Transition-Metal Mediated Fluorination and Fluoroalkylation Reactions

By

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Abstract

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The following dissertation discusses the development, study, and applications of methods to prepare perfluoroalkyl arenes, difluoromethyl arenes, aryl difluoromethyl ethers, and aryl fluorides. The final section discusses the use of a C-H fluorination reaction for the synthesis and late-stage functionalization of complex molecules. In addition to developing reactions to prepare fluorinated compounds, the mechanisms were investigated through experimental and computational methods.

Chapter 1 provides a review of the importance of fluorinated compounds and how such compounds are typically prepared. The challenges involved with developing new reactions to form Ar-F or Ar-CF_2R bonds are discussed, along with the approaches that have been taken to address these challenges. A detailed discussion of state of the art methods follows, particularly focused on reactions with transition metal reagents or catalysts. Comments on how these new reactions have expanded the field of fluorination and fluoroalkylation are provided. Each section closes with a forward looking statement on what major challenges remain, and how such issues may be overcome.

Chapter 2 describes a method for the synthesis of perfluoroalkyl arenes from aryl boronate esters. This method was extended to the perfluoroalkylation of Ar-H and Ar-Br bonds through initial formation of ArBPin reagents in-situ.

Chapter 3 discusses a reaction to extend the scope of perfluoroalkylation chemistry to include a variety of heteroarylbromide substrates as reacting partners. These reactions occur with remarkable scope and functional group tolerance for the preparation of trifluoromethyl heteroarenes.

Chapter 4 discusses the development of the first difluoromethylation cross-coupling reaction. These reactions occur with simple reagents and occur in good yields for the difluoromethylation of electron-neutral and electron-rich aryl iodides.

Chapter 5 describes the development of a broadly applicable method for preparing aryl difluoromethyl ethers. These reactions occur under mild conditions within seconds at room temperature.

Chapter 6 describes the design of a new copper reagent for the fluorination of aryl iodides with AgF. This work was the first example of copper in the synthesis of functionalized aryl fluorides, and the first example for the fluorination of unactivated aryl halides.

Chapter 7 discusses the extension of the work in Chapter 6 for the fluorination of aryl boron reagents with our newly designed copper reagent. The mechanism of this transformation was investigated, and our data is consistent with the formation of the aryl fluoride from an Ar-Cu(III)-F species.

Chapter 8 describes a simple and general method for prepare fluorinated heteroarenes directly through C-H fluorination. The design of such a fluorination reaction was inspired by a classic C-H amination reaction.

Chapter 9 extends from the work discussed in Chapter 8 and demonstrates how the C-H fluorination reaction can be used as a versatile reaction for accessing a variety of 2-heteroaryl compounds. The utility of this was demonstrated in several syntheses and late-stage functionalization reactions of important medicinal compounds.

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Acknowledgements

It is surreal that I am receiving a receiving a PhD in chemistry from UC Berkeley. This is mostly surprising because I was not admitted when I applied to Berkeley for graduate school in the fall of 2009. While my dreams of attending Berkeley and moving to California vanished when I received that rejection letter, I was thrilled to attend the University of Illinois. Though I only spent a year at UIUC before our group moved to UC Berkeley, the UIUC chemistry department was an incredible place to be. I learned a lot about chemistry, made many great friends, and would have been happy to finish my degree there. However, I certainly can't complain about how things ended up. My time at Berkeley has been enjoyable, and I wouldn't change anything about how the events unfolded. I am thankful to many people I interacted with throughout my academic path, and some of the most notable are acknowledged below.

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CHAPTER 1

Overview of Methods for the Synthesis of Fluoroalkylarenes and Aryl Fluorides

1.1 Applications of Fluorinated Compounds

Fluorine has become a mainstay in the design and development of new bioactive small molecules. Approximately 20% of currently marketed drugs, and nearly half of the small molecules approved by the FDA in 2013,[1] contain at least one fluorine atom. Most commonly, fluorine is found attached directly to an arene (ArF), or as 2 or 3 fluorine atoms at a benzylic position ($ArCF_2H$, $ArCF_2R$, $ArCF_3$). The wide spread prevalence of these fluorinated moieties in drugs is surprising if one considers that none of these are naturally occurring in nature. Two examples of drugs containing fluorine are shown in Figure 1.1; Isentress (reltegravir) is a first-in-class integrase inhibitor used to treat HIV infection, and Januvia (sitagliptin) is a DPP-4 inhibitor used in the treatment of diabetes mellitus type 2. Of course, the applications of fluorinated compounds extend far beyond pharmaceutical compounds, as fluorine is commonplace in several other areas of chemistry, including agrochemicals, polymer chemistry (Teflon, Nafion), materials, electronics, refrigerants, and dyes. Yet, despite the tremendous importance and widespread applications of fluorinated organic compounds, there remain significant limitations in the methods for forming Ar-F or Ar-CF_2R bonds. The challenges and limitations that need to be addressed will be discussed in the next three sections of this introduction chapter, as well as the introductory portion of the remaining chapters.

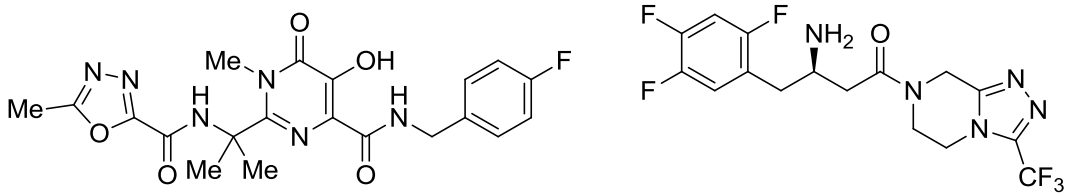


Figure 1.1 Examples of fluorine-containing pharmaceutical compounds

The replacement of a hydrogen atom by fluorine in a drug candidate can impart subtle or drastic effects on a variety of physical and biological properties.[2] The incorporation of an electron-withdrawing fluorine or fluorinated group will result in a decrease in basicity, or an increase in acidity, of neighboring functionality. This impact on pK_a can impact hydrogen-bonding and other binding interactions between a compound and target. The attachment of fluorine or a fluoroalkyl group to an arene most often leads to an increase in lipophilicity, which can lead to enhanced membrane permeability, absorption, and bioavailability. Since fluorine is the most electronegative element, its incorporation in a molecule tends to decrease the susceptibility of a compound to oxidation, a common enzymatic degradation method that leads to removal of a drug from the system. By impeding this metabolic process, fluorine incorporation often leads to an increased half-life of a drug candidate and can prevent the formation of toxic byproducts that result from such oxidation processes. Taken together, these effects of fluorine in a bioactive small molecule can improve the biological activity and efficacy of a drug candidate. Some examples of this are illustrated in Figure 1.2. In the development of Zetia (ezetimibe), a drug used to inhibit intestinal absorption of cholesterol, the replacement of a hydrogen atom by fluorine prevented oxidative arene degradation.[3] In

the development of Emend (aprepitant), a drug used to treat nausea, the two trifluoromethyl groups provided a significant increase in CNS permeability, and the incorporation of a fluorine atom on the other arene led to a further 2-fold increase in potency.[4]

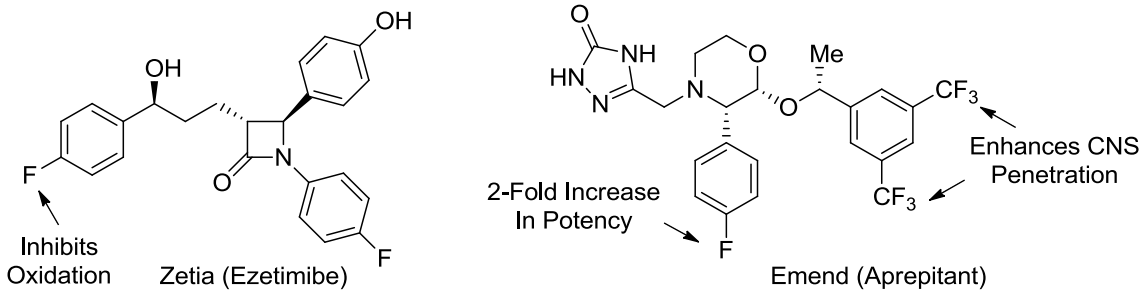


Figure 1.2 Examples demonstrating the impact of fluorine on biological activity

Despite the growing importance of fluorinated compounds, methods that are used to form the C-F or C-CF_2R (R = H, F, organyl) bonds in these molecules have required toxic reagents and forcing reaction conditions that are not practical in a typical laboratory setting or for the fluorination of functionalized substrates. Because of this, the fluorine atoms in pharmaceutical compounds are most commonly introduced using pre-fluorinated building blocks. While this approach has advantages for large-scale manufacturing, the use of pre-fluorinated building blocks can limit synthetic efficiency in drug discovery, and can limit the diversity of compounds that can be accessed. To address the severe synthetic limitations of classic methods, the unique reactivity of transition metal catalysts and reagents has been used to greatly improve the scope of fluoroalkylation and fluorination chemistry.

This remainder of this introductory chapter is divided into three sections; 1.2) methods for preparing $ArCF_3$ compounds, 1.3) methods for preparing $ArCF_2H$ compounds, and 1.4) methods for preparing aryl fluorides. Each section contains a brief discussion of traditional methods to prepare that class of compound, challenges for employing transition metal catalysts/reagents, current state of the art methods, and a summary of what major limitations remain and potential solutions.

1.2 Methods for Preparing $ArCF_3$ Compounds

Trifluoromethylarenes are among the most common fluorinated compounds and are found in many top-selling drugs (Prozac, Celebrex) and agrochemicals (Lariam, Fipronil). On an industrial scale, $ArCF_3$ compounds are prepared from the corresponding $ArCH_3$ precursor in two steps through benzylic chlorination followed by fluoride displacement with SbF_3 (Swarts reaction, Figure 1.3).[5] While this route to $ArCF_3$ compounds is reliable for preparing simple trifluoromethyl-containing building blocks, its use in a typical laboratory setting is not practical, and the harsh reaction conditions are not compatible with complex molecules. Alternatively, trifluoroacetic anhydride is an inexpensive and reliable source of a C(sp^2)-CF_3 unit through annulation/condensation type reactions at the carboxyl group. This approach has been applied in the large scale

synthesis of numerous heteroaryl-CF_3 compounds, including Januvia (Figure 1.1) and Celebrex.

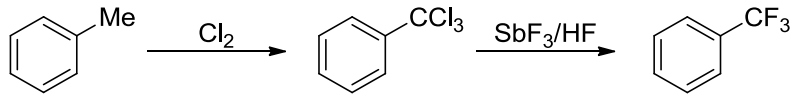


Figure 1.3 The Swarts reaction used to prepare $ArCF_3$ from $ArCH_3$

To address the severe synthetic limitations of the Swarts reaction, several alternative reactions have been developed which form the Ar-CF_3 bond under milder conditions than forming the ArC-F_3 bonds.[6] The majority of the work in this area has employed copper reagents or catalysts to couple aryl electrophiles or nucleophiles with a CF_3 unit. Several challenges exist in the development of these trifluoromethylation reactions, which are shown schematically in Figure 1.4 for a generic catalytic cycle between an aryl halide and a CF_3 nucleophile. With the exception of one Pd/phosphine catalyst, all cross coupling reactions with CF_3 have been developed with copper.

The major challenges that must be overcome in the development of copper-mediate trifluoromethylation reactions mostly revolve around the unstable CF_3 anion. Most trifluoromethyl anions are known to undergo rapid loss of fluoride to generate difluorocarbene (faster decomposition with harder counter cations). The difluorocarbene liberated can react with M-CF_3 species to generate homologated M-CF_2CF_3 species which lead to ArC_2F_5 side products. Trifluoromethyl anions are also strong nucleophiles that readily add to electrophiles, including the amides that are employed as the reaction solvent (DMF, DMA, etc.). The nucleophilic CF_3 anion can also displace the datively bound ligands of the metal complexes that are involved in the catalytic cycle. For these reasons, the concentration of unstable CF_3 anions must be minimized, and this has been addressed by using CF_3 anion surrogates. Most commonly trifluoromethylsilanes (Me_3SiCF_3, Et_3SiCF_3) have been employed which react with an exogenous Lewis base, such as fluoride, to generate pentacoordiante silicates that can transfer the anionic CF_3 group to the transition metal while avoiding the above mentioned side reactions. However, such an approach requires a careful balance of the reactivity of the silane and Lewis base with that of the transition metal catalyst/reagent. Because the penta-coordinate silicate can release CF_3 anions into solution, preformed Cu-CF_3 complexes have recently been used to avoid the above mentioned side-reactions.

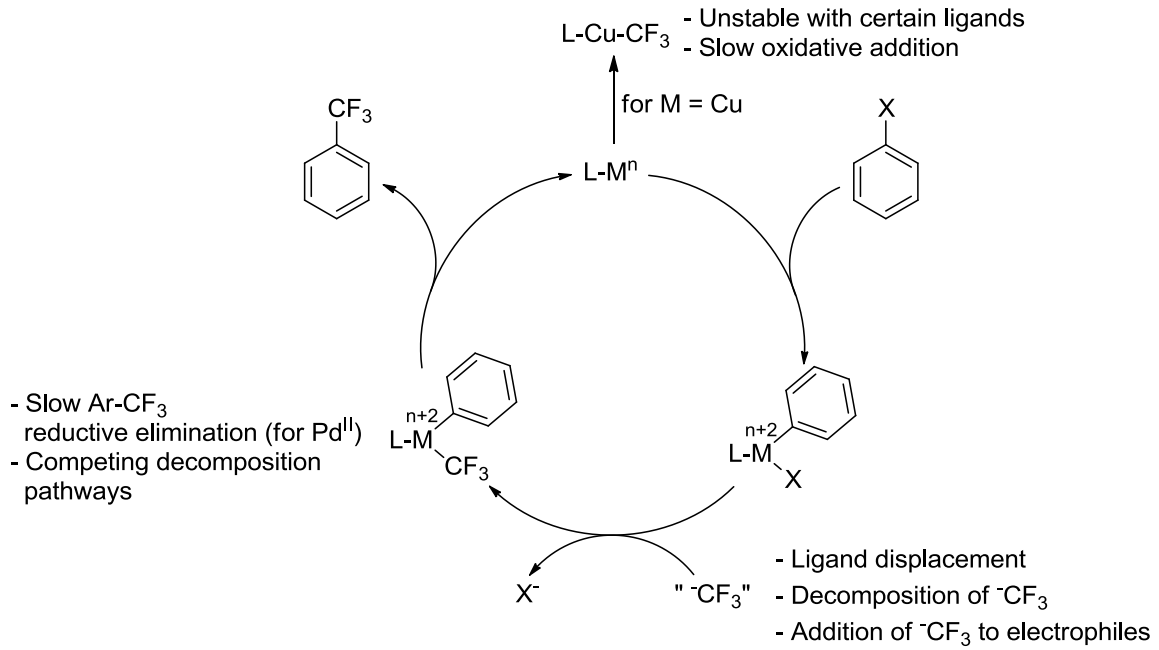


Figure 1.4 Potential catalytic cycle for the trifluoromethylation of an aryl electrophile and challenges associated with each step

As mentioned above, most trifluoromethylation reactions have used Cu instead of Pd. Besides the challenges associated with trifluoromethyl anions, the major roadblock in developing a trifluoromethylation reaction with Pd is the slow reductive elimination step that forms the Ar-CF_3 bond from an Ar-Pd(II)-CF_3 intermediate. The strong, polarized Pd-CF_3 bond must be partially broken in the transition state to form the Ar-CF_3 bond. The high electronegativity of the CF_3 group also means that the electron density in the Pd-CF_3 bond is polarized towards CF_3, resulting in poor orbital overlap with the Pd-Ar bond. Finally, the CF_3 is sufficiently large such that a large entropic barrier must be overcome to bring the aryl group and CF_3 group together for reductive elimination. Notably, these issues are easily overcome in copper-mediated reactions, since the analogous Cu(III) intermediate is smaller size and is more electronegative than Pd(II), and reductive elimination from a higher valent metal is faster than a comparable, isoelectronic, lower valent metal. Futhermore, reductive elimination is faster from a first row transition-metal than a second row transition-metal.

Seminal, in-depth stoichiometric studies aimed at promoting Ar-CF_3 reductive elimination from Ar-Pd(II)-CF_3 complexes were performed by Grushin and Marshall.[7] It was found that Ar-CF_3 reductive elimination could be promoted by the wide bite-angle bisphosphine XantPhos (Figure 1.5), however, attempts to make the reaction catalytic were unsuccessful due to competing ligand displacement of XantPhos by CF_3 anion. Later, Buchwald and coworkers developed a catalytic trifluoromethylation reaction of aryl chlorides with Et_3SiCF_3.[8] The use of Et_3SiCF_3 in place of the trimethylsilyl reagent was essential to slow down the rate of the competitive background decomposition of the trifluoromethylsilane. Ar-CF_3 reductive elimination in these reactions, confirmed by stoichiometric reactions with L-Pd(Ar)(CF_3) complexes, was promoted by bulky monophosphine ligands (L = BrettPhos or RuPhos). While this represents a major

achievement in the field, the reactions require high loadings of palladium (6-8 mol % Pd) as well as the expensive ligands (9-12 mol %). Although aryl chlorides are much more attractive electrophiles than aryl iodides, the scope of these reactions is significantly less than reported Cu based systems.

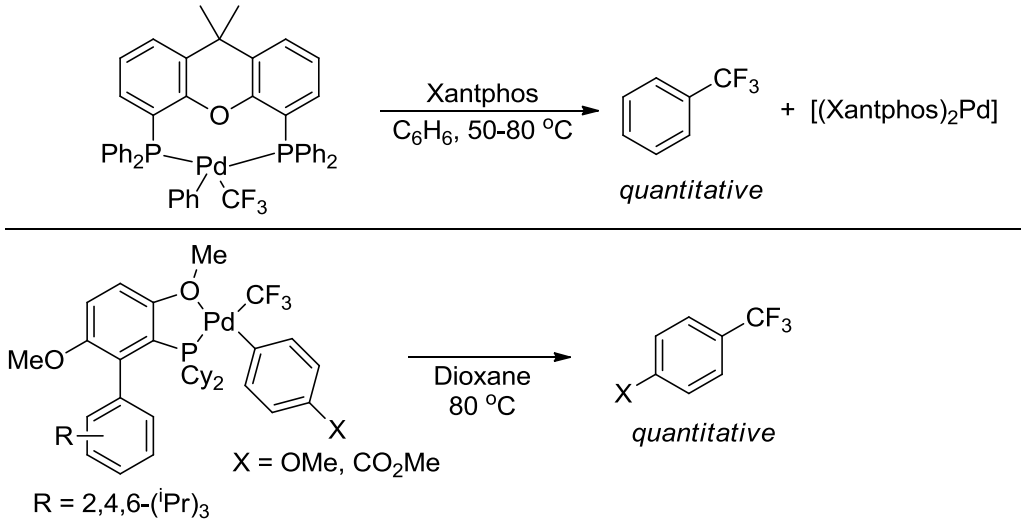


Figure 1.5 Ar-CF_3 reductive elimination from Pd(II)

The first cross-coupling reaction with a perfluoroalkyl group was published by McLoughlin and Thrower in 1969.[9] In these reactions, stoichiometric copper metal was employed to mediate the reductive coupling between aryl iodides with perfluoroalkyl iodides. Since this landmark publication, significant work has been done to use copper(I) salts to mediate or catalyze the coupling of aryl iodides with a CF_3 anion source; most commonly $TMSCF_3$, CF_3CO_2Na, $ClCF_2CO_2Me$ + F^-, $FSO_2CF_2CO_2Me$, and recently HCF_3[10] (Figure 1.6).[6] Most often, stoichiometric quantities of a copper salt are added to the reaction, and only recently has copper catalyzed trifluoromethylation been realized. In 2009 Amii reported the use of catalytic CuI and phen (10 mol % each) with Et_3SiCF_3 and KF for the trifluoromethylation of aryl iodides.[11] Subsequent copper catalyzed trifluoromethylation reactions were reported in 2011 by Amii with a fluoral hemiaminal,[12] and by Goossen with $CF_3B(OMe)_3K$, also in 2011.[13]

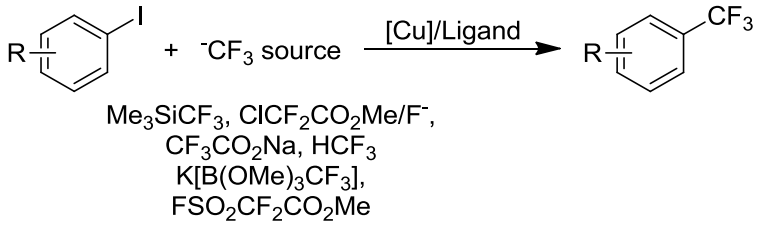


Figure 1.6 Copper mediated trifluoromethylation reactions of aryl iodides

The best functional group tolerance and broadest substrate scope for the trifluoromethylation of aryl iodides is realized with preformed [Cu-CF_3] complexes

(Figure 1.7), most notably (phen)$CuCF_3$ developed by the Hartwig group,[14] and to a lesser extent $(Ph_3P)_3CuCF_3$ developed by Grushin,[15] and NHC-Cu-CF_3 complexes developed by Vicic.[16] These preformed and pre-ligated Cu-CF_3 complexes prevent decomposition reactions that are observed when CF_3 anions are generated and pre-ligation improves the tolerance towards basic functionality.

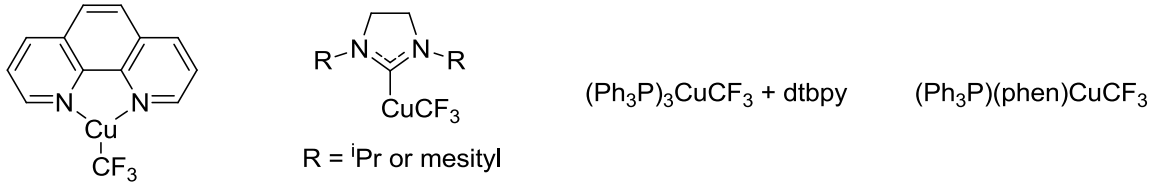


Figure 1.7 Well-defined $CuCF_3$ complexes used in stoichiometric trifluoromethylation reactions

An alternative approach to preparing $ArCF_3$ compounds involves the reactions of aryl nucleophiles with electrophilic CF_3 reagents under redox neutral conditions, or with nucleophilic CF_3 reagents under oxidizing conditions. These alternative approaches can occur with different functional group compatibility and substrate scope than the reactions described above with aryl electrophiles. The most common and synthetically attractive nucleophiles are aryl boronic acids or derivatives, which have been the focus of several trifluoromethylation reactions. The mechanisms by which these processes operate have not been determined with certainty, and several possible mechanisms could be operative depending on the reaction conditions.

Examples for the electrophilic trifluoromethylation of aryl boronic acids are shown in Figure 1.8. In 2011, Shen reported the coupling of aryl boronic acids with Togni's hypervalent λ-3-iodane reagent with 5 mol% CuI and 10% phen in the presence of K_2CO_3 under mild conditions.[17] The same year, the groups of Liu[18] and Xiao[19] independently reported the use of *S*-trifluoromethylsulfonium reagents with catalytic CuOAc, or super stoichiometric Cu metal, respectively, for the trifluoromethylation of aryl boronic acids.

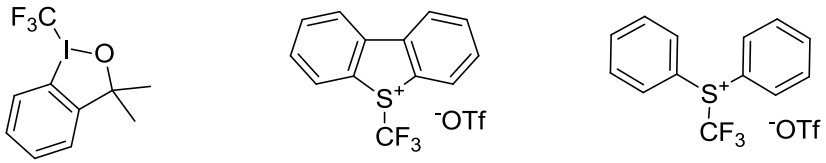
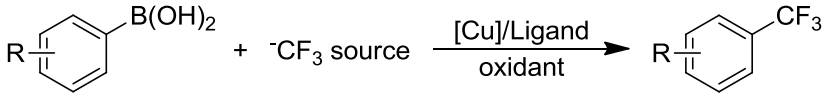


Figure 1.8 Reagents and reaction conditions for the electrophilic trifluoromethylation of aryl boronic acids

Oxidative coupling reactions of aryl boronic acids with nucleophilic CF_3 reagents have also been developed. These oxidative reactions avoid the expensive and potentially explosive electrophilic CF_3 reagents. The first example of this was reported by Qing and coworkers in October of 2010.[20] These reactions occurred with stoichiometric amounts of an expensive air and moisture sensitive copper reagent, $[Cu(OTf)]_2 \bullet C_6H_6$, with 1 equiv of

Ag_2CO_3 as the stoichiometric oxidant (Figure 1.9). Two years later, the same group reported that the same reaction conditions could be used with catalytic amounts of the copper triflate reagent (20 mol % Cu) if the boronic acid and $TMSCF_3$ were added slowly with a syringe-pump.[21]

Significantly improved reaction conditions were reported 3 months later by Buchwald[22] in January of 2011 using inexpensive and air-stable, though still stoichiometric, $Cu(OAc)_2$ in combination with phen, $TMSCF_3$, and CsF at room temperature (Figure 1.9). In these reactions, at atmosphere of O_2 was used as the terminal oxidant. Over a year later, Grushin reported a similar oxidative coupling reaction with unligated $CuCF_3$, formed by the direct cupration of HCF_3, under an atmosphere of air.[23] The authors stress that the benefit of this reaction is that fluoroform is cheaper than $TMSCF_3$, however the cost of $TMSCF_3$ is negligible on laboratory scale (less than \$1/g for 100 g from Oakwood Chemical), and in most cases the overall cost of the reaction will depend mostly on the cost of the boronic acid reagent. In addition, the use of a gaseous reagent is not as practical as using a liquid reagent, and the cost per gram of HCF_3 on decagram scale from commercial suppliers is more expensive than $TMSCF_3$ due to the added cost of the gas cylinder (\$125 for 50 g from Synquest). Finally, the demonstrated functional group tolerance for the reactions with $CuCF_3$ from HCF_3 is limited (demonstrated with aldehydes, ketones, esters) compared to that of the Buchwald system with $TMSCF_3$ (demonstrated with ketones, esters, carbamates, silyl ethers, free N-H bonds, and several nitrogen heterocycles).



$[Cu(OTf)]_2 \cdot C_6H_6$ (1.2 equiv Cu)	Cu(OAc) (1.0 equiv)	1) CuCl (2 equiv)	ligandless $CuCF_3$
phen (1.2 equiv)	phen (1.1 equiv)	KO^tBu (4 equiv)	
Ag_2CO_3 (1.0 equiv)	CsF (2.0 equiv)	HCF_3 (excess)	
KF (5.0 equiv)	Me_3SiCF_3 (2.0 equiv)	$Et_3N(HF)_3$ (0.67 equiv)	
K_3PO_4 (3.0 equiv)	Molecular sieves	2) add $ArB(OH)_2$	
Me_3SiCF_3 (5.0 equiv)	DCE or ^{i}PrCN	DMF +/- PhMe	
DMF, 45 °C	O_2 atmosphere, rt	air atmosphere, rt	
Qing	**Buchwald**	**Grushin**	

Figure 1.9 Reagents and reaction conditions for the oxidative trifluoromethylation of aryl boronic acids

An alternative approach to the trifluoromethylation of boronic acids was reported by the Sanford group. Two similar copper-mediated reactions of aryl boronic acids with CF_3 radicals were published in 2012. The CF_3 radicals were generated from gaseous CF_3I with a photocatalyst,[24] or from a more practical salt, $NaSO_2CF_3$ (Langlois' reagent) with ^{t}BuOOH.[25] These radical reactions occur with comparable scope to other trifluoromethylation reactions of $ArB(OH)_2$. Notably, these reactions are performed with water as a co-solvent; which offers a practical advantage to nearly all other trifluoromethylation reactions which require anhydrous reaction conditions.

The reactions discussed in the previous paragraphs for the trifluoromethylation of aryl boronic acids were not demonstrated to work for the trifluoromethylation of the more

synthetically accessible pinacol boronate esters (ArBPin). ArBPin reagents are attractive alternatives to $ArB(OH)_2$ since they can be prepared through several different C-H borylation reactions,[26] and are the most common products of Miyaura borylation (ArX to ArBPin). Furthermore, because the most common routes to $ArB(OH)_2$ involve the addition of ArLi or ArMgX reagents to $B(OR)_3$ with subsequent hydrolysis, the diversity of aryl boronic acids that can be directly accessed is limited due to the use of organometal species. In many cases, $ArB(OH)_2$ substrates are prepared from the corresponding ArBPin compound through oxidative hydrolysis of pinacol, however this method requires a separate synthetic step, is often low yielding, and is not tolerant of acid- or oxidant-sensitive substrates. Thus, a route to $ArCF_3$ products directly from ArBPin reagents would be a significant advance in the field.

Chapter 2 describes the development of a trifluoromethylation reaction of ArBPin reagents with $(phen)CuCF_3$ and KF in air, and will not be discussed in detail here.[27] Simultaneous with our work, Shen[28] and coworkers developed a similar reaction for the trifluoromethylation of ArBPin reagents with Togni's electrophilic CF_3 reagent (structure shown in Fig 1.8) catalyzed by the combination of CuTC (10 mol %) and phen (20 mol %) with $LiOH•H_2O$ as the base. In these two reports, published back-to-back in 2012, the synthetic utility was demonstrated by performing tandem C-H borylation followed by trifluoromethylation of the crude reaction mixture for an overall 2-step, 1-pot C-H trifluoromethylation reaction (Figure 1.10). A few weeks later, Goossen and coworkers described the oxidative trifluoromethylation of ArBPin with $CF_3B(OMe)_3K$ and 1 equiv of CuOAc.[29] In contrast to the reactions of ArBPin reagents with preformed $(phen)CuCF_3$, the use of the nucleophilic borate salt does not allow for these reactions to be performed with substrates containing common electrophilic functionality.

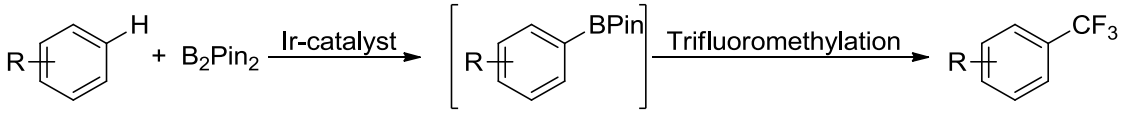


Figure 1.10 Trifluoromethylation of ArBPin reagents, and formal C-H trifluoromethylation

Despite the tremendous progress in the development of mild and general trifluoromethylation reactions, several challenges remain to be addressed. The substrate scope and reliability for several of the state of the art methods described above, most notably for reactions with stoichiometric $(phen)CuCF_3$, are on par with many widely used cross-coupling reactions. The major limitation in this area is that there are no reports of broadly applicable trifluoromethylation reactions for aryl bromides or phenol-derived electrophiles. This limitation is significant since these electrophiles are much more common and significantly less expensive than aryl iodides. We partially addressed this limitation by developing a method for the trifluoromethylation of a wide range of heteroaryl bromides with $(phen)CuCF_3$ (see Chapter 3).

To extend the scope of electrophiles that react with Cu, ligands and reaction conditions must be identified which increase the rate of oxidative addition of Cu(I) such that non-activated aryl bromides can react. Solving this problem is not trivial, as $CuCF_3$ complexes, if formed under the reaction conditions, are much less electron rich than other Cu(I) salts, and are less reactive towards oxidative addition.[30] One approach would be to

design a system where the CF_3 group does not transmetallate to Cu(I), but rather to Cu(III) after oxidative addition of the aryl halide to Cu(I). Such a mechanism would require the identification or development of a weakly nucleophilic CF_3 reagent. In the design of new L-Cu-CF_3 reagents/catalysts, the appropriate ligand must not only increase the rate of oxidative addition, but also be able to mediate the other steps of the catalytic cycle. If the reagent will be used stoichiometrically, as with (phen)$CuCF_3$, the dative ligand must also be inexpensive.

It is likely that the future of trifluoromethylation chemistry will rely, at least partially, on the development of nickel catalysts. Ni(0) complexes are well known to undergo facile oxidative addition with a wide variety of aryl halides, including unactivated aryl chlorides, as well as numerous phenol-derived electrophiles. The challenges in developing Ni-catalysts for trifluoromethylation are similar to those faced for Pd-catalysts (*vide supra*). Preliminary work in this area has been done by Vicic, confirming the predictions that the reductive elimination from an isolated Ar-Ni(II)-CF_3 species is slow.[31] However, only a single bisphosphine ligand (dippe) was examined in this study! The investigation of other ligands will certainly increase the likelihood of finding reaction conditions that can mediate Ar-CF_3 bond formation from Ni(II), and this approach should be the first step to solving this problem. Similarly, efforts should be made to improve upon the current Pd-based catalysts for the trifluoromethylation of aryl chlorides.

As mentioned above, the cost of $TMSCF_3$ is negligible on laboratory scale and is available from numerous suppliers. The use of $TMSCF_3$ could be practical on large scale. However, it is unlikely that Ar-CF_3 coupling reactions will replace the Swarts reaction for the synthesis of simple $ArCF_3$ building blocks in the near future due to the cost of the other reaction components. Yet, there is potential for Ar-CF_3 coupling reactions to be applied to the kg-scale synthesis of more specialized $ArCF_3$ compounds on large scale if the value of the final compound justifies the use of expensive iodide or boronic acid starting materials.

As the development of new trifluoromethylation reactions progresses, new $ArCF_3$ scaffolds and substitution patterns will be accessible within drug discovery that may not have been available from commercially available trifluoromethyl building blocks. As such compounds are explored and developed into potential drug candidates, and the (precursors to) such compounds are not available through Ar$C\text{-}F_3$ bond formation, then reactions must be developed to perform the Ar-CF_3 bond formation on scale. Indeed, this type of situation has recently been encountered. Notably, two multi-kg scale trifluoromethylation reactions have been reported with aryl and vinyl iodide substrates to prepare pharmaceutical compounds, where the appropriate CF_3-containing building blocks were inaccessible. In 2013, chemists at Boehringer-Ingelheim reported the trifluoromethylation of a 3-iodopyridine (7 kg) with $ClCF_2CO_2Me$ (3.0 equiv), CuI (1.5 equiv), and KF (1.1 equiv) in NMP at 120 ^oC.[32] In 2014, process chemists at Merck reported the trifluoromethylation of a vinyl iodide (36 kg) with $FSO_2CF_2CO_2Me$ (2.0 equiv), CuI (20 mol %), 2,6-lutidine (20 mol %) in DMF at 90 ^oC.[33]

1.3 Methods for Preparing $ArCF_2H$ Compounds

Similar to arenes bearing a trifluoromethyl group, those bearing a difluoromethyl group are also prevalent in biologically active small molecules. Unlike the CF_3 group, the CF_2H group can participate as a hydrogen-bond donor,[34] and is often invoked as a lipophilic bioisostere of alcohols and thiols.[35] Despite the importance of difluoromethylarenes, methods for their synthesis are significantly less developed than methods to prepare trifluoromethylarenes.[36]

The most common route to $ArCF_2H$ compounds involves the fluoro-deoxygenation of the corresponding benzaldehyde with a S(IV) fluoride reagent.[37] The most common reagents to perform this reaction are DAST (diethylaminosulfur trifluoride), or the more thermally stable analog Deoxo-Fluor, Bis(2-methoxyethyl)aminosulfur trifluoride (Figure 1.11). Although these reagents have become routine in organofluorine chemistry, care must be taken with these reagents since they readily release toxic HF upon contact with moisture. However, this route to difluoromethylarenes requires access to the corresponding benzaldehyde, which is often prepared in one or more steps from the corresponding aryl halide (i.e. carbonylation with CO/H_2 or reaction of the Grignard or lithium reagent with DMF), or reduction of the benzoic acid derivative. An attractive alternative to this multi-step approach would be to directly convert an aryl halide to a difluoromethylarene.

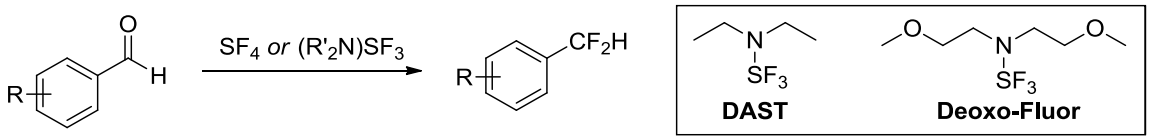


Figure 1.11 Traditional methods to prepare difluoromethylarenes through fluoro-deoxygenation with S(IV) fluoride reagents

Several challenges exist for the cross-coupling of a difluoromethyl group with an aryl electrophile or nucleophile. In contrast to the handful of thermally stable trifluoromethyl-copper complexes (Figure 1.7), no thermally stable difluoromethyl-copper complexes have been prepared. While trifluoromethyl-copper complexes undergo decomposition through α-fluoride elimination to generate difluorocarbene, difluoromethyl-copper undergoes bimolecular decomposition to generate tetrafluoroethane and 1,2-difluoroethylene.[38] Furthermore, the same challenges that were discussed above involving the CF_3 anion are also true for the CF_2H anion (addition to electrophiles, ligand displacement, and decomposition to carbene).

The challenge of cross coupling with CF_2H vs CF_3 is further complicated by the much fewer sources of $^-CF_2H$ compared to $^-CF_3$. While several trifluoroacetic acid derivatives can be used as CF_3 sources (CF_3CO_2Na, $ClCF_2CO_2Me + F^-$, $FSO_2CF_2CO_2Me$, etc.), analogous reagents that generate difluoromethyl anions are unknown (i.e. the decarboxylation of HCF_2CO_2Na), this is because the trifluoromethyl precursors proceed through the concerted loss of CO_2 and X^- to generate difluorocarbene which then reacts with the liberated or exogenous fluoride anion to generate $^-CF_3$.

The use of M-CF_2H reagents (M = SiR_3, SnR_3) as CF_2H sources can present several challenges when compared to analogous M-CF_3 reagents. First, the lower

electronegativity of CF_2H compared to CF_3 means that M is less Lewis basic, and therefore has a decreased propensity to form a penta-coordinate metallate. The penta-coordinate metallate must be formed prior to transfer of the anionic group from M. Similarly, it is likely that transfer of the CF_2H anion from the penta-coordinated metallate will occur at a lower rate compared to the analogous transfer of CF_3 anion.

Finally, electrophilic CF_2H sources are much less developed than analogous electrophilic CF_3 sources, and are also much less stable. With the exception of (pseudo)halodifluoromethanes, only one stable $^+CF_2H$ reagent has been reported, $[Ar_2S\text{-}CF_2H]BF_4$.[39] This reagent has been employed in the difluoromethylation of weak nucleophiles under essentially neutral reaction conditions (sulfonate salts, imidazoles, phosphines, and tertiary amines). The challenge in using electrophilic CF_2H reagents for preparing $ArCF_2H$ compounds lies in the fact that reactions with nucleophiles (i.e. aryl boronic acids) occur under basic conditions which leads to the rapid and irreversible decomposition of the electrophilic CF_2H reagent to difluorocarbene. These deprotonation reactions are fast for many [X] groups (Figure 1.12), and is a reliable route to generate difluorocarbene for the synthesis of aryl difluoromethyl ethers (see Chapter 5).

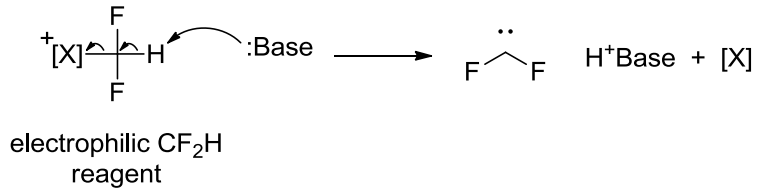


Figure 1.12 Reactions of electrophilic CF_2H reagents under basic conditions

At the time we began our work on difluoromethyl cross-coupling (Chapter 4), there had only been one report to form difluoromethylarenes from iodoarenes (Figure 1.13). Amii reported the coupling reaction of the TMS enolate of ethyl difluoroacetate with iodoarenes to generate ethyl α-aryl-α,α-difluoroacetates. The esters were then subjected to hydrolysis to generate the difluoroacetic acid derivatives. Decarboxylation of the carboxylic acid was effected at high temperature, but was only reported to work when an electron-withdrawing group was present on the arene ring, or when the arene component was pyridine.[40] This 3-step procedure was, at the time, the only route to form $ArCF_2H$ compounds from aryl halides, albeit with limited scope and generality.

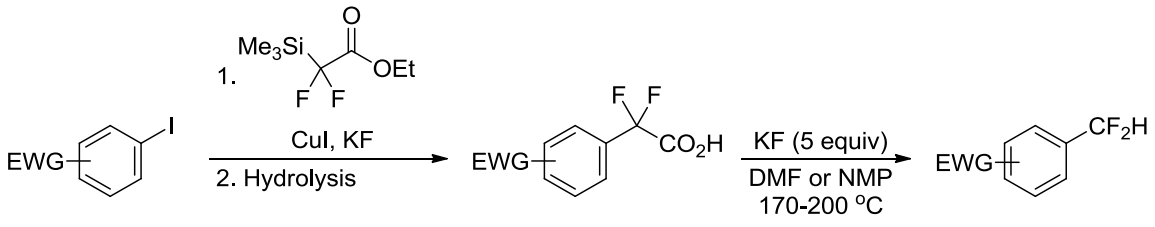


Figure 1.13 3-step synthesis of difluoromethylarenes from aryl iodides with $Me_3SiCF_2CO_2Et$

In March of 2012, we published the first example for the direct cross coupling with CF_2H for the synthesis of $ArCF_2H$ compounds from aryl iodides with CuI, CsF and $TMSCF_2H$ (see Chapter 4). The scope of this reaction encompassed a range of electron-neutral and electron-rich aryl and vinyl iodides. In October of 2012, Prakash and

coworkers reported a complimentary approach to prepare $ArCF_2H$ compounds from aryl iodides with Bu_3SnCF_2H, CuI and KF (Figure 1.14).[41] Despite the similar reaction conditions to our work, surprisingly their reaction worked best for electron-deficient aryl iodides. This finding suggests that different mechanisms are operative, and that the Cu intermediates that are formed in the reactions with the silane react with different scope than the Cu intermediates formed in the reactions with the stannane reagent. Both of these reactions operate at 100-120 ^oC in an amide solvent without a strongly coordinating dative ligand. This is in contrast to the fact that most trifluoromethylation reactions employ phenanthroline or a similar pyridine-type ligand and typically occur at lower temperatures.

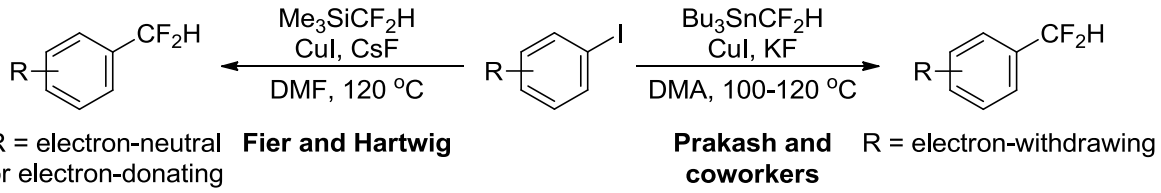


Figure 1.14 Direct difluoromethylation of aryl iodides with CuI and [M]-CF_2H reagents

Following these two reports, two other methods have been reported to prepare $ArCF_2H$ compounds from aryl halides. The Hartwig group reported a Pd-catalyzed α-arylation reaction of α,α-difluoroacetophenone with aryl bromides and chlorides, followed by cleavage of the $ArCF_2$-COPh bond with concentrated KOH. This is the first example for the synthesis of difluoromethylarenes from unactivated aryl bromides and chlorides; however a direct cross-coupling reaction with CF_2H should be the focus of future studies. Earlier this year, Qing and coworkers described the direct difluoromethylation of electron-poor aryl iodides, comparable to Prakash's work described in the previous paragraph, with 1.2 equiv each of CuCl and phen, and 2.4 equiv each of $TMSCF_2H$ and KO^tBu.[42] Notably, these reactions were reported to occur in DMF at room temperature.

As discussed in the previous section, a handful of methods exist for the cross coupling of aryl boronic acids with CF_3 sources (see section 1.2). However, analogous methods for the difluoromethylation of boronic acids have yet to be reported. This is due to a combination of the instability of $^+CF_2H$ reagents, discussed above (Figure 1.12), and the instability of Cu-CF_2H reagents. The challenges in developing such a direct transformation of $ArB(OH)_2$ to $ArCF_2H$ means that work in the near future in this area will likely rely on the use of CF_2H surrogates to generate a functionalized intermediate, $ArCF_2$-[FG], followed by a subsequent transformation of $ArCF_2$-[FG] to $ArCF_2H$ (i.e. FG = SO_2Ph with reductive cleavage, FG = CO_2H with decarboxylation, or FG = $SiMe_3$ with proto-desilylation). Alternatively, the reaction of aryl boronic acids with CF_2H radicals could be a promising direction for preparing difluoromethylarenes from aryl boronic acids, analogous to the work performed by Sanford described in Section 1.2.[24-25] Notably, the Baran group has demonstrated that $Zn(SO_2CF_2H)_2$ in the presence of ^tBuOOH is a convenient source of difluoromethyl radicals,[43] and exploring reactions of aryl boronic acids with this zinc sulfinate reagent could be a fruitful pursuit.

Future work in difluoromethylation should also investigate Pd-catalyzed cross-coupling reactions of $^{-}CF_2H$ with aryl bromides and chlorides. Such a direct reaction will represent a major breakthrough in the field. Although it is likely that reductive elimination from Ar-Pd(II)-CF_2H species will be faster than Ar-Pd(II)-CF_3 complexes, it is unclear if such Pd(II) compounds will react through other decomposition pathways (i.e. α-hydride elimination), and if these intermediates can be accessed under catalytic conditions. The synthesis, isolation, and study of Ar-Pd(II)-CF_2H complexes will lay the foundation for developing catalytic reactions that occur through these intermediates.

In summary, while numerous reactions to reliably prepare diverse trifluoromethylarenes have been developed, especially within the past 5 years, analogous methods to form difluoromethylarenes are lagging far behind. The limited scope and generality of current difluoromethylation reactions, combined with few commercially available difluoromethylarene building blocks, severely limits the accessibility to $ArCF_2H$ compounds, notably in drug discovery chemistry. With the development of new routes to prepare this class of compounds, the prevalence of difluoromethylarenes in the development of new biologically active small molecules is likely to increase given the unique properties of the CF_2H group as a lipophilic hydrogen bond donor and as a metabolically stable bioisostere of alcohols and thiols.

1.4 Methods for Preparing Aryl Fluorides

Aryl fluorides are the most common fluorinated moiety in pharmaceuticals and agrochemicals. As with fluoroalkylarenes, aryl fluorides are often installed in a molecule through incorporation of a pre-fluorinated building block. This approach is certainly the most reliable and cost effective route to prepare compounds containing simple aryl fluoride units. Aryl fluoride building blocks are widely available, and are most commonly prepared by two classic C-F bond forming reactions. The most common route to aryl fluorides is the Balz-Schiemann reaction (Figure 1.15). This reaction occurs in 2 steps from an aniline substrate, first with diazotization under strongly acidic conditions, followed by thermally induced loss of N_2 to generate a transient aryl cation that is trapped by a fluoride of BF_4. The second most common route to prepare aryl fluorides is through nucleophilic aromatic substitution of an electron-poor aryl chloride or nitroarene with a nucleophilic fluoride salt (most commonly KF) at high temperatures (Figure 1.15). Although these methods are reliable to prepare simple aryl fluoride building blocks, the harsh reaction conditions limit these to simple substrates at an early stage in a synthesis. It should also be mentioned here that the Ritter group has developed a reagent for the fluoro-deoxygenation of phenols that occurs with broad scope, however this reagent is prohibitively expensive for large-scale.[44]

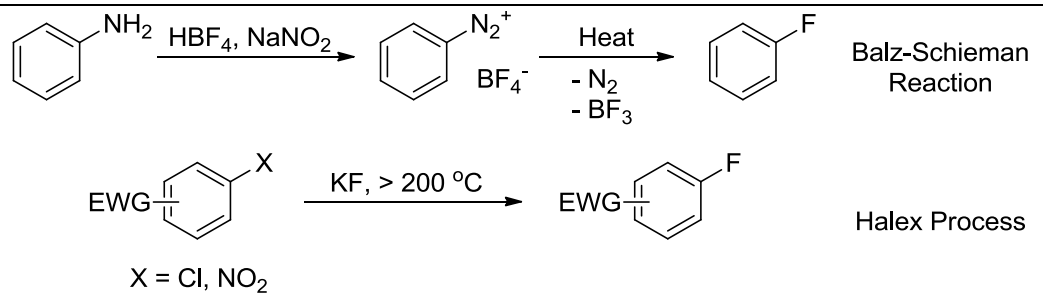


Figure 1.15 Classic methods to prepare aryl fluorides

As with fluoroalkylarenes, reactions with transition metals have been explored to form aryl fluorides under milder conditions than classic methods. Several challenges exist in developing a reaction for Ar-F synthesis, and these issues are illustrated in the generic catalytic cycle shown below for the fluorination of an aryl halide with a fluoride salt (Figure 1.16). First, the catalytic cycle will be discussed for M = Pd(0).

Oxidative addition of an aryl halide to Pd(0) is common to most cross coupling reactions, and is not considered a challenge for developing a fluorination reaction. After oxidative addition, exchange of the Pd halide with fluoride can be challenging due to the low solubility of many fluoride salts. More soluble and nucleophilic fluoride reagents can lead to competitive displacement of the datively bound ligand (L). The sonication of an Ar-Pd(II)-I complex with AgF in benzene for 1-6 hours has been demonstrated to form the corresponding Ar-Pd(II)-F complex.[45] Similarly, Buchwald reported the reaction of Ar-Pd(II)-Br complexes with AgF in DCM to generate Ar-Pd(II)-F complexes.[46] Notably, this halogen exchange reaction has not been demonstrated with alkali metal fluorides, which are much less expensive and more practical than AgF.

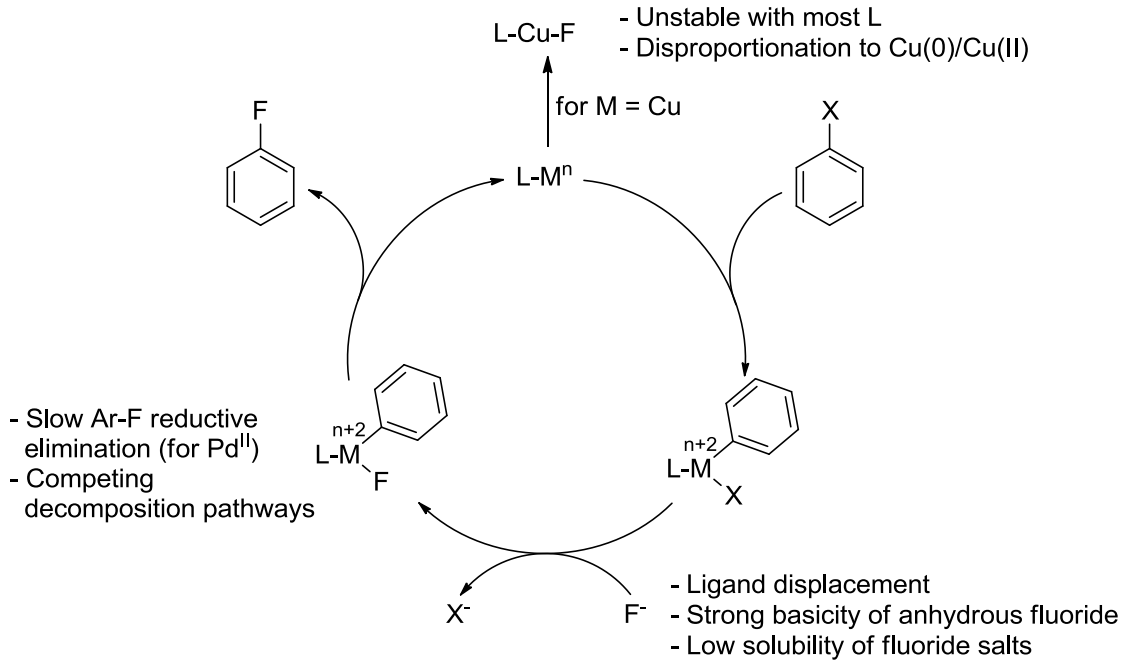


Figure 1.16 Potential catalytic cycle for the fluorination of an aryl electrophile and challenges associated with each step

Similar to the slow reductive elimination of Ar-CF_3 from Ar-Pd(II)-CF_3 complexes discussed in section 1.2, reductive elimination from Ar-Pd(II)-F complexes to form the Ar-F product is kinetically unfavorable and slower than competing side reactions. Pioneering work by Grushin and coworkers found that instead of Ar-F reductive elimination, competing reductive elimination reactions occur with the dataive phosphine ligands to generate $[Ar\text{-}PR_3]^+$ and $[F\text{-}PR_3]^+$ side products, leading to decomposition of the Pd species.[47] The first example of Ar-F bond formation from Ar-Pd(II)-F complexes was reported by Buchwald with ortho-substituted, electron-poor aryl groups and BrettPhos as ligand in 15-25% yield from the isolated complex.[46a] The details surrounding the Ar-F reductive elimination reaction are still unclear. It has been shown that ligand modification occurs in some cases prior to Ar-F formation, and in many cases, isomeric arylfluorides are formed, suggesting a benzyne-type intermediate may be forming.[46b] In stoichiometric reductive elimination studies, the yields of the Ar-F products are much lower than those observed in the catalytic reaction.[46]

In spite of these challenges for developing a Pd-catalyzed fluorination reaction, the Buchwald group reported their landmark discovery in 2009 that a complex formed from ^{t}BuBrettPhos (6 mol %), and $[(cinnamyl)PdCl]_2$ (4 mol % Pd) catalyzes the coupling of aryl triflates with CsF. While representing a major breakthrough in the field, the reaction only worked well for electron-poor aryl triflates, and isomeric aryl fluorides and arene side-products were formed in many cases. Very similar reaction conditions were reported 4 and a half years later by the same group for the fluorination of aryl bromides with a slightly different ligand (AdBrettPhos) and Pd-precatalyst.[48] Given the similar reaction conditions to the aryl triflate chemistry, the formation of regioisomers plagues this reaction as well. It should be mentioned here that avoiding the formation of arene side products is a particular challenge in fluorination chemistry, especially since it is challenging, or impossible, to separate the desired Ar-F product from the Ar-H side-product.

An alternative approach that could potentially overcome the issues with Pd catalysts would be to use Cu. Similar to the discussion on why Ar-CF_3 reductive elimination is faster from copper vs. palladium (Section 1.2), reductive elimination from an Ar-Cu(III)-F species should be more facile than from a comparable Ar-Pd(II)-F complex. However, competing decomposition reactions involving the ligand or other X-type ligand on Cu could lead to decomposition (*vide infra*). If we assume that a system could be identified to form Ar-F products from Ar-Cu(III)-F, we must now consider the other steps in the cycle and what the role of ligand and other anionic ligand on Cu(III) will have.

For simplicity, the following discussion will assume that the reactions will be performed with an aryl iodide substrate. Oxidative addition of an aryl iodide to CuX is slow and reversible, leading to a low concentration of the resulting Ar-Cu-(X)(I) species. From here, fluoride must transmetallate to Cu(III), and two possibilities exist. If fluoride displaces X, the resulting species will be Ar-Cu-(F)(I); if fluoride displaces I, the resulting species will be Ar-Cu-(F)(X). The rates of Ar-F reductive elimination will be different from each species, and will have to be faster than the rate of Ar-I or Ar-X reductive elimination. Although Ar-I or Ar-X reductive elimination from these intermediates appears to be the reverse of the oxidative addition step, this process would lead to the formation of a Cu(F) complex, which are known to undergo rapid

disproportionation to Cu metal and CuF_2. Similarly, a ligand must be identified that can stabilize the Cu intermediates but not participate in competing side reactions.

Finally, the use of CuX reagents/catalysts in the presence of nucleophilic fluoride salts can lead to the formation of CuF species, which, as mentioned above, are unstable. Thus, a careful choice of CuX and fluoride is crucial for successfully developing a copper-mediated fluorination reaction.

Having carefully considered the above challenges in the development of a copper-mediated fluorination reaction, we designed a new copper reagent, $(^tBuCN)_2CuOTf$, that mediates the coupling of aryl iodides with AgF. These reactions were the first examples for the fluorination of unactivated aryl halides, and the first use of copper in the synthesis of functionalized aryl fluorides. This work will be discussed in detail in chapter 6.[49] Following our lead, the Sanford group reported a similar reaction for the fluorination of diaryliodonium salts with a copper triflate catalyst (Figure 1.17).[50] These reactions occur through initial in-situ reduction of Cu(II) to Cu(I).[51] Aryl iodonium salts are more reactive than aryl iodides, but are much less attractive substrates, since they must be prepared from the corresponding aryl iodide or aryl boronic acid. Likewise, Liu and coworkers built off of our work and used similar reaction conditions to our aryl iodide fluorination for the fluorination of aryl bromides containing a directing group (Figure 1.17).[52] However, there are limited practical applications of these reactions because of the requirement for a non-removable directing group and the esoteric products that are prepared.

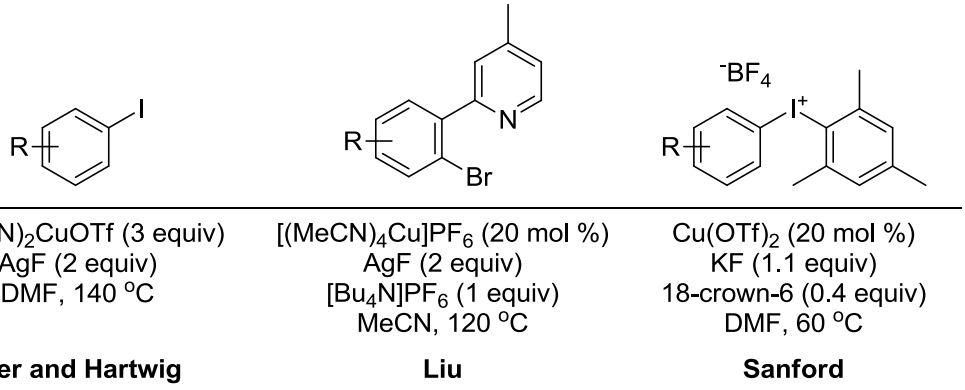
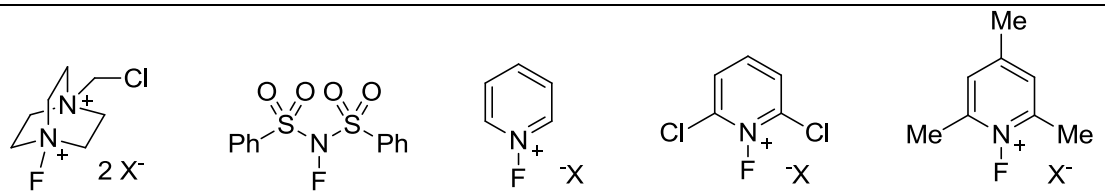


Figure 1.17 Methods for the fluorination of aryl electrophiles with copper

Aryl fluorides have also been prepared from aryl nucleophiles with electrophilic fluorine reagents, and more recently with fluoride salts under oxidizing conditions. Common electrophilic fluorine reagents (F^+ reagents) are shown in Figure 1.18. Early work in this area was reported in back-to-back publications by Knochel[53] and Beller[54] for the fluorination of aryl Grignard reagents with NFSI or $[Me_3pyF]BF_4$, respectively. These reactions occur rapidly in modest to good yields. However the functional group compatibility is limited by the high reactivity of Grignard reagents, and significant amounts of arene side products are formed in some cases. Notably, these reactions were applied to the synthesis of some heteroaryl fluorides as well, which can be challenging to prepare with other state of the art fluorination methods.



Selectfluor, F-TEDA-X | **NFSI, NFBS** | **[pyF]X** | **[Cl_2pyF]X** | **[Me_3pyF]X**

Figure 1.18 Common electrophilic fluorine reagents (F^+ reagents) for the fluorination of nucleophiles

Several methods for the fluorination of aryl nucleophiles with transition metals have been reported. An early proof-of-concept in this area was demonstrated in 2008 by Ritter; he showed that pre-formed Ar-Pd(II) species, formed stoichiometrically from aryl boronic acids, react with F-TEDA-BF_4 to form Ar-F products.[55] These reactions were reported to occur through oxidation of Pd(II) by F-TEDA-BF_4 to generate a Pd(IV) species from which the Ar-F is formed from reductive elimination.[56] Notably, reductive elimination from Pd(IV) is much faster than from Pd(II), making Pd(II)/(IV) cycles a feasible route to form aryl fluorides. Similar findings were reported by Sanford who conducted the reaction of an Ar-Pd(II)-F complex with XeF_2 to form a Pd(IV) complex. This intermediate, with or without additives, could form the corresponding Ar-F products in modest yields.[57]

The Ritter group has reported direct routes to aryl fluorides from aryl stannanes,[58] and aryl triethoxysilanes[59] with 2-4 equivalents of Ag(I) salts and F-TEDA-X. However, aryl stannanes are toxic, and aryl triethoxysilanes are uncommon aryl nucleophiles. The same group also reported a two-step procedure for the fluorination of aryl boronic acids through initial formation of an Ar-Ag(I) species that are isolated as crude mixtures, followed by the addition of Selectfluor.[60] The need to isolate the Ar-Ag intermediates makes these reactions less attractive than the direct fluorination of aryl boron reagents (*vide infra*). The same group also developed a silver *catalyzed* fluorination of aryl stannanes with good functional group compatibility.[61] Although several complex molecules could be used in these fluorination reactions, the use of toxic aryl stannanes limits the appeal of this reaction. The exact mechanism by which these silver mediated/catalyzed reactions occur is not well understood; the authors propose that multimetallic silver species are formed and that Ar-F formation is promoted by 'redox synergy.'

Aryl boronic acids and ArBPin reagents are the most common and accessible aryl nucleophiles, and the direct fluorination of these substrates would be the most desirable in electrophilic fluorination. Thus, we developed a method for the direct fluorination of ArBPin reagents using our previously developed (^{t}BuCN)$_2$CuOTf reagent with [Me_3pyF]PF_6 (see Chapter 7).[62] These reactions occur with good substrate scope, and the use of tandem C-H borylation/fluorination allowed for the synthesis of aryl fluorides from arenes. The same reaction conditions could be applied for the direct fluorination of $ArB(OH)_2$, $ArBF_3K$, and other $ArB(OR)_2$ reagents. Our mechanistic studies support the proposal that the Ar-F is formed by rapid reductive elimination from a Cu(III) species. This work was reported in February 2013, and one month later the Sanford group reported nearly identical conditions to ours for the fluorination of $ArBF_3K$ and $ArSnBu_3$

reagents (Figure 1.19). Given the similar reaction conditions, the substrate scope and yields reported in these two papers were comparable. Reactions with ArBPin reagents require an added base (AgF) to promote the reaction, which is not necessary for the more reactive $ArBF_3K$ and $ArSnBu_3$ substrates. In September 2013, the Ritter group reported the Pd-catalyzed fluorination of aryl trifluoroborates ($ArBF_3K$) with F-TEDA-BF_4.[63] These reactions occur with broad scope, however the more common $ArB(OH)_2$ and ArBPin derivatives must be converted to the trifluoroborates salts. A single $ArB(OH)_2$ and ArBPin substrate, which are more common and accessible than $ArBF_3K$, were demonstrated to undergo the fluorination reaction through in-situ formation of the $ArBF_3K$, however it is not clear if this approach is general.

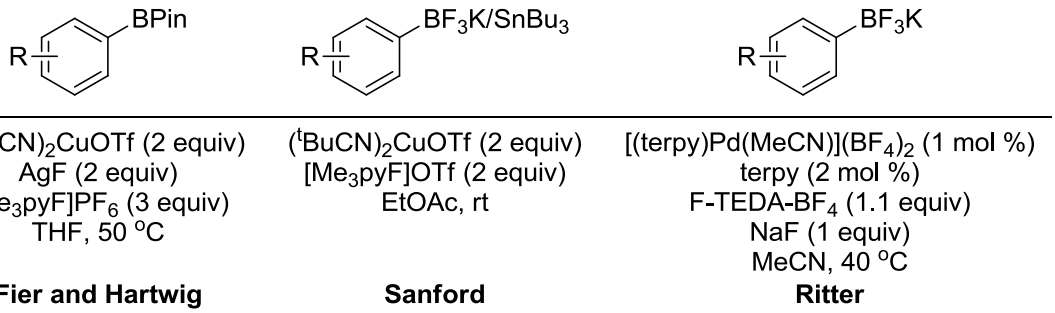
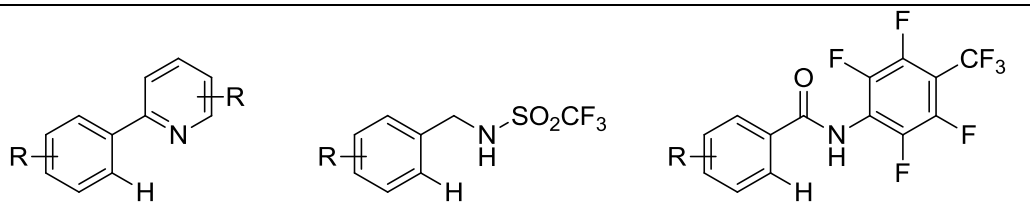


Figure 1.19 Direct fluorination of aryl boron substrates with F+ reagents

The synthesis of aryl fluorides has also been performed from aryl boron reagents with nucleophilic fluoride salts under oxidizing conditions. The Sanford group reported that 4 equiv each of $Cu(OTf)_2$ and KF in MeCN at 60 °C mediates the fluorination of aryl trifluoroborate reagents.[64] The mechanism of these reactions are proposed to be similar to Chan-Lam-Evans reactions in which an intermediate Ar-Cu(II) species is oxidized by a second equivalent of Cu(II) to form an Ar-Cu(III)-F complex from which the Ar-F bond is formed. A similar reaction was recently employed for the synthesis of ^{18}F-labeled aryl fluorides from ArBPin reagents.[65]

Finally, the fluorination of C-H bonds in arenes has also been developed, most commonly for substrates that contain a directing group. In 2006, Sanford demonstrated that the combination of $Pd(OAc)_2$ (10 mol %) and $[pyF]BF_4$ can promote the fluorination of substrates containing a pyridyl directing group in about 50% yield with microwave irradiation (Figure 1.20).[66] Following this work, the Yu group reported in 2009 that $Pd(OTf)_2 \cdot 2H_2O$ (10 mol %) and $[Me_3pyF]OTf$ effects the fluorination of C-H bonds adjacent to a triflamide directing group (Figure 1.20).[67] In both of these reactions, it was difficult to prevent difluorination of substrates containing two sterically accessible ortho C-H bonds. The Yu group subsequently published similar reaction conditions for the directed C-H fluorination of benzamide derivatives (Figure 1.20).[68] The reaction conditions allowed for selective mono-fluorination, and the amide directing group could be cleaved with KOH to form the 2-fluorobenzoic acid product. Although C-H fluorination reactions are potentially powerful, it is important to note that the product and starting materials are often inseparable by silica gel chromatography, requiring the use of HPLC or SFC to obtain pure products.[69]



Pd(OAc) (10 mol %) [pyF]BF_4 (2.5-4.5 equiv) MeCN, $PhCF_3$ microwave, 150 °C	$Pd(OTf)_2$ $2H_2O$ (10 mol %) $[Me_3pyF]OTf$ (1.5-3.0 equiv) NMP (0.5 equiv) DCE, 120 °C	$[(MeCN)_4Pd](OTf)_2$ (10 mol %) $[Me_3pyF]OTf$ (1.5-3.0 equiv) NMP (0.2 equiv) MeCN, 120 °C
Sanford	**Yu**	**Yu**

Figure 1.20 Pd-catalyzed directed C-H fluorination

Although most work for arene C-H fluorination has been with Pd catalysts, a recent report by Daugulis demonstrated that copper systems are also viable.[70] In these reactions, benzamide substrates derived from 8-aminoquinoline undergo selective mono C-H fluorination with CuI (10-25 mol %) and AgF (3.5-4 equiv) with NMO as the oxidant (4.5-5 equiv). The reactions occur rapidly (30 to 120 min) at 50 to 120 °C in DMF. Changing the stoichiometry and adding pyridine allows for selective difluorination. This reaction is comparable to Yu's system for C-H fluorination of benzamide derivatives.

While numerous methods have been developed to form aryl fluorides from aryl halides, aryl nucleophiles, and arenes, major limitations remain to be addressed. First, most reactions have not been demonstrated to work with heteroaryl substrates, or occur only with electron-poor heteroaryl substrates with limited generality. Second, the formation of minor amounts of Ar-H impurities in many reactions used to form Ar-F products complicates purification. Because HPLC or SFC separation is often required, such reactions are unlikely to be ever used on scale. Current fluorination reactions with transition metals are also not scalable since each of these reactions has at least one prohibitively expensive component (Ag^+, electrophilic fluorine reagents, diaryliodonium substrates, 4 equivalents of $Cu(OTf)_2$, high loadings of Pd). The ideal fluorination reaction would use the most common aryl halides (ArBr, ArCl), simple inorganic fluoride salts (NaF, KF), and low loadings of an inexpensive catalyst. Ideally, the same reaction would be tolerant of trace oxygen and water and would not form Ar-H or isomeric side products. The development of such a reaction may rely on Ni catalysts. A single report of stoichiometric Ar-F formation from high-valent nickel has been reported, notably this reaction was tolerant of water.[71] However, it is unclear if the Ar-F formation occurs from Ni(III), and if such a species could be generated under catalytic conditions. Although studies focused on promoting Ar-F reductive elimination from Pd(II) have been performed, analogous studies with Ni(II) complexes have not been reported. Future work should also focus on designing more reactive copper complexes that can react with aryl halides other than ArI, $[Ar_2I]BF_4$, or activated ArBr substrates.

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CHAPTER 2

Perfluoroalkylation of Arenes and Arylbromides via Arylboronate Esters and [(phen)CuR_F]

2.1 Introduction

A large number of existing and candidate pharmaceuticals contain perfluoroalkyl groups because these moieties can favorably affect the physical and biological properties of a compound.[1] Accordingly, the development of methods to introduce perfluoroalkyl groups into aromatic compounds has become increasingly important. To introduce the CF_3 moiety, the simplest perfluoroalkyl group, most current industrial methods rely on the Swarts reaction,[2] wherein benzotrichlorides are treated with HF or SbF_5 under forcing conditions. While effective for the bulk synthesis of simple commodity chemicals, the harsh nature of this reaction significantly limits its utility in complex molecule synthesis, particularly with respect to late-stage SAR studies. Furthermore, this classical route to trifluoromethylarenes does not provide access to higher order perfluoroalkylarenes.

In recent years, synthetic methods have been developed for the preparation of perfluoroalkyl arenes from aryl iodides[3] and aryl chlorides.[4] However, analogous methods to prepare these compounds from aryl bromides, which are particularly desirable starting materials, due to their ease of synthesis and wide commercial availability, are notably lacking. Similarly, methods to prepare perfluoroalkyl arenes directly from arenes would be valuable because the halogenation step is avoided altogether. Existing methods for the perfluoroalkylation of arenes require a directing group or occur with low selectivity,[5] and no methods currently exist for the perfluoroalkylation of bromoarenes with a broad substrate scope.[6,7] Here, we report a general strategy for accessing perfluoroalkyl arenes from arenes and aryl bromides without directing groups, high temperatures, or acidic conditions.

2.2 Results and Discussion

Our strategy for the synthesis of perfluoroalkyl arenes from arenes and aryl bromides, shown in Scheme 1, starts from the formation of an arylboronate ester *in situ*, either by iridium-catalyzed borylation of arenes or palladium-catalyzed borylation of aryl bromides. The arylboronate ester is then converted to the perfluoroalkylarene by reaction with (Phen)CuR_f (**1**) in air.[8] These two sequences are complementary because bromination of arenes is typically controlled by the electronic properties of the arene and iridium-catalyzed borylation is controlled by the steric properties of the arene.[9]

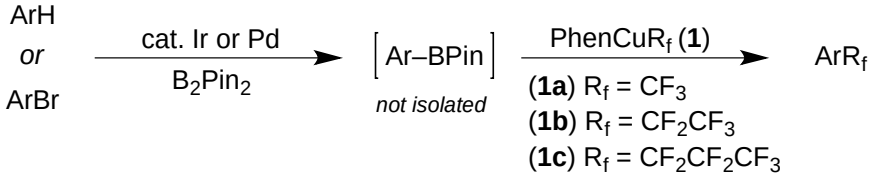


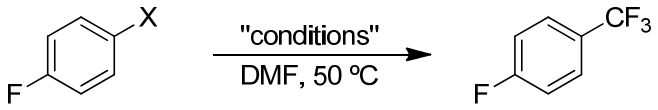
Figure 2.1 General strategies for the perfluoroalkylation of arene C-H bonds and aryl bromides via the in-situ formation of ArBPin.

The coupling of arylboronic acids with electrophilic sources of CF_3 to give benzotrifluorides have been described recently, but arylboronate esters tend to be much less reactive than boronic acids.[10] We hypothesized that (Phen)$CuCF_3$ (**1a**), a reagent we recently reported,[7] and its higher perfluoroalkyl congeners (**1b**, **1c**) could convert arylboronate esters to the corresponding perfluoroalkylarenes under oxidative Chan-Lam-

type conditions. Reactions of this reagent would circumvent the need for excess quantities (2-5 equiv) of $TMSCF_3$ (Ruppert's reagent) typically used to compensate for the decompostion of CF_3^-. Compound **1** is simple to use because it is a solid that is commercially available, stable indefinitely under nitrogen, and sufficiently stable to oxygen and moisture that it can be weighed in air.

We initiated our studies by examining conditions for the conversion of 4-fluorophenylboronates to the corresponding benzotrifluoride (Table 2.1). After surveying a range of bases, solvents and oxidants, we found that reactions conducted in DMF with air as the oxidant in conjunction with one equivalent of KF to activate the boronate ester occurred in higher yields than those conducted other oxidants we tested. With air and added KF, 77% yield of the desired benzotrifluoride was formed from the pinacolatoboronate ester, as determined by ^{19}F NMR spectroscopy (Table 2.1, entry 2). Reactions with pre-formed $(Phen)CuCF_3$ occurred in higher yields than those conducted with the reagent generated *in situ* (entries 1 and 2).

Table 2.1. Trifluoromethylation of arylboron reagents[a]



entry	X	conditions	yield (%)[a]
1	Bpin	CuI, phen, KOtBu, CF_3TMS, KF, air	49
2	Bpin	$PhenCuCF_3$, KF, air	77
3	$B(OH)_2$	"	36
4	Bnpg	"	67
5	Bcat	"	16
6	BMIDA	"	10
7	BF_3K	"	np
8	Bpin	20 mol % $PhenCuCF_3$ 1.2 equiv CF_3TMS, KF, air	42

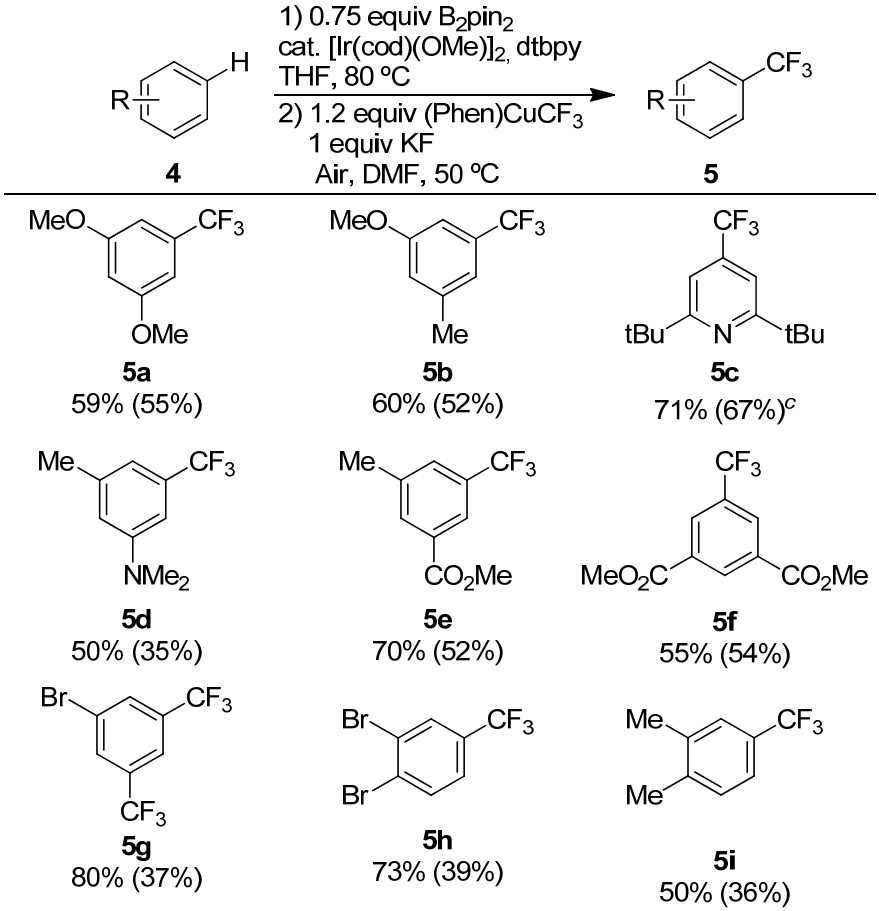
[a]Reactions were run on a 0.1 mmol scale and the yields were determined by ^{19}F NMR spectroscopy with 4-trifluoromethoxyanisole as an internal standard.

In addition to studying the trifluoromethylation of pinacolatoboronate esters, we studied the trifluoromethylation of a variety of less hindered boronate esters and boronic acids. Reactions of boronic acids under the standard conditions gave the corresponding trifluromethylated product, but the yields were lower than those of the reactions of pinacolatoboronate esters (entry 3). Arylboronic acids containing electron-withdrawing substituents on the aryl group did, however, react in higher yields than those with a relatively electron-neutral fluorine substituent (see SI for additional substrates). Although reactions conducted with catecholboronate esters and trifluoroborate salts did not give benzotrifluoride products in high yield, reactions of the corresponding neopentylglycolboronate ester proceeded in good yield (entry 4). Finally, we briefly examined the reaction of the pinacolatoboronate ester with Ruppert's reagent in the presence of $(Phen)CuCF_3$ as a catalyst (entry 8). Some turnover was observed, but higher

yields were observed with (Phen)$CuCF_3$ as reagent, and the latter conditions were explored further.

Based on these conditions that we developed for the trifluoromethylation of aryl boronate esters, a one-pot sequence for the generation of benzotrifluorides from arenes was developed. This sequence consists of Ir-catalyzed borylation of the arene,[9] followed by removal of the volatile components and subsequent copper-mediated trifluoromethylation with (Phen)$CuCF_3$. Because the regioselectivity of the iridium-catalyzed borylation of arenes is controlled by steric effects, 1,3-disubstituted arenes generate 1,3,5-trisubstituted arylboronate esters, symmetric 1,2-disubstituted arenes give 1,2,4-trisubstiuted arylboronate esters, and 1,4-disubstituted arenes give products from functionalization adjacent to the smaller substituent.[9] Despite the presence of Ir and other by-products from the borylation process, the trifluoromethylation of the boronate ester occurred in the same reaction vessel, and good yields of benzotrifluorides were obtained over the two-step process.

Table 2.2 Scope of the one-pot borylation/trifluoromethylation sequence with disubstituted arenes[a]

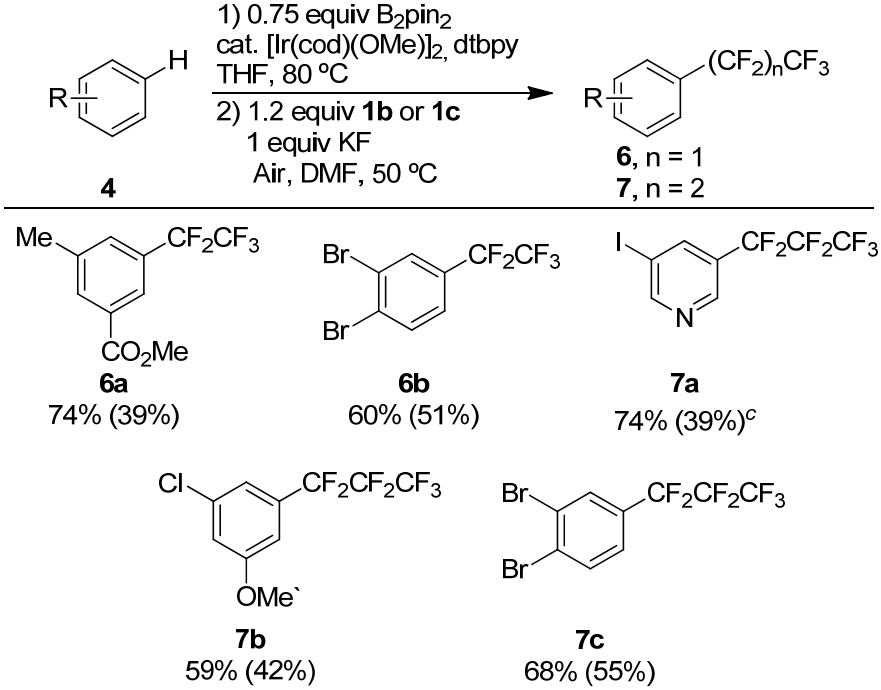


[a]Reactions run on a 0.1 mmol scale to determine ^{19}F NMR yields and run on a 0.5 mmol scale to obtain isolated yields. ^{19}F NMR yields are listed first followed by isolated yields in parenthesis. [b]Reaction conditions: 0.75 equiv B_2Pin_2, 0.1 mol % $[Ir(COD)OMe]_2$, 0.2 mol % dtbpy, 0.5M THF, 80 ºC. [c]3 mol % $[Ir(COD)OMe]_2$, 6 mol % dtbpy. [d]Yields determined by ^{19}F NMR spectroscopy with 4-trifluoromethoxyanisole as an internal standard.

The scope of the trifluoromethylation of arenes is shown in Table 2.2. Amines, pyridines, and esters were tolerated by the reaction conditions. Although silyl-protected alcohols were tolerated by the conditions of the Ir-catalyzed borylation, the silicon-oxygen bond was cleaved during the trifluoromethylation step. Aryl halides reacted to form benzotrifluorides by cleavage of a C–H bond, not by cleavage of the carbon-halogen bond. Based on the selectivity for Ir-catalyzed C–H borylation, symmetric 1,2-substitued arenes formed products containing a trifluoromethyl group at the 4-position. The aldehyde function was not tolerated by the conditions of the borylation step, but was tolerated by the conditions of the trifluoromethylation step (*vide infra*).

Like the trifluoromethyl moiety, the pentafluoroethyl and heptafluoropropyl moieties are valuable for modulating the properties of molecules of interest to the pharmaceutical and agrochemical industries.[1b] However, methods to prepare perfluoroalkyl arenes are limited because they cannot be prepared by halogenation of the corresponding alkylarene.[3c,11] Fortunately, perfluoroalkyl analogs of (Phen)$CuCF_3$, such as (Phen)$CuCF_2CF_3$ and (Phen)$CuCF_2CF_2CF_3$, are easily prepared.[7] These reagents react with arylboronate esters in a fashion similar to that of (Phen)$CuCF_3$, giving perfluoroalkyl arenes in good yields. Table 2.3 shows the scope of the one-pot sequence of borylation and perfluoroalkylation. The reaction yields were generally unaffected by the nature of the (Phen)CuR_f reagent; sequences that lead to products of trifluoromethylation, perfluoroethylation and perfluoropropylation occurred in similar yields with the same arene.

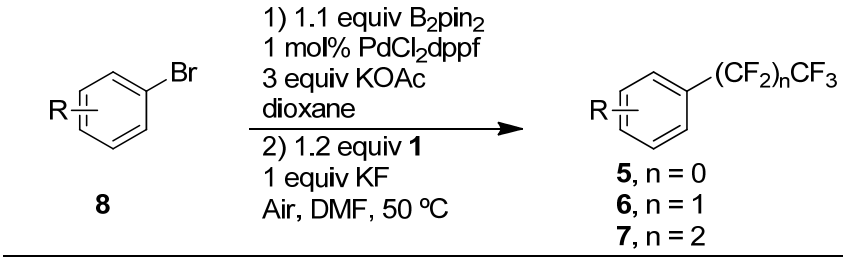
Table 2.3 Scope of the one-pot borylation/perfluoroalkylation sequence with disubstituted arenes.

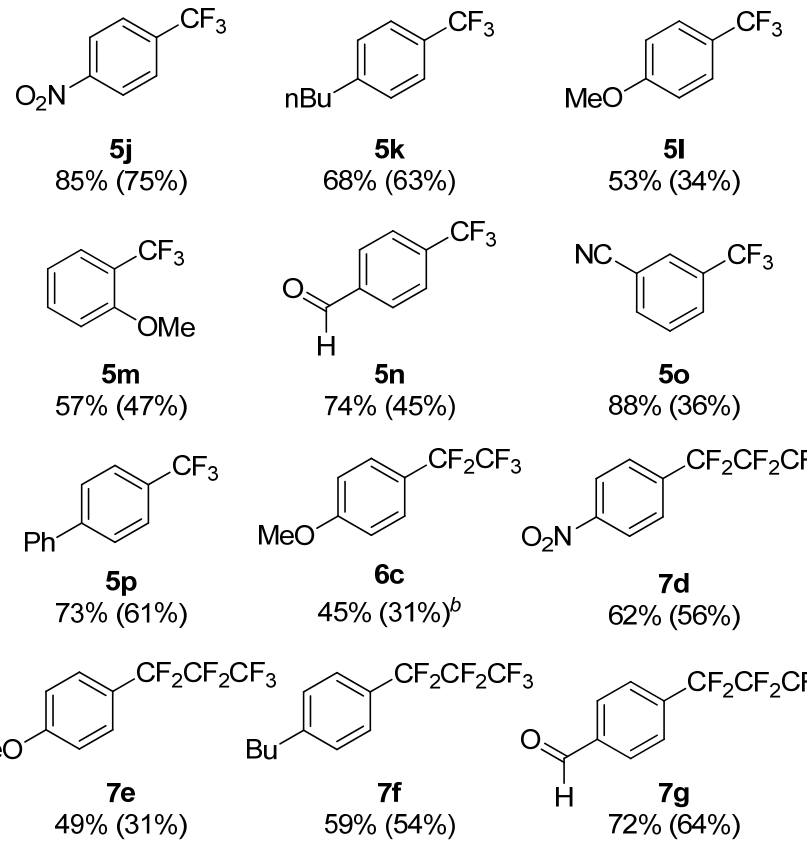


[a]Reactions run on a 0.1 mmol scale to determine ^{19}F NMR yields and run on a 0.5 mmol scale to obtain isolated yields. [b]Reaction conditions: 0.75 equiv B_2Pin_2, 0.1 mol % $[Ir(COD)OMe]_2$, 0.2 mol % dtbpy, 0.5 M THF, 80 °C. [c]3 mol % $[Ir(COD)OMe]_2$, 6 mol % dtbpy. [d]Yields determined by ^{19}F NMR spectroscopy with 4-trifluoromethoxyanisole as an internal standard.

The success of our one-pot sequence consisting of C–H borylation and trifluoromethylation prompted us to investigate the combination of the borylation and trifluoromethylation of aryl bromides. Despite the widespread utility of aryl bromides as building blocks for the synthesis of complex arenes, the development of trifluoromethylations of aryl bromides has been challenging. We anticipated that perfluoroalkyl arenes could be accessed from aryl bromides by first forming the arylboronate ester *in situ*. We sought to identify conditions for the borylation of aryl bromides that would be compatible with the perfluoroalkylation of arylboronate esters.

Table 2.4 Scope of the tandem Miyaura borylation and trifluoromethylation of arylbromides.





[a]Reactions run on a 0.1 mmol scale to determine ^{19}F NMR yields and run on a 0.5 mmol scale to obtain isolated yields. [b]A small amount of starting material could not be separated from the desired product. [c]Yields determined by ^{19}F NMR spectroscopy with 4-trifluoromethoxyanisole as an internal standard.

After examining several sets of conditions, we found the palladium-catalyzed borylation of aryl bromides reported by Miyaura were most compatible with the

subsequent trifluoromethylation.[8d] Three equivalents of KOAc were required for the borylation of the aryl bromide to proceed in high conversion. Unfortunately, the excess KOAc caused the trifluoromethylation step to occur in low yield. However, filtration of the crude reaction mixture through a small plug of Celite before the trifluoromethylation step led to formation of the trifluoromethylarene in higher yields.

Several examples of the perfluoroalkylation of aryl bromides are shown in Table 2.4. Trifluoromethylarenes, pentafluoroethylarenes, and heptafluoropropylarenes are formed in good yield from the arylbromide precursor. Notably, electron-rich arylbromides, which are typically unreactive in other copper-mediated trifluoromethylation methods, give good yields of the corresponding perfluroalkylarenes. Electrophilic functionality such as nitriles, esters, and aldehydes were tolerated. This method allows access to 1, 2–, 1, 3–, and 1, 4–disubstituted arenes, complementing the selectivity observed for the Ir-catalyzed borylation of arenes (vide supra).

2.3 Conclusions

In summary, we have developed a versatile method for the synthesis of perfluoroalkyl arenes from two common classes of aromatic reactants. Disubstituted or trisubstituted arenes and a range of aryl bromides are converted regioselectively to an arylboronate ester *in situ,* and this ester readily undergoes perfluoroalkylation under mild conditions with a stable, pre-formed copper reagent. By this sequence, arenes are selectively functionalized with regioselectivity that contrasts that of directed arene perfluoroalkylations. In addition, a variety of aryl bromides are converted to benzotrifluorides for the first time under mild conditions. The two processes we report are complementary because the borylation of arenes is controlled by steric effects and the bromination that forms the aryl bromide reagent is controlled by electronic effects. Both methods are based on recently developed copper reagents that are thermally stable, easily handled solids.

2.4 Experimental

All manipulations were conducted under an inert atmosphere with a nitrogen-filled glovebox (Innovative Technologies, Newburyport, Massachusetts) equipped with an oxygen sensor (working oxygen level <20.0 ppm) and low-temperature refrigeration unit (–30 °C), unless otherwise noted. All reactions were conducted in oven-dried 4-mL or 20-mL vials fitted with a Teflon-lined screw cap under an atmosphere of nitrogen unless otherwise noted.

$[Ir(cod)OMe]_2$ was obtained from Johnson-Matthey and used as received. 2-Mesitylmagnesium bromide was purchased as a 1.0M THF solution from Sigma-Aldrich. Copper(I) chloride (99.999%) was purchased from Strem and used as received. 4,4'-Di-tert-butylbipyridine was obtained from Sigma-Aldrich and used as received. B_2pin_2 was obtained from Allychem and used as received. Arenes and aryl bromides were purchased from Sigma-Aldrich and used as received, except 4-butyliodobenzene and 3-iodopyridine, which were purchased from Alfa Aesar and used as received. (Pentafluoroethyl)trimethylsilane ($TMSCF_2CF_3$) was purchased from Combi-Blocks. (Perfluoropropyl)trimethylsilane ($TMSCF_2CF_2CF_3$), and 4-(trifluoromethoxy)anisole

(internal standard for ^{19}F NMR analysis) were purchased from Aldrich. (Trifluoromethyl)trimethylsilane ($TMSCF_3$, Ruppert's reagent) was purchased from Matrix Scientific. KF and KOAc were purchased from Sigma-Aldrich and dried in a vacuum oven overnight before use. Mesitylcopper was prepared according to the literature procedure. (1,10-phenanthroline)(heptafluoropropyl)copper(I) [$(phen)CuCF_2CF_2CF_3$] was prepared according to the published procedure. $PhenCuCF_3$ was synthesized as described below, but it can now be purchased from Sigma-Aldrich.

Organic solutions were concentrated by rotary evaporation. Flash column chromatography was performed on Silicylce Siala-P silica gel or on a Teledyne Isco CombiFlash Rf automated chromatography system with 4 g RediSep Rf Gold normal-phase silica columns. The products were visualized by UV light and stained with ceric ammonium molybdate (CAM) or potassium permanganate ($KMnO_4$).

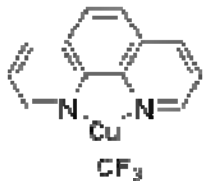
NMR spectra were acquired on 400 MHz and 500 MHz Varian Unity or Innova instruments at the University of Illinois VOICE NMR facility. NMR spectra were processed with MestReNova 5.0 (Mestrelab Research SL). Chemical shifts are reported in ppm and referenced to residual solvent peaks ($CHCl_3$ in $CDCl_3$: 7.26 ppm for ^1H and 77.0 ppm for ^{13}C; DMF-d_6 in DMF-d_7: 2.91 ppm for ^1H and 162.7 ppm for ^{13}C) or to an external standard (1% $CFCl_3$ in $CDCl_3$: 0 ppm for ^{19}F). Coupling constants are reported in hertz.

All GC-MS analyses were conducted with an Agilent 6890N GC equipped with an HP-5 column (25 m x 0.20 mm ID x 0.33 μm film) and an Agilent 5973 Mass Selective Detector. The temperature for each run was held at 50 °C for 2 min, ramped from 50 °C to 300 °C at 40 °C/min, and held at 300 °C for 5 min.

Elemental analyses were performed by the University of Illinois at Urbana-Champaign Microanalysis Laboratory and by Robertson Microlit Laboratories, Inc. (Madison, NJ).

Preparation of Reagents and Products

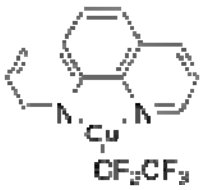
(1,10-phenanthroline)(trifluoromethyl)copper, $(phen)CuCF_3$



To an oven-dried 500-mL round-bottomed flask equipped with a stir bar was added $[Cu(Mesityl)]_5$ (9.14 g, 12.5 mmol, 50.0 mmol of monomeric [Cu(Mesityl)] units), and benzene (160 mL). The resulting light yellow solution was stirred vigorously while anhydrous ^tBuOH (5.3 mL, 55.0 mmol, 1.1 equiv) was added dropwise. The flask was sealed with a septum, and the light yellow solution was stirred at room temperature for 1 h. 1,10-phenanthroline (9.01 g, 50.0 mmol, 1.0 equiv) was added with an additional 170 mL of benzene. The dark purple solution was stirred at room temperature for 30 min. $TMSCF_3$ (8.1 mL, 55.0 mmol, 1.1 equiv) was then added dropwise. The mixture was stirred at room temperature for 18 h to give a red-orange suspension. The suspension was filtered through a medium fritted funnel, and the solid was washed with Et_2O (50 mL) and dried under vacuum to give (1,10-phenanthroline)(trifluoromethyl)copper(I) as an orange solid (12.63 g, 40.4 mmol, 81% yield). The product consists of a 21:79 ratio of isomers $(Phen)CuCF_3$ and $[(Phen)_2Cu][Cu(CF_3)_2]$.

Major isomer: ^{1}H NMR (400 MHz, DMF-d_7, -25 ºC) δ 9.23 (s, 4H), 8.93 (s, 4H), 8.79 (s, 2H), 8.36 (s, 4H), 8.11 (br s, 4H).
Minor isomer: ^{1}H NMR (400 MHz, DMF-d_7, -25 ºC) δ 9.10 (s, 2H), 8.79 (s, 2H), 8.11 (br s, 4H). ^{13}C NMR (100 MHz, DMF-d_7) δ 150.4, 144.2, 138.3, 130.0, 127.8, 126.5 (note that a carbon resonance for CF_3 was not observed due to (1) dynamic behavior of the complex (see below), (2) broadening of the resonance by Cu-C coupling and (3) splitting of the resonance by C-F coupling).
^{19}F NMR (376 MHz, DMF-d_7): δ –22.6 (br), –30.9 (s).
Anal. Calcd for $C_{13}H_8CuN_2F_3$: C, 49.92; H, 2.58; N, 8.96; F, 18.22; Found: C, 49.74; H, 2.52; N, 8.99; F, 18.17.

(1,10-phenanthroline)(pentafluoroethyl)copper, (phen)CuCF$_2$CF$_3$



To an oven-dried 50-mL round-bottomed flask equipped with a stir bar was added $[Cu(Mesityl)]_5$ (859 mg, 0.94 mmol, 4.7 mmol of the monomeric [Cu(Mesityl)] unit), and benzene (16 mL). The resulting light yellow solution was stirred vigorously while anhydrous ^{t}BuOH (500 μL, 5.2 mmol, 1.1 equiv) was added dropwise. The flask was sealed with a septum, and the light yellow solution was stirred at room temperature for 1 h. 1,10-phenanthroline (847 mg, 4.7 mmol, 1.0 equiv) was added with an additional 16 mL of benzene. The dark purple solution was stirred at room temperature for 30min. $TMSCF_2CF_3$ (1.0 g, 5.2 mmol, 1.1 equiv) was then added dropwise. The mixture was stirred at room temperature for 18 h to give a red-orange suspension. The suspension was filtered through a medium fritted funnel, and the solid was washed with Et_2O (5 mL) and dried under vacuum to give (1,10-phenanthroline)(pentafluoroethyl)copper(I) as an orange solid (1.33 g, 3.67 mmol, 78% yield). As for (Phen)$CuCF_3$, neutral (Phen)CuCF2CF3 equilibrates with its anionic form. Two sets of ^{19}F NMR peaks for the pentafluoroethyl group were observed in a 52:48 ratio, reflecting a 69:31 ratio of the neutral to anionic form after correcting for the number of equivalent fluorine resonances in the ionic form.
Major Isomer: ^{1}H NMR (500 MHz, DMF) δ 9.19 (d, J = 4.6, 2H), 8.89 (d, J = 8.2 Hz, 2H), 8.30 (s, 2H), 8.10 (dd, J = 8.2, 4.6 Hz, 2H).
^{19}F NMR (470 MHz, DMF) δ -84.01 (s), -117.31 (s).
Minor Isomer: ^{1}H NMR (500 MHz, DMF) δ 9.19 (d, J = 4.6 Hz, 2H), 8.89 (d, J = 8.1 Hz, 2H), 8.30 (s, 2H), 8.10 (dd, J = 8.1, 4.6 Hz, 2H).
^{19}F NMR (470 MHz, DMF) δ -84.03 (s), -110.01 (br s).
Anal. Calcd. for $C_{14}H_8CuF_5N_2$: C, 46.35; H, 2.22; N, 7.72; Found: C, 46.42; H, 2,42; N, 8.05.

General Procedure for One-Pot Generation of Perfluoroalkyl Arenes via Ir-Catalyzed C–H Borylation

In a nitrogen-filled glove box, the arene (0.500 mmol, 1 equiv) and a stock solution of B_2Pin_2, $[Ir(cod)OMe]_2$, and dtbpy were combined in a 20 mL vial. The stock solution contained B_2Pin_2 (95.3 mg, 0.375 mmol, 0.75 equiv), $[Ir(cod)OMe]_2$ (0.1 – 3.0 mol%) and dtbpy (0.2 – 6.0 mol%) per 1 mL of THF (0.5M) (See specific catalyst and

ligand loadings below). The reaction mixture was heated in a sealed vessel at 80 ºC for 18 h. The dark red solution was then cooled to room temperature, and the volatile materials were evaporated under reduced pressure for 2-4 h. The reaction vessel was returned to the glove box where (Phen)$CuCF_3$ (188 mg, 0.600 mmol, 1.2 equiv) or (Phen)$CuCF_2CF_3$ (218 mg, 0.600 mmol, 1.2 equiv) or (Phen)$CuCF_2CF_2CF_3$ (248 mg, 0.600 mmol, 1.2 equiv), KF (29.1 mg, 0.500 mmol, 1.0 equiv) and DMF (5 mL, 0.1M) were added, and the vial was sealed with a screw cap fitted with a septum. Outside of the glove box, air from a balloon was bubbled into the DMF solution or 5-10 min. The balloon was removed, and the vial was placed in a 50 ºC heating bath. After 18 h, the reaction mixture was cooled to room temperature and diluted with 5 mL of Et_2O. The mixture was filtered over Celite, washed with an additional 20 mL of Et_2O, and transferred to a separatory funnel. The mixture was washed with 4 x 40 mL of H_2O and 1 x 25 mL brine, dried with $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel with pentane or pentane/Et_2O mixtures as the eluent.

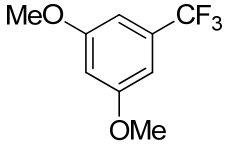
General Procedure for One-Pot Generation of Perfluoroalkyl Arenes via Palladium-Catalyzed C–Br Borylation

In a nitrogen-filled glove box, the aryl bromide (0.500 mmol, 1 equiv), B_2Pin_2 (139 mg, 0.550 mmol, 1.1 equiv), KOAc (147 mg, 1.50 mmol, 3 equiv), $PdCl_2$•dppf (12.2 mg, 0.015 mmol, 3 mol%), and 2.5 mL dioxane (0.2M) were combined in a 20 mL vial. The reaction vessel was sealed with a Teflon-lined cap and heated at 80 ºC for 18 h, or until the starting material was consumed, as determined by GC-MS. The solution was then allowed to cool to room temperature and filtered through a plug of Celite. The Celite plug was rinsed with a minimal volume of EtOAc (~2 mL), and the resulting solution was concentrated under vacuum for 2-4 h. The reaction vessel was returned to the glove box where (Phen)$CuCF_3$ (188 mg, 0.600 mmol, 1.2 equiv) or (Phen)$CuCF_2CF_3$ (218 mg, 0.600 mmol, 1.2 equiv) or (Phen)$CuCF_2CF_2CF_3$ (248 mg, 0.600 mmol, 1.2 equiv), KF (29 mg, 0.500 mmol, 1.0 equiv) and DMF (5 mL, 0.1M) were added, and the vial was sealed with a screw cap fitted with a septum. Outside of the glove box, air from a balloon was bubbled into the DMF solution for 5-10 min. The balloon was removed, and the vial was placed in a 50 ºC heating bath. After 18 h, the reaction mixture was cooled to room temperature and diluted with 5 mL of Et_2O. The mixture was filtered over Celite, washed with an additional 20 mL of Et_2O, and transferred to a separatory funnel. The mixture was washed with 4 x 40 mL of H_2O and 1 x 25 mL brine, dried with $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel with pentane or pentane/Et_2O mixtures as the eluent.

Specific procedures and characterization of perfluoroalkyl arenes not previously reported

1,3-dimethoxy-5-(trifluoromethyl)benzene (5a)

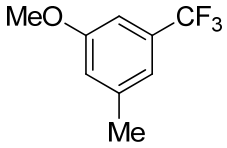
The reaction was performed according to the general procedure for the trifluoromethylation of arenes on a 0.500 mmol scale (65.8 μL **4a**) with 1.0 mol % $[Ir(COD)OMe]_2$ and 2.0 mol % dtbpy in the first step. The crude



mixture was purified by silica gel chromatography (4 g of silica, 100:0 → 90:10 pentane:Et_2O) to give **5a** (56.4 mg, 55% yield) (Average isolated yield: 55%).
R_f = 0.47 (8:1 hexanes:EtOAc)
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (d, *J* = 2.3 Hz, 2H), 6.60 (t, *J* = 2.2 Hz, 1H), 3.83 (s, 6H).^{13}C NMR (126 MHz, $CDCl_3$) δ 161.20 (s), 132.58 (q, *J* = 32.3 Hz), 124.10 (q, *J* = 272.5 Hz), 103.83 (s), 103.47 (dd, *J* = 7.5, 3.7 Hz), 55.77 (s).
^{19}F NMR (376 MHz, $CDCl_3$) δ -63.35 (s).

1-methoxy-3-methyl-5-(trifluoromethyl)benzene (5b)

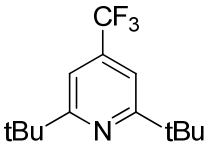
The reaction was performed according to the general procedure for the trifluoromethylation of arenes on a 0.500 mmol scale (63.1 μL **4b**) with 0.1 mol % $[Ir(COD)OMe]_2$ and 0.2 mol % dtbpy in the first step. The crude mixture was purified by silica gel chromatography (4 g of silica, 100:0 → 90:10 pentane:Et_2O) to give **5b** (60.0 mg, 63% yield) (Average isolated yield: 52%).



R_f = 0.63 (8:1 hexanes:EtOAc)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (s, 1H), 6.94 (s, 1H), 6.88 (s, 1H), 3.83 (s, 3H), 2.38 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.67 (s), 140.33 (s), 131.54 (q, *J* = 32.0 Hz), 124.07 (q, *J* = 272.4 Hz), 120.57 (s), 118.11 (q, *J* = 3.9 Hz), 107.63 (q, *J* = 3.8 Hz), 55.34 (s), 21.41 (s).
^{19}F NMR (470 MHz, $CDCl_3$) δ -63.09 (s).

2,6-di-tert-butyl-4-(trifluoromethyl)pyridine (5c)

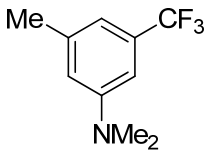
The reaction was performed according to the general procedure for the trifluoromethylation of arenes on a 0.500 mmol scale (108.1 μL **4c**) with 3.0 mol % $[Ir(COD)OMe]_2$ and 6.0 mol % dtbpy in the first step. The crude mixture was purified by silica gel chromatography (4 g of silica, 100:0 → 90:10 pentane:Et_2O) to give **5c** (88.5 mg, 68% yield) (Average isolated yield: 67%).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 2H), 1.37 (s, 18H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.29 (s), 138.48 (q, *J* = 32.6 Hz), 123.63 (q, *J* = 273.4 Hz), 111.22 (q, *J* = 2.8 Hz), 38.01 (s), 29.98 (s).
^{19}F NMR (376 MHz, $CDCl_3$) δ -64.68 (s).

***N*,*N*,3-trimethyl-5-(trifluoromethyl)aniline (5d)**

The reaction was performed according to the general procedure for the trifluoromethylation of arenes on a 0.500 mmol scale (72.7 μL **4d**) with 0.1 mol % $[Ir(COD)OMe]_2$ and 0.2 mol % dtbpy in the first step. The crude mixture was purified by silica gel chromatography (4 g of silica, 100:0 → 90:10 pentane:Et_2O) to give **5d** (36.3 mg, 35% yield) (Average isolated yield: 35%).

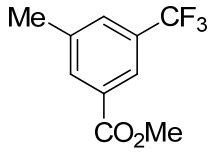


R_f = 0.60 (8:1 hexanes:EtOAc)
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79 (s, 1H), 6.74 (s, 1H), 6.68 (s, 1H), 2.99 (s, 6H), 2.37 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.76 (s), 139.64 (s), 131.43 (q, *J* = 31.0 Hz), 124.85 (q, *J* = 272.6 Hz), 116.06 (s), 113.83 (q, *J* = 3.8 Hz), 106.17 (q, *J* = 4.0 Hz), 40.65 (s), 22.04 (s).
^{19}F NMR (470 MHz, $CDCl_3$) δ -63.08 (s).

methyl 3-methyl-5-(trifluoromethyl)benzoate (5e)

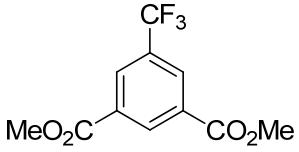
The reaction was performed according to the general procedure for the trifluoromethylation of arenes on a 0.500 mmol scale (70.8 μL **4e**) with 0.1 mol % $[Ir(COD)OMe]_2$ and 0.2 mol % dtbpy in the first step. The crude mixture was purified by silica gel chromatography (4 g of silica, 100:0 → 90:10 pentane:Et_2O) to give **5e** (58.8 mg, 54% yield) (Average isolated yield: 52%).



R_f = 0.52 (8:1 hexanes:EtOAc)
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 1H), 8.03 (s, 1H), 7.61 (s, 1H), 3.94 (s, 3H), 2.47 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 165.95 (s), 139.32 (s), 133.36 (s), 130.92 (q, *J* = 32.6 Hz), 130.82 (s), 130.02 (s), 123.71 (q, *J* = 272.3 Hz), 123.66 (s), 52.41 (s), 21.18 (s).
^{19}F NMR (376 MHz, $CDCl_3$) δ -63.22 (s).

dimethyl 5-(trifluoromethyl)isophthalate (5f)

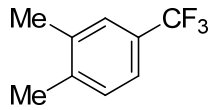
The reaction was performed according to the general procedure for the trifluoromethylation of arenes on a 0.500 mmol scale (97.1 mg **4f**) with 0.1 mol % $[Ir(COD)OMe]_2$ and 0.2 mol % dtbpy in the first step. The crude mixture was purified by silica gel chromatography (4 g of silica, 100:0 → 90:10 pentane:Et_2O) to give **5f** (85.0 mg, 65% yield) (Average isolated yield: 54%).



R_f = 0.39 (8:1 hexanes:EtOAc)
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.46 (s, 2H), 3.98 (s, 6H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 164.87 (s), 133.63 (s), 131.62 (s), 131.59 (q, *J* = 33.8 Hz), 130.40 (q, *J* = 3.6 Hz), 123.13 (q, *J* = 272.9 Hz), 52.75 (s).
^{19}F NMR (470 MHz, $CDCl_3$) δ -63.36 (s).

1,2-dimethyl-4-(trifluoromethyl)benzene (5i)

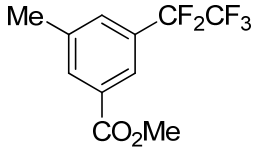
The reaction was performed according to the general procedure for the trifluoromethylation of arenes on a 0.500 mmol scale (60.3 μL **4i**) with 0.1 mol % $[Ir(COD)OMe]_2$ and 0.2 mol % dtbpy in the first step. The crude mixture was purified by silica gel chromatography (4 g of silica, 100:0 → 90:10 pentane:Et_2O) to give **5i** (34.0 mg, 39% yield) (Average isolated yield: 36%).



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (s, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 1H), 2.33 (s, 6H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 140.87 (s), 137.43 (s), 130.02 (s), 128.34 (q, *J* = 32.1 Hz), 126.40 (q, *J* = 3.8 Hz), 124.66 (q, *J* = 271.8 Hz), 122.80 (q, *J* = 3.9 Hz), 19.99 (s), 19.97 (s).
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.68 (s).

methyl 3-methyl-5-(perfluoroethyl)benzoate (6a)

The reaction was performed according to the general procedure for the perfluoroalkylation of arenes on a 0.500 mmol scale (70.6 μL methyl 3-methylbenzoate) with 0.1 mol % $[Ir(COD)OMe]_2$ and 0.2 mol % dtbpy in the first step. The crude mixture was purified by silica gel chromatography (4 g of silica, 100:0 → 90:10 pentane:Et_2O) to give **6a** (55.2 mg, 41% yield) (Average isolated yield: 39%).

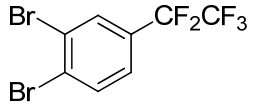


^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 8.06 (s, 1H), 7.58 (s, 1H), 3.95 (s, 3H), 2.48 (s, 3H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -85.14 (s), -115.31 (s).

1,2-dibromo-4-(perfluoroethyl)benzene (6b)

The reaction was performed according to the general procedure for the perfluoroalkylation of arenes on a 0.500 mmol scale (60.5 μL 1,2-dibromobenzene) with 0.1 mol % $[Ir(COD)OMe]_2$ and 0.2 mol % dtbpy in the first step. The crude mixture was purified by silica gel chromatography (4 g of silica, 100:0 → 90:10 pentane:Et_2O) to give **6b** (90.3 mg, 51% yield) (Average isolated yield: 51%).

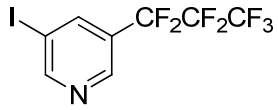


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 2.0 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.40 (dd, J = 8.4, 1.9 Hz, 1H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -85.13 (s), -115.58 (s).

3-iodo-5-(perfluoropropyl)pyridine (7a)

The reaction was performed according to the general procedure for the perfluoroalkylation of arenes on a 0.500 mmol scale (102.5 mg 3-iodopyridine) with 3.0 mol % $[Ir(COD)OMe]_2$ and 6.0 mol % dtbpy in the first step. The crude mixture was purified by silica gel chromatography (4 g of silica, 100:0 → 90:10 pentane:Et_2O) to give **7a** (70.9 mg, 38% yield) (Average isolated yield: 39%).

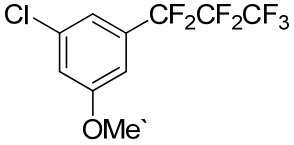


^{1}H NMR (500 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.77 (s, 1H), 8.21 (s, 1H).

^{19}F NMR (470 MHz, $CDCl_3$) δ -80.21 (t, J = 8.8 Hz), -112.89 (m), -126.52 (s).

1-chloro-3-methoxy-5-(perfluoropropyl)benzene (7b)

The reaction was performed according to the general procedure for the perfluoroalkylation of arenes on a 0.500 mmol scale (61.5 μL 3-chloroanisole) with 0.1 mol % $[Ir(COD)OMe]_2$ and 0.2 mol % dtbpy in the first step. The crude mixture was purified by silica gel chromatography (4 g of silica, 100:0 → 90:10 pentane:Et_2O) to give **7b** (71.4 mg, 46% yield) (Average isolated yield: 42%).

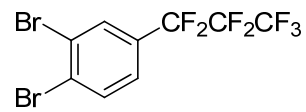


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (s, 1H), 7.11 (t, J = 2.0 Hz, 1H), 7.01 (s, 1H), 3.87 (s, 3H).

^{19}F NMR (470 MHz, $CDCl_3$) δ -80.52 (t, J = 9.8 Hz), -112.27 (q, J = 9.8 Hz), -126.82 (s).

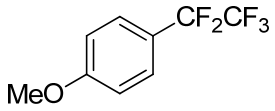
1,2-dibromo-4-(perfluoropropyl)benzene (7c)

The reaction was performed according to the general procedure for the perfluoroalkylation of arenes on a 0.500 mmol scale (60.5 μL



1,2-dibromobenzene) with 0.1 mol % $[Ir(COD)OMe]_2$ and 0.2 mol % dtbpy in the first step. The crude mixture was purified by silica gel chromatography (4 g of silica, 100:0 → 90:10 pentane:Et_2O) to give **7c** (115.1 mg, 57% yield) (Average isolated yield: 55%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 2.0 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.39 (dd, *J* = 8.4, 2.0 Hz, 1H).
^{19}F NMR (470 MHz, $CDCl_3$) δ -80.41 (t, *J* = 9.6 Hz), -112.43 (q, *J* = 9.5 Hz), -126.71 (s).

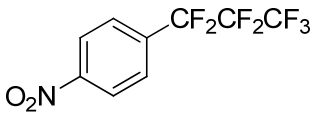
1-methoxy-4-(perfluoroethyl)benzene (6c)



The reaction was performed according to the general procedure for the perfluoroalkylation of aryl bromides on a 0.500 mmol scale (62.8 μL 4-bromoanisole). The crude mixture was purified by silica gel chromatography (4g silica, 100% pentane) to give **6c** (34.5 mg, 31% yield) (Average isolated yield: 30%).

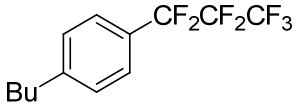
R_f = 0.58 (8:1 hexanes:EtOAc)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.8 Hz, 2 H), 7.03 (d, *J* = 8.9 Hz, 2 H), 3.90 (s, 3 H).
^{19}F NMR (376 MHz, $CDCl_3$) δ -85.41 (s), -114.29 (s).

1-nitro-4-(perfluoropropyl)benzene (7d)



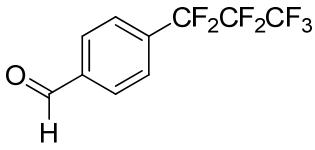
The reaction was performed according to the general procedure for the perfluoroalkylation of aryl bromides on a 0.500 mmol scale (101.0 mg 1-bromo-4-nitrobenzene). The crude mixture was purified by silica gel chromatography (4 g of silica, 100:0 → 90:10 pentane:Et_2O) to give **7d** (83.1 mg, 57% yield) (Average isolated yield: 56%).
^{1}H NMR (376 MHz, $CDCl_3$) δ 8.46 (d, *J* = 8.7 Hz, 2H), 7.85 (d, *J* = 8.7 Hz, 2H).
^{19}F NMR (376 MHz, $CDCl_3$) δ -80.26 (t, *J* = 9.8 Hz), -112.63 (q, *J* = 9.7 Hz), -126.51 (s).

1-butyl-4-(perfluoropropyl)benzene (7e)



The reaction was performed according to the general procedure for the perfluoroalkylation of aryl bromides on a 0.500 mmol scale (88.2 μL 1-bromo-4-butylbenzene). The crude mixture was purified by silica gel chromatography (4 g of silica, 100:0 → 90:10 pentane:Et_2O) to give **7f** (86.3 mg, 57% yield) (Average isolated yield: 54%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 2.68 (t, *J* = 7.8 Hz, 2H), 1.62 (m, 2H), 1.36 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).
^{19}F NMR (376 MHz, $CDCl_3$) δ -80.43 (t, *J* = 9.9 Hz), -111.79 (q, *J* = 9.8 Hz), -126.93 (s).

4-(perfluoropropyl)benzaldehyde (7f)



The reaction was performed according to the general procedure for the perfluoroalkylation of aryl bromides on a 0.500 mmol scale (92.5 mg 4-bromobenzaldehyde). The crude mixture was purified by silica gel chromatography (4 g of silica, 100:0 → 90:10 pentane:Et_2O) to give **7g** (93.4 mg, 68% yield) (Average isolated yield: 64%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.12 (s, 1H), 8.03 (d, *J* = 8.2 Hz, 2H), 7.78 (d, *J* = 8.2 Hz, 2H).
^{19}F NMR (376 MHz, $CDCl_3$) δ -80.34 (t, *J* = 9.7 Hz), -112.71 (q, *J* = 9.7 Hz), -126.68 (s).

2.5 References

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"A General Strategy for the Perfluoroalkylation of Arenes and Arylbromides by Using Arylboronate Esters and [(phen)CuR_F]"
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CHAPTER 3

Perfluoroalkylation of Heteroarylbromides with [(phen)CuR_F]

3.1 Introduction

The trifluoromethyl group is present in numerous pharmaceuticals, agrochemicals and materials. As a result, there has been considerable interest in developing practical reactions to incorporate perfluoroalkyl groups into organic compounds under mild conditions. In medicinal and agrochemistry, the introduction of a trifluoromethyl group can lead to increases in activity and stability.[1] The top selling drugs fluoxetine (Prozac) and mefloquine (Lariam) and the leading agrochemical fluazinam contain CF_3 groups (Figure 3.1).

The Swarts reaction, which involves the treatment of benzotrichlorides with HF or SbF_5, remains the most prevalent method for the industrial-scale synthesis of trifluoromethyl arenes and certain heteroarenes.[2a] Although this method is effective in the bulk production of simple benzotrifluorides, its utility on laboratory scale for the synthesis of complex molecules and late-stage functionalization is limited by the low functional group compatibility and toxic reagents. Furthermore, the Swarts reaction cannot be applied to the synthesis of longer-chain perfluoroalkyl moieties, such as the C_2F_5 group.

Although there has been considerable progress in copper-mediated perfluoroalkylation reactions in recent years, these reactions are mostly limited to aryl iodide and arylboron substrates.[2] Perfluoroalkylation reactions of aryl bromides, which are more commercially and synthetically available than aryl iodides, have been limited to substrates containing electron-withdrawing groups. A single report for the trifluoromethylation of aryl chlorides with Pd has been reported.[3] However, these reactions require an expensive palladium precatalyst, ligand, and CF_3 source. Most relevant to our current work, the majority of the current methods have not been demonstrated to be applicable to the synthesis of fluoroalkyl *hetero*arenes with significant scope. This limitation is important because of the prevalence of heteroarenes in medicinal and agrochemistry.

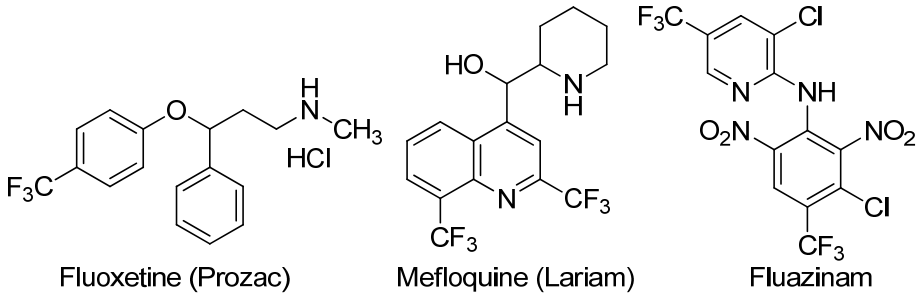


Figure 3.1 Selected Bioactive Compounds Containing CF_3 Groups

The difference in availability of aryl iodides and bromides is even greater for heteroaryl halides. There are only about $1/5^{th}$ as many commercially available iodopyridines compared to bromopyridines, and the price of 2-iodopyridine is nearly forty times higher than that of 2-bromopyridine per mole.[4] A Reaxys search shows that there are also twice as many procedures to synthesize any bromopyridine isomer compared to procedures to synthesize the corresponding iodopyridines.

Grushin has recently reported the perfluoroalkylation of heteroaryl bromides with $CuCF_3$ formed by the direct cupration of HCF_3.[5] Although the functional group tolerance and yields of this method are high, the $CuCF_3$ reagent cannot be stored. Thus, each reaction must be initiated by generation of $CuCF_3$ from gaseous HCF_3, and such a transformation is challenging to conduct in common laboratory settings.

Methods for the radical trifluoromethylation of heteroarenes have also been reported recently.[6] While these methods do not require prefunctionalized substrates, the yields and regioselectivities of these reactions are often modest, and limited functional group compatibility has been demonstrated. Thus, methods for the synthesis of fluoroalkylheteroarenes from heteroaryl bromides with easily handled reagents that occur with broad scope and complete site selectivity is desirable.

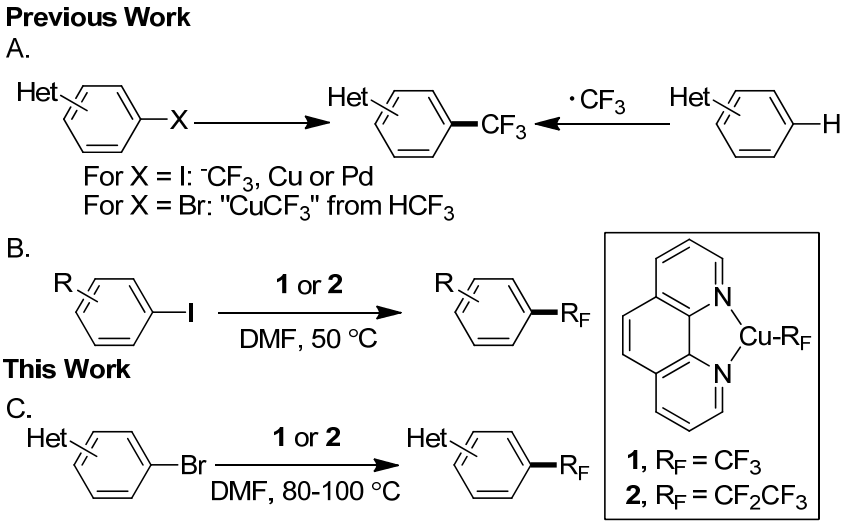


Figure 3.2 Methods for the synthesis of Perfluoroalkyl Heteroarenes.

Our group recently reported the trifluoromethylation of aryl iodides with a phenanthroline-$CuCF_3$ complex, (phen)$CuCF_3$ (**1**) (Figure 3.2, B).[7a] This thermally-stable, commercially-available solid reacts with a variety of aryl iodides and electron-deficient aryl bromides under mild conditions. We also showed that aryl bromides can be converted to trifluoromethylarenes indirectly by initial conversion to arylboronate esters, followed by reaction of the boronate with **1** in air.[7b]

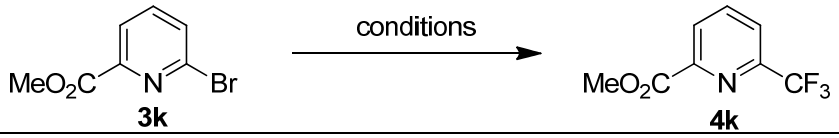
3.2 Results and Discussion

Because pyridines are more electron-deficient than arenes, we considered that the reactions of **1** with bromopyridines would occur similarly to the reactions of **1** with electron-deficient bromoarenes. However, reactions of $CuCF_3$ reagents with bromopyridines could be challenging because pyridines can bind to the metal center and alter the inherent reactivity. Moreover, bromopyridines are less reactive towards oxidative addition than iodopyridines, and the oxidative addition step is likely the rate-limiting step for reactions with copper centers containing electron-withdrawing perfluoroalkyl groups.[9] We hypothesized that the chelating phen ligand in pre-formed **1**

would minimize bonding of the pyridine to the copper center, in addition to rendering the copper complex isolable and easy to handle. Herein, we report that copper complexes **1** and **2** react with a range of heteroaryl bromides to form perfluoroalkylheteroarenes in good yields. The reactivity and functional group compatibility for the reaction of bromopyridines with **1** is higher than prior fluoroalkylation methods of heteroarenes.

Table 3.1 shows a comparison of the yield for the trifluoromethylation of methyl 6-bromopicolinate, a representative bromopyridine containing a potentially reactive ester. Although the 2-position is activated, the prior methods reported for trifluoromethylation generate the 2-trifluoromethylpyridine in low to modest yield. In contrast, the reaction of this bromopyridine with **1** occurs in essentially quantitative yield.

Table 3.1 Comparison of copper-mediated trifluoromethylation reactions of a functionalized bromopyridine with previously reported methods.[a]



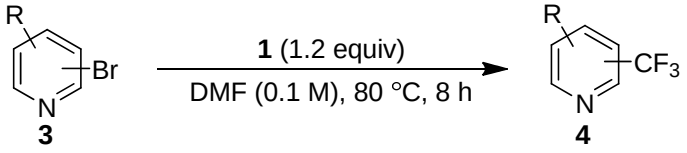
3k **4k**

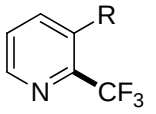
conditions	yield
(phen)$CuCF_3$, DMF, 80 °C	96%
$(PPh_3)_3CuCF_3$ (1.0 equiv), ^{t}BuBipy, PhMe, 80 °C	56% [b]
$K[(MeO)_3BCF_3]$, CuI (20 mol%), phen (20 mol%), DMSO, 60 °C	17% [c]
$TESCF_3$, KF, CuI (10 mol%), phen (10 mol%), DMF/NMP, 60 °C	20% [d]
MeO_2CCF_3, CsF, CuI (10 mol%), DMF, 160 °C	24% [e]
$TESCF_3$, KF, CuI (1.5 equiv), DMF/NMP, 80 °C	< 5% [f]

[a] Yields were determined by ^{19}F NMR spectroscopy. [b] ref. 8a. [c] ref. 8b. [d] ref. 8c. [e] ref. 8d. [f] ref. 8e.

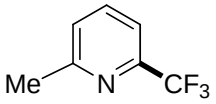
The scope of the trifluoromethylation reaction of various 2-, 3- and 4-bromopyridines with complex **1** is shown in Table 3.2. 2-Bromopyridines containing both electron-donating and electron-withdrawing substituents at each position of the ring afforded the products in excellent yields within 8 hours. Substrates bearing aldehyde, ketone, ester and the Weinreb amide functionality (**3f-k**) reacted in good yields; side-products resulting from nucleophilic addition of CF_3 to the carbonyl group were not observed. Competitive addition to a carbonyl group is commonly observed in systems using nucleophilic CF_3 reagents.[8] In addition, substrates containing nitro and cyano groups (**4e** and **4l**) reacted in high yields. Ortho-substituted 2-bromopyridines (**4b**, **4f**, **4g**, **4p**) formed the products in 74-94% yield. Protic X-H bonds of alcohols, amides and carbamates were tolerated under the reaction conditions. However, a lower yield (**4m**, 40%) was observed in the reaction of a substrate containing a secondary amide compared to a substrate containing a tertiary amide (**4n**, 92%).

Table 3.2 Trifluoromethylation reactions of bromopyridines with (phen)$CuCF_3$[a]

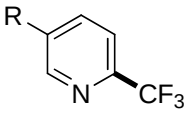




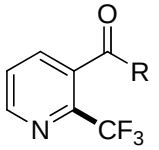
4a, R = H, 94%
4b, R = Me, 92%



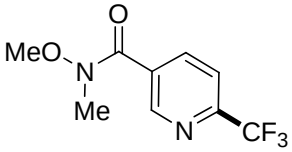
4c, 83%



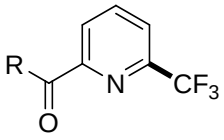
4d, R = Br, 63% {15%} [b]
4e, R = NO_2, 99% (85%)



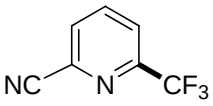
4f, R = H, 74%
4g, R = OMe, 94% (70%)



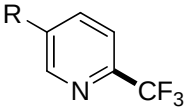
4h, 91%



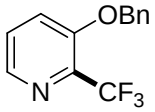
4i, R = H, 78% [c]
4j, R = Me, 76% [c]
4k, R = OMe, 96% (80%)



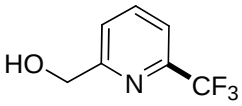
4l, 88% (79%)



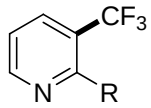
4m, R = NHAc, 40% (39%)[e]
4n, R = N(Me)Ac, 92% (86%)[e]
4o, R = OBn, 86% (85%)[e]



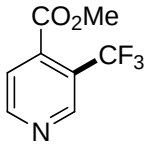
4p, 84% (60%)



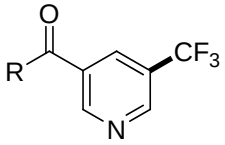
4q, 71%



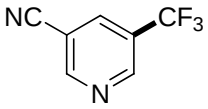
4r, R = H, 50% [c]
4s, R = Cl, 50% [c]



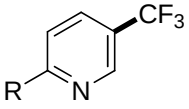
4t, 88% (74%) [c]



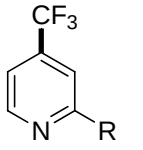
4u, R = H, 51% [c]
4v, R = OMe, 70% [c]



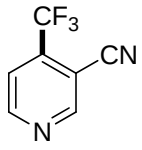
4w, 66% [c]



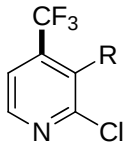
4x, R = NHBoc, 42% [c]
4y, R = OMe, 32% [c]



4z, R = H, 75% [c]
4aa, R = Me, 59% [c, d]
4ab, R = OMe, 58% [c, d]



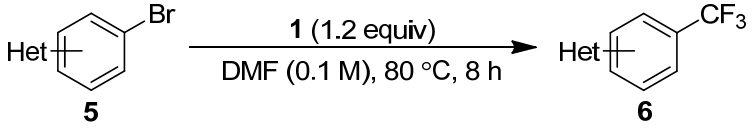
4ac, 92%



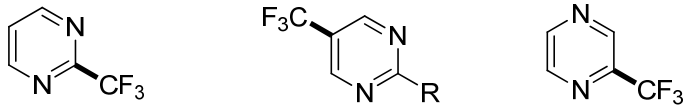
4ad, R = H, 68%
4ae, R = CO_2Me, 70%

[a]Reaction conditions: bromopyridine (**3**, 0.10 mmol) and **1** (0.12 mmol) in DMF (1 mL) at 80 or 100 °C for 8 h. Yields were determined by ^{19}F NMR spectroscopy. Yields in parentheses are isolated yields. [b]Yield of bis-trifluoromethylated product. [c]Reaction was run at 100 °C. [d] 1.5 equiv of **1** was used. [e] Isolated product contains trace (2-3%) perfluoroethyl product.

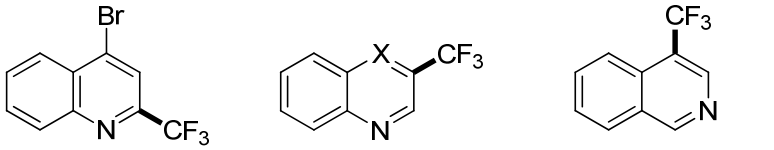
Table 3.3 Trifluoromethylation of Heteroaryl Bromides with (phen)$CuCF_3$[a]



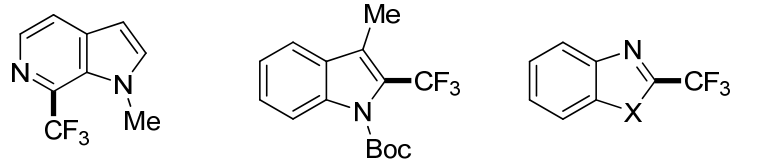
5 **6**



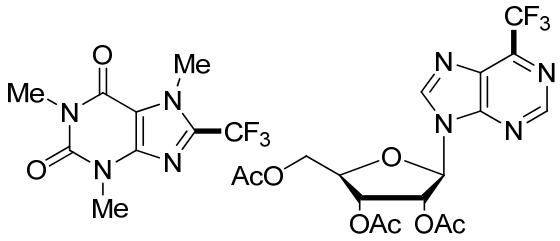
6a, 97% **6b**, R = CN, 86% [c] **6c**, R = NPr(Boc), 64% (59%)[e] **6d**, 98%



6e, 65% {18%} [b] **6f**, X = CH, 78% [c, d] **6g**, X = N, 99% (88%) **6h**, 67% [c, d]



6i, 99% (95%) **6j**, 76% **6k**, X = O, 84% (71%) **6l**, X = NMe, 87% (68%)



6m, 91% (72%) [f] **6n**, 86%

[a] Reaction conditions: bromoheteroarene (**5**, 0.10 mmol) and **1** (0.12 mmol) in DMF (1 mL) at 80 or 100 °C for 8 h. Yields were determined by ^{19}F NMR spectroscopy. Yields in parentheses are isolated yields. [b] Yield of bis-trifluoromethylated product. [c] Reaction was run at 100 °C. [d] 1.5 equiv of **1** was used. [e] Isolated product contains 20% perfluoroethyl product. [f] Isolated on a 4.8 mmol scale.

For certain compounds (**4m-o**), the isolated product was found to contain trace (2-3%) perfluoroethyl-product resulting from difluorocarbene insertion into the $CuCF_3$ reagent. The reaction of 2,5-dibromopyridine (**3d**) occurred preferentially at the 2-position over the 5-position, but the product from trifluoromethylation at both the 2- and 5-position formed in 15% yield. No product was observed corresponding to trifluoromethylation at the 5-position alone. 2-Chloropyridines and pyrimidines were also investigated for their reactivity towards **1**. However, low yields (5-20%) of the trifluoromethylated products were obtained from the heteroaryl chlorides.

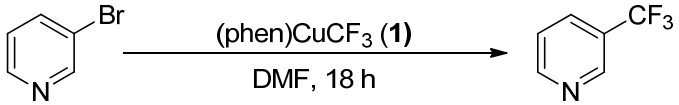
Pyridines containing bromine at the 4-position were less reactive than those containing bromine at the 2-position. High yields were observed when the bromoheteroarene contained electron-withdrawing groups (**3ac-ae**). The product of trifluoromethylation was obtained in modest yield from 4-bromopyridines bearing

electron-donating groups (**4aa**, **4ab**).

3-Bromopyridines were less reactive toward this process than 2- and 4-bromopyridines, but synthetically useful amounts of the 3-trifluoromethylpyridines did form. We presume the lower reactivity is due to the greater electron-density at the 3-position of pyridines, compared to the 2 and 4-positions, making them more akin to bromoarenes and less prone to undergo oxidative addition to the Cu(I) reagent. Consistent with this assertion, the reactions of 3-bromopyridines required heating at a higher temperature (100 ºC) than the reactions with 2-bromopyridines (80 ºC). The trifluoromethylation of 3-bromopyridines containing electron-donating substituents (**3x**, **3y**) afforded products in modest yields. However, the trifluoromethylation of 3-bromopyridines containing electron-withdrawing substituents (**3s-w**) formed the products in good yields. Thus, this simple reaction provides a method to form a range of 3-trifluoromethylpyridine derivatives.

To enhance the reactivity of 3-bromopyridines toward **1**, we tested several changes to the reaction conditions (see Table 3.4). However, changes to the temperature, equivalents of **1**, reaction time, concentration, ligand and solvent had little effect on the yield. Catalytic quantities of Lewis acids to bind to pyridine and decrease electron density at the 3-position led to no reaction. Reactions of the corresponding pyridine-*N*-oxide and *N*-(TBS)pyridinium triflate formed the trifluoromethylpyridine derivatives in trace quantities. We are continuing to investigate methods to increase the reactivity of electron-rich 3-bromopyridines toward **1**.

Table 3.4 Screen of reaction conditions for improving the reactivity of 3-bromopyridines with (phen)$CuCF_3$.



3a **4a**

entry	[**3a**]	°C	equiv (**1**)	additive	yield
1	0.1	100	1.2	-	50%
2	0.1	100	1.5	-	46%
3	0.1	120	1.2	-	40%
4	0.2	100	1.2	-	49%
5	0.4	100	1.2	-	46%
6	0.1	100	1.2	$Zn(OTf)_2$	< 5% [b]
7	0.1	100	1.2	$Al(OTf)_3$	< 5% [b]
8	0.1	100	1.2	$In(OTf)_3$	< 5% [b]
9	0.1	100	1.2	$ZnCl_2$	< 5% [b]
10	0.1	100	1.2	BPh_3	< 5% [b]
11 [c]	0.1	100	1.2	-	< 5%
12 [d]	0.1	100	1.2	-	< 5%
13 [e]	0.1	100	1.2	-	26%
14	0.1	100	2.5	-	53%
15 [f]	0.1	100	2.5	-	60%

[a] Reaction conditions: **3** (0.10 mmol) and **1** (0.12 mmol) in DMF (1 mL) at 100 °C for 18 h. Yields were determined by ^{19}F NMR spectroscopy with 4-$CF_3OC_6H_4OMe$ as internal standard. [b] No significant product formation was observed with DMF or PhMe as solvent. [c] 3-bromopyridine *N*-oxide was used as substrate. [d] 3-bromo-1-(tert-butyldimethylsilyl)pyridinium triflate was used as substrate. [e] (bipy)CuCF3 was used as CF_3 source. [f] 1.0 equiv of **1** added initially, followed by an additional 1.5 equiv after 6 h.

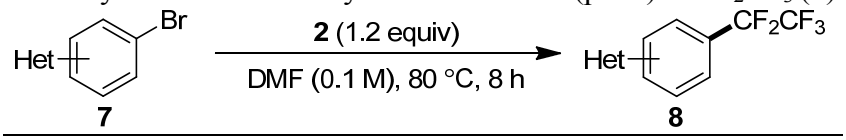
The scope of the trifluoromethylation reaction with **1** encompassed reactions with other brominated nitrogen-heterocycles (Table 3.3). For example, 2- and 5-bromopyrimidines reacted with **1** to form the corresponding trifluoromethylpyrimidines in good yield (**6a-c**). Complex **1** also reacted with a range of bromopyrazines (**5d**), quinolines (**5e, 5f**), quinoxolines (**5g**), isoquinolines (**5h**), and aza-indoles (**5i**) when bromine was located adjacent to nitrogen. The reaction with 2,4-dibromoquinoline occurred selectively at the 2-position; only 18% of the bis-trifluoromethylated side-product (**6e**) formed.

The electron-rich property of 5-membered heterocycles might lead one to expect that these systems would not react readily with **1**. However, complex **1** does react with certain 5-membered heterocycles containing bromine in the 2-position. The reactions of **1** with 2-bromo indole (**5j**), benzimidazole (**5l**) and benzoxazole (**5k**) formed the trifluoromethylated products in good to high yield. Brominated caffeine was also transformed to the trifluoromethylated product and isolated on gram-scale in high yield (**6m**), demonstrating the applicability of this method for the large-scale trifluoromethylation of complex heterocyclic substrates. Finally, the nucleoside derivative **5n** underwent trifluoromethylation in high yield. Reactions of 2-bromofurans and 2-bromothiophenes also were explored, but only low yields of the trifluoromethylation product were obtained. Furthermore, unprotected N-H derivatives of **5i** and **5l** did not react with **1** to form trifluoromethylated products.

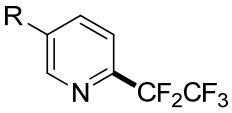
Given the limited synthetic procedures for the incorporation of longer chain perfluoroalkyl groups, we investigated the extension of this reaction to the perfluoroethylation of bromo-heteroarenes with (phen)$CuCF_2CF_3$ (**2**) (Table 3.5). In fact, the perfluoroethyl heteroarene products were generated in higher yield than the trifluoromethyl analogues. This higher yield was observed for 2-, 3- and 4-bromopyridines. For example, 3-bromopyridine reacted with **2** to form 3-pentafluoroethylpyridine in 74% yield, and 2-methoxy-3-bromopyridine reacted with **2** to form the $-C_2F_5$ product in 65% yield. We propose the increased yields with **2** results, in part, from greater thermal stability of **2** compared to **1**. Heating complexes **1** and **2** separately in DMF at 80 ºC caused 80% of **1** to decompose, compared to only 6% of **2** after 24 h.

The reactions of bromopyridines with **2** occurred with similar functional group compatibility as was observed for the reactions of **1** (Table 3.5). Although the yields were high in almost all cases, bromopyridines bearing electron-withdrawing substituents generally reacted in higher yields than those bearing electron-donating substituents. Various diazines also underwent the perfluoroethylation reaction.

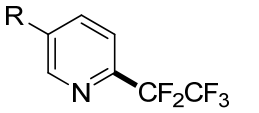
Table 3.5 Perfluoroethylation of Heteroaryl Bromides with (phen)$CuCF_2CF_3$ (2).[a]



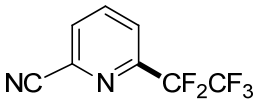
7 **8**



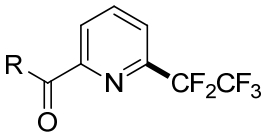
8a, R = H, 98%
8b, R = Br, 59% {17%} [b]
8c, R = NO_2, 99% (93%)



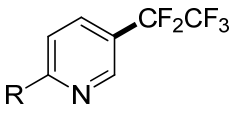
8d, R = NHAc, 84% (79%)
8e, R = OBn, 87% (80%)



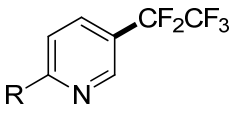
8f, 95% (89%)



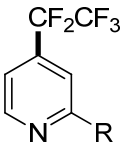
8g, R = Me, 68% (57%) [c]
8h, R = OMe, 98% (90%)



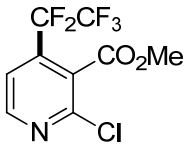
8i, R = H, 74% [c]
8j, R = CN, 72% [c]



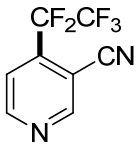
8k, R = OMe, 61% [c]
8l, R = NHBoc, 56% (42%) [c]



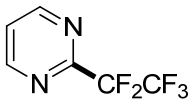
8m, R = H, 68% [c]
8n, R = OBn, 82% (75%) [c, d]



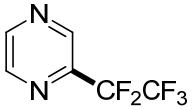
8o, 90% (81%) [c, e]



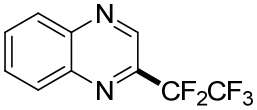
8p, 99% (62%) [c]



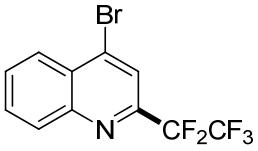
8q, 99%



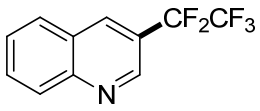
8r, 99%



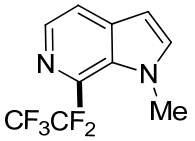
8s, 95%



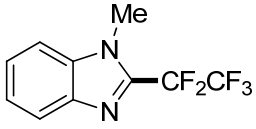
8t, 60% {30%} [b]



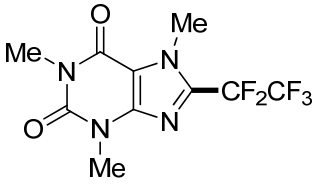
8u, 92% [c]



8v, 98% (85%)



8w, 93% (69%)



8x, 98% (79%)

[a] Reaction conditions: bromoheteroarene (**7**, 0.10 mmol) and **2** (0.12 mmol) in DMF (1 mL) at 80 or 100 °C for 8 h. Yields were determined by ^{19}F NMR spectroscopy. Yields in parentheses are isolated yields. [b] Yield of bis-perfluoroethylated product. [c] Reaction was run at 100 °C. [d] Isolated product contains 7% of **7n**. [e] Isolated product contains 5% bis-perfluoroethylated product.

3.3 Conclusions

In summary, we developed a simple synthetic procedure for the generation of perfluoroalkyl heteroarenes from reactions of stable $CuCF_3$ and CuC_2F_5 complexes **1** and **2** with heteroaryl bromides. These reactions are an improvement over current perfluoroalkylation reactions of heteroaryl iodides because heteroaryl bromides are significantly less expensive and more readily available than heteroaryl iodides. The high reactivity of complexes **1** and **2**, as well as the mild reaction conditions, allowed for the perfluoroalkylation of heteroaryl bromides containing both electron-donating and electron-withdrawing groups as well as electrophilic and protic functional groups. We anticipate that this process will enable the synthesis of perfluoroalkyl derivatives of a wide range of heteroarenes as part of studies on structure-reactivity relationships.

3.4 Experimental

All manipulations were conducted under an inert atmosphere with a nitrogen-filled glove box (Innovative Technologies, Newburyport, Massachusetts) equipped with an oxygen sensor (working oxygen level <20.0 ppm) and low-temperature refrigeration unit (–30 °C), unless otherwise noted. All reactions were conducted in 4 mL or 20 mL vials fitted with a Teflon-lined screw cap unless otherwise noted.

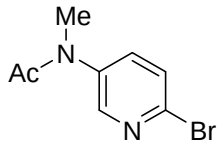
Compounds **1**, **2**, **3h**, **3m**, **3o**, **3p**, and **3x** were prepared according to the published literature procedures. The preparations of reactants **3n**, **5c**, and **5i**, are described below. All other reagents were purchased from commercial suppliers and used as received.

The fluoroalkyl heteroarenes were synthesized and isolated by the general procedures described below. The new compound **8r** was not isolated due to high volatility, and product identity was confirmed by ^{19}F NMR spectroscopy and by GC-mass spectrometry. The yields of fluoroalkyl heteroarenes that were not isolated and reported previously in the literature were determined by ^{19}F NMR spectroscopy following the general procedure described below. The identity of the products previously reported in the literature was confirmed by comparison of the acquired ^{19}F NMR spectrum to the published data and by GC-mass spectrometry.

NMR spectra were acquired on 400 MHz, 500 MHz, or 600 MHz Bruker instruments at the University of California, Berkeley. NMR spectra were processed with MestReNova 5.0 (Mestrelab Research SL). Chemical shifts are reported in ppm and referenced to residual solvent peaks (CHCl3 in CDCl3: 7.26 ppm for 1H and 77.0 ppm for 13C) or to an external standard (1% CFCl3 in CDCl3: 0 ppm for 19F). Coupling constants are reported in hertz.

All GC-MS analyses were conducted with an Agilent 6890N GC equipped with an HP-5 column (25 m x 0.20 mm ID x 0.33 μm film) and an Agilent 5973 Mass Selective Detector. The temperature for each run was held at 50 °C for 2 min, ramped from 50 °C to 300 °C at 40 °C/min, and held at 300 °C for 5 min.

Preparation of N-(6-bromopyridin-3-yl)-N-methylacetamide (3n)



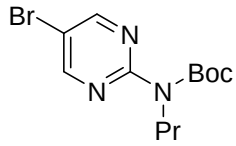
To an oven-dried flask under inert atmosphere was added NaH (1.1 mmol, 1.1 equiv) in THF (2 mL). Reactant **3m** (1.0 mmol, 1.0 equiv) was added slowly over 3 minutes. The reaction was allowed to stir at room temperature for 2 minutes, and then MeI (1.1 mmol, 1.1 equiv) was added dropwise over 2 minutes. The reaction was allowed to stir at room temperature for 13 h, at which point full conversion was determined by TLC analysis. The solvent was removed by rotary evaporation and the crude material was purified by silica gel chromatography (100% EtOAc) to give **3n** as a white solid (186 mg, 81% yield).

Note: The peaks in the ^{1}H and ^{13}C spectra were broadened due to the slow interconversion of the amide diastereomers.

^{1}H NMR (600 MHz, DMSO) δ 8.44 (s, 1H), 7.81 – 7.72 (m, 2H), 3.16 (bs, 3H), 1.81 (bs, 3H).

^{13}C NMR (151 MHz, DMSO) δ 169.4, 149.5, 141.0, 139.6, 138.6, 129.0, 36.9, 22.8.

Preparation of tert-butyl (5-bromopyrimidin-2-yl)(propyl)carbamate (5c)

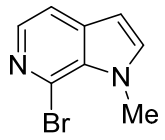


To an oven-dried flask under inert atmosphere was added 5-bromo-N-propylpyrimidin-2-amine (1.0 mmol, 1.0 equiv), Et_3N (1.5 mmol, 1.5 equiv), and DMAP (8.2 mol%) in THF (2 mL). The reaction was warmed to 55 ºC and then Boc_2O (3.0 mmol, 3.0 equiv) was added slowly over 1 minute. The reaction was allowed to stir at 55 ºC for 18 h and then cooled to room temperature. The solvent was removed by rotary evaporation and the crude material was purified by silica gel chromatography (9:1 hexanes-EtOAc) to give **5c** as a colorless oil (280 mg, 82% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.55 (s, 2H), 3.85 – 3.71 (m, 2H), 1.58 (sext, J = 7.5 Hz, 2H), 1.44 (s, 9H), 0.82 (t, J = 7.5 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 159.3, 158.0, 153.3, 113.6, 81.5, 49.4, 28.1, 22.0, 11.2.

Preparation of 1-methyl-7-bromo-6-azaindole (5i)



To an oven-dried flask under inert atmosphere was added NaH (1.6 mmol, 1.1 equiv) in THF (3 mL). 7-Bromo-6-azaindole (1.5 mmol, 1.0 equiv) was added slowly over 3 minutes. The reaction was allowed to stir at room temperature for 5 minutes, and then a solution of MeI (1.6 mmol, 1.1 equiv) in THF (0.5 mL) was added dropwise over 2 minutes. The reaction was allowed to stir at room temperature overnight. The solvent was removed by rotary evaporation and the crude material was purified by silica gel chromatography (6:1 hexanes-EtOAc) to give **5i** as a white solid (198 mg, 63% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 (d, J = 5.3 Hz, 1H), 7.43 (d, J = 5.3 Hz, 1H), 7.16 (d, J = 3.1 Hz, 1H), 6.47 (d, J = 3.1 Hz, 1H), 4.17 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 138.1, 136.2, 135.0, 131.0, 123.9, 115.5, 101.0, 36.9.

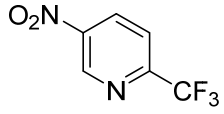
General Procedure for the Perfluoroalkylation of Heteroaryl Bromides with 1 and 2 for Characterization by ^{19}F NMR Spectroscopy

To an oven-dried 4 mL vial was added heteroaryl bromide (0.10 mmol, 1.0 equiv) and a solution containing **1** or **2** (0.12 mmol, 1.2 equiv) in 1.0 mL of DMF solvent. The vial was sealed with a Teflon-lined cap and heated at 80 ºC or 100 ºC for 8 h. The solution was allowed to cool to room temperature. 4-Trifluoromethoxyanisole (0.10 mmol, 1.0 equiv) was then added as internal standard, then the reaction mixture was directly transferred to an NMR tube for characterization by ^{19}F NMR spectroscopy

General Procedure for the Synthesis of Perfluoroalkyl Heteroarenes from the Reaction of Heteroaryl Bromides with 1 and 2.

To an oven-dried 20 mL vial was added heteroaryl bromide (0.50 mmol, 1.0 equiv) and a solution containing **1** or **2** (0.60 mmol, 1.2 equiv) in 5.0 mL of DMF solvent. The vial was sealed with a Teflon-lined cap and heated at 80 ºC or 100 ºC for 8 h. The solution was allowed to cool to room temperature, and the reaction mixture was diluted with 30 mL EtOAc. The reaction mixture was washed with H_2O (3 x 20 mL) and brine (1 x 10 mL) and then the organic layer was dried with anhydrous Na_2SO_4, concentrated, and purified by silica gel chromatography.

5-nitro-2-(trifluoromethyl)pyridine (4e)



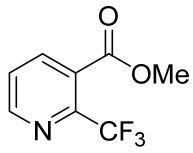
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 20:1 hexanes-EtOAc to give **4e** as a white solid (82 mg, 85% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.54 (d, J = 2.5 Hz, 1H), 8.70 (dd, J = 8.5, 2.5 Hz, 1H), 7.94 (d, J = 8.5 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 152.7 (q, J = 36.0 Hz), 145.6, 145.5, 133.1, 121.4, 120.6 (q, J = 274.9 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -68.0.

methyl 2-(trifluoromethyl)nicotinate (4g)



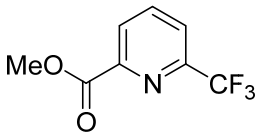
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 6:1 hexanes-EtOAc to give **4g** as a colorless oil (72 mg, 70% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.77 (d, J = 4.4 Hz, 1H), 8.08 (d, J = 7.8 Hz, 1H), 7.56 (dd, J = 7.9, 4.8 Hz, 1H), 3.93 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 165.9, 150.9, 145.7 (q, J = 35.2 Hz), 138.4, 127.8, 126.1, 121.2 (q, J = 275.0 Hz), 53.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ -64.6.

methyl 6-(trifluoromethyl)picolinate (4k)



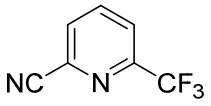
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 6:1 hexanes-EtOAc to give **4k** as a white solid (82 mg, 80% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.27 (d, J = 7.9 Hz, 1H), 8.05 (t, J = 7.9 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H), 3.98 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 164.5, 148.5, 148.3 (q, J = 35.4 Hz), 138.8, 127.5, 123.4, 121.0 (q, J = 274.6 Hz), 53.1.

^{19}F NMR (376 MHz, $CDCl_3$) δ -67.8.

6-(trifluoromethyl)picolinonitrile (4l)



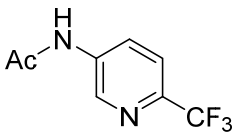
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 6:1 hexanes-EtOAc to give **4l** as a white solid (68 mg, 79% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 (t, J = 7.9 Hz, 1H), 7.96 – 7.89 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 149.7 (q, J = 36.6 Hz), 139.2, 134.0, 130.8, 123.7, 120.4 (q, J = 274.8 Hz), 115.9.

^{19}F NMR (376 MHz, $CDCl_3$) δ -68.2.

N-(6-(trifluoromethyl)pyridin-3-yl)acetamide (4m)



The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 100% EtOAc to give **4m** as a tan solid (40 mg, 39% yield).

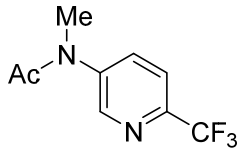
Note: Isolated **4m** contained 2% of perfluoroethyl-substituted product.

^{1}H NMR (600 MHz, DMSO-d_6) δ 10.54 (s, 1H), 8.83 (s, 1H), 8.30 (d, J = 8.1 Hz, 1H), 7.81 (d, J = 8.7 Hz, 1H), 2.11 (s, 3H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 169.5, 140.4, 140.2 (q, J = 33.8 Hz), 138.7, 126.2, 121.7 (q, J = 273.0 Hz), 121.1, 23.9.

^{19}F NMR (376 MHz, $CDCl_3$) δ -67.1.

N-methyl-N-(6-(trifluoromethyl)pyridin-3-yl)acetamide (4n)



The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 100% EtOAc to give **4n** as a colorless oil (94 mg, 86% yield).

Note: The peaks in the ^{1}H and ^{13}C spectra were broadened due to the slow interconversion of the amide diastereomers.

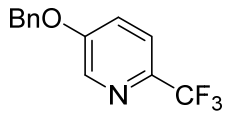
Note: Isolated **4n** contained 3% of perfluoroethyl-substituted product.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.73 – 7.71 (m, 2H), 3.29 (s, 3H), 1.90 (br s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.9, 148.5, 143.1, 135.3, 122.0, 121.1, 120.2, 37.2, 22.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ -72.0.

5-(benzyloxy)-2-(trifluoromethyl)pyridine (4o)



The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 6:1 hexanes-EtOAc to give **4o** as a colorless oil (108 mg, 85% yield).

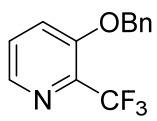
Note: Isolated **4o** contained 2% of perfluoroethyl-substituted product.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.60 (d, J = 8.7 Hz, 1H), 7.52 – 7.25 (m, 6H), 5.15 (s, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 156.7, 140.4 (q, J = 34.8 Hz), 138.9, 135.3, 128.9, 128.6, 127.6, 121.9 (q, J = 273.0 Hz), 121.4, 121.3, 70.7.

^{19}F NMR (376 MHz, $CDCl_3$) δ -66.6.

3-(benzyloxy)-2-(trifluoromethyl)pyridine (4p)



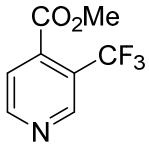
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with a gradient from 100% hexanes to 6:1 hexanes-EtOAc to give **4p** as a colorless oil (76 mg, 60% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.26 (dd, J = 4.2, 1.6 Hz, 1H), 7.44 – 7.37 (m, 6H), 7.36 – 7.31 (m, 1H), 5.22 (s, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 153.3, 140.6, 137.1 (q, J = 33.7 Hz), 135.4, 128.8, 128.4, 127.6, 127.0, 121.9 (q, J = 274.6 Hz), 121.5, 70.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ -66.0.

methyl 3-(trifluoromethyl)isonicotinate (4t)



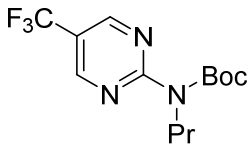
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 6:1 hexanes-EtOAc to give **4t** as a colorless oil (76 mg, 74% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.89 (d, J = 5.0 Hz, 1H), 7.62 (d, J = 4.9 Hz, 1H), 3.94 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 165.4, 153.8, 148.0 (q, J = 5.8 Hz), 138.5, 123.5 (q, J = 32.8 Hz), 122.8 (q, J = 273.8 Hz), 123.1, 53.4.

^{19}F NMR (376 MHz, $CDCl_3$) δ -59.7.

tert-butyl propyl(5-(trifluoromethyl)pyrimidin-2-yl)carbamate (6c)



The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 20:1 hexanes-EtOAc to give **6c** as a colorless oil (90 mg, 59% yield).

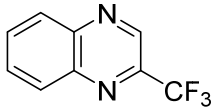
Note: Isolated **6c** contained 20% of perfluoroethyl-substituted product.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.79 (s, 2H), 3.93 (t, J = 7.4 Hz, 2H), 1.68 (sext, J = 7.5 Hz, 2H), 1.53 (s, 9H), 0.91 (t, J = 7.3 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 156.1 (t, J = 6.8 Hz), 155.2 (q, J = 3.5 Hz), 153.3, 123.3 (q, J = 271.1 Hz), 119.0 (q, J = 34.0 Hz), 82.4, 49.5, 28.2, 22.1, 11.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ -61.7.

2-(trifluoromethyl)quinoxaline (6g)



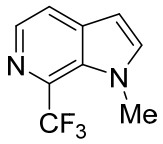
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 9:1 hexanes-EtOAc to give **6g** as a white solid (86 mg, 88% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.15 (s, 1H), 8.18 (t, J = 9.5 Hz, 2H), 7.94 – 7.80 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 143.9, 142.9 (q, J = 35.2 Hz), 141.0 – 140.9 (2C), 132.4, 131.6, 130.1, 129.6, 121.3 (q, J = 275.5 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -67.1.

1-methyl-7-(trifluoromethyl)-6-azaindole (6i)



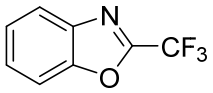
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 6:1 hexanes-EtOAc to give **6i** as a white solid (95 mg, 95% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.25 (d, J = 5.1 Hz, 1H), 7.66 (d, J = 5.0 Hz, 1H), 7.20 (s, 1H), 6.56 (s, 1H), 3.94 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 137.5, 136.4, 135.9, 131.0 (q, J = 35.6 Hz), 129.7, 122.4 (q, J = 272.6 Hz), 119.1, 101.5, 36.7 (q, J = 5.9 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -59.2.

2-(trifluoromethyl)benzo[d]oxazole (6k)



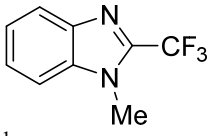
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 20:1 hexanes-EtOAc to give **6k** as a light yellow oil (66 mg, 71% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 8.3 Hz, 1H), 7.54 (t, J = 7.5 Hz, 1H), 7.49 (t, J = 7.7 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 151.7 (q, J = 43.0 Hz), 150.6, 139.5, 127.8, 125.9, 121.9, 116.8 (q, J = 271.5 Hz), 111.6.

^{19}F NMR (376 MHz, $CDCl_3$) δ -66.6.

1-methyl-2-(trifluoromethyl)-1H-benzo[d]imidazole (6l)



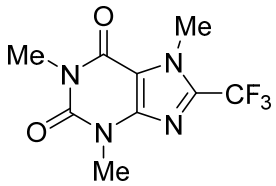
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 6:1 hexanes-EtOAc to give **6l** as a white solid (68 mg, 68% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 (d, J = 8.1 Hz, 1H), 7.44 – 7.38 (m, 2H), 7.38 – 7.32 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 141.1, 140.9 (q, J = 38.5 Hz), 136.1, 125.4, 123.7, 121.6, 119.2 (q, J = 271.3 Hz), 110.1, 30.8.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.7.

8-(perfluoroethyl)caffeine (6m)



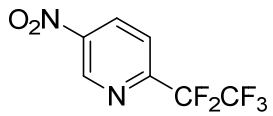
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 4.8 mmol scale. The product was purified by silica gel chromatography eluting with 4:1 hexanes-EtOAc to give **6m** as a white solid (0.90 g, 72% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.14 (s, 3H), 3.58 (s, 3H), 3.40 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 155.4, 151.3, 146.6, 138.9 (q, J = 40.0 Hz), 118.3 (q, J = 271.3 Hz), 109.7, 33.2, 29.9, 28.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.4.

5-nitro-2-(perfluoroethyl)pyridine (8c)



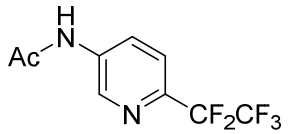
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 20:1 hexanes-EtOAc to give **8c** as a colorless oil (113 mg, 93% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.54 (s, 1H), 8.71 (dd, J = 8.6, 2.5 Hz, 1H), 7.97 (d, J = 8.6 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 152.5 (t, J = 26.3 Hz), 145.5, 145.3, 132.7, 122.7, 118.5 (qt, J = 286.8, 36.8 Hz), 110.6 (tq, J = 256.4, 38.5 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -83.2 (s, 3F), -116.7 (s, 2F).

N-(6-(perfluoroethyl)pyridin-3-yl)acetamide (8d)



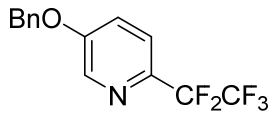
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 1:1 hexanes-EtOAc to give **8d** as a colorless oil (100 mg, 79% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.73 (s, 1H), 8.32 (d, J = 7.1 Hz, 1H), 7.62 (d, J = 8.5 Hz, 1H), 2.19 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.2, 142.1 (t, J = 26.5 Hz), 140.9, 137.8, 127.4, 122.7, 119.0 (qt, J = 286.2, 38.0 Hz), 111.3 (tq, J = 254.9, 38.2 Hz), 24.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ -83.5 (s, 3F), -115.8 (s, 2F).

5-(benzyloxy)-2-(perfluoroethyl)pyridine (8e)



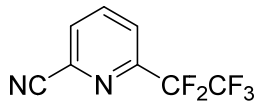
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 6:1 hexanes-EtOAc to give **8e** as a colorless oil (121 mg, 80% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.63 (d, J = 8.7 Hz, 1H), 7.49 – 7.26 (m, 6H), 5.17 (s, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 156.7, 139.6 (t, J = 26.2 Hz), 138.9, 135.2, 128.8, 128.58, 127.5, 122.8, 121.4, 119.0 (qt, J = 286.5, 38.2 Hz), 111.4 (tq, J = 253.5, 37.6 Hz), 70.6.

^{19}F NMR (376 MHz, $CDCl_3$) δ -83.5 (s, 3F), -115.3 (s, 2F).

6-(perfluoroethyl)picolinonitrile (8f)



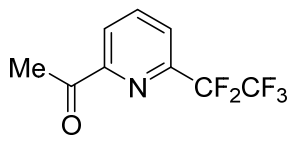
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with a gradient from 100% hexanes to 6:1 to give **8f** as a colorless oil (99 mg, 89% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (t, J = 8.0 Hz, 1H), 7.95 (t, J = 8.6 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 149.5 (t, J = 26.7 Hz), 139.3, 134.2, 131.0, 125.3, 118.6 (qt, J = 286.4, 36.8 Hz), 116.1, 110.5 (tq, J = 256.3, 38.2 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -83.5 (s, 3F), -117.1 (s, 2F).

1-(6-(perfluoroethyl)pyridin-2-yl)ethan-1-one (8g)



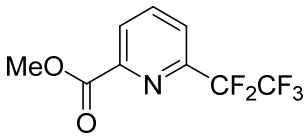
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 20:1 hexanes-EtOAc to give **8g** as a colorless oil (68 mg, 57% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (d, J = 7.9 Hz, 1H), 8.04 (t, J = 7.9 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 2.72 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 199.0, 153.5, 147.5 (t, J = 26.3 Hz), 138.6, 125.0, 124.0, 119.0 (qt, J = 286.5, 37.1 Hz), 111.1 (tq, J = 254.8, 38.0 Hz), 25.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ -83.2 (s, 3F), -116.3 (s, 2F).

methyl 6-(perfluoroethyl)picolinate (8h)



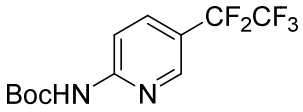
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 6:1 hexanes-EtOAc to give **8h** as a colorless oil (115 mg, 90% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.27 (d, J = 7.9 Hz, 1H), 8.05 (t, J = 7.9 Hz, 1H), 7.85 (d, J = 7.9 Hz, 1H), 3.96 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 164.7, 148.8, 148.0 (t, J = 26.0 Hz), 138.7, 127.6, 125.0, 118.9 (qt, J = 286.2, 37.1 Hz), 111.0 (tq, J = 255.4, 38.0 Hz), 53.1.

^{19}F NMR (376 MHz, $CDCl_3$) δ -83.5 (s, 3F), -116.7 (s, 2F).

tert-butyl (5-(perfluoroethyl)pyridin-2-yl)carbamate (8l)



The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 6:1 hexanes-EtOAc to give **8l** as a white solid (66 mg, 42% yield).

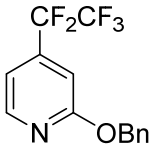
Note: The peaks in the ^{1}H and ^{13}C spectra were broadened due to the slow interconversion of the amide diastereomers.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.23 (bs, 1H), 7.64 (d, J = 8.7 Hz, 1H), 6.73 (bs, 1H), 1.54 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 152.2, 141.4 (t, J = 26.3 Hz), 139.8, 137.8, 125.5, 122.6, 120.1, 111.4 (m), 82.3, 28.4.

^{19}F NMR (376 MHz, $CDCl_3$) δ -83.5 (s, 3F), -115.8 (s, 2F).

2-(benzyloxy)-4-(perfluoroethyl)pyridine (8n)



The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 20:1 hexanes-EtOAc to give **8n** as a colorless oil (114 mg, 75% yield).

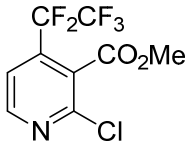
Note: Isolated **8n** contained 7% of **7n**.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.37 (d, J = 5.2 Hz, 1H), 7.65 – 7.30 (m, 5H), 7.11 – 7.10 (m, 2H), 5.49 (s, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 164.1, 148.2, 139.8 (t, J = 24.9 Hz), 136.8, 128.7, 128.2, 128.1, 118.9 (qt, J = 286.1, 38.0 Hz), 113.5 (t, J = 5.3 Hz), 112.4 (tq, J = 254.6, 38.6 Hz), 109.5 (t, J = 6.7 Hz), 68.4.

^{19}F NMR (376 MHz, $CDCl_3$) δ -85.2 (s, 3F), -117.1 (s, 2F).

methyl 2-chloro-4-(perfluoroethyl)nicotinate (8o)



The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with a gradient from 100% hexanes to 6:1 hexanes-EtOAc to give **8o** as a colorless oil (117 mg, 81% yield).

Note: Isolated **8o** contained 4% of 2,4-bis-perfluoroethyl-substituted product.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.64 (d, J = 5.2 Hz, 1H), 7.46 (d, J = 5.2 Hz, 1H), 3.98 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 164.1, 150.7, 149.7, 136.3 (t, J = 24.7 Hz), 128.5, 120.5, 118.4 (qt, J = 287.2, 37.2 Hz), 112.1 (tq, J = 257.7, 39.9 Hz), 53.6.

^{19}F NMR (376 MHz, $CDCl_3$) δ -84.1 (s, 3F), -113.2 (s, 2F).

4-(perfluoroethyl)nicotinonitrile (8p)

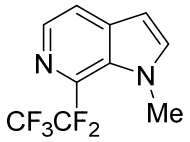
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with a gradient from 100% hexanes to 6:1 hexanes-EtOAc to give **8p** as a colorless oil (69 mg, 62% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.11 (s, 1H), 9.03 (d, J = 5.2 Hz, 1H), 7.68 (d, J = 5.1 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 155.1, 153.8, 138.9 (t, J = 24.8 Hz), 122.0 (t, J = 6.5 Hz), 118.5 (qt, J = 287.1, 36.8 Hz), 113.7, 111.7 (tq, J = 258.4, 40.1 Hz), 107.9 (t, J = 3.6 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -84.4 (s, 3F), -115.0 (s, 2F).

1-methyl-7-(perfluoroethyl)-6-azaindole (8v)



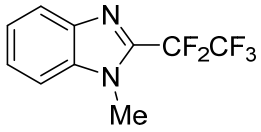
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with a gradient from 100% hexanes to 6:1 to give **8v** as a white solid (106 mg, 85% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.28 (d, J = 5.2 Hz, 1H), 7.70 (d, J = 5.2 Hz, 1H), 7.24 (d, J = 3.1 Hz, 1H), 6.61 (d, J = 3.0 Hz, 1H), 4.00 (t, J = 3.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 137.7, 136.2, 136.0, 131.7 (t, J = 30.1 Hz), 130.7, 119.5 (qt, J = 285.8, 36.0 Hz), 119.0, 113.6 (tq, J = 251.1, 35.4 Hz), 101.8, 37.7 (t, J = 9.4 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -79.4 (s, 3F), -99.2 (s, 2F).

1-methyl-2-(perfluoroethyl)-1H-benzo[d]imidazole (8w)



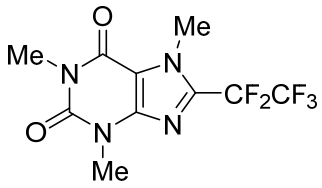
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with a gradient from 100% hexanes to 6:1 to give **8w** as a white solid (86 mg, 69% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (d, J = 8.3 Hz, 1H), 7.47 – 7.43 (m, 1H), 7.40 – 7.35 (m, 2H), 3.97 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 141.6, 139.7 (t, J = 27.4 Hz), 136.3, 125.5, 123.7, 121.7, 118.6 (dt, J = 286.1, 36.0 Hz), 110.2 (tq, J = 253.0, 39.5 Hz), 110.1, 31.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ -82.4 (s, 3F), -109.9 (s, 2F).

8-(perfluoroethyl)caffeine (8x)



The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with a gradient from 100% hexanes to 6:1 Hexanes-EtOAc to give **8x** as a white solid (123 mg, 79% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.18 (s, 3H), 3.57 (s, 3H), 3.40 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 155.4, 151.3, 146.9, 137.7 (t, J = 28.8 Hz), 118.2 (qt, J = 286.0, 36.5 Hz), 110.1, 109.4 (tq, J = 254.3, 40.3 Hz), 33.6, 29.9, 28.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ -83.0 (s, 3F), -111.2 (s, 2F).

3.5 References

Parts of this chapter were reprinted with permission from:
"Copper-Mediated Perfluoroalkylation of Heteroaryl Bromides with (phen)CuR_F"
Mormino, M. G.; Fier, P. S.; Hartwig, J. F. *Org. Lett.* **2014**, *16*, 1744.

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(8) (a) Tomashenko, O. A.; Escudero-Adán, E. C.; Belmonte, M. M.; Grushin, V. V. *Angew. Chem. Int. Ed.* **2011**, *50*, 7655. (b) Knauber, T.; Arikan, F.; Röshenthaler, G.-V.; Gooßen, L. J. *Chem. Eur. J.* **2011**, *17*, 2689. (c) Oishi, M.; Kondo, H.; Amii, H. *Chem. Commun*. **2009**, 1909. (d) Schareina, T.; Wu, X.-F.; Zapf, A.; Cotté, A.; Gotta, M.; Beller, M. *Top. Catal.* **2012**, *55*, 426. (e) Urata, H.; Fuchikami, H. *Tet. Lett.* **1991**, *32*, 91.
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CHAPTER 4

Copper-Mediated Difluoromethylation of Aryl and Vinyl Iodides with Me_3SiCF_2H

4.1 Introduction

The unique stability, reactivity and biological properties of fluorinated compounds contribute to their widespread use in many chemical disciplines. Compounds containing a trifluromethyl group have been studied extensively. Compounds containing partially fluorinated alkyl groups, such as a difluoromethyl group, should be similarly valuable for medicinal chemistry because such groups could act as lipophilic hydrogen bond donors and as bio-isosteres of alcohols and thiols.[1,2] However, methods for the introduction of a difluoromethyl group are limited, and methods for the introduction of a difluoromethyl group onto arenes are even more limited. Hence there is a current need for new procedures to generate difluoromethylarenes.[3]

Most current syntheses of difluoromethylarenes require hazardous reagents or multi-step sequences (Figure 4.1). Fluoro-deoxygenation of aldehydes with sulfur tetrafluoride or aminosulfurtrifluorides (DAST, Deoxofluor) is the most common route to difluoromethyl compounds. However, these reagents release hydrogen fluoride upon contact with water and may undergo explosive decomposition when heated.[4] Amii and coworkers recently reported a three-step route to difluoromethylarenes; however, the final step of this process only occurred with electron-deficient aryl iodides, and the three-step process with electron-poor arenes occurred in modest overall yields (Figure 4.1).[5] Baran recently reported a new reagent that leads to the addition of difluoromethyl radicals to heteroaromatic systems under mild conditions.[6] However, reactions with arenes were not reported. Thus, methods for the introduction of a difluoromethyl group onto arenes and methods for the introduction of the difluoromethyl group with regioselectivities that complement those resulting from radical-based reactions are needed.

In contrast to the recent success in developing copper mediated trifluoromethylation of aryl halides[7] methods for related copper-mediated difluoromethylation of aryl halides have not been developed. Difluoromethyl copper complexes are much less stable than trifluoromethyl copper complexes and are known to be unstable toward the formation of tetrafluoroethane and *cis*-difluoroethylene.[3,8] Despite this instability, we have identified conditions for copper-mediated difluoromethylation of aryl iodides. We report our results on this difluoromethylation process. The difluoromethylation reaction occurs with aryl iodides containing a wide range of functional groups, as well as vinyl iodides, in a single step with inexpensive and readily available reagents.

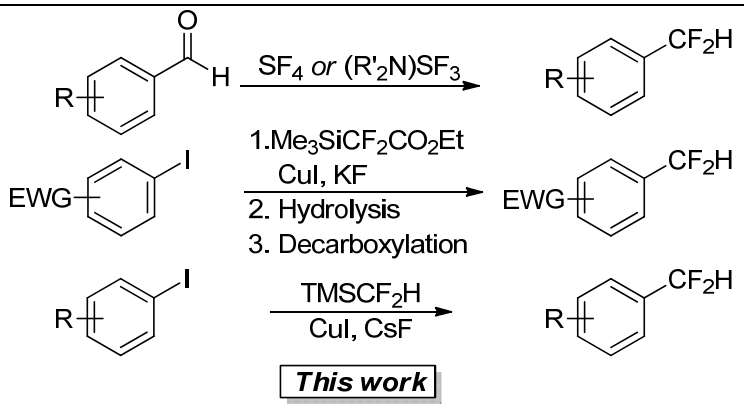
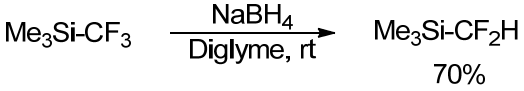


Figure 4.1 Methods for the synthesis of difluoromethylarenes

4.2 Results and Discussion

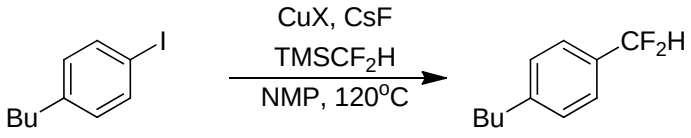
We chose to develop difluoromethylations with trimethylsilyl difloromethane ($TMSCF_2H$) as the source of the CF_2H group because fluoroalkylsilanes are accessible, commercially available, stable, and readily prepared on large scale. Most important for the current work, $TMSCF_2H$ is accessible on multi-gram scale, as shown in equation 4.1, by sodium borohydride reduction of the Ruppert-Prakash reagent ($TMSCF_3$).[9] Initial attempts to extend our previously published work on the trifluoromethylation of aryl iodides[10] with (1,10-phenanthroline)$CuCF_3$ to the difluoromethylation of aryl iodides with pre-formed or *in-situ* generated (1,10-phenanthroline)$CuCF_2H$ gave large amounts of arene. Only trace amounts of the difluoromethylarene product were formed. Reactions of 1-butyl-4-iodobenzene conducted with *tert*-butoxide or fluoride to activate the silane and a broad range of copper (I) sources and exogenous ligands gave similar product distibutions.



Equation 4.1 Synthesis of Me_3SiCF_2H from Me_3SiCF_3

However, reactions conducted without added ligand resulted in high conversion to the difluoromethylarene. Various copper(I) sources were found to mediate the difluoromethylation of 1-butyl-4-iodobenzene, but reactions conducted with CuI provided higher yields than did those with CuBr, CuBr-SMe_2, or CuCl (Table 4.1). Reactions conducted with cesium fluoride led to transfer of the difluoromethyl group from $TMSCF_2H$ without significant background decomposition of the silane. Studies with various ratios of reagents showed that reactions with 1 equiv of CuI, 3 equiv of CsF and 5 equiv of $TMSCF_2H$ occurred in reproducibly high yields. Reactions conducted with less CsF or $TMSCF_2H$ resulted in moderate to good yields (Table 4.1, entries 6-8). The excess $TMSCF_2H$ in the reaction likely converts $CuCF_2H$ to the cuprate, $Cu(CF_2H)_2^-$ (*vide infra*).

Table 4.1 Development of a copper-mediated difluoromethylation reaction of aryl iodides



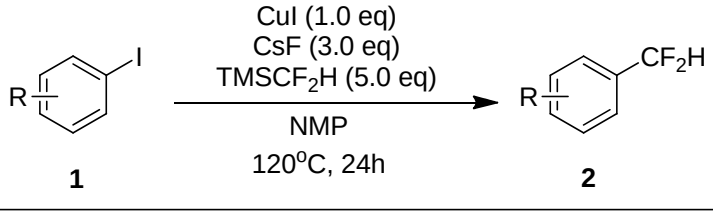
Entry	CuX (eq)	CsF (eq)	$TMSCF_2H$ (eq)	yield (%)
1	CuBr (1.0)	2.0	5.0	84
2	CuBr-SMe_2 (1.0)	2.0	5.0	70
3	CuCl (1.0)	2.0	5.0	53
4	CuI (1.5)	1.5	1.5	26
5	CuI (3.0)	3.0	3.0	36
6	CuI (1.0)	1.0	5.0	55
7	CuI (1.0)	2.0	5.0	91
8	CuI (1.0)	3.0	3.0	75
9	CuI (1.0)	3.0	5.0	100

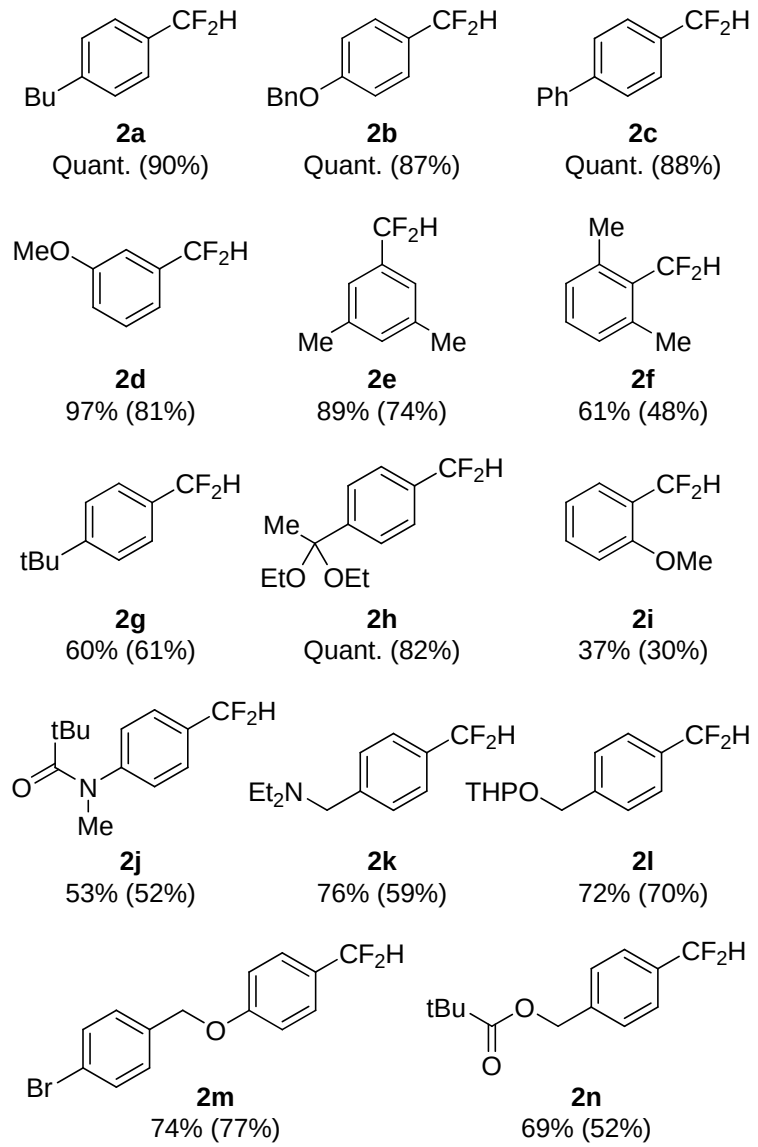
[a]Reactions were performed with 0.1 mmol of 1-butyl-4-iodobenzene in 0.5 mL of NMP for 24 hours. The yield was determined by ^{19}F NMR with 1-bromo-4-fluorobenzene as an internal standard added after the reaction.

The reaction conditions developed for the difluoromethylation of 1-butyl-4-iodobenzene were suitable for the conversion of a range of aryl iodides **1** to difluoromethylarenes **2** (Table 4.2). Electron-neutral, electron-rich, and sterically hindered aryl iodides reacted in high yield. Amine, ether, amide, ester, aromatic bromide and protected alcohol functionality were tolerated under the standard reaction conditions. While ketones and aldehydes underwent competing direct addition of the difluoromethyl group,[11] acetal-protected ketone **1h** gave quantitative conversion to difluoromethylarene **2h**. In contrast to reactions of electron-rich and electron-neutral aryl iodides, reactions of electron-deficient aryl iodides formed arene as the major product, along with trace amounts of trifluoromethyl and tetrafluoroethylarene. The latter products, presumably, form by a sequence similar to the one that forms pentafluoroethylarenes during copper-mediated trifluoromethylation of aryl halides involving difluorocarbene.[7] The volatility of difluoromethylarenes and similar polarity to side-products often contribute to lower isolated yields.

This difluoromethylation protocol was also suitable for the difluoromethylation of vinyl iodides **3** to prepare allylic difluorinated alkenes **4** (Table 3). This family of products has been prepared by the reaction of sulfur tetrafluoride or aminosulfurtrifluorides and α-ß unsaturated aldehydes; however formation of products from allylic substitution and rearrangements of reaction intermediates occur in these systems, resulting in a mixture of isomers.[4] In addition, the cross-coupling of vinyl iodides with $TMSCF_2H$ avoids the use of hazardous sulfurfluoride reagents and reactive, electrophilic α,ß-unsaturated aldehydes. *Cis* and *trans* alkenes, as well as styrenyl iodides, reacted in good yield to give a single stereoisomer of the coupled product.

Table 4.2 Scope of the difluoromethylation of aryl iodides with CuI, CsF and Me_3SiCF_2H





2a Quant. (90%) **2b** Quant. (87%) **2c** Quant. (88%)

2d 97% (81%) **2e** 89% (74%) **2f** 61% (48%)

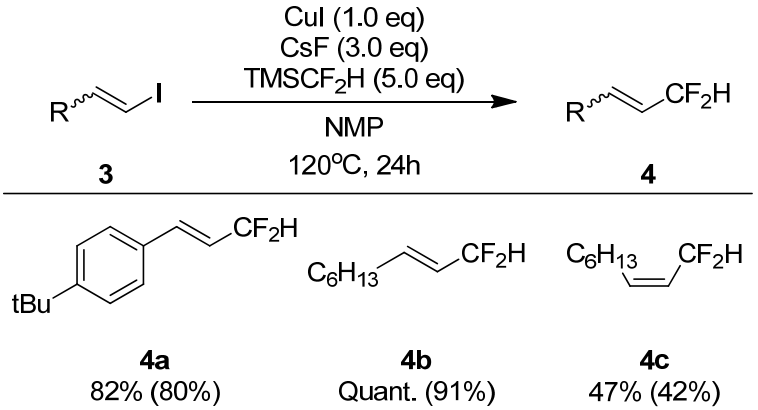
2g 60% (61%) **2h** Quant. (82%) **2i** 37% (30%)

2j 53% (52%) **2k** 76% (59%) **2l** 72% (70%)

2m 74% (77%) **2n** 69% (52%)

[a]Reactions were performed with 0.1 mmol of aryl iodide to determine ^{19}F NMR yields with 1-bromo-4-fluorobenzene as an internal standard added after the reaction. Isolated yields, shown in parenthesis, were obtained from reactions performed with 0.5 mmol of aryl iodide.

Table 4.2 Difluoromethylation of vinyl iodides with CuI, CsF and Me_3SiCF_2H



[a]Reactions were performed with 0.1 mmol of vinyl iodide to determine ^{19}F NMR yields with 1-bromo-4-fluorobenzene as an internal standard added after the reaction. Isolated yields, shown in parenthesis, were obtained from reactions with 0.5 mmol of vinyl iodide.

Reactions of aryl halides with Cu(I) species have been proposed in some cases to occur by radical intermediates[12] and in other cases to occur through Cu(III) intermediates formed by oxidative addition of organic halides to a Cu(I) intermediate.[13] Although the current evidence disfavors radical reactions of aryl halides with copper complexes containing neutral dative nitrogen ligands,[14] the difluoromethylation in the current work occurs through complexes lacking such ligands and, therefore, could follow a different pathway. To probe the potential intermediacy of aryl radicals during this difluoromethylation reaction, we conducted the difluoromethylation of 1-(allyloxy)-2-iodobenzene (Figure 4.2). The corresponding aryl radical undergoes 5-exo-trig cyclization with a rate constant of 10^{10} s^{-1} to form 3-methyl-2,3-dihydrobeznofuran after hydrogen atom abstraction from the solvent.[15] Thus, if products from cyclization are not observed, then the reaction of the aryl radical with the fluoroalkyl species must occur with an effective first order rate constant of 10^{12} s^{-1} – 10^{13} s^{-1}, which approaches the time scale of a vibration and the diffusion-controlled limit. The reaction of 1-(allyloxy)-2-iodobenzene with CuI, CsF and $TMSCF_2H$ did not give any products resulting from cyclization. Instead, this reaction formed allyloxybenzene and the difluoromethylarene. Although the yield of difluoromethylarene was low (13%), in agreement with the result from the reaction of ortho-iodoansole, this result argues against a mechanism involving an aryl radical intermediate.

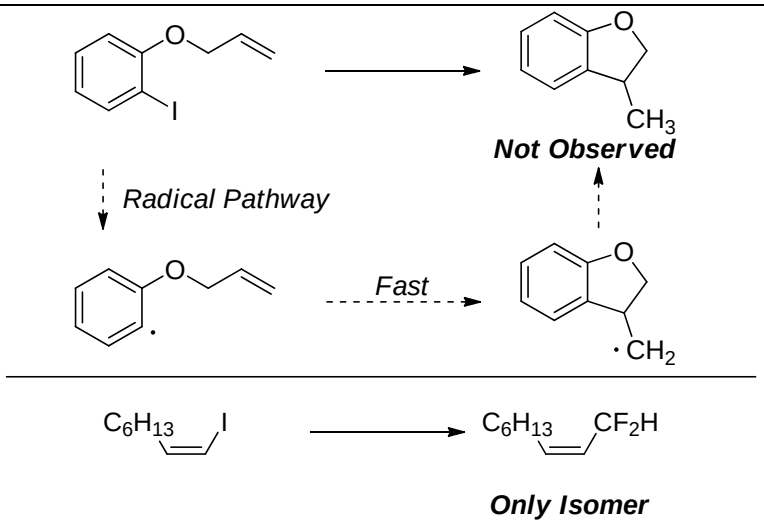
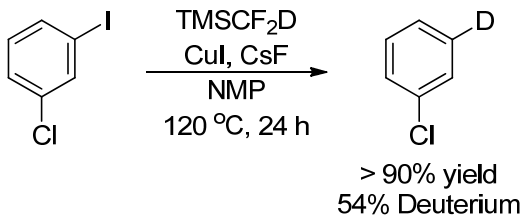


Figure 4.2 Evidence against a radical pathway in the difluoromethylation reaction

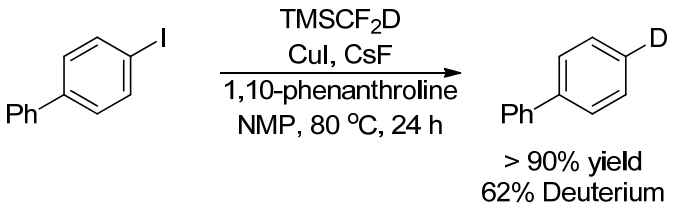
Reactions of vinyl iodides also provide evidence against a radical intermediate. The difluoromethylation of Z-1-iodo-1-octene formed the difluoroallyl product with complete retention of the olefin geometry. Because of the configurational instability of vinyl radicals a mixture of stereoisomers of the coupled products would be expected to form if a vinyl radical were formed. Only one stereoisomer was observed (Figure 4.2).

An unusual feature of the scope of this coupling process is the higher yields obtained from reactions of electron-rich aryl iodides than from reactions of electron-poor aryl iodides. Most often, electron-deficient electrophiles react faster and in higher yields than electron-rich electrophiles in cross-coupling reactions. To elucidate the origin of the effect of arene electronics on the yield of the difluoromethylation reaction, we conducted experiments with deuterium labeled $TMSCF_2D$, prepared from $TMSCF_3$ and $NaBD_4$. The reaction of 1-chloro-3-iodobenzene with CuI, CsF and $TMSCF_2D$ resulted in greater than 50% deuterium incorporation at the iodide position of the arene product (equation 4.2). Thus, the arene product appears to form, at least in part, by an overall hydride transfer from trimethyl(difluoromethyl)silane.



Equation 4.2 Reaction of an electron-deficient aryl iodide with $TMSCF_2D$

Similar results were obtained from reactions conducted with exogenous ligand. The reaction of 4-iodo-1,1'-biphenyl with $TMSCF_2D$ in the presence of CuI, CsF and 1,10-phenanthroline formed arene in greater than 90% yield, and the arene contained greater than 60% deuterium at the iodide position (equation 4.3). Reactions conducted in deuterated solvent did not lead to incorporation of deuterium into the arene, showing that the solvent is not a source of hydrogen for the hydrodehalogenation process.



Equation 4.3 Reaction of an aryl iodide with $TMSCF_2D$ in the presence of added phenanthroline

The observation of tetrafluoroethyl and trifluoromethyl side products from reactions of electron-deficient aryl iodides suggests that difluorocarbene may be formed under the reaction conditions (*vide supra*). However, reactions conducted with added cyclohexene or styrene to trap difluorocarbene gave only trace amounts or no detectable amount of products resulting from cyclopropanation, respectively.

Difluoromethylcopper(I) has been reported to undergo a combination of disproportionation and homo-coupling to form *cis*-difluoroethylene and 1,1,2,2-tetrafluoroethane, even below room temperature.[8] If the reaction we report occurs through $CuCF_2H$, the reaction of this complex with aryl iodide must be faster than decomposition. However, the reactions of aryl iodides with Cu(I) species typically require elevated temperatures, and electron-poor aryl iodides typically react with Cu(I) faster than electron-rich aryl iodides.[16] Thus, we suggest that two different reaction pathways are likely to form the difluoromethylarene and the arene, and the rate of formation of arene would be faster with electron-poor arenes than with electron-rich arenes.

To assess the identity of the difluoromethyl copper species that could react with the aryl iodide, we combined CuI, CsF, and $TMSCF_2H$ and heated the mixture at 120 ° C in the absence of aryl iodide. Within 5 min, this reaction formed a product with ^{19}F NMR chemical shift and $J_{H\text{-}F}$ values (-116.6 ppm, J = 44 Hz) that matched those reported previously for the cuprate $Cu(CF_2H)_2^-$.[8,17, 18] This difluoromethylcuprate species in this difluoromethylation reaction is clearly more stable than the neutral $CuCF_2H$.

Although speculative, we provide a rationalization of our ability to develop copper-mediated difluoromethylation, despite the instability of $CuCF_2H$. We suggest that $Cu(CF_2H)_2^-$ acts as a stable reservoir for the neutral $CuCF_2H$. Because prior studies have shown that two-coordinate cuprates react more slowly with haloarenes than do neutral complexes,[14a-c] we suggest that $CuCF_2H$ reacts with the haloarene. The low concentrations of $CuCF_2H$ should decrease the rate of bimolecular decomposition, relative to reaction with the haloarene. Future studies will assess these mechanistic hypotheses.

4.3 Conclusions

In summary, we have described a one-step procedure for the difluoromethylation of aryl and vinyl iodides that occurs with readily available and non-hazardous reagents. This reaction tolerates amine, ether, amide, ester, aromatic bromide and protected alcohol functionalities and occurs in high yield with sterically hindered aryl iodides. The simplicity and generality of this method makes it attractive for the introduction of a CF_2H group into functionally diverse iodoarenes. Work is ongoing to develop conditions for

difluormethylation of electron-poor aryl iodides, to develop reactions of heteroaryl iodides, and to develop reactions of higher difluoroalkyl groups.

4.4 Experimental

All manipulations were conducted under an inert atmosphere with a nitrogen-filled glovebox unless otherwise noted. All reactions were conducted in oven-dried 4-mL or 20-mL vials fitted with a Teflon-lined screw cap under an atmosphere of nitrogen unless otherwise noted.

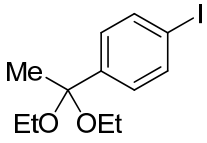
Cesium fluoride was purchased from Sigma-Aldrich and dried at 140°C under vacuum (100 mtorr) for 12 hours prior to use. Trimethyl(trifluoromethyl) silane ($TMSCF_3$, Ruppert's reagent) was purchased from Matrix Scientific. N-Methylpyrrolidone (NMP), 99.5%, Extra Dry over Molecular Sieves, was purchased from Acros and used without further purification. Unless otherwise noted, all other reagents were purchased from commercial suppliers and used as received. Trimethyl(difluoromethyl)silane, 2-((4-iodobenzyl)oxy)tetrahydro-2H-pyran (**1l**) and Z-1-iodo-1-octene (**4a**) were prepared according to literature procedures.

Organic solutions were concentrated by rotary evaporation. Flash column chromatography was performed on Silicylce Siala-P silica gel or on a Teledyne Isco CombiFlash Rf automated chromatography system with 12 g RediSep Rf Gold normal-phase silica columns. The products were visualized by UV light and stained with potassium permanganate ($KMnO_4$).

NMR spectra were acquired on 400 MHz, 500 MHz, or 600 MHz Bruker instruments at the University of California. NMR spectra were processed with MestReNova 5.0 (Mestrelab Research SL). Chemical shifts are reported in ppm and referenced to residual solvent peaks ($CHCl_3$ in $CDCl_3$: 7.26 ppm for ^1H and 77.0 ppm for ^{13}C) or to an external standard (1% $CFCl_3$ in $CDCl_3$: 0 ppm for ^{19}F). Coupling constants are reported in hertz.

All GC-MS analyses were conducted with an Agilent 6890N GC equipped with an HP-5 column (25 m x 0.20 mm ID x 0.33 μm film) and an Agilent 5973 Mass Selective Detector. The temperature for each run was held at 50 °C for 2 min, ramped from 50 °C to 300 °C at 40 °C/min, and held at 300 °C for 5 min.

Preparation of 1-(1,1-diethoxyethyl)-4-iodobenzene (1h)

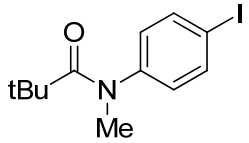


To a 3 mL vial was added 4'-iodoacetophenone (492 mg, 2.0 mmol), tetrabutylammonium tribromide (14 mg, 0.03 mmol) and 2 mL of ethanol. Triethylorthoformate (730 μL, 4.4 mmol) was added and the resulting solution was stirred at room temperature for 10 hours. The reaction was poured into 5 mL of saturated $NaHCO_3$ and extracted with ethyl acetate. The organic layer was dried with Na_2SO_4 and concentrated to an orange oil (530 mg, 1.7 mmol, 85% yield).

^1H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.5 Hz, 2H), 3.48 (dq, J = 9.3, 7.1 Hz, 2H), 3.40 – 3.29 (m, 2H), 1.53 (s, 3H), 1.22 (t, J = 7.1 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.68 (s), 137.07 (s), 128.27 (s), 100.88 (s), 93.18 (s), 56.69 (s), 26.92 (s), 15.31 (s).

Preparation of N-(4-iodophenyl)-N-methylpivalamide (1j)



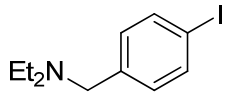
4-iodoaniline (2.19 g, 10 mmol), 4-dimethylaminopyridine (DMAP, 12 mg, 0.1 mmol), and pyridine (1.6 mL, 20 mmol) were dissolved in 20 mL of CH_2Cl_2 and cooled to 0 ^oC. Pivaloyl chloride (1.35 mL, 11 mmol) was added dropwise, and the resulting solution was allowed to warm to room temperature and stirred a total of 3 h. The solution was poured into a separatory funnel and washed with 1 x 20 mL of 1 M HCl and 1 x 20 mL of saturated $NaHCO_3$. The organic layer was dried with $MgSO_4$ and concentrated to a white solid (2.90 g, 9.6 mmol).

500 mg of the white solid, N-(4-iodophenyl)pivalamide (1.65 mmol), was dissolved in 2 mL of anhydrous THF and added dropwise to a suspension of 60% NaH (79 mg, 2.0 mmol) in 1 mL of anhydrous THF. The resulting solution was stirred at room temperature for 30 minutes, and methyl iodide (160 μL, 2.5 mmol) was added dropwise. After stirring for 3 h, water was added, and the product was extracted with ether. Drying with $MgSO_4$ and removal of the solvent gave **1j** as a white solid (480 mg, 1.5 mmol, 92% yield).

^1H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.70 (m, 2H), 6.99 – 6.95 (m, 2H), 3.18 (s, 3H), 1.05 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.93 (s), 145.12 (s), 138.49 (s), 130.70 (s), 92.73 (s), 41.22 (s), 40.80 (s), 29.45 (s).

Preparation of N-ethyl-N-(4-iodobenzyl)ethanamine (1k)

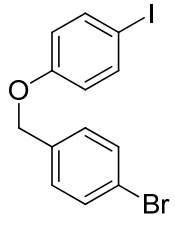


4-iodobenzylbromide (891 mg, 3.0 mmol) was dissolved in 3 mL of CH_2Cl_2 and diethylamine (930 μL, 9.0 mmol) was added at once. After 20 min at room temperature, the reaction was complete, as judged by TLC analysis. The solution was poured into a separatory funnel containing ethyl acetate and washed with 2 x 10 mL of 3 M KOH and 1 x 10 mL of brine. The organic layer was dried over sodium sulfate and concentrated to give **1k** as a light yellow oil (830 mg, 2.9 mmol, 96% yield).

^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J = 8.2 Hz, 2H), 7.09 (d, J = 8.2 Hz, 2H), 3.49 (s, 2H), 2.49 (q, J = 7.1 Hz, 4H), 1.02 (t, J = 7.1 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.93 (s), 137.14 (s), 130.80 (s), 91.80 (s), 57.00 (s), 46.73 (s), 11.75 (s).

Preparation of 1-bromo-4-((4-iodophenoxy)methyl)benzene (1m)

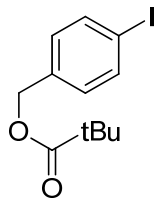


Sodium hydride (60% wt/wt in mineral oil, 132 mg, 3.3 mmol) was suspended in 2 mL of anhydrous THF. 4-Iodophenol (660 mg, 3.0 mmol) in 2 mL of THF was added dropwise to the NaH suspension and stirred at room temperature for 5 min. 4'-Bromo-benzylbromide in 2 mL of THF was added dropwise and stirred at 80 ^oC for 8 h. The solution was washed with water and extracted with ether. The organic layer was washed with 1 x 10 mL of brine, dried with magnesium sulfate, and concentrated and purified by silica gel chromatography eluting with hexanes (R_f=0.15). White solid (1.01 g, 2.6 mmol, 87% yield).

^1H NMR (500 MHz, $CDCl_3$) δ 7.58 – 7.54 (m, 2H), 7.53 – 7.49 (m, 2H), 7.28 (d, J = 8.5 Hz, 2H), 6.75 – 6.69 (m, 2H), 4.98 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.35 (s), 138.31 (s), 135.54 (s), 131.77 (s), 128.99 (s), 122.03 (s), 117.26 (s), 83.31 (s), 69.32 (s).

Preparation of 4-iodobenzyl pivalate (1n)

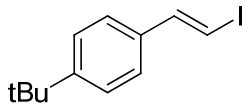


Sodium hydride (60% wt/wt in mineral oil, 132 mg, 3.3 mmol) was suspended in 3 mL of anhydrous THF. 4'-Iodo-benzylalcohol in 2 mL of THF was added dropwise to the NaH suspension and stirred at room temperature for 10 min. Pivaloyl chloride (406 μL, 3.3 mmol) was added dropwise, and the resulting solution was stirred at room temperature for 2 h. The solution was poured into water and extracted with ether. The organic layer was washed with 1 x 10 mL of saturated $NaHCO_3$ and 1 x 10 mL of brine, dried with magnesium sulfate, and concentrated to give **1n** as a light yellow oil (905 mg, 2.8 mmol, 95% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 8.2 Hz, 2H), 7.08 (d, J = 8.2 Hz, 2H), 5.04 (s, 2H), 1.22 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 178.17 (s), 137.59 (s), 136.09 (s), 129.59 (s), 93.57 (s), 65.30 (s), 38.75 (s), 27.13 (s).

Preparation of (E)-1-(tert-butyl)-4-(2-iodovinyl)benzene (3a)



To 4-(tert-butyl)-phenylacetylene (1.27 g, 8.0 mmol) in a small vial was slowly added catecholborane (853 μL, 8.0 mmol). The resulting mixture was heated at 70 ^{o}C for 2 h and allowed to cool to room temperature, forming an orange solid. The orange solid was dissolved in 20 mL of THF and 8 mL of 3 M NaOH was added slowly and stirred at room temperature for 10 min. A solution of I_2 (4.06 g, 16 mmol) in 80 mL of THF was added by an addition funnel over 2 h. The dark reaction mixture was filtered thru Celite, diluted with ethyl acetate and washed 2 x 20 mL with saturated sodium thiosulfate and 1 x 10 mL brine. The organic layer was dried with magnesium sulfate and purified by silica gel chromatography eluting with hexanes (R_f = 0.5) to give a light yellow oil that solidified upon standing (1.43 g, 5.0 mmol, 62% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 14.9 Hz, 1H), 7.34 (d, J = 8.1 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 6.76 (d, J = 14.9 Hz, 1H), 1.31 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 151.54 (s), 144.71 (s), 134.99 (s), 125.70 (s), 125.61 (s), 75.55 (s), 34.67 (s), 31.17 (s).

General Procedure for the Difluoromethylation of Aryl and Vinyl Iodides

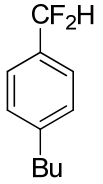
In a nitrogen-filled glove box, aryl or vinyl iodide (0.5 mmol, 1 equiv), copper iodide (0.5 mmol, 1 eq), and cesium fluoride (1.5 mmol, 1 equiv) were combined in a 20 mL vial. To this vial was added 2.5 mL of anhydrous NMP, followed by trimethyl(difluoromethyl)silane (2.5 mmol, 5 equiv). The reaction mixture was heated in a sealed vessel at 120 ºC for 24 h. **Note:** the pressure increases during the reaction due to the formation of volatile fluorotrimethylsilane (Me_3SiF) as a stoichiometric product. The dark red solution was then cooled to room temperature, and diluted with 15 mL of Et_2O. The mixture was filtered over Celite, washed with an additional 20 mL of Et_2O, and transferred to a separatory funnel. The mixture was washed with 5 x 20 mL of H_2O and 1 x 20 mL of brine, dried with $MgSO_4$, filtered, and concentrated under vacuum. The crude

product was purified by column chromatography on silica gel with pentane or pentane/Et_2O mixtures as the eluent.

Specific Procedures and Characterization of Products

1-butyl-4-(difluoromethyl)benzene (2a)

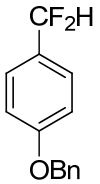
The reaction was performed according to the general procedure for difluoromethylation on a 0.5 mmol scale (89 μL **1a**). The crude mixture was purified by silica gel chromatography (12 g of silica, 100:0 → 90:10 pentane:Et_2O) to give **2a** (83 mg, 90% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 7.7 Hz, 2H), 7.27 (d, J = 7.2 Hz, 2H), 6.63 (t, J = 56.6 Hz, 1H), 1.67 – 1.56 (m, 2H), 1.37 (dt, J = 14.9, 7.3 Hz, 2H), 0.94 (t, J = 7.3 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 145.82 (t, J = 1.9 Hz), 131.77 (t, J = 22.4 Hz), 128.68 (s), 125.47 (t, J = 6.0 Hz), 114.95 (t, J = 238.0 Hz), 35.49 (s), 33.42 (s), 22.28 (s), 13.88 (s).
^{19}F NMR (376 MHz, $CDCl_3$) δ -110.06 (d, J = 56.6 Hz).

1-(benzyloxy)-4-(difluoromethyl)benzene (2b)

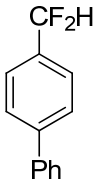


The reaction was performed according to the general procedure for difluoromethylation on a 0.5 mmol scale (155 mg **1b**). The crude mixture was purified by silica gel chromatography (12 g of silica, 100:0 → 90:10 pentane:Et_2O) to give **2b** (102 mg, 87% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.31 (m, 7H), 7.03 (d, J = 8.5 Hz, 2H), 6.60 (t, J = 56.7 Hz, 1H), 5.10 (s, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 160.51 (t, J = 1.6 Hz), 136.46 (s), 128.66 (s), 128.14 (s), 127.43 (s), 127.13 (t, J = 5.9 Hz), 127.01 (s), 114.92 (s), 114.83 (t, J = 237.5 Hz), 70.09 (s).
^{19}F NMR (376 MHz, $CDCl_3$) δ -108.77 (d, J = 57.0 Hz).

4-(difluoromethyl)-1,1'-biphenyl (2c)

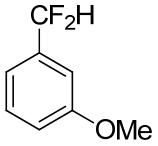


The reaction was performed according to the general procedure for difluoromethylation on a 0.5 mmol scale (140 mg **1c**). The crude mixture was purified by silica gel chromatography (12 g of silica, 100:0 → 90:10 pentane:Et_2O) to give **2c** (90 mg, 88% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.0 Hz, 2H), 7.60 (t, J = 7.2 Hz, 4H), 7.47 (t, J = 7.5 Hz, 2H), 7.39 (t, J = 6.9 Hz, 1H), 6.70 (t, J = 56.5 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 143.70 (t, J = 2.0 Hz), 140.18 (s), 133.20 (t, J = 22.2 Hz), 128.90 (s), 127.89 (s), 127.42 (s), 127.24 (s), 126.01 (t, J = 6.0 Hz), 114.73 (t, J = 238.5 Hz).
^{19}F NMR (376 MHz, C_6D_6) δ -111.35 (d, J = 57.0 Hz).

1-(difluoromethyl)-3-methoxybenzene (2d)



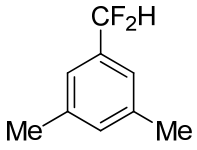
The reaction was performed according to the general procedure for difluoromethylation on a 0.5 mmol scale (59.5 μL **1d**). The crude mixture was purified by silica gel chromatography (12 g of silica, 100:0 → 90:10 pentane:Et_2O) to give **2d** (64 mg, 81% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 (t, J = 7.9 Hz, 1H), 7.08 (d, J = 7.5 Hz, 1H), 7.04 (s, 1H), 7.01 (d, J = 8.3 Hz, 1H), 6.61 (t, J = 56.5 Hz, 1H), 3.84 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 159.82 (s), 135.75 (t, J = 22.3 Hz), 129.86 (s), 117.82 (t, J = 6.3 Hz), 116.59 (t, J = 1.8 Hz), 114.55 (t, J = 239.0 Hz), 110.66 (t, J = 6.1 Hz), 55.36 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -111.12 (d, J = 56.5 Hz).

1-(difluoromethyl)-3,5-dimethylbenzene (2e)



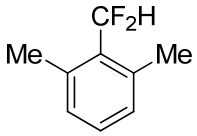
The reaction was performed according to the general procedure for difluoromethylation on a 0.5 mmol scale (72.2 μL **1e**). The crude mixture was purified by silica gel chromatography (12 g of silica, 100:0 → 90:10 pentane:Et_2O) to give **2e** (58 mg, 74% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.12 (s, 2H), 7.10 (s, 1H), 6.57 (t, J = 56.6 Hz, 1H), 2.36 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 138.44 (s), 134.30 (t, J = 21.7 Hz), 132.27 (t, J = 1.9 Hz), 123.20 (t, J = 6.0 Hz), 114.99 (t, J = 238.4 Hz), 21.21 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -110.61 (d, J = 56.7 Hz).

2-(difluoromethyl)-1,3-dimethylbenzene (2f)



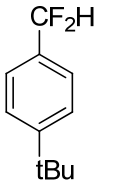
The reaction was performed according to the general procedure for difluoromethylation on a 0.5 mmol scale (116 mg **1f**). The crude mixture was purified by silica gel chromatography (12 g of silica, 100:0 → 90:10 pentane:Et_2O) to give **2f** (75 mg, 48% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22 (t, J = 7.6 Hz, 1H), 7.05 (d, J = 7.6 Hz, 2H), 6.99 (t, J = 54.3 Hz, 1H), 2.48 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 137.05 (t, J = 4.0 Hz), 130.31 (t, J = 1.5 Hz), 130.00 (t, J = 20.3 Hz), 129.18 (s), 114.48 (t, J = 236.2 Hz), 19.45 (t, J = 1.4 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -113.15 (d, J = 54.3 Hz).

1-(tert-butyl)-4-(difluoromethyl)benzene (2g)



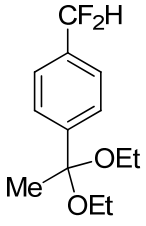
The reaction was performed according to the general procedure for difluoromethylation on a 0.5 mmol scale (130 mg **1g**). The crude mixture was purified by silica gel chromatography (12 g of silica, 100:0 → 90:10 pentane:Et_2O) to give **2g** (113 mg, 61% yield). A small amount (<10%) of unreacted **1g** was unable to be separated from the product.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (q, J = 8.5 Hz, 4H), 6.63 (t, J = 56.6 Hz, 1H), 1.34 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 154.00 (t, J = 2.0 Hz), 131.54 (t, J = 22.4 Hz), 125.61 (s), 125.30 (t, J = 6.0 Hz), 114.90 (t, J = 238.0 Hz), 34.85 (s), 31.21 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -110.24 (d, J = 56.6 Hz).

1-(1,1-diethoxyethyl)-4-(difluoromethyl)benzene (2h)



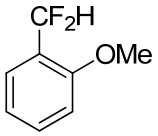
The reaction was performed according to the general procedure for difluoromethylation on a 0.5 mmol scale (160 mg **1h**). The crude mixture was purified by silica gel chromatography (12 g of silica, 100:0 → 90:10 pentane:Et_2O) to give **2h** (101 mg, 82% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (d, J = 7.8 Hz, 2H), 7.48 (d, J = 7.8 Hz, 2H), 6.65 (t, J = 56.4 Hz, 1H), 3.53 – 3.44 (m, 2H), 3.39 – 3.31 (m, 2H), 1.22 (t, J = 7.0 Hz, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 146.74 (s), 133.43 (t, J = 22.4 Hz), 126.58 (s), 125.27 (t, J = 5.9 Hz), 114.76 (t, J = 238.3 Hz), 100.94 (s), 56.77 (s), 27.04 (s), 15.29 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -110.72 (d, J = 56.5 Hz).

1-(difluoromethyl)-2-methoxybenzene (2i)



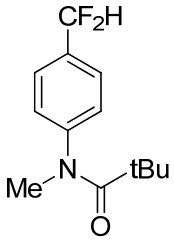
The reaction was performed according to the general procedure for difluoromethylation on a 0.5 mmol scale (117 mg **1i**). The crude mixture was purified by silica gel chromatography (12 g of silica, 100:0 → 90:10 pentane:Et_2O) to give **2i** (24 mg, 30% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (d, J = 7.5 Hz, 1H), 7.43 (t, J = 7.8 Hz, 1H), 7.04 (d, J = 8.3 Hz, 1H), 6.95 (t, J = 47.5 Hz, 1H), 6.94 (d, J = 8.4 Hz, 1H), 3.87 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 157.27 (t, J = 6.0 Hz), 131.94 (t, J = 1.9 Hz), 126.22 (t, J = 5.8 Hz), 122.71 (t, J = 22.0 Hz), 120.59 (s), 113.13 (s), 110.82 (t, J = 117.7 Hz), 55.59 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -115.84 (d, J = 55.7 Hz).

N-(4-(difluoromethyl)phenyl)-N-methylpivalamide (2j)



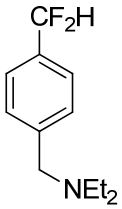
The reaction was performed according to the general procedure for difluoromethylation on a 0.5 mmol scale (159 mg **1j**). The crude mixture was purified by silica gel chromatography (6:1 Hexanes:Ethyl Acetate, R_f=0.13) to give **2j** (63 mg, 52% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 6.67 (t, J = 56.3 Hz, 1H), 3.21 (s, 3H), 1.04 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 178.01 (s), 147.52 (t, J = 2.0 Hz), 133.74 (t, J = 22.7 Hz), 129.05 (s), 126.64 (t, J = 5.9 Hz), 114.04 (t, J = 239.2 Hz), 41.22 (s), 40.82 (s), 29.39 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -111.24 (d, J = 56.3 Hz).

N-(4-(difluoromethyl)benzyl)-N-ethylethanamine (2k)



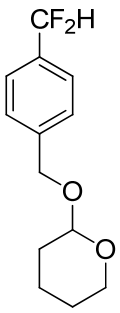
The reaction was performed according to the general procedure for difluoromethylation on a 0.5 mmol scale (145 mg **1k**). The crude mixture was purified by silica gel chromatography (3:1 Hexanes:Ethyl Acetate, R_f=0.2) to give **2k** (63 mg, 59% yield). A small amount (<5%) of unreacted **1k** was unable to be separated from the product.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 – 7.40 (m, 4H), 6.63 (t, J = 56.6 Hz, 1H), 3.59 (s, 2H), 2.52 (q, J = 7.1 Hz, 4H), 1.04 (t, J = 7.1 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.20 (s), 132.74 (t, J = 22.3 Hz), 128.97 (s), 125.37 (t, J = 6.0 Hz), 114.86 (t, J = 238.1 Hz), 57.23 (s), 46.79 (s), 11.75 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -111.17 (d, J = 56.6 Hz).

2-((4-(difluoromethyl)benzyl)oxy)tetrahydro-2H-pyran (2l)



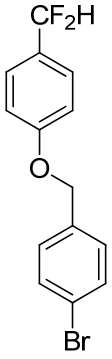
The reaction was performed according to the general procedure for difluoromethylation on a 0.5 mmol scale (159 mg **1l**). The crude mixture was purified by silica gel chromatography (6:1 Hexanes:Ethyl Acetate, R_f=0.49) to give **2l** (85 mg, 70% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (dd, J = 18.5, 8.2 Hz, 4H), 6.64 (t, J = 56.5 Hz, 1H), 4.83 (d, J = 12.5 Hz, 1H), 4.71 (t, J = 3.5 Hz, 1H), 4.55 (d, J = 12.5 Hz, 1H), 3.91 (ddd, J = 11.4, 8.6, 2.9 Hz, 1H), 3.58 – 3.53 (m, 1H), 1.92 – 1.83 (m, 1H), 1.80 – 1.72 (m, 1H), 1.71 – 1.51 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.23 (t, J = 1.9 Hz), 133.49 (t, J = 22.4 Hz), 127.78 (s), 125.61 (t, J = 6.0 Hz), 114.68 (t, J = 238.4 Hz), 97.90 (s), 68.19 (s), 62.16 (s), 30.50 (s), 25.41 (s), 19.29 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -111.33 (d, J = 56.6 Hz).

1-bromo-4-((4-(difluoromethyl)phenoxy)methyl)benzene (2m)



The reaction was performed according to the general procedure for difluoromethylation on a 0.5 mmol scale (195 mg **1m**). The crude mixture was purified by silica gel chromatography (12 g of silica, 100:0 → 90:10 pentane:Et_2O) to give **2m** (121 mg, 77% yield). A small amount (<5%) of unreacted **1m** was unable to be separated from the product.

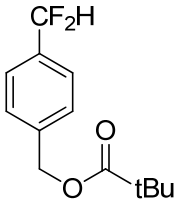
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.1 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H), 6.60 (t, J = 56.7 Hz, 1H), 5.05 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.16 (t, J = 1.8 Hz), 135.43 (s), 131.77 (s), 129.51 (s), 129.01 (s), 127.17 (t, J = 5.9 Hz), 122.05 (s), 114.84 (s), 114.74 (t, J = 237.6 Hz), 69.26 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -108.86 (d, J = 56.7 Hz).

4-(difluoromethyl)benzyl pivalate (2n)

The reaction was performed according to the general procedure for difluoromethylation on a 0.5 mmol scale (159 mg **1n**). The crude mixture was purified by silica gel chromatography (12 g of silica, 100:0 → 90:10 pentane:Et_2O) to give **2n** (63 mg, 52% yield). A small amount (<5%) of unreacted **1n** was unable to be separated from the product.

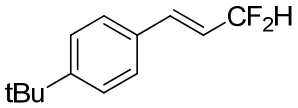


^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51 (d, J = 7.7 Hz, 1H), 7.42 (d, J = 7.7 Hz, 1H), 6.65 (t, J = 56.5 Hz, 1H), 5.14 (s, 1H), 1.24 (s, 4H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 178.19 (s), 139.26 (t, J = 1.8 Hz), 134.04 (t, J = 22.5 Hz), 127.79 (s), 125.78 (t, J = 6.0 Hz), 114.50 (t, J = 238.8 Hz), 65.35 (s), 38.81 (s), 27.16 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -111.03 (d, J = 56.7 Hz).

(E)-1-(tert-butyl)-4-(3,3-difluoroprop-1-en-1-yl)benzene (4a)



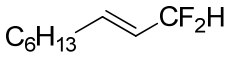
The reaction was performed according to the general procedure for difluoromethylation on a 0.5 mmol scale (143 mg **3a**). The crude mixture was purified by silica gel chromatography (Hexanes, R_f=0.27) to give **4a** (84 mg, 80% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.36 (m, 4H), 6.90 – 6.82 (m, 1H), 6.38 – 6.12 (m, 2H), 1.34 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.75 (s), 136.93 (t, J = 12.2 Hz), 131.63 (s), 127.01 (s), 125.74 (s), 120.12 (t, J = 23.9 Hz), 115.61 (t, J = 233.3 Hz), 34.74 (s), 31.18 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -109.42 – -109.69 (m).

(E)-1,1-difluorononon-2-ene (4b)



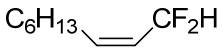
The reaction was performed according to the general procedure for difluoromethylation on a 0.5 mmol scale (119 mg **3b**). The crude mixture was purified by silica gel chromatography (12 g of silica, 100:0 → 90:10 pentane:Et_2O) to give **4b** (74 mg, 91% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.07 (ddd, J = 9.8, 7.0, 3.3 Hz, 1H), 6.02 (td, J = 56.2, 6.0 Hz, 1H), 5.63 (dt, J = 15.4, 7.6 Hz, 1H), 2.17 – 2.08 (m, 2H), 1.45 – 1.38 (m, 2H), 1.34 – 1.25 (m, 6H), 0.89 (t, J = 6.6 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 140.26 (t, J = 11.9 Hz), 123.17 (t, J = 23.8 Hz), 115.57 (t, J = 232.8 Hz), 31.79 (s), 31.59 (s), 28.72 (s), 28.20 (t, J = 1.9 Hz), 22.54 (s), 14.02 (s).

^{19}F NMR (376 MHz $CDCl_3$) δ -110.86 – -111.08 (m).

(Z)-1,1-difluorononon-2-ene (4c)



The reaction was performed according to the general procedure for difluoromethylation on a 0.5 mmol scale (119 mg **3b**). The crude mixture was purified by silica gel chromatography (12 g of silica, 100:0 → 90:10 pentane:Et_2O) to give **4b** (34 mg, 42% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39 (td, J = 56.0, 6.9 Hz, 1H), 5.93 – 5.83 (m, 1H), 5.65 – 5.51 (m, 1H), 2.17 (q, J = 7.5 Hz, 2H), 1.45 – 1.36 (m, 2H), 1.36 – 1.22 (m, 6H), 0.88 (t, J = 6.5 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.04 (t, J = 12.1 Hz), 122.75 (t, J = 25.1 Hz), 111.91 (t, J = 231.0 Hz), 31.55 (s), 29.07 (t, J = 1.7 Hz), 28.69 (s), 27.90 (t, J = 1.4 Hz), 22.53 (s), 14.01 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -111.16 (d, J = 56.0 Hz).

4.5 References

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"Copper-Mediated Difluoromethylation of Aryl and Vinyl Iodides"
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CHAPTER 5

Synthesis of Difluoromethyl Ethers with HCF_2OTf

5.1 Introduction

Difluoromethyl ethers are found increasingly in pharmaceuticals, agrochemicals, and materials.[1] Aryl difluoromethyl ethers are found in medicinally important compounds that include enzyme inhibitors,[2] anti-HIV agents[3] and atimicrobial agents.[4] Pantoprazole (Protonix®), a proton-pump inhibitor, is among the top 100 pharmaceuticals and contains a difluoromethyl ether.[5]

However, current syntheses of difluoromethyl ethers require the ozone-depleting compound HCF_2Cl (Freon 22) that is difficult to handle because it is a gas (Figure 5.1).[6] Non-ozone-depleting sources have been reported for the formation of difluoromethyl ethers from phenols,[7] but the reactions with these reagents often require high-temperatures, long reaction times, and have only been demonstrated to work with simple substrates.

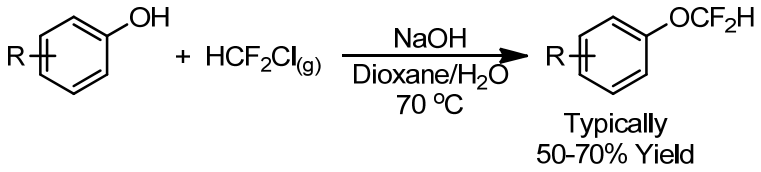
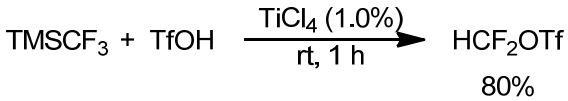


Figure 5.1 Traditional route to of aryl difluoromethyl ethers

We report a procedure for the difluoromethylation of phenols and thiophenols that occurs with broad scope starting with difluoromethyltriflate (HCF_2OTf), a non-ozone-depleting liquid. The fast rates, tolerance for additional functionality and tolerance of byproducts formed by prior reactions made possible the development of one-pot protocols for the conversion of aryl halides, aryl boronic acids, and even arenes, to difluoromethyl ethers.

5.2 Results and Discussion

Difluoromethyltriflate is an attractive source of a difluoromethyl unit because it can be prepared in multi-gram scale from readily available, non-ozone-depleting reagents. The reaction between $TMSCF_3$ (the Ruppert-Prakash reagent) and triflic acid with catalytic $TiCl_4$ at room temperature provides difluoromethyltriflate (HCF_2OTf) in good yield (equation 5.1).[8] HCF_2OTf is an air-stable liquid which makes handling the reagent easier than gaseous HCF_2Cl.

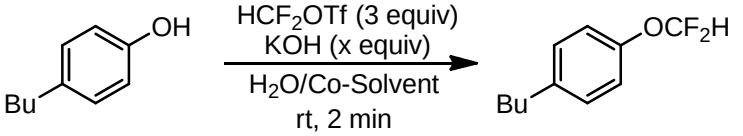


Equation 5.1 Synthesis of HCF_2OTf from Me_3SiCF_3 and TfOH with catalytic $TiCl_4$

Reaction conditions were examined for the difluoromethylation of 4-butylphenol with HCF_2OTf (Table 5.1). Initial results showed that reactions conducted with aqueous base occurred in significantly higher yields than reactions conducted under anhydrous conditions. Reactions conducted with aqueous KOH formed the desired product in higher yield than those conducted with LiOH or NaOH (Table 5.1, entries 12 and 13). Reactions

with MeCN were found to give higher yields than those in other co-solvents examined. Under the reaction conditions shown in Table 5.1, the difluoromethylation of 4-butylphenol was complete within minutes at room temperature and formed minimal side-products. The reactions are trivial to perform; they simply involve the addition of HCF_2OTf to a solution of phenol in 1:1 MeCN/6M KOH at ambient temperature (entry 6).

Table 5.1 Development of reaction conditions for the difluoromethylation of phenols with HCF_2OTf[a]



Entry	KOH (equiv)	Co-Solvent	$ArOCF_2H$ (%)	ArOTf (%)
1	12	DMF	43	34
2	12	DMSO	59	5
3	12	Dioxane	54	16
4	12	THF	62	7
5	12	Water	5	2
6	12	MeCN	75	12
7	8	MeCN	59	6
8	10	MeCN	70	19
9	16	MeCN	54	11
10	20	MeCN	61	7
11	24	MeCN	56	7
12	12	MeCN	38	11[b]
13	12	MeCN	61	10[c]

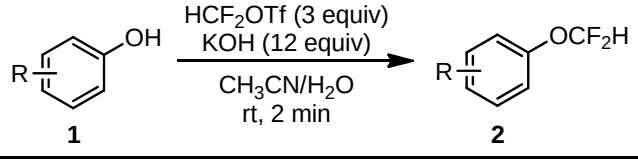
[a]Reactions were performed on a 0.1 mmol scale and the yields were determined by GC with 1-bromo-4-fluorobenzene as an internal standard. [b]The reaction was performed with LiOH in place of KOH. [c]The reaction was performed with NaOH in place of KOH.

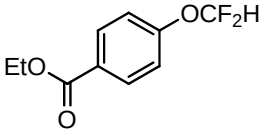
The reaction conditions identified for the difluoromethylation of 4-butylphenol (Table 5.1, entry 6) were evaluated for the synthesis of difluoromethyl ethers from a range of phenols (Table 5.2). Electron-rich, electron-deficient and sterically hindered phenols reacted under the standard conditions. The short reaction time and mild conditions were tolerant of esters, amides, ketones, acetals, nitriles, aldehydes, aryl halides, and heterocycles. In each reaction, the only by-products observed were unreacted phenol and varying amounts of aryl-triflate.[9] Stable enols (**1s**, **1t**) also underwent the difluoromethylation reaction in high yield. Capsaicin and estrone reacted to form the difluoromethyl ethers **2w** and **2x** in modest yield. The same reaction conditions for the difluoromethylation of phenols also led to difluoromethylsulfides **2u** and **2v** from the corresponding thiophenols. The substrate scope and generality demonstrated here is unrivaled for the synthesis of difluoromethyl ethers.

The aryl difluoromethyl ether products are stable and were isolated by silica gel chromatography. Difluoromethyl ethers **2a**, **2f**, **2g**, and **2p**, which contain an electron-withdrawing group, were obtained in analytically pure form after an aqueous workup. Isolated yields of the reactions performed with 0.5 mmol of substrate were comparable to the yields determined by ^{19}F NMR spectroscopy for reactions performed on a 0.1 mmol

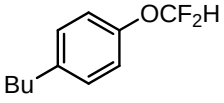
scale. The volatility of some products prevented their isolation in high yield, and the yields determined by ^{19}F NMR spectroscopy are given in those cases.

Table 5.2 Scope of the difluoromethylation reaction with HCF_2OTf[a]

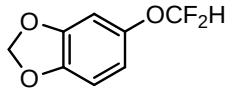




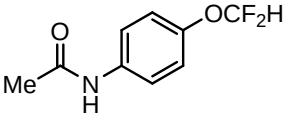
2a, 93% (90%)



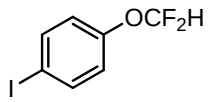
2b, 75% (68%)



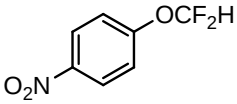
2c, 69% (52%), 78%[b]



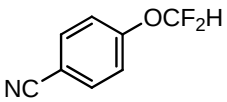
2d, 68% (70%)



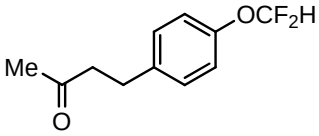
2e, 72% (72%), 94%[b]



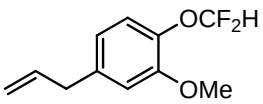
2f, Quant (94%)



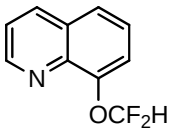
2g, 98% (88%)



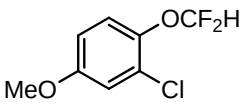
2h, 70% (66%)



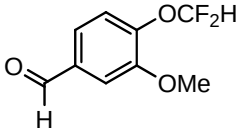
2i, 51%, 74%[b]



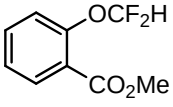
2j, 61%



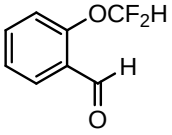
2k, 57% (53%)



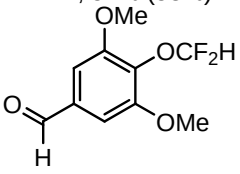
2l, 84% (81%)



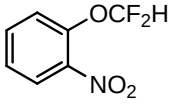
2m, 74% (65%)



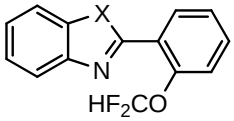
2n, 68%



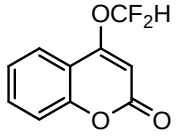
2o, 68% (62%)



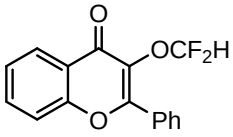
2p, Quant. (92%)



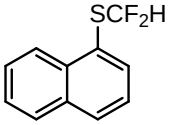
2q, X = O, 90% (85%)
2r, X = S, 80% (77%)



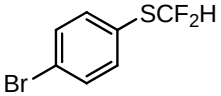
2s, 90% (89%)



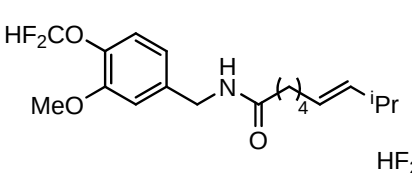
2t, 88% (79%)



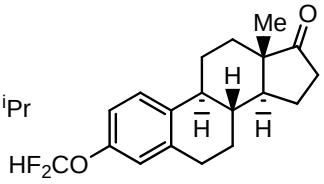
2u, 88%



2v, 83%



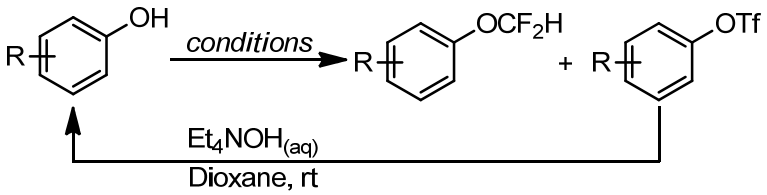
2w, 53% (45%)
Capsaicin



2x, 53% (50%), 79%[b]
Estrone

[a]Reactions were performed on a 0.1 mmol scale to determine yields by ^{19}F NMR spectroscopy with $PhCF_3$ as an internal standard. Isolated yields are shown in parenthesis for reactions performed on a 0.5 mmol scale. [b]Reactions were performed on a 0.1 mmol scale with HCF_2ONf in place of HCF_2OTf and yields were determined by ^{19}F NMR spectroscopy.

The aryl-triflate side products are most prevalent in the reactions of phenol substrates bearing electron-donating groups. It was proposed that nucleophilic attack at the sulfur atom of HCF_2OTf would be inhibited by the use of a bulkier sulfonate group. Thus, we prepared difluoromethylnonaflate (HCF_2ONf) according to the literature procedure by the reaction of nonafluorobutanesulfonic acid (NfOH) with $TMSCF_3$ (equation 5.1).[8] Phenols **1c**, **1e**, **1i**, and **1x**, which formed significant amounts of ArOTf in the reactions with HCF_2OTf, gave measurably higher yields of the difluoromethyl ethers when HCF_2ONf was used as the difluoromethyl source (Table 5.2). It is important to note that the aryl triflate from reactions with HCF_2OTf can be recycled to the starting phenol by basic hydrolysis (equation 5.2).[10]



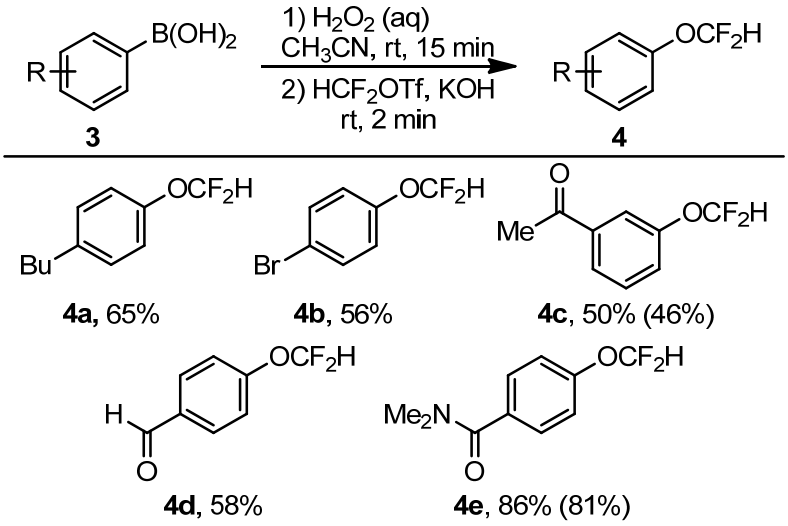
Equation 5.2 Formation of aryl triflate side-product and recycling to phenol with $[Et_4N]OH$

Because these reactions occur rapidly under mild conditions, we considered that they would tolerate byproducts from the synthesis of phenols. If so, then the difluoromethylation could be used in combination with several processes that form phenols from common precursors, such as arylboronates, aryl halides and arenes themselves.

Phenols can be prepared by oxidation of aryl boronic acids with aqueous hydrogen peroxide. We proposed that aryl boronic acids could be transformed to aryl difluoromethyl ethers by first forming the phenol *in-situ*. Indeed, the reaction between arylboronic acids in MeCN with 30% aqueous H_2O_2 for 15 minutes, followed by the addition of KOH and HCF_2OTf provided difluoromethyl ethers from aryl boronic acids (Table 5.3). The two-step, one-pot reaction sequence was tolerant of ketones, aldehydes and amides.[11]

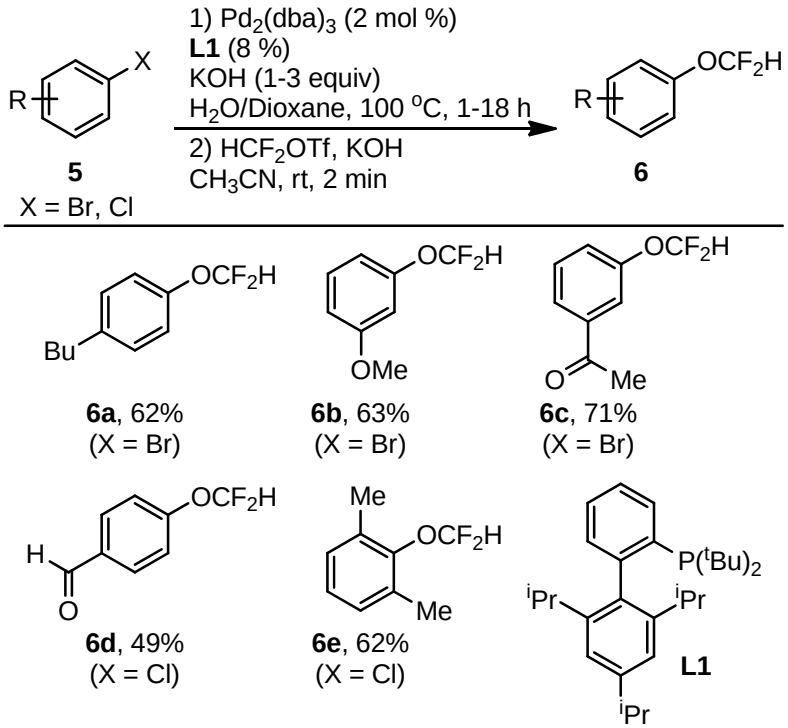
Phenols can also be prepared by the hydroxylation of aryl halides catalyzed by transition-metal complexes. We envisioned a two-step sequence for the conversion of aryl halides to difluoromethoxyarenes based on the palladium-catalyzed conversion of aryl halides to phenols and *in-situ* conversion of the resulting phenoxides with HCF_2OTf. Indeed, we found that the phenols formed in the Pd-catalyzed hydroxylation were readily transformed into difluoromethyl ethers (Table 5.4).[12] The phenols formed in the first step were used without purification. Dilution of the crude reaction with MeCN and additional aqueous KOH, and treatment of this solution with HCF_2OTf, gave the difluoromethyl ether products in good yield. Aryl bromides and aryl chlorides both underwent the two step process in good yield.[13]

Table 5.3 One-pot difluoromethoxylation of arylboronic acids[a]



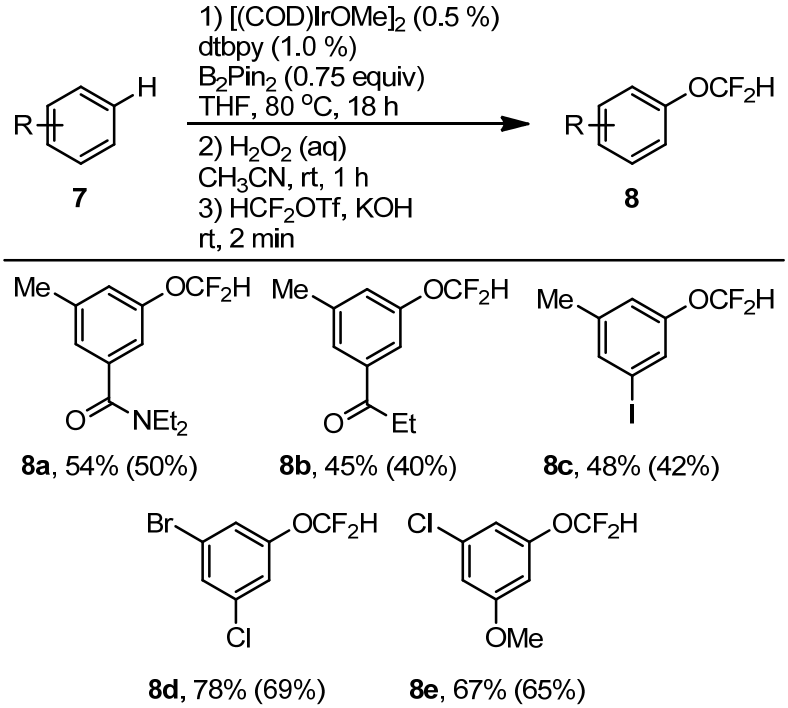
[a]Reactions were performed on a 0.1 mmol scale to determine yields by ^{19}F NMR spectroscopy with $PhCF_3$ as an internal standard added after the reaction. Isolated yields are shown in parenthesis for reactions performed on a 0.5 mmol scale.

Table 5.4 One-pot difluoromethoxylation of aryl halides[a]



[a]Reactions were performed on a 0.5 mmol scale to determine yields by ^{19}F NMR spectroscopy with $PhCF_3$ as an internal standard added after the reaction.

Table 5.5 One-pot difluoromethoxylation of arenes through Ir-catalyzed C-H borylation[a]

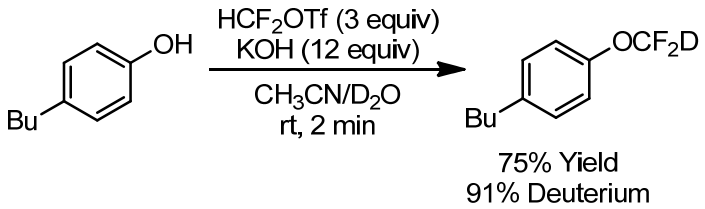


[a]Reactions were performed on a 0.1 mmol scale to determine yields by ^{19}F NMR spectroscopy with $PhCF_3$ as an internal standard added after the reaction. Isolated yields are shown in parenthesis for reactions performed on a 0.5 mmol scale.

Finally, we considered that a one-pot route could be developed for the conversion of arenes to aryl difluoromethyl ethers by sequential C-H borylation, oxidation, and difluoromethylation. Tandem reactions involving initial C-H borylation are useful for preparing diversely functionalized arenes,[14] due in part to the high selectivity of the borylation reaction for the least-hindered C-H bond.[15] The results for the overall conversion of Ar-H to Ar-OCF_2H are shown in Table 5.5. Synthetically useful yields of the difluoromethyl ether were obtained with substrates containing amides, ketones and aryl halides. The aryl boronate esters formed in the first step were used without purification. However, a change in solvent from THF to MeCN was necessary after the borylation reaction. Thus, the three-step sequence reported here provides an unusual conversion of arenes to 3,5-disubsituted aryl difluoromethyl ethers.

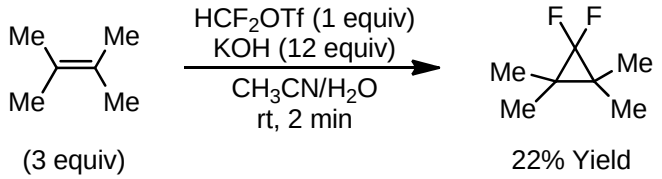
The mechanism of the reactions of phenols with HCF_2OTf was studied experimentally. All reactions that have been reported for the difluoromethylation of phenols are proposed to occur through initial formation of difluorocarbene.[16] To determine if the reaction of phenols with HCF_2OTf proceeds through the formation of difluorocarbene or by nucleophilic displacement of the triflate of HCF_2OTf by phenol, we performed reactions with D_2O. If the reaction with phenol occurs by nucleophilic displacement of triflate, than the unlabeled product $ArOCF_2H$ would be expected to form. However, if the reaction proceeds by nucleophilic addition to difluorocarbene, then the deuterium-labeled product $ArOCF_2D$ would be expected to form by protonation of the intermediate $ArOCF_2^-$ with D_2O. These labeling experiments reflect the reaction pathway because no H-D exchange occurs to generate DCF_2OTf in the presence of D_2O and KOH,

and the difluoromethyl ether product does not undergo H-D exchange under the reaction conditions. In the event, the reaction with D_2O gave 91% incorporation of deuterium at the difluoromethyl group of the ether (equation 5.3).[17]



Equation 5.3 Deuterium labeling study with D_2O to determine the mechanism of the difluoromethylation reaction.

We further evaluated whether difluorocarbene is formed under the reaction conditions by conducting the reaction of HCF_2OTf with an alkene under the same conditions as the difluoromethylation of phenol. The reaction of tetramethylethylene with HCF_2OTf and KOH in CH_3CN/H_2O provided the difluorocyclopropane product in 22% yield, as determined by ^{19}F NMR spectroscopy (equation 5.4). The difluorocarbene formed undergoes competing hydrolysis with water to form formate and fluoride ions, which accounts for the low yield of the difluorocyclopropane. Nevertheless, the observation of the cyclopropane further supports the formation of difluorocarbene from the reaction of KOH with HCF_2OTf. These results are consistent with a mechanism for the formation of a difluoromethyl ether by reaction of the phenol (or phenolate) with difluorocarbene, not by nucleophilic displacement of the triflate of HCF_2OTf by phenoxide.



Equation 5.4 Trapping experiment with tetramethylethylene to confirm that difluorocarbene is formed

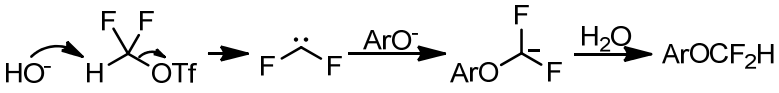


Figure 5.2 Proposed mechanism for the reaction of phenols with HCF_2OTf.

5.3 Conclusions

In summary, we have developed a simple method for the difluoromethylation of phenols and thiophenols with a readily available and non-ozone-depleting liquid reagent, HCF_2OTf. This method allows difluoromethyl ethers and sulfides to be prepared within minutes at room temperature in aqueous solvent. The broad functional group tolerance and mild conditions of this reaction make possible the difluoromethylation of a wide range of complex phenols, including phenols generated *in-situ* by a series of catalytic and

oxidation processes. One-pot procedures have been developed for the difluoromethyoxylation of aryl boronic acids, aryl halides and arenes. The direct conversion of arenes, boronic acids, and aryl halides to difluoromethoxyarenes has been challenging, in part, because of the instability of the $^{-}OCF_2H$ anion. A series of mechanistic studies show that the difluoromethylation of phenols reported here proceeds through initial formation of difluorocarbene and subsequent nucleophilic addition of the phenolate or thiophenolate anion to difluorocarbene.

5.4 Experimental

All manipulations were conducted on the benchtop without any exclusion of air or moisture, unless otherwise noted. All reactions were conducted in 4 mL or 20 mL vials fitted with a Teflon-lined screw cap unless otherwise noted. HCF_2OTf and HCF_2ONf were prepared according to the published procedure. All other reagents were purchased from commercial suppliers and used as received.

NMR spectra were acquired on 400 MHz, 500 MHz, or 600 MHz Bruker instruments at the University of California, Berkeley. NMR spectra were processed with MestReNova 5.0 (Mestrelab Research SL). Chemical shifts are reported in ppm and referenced to residual solvent peaks ($CHCl_3$ in $CDCl_3$: 7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C) or to an external standard (1% $CFCl_3$ in $CDCl_3$: 0 ppm for ^{19}F). Coupling constants are reported in hertz.

All GC-MS analyses were conducted with an Agilent 6890N GC equipped with an HP-5 column (25 m x 0.20 mm ID x 0.33 μm film) and an Agilent 5973 Mass Selective Detector. The temperature for each run was held at 50 °C for 2 min, ramped from 50 °C to 300 °C at 40 °C/min, and held at 300 °C for 5 min.

General Procedure for the Difluoromethylation of Phenols and Thiophenols

Into a 20 mL vial was placed the phenol or thiophenols (0.5 mmol, 1.0 equiv), acetonitrile (1.0 mL) and 6M aqueous KOH (1.0 mL). The mixture was stirred rapidly at room temperature and HCF_2OTf (210 μL, 1.5 mmol, 3.0 equiv) was added at once. Note: the reactions are exothermic. The mixture was stirred vigorously for 2 minutes. The reaction was diluted with H_2O (8 mL) and extracted with ether (2 x 8 mL). The combined organic layers were dried over $MgSO_4$, concentrated, and purified by silica gel chromatography.

General Procedure for the Difluoromethoxylation of Aryl Boronic Acids

To a 20 mL vial was added the aryl boronic acid (0.5 mmol, 1.0 equiv), acetonitrile (1.0 mL) and 30% aqueous hydrogen peroxide (500 μL). The reaction was stirred at room temperature for 15 minutes. After this time, 12M KOH (500 μL) was added carefully. Note: the addition of KOH causes rapid decomposition of the unreacted hydrogen peroxide. This reaction is exothermic, and gas is evolved. The resulting mixture was stirred rapidly at room temperature, and HCF_2OTf (210 μL, 1.5 mmol, 3.0 equiv) was added at once. Note: the reactions are exothermic. The mixture was stirred vigorously for 2 minutes. The reaction was diluted with H_2O (8 mL) and extracted with ether (2 x 8

mL). The combined organic layers were dried over $MgSO_4$, concentrated, and purified by silica gel chromatography.

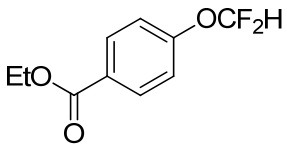
General Procedure for the Difluoromethoxylation of Aryl Bromides and Aryl Chlorides

Note: The hydroxylation reaction was set-up under an inert atmosphere according to the literature procedure.[12] To an oven-dried 4 mL vial was added $Pd_2(dba)_3$ (9.2 mg, .010 mmol, 4.0 mol % Pd), 2-Di-tert-butylphosphino-2′,4′,6′-triisopropylbiphenyl (^{t}Bu-XPhos, 17.0 mg, .040 mmol, 8.0 mol %), KOH (1.0-3.0 equiv), degassed H_2O (150-300 μL) and dioxane (250-500 μL). The aryl halide (0.5 mmol, 1.0 equiv) was added (solid aryl halides were weighed into the vial prior to adding solvent, and liquid aryl bromides were added neat by syringe after the addition of solvent). The vial was sealed with a Teflon-lined cap and heated at 100 ^{o}C for 1-18 h. The solution was allowed to cool, and the reaction was diluted with acetonitrile (500-750 μL, such that the total volume of dioxane and acetonitrile is 1.0 mL) and 6M KOH (700-850 μL, such that the final aqueous solvent volume is 1.0 mL). The resulting mixture was stirred rapidly at room temperature, and HCF_2OTf (210 μL, 1.5 mmol, 3.0 equiv) was added at once. Note: the reactions are exothermic. The mixture was stirred vigorously for 2 minutes. The reaction was diluted with H_2O (8 mL) and extracted with ether (2 x 8 mL). The combined organic layers were dried over $MgSO_4$, concentrated, and purified by silica gel chromatography.

General Procedure for the Difluoromethoxylation of Arenes through Ir-Catalyzed C-H Borylation

Note: The borylation reaction was set-up under an inert atmosphere. To an oven-dried 20 mL vial was added arene (0.5 mmol, 1.0 equiv), and 1.0 mL of a stock solution containing 0.5 mol % $[Ir(COD)OMe]_2$, 1.0 mol % 4,4'-di-tert-butyl bipyridine (dtbpy), and 0.75 equiv of B_2Pin_2. The vial was sealed with a Teflon-lined cap and heated at 80 ^{o}C for 18 h. The solution was allowed to cool, and the volatile components were removed in vacuo. To the crude ArBPin was added acetonitrile (1.0 mL) and 30% aqueous hydrogen peroxide (500 μL). The reaction was stirred at room temperature for 15 minutes. After this time, 12M KOH (500 μL) was added carefully. Note: the addition of KOH causes rapid decomposition of the unreacted hydrogen peroxide. This reaction is exothermic, and gas is evolved. The resulting mixture was stirred rapidly at room temperature, and HCF_2OTf (210 μL, 1.5 mmol, 3.0 equiv) was added at once. Note: the reactions are exothermic. The mixture was stirred vigorously for 2 minutes. The reaction was diluted with H_2O (8 mL) and extracted with ether (2 x 8 mL). The combined organic layers were dried over $MgSO_4$, concentrated, and purified by silica gel chromatography.

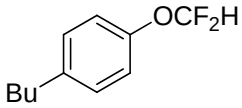
Ethyl 4-(difluoromethoxy)benzoate (2a)



The reaction was performed according to the general procedure for the difluoromethylation of phenols on a 0.5 mmol scale. The product was purified by silica gel chromatography to give **2a** as a clear oil (98 mg, 90% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J = 8.7 Hz, 2H), 7.15 (d, J = 8.5 Hz, 2H), 6.59 (t, J = 73.2 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 165.66 (s), 154.61 (t, J = 2.4 Hz), 131.60 (s), 127.47 (s), 118.59 (s), 115.40 (t, J = 261.0 Hz), 61.13 (s), 14.29 (s).
^{19}F NMR (376 MHz, $CDCl_3$) δ -84.25 (d, J = 73.2 Hz).

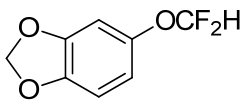
1-butyl-4-(difluoromethoxy)benzene (2b)



The reaction was performed according to the general procedure for the difluoromethylation of phenols on a 0.5 mmol scale. The product was purified by silica gel chromatography to give **2b** as a clear oil (68 mg, 68% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.16 (d, J = 8.2 Hz, 2H), 7.03 (d, J = 8.0 Hz, 2H), 6.47 (t, J = 74.3 Hz, 1H), 2.59 (t, J = 7.7 Hz, 2H), 1.62 – 1.54 (m, 2H), 1.35 (dd, J = 14.8, 7.4 Hz, 2H), 0.93 (t, J = 7.3 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 149.19 (t, J = 2.8 Hz), 140.17 (s), 129.61 (s), 119.45 (s), 116.15 (t, J = 258.9 Hz), 34.89 (s), 33.61 (s), 22.25 (s), 13.89 (s).
^{19}F NMR (376 MHz, $CDCl_3$) δ -82.61 (d, J = 74.3 Hz).

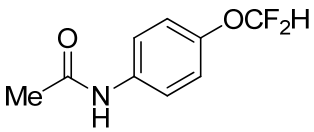
5-(difluoromethoxy)benzo[d][1,3]dioxole (2c)



The reaction was performed according to the general procedure for the difluoromethylation of phenols on a 0.5 mmol scale. The product was purified by silica gel chromatography to give **2c** as a clear oil (49 mg, 52% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.75 (d, J = 8.4 Hz, 1H), 6.67 (s, 1H), 6.59 (d, J = 8.4 Hz, 1H), 6.40 (t, J = 74.1 Hz, 1H), 5.99 (s, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 148.27 (s), 145.47 (t, J = 3.1 Hz), 145.32 (s), 116.19 (t, J = 260.0 Hz), 112.72 (s), 108.07 (s), 102.80 (s), 101.78 (s).
^{19}F NMR (376 MHz, $CDCl_3$) δ -82.74 (d, J = 74.1 Hz).

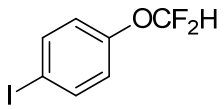
N-(4-(difluoromethoxy)phenyl)acetamide (2d)



The reaction was performed according to the general procedure for the difluoromethylation of phenols on a 0.5 mmol scale. The product was purified by silica gel chromatography to give **2d** as a white solid (70 mg, 70% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 (d, J = 8.7 Hz, 2H), 7.25 (br s, 1H), 7.08 (d, J = 8.6 Hz, 2H), 6.46 (t, J = 74.0 Hz, 1H), 2.18 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 168.36 (s), 147.31 (t, J = 2.3 Hz), 135.32 (s), 121.32 (s), 120.40 (s), 115.94 (t, J = 260.0 Hz), 24.42 (s).
^{19}F NMR (376 MHz, $CDCl_3$) δ -82.52 (d, J = 74.0 Hz).

1-(difluoromethoxy)-4-iodobenzene (2e)



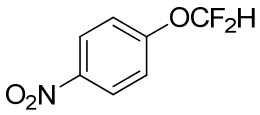
The reaction was performed according to the general procedure for the difluoromethylation of phenols on a 0.5 mmol scale. The product was purified by silica gel chromatography to give **2e** as a clear oil (98 mg, 72% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.9 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.48 (t, J = 73.4 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 150.89 (t, J = 2.9 Hz), 138.82 (s), 121.80 (s), 115.54 (t, J = 261.2 Hz), 89.08 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -83.62 (d, J = 73.4 Hz).

1-(difluoromethoxy)-4-nitrobenzene (2f)



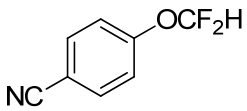
The reaction was performed according to the general procedure for the difluoromethylation of phenols on a 0.5 mmol scale. The product obtained from the aqueous workup as a white solid (**2f**) was not subjected to further purification (88 mg, 94% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.27 (d, J = 8.5 Hz, 2H), 7.25 (d, J = 8.1 Hz, 2H), 6.63 (t, J = 72.2 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 155.52 (t, J = 2.8 Hz), 144.81 (s), 125.75 (s), 119.34 (s), 114.99 (t, J = 263.7 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -85.19 (d, J = 72.2 Hz).

4-(difluoromethoxy)benzonitrile (2g)



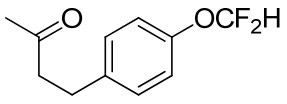
The reaction was performed according to the general procedure for the difluoromethylation of phenols on a 0.5 mmol scale. The product obtained from the aqueous workup as a white solid (**2g**) was not subjected to further purification (88 mg, 94% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, J = 8.6 Hz, 2H), 7.22 (d, J = 8.5 Hz, 2H), 6.59 (t, J = 72.4 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 154.09 (t, J = 2.8 Hz), 134.14 (s), 119.84 (s), 118.00 (s), 115.05 (t, J = 263.2 Hz), 109.17 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -84.85 (d, J = 72.4 Hz).

4-(4-(difluoromethoxy)phenyl)butan-2-one (2h)



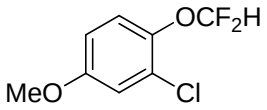
The reaction was performed according to the general procedure for the difluoromethylation of phenols on a 0.5 mmol scale. The product was purified by silica gel chromatography to give **2h** as a clear oil (71 mg, 66% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.17 (d, J = 8.3 Hz, 2H), 7.03 (d, J = 8.3 Hz, 2H), 6.47 (t, J = 74.1 Hz, 1H), 2.88 (t, J = 7.5 Hz, 2H), 2.75 (t, J = 7.5 Hz, 2H), 2.14 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 207.48 (s), 149.49 (t, J = 2.9 Hz), 138.29 (s), 129.62 (s), 119.70 (s), 116.00 (t, J = 259.4 Hz), 44.98 (s), 30.04 (s), 28.88 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -82.71 (d, J = 74.1 Hz).

2-chloro-1-(difluoromethoxy)-4-methoxybenzene (2k)



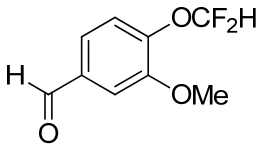
The reaction was performed according to the general procedure for the difluoromethylation of phenols on a 0.5 mmol scale. The product was purified by silica gel chromatography to give **2k** (56 mg, 53% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.17 (d, J = 9.0 Hz, 1H), 6.97 (d, J = 3.0 Hz, 1H), 6.78 (dd, J = 9.0, 3.0 Hz, 1H), 6.44 (t, J = 74.0 Hz, 1H), 3.79 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 157.69 (s), 140.31 (t, J = 3.1 Hz), 127.38 (s), 123.54 (s), 116.04 (t, J = 262.1 Hz), 115.69 (s), 113.40 (s), 55.80 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -83.09 (d, J = 74.1 Hz).

4-(difluoromethoxy)-3-methoxybenzaldehyde (2l)



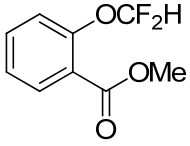
The reaction was performed according to the general procedure for the difluoromethylation of phenols on a 0.5 mmol scale. The product was purified by silica gel chromatography to give **2l** as a white solid (81 mg, 81% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (s, 1H), 7.50 (s, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 6.67 (t, J = 74.2 Hz, 1H), 3.96 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 190.81 (s), 151.46 (s), 144.86 (t, J = 2.6 Hz), 134.45 (s), 124.98 (s), 121.40 (s), 115.52 (t, J = 261.6 Hz), 110.91 (s), 56.13 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -83.73 (d, J = 74.2 Hz).

Methyl 2-(difluoromethoxy)benzoate (2m)



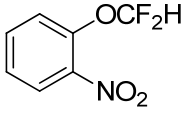
The reaction was performed according to the general procedure for the difluoromethylation of phenols on a 0.5 mmol scale. The product was purified by silica gel chromatography to give **2m** (66 mg, 65% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (d, J = 7.8 Hz, 1H), 7.54 (t, J = 7.8 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 7.26 (d, J = 8.2 Hz, 1H), 6.57 (t, J = 74.7 Hz, 1H), 3.92 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 165.50 (s), 149.89 (t, J = 3.2 Hz), 133.55 (s), 131.70 (s), 125.96 (s), 124.35 (s), 122.92 (s), 116.43 (t, J = 260.6 Hz), 52.37 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -83.47 (d, J = 74.7 Hz).

1-(difluoromethoxy)-2-nitrobenzene (2o)



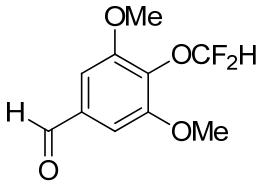
The reaction was performed according to the general procedure for the difluoromethylation of phenols on a 0.5 mmol scale. The product obtained from the aqueous workup as a clear oil (**2o**) was not subjected to further purification (87 mg, 92% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 (d, J = 8.0 Hz, 1H), 7.63 (t, J = 7.9 Hz, 1H), 7.40 (m, 2H), 6.62 (t, J = 73.0 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 143.07 (t, J = 3.2 Hz), 142.88 (s), 134.09 (s), 126.38 (s), 125.62 (s), 123.56 (s), 115.61 (t, J = 265.2 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -84.01 (d, J = 73.0 Hz).

4-(difluoromethoxy)-3,5-dimethoxybenzaldehyde (2p)



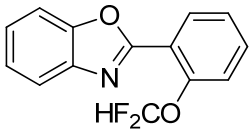
The reaction was performed according to the general procedure for the difluoromethylation of phenols on a 0.5 mmol scale. The product was purified by silica gel chromatography to give **2p** as a white solid (72 mg, 62% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 1H), 7.16 (s, 2H), 6.66 (t, J = 75.9 Hz, 1H), 3.96 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 190.73 (s), 153.54 (s), 134.10 (s), 134.03 (t, J = 2.8 Hz), 116.16 (t, J = 261.4 Hz), 106.34 (s), 56.53 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -83.00 (d, J = 75.9 Hz).

2-(2-(difluoromethoxy)phenyl)benzo[d]oxazole (2q)



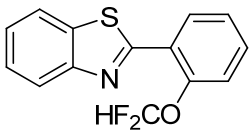
The reaction was performed according to the general procedure for the difluoromethylation of phenols on a 0.5 mmol scale. The product was purified by silica gel chromatography to give **2q** as a white solid (111 mg, 85% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 7.7 Hz, 1H), 7.85 – 7.79 (m, 1H), 7.62 (dd, J = 5.0, 3.9 Hz, 1H), 7.56 (td, J = 8.2, 1.2 Hz, 1H), 7.45 – 7.36 (m, 4H), 6.75 (t, J = 74.3 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 160.05 (s), 150.63 (s), 149.02 (t, J = 2.7 Hz), 141.74 (s), 132.57 (s), 131.24 (s), 126.25 (s), 125.51 (s), 124.64 (s), 122.76 (s), 120.58 (s), 120.43 (s), 116.24 (t, J = 261.7 Hz), 110.69 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -83.59 (d, J = 74.3 Hz).

2-(2-(difluoromethoxy)phenyl)benzo[d]thiazole (2r)



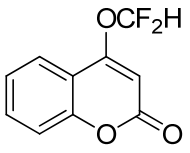
The reaction was performed according to the general procedure for the difluoromethylation of phenols on a 0.5 mmol scale. The product was purified by silica gel chromatography to give **2r** as a white solid (107 mg, 77% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.54 (d, J = 7.9 Hz, 1H), 8.16 (d, J = 8.1 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.53 (dt, J = 12.3, 7.9 Hz, 2H), 7.44 (t, J = 7.6 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.31 (d, J = 8.2 Hz, 1H), 6.71 (t, J = 73.2 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 161.96 (s), 152.14 (s), 148.78 (t, J = 2.5 Hz), 135.92 (s), 131.77 (s), 130.62 (s), 126.33 (s), 125.92 (s), 125.44 (s), 125.38 (s), 123.21 (s), 121.41 (s), 119.54 (s), 116.12 (t, J = 261.9 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -82.68 (d, J = 73.2 Hz).

4-(difluoromethoxy)-2H-chromen-2-one (2s)



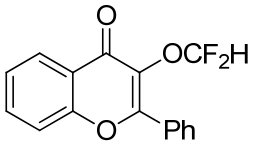
The reaction was performed according to the general procedure for the difluoromethylation of phenols on a 0.5 mmol scale. The product was purified by silica gel chromatography to give **2s** (94 mg, 89% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 7.8 Hz, 1H), 7.63 (t, J = 7.4 Hz, 1H), 7.36 (m, 2H), 6.81 (t, J = 71.2 Hz, 1H), 5.97 (s, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 160.96 (s), 158.93 (t, J = 3.2 Hz), 153.52 (s), 133.40 (s), 124.53 (s), 123.00 (s), 114.41 (t, J = 264.8 Hz), 114.05 (s), 96.43 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -87.63 (d, J = 71.2 Hz).

3-(difluoromethoxy)-2-phenyl-4H-chromen-4-one (2t)



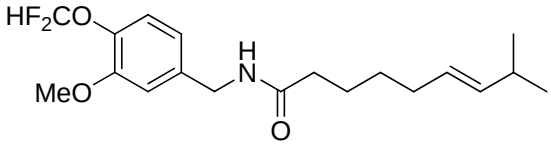
The reaction was performed according to the general procedure for the difluoromethylation of phenols on a 0.5 mmol scale. The product was purified by silica gel chromatography to give **2t** as a white solid (114 mg, 79% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 8.0 Hz, 1H), 8.10 – 8.04 (m, 2H), 7.75 (t, J = 7.8 Hz, 1H), 7.62 – 7.51 (m, 4H), 7.47 (t, J = 7.6 Hz, 1H), 7.20 (t, J = 76.9 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.32 (s), 157.42 (s), 155.35 (s), 134.21 (s), 133.68 (t, J = 4.0 Hz), 131.46 (s), 129.67 (s), 128.94 (s), 128.56 (s), 125.84 (s), 125.37 (s), 123.74 (s), 118.12 (s), 115.65 (t, J = 262.6 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -84.38 (d, J = 76.9 Hz).

Difluoromethyl-capsaicin (2w)



Note: Commercially available capsaicin from natural sources (TCI Chemicals) is a 1.9:1 mixture of capsaicin and dihydrocapsaicin. The mixture of capsaicin and dihydrocapsaicin was used as received. The reaction was performed according to the general procedure for the difluoromethylation of phenols on a 0.5 mmol scale. The product was purified by silica gel chromatography to give **2w** as a white solid (80 mg, 45% yield) as an inseparable 1.9:1 mixture of difluoromethyl-capsaicin and difluoromethyl-dihydrocapsaicin.

Difluoromethyl-capsaicin:

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.09 (d, J = 8.1 Hz, 1H), 6.89 (s, 1H), 6.81 (d, J = 8.1 Hz, 1H), 6.51 (t, J = 75.2 Hz, 1H), 5.84 (s, 1H), 5.46 – 5.23 (m, 2H), 4.40 (d, J = 5.8 Hz, 2H), 3.85 (s, 3H), 2.21 (t, J = 7.5 Hz, 2H), 1.65 (dd, J = 15.1, 7.6 Hz, 2H), 1.43 – 1.34 (m, 2H), 1.34 – 1.22 (m, 3H), 0.94 (d, J = 6.7 Hz, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.03 (s), 151.13 (s), 139.04 (t, J = 3.0 Hz), 138.05 (s), 137.42 (s), 126.34 (s), 122.30 (s), 119.83 (s), 116.07 (t, J = 259.8 Hz), 112.13 (s), 55.86 (s), 43.05 (s), 36.46 (s), 32.13 (s), 30.87 (s), 29.20 (s), 25.19 (s), 22.54 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -82.92 (d, J = 75.2 Hz).

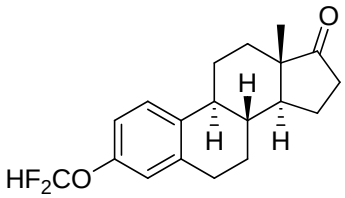
Difluoromethyl-dihydrocapsaicin:

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.09 (d, J = 8.1 Hz, 1H), 6.89 (s, 1H), 6.81 (d, J = 8.1 Hz, 1H), 6.51 (t, J = 75.2 Hz, 1H), 5.84 (s, 1H), 4.40 (d, J = 5.8 Hz, 2H), 3.85 (s, 3H), 1.98 (dd, J = 14.1, 7.0 Hz, 2H), 1.65 (dd, J = 15.1, 7.6 Hz, 2H), 1.54 – 1.45 (m, 1H), 1.35 – 1.20 (m, 8H), 0.85 (d, J = 6.6 Hz, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.15 (s), 151.13 (s), 139.04 (t, J = 3.0 Hz), 137.44 (s), 122.30 (s), 119.83 (s), 116.07 (t, J = 259.8 Hz), 112.13 (s), 55.86 (s), 43.05 (s), 38.87 (s), 36.63 (s), 29.54 (s), 29.29 (s), 27.85 (s), 27.16 (s), 25.72 (s), 22.52 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -82.92 (d, J = 75.2 Hz).

Difluoromethyl-estrone (2x)



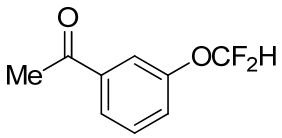
The reaction was performed according to the general procedure for the difluoromethylation of phenols on a 0.5 mmol scale. The product was purified by silica gel chromatography to give **2x** (81 mg, 50% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 8.6 Hz, 1H), 6.86 (s, 1H), 6.47 (t, J = 74.3 Hz, 1H), 2.91 (dd, J = 8.7, 3.6 Hz, 2H), 2.51 (dd, J = 19.1, 8.8 Hz, 1H), 2.43 – 2.38 (m, 1H), 2.27 (t, J = 10.8 Hz, 1H), 2.05 (ddd, J = 23.9, 13.4, 5.9 Hz, 2H), 1.97 (d, J = 10.5 Hz, 1H), 1.69 – 1.40 (m, 7H), 0.91 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 220.57 (s), 149.20 (t, J = 2.6 Hz), 138.46 (s), 137.01 (s), 126.71 (s), 119.68 (s), 116.86 (s), 116.07 (t, J = 259.1 Hz), 50.42 (s), 47.91 (s), 44.05 (s), 38.06 (s), 35.82 (s), 31.54 (s), 29.43 (s), 26.29 (s), 25.79 (s), 21.57 (s), 13.81 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -82.49 (d, J = 74.3 Hz).

3'-(difluoromethoxy)acetophenone (4c)



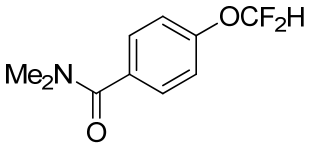
The reaction was performed according to the general procedure for the difluoromethoxylation of boronic acids on a 0.5 mmol scale. The product was purified by silica gel chromatography to give **4c** as a clear oil (43 mg, 46% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, J = 7.7 Hz, 1H), 7.70 (s, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.33 (d, J = 8.1 Hz, 1H), 6.57 (t, J = 73.3 Hz, 1H), 2.61 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 196.80 (s), 151.26 (t, J = 2.8 Hz), 138.79 (s), 130.06 (s), 125.32 (s), 124.26 (s), 118.93 (s), 115.60 (t, J = 261.1 Hz), 26.59 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -83.61 (d, J = 73.3 Hz).

4-(difluoromethoxy)-N,N-dimethylbenzamide (4e)



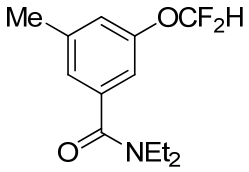
The reaction was performed according to the general procedure for the difluoromethoxylation of boronic acids on a 0.5 mmol scale. The product was purified by silica gel chromatography to give **4e** as a white solid (87 mg, 81% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 8.1 Hz, 2H), 6.54 (t, J = 73.4 Hz, 1H), 3.10 (s, 3H), 3.01 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.62 (s), 151.89 (t, J = 2.8 Hz), 133.41 (s), 129.01 (s), 119.25 (s), 115.61 (t, J = 260.7 Hz), 39.50 (br, s), 35.46 (br, s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -83.51 (d, J = 73.4 Hz).

3-(difluoromethoxy)-N,N-diethyl-5-methylbenzamide (8a)



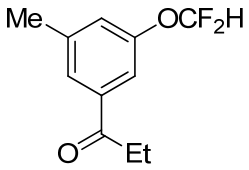
The reaction was performed according to the general procedure for the difluoromethoxylation of arenes on a 0.5 mmol scale. The product was purified by silica gel chromatography to give **8a** as a white solid (64 mg, 50% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.01 (s, 1H), 6.94 (s, 1H), 6.91 (s, 1H), 6.49 (t, J = 73.8 Hz, 1H), 3.52 (d, J = 5.6 Hz, 2H), 3.22 (d, J = 5.5 Hz, 2H), 2.36 (s, 3H), 1.23 (s, 3H), 1.10 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.99 (s), 150.94 (t, J = 2.7 Hz), 140.63 (s), 138.78 (s), 123.92 (s), 120.74 (s), 115.77 (t, J = 260.0 Hz), 114.34 (s), 43.23 (s), 39.25 (s), 21.27 (s), 14.10 (s), 12.79 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -83.16 (d, J = 73.8 Hz).

1-(3-(difluoromethoxy)-5-methylphenyl)propan-1-one (8b)



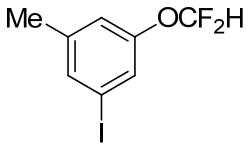
The reaction was performed according to the general procedure for the difluoromethoxylation of arenes on a 0.5 mmol scale. The product was purified by silica gel chromatography to give **8b** (43 mg, 40% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.50 (s, 1H), 7.13 (s, 1H), 6.54 (t, J = 73.6 Hz, 1H), 2.98 (q, J = 7.1 Hz, 2H), 2.42 (s, 3H), 1.22 (t, J = 7.2 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 199.79 (s), 151.25 (t, J = 2.8 Hz), 140.51 (s), 138.47 (s), 125.66 (s), 124.61 (s), 115.90 (s), 115.72 (t, J = 260.5 Hz), 31.95 (s), 21.31 (s), 8.12 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -83.37 (d, J = 73.6 Hz).

1-(difluoromethoxy)-3-iodo-5-methylbenzene (8c)



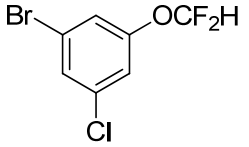
The reaction was performed according to the general procedure for the difluoromethoxylation of arenes on a 0.5 mmol scale. The product was purified by silica gel chromatography to give **8c** (60 mg, 42% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.29 (s, 1H), 6.90 (s, 1H), 6.47 (t, J = 73.5 Hz, 1H), 2.32 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 151.20 (t, J = 2.9 Hz), 141.81 (s), 135.29 (s), 125.71 (s), 119.86 (s), 115.63 (t, J = 260.7 Hz), 93.72 (s), 20.91 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -83.44 (d, J = 73.5 Hz).

1-bromo-3-chloro-5-(difluoromethoxy)benzene (8d)



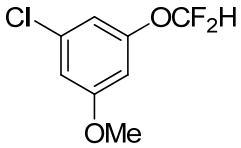
The reaction was performed according to the general procedure for the difluoromethoxylation of arenes on a 0.5 mmol scale. The product was purified by silica gel chromatography to give **8d** as a clear oil (89 mg, 69% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.21 (s, 1H), 7.10 (s, 1H), 6.50 (t, J = 72.6 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 151.57 (t, J = 2.7 Hz), 135.88 (s), 128.63 (s), 122.99 (s), 121.49 (s), 119.17 (s), 115.22 (t, J = 263.2 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -84.55 (d, J = 72.6 Hz).

1-chloro-3-(difluoromethoxy)-5-methoxybenzene (8e)



The reaction was performed according to the general procedure for the difluoromethoxylation of arenes on a 0.5 mmol scale. The product was purified by silica gel chromatography to give **8e** as a clear oil (68 mg, 65% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.74 (d, J = 14.0 Hz, 1H), 6.56 (s, 1H), 6.49 (t, J = 73.4 Hz, 1H), 3.79 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 161.08 (s), 152.32 (t, J = 3.0 Hz), 135.54 (s), 115.59 (t, J = 260.8 Hz), 112.06 (s), 111.51 (s), 104.40 (s), 55.72 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -83.90 (d, J = 73.4 Hz).

5.5 References

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(17) The protons in KOH and ArOH, and HCF_2OTf limit the maximum deuterium incorporation to 93% based on the amount of O-H and O-D bonds in the reaction. This value is in good agreement with our experimental results.

CHAPTER 6

Copper-Mediated Fluorination of Aryl Iodides with (^{t}BuCN)$_2$CuOTf

6.1 Introduction

The unique stability, reactivity and biological properties of fluorinated compounds make them useful in many chemical disciplines. Compounds containing an aryl fluoride moiety are common in pharmaceuticals and agrochemicals because the site containing fluorine is stable toward degradation, and this stability improves biological activity.

The conditions typically used to form aryl-fluorine bonds are harsh; thus the fluorine is usually introduced into the arene ring at the beginning of a synthesis or as part of a building block. Improved methods for late-stage aromatic fluorination would be important for diversification in medicinal chemistry. Moreover, methods for aromatic fluorination with simple fluoride sources would be valuable for the preparation of ^{18}F labeled compounds used in PET imaging. Yet, no general method has been reported for the fluorination of aryl halides.

Instead, aryl fluorides have been prepared by the Balz-Schiemann reaction involving the decomposition of aryldiazonium salts (Figure 6.1).[1] The acidic conditions, the toxicity of the reagents, and the potential for explosions limit the synthetic utility of the Balz-Schiemann reaction.[1] Alternatively, aryl fluorides bearing electron-withdrawing groups have been prepared by the halogen exchange (halex) process in which electron deficient aryl chlorides or nitroarenes undergo nucleophilic aromatic substitution with fluoride at high temperatures (Figure 6.1).[2] However, this reaction occurs only with substrates that are activated toward nucleophilic attack.

Recently, transition metal complexes have been used to prepare fluoroarenes.[3] Palladium-catalyzed fluorination of aryl triflates has been reported (Figure 6.2).[4] Although these findings demonstrated that aryl electrophiles can undergo fluorination in the presence of a transition metal catalyst, the formation of a single product occurred only with substrates bearing electron-withdrawing groups.[4] The triflates for this reaction are formed from phenols, and a reagent for the conversion of phenols to aryl fluorides was reported more recently.[5] Methods for the conversion of aryl stannanes,[6] boronic acids,[7] and silanes[8] to aryl fluorides with silver or palladium and an electrophilic fluoride source also have been published, but the aryl nucleophiles in these reactions are often prepared from the aryl halide, and therefore a method to convert aryl halides to the corresponding aryl fluorides would be more direct than the reactions of main group-aryl reagents.

Here, we report the fluorination of a set of functionally diverse aryl iodides with a simple copper reagent and fluoride source. The success of this reaction with a nucleophilic fluoride reagent rests on the identification of an appropriate ligand for copper. With the proper choice of ligand and source of fluoride, the rapid decomposition of copper(I) fluorides is avoided.

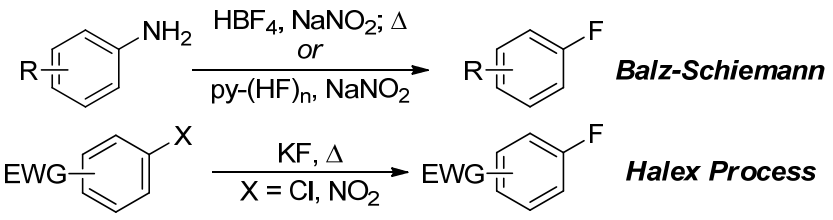


Figure 6.1 Conventional routes to fluoroarenes

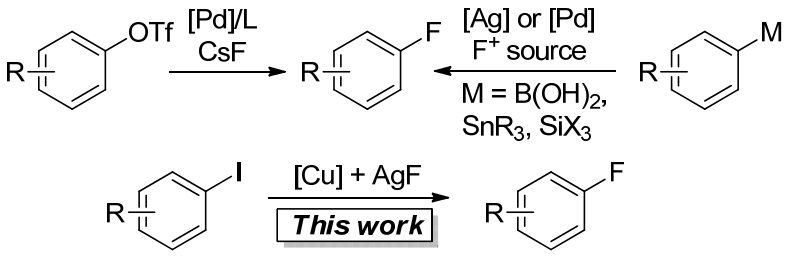


Figure 6.2 Methods for the synthesis of aryl fluorides with transition metals

6.2 Results and Discussion

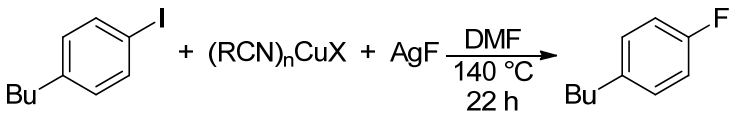
Having recently developed copper-mediated fluoroalkylation[9] of arenes, including reactions through unstable fluoroalkyl intermediates, we studied copper systems for for the fluorination of aryl iodides. The strong metal-fluorine bond causes C-F reductive elimination to be slower than competing side-reactions.[3,10] However, Ribas and coworkers have shown that a macrocyclic aryl-copper(III) complex undergoes C-F bond formation, suggesting that copper mediated fluorination of aryl electrophiles through high-valent copper is feasible.[11] We hypothesized that reductive elimination from an arylcopper(III) fluoride species would be facilitated by a non-coordinating counterion and weakly-donating ligands. Based on this logic, we found that the reaction of 4-butyl-1-iodobenzene with $(MeCN)_4CuBF_4$ and AgF gave detectable amounts of aryl fluoride. No reaction occurred in the absence of copper, demonstrating that a direct reaction between AgF and ArI is not occurring.

$$Cu_2O + HX \xrightarrow[rt]{RCN} (RCN)_4CuX$$

Equation 6.1 Synthesis of nitrile ligated copper complexes with a weakly coordinating counterion

This initial result led us to investigate the effect of nitrile ligands and counterions on the halogen exchange reaction. Cationic copper complexes ligated by nitriles can be prepared in multi-gram quantities within minutes from the reaction of Cu_2O with strong acids in the nitrile solvent (Equation 6.1). By this route, we prepared copper complexes containing different nitriles and counterions (see supporting information). These complexes were tested as mediators of the fluorination of 1-butyl-4-iodobenzene with AgF (Table 6.1). Reaction of this aryl iodide with AgF in the presence of the complexes ligated by ^{t}BuCN occurred in higher yields than those conducted with complexes ligated by MeCN, ^{i}PrCN, and PhCN. Reactions conducted with copper complexes containing SbF_6 and OTf as counterion occurred in higher yields than those conducted with copper complexes containing BF_4 and PF_6. Reactions conducted with ^{t}BuCN-ligated CuOTf were more reproducible than those conducted with ^{t}BuCN-ligated $CuSbF_6$. An excess of copper, relative to AgF, was critical for the reaction to occur in high yields (see supporting information). Reactions conducted with CsF in place of AgF gave the same aryl fluoride product, but in a 34% yield with 30% of the arene side-product.

Table 6.1 Effect of nitrile and counterion on the fluorination of an aryl iodide with AgF[a]



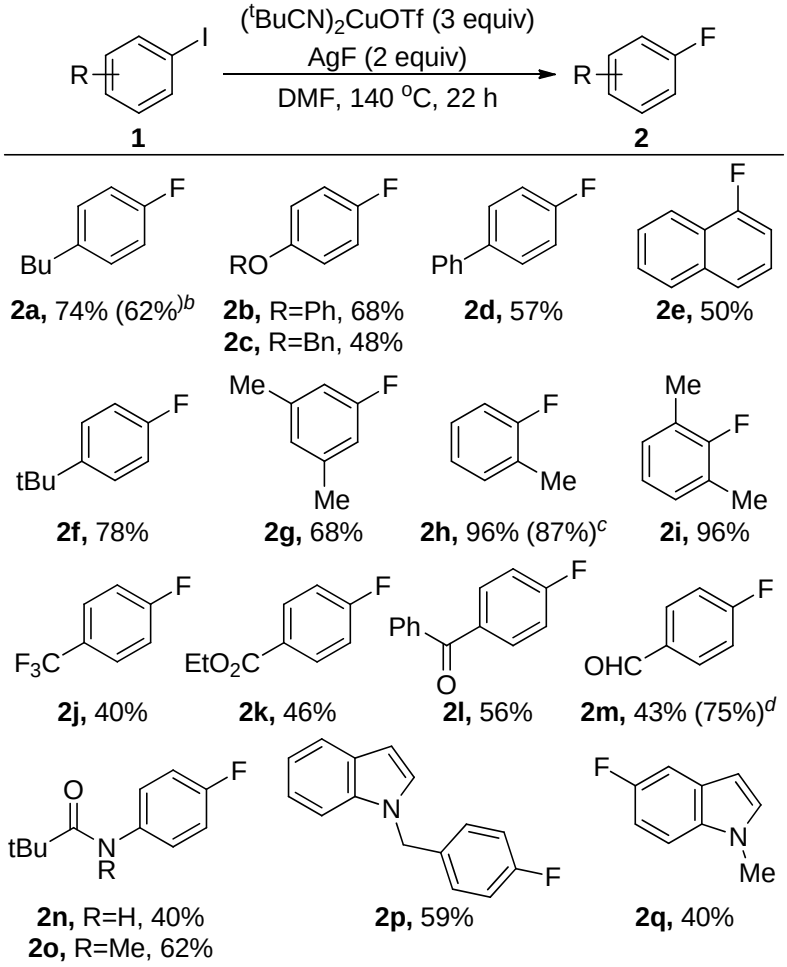
Entry	RCN	X	ArI : [Cu] : AgF	yield (%)
1	MeCN	BF_4	1:1:1	7
2	MeCN	PF_6	1:1:1	16
3	MeCN	SbF_6	1:1:1	11
4	^{i}PrCN	PF_6	1:1:1	3
5	^{i}PrCN	SbF_6	1:1:1	39
6	PhCN	SbF_6	1:1:1	24
7	^{t}BuCN	SbF_6	1:1:1	36
8	^{t}BuCN	OTf	1:1:1	28
9	^{t}BuCN	OTf	1:2:1	65
10	^{t}BuCN	OTf	1:1:2	6
11	^{t}BuCN	OTf	1:3:2	74 (58)[b]

[a]Reactions were performed with 0.1 mmol of 1-butyl-4-iodobenzene in 0.5 mL of DMF for 22 h. The yield was determined by ^{19}F NMR with 1-bromo-4-fluorobenzene as an internal standard added after the reaction. [b]The reaction was conducted at 120 °C for 22 h.

^{t}BuCN-ligated CuOTf was prepared in multi-gram quantites from Cu_2O, triflic acid and ^{t}BuCN (*vide supra*). When the ^{t}BuCN-ligated CuOTf complex is prepared, four nitriles are bound in a tetrahedral geometry. However, placing the solid under vacuum at room temperature resulted in the loss of two nitriles to give a compound with the formula $(^{t}BuCN)_2CuOTf$, as determined by elemental analysis[12] and X-ray crystallography. This complex is stable to oxygen and absorbs moisture from the air only slowly. Thus, this species can be weighed quickly on the benchtop.

Reactions of the combination of $(^{t}BuCN)_2CuOTf$ and AgF with a range of aryl iodides are shown in Table 6.2. These data show that electron-rich and electron-poor iodoarenes react to form the aryl fluorides in good yields, as determined by NMR spectroscopy. Sterically hindered aryl iodides (**1h**, **1i**) reacted to provide nearly quantitative yields of the aryl fluoride. Esters, amides, aldehydes, ketones, and indole heterocycles were tolerated under the reaction conditions. Reactions conducted with AgF as the limiting reagent and an excess of aryl iodide provided high yields of the aryl fluoride **2m**. Conditions for conducting fluorinations with limiting fluoride are important for the use of this process to provide ^{18}F-lableled product for PET imaging. The aryl fluoride **2a** was isolated in good yield on a 0.5 mmol scale. The greatest challenge in the current reactions is the separation of the major aryl fluoride product from the arene side-product. Methods for separation from the arene, and conditions for minimizing formation of the arene are currently being studied.

Table 6.2 Scope of the fluorination reaction with (^{t}BuCN)$_2$CuOTf and AgF

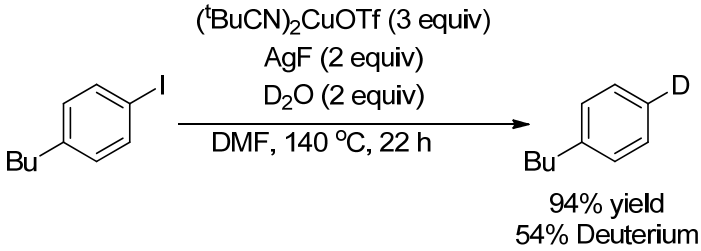


[a]Reactions were performed with 0.1 mmol of aryl iodide to determine yields by ^{19}F NMR spectroscopy with 1-bromo-4-fluorobenzene as an internal standard added after the reaction. ^{19}F NMR chemical shifts were compared with those of the authentic aryl fluorides. [b]Isolated yield from a reaction with 0.5 mmol of ArI. [c]Reactions were conducted with 1 eq ArI, 2 equiv of (^{t}BuCN)$_2$CuOTF and 1 equiv of of AgF. [d]Reactions were conducted with 3 equiv of ArI, 2 equiv of (^{t}BuCN)$_2$CuOTF and 1 equiv of AgF.

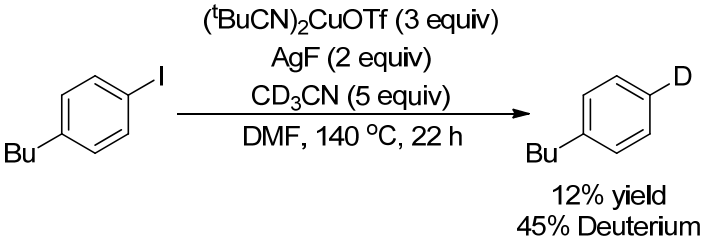
The source of hydride leading to the arene side-product was investigated by deuterium-labeling experiments. The reaction between **1a**, (^{t}BuCN)$_2$CuOTf, and AgF with 2 equivalents of D_2O formed the arene in 94% yield, with 54% incorporation of deuterium into this product (Equation 6.2). These data suggest that adventitious water is one source of the hydro-dehalogenation product, despite the use of anhydrous DMF[13] and oven dried glassware. Indeed, the rigorous exclusion of water is essential for high yields.

The reaction of **1a** under the standard conditions with 5 equivalents of CD_3CN produced 12% of the arene side product with 45% incorporation of deuterium (Equation 6.3). This finding shows that the alpha proton of the nitrile is also a source of hydride in the hydrodehalogenation process. Thus, the higher yields from reactions mediated by complexes of ^{t}BuCN than from those of the other nitriles can be attributed, in part, to the absence of acidic protons on the ligand. The arene side product from reactions run in

DMF-d_7 did not containing deuterium, showing that arene does not form from hydrogen atom abstraction from the solvent.



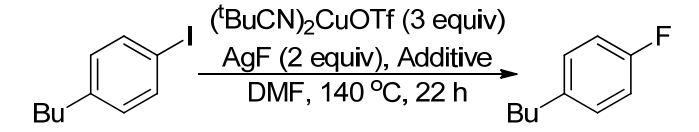
Equation 6.2 Deuterium labeling experiment with added D_2O to determine the source of the arene side-product



Equation 6.3 Deuterium labeling experiment with CD_3CN to determine the source of the arene side-product

Lower yields and conversions were obtained when the reactions were conducted with an excess of AgF, relative to (^{t}BuCN)$_2$CuOTf. To understand the deleterious effect of excess AgF, we conducted reactions under the standard conditions, but with added AgOTf and with added CsF (Table 6.3). Reactions run with 1 or 2 equivalents of added AgOTf proceeded in much lower yields and lower conversions than those without added AgOTF. However, reactions run under the standard conditions with 1 or 2 equivalents of added CsF were not as inhibited as the reactions with added AgOTf. These findings suggest that the lower yields in the presence of excess AgF result from the silver ion, rather than fluoride. The AgF may mediate an unproductive redox reaction with copper to generate a copper(0) or copper(II) species that does not mediate the fluorination of aryl iodides.

Table 6.3 Effect of excess Ag^+ or F^- in the fluorination reaction



Entry	Additive	ArF (%)	ArH (%)	Conversion (%)
1	AgOTf (1 eq)	18	13	60
2	AgOTf (2 eq)	5	22	51
3	CsF (1 eq)	71	23	100
4	CsF (2 eq)	59	25	92

Reactions of aryl halides with Cu(I) species have been proposed in some cases to occur by radical intermediates[14] and in other cases to occur through Cu(III) intermediates formed by oxidative addition of organic halides to a Cu(I) species.[15] To probe the potential intermediacy of aryl radicals during this fluorination reaction, we conducted the process with *o*-(3-butenyl)-iodobenzene (Figure 6.3). The corresponding aryl radical undergoes 5-exo-trig cyclization with a rate constant of 10^8 s^{-1} to form 1-methyl-indane after hydrogen atom abstraction.[16] The reaction of *o*-(3-butenyl)-iodobenzene under the standard conditions gave less than 5% of the cyclized product, with 15% of the aryl fluoride product; the remaining mass balance consisted of 4-phenyl-1-butene. This finding suggests that the formation of aryl fluoride does not occur through an aryl radical intermediate because the rate of cyclization should be much faster than the intermolecular reaction of a Cu(II) intermediate with the fluoride source. However, a fraction of the aryl iodide appears to react through a radical pathway, as deduced by observation of some cyclized product. We suggest that this radical pathway is due to the formation of a copper side product during the reaction.[17]

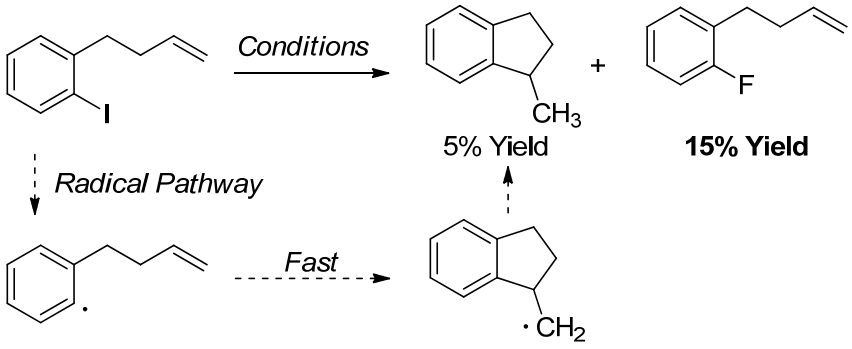
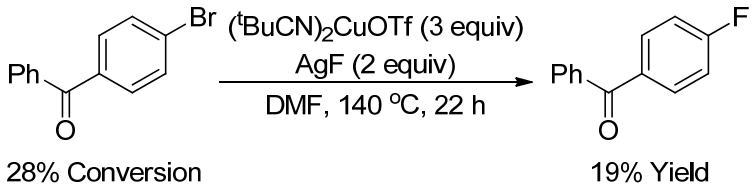


Figure 6.3 Probe for Aryl Radical Intermediates

To gain additional data on whether this fluorination process occurs through an initial electron-transfer reaction, we tested the fluorination of 4-bromobenzophenone. The reduction potential of this bromoarene is higher than that of some of the aryl iodides in Table 6.2.[18] Thus, the formation of an aryl radical by an outer-sphere electron transfer with this aryl bromide should occur at a rate that is comparable to the rate of the reactions of aryl iodides.[18] However the aryl bromide reacted to less than 30% conversion and formed the aryl fluoride in only 19% yield (equation 6.4). A higher conversion of the aryl bromide would be expected if the copper system reacted with the aryl halide by a single-electron transfer pathway.



Equation 6.4 Fluorination of an electron-deficient aryl bromide

Additional data were consistent with the absence of aryl radicals. The reaction of 1-butyl-4-iodobenzene under the standard fluorination conditions, but with 1 equiv of

TEMPO as a free radical trap, yielded the aryl fluoride in 74% yield with 93% conversion of the aryl iodide. In addition, reactions in DMF-d_7 did not lead to incorporation of deuterium into the arene side product. If an aryl radical were formed, hydrogen atom abstraction from the solvent, rather than from adventitious water (*vide supra*), would be expected because DMF is present in higher concentrations and has weaker X-H bonds than those in water. Reactions run in the dark gave identical results to those run in room light.

Nucleophilic attack of fluoride on an aryl iodide coordinated to copper through the π system is an alternative mechanism. However, the observation of arene side-product suggests that protonolysis of an aryl-copper species occurs. Such a protonolysis would not be expected to occur during nucleophilic attack on a π-coordinated arene.[15d,19]

Finally, fluorinations of aryl halides could occur through a benzyne intermediate. Grushin and Marshall reported a fluorination of aryl triflates with tetramethylammonium fluoride, which resulted in constitutional isomers that were consistent with an aryne intermediate.[20] We detect only one isomer in each reaction, and the fluorination of 2,6-dimethyliodobenzene occurs in high yield. These data are inconsistent with reaction through an aryne intermediate.

A copper(I) fluoride species is a potential intermediate in the fluorination of aryl iodides. Unligated copper(I) fluoride is unstable toward rapid and exothermic decomposition to Cu(0) and CuF_2,[21] and only two copper(I) fluorides have been reported. Both of these complex contain strongly bound ancillary ligands.[22] To test the properties of a ^{t}BuCN-ligated copper(I) fluoride, (^{t}BuCN)$_2$CuOTf and AgF were combined in DMF and allowed to react between room temperature and 140 °C. No new species were observed by ^{19}F NMR spectroscopy over the course of 8 h at room temperature, 80, 100, or 140 °C.. The reaction between (^{t}BuCN)$_2$CuOTf and the more reactive anhydrous tetra-*n*-butylammonium fluoride led to rapid decomposition of the nitrile-ligated copper triflate at room temperature without formation of a species that could be detected by ^{19}F NMR spectroscopy. The higher yields obtained with AgF than with other fluorides might be due, at least in part, to the low solubility of this fluoride source. The slow background reaction with (^{t}BuCN)$_2$CuOTf leads to a lower concentration of CuF and thus a lower rate of decomposition.

A proposed reaction mechanism that is consistent with our data and known chemistry of copper is shown in Figure 6.4. In this pathway, reversible oxidative addition of an aryl iodide to a nitrile-ligated CuOTf forms an aryl copper(III) iodide containing a coordinated or loosely bound triflate. The rate and equilibrium for oxidative addition is likely faster to copper complexes containing the more donating ^{t}BuCN than to those containing other nitriles, and this expectation is consistent with the higher yields from reactions conducted with this ligand than from those conducted with other nitriles. The electrophilicity of a Cu(III) triflate might favor transmetallation of AgF with this species, and we propose this reaction occurs to form an aryl copper(III) fluoride that undergoes C-F bond formation.

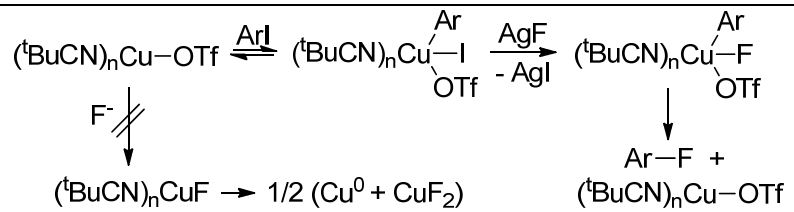


Figure 6.4 Proposed Mechanism for the Fluorination of aryl iodies with $(^tBuCN)_2CuOTf$ and AgF.

6.3 Conclusions

In summary, we have developed an operationally simple fluorination of aryl iodides with readily available reagents. This reaction tolerates ether, amide, ester, ketone, and aldehyde functional groups and occurs with some heterocyclic systems. Moreover, it occurs in high yield with sterically hindered aryl iodides. We propose that this reaction occurs by oxidative addition to form a Cu(III) intermediate and C-F reductive elimination from an aryl copper(III) fluoride. Work is ongoing to extend the work described here to the synthesis of ^{18}F labeled compounds for PET imaging.

6.4 Experimental

All manipulations were conducted under an inert atmosphere with a nitrogen-filled glovebox unless otherwise noted. All reactions were conducted in oven-dried 4-mL vials fitted with a Teflon-lined screw cap under an atmosphere of nitrogen unless otherwise noted.

Silver fluoride (>99%) was purchased from Acros and used as received. N,N-Dimethylformamide (DMF), 99.8%, Extra Dry over Molecular Sieves, was purchased from Acros and used without further purification. Unless otherwise noted, all other reagents were purchased from commercial suppliers and used as received. N-(4-iodophenyl)pivalamide (**1n**), N-(4-iodophenyl)-N-methylpivalamide (**1o**) and 5-iodo-1-methyl-1H-indole (**1q**) were prepared according to literature procedures.

NMR spectra were acquired on 400 MHz, 500 MHz, or 600 MHz Bruker instruments at the University of California. NMR spectra were processed with MestReNova 5.0 (Mestrelab Research SL). Chemical shifts are reported in ppm and referenced to residual solvent peaks ($CHCl_3$ in $CDCl_3$: 7.26 ppm for ^1H and 77.0 ppm for ^{13}C) or to an external standard (1% $CFCl_3$ in $CDCl_3$: 0 ppm for ^{19}F). Coupling constants are reported in hertz.

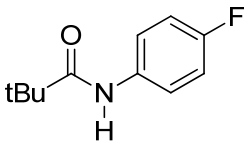
All GC-MS analyses were conducted with an Agilent 6890N GC equipped with an HP-5 column (25 m x 0.20 mm ID x 0.33 μm film) and an Agilent 5973 Mass Selective Detector. The temperature for each run was held at 50 °C for 2 min, ramped from 50 °C to 300 °C at 40 °C/min, and held at 300 °C for 5 min.

Preparation of $(^tBuCN)_2CuOTf$

A similar procedure was used for the preparation of all nitrile ligated copper complexes reported in the manuscript. This procedure was carried out in a fumehood without any exclusion of moisture or oxygen until the product was isolated. 1.8 g Cu_2O (12.6 mmol) and 20 mL of ^tBuCN were stirred vigorously in a 50 mL round bottom flask

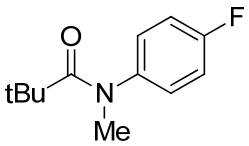
at room temperature. Trifluoromethanesulfonic acid (1.5 mL, 17 mmol) was added over 1 minute. The exothermic reaction was stirred for 5 minutes and quickly filtered through celite and rinsed with a small amount of diethyl ether. The clear, light orange filtrate was poured into 100 mL of diethyl ether and cooled to -20 °C. White needles formed within 15 minutes and were collected on a fritted funnel under a blanket of nitrogen. The white needles were placed under vacuum (100 mtorr) at room temperature overnight. 4.3 grams (11.3 mmol) of white needles were obtained and were stored in an inert atmosphere.
Elemental Analysis Calc'd: C: 34.87; H: 4.79; N: 7.39. Found: C: 34.96; H: 4.88; N: 7.53.

Independent Synthesis of Authentic N-(4-fluorophenyl)pivalamide (2n)



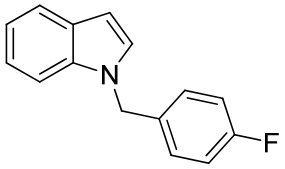
4-Fluoroaniline (947 µL, 10.0 mmol), 4-dimethylaminopyridine (DMAP, 12 mg, 0.1 mmol), and pyridine (1.6 mL, 20 mmol) were dissolved in 20 mL of CH_2Cl_2 and cooled to 0 °C. Pivaloyl chloride (1.35 mL, 11.0 mmol) was added dropwise, and the resulting solution was allowed to warm to room temperature and stirred a total of 12 h. The solution was poured into a separatory funnel and washed with 1 x 20 mL of 1 M HCl and 1 x 20 mL of saturated $NaHCO_3$. The organic layer was dried with $MgSO_4$ and concentrated to afford a white solid (1.80 g, 9.2 mmol, 92% yield).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 (dd, J = 7.7, 5.0 Hz, 2H), 7.30 (s, 1H), 7.01 (t, J = 8.4 Hz, 2H), 1.31 (s, 9H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 176.52 (s), 159.33 (d, J = 243.4 Hz), 134.00 (d, J = 2.7 Hz), 121.86 (d, J = 7.9 Hz), 115.53 (d, J = 22.4 Hz), 39.51 (s), 27.60 (s).
^{19}F NMR (376 MHz, $CDCl_3$) δ -122.20 – -122.38 (m).

Independent Synthesis of Authentic N-(4-fluorophenyl)-N-methylpivalamide (2o)



N-(4-Fluorophenyl)pivalamide (586 mg, 3.0 mmol) was dissolved in 3 mL of anhydrous THF, and the resulting solution was added dropwise to a suspension of 60% NaH (143 mg, 3.6 mmol) in 6 mL of anhydrous THF. The resulting solution was stirred at room temperature for 30 minutes, and methyl iodide (280 µL, 4.5 mmol) was added dropwise. After stirring for 2 h, water was added, and the product was extracted with ether. Drying with $MgSO_4$ and removal of the solvent gave **2o** as a clear oil (581 mg, 2.8 mmol, 93% yield).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 – 7.16 (m, 2H), 7.07 (t, J = 7.9 Hz, 2H), 3.19 (s, 3H), 1.04 (s, 9H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 178.10 (s), 161.70 (d, J = 248.1 Hz), 141.33 (d, J = 2.5 Hz), 130.40 (d, J = 8.5 Hz), 116.09 (d, J = 22.6 Hz), 41.39 (s), 40.74 (s), 29.45 (s).
^{19}F NMR (376 MHz, $CDCl_3$) δ -116.28 – -116.50 (m).

Independent Synthesis of Authentic 1-(4-fluorobenzyl)-1H-indole (2p)

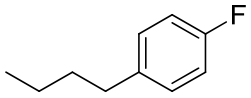


Indole (352 mg, 3.0 mmol) and potassium hydroxide (202 mg, 3.6 mmol) were suspended in 3 mL of anhydrous DMF. 4-Fluorobenzyl bromide (374 µL, 3.0 mmol) was dissolved in 2 mL of anhydrous DMF, and the resulting solution was added dropwise. After stirring for 12 h, water was added, and the product was extracted with ether. Drying with $MgSO_4$ and removal of the solvent gave crude **2p**. The product was purified by silica gel chromatography with 9:1 hexanes : ethyl acetate (R_f=0.64) to afford **2p** as a clear oil (500 mg, 2.2 mmol, 74% yield).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66 (d, J = 7.8 Hz, 1H), 7.27 (d, J = 6.6 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.12 (t, J = 7.4 Hz, 2H), 7.10 – 7.05 (m, 2H), 6.98 (t, J = 8.5 Hz, 2H), 6.56 (d, J = 3.0 Hz, 1H), 5.30 (s, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 162.22 (d, J = 245.9 Hz), 136.17 (s), 133.25 (d, J = 3.2 Hz), 128.77 (s), 128.41 (d, J = 8.1 Hz), 128.03 (s), 121.77 (s), 121.04 (s), 119.62 (s), 115.65 (d, J = 21.6 Hz), 109.56 (s), 101.88 (s), 49.41 (s).
^{19}F NMR (376 MHz, $CDCl_3$) δ -117.64 – -117.83 (m).

General Procedure for the Fluorination of Aryl Iodides

To an oven-dried 4 mL vial was added AgF (25 mg, 0.2 mmol, 2.0 equiv), (^{t}BuCN)$_2$CuOTf (114 mg, 0.3 mmol, 3.0 equiv) and DMF (0.5 mL). Aryl iodide (0.1 mmol, 1.0 equiv) is added (solid aryl iodides were weighed in the vial prior to adding DMF, and liquid aryl iodides were added neat by syringe after the addition of DMF). The vial is sealed with a Teflon-lined cap and heated at 140 ^{o}C with vigorous stirring for 22 h. The solution is allowed to cool to room temperature and 11.0 µL (0.1 mmol, 1.0 equiv) of 1-bromo-4-fluorobenzene is added as an internal standard. The crude reaction mixture is analyzed by ^{19}F NMR spectroscopy to determine the yield of aryl fluoride. ^{19}F NMR chemical shifts were compared to authentic samples of the aryl fluoride product to confirm the identity of the product. The identities of the products were further confirmed by GC/MS.

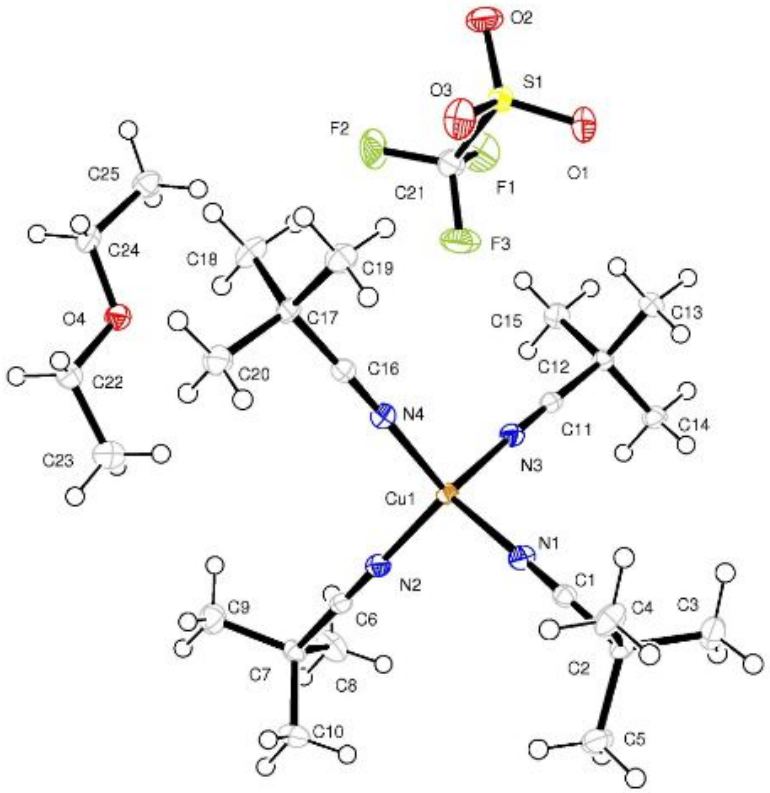
Synthesis of 1-butyl-4-fluorobenzene (2a)



To an oven-dried 20 mL vial was added AgF (127 mg, 1.0 mmol, 2.0 equiv), (^{t}BuCN)$_2$CuOTf (568 mg, 1.5 mmol, 3.0 equiv) and DMF (2.5 mL). 1-butyl-4-iodobenzene (89 µL, 1.0 mmol, 1.0 equiv) was added, and the reaction was heated at 140 ^{o}C for 22 h. The reaction was cooled, diluted with 15 mL of ether and filtered through Celite. The organic layer was washed with water (5 x 15 mL) and brine (1 x 15 mL). The organic layer was dried with $MgSO_4$, concentrated, and purified by silica gel chromatography eluting with hexanes to afford a clear oil (47 mg, 0.31 mmol, 62% yield).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 – 7.08 (m, 2H), 6.99 – 6.90 (m, 2H), 2.61 – 2.54 (m, 2H), 1.62 – 1.49 (m, 2H), 1.34 (dq, J = 14.6, 7.3 Hz, 2H), 0.92 (t, J = 7.3 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 161.13 (d, J = 242.8 Hz), 138.43 (d, J = 3.2 Hz), 129.63 (d, J = 7.7 Hz), 114.88 (d, J = 21.0 Hz), 34.81 (s), 33.75 (s), 22.23 (s), 13.90 (s).
^{19}F NMR (376 MHz, $CDCl_3$) δ -120.52 – -120.61 (m).

X-ray Crystallographic Analysis of (^{t}BuCN)$_4$CuOTf

A colorless needle 0.15 x 0.06 x 0.04 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 40 mm and exposure time was 10 seconds per frame using a scan width of 0.5°. 5926 reflections were found to be symmetry independent, with an R_{int} of 0.0310. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P2(1)/n (No. 14). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SIR-2011) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-97). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-97.



Empirical formula	C25 H46 Cu F3 N4 O4 S	
Formula weight	619.26	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 12.965(4) Å	□= 90°.
	b = 11.375(3) Å	□= 91.863(14)°.
	c = 22.117(7) Å	□ = 90°.
Volume	3259.8(17) Å^3	
Z	4	
Density (calculated)	1.262 Mg/m^3	
Absorption coefficient	0.784 mm^{-1}	
F(000)	1312	
Crystal size	0.15 x 0.06 x 0.04 mm^3	

Crystal color/habit	colorless needle
Theta range for data collection	1.80 to 25.47°.
Index ranges	-13<=h<=15, -13<=k<=13, -26<=l<=26
Reflections collected	31958
Independent reflections	5926 [R(int) = 0.0310]
Completeness to theta = 25.00°	99.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9693 and 0.8914
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5926 / 0 / 357
Goodness-of-fit on F^2	1.043
Final R indices [I>2sigma(I)]	R1 = 0.0257, wR2 = 0.0632
R indices (all data)	R1 = 0.0335, wR2 = 0.0671
Largest diff. peak and hole	0.305 and -0.350 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	7746(1)	4042(1)	6351(1)	15(1)
C(2)	7869(1)	4759(1)	5796(1)	16(1)
C(3)	7092(1)	4336(2)	5308(1)	24(1)
C(4)	7680(1)	6054(1)	5958(1)	23(1)
C(5)	8979(1)	4604(2)	5588(1)	24(1)
C(6)	9513(1)	1060(1)	7843(1)	15(1)
C(7)	10421(1)	303(1)	7985(1)	16(1)
C(8)	10133(1)	-968(2)	7816(1)	28(1)
C(9)	10691(1)	410(2)	8667(1)	28(1)
C(10)	11324(1)	724(2)	7608(1)	25(1)
C(11)	5713(1)	744(1)	7324(1)	15(1)
C(12)	4802(1)	-13(1)	7184(1)	15(1)
C(13)	3880(1)	808(1)	7072(1)	19(1)
C(14)	5015(1)	-732(2)	6610(1)	20(1)
C(15)	4611(1)	-826(1)	7724(1)	20(1)
C(16)	7005(1)	4298(1)	8597(1)	15(1)
C(17)	6795(1)	5083(1)	9117(1)	17(1)
C(18)	6446(1)	4308(2)	9646(1)	25(1)
C(19)	5941(1)	5952(2)	8932(1)	24(1)
C(20)	7797(1)	5730(2)	9294(1)	26(1)
C(21)	3934(1)	2210(2)	8908(1)	23(1)
C(22)	9044(1)	2824(2)	10450(1)	26(1)
C(23)	9607(2)	2516(2)	9882(1)	35(1)
C(24)	7443(1)	2562(1)	10927(1)	21(1)
C(25)	6406(1)	1983(2)	10839(1)	24(1)
N(1)	7656(1)	3486(1)	6781(1)	18(1)
N(2)	8806(1)	1634(1)	7731(1)	17(1)
N(3)	6391(1)	1370(1)	7417(1)	17(1)
N(4)	7184(1)	3670(1)	8206(1)	16(1)
O(1)	2650(1)	3181(1)	8153(1)	26(1)

O(2)	2234(1)	3139(1)	9222(1)	33(1)
O(3)	3595(1)	4424(1)	8873(1)	30(1)
O(4)	8072(1)	2243(1)	10434(1)	21(1)
F(1)	3504(1)	1144(1)	8846(1)	38(1)
F(2)	4353(1)	2265(1)	9470(1)	37(1)
F(3)	4706(1)	2259(1)	8521(1)	38(1)
S(1)	2991(1)	3378(1)	8773(1)	18(1)
Cu(1)	7521(1)	2551(1)	7542(1)	13(1)

Table 3. Bond lengths [Å] and angles [°].

C(1)-N(1)	1.151(2)
C(1)-C(2)	1.487(2)
C(2)-C(3)	1.529(2)
C(2)-C(5)	1.535(2)
C(2)-C(4)	1.538(2)
C(3)-H(3A)	0.9800
C(3)-H(3B)	0.9800
C(3)-H(3C)	0.9800
C(4)-H(4A)	0.9800
C(4)-H(4B)	0.9800
C(4)-H(4C)	0.9800
C(5)-H(5A)	0.9800
C(5)-H(5B)	0.9800
C(5)-H(5C)	0.9800
C(6)-N(2)	1.146(2)
C(6)-C(7)	1.484(2)
C(7)-C(10)	1.536(2)
C(7)-C(8)	1.537(2)
C(7)-C(9)	1.541(2)
C(8)-H(8A)	0.9800
C(8)-H(8B)	0.9800
C(8)-H(8C)	0.9800
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800
C(10)-H(10A)	0.9800
C(10)-H(10B)	0.9800
C(10)-H(10C)	0.9800
C(11)-N(3)	1.145(2)
C(11)-C(12)	1.485(2)
C(12)-C(13)	1.531(2)
C(12)-C(15)	1.536(2)
C(12)-C(14)	1.543(2)

C(13)-H(13A)	0.9800
C(13)-H(13B)	0.9800
C(13)-H(13C)	0.9800
C(14)-H(14A)	0.9800
C(14)-H(14B)	0.9800
C(14)-H(14C)	0.9800
C(15)-H(15A)	0.9800
C(15)-H(15B)	0.9800
C(15)-H(15C)	0.9800
C(16)-N(4)	1.151(2)
C(16)-C(17)	1.488(2)
C(17)-C(19)	1.530(2)
C(17)-C(20)	1.533(2)
C(17)-C(18)	1.544(2)
C(18)-H(18A)	0.9800
C(18)-H(18B)	0.9800
C(18)-H(18C)	0.9800
C(19)-H(19A)	0.9800
C(19)-H(19B)	0.9800
C(19)-H(19C)	0.9800
C(20)-H(20A)	0.9800
C(20)-H(20B)	0.9800
C(20)-H(20C)	0.9800
C(21)-F(1)	1.339(2)
C(21)-F(3)	1.339(2)
C(21)-F(2)	1.342(2)
C(21)-S(1)	1.8237(18)
C(22)-O(4)	1.422(2)
C(22)-C(23)	1.514(3)
C(22)-H(22A)	0.9900
C(22)-H(22B)	0.9900
C(23)-H(23A)	0.9800
C(23)-H(23B)	0.9800
C(23)-H(23C)	0.9800
C(24)-O(4)	1.429(2)

C(24)-C(25)	1.505(2)
C(24)-H(24A)	0.9900
C(24)-H(24B)	0.9900
C(25)-H(25A)	0.9800
C(25)-H(25B)	0.9800
C(25)-H(25C)	0.9800
N(1)-Cu(1)	2.0037(15)
N(2)-Cu(1)	1.9981(14)
N(3)-Cu(1)	2.0006(14)
N(4)-Cu(1)	2.0023(14)
O(1)-S(1)	1.4440(13)
O(2)-S(1)	1.4442(13)
O(3)-S(1)	1.4372(13)

N(1)-C(1)-C(2)	179.65(17)
C(1)-C(2)-C(3)	108.90(13)
C(1)-C(2)-C(5)	108.10(13)
C(3)-C(2)-C(5)	110.76(14)
C(1)-C(2)-C(4)	108.08(13)
C(3)-C(2)-C(4)	111.13(14)
C(5)-C(2)-C(4)	109.76(14)
C(2)-C(3)-H(3A)	109.5
C(2)-C(3)-H(3B)	109.5
H(3A)-C(3)-H(3B)	109.5
C(2)-C(3)-H(3C)	109.5
H(3A)-C(3)-H(3C)	109.5
H(3B)-C(3)-H(3C)	109.5
C(2)-C(4)-H(4A)	109.5
C(2)-C(4)-H(4B)	109.5
H(4A)-C(4)-H(4B)	109.5
C(2)-C(4)-H(4C)	109.5
H(4A)-C(4)-H(4C)	109.5
H(4B)-C(4)-H(4C)	109.5
C(2)-C(5)-H(5A)	109.5
C(2)-C(5)-H(5B)	109.5

H(5A)-C(5)-H(5B)	109.5
C(2)-C(5)-H(5C)	109.5
H(5A)-C(5)-H(5C)	109.5
H(5B)-C(5)-H(5C)	109.5
N(2)-C(6)-C(7)	179.29(17)
C(6)-C(7)-C(10)	108.54(13)
C(6)-C(7)-C(8)	108.05(13)
C(10)-C(7)-C(8)	110.13(14)
C(6)-C(7)-C(9)	108.41(13)
C(10)-C(7)-C(9)	110.65(14)
C(8)-C(7)-C(9)	110.99(15)
C(7)-C(8)-H(8A)	109.5
C(7)-C(8)-H(8B)	109.5
H(8A)-C(8)-H(8B)	109.5
C(7)-C(8)-H(8C)	109.5
H(8A)-C(8)-H(8C)	109.5
H(8B)-C(8)-H(8C)	109.5
C(7)-C(9)-H(9A)	109.5
C(7)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(7)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
C(7)-C(10)-H(10A)	109.5
C(7)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	109.5
C(7)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5
N(3)-C(11)-C(12)	176.77(16)
C(11)-C(12)-C(13)	106.93(13)
C(11)-C(12)-C(15)	109.60(13)
C(13)-C(12)-C(15)	110.37(13)
C(11)-C(12)-C(14)	108.42(13)
C(13)-C(12)-C(14)	110.43(13)

C(15)-C(12)-C(14)	110.99(13)
C(12)-C(13)-H(13A)	109.5
C(12)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5
C(12)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5
C(12)-C(14)-H(14A)	109.5
C(12)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	109.5
C(12)-C(14)-H(14C)	109.5
H(14A)-C(14)-H(14C)	109.5
H(14B)-C(14)-H(14C)	109.5
C(12)-C(15)-H(15A)	109.5
C(12)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15B)	109.5
C(12)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15C)	109.5
H(15B)-C(15)-H(15C)	109.5
N(4)-C(16)-C(17)	178.03(17)
C(16)-C(17)-C(19)	109.23(14)
C(16)-C(17)-C(20)	108.14(13)
C(19)-C(17)-C(20)	110.99(14)
C(16)-C(17)-C(18)	107.96(13)
C(19)-C(17)-C(18)	110.16(14)
C(20)-C(17)-C(18)	110.28(14)
C(17)-C(18)-H(18A)	109.5
C(17)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
C(17)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5
C(17)-C(19)-H(19A)	109.5
C(17)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5

C(17)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5
C(17)-C(20)-H(20A)	109.5
C(17)-C(20)-H(20B)	109.5
H(20A)-C(20)-H(20B)	109.5
C(17)-C(20)-H(20C)	109.5
H(20A)-C(20)-H(20C)	109.5
H(20B)-C(20)-H(20C)	109.5
F(1)-C(21)-F(3)	106.88(14)
F(1)-C(21)-F(2)	106.97(14)
F(3)-C(21)-F(2)	107.55(14)
F(1)-C(21)-S(1)	111.61(12)
F(3)-C(21)-S(1)	112.05(12)
F(2)-C(21)-S(1)	111.48(12)
O(4)-C(22)-C(23)	108.77(14)
O(4)-C(22)-H(22A)	109.9
C(23)-C(22)-H(22A)	109.9
O(4)-C(22)-H(22B)	109.9
C(23)-C(22)-H(22B)	109.9
H(22A)-C(22)-H(22B)	108.3
C(22)-C(23)-H(23A)	109.5
C(22)-C(23)-H(23B)	109.5
H(23A)-C(23)-H(23B)	109.5
C(22)-C(23)-H(23C)	109.5
H(23A)-C(23)-H(23C)	109.5
H(23B)-C(23)-H(23C)	109.5
O(4)-C(24)-C(25)	108.68(13)
O(4)-C(24)-H(24A)	110.0
C(25)-C(24)-H(24A)	110.0
O(4)-C(24)-H(24B)	110.0
C(25)-C(24)-H(24B)	110.0
H(24A)-C(24)-H(24B)	108.3
C(24)-C(25)-H(25A)	109.5
C(24)-C(25)-H(25B)	109.5

H(25A)-C(25)-H(25B)	109.5
C(24)-C(25)-H(25C)	109.5
H(25A)-C(25)-H(25C)	109.5
H(25B)-C(25)-H(25C)	109.5
C(1)-N(1)-Cu(1)	178.48(13)
C(6)-N(2)-Cu(1)	176.60(13)
C(11)-N(3)-Cu(1)	175.75(13)
C(16)-N(4)-Cu(1)	178.37(13)
C(22)-O(4)-C(24)	112.92(13)
O(3)-S(1)-O(1)	115.02(7)
O(3)-S(1)-O(2)	115.42(8)
O(1)-S(1)-O(2)	115.39(8)
O(3)-S(1)-C(21)	102.66(8)
O(1)-S(1)-C(21)	103.03(8)
O(2)-S(1)-C(21)	102.54(8)
N(2)-Cu(1)-N(3)	106.28(6)
N(2)-Cu(1)-N(4)	112.22(6)
N(3)-Cu(1)-N(4)	110.56(6)
N(2)-Cu(1)-N(1)	110.98(5)
N(3)-Cu(1)-N(1)	108.95(6)
N(4)-Cu(1)-N(1)	107.82(6)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for hartwig07. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	13(1)	15(1)	18(1)	-3(1)	1(1)	1(1)
C(2)	19(1)	15(1)	13(1)	2(1)	2(1)	1(1)
C(3)	30(1)	26(1)	17(1)	2(1)	-3(1)	-4(1)
C(4)	36(1)	17(1)	17(1)	2(1)	4(1)	3(1)
C(5)	23(1)	29(1)	20(1)	5(1)	7(1)	4(1)
C(6)	17(1)	15(1)	14(1)	-2(1)	4(1)	-4(1)
C(7)	14(1)	15(1)	20(1)	-2(1)	0(1)	2(1)
C(8)	22(1)	18(1)	44(1)	-4(1)	-4(1)	3(1)
C(9)	27(1)	33(1)	24(1)	0(1)	-3(1)	8(1)
C(10)	17(1)	27(1)	31(1)	-1(1)	6(1)	0(1)
C(11)	17(1)	15(1)	13(1)	1(1)	3(1)	3(1)
C(12)	13(1)	15(1)	16(1)	-1(1)	1(1)	-2(1)
C(13)	16(1)	20(1)	21(1)	0(1)	0(1)	-1(1)
C(14)	18(1)	22(1)	19(1)	-4(1)	2(1)	-2(1)
C(15)	21(1)	18(1)	21(1)	2(1)	2(1)	-4(1)
C(16)	15(1)	14(1)	17(1)	4(1)	1(1)	-1(1)
C(17)	21(1)	15(1)	15(1)	-3(1)	2(1)	0(1)
C(18)	37(1)	22(1)	16(1)	1(1)	6(1)	0(1)
C(19)	28(1)	19(1)	24(1)	-3(1)	4(1)	4(1)
C(20)	25(1)	27(1)	25(1)	-9(1)	2(1)	-4(1)
C(21)	23(1)	25(1)	22(1)	4(1)	2(1)	1(1)
C(22)	21(1)	32(1)	26(1)	-3(1)	0(1)	-6(1)
C(23)	26(1)	48(1)	30(1)	-5(1)	6(1)	-4(1)
C(24)	26(1)	21(1)	17(1)	-2(1)	-1(1)	2(1)
C(25)	27(1)	24(1)	21(1)	1(1)	4(1)	-2(1)
N(1)	19(1)	17(1)	17(1)	1(1)	3(1)	1(1)
N(2)	17(1)	18(1)	17(1)	0(1)	3(1)	-1(1)
N(3)	16(1)	17(1)	17(1)	1(1)	2(1)	0(1)
N(4)	18(1)	15(1)	16(1)	1(1)	1(1)	0(1)
O(1)	29(1)	26(1)	22(1)	0(1)	-8(1)	2(1)

O(2)	28(1)	42(1)	30(1)	3(1)	12(1)	5(1)
O(3)	41(1)	18(1)	30(1)	-2(1)	-6(1)	-6(1)
O(4)	20(1)	23(1)	21(1)	-5(1)	2(1)	-2(1)
F(1)	48(1)	16(1)	51(1)	3(1)	2(1)	2(1)
F(2)	38(1)	47(1)	27(1)	13(1)	-11(1)	3(1)
F(3)	27(1)	49(1)	39(1)	10(1)	13(1)	14(1)
S(1)	19(1)	16(1)	17(1)	-1(1)	0(1)	2(1)
Cu(1)	14(1)	13(1)	13(1)	0(1)	1(1)	0(1)

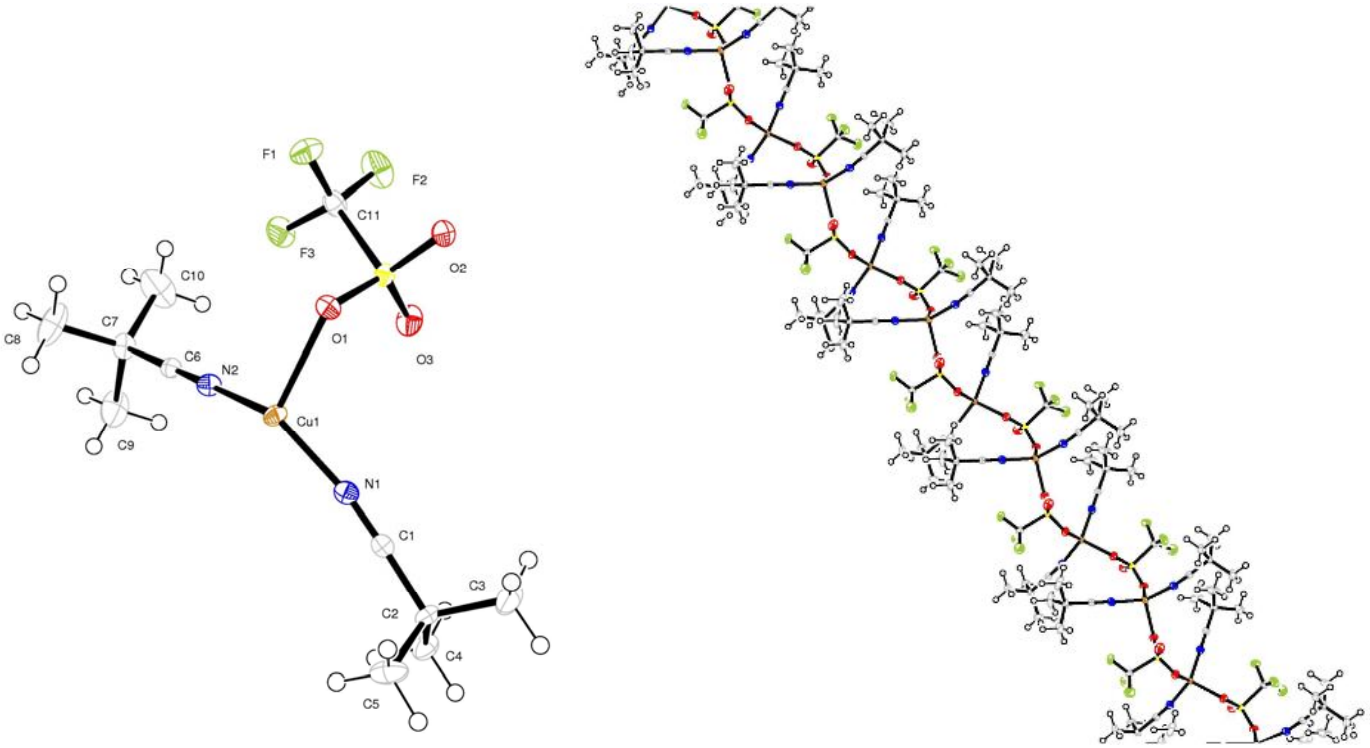
Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3).

	x	y	z	U(eq)
H(3A)	7255	3525	5195	37
H(3B)	7131	4844	4951	37
H(3C)	6394	4369	5464	37
H(4A)	6982	6142	6108	35
H(4B)	7754	6544	5598	35
H(4C)	8185	6301	6273	35
H(5A)	9463	4882	5906	36
H(5B)	9074	5061	5218	36
H(5C)	9108	3771	5507	36
H(8A)	9556	-1227	8058	42
H(8B)	10729	-1482	7896	42
H(8C)	9932	-1006	7385	42
H(9A)	10868	1227	8764	42
H(9B)	11281	-99	8770	42
H(9C)	10096	169	8899	42
H(10A)	11123	696	7178	37
H(10B)	11922	211	7685	37
H(10C)	11505	1532	7722	37
H(13A)	3753	1255	7441	29
H(13B)	3268	342	6961	29
H(13C)	4030	1353	6743	29
H(14A)	5113	-195	6270	29
H(14B)	4427	-1250	6517	29
H(14C)	5639	-1206	6678	29
H(15A)	5211	-1338	7794	30
H(15B)	3998	-1308	7636	30
H(15C)	4502	-351	8085	30
H(18A)	5808	3896	9526	37
H(18B)	6323	4805	9998	37
H(18C)	6986	3733	9749	37

H(19A)	6161	6419	8586	35
H(19B)	5805	6475	9272	35
H(19C)	5311	5518	8817	35
H(20A)	8337	5156	9399	38
H(20B)	7680	6238	9644	38
H(20C)	8014	6211	8954	38
H(22A)	9457	2572	10812	32
H(22B)	8942	3685	10474	32
H(23A)	9700	1662	9861	52
H(23B)	10283	2902	9892	52
H(23C)	9202	2785	9527	52
H(24A)	7360	3426	10941	25
H(24B)	7774	2301	11314	25
H(25A)	6086	2238	10454	36
H(25B)	5962	2206	11171	36
H(25C)	6492	1127	10836	36

X-ray Crystallographic Analysis of (^{t}BuCN)$_2$CuOTf

A colorless needle 0.06 x 0.05 x 0.03 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 40 mm and exposure time was 5 seconds per frame using a scan width of 0.5°. Data collection was 100.0% complete to 25.00° in θ. A total of 13340 reflections were collected covering the indices, -11<=*h*<=11, -12<=*k*<=10, -21<=*l*<=17. 2993 reflections were found to be symmetry independent, with an R_{int} of 0.0300. Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be P2(1)2(1)2(1) (No. 19). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SIR-2011) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-97). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-97.



Empirical formula	C11 H18 Cu F3 N2 O3 S
Formula weight	378.87

Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 9.2021(3) Å	α= 90°.
	b = 10.0062(4) Å	β= 90°.
	c = 17.8241(6) Å	γ = 90°.
Volume	1641.21(10) $Å^3$	
Z	4	
Density (calculated)	1.533 Mg/m^3	
Absorption coefficient	1.497 mm^{-1}	
F(000)	776	
Crystal size	0.06 x 0.05 x 0.03 mm^3	
Crystal color/habit	colorless needle	
Theta range for data collection	2.29 to 25.37°.	
Index ranges	-11<=h<=11, -12<=k<=10, -21<=l<=17	
Reflections collected	13340	
Independent reflections	2993 [R(int) = 0.0300]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9565 and 0.9156	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2993 / 0 / 196	
Goodness-of-fit on F^2	1.025	
Final R indices [I>2sigma(I)]	R1 = 0.0227, wR2 = 0.0516	
R indices (all data)	R1 = 0.0250, wR2 = 0.0526	
Absolute structure parameter	-0.011(10)	
Largest diff. peak and hole	0.230 and -0.210 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	9232(2)	6179(2)	7378(1)	16(1)
C(2)	10772(2)	6150(2)	7135(1)	18(1)
C(3)	11234(3)	4706(2)	6998(2)	31(1)
C(4)	11695(2)	6780(3)	7757(1)	24(1)
C(5)	10878(3)	6968(3)	6411(1)	31(1)
C(6)	4588(2)	8273(2)	9068(1)	15(1)
C(7)	3866(3)	9074(2)	9658(1)	20(1)
C(8)	2576(3)	9804(3)	9308(2)	41(1)
C(9)	4954(3)	10106(3)	9947(2)	40(1)
C(10)	3405(4)	8149(3)	10289(2)	52(1)
C(11)	3585(3)	3932(2)	9077(1)	21(1)
N(1)	8046(2)	6246(2)	7562(1)	18(1)
N(2)	5154(2)	7650(2)	8619(1)	18(1)
O(1)	4880(2)	4714(1)	7870(1)	18(1)
O(2)	4975(2)	2351(2)	8195(1)	19(1)
O(3)	6365(2)	3967(2)	8922(1)	27(1)
F(1)	2328(1)	3723(2)	8725(1)	31(1)
F(2)	3647(2)	3079(2)	9649(1)	37(1)
F(3)	3551(2)	5163(1)	9362(1)	32(1)
S(1)	5136(1)	3721(1)	8448(1)	16(1)
Cu(1)	6101(1)	6623(1)	7861(1)	16(1)

Table 3. Bond lengths [Å] and angles [°]

C(1)-N(1)	1.142(3)
C(1)-C(2)	1.482(3)
C(2)-C(3)	1.526(3)
C(2)-C(5)	1.531(3)
C(2)-C(4)	1.532(3)
C(3)-H(3A)	0.9800
C(3)-H(3B)	0.9800
C(3)-H(3C)	0.9800
C(4)-H(4A)	0.9800
C(4)-H(4B)	0.9800
C(4)-H(4C)	0.9800
C(5)-H(5A)	0.9800
C(5)-H(5B)	0.9800
C(5)-H(5C)	0.9800
C(6)-N(2)	1.140(3)
C(6)-C(7)	1.480(3)
C(7)-C(10)	1.518(4)
C(7)-C(8)	1.526(4)
C(7)-C(9)	1.528(4)
C(8)-H(8A)	0.9800
C(8)-H(8B)	0.9800
C(8)-H(8C)	0.9800
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800
C(10)-H(10A)	0.9800
C(10)-H(10B)	0.9800
C(10)-H(10C)	0.9800
C(11)-F(2)	1.331(3)
C(11)-F(3)	1.333(3)
C(11)-F(1)	1.333(3)
C(11)-S(1)	1.827(2)
N(1)-Cu(1)	1.905(2)
N(2)-Cu(1)	1.908(2)

O(1)-S(1)	1.4496(17)
O(1)-Cu(1)	2.2169(15)
O(2)-S(1)	1.4509(16)
O(2)-Cu(1)#1	2.2481(16)
O(3)-S(1)	1.4334(17)
Cu(1)-O(2)#2	2.2481(16)

N(1)-C(1)-C(2)	177.7(3)
C(1)-C(2)-C(3)	109.4(2)
C(1)-C(2)-C(5)	107.26(19)
C(3)-C(2)-C(5)	110.7(2)
C(1)-C(2)-C(4)	108.1(2)
C(3)-C(2)-C(4)	110.54(19)
C(5)-C(2)-C(4)	110.7(2)
C(2)-C(3)-H(3A)	109.5
C(2)-C(3)-H(3B)	109.5
H(3A)-C(3)-H(3B)	109.5
C(2)-C(3)-H(3C)	109.5
H(3A)-C(3)-H(3C)	109.5
H(3B)-C(3)-H(3C)	109.5
C(2)-C(4)-H(4A)	109.5
C(2)-C(4)-H(4B)	109.5
H(4A)-C(4)-H(4B)	109.5
C(2)-C(4)-H(4C)	109.5
H(4A)-C(4)-H(4C)	109.5
H(4B)-C(4)-H(4C)	109.5
C(2)-C(5)-H(5A)	109.5
C(2)-C(5)-H(5B)	109.5
H(5A)-C(5)-H(5B)	109.5
C(2)-C(5)-H(5C)	109.5
H(5A)-C(5)-H(5C)	109.5
H(5B)-C(5)-H(5C)	109.5
N(2)-C(6)-C(7)	179.3(2)
C(6)-C(7)-C(10)	108.8(2)
C(6)-C(7)-C(8)	108.53(19)
C(10)-C(7)-C(8)	112.2(3)
C(6)-C(7)-C(9)	108.1(2)
C(10)-C(7)-C(9)	110.2(2)
C(8)-C(7)-C(9)	108.9(2)
C(7)-C(8)-H(8A)	109.5
C(7)-C(8)-H(8B)	109.5
H(8A)-C(8)-H(8B)	109.5

C(7)-C(8)-H(8C)	109.5
H(8A)-C(8)-H(8C)	109.5
H(8B)-C(8)-H(8C)	109.5
C(7)-C(9)-H(9A)	109.5
C(7)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(7)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
C(7)-C(10)-H(10A)	109.5
C(7)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	109.5
C(7)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5
F(2)-C(11)-F(3)	107.61(19)
F(2)-C(11)-F(1)	107.26(19)
F(3)-C(11)-F(1)	107.68(19)
F(2)-C(11)-S(1)	111.29(16)
F(3)-C(11)-S(1)	111.01(16)
F(1)-C(11)-S(1)	111.78(17)
C(1)-N(1)-Cu(1)	171.9(2)
C(6)-N(2)-Cu(1)	179.4(2)
S(1)-O(1)-Cu(1)	120.87(9)
S(1)-O(2)-Cu(1)#1	127.66(9)
O(3)-S(1)-O(1)	115.45(10)
O(3)-S(1)-O(2)	115.19(10)
O(1)-S(1)-O(2)	114.22(9)
O(3)-S(1)-C(11)	103.55(11)
O(1)-S(1)-C(11)	103.31(10)
O(2)-S(1)-C(11)	102.71(11)
N(1)-Cu(1)-N(2)	137.21(8)
N(1)-Cu(1)-O(1)	107.92(7)
N(2)-Cu(1)-O(1)	103.15(7)
N(1)-Cu(1)-O(2)#2	104.09(7)

N(2)-Cu(1)-O(2)#2	102.54(7)
O(1)-Cu(1)-O(2)#2	93.56(6)

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,y-1/2,-z+3/2 #2 -x+1,y+1/2,-z+3/

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$). The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	21(1)	15(1)	12(1)	0(1)	-1(1)	-1(1)
C(2)	11(1)	22(1)	20(1)	-1(1)	2(1)	0(1)
C(3)	20(1)	31(1)	40(2)	-12(1)	1(1)	4(1)
C(4)	17(1)	27(1)	27(1)	-7(1)	-2(1)	-1(1)
C(5)	25(1)	46(2)	22(1)	9(1)	4(1)	-9(1)
C(6)	15(1)	16(1)	14(1)	1(1)	-2(1)	-1(1)
C(7)	24(1)	21(1)	14(1)	-4(1)	-2(1)	3(1)
C(8)	33(2)	58(2)	33(2)	-24(2)	-11(1)	21(2)
C(9)	41(2)	32(2)	48(2)	-21(1)	-12(2)	7(1)
C(10)	89(3)	36(2)	32(2)	0(2)	37(2)	6(2)
C(11)	28(1)	17(1)	18(1)	0(1)	3(1)	1(1)
N(1)	20(1)	19(1)	14(1)	2(1)	-1(1)	-1(1)
N(2)	18(1)	20(1)	16(1)	-1(1)	1(1)	-2(1)
O(1)	21(1)	17(1)	16(1)	-1(1)	-2(1)	-2(1)
O(2)	22(1)	18(1)	16(1)	-3(1)	-1(1)	1(1)
O(3)	24(1)	28(1)	29(1)	-7(1)	-12(1)	3(1)
F(1)	21(1)	39(1)	32(1)	-2(1)	5(1)	-3(1)
F(2)	62(1)	32(1)	17(1)	7(1)	10(1)	4(1)
F(3)	42(1)	21(1)	34(1)	-10(1)	14(1)	1(1)
S(1)	16(1)	16(1)	15(1)	-3(1)	-2(1)	2(1)
Cu(1)	14(1)	20(1)	15(1)	-2(1)	3(1)	0(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3).

	x	y	z	U(eq)
H(3A)	11032	4171	7446	46
H(3B)	12277	4676	6887	46
H(3C)	10691	4342	6571	46
H(4A)	11403	7713	7828	35
H(4B)	12723	6743	7615	35
H(4C)	11549	6286	8226	35
H(5A)	10243	6576	6029	47
H(5B)	11884	6963	6231	47
H(5C)	10575	7890	6511	47
H(8A)	2922	10388	8904	62
H(8B)	2089	10343	9692	62
H(8C)	1891	9150	9103	62
H(9A)	5798	9646	10161	60
H(9B)	4492	10657	10334	60
H(9C)	5271	10677	9531	60
H(10A)	2714	7487	10096	78
H(10B)	2942	8672	10688	78
H(10C)	4261	7690	10491	78

6.5 References

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CHAPTER 7

Copper-Mediated Fluorination of Aryl Boronate Esters with $(^{t}BuCN)_2CuOTf$

7.1 Introduction

A wide range of materials and biologically active molecules contain fluoroarenes. The presence of fluorine atoms in these arenes often affects reactivity, solubility, and stability of the molecule. In medicinal chemistry, a fluorine atom is used to block metabolic degradation and, thereby, to improve the efficacy of lead compounds. In addition, fluorinated compounds enriched in ^{18}F are used as PET-imaging agents in medicine. However, methods to synthesize aryl fluorides under mild reaction conditions are limited.

To overcome the limitations of classical methods for the synthesis of aryl fluorides by the Halex[1] or Balz-Schieman reactions (Figure 7.1),[2] modern methods based on transition metal complexes have been sought (Figure 7.2). Aryl triflates react with CsF in the presence of a palladium catalyst to form aryl fluorides, but isomeric products were obtained in many cases.[3] Arylstannanes,[4] arylsilver,[5] arylpalladium,[6] and arylnickel[7] complexes have been reported to form aryl fluorides, but the stannanes are toxic, and the silver, palladium, and nickel complexes must be isolated after synthesis from arylboronic acids (Ag, Pd) or aryl bromides (Ni). More recently, Ritter and coworkers reported the direct conversion of phenols to aryl fluorides with a difluoroimidazoline reagent,[8] and we disclosed the conversion of aryl iodides to aryl fluorides with (^{t}BuCN)$_2$CuOTf and AgF.[9]

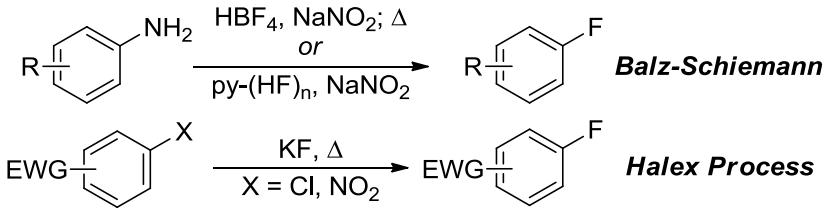


Figure 7.1 Conventional routes to fluoroarenes

Arylboron reagents are valuable alternative sources of aryl groups for the synthesis of aryl fluorides because they are readily available, non-toxic, shelf-stable, and often react under mild-conditions with good functional group tolerance. Moreover, they can be prepared by methods, such as C-H bond functionalization, that complement those used to form aryl iodides and phenols. Finally, reactions of arylboronate esters can occur with reactivity that is orthogonal to that of aryl iodides. However, no direct conversion of arylboron reagents to aryl fluorides has been reported.

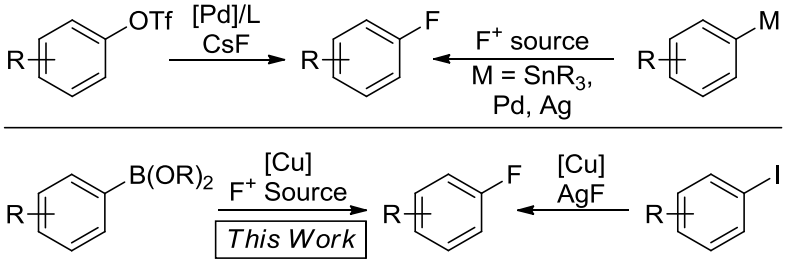


Figure 7.2 Methods for the synthesis of aryl fluorides with transition metals

We report a straightforward copper-mediated fluorination of arylboronate esters under mild conditions with good substrate scope. We show that this reaction can be used

in tandem with the borylation of aryl C-H bonds to effect an overall C-H bond fluorination and that it can be used in tandem with the borylation of aryl bromides to convert aryl bromides to aryl fluorides. Mechanistic experiments suggest that the fluorination of arylboronate esters occurs by initial formation of a cationic Cu(III) fluoride complex, which was identified spectroscopically. Stoichiometric reactions of this Cu(III) species show that it is competent to be an intermediate in the fluorination process.

7.2 Results and Discussion

To develop a method for the conversion of arylboron nucleophiles to aryl fluorides (Figure 7.3), we focused initially on the fluorination of pinacol-derived arylboronate esters (ArBPin). Pinacolate esters can be prepared in quantitative yield by the reaction of boronic acids with equimolar amounts of pinacol and can be prepared by C-H bond functionalization and coupling of aromatic electrophiles with boron reagents.[10] ArBPin reagents are more stable to air and moisture than other arylboronate esters and boronic acids, and they can be purified by silica gel chromatography. They are indefinitely stable on the bench. Finally, ArBPin reagents are inert under many reaction conditions. Thus the ArBPin can be carried through a synthetic sequence conveniently without cleaving the C-B bond.[10]

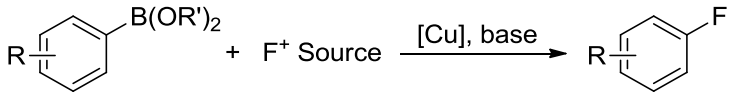
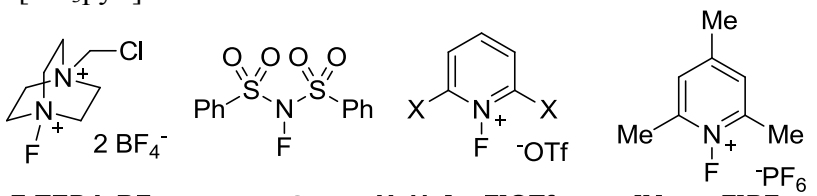


Figure 7.3 Electrophilic fluorination of aryl boron reagents

A variety of electrophilic fluorine sources (Figure 7.4) are commercially available. These reagents vary in their reactivity, solubility and stability. We tested the reactivity of the pinacol ester of 4-butylphenylboronic acid (**1a**) with electrophilic fluorine sources in the presence of a base and copper source. The reactions of this arylboronic ester with the sterically hindered and electron-rich 1-fluoro-2,4,6-trimethylpyridinium (Me_3pyF^+) reagent formed the aryl fluoride in higher yields, when combined with ($^tBuCN)_2CuOTf$ and AgF,[11] than those conducted with other F^+ sources (Table 7.1). The higher yields with $[Me_3pyF]^+$ reagents than with other F^+ sources appear to result, in part, from a slower rate of thermal and base-induced decomposition of the F^+ source. In addition, the ligating ability of 2,4,6-trimethylpyridine appeared to be important (*vide infra*). The counterion of $[Me_3pyF]^+$ affected the yield; the reactions conducted with $[Me_3pyF]PF_6$ occurred in higher yields than the reactions conducted with $[Me_3pyF]BF_4$ and $[Me_3pyF]OTf$.

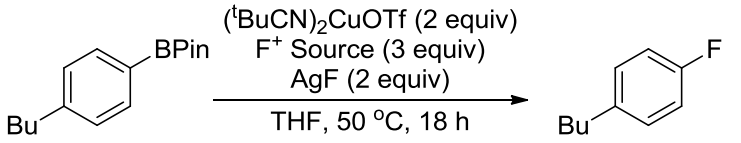


F-TEDA-BF$_4$ (Selectfluor) NFSI **X=H, [pyF]OTf** **X=Cl, [Cl$_2$pyF]OTf** **[Me$_3$pyF]PF$_6$**

Figure 7.4 Electrophilic Fluorine (F^+) Reagents.

Electrophilic fluorine sources are susceptible to base-induced decomposition. Thus, a base that promotes transmetallation of the ArBPin without decomposing the F^+ source is essential for high conversion of ArBpin reagents to the corresponding aryl fluoride. Reactions conducted with a series of alkoxide bases gave modest yields (10 - 15%) of the aryl fluoride product in the presence of $(^tBuCN)_2CuOTf$ and $[Me_3pyF]PF_6$. Reactions conducted with fluoride bases occurred in significantly higher yields than those conducted with alkoxide bases. Reactions conducted with AgF as base occurred in significantly higher yields than reactions conducted with other fluoride bases we tested (Table 7.1, entries 8-10). We propose that higher yields are obtained with AgF than with other bases because the low solubility and low nucleophilicity of AgF prevent it from promoting transmetallation of the ArBPin to Cu(I) (*vide infra)*. Also, in contrast to stronger bases, AgF does not lead to the decomposition of the F^+ source. Finally, AgF does not react with Cu(I) to form an unstable Cu(I)F species.[12]

Table 7.1 Screen of F^+ reagents for the fluorination of **1a** with $(^tBuCN)_2CuOTf$ and AgF[a]



1a **2a**

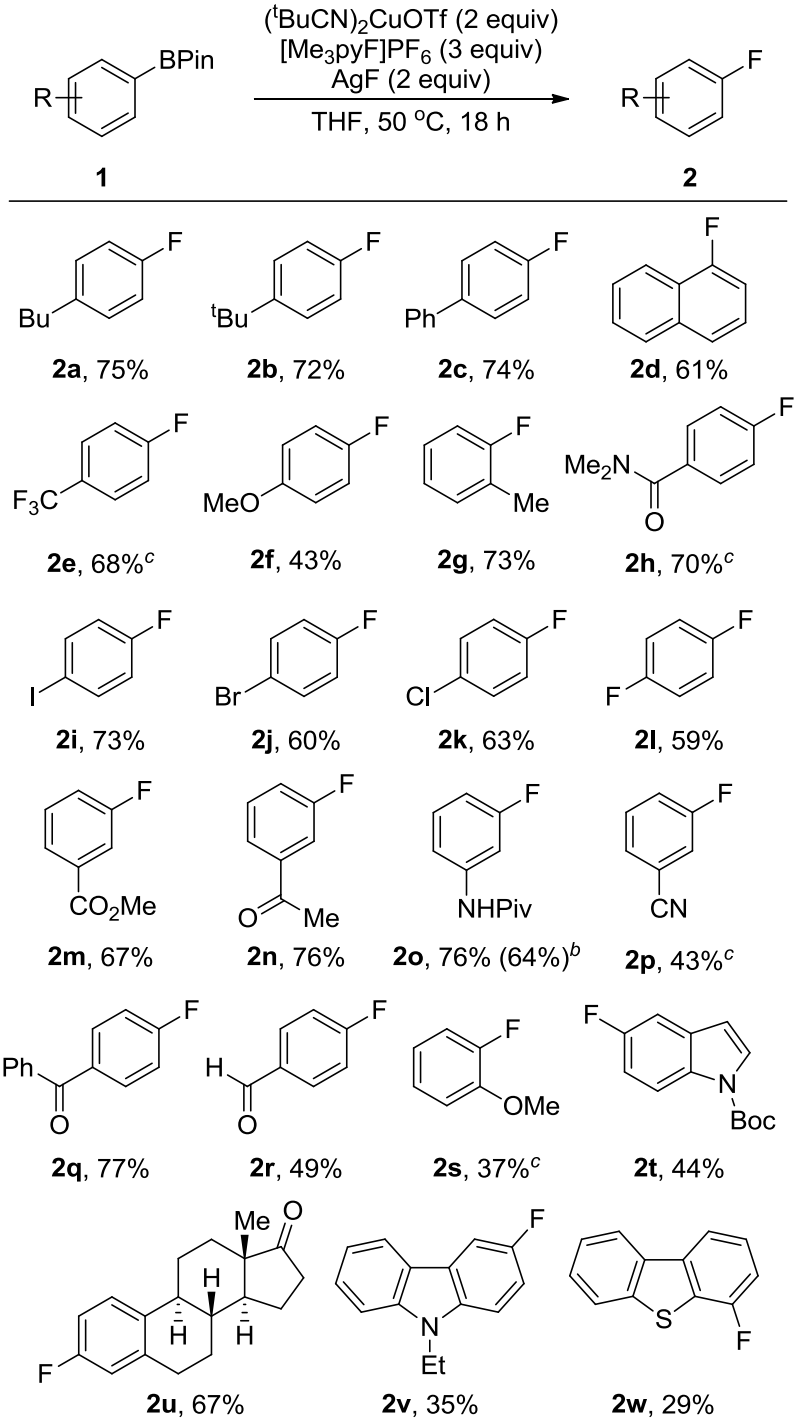
Entry	F^+ Source	Conversion (%)	ArH (%)	ArF (%)
1	F-TEDA-BF_4	91	37	27
2	F-TEDA-PF_6	100	73	26
3	NFSI	100	90	10
4	$[Cl_2pyF]OTf$	100	100	0
5	[pyF]OTf	100	87	1
6	$[Me_3pyF]BF_4$	84	9	56
7	$[Me_3pyF]OTf$	82	13	64
8	$[Me_3pyF]PF_6$	88	12	75
9	$[Me_3pyF]PF_6$	97	57	24
10	$[Me_3pyF]PF_6$	100	39	38

[a]Reactions were performed with 0.1 mmol of **1a** in 2.0 mL of THF for 18 h. Yields were determined by gas chromatography with 1-bromo-4-fluorobenzene as an internal standard added after the reaction. [b]Reactions were performed with KF in place of AgF. [c]Reactions were performed with CsF in place of AgF.

The combination of $(^tBuCN)_2CuOTf$, $[Me_3pyF]PF_6$ and AgF converted a range of arylboronate esters to the corresponding aryl fluoride, and the scope of this process is summarized in Table 7.2. The same reaction conditions were suitable for the reactions of both electron-rich and electron-deficient arylboronate esters. Substrates containing esters, ketones, aldehydes, amides, nitriles, aryl hlides, and some heterocycles underwent fluorination in moderate to good yield. In addition, the ortho-substituted boronate ester **1g** provided 2-fluorotoluene in 73% yield. The corresponding *ortho*-anisylboronic ester (**1s**) also gave the aryl fluoride product, but in lower yield. Amide-containing aryl fluoride **2o** was isolated in good yield on a 0.5 mmol scale from boronate ester **1o**. The boron byproduct in these fluorination reactions is F-BPin. F-BPin undergoes hydrolysis to HO-BPin during aqueous workup and is easily separated from the aryl fluoride product. The

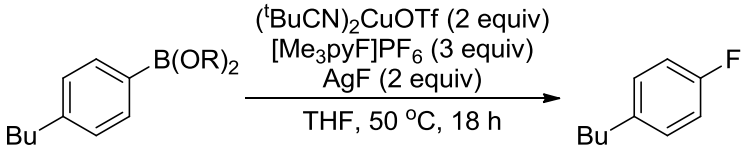
conditions we developed for the fluorination of pinacolate esters also induced the fluorination of boronic acids and other boronic acid derivatives (Table 3).

Table 7.2 Scope of the fluorination of ArBPin reagents with $(^tBuCN)_2CuOTf$, $[Me_3pyF]PF_6$ and AgF[a]



[a]Reactions were performed with 0.1 mmol of **1** to determine yields by ^{19}F NMR spectroscopy with 1-bromo-4-fluorobenzene as an internal standard added after the reaction. [b]Isolated yield from a reaction with 0.5 mmol of ArBPin. [c]Reactions were conducted at 80 °C.

Table 7.3 Fluorination of boronic acid derivatives

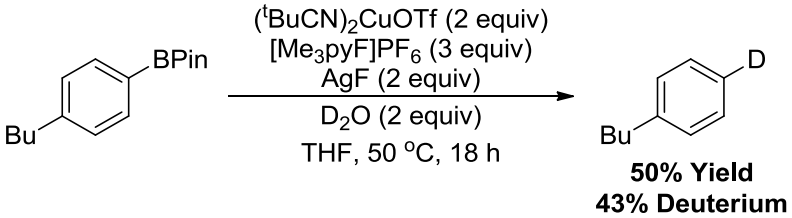


Entry	$(OR)_2$	ArH (%)	ArF (%)
1	$(OH)_2$	5	45
2	BF_3K	37	46
3	MIDA	23	18
4	Catechol	60	0
5	Neopentylglycol	15	70
6	Pinacol	12	75

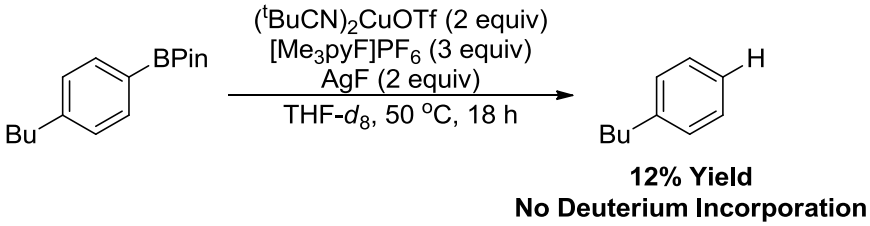
[a]Reactions were performed with 0.1 mmol of aryl-boron in 2.0 mL of THF for 18 h. Yields were determined by gas chromatography with 1-bromo-4-fluorobenzene as an internal standard added after the reaction.

The major side-reaction in the fluorination of arylboronate esters is protodeborylation to form the corresponding arene. This side-reaction occurs commonly during reactions of aryl-boron reagents. The hydrogen atom in this process may originate from multiple sources, including the solvent or adventitious water.

To determine the source of the product of proto-deborylation, a deuterium labeling experiment was conducted. The reaction of **1a** under the standard reaction conditions with two equivalents of added D_2O formed the arene side product in 50% yield with 43% incorporation of deuterium in the arene (Equation 7.1). The arene side product from the reaction of **1a** under the standard reaction conditions in THF-d_8 did not contain deuterium (Equation 7.2). Thus, we suggest that the arene side-product in the fluorination of ArBPin results, in part, from a reaction with adventitious water.



Equation 7.1 Formation of arene side product through reaction with adventitious water

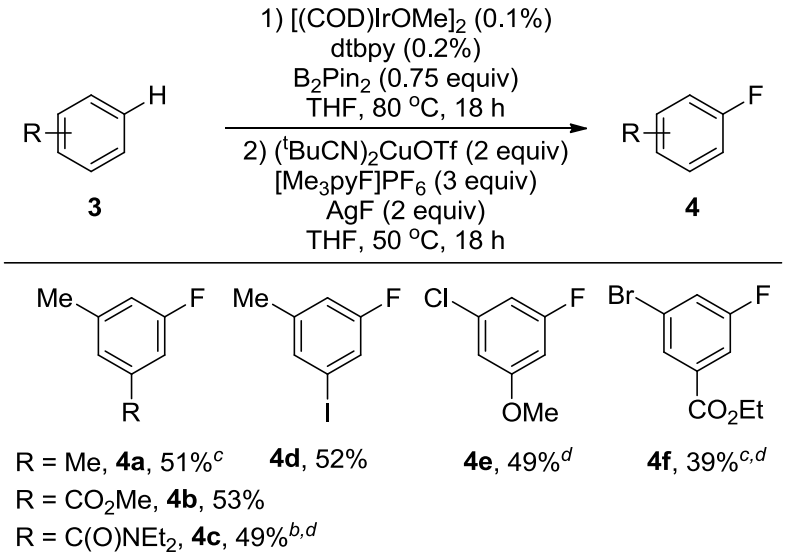


Equation 7.2 Reaction performed in THF-d_8 to determine if the solvent contributes to arene formation

Arylboronate esters can be prepared by iridium catalyzed C-H borylation,[13] and this process leads to the borylation at the least hindered C-H bond of arenes. Our group has shown that Ir-catalyzed C-H borylation can be used in tandem with reactions of the

resulting ArBPin as a two-step, one-pot route to diversely functionalized arenes.[14] We considered that a similar tandem process could be used to achieve the fluorination of C-H bonds. Indeed, C-H borylation with B_2Pin_2 catalyzed by the combination of $[Ir(COD)OMe]_2$ and dtbpy provided crude ArBPin intermediates that underwent subsequent copper-mediated fluorination. The ArBPin formed by C-H borylation could be used without purification. Conversion of the crude ArBpin to the corresponding aryl fluoride occurred such that the two-step process gave a good yield of the aryl fluoride (Table 7.4). Arenes containing electron-donating and electron-withdrawing groups reacted in comparable yield. Ketones, esters, amides and aryl halides were tolerated over the two-step procedure. This sequence represents a simple strategy for a regioselective C-H fluorination of arenes.

Table 7.4 Tandem C-H borylation and fluorination of arenes[a]



R = Me, **4a**, 51%[c] **4d**, 52% **4e**, 49%[d] **4f**, 39%[c,d]

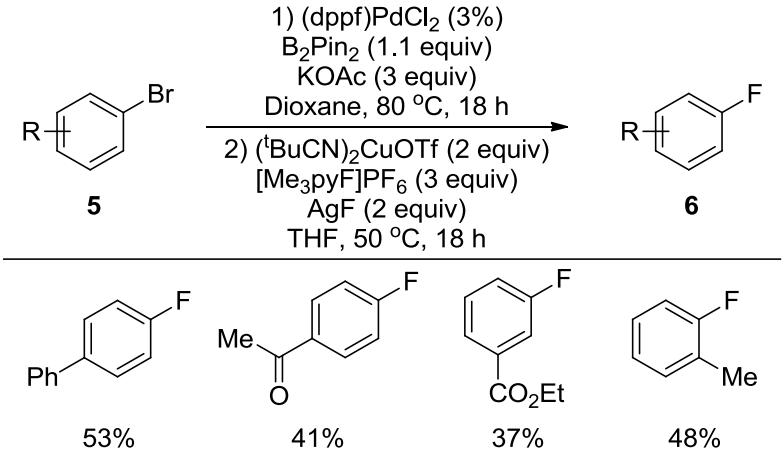
R = CO_2Me, **4b**, 53%

R = $C(O)NEt_2$, **4c**, 49%[b,d]

[a]Reactions were performed with 0.1 mmol of arene. Yields were determined by ^{19}F NMR spectroscopy with 1-bromo-4-fluorobenzene as an internal standard added after the reaction. [b]The borylation reaction was performed with 1.5% [Ir] and 3.0% dtbpy. [c]The borylation reaction was performed with 0.5% [Ir] and 1.0% dtbpy. [d]The fluorination reaction was performed at 80 °C for 18 h.

An alternative method to prepare arylboronate esters is the borylation of aryl halides catalyzed by transition metals. Thus, we evaluated whether aryl bromides would react in a one-pot sequence to convert aryl bromides to aryl fluorides through ArBPin intermediates. The combination of a simple palladium pre-catalyst, B_2Pin_2, and KOAc[15] led to the high conversion of aryl bromides to ArBPin intermediates under conditions suitable for the conversion of the ArBPin to the corresponding ArF. The crude mixture from the borylation reaction was filtered, concentrated, and subjected to the fluorination conditions described above. Good yields of the aryl fluorides were obtained over the two-step sequence without purification of the intermediate ArBPin (Table 7.5). Because methods for the direct fluorination of aryl bromides have not been reported, this two-step strategy provides a unique conversion of aryl bromides to aryl fluorides.

Table 7.5 Tandem C-Br borylation and fluorination of aryl bromides[a]



[a]Reactions were performed with 0.1 mmol of aryl bromide. Yields were determined by ^{19}F NMR spectroscopy with 1-bromo-4-fluorobenzene as an internal standard added after the reaction.

The mechanism of the copper-mediated fluorination of arylboronate esters was studied experimentally. Two simplified reaction pathways are shown in Scheme 4. One mechanism (Figure 7.4, A) begins with transmetallation of the ArBPin to Cu(I), followed by reaction of the arylcopper(I) species with $[Me_3pyF]PF_6$. The second mechanism (Figure 7.4, B) begins with formation of a Cu(III) species from reaction of a Cu(I) complex with an F^+ source.

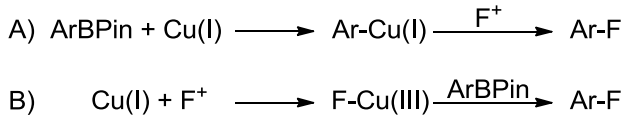
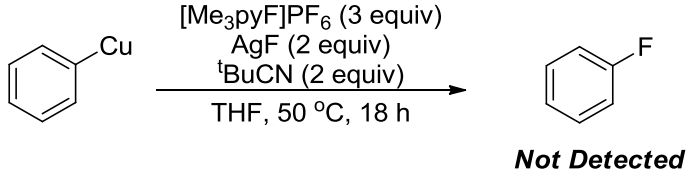
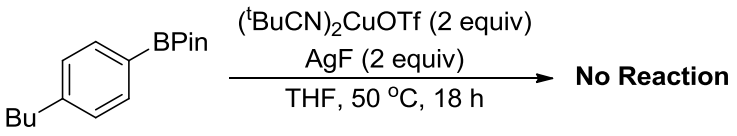


Figure 7.4 Potential reaction pathways for the fluorination of ArBPin with $(^tBuCN)_2CuOTf$ and $[Me_3pyF]PF_6$

To evaluate the potential that mechanism A occurs, we conducted the reaction between the known phenyl-copper[16] with $[Me_3pyF]PF_6$, AgF and ^tBuCN in THF. After 18 h at 50 °C no fluorobenzene was detected by ^{19}F NMR spectroscopy (Equation 7.3). Furthermore, no reaction occurred between aryl pinacolboronate **1a** and $(^tBuCN)_2CuOTf$ with added AgF in the absence of $[Me_3pyF]PF_6$ over 18 h at 50 °C (Equation 7.4). These results argue against a mechanism involving initial formation of an arylcopper(I) species.



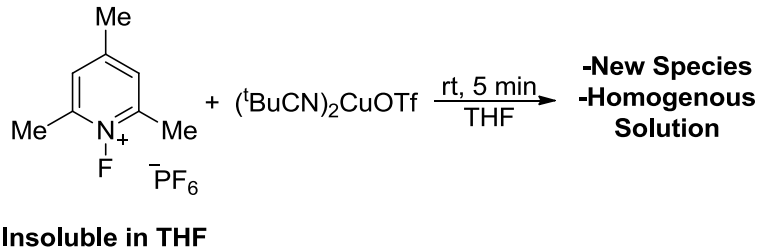
Equation 7.3 Attempted fluorination reaction with an isolated aryl-copper reagent



Equation 7.4 Reactivity of an ArBPin reagent in the absence of the electrophilic fluorine reagent

We also assessed whether arylsilver species are formed in the reaction. Arylsilver species generated from arylboron reagents have been shown to react with electrophilic fluorine sources to provide aryl fluorides.[5] Yet, we did not detect any reaction of arylboronate **1a** with AgF in THF at 50 °C over 18 h. Furthermore, many of the reactions we conducted between arylboronates and $[Me_3pyF]PF_6$ with other fluoride sources (KF, CsF) formed aryl fluorides. Reactions conducted with AgF occurred in higher yield than those with KF and CsF, but the presence of AgF was not required for product to form. Thus, the fluorination of aryl boronates with $[Me_3pyF]PF_6$ is unlikely to occur through arylsilver intermediates. Finally, no aryl fluoride was formed in the absence of copper.

To assess the potential that mechanism B of Figure 7.4 occurs, we conducted a series of NMR spectroscopic measurements of the reaction of $(^tBuCN)_2CuOTf$ with $[Me_3pyF]PF_6$. The ^{19}F NMR spectrum of $(^tBuCN)_2CuOTf$ consists of a sharp singlet at -77.7 ppm in THF. $[Me_3pyF]PF_6$ is insoluble in THF, and no ^{19}F NMR signals were observed for a sample of $[Me_3pyF]PF_6$ suspended in THF.[17] However, equimolar amounts of $(^tBuCN)_2CuOTf$ and $[Me_3pyF]PF_6$ in THF generated a colorless, homogenous solution within 5 min at room temperature (Equation 7.5). A new species was formed, as determined by ^1H and ^{19}F NMR spectroscopic and ESI-MS measurements. Attempts to isolate this species in pure form have been unsuccessful. Thus, we characterized this copper complex in solution.



Equation 7.5 Reaction of $[Me_3pyF]PF_6$ with $(^tBuCN)_2CuOTf$

The ^{19}F NMR spectrum of the reaction between equimolar amounts of $(^tBuCN)_2CuOTf$ and $[Me_3pyF]PF_6$ in THF at room temperature consisted of a doublet at -72.0 ppm due to the PF_6 anion (J = 710 Hz), a broad peak at -71.4 ppm due to the OTf group, and a doublet of doublets at -110.8 ppm that we propose to correspond to a copper-bound fluoride (J = 66, 26 Hz). The chemical shift of the triflate peak in the new complex was 6.3 ppm downfield of the chemical shift of $(^tBuCN)_2CuOTf$, suggesting that the triflate is bound to an electrophilic site, such as the Cu(III) center in the proposed product. Fluoride complexes of d^8 transition metal centers containing weakly donating ligands have not been reported. The ^{19}F NMR spectra of phosphine-ligated Pd(II)-F complexes typically contain resonances near -300 ppm. In contrast, the ^{19}F NMR spectra of Pt(II)-F complexes contain signals as far downfield as -107.6 ppm for *trans*-

[Pt(Ph)(F)(PPh_3)$_2$].[18] The ^{19}F chemical shifts of alkali-metal fluorides are near -150 ppm. Thus, the ^{19}F chemical shift of the new copper species at -110.8 ppm is consistent with that for a fluoride bound to a cationic Cu(III) site. The sharp, well-resolved peaks in the NMR spectra argue against the formation of a paramagnetic Cu(II) species.

We propose that the doublet of doublets pattern of the fluoride signal (J = 66, 26 Hz) results from scalar coupling between the fluoride ligand and inequivalent α-protons of a bound THF. This coupling could result from a hydrogen-bonding interaction or through-space coupling due to the electron pairs on the fluroride and the electron density in the C-H bonds.[19] The coupling constants for the fluoride peak are similar in magnitude to ^1J values from H-F hydrogen bonds.[19-20] Because coupling constants are largely dependent on the relative locations and electron density of the coupled atoms, conclusions about the origin of the splitting could not be made based on the magnitude of the coupling constants alone. Thus, further experiments were performed to elucidate the structure of the copper species formed in the reaction between (^{t}BuCN)$_2$CuOTf and [Me_3pyF]PF_6.

To assess our proposal that the observed splitting is due to coupling between the fluoride and a bound THF, we generated this compound in THF-d_8. The ^{19}F NMR spectrum of the complex generated in THF-d_8 contains a singlet – rather than a doublet of doublets – for the fluoride, and this signal lies upfield (-112.1 ppm) of that for the same peak in the ^{19}F NMR spectrum of the sample in THF (-110.8 ppm). The magnitude of this upfield shift is similar to deuterium isotope effects observed on the chemical shifts of alkyl and vinyl fluorides containing vicinal deuterium atoms.[19,21] These data show that the fluoride is coupled to a bound THF.

To assess further how THF is coordinated to copper, the copper complex was generated in 2,2-dideuteriotetrahydrofuran. If the coupling to fluorine occurred through interactions with one hydrogen atom on each of carbons 2 and 5, a doublet in the ^{19}F NMR spectrum would be expected to be observed, rather than the observed doublet of doublets in fully protiated THF. However, if coupling occurred to two inequivalent hydrogen atoms on the same carbon of the bound THF, then two separate resonances, one a doublet of doublets and one a singlet would be expected to be observed in THF-d_2 because both isomers would be present in solution in similar amounts (Figure 7.5).

When the copper complex was generated in THF-d_2, two resonances in the ^{19}F NMR spectrum were observed for the fluorine atom, a doublet of doublets at -110.8 ppm and a singlet at -112.0 ppm. The two isomers were present in solution in a ratio of 1.5:1, favoring the isomer with hydrogen-fluorine coupling by 0.2 kcal/mol.[22] The coupling observed in the ^{19}F NMR spectrum demonstrates that the THF ligand is in a conformation or a coordination sphere in which the geminal α-protons of the bound THF molecule are inequivalent on the NMR time scale.

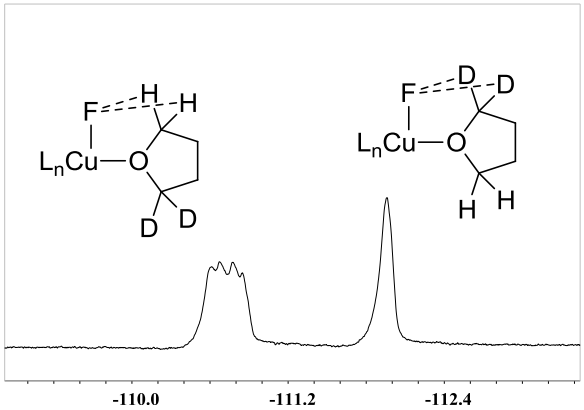


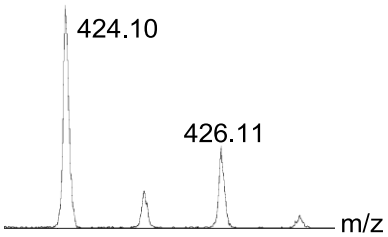
Figure 7.5 Fluoride peaks in the ^{19}F NMR spectrum of the reaction between (^{t}BuCN)$_2$CuOTf and [Me$_3$pyF]PF$_6$ in THF-d_2

The ^{1}H NMR spectra of the new species reveals the identity of the dative nitrogen ligands bound to copper. The ^{1}H NMR spectrum of (^{t}BuCN)$_2$CuOTf in THF-d_8 consists of one singlet at 1.41 ppm (free ^{t}BuCN resonates at 1.32 ppm). The ^{1}H NMR spectrum of the new species in THF-d_8 contains a singlet at 1.33 ppm for free ^{t}BuCN and no signals that could be attributed to a bound nitrile. The spectrum also contains resonances at δ 7.49, 2.66, and 2.48 ppm for a 2,4,6-trimethylpyridine unit. These resonances are located downfield of those of free 2,4,6-trimethylpyridine (δ 6.75, 2.36, and 2.20 ppm), and this chemical shift implies that 2,4,6-trimethylpyridine is bound to copper.

A ^{13}C NMR spectrum of the copper species was also obtained. Because the copper species slowly decomposes at room temperature, the ^{13}C NMR spectrum was acquired at -60 ^{o}C. The ^{13}C NMR spectrum in THF-d_8 contained resonances for a bound Me$_3$py (δ 158.9, 151.3, 124.4, 20.0 and 17.4 ppm), which were distinct from those for free Me$_3$py (δ 158.1, 147.6, 121.3, 24.4, 20.7 ppm). These spectral data agree with the ^{1}H NMR spectral data indicating that Me$_3$py is ligated to copper.

An assessment of whether the triflate was free or bound and, if bound, what binding mode it adopts was conducted by IR spectroscopy. The IR spectrum of this complex in THF contained characteristic bands for ν_{as}(SO) at 1251 and 1292 cm^{-1}. The presence of two vibrations and the 40 cm^{-1} difference between the two vibrations is consistent with a bound, κ^1 triflate ligand.[23]

Finally, the product of the reaction of (^{t}BuCN)$_2$CuOTf with [Me$_3$pyF]PF$_6$ was analyzed by ESI-MS under an inert atmosphere.[24] A 1:1 ratio of (^{t}BuCN)$_2$CuOTf and [Me$_3$pyF]PF$_6$ was allowed to react at room temperature, and the solution was continuously monitored on a Micromass Q-ToF spectrometer in positive-ion mode over 10 minutes under an inert atmosphere with electrospray ionization. The ions (^{t}BuCN)$_2$Cu^{+} and [(Me$_3$py)(THF)Cu(F)(OTf)]$^{+}$ were observed as the major peaks in the mass spectrum. The signal attributed to the cation [(Me$_3$py)(THF)Cu(F)(OTf)]$^{+}$, has a mass to charge ratio of 424.10 for the base peak and the characteristic isotope pattern of copper. Together, these data indicate that the species formed from the reaction between (^{t}BuCN)$_2$CuOTf and [Me$_3$pyF]PF$_6$ has the general formula [(Me$_3$py)(THF)Cu(F)(OTf)(PF$_6$)]



$[(Me_3py)(THF)Cu(F)(OTf)]^+$

Figure 7.6 Proposed formula and ESI-MS of the cationic portion of the Cu(III)-fluoride intermediate.

We used computational methods with DFT to assess potential structures the Cu(III) fluoride species detected by NMR spectroscopy and mass spectrometry. Energy minimizations of a complex containing one fluoride, one triflate, one bound THF, one trimethylpyridine and one PF_6 unit were conducted with DFT using WB97XD functionals that include empirical dispersion corrections. These calculations indicated that the stereoisomer shown in Figure 7.7 with the Me_3py trans and the triflate cis to THF is 9.3 kcal/mol more stable in the gas phase than the isomer with the Me_3py cis and the triflate trans to THF. These calculations also indicated that the ground state of $[(Me_3py)(THF)Cu(F)(OTf)(PF_6)]$ is approximately square pyramidal with hexafluorophosphate bound in the apical position (Figure 7.7). Calculations performed with a THF solvent continuum indicated that the neutral complex containing a bound PF_6 anion is more stable than the separated ions by ΔH = 14.2 kcal/mol and ΔG = 2.1 kcal/mol. Although further work on stable analogs of the new species is clearly needed, binding of PF_6 or slow rotation of the THF would cause the complex to be chiral on the NMR time scale; this property would render the geminal protons at THF diastereotopic and chemically inequivalent. In the computed structure, the four inequivalent alpha protons of the bound THF lie in an orientation with short (2.4 and 2.6 Å) H-F distances that are consistent with the observation of $^1J_{HF}$ coupling in the ^{19}F NMR spectra (*vide supra*). Studies toward analogs of this Cu(III) species that are sufficiently stable for isolation are ongoing.

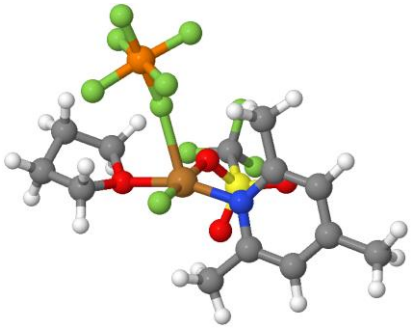
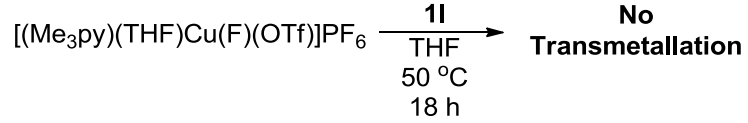


Figure 7.7 Computed ground state structure of $[(Me_3py)(THF)Cu(F)(OTf))PF_6)]$ in a THF solvent continuum.

The reactivity of the cationic copper(III)-fluoride species was investigated to assess the competence of this species to be an intermediate and to determine which reagents react with this complex to form the aryl fluoride product. The reaction of metal fluorides with aryl-boron reagents to generate aryl-metal species has been shown to occur during palladium-catalyzed Suzuki cross-coupling.[25] Thus, the Cu(III)-fluoride could

react directly with the arylboronate ester to generate an arylCu(III) species and F-BPin. However, the copper(III)-fluoride species (generated *in-situ*) did not undergo transmetallation with *p*-fluorophenylboronate **1l**, as determined by ^{19}F NMR spectroscopy (Equation 7.6). The reaction of $(^tBuCN)_2CuOTf$ with $[Me_3pyF]PF_6$ and **1l** in the absence of AgF did not lead to any detectable conversion of the arylboronate ester over 18 h at 50 °C.



Equation 7.6 Reaction of $[(Me_3py)(THF)Cu(F)(OTf)]PF_6$ with an ArBPin

The potential that the copper(III)-fluoride species reacts with AgF to form a copper(III) species containing two fluorides was also investigated. If formed, a copper(III) difluoride could react with the arylboronate ester to give an aryl-copper(III)fluoride. However, no new copper species from the reaction between the copper(III)-fluoride intermediate and AgF in THF after 18 h at 50 °C was detected by ^{19}F NMR spectroscopy. The reaction of the copper(III)-fluoride with the more reactive, and more soluble, tetrabutylammonium fluoride (TBAF) resulted in the rapid formation of paramagnetic copper(II) species, as determined by characteristic broad peaks in the NMR spectrum. The formation of Cu(II) could result from N-F reductive elimination of $[Me_3pyF]^+$ from an unstable Cu(III) difluoride to form a copper(I) fluoride. Copper(I) fluoride complexes are known to disproportionate rapidly to Cu(0) and CuF_2, and this disproportionation would account for the paramagnetic species observed in the ^{19}F NMR spectrum.[12]

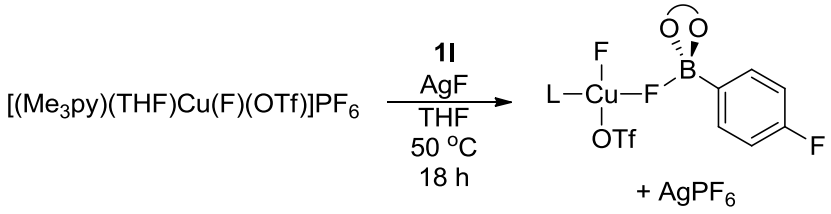
Finally, the reaction of *p*-fluorophenylboronate **1l** with $(^tBuCN)_2CuOTf$, $[Me_3pyF]PF_6$ and AgF under the standard reaction conditions was monitored, and this reaction led to a new species that appears to be a second intermediate in the fluorination of arylboronate esters The ^{19}F NMR spectrum after 20 minutes of the reaction of *p*-fluorophenylboronate **1l** with $(^tBuCN)_2CuOTf$ at 50 °C showed that greater than 90% of the arylboronate ester was converted to a new species. New resonances in the ^{19}F NMR spectrum were observed. A new signal corresponding to the *p*-fluorine atom on the aryl ring (-115.7 ppm) resonated upfield of that on the starting, free arylboronate ester (-108.7 ppm). The peak corresponding to the Cu(III)-F species described above was quickly consumed and was replaced by a broad peak at -138 ppm. The intensity of the peak at -138 ppm was twice that of the peak from the fluorine atom on the aryl group. The resonance from the triflate was observed at -76 ppm, and this peak was sharper and located upfield of the triflate peak of the cationic Cu(III)-fluoride (-71.4 ppm, broad). The other peaks observed in the ^{19}F NMR spectrum were 1,4-difluorobenzene (the product of fluorination of the aryl boronate ester), fluorobenzene (formed by proto-deborylation), internal standard, and F-BPin. F-BPin and 1,4-difluorobenzene were formed in concert with consumption of the copper species corresponding to the resonances at -115.7 and -138 ppm.

The new species formed from the reaction between arylboronate **1l**, $(^tBuCN)_2CuOTf$, $[Me_3pyF]PF_6$ and AgF was further characterized by ^1H NMR

spectroscopy. The aryl protons of the boronate ester **1l** resonate at 7.76 ppm and 7.07 ppm in THF-d_8. The aromatic protons of the new species resonated further upfield at 7.68 ppm, and 6.99 ppm. The ^{1}H NMR spectrum of the reaction solution also contained resonances for ligated trimethylpyridine at δ 7.49, 2.63, and 2.46 ppm and ^{t}BuCN (δ 1.33 ppm). These chemical shifts are similar to those of the trimethylpyridine ligand in [(Me_3py)Cu(F)(OTf)(THF)(PF_6)] (δ 7.49, 2.66, and 2.48 ppm). The proton resonances for the pinacolate group (δ 1.25 ppm) were shifted upfield of those for the pinacolate group of **1l** (δ 1.32 ppm).

The ^{11}B NMR spectrum of the reaction between arylboronate **1l**, (^{t}BuCN)$_2$CuOTf, [Me_3pyF]PF_6 and AgF under the standard reaction conditions showed >90% conversion of **1l** (δ 30.4 ppm) to a new species within 20 minutes at 50 ^{o}C. This new species corresponded to a ^{11}B resonance at 4.5 ppm. As the reaction progressed, the peak at 4.5 ppm decayed in concert with the formation of F-BPin (0.6 ppm). The chemical shift of 4.5 ppm is consistent with the formation of a four-coordinate anionic arylboronate. These results suggest that the Ar-B bond is present in the observed species.

We propose that the copper complex formed from the reaction of *p*-fluorophenylboronate **1l** with (^{t}BuCN)$_2$CuOTf, [Me_3pyF]PF_6 and AgF is a neutral arylboronate-Cu(III)-fluoride. A potential structure of this complex is shown in Equation 7.7. We propose that the two fluorine atoms give rise to a single broad ^{19}F resonance due to a combination of stereoisomerism and transfer of the boron center from one fluorine to the other. This species was formed in 90% yield (based on the conversion of ArBPin).



Equation 7.7 Reaction of [(Me_3py)(THF)Cu(F)(OTf)]PF_6 with an ArBPin and AgF

We propose the arylboronate-Cu(III)-fluoride complex undergoes rate-limiting transmetallation of the aryl group to copper. The aryl-Cu(III)-fluoride complex formed from transmetallation would then undergo fast reductive elimination of the Ar-F product. Fast reductive elimination of an aryl fluoride is consistent with a recent report by Ribas and coworkers in which an aryl-Cu(III)-fluoride complex was proposed to be formed as an unobserved, reactive intermediate during the reaction of a macrocylic aryl-Cu(III) complex with fluoride to form a macrocyclic fluoroarene.[26]

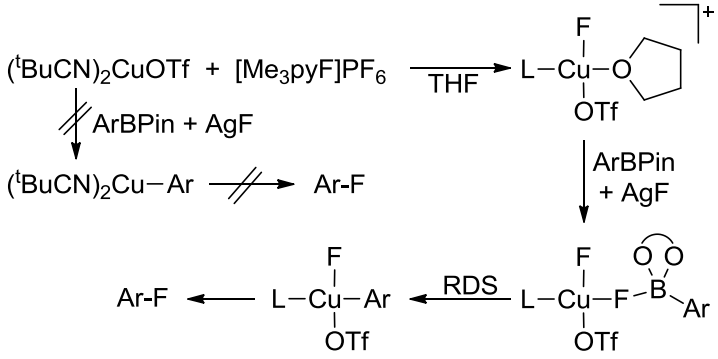


Figure 7.8 Proposed Mechanism for the Fluorination of ArBPin with (^{t}BuCN)$_2$CuOTf and Me$_3$pyF-PF$_6$.

Figure 7.8 shows a mechanism for the fluorination of arylboronate esters with (^{t}BuCN)$_2$CuOTf, [Me$_3$pyF]PF$_6$ and AgF that is consistent with our data. Our data indicate that the fluorination of aryl boronate esters does not occur by the formation of arylcopper(I) species. Instead, the fluorination reactions appear to occur by generation of a cationic copper(III)-fluoride intermediate that reacts with the combination of fluoride and arylboronic ester. Rate-limiting transmetallation of the aryl group to Cu(III) is proposed to form an aryl-Cu(III)-fluoride from which rapid reductive elimination of the Ar-F product occurs.

7.3 Conclusions

In summary, we have developed an operationally simple, direct method for the fluorination of arylboronate esters and revealed the formation of two copper(III) fluoride intermediates. This reaction occurs with readily available reagents under mild conditions. Electron-rich, electron-deficient, ortho-substituted and diversely functionalized arylboronate esters undergo fluorination in good yield. In addition, sequential, one-pot processes allow the fluorination of arenes and aryl bromides to occur through arylboronate ester intermediates generated *in-situ*. We provide evidence that the fluorination of arylboronate esters with (^{t}BuCN)$_2$CuOTf and [Me$_3$pyF]PF$_6$ occurs by facile formation of a cationic copper(III)-fluoride complex, which reacts with AgF and ArBpin to form a neutral fluoroarylboronate complex. This fluoroarylboronate undergoes transmetallation to form an arylcopper(III) fluoride, which undergoes reductive elimination to form the aryl fluoride product.

7.4 Experimental

All manipulations were conducted under an inert atmosphere with a nitrogen-filled glovebox unless otherwise noted. All reactions were conducted in oven-dried 4-mL vials fitted with a Teflon-lined screw cap under an atmosphere of nitrogen unless otherwise noted.

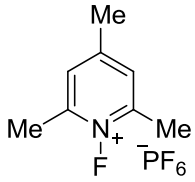
Silver fluoride (>99%) was purchased from Acros and used as received. THF was sparged with N_2, passed through activated alumina and stored over 3 Å molecular sieves prior to use. (^{t}BuCN)$_2$CuOTf was prepared according to our previously published

procedure. Unless otherwise noted, all other reagents were purchased from commercial suppliers and used as received.

NMR spectra were acquired on 400 MHz, 500 MHz, or 600 MHz Bruker instruments at the University of California. NMR spectra were processed with MestReNova 5.0 (Mestrelab Research SL). Chemical shifts are reported in ppm and referenced to residual solvent peaks ($CHCl_3$ in $CDCl_3$: 7.26 ppm for ^1H and 77.0 ppm for ^{13}C) or to an external standard (1% $CFCl_3$ in $CDCl_3$: 0 ppm for ^{19}F). Coupling constants are reported in hertz.

All GC-MS analyses were conducted with an Agilent 6890N GC equipped with an HP-5 column (25 m x 0.20 mm ID x 0.33 μm film) and an Agilent 5973 Mass Selective Detector. The temperature for each run was held at 50 °C for 2 min, ramped from 50 °C to 300 °C at 40 °C/min, and held at 300 °C for 5 min.

Preparation of 1-fluoro-2,4,6-trimethylpyridinium hexafluorophosphate, [Me$_3$pyF]PF$_6$

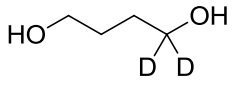


1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate ([Me$_3$pyF]BF_4, 4.54 g, 20.0 mmol) was dissolved in water (80 mL), and ammonium hexafluorophosphate (19.56 g, 120.0 mmol) was added to the resulting solution at once. A white precipitant formed quickly, and the resulting suspension was stirred at room temperature for 2 h. The white solid was collected on a funnel, washed with 3 x 15 mL of water, 2 x 15 mL of ether, and dried in vacuo (20 mtorr). 5.00 g (17.5 mmol) of a white powder was obtained, 88% yield.

^1H NMR (400 MHz, CD_3CN) δ 7.65 (d, J = 6.4 Hz, 2H), 2.74 (d, J = 4.0 Hz, 6H), 2.55 (s, 3H).

^{19}F NMR (376 MHz, CD_3CN) δ 17.48 (s), -71.40 (d, J = 706.4 Hz).

Preparation of 1,1-dideuterio-1,4-butanediol

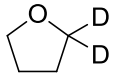


1,1-dideuterio-1,4-butanediol was prepared by the reduction of γ-butyrolactone according to a similar procedure as that reported in J. Org. Chem. **1982**, 47, 4702. Sodium borodeuteride ($NaBD_4$, 576 mg, 13.8 mmol) and LiCl (583 mg, 13.8 mmol) were suspended in THF (10 mL) and stirred at room temperature for 1 h. γ-butyrolactone (1.9 mL, 25 mmol) and toluene (4 mL) were added and the resulting mixture was heated at 80 ^oC for 12 hours. The bulk of the solvent was distilled off at 120 ^oC and the remaining liquid was removed by vacuum distillation at 120 ^oC. The flask was allowed to cool to room temperature and the white solid was hydrolyzed with 1 M HCl (20 mL) over 3 hours. K_2CO_3 was added to saturate the aqueous layer followed by extraction with THF (3 x 20 mL). The THF was dried over anhydrous K_2CO_3, concentrated and dried in-vacuo (20 mtorr) overnight to afford the title compound as a viscous oil (1.52 g, 16.5 mmol, 66% yield).

^1H NMR (400 MHz, $CDCl_3$) δ 3.68 (t, J = 5.8 Hz, 2H), 2.52 (s, 2H), 1.68 (m, 4H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 62.52 (s), 61.85 (m), 29.72 (s), 29.58 (s).

Preparation of 2,2-dideuteriotetrahydrofuran (THF-d$_2$)



A similar procedure was used as that reported in J. Org, Chem.**1959**, 24, 1259. To a Schlenk flask was added 1,1-dideuterio-1,4-butanediol (1.5 g, 16 mmol)

and 85% aqueous phosphoric acid (400 μL). The resulting solution was heated at 125 °C for 24 hours. The reaction was cooled to room temperature and the THF-d_2 formed was vacuum transferred to a separate Schlenk flask. The THF-d_2 was dried over sodium metal with benzophenone as an indicator. Once the THF-d_2 was dry (3 days), it was vacuum transferred to an oven dried flask to afford the title compound as a clear liquid (ca. 900 μL). Note: the THF initially contains a large amount of water and the sodium metal should be added carefully.
^{1}H NMR (600 MHz, $CDCl_3$) δ 3.73 (t, J = 6.5 Hz, 2H), 1.84 (m, 4H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 67.94 (s), 67.32 (m), 25.59 (s), 25.36 (s).

General Procedure for the Synthesis of Aryl Pinacol Boronate Esters

Into a 20 mL vial was placed the aryl boronic acid (2.00 mmol, 1.00 equiv), pinacol (236 mg, 2.00 mmol, 1.00 equiv), powdered 4 Å molecular sieves (~300 mg), and 5 mL of ether. The mixture was stirred at room temperature overnight. The molecular sieves were removed by filtration, and the filtrate was concentrated to afford aryl pinacol boronate esters as colorless solids or oils. Further purification of the aryl boronate ester was rarely needed.

General Procedure for the Fluorination of Aryl Boronate Esters

To an oven-dried 4 mL vial was added AgF (25 mg, 0.20 mmol, 2.0 equiv), (^{t}BuCN)$_2$CuOTf (76 mg, 0.20 mmol, 2.0 equiv), [Me_3pyF]PF_6 (86 mg, 0.30 mmol, 3.0 equiv) and THF (2.0 mL). The aryl boronate ester (0.10 mmol, 1.0 equiv) was added (solid aryl boronate esters were weighed in the vial prior to adding THF, and liquid aryl boronate esters were added neat by syringe after the addition of THF). The vial was sealed with a Teflon-lined cap and heated at 50 °C with vigorous stirring for 18 h. The solution was allowed to cool to room temperature, and 11.0 μL (0.100 mmol, 1.00 equiv) of 1-bromo-4-fluorobenzene was added as an internal standard. The crude reaction mixture was analyzed by ^{19}F NMR spectroscopy to determine the yield of aryl fluoride. ^{19}F NMR chemical shifts were compared to authentic samples of the aryl fluoride product to confirm the identity of the product, and the identities of the products were further assessed by GC/MS.

General Procedure for the Fluorination of Arenes through Ir-Catalyzed C-H Borylation

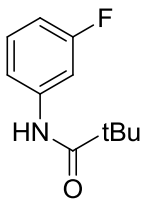
To an oven-dried 4 mL vial was added arene (0.10 mmol, 1.0 equiv), and 0.2 mL of a stock solution containing 0.1 mol% [Ir(COD)OMe]$_2$, 0.2 mol% 4,4'-di-tert-butyl bipyridine (dtbpy), and 0.75 equiv of B_2Pin_2. The vial was sealed with a Teflon-lined cap and heated at 80 °C for 18 h. The solution was allowed to cool, and the volatile components were removed in vacuo. To the crude ArBPin was added AgF (25 mg, 0.20 mmol, 2.0 equiv), (^{t}BuCN)$_2$CuOTf (76 mg, 0.20 mmol, 2.0 equiv), [Me_3pyF]PF_6 (86 mg, 0.30 mmol, 3.0 equiv) and THF (2.0 mL). The vial was sealed with a Teflon-lined cap and heated at 50 °C with vigorous stirring for 18 h. The solution was allowed to cool to room temperature, and 11.0 μL (0.100 mmol, 1.00 equiv) of 1-bromo-4-fluorobenzene

was added as an internal standard. The crude reaction mixture was analyzed by ^{19}F NMR spectroscopy to determine the yield of aryl fluoride. ^{19}F NMR chemical shifts were compared to authentic samples of the aryl fluoride product to confirm the identity of the product, and the identities of the products were further confirmed by GC/MS.

General Procedure for the Fluorination of Aryl Bromides through Pd-Catalyzed C-Br Borylation

To an oven-dried 4 mL vial was added (dppf)$PdCl_2$ (2.2 mg, .0030 mmol, 3.0 mol%), KOAc (29 mg, 0.30 mmol, 3.0 equiv), B_2Pin_2 (28 mg, 0.11 mmol, 1.1 equiv) and dioxane (0.5 mL). The aryl bromide (0.10 mmol, 1.0 equiv) was added (solid aryl bromides were weighed in the vial prior to adding dioxane, and liquid aryl bromides were added neat by syringe after the addition of dioxane). The vial was sealed with a Teflon-lined cap and heated at 80 °C for 18 h. The solution was allowed to cool and filtered through a short plug of Celite with EtOAc, and the volatile components were removed in vacuo. To the crude ArBPin was added AgF (25 mg, 0.20 mmol, 2.0 equiv), (^{t}BuCN)$_2$CuOTf (76 mg, 0.20 mmol, 2.0 equiv), [Me_3pyF]PF_6 (86 mg, 0.30 mmol, 3.0 equiv) and THF (2.0 mL). The vial was sealed with a Teflon-lined cap and heated at 50 °C with vigorous stirring for 18 h. The solution was allowed to cool to room temperature, and 11.0 μL (0.100 mmol, 1.00 equiv) of 1-bromo-4-fluorobenzene was added as an internal standard. The crude reaction mixture was analyzed by ^{19}F NMR spectroscopy to determine the yield of aryl fluoride. ^{19}F NMR chemical shifts were compared to authentic samples of the aryl fluoride product to confirm the identity of the product. The identities of the products were further confirmed by GC/MS.

Synthesis of N-(3-fluorophenyl)pivalamide (2o)



To an oven-dried 20 mL vial was added AgF (127 mg, 1.00 mmol, 2.00 equiv), (^{t}BuCN)$_2$CuOTf (379 mg, 1.00 mmol, 2.00 equiv), 1-fluoro-2,4,6-trimethylpyridinium hexafluorophosphate (428 mg, 1.50 mmol, 3.00 equiv), **1o** (152 mg, 0.500 mmol, 1.00 equiv) and THF (10 mL). The vial was sealed with a Teflon-lined cap, and the reaction was heated at 50 °C for 18 h. The reaction was cooled, diluted with 15 mL of ether, and filtered through Celite. The filtrate was concentrated and purified by silica gel chromatography eluting with 9:1 hexanes:ethyl acetate (R_f=0.18) to afford a white solid (63 mg, 0.32 mmol, 64% yield).

^1H NMR (600 MHz, $CDCl_3$) δ 7.54 (d, J = 11.0 Hz, 1H), 7.35 (s, 1H), 7.25 (t, J = 11.4 Hz, 1H), 7.13 (d, J = 8.1 Hz, 1H), 6.83 – 6.77 (m, 1H), 1.31 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 176.60 (s), 163.04 (d, J = 244.7 Hz), 139.58 (d, J = 11.0 Hz), 129.94 (d, J = 9.4 Hz), 115.01 (d, J = 2.9 Hz), 110.85 (d, J = 21.4 Hz), 107.44 (d, J = 26.4 Hz), 39.70 (s), 27.56 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -111.51 – -111.61 (m).

Solution NMR Analysis of the Reaction Between (^{t}BuCN)$_2$CuOTf and [Me_3pyF]PF_6

To an oven-dried 4 mL vial was added (^{t}BuCN)$_2$CuOTf (38 mg, 0.10 mmol, 1.0 equiv), [Me_3pyF]PF_6 (29 mg, 0.10 mmol, 1.0 equiv) and THF (1.0 mL) or THF-d_8 (1.0 mL). The

suspension was stirred at room temperature until the solution became homogenous (5-10 min). The solution was transferred to an oven-dried NMR tube and analyzed by ^{1}H and ^{19}F NMR spectroscopy.
^{1}H NMR (600 MHz, THF-d_8) δ 7.49 (s, 2H), 2.66 (s, 6H), 2.48 (s, 3H), 1.33 (s, 18H).
^{13}C NMR (101 MHz, THF-d_8) δ 158.86, 151.34, 124.41, 25.81, 20.03, 17.37.
^{19}F NMR (376 MHz, THF-d_8) δ -71.00 (br, s), -72.17 (d, J = 710.1 Hz), -112.12 (s).
^{19}F NMR (376 MHz, THF-H_8) δ -71.5 (br, s), -72.00 (d, J = 710.4 Hz), -110.80 (dd, J = 66.2, 26.3 Hz).

ESI-MS Analysis of the Reaction Between (^{t}BuCN)$_2$CuOTf and [Me$_3$pyF]PF$_6$

To an oven-dried flask was added (^{t}BuCN)$_2$CuOTf (38 mg, 0.10 mmol, 1.0 equiv), [Me$_3$pyF]PF$_6$ (29 mg, 0.10 mmol, 1.0 equiv),THF (1.0 mL) and fluorobenzene (1.0 mL). The reaction was stirred at room temperature, and the solution was continuously monitored on a Micromass Q-ToF micro mass spectrometer in positive-ion mode over 10 minutes under an inert atmosphere using electrospray ionization. Capillary voltage: 2900 V. Cone voltage: 15 V. Extraction voltage: 0.5 V. Source temperature: 91°C. Desolvation temperature: 191°C. cone gas flow rate, 100 L/h; desolvation gas flow, 200 L/h; collision voltage, 2 V; MCP voltage, 2700 V.

Solution IR Spectroscopy of the Reaction Between (^{t}BuCN)$_2$CuOTf and [Me$_3$pyF]PF$_6$

To an oven-dried vial was added (^{t}BuCN)$_2$CuOTf (38 mg, 0.10 mmol, 1.0 equiv), [Me$_3$pyF]PF$_6$ (29 mg, 0.10 mmol, 1.0 equiv) and THF (1.0 mL). The reaction mixture was stirred at room temperature for 5 minutes. This reaction mixture was transferred to an IR solution cell and analyzed by FT-IR spectroscopy (Thermo Scientific Nicolet iS5 FT-IR). A blank sample of THF was acquired and subtracted from the spectrum of the reaction..

Solution NMR Analysis of the Reaction Between (^{t}BuCN)$_2$CuOTf, [Me$_3$pyF]PF$_6$, AgF and 1l

To an oven-dried 4 mL vial was added (^{t}BuCN)$_2$CuOTf (38 mg, 0.10 mmol, 2.0 equiv), [Me$_3$pyF]PF$_6$ (43 mg, 0.15 mmol, 3.0 equiv), 4-fluorophenyl pinacolboronate (**1l**, 11 mg, .050 mmol, 1.0 equiv), AgF (13 mg, 0.10 mmol, 2.0 equiv) and THF (1.0 mL) or THF-d_8 (1.0 mL). 1-bromo-4-fluorobenzne (11.0 μL, 0.100 mmol) was added as an internal standard for reactions monitored by ^{19}F NMR spectroscopy. The reaction mixture was stirred at 50 ^{o}C for the indicated time. The solution was transferred to an oven-dried NMR tube and analyzed by ^{1}H, ^{11}B and ^{19}F NMR spectroscopy.

DFT Calculations

WB97XD/6-31G++(d,p) calculations were performed with Gaussian 09. Structure optimizations were performed in both the gas-phase and in a THF solvent continuum. All

structures were confirmed to be stationary points by the absence of negative frequency values.

Cartesian Coordinates for WB97XD/6-31G++(d,p) optimized stationary points in the gas-phase.

$C_{13}H_{19}CuF_4NO_4S(1+)$
$[(Me_3py)(THF)Cu(F)(OTf)]^+$

	Atomic Number		X	Y	Z
1	29	0	-0.111435	-0.876319	-0.050266
2	8	0	1.718854	-1.311257	-0.034244
3	6	0	2.275541	-1.898616	1.201726
4	6	0	2.232782	-2.009915	-1.211820
5	6	0	3.215434	-2.993544	0.714236
6	1	0	2.770531	-1.068311	1.706099
7	1	0	1.444688	-2.269855	1.803285
8	6	0	3.554821	-2.567921	-0.720190
9	1	0	1.526604	-2.802828	-1.480892
10	1	0	2.306509	-1.262351	-2.002542
11	1	0	2.707344	-3.961408	0.715449
12	1	0	4.099633	-3.067379	1.349305
13	1	0	3.893140	-3.400816	-1.338837
14	1	0	4.321702	-1.789016	-0.731602
15	9	0	-0.527849	-2.525027	0.321518
16	7	0	-1.926774	-0.443538	-0.055183
17	6	0	-2.533969	-0.344122	-1.257910
18	6	0	-2.556658	-0.260047	1.124218
19	6	0	-3.872473	0.008042	-1.291653
20	6	0	-3.897374	0.100176	1.097882
21	6	0	-4.579073	0.251545	-0.109832
22	1	0	-4.363005	0.089354	-2.255558
23	1	0	-4.406298	0.253318	2.043145
24	6	0	-1.805461	-0.484636	2.400915
25	1	0	-1.522557	-1.539121	2.479859
26	1	0	-0.901372	0.130858	2.451213
27	1	0	-2.432797	-0.230117	3.255080
28	6	0	-1.736552	-0.637704	-2.493767
29	1	0	-0.962592	0.121217	-2.642748
30	1	0	-1.270596	-1.627459	-2.423369
31	1	0	-2.384502	-0.640574	-3.370407
32	6	0	-6.018990	0.668924	-0.144390
33	1	0	-6.082809	1.750259	-0.308268
34	1	0	-6.553240	0.178501	-0.961238
35	1	0	-6.524987	0.442333	0.795701

36	8	0	0.265570	0.813629	-0.648277
37	16	0	0.815689	1.800501	0.439357
38	8	0	1.059202	1.038703	1.658616
39	8	0	0.044737	3.015571	0.459595
40	6	0	2.478961	2.216078	-0.300290
41	9	0	3.218849	1.112231	-0.398249
42	9	0	2.308852	2.736750	-1.505589
43	9	0	3.083901	3.082787	0.492359

$F_6P(1-)$
$(PF_6)^-$

	Atomic Number		**X**	**Y**	**Z**
1	15	0	0.000069	0.000275	-0.000209
2	9	0	0.572828	0.355880	-1.493232
3	9	0	-0.999615	1.296907	-0.073233
4	9	0	1.167003	0.936752	0.669666
5	9	0	-0.573245	-0.356177	1.492786
6	9	0	0.999864	-1.297561	0.074447
7	9	0	-1.166949	-0.936258	-0.670085

$C_{13}H_{19}CuF_{10}NO_4PS$
$[(Me_3py)(THF)Cu(F)(OTf)]PF_6$

	Atomic Number		**X**	**Y**	**Z**
1	29	0	0.077445	0.245901	0.861356
2	8	0	-1.097446	-1.000291	1.728407
3	6	0	-2.088124	-0.454979	2.668134
4	6	0	-1.692318	-2.110910	0.960045
5	6	0	-3.101925	-1.574098	2.809824
6	1	0	-1.543418	-0.200982	3.576114
7	1	0	-2.525063	0.436029	2.216124
8	6	0	-3.146834	-2.152006	1.393592
9	1	0	-1.558951	-1.904345	-0.099076
10	1	0	-1.119938	-2.994792	1.250673
11	1	0	-4.067051	-1.181389	3.135820
12	1	0	-2.761484	-2.321549	3.534261
13	1	0	-3.747671	-1.517830	0.738749
14	1	0	-3.540139	-3.170262	1.359089
15	9	0	-0.431982	1.522157	1.930415
16	7	0	1.573162	1.308698	0.455320
17	6	0	1.669240	1.945004	-0.731346
18	6	0	2.532171	1.359921	1.411298

19	6	0	2.824087	2.675633	-0.989924
20	6	0	3.685517	2.079807	1.152884
21	6	0	3.856793	2.745934	-0.062395
22	1	0	2.903082	3.180055	-1.946357
23	1	0	4.456068	2.111421	1.915205
24	6	0	2.317247	0.642499	2.710377
25	1	0	1.454402	1.065320	3.230746
26	1	0	2.153323	-0.427157	2.540015
27	1	0	3.201009	0.744582	3.340510
28	6	0	0.551727	1.864131	-1.715442
29	1	0	0.301241	0.826094	-1.942804
30	1	0	-0.348467	2.340596	-1.316820
31	1	0	0.831642	2.367945	-2.640201
32	6	0	5.127571	3.486431	-0.362533
33	1	0	5.877759	2.783228	-0.740321
34	1	0	4.973344	4.254327	-1.123347
35	1	0	5.534509	3.956526	0.535930
36	8	0	0.618273	-1.047961	-0.325317
37	16	0	2.035180	-1.676766	-0.371833
38	8	0	2.463591	-2.113030	0.945944
39	8	0	2.946489	-0.918710	-1.204790
40	6	0	1.568693	-3.199395	-1.339533
41	9	0	0.702285	-3.935031	-0.646960
42	9	0	1.026872	-2.858037	-2.500205
43	9	0	2.670254	-3.910043	-1.555117
44	15	0	-3.166056	1.173606	-1.054301
45	9	0	-4.502073	1.906568	-1.562093
46	9	0	-3.758601	1.045103	0.466031
47	9	0	-2.467212	2.590729	-0.651400
48	9	0	-1.753126	0.392892	-0.506731
49	9	0	-2.484845	1.254006	-2.526227
50	9	0	-3.765417	-0.299852	-1.397810

Cartesian Coordinates for WB97XD/6-31G++(d,p) optimized stationary points in a THF solvent continuum.

$C_{13}H_{19}CuF_4NO_4S(1+)$
$[(Me_3py)(THF)Cu(F)(OTf)]^+$

	Atomic Number		**X**	**Y**	**Z**
1	29	0	0.111435	-0.876319	0.050266
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5	6	0	-3.215434	-2.993544	-0.714236

6	1	0	-2.770531	-1.068311	-1.706099
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8	6	0	-3.554821	-2.567921	0.720190
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18	6	0	2.556658	-0.260047	-1.124218
19	6	0	3.872473	0.008042	1.291653
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23	1	0	4.406298	0.253318	-2.043145
24	6	0	1.805461	-0.484636	-2.400915
25	1	0	1.522557	-1.539121	-2.479859
26	1	0	0.901372	0.130858	-2.451213
27	1	0	2.432797	-0.230117	-3.255080
28	6	0	1.736552	-0.637704	2.493767
29	1	0	0.962592	0.121217	2.642748
30	1	0	1.270596	-1.627459	2.423369
31	1	0	2.384502	-0.640574	3.370407
32	6	0	6.018990	0.668924	0.144390
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35	1	0	6.524987	0.442333	-0.795701
36	8	0	-0.265570	0.813629	0.648277
37	16	0	-0.815689	1.800501	-0.439357
38	8	0	-1.059202	1.038703	-1.658616
39	8	0	-0.044737	3.015571	-0.459595
40	6	0	-2.478961	2.216078	0.300290
41	9	0	-3.218849	1.112231	0.398249
42	9	0	-2.308852	2.736750	1.505589
43	9	0	-3.083901	3.082787	-0.492359

F_6P(1-)
$(PF_6)^-$

	Atomic Number		**X**	**Y**	**Z**
1	15	0	-0.000107	-0.000220	-0.000030
2	9	0	0.660138	0.267397	-1.476256

3	9	0	-0.810148	-1.294799	-0.596349
4	9	0	-1.263400	0.969867	-0.389254
5	9	0	-0.660310	-0.267218	1.476654
6	9	0	0.810088	1.294858	0.596197
7	9	0	1.263811	-0.969738	0.389058

$C_{13}H_{19}CuF_{10}NO_4PS$
$[(Me_3py)(THF)Cu(F)(OTf)]PF_6$

	Atomic Number		**X**	**Y**	**Z**
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2	8	0	1.097446	1.000291	1.728407
3	6	0	2.088124	0.454979	2.668134
4	6	0	1.692318	2.110910	0.960045
5	6	0	3.101925	1.574098	2.809824
6	1	0	1.543418	0.200982	3.576114
7	1	0	2.525063	-0.436029	2.216124
8	6	0	3.146834	2.152006	1.393592
9	1	0	1.558951	1.904345	-0.099076
10	1	0	1.119938	2.994792	1.250673
11	1	0	4.067051	1.181389	3.135820
12	1	0	2.761484	2.321549	3.534261
13	1	0	3.747671	1.517830	0.738749
14	1	0	3.540139	3.170262	1.359089
15	9	0	0.431982	-1.522157	1.930415
16	7	0	-1.573162	-1.308698	0.455320
17	6	0	-1.669240	-1.945004	-0.731346
18	6	0	-2.532171	-1.359921	1.411298
19	6	0	-2.824087	-2.675633	-0.989924
20	6	0	-3.685517	-2.079807	1.152884
21	6	0	-3.856793	-2.745934	-0.062395
22	1	0	-2.903082	-3.180055	-1.946357
23	1	0	-4.456068	-2.111421	1.915205
24	6	0	-2.317247	-0.642499	2.710377
25	1	0	-1.454402	-1.065320	3.230746
26	1	0	-2.153323	0.427157	2.540015
27	1	0	-3.201009	-0.744582	3.340510
28	6	0	-0.551727	-1.864131	-1.715442
29	1	0	-0.301241	-0.826094	-1.942804
30	1	0	0.348467	-2.340596	-1.316820
31	1	0	-0.831642	-2.367945	-2.640201
32	6	0	-5.127571	-3.486431	-0.362533
33	1	0	-5.877759	-2.783228	-0.740321
34	1	0	-4.973344	-4.254327	-1.123347
35	1	0	-5.534509	-3.956526	0.535930

36	8	0	-0.618273	1.047961	-0.325317
37	16	0	-2.035180	1.676766	-0.371833
38	8	0	-2.463591	2.113030	0.945944
39	8	0	-2.946489	0.918710	-1.204790
40	6	0	-1.568693	3.199395	-1.339533
41	9	0	-0.702285	3.935031	-0.646960
42	9	0	-1.026872	2.858037	-2.500205
43	9	0	-2.670254	3.910043	-1.555117
44	15	0	3.166056	-1.173606	-1.054301
45	9	0	4.502073	-1.906568	-1.562093
46	9	0	3.758601	-1.045103	0.466031
47	9	0	2.467212	-2.590729	-0.651400
48	9	0	1.753126	-0.392892	-0.506731
49	9	0	2.484845	-1.254006	-2.526227
50	9	0	3.765417	0.299852	-1.397810

7.5 References

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"Copper-Mediated Fluorination of Arylboronate Esters. Identification of a Copper(III) Fluoride Complex"
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CHAPTER 8

Site-Selective C-H Fluorination of Pyridines and Diazines

8.1 Introduction

The selective introduction of fluorine into small molecules can lead to subtle or profound effects on the pK_a, conformation, solubility and stability compared to the non-fluorinated counterpart. In particular, the introduction of fluorine into a basic heterocycle can modulate the basicity and binding properties with only a small change in the steric environment.[1] These effects are especially prevalent in 2-fluoropyridines where fluorine and nitrogen are juxtaposed. For example, the 2-fluoropyridyl containing anti-cancer compound BMS-754807 has higher potency, cell activity, and selectivity than the non-fluorinated analogue.[2]

A valuable strategy for creating molecular diversity is to form a synthetic intermediate by C-H bond cleavage that can be converted to a variety of products. Because many nucleophiles react with 2-fluoropyridines and related 2-fluoroazines to form products containing new carbon-heteroatom or carbon-carbon bonds, a conversion of heteroarenes to 2-fluoroheteroarenes would be a valuable platform for the preparation of an array of functionalized products. Substitution reactions of 2-fluoroazines occur under milder reaction conditions than the substitution reactions of other 2-haloazines because of the strong electron-withdrawing properties of fluorine.

Although 2-fluoropyridines and diazines have favorable physical properties and are valuable synthetic intermediates, they are difficult to prepare when the heterocycle contains functional groups. The direct fluorination of pyridines and diazines with F_2 is known, but F_2 gas is too hazardous for use in most laboratories, and the reactions with F_2 occur in low yield, even with very simple pyridines and diazines.[3] Alternative routes (Figure 8.1) to these products include the Balz-Schiemann reaction and nucleophilic aromatic substitution of 2-chloro or 2-nitroazines with anhydrous fluoride. However, the Balz-Schiemann reaction involves strongly acidic and oxidizing conditions to form a diazonium salt intermediate. This potentially explosive species is then heated in anhydrous HF or as an isolated tetrafluoroborate salt to induce fluorination.[4] Nucleophilic aromatic substitution [5] is limited because it occurs in high yields only with strongly electron-deficient heteroarenes. Moreover, both reaction classes require pre-functionalized substrates, which may be inaccessible directly from a complex molecule.

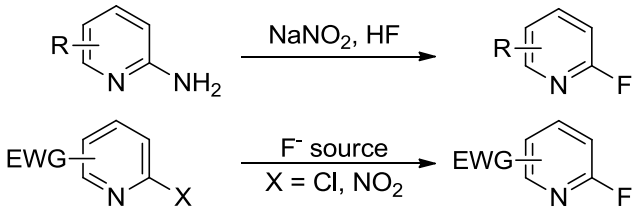


Figure 8.1 Methods for the synthesis of 2-fluoropyridines

Thus, a method to form 2-fluoropyridines and 2-fluorodiazines directly from pyridines and diazines containing additional functional groups under mild conditions with simple reagents would provide an important tool for synthetic and medicinal chemistry. Here, we report a mild C-H bond fluorination reaction of a broad range of pyridines and diazines with a single, commercially available reagent. The fluorination of several

medicinally important compounds and the application of this fluorination reaction to the synthesis of a range of 2-pyridyl compounds via 2-fluoropyridines are demonstrated.

8.2 Results and Discussion

Our design of a direct fluorination of pyridines and diazines was based on the mechanism of a classic reaction of pyridines, the Chichibabin reaction. In this reaction, pyridines react with $NaNH_2$ to form 2-aminopyridines (Figure 8.2)[6] by initial coordination of pyridine to the sodium cation, followed by dearomative nucleophilic addition of the amide to the 2-position and subsequent loss of hydride. We considered that a similar reaction could be developed for the fluorination of pyridine C-H bonds if a reagent or set of reagents could be identified having (i) a sufficiently Lewis acidic site to bind the pyridine, thereby increasing the electrophilicity of the adjacent carbon atom; (ii) a sufficiently nucleophilic fluoride to add to the activated carbon of the pyridine; and (iii) the oxidizing potential to aromatize the intermediate σ-adduct.

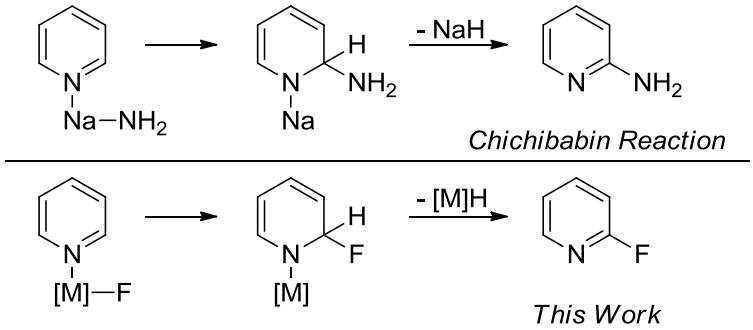
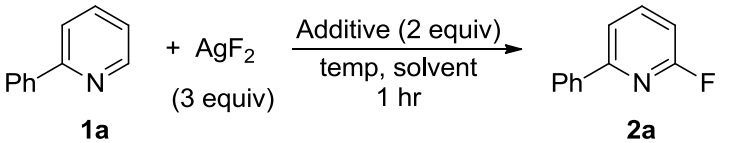


Figure 8.2 Chichibabin amination reaction and the proposed C-H fluorination reaction

With these considerations in mind, we investigated reactions with commercially available AgF_2. AgF_2 is an attractive fluorinating agent because it is commercially available in multi-gram to kilogram quantities and is cheaper than many common fluorinating reagents.[7] Many years ago, AgF_2 was reported to react with an excess of benzene in refluxing hexane, but a mixture of fluorinated products formed.[8] Even earlier, AgF_2 was reported to react with 2,4,6-trifluoropyrimidine, but this reaction occurred in low yield, required high temperature, and has not been investigated since.[9] We sought to determine if reactions of AgF_2 with heteroarenes would occur in a milder and more controlled fashion by a transformation analogous to the Chichibabin reaction. To do so, we studied the fluorination of 2-phenylpyridine. Reactions with this substrate would show whether AgF_2 is selective for fluorination of the heteroarene over fluorination of an arene and whether fluorination of the heteroarene would be regioselective for the 2-position as we envisioned. These studies (Table 8.1) showed that the reaction between 2-phenylpyridine and 2 equivalents of AgF_2 in acetonitrile (MeCN) at room temperature formed 2-fluoro-6-phenylpyridine in 56% yield as the only fluorinated product detectable by ^{19}F NMR spectroscopy. The only organic material detected by gas chromatography was the starting 2-phenylpyridine and 2-fluoro-6-phenylpyridine. Reactions performed in solvents other than MeCN did not afford the fluorinated product in appreciable amounts. During the course of the reaction, AgF_2 is reduced to form the yellow solid AgF, which

was characterized by ^{19}F NMR spectroscopy.[10] The addition of an additional equivalent of AgF_2 at the beginning of the reaction increased the yield of the fluorinated product to 88% (Table 8.1). Although only 2 equivalents of AgF_2 are present in the balanced equation, some of the silver reagent is consumed through unproductive reactions with the solvent. Even though HF is formally generated as a stoichiometric byproduct in the reaction, and one might envision that this side product would interfere with the reaction or react with auxiliary functional groups, the yield and scope of the reaction was not altered by the addition of base. Likewise, the reactions with AgF_2 are insensitive to light.

Table 8.1 Effect of solvent, temperature, and additives on the fluorination of 2-phenylpyridine with AgF_2[a]



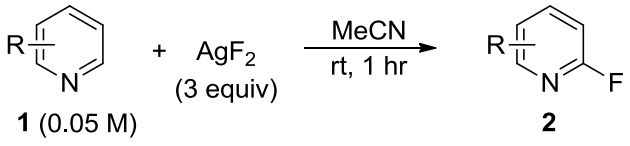
1a **2a**

Entry	Solvent	Additive	Temp (°C)	**2a** (%)
1	THF	-	rt	0
2	DMF	-	rt	0
3	Toluene	-	rt	0
4	Pentane	-	rt	0
5	MeCN	-	rt	88
6[b]	MeCN	-	rt	56
7	EtCN	-	rt	2
8	^{i}PrCN	-	rt	0
9	^{t}BuCN	-	rt	0
10	MeCN	-	50	57
11	MeCN	-	80	27
12	MeCN	KF	rt	78
13	MeCN	CsF	rt	0
14	MeCN	Na_3PO_4	rt	71
15	MeCN	Me_3py	rt	45
16[c]	MeCN	HBF_4	rt	0

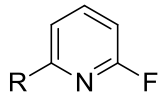
[a]Reactions were performed with 0.1 mmol of 2-phenylpyridine (0.05 M) and the yields were determined by 19F NMR spectroscopy with PhCF3 as an internal standard. [a]The reaction was performed with 2 equivalents of AgF_2. [c]Isolated 2-phenylpyridinium tetrafluoroborate was used as the substrate.

The fluorination of a broad range of substituted pyridines occurs with AgF_2 (Table 8.2). Both electron-donating and electron-withdrawing groups at each position of the ring are tolerated. Pyridines containing ketones, esters, amides, acetals, protected alcohols and amines, nitriles, alkyl tosylates, and enolizable carbonyls underwent the fluorination in good yield [11]. Notably, bromide and chloride substituents in the 2-position of the pyridine, which are susceptible to nucleophilic displacement, remained intact during the reaction. Carboxylic acids and aldehydes were transformed to the corresponding acyl fluorides without formation of the 2-fluoropyridine products.

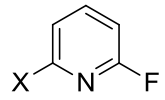
Table 8.2 Scope of the fluorination of pyridines with AgF_2[a]



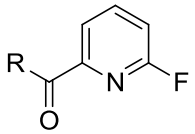
1 (0.05 M) **2**



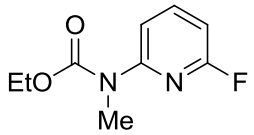
2a, R = Ph, 88% (82%)
2b, R = Et, 94%*
2c, R = ^{t}Bu, 50%



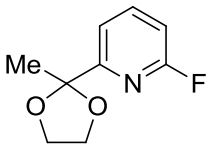
2d, X = OMe, 57%*
2e, X = Cl, 41%#
2f, X = Br, 43%#



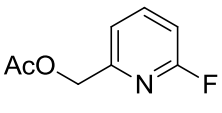
2g, R = Ph, 59% (54%)
2h, R = OEt, 73% (67%)
2i, R = NEt_2, 83% (75%)



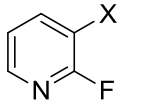
2j, 62%† (49%)



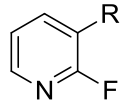
2k, 96% (91%)



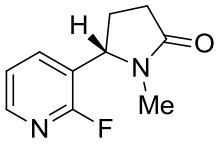
2l, 81% (71%)



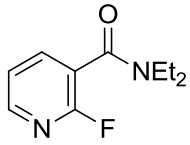
2m, X = F, 55%*
2n, X = Cl, 64%#
2o, X = Br, 72%



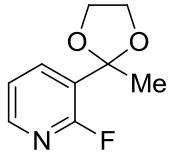
2p, R = CF_3, 97%
2q, R = CN, 53%
2r, R = OMe, 70%



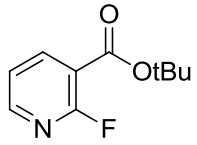
2s, 75%‡ (60%), 5.3:1



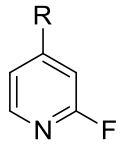
2t, 77%# (70%) 4.5:1



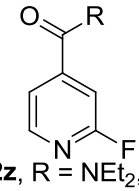
2u, 79%# (72%), 2.3:1



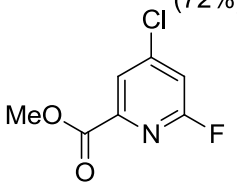
2v, 86%* (63%), 2.0:1



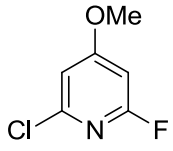
2w, R = ^{t}Bu, 80%#
2x, R = OMe, 75%*
2y, R = Cl, 62%*



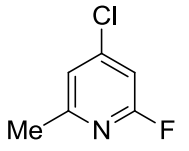
2z, R = NEt_2, 78% (66%)
2aa, R = OEt, 51%#,‡ (44%)



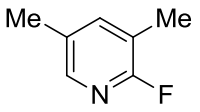
2ab, 74%* (72%)



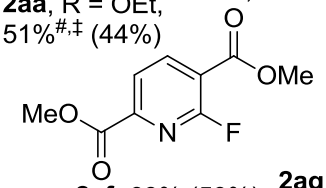
2ac, 57%#



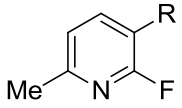
2ad, 75%*



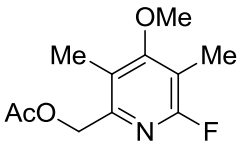
2ae, 44%#



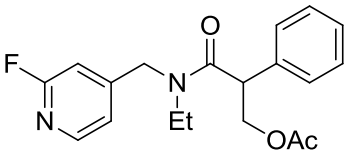
2af, 63% (59%)



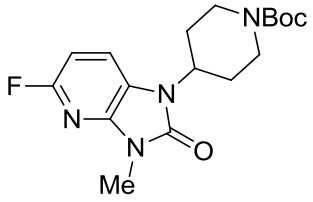
2ag, R = Me, 74%*
2ah, R = OBn, 99%* (75%)



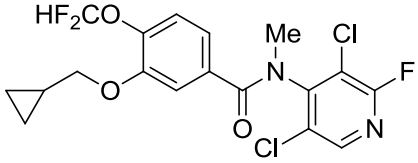
2ai, 94% (81%)



2aj, 70%#,‡ (74%)



2ak, 82% (75%)



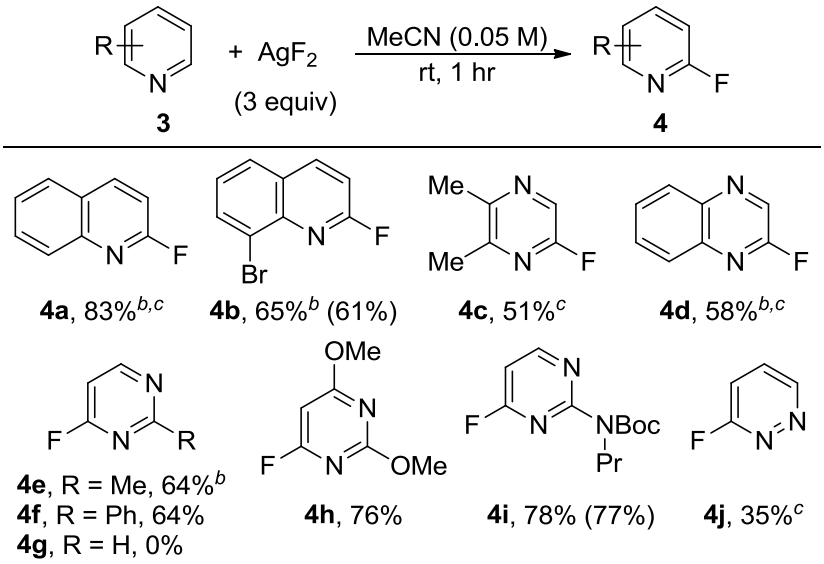
2al, 69% (67%)

[a]Reactions were performed with 0.1 mmol of pyridine to determine yields by ^{19}F NMR spectroscopy with $PhCF_3$ as an internal standard. Isolated yields for reactions performed on a 0.5 mmol scale are shown in parenthesis. *Reactions performed at 0.1 M. #Reactions performed at 0.025 M. †Reactions performed for 2 hrs. ‡Reactions performed at 50 °C.

The reactions with pyridines containing functional groups in the 3 positions formed the 2-fluoro-3-functionalized pyridine products preferentially. In some cases, a mixture of 2,3 and 2,5 functionalized products were formed, but these products were separable by silica gel chromatography. The C-H fluorination reaction also proceeded with several pyridines containing more than one substituent to form valuable disubstituted fluoropyridines **2ab-2ah** suitable for multiple further derivatizations (vide infra). The fluorination reaction also occurred with **1ai**, the precursor to the well-known drug Prilosec (omeprazole), in high yield to form the fully substituted fluoropyridine **2ai**.

The reaction conditions developed for the fluorination of pyridines led to the fluorination of a range of other types of six-membered nitrogen heterocycles. As shown in Table 8.3, quinolines, pyrazines, pyrimidines, and pyridazines reacted to afford mono-fluorinated products. Pyrimidines containing an alkyl, aryl, oxygen, or nitrogen group in the 2-position reacted to form the corresponding 4-fluoropyrimidines in good yield. In contrast, AgF_2 reacted with the π-excessive 5-membered aromatic heterocycles to form complex mixtures of products.[12]

Table 8.3 C-H Fluorination of other heteroarenes with AgF_2[a]



[a]Reactions were performed with 0.1 mmol of pyridine to determine yields by ^{19}F NMR spectroscopy with $PhCF_3$ as an internal standard. Isolated yields for reactions performed on a 0.5 mmol scale are shown in parenthesis. [#]Reactions performed at 0.025 M. [‡]Reactions performed at 50 °C.

Isolated yields of the reactions performed with 0.5 mmol of substrate were comparable to the yields determined by ^{19}F NMR spectroscopy for reactions performed on a 0.1 mmol scale. The volatility of some products prevented their isolation in high yield; in these cases, the yields determined by ^{19}F NMR spectroscopy are reported. In each reaction, only the mono-fluorination product is observed. Furthermore, the organic material in these reactions consists solely of the mono-fluorinated product and unreacted starting material (as determined by TLC and GC/MS). Because the presence of fluorine adjacent to nitrogen decreases the basicity and polarity of the products, relative to the starting material, the products are easily purified by silica gel chromatography or acid/base extractions.

To demonstrate the utility of these reactions for medicinal chemistry, the fluorination reactions were performed on several medicinally relevant compounds (Table 8.2). The fluorination of acetyl-Mydriacil (tropicamide, **1aj**), an anticholinergic drug containing a base-sensitive acetate and an acidic α-phenyl amide, reacted with AgF_2 to form **2aj** in 74% isolated yield. Compound **1ak**, containing a 1-(piperidin-4-yl)-1*H*-imidazo[4,5-*b*]-pyridin-2-(3H)-one core found in over 1000 calcitonin gene-related peptide (CGRP) receptor antagonists [13] also reacted smoothly to form **2ak** in high yield. Finally, **1al** reacted with AgF_2 to form a 2-fluorinated analogue of Daliresp (roflumilast), a drug used in the treatment of chronic obstructive pulmonary disease (COPD). These results demonstrate that the fluorination chemistry described herein can be used for the late-stage fluorination of medicinally important compounds.

The ability to conduct the fluorination reaction on multi-gram scale was assessed. The fluorination of 2,5-disubstituted pyridine **1am** on a 5-mmol scale (Figure 8.3) gave 1.34 grams of pure **2am** in 83% yield. The product of this reaction was then converted in one step to a fluorinated analogue of the anti-diabetic drug Actos (pioglitazone).

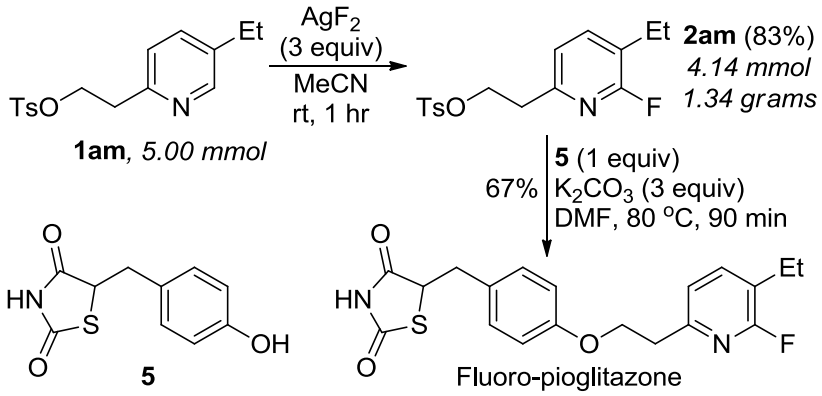


Figure 8.3 Gram-scale fluorination and the synthesis of fluoro-pioglitazone

As noted in the introduction, a fluorine atom in the 2-position of pyridines and azines allows several transformations to be conducted that cannot be conducted on the parent heteroarene or derivatives of it. For example, 2-fluoropyridines undergo selective lithiation in the 3-position of the ring with lithium diisopropylamide (LDA), and the resulting 3-pyridyl anion can be quenched with a variety of electrophiles.[14] 2-Fluoropyridines also undergo acid catalyzed hydrolysis to 2-pyridones.[15]

However, the most common reactions of 2-fluoropyridines are nucleophilic substitutions with a range of carbon and heteroatom nucleophiles.[16] Fluoroarenes are known to be more reactive than the other haloarenes toward nucleophilic aromatic substitution. With a mild method to prepare 2-fluoropyridines, a range of 2-pyridyl compounds can now be synthesized on a readily available intermediate. To demonstrate the utility of 2-fluoropyridines in structure-activity-relationship (SAR) studies, the C-H fluorination reaction was performed to prepare a model compound containing a benzyl-protected 2-pyridyl alcohol and a morpholine-derived amide (Figure 8.4). This 2-fluoropyridine reacted under mild conditions with oxygen, nitrogen, and carbon

nucleophiles in good yields. This sequence of C-H bond fluorination and substitution can be valuable for late-stage diversification of lead compounds.

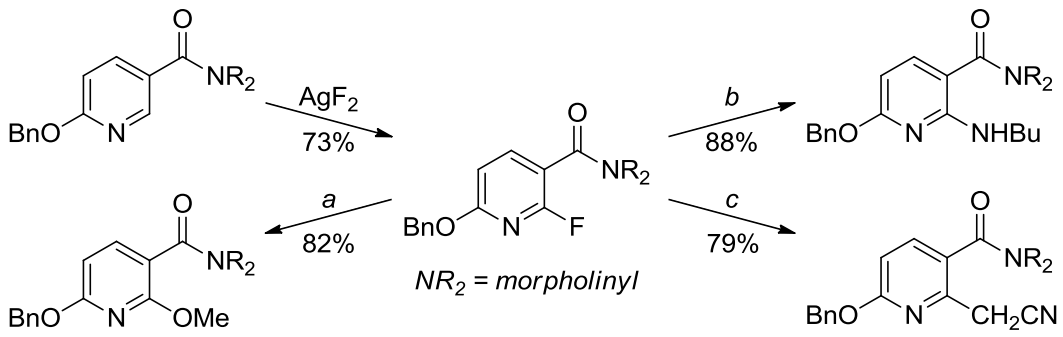
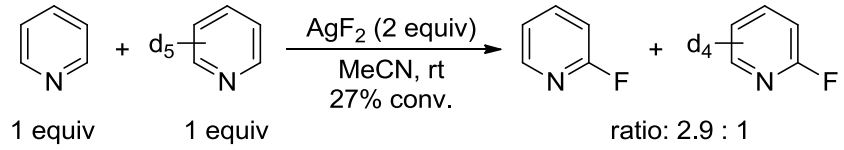


Figure 8.4 Synthetic utility of the 2-fluoropyridine products

A series of experiments were performed to gain insight into the mechanism of the reactions between pyridines and AgF_2. The insolubility and paramagnetism of AgF_2 prevented our gaining detailed data from NMR spectroscopic experiments. However, the ^{1}H NMR resonances of Me_3py did shift downfield in the presence of 3 equivalents of AgF_2,[17] suggesting that pyridines bind to AgF_2.

A kinetic isotope effect (KIE) was measured to assess the reversibility of the C-H bond cleavage process. The reaction of AgF_2 with equivalent amounts of pyridine and pyridine-d_5 revealed a kinetic isotope effect (KIE) of 2.9±0.1 after 27% conversion (Equation 8.1).



Equation 8.1 Competition experiment between pyridine and pyridine-d_5

An *N*-fluoropyridinium salt could be an intermediate in the reaction because *N*-fluoropyridinium fluoride, which is formed by the reaction of pyridine with F_2, is known to rearrange to 2-fluoropyridine at low temperature.[18] Isolated *N*-fluoropyridinium salts are also known to undergo base induced rearrangement to 2-fluoropyridines at ambient temperature.[19] Particularly relevant to our results, 2-fluoro-3-substituted pyridines are formed preferentially from 3-substituted *N*-fluoropyridium salts. This selectivity mirrors that of our reactions of 3-substituted pyridines with AgF_2.

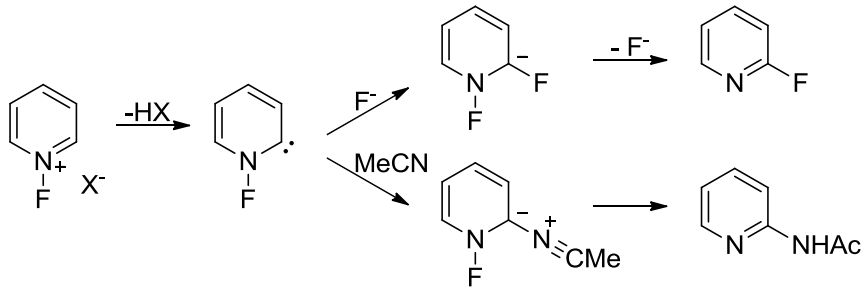


Figure 8.5 Exploring the possibility of an N-fluoropyridinium intermediate

However, the base induced rearrangements of isolated *N*-fluoropyridinium salts has been demonstrated to occur through electrophilic carbene intermediates (Figure 8.5),[19] which are known to react rapidly with MeCN to form pyridyl acetamides after hydrolysis.[20] Because our fluorination reactions are performed in MeCN, it is unlikely that a similar mechanism occurs for the reactions with AgF_2. Furthermore, reactions with AgF_2 in the presence of added base or fluoride occurred in yields that were similar to those obtained in the absence of these additives (Table 8.1). The base and fluoride should increase the rate of formation of the carbene intermediate and of the subsequent reaction with fluoride, respectively. Taken together, these results are inconsistent with the reactions of AgF_2 occurring through the intermediacy of an *N*-fluoropyridinium cation.

An alternative mechanism is one that involves addition of a fluorine radical from AgF_2 to the pyridine form a delocalized radical and AgF. However, several pieces of data are inconsistent with such a pathway. First, the exclusive selectivity for fluorination at the 2-position of pyridines contrasts the mixture of isomeric products formed in varying amounts, depending on the steric and electronic properties of the reactants, for the addition of alkyl, aryl, and fluoroalkyl radicals to pyridines.[21] Second, if the fluorine radical is nucleophilic, then the reaction would be expected to proceed in higher yield with more electron deficient azines, and if the radical is electrophilic, then fluorination of benzo-fused or free aryl rings would be expected compete with fluorination of the heteroarene, and neither prediction is observed. Third, 2,6-dimethylpyridine does not undergo fluorination, and a radical should add to the 3 or 4-position. Finally, the observed KIE of 2.9 would require reversible transfer of the fluorine radical from silver to the heteroarene, and the transfer of a fluorine radical from the arene to silver most likely has an inaccessibly high kinetic barrier and must occur faster than a more typical hydrogen-atom abstraction.

Instead, we propose that the fluorination occurs by a mechanism similar to that of the Chichibabin reaction (*vide supra*). This mechanism would involve initial coordination of AgF_2 to pyridine, followed by addition of the [Ag]-F bond across the π-system of the pyridine to form an amido-silver(II)-fluoride complex (Figure 8.6). Subsequent hydrogen atom abstraction by a second equivalent of AgF_2 from **7** would then form 2 equivalents of AgF and 1 equivalent of HF.[22] Alkyl and allyl, acyl, silyl and amido complexes of several metal complexes are known to add across the C=N bond of pyridines, including those of Ni and Cu[23] at or below room temperature. To determine if the analogous product from reaction of pyridine with AgF_2 lies at an accessible energy, we computed the relative ground-state energies of the pyridine-AgF_2 coordination complex (Figure 8.6, **6**) and the addition product (**7**) in an acetonitrile solvent continuum by DFT methods.[24] Compound

7 was calculated to lie only 9.6 kcal/mol higher in free energy at room temperature in acetonitrile than the pyridine-AgF_2 coordination complex **6**. These results imply that the proposed intermediate is accessible at room temperature. To account for the observed KIE of 2.9 and an overall barrier commensurate with the reaction times and temperatures, we propose that the coordination of pyridine to AgF_2 and the addition step are reversible; the transition state for hydrogen-atom abstraction would then lie at the highest energy along the reaction coordinate. In this case, the regioselectivity observed with 3-substituted pyridines would be controlled by the relative concentrations of the isomeric addition products and the relative rates of reaction of these two isomers with a second equivalent of AgF_2. The same trend in regioselectivity is observed in the Chichibabin reaction.[6]

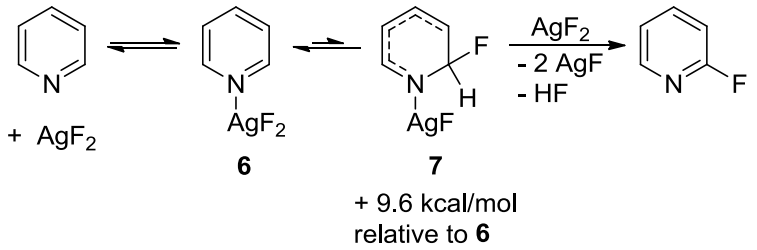


Figure 8.6 Proposed mechanism for the fluorination of pyridines with AgF_2

8.3 Conclusions

The halogenation of arenes and heteroarenes is a classic reaction in organic chemistry, but the fluorination of these reagents has required multiple steps. Even for laboratories equipped to use fluorine gas, the fluorination of functionalized pyridines occurs in low yields. Thus, the mild conditions, fast reaction times, broad scope, high tolerance for auxiliary functionality, and commercial availability of the reagent for the fluorination we report create the ability to generate fluorinated pyridines and diazines. Considering the high interest in generating fluorinated drug and agrochemical candidates and the high utility of fluorinated heteroarenes as synthetic intermediates, we anticipate that synthetic chemists will rapidly adopt this class of halogenation reaction.

8.4 Experimental

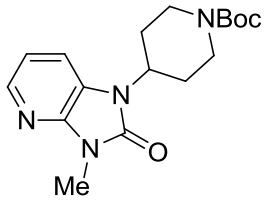
All manipulations were conducted under an inert atmosphere with a nitrogen-filled glovebox unless otherwise noted. All reactions were conducted in oven-dried vials fitted with a Teflon-lined screw cap under an atmosphere of nitrogen unless otherwise noted.

Silver difluoride (AgF_2) was purchased from Alfa Aesar and used as received. Acetonitrile was distilled from CaH_2 and stored over molecular sieves. Unless otherwise noted, all other reagents were purchased from commercial suppliers and used as received. 2-*tert*-butylpyridine (1c), 2-(2-methyl-1,3-dioxolan-2-yl)pyridine (**1k**), 2-pyridylmethyl acetate (**1l**), 3-(2-methyl-1,3-dioxolan-2-yl)pyridine (**1u**), *tert*-butyl nicotinate (**1v**), 4-chloropyridine (**1y**), toluene-4-sulfonic acid-2-(5-ethylpyridin-2-yl)-ethyl ester (**1am**), 5-(benzyloxy)-2-methylpyridine (**1ah**), 2-phenylpyrimidine (**3f**) and 5-(4-

hydroxybenzyl)thiazolidine-2,4-dione (**5**) were prepared according to literature procedures.

NMR chemical shifts are reported in ppm and referenced to residual solvent peaks ($CHCl_3$ in $CDCl_3$: 7.26 ppm for ^1H and 77.0 ppm for ^{13}C) or to an external standard (1% $CFCl_3$ in $CDCl_3$: 0 ppm for ^{19}F). Coupling constants are reported in hertz.

Synthesis of tert-butyl 4-(3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate (1ak)



To a vial was added sodium hydride (60% wt/wt in mineral oil, 44 mg, 1.1 mmol, 1.1 equiv) and DMF (4 mL). To the resulting suspension was added tert-butyl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate[13] over 5 minutes with rapid stirring. Iodomethane (70 µL, 1.1 mmol, 1.1 equiv) was then added dropwise and the resulting reaction mixture was stirred at room temperature for 90 min. The reaction was quenched with saturated aqueous ammonium chloride (3 mL) and diluted with water (10 mL). The aqueous mixture was extracted with EtOAc (3 x 20 mL) and the combined organic fractions were washed with water (3 x 50 mL) to remove DMF. The organic layer was dried with $MgSO_4$ and concentrated to a solid. The product was purified by silica gel chromatography eluting with 10:1 CH_2Cl_2 : MeOH to afford **1ak** as a beige solid (323 mg, 0.97 mmol, 97% yield).

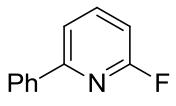
^1H NMR (600 MHz, $CDCl_3$) δ 8.04 (d, J = 4.1 Hz, 1H), 7.29 (d, J = 7.7 Hz, 1H), 6.96 (t, J = 6.3 Hz, 1H), 4.52 (t, J = 12.3 Hz, 1H), 4.31 (br, 2H), 3.49 (s, 3H), 2.86 (br, 2H), 2.19 (m, 2H), 1.83 (d, J = 11.6 Hz, 2H), 1.49 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 154.63 (s), 153.33 (s), 143.81 (s), 140.24 (s), 122.46 (s), 116.51 (s), 114.75 (s), 79.99 (s), 50.87 (s), 43.40 (s), 29.45 (s), 28.43 (s), 26.02 (s).

General Procedure for the Fluorination of Pyridines

To an oven-dried vial was added the pyridine substrate (0.50 mmol, 1.0 equiv) and MeCN (5.0 - 20.0 mL). While the solution was stirring rapidly, AgF_2 (219 mg, 1.50 mmol, 3.00 equiv) was added at once. The vial was sealed with a Teflon-lined cap and stirred at room temperature for 1 hour. The reaction was poured into a separatory funnel containing 20 mL of saturated aqueous $NaHCO_3$ and extracted with 30 mL of Et_2O. The organic layer was washed once with 20 mL of brine, dried over $MgSO_4$, and concentrated. The fluoropyridine product was purified by silica gel chromatography.

Synthesis of 2-fluoro-6-phenylpyridine (2a)

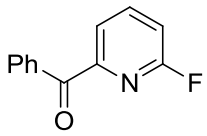


The general procedure for the fluorination of pyridines was performed with 2-phenylpyridine (78 mg, 0.50 mmol, 1.0 equiv), AgF_2 (219 mg, 1.50 mmol, 3.00 equiv) and 10 mL of MeCN. The product was purified by silica gel chromatography eluting with 9:1 hexanes : ethyl acetate (R_f = 0.54) to afford **2a** as a clear oil (71 mg, 0.41 mmol, 82% yield).

^1H NMR (600 MHz, $CDCl_3$) δ 8.01 (m, 2H), 7.84 (m, 1H), 7.63 (dd, J = 7.5, 2.5 Hz, 1H), 7.50 – 7.42 (m, 3H), 6.87 (dd, J = 8.1, 3.0 Hz, 1H).

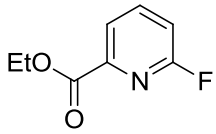
^{13}C NMR (151 MHz, $CDCl_3$) δ 163.3 (d, J = 238.1 Hz), 156.1 (d, J = 13.4 Hz), 141.6 (d, J = 7.7 Hz), 137.4 (s), 129.5 (s), 128.7 (s), 126.8 (s), 117.2 (d, J = 3.8 Hz), 107.5 (d, J = 37.7 Hz).
^{19}F NMR (376 MHz, $CDCl_3$) δ -69.6 (s).

Synthesis of 6-fluoro-2-benzoylpyridine (2g)



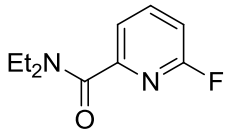
The general procedure for the fluorination of pyridines was performed with 2-benzoylpyridine (92 mg, 0.50 mmol, 1.0 equiv), AgF_2 (219 mg, 1.50 mmol, 3.00 equiv) and 10 mL of MeCN. The product was purified by silica gel chromatography eluting with 9:1 hexanes : ethyl acetate (R_f = 0.48) to afford **2g** as a white solid (54 mg, 0.27 mmol, 54% yield).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (dd, J = 8.3, 1.3 Hz, 2H), 8.02 (dd, J = 15.5, 7.7 Hz, 1H), 7.95 (ddd, J = 7.4, 2.2, 0.7 Hz, 1H), 7.64 – 7.59 (m, 1H), 7.53 – 7.47 (m, 2H), 7.17 (ddd, J = 8.1, 2.9, 0.7 Hz, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 191.8 (s), 161.9 (d, J = 242.2 Hz), 153.1 (d, J = 12.3 Hz), 142.0 (d, J = 7.5 Hz), 135.6 (s), 133.1 (s), 130.8 (s), 128.2 (s), 122.1 (d, J = 3.9 Hz), 112.8 (d, J = 36.9 Hz).
^{19}F NMR (376 MHz, $CDCl_3$) δ -69.3 (s).

Synthesis of ethyl 6-fluoropicolinate (2h)



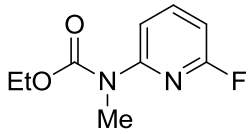
The general procedure for the fluorination of pyridines was performed with ethyl picolinate (76 mg, 0.50 mmol, 1.0 equiv), AgF_2 (219 mg, 1.50 mmol, 3.00 equiv) and 10 mL of MeCN. The product was purified by silica gel chromatography eluting with 3:1 hexanes : ethyl acetate (R_f = 0.56) to afford **2h** as a clear oil (57 mg, 0.34 mmol, 67% yield).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (dd, J = 7.6, 1.8 Hz, 1H), 7.95 (dd, J = 15.5, 7.7 Hz, 1H), 7.15 (dd, J = 8.1, 2.8 Hz, 1H), 4.46 (q, J = 7.1 Hz, 2H), 1.43 (t, J = 7.1 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 163.8 (s), 162.8 (d, J = 242.8 Hz), 146.5 (d, J = 12.6 Hz), 142.0 (d, J = 7.5 Hz), 122.5 (d, J = 3.8 Hz), 113.6 (d, J = 36.9 Hz), 62.1 (s), 14.1 (s).
^{19}F NMR (376 MHz, $CDCl_3$) δ -68.7 (s).

Synthesis of N,N-diethyl 6-fluoropicolinamide (2i)



The general procedure for the fluorination of pyridines was performed with N,N-diethyl picolinamide (89 mg, 0.50 mmol, 1.0 equiv), AgF_2 (219 mg, 1.50 mmol, 3.00 equiv) and 10 mL of MeCN. The product was purified by silica gel chromatography eluting with 3:1 hexanes : ethyl acetate (R_f = 0.25) to afford **2i** as a clear oil (74 mg, 0.38 mmol, 75% yield).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (dd, J = 15.6, 8.0 Hz, 1H), 7.50 (ddd, J = 7.4, 2.1, 0.5 Hz, 1H), 6.97 (ddd, J = 8.3, 2.7, 0.4 Hz, 1H), 3.54 (q, J = 7.1 Hz, 2H), 3.37 (q, J = 7.1 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 166.6 (s), 161.8 (d, J = 241.4 Hz), 153.1 (d, J = 12.9 Hz), 141.8 (d, J = 7.6 Hz), 120.5 (d, J = 4.1 Hz), 110.1 (d, J = 36.5 Hz), 43.1 (s), 40.2 (s), 14.0 (s), 12.6 (s).
^{19}F NMR (376 MHz, $CDCl_3$) δ -69.9 (s).

Synthesis of ethyl (6-fluoropyridin-2-yl)(methyl)carbamate (2j)



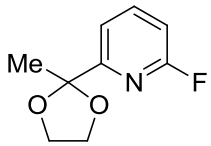
The general procedure for the fluorination of pyridines was performed with ethyl methyl(pyridin-2-yl)carbamate (90 mg, 0.50 mmol, 1.0 equiv), AgF_2 (219 mg, 1.50 mmol, 3.00 equiv) and 20 mL of MeCN. The product was purified by silica gel chromatography eluting with 10:1 hexanes : ethyl acetate (R_f = 0.45) to afford **2j** as a clear oil (49 mg, 0.25 mmol, 49% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 – 7.66 (m, 2H), 6.65 – 6.57 (m, 1H), 4.26 (q, J = 7.1 Hz, 2H), 3.42 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 161.5 (d, J = 238.4 Hz), 155.0 (s), 153.0 (d, J = 13.6 Hz), 141.7 (d, J = 7.4 Hz), 114.5 (d, J = 4.5 Hz), 103.2 (d, J = 36.1 Hz), 62.2 (s), 33.6 (s), 14.4 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -71.3 (s).

Synthesis of 2-fluoro-6-(2-methyl-1,3-dioxolan-2-yl)pyridine (2k)



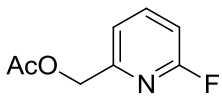
The general procedure for the fluorination of pyridines was performed with 2-(2-methyl-1,3-dioxolan-2-yl)pyridine (83 mg, 0.50 mmol, 1.0 equiv), AgF_2 (219 mg, 1.50 mmol, 3.00 equiv) and 10 mL of MeCN. The product was purified by silica gel chromatography eluting with 3:1 hexanes : ethyl acetate with 2% Et_3N (R_f = 0.51) to afford **2k** as a clear oil (83 mg, 0.45 mmol, 91% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (dd, J = 15.6, 8.0 Hz, 1H), 7.43 (ddd, J = 7.4, 2.3, 0.5 Hz, 1H), 6.86 (ddd, J = 8.1, 2.9, 0.4 Hz, 1H), 4.09 (m, 2H), 3.92 – 3.84 (m, 2H), 1.70 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 163.1 (d, J = 240.4 Hz), 159.9 (d, J = 12.0 Hz), 141.4 (d, J = 7.4 Hz), 116.5 (d, J = 4.0 Hz), 108.7 (d, J = 37.1 Hz), 107.7 (s), 64.9 (s), 24. 8 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -70.1 (s).

Synthesis of (6-fluoro-2-pyridinyl)methyl acetate (2l)



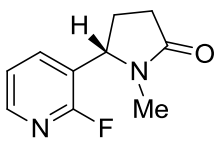
The general procedure for the fluorination of pyridines was performed with 2-pyridinylmethyl acetate (76 mg, 0.50 mmol, 1.0 equiv), AgF_2 (219 mg, 1.50 mmol, 3.00 equiv) and 10 mL of MeCN. The product was purified by silica gel chromatography eluting with 3:1 hexanes : ethyl acetate (R_f = 0.52) to afford **2l** as a clear oil (60 mg, 0.35 mmol, 71% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (dd, J = 15.7, 8.0 Hz, 1H), 7.23 (dd, J = 7.4, 2.1 Hz, 1H), 6.87 (dd, J = 8.2, 2.7 Hz, 1H), 5.15 (s, 2H), 2.17 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.3 (s), 163.0 (d, J = 240.5 Hz), 154.8 (d, J = 10.5 Hz), 141.7 (d, J = 7.5 Hz), 118.7 (d, J = 3.4 Hz), 108.6 (d, J = 36.6 Hz), 65.6 (s), 20.7 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -70.3 (s).

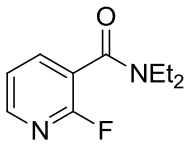
Synthesis of 2-fluorocotinine (2s)



The general procedure for the fluorination of pyridines was performed with (-)-cotinine (88 mg, 0.50 mmol, 1.0 equiv), AgF_2 (219 mg, 1.50 mmol, 3.00 equiv) and 10 mL of MeCN at 50 ^{o}C. The major isomer was purified by silica gel chromatography eluting with 99:1 ethyl acetate : triethylamine (R_f = 0.26) to afford **2s** as a clear oil (58 mg,

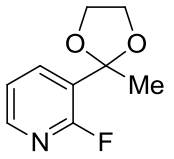
0.30 mmol, 60% yield).
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 (d, J = 4.1 Hz, 1H), 7.54 (t, J = 8.5 Hz, 1H), 7.24 – 7.20 (m, 1H), 4.80 (dd, J = 8.0, 4.6 Hz, 1H), 2.71 (s, 3H), 2.57 – 2.38 (m, 3H), 1.87 (m, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 175.4 (s), 161.1 (d, J = 239.1 Hz), 147.0 (d, J = 15.0 Hz), 137.7 (d, J = 4.6 Hz), 122.9 (d, J = 27.4 Hz), 121.9 (d, J = 3.7 Hz), 57.7 (s), 29.4 (s), 28.3 (s), 26.5 (s).
^{19}F NMR (376 MHz, $CDCl_3$) δ -75.6 (s).

Synthesis of N,N-diethyl-2-fluoronicotinamide (2t)



The general procedure for the fluorination of pyridines was performed with N,N-diethylnicotinamide (89 mg, 0.50 mmol, 1.0 equiv), AgF_2 (219 mg, 1.50 mmol, 3.00 equiv) and 20 mL of MeCN. Both isomers of the product were purified by silica gel chromatography eluting with 1:1 hexanes : ethyl acetate to afford **2t** as a clear oil (63 mg, 0.32 mmol, 64% yield) and iso-**2t** as a clear oil (6 mg, 0.03 mmol, 6%).
Spectral data for **2t**:
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.27 (d, J = 3.3 Hz, 1H), 7.80 (t, J = 8.1, 1H), 7.27 (d, J = 6.4 Hz, 1H), 3.58 (q, J = 7.1, 2H), 3.21 (q, J = 7.0 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H), 1.11 (t, J = 7.1 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 164.32 (d, J = 3.8 Hz), 158.54 (d, J = 238.2 Hz), 148.30 (d, J = 14.3 Hz), 139.51 (d, J = 4.4 Hz), 121.60 (d, J = 4.2 Hz), 120.00 (d, J = 34.2 Hz), 43.07 (s), 39.38 (s), 13.88 (s), 12.71 (s).
^{19}F NMR (376 MHz, $CDCl_3$) δ -73.0 (s).
Spectral data for **iso-2t**:
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.85 (t, J = 7.5 Hz, 1H), 6.99 (d, J = 8.3 Hz, 1H), 3.55 (br, 2H), 3.28 (br, 2H), 1.25 (br, 3H), 1.16 (br, 3H).
^{19}F NMR (376 MHz, $CDCl_3$) δ -69.2 (s).

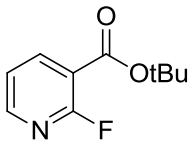
Synthesis of 2-fluoro-3-(2-methyl-1,3-dioxolan-2-yl)pyridine (2u)



The general procedure for the fluorination of pyridines was performed with 3-(2-methyl-1,3-dioxolan-2-yl)pyridine (83 mg, 0.50 mmol, 1.0 equiv), AgF_2 (219 mg, 1.50 mmol, 3.00 equiv) and 20 mL of MeCN. Both isomers of the product were purified by silica gel chromatography eluting with 9:1 hexanes : ethyl acetate to afford **2u** as a clear oil (43 mg, 0.23 mmol, 47% yield) and iso-**2u** as a clear oil (23 mg, 0.13 mmol, 25%).
Spectral data for **2u**:
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 – 8.11 (m, 1H), 7.90 (ddd, J = 9.6, 7.4, 2.0 Hz, 1H), 7.14 (ddd, J = 7.1, 4.9, 1.9 Hz, 1H), 4.10 – 4.01 (m, 2H), 3.85 – 3.77 (m, 2H), 1.72 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 160.6 (d, J = 241.6 Hz), 147.1 (d, J = 14.9 Hz), 137.9 (d, J = 4.5 Hz), 124.9 (d, J = 27.9 Hz), 121.0 (d, J = 4.4 Hz), 106.4 (d, J = 6.6 Hz), 64.8 (s), 25.6 (d, J = 3.0 Hz).
^{19}F NMR (376 MHz, $CDCl_3$) δ -69.2 (s).
Spectral data for **iso-2u**:

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.85 (td, J = 8.1, 2.4 Hz, 1H), 6.88 (dd, J = 8.5, 2.8 Hz, 1H), 4.08 – 4.01 (m, 2H), 3.80 – 3.73 (m, 2H), 1.63 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 163.3 (d, J = 238.8 Hz), 145.1 (d, J = 15.1 Hz), 138.7 (d, J = 8.0 Hz), 136.7 (d, J = 4.4 Hz), 108.9 (d, J = 37.4 Hz), 107.4 (s), 64.6 (s), 27.6 (s)
^{19}F NMR (376 MHz, $CDCl_3$) δ -72.6 (s).

Synthesis of tert-butyl 2-fluoronicotinate (2v)

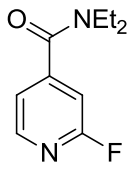


The general procedure for the fluorination of pyridines was performed with tert-butyl nicotinate (90 mg, 0.50 mmol, 1.0 equiv), AgF_2 (219 mg, 1.50 mmol, 3.00 equiv) and 5 mL of MeCN. Both isomers of the product were purified by silica gel chromatography eluting with 9:1 hexanes : ethyl acetate to afford **2v** as a clear oil (41 mg, 0.21 mmol, 42% yield) and iso-**2v** as a clear oil (21 mg, 0.11 mmol, 21%).

Spectral data for **2v**:
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.32 (d, J = 4.1 Hz, 1H), 8.28 (t, J = 8.4 Hz, 1H), 7.26 – 7.23 (m, 1H), 1.57 (s, 9H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 162.2 (d, J = 7.9 Hz), 161.5 (d, J = 249.2 Hz), 150.9 (d, J = 15.3 Hz), 142.9 (s), 121.2 (d, J = 4.7 Hz), 115.6 (d, J = 24.8 Hz), 82.8 (s), 28.1 (s).
^{19}F NMR (376 MHz, $CDCl_3$) δ -65.9 (s).

Spectral data for **iso-2v**:
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.80 (d, J = 2.2 Hz, 1H), 8.33 (td, J = 8.1, 2.4 Hz, 1H), 6.96 (dd, J = 8.5, 2.8 Hz, 1H), 1.59 (s, 9H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 165.6 (d, J = 244.7 Hz), 163.3 (s), 150.1 (d, J = 16.4 Hz), 142.4 (d, J = 9.2 Hz), 126.1 (d, J = 4.5 Hz), 109.2 (d, J = 37.5 Hz), 82.3 (s), 28.1 (s)
^{19}F NMR (376 MHz, $CDCl_3$) δ -65.2 (s).

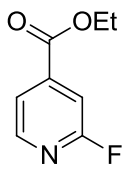
Synthesis of N,N-diethyl-2-fluoroisonicotinamide (2z)



The general procedure for the fluorination of pyridines was performed with N,N-diethyl isonicotinamide (89 mg, 0.50 mmol, 1.0 equiv), AgF_2 (219 mg, 1.50 mmol, 3.00 equiv) and 10 mL of MeCN. The product was purified by silica gel chromatography eluting with 3:1 hexanes : ethyl acetate to afford **2z** as a clear oil (65 mg, 0.33 mmol, 66% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, J = 5.0 Hz, 1H), 7.16 – 7.14 (m, 1H), 6.91 (d, J = 2.3 Hz, 1H), 3.54 (q, J = 7.1 Hz, 2H), 3.20 (q, J = 7.1 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H), 1.12 (t, J = 7.1 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 167.2 (d, J = 3.4 Hz), 163.6 (d, J = 240.7 Hz), 150.1 (d, J = 7.1 Hz), 148.3 (d, J = 14.8 Hz), 118.6 (d, J = 4.3 Hz), 107.0 (d, J = 38.8 Hz), 43.1 (s), 39.4 (s), 14.2 (s), 12.7 (s).
^{19}F NMR (376 MHz, $CDCl_3$) δ -69.0 (s).

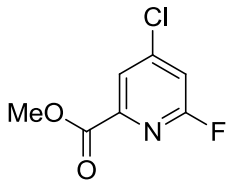
Synthesis of ethyl 2-fluoroisonicotinate (2aa)



The general procedure for the fluorination of pyridines was performed with ethyl isonicotinate (76 mg, 0.50 mmol, 1.0 equiv), AgF_2 (219 mg, 1.50 mmol, 3.00 equiv) and 20 mL of MeCN at 50 ^{o}C. The product was purified by silica gel chromatography eluting with 3:1 hexanes : ethyl acetate to afford **2aa** as a clear oil (37 mg, 0.22 mmol, 44% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, J = 5.0 Hz, 1H), 7.74 (d, J = 4.9 Hz, 1H), 7.49 (s, 1H), 4.42 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 164.2 (d, J = 240.0 Hz), 163.8 (d, J = 3.9 Hz), 148.5 (d, J = 14.5 Hz), 143.2 (d, J = 7.9 Hz), 120.7 (d, J = 4.5 Hz), 109.7 (d, J = 39.1 Hz), 62.2 (s), 14.1 (s).
^{19}F NMR (376 MHz, $CDCl_3$) δ -69.5 (s).

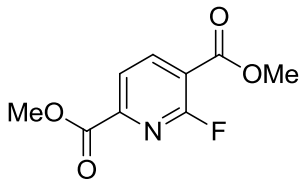
Synthesis of methyl 4-chloro-6-fluoropicolinate (2ab)



The general procedure for the fluorination of pyridines was performed with methyl 4-chloropicolinate (86 mg, 0.50 mmol, 1.0 equiv), AgF_2 (219 mg, 1.50 mmol, 3.00 equiv) and 5 mL of MeCN. The product was purified by silica gel chromatography eluting with 6:1 hexanes : ethyl acetate (R_f = 0.45) to afford **2ab** as a white solid (68 mg, 0.36 mmol, 72% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.18 (dd, J = 2.3, 1.7 Hz, 1H), 4.01 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 163.3 (s), 163.1 (d, J = 244.7 Hz), 148.7 (d, J = 9.9 Hz), 146.8 (d, J = 14.5 Hz), 123.5 (d, J = 4.3 Hz), 113.9 (d, J = 40.5 Hz), 53.2 (s)
^{19}F NMR (376 MHz, $CDCl_3$) δ -67.2 (s).

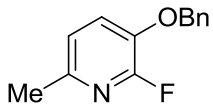
Synthesis of dimethyl 6-fluoropyridine-2,5-dicarboxylate (2af)



The general procedure for the fluorination of pyridines was performed with dimethyl pyridine-2,5-dicarboxylate (98 mg, 0.50 mmol, 1.0 equiv), AgF_2 (219 mg, 1.50 mmol, 3.00 equiv) and 10 mL of MeCN. The product was purified by silica gel chromatography eluting with 5:1 hexanes : ethyl acetate (R_f = 0.25) to afford **2af** as a white solid (63 mg, 0.30 mmol, 59% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (dd, J = 8.7, 7.8 Hz, 1H), 8.11 (dd, J = 7.7, 1.4 Hz, 1H), 4.03 (s, 3H), 3.99 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 163.5 (s), 162.7 (d, J = 7.9 Hz), 160.6 (d, J = 253.4 Hz), 148.9 (d, J = 13.2 Hz), 144.4 (s), 122.4 (d, J = 4.5 Hz), 117.0 (d, J = 25.2 Hz), 53.2 (s), 53.0 (s).
^{19}F NMR (376 MHz, $CDCl_3$) δ -65.1 (s).

Synthesis of 3-(benzyloxy)-2-fluoro-6-methylpyridine (2ah)

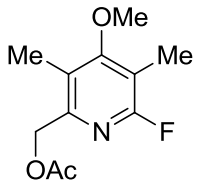


The general procedure for the fluorination of pyridines was performed with 5-benzyloxy-2-methylpyridine (100 mg, 0.50 mmol, 1.0 equiv), AgF_2 (219 mg, 1.50 mmol, 3.00 equiv) and 5 mL of MeCN. The product was purified by silica gel chromatography eluting with 6:1 hexanes : ethyl acetate (R_f = 0.50) to afford **2ah** as a clear oil (82 mg, 0.38 mmol, 75% yield).

^{1}H NMR (500 MHz, CDCl3) δ 7.44 – 7.29 (m, 5H), 7.20 (dd, J = 10.2, 8.0 Hz, 1H), 6.89 (d, J = 7.9 Hz, 1H), 5.12 (s, 2H), 2.41 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 153.0 (d, J = 237.7 Hz), 147.2 (d, J = 12.3 Hz), 139.1 (d, J = 25.7 Hz), 135.8 (s), 128.5 (s), 128.2 (s), 127.3 (s), 124.9 (d, J = 3.7 Hz), 120.5 (d, J = 4.3 Hz), 71.4 (s), 22.6 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -87.4 (s).

Synthesis of (6-fluoro-4-methoxy-3,5-dimethylpyridin-2-yl)methyl acetate (2ai)



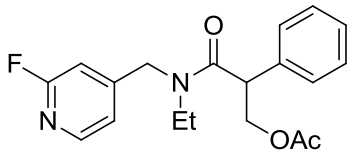
The general procedure for the fluorination of pyridines was performed with (4-methoxy-3,5-dimethylpyridin-2-yl)methyl acetate (105 mg, 0.500 mmol, 1.00 equiv), AgF_2 (219 mg, 1.50 mmol, 3.00 equiv) and 10 mL of MeCN. The product was purified by silica gel chromatography eluting with 3:1 hexanes : ethyl acetate (R_f = 0.51) to afford **2ai** as a clear oil (92 mg, 0.40 mmol, 81% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.09 (s, 2H), 3.78 (s, 3H), 2.22 (s, 3H), 2.18 (s, 3H), 2.12 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.52 (s), 167.22 (d, J = 7.9 Hz), 160.85 (d, J = 235.0 Hz), 148.88 (d, J = 16.1 Hz), 123.64 (d, J = 5.3 Hz), 112.17 (d, J = 32.9 Hz), 64.63 (s), 60.24 (s), 20.62 (s), 10.59 (s), 8.24 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -76.19 (s).

Synthesis of acyl 2-fluorotropicamide (2aj)



The general procedure for the fluorination of pyridines was performed with acyl tropicamide (163 mg, 0.500 mmol, 1.00 equiv), AgF_2 (219 mg, 1.50 mmol, 3.00 equiv) and 20 mL of MeCN at 50 ^{o}C. The product was purified by silica gel chromatography eluting with ethyl acetate (R_f = 0.75) to afford **2aj** as a clear oil (127 mg, 0.37 mmol, 74% yield).

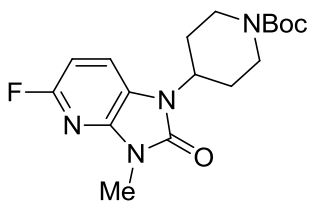
The compound exists as a 2.5:1 ratio of amide diastereomers on the NMR time scale.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (d, J = 5.1 Hz), 8.09 (d, J = 5.1 Hz), 7.43 – 7.27 (m), 7.24 (d, J = 6.7 Hz), 6.93 (d, J = 5.0 Hz), 6.89 (d, J = 5.0 Hz), 6.64 (s), 4.73 – 4.50 (m), 4.38 – 4.17 (m), 4.14 – 4.09 (m), 3.86 (dd, J = 9.2, 5.1 Hz), 3.70 (dq, J = 14.0, 7.1 Hz), 3.51 – 3.38 (m), 3.23 – 3.13 (m), 2.06 (s), 2.03 (s), 1.23 (dt, J = 33.9, 7.1 Hz), 1.10 (t, J = 7.1 Hz), 1.05 (t, J = 7.1 Hz).

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.81 (s), 170.51 – 170.30 (m), 164.04 (d, J = 239.0 Hz), 163.90 (d, J = 238.3 Hz), 153.02 (d, J = 7.6 Hz), 152.40 (d, J = 7.4 Hz), 147.79 (d, J = 15.2 Hz), 147.37 (d, J = 15.3 Hz), 135.00 (s), 134.65 (s), 128.99 (s), 128.93 (s), 127.93 (s), 127.75 (s), 119.70 (d, J = 3.9 Hz), 118.88 (d, J = 3.9 Hz), 107.33 (d, J = 38.1 Hz), 106.69 (d, J = 38.5 Hz), 66.30 (s), 66.17 (s), 48.88 (d, J = 2.8 Hz), 48.04 (s), 47.50 (s), 42.54 (s), 41.50 (s), 20.57 (s), 20.51 (s), 13.80 (s), 12.19 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -70.9 (s), -71.9 (s).

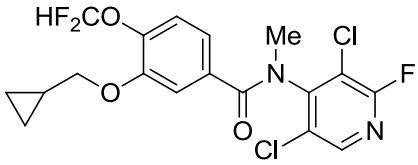
Synthesis of tert-butyl 4-(5-fluoro-3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate (2ak)



The general procedure for the fluorination of pyridines was performed with **1ak** (166 mg, 0.500 mmol, 1.00 equiv), AgF_2 (219 mg, 1.50 mmol, 3.00 equiv) and 10 mL of MeCN. The product was purified by silica gel chromatography eluting with 2:1 hexanes : ethyl acetate to afford **2ak** as a white solid (132 mg, 0.38 mmol, 75% yield).

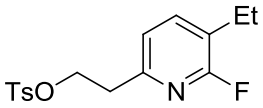
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (dd, J = 8.1, 6.4 Hz, 1H), 6.57 (d, J = 8.3 Hz, 1H), 4.50 (tt, J = 12.5, 4.1 Hz, 1H), 4.30 (br, 2H), 3.45 (s, 3H), 2.85 (s, 2H), 2.20 – 2.04 (br, 2H), 1.84 (d, J = 12.0 Hz, 2H), 1.49 (s, 9H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 159.01 (d, J = 235.8 Hz), 154.55 (s), 153.37 (s), 141.52 (d, J = 18.3 Hz), 119.55 (d, J = 3.6 Hz), 118.78 (d, J = 8.5 Hz), 99.69 (d, J = 37.9 Hz), 80.00 (s), 51.02 (s), 43.26 (s), 29.50 (s), 28.37 (s), 26.17 (s).
^{19}F NMR (376 MHz, $CDCl_3$) δ -83.7 (s).

Synthesis of 3-(cyclopropylmethoxy)-N-(3,5-dichloro-2-fluoropyridin-4-yl)-4-(difluoromethoxy)-N-methylbenzamide (2al)



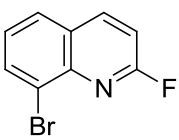
The general procedure for the fluorination of pyridines was performed with **1al**[25] (104 mg, 0.250 mmol, 1.00 equiv), AgF_2 (109 mg, 0.75 mmol, 3.00 equiv) and 5 mL of MeCN. The product was purified by silica gel chromatography eluting with 6:1 hexanes : ethyl acetate (R_f = 0.37) to afford **2al** as a clear oil (73 mg, 0.17 mmol, 67% yield).
The compound exists as a 10:1 ratio of amide diastereomers on the NMR time scale.
Spectral data for major diastereomer:
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.10 (s, 1H), 6.97 (d, J = 8.0 Hz, 1H), 6.90 (d, J = 7.9 Hz, 1H), 6.60 (t, J = 74.8 Hz, 1H), 3.78 (d, J = 6.2 Hz, 2H), 3.32 (s, 3H), 1.21 (s, 1H), 0.64 (d, J = 6.0 Hz, 2H), 0.33 (s, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 169.31 (s), 158.35 (d, J = 241.4 Hz), 150.77 (d, J = 2.9 Hz), 149.81 (s), 144.57 (d, J = 15.6 Hz), 142.48 (s), 132.44 (s), 128.39 (d, J = 6.0 Hz), 121.32 (s), 120.04 (s), 117.37 (s), 115.72 (t, J = 277.9 Hz), 113.81 (s), 73.84 (s), 34.78 (s), 9.82 (s), 3.10 (s).
^{19}F NMR (376 MHz, $CDCl_3$) δ -71.17 (s), -85.19 (d, J = 74.8 Hz).

Synthesis of 2-(5-ethyl-6-fluoro-2-pyridinyl)ethyl 4-methylbenzenesulfonate (2am)



The general procedure for the fluorination of pyridines was performed with 2-(5-ethyl-2-pyridinyl)ethyl 4-methylbenzenesulfonate (153 mg, 0.500 mmol, 1.00 equiv), AgF_2 (219 mg, 1.50 mmol, 3.00 equiv) and 5 mL of MeCN. The product was purified by silica gel chromatography eluting with 3:1 hexanes : ethyl acetate (R_f = 0.55) to afford **2am** as a white solid (133 mg, 0.41 mmol, 82% yield).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 8.3 Hz, 2H), 7.50 (dd, J = 9.9, 7.5 Hz, 1H), 7.28 (d, J = 8.1 Hz, 2H), 6.97 (dd, J = 7.4, 1.4 Hz, 1H), 4.37 (t, J = 6.4 Hz, 2H), 3.01 (t, J = 6.4 Hz, 2H), 2.61 (q, J = 7.6 Hz, 2H), 2.44 (s, 3H), 1.22 (t, J = 7.6 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 161.1 (d, J = 238.9 Hz), 152.1 (d, J = 13.4 Hz), 144.6 (s), 140.2 (d, J = 6.2 Hz), 132.5 (s), 129.6 (s), 127.6 (s), 123.3 (d, J = 30.9 Hz), 121.1 (d, J = 4.0 Hz), 68.8 (s), 36.1 (s), 21.5 (s), 21.4 (s), 13.5 (s).
^{19}F NMR (376 MHz, $CDCl_3$) δ -75.6 (s).

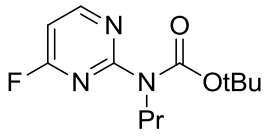
Synthesis of 8-bromo-2-fluoroquinoline (4b)



The general procedure for the fluorination of pyridines was performed with 8-bromoquinoline (104 mg, 0.500 mmol, 1.00 equiv), AgF_2 (219 mg, 1.50 mmol, 3.00 equiv) and 20 mL of MeCN. The product was

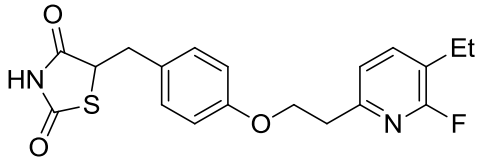
purified by silica gel chromatography eluting with 6:1 hexanes : ethyl acetate (R_f = 0.43) to afford **4b** as a white solid (69 mg, 0.31 mmol, 61% yield).
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.28 (t, J = 8.3 Hz, 1H), 8.07 (d, J = 7.5 Hz, 1H), 7.83 (d, J = 8.1 Hz, 1H), 7.41 (t, J = 7.8 Hz, 1H), 7.15 (dd, J = 8.7, 2.9 Hz, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 161.4 (d, J = 244.2 Hz), 143.1 (d, J = 16.3 Hz), 142.7 (d, J = 9.9 Hz), 134.1 (s), 127.9 (d, J = 1.6 Hz), 127.2 (s), 126.5 (d, J = 2.1 Hz), 122.6 (s), 110.9 (d, J = 42.4 Hz).
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.2 (s).

Synthesis of tert-butyl (4-fluoropyrimidin-2-yl)(propyl)carbamate (4i)



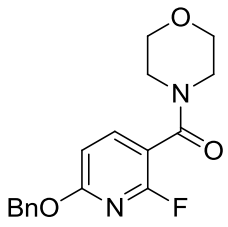
The general procedure for the fluorination of pyridines was performed with tert-butyl (pyrimidin-2-yl)(propyl)carbamate (119 mg, 0.500 mmol, 1.00 equiv), AgF_2 (219 mg, 1.50 mmol, 3.00 equiv) and 10 mL of MeCN. The product was purified by silica gel chromatography eluting with 6:1 hexanes : ethyl acetate (R_f = 0.50) to afford **4i** as a clear oil (99 mg, 0.39 mmol, 77% yield).
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.65 – 8.58 (m, 1H), 6.60 (m, 1H), 3.88 (m, 2H), 1.73 – 1.63 (m, 2H), 1.53 (s, 9H), 0.91 (m, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 169.29 (d, J = 252.5 Hz), 161.06 (d, J = 6.5 Hz), 160.87 (d, J = 15.5 Hz), 152.90 (s), 100.89 (d, J = 29.6 Hz), 81.63 (s), 49.01 (s), 27.83 (s), 21.73 (s), 10.93 (s).
^{19}F NMR (376 MHz, $CDCl_3$) δ -61.25 (s).

Synthesis of fluoro-pioglitazone



To a vial was added **2am** (323 mg, 1.00 mmol, 1.00 equiv), 5-(4-hydroxybenzyl)thiazolidine-2,4-dione (223 mg, 1.00 mmol, 1.00 equiv), K_2CO_3 (415 mg, 3.00 mmol, 3.00 equiv) and DMF (5 mL). The resulting reaction mixture was heated at 80 ^{o}C for 90 minutes. The reaction mixture was diluted with EtOAc (40 mL) and washed with H_2O (3 x 20 mL) and brine (1 x 20 mL). The EtOAc layer was dried over $MgSO_4$ and concentrated to an oil. The product was purified by silica gel chromatography eluting with 1:1 hexanes : ethyl acetate (R_f = 0.64) to afford fluoro-pioglitazone as a light yellow oil which solidified upon standing (251 mg, 0.670 mmol, 67% yield).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (dd, J = 9.9, 7.5 Hz, 1H), 7.08 (d, J = 8.5 Hz, 2H), 6.90 (dd, J = 7.4, 1.4 Hz, 1H), 6.79 (d, J = 8.5 Hz, 2H), 5.81 (br, 1H), 4.37 (dd, J = 9.5, 3.8 Hz, 1H), 3.91 (td, J = 7.0, 1.9 Hz, 2H), 3.40 (dd, J = 14.1, 3.8 Hz, 1H), 3.04 (dd, J = 14.1, 9.5 Hz, 1H), 2.89 (t, J = 7.1 Hz, 2H), 2.62 (q, J = 7.6 Hz, 2H), 1.21 (t, J = 7.6 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 173.89 (s), 171.28 (s), 161.29 (d, J = 239.9 Hz), 155.56 (s), 153.45 (d, J = 12.9 Hz), 140.61 (d, J = 6.2 Hz), 130.41 (s), 127.25 (s), 123.44 (d, J = 30.4 Hz), 120.73 (d, J = 4.0 Hz), 115.62 (s), 51.69 (s), 41.06 (s), 37.67 (s), 33.99 (s), 21.52 (s), 13.51 (s).
^{19}F NMR (376 MHz, $CDCl_3$) δ -74.91 (d, J = 9.8 Hz).

Synthesis of (6-(benzyloxy)-2-fluoropyridin-3-yl)(morpholino)methanone



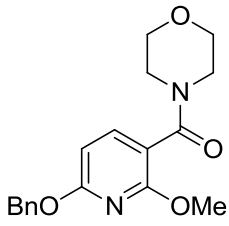
The general procedure for the fluorination of pyridines was performed with (6-(benzyloxy)pyridin-3-yl)(morpholino)methanone (1.49 g, 5.00 mmol, 1.00 equiv), AgF_2 (2.19 g, 15.0 mmol, 3.00 equiv) and 100 mL of MeCN. The product was purified by silica gel chromatography eluting with 1:1 hexanes : ethyl acetate (R_f = 0.43) to afford (6-(benzyloxy)-2-fluoropyridin-3-yl)(morpholino)methanone as a colorless oil which solidified to a white solid upon standing (1.17 g, 3.70 mmol, 74% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (m, 1H), 7.45 (d, J = 7.3 Hz, 2H), 7.39 (t, J = 7.4 Hz, 2H), 7.35 (t, J = 7.3 Hz, 1H), 6.75 (dd, J = 8.2, 1.0 Hz, 1H), 5.36 (s, 2H), 3.78 (s, 4H), 3.68 (s, 2H), 3.40 (s, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 164.16 (d, J = 4.7 Hz), 163.65 (d, J = 13.8 Hz), 157.05 (d, J = 241.3 Hz), 143.14 (d, J = 4.0 Hz), 135.97 (s), 128.56 (s), 128.26 (s), 128.18 (s), 108.95 (d, J = 31.0 Hz), 108.66 (d, J = 5.0 Hz), 68.83 (s), 66.74 (s), 66.73 (s), 47.69 (s), 42.71 (s).

^{19}F NMR (376 MHz, C_6D_6) δ -72.46 (s).

Synthesis of (6-(benzyloxy)-2-methoxypyridin-3-yl)(morpholino)methanone

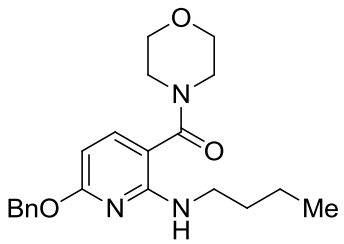


To a vial was added (6-(benzyloxy)-2-fluoropyridin-3-yl)(morpholino)methanone (32 mg, 0.10 mmol, 1.0 equiv) and anhydrous methanol (400 µL). Potassium tert-butoxide (56 mg, 0.50 mmol, 5.0 equiv) was added and the resulting reaction mixture was heated at 65 ^{o}C for 2.5 hours. The reaction mixture was quenched with aqueous ammonium acetate (2 mL) and diluted with EtOAc (2 mL). The organic layer was collected and the aqueous layer was extracted with EtOAc (2 x 3 mL). The combined organic layers were dried over $MgSO_4$, and concentrated to an oil. The product was purified by silica gel chromatography eluting with 1:1 hexanes : ethyl acetate (R_f = 0.40) to afford the title compound as a colorless oil (28 mg, 0.085 mmol, 85% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (d, J = 8.1 Hz, 1H), 7.43 (d, J = 7.3 Hz, 2H), 7.36 (t, J = 7.5 Hz, 2H), 7.31 (t, J = 7.3 Hz, 1H), 6.42 (d, J = 8.1 Hz, 1H), 5.38 (s, 2H), 3.93 (s, 3H), 3.77 (br, 2H), 3.75 (br, 2H), 3.62 (br, 2H), 3.30 (br, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 166.73 (s), 163.08 (s), 158.27 (s), 141.08 (s), 137.09 (s), 128.46 (s), 127.91 (s), 127.78 (s), 110.26 (s), 102.42 (s), 67.95 (s), 66.86 (s), 66.81 (s), 53.65 (s), 47.56 (s), 42.38 (s).

Synthesis of (6-(benzyloxy)-2-(butylamino)pyridin-3-yl)(morpholino)methanone



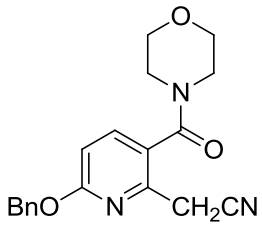
To a vial was added (6-(benzyloxy)-2-fluoropyridin-3-yl)(morpholino)methanone (32 mg, 0.10 mmol, 1.0 equiv) and n-butylamine (500 µL). The resulting reaction mixture was stirred at room temperature for 45 minutes. To the reaction mixture was added water (5 mL) and EtOAc (3 mL). The organic layer was collected and the aqueous layer was extracted with EtOAc (3 x 3 mL). The combined organic layers were dried over $MgSO_4$ and concentrated.

The product was purified by silica gel chromatography eluting with 3:1 hexanes : ethyl acetate (R_f = 0.42) to afford the title compound as a colorless oil (32 mg, 0.087 mmol, 87% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, J = 7.4 Hz, 2H), 7.36 (t, J = 7.5 Hz, 2H), 7.30 (t, J = 7.3 Hz, 1H), 7.26 (d, J = 8.2 Hz, 1H), 6.60 (br, 1H), 5.97 (d, J = 8.2 Hz, 1H), 5.38 (s, 2H), 3.71 – 3.67 (m, 4H), 3.62 – 3.58 (m, 4H), 3.41 (t, J = 7.1 Hz, 2H), 1.61 – 1.54 (m, 2H), 1.45 – 1.35 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.74 (s), 163.98 (s), 157.63 (s), 140.00 (s), 137.64 (s), 128.38 (s), 127.84 (s), 127.70 (s), 102.12 (s), 95.95 (s), 67.33 (s), 67.02 (s), 46.14 (s), 40.94 (s), 31.77 (s), 20.31 (s), 13.91 (s).

Synthesis of 2-(6-(benzyloxy)-3-(morpholine-4-carbonyl)pyridin-2-yl)acetonitrile



The reaction was performed similarly to the procedure reported by the Merck process group. To a round bottom flask was added (6-(benzyloxy)-2-fluoropyridin-3-yl)(morpholino)methanone (47 mg, 0.15 mmol, 1.0 equiv), acetonitrile (12 µL, 0.23 mmol, 1.5 equiv) and toluene (100 µL). The reaction mixture was cooled to 0^{o}C and a 0.5 M solution of KHMDS in PhMe (900 µL, 0.45 mmol, 3.0 equiv) was added dropwise. The resulting reaction mixture was stirred at 0^{o}C for 1 hour then warmed to room temperature and stirred for an additional 6 hours. The reaction was quenched with a saturated ammonium chloride solution (2 mL) and extracted with PhMe (3 x 3 mL). The combined organic layers were concentrated. The product was purified by silica gel chromatography eluting with 1:1 hexanes : ethyl acetate (R_f= 0.27) to afford the title compound as a colorless oil (40 mg, 0.12 mmol, 79% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (d, J = 7.3 Hz, 2H), 7.45 (d, J = 8.4 Hz, 1H), 7.39 (t, J = 7.3 Hz, 2H), 7.34 (t, J = 7.1 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 5.44 (s, 2H), 3.96 (s, 2H), 3.79 (br, 4H), 3.66 (br, 2H), 3.39 (br, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 167.35 (s), 163.34 (s), 146.71 (s), 137.85 (s), 136.47 (s), 128.49 (s), 128.40 (s), 128.12 (s), 123.08 (s), 116.69 (s), 110.56 (s), 68.34 (s), 66.66 (s, 2C), 47.89 (s), 42.43 (s), 24.65 (s).

DFT Calculations

SDD/6-31+G* calculations were performed with Gaussian 09. SDD functionals have been shown to be suitable for computing the energies of Ag complexes.[24] Structure optimizations were performed in both the gas-phase and in an acetonitrile solvent continuum. All structures were confirmed to be stationary points by the absence of negative frequency values.

Cartesian Coordinates for SDD/6-31+G* optimized stationary points.

Pyridine-AgF_2 coordination complex, gas phase (Figure 8.6, A)

	Atomic Number		X	Y	Z
1	47	0	1.200051	0.000005	0.000005
2	7	0	-0.839949	-0.000097	-0.000050
3	6	0	-1.541686	-0.906603	-0.707704
4	6	0	-1.541917	0.906471	0.707668
5	6	0	-2.947627	-0.947094	-0.739269
6	1	0	-0.941891	-1.637763	-1.278455
7	6	0	-2.947936	0.947167	0.739280
8	1	0	-0.942018	1.637686	1.278383
9	6	0	-3.658636	0.000078	-0.000099
10	1	0	-3.467435	-1.708895	-1.334087
11	1	0	-3.467592	1.709128	1.334039
12	1	0	-4.757900	-0.000785	0.000457
13	9	0	2.160080	-1.206534	1.144123
14	9	0	2.160021	1.206640	-1.144062

Pyridine-AgF_2 coordination complex, MeCN solvent continuum (Figure 8.6, A)

	Atomic Number		X	Y	Z
1	47	0	1.399751	0.000004	-0.000065
2	7	0	-0.814923	-0.000010	-0.000028
3	6	0	-1.472780	-1.171030	-0.000013
4	6	0	-1.472782	1.171010	-0.000006
5	6	0	-2.866397	-1.205702	-0.000006
6	1	0	-0.850206	-2.061152	-0.000005
7	6	0	-2.866397	1.205684	0.000008
8	1	0	-0.850199	2.061126	0.000057
9	6	0	-3.571821	-0.000008	0.000013
10	1	0	-3.379139	-2.162335	0.000039
11	1	0	-3.379139	2.162317	0.000008
12	1	0	-4.658437	-0.000006	0.000036
13	9	0	1.474169	-1.982557	0.000179
14	9	0	1.474091	1.982577	0.000167

Insertion compound, gas phase (Figure 8.6 B)

	Atomic Number		X	Y	Z
1	6	0	2.276898	-0.252796	1.141705
2	6	0	2.585337	1.038524	0.863159
3	6	0	2.002004	1.681461	-0.283445
4	6	0	1.045203	1.029518	-1.029048
5	7	0	0.542164	-0.218472	-0.663344
6	1	0	3.289553	1.589590	1.478455
7	1	0	2.719881	-0.787826	1.972905
8	1	0	2.315516	2.684140	-0.553337
9	1	0	0.579653	1.456521	-1.910454
10	6	0	1.362424	-1.014562	0.236298
11	1	0	0.746209	-1.775993	0.713863
12	47	0	-1.303154	-0.035401	-0.073969
13	9	0	-3.131880	0.155503	0.687229
14	9	0	2.262001	-1.807297	-0.593172

Insertion compound, MeCN solvent continuum (Figure 8.6, B)

	Atomic Number		X	Y	Z
1	6	0	-2.923871	0.837585	0.289551
2	6	0	-3.530655	-0.366578	0.057636
3	6	0	-2.729471	-1.509856	-0.154242
4	6	0	-1.314447	-1.379705	-0.152036
5	7	0	-0.673039	-0.252533	0.061525
6	1	0	-4.613681	-0.444079	0.023935
7	1	0	-3.487635	1.751232	0.451501
8	1	0	-3.168403	-2.481737	-0.351801
9	1	0	-0.699905	-2.252961	-0.355900
10	6	0	-1.433628	0.954145	0.347174
11	1	0	-1.107780	1.326369	1.329250
12	47	0	1.441812	-0.093830	0.021908
13	9	0	3.427481	-0.042698	0.028681
14	9	0	-1.025711	1.938851	-0.571554

8.5 References

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"Selective C-H Fluorination of Pyridines and Diazines Inspired by a Classic Amination Reaction"
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(10) Commercial AgF_2 is a black crystalline solid.
(11) The direct fluorination of pyridines with F_2 gas has been demonstrated for alkyl, chloro, and ester substituted pyridines in 31-70% yields. The direct fluorination with F_2 gas of pyridines containing benzy, acyl, or bromo substituents resulted in less than 30% yield. See references 5-7.
(12) The presence of 5-membered aromatic heterocycles are not tolerated in the fluorination of pyridines.
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CHAPTER 9

Synthesis and Late-Stage Functionalization of Complex Molecules through C-H Fluorination and S_NAr

9.1 Introduction

Pyridines and diazines are among the most prevalent heterocycles in biologically active compounds. They are found in 2 of the 5 top-selling pharmaceuticals,[1] and 6 of the 23 small molecules approved by the FDA in 2013.[2] 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, multi-step 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 occur by the addition of carbon-centered radicals to heteroarenes (Figure 9.1).[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.[3a,5]

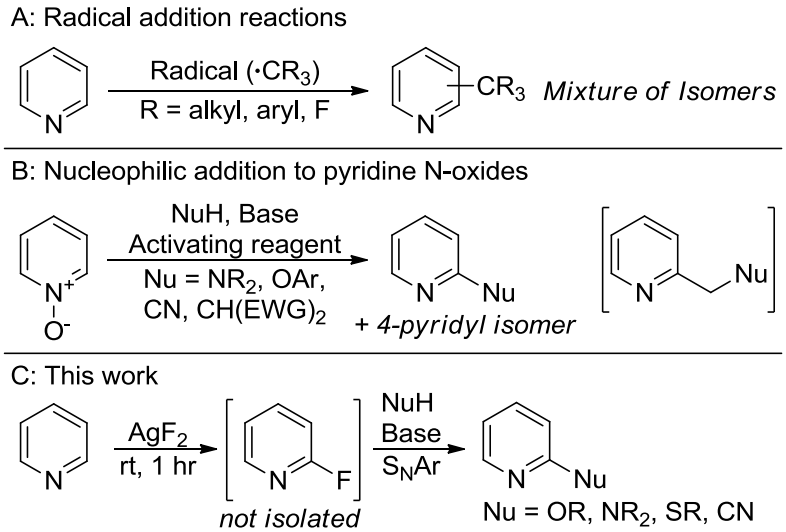


Figure 9.1 Strategies for the C-H functionalization of pyridines

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 (Figure 9.1). 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 (pK_a 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 S_NAr. 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 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 heteroarenes by conversion of the heteroarene to the corresponding heteroarylboronate 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 heteroarenes. 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 diazines[10] at the position α to nitrogen with AgF_2 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-fluoro 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 (Figure 9.1). In addition to revealing the potential of this reaction for the functionalization of complex heteroarenes, we demonstrate how the combination of CHF 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.

9.2 Results and Discussion

S_NAr reactions of 2- or 4-halopyridines 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 hydroxypyridines with neat POX_3 (X = Br, Cl) at high temperatures.

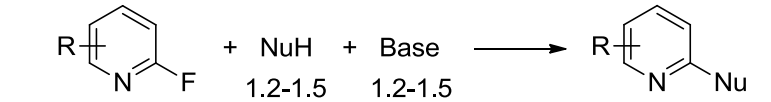
The majority of S_NAr reactions with halopyridines have been performed with chloropyridines. Chloropyridines are more available commercially than other halopyridines, but the reactions of fluoropyridines are likely to be faster than those of chloropyridines. As for S_NAr reactions of arenes, the S_NAr 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 fluoro*arenes* 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 ($LiBH_3NR_2$), 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, these reports are of limited use to the practicing organic chemist. Most reactions that have been reported in the patent literature for a given class of nucleophile react under different conditions, and therefore, the scope of each set of reaction conditions is ambiguous. In most cases, the S_NAr reactions were performed with activated 2-fluoropyridine substrates. Thus, it was unclear from these limited studies if mild and general S_NAr reactions with fluoroheteroarenes 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 thiols under relatively mild conditions. The reaction conditions we identified afforded *quantitative* conversion to the substitution products, as indicated by GC/MS and TLC (Table 9.1). 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.

Table 9.1 Reaction conditions for the S_NAr of 2-fluoropyridines



R = 6-Ph or 5-Me

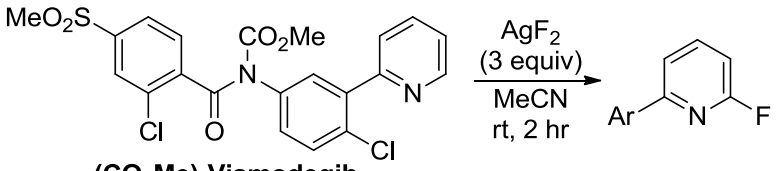
NuH	Base	Solvent	Temp	Time (h)
1°, 2°, or 3° alcohol	KO^{t}Bu	THF	50 °C	3
ArOH	KO^{t}Bu	DMF	80 °C	6
1° or 2° amine	^{i}Pr$_2$NEt	DMSO	120 °C	18
Amide (N-H)	NaH	DMF	100 °C	3
N-heterocycle	NaH	DMF	100 °C	1-3
KCN (3 equiv)	-	DMSO	120 °C	18
NaSR	-	THF	50 °C	3

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 reactions through a short silica-filled pipette and evaporating the solvent was sufficient to perform the subsequent S_NAr reactions. Yields of the S_NAr reactions conducted after filtering the reaction through Celite were low, due to the presence of soluble Ag salts.

For the fluorination-S_NAr sequence to be used broadly, procedures for conducting the reaction without specialized equipment for excluding air and moisture are needed. AgF_2 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.[10] However, despite the water sensitivity of AgF_2, 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 (CO_2Me)-vismodegib, a drug recently approved for the treatment of basal-cell carcinoma (Table 9.2). Assembling the fluorination reaction in a glovebox (oxygen and water content <1 ppm), in an oven-dried vial, with MeCN that had been rigorously dried over CaH_2, afforded the fluorinated vismodegib derivative in 99% yield by ^{19}F NMR spectroscopy.

Table 9.2 Assessing the impact of water and air on the fluorination reaction with AgF_2[a]



(CO_2Me)-Vismodegib

Method of drying MeCN	Rxn vial dried	Solids weighed	Atmosphere	Yield (NMR)
CaH_2	Yes	In glovebox	N_2	99%
CaH_2	Yes	In air	N_2	84%
CaH_2	No	In air	Air	79%
Molecular Sieves	No	In air	Air	85%
None	No	In air	Air	65%

[a] Reactions were performed with 0.2 mmol of (CO_2Me)-vismodegib with 2 mL of MeCN in 4 mL vials.

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 CaH_2. AgF_2 was weighed quickly in air, added to the pyridine solution, and the vial was sealed under an atmosphere of N_2. The reaction assembled in this manner afforded the 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 fluoropyridine product (79%).

Acetonitrile dried with 5 weight % of 3Å molecular sieves for 24 h was a suitable solvent; The reaction of (CO_2Me)-vismodegib with AgF_2 assembled by weighing the solid reagents in air in a non-dried vial sealed under an atmosphere of air, afforded the fluorinated product in 85% yield. The water content in MeCN dried over 5 wt % molecular sieves for 24 hours is near 4 ppm, and the water content further decreases with time.[14] 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 AgF_2 is sensitive to water and should be stored under an inert atmosphere. Reactions performed on the bench top occur in yields that are comparable to those performed under rigorously anhydrous reaction conditions.

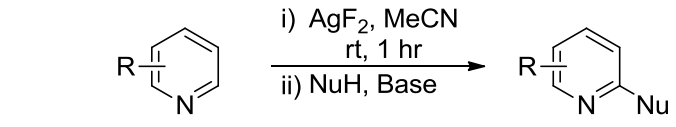
AgF_2 is supplied as a black, microcrystalline solid that should be stored under an inert atmosphere. As AgF_2 undergoes decomposition with moisture, a noticeable color change from black to yellow or brown is observed. For all reactions reported here, and in our previous report, AgF_2 was used as received from Alfa Aesar and stored in a nitrogen-filled glovebox in a plastic bottle. In our experience, reactions with AgF_2 supplied from Strem provide comparable results to reactions performed with AgF_2 from Alfa Aesar.

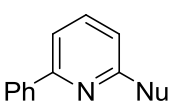
Having identified convenient methods for conducting both the fluorination and S_NAr reactions and having developed a protocol to conduct the two reactions in sequence, we investigated the scope of the fluorination-S_NAr process. Representative examples illustrating the scope of the combined reactions are shown in Tables 9.3 and 9.4. 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 (**2**, **4**, **11**, **12**, **14**, **15**) and/or electronically deactivated (**2**, **9**, **13**, **15**) towards S_NAr reactions afforded the substitution products in good yields. Substrates containing alkyl groups in the 2-position reacted uneventfully (**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 (Figure 9.1). A wide range of functional groups were tolerated, including ethers, halides, ketones, acetals, esters, amides, ethyl and

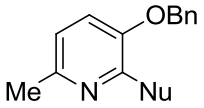
t-butyl carbamates, nitriles, and sulfones. It is notable that the azetidine in **11** (Table 9.4) did not undergo ring opening, a competing reaction observed under acidic conditions.[15]

Table 9.3 General scope of the tandem C-H fluorination and S_NAr reactions

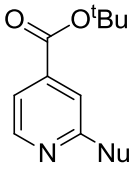




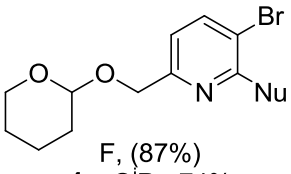
F, (88%)
1a, OBu, 84%
1b, O^{i}Pr, 84%
1c, O^{t}Bu, 81%
1d, O-(*p*-Bu-C_6H_4), 73%
1e, NHC_8H_{17}, 60%
1f, morpholino, 75%
1g, CN, 61%



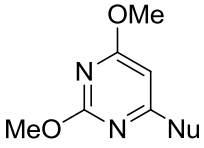
F, (99%)
2a, OBu, 77%
2b, O^{i}Pr, 78%
2c, O^{t}Bu, 77%
2d, pyrrolyl, 59%



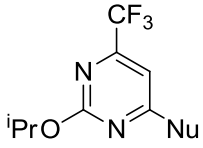
F, (64%)
3a, O-(*m*-Br-C_6H_4), 40%
3b, pyrrolidinonyl, 46%
3c, pyrrolyl, 45%



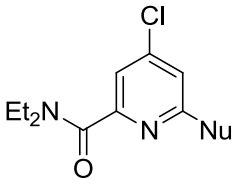
F, (87%)
4a, O^{i}Pr, 74%
4b, NHC_8H_{17}, 70%
4c, S^{t}Bu, 51%



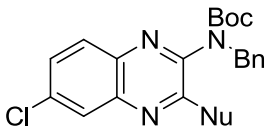
F, (76%)
5a, O^{t}Bu, 71%
5b, NHC_8H_{17}, 71%
5c, pyrrolidinonyl, 63%



F, (75%)
6a, O-(*m*-OMe-C_6H_4), 50%
6b, morpholino, 50%



F, (82%)
7a, O^{t}Bu, 70%
7b, NBu_2, 71%
7c, indolyl, 61%



F, (99%)
8a, OBu, 92%
8b, furfurylamino, 82%[b]
8c, imidazolyl, 83%
8d, 3,5-Me_2pyrazolyl, 68%

[a] Isolated yields from the 2-step sequence for reactions performed with 0.2 mmol of heteroarene. Yields in parentheses were determined by ^{19}F NMR spectroscopy for the independent fluorination reaction. [b] The isolated product contained ~5% of an inseparable impurity. [c] The Boc-group was cleaved during the S_NAr reaction.

The reactions of chloropyridines **7** and **11** revealed a high selectivity for substitution of a fluoride over a chloride under the S_NAr reaction conditions shown in Table 9.1. This high selectivity, along with the high functional group compatibility, is attributed to the milder reaction conditions we developed for the S_NAr 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

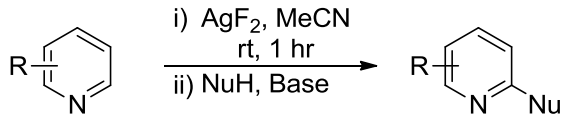
reactions under conditions much milder than previously reported and can be performed in the presence of a wide range of functional groups, including electrophilic functional groups.

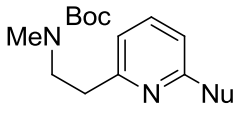
Six-membered heteroarenes containing two nitrogen atoms (diazines) are prevalent subunits in medicinal chemistry. Radical addition reactions to diazines are commonplace[3] (Figure 9.1), but a single example of nucleophilic addition of a heteroatom to a diazine-*N*-oxide for C-H functionalization has been demonstrated.[6c] Like pyridines, diazines react with AgF_2 with exclusive selectivity for fluorination adjacent to nitrogen.[10] Thus, we considered that the combination of C-H bond fluorination and S_NAr reactions could be conducted with these heterocycles to form functionalized diazine products. Indeed, pyrimidines (**5**, **6**) and pyrazines (**8**) reacted in the 2-step sequence following the standard conditions we developed for the fluorination and S_NAr reactions reported in Table 9.1. This sequence allowed several poly-substituted diazines to be prepared through C-H functionalization. Because the conditions for both the fluorination and the S_NAr reactions with diazines are the same as those for pyridines, the substrate scope with respect to pendant functionality is likely to be comparable for functionalized pyridines and diazines. This C-H fluorination-S_NAr sequence was also applied to the synthesis of a reverse transcriptase inhibitor containing a tetra-substituted pyrimidine (*vide infra*).

With conditions established for the fluorination and S_NAr 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 Meniere's disease. Reaction of **9** with AgF_2 formed the corresponding 2-fluoropyridine in nearly quantitative yield (98%). This electronically deactivated fluoropyridine intermediate reacted with nucleophiles derived from butanol, morpholine and indole to provide several 2-substituted analogs of betahistine. Although betahistine is a relatively simple compound that can be prepared in one step form 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 fluorinatin/S_NAr strategy for late-stage functionalization avoids lengthy synthetic sequences to prepare derivatives of betahistine.

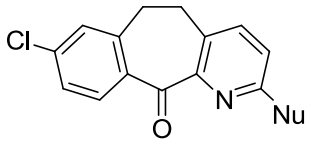
We also conducted the fluorination of compound **10**, the direct precursor to loratadine (Claritin) and desloratadine (Clarinex), two common antihistamines. Compound **10** is prepared in 2 steps from 3-methylpicolinic acid under relatively harsh reaction conditions (^nBuLi, KO^tBu for the first step; $SOCl_2$, $AlCl_3$ 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 analogs of **10** more directly through fluorination and S_NAr 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 analogs of **10**.

Table 9.4 Tandem C-H fluorination and S_NAr reactions of medicinally relevant compounds

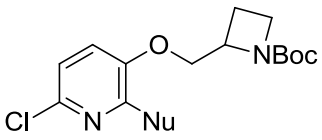




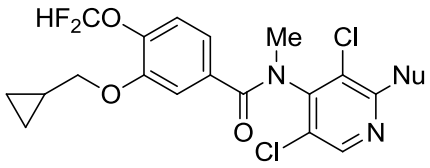
(Boc)-Betahistine
F, (98%)
9a, OBu, 60%
9b, morpholino, 47%
9c, indolyl, 51%



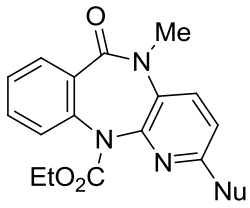
Precursor to Loratadine and Desloratadine
F, (53%)
10a, 1,2-isopropylideneglycerol, 47%
10b, piperidino, 31%
10c, pyrazolyl, 40%



(Boc)-Tebanicline
F, (65%)
11a, OBu, 53%
11b, NHC_8H_{17}, 56%
11c, imidazolyl, 38%



(Me)-Roflumilast
F, (69%)
12a, O^{i}Pr, 44%
12b, NHC_8H_{17}, 47%



Precursor to Pirenzepine
F, (57%)
13a, O^{t}Bu, 43%
13b, S^{t}Bu, 53%
13c, O-(*m*-Cl-C_6H_4), 48%

[a]Isolated yields from the 2-step sequence for reactions performed with 0.2 mmol of heteroarene. Yields in parentheses were determined by ^{19}F NMR spectroscopy for the independent fluorination reaction. [b]The isolated product contained ~5% of an inseparable impurity.

Our C-H functionalization method also gave access to a series of (Boc-protected) derivatives of tebanicline (**11**), a potent non-opiod 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_NAr also led to a convenient synthesis of 2-alkoxy and 2-amino analogs 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-aminopyridine. Thus, the syntheses of the 2-substituted analogs 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 multi-step syntheses of the appropriate pyridine, in addition to performing the subsequent amide-bond formation for each derivative. In contrast, the CHF-S_NAr strategy we report allows rapid access to analogs that would otherwise require several synthetic steps to prepare.

In a similar manner, analogs 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 aryloxy 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 3 steps from 2-chloro-3-aminopyridine.

Because many medicinally important compounds contain multiple heteroaryl rings it would be valuable if the fluorination were 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 (Figure 9.2) 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_5 demonstrated that coordination of AgF_2 to pyridine is reversible and that cleavage of the C-H bond is irreversible.[10]

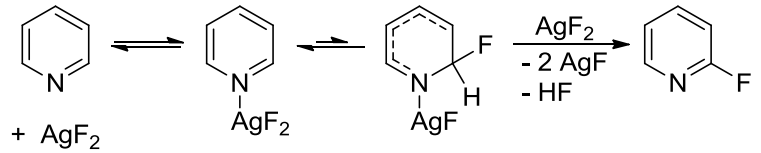
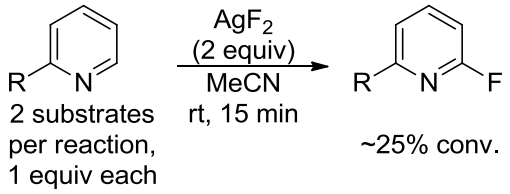


Figure 9.2 Proposed mechanism for the fluorination of pyridines with AgF_2

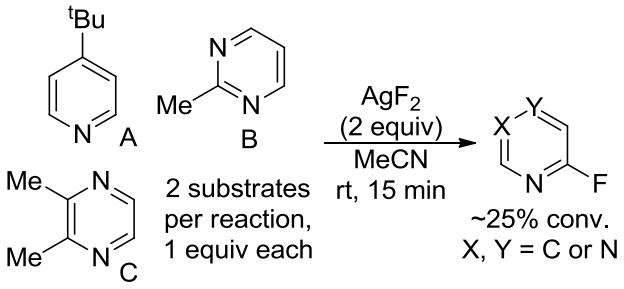
To determine how the electronic properties of the heteroarene influence the relative rates of fluorination, we conducted a series of competition experiments. In these experiments, AgF_2 was allowed to react with a 1:1 mixture of two different pyridines and diazines. Because the yield of the fluorination reactions conducted with a large excess of pyridine, relative to AgF_2, is low, reactions containing 1 equivalent of each heteroarene (0.1 mmol each) and 2 equivalents of AgF_2 (0.2 mmol) were run, and the reactions were quenched after 15 minutes 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 9.5. 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-alkyl pyridine over two alkyl-substituted diazines was observed; the competition between 2-methylpyridimidine and 2,3-dimethylpyrazine showed that the pyrimidine was the more reactive diazine by a factor of 3.3.

Table 9.5 Competition experiments between electronically different pyridines and diazines with AgF_2[a]



	R = Et	R = OMe	R = Cl
Substrate pKa	5.97	3.28	0.72
Yield of independent fluorination reaction	94%	57%	41%
2-Fluoropyridine product ratio in competition experiment	>20 >20 --	<1 -- >20	-- <1 <1



	A	B	C
Substrate pKa:	5.99	2.3	2.2
Yield of independent fluorination reaction:	80%	64%	51%
Fluoroheteroarene product ratio:	>20 : >20 : –	<1 -- 3.3 :	-- <1 1

[a] Product ratios were determined by ^{19}F NMR spectroscopy of the crude reaction mixture after quenching with aqueous $NaHCO_3$.

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 equivalents of AgF_2 to give 38% yield of the 6-fluoropyridine after 15 minutes. Similarly, 2-methoxypyridine reacts in 36% yield, and 2-chloropyridine reacts in 9% yield after 15 minutes. 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.

To assess the relative reactivity of multiple pyridines in the context of a medicinally important compound, we conducted the fluorination and S_NAr reaction of etoricoxib (Figure 9.3), 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.

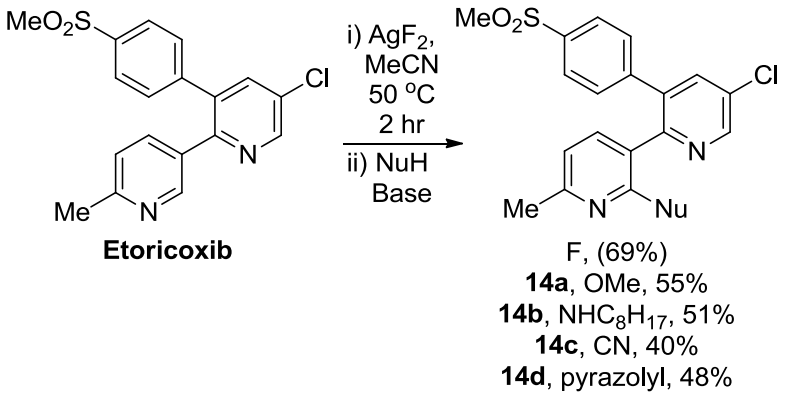
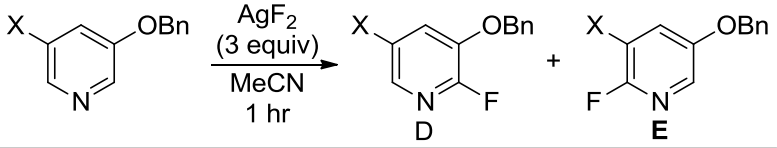


Figure 9.3 Site-selective C-H functionalization of etoricoxib

Many medicinally active pyridines contain two inequivalent 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-fluoropyridine isomers include those containing 3-alkyl, 3-CO_2R, and 3-$C(O)NR_2$ 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 site-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 9.6).

Table 9.6 Fluorination of 3,5-disubstituted pyridines with AgF_2[a]



X	Temp (°C)	concentration (M)	ratio (D:E)	Combined yield (D+E)
Br	50	.050	15:1	49%
Cl	50	.025	8.1:1	64%
Me	50	.025	>20:1	62%
Ph	50	.050	4.2:1	68%
CN	50	.025	12:1	67%
CF_3	rt	.050	20:1	85%

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 (Figure 9.4), a drug used for the treatment of metastatic non-small cell lung cancer, contains such a heteroaromatic unit. Reaction of crizotinib 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-benzyloxypyridine (Table 9.6), 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 benzyloxy group of Crizotinib 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 benzyloxy 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.

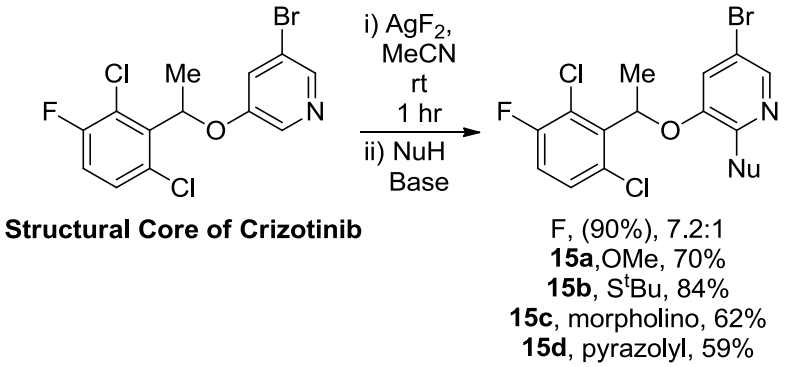


Figure 9.4 Preparation of several analogs of the precursor to crizotinib

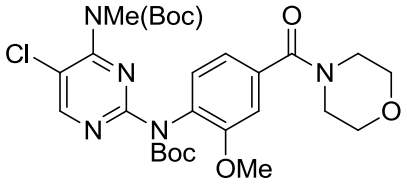
Even though the 2-fluoro-3-benzyloxypydridine intermediate is both sterically and electronically deactivated towards S_NAr, several 2-substituted derivatives were prepared under the standard conditions for the S_NAr step shown in Table 9.1. Even a

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_NAr reactions were not separable by standard silica gel chromatography, even though the 2-fluoropyridine isomers could be separated by HPLC and GC.

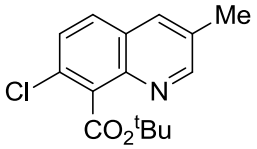
Although we have demonstrated that the C-H fluorination and S_NAr reactions occur with broad scope and can be conducted on complex molecules, there are some limitations. As we reported previously,[10] the fluorination reaction is not compatible with free amines or alcohols, carboxylic acids, aldehydes, or electron-rich 5-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 9.7. 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_NAr reaction conditions can be employed for substitution reactions on a variety of 2-fluoroheteroarenes. However, we did find substrates that underwent competing side-reactions faster than they underwent S_NAr (Table 9.7). Fluorinated analogs of tropicamide underwent retro-Michael addition under the basic reaction conditions. Although we demonstrated that *tert*-butyl esters remain intact during the S_NAr reactions (Table 9.3, substrate **3**), we found that aryl acetates are cleaved faster than substitution of fluoride. This cleavage was observed when attempting S_NAr reactions of bisacodyl. Finally, very electron-rich and sterically hindered pyridines, such as the precursor to Nexium, underwent the S_NAr step in low yields; more forcing conditions resulted in the formation of side-products.

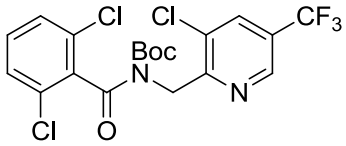
Table 9.7 Substrates that reacted in low yields for the C-H fluorination or S_NAr reactions



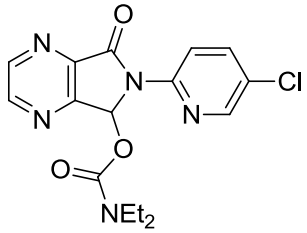
$(Boc)_2$-HG-10-102-01
Low yield for fluorination



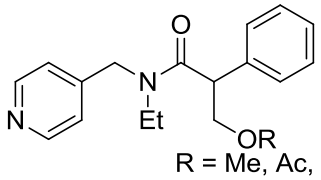
Quinmerac, ^{t}Bu-ester
Low yield for fluorination



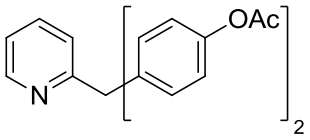
(Boc)-Fluopicolide
No fluorination



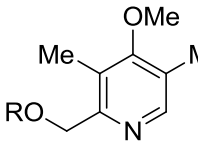
Zopiclone Analog
No fluorination



Tropicamide derivatives
>65% yield for fluorination
Retro-Michael addition during S_NAr



Bisacodyl
93% yield for fluorination
Acetate cleavage during S_NAr



R = Me, Ac, Piv

Precursor to Nexium
>90% yield for fluorination
Low reactivity in S_NAr

Having demonstrated the potential of the C-H fluorination-S_NAr 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_NAr 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 (Figure 9.5, **16**). Compound **16** is a precursor to several important compounds, including the integrin inhibitor SB-273005 (Figure 9.5, C). Although **16** is structurally simple, the two reported syntheses of **16** by medicinal chemists were conducted in 5 and 7 steps from 2-amino-6-methylpyridine (Figure 9.5, A). We considered that the 2-methylamino group could be installed through C-H bond fluorination and S_NAr from a derivative of 2-pyridineethanol.

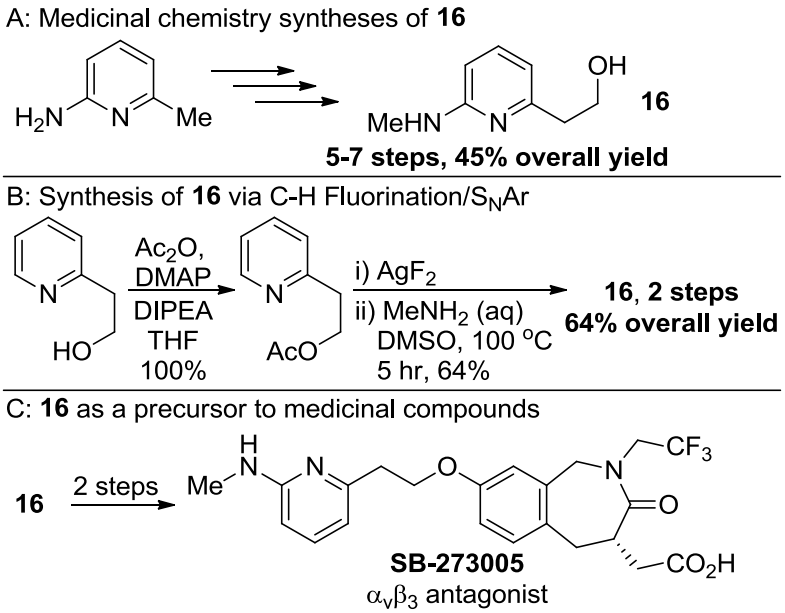


Figure 9.5 Synthesis of 6-(methylamino)-2-pyridineethanol through C-H fluorination

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_NAr 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* cleaveage of the acetyl-group to reveal the free alcohol. This route gave **16** with only 2 isolation steps in 64% overall yield, a significantly shorter and higher-yielding approach than the reported syntheses requiring 5 or 7 steps. Although our route requires stoichiometric silver, it is worthy to note that an improved process used to prepare 30 grams of **16** still required 4 steps and occurred in only 39% overall yield.[18]

The combination of C-H bond fluorination and S_NAr also shortened the synthesis of PF-1247324, a potent and selective $Na_V1.8$ inhibitor (Figure 9.6).[19] The medicinal chemistry route to this compound comprised 6 steps and occurred in less than 1% yield; an advanced intermediate was outsourced for the kilogram-scale synthesis of PF-1247324.[20] Our route to this compound began with the fluorination of methyl 5-bromopicolinate. The fluoropyridine intermediate contains two electrophilic sites for nucleophilic substitution: a methyl ester and a 2-fluoropyridine. We demonstrated (Tables 9.3 and 9.4) 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 $MeNH_2$ 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.*

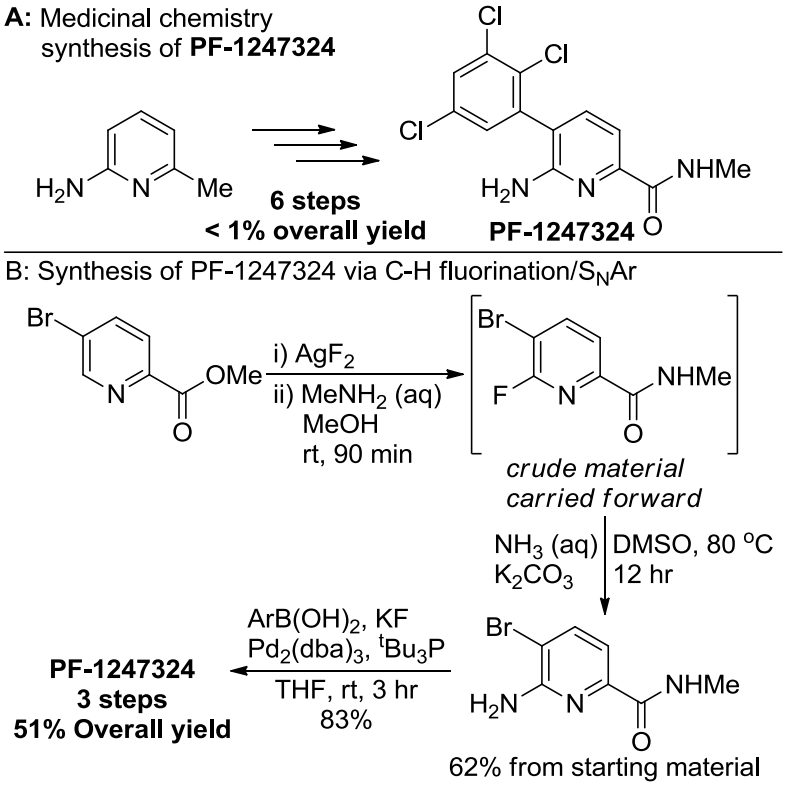


Figure 9.6 Synthesis of PF-1247324 through C-H fluorination

After aqueous workup, the crude reaction mixture was treated with ammonium hydroxide in DMSO to substitute an NH_2 group for the fluoride. Finally, the 3-bromopyridine was subjected to the reported Suzuki cross-coupling reaction conditions[20] to provide the title compound. By our route, the synthesis of PF-1247324 involving C-H fluorination was completed in 3 isolation steps 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 hours of total reaction time, while the route we report here required less than 18 hours.

Finally, we used our chemistry to prepare the non-nucleoside reverse transcriptase inhibitor Intelence (etravirine, Figure 9.7), a compound used in the treatment of HIV. The route to this compound developed by medicinal chemists occurred in 5 steps and 9% yield from *N*-(4-cyanophenyl)guanidine hydrochloride.[21] An alternative route used to prepare etravirine on kilogram scale required 4 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-aminobenzontirile and Boc-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 ^{19}F NMR spectroscopy), substitution with aqueous ammonia, and addition of $HCl_{(aq)}$ to cleave the Boc group. Through this route, etravirine was prepared with 3 isolation steps in 45% overall yield in under 6 hours of total reaction time.

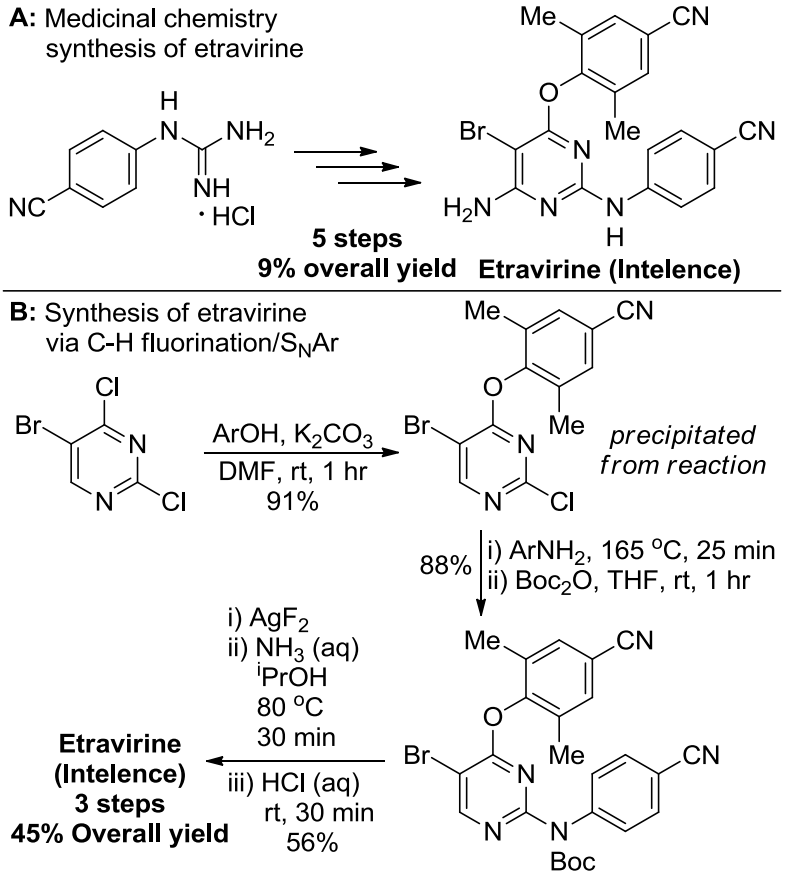


Figure 9.7 Synthesis of Intelence (etravirine) through C-H fluorination

9.3 Conclusions

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, aryloxy, 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 reaction conditions. 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 S_NAr 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.

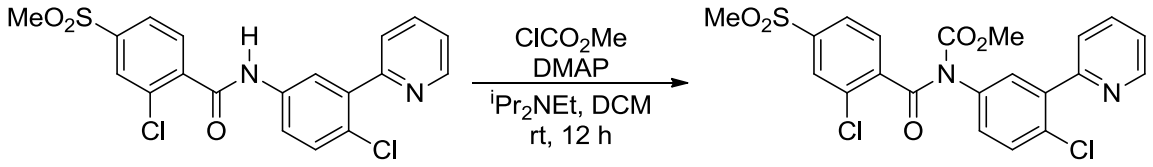
9.4 Experimental

Unless otherwise noted, all reactions were assembled under an inert atmosphere with a nitrogen-filled glovebox except for reactions involving aqueous solutions. All reactions were conducted in oven-dried 4-mL or 20-mL vials fitted with a Teflon-lined screw cap under an atmosphere of nitrogen unless otherwise noted.

Silver difluoride (AgF_2) was purchased from Alfa Aesar and used as received (black microcrystalline solid). Acetonitrile was distilled from CaH_2 and stored over molecular sieves. THF was collected from a solvent purification system containing a column of activated alumina under nitrogen. Anhydrous DMF and DMSO (extra dry over molecular sieves, AcroSeal) were purchased from Acros and used as received. Substrates **1**, **5**, and **10** were purchased from commercial suppliers and used as received. Substrates **2**, **3**, **4**, **9**, **11**, **12**, and **14** were prepared according to literature procedures. **(CO_2Me)-Vismodegib**, and substrates **6**, **7**, **8**, **13**, and **15** were prepared according to the procedures described below. All other reagents were purchased from commercial suppliers and used as received.

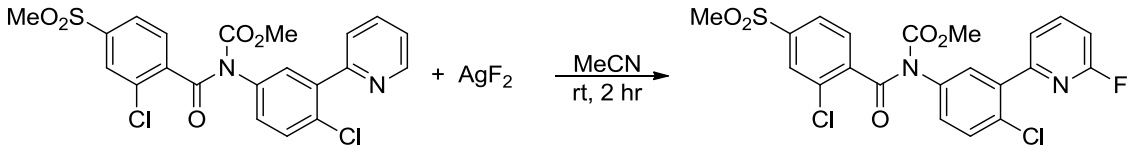
NMR chemical shifts are reported in ppm and referenced to residual solvent peaks ($CHCl_3$ in $CDCl_3$: 7.26 ppm for ^1H and 77.0 ppm for ^{13}C) or to an external standard (1% $CFCl_3$ in $CDCl_3$: 0 ppm for ^{19}F). Coupling constants are reported in hertz.

Preparation of (CO_2Me)-Vismodegib:



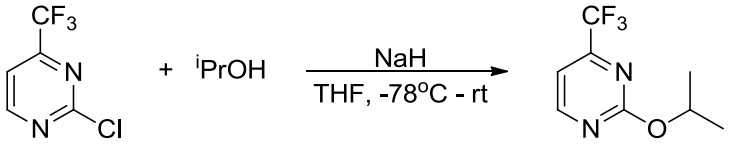
To a 25 mL round bottom flask was added vismodegib (632 mg, 1.50 mmol, 1.00 equiv), DMAP (18 mg, 0.15 mmol, 0.10 equiv), $^iPr_2NEt$ (520 μL, 3.0 mmol, 2.0 equiv) and CH_2Cl_2 (15 mL). The reaction vessel was sparged with N_2 for 5 minutes, and $ClCO_2Me$ (230 μL, 3.0 mmol, 2.0 equiv) was added at once. The reaction mixture was stirred at room temperature for 12 h; a change in the color of the solution from light yellow to orange occurred over the first hour. The mixture was diluted with CH_2Cl_2 (15 mL), and washed once with H_2O (30 mL). The organic phase was concentrated, and the product was purified by silica gel chromatography eluting with 1:3 hexanes : ethyl acetate to afford (CO_2Me)-vismodegib as a light yellow solid (683 mg, 1.42 mmol, 95% yield).
Note: A trace amount of EtOAc remained bound to the solid even after prolonged drying under vacuum at 50 °C.
^1H NMR (600 MHz, Chloroform-d) δ 8.78 – 8.73 (m, 1H), 7.99 (d, J = 1.6 Hz, 1H), 7.93 (dd, J = 8.0, 1.7 Hz, 1H), 7.82 (td, J = 7.7, 1.7 Hz, 1H), 7.77 (m, 1H), 7.64 – 7.59 (m, 3H), 7.37 – 7.32 (m, 1H), 7.30 (dd, J = 8.5, 2.6 Hz, 1H), 3.68 (s, 3H), 3.10 (s, 3H).
^{13}C NMR (151 MHz, Chloroform-d) δ 167.61, 155.23, 153.18, 149.48, 142.28, 141.76, 140.04, 136.04, 135.30, 132.69, 131.25, 131.14, 130.80, 129.18, 128.57, 128.21, 125.91, 124.93, 122.81, 54.45, 44.29.

Preparation of Fluoro-(CO_2Me)-vismodegib:



To an oven-dried vial was added (CO_2Me)-vismodegib (96 mg, 0.20 mmol, 1.0 equiv) and MeCN (2.0 mL). While the solution was stirring rapidly, AgF_2 (88 mg, 0.60 mmol, 3.0 equiv) was added at once. The vial was sealed with a Teflon-lined cap and stirred at room temperature for 2 h. The reaction was poured into a separatory funnel containing 10 mL of saturated aqueous $NaHCO_3$ and extracted with 10 mL of Et_2O. The organic layer was washed once with 10 mL of brine, dried over $MgSO_4$, and concentrated. The product was purified by silica gel chromatography eluting with 1:1 hexanes : ethyl acetate (R_f = 0.32) to afford the title compound as a pale yellow solid (90 mg, 0.18 mmol, 90% yield).
^{1}H NMR (600 MHz, Chloroform-d) δ 8.00 (d, J = 1.6 Hz, 1H), 7.95 – 7.88 (m, 2H), 7.69 (dd, J = 7.4, 2.1 Hz, 1H), 7.64 – 7.59 (m, 3H), 7.31 (dd, J = 8.5, 2.6 Hz, 1H), 6.99 (dd, J = 8.1, 2.6 Hz, 1H), 3.68 (s, 3H), 3.10 (s, 3H).
^{13}C NMR (151 MHz, Chloroform-d) δ 167.71, 163.10 (d, J = 240.0 Hz), 153.67 (d, J = 13.3 Hz), 153.22, 142.41, 141.80, 141.15 (d, J = 7.7 Hz), 138.48, 135.44, 132.84, 131.43, 131.42, 130.95, 129.64, 128.68, 128.37, 126.03, 122.39 (d, J = 4.1 Hz), 108.84 (d, J = 36.8 Hz), 54.59, 44.46.
^{19}F NMR (376 MHz, Chloroform-d) δ -69.09.

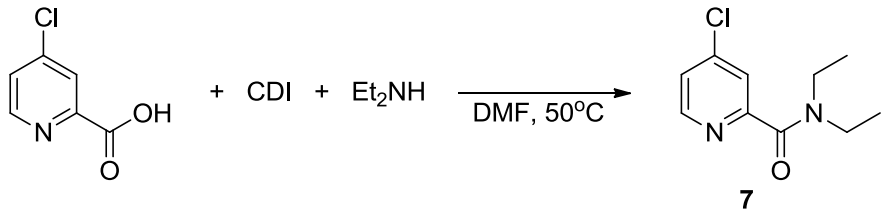
Preparation of Substrate 6:



6

To a 25 mL round bottom flask was added NaH (180 mg, 7.5 mmol, 1.5 equiv) and THF (10 mL). The suspension was cooled to 0 °C, and ^{i}PrOH (570 µL, 7.5 mmol, 1.5 equiv) was added dropwise over 10 minutes. The resulting solution was cooled to -78 °C, and 2-chloro-4-trifluoromethylpyrimidine (600 µL, 5.0 mmol, 1.0 equiv) was added dropwise over 5 minutes. The reaction mixture was allowed to slowly warm to room temperature over ~30 minutes and quenched with aqueous NH_4Cl (5 mL) and H_2O (15 mL). The mixture was extracted 2 x 20 mL EtOAc. The organic phase was concentrated, and the product was purified by silica gel chromatography eluting with 9:1 hexanes : ethyl acetate to afford **6** as a clear oil (800 mg, 3.90 mmol, 78% yield).
^{1}H NMR (400 MHz, Chloroform-d) δ 8.73 (d, J = 4.8 Hz, 1H), 7.21 (d, J = 4.9 Hz, 1H), 5.34 (hept, J = 6.2 Hz, 1H), 1.42 (d, J = 6.2 Hz, 6H).
^{13}C NMR (151 MHz, Chloroform-d) δ 165.09, 161.85, 157.63 (q, J = 36.3 Hz), 120.12 (q, J = 275.3 Hz), 109.82, 71.68, 21.60.

Preparation of Substrate 7:

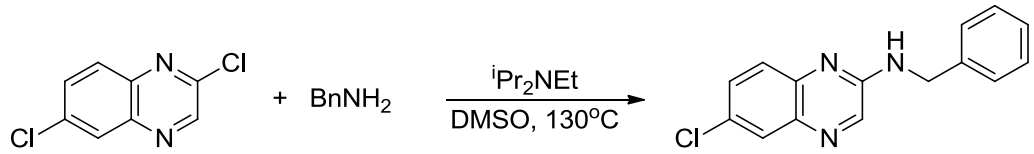


7

To a 25 mL round bottom flask was added 4-chloropicolinic acid (473 mg, 3.00 mmol, 1.00 equiv) and DMF (4 mL). The suspension was heated at 50 °C, and a solution of 1,1'-carbonyldiimidazole (486 mg, 3.00 mmol, 1.00 equiv) in 5 mL of DMF was added over 3 minutes. The resulting solution was stirred at 50 °C for 30 minutes. Et_2NH (680 µL, 6.6 mmol, 2.2 equiv) was added over 5 minutes, and the resulting mixture was stirred at 50 °C for 12 hours. The solution was cooled, diluted with EtOAc (40 mL), and washed 3 x 20 mL with a 50% saturated aqueous NaCl solution. The organic phase was concentrated, and the product was purified by silica gel chromatography eluting with 2:1 hexanes : ethyl acetate to afford **7** as a clear oil (510 mg, 2.40 mmol, 80% yield).
^{1}H NMR (600 MHz, Chloroform-d) δ 8.48 (s, 1H), 7.61 (s, 1H), 7.33 (dd, J = 5.2, 1.7 Hz, 1H), 3.55 (q, J = 7.1 Hz, 2H), 3.37 (q, J = 7.1 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H), 1.17 (t, J = 7.1 Hz, 3H).
^{13}C NMR (151 MHz, Chloroform-d) δ 167.06, 156.22, 149.09, 145.03, 124.46, 123.66, 43.17, 40.22, 14.22, 12.71.

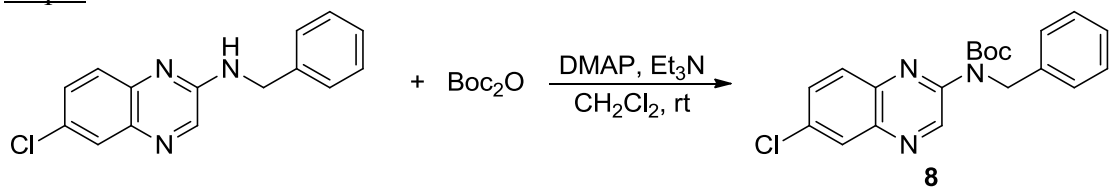
Preparation of Substrate 8:

Step 1:



To an oven dried vial was added 2,6-dichloroquinoxaline (398 mg, 2.00 mmol, 1.00 equiv), ^{i}Pr$_2$NEt (380 µL, 2.2 mmol, 1.1 equiv), DMSO (2 mL) and benzylamine (240 µL, 2.2 mmol, 1.1 equiv). The vial was sealed with a Teflon-lined cap and stirred at 130°C for 12 h. The reaction was diluted with EtOAc (20 mL) and washed 3 x 20 mL H_2O. The organic phase was concentrated, and the product was purified by silica gel chromatography eluting with 3:1 hexanes : ethyl acetate to afford N-benzyl-6-chloroquinoxalin-2-amine as a dark oil (540 mg, 2.00 mmol, quantitative yield) that was used directly in step 2.

Step 2:



8

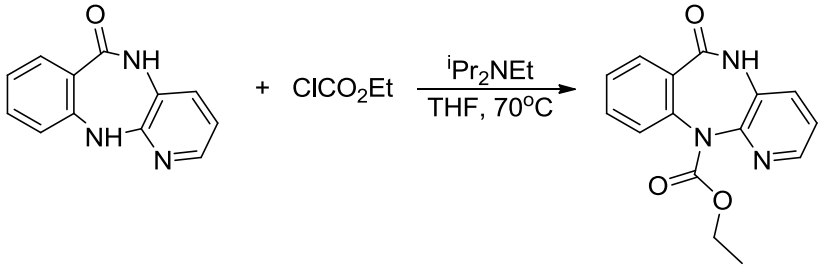
To a round bottom flask was added N-benzyl-6-chloroquinoxalin-2-amine (540 mg, 2.0 mmol, 1.0 equiv), Et_3N (420 µL, 3.0 mmol, 1.5 equiv), DMAP (12 mg, 0.1 mmol, 5 mol %) and CH_2Cl_2 (5 mL). To this solution was added Boc_2O (510 µL, 2.2 mmol, 1.1 equiv) and the resulting mixture was stirred at room temperature for 14 hours. The solvent was removed in vacuo, and the product was purified by silica gel chromatography eluting with 6:1 hexanes : ethyl acetate to afford **8** as a white solid (621 mg, 1.68 mmol, 84% yield).

^{1}H NMR (500 MHz, Chloroform-d) δ 9.31 (s, 1H), 8.03 (d, J = 2.3 Hz, 1H), 7.81 (d, J = 8.9 Hz, 1H), 7.62 (dd, J = 8.9, 2.3 Hz, 1H), 7.36 (d, J = 7.4 Hz, 2H), 7.28 (t, J = 7.4 Hz, 2H), 7.23 (t, J = 7.3 Hz, 1H), 5.30 (s, 2H), 1.47 (s, 9H).

^{13}C NMR (151 MHz, Chloroform-d) δ 153.64, 149.68, 143.74, 139.16, 138.92, 138.47, 133.57, 130.79, 129.18, 128.28, 127.70, 127.51, 127.07, 82.94, 49.58, 28.05.

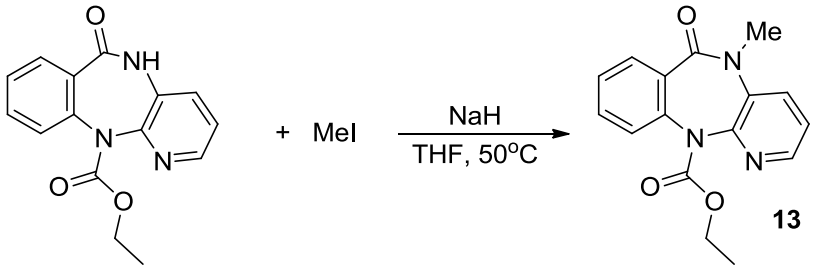
Preparation of Substrate 13:

Step 1:



To an 25 mL round bottom flask was added 5,6-Dihydro-6-oxo-11H-pyrido-[2,3-b][1,4]benzodiazepine (1.06 g, 5.00 mmol, 1.00 equiv; from Matrix Scientific, CAS # 885-70-1), ^{i}Pr$_2$NEt (1.1 mL, 6.0 mmol, 1.2 equiv) and THF (10 mL). The suspension was heated to 70 °C, and $ClCO_2Et$ was added over 3 minutes. The reaction was held at 70 °C for 1 h, and then at room temperature for 12 h. H_2O was added (70 mL) to precipitate the product as a tan solid. The solid was collected, washed with H_2O (2 x 15 mL), and dried to afford the product as a tan solid (1.16 g, 4.09 mmol, 82% yield) that was used directly in step 2.

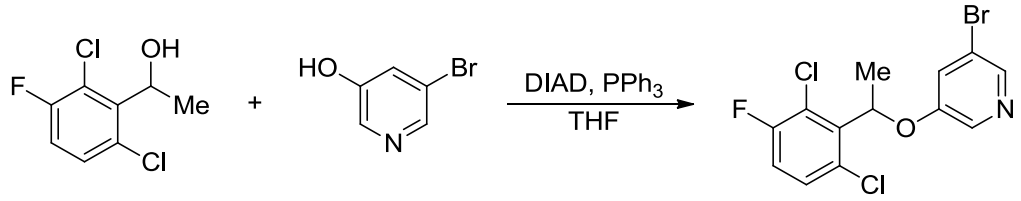
Step 2:



To a round bottom flask was added NaH (40 mg, 1.7 mmol, 1.1 equiv) and THF (3 mL). The solid from step 1 (425 mg, 1.50 mmol, 1.00 equiv) was added in portions over 5 minutes. The suspension was stirred at room temperature for 15 minutes, during which the solution became clear and homogeneous. MeI (100 µL, 1.7 mmol, 1.1 equiv) was added, and the mixture was heated to 50 °C for 90 minutes at which time ^{1}H NMR

analysis of an aliquot showed complete conversion of the starting material to **13** (Note: the starting material and product have identical R_f values by TLC; therefore reaction conversion must be measured by an alternative method). The reaction was quenched with aqueous NH_4Cl (200 μL). The solvent was removed in vacuo and the product was purified by silica gel chromatography eluting with ethyl acetate (R_f = 0.56) to afford **13** as a light yellow solid (370 mg, 1.25 mmol, 83% yield).
^{1}H NMR (600 MHz, Chloroform-d) δ 8.37 (d, J = 4.1 Hz, 1H), 7.85 (d, J = 7.9 Hz, 1H), 7.65 (d, J = 8.1 Hz, 1H), 7.52 (m, 2H), 7.41 – 7.29 (m, 2H), 4.36 – 4.15 (m, 2H), 3.59 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H).
^{13}C NMR (151 MHz, Chloroform-d) δ 166.67, 153.12, 148.28, 145.55, 141.37, 135.58, 132.47, 131.38, 131.30, 129.42, 127.62, 127.12, 123.63, 62.58, 37.00, 14.25.

Preparation of Substrate 15:



To a 25 mL round bottom flask was added PPh_3 (1.47 g, 5.60 mmol, 1.4 equiv) and THF (20 mL). The solution was cooled to 0 °C and DIAD (1.1 mL, 5.6 mmol, 1.4 equiv) was added. The resulting slurry was stirred at 0 °C for 5 minutes after which time a solution was added containing 1-(2,6-dichloro-3-fluorophenyl)ethanol[9] (836 mg, 4.00 mmol, 1.00 equiv) and 5-bromo-3-hydroxypyridine (766 mg, 4.4 mmol, 1.1 equiv) in 10 mL of THF. The clear orange solution was stirred at room temperature for 4 h and the solvent was removed in vacuo. The product was purified by silica gel chromatography eluting with 6:1 hexanes : ethyl acetate to afford **15** as a white solid (1.3 g, 3.6 mmol, 89% yield).
^{1}H NMR (500 MHz, Chloroform-d) δ 8.26 (s, 1H), 8.17 (s, 1H), 7.36 (t, J = 2.1 Hz, 1H), 7.30 (dd, J = 8.9, 4.8 Hz, 1H), 7.11 – 7.05 (m, 1H), 6.05 (q, J = 6.7 Hz, 1H), 1.83 (d, J = 6.7 Hz, 3H).
^{13}C NMR (151 MHz, Chloroform-d) δ 157.42 (d, J = 250.1 Hz), 153.54, 143.23, 136.17, 136.09, 129.94, 128.71 (d, J = 3.7 Hz), 125.38, 121.76 (d, J = 19.3 Hz), 120.26, 116.79 (d, J = 23.2 Hz), 73.33, 18.90.

General Procedure for Tandem C-H fluorination/S_NAr
To an oven-dried vial was added the heteroarene (0.20 mmol, 1.0 equiv) and MeCN (2.0 - 8.0 mL). While the solution was stirring rapidly, AgF_2 (88 mg, 0.60 mmol, 3.0 equiv) was added at once. The vial was sealed with a Teflon-lined cap, and stirred at room temperature for 1 h, unless otherwise noted below. The reaction was filtered into a 20 mL vial through a pipette containing ~500 mg of silica wet with Et_2O. The silica was rinsed with 4-5 mL of Et_2O, and the filtrate was concentrated in vacuo. The resulting crude material was subjected to the following S_NAr reaction conditions:

Reactions with 1°, 2°, or 3° alcohols:
The crude material from the fluorination reaction was dissolved in 1 mL of THF and the 1° or 2° alcohol (0.24 mmol, 1.2 equiv) was added followed by KO^{t}Bu (0.24 mmol, 1.2

equiv). For 3° alcohol nucleophiles, the potassium 3° alkoxide salt (0.24 mmol, 1.2 equiv) was used directly. The vial was sealed with a Teflon-lined cap, and stirred at 50 °C for 3 h. The reaction mixture was concentrated in vacuo, and the crude material was purified by silica gel chromatography.

Reactions with phenols:
The crude material from the fluorination reaction was dissolved in 1 mL of DMF and the phenol (0.24 mmol, 1.2 equiv) was added followed by KO^{t}Bu (0.24 mmol, 1.2 equiv). The vial was sealed with a Teflon-lined cap, and stirred at 80 °C for 6 h. The reaction mixture was diluted with EtOAc (20 mL) and washed 4 x 20 mL H_2O (or 4 x 20 mL brine). The organic layer was concentrated and purified by silica gel chromatography.

Reactions with 1° or 2° amines:
The crude material from the fluorination reaction was dissolved in 500 µL of DMSO and ^{i}Pr$_2$NEt (0.30 mmol, 1.5 equiv) and amine (0.30 mmol, 1.5 equiv) were added. The vial was sealed with a Teflon-lined cap, and stirred at 120 °C for 18 h. The reaction mixture was diluted with EtOAc (20 mL) and washed 4 x 20 mL H_2O (or 4 x 20 mL brine). The organic layer was concentrated and purified by silica gel chromatography.

Reactions with amides:
The crude material from the fluorination reaction was dissolved in 1 mL of DMF, and amide (0.24 mmol, 1.2 equiv) was added. NaH (0.24 mmol, 1.2 equiv) was added slowly, and the resulting mixture was stirred at room temperature for 5 minutes, or until H_2 evolution stopped. The vial was sealed with a Teflon-lined cap, and stirred at 100 °C for 3 h. The reaction mixture was diluted with EtOAc (20 mL) and washed with 4 x 20 mL of H_2O (or 4 x 20 mL brine). The organic layer was concentrated and purified by silica gel chromatography.

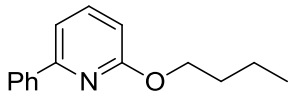
Reactions with nitrogen heterocycles:
The crude material from the fluorination reaction was dissolved in 1 mL of DMF and the nitrogen heterocycle (0.24 mmol, 1.2 equiv) was added. NaH (0.24 mmol, 1.2 equiv) was added slowly, and the resulting mixture was stirred at room temperature for 5 minutes, or until H_2 evolution stopped. The vial was sealed with a Teflon-lined cap, and stirred at 100 °C for 1-3 h. The reaction mixture was diluted with EtOAc (20 mL) and washed with 4 x 20 mL of H_2O (or 4 x 20 mL brine). The organic layer was concentrated and purified by silica gel chromatography.

Reactions with KCN:
The crude material from the fluorination reaction was dissolved in 500 µL of DMSO and KCN (0.60 mmol, 3.0 equiv) was added. The vial was sealed with a Teflon-lined cap, and stirred at 120 °C for 18 h. The reaction mixture was diluted with EtOAc (20 mL) and washed with 4 x 20 mL of H_2O (or 4 x 20 mL brine). The organic layer was concentrated and purified by silica gel chromatography.

Reactions with sodium thiolate salts:

The crude material from the fluorination reaction was dissolved in 1 mL of THF and the sodium thiolate salt (0.24 mmol, 1.2 equiv) was added. The vial was sealed with a Teflon-lined cap, and stirred at 50 °C for 3 h. The reaction mixture was concentrated in vacuo, and the crude material was purified by silica gel chromatography.

Synthesis of 2-butoxy-6-phenylpyridine (1a)



The general procedure for tandem C-H fluorination/S_NAr was performed with 2-phenylpyridine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 9:1 hexanes : ethyl acetate (R_f = 0.44) to afford **1a** as a colorless oil (38 mg, 0.17 mmol, 84% yield).

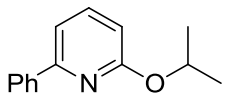
^{1}H NMR (600 MHz, Chloroform-d) δ 8.06 (d, J = 7.4 Hz, 2H), 7.63 (t, J = 7.8 Hz, 2H), 7.48 (t, J = 7.5 Hz, 2H), 7.41 (t, J = 7.3 Hz, 1H), 7.34 (d, J = 7.4 Hz, 1H), 6.69 (d, J = 8.1 Hz, 1H), 4.46 (t, J = 6.6 Hz, 2H), 1.84 (p, J = 6.8 Hz, 2H), 1.55 (h, J = 7.4 Hz, 2H), 1.02 (t, J = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-d) δ 163.65, 154.58, 139.14, 139.04, 128.71, 128.53, 126.64, 112.53, 109.33, 65.49, 31.19, 19.37, 13.93.

Calculated exact mass: 227.13

EI Mass Spectrum: 227.1 (M^+, 13% relative intensity), 171.1 ($[M-56]^+$, base peak)

Synthesis of 2-isopropoxy-6-phenylpyridine (1b)



The general procedure for tandem C-H fluorination/S_NAr was performed with 2-phenylpyridine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 20:1 hexanes : ethyl acetate (R_f = 0.59) to afford **1b** as a colorless oil (36 mg, 0.17 mmol, 84% yield).

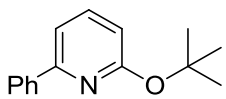
^{1}H NMR (600 MHz, Chloroform-d) δ 8.06 (d, J = 7.6 Hz, 2H), 7.62 (t, J = 7.8 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 7.41 (t, J = 7.3 Hz, 1H), 7.33 (d, J = 7.4 Hz, 1H), 6.66 (d, J = 8.2 Hz, 1H), 5.54 (hept, J = 6.2 Hz, 1H), 1.45 (d, J = 6.2 Hz, 6H).

^{13}C NMR (151 MHz, Chloroform-d) δ 163.04, 154.50, 139.20, 139.09, 128.67, 128.52, 126.60, 112.28, 109.86, 67.72, 22.07.

Calculated exact mass: 213.12

EI Mass Spectrum: 213.1 (M^+, 22% relative intensity), 171.1 ($[M-42]^+$, base peak)

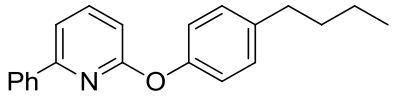
Synthesis of 2-(tert-butoxy)-6-phenylpyridine (1c)



The general procedure for tandem C-H fluorination/S_NAr was performed with 2-phenylpyridine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 20:1 hexanes : ethyl acetate (R_f = 0.57) to afford **1c** as a colorless oil (37 mg, 0.16 mmol, 81% yield).

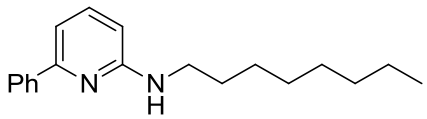
^{1}H NMR (600 MHz, Chloroform-d) δ 8.02 (d, J = 7.6 Hz, 2H), 7.58 (t, J = 7.8 Hz, 1H), 7.46 (t, J = 7.6 Hz, 2H), 7.39 (t, J = 7.3 Hz, 1H), 7.31 (d, J = 7.4 Hz, 1H), 6.60 (d, J = 8.2 Hz, 1H), 1.69 (s, 9H).
^{13}C NMR (151 MHz, Chloroform-d) δ 163.55, 154.22, 139.42, 138.84 (two overlapping peaks), 128.56, 126.62, 112.15, 111.64, 79.38, 28.81.
Calculated exact mass: 227.13
EI Mass Spectrum: 227.1 (M^+, 3% relative intensity), 171.1 ($[M-56]^+$, base peak)

Synthesis of 2-(4-butylphenoxy)-6-phenylpyridine (1d)



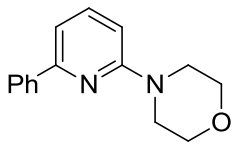
The general procedure for tandem C-H fluorination/S_NAr was performed with 2-phenylpyridine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 20:1 hexanes : ethyl acetate (R_f = 0.51) to afford **1d** as a colorless oil (44 mg, 0.15 mmol, 73% yield).
^{1}H NMR (600 MHz, Chloroform-d) δ 7.96 (d, J = 7.2 Hz, 2H), 7.71 (t, J = 7.8 Hz, 1H), 7.47 (d, J = 7.5 Hz, 1H), 7.42 (t, J = 7.3 Hz, 2H), 7.38 (t, J = 7.2 Hz, 1H), 7.22 (d, J = 8.3 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 6.75 (d, J = 8.1 Hz, 1H), 2.68 – 2.63 (m, 2H), 1.65 (p, J = 7.6 Hz, 2H), 1.40 (h, J = 7.3 Hz, 2H), 0.97 (t, J = 7.4 Hz, 3H).
^{13}C NMR (151 MHz, Chloroform-d) δ 163.64, 155.56, 152.08, 139.92, 139.00, 138.40, 129.34, 129.00, 128.54, 126.75, 120.91, 114.39, 109.04, 35.01, 33.67, 22.29, 13.96.
Calculated exact mass: 303.16
EI Mass Spectrum: 303.2 (M^+, 67% relative intensity), 302.2 ($[M-1]^+$, base peak)

Synthesis of N-octyl-6-phenylpyridin-2-amine (1e)



The general procedure for tandem C-H fluorination/S_NAr was performed with 2-phenylpyridine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 20:1 hexanes : ethyl acetate (R_f = 0.29) to afford **1e** as a colorless oil (34 mg, 0.12 mmol, 60% yield).
^{1}H NMR (600 MHz, Chloroform-d) δ 7.96 (d, J = 7.7 Hz, 2H), 7.50 (t, J = 7.8 Hz, 1H), 7.44 (t, J = 7.6 Hz, 2H), 7.37 (t, J = 7.2 Hz, 1H), 7.02 (d, J = 7.4 Hz, 1H), 6.34 (d, J = 8.2 Hz, 1H), 4.71 (br, 1H), 3.32 (q, J = 6.6 Hz, 2H), 1.66 (p, J = 7.2 Hz, 2H), 1.43 (p, J = 6.8 Hz, 2H), 1.38 – 1.25 (m, 8H), 0.89 (t, J = 6.8 Hz, 3H).
^{13}C NMR (151 MHz, Chloroform-d) δ 158.70, 155.70, 139.80, 138.12 (two overlapping peaks), 128.44, 126.75, 109.40, 104.70, 42.38, 31.82, 29.64, 29.38, 29.25, 27.12, 22.64, 14.08.
Calculated exact mass: 282.21
EI Mass Spectrum: 282.2 (M^+, 25% relative intensity), 183.1 ($[M-99]^+$, base peak)

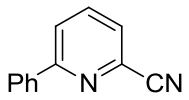
Synthesis of 4-(6-phenylpyridin-2-yl)morpholine (1f)



The general procedure for tandem C-H fluorination/S_NAr was performed with 2-phenylpyridine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 9:1

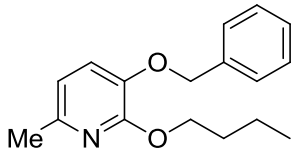
hexanes : ethyl acetate (R_f = 0.28) to afford **1f** as a colorless oil (36 mg, 0.15 mmol, 75% yield).
^{1}H NMR (600 MHz, Chloroform-d) δ 8.04 (d, J = 7.3 Hz, 2H), 7.61 – 7.55 (m, 1H), 7.46 (t, J = 7.6 Hz, 2H), 7.39 (t, J = 7.3 Hz, 1H), 7.17 (d, J = 7.5 Hz, 1H), 6.59 (d, J = 8.4 Hz, 1H), 3.88 – 3.86 (m, 4H), 3.64 – 3.60 (m, 4H).
^{13}C NMR (151 MHz, Chloroform-d) δ 159.06, 155.11, 139.64, 138.17, 128.56, 128.40, 126.66, 110.12, 105.22, 66.76, 45.52.
Calculated exact mass: 240.13
EI Mass Spectrum: 240.1 (M^+, 57% relative intensity), 209.1 ($[M-31]^+$, base peak)

Synthesis of 6-phenylpicolinonitrile (1g)



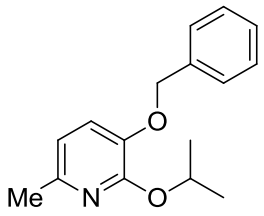
The general procedure for tandem C-H fluorination/S_NAr was performed with 2-phenylpyridine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 6:1 hexanes : ethyl acetate (R_f = 0.33) to afford **1g** as a white solid (22 mg, 0.12 mmol, 61% yield).
NMR spectra were in accord with previously reported spectral data.[10]
^{1}H NMR (600 MHz, Chloroform-d) δ 8.02 (d, J = 7.1 Hz, 2H), 7.94 (d, J = 8.1 Hz, 1H), 7.88 (t, J = 7.8 Hz, 1H), 7.61 (d, J = 7.5 Hz, 1H), 7.49 (m, 3H).
^{13}C NMR (151 MHz, Chloroform-d) δ 158.86, 137.68, 137.09, 133.69, 130.10, 128.91, 126.97, 126.52, 123.43, 117.37.

Synthesis of 3-(benzyloxy)-2-butoxy-6-methylpyridine (2a)



The general procedure for tandem C-H fluorination/S_NAr was performed with 5-(benzyloxy)-2-methylpyridine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 9:1 hexanes : ethyl acetate (R_f = 0.67) to afford **2a** as a colorless oil (42 mg, 0.15 mmol, 77% yield).
^{1}H NMR (600 MHz, Chloroform-d) δ 7.43 (d, J = 7.6 Hz, 2H), 7.37 (t, J = 7.5 Hz, 2H), 7.31 (t, J = 7.3 Hz, 1H), 6.95 (d, J = 7.8 Hz, 1H), 6.56 (d, J = 7.8 Hz, 1H), 5.11 (s, 2H), 4.41 (t, J = 6.7 Hz, 2H), 2.37 (s, 3H), 1.84 (p, J = 6.9 Hz, 2H), 1.53 (h, J = 7.4 Hz, 2H), 1.01 (t, J = 7.4 Hz, 3H).
^{13}C NMR (151 MHz, Chloroform-d) δ 154.39, 147.10, 140.45, 137.04, 128.42, 127.77, 127.23, 122.34, 114.91, 71.36, 65.63, 31.17, 23.21, 19.34, 13.92.
Calculated exact mass: 271.16
EI Mass Spectrum: 271.1 (M^+, 12% relative intensity), 91.1 ($[C_7H_7]^+$, base peak)

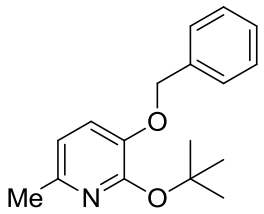
Synthesis of 3-(benzyloxy)-2-isopropoxy-6-methylpyridine (2b)



The general procedure for tandem C-H fluorination/S_NAr was performed with 5-(benzyloxy)-2-methylpyridine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 9:1 hexanes : ethyl acetate (R_f = 0.69) to afford **2b** as a colorless oil (40 mg, 0.16 mmol, 78% yield).
^{1}H NMR (600 MHz, Chloroform-d) δ 7.43 (d, J = 7.5 Hz, 2H),

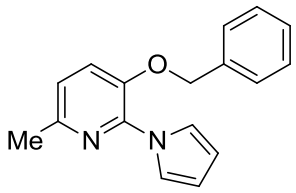
7.37 (t, J = 7.5 Hz, 2H), 7.30 (t, J = 7.3 Hz, 1H), 6.95 (d, J = 7.8 Hz, 1H), 6.53 (d, J = 7.8 Hz, 1H), 5.46 (hept, J = 6.1 Hz, 1H), 5.12 (s, 2H), 2.36 (s, 3H), 1.42 (d, J = 6.2 Hz, 6H).
^{13}C NMR (151 MHz, Chloroform-d) δ 153.93, 147.26, 140.56, 137.19, 128.39, 127.72, 127.23, 122.96, 114.67, 71.52, 67.90, 23.28, 22.11.
Calculated exact mass: 257.14
EI Mass Spectrum: 257.1 (M^+, 11% relative intensity), 91.0 ($[C_7H_7]^+$, base peak)

Synthesis of 3-(benzyloxy)-2-(tert-butoxy)-6-methylpyridine (2c)



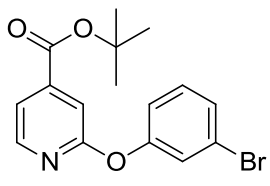
The general procedure for tandem C-H fluorination/S_NAr was performed with 5-(benzyloxy)-2-methylpyridine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 9:1 hexanes : ethyl acetate (R_f = 0.69) to afford **2c** as a colorless oil (42 mg, 0.15 mmol, 77% yield).
^{1}H NMR (600 MHz, Chloroform-d) δ 7.43 (d, J = 7.6 Hz, 2H), 7.36 (t, J = 7.4 Hz, 2H), 7.30 (t, J = 7.3 Hz, 1H), 6.98 (d, J = 7.8 Hz, 1H), 6.56 (d, J = 7.8 Hz, 1H), 5.06 (s, 2H), 2.36 (s, 3H), 1.64 (s, 9H).
^{13}C NMR (151 MHz, Chloroform-d) δ 154.23, 147.30, 141.74, 137.33, 128.37, 127.72, 127.36, 123.65, 115.10, 80.12, 71.74, 28.82, 23.32.
Calculated exact mass: 271.16
EI Mass Spectrum: 271.1 (M^+, 1% relative intensity), 215.1 ($[M-56]^+$, 33% relative intensity), 91.1 ($[C_7H_7]^+$, base peak)

Synthesis of 3-(benzyloxy)-6-methyl-2-(1H-pyrrol-1-yl)pyridine (2d)



The general procedure for tandem C-H fluorination/S_NAr was performed with 5-(benzyloxy)-2-methylpyridine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 9:1 hexanes : ethyl acetate (R_f = 0.41) to afford **2d** as a light yellow oil (31 mg, 0.12 mmol, 59% yield).
^{1}H NMR (600 MHz, Chloroform-d) δ 7.69 (t, J = 2.2 Hz, 2H), 7.40 (d, J = 6.8 Hz, 4H), 7.35 (m, 1H), 7.27 (d, J = 8.1, 1H), 6.92 (d, J = 8.2 Hz, 1H), 6.32 – 6.30 (m, 2H), 5.10 (s, 2H), 2.49 (s, 3H).
^{13}C NMR (151 MHz, Chloroform-d) δ 149.15, 143.24, 141.13, 136.00, 128.66, 128.17, 127.32, 123.29, 120.88, 120.17, 109.52, 71.37, 23.28.

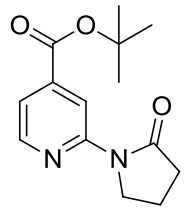
Synthesis of tert-butyl 2-(3-bromophenoxy)isonicotinate (3a)



The general procedure for tandem C-H fluorination/S_NAr was performed with tert-butyl isonicotinate. The fluorination step was performed with 4 mL of MeCN at 50 ^{o}C for 2 h. The product was purified by silica gel chromatography eluting with 9:1 hexanes : ethyl acetate to afford **3a** as a colorless oil (28 mg, 0.080 mmol, 40% yield).

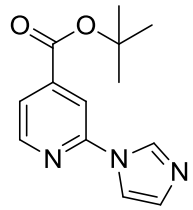
^{1}H NMR (600 MHz, Chloroform-d) δ 8.28 (d, J = 5.1 Hz, 1H), 7.52 (d, J = 5.1 Hz, 1H), 7.45 (s, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 1.9 Hz, 1H), 7.29 – 7.25 (m, 1H), 7.09 (dd, J = 8.1, 2.1 Hz, 1H), 1.61 (s, 9H).
^{13}C NMR (101 MHz, Chloroform-d) δ 163.72, 163.45, 154.50, 148.11, 143.32, 130.71, 128.05, 124.58, 122.67, 119.93, 118.20, 111.73, 82.71, 28.02.
Calculated exact mass: 349.03 (100.0%), 351.03 (97.3%)
EI Mass Spectrum: 349.0 ([M with ^{79}Br]$^{+}$, 18% relative intensity), 351.1 ([M with ^{81}Br]$^{+}$, 18% relative intensity), 293.9 ([M-55]$^{+}$, base peak)

Synthesis of tert-butyl 2-(2-oxopyrrolidin-1-yl)isonicotinate (3b)



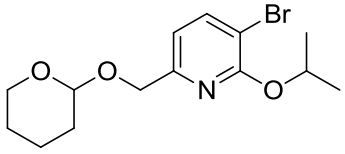
The general procedure for tandem C-H fluorination/S_NAr was performed with tert-butyl isonicotinate. The fluorination step was performed with 4 mL of MeCN at 50 °C for 2 h. The product was purified by silica gel chromatography eluting with 3:1 hexanes : ethyl acetate (R_f = 0.27) to afford **3b** as a light yellow oil (24 mg, 0.091 mmol, 46% yield).
^{1}H NMR (600 MHz, Chloroform-d) δ 8.86 (s, 1H), 8.43 (d, J = 5.1 Hz, 1H), 7.55 – 7.49 (m, 1H), 4.10 (t, J = 7.1 Hz, 2H), 2.67 (t, J = 8.1 Hz, 2H), 2.14 (p, J = 7.8 Hz, 2H), 1.59 (s, 9H).
^{13}C NMR (151 MHz, Chloroform-d) δ 174.94, 164.11, 152.53, 147.84, 141.03, 118.49, 114.24, 82.31, 47.49, 33.52, 28.00, 17.65.
Calculated exact mass: 262.13
EI Mass Spectrum: 262.1 (M^{+}, 12% relative intensity), 151.0 ([M-111]$^{+}$, base peak)

Synthesis of tert-butyl 2-(1H-imidazol-1-yl)isonicotinate (3c)



The general procedure for tandem C-H fluorination/S_NAr was performed with tert-butyl isonicotinate. The fluorination step was performed with 4 mL of MeCN at 50 °C for 2 h. The product was purified by silica gel chromatography eluting with 99:1 ethyl acetate : triethylamine (R_f = 0.16) to afford **3c** as a light yellow oil (22 mg, 0.090 mmol, 45% yield).
^{1}H NMR (600 MHz, Chloroform-d) δ 8.58 (d, J = 5.0 Hz, 1H), 8.46 (s, 1H), 7.85 (s, 1H), 7.72 (dd, J = 5.0, 1.1 Hz, 1H), 7.69 (s, 1H), 7.23 (s, 1H), 1.62 (s, 9H).
^{13}C NMR (151 MHz, Chloroform-d) δ 163.04, 149.82, 149.64, 142.53, 134.94, 130.46, 121.26, 116.21, 111.70, 83.29, 28.00.

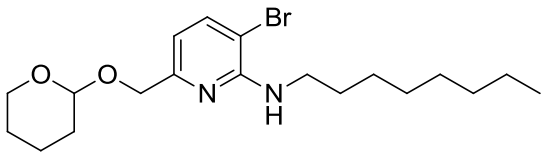
Synthesis of 3-bromo-2-isopropoxy-6-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)pyridine (4a)



The general procedure for tandem C-H fluorination/S_NAr was performed with 5-bromo-2-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)pyridine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 9:1 hexanes : ethyl acetate (R_f = 0.67) to afford **4a** as a colorless oil (49 mg, 0.15 mmol, 74% yield).
^{1}H NMR (600 MHz, Chloroform-d) δ 7.74 (d, J = 7.8 Hz, 1H), 6.86 (d, J = 7.7 Hz, 1H), 5.32 (hept, J = 6.1 Hz, 1H), 4.76 (t, J = 3.3 Hz, 1H), 4.70 (d, J = 13.8 Hz, 1H), 4.48 (d, J

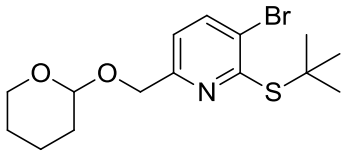
= 13.8 Hz, 1H), 3.93 – 3.88 (m, 1H), 3.55 (dd, J = 10.3, 5.0 Hz, 1H), 1.92 – 1.84 (m, 1H), 1.80 – 1.73 (m, 1H), 1.70 (m, 1H), 1.65 – 1.51 (m, 3H), 1.36 (dd, J = 6.2, 2.0 Hz, 6H).
^{13}C NMR (151 MHz, Chloroform-d) δ 158.67, 155.11, 141.79, 114.39, 105.42, 98.19, 69.44, 68.92, 62.08, 30.50, 25.40, 21.89, 19.25.
Chemical formula: $C_{14}H_{20}BrNO_3$
Calculated exact mass: 329.0627
Observed formula by ESIMS: $C_{14}H_{21}BrNO_3$
Observed exact mass: 330.0702 (calculated exact mass + ^{1}H)

Synthesis of 3-bromo-N-octyl-6-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)pyridin-2-amine (4b)



The general procedure for tandem C-H fluorination/S_NAr was performed with 5-bromo-2-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)pyridine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 20:1 hexanes : ethyl acetate to afford **4b** as a colorless oil (56 mg, 0.14 mmol, 70% yield).
^{1}H NMR (600 MHz, Chloroform-d) δ 7.55 (d, J = 7.8 Hz, 1H), 6.57 (d, J = 7.8 Hz, 1H), 4.95 (br, 1H), 4.77 (t, J = 3.3 Hz, 1H), 4.68 (d, J = 13.7 Hz, 1H), 4.46 (d, J = 13.7 Hz, 1H), 3.96 – 3.88 (m, 1H), 3.53 (dt, J = 10.2, 4.4 Hz, 1H), 3.42 (q, J = 6.7 Hz, 2H), 1.89 (m, 1H), 1.76 (m,, 1H), 1.69 (m, 1H), 1.65 – 1.51 (m, 5H), 1.40 – 1.22 (m, 10H), 0.88 (t, J = 6.9 Hz, 1H).
^{13}C NMR (151 MHz, Chloroform-d) δ 156.02, 153.95, 139.55, 110.12, 103.56, 98.14, 69.30, 62.02, 41.65, 31.79, 30.52, 29.58, 29.33, 29.21, 27.00, 25.44, 22.61, 19.28, 14.05.
Chemical formula: $C_{19}H_{31}BrN_2O_2$
Calculated exact mass: 398.1569
Observed formula by ESIMS: $C_{19}H_{32}BrN_2O_2$
Observed exact mass: 399.1642 (calculated exact mass + ^{1}H)

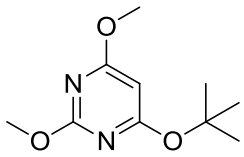
Synthesis of 3-bromo-2-(tert-butylthio)-6-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)pyridine (4c)



The general procedure for tandem C-H fluorination/S_NAr was performed with 5-bromo-2-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)pyridine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 20:1 hexanes : ethyl acetate (R_f = 0.37) to afford **4c** as a colorless oil (37 mg, 0.10 mmol, 51% yield).
^{1}H NMR (600 MHz, Chloroform-d) δ 7.67 (d, J = 8.0 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 4.81 (d, J = 13.7 Hz, 1H), 4.77 (t, J = 3.3 Hz, 1H), 4.56 (d, J = 13.7 Hz, 1H), 3.93 – 3.87 (m, 1H), 3.59 – 3.52 (m, 1H), 1.88 (m, 1H), 1.78 (m, 1H), 1.74 – 1.67 (m, 1H), 1.64 – 1.53 (m, 12H).
^{13}C NMR (151 MHz, Chloroform-d) δ 159.03, 156.60, 139.71, 117.27, 117.18, 98.43, 69.19, 62.12, 48.66, 30.51, 30.07, 25.39, 19.23.

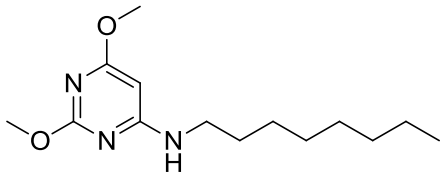
Chemical formula: $C_{15}H_{22}BrNO_2S$
Calculated exact mass: 359.0555 for **4c** with ^{79}Br isotope
Observed formula by ESIMS: $C_{15}H_{22}BrNO_2SNa$
Observed exact mass: 382.0447 (calculated exact mass + ^{23}Na)

Synthesis of 4-(tert-butoxy)-2,6-dimethoxypyrimidine (5a)



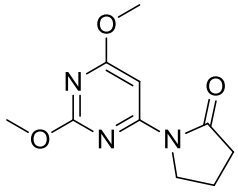
The general procedure for tandem C-H fluorination/S_NAr was performed with 2,4-dimethoxypyrimidine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 20:1 hexanes : ethyl acetate (R_f = 0.41) to afford **5a** as a colorless oil (30 mg, 0.14 mmol, 71% yield).
^1H NMR (600 MHz, Chloroform-d) δ 5.62 (s, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 1.58 (s, 9H).
^{13}C NMR (151 MHz, Chloroform-d) δ 172.58, 172.09, 164.35, 85.49, 81.33, 54.60, 53.76, 28.69.
Calculated exact mass: 212.12
EI Mass Spectrum: 212.1 (M^+, 3% relative intensity), 156.0 ($[M-56]^+$, base peak)

Synthesis of 2,6-dimethoxy-N-octylpyrimidin-4-amine (5b)



The general procedure for tandem C-H fluorination/S_NAr was performed with 2,4-dimethoxypyrimidine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 3:1 hexanes : ethyl acetate (R_f = 0.44) to afford **5b** as a colorless oil which solidified to a white solid on standing (38 mg, 0.14 mmol, 71% yield).
^1H NMR (600 MHz, Chloroform-d) δ 5.31 (s, 1H), 4.92 (s, 1H), 3.86 (two overlapping methyl peaks, 6H), 3.16 (s, 2H), 1.55 (q, J = 6.8 Hz, 2H), 1.38 – 1.17 (m, 10H), 0.85 (t, J = 6.5 Hz, 3H).
^{13}C NMR (151 MHz, Chloroform-d) δ 172.00, 165.51, 164.90, 78.34, 54.05, 53.42, 41.74, 31.70, 29.20 (2 overlapping peaks), 29.12, 26.86, 22.54, 13.98.
Calculated exact mass: 267.19
EI Mass Spectrum: 267.2 (M^+, 16% relative intensity), 168.0 ($[M-99]^+$, base peak)

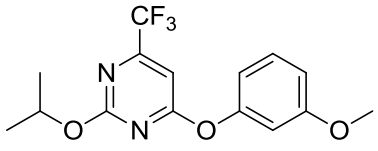
Synthesis of 1-(2,6-dimethoxypyrimidin-4-yl)pyrrolidin-2-one (5c)



The general procedure for tandem C-H fluorination/S_NAr was performed with 2,4-dimethoxypyrimidine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 2:1 hexanes : ethyl acetate (R_f = 0.36) to afford **5c** as a white solid (28 mg, 0.13 mmol, 63% yield).
^1H NMR (600 MHz, Chloroform-d) δ 7.41 (s, 1H), 4.05 (t, J = 7.2 Hz, 2H), 3.93 (two overlapping peaks, 6H), 2.61 (t, J = 8.1 Hz, 2H), 2.09 (p, J = 7.8 Hz, 2H).

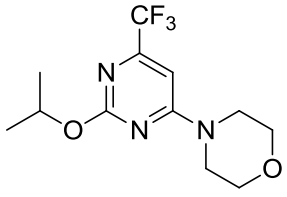
^{13}C NMR (151 MHz, Chloroform-d) δ 175.53, 172.88, 164.27, 159.27, 88.48, 54.47, 54.01, 46.87, 33.59, 17.56.
Calculated exact mass: 223.10
EI Mass Spectrum: 223.1 (M^+, 46% relative intensity), 168.1 ($[M-55]^+$, base peak)

Synthesis of 2-isopropoxy-4-(3-methoxyphenoxy)-6-(trifluoromethyl)pyrimidine (6a)



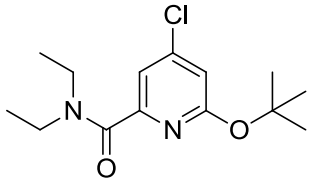
The general procedure for tandem C-H fluorination/S_NAr was performed with 2-isopropoxy-4-(trifluoromethyl)pyrimidine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 20:1 hexanes : ethyl acetate (R_f = 0.26) to afford **6a** as a colorless oil (33 mg, 0.10 mmol, 50% yield).
^{1}H NMR (600 MHz, Chloroform-d) δ 7.33 (t, J = 8.2 Hz, 1H), 6.83 (dd, J = 8.3, 1.8 Hz, 1H), 6.76 (s, 1H), 6.75 – 6.72 (m, 1H), 6.69 (s, 1H), 5.11 (hept, J = 6.2 Hz, 1H), 3.81 (s, 3H), 1.32 (d, J = 6.2 Hz, 6H).
^{13}C NMR (151 MHz, Chloroform-d) δ 172.24, 165.22, 160.84, 158.88 (q, J = 35.9 Hz), 152.82, 130.19, 120.15 (q, J = 274.9 Hz), 113.54, 111.90, 107.46, 97.72 (q, J = 2.9 Hz), 71.92, 55.47, 21.55.
Calculated exact mass: 328.10
EI Mass Spectrum: 328.1 (M^+, 27% relative intensity), 149.0 ($[M-179]^+$, base peak)

Synthesis of 4-(2-isopropoxy-6-(trifluoromethyl)pyrimidin-4-yl)morpholine (6b)



The general procedure for tandem C-H fluorination/S_NAr was performed with 2-isopropoxy-4-(trifluoromethyl)pyrimidine. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 6:1 hexanes : ethyl acetate (R_f = 0.24) to afford **6b** as a colorless oil (29 mg, 0.10 mmol, 50% yield).
^{1}H NMR (600 MHz, Chloroform-d) δ 6.44 (s, 1H), 5.23 (hept, J = 6.1 Hz, 1H), 3.79 – 3.74 (m, 4H), 3.70 (br, 4H), 1.36 (d, J = 6.2 Hz, 6H).
^{13}C NMR (151 MHz, Chloroform-d) δ 164.98, 164.33, 156.61 (q, J = 34.5 Hz), 120.75 (q, J = 274.7 Hz), 92.79 (q, J = 3.2 Hz), 70.44, 66.34, 44.43, 21.77.

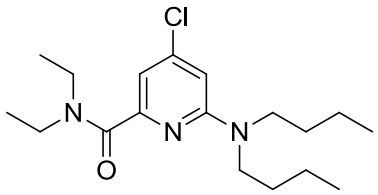
Synthesis of 6-(tert-butoxy)-4-chloro-N,N-diethylpicolinamide (7a)



The general procedure for tandem C-H fluorination/S_NAr was performed with 4-chloro-N,N-diethylpicolinamide. The fluorination step was performed with 4 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 6:1 hexanes : ethyl acetate (R_f = 0.29) to afford **7a** as a colorless oil (40 mg, 0.14 mmol, 70% yield).
^{1}H NMR (600 MHz, Chloroform-d) δ 7.00 (d, J = 1.7 Hz, 1H), 6.66 (d, J = 1.7 Hz, 1H), 3.52 (q, J = 7.1 Hz, 2H), 3.34 (q, J = 7.1 Hz, 2H), 1.53 (s, 9H), 1.22 (t, J = 7.1 Hz, 3H), 1.10 (t, J = 7.1 Hz, 3H).

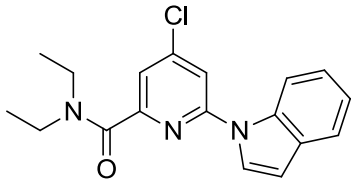
^{13}C NMR (151 MHz, Chloroform-d) δ 167.50, 163.45, 153.23, 145.56, 115.68, 113.61, 80.96, 42.43, 39.41, 28.54, 14.29, 12.68.
Calculated exact mass: 284.13
EI Mass Spectrum: 284.1 (M^+, 1% relative intensity), 227.0 ($[M-57]^+$, 13% relative intensity), 72.1 ($[C_4H_{10}N]^+$, base peak)

Synthesis of 4-chloro-6-(dibutylamino)-N,N-diethylpicolinamide (7b)



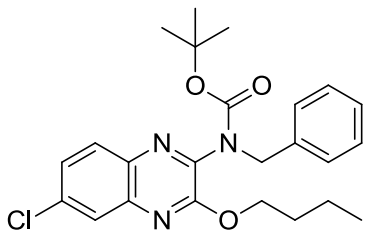
The general procedure for tandem C-H fluorination/S_NAr was performed with 4-chloro-N,N-diethylpicolinamide. The fluorination step was performed with 4 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 6:1 hexanes : ethyl acetate (R_f = 0.28) to afford **7b** as a colorless oil (48 mg, 0.14 mmol, 71% yield).
^{1}H NMR (600 MHz, Chloroform-d) δ 6.67 (s, 1H), 6.35 (s, 1H), 3.49 (q, J = 6.6 Hz, 2H), 3.36 (m, 6H), 1.51 (m, 4H), 1.29 (m, 4H), 1.19 (t, J = 6.8 Hz, 3H), 1.13 (t, J = 6.7 Hz, 3H), 0.91 (t, J = 7.1 Hz, 6H).
^{13}C NMR (151 MHz, Chloroform-d) δ 168.20, 157.45, 154.55, 144.85, 110.02, 105.09, 48.40, 42.58, 39.50, 29.51, 20.13, 14.28, 13.83, 12.65.
Calculated exact mass: 339.21
EI Mass Spectrum: 339.2 (M^+, 52% relative intensity), 240.1 ($[M-99]^+$, base peak)

Synthesis of 4-chloro-N,N-diethyl-6-(1H-indol-1-yl)picolinamide (7c)



The general procedure for tandem C-H fluorination/S_NAr was performed with 4-chloro-N,N-diethylpicolinamide. The fluorination step was performed with 4 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 6:1 hexanes : ethyl acetate to afford **7c** as a light yellow oil (40 mg, 0.12 mmol, 61% yield).
^{1}H NMR (600 MHz, Chloroform-d) δ 8.17 (d, J = 8.3 Hz, 1H), 7.72 (s, 1H), 7.66 (d, J = 7.7 Hz, 1H), 7.55 (s, 1H), 7.44 (s, 1H), 7.32 (t, J = 7.6 Hz, 1H), 7.24 (t, J = 7.3 Hz, 1H), 6.73 (s, 1H), 3.60 (q, J = 6.7 Hz, 2H), 3.43 (q, J = 6.6 Hz, 2H), 1.30 (t, J = 6.9 Hz, 3H), 1.21 (t, J = 6.7 Hz, 3H).
^{13}C NMR (151 MHz, Chloroform-d) δ 166.68, 155.37, 151.83, 146.61, 134.85, 130.62, 125.65, 123.54, 121.86, 121.25, 119.46, 114.31, 113.09, 106.64, 43.14, 40.16, 14.37, 12.73.
Calculated exact mass: 327.11
EI Mass Spectrum: 327.1 (M^+, 13% relative intensity), 72.1 ($[C_4H_{10}N]^+$, base peak)

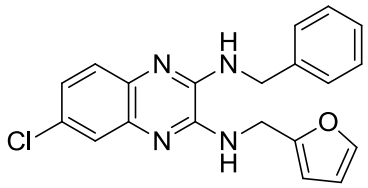
Synthesis of tert-butyl benzyl(3-butoxy-6-chloroquinoxalin-2-yl)carbamate (8a)



The general procedure for tandem C-H fluorination/S_NAr was performed with tert-butyl benzyl(6-chloroquinoxalin-2-yl)carbamate. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography with 20:1

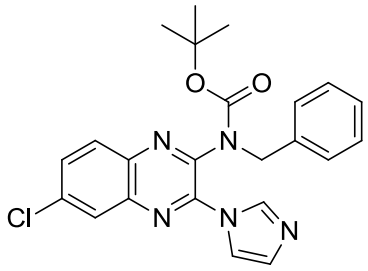
hexanes : ethyl acetate to afford **8a** as a light yellow oil (81 mg, 0.18 mmol, 92% yield).
^{1}H NMR (600 MHz, Chloroform-d) δ 7.80 (d, J = 8.8 Hz, 1H), 7.76 (s, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.35 (d, J = 7.5 Hz, 2H), 7.23 (t, J = 7.4 Hz, 2H), 7.18 (t, J = 7.2 Hz, 1H), 5.08 (s, 2H), 4.40 (s, 2H), 1.75 (p, J = 6.8 Hz, 2H), 1.44 (m, 2H), 1.40 (s, 9H), 0.96 (t, J = 7.4 Hz, 3H).
^{13}C NMR (151 MHz, Chloroform-d) δ 154.48, 153.60, 143.08, 140.13, 137.93, 135.83, 134.80, 129.03, 128.13, 127.73, 127.16, 127.06, 125.64, 81.40, 66.79, 51.80, 30.72, 28.05, 19.12, 13.75.
Calculated exact mass: 441.18
EI Mass Spectrum: 341.1 ($[M\text{-}Boc]^+$, 57% relative intensity), 91.0 ($[C_7H_7]^+$, base peak)

Synthesis of N2-benzyl-6-chloro-N3-(furan-2-ylmethyl)quinoxaline-2,3-diamine (8b)



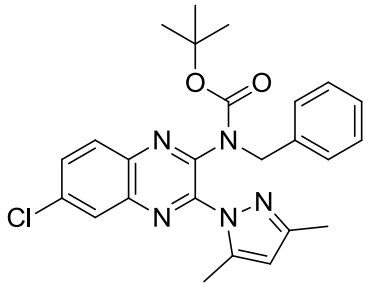
The general procedure for tandem C-H fluorination/S_NAr was performed with tert-butyl benzyl(6-chloroquinoxalin-2-yl)carbamate. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 3:1 hexanes : ethyl acetate to afford **8b** as a white solid (60 mg, 0.16 mmol, 82% yield).
Note: The Boc group was cleaved during the S_NAr reaction.
^{1}H NMR (600 MHz, Chloroform-d) δ 7.95 (s, 1H), 7.86 (d, J = 8.7 Hz, 1H), 7.56 (d, J = 7.2 Hz, 2H), 7.49 (d, J = 8.6 Hz, 1H), 7.36 – 7.31 (m, 3H), 7.31 – 7.26 (m, 1H), 6.49 (s, 1H), 6.32 (s, 1H), 5.18 (two overlapping peaks, 4H).
^{13}C NMR (151 MHz, Chloroform-d) δ 153.54, 148.35, 142.69, 139.75, 139.57, 139.46, 137.57, 135.51, 132.28, 128.81, 128.71, 128.11, 127.55, 126.93, 110.53, 109.56, 43.58, 36.22.

Synthesis of tert-butyl benzyl(6-chloro-3-(1H-imidazol-1-yl)quinoxalin-2-yl)carbamate (8c)



The general procedure for tandem C-H fluorination/S_NAr was performed with tert-butyl benzyl(6-chloroquinoxalin-2-yl)carbamate. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 1:1 hexanes : ethyl acetate (R_f = 0.32) to afford **8c** as a light yellow oil (72 mg, 0.17 mmol, 83% yield).
^{1}H NMR (600 MHz, Chloroform-d) δ 8.05 (s, 1H), 7.98 (m, 2H), 7.71 (d, J = 8.9 Hz, 1H), 7.37 (d, J = 7.3 Hz, 2H), 7.34 – 7.23 (m, 4H), 7.09 (s, 1H), 5.28 (s, 2H), 1.16 (br, 9H).
^{13}C NMR (151 MHz, Chloroform-d) δ 152.54, 142.90, 141.74, 139.44, 138.20, 136.65, 136.35, 136.02, 131.26, 129.20, 129.04 (two overlapping peaks), 128.79, 128.10, 127.17, 117.58, 83.08, 51.74, 27.53.
Chemical formula: $C_{24}H_{23}ClN_4O_2$
Calculated exact mass: 434.1510
Observed formula by ESIMS: $C_{24}H_{25}ClN_4O_2$
Observed exact mass: 436.1535 (calculated exact mass + $^{1}H_2$)

Synthesis of tert-butyl benzyl(6-chloro-3-(3,5-dimethyl-1H-pyrazol-1-yl)quinoxalin-2-yl)carbamate (8d)



The general procedure for tandem C-H fluorination/S_NAr was performed with tert-butyl benzyl(6-chloroquinoxalin-2-yl)carbamate. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 9:1 hexanes : ethyl acetate (R_f = 0.61) to afford **8d** as a white solid (63 mg, 0.14 mmol, 68% yield).

^{1}H NMR (600 MHz, Chloroform-d) δ 7.98 – 7.96 (m, 1H), 7.90 (d, J = 8.9 Hz, 1H), 7.64 (dd, J = 8.9, 1.9 Hz, 1H), 7.60 (d, J = 7.6 Hz, 2H), 7.32 (t, J = 7.5 Hz, 2H), 7.25 (d, J = 8.9 Hz, 1H), 6.01 (s, 1H), 5.08 (br, 2H), 2.56 (s, 3H), 2.28 (s, 3H), 1.11 (s, 9H).

^{13}C NMR (151 MHz, Chloroform-d) δ 152.86, 150.17, 143.75, 142.17, 138.96, 138.83, 138.15, 135.15, 130.52, 129.29, 128.20 (two overlapping peaks), 127.99, 127.04, 126.86, 108.01, 81.16, 53.23, 27.59, 13.67, 12.93.

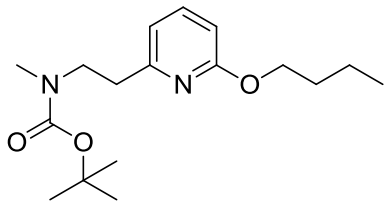
Chemical formula: $C_{26}H_{27}ClN_4O_2$

Calculated exact mass: 462.1823

Observed formula by ESIMS: $C_{26}H_{29}ClN_4O_2$

Observed exact mass: 464.1846 (calculated exact mass + $^1H_2$)

Synthesis of tert-butyl (2-(6-butoxypyridin-2-yl)ethyl)(methyl)carbamate (9a)



The general procedure for tandem C-H fluorination/S_NAr was performed with Boc-betahistine. The fluorination step was performed with 4 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 9:1 hexanes : ethyl acetate (R_f = 0.43) to afford **9a** as a colorless oil (37 mg, 0.12 mmol, 60% yield).

Note: Slow rotation about the R_2N-$CO_2{}^tBu$ bond results in the appearance of broad and/or diastereomeric peaks in the ^{1}H and ^{13}C NMR spectra corresponding to the atoms to the left of the pyridine ring.

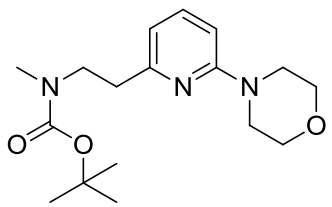
^{1}H NMR (600 MHz, Chloroform-d) δ 7.43 (t, J = 7.6 Hz, 1H), 6.67 (d, J = 34.9 Hz, 1H), 6.52 (d, J = 6.6 Hz, 1H), 4.25 (t, J = 6.5 Hz, 2H), 3.54 (s, 2H), 2.80 (m, 5H), 1.73 (p, J = 6.8 Hz, 2H), 1.50 – 1.34 (m, 11H), 0.95 (t, J = 7.3 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-d) δ 163.64, 157.10, 155.59, 138.69, 115.55, 107.93, 79.04, 65.47, 49.08, 36.46, 34.28, 31.18, 28.34, 19.27, 13.85.

Calculated exact mass: 308.21

EI Mass Spectrum: 308.2 (M^+, 10% relative intensity), 109.0 ($[M-199]^+$, base peak)

Synthesis of tert-butyl methyl(2-(6-morpholinopyridin-2-yl)ethyl)carbamate (9b)



The general procedure for tandem C-H fluorination/S_NAr was performed with Boc-betahistine. The fluorination step was performed with 4 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography

eluting with 3:1 hexanes : ethyl acetate to afford **9b** as a colorless oil (30 mg, 0.093 mmol, 47% yield).

Note: Slow rotation about the $R_2N\text{-}CO_2{}^tBu$ bond results in the appearance of broad and/or diastereomeric peaks in the ^1H and ^{13}C NMR spectra corresponding to the atoms to the left of the pyridine ring.

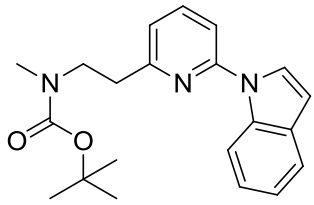
^1H NMR (600 MHz, Chloroform-d) δ 7.39 (t, J = 7.5 Hz, 1H), 6.59 – 6.41 (m, 2H), 3.84 – 3.77 (m, 4H), 3.51 (m, 6H), 2.81 (s, 5H), 1.40 (9H).

^{13}C NMR (151 MHz, Chloroform-d) δ 159.16, 157.63, 155.62, 137.81, 113.10, 104.19, 79.02, 66.77, 49.13, 45.59, 36.77, 34.35, 28.38.

Calculated exact mass: 321.21

EI Mass Spectrum: 321.2 (M^+, 9% relative intensity), 178.1 ($[M\text{-}143]^+$, base peak)

Synthesis of tert-butyl (2-(6-(1H-indol-1-yl)pyridin-2-yl)ethyl)(methyl)carbamate (9c)



The general procedure for tandem C-H fluorination/S_NAr was performed with Boc-betahistine. The fluorination step was performed with 4 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 6:1 hexanes : ethyl acetate (R_f = 0.24) to afford **9c** as a colorless oil (36 mg, 0.10 mmol, 51% yield).

Note: Slow rotation about the $R_2N\text{-}CO_2{}^tBu$ bond results in the appearance of broad and/or diastereomeric peaks in the ^1H and ^{13}C NMR spectra corresponding to the atoms to the left of the pyridine ring.

^1H NMR (600 MHz, Chloroform-d) δ 8.25 (s, 1H), 7.76 – 7.69 (m, 2H), 7.66 (d, J = 7.8 Hz, 1H), 7.34 (d, J = 6.2 Hz, 1H), 7.29 (t, J = 7.7 Hz, 1H), 7.21 (t, J = 7.4 Hz, 1H), 7.04 (d, J = 48.4 Hz, 1H), 6.71 (s, 1H), 3.68 (br, 2H), 3.07 (br, 2H), 2.87 (d, J = br, 3H), 1.41 (br, 9H).

^{13}C NMR (151 MHz, Chloroform-d) δ 159.13, 155.62, 152.14, 138.68, 135.05, 130.43, 125.99, 122.95, 121.14, 121.00, 119.50, 113.20, 111.89, 105.33, 79.29, 49.15, 36.73, 34.44, 28.39.

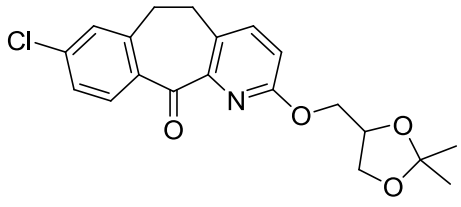
Chemical formula: $C_{21}H_{25}N_3O_2$

Calculated exact mass: 351.1947

Observed formula by ESIMS: $C_{21}H_{28}N_3O_2$

Observed exact mass: 354.1812 (calculated exact mass + $^1H_3$)

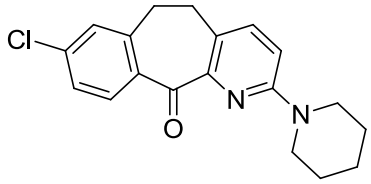
Synthesis of 8-chloro-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11(6H)-one (10a)



The general procedure for tandem C-H fluorination/S_NAr was performed with 8-chloro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11(6H)-one. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 3:1 hexanes : ethyl acetate (R_f = 0.27) to afford **10a** as a colorless oil (35 mg, 0.94 mmol, 47% yield).

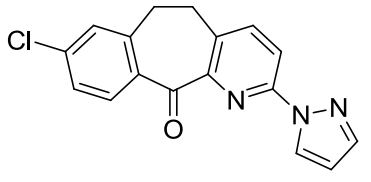
^{1}H NMR (600 MHz, Chloroform-d) δ 7.97 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 8.3 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.22 (s, 1H), 6.89 (d, J = 8.3 Hz, 1H), 4.50 (td, J = 12.1, 9.9, 4.7 Hz, 2H), 4.40 (dd, J = 10.4, 6.0 Hz, 1H), 4.13 (t, J = 7.3 Hz, 1H), 3.84 (t, J = 7.3 Hz, 1H), 3.17 – 3.13 (m, 2H), 3.09 – 3.05 (m, 2H), 1.45 (s, 3H), 1.39 (s, 3H).
^{13}C NMR (151 MHz, Chloroform-d) δ 192.65, 161.93, 150.35, 143.10, 140.77, 138.58, 135.98, 132.61, 130.69, 129.39, 127.08, 114.87, 109.72, 74.21, 66.77, 66.44, 34.53, 31.54, 26.69, 25.48.
Chemical formula: $C_{20}H_{20}ClNO_4$
Calculated exact mass: 373.1081
Observed formula by ESIMS: $C_{20}H_{20}ClNO_4Na$
Observed exact mass: 396.0972 (calculated exact mass + ^{23}Na)

Synthesis of 8-chloro-2-(piperidin-1-yl)-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11(6H)-one (10b)



The general procedure for tandem C-H fluorination/S_NAr was performed with 8-chloro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11(6H)-one. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 3:1 hexanes : ethyl acetate (R_f = 0.38) to afford **10b** as a yellow oil (20 mg, 0.061 mmol, 31% yield).
^{1}H NMR (500 MHz, Chloroform-d) δ 7.95 (d, J = 8.5 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.28 (dd, J = 8.5, 2.0 Hz, 1H), 7.20 (d, J = 1.9 Hz, 1H), 6.82 (br, 1H), 3.57 (m, 4H), 3.15 – 3.09 (m, 2H), 3.02 – 2.98 (m, 2H), 1.64 (br, 6H).
^{13}C NMR (151 MHz, Chloroform-d) δ 193.81, 157.94, 143.26, 139.43 (two overlapping peaks), 138.16, 136.48, 132.56, 129.27, 126.87, 125.76, 110.69, 46.23, 34.80, 31.42, 25.51, 24.52.
Chemical formula: $C_{19}H_{19}ClN_2O$
Calculated exact mass: 326.1186
Observed formula by ESIMS: $C_{19}H_{20}ClN_2O$
Observed exact mass: 327.1258 (calculated exact mass + ^{1}H)

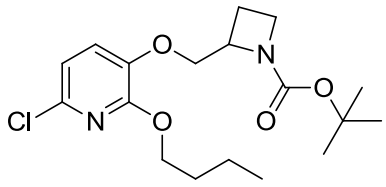
Synthesis of 8-chloro-2-(1H-pyrazol-1-yl)-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11(6H)-one (10c)



The general procedure for tandem C-H fluorination/S_NAr was performed with 8-chloro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11(6H)-one. The fluorination step was performed with 2 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 1:1 hexanes : ethyl acetate (R_f = 0.28) to afford **10c** as a yellow oil (25 mg, 0.081 mmol, 40% yield).
Note: The product was contaminated with ~8% of an inseparable impurity
^{1}H NMR (500 MHz, Chloroform-d) δ 8.68 (d, J = 2.4 Hz, 1H), 8.07 (dd, J = 15.8, 8.4 Hz, 2H), 7.79 – 7.73 (m, 2H), 7.36 (dd, J = 8.4, 1.9 Hz, 1H), 7.28 (d, J = 2.8 Hz, 1H), 6.49 – 6.47 (m, 1H), 3.27 – 3.23 (m, 2H), 3.23 – 3.19 (m, 2H).

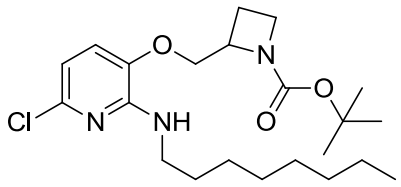
^{13}C NMR (101 MHz, Chloroform-d) δ 192.41, 152.19, 150.44, 143.15, 142.20, 140.39, 139.01, 135.49, 134.23, 132.76, 129.70, 127.52, 127.26, 115.30, 107.91, 34.49, 31.70.
Chemical formula: $C_{17}H_{12}ClN_3O$
Calculated exact mass: 309.0669
Observed formula by ESIMS: $C_{17}H_{12}ClN_3ONa$
Observed exact mass: 332.0560 (calculated exact mass + ^{23}Na)

Synthesis of N-Boc-2-butoxytebanicline (11a)



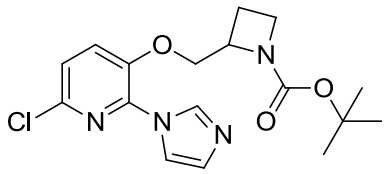
The general procedure for tandem C-H fluorination/S_NAr was performed with Boc-tebanicline. The fluorination step was performed with 4 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 6:1 hexanes : ethyl acetate (R_f = 0.34) to afford **11a** as a colorless oil (39 mg, 0.11 mmol, 53% yield).
^{1}H NMR (600 MHz, Chloroform-d) δ 7.08 (d, J = 7.7 Hz, 1H), 6.76 (d, J = 8.4 Hz, 1H), 4.46 (s, 1H), 4.32 (two overlapping peaks, 3H), 4.07 (d, J = 10.2 Hz, 1H), 3.91 – 3.80 (m, 2H), 2.32 (m, 2H), 1.77 (p, J = 6.8 Hz, 2H), 1.47 (h, J = 7.4 Hz, 2H), 1.38 (s, 9H), 0.96 (t, J = 7.3 Hz, 3H).
^{13}C NMR (151 MHz, Chloroform-d) δ 155.99, 154.43, 142.42, 138.27, 123.14, 115.49, 79.51, 69.91, 66.58, 60.31, 47.34, 30.88, 28.35, 19.22, 19.03, 13.81.
Calculated exact mass: 370.17
EI Mass Spectrum: 370.2 (M^+, 3% relative intensity), 70.1 (base peak)

Synthesis of N-Boc-2-octylaminotebanicline (11b)



The general procedure for tandem C-H fluorination/S_NAr was performed with Boc-tebanicline. The fluorination step was performed with 4 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 3:1 hexanes : ethyl acetate (R_f = 0.49) to afford **11b** as a light yellow oil (48 mg, 0.11 mmol, 56% yield).
^{1}H NMR (600 MHz, Chloroform-d) δ 6.75 (d, J = 7.9 Hz, 1H), 6.41 – 6.37 (d, J = 7.9 Hz, 1H), 4.53 (s, 1H), 4.24 – 4.17 (m, 1H), 4.06 – 3.99 (s, 1H), 3.93 – 3.82 (m, 2H), 3.39 (s, 2H), 2.35 (dt, J = 17.2, 9.2 Hz, 1H), 2.14 (s, 1H), 1.62 (p, J = 7.3 Hz, 2H), 1.46 – 1.22 (m, 19H), 0.86 (t, J = 6.9 Hz, 3H).
^{13}C NMR (151 MHz, Chloroform-d) δ 156.31, 150.27, 140.22, 140.01, 117.33, 109.04, 79.75, 70.02, 59.97, 47.35, 41.02, 31.80, 29.58, 29.34, 29.20, 28.34, 27.03, 22.61, 18.97, 14.05.
Chemical formula: $C_{22}H_{36}ClN_3O_3$
Calculated exact mass: 425.2445
Observed formula by ESIMS: $C_{22}H_{37}ClN_3O_3$
Observed exact mass: 426.2516 (calculated exact mass + ^{1}H)

Synthesis of N-Boc-2-imidazolyltebanicline (11c)



The general procedure for tandem C-H fluorination/S_NAr was performed with Boc-tebanicline. The fluorination step was performed with 4 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 99:1 ethyl acetate : triethylamine (R_f = 0.38) to afford **11c** as a light yellow oil (28 mg, 0.077 mmol, 38% yield).

^{1}H NMR (600 MHz, Chloroform-d) δ 8.61 (s, 1H), 7.85 (s, 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.23 (d, J = 8.5 Hz, 1H), 7.19 (s, 1H), 4.55 (s, 1H), 4.47 (s, 1H), 4.22 (dd, J = 10.2, 2.4 Hz, 1H), 3.92 – 3.84 (m, 1H), 3.80 (m, 1H), 2.37 – 2.28 (m, 1H), 2.21 (m, 1H), 1.39 (s, 9H).

^{13}C NMR (151 MHz, Chloroform-d) δ 156.25, 144.89, 140.49, 137.80, 136.65, 127.56, 125.02, 123.05, 118.59, 80.09, 70.30, 59.49, 47.39, 28.30, 18.93.

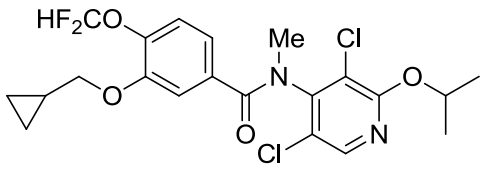
Chemical formula: $C_{17}H_{21}ClN_4O_3$

Calculated exact mass: 364.1302

Observed formula by ESIMS: $C_{17}H_{22}ClN_4O_3$

Observed exact mass: 365.1374 (calculated exact mass + ^{1}H)

Synthesis of N-methyl-2-isopropoxyroflumilast (12a)



The general procedure for tandem C-H fluorination/S_NAr was performed with N-methylroflumilast. The fluorination step was performed with 4 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 6:1 hexanes : ethyl acetate to afford **12a** as a colorless oil (42 mg, 0.088 mmol, 44% yield).

Note: The product exists as two amide diastereomers (~10:1) that do not interconvert on the NMR time scale

Major diastereomer:

^{1}H NMR (600 MHz, Chloroform-d) δ 7.98 (s, 1H), 7.06 (s, 1H), 6.96 (m, 2H), 6.57 (t, J = 75.0 Hz, 1H), 5.23 (hept, J = 5.3, 1H), 3.78 – 3.67 (m, 2H), 3.27 (s, 3H), 1.36 – 1.30 (m, 6H), 1.22 – 1.15 (m, 1H), 0.61 (d, J = 7.5 Hz, 2H), 0.30 (d, J = 4.5 Hz, 2H).

^{13}C NMR (151 MHz, Chloroform-d) δ 169.67, 158.96, 149.54, 148.38, 144.01, 142.15 (t, J = 3.1 Hz), 133.08, 122.46, 121.39, 120.41, 118.12, 115.82 (t, J = 260.2 Hz), 113.80, 73.86, 71.07, 34.76, 21.74, 9.93, 3.17.

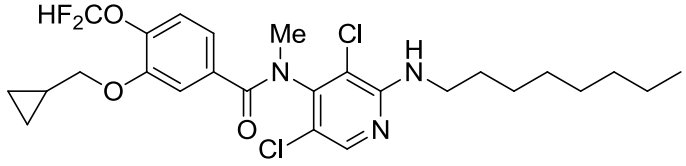
Chemical formula: $C_{21}H_{22}Cl_2F_2N_2O_4$

Calculated exact mass: 474.0925

Observed formula by ESIMS: $C_{21}H_{22}Cl_2F_2N_2O_4Na$

Observed exact mass: 497.0825 (calculated exact mass + ^{23}Na)

Synthesis of N-methyl-2-octylaminoroflumilast (12b)



The general procedure for tandem C-H fluorination/S_NAr was performed with N-methylroflumilast. The

fluorination step was performed with 4 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 6:1 hexanes : ethyl acetate to afford **12b** as a colorless oil (51 mg, 0.094 mmol, 47% yield).

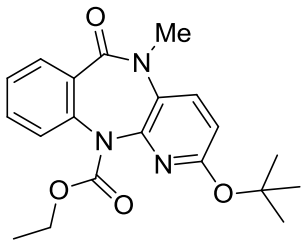
Note: The product exists as two amide diastereomers (~10:1) that do not interconvert on the NMR time scale

Major diastereomer:

^{1}H NMR (600 MHz, Chloroform-d) δ 7.97 (s, 1H), 7.06 (s, 1H), 7.00 (d, J = 8.3 Hz, 1H), 6.96 (d, J = 8.2 Hz, 1H), 6.58 (t, J = 75.0 Hz, 1H), 4.97 (t, J = 4.4 Hz, 1H), 3.72 (d, J = 6.9 Hz, 2H), 3.40 (m, 1H), 3.32 (m, 1H), 3.26 (s, 3H), 1.58 (m, 2H), 1.30 (m, 10H), 0.87 (t, J = 6.6 Hz, 3H), 0.60 (d, J = 7.6 Hz, 2H), 0.29 (d, J = 4.4 Hz, 2H).

^{13}C NMR (151 MHz, Chloroform-d) δ 169.65, 154.08, 149.46, 146.33, 145.84, 142.14 (t, J = 3.1 Hz), 133.13, 121.35, 120.51, 117.26, 115.86 (t, J = 260.0 Hz), 113.86, 113.79, 73.87, 41.90, 34.85, 31.76, 29.36, 29.25, 29.15, 26.93, 22.59, 14.03, 9.94, 3.20.

Synthesis of ethyl 2-(tert-butoxy)-5-methyl-6-oxo-5H-benzo[e]pyrido[3,2-b][1,4]diazepine-11(6H)-carboxylate (13a)

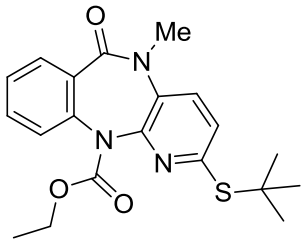


The general procedure for tandem C-H fluorination/S_NAr was performed with ethyl 5-methyl-6-oxo-5H-benzo[e]pyrido[3,2-b][1,4]diazepine-11(6H)-carboxylate. The fluorination step was performed with 4 mL of MeCN at room temperature for 2 h. The product was purified by silica gel chromatography eluting with 1:1 hexanes : ethyl acetate (R_f = 0.48) to afford **13a** as a colorless oil (32 mg, 0.087 mmol, 43% yield).

^{1}H NMR (600 MHz, Chloroform-d) δ 7.83 (d, J = 7.7 Hz, 1H), 7.50 – 7.42 (m, 3H), 7.33 – 7.29 (m, 1H), 6.61 (d, J = 8.7 Hz, 1H), 4.24 (q, J = 6.7 Hz, 2H), 3.51 (s, 3H), 1.57 (s, 9H), 1.23 (t, J = 7.0 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-d) δ 166.91, 160.03, 153.20, 144.88, 142.20, 133.75, 132.01, 131.22, 129.94, 127.48, 127.25, 126.72, 113.14, 80.65, 62.31, 36.78, 28.34, 14.34.

Synthesis of ethyl 2-(tert-butylthio)-5-methyl-6-oxo-5H-benzo[e]pyrido[3,2-b][1,4]diazepine-11(6H)-carboxylate (13b)



The general procedure for tandem C-H fluorination/S_NAr was performed with ethyl 5-methyl-6-oxo-5H-benzo[e]pyrido[3,2-b][1,4]diazepine-11(6H)-carboxylate. The fluorination step was performed with 4 mL of MeCN at room temperature for 2 h. The product was purified by silica gel chromatography eluting with 2:1 hexanes : ethyl acetate (R_f = 0.36) to afford **13b** as a colorless oil (41 mg, 0.11 mmol, 53% yield).

^{1}H NMR (600 MHz, Chloroform-d) δ 7.82 (d, J = 7.5 Hz, 1H), 7.49 (m, 2H), 7.42 (d, J = 8.4 Hz, 1H), 7.34 – 7.30 (m, 1H), 7.20 (d, J = 8.4 Hz, 1H), 4.29 – 4.17 (m, 2H), 3.54 (s, 3H), 1.53 (s, 9H), 1.22 (t, J = 7.1 Hz, 3H).

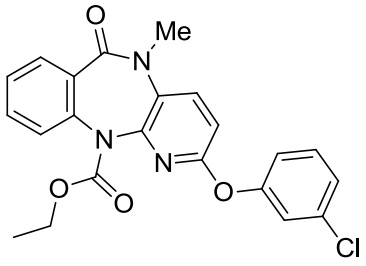
^{13}C NMR (151 MHz, Chloroform-d) δ 166.72, 155.13, 153.09, 147.36, 141.60, 132.35, 131.98, 131.25, 131.12, 129.58, 127.48, 126.97, 125.68, 62.47, 48.24, 36.84, 30.59, 14.31.

Chemical formula: $C_{20}H_{23}N_3O_3S$

Calculated exact mass: 385.1460

Observed formula by ESIMS: $C_{20}H_{24}N_3O_3S$
Observed exact mass: 386.1536 (calculated exact mass + ^{1}H)

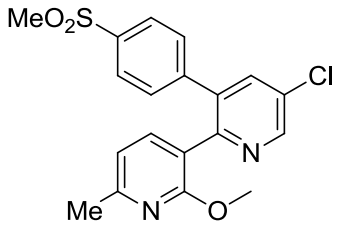
Synthesis of ethyl 2-(3-chlorophenoxy)-5-methyl-6-oxo-5H-benzo[e]pyrido[3,2-b][1,4]diazepine-11(6H)-carboxylate (13c)



The general procedure for tandem C-H fluorination/S_NAr was performed with ethyl 5-methyl-6-oxo-5H-benzo[e]pyrido[3,2-b][1,4]diazepine-11(6H)-carboxylate. The fluorination step was performed with 4 mL of MeCN at room temperature for 2 h. The product was purified by silica gel chromatography eluting with 1:1 hexanes : ethyl acetate (R_f = 0.46) to afford **13c** as a colorless oil (41 mg, 0.10 mmol, 48% yield).

^{1}H NMR (600 MHz, Chloroform-d) δ 7.83 (d, J = 7.7 Hz, 1H), 7.64 (d, J = 8.7 Hz, 1H), 7.47 (s, 2H), 7.35 – 7.28 (m, 2H), 7.17 (m, 2H), 7.04 (d, J = 8.1 Hz, 1H), 6.89 (d, J = 8.6 Hz, 1H), 4.27 – 4.18 (m, 2H), 3.56 (s, 3H), 1.23 (t, J = 7.0 Hz, 3H).
^{13}C NMR (151 MHz, Chloroform-d) δ 166.75, 158.46, 154.57, 152.94, 146.10, 141.61, 134.97, 134.73, 132.31, 131.30, 130.92, 130.26, 129.51, 127.56, 127.12, 124.80, 120.91, 118.69, 111.81, 62.60, 37.05, 14.33.
Chemical formula: $C_{22}H_{18}ClN_3O_4$
Calculated exact mass: 423.0986
Observed formula by ESIMS: $C_{22}H_{18}ClN_3O_4Na$
Observed exact mass: 446.0878 (calculated exact mass + ^{23}Na)

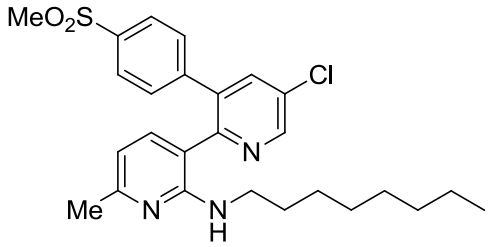
Synthesis of 2-methoxyetoricoxib (14a)



The general procedure for tandem C-H fluorination/S_NAr was performed with etoricoxib. The fluorination step was performed with 2 mL of MeCN at 50 ^{o}C for 2 h. The product was purified by silica gel chromatography eluting with 1:1 hexanes : ethyl acetate (R_f = 0.52) to afford **14a** as a white solid (43 mg, 0.11 mmol, 55% yield).

^{1}H NMR (600 MHz, Chloroform-d) δ 8.67 (d, J = 2.3 Hz, 1H), 7.84 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 2.3 Hz, 1H), 7.65 (d, J = 7.4 Hz, 1H), 7.34 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 7.4 Hz, 1H), 3.38 (s, 3H), 3.03 (s, 3H), 2.42 (s, 3H).
^{13}C NMR (151 MHz, Chloroform-d) δ 158.82, 157.68, 151.99, 147.76, 144.54, 140.15, 139.60, 136.94, 136.63, 130.87, 129.16, 127.19, 118.61, 116.18, 52.46, 44.43, 24.01.
Chemical formula: $C_{19}H_{17}ClN_2O_3S$
Calculated exact mass: 388.0648
Observed formula by ESIMS: $C_{19}H_{18}ClN_2O_3S$
Observed exact mass: 389.0725 (calculated exact mass + ^{1}H)

Synthesis of 2-octylaminoetoricoxib (14b)



The general procedure for tandem C-H fluorination/S_NAr was performed with etoricoxib. The fluorination step was performed with 2 mL of MeCN at 50 ^oC for 2 h. The product was purified by silica gel chromatography eluting with 2:1 hexanes : ethyl acetate (R_f = 0.46) to afford **14b** as a light yellow oil (50 mg, 0.10 mmol, 51% yield).

^1H NMR (600 MHz, Chloroform-d) δ 8.63 (d, J = 2.4 Hz, 1H), 7.86 (d, J = 8.3 Hz, 2H), 7.76 (d, J = 2.4 Hz, 1H), 7.37 (d, J = 8.4 Hz, 2H), 6.64 (d, J = 7.5 Hz, 1H), 6.18 (br, 1H), 6.10 (d, J = 7.6 Hz, 1H), 3.47 – 3.40 (m, 2H), 3.05 (s, 3H), 2.35 (s, 3H), 1.57 (p, J = 7.3 Hz, 2H), 1.31 m, 10H), 0.87 (t, J = 7.0 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-d) δ 157.67, 155.85, 154.02, 147.25, 144.10, 139.81, 139.65, 138.52, 136.30, 130.27, 130.03, 127.69, 112.98, 110.65, 44.38, 41.46, 31.78, 29.63, 29.32, 29.22, 27.11, 24.42, 22.61, 14.06.

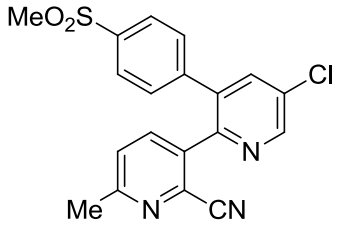
Chemical formula: $C_{26}H_{32}ClN_3O_2S$

Calculated exact mass: 485.1904

Observed formula by ESIMS: $C_{26}H_{33}ClN_3O_2S$

Observed exact mass: 486.1972 (calculated exact mass + ^1H)

Synthesis of 2-cyanoetoricoxib (14c)



The general procedure for tandem C-H fluorination/S_NAr was performed with etoricoxib. The fluorination step was performed with 2 mL of MeCN at 50 ^oC for 2 h. The product was purified by silica gel chromatography eluting with 1:1 hexanes : ethyl acetate to afford **14c** as a light yellow oil (31 mg, 0.081 mmol, 40% yield).

^1H NMR (500 MHz, Chloroform-d) δ 8.77 (d, J = 2.3 Hz, 1H), 7.89 (d, J = 8.4 Hz, 2H), 7.84 (d, J = 2.3 Hz, 1H), 7.55 (d, J = 8.1 Hz, 1H), 7.37 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.1 Hz, 1H), 3.07 (s, 3H), 2.61 (s, 3H).

^{13}C NMR (151 MHz, Chloroform-d) δ 160.39, 149.90, 148.61, 142.24, 140.54, 138.52, 137.86, 136.61, 136.59, 132.80, 132.49, 130.57, 127.83, 126.25, 116.27, 44.39, 24.20.

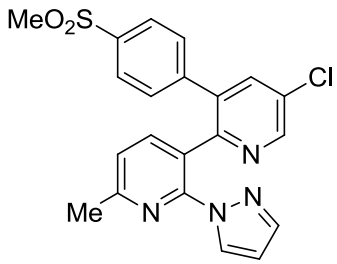
Chemical formula: $C_{19}H_{14}ClN_3O_2S$

Calculated exact mass: 383.0495

Observed formula by ESIMS: $C_{19}H_{14}ClN_3O_2SNa$

Observed exact mass: 406.0391 (calculated exact mass + ^{23}Na)

Synthesis of 2-pyrazolyletoricoxib (14d)

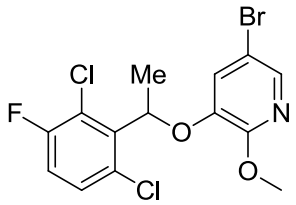


The general procedure for tandem C-H fluorination/S_NAr was performed with etoricoxib. The fluorination step was performed with 2 mL of MeCN at 50 ^oC for 2 h. The product was purified by silica gel chromatography eluting with 1:2 hexanes : ethyl acetate to afford **14d** as a white solid (41 mg, 0.10 mmol, 48% yield).

^1H NMR (500 MHz, Chloroform-d) δ 8.64 (d, J = 2.3 Hz,

1H), 7.73 – 7.66 (m, 4H), 7.58 (d, J = 2.3 Hz, 1H), 7.35 (s, 1H), 7.14 (d, J = 7.8 Hz, 1H), 7.08 (d, J = 8.4 Hz, 2H), 6.20 – 6.17 (m, 1H), 3.01 (s, 3H), 2.56 (s, 3H).
^{13}C NMR (151 MHz, Chloroform-d) δ 158.22, 153.66, 148.01, 147.67, 142.70, 141.71, 141.30, 139.58, 136.60, 135.78, 130.85, 129.52, 128.14, 127.14, 122.97, 121.51, 106.96, 44.40, 24.07.
Chemical formula: $C_{21}H_{17}ClN_4O_2S$
Calculated exact mass: 424.0761
Observed formula by ESIMS: $C_{21}H_{18}ClN_4O_2S$
Observed exact mass: 425.0836 (calculated exact mass + ^{1}H)

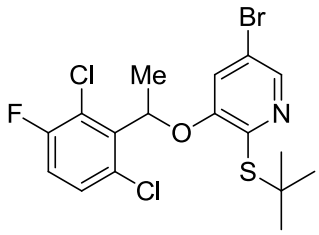
Synthesis of 5-bromo-3-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)-2-methoxypyridine (15a)



The general procedure for tandem C-H fluorination/S_NAr was performed with 3-bromo-5-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridine. The fluorination step was performed with 8 mL of MeCN at room temperature for 1 h. The product was purified by silica gel chromatography eluting with 20:1 hexanes : ethyl acetate to afford **15a** as a white solid (55 mg, 0.14 mmol, 70% yield).

The product was obtained as a 7:1 mixture of regioisomeric products
Major isomer:
^{1}H NMR (600 MHz, Chloroform-d) δ 7.74 (s, 1H), 7.28 (m, 1H), 7.05 (t, J = 8.4 Hz, 1H), 6.97 (s, 1H), 5.99 (q, J = 6.6 Hz, 1H), 3.97 (s, 3H), 1.83 (d, J = 6.7 Hz, 3H).
^{13}C NMR (101 MHz, Chloroform-d) δ 157.46 (d, J = 249.0 Hz), 154.38, 141.90, 138.43, 136.55, 131.23 (d, J = 2.2 Hz), 128.97 (d, J = 3.7 Hz), 124.20, 122.07 (d, J = 19.3 Hz), 116.65 (d, J = 23.2 Hz), 110.55, 73.94, 53.95, 18.96.

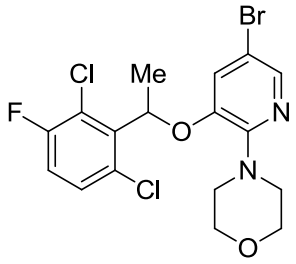
Synthesis of 5-bromo-2-(tert-butylthio)-3-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridine (15b)



The general procedure for tandem C-H fluorination/S_NAr was performed with 3-bromo-5-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridine. The fluorination step was performed with 8 mL of MeCN at room temperature for 1 h. The S_NAr step was performed with 3 equivalents of sodium thiolate salt. The product was purified by silica gel chromatography eluting with 20:1 hexanes : ethyl acetate to afford **15b** as a colorless oil (76 mg, 0.17 mmol, 84% yield).

The product was obtained as a 7:1 mixture of regioisomeric products
Major isomer:
^{1}H NMR (600 MHz, Chloroform-d) δ 8.07 (d, J = 1.8 Hz, 1H), 7.29 (dd, J = 8.9, 4.8 Hz, 1H), 7.08 – 7.03 (m, 1H), 6.82 (d, J = 1.8 Hz, 1H), 5.91 (q, J = 6.7 Hz, 1H), 1.83 (d, J = 6.7 Hz, 3H), 1.59 (s, 9H).
^{13}C NMR (151 MHz, Chloroform-d) δ 157.45 (d, J = 247.6 Hz), 150.55, 150.17, 141.31, 136.36, 129.72, 128.95 (d, J = 3.0 Hz), 122.16 (d, J = 18.1 Hz), 120.48, 116.67 (d, J = 23.3 Hz), 115.06, 73.79, 47.06, 30.50, 18.93.

Synthesis of 4-(5-bromo-3-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridin-2-yl)morpholine (15c)



The general procedure for tandem C-H fluorination/S_NAr was performed with 3-bromo-5-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridine. The fluorination step was performed with 8 mL of MeCN at room temperature for 1 h. The S_NAr step was performed with 3 equivalents of sodium thiolate salt. The product was purified by silica gel chromatography eluting with 9:1 hexanes : ethyl acetate (R_f = 0.38) to afford **15c** as a light yellow oil (56 mg, 0.12 mmol, 62% yield).

The product was obtained as a 7:1 mixture of regioisomeric products

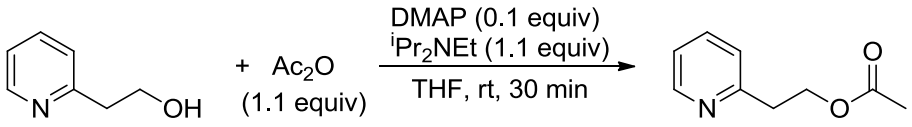
Major isomer:

^{1}H NMR (600 MHz, Chloroform-d) δ 7.86 (d, J = 1.9 Hz, 1H), 7.31 (dd, J = 8.9, 4.8 Hz, 1H), 7.08 (t, J = 8.4 Hz, 1H), 6.97 (d, J = 1.9 Hz, 1H), 5.98 (q, J = 6.7 Hz, 1H), 3.81 (m, 4H), 3.47 (m, 4H), 1.80 (d, J = 6.7 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-d) δ 157.47 (d, J = 249.1 Hz), 150.88, 144.81, 139.82, 136.58, 129.96, 128.86 (d, J = 3.7 Hz), 124.37, 121.96 (d, J = 19.3 Hz), 116.80 (d, J = 23.2 Hz), 110.37, 74.20, 66.90, 48.77, 18.89.

Synthesis of 2-methylamino-6-(2-hydroxyethyl)pyridine (16)

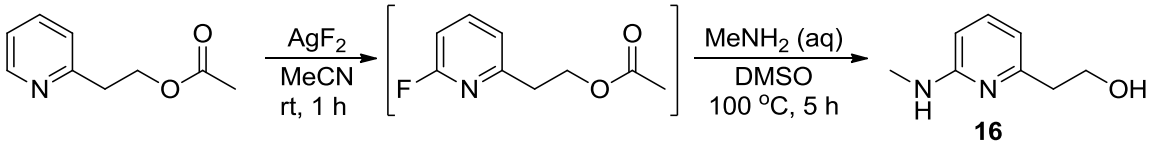
Step 1:



To a 100 mL round bottom flask was added 2-pyridineethanol (560 µL, 5.0 mmol, 1.0 equiv), DMAP (61 mg, 0.50 mmol, 0.10 equiv), ^{i}Pr$_2$NEt (960 µL, 5.5 mmol, 1.1 equiv) and THF (15 mL). Acetic anhydride (520 µL, 5.5 mmol, 1.1 equiv) was added over 1 minute. The resulting pale yellow solution was stirred at room temperature for 30 minutes and the solvent was removed in vacuo. The resulting oil was filtered through ~10 grams of silica with 40 mL of ethyl acetate and the filtrate was concentrated to afford 2-(2-pyridinyl)ethyl acetate as a light yellow oil (822 mg, 4.98 mmol, quantitative yield).

^{1}H NMR (600 MHz, Chloroform-d) δ 8.55 (d, J = 4.6 Hz, 1H), 7.63 (t, J = 7.2 Hz, 1H), 7.21 – 7.12 (m, 2H), 4.46 (t, J = 6.7 Hz, 2H), 3.12 (t, J = 5.9 Hz, 2H), 2.01 (s, 3H).

Step 2:



To an oven-dried vial was added 2-(2-pyridinyl)ethyl acetate (83 mg, 0.50 mmol, 1.0 equiv) and MeCN (5.0 mL). While the solution was stirring rapidly, AgF_2 (220 mg, 1.5

mmol, 3.0 equiv) was added at once. The vial was sealed with a Teflon-lined cap and stirred at room temperature for 1 h. The reaction was filtered into a 20 mL vial through a pipette containing ~500 mg of silica wet with Et_2O. The silica was rinsed with 4-5 mL of Et_2O and the filtrate was concentrated in vacuo. The resulting crude material was dissolved in 2 mL of DMSO and 40% aqueous $MeNH_2$ (1 mL, 12 mmol, 24 equiv) was added. The vial was sealed with a Teflon-lined cap and stirred at 100 ^oC for 5 h. The reaction mixture was diluted with saturated aqueous NH_4Cl (10 mL) and brine (10 mL) and extracted with ethyl acetate (3 x 15 mL). The organic layer was washed 1 x 10 mL brine and concentrated. The product was purified by silica gel chromatography eluting with 3% methanol in dichloromethane to afford **16** as a light yellow oil (49 mg, 0.32 mmol, 64% yield).

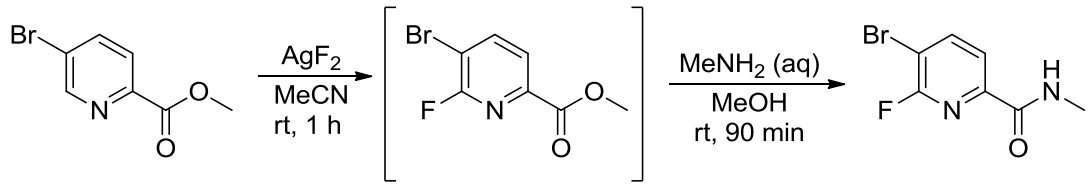
NMR spectra were in accord with previously reported spectral data.[11]

^1H NMR (600 MHz, Chloroform-d) δ 7.35 (t, J = 7.7 Hz, 1H), 6.40 (d, J = 7.2 Hz, 1H), 6.26 (d, J = 8.3 Hz, 1H), 4.98 (br, 1H), 4.78 (br, 1H), 3.95 (t, J = 5.2 Hz, 2H), 2.88 (s, 3H), 2.83 (t, J = 5.2 Hz, 2H).

^{13}C NMR (151 MHz, Chloroform-d) δ 158.87, 158.52, 138.22, 111.58, 104.26, 62.00, 38.07, 28.90.

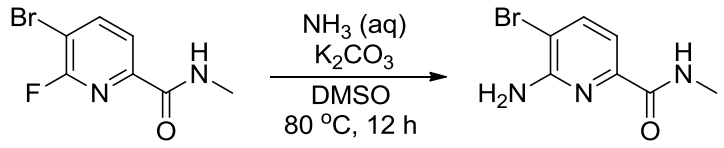
Synthesis of PF-1247324

Step 1:



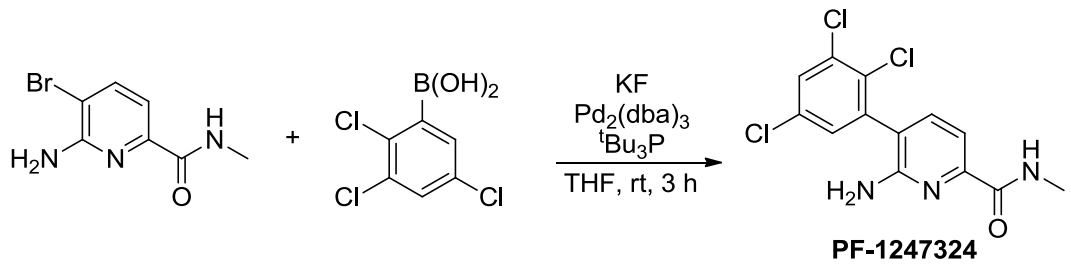
To an oven-dried vial was added methyl 5-bromopicolinate (108 mg, 0.50 mmol, 1.0 equiv) and MeCN (5.0 mL). While the solution was stirring rapidly, AgF_2 (220 mg, 1.5 mmol, 3.0 equiv) was added at once. The vial was sealed with a Teflon-lined cap and stirred at room temperature for 1 h. The reaction was filtered into a 20 mL vial through a pipette containing ~500 mg of silica wet with Et_2O. The silica was rinsed with 4-5 mL of Et_2O and the filtrate was concentrated in vacuo. The resulting crude material was dissolved in 5 mL of MeOH and 40% aqueous $MeNH_2$ (220 μL, 2.5 mmol, 5.0 equiv) was added. The vial was sealed with a Teflon-lined cap and stirred at room temperature for 90 min. The reaction mixture was diluted with brine (15 mL) and extracted with ethyl acetate (2 x 15 mL). The organic layer was dried with $MgSO_4$ and concentrated to afford crude 5-bromo-6-fluoro-N-methylpicolinamide as a white solid (114 mg crude mass, about 0.49 mmol). The crude material was used directly in step 2.

Step 2:



The crude material from step 1 was dissolved in 2 mL of DMSO in a 20 mL vial. K_2CO_3 (140 mg, 1.0 mmol, 2.0 equiv) was added, followed by aqueous ammonium hydroxide (1 mL, 15 mmol, 30 equiv). The vial was sealed with a Teflon-lined cap and stirred at 80 °C for 12 h. The reaction mixture was diluted with brine (15 mL) and extracted with ethyl acetate (2 x 15 mL). The product was purified by silica gel chromatography eluting with 1:5 hexanes : ethyl acetate to afford 6-amino-5-bromo-N-methylpicolinamide as a white solid (71 mg, 0.31 mmol, 62% yield from methyl 5-bromopicolinate).
^{1}H NMR (600 MHz, Chloroform-d) δ 7.73 (br, 2H), 7.39 (d, J = 7.8 Hz, 1H), 5.03 (br, 2H), 2.93 (d, J = 4.6 Hz, 3H).
^{13}C NMR (151 MHz, Chloroform-d) δ 164.49, 153.93, 147.18, 141.27, 113.58, 107.55, 25.95.

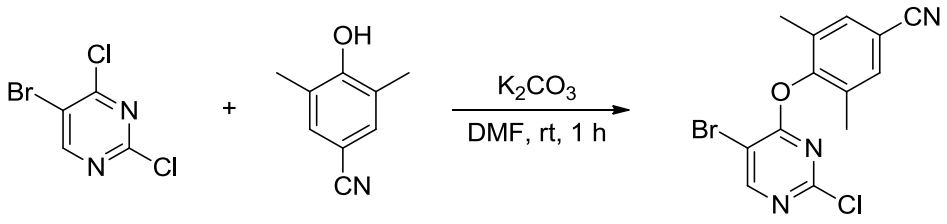
Step 3:



To an oven-dried round bottom flask was added 6-amino-5-bromo-N-methylpicolinamide (46 mg, 0.20 mmol), KF (38 mg, 0.66 mmol, 3.3 equiv), THF (600 µL) and H_2O (4 µL). A solution of $Pd_2(dba)_3$ (5.5 mg, 6.0 mol % Pd) and $^tBu_3P$ (2.4 mg, 6.0 mol %) in 200 µL THF was added, and the resulting mixture was stirred at room temperature for 2 minutes. A solution of 2,3,5-trichlorobenzeneboronic acid (50 mg, 0.22 mmol, 1.1 equiv) in 200 µL of THF was added and the reaction was stirred at room temperature for 3 h. The solvent was removed in vacuo and the residue was purified by silica gel chromatography eluting with ethyl acetate to afford PF-1247324 as a white solid (55 mg, 0.17 mmol, 83% yield).
NMR spectra were in accord with previously reported spectral data.[12]
^{1}H NMR (600 MHz, Methanol-d_4) δ 7.68 (d, J = 2.0 Hz, 1H), 7.46 (d, J = 7.5 Hz, 1H), 7.41 (d, J = 7.5 Hz, 1H), 7.34 (d, J = 2.0 Hz, 1H), 2.95 (s, 3H).^{13}C NMR (151 MHz, Methanol-d_4) δ 167.14, 156.69, 148.96, 140.61, 140.53, 135.63, 134.39, 132.14, 131.29, 131.02, 122.51, 111.85, 26.37.

Synthesis of Intelence (etravirine)

Step 1:

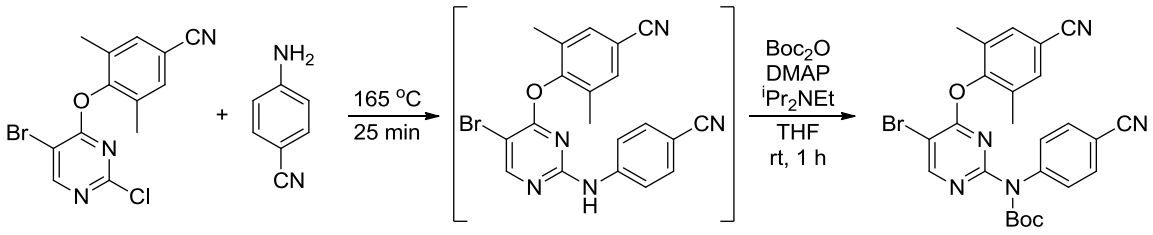


To a 100 mL round bottom flask was added 2,4-dichloro-5-bromopyrimidine (1.14 g, 5.00 mmol, 1.00 equiv), K_2CO_3 (760 mg, 5.5 mmol, 1.1 equiv) and DMF (15 mL). While the suspension was stirring rapidly, a solution of 2,6-dimethyl-4-cyanophenol in DMF (5 mL) was added over 5 minutes. The resulting mixture was stirred at room temperature for 1 h, during which the product began to precipitate. After 1 h, 50 mL of H_2O was added and stirring was continued for 5 minutes. The white solid was collected by suction filtration, washed with H_2O (2 x 20 mL) and Et_2O (1 x 20 mL) and dried under vacuum to afford 4-((5-bromo-2-chloropyrimidin-4-yl)oxy)-3,5-dimethylbenzonitrile as a white solid (1.54 g, 4.54 mmol, 91% yield).

^{1}H NMR (600 MHz, DMSO-d_6) δ 8.98 (s, 1H), 7.76 (s, 2H), 2.10 (s, 6H).

^{13}C NMR (151 MHz, Chloroform-d) δ 164.61, 161.35, 158.90, 152.51, 132.74, 132.15, 118.31, 110.50, 104.51, 16.29.

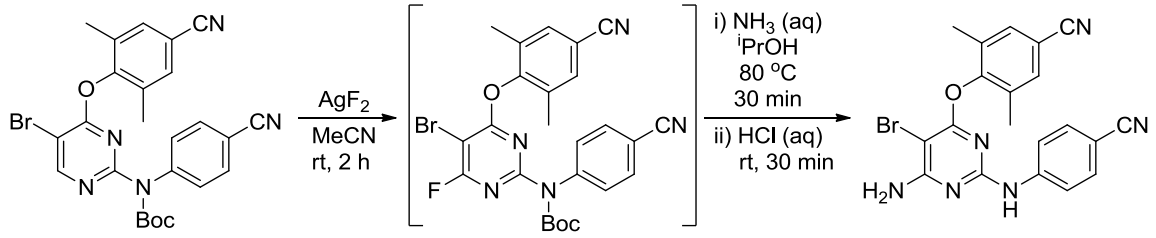
Step 2:



To a 20 mL vial was added 4-((5-bromo-2-chloropyrimidin-4-yl)oxy)-3,5-dimethylbenzonitrile (339 mg, 1.00 mmol, 1.00 equiv) and 4-aminobenzonitrile (154 mg, 1.30 mmol, 1.3 equiv) and the solids were mixed evenly. The vial was sealed with a Teflon-lined cap and heated at 165 °C for 15 minutes. The solids were mixed again and heated for an additional 10 minutes at 165 °C. The resulting solid residue was triturated with 1 M HCl (3 mL) and H_2O (3 x 3 mL). THF (5 mL), ^{i}Pr$_2$Net (350 µL, 2.0 mmol, 2.0 equiv) and DMAP (12 mg, 0.10 mmol, 10 mol %) were added, followed by Boc_2O (510 µL, 2.2 mmol, 2.2 equiv). The solution was stirred at room temperature for 1 h and the solvent was removed in vacuo. The residue was purified by silica gel chromatography eluting with 5:1 hexanes : ethyl acetate to afford tert-butyl (5-bromo-4-(4-cyano-2,6-dimethylphenoxy)pyrimidin-2-yl)(4-cyanophenyl)carbamate as a white solid (460 mg, 0.88 mmol, 88% yield).

^{1}H NMR (400 MHz, Chloroform-d) δ 8.64 (s, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.32 (s, 2H), 7.07 (d, J = 8.4 Hz, 2H), 2.03 (s, 6H), 1.32 (s, 9H).
^{13}C NMR (151 MHz, Chloroform-d) δ 164.02, 160.87, 158.49, 152.84, 151.47, 144.57, 132.64, 132.37, 132.24, 127.88, 118.16, 118.08, 110.54, 110.02, 100.80, 83.52, 27.76, 16.20.

Step 3:



Etravirine (Intelence)

To an oven-dried vial was added tert-butyl (5-bromo-4-(4-cyano-2,6-dimethylphenoxy)pyrimidin-2-yl)(4-cyanophenyl)carbamate (260 mg, 0.50 mmol, 1.0 equiv) and MeCN (10.0 mL). While the solution was stirring rapidly, AgF_2 (220 mg, 1.5 mmol, 3.0 equiv) was added at once. The vial was sealed with a Teflon-lined cap and stirred at room temperature for 2 h. The reaction was filtered into a 20 mL vial through a pipette containing ~500 mg of silica wet with Et_2O. The silica was rinsed with 4-5 mL of Et_2O and the filtrate was concentrated in vacuo. The resulting crude material was dissolved in 2.5 mL of ^{i}PrOH and ammonium hydroxide (100 µL, 1.5 mmol, 3.0 equiv) was added and the mixture was stirred at 80 ^{o}C for 30 minutes. The reaction was cooled to room temperature and concentrated HCl (1.3 mL, 16 mmol, 32 equiv) was added over 2 minutes. The mixture was stirred at room temperature for 30 minutes, diluted with 20 mL of H_2O and basified to pH = 8 with 10% aqueous K_2CO_3. The aqueous mixture was extracted with 2 x 30 mL dichloromethane, dried with $MgSO_4$ and concentrated onto ~2 grams of silica gel. The product was purified by silica gel chromatography eluting with 2:1 hexanes : ethyl acetate (R_f = 0.35) to afford etravirine as a white solid (122 mg, 0.280 mmol, 56% yield).
^{1}H NMR (500 MHz, DMSO-d_6) δ 9.59 (s, 1H), 7.72 (d, J = 3.6 Hz, 2H), 7.54 (s, 2H), 7.47 – 7.33 (m, 2H), 7.11 (br, 2H), 2.12 (s, 6H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 163.77, 162.90, 157.04, 154.47, 145.29, 133.10, 132.89, 132.78, 119.89, 119.03, 118.52, 108.72, 102.49, 74.75, 16.13.

Competition experiments between pyridines and diazines with AgF_2

To an oven-dried vial was added MeCN (1 mL) and 0.10 mmol each (1.0 equiv. each) of two heteroarenes. While the solution was stirring rapidly, AgF_2 (29mg, 0.20 mmol, 2.0 equiv) was added at once. The vial was sealed with a Teflon-lined cap, and stirred at room temperature for 15 minutes (25% ± 2% conversion). The reaction was quenched by the addition of 100 µL of saturated aqueous $NaHCO_3$. $PhCF_3$ (0.033 mmol, 0.10 mmol of ^{19}F, 1.0 equiv of ^{19}F) was added as an internal standard, and the reaction mixture was analyzed by ^{19}F NMR spectroscopy to determine the amounts and relative ratios of products resulting from fluorination of each heteroarene.

9.5 References

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