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By

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Committee in charge:
Professor John F. Hartwig, Chair
Professor F. Dean Toste
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Professor Alexander Katz

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Abstract

The Development of Transition Metal-Catalyzed Fluoroalkylation Reactions of Aryl Electrophiles

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Professor John F. Hartwig, Chair

The following dissertation discusses the development and study of reactions that introduce fluorine-containing substituents to functionalized aromatic compounds. In particular, the focus of this work will be directed towards transition metal-catalyzed or -mediated reactions that couple abundant aryl halide or aryl pseudohalide electrophiles with trifluoromethyl, pentafluoroethyl, difluorobenzoyl, difluoromethyl, or aryldifluoromethyl groups.

Chapter 1 provides a review of the properties and applications of fluorinated organic compounds, as well as synthetic methods to prepare such compounds. The challenges associated with preparing organic compounds that possess fluorinated-substituents are also discussed along with the progress that has been made towards addressing these challenges. In addition, this chapter highlights unsolved challenges in the fluoroalkylation reactions of functionalized aromatic compounds and provides the author's opinion on future directions for research in this area.

Chapter 2 discusses the perfluoroalkylation of abundant heteroaryl bromide electrophiles with stoichiometric perfluoroalkylcopper complexes, (phen)CuR_F. These reactions occurred with excellent scope and functional group compatibility for the preparation of medicinally-relevant trifluoromethyl-substituted heterocycles.

Chapter 3 discusses a new procedure for the copper-catalyzed trifluoromethylation and pentafluoroethylation of aryl iodides and heteroaryl bromides. These reactions occurred under mild conditions and could be conducted with as little as 5% of a Cu-catalyst. In addition, the preparation and reactivity of new (L)CuCF_2CF_3 complexes were studied to gain insight on how the electron-donating properties of the ligand on copper affect the perfluoroalkylation reaction.

Chapter 4 discusses a route for the α-arylation of α,α-difluoroacetophenone with phenol derivatives that is catalyzed by palladium complexes. Different catalyst systems were developed to allow for the coupling of assorted aryl sulfonate electrophiles. The products of this reaction have been previously reported to undergo base-induced cleavage to difluoromethylarenes. The overall transformation provides a route from phenols to difluoromethylarenes, a phenol bioisostere.

Chapter 5 discusses the synthesis of diaryldifluoromethane compounds by a palladium-catalyzed cross-coupling of aryl bromides with aryldifluoromethyl trimethylsilanes. This work is the first example of the coupling of an aryldifluoromethyl group with an aryl electrophile.

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Acknowledgements

And so I have come to the end of this fantastic voyage. I am incredibly excited to be receiving a PhD from UC Berkeley. These past 5 years have been an absolutely incredible time of growth and learning. I know that I could very nearly write an entire additional chapter dedicated to the people who have helped me reach this goal, but I'll try my best to keep this communication from becoming a full article.

First and foremost, I would like to thank my family. I can't possibly imagine the sort of person I might have been without the love and support of my large Italian family. My parents were always encouraging me in my scholarly endeavors. They taught me the value of hard work and creativity, and most importantly, how to treat others with warmth and kindness. My big sister was my role model growing up, and I can't put into words how much she has helped me throughout the years. And of course, if it weren't from my wonderful older brother keeping me safe from the evil monsters that lived in my closet when I was a small child, I don't think I would be here writing this. In addition to my immediate family, I also want to thank my loving grandparents, aunts, uncles, and cousins. You all mean the world to me. And finally, one more thanks to the family that I chose, my lifelong friends and brothers, Kory and Gavin. They were always there for me despite the 3-hour time difference between us and they made my visits home all the brighter.

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Chapter 1

Synthetic Methods for the Preparation of Fluoroalkyl-substituted Arenes

1.1 Properties and Applications of Fluorinated Compounds

Fluorinated compounds have emerged as potent bioactive molecules in pharmaceutical chemistry and agrochemistry.[1-4] Approximately 20% of all pharmaceutical compounds and 30-40% of agrochemicals contain at least one fluorine atom. The fluorine atom is commonly present as an aryl fluoride motif or as a trifluoromethyl group, with fewer examples of longer chain perfluoroalkyl-substituted arenes or partially fluorinated substituents. Despite the abundance of fluorinated molecules in drugs and agrochemicals, the occurrence of fluorine-containing compounds in nature is rare. Several examples of fluorine-containing bioactive molecules are depicted in Figure 1.1. In addition to their application as drugs and agrochemicals, fluorinated molecules are also common in materials chemistry, polymer chemistry, electronics, refrigerants, and dyes.[5-6] The widespread application of fluorinated organic molecules has driven the development of reactions to prepare such compounds. Despite extensive research into this area, there still remain significant challenges associated with the preparation of fluoroalkyl-substituted or partially fluorinated compounds. These limitations will be addressed in the remainder of this introduction chapter as well as in the introduction portion of the following chapters.

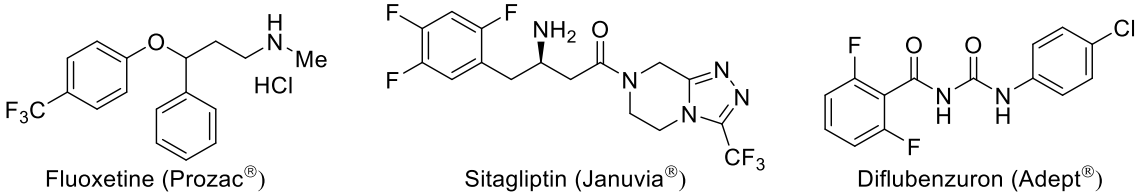


Figure 1.1 Examples of fluorinated pharmaceuticals and agrochemicals

Certain physical and biological properties can be altered by the incorporation of fluorine or fluorine-containing substituents onto organic molecules. The substitution of a hydrogen atom for a fluorine atom will generally confer increased lipophilicity, thereby improving the membrane permeability, bioavailability, and absorption of a drug. The log*D*, a measure of lipophilicity, was measured for 293 pairs of nonfluorinated and monofluorinated molecules. An average increase in log*D* of 0.25 was observed for replacement of one hydrogen atom by a fluorine atom.[1] The electron-withdrawing nature of fluorine and fluorine-containing substituents can also impart drastic changes to the pK_a of neighboring groups, increasing acidity significantly. An example of this effect is shown in Figure 1.2 for a series of $5HT_{1D}$ agonists explored for the treatment of migraines.[7]

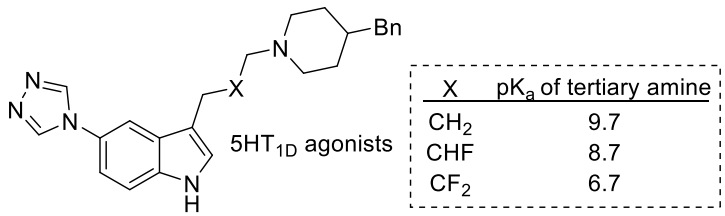


Figure 1.2 Decrease in pK_a of a $5HT_{1D}$ agonist upon fluorination

Due to the highly polarized nature of the C-F bond, fluorine is also known to be a weak hydrogen-bond acceptor, forming hydrogen bonds with an average distance of 2.5-3.0 Å.[8] These effects can impact the binding of fluorinated substrates to the active site of an enzyme. Due to its electronegativity, the incorporation of fluorine will deactivate bioactive molecules towards oxidative metabolic processes. These processes are common pathways for removal of drugs from biological systems. By impeding these pathways, drugs are rendered more potent by increasing their half-life and preventing oxidation to undesired byproducts. The development of the cholesterol absorption inhibitor, Ezetimibe, from a lead compound demonstrates the effectiveness of improving a drug's potency by replacing metabolically labile sites with fluorine (Figure 1.3).[9]

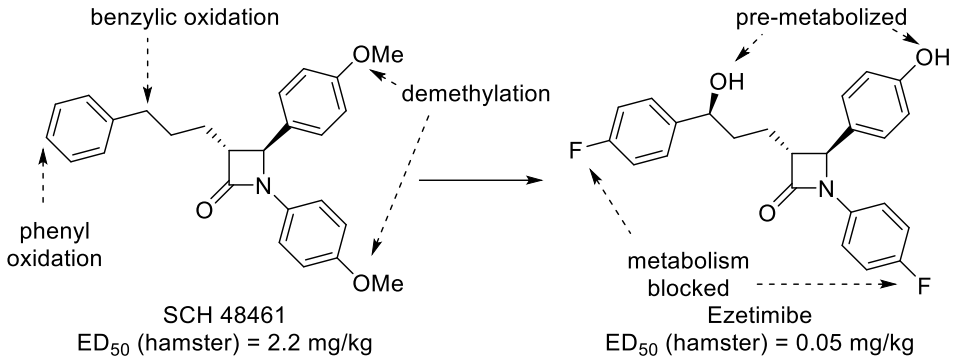


Figure 1.3 Improved drug efficacy upon fluorination at metabolically labile sites

Currently, the synthesis of most fluorine-containing compounds produced on industrial scale involves harsh reaction conditions or toxic reagents. These conditions are not compatible with many functional groups and are typically not practical to be conducted in most laboratory settings. Because of this limitation, fluorine is commonly incorporated in early synthetic steps, and many pharmaceutical compounds are made from commercially available pre-fluorinated building blocks. The development of mild, functional-group compatible procedures for the introduction of fluorinated substituents onto organic molecules allows for these groups to be installed at a later synthetic step. Late-stage functionalization improves the ability to rapidly prepare many variants of a target in drug discovery. To that effect, progress has been made in developing various fluoroalkylation reactions either mediated or catalyzed by transition metal complexes. These procedures significantly improve access to this important class of compounds.

This chapter will aim to give a brief review of the development of reactions that incorporate fluorine-based substituents onto organic compounds. In particular, reactions that introduce perfluoroalkyl (Section 1.2) or difluoro-functionalized (-CF_2R) substituents (Section 1.3) will be the primary focus because these transformations are most relevant to the reactions disclosed in this thesis. The current state of the art, ongoing challenges, and future outlook will be discussed for each transformation.

1.2 Perfluoroalkylation of Aryl Electrophiles

Many pharmaceutical and agrochemical compounds contain trifluoromethyl-substituted arenes. The trifluoromethyl group is typically prepared on an industrial scale by the Swarts reaction (Figure 1.4).[10] This reaction involves the treatment of toluene derivatives ($ArCH_3$) with chlorine gas to generate benzotrichlorides ($ArCCl_3$) which are then converted to benzotrifluorides ($ArCF_3$) with SbF_3 or HF. The Swarts reaction is typically conducted under highly acidic conditions and with high reaction temperatures, rendering this reaction only amenable to simple building blocks. The reaction is also immensely waste-intensive. Large excesses of hazardous reagents, Cl_2, SbF_3, or HF, are typically required, and six moles of waste HCl are generated per every mole of $ArCF_3$ produced.

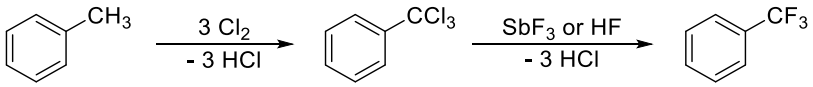


Figure 1.4 The Swarts reaction

Various coupling strategies that occur under milder conditions than the Swarts reaction have been developed to prepare the C-CF_3 bond of benzotrifluorides.[11-12] Multiple iterations of aryl and CF_3 sources have been explored (Figure 1.5). The trifluoromethylation of aryl halides is the most studied class of this reaction and will be the focus of this section. The C-H bonds of arenes have also been reported to undergo trifluoromethylation with radical[13-16] or electrophilic CF_3 sources.[17-18] In the former case of radical C-H trifluoromethylation, the reaction scope is generally limited to heteroarene or electron-rich arene substrates, and regioselectivity can be poor to modest in certain cases. In the case of electrophilic C-H trifluoromethylation, the installation of a directing group is necessary to prepare the C-CF_3 bond, rendering additional synthetic steps necessary for bond construction, and limiting the scope of arenes that can undergo trifluoromethylation.

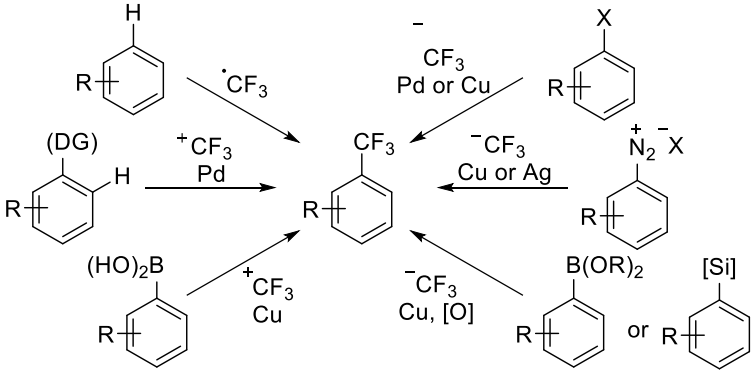


Figure 1.5 Various strategies for the generation of Ar-CF_3 bonds

Aryl boron[19-26] or aryl silicon nucleophiles[27] can react with nucleophilic CF_3 sources in an oxidative process or with electrophilic CF_3 sources. While the coupling of aryl nucleophiles offers an alternative strategy to the coupling reactions of aryl electrophiles, the starting materials are

generally less synthetically and commercially available. Also, the electrophilic CF_3 reagents commonly employed in these reactions are often difficult to prepare and are expensive.[28] Nucleophilic trifluoromethylation of aryl diazoniums has also been reported, but similar to the reactions of aryl nucleophiles, access to the starting materials is more restricted than access to aryl halides.[29-31]

The majority of perfluoroalkylation reactions of aryl halides have been reported to proceed with copper as either a stoichiometric or catalytic additive. While progress has been made in the development of these reactions, there are various challenges associated with the fundamental steps of a transition metal-mediated trifluoromethylation reaction. A general mechanism of this transformation is depicted in Figure 1.6. Initial complexation of the trifluoromethyl group to copper is challenging due to the instability and nucleophilicity of the CF_3 anion.[11] The trifluoromethyl anion is known to displace fluoride and generate difluorocarbene. The resultant difluorocarbene can insert into M-CF_3 bonds and generate higher order perfluoroalkyl species, M-CF_2CF_3, which then react to form longer-chain $ArCF_2CF_3$ byproducts. This loss of fluoride is typically rapid, and only recently has a long-lived CF_3 anion been characterized under cryogenic conditions and with a sequestered counter-cation.[32-33] Trifluoromethyl anions are also known to be good nucleophiles and can readily add to aldehydes, ketones, esters, and amides.[34] Trifluoromethyl nucleophiles can also displace dative ligands on a transition metal to generate inactive species. To limit the impact of these undesired pathways, the concentration of CF_3 anion is generally kept low by slow liberation from a CF_3 anion surrogate. The most common CF_3 anion surrogate is the Ruppert-Prakash reagent (Me_3SiCF_3 or Et_3SiCF_3), which reacts with Lewis bases, commonly a fluoride source, to generate a penta-coordinate silicate which then can liberate CF_3 anion.[35]

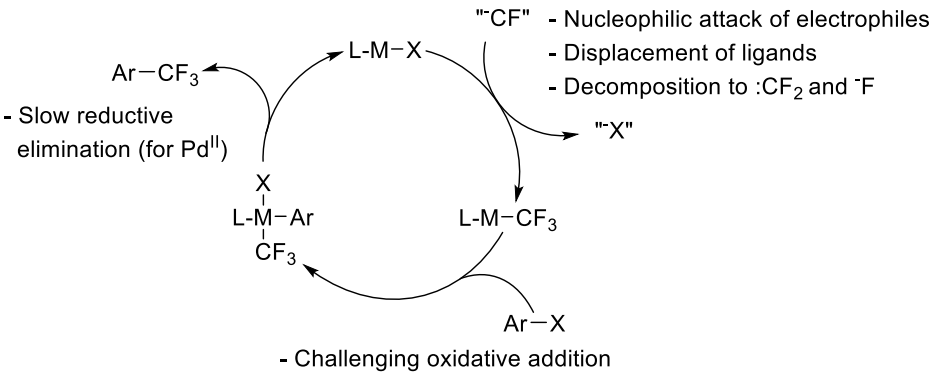


Figure 1.6 A general mechanism for catalytic trifluoromethylation of aryl halides

Oxidative addition of aryl halides to perfluoroalkyl copper species are challenging because the electron-withdrawing perfluoroalkyl substituent results in lower electron density at copper and makes oxidative processes less favorable. In this respect, it is commonly observed that aryl iodides, which generally exhibit faster rates of oxidative addition to Cu(I) than those of ArBr and ArCl, are the most common electrophiles to react. Within the class of aryl iodides, it is also observed that substrates bearing electron-withdrawing groups, which are activating groups towards oxidative addition, react faster than aryl iodides possessing electron-donating substituents.

The challenges associated with the reductive elimination of Ar-CF_3 from a transition metal complex are most apparent when examining trifluoromethyl palladium complexes. Hartwig reported the facile reductive elimination of Ar-CH_3 from a 1,2-bis(diphenylphosphino)benzene-ligated Ar-Pd(II)-CH_3 species. However, reductive elimination of Ar-CF_3 from the analogous Ar-Pd(II)-CF_3 was not observed, and this complex remains inert at elevated temperature for days (Figure 1.7).[36] The reductive elimination from palladium is challenging because in the transition state to form the Ar-CF_3 product, a highly polarized, strong Pd-CF_3 bond must be partially broken for the reaction to occur. Because reductive elimination is faster for higher valent metals over lower valent metals, and from first-row metals than from second-row metals, it is expected that reductive elimination from a Cu(III) intermediate should be faster than from a Pd(II) complex.

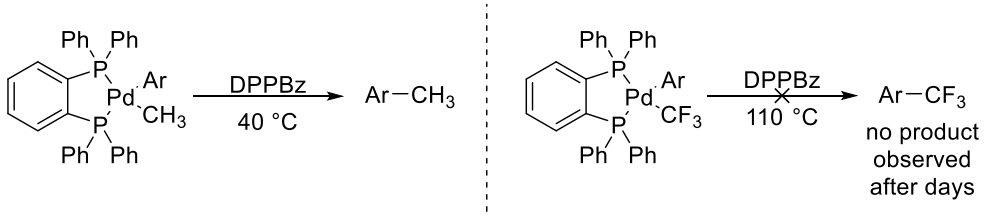


Figure 1.7 Slower reductive elimination of Ar-CF_3 than of Ar-CH_3

The first example of reductive elimination from an Ar-Pd(II)-CF_3 complex was reported by Grushin (Figure 1.8, a).[37-38] Ligating the palladium complex with a wide bite-angle ligand, Xantphos, was critical to force the aryl and trifluoromethyl substituents into close proximity, facilitating reductive elimination. Attempts to render the reaction catalytic with a Xantphos-ligated palladium species were unsuccessful because the trifluoromethyl anion was found to displace the bisphosphine ligand, generating inactive palladium species. The first palladium-catalyzed trifluoromethylation reaction was later reported by Buchwald with aryl chlorides and Et_3SiCF_3 (Figure 1.8, b).[39] This work also demonstrated the necessity of bulky ligands (BrettPhos or RuPhos) to promote reductive elimination of Ar-CF_3. Although this reaction allows for the trifluoromethylation of widely available and inexpensive aryl chlorides, there are also factors that prevent broad adoption of this method. The loadings of palladium (6-8 mol %) and of an expensive phosphine ligand (9-12 mol %) are high. Additionally, the scope of the reaction is limited when compared to analogous systems based on copper.

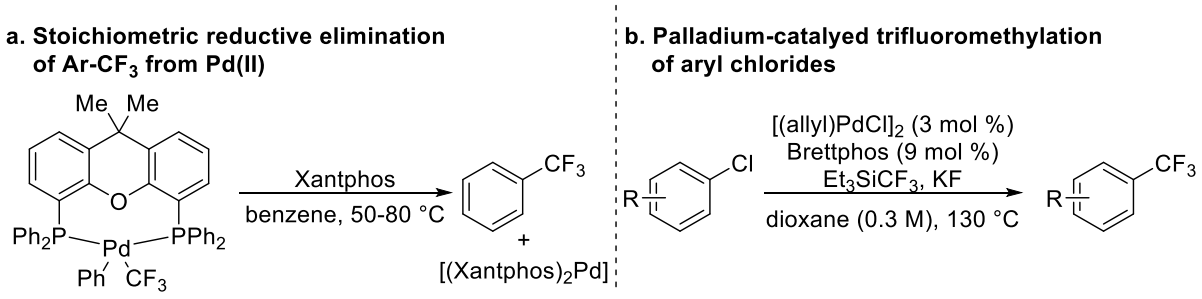


Figure 1.8 Construction of Ar-CF_3 bonds by palladium

McLoughlin and Thrower were the first to report a copper-mediated perfluoroalkylation reaction in 1969.[40] In this system, stoichiometric quantities of Cu^0 were required to mediate the reductive coupling of aryl iodides with perfluoroalkyl iodides at temperatures ranging from 100-180 °C. These reactions typically proceed in yields of only 40-70%. To prepare the desirable $ArCF_3$ and $ArCF_2CF_3$ products, expensive and difficult to handle gaseous reagents, CF_3I and CF_3CF_2I, respectively, are required. Subsequent copper-mediated reactions were developed that employed nucleophilic CF_3 sources. Among the CF_3 sources studied were species that undergo decarboxylation to generate CF_3 anion directly (CF_3CO_2Na or CF_3CO_2Me)[41-42] or by generating difluorocarbene and fluoride, which then combine to generate the nucleophilic CF_3 anion ($MeCO_2CF_2Cl$ + F^- or $MeCO_2CF_2SO_2F$).[43-44] Perfluoroalkyl silanes ($R_3Si\text{-}C_nF_{2n+1}$), such as the Ruppert-Prakash reagent, were also found to be efficient sources of CF_3 anion and are the most common nucleophilic CF_3 source.[45-46] Deprotonation of HCF_3 or displacement of CF_3 from trifluoroacetophenone by a strong alkoxide base have also been demonstrated to generate $CuCF_3$ in the presence of a Cu(I) salt.[47-48] The resultant trifluoromethylcopper species could then be readily coupled with ArI under mild conditions.

In addition to the aforementioned reports in which a copper salt is reacted with a CF_3 source to prepare $CuCF_3$ in-situ, discrete, preformed $CuCF_3$ complexes have been reported over the past several years that react with a large scope of ArI and demonstrate excellent functional group tolerance. By preforming the $CuCF_3$ species, the problems associated with generation of CF_3 anion during the trifluoromethylation reaction, such as difluorocarbene formation and nucleophilic attack of CF_3 on electrophilic functional groups, are avoided. Also, pre-ligation of copper prevents basic functional groups on the substrate from coordinating to the reactive metal center. In 2008, Vicic reported the first well-defined $Cu(I)CF_3$ complex as a NHC-Cu-CF_3 compound.[49-50] Grushin later reported the first example of an air-stable, isolable trifluoromethyl complex, $(PPh_3)_3CuCF_3$.[51] The reactivity of these complexes with aryl iodides was modest to good.

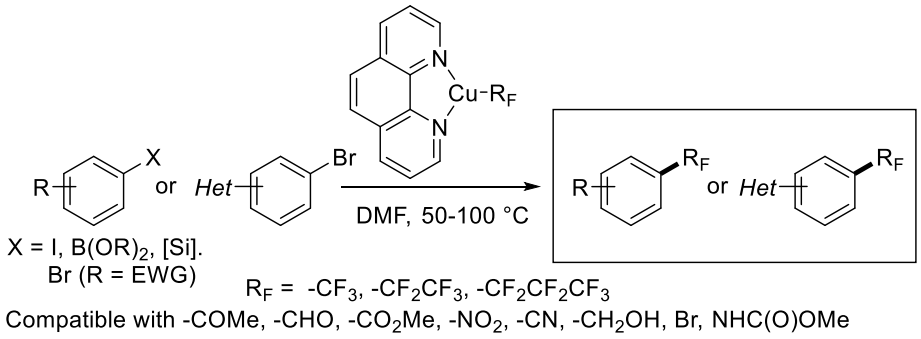


Figure 1.9 Reactions of aryl electrophiles and nucleophiles with pre-formed (phen)CuR_F as a stoichiometric reagent

In 2011, Hartwig reported the preparation and reactivity of (phen)$CuCF_3$ (Figure 1.9).[52] The reactions of aryl iodides with this complex currently hold the distinction of possessing the largest scope, functional group tolerance, and reliability of any reported trifluoromethylation procedure either stoichiometric or catalytic in copper. Whereas most of the trifluoromethylation reactions previously discussed tend to react in high yield only for electron-deficient aryl iodides,

(phen)$CuCF_3$ was found to react with both electron-deficient and electron-rich aryl iodides, as well as activated aryl bromides, under mild reaction conditions and temperatures. A two-step strategy to allow for the trifluoromethylation of unactivated aryl bromides was also developed in which ArBr are converted to aryl pinacol boronate esters (ArBpin) under Pd catalysis. The ArBpin intermediates can then undergo an oxidative reaction with (phen)$CuCF_3$ to prepare $ArCF_3$ in high yield and scope.[26] In addition to the observed reactivity of this complex with activated aryl bromides, Chapter 2 describes the reaction of (phen)$CuCF_3$ with *hetero*aryl bromides to synthesize a variety of pharmacologically relevant trifluoromethyl-substituted heterocycles.[53]

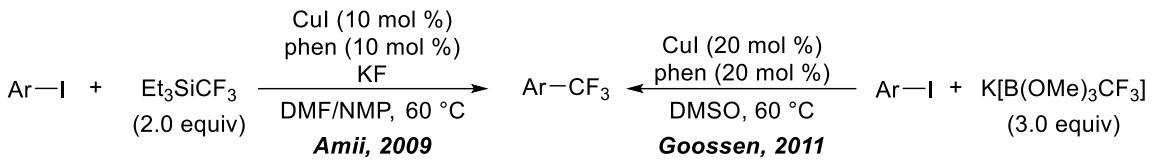


Figure 1.10 Selected trifluoromethylation reactions of aryl iodides that are catalytic in copper

Although copper-mediated trifluoromethylation reactions have been developed over the past several years, less progress has been made on the development of reactions that are catalytic in copper (Figure 1.10).[54] The first catalytic trifluoromethylation was reported by Amii in 2009 with Et_3SiCF_3 as a CF_3 anion source, KF as activator, and CuI/phen (10 mol % each).[46] While this reaction provided an important precedence, limited reactivity was observed for electron-rich aryl iodide substrates and electrophilic functionality was not well tolerated. Since this landmark publication, other copper-catalyzed trifluoromethylation reactions have been disclosed. In 2011, Amii also reported the use of a fluoral hemiaminal as a less expensive CF_3 surrogate than Et_3SiCF_3.[55] However, similar to their earlier report, only electron-deficient aryl iodides could be converted to product in high yield. In the same year, Goossen reported the reaction of both electron-rich and electron-poor aryl iodides with $K[B(OMe_3)CF_3]$ that proceeds with 20 mol % CuI and phen at mild temperatures.[56] While this procedure uses a large excess of the borate salt and does not tolerate electrophilic functional groups, it is currently the mildest and most efficient copper-*catalyzed* trifluoromethylation of aryl halides to date. Other Cu-catalyzed trifluoromethylation reactions of aryl halides include procedures that employ trifluoromethylzinc(II) species prepared from CF_3I, an expensive gas,[57-58] and a decarboxylative trifluoromethylation with $MeCO_2CF_3$, which occurs at very high temperature.[59] Chapter 3 discusses the development of new mild, copper-catalyzed perfluoroalkylation reactions of aryl iodides and heteroaryl bromides.

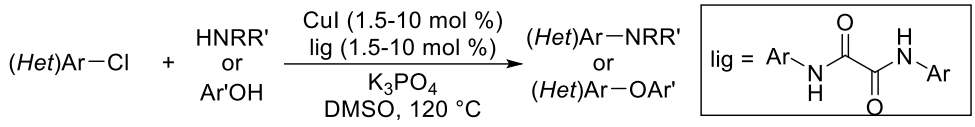


Figure 1.11 Cu-catalyzed transformations of ArCl with high turnover enabled by oxalic diamide ligands

Many significant challenges still remain to be addressed in the future development of perfluoroalkylation reactions. The most notable of these challenges is that many procedures require the coupling of aryl iodide substrates and that there are still no direct and effective strategies to prepare $ArCF_3$ compounds from more synthetically accessible and inexpensive aryl bromide or phenol-based electrophiles. To address this issue, reaction conditions must be developed that increase the rate of oxidative addition to Cu(I)-CF_3. As discussed previously in this section, the electron-poor nature of trifluoromethyl copper species can retard rates of oxidative addition. The discovery of a suitable ligand system on copper could allow for access to weaker aryl electrophiles. Ma has reported various Cu-catalyzed couplings of ArCl with various nitrogen- and oxygen-based nucleophiles that occur with remarkable catalyst turnovers (Figure 1.11).[60-63] The development of oxalic diamide ligands was critical to achieve the observed reactivity. Because these reactions are conducted under basic conditions, it is likely that the oxalic diamide ligands could be deprotonated and the active Cu(I) species in these transformations is a negatively charged cuprate species. Due to their electron-rich nature, oxidative addition to cuprates should be much more facile than to a neutral Cu(I) species. To this end, the development of a ligand system that could result in a CF_3 containing cuprate species should be much more reactive towards oxidative addition of weaker electrophiles such as ArBr and ArCl. Alternatively, ligands that are more donating to neutral Cu(I) complexes can potentially offset the electron-withdrawing nature of the fluoroalkyl ligand. However, the ligand must not only accelerate the rate of oxidative addition, but also not interfere with rates of reductive elimination or transmetalation of the fluorinated substituent.

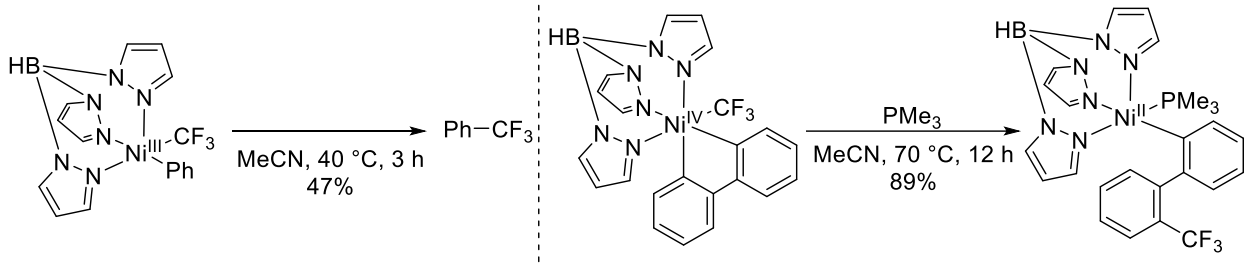


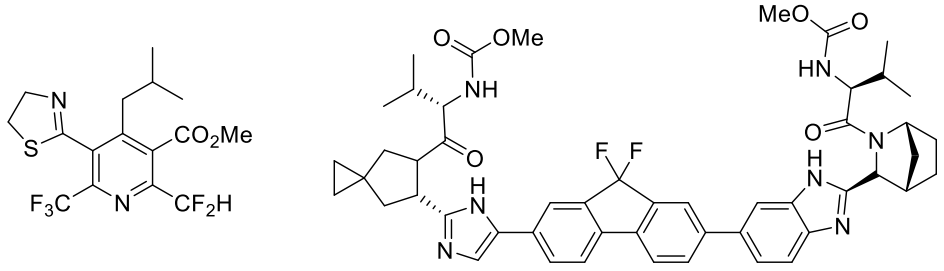
Figure 1.12 Reductive elimination of Ar-CF_3 from Ni(III) and Ni(IV) complexes

Access to weaker aryl electrophiles could also be solved by further studies into trifluoromethylation reactions with group 10 metals, palladium and nickel. Nickel, in particular, undergoes facile oxidative addition to unactivated aryl chlorides as well as to a variety of aryl pseudohalides. While the problems with the development of nickel-based trifluoromethylation systems are similar to those previously discussed for palladium, the feasibility of Ni-catalyzed fluoroalkylation processes has been studied. Slow reductive elimination from an Ar-Ni(II)-CF_3 complex ligated by the bisphosphine ligand, dippe, was demonstrated by Vicic in 2008.[64] Later, Grushin used computational methods to explore the viability of various bisphosphine-ligated Ar-Ni(II)-CF_3 species to undergo reductive elimination.[65] While several ligands, notably dtbpb and dippf, were calculated to form complexes with the lowest barriers to Ar-CF_3 reductive elimination, the authors were unsuccessful at preparing the [(PP)Ni(Ar)(CF_3)] complexes and did not experimentally demonstrate Ar-CF_3 formation. Recently, the Sanford group has experimentally

demonstrated reductive elimination of benzotrifluorides from high-valent Ni(III) and Ni(IV) complexes (Figure 1.12).[66-67] A cross-coupling strategy that employs a group 10 metal as a catalyst that can undergo oxidative addition of weak electrophiles, and then reductive elimination of Ar-CF_3 from a high-valent intermediate could serve as a valuable strategy for the trifluoromethylation of ArCl and ArOR.

The discovery of new CF_3 sources would also be beneficial for the development of more functional group tolerant reactions and more efficient copper-catalyzed processes. The nucleophilicity of CF_3 anion often renders substrates possessing electrophilic aldehydes or ketones incompatible with most coupling procedures. While these problems are obviated by the use of pre-made trifluoromethyl copper species, such as (phen)CuCF_3, or by the umpolung reaction of aryl boron or silicon reagents with electrophilic CF_3 sources, the development of a stable CF_3 reagent that undergoes faster rates of transmetalation to a reactive metal species than rates of addition to electrophilic functionality is desirable. In addition, such a reagent could facilitate the development of catalytic reactions that occur with higher turnovers than existing processes. Catalyst decomposition can arise as a result of unproductive pathways involving the nucleophilicity of CF_3 anion or its decomposition products, difluorocarbene and fluoride. Attenuating the nucleophilicity of CF_3 could prevent these undesired pathways. In most coupling procedures, a large excess of the CF_3 surrogate is usually required to offset decomposition to fluoroform or difluorocarbene side products. As demonstrated by the greater occurrence of the more stable Et_3SiCF_3 variant of the Ruppert-Prakash reagent over the Me_3SiCF_3 variant in Cu-catalyzed and Cu-mediated coupling procedures, enhancements to the stability of the reagent will allow for the CF_3 source to remain long-lived in the reaction and to be used in lower excess with respect to the ArX coupling partner.

1.3 Preparation of Difluorofunctionalized Arenes



Thiazopyr (Pesticide)

Ledipasvir (Component of Harvoni®) (Treatment of Hepatitis C)

Figure 1.13 Examples of bioactive compounds possessing Ar-CF_2R structural motifs

Although most fluorination of bioactive molecules is in the form of an ArF or ArCF_3, partially fluorinated substituents (CF_2R) are also desirable structural motifs. The difluoromethylene motif (CF_2) is often regarded as a bioisostere to oxygen.[68-69] Examples of bioactive compounds with difluoromethylene units are shown in Figure 1.13. This family of compounds is classically prepared by deoxyfluorination of aryl aldehydes or ketones with S(IV) fluoride reagents or by the analogous fluorodesulfurization reactions of 1,3-dithiolane-protected

carbonyls (Figure 1.14, a & b).[70] Deoxyfluorination reactions of aldehydes or ketones are most commonly achieved by reaction with DAST (diethylaminosulfur trifluoride) or the more thermally stable variant, Deoxo-fluor®, bis-(2-methoxyethyl)sulfur trifluoride.[71-72] These reagents are undesirable due to their proclivity to release toxic HF upon exposure to moisture. Fluorodesulfurization of 1,3-dithiolanes is a more reliable strategy that typically requires treatment with an oxidant and nucleophilic fluoride source.[73] However, these reactions require extra synthetic steps to prepare the protected ketone or aldehyde and often suffer from poor scope and functional group compatibility. To a lesser extent, benzylic *gem*-difluorination with electrophilic or radical sources of fluorine can also provide access to $ArCF_2R$ compounds (Figure 1.14, c), but typically these procedures suffer from poor site-selectivity or result in a mixture of mono- and difluorinated benzyl products.[74-77] Transition metal-mediated formation of C-CF_2R bonds is desirable to prepare these compounds in a mild and reliable manner.

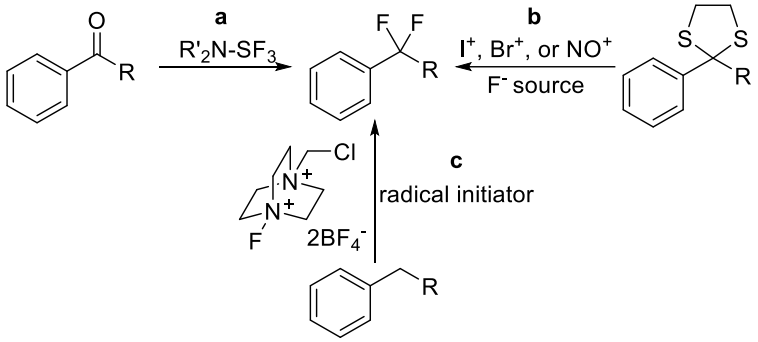
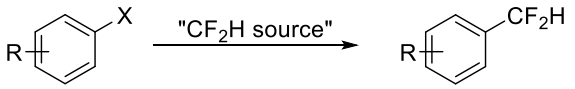


Figure 1.14 Strategies to prepare $ArCF_2R$ compounds by C-F bond formation

1.3.1 Strategies for the Synthesis of Difluoromethylarenes

The most explored class of CF_2-containing compounds aside from benzotrifluorides are difluoromethyl-substituted arenes ($ArCF_2H$).[78] In addition to possessing the physical and biological properties associated with fluorinated compounds, difluoromethylarenes are capable of engaging in weak hydrogen-bonding interactions with basic functionality (CF_2H---X).[79] This attribute can result in conformational changes from the parent compound and altered binding to proteins. Unlike sources of CF_3, there are few CF_2H sources that have been reported for cross coupling with aryl halides. Notable examples of direct difluoromethylation of aryl halides are depicted in Figure 1.15. Because of the excellent scope and functional group compatibility that are observed for reactions of isolated Cu(I)CF_3 complexes, such as (phen)CuCF_3, analogous Cu(I)CF_2H compounds would be desirable reagents. However, no examples of discrete, isolable Cu(I)CF_2H complexes have been reported because these compounds are thermally unstable and decompose unproductively to tetrafluoroethane or 1,2-difluoroethylene.[80-81] The most common nucleophilic CF_2H source is the difluoromethyl variant of the Ruppert-Prakash reagent, Me_3SiCF_2H.[82] Hartwig reported the first example of a direct, copper-mediated coupling of this reagent with aryl iodides.[83] These reactions proceed at high temperature (> 100 °C), and only electron-neutral and electron-rich aryl iodides were viable substrates. As is the case for couplings

involving Me_3SiCF_3, electrophilic groups required protection from nucleophilic attack of CF_2H anion. Prakash demonstrated the coupling of electron-deficient aryl iodides under nearly identical conditions to those developed by Hartwig, but substituting Me_3SiCF_2H with $^nBu_4SnCF_2H$.[84] Qing later reported the difluoromethylation of electron-poor aryl iodides that proceeds at room temperature with Me_3SiCF_2H, KO^{t}Bu, and stoichiometric CuCl ligated by phenanthroline.[85] In 2014, Shen reported the first example of direct Pd-catalyzed difluoromethylation of either electron-rich or electron-poor ArI and ArBr.[86] While a notable first example, the strongly basic conditions and high loadings of Pd (5-7 mol %) and of a requisite, expensive NHC-ligated AgCl salt (20 mol %) are severe limitations of this procedure. The same group has explored (SIPr)AgCF_2H as a stoichiometric difluoromethylation reagent.[87-88] Recently, (L)$Zn^{II}(CF_2H)_2$ complexes have emerged as CF_2H sources that do not require basic activators. Vicic reported the use of $(DMPU)_2Zn(CF_2H)_2$ in the Ni-catalyzed coupling of electron-poor aryl iodides, bromides, and triflates.[89] Mikami also found this reagent to react with electron-poor aryl iodides under Cu(I) catalysis,[90] and later developed a Pd-catalyzed Negishi coupling of electron-rich and electron-deficient ArI or ArBr with the related compound, $(TMEDA)Zn(CF_2H)_2$.[91]



	X	R	conditions
Hartwig	I	EDG	CuI Me_3SiCF_2H, CsF NMP, 120 °C
Prakash	I	EWG	CuI $^nBu_4SnCF_2H$, KF NMP, 100 °C
Qing	I	EWG	CuCl/phen Me_3SiCF_2H, KO^{t}Bu DMF, 25 °C

	X	R	conditions
Shen	I, Br	EWG, EDG	$[Pd(dba)_2]$ (5-7 mol %) dppf (10-14 mol %) (SIPr)AgCl (20 mol %) Me_3SiCF_2H, NaO^{t}Bu PhMe or dioxane, 80 °C
Vicic	I, Br, OTf	EWG	(dppf)Ni(cod) (15 mol %) $(DMSO)Zn(CF_2H)_2$ DMSO, 80 °C
Mikami, Cu	I	EWG	CuI (10 mol %) $(DMSO)Zn(CF_2H)_2$ DMPU, 60 °C
Mikami, Pd	I, Br	EWG, EDG	$[Pd(dba)_2]$ (5 mol %) dppf (10 mol %) $(TMEDA)Zn(CF_2H)_2$ dioxane, 120 °C

Figure 1.15 Strategies for the direct coupling of CF_2H nucleophiles with aryl electrophiles

Owing to the lack of electrophilic $^+CF_2H$ sources, difluoromethylation reactions of aryl nucleophiles are less developed and typically proceed by reaction with CF_2H radicals or by difluorocarbene insertion. Baran reported the radical difluoromethylation of heteroarenes with $Zn(SO_2CF_2H)_2$ and a peroxide initiator (Figure 1.16, a).[92] As with other radical-based C-H fluoroalkylation reactions, yields were modest and site-selectivity can often be poor. Various Pd-catalyzed difluoromethylation reactions of arylboronic acids have been developed recently (Figure 1.16, b). In these systems, palladium difluorocarbene species ($Pd{=}CF_2$) have been implied as active

intermediates in the reaction mechanism. Difluorocarbene sources that have been explored in the coupling with $ArB(OH)_2$ include $BrCF_2CO_2Et$, $Ph_3P^+CF_2CO_2^-$ (PDFA), and recently HCF_2Cl, a widely-available, inexpensive gas.[93-95]

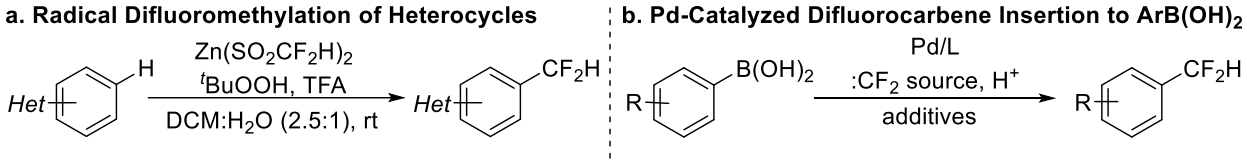


Figure 1.16 Difluoromethylation reactions of aryl nucleophiles

1.3.2 Strategies for the Difluoroalkylation of Aromatic Systems

In addition to difluoromethylarenes, the preparation of aryldifluoromethylated carboxylic acid derivatives ($ArCF_2CO_2R$ or $ArCF_2C(O)NR_2$) and aryldifluoromethyl ketones ($ArCF_2C(O)R$) has also been of considerable interest because these compounds possess interesting bioactive properties and can also be readily functionalized to other valuable difluoromethylene-containing products. Aryldifluoromethyl phosphonates ($ArCF_2P(O)(OR)_2$) are also desirable structural motifs, because replacement of the phosphoryl ester oxygen in phosphate-containing bioactive molecules with the bioisosteric CF_2 can prevent hydrolytic degradation of this class of compounds in biological systems.[96-97] Although progress has been made to prepare the Ar-CF_2R bonds of these compounds by transition metal-mediated processes, the coupling of CF_2-containing enolates to functionalized arenes presents unique challenges. Fluorinated enolate nucleophiles are often unstable and can decompose to intractable mixtures of side-products. One such side-product can be the Aldol- or Claisen-type products that result from attack of the difluoroenolate on its protonated difluoroketone or ester form.[98-100] Indeed, the presence of α-fluorine substituents on esters, amides, and ketones can drastically enhance the electrophilicity of the carbonyl group, so the concentration of the reactive enolate must be kept low such that Aldol and condensation products do not form. Because they possess two highly electronegative atoms on the reactive carbon anion, the nucleophilicity of difluoroenolates is less than that of nonfluorinated enolates. As such, coupling with nucleophilic $CF_2C(O)R$ sources is more challenging than coupling of the related nonfluorinated enolates. As with reductive elimination to form Ar-CF_3 bonds, reductive elimination to form Ar-CF_2R bonds from group 10 transition metals also can be challenging and require elevated temperatures to proceed at reasonable rates.

The first coupling reaction to form aryldifluoromethyl esters was reported by Kobayashi in 1986.[101] Super-stoichiometric quantities of Cu^0 were required as a reductant for the coupling of ICF_2CO_2Me with aryl iodides, vinyl iodides, vinyl bromides, and allyl/benzyl bromides. Owing to the poor stability, difficulty of use, and lack of commercial availability of ICF_2CO_2Me, a similar Cu^0-mediated reductive coupling was later demonstrated with the more stable and accessible $BrCF_2CO_2Et$.[101] For both of these procedures, only relatively simple molecules are tolerated. In 2011, Amii reported the coupling of aryl iodides with $Me_3SiCF_2CO_2Et$ mediated by CuI (Figure 1.17, a).[102] This procedure allows for the synthesis of a reasonably diverse array of

aryldifluoromethyl esters. Products of this reaction bearing electron-deficient aryl groups were also able to undergo hydrolysis to the corresponding carboxylic acid, then decarboxylation to afford difluoromethylarenes. Early procedures forming aryldifluoromethyl phosphonates relied on the Cu(I)-promoted reaction of ArI with M-$CF_2P(O)(OEt)_2$ reagents, in which M = Cd(II) or Zn(II).[103-104] The functional group compatibility and scope of these reactions are poor, and the use of toxic cadmium reagents is undesirable.

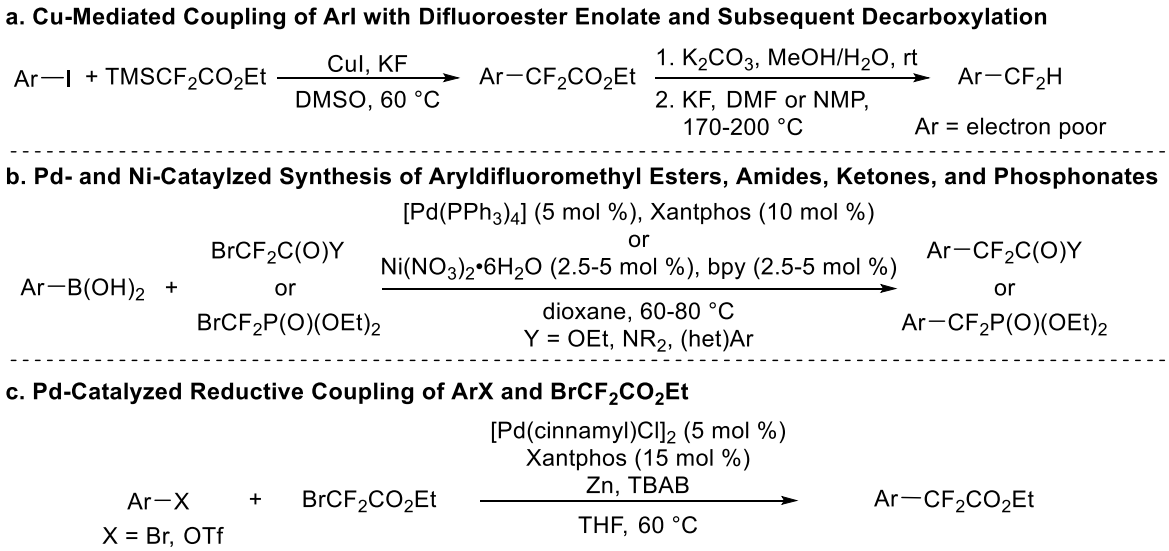


Figure 1.17 Current Synthetic Methods for the Preparation of Aryldifluoromethyl Ester and Phosphonates

More recent syntheses of $ArCF_2CO_2R$ and $ArCF_2P(O)(OR_2)$ rely on the coupling of aryl boronic acid nucleophiles with halodifluoromethyl-substituted electrophiles (Figure 1.17, b). In 2014, Zhang found that a combination of $[Pd(PPh_3)_4]$ and Xantphos allows for the reaction of $ArB(OH)_2$ with either $BrCF_2CO_2Et$ or $BrCF_2P(O)(OEt)_2$.[105] These reactions proceed with good scope and excellent functional group compatibility under mildly basic conditions and moderate temperatures. However, as with many Pd-catalyzed fluoroalkylation reactions, the loadings of Pd (5 mol %) and ligand (10 mol %) are high. Later the same year, Zhang disclosed a Ni-catalyzed variant of the same reactions.[106] The catalyst for this reaction is a combination of the air-stable and inexpensive $Ni(NO_3)_2 \cdot 6H_2O$, and 2,2'-bipyridine as ligand. Similar scope is observed to that of the Pd-catalyzed reaction, but low loadings (2.5 mol %) of an abundant Ni-catalyst and an inexpensive ligand render this system significantly more attractive. In addition to the coupling of esters and phosphonates, a few examples of the coupling of bromodifluoromethyl ketones and amides with $ArB(OH)_2$ were reported as well. While these reactions constitute a state of the art in the formation of aryldifluoromethyl esters or phosphonates, it would be preferable to develop the reactions of more abundant and accessible aryl halides. Recently, Liao and Hartwig reported a reductive, Pd-catalyzed coupling of ArBr or ArOTf with $BrCF_2CO_2Et$ (Figure 1.17, c).[107] While this procedure uses readily available reagents and operates under mild reaction conditions, the

functional group compatibility is modest, and activated ArBr and ArOTf are required to obtain products in high yield.

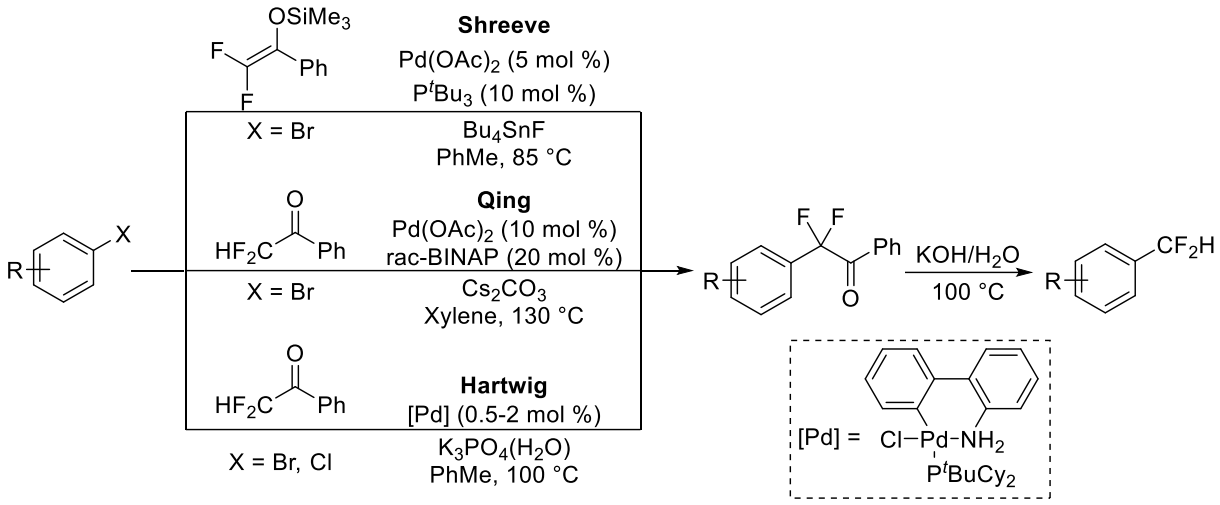


Figure 1.18 Strategies to prepare aryldifluoromethyl ketones

Considerably less attention has been paid to the development of procedures that generate aryldifluoromethyl ketones (Figure 1.18). In 2007, Shreeve reported the coupling of aryl bromides with the trimethylsilyl-protected silyl enol ether of 2,2-difluoroacetophenone.[108] A large excess of toxic Bu_3SnF was required as activator, and high loadings of $Pd(OAc)_2$ (5 mol %) and P^tBu_3 (10 mol %) were necessary. In addition, the silyl enol ether of 2,2-difluoroacetophenone is very moisture sensitive and decomposes over time. Qing later reported the Pd-catalyzed coupling of ArBr with 2,2-difluoroacetophenone.[109] The use of a mild, insoluble base, Cs_2CO_3, was required to maintain a low concentration of the reactive difluoroenolate species. While the issues relating to the poor stability of the nucleophile and the necessity of toxic reagents were addressed in this method, even higher loadings of $Pd(OAc)_2$ and rac-BINAP ligand were required (10 mol % and 20 mol %, respectively). The reaction also employed the ArBr coupling partner in excess (2 equiv), which is not desirable for the functionalization of complex, valuable aryl halides. Hartwig improved upon this procedure in 2011 by changing the precatalyst to a preformed palladacycle containing P^tBuCy_2 as ligand.[110] Unlike Qing's method, the ArX component could be used as the limiting reagent with 2,2-difluoroacetophenone and $K_3PO_4(H_2O)$ in excess. This report was also the first to demonstrate that not only ArBr, but also the less expensive and readily available ArCl coupled with aryldifluoromethyl ketones in excellent yield with great scope and functional group compatibility. The products of this reaction could be transformed in a one-pot procedure to the more valuable difluoromethyl arenes by base-induced Haller-Bauer cleavage of the benzoyl moiety. Unlike Amii's decarboxylation of aryldifluoromethyl esters to generate $ArCF_2H$, the cleavage of aryldifluoromethyl ketones to $ArCF_2H$ proceeded with both electron-poor and electron-rich aromatic systems.

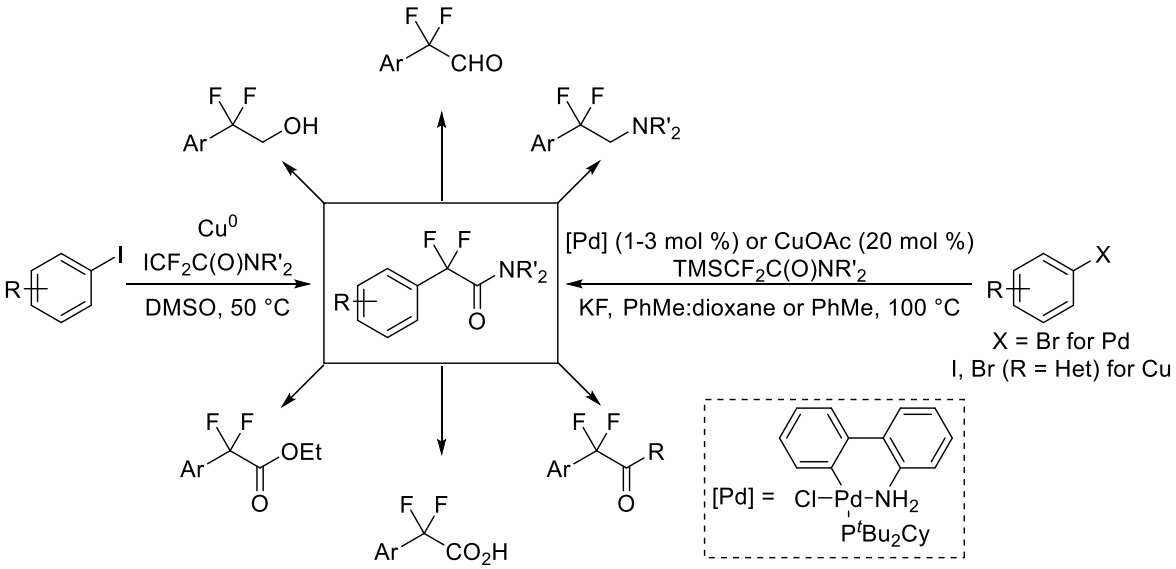


Figure 1.19 Preparation of aryldifluoromethyl amides and product derivatization

There are few reported examples for the coupling of difluoromethyl amides to functionalized arenes (Figure 1.19). Hu developed a Cu^0-mediated reductive coupling of ArI with $ICF_2C(O)NR_2$.[111] While a notable first example of this class of reaction, no synthetically valuable functional groups were tolerated, and yields of the aryldifluoromethyl amide products were only modest. Due to the weaker acidity of 1,1-difluorocarboxylic acid derivatives compared to their nonfluorinated analogs, strategies to generate nucleophilic amide enolates by direct deprotonation can be challenging and have not been developed for transition metal-catalyzed coupling reactions.[112] To generate the amide enolate species under mild conditions, Hartwig reported the use of trimethylsilyl-protected difluoroacetamide enolates in conjunction with a fluoride activator for the cross coupling reactions with aryl bromides.[113-114] The protected difluoroacetamide enolates can be readily prepared on large scale in a two-step procedure from the treatment of inexpensive chlorodifluoroacetic anhydride with a variety of amines to generate chlorodifluoroacetamides, which then undergo Mg-mediated reductive silylation to furnish the protected amide enolate. A notable feature of these difluoroamide enolates is that the silicon rests on the α-carbon, like it does on $Me_3SiCF_2CO_2Et$, instead of on the oxygen, as in the case of silyl enol ethers of difluoroketones. The amide enolates were also found to be remarkably stable and could be subjected to column chromatography and stored for months without decomposition. A Pd-catalyzed coupling with ArBr was first disclosed in 2014.[113] A trialkylphosphine-ligated palladacycle that is similar to that used in the related coupling of difluoroketones was found to be an effective precatalyst. While an impressive scope and functional group tolerance was demonstrated for this reaction, incompatibility with certain medicinally relevant heterocycles and the high cost of palladium led the group to develop an equally impressive Cu-catalyzed coupling procedure with ArI or HetBr in 2016.[114] The aryldifluoromethyl amide products of these reactions were found to be extremely valuable starting materials in the preparation of versatile $ArCF_2$-containing compounds. Reduction to fluorinated alcohols, amines, or aldehydes occurred in good yield. Addition of aryl or alkyl

nucleophiles generated aryldifluoromethyl ketones, and alcoholysis of the amide afforded aryldifluoromethyl esters. Basic hydrolysis of the amide to difluoroacetic acid derivatives was also demonstrated.

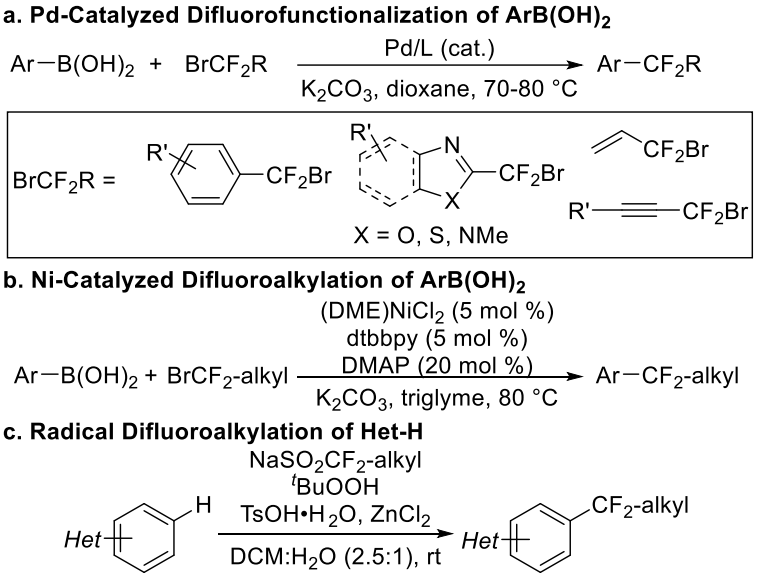


Figure 1.20 Examples of other classes of difluorofunctionalization reactions of (hetero)aryl nucleophiles

Owing to the poor nucleophilicity of fluorinated compounds, coupling of aryl nucleophiles with fluorinated electrophiles offers a general strategy to prepare $ArCF_2R$ compounds other than those discussed previously in this section. Work from Zhang has demonstrated a variety of difluorofunctionalization reactions of $ArB(OH)_2$ that have yet to be developed for ArX (Figure 1.20, a). Suitable Pd-catalysts allow for the *gem*-difluoroallylation,[115] *gem*-difluoro-propargylation,[116] and (hetero)aryldifluoromethylation of arylboron nucleophiles.[117-118] Like previous reports from this group on the coupling of $ArB(OH)_2$ with $BrCF_2R$ reagents, the mild conditions allowed for excellent functional group compatibility. A Ni-catalyzed reaction of $ArB(OH)_2$ with unactivated bromodifluoroalkanes was also recently disclosed by Zhang (Figure 1.20, b).[119] This work offers a route to 1,1-difluoroalkylated (hetero)arenes that complements earlier work by Baran on the radical difluoroalkylation of heterocycles with NaO_2SCF_2R reagents (Figure 1.20, c).[120]

1.3.3 Outlook on Difluoroalkylation Reactions of Functionalized Arenes

Many challenges remain to be addressed in the synthesis of difluorofunctionalized arenes. Most of these challenges are the same as those previously discussed for reactions to generate trifluoromethylated arenes. Unlike reactions for the synthesis of benzotrifluorides, there are many difluorofunctionalization reactions that are catalyzed by group 10 metals, Pd and Ni. Although reductive elimination of Ar-CF_2R from Pd or Ni occurs more readily than the analogous reductive elimination to form Ar-CF_3, many of the reported examples of this class of coupling reaction still

require high loadings of Pd catalyst and ligand (>5 mol %). Zhang's Ni-catalyzed difluorofunctionalization reactions of aryl boronic acids and Hartwig's Pd-catalyzed couplings of α,α-difluoroketones or α,α-difluoroacetamides with ArX constitute notable examples of this class of reactions that proceed with low loadings of transition metal catalysts (2.5 mol % and 1 mol %, respectively). Like trifluoromethylation reactions, there are still limited examples of broadly applicable difluorofunctionalization reactions of widely-accessible ArCl or ArOR electrophiles. Because difluoromethylarenes are proposed to be bioisosteric to phenols, reactions of phenol-derived electrophiles to $ArCF_2H$ would be an especially valuable tool for structure-activity relationship studies in medicinal chemistry. While Vicic's Ni-catalyzed difluoromethylation of ArOTf with $(DMSO)Zn(CF_2H)_2$ is an example of this class of reaction, the reported scope was poor and only tolerated electron-deficient ArOTf. Chapter 4 outlines progress towards a Pd-catalyzed strategy for the coupling of electron-poor and electron-rich aryl sulfonates with α,α-difluoroacetophenone to generate α-aryl-α,α-difluoroketones, which can then be readily cleaved to the corresponding difluoromethylarenes.

The development of novel difluoromethylene-containing coupling partners is also desirable. The two most commonly used difluoromethylation reagents, Me_3SiCF_2H and $(L)Zn^{II}(CF_2H)_2$, each possess qualities that limit their broad application. The high cost of Me_3SiCF_2H renders large-scale synthesis with this reagent impractical. Because CF_2H is a weaker electron-withdrawing group than CF_3, the Si atom of this reagent is less Lewis acidic than that of Me_3SiCF_3. As a result, formation of the penta-coordinate silicate species that precedes transfer of CF_2H anion is slower than the analogous penta-coordinate silicate formation from Me_3SiCF_3. The difluoromethylzinc(II) species that have been reported are not commercially available, and their preparation requires the expensive and difficult to handle gas, HCF_2I.[89-91] Other $-CF_2R$ sources are similarly problematic. While diethyl (bromodifluoromethyl)phosphonate and ethyl bromo-difluoroacetate are commercially available at reasonable prices, other α,α-difluorocarbonyl compounds are not commercially available or are prohibitively expensive. Typically, multiple synthetic steps are required to prepare these compounds from readily available CF_2-containing building blocks. The lack of readily-available CF_2-containing building blocks are especially apparent for the coupling of difluoroallyl, difluoropropargyl, difluoro(hetero)aryl, and difluoroalkyl moieties. Many different synthetic routes were required to prepare the $BrCF_2R$ variants of these groups for cross couplings with $ArB(OH)_2$. While 3-bromo-3,3-difluoropropene is commercially available, it is very expensive. Difluoroalkyl- and difluoropropargyl bromides are prepared from treatment of alkyl- or alkynyllithium species with expensive and ozone-depleting CF_2Br_2 gas.[121] Bromodifluoromethylarenes are made from radical bromination of $ArCF_2H$, which are limited in commercial availability and, as previously discussed, challenging to synthesize.[122] Preparation and coupling of nucleophilic sources of these lesser-explored CF_2-containing fragments with ArX would be desirable to prepare novel fluorinated compounds. Chapter 4 outlines work towards the Pd-catalyzed coupling of ArBr or ArCl with Me_3SiCF_2Ar, which can be prepared in one step from inexpensive, commercially available $ArCF_3$ compounds.

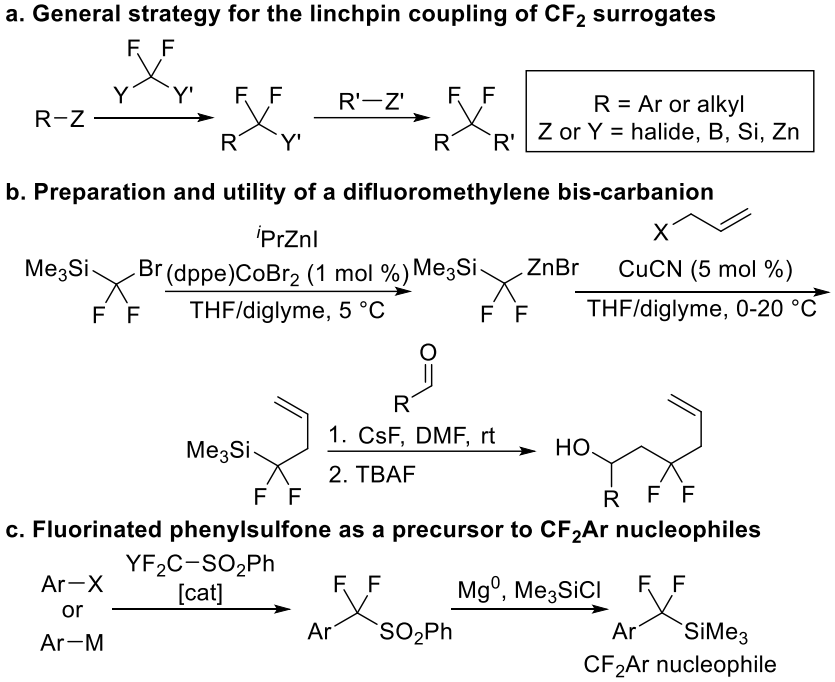


Figure 1.21 Reported and proposed reactions of difunctionalized CF_2-containing reagents

The development of a suitable difunctionalized CF_2-containing reagent that could act as a linchpin between more widely available coupling partners would be immensely valuable for the preparation of $ArCF_2R$ compounds (Figure 1.21, a). Various haloalkanes, such as Br_2CF_2, Cl_2CF_2, and $ClCF_2Br$, constitute examples of doubly electrophilic XCF_2X' compounds. However, these ozone depleting gases are not only difficult to handle in most common laboratory settings, but are also immensely expensive from commercial suppliers. Doubly nucleophilic MCF_2M' compounds where M = Si or B currently do not exist. One example of a difluoromethyl bis-carbanion, Me_3SiCF_2ZnBr, has been reported.[123] This compound was found to undergo Cu-catalyzed allylic substitution to form Me_3SiCF_2R compounds, which were then added to aldehydes (Figure 1.21, b). A Negishi coupling of this reagent with ArX could potentially form valuable $ArCF_2SiMe_3$ nucleophiles. However, this fluoroalkylzinc compound is not thermally stable and will likely not tolerate the temperatures required for efficient Ar-CF_2R reductive elimination from Pd or Ni. While not an example of a doubly nucleophilic CF_2 source, reported compounds of the type $PhSO_2CF_2Y$ (Y = H, $SiMe_3$, or X) could feasibly be coupled with aryl electrophiles or aryl nucleophiles with a suitable transition metal catalyst. The resultant $ArCF_2SO_2Ph$ compounds could readily undergo reductive silylation to form $ArCF_2SiMe_3$,[124-125] or desulfurization to form $ArCF_2H$ (Figure 1.21, c).[126]

Ambiphilic CF_2 sources should also be studied for cross coupling reactions. While Me_3SiCF_2X reagents (X= Br, Cl) are known and are commercially available, coupling of these reagents in the same manner as Me_3SiCF_3 to prepare $ArCF_2X$ could be problematic.[127-128] The CF_2X anion will likely undergo rapid decomposition to difluorocarbene and ^-X. It has been shown, however, that a soluble source of ^-X as activator could push the equilibrium towards CF_2X anion.

This strategy was successful for the addition of CF_2Br anion to aldehyde and iminium electrophiles with Me_3SiCF_2Br and Bu_4NBr.[129-130] Conceivably, oxidative addition of the X-CF_2SiMe_3 bond to a transition metal could occur, which could then react with an aryl nucleophile, or aryl electrophile with a suitable reductant, to form $ArCF_2SiMe_3$ species. Because the X-CF_2SiMe_3 bond is less polarized than those of X-R_F or X-$CF_2C(O)R$ species, this oxidative addition is likely to be more challenging than that of related fluorinated compounds.

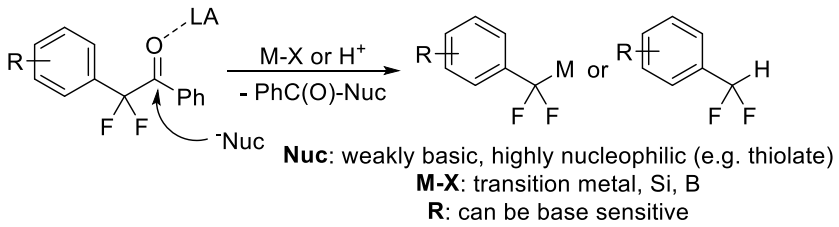


Figure 1.22 Mild Haller-Bauer cleavage of α-aryl-α,α-difluoroketones for generation of CF_2Ar nucleophiles

A final strategy to access $ArCF_2R$ compounds from a CF_2-linchpin strategy could involve improving the Haller-Bauer cleavage of α-aryl-α,α-difluoroketones prepared by the Pd-catalyzed coupling of α,α-difluoroacetophenone with ArBr or ArCl (Figure 1.22).[110] Currently, this cleavage is conducted at elevated temperature in an aqueous KOH solution to form $ArCF_2H$. If a suitable combination of nucleophile and Lewis acid activator could be discovered that would allow this cleavage to occur in an organic solvent at lower temperatures, and under less basic conditions, then this strategy could generate $ArCF_2H$ with a greater functional group compatibility than currently reported, and could potentially act as a source of $^-CF_2Ar$ nucleophiles for subsequent metal-catalyzed processes.

These strategies could offer an improved route to a diverse array of $ArCF_2$-containing compounds. Because of the abundance of bioactive molecules possessing fluorine or trifluoromethyl groups, it is likely that these partially-fluorinated compounds could serve as novel drug or agrochemical compounds. It is therefore valuable to develop or improve strategies that allow for the facile coupling of partially fluorinated moieties onto (hetero)aromatic systems.

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Chapter 2

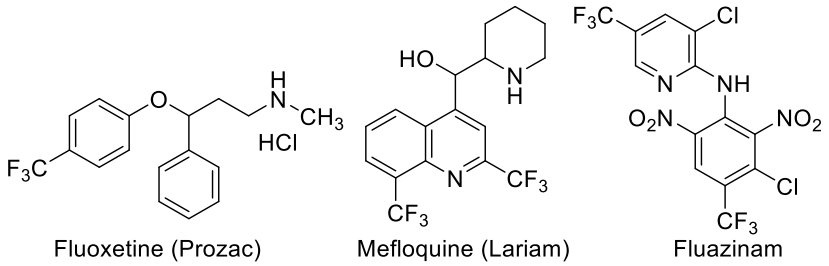
Copper-Mediated Perfluoroalkylation of Heteroaryl Bromides with (phen)CuR_F

2.1 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 2.1).

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.



Fluoxetine (Prozac) Mefloquine (Lariam) Fluazinam

Figure 2.1 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.[5a,b] Although the functional group tolerance and yields of this method are high, the $CuCF_3$ reagent cannot be stored.[5c] 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.

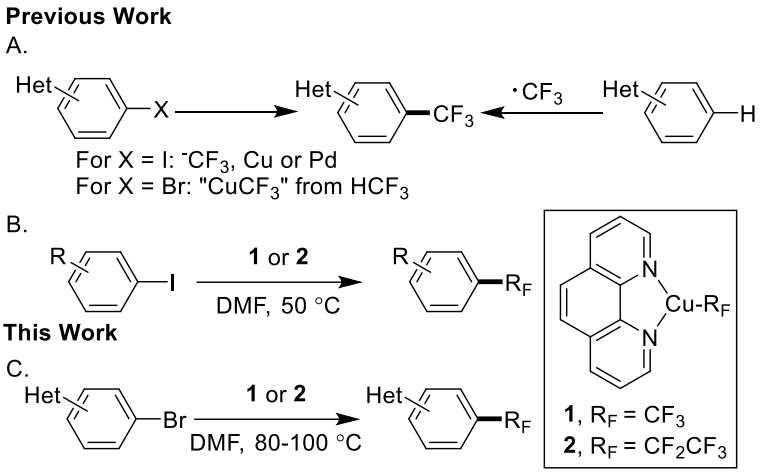


Figure 2.2 Methods for the synthesis of perfluoroalkyl heteroarenes

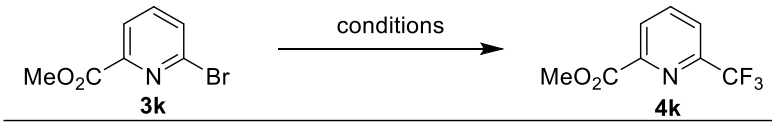
Our group recently reported the trifluoromethylation of aryl iodides with a phenanthroline-$CuCF_3$ complex, (phen)$CuCF_3$ (**1**) (Figure 2.2, B).[7a] This thermally-stable, commercially-available solid reacts with a variety of aryl iodides and electron-deficient aryl bromides under mild conditions. 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]

2.2 Results and Discussion

Because **1** was shown to react with electron-deficient *aryl*bromides, we considered that **1** would react similarly with *hetero*arylbromides that are inherently more electron-deficient than the corresponding arenes, such as pyridines and diazines. 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 2.1 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 2.1 Comparison of copper-mediated trifluoromethylations of a functionalized bromopyridine with previously reported methods.[a]



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.

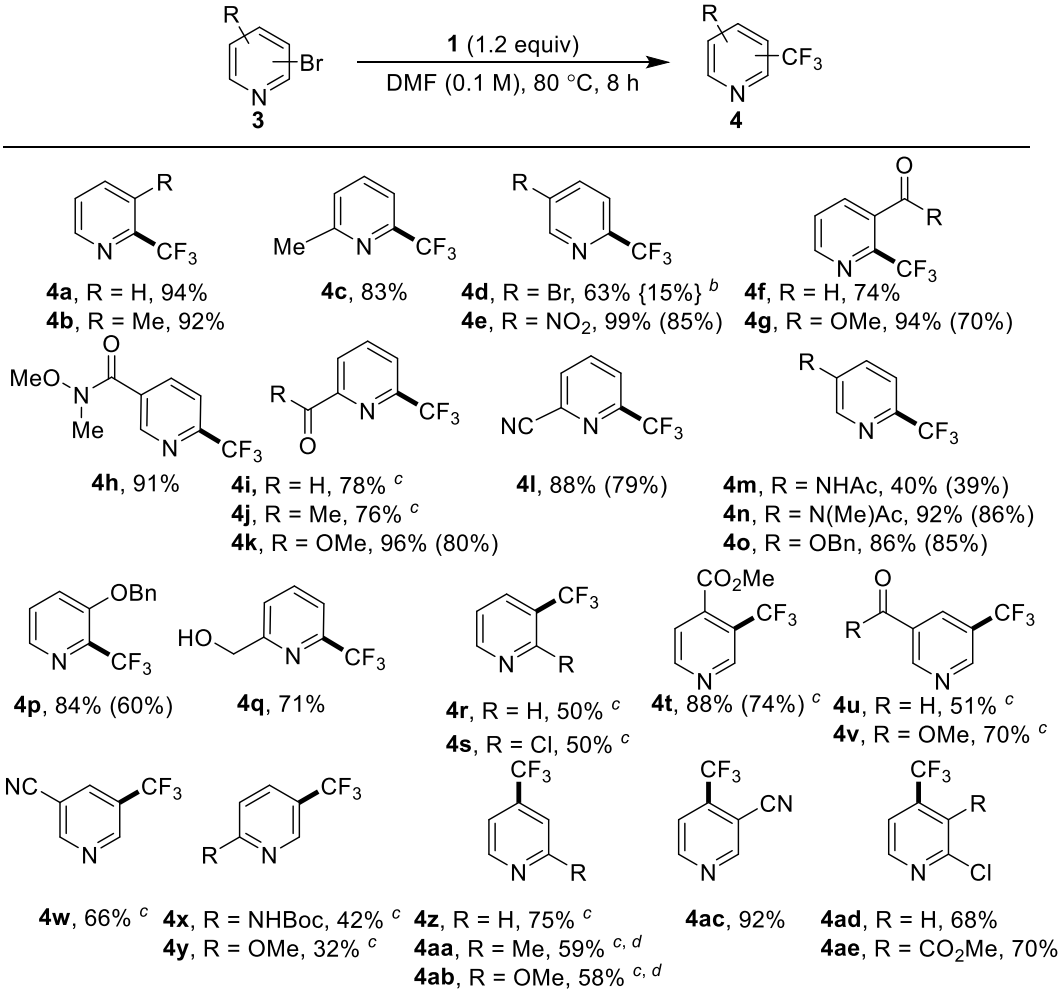
The scope of the trifluoromethylation reaction of various 2-, 3- and 4- bromopyridines with complex **1** is shown in Table 2.2. 2-Bromopyridines containing both electron-donating and electron-withdrawing substituents at each position of the ring afforded the products in excellent yields within 8 hours. 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%).

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.[5c] 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**).

Table 2.2 Trifluoromethylation reactions of bromopyridines with (phen)$CuCF_3$.[a]



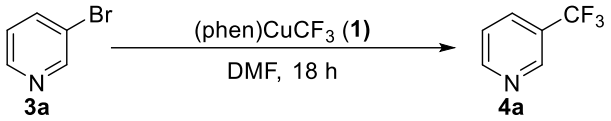
[a] Reaction conditions: bromopyridine (**3**, 0.10 mmol) and **1** (0.12 mmol) in DMF (1 mL) at 80 or 100 °C for 8 h. Yields were determined by ^{19}F NMR spectroscopy. Yields in parentheses are isolated yields. [b] Yield of bis-trifluoromethylated product. [c] Reaction was run at 100 °C. [d] 1.5 equiv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

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 (Table 2.3). 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 2.3 Screen of reaction conditions for improving the reactivity of 3-bromopyridines with (phen)$CuCF_3$.[a]



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%

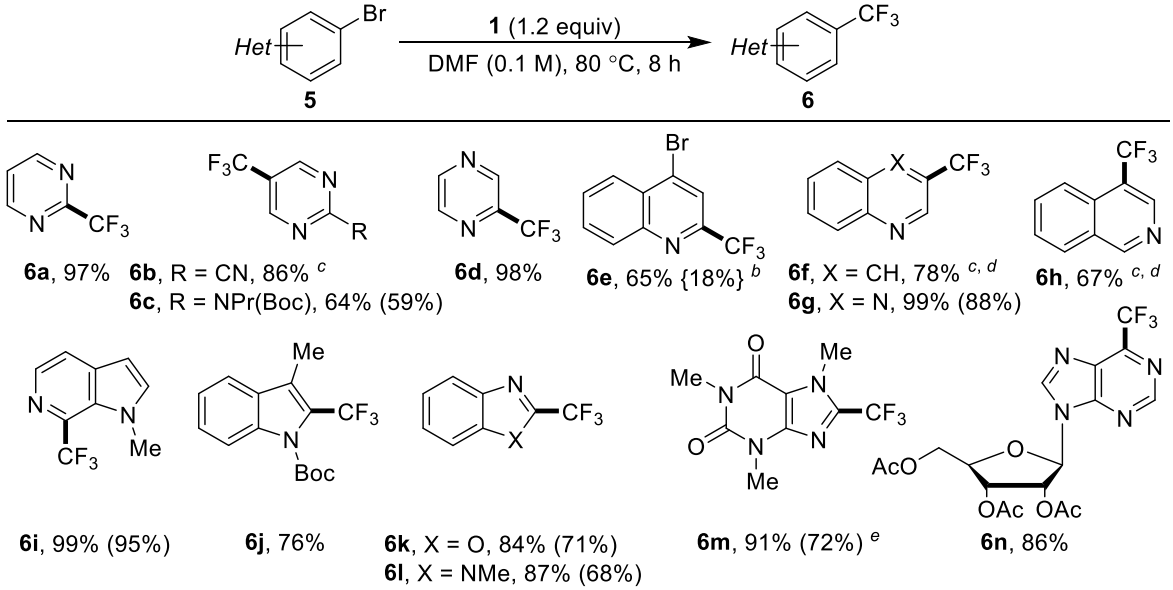
[a] Reaction conditions: bromopyridine (**3**, 0.10 mmol) and **1** (0.12 mmol) in DMF (1 mL) at 100 °C for 18 h. Yields were determined by ^{19}F NMR spectroscopy with 4-$CF_3OC_6H_4OMe$ as internal standard. [b] No significant product formation was observed with DMF or PhMe as solvent. [c] 3-bromopyridine *N*-oxide was used as substrate. [d] 3-bromo-1-(tert-butyldimethylsilyl)pyridinium triflate was used as substrate. [e] (bipy)$CuCF_3$ 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 2.4). 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.

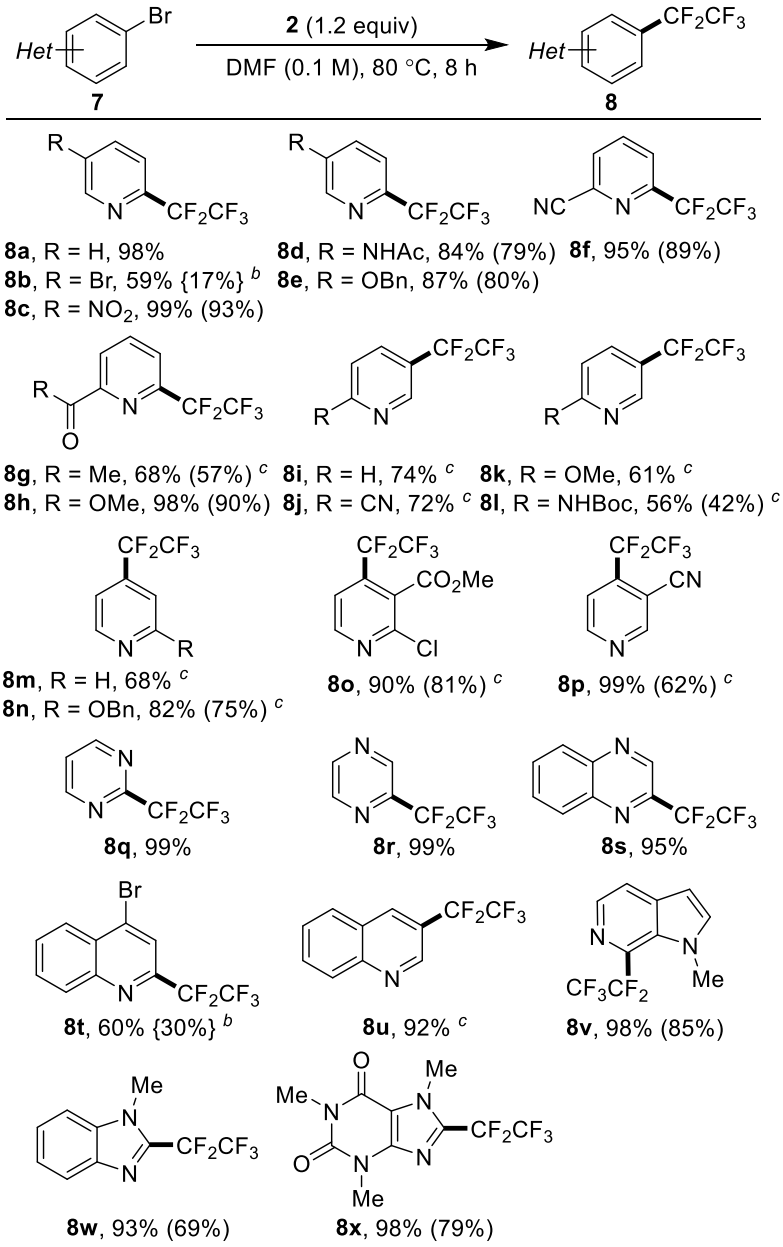
Table 2.4 Trifluoromethylation of heteroaryl bromides with (phen)$CuCF_3$.[a]



[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.

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 2.5). 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** result, 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.

Table 2.5 Perfluoroethylation of heteroaryl bromides with (phen)$CuCF_2CF_3$.[a]



[a] Reaction conditions: bromoheteroarene (**5**, 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 4% bis-perfluroethylated product.

The reactions of bromopyridines with **2** occurred with similar functional group compatibility as was observed for the reactions of **1** (Table 2.5). 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.

2.3 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.

2.4 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.

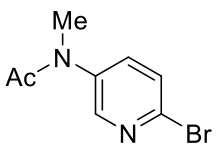
Compounds **1**, **2**, **3h**, **3m**, **3o**, **3p**, and **3x** were prepared according to the published literature procedures.[7, 10-11] The preparations of reactants **3n**, **5c**, and **5i**, are described below. All other reagents were purchased from commercial suppliers and used as received.

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 ($CHCl_3$ 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.

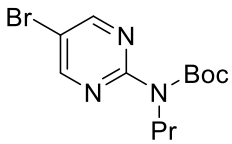
Preparation of N-(6-bromopyridin-3-yl)-N-methylacetamide (3n)



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

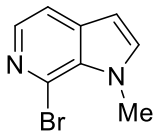
minutes. The reaction was allowed to stir at room temperature for 13 h, at which point full conversion was determined by TLC analysis. The solvent was removed by rotary evaporation and the crude material was purified by silica gel chromatography (100% EtOAc) to give **3n** as a white solid (186 mg, 81% yield).
Note: The peaks in the ^{1}H and ^{13}C spectra were broadened due to the slow interconversion of the amide rotamers.
^{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[3] (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.

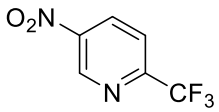
General Procedure for the Perfluoroalkylation of Heteroaryl Bromides with 1 and 2 for Characterization by ^{19}F NMR Spectroscopy

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)



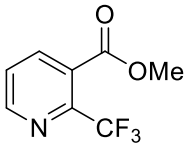
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 20:1 hexanes-EtOAc to give **4e** as a white solid (82 mg, 85% yield).

^{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)



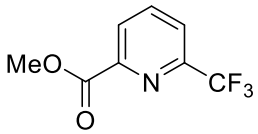
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 6:1 hexanes-EtOAc to give **4g** as a colorless oil (72 mg, 70% yield).

^{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)



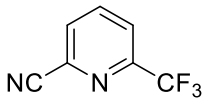
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 6:1 hexanes-EtOAc to give **4k** as a white solid (82 mg, 80% yield).

^{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.

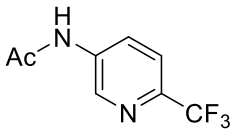
6-(trifluoromethyl)picolinonitrile (4l)



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)**

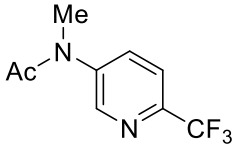


The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 100% EtOAc to give **4m** as a tan solid (40 mg, 39% yield).

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)**



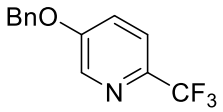
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 100% EtOAc to give **4n** as a colorless oil (94 mg, 86% yield).

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)



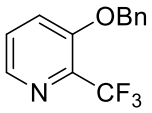
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 6:1 hexanes-EtOAc to give **4o** as a colorless oil (108 mg, 85% yield).

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)



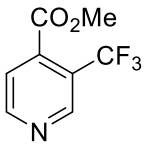
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with a gradient from 100% hexanes to 6:1 hexanes-EtOAc to give **4p** as a colorless oil (76 mg, 60% yield).

^{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)



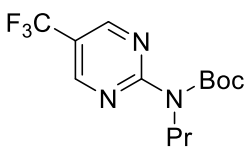
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 6:1 hexanes-EtOAc to give **4t** as a colorless oil (76 mg, 74% yield).

^{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).

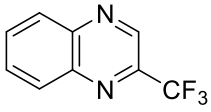
Note: Isolated **6c** contained 20% of perfluoroethyl-substituted product.

^{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)



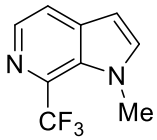
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 9:1 hexanes-EtOAc to give **6g** as a white solid (86 mg, 88% yield).

^{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)



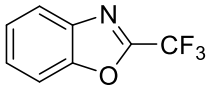
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 6:1 hexanes-EtOAc to give **6i** as a white solid (95 mg, 95% yield).

^{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)



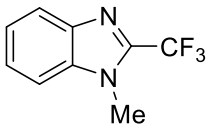
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 20:1 hexanes-EtOAc to give **6k** as a light yellow oil (66 mg, 71% yield).

^{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)



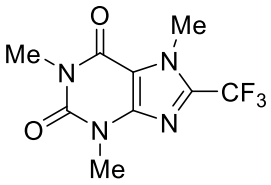
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 6:1 hexanes-EtOAc to give **6l** as a white solid (68 mg, 68% yield).

^{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)



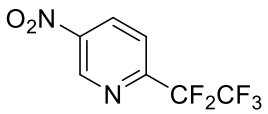
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 4.8 mmol scale. The product was purified by silica gel chromatography eluting with 4:1 hexanes-EtOAc to give **6m** as a white solid (0.90 g, 72% yield).

^{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)



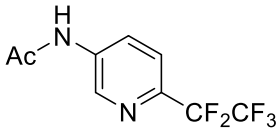
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 20:1 hexanes-EtOAc to give **8c** as a colorless oil (113 mg, 93% yield).

^{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)**



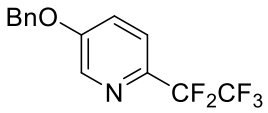
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 1:1 hexanes-EtOAc to give **8d** as a colorless oil (100 mg, 79% yield).

^{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)



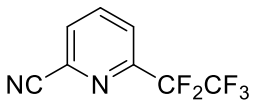
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 6:1 hexanes-EtOAc to give **8e** as a colorless oil (121 mg, 80% yield).

^{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)



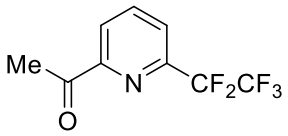
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with a gradient from 100% hexanes to 6:1 to give **8f** as a colorless oil (99 mg, 89% yield).

^{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)



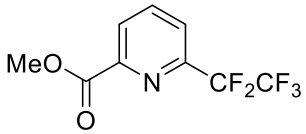
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 20:1 hexanes-EtOAc to give **8g** as a colorless oil (68 mg, 57% yield).

^{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)



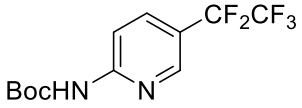
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 6:1 hexanes-EtOAc to give **8h** as a colorless oil (115 mg, 90% yield).

^{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).

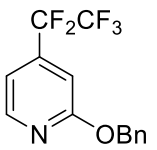
Note: The peaks in the ^{1}H and ^{13}C spectra were broadened due to the slow interconversion of the amide diastereomers.

^{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)



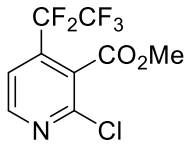
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with 20:1 hexanes-EtOAc to give **8n** as a colorless oil (114 mg, 75% yield).

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)

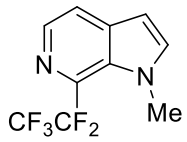


The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with a gradient from 100% hexanes to 6:1 hexanes-EtOAc to give **8o** as a colorless oil (117 mg, 81% yield).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

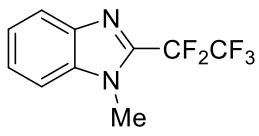
The reaction was performed according to the general procedure for the synthesis of perfluoroalkyl heteroarenes on a 0.50 mmol scale. The product was purified by silica gel chromatography eluting with a gradient from 100% hexanes to 6:1 hexanes-EtOAc to give **8p** as a colorless oil (69 mg, 62% yield).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

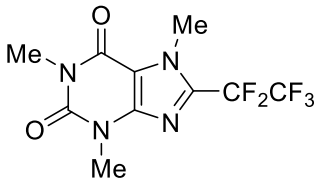
1-methyl-2-(perfluoroethyl)-1H-benzo[d]imidazole (8w)



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).

2.5 References

Parts of this chapter were reprinted with permission from:
"Copper-Mediated Perfluoroalkylation of Heteroaryl Bromides with (phen)CuR_F"
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Chapter 3

Development of a Broadly Applicable Copper-Catalyzed Perfluoroalkylation of Aryl Iodides and Heteroaryl Bromides

3.1 Introduction

Over the past 50 years, there has been considerable interest in the development of reactions that introduce trifluoromethyl substituents onto organic compounds.[1-2] Methods to prepare trifluoromethyl-substituted (hetero)arenes are of particular interest due to their unique physical and biological properties, as well as their prevalence in medicinal chemistry.[3-6] Examples of pharmaceuticals that contain trifluoromethyl groups are shown in Figure 3.1. Perfluoroalkylarenes have broad application in the fields of agrochemistry and materials.[7-8]

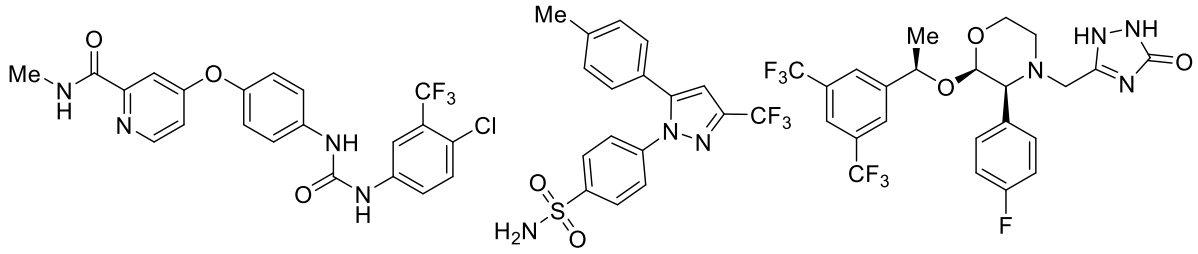


Figure 3.1 Examples of trifluoromethyl-containing pharmaceutical compounds

Trifluoromethylarenes are industrially prepared by the Swarts reaction.[9] This reaction involves exhaustive benzylic chlorination with chlorine gas, generating a benzotrichloride intermediate, followed by reaction with SbF_3 to produce benzotrifluoride. While this procedure is viable for the large-scale synthesis of relatively simple trifluoromethylarenes, the harsh reaction conditions and the necessity of hazardous and toxic reagents limit the broad application of this method to prepare complex, functionalized CF_3-containing arenes in a common laboratory setting. In addition, longer-chain perfluoroalkyl groups (R_F), such as the pentafluoroethyl substituent, cannot be introduced by this reaction.

Various transition metal-mediated reactions have been reported to prepare the C-R_F bonds of perfluoroalkylarenes under milder conditions than those for the Swarts reaction. In 1969, McLoughlin and Thrower reported the reductive coupling of aryl iodides with perfluoroalkyl iodides in the presence of stoichiometric quantities of Cu^0.[10] While a notable first example of this valuable class of cross-coupling reactions, limitations of this procedure include modest yields of products, high reaction temperatures, and the necessity of a difficult to handle gas, CF_3I, to prepare $ArCF_3$. Since this landmark publication, strategies to prepare $ArCF_3$ from diverse starting materials have been developed. Trifluoromethylarenes can be prepared by the reactions of aryl boron[11-18] or aryl silicon nucleophiles[19] with electrophilic CF_3 sources, or nucleophilic CF_3 sources under oxidative conditions. While these reactions occur under mild conditions and in excellent yields, aryl nucleophiles are less commercially and synthetically available than aryl halides, limiting the ability to prepare many diverse ArR_F products. In addition, many electrophilic CF_3 sources required for these reactions are difficult to prepare and expensive.[20] The C-H bonds of (hetero)arenes can be trifluoromethylated by reaction with CF_3 radicals,[21-24] or under palladium

catalysis with electrophilic CF_3 sources.[25-26] Although arenes are abundant starting materials, poor regioselectivity is often obtained for the reactions of (hetero)arenes with CF_3 radical, and directing groups are required to obtain regioselectivity in the Pd-catalyzed C-H trifluoromethylation reactions. Recently, trifluoromethylation of aryl diazonium electrophiles have been reported.[27-29] However, aryl diazoniums are potentially explosive and less available than aryl halides.

The coupling of aryl halides with a nucleophilic perfluoroalkyl source is the most developed route to ArR_F. These reactions are typically conducted in the presence of stoichiometric quantities of Cu(I) salts, which combine with a perfluoroalkyl anion to form an active "CuR_F" species. Decarboxylation of fluorinated carboxylic acid derivatives,[30-34] deprotonation of HR_F,[35-36] or displacement of R_F from fluorinated ketones or esters are some strategies to generate perfluoroalkyl anions.[37-38] The most common nucleophilic perfluoroalkyl sources are derivatives of the Ruppert-Prakash reagent (Me_3SiCF_3, Et_3SiCF_3, $Me_3SiCF_2CF_3$).[39] Discrete, isolable (L)CuR_F complexes have also been developed that react with aryl iodides in excellent yields and under mild conditions.[40-42] In particular, (phen)$CuCF_3$ and the related compound (phen)$CuCF_2CF_3$ were reported to react with a broad range of functionalized arenes, including aryl iodides, activated aryl bromides, heteroaryl bromides, arylboronate esters, and aryl silanes.[18-19, 43-44]

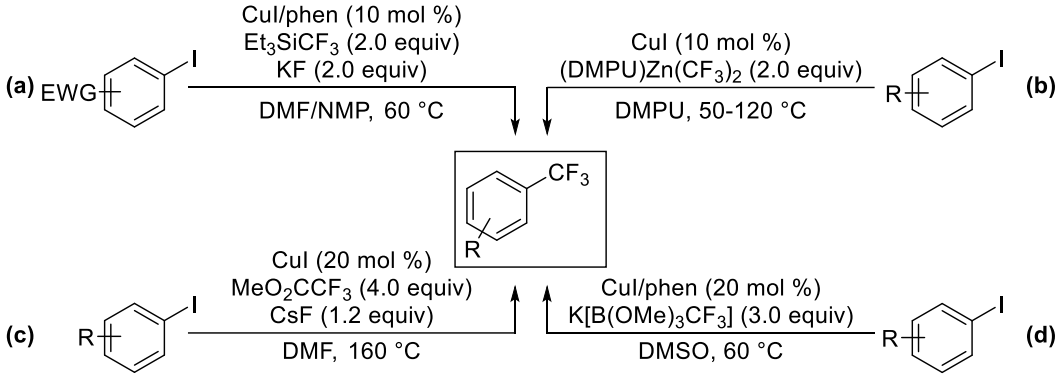


Figure 3.2 Previously-reported copper-catalyzed trifluoromethylation reactions of aryl iodides

Although many examples of copper-mediated perfluoroalkylation reactions of aryl halides have been disclosed, fewer transition metal-*catalyzed* systems that generate perfluoroalkylarenes have been reported. A single Pd-catalyzed trifluoromethylation of widely-available aryl chlorides has been developed.[45] However, the poor reaction scope and the high loadings of Pd and of an expensive phosphine ligand are limitations of this procedure. The majority of catalytic trifluoromethylation or pentafluoroethylation reactions are conducted with Cu(I) salts, often possessing phenanthroline as ligand (Figure 3.2). Amii reported the trifluoromethylation of electron-poor aryl iodides with Et_3SiCF_3 that is catalyzed by 10 mol % of CuI and phenanthroline (Figure 3.2, a).[46] Other trifluoromethylation reagents have been explored for CuI-catalyzed couplings with aryl iodides. Mikami has developed $(DMPU)_2Zn(R_F)_2$ as a reagent for perfluoroalkylation (Figure 3.2, b).[47-48] These compounds are not commercially available and require preparation by treatment of pyrophoric Et_2Zn with expensive gases, CF_3I or CF_2CF_3I. Methyl trifluoroacetate is a readily available and inexpensive compound that can decarboxylate to

generate CF_3 anion in a catalytic trifluoromethylation of aryl iodides (Figure 3.2, c).[49] However, this decarboxylation requires high temperatures (160 °C), limiting the functional groups that are tolerated.

Goossen reported $K[B(OMe)_3CF_3]$ as a CF_3 source for a trifluoromethylation of aryl iodides that is catalyzed by CuI and phen (20 mol %).[50] This reagent coupled with an array of electron-poor or electron-rich aryl iodides under mild reaction conditions (Figure 3.2, d). This compound is prepared from Me_3SiCF_3, KF, and $B(OMe)_3$. Trifluoromethylation reactions conducted with these individual components can form $K[B(OMe)_3CF_3]$ in situ, but typically occur with a more limited scope than reactions of the isolated reagent.[51] The related compound $K[B(OMe)_3CF_2CF_3]$ has also been recently reported for the Cu-catalyzed pentafluoroethylation of aryl iodides.[52] While the scope of the reaction with preformed $K[B(OMe)_3CF_3]$ is greater than that for other Cu-catalyzed trifluoromethylation reactions, a large excess (3.0 equiv) of this compound is required to obtain products in good yields. In addition, this reagent is not commercially available and must be synthesized.

Thus, current methods for catalytic perfluoroalkylation of aryl halides have significant limitations. Most catalytic perfluoroalkylation reactions proceed with high loadings of a copper catalyst (20 mol %). Although copper is an earth-abundant metal, reactions that occur in high turnover are desirable. There are also few examples of catalytic perfluoroalkylation reactions that occur with both electron-deficient and electron-rich aryl iodides. Even fewer examples of the trifluoromethylation of abundant (hetero)aryl bromide electrophiles have been reported. In addition, most catalytic reactions require a large excess of a trifluoromethyl source that is often expensive or challenging to access. To address these issues, we have developed a trifluoromethylation and a pentafluoroethylation reaction of diverse aryl iodides and heteroaryl bromides that occurs under mild conditions with commercially available starting materials. Reactions can be conducted with as little as 5 mol % of a Cu-catalyst. We have also studied the effect of ancillary ligands on the copper catalysts for the perfluoroalkylation reactions in an effort to improve the catalytic process.

3.2 Results and Discussion

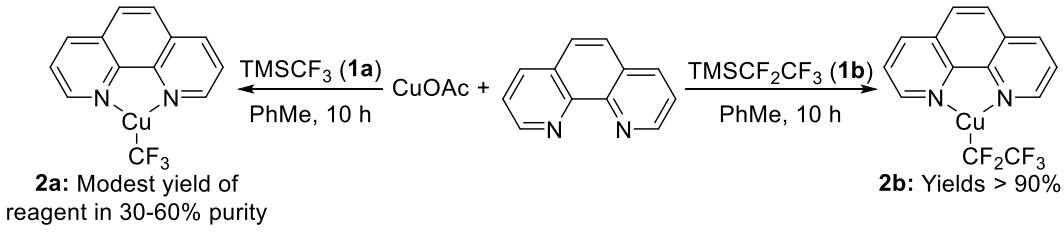


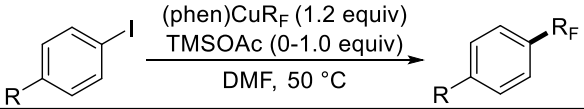
Figure 3.3 Preparation and isolation of (phen)CuR_F from (phen)CuOAc

To model the transmetalation step of the catalytic perfluoroalkylation reaction, various (phen)CuX complexes were treated with Me_3SiCF_3 (**1a**) or $Me_3SiCF_2CF_3$ (**1b**) to prepare and isolate (phen)CuR_F (**2a**, $R_F = CF_3$. **2b**, $R_F = CF_2CF_3$). Reagents **2a** and **2b** are currently prepared by the reaction of **1a** or **1b**, respectively, with (phen)CuO^tBu.[43] We considered that studies on the

transmetalation of perfluoroalkyl groups to copper complexes bearing anionic ligands that are less basic than *tert*-butoxide could point towards additives that could accelerate this step of a catalytic reaction under mild conditions. We were unable to form either **2a** or **2b** from phenanthroline-ligated Cu(I)-phenoxides, -amidates, -silanoates, -thiolates, -carboxylates, or -phosphinates. Reactions of (phen)CuOAc with **1b** afforded isolable **2b** in high yield and purity. However, the analogous preparation of **2a** from (phen)CuOAc only occurred in modest yields and afforded product in low purity (Figure 3.3).

To determine the potential cause for the low yields and purity of **2a** obtained from (phen)CuOAc, we evaluated the effect of TMSOAc, the sole byproduct of this reaction, on the stoichiometric perfluoroalkylation of aryl iodides (Table 3.1). Indeed, while the pentafluoroethylation reactions of 4-butyl-iodobenzene or 4-cyano-iodobenzene with **2b** proceeded in high yields with or without an added equivalent of TMSOAc, the analogous trifluoromethylation reactions of these aryl iodides with **2a** occurred in significantly lower yields when TMSOAc is present in solution. This result indicates that **2a** decomposes in the presence of TMSOAc, but under the same conditions **2b** remains stable. Indeed, the CF_3 signals in the ^{19}F NMR spectrum of **2a** persist for hours at room temperature, but decayed when TMSOAc was added. This same decay was not observed for the CF_2CF_3 signals in the ^{19}F NMR spectrum of **2b**. These results are also consistent with the reported greater stability of "$CuCF_2CF_3$" complexes compared to "$CuCF_3$" complexes.[34, 36, 38, 52]

Table 3.1 Incompatibility of **2a** with TMSOAc in stoichiometric perfluoroalkylation reactions.[a]



	(phen)$CuCF_2CF_3$ (**2b**)		(phen)$CuCF_3$ (**2a**)	
	No TMSOAc	TMSOAc	No TMSOAc	TMSOAc
R = Bu	85%	84%	88%	15%
R = CN	99%	96%	99%	54%

[a] Yields were determined by ^{19}F NMR spectroscopy.

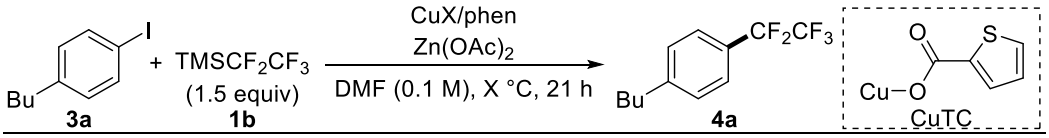
3.2.1 Catalytic Pentafluoroethylation of Aryl Iodides and Heteroaryl Bromides

Because **2b** readily formed from the reaction of **1b** and (phen)CuOAc, we assessed the activity of this copper complex in a catalytic reaction. Aryl iodide **3a** was allowed to react with pentafluoroethyl silane **1b** in the presence of various metal acetates and a catalytic amount of CuOAc and phen. Because $Zn^{II}(R_F)_2$ complexes are known to be stable species, $Zn(OAc)_2$ was chosen as a suitable acetate source that could act as a reservoir of the pentafluoroethyl anion.[48] Indeed, reactions conducted with $Zn(OAc)_2$ afforded product **4a** in moderate yields (Table 3.2, entry 1). Reactions with other metal acetates occurred in lower yields (Table 3.2, entries 2 & 3). By reducing the equivalents of $Zn(OAc)_2$ and increasing the loading of CuOAc and phen, product **4a** was obtained in high yield (Table 3.2, entry 5). Other Cu(I) sources were evaluated (Table 3.2, entries 7-10), and reactions conducted with air-stable and commercially available copper(I)

thiophene-carboxylate, CuTC, occurred in excellent yields (Table 3.2, entries 10 & 11). Reactions performed in the absence of a copper salt did not form product (Table 3.2, entry 12).

Reactions conducted in the absence of $Zn(OAc)_2$ or at room temperature (Table 3.1, entries 13 & 14) both formed the product in ~20% yield. The results from the reaction conducted without $Zn(OAc)_2$ suggest that the 20 mol % of (phen)CuTC readily undergoes transmetalation with **1b** at 80 °C to form ~20 mol % of pentafluoroethylcopper complex **2b**, which can react with **3a** to form 19% of product **4a**. The absence of catalytic turnover indicates that the (phen)CuI formed after the reaction does not undergo transmetalation with $TMSCF_2CF_3$ in the absence of an acetate source. The results from the reaction conducted at room temperature suggest that transmetalation of silane **1b** to a copper carboxylate species to form **2b**, and the coupling of this complex, can occur at lower temperatures. However, the single turnover indicates that (phen)CuI cannot form (phen)$CuCF_2CF_3$ at room temperature in the presence of an acetate source.

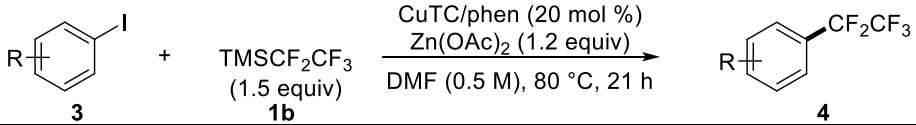
Table 3.2 Evaluation of conditions for the Cu-catalyzed pentafluoroethylation of aryl iodides.[a]

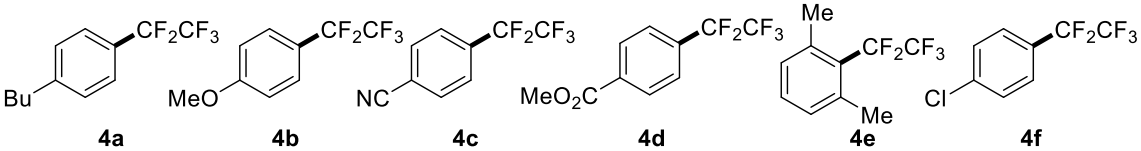


entry	CuX	[Cu/L] (mol %)	$Zn(OAc)_2$ (equiv)	°C	yield
1	CuOAc	10	2.0	80	47%
2	CuOAc	10	2.0 (NaOAc)	80	20%
3	CuOAc	10	2.0 (Bu_4NOAc)	80	5%
4	CuOAc	10	1.2	80	58%
5	CuOAc	20	1.2	80	81%
6	CuOAc	20	1.2	50	19%
7	CuI	20	1.2	80	66%
8	$(MeCN)_4CuBF_4$	20	1.2	80	76%
9	CuSCN	20	1.2	80	63%
10	CuTC	20	1.2	80	84%
11[b]	CuTC	20	1.2	80	90%
12	CuTC	0	1.2	80	0%
13	CuTC	20	0.0	80	19%
14	CuTC	20	1.2	25	17%

[a] Yields were determined by ^{19}F NMR spectroscopy. [b] Reaction concentration was 0.5 M [ArI].

Table 3.3 Cu-catalyzed pentafluoroethylation of aryl iodides with phenanthroline as ligand.[a]





4a	**4b**	**4c**	**4d**	**4e**	**4f**
90% (69%)[b]	96% (69%)[b]	94% (84%)[b]	97% (74%)[b]	61% (52%)[b]	91% (73%)[b]

[a] Yields were determined by ^{19}F NMR spectroscopy. [b] Reaction was performed in the absence of phenanthroline.

The reactions of various aryl iodides were conducted under the developed conditions (Table 3.3). In addition to obtaining excellent yields of trifluoromethylated products from electron-poor aryl iodides, excellent yields of product **4b** were obtained from the reaction of electron-rich 4-iodoanisole. Sterically hindered aryl iodides underwent the coupling reactions in modest yields (**4e**). Aryl bromides possessing synthetically valuable aryl nitriles (**4c**), esters (**4d**), and chlorides (**4f**) were tolerated under the reaction conditions. In the absence of phenanthroline ligand, the pentafluoroethylarene products were also obtained in lower, but still synthetically useful, yields with 20 mol % CuTC as catalyst. In addition, these conditions were extended to the synthesis of longer-chain perfluoroalkyl arenes, as demonstrated by the heptafluoropropylation of an unactivated aryl iodide **3a** with $Me_3SiCF_2CF_2CF_3$ (**1c**) (Figure 3.4).

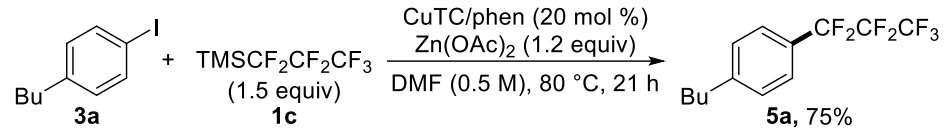
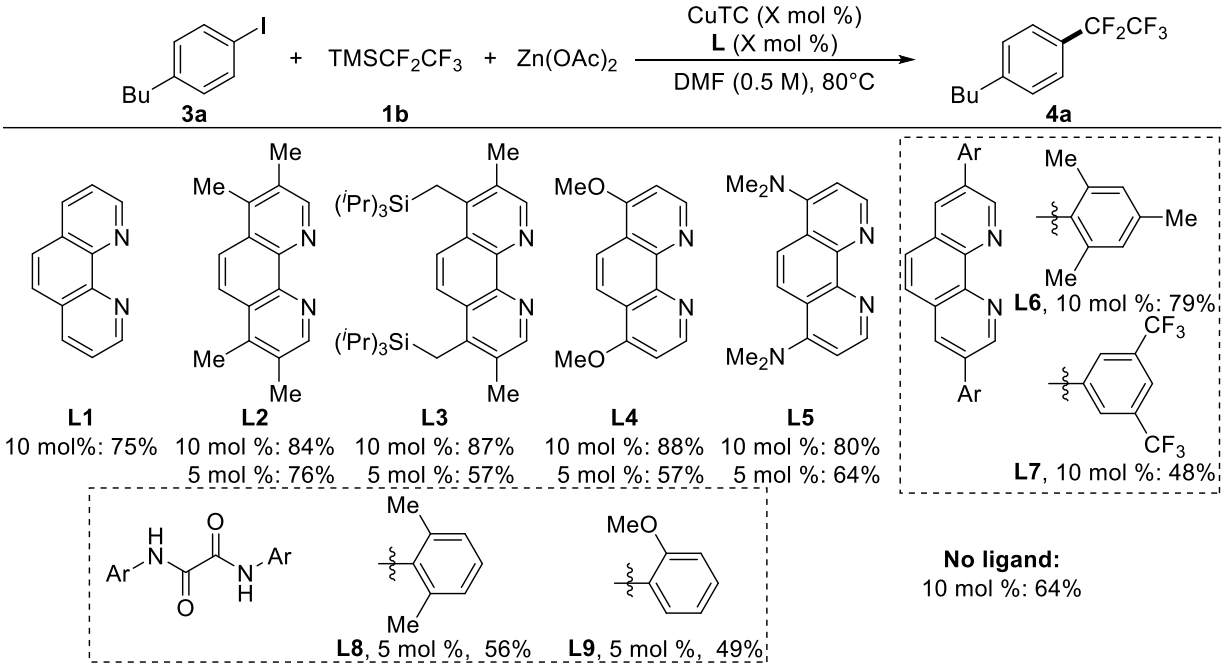


Figure 3.4 Catalytic heptafluoropropylation of an aryl iodide with **1c**

Table 3.4 Evaluation of ligands for pentafluoroethylation at lower loadings of catalyst.[a]



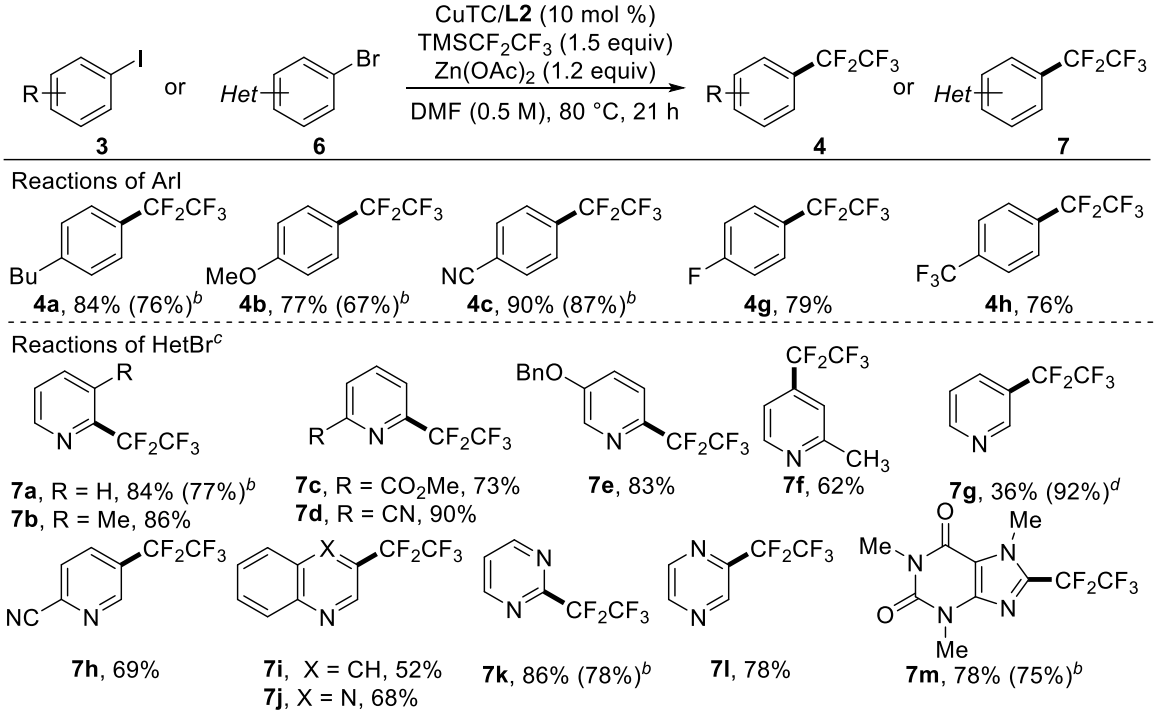
[a] Yields were determined by ^{19}F NMR spectroscopy.

To determine if modifications of the copper catalyst could allow for the pentafluoro-ethylation reaction to proceed with higher turnover numbers than the reaction with CuTC and phen, combinations of CuTC and chelating *N*,*N*-ligands were assessed as catalysts for the coupling of aryl iodide **3a** with **1b** at low loadings of catalyst (Table 3.4). With 10 mol % of catalyst, the yields of reactions with phenanthroline ligands bearing electron-donating substituents (**L2-L5**) were

slightly higher than the yields obtained for reactions with a catalyst consisting of phenanthroline (**L1**). Phenanthroline ligands with aryl substituents in the 3- and 8-positions were also evaluated. A phenanthroline with electron-rich aryl substituents formed catalysts that coupled **3a** and **1b** in excellent yields (**L6**). However, a phenanthroline with electron-poor aryl substituents formed catalysts that afforded **4a** in yields lower than those obtained for reactions conducted without a ligand (**L7** versus no ligand).

Reactions were conducted with 5 mol % of CuTC and ligand to compare the activity of a series of catalysts at loadings lower than 10-20 mol %. In addition to the electron-rich phenanthroline derivatives (**L2-L5**), oxalic diamide ligands were investigated (**L8** & **L9**). These ligands have been previously developed for Cu-catalyzed amination and etherification reactions of aryl chlorides that occur with as little as 1.5 mol % of catalyst.[53-56] However, the yields of pentafluoroethylation reactions conducted with oxalic diamide ligands were lower than those obtained in the ligandless reaction. Because tetramethylphenanthroline (Me_4phen, **L2**) formed a catalyst that afforded pentafluoroethylarene **4a** in good yields, even at 5 mol %, this ligand was chosen for further evaluation.

Table 3.5 Cu-catalyzed Pentafluoroethylation of aryl iodides or heteroaryl bromides with Me_4phen as ligand.[a]



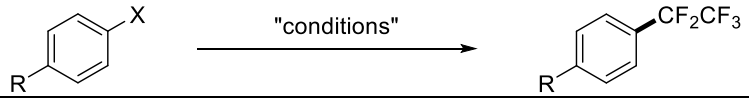
[a] Yields were determined by ^{19}F NMR spectroscopy. [b] Reactions were conducted with 5 mol % of CuTC and Me_4phen. [c] Reactions were run at 100 °C. [d] Reaction was conducted on 3-iodopyridine with 20 mol % of CuTC and phen.

Reactions of either electron-rich or electron-deficient aryl iodides proceeded to form products in good yields with 10 mol % of CuTC and **L2** (Table 3.5, **4a-4h**). The yields of reactions

with 5 mol % of catalyst were slightly lower than the yields of reactions with 10 mol % of catalyst, but still synthetically useful. Because stoichiometric reactions conducted with pentafluoroethylcopper complex **2b** were reported previously to convert either aryl iodides or heteroaryl bromides to pentafluoroethyl-substituted (hetero)arenes, we considered the catalytic pentafluoroethylation reaction also could occur with heteroaryl bromides for the synthesis of medicinally-relevant perfluoroalkyl-substituted heteroarenes. Indeed, the reactions of various 2- and 4-bromopyidines occurred in good to excellent yields (**7a-7f**). Like the couplings of aryl iodides, the couplings of heteroaryl bromides possessing ortho-substituents (**7b**), esters (**7c**), or cyano groups (**7d** and **7h**) afforded products in good yields.

Similar to what was observed in the stoichiometric pentafluoroethylation reactions of heteroaryl bromides with **2b**, the catalytic pentafluoroethylation reactions of 3-bromopyridines occurred in low yields. The 3-position of a pyridine ring is more electron-rich than the 2- or 4-positions. As a result, oxidative addition at the 3-position of a pyridine ring occurs more slowly than oxidative addition at the 2- or 4-positions. The slower rates of oxidative addition could result in the lower yields of **7g**. However, the more reactive, but less commercially and synthetically accessible, 3-iodopyridine underwent the coupling reaction catalyzed by 20 mol % CuTC and phen to afford **7g** in excellent yields. Various other heteroaryl bromides reacted to form products in high yields, including bromo-quinolines (**7i**), -quinoxalines (**7j**), -pyrimidines (**7k**), -pyrazines (**7l**), and -caffeine (**7m**).

Table 3.6 Pentafluoroethylation of aryl iodides under various conditions developed for catalytic perfluoroalkylation.[a]



	conditions	X	R	yield
(a)	$TMSCF_2CF_3$, KF, $[(allyl)PdCl]_2$ (3 mol %), Brettphos (9 mol %), dioxane, 130 °C	Cl	CO_2Et	0%
		Cl	OMe	0%
(b)	$TMSCF_2CF_3$, KF, CuI/phen (10 mol %), NMP:DMF, 65 °C	I	CO_2Et	39%
		I	OMe	23%
(c)	$TMSCF_2CF_3$, KF, $B(OMe)_3$ CuI/phen (20 mol %), DMSO, 65 °C	I	CO_2Et	67%
		I	OMe	20%
(d)	$TMSCF_2CF_3$, $Zn(OAc)_2$, CuTC/phen (20 mol %) DMF, 80 °C	I	CO_2Me	97%
		I	OMe	96%

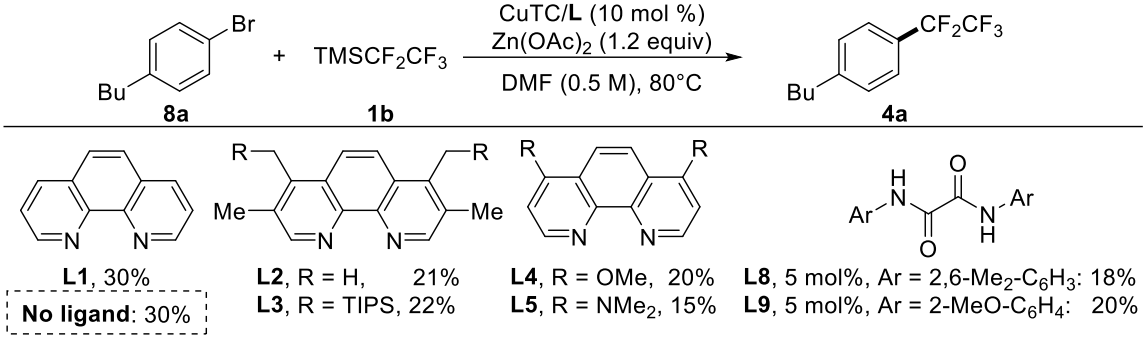
[a] Yields were determined by ^{19}F NMR spectroscopy.

Although many conditions reported for catalytic trifluoromethylation reactions are not extended towards the synthesis of longer chain perfluoroalkylarenes, Table 3.6 shows the comparison of our developed conditions for the pentafluoroethylation of aryl iodides to various conditions previously reported for catalytic trifluoromethylation with Me_3SiCF_3 (**1a**) or Et_3SiCF_3 (**1d**). By substituting **1d** with pentafluoroethyl silane **1b**, we assessed the ability to prepare

pentafluoroethylarenes from the conditions developed by Buchwald for the Pd-catalyzed trifluoromethylation of aryl chlorides (Table 3.6, a).[45] Pentafluoroethylated product was not obtained from reactions of either 4-chloroanisole or ethyl 4-chlorobenzoate. Likewise, low yields of products were obtained from the coupling of aryl iodides with **1d** in the place of **1b** under the conditions developed by Amii for Cu-catalyzed trifluoromethylation (Table 3.6, b).[46]

Because $Et_3SiCF_2CF_3$ is not commercially available, and the few procedures reported generate this reagent from expensive HCF_2CF_3,[57] it is challenging to directly compare the reactivity of pentafluoroethyl silicon reagents in trifluoromethylation procedures that normally require **1d** instead of **1a**. Indeed, the enhanced stability of triethylsilyl reagent **1d** is often required to prevent rapid protodesilylation to HCF_3.[45-46] Novak has reported Cu-catalyzed trifluoromethylation with $K[B(OMe)_3CF_3]$ prepared in situ from KF, $B(OMe)_3$, and **1a**.[51] By replacing trimethylsilyl reagent **1a** with its pentafluoroethyl variant **1b**, the coupling of an activated, electron-deficient aryl iodide was achieved in 67% yield, but the reaction of electron-rich 4-iodoanisole occurred in low yields (Table 3.6, c). In contrast, the system we developed afforded $ArCF_2CF_3$ in excellent yields with a broad scope of aryl iodides (Table 3.6, d & Table 3.3).

Table 3.7 Evaluation of ligands for the pentafluoroethylation of an unactivated aryl bromide.[a]



[a] Yields were determined by ^{19}F NMR spectroscopy.

Having achieved the pentafluoroethylation of aryl iodides and heteroaryl bromides, we investigated the pentafluoroethylation of unactivated aryl bromides under the developed conditions (Table 3.7). A general catalytic or stoichiometric strategy for the direct perfluoroalkylation of unactivated aryl bromides has not been reported. We assessed the reaction of aryl bromide **8a** with **1b** in the presence of catalytic quantities of CuTC and various *N*,*N*-ligands. Although some turnover was observed, the identity of the yields obtained from reactions with **L1** as ligand and from reactions with no added ligand suggest that the observed product formed from a ligandless copper intermediate. Reactions conducted with more electron-rich phenanthroline ligands, or oxalic diamide ligands, resulted in the formation of product **4a** in low yield.

Copper-catalyzed transformations of aryl halides have been proposed in some cases to proceed via the intermediacy of aryl radicals, and in other cases to proceed through a Cu(I)/(III) cycle without the intermediacy of aryl radicals.[58] To investigate whether the catalytic pentafluoroethylation reaction occurs through aryl radical intermediates, we conducted the

reaction of **1b** with 1-(allyloxy)-2-iodobenzene (**3q**) (Figure 3.5). The corresponding aryl radical of **3q** has been reported to undergo cyclization to form 3-methyl-2,3-dihydrobenzofuran with a rate constant of 9.6 $\times 10^9$ s^{-1}.[59] The reaction of **3q** with **1b** catalyzed by a combination of CuTC and **L2** did not form cyclized products. Pentafluoroethylarene **4q** was formed in 37% yield. These results indicate that the reaction likely occurs without the intermediacy of an aryl radical.

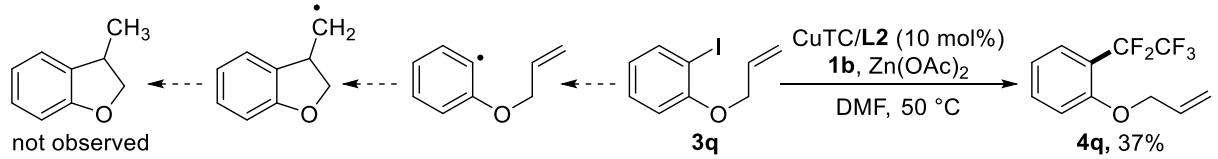
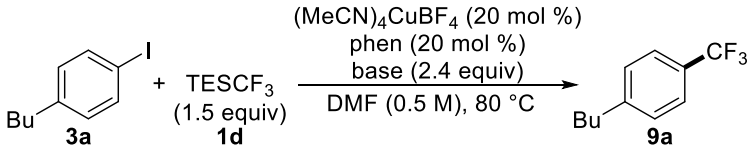


Figure 3.5 Probe for the intermediacy of aryl radicals in the catalytic pentafluoroethylation reaction of aryl iodides

3.2.2 Catalytic Trifluoromethylation of Aryl Iodides and Heteroaryl Bromides

Under the conditions developed for the catalytic pentafluoroethylation of aryl iodides or heteroaryl bromides with **1b**, we were unable to achieve the trifluoromethylation of aryl halides with trifluoromethyl silanes **1a** or **1d**. Reactions of aryl iodide **3a** with either **1a** or **1d** were conducted in the presence of various metal acetate salts, but in all cases the potential $ArCF_3$ product formed in < 10% yield (Table 3.8, entry 1). To avoid the formation of TMSOAc, which we showed to decompose trifluoromethylcopper complex **2a**, the reactions of aryl iodides with the more stable Et_3SiCF_3 **1d** were performed with mild carbonate or phosphate bases. Although reactions containing Cs_2CO_3, Na_2CO_3, or Na_3PO_4 afforded **9a** in trace quantities (Table 3.8, entries 2-4), reactions with either K_3PO_4 or K_2CO_3 formed product in > 20% (Table 3.8, entries 5-6).

Table 3.8 Mild acetate, carbonate, or phosphate bases for catalytic trifluoromethylation of aryl iodides.[a]



entry	base	yield	entry	base	yield
1[b]	$M(OAc)_n$	< 10%	4	Na_3PO_4	5%
2	Cs_2CO_3	0%	5	K_2CO_3	26%
3	Na_2CO_3	11%	6	K_3PO_4	28%

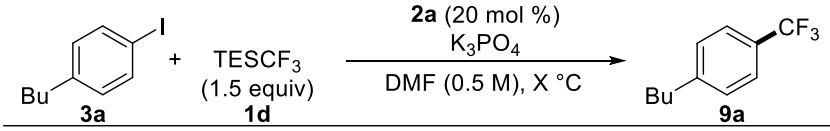
$M(OAc)_2$ = $Zn(OAc)_2$, LiOAc, NaOAc, KOAc, CsOAc, AgOAc, $Cu(OAc)_2$

[a] Yields were determined by ^{19}F NMR spectroscopy. [b] Reactions were also conducted with $TMSCF_3$ (**1a**).

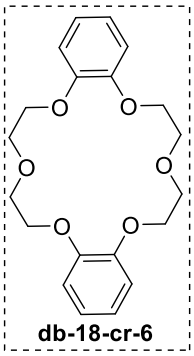
By changing the precatalyst of this reaction from a combination of $(MeCN)_4CuBF_4$ and phen to the preformed trifluoromethylcopper complex **2a**, **9a** was formed in 49% with K_3PO_4 to activate **1d** (Table 3.9, entry 1). No improvements in the yield of product **9a** were obtained by conducting the reaction with 3.0 equiv of **1d** (Table 3.9, entry 2). Reactions conducted with **1a** instead of **1d** were not catalytic, forming only ~20% of product by the stoichiometric reaction of

aryl iodides **3a** with **2a**. Reducing the reaction temperature and the quantity of K_3PO_4 had little impact on the yield of product, but increasing temperature of the reaction to 120 °C resulted in rapid protodesilylation of **1d** and low yields of **9a** (Table 3.9, entries 4-7). We considered that the poor solubility of K_3PO_4 in DMF could result in slow transfer of CF_3 from **1d**. Crown ethers are known to solubilize many potassium salts, In addition, crown ethers were required in a recent report to prepare and characterize free CF_3 anion with a non-coordinated [18-crown-6]K cation.[60] By conducting the reaction with dibenzo-18-crown-6 (db-18-cr-6), a commercially available solid ($0.95/g), we obtained **9a** in ~60% yield (Table 3.9, entries 9-10).

Table 3.9 Evaluation of conditions for the trifluoromethylation of aryl iodides with **2a** as catalyst.[a]



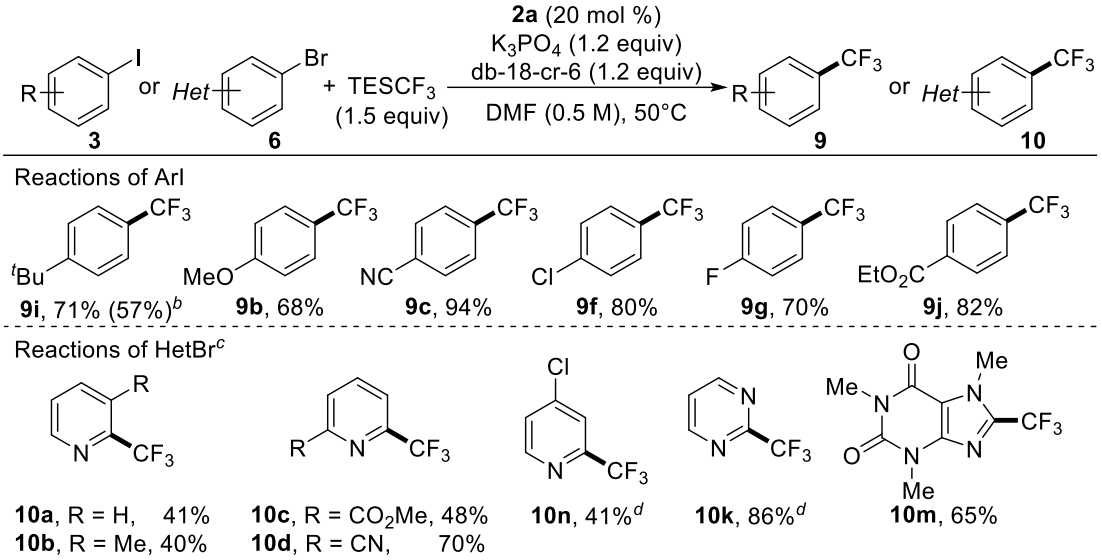
entry	K_3PO_4 equiv	X °C	additive	yield
1	2.4	80	none	49%
2[b]	2.4	80	none	48%
3[c]	2.4	80	none	21%
4	1.2	80	none	44%
5	2.4	50	none	51%
6	2.4	120	none	32%
7	1.2	50	none	45%
8	1.2	50	db-18-cr-6 (0.2 equiv)	48%
9	1.2	50	db-18-cr-6 (0.6 equiv)	62%
10	1.2	50	db-18-cr-6 (1.2 equiv)	63%



[a] Yields were determined by ^{19}F NMR spectroscopy. [b] Reaction was conducted with 3.0 equiv of **1d**. [c] Reaction was conducted with $TMSCF_3$ (**1a**) instead of **1d**.

Trifluoromethylation reactions catalyzed by phen-ligated trifluoromethyl complex **2a**, with **1d**, K_3PO_4, and db-18-cr-6 afforded $ArCF_3$ products from both electron-rich and electron-poor aryl iodides in good yields (Table 3.10). Modest yields (57%) of **9i** were obtained when the loading of catalyst was a lower 10 mol %. The set of functional groups tolerated in this reaction was similar to that tolerated in the catalytic pentafluoroethylation reaction presented above. In addition to reactions of aryl iodides, reactions of heteroaryl bromides occurred in modest to good yield. Typically, yields of $HetCF_3$ products were lower when the reaction was conducted with db-18-cr-6 than when conducted without the crown ether additive. Although the reason this crown ether additive is beneficial for the couplings of aryl iodides, but not for heteroaryl bromides is unknown, reactions to prepare $HetCF_3$ products were performed with a larger excess of base and without crown ether additive. In general, reactions of the less reactive 3-bromopyridines did not form products in > 20% yield. Because oxidative addition occurs more readily for electron-poor aryl halides, bromopyridine **6d**, which contains an electron-withdrawing cyano group, and bromopyrimidine **6k**, which has a more electron-deficient π-system than that of pyridine, coupled to form **10d** and **10k**, respectively, in excellent yields.

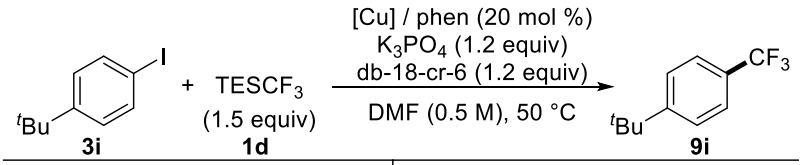
Table 3.10 Cu-catalyzed Trifluoromethylation of aryl iodides or heteroaryl bromides with **2a** as catalyst.[a]



[a] Yields were determined by ^{19}F NMR spectroscopy. [b] Reaction was conducted with 10 mol % of **2a**. [c] Reactions were conducted with 2.4 equiv of K_3PO_4 and no added db-18-cr-6. [d] Reactions were conducted at 80 °C with no added db-18-cr-6.

Because reactions catalyzed by phen-ligated trifluoromethyl complex **2a** require the synthesis of this copper complex from air and moisture sensitive CuO^{t}Bu, we examined the combination of phen and various Cu(I) salts as precatalysts in the reaction (Table 3.11). Reactions with catalysts prepared from copper halide salts or from cationic copper complexes afforded the trifluoromethylarene products in modest yields. However, like the developed pentafluoroethylation reaction, the trifluoromethylation reaction catalyzed by a combination of CuTC and phen produced perfluoroalkylarene **9i** in good yields.

Table 3.11 Assessment of CuX compounds as the source of Cu in catalytic trifluoromethylation of aryl iodides.[a]



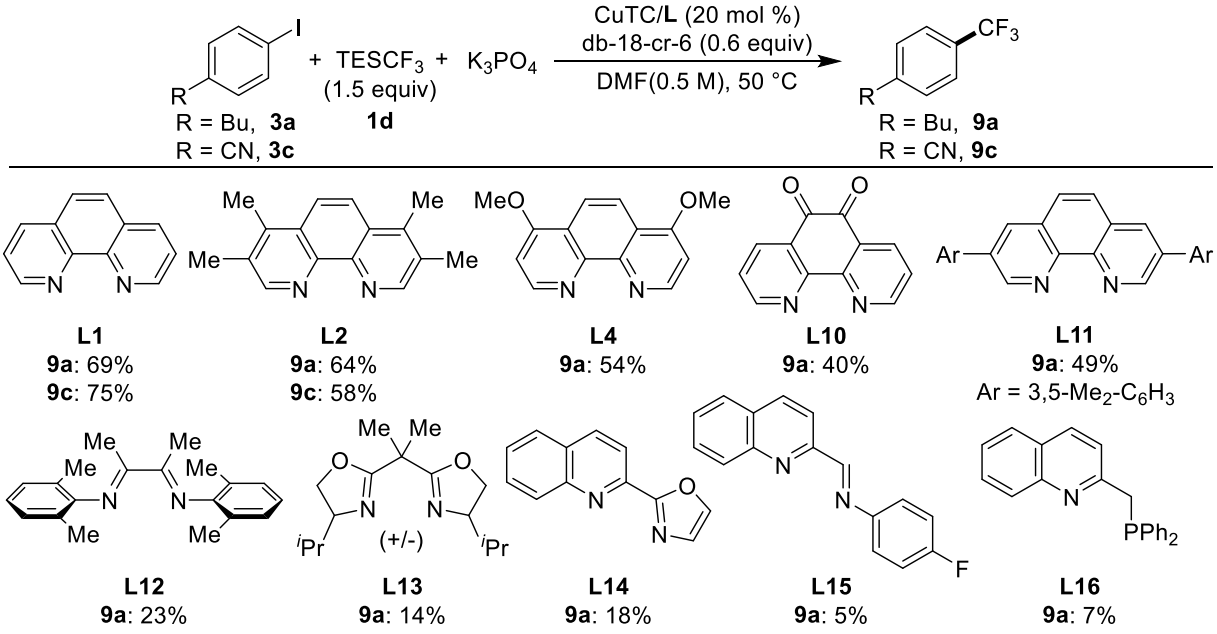
entry	copper source	yield	entry	copper source	yield
1	CuI	43%	5	CuTC	61%
2	CuBr	34%	6	$[Bu_4N][CuI_2]$	34%
3	CuCl	37%	7	$(MeCN)_4CuBF_4$	28%
4	CuOAc	46%	8	$(^tBuCN)_2CuOTf$	32%

[a] Yields were determined by ^{19}F NMR spectroscopy.

Various chelating, nitrogen-based ligands were evaluated in the catalytic trifluoromethylation reaction (Table 3.12). Although the previously discussed pentafluoroethylation reactions catalyzed by a complex containing **L2** proceeded in higher yields than those

containing the unsubstituted phenanthroline **L1**, the trifluoromethylation reactions of **3a** catalyzed by the complex of **L2** occurred in similar yields as those catalyzed the complex of **L1**. The yield of **9c** from the reaction of the electron deficient iodoarene **3c** catalyzed by the system generated from **L2** was lower than that of reactions catalyzed by the system generated from **L1**. The yields of reactions catalyzed by other phenanthroline complexes, including those of phenanthrolines containing electron-donating methoxy groups (**L4**), or a more electron-deficient π-system (**L10**), were lower than those catalyzed by the complex of **L1**. Other *N*,*N*-ligands were assessed, including bis-imine **L12**, racemic bisoxazoline **L13**, and quinoline-based ligands **L14** and **L15**. However, reactions conducted with these ligands afforded trifluoromethylarenes in very low yields. In addition to *N*,*N*-ligands, an *N*,*P*-ligand **L16** was also evaluated for the Cu-catalyzed trifluoromethylation, but the reactions with this ligand formed **9a** in only 7% yield. Currently, no modifications of phenanthroline have resulted in ligands that form more active catalysts than those formed from unsubstituted phenanthroline.

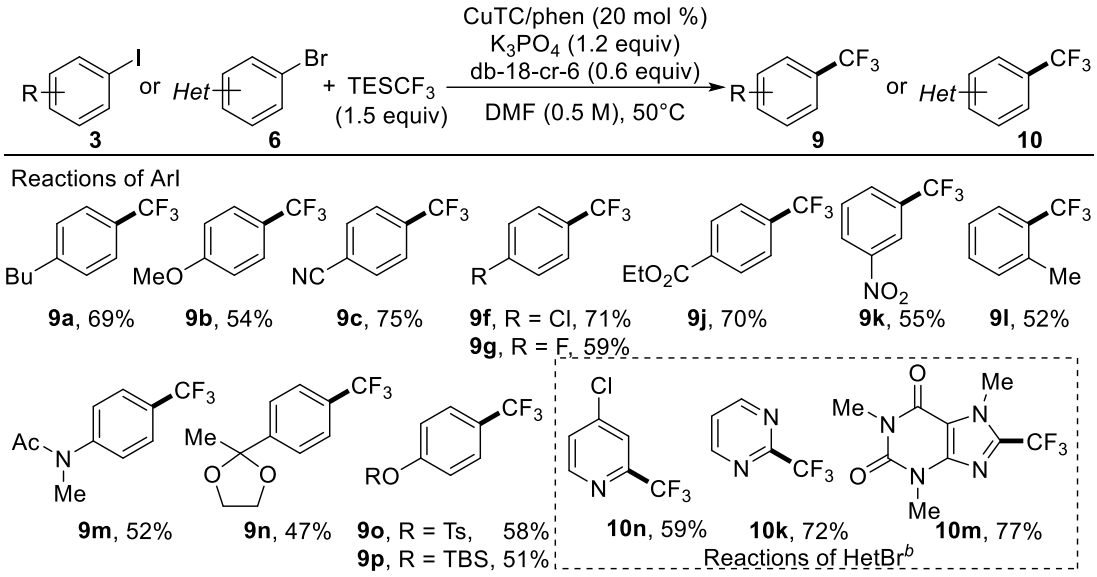
Table 3.12 Evaluation of ligands in Cu-catalyzed trifluoromethylation of aryl iodides.[a]



[a] Yields were determined by ^{19}F NMR spectroscopy.

Reactions catalyzed by a combination of CuTC and **L1** typically occurred in lower yields than those catalyzed by preformed complex **2a**. However, synthetically useful quantities of $ArCF_3$ or $HetCF_3$ were obtained from functionalized (hetero)aryl halides (Table 3.13). The reaction did not tolerate the protic N-H bonds of anilines or enolizable ketones, but protecting these functional groups allowed the formation of acetanilide compound **9m** or ketal-protected **9n** to occur in moderate yields. Protic phenols were also not tolerated under the reaction conditions. Converting the phenol to a tosylate group allowed for the formation of **9o** in good yields and provided a valuable substituent for further synthetic transformations.

Table 3.13 Cu-catalyzed trifluoromethylation of aryl iodides or heteroaryl bromides with CuTC and phen as precatalyst.[a]



[a] Yields were determined by ^{19}F NMR spectroscopy. [b] Reactions were conducted with 2.4 equiv of K_3PO_4 and no added db-18-cr-6.

4-Iodophenol was also protected with a *tert*-butyldimethylsilyl (TBS) group (Table 3.13, **3p**). Although the coupling of this compound occurred in only 51% yield, stoichiometric reactions of **3p** with Cu-complex **2a** did not form product **9p** (Figure 3.6, a). We also subjected **3p** to the conditions developed by Amii for the trifluoromethylation of aryl iodides catalyzed by CuI and phen (Figure 3.6, b). The KF required in this reaction to liberate the CF_3 anion from silane **1d** also cleaved the O-Si bond, resulting in no formation of the coupled product.

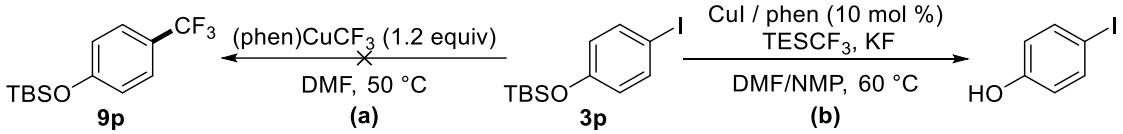


Figure 3.6 Reactions of **3p** under conditions previously reported for Cu-mediated or -catalyzed trifluoromethylation of aryl iodides

3.2.3 Studies on the Effect of Ligands in Cu-Mediated Perfluoroalkylation Reactions

Although we have developed a procedure for the catalytic trifluoromethylation or pentafluoroethylation of (hetero)aryl halides, the yields of these reactions are often modest, and 20 mol % of a copper catalyst are typically required. A copper catalyst that is able to transform aryl iodides or heteroaryl bromides in higher yields and turnover numbers than what has been previously reported is desirable. In addition, the discovery of a more reactive copper catalyst or reagent could allow for the transformations of challenging unactivated ArBr electrophiles. To gain insight on how the electron-donating ability of the ligand on copper affects the perfluoroalkylation

reaction, we prepared electronically diverse (L)CuR_F species to study in the stoichiometric reactions of these complexes with aryl iodides.

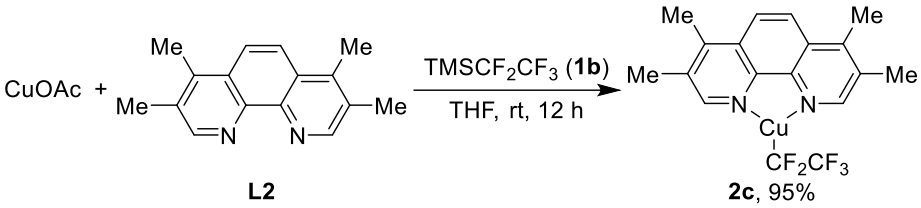


Figure 3.7 Synthesis of **2c** from CuOAc

Because catalysts containing the electron-rich ligand Me_4phen (**L2**) coupled aryl iodides and perfluoroethyl **1b** in high yields, we prepared the pentafluoroethylcopper complex containing this ligand, (Me_4phen)CuCF_2CF_3 (**2c**). This complex formed in high yields from CuOAc, Me_4phen, and **1b** (Figure 3.7). The stoichiometric pentafluoroethylation of aryl iodide **3a** was performed with reagents **2b** or **2c**. After 24 h, product **4a** was obtained in high yields from reactions conducted with either **2b** or **2c**. However, reactions conducted with **2c** to form the trifluoromethylarene were slower than those conducted with **2b** (Figure 3.8). The slow conversion of **3a** with this complex was likely due to the poor solubility of complex **2c** in DMF.

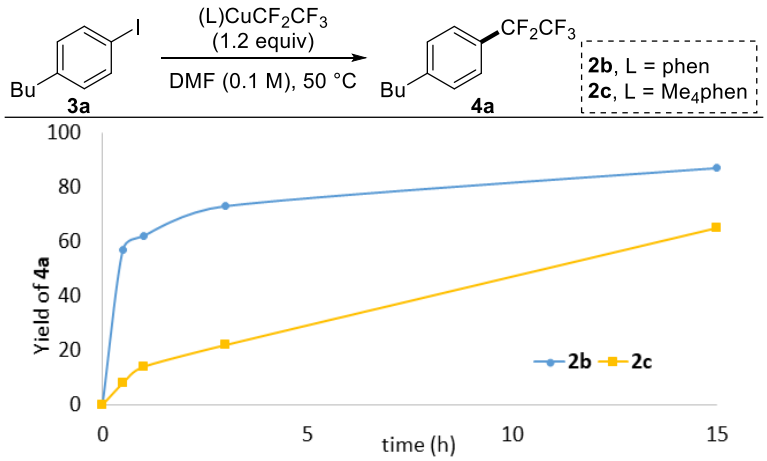


Figure 3.8 Formation **4a** from the stoichiometric reactions of **3a** with **2b** or **2c**

Because the poor solubility of **2c** in DMF rendered the analysis of stoichiometric reactions with this complex challenging, we prepared more soluble complexes based on 2,2-bipyridyl (bipy) ligands (**L17**). This class of ligand is structurally analogous to phenanthroline. In addition to the commercial availability of bipy derivatives being higher than that of phenanthroline derivatives, the number of steps in the synthesis of these ligands is lower than that needed to prepare phenanthroline compounds. The rapid access to a variety of bipy derivatives allows for the synthesis and evaluation of diverse electron-rich or electron-poor (L)CuCF_2CF_3 complexes. We prepared unsubstituted parent compound (bipy)CuCF_2CF_3 (**2d**) and compared the reaction of this

complex with either **3b** or **3c** to reactions of these aryl iodides with **2b** (Figure 3.9). The rate of reactions of activated aryl iodide **3c** with **2d** to form product **4c** was similar to that of the reaction of **3c** with **2b**. Reactions of **3b** with **2d** were only marginally slower than reactions of **3b** with **2b**. These results suggest that the rate of reactions of (phen)$CuCF_2CF_3$ with aryl iodides are similar to those of reactions of (bipy)$CuCF_2CF_3$ with aryl iodides.

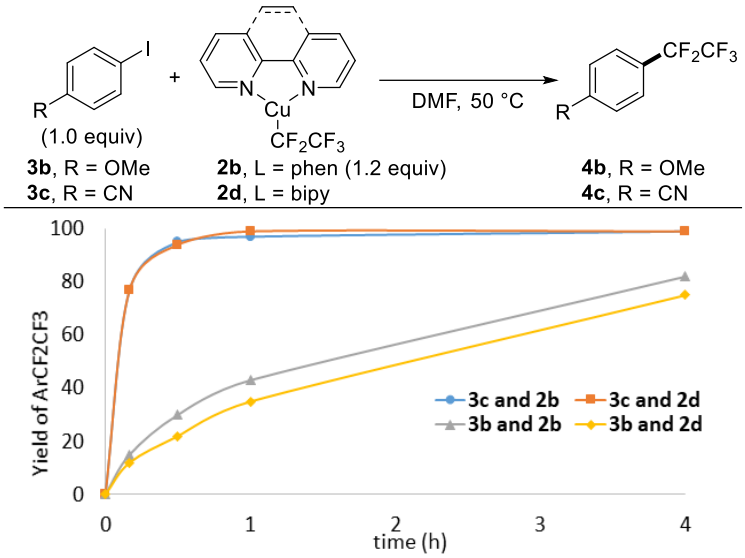
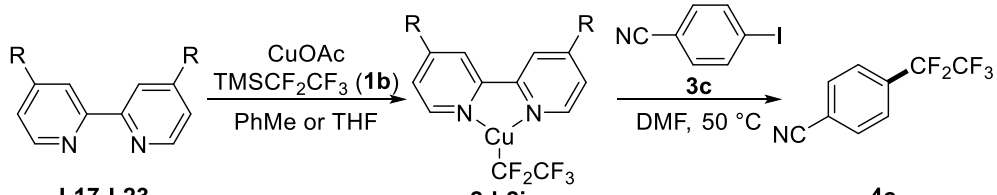


Figure 3.9 Formation of **4b** or **4c** from stoichiometric reactions with complexes **2b** or **2d**

Table 3.14 Synthesis and reactivity of substituted (bipy)$CuCF_2CF_3$ derivatives.



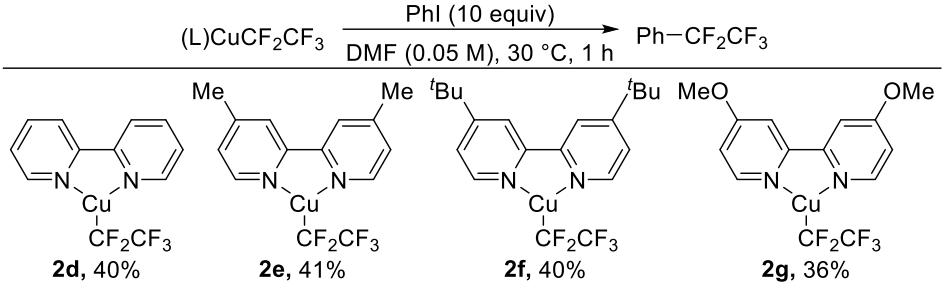
L17-L23		2d-2j	4c
ligand	R =	yield of (L)$CuCF_2CF_3$	yield of **4c**[a]
L17	R = H	**2d**, 96%	99%
L18	R = Me	**2e**, 74%	99%
L19	R = ^{t}Bu	**2f**, 75%	99%
L20	R = OMe	**2g**, 90%	80%
L21	R = NMe_2	**2h**, 86%	95%
L22	R = CN	**2i**, 0%	-%
L23	R = CF_3	**2j**, 0%	-%
L24	R = Cl	**2k**, 0%	-%

[a] Yields were determined by ^{19}F NMR spectroscopy. Reactions were conducted on a 0.05 mmol scale with 1.0 equiv of aryl iodide and 1.2 equiv of (L)$CuCF_2CF_3$ complex

CuOAc and **1b** were treated with an assortment of bipy ligands (Table 3.14). Parent compound **2d** and derivatives of this complex possessing electron-donating methyl (**2e**), *tert*-butyl (**2f**), methoxy (**2g**), or dimethylamino (**2h**) substituents formed and were isolated in high yield. In

addition, these complexes reacted with 4-iodobenzonitrile to form **4c** in high yields. Derivatives of bipy with electron-withdrawing substituents (**L22-L24**) did not form the trifluoromethyl complexes **2i-2k**. It is likely that the electron-poor nature of these ligands resulted in weak binding to Cu(I), and the resultant unligated perfluoroalkylcopper species underwent decomposition. The preparation of (L)CuCF_2CF_3 from electron-poor ligands related to bipy was also attempted. Similar to the reactions with **L22-L24**, the reactions with 4,5-diazafluoren-9-one formed a solid product that did not possess any fluorine-containing groups, as determined by ^{19}F NMR spectroscopy. Reactions to form a complex possessing a 2,2-bipyrimidine ligand did form some pentafluoroethylcopper complex in low purity, but reactions of this complex with iodoarene **3c** afforded product **4c** in only 31% yield.

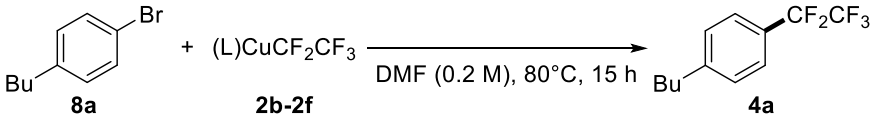
Table 3.15 Comparison of the partial conversions of complexes **2d-2g** to $PhCF_2CF_3$.[a]



[a] Yields were determined by ^{19}F NMR spectroscopy.

The stoichiometric reactions of complexes **2d-2g** with an excess of PhI were conducted at 30 °C (Table 3.15). Reactions were quenched after 1 h to determine the copper complex that underwent the highest partial conversion to pentafluoroethyl benzene. Despite these complexes bearing ligands with varying degrees of electron-donating ability, pentafluoroethyl benzene was formed in approximately 40% yield for each of these complexes after 1 h. These results suggest that the ancillary ligand on copper has a minimal effect on the rate of formation of pentafluoroethylarenes.

Table 3.16 Stoichiometric pentafluoroethylation of **8a** with complexes **2b-2f**.[a]



L	complex	yield of **4a**
phen	**2b**	22%
Me_4phen	**2c**	0%
bipy	**2d**	20%
Me_2bipy	**2e**	28%
(^{t}Bu)$_2$bipy	**2f**	23%
(MeO)$_2$bipy	**2g**	49%

[a] Yields were determined by ^{19}F NMR spectroscopy.

Because the perfluoroalkylation of unactivated ArBr remains a challenge, we also assessed reactions of the pentafluoroethylcopper complexes **2b-2g** with the unactivated bromoarene **8a** (Table 3.16). Reactions of **8a** with complex **2c** did not form **4a**. Plating of Cu^0 was observed on the vial during this reaction, indicating decomposition of the copper reagent. Reactions of **2b** and **2d-2f** with bromoarene **8a** all formed the perfluoroethylarene product in ~20-30% yield. Reactions of electron-rich copper complex **2g** afforded product **4a** in 49% yield. Further modification of this ligand scaffold or the reaction conditions could potentially allow for the Cu-mediated formation of $ArCF_2CF_3$ from unactivated ArBr in good yields.

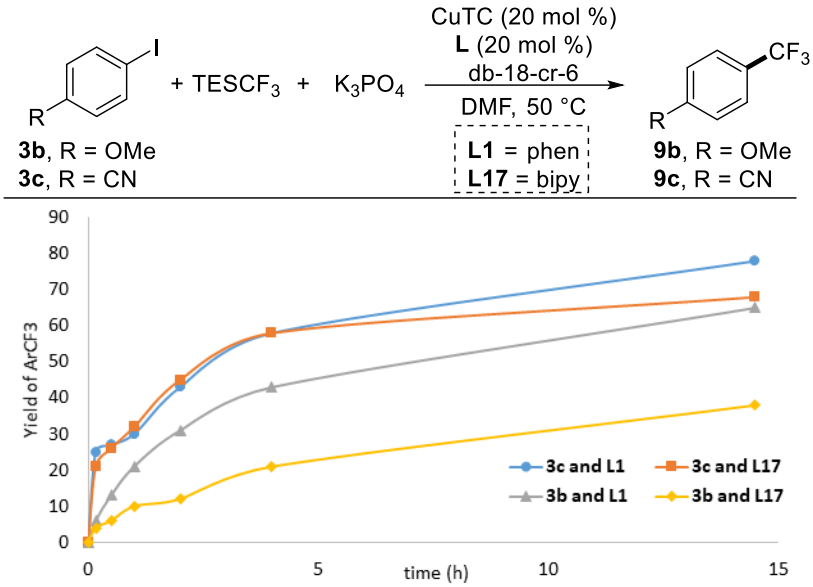


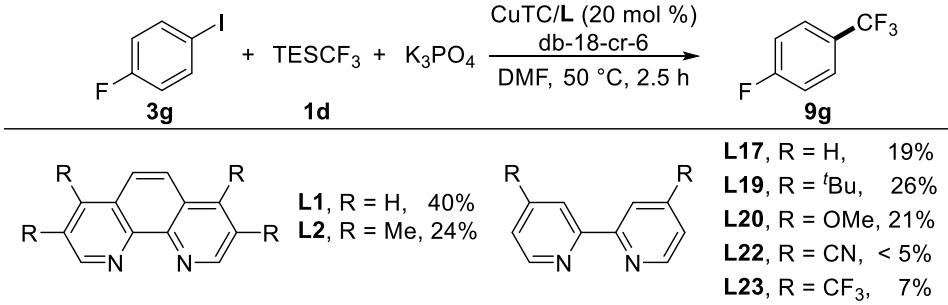
Figure 3.10 Formation of **4b** or **4c** from catalytic reactions with CuTC and **L1** or **L17**

Unlike reactions to prepare $(L)CuCF_2CF_3$ compounds, reactions to prepare $(L)CuCF_3$ species did not afford isolable complexes with Me_4phen or various substituted bipy ligands. Because the reaction to prepare $(phen)CuCF_3$ occurs from CuO^tBu, it is possible that the ligation with a phen or bipy derivative, and subsequent transmetalation of CF_3 to this complex, are more sensitive to the nature of the ancillary ligand than is the transmetalation of CF_2CF_3 to (L)CuOAc. As a result, we compared the effect of the electronic properties of the ligand on the Cu-catalyzed formation of electron-rich anisole **9b** or electron-poor nitrile **9c** (Figure 3.10). Although the reactions of iodobenzonitrile **3c** conducted with **L1** were similar in rate to those conducted with **L17**, reactions of anisole derivative **3b** catalyzed by a combination of CuTC and **L17** were slower than those with **L1**. Although the formation of pentafluoroethyl product **4b** from the stoichiometric reactions of $(phen)CuCF_2CF_3$ or $(bipy)CuCF_2CF_3$ with **3c** occurs at similar rates (see Figure 3.9), the formation of the trifluoromethyl-analogue **9b** from the catalytic reaction of **3c** with **1d** was slower when conducted with bipy than when conducted with phen.

Catalytic trifluoromethylation reactions of 4-fluoroiodobenzene (**3g**) were performed with various substituted phenanthroline or 2,2'-bipyridine derivatives and quenched after 2.5 hours at

50 °C (Table 3.17). Reactions catalyzed by a complex containing **L1** formed **9g** in the highest yield after this time. These results were consistent with those depicted in Table 3.12, in which reactions with **L1** as ligand formed products **9a** or **9c** in higher yields than reactions with other *N*,*N*- or *N*,*P*-ligands. The yields of reactions of **3g** with **1d** catalyzed by CuTC and **L17**, **L19**, or **L20** were similar to one another. High yields of **9g** were not obtained from reactions with more electron-rich Cu-complexes, which are expected to undergo oxidative addition of aryl iodides faster than more electron-poor Cu-complexes. Reactions with electron-poor bipy derivatives, which bind weakly to copper, formed product in only trace yield. Because of this low yield, it is difficult to determine a clear correlation between the electronic properties of the ligand on copper and the rate of the catalytic trifluoromethylation of aryl iodides.

Table 3.17 Evaluation of phen and bipy ligands in catalytic trifluoromethylation of **3g**.[a]



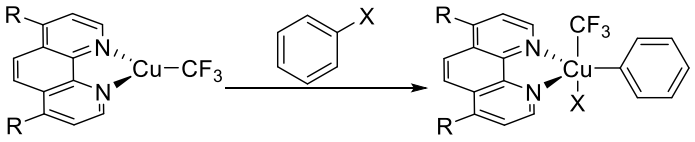
[a] Yields were determined by ^{19}F NMR spectroscopy.

Because our experiments to deduce the effect of the electronic properties of the ligand on the rate and yield of the trifluoromethylation reactions were inconclusive, we conducted computational studies on the energy barriers to oxidative addition of various aryl halides to substituted (phen)$CuCF_3$ reagents. The calculated barrier to oxidative addition of PhI to complex **2a** was 16.5 kcal/mol (Table 3.18, entry 1). This barrier is consistent with the mild temperatures required for trifluoromethylation of aryl iodides with this complex. A higher barrier was calculated for the oxidative addition of aryl bromides (Table 3.18, entry 2), which react with **2a** at elevated temperatures when possessing an electron-deficient aryl group. A barrier of 22.4 kcal/mol was calculated for the oxidative addition of aryl chlorides, which do not react with complex **2a** (Table 3.18, entry 3).

The barriers for oxidative addition of aryl halides to methoxy- or trifluoromethyl-substituted (phen)$CuCF_3$ complexes were also calculated (Table 3.18, entries 4-7). In general, the computed barrier for the oxidative addition of iodobenzene to the electron-rich [$(MeO)_2$phen]$CuCF_3$ was slightly higher than that for the oxidative addition of iodobenzene to **2a** (17.8 kcal/mol vs. 16.5 kcal/mol). The computed barriers for the oxidative addition of iodobenzene to **2a** was identical to that for the oxidative addition of this compound to electron-deficient [$(CF_3)_2$phen]$CuCF_3$ (16.5 kcal/mol vs. 16.4 kcal/mol). The observed trend for the oxidative additions of aryl bromides to these complexes was similar to that for the oxidative addition of aryl iodides (Table 3.18, entries 2, 5, & 7). In general, the differences in energy barriers to oxidative addition of aryl halides to electronically-diverse phenanthroline-ligated trifluoromethylcopper

complexes are relatively small (< 2 kcal/mol), suggesting that the ancillary ligand on copper has little effect on the barrier to oxidative addition. This conclusion is consistent with the results from the partial conversion of complexes **2d-2g** to $PhCF_2CF_3$ presented in Table 3.15.

Table 3.18 Calculated barriers to oxidative addition for ArX to (L)$CuCF_3$ complexes.[a]



entry	R	X	calculated barrier to OA (kcal/mol)
1	H	I	16.5
2	H	Br	18.4
3	H	Cl	22.4
4	OMe	I	17.8
5	OMe	Br	19.2
6	CF_3	I	16.4
7	CF_3	Br	18.2

[a] B3LYP functional (gd3 dispersion correction), LANL2DZ basis set for Cu, Br and I and 6-31g(d,p) basis set for all other atoms.

3.3 Conclusions and Outlook

We have reported the catalytic pentafluoroethylation and trifluoromethylation of both electron-rich and electron-poor aryl iodides, as well as perfluoroalkylation of a variety of widely available heteroaryl bromides. These reactions are conducted under mild conditions with commercially available perfluoroalkylsilane reagents used in a slight excess with respect to the aryl halide coupling partner. Reactions conducted with a mild $Zn(OAc)_2$ base allow the pentafluoroethylation of various aryl halides to occur with as little as 5 mol % of the combination of Me_4phen and CuTC as catalyst. Reactions conducted with a combination of K_3PO_4 and a crown ether additive allow for the trifluoromethylation of aryl halides that is catalyzed either by preformed (phen)$CuCF_3$ or a combination of CuTC and phen. Although the scope and functional group compatibility of this reaction were good, yields were often modest.

The discovery of a catalyst that couples aryl iodides with perfluoroalkyl groups with high turnover numbers, or to transform unactivated ArBr, would be a significant development towards the facile preparation of perfluoroalkylarenes. To explore the effect of ancillary ligands on copper catalysts for the perfluoroalkylation of aryl iodides, we reported the synthesis and the reactivity of various pentafluoroethylcopper reagents. Preliminary results suggest that the reactivity of aryl iodides with (bipy)$CuCF_2CF_3$ derivatives is similar to that with (phen)$CuCF_2CF_3$, and that the effect of the substituents on the bipy of bipy-ligated copper complexes on the conversion to pentafluoroethylarenes are small. The design and synthesis of (L)$CuCF_2CF_3$ complexes with a broader range of electron-rich or electron-poor ligands, and additional kinetic analysis of the

reactions of these complexes with ArX, would offer greater insight towards the design of novel ligands that accelerate slow steps of the catalytic cycle for perfluoroalkylation.

Although we have prepared isolable pentafluoroethylcopper complexes to evaluate the effect of electron density at copper on the formation of $ArCF_2CF_3$, we were not able to prepare many analogous trifluoromethylcopper complexes. As demonstrated by the different reaction conditions for the previously discussed pentafluoroethylation and trifluoromethylation reactions, reactions of copper complexes that incorporate pentafluoroethyl substituents could be poor models for reactions that introduce trifluoromethyl groups. Although we have not been able to prepare various $(L)CuCF_3$ from CuOAc or CuO^{t}Bu, an alternative strategy would be to generate unligated "$CuCF_3$" in-situ, then ligate this complex with substituted ligands, preparing $(L)CuCF_3$ reagents as solutions in DMF for kinetic analysis.[35, 37] Preliminary data has been obtained demonstrating the ability of this procedure to prepare solutions of trifluoromethylcopper complexes ligated by phen, bipy, ^{t}Bu$_2$bipy, or bathophenanthroline.

To achieve catalytic transformations with lower quantities of a Cu-catalyst, the reaction of (L)CuX complexes with perfluoroalkyl silane reagents to form $(L)CuR_F$ species should also be studied. Assessing the rates of this reaction with or without various additives, including acetate or phosphate, could suggest additives or other bases that improve catalytic turnover. In addition to studies on transmetalation between copper halide species and Me_3SiR_F or Et_3SiR_F, a systematic evaluation of the transmetalation from novel perfluoroalkyl silicon reagents containing other silyl groups (e.g. $SiMe_2Ph$, $SiMe_2{}^t$Bu, $Si(SiMe_3)_3$) would be valuable to identify perfluoroalkylation reagents that could be more stable towards decomposition to $H\text{-}R_F$, allowing for these reagent to be used in a smaller excess.

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.

Copper complex **2a**,[18, 43] ligands **L3**, **L6-L9**, **L12**, **L14-L16**, **L21-L24**,[54, 61-69] iodoarenes **3m-3p**,[50, 70-72] and bromopyridine **6e**[73] were prepared according to the reported literature procedures. The syntheses of pentafluoroethyl copper complexes **2b-2h** from CuOAc are described below. Complex **2b** has been previously reported.[18] The characterizations of **2c-2h** are reported below. All other ligands, reagents, and solvents were purchased from commercial sources and used as received.

Pentafluoroethyl products **4a-4h**[36, 52, 74] and **7a-7m**,[44] heptafluoropropyl product **5a**,[18] and trifluoromethyl products **9a-9c**, **9f**, **9g**, **9i-9p**[11, 37, 43, 50, 75-77] and **10k**, **10m**, **10n**[44] have been previously reported in the literature and the identity of these products was confirmed by comparison of the acquired ^{19}F NMR spectrum to the published data and by GC-mass spectrometry.

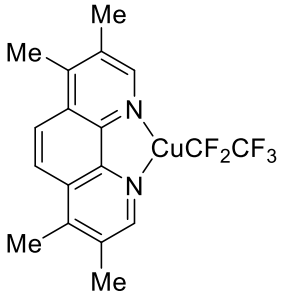
NMR spectra were acquired on 400 MHz, 500 MHz, or 600 MHz Bruker instruments at the University of California, Berkeley. NMR spectra were processed with MestReNova 5.0 (Mestrelab Research SL). Chemical shifts are reported in ppm and referenced to residual solvent peaks ($CHCl_3$ in $CDCl_3$: 7.26 ppm 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.

General Procedure for the Synthesis of Pentafluoroethylcopper Complexes

To an oven-dried, 20 mL vial equipped with a magnetic stir bar was added phenanthroline or 2,2'-bipyridine derivative (1.1 equiv) and toluene or THF (such that the concentration of the phen/bipy derivative is 0.15 M). To the rapidly stirring solution was added CuOAc (1.0 equiv). The vial was then sealed with a Teflon-lined cap, and the suspension was allowed to stir at room temperature for 45 min. Pentafluoroethyl trimethylsilane (1.2 equiv) was added dropwise to the stirring suspension, and then the solution was allowed to stir for 12 h at room temperature. The precipitated solids were removed from the solution by vacuum filtration through a medium fritted funnel. The solids were washed with Et_2O until the eluent was colorless, and then dried under vacuum to afford product as a pure solid. As has been previously reported for complexes **2a** and **2b**, pentafluoroethylcopper complexes **2c-2h** exist as a mixture of two equilibrating isomers: the neutral species $(L)CuCF_2CF_3$ and the ionic species $[(L)_2Cu][Cu(CF_2CF_3)_2]$.[18, 43] Due to this dynamic behavior, broad signals were obtained in the ^1H NMR spectrum of these compounds. Likewise, characterization of these compounds by ^{13}C NMR spectroscopy was complicated by (1) the dynamic behavior of these complexes; (2) broadening of resonances by Cu-C coupling; and (3) splitting of resonances by C-F coupling.

Preparation of (3,4,7,8-Tetramethyl-1,10-phenanthroline)(pentafluoroethyl)copper(I) (2c)

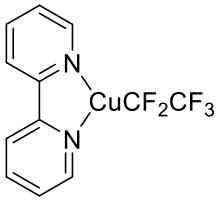


The reaction was performed according to the general procedure in THF on a 0.5 mmol scale. Product was obtained as a yellow-orange solid (199 mg, 95%). Two sets of ^{19}F NMR peaks for the pentafluoroethyl group were observed in a 50:50 ratio, reflecting a 67:33 ratio of the neutral to ionic form after correcting for the number of equivalent fluorine resonances in the ionic form.

^1H NMR (600 MHz, DMF-d7) δ 8.90 (s, 2H), 8.03 (s, 2H), 2.81 (s, 3H), 2.61 (s, 3H).

^{19}F NMR (376 MHz, DMF-d7) δ -82.7 (s, 3F major), -82.8 (s, 6F minor), -116.1 (s, 2F major). **Note**: The signal corresponding to the CF_2 of the minor ionic form was not detected. The corresponding peak in the analogous complex $(phen)CuCF_2CF_3$ was reported as a broad singlet with a poor signal-to-noise ratio at -110.0 ppm.[18]

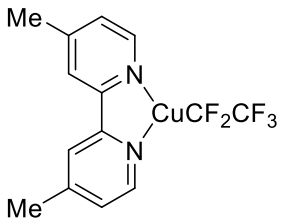
Preparation of (2,2'-bipyridine)(pentafluoroethyl)copper(I) (2d)



The reaction was performed according to the general procedure in PhMe on a 0.5 mmol scale. Product was obtained as an orange solid (167 mg, 96%). Two sets of ^{19}F NMR peaks for the pentafluoroethyl group were observed in a 60:40 ratio, reflecting a 75:25 ratio of the neutral to ionic form after correcting for the number of equivalent fluorine resonances in the ionic form.

^{1}H NMR (600 MHz, DMF-d7) δ 8.77 (s, 4H), 8.31 (s, 2H), 7.80 (s, 2H).
^{19}F NMR (376 MHz, DMF-d7) δ -82.8 (s, 3F, major), -82.9 (s, 6F minor), -108.6 (s, 4F minor), -116.1 (s, 3F, major).

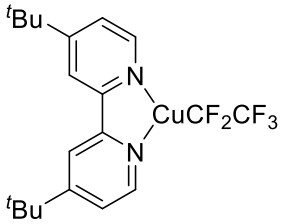
Preparation of (4,4′-di-methyl-2,2′-dipyridyl)(pentafluoroethyl)copper(I) (2e)



The reaction was performed according to the general procedure in THF on a 0.4 mmol scale. Product was obtained as an orange solid (109 mg, 74%). Two sets of ^{19}F NMR peaks for the pentafluoroethyl group were observed in a 57:43 ratio, reflecting a 73:27 ratio of the neutral to ionic form after correcting for the number of equivalent fluorine resonances in the ionic form.

^{1}H NMR (600 MHz, DMF-d7) δ 8.64 (s, 2H), 8.55 (s, 2H), 7.59 (s, 2H), 2.56 (s, 6H).
^{19}F NMR (376 MHz, DMF-d7) δ -82.8 (s, 3F major), -82.9 (s, 6F minor), -108.4 (s, 4F minor), -116.1 (s, 2F major).

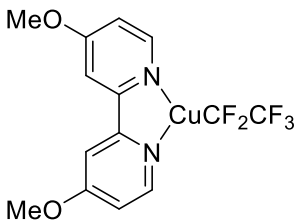
Preparation of (4,4′-di-tert-butyl-2,2′-dipyridyl)(pentafluoroethyl)copper(I) (2f)



The reaction was performed according to the general procedure in THF on a 0.4 mmol scale. Product was obtained as an orange solid (135 mg, 75%). Two sets of ^{19}F NMR peaks for the pentafluoroethyl group were observed in a 57:43 ratio, reflecting a 73:27 ratio of the neutral to ionic form after correcting for the number of equivalent fluorine resonances in the ionic form.

^{1}H NMR (600 MHz, DMF-d7) δ 9.02 – 8.38 (m, 4H), 7.77 (s, 2H), 1.46 (s, 18H).
^{19}F NMR (376 MHz, DMF-d7) δ -82.8 (s, 3F major), -82.9 (s, 6F minor), -108.4 (s, 4F minor), -116.1 (s, 2F major).

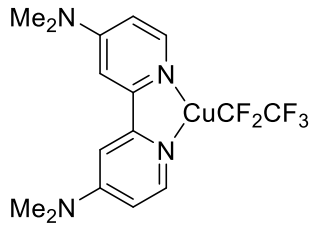
Preparation of (4-4′-dimethoxy-2-2′-bipyridine)(pentafluoroethyl)copper(I) (2g)



The reaction was performed according to the general procedure in PhMe on a 0.4 mmol scale. Product was obtained as a brown solid (144 mg, 90%). The reaction was also performed in THF on a 0.3 mmol scale. Product was obtained as a light orange solid (92 mg, 77%). Two sets of ^{19}F NMR peaks for the pentafluoroethyl group were observed in a 35:65 ratio, reflecting a 52:48 ratio of the neutral to ionic form after correcting for the number of equivalent fluorine resonances in the ionic form.

^{1}H NMR (600 MHz, DMF-d7) δ 8.57 (s, 2H), 8.30 (s, 2H), 7.34 (s, 2H), 4.11 (s, 6H).
^{19}F NMR (376 MHz, DMF-d7) δ -83.2 (s, 3F major), -83.3 (s, 6F minor), -108.6 (s, 4F minor), -116.5 (s, 2F major).

Preparation of (4,4'-Bis(*N*,*N*-dimethylamino)-2,2'-bipyridine)(pentafluoroethyl)copper(I) (2h)



The reaction was performed according to the general procedure in THF on a 0.3 mmol scale. Product was obtained as a tan solid (109 mg, 86%). One set of ^{19}F NMR peaks for the pentafluoroethyl group was observed corresponding to the ionic [((Me$_2$N)$_2$bipy)$_2$Cu][Cu(CF$_2$CF$_3$)] form of the complex.
^{1}H NMR (600 MHz, DMF-d7) δ 8.28 (d, J = 5.5 Hz, 2H), 7.64 (s, 2H), 6.86 (s, 2H), 3.20 (s, 12H).
^{19}F NMR (376 MHz, DMF-d7) δ -83.2 (s, 6F), -107.7 (s, 4F).

General Procedure for the Catalytic Pentafluoroethylation or Heptafluoropropylation of aryl iodides or heteroaryl bromides

To an oven-dried, 4 mL vial equipped with a magnetic stir bar was added either a combination of phen (0.02 mmol, 20 mol %) and CuTC (0.02 mmol, 20 mol %) or Me$_4$phen (0.01 mmol, 10 mol %) and CuTC (0.01 mmol, 10 mol %). DMF (100 μL) was then added, followed by a solution of aryl halide (0.1 mmol, 1.0 equiv) and **1b** or **1c** (0.15 mmol, 1.5 equiv) in additional DMF (100 μL). To the vial was added Zn(OAc)$_2$ (0.12 mmol, 1.2 equiv). The vial was then sealed with a Teflon-lined cap and heated at 80 ºC for 15 h. The solution was allowed to cool to room temperature. 4,4'-Difluorobenzophenone (0.1 mmol, 1.0 equiv) was added as an internal standard. The solution was diluted with 1 mL of EtOAc and then solids were removed by filtration through a short plug of silica. The eluent was transferred directly to an NMR tube for characterization by ^{19}F NMR spectroscopy.

General Procedure for the Catalytic Trifluoromethylation of aryl iodides or heteroaryl bromides

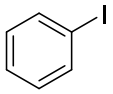
To an oven-dried, 4 mL vial equipped with a magnetic stir bar was added either **2a** (0.02 mmol, 20 mol %) or a combination of phen (0.02 mmol, 20 mol %) and CuTC (0.02 mmol, 20 mol %). DMF (100 μL) was then added, followed by a solution of aryl halide (0.1 mmol, 1.0 equiv) and **1d** (0.15 mmol, 1.5 equiv) in additional DMF (100 μL). To the vial was added db-18-cr-6 (0.06-0.12 mmol, 0.6-1.2 equiv for aryl iodides), followed by K$_3$PO$_4$ (0.12 mmol, 1.2 equiv for aryl iodides, 0.24 mmol, 2.4 equiv for heteroaryl bromides). The vial was then sealed with a Teflon-lined cap and heated at 50 ºC for 15 h. The solution was allowed to cool to room temperature. 4-Trifluoromethoxyanisole (0.1 mmol, 1.0 equiv) was added as an internal standard. The solution was diluted with 1 mL of EtOAc and then solids were removed by filtration through a short plug of silica. The eluent was transferred directly to an NMR tube for characterization by ^{19}F NMR spectroscopy.

Supporting Information for Calculations

DFT calculations were performed with the Gaussian 09 software package. B3LYP functionals (with gd3 dispersion correction), and LANL2DZ basis set for Cu, I, and Br, and 6-31g(d,p) basis set for all other atoms was applied for geometry optimizations. Cartesian coordinates and Gibbs energy are given.

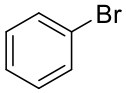
Iodobenzene

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.662288	-1.207147	0.000001
2	6	0	-1.265019	-1.215941	0.000000
3	6	0	-0.581792	-0.000020	-0.000004
4	6	0	-1.265009	1.215933	-0.000003
5	6	0	-2.662254	1.207167	0.000003
6	6	0	-3.362729	0.000006	0.000000
7	1	0	-3.199159	-2.151461	0.000006
8	1	0	-0.723170	-2.155021	-0.000003
9	1	0	-0.723115	2.154988	-0.000004
10	1	0	-3.199143	2.151471	0.000008
11	1	0	-4.448491	0.000035	-0.000003
12	53	0	1.567691	0.000000	0.000000



G^0 = -242.978882 Hartrees

Bromobenzene



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
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3	6	0	0.134258	0.000001	0.000000
4	6	0	0.807971	-1.218193	0.000001
5	6	0	2.205187	-1.208336	0.000002
6	6	0	2.904612	0.000000	0.000003
7	1	0	2.743129	2.151833	0.000003

8	1	0	0.256735	2.151612	0.000000
9	1	0	0.256732	-2.151611	0.000000
10	1	0	2.743128	-2.151833	0.000003
11	1	0	3.990312	-0.000001	0.000004
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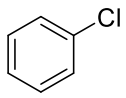
G^0 = -244.758653 Hartrees

Chlorobenzene



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.583527	1.208591	0.000002
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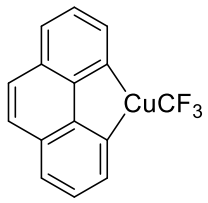
3	6	0	-0.485725	0.000000	-0.000001
4	6	0	0.186934	-1.217932	0.000000
5	6	0	1.583526	-1.208591	0.000002
6	6	0	2.283047	0.000000	0.000002
7	1	0	2.121720	2.151800	0.000002
8	1	0	-0.370768	2.147490	0.000000
9	1	0	-0.370768	-2.147490	0.000000
10	1	0	2.121720	-2.151800	0.000003
11	1	0	3.368688	0.000000	0.000004
12	17	0	-2.288239	0.000000	-0.000002

G^0 = -246.540815 Hartrees

(phen)$CuCF_3$



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.222454	2.670247	-0.010479
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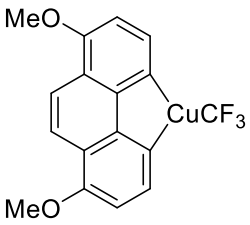
3	6	0	2.622624	2.835292	0.002547
4	6	0	2.687420	1.423385	0.003411
5	6	0	3.917524	0.681979	0.010333

6	1	0	4.853835	1.232714	0.015615
7	6	0	3.917544	-0.681887	0.010334
8	1	0	4.853871	-1.232594	0.015616
9	6	0	2.687462	-1.423330	0.003411
10	6	0	2.622709	-2.835238	0.002548
11	6	0	1.390312	-3.459480	-0.004631
12	6	0	0.222535	-2.670267	-0.010480
13	6	0	1.456993	-0.721942	-0.003001
14	6	0	1.456972	0.721961	-0.003001
15	7	0	0.253123	1.343205	-0.009544
16	7	0	0.253162	-1.343224	-0.009545
17	1	0	1.307237	4.540913	-0.005742
18	1	0	1.307374	-4.540900	-0.005741
19	29	0	-1.444642	-0.000050	-0.006787
20	1	0	3.542049	-3.414381	0.007419
21	1	0	-0.764926	-3.122412	-0.016527
22	1	0	-0.765022	3.122359	-0.016526
23	1	0	3.541946	3.414463	0.007417
24	6	0	-3.380677	-0.000009	0.003248
25	9	0	-3.932838	-0.000223	1.273097
26	9	0	-3.967452	1.091162	-0.617947
27	9	0	-3.967512	-1.090918	-0.618344

G^0 = -1105.314056 Hartrees

((MeO)$_2$phen)CuCF$_3$



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
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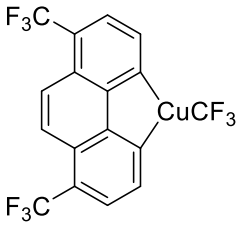
3	6	0	1.974058	2.841834	-0.000328
4	6	0	2.035439	1.415299	-0.000030
5	6	0	3.265206	0.683341	0.005360
6	1	0	4.196323	1.237593	0.009493
7	6	0	3.265254	-0.683131	0.005360
8	1	0	4.196411	-1.237316	0.009493
9	6	0	2.035539	-1.415177	-0.000030
10	6	0	1.974263	-2.841716	-0.000327

11	6	0	0.731266	-3.462047	-0.006071
12	6	0	-0.425509	-2.662675	-0.010859
13	6	0	0.805665	-0.721748	-0.005209
14	6	0	0.805614	0.721781	-0.005210
15	7	0	-0.405292	1.337352	-0.010348
16	7	0	-0.405198	-1.337407	-0.010347
17	1	0	0.626820	4.539159	-0.006861
18	1	0	0.627148	-4.539140	-0.006859
19	29	0	-2.099423	-0.000110	-0.007330
20	1	0	-1.409761	-3.122325	-0.015687
21	1	0	-1.409988	3.122195	-0.015690
22	6	0	-4.035344	-0.000093	0.004030
23	9	0	-4.589086	-0.000313	1.274539
24	9	0	-4.625998	1.091022	-0.616467
25	9	0	-4.626035	-1.090956	-0.616866
26	8	0	3.162179	-3.478827	0.005131
27	8	0	3.161928	3.479031	0.005131
28	6	0	3.174672	-4.906225	0.006106
29	1	0	4.226082	-5.193602	0.011391
30	1	0	2.681008	-5.305941	0.899609
31	1	0	2.689703	-5.307154	-0.891606
32	6	0	3.174317	4.906430	0.006107
33	1	0	2.680625	5.306110	0.899611
34	1	0	4.225707	5.193883	0.011391
35	1	0	2.689318	5.307324	-0.891604

G^0 = -1334.322158 Hartrees

((CF$_3$)$_2$phen)CuCF$_3$



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
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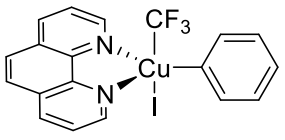
4	6	0	1.467338	1.429120	-0.001658
5	6	0	2.694416	0.682063	0.005621
6	1	0	3.636315	1.215332	0.011139
7	6	0	2.694475	-0.681852	0.005621

8	1	0	3.636421	-1.215039	0.011139
9	6	0	1.467463	-1.429017	-0.001658
10	6	0	1.379653	-2.847807	-0.003221
11	6	0	0.140809	-3.456205	-0.010654
12	6	0	-1.018255	-2.656278	-0.015880
13	6	0	0.240148	-0.722777	-0.007821
14	6	0	0.240085	0.722772	-0.007821
15	7	0	-0.970390	1.332364	-0.014301
16	7	0	-0.970275	-1.332477	-0.014300
17	1	0	0.055976	4.535748	-0.012232
18	1	0	0.056377	-4.535770	-0.012230
19	29	0	-2.673219	-0.000159	-0.008519
20	1	0	-2.009040	-3.100157	-0.021821
21	1	0	-2.009316	3.099947	-0.021826
22	6	0	-4.607363	-0.000137	0.007166
23	9	0	-5.152379	-0.000356	1.278458
24	9	0	-5.192262	1.091176	-0.612412
25	9	0	-5.192312	-1.091189	-0.612814
26	6	0	2.636370	-3.688455	0.003724
27	6	0	2.636044	3.688663	0.003725
28	9	0	2.364597	-5.005082	0.000193
29	9	0	3.386835	-3.424623	1.096276
30	9	0	3.401218	-3.421882	-1.078154
31	9	0	2.364153	5.005265	0.000196
32	9	0	3.386534	3.424895	1.096276
33	9	0	3.400915	3.422160	-1.078155

G^0 = -1779.380447 Hartrees

Oxidative Addition Complex of PhI to (phen)CuCF$_3$



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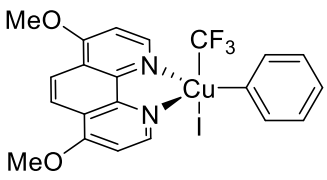
2	6	0	2.239501	0.881979	3.353231
3	6	0	3.466245	0.674697	2.752460
4	6	0	3.526196	0.409081	1.366719
5	6	0	4.752242	0.179600	0.655254
6	1	0	5.685974	0.213510	1.209261

7	6	0	4.750810	-0.078214	-0.683324
8	1	0	5.683385	-0.252759	-1.212246
9	6	0	3.523186	-0.129038	-1.426582
10	6	0	3.460255	-0.396929	-2.811723
11	6	0	2.232089	-0.426998	-3.443944
12	6	0	1.069673	-0.191560	-2.686151
13	6	0	2.295812	0.096237	-0.755083
14	6	0	2.297336	0.369520	0.662058
15	7	0	1.104455	0.571312	1.263495
16	7	0	1.101385	0.059081	-1.385559
17	1	0	2.159435	1.086338	4.415300
18	1	0	2.149718	-0.631037	-4.505899
19	29	0	-0.660547	0.277414	-0.051695
20	1	0	4.377577	-0.577990	-3.365039
21	1	0	0.086766	-0.212677	-3.146666
22	1	0	0.093556	0.972762	3.001877
23	1	0	4.384798	0.711542	3.331539
24	6	0	-0.936865	2.251442	-0.429396
25	9	0	-2.134224	2.848207	-0.550177
26	9	0	-0.279258	2.916875	0.561081
27	9	0	-0.267386	2.506392	-1.588328
28	6	0	-2.591621	0.267586	-0.051845
29	6	0	-3.264773	0.474887	1.144631
30	6	0	-3.261279	0.016761	-1.241879
31	6	0	-4.661601	0.399676	1.150557
32	1	0	-2.722657	0.675763	2.062554
33	6	0	-4.658071	-0.056324	-1.223569
34	1	0	-2.716208	-0.136246	-2.167254
35	6	0	-5.357466	0.133993	-0.030324
36	1	0	-5.200740	0.548115	2.082407
37	1	0	-5.194407	-0.264006	-2.145670
38	1	0	-6.442078	0.077984	-0.021213
39	53	0	-0.646137	-2.326323	0.449393

G^0 = -1348.276640 Hartrees

Oxidative Addition Complex of PhI to ((MeO)$_2$phen)CuCF$_3$



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
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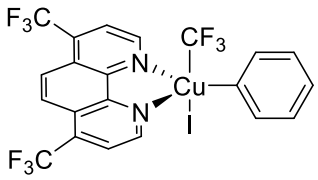
4	6	0	-2.933714	1.670407	-0.440332
5	6	0	-4.246367	1.106174	-0.368817
6	1	0	-5.099143	1.770789	-0.441200
7	6	0	-4.420323	-0.238385	-0.208495
8	1	0	-5.413848	-0.667292	-0.155019
9	6	0	-3.293128	-1.111137	-0.085049
10	6	0	-3.424710	-2.516379	0.122237
11	6	0	-2.278848	-3.289396	0.260398
12	6	0	-1.028835	-2.654564	0.203518
13	6	0	-1.982063	-0.585173	-0.147965
14	6	0	-1.796580	0.832457	-0.362089
15	7	0	-0.523762	1.293162	-0.455063
16	7	0	-0.870576	-1.353307	0.008700
17	1	0	-1.156678	4.586941	-0.704831
18	1	0	-2.320899	-4.358662	0.420802
19	29	0	0.953933	-0.297700	0.314365
20	1	0	-0.113588	-3.228598	0.320249
21	1	0	0.689903	2.934492	-0.587489
22	6	0	1.011044	0.469176	2.170423
23	9	0	1.270387	1.831377	2.134805
24	9	0	-0.204514	0.371963	2.824166
25	9	0	1.933893	-0.026040	3.071523
26	6	0	2.905009	0.262565	-0.278554
27	6	0	2.740027	1.236610	-1.268457
28	6	0	3.821531	0.422730	0.765469
29	6	0	3.434622	2.444604	-1.141721
30	1	0	2.063877	1.065670	-2.097614
31	6	0	4.503885	1.630592	0.868455
32	1	0	3.925853	-0.345418	1.520028
33	6	0	4.314699	2.644570	-0.078871
34	1	0	3.296656	3.216650	-1.894479
35	1	0	5.179312	1.785424	1.704963
36	1	0	4.861877	3.578342	0.007792

37	53	0	2.578745	-1.978297	-1.109110
38	8	0	-3.803466	3.846262	-0.652426
39	8	0	-4.688667	-2.987116	0.169880
40	6	0	-3.637428	5.258011	-0.760251
41	1	0	-4.644438	5.674409	-0.795533
42	1	0	-3.104278	5.662418	0.108349
43	1	0	-3.098788	5.526070	-1.677242
44	6	0	-4.890439	-4.381505	0.391234
45	1	0	-4.472284	-4.694628	1.355199
46	1	0	-5.970710	-4.527967	0.398076
47	1	0	-4.445365	-4.979391	-0.413049

G^0 = -1577.272673 Hartrees

Oxidative Addition Complex of PhI to ((CF$_3$)$_2$phen)CuCF$_3$



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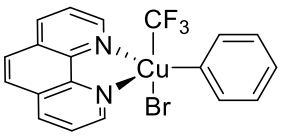
3	6	0	-2.230506	2.948782	-0.502567
4	6	0	-2.443952	1.549480	-0.392678
5	6	0	-3.733836	0.936199	-0.244725
6	1	0	-4.616453	1.562331	-0.230754
7	6	0	-3.866126	-0.413687	-0.119074
8	1	0	-4.852279	-0.845827	-0.011169
9	6	0	-2.718212	-1.276474	-0.103792
10	6	0	-2.778153	-2.684717	0.065212
11	6	0	-1.609726	-3.421781	0.095793
12	6	0	-0.380715	-2.754810	-0.024244
13	6	0	-1.428476	-0.703363	-0.246719
14	6	0	-1.290231	0.725138	-0.430199
15	7	0	-0.038757	1.213840	-0.605864
16	7	0	-0.291455	-1.441868	-0.187930
17	1	0	-0.758970	4.498932	-0.693990
18	1	0	-1.635946	-4.496845	0.222403
19	29	0	1.481728	-0.335264	0.182846
20	1	0	0.561528	-3.293808	0.016968
21	1	0	1.151158	2.873125	-0.771917

22	6	0	1.192994	0.408854	2.037588
23	9	0	1.437352	1.769244	2.086271
24	9	0	-0.121649	0.282366	2.457769
25	9	0	1.946801	-0.114513	3.062986
26	6	0	3.433680	0.357774	-0.131817
27	6	0	3.365689	1.351933	-1.112422
28	6	0	4.189433	0.516854	1.033007
29	6	0	3.992021	2.578418	-0.863493
30	1	0	2.821378	1.178726	-2.033422
31	6	0	4.805104	1.744629	1.257022
32	1	0	4.221961	-0.269605	1.775650
33	6	0	4.709219	2.776830	0.315728
34	1	0	3.932464	3.365824	-1.610316
35	1	0	5.353564	1.899193	2.181610
36	1	0	5.204061	3.725604	0.498623
37	53	0	3.294361	-1.879978	-1.068638
38	6	0	-4.112286	-3.377606	0.217431
39	6	0	-3.400054	3.904137	-0.472382
40	9	0	-4.900283	-3.158226	-0.860088
41	9	0	-4.781556	-2.916373	1.297023
42	9	0	-3.978466	-4.709308	0.358741
43	9	0	-4.266281	3.644833	-1.479921
44	9	0	-4.094520	3.793473	0.681482
45	9	0	-3.010247	5.186832	-0.592979

G^0 = -2022.333264 Hartrees

Oxidative Addition Complex of PhBr to (phen)CuCF$_3$



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
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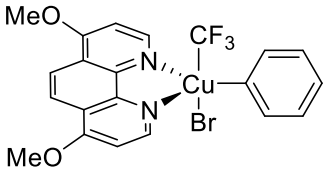
5	6	0	-4.521294	1.406496	-0.432335
6	1	0	-5.315046	2.142857	-0.522524
7	6	0	-4.815080	0.101205	-0.174148
8	1	0	-5.846111	-0.221085	-0.059387

9	6	0	-3.773071	-0.875491	-0.026186
10	6	0	-4.022954	-2.232460	0.273589
11	6	0	-2.962143	-3.105328	0.425759
12	6	0	-1.652658	-2.610081	0.298084
13	6	0	-2.418981	-0.476347	-0.167420
14	6	0	-2.108558	0.897745	-0.494282
15	7	0	-0.809466	1.229310	-0.677977
16	7	0	-1.389068	-1.339098	0.017088
17	1	0	-1.161246	4.544167	-1.151042
18	1	0	-3.121943	-4.153782	0.652815
19	29	0	0.537574	-0.462315	0.220261
20	1	0	-5.048019	-2.575278	0.384936
21	1	0	-0.786417	-3.253287	0.426437
22	1	0	0.557720	2.721430	-0.985034
23	1	0	-3.581316	3.941192	-0.921956
24	6	0	0.686390	0.545678	1.939545
25	9	0	1.118875	1.843024	1.727130
26	9	0	-0.538128	0.688676	2.566343
27	9	0	1.530300	0.056439	2.911305
28	6	0	2.520594	-0.165269	-0.412852
29	6	0	2.469361	0.761945	-1.453972
30	6	0	3.489201	-0.120007	0.589400
31	6	0	3.349019	1.848864	-1.410826
32	1	0	1.743869	0.651698	-2.251053
33	6	0	4.355822	0.969615	0.606230
34	1	0	3.503799	-0.867057	1.371840
35	6	0	4.288876	1.955894	-0.385616
36	1	0	3.306791	2.596536	-2.198556
37	1	0	5.082449	1.052623	1.409322
38	1	0	4.978069	2.794336	-0.364279
39	35	0	1.851853	-2.234247	-1.076056

G^0 = -1350.043378 Hartrees

Oxidative Addition Complex of PhBr to ((MeO)$_2$phen)CuCF$_3$



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
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3	6	0	-2.127767	3.264563	-0.416769
4	6	0	-2.542441	1.901765	-0.338814
5	6	0	-3.915593	1.511145	-0.245171
6	1	0	-4.674461	2.284685	-0.250767
7	6	0	-4.262028	0.193918	-0.149446
8	1	0	-5.301774	-0.103162	-0.081731
9	6	0	-3.257545	-0.824678	-0.112797
10	6	0	-3.566809	-2.210618	0.026442
11	6	0	-2.529729	-3.133543	0.080529
12	6	0	-1.208669	-2.664241	0.016063
13	6	0	-1.891098	-0.471568	-0.194175
14	6	0	-1.525126	0.918953	-0.348104
15	7	0	-0.206651	1.211855	-0.474508
16	7	0	-0.887155	-1.384990	-0.111045
17	1	0	-0.401654	4.568907	-0.535796
18	1	0	-2.708519	-4.195645	0.184242
19	29	0	1.069244	-0.607370	0.194355
20	1	0	-0.373074	-3.356969	0.070650
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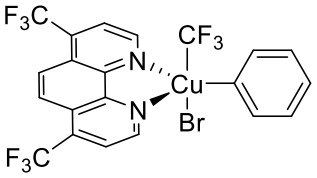
22	6	0	1.314046	0.122896	2.039432
23	9	0	1.773124	1.429557	2.003892
24	9	0	0.117829	0.198480	2.729625
25	9	0	2.179135	-0.518695	2.900331
26	6	0	3.049960	-0.315994	-0.459521
27	6	0	3.000445	0.714633	-1.399560
28	6	0	4.045039	-0.395778	0.515149
29	6	0	3.909201	1.770232	-1.269228
30	1	0	2.252197	0.704177	-2.182858
31	6	0	4.940652	0.664669	0.619523
32	1	0	4.057317	-1.217512	1.218599
33	6	0	4.876419	1.749214	-0.264330
34	1	0	3.867567	2.595248	-1.975738
35	1	0	5.688592	0.647348	1.407063
36	1	0	5.588549	2.563963	-0.176749
37	35	0	2.317380	-2.282429	-1.312485
38	8	0	-4.879711	-2.514171	0.098616
39	8	0	-3.119505	4.181827	-0.401277
40	6	0	-5.257534	-3.879260	0.265601
41	1	0	-4.851971	-4.291561	1.197151
42	1	0	-6.346808	-3.882715	0.309712

43	1	0	-4.924003	-4.490460	-0.581522
44	6	0	-2.769771	5.563258	-0.441363
45	1	0	-3.712434	6.110072	-0.408086
46	1	0	-2.154175	5.841739	0.422237
47	1	0	-2.235665	5.811506	-1.366533

G^0 = -1579.050261 Hartrees

Oxidative Addition Complex of PhBr to ($(CF_3)_2$phen)CuCF_3



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
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7	6	0	-3.726810	-0.081411	-0.077052
8	1	0	-4.755841	-0.399223	0.027367
9	6	0	-2.688148	-1.072609	-0.103316
10	6	0	-2.910703	-2.470181	0.013961
11	6	0	-1.836631	-3.339276	0.002716
12	6	0	-0.538069	-2.815647	-0.102523
13	6	0	-1.341232	-0.649091	-0.238678
14	6	0	-1.037777	0.758629	-0.383727
15	7	0	0.259086	1.101013	-0.570767
16	7	0	-0.298515	-1.516404	-0.213778
17	1	0	-0.068799	4.448941	-0.563445
18	1	0	-1.988586	-4.408054	0.086604
19	29	0	1.619141	-0.666127	0.113572
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21	1	0	1.635613	2.610647	-0.718184
22	6	0	1.644904	0.121205	1.953704
23	9	0	2.087774	1.430389	1.939486
24	9	0	0.378063	0.190482	2.505331
25	9	0	2.419652	-0.497470	2.905301
26	6	0	3.616496	-0.265296	-0.365863

27	6	0	3.622003	0.785279	-1.283337
28	6	0	4.523205	-0.352576	0.689199
29	6	0	4.493370	1.855143	-1.050505
30	1	0	2.949454	0.775740	-2.132810
31	6	0	5.382188	0.723816	0.895837
32	1	0	4.494899	-1.193025	1.369976
33	6	0	5.369316	1.827968	0.034778
34	1	0	4.496605	2.695852	-1.739210
35	1	0	6.059364	0.702282	1.744726
36	1	0	6.052168	2.654760	0.203200
37	35	0	2.989472	-2.238953	-1.334811
38	6	0	-4.315655	-3.008716	0.156442
39	6	0	-2.759686	4.161635	-0.312522
40	9	0	-5.082850	-2.654285	-0.899616
41	9	0	-4.915281	-2.516887	1.263134
42	9	0	-4.337011	-4.351555	0.242368
43	9	0	-2.225843	5.393063	-0.409883
44	9	0	-3.665755	4.029562	-1.309627
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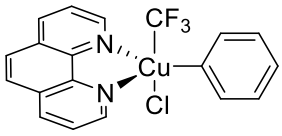
G^0 = -2024.110043 Hartrees

Oxidative Addition Complex of PhCl to (phen)CuCF$_3$



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
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5	6	0	-4.242354	1.657810	-0.124339
6	1	0	-4.964759	2.466512	-0.057130
7	6	0	-4.648374	0.359592	-0.043136
8	1	0	-5.699167	0.115956	0.085505
9	6	0	-3.699335	-0.716229	-0.103466
10	6	0	-4.064062	-2.076007	0.006565
11	6	0	-3.086353	-3.052223	-0.035122
12	6	0	-1.742056	-2.660132	-0.162478
13	6	0	-2.321167	-0.421218	-0.263815

14	6	0	-1.895069	0.953864	-0.406728
15	7	0	-0.580746	1.193796	-0.622104
16	7	0	-1.371818	-1.389137	-0.266199
17	1	0	-0.636470	4.560434	-0.595412
18	1	0	-3.335991	-4.104823	0.042593
19	29	0	0.634317	-0.725947	-0.013753
20	1	0	-5.111204	-2.340204	0.126508
21	1	0	-0.935558	-3.388150	-0.178872
22	1	0	0.905550	2.590098	-0.800828
23	1	0	-3.088415	4.144440	-0.300386
24	6	0	0.882696	0.023749	1.816105
25	9	0	1.436763	1.288619	1.780352
26	9	0	-0.325785	0.193222	2.467255
27	9	0	1.671428	-0.675680	2.699432
28	6	0	2.622325	-0.516762	-0.631931
29	6	0	2.676474	0.557675	-1.517066
30	6	0	3.608084	-0.775688	0.316699
31	6	0	3.699784	1.494712	-1.340863
32	1	0	1.926287	0.667804	-2.290790
33	6	0	4.618018	0.172016	0.466469
34	1	0	3.536221	-1.639399	0.964268
35	6	0	4.666676	1.307067	-0.352382
36	1	0	3.746417	2.358455	-1.998837
37	1	0	5.368359	0.024074	1.237806
38	1	0	5.466642	2.030383	-0.229547
39	17	0	1.719686	-2.238653	-1.545212

G^0 = -1351.819201

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Chapter 4

Pd-Catalyzed α-Arylation of α,α-Difluoroacetophenone with Aryl Sulfonates: A Route to Difluoromethylarenes from Phenols

4.1 Introduction

Aromatic compounds bearing fluorine or fluorine-containing substituents are common structures in medicinal chemistry and agrochemistry.[1-5] Fluorination will often alter the physical and biological properties of a compound, such as improving metabolic stability, increasing lipophilicity, and altering the non-covalent interactions of the molecule. Although many methods have been reported to install fluorine or trifluoromethyl groups onto aromatic rings, fewer examples of the introduction of partially fluorinated moieties have been reported.[6-7]

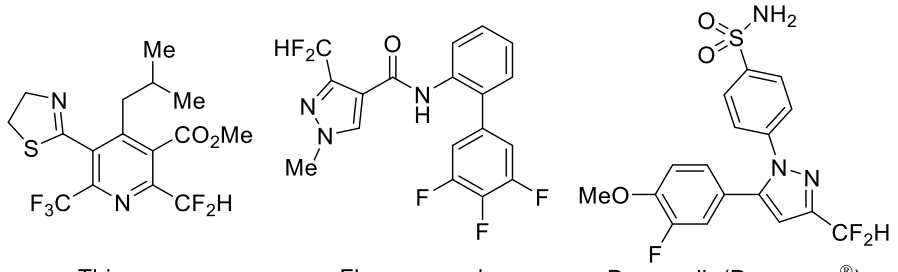


Figure 4.1 Bioactive compounds containing difluoromethyl substituted (hetero)arenes

The difluoromethyl group is a particularly desirable moiety.[8] Figure 4.1 shows various biologically active compounds that possess difluoromethyl groups. In addition to imparting properties characteristic of fluorinated compounds, the polarization of the CF_2-H bond in a difluoromethyl group renders these substituents weak hydrogen-bond donors.[9] The ability of difluoromethylarenes to engage in hydrogen-bonding interactions can alter the conformation of these compounds and impact their ability to interact with biological targets. The higher activity of a difluoromethyl-containing pyrazole carboxamide fungicide over its trifluoromethyl-containing structural analogue has been attributed to a weak CF_2H---O hydrogen-bond (Figure 4.2).

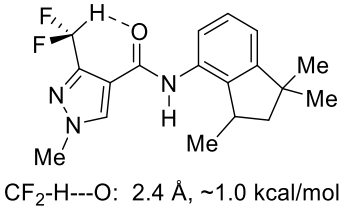


Figure 4.2 Intramolecular hydrogen-bonding interactions in a difluoromethyl-containing fungicide

Because the difluoromethyl group is able to engage in hydrogen-bonding interactions, difluoromethylarenes are often proposed to be lipophilic bioisosteres of phenols.[10-11] Phenols are a structural motif found in many important drug compounds (Figure 4.3). Substitution of a phenolic hydroxyl group with a difluoromethyl group could result in drugs that possess similar capabilities for non-covalent binding interactions, while improving the ability of these compounds to permeate cell membranes. In addition, difluoromethylarenes are less prone to decomposition

pathways common to phenols, including phosphorylation and oxidatiation. As such, the ability to convert phenols readily to the related $ArCF_2H$ compounds would be a valuable tool for studies of structure-activity relationships and the discovery of new pharmaceuticals and agrochemicals.

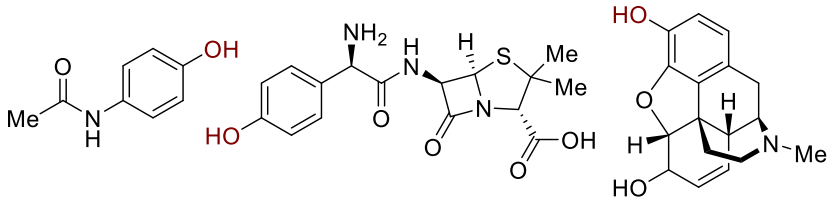


Figure 4.3 Phenol-containing compounds with bioactive properties

Simple difluoromethylarenes are prepared by the deoxyfluorination of benzaldehyde derivatives with toxic and thermally unstable sulfur(IV) fluoride reagents (Figure 4.4, a).[12-13] The most commonly employed deoxyfluorination reagents are diethylaminosulfur trifluoride (DAST) or its more thermally-stable variant, bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor). These reagents release hazardous HF upon exposure to moisture. In addition, the harsh reaction conditions required for these reactions limit the ability to convert functionalized benzaldehyde derivatives to more complex difluoromethylarene products.

To prepare difluoromethylarenes under milder reaction conditions, transition metal-mediated processes have been developed for the difluoromethylation of functionalized arenes. A few routes have been reported to prepare difluoromethylarenes from aryl nucleophiles, such as aryl boronic acids[14-16] or electron-rich (hetero)arenes,[17] but most of the procedures for difluoromethylation involve coupling of a nucleophilic source of CF_2H with aryl halides or pseudo-halide electrophiles. Amii reported a Cu-mediated reaction of aryl iodides with ethyl α-trimethylsilyl-α,α-difluoroacetate to generate α-aryl-α,α-difluoroesters, which can then be hydrolyzed to the corresponding acid and then decarboxylated to form difluoromethylarenes (Figure 4.4, b).[18] While this example was the first process to prepare difluoromethylarenes by a C-C bond forming reaction, the decarboxylation step occurred only with fluorinated carboxylic acids bearing electron deficient arenes.

Direct difluoromethylation of aryl halides catalyzed or mediated by transition-metal complexes have been achieved with difluoromethylsilicon or difluoromethyltin reagents (Figure 4.4, c). Early reports of this class of reactions involve the copper-mediated coupling of aryl iodides with Me_3SiCF_2H, or the related Bu_4SnCF_2H reagent.[19-21] Shen reported a Pd-catalyzed reaction of more accessible aryl bromide starting materials with Me_3SiCF_2H.[22-24] Although this procedure offers a route to diverse difluoromethylarenes, broad application of this procedure is limited by the strongly basic conditions (NaO^tBu) and the necessity of an expensive *N*-heterocyclic carbene-ligated Ag(I) co-catalyst. Recently, $(L)Zn(CF_2H)_2$ reagents have been developed that allow for difluoromethylation of aryl iodide, aryl bromides, or activated aryl trifluoromethanesulfonates

(Figure 4.4, d).[25-27] While these reagents allow for reactions to occur under neutral conditions, they are typically prepared from the expensive and difficult-to-handle gaseous reagent HCF_2I.

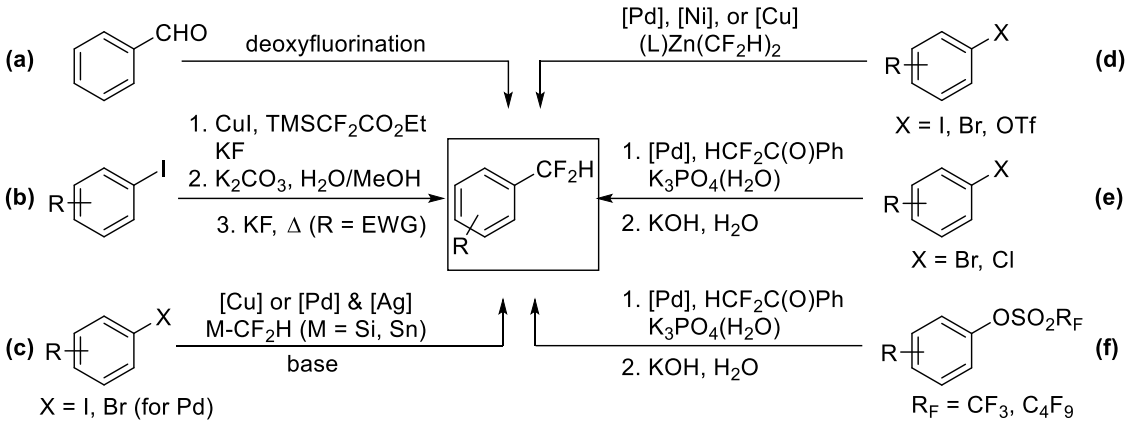


Figure 4.4 Common synthetic routes to prepare difluoromethylarenes (**a-e**) and this work (**f**)

Our group reported a two-step, one-pot procedure to prepare difluoromethylarenes from readily available, inexpensive aryl chloride or aryl bromide starting materials (Figure 4.4, e).[28] This strategy involves a Pd-catalyzed α-arylation reaction of α,α-difluoroacetophenone that proceeds under mildly basic conditions to furnish α-aryl-α,α-difluoroketones. The fluorinated ketones underwent hydroxide-induced Haller-Bauer cleavage of the benzoyl moiety to afford either electron-rich or electron-deficient difluoromethylarene products.

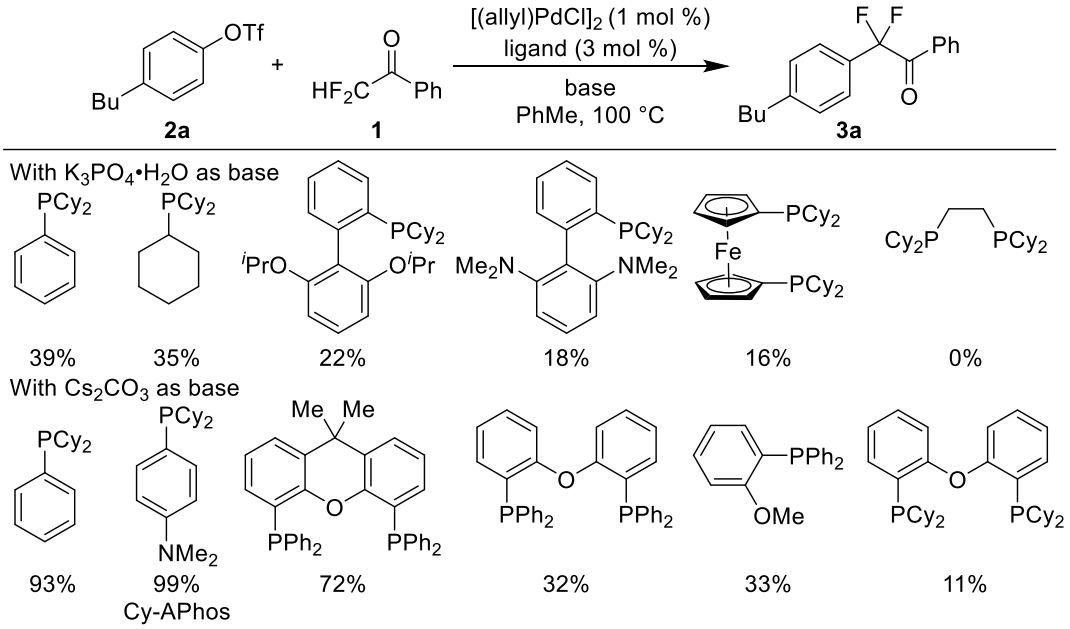
Due to the wide scope of the Pd-catalyzed α-arylation reaction and the inexpensive and readily-available reagents, we considered expanding the reactivity of this system to include aryl sulfonate derivatives as electrophiles (Figure 4.4, f). Because aryl sulfonates are prepared from phenols, such a coupling could convert phenol to the corresponding difluoromethylarenes. By employing an appropriate phosphine ligand, we were able to achieve Pd-catalyzed α-arylation reaction of α,α-difluoroacetophenones with readily prepared aryl trifluoromethanesulfonates (ArOTf; triflates) and the more stable variants, aryl nonafluorobutane-sulfonates (ArONf; nonaflates).

4.2 Results and Discussion

Due to their high reactivity and ease of preparation, aryl triflates were chosen initially as the aryl sulfonate electrophile for developing the coupling of difluoroacetophenone (**1**) with an aryl sulfonate. Initial investigations were conducted under reaction conditions that were similar to those previously reported for the related reaction of aryl chlorides and aryl bromides (Table 4.1). The combination of $[(allyl)PdCl]_2$ and a series of monophosphine and bisphosphine ligands were evaluated as catalysts for the reaction with $K_3PO_4 \cdot H_2O$ as base. Catalysts ligated by PCy_3 or PCy_2Ph furnished the desired α-aryl-α,α-difluoroketone product. However, the product was obtained in low yield from reactions in which $K_3PO_4 \cdot H_2O$ was employed as base. By substituting

this base for the equally mild Cs_2CO_3, the desired product was obtained in high yield with a catalyst consisting of PCy_2Ph or the more electron-rich 4-dimethylaminophenyl variant of this ligand, Cy-APhos.

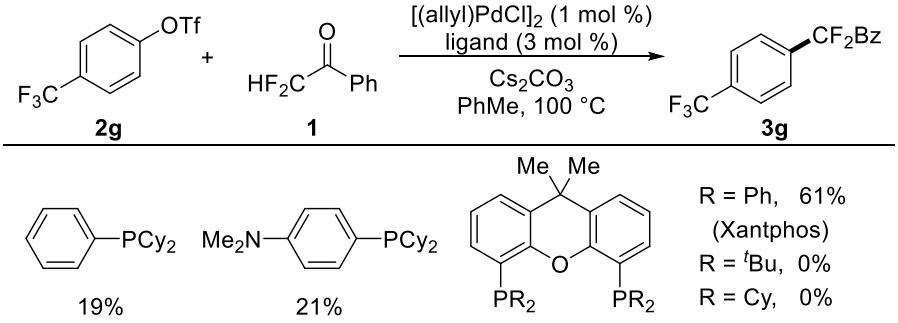
Table 4.1 Initial evaluation of ligands for the α-arylation reaction with an electron-neutral aryl triflate.[a]



[a] Yields were determined by ^{19}F NMR spectroscopy.

Although complexes containing Cy-APhos catalyzed the coupling of electron-neutral or electron-rich aryl triflates, low yields (~5-20%) of products were obtained for reactions of electron-deficient aryl triflates. Aryl triflates bearing electron-withdrawing substituents are more likely to undergo hydrolysis to the corresponding phenol than aryl triflates with electron-donating groups. Indeed, 4-trifluoromethyl phenol formed during the coupling of **1** with 4-trifluoromethylphenyl triflate catalyzed by a Pd-complex with Cy-Aphos as ligand. The decomposition of these compounds could be a potential cause for the observed low conversion to product.

Table 4.2 Initial ligand evaluation for the α-arylation reaction with an electron-poor aryl triflate.[a]

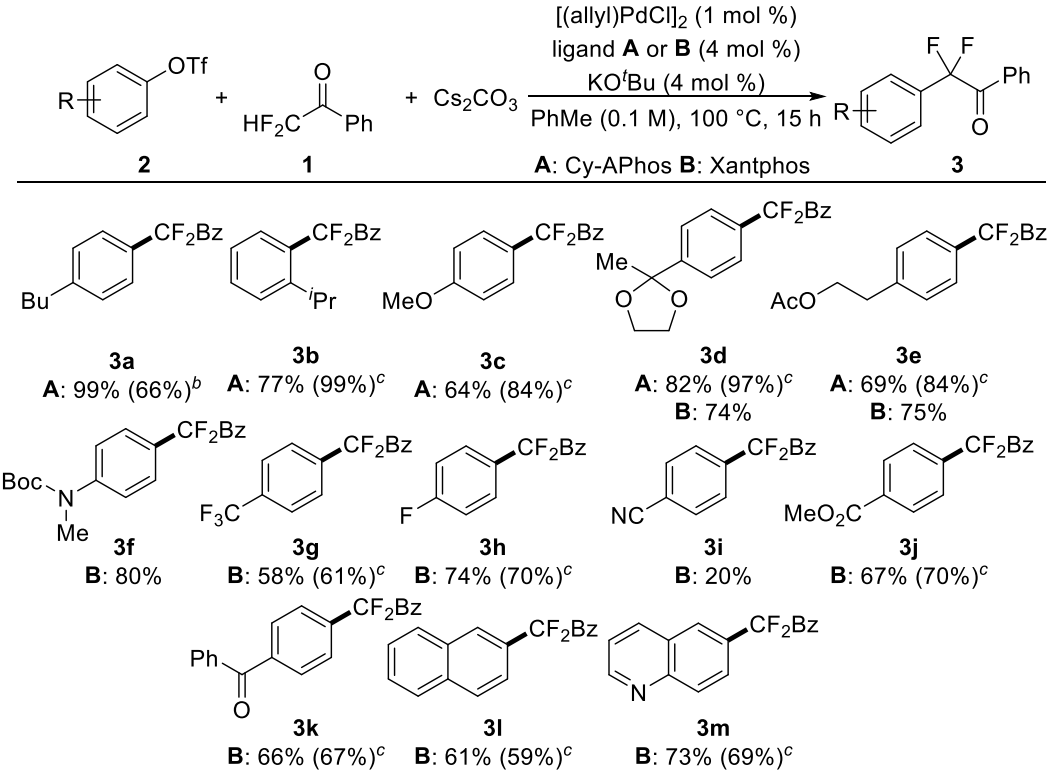


[a] Yields were determined by ^{19}F NMR spectroscopy.

Higher yields of products from the reactions of electron-poor aryl triflates were obtained by changing the ligand on the catalyst to Xantphos (Table 4.2). Because oxidative addition of electron-deficient aryl triflates to Pd^0 would be expected to be faster than oxidative addition of electron-rich aryl triflates, it is likely that a higher concentration of potentially unstable cationic Pd^{II} species exist in solution during reactions with electron-poor ArOTf. The higher yields of products from reactions of electron-poor aryl triflates when Xantphos is employed as ligand could result from the ability of this chelating ligand to better stabilize cationic Pd-intermediates. In addition, this bulky, wide bite-angle ligand could also accelerate the C-C bond-forming reductive elimination reaction and regenerate active Pd^0.

With the discovery of one system that catalyzes the coupling of **1** with electron-rich ArOTf or electron-neutral ArOTf and one that catalyzes the coupling of electron-deficient ArOTf, we explored the scope of the reaction (Table 4.3). Addition of a catalytic quantity of potassium *tert*-butoxide improved the yields of products. Because a preformed palladium complex was employed for the analogous α-arylation reaction of aryl bromides and aryl chlorides, a preformed complex, $(Cy\text{-}APhos)_2PdCl_2$, was evaluated as a precatalyst for the reaction of **2a**, but the reaction catalyzed by this dichloride complex resulted in formation of **3a** in only modest yield (66%).

Table 4.3 Pd-catalyzed α-arylation of **1** with ArOTf.[a]

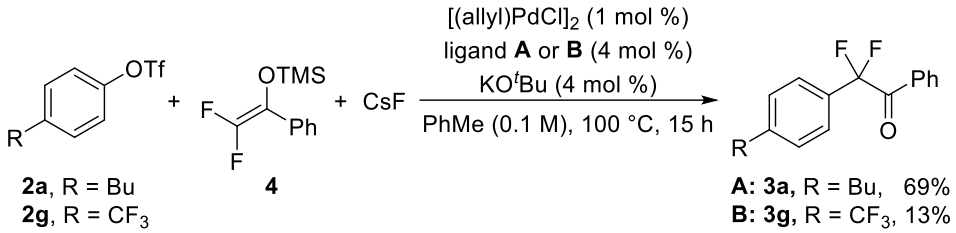


[a] Yields were determined by ^{19}F NMR spectroscopy. [b] Reaction was conducted with 2 mol % $(Cy\text{-}APhos)_2PdCl_2$ as a preformed complex instead of $[(allyl)PdCl]_2$ and Cy-APhos. [c] Reaction was run with 2 mol % of $[(allyl)PdCl]_2$, 8 mol % of ligand, and 8 mol % of KO^{t}Bu.

Aryl triflates with large *ortho*-substituents underwent the coupling reaction in good yield (**3b)**. Although aryl triflates bearing protic functionality were not tolerated, aryl triflates containing enolizable ketones protected as ketals (**2d**), alcohols protected with an acetyl group (**2e**), or carbamate-protected anilines (**2f**) reacted to form products in good yield with either a catalyst consisting of Cy-APhos or Xantphos. Reactions of electron-deficient aryl triflates typically occurred in modest to good yields (**3g-3l**). Unlike the higher yields of products obtained when increasing the amount of catalyst for reactions of electron-rich or electron-neutral aryl triflates, higher yields of products from electron-deficient aryl triflates were not obtained by increasing the catalyst loading for reactions of this class of ArOTf. Products containing synthetically valuable esters (**3j**) and non-enolizable ketones (**3k**) were prepared in good yield. Basic heterocycles were also tolerated, as demonstrated by quinoline-containing product **3m**. Similar to the previously reported reaction of ArCl and ArBr, benzonitrile derivatives (**2i**) were poor substrates for the coupling with **1** and formed little product.

We considered that slow deprotonation of **1** by an insoluble base could reduce the concentration of reactive enolate species, leading to the observed modest yields of products. The generation of the enolate by treatment of a silyl enol ether of α,α-difluoroacetophenone, **4**, with an appropriate fluoride source was considered as a means to access a reactive difluoroenolate species more readily. Although the generation of fluoroalkyl nucleophiles from fluoroalkyl silicon compounds is well-precedented,[29] the yields of reactions of aryl triflates with **4** and a fluoride source were lower yield than those from the reactions conducted with **1** and Cs_2CO_3.

Table 4.4 Pd-catalyzed α-arylation of **4** with ArOTf.[a]

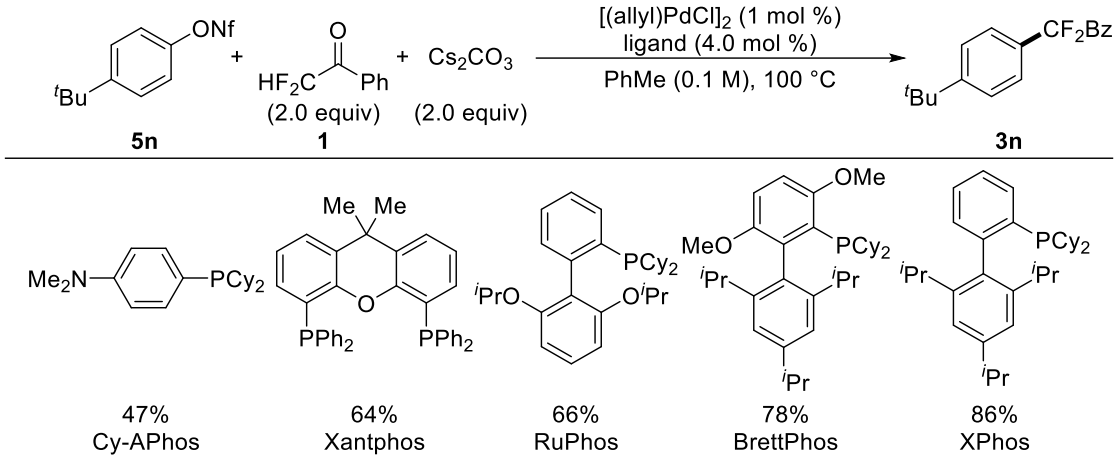


[a] Yields were determined by ^{19}F NMR spectroscopy.

To broaden the scope of aryl sulfonates that are able to couple with **1**, the reactivity of related aryl nonaflate electrophiles was explored for the Pd-catalyzed α-arylation reaction. Aryl nonaflates are more stable surrogates of aryl triflates.[30-31] In addition to possessing a better leaving group than aryl triflates, these compounds are readily prepared from phenols and inexpensive ($0.34/g) nonafluorobutanesulfonyl fluoride (NfF), which is in turn prepared by electrochemical fluorination of the industrial solvent, sulfolane.[32]

Although reactions catalyzed by a complex bearing Cy-APhos ligands were able to transform electron-rich or electron-neutral aryl triflates to products, reactions of ArONf conducted with this ligand occurred in low yield. From a brief evaluation of phosphine ligands, the bulky, electron-rich ligand, XPhos, was found to form an active Pd-catalyst for the α-arylation of ketone **1** with aryl nonaflates (Table 4.5).

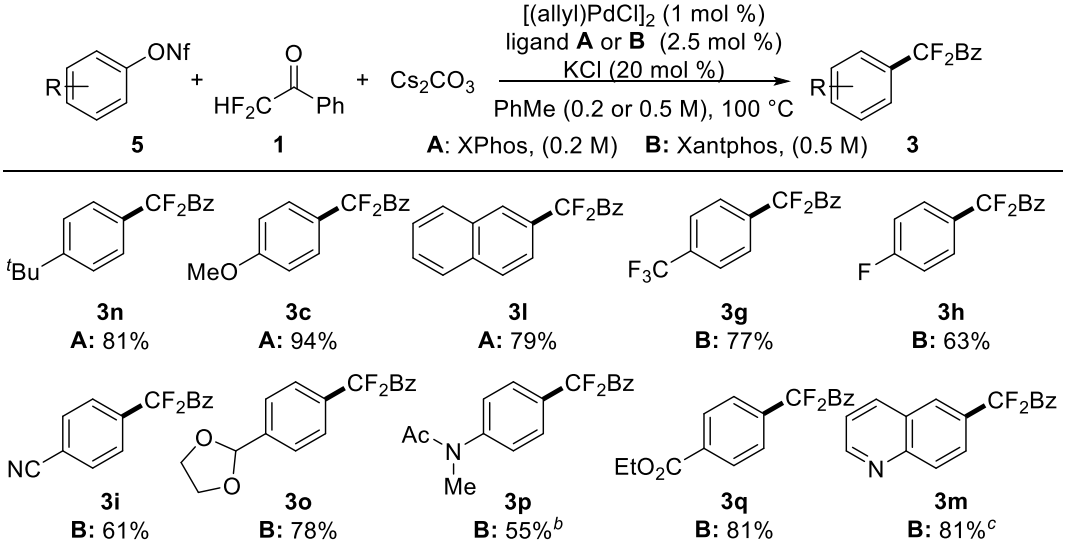
Table 4.5 Evaluation of phosphine ligands for the α-arylation of **1** with an electron-rich ArONf.[a]



[a] Yields were determined by ^{19}F NMR spectroscopy.

The scope of the reaction of aryl nonaflates with **1** was explored (Table 4.6). The functional group compatibility for the reactions of ArONf was similar to that obtained for the reaction of aryl triflates. Reactions of electron-deficient aryl nonaflates were conducted with Xantphos as ligand and at slightly higher concentrations than those for the reactions of electron-rich ArONf. In general, higher yields of electron-poor α-aryl-α,α-difluoroketone products were obtained from the reaction of aryl nonaflates than the yields of products that were obtained from the coupling of the corresponding aryl triflates. While the reaction of an aryl triflate containing a cyano group occurred in low yield (Table 4.3, **3i**, 20%), the reaction of the corresponding aryl nonaflate afforded product in synthetically useful quantities (Table 4.6, **3i**, 61%).

Table 4.6 Pd-catalyzed α-arylation of **1** with ArONf.[a]

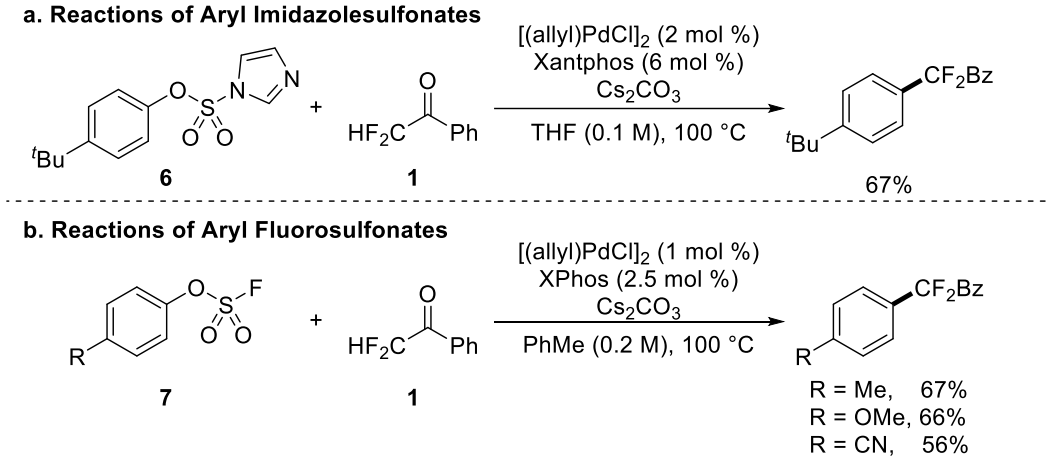


[a] Yields were determined by ^{19}F NMR spectroscopy. [b] Reaction was conducted without KCl additive. [c] Reaction was run in a 3:1 mixture of PhMe/dimethoxyethane as solvent.

Efforts to expand the α-arylation reaction to other common aryl sulfonate derivatives, such as aryl methanesulfonates (ArOMs, mesylates) or aryl *p*-toluenesulfonates (ArOTs, tosylate), were also attempted, but these aryl sulfonates did not couple with **1** to form product. In these reactions, aryl tosylates typically remained unconverted, and aryl mesylates underwent significant hydrolysis to the corresponding phenol. Aryl imidazolesulfonates (imidazylates) have been recently applied to various transition metal-catalyzed cross-coupling reactions.[33-36] Aryl imidazylates are more reactive than ArOTs or ArOMs and are more stable and inexpensive to prepare than ArOTf. Increasing the loading of palladium catalyst with Xantphos as ligand allowed for an aryl imidazylate **6** to undergo the desired reaction with **1** to form product in good yield (Table 4.7, a).

Aryl fluorosulfonates also have been developed as sulfonate electrophiles.[37-38] These compounds are prepared by the reaction of phenols with sulfuryl fluoride, a common fumigant insecticide. Reactions occurred in good yield for an electron-neutral, electron-rich, and electron-poor aryl fluorosulfonate (Table 4.7, b). However, the yields of reactions with aryl fluorosulfonates were lower than the yields of the corresponding reactions with aryl nonaflates.

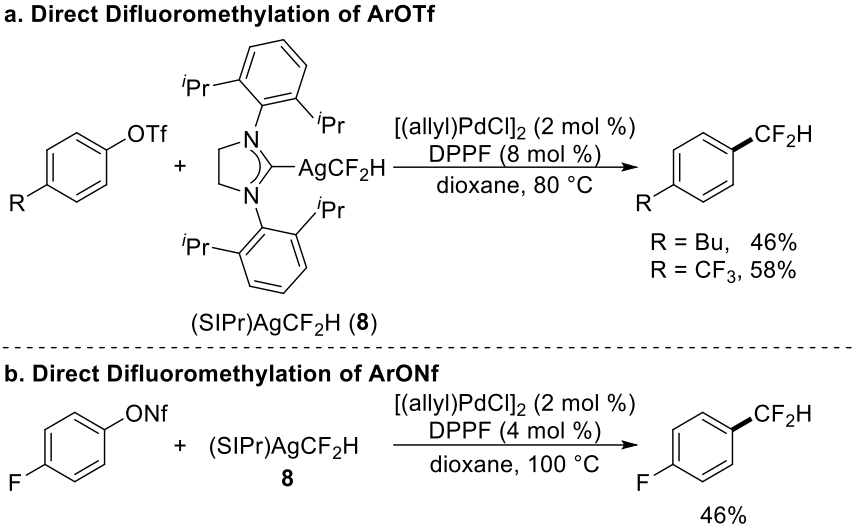
Table 4.7 Pd-catalyzed α-arylation of **1** with other aryl sulfonate electrophiles.[a]



[a] Yields were determined by ^{19}F NMR spectroscopy.

Although reactions have been developed for the α-arylation of difluoroketone **1** with various aryl sulfonate derivatives, an additional step is still required for the generation of the more valuable difluoromethylarene products. The reported Haller-Bauer cleavage of the cross-coupled products is conducted with aqueous KOH at 100 °C. While the cleavage was demonstrated to produce a variety of difluoromethylarenes, the strongly basic conditions at elevated temperatures could limit the applicability of this step for the conversion of phenol-containing complex molecules to the corresponding bioisosteric difluoromethyl-containing compounds. Shen reported the difluoromethylation of *vinyl* triflates and nonaflates with difluoromethylsilver complex **8**.[39] We investigated the reaction of this reagent with aryl triflates and nonaflates under the previously reported conditions for vinyl electrophiles (Table 4.8). Although this reaction would offer a more direct route to $ArCF_2H$, only modest yields of products were obtained from these starting materials.

Table 4.8 Direct difluoromethylation of ArOTf and ArONf with (SIPr)$AgCF_2H$ (**8**).[a]



[a] Yields were determined by ^{19}F NMR spectroscopy.

4.3 Conclusions and Outlook

Conditions have been discovered that allow for the Pd-catalyzed α-arylation reactions of α,α-difluoroacetophenone with various aryl sulfonate electrophiles, including aryl triflates, nonaflates, imidazylates, and fluorosulfonates. The reaction of these substrates to form α-aryl-α,α-difluoroketones, which can then be transformed to difluoromethylarenes, provides a synthetic route to convert bioactive phenols to their lipophilic isosteric CF_2H analogs. Reactions of electron-neutral or electron-rich aryl sulfonates typically proceeded with catalysts consisting of a bulky, electron-rich, monophosphine ligand. The reactions of electron-poor aryl sulfonates typically required Xantphos as ligand. In general, reactions of the more stable aryl nonaflates occurred in higher yields than the corresponding reactions of aryl triflates. Direct couplings of aryl sulfonates were briefly investigated with a stoichiometric difluoromethylsilver reagent, but poor yields of product were obtained.

As previously discussed, the products from α-arylation require treatment with a strong base, KOH, at high temperature to obtain the desired difluoromethylarenes (Figure 4.5, a). Complex molecules with base-sensitive functional groups may not be tolerated under these forcing conditions. Because *gem*-difluorination in the position α to a carbonyl enhances its electrophilicity, it is likely that a less basic nucleophile (e.g. thiolates, silanoates, etc.) could add to the fluorinated ketone products and liberate the difluoromethylarene under milder reaction conditions. Indeed, in the reactions of aryl chlorides or bromides with **1**, cleavage of the ketone product from the reaction of 4-bromoquinoline was observed in the absence of added KOH (Figure 4.5, b). This result indicates that the basic quinoline functionality was itself sufficient to generate some quantity of the difluoromethylarene, and that other nitrogen-based heterocycles could serve a similar function. Lewis acid additives could also help further activate the carbonyl towards nucleophilic attack by

weaker bases, rendering this α-arylation/ketone cleavage strategy much more amenable to transformations of complex molecules (Figure 4.5, c).

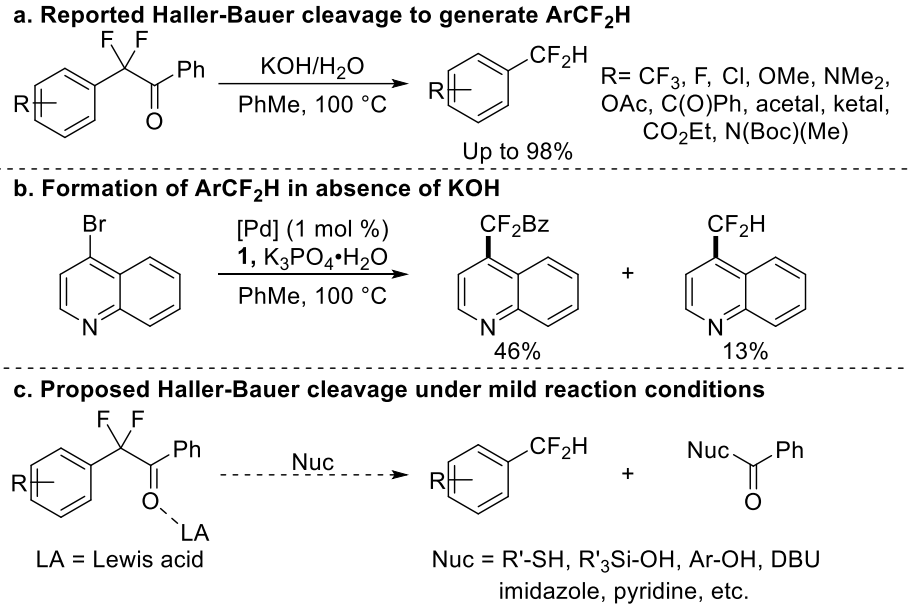


Figure 4.5 Generation of difluoromethylarenes from α-aryl-α,α-difluoroketones

Although reactions of aryl triflates and aryl nonaflates are common, it would be desirable to extend this methodology to less reactive aryl mesylates or aryl tosylates. The synthesis of these compounds requires significantly less expensive reagents. Trifluoromethanesulfonic anhydride (Tf_2O) and nonafluorobutanesulfonyl fluoride (NfF) are $115/mol and $103/mol, respectively, whereas *p*-toluenesulfonyl chloride (TsCl) is $8/mol and methanesulfonyl chloride (MsCl) is $3/mol. Cross-coupling reactions of the more challenging aryl mesylate or aryl tosylate electrophiles are commonly achieved with Ni-catalysts because oxidative addition of aryl sulfonates to nickel is more facile than to palladium.[40] The discovery of a Ni-catalyst that can activate inexpensive aryl sulfonates for the coupling with α,α-difluoroacetophenone would be desirable as a more cost-effective route to difluoromethylarenes from phenols.

Further work should also focus on reagents that can allow for the direct difluoromethylation of aryl sulfonates. Because bioactive phenol derivatives must first be reacted with Tf_2O, NfF, or other sulfonylating reagents, two additional steps (Pd-catalyzed coupling and ketone cleavage) are needed before obtaining the desired difluoromethyl-containing compounds. Although modest yields of difluoromethylarenes were obtained by the reactions of ArOTf or ArONf with (SIPr)AgCF_2H, this reagent is expensive to prepare. Similarly, Vicic has reported the Ni-catalyzed difluoromethylation of electron-poor ArOTf with (DMPU)Zn$(CF_2H)_2$, but this difluoromethylation reagent is also expensive to prepare from gaseous HCF_2I.[25] A cheap, readily available reagent to directly prepare difluoromethylarenes from phenols under mild conditions would greatly improve the ability for pharmaceutical chemists to apply this methodology to new drug compounds.

4.4 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.

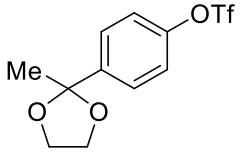
α,α-Difluoroacetophenone **1**, its silyl enol ether **4**,[41] and (SIPr)AgCF$_2$H **8**[23] were prepared according to the literature procedures. Aryl triflates **2a-2c**, **2e**, **2g-2m**,[42-51] aryl nonaflates **5c**, **5g-5i**, **5l-n**, **5q**,[52-55] and aryl imidazylate **6**[56] have been previously reported and were prepared according to published procedures. The synthesis and characterization of previously unreported aryl triflates **2d** and **2f**, and aryl nonaflates **5o** and **5p** are described below. Aryl fluorosulfonates **7** were received from Dr. Patrick Hanley at Dow Chemical Company and used as received. All other ligands, reagents, and solvents were purchased from commercial sources and used as received.

Products from α-arylation **3b**, **3c**, **3e-3i**, **3k-3n** and **3q** have been previously reported and the identity of these products was confirmed by comparison of the acquired ^{19}F NMR spectrum to the published data and by GC-mass spectrometry.[28, 57-58] The yields and identity of the remaining α-arylation products **3a**, **3d**, **3j**, **3o**, and **3p** were determined by ^{19}F NMR spectroscopy and by GC-mass spectrometry following the general procedure described below.

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.

Synthesis of 4-(2-methyl-1,3-dioxolan-2-yl)phenyl triflate (2d)

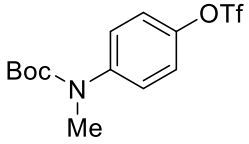


To an oven-dried flask equipped with a magnetic stir bar was added 4-acetylphenyl triflate (1.0 g, 3.7 mmol, 1.0 equiv), ethylene glycol (0.42 mL, 7.5 mmol, 2.0 equiv), *p*-toluenesulfonic acid monohydrate (0.14 g, 0.75 mmol, 20 mol %), and toluene (30 mL). The flask was fitted with a reflux condenser and Dean-Stark apparatus and then heated at reflux. After completion of the reaction, the solvent was evaporated from the resulting solution under reduced pressure. The obtained crude product was purified by silica gel column chromatography with a gradient of 100% hexanes to 2:1 hexanes-EtOAc to afford pure product as a white solid (0.62 g, 53%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.7 Hz, 2H), 7.25 (d, J = 8.8 Hz, 2H), 4.16 – 3.86 (m, 2H), 3.87 – 3.57 (m, 2H), 1.65 (s, 3H).

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

Synthesis of 4-((tert-butoxycarbonyl)(methyl)amino)phenyl triflate (2f)

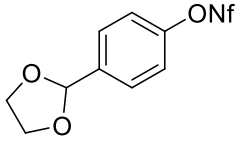


To an oven-dried flask equipped with a magnetic stir bar was added the known compound 4-((tert-butoxycarbonyl)amino)phenyl triflate (0.50 g, 1.5 mmol, 1.0 equiv)[48] and DMF (10 mL). To the flask was added NaH (53 mg, 2.2 mmol, 1.5 equiv) with stirring. After cessation of the evolution of gas, the flask was fitted with a rubber septum. The flask was cooled to 0 °C, and then MeI (360 μL, 5.8 mmol, 4.0 equiv) was added dropwise. The reaction was allowed to warm to room temperature and stirred for 12 h. After the reaction was complete, the solution was transferred to a separatory funnel, and then DCM and H_2O were added. The organic layer was extracted with DCM, and the combined organic layers were then washed with brine, dried with anhydrous Na_2SO_4, and filtered. Solvent was evaporated from the resulting solution under reduced pressure, and the crude product then was purified by silica gel chromatography with a gradient from 100% hexanes to 2:1 hexanes-EtOAc to afford product as a yellow oil (0.34 g, 66%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 9.0 Hz, 2H), 3.28 (s, 3H), 1.47 (s, 9H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -72.1 (s, 3F).

Synthesis of 4-(1,3-dioxolan-2-yl)phenyl nonaflate (5o)

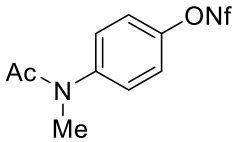


To a vial equipped with a magnetic stir bar was added known compound 4-formylphenyl nonaflate (1.0 g, 2.5 mmol, 1.0 equiv),[53] ethylene glycol (0.56 mL, 10.0 mmol, 4.0 equiv), triethyl orthoformate (0.47 mL, 2.8 mmol, 1.1 equiv) and Bu_4NBr_3 (24 mg, 0.05 mmol, 2 mol %). The vial was sealed with a PTFE-lined screw cap. The reaction was stirred at room temperature for 12 h. After completion, the solution was poured onto a saturated aqueous solution of $NaHCO_3$. The mixture was extracted with EtOAc (2 x 12 mL), and the combined organic layers were dried with anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The crude product was dissolved in a minimal amount of EtOAc and then passed through a short pad of silica. After removal of EtOAc, the product was obtained as a white solid (0.45 g, 40%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.5 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 5.84 (s, 1H), 4.18 – 4.02 (m, 4H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -79.9 (t, J = 10.0 Hz, 3F), -108.2 (t, J = 14.0 Hz, 2F), -120.2 (bs, 2F), -124.9 – -125.5 (m, 2F).

Synthesis of 4-(*N*-methylacetamido)phenyl nonaflate (5p)



To an oven-dried flask equipped with a magnetic stir bar was added NaH (33 mg, 13.8 mmol, 2.0 equiv) and DMF (14 mL). The flask was sealed with a rubber septum and then cooled to 0 °C. To the cooled suspension was added a solution of known compound 4-acetamidophenyl nonaflate (3.0 g, 6.9 mmol, 1.0 equiv)[52] in DMF (7 mL) dropwise. The reaction was allowed to stir at 0 °C for 1 h, after which MeI (0.9 mL, 13.8 mmol, 2.0 equiv) was then added dropwise. The reaction was allowed to warm to room temperature, then stirred for 12 h. To the solution was added excess water to quench

unreacted NaH. The organic layer was extracted with EtOAc (3 x 20 mL), and the combined organic layers were dried with anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The crude product was purified by silica gel column chromatography with 3:1 hexanes-EtOAc to afford product as a white solid (2.1 g, 68%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 4H), 3.28 (s, 3H), 1.90 (s, 3H).
^{19}F NMR (376 MHz, $CDCl_3$) δ -79.7 (t, J = 9.7 Hz), -107.9, -120.0, -125.0 (t, J = 14.2 Hz).

General Procedure for the α-Arylation of 1 or 4 with Aryl Triflates
To an oven-dried 4 mL vial equipped with a magnetic stir bar was added ligand (4.0 μmol, 4.0 mol %) (Cy-APhos for conditions **A** or Xantphos for conditions **B**), $[(allyl)PdCl]_2$ (1.0 μmol, 1.0 mol % of dimer), KO^{t}Bu (4.0 μmol, 4.0 mol %), aryl triflate (0.10 mmol, 1.0 equiv), **1** or **4** (0.20 mmol, 2.0 equiv), and PhMe (1.0 ml). To the vial was added base (0.20 mmol, 2.0 equiv)(Cs_2CO_3 for reactions with **1**, or CsF for reactions with **4**), and then the vial was sealed with a Teflon-lined cap and heated at 100 ºC for 15 h. The solution was allowed to cool to room temperature. 4,4'-Difluorobenzophenone (0.10 mmol, 1.0 equiv) was then added as internal standard, and the reaction mixture was directly transferred to an NMR tube for characterization by ^{19}F NMR spectroscopy.

General Procedure for the α-Arylation of 1 with Aryl Nonaflates
To an oven-dried 4 mL vial equipped with a magnetic stir bar was added ligand (2.5 μmol, 2.5 mol %) (XPhos for conditions **A** or Xantphos for conditions **B**), $[(allyl)PdCl]_2$ (1.0 μmol, 1.0 mol % of dimer), KCl (0.2 mmol, 20 mol %), aryl nonaflate (0.10 mmol, 1.0 equiv), **1** (0.20 mmol, 2.0 equiv), and PhMe (0.5 mL for conditions **A** or 0.2 mL for conditions **B**). To the vial was added Cs_2CO_3 (0.20 mmol, 2.0 equiv).The vial was then sealed with a Teflon-lined cap and heated at 100 ºC for 12 h. The solution was allowed to cool to room temperature. 4,4'-Difluorobenzophenone (0.10 mmol, 1.0 equiv) was then added as internal standard, and the reaction mixture was directly transferred to an NMR tube for characterization by ^{19}F NMR spectroscopy.

General Procedure for the α-Arylation of 1 with Aryl Imidazylate or Aryl Fluorosulfonates
To an oven-dried, 4 mL vial equipped with a magnetic stir bar was added ligand (Xantphos: 6.0 μmol, 6.0 mol % for aryl imidazylate, or XPhos: 2.5 μmol, 2.5 mol % for aryl fluorosulfonates), $[(allyl)PdCl]_2$ (2.0 μmol, 2.0 mol % of dimer for aryl imidazylates, or 1.0 μmol, 1.0 mol % of dimer for aryl fluorosulfonates), aryl sulfonate derivative (0.10 mmol, 1.0 equiv), **1** (0.20 mmol, 2.0 equiv), and solvent (1.0 ml PhMe for aryl imidazylate, or 0.5 mL THF for aryl fluorosulfonates). To the vial was added Cs_2CO_3 (0.20 mmol, 2.0 equiv), and then the vial was sealed with a Teflon-lined cap and heated at 100 ºC for 12 h. The solution was allowed to cool to room temperature. 4,4'-Difluorobenzophenone (0.10 mmol, 1.0 equiv) was then added as internal standard, and the reaction mixture was directly transferred to an NMR tube for characterization by ^{19}F NMR spectroscopy.

General Procedure for the Direct Difluoromethylation of Aryl Triflates or Nonaflates with 8
To an oven-dried 4 mL vial equipped with a magnetic stir bar was added DPPF (8.0 μmol, 8.0 mol % for ArOTf, 4.0 μmol, 4.0 mol % for ArONf), $[(allyl)PdCl]_2$ (2.0 μmol, 2.0 mol % of dimer), the aryl sulfonate derivative (0.10 mmol, 1.0 equiv), silver complex **8** (0.60 mmol, 1.2 equiv), and dioxane (1.0 mL). The vial was sealed with a Teflon-lined cap and heated at 80-100 ºC for 12 h. The solution was allowed to cool to room temperature. 4,4'-Difluorobenzophenone (0.10 mmol, 1.0 equiv) was then added as internal standard, and the reaction mixture was transferred directly to an NMR tube for characterization by ^{19}F NMR spectroscopy.

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Chapter 5

Palladium-Catalyzed Aryldifluoromethylation of Aryl Halides

5.1 Introduction

Due to their interesting physical and biological properties, fluorinated compounds have found considerable application in the fields of pharmaceutical chemistry, agrochemistry, and materials chemistry.[1-5] While significant effort has been made towards the development of transition metal-mediated reactions that can introduce a fluorine or perfluoroalkyl substituent onto a functionalized arene, fewer examples have been reported on the incorporation of partially fluorinated substituents.[6-7] Many of the reactions that form arenes bound to partially fluorinated alkyl groups incorporate difluoromethyl groups[8] or α,α-difluorinated carbonyl compounds, such as difluoroketones,[9-11] difluoroesters,[12-15] and difluoroamides.[16-18] Less progress has been made towards developing methods to introduce CF_2-containing moieties with weaker electron-withdrawing groups or electron-donating groups attached to carbon, such as aryldifluoromethyl[19-20] or alkyldifluoromethyl fragments.[21] The ability to couple a more diverse array of partially fluorinated substituents onto aromatic compounds can broaden access to unique fluorine-containing structural motifs. Such compounds may possess novel and desirable properties that lead to the discovery of new drugs or agrochemical compounds.

Diaryldifluoromethanes are particularly interesting structural units containing fluorine. Because difluoromethylene groups are proposed to be lipophilic bioisosteres to oxygen, diaryldifluoromethanes could act as surrogates to bioactive diarylethers.[22-23] Replacing an oxygen linker with a difluoromethylene linker could result in compounds that exhibit enhanced bioavailability and metabolic stability, because these traits are common to fluorinated molecules. Indeed, the IC_{50} of a leukotriene A_4 inhibitor containing a difluoromethylene linker between two aromatic groups is lower than that of either structurally analogous compound bearing a methylene or oxygen linker (Figure 5.1, a).[24] Likewise, Ledipasvir, a diaryl-difluoromethane-containing oral NS5A inhibitor, is a component of Harvoni, a drug for the treatment of hepatitis C (Figure 5.1, b).[25]

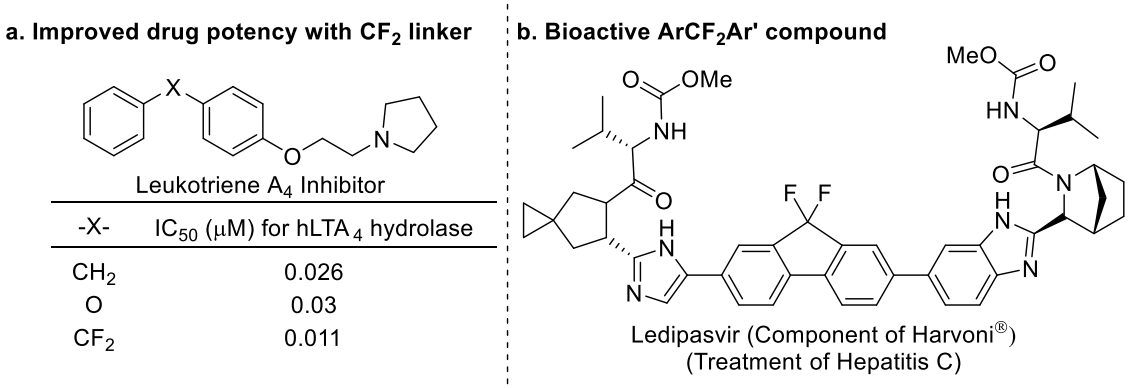


Figure 5.1 Examples of diaryldifluoromethanes as bioactive compounds

Classical strategies for the synthesis of diaryldifluoromethanes include fluorodeoxygenation of diarylketones with S(IV) reagents, such as DAST or Deoxo-fluor, or the analogous fluorodesulfurization of 2,2-diaryl-1,3-dithiolanes (Figure 5.2, a).[26-29] These procedures

typically require toxic reagents and harsh reaction conditions that limit their applicability for late-stage derivatization of complex molecules. Another strategy for the preparation of the C-F bonds of these compounds is benzylic difluorination of diarylmethanes (Figure 5.2, b).[30-33] Typically, these reactions occur with expensive electrophilic fluorine sources under strongly basic conditions to generate benzylic anions or under oxidative conditions to generate benzylic radicals. While the functional-group compatibility of is greater than that observed for fluorodeoxygenation or fluorodesulfurization, poor benzylic site-selectivity, low reaction yields, and poor selectivity for mono- vs. di-fluorinated products render these reactions undesirable.

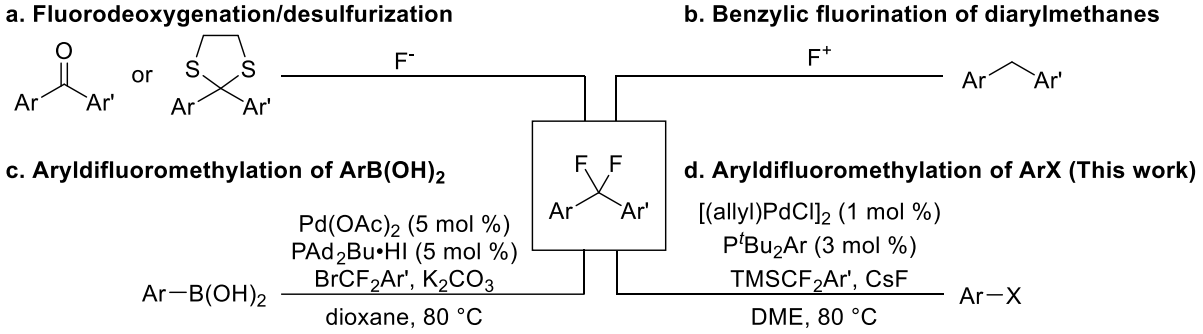


Figure 5.2 Synthetic strategies to prepare diaryldifluoromethanes by C-F or C-C bond formation

Construction of the Ar-CF_2Ar' bond of these molecules would be an improved route to this class of compound. Only one example has been reported of the direct installation of aryldifluoromethyl groups to functionalized arenes. Zhang reported the palladium-catalyzed reaction of arylboronic acids with aryldifluoromethyl bromides (Figure 5.2, c).[20] This reaction allows for the preparation of diaryldifluoromethanes in modest to good yields, and the mild conditions allow many synthetically useful functional groups to be tolerated. While a notable first example of this class of cross-coupling reaction, there are significant limitations that prevent the broad applicability of this procedure. The synthetic and commercial availability of arylboronic acids are limited compared to that of abundant aryl halides, which can be readily prepared or purchased. For this reason, a coupling strategy that employs the more ubiquitous aryl halide coupling partners would be preferred. Moreover, the aryldifluoromethyl bromide reagents in this reaction are not simple to access. They were prepared by radical bromination of difluoromethylarenes.[34] Due to the difficulty associated with their preparation, difluoromethylarenes have limited commercial availability and are often expensive, making them undesirable starting materials for coupling reactions. Low yields of products are also obtained from reactions of aryldifluoromethyl bromides other than 4-(bromodifluoromethyl)-1,1'-biphenyl, limiting the ability of this procedure to furnish a large scope of diaryldifluoromethanes.

To address these limitations, we sought to develop a reaction that couples aryl halides with a readily accessible nucleophilic source of CF_2Ar (Figure 5.2, d). We show that an appropriate catalyst and reaction conditions allow for the coupling of aryl bromides or aryl chlorides with the nucleophilic aryldifluoromethylation reagent, $TMSCF_2Ph$. We also show that limitations on the

process result from poor functional-group compatibility and difficulty in accessing varied R_3SiCF_2Ar reagents.

5.2 Results and Discussion

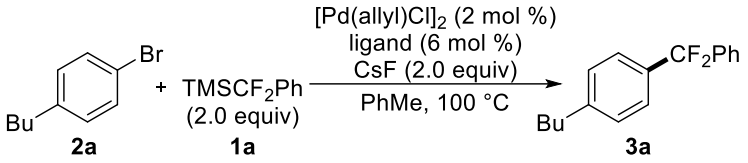
Given the wide application of the Ruppert-Prakash reagent, $TMSCF_3$, in transition metal-mediated trifluoromethylation reactions of aryl halides,[35] we sought to prepare an aryldifluoromethyl variant of this reagent, $TMSCF_2Ph$ (**1a**), for the coupling of aryldifluoromethyl nucleophiles with aryl halides. The synthesis of phenyldifluoromethyl trimethylsilane was reported previously for use in the addition of aryldifluoromethyl groups to aldehydes and ketones.[36-38] This column-stable, easy to handle reagent can be readily prepared on multi-gram scale by a Mg-mediated reductive silylation of inexpensive, commercially available benzotrifluorides.

Due to the abundance of copper-mediated perfluoroalkylation reactions, we investigated the coupling of this regent with aryl iodides in the presence of various copper(I) salts. After extensive investigation, no conditions were discovered that allowed for the conversion of iodoarenes to phenyldifluoromethyl-arenes. Our group has developed a stoichiometric trifluoromethylation reagent, $(phen)CuCF_3$, which was found to react with aryl iodides and activated (hetero)aryl bromides to form trifluoromethyl (hetero)arenes in good yields.[39-40] Attempts were made to prepare the analogous $(phen)CuCF_2Ph$ reagent, but were not successful. Instead, rapid decomposition of **1a** to an intractable mixture of fluorinated byproducts was observed for many reactions of this reagent with Cu(I) salts and a base activator.

Although a single example of a palladium-catalyzed trifluoromethylation reaction of aryl chlorides has been reported,[41] palladium catalysts have been applied broadly to the coupling of partially fluorinated nucleophiles, such as difluoroketones and difluoroamides. The necessity to break strong $Pd\text{-}CF_3$ bonds has been implied as a potential cause for the slow reductive elimination of $Ar\text{-}CF_3$ from Pd.[6] Because phenyl groups are less inductively withdrawing than fluorine or carbonyl-based substituents, we considered that $Pd\text{-}CF_2Ar$' bonds could be weaker and less polarized than analogous bonds to CF_3 or $CF_2C(O)R$, and undergo faster product-forming reductive elimination.

To assess the feasibility of a Pd-catalyzed phenyldifluoromethylation reaction of aryl halides, we investigated the reaction of an unactivated aryl bromide with silicon compound **1a**, CsF as activator, a suitable palladium precursor, and various phosphine ligands (Table 5.1). Given the necessity of bulky monophosphine ligands in the reported Pd-catalyzed trifluoromethylation of ArCl (BrettPhos) and in Zhang's aryldifluoromethylation of arylboronic acids (PAd_2Bu), we examined reactions with this class of ligand. Although little or no conversion to product was observed for reactions with BrettPhos or PAd_2Bu as ligands, we found that reactions catalyzed by a palladium complex bearing di-*tert*-butyl(phenyl)phosphine as ligand could furnish the expected diaryldifluoromethane product in good yield.

Table 5.1 Evaluation of phosphine ligands on the Pd-catalyzed aryldifluoromethylation reaction of ArBr.[a]



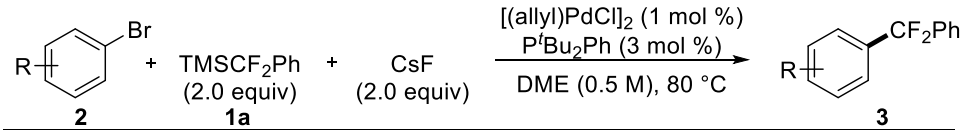
2a **1a** **3a**

ligand	yield	ligand	yield
P^tBu_3	17%	PAd_2Bu	0%
PCy_3	< 5%	QPhos	0%
P^tBuCy_2	< 5%	JohnPhos	< 5%
PCy_2Ph	17%	SPhos	25%
$PCyPh_2$	36%	RuPhos	0%
P^tBu_2Ph	48%	CPhos	0%
P^tBuPh_2	39%	BrettPhos	14%

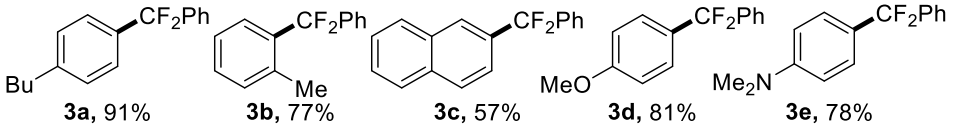
[a] Yields were determined by ^{19}F NMR spectroscopy.

By changing the reaction solvent to the more polar dimethoxyethane (DME) and lowering the temperature of the reaction to 80 °C, we were able to decrease the loading of $[(allyl)PdCl]_2$ and P^tBu_2Ph, while still obtaining synthetically useful yields of diaryldifluoromethanes (Table 5.2). Although reactions of electron-neutral and electron-rich aryl bromides afforded products in good yield (**3a-3e**), electron-deficient aryl bromides could be coupled with **1a** in only low yields (**3f-3i**). By increasing the loading of catalyst, the formation of these compounds could be increased only marginally.

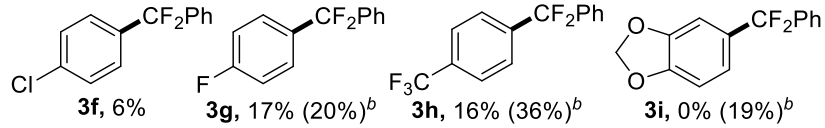
Table 5.2 Reactions of ArBr with $TMSCF_2Ar$ catalyzed by a Pd-complex bearing P^tBu_2Ph as ligand.[a]



2 **1a** **3**



3a, 91% **3b,** 77% **3c,** 57% **3d,** 81% **3e,** 78%



3f, 6% **3g,** 17% (20%)[b] **3h,** 16% (36%)[b] **3i,** 0% (19%)[b]

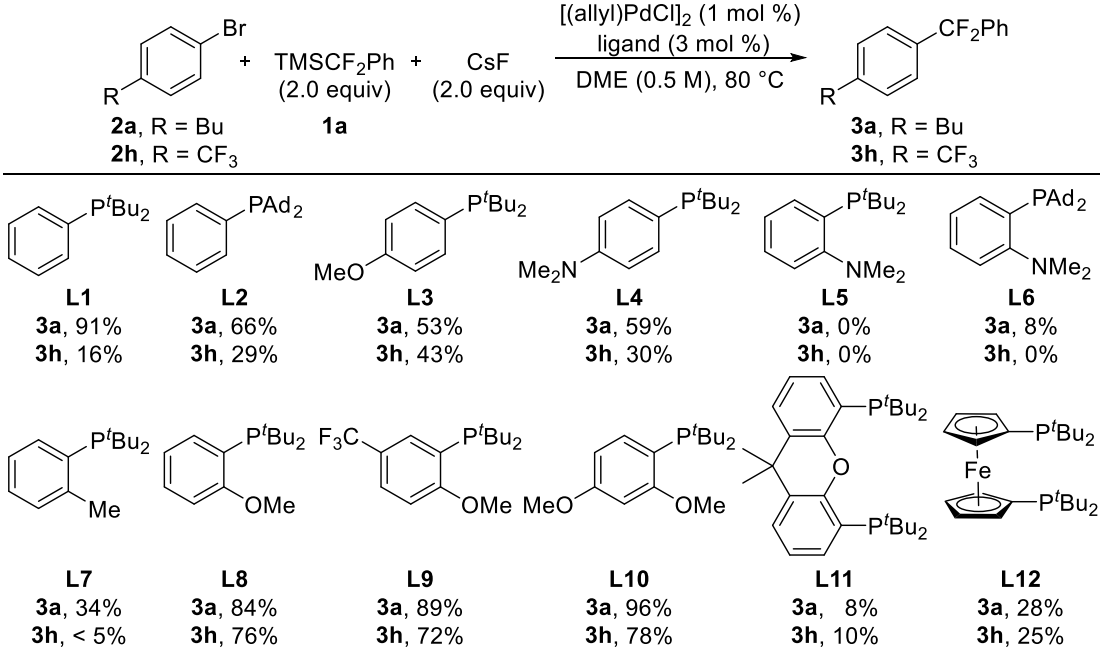
[a] Yields were determined by ^{19}F NMR spectroscopy. [b] Reactions were conducted with $[(allyl)PdCl]_2$ (2 mol %) and P^tBu_2Ph (6 mol %).

We considered that variation of the P^tBu_2Ph (**L1**) ligand scaffold could result in a catalyst that is more active in the transformation of electron-deficient aryl bromides. The couplings of both 4-butyl bromobenzene (**2a**) and 4-trifluoromethyl bromobenzene (**2h**) were evaluated with various dialkyl-arylphosphine ligands (Table 5.3). Replacement of the *tert*-butyl groups in **L1** with

adamantyl groups in **L2**, or introduction of electron-donating groups in the 4-position of the aromatic ring on the phosphine (**L3** and **L4**), resulted in a slight increase in the yield of electron-deficient product **3h**, but a decrease in the yield of a more electron-rich product **3a**.

Substitution at the 2-position of the aromatic ring on phosphorus was considered as a method to increase steric bulk and, thereby, facilitate reductive elimination from the fluoroalkylpalladium intermediate to form the C-C bond. Because of the low reactivity observed with JohnPhos ((2-Biphenyl)di-*tert*-butylphosphine) as ligand during initial evaluation of reaction conditions (see Table 5.1), the synthesis of ligands with *ortho*-substituents that are smaller than a phenyl group were considered (**L5**-**L7**). These ligands were found to form inactive catalysts that did not afford diaryl-difluoromethane products in useful yields. Chelating, wide bite-angle, bis-phosphine ligands (**L11** and **L12**) were also explored as a means to facilitate reductive elimination, or to better stabilize catalytic palladium intermediates, but reactions catalyzed by complexes bearing these ligands resulted in a lower yield of product than those containing **L1**.

Table 5.3 Re-evaluation of phosphine ligands for coupling of both electron-rich and electron-deficient ArBr.[a]



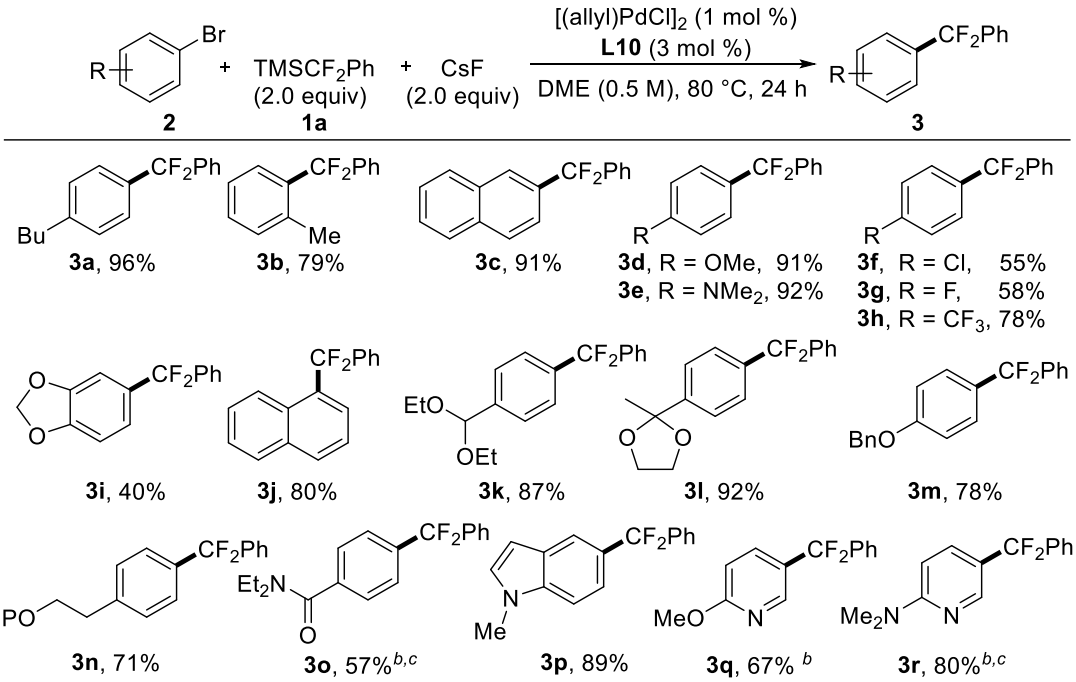
[a] Yields were determined by ^{19}F NMR spectroscopy.

Incorporating a donating methoxy group in the *ortho*-position of the aromatic ring of P^{t}Bu$_2$Ph (**L8**) led to a more active catalyst. The reaction of **2h** with **1a** catalyzed by a complex containing ligand **L8** formed **3h** in yields that were much higher than those obtained for reactions in which **L1** was ligand. Similar high yields of **3a** were obtained in a reaction with **L8** as ligand as those obtained with **L1** as ligand. In addition to donating electrons to the aromatic system, this substituent could also bind to Pd, resulting in a chelating P,O-ligand. The electronic effects of this new class of ligand were explored by addition of an electron-withdrawing trifluoromethyl group in the 5-position of the ring (**L9**) or by further increasing electron density by addition of a second

methoxy group in the 4-position of the 2-anisyl substituent (**L10**). These modifications had little effect on the yields of **3a** and **3h**. Nevertheless, due to the modest increase in yields observed for reactions containing **L10**, this ligand was chosen for further investigations in the catalytic reaction.

Table 5.4 shows the scope of the coupling reactions with **L10** as ligand. In addition to improvements in the yields of products from electron-rich and electron-neutral ArBr (**3a**-**3e**), a catalyst containing **L10** led to the coupling of electron-deficient ArBr that were previously explored with **L1** as ligand to proceed in synthetically useful yields (**3f-3i**). Reactions of sterically hindered ArBr (**2b**, **2j**) were demonstrated to occur in good yield. Compounds possessing aldehydes or ketones protected as acetals and ketals, respectively, can be coupled in excellent yield (**3k**, **3l**). While free –OH groups were not tolerated under the reaction conditions, benzyl protected phenols (**3m**) and aliphatic alcohols protected as tetrahydropyranyl ethers (**3n**) readily underwent the phenyldifluoromethylation reaction. At elevated reaction temperatures and catalyst loading, the coupling of **1a** with amide-containing **2o** proceeded to generate product **3o** in synthetically useful quantities. In addition to reactions with aryl bromides, the reactions of **1a** were explored with a variety of *hetero*aryl bromides. Indole-containing product **3p** was generated in good yield, but reactions of 3-bromopyridines were found to require starting materials bearing electron-donating groups at the 6-position (**3q, 3r**).

Table 5.4 Phenyldifluoromethylation of ArBr with **L10** as ligand.[a]

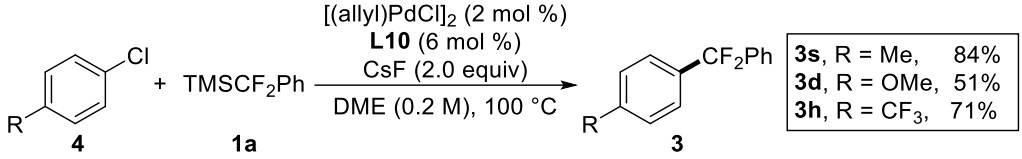


[a] Yields were determined by ^{19}F NMR spectroscopy. [b] Reaction was conducted with 2.5 mol % of $[(allyl)PdCl]_2$ and 7.5 mol % of **L10**. [c] Reaction was run at 100 °C.

Because aryl chlorides are more widely available and less expensive than aryl bromides, we explored the coupling of this class of compound with **1a** (Table 5.5). Due to the slower rates

of oxidative addition to palladium, couplings of ArCl are often more challenging than those of ArBr. By increasing the loading of catalyst and the reaction temperature, reactions with **L10** as ligand were found to react with various aryl chlorides to form the corresponding diaryldifluoromethanes. Reactions of an electron-rich, electron-neutral, and electron-poor aryl chloride to the corresponding diaryldifluoromethanes occurred in moderate to good yield.

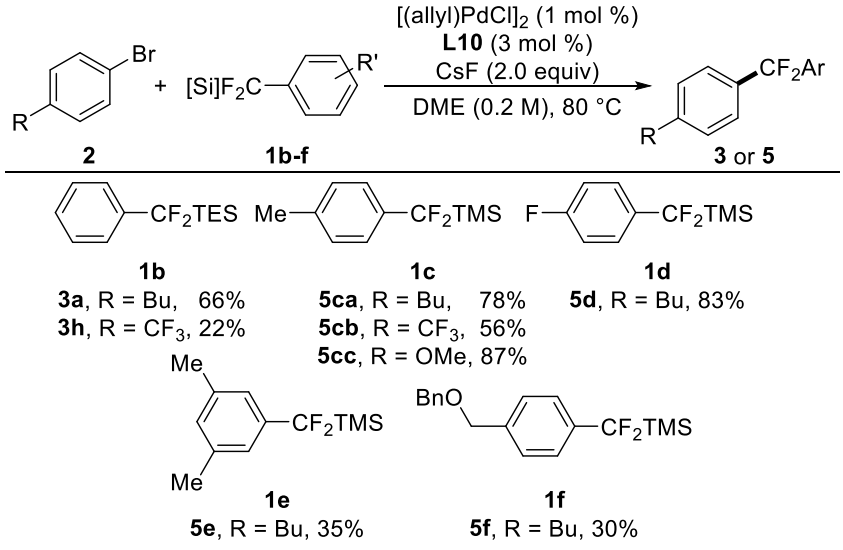
Table 5.5 Pd-Catalyzed phenyldifluoromethylation reactions of ArCl with **1a**.[a]



[a] Yields were determined by ^{19}F NMR spectroscopy.

Table 5.6 shows the reactions of structural analogues of phenyldifluoromethyl silane **1a** with ArBr. By changing the trimethylsilyl group in **1a** to the bulkier triethylsilyl group in **1b**, we anticipated the stability of this reagent would be increased and that this greater stability could reduce unproductive protodesilylation to difluoromethylbenzene. Reactions conducted with **1b** were found to result in lower formation of products than those conducted with **1a**. In a similar manner to $TMSCF_3$,[35] phenyldifluoromethyl trialkylsilanes likely first form a penta-coordinate silicate species by reaction with fluoride before transfer of CF_2Ph. Formation of this silicate could be more challenging with the hindered **1b**, resulting in slow rates of CF_2Ph transfer. Reactions to couple (4-tolyl)difluoromethyl (**1c**) and (4-fluorophenyl)difluoromethyl (**1d**) groups with aryl bromides occurred in good yields, allowing for the preparation of more structurally diverse diaryldifluoromethane products. The coupling of a more sterically demanding aryldifluoromethyl nucleophile **1e,** or a silane reagent bearing a benzyl-protected benzylic alcohol **1f,** was found to form products from reaction with 4-butyl bromobenzene in low yield.

Table 5.6 Variation upon the aryldifluoromethyl silane coupling partners (**1b-f**).[a]



[a] Yields were determined by ^{19}F NMR spectroscopy.

Although a variety of diaryldifluoromethane products can be formed from reactions of aryl bromide or aryl chlorides, the scope and functional group compatibility of this reaction is still limited. Figure 5.3 shows the (hetero)aryl bromide substrates that did not couple with **1a** to form diaryldifluoromethane products. Aryl bromides containing strong, electron-withdrawing groups, such as a cyano (**2s**) or nitro group (**2t**) did not react to form product. The presence of an equivalent of added benzonitrile resulted in no formation of product from reactions of ArBr that typically couple in high yield, indicating an inhibitory effect of aryl nitriles on the catalyst. The reaction could also not be extended to aryl bromides containing protic OH functionality (**2u**) or non-enolizable ketones (**2v**), or to vinyl bromides (**2w**). Acetyl (**2x**) or pivaloyl (**2y**) protected 4-bromophenol were not suitable for the reaction. Conversion of this phenol to the synthetically useful tosylate group (**2z**) could allow for further derivatization of the coupled product, but this compound did not react. Aryl bromides containing protected aniline functionality were also not suitable for the coupling reaction (**2aa-2ee**). Compounds containing acyclic esters (**2ff, 2gg**), cyclic esters (**2hh**), or ester surrogates such as orthoesters (**2ii**) and oxazolines (**2jj**), were not amenable to the reaction. In general, aryl bromides containing esters or ketones underwent side reactions to generate mixtures of multiple unidentified products at room temperature. These unproductive reactions occur in the absence of a catalyst.

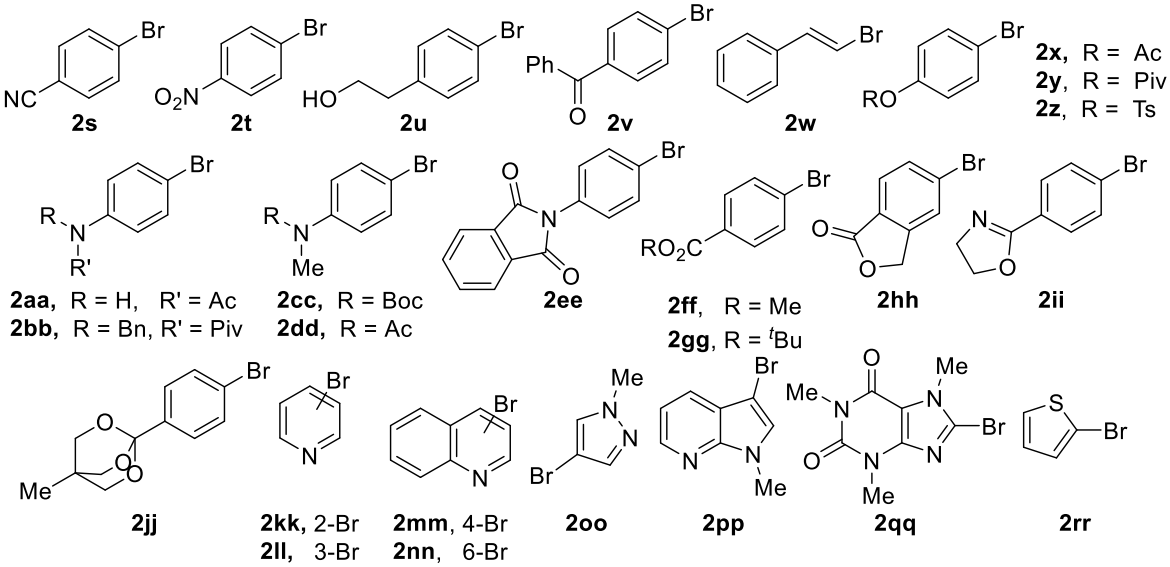


Figure 5.3 (Hetero)aryl bromides that did not undergo the Pd-catalyzed aryldifluoromethylation reaction

We were also unable to demonstrate couplings of many basic heteroaryl bromides, limiting the applicability of this procedure towards the synthesis of pharmacologically relevant compounds containing heterocycles. Unsubstituted bromopyridines and bromoquinolines were not reactive (**2kk-2nn**). Although the coupling reaction of (hetero)aryl bromides bearing electron-donating groups occurs in good yields, reactions of more electron-rich 5-membered bromoheteroarenes did not occur (**2oo-rr**).

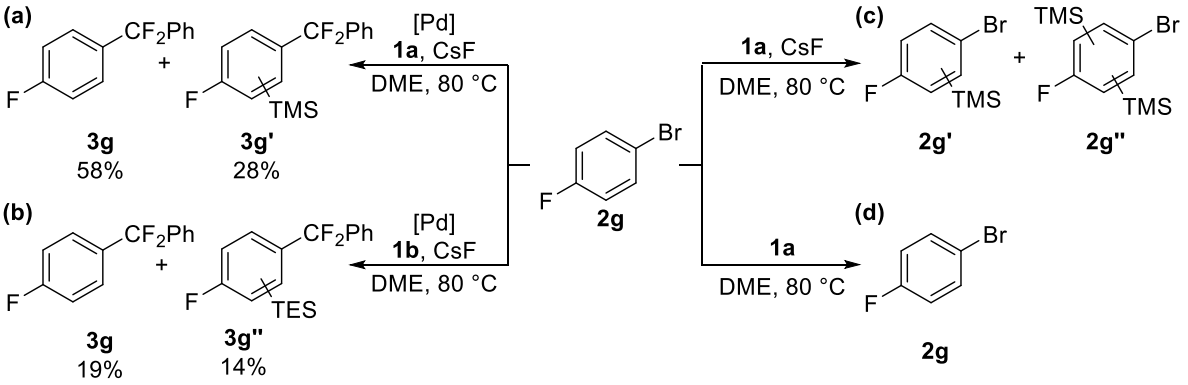
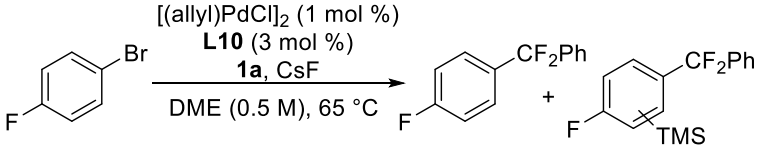


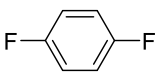
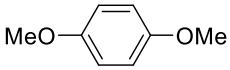
Figure 5.4 Potential undesired side-product in reaction of **2g**

Undesired side reactions were observed for some aryl bromides that are able to couple with **1a**. In addition to the peaks corresponding to the desired product **3g** from the reaction of 4-fluoro bromobenzene, a second set of signals with similar chemical shifts were observed in the ^{19}F NMR spectrum. Analysis of the reaction mixture by GC-mass spectrometry indicated the major product of this reaction is **3g** and the mass of the minor product matched that of a compound in which a hydrogen is replaced by a trimethylsilyl group **3g'** (Figure 5.4, a). Although **3g** and the observed side-product **3g'** could not be easily separated by column chromatography, a ^{1}H NMR spectrum of the mixture of these compounds contained a singlet peak with a chemical shift indicative of a trimethylsilyl group. Phenyldifluoromethyl silane **1a** was completely consumed during the reaction to form product and $PhCF_2H$, so the trimethylsilyl group did not arise from unreacted **1a**.

Table 5.7 Additives to suppress the formation of side-product **3g'** in the reaction of **2g**.[a]



2g **3g** **3g'**

variation on reaction	yield **3g**	yield **3g'**	**3g/3g'**
none	58%	28%	2.1:1
 (2.0 equiv)	57%	10%	5.7:1
 (2.0 equiv)	61%	22%	2.8:1

[a] Yields were determined by ^{19}F NMR spectroscopy.

To explore the origin of this unusual side-product further, aryl bromide **2g** was allowed to react with triethylsilyl-containing reagent **1b**. Two sets of peaks corresponding to the aryl fluoride and difluoromethylene groups of two different compounds were observed in the ^{19}F NMR spectrum. Analysis by GC-mass spectrometry indicated that the minor product was the triethylsilyl-containing diaryldifluoromethane product, **3g''** (Figure 5.4, b). In the absence of a palladium catalyst, we observed the consumption of aryl bromide **2g** and noted the formation of two compounds with molecular weights corresponding to mono-silylated and bis-silylated starting material (Figure 5.4, c). Omitting both a palladium catalyst and the CsF activator required for the cleavage of the CF_2-Si bond resulted in recovery of **2g** with no detectable side-product formation (Figure 5.4, d). Although the structure of this side-product is not confirmed, we were able to slightly suppress its formation by addition of an appropriate additive (Table 5.7).

To prepare a wide array of diaryldifluoromethane motifs, it would be desirable to synthesize more variants of the aryldifluoromethyl silane reagents explored in this coupling. Although the reported reductive silylation reaction of benzotrifluorides can be used to form simple aryldifluoromethylation reagents, the C-F bond activation of this transformation was found to be very sensitive to the electronic properties of the aromatic ring.[36] Trifluoromethylarenes with strong electron-donating substituents did not react. Halogenated benzotrifluorides reacted to form the CF_2-Si bond, but the halogen substituent underwent magnesiation and was quenched by TMSCl to form the corresponding trimethylsilylarene.[36] We subjected various benzotrifluorides that were not explored in the original publication to the reported reaction conditions, but were unable to form the desired $TMSCF_2Ar$ reagents (Figure 5.5). The benzotrifluorides examined contained groups that could later be manipulated by further transformations, including boronic acids, boronate esters, ketones, esters, ketals, thioketals, alkenyl groups, and alkynyl substituents. The reductive silylation reactions of trifluoromethyl-substituted heteroaryl compounds were also investigated. In these reactions, the starting materials either remain inert, undergo decomposition of the functional groups on the aromatic ring, or over-reduce to $CF(TMS)_2$-containing products.

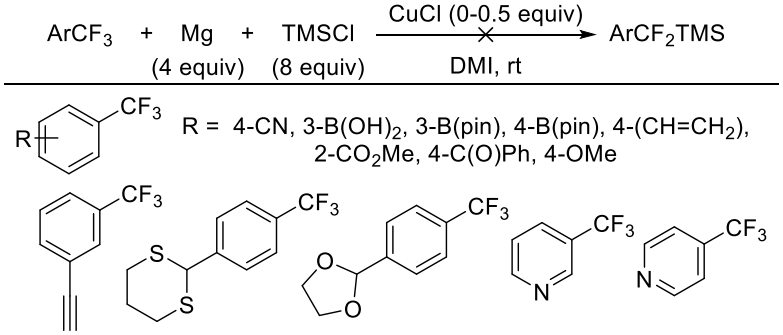


Figure 5.5 (Het)$ArCF_3$ compounds that did not undergo reductive silylation reaction

To broaden access to more complex $TMSCF_2Ar$ reagents, we explored various potential new synthetic routes to such compounds (Figure 5.6). We attempted the deprotonation of difluoromethylarenes with alkyllithium or potassium amide bases to generate aryldifluoromethyl anions, which could then be trapped by TMSCl (Figure 5.6, i). Although analogous deprotonation

reactions of fluoroform have been reported with these bases,[42] we were not able to find conditions that formed the desired silicon-containing compound in good yield.

Construction of the C-F bonds of this reagent by benzylic *gem*-difluorination was attempted by the reaction of benzyltrimethylsilane with the electrophilic fluorinating reagent, Selectfluor, and either a silver-based or a photochemical oxidant (Figure 5.6, ii). No fluorinated product was observed. Reported benzylic *gem*-difluorination reactions are typically conducted on unhindered methylarenes or ethylarenes, so it is likely that a large trimethylsilyl group on the benzylic position hinders the ability of the proposed benzyl radicals generated in this system to react with Selectfluor. Additionally, benzyltrimethylsilanes are not widely accessible starting materials for the synthesis of $TMSCF_2Ar$ reagents.

Bromodifluoromethyl trimethylsilane is a commercially available reagent that can also be prepared in one step from inexpensive $TMSCF_3$.[43] While this reagent has been employed as a difluorocarbene source, activation of the C-Br bond by a transition metal could potentially give access to a reactive CF_2TMS species. We explored the reaction of an arylboronic acid with this reagent under various transition metal-mediated or -catalyzed conditions (Figure 5.6, iii). We did not observe the desired products. A Cu-mediated reductive coupling of $TMSCF_2Br$ with aryl iodides was attempted, but no product was observed (Figure 5.6, iv). The low stability of $TMSCF_2Br$ and its decomposition to difluorocarbene were the primary reasons for the unsuccessful coupling reactions.

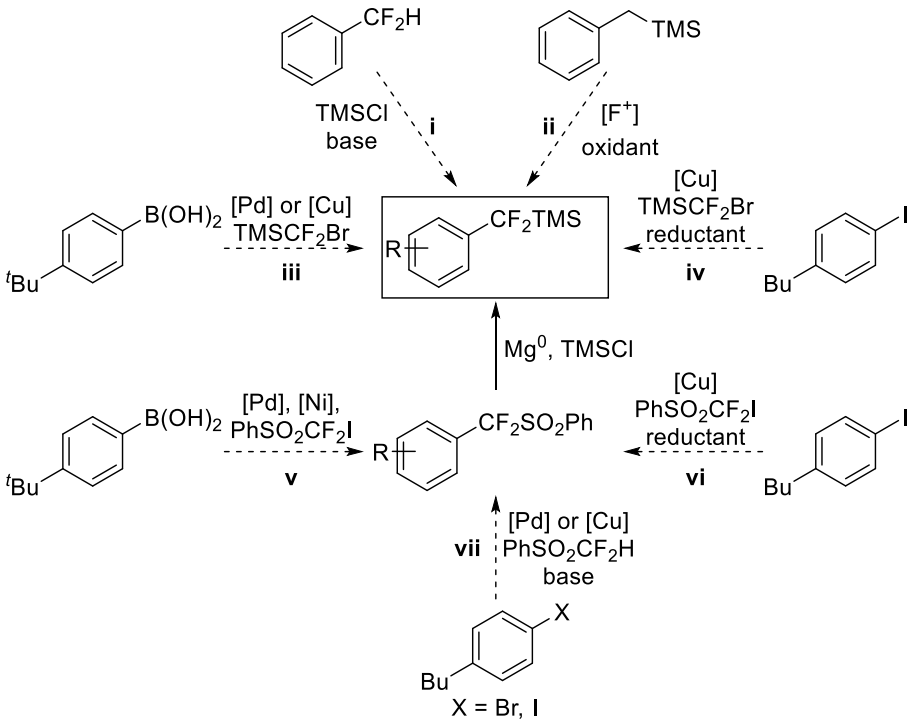


Figure 5.6 Attempted alternative synthetic routes to aryldifluoromethyl trimethylsilane reagents

The reductive silylation of fluoroalkylated phenylsulfones has been previously reported for the synthesis of trifluoromethyl, difluoromethyl, and 1,1-difluoroethyl silicon reagents.[44-45] Because the phenylsulfonyl group can be ready converted to a trialkylsilyl group, we considered the preparation of aryldifluoromethyl phenylsulfones as a precursor to aryldifluoromethyl silanes. Under reaction conditions that have been previously applied to the Pd-,[14] or Ni-catalyzed[15, 46] coupling of $ArB(OH)_2$ with halodifluoromethyl-esters, -amides, or -phosphonates, we were unable to couple $ArB(OH)_2$ to the analogous iododifluoromethyl phenylsulfone (Figure 5.6, v). The McLoughlin-Thrower reaction involves a Cu-mediated reductive coupling of aryl iodides with perfluoroalkyl iodides.[47] We found that this reaction could not be extended to the coupling of ICF_2SO_2Ph (Figure 5.6, vi).

Direct deprotonation of commercially-available phenyl(difluoromethyl)sulfone has been shown to occur with *tert*-butoxide bases at low temperature.[48] We sought to generate this anion for the palladium-catalyzed or copper-mediated coupling of aryl halides with phenyl(difluoromethyl)-sufone (Figure 5.6, vii). Deprotonation of fluoroalkyl groups has been previously shown to generate reactive nucleophiles for transition metal-mediated couplings. Direct deprotonation of α,α-difluoroacetophenone to generate reactive difluoroketone enolates that can then couple to aryl halides with a palladium catalyst has been achieved.[11] A method for deprotonation and cupration of HCF_3 has also been demonstrated for the preparation of $ArCF_3$.[42] Despite the success in related couplings of difluoroketone enolates or trifluoromethyl anions, no coupled product was observed between aryl halides and phenyl(difluoromethyl)sulfone.

5.3 Conclusions and Outlook

We have disclosed the first example of a palladium-catalyzed coupling of aryldifluoromethyl groups to widely available aryl bromides and aryl chlorides. This reaction was enabled by the use of a readily accessible phenyldifluoromethyl anion surrogate, **1a**. While high yields of product could be obtained in reactions catalyzed by a palladium complex containing an electron-rich (2,4-dimethoxyphenyl)di-*tert*-butyl phosphine ligand, **L10**, the functional group compatibility of this system was found to be poor. In addition, a limited range of aryldifluoromethyl components could be accessed through the reported literature procedure for the synthesis of these compounds. Although the previously discussed exploratory routes to such compounds were not successful, further investigation of these reactions could result in a method to prepare more complex aryldifluoromethylsilanes from abundant starting materials. Indeed, a recent report from the Hu group has demonstrated the Cu-mediated oxidative coupling of phenyl(difluoromethyl)sulfone with arylboronic acids.[49] Reductive silylation of these compounds should afford aryldifluoromethyl trialkylsilanes reagents.

While modification of the palladium catalyst could allow for the coupling of unreactive aryl bromides, or accelerate the reaction of ArBr that formed products in low yields, many of the functionalized starting materials of this reaction undergo room temperature, uncatalyzed formation of side products. These undesired side reactions indicate that the poor functional group compatibility is likely a consequence of the reactivity of silane **1a**, and not of any palladium-

catalyzed process. To address this limitation, the effect of additives that could better stabilize CF_2Ar anions or act as a reservoir for these reactive species should be explored. Indeed, such a strategy has been demonstrated in previously reported fluoroalkylation reactions. The addition of trimethylborate as a Lewis acid was found to improve a Cu-catalyzed trifluoromethylation reaction of ArI with $TMSCF_3$,[50] and the presence of an NHC-ligated Ag(I) salt greatly improved a palladium-catalyzed difluoromethylation reaction of aryl bromides with $TMSCF_2H$.[51]

Alternatively, new sources of aryldifluoromethyl nucleophiles should be investigated that could allow these reactions to occur with greater functional group compatibility (Figure 5.7). Trifluoroacetates have been demonstrated as sources of nucleophilic CF_3 after decarboxylation, and trifluoroacetophenone has been reported to generate CF_3 anion upon treatment with *tert*-butoxide base.[52] Analogous aryldifluoromethyl esters or ketones could be readily prepared through literature-reported α-arylation reactions and reactions of these compounds could serve as a strategy to access diverse CF_2Ar nucleophiles. Trifluoromethyl-[53] and difluoromethyl-zinc(II)[54-56] species have been broad applicability in mild trifluoromethylation and difluoromethylation reactions, respectively. The synthesis and reactivity of an aryldifluoromethyl zinc(II) could also be investigated.

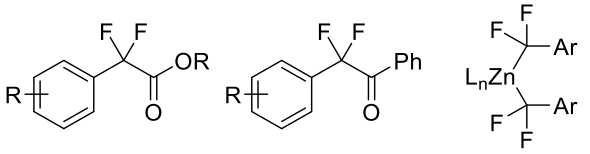


Figure 5.7 Alternative nucleophilic sources of CF_2Ar

Gaining insight into the mechanism of this Pd-catalyzed coupling, and into the formation of the undesired side-products observed in the reactions of certain ArBr, could be beneficial in improving the utility of this synthetic method. Understanding the salient mechanistic features of this reaction will be critical for the discovery of modifications that can improve the yields of products and result in the construction of more complex, highly-functionalized, diaryldifluoromethane structures.

5.4 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.

Aryl bromides and aryl chlorides were purchased from commercial suppliers or prepared according to the published literature procedures. Aryldifluoromethyl silicon reagents **1a**, **1c**-**1e** are previously reported compounds and were prepared according to the literature procedure.[36] The preparation and characterization of reagents **1b** and **1f** are described below. Ligands **L2, L3**, **L7**, and **L8** were prepared according to reported literature procedures.[57-59] The preparation and

characterization of ligands **L2**, **L7**, **L9** and **L10** are described below. All other ligands, reagents, and solvents were purchased from commercial sources and used as received.

Diaryldifluoromethane products **3d**, **3f**, **3g**, and **3s** have been previously reported in the literature and the identity of these products was confirmed by comparison of the acquired ^{19}F NMR spectrum to the published data and by GC-mass spectrometry.[60-64] The yields and identity of the remaining diaryldifluoromethane products were determined by ^{19}F NMR spectroscopy and by GC-mass spectrometry following the general procedure described below. Isolation of these compounds was made difficult by poor separation of the products from $PhCF_2H$ or by the formation of previously unobserved side products upon increasing the scale of the reaction.

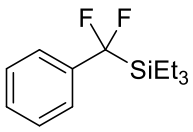
NMR spectra were acquired on 400 MHz, 500 MHz, or 600 MHz Bruker instruments at the University of California, Berkeley. NMR spectra were processed with MestReNova 5.0 (Mestrelab Research SL). Chemical shifts are reported in ppm and referenced to residual solvent peaks ($CHCl_3$ in $CDCl_3$: 7.26 ppm for ^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.

General Procedure for the Synthesis of Aryldifluoromethyl Silanes (1a-1f)

To an oven dried flask equipped with a magnetic stir bar was added Mg (4.0 equiv), CuCl (0.5 equiv), and 1,3-dimethyl-2-imidazolidinone (DMI) (0.25 M with respect to the benzotrifluoride derivative). The flask was fitted with a rubber septum, and TMSCl (8.0 equiv) was added to the suspension. The reaction was allowed to stir for 15 minutes at room temperature, at which time a benzotrifluoride derivative (1.0 equiv) was added dropwise. The solution was then allowed to continue stirring at room temperature for 10 h or until consumption of $ArCF_3$ was observed by ^{19}F NMR spectroscopy. Hexanes were added to the flask, and solids were removed from the solution by filtration through a pad of *Celite*. The resulting hexanes layer was extracted from the DMI layer with additional hexanes, and the combined hexanes layers were washed with 1.0 M HCl and then brine. The solution was dried with anhydrous Na_2SO_4 and filtered, and the solvent was evaporated from the resulting solution under reduced pressure. The crude product was purified by silica gel chromatography with hexanes as eluent.

(difluoro(phenyl)methyl)triethylsilane (1b)



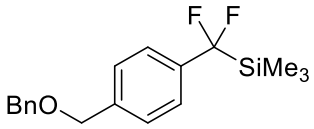
The product was prepared on a 20.0 mmol scale according to the general procedure for the synthesis of aryldifluoromethyl silanes to afford **1b** as a colorless oil (1.6 g, 32% yield).

^1H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.31 (m, 5H), 1.00 (t, J = 8.0 Hz, 9H), 0.72 (q, J = 8.0 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.9 (t, J = 20.1 Hz), 129.4 (t, J = 266.2 Hz), 128.8 (t, J = 2.5 Hz), 128.3, 124.5 (t, J = 8.0 Hz), 6.9, 0.9.

^{19}F NMR (565 MHz, $CDCl_3$) δ -106.3

((4-((benzyloxy)methyl)phenyl)difluoromethyl)trimethylsilane (1f)



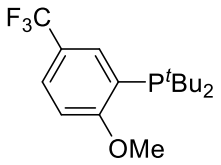
The product was prepared on a 3.75 mmol scale according to the general procedure for the synthesis of aryldifluoromethyl silanes to afford **1f** as a colorless oil (724 mg, 60% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.40 (m, 2H), 7.39 – 7.35 (m, 4H), 7.34 – 7.29 (m, 3H), 4.59 (s, 2H), 4.58 (s, 2H), 0.14 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.2 (t, J = 2.4 Hz), 138.2, 137.7 (t, J = 20.4 Hz), 128.6, 128.0, 127.9, 127.7, 125.0 (t, J = 7.9 Hz), 72.6, 71.9, -4.7. (Note: The triplet corresponding to the CF_2 carbon overlapped with signals for aromatic carbons and was not observed)

^{19}F NMR (565 MHz, $CDCl_3$) δ -111.1.

Synthesis of di-*tert*-butyl(2-methoxy-5-(trifluoromethyl)phenyl)phosphine (L9)



To an oven dried 4 mL vial was added di-*tert*-butylchlorophosphine (361 mg, 2.00 mmol) and ether (2 ml). 2-Methoxy-5-(trifluoromethyl)phenyllithium (400 mg, 2.20 mmol, 1.10 equiv) was dissolved in ether (1 ml + 1 ml rinse) and added dropwise with stirring to the reaction vial. The vial was sealed with a Teflon-lined cap, and the reaction mixture was stirred at ambient temperature for 24 h. The reaction mixture was filtered through a plug of silica, which was rinsed with ether (6 ml). The volatile materials were removed *in vacuo*. The crude product was purified by column chromatography (5% to 15% Et_2O/pentane gradient) to give the title compound as a clear and colorless oil (500 mg, 1.56 mmol, 78% yield).

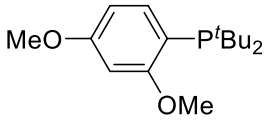
This compound exists as a mixture (60:40 in C_6D_6, 75:25 in $CDCl_3$) of two rotamers (P–C(sp^2) rotation). NMR signals were assigned to major/minor by their integrations when possible. The two sets of ^{1}H NMR resonances were coalesced at 90 °C in C_6D_6.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 – 7.88 (m, 1H major+minor), 7.64 – 7.55 (m, 1H major+minor), 6.96 (dd, *J* = 8.5, 4.5 Hz, 1H major), 6.92 (d, *J* = 8.5 Hz, 1H minor), 3.88 (s, 3H major) 3.85 (s, 3H minor), 1.20 (d, *J* = 12.0 Hz, 18H major) 1.19 (d, *J* = 12.2 Hz, 18H minor).

^{19}F NMR (565 MHz, $CDCl_3$) δ -62.5 (minor), -62.6 (major).

^{31}P NMR (243 MHz, $CDCl_3$) δ 56.5 (minor), 9.6 (major).

Synthesis of di-*tert*-butyl(2,4-dimethoxyphenyl)phosphine (L10)



To an oven dried flask equipped with a magnetic stir bar was added Mg (91 mg, 3.8 mmol, 1.5 equiv) and THF (8 mL). 2,4-Dimethoxybromobenzene (0.1 mL, 0.7 mmol) was added to the reaction to initiate formation of the Grignard reagent. The reaction was heated at 75 °C, and an additional portion of the aryl bromide was added (0.1 mL, 0.7 mmol). The flask was removed from heat and allowed to cool to room temperature. The remainder of the aryl bromide was added dropwise (340 μL, 2.4 mmol). To the flask containing the Grignard reagent was slowly added a solution of P^{t}Bu$_2$Cl (480 μL, 2.5 mmol, 1.0 equiv) and CuCl (15 mg, 150 μmol, 6 mol %) in THF (4 mL). The reaction was refluxed for 12 h, and conversion of P^{t}Bu$_2$Cl was monitored by ^{31}P NMR spectroscopy. After full conversion of the chlorophosphine, Et_2O (15 mL) and H_2O (10 mL,

sparged with N_2 for 30 min) were added to the flask. The reaction was extracted with Et_2O (4 x 7 mL), and the combined organic layers were concentrated under reduced vacuum. The crude phosphine was purified by silica gel chromatography under inert atmosphere (100% pentane to 5% Et_2O/pentane gradient) to afford **L10** as a colorless oil (240 mg, 34%).
This compound exists as a mixture (53:47 in C_6D_6, 72:28 in $CDCl_3$) of two rotamers (P–C(sp^2) rotation). NMR signals were assigned to major/minor by their integrations when possible.
^{1}H NMR (500 MHz, C_6D_6) δ 7.86 (dd, J = 14.1, 8.3 Hz, 1H), 7.64 (dd, J = 8.2, 1.9 Hz, 1H), 6.47 – 6.33 (m, 3H), 6.31 – 6.21 (m, 1H), 3.35 (s, 3H minor), 3.34 (s, 3H minor), 3.30 (s, 3H major), 3.16 (s, 3H major), 1.36 (d, J = 11.9 Hz, 18H major), 1.29 (d, J = 11.5 Hz, 18H minor).
^{31}P NMR (202 MHz, C_6D_6) δ 52.22 (major), 8.10 (minor).

General Procedure for the Aryldifluoromethylation of (Hetero)aryl Bromides and Aryl Chlorides for Characterization by ^{19}F NMR Spectroscopy

To an oven-dried 4 mL vial was added **L10** (3.0 μmol, 3.0 mol %), $[(allyl)PdCl]_2$ (1.0 μmol, 1.0 mol % of dimer), and dimethoxyethane (DME) (0.2 mL). Aryl halide (0.10 mmol, 1.0 equiv) and aryldifluoromethyl silane (0.20 mmol, 2.0 equiv) were added, followed by CsF (0.20 mmol, 2.0 equiv). The vial was sealed with a Teflon-lined cap and heated at 80 ºC for 12 h. The solution was allowed to cool to room temperature. 4,4'-Difluorobenzophenone (0.10 mmol, 1.0 equiv) was then added as internal standard, and the reaction mixture was directly transferred to an NMR tube for characterization by ^{19}F NMR spectroscopy. Formation of products and yields of reactions were based on the presence of an indicative singlet peak between approximately -87.0 ppm and -91.0 ppm in the ^{19}F NMR spectrum, Singlets within this range of chemical shifts are observed for previously reported diaryldifluoromethane compounds.[60-64] Analysis of the crude reaction mixture by GC-mass spectrometry confirmed the presence of expected product molecular weights, and indicated characteristic benzylic C-F cleavage as a major fragmentation for these compounds.

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