The Development of Transition Metal-Catalyzed Fluoroalkylation and Fluoroenolate Arylation Reactions

By

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Professor F. Dean Toste
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Abstract

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The following dissertation discusses the development and mechanistic study of reactions that form bonds between fluorine-containing substituents and functionalized aromatic compounds. In particular, this work focuses on transition metal-catalyzed reactions that form aryldifluoromethylcarboxylic acid derivatives and trifluoromethylarenes.

Chapter 1 discusses the properties and applications of fluorine-containing organic compounds and provides an overview of methods for the synthesis of fluoroalkylarenes. The challenges associated with developing transition metal-catalyzed reactions that form aryldifluoromethyl carboxylic acid derivatives and trifluoromethylarenes are also described, and strategies to address these challenges are discussed.

Chapter 2 describes the development of a copper-catalyzed cross-coupling reaction to form aryldifluoroamides from α-silyldifluoroamides and aryl iodides, vinyl iodides, or heteroaryl bromides. The reactions tolerate a variety of functional groups, and the aryldifluoroamide products can be converted to a diverse array of difluoroalkylarenes. The application of this reaction to the synthesis of fluorinated compounds of potential biological interest is also described.

Chapter 3 describes the synthesis, characterization, and reactivity of fluoroenolate complexes of palladium. A systematic study of reductive elimination from fluorinated ester, amide, and nitrile enolate complexes was conducted, and factors influencing the rate of reductive elimination were determined.

Chapter 4 discusses the development of a cross-coupling reaction to form aryldifluoronitriles. In the presence of copper, an α-silyldifluoroacetronitrile reagent couples with aryl halides in moderate to high yields.

Chapter 5 describes the investigation of reductive elimination to form an aryl-trifluoromethyl bond by treatment of arylnickel(II) trifluoromethyl complexes with single-electron oxidants. The reactions occur at room temperature in up to 70% yield.

Chapter 6 discusses the identification of new classes of ligands that promote reductive elimination to form trifluoromethylarenes from arylpalladium(II) trifluoromethyl complexes. The reductive elimination reactions occur under mild conditions and at moderate temperatures.

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Chapter 1

Overview of Methods for the Synthesis of Aryldifluoromethyl Carboxylic Acid Derivatives and Fluoroalkylarenes

1.1 Overview of Properties and Applications of Fluorine-Containing Compounds

The incorporation of fluorine atoms and fluorine-containing functional groups is a common strategy to improve the biological and physical properties of pharmaceuticals, agrochemicals, and materials.[1-5] Of the 50 drugs approved by the FDA between January 2017 and February 2018, 13 contain fluorine (see Figure 1.1 for selected examples). Among the drugs approved, a total of 47 fluorine atoms were incorporated, mainly as aryl fluoride or trifluoromethylarene motifs.

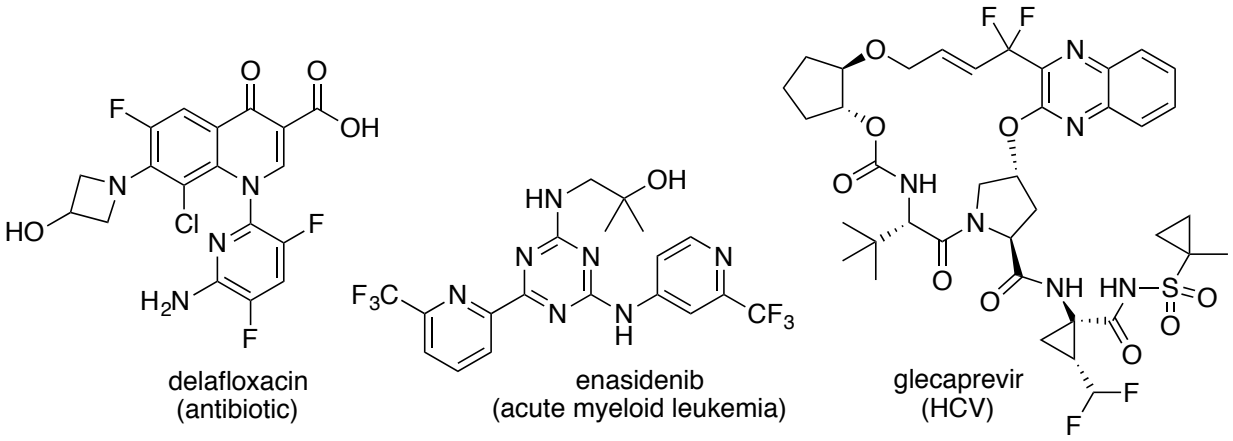
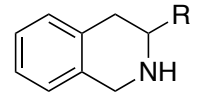


Figure 1.1 Examples of fluorinated pharmaceuticals approved by the FDA in 2017.

Many of the desirable effects of incorporating fluorine atoms can be attributed to a combination of fluorine's small size, high electronegativity, and ability to form strong, highly polarized bonds to carbon. The van der Waals radius of fluorine (1.47 Å) is intermediate between than of hydrogen (1.2 Å) and oxygen (1.52 Å),[6] and fluorine is the most electronegative element ($\chi = 4.0$).[7] Fluorine has been used extensively in drug development to replace both hydrogen and oxygen atoms.[8] In the former case, substitution is the most conservative option on steric grounds; in the latter, substitution provides a comparable size match and replaces one electronegative atom with another.

In medicinal chemistry, fluorinated compounds often display differences in lipophilicity, metabolic stability, and overall activity relative to their non-fluorinated analogs.[9-12] Modulating the lipophilicity of a biologically active compound can control bioavailability, absorption, and membrane permeability. The effects of fluorination on lipophilicity are variable;[12] however, on average, a modest increase in log *D* is observed upon substitution of a hydrogen atom by a fluorine atom.[13] The incorporation of fluorine can also modulate the pK_a of neighboring functional groups such as amines and acids.[14-16] For example, significant changes in pK_a were observed upon increasing fluorine substitution for a series of phenylethanoloamine *N*-methyltransferase (PNMT) inhibitors (Figure 1.2).[14]



PNMT inhibitors

R	pK_a
CH_3	9.42
CH_2F	7.88
CHF_2	6.42
CF_3	4.88

Figure 1.2 Effect of fluorine incorporation on pK_a of PNMT inhibitors.

Targeted incorporation of fluorine atoms at metabolically labile sites can block oxidative metabolism pathways mediated by P450 enzymes, thereby increasing the half-life of drug candidates and preventing the formation of potentially toxic metabolites. For instance, identification of a site of metabolic hydroxylation and substitution of fluorine for hydrogen at that position decreased the clearance rate of the CCR1 antagonist shown in Figure 1.3 dramatically while maintaining binding efficacy.[17]

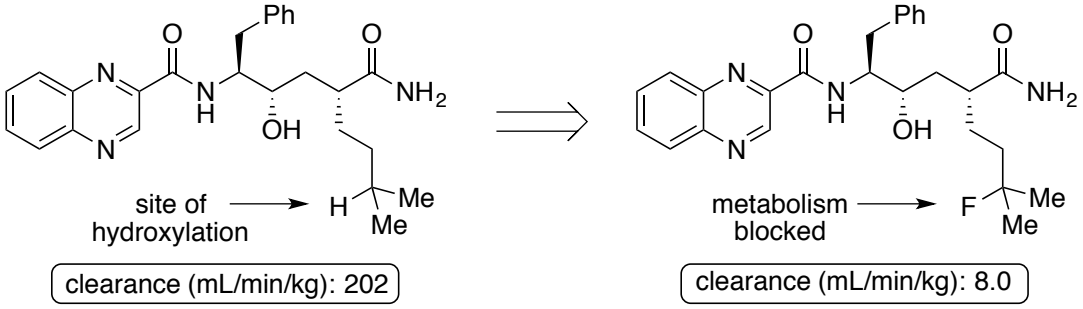


Figure 1.3 Improvement in metabolic stability upon incorporation of fluorine.

Although fluorine is the most abundant halogen in the earth's crust, very few fluorine-containing natural products have been isolated. Halogenating enzymes that form bonds between carbon and chlorine, bromine, or iodine give rise to the >5,000 halogenated natural products that have been reported in the literature.[18] Haloperoxidases and halogenases transform halide anions (X^-) to reactive halonium (X^+) or halide radical ($X^\cdot$) species that participate in carbon-halogen bond-forming reactions. However, the oxidation potential of hydrogen peroxide (-1.8 eV) is insufficient to oxidize fluoride (-2.87 eV), rendering haloperoxidases ineffective for fluorination reactions.[19] In addition, accessing the nucleophilic reactivity of fluoride in an aqueous environment is challenging due to its highly exothermic heat of hydration (-120 kcal/mol).[20] The first fluorinase enzyme was identified in 2002 by O'Hagan and coworkers and was shown to mediate the desolvation of fluoride and its subsequent reaction with S-adenosyl-L-methionine (SAM) to form 5'-fluorodeoxyadenosine (5'-FDA).[21-22] Further biosynthetic steps convert 5'-FDA to the potent toxin fluoroacetate and to 4-fluoro-L-threonine. Although additional fluorinase enzymes have been reported,[23-24] examples of fluorinated natural products remain limited to a handful of compounds that contain C(sp^3)-F bonds (see Figure 1.4). No examples of natural products

containing difluoromethylene, trifluoromethyl, or C(sp^2)-F motifs have been definitively identified.[25]

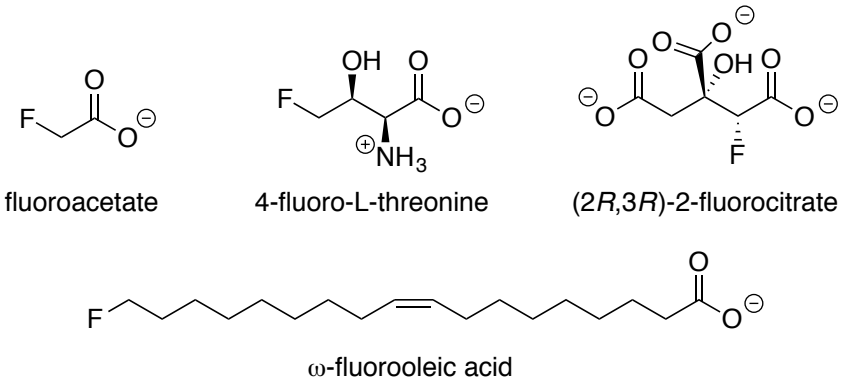


Figure 1.4 Fluorine-containing natural products.

To expand access to fluorine-containing organic compounds beyond the limited examples found in nature, a wide range of synthetic strategies for the incorporation of fluorine into organic compounds have been pursued. Currently, most fluorine atoms and fluorine-containing functional groups in pharmaceuticals and agrochemicals are incorporated in early synthetic steps in the form of simple fluorine-containing building blocks. While this strategy is amenable to large-scale manufacturing processes, reactions that allow these groups to be installed at a later synthetic step are desirable for applications in drug discovery. For example, reactions that afford access to a diverse array of fluorine-containing compounds are valuable for analyses of structure-activity relationships. The development of fluoroalkylation reactions that are mediated or catalyzed by transition metal complexes has the potential to improve access to this important class of compounds.

The remainder of this chapter presents a review of methods for the synthesis of aryldifluoromethyl carboxylic acid derivatives (Section 1.2) and trifluoromethylarenes (Section 1.3). Each section includes a discussion of traditional synthetic methods to access each class of compound, as well as the challenges, prior art, and future outlook associated with the development of transition metal-catalyzed transformations.

1.2 Synthesis of Aryldifluoromethyl Carboxylic Acid Derivatives

1.2.1. Motivation for the Synthesis of Aryldifluoromethyl Carboxylic Acid Derivatives

Aryldifluorocarbonyl groups and aryldifluoronitriles are present in several biologically active compounds, including inhibitors and modulators of FKBP12,[26] AMPAR,[27] and prostaglandin D_2 receptors,[28] as well as anti-inflammatory compounds[29] (Figure 1.5). The incorporation of a benzylic difluoromethylene (CF_2) group in these molecules is of particular interest because the CF_2 group can serve as a bioisostere of carbonyl groups and ethers[26] and can modulate the pK_a value of nearby functional groups such as amines and acids.[14-16] The presence of fluorine atoms can also block oxidation at metabolically labile benzylic positions.[26-27, 30] In

addition, difluoroester, -amide, -nitrile, and -acid groups can be further transformed to generate amines, alcohols, ketones, esters, amides, and acids.

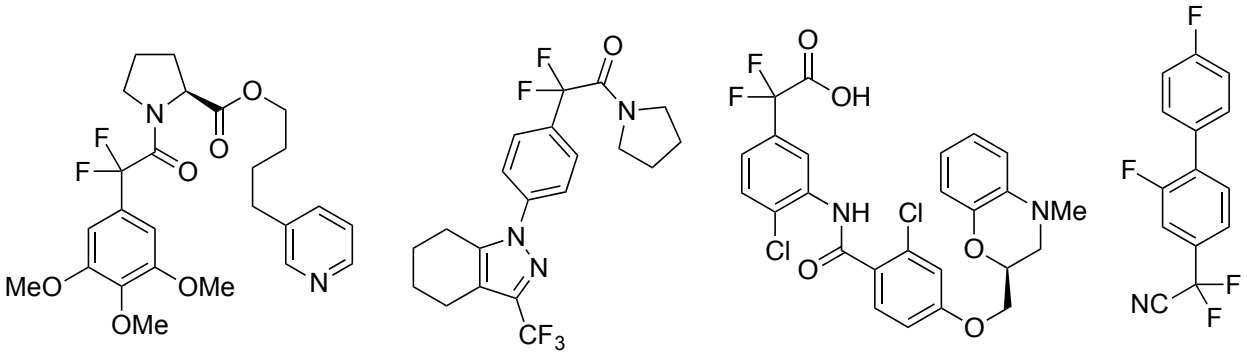


Figure 1.5 Selected biologically active aryldifluorocarboxylic acid derivatives and aryldifluoronitriles.

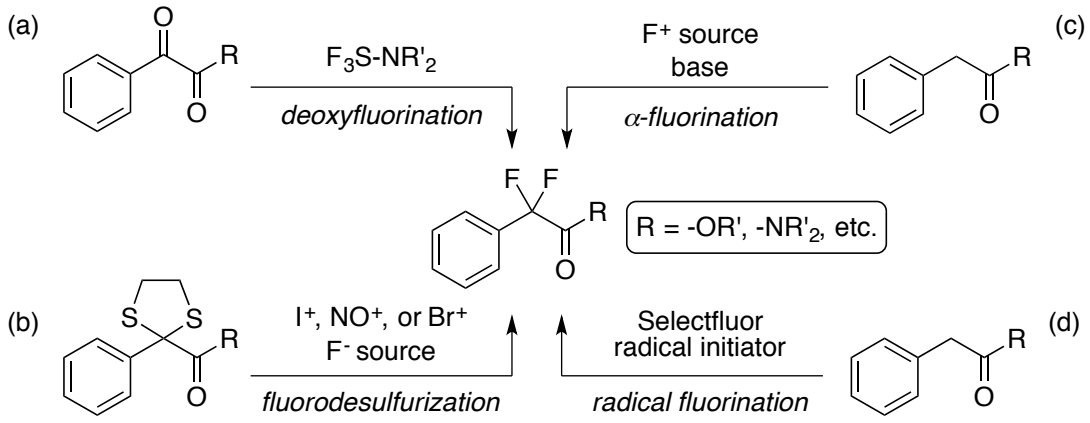
1.2.2 Synthesis of Aryldifluoromethyl Carboxylic Acid Derivatives by C-F Bond Formation or Radical Addition

Despite the biological and synthetic potential of aryldifluorocarbonyl compounds, current methods for their synthesis are limited. Aryldifluoroesters and -amides can by prepared by deoxyfluorination of the corresponding α-keto amide or ester with diethylaminosulfur trifluoride (DAST) or related aminosulfur trifluorides (Scheme 1.1a),[31-33] and aryldifluoronitriles have been prepared by treatment of the corresponding acyl cyanides with DAST.[34] However, DAST and related fluorinating reagents release toxic HF upon contact with water and can undergo explosive decomposition upon heating. The functional group compatibility of these reactions is also often limited. Although more stable and easier-to-handle deoxyfluorination reagents have been developed, they suffer from high costs and/or low reactivity in difluorination reactions of carbonyl groups.[35-38] In addition, this route is not suitable for the synthesis of aryldifluoroketones because the corresponding 1,2-diketone substrates react at both carbonyl groups.

Alternatively, fluorodesulfurization reactions of benzylic thioketals enable *gem* difluorination at benzylic positions (Scheme 1.1b).[39] Although this strategy often affords the difluoromethylene-containing product in higher yields than the corresponding deoxyfluorination reaction of a 1,2-dicarbonyl compound, this strategy requires additional synthetic steps to prepare the 1,3-dithiolane substrate.

Fluorination reactions alpha to esters, amides, nitriles, and nitro groups in the presence of a base and an electrophilic fluorinating reagent have been reported (Scheme 1.1c),[40-45] but yields and selectivity for the difluorinated product over monofluorinated byproducts are often low. Similarly, examples of radical-based benzylic fluorination reactions that selectively form difluoroalkylarenes, rather than the corresponding monofluoroalkylarenes, are rare (Scheme 1.1d).[46-47] These silver- or visible light-catalyzed reactions require up to 5 equivalents of

fluorinating reagent, and the difluoroalkylarene products can be difficult to separate from monofluorinated byproducts.



Scheme 1.1 Methods to prepare $ArCF_2COR$ compounds by C-F bond formation.

Methods to generate radicals from α-halodifluorocarbonyl compounds such as ethyl bromodifluoroacetate have been developed.[48-52] Light, silver salts, or persulfate salts can promote carbon-halogen bond cleavage of α-halodifluorocarbonyl compounds to form the corresponding difluoroalkyl radicals. These radicals then add to radical acceptors. However, these reactions are generally applicable only to heteroarene substrates and often afford mixtures of isomeric products.

1.2.3 Challenges and Strategies for the Synthesis of Aryldifluoromethyl Carboxylic Acid Derivatives by Transition Metal-Catalyzed Cross-Coupling

Cross-coupling reactions to form aryldifluoromethyl carboxylic acid derivatives are desirable because they can allow variation of both the arene and difluoroenolate coupling partner, thereby enabling access to a wide range of products. Figure 1.6 depicts general catalytic cycles for cross-coupling reactions of aryl halides (left) and aryl boronic acids (right). Alpha-arylation reactions of non-fluorinated enolates are well-established synthetic methods to generate α-aryl carbonyl compounds.[53-54] However, several challenges are associated with the development of analogous reactions of fluorinated enolates.

First, the alkali metal enolates of difluorocarbonyl compounds are unstable at the temperatures required for typical cross-coupling reactions.[55-56] The presence of α-fluorine substituents enhances the electrophilicity of the parent carbonyl compounds, promoting decomposition pathways involving attack of a difluoroenolate on the difluorocarbonyl comopound to generate aldol- or Claisen-type products.[57-59] In addition, generating a difluoroenolate by deprotonation under basic conditions can limit the functional group tolerance of the reaction.

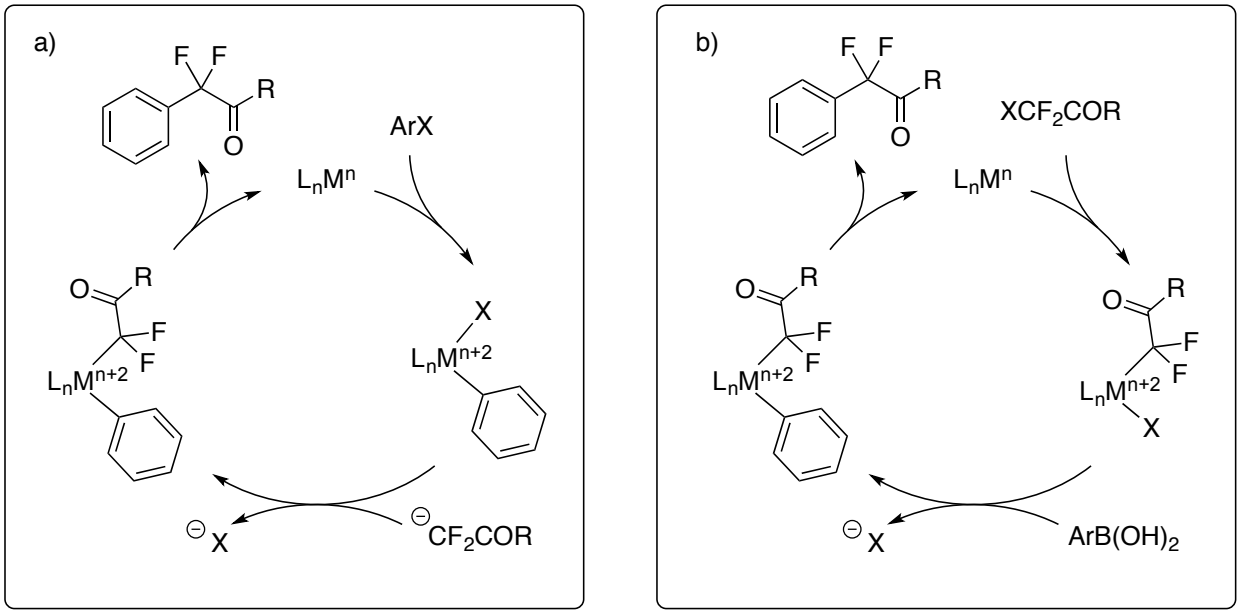


Figure 1.6 General catalytic cycles for transition metal-catalyzed syntheses of aryldifluorocarboxylic acid derivatives from a) aryl halides and b) arylboronic acids. For simplicity, only carbon-bound metal enolate intermediates are depicted.

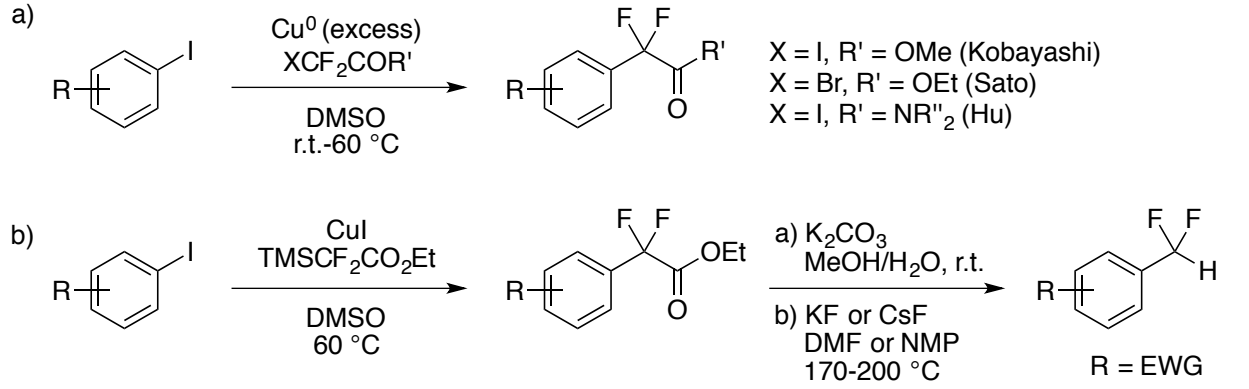
To address these challenges, silyl-protected difluoroenolate equivalents have been employed in cross-coupling reactions. These reagents can be activated *in situ* by fluoride or another suitable Lewis base to promote transmetallation to a transition metal catalyst. Limiting the concentration of difluoroenolate anion in solution can help prevent decomposition and unproductive side reactions. Alternatively, coupling reactions of aryl nucleophiles with halodifluorocarbonyl electrophiles can be conducted. Although fewer aryl nucleophiles, such as arylboronic acids, are commercially available or accessible compared to aryl halides, this strategy allows for the direct generation of a metal difluoroenolate by oxidative addition (Figure 1.6, right), rather than by transmetallation with a potentially unstable difluoroenolate anion (Figure 1.6, left).

The product-forming step of a transition metal-catalyzed fluoroenolate arylation reaction is reductive elimination from an arylmetal difluoroenolate intermediate. This step is likely to be more challenging for complexes containing fluorinated enolates than for complexes containing the analogous non-fluorinated enolates, as the presence of fluorine on the α-carbon of an arylmetal alkyl intermediate raises the barrier to reductive elimination[60] (see Section 1.3 for further discussion of the effects of fluorine on reductive elimination reactions). The rate of reductive elimination can be increased with a judicious selection of ligand, or by accessing arylmetal difluoroenolate intermediates from which reductive elimination may be more facile (e.g. Cu^{III} rather than Pd^{II}).

1.2.4 Transition Metal-Mediated and -Catalyzed Syntheses of Aryldifluoromethyl Carboxylic Acid Derivatives

Cross-coupling reactions of aryl electrophiles with α-iododifluoroacetates mediated by copper were first reported by Kobayashi in 1986 (Scheme 1.2a).[61] In the presence of super-stoichiometric quantities of copper powder, reductive couplings of aryl iodides, vinyl iodides and bromides, and allyl and benzyl bromides with methyl iododifluoroacetate were achieved. Subsequently, Sato and coworkers demonstrated that ethyl bromodifluoroacetate, which is more stable and more readily available than iododifluoroacetate derivatives, coupled with aryl iodides under similar conditions.[62] The first reductive couplings of aryl and vinyl iodides with iododifluoroacetamides were reported by Hu in 2010.[63]

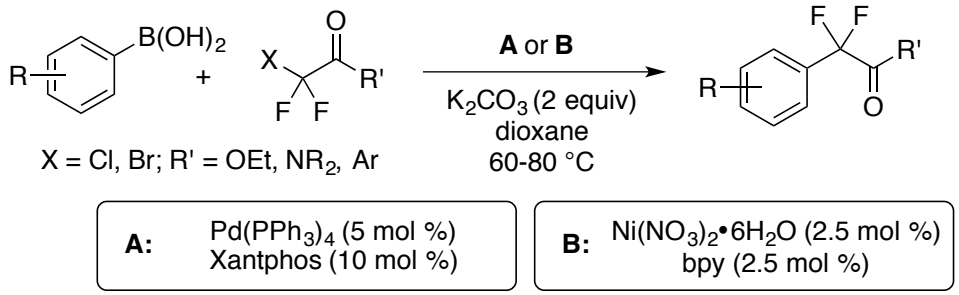
Copper-mediated and -catalyzed reactions of aryl electrophiles and difluoroenolate nucleophiles also have been developed. In 2011, Amii and coworkers reported a coupling of α-trimethylsilyldifluoroacetates with aryl iodides mediated by stoichiometric CuI (Scheme 1.2b).[64] The reaction also proceeded with catalytic amounts of CuI (20 mol %), but yields were variable (40-71%), and the reaction was limited to electron-deficient substrates. A related coupling of halopyridines was reported, but required two equivalents of CuI.[65] Amii also demonstrated that the aryldifluoroester products readily underwent hydrolysis to the corresponding carboxylic acids and that electron-deficient aryldifluoroacetic acids could be converted to the corresponding difluoromethylarenes by decarboxylation, albeit at high temperatures (170-200 ºC) and in the presence of excess base (5 equivalents KF or CsF).



Scheme 1.2 Summary of copper-mediated and -catalyzed methods to prepare aryldifluoroesters and -amides.

More recently, palladium- and nickel-catalyzed reactions for the synthesis of aryldifluorocarboxylic acid derivatives have been reported. In 2014, Zhang reported the coupling of arylboronic acids with bromodifluorophosphonates, -esters, and -amides in the presence of a combination of $Pd(PPh_3)_4$ and Xantphos (Scheme 1.3, conditions A).[66] The reaction proceeds in high yield with both electron-rich and electron-poor arylboronic acids and tolerates base-sensitive functional groups including esters, ketones, and aldehydes. A single example of the coupling of

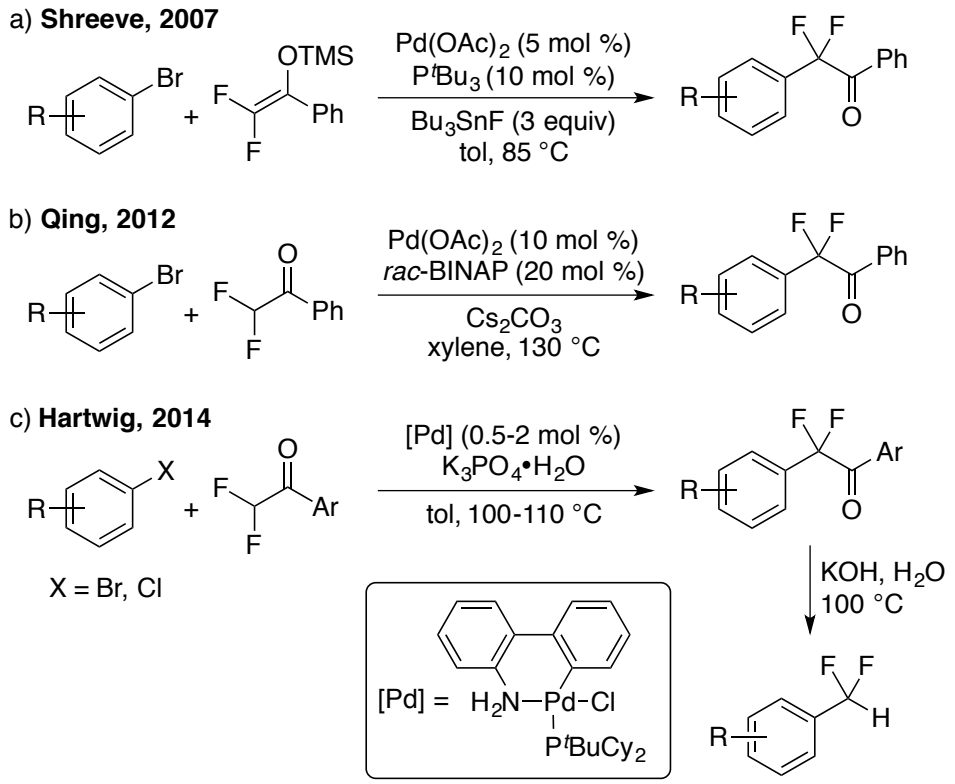
the pinacol ester of an arylboronic acid (*p*-$CF_3C_6H_4$-BPin) with ethyl bromodifluoroacetate was also reported.



Scheme 1.3 Pd- and Ni-catalyzed coupling reactions of arylboronic acids for the synthesis of arylldifluoroesters, -amides, and -ketones.

Although detailed mechanistic studies were not performed, reactions conducted in the presence of the radical inhibitors 1,4-dinitrobenzene or hydroquinone proceeded in substantially lower yield than those conducted in the absence of either additive. On the basis of these observations, the authors proposed that a single-electron transfer pathway for oxidative addition was likely operative.

Zhang later reported a nickel-catalyzed system for the difluoroalkylation of arylboronic acids (Scheme 1.3, conditions B).[67] The reaction is catalyzed by the combination of inexpensive, air-stable $Ni(NO_3)_2$•$6H_2O$ and 2,2'-bipyridine as ligand. The scope of the reaction is comparable to that of the analogous Pd-catalyzed reaction, tolerating variation of the electronic properties of the arylboronic acid coupling partner as well as base-sensitive functional groups including ketones, nitriles, and esters. In addition, aryl bromide and benzyl bromide functional groups are compatible with the reaction conditions. Functionalized difluoromethyl bromides and chlorides are both suitable coupling partners, and reactions of halodifluoroesters, -amides, -ketones, and -heteroarenes (benzothiazole, benzimidazole, and thiazole) proceed in high yield. The authors propose that the reaction proceeds through a Ni^{I}/Ni^{III} cycle involving: a) initial reduction of the Ni^{II} precatalyst to an active Ni^{I} species; b) transmetallation with an arylboronic acid to generate a [Ni^{I}]-Ar species; c) oxidative addition of the fluoroalkyl halide to generate a Ni^{III} intermediate; and d) reductive elimination to afford the functionalized difluoromethylarene product and regenerate a Ni^{I} species.

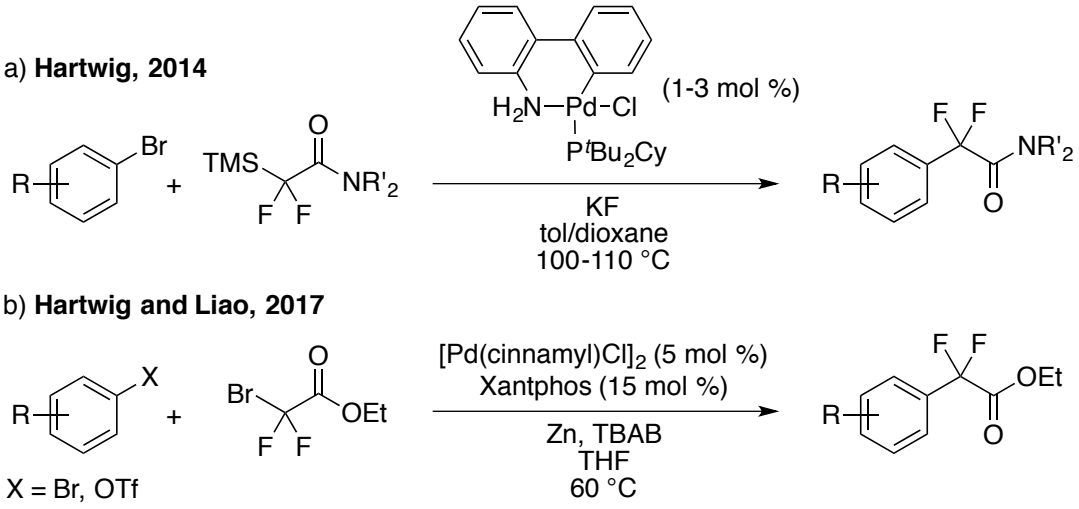


Scheme 1.4 Pd-catalyzed α-arylation reactions of 2,2-difluoroacetophenone and its derivatives.

While the Ni- and Pd-catalyzed reactions of arylboronic acids reported by Zhang afford access to a variety of difluoroalkylarenes, the development of complementary coupling reactions of cheaper, more readily available aryl halides is also valuable. In 2007, Shreeve reported a method for the palladium-catalyzed cross-coupling of aryl bromides with the trimethylsilyl enol ether of 2,2-difluoroacetophenone (Scheme 1.4a).[68] The reaction is catalyzed by a combination of $Pd(OAc)_2$ (5 mol %) and P^tBu_3 (10 mol %) and requires an excess of toxic Bu_3SnF, presumably to form a stannyl enolate *in situ* that undergoes transmetallation with an arylpalladium(II) halide intermediate. Qing subsequently reported a direct α-arylation of 2,2-difluoroacetophenone with aryl bromides (Scheme 1.4b).[69] However, the reaction required high Pd and ligand loadings (10 mol % $Pd(OAc)_2$ and 20 mol % *rac*-BINAP), high temperatures (130 ºC), and an excess of the aryl bromide coupling partner (2 equiv) relative to 2,2-difluoroacetophenone. Hartwig reported an improved system for the α-arylation of 2,2-difluoroacetophenone and its derivatives catalyzed by an air- and moisture-stable palladacyle containing P^tBuCy_2 as ligand (Scheme 1.4c).[70] Both aryl bromides and aryl chlorides underwent coupling in high yield, and a variety of functional groups were tolerated on both coupling partners. In addition, a one-pot synthesis of difluoromethylarenes by a sequence of α-arylation and subsequent Haller-Bauer cleavage of the benzoyl moiety was reported.

Cross-coupling reactions of aryl halides with difluoroamide and -ester enolates and enolate equivalents also have been developed. Hartwig reported a palladium-catalyzed coupling of aryl

bromides with α-silyldifluoroacetamides in the presence of a palladacyclic precatalyst containing P^tBu_2Cy as ligand (Scheme 1.5a).[71] The reaction has broad substrate scope, but does not occur with many medicinally relevant heterocycles, such as 2-halopyridines. In 2017, Hartwig and Liao reported a Negishi-type coupling of aryl bromides and aryl triflates with ethyl bromodifluoroacetate (Scheme 1.5b).[72] The reaction relies on the generation of a Reformatsky reagent ($BrZnCF_2CO_2Et$), which is formed *in situ* from Zn^0 and $BrCF_2CO_2Et$.[57] The reaction proceeds in moderate to high yields with both electron-rich and electron-poor aryl bromides and triflates, but does not tolerate electrophilic functional groups such as aldehydes and ketones.



Scheme 1.5 Pd-catalyzed methods for the synthesis of aryldifluoroamides and -esters.

1.2.5 Outlook on the Synthesis of Aryldifluoromethyl Carboxylic Acid Derivatives

Interest in the bioactivity of aryldifluoromethyl carboxylic acid derivatives as well as their potential to serve as fluorinated building blocks for the synthesis of diverse difluoroalkylarenes has motivated the development of a variety of methods for their synthesis. However, significant challenges remain to be addressed to ensure straightforward and efficient access to a variety of functionalized aryldifluoromethyl carboxylic acid derivatives.

Methods that rely on C-F bond formation (e.g. deoxyfluorination of 1,2-dicarbonyl compounds or radical fluorination) typically suffer from a combination of poor functional group tolerance, harsh reaction conditions, and the formation of mixtures of products. Cross-coupling methods present an attractive alternative because they enable facile variation of both the aryl and difluorocarbonyl coupling partners. Cu-mediated couplings of aryl iodides with XCF_2CO_2Et or $R_3SiCF_2CO_2Et$ are well-established, but broadly-applicable Cu-catalyzed reaction conditions had not been reported prior to our Cu-catalyzed synthesis of aryldifluoroamides described in Chapter 2. In addition, transformations of aryldifluoroamides and investigations of their potential utility as synthetic building blocks had not been previously described.

Several examples of difluoroenolate arylations catalyzed by Ni and Pd have been reported recently. Many require high catalyst and ligand loadings, though notable exceptions include

Zhang's Ni-catalyzed difluorofunctionalization of arylboronic acids (2.5 mol% [Ni], 2.5 mol % bpy) and Hartwig's alpha-arylation of difluoroketones (0.5 mol% of a Pd/P^{t}BuCy$_2$ pre-catalyst). Ni-catalyzed reactions for the synthesis of aryldifluoromethyl carboxylic acid derivatives are currently limited to arylboronic acid substrates, rather than more widely available and cheaper aryl halides. With Pd, few examples of coupling reactions of aryl chlorides or aryl triflates with fluoroenolates have been reported, and the reactions are often incompatible with medicinally-relevant heteroarenes.

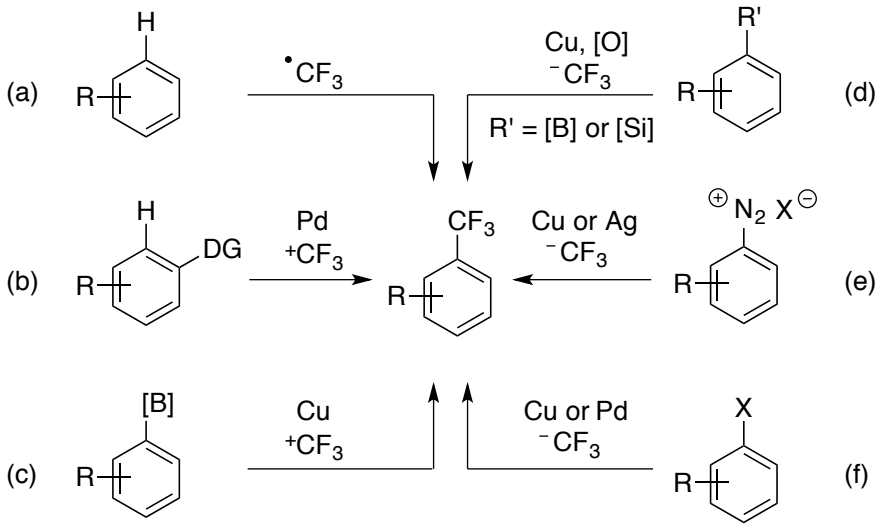
A detailed mechanistic understanding of α-arylation reactions of fluorinated enolates has not been established, and the structures and properties of intermediates relevant to cross-coupling reactions of difluoroenolates have not been elucidated. The development of Pd-catalyzed α-arylation reactions of difluorocarbonyl compounds at moderate temperatures and with several different classes of ligands suggests that reductive elimination to form an aryl-fluoroenolate bond is likely to be more facile than reductive elimination to form an analogous aryl-trifluoromethyl bond. However, prior to our studies of Pd-fluoroenolate complexes described in Chapter 3, no arylmetal fluoroenolate complexes had been detected or demonstrated to undergo reductive elimination.

Despite interest in aryldifluoronitriles in materials science[34] and drug discovery,[29] cross-coupling routes to this class of compounds have not been reported. Aryldifluoronitriles can be synthesized by deoxyfluorination reactions of acyl cyanides, or, more commonly, by multi-step sequences involving synthesis of an aryldifluoroester, treatment with ammonia to afford the corresponding aryldifluoroacetamide, and dehydration of the acetamide to form the nitrile. Streamlining synthetic access to aryldifluoronitriles would encourage further study of their potential as materials, pharmaceuticals, and agrochemicals. Key to this effort is identification of a suitable difluoronitrile anion source for the cross-coupling reaction that is synthetically accessible, easy to handle, and sufficiently stable to withstand the conditions required for cross-coupling, while also readily transferring a difluoronitrile group to a metal complex. Efforts to develop a cross-coupling reaction for the synthesis of aryldifluoronitriles are described in Chapter 4.

1.3 Synthesis of Trifluoromethyl-Substituted Arenes

1.3.1 Overview of Methods for the Synthesis of Trifluoromethylarenes

The incorporation of trifluoromethyl substituents on aryl groups is a powerful strategy to improve the physical and biological properties of compounds of interest for medicinal and agrochemical applications. The Swarts reaction[73] is the most common method for industrial-scale syntheses of trifluoromethylarenes.[74] In this reaction, a benzotrichloride is converted to the corresponding benzotrifluoride by halogen exchange with HF and/or metal halides such as SbF_5. Although this is an effective strategy for preparing simple trifluoromethyl-containing building blocks on large scale, functionalized substrates are incompatible with the high temperatures and strongly acidic reaction conditions, and the requisite excess of toxic and hazardous reagents limits the practicality of the reaction on a laboratory scale.



Scheme 1.6 Summary of methods for the synthesis of trifluoromethylarenes.

A variety of strategies have been explored for both the direct trifluoromethylation of arenes and for the trifluoromethylation of pre-functionalized arenes (Scheme 1.6). The direct trifluoromethylation of C-H bonds in arenes and heteroarenes with various trifluoromethyl radical sources has been reported (Scheme 1.6a), but mixtures of trifluoromethylarene products are formed, and the substrate scope is generally limited to C-H bonds of heteroarenes or electron-rich arenes.[75-80] Directing groups can increase the regioselectivity of C-H trifluoromethylation reactions (Scheme 1.6b), as demonstrated by the directed, Pd-catalyzed electrophilic trifluoromethylation reactions reported by Yu[81-83] and Sanford.[84] However, installation and removal of the directing group require additional synthetic steps.

Aryl nucleophiles, including aryl boron[85-95] and aryl silicon[96] compounds, can be transformed to the corresponding trifluoromethylarenes under copper-mediated conditions with electrophilic CF_3 sources (Scheme 1.6c) or with nucleophilic CF_3 sources and an oxidant (Scheme 1.6d). These reactions are particularly valuable when combined with metal-catalyzed, sterically-controlled borylation and silylation reactions of C-H bonds. Copper- and silver-mediated trifluoromethylation of aryl diazonium salts also has been reported (Scheme 1.6e).[97-100] However, the availability of aryl boron, aryl silicon, and aryl diazonium compounds is considerably more limited than that of aryl halides.

1.3.2 Challenges and Strategies for Transition Metal-Mediated and -Catalyzed Trifluoromethylation of Aryl Halides

Cross-coupling reactions of synthetically accessible and widely commercially available aryl halide electrophiles with CF_3 nucleophiles (Scheme 1.6f) have the potential to enable incorporation of trifluoromethyl groups into aromatic compounds under mild conditions, with complete site selectivity, and in functionalized substrates. However, several challenges are associated with the development of this class of trifluoromethylation reactions.

The trifluoromethyl anion is unstable under conditions relevant for cross coupling and can decompose to release fluoride and difluorocarbene.[74] For example, deprotonation of CF_3H with KO^{t}Bu or dimsyl potassium at low temperature leads to formation of difluorocarbene unless the reaction is carried out in a solvent such as DMF that forms a stabilized adduct with the trifluoromethyl anion.[101-104] Insertion of difluorocarbene into M-CF_3 intermediates generates M-CF_2CF_3 species that can react to form pentafluoroethylarene byproducts.[105] In addition, the trifluoromethyl anion is nucleophilic and can displace ancillary ligands on a metal center[106-108] or add to electrophilic functional groups including aldehydes, ketones, esters, and amides.[109]

To prevent decomposition of the trifluoromethyl source and formation of byproducts, strategies to limit the concentration of the trifluoromethyl anion have been developed. Most commonly, the source of trifluoromethyl nucleophile is a trifluoromethylsilyl compound ($TMSCF_3$ or $TESCF_3$) that is activated by a Lewis base (typically fluoride).[110] Under appropriate conditions, the resulting pentacoordinate silicate can transfer a CF_3 group to a transition metal. The challenge of the limited stability and problematic nucleophilicity of the trifluoromethyl anion also has been addressed by conducting reactions with stoichiometric quantities of pre-formed trifluoromethyl copper complexes (see Section 1.3.3).

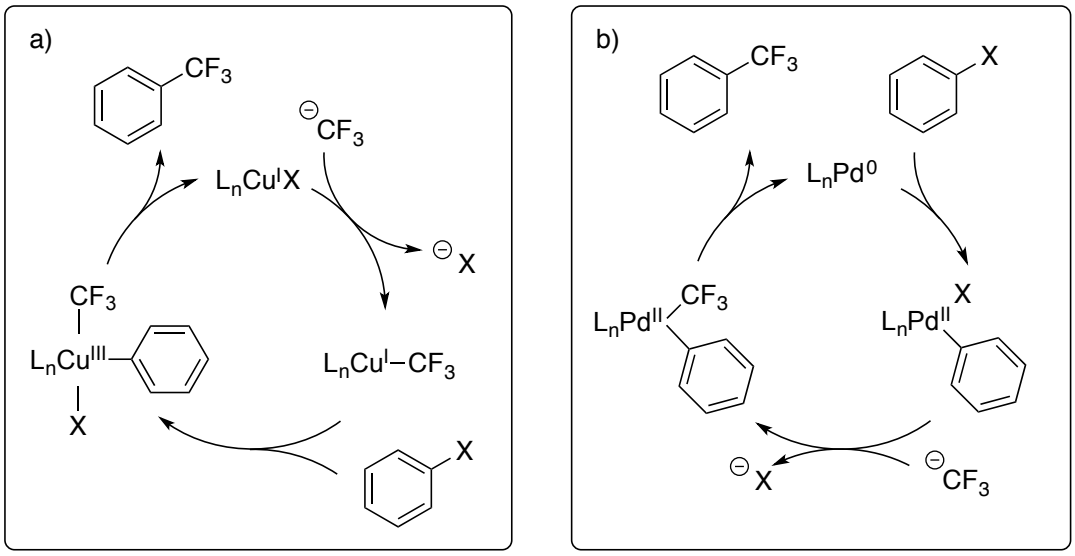
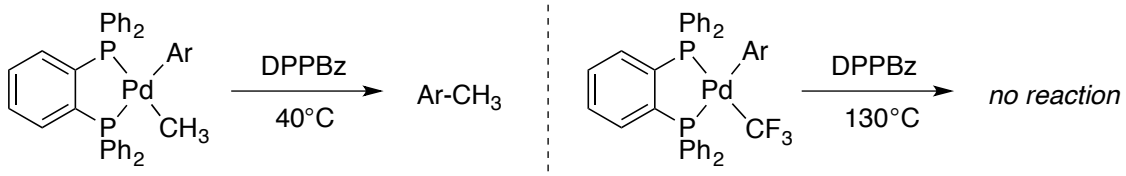


Figure 1.7 General catalytic cycles for Cu- and Pd-catalyzed trifluoromethylation reactions of aryl halides.

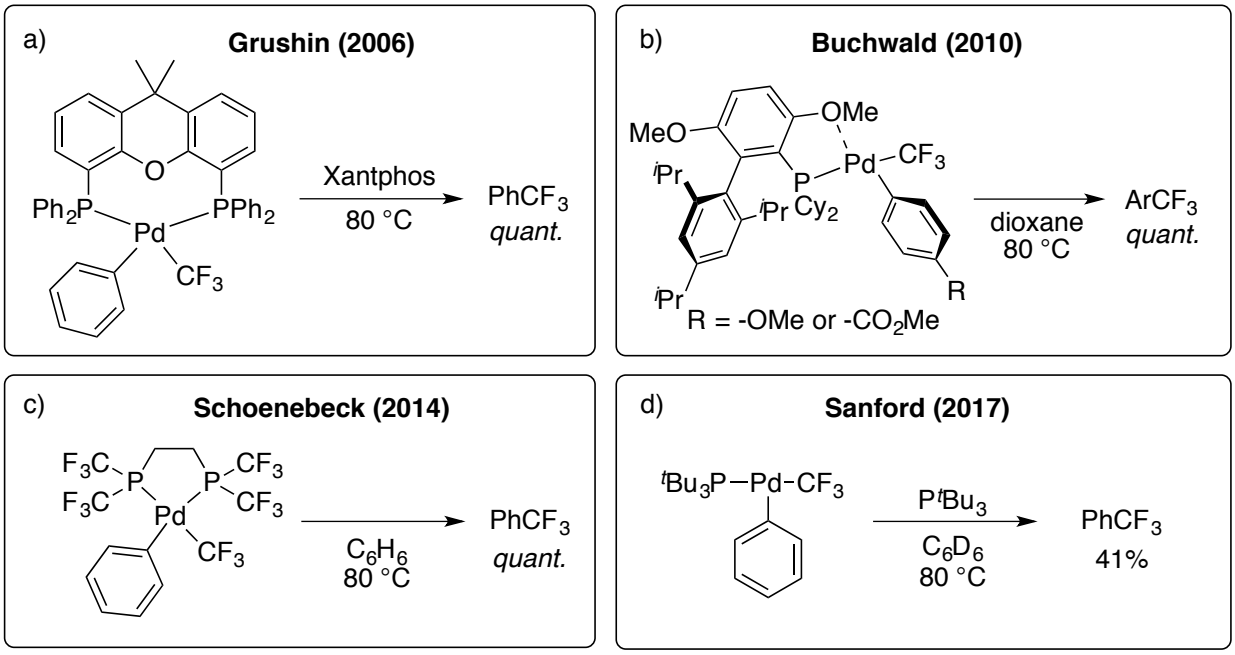
Because the trifluoromethyl group is strongly electron-withdrawing, oxidative addition of aryl halides to M-CF_3 complexes is challenging.[111-112] In a general mechanism for Cu-catalyzed trifluoromethylation of aryl halides (Figure 1.7a), a L_nCuCF_3 species reacts with an aryl halide to generate a copper(III) intermediate. Due to the high barrier associated with this oxidative addition step, copper-mediated or -catalyzed trifluoromethylation reactions are restricted to more reactive electrophiles (typically aryl iodides and activated aryl bromides) as substrates and are ineffective for cheaper, more commercially available aryl bromide and chloride substrates.

The product-forming step in trifluoromethylation reactions of aryl halides is reductive elimination to form an Ar-CF_3 bond. Reductive elimination is widely considered the most challenging fundamental step in the Pd-catalyzed trifluoromethylation of aryl halides.[74, 113] To gain insight into the effect of the electronic and steric properties of ancillary ligands on reductive elimination to form an Ar-CF_3 bond, experiments with isolated arylpalladium trifluoromethyl complexes bearing mono- and bisphosphine ligands have been conducted. Studies of reductive elimination to form aryl-alkyl bonds from arylpalladium(II) alkyl complexes revealed that the presence of fluorine on the α-carbon of the alkyl group dramatically retards the rate of reductive elimination relative to complexes containing the corresponding non-fluorinated alkyl group. For example, a bisphosphine-ligated arylpalladium complex bearing a methyl group underwent reductive elimination of Ar-CH_3 with a half-life of 23 minutes at 40 degrees °C.[60] In contrast, the analogous complex bearing a trifluoromethyl group did not undergo reductive elimination when heated for several days at 130 °C (Scheme 1.7).



Scheme 1.7 Reductive elimination to form an aryl-alkyl bond is slowed by the presence of fluorine on the α-carbon of the alkyl group.

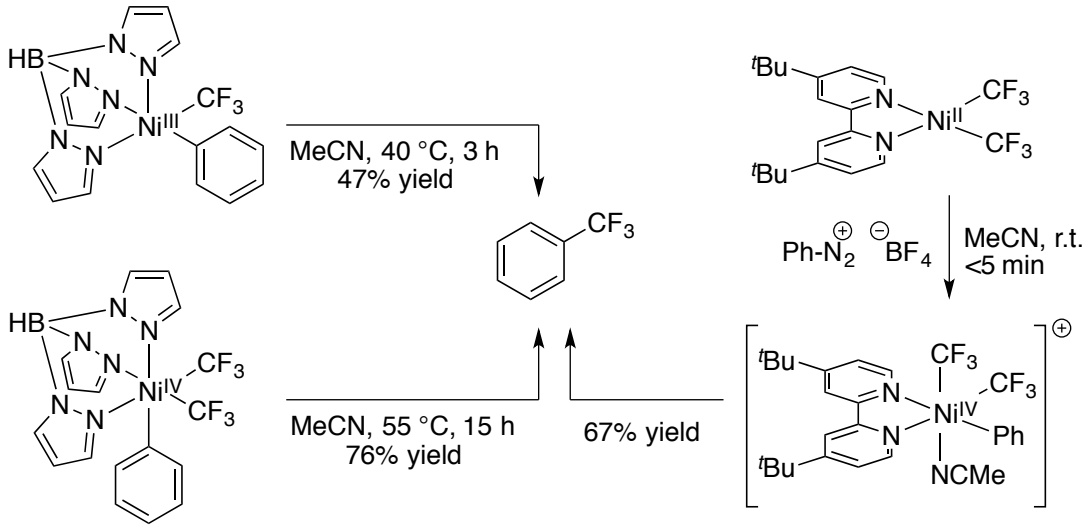
In 2006, Grushin reported the first example of reductive elimination from an isolated palladium complex to form an Ar-CF_3 bond (Scheme 1.8a).[107] Key to the success of this transformation was ligation of the palladium center with Xantphos, a bisphosphine ligand with a wide bite angle (111°).[114] Since this initial report, a series of ligands have been identified that promote reductive elimination of Ar-CF_3 from isolated palladium(II) complexes. These ligands include both mono- and bisphosphines. Isolated complexes ligated by the bulky monophosphine ligand BrettPhos undergo reductive elimination to form trifluoromethylarenes.[115] Schoenebeck demonstrated that reductive elimination can be accelerated by ligation of the arylpalladium trifluoromethyl complex with a highly electron-deficient bisphosphine ligand,[116] and Sanford demonstrated that moderate yields can be obtained from reductive elimination reactions with P^tBu_3 as an ancillary ligand.[117]



Scheme 1.8 Reductive elimination to form Ar-CF_3 bonds from isolated palladium complexes.

However, ligands that promote reductive elimination from isolated arylpalladium trifluoromethyl complexes are not necessarily effective for Pd-catalyzed trifluoromethyation of aryl halides. For example, attempts by Grushin and coworkers to develop a Pd-catalyzed trifluoromethylation with a Xantphos-ligated palladium species as catalyst were thwarted due to displacement of Xantphos by the trifluoromethyl anion under catalytically relevant conditions.[74] Off-cycle side reactions can also compete with reductive elimination, as observed in Sanford's studies of palladium complexes ligated by P^{t}Bu$_3$, in which α-fluoride elimination competed with reductive elimination.[117] In spite of these challenges, a palladium-catalyzed trifluoromethylation reaction of aryl chlorides with Brettphos or Ruphos as ligand was reported by Buchwald in 2010 (see section 1.3.4).[115]

Studies to investigate Ar-CF_3 bond formation from Ni complexes have also been conducted. Vicic studied the reactivity of isolated (dippe)Ni(Ar)(CF_3) complexes (dippe = 1,2-bis(diisopropylphosphino)ethane), but heating the complexes resulted in decomposition, and low yields of trifluoromethylarene (11-22%) were formed upon addition of PhZnBr, $ZnBr_2$, or water.[118] Preparing related complexes has also proven challenging: a computational study of the barriers to reductive elimination of Ar-CF_3 from nickel complexes bearing bisphosphine ligands identified several ligands of potential interest, but attempts to synthesize the relevant complexes were unsuccessful.[119] Reductive elimination can be accelerated by accessing higher oxidation states, and Ar-CF_3 bond formation has been demonstrated from isolated Ni^{III} and Ni^{IV} complexes and from a transiently formed Ni^{IV} species (Scheme 1.9).[120-122] However, nickel-catalyzed trifluoromethylation reactions of aryl halides have not been reported.



Scheme 1.9 Reductive elimination to form $PhCF_3$ from high-valent nickel species.

1.3.3 Copper-Mediated and -Catalyzed Trifluoromethylation of Aryl Halides

The first copper-mediated trifluoromethylation reaction of aryl iodides was reported by McLoughlin and Thrower in 1969.[123] The reductive coupling of aryl iodides with trifluoromethyl iodide and other fluoroalkyl halides mediated by stoichiometric quantities of Cu^0 afforded the corresponding benzotrifluorides and fluoroalkylarenes. However, yields were moderate, superstoichiometric quantities of Cu^0 were required, and the reactions were conducted at high temperatures with gaseous reagents, such as CF_3I.

Subsequent efforts to identify more convenient CF_3 sources and milder conditions for Cu-mediated trifluoromethylation focused on coupling reactions of nucleophilic CF_3 sources with aryl halides. Copper-mediated trifluoromethylation reactions have been conducted with compounds, such as sodium trifluoroacetate[124] or methyl trifluoroacetate,[125] that undergo decarboxylation upon heating or with the addition of base to generate a trifluoromethyl nucleophile. Alternatively, the combination of a difluorocarbene precursor and fluoride can generate a trifluoromethyl anion *in situ* to serve as a nucleophile in copper-mediated couplings.[126-127] Fluoroalkyl silanes, including the Ruppert-Prakash reagent ($TMSCF_3$), have been widely employed as convenient nucleophilic CF_3 sources for Cu-mediated coupling on a laboratory scale.[110, 128-129] Fluoroform (HCF_3) is an attractive source of trifluoromethyl nucleophile because it is inexpensive and available on a large scale as a byproduct from the manufacture of polytetrafluoroethylene (PTFE). Several reports have demonstrated the feasibility of deprotonation of fluoroform and subsequent stabilization or trapping of the resulting trifluoromethyl anion,[101-104, 130-131] and Grushin demonstrated that deprotonation of CF_3H in DMF in the presence of a Cu(I) salt afforded a $CuCF_3$ species that coupled with iodoarenes under mild conditions.[132]

To avoid decomposition of the trifluoromethyl anion and reduce its propensity to attack electrophilic functional groups and displace ligands on metal centers, pre-formed, discrete trifluoromethylcopper complexes have been synthesized as stoichiometric trifluoromethylating

agents (Figure 1.8). Vicic reported the first isolated Cu(I)-trifluoromethyl complex in 2008, and demonstrated that this complex, ligated by an *N*-heterocyclic carbene (NHC), mediated the trifluoromethylation of aryl iodides in high yield under mild conditions.[133] Grushin subsequently reported the synthesis and isolation of the air-stable trifluoromethylcopper complexes $(PPh_3)_3CuCF_3$ and $(phen)(PPh_3)CuCF_3$, as well as their reactions with aryl iodides to afford the corresponding benzotrifluorides in moderate to high yields.[74]

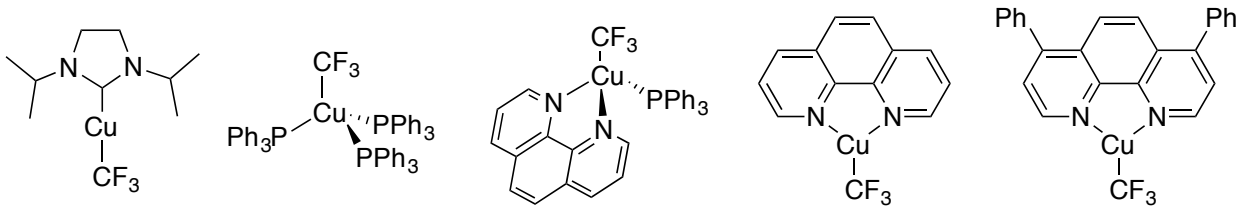
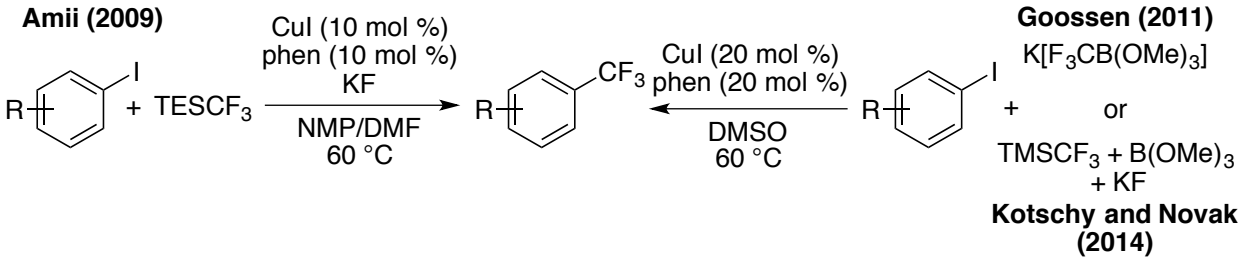


Figure 1.8 Discrete, isolable trifluoromethylcopper complexes that react with aryl iodides to form benzotrifluorides.

In 2011, Hartwig and coworkers reported the synthesis of $(phen)CuCF_3$ and related $(phen)Cu(CF_2)_nCF_3$ complexes, as well as reactivity of these complexes with a wide range of aryl iodides.[134] Electron-rich, electron-neutral, and electron-poor aryl iodides underwent coupling in high yield, and a diverse variety of functional groups were tolerated, including electrophilic and protic functional groups such as aldehydes, ketones, esters, and unprotected alcohols. The scope of the reaction was later expanded to heteroaryl bromides to afford a series of pharmacologically relevant heterocycles bearing trifluoromethyl and pentafluoroethyl groups.[135] In addition, a two-step sequence was developed in which aryl bromides were transformed to the corresponding arylboronate esters prior to oxidative coupling with $(phen)CuCF_3$.[93] Feng and Huang reported the isolation of the related complex $(bathophen)CuCF_3$ and described its reactivity with 4-iodobenzonitrile as part of their mechanistic studies of the effects of silver additives on copper-catalyzed trifluoromethylation.[136]



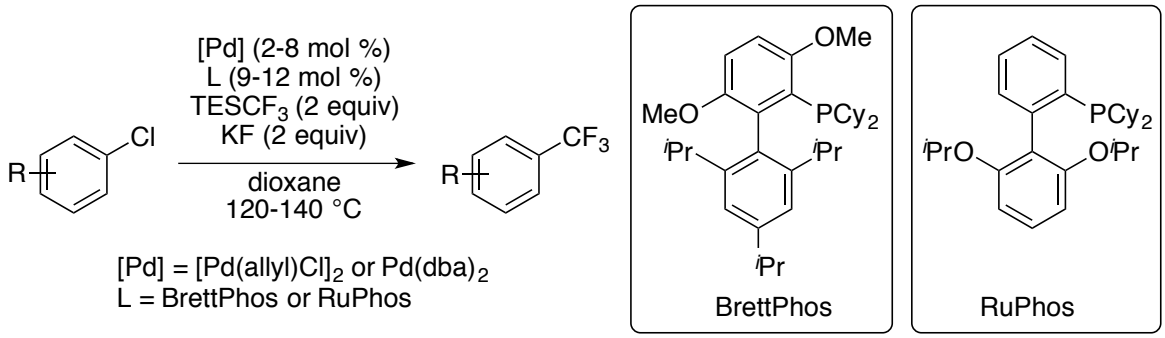
Scheme 1.10 Copper-catalyzed trifluoromethylation of aryl iodides.

Despite progress in developing copper-mediated trifluoromethylation reactions that occur with broad scope under mild conditions, developing reactions that are catalytic in copper remains an area of ongoing interest. In 2009, Amii reported the first copper-catalyzed trifluoromethylation

of aryl iodides (Scheme 1.10).[129] However, high yields were obtained only for electron-deficient aryl iodides as substrates. In the initial report, $TESCF_3$ was employed as the trifluoromethyl nucleophile source. A fluoral hemiaminal reagent was later shown to serve as a comparably effective and less expensive alternative to $TESCF_3$.[137] In 2011, Goossen reported a method for copper-catalyzed trifluoromethylation with $K[F_3CB(OMe)_3]$ as the trifluoromethyl source.[138] As in the conditions reported by Amii, a combination of CuI and phen generates the active catalyst *in situ*. The conditions reported by Goossen convert electron-rich, electron-poor, and sterically hindered aryl iodides to the corresponding trifluoromethylarenes in high yield under mild conditions, although an excess of the borate salt is required (3 equivalents) and catalyst and ligand loadings are high (20 mol %). Comparable results were later reported when the reaction was conducted with a combination of $TMSCF_3$, $B(OMe)_3$, and KF rather than with the isolated trifluoromethylborate salt.[139] Other strategies for copper-catalyzed trifluoromethylation include reactions of trifluoromethylzinc(II) species prepared from CF_3I[140-141] or decarboxylative trifluoromethylation reactions of methyl trifluoroacetate that occur at high temperatures (160 °C).[142]

1.3.4 Palladium-Catalyzed Trifluoromethylation of Aryl Halides

The palladium-catalyzed trifluoromethylation of aryl halides was reported in 2010 by Buchwald and coworkers (Scheme 1.11).[115] The reaction couples aryl chlorides with $TESCF_3$ in the presence of $[Pd(allyl)Cl]_2$ (2-4 mol %) or $Pd(dba)_2$ (6-8 mol %) with bulky monophosphines BrettPhos or RuPhos (9-12 mol %) as ligand. A variety of aryl chlorides were transformed to the corresponding benzotrifluorides in moderate to high yield. However, the reaction requires high temperatures (120-140 °C) and high loadings of palladium and expensive phosphine ligands. In addition, substrates bearing aldehyde, ketone, and unprotected -OH or -NH groups were not suitable coupling partners. Attempts by other groups to develop efficient Pd-catalyzed trifluoromethylation reactions of aryl halides have thus far been unsuccessful; for example, Sanford's studies with P^tBu_3 as a ligand resulted in only 22% yield of trifluoromethylarene with 10 mol % $Pd(P^tBu_3)_2$ as catalyst.[117]



Scheme 1.11 Palladium-catalyzed trifluoromethylation of aryl chlorides.

1.3.5 Outlook on the Development of Transition Metal-Catalyzed Trifluoromethylation of Aryl Halides

Several opportunities exist to address challenges associated with transition metal-catalyzed trifluoromethylation reactions of aryl halides. The limited stability of the CF_3 anion and its surrogates under conditions relevant to catalysis means that excess quantities of the CF_3 source are typically required to achieve high yields of trifluoromethylarene products. In addition, the trifluoromethyl anion readily adds to electrophilic functional groups, displaces ligands and thereby inactivates metal catalysts, and can decompose to difluorocarbene and generate other fluoroalkyl byproducts. Simple modifications to CF_3 surrogates to enhance stability can substantially increase yields; for example, employing $TESCF_3$ rather than $TMSCF_3$ was key to achieving high yields in the Pd-catalyzed trifluoromethylation of aryl chlorides.[115] The development of CF_3 sources that are stable under conditions relevant to catalysis and can be activated toward transmetallation to metal complexes under mild conditions would therefore be valuable.

Substantial progress has been made in developing copper-mediated and -catalyzed reactions for the trifluoromethylation of aryl iodides. The scope of these reactions is broad, and reactions occur under mild conditions, although high catalyst loadings or stoichiometric quantities of copper are typically required to achieve high yields. The most significant limitation of current procedures for trifluoromethylation with copper is the lack of reactivity with unactivated aryl bromide and aryl chloride electrophiles. As discussed in section 1.3.2, oxidative addition to an electron-poor trifluoromethylcopper(I) complex is inherently challenging. The application of new classes of ligands that are more donating to copper may be required to accelerate this step and expand reactivity to aryl bromides and chlorides. For example, anionic ligands that can stabilize negatively charged trifluoromethylcuprate species may be effective in promoting oxidative addition reactions that do not occur with neutral Cu(I)-CF_3 species. Recently, Ma and coworkers have demonstrated that copper complexes ligated by oxalic diamide ligands catalyze amination and alkoxylation reactions of aryl bromides and chlorides.[143-146] These reactions likely proceed through cuprate intermediates formed upon deprotonation of the ligand under basic conditions, suggesting that employing anionic ligands may be a viable strategy for expanding the scope of electrophiles for copper-catalyzed trifluoromethylation reactions.

An alternative strategy would be to develop trifluoromethylation reactions catalyzed by metals such as nickel that are known to undergo facile oxidative addition to aryl bromides, chlorides, and pseudohalides. However, ligands that promote reductive elimination from $L_nNi^{II}(Ar)(CF_3)$ complexes in high yield have not been identified. Conducting a wider survey of ligands would be beneficial to determine the feasibility of this reductive elimination step. Reductive elimination from Ni^{III} and Ni^{IV} species to form an Ar-CF_3 bond have been reported by Sanford and co-workers.[120-122] However, studies have largely focused on ligands designed to stabilize and enable isolation and characterization of high-valent nickel species, rather than ligands more likely to be relevant to catalysis. The advent of photoredox catalysis has provided a means of accessing Ni(III) intermediates under mild conditions and has enabled cross-coupling reactions that involve challenging reductive elimination steps.[147] However, translating this strategy to fluoroalkylation reactions of aryl halides requires efficient reductive elimination from an arylnickel(III) trifluoromethyl complex. Chapter 5 describes work to assess the feasibility of this

fundamental step by studying reductive elimination of Ar-CF_3 induced by single-electron oxidation of Ni(II) complexes.

To date, only a single system for Pd-catalyzed trifluoromethylation of aryl halides in high yield has been reported,[115] and the development of other Pd-catalyzed reactions that occur under mild conditions, require low catalyst and ligand loadings, and are effective for a broad range of functionalized substrate would be valuable. The slow rate of reductive elimination from $L_nPd^{II}(Ar)(CF_3)$ complexes is well-established, and only a handful of ligands have been reported to be effective at promoting reductive elimination from isolated Pd complexes. Identifying new classes of ligands that promote reductive elimination of Ar-CF_3 from Pd(II) would help guide the development of catalytic trifluoromethylation reactions. Efforts toward this goal are described in Chapter 6.

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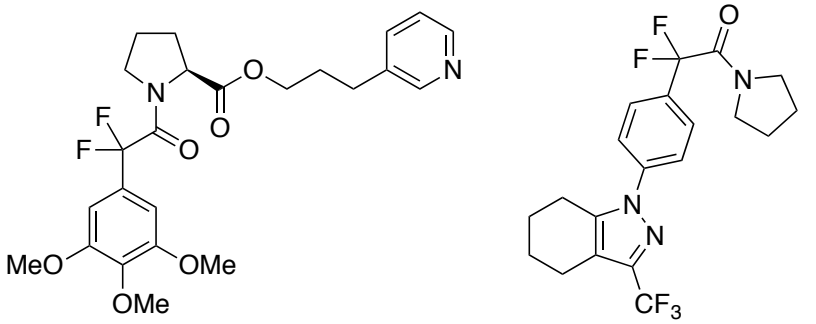
Chapter 2

Synthesis of Aryldifluoroamides by Copper-Catalyzed Cross-Coupling

2.1 Introduction

Fluorinated compounds are common in pharmaceuticals, agrochemicals, and materials, due to their favorable biological and physical properties (see Chapter 1).[1-5] In medicinal chemistry, fluorinated substituents can alter the lipophilicity, metabolic stability, and overall activity of biologically active compounds, relative to their non-fluorinated counterparts.[6-9] The difluoromethylene (CF_2) group has particular value because it is considered a bioisostere of carbonyl groups and ethers[10] and can modulate the pK_a of neighboring functional groups, such as amines.[11-13]

Aryldifluoroamides are present in several biologically active compounds, including the inhibitor of FKBP12[10] and the modulator of AMPAR[14] shown in Figure 2.1. Moreover, amides can be transformed into amines, alcohols, acids, esters, and ketones, making aryldifluoroamides versatile precursors to a variety of difluoroalkylarenes. Despite the biological and synthetic potential of this class of compound, current methods for the synthesis of difluoroamides are limited. Aryldifluoroamides can by prepared by deoxyfluorination of dicarbonyl compounds with diethylaminosulfur trifluoride (DAST) or related aminosulfur trifluorides.[15-17] However, these fluorinating reagents release toxic HF upon contact with water and can undergo explosive decomposition upon heating. Alpha-fluorination reactions of amides have also been reported, but the reactions are often low-yielding, typically require strong bases, and form mixtures of mono- and bis-fluorinated products that can be challenging to separate.[14]



FKBP12 inhibitor AMPAR allosteric modulator

Figure 2.1 Bioactive compounds containing aryldifluoroamide groups.

The cross coupling of aryl halides with difluorinated enolates would be a valuable approach to the synthesis of aryldifluorocarboxylic acid derivatives. Cross-coupling reactions of aryl nucleophiles, such as arylboronic acids, with difluorocarboxylic acid derivatives as electrophiles have been reported,[18-19] but reactions of the more widely accessible aryl halides with a carbonyl derivative as the nucleophile would be a more direct method from chemical feedstocks.

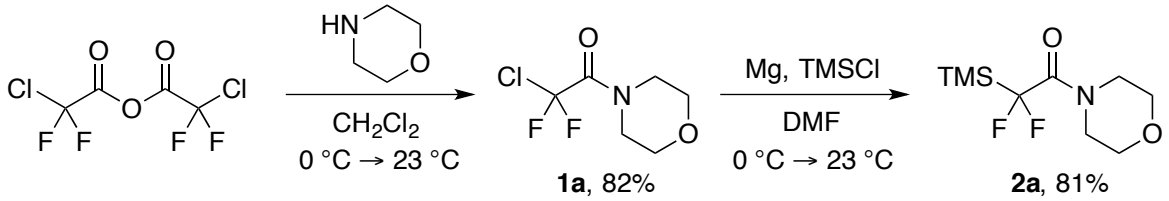
A synthesis of aryldifluoroamides by the reductive coupling of aryl iodides and iododifluoroamides has been reported,[20] but the reaction requires excess copper (6 equivalents) and displays limited scope and functional group tolerance. For example, the reaction occurs in low yields with electron-rich or sterically hindered aryl iodides, and coupling reactions of heteroaryl

iodides were not reported. Our group recently reported a palladium-catalyzed coupling of aryl bromides with silyldifluoroamides.[21] This reaction occurs with broad scope, but did not occur with many medicinally relevant heterocycles, such as 2-halopyridines. In addition, this reaction required palladium as the central metal of the catalyst, and we sought to develop a catalytic coupling reaction based on a cost-effective and earth-abundant first-row metal. Amii and coworkers reported a coupling of α-silyldifluoroesters with aryl iodides in the presence of stoichiometric copper(I) iodide. The reaction also proceeded with catalytic copper(I) iodide, but yields were variable (40-71%), and the reaction was limited to electron-deficient substrates.[22] A related coupling of halopyridines was also reported, but required two equivalents of copper(I) iodide.[23]

We report the cross coupling of aryl halides with α-silyldifluoroamides in the presence of a catalytic quantity of copper(I) acetate. The reactions encompass aryl and heteroaryl iodides containing a range of functional groups and steric and electronic properties and occur with a commercially available copper catalyst without the need for any added ligand. We report a series of transformations of the aryl- and heteroaryldifluoroamide products to esters, acids, alcohols, amines, and ketones. Furthermore, we demonstrate that the aryldifluoroamide products are synthetically useful precursors to difluorinated analogs of the biologically active compounds pioglitazone, verapamil, and ropinirole.

2.2 Results and Discussion

The arylation of α-silyldifluoroamide **2a** with 1-butyl-4-iodobenzene was chosen as a model system to identify a copper catalyst and reaction conditions for the cross-coupling reaction. By employing a pre-formed silyl amide enolate as the nucleophilic coupling partner, we sought to avoid the requirement for a strong base required to generate a difluoroamide enolate *in situ* via deprotonation of a difluoroamide. We envisioned that the silyldifluoroamide could be activated by a fluoride source under mild conditions.

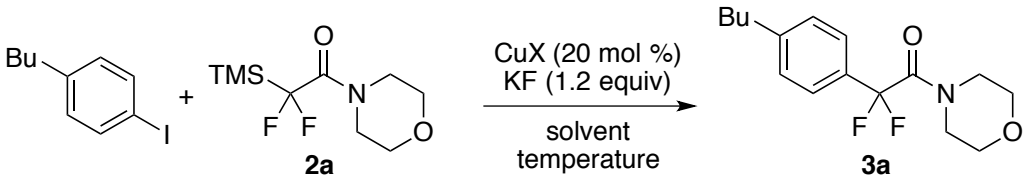


Scheme 2.1 Synthesis of *α*-(trimethylsilyl)difluoroamide **2a**.

A two-step procedure to prepare *α*-silyl difluoroamide **2a** from chlorodifluoroamide **1a** was developed. First, *α*-chlorodifluoroamide **1a** was prepared from commercially available chlorodifluoroacetic anhydride and morpholine in 82% yield (Scheme 2.1). Next, *α*-silyl difluoroamide **2a** was synthesized in 81% yield from chlorodifluoroamide **1a** in the presence of magnesium and chlorotrimethylsilane, based on a modification of a procedure previously reported for the synthesis of *α*-silyl difluoroacetates.[22] Compound **2** was prepared on multi-gram scale and is an air-stable, crystalline solid that can be stored. After two months under air, no decomposition

of compound **2a** was observed by ^{1}H or ^{19}F NMR spectroscopy. Compound **2a** displays a singlet ^{19}F NMR resonance in solution at –114.6 ppm, suggesting that the trimethylsilyl group is bound to the α-carbon and not to oxygen. Inequivalent fluorine signals and fluorine-fluorine coupling would be expected if the silyl enol ether product were formed.[24] Electron-neutral 1-butyl-4-iodobenzene was selected as the coupling partner for initial experiments, and the yields of the aryldifluoroamide product were evaluated by ^{19}F NMR spectroscopy with 3-nitrofluorobenzene as an internal standard.

Table 2.1 Effect of reaction conditions on the coupling of 1-butyl-4-iodobenzene with α-silyldifluoroamide **2a**.[a]

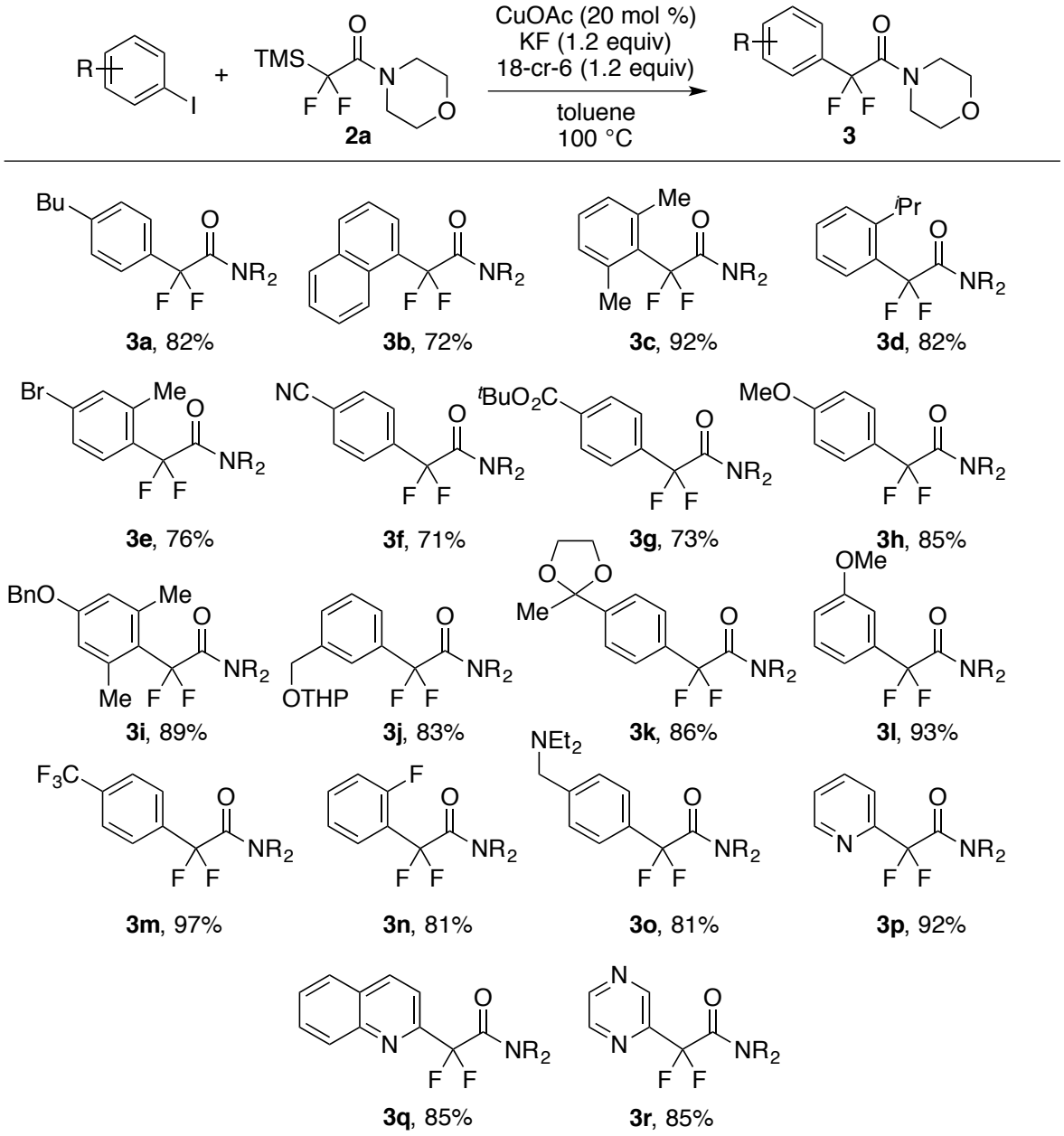


entry	solvent	temperature	CuX	yield[b]
1	DMSO	80 °C	CuCl	<5%
2	DMSO	80 °C	CuBr•SMe_2	14%
3	DMSO	80 °C	CuI	18%
4	DMSO	80 °C	CuCN	12%
5	DMSO	80 °C	CuOAc	89%
6[c]	toluene	100 °C	CuOAc	87%

[a]General conditions: 0.100 mmol aryl iodide, 0.120 mmol **2a**, and 0.0200 mmol CuX in 0.25 mL of solvent. [b]Yields were determined by ^{19}F NMR spectroscopy. [c]1.2 equiv 18-cr-6 and 2.0 equiv **2a**.

Various copper(I) sources were found to effect the coupling of **2a** and 1-butyl-4-iodobenzene. Reactions catalyzed by CuOAc proceeded in higher yields than those catalyzed by CuI, CuBr•SMe_2, CuCl, or CuCN (Table 2.1). None of the copper(II) sources tested catalyzed the coupling process (see Table S2.1 in the Experimental section). Reactions conducted with CuOAc without added ligand proceeded in higher yields than those conducted with added ligand (see Table S2.2 in the Experimental section). The reaction catalyzed by CuOAc (20 mol %) in toluene in the presence of KF and 18-crown-6 formed the coupled product in 87% yield, as measured by ^{19}F NMR spectroscopy, and in 82% isolated yield. The reaction of **1a** and **2a** conducted in DMSO in the absence of 18-cr-6 (entry 5) proceeded in yields that are comparable to those from the conditions described in entry 6. However, the conditions described in entry 6 were applicable to a wider range of substrates, and afforded the coupling products of electron-rich aryl iodides in higher yield than the conditions described in entry 5.

Table 2.2 Copper-catalyzed coupling of silyldifluoroamide **2a** with aryl iodides.[a]



[a]Isolated yields. General conditions: aryl iodide (0.400 mmol), **2a** (0.800 mmol), CuOAc (0.0800 mmol), KF (0.480 mmol), 18-crown-6 (0.480 mmol), toluene (1 mL), 100 °C, 24 h.

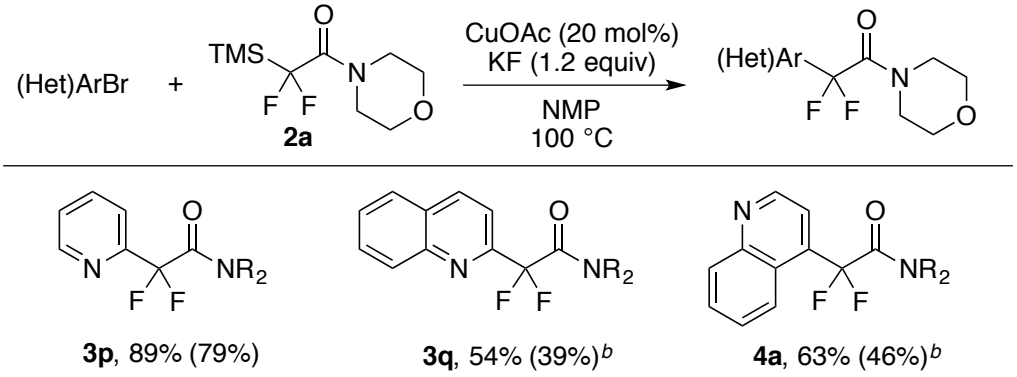
Having identified conditions for the coupling of **2a** with 1-butyl-4-iodobenzene, we investigated the conversion of a variety of aryl iodides to the corresponding aryldifluoroamides (Table 2.2). Electron-rich, electron-neutral, and electron-poor aryl iodides coupled with **2** in high yield. In contrast to many copper-catalyzed coupling reactions, which occur in significantly lower

yields with sterically hindered aryl iodides,[25] the reactions of **2a** with aryl iodides containing mono- or di-substitution adjacent to the iodine atom occurred in high yield to afford products **3c-3e**, **3i**, and **3n**. The reaction conditions were found to tolerate ester (**3g**), nitrile (**3f**), tertiary amine (**3o**), ether (**3h-3l**), and aromatic bromide (**3e**) groups. Although free hydroxyl groups, primary or secondary amines, and enolizable ketones were found to be incompatible with the reaction conditions, aryl iodides containing protected alcohol and ketone groups coupled in high yields to afford aryldifluoroamides **3j** and **3k**, respectively.

Heteroarenes are ubiquitous in pharmaceuticals, agrochemicals, and materials,[26] but the metal-catalyzed coupling of basic heteroarenes can be challenging to effect because they can coordinate to and potentially deactivate transition metal catalysts. However, electron-poor heteroaryl iodides, such 2-iodo pyridine, quinoline, and pyrazine, coupled with silyl difluoroamide **2a** in the presence of catalytic CuOAc to afford the corresponding heteroaryldifluoroamides (**3p-3r**) in high yield.

Recent studies in our group demonstrated that heteroaryl bromides react with (phen)CuR_F complexes to form perfluoroalkylarenes in high yield,[27] and studies by other groups have shown that ligandless perfluoroalkyl copper compounds generated *in situ* also react with heteroaryl halides.[28-31] Therefore, we investigated the copper-catalyzed reactions of α-silyldifluoroamides with heteroaryl bromides to form α,α-difluoro-α-heteroaryl amides.

Table 2.3 Copper-catalyzed coupling of silyldifluoroamide **2a** with heteroaryl bromides.[a]



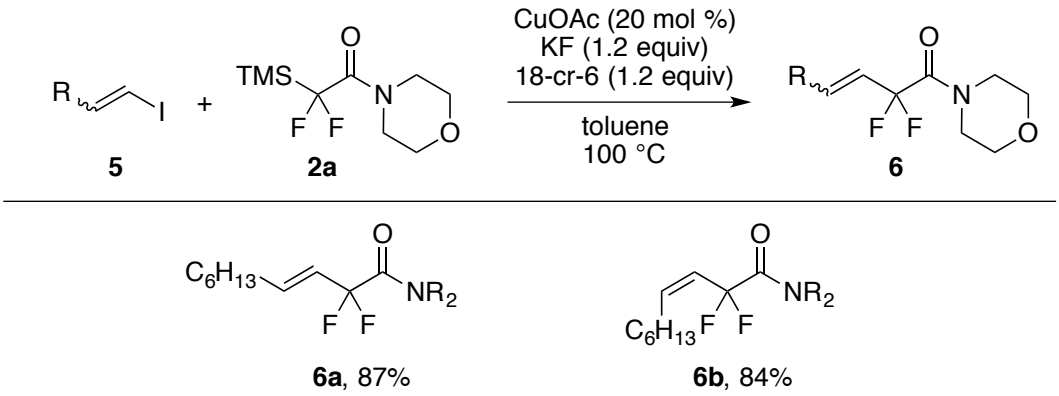
[a]Reactions were performed on a 0.100 mmol scale to determine yields by ^{19}F NMR spectroscopy. Yields of isolated products are shown in parentheses for reactions performed on a 0.400 mmol scale. General conditions: aryl bromide (1 equiv), **2a** (1.5 equiv), CuOAc (20 mol %), KF (1.2 equiv), 100 °C, 24 h. [b]Reactions performed with toluene as solvent and 18-cr-6 (1.2 equiv) as additive.

Coupling of halopyridines and -quinolines at the electron-poor 2- and 4- positions is challenging with palladium catalysts, often requiring high catalyst loadings and occurring in low yields and with limited scope. For example, 2-bromopyridine and 2-bromoquinoline did not undergo coupling with α-silyldifluoroamides under the palladium-catalyzed conditions previously reported by our group.[21] To investigate the reactivity of these substrates in the presence of a copper catalyst, the coupling of 2-bromopyridine with α-silyldifluoroamide **2a** was chosen as a model reaction. The conditions identified for the coupling of **2a** with iodoarenes (*vide supra*) resulted in

only 21% yield of the product from coupling of **2a** with 2-bromopyridine. However, the same reaction conducted with KF as an additive in NMP as solvent in place of toluene resulted in 79% yield of the product from coupling of the bromopyridine. Other nitrogen-containing heteroaryl bromides, such as 2- and 4-bromoquinoline, coupled with **2a** in moderate yield (Table 2.3).

Vinyl iodides also coupled with **2a** in high yield (Table 2.4). The coupling reactions of both *trans* vinyl iodide **5a** and *cis* vinyl iodide **5b** afforded the corresponding vinyldifluoroamides (**6a** and **6b**, respectively) as single stereoisomers with retention of the alkene geometry.

Table 2.4 Copper-catalyzed coupling of silyldifluoroamide **2** with vinyl iodides.[a]

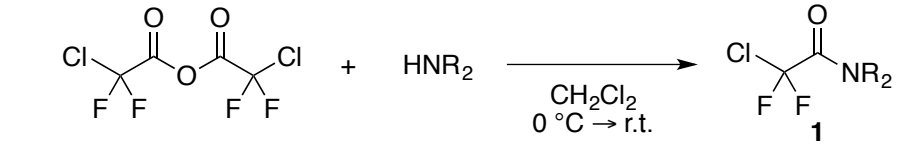


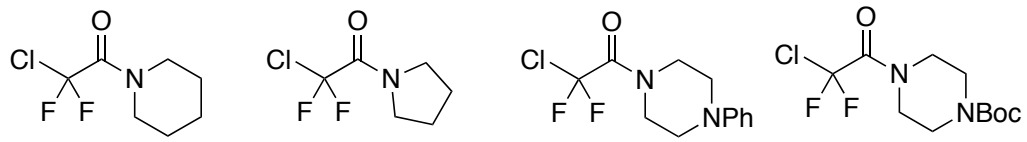
[a]Isolated yields. General conditions: vinyl iodide (0.400 mmol), **2a** (0.800 mmol), CuOAc (0.0800 mmol), KF (0.480 mmol), 18-crown-6 (0.480 mmol), toluene (1 mL), 100 °C, 24 h.

To evaluate the scope of the reaction with respect to the difluoroamide coupling partner, a series of α-silyldifluoroamides were synthesized (Table 2.5). The α-chlorodifluoroamide compounds were prepared from chlorodifluoroacetic anhydride and the corresponding amine in 70-100% yield. Both cylic and acyclic secondary amines were suitable substrates, and hindered α-chlorodifluoroamides such as di-isopropyl amide **1h** were prepared in high yield.

The α-chlorodifluoroamides were then treated with magnesium and chlorotrimethylsilane to afford α-(trimethylsilyl)difluoroamides **2b**-**2i** in 54-87% yield (Table 2.6). In each case, the silyl group in the α-silyldifluoroamide was bound to carbon rather than oxygen, as confirmed by ^{19}F and ^{13}C NMR spectroscopy.

Table 2.5 Synthesis of α-chlorodifluoroamides.





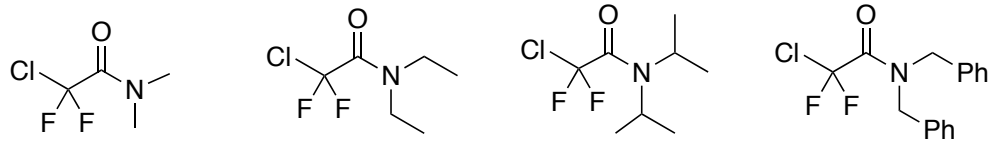
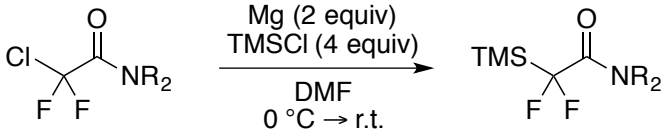
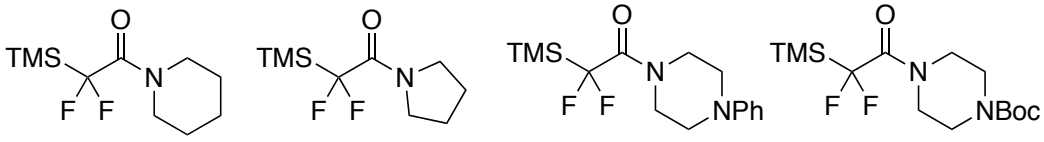
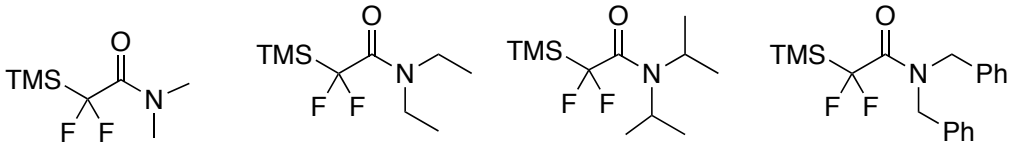


Table 2.6 Synthesis of α-silyldifluoroamides.



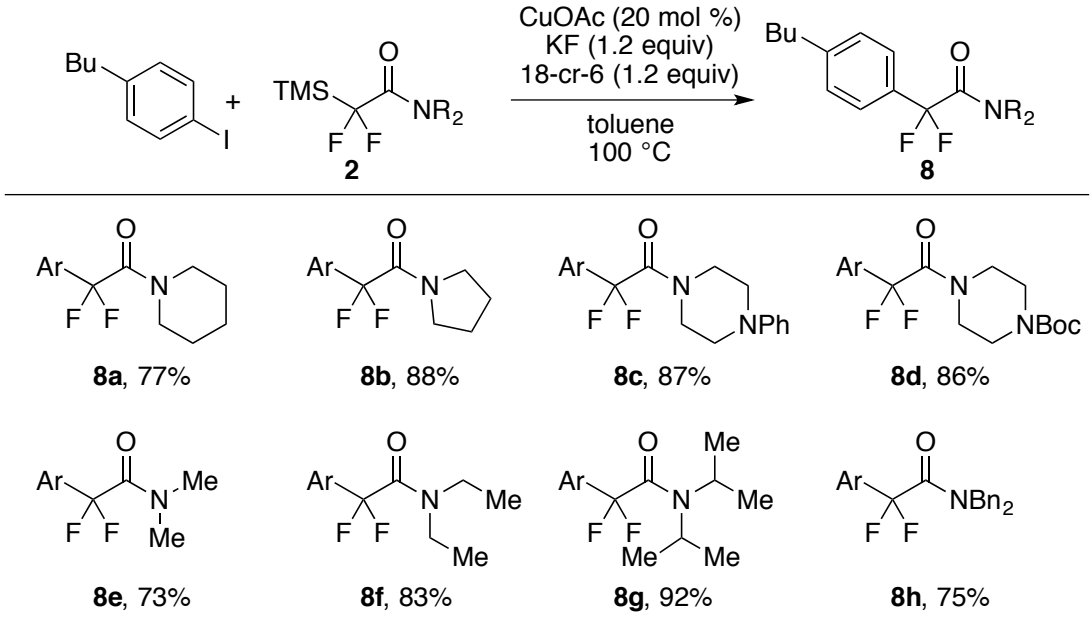




A variety of α-silyldifluoroamides coupled with aryl iodides under the reaction conditions (Table 2.7). Tertiary amides containing both cyclic and acyclic groups on nitrogen coupled with 1-butyl-4-iodobenzene in high yield. Varying degrees of steric bulk at the amide nitrogen atom were tolerated; dialkyl amides ranging from dimethyl- to diisopropylamides underwent coupling with 1-butyl-4-iodobenzene in 73 to 92% yield. Secondary *α*-silyl difluoroamides were also tested

in cross-coupling reactions with 1-butyl-4-iodobenzene; however, the aryldifluoroamide coupling products were not formed. In these reactions, the aryl iodide starting material was recovered, but quantitative protodesilylation of the α-silyl amide occurred, as was observed in reactions of aryl iodides containing protic functional groups.

Table 2.7 Copper-catalyzed coupling of 1-butyl-4-iodobenzene with α-silyldifluoroamides.[a]

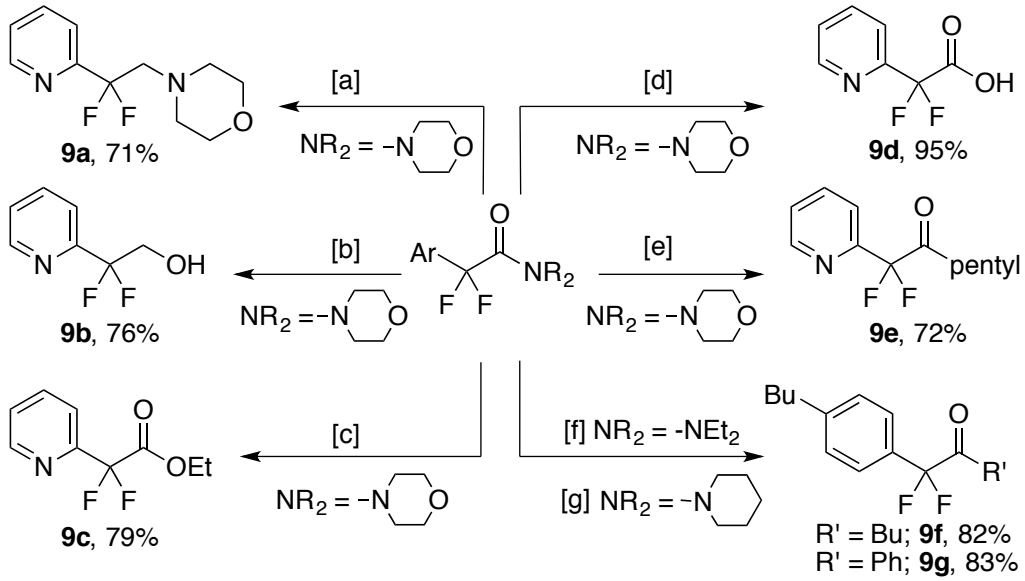


[a]Isolated yields. General conditions: aryl iodide (0.400 mmol), α-silyldifluoroamide (0.800 mmol), KF (0.480 mmol), CuOAc (0.0800 mmol), 18-crown-6 (0.480 mmol), toluene (1 mL), 100 °C, 24 h.

Aryldifluoroacetamides can serve as precursors to a variety of difluoroalkylarenes.[21] Because of the unique access to 2-pyridyldifluoroamides by this coupling chemistry, we investigated the transformation of a 2-pyridyl amide into a range of 2-difluoroalkylpyridines (Scheme 2.2). This pyridyl amide underwent transformations under conditions related to those we reported to occur with electron-neutral aryldifluoroamides.[21] The morpholinoamide **3p** was reduced to amine **9a** with BH_3•THF in 71% yield, and to alcohol **9b** with excess sodium borohydride in 76% yield. Pyridyldifluoroamide **3p** also underwent addition of a single equivalent of an alkyl Grignard reagent in 72% yield to afford a product (**9e**) equivalent to the unknown coupling of an aryl halide at the difluoromethyl group of the enolate of an alkyl difluoromethyl ketone. Monoaddition of alkyl- and arylmetal reagents is not limited to morpholinoamides: diethyl and piperidinyl amides were also converted to ketones **9f** and **9g** in high yield.

We reasoned that the fluorine atoms in the α-position to the amide carbonyl group render the carbon more electrophilic than that in a typical amide. Consistent with this hypothesis, hydrolysis or alcoholysis of difluoroamide **3p** to the corresponding carboxylic acid (**9d**) or ester (**9c**) occurred under mild conditions in 76 and 79% yield, respectively. The conditions for this hydrolysis were milder than those for hydrolysis of non-fluorinated amides, suggesting that

selective hydrolysis of an aryldifluoramide group in the presence of non-fluorinated amides is feasible.

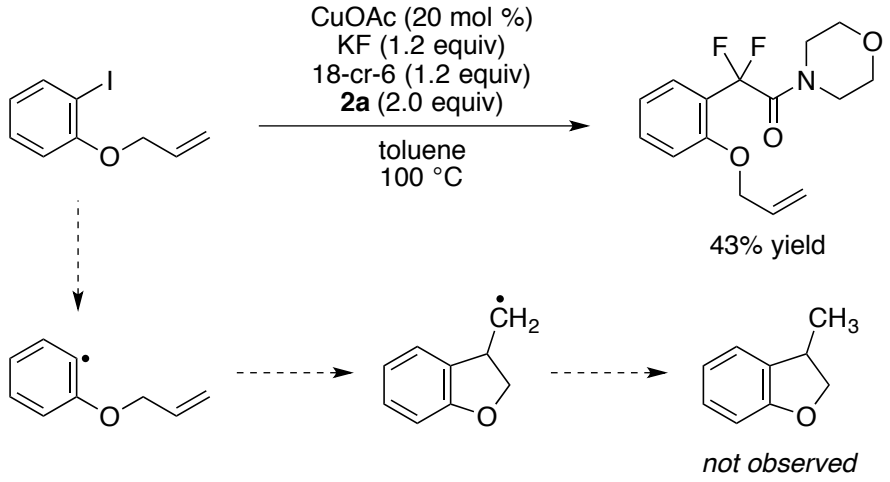


Scheme 2.2 Isolated yield for a reaction of 0.500 mmol **3p** unless otherwise stated. [a] BH_3•THF, THF, reflux. [b] $NaBH_4$, EtOH, reflux. [c] TMSCl, EtOH, reflux. [d] NaOH, EtOH, r.t. Yield was determined by ^{19}F NMR spectroscopy. [e] Pentylmagnesium bromide, THF, -78 °C. [f] Reaction of 0.300 mmol **8f**. *n*-Butyllithium, THF, -78 °C. [g] Reaction of 0.300 mmol **8a**. Phenyllithium, THF, -78 °C.

Copper-catalyzed enolate arylation reactions of aryl halides have been proposed in some cases to proceed via the intermediacy of aryl radicals,[32-33] and in other cases to proceed through a copper(I)/(III) cycle without the intermediacy of aryl radicals.[34] To investigate the potential that the coupling reactions of difluoroamide enolates occur through aryl radicals, we conducted the coupling reaction with 1-(allyloxy)-2-iodobenzene (Scheme 2.3). The corresponding aryl radical has been reported to undergo cyclization with a rate constant of $9.6*10^9$ s^{-1}.[35] The absence of 3-methyl-2,3-dihydrobenzofuran, which would be formed after hydrogen-atom abstraction from the solvent by the product of cyclization of the aryl radical, would provide evidence against the intermediacy of aryl radicals. The reaction of 1-(allyloxy)-2-iodobenzene under the standard CuOAc-catalyzed coupling conditions did not form cyclized products, implying that this reaction occurs, like other copper-catalyzed coupling reactions, without the intermediacy of an aryl radical. In addition, the coupling of (*Z*)-iodooctene proceeds with complete retention of the olefin geometry. If the reaction occurred through a vinyl radical, a mixture of (*E*) and (*Z*) stereoisomers of the coupled products would be expected to form.

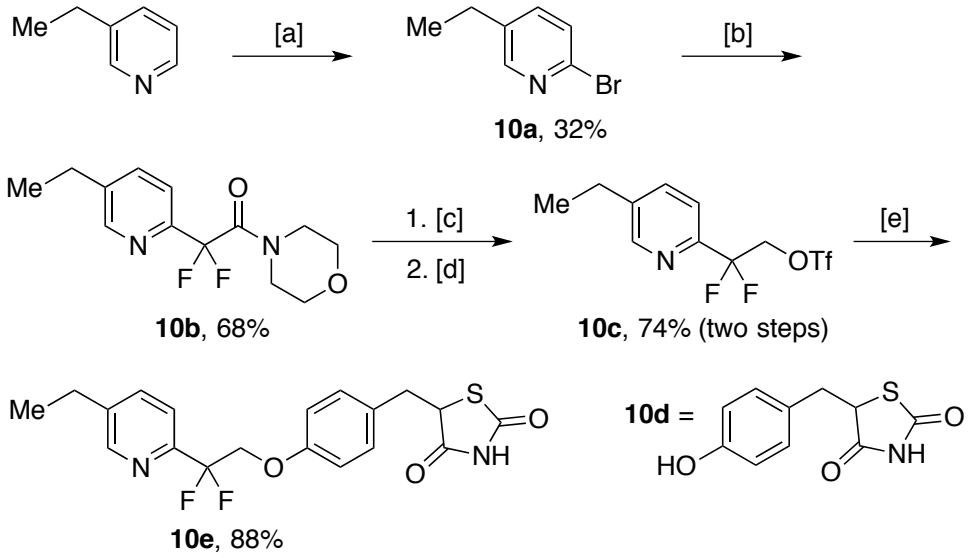
Due to the versatility of both the copper-catalyzed coupling reaction and the transformations of the coupled products, we sought to apply our methodology to the synthesis of difluoro derivatives of biologically active compounds. Substituting fluorine atoms for hydrogen atoms at positions prone to oxidation has become a common strategy for increasing the metabolic

stability of medicinal compounds.[6] Because benzylic positions are common sites of metabolic oxidation, we targeted analogs of biologically active compounds containing two fluorine atoms at a benzylic position.



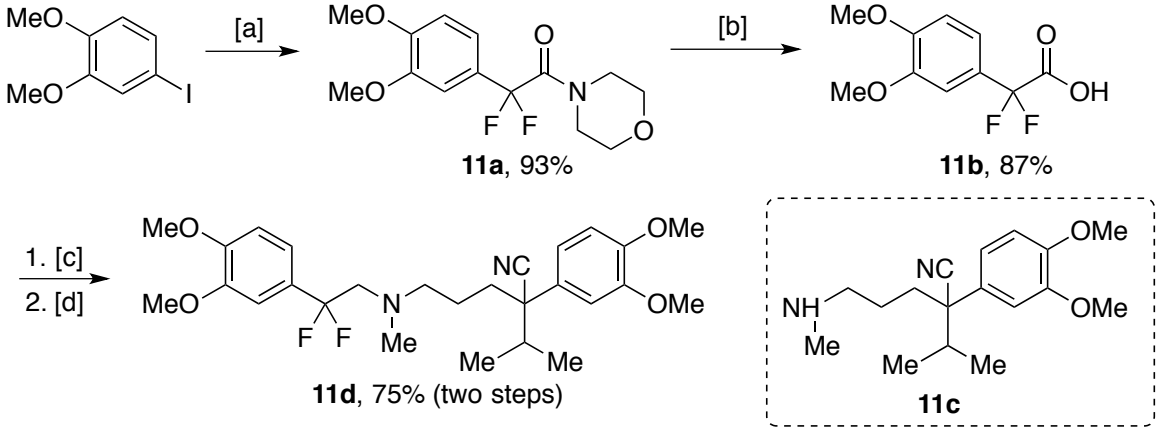
Scheme 2.3 Probe for the intermediacy of aryl radicals.

By the coupling chemistry in this work, we synthesized a difluorinated analog of pioglitazone, a drug for the treatment of type 2 diabetes (Scheme 2.4). The reaction of a 2-bromopyridine with compound **2a** formed **10b**, which was reduced to the corresponding alcohol. The alcohol was converted to the corresponding tosylate, but the aryldifluoroalkyl tosylate was less reactive toward substitution than the unfluorinated analog, and substitution with phenol derivative **10d** did not occur. However, alkyl triflate **10c** underwent Williamson etherification with phenol derivative **10d** to afford difluoro-pioglitazone (**10e**) in 88% yield.



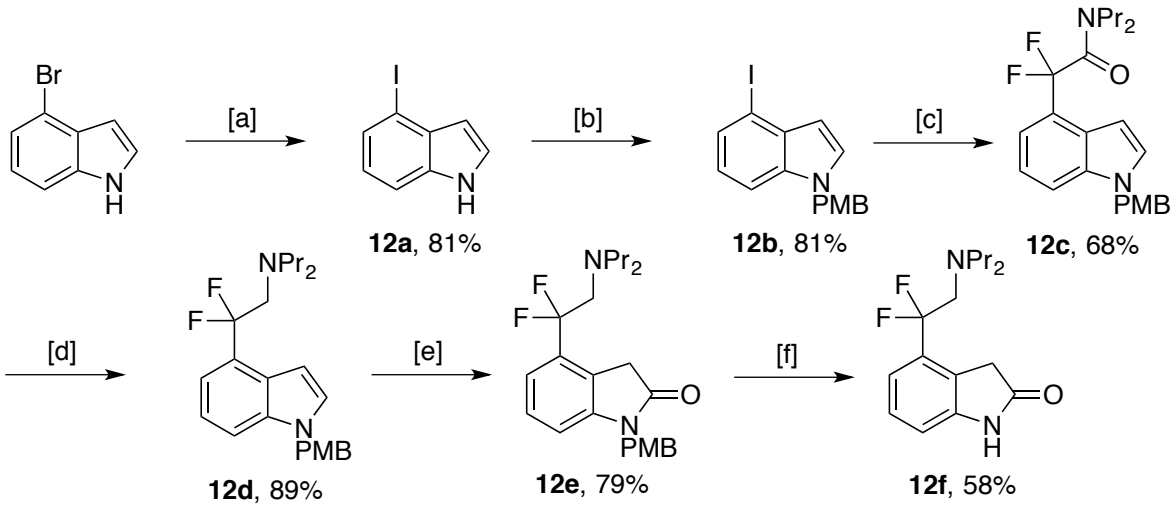
Scheme 2.4 Synthesis of difluoro-pioglitazone. [a] *n*BuLi, $Me_2N(CH_2)_2OH$, CBr_4, hexane, 0 °C → r.t. [b] CuOAc (20 mol %), KF (1.2 equiv), **2a** (2 equiv), NMP, 100 °C. [c] $NaBH_4$, EtOH, reflux. [d] Tf_2O, pyr, CH_2Cl_2, r.t. [e] NaH, **10d**, DMF, 50 °C.

The copper-catalyzed reaction of an electron-rich aryl iodide with an α-silyldifluoroamide was exploited for the synthesis of a difluoro analog of the cardiac drug verapamil (Scheme 2.5). 3,4-Dimethoxyiodobenzene coupled with **2a** in the presence of CuOAc in 93% yield. Compound **11a** was then converted to the corresponding acid in 87% yield and coupled with amine **11c**. The resulting amide was reduced to the amine to afford difluoro-verapamil (**11d**) in 75% yield over the last two steps and in 61% yield over the four-step sequence.



Scheme 2.5 Synthesis of difluoro-verapamil. [a] CuOAc (20 mol %), KF (1.2 equiv), 18-cr-6 (1.2 equiv), **2a** (2 equiv), toluene, 100 °C. [b] NaOH, EtOH, 65 °C. [c] CDI, DMAP, **11c**, CH_2Cl_2, r.t. [d] $Zn(OAc)_2$, $HSiMe(OEt)_2$, THF, 65 °C.

Finally, we synthesized a difluorinated analog of ropinirole, a drug for the treatment of Parkinson's disease (Scheme 2.6). Protected indole **12b** participated in the copper-catalyzed coupling, which enabled the synthesis of indole **12c**. Compound **12c** was then reduced to amine **12d** in 89% yield. Finally, oxidation of the indole to the corresponding oxindole (**12e**), followed by deprotection, afforded difluoro-ropinirole (**12f**).



Scheme 2.6 Synthesis of difluoro-ropinirole. [a] CuI, DMEDA, NaI, dioxane, 110 °C. [b] NaH, PMBCl, DMF, 0 °C → r.t. [c] CuOAc (20 mol %), KF (1.2 equiv), 18-cr-6 (1.2 equiv), $TMSCF_2CONPr_2$ (2 equiv), toluene, 100 °C. [d] $Zn(OAc)_2$, $HSiMe(OEt)_2$, THF, 65 °C. [e] NCS, toluene/HCl, 100 °C. [f] PhOMe, H_2SO_4, TFA, 100 °C.

2.3 Conclusion

In summary, we have developed a procedure for the synthesis of aryldifluoroamides from aryl halides and α-silyldifluoroamides. The reaction is catalyzed by commercially available CuOAc, does not require the addition of an exogenous ligand, and is applicable to the coupling of electron-rich, electron-poor, and sterically hindered aryl and heteroaryl iodides with a variety of α-silyldifluoroamides. Several heteroaryl bromides that did not undergo coupling under Pd-catalyzed cross-coupling conditions were transformed to the corresponding heteroaryldifluoroamides when subjected to Cu-catalyzed cross-coupling conditions. The results of cross-coupling reactions of substrates that can serve as radical probes are consistent with a reaction mechanism that does not involve aryl or vinyl radical intermediates. We demonstrated that the aryldifluoroamide products can be converted to a range of difluoroalkylarenes that would otherwise be difficult to access, and that aryldifluoroamides serve as versatile intermediates for the synthesis of compounds of biological interest.

2.4 Experimental

General Experimental Details

All reactions were conducted under inert atmosphere in a nitrogen-filled glovebox or with standard Schlenk techniques, unless otherwise specified. Vessels used in air-free reactions were oven-dried prior to use. Vials used as a reaction vessel were sealed with Teflon-lined caps. Silica-gel chromatography was performed with Silicycle SiliaFlash P60 silica gel. Toluene, tetrahydrofuran, and dichloromethane were purged with nitrogen and dried with an Innovative

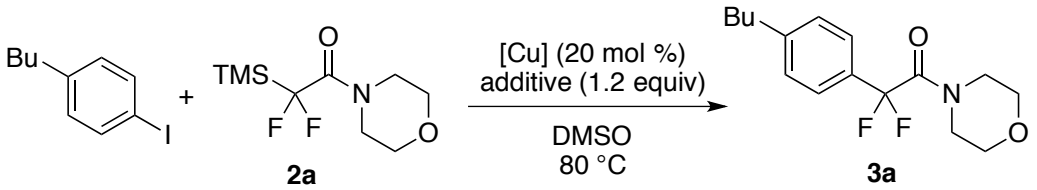
Pure-Solv solvent purification system. Anhydrous dimethylsulfoxide, dimethylformamide, dioxane, and *N*-methylpyrrolidone were purchased from Acros Organics. All other solvents were purchased from Fisher Scientific. Copper(I) acetate was purchased from Strem. $CDCl_3$ was purchased from Cambridge Isotope Laboratories. Aryl and vinyl iodides, aryl bromides, amines, chlorodifluoroacetic anhydride, and ligands were purchased from Sigma Aldrich, Alpha Aesar, Oakwood Chemical, Santa Cruz Biotechnologies, VWR International, and Fisher Scientific. Compounds were used as received unless otherwise noted. *Tert*-butyl 4-iodobenzoate,[36] *N*-ethyl-*N*-(4-iodobenzyl)ethanamine,[37] 2-(4-iodophenyl)-2-methyl-1,3-dioxolane,[38] 1-(allyloxy)-2-iodobenzene,[39] and 4-(3,4-dimethoxyphenyl)-4-isocyano-*N*,5-dimethylhexan-1-amine (**11c**)[40] were prepared according to literature procedures.

NMR spectra were acquired on Bruker AVB-400, AVQ-400, and AV-600 spectrometers at the University of California, Berkeley NMR facility. ^1H and ^{13}C chemical shifts were reported relative to residual solvent peaks ($CDCl_3$ = 7.26 ppm for ^1H and 77.2 ppm for ^{13}C). High-resolution mass spectra were obtained at the University of California, Berkeley Mass Spectrometry Facility with EI or ESI techniques with a Thermo Finnigan LTQ FT instrument.

Investigation of Reaction Conditions

In a nitrogen-filled glovebox, the copper salt (0.0200 mmol, 0.200 equiv), additive (0.120 mmol, 1.20 equiv), and **2** (28.5 mg, 0.120 mmol, 1.20 equiv) were added to a 4 mL vial equipped with a stir bar. If applicable, the ligand was added, if solid at room temperature (0.0200 mmol, 0.200 equiv). Solvent (0.25 mL) was added, followed by 1-butyl-4-iodobenzene (17.8 μL, 0.100 mmol, 1.00 equiv). If applicable, the ligand was added, if liquid at room temperature (0.0200 mmol, 0.200 equiv). The reaction was sealed with a Teflon-lined cap and heated at 80 or 100 °C for 6 h. After 6 h, the reaction was allowed to cool to room temperature. The internal standard, 3-nitrofluorobenzene (21.3 μL, 0.200 mmol, 2.00 equiv), was added, and the yield of the reaction was determined by ^{19}F NMR spectroscopy by comparing the ^{19}F NMR resonance of the desired product to that of the internal standard.

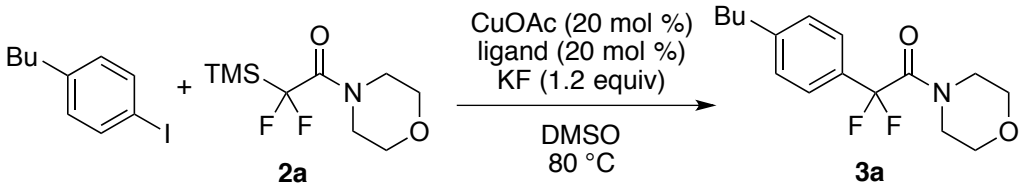
Table S2.1 Effect of copper and fluoride salts on coupling with α-silyldifluoroamide **2a**.[a]



entry	[Cu]	additive	yield[b]
1	$CuBr_2$	KF	<5%
2	$Cu(OAc)_2$	KF	<5%
3	CuO	KF	<5%
4	CuOAc	KF	89%
5	CuOAc	NaF	76%
6	CuOAc	CsF	31%
7	-	KF	<5%
8c	CuOAc	KF	<5%

[a]General conditions: 0.100 mmol aryl iodide, 0.120 mmol **2a**, and 0.0200 mmol CuX in 0.25 mL of DMSO under nitrogen atmosphere unless otherwise stated. [b]Yields were determined by ^{19}F NMR spectroscopy. [c]The reaction was carried out under air.

Table S2.2 Effect of added ligands on the coupling with α-silyldifluoroamide **2a**.[a]

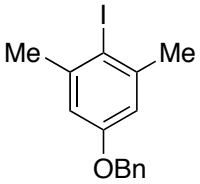


entry	ligand	yield[b]
1	Me_2N NMe_2	68%
2	MeHN NHMe	14%
3	H_2N NH_2	< 5%
4	N N	74%
5	N N	85%
6	none	89%

[a]General conditions: 0.100 mmol aryl iodide and 0.120 mmol **2a** in 0.25 mL of DMSO. [b]Yields were determined by ^{19}F NMR spectroscopy.

Synthesis of Aryl Iodides

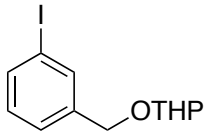
5-(benzyloxy)-2-iodo-1,3-dimethylbenzene (S1)



To an oven-dried round bottom flask under nitrogen was added K_2CO_3 (1.11 g, 8.00 mmol, 2.00 equiv) and 4-iodo-3,5-dimethylphenol (992 mg, 4.00 mmol, 1.00 equiv), followed by anhydrous acetone (10 mL). Benzyl bromide (476 μL, 4.00 mmol, 1.00 equiv) was added dropwise, and the reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated *in vacuo*, and the crude residue was purified by silica gel chromatography with 20:1 hexanes:EtOAc as eluent. The product was isolated as a fluffy white solid (1.14 g, 3.33 mmol, 83% yield).

^1H NMR (600 MHz, $CDCl_3$) δ 7.49-7.44 (m, 2H), 7.44-7.39 (m, 2H), 7.39-7.34 (m, 3H), 4.79 (s, 2H), 2.25 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.0, 137.8, 137.4, 134.0, 128.8, 128.3, 128.0, 88.0, 74.3, 16.3. HRMS (EI+) calc'd for $C_{15}H_{15}IO$: 338.0168, found: 338.0166.

2-((3-iodobenzyl)oxy)tetrahydro-2*H*-pyran (S2)

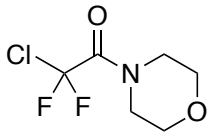


To a round bottom flask was added PPTS (101 mg, 0.400 mmol, 0.100 equiv), followed by CH_2Cl_2 (40 mL). 3,4-dihydro-2*H*-pyran (678 μL, 8.00 mmol, 2.00 equiv) was added, followed by (3-iodophenyl)methanol (508 μL, 4.00 mmol, 1.00 equiv). The reaction mixture was stirred for 4.5 h at room temperature. The solvent was evaporated in vacuo, and the crude residue was purified by silica gel chromatography with 4:1 hexanes:EtOAc as eluent. The product was isolated as a colorless oil (1.20 g, 3.76 mmol, 94% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.61 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 7.7 Hz, 1H), 4.72 (d, *J* = 12.4 Hz, 1H), 4.69 (t, *J* = 3.6 Hz, 1H), 4.43 (d, *J* = 12.3 Hz, 1H), 3.89 (ddd, *J* = 11.5, 8.6, 2.9 Hz, 1H), 3.59-3.48 (m, 1H), 1.91-1.81 (m, 1H), 1.78-1.70 (m, 1H), 1.70-1.50 (m, 5H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 140.9, 136.7, 136.6, 130.2, 127.0, 98.0, 94.5, 68.0, 62.3, 30.6, 25.6, 19.4. HRMS (EI+) calc'd for $C_{12}H_{15}IO_2$: 318.0117, found: 318.0110.

Synthesis of Chlorodifluoroamides

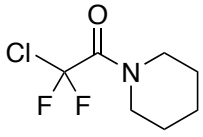
2-Chloro-2,2-difluoro-1-mormpholinoethan-1-one (1a)



To an oven-dried round bottom flask under nitrogen was added anhydrous CH_2Cl_2 (10 mL) and morpholine (3.85 mL, 44.0 mmol, 2.20 equiv). The reaction mixture was cooled in an ice bath for 15 min. Chlorodifluoroacetic anhydride (3.48 mL, 20.0 mmol, 1.00 equiv) was added dropwise. After addition was complete, the reaction mixture was stirred in an ice bath for 15 min, then allowed to warm to room temperature and stirred for 2 h. The reaction mixture was poured into a separatory funnel, and 1 M HCl (15 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3x15 mL) and washed with H_2O (3x15 mL). The combined organic extracts were dried over Na_2SO_4, and the solvent was removed *in vacuo*. The product was isolated as a colorless oil (3.26 g, 16.3 mmol, 82% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86–3.52 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.6 (d, *J* = 29.5 Hz), 118.6 (t, *J* = 301.9 Hz), 66.6, 66.4, 47.1, 44.0.^{19}F NMR (376 MHz, $CDCl_3$) δ –57.0. HRMS (EI) calc'd: 199.0212, found: 199.0206.

2-chloro-2,2-difluoro-1-(piperidin-1-yl)ethan-1-one (1b)

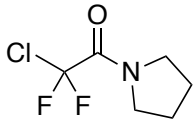


To an oven-dried round bottom flask under nitrogen was added anhydrous CH_2Cl_2 (10 mL) and piperidine (4.35 mL, 44.0 mmol, 2.20 equiv). The reaction mixture was cooled in an ice bath for 15 min. Chlorodifluoroacetic anhydride (3.48 mL, 20.0 mmol, 1.00 equiv) was added dropwise. After addition was complete, the reaction mixture was stirred in an ice bath for 15 min, then allowed to warm to room temperature and stirred for 2 h. The reaction mixture was poured into a separatory funnel, and 1 M HCl (15 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3x15 mL) and

washed with H_2O (3x15 mL). The combined organic extracts were dried over Na_2SO_4, and the solvent was removed *in vacuo*. The product was isolated as a colorless oil (3.94 g, 19.9 mmol, 100% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75–3.24 (m, 4H), 1.72–1.45 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.1 (t, J = 29.0 Hz), 118.7 (t, J = 301.0 Hz), 47.4 (t, J = 3.9 Hz), 44.9, 26.0, 25.4, 24.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ –56.8.

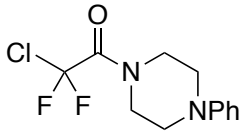
2-chloro-2,2-difluoro-1-(pyrrolidin-1-yl)ethan-1-one (1c)



To an oven-dried round bottom flask under nitrogen was added anhydrous CH_2Cl_2 (10 mL) and pyrrolidine (3.67 mL, 44.0 mmol, 2.20 equiv). The reaction mixture was cooled in an ice bath for 15 min. Chlorodifluoroacetic anhydride (3.48 mL, 20.0 mmol, 1.00 equiv) was added dropwise. After addition was complete, the reaction mixture was stirred in an ice bath for 15 min, then allowed to warm to room temperature and stirred for 2 h. The reaction mixture was poured into a separatory funnel, and 1 M HCl (15 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3x15 mL) and washed with H_2O (3x15 mL). The combined organic extracts were dried over Na_2SO_4, and the solvent was removed *in vacuo*. The product was isolated as a colorless oil (3.69 g, 20.0 mmol, 100% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.59 (t, J = 6.9 Hz, 2H), 3.49 (t, J = 7.1 Hz, 2H), 1.99–1.90 (m, 2H), 1.89–1.79 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4 (t, J = 29.9 Hz), 119.0 (t, J = 301.6 Hz), 47.9, 47.3 (t, J = 4.4 Hz), 26.4, 23.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ –59.9. HRMS (ESI+) calc'd for [$C_6H_8ClF_2NONa^+$]: 206.0160, found: 206.0155.

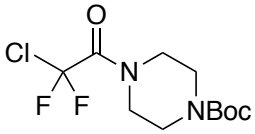
2-Chloro-2,2-difluoro-1-(4-phenylpiperazin-1-yl)ethan-1-one (1d)



To an oven-dried round bottom flask under N_2 was added ethyl chlorodifluoroacetate (2.00 g, 1.60 mL, 12.6 mmol, 1.00 equiv), followed by 1-phenylpiperazine (10.2 g, 9.64 mL, 63.1 mmol, 5.00 equiv). The reaction mixture was stirred at room temperature for 4 h, followed by the addition of 2M HCl (15 mL). The mixture was extracted with EtOAc (3x15 mL), and the combined organic extracts were washed with 2M HCl (3x15 mL) and brine (15 mL). The solvent was evaporated *in vacuo*. The product was isolated as a colorless solid (2.44 g, 8.88 mmol, 70% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (t, J = 7.8 Hz, 2H), 6.95 (dd, J = 7.8, 4.7 Hz, 3H), 3.90-3.80 (m, 4H), 3.31-3.20 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.4 (t, J = 29.2 Hz), 150.5, 129.3, 121.0, 118.5 (t, J = 301.3 Hz), 116.8, 49.5, 49.2, 46.3 (t, J = 3.9 Hz), 43.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ -56.72. HRMS (ESI+) calc'd for $C_{12}H_{14}ClF_2N_2O^+$ $[M+H]^+$: 275.0763, found: 275.0757.

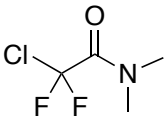
tert-Butyl 4-(2-chloro-2,2-difluoroacetyl)piperazine-1-carboxylate (1e)



To an oven-dried round bottom flask under N_2 was added *tert*-butyl piperazine-1-carboxylate (410 mg, 2.20 mmol, 2.20 equiv) and CH_2Cl_2 (5 mL). The solution was cooled at 0 °C, and chlorodifluoroacetic anhydride (174 μL, 1.00 mmol, 1.00 equiv) was added dropwise. The solution was stirred at 0 °C, then allowed to warm to room temperature and stirred for 2 h. To the reaction mixture was added 1M HCl (5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3x5 mL). The combined organic extracts were washed with 1M HCl (2x5 mL) and H_2O (2x5 mL) and dried with Na_2SO_4. The solvent was evaporated in *vacuo*. The product was isolated as a colorless oil (263 mg, 0.882 mmol, 88% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.57-3.49 (m, 4H), 3.44-3.32 (m, 4H), 1.35 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4 (t, *J* = 29.2 Hz), 154.1, 118.3 (t, *J* = 301.0 Hz), 80.4, 46.1, 43.4, 28.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ -56.8. HRMS (EI+) calc'd for $C_{11}H_{17}ClF_2N_2O_3$: 298.0896, found: 298.0899.

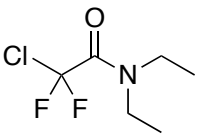
2-chloro-2,2-difluoro-N,N-dimethylacetamide (1f)



To an oven-dried round bottom flask under nitrogen was added dimethylamine hydrochloride (489 mg, 6.00 mmol, 2.00 equiv), anhydrous CH_2Cl_2 (5 mL), and chlorodifluoroacetic anhydride (522 μL, 3.00 mmol, 1.00 equiv). The reaction mixture was cool in an ice bath for 15 min. Pyridine (1.62 mL, 20.0 mmol, 4.00 equiv) was added dropwise. After addition was complete, the reaction mixture was stirred in an ice bath for 15 min, then allowed to warm to room temperature and stirred for 2 h. The reaction mixture was poured into a separatory funnel, and 1 M HCl (10 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3x10 mL) and washed with 1 M HCl (3x10 mL) and sat. aqueous $NaHCO_3$ (3x10 mL). The combined organic extracts were dried over Na_2SO_4, and the solvent was removed *in vacuo*. The product was isolated as a light yellow oil (459 mg, 2.91 mmol, 97% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.13 (s, 3H), 2.99 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7 (t, J = 28.5 Hz), 118.6 (t, J = 301 Hz), 37.5, 37.3. 19F NMR (376 MHz, CDCl3) δ -57.2 (s).

2-chloro-N,N-diethyl-2,2-difluoroacetamide (1g)

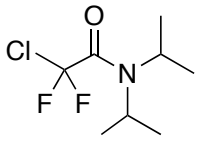


To an oven-dried round bottom flask under nitrogen was added anhydrous CH_2Cl_2 (5 mL) and diethylamine (1.03 mL, 10.0 mmol, 2.00 equiv). The reaction mixture was cooled in an ice bath for 15 min. Chlorodifluoroacetic anhydride (871 μL, 5.00 mmol, 1.00 equiv) was added dropwise. After addition was complete, the reaction mixture was stirred in an ice bath for 15 min, then allowed to warm to room temperature and stirred for 2 h. The reaction mixture was poured into a separatory funnel, and 1 M HCl (10 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3x10 mL) and washed with H_2O (3x10 mL). The combined organic extracts were dried over Na_2SO_4, and the

solvent was removed *in vacuo*. The product was isolated as a light yellow oil (890 mg, 4.80 mmol, 96% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.46 (q, J = 6.9 Hz, 2H), 3.38 (q, J = 7.0 Hz, 2H), 1.20 (t, J = 7.0 Hz, 3H), 1.15 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1 (t, J = 29.1 Hz), 118.9 (t, J = 302 Hz), 42.5 (t, J = 3.7 Hz), 41.9, 13.8, 11.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ –57.2 (s). The NMR spectra correspond to those that have been previously reported.[41]

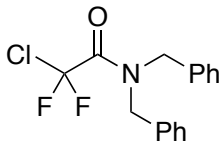
2-Chloro-2,2-difluoro-*N*,*N*-diisopropylacetamide (1h)



To an oven-dried round bottom flask under N_2 was added diisopropylamine (6.17 mL, 44.0 mmol, 2.20 equiv) and CH_2Cl_2 (25 mL). The solution was cooled at 0 °C, and chlorodifluoroacetic anhydride (3.48 mL, 20.0 mmol, 1.00 equiv) was added dropwise. The solution was stirred at 0 °C, then allowed to warm to room temperature and stirred for 2 h. To the reaction mixture was added 1M HCl (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3x15 mL). The combined organic extracts were washed with 1M HCl (2x20 mL) and H_2O (2x20 mL) and dried with Na_2SO_4. The solvent was evaporated *in vacuo*. The product was isolated as a colorless oil (3.78 g, 17.7 mmol, 89% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 (hept, *J* = 6.5 Hz, 1H), 3.50 (hept, *J* = 6.8 Hz, 1H), 1.40 (d, *J* = 6.9 Hz, 6H), 1.22 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2 (t, *J* = 28.1 Hz), 118.9 (t, *J* = 301.3 Hz), 49.6 (t, *J* = 4.3 Hz), 47.5, 20.3, 19.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.2. HRMS (ESI+) calc'd for $C_8H_{15}ClF_2NO^+$ $[M+H]^+$: 214.0810, found: 214.0805.

***N*,*N*-Dibenzyl-2-chloro-2,2-difluoroacetamide (1i)**

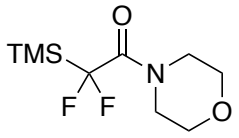


To an oven-dried round bottom flask under N_2 was added dibenzylamine (1.15 mL, 6.00 mmol, 2.00 equiv) and CH_2Cl_2 (10 mL). The solution was cooled at 0 °C, and chlorodifluoroacetic anhydride (522 µL, 3.00 mmol, 1.00 equiv) was added dropwise. The solution was stirred at 0 °C, then allowed to warm to room temperature and stirred for 2 h. To the reaction mixture was added 1M HCl (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The combined organic extracts were washed with 1M HCl (2x10 mL) and H_2O (2x10 mL) and dried with Na_2SO_4. The solvent was evaporated *in vacuo*. The product was isolated as a colorless solid (889 mg, 2.87 mmol, 96% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.31 (m, 6H), 7.30-7.21 (m, 4H), 4.69 (s, 2H), 4.60 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4 (t, *J* = 29.0 Hz), 135.2, 134.6, 129.0, 128.8, 128.2, 128.2, 128.0, 127.3, 119.0 (t, *J* = 301.7 Hz), 50.1, 48.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -55.9. HRMS (ESI+) calc'd for $C_{16}H_{15}ClF_2NO^+$ $[M+H]^+$: 310.0805, found: 310.0807.

Synthesis of α-Silyl Difluoroamides

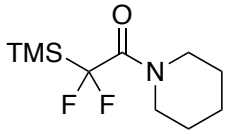
2,2-Difluoro-1-morpholino-2-(trimethylsilyl)ethan-1-one (2a)



To an oven-dried round bottom flask under N_2 was added Mg (972 mg, 40.0 mmol, 2.00 equiv), anhydrous DMF (50 mL), and TMSCl (10.2 mL, 80.0 mmol, 4.00 equiv). The reaction mixture was cooled at 0 °C. Compound **1** (3.99 g, 20.0 mmol, 1.00 equiv) was added, and the reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 20 h, the reaction was quenched with H_2O (100 mL) and extracted with Et_2O (3x50 mL). The combined organic extracts were washed with H_2O (3x50 mL) and brine (50 mL) and dried with Na_2SO_4. The solvent was evaporated *in vacuo*, and the crude residue was purified by silica gel chromatography with Et_2O:pentane (1:5) as eluent. Compound **2a** was isolated as a colorless crystalline solid (3.84 g, 16.2 mmol, 81% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.77–3.74 (m, 2H), 3.74–3.71 (m, 2H), 3.71–3.67 (m, 2H), 3.62–3.56 (m, 2H), 0.24 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.6 (t, J = 24.1 Hz), 126.3 (t, J = 274.6 Hz), 67.1, 66.9, 45.9 (t, J = 6.3 Hz), 42.9, –3.9 (t, J = 1.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ –114.6.

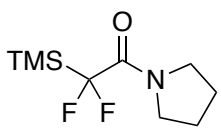
2,2-difluoro-1-(piperidin-1-yl)-2-(trimethylsilyl)ethan-1-one (2b)



To an oven-dried round bottom flask under N_2 was added Mg (123 mg, 5.06 mmol, 2.00 equiv), anhydrous DMF (8 mL), and TMSCl (1.28 mL, 10.1 mmol, 4.00 equiv). The reaction mixture was cooled at 0 °C. Compound **1b** (500 mg, 2.53 mmol, 1.00 equiv) was added, and the reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 20 h, the reaction was quenched with H_2O (50 mL) and extracted with Et_2O (3x20 mL). The combined organic extracts were washed with H_2O (3x20 mL) and brine (20 mL) and dried with Na_2SO_4. The solvent was evaporated *in vacuo*, and the crude residue was purified by silica gel chromatography with hexanes:EtOAc 8:1 as eluent. Compound **2b** was isolated as a colorless oil (322 mg, 1.37 mmol, 54% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (t, J = 5.3 Hz, 2H), 3.51 (t, J = 5.3 Hz, 2H), 1.74–1.47 (m, 6H), 0.23 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.2 (t, J = 23.8 Hz), 126.5 (t, J = 275.1 Hz), 46.1, 43.8, 26.6, 25.7, 24.6, –3.9 (t, J = 1.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ –114.6.

2,2-difluoro-1-(pyrrolidin-1-yl)-2-(trimethylsilyl)ethan-1-one (2c)

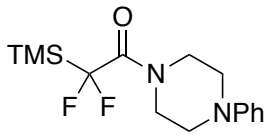


To an oven-dried round bottom flask under N_2 was added Mg (530 mg, 21.8 mmol, 2.00 equiv), anhydrous DMF (30 mL), and TMSCl (5.53 mL, 43.6 mmol, 4.00 equiv). The reaction mixture was cooled at 0 °C. Compound **1c** (2.00 g, 10.9 mmol, 1.00 equiv) was added, and the reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 20 h, the reaction

was quenched with H_2O (75 mL) and extracted with Et_2O (3x40 mL). The combined organic extracts were washed with H_2O (3x40 mL) and brine (40 mL) and dried with Na_2SO_4. The solvent was evaporated *in vacuo*, and the crude residue was purified by silica gel chromatography with hexanes:EtOAc 8:1 as eluent. Compound **2c** was isolated as a colorless oil colorless oil (1.52 g, 6.87 mmol, 63% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.61 (t, *J* = 7.0 Hz, 2H), 3.40 (t, *J* = 7.2 Hz, 2H), 1.90–1.80 (m, 2H), 1.80–1.70 (m, 2H), 0.15 (d, *J* = 2.4 Hz, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.6 (t, *J* = 24.4 Hz), 125.0 (t, *J* = 272.8 Hz), 46.8, 45.7 (t, *J* = 6.2 Hz), 26.4 (t, *J* = 1.5 Hz), 23.2, –4.1 (t, *J* = 1.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ –118.2.

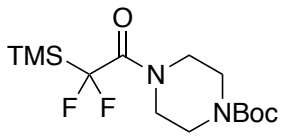
2,2-Difluoro-1-(4-phenylpiperazin-1-yl)-2-(trimethylsilyl)ethan-1-one (2d)



To an oven-dried round bottom flask under N_2 was added Mg (79.6 mg, 3.28 mmol, 2.00 equiv), anhydrous DMF (5 mL), and TMSCl (832 µL, 6.55 mmol, 4.00 equiv). The reaction mixture was cooled at 0 °C. Compound **1d** (450 mg, 1.64 mmol, 1.00 equiv) was added, and the reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 20 h, the reaction was quenched with H_2O (50 mL) and extracted with Et_2O (3x20 mL). The combined organic extracts were washed with H_2O (3x20 mL) and brine (20 mL) and dried with Na_2SO_4. The solvent was evaporated *in vacuo*, and the crude residue was purified by silica gel chromatography with hexanes:EtOAc 8:1 as eluent. Compound **2d** was isolated as a colorless solid (370 mg, 1.18 mmol, 74% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (t, *J* = 8.6 Hz, 2H), 6.96-6.88 (m, 3H), 3.91 (t, *J* = 5.0 Hz, 2H), 3.76 (t, *J* = 4.2 Hz, 2H), 3.25-3.17 (m, 4H), 0.26 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.5 (t, *J* = 23.8 Hz), 151.1, 129.4, 126.3 (t, *J* = 274.6 Hz), 120.8, 116.9, 50.1, 49.5, 45.1 (t, *J* = 6.3 Hz), 42.6, -3.79 (t, *J* = 1.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) -114.3. HRMS (EI+) calc'd for $C_{15}H_{22}F_2N_2OSi$: 312.1469, found: 312.1471.

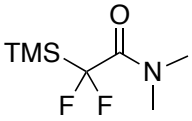
***tert*-Butyl 4-(2,2-difluoro-2-(trimethylsilyl)acetyl)piperazine-1-carboxylate (2e)**



To an oven-dried round bottom flask under N_2 was added Mg (40.7 mg, 1.67 mmol, 2.00 equiv), anhydrous DMF (5 mL), and TMSCl (425 µL, 3.35 mmol, 4.00 equiv). The reaction mixture was cooled at 0 °C. Compound **1e** (250 mg, 0.837 mmol, 1.00 equiv) was added, and the reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 20 h, the reaction was quenched with H_2O (20 mL) and extracted with Et_2O (3x50 mL). The combined organic extracts were washed with H_2O (3x50 mL) and brine (10 mL) and dried with Na_2SO_4. The solvent was evaporated *in vacuo*, and the crude residue was purified by silica gel chromatography with hexanes:EtOAc 10:1 as eluent. Compound **2e** was isolated as a colorless solid (214 mg, 0.636 mmol, 76% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (t, *J* = 5.0 Hz, 2H), 3.50 (t, *J* = 5.0 Hz, 2H), 3.41 (m, 4H), 1.41 (s, 9H), 0.18 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4 (t, *J* = 24.3 Hz), 154.5, 126.1 (t, *J* = 274.6 Hz), 80.3, 44.9, 42.4, 28.4, -4.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.5. HRMS (EI+) calc'd for $C_{14}H_{26}F_2N_2O_3Si$: 336.1681, found: 336.1683.

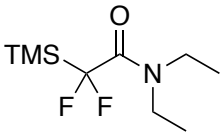
2,2-difluoro-N,N-dimethyl-2-(trimethylsilyl)acetamide (2f)



To an oven-dried round bottom flask under N_2 was added Mg (136 mg, 5.83 mmol, 2.00 equiv), anhydrous DMF (15 mL), and TMSCl (1.48 mL, 11.7 mmol, 4.00 equiv). The reaction mixture was cooled at 0 °C. Compound **1f** (459 mg, 2.91 mmol, 1.00 equiv) was added, and the reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 20 h, the reaction was quenched with H_2O (15 mL) and extracted with Et_2O (3x15 mL). The combined organic extracts were washed with H_2O (3x15 mL) and brine (15 mL) and dried with Na_2SO_4. The solvent was evaporated *in vacuo*. Compound **2f** was isolated as a colorless oil (386 mg, 1.98 mmol, 68% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.11 (s, 3H), 2.90 (s, 3H), 0.18 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6 (t, J = 23.9 Hz), 125.8 (t, J = 275 Hz), 36.0, 35.9 (t, J = 6.9 Hz), -4.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ –115.1.

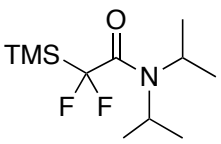
N,N-diethyl-2,2-difluoro-2-(trimethylsilyl)acetamide (2g)



To an oven-dried round bottom flask under N_2 was added Mg (233 mg, 9.60 mmol, 2.00 equiv), anhydrous DMF (20 mL), and TMSCl (2.44 mL, 19.2 mmol, 4.00 equiv). The reaction mixture was cooled at 0 °C. Compound **1g** (890 mg, 4.80 mmol, 1.00 equiv) was added, and the reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 20 h, the reaction was quenched with H_2O (100 mL) and extracted with Et_2O (3x30 mL). The combined organic extracts were washed with H_2O (3x30 mL) and brine (30 mL) and dried with Na_2SO_4. The solvent was evaporated *in vacuo*, and the crude residue was purified by silica gel chromatography with hexanes:EtOAc 10:1 as eluent. Compound **2g** was isolated as a light yellow oil (819 mg, 3.65 mmol, 76% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55–3.45 (m, 2H), 3.35–3.25 (m, 2H), 1.20–1.08 (m, 6H), 0.19 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4 (t, *J* = 23.8 Hz), 126.3 (t, *J* = 274.9 Hz), 41.1 (t, *J* = 6.2 Hz), 40.9, 14.5, 12.5, –3.8 (t, *J* = 1.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ –115.1.

2,2-Difluoro-*N*,*N*-diisopropyl-2-(trimethylsilyl)acetamide (2h)

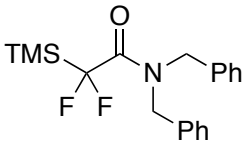


To an oven-dried round bottom flask under N_2 was added Mg (314 mg, 12.9 mmol, 2.00 equiv), anhydrous DMF (20 mL), and TMSCl (3.27 mL, 25.8 mmol, 4.00 equiv). The reaction mixture was cooled at 0 °C. Compound **1h** (1.38 g, 6.44 mmol, 1.00 equiv) was added, and the reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 20 h, the reaction

was quenched with H_2O (100 mL) and extracted with Et_2O (3x30 mL). The combined organic extracts were washed with H_2O (3x30 mL) and brine (30 mL) and dried with Na_2SO_4. The solvent was evaporated *in vacuo*, and the crude residue was purified by silica gel chromatography with hexanes:EtOAc 15:1 as eluent. Compound **2h** was isolated as a colorless oil (959 mg, 3.81 mmol, 59% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.53 (hept, J = 6.6 Hz, 1H), 3.41 (hept, J = 6.8 Hz, 1H), 1.37 (d, J = 6.9 Hz, 6H), 1.17 (d, J = 6.8 Hz, 6H), 0.20 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.1 (t, J = 22.8 Hz), 127.6 (t, J = 277.3 Hz), 47.6 (t, J = 7.5 Hz), 46.6, 20.8, 20.1, -3.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.96. HRMS (EI+) calc'd for $C_{11}H_{23}F_2NOSi$: 251.1517, found: 251.1515.

_N_,_N_-Dibenzyl-2,2-difluoro-2-(trimethylsilyl)acetamide (2i)



To an oven-dried round bottom flask under N_2 was added Mg (140 mg, 5.74 mmol, 2.00 equiv), anhydrous DMF (10 mL), and TMSCl (1.46 mL, 11.5 mmol, 4.00 equiv). The reaction mixture was cooled at 0 °C. Compound **1i** (889 mg, 2.87 mmol, 1.00 equiv) was added, and the reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 20 h, the reaction was quenched with H_2O (60 mL) and extracted with Et_2O (3x20 mL). The combined organic extracts were washed with H_2O (2x30 mL) and brine (20 mL) and dried with Na_2SO_4. The solvent was evaporated *in vacuo*, and the residue was used without further purification. Compound **2i** was isolated as a colorless oil (616 mg, 1.59 mmol, 87% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.10 (m, 10H), 4.75 (s, 2H), 4.55 (s, 2H), 0.42 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1 (t, J = 23.9 Hz), 136.1, 136.1, 128.7, 128.6, 128.1, 127.7, 127.7, 127.5, 126.3 (t, J = 275.9 Hz), 48.8 (t, J = 6.2 Hz), 47.3, -3.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.0. HRMS (EI+) calc'd for $C_{19}H_{23}F_2NOSi$: 347.1517, found: 347.1510.

*Arylation of 2,2-Difluoro-1-morpholino-2-(trimethylsilyl)ethan-1-one (**2a**)*

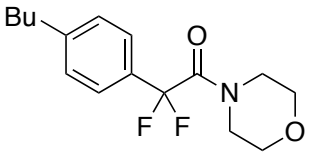
General Procedure Ia

In a nitrogen-filled glovebox, CuOAc (9.8 mg, 0.080 mmol, 0.20 equiv), KF (27.9 mg, 0.480 mmol, 1.20 equiv), 18-crown-6 (127 mg, 0.480 mmol, 1.20 equiv), compound **2a** (0.800 mmol, 2.00 equiv), and the aryl or vinyl iodide, if solid at r.t. (0.400 mmol, 1.00 equiv) were added to a 4 mL vial equipped with a stir bar. Toluene (1 mL) was added, followed by the aryl or vinyl iodide, if liquid at r.t. (0.400 mmol, 1.00 equiv). The reaction was sealed with a Teflon-lined cap and heated at 100 °C for 24 h. After 24 h, the reaction was allowed to cool to room temperature. The reaction mixture was filtered through Celite, eluting with EtOAc, and the solvent was evaporated *in vacuo*. The crude residue was purified by silica gel chromatography.

General Procedure Ib: Alternative Procedure without the Use of a Glovebox

NOTE**:** CuOAc should be stored under an inert atmosphere, but can be weighed under air without a decrease in reaction yield. Under air, CuOAc (9.8 mg, 0.080 mmol, 0.20 equiv), KF (27.9 mg, 0.480 mmol, 1.20 equiv), 18-crown-6 (127 mg, 0.480 mmol, 1.20 equiv), and compound **2a** (0.800 mmol, 2.00 equiv) were added to a 4 mL vial equipped with a stir bar. The vial was sealed with a septum cap, and was then evacuated and refilled with nitrogen three times. Anhydrous toluene (1 mL) was added, followed by 1-butyl-4-iodobenzene (104 mg, 71.2 μL, 0.400 mmol, 1.00 equiv). The vial was removed from the nitrogen line and heated at 100 °C for 24 h. After 24 h, the reaction was allowed to cool to room temperature. The reaction mixture was filtered through Celite, eluting with EtOAc, and the solvent was evaporated *in vacuo*. The crude residue was purified by silica gel chromatography with 3:1 hexanes:EtOAc as eluent. The product was isolated as a colorless oil (102 mg, 0.343 mmol, 86% yield).

2-(4-butylphenyl)-2,2-difluoro-1-morpholinoethan-1-one (3a)

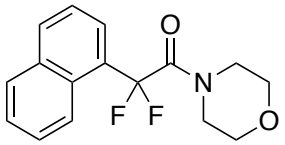


3a

Compound **3a** was prepared according to general procedure Ia with 1-butyl-4-iodobenzene (104 mg, 71.2 μL, 0.400 mmol, 1.00 equiv) and compound **2a** (190 mg, 0.800 mmol, 2.00 equiv). The product was isolated after silica gel chromatography with 3:1 hexanes:EtOAc as eluent. The product was isolated as a colorless oil (97.0 mg, 0.326 mmol, 82% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.9 Hz, 2H), 7.27 (d, *J* = 7.9 Hz, 2H), 3.70 (s, 4H), 3.46 (s, 4H), 2.65 (t, *J* = 7.8 Hz, 2H), 1.66-1.58 (m, 2H), 1.35 (hept, *J* = 7.4 Hz, 2H), 0.93 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4, 146.3, 130.8 (t, *J* = 25.0 Hz), 128.9, 125.1 (t, *J* = 5.6 Hz), 115.6 (t, *J* = 245.1 Hz), 66.7, 66.4, 46.7, 43.5, 35.5, 33.3, 22.4, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -93.2. HRMS (EI+) calc'd for $C_{16}H_{21}F_2NO_2$: 297.1540, found: 297.1538.

2,2-difluoro-1-morpholino-2-(naphthalen-1-yl)ethan-1-one (3b)

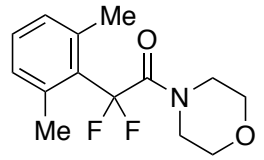


3b

Compound **3b** was prepared according to general procedure Ia with 1-iodonaphthalene (102 mg, 0.400 mmol, 1.00 equiv) and compound **2a** (190 mg, 0.800 mmol, 2.00 equiv). The product was isolated after silica gel chromatography with 3:1 hexanes:EtOAc as eluent. The product was isolated as a colorless solid (129 mg, 0.288 mmol, 72% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.4 Hz, 1H), 7.98 (d, *J* = 8.2 Hz, 1H), 7.91 (d, *J* = 7.9 Hz, 1H), 7.76 (d, *J* = 7.2 Hz, 1H), 7.63-7.52 (m, 2H), 7.51 (t, *J* = 7.7 Hz, 1H), 3.73 (t, *J* = 4.6 Hz, 2H), 3.68 (t, *J* = 4.7 Hz, 2H), 3.52 (t, *J* = 4.7 Hz, 2H), 3.43 (t, *J* = 4.8 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.5 (t, *J* = 30.5 Hz), 134.2, 132.2, 129.8, 129.4 (t, *J* = 22.1 Hz), 128.9, 127.6, 126.7, 124.8, 124.6 (t, *J* = 8.4 Hz), 124.4, 116.7 (d, *J* = 250.1 Hz), 66.9, 66.5, 47.0, 43.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -91.4. HRMS (EI+) calc'd for $C_{16}H_{15}F_2NO_2$: 291.1071, found: 291.1073.

2-(2,6-dimethylphenyl)-2,2-difluoro-1-morpholinoethan-1-one (3c)

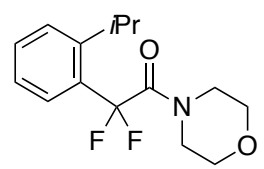


3c

Compound **3c** was prepared according to general procedure Ia with 2-iodo-1,3-dimethylbenzene (92.8 mg, 0.400 mmol, 1.00 equiv) and compound **2a** (190 mg, 0.800 mmol, 2.00 equiv). The product was isolated after silica gel chromatography with 3:1 hexanes:EtOAc as eluent. The product was isolated as a colorless solid (99.1 mg, 0.368 mmol, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (t, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 7.6 Hz, 2H), 3.77-3.66 (m, 4H), 3.65-3.53 (m, 4H), 2.38 (t, *J* = 4.1 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.5 (t, *J* = 31.1 Hz), 137.0 (t, *J* = 3.6 Hz), 131.1 (t, *J* = 22.1 Hz), 130.4, 129.9, 118.8 (t, *J* = 254.6 Hz), 66.9, 66.7, 46.6, 43.7, 22.0 (t, *J* = 5.1 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -88.7. HRMS (EI+) calc'd for $C_{14}H_{17}F_2NO_2$: 269.1227, found: 269.1226.

2,2-difluoro-2-(2-isopropylphenyl)-1-morpholinoethan-1-one (3d)

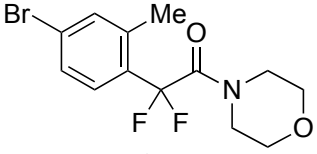


3d

Compound **3d** was prepared according to general procedure Ia with 1-iodo-2-isopropylbenzene (98.4 mg, 0.400 mmol, 1.00 equiv) and compound **2a** (190 mg, 0.800 mmol, 2.00 equiv). The product was isolated after silica gel chromatography with 3:1 hexanes:EtOAc as eluent. The product was isolated as a colorless solid (92.9 mg, 0.328 mmol, 82% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.9 Hz, 1H), 7.47-7.42 (m, 2H), 7.26-7.22 (m, 1H), 3.72 (s, 4H), 3.53 (s, 4H), 3.23 (hept, *J* = 6.7 Hz, 1H), 1.22 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.6 (t, *J* = 30.8 Hz), 148.7, 131.2, 130.6 (t, *J* = 23.5 Hz), 127.6, 125.8, 125.4 (t, *J* = 8.9 Hz), 116.7 (t, *J* = 251.4 Hz), 66.8, 66.6, 46.9, 43.7, 29.5 (t, *J* = 1.9 Hz), 24.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -91.0. HRMS (ESI+): calc'd for $C_{15}H_{20}F_2NO_2^+$ $[M+H]^+$: 284.1457, found: 284.1458

2-(4-bromo-2-methylphenyl)-2,2-difluoro-1-morpholinoethan-1-one (3e)

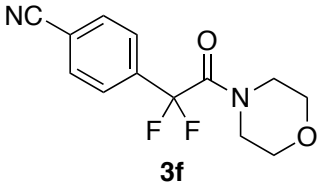


3e

Compound **3e** was prepared according to general procedure Ia with 4-bromo-1-iodo-2-methylbenzene (119 mg, 0.400 mmol, 1.00 equiv) and compound **2a** (190 mg, 0.800 mmol, 2.00 equiv). The product was isolated after silica gel chromatography with 3:1 hexanes:EtOAc as eluent. The product was isolated as a colorless solid (101 mg, 0.302 mmol, 76% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7,62 (d, *J* = 8.3 Hz, 1H), 7.39 (d, *J* = 2.2 Hz, 1H), 7.21 (dd, *J* = 8.3, 2.2 Hz, 1H), 3.78-3.63 (m, 4H), 3.60-3.41 (m, 4H), 2.43 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) 161.9 (t, *J* = 30.3 Hz), 139.0, 132.9, 132.7 (t, *J* = 25.4 Hz), 128.0, 127.6 (t, *J* = 5.7 Hz), 124.2 (t, *J* = 5.9 Hz), 115.6 (t, *J* = 252.0 Hz), 66.8, 66.6, 46.8, 43.7, 23.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -94.1. HRMS (EI+) calc'd for $C_{13}H_{14}BrF_2NO_{22}$: 333.0176, found: 333.0178.

4-(1,1-difluoro-2-morpholino-2-oxoethyl)benzonitrile (3f)

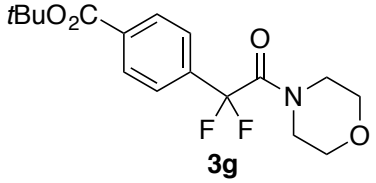


3f

Compound **3f** was prepared according to general procedure Ia with 4-iodobenzonitrile (91.6 mg, 0.400 mmol, 1.00 equiv) and compound **2a** (190 mg, 0.800 mmol, 2.00 equiv). The product was isolated after silica gel chromatography with 2:1 hexanes:EtOAc as eluent. The product was isolated as a colorless solid (75.7 mg, 0.284 mmol, 71% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 2H), 3.74-3.68 (m, 2H), 3.68-3.59 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.2 (t, *J* = 30.3 Hz), 138.1 (t, *J* = 25.3 Hz), 132.4, 126.5 (t, *J* = 6.2 Hz), 117.8, 115.6 (t, *J* = 255.2 Hz), 114.9, 66.6, 66.5, 46.6 (t, *J* = 4.9 Hz), 43.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ -95.8. HRMS (EI+) calc'd for $C_{13}H_{12}F_2N_2O_2$: 266.0867, found: 266.0867.

***tert*-butyl 4-(1,1-difluoro-2-morpholino-2-oxoethyl)benzoate (3g)**

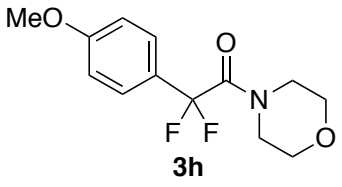


3g

Compound **3g** was prepared according to general procedure Ia with *tert*-butyl 4-iodobenzoate (122 mg, 0.400 mmol, 1.00 equiv) and compound **2a** (190 mg, 0.800 mmol, 2.00 equiv). The product was isolated after silica gel chromatography with 4:1→3:1 hexanes:EtOAc as eluent. The product was isolated as a colorless oil (99.7 mg, 0.292 mmol, 73% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.1 Hz, 2H), 7.56 (d, *J* = 8.1 Hz, 2H), 3.65 (s, 4H), 3.45 (s, 4H), 1.55 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) 164.6, 161.6 (t, *J* = 30.1 Hz), 137.1 (t, *J* = 24.9 Hz), 134.4, 129.8, 125.2 (t, *J* = 5.7 Hz), 115.4 (t, *J* = 252.2 Hz), 81.7, 66.6, 66.3, 46.6, 43.5, 28.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ -94.81. HRMS (EI+) calc'd for $C_{17}H_{21}F_2NO_4$: 341.1439, found: 349.1438.

2,2-difluoro-2-(4-methoxyphenyl)-1-morpholinoethan-1-one (3h)

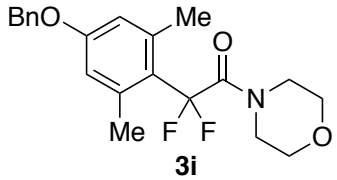


3h

Compound **3h** was prepared according to general procedure Ia with 4-iodoanisole (93.6 mg, 0.400 mmol, 1.00 equiv) and compound **2a** (190 mg, 0.800 mmol, 2.00 equiv). The product was isolated after silica gel chromatography with 2:1 hexanes:EtOAc as eluent. The product was isolated as a colorless oil (92.6 mg, 0.341 mmol, 85% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.0 Hz, 2H), 6.95 (d, *J* = 7.9 Hz, 2H), 3.82 (s, 3H), 3.69 (s, 4H), 3.46 (s, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.5 (t, *J* = 30.5 Hz), 161.6, 126.9 (t, *J* = 5.6 Hz), 125.7 (t, *J* = 25.2 Hz), 115.8 (t, *J* = 249.5 Hz), 114.3, 66.8, 66.5, 55.5, 46.8, 43.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ -92.8. HRMS (EI+) calc'd for $C_{13}H_{15}F_2NO_3$: 271.1020, found: 271.1025.

2-(4-(benzyloxy)-2,6-dimethylphenyl)-2,2-difluoro-1-morpholinoethan-1-one (3i)

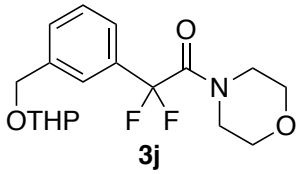


3i

Compound **3i** was prepared according to general procedure Ia with 5-(benzyloxy)-2-iodo-1,3-dimethylbenzene (135 mg, 0.400 mmol, 1.00 equiv) and compound **2a** (190 mg, 0.800 mmol, 2.00 equiv). The product was isolated after silica gel chromatography with 2:1 hexanes:EtOAc as eluent. The product was isolated as a colorless solid (133 mg, 0.354 mmol, 89% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.0 Hz, 2H), 7.42-7.38 (m, 2H), 7.37-7.35 (m, 1H), 7.23 (s, 2H), 4.84 (s, 2H), 3.70 (s, 4H), 3.48 (s, 4H), 2.32 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.3 (t, *J* = 30.6 Hz), 157.8, 137.1, 132.1, 128.9 (t, *J* = 24.7 Hz), 128.6, 128.2, 127.8, 125.7 (t, *J* = 5.4 Hz), 115.6 (t, *J* = 250.0 Hz), 74.1, 66.7, 66.4, 46.7, 43.5, 16.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ -93.5. HRMS (EI+) calc'd for $C_{21}H_{23}F_2NO_3$: 275.1646, found: 375.1647.

2,2-difluoro-1-morpholino-2-(3-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)phenyl)ethan-1-one (3j)

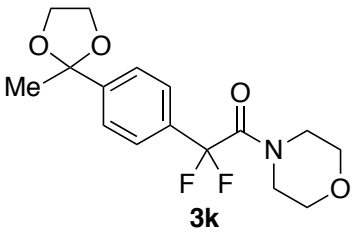


3j

Compound **3j** was prepared according to general procedure Ia with 2-((3-iodobenzyl)oxy)tetrahydro-2*H*-pyran (137 mg, 0.400 mmol, 1.00 equiv) and compound **2a** (190 mg, 0.800 mmol, 2.00 equiv). The product was isolated after silica gel chromatography with 2:1 hexanes:EtOAc as eluent. The product was isolated as a colorless oil (118 mg, 0.332 mmol, 83% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.49-7.38 (m, 3H), 4.78 (d, *J* = 12.4 Hz, 1H), 4.66 (t, *J* = 3.6 Hz, 1H), 4.50 (d, *J* = 12.4 Hz, 1H), 3.85 (ddd, *J* = 11.2, 8.3, 3.2 Hz, 1H), 3.66 (s, 4H), 3.56-3.46 (m, 1H), 3.43 (s, 4H), 1.87-1.44 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.0 (t, *J* = 30.2 Hz), 139.5, 133.8, 130.1, 128.9, 124.2 (t, *J* = 5.6 Hz), 115.5 (t, *J* = 250.6 Hz), 98.1, 68.2, 66.6, 66.3, 62.2, 46.7, 43.4, 30.5, 25.4, 19.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ -95.2. HRMS (ESI+) calc'd for $C_{18}H_{23}F_2NNaO_4^+$ $[M+Na]^+$: 378.1487, found: 378.1491

2,2-difluoro-2-(4-(2-methyl-1,3-dioxolan-2-yl)phenyl)-1-morpholinoethan-1-one (3k)



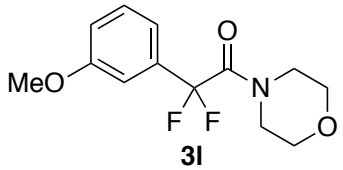
3k

Compound **3k** was prepared according to general procedure Ia with 2-(4-iodophenyl)-2-methyl-1,3-dioxolane (116 mg, 0.400 mmol, 1.00 equiv) and compound **2a** (190 mg, 0.800 mmol, 2.00 equiv). The product was isolated after silica gel chromatography with 2:1 hexanes:EtOAc as eluent. The product was isolated as a colorless solid (112 mg, 0.342 mmol, 86% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.2 Hz, 2H), 7.49 (d, *J* = 8.2 Hz, 2H), 4.05-3.99 (m, 2H), 3.76-3.70 (m, 2H), 3.67 (s, 4H), 3.47 (s, 4H), 1.61 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.1 (t, *J* = 30.4 Hz), 146.6, 133.0 (t, *J* = 24.8 Hz), 125.8, 125.3 (t, *J* = 5.7 Hz), 115.7 (t, *J* = 251.0

Hz), 108.4, 66.7, 66.4, 64.6, 46.7, 43.6, 27.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ -93.6. HRMS (ESI+) calc'd for $C_{16}H_{20}F_2NO_4^+$ $[M+H]^+$: 328.1355, found: 328.1357

2,2-difluoro-2-(3-methoxyphenyl)-1-morpholinoethan-1-one (3l)

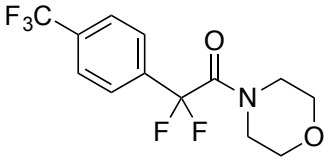


3l

Compound **3l** was prepared according to general procedure Ia with 3-iodoanisole (93.6 mg, 0.400 mmol, 1.00 equiv) and compound **2a** (190 mg, 0.800 mmol, 2.00 equiv). The product was isolated after silica gel chromatography with 2:1 hexanes:EtOAc as eluent. The product was isolated as a colorless oil (101 mg, 0.372 mmol, 93% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (t, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 7.7 Hz, 1H), 7.02 (t, *J* = 2.1 Hz, 1H), 6.97 (dd, *J* = 8.3, 2.4 Hz, 1H), 3.77 (s, 3H), 3.64 (s, 4H), 3.40 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.9 (t, *J* = 30.2 Hz), 159.8, 134.7 (t, *J* = 24.8 Hz), 130.1, 117.2 (t, *J* = 5.8 Hz), 116.6, 115.2 (t, *J* = 250.6 Hz), 110.5 (t, *J* = 5.8 Hz), 66.6, 66.2, 55.4, 46.6, 43.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -93.8. HRMS (EI+) calc'd for $C_{13}H_{15}F_2NO_3$: 271.1020, found: 271.1025.

2,2-difluoro-1-morpholino-2-(4-(trifluoromethyl)phenyl)ethan-1-one (3m)

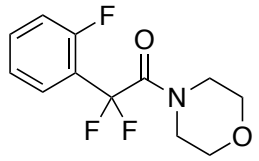


3m

Compound **3m** was prepared according to general procedure Ia with 1-iodo-4-(trifluoromethyl)benzene (109 mg, 0.400 mmol, 1.00 equiv) and compound **2a** (190 mg, 0.800 mmol, 2.00 equiv). The product was isolated after silica gel chromatography with 5:1 hexanes:EtOAc as eluent. The product was isolated as a colorless oil (120 mg, 0.388 mmol, 97% yield).

^{1}H NMR (400 MHz, $CDCl_3$) NMR δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 2H), 3.75-3.63 (m, 4H), 3.59 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.6 (t, *J* = 30.2 Hz), 137.3 (t, *J* = 25.0 Hz), 133.0 (q, *J* = 33.1 Hz), 126.1 (t, *J* = 6.0 Hz), 125.8 (q, *J* = 3.8 Hz), 123.6 (q, *J* = 272.5 Hz), 115.6 (t, *J* = 253.8 Hz), 66.7, 66.6, 46.7, 43.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.3, -95.1. HRMS (EI+) calc'd for $C_{13}H_{12}F_5NO_2$: 309.0788, found: 309.0788.

2,2-difluoro-2-(2-fluorophenyl)-1-morpholinoethan-1-one (3n)



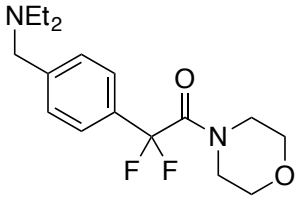
3n

Compound **3n** was prepared according to general procedure Ia with 1-iodo-2-fluorobenzene (88.8 mg, 0.400 mmol, 1.00 equiv) and compound **2a** (190 mg, 0.800 mmol, 2.00 equiv). The product was isolated after silica gel chromatography with 4:1 hexanes:EtOAc as eluent. The product was isolated as a colorless solid (83.8 mg, 0.323 mmol, 81% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (td, *J* = 7.6, 1.7 Hz, 1H), 7.50 (tdd, *J* = 7.5, 5.1, 1.6 Hz, 1H), 7.24 (t, *J* = 7.7 Hz, 1H), 7.20-7.12 (m, 1H), 3.76-3.62 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.1 (t, *J* = 30.1 Hz), 158.6, 133.0 (d, *J* = 8.4 Hz), 126.7 (td, *J* = 7.2, 2.2 Hz), 124.2 (d, *J* = 3.7

Hz), 121.8 (td, *J* = 25.5, 12.4 Hz), 116.5 (d, *J* = 20.9 Hz), 115.1 (t, *J* = 254.1 Hz), 66.7, 66.6, 46.6 (t, *J* = 4.9 Hz), 43.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ -96.0, -113.2. HRMS (EI+) calc'd for $C_{12}H_{12}F_3NO_2$: 259.0820, found: 259.0824.

2-(4-(diethylamino)phenyl)-2,2-difluoro-1-morpholinoethan-1-one (3o)

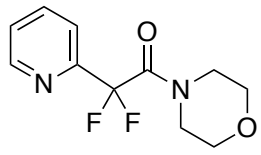


3o

Compound **3o** was prepared according to general procedure Ia with *N*,*N*-diethyl-4-iodoaniline (116 mg, 0.400 mmol, 1.00 equiv) and compound **2a** (190 mg, 0.800 mmol, 2.00 equiv). The product was isolated after silica gel chromatography with 1:2 hexanes:EtOAc with 1% added NEt_3 as eluent. The product was isolated as a colorless oil (83.8 mg, 0.323 mmol, 81% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.37 (m, 4H), 3.66 (s, 4H), 3.56 (s, 2H), 3.42 (s, 4H), 2.48 (q, *J* = 7.2 Hz, 4H), 1.00 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3 (t, *J* = 30.4 Hz), 143.8, 1131.7 (t, *J* = 24.9 Hz), 129.1, 125.0 (t, *J* = 5.6 Hz), 115.6 (t, *J* = 250.1 Hz), 66.7, 66.3, 57.2, 47.0, 46.7, 43.5, 11.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -94.5. HRMS (EI+) calc'd for $C_{17}H_{24}F_2N_2O_2$: 326.1806, found: 326.1808.

2,2-difluoro-1-morpholino-2-(pyridin-2-yl)ethan-1-one (3p)

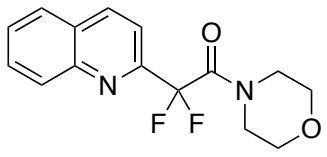


3p

Compound **3p** was prepared according to general procedure Ia with 2-iodopyridine (82.0 mg, 0.400 mmol, 1.00 equiv) and compound **2a** (190 mg, 0.800 mmol, 2.00 equiv). The product was isolated after silica gel chromatography with 1:1 hexanes:EtOAc as eluent. The product was isolated as a colorless oil (88.7 mg, 0.366 mmol, 92% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.65 (d, *J* = 4.6 Hz, 1H), 7.86 (t, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 7.9 Hz, 1H), 7.42 (t, *J* = 6.3 Hz, 1H), 3.71 (s, 4H), 3.60 (m, 2H), 3.57 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.9 (t, *J* = 27.5 Hz), 152.7 (t, *J* = 27.1 Hz), 149.4, 137.6, 125.7, 120.9 (t, *J* = 3.3 Hz), 114.3 (t, *J* = 251.9 Hz), 66.8, 66.7, 46.9 (t, *J* = 4.7 Hz), 43.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ -97.4. HRMS (EI+) calc'd for $C_{11}H_{12}F_2N_2O_2$: 242.0867, found: 242.0867.

2,2-difluoro-1-morpholino-2-(quinolin-2-yl)ethan-1-one (3q)



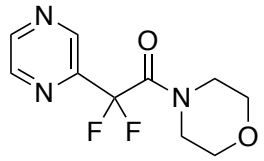
3q

Compound **3q** was prepared according to general procedure Ia with 2-iodoquinoline (102 mg, 0.400 mmol, 1.00 equiv) and compound **2a** (190 mg, 0.800 mmol, 2.00 equiv). The product was isolated after silica gel chromatography with 1:1 hexanes:EtOAc as eluent. The product was isolated as a colorless oil (99.7 mg, 0.341 mmol, 85% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.6 Hz, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.82-7.74 (m, 2H), 7.63 (t, *J* = 7.5 Hz, 1H), 3.76 (s, 4H), 3.64 (t, *J* = 4.8 Hz, 2H), 3.57 (t,

J = 4.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.0 (t, J = 28.1 Hz), 152.2 (t, J = 28.6 Hz), 146.9, 138.2, 130.6, 129.9, 128.6, 128.4, 127.8, 117.4 (t, J = 2.5 Hz), 114.6 (t, J = 251.4 Hz), 66.8, 66.6, 47.1, 43.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ -96.4. HRMS (ESI+) calc'd for $C_{15}H_{15}F_2N_2O_2^+$ $[M+H]^+$: 293.1096, found: 293.1098.

2,2-difluoro-1-morpholino-2-(pyrazin-2-yl)ethan-1-one (3r)



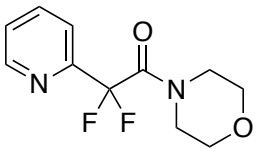
3r

Compound **3r** was prepared according to general procedure Ia with 2-iodoquinoline (102 mg, 0.400 mmol, 1.00 equiv) and compound **2a** (190 mg, 0.800 mmol, 2.00 equiv). The product was isolated after silica gel chromatography with 1:1 hexanes:EtOAc as eluent. The product was isolated as a colorless oil (99.7 mg, 0.341 mmol, 85% yield). Note: the isolated product contained a minor fluorinated impurity at -100.8 ppm (95:5 ratio of product:minor impurity by ^{19}F NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.68 (s, 1H), 8.58 (s, 1H), 3.65-3.57 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.0 (t, J = 28.6), 148.0 (t, J = 28.1 Hz), 146.7, 143.7, 142.7 (t, J = 4.2 Hz), 114.1 (t, J = 254.5 Hz), 66.6, 46.7 (t, J = 5.3 Hz), 43.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ -99.0. HRMS (EI+) calc'd for $C_{10}H_{11}F_2N_3O_2$: 243.0819, found: 243.0820.

*Coupling of Heteroaryl Bromides with 2,2-Difluoro-1-morpholino-2-(trimethylsilyl)ethan-1-one (**2a**)*

2,2-difluoro-1-morpholino-2-(pyridin-2-yl)ethan-1-one (3p)



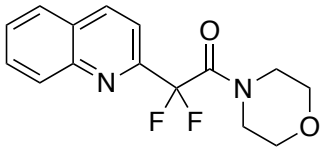
3p

Procedure for determination of yields by ^{19}F NMR spectroscopy: In a nitrogen-filled glovebox, CuOAc (2.5 mg, 0.020 mmol, 0.20 equiv), KF (7.0 mg, 0.12 mmol, 1.2 equiv), compound **2a** (35.6 mg, 0.150 mmol, 1.50 equiv), and 2-bromopyridine (15.8 mg, 0.100 mmol, 1.00 equiv) were added to a 4 mL vial equipped with a stir bar. NMP (0.25 mL) was added. The reaction was sealed with a Teflon-lined cap and heated at 100 °C for 24 h. After 24 h, the reaction was allowed to cool to room temperature, and 3-nitrofluorobenzene (21.3 μL, 0.200 mmol, 2.00 equiv) was added. The yield of the reaction was determined by ^{19}F NMR spectroscopy by comparing the ^{19}F NMR resonance of the desired product to that of the internal standard. ^{19}F NMR yield: 89%.

Procedure for determination of yields of isolated product: In a nitrogen-filled glovebox, CuOAc (9.8 mg, 0.080 mmol, 0.20 equiv), KF (27.9 mg, 0.480 mmol, 1.20 equiv), compound **2a** (142 mg, 0.600 mmol, 1.50 equiv), and 2-bromopyridine (63.2 mg, 0.400 mmol, 1.00 equiv) were added to a 4 mL vial equipped with a stir bar. NMP (1 mL) was added. The reaction was sealed with a Teflon-lined cap and heated at 100 °C for 24 h. After 24 h, the reaction was allowed to cool to room temperature and diluted with 20 mL H_2O. The aqueous layer was extracted with EtOAc (3x5 mL), and the combined organic layers were washed with H_2O (3x5 mL) and brine (5 mL). The combined organic layers were dried with Na_2SO_4, and the solvent was evaporated *in vacuo*. The

crude residue was purified by silica gel chromatography with hexanes:EtOAc 1:1 as eluent. The product was isolated as a colorless oil (76.5 mg, 0.316 mmol, 79% yield).

2,2-difluoro-1-morpholino-2-(quinolin-2-yl)ethan-1-one (3q)

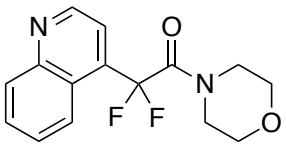


3q

Procedure for yield determination by ^{19}F NMR spectroscopy: In a nitrogen-filled glovebox, CuOAc (2.5 mg, 0.020 mmol, 0.20 equiv), KF (7.0 mg, 0.12 mmol, 1.2 equiv), 18-crown-6 (31.7 mg, 0.12 mmol, 1.2 equiv), compound **2a** (35.6 mg, 0.150 mmol, 1.50 equiv), and 2-bromoquinoline (20.8 mg, 0.100 mmol, 1.00 equiv) were added to a 4 mL vial equipped with a stir bar. Toluene (0.25 mL) was added. The reaction was sealed with a Teflon-lined cap and heated at 100 °C for 24 h. After 24 h, the reaction was allowed to cool to room temperature, and 3-nitrofluorobenzene (21.3 μL, 0.200 mmol, 2.00 equiv) was added. The yield of the reaction was determined by ^{19}F NMR spectroscopy by comparing the ^{19}F NMR resonance of the desired product to that of the internal standard. ^{19}F NMR yield: 54%.

Procedure for determination of yields of isolated product: In a nitrogen-filled glovebox, CuOAc (9.8 mg, 0.080 mmol, 0.20 equiv), KF (27.9 mg, 0.480 mmol, 1.20 equiv), 18-crown-6 (127 mg, 0.480 mmol, 1.20 equiv), compound **2a** (142 mg, 0.600 mmol, 1.50 equiv), and 2-bromoquinoline (83.2 mg, 0.400 mmol, 1.00 equiv) were added to a 4 mL vial equipped with a stir bar. Toluene (1.0 mL) was added. The reaction was sealed with a Teflon-lined cap and heated at 100 °C for 24 h. After 24 h, the reaction was allowed to cool to room temperature. After 24 h, the reaction was allowed to cool to room temperature. The reaction mixture was filtered through Celite, eluting with EtOAc, and the solvent was evaporated *in vacuo*. The crude residue was purified by silica gel chromatography with 1:1 hexanes:EtOAc as eluent. The product was isolated as a yellow oil (45.8 mg, 0.157 mmol, 39% yield).

2,2-difluoro-1-morpholino-2-(quinolin-4-yl)ethan-1-one (4a)



4a

Procedure for yield determination by ^{19}F NMR spectroscopy: In a nitrogen-filled glovebox, CuOAc (2.5 mg, 0.020 mmol, 0.20 equiv), KF (7.0 mg, 0.12 mmol, 1.2 equiv), 18-crown-6 (31.7 mg, 0.12 mmol, 1.2 equiv), compound **2a** (35.6 mg, 0.150 mmol, 1.50 equiv), and 4-bromoquinoline (20.8 mg, 0.100 mmol, 1.00 equiv) were added to a 4 mL vial equipped with a stir bar. Toluene (0.25 mL) was added. The reaction was sealed with a Teflon-lined cap and heated at 100 °C for 24 h. After 24 h, the reaction was allowed to cool to room temperature, and 3-nitrofluorobenzene (21.3 μL, 0.200 mmol, 2.00 equiv) was added. The yield of the reaction was determined by ^{19}F NMR spectroscopy by comparing the ^{19}F NMR resonance of the desired product to that of the internal standard. ^{19}F NMR yield: 63%.

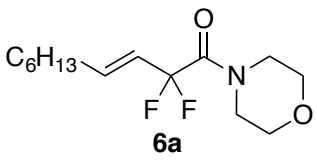
Procedure for determination of yields of isolated product: In a nitrogen-filled glovebox, CuOAc (9.8 mg, 0.080 mmol, 0.20 equiv), KF (27.9 mg, 0.480 mmol, 1.20 equiv), 18-crown-6 (127 mg, 0.480 mmol, 1.20 equiv), compound **2a** (142 mg, 0.600 mmol, 1.50 equiv), and 4-bromoquinoline

(83.2 mg, 0.400 mmol, 1.00 equiv) were added to a 4 mL vial equipped with a stir bar. Toluene (1.0 mL) was added. The reaction was sealed with a Teflon-lined cap and heated at 100 °C for 24 h. After 24 h, the reaction was allowed to cool to room temperature. After 24 h, the reaction was allowed to cool to room temperature. The reaction mixture was filtered through Celite, eluting with EtOAc, and the solvent was evaporated *in vacuo*. The crude residue was purified by silica gel chromatography with 98:2 EtOAc:NEt_3 as eluent. The product was isolated as a yellow oil (53.4 mg, 0.183 mmol, 46% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (d, *J* = 4.4 Hz, 1H), 8.22 (d, *J* = 8.5 Hz, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.79 (t, *J* = 7.7 Hz, 1H), 7.70 – 7.59 (m, 2H), 3.74 – 3.59 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.2 (t, *J* = 29.7 Hz), 149.5, 148.9, 138.2 (t, *J* = 24.2 Hz), 130.4, 129.9, 127.9, 124.6, 124.1, 117.7 (t, *J* = 8.1 Hz), 115.9 (t, *J* = 255.0 Hz), 66.7, 66.5, 46.7, 43.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ -94.4. HRMS (ESI+) calc'd for $C_{15}H_{15}F_2N_2O_2^+$ $[M+H]^+$: 293.1096, found: 293.1097.

*Vinylation of 2,2-Difluoro-1-morpholino-2-(trimethylsilyl)ethan-1-one (**2a**)*

(*E*)-2,2-difluoro-1-morpholinodec-3-en-1-one (6a)

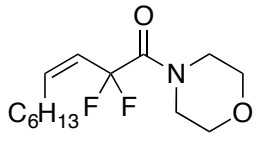


6a

Compound **6a** was prepared according to general procedure Ia with (*E*)-1-iodooct-1-ene (95.2 mg, 0.400 mmol, 1.00 equiv) and compound **2a** (190 mg, 0.800 mmol, 2.00 equiv). The product was isolated after silica gel chromatography with 4:1 hexanes:EtOAc as eluent. The product was isolated as a colorless oil (95.9 mg, 0.348 mmol, 87% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.20-6.05 (m, 1H), 5.88-5.59 (m, 1H), 3.66 (d, *J* = 5.1 Hz, 2H), 3.64-3.55 (m, 6H), 2.11 (dt, *J* = 7.1, 3.5 Hz, 2H), 1.43-1.32 (m, 2H), 1.30-1.19 (m, 6H), 0.83 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2 (t, *J* = 30.5 Hz), 138.9 (t, *J* = 9.2 Hz), 122.0 (t, *J* = 24.7 Hz), 114.8 (t, *J* = 247.9 Hz), 66.7, 66.6, 46.7, 43.3, 31.9, 31.6, 28.8, 28.2, 22.5, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -94.2 (d, *J* = 10.3 Hz). HRMS (EI+) calc'd for $C_{14}H_{23}F_2NO_2$: 275.1697, found: 275.1697.

(*E*)-2,2-difluoro-1-morpholinodec-3-en-1-one (6b)



6b

Compound **6b** was prepared according to general procedure Ia with (*Z*)-1-iodooct-1-ene (95.2 mg, 0.400 mmol, 1.00 equiv) and compound **2a** (190 mg, 0.800 mmol, 2.00 equiv). The product was isolated after silica gel chromatography with 4:1 hexanes:EtOAc as eluent. The product was isolated as a colorless oil (92.5 mg, 0.336 mmol, 84% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96-5.85 (m, 1H), 5.76-5.59 (m, 1H), 3.68 (d, *J* = 4.9 Hz, 2H), 3.67-3.61 (m, 4H), 3.57 (t, *J* = 4.9 Hz, 2H), 2.21 (m, 2H), 1.36 (dd, *J* = 10.2, 4.8 Hz, 2H), 1.31-1.18 (m, 6H), 0.85 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6 (t, *J* = 30.8 Hz), 142.0 (t, *J* = 7.5 Hz), 121.7 (t, *J* = 25.7 Hz), 114.6 (t, *J* = 248.0 Hz), 66.8, 66.6, 46.7, 43.5, 31.7, 29.1,

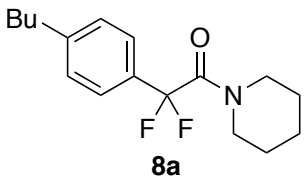
28.9, 28.5, 22.6, 14.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ -90.7 (d, J = 12.9 Hz). HRMS (EI+) calc'd for $C_{14}H_{23}F_2NO_2$: 275.1697, found: 275.1694.

Difluoroamidation of 1-Butyl-4-iodobenzene

General Procedure II

In a nitrogen-filled glovebox, CuOAc (9.8 mg, 0.0800 mmol, 0.200 equiv), KF (27.9 mg, 0.480 mmol, 1.20 equiv), 18-crown-6 (127 mg, 0.480 mmol, 1.20 equiv), and the α-silyl difluoroamide, if solid at room temperature (0.800 mmol, 2.00 equiv) were added to a 4 mL vial equipped with a stir bar. Toluene (1 mL) was added, followed by 1-butyl-4-iodobenzene (104 mg, 71.2 μL, 0.400 mmol, 1.00 equiv) and the α-silyl difluoroamide, if liquid at r.t. (0.400 mmol, 1.00 equiv). The reaction was sealed with a Teflon-lined cap and heated at 100 °C for 24 h. After 24 h, the reaction was allowed to cool to room temperature. The reaction mixture was filtered through Celite, eluting with EtOAc, and the solvent was evaporated *in vacuo*. The crude residue was purified by silica gel chromatography.

2-(4-butylphenyl)-2,2-difluoro-1-(piperidin-1-yl)ethan-1-one (8a)

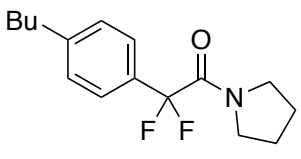


8a

Compound **8a** was prepared according to general procedure II with 1-butyl-4-iodobenzene (104 mg, 71.2 μL, 0.400 mmol, 1.00 equiv) and 2,2-difluoro-1-(piperidin-1-yl)-2-(trimethylsilyl)ethan-1-one (**2b**) (188 mg, 0.800 mmol, 2.00 equiv). The product was isolated after silica gel chromatography with 5:1 hexanes:EtOAc as eluent. The product was isolated as a colorless oil (91.0 mg, 0.308 mmol, 77% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 7.9 Hz, 2H), 3.60 (d, J = 5.0 Hz, 2H), 3.32 (t, J = 5.6 Hz, 2H), 2.62 (t, J = 7.8 Hz, 2H), 1.64-1.52 (m, 6H), 1.37-1.26 (m, 4H), 0.90 (t, J = 7.3 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.0 (t, J = 29.8 Hz), 145.9, 131.3 (t, J = 25.1 Hz), 128.8, 125.1 (t, J = 5.4 Hz), 115.8 (t, J = 249.0 Hz), 47.1, 44.4, 35.5, 33.4, 25.9, 25.6, 24.4, 22.3, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -92.9. HRMS (EI+) calc'd for $C_{17}H_{23}F_2NO$: 295.1748, found: 295.1746.

2-(4-butylphenyl)-2,2-difluoro-1-(pyrrolidin-1-yl)ethan-1-one (8b)



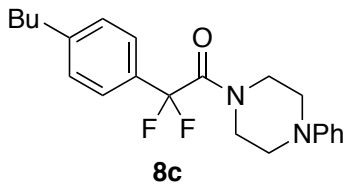
8b

Compound **8b** was prepared according to general procedure II with 1-butyl-4-iodobenzene (104 mg, 71.2 μL, 0.400 mmol, 1.00 equiv) and 2,2-difluoro-1-(pyrrolidin-1-yl)-2-(trimethylsilyl)ethan-1-one (**2c**) (177 mg, 0.800 mmol, 2.00 equiv). The product was isolated after silica gel chromatography with 8:1→4:1 hexanes:EtOAc as eluent. The product was isolated as a colorless oil (98.5 mg, 0.358 mmol, 88% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 7.9 Hz, 2H), 7.52 (d, J = 7.9 Hz, 2H), 3.83 (t, J = 6.6 Hz, 2H), 3.70 (t, J = 6.8 Hz, 2H), 2.91 (t, J = 7.8 Hz, 2H), 2.13-1.94 (m, 4H), 1.87 (p, J = 7.8 Hz,

2H), 1.62 (hept, J = 6.8 Hz, 2H), 1.19 (t, J = 7.3 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.4 (t, J = 31.7 Hz), 145.9, 130.6 (t, J = 25.3 Hz), 128.7, 125.4, 115.6 (t, J = 250.0 Hz), 47.5, 46.8, 35.5, 33.4, 26.4, 23.4, 22.4, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -97.0. HRMS (ESI+) calc'd for $C_{16}H_{22}F_2NO^+$ $[M+H]^+$: 282.1664, found: 282.1666.

2-(4-butylphenyl)-2,2-difluoro-1-(4-phenylpiperazin-1-yl)ethan-1-one (8c)

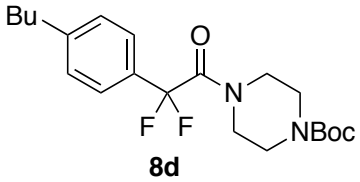


8c

Compound **8c** was prepared according to general procedure II with 1-butyl-4-iodobenzene (104 mg, 71.2 μL, 0.400 mmol, 1.00 equiv) and 2,2-difluoro-1-(4-phenylpiperazin-1-yl)-2-(trimethylsilyl)ethan-1-one (**2d**) (250 mg, 0.800 mmol, 2.00 equiv). The product was isolated after silica gel chromatography with 3:1 hexanes:EtOAc as eluent. The product was isolated as a colorless solid (129 mg, 0.346 mmol, 87% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 8.0 Hz, 2H), 7.32-7.25 (m, 4H), 6.94-6.86 (m, 3H), 3.88 (t, J = 5.2 Hz, 2H), 3.62 (t, J = 5.0 Hz, 2H), 3.20 (t, J = 5.2 Hz, 2H), 2.95 (t, J = 5.0 Hz, 2H), 2.67 (t, J = 7.8 Hz, 2H), 1.70-1.57 (m, 2H), 1.38 (hept, J = 7.3 Hz, 2H), 0.95 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2 (t, J = 30.3 Hz), 150.7, 146.2, 130.9 (t, J = 25.0 Hz), 129.2, 128.9, 125.1 (t, J = 5.5 Hz), 120.7, 116.6, 115.7 (t, J = 249.8 Hz), 49.3, 49.2, 45.9, 43.1, 35.5, 33.3, 22.3, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -93.0. HRMS (ESI+) calc'd for $C_{22}H_{27}F_2N_2O^+$ $[M+H]^+$: 373.2086, found: 373.2076.

***tert*-butyl 4-(2-(4-butylphenyl)-2,2-difluoroacetyl)piperazine-1-carboxylate (8d)**

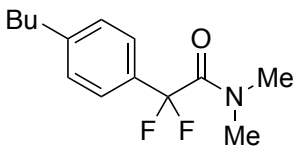


8d

Compound **8d** was prepared according to general procedure II with 1-butyl-4-iodobenzene (104 mg, 71.2 μL, 0.400 mmol, 1.00 equiv) and *tert*-butyl 4-(2,2-difluoro-2-(trimethylsilyl)acetyl)piperazine-1-carboxylate (**2e**) (269 mg, 0.800 mmol, 2.00 equiv). The product was isolated after silica gel chromatography with 5:1 hexanes:EtOAc as eluent. The product was isolated as a colorless solid (136 mg, 0.343 mmol, 86% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 3.62 (t, J = 5.2 Hz, 2H), 3.44-3.33 (m, 4H), 3.16 (t, J = 5.1 Hz, 2H), 2.60 (t, J = 7.8 Hz, 2H), 1.62-1.51 (m, 2H), 1.40 (s, 9H), 1.31-1.29 (m, 2H), 0.88 (t, J = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.4 (t, J = 30.5 Hz), 154.4, 146.2, 130.7 (t, J = 24.6 Hz), 128.9, 125.0 (t, J = 5.4 Hz), 115.6 (t, J = 249.6 Hz), 80.4, 45.9, 43.0, 35.4, 33.3, 28.3, 22.3, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -93.2. HRMS (ESI+) calc'd for $C_{21}H_{31}F_2N_2O_3^+$ $[M+H]^+$: 397.2297, found: 397.2304.

2-(4-butylphenyl)-2,2-difluoro-*N*,*N*-dimethylacetamide (8e)

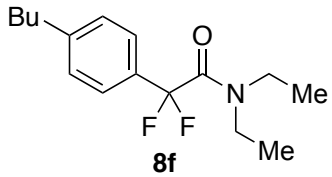


8e

Compound **8e** was prepared according to general procedure II with 1-butyl-4-iodobenzene (104 mg, 71.2 μL, 0.400 mmol, 1.00 equiv) and 2,2-difluoro-*N*,*N*-dimethyl-2-(trimethylsilyl)acetamide (**2f**) (156 mg, 0.800 mmol, 2.00 equiv). The product was isolated after silica gel chromatography with 5:1 hexanes:EtOAc as eluent. The product was isolated as a colorless oil (74.9 mg, 0.293 mmol, 73% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 3.02 (s, 3H), 2.93 (t, *J* = 1.8 Hz, 3H), 2.63 (t, *J* = 7.8 Hz, 2H), 1.65-1.53 (m, 2H), 1.34 (hept, *J* = 7.3 Hz, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7 (t, *J* = 30.3 Hz), 146.0, 130.9 (t, *J* = 25.1 Hz), 128.8, 125.2 (t, *J* = 5.6 Hz), 115.8 (t, *J* = 249.5 Hz), 37.4 (t, *J* = 4.9 Hz), 37.0, 35.5, 33.4, 22.4, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -93.5. HRMS (ESI+) calc'd for $C_{14}H_{19}F_2NNaO^+$ $[M+Na]^+$: 278.1327, found: 278.1329.

2-(4-butylphenyl)-*N*,*N*-diethyl-2,2-difluoroacetamide (8f)

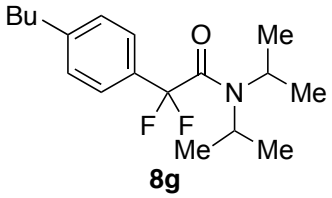


8f

Compound **8f** was prepared according to general procedure II with 1-butyl-4-iodobenzene (104 mg, 71.2 μL, 0.400 mmol, 1.00 equiv) and *N*,*N*-diethyl-2,2-difluoro-2-(trimethylsilyl)acetamide (**2g**) (179 mg, 0.800 mmol, 2.00 equiv). The product was isolated after silica gel chromatography with 8:1 hexanes:EtOAc as eluent. The product was isolated as a colorless oil (94.1 mg, 0.332 mmol, 83% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.9 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 3.42 (q, *J* = 7.1 Hz, 2H), 3.23 (q, *J* = 7.0 Hz, 2H), 2.64 (t, *J* = 7.8 Hz, 2H), 1.66-1.51 (m, 2H), 1.35 (hept, *J* = 7.4 Hz, 2H), 1.17 (t, *J* = 7.1 Hz, 3H), 1.02 (t, *J* = 7.0 Hz, 3H), 0.93 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.1 (t, *J* = 30.0 Hz), 146.0, 131.4 (t, *J* = 25.6 Hz), 128.9, 125.2 (t, *J* = 5.5 Hz), 115.8 (t, *J* = 256.3 Hz), 42.2, 41.5, 35.6, 33.4, 22.4, 14.0, 13.9, 12.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -93.3. HRMS (ESI+) calc'd for $C_{16}H_{24}F_2NO^+$ $[M+H]^+$: 284.1820, found: 284.1822.

2-(4-butylphenyl)-2,2-difluoro-*N*,*N*-diisopropylacetamide (8g)



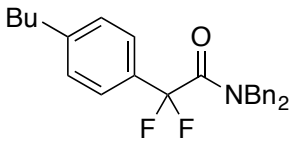
8g

Compound **8g** was prepared according to general procedure II with 1-butyl-4-iodobenzene (104 mg, 71.2 μL, 0.400 mmol, 1.00 equiv) and 2,2-difluoro-*N*,*N*-diisopropyl-2-(trimethylsilyl)acetamide (**2h**) (201 mg, 0.800 mmol, 2.00 equiv). The product was isolated after silica gel chromatography with 10:1 hexanes:EtOAc as eluent. The product was isolated as a colorless oil (115 mg, 0.369 mmol, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.8 Hz, 2H), 7.24 (d, *J* = 7.9 Hz, 2H), 3.99 (hept, *J* = 6.2 Hz, 1H), 3.39 (hept, *J* = 6.6 Hz, 1H), 2.63 (t, *J* = 7.7 Hz, 2H), 1.64-1.52 (m, 2H), 1.45 (d, *J* = 6.8 Hz, 6H), 1.37-1.27 (m, 2H), 0.95-0.86 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2 (t, *J* =

29.1 Hz), 145.8, 131.6 (t, J = 24.8 Hz), 128.8, 125.0 (t, J = 5.2 Hz), 115.3 (t, J = 248.9 Hz), 48.8 (t, J = 4.1 Hz), 46.9, 35.5, 33.4, 22.3, 19.9, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -93.3. HRMS (ESI+) calc'd for $C_{18}H_{28}F_2NO^+$ $[M+H]^+$: 312.2133, found: 312.2128.

_N_,_N_-dibenzyl-2-(4-butylphenyl)-2,2-difluoroacetamide (8h)



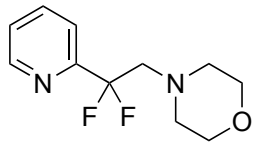
8h

Compound **8h** was prepared according to general procedure II with 1-butyl-4-iodobenzene (104 mg, 71.2 μL, 0.400 mmol, 1.00 equiv) and *N*,*N*-dibenzyl-2,2-difluoro-2-(trimethylsilyl)acetamide (**2i)** (278 mg, 0.800 mmol, 2.00 equiv). The product was isolated after silica gel chromatography with 10:1 hexanes:EtOAc as eluent. The product was isolated as a colorless oil (123 mg, 0.301 mmol, 75% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.0 Hz, 2H), 7.38-7.27 (m, 8H), 7.24-7.19 (m, 2H), 7.06 (dd, J = 7.3, 2.2 Hz, 2H), 4.58 (s, 2H), 4.43 (s, 2H), 2.68 (t, J = 7.8 Hz, 2H), 1.71-1.56 (m, 2H), 1.39 (hept, J = 7.3 Hz, 2H), 0.98 (t, J = 7.3 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.3 (t, J = 30.2 Hz), 146.1, 136.1, 135.4, 131.0 (t, J = 24.8 Hz), 128.9, 128.8, 128.7, 128.5, 127.9, 127.7, 127.5, 116.0 (t, J = 250.5 Hz), 49.8, 48.1, 35.5, 33.4, 22.3, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -92.6. HRMS (ESI+) calc'd for $C_{26}H_{28}F_2NO^+$ $[M+H]^+$: 408.2133, found: 408.2136.

Transformations of Aryldifluoroamides

4-(2,2-difluoro-2-(pyridin-2-yl)ethyl)morpholine (9a)

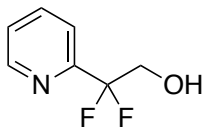


9a

To an oven-dried round bottom flask under N_2 equipped with a reflux condenser was added 2,2-difluoro-1-morpholino-2-(pyridin-2-yl)ethan-1-one (**3p**) (121 mg, 0.500 mmol, 1.00 equiv), anhydrous THF (5 mL), and BH_3•THF (1.0 M in THF, 2.50 mL, 2.50 mmol, 5.00 equiv). The flask was heated at reflux for 22 h, then allowed to cool to room temperature. The solvent was evaporated *in vacuo*, and the crude residue was purified by silica gel chromatography with 100% EtOAc as eluent. The product was obtained as a light yellow oil (81.4 mg, 0.357 mmol, 71% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 4.6 Hz, 1H), 7.78 (td, J = 7.7, 1.8 Hz, 1H), 7.63 (dt, J = 7.8, 1.1, Hz, 1H), 7.38-7.29 (m, 1H), 3.61-3.51 (m, 4H), 3.19 (t, J = 14.5 Hz, 2H), 2.78-2.42 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4 (t, J = 28.3 Hz), 149.3, 136.9, 124.7, 120.6 (t, J = 251.6 Hz), 120.6 (t, J = 5.1 Hz), 67.1, 61.7 (t, J = 26.9 Hz), 54.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -102.0 (t, J = 14.4 Hz). HRMS (ESI+) calc'd for $C_{11}H_{15}F_2N_2O^+$ $[M+H]^+$: 229.1147, found: 229.1148.

2,2-difluoro-2-(pyridin-2-yl)ethan-1-ol (9b)

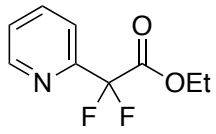


9b

To a round bottom flask was added 2,2-difluoro-1-morpholino-2-(pyridin-2-yl)ethan-1-one (**3p**) (121 mg, 0.500 mmol, 1.00 equiv), $NaBH_4$ (284 mg, 7.50 mmol, 15.0 equiv), and EtOH (5 mL). The flask was equipped with a reflux condenser and heated at reflux for 12 h. After 12 h, the reaction mixture was allowed to cool to room temperature, and 20 mL H_2O was added. The layers were separated, and the aqueous layer was extracted with EtOAc (3x20 mL). The combined organic layers were washed with brine (3x20 mL) and dried with Na_2SO_4, and the solvent was evaporated *in vacuo*. The crude residue was purified by silica gel chromatography with hexanes:EtOAc 1:1 as eluent. The product was obtained as a colorless solid (60.5 mg, 0.380 mmol, 76% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 4.8 Hz, 1H), 7.84 (t, *J* = 7.7 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.39 (dd, *J* = 7.6, 4.9 Hz, 1H), 4.19 (t, *J* = 12.7 Hz, 2H), 4.03 (br. s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.8 (t, *J* = 29.3 Hz), 148.9, 137.7, 125.4, 121.1, 118.1 (t, *J* = 243.3 Hz), 64.3 (t, *J* = 31.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -106.6 (t, *J* = 12.9 Hz). HRMS (EI+) calc'd for $C_7H_7F_2NO$: 159.0496, found: 159.0498

Ethyl 2,2-difluoro-2-(pyridin-2-yl)acetate (9c)

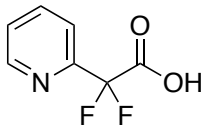


9c

To a 20 mL vial equipped with a stir bar containing 2,2-difluoro-1-morpholino-2-(pyridin-2-yl)ethan-1-one (**3p**) (121 mg, 0.500 mmol, 1.00 equiv) was added EtOH (1 mL) and TMSCl (109 mg, 127 μL, 1.00 mmol, 2.00 equiv). The vial was sealed with a Teflon-lined cap and heated at 80 °C for 24 h. After 24 h, the reaction mixture was allowed to cool to room temperature, and the solvent was evaporated *in vacuo*. The crude residue was purified by silica gel chromatography with hexanes:EtOAc 4:1 as eluent. The product was obtained as a colorless oil (79.2 mg, 0.394 mmol, 79% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 4.6 Hz, 1H), 7.87 (td, *J* = 7.7, 1.7 Hz, 1H), 7.74 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.46-7.40 (m, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5 (t, *J* = 32.8 Hz), 151.8 (t, *J* = 28.1 Hz), 149.6, 137.4, 125.7, 120.5 (t, *J* = 3.5 Hz), 112.2 (t, *J* = 251.6 Hz), 63.3, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.5. HRMS (EI+) calc'd for $C_9H_9F_2NO_2$: 201.0601, found: 201.0599.

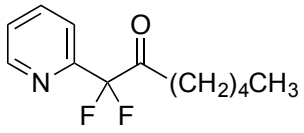
2,2-difluoro-2-(pyridin-2-yl)acetic acid (9d)



9d

To a 20 mL vial was added 2,2-difluoro-1-morpholino-2-(pyridin-2-yl)ethan-1-one (**3p**) (121 mg, 0.500 mmol, 1.00 equiv), EtOH (3 mL), and 2M NaOH (3 mL). The reaction was sealed with a Teflon-lined cap and stirred at room temperature for 8 h. After 8 h, the internal standard, 3-nitrofluorobenzene (106 µL, 1.00 mmol, 2.00 equiv), was added, and the yield of the reaction was determined by ^{19}F NMR spectroscopy by comparing the ^{19}F NMR resonance of the desired product to that of the internal standard. ^{19}F NMR yield: 95%.

1,1-difluoro-1-(pyridin-2-yl)heptan-2-one (9e)

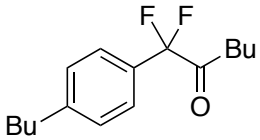


9e

To an oven-dried round bottom flask under N_2 was added 2,2-difluoro-1-morpholino-2-(pyridin-2-yl)ethan-1-one (**3p**) (121 mg, 0.500 mmol, 1.00 equiv) and anhydrous THF (5 mL). The solution was cooled at -78 °C, and pentylmagnesium bromide (2.0 M in Et_2O, 275 µL, 0.550 mmol, 1.10 equiv) was added dropwise. The reaction mixture was stirred at -78 °C for 30 minutes, then allowed to warm to room temperature and quenched with sat. aqueous NH_4Cl (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3x15 mL). The combined organic layers were washed with H_2O (3x15 mL) and dried with Na_2SO_4, and the solvent was evaporated *in vacuo*. The crude residue was purified by silica gel chromatography with hexanes:EtOAc 10:1 as eluent. The product was obtained as a colorless oil (81.7 mg, 0.360 mmol, 72% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (dd, J = 4.9, 1.5 Hz, 1H), 7.83 (td, J = 7.8, 1.7 Hz, 1H), 7.69 (dt, J = 8.0, 1.1 Hz, 1H), 7.44-7.35 (m, 1H), 2.81 (t, J = 7.3 Hz, 2H), 1.64 (p, J = 7.3 Hz, 2H), 1.34-1.20 (m, 4H), 0.86 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.4 (t, J = 29.0 Hz), 152.1 (t, J = 28.0 Hz), 149.6, 137.5, 125.6, 121.0 (t, J = 3.8 Hz), 113.9 (t, J = 253.9 Hz), 37.8, 31.1, 22.4, 22.4, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -107.3. HRMS (ESI+) calc'd for $C_{12}H_{16}F_2NO^+$ $[M+H]^+$: 228.1194, found: 228.1195.

1-(4-butylphenyl)-1,1-difluorohexan-2-one (9f)

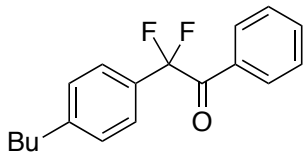


9f

To an oven-dried round bottom flask under N_2 was added 2-(4-butylphenyl)-*N*,*N*-diethyl-2,2-difluoroacetamide **(8f)** (85.0 mg, 0.300 mmol, 1.00 equiv) and anhydrous THF (3 mL). The solution was cooled at -78 °C, and *n*-butyllithium (2.5 M in hexanes, 132 µL, 0.330 mmol, 1.10 equiv) was added dropwise. The reaction mixture was stirred at -78 °C for 15 minutes, then allowed to warm to room temperature and quenched with sat. aqueous NH_4Cl (5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3x5 mL). The combined organic layers were washed with brine (5 mL) and dried with Na_2SO_4, and the solvent was evaporated *in vacuo*. The crude residue was purified by silica gel chromatography with hexanes:EtOAc 15:1 as eluent. The product was obtained as a light yellow oil (65.9 mg, 0.246 mmol, 82% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 2.69 (m, 4H), 1.69–1.53 (m, 4H), 1.44–1.35 (m, 2H), 1.35–1.24 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H), 0.90 (t, *J* = 7.3 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 200.5 (t, *J* = 31.8 Hz), 146.2, 129.5 (t, *J* = 25.6 Hz), 128.9, 125.6 (t, *J* = 6.2 Hz), 116.3 (t, *J* = 253.8 Hz), 36.1, 35.6, 33.5, 25.0, 22.4, 22.1, 14.0, 13.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -105.6. HRMS (EI+): calc'd for $C_{16}H_{22}F_2O$: 268.1639, found: 268.1644.

2-(4-butylphenyl)-2,2-difluoro-1-phenylethan-1-one (9g)



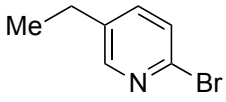
9g

To an oven-dried round bottom flask under N_2 was added 2-(4-butylphenyl)-2,2-difluoro-1-(piperidin-1-yl)ethan-1-one **(8a)** (88.6 mg, 0.300 mmol, 1.00 equiv) and anhydrous THF (3 mL). The solution was cooled at -78 °C, and phenyllithium (1.8 M in dibutyl ether, 200 µL, 0.360 mmol, 1.20 equiv) was added dropwise. The reaction mixture was stirred at -78 °C for 15 minutes, then allowed to warm to room temperature and quenched with sat. aqueous NH_4Cl (5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3x5 mL). The combined organic layers were washed with brine (5 mL) and dried with Na_2SO_4, and the solvent was evaporated *in vacuo*. The crude residue was purified by silica gel chromatography with hexanes:EtOAc 15:1 as eluent. The product was obtained as a yellow oil (72.0 mg, 0.250 mmol, 83% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (dt, *J* = 7.4, 1.1 Hz, 2H), 7.61–7.56 (m, 1H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.48–7.41 (m, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 2.65 (t, *J* = 7.8 Hz, 2H), 1.66–1.54 (m, 2H), 1.42–1.30 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.3 (t, *J* = 31.2 Hz), 146.2, 134.2, 132.4, 130.5 (t, *J* = 25.2 Hz), 130.4 (t, *J* = 3.0 Hz), 129.0, 128.7, 125.7 (t, *J* = 5.9 Hz), 117.2 (t, *J* = 252.7 Hz), 35.6, 33.4, 22.4, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -96.2. HRMS (EI+): calc'd for $C_{18}H_{18}F_2O$: 288.1326, found: 288.1328.

Synthesis of Difluoro-pioglitazone

2-Bromo-5-ethylpyridine (10a)



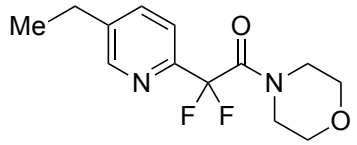
10a

Compound **10a** was synthesized in analogy to the synthesis of 2-bromo-5-heptylpyridine.[42] To an oven-dried round bottom flask under N_2 was added hexane (10 mL) and 2-(dimethylamino)ethanol (2.50 g, 28.0 mmol, 3.00 equiv). The solution was cooled at 0 °C, and *n*BuLi (2.5 M in hexane, 22.4 mL, 56.0 mmol, 6.00 equiv) was added dropwise. 3-Ethylpyridine (1.00 g, 9.33 mmol, 1.00 equiv) was added dropwise, and the solution was stirred at 0 °C for 1 h. A solution of CBr_4 (11.1 g, 33.6 mmol, 3.60 equiv) in THF (15 mL) was added dropwise, and the resulting solution was allowed to warm to room temperature and stirred at room temperature for 12 h. To the solution was added H_2O (100 mL) and CH_2Cl_2 (50 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3x50 mL), and the combined organic layers were washed with H_2O (50 mL) and dried with Na_2SO_4. The solvent was evaporated *in vacuo*, and the

crude residue was purified by silica gel chromatography with hexanes:EtOAc 10:1 as eluent. The product was isolated as a light yellow oil (555 mg, 2.99 mmol, 32% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (t, *J* = 1.6 Hz, 1H), 7.38-7.28 (m, 2H), 2.55 (q, *J* = 7.6 Hz, 2H), 1.18 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.7, 139.2, 138.6, 138.2, 127.6, 25.4, 15.1. HRMS (ESI+): calc'd for $C_7H_9BrN^+$ $[M+H]^+$: 185.9913, found: 185.9910.

2-(5-ethylpyridin-2-yl)-2,2-difluoro-1-morpholinoethan-1-one (10b)

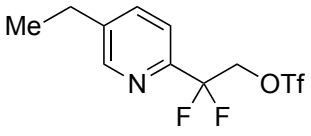


10b

In a nitrogen-filled glovebox, CuOAc (36.8 mg, 0.300 mmol, 0.200 equiv), KF (1.05 mg, 1.80 mmol, 1.20 equiv), and compound **2a** (534 mg, 2.25 mmol, 1.50 equiv) were added to a 4 mL vial equipped with a stir bar. NMP (1 mL) was added, followed by 2-bromo-5-ethylpyridine (279 mg, 1.50 mmol, 1.00 equiv). The reaction was sealed with a Teflon-lined cap and heated at 100 °C for 24 h. After 24 h, the reaction was allowed to cool to room temperature, and H_2O (15 mL) was added. The reaction mixture was extracted with EtOAc (3x10 mL), and the combined organic extracts were washed with brine (3x10 mL) and dried with Na_2SO_4. The solvent was evaporated *in vacuo*, and the crude reside was purified by silica gel chromatography with hexanes:EtOAc 1:1 as eluent. The product was obtained as a colorless oil (312 mg, 1.16 mmol, 77% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 2.1 Hz, 1H), 7.64 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 3.66 (s, 4H), 3.59-3.47 (m, 4H), 2.66 (q, *J* = 7.6 Hz, 2H), 1.21 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.0 (t, *J* = 28.8 Hz), 149.8 (t, *J* = 28.1 Hz), 149.0, 141.7, 136.7, 120.3 (t, *J* = 3.0 Hz), 114.3 (t, *J* = 250.8 Hz), 66.6, 66.5, 46.8 (t, *J* = 4.7 Hz), 43.4, 25.9, 15.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -96.8. HRMS (ESI+) calc'd for $C_{13}H_{17}F_2N_2O_2^+$ $[M+H]^+$: 271.1253, found: 271.1251.

2-(5-ethylpyridin-2-yl)-2,2-difluoroethyl trifluoromethanesulfonate (10c)



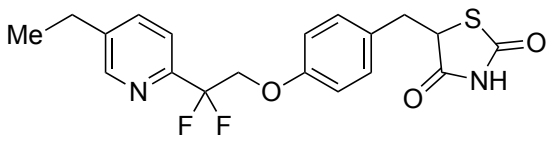
10c

To a round bottom flask was added $NaBH_4$ (315 mg, 8.33 mmol, 15.0 equiv), EtOH (10 mL), and compound **10b** (150 mg, 0.555 mmol, 1.00 equiv). The flask was equipped with a reflux condenser and heated at reflux for 2 h. After 2 h, the reaction mixture was allowed to cool to room temperature, and 15 mL H_2O was added. The layers were separated, and the aqueous layer was extracted with EtOAc (3x15 mL). The combined organic layers were washed with H_2O (3x15 mL) and brine (15 mL) and dried with Na_2SO_4, and the solvent was evaporated *in vacuo*. A solution of the crude residue in CH_2Cl_2 (2 mL) was added to an oven-dried round bottom flask containing pyridine (25.4 mg, 26.0 μL, 0.321 mmol, 1.00 equiv), Tf_2O (109 mg, 64.8 μL, 0.385 mmol, 1.20 equiv), and CH_2Cl_2 (3 mL). The solution was stirred at room temperature for 1 h, followed by the addition of 15 mL H_2O. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were washed with H_2O (3x10 mL) and dried with Na_2SO_4, and the solvent was evaporated *in vacuo*. The crude residue was purified by silica gel chromatography with

hexanes:EtOAc 10:1 as eluent. The product was obtained as a colorless solid (90.1 mg, 0.411 mmol, 74% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 5.10 (t, *J* = 12.0 Hz, 2H), 2.73 (q, *J* = 7.6 Hz, 2H), 1.28 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.5, 148.3 (t, *J* = 27.9 Hz), 142.3, 136.9, 120.6 (t, *J* = 3.5 Hz), 118.7 (q, *J* = 319.6 Hz), 114.6 (t, *J* = 247.7 Hz), 72.9 (t, *J* = 31.6 Hz), 26.1, 15.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ -73.5, -105.4.

5-(4-(2-(5-ethylpyridin-2-yl)-2,2-difluoroethoxy)benzyl)thiazolidine-2,4-dione (10e)



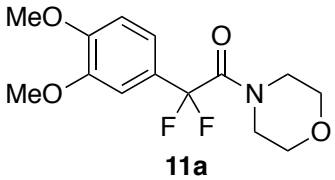
10e

To a suspension of NaH (11.3 mg, 0.471 mmol, 3.00 equiv) in DMF (2 mL) in an oven-dried, septum-capped vial under N_2 was added 5-(4-hydroxybenzyl)thiazolidine-2,4-dione (**10d**) (35.0 mg, 0.157 mmol, 1.00 equiv). The reaction mixture was stirred at room temperature for 2 h. After 2 h, a solution of compound **10c** in 1 mL DMF was added, and the reaction mixture was heated at 50 °C for 1 h. The reaction was quenched with H_2O (10 mL) and extracted with EtOAc (3x10 mL). The combined organic extracts were dried with Na_2SO_4, and the solvent was evaporated *in vacuo*. The crude residue was purified by silica gel chromatography with hexanes:EtOAc 2:1 as eluent. The product was obtained as a colorless solid (54.1 mg, 0.138 mmol, 88% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.18 (br. s, 1H), 7.67 (t, *J* = 1.2, 2H), 7.13 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.64 (t, *J* = 12.2 Hz, 2H), 4.48 (dd, *J* = 9.4, 3.9 Hz, 1H), 3.44 (dd, *J* = 14.2, 4.0 Hz, 1H), 3.10 (dd, *J* = 14.2, 9.4 Hz, 1H), 2.71 (q, *J* = 7.6 Hz, 2H), 1.28 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.7, 170.9, 157.7, 150.1 (t, *J* = 29.6 Hz), 149.2, 141.3, 136.5, 130.4, 129.0, 120.8, 118.5 (t, *J* = 243.7 Hz), 115.4, 68.8 (t, *J* = 31.9 Hz), 53.8, 37.9, 26.0, 15.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ -105.9 (t, *J* = 12.3 Hz). HRMS (ESI+) calc'd for $C_{19}H_{19}F_2N_2O_3S^+$ $[M+H]^+$: 393.1079, found: 393.1074.

Synthesis of Difluoro-verapamil

2-(3,4-dimethoxyphenyl)-2,2-difluoro-1-morpholinoethan-1-one (11a)

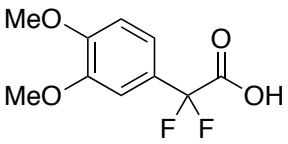


11a

In a nitrogen-filled glovebox, CuOAc (92.8 mg, 0.757 mmol, 0.200 equiv), KF (264 mg, 4.54 mmol, 1.20 equiv), 18-cr-6 (1.20 g, 4.54 mmol, 1.20 equiv), compound **2a** (1.35 g, 5.68 mmol, 2.00 equiv), and 4-iodo-1,2-dimethoxybenzene (1.00 g, 3.79 mmol, 1.00 equiv) were added to a 20 mL vial equipped with a stir bar. Toluene (5 mL) was added, and the reaction was sealed with a Teflon-lined cap and heated at 100 °C for 24 h. After 24 h, the reaction was allowed to cool to room temperature and filtered through Celite, eluting with EtOAc. The solvent was evaporated *in vacuo*, and the crude reside was purified by silica gel chromatography with hexanes:EtOAc 2:3 as eluent. The product was obtained as a colorless solid (1.05 g, 0.349 mmol, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.5 Hz, 1H), 6.99 (d, *J* = 2.1 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.66 (s, 4H), 3.43 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.0 (t, *J* = 30.6 Hz), 150.9, 149.1, 125.4 (t, *J* = 25.1 Hz), 117.9 (t, *J* = 6.1 Hz), 114.0 (t, *J* = 249.5 Hz), 110.6, 107.7, 66.4, 66.1, 55.8, 55.8, 46.5, 43.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -92.1. HRMS (ESI+) calc'd for $C_{14}H_{18}F_2NO_4^+$ $[M+H]^+$: 302.1198, found: 302.1199.

2-(3,4-dimethoxyphenyl)-2,2-difluoroacetic acid (11b)

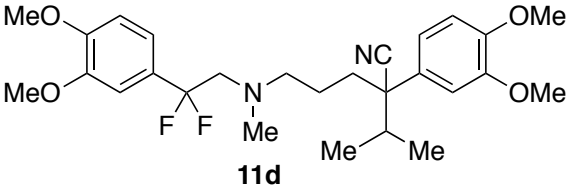


11b

To a 20 mL vial equipped with a stir bar containing compound **11a** (151 mg, 0.500 mmol, 1 equiv) was added 3M NaOH (4 mL). The vial was sealed with a Teflon-lined cap and heated at 65 °C for 1 h. After 1 h, the solution was allowed to cool to room temperature. The solution was washed with Et_2O (3x15 mL), then acidified to pH 1 with 2M HCl and extracted with Et_2O (3x20 mL). The combined organic extracts were dried with Na_2SO_4, and the solvent was evaporated in vacuo. The product was obtained as a light yellow oil (101 mg, 0.437 mmol, 87% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (br. s, 1H), 7.20 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.09 (d, *J* = 2.2 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 3.90 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3 (t, *J* = 39.4 Hz), 151.3, 149.1, 124.6 (t, *J* = 25.9 Hz), 118.8 (t, *J* = 5.9 Hz), 113.3 (t, *J* = 240.6 Hz), 111, 108.4 (t, *J* = 5.4 Hz), 56.1, 56.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ -103.2. HRMS (ESI-) calc'd for $C_{10}H_9F_2O_4^-$ $[M-H]^+$: 231.0474, found: 231.0474.

2-(3,4-dimethoxyphenyl)-5-((2-(3,4-dimethoxyphenyl)-2,2-difluoroethyl)(methyl)amino)-2-isopropylpentanenitrile (11d)



11d

To a round bottom flask under N_2 was added compound **11c** (201 mg, 0.866 mmol, 1 equiv) and CH_2Cl_2 (10 mL). DMAP (52.9 mg, 0.433 mmol, 0.500 equiv) and CDI (352 mg, 2.17 mmol, 2.50 equiv) were added, and the solution was stirred at room temperature for 2 h. The reaction was then equipped with a reflux condenser and heated at reflux for 15 h. The solution was then allowed to cool to room temperature, and amine **11c** (503 mg, 1.73 mmol, 2.00 equiv) was added. The solution was stirred at room temperature for 2 h, followed by the addition of 2M HCl (20 mL). The layers were separated, and the organic layer was extracted with CH_2Cl_2 (4x15 mL). The combined organic layers were washed with H_2O (15 mL) and dried with Na_2SO_4. The solvent was evaporated *in vacuo*.

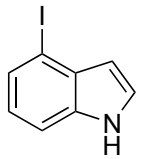
In a nitrogen-filled glovebox, $Zn(OAc)_2$ (18.3 mg, 0.100 mmol, 0.200 equiv) and $HSi(OEt)_2Me$ (403 mg, 481 μL, 3.00 mmol, 6.00 equiv) were added to a 4 mL vial equipped with a stir bar. THF (1 mL) was added, and the reaction mixture was sealed with a Teflon-lined cap, removed from the glovebox, and heated at 65 °C for 30 min. The reaction mixture was then returned to the glovebox, and a solution of the crude amide residue in THF (1 mL) was added. The reaction mixture was sealed with a Teflon-lined cap, removed from the glovebox, and heated at 65

°C for 13 h. The reaction was then allowed to cool to room temperature, and 1M NaOH (2 mL) was added. The reaction was stirred at room temperature for 1 h, then extracted with EtOAc (3x15 mL). The combined organic layers were washed with 1M NaOH (3x15 mL) and dried over Na_2SO_4, and the solvent was evaporated *in vacuo*. The crude residue was purified by silica gel chromatography with hexanes:EtOAc 1:1 as eluent. The product was obtained as a colorless solid (185 mg, 0.377 mmol, 75% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.91 (d, *J* = 2.1 Hz, 1H), 6.88-6.73 (m, 4H), 3.84 (s, 6H), 3.82 (s, 6H), 2.83 (t, *J* = 14.3 Hz, 2H), 2.36 (t, *J* = 6.6 Hz, 2H), 2.15 (s, 3H), 1.96 (m, 2H), 1.69 (td, *J* = 13.5, 4.2 Hz, 1H), 1.38 (m, 1H), 1.09 (d, *J* = 6.6 Hz, 3H), 1.06-0.92 (m, 1H), 0.72 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.0, 148.9, 148.6, 148.2, 130.6, 129.0 (t, *J* = 26.4 Hz), 123.4 (t, *J* = 244.3 Hz), 121.4, 118.7, 118.1 (t, *J* = 6.6 Hz), 111.0, 110.5, 109.4, 108.5 (t, *J* = 6.3 Hz), 63.1 (t, *J* = 29.6 Hz), 58.1, 55.9, 55.9, 55.8, 55.8, 53.2, 43.5, 37.9, 35.1, 23.6, 18.9, 18.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -96.8. HRMS (ESI+) calc'd for $C_{27}H_{37}F_2N_2O_4^+$ $[M+H]^+$: 491.2716, found: 491.2719.

Synthesis of Difluoro-ropinirole

4-Iodoindole (12a)

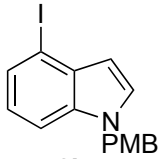


12a

4-Iodoindole was synthesized in analogy to the previously reported synthesis of 5-iodoindole.[43] In a nitrogen-filled glovebox, NaI (1.53 g, 10.2 mmol, 2.00 equiv), CuI (97.1 mg, 0.510 mmol, 0.100 equiv), dioxane (5 mL), 4-bromoindole (2.94 g, 15.0 mmol, 1.00 equiv), and DMEDA (89.9 mg, 110 μL, 1.02 mmol, 0.200 equiv) were added to a 20 mL vial equipped with a stir bar. The reaction mixture was removed from the glovebox and heated at 110 °C for 48 h, then allowed to cool to room temperature and poured into sat. aqueous NH_4OH (15 mL). The solution was extracted with CH_2Cl_2 (3x20 mL), and the combined organic extracts were washed with brine (20 mL) and dried with Na_2SO_4, and the solvent was evaporated *in vacuo*. The product was obtained as a brown oil (2.96 g, 12.2 mmol, 81% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.22 (t, *J* = 2.9 Hz, 1H), 6.96 (t, *J* = 7.8 Hz, 1H), 6.52 (t, *J* = 2.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.7, 132.4, 129.4, 124.6, 123.4, 111.2, 106.3, 87.5.

4-iodo-1-(4-methoxybenzyl)-1*H*-indole (12b)



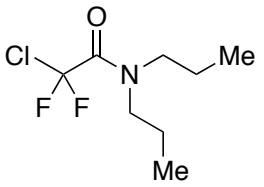
12b

A solution of 4-iodoindole (**12a**) (1.22 g, 5.00 mmol, 1.00 equiv) in DMF (25 mL) was added to an oven-dried round bottom flask under N_2 and cooled at 0 °C. After 10 min, NaH (240 mg, 10.0 mmol, 2.00 equiv) was added in one portion, and bubbling was observed. The reaction mixture was stirred at 0 °C for 5 min, then allowed to warm to room temperature and stirred for 1 h. The reaction was quenched by the dropwise addition of H_2O (50 mL), then extracted with EtOAc (3x35 mL). The combined organic extracts were washed with H_2O (3x35 mL) and brine (30 mL)

and dried with Na_2SO_4. The solvent was evaporated *in vacuo*, and the crude residue was purified by silica gel chromatography with hexanes:EtOAc 12:1. The product was isolated as a pale yellow solid (1.47 g, 4.06 mmol, 81% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.27 (d, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 3.2 Hz, 1H), 7.05 (d, *J* = 8.6 Hz, 2H), 6.90 (dd, *J* = 8.2, 7.5 Hz, 1H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.46 (dd, *J* = 3.2, 0.8 Hz, 1H), 5.23 (s, 2H), 3.78 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 135.4, 133.3, 129.1, 129.0, 128.6, 128.3, 123.0, 114.3, 109.9, 105.3, 87.9, 55.4, 50.2. HRMS (EI+) calc'd for $C_{16}H_{14}INO$: 363.0120, found: 363.0125.

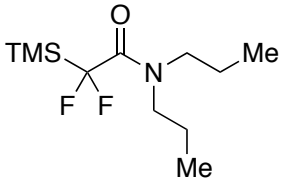
2-chloro-2,2-difluoro-*N*,*N*-dipropylacetamide (S3)



To an oven-dried round bottom flask under N_2 was added dipropylamine (6.03 mL, 44.0 mmol, 2.20 equiv) and CH_2Cl_2 (25 mL). The solution was cooled at 0 °C, and chlorodifluoroacetic anhydride (3.48 mL, 20.0 mmol, 1.00 equiv) was added dropwise. The solution was stirred at 0 °C, then allowed to warm to room temperature and stirred for 12 h. To the reaction mixture was added 1M HCl (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3x30 mL). The combined organic extracts were washed with H_2O (3x30 mL) and brine (30 mL) and dried with Na_2SO_4. The solvent was evaporated in *vacuo*. Compound **S3** was isolated as a colorless oil (4.59 g, 21.1 mmol, 48% yield based on amine).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.34-3.11 (m, 4H), 1.61-1.45 (m, 4H), 0.80 (t, *J* = 7.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4 (t, *J* = 28.8 Hz), 118.9 (t, *J* = 301.5 Hz), 49.6 (t, *J* = 3.6 Hz), 48.7, 21.7, 19.9, 10.9, 10.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.6. HRMS (ESI+) calc'd for $C_8H_{15}ClF_2NO^+$ $[M+H]^+$: 214.0805, found: 214.0804.

2,2-difluoro-*N*,*N*-dipropyl-2-(trimethylsilyl)acetamide (S4)

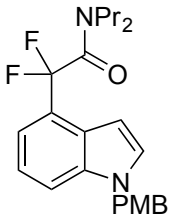


To an oven-dried round bottom flask under N_2 was added Mg (1.03 g, 21.1 mmol, 2.00 equiv), anhydrous DMF (50 mL), and TMSCl (9.17 g, 10.6 mL, 84.4 mmol, 4.00 equiv). The reaction mixture was cooled at 0 °C. Compound **S3** (4.50 g, 21.1 mmol, 1.00 equiv) was added dropwise, and the reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 20 h, the reaction was quenched with H_2O (100 mL) and extracted with Et_2O (3x50 mL). The combined organic extracts were washed with H_2O (3x50 mL) and brine (50 mL) and dried with Na_2SO_4. The solvent was evaporated *in vacuo*, and the material was used without further purification. Compound **S4** was isolated as a colorless oil (4.70 g, 18.7 mmol, 93% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.39 (t, *J* = 7.9 Hz, 2H), 3.26-3.18 (m, 2H), 1.58 (m, 4H), 0.87 (t, *J* = 7.5 Hz, 6H), 0.20 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7 (t, *J* = 23.7 Hz), 126.4 (t, *J* =

275.4 Hz), 48.4 (t, *J* = 5.9 Hz), 48.1, 22.3, 20.4, 11.4, 11.1, -3.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.6. HRMS (EI+) calc'd for $C_8H_{14}ClF_2NO$: 251.1517, found: 251.1521.

2,2-difluoro-2-(1-(4-methoxybenzyl)-1*H*-indol-4-yl)-*N*,*N*-dipropylacetamide (12c)

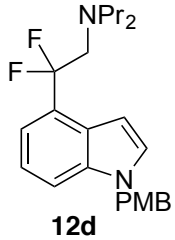


12c

In a nitrogen-filled glovebox, CuOAc (24.5 mg, 0.200 mmol, 0.200 equiv), KF (69.7 mg, 1.20 mmol, 1.20 equiv), 18-cr-6 (317 mg, 1.20 mmol, 1.20 equiv), compound **12b** (363 mg, 1.00 mmol, 2.00 equiv), toluene (2 mL), and compound **S3** (302 mg, 1.20 mmol, 1.20 equiv) were added to a 4 mL vial equipped with a stir bar. The reaction was sealed with a Teflon-lined cap and heated at 100 °C for 24 h. The reaction was allowed to cool to room temperature and filtered through Celite, eluting with EtOAc. The solvent was evaporated *in vacuo*, and the crude reside was purified by silica gel chromatography with hexanes:EtOAc 6:1→2:1 as eluent. The product was obtained as a colorless solid (284 mg, 0.684 mmol, 68% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.2 Hz, 1H), 7.30 (d, *J* = 7.4 Hz, 1H), 7.19-7.16 (m, 2H), 7.03 (d, *J* = 8.2 Hz, 2H), 6.85-6.75 (m, 3H), 5.25 (s, 2H), 3.75 (s, 3H), 3.32 (t, *J* = 7.7 Hz, 2H), 3.11 (t, *J* = 7.9 Hz, 2H), 1.60 (d, *J* = 7.6 Hz, 2H), 1.23 (d, *J* = 8.0 Hz, 2H), 0.88 (t, *J* = 7.4 Hz, 3H), 0.57 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6 (t, *J* = 30.3 Hz), 159.2, 136.8, 129.6, 129.0, 128.2, 125.6 (t, *J* = 25.1 Hz), 125.2 (t, *J* = 3.2 Hz), 121.0, 116.8 (t, *J* = 7.0 Hz), 116.2 (t, *J* = 248.6 Hz), 114.2, 112.4, 101.0, 55.3, 49.8, 49.4, 48.5, 21.5, 20.3, 11.4, 10.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -93.0. HRMS (ESI+) calc'd for $C_{24}H_{29}F_2N_2O_2^+$ $[M+H]^+$: 415.2192, found: 415.2188.

***N*-(2,2-difluoro-2-(1-(4-methoxybenzyl)-1*H*-indol-4-yl)ethyl)-*N*-propylpropan-1-amine (12d)**



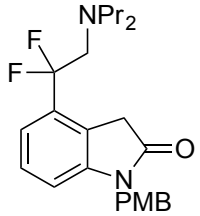
12d

In a nitrogen-filled glovebox, $Zn(OAc)_2$ (9.2 mg, 0.0500 mmol, 0.100 equiv) and $HSi(OEt)_2Me$ (275 mg, 328 μL, 1.50 mmol, 3.00 equiv) were added to a 4 mL vial equipped with a stir bar. THF (1 mL) was added, and the reaction mixture was sealed with a Teflon-lined cap, removed from the glovebox, and heated at 65 °C for 30 min. The reaction mixture was then returned to the glovebox, and a solution of compound **12c** (207 mg, 0.500 mmol, 1.00 equiv) in THF (1 mL) was added. The reaction mixture was sealed with a Teflon-lined cap, removed from the glovebox, and heated at 65 °C for 16 h. The reaction was then allowed to cool to room temperature, and 1M NaOH (2 mL) was added. The reaction was stirred at room temperature for 1 h, then extracted with EtOAc (3x20 mL). The combined organic layers were washed with brine (3x20 mL) and dried over Na_2SO_4, and the solvent was evaporated *in vacuo*. The product was isolated as a light yellow oil (178 mg, 0.445 mmol, 89% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.2 Hz, 1H), 7.30 (d, *J* = 7.3 Hz, 1H), 7.21 (d, *J* = 7.9 Hz, 1H), 7.18 (d, *J* = 3.2 Hz, 1H), 7.04 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.70 (d, *J* = 2.6 Hz, 1H), 5.27 (s, 2H), 3.78 (s, 3H), 3.24 (t, *J* = 14.8 Hz, 2H), 2.59 – 2.38 (m, 4H), 1.37 (m, 4H), 0.78 (t, *J* = 7.4 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 136.7, 129.3, 128.9, 128.7 (t,

J = 26.1 Hz), 128.1, 125.4 (t, *J* = 3.6 Hz), 123.6 (t, *J* = 245.0 Hz), 121.0, 117.4 (t, *J* = 7.4 Hz), 114.2, 111.3, 101.1, 60.1 (t, *J* = 28.4 Hz), 57.6, 55.3, 49.7, 20.6, 11.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ -98.4 (t, *J* = 14.9 Hz). HRMS (ESI+) calc'd for $C_{24}H_{31}F_2N_2O^+$ $[M+H]^+$: 401.2399, found: 401.2390.

4-(2-(dipropylamino)-1,1-difluoroethyl)-1-(4-methoxybenzyl)indolin-2-one (12e)

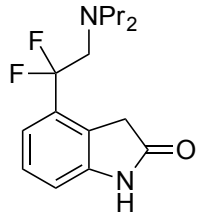


12e

To a 4 mL vial equipped with a stir bar was added compound **12d** (207 mg, 0.500 mmol, 1.00 equiv), NCS (134 mg, 1.00 mmol, 2.00 equiv), and toluene (1 mL). The vial was sealed with a Teflon-lined cap and stirred at room temperature for 2.5 h. 1M NaOH (5 mL) was added, and the layers were separated. The aqueous layer was extracted with toluene (2x2 mL). The combined organic layers and 1M HCl (5 mL) were added to a 20 mL vial sealed with a Teflon-lined cap, and the reaction was heated at 100 °C for 5 h. To the reaction mixture was added 0.5M NaOH to pH 10. The layers were separated, and the aqueous layer was extracted with EtOAc (5x15 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (3x15 mL) and brine (15 mL) and dried with Na_2SO_4. The solvent was evaporated *in vacuo*, and the crude residue was purified by silica gel chromatography with hexanes:EtOAc 4:1 as eluent. The product was obtained as a colorless oil (164 mg, 0.394 mmol, 79% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.15 (m, 3H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 2H), 6.75 (d, *J* = 7.8 Hz, 1H), 4.86 (s, 2H), 3.81 (d, *J* = 2.9 Hz, 2H), 3.75 (s, 3H), 3.02 (t, *J* = 13.9 Hz, 2H), 2.50-2.33 (m, 4H), 1.42-1.09 (m, 4H), 0.71 (t, *J* = 7.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1, 159.1, 144.7, 133.0 (t, *J* = 13.4 Hz), 128.6, 127.9, 127.7, 122.6, 122.5 (t, *J* = 245.0 Hz), 119.7 (t, *J* = 6.5 Hz), 114.2, 110.2, 60.6, 57.6, 55.3, 43.2, 36.2, 20.3, 11.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ -99.1 (t, *J* = 14.7 Hz). HRMS (ESI+) calc'd for $C_{24}H_{31}F_2N_2O_2^+$ $[M+H]^+$: 417.2348, found: 417.2351.

4-(2-(dipropylamino)-1,1-difluoroethyl)indolin-2-one (12f)



12f

To a 20 mL vial equipped with a stir bar was added compound **12e** (104 mg, 0.250 mmol, 1.00 equiv), anisole (1.08 g, 1.09 µL, 10.0 mmol, 40.0 equiv), TFA (2 mL) and H_2SO_4 (100 µL). The vial was sealed with a Teflon-lined cap and heated at 80 °C for 17 h. The reaction was allowed to cool to room temperature and poured into 50 mL sat. aq. $NaHCO_3$. The reaction mixture was extracted with EtOAc (3x20 mL), and the combined organic layers were washed with sat. aq. $NaHCO_3$ (2x20 mL) and brine (20 mL). The organic layers were dried with Na_2SO_4, and the solvent was evaporated *in vacuo*. The crude reside was purified by silica gel chromatography with hexanes:EtOAc 5:1 → 2:1 as eluent. The product was obtained as a colorless solid (43.0 mg, 0.145 mmol, 58% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (d, *J* = 6.8 Hz, 1H), 7.29 (t, *J* = 7.1 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 7.8 Hz, 1H), 3.79 (s, 2H), 3.08 (t, *J* = 13.8 Hz, 2H), 2.48-2.42 (m, 4H), 1.37-1.30 (m, 4H), 0.77 (t, *J* = 7.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.4, 143.1, 133.2 (t, *J* =

13.6 Hz) 128.0, 125.6 (t, J = 245.0 Hz), 123.3, 119.7 (t, J = 6.8 Hz), 111.1, 60.5, 57.5, 36.8, 20.2, 11.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ -99.0. HRMS (ESI+) calc'd for $C_{16}H_{23}F_2N_2O^+$ $[M+H]^+$: 297.1773, found: 297.1767.

2.5 References

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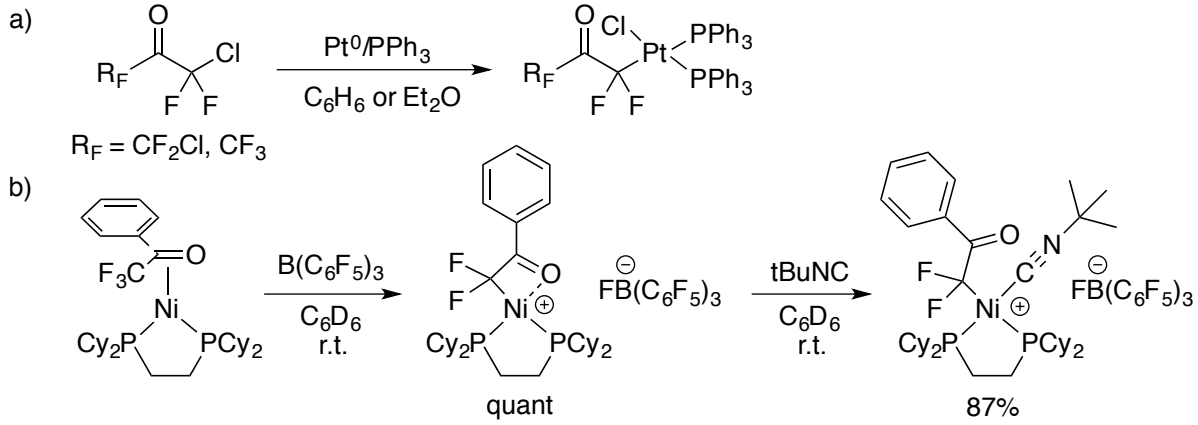
Chapter 3

Synthesis, Characterization, and Reactivity of Palladium Fluoroenolate Complexes

3.1 Introduction

The importance of fluorinated compounds in pharmaceuticals, agrochemicals, and materials has prompted the development of transition metal-catalyzed methods for the synthesis of fluoroalkyl arenes (see Chapter 1).[1-6] Palladium-catalyzed coupling reactions for the synthesis of aryldifluoromethyl carboxylic acid derivatives have been reported recently. The α-arylations of α,α-difluoroketones,[7-8] α,α-difluoroesters,[9] and α,α-difluoroacetamides[10] with aryl halides all occur with broad scope. In addition, palladium-catalyzed cross-couplings of arylboronic acids with bromodifluoroacetates and –acetamides ($BrCF_2CO_2Et$, $BrCF_2C(O)NRR'$) have been developed.[11] The aryl-fluoroalkyl bond could form in these catalytic processes by reductive elimination from an arylpalladium difluoroenolate complex. However, the isolation and reactivity of such complexes have not been reported. Reductive elimination reactions of alkylpalladium complexes containing fluorine atoms on the α-carbon of an alkyl group are significantly slower than those of their non-fluorinated analogs.[12] Reductive elimination reactions to form aryl-fluoroalkyl bonds from isolated fluoroalkyl palladium complexes are rare and are limited to trifluoromethyl,[13-23] pentafluoroethyl,[19, 21] and difluoromethyl[24] compounds.

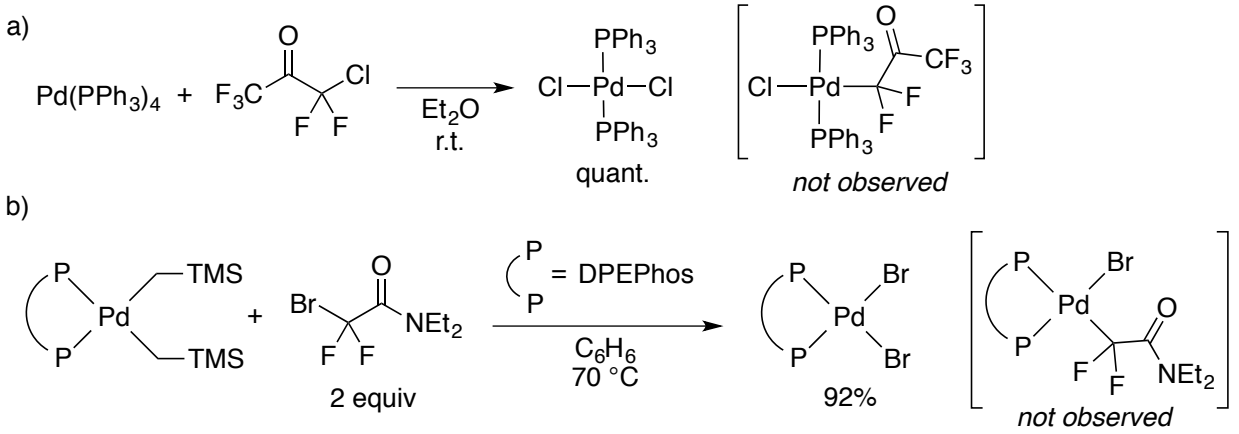
Previous examples of isolated transition-metal fluoroenolates are limited, and complexes relevant to metal-catalyzed fluoroenolate arylations have not been isolated. Two chloroplatinum difluoroketone complexes have been prepared (Scheme 3.1a),[25-26] but no reactions of the isolated complexes were reported, and platinum-catalyzed fluoroenolate arylations are unknown. In 2015, a nickel difluoroketone enolate was prepared by fluoride abstraction from a Ni^0-trifluoroacetophenone complex (Scheme 1b),[27] but reactions relevant to catalytic coupling between fluoroenolates and aryl groups were not reported.



Scheme 3.1 Previously reported syntheses of metal fluoroenolate complexes.

Unsuccessful attempts to prepare Pd-difluoroenolate complexes have been previously reported (Scheme 3.2). Palladium complexes containing monodentate phosphine ligands (Scheme 3.2a, L = PPh_3)[26] and bidentate phosphine ligands (Scheme 3.2b, L = DPEPhos)[28] were treated with chlorodifluoroketones and bromodifluoroamides, respectively. In each case, halopalladium

difluoroenolate complexes were not detected, and only palladium dihalide complexes were observed.



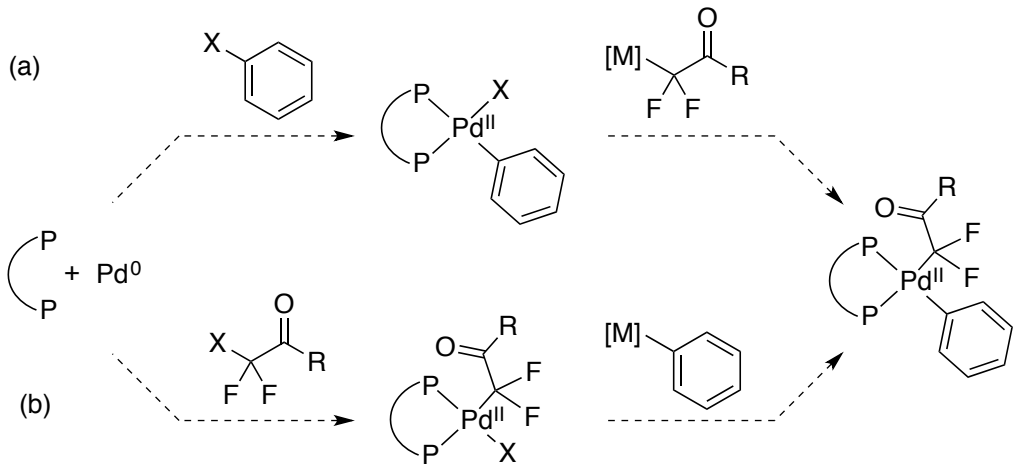
Scheme 3.2 Previous attempts to prepare palladium difluoroenolate complexes.

We report the synthesis and structural characterization of a series of phosphine-ligated arylpalladium complexes of C-bound fluorinated enolates. Arylpalladium complexes ligated by DPPF underwent reductive elimination in high yield, allowing an assessment of the effects of the steric and electronic properties of the aryl and enolate ligands on the rates of this reaction. Synthesis of complexes containing various phosphines allowed an assessment of the effect of the ancillary ligands and a direct comparison of reductive elimination from a difluoroenolate complex and an analogous trifluoromethyl complex.

3.2 Results and Discussion

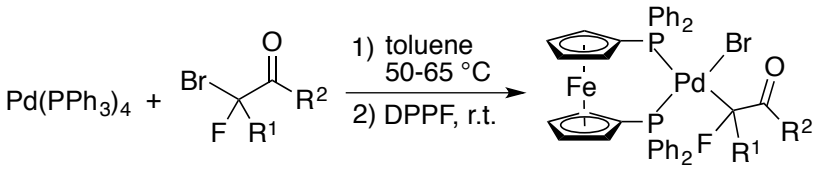
Our studies began with efforts to synthesize and isolate stable arylpalladium difluoroenolate complexes. Two strategies for the synthesis of arylpalladium fluoroenolate complexes were pursued: 1) oxidative addition of an aryl halide, followed by transmetallation with a pre-formed fluoroenolate (Scheme 3.3a) and 2) oxidative addition of a halodifluorocarbonyl compound, followed by transmetallation with an arylmetal species (Scheme 3.3b).

Oxidative addition of aryl halides to phosphine-ligated Pd^0 complexes is well-precedented.[29] However, subjecting the resulting Pd^{II} aryl halide complexes to transmetallation with pre-formed silyldifluoroesters or zinc difluoroester enolates did not result in the formation of isolable arylpalladium difluoroenolate complexes.



Scheme 3.3 Proposed syntheses of arylpalladium difluoroenolate complexes.

We therefore pursued an alternative route, beginning with the synthesis of a series of bromopalladium fluoroenolate complexes ligated by DPPF (Scheme 3.4). The complexes were prepared by oxidative addition of a carbon-bromine bond of bromodifluoromethyl and bromofluoromethyl esters and amides to $Pd(PPh_3)_4$, followed by ligand exchange with DPPF. The C-bound difluoroester enolate 1a was prepared in 90% isolated yield by oxidative addition of ethyl bromodifluoroacetate, followed by ligand exchange of DPPF for PPh_3. A series of palladium monofluoroester (1b) and difluoroamide (1c-e) complexes ligated by DPPF were prepared in 73-94% yield by analogous routes involving oxidative addition of the corresponding bromofluorocarbonyl compound (Scheme 3).



1a R^1 = F, R^2 = OEt 90%
1b R^1 = H, R^2 = OEt 93% **1d** R^1 = F, R^2 = NMe_2 94%
1c R^1 = F, R^2 = N⌒O 83% **1e** R^1 = F, R^2 = NEt_2 73%

Scheme 3.4 Synthesis of DPPF-ligated bromopalladium fluoroenolate complexes.

The bromopalladium fluoroenolate complexes were characterized by NMR spectroscopy, and the connectivity of complex 1a was confirmed by single-crystal x-ray diffraction (Figure 3.1). Like the previously reported platinum[25-26] and nickel[27] difluoroketone enolates, palladium enolate 1a was C-bound. The carbon-oxygen bond lengths of the difluoroester group in **1a** (1.19(1) Å and 1.335(9) Å) were consistent with typical values for a C-O double bond and a C-O single bond, respectively, supporting the assignment of the complex as an η^1-C-bound enolate.

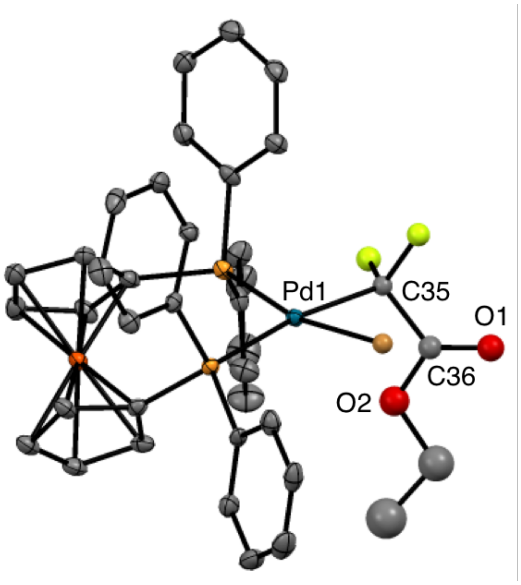
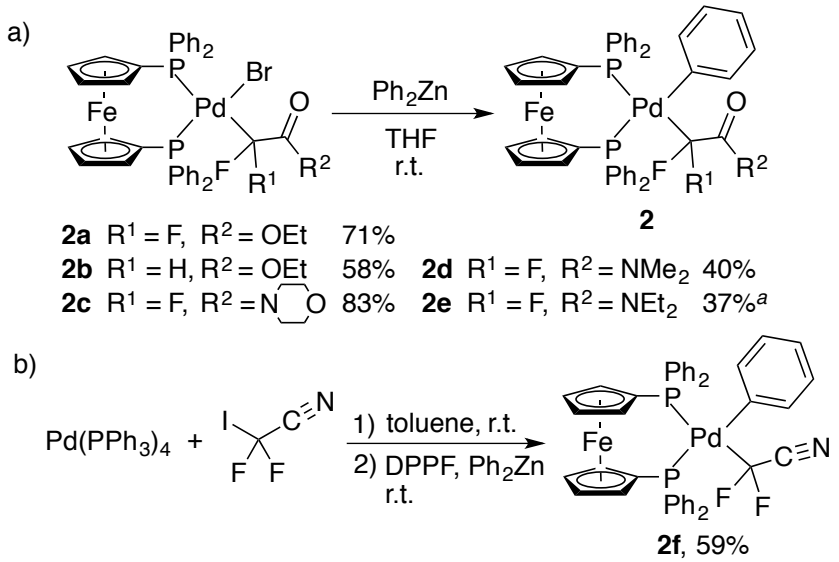


Figure 3.1 ORTEP diagram of complex **1a**. Selected bond lengths: Pd1-C35, 2.135(7) Å; C36-O1, 1.19(1) Å; C36-O2, 1.335(9) Å. Ellipsoids are shown at 50% probability, and hydrogen atoms and solvents of crystallization are omitted for clarity.

Bromopalladium fluoroenolate complexes **1a-e** were converted to the corresponding arylpalladium fluoroenolates by reactions with aryl nucleophiles. The reaction of bromopalladium fluoroenolates **1a-1d** with diphenylzinc occurred rapidly in THF at room temperature to afford the corresponding phenylpalladium fluoroenolate complexes (**2a-d**) in 40-83% isolated yield (Scheme 3.5). Complex **2e** was prepared by a transmetallation reaction between complex **1e** and phenylboronic acid in 37% isolated yield. A modified synthetic route afforded difluorocyanomethyl complex 2f in 59% isolated yield (Scheme **2b**). The ^{19}F NMR spectra of the arylpalladium fluoroenolate complexes consisted of a single fluorine resonance with ^{31}P-^{19}F coupling between fluorine and two inequivalent phosphorus nuclei ($J_{F\text{-}P}$ = 44.0, 37.3 Hz for difluoroester enolate **2a**). The ^{31}P NMR spectra consisted of two triplets of doublets, due to ^{31}P-^{19}F and ^{31}P-^{31}P coupling.



Scheme 3.5 Synthesis of DPPF-ligated arylpalladium fluoroenolate complexes. [a]Prepared by transmetallation with $PhB(OH)_2$.

The structures of DPPF-ligated arylpalladium fluoroenolate complexes **2a-c** and **2f** were confirmed by single-crystal, x-ray crystallography (Figure 3.2). The geometry about the palladium atom is square planar in each complex. The Pd-C(aryl) bond lengths are nearly constant, ranging from 2.051(2)-2.058(3) Å. The enolates are η^1-C-bound in all cases, but the Pd-C(enolate) bond lengths vary over a wide range from 2.089(3)-2.188(3) Å. Among the complexes of difluorinated enolates (**2a**, **2c**, and **2f**), the Pd-C(enolate) bond is shorter for enolates containing more electron-withdrawing groups. The Pd-C(enolate) bond is shortest in difluorocyanomethyl complex **2f** (2.089(3) Å), followed by difluoroester complex **2a** (2.099(3) Å). The Pd-C(enolate) bond is longest in difluoroamide complex **2c** (2.188(3) Å).

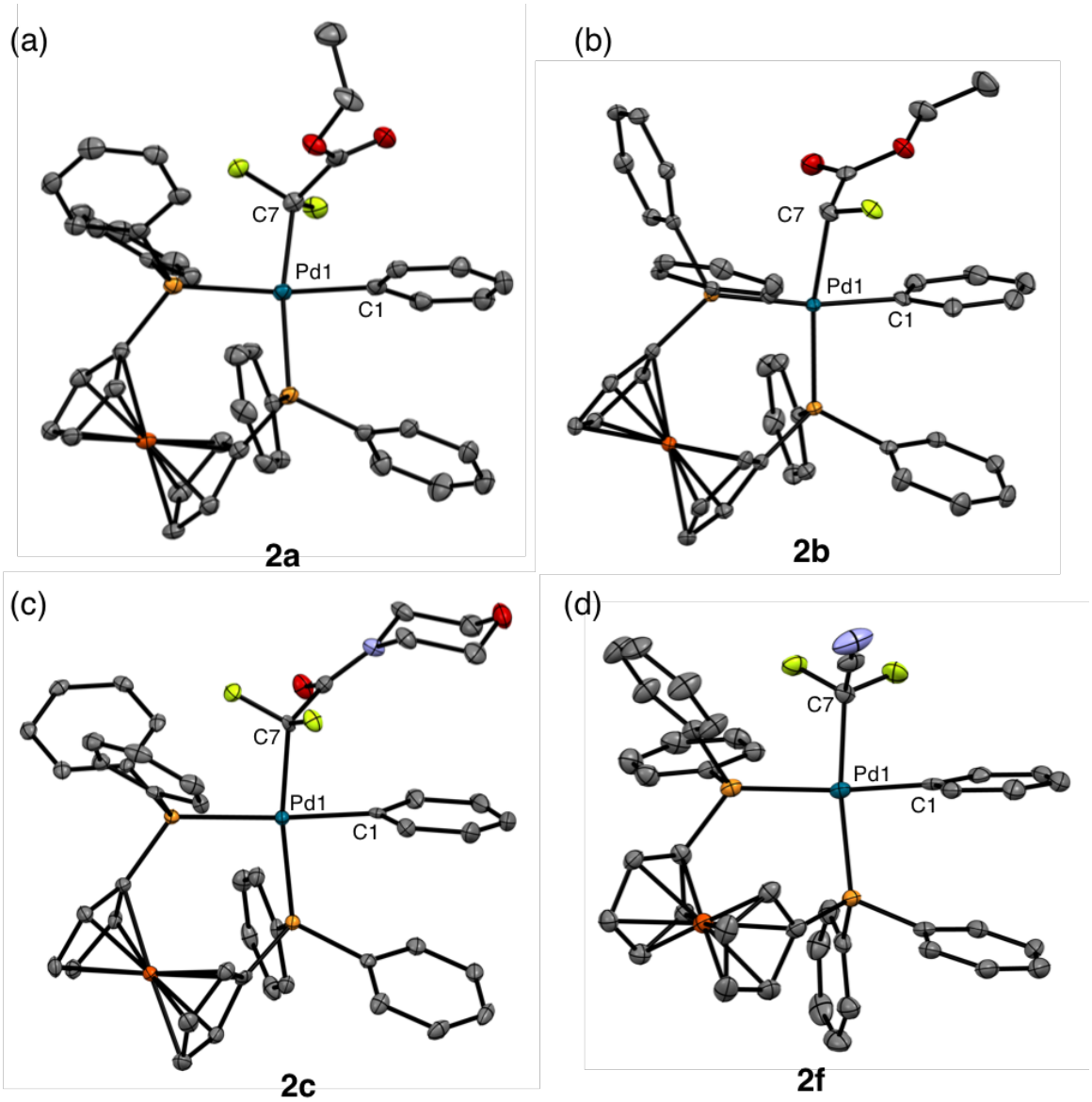
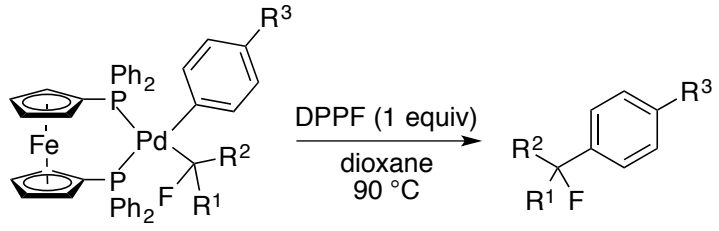


Figure 3.2 ORTEP diagrams of complexes **2a-c** and **2f**. Selected bond lengths: (a) Pd1-C1, 2.053(3) Å; Pd1-C7, 2.099(3) Å; (b) Pd1-C1, 2.051(2) Å; Pd1-C7, 2.105(3) Å; (c) Pd1-C1, 2.055(5) Å; Pd1-C7, 2.188(3) Å; (d) Pd1-C1, 2.058(3)Å; Pd1-C7, 2.089(3) Å.[30] Ellipsoids are shown at 50% probability, and hydrogen atoms and solvents of crystallization are omitted for clarity.

Arylpalladium fluoroenolate complexes **2a-e**, containing difluoroester, monofluoroester, and difluoroamide enolates, and complex **2f**, containing a difluorocyanomethyl ligand, underwent reductive elimination to form the corresponding aryl fluorocarbonyl and -nitrile compounds in 92-99% yield (Table 3.1). The effect of the electronic and steric properties of the enolate was assessed

by measuring the rate constants for the reaction of a series of fluoroenolate complexes ligated by DPPF. The rate constants were measured from the decay of the Pd-fluoroenolate complexes by ^{19}F NMR spectroscopy in the presence of 1 equiv of DPPF.[31] These data fit a first-order exponential decay, from which the rate constants and half-lives for reductive elimination were determined.

Table 3.1 Reductive elimination from Pd-fluoroenolate complexes.



entry	complex	R^1	R^2	R^3	yield[a]	$t_{1/2}$ (min)[b]
1	**2a**	F	CO_2Et	H	99%	213
2	**2b**	H	CO_2Et	H	93% (98%)[c]	<5 (83)[c]
3	**2c**	F	C(O)N⌒O	H	98%	42
4	**2d**	F	$C(O)NMe_2$	H	93%	53
5	**2e**	F	$C(O)NEt_2$	H	95%	30
6	**2f**	F	CN	H	92%[d]	845
7	**2g**[e]	F	CO_2Et	OMe	99%	223
8	**2h**[e]	F	CO_2Et	Cl	84%[f]	811

[a]Determined after 24 h by ^{19}F NMR spectroscopy. [b]Determined by monitoring the decay of the Pd complex by ^{19}F NMR spectroscopy. [c]At 50 ºC. [d]Yield after 72 h. [e]Prepared by transmetallation between complex **1a** and the corresponding arylboronic acid (see Experimental section for synthetic details). [f]Yield after 36 h.

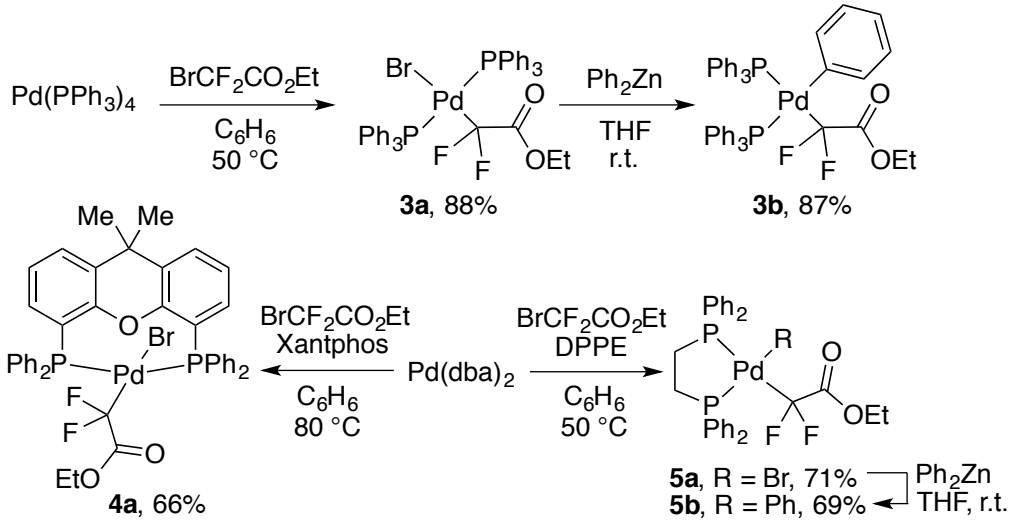
Comparison of these half-lives show that complexes of more electron-rich enolates underwent reductive elimination at lower temperatures and with faster rates than did complexes of more electron-poor enolates. Difluoroamide complex **2c** reacted approximately 4 times faster than difluoroester complex **2a** and approximately 20 times faster than difluoronitrile complex **2f**. The number of fluorine atoms on the α-carbon of the enolate also significantly affected the rate of reductive elimination of the corresponding Pd enolate complex; monofluoroester complex **2b** underwent reductive elimination in 98% yield upon heating at 50 °C, whereas difluoroester complex **2a** reacted to <5% conversion after 24 hours at the same temperature. Overall, the trend in rates of reductive elimination of the palladium fluoroenolate complexes was: monofluoroester > difluoroamide > difluoroester > difluoronitrile.

The relationships between these relative rates and the structures of the enolate complexes can be assessed by comparing the data in Table 3.1 to the structures of the complexes determined by x-ray diffraction (Figure 3.2). Among the complexes of difluorinated ester (**2a**), amide (**2c**), and nitrile (**2f**) enolates, a correlation between a longer Pd-C(enolate) bond and a faster rate of reductive elimination was observed.

Complexes of more sterically hindered enolates underwent reductive elimination with faster rates than those of less hindered enolates: at 90 °C, the half-life for reaction of dimethylamide complex **2d** was 53 minutes, whereas the half-life for reaction of the analogous diethylamide complex **2e** was 30 minutes. The magnitude of this effect is comparable to that observed for reductive elimination from arylpalladium complexes of non-fluorinated enolates of dimethyl- and diethylamides.[12]

The relative rates of reductive elimination from complexes **2a**, **2g**, and **2h** containing hydrogen, methoxy and chloro substituents on the palladium-bound aryl group were measured (Table 3.1, entries 1 and 7-8). The half-life for reductive elimination from the more electron-rich *para*-anisylpalladium complex **2g** was nearly identical to that for reductive elimination from the phenylpalladium complex **2a**; the half-life for reaction of *para*-chlorophenyl complex **2h** was longer than that for the reactions of **2a** or **2g**. In previous studies of reductive elimination from arylpalladium cyano complexes[32] and arylpalladium complexes of non-fluorinated ketone enolates,[12] the reactions of *para*-chlorophenyl complexes were slower than those of the parent phenyl complexes, just as observed for complexes **2h** and **2a** of the fluorinated enolates.

Finally, we investigated the effect of the ancillary phosphine ligand on this class of reductive elimination. A series of phosphine-ligated difluoroester complexes were prepared by oxidative addition of a carbon-halogen bond to the Pd^0 precursors $Pd(PPh_3)_4$ or $Pd(dba)_2$. Complex **3a** was isolated from the oxidative addition of ethyl bromodifluoroacetate to $Pd(PPh_3)_4$ in 88% yield. Oxidative addition of ethyl bromodifluoroacetate to $Pd(dba)_2$ in the presence of a chelating bisphosphine afforded difluoroester complexes **4a**, ligated by Xantphos, and **5a**, ligated by DPPE (DPPE=1,2-bis(diphenylphosphino)ethane), in 66 and 71% yield, respectively (Scheme 3.6). The connectivity of Xantphos complex **4a** was confirmed by x-ray crystallography (Figure 3.3). Transmetallation with diphenylzinc afforded triphenylphosphine- and DPPE-ligated complexes **3b** and **5b** in 87% and 69% yield, respectively.



Scheme 3.6 Synthesis of phosphine-ligated palladium difluoroester enolate complexes.

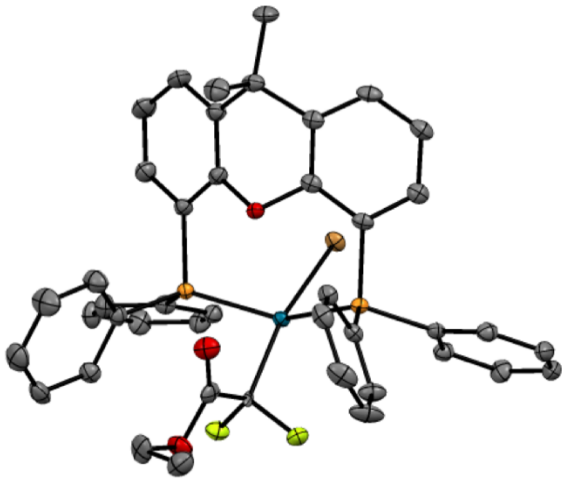
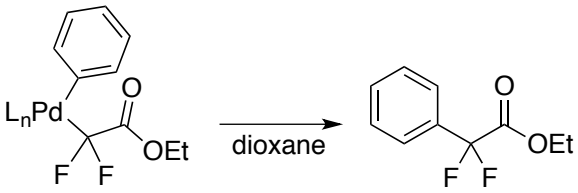


Figure 3.3 ORTEP diagram of complex **4a**. Ellipsoids are shown at 50% probability, and hydrogen atoms are omitted for clarity.

Reductive elimination to form ethyl phenyldifluoroacetate from arylpalladium difluoroester enolate complexes ligated by monophosphines and bisphosphines occurred with rates and yields that depended strongly on the identity of the ancillary ligand (Table 3.2). Triphenylphosphine-ligated arylpalladium difluoroester complex **3b** did not undergo reductive elimination in high yield; only 31% yield of ethyl phenyldifluoroacetate was obtained upon heating of **3b** at 90 °C for 24 h, although full consumption of **3b** was observed.

Table 3.2 Reductive elimination of arylpalladium difluoroester complexes.



entry	complex	ligand	temperature	yield[a]
1	**2a**	DPPF	90 °C	97%[b]
2	**3b**	PPh_3	90 °C	31%[b]
3	**4b**[c]	Xantphos	r.t.	94%[d,b]
4	**5b**	DPPE	90 °C	0%[e] (25%)[b,f]

[a]Determined after 24 h by ^{19}F NMR spectroscopy with fluorobenzene as internal standard. [b]Full conversion of the starting material was observed. [c]Formed *in situ* from complex 4a and Ph_2Zn with THF as solvent. [d]Yield after 30 min. [e]<5% conversion of the starting material was observed. [f]At 100 ºC for 72 h.

While reductive elimination from difluoroester enolate complex **2a**, ligated by DPPF (bite angle = 99.1°[33]), proceeded in high yield (*vide supra*), the analogous elimination from complex **5b**, ligated by DPPE (bite angle = 85.8°[34]), proceeded in low yield. Complex **5b** required heating at 100 °C for 72 hours for full conversion, and only 25% yield of ethyl phenyldifluoroacetate was obtained.

The reaction of a Xantphos-ligated difluoroester enolate complex allows a comparison of the rate of reductive elimination from a difluoroenolate to that of reductive elimination from trifluoromethyl compound. Treatment of complex **4a**, ligated by Xantphos (bite angle = 111°[35]), with diphenylzinc formed the corresponding arylpalladium difluoroester enolate **4b**, which was characterized *in situ*. Consistent with the high yields obtained from arylation reactions of difluorocarbonyl compounds catalyzed by palladium and Xantphos[9, 11] and the effect of large bite angles on the rates of reductive elimination, reductive elimination of ethyl phenyldifluoroacetate occurred in 94% yield after just 30 min at room temperature. Reductive elimination from this compound was much faster than reductive elimination of trifluoromethylbenzene from the (Xantphos)Pd(Ph)(CF_3) complex studied by Grushin, which required heating for 3 hours at 80 °C for reductive elimination to occur in high yield.[15]

3.3 Conclusion

We report the first examples of isolated fluoroenolate complexes of palladium, as well as the first reductive elimination reactions of isolated fluoroenolate complexes. DPPF-ligated arylpalladium complexes of C-bound fluorinated ester, amide, and nitrile enolates were isolated, characterized, and shown to undergo reductive elimination in high yield upon heating. The combination of structural data and rates of reductive elimination reveal that complexes containing more electron-donating fluoroenolate groups, which have longer Pd–C(enolate) bonds, react significantly faster than those with less electron-donating groups and shorter Pd–C(enolate) bonds. Future work will examine the reactivity of metal fluoroenolate and fluoroalkyl complexes ligated with a range of ancillary ligands, as well as the development of new catalytic reactions involving these classes of complexes.

3.4 Experimental

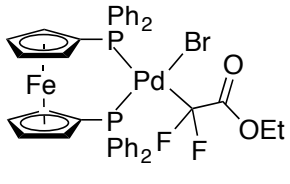
General Experimental Details

All reactions were conducted under inert atmosphere in a nitrogen-filled glovebox or with standard Schlenk techniques, unless otherwise specified. Vessels used in air-free reactions were oven-dried prior to use. Vials used as a reaction vessel were sealed with Teflon-lined caps. Toluene, tetrahydrofuran, diethyl ether, and dichloromethane were purged with nitrogen and dried with an Innovative Pure-Solv solvent purification system. Anhydrous benzene and dioxane were purchased from Acros Organics. All other solvents were purchased from Fisher Scientific. $Pd(PPh_3)_4$ was purchased from Strem. $Pd(dba)_2$ was purchased from Combi-Blocks. $CDCl_3$, CD_2Cl_2, and C_6D_6 were purchased from Cambridge Isotope Laboratories. Ethyl bromodifluoroacetate, ethyl bromofluoroacetate, and ligands were purchased from Sigma Aldrich, Alpha Aesar, Oakwood Chemical, and Fisher Scientific. Compounds were used as received unless

otherwise noted. 2-bromo-2,2-difluoro-1-morpholinoethan-1-one[28] and 2,2-difluoro-2-iodoacetonitrile[36] were prepared according to literature procedures. NMR spectra were acquired on Bruker 300, 400, 500, or 600 MHz spectrometers at the University of California, Berkeley NMR facility. ^{1}H and ^{13}C chemical shifts were reported relative to residual solvent peaks ($CDCl_3$ = 7.26 ppm for ^{1}H and 77.2 ppm for ^{13}C; CD_2Cl_2 = 5.32 ppm for ^{1}H and 53.8 ppm for ^{13}C; C_6D_6 = 7.16 ppm for ^{1}H and 128.1 ppm for ^{13}C). Elemental analysis was performed by the University of California, Berkeley Microanalytical Laboratory. High-resolution mass spectra were obtained at the University of California, Berkeley Mass Spectrometry Facility with ESI techniques with a Thermo Finnigan LTQ FT instrument.

Synthesis of DPPF-Ligated Palladium Fluoroenolate Bromide Complexes

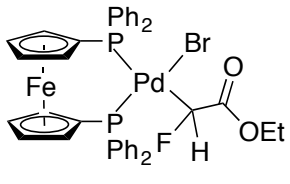
(DPPF)Pd(Br)(CF_2CO_2Et) (1a)



In a nitrogen-filled glovebox, $Pd(PPh_3)_4$ (462 mg, 0.400 mmol, 1.00 equiv) was added to a 20 mL vial equipped with a stir bar. Toluene (15 mL) was added, followed by ethyl bromodifluoroacetate (61.5 μL, 97.4 mg, 0.480 mmol, 1.20 equiv). The reaction was sealed with a Teflon-lined cap and heated at 50 °C for 2.5 h. After 2.5 h, the reaction was allowed to cool to room temperature and DPPF (244 mg, 0.440 mmol, 1.10 equiv) was added. The reaction mixture was stirred at room temperature for 10 h. After 10 h, pentane (5 mL) was added, and the reaction mixture was filtered. The solid was washed with pentane (3x5 mL) and dried under vacuum. The product was isolated as a yellow-orange solid (312 mg, 0.361 mmol, 90% yield). Crystals suitable for x-ray diffraction were grown by vapor diffusion of Et_2O into a solution of 1a in CH_2Cl_2 at 0 °C.

^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.03–7.76 (m, 8H), 7.59–7.33 (m, 12H), 4.44 (s, 2H), 4.41 (s, 2H), 4.26 (s, 2H), 4.15 (q, J = 7.2 Hz, 2H), 3.87–3.77 (m, 2H), 1.30 (t, J = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, CD_2Cl_2) δ -79.3 (app. t, J = 54.2 Hz). ^{31}P NMR (162 MHz, CD_2Cl_2) δ 31.7 (td, J = 55.9, 36.5 Hz), 14.7 (td, J = 52.3, 36.2 Hz). HRMS (ESI+) Calcd for $C_{38}H_{33}F_2FeO_2P_2Pd^+$ $[M\text{-}Br]^+$: 783.0303. Found: 783.0340.

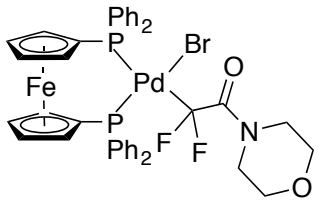
(DPPF)Pd(Br)($CFHCO_2Et$) (1b)



In a nitrogen-filled glovebox, $Pd(PPh_3)_4$ (462 mg, 0.400 mmol, 1.00 equiv) was added to a 20 mL vial equipped with a stir bar. Toluene (15 mL) was added, followed by ethyl bromofluoroacetate (56.7 μL, 88.8 mg, 0.480 mmol, 1.20 equiv). The reaction was sealed with a Teflon-lined cap and heated at 50 °C for 2.5 h. After 2.5 h, the reaction was allowed to cool to room temperature and DPPF (244 mg, 0.440 mmol, 1.10 equiv) was added. The reaction mixture was stirred at room temperature for 22 h. After 22 h, pentane (5 mL) was added, and the reaction mixture was filtered. The solid was washed with pentane (3x5 mL) and dried under vacuum. The product was isolated as a light yellow-orange solid (315 mg, 0.373 mmol, 93% yield).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.92 (m, 4H), 7.69 (m, 4H), 7.48 (m, 8H), 7.33 (m, 4H), 5.01 (ddd, *J* = 51.6, 18.3, 7.4 Hz, 1H), 4.87 (s, 1H), 4.79 (s, 1H), 4.59 (s, 1H), 4.55 (s, 1H), 4.18 (s, 2H), 4.16–3.97 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, CD_2Cl_2) δ -178.9 (ddd, *J* = 50.4, 39.7, 10.7 Hz). ^{31}P NMR (162 MHz, CD_2Cl_2) δ 33.2 (dd, *J* = 33.6, 9.8 Hz), 13.8 (dd, *J* = 38.1, 33.3 Hz). HRMS (ESI+) Calcd for $C_{38}H_{34}FFeO_2P_2Pd^+$ $[M\text{-}Br]^+$: 765.0397. Found: 765.0433.

(DPPF)Pd(Br)($CF_2C(O)N(CH_2CH_2)_2O$) (1c)

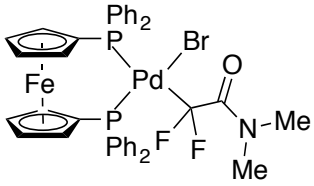


In a nitrogen-filled glovebox, $Pd(PPh_3)_4$ (462 mg, 0.400 mmol, 1.00 equiv) was added to a 20 mL vial equipped with a stir bar. Toluene (15 mL) was added, followed by 2-bromo-2,2-difluoro-1-morpholinoethan-1-one (117 mg, 0.480 mmol, 1.20 equiv). The reaction was sealed with a Teflon-lined cap and heated at 50 °C for 4.5 h. After 4.5 h, the reaction was allowed to cool to room temperature and DPPF (244 mg, 0.440 mmol, 1.10 equiv) was added. The reaction mixture was stirred at room temperature for 16 h. After 16 h, pentane (5 mL) was added, and the reaction mixture was filtered. The solid was washed with pentane (3x5 mL) and dried under vacuum. The product was isolated as a light orange solid (303 mg, 0.334 mmol, 83% yield).

Note: The isolated product contained 6% of $(DPPF)Pd(Br)_2$ as an impurity, but was used without further purification in subsequent transmetallation reactions.

^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95–7.85 (m, 4H), 7.76 (dd, *J* = 12.4, 7.7 Hz, 4H), 7.48–7.37 (m, 8H), 7.29–7.23 (m, 4H), 4.70–4.67 (m, 2H), 4.52–4.49 (m, 2H), 4.18–4.14 (m, 2H), 3.75 (br. s, 2H), 3.60 (br. s, 4H), 3.50 (br. s, 2H), 3.41 (q, *J* = 1.8 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -72.7 (app. t, *J* = 56.6 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.9 (td, *J* = 60.1, 40.2 Hz), 11.9 (td, *J* = 52.8, 40.2 Hz). HRMS (ESI+) Calcd for $C_{40}H_{36}F_2FeNO_2P_2Pd^+$ $[M\text{-}Br]^+$: 824.0568. Found: 824.0603.

(DPPF)Pd(Br)($CF_2C(O)NMe_2$) (1d)

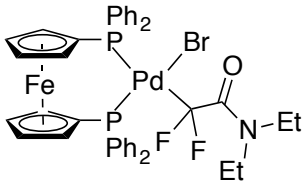


In a nitrogen-filled glovebox, $Pd(PPh_3)_4$ (462 mg, 0.400 mmol, 1.00 equiv) was added to a 20 mL vial equipped with a stir bar. Toluene (15 mL) was added, followed by 2-bromo-*N*,*N*-dimethyl-2,2-difluoroacetamide (97.4 mg, 0.480 mmol, 1.20 equiv). The reaction was sealed with a Teflon-lined cap and heated at 50 °C for 24 h. After 24 h, the reaction was allowed to cool to room temperature and DPPF (244 mg, 0.440 mmol, 1.10 equiv) was added. The reaction mixture was stirred at room temperature for 3.5 h. After 3.5 h, pentane (5 mL) was added, and the reaction mixture was filtered. The solid was washed with pentane (3x5 mL) and dried under vacuum. The product was isolated as a light orange solid (325 mg, 0.377 mmol, 94% yield).

Note: The isolated product contained 14% of $(DPPF)Pd(Br)_2$ as an impurity, but was used without further purification in subsequent transmetallation reactions.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98–7.89 (m, 4H), 7.78 (dd, *J* = 12.4, 7.8 Hz, 4H), 7.50–7.38 (m, 8H), 7.29–7.23 (m, 4H), 4.75 (s, 2H), 4.54 (s, 2H), 4.19 (s, 2H), 3.39 (s, 2H), 3.18 (s, 3H), 2.83 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -71.1 (app. t, *J* = 57.6 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.9 (td, *J* = 61.2, 40.7 Hz), 11.6 (td, *J* = 53.7, 41.0 Hz). HRMS (ESI+) Calcd for $C_{38}H_{34}F_2FeNOP_2Pd^+$ [M-Br]$^+$: 782.0463. Found: 782.0498.

(DPPF)Pd(Br)($CF_2C(O)NEt_2$) (1e)



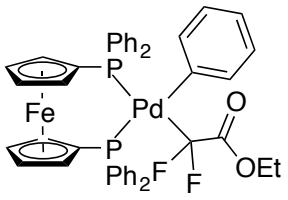
In a nitrogen-filled glovebox, $Pd(PPh_3)_4$ (231 mg, 0.200 mmol, 1.00 equiv) was added to a 20 mL vial equipped with a stir bar. Toluene (7.5 mL) was added, followed by 2-bromo-*N*,*N*-diethyl-2,2-difluoroacetamide (55.2 mg, 0.240 mmol, 1.20 equiv). The reaction was sealed with a Teflon-lined cap and heated at 50 °C for 24 h. After 24 h, the reaction was allowed to cool to room temperature and DPPF (122 mg, 0.220 mmol, 1.10 equiv) was added. The reaction mixture was stirred at room temperature for 3.5 h. After 3.5 h, pentane (5 mL) was added, and the reaction mixture was filtered. The solid was washed with pentane (3x5 mL) and dried under vacuum. The product was isolated as a light orange solid (130 mg, 0.146 mmol, 73% yield).

Note: The isolated product contained 10% of $(DPPF)Pd(Br)_2$ as an impurity, but was used without further purification in subsequent transmetallation reactions.

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.96–7.87 (m, 4H), 7.82–7.74 (m, 4H), 7.55–7.42 (m, 8H), 7.34–7.27 (m, 4H), 4.73 (q, *J* = 2.1 Hz, 2H), 4.52 (t, *J* = 1.9 Hz, 2H), 4.17 (t, *J* = 1.9 Hz, 2H), 3.72 (q, *J* = 7.1 Hz, 2H), 3.47–3.42 (m, 2H), 3.20 (q, *J* = 7.1 Hz, 2H), 1.04 (t, *J* = 7.0 Hz, 6H). ^{19}F NMR (376 MHz, CD_2Cl_2) δ -66.5 (app. t, *J* = 59.4 Hz). ^{31}P NMR (162 MHz, CD_2Cl_2) δ 33.60 (td, *J* = 62.3, 42.4 Hz), 13.71 (td, *J* = 56.0, 42.0 Hz). HRMS (ESI+) Calcd for $C_{40}H_{38}F_2FeNOP_2Pd^+$ [M-Br]$^+$: 810.0775. Found: 810.0814.

Synthesis of DPPF-Ligated Palladium Aryl Fluoroenolate Complexes

(DPPF)Pd(Ph)(CF_2CO_2Et) (2a)

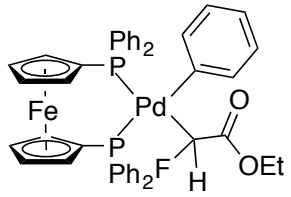


In a nitrogen-filled glovebox, (DPPF)Pd(Br)(CF_2CO_2Et) (**1a**) (173 mg, 0.200 mmol, 1.00 equiv) was added to a 20 mL vial equipped with a stir bar. THF (4 mL) was added, followed by Ph_2Zn (43.9 mg, 0.200 mmol, 1.00 equiv). The reaction was sealed with a Teflon-lined cap and stirred at room temperature for 5 min, during which time the reaction mixture became homogeneous and turned dark orange. After 5 min, the reaction was filtered. The filtrate was layered with pentane (15 mL) and cooled at 0 °C for 18 h. After 18 h, the reaction mixture was decanted, and the solid was triturated with pentane (3x5 mL) and dried under vacuum. The product was isolated as a yellow solid (122 mg, 0.141 mmol, 71% yield).

Crystals suitable for x-ray diffraction were grown by vapor diffusion of pentane into a solution of 2a in 1,2-dichloroethane.

^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.19–8.08 (m, 4H), 7.59–7.51 (m, 6H), 7.38–7.30 (m, 4H), 7.30–7.23 (m, 2H), 7.14–7.06 (m, 4H), 7.05–6.98 (m, 2H), 6.54 (m, 3H), 4.62 (s, 2H), 4.47 (s, 2H), 4.12 (s, 2H), 3.63 (q, *J* = 7.1 Hz, 2H), 3.54 (s, 2H), 1.10 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, CD_2Cl_2) δ -85.0 (dd, *J* = 44.0, 37.1 Hz). ^{31}P NMR (162 MHz, CD_2Cl_2) δ 21.5 (td, *J* = 37.5, 26.7 Hz), 15.1 (td, *J* = 43.9, 26.3 Hz). Anal. Calcd for $C_{44}H_{38}F_2FeO_2P_2Pd$: C, 61.38; H, 4.45. Found: C, 61.19; H, 4.47.

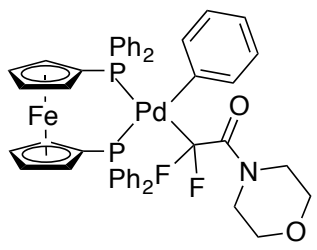
(DPPF)Pd(Ph)(CFHCO$_2$Et) (2b)



In a nitrogen-filled glovebox, (DPPF)Pd(Br)(CFHCO$_2$Et) (**1b**) (169 mg, 0.200 mmol, 1.00 equiv) was added to a 20 mL vial equipped with a stir bar. THF (4 mL) was added, followed by Ph_2Zn (43.9 mg, 0.200 mmol, 1.00 equiv). The reaction was sealed with a Teflon-lined cap and stirred at room temperature for 5 min, during which time the reaction mixture became homogeneous. After 5 min, the reaction was filtered. The filtrate was layered with pentane (15 mL) and cooled at 0 °C for 21 h. After 21 h, the reaction mixture was decanted, and the solid was triturated with pentane (3x5 mL) and dried under vacuum. The product was isolated as a yellow solid (98.4 mg, 0.117 mmol, 58% yield). Crystals suitable for x-ray diffraction were grown by vapor diffusion of Et_2O into a solution of 2b in CH_2Cl_2.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (ddd, *J* = 10.0, 6.5, 2.9 Hz, 2H), 7.95 (ddd, *J* = 9.8, 6.6, 3.0 Hz, 2H), 7.55–7.48 (m, 6H), 7.33–7.24 (m, 6H), 7.19–7.06 (m, 4H), 6.86 (t, *J* = 7.0 Hz, 1H), 6.65–6.59 (m, 1H), 6.54 (q, *J* = 5.4, 3.2 Hz, 2H), 5.62 (ddd, *J* = 51.7, 19.3, 5.7 Hz, 1H), 4.49 (t, *J* = 2.0 Hz, 1H), 4.45 (t, *J* = 2.1 Hz, 1H), 4.43–4.39 (m, 2H), 4.18 (t, *J* = 2.0 Hz, 2H), 3.88–3.87 (m, 1H), 3.87–3.84 (m, 1H), 3.67 (dq, *J* = 10.4, 7.1 Hz, 1H), 3.39 (dq, *J* = 10.5, 7.1 Hz, 1H), 0.92 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, CD_2Cl_2) δ -197.7 (ddd, *J* = 51.7, 19.6, 5.2 Hz). ^{31}P NMR (162 MHz, CD_2Cl_2) δ 22.4 (dd, *J* = 26.5, 19.5 Hz), 19.2 (dd, *J* = 26.6, 5.1 Hz). Anal. Calcd for $C_{44}H_{39}FFeO_2P_2Pd$: C, 62.69; H, 4.66. Found: C, 62.59; H, 4.90.

(DPPF)Pd(Ph)(CF$_2$C(O)N(CH$_2$CH$_2$)$_2$O) (2c)

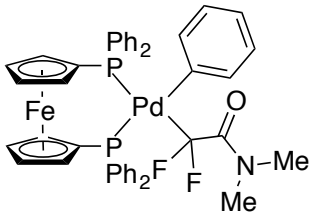


In a nitrogen-filled glovebox, (DPPF)Pd(Br)(C(O)N(CH$_2$CH$_2$)$_2$O) (**1c**) (181 mg, 0.200 mmol, 1.00 equiv) was added to a 20 mL vial equipped with a stir bar. THF (4 mL) was added, followed by Ph_2Zn (43.9 mg, 0.200 mmol, 1.00 equiv). The reaction was sealed with a Teflon-lined cap and stirred at room temperature for 5 min, during which time the reaction mixture became homogeneous. After 5 min, the reaction was filtered. The filtrate was layered with pentane (15 mL) and cooled at 0 °C for 24 h. After 24 h, the reaction mixture was decanted, and the solid was triturated with pentane (3x5 mL) and dried under vacuum. The product was isolated as a yellow solid (149 mg, 0.165

mmol, 83% yield). Crystals suitable for x-ray diffraction were grown by vapor diffusion of Et_2O into a solution of 2c in CH_2Cl_2.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11–8.03 (m, 4H), 7.54–7.46 (m, 6H), 7.37–7.29 (m, 4H), 7.29–7.23 (m, 2H), 7.15–7.07 (m, 4H), 7.02–6.95 (m, 2H), 6.53–6.45 (m, 3H), 4.55–4.49 (m, 2H), 4.42 (s, 2H), 4.09 (s, 2H), 3.73–3.67 (m, 2H), 3.38 (t, J = 4.9 Hz, 2H), 3.13–3.05 (m, 6H).
^{19}F NMR (376 MHz, $CDCl_3$) δ -76.9 (app. t, J = 40.4 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.2 (td, J = 38.8, 25.5 Hz), 13.8 (td, J = 41.8, 25.6 Hz). Anal. Calcd for $C_{46}H_{41}F_2FeNO_2P_2Pd$: C, 61.25; H, 4.58; N, 1.55. Found: C, 60.93; H, 4.96; N, 1.45.

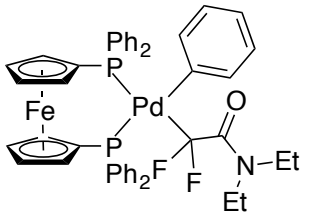
(DPPF)Pd(Ph)($CF_2C(O)NMe_2$) (2d)



In a nitrogen-filled glovebox, (DPPF)Pd(Br)($CF_2C(O)NMe_2$) (**1d**) (173 mg, 0.200 mmol, 1.00 equiv) was added to a 20 mL vial equipped with a stir bar. THF (4 mL) was added, followed by Ph_2Zn (43.9 mg, 0.200 mmol, 1.00 equiv). The reaction was sealed with a Teflon-lined cap and stirred at room temperature for 25 min, during which time the reaction mixture became homogeneous. After 25 min, the reaction was filtered. The filtrate was layered with Et_2O (15 mL) and cooled at 0 °C for 24 h. After 24 h, the reaction mixture was decanted, and the solid was triturated with Et_2O (3x2 mL) and dried under vacuum. The product was isolated as a yellow solid (69.2 mg, 0.0805 mmol, 40% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 (t, J = 8.9 Hz, 4H), 7.53–7.45 (m, 6H), 7.31 (t, J = 9.1 Hz, 4H), 7.28–7.22 (m, 2H), 7.10–7.06 (m, 4H), 7.05–7.01 (m, 2H), 6.52–6.45 (m, 3H), 4.53 (s, 2H), 4.41 (s, 2H), 4.08 (s, 2H), 3.64 (s, 2H), 2.42 (s, 3H), 2.40 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.4 (app. t, J = 42.2 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.4 (td, J = 39.9, 25.8 Hz), 14.3 (td, J = 44.3, 25.7 Hz). Anal. Calcd for $C_{44}H_{39}F_2FeNOP_2Pd$: C, 61.45; H, 4.57; N, 1.63. Found: C, 61.12; H, 4.78; N, 1.77.

(DPPF)Pd(Ph)($CF_2C(O)NEt_2$) (2e)

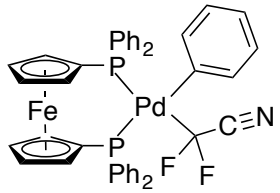


In a nitrogen-filled glovebox, (DPPF)Pd(Br)($CF_2C(O)NEt_2$) (**1e**) (178 mg, 0.200 mmol, 1.00 equiv), $PhB(OH)_2$ (97.5 mg, 0.800 mmol, 4.00 equiv), and K_2CO_3 (221 mg, 1.60 mmol, 8.00 equiv) were added to a 20 mL vial equipped with a stir bar. THF (5 mL) was added, and the reaction was sealed with a Teflon-lined cap and heated at 50 °C for 4.5 h. The reaction mixture was concentrated *in vacuo*, and the crude reside was purified under air by column chromatography with 2:1 hexanes/EtOAc as eluent. The product was further purified by recrystallization from THF/Et_2O. The product was isolated as a yellow solid (69.5 mg, 0.0733 mmol, 37% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11–8.06 (m, 4H), 7.50–7.45 (m, 6H), 7.35–7.30 (m, 4H), 7.25–7.22 (m, 2H), 7.08 (td, J = 7.8, 2.1 Hz, 4H), 7.03–6.99 (m, 2H), 6.47–6.43 (m, 3H), 4.56–4.52 (m, 2H), 4.40 (t, J = 1.9 Hz, 2H), 4.08 (t, J = 1.9 Hz, 2H), 3.67–3.61 (m, 2H), 2.98 (q, J = 7.2 Hz, 2H),

2.87 (q, J = 7.1 Hz, 2H), 0.81 (t, J = 7.1 Hz, 3H), 0.67 (t, J = 7.0 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.6 (app. t, J = 42.0 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.0 (td, J = 40.0, 25.6 Hz), 13.7 (td, J = 44.0, 25.6 Hz). Anal. Calcd for $C_{46}H_{43}F_2FeNOP_2Pd$: C, 62.21; H, 4.88; N, 1.58. Found: C, 62.52; H, 4.80, N, 1.65.

(DPPF)Pd(Ph)(CF_2CN) (2f)

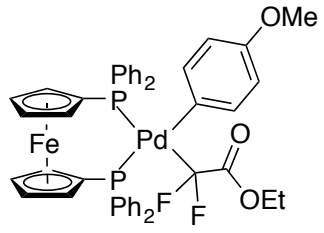


Step 1: In a nitrogen-filled glovebox, $Pd(PPh_3)_4$ (462 mg, 0.400 mmol, 1.00 equiv) was added to a 20 mL vial equipped with a stir bar. Toluene (15 mL) was added, followed by 2,2-difluoro-2-iodoacetonitrile (97.4 mg, 0.480 mmol, 1.20 equiv). The reaction was sealed with a Teflon-lined cap and stirred at room temperature for 2 h. After 2 h, the solvent was removed *in vacuo*. To the crude residue was added Et_2O (10 mL), and the resulting mixture was filtered. The solid was washed with Et_2O (3 mL) and pentane (3x3 mL). The bright yellow solid (280 mg) consisted of a 1.00:0.29 mixture of $(PPh_3)_2Pd(I)(CF_2CN)$ and $(PPh_3)_2PdI_2$, and was used without further purification for the synthesis of (DPPF)Pd(Ph)(CF_2CN) (*vide infra*).

Step 2: In a nitrogen-filled glovebox, $(PPh_3)_2Pd(I)(CF_2CN)$ (125 mg, 0.150 mmol, 1.00 equiv) and DPPF (91.5 mg, 0.165 mmol, 1.10 equiv) were added to a 20 mL vial equipped with a stir bar. THF (3 mL) was added, followed by Ph_2Zn (33.0 mg, 0.150 mmol, 1.00 equiv). The reaction was sealed with a Teflon-lined cap and stirred at room temperature for 4.5 h. After 4.5 h, the reaction was filtered. The filtrate was layered with pentane (3 mL) and cooled at 0 °C for 24 h. After 24 h, the reaction mixture was decanted, and the solid was triturated with pentane (5x1 mL) and dried under vacuum. The product was isolated as a yellow solid (71.6 mg, 0.0880 mmol, 59% yield). Crystals suitable for x-ray diffraction were grown by layering a solution of **2f** in THF with pentane.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.98–7.91 (m, 4H), 7.57–7.50 (m, 6H), 7.32–7.24 (m, 6H), 7.18–7.14 (m, 2H), 7.09 (dt, J = 7.8, 3.9 Hz, 4H), 6.63–6.57 (m, 3H), 4.59 (s, 2H), 4.47 (s, 2H), 4.11 (s, 2H), 3.53 (s, 2H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.2 (td, J = 32.5, 27.8 Hz), 15.3 (td, J = 35.3, 27.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -79.1 (t, J = 34.0 Hz). Anal. Calcd for $C_{42}H_{33}F_2FeNP_2Pd$: C, 61.98; H, 4.09; N, 1.72. Found: C, 62.01; H, 4.09; N, 1.92.

(DPPF)Pd((4-OMe)C_6H_4)(CF_2CO_2Et) (2g)

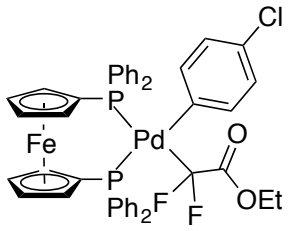


In a nitrogen-filled glovebox, (DPPF)Pd(Br)(CF_2CO_2Et) (**1a**) (104 mg, 0.120 mmol, 1.00 equiv), 4-methoxyphenylboronic acid (73.0 mg, 0.480 mmol, 4.00 equiv), and potassium carbonate (132 mg, 0.960 mmol, 8.00 equiv) were added to a 20 mL vial equipped with a stir bar. THF (5 mL) was added, and the reaction was sealed with a Teflon-lined cap and heated at 40 °C for 25 h. After 25 h, the reaction was allowed to cool to room temperature and filtered through a pad of Celite, eluting with THF (5 mL). The filtrate was concentrated to ~2 mL, and Et_2O (10 mL) was added. The mixture was filtered, and the solid was washed with Et_2O (3x2 mL) and pentane (3x2

mL) and dried under vacuum. The product was isolated as a yellow solid (77.5 mg, 0.0870 mmol, 72% yield).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.14–8.04 (m, 4H), 7.58–7.47 (m, 6H), 7.35–7.21 (m, 6H), 7.14–7.04 (m, 4H), 6.82–6.74 (m, 2H), 6.22–6.13 (m, 2H), 4.57 (q, *J* = 2.1 Hz, 2H), 4.43 (t, *J* = 1.9 Hz, 2H), 4.09 (t, *J* = 1.9 Hz, 2H), 3.60 (q, *J* = 7.2 Hz, 2H), 3.53 (s, 3H), 1.06 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, CD_2Cl_2) δ -85.1 (dd, *J* = 43.7, 38.1 Hz). ^{31}P NMR (162 MHz, CD_2Cl_2) δ 21.5 (td, *J* = 38.5, 26.1 Hz), 15.4 (td, *J* = 44.6, 26.2 Hz). Anal. Calcd for $C_{45}H_{40}F_2FeO_3P_2Pd$: C, 60.66; H, 4.53. Found: C, 60.56; H, 4.83.

(DPPF)Pd((4-Cl)C$_6$H$_4$)(CF$_2$CO$_2$Et) (2h)



In a nitrogen-filled glovebox, (DPPF)Pd(Br)(CF_2CO_2Et) (**1a**) (173 mg, 0.200 mmol, 1.00 equiv), 4-chlorophenylboronic acid (125 mg, 0.800 mmol, 4.00 equiv), and potassium carbonate (205 mg, 1.60 mmol, 8.00 equiv) were added to a 20 mL vial equipped with a stir bar. THF (5 mL) was added, and the reaction was sealed with a Teflon-lined cap and heated at 65 °C for 19 h. After 19 h, the reaction was allowed to cool to room temperature and filtered through a pad of Celite, eluting with THF (2 mL). The filtrate was concentrated to ~2 mL and layered with Et_2O (12 mL) and pentane (4 mL) and cooled at 0 °C overnight. The mixture was filtered, and the solid was washed with Et_2O (3 mL) and pentane (3 mL) and dried under vacuum. The product was isolated as a yellow solid (60.1 mg, 0.0671 mmol, 34% yield).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.17–8.07 (m, 4H), 7.63–7.53 (m, 6H), 7.40–7.29 (m, 6H), 7.20–7.12 (m, 4H), 6.94 (dd, *J* = 8.0, 6.1 Hz, 2H), 6.55 (dd, *J* = 8.3, 1.9 Hz, 2H), 4.64 (q, *J* = 2.1 Hz, 2H), 4.51 (t, *J* = 1.9 Hz, 2H), 4.16–4.14 (m, 2H), 3.66 (q, *J* = 7.1 Hz, 2H), 3.53 (q, *J* = 1.9 Hz, 2H), 1.11 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, CD_2Cl_2) δ -85.5 (dd, *J* = 43.8, 38.0 Hz). ^{31}P NMR (162 MHz, CD_2Cl_2) δ 20.7 (td, *J* = 38.2, 27.5 Hz), 15.2 (td, *J* = 43.6, 27.1 Hz). Anal. Calcd for $C_{44}H_{37}ClF_2FeO_2P_2Pd$: C, 59.02; H, 4.17. Found: C, 58.97; H, 4.52.

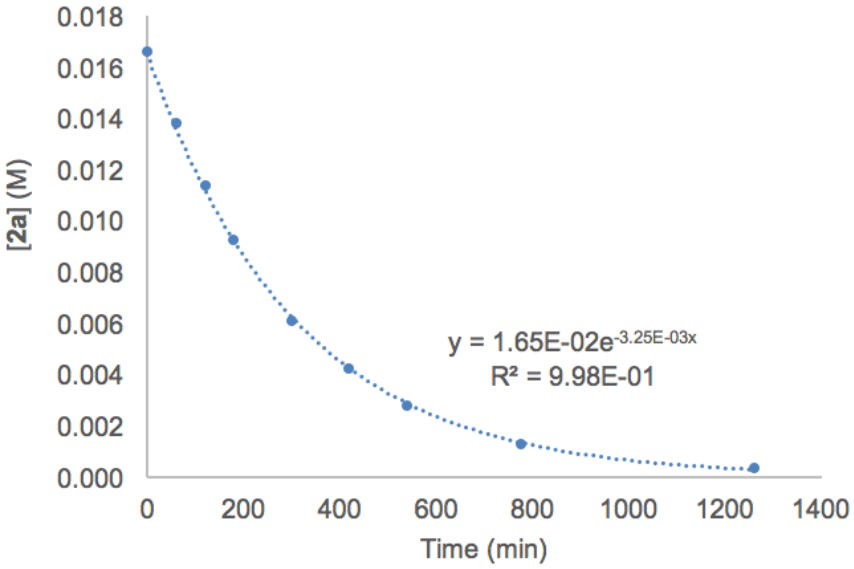
Procedure for Kinetic Analysis of Reductive Elimination

Reductive Elimination of Pd-Fluoroenolate Complexes (Table 1)

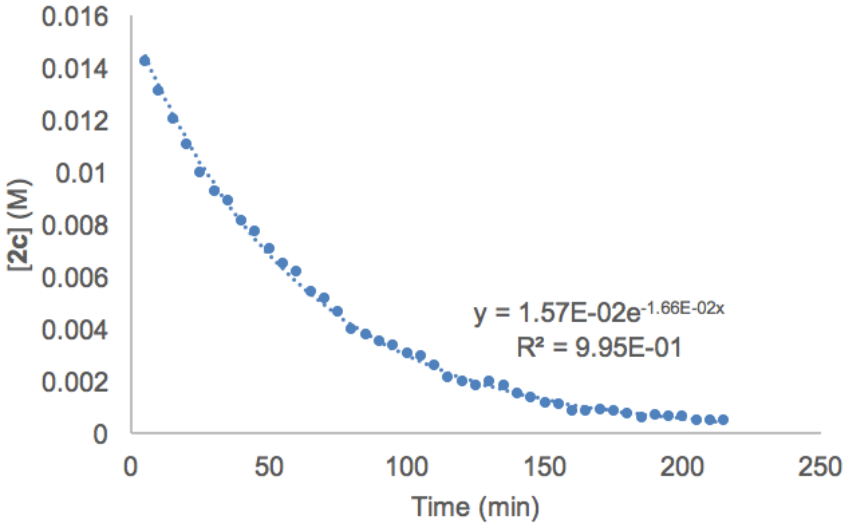
In a nitrogen-filled glovebox, the Pd complex (2a-h) (0.0100 mmol, 1.00 equiv), DPPF (5.5 mg, 0.0100 mmol, 1.00 equiv), and a stock solution of 1-fluoro-4-(trifluoromethyl)benzene (0.100 M in dioxane, 100 μL, 0.0100 mmol, 1.00 equiv) were added to a 4 mL vial. Dioxane (500 μL) was added, and the reaction mixture was transferred to a J-Young NMR tube. The tube was then either inserted into a 500 MHz NMR probe pre-heated at the indicated temperature (complexes **2b-e**, entries 2-5) or heated in a temperature controlled oil bath (complexes **2a** and **2f-h**, entries 1 and 6-8). The concentration of the Pd complex was monitored by ^{19}F NMR spectroscopy over >3 half-lives. The spectra were integrated and fit to an exponential decay to determine the rate constant for reductive elimination, from which the half-life was determined. The yield of the

reductive elimination product was determined by ^{19}F NMR spectroscopy after heating for 24 h (unless indicated otherwise in Table 1).

Representative plot (decay of 2a vs. time):

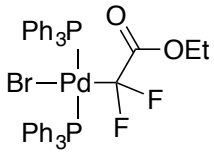


Representative plot (decay of 2c vs. time):



Synthesis of $L_nPd(Br)(CF_2CO_2Et)$ Complexes

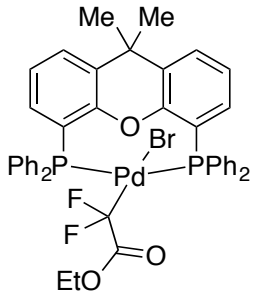
$(PPh_3)_2Pd(Br)(CF_2CO_2Et)$ (3a)



In a nitrogen-filled glovebox, $Pd(PPh_3)_4$ (578 mg, 0.500 mmol, 1.00 equiv) and ethyl bromodifluoroacetate (77.1 μL, 122 mg, 0.600 mmol, 1.20 equiv) were added to a 20 mL vial equipped with a stir bar. Benzene (10 mL) was added, and the reaction was sealed with a Teflon-lined cap and heated at 50 °C for 6 h. After 6 h, the reaction was allowed to cool to room temperature and the solvent was evaporated *in vacuo*. To the crude residue was added Et_2O (20 mL). The mixture was filtered, and the solid was washed with Et_2O (3x5 mL) and dried under vacuum. The product was isolated as a pale yellow solid (376 mg, 0.440 mmol, 88% yield).

^{1}H NMR (400 MHz, C_6D_6) δ 8.08–8.00 (m, 12H), 7.10–6.94 (m, 18H), 3.44 (q, J = 7.1 Hz, 2H), 0.70 (t, J = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, C_6D_6) δ -60.9 (t, J = 41.3 Hz). ^{31}P NMR (162 MHz, C_6D_6) δ 25.6 (t, J = 41.3 Hz). Anal. Calcd for $C_{40}H_{35}BrF_2O_2P_2Pd$: C, 57.61; H, 4.23. Found: C, 57.70; H, 4.28.

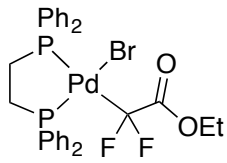
(Xantphos)Pd(Br)(CF_2CO_2Et) (4a)



In a nitrogen-filled glovebox, $Pd(dba)_2$ (575 mg, 1.00 mmol, 1.00 equiv) and Xantphos (579 mg, 1.00 mmol, 1.00 equiv) were added to a 20 mL vial equipped with a stir bar. Benzene (10 mL) was added, followed by ethyl bromodifluoroacetate (154 μL, 244 mg, 1.20 mmol, 1.20 equiv). The reaction was sealed with a Teflon-lined cap and heated at 80 °C for 23 h. After 23 h, the reaction was allowed to cool to room temperature and filtered. The solid was washed with pentane (5 mL) and recrystallized from benzene. The product was isolated as a yellow solid (586 mg, 0.660 mmol, 66% yield). Crystals suitable for x-ray diffraction were grown by vapor diffusion of Et_2O into a solution of 4a in CH_2Cl_2 at 0 °C.

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.86–7.77 (m, 8H), 7.61 (dd, J = 7.7, 1.6 Hz, 2H), 7.51–7.44 (m, 4H), 7.43 – 7.38 (m, 8H), 7.28–7.20 (m, 2H), 7.15 (t, J = 7.7 Hz, 2H), 3.68 (q, J = 7.2 Hz, 2H), 1.74 (s, 6H), 1.00 (t, J = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, CD_2Cl_2) δ -68.0 (t, J = 48.7 Hz). ^{31}P NMR (162 MHz, CD_2Cl_2) δ 12.5 (t, J = 48.6 Hz). HRMS (ESI+) Calcd for $C_{43}H_{37}F_2O_3P_2Pd^+$ [M-Br]$^+$: 807.1215. Found: 807.1246.

(DPPE)Pd(Br)(CF_2CO_2Et) (5a)



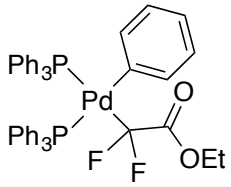
In a nitrogen-filled glovebox, $Pd(dba)_2$ (288 mg, 0.500 mmol, 1.00 equiv) and DPPE (209 mg, 0.525 mmol, 1.05 equiv) were added to a 20 mL vial equipped with a stir bar. Benzene (10 mL) was added, followed by ethyl bromodifluoroacetate (77.1 μL, 122 mg, 0.600 mmol, 1.20 equiv). The

reaction was sealed with a Teflon-lined cap and heated at 50 °C for 1.5 h. After 1.5 h, the reaction was allowed to cool to room temperature and filtered through Celite. The solvent was evaporated *in vacuo* from the filtrate. The crude residue was dissolved in benzene (2 mL) and precipitated with Et_2O (10 mL). The mixture was filtered, and the solid was washed with Et_2O (3x5 mL) and dried under vacuum. The product was isolated as an off-white solid (252 mg, 0.356 mmol, 71% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93–7.80 (m, 8H), 7.62–7.43 (m, 12H), 4.30 (q, J = 7.2 Hz, 2H), 2.52–2.30 (m, 2H), 2.30–2.15 (m, 2H), 1.36 (t, J = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -79.0 (dd, J = 49.7, 46.3 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 56.5 (td, J = 49.8, 30.0 Hz), 38.39 (td, J = 46.3, 30.0 Hz). Anal. Calcd for $C_{30}H_{29}BrF_2O_2P_2Pd$: C, 50.91; H, 4.13. Found: C, 51.23; H, 4.02.

Synthesis of $L_nPd(Ph)(CF_2CO_2Et)$ Complexes

$(PPh_3)_2Pd(Ph)(CF_2CO_2Et)$ (3b)

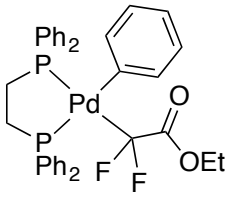


In a nitrogen-filled glovebox, $(PPh_3)_2Pd(Br)(CF_2CO_2Et)$ (**3a**) (125 mg, 0.150 mmol, 1.00 equiv) was added to a 4 mL vial equipped with a stir bar. THF (1 mL) was added, followed by the dropwise addition of a solution of Ph_2Zn (16.6 mg, 0.0758 mmol, 0.505 equiv) in 1 mL THF. The reaction was sealed with a Teflon-lined cap and stirred at room temperature for 30 min. After 30 min, the reaction was filtered. The filtrate was layered with pentane (8 mL) and cooled at 0 °C for 24 h. After 24 h, the reaction mixture was decanted, and the solid was triturated with pentane (3x5 mL) and dried under vacuum. The product was isolated as a light yellow solid (108 mg, 0.130 mmol, 87% yield).

Note: At earlier time points, a mixture of *cis*- and *trans*-PPh_3 complexes was observed by ^{31}P NMR spectroscopy of an aliquot of the crude reaction mixture. However, the only the *cis*-PPh_3 complex was isolated.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, J = 10.3, 7.8 Hz, 6H), 7.28–7.19 (m, 12H), 7.19–7.12 (m, 8H), 7.03 (td, J = 7.8, 2.1 Hz, 6H), 6.55 (dt, J = 7.7, 4.0 Hz, 2H), 6.49 (t, J = 7.2 Hz, 1H), 3.58 (q, J = 7.1 Hz, 2H), 0.96 (t, J = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -85.2 (dd, J = 41.8, 37.0 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.7 (td, J = 37.0, 23.9 Hz), 21.8 (td, J = 42.0, 23.9 Hz). Anal. Calcd for $C_{46}H_{40}F_2O_2P_2Pd$: C, 66.47; H, 4.85. Found: C: 65.78; H, 4.98.

(DPPE)Pd(Ph)(CF_2CO_2Et) (5b)



In a nitrogen-filled glovebox, (DPPE)Pd(Br)(CF_2CO_2Et) (**5a**) (70.8 mg, 0.100 mmol, 1.00 equiv) was added to a 4 mL vial equipped with a stir bar. THF (0.75 mL) was added, followed by the dropwise addition of a solution of Ph_2Zn (16.5 mg, 0.0750 mmol, 0.750 equiv) in 0.75 mL THF. The reaction was sealed with a Teflon-lined cap and stirred at room temperature for 2 h. After 2 h, the reaction was filtered. The filtrate was reduced in volume to 1 mL *in vacuo*, layered with pentane (5 mL), and cooled at 0 °C for 24 h. After 24 h, the reaction mixture was decanted, and the solid was triturated with pentane (3x5 mL) and dried under vacuum. The product was isolated as an off-white solid (48.9 mg, 0.0693 mmol, 69% yield).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.92–7.83 (m, 4H), 7.56–7.47 (m, 6H), 7.43–7.37 (m, 2H), 7.33–7.21 (m, 8H), 7.11–7.03 (m, 2H), 6.79–6.70 (m, 3H), 3.63 (q, J = 7.1 Hz, 2H), 2.37–2.13 (m, 4H), 1.06 (t, J = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, CD_2Cl_2) δ -83.9 (dd, J = 45.0, 37.2 Hz). ^{31}P NMR (162 MHz, CD_2Cl_2) δ 38.9 (td, J = 44.9, 14.8 Hz), 38.5 (td, J = 37.3, 14.8 Hz). Anal. Calcd for $C_{36}H_{34}F_2O_2P_2Pd$: C, 61.33; H, 4.86. Found: C, 60.99; H, 5.09.

Reductive Elimination from Arylpalladium Difluoroester Complexes

General Procedure (Table 2):

In a nitrogen-filled glovebox, the Pd complex (0.0200 mmol, 1.00 equiv) and dioxane (0.5 mL) were added to a 4 mL vial equipped with a stir bar. The reaction was sealed with a Teflon-lined cap and heated at the indicated temperature for 24 h. After 24 h, the reaction was allowed to cool to room temperature, and fluorobenzene (3.8 mg, 3.8 μL, 0.0400 mmol, 2.00 equiv) was added as an internal standard. The yield of ethyl phenyldifluoroacetate was determined by ^{19}F NMR spectroscopy.

Procedure with Xantphos as Ligand (Table 2, entry 3):

In a nitrogen-filled glovebox, (Xantphos)Pd(Br)(CF_2CO_2Et) (**4a**) (17.8 mg, 0.0200 mmol, 1.00 equiv) and THF (0.5 mL) were added to a 4 mL vial equipped with a stir bar. To this vial was added a solution of Ph_2Zn (2.3 mg, 0.0105 mmol, 0.525 equiv) in THF (0.5 mL). The reaction was sealed with a Teflon-lined cap and stirred at room temperature for 30 min. After 30 min, fluorobenzene (3.8 mg, 3.8 μL, 0.0400 mmol, 2.00 equiv) was added as an internal standard, and the yield of ethyl phenyldifluoroacetate was determined by ^{19}F NMR spectroscopy. Putative intermediate (Xantphos)Pd(Ph)(CF_2CO_2Et) (**4b**) was detected by ^{19}F NMR spectroscopy of the crude reaction mixture after 10 minutes (see below). ^{19}F NMR (376 MHz, THF) δ -78.8 (t, J = 42.6 Hz).

Crystallographic Data

Crystallographic Data for (DPPF)Pd(Br)(CF_2CO_2Et) (1a)

An orange plate 0.080 x 0.070 x 0.040 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K. Crystal-to-detector distance was 50 mm and exposure time was 10 seconds per frame using a scan width of 1.0°. Data collection was 99.9% complete to 25.000° in θ. A total of 71579 reflections were collected covering the indices, -13<=*h*<=13, -37<=*k*<=38, -13<=*l*<=13. 6667 reflections were found to be symmetry independent, with an R_{int} of 0.0346. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21/n (No. 14). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT-2014) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms with the exception of the bromine and difluoroester moieties were refined anisotropically by full-matrix least-squares (SHELXL-2014). The bromine and difluoroester moieties were refined isotropically due to positional disorder. All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

Table S3.1 Crystal data and structure refinement for (DPPF)Pd(Br)(CF_2CO_2Et) (**1a**)

Empirical formula	$C_{39}H_{35}BrCl_2F_2FeO_2P_2Pd$	
Formula weight	948.67	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 10.9180(6) Å	α= 90°.
	b = 32.2289(19) Å	β= 113.1060(10)°.
	c = 11.2271(7) Å	γ = 90°.
Volume	3633.6(4) $Å^3$	
Z	4	
Density (calculated)	1.734 Mg/m^3	
Absorption coefficient	2.275 mm^{-1}	
F(000)	1896	
Crystal size	0.080 x 0.070 x 0.040 mm^3	
Theta range for data collection	1.264 to 25.367°.	
Index ranges	-13<=h<=13, -37<=k<=38, -13<=l<=13	
Reflections collected	71579	

Independent reflections	6667 [R(int) = 0.0346]
Completeness to theta = 25.000°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.928 and 0.724
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6667 / 3 / 432
Goodness-of-fit on F^2	1.064
Final R indices [I>2sigma(I)]	R1 = 0.0659, wR2 = 0.1664
R indices (all data)	R1 = 0.0695, wR2 = 0.1690
Extinction coefficient	n/a
Largest diff. peak and hole	5.024 and -2.379 e.$Å^{-3}$

Crystallographic Data for (DPPF)Pd(Ph)(CF_2CO_2Et) (2a)

A yellow needle 0.060 x 0.030 x 0.020 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K. Crystal-to-detector distance was 40 mm and exposure time was 10 seconds per frame using a scan width of 1.0°. Data collection was 99.9% complete to 25.000° in θ. A total of 142182 reflections were collected covering the indices, -19<=*h*<=19, -19<=*k*<=19, -23<=*l*<=23. 8421 reflections were found to be symmetry independent, with an R_{int} of 0.0898. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21/n (No. 14). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT-2014) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

Table S3.2 Crystal data and structure refinement for (DPPF)Pd(Ph)(CF_2CO_2Et) (**2a**)

Empirical formula	$C_{46}H_{42}Cl_2F_2FeO_2P_2Pd$	
Formula weight	959.88	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 15.9427(5) Å	α= 90°.
	b = 16.2365(6) Å	β= 114.0630(10)°.

	c = 19.4196(8) Å γ = 90°.
Volume	4590.0(3) $Å^3$
Z	4
Density (calculated)	1.389 Mg/m^3
Absorption coefficient	0.937 mm^{-1}
F(000)	1952
Crystal size	0.060 x 0.030 x 0.020 mm^3
Theta range for data collection	1.402 to 25.371°.
Index ranges	-19<=h<=19, -19<=k<=19, -23<=l<=23
Reflections collected	142182
Independent reflections	8421 [R(int) = 0.0898]
Completeness to theta = 25.000°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.928 and 0.772
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8421 / 0 / 506
Goodness-of-fit on F^2	1.026
Final R indices [I>2sigma(I)]	R1 = 0.0398, wR2 = 0.0841
R indices (all data)	R1 = 0.0687, wR2 = 0.0954
Extinction coefficient	n/a
Largest diff. peak and hole	1.057 and -1.002 $e.Å^{-3}$

Crystallographic Data for (DPPF)Pd(Ph)($CFHCO_2Et$) (2b)

A yellow plate 0.060 x 0.050 x 0.030 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K. Crystal-to-detector distance was 40 mm and exposure time was 10 seconds per frame using a scan width of 1.0°. Data collection was 100.0% complete to 25.000° in θ. A total of 100894 reflections were collected covering the indices, -50<=*h*<=52, -13<=*k*<=13, -20<=*l*<=20. 7079 reflections were found to be symmetry independent, with an R_{int} of 0.0383. Indexing and unit cell refinement indicated a C-centered, monoclinic lattice. The space group was found to be C 2/c (No. 15). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT-2014) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

Table S3.3 Crystal data and structure refinement for (DPPF)Pd(Ph)($CFHCO_2Et$) (**2b**)

Empirical formula	$C_{92}H_{88}F_2Fe_2O_5P_4Pd_2$	
Formula weight	1760.00	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C 2/c	
Unit cell dimensions	a = 43.7168(17) Å	α= 90°.
	b = 11.0409(4) Å	β= 112.599(2)°.
	c = 17.2876(7) Å	γ = 90°.
Volume	7703.6(5) $Å^3$	
Z	4	
Density (calculated)	1.518 Mg/m^3	
Absorption coefficient	0.972 mm^{-1}	
F(000)	3608	
Crystal size	0.060 x 0.050 x 0.030 mm^3	
Theta range for data collection	1.009 to 25.395°.	
Index ranges	-50<=h<=52, -13<=k<=13, -20<=l<=20	
Reflections collected	100894	
Independent reflections	7079 [R(int) = 0.0383]	
Completeness to theta = 25.000°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.928 and 0.861	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7079 / 0 / 495	
Goodness-of-fit on F^2	1.089	
Final R indices [I>2sigma(I)]	R1 = 0.0300, wR2 = 0.0658	
R indices (all data)	R1 = 0.0338, wR2 = 0.0681	
Extinction coefficient	n/a	
Largest diff. peak and hole	1.274 and -0.490 $e.Å^{-3}$	

Crystallographic Data for (DPPF)Pd(Ph)($CF_2C(O)N(CH_2CH_2)_2O$) (2c)

A yellow prism 0.030 x 0.030 x 0.020 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K. Crystal-to-detector distance was 40 mm and exposure time was 10 seconds per frame using a scan width of 0.5°. Data collection was 95.3% complete to 25.000° in θ. A total of 11745 reflections were collected covering the indices, -13<=*h*<=13, -15<=*k*<=15, -17<=*l*<=17. 11745 reflections were found to be symmetry independent, with an R_{int} of 0.0421. Indexing and unit cell refinement indicated a primitive, triclinic lattice. The space group was found to be P -1 (No. 2). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT-2014) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

Table S3.4 Crystal data and structure refinement for (DPPF)Pd(Ph)($CF_2C(O)N(CH_2CH_2)_2O$) (**2c**)

Empirical formula	$C_{46}H_{41}F_2FeNO_2P_2Pd$	
Formula weight	901.99	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 10.9331(7) Å	α= 106.347(3)°.
	b = 12.8305(8) Å	β= 90.868(3)°.
	c = 14.1647(8) Å	γ = 97.639(4)°.
Volume	1886.8(2) $Å^3$	
Z	2	
Density (calculated)	1.588 Mg/m^3	
Absorption coefficient	0.998 mm^{-1}	
F(000)	920	
Crystal size	0.030 x 0.030 x 0.020 mm^3	
Theta range for data collection	1.500 to 25.394°.	
Index ranges	-13<=h<=13, -15<=k<=15, -17<=l<=17	
Reflections collected	11745	
Independent reflections	11745 [R(int) = ?]	
Completeness to theta = 25.000°	95.3 %	

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.928 and 0.805
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	11745 / 0 / 498
Goodness-of-fit on F^2	1.039
Final R indices [I>2sigma(I)]	R1 = 0.0391, wR2 = 0.0980
R indices (all data)	R1 = 0.0511, wR2 = 0.1048
Extinction coefficient	n/a
Largest diff. peak and hole	1.077 and -0.513 e.$Å^{-3}$

Crystallographic Data for (DPPF)Pd(Ph)(CF_2CN) (2f)

A yellow plate 0.050 x 0.050 x 0.030 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K. Crystal-to-detector distance was 40 mm and exposure time was 10 seconds per frame using a scan width of 1.0°. Data collection was 99.7% complete to 25.000° in θ. A total of 97557 reflections were collected covering the indices, -13<=*h*<=13, -21<=*k*<=21, -24<=*l*<=23. 13821 reflections were found to be symmetry independent, with an R_{int} of 0.0388. Indexing and unit cell refinement indicated a primitive, triclinic lattice. The space group was found to be P -1 (No. 2). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT-2014) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

Table S3.5 Crystal data and structure refinement for (DPPF)Pd(Ph)(CF_2CN) (**2f**)

Empirical formula	C89 H78 F4 Fe2 N2 P4 Pd2	
Formula weight	1699.91	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 11.2279(4) Å	α= 99.6640(10)°.
	b = 18.1228(6) Å	β= 103.879(2)°.
	c = 19.9202(7) Å	γ = 100.6330(10)°.
Volume	3770.7(2) $Å^3$	

Z	2
Density (calculated)	1.497 Mg/m^3
Absorption coefficient	0.990 mm^{-1}
F(000)	1732
Crystal size	0.050 x 0.050 x 0.030 mm^3
Theta range for data collection	1.080 to 25.433°.
Index ranges	-13<=h<=13, -21<=k<=21, -24<=l<=23
Reflections collected	97557
Independent reflections	13821 [R(int) = 0.0388]
Completeness to theta = 25.000°	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.928 and 0.861
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	13821 / 0 / 930
Goodness-of-fit on F^2	1.041
Final R indices [I>2sigma(I)]	R1 = 0.0374, wR2 = 0.0852
R indices (all data)	R1 = 0.0538, wR2 = 0.0944
Extinction coefficient	n/a
Largest diff. peak and hole	1.119 and -0.799 $e.Å^{-3}$

Crystallographic Data for (Xantphos)Pd(Br)(CF_2CO_2Et) (4a)

An orange prism 0.080 x 0.060 x 0.040 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K. Crystal-to-detector distance was 50 mm and exposure time was 10 seconds per frame using a scan width of 2.0°. Data collection was 100.0% complete to 25.000° in θ. A total of 92271 reflections were collected covering the indices, -21<=*h*<=21, -12<=*k*<=12, -27<=*l*<=27. 7584 reflections were found to be symmetry independent, with an R_{int} of 0.0395. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21/c (No. 14). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT-2014) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

Table S3.6 Crystal data and structure refinement for (Xantphos)Pd(Br)(CF_2CO_2Et) (**4a**)

Empirical formula	$C_{43}H_{37}BrF_2O_3P_2Pd$	
Formula weight	887.97	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 18.0490(10) Å	α= 90°.
	b = 10.5004(6) Å	β= 109.9770(10)°.
	c = 23.2270(12) Å	γ = 90°.
Volume	4137.1(4) $Å^3$	
Z	4	
Density (calculated)	1.426 Mg/m^3	
Absorption coefficient	1.537 mm^{-1}	
F(000)	1792	
Crystal size	0.080 x 0.060 x 0.040 mm^3	
Theta range for data collection	1.842 to 25.365°.	
Index ranges	-21<=h<=21, -12<=k<=12, -27<=l<=27	
Reflections collected	92271	
Independent reflections	7584 [R(int) = 0.0395]	
Completeness to theta = 25.000°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.862 and 0.788	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7584 / 0 / 472	
Goodness-of-fit on F^2	1.090	
Final R indices [I>2sigma(I)]	R1 = 0.0298, wR2 = 0.0681	
R indices (all data)	R1 = 0.0367, wR2 = 0.0724	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.969 and -0.539 e.$Å^{-3}$	

3.5 References

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Chapter 4

Copper-Mediated Synthesis of Aryldifluoronitriles

4.1 Introduction

The incorporation of fluorine atoms is a common strategy for improving the physical properties and biological activity of agrochemicals and drug candidates (see Chapter 1). Aryl fluorides and trifluoromethylarenes are the most common fluorinated motifs present in pharmaceuticals, but there has been increasing interest in the incorporation of other types of fluorine-containing functional groups to tune molecular properties such as metabolic stability, lipophilicity, and binding specificity for an enzymatic target.

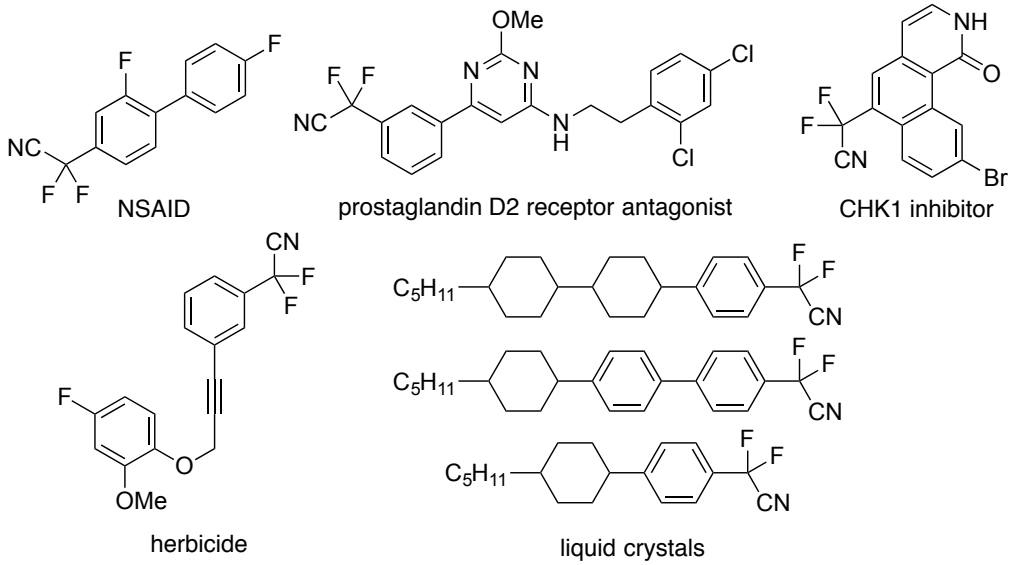


Figure 4.1 Compounds containing aryldifluoronitrile groups.

Although relatively few compounds containing aryldifluoronitrile motifs have been reported, several possess desirable biological or physical properties. For example, compounds containing aryldifluoronitrile groups have been studied as NSAIDs,[1] prostaglandin D2 receptor antagonists,[2] CHK1 inhibitors,[3] herbicides,[4] and liquid crystals (Figure 4.1).[5]

The difluoronitrile group is a relatively small, highly polar, and strongly electron-withdrawing group. In biologically active compounds, nitriles often serve as hydrogen bond acceptors.[6-7] Several crystal structures show hydrogen bonding interactions between the nitrogen atom of a bioactive nitrile and an amino acid residue or water molecule present in the binding pocket of an enzymatic target.[8-9] The incorporation of fluorine alpha to a nitrile substituent would allow the strength of these hydrogen-bonding interactions to be tuned, as difluoronitriles are likely to be much weaker hydrogen-bond acceptors than their non-fluorinated analogs (Figure 4.2). In addition, incorporating an electron-withdrawing difluoronitrile group onto an aromatic ring would deactivate the ring toward metabolic oxidation, and could also enable new polar interactions, even in sterically congested environments.

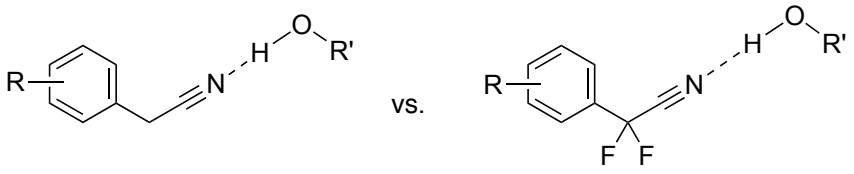
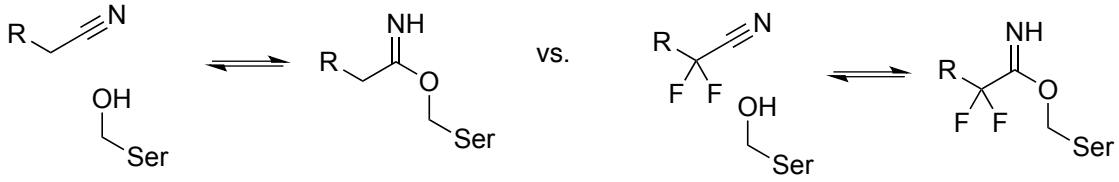


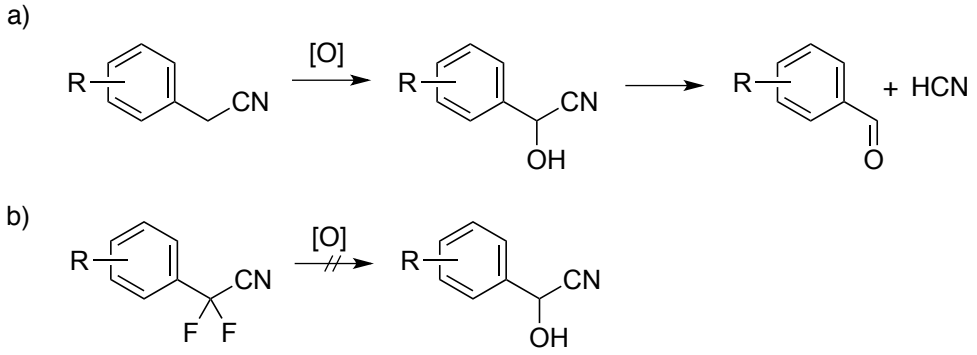
Figure 4.2 Hydrogen bonding interactions upon fluorine substitution alpha to a nitrile.

Nitrile-containing compounds, such as the diabetes drug saxagliptin, can serve as reversible covalent inhibitors of serine and cysteine proteases.[10-13] In these compounds, attack of a nucleophilic amino acid side chain on the carbon atom of the nitrile reversibly forms an imidate or thioimidate linkage.[14-16] Relative to their non-fluorinated counterparts, difluoronitriles are likely to be more susceptible to nucleophilic attack and may form stronger covalent linkages to amino acid residues in an enzyme active site (Scheme 4.1).



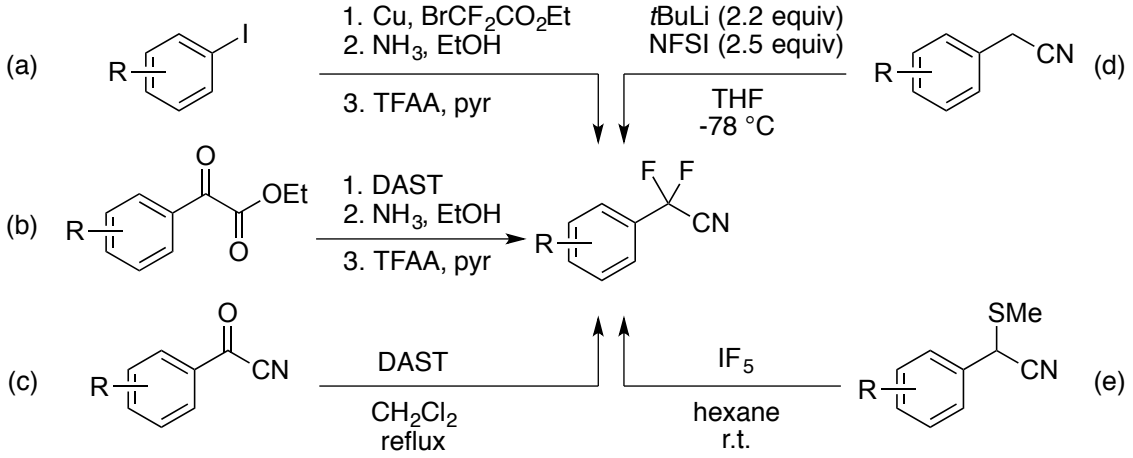
Scheme 4.1 Alpha-fluorination of nitriles to tune their properties as reversible, covalent protease inhibitors.

In pharmaceuticals, nitrile groups are generally robust toward metabolism and are not readily oxidized or hydrolyzed.[17-19] However, alkylnitriles containing α-hydrogen atoms are rare in drugs because α-oxidation to form the corresponding cyanohydrin can occur, followed by release of cyanide (Scheme 4.2a).[6, 20] Benzylic nitriles are particularly problematic in this respect due to the metabolic lability of benzylic C-H bonds. The toxicity of benzylic cyanohydrins is well established: the major pathway for metabolism of mandelonitrile (benzaldehyde cyanohydrin), present in apricot pits and bitter almonds, releases cyanide.[21] The presence of two fluorine atoms alpha to the nitrile group in an aryldifluoronitrile would block this pathway for metabolic degradation (Scheme 4.2b).



Scheme 4.2 Metabolic degradation of benzylic nitriles is blocked by the introduction of two benzylic fluorine atoms.

Traditional routes to aryldifluoronitriles involve multi-step syntheses. These routes typically begin with preparation of an aryldifluoroester by copper-mediated reductive coupling of an aryl iodide with ethyl bromodifluoroacetate or by deoxyfluorination of an α-keto ester (Scheme 4.3a and b). Subsequent addition of ammonia generates the corresponding primary acetamide, and a final dehydration step affords the aryldifluoronitrile.[22] These routes are typically low-yielding, do not tolerate sensitive functional groups, and are impractical for the synthesis of a wide array of aryldifluoronitriles with different substituents on the aryl group.



Scheme 4.3 Methods for the synthesis of aryldifluoronitriles.

Approaches for the synthesis of aryldifluoronitriles by C-F bond formation have also been explored, but suffer from a combination of poor yields, limited scope and functional group tolerance, and the requirement for harsh conditions and sensitive reagents. In 1993, Bartmann and coworkers reported the deoxyfluorination of acyl cyanides with DAST (Figure 4.3c), but yields were low (17-40%).[5] Alpha-fluorination of benzylic nitriles has also been reported (Figure 4.3d), but yields were variable (5-56%) and the functional group tolerance of the reaction was poor.[23] A

single example of a desulfurizing difluorination reaction to form an aryldifluoronitrile has been reported. However, the fluorinating reagent required for the transformation, iodine pentafluoride, readily releases HF upon exposure to atmospheric moisture, and additional synthetic steps are required to introduce the benzylic thioether group in the starting material.[24]

To address the lack of suitable methods to prepare aryldifluoronitriles and provide improved access to new compounds of potential biological interest, we sought to develop a reaction that couples readily available aryl halides with an accessible difluoronitrile nucleophile. Both palladium and copper complexes were evaluated as catalysts for the synthesis of aryldifluoronitriles. We report a cross-coupling of aryl iodides with α-(trimethylsilyl)difluoroacetonitrile mediated by copper. We explore the scope of the reaction and identify challenges to developing mild, transition metal-catalyzed methods for the synthesis of aryldifluoronitriles.

4.2 Results and Discussion

We considered two potential pathways for a transition metal-catalyzed or -mediated coupling of aryl halides with a difluoronitrile nucleophile (Figure 4.3). In Figure 4.3a, a simplified catalytic cycle for a group 10 metal such as palladium is depicted. The cycle begins with oxidative addition of an aryl halide to a Pd^0 species. Transmetallation with a difluoronitrile anion or anion equivalent generates an arylpalladium(II) difluoronitrile complex, which undergoes reductive elimination to form an aryldifluoronitrile.

Our studies of reductive elimination from Pd-fluoroenolate complexes revealed that the barrier to reductive elimination from a DPPF-ligated arylpalladium difluoronitrile complex was significantly greater than that of the analogous arylpalladium difluoroamide or difluoroester enolate complex (see Chapter 3).[25] However, at elevated temperatures, reductive elimination occurred in high yield (92%) from an isolated arylpalladium difluoronitrile complex. In addition, we found that the ancillary ligand had a dramatic impact on the yield and rate of reductive elimination for arylpalladium difluoroenolate complexes ligated by mono- and bisphosphines. These results suggested that reductive elimination may be a challenging step in the Pd-catalyzed synthesis of aryldifluoronitriles, and that a variety of ligands of varying steric and electronic properties should be evaluated for their ability to promote the desired coupling reaction.

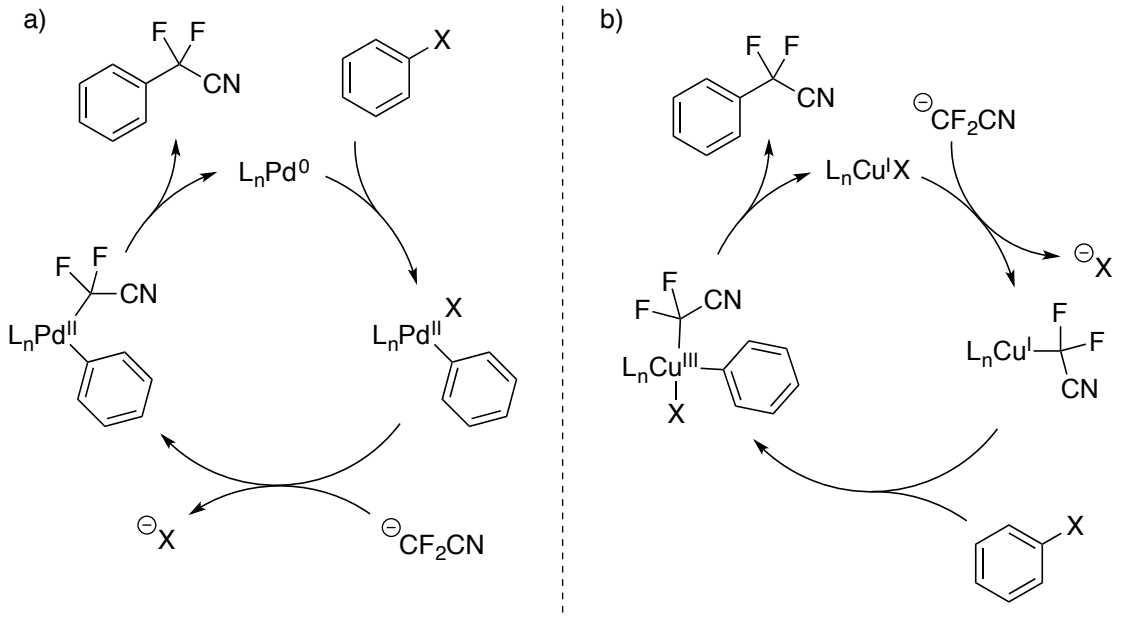


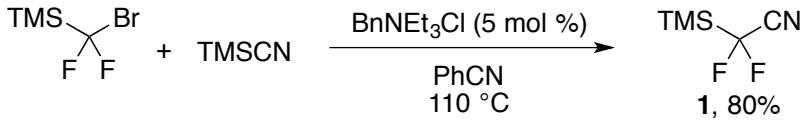
Figure 4.3 Potential catalytic cycles for (a) palladium- and (b) copper-catalyzed synthesis of aryldifluoronitriles.

We also considered a copper-catalyzed or -mediated coupling of aryl halides with a difluoronitrile nucleophile (Figure 4.3b). Such a reaction would likely proceed by transmetallation between a copper(I) salt and a difluoronitrile nucleophile source to generate a Cu^I-difluoronitrile species. Oxidative addition of an aryl halide would generate a Cu^{III} species, and reductive elimination would afford the aryldifluoronitrile product and regenerate a Cu^I complex. Oxidative addition to electron-deficient metal centers is challenging, and is proposed to be the rate-determining step for cross-coupling reactions of aryl halides that involve perfluoroalkyl Cu intermediates.[26-27] The Taft polar substituent constant (σ^*) of a cyano group (+1.30) is greater than that of fluorine (+1.10).[28] This implies that a difluoronitrile group is more inductively withdrawing than a trifluoromethyl group, and that oxidative addition to a Cu(I) difluoronitrile complex may therefore be more challenging than oxidative addition to the analogous Cu(I) trifluoromethyl complex. This could potentially restrict the scope of the reaction to aryl iodides and activated heteroaryl bromides as the electrophilic coupling partner.

We first sought to identify a suitable difluoronitrile source for the coupling reaction. A difluoronitrile anion could be generated *in situ* by deprotonation of difluoroacetonitrile. However, the requirement for a base could limit the scope and functional group tolerance of the reaction, and the low boiling point of difluoroacetonitrile (23 °C)[29] makes its handling less convenient on a laboratory scale than higher-boiling liquid or solid reagents.

We therefore employed a pre-formed difluoronitrile anion equivalent that we envisioned could be activated toward transmetallation to a metal complex *in situ*. We began with the synthesis of compound **1** by the method reported by Dilman and coworkers in 2012 (Scheme 4.4).[30] The formation of $TMSCF_2CN$ is proposed to occur by generation of a difluorocarbene intermediate from attack of chloride on $TMSCF_2Br$, followed by insertion of difluorocarbene into the silicon-

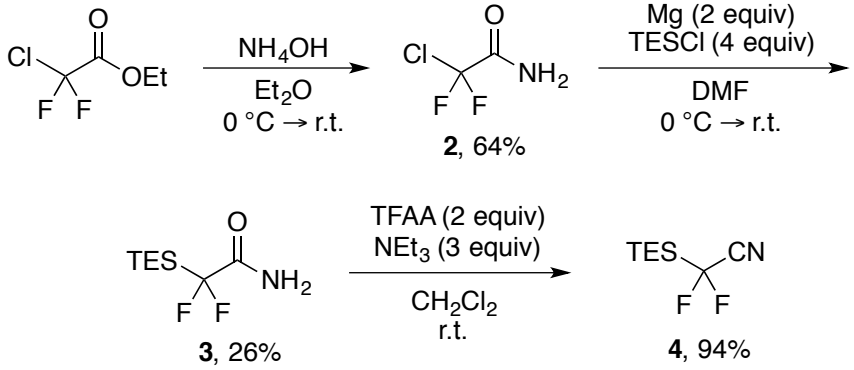
carbon bond of TMSCN. In the initial report of the synthesis of **1**, mild activating agents, including fluoride and acetate salts, were shown to be capable of promoting addition reactions of compound **1** to aldehydes and *N*-tosylimines. However, no examples of metal-mediated or -catalyzed cross-coupling reactions of compound **1** were reported.



Scheme 4.4 Synthesis of $TMSCF_2CN$ (**1**).[30]

The identity of the silyl group in fluoroalkylsilane reagents has a significant influence on the stability and rate of activation of the nucleophile. For instance, in Amii's synthesis of aryldifluoroesters, $TMSCF_2CO_2Et$ was an effective coupling partner when stoichiometric quantities of copper were employed, but $TESCF_2CO_2Et$ was required to achieve moderate yields with catalytic quantities of copper.[31] Similarly, the Pd-catalyzed trifluoromethylation reported by Buchwald required $TESCF_3$ rather than $TMSCF_3$ as the CF_3 source.[32]

Initially, attempts were made to synthesize $TESCF_2CN$ through a route analogous to that shown in Scheme 4.4 by employing TESCN instead of TMSCN. However, formation of $TESCF_2CN$ was not observed, and a complex mixture of fluorinated compounds was observed by ^{19}F NMR spectroscopy. We therefore developed the alternate route to $TESCF_2CN$ shown in Scheme 4.5. Ethyl chlorodifluoroacetate was treated with ammonium hydroxide to generate the corresponding primary acetamide (**2**) in 64% yield. Subsequent treatment of compound **2** with magnesium and chlorotriethylsilane afforded α-triethylsilyl difluoroamide **3** in 26% yield. The yield of this reaction was limited by competitive formation of 2,2-difluoroacetamide, the product of protodechlorination of starting material **2**. Dehydration of compound **3** was achieved with trifluoroacetic anhydride and triethylamine to afford $TESCF_2CN$ (**4**) in 94% yield.

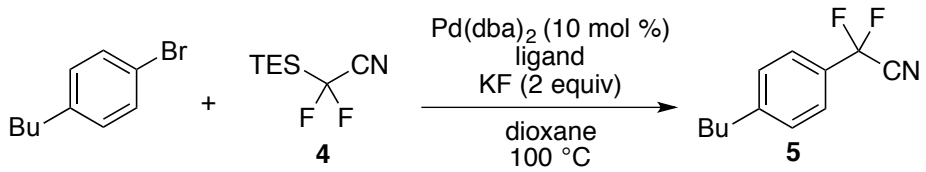


Scheme 4.5 Synthesis of $TESCF_2CN$ (**4**).

Initial experiments to identify conditions for palladium-catalyzed coupling were conducted with $TMSCF_2CN$ and electron-neutral 1-butyl-4-bromobenzene as coupling partners, and the yield of the aryldifluoronitrile product was evaluated by ^{19}F NMR spectroscopy with 3-

nitrofluorobenzene as an internal standard. A series of mono- and bidentate phosphines were evaluated as ligands in the palladium-catalyzed coupling reaction, including ligands that have been demonstrated to effect the arylation of difluoroketones[33] and difluoroamides.[34] Reactions were conducted with potassium fluoride as an additive to activate $TMSCF_2CN$ toward transmetallation. However, coupling product **5** was not formed, and full conversion of $TMSCF_2CN$ was observed by ^{19}F NMR spectroscopy, accompanied by the formation of difluoroacetontrile and trimethylsilylfluoride.

Table 4.1 Pd-catalyzed synthesis of aryldifluoronitriles.[a]



entry	ligand	yield[b]	entry	ligand	yield[b]
1	P^{t}Bu$_2$Cy	0%	7	QPhos	0%
2	P^{t}BuCy$_2$	0%	8	DPPF	0%
3	P^{t}Bu$_3$	0%	9	^{t}Bu-Xantphos	0%
4	BrettPhos	0%	10	Xantphos	5%
5	SPhos	0%	11[c]	Xantphos	13%
6	XPhos	0%	12[d]	Xantphos	28%

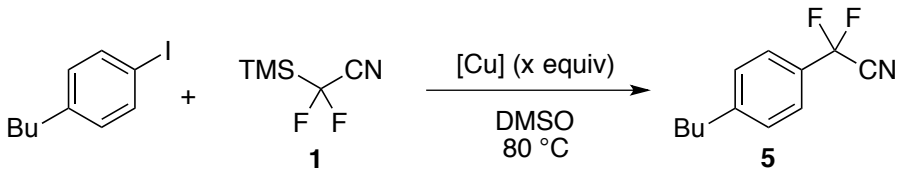
[a]See Experimental section for detailed conditions. [b]Yields were determined by ^{19}F NMR spectroscopy with 3-nitrofluorobenzene as internal standard. [c]The reaction was conducted with $[(allyl)PdCl]_2$ in THF at 80 °C. [d]The reaction was conducted with $[(allyl)PdCl]_2$ and CsF in THF at 80 °C.

To address the evident instability of $TMSCF_2CN$ under the reaction conditions, a series of reactions were conducted with $TESCF_2CN$ as an alternative difluoronitrile nucleophile source (Table 4.1). Among the ligands tested, only reactions conducted with Xantphos as ligand afforded product **5** (entries 10-12), potentially due to the wide bite angle of Xantphos (111°)[35] and its ability to accelerate challenging reductive eliminations.[36] The reaction catalyzed by a combination of $[Pd(allyl)Cl]_2$ (2.5 mol %) and Xantphos (6 mol %) formed coupled product **5** in 28% yield, as measured by ^{19}F NMR spectroscopy (entry 12). However, changing reaction parameters including the solvent, temperature, concentration, and type of Lewis basic additive (including halide, acetate, and *tert*-butoxide salts) failed to improve the yield of compound **5**. The Pd-catalyzed direct arylation of difluoracetronitrile in the presence of a variety of bases was also investigated, but coupling products were not formed under the conditions tested. Additionally, coupling reactions of arylboronic acids with a difluoronitrile electrophile (ICF_2CN) were investigated, but suitable conditions for coupling were not identified.

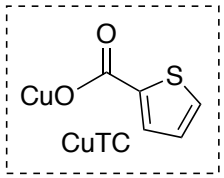
The low yields obtained in palladium-catalyzed coupling reactions prompted us to consider alternative systems for the synthesis of aryldifluoronitriles. Copper-catalyzed fluoroalkylation reactions have been developed for the synthesis of trifluoromethylarenes,[37-40] aryldifluoroesters,[31]

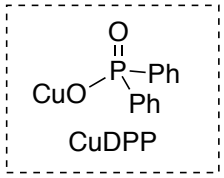
and aryldifluoroamides (see Chapter 2).[41] To determine if related reaction conditions were applicable to the synthesis of aryldifluoronitriles, we conducted a series of experiments with 1-butyl-4-iodobenzene as substrate. Initial studies were conducted with $TMSCF_2CN$ as the difluoronitrile source, and the yields of the reactions were evaluated by ^{19}F NMR spectroscopy. Reactions were conducted with an excess of $TMSCF_2CN$ (**1**) due to competing decomposition of the reagent under the reaction conditions.

Table 4.2 Evaluation of reaction conditions on the coupling of 1-butyl-4-iodobenzene with α-silyldifluoroacetonitrile **1**.[a]



entry	equiv. [Cu]	[Cu]	yield[b]
1	0.200	CuI	0%
2	0.500	CuI	6%
3	1.00	CuI	19%
4	2.00	CuI	27%
5	5.00	CuI	48%
6	2.00	CuCl	65%
7	2.00	CuBr	41%
8	2.00	$CuBr•SMe_2$	50%
9	2.00	CuOAc	65%
10	2.00	CuTC	72%
11	2.00	CuDPP	84%
12[c]	2.00	CuDPP	84%

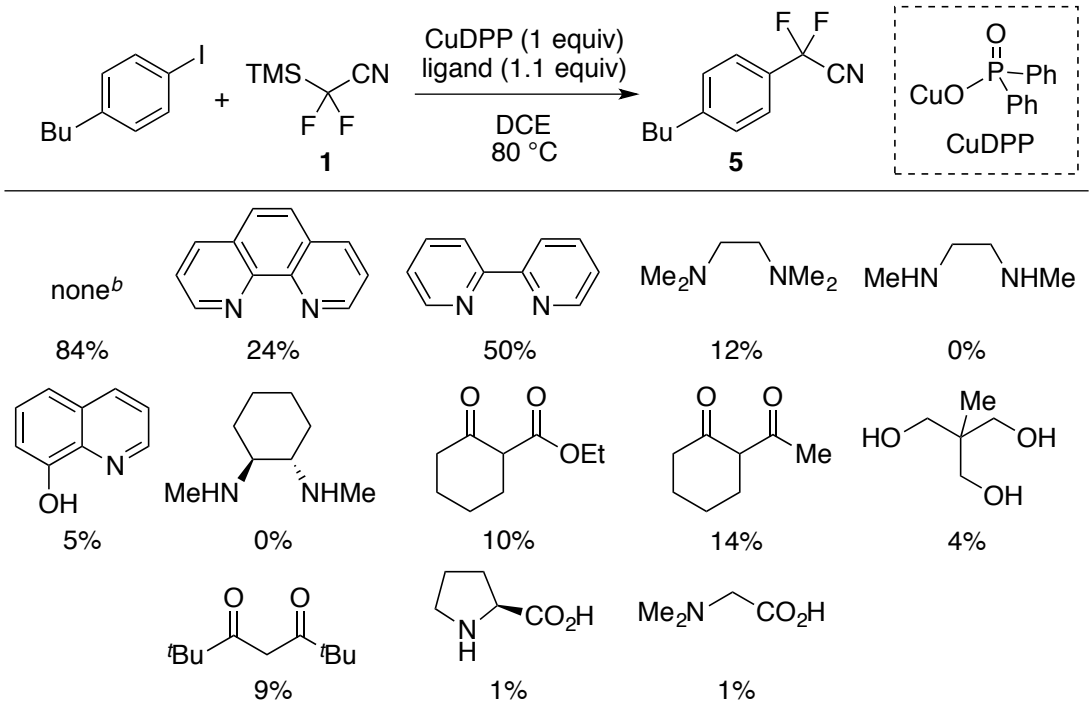




[a]See Experimental section for detailed conditions. [b]Yields were determined by ^{19}F NMR spectroscopy with 3-nitrofluorobenzene as internal standard. [c]The reaction was conducted with DCE as solvent.

Reactions conducted with 20 mol % of CuI failed to afford coupling product **5**. However, the formation of aryldifluoronitrile **5** was observed in reactions conducted with larger quantities of CuI, and 48% yield was obtained with 5 equivalents of CuI (Table 4.2, entry 5). A variety of copper(I) sources were effective mediators of the coupling between silyldifluoronitrile **1** and 1-butyl-4-iodobenzene. The reaction mediated by 2 equivalents of copper(I) diphenylphosphinate formed the coupled product in 84% yield, as measured by ^{19}F NMR spectroscopy (entry 11). Reactions conducted in DMSO and DCE proceeded in the same yield (entries 11-12).

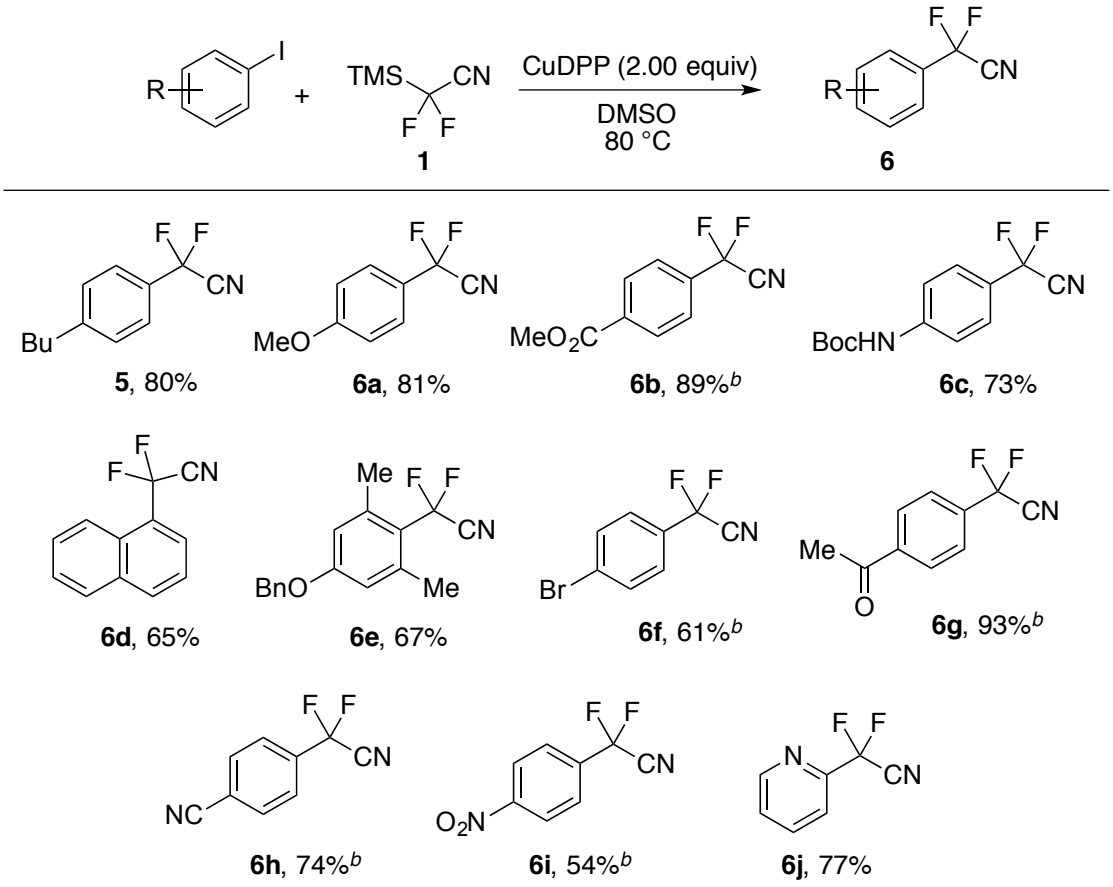
Table 4.3 Effect of ligands on the copper-mediated coupling of aryl iodides and $TMSCF_2CN$ (**1**)[a]



[a]See Experimental section for detailed conditions. Yields were determined by ^{19}F NMR spectroscopy with 3-nitrofluorobenzene as internal standard. [b]The reaction was conducted with 2.00 equiv CuDPP.

Reactions conducted with added N- and O-donor ligands commonly employed in Cu-catalyzed coupling reactions proceeded in lower yields than reactions conducted without added ligands (Table 4.3). In contrast to copper-mediated or -catalyzed arylation reactions of silyldifluoroesters[31] or -amides[41], the copper-mediated arylation of $TMSCF_2CN$ did not require the addition of a fluoride salt as an activating agent (see Table S4.1 in the Experimental section). Additives including halide, acetate, carboxylate, carbonate, phosphonate, and phosphinate salts were also evaluated, but yields were comparable or lower than the analogous reactions conducted without additives.

Table 4.4 Copper-mediated coupling of aryl iodides with $TMSCF_2CN$ (**1**).[a]



[a]Isolated yield. General conditions: aryl iodide (0.400 mmol), **1** (2.00 mmol), and CuDPP (0.800 mmol) in 2 mL of DMSO at 80 °C. [b]Reaction was conducted with DCE (2 mL) as solvent.

A series of aryl iodides were subjected to the CuDPP-mediated coupling conditions to afford the corresponding aryldifluoronitriles (Table 4.4). Because both DMSO and DCE were effective solvents for coupling reactions of 1-butyl-4-iodobenzene (Table 4.2, entries 11 and 12), both were evaluated as solvents for reactions of other aryl iodides. For most substrates, comparable yields were obtained in both solvents. However, the coupling to form **6b** proceeded in significantly higher yield in DCE than in DMSO, and the coupling to form **6c** displayed the opposite trend.

Both electron-rich (**6a**, **6c**, **6e**) and electron-poor (**6b**, **6g-i**) aryldifluoronitriles were formed in moderate to high yields under the coupling conditions. An *ortho*-substituted aryl iodide containing disubstitution adjacent to iodine coupled with **1** to afford product **6e** in 67% yield. Ester (**6b**) and protected amine (**6c**) functional groups were also tolerated. A substrate bearing both iodine and bromine coupled exclusively at the iodine group to form **6f** in 61% isolated yield. Electrophilic groups including ketones (**6g**), nitriles (**6h**), and nitro groups (**6i**) were compatible with the coupling conditions. In addition, 2-iodopyridine underwent coupling to form **6j** in 77% yield. However, substrates containing aldehydes, hydroxyl groups, and unprotected N-H groups

were incompatible with the reaction conditions, and heterocycles such as 3- or 4-iodopyridine and 2-iodopyrazine did not undergo coupling (Figure 4.5).

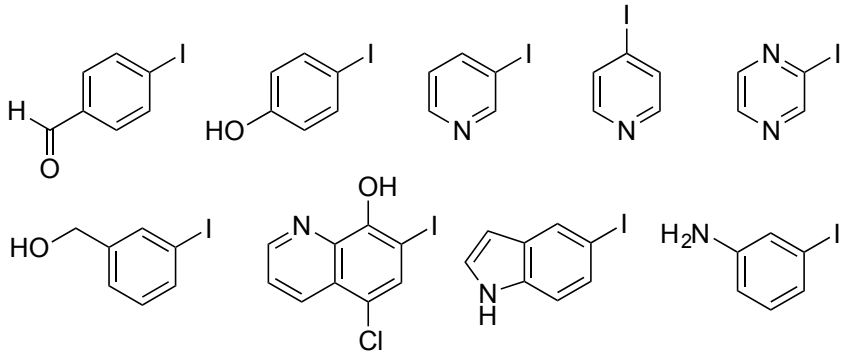


Figure 4.5 Unsuccessful substrates for CuDPP-mediated coupling of aryl iodides and $TMSCF_2CN$ (**1**).

4.3 Conclusion

We report the development of the first cross-coupling reaction for the synthesis of aryldifluoronitriles from reactions of α-silyldifluoroacetronitrile reagents with aryl halides. Reactions catalyzed by a combination of $[Pd(allyl)Cl]_2$ and Xantphos enabled the transformation of aryl bromides to the corresponding aryldifluoronitriles, but yields were low. A copper-mediated coupling of aryl iodides with $TMSCF_2CN$ was developed and found to be applicable to the coupling of electron-poor, electron-neutral, electron-rich, and sterically hindered aryl iodide substrates. The reaction proceeds without the addition of an exogenous ligand and employs a commercially available copper(I) source, copper(I) diphenylphosphinate, and a difluoronitrile nucleophile, $TMSCF_2CN$, that is available in one step from commercially available starting materials. The copper-mediated coupling reaction offers an alternative to current methods for the synthesis of aryldifluoronitriles, which often require multiple steps, display poor functional group tolerance, require pre-functionalization of substrates, or form mixtures of products. We anticipate that this method will allow the synthesis of a diverse range of aryldifluoronitriles for applications in materials science, medicinal chemistry, and agrochemistry.

Future directions for investigation include the development of alternative difluoronitrile nucleophile sources with increased stability. Because $TMSCF_2CN$ decomposes under the copper-mediated cross-coupling conditions, a large excess of the reagent relative to the aryl iodide coupling partner is required to obtain high yields. Tuning the reactivity of the α-silyl difluoronitrile reagent by altering the steric and electronic properties of the silyl group and controlling activation of the reagent with a Lewis basic additive may enable reactions to be conducted without a large excess of the difluoronitrile source. Alternatively, conducting coupling reactions with isolated L_nCuCF_2CN complexes may be a viable strategy to expand the scope and improve the functional group compatibility of the reaction, as was observed for trifluoromethylation reactions conducted with isolated $(phen)CuCF_3$.[26,42] Developing conditions for coupling reactions of heteroaryl bromides would also be useful for applications in medicinal chemistry. Improved access to aryldifluoronitriles by metal-mediated or -catalyzed cross-coupling will also enable the evaluation

of this class of compound for biological applications as metabolically stable analogs of benzylic nitriles and as potential covalent inhibitors.

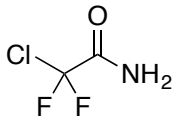
4.4 Experimental

General Experimental Details

All reactions were conducted under inert atmosphere in a nitrogen-filled glovebox or with standard Schlenk techniques, unless otherwise specified. Vessels used in air-free reactions were oven-dried prior to use. Vials used as a reaction vessel were sealed with Teflon-lined caps. Silica-gel chromatography was performed with Silicycle SiliaFlash P60 silica gel. Toluene, tetrahydrofuran, diethyl ether, and dichloromethane were purged with nitrogen and dried with an Innovative Pure-Solv solvent purification system. Anhydrous dioxane, DMF, and DMSO were purchased from Acros Organics. All other solvents were purchased from Fisher Scientific. $Pd(dba)_2$ was purchased from Strem. $[Pd(allyl)Cl]_2$ was purchased from Sigma Aldrich. CuDPP was purchased from Combi Blocks. Ethyl chlorodifluoroacetate, $TMSCF_2Br$, TMSCN, benzyltriethylammonium chloride, and ligands were purchased from Sigma Aldrich, Alpha Aesar, Oakwood Chemical, and Fisher Scientific. Deuterated solvents were purchased from Cambridge Isotope Laboratories. Compounds were used as received unless otherwise noted. Alpha-trimethylsilyl difluoroacetonitrile (**1**)[30] and iododifluoroacetonitrile[43] were synthesized according to procedures reported in the literature. NMR spectra were acquired on Bruker 300, 400, 500, or 600 MHz spectrometers at the University of California, Berkeley NMR facility. ^1H and ^{13}C chemical shifts were reported relative to residual solvent peaks ($CDCl_3$ = 7.26 ppm for ^1H and 77.2 ppm for ^{13}C; CD_2Cl_2 = 5.32 ppm for ^1H and 53.8 ppm for ^{13}C; C_6D_6 = 7.16 ppm for ^1H and 128.1 ppm for ^{13}C). GC/MS analyses were conducted with a system consisting of an Agilent 6890N GC and an Agilent 5973 Mass Selective Detector. The instrument was equipped with an HP-5 column (25m x 0.20mm ID x 0.33 μm film). High-resolution mass spectra were obtained at the University of California, Berkeley Mass Spectrometry Facility with ESI or EI techniques with a Thermo Finnigan LTQ FT instrument

*Synthesis of $TESCF_2CN$ (**4**)*

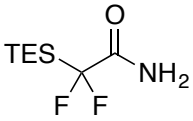
2-chloro-2,2-difluoroacetamide (2)



To a round-bottom flask under air equipped with a stir bar was added 30% aq. NH_4OH (40 mL) and Et_2O (40 mL). The mixture was cooled in an ice bath, and ethyl chlorodifluoroacetate (2.53 mL, 3.17 g, 20.0 mmol, 1.00 equiv) was added dropwise. After addition of ethyl chlorodifluoroacetate was complete, the reaction mixture was allowed to warm to room temperature and stirred for an additional 2 h. After 2 h, the reaction mixture was transferred to a separatory funnel, and the layers were separated. The aqueous phase was extracted with Et_2O (2x50 mL). The combined organic extracts were washed with H_2O (50 mL) and brine (50 mL) and dried over Na_2SO_4. Removal of the solvent *in vacuo* afforded the product as a colorless solid (1.65 g, 12.7 mmol, 64% yield).

The ^{1}H, ^{19}F, and ^{13}C NMR spectra correspond to those that have been previously reported.[44]

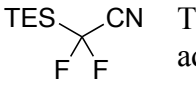
2,2-difluoro-2-(triethylsilyl)acetamide (3)



To an oven-dried round-bottom flask under nitrogen equipped with a stir bar was added Mg (1.22 g, 50.0 mmol, 2.00 equiv), anhydrous DMF (75 mL), and chlorotriethylsilane (16.8 mL, 15.1 g, 100 mmol, 4.00 equiv). The reaction mixture was cooled in an ice bath, and a solution of compound **2** (3.24 g, 25.0 mmol, 1.00 equiv) in 15 mL anhydrous DMF was added dropwise. After addition was complete, the reaction was allowed to slowly warm to room temperature over 1 h and stirred at room temperature for an additional 20 h. Conversion of compound **2** was measured by ^{19}F NMR spectroscopy of an aliquot of the reaction mixture. After 20 h, full consumption of compound **2** was observed, and the reaction was quenched with H_2O (100 mL). The reaction mixture was filtered to remove residual magnesium and magnesium salts and transferred to a separatory funnel. Et_2O (75 mL) was added, and the layers were separated. The aqueous phase was extracted with Et_2O (3x50 mL), and the combined organic extracts were washed with H_2O (3x50 mL) and brine (50 mL) and dried over Na_2SO_4. The solvent was evaporated *in vacuo*, and the crude residue was purified by silica gel chromatography with hexanes:EtOAc 100:1 → 3:1 as eluent. The product was isolated as a colorless, crystalline solid (1.38 g, 6.57 mmol, 26% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16 (br. s, 1H), 5.61 (br. s, 1H), 1.03 (t, J = 7.9 Hz, 9H), 0.81 (q, J = 7.9 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.7 (t, J = 23.1 Hz), 123.4 (t, J = 272.6 Hz), 6.9, 1.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.6. HRMS (ESI+) calc'd for $C_8H_{18}F_2NOSi^+$ $[M+H]^+$: 210.1120, found: 210.1120.

2,2-difluoro-2-(triethylsilyl)acetonitrile (4)



To an oven-dried round-bottom flask under nitrogen equipped with a stir bar was added compound **3** (209 mg, 1.00 mmol, 1.00 equiv), anhydrous CH_2Cl_2 (10 mL), and triethylamine (418 μL, 304 mg, 3.00 mmol, 3.00 equiv). The solution was stirred at room temperature, and trifluoroacetic anhydride (278 μL, 420 mg, 2.00 mmol, 2.00 equiv) was added dropwise. The light yellow solution was stirred at room temperature for 1 h. After 1 h, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and H_2O (30 mL). The reaction mixture was transferred to a separatory funnel, and the layers were separated. The organic layer was washed with sat. aq. $NaHCO_3$ (30 mL) and brine (30 mL) and dried over Na_2SO_4. Removal of the solvent *in vacuo* afforded the product as a colorless oil (179 mg, 0.936 mmol, 94% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (t, J = 7.9 Hz, 9H), 0.87 (q, J = 7.8 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 116.7 (t, J = 266.7 Hz), 113.8 (t, J = 37.2 Hz), 6.5, 0.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.2.

Investigation of Reaction Conditions for Pd-Catalyzed Coupling

General procedure for evaluation of ligands for Pd-catalyzed synthesis of aryldifluoronitriles (Table 4.1, entries 1-10)

In a nitrogen-filled glovebox, $Pd(dba)_2$ (1.4 mg, 0.0025 mmol, 0.10 equiv), ligand, if solid at room temperature, (0.0055 mmol, 0.10 equiv for entries 1-6; 0.0030 mmol for entries 7-12), and KF (2.9 mg, 0.05 mmol, 2.0 equiv) were added to a 4 mL vial equipped with a stir bar. Dioxane (0.25 mL) was added, followed by the ligand, if liquid at room temperature (0.0055 mmol, 0.10 equiv for entries 1-6; 0.0030 mmol for entries 7-12), and KF (2.9 mg, 0.05 mmol, 2.0 equiv), 1-butyl-4-bromobenzene (5.3 mg, 0.025 mmol, 1.0 equiv) and $TESCF_2CN$ (**4**) (9.6 mg, 0.050 mmol, 2.0 equiv). The reaction was sealed with a Teflon-lined cap and heated at 100 °C for 15 h. After 15 h, the reaction was allowed to cool to room temperature. Internal standard (3-nitrofluorobenzene) was added, and the yield of the reaction was determined by ^{19}F NMR spectroscopy.

Procedure for Pd-catalyzed coupling in THF with Xantphos as ligand (Table 4.1, entries 11-12)

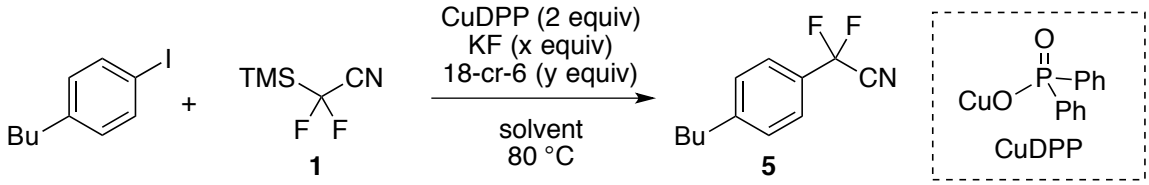
In a nitrogen-filled glovebox, $[Pd(allyl)Cl]_2$ (0.9 mg, 0.0025 mmol, 0.050 equiv), Xantphos (3.5 mg, 0.0060 mmol, 0.120 equiv), and the fluoride source (0.150 mmol, 3.00 equiv) were added to a 4 mL vial equipped with a stir bar. THF (0.5 mL) was added, followed by 1-butyl-4-bromobenzene (10.7 mg, 0.0500 mmol, 1.00 equiv) and $TESCF_2CN$ (**4**) (19.1 mg, 0.100 mmol, 2.00 equiv). The reaction was sealed with a Teflon-lined cap and heated at 80 °C for 15 h. After 15 h, the reaction was allowed to cool to room temperature. Internal standard (3-nitrofluorobenzene) was added, and the yield of the reaction was determined by ^{19}F NMR spectroscopy.

Investigation of Reaction Conditions for Cu-Mediated Coupling

General procedure for evaluation of conditions for Cu-mediated synthesis of aryldifluoronitriles

In a nitrogen-filled glovebox, the copper salt (0.200-5.00 equiv) was added to a 4 mL vial equipped with a stir bar. Solvent (0.25 mL) was added, followed by $TMSCF_2CN$ (**1**) (18.7 mg, 0.125 mmol, 5.00 equiv) and 1-butyl-4-iodobenzene (6.5 mg, 0.0250 mmol, 1.00 equiv). The reaction was sealed with a Teflon-lined cap and heated at 80 °C for 12 h. After 12 h, the reaction was allowed to cool to room temperature and internal standard (3-nitrofluorobenzene) was added. The yield of the reaction was determined by ^{19}F NMR spectroscopy.

Table S4.1 Evaluation of additives for Cu-mediated synthesis of aryldifluoronitriles.[a]



entry	equiv. KF	equiv. 18-cr-6	solvent	yield[b]
1	0.00	0.00	DCE	84%
2	0.500	0.00	DCE	61%
3	0.500	0.500	DCE	52%
4	1.20	0.00	DCE	74%
5	1.20	1.20	DCE	61%
6	5.00	0.00	DCE	64%
7	5.00	5.00	DCE	10%
8[c]	1.20	1.20	toluene	56%
9[c]	1.20	1.20	dioxane	41%
10	1.20	1.20	DMSO	55%

[a]General conditions: 1-butyl-4-iodobenzene (0.0250 mmol), **1** (0.125 mmol), and CuDPP (0.0500 mmol) in 0.25 mL solvent at 80 °C. [b]Yields were determined by ^{19}F NMR spectroscopy with 3-nitrofluorobenzene as internal standard. [c]The reaction was conducted at 100 °C.

General procedures for evaluation of scope of Cu-mediated synthesis of aryldifluoronitriles

General Procedure A

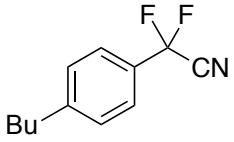
In a nitrogen-filled glovebox, CuDPP (225 mg, 0.800 mmol, 2.00 equiv) and aryl iodide, if solid at room temperature, (0.400 mmol, 1.00 equiv) were added to a 4 mL vial equipped with a stir bar. DMSO (2 mL) was added, followed by aryl iodide, if liquid at room temperature, (0.400 mmol, 1.00 equiv) and $TMSCF_2CN$ (**1**) (298 mg, 2.00 mmol, 5.00 equiv). The reaction was sealed with a Teflon-lined cap and heated at 80 °C for 12 h. After 12 h, the reaction was allowed to cool to room temperature and transferred to a separatory funnel. Water (10 mL) and EtOAc (10 mL) were added, and the layers were separated. The aqueous layer was extracted with EtOAc (3x10 mL), and the combined organic layers were washed with water (10 mL) and brine (10 mL) and dried over Na_2SO_4. The solvent was evaporated *in vacuo*, and the crude residue was purified by silica gel chromatography with a mixture of hexanes and EtOAc as eluent.

General Procedure B

In a nitrogen-filled glovebox, CuDPP (225 mg, 0.800 mmol, 2.00 equiv) and aryl iodide, if solid at room temperature, (0.400 mmol, 1.00 equiv) were added to a 4 mL vial equipped with a stir bar. DCE (2 mL) was added, followed by aryl iodide, if liquid at room temperature, (0.400

mmol, 1.00 equiv) and $TMSCF_2CN$ (**1**) (298 mg, 2.00 mmol, 5.00 equiv). The reaction was sealed with a Teflon-lined cap and heated at 80 °C for 12 h. After 12 h, the reaction was allowed to cool to room temperature. The crude reaction mixture was filtered through Celite, eluting with EtOAc (5 mL). The solvent was evaporated *in vacuo*, and the crude residue was purified by silica gel chromatography with a mixture of hexanes and EtOAc as eluent.

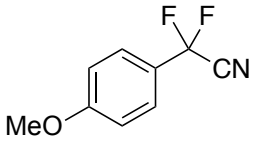
2-(4-butylphenyl)-2,2-difluoroacetonitrile (5)



Compound **5** was prepared according to General Procedure A with 1-butyl-4-iodobenzene (104 mg, 0.400 mmol, 1.00 equiv) as substrate and DMSO as solvent. The product was isolated after silica gel chromatography with hexanes as eluent. The product was isolated as a colorless oil (67.0 mg, 0.320 mmol, 80% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 2.69 (t, *J* = 7.8 Hz, 2H), 1.62 (tt, *J* = 9.2, 6.9 Hz, 2H), 1.37 (h, *J* = 7.4 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 148.2, 129.4, 128.8 (t, *J* = 25.3 Hz), 125.3 (t, *J* = 5.0 Hz), 112.9 (t, *J* = 48.5 Hz), 109.2 (t, *J* = 249.1 Hz), 35.7, 33.4, 22.4, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -81.6. HRMS (EI+) calc'd for $C_{12}H_{13}F_2N$: 209.1016; found: 209.1019.

2,2-difluoro-2-(4-methoxyphenyl)acetonitrile (6a)

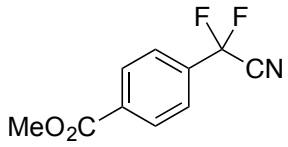


Compound **6a** was prepared according to General Procedure A with 4-iodoanisole (93.6 mg, 0.400 mmol, 1.00 equiv) as substrate and DMSO as solvent. The product was isolated after silica gel chromatography with 20:1 hexanes:EtOAc as eluent. The product was isolated as a colorless oil (59.0 mg, 0.322 mmol, 81% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.5 Hz, 2H), 7.00 (d, *J* = 8.5 Hz, 2H), 3.86 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.9, 127.2 (t, *J* = 5.0 Hz), 123.5 (t, *J* = 25.4 Hz), 114.7, 112.9 (t, *J* = 49.0 Hz), 109.2 (t, *J* = 241.8 Hz), 55.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ -80.1.

The ^{1}H, ^{19}F, and ^{13}C NMR spectra correspond to those that have been previously reported.[23]

Methyl 4-(cyanodifluoromethyl)benzoate (6b)



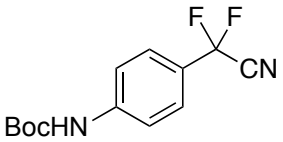
Compound **6b** was prepared according to General Procedure B with methyl 4-iodobenzoate (105 mg, 0.400 mmol, 1.00 equiv) as substrate and DCE as solvent. The product was isolated after silica gel chromatography with 20:1 hexanes:EtOAc as eluent. The product was isolated as a colorless oil (75.2 mg, 0.356 mmol, 89% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.8 Hz, 2H), 7.76 (d, *J* = 8.8 Hz, 2H), 3.97 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.7, 135.2 (t, *J* = 25.3 Hz), 134.3, 130.6, 125.6 (t, *J* = 5.0 Hz), 112.3

(t, J = 47.8 Hz), 108.4 (t, J = 244.0 Hz), 52.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -83.5. HRMS (EI+) calc'd for $C_{10}H_7F_2NO_2$: 211.0445; found: 211.0444.

Note: the isolated product contained a small amount of an unidentified impurity.

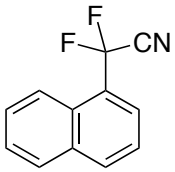
***Tert*-butyl (4-(cyanodifluoromethyl)phenyl)carbamate (6c)**



Compound **6c** was prepared according to General Procedure A with *tert*-butyl (4-iodophenyl)carbamate (128 mg, 0.400 mmol, 1.00 equiv) as substrate and DMSO as solvent. The product was isolated after silica gel chromatography with 8:1 hexanes:EtOAc as eluent. The product was isolated as a colorless solid (78.3 mg, 0.292 mmol, 73% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 9.1 Hz, 2H), 7.53 (d, J = 8.9 Hz, 2H), 6.84 (br. s, 1H), 1.52 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.4, 142.6, 126.5 (t, J = 5.0 Hz), 125.2 (t, J = 25.5 Hz), 118.4, 112.8 (t, J = 48.7 Hz), 108.9 (t, J = 242.2 Hz), 81.6, 28.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -80.9. HRMS (EI+) calc'd for $C_{13}H_{14}F_2N_2O_2$: 268.1023; found: 268.1025.

2,2-difluoro-2-(naphthalen-1-yl)acetonitrile (6d)

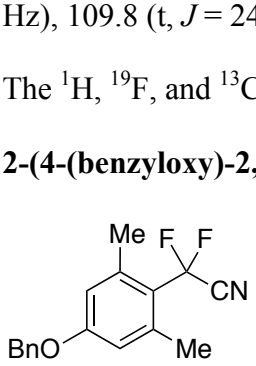


Compound **6d** was prepared according to General Procedure A with 1-iodonaphthalene (102 mg, 0.400 mmol, 1.00 equiv) as substrate and DMSO as solvent. The product was isolated after silica gel chromatography with 25:1 hexanes:EtOAc as eluent. The product was isolated as a colorless oil (53.1 mg, 0.261 mmol, 65% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.23 (d, J = 8.6 Hz, 1H), 8.08 (d, J = 8.3 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 7.94 (d, J = 7.3 Hz, 1H), 7.69 (ddd, J = 8.5, 7.0, 1.2 Hz, 1H), 7.63 (dd, J = 8.2, 6.8 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 134.2, 133.9, 129.3, 128.7, 128.3, 127.2, 126.3 (t, J = 23.3 Hz), 125.5 (t, J = 8.0 Hz), 124.4, 123.6 (t, J = 2.7 Hz), 112.9 (t, J = 47.8 Hz), 109.8 (t, J = 243.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -81.7.

The ^{1}H, ^{19}F, and ^{13}C NMR spectra correspond to those that have been previously reported.[23]

2-(4-(benzyloxy)-2,6-dimethylphenyl)-2,2-difluoroacetonitrile (6e)

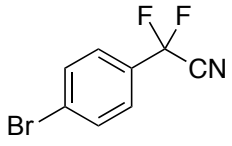


Compound **6e** was prepared according to General Procedure A with 5-(benzyloxy)-2-iodo-1,3-dimethylbenzene (338 mg, 0.400 mmol, 1.00 equiv) as substrate and DMSO as solvent. The product was isolated after silica gel chromatography with 50:1 hexanes:EtOAc as eluent. The product was isolated as a colorless oil (77.4 mg, 0.269 mmol, 67% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 (d, J = 7.0 Hz, 2H), 7.43 (t, J = 7.4 Hz, 2H), 7.38 (t, J = 7.1 Hz, 1H), 7.35 (s, 2H), 4.86 (s, 2H), 2.36 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.3, 137.0,

132.9, 128.8, 128.5, 128.0, 126.7 (t, J = 24.9 Hz), 126.0 (t, J = 4.9 Hz), 112.9 (t, J = 48.9 Hz), 109.0 (t, J = 242.6 Hz), 74.4, 16.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -81.2. HRMS (EI+) calc'd for $C_{17}H_{15}F_2NO$: 287.1122; found: 287.1125.

2-(4-bromophenyl)-2,2-difluoroacetonitrile (6f)

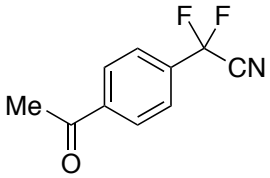


Compound **6f** was prepared according to General Procedure B with 1-bromo-4-iodobenzene (113 mg, 0.400 mmol, 1.00 equiv) as substrate and DCE as solvent. The product was isolated after silica gel chromatography with hexanes as eluent. The product was isolated as a colorless oil (56.5 mg, 0.244 mmol, 61% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.5 Hz, 1H), 7.55 (d, J = 8.2 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 132.8, 130.4 (t, J = 25.6 Hz), 127.6 (t, J = 2.4 Hz), 127.0 (t, J = 5.0 Hz), 112.3 (t, J = 48.0 Hz), 108.5 (t, J = 243.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -83.4.

The ^{1}H, ^{19}F, and ^{13}C NMR spectra correspond to those that have been previously reported.[23]

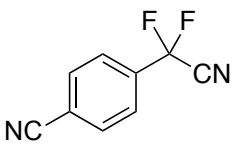
2-(4-acetylphenyl)-2,2-difluoroacetonitrile (6g)



Compound **6g** was prepared according to General Procedure B with 1-(4-iodophenyl)ethan-1-one (98.4 mg, 0.400 mmol, 1.00 equiv) as substrate and DCE as solvent. The product was isolated after silica gel chromatography with 20:1 hexanes:EtOAc as eluent. The product was isolated as a colorless oil (72.8 mg, 0.373 mmol, 93% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 7.9 Hz, 2H), 7.78 (d, J = 8.0 Hz, 2H), 2.66 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 196.8, 140.4, 135.2 (t, J = 25.5 Hz), 129.2, 125.9 (t, J = 5.0 Hz), 112.2 (t, J = 47.5 Hz), 108.4 (d, J = 243.1 Hz), 26.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -84.7 ppm. HRMS (EI+) calc'd for $C_{10}H_7F_2NO$: 195.0496; found: 195.0493.

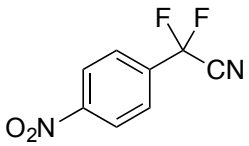
4-(cyanodifluoromethyl)benzonitrile (6h)



Compound **6h** was prepared according to General Procedure B with 4-iodobenzonitrile (91.6 mg, 0.400 mmol, 1.00 equiv) as substrate and DCE as solvent. The product was isolated after silica gel chromatography with 25:1 hexanes:EtOAc as eluent. The product was isolated as a colorless oil (51.6 mg, 0.290 mmol, 74% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.8 Hz, 2H), 7.83 (d, J = 8.7 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 135.2 (t, J = 25.8 Hz), 133.1, 126.2 (t, J = 5.0 Hz), 117.0, 116.8, 111.6 (t, J = 47.9 Hz), 107.6 (t, J = 245.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -84.2. HRMS (EI+) calc'd for $C_9H_4F_2N_2$: 178.0343; found: 178.0340.

2,2-difluoro-2-(4-nitrophenyl)acetonitrile (6i)

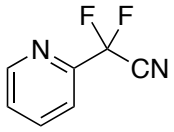


Compound **6i** was prepared according to General Procedure B with 1-iodo-4-nitrobenzene (99.6 mg, 0.400 mmol, 1.00 equiv) as substrate and DCE as solvent. The product was isolated after silica gel chromatography with 50:1 hexanes:EtOAc as eluent. The product was isolated as a colorless oil (42.2 mg, 0.214 mmol, 54% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 8.5 Hz, 2H), 7.91 (d, J = 8.6 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 150.5, 136.9 (t, J = 25.7 Hz), 127.0 (t, J = 5.0 Hz), 124.7, 111.8 (t, J = 47.4 Hz), 107.6 (t, J = 245.1 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -83.9.

The ^{1}H, ^{19}F, and ^{13}C NMR spectra correspond to those that have been previously reported.[23]

2,2-difluoro-2-(pyridin-2-yl)acetonitrile (6j)

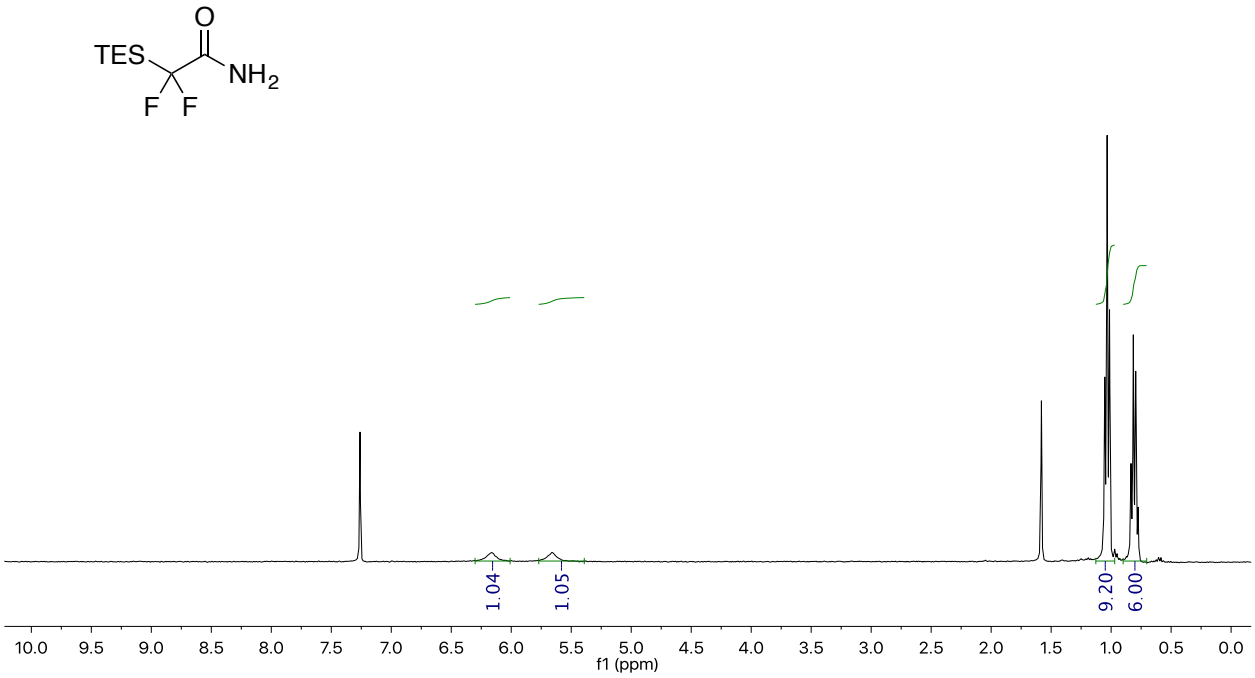


Compound **6j** was prepared according to General Procedure A with 2-iodopyridine (82.0 mg, 0.400 mmol, 1.00 equiv) as substrate and DCE as solvent. The product was isolated after silica gel chromatography with 25:1 hexanes:EtOAc as eluent. The product was isolated as a colorless oil (47.5 mg, 0.308 mmol, 77% yield).

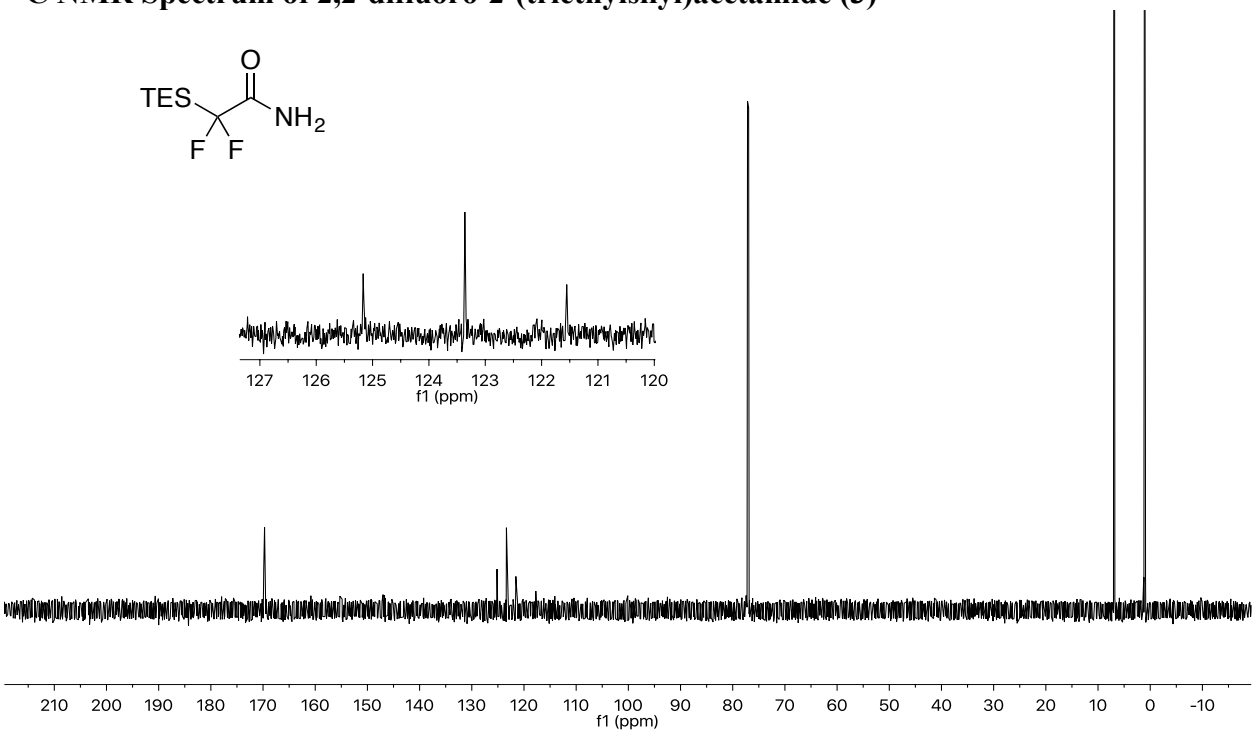
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.75 (d, J = 4.6 Hz, 1H), 7.93 (t, J = 7.8 Hz, 1H), 7.71 (d, J = 7.9 Hz, 1H), 7.54 (dd, J = 7.6, 4.9 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 150.2, 149.4 (t, J = 28.1 Hz), 138.1 (d, J = 2.9 Hz), 127.1, 120.1 (t, J = 2.6 Hz), 112.1 (t, J = 45.4 Hz), 108.3 (t, J = 244.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -86.6. HRMS (ESI+) calc'd for $C_7H_5F_2N_2^+$ $[M+H]^+$: 155.0415, found: 155.0414.

4.5 NMR Spectra

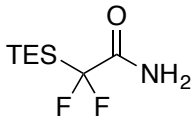
^{1}H NMR Spectrum of 2,2-difluoro-2-(triethylsilyl)acetamide (3)

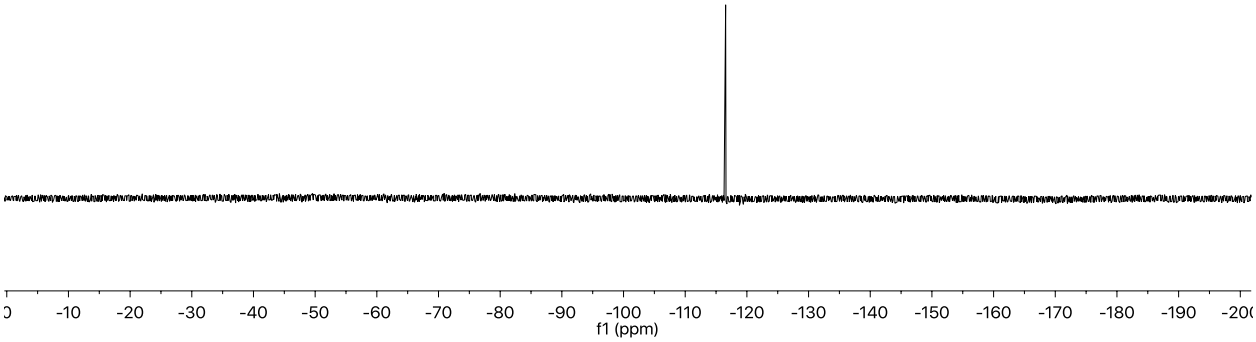


^{13}C NMR Spectrum of 2,2-difluoro-2-(triethylsilyl)acetamide (3)

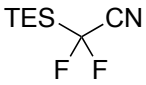


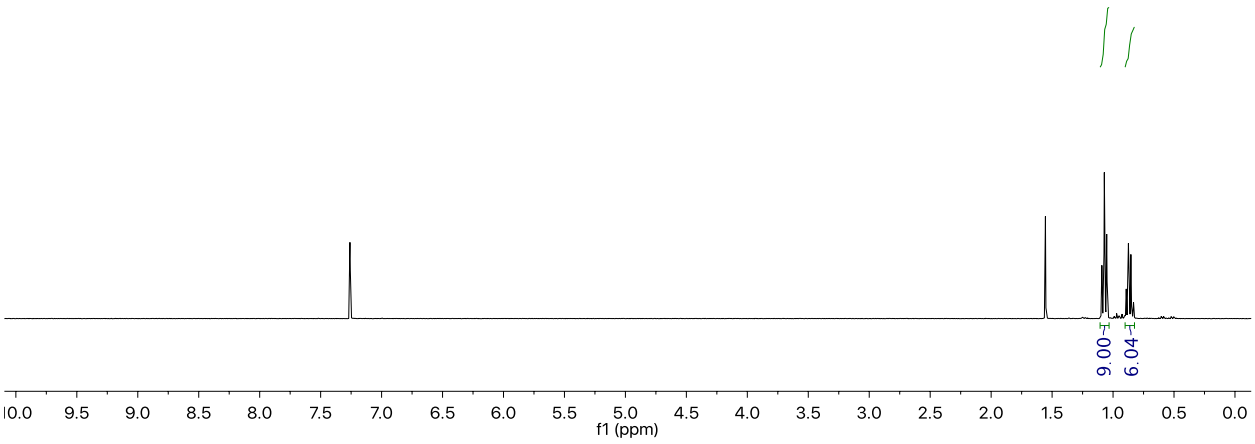
^{19}F NMR Spectrum of 2,2-difluoro-2-(triethylsilyl)acetamide (3)



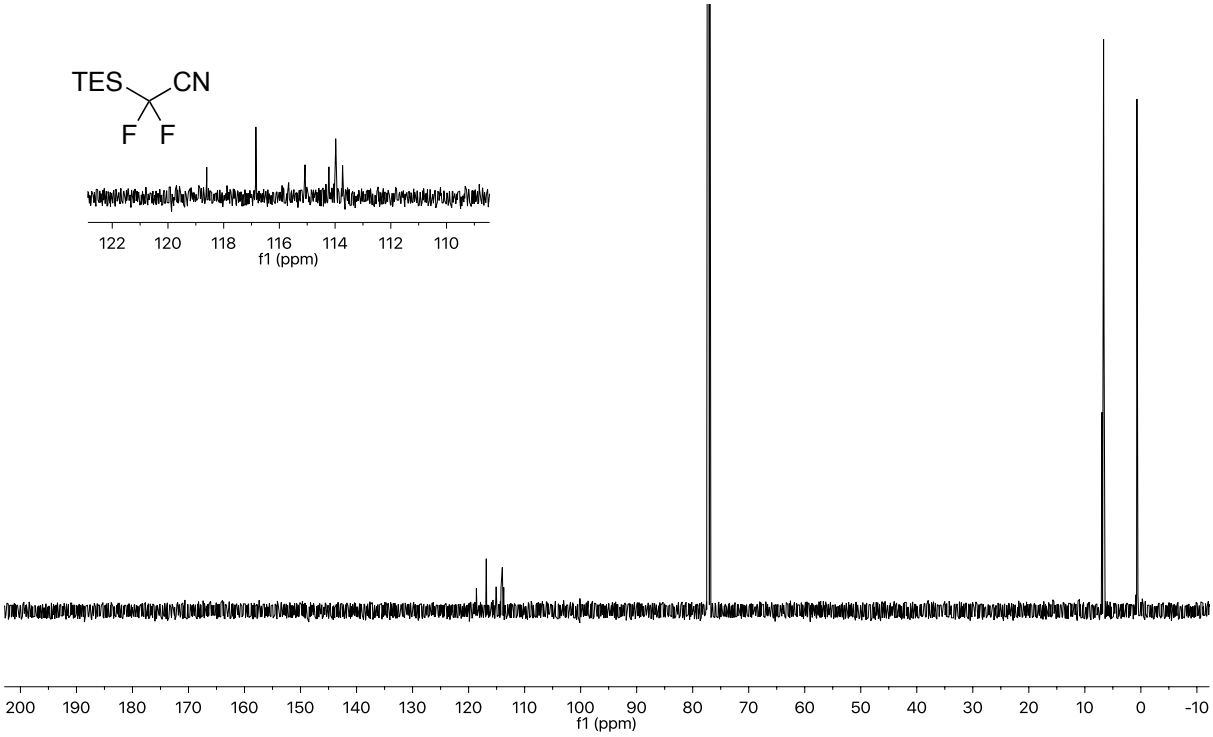


^{1}H NMR Spectrum of 2,2-difluoro-2-(triethylsilyl)acetonitrile (4)

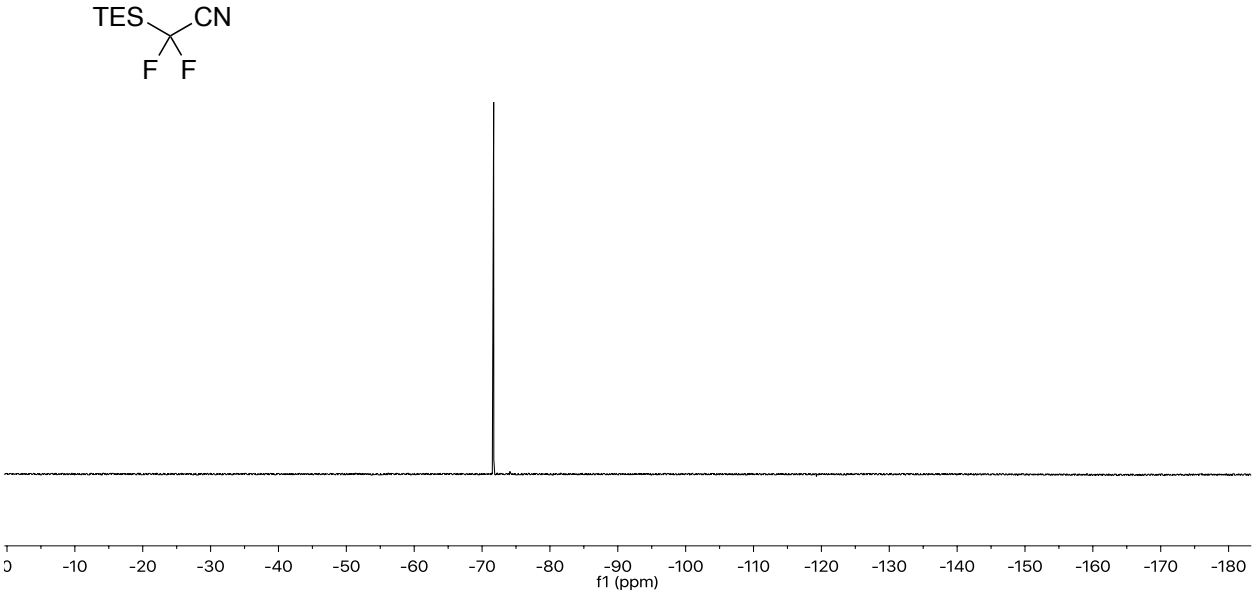




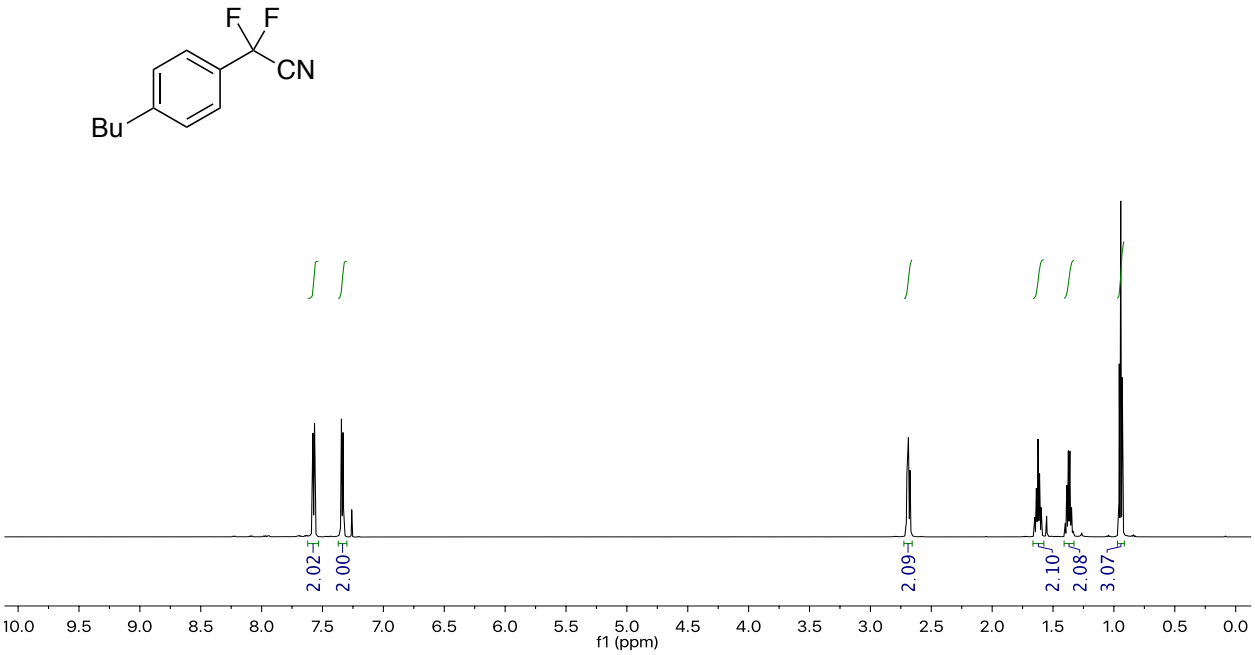
^{13}C NMR Spectrum of 2,2-difluoro-2-(triethylsilyl)acetonitrile (4)



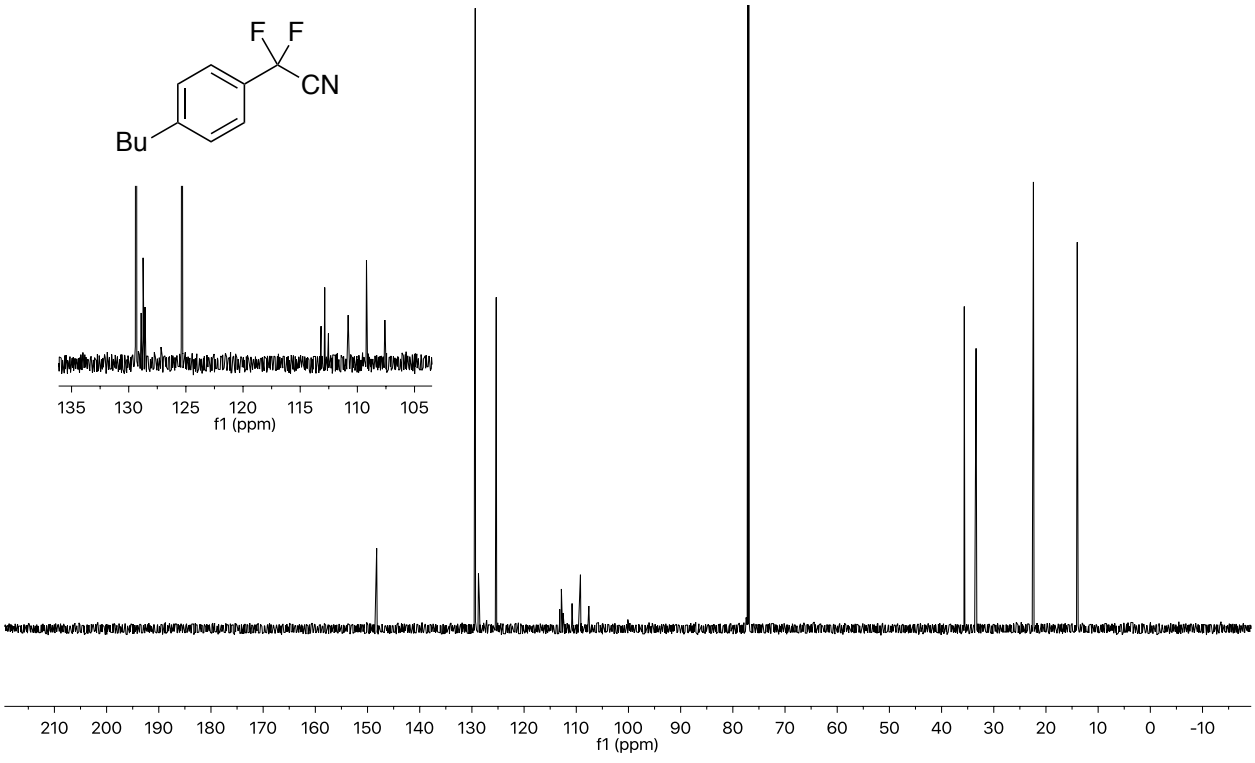
^{19}F NMR Spectrum of 2,2-difluoro-2-(triethylsilyl)acetonitrile (4)



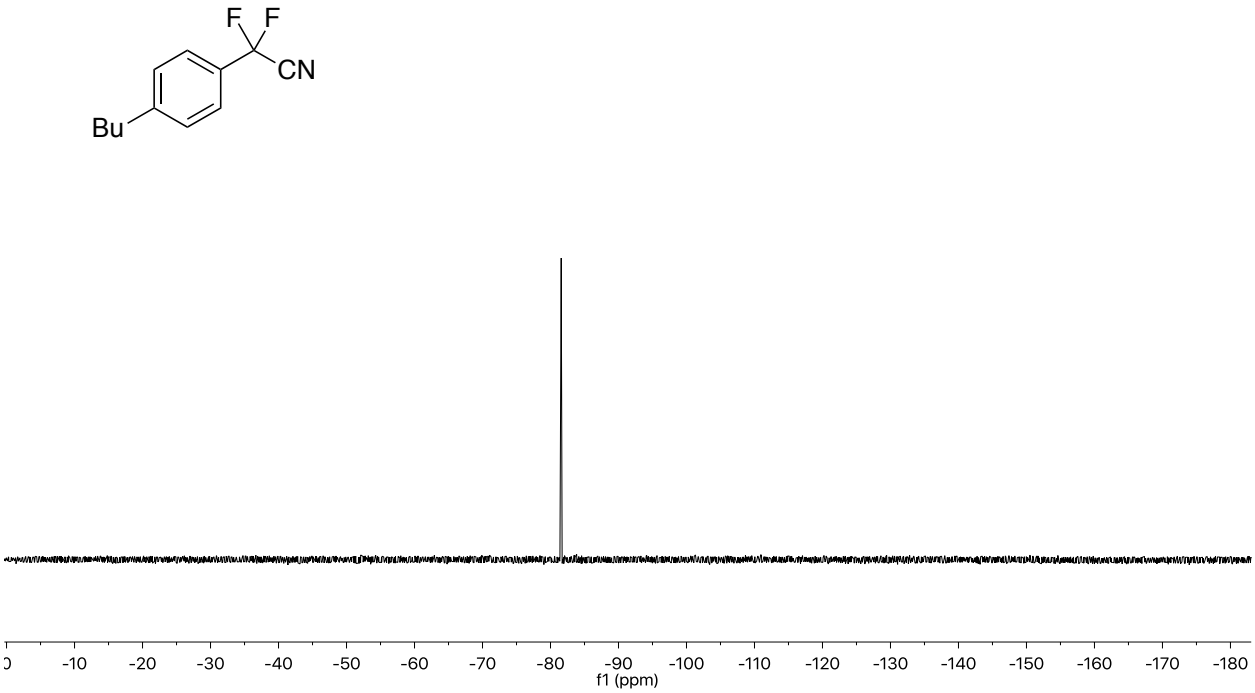
^{1}H NMR Spectrum of 2-(4-butylphenyl)-2,2-difluoroacetonitrile (5)



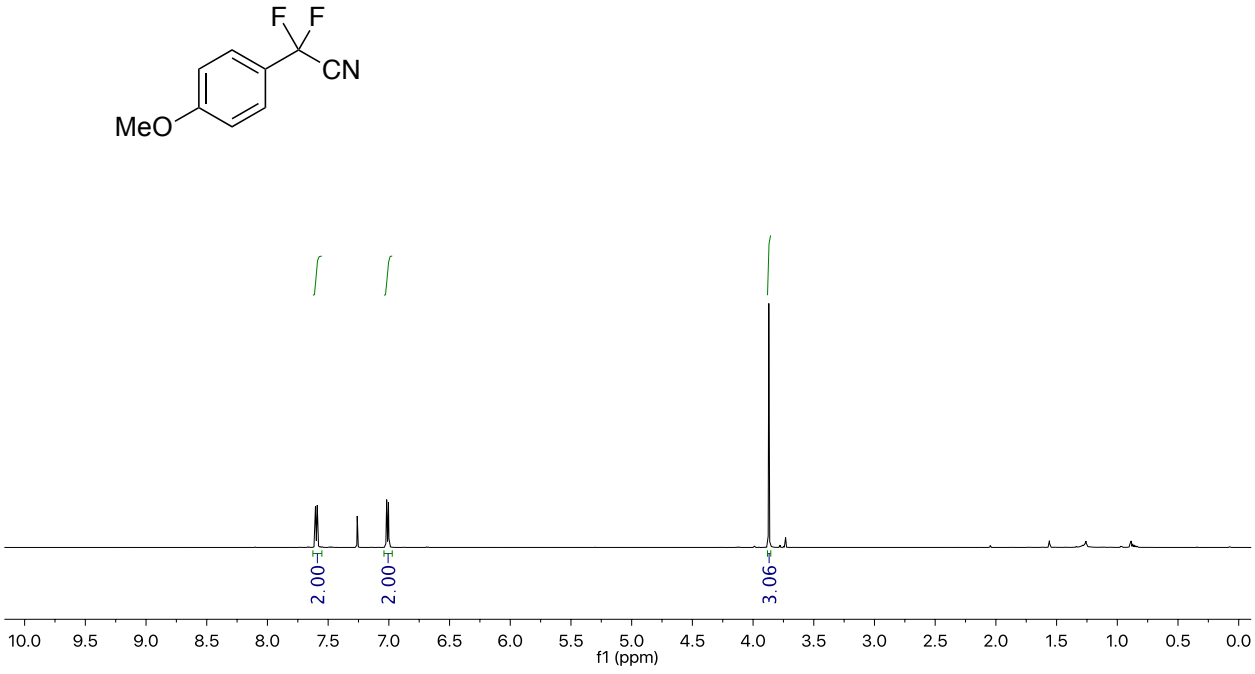
^{13}C NMR Spectrum of 2-(4-butylphenyl)-2,2-difluoroacetonitrile (5)



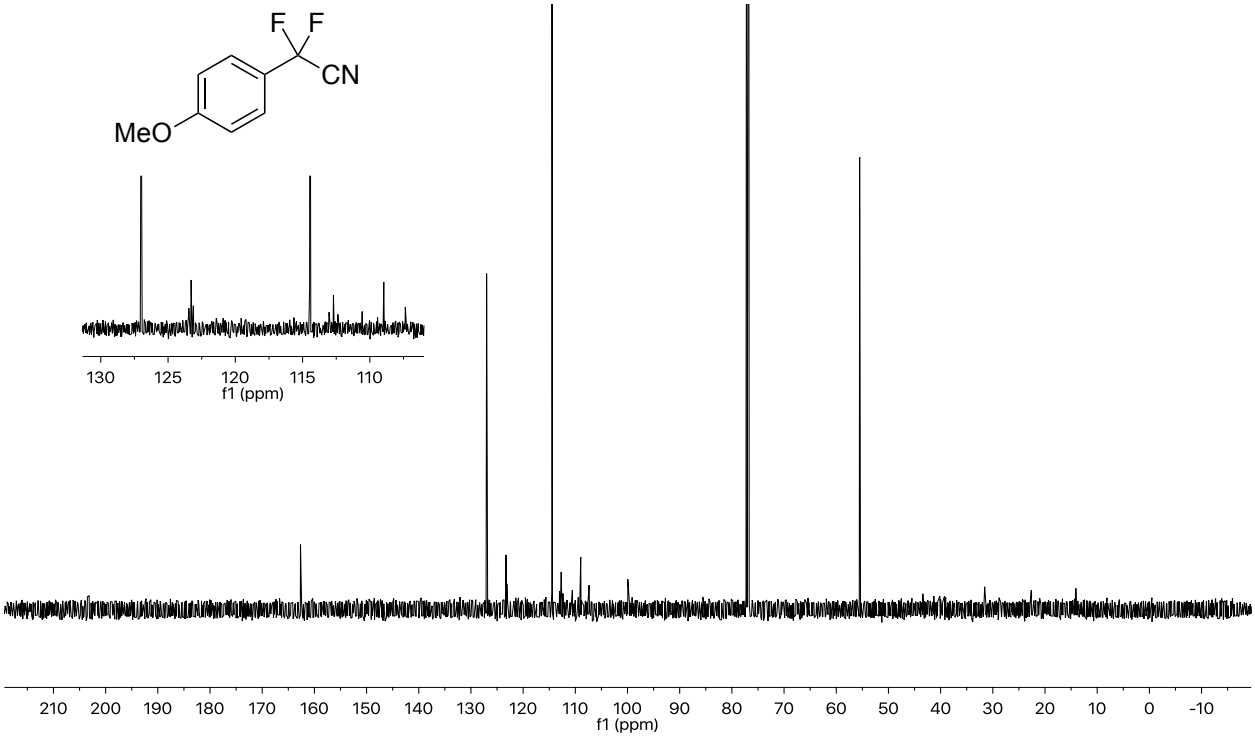
^{19}F NMR Spectrum of 2-(4-butylphenyl)-2,2-difluoroacetonitrile (5)



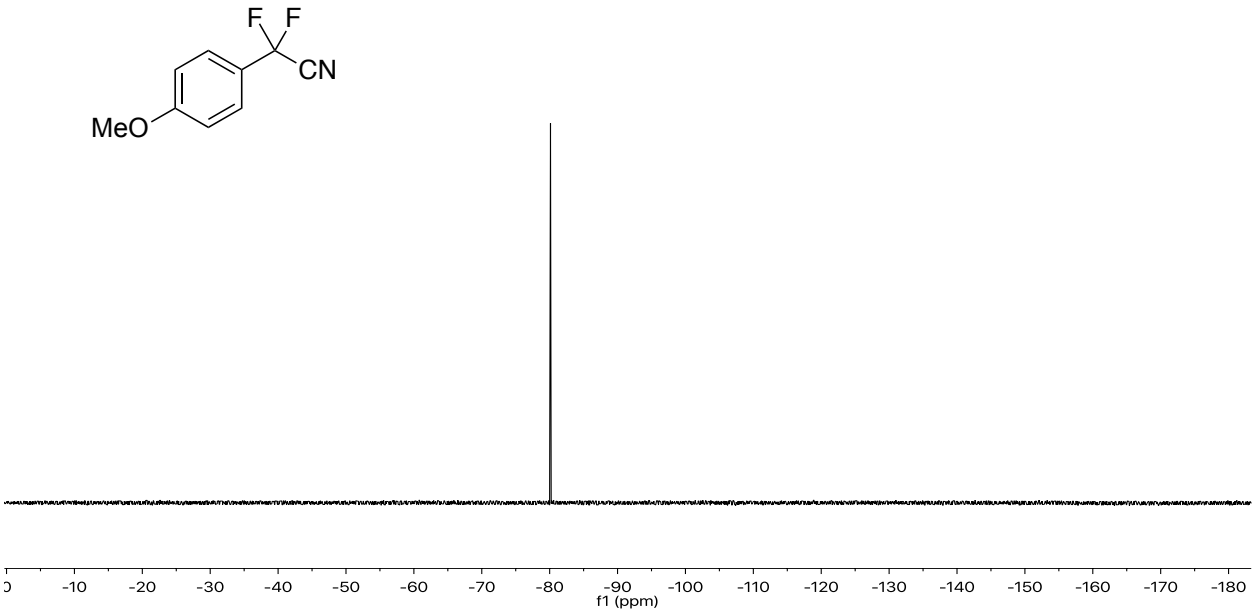
^{1}H NMR Spectrum of 2,2-difluoro-2-(4-methoxyphenyl)acetonitrile (6a)



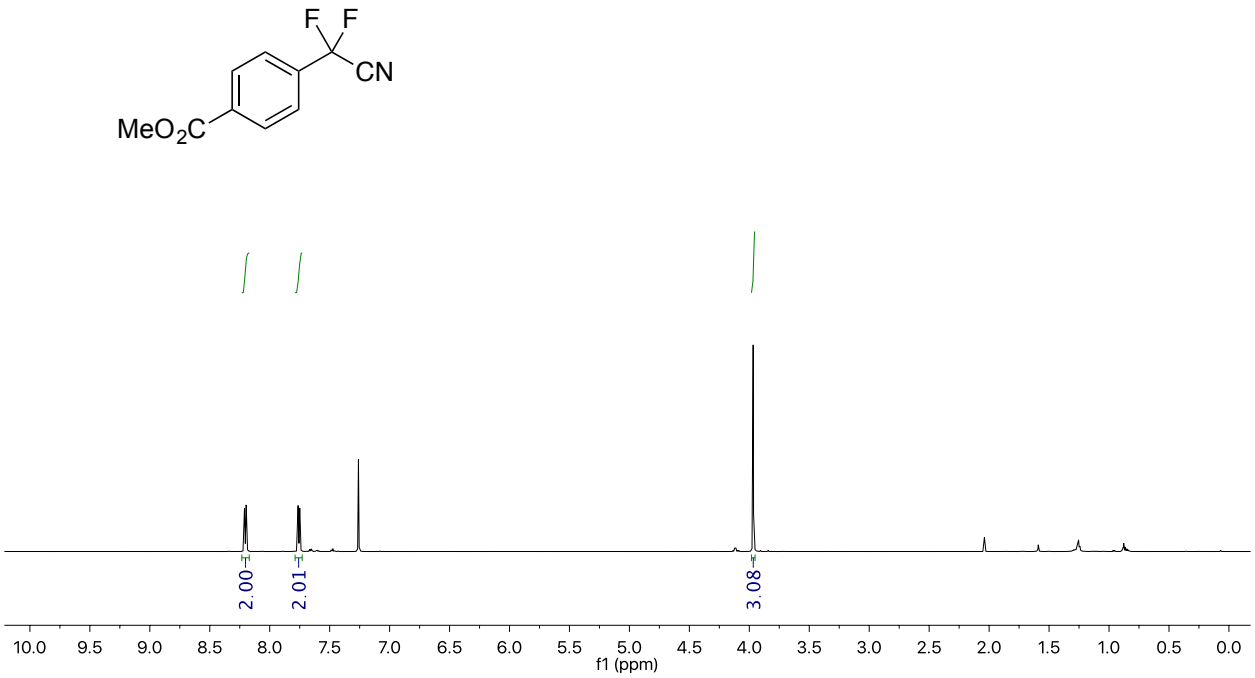
^{13}C NMR Spectrum of 2,2-difluoro-2-(4-methoxyphenyl)acetonitrile (6a)



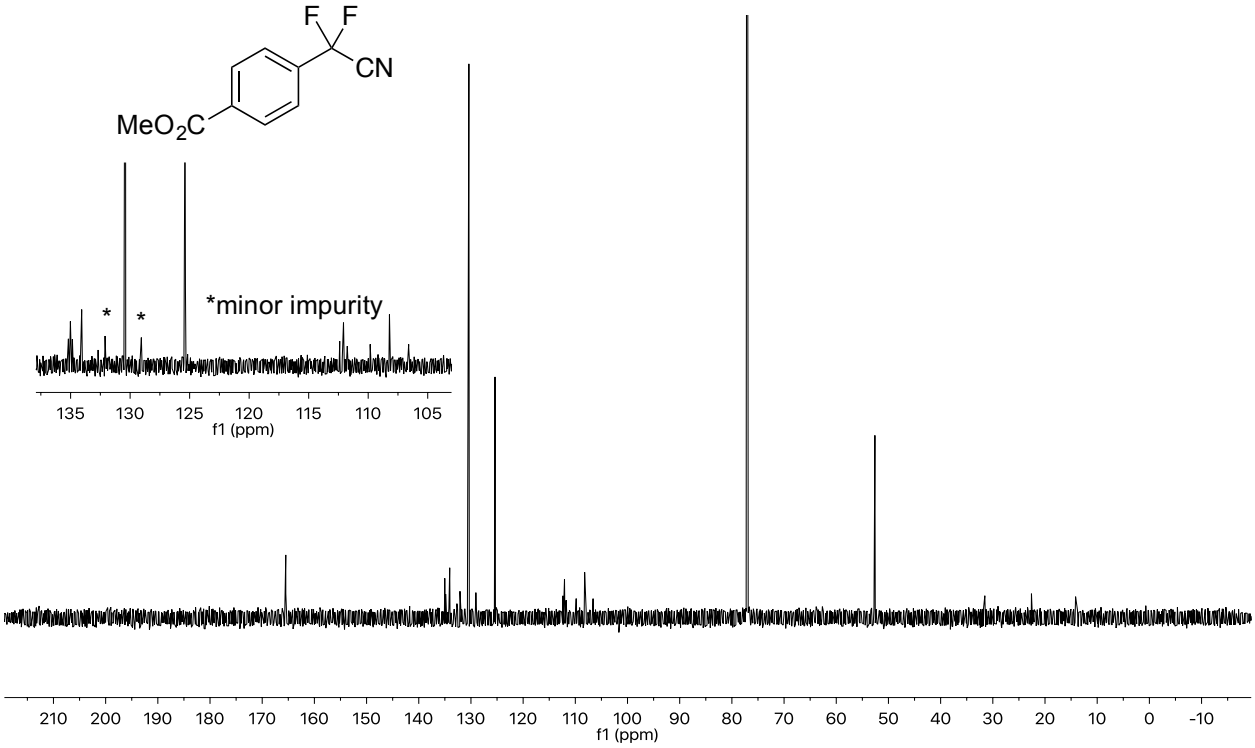
^{19}F NMR Spectrum of 2,2-difluoro-2-(4-methoxyphenyl)acetonitrile (6a)



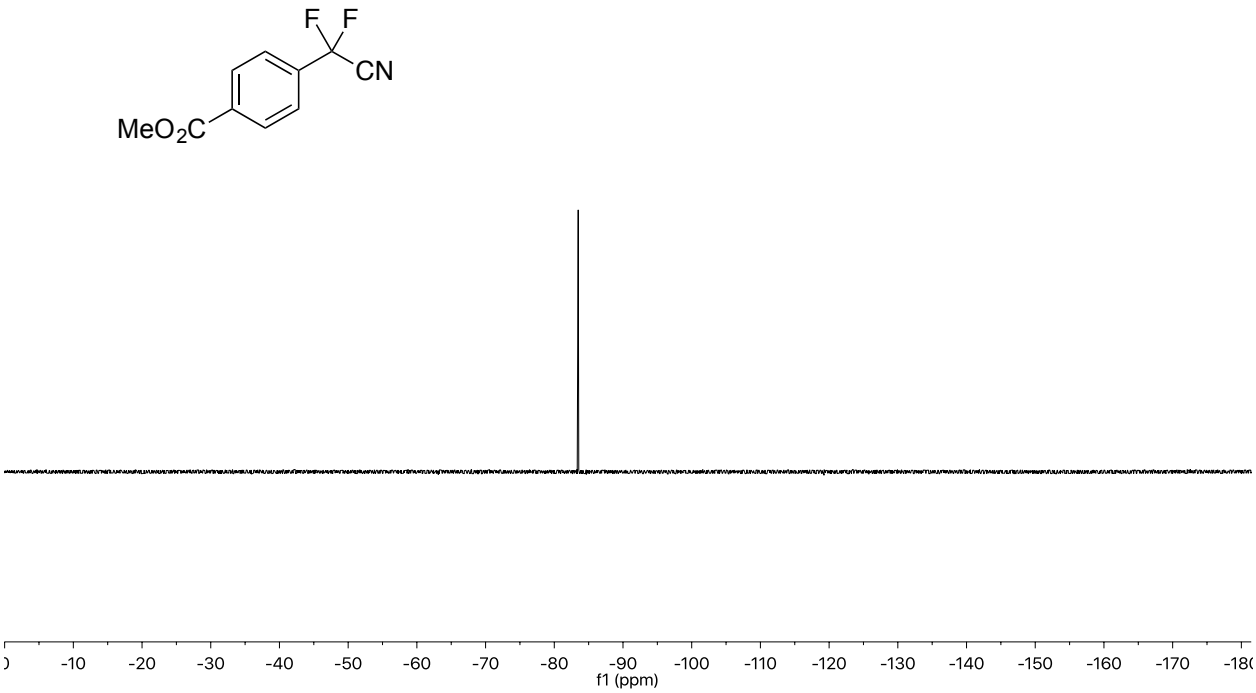
^{1}H NMR Spectrum of Methyl 4-(cyanodifluoromethyl)benzoate (6b)



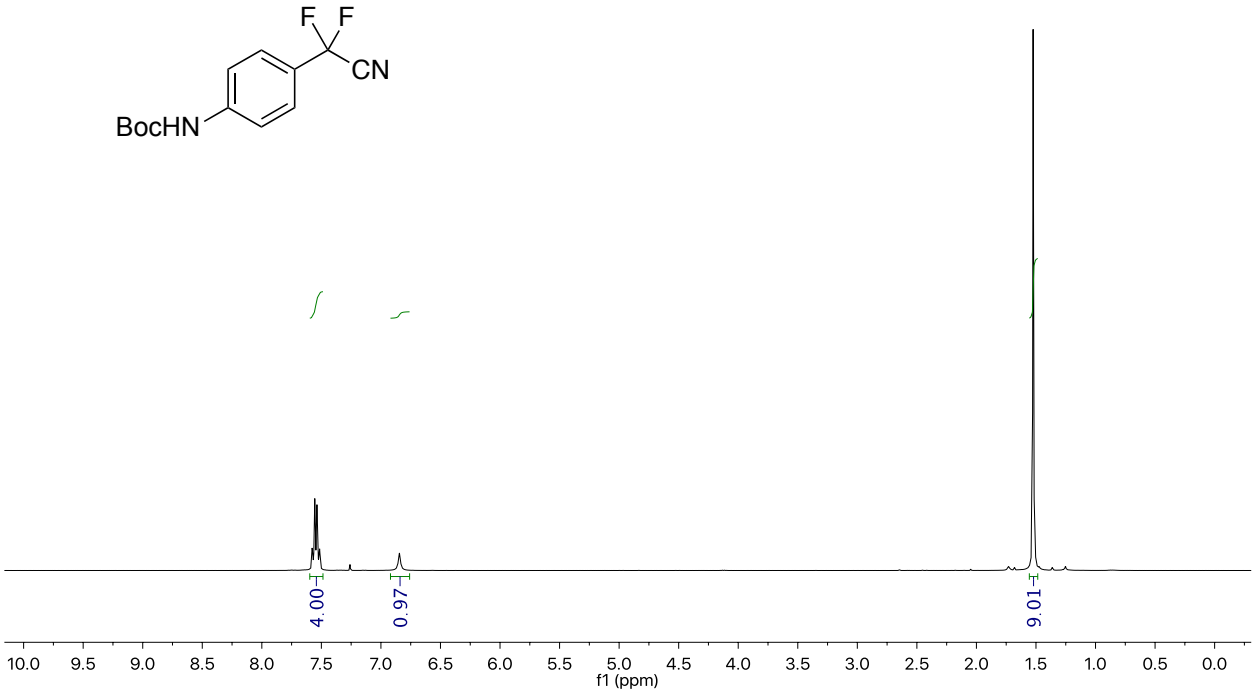
^{13}C NMR Spectrum of Methyl 4-(cyanodifluoromethyl)benzoate (6b)



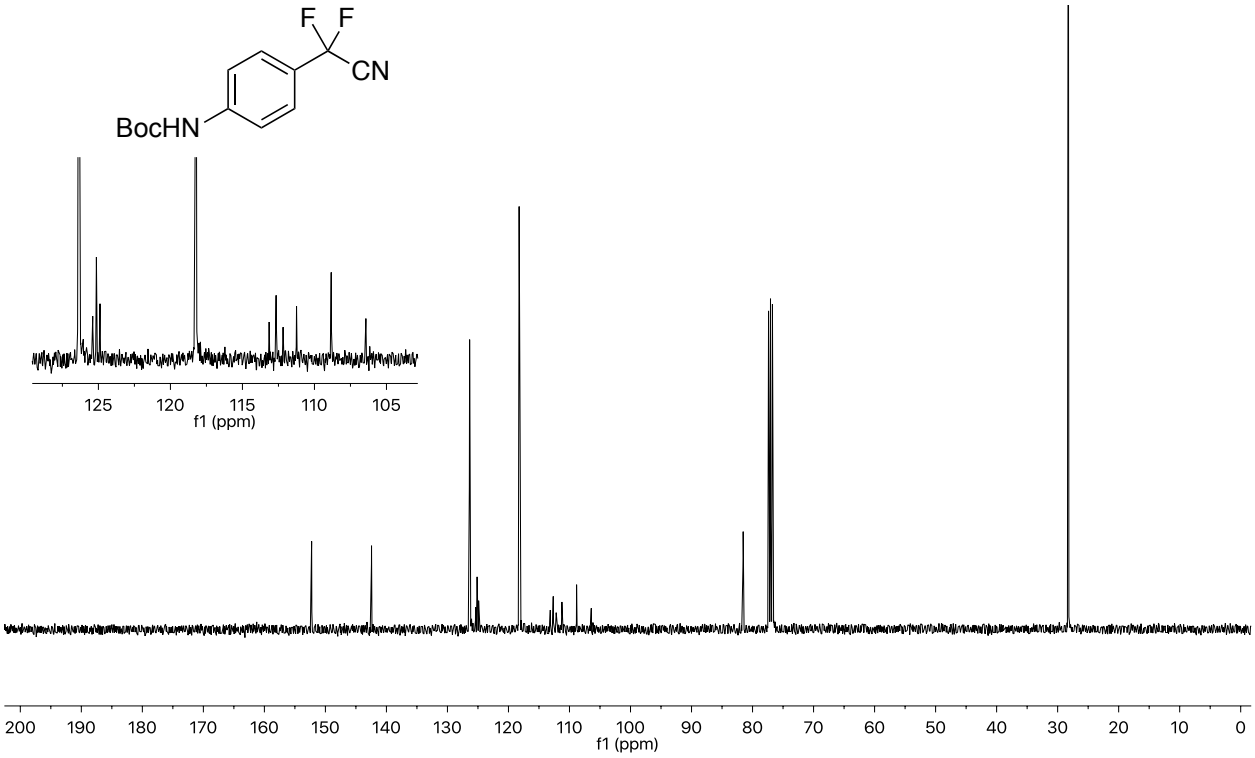
^{19}F NMR Spectrum of Methyl 4-(cyanodifluoromethyl)benzoate (6b)



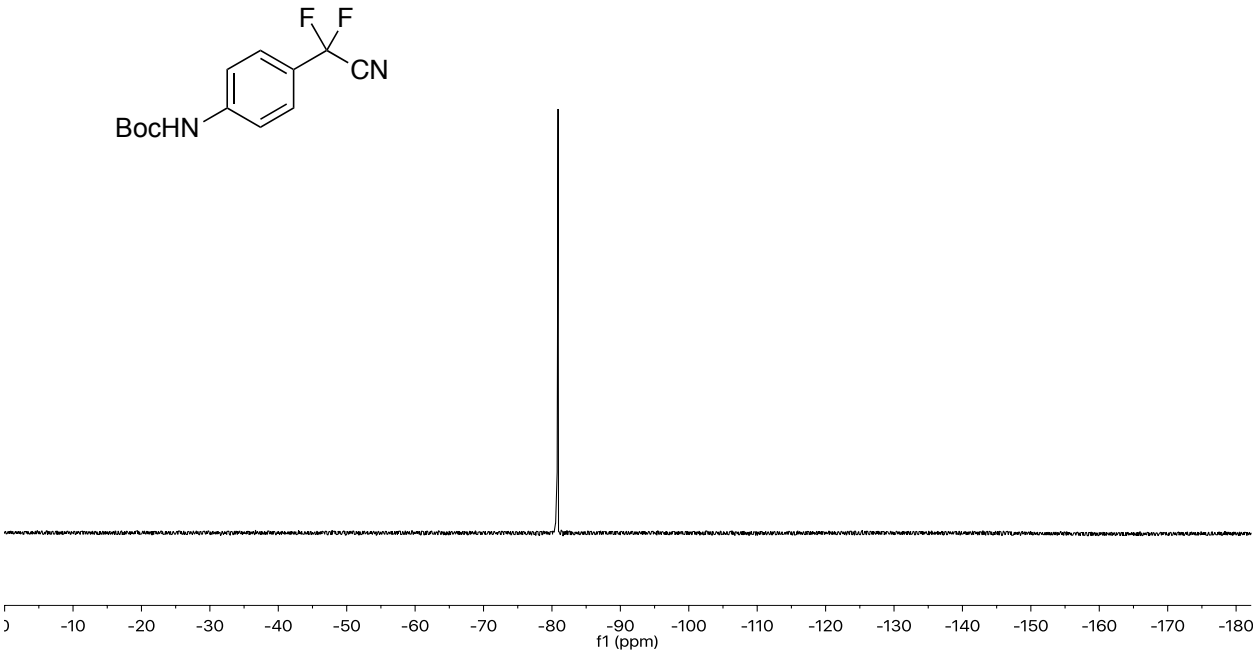
^{1}H NMR Spectrum of *tert*-butyl (4-(cyanodifluoromethyl)phenyl)carbamate (6c)



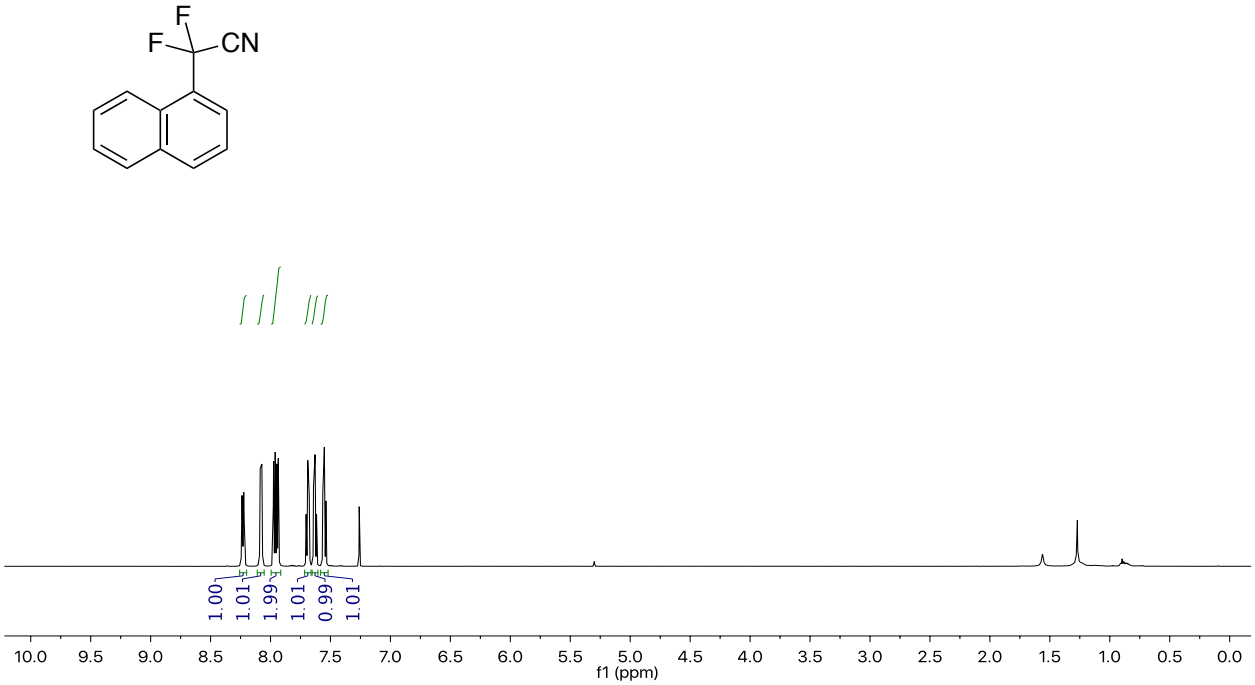
^{13}C NMR Spectrum of *tert*-butyl (4-(cyanodifluoromethyl)phenyl)carbamate (6c)



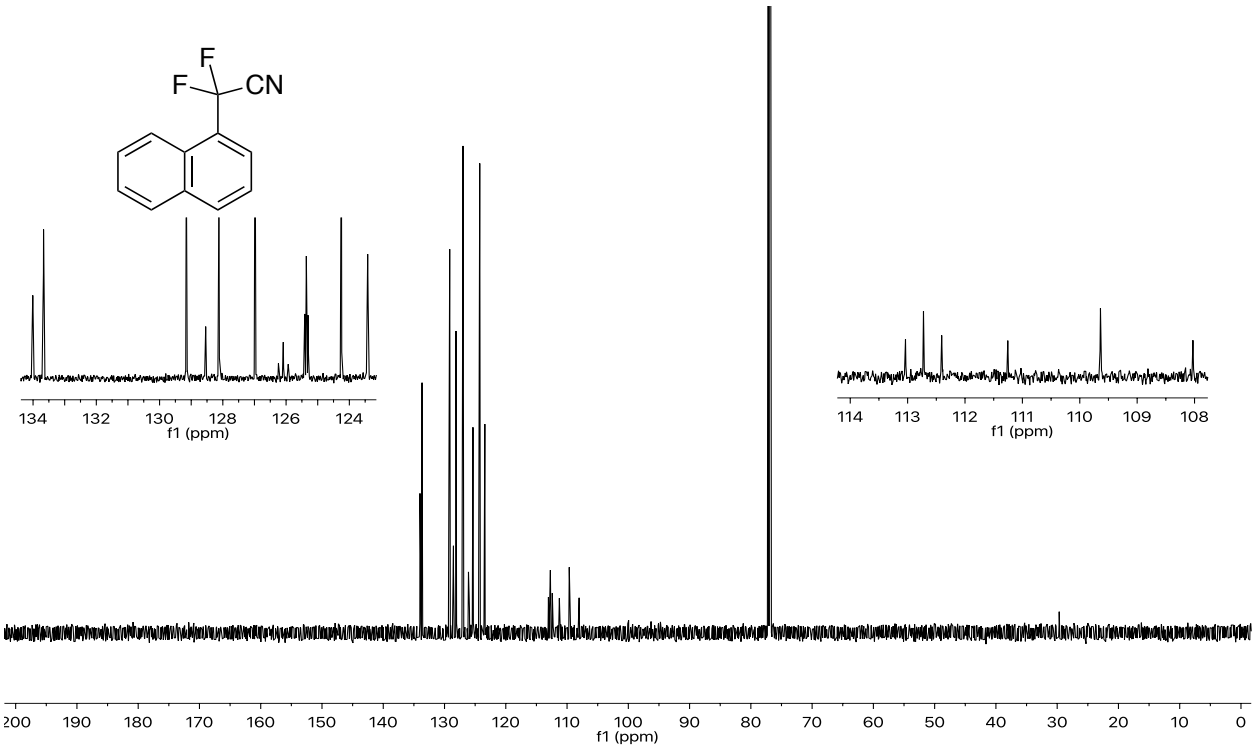
^{19}F NMR Spectrum of t*ert*-butyl (4-(cyanodifluoromethyl)phenyl)carbamate (6c)



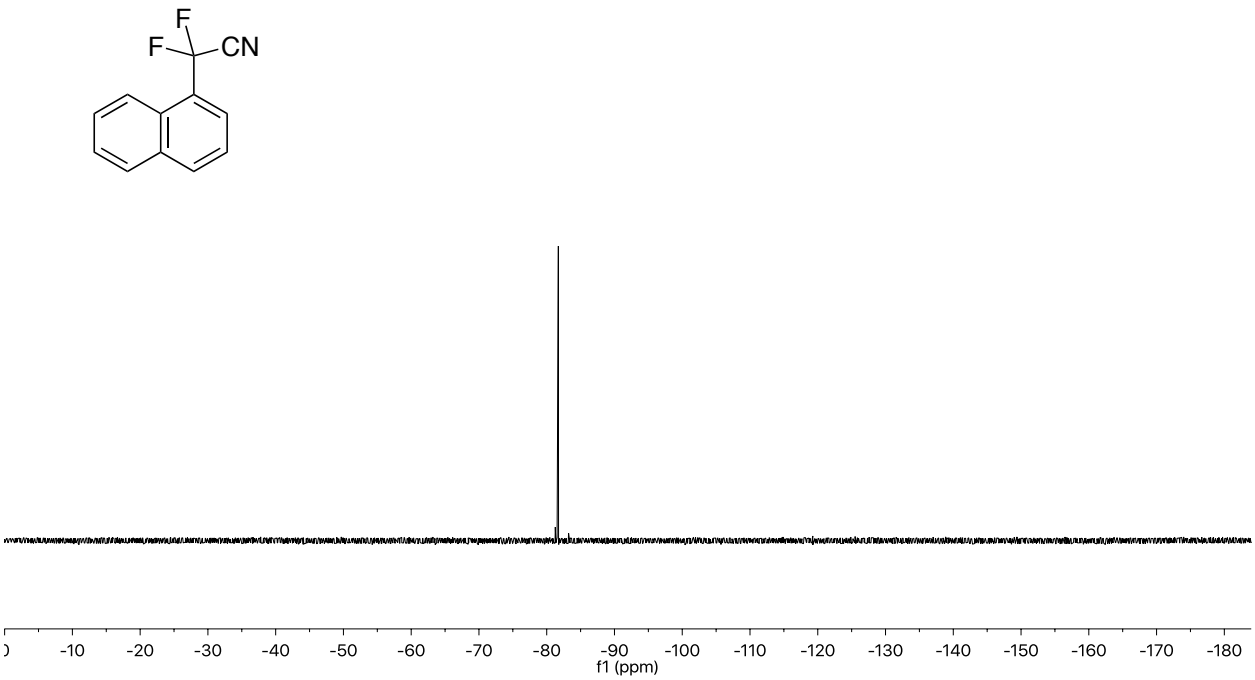
^{1}H NMR Spectrum of 2,2-difluoro-2-(naphthalen-1-yl)acetonitrile (6d)



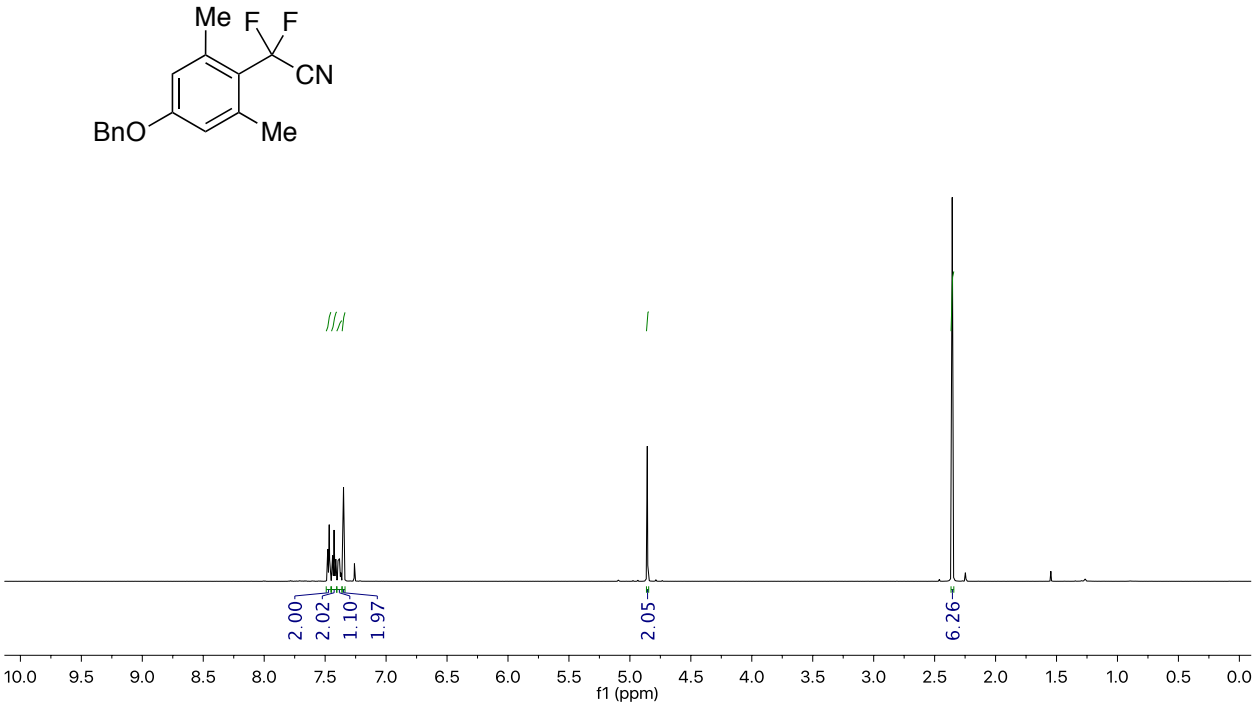
^{13}C NMR Spectrum of 2,2-difluoro-2-(naphthalen-1-yl)acetonitrile (6d)



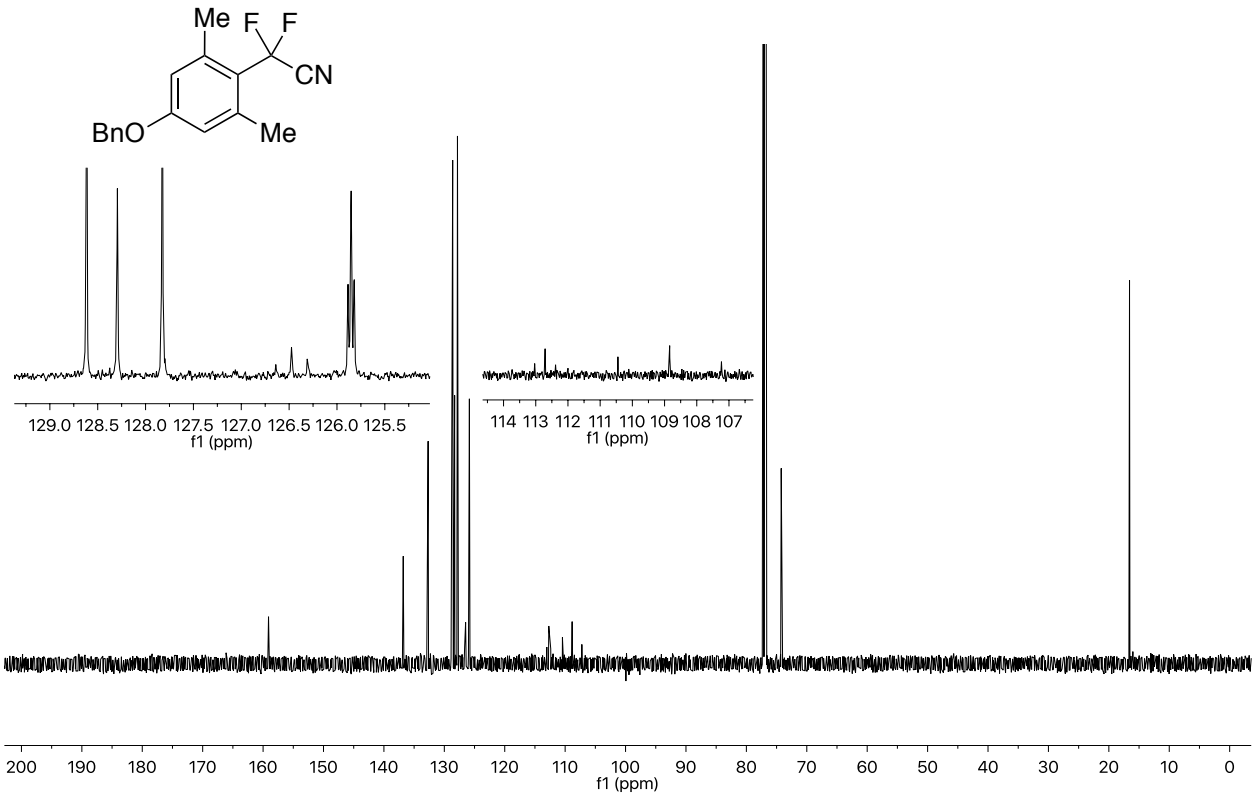
^{19}F NMR Spectrum of 2,2-difluoro-2-(naphthalen-1-yl)acetonitrile (6d)



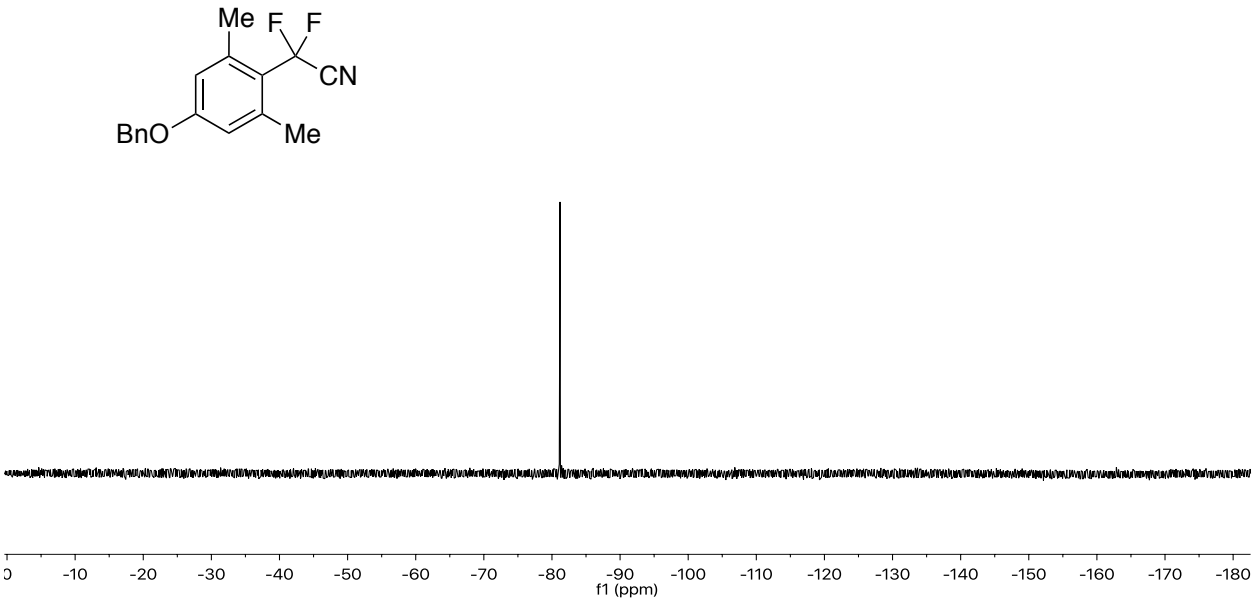
^{1}H NMR Spectrum of 2-(4-(benzyloxy)-2,6-dimethylphenyl)-2,2-difluoroacetonitrile (6e)



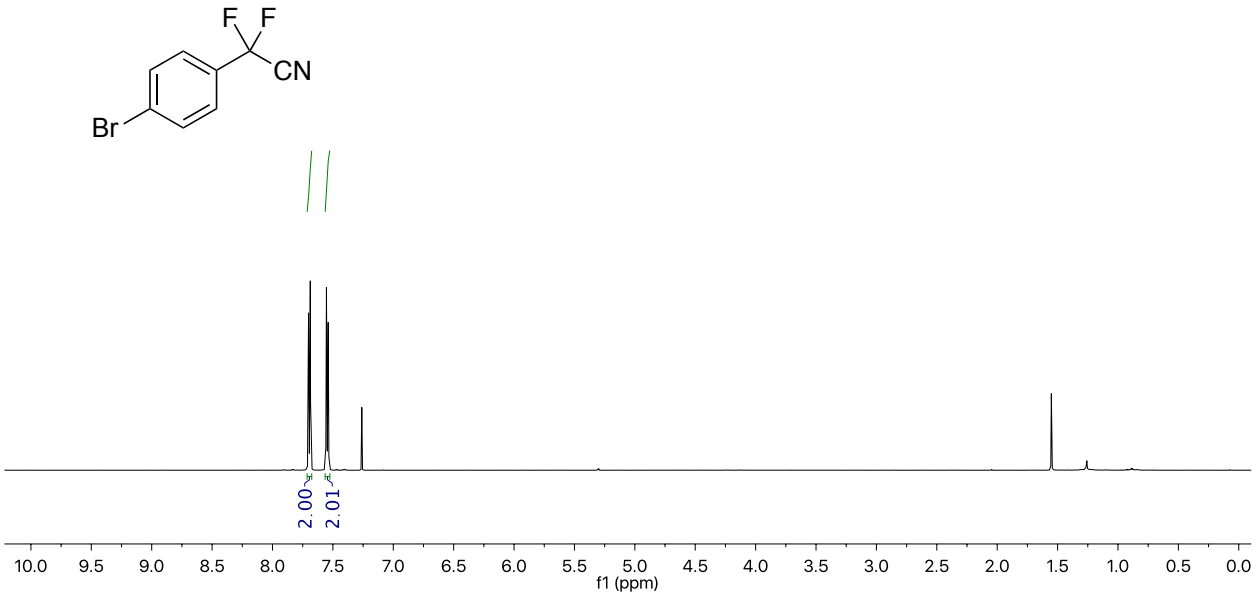
^{13}C NMR Spectrum of 2-(4-(benzyloxy)-2,6-dimethylphenyl)-2,2-difluoroacetonitrile (6e)



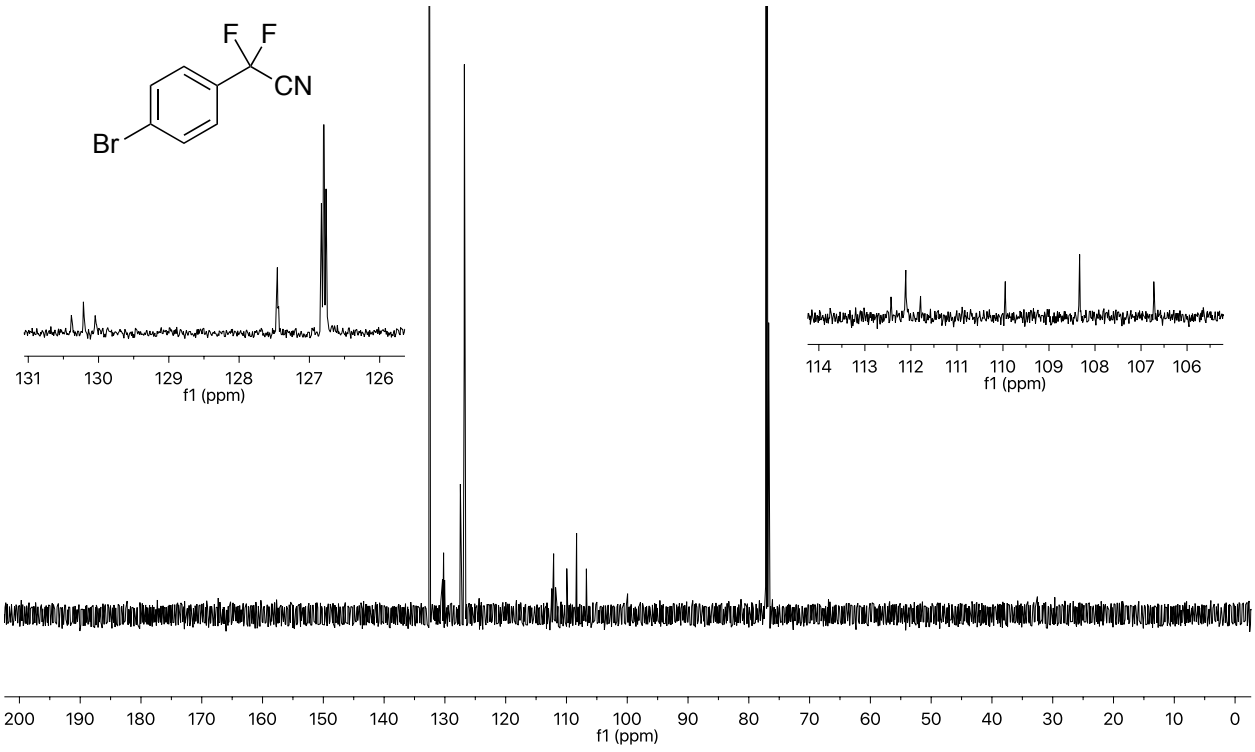
^{19}F NMR Spectrum of 2-(4-(benzyloxy)-2,6-dimethylphenyl)-2,2-difluoroacetonitrile (6e)



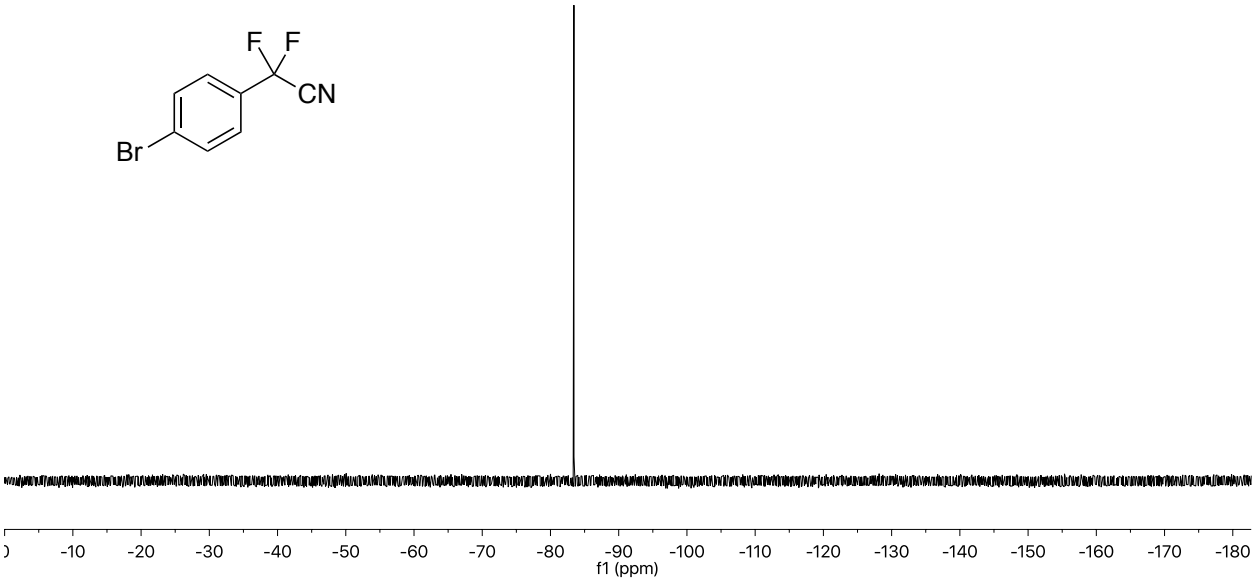
^{1}H NMR Spectrum of 2-(4-bromophenyl)-2,2-difluoroacetonitrile (6f)



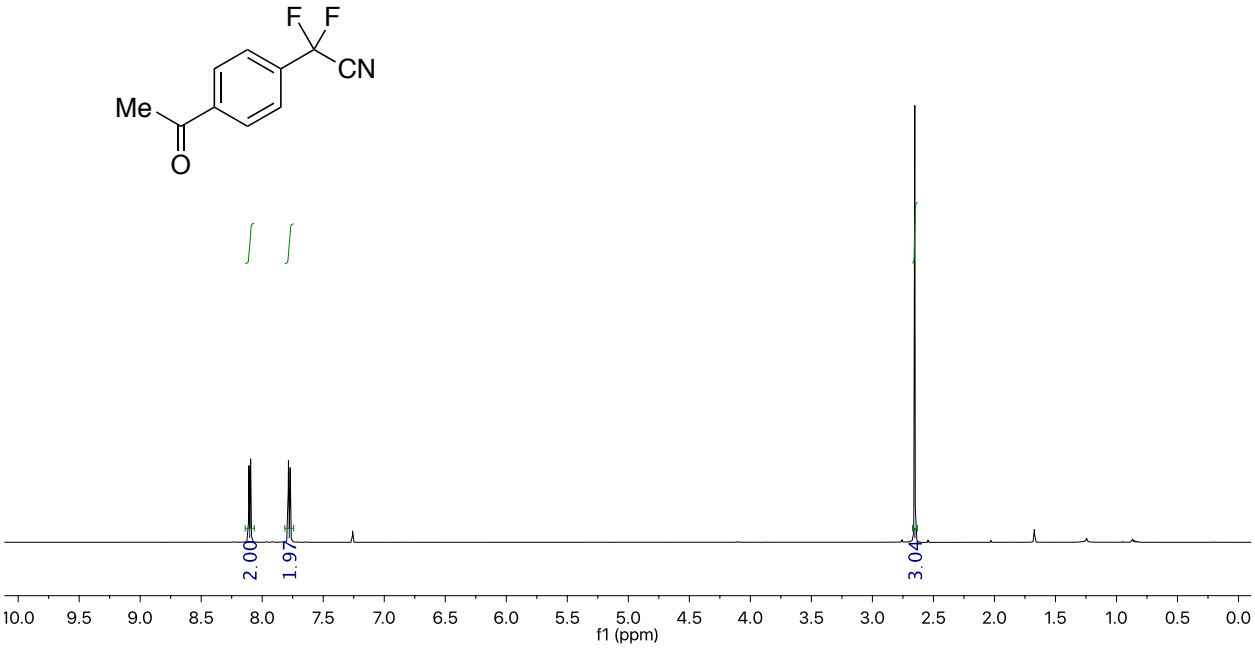
^{13}C NMR Spectrum of 2-(4-bromophenyl)-2,2-difluoroacetonitrile (6f)



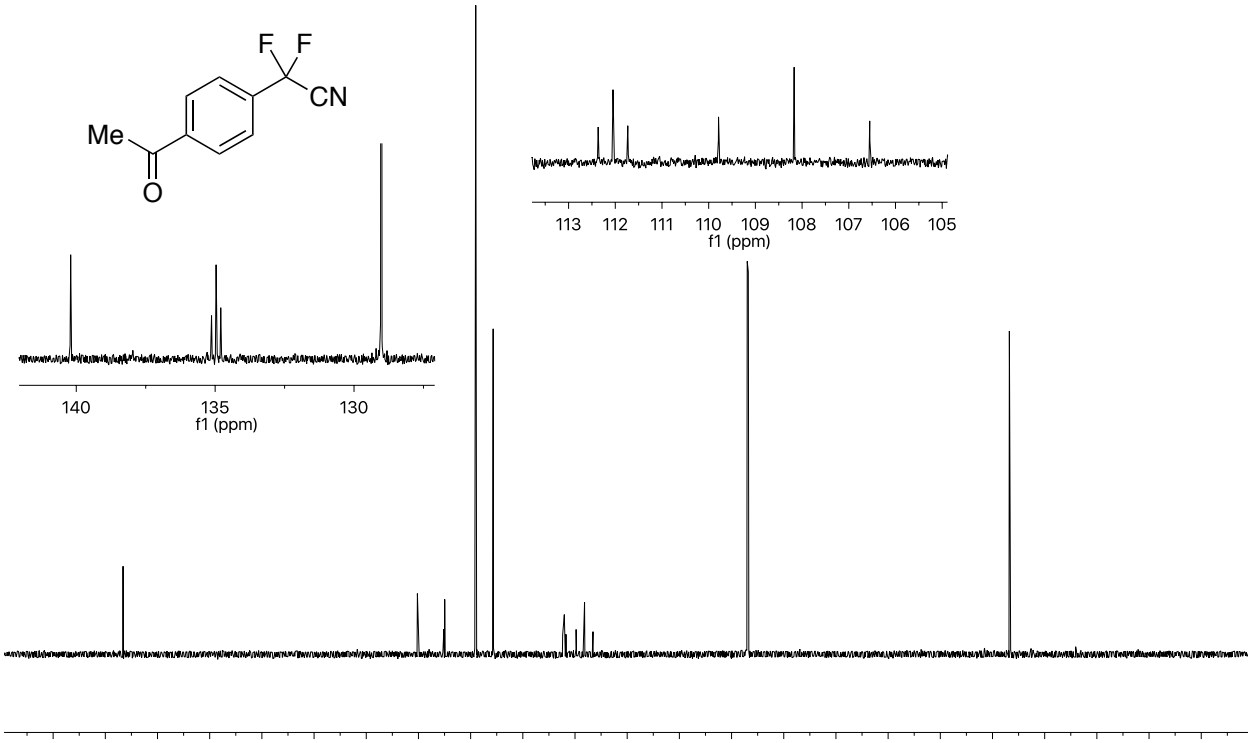
^{19}F NMR Spectrum of 2-(4-bromophenyl)-2,2-difluoroacetonitrile (6f)



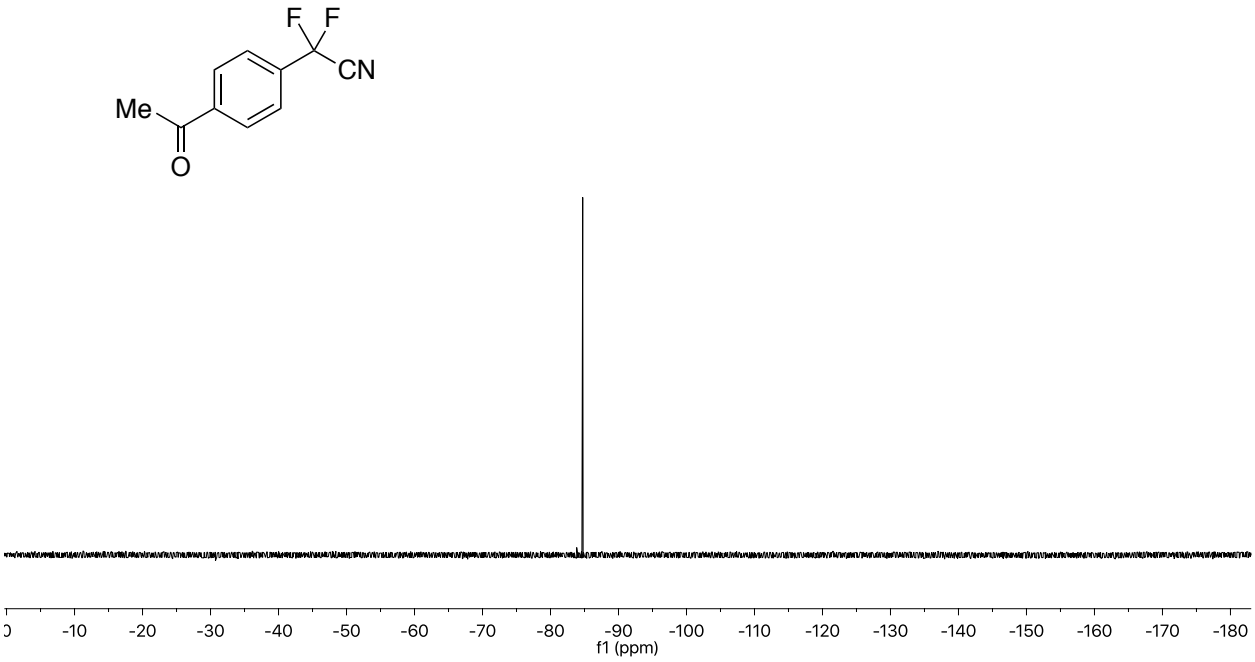
^{1}H NMR Spectrum of 2-(4-acetylphenyl)-2,2-difluoroacetonitrile (6g)



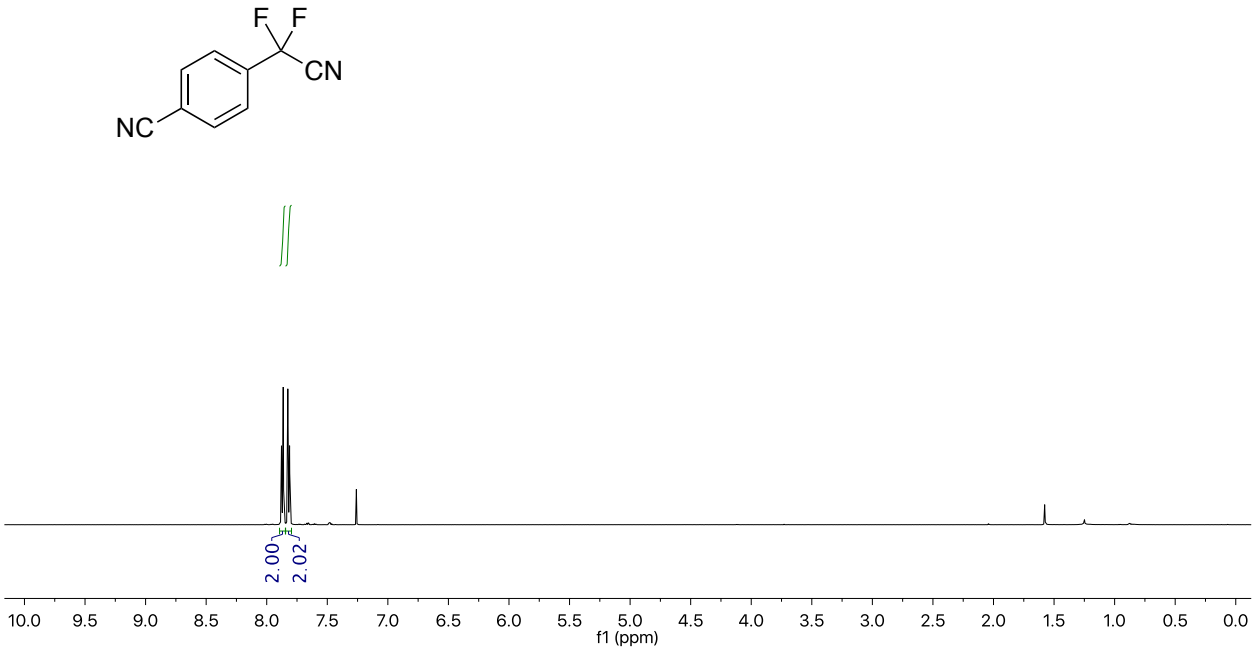
^{13}C NMR Spectrum of 2-(4-acetylphenyl)-2,2-difluoroacetonitrile (6g)



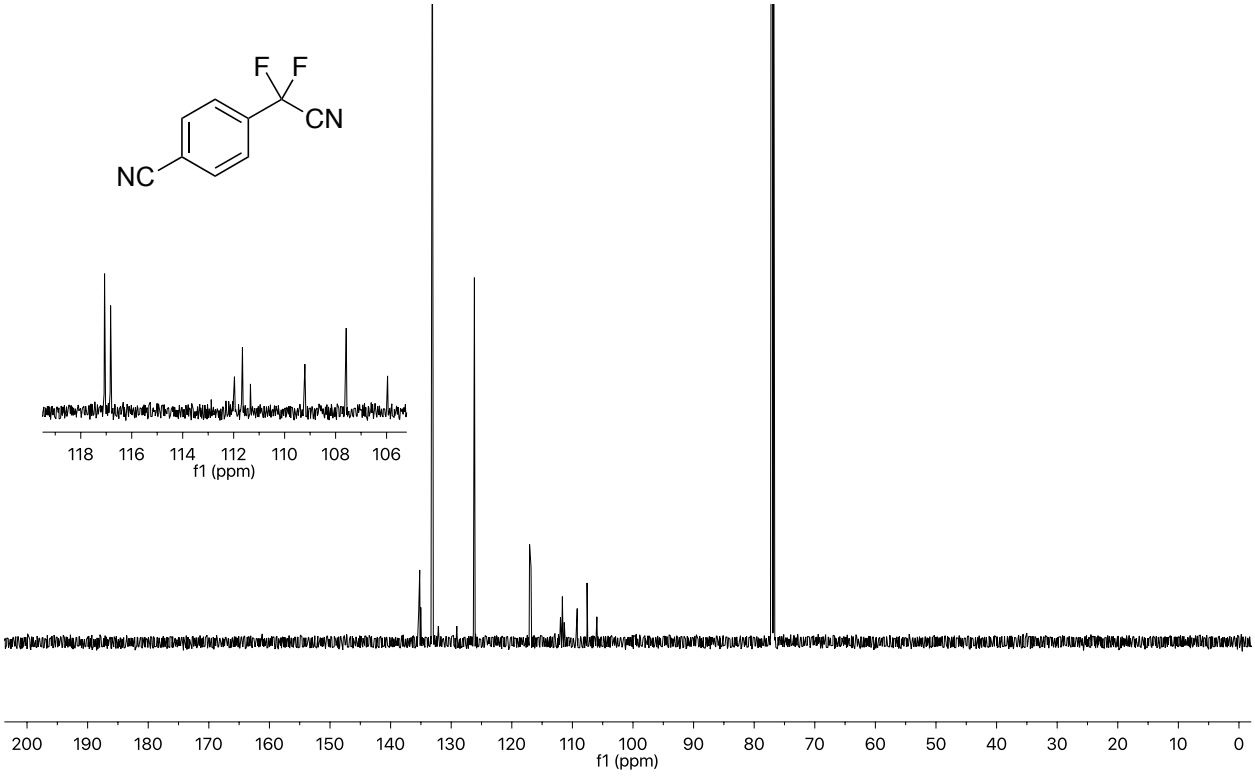
^{19}F NMR Spectrum of 2-(4-acetylphenyl)-2,2-difluoroacetonitrile (6g)



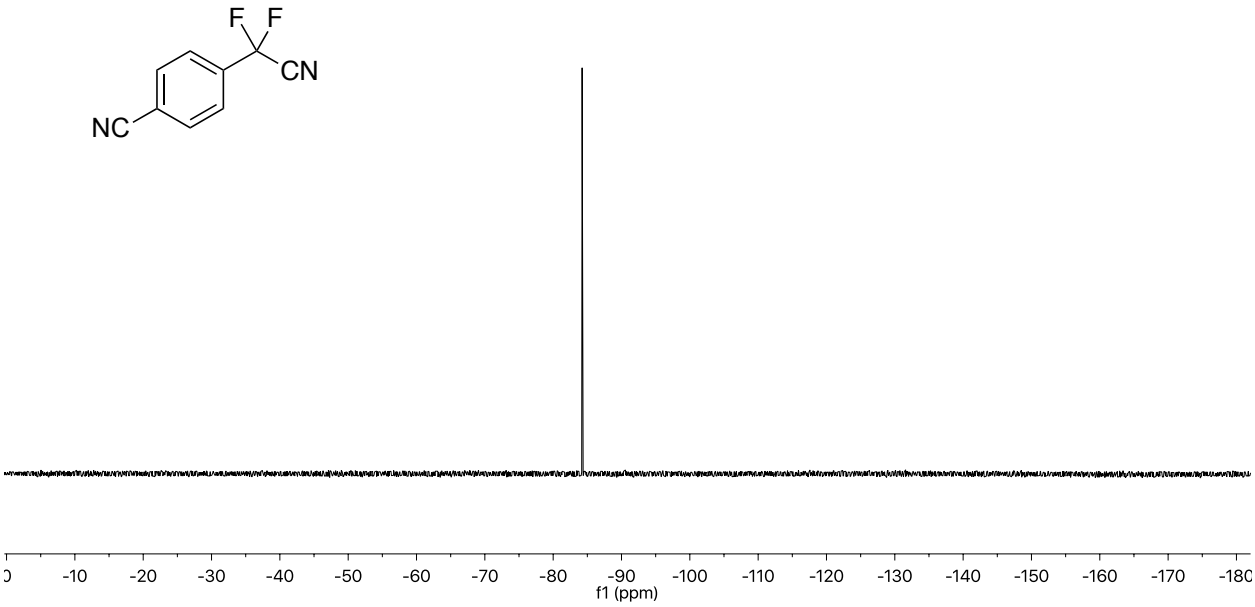
^{1}H NMR Spectrum of 4-(cyanodifluoromethyl)benzonitrile (6h)



^{13}C NMR Spectrum 4-(cyanodifluoromethyl)benzonitrile (6h)



^{19}F NMR Spectrum 4-(cyanodifluoromethyl)benzonitrile (6h)



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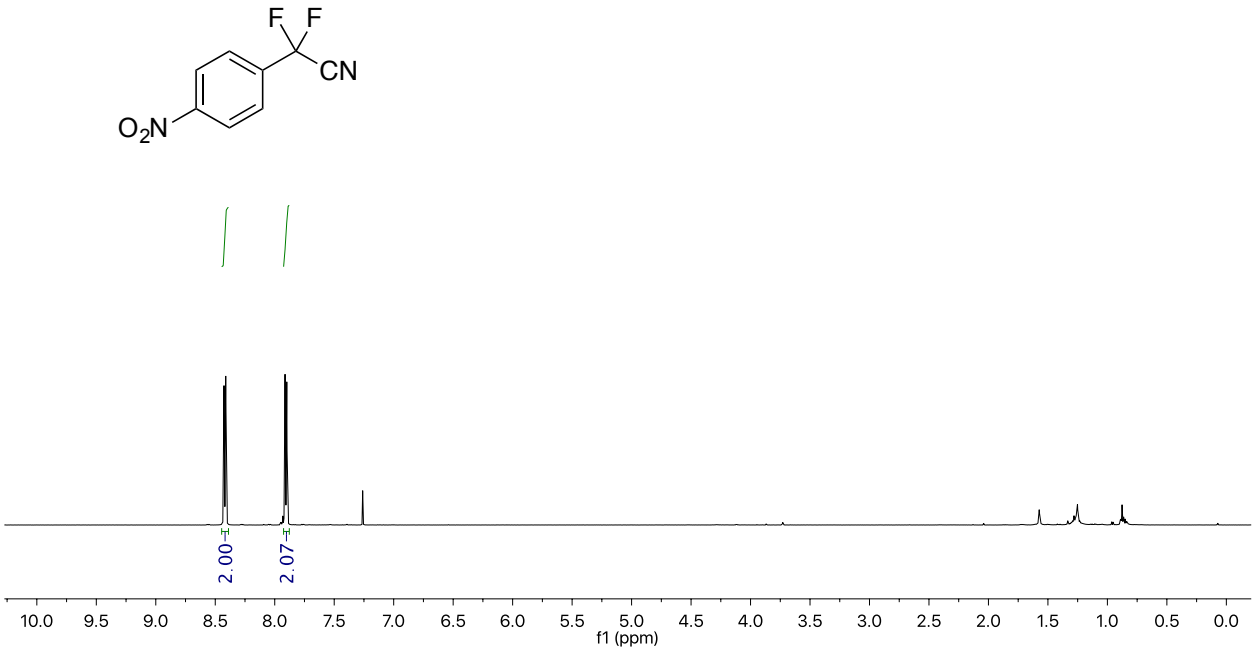
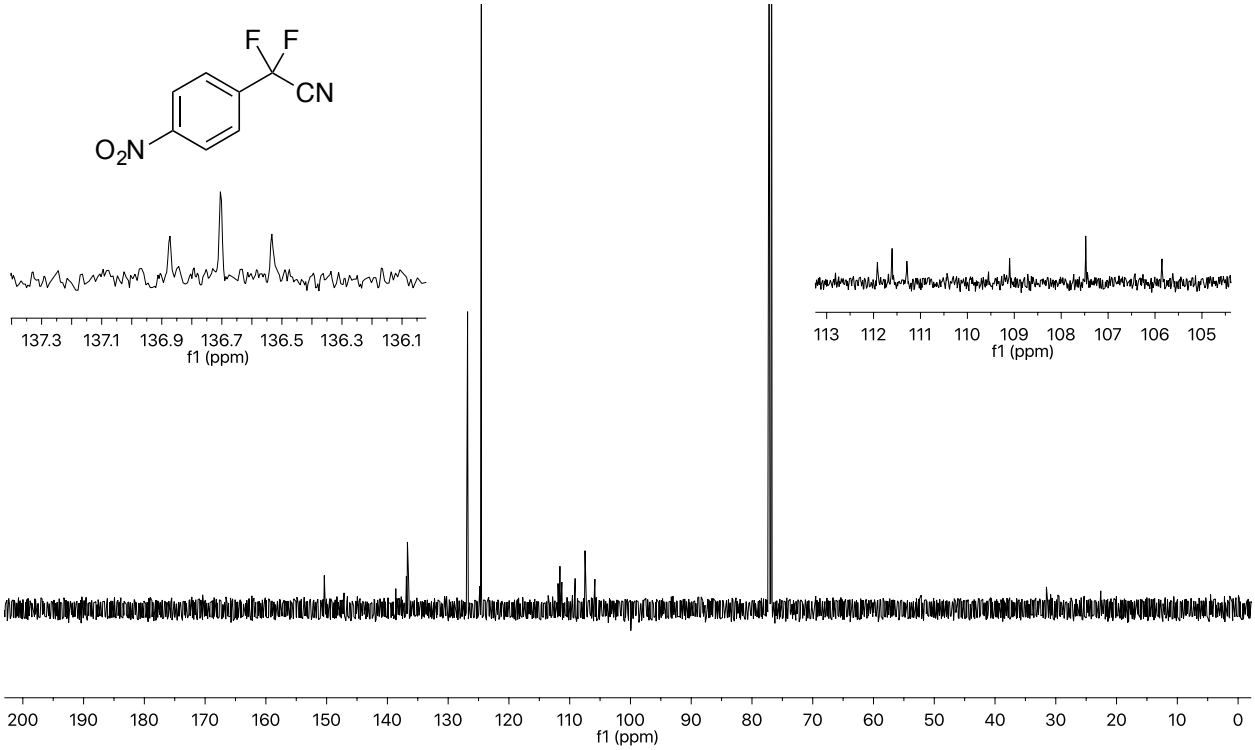
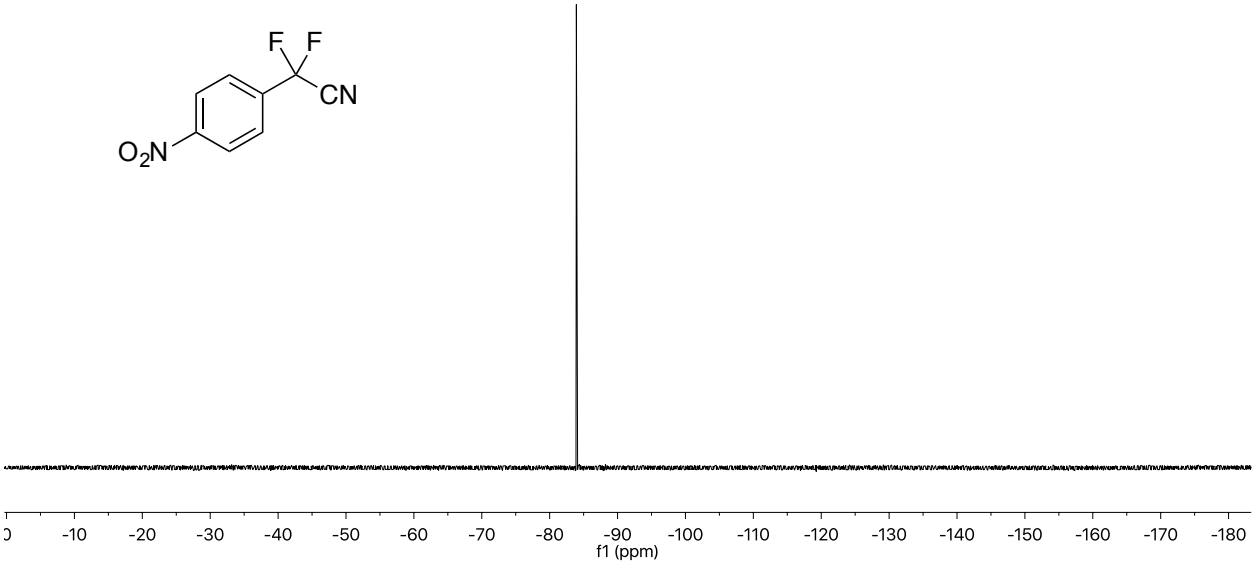


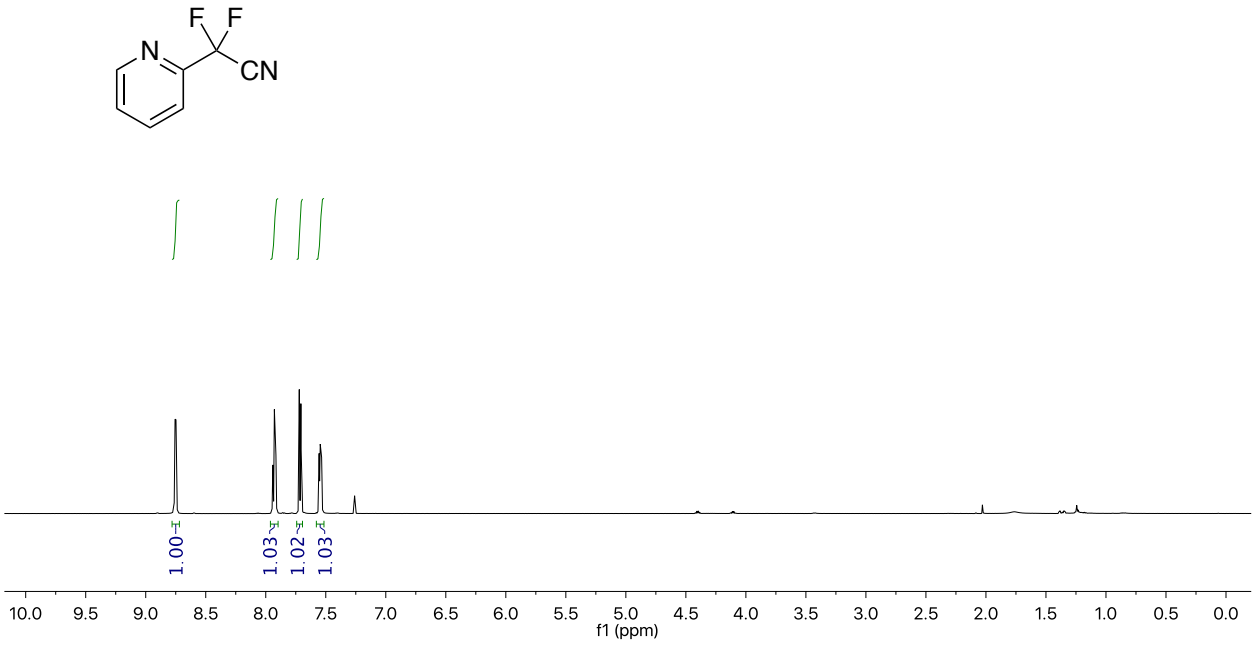
^{13}C NMR Spectrum of 2,2-difluoro-2-(4-nitrophenyl)acetonitrile (6i)



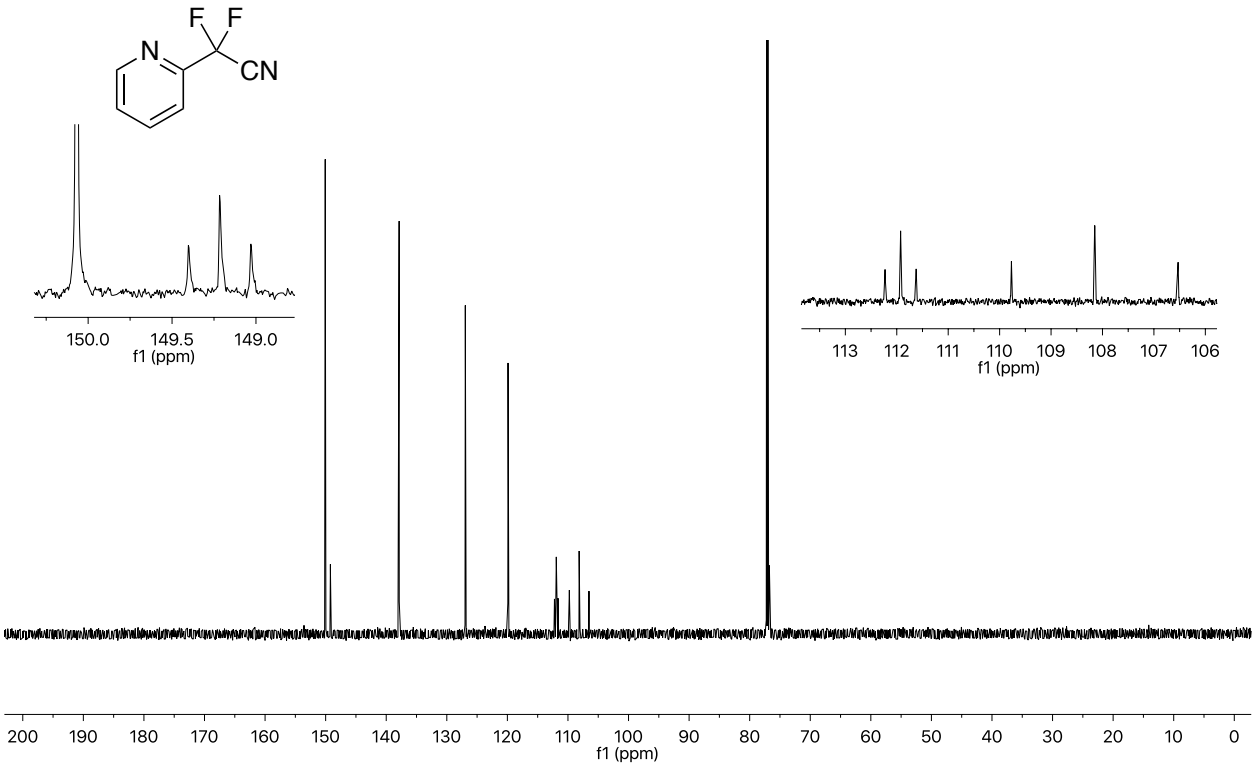
^{19}F NMR Spectrum of 2,2-difluoro-2-(4-nitrophenyl)acetonitrile (6i)



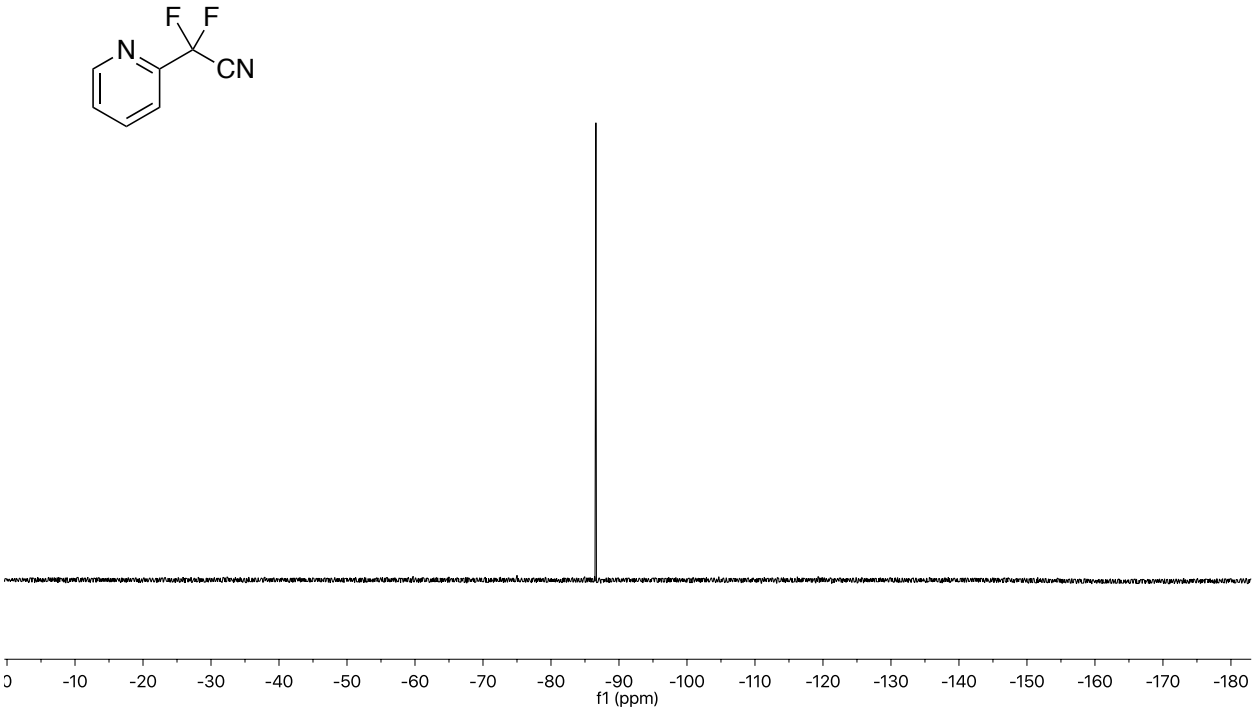
^{1}H NMR Spectrum of 2,2-difluoro-2-(pyridin-2-yl)acetonitrile (6j)



^{13}C NMR Spectrum of 2,2-difluoro-2-(pyridin-2-yl)acetonitrile (6j)



^{19}F NMR Spectrum of 2,2-difluoro-2-(pyridin-2-yl)acetonitrile (6j)



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Chapter 5

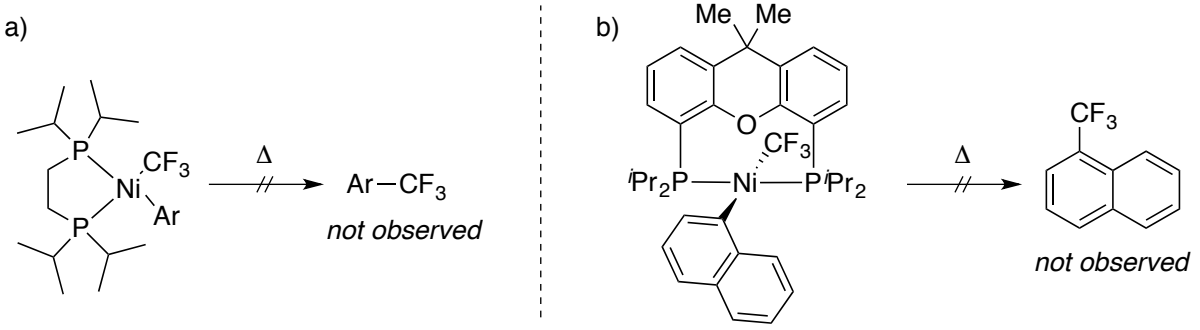
Oxidatively-Induced Reductive Elimination from Arylnickel Trifluoromethyl Complexes

5.1 Introduction

Cross-coupling reactions of aryl halides and trifluoromethyl nucleophiles are an attractive strategy for the synthesis of trifluoromethylarenes from widely available starting materials. However, only a single system for high-yielding catalytic trifluoromethylation with a group 10 metal has been reported. In 2010, Buchwald reported a palladium-catalyzed coupling reaction for the synthesis of trifluoromethylarenes, but the reaction requires high temperatures (120-140 °C) and the substrate scope is limited to aryl chlorides that do not contain electrophilic functional groups such as aldehydes and ketones or protic groups such as unprotected alcohols and amines.[1] No examples of nickel-catalyzed trifluoromethylation reactions of aryl halides have been reported. However, such transformations would be desirable because nickel is significantly less expensive and more abundant than palladium and because nickel-catalyzed coupling reactions may occur with a scope complementary to that of palladium-catalyzed reactions.

Reductive elimination has been identified as a slow and often low-yielding step in the palladium-catalyzed trifluoromethylation of aryl halides. Complexes containing a fluorine atom on the α-carbon of an alkyl group undergo reductive elimination more slowly than those containing the analogous non-fluorinated alkyl group.[2] As a result, Ar-CF_3 bond formation from palladium(II) complexes requires high temperatures and/or ligands that are sterically bulky, are highly-electron deficient, or have a wide bite angle.[1, 3-6]

Reductive elimination reactions from trifluoromethyl complexes of nickel also have been explored. Vicic and coworkers prepared a series of (dippe)Ni(Ar)(CF_3) complexes (dippe = 1,2-bis(diisopropylphosphino)ethane), but found that the complexes decomposed without formation of an Ar-CF_3 bond when heated or upon addition of oxidants (Scheme 5.1a).[7] Low yields (11-22%) of trifluoromethylarene were formed upon addition of excess PhZnBr, $ZnBr_2$, or water.



Scheme 5.1 Unsuccessful attempts to achieve reductive elimination of Ar-CF_3 from isolated Ni^{II} complexes.

A computational study to predict which bidentate phosphine ligands would promote reductive elimination from Ni(II) complexes to form an Ar-CF_3 bond identified several candidate ligands that were predicted to form LNi(Ph)(CF_3) complexes with moderate barriers to reductive elimination.[8] For instance, the computed barrier for reductive elimination of Ph-CF_3 from a phosphine-ligated arylnickel trifluoromethyl complex was 22.6 kcal/mol with dippf (dippf = 1,1′-bis(diisopropylphosphino)ferrocene) as ligand and 23.2 kcal/mol for dcypf (dcypf = 1,1′-

bis(dicyclohexylphosphino)ferrocene) as ligand. However, the authors reported that attempts to prepare these complexes in order to study their reductive elimination reactions were unsuccessful. In the same study, the synthesis of (^{i}PrXantphos)Ni(1-Np)(CF_3) was described. However, heating this complex at 120 ºC resulted in decomposition of the metal complex without concomitant formation of 1-NpCF_3 (Scheme 5.1b).

The ability of Ni to access a range of oxidation states raises the possibility of accelerating reductive elimination by accessing a higher oxidation state than Ni(II). Hillhouse demonstrated that reductive elimination reactions that are slow and occur in low yield from Ni(II) complexes occur rapidly and in higher yield upon addition of an oxidant. This accelerating affect was attributed to the generation of Ni(III) species that undergo facile reductive elimination.[9-10]

More recently, a series of Ni-catalyzed cross-coupling reactions that occur in the presence of a photocatalyst and visible light have been described. In several reports, oxidation of a Ni(II) intermediate to a Ni(III) species that undergoes fast reductive elimination has been proposed as a key step to achieve efficient catalysis.[11] For example, MacMillan and coworkers reported a system for the etherification of aryl bromides in which formation of an Ar-OR bond is proposed to proceed from a Ni(III) intermediate (Figure 5.1).[12]

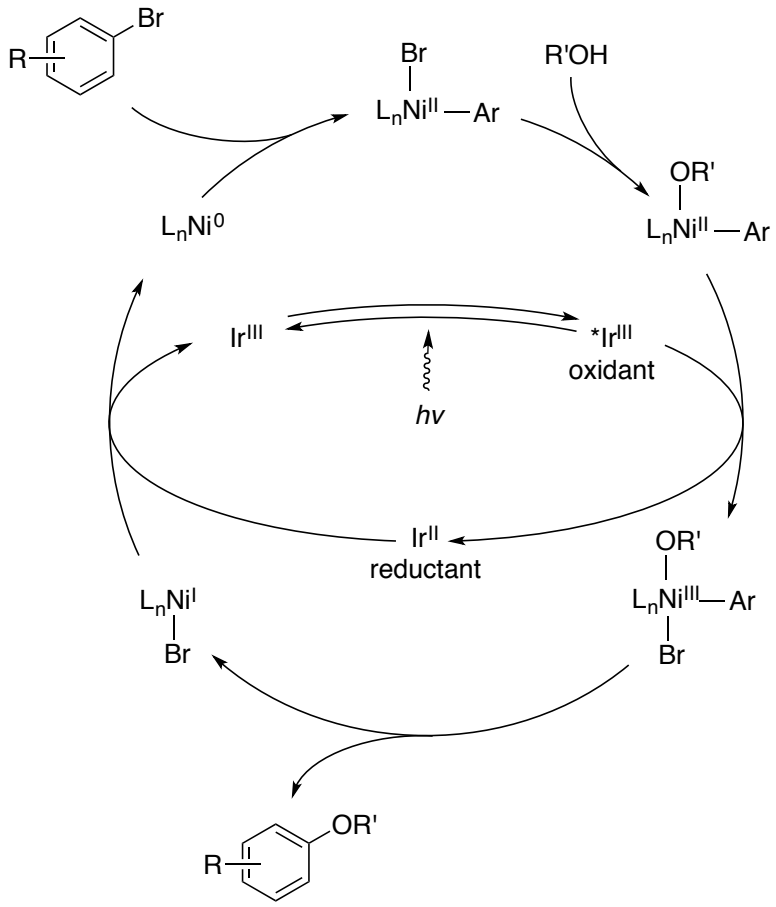


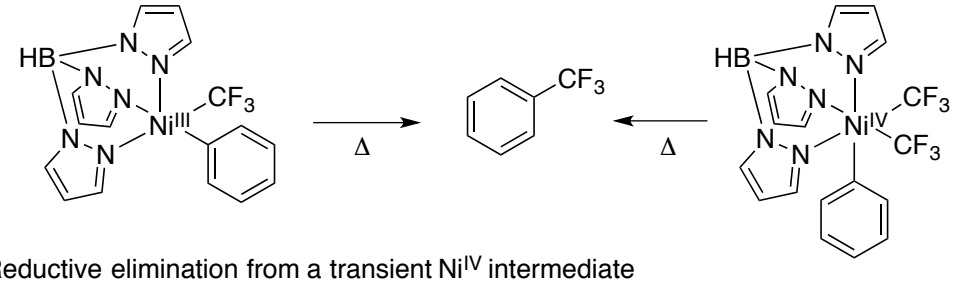
Figure 5.1 Etherification of aryl halides enabled by oxidation of Ni(II) to Ni(III).

Other reactions involving Ni/Ir dual photocatalysis have been proposed to proceed by direct energy transfer from an iridium photosensitizer to a nickel catalyst to generate a nickel complex in an excited state. Reductive elimination occurs more readily from the nickel complex in an excited state than from the nickel complex in its ground state. Direct energy transfer has been proposed to enable C-O bond formation between aryl bromides and carboxylic acids in the presence of Ni and Ir catalysts and visible light.[13]

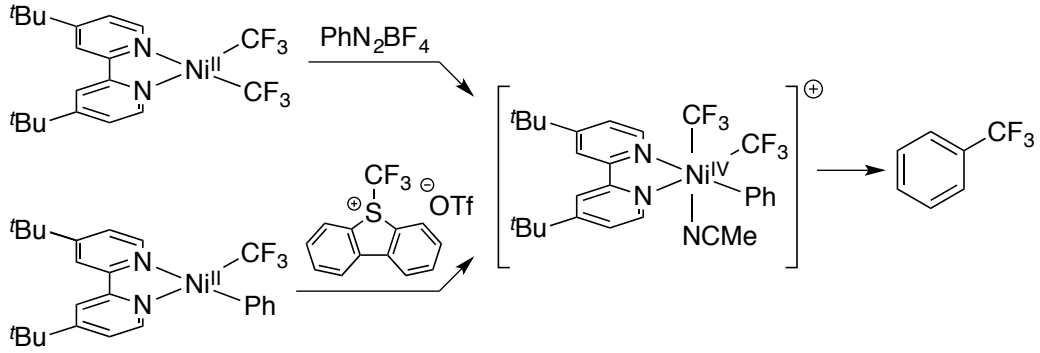
We considered the possibility of developing an analogous fluoroalkylation reaction in which reductive elimination to form an Ar-CF_3 bond would proceed from a Ni(III) intermediate or from a Ni(II) complex that had undergone photoexcitation by direct energy transfer. However, the feasibility of this reductive elimination step was unclear. During the course of our work, Sanford reported the synthesis and reactivity of a series of arylnickel(III) complexes.[14] A $TpNi^{III}(Ph)(CF_3)$ (Tp = tris(pyrazolyl)borate) complex was isolated and formed trifluoromethylbenzene upon heating (Scheme 5.2a). Mechanistic studies supported direct reductive elimination from Ni(III) as the most likely pathway for Ph-CF_3 bond formation. Aryl-CF_3 bond formation has also been demonstrated from isolated Ni(IV) complexes bearing Tp ligands (Scheme 5.2a).[15-16] Sanford reported in 2015 that two-electron oxidation of dtbbpy-ligated Ni(II) complexes resulted in Ar-CF_3 reductive elimination at room temperature, and the authors observed a putative Ni(IV) intermediate at low temperature (Scheme 5.2b).[15]

The aforementioned reductive elimination reactions from Ni(III) and Ni(IV) to form trifluoromethylarenes have mainly focused on the study of stable, isolable complexes. Less attention has been paid to identifying nickel complexes that undergo rapid reductive elimination to form trifluoromethylarenes in high yield upon oxidation. Here, we report studies of oxidatively-induced reductive elimination from nickel complexes ligated by phosphorus and nitrogen-donor ligands and show that complexes of a common bipyridine ligand undergo this process rapidly, under mild conditions, and in high yield (Scheme 5.2c).

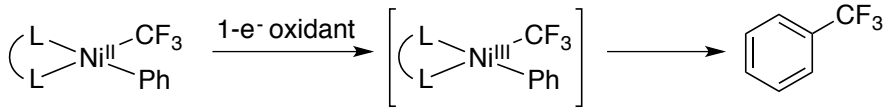
a) Reductive elimination from isolated Ni^{III} and Ni^{IV} complexes



b) Reductive elimination from a transient Ni^{IV} intermediate



c) **This work:** oxidatively-induced Ar-CF_3 bond formation from Ni^{III}



Scheme 5.2 Ar-CF_3 bond formation from Ni^{III} and Ni^{IV} complexes.

5.2 Results and Discussion

We began our studies by considering the possibility of developing a nickel/photoredox dual catalyst system for trifluoromethylation and related fluoroalkylation reactions of aryl halides. A potential catalytic cycle for such a reaction is shown in Figure 5.2. A nickel(0) species would undergo oxidative addition with an aryl halide or pseudohalide to form the corresponding nickel(II) species. Transmetallation with a fluoroalkyl nucleophile (e.g. a fluoride-activated fluoroalkylsilane) would generate an arylnickel(II) fluoroalkyl complex. A photocatalyst with an appropriate oxidation potential would oxidize this Ni(II) species to the corresponding Ni(III) complex, from which reductive elimination would occur to generate a fluoroalkylarene. Reduction of the resulting Ni(I) species by the reduced state of the photocatalyst would regenerate both the Ni(0) species and the photocatalyst.

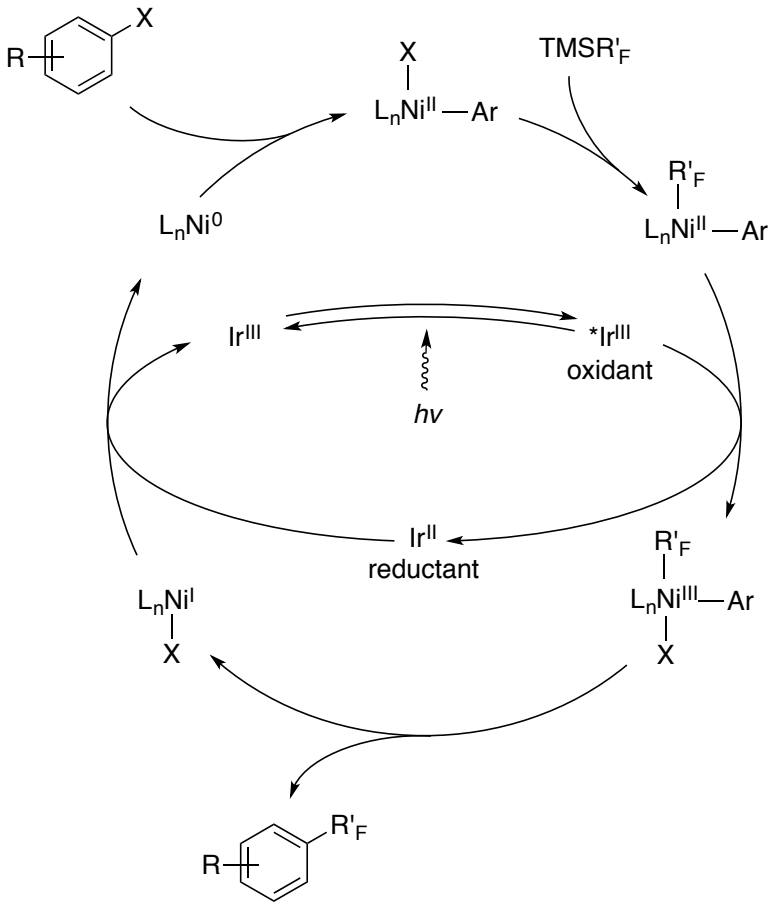
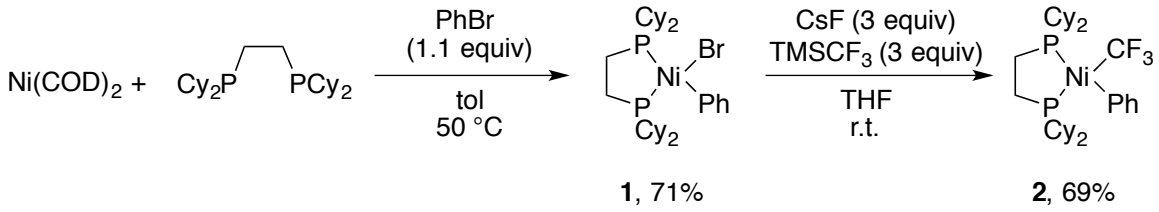


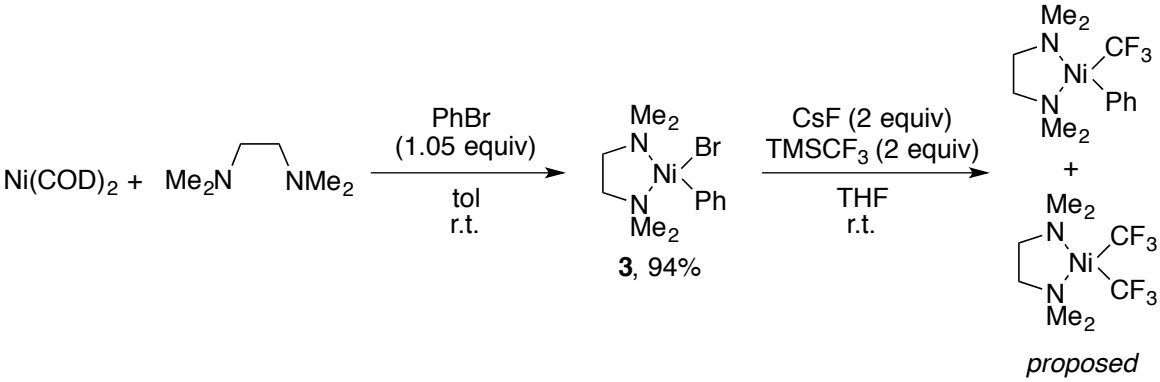
Figure 5.2 Proposed catalytic cycle for catalytic fluoroalkylation of aryl halides through Ni/photoredox dual catalysis.

We first sought to assess the feasibility of the reductive elimination step in the proposed cycle and to determine whether single-electron oxidation of a Ni(II) complex can promote Ar-CF3 reductive elimination. Our studies began with the synthesis of arylnickel(II) trifluoromethyl complexes bearing a series of ancillary ligands. Complex 2, ligated by dcype (dcype = 1,2-bis(dicyclohexylphosphino)ethane) was synthesized by a procedure consisting of oxidative addition of bromobenzene to a mixture of $Ni(COD)_2$ and dcype to form arylnickel(II) complex **1** in 71% yield, followed by transmetallation in the presence of cesium fluoride and trimethyl(trifluoromethyl)silane to afford the corresponding trifluoromethyl complex in 69% yield (Scheme 5.3).



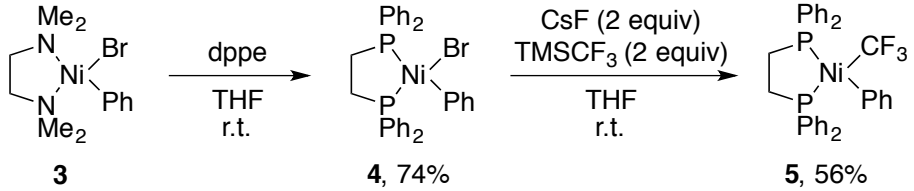
Scheme 5.3 Synthesis of (dcype)Ni(Ph)(CF_3) (**2**).

Complexes bearing the bidentate nitrogen-donor ligand TMEDA (TMEDA = *N*,*N*,*N*,*N*-tetramethylethylenediamine) were also investigated (Scheme 5.4). Oxidative addition of bromobenzene to $Ni(COD)_2$ in the presence of TMEDA afforded (TMEDA)Ni(Ph)(Br) (**3**) in 94% isolated yield. Treatment of complex **3** with cesium fluoride and trimethyl(trifluoromethyl)silane generated a mixture of products, including two species observed by ^{19}F NMR that were tentatively assigned as (TMEDA)Ni(Ph)(CF_3) and (TMEDA)Ni(CF_3)$_2$.[17] However, attempts to isolate (TMEDA)Ni(Ph)(CF_3) in pure form by recrystallization were unsuccessful.



Scheme 5.4 Attempted synthesis of (TMEDA)Ni(Ph)(CF_3).

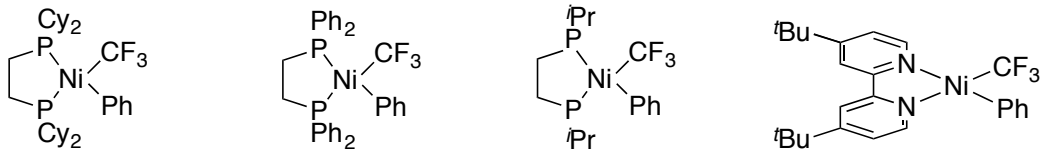
Complex **3** was converted to (dppe)Ni(Ph)(CF_3) (**5**) by a two-step sequence (Scheme 5.5). First, ligand exchange of dppe for TMEDA afforded complex **4** in 74% yield. Transmetallation with $TMSCF_3$ in the presence of CsF formed trifluoromethyl complex **5** in 56% yield. In addition, the analogous complex ligated by dippe (**6**) was prepared by the procedure previously reported by Vicic.[7]



Scheme 5.5 Synthesis of (dppe)Ni(Ph)(CF_3).

The ^{19}F NMR spectra of bisphosphine-ligated arylnickel(II) trifluoromethyl complexes **2**, **5**, and **6** each consisted of a single fluorine resonance with a doublet of doublets splitting pattern due to ^{31}P-^{19}F coupling between fluorine and the two inequivalent phosphorus nuclei of each ligand ($J_{F\text{-}P}$ = 34.6, 15.2 Hz for complex **2**). The ^{31}P NMR spectra of the complexes consisted of two quartets of doublets, due to ^{31}P-^{19}F and ^{31}P-^{31}P coupling between the trifluoromethyl group and the inequivalent phosphorus nuclei.

A route previously reported by Sanford[15] afforded trifluoromethyl complex **7**, ligated by dtbbpy. Attempts were also made to prepare arylnickel trifluoromethyl complexes bearing other bidentate, N-donor ligands such as 1,10-phenanthroline and its derivatives, as well as bipyridine ligands with varying electronic and steric properties. However, synthetic routes analogous to that shown in Scheme 5.5 did not afford the corresponding $L_nNi(Ph)(CF_3)$ complexes bearing these ligands. In many cases, biphenyl formation was observed, likely arising from competing transmetallation processes between $L_nNi(Ph)(X)$ and/or $L_nNi(Ph)(CF_3)$ complexes to form $L_nNi(Ph)(Ph)$ complexes that undergo reductive elimination to form a Ph-Ph bond. We therefore explored the synthesis of complexes bearing *ortho*-tolyl substituents instead of phenyl groups because hindered aryl groups have been demonstrated to confer enhanced stability to nickel complexes by hindering associative substitution pathways.[18-20] However, nickel complexes bearing *ortho*-tolyl groups and substituted phenanthroline or bipyridine-based ligands were not isolated in sufficient purity to allow for further investigations.

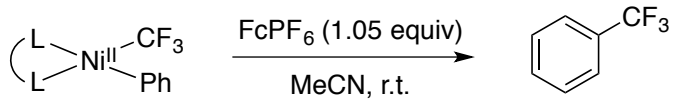


2 **5** **6** **7**

Figure 5.3 $Ni^{II}(Ph)(CF_3)$ complexes evaluated for oxidatively-induced reductive elimination.

Arylnickel trifluoromethyl complexes **2**, **5**, **6**, and **7** were treated with the 1-e^- oxidant ferrocenium hexafluorophosphate ($FcPF_6$) to promote oxidation of the Ni^{II} complexes to Ni^{III}, and the yield of trifluorotoluene was evaluated by ^{19}F NMR spectroscopy (Table 5.1). Bisphosphine-ligated complexes **2**, **5**, and **6** did not react to form trifluoromethylbenzene. This result is consistent with the observation by Vicic that complex **6** did not undergo reductive elimination when treated with Fe(III) or Ce(IV)-based oxidants.[7] In contrast, complex **7**, ligated by dtbbpy, formed trifluoromethylbenzene in 41% yield under the same conditions.

Table 5.1 Oxidation of $L_nNi(Ph)(CF_3)$ complexes with ferrocenium hexafluorophosphate.

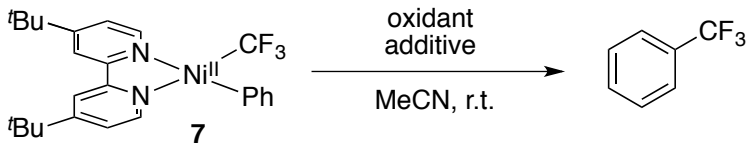


entry	complex	ligand	yield[a]
1	**2**	dcype	0%
2	**5**	dppe	0%
3	**6**	dippe	0%
4	**7**	dtbbpy	41%

[a]Determined by ^{19}F NMR spectroscopy.

We hypothesized that the moderate yield of trifluoromethyl benzene obtained in the oxidatively-induced reductive elimination reaction of complex **7** was due to undesired side reactions that consume the oxidant, complex **7**, or both. The direct product of reductive elimination from an arylnickel(III) trifluoromethyl intermediate is likely an unsaturated, low-valent nickel(I) species. The rate of oxidation of this Ni^{I} species would likely outcompete that of Ni^{II} complex **7**, thereby consuming the oxidant in an unproductive pathway that does not generate trifluoromethylbenzene. Consistent with this hypothesis, addition of 5 equivalents of oxidant increased the yield of trifluoromethylbenzene to 70% (Table 5.2, entry 2). A similar increase in yield of trifluoromethylbenzene was observed by Sanford when the thermolysis of $TpNi^{III}(Ph)(CF_3)$ was carried out in the presence of excess $Cp^*_2FeBF_4$.[14]

Table 5.2 Effect of oxidants and additives on the yield of trifluoromethylbenzene.



entry	oxidant[a]	additive[b]	yield[c]
1	$FcPF_6$	-	41%
2[d]	$FcPF_6$	-	70%
3	$FcPF_6$	pyridine	37%
4	$FcPF_6$	PEt_3	5%
5	$AgBF_4$	-	35%
6	$AcFcBF_4$	-	45%

[a]1.05 equiv. oxidant unless stated otherwise. [b]1.05 equiv. additive. [c]Determined by ^{19}F NMR spectroscopy. [d]5.00 equiv oxidant.

A Ni^{I} species formed upon reductive elimination could also react with complex **7** in ligand exchange or transmetallation reactions that consume the Ni^{II} starting material without generation of $PhCF_3$, limiting the yield of the oxidatively-induced reductive elimination. In reductive elimination reactions of isolated Pd complexes, the addition of exogenous ligands to trap the low-valent metal products of reductive elimination and prevent undesired reactivity is often required to achieve high yields.[21-22] We therefore conducted reactions of **7** in the presence of pyridine and phosphine additives that could chelate low-valent Ni^{I} species. The addition of pyridine had a negligible effect on the yield of trifluoromethylbenzene (Table 5.2, entry 3). In contrast, the addition of triethylphosphine reduced the yield of trifluoromethylbenzene significantly (Table 5.2, entry 4), potentially due to the ability of a phosphine ligand to displace dtbbpy from complex **7** to form a phosphine-ligated nickel complex that does not undergo oxidatively-induced reductive elimination.

Oxidatively-induced reductive elimination of complex **7** was not exclusive to ferrocenium hexafluorophosphate as oxidant. Treatment of complex **7** with 1.05 equivalents of silver tetrafluoroborate afforded $PhCF_3$ in 35% yield (Table 5.2, entry 5). No significant correlation between the strength of the oxidant and the yield of the reductive elimination reaction was observed. The reaction conducted with acetylferrocenium tetrafluoroborate (E^0 = +0.27V)[23] proceeded in 45% yield, while the reaction conducted with ferrocenium hexafluorophosphate (E^0 = +0.0V) proceeded in 41% yield.

Cyclic voltammetry of complex **7** was conducted to determine the potential required to oxidize the complex from Ni(II) to Ni(III). Cyclic voltammetry of complex **7** showed irreversible 1-e^- oxidation at a scan rate of 100 mV/s in acetonitrile (i_{pc}/i_{pa} = 7.8) (Figure 5.4). The oxidation peak with a maximum at -0.001V and an onset potential of approximately -0.24V can be attributed to a Ni^{II}/Ni^{III} couple. This potential is consistent with our observations of oxidatively-induced reductive elimination with Fc^+ (E^0 = +0.0V), Ag^+ (E^0 = +0.04V),[24] and acetylferrocenium (E^0 = +0.27V)[23] salts as oxidants. For comparison, Vicic measured the oxidation potential of a (dippe)Ni^{II}(Ar)(CF_3) complex to be +0.61V,[25] which may explain the lack of trifluoromethylarene formation from complex **6**. Oxidation of complex **7** remained irreversible at scan rates as high as 500 mV/s (Figure 5.5).

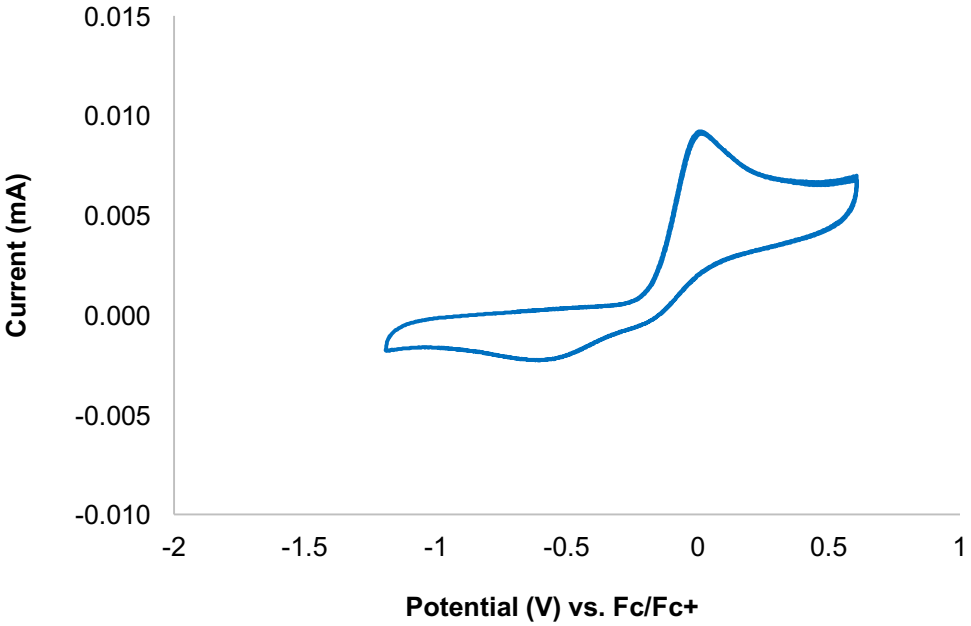


Figure 5.4 Cyclic voltammogram of complex **7** [1.0 mM] with NBu_4PF_6 (0.1M) in MeCN at a scan rate of 100 mV/s.

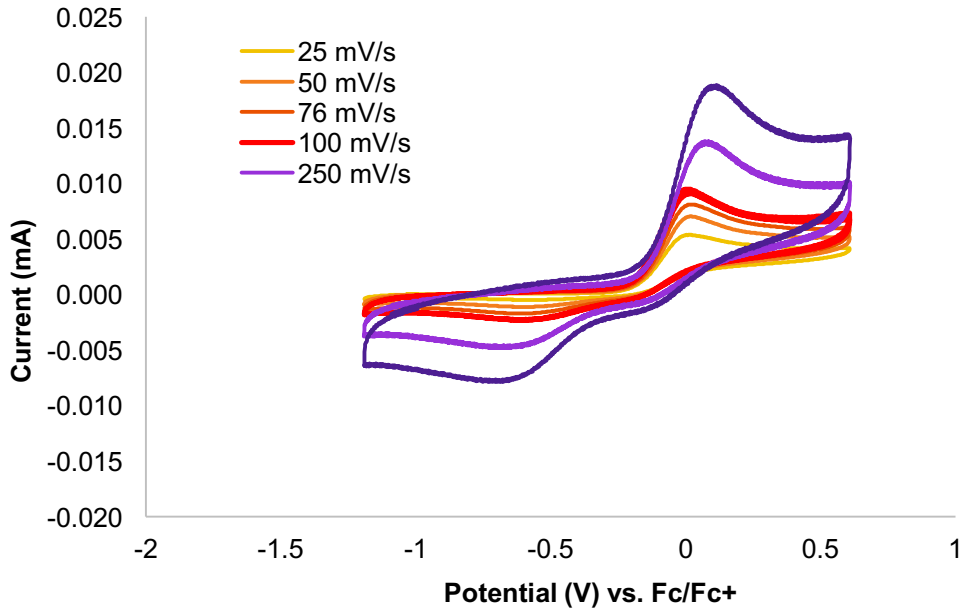
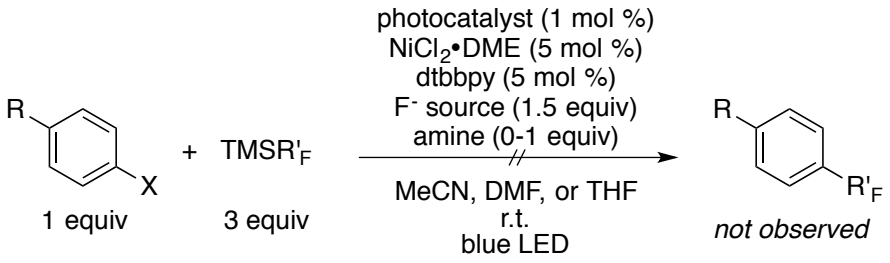
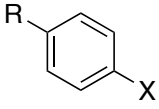


Figure 5.5 Cyclic voltammograms of complex **7** [1.0 mM] with NBu_4PF_6 (0.1M) in MeCN at variable scan rates.

Having demonstrated the feasibility of oxidatively-induced reductive elimination to form an Ar-CF_3 bond, we conducted a series of experiments designed to identify conditions for catalytic coupling reactions in the presence of a nickel catalyst, a photocatalyst, and visible light. A series of fluoroalkylation reactions were conducted with a combination of dtbbpy and a Ni precatalyst. Electron-rich, electron-neutral, and electron-poor aryl iodides, bromides, and chlorides were evaluated as electrophilic coupling partners. A series of fluoroalkyl silanes containing trifluoromethyl, pentafluoroethyl, difluoroester, difluoroamide, and difluoronitrile groups were tested, and fluoride salts were added to activate the silane coupling partner. Iridium, ruthenium, and acridinium-based photocatalysts of varying redox potentials were added as co-catalysts, and reactions were irradiated with blue LEDs. The effect of amine additives was also explored. These screening efforts are summarized in Scheme 5.3. However, extensive screening of reaction conditions failed to identify suitable conditions for catalytic fluoroalkylation. Decomposition of the fluoroalkyl silane was observed, and several products of undesired side reactions (e.g. formation of biaryl compounds) were identified.



aryl halide	$TMSR'_F$	photocatalyst	F^- source	amine
 R = OMe, CF_3, CN, F, H X = I, Br, Cl	$TMSCF_3$ $TESCF_3$ $TMSCF_2CF_3$ $TMSCF_2CO_2Et$ $TMSCF_2CONR_2$ $TMSCF_2CN$	$Ru(bpy)_3(PF_6)_2$ $Ru(bpz)_3(PF_6)_2$ $[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$ $[Ir(dtbbpy)(ppy)_2][PF_6]$ 9-Mes-10-Ph-acridinium BF_4	KF CsF TBAT	NEt_3 NPh_3 $^iPr_2NEt$ DMAP quinuclidine

Scheme 5.6 Evaluation of reaction conditions for Ni/photoredox-catalyzed fluoroalkylation of aryl halides.

5.3 Conclusion

We report reductive elimination to form an aryl-trifluoromethyl bond by treatment of arylnickel(II) trifluoromethyl complexes with a single-electron oxidant. The reductive elimination reactions occur at room temperature in up to 70% yield with 4,4'-di-tert-butyl-2,2'-dipyridyl (dtbbpy) as ligand and ferrocenium hexafluorophosphate ($FcPF_6$) as oxidant. Related complexes bearing bisphosphines as ligands did not undergo oxidatively-induced reductive elimination under analogous conditions. One possible explanation for this observed difference in reactivity is that a redox-active ligand may be necessary to promote the desired reductive elimination pathway.

This study suggests that reductive elimination from Ni^{III} complexes bearing simple bidentate nitrogen-donor ligands may be a viable fundamental step in Ni-catalyzed trifluoromethylation reactions of aryl halides. However, initial attempts to develop a catalytic trifluoromethylation of aryl halides under nickel/photoredox dual catalysis were unsuccessful. Future studies will investigate the reactivity of related complexes bearing other redox-active ligands, as well as the possibility of incorporating reductive elimination from Ni^{III} as a fundamental step in nickel-catalyzed trifluoromethylation and fluoroalkylation reactions.

5.4 Experimental

General Experimental Details

All reactions were conducted under inert atmosphere in a nitrogen-filled glovebox or with standard Schlenk techniques, unless otherwise specified. Vessels used in air-free reactions were oven-dried prior to use. Vials used as a reaction vessel were sealed with Teflon-lined caps. Toluene, tetrahydrofuran, diethyl ether, and pentane were purged with nitrogen and dried with an Innovative Pure-Solv solvent purification system. Anhydrous acetonitrile was purchased from Acros Organics. All other solvents were purchased from Fisher Scientific. $Ni(COD)_2$ and $NiCl_2$•DME were purchased from Strem. Photocatalysts $Ru(bpy)_3(PF_6)_2$, $Ru(bpz)_3(PF_6)_2$, $[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$ and $[Ir(dtbbpy)(ppy)_2][PF_6]$ were purchased from Aspira, and [9-Mes-10-Ph-acridinium]BF_4 was purchased from Sigma Aldrich. $CDCl_3$, CD_2Cl_2, and C_6D_6 were purchased from Cambridge Isotope Laboratories. $TMSCF_3$, $TESCF_3$, aryl halides, fluoride sources, bases, and ligands were purchased from Sigma Aldrich, Alpha Aesar, Oakwood Chemical, and Fisher Scientific. Compounds were used as received unless otherwise noted. $TMSCF_2H$[26], $TMSCF_2CO_2Et$[27], $TMSCF_2CO$(morpholine),[28] and $TMSCF_2CN$[29] were prepared according to literature procedures. Complex **6** was prepared by the procedure previously reported by Vicic.[7] Complex **7** was prepared by the procedure previously reported by Sanford.[15]

NMR spectra were acquired on Bruker 300, 400, 500, or 600 MHz spectrometers at the University of California, Berkeley NMR facility. ^1H and ^{13}C chemical shifts were reported relative to residual solvent peaks ($CDCl_3$ = 7.26 ppm for ^1H and 77.2 ppm for ^{13}C; CD_2Cl_2 = 5.32 ppm for ^1H and 53.8 ppm for ^{13}C; C_6D_6 = 7.16 ppm for ^1H and 128.1 ppm for ^{13}C). Elemental analysis was performed by the University of California, Berkeley Microanalytical Laboratory. High-resolution mass spectra were obtained at the University of California, Berkeley Mass Spectrometry Facility with ESI techniques with a Thermo Finnigan LTQ FT instrument.

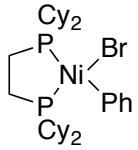
Evaluation of reaction conditions for Ni/photoredox-catalyzed fluoroalkylation of aryl halides

In a nitrogen-filled glovebox, $NiCl_2$•DME (1.4 mg, 0.0063 mmol, 0.050 equiv), dtbbpy (1.7 mg, 0.0063 mmol, 0.050 equiv), photocatalyst (0.0013 mmol, 0.0100 equiv), and fluoride source (0.188 mmol, 1.50 equiv) were added to a 4 mL vial equipped with a stir bar. If solid at room temperature, the aryl halide (0.125 mmol, 1.00 equiv), fluoroalkyl silane (0.375 mmol, 3.00 equiv), and amine (0.0125 or 0.125 mmol, 0.100 or 1.00 equiv) were also added. Solvent (0.5 mL) was added, followed by the aryl halide (0.125 mmol, 1.00 equiv), fluoroalkyl silane (0.375 mmol, 3.00 equiv), and amine (0.0125 or 0.125 mmol, 0.100 or 1.00 equiv), if liquid at room temperature.

The reaction was sealed with a Teflon-lined cap and placed 2 cm away from a Kessil H150 blue LED lamp. The reaction was stirred vigorously and irradiated with blue LEDs for 12h under fan cooling to maintain the reaction mixture at room temperature. After 12 h, the reaction mixture was analyzed by GC/MS and ^{19}F NMR spectroscopy with 1-nitro-3-fluorobenzene as an internal standard.

Synthesis of $L_nNi(X)(CF_3)$ complexes

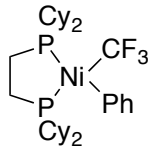
(dcype)Ni(Ph)(Br) (1)



In a nitrogen-filled glovebox, $Ni(COD)_2$ (110 mg, 0.400 mmol, 1.00 equiv) and 1,2-bis(dicyclohexylphosphino)ethane (169 mg, 0.400 mmol, 1.00 equiv) were added to a 20 mL vial equipped with a stir bar. Toluene (5 mL) was added, and the reaction was sealed with a Teflon-lined cap and stirred at room temperature for 10 min. After 10 min, bromobenzene (69.1 mg, 46.3 µL, 0.440 mmol, 1.10 equiv) was added, and the reaction mixture was sealed, removed from the glovebox, and heated at 50 °C for 13 h. After 13 h, the reaction mixture was returned to the glovebox and reduced in volume to 2 mL *in vacuo*. The reaction mixture was filtered, and the yellow solid was washed with pentane (5x2 mL) and dried under vacuum. The product was isolated as a bright yellow solid (182 mg, 0.285 mmol, 71% yield).

^1H NMR (400 MHz, $CDCl_3$) δ 9.38 (t, *J* = 6.5 Hz, 2H), 8.88 (t, *J* = 7.3 Hz, 2H), 8.70 (t, *J* = 7.2 Hz, 1H), 4.39–4.27 (m, 2H), 4.05 (dt, *J* = 9.0, 4.7 Hz, 4H), 3.87–3.35 (m, 28H), 3.34–3.04 (m, 12H), 2.70 (qt, *J* = 12.6, 3.8 Hz, 2H). ^{31}P NMR (162 MHz, CD_2Cl_2) δ 67.9 (d, *J* = 19.8 Hz), 63.2 (d, *J* = 20.7 Hz). Anal. Calcd for $C_{32}H_{53}BrNiP_2$: C, 60.21; H, 8.37. Found: C, 59.91; H, 8.00.

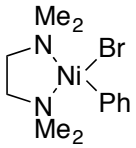
(dcype)Ni(Ph)(CF_3) (2)



In a nitrogen-filled glovebox, (dcype)Ni(Ph)(Br) (**1**) (34.3 mg, 0.0500 mmol, 1.00 equiv) and CsF (15.2 mg, 0.100 mmol, 2.00 equiv) were added to a 4 mL vial equipped with a stir bar. THF (1.25 mL) was added, followed by $TMSCF_3$ (14.2 mg, 14.8 µL, 0.100 mmol, 2.00 equiv). The reaction was sealed with a Teflon-lined cap and stirred at room temperature for 17 h. After 17 h, additional portions of CsF (7.6 mg, 0.050 mmol, 1.0 equiv) and $TMSCF_3$ (7.1 mg, 7.4 µL, 0.050 mmol, 1.0 equiv) were added, and the reaction mixture was stirred at room temperature for 4 h. Conversion of complex **1** to complex **2** was monitored by ^{31}P NMR spectroscopy of an aliquot of the reaction mixture (^{31}P NMR shifts: 67.9 (d, J = 19.8 Hz), 63.2 (d, J = 20.7 Hz) for complex **1**; 69.01 (qd, J = 16.1, 9.5 Hz), 56.03 (qd, J = 35.5, 9.0 Hz) for complex **2**). After 4 h, full conversion of complex **1** was observed. The reaction mixture was filtered through a syringe filter and the filtrate was concentrated in vacuo. The crude residue was dissolved in toluene (0.25 mL) and precipitated with pentane. The solution was decanted, and the solid was triturated with pentane (3x2 mL) and dried under vacuum. The product was isolated as a yellow solid (21.6 mg, 0.0344 mmol, 69% yield).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.44 (t, J = 6.0 Hz, 2H), 6.96 (t, J = 7.3 Hz, 2H), 6.80 (t, J = 7.3 Hz, 1H), 2.24 (d, J = 6.7 Hz, 2H), 2.03–1.07 (m, 44H), 0.65 (qt, J = 12.6, 3.7 Hz, 2H). ^{31}P NMR (162 MHz, CD_2Cl_2) δ 69.01 (qd, J = 16.1, 9.5 Hz), 56.03 (qd, J = 35.5, 9.0 Hz). ^{19}F NMR (376 MHz, CD_2Cl_2) δ -16.4 (dd, J = 34.6, 15.2 Hz). Anal. Calcd for $C_{33}H_{53}F_3NiP_2$: C 63.17, H 8.51; C: 62.83, H 8.20.

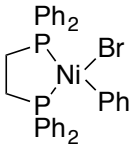
(TMEDA)Ni(Ph)(Br) (3)



In a nitrogen-filled glovebox, $Ni(COD)_2$ (138 mg, 0.500 mmol, 1.00 equiv) was added to a 20 mL vial. Toluene (3 mL) was added, followed by tetramethylethylenediamine (TMEDA) (61.0 mg, 78.7 µL, 0.525 mmol, 1.05 equiv) and bromobenzene (82.4 mg, 55.3 µL, 0.525 mmol, 1.05 equiv). The reaction mixture was stirred at room temperature for 14 h. After 14 h, pentane was added (14 mL) and a pink precipitate formed. The reaction mixture was filtered, and the solid was washed with pentane (3x3 mL) and dried under vacuum. The product was isolated as a salmon-pink solid (156 mg, 0.470 mmol, 94% yield).

^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.48 (d, J = 7.5 Hz, 2H), 6.78 (t, J = 7.3 Hz, 2H), 6.61 (t, J = 7.2 Hz, 1H), 2.74–2.02 (br. m, 16H). Note: broad signals resulting from the TMEDA ligand have been reported for similar (TMEDA)Ni(Ar)(X) complexes.[30-31] Anal. Calcd for $C_{12}H_{21}BrN_2Ni$: C, 43.42; H, 6.38; N, 8.44. Found: C, 43.25; H, 6.35; N, 8.33.

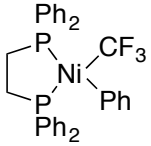
(dppe)Ni(Ph)(Br) (4)



In a nitrogen-filled glovebox, (TMEDA)Ni(Ph)(Br) (**3**) (83.0 mg, 0.250 mmol, 1.00 equiv) and 1,2-bis(diphenylphosphino)ethane (dppe) (110 mg, 0.275 mmol, 1.10 equiv) were added to a 4 mL vial. THF (2.5 mL) was added, and the orange reaction mixture was stirred at room temperature for 24 h. A bright yellow precipitate formed over the course of the reaction. After 24 h, the reaction mixture was filtered, and the solid was washed with pentane (3x2 mL) and dried under vacuum. The product was isolated as a bright yellow solid (114 mg, 0.185 mmol, 74% yield).

The NMR spectra of complex **4** corresponded to previously reported data for the complex.[32]

(dppe)Ni(Ph)(CF_3) (5)



In a nitrogen-filled glovebox, (dppe)Ni(Ph)(Br) (**4**) (61.4 mg, 0.100 mmol, 1.00 equiv) and CsF (30.4 mg, 0.200 mmol, 2.00 equiv) were added to a 4 mL vial equipped with a stir bar. THF (0.5 mL) was added, followed by $TMSCF_3$ (28.2 mg, 29.6 µL, 0.200 mmol, 2.00 equiv). The reaction was sealed with a Teflon-lined cap and stirred at room temperature for 20 h. After 20 h, the reaction mixture was filtered with a syringe filter. The yellow-orange solution was layered with pentane (1 mL) and cooled at 0 °C for 2 days. After 2 days, the solution was decanted, and the solid was washed with pentane

(3x0.25 mL) and dried under vacuum. The product was isolated as a yellow crystalline solid (65.1 mg, 0.0561 mmol, 56% yield).

^{1}H NMR (400 MHz, THF-d_8) δ 7.91–7.84 (m, 4H), 7.51–7.33 (m, 12H), 7.28 (t, J = 7.7 Hz, 4H), 7.08 (t, J = 5.5 Hz, 2H), 6.52 (t, J = 7.1 Hz, 8H), 6.45 (t, J = 6.8 Hz, 1H), 2.27–2.19 (m, 2H), 2.14–2.06 (m, 2H). ^{31}P NMR (162 MHz, THF-d_8) δ 47.0 (qd, J = 36.2, 6.6 Hz), 46.7 (qd, J = 21.2, 6.4 Hz). ^{19}F NMR (376 MHz, THF-d_8) δ -20.3 (dd, J = 36.6, 20.6 Hz). Anal. Calcd for $C_{33}H_{29}F_3NiP_2$: C 65.71, H: 4.85; found: C 65.45, H: 5.14.

Oxidatively-induced reductive elimination of $L_nNi(Ph)(CF_3)$ complexes

General procedure for oxidation of $LnNi(Ph)(CF_3)$ complexes with ferrocenium hexafluorophosphate (Table 5.1)

In a nitrogen-filled glovebox, $L_nNi(Ph)(CF_3)$ (0.0100 mmol, 1.00 equiv) and ferrocenium hexafluorophosphate (3.5 mg, 0.0105 mmol, 1.05 equiv) were added to a 4 mL vial equipped with a stir bar. MeCN (0.5 mL) was added, and the reaction was sealed with a Teflon-lined cap and stirred at room temperature for 12 h. After 12 h, 4-(trifluoromethoxy)anisole was added as an internal standard, and the yield of the reaction was determined by ^{19}F NMR spectroscopy.

General procedure for evaluation of oxidants and additives on oxidation of (dtbbpy)Ni(Ph)(CF_3) complexes with ferrocenium hexafluorophosphate (Table 5.2)

In a nitrogen-filled glovebox, (dtbbpy)Ni(Ph)(CF_3) (**7**) (7.1 mg, 0.0150 mmol, 1.00 equiv), MeCN (0.25 mL), and the additive, if applicable, (0.0158 mmol, 1.05 equiv) were added to a 4 mL vial equipped with a stir bar. A solution of the oxidant (0.0158 mmol or 0.0750 mmol, 1.05 or 5.00 equiv) in MeCN (0.25 mL) was added, and the reaction was sealed with a Teflon-lined cap and stirred at room temperature for 12 h. After 12 h, 4-(trifluoromethoxy)anisole was added as an internal standard, and the yield of the reaction was determined by ^{19}F NMR spectroscopy.

Electrochemistry

General procedure for cyclic voltammetry

Cyclic voltammetry experiments on complex **7** were performed in a 3-electrode cell employing a glassy carbon disc working electrode, a platinum wire counter electrode, and a $Ag/AgNO_3$ reference electrode (0.1 M [nBu_4N][PF_6], $AgNO_3$ (satd.) in MeCN). Measurements were made with a BASi EC Epsilon potentiostat/galvanostat and a PWR-3 Power Module. Data analysis, including peak-finding and baseline determination employing linear regression, was performed with EC-Lab (v. 10.40).

Cyclic voltammagrams were recorded for a 1.0 mM solution of complex **7** in 0.1 M [nBu_4N][PF_6] in MeCN at room temperature with software-determine iR compensation applied. Cyclic voltammagrams for complex **7** were recorded at scan rates of 25, 50, 76, 100, and 250

mV/s. After obtaining the cyclic voltammetry data for complex **7**, ferrocene was added as an internal reference.

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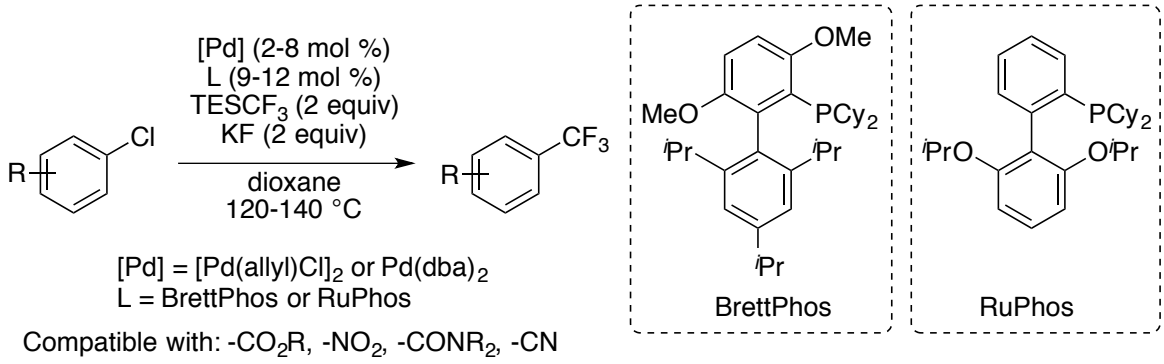
Chapter 6

Reductive Elimination from Arylpalladium(II) Trifluoromethyl Complexes

6.1 Introduction

The wide-ranging applications of trifluoromethylarenes in medicinal chemistry, agrochemistry, and materials science has driven the development of diverse strategies for incorporating trifluoromethyl groups into aromatic compounds (see Chapter 1). Although the Swarts reaction is the most economical strategy currently available for the large-scale synthesis of simple fluorinated building blocks, it is impractical to carry out on a laboratory scale and does not tolerate a range of functional groups.[1] Other strategies for trifluoromethylation also suffer from significant drawbacks; for example, radical trifluoromethylation reactions generate mixtures of products, and trifluoromethylation reactions of aryl boron, aryl silicon, or aryl diazonium compounds require starting materials that are less widely available than aryl halides. Copper-mediated and -catalyzed trifluoromethylation reactions offer a means for site-selective incorporation of a trifluoromethyl group, but the reactions typically occur only with aryl iodides and activated aryl bromides as substrates, rather than with cheaper and more widely available aryl chlorides.



Scheme 4.1 Pd-catalyzed trifluoromethylation of aryl chlorides reported by Buchwald.

Palladium-catalyzed cross-coupling reactions have emerged as powerful methods for constructing carbon-carbon and carbon-heteroatom bonds.[2] However, only a single report of the palladium-catalyzed trifluoromethylation of aryl halides in high yield has been disclosed. In 2010, Buchwald described a Pd-catalyzed trifluoromethylation of aryl chlorides catalyzed by a combination of a Pd source ($[Pd(allyl)Cl]_2$ or $Pd(dba)_2$) and a bulky monophosphine ligand (BrettPhos or RuPhos).[3] $TESCF_3$ served as the trifluoromethyl nucleophile source. The reaction proceeded in high yield with electron-rich and electron-poor aryl chlorides bearing a variety of functional groups, including esters, nitro groups, amides, and nitriles. However, substrates bearing aldehydes or ketones were not tolerated, presumably due to competing addition of the trifluoromethyl anion to electrophilic functional groups. Substrates containing unprotected -OH or -NH groups did not undergo coupling, possibly due to protonation of the trifluoromethyl anion to form CHF_3 or due to competing coordination of the functional group to the palladium center rendering the catalyst inactive. Although this report marked a significant advance in the development of transition metal-catalyzed trifluoromethylation, the reaction requires temperatures

of 120-140 °C, occurs with high catalyst and ligand loadings, and occurs with limited substrate scope.

A generalized catalytic cycle for Pd-catalyzed trifluoromethylation of aryl halides in shown in Figure 6.1. Combining a ligand and a Pd source generates a Pd(0) species that reacts with an aryl halide to form an arylpalladium(II) halide complex. Transmetallation with a CF_3 source generates the corresponding arylpalladium(II) trifluoromethyl complex. Reductive elimination forms an Ar-CF_3 bond and regenerates a Pd(0) species.

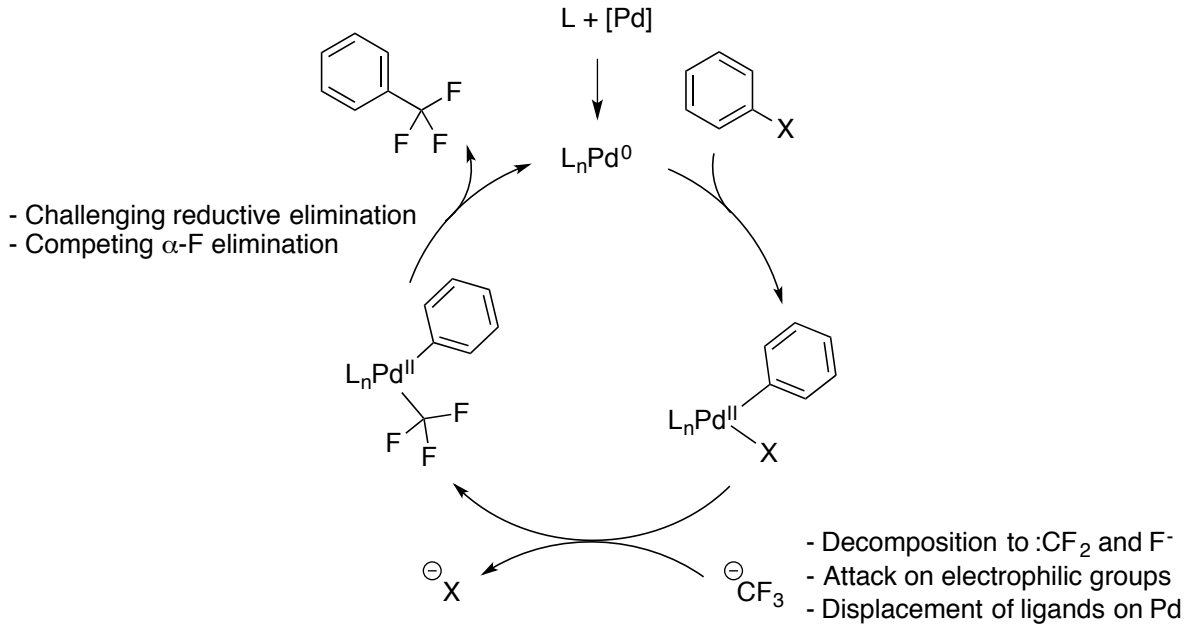


Figure 6.1 Generalized catalytic cycle and associated challenges for Pd-catalyzed trifluoromethylation of aryl halides.

To develop a trifluoromethylation reaction that occurs under mild conditions and with broad scope, several challenges must be addressed. An appropriate source of trifluoromethyl nucleophile must be identified that efficiently transfers a CF_3 group to Pd without competing decomposition of the trifluoromethyl anion or nucleophilic attack on electrophilic functional groups or the palladium center. In addition, reductive elimination from Pd(II) to form an Ar-CF_3 bond is challenging because the transition state requires the partial breaking of a strong and highly polarized Pd-CF_3 bond. Currently, only five ligands have been demonstrated to promote this step: Xantphos,[4] BrettPhos and RuPhos,[3] dfmpe,[5] and P^{t}Bu$_3$[6] (Figure 6.2). Although this data set is limited, it suggests that reductive elimination can occur from Pd complexes containing bisphosphine ligands with a wide bite angle (Xantphos) or with strong electron-withdrawing groups (dfmpe), or from complexes bearing bulky monophosphine ligands (BrettPhos, RuPhos, and P^{t}Bu$_3$). However, only BrettPhos and RuPhos have been successfully employed in catalytic trifluoromethylation of aryl halides. In addition to promoting reductive elimination, ligands for Pd-catalyzed trifluoromethylation reactions must facilitate other steps in the catalytic cycle,

including oxidative addition of the aryl halide substrate and transmetallation with a CF_3 source. Reactions conducted with ligands other than BrettPhos or Ruphos may be low-yielding because the ligands are displaced from the Pd complex under catalytic conditions by fluoride or by the trifluoromethyl anion, or because $L_nPd(Ar)(CF_3)$ complexes undergo competing side reactions such as α-fluoride elimination.

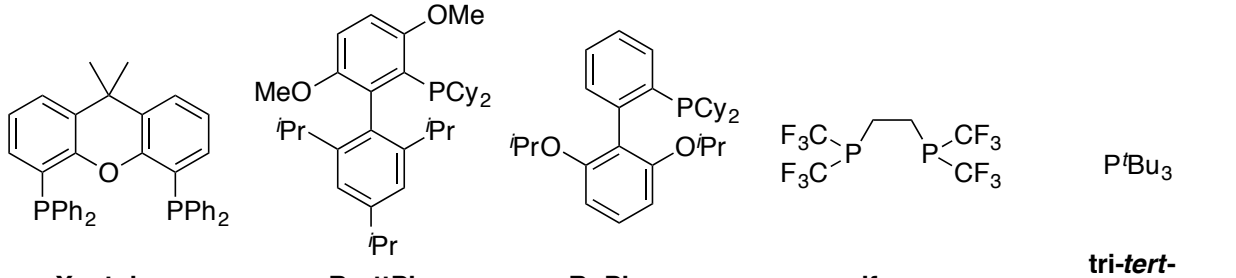
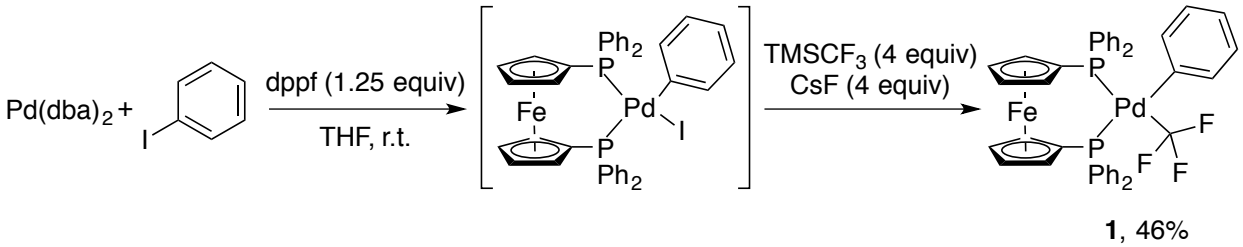


Figure 6.2 Ligands that promote Ar-CF_3 reductive elimination from Pd(II).

To inform the development of new Pd-catalyzed trifluoromethylation reactions, we sought to determine whether reductive elimination of Ar-CF_3 was unique to Pd(II) complexes of ligands that have wide bite angles, are highly sterically hindered, or are very electron-poor, or whether reductive elimination could be achieved with other classes of ligands that did not fulfill those criteria. We report a series of mono- and bisphosphine ligands that promote reductive elimination of Ar-CF_3 from arylpalladium trifluoromethyl complexes under mild conditions. We also describe efforts toward developing catalytic trifluoromethylation reactions with these ligands.

6.2 Results and Discussion

In the course of studying reductive elimination reactions of DPPF-ligated arylpalladium fluoroenolates (see Chapter 3), we synthesized a DPPF-ligated arylpalladium trifluoromethyl complex (**1**) to compare its reactivity to that of the analogous fluoroenolate complexes. To prepare trifluoromethyl complex **1**, (DPPF)Pd(Ph)(I) was formed *in situ* from $Pd(dba)_2$, DPPF, and iodobenzene. Subsequent addition of excess CsF and $TMSCF_3$ afforded complex **1** in 46% overall yield (Scheme 6.2).



Scheme 6.2 Synthesis of (DPPF)Pd(Ph)(CF_3) (**1**).

Complex **1** was characterized by NMR spectroscopy and elemental analysis. The ^{19}F NMR spectrum of complex **1** consisted of a fluorine resonance at -17.8 ppm with ^{19}F-^{31}P coupling between fluorine and the two inequivalent phosphorus nuclei of the DPPF ligand (dd, J = 48.1, 15.8 Hz). The ^{31}P NMR spectrum consisted of two quartets of doublets resulting from ^{31}P-^{19}F and ^{31}P-^{31}P coupling. The structure and connectivity of complex **1** were confirmed by single-crystal x-ray crystallography (Figure 6.3).

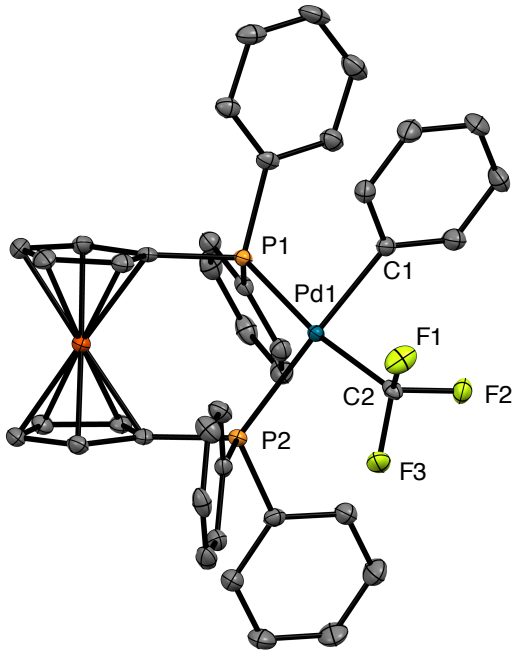


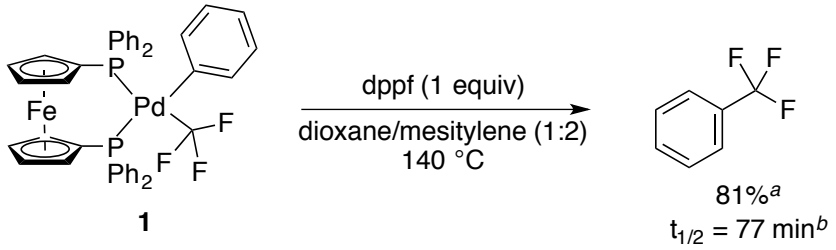
Figure 6.3 ORTEP diagram of complex **1**. Selected bond lengths and angles: Pd1-P1, 2.3335(7) Å; Pd1-P2, 2.3737(7) Å; Pd1-C1 2.051(3) Å; Pd1-C2, 2.091(3) Å; ∠C1-Pd1-C2, 83.3(1)°. Ellipsoids are shown at 50% probability, and hydrogen atoms and solvents of crystallization are omitted for clarity.

Selected bond metrics obtained from crystal structures of isolated $L_nPd(Ar)(CF_3)$ complexes with DPPF (**1**), DPPBz,[7] Xantphos,[8] and BrettPhos[3] as the ancillary ligand are provided in Table 6.1. The Pd-CF_3 bond length in complex **1** is significantly longer than that in complexes containing Xantphos or BrettPhos as ligand, but shorter than the Pd-CF_3 bond in the DPPBz-ligated complex. The Ar-Pd-CF_3 angle of complex **1** (83.3°) was closer to that of the complex ligated by the wide bite-angle bisphosphine Xantphos (82.1°) than that of complexes ligated by DPPBz (87.0°) or Brettphos (86.09°).

Table 6.1 Selected bond lengths and angles for isolated $L_nPd(Ar)(CF_3)$ complexes.[3, 7-8]

complex	Pd-C_{CF3} (Å)	Pd-C_{aryl} (Å)	∠C_{CF3}-Pd-C_{aryl} (°)
(DPPF)Pd(Ph)(CF_3) (1)	2.091(3)	2.051(3)	83.3(1)
(DPPBz)Pd(Ph)(CF_3)	2.137(6)	2.070(4)	87.0(2)
(Xantphos)Pd(Ph)(CF_3)	2.069(4)	2.068(3)	82.1(1)
(BrettPhos)Pd(Ar)(CF_3)	2.055(2)	1.983(2)	86.09(7)

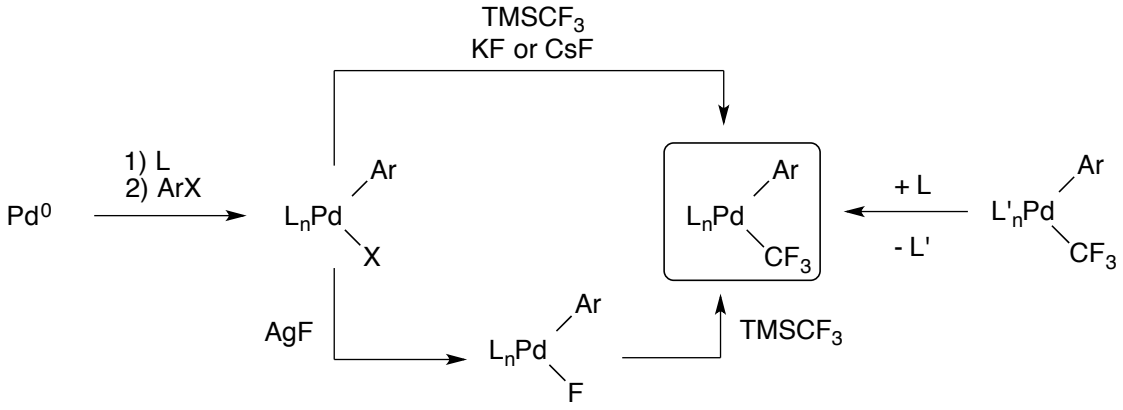
Reductive elimination to form trifluoromethylbenzene was not observed upon heating complex **1** at 100 °C for 24 hours. However, reductive elimination did occur slowly at 120 °C (59% conversion of **1** after 24 hours), and occurred in 81% yield when heated at 140 °C for 24 hours in a mixture of dioxane and mesitylene (Scheme 6.3). While the rate of reductive elimination to form a Ph-CF_3 bond ($t_{1/2}$ = 77 minutes at 140 °C) was significantly slower than the rates of reductive elimination to form Ph-fluoroenolate bonds (see Chapter 3), the yield of the reductive elimination reaction of **1** to form trifluoromethylbenzene was high (81%).



Scheme 6.3 Reductive elimination to form an Ar-CF_3 bond. [a]Determined after 24 h by ^{19}F NMR spectroscopy. [b]Determined by monitoring the decay of the Pd complex by ^{19}F NMR spectroscopy (see Experimental section for details).

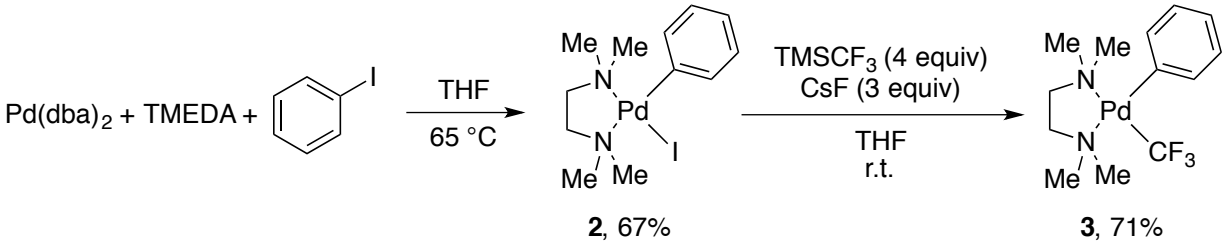
The observation that a simple bisphosphine ligand such as DPPF could promote reductive elimination to form an Ar-CF_3 bond in high yield encouraged us to evaluate other phosphine ligands to identify those that could promote reductive elimination in high yield at lower temperatures. A method to access a series of arylpalladium(II) trifluoromethyl complexes was therefore developed. Complex **1** was prepared in moderate yield from the corresponding arylpalladium halide complex by transmetallation with $TMSCF_3$ in the presence of a fluoride additive. However, this synthetic route (Scheme 6.4, top) was not general for many classes of phosphine ligands. Grushin reported that treating (Xantphos)Pd(Ph)(I) with $TMSCF_3$ and CsF resulted in ligand displacement and formation of side products and was therefore ineffective for the synthesis of (Xantphos)Pd(Ph)(CF_3).[8] Our attempts to prepare other $L_nPd(Ar)(CF_3)$ complexes under similar conditions often resulted in sluggish conversion, ligand displacement, and formation of byproducts.

Alternatively, an arylpalladium bromide, chloride, or iodide complex can be treated with AgF to generate the corresponding fluoride complex, which reacts rapidly with $TMSCF_3$ to form the desired trifluoromethyl complex (Scheme 6.4, bottom). This strategy was employed successfully by Grushin in the synthesis of (Xantphos)Pd(Ph)(CF_3).[8] However, attempted halide exchange reactions conducted with phosphine-ligated arylpalladium(II) bromide or iodide complexes and AgF proceeded in low yield for a variety of ligands, even in the presence of excess AgF and upon extended sonication. Decomposition of the palladium starting material and formation of palladium black was also observed in many cases.



Scheme 6.4 Strategies for the synthesis of $L_nPd(Ar)(CF_3)$ complexes.

We therefore pursued an alternative strategy to evaluate the ability of a ligand to promote reductive elimination of Ar-CF_3. This method relied on ligand exchange with an easily accessible arylpalladium (II) trifluoromethyl complex (Scheme 6.4, right), avoiding the need to optimize the protocol for transmetallation of a CF_3 group to Pd for each ligand being evaluated. We began with the two-step synthesis of (TMEDA)Pd(Ph)(CF_3) shown in Scheme 6.5. Oxidative addition of iodobenzene to $Pd(dba)_2$ in the presence of TMEDA afforded complex **2** in 67% yield. Treating complex **2** with excess $TMSCF_3$ and CsF afforded complex **3** in 71% yield.

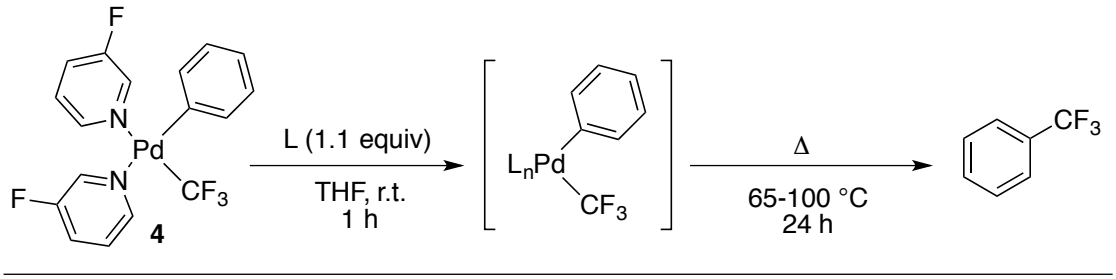


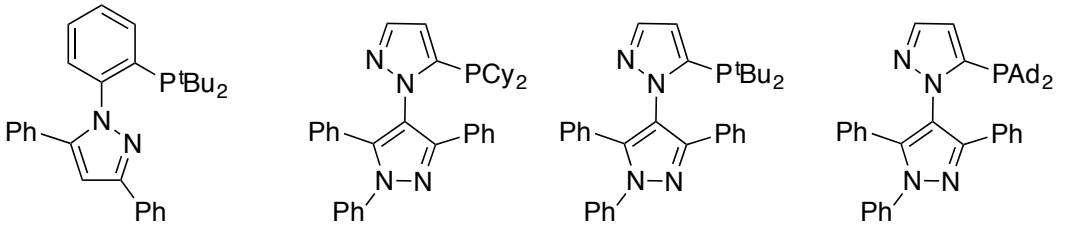
Scheme 6.5 Synthesis of (TMEDA)Pd(Ar)(CF_3) (**3**).

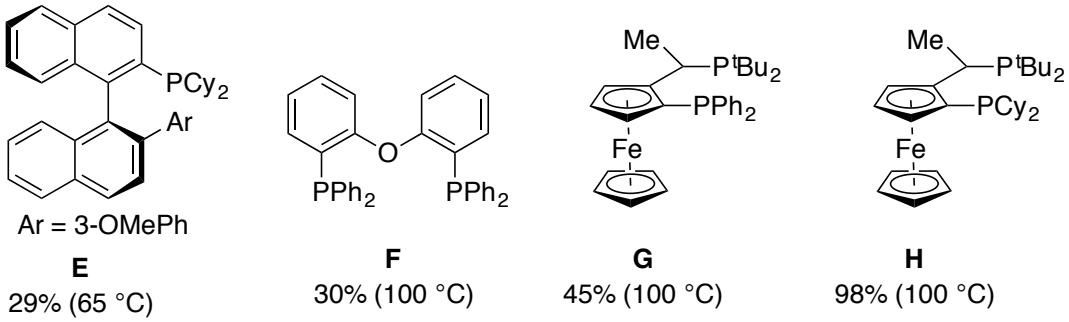
Although complex **3** has been previously reported to undergo ligand exchange with dppe (1,2-bis(diphenylphosphino)ethane) and dppp (1,3-bis(diphenylphosphino)propane),[9] ligand exchange only occurred after extended heating at elevated temperatures with other phosphine

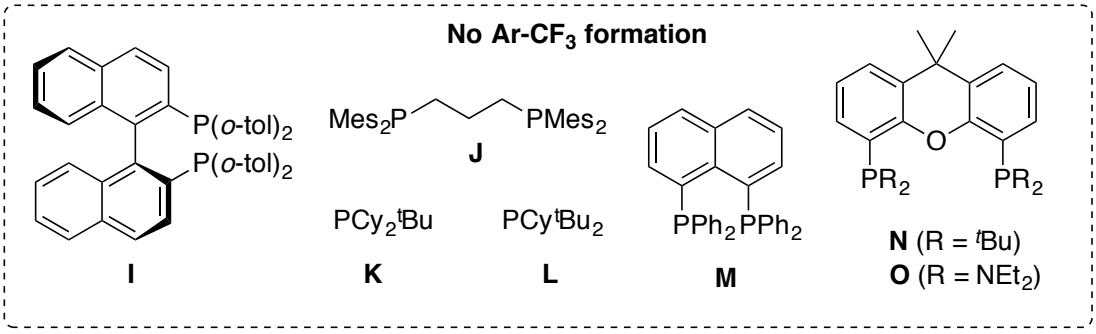
ligands. We therefore prepared complex **4**, first reported by Schoenebeck as a precursor to (dfmpe)Pd(Ph)(CF_3),[5] hypothesizing that the monodentate 3-fluoropyridine ligands of complex **4** would be more readily displaced than the TMEDA ligand of complex **3**.

Table 6.2 Evaluation of ligands for reductive elimination of Ar-CF_3.







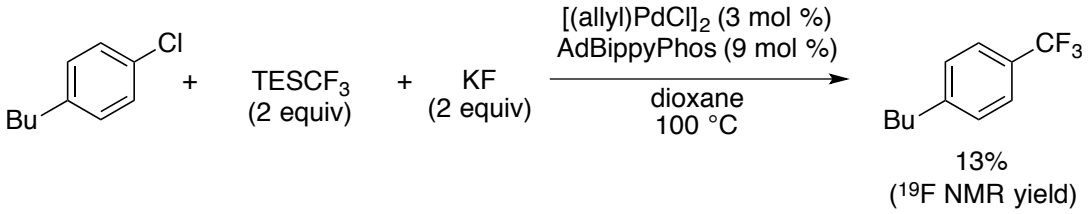


General procedure: Complex **4** (0.020 mmol, 1.0 equiv) and ligand (0.022 mmol, 1.1 equiv) in 0.5 mL of THF. Reductive elimination was monitored by ^{19}F NMR spectroscopy (see Experimental section for details).

Complex **4** was treated with a variety of mono- and bisphosphine ligands with varying steric and electronic properties to form phosphine-ligated arylpalladium trifluoromethyl complexes *in situ*. The resulting reaction mixtures were heated, and formation of trifluoromethylbenzene was monitored by ^{19}F NMR spectroscopy (see Experimental section for details).

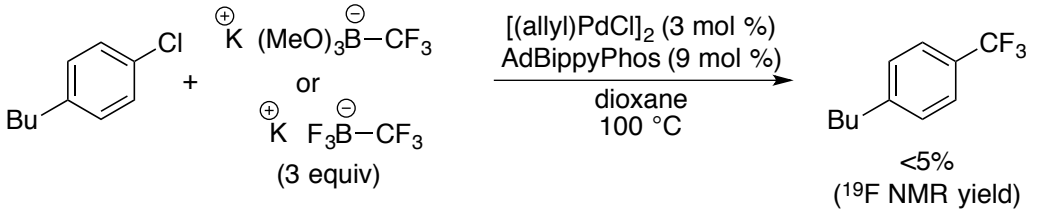
When mixtures of complex **4** and ligand were heated, reductive elimination to form an Ar-CF_3 bond was observed for a variety of ligands (Table 6.2). Bulky monophosphines **A**-**E** promoted reductive elimination in varying yields (20-73%) at moderate temperatures (65-80 °C). Increased steric bulk on phosphorus was associated with a higher yield of trifluoromethylbenzene for substituted BippyPhos derivatives bearing cylohexyl (**B**, 20% yield), *tert*-butyl (**C**, 56% yield) and adamantyl (**D**, 73% yield) groups on phosphorus. Among the ligands evaluated, higher temperatures were required to promote reductive elimination reactions conducted with bisphosphine ligands than with monophosphine ligands. Reactions conducted with DPEPhos (**F**) and JosiPhos ligand **G** formed trifluoromethylbezene in low to moderate yield (30% and 45%, respectively). In contrast, the reaction conducted with JosiPhos ligand **H** afforded trifluoromethylbenzene in 98% yield by ^{19}F NMR spectroscopy after heating for 24 hours at 100 °C. Overall, the studies summarized in Table 6.2 demonstrate that reductive elimination to form trifluoromethylarenes from Pd(II) complexes can be promoted by both mono- and bisphosphine ligands at moderate temperatures (65-100 °C).

Ligands **A**-**H** were evaluated in the Pd-catalyzed coupling of aryl halides. $Pd(dba)_2$ and $[Pd(allyl)Cl]_2$ were evaluated as Pd sources, and $TMSCF_3$ and $TESCF_3$, activated with KF or CsF, served as the CF_3 source. However, only low yields of trifluoromethylarene were obtained in the catalytic coupling reactions. For example, 13% yield of coupling product was obtained with AdBippyPhos (ligand **D**, 9 mol %) and $[Pd(allyl)Cl]_2$ (3 mol %) (Scheme 6.6).



Scheme 6.6 Low yield in the catalytic trifluoromethylation of aryl chlorides with AdBippyPhos as ligand.

Because consumption of $TESCF_3$ and formation of TESF and HCF_3 were observed by ^{19}F spectroscopy under the conditions described in Scheme 6.6, we reasoned that the instability of $TESCF_3$ under the reaction conditions and/or the inability of $TESCF_3$ to efficiently transfer a CF_3 group to Pd might account for the low yield of the reaction. However, an evaluation of alternative CF_3 sources, such as $K[F_3CB(OMe)_3]$[10] or $K[F_3CBF_3]$,[11] did not result in increased yields in attempted catalytic coupling reactions (Scheme 6.7).



Scheme 6.7 Evaluation of borate salts as CF_3 sources for Pd-catalyzed trifluoromethylation.

6.3 Conclusion

In summary, we report new examples of ligands that promote reductive elimination of Ar-CF_3 from arylpalladium(II) trifluoromethyl complexes under mild conditions and at moderate temperatures. Initial studies with (DPPF)Pd(Ph)(CF_3) demonstrated that reductive elimination was possible at elevated temperatures from complexes bearing a simple bisphosphine ligand. A protocol based on ligand exchange enabled the evaluation of a series of mono- and bisphosphine ligands. Bisphosphine ligands based on the JosiPhos scaffold were effective at promoting reductive elimination in high yield, as were bulky monophosphine ligands derived from the BippyPhos scaffold.

Initial attempts to develop catalytic trifluoromethylation reactions with JosiPhos and BippyPhos ligands resulted in low yields. Potential challenges limiting the yield of the reaction include decomposition of the CF_3 source, inefficient transmetallation of the CF_3 group to Pd, or displacement of ligands on Pd by fluoride or the trifluoromethyl anion. Future work should focus on the development of effective CF_3 sources for catalytic trifluoromethylation, and on the identification of ligands that promote reductive elimination to form an Ar-CF_3 bond and are also compatible with the conditions required for other steps of the catalytic cycle.

6.4 Experimental

General Experimental Details

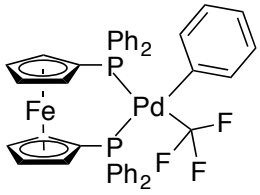
All reactions were conducted under inert atmosphere in a nitrogen-filled glovebox or with standard Schlenk techniques, unless otherwise specified. All reactions were conducted under inert atmosphere in a nitrogen-filled glovebox or with standard Schlenk techniques, unless otherwise specified. Vessels used in air-free reactions were oven-dried prior to use. Vials used as a reaction vessel were sealed with Teflon-lined caps. Silica-gel chromatography was performed with Silicycle SiliaFlash P60 silica gel. Toluene, tetrahydrofuran, diethyl ether, and pentane were purged with nitrogen and dried with an Innovative Pure-Solv solvent purification system. Anhydrous dioxane was purchased from Acros Organics. All other solvents were purchased from Fisher Scientific. $Pd(dba)_2$ was purchased from Strem. $[Pd(allyl)Cl]_2$ was purchased from Sigma Aldrich. $TMSCF_3$, $TESCF_3$, CsF, KF, and ligands were purchased from Sigma Aldrich, Alpha Aesar, Oakwood Chemical, Combi-Blocks, and Fisher Scientific. Deuterated solvents were purchased from Cambridge Isotope Laboratories. Compounds were used as received unless

otherwise noted. Potassium trifluoromethyl trimethoxyborate[10] and (3-F-pyridine)$_2$Pd(Ph)(CF$_3$) (complex **4**)[5] were synthesized according to procedures reported in the literature.

NMR spectra were acquired on Bruker 300, 400, 500, or 600 MHz spectrometers at the University of California, Berkeley NMR facility. ^{1}H and ^{13}C chemical shifts were reported relative to residual solvent peaks ($CDCl_3$ = 7.26 ppm for ^{1}H and 77.2 ppm for ^{13}C; CD_2Cl_2 = 5.32 ppm for ^{1}H and 53.8 ppm for ^{13}C; C_6D_6 = 7.16 ppm for ^{1}H and 128.1 ppm for ^{13}C). Elemental analysis was performed by the University of California, Berkeley Microanalytical Laboratory. GC/MS analyses were conducted with a system consisting of an Agilent 6890N GC and an Agilent 5973 Mass Selective Detector. The instrument was equipped with an HP-5 column (25m x 0.20mm ID x 0.33 μm film).

*Synthesis of (DPPF)Pd(Ph)(CF$_3$) (**1**)*

(DPPF)Pd(Ph)(CF$_3$) (1)

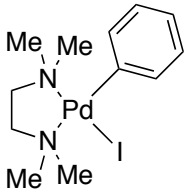


In a nitrogen-filled glovebox, Pd(dba)$_2$ (230 mg, 0.400 mmol, 1.00 equiv) and DPPF (277 mg, 0.500 mmol, 1.25 equiv) were added to a 20 mL vial equipped with a stir bar. THF (4 mL) was added, followed by iodobenzene (1 mL). The reaction mixture was stirred at room temperature for 1.5 h. After 1.5 h, CsF (122 mg, 0.800 mmol, 2.00 equiv) and TMSCF$_3$ (114 mg, 0.800 mmol, 2.00 equiv) were added, and the reaction mixture was stirred at room temperature for 12 h. After 12 h, additional portions of CsF (122 mg, 0.800 mmol, 2.00 equiv) and TMSCF$_3$ (114 mg, 0.800 mmol, 2.00 equiv) were added, and the reaction mixture was stirred at room temperature for 24 h. After 24 h, the reaction mixture was filtered. Pentane (15 mL) was added to the filtrate, and the resulting reaction mixture was stirred at room temperature for 2 h. After 2 h, the reaction mixture was filtered to collect a yellow solid. The solid was washed with pentane (3x5 mL) and dried under vacuum. The product was isolated as a yellow solid (147 mg, 0.182 mmol, 46% yield). Crystals of **1** suitable for x-ray diffraction were grown by vapor diffusion of Et$_2$O into a solution of **1** in CH_2Cl_2 at 0 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04–7.94 (m, 4H), 7.57–7.48 (m, 6H), 7.36–7.23 (m, 6H), 7.14–7.05 (m, 6H), 6.62–6.54 (m, 3H), 4.59 (q, *J* = 2.0 Hz, 2H), 4.46 (t, *J* = 1.9 Hz, 2H), 4.11 (t, *J* = 1.9 Hz, 2H), 3.54 (q, *J* = 1.9 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -17.8 (dd, *J* = 48.1, 15.8 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.5 (qd, *J* = 48.1, 27.4 Hz), 15.1–14.23 (m). Anal. Calcd for $C_{41}H_{33}F_3FeP_2Pd$: C, 61.03; H, 4.12. Found: C, 61.10; H, 4.25.

Synthesis of (TMEDA)Pd(Ph)(X) Complexes

(TMEDA)Pd(Ph)(I) (2)

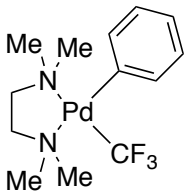


The procedure for the synthesis of complex **2** was based on the conditions reported by Sanford and coworkers for the synthesis of (TMEDA)Pd(Ar)(I).[12]

In a nitrogen-filled glovebox, $Pd(dba)_2$ (1.00 g, 1.74 mmol, 1.00 equiv) and THF (25 mL) were added to an oven-dried round bottom flask equipped with a stir bar. TMEDA (526 mg, 678 μL, 4.52 mmol, 2.60 equiv) and iodobenzene (994 mg, 545 μL, 4.87 mmol, 2.80 equiv) were added, and the reaction mixture was sealed and heated at 65 °C for 30 min. After 30 min, the reaction mixture filtered through Celite under air to remove Pd black. The Celite was rinsed with THF (3x1 mL), and the filtrate was concentrated *in vacuo*. The resulting solid was triturated with hexanes (3x10 mL) and Et_2O (3x25 mL) and dried under vacuum. The product was isolated as a yellow solid (500 mg, 1.17 mmol, 67% yield).

The NMR spectra of complex **2** corresponded to previously reported data for the complex.[13]

(TMEDA)Pd(Ph)(CF_3) (3)



The procedure for the synthesis of complex **3** was based on the conditions reported by Sanford and coworkers for the synthesis of (TMEDA)Pd(Ar)(CF_3).[12]

In a nitrogen-filled glovebox, (TMEDA)Pd(Ph)(I) (**2**) (500 mg, 1.17 mmol, 1.00 equiv) and CsF (533 mg, 3.51 mmol, 3.00 equiv) were added to a 20 mL vial equipped with a stir bar. THF (8 mL) was added, and the reaction mixture was stirred vigorously at r.t. for 5 min. After 5 min, $TMSCF_3$ (333 mg, 346 μL, 2.34 mmol, 2.00 equiv) was added, and the reaction mixture was stirred at r.t. for 3 h. Conversion was monitored by ^1H NMR spectroscopy of an aliquot of the reaction mixture. After 3 h, additional $TMSCF_3$ (333 mg, 346 μL, 2.34 mmol, 2.00 equiv) was added, and the reaction mixture was stirred at r.t. for an additional 15 h. After 15 h, the reaction mixture was concentrated *in vacuo*. The crude reside was dissolved in CH_2Cl_2 (7.5 mL) and filtered through Celite. The Celite was rinsed with CH_2Cl_2 (2x2.5 mL), and the filtrate was concentrated *in vacuo* to a volume of 1 mL. Pentane (20 mL) was added, and the resulting precipitate was collected by filtration. The solid was washed with hexane (3x5 mL) and Et_2O (2x1 mL) and dried under vacuum. The product was isolated as a light yellow solid (308 mg, 0.835 mmol, 71% yield).

The NMR spectra of complex **3** corresponded to previously reported data for the complex.[9]

Procedure for Kinetic Analysis of Reductive Elimination

In a nitrogen-filled glovebox, Pd complex **1** (8.7 mg, 0.010 mmol, 1.0 equiv), DPPF (5.5 mg, 0.010 mmol, 1.0 equiv), and a stock solution of 1-fluoro-4-(trifluoromethyl)benzene (0.100

M in dioxane, 100 μL, 0.0100 mmol, 1.00 equiv) were added to a 4 mL vial. A mixture of dioxane and mesitylene (1:2, 500 μL total volume) was added, and the reaction mixture was transferred to a J-Young NMR tube. The tube was then heated in a temperature controlled oil bath at 140 °C. The concentration of the Pd complex was monitored by ^{19}F NMR spectroscopy over approximately 3 half-lives. The spectra were integrated and fit to an exponential decay to determine the rate constant for reductive elimination, from which the half-life was determined. The yield of the reductive elimination product was determined by ^{19}F NMR spectroscopy after heating for 24 h.

General Procedure for Evaluation of Ligands for Reductive Elimination of Ar-CF_3

In a nitrogen-filled glovebox, the ligand (0.0220 mmol, 1.10 equiv) and THF (0.5 mL) were added to a 4 mL vial equipped with a stir bar. In a separate vial, a stock solution was prepared containing complex **4** (0.200 M) and the internal standard 4-trifluoromethoxyanisole (0.200 M) in THF. The stock solution (100 μL, 0.0200 mmol, 1.00 equiv of both **4** and internal standard) was added to the vial containing the ligand, and the reaction mixture was stirred at r.t. for 1 h. After 1 h, the reaction mixture was heated at 65 °C for 2 h. After 2 h, formation of $PhCF_3$ was evaluated by ^{19}F NMR spectroscopy. This procedure was repeated at 80 °C and 100 °C. The lowest temperature at which reductive elimination occurred in >5% yield after 2 h is indicated in Table 6.2. After heating for 24 h, the yield of the reaction was measured by ^{19}F NMR spectroscopy.

General Procedure for Palladium-Catalyzed Trifluoromethylation with AdBippyPhos as Ligand

In a nitrogen-filled glovebox, $[Pd(allyl)Cl]_2$ (0.5 mg, 0.002 mmol, 0.03 equiv), AdBippyPhos (3.0 mg, 0.0045 mmol, 0.090 equiv), KF (5.8 mg, 0.10 mmol, 2.0 equiv), and the CF_3 source (0.10 mmol, 2.0 equiv), if solid at room temperature, were added to a 4 mL vial equipped with a stir bar. Dioxane (0.25 mL) was added, followed by 1-butyl-4-chloro-benzene (8.4 mg, 8.4 μL, 0.050 mmol, 1.0 equiv) and the CF_3 source (0.10 mmol, 2.0 equiv), if liquid at room temperature. The reaction mixture was stirred at room temperature for 5 min, then heated at 100 °C for 16 h. After 16 h, the reaction was allowed to cool to r.t., and 3-nitrofluorobenzene was added as an internal standard. The yield of the reaction was evaluated by ^{19}F NMR spectroscopy.

Crystallographic Data

Table S6.1 Crystal data and structure refinement for (DPPF)Pd(Ph)(CF_3) (**1**).

Empirical formula	$C_{42}H_{33}ClF_3FeP_2Pd$
Formula weight	854.32
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P 21/c

Unit cell dimensions	a = 12.4826(5) Å	α = 90°.
	b = 13.2243(6) Å	β= 104.9245(17)°.
	c = 21.9347(10) Å	γ = 90°.
Volume	3498.7(3) $Å^3$	
Z	4	
Density (calculated)	1.622 Mg/m^3	
Absorption coefficient	1.144 mm^{-1}	
F(000)	1724	
Crystal size	0.180 x 0.120 x 0.080 mm^3	
Theta range for data collection	1.688 to 25.397°.	
Index ranges	-15<=h<=15, -14<=k<=15, -26<=l<=26	
Reflections collected	102810	
Independent reflections	6414 [R(int) = 0.0273]	
Completeness to theta = 25.000°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.745 and 0.674	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6414 / 12 / 451	
Goodness-of-fit on F^2	1.114	
Final R indices [I>2sigma(I)]	R1 = 0.0324, wR2 = 0.0839	
R indices (all data)	R1 = 0.0343, wR2 = 0.0853	
Extinction coefficient	n/a	
Largest diff. peak and hole	1.227 and -2.075 $e.Å^{-3}$	

6.5 References

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