DISSERTATION

SYNTHESIS OF α,α-DIFLUOROBENZYLIC STRUCTURES VIA NEW BASE-PROMOTED REDUCTIVE AND OXIDATIVE COUPLING REACTIONS

Submitted by

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ABSTRACT

SYNTHESIS OF α,α-DIFLUOROBENZYLIC STRUCTURES VIA NEW BASE-PROMOTED REDUCTIVE AND OXIDATIVE COUPLING REACTIONS

α,α-Difluorobenzylic substructures have been a desired product in a variety of industries from pharmaceuticals to agrochemicals to electronic materials. This thesis highlights the traditional and fundamental challenges associated with accessing these valuable products from trifluoromethylarenes and difluoromethylarenes, respectively, with an emphasis on base-promoted strategies to facilitate these transformations. Both a general Lewis base-promoted reductive coupling strategy and a Brønsted base-promoted oxidative coupling strategy have been developed with the purpose of achieving more modular access to α,α-difluorobenzylic substructures.

Chapter One describes the significance of defluorinative strategies on small molecule organofluorines and the background of defluorinative strategies on trifluoromethylarenes, specifically, including previous and current work by the Bandar Group. The monoselective defluorofunctionalization of trifluoromethylarenes has been a long-standing challenge within the chemistry community and in 2019 the Bandar Group began to expand this methodology to include Lewis-base promoted approaches to access value-added products. Chapter One is intended to be the foundation of this thesis and convey the importance of fluorinated small molecules in a variety of applications with a specific emphasis on defluorinative strategies to functionalize trifluoromethylarenes.

Chapter Two describes the long-standing challenges for selective defluorofunctionalization of trifluoromethylarenes, specifically of electronically unactivated arenes. Insight gained from the

Bandar Group's reported Lewis base-promoted strategy was used to pragmatically develop an approach for selective functionalization of electron-neutral trifluoromethylarenes. This chapter will provide background on the prevalence of trifluoromethylarenes, strategies that selectively functionalize unactivated systems, and my efforts to expand Lewis-base promoted functionalization to this class of arenes.

Chapter Three describes the fundamental challenge of deprotonative strategies that result in unstable carbanions, particularly α,α-difluoromethylarenes and our approach to achieve their productive functionalization. Difluorobenzylic substructures are valuable in a variety fields such as pharmaceuticals, agrochemicals, and electronic materials. Our group's Halogen transfer platform provides an approach to rapidly capture unstable carbanions with base-stable halogen oxidants (2-halothiophenes) which was sequenced with substitution *via in situ* pronucleophiles. The scope is highly general and provides alternative selectivity to traditional nucleophilic fluorination or radical halogenation methods, while pronucleophiles can be aliphatic alcohols or aromatic alcohols and thiols to achieve value-added products.

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d encouraging me to set up “just a few more reactions” every day – your continued support and belief in me has truly been invaluable over the years.

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possible. Kennan, thank you for going out of your way to essentially stock my new apartment after my divorce, giving me an escape from reality and supporting me through a difficult time. Hayden, thank you for making a point to stop by and spend fun-filled evenings on the town, discussing philosophies and our own experiences with human interactions. You all have been a consistent force in the life, and for that I am grateful. To my extended family, Shirley, Ray, Carl, Renee, Sophia, Lauren, Caroline, Anita, Ben, James, and Belle, thank you for always showing up and showing up in style and with all of the energy for a good time. I have been privileged to have been able to attend family trips to see you all, celebrate your own accomplishments, and tease you the way the Hooker family has always done.

To my friends, I do not have the space to describe your immeasurable impact on my life through the years, but I will try to mention you in a brief manner. The friends back home in Montana, Lexi and Mateo, you have been my closest friends for almost as long as I can remember and even though we have all grown and moved to different places, I am so thankful that you are still in my life and the distance completely dissipates when we get together. To Haley, it's crazy to think that we met almost a decade ago through a Craigslist ad and now you are still one of my closest friends, thank you for being a phone call away and for always being understanding as well as your firery self. To the graduate students I've met in my time at CSU, Felipe, Celine, Celena and Bryce, Heidi Klem, Trey, Ethan, and Liam, thank you for always being down for an adventure to Old Town, the mountains, or Red Rocks. Your friendship has made the graduate school experience one of the most rewarding so far in my life. To Lacey, Lexi, Danni, Ryan, and Nina, thank you for your love, acceptance, and friendship over the past few years. Meeting you all and being included in the many shenanigans you get up to has been so appreciated.

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CHAPTER ONE

ORGANOFLUORINES IN SYNTHETIC CHEMISTRY

1.1 Chapter Overview

Organofluorine chemicals are abundantly available from commercial suppliers and through well-established synthetic protocols.[1] Reliable access to these compounds in modular and scalable fashions is the result of tremendous development in fluorination methods as well as the invention and use of fluorinated building blocks.[2] I, along with my advisor Prof. Dr. Jeffery Bandar, recently authored a review highlighting the synthetic advantages of defluorinative C–F bond functionalization, featuring the main challenges, advances and applications for each type of C–F bond to guide synthetic chemists and to motivate researchers to devise new C–F functionalization methods.[3] This chapter will describe the significance of defluorinative strategies on small molecule organofluorines and the background of defluorinative strategies on trifluoromethylarenes, specifically, including previous and current work by the Bandar Group. The monoselective defluorofunctionalization of trifluoromethylarenes has been a long-standing challenge within the chemistry community and in 2019 the Bandar Group began to expand this methodology to include Lewis-base promoted approaches to access value-added products. Chapter One is intended to be the foundation of this thesis and convey the importance of fluorinated small molecules in a variety of applications with a specific emphasis on defluorinative strategies to functionalize trifluoromethylarenes.

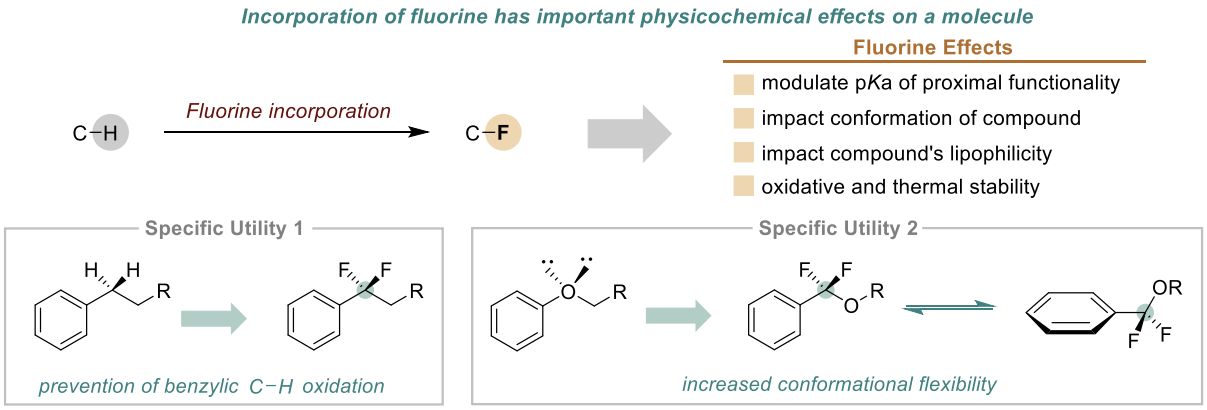

Figure 1-1. Beneficial effects of fluorine incorporation into small molecules.

1.2 Organofluorine Synthetic Utility

Fluorine has been incorporated into organic small molecules in a variety of applications from pharmaceuticals and agrochemicals to materials and electronics.[4] Efforts to integrate fluorine into organic small molecules are generally motivated by the widespread use of fluorine incorporation as a means to modulate a molecule's properties, especially within medicinal, agrochemical, materials and commercial product (e.g., refrigerants and polyfluoroalkyl substances) applications.[4] In these contexts, fluorine's high electronegativity and the high strength of C–F bonds can improve a compound's metabolic or oxidative stability, lipophilicity and solubility, and can modulate key properties such as pK_a or conformational preferences (Figure 1-1).[5] In material and technological applications, difluoroaryl motifs can enhance the dielectric anisotropy and stability of liquid crystals while broadening the range of the nematic phase range.[6] Traditionally, these compounds are prepared *via* deoxyfluorination methods that require toxic chemicals that react violently with water and are not ideal conditions for a general protocol (Figure 1-2a).[7] Alternatively, access to the halogenated intermediate (e.g., ArCF_2–Br) would offer a modular approach to difluoromethylarene derivatives, however mechanistic challenges exist for access to these synthetic precursors (Figure 1-2b).[8,39]

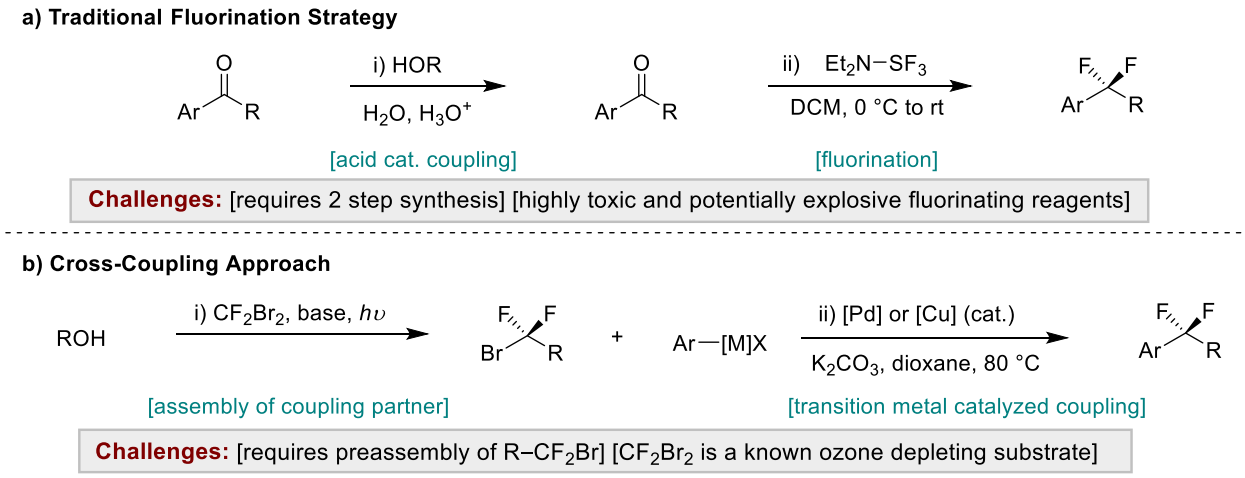

Figure 1-2. (a) Traditional nucleophilic fluorination to access difluorobenzylic structures. (b) Traditional cross-coupling protocol to access difluorobenzylic substructures.

1.3 Defluorinative Strategies of Organofluorines

Chemists have made significant advances in C–F bond functionalization methodology, a task often inspired by the fundamental challenges associated with activating such strong bonds. This progress is the subject of numerous reviews that are often dedicated to a specific class of C–F bond (e.g., aryl fluorides) or mechanistic strategy (e.g., metal catalysis).[9-10] However, given the increasing availability of fluorinated chemicals and advances in C–F functionalization, an overview of the key synthetic advantages that motivate defluorinative methods and applications would be useful. The advantages of defluorinative strategies can generally be classified as benefits to either an overall synthetic route or to the mechanism of a desired reaction.

Synthetic route advantages of defluorofunctionalization typically stem either from the availability of a fluorinated starting material or the chemoselectivity of a targeted reaction. For example, certain small molecule organofluorines are less expensive than alternately halogenated analogues. Strong C–F bonds are also inert under many standard reaction conditions and can often be carried through multistep syntheses for downstream functionalization, unlike other C–X bonds.[5] Alternatively, chemoselective activation of functionalized or multihalogenated

organofluorines allows for regioselective multistep syntheses.[11] Defluorofunctionalization is also advantageous when the reaction generates a new, but more valuable, fluorinated product. This is exemplified by methods that activate C–F bonds for isomerization or insertion processes in order to transform simple organofluorines into complex fluorinated products. Similarly, the preparation or purchase of polyfluorinated starting materials for use in partial defluorofunctionalization can be a cost-effective and modular route to fluorine-containing compounds.[12]

There are several mechanistic features of defluorinative reactions that can enable desired transformations over alternative organohalide starting materials. Due to the small size of fluorine and the high bond polarization, certain C–F bonds (e.g. acyl and aryl fluorides) undergo uniquely facile substitution reactions with anionic and sterically-encumbered nucleophiles. The polarization also leads to low-lying C–F anti-bonding orbitals that stabilize β-carbanions, an enabling feature for addition/fluoride elimination sequences of allyl and vinyl fluorides.[13] Defluorination also frequently generates fluoride byproducts that play a pivotal role in reaction mechanisms, often as bases for pronucleophile activation or generation of unstable anionic species *in situ*.[14] Similarly, metal-catalyzed defluorinative reactions can proceed *via* metal fluoride complexes that react with a reagent for reaction propagation.[15] C–F bonds are also often reactive towards Lewis acids and can generate strong fluorine bonds with a reagent or catalyst (e.g., Si–F bond formation).[16] Lewis acidic activation can therefore enable non-traditional substitution selectivity and provide a driving force for thermodynamically challenging reactions or those that proceed through high-energy intermediates (e.g., aryl cation generation).

1.4 Trifluoromethylarene Defluorinative Strategies

The advantages of these starting materials stem from their abundance and availability relative to prefunctionalized motifs (e.g., $ArCF_2$–Br). The resulting products, especially α,α-difluorobenzylic derivatives, are highly sought after in medicinal chemistry as benzylic fluorination can address metabolic stability concerns of analogous C–H bonds.[5b] This substructure also functions as a less oxidizable bioisostere of aryl ethers.[17] Given the abundance of trifluoromethylarenes, their selective defluorofunctionalization could improve the economics of largescale syntheses and enhance access to fluorinated libraries. It should also be noted that typically "inert" perfluoroalkyl groups can be carried through multistep syntheses and are frequently found in complex bioactive molecules, making their use in late-stage derivatization attractive. Despite these advantages, general protocols for monoselective defluorofunctionalization have only recently emerged due to the mechanistic difficulty associated with such processes.[18] The central challenge is that C–F bond strengths of perfluoroalkyl arenes (e.g., $PhCF_3$: 115 kcal/mol) decrease upon removal of each fluorine atom (e.g., $PhCH_2F$: 95 kcal/mol), thus rendering it difficult to activate a C–F bond in the starting material while leaving a weaker C–F bond in the product intact.[19] Despite this fundamental challenge, there have been four distinct mechanistic strategies developed to achieve monoselective defluorofunctionalization of $ArCF_3$s: metal or electrochemical reduction, photoredox, Lewis-acid or frustrated Lewis-pairs activation, and Lewis-base promotion.

In 1989, monoselective trifluoromethylarene defluorofunctionalization was achieved electrochemically by Troupel and coworkers.[20] This process operates *via* reduction of the trifluoromethylarene to an aryl radical anion that undergoes mesolytic C–F cleavage to form a benzylic radical. This radical is further reduced to a difluorobenzylic carbanion that can be

captured *in situ* with chlorosilane or carbonyl electrophiles (Figure 1-3, top).[21] This early work was highly influential as it illustrated that monoselective defluorofunctionalization could be achieved under single electron reducing conditions as the $ArCF_3$ starting materials are easier to reduce than the $ArCF_2R$ products.[22] Recently, Lennox and co-workers developed an improved electrochemical method that expands the scope of hydrodefluorination to enable the direct conversion of bioactive and electron-rich trifluoromethylarenes to difluoromethyl variants (Figure 1-3, bottom).[23] Electrochemical methods to derivatize $ArCF_3$s is limited to simple arenes as other more reducible functional groups (e.g., carbonyls, carbonitriles, halogens) are generally not tolerated due to the need for strong reducing conditions. More mild reducing conditions can be employed on electron-deficient systems which allow for a slight increase in functional group tolerance, but is limiting as the $ArCF_3$ substrate must be sufficiently activated by electron-withdrawing groups (EWGs).

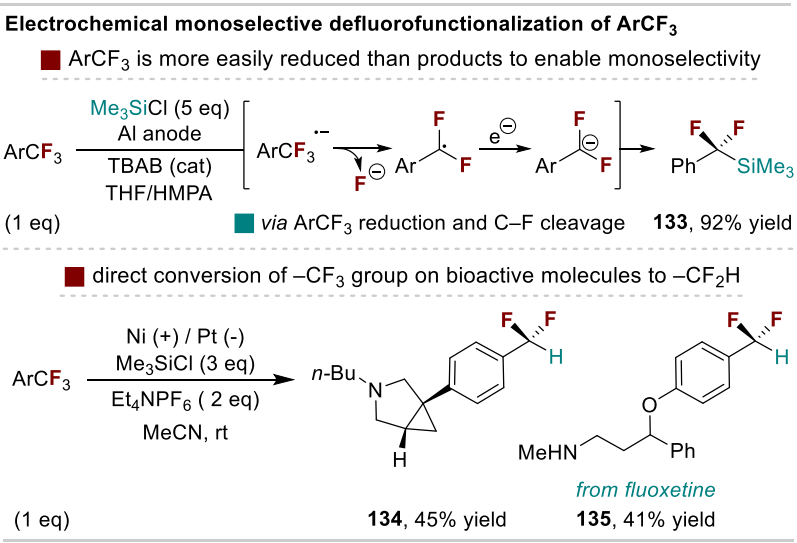

Figure 1-3. Electrochemical strategies for selective defluorofucntionalization of trifluoromethylarenes.

In 2017 and 2018, the Gschwind and König[24] and Jui[25] Groups reported photoredox-catalyzed, monoselective defluoroalkylation of electron-deficient trifluoromethylarenes that also

exploits a decrease in reduction potential upon C–F substitution. Here, $ArCF_3$ reduction and C–F cleavage generate a difluorobenzylic radical that is intercepted by an alkene. These methods are represented in Figure 1-4a by an improved protocol, developed by Jui and co-workers in 2019, that includes electron-neutral trifluoromethylarenes and facilitates rapid access to key fragments of medicinal compounds.[26] Following these pioneering reports, photopromoted processes have been expanded to include hydrodefluorination, defluoroarylation and defluorocarboxylation, as summarized in Figure 1-4b. [27] It is likely that future work will continue to exploit benzylic C–F bonds as radical precursors for other coupling reactions.[28] Photoredox strategies have been employed on a wide range of $ArCF_3$s from electron-deficient to electron-rich arenes, however the need for niche photocatalysts and light activation limit the broad use of these strategies.

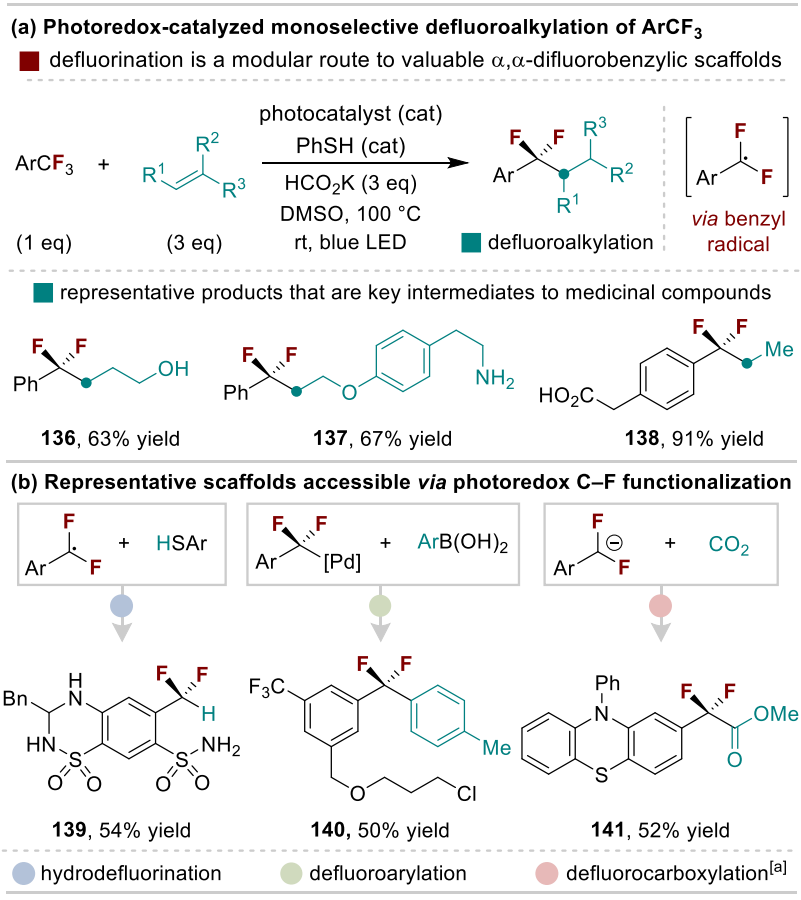

Figure 1-4. (a) Selected examples of photoredox-promoted selective functionalization of trifluoromethylarenes. (b) Scaffolds that are accessible *via* photoredox defluorinativefunctionalization

Lewis acid C–F bond activation strategies of polyfluoroalkylarenes typically lead to multiple C–F substitutions.[29] Yoshida, Hosoya and co-workers addressed this challenge through the generation of *ortho*-silylium ions on trifluoromethylarenes that abstract a single fluoride to generate versatile difluorobenzylic cation intermediates (Figure 1-5a).[30] Young and co-workers disclosed a major breakthrough in 2020 through their use of frustrated Lewis pairs (FLPs),[31] as a general defluorofunctionalization method of di- and trifluoromethylarenes to form pyridinium and phosphonium salts (Figure 1-5b).[32] The obtained salts are versatile for diverse coupling methods as represented in Figure 1-5b. This approach also enables ^{18}F radiofluorination of di- and trifluoromethyl groups in bioactive polyfluoroalkylarenes for potential use in Positron-Emission-Tomography (PET) imaging (Figure 1-5c).[33,34] Limitations to these strategies are that they often require an *ortho*-silyl group to facilitate formation of difluorobenzylic cations or the use of specific FLP systems (e.g., $B(C_6F_5)_3$ and phosphonium or pyridinium salts) to activate $ArCF_3$ substrates for nucleophilic substitutions.

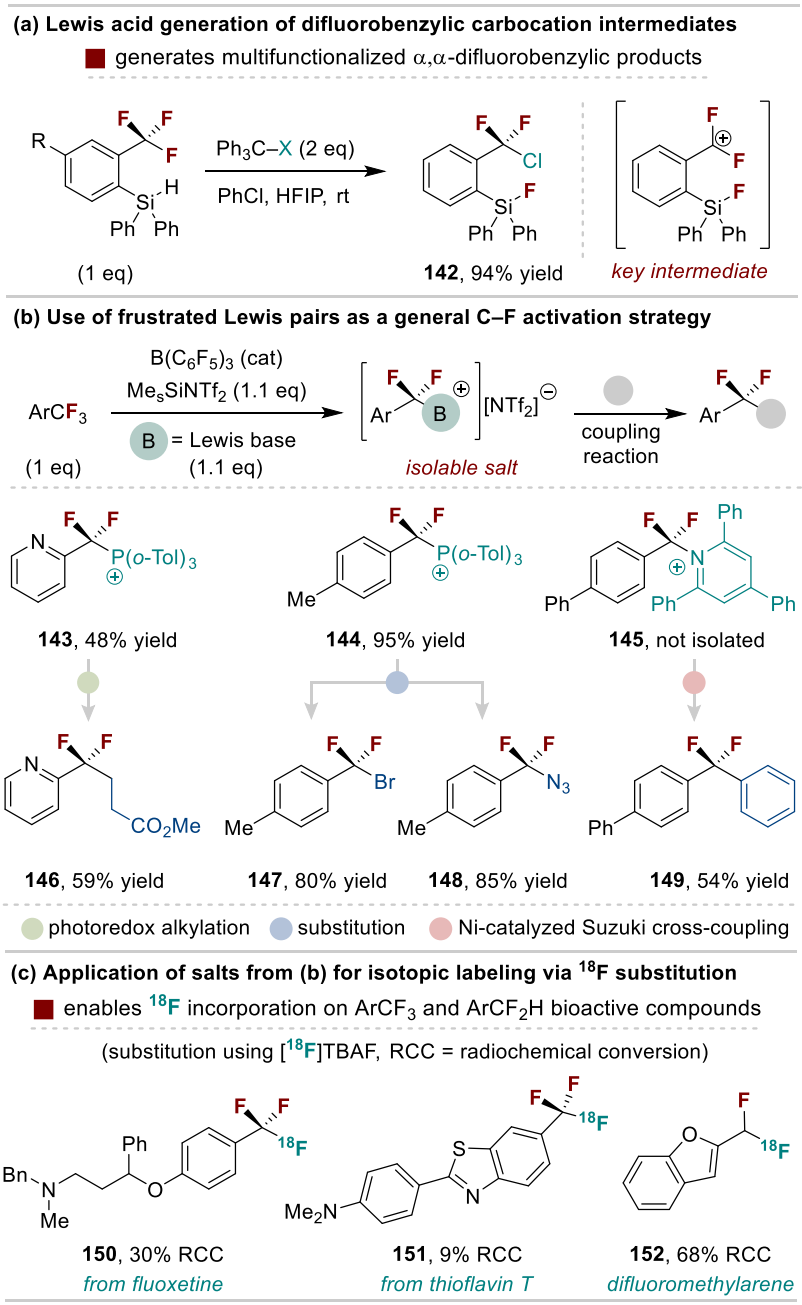

Figure 1-5. (a) Lewis acid-promoted selective defluorofunctionalization. (b) FLP-facilitated selective defluorofunctionalization. (c) application of cationic salts for isotopic labeling.

In 2019, our group discovered a fluoride-promoted defluoroallylation reaction of electron-deficient trifluoromethylarenes using allyltrimethylsilanes, which is proposed to proceed *via* single electron transfer (SET) from an anionic silicate intermediate to the $ArCF_3$ (Figure 1-6a).[35] Our group subsequently expanded the scope of accessible $ArCF_2R$ products *via* a Lewis base-promoted

reductive coupling reaction with formamides (Figure 1-6b).[36] Jiao and co-workers developed an alternative protocol for defluoroallylation of CF_3-substituted *N*-heteroarenes (Figure 1-6c).[37] Here, an *N*-heteroarene and base-activated B_2pin_2 react to reduce a C–F bond, thus generating a difluorobenzylic anion that undergoes enantioselective allylation using a chiral Ir catalyst. These methods have largely been limited to electron-deficient arenes, similar to electrochemical methods, the specifics of the Bandar Group's Lewis-base approach is discussed in section 1.5.

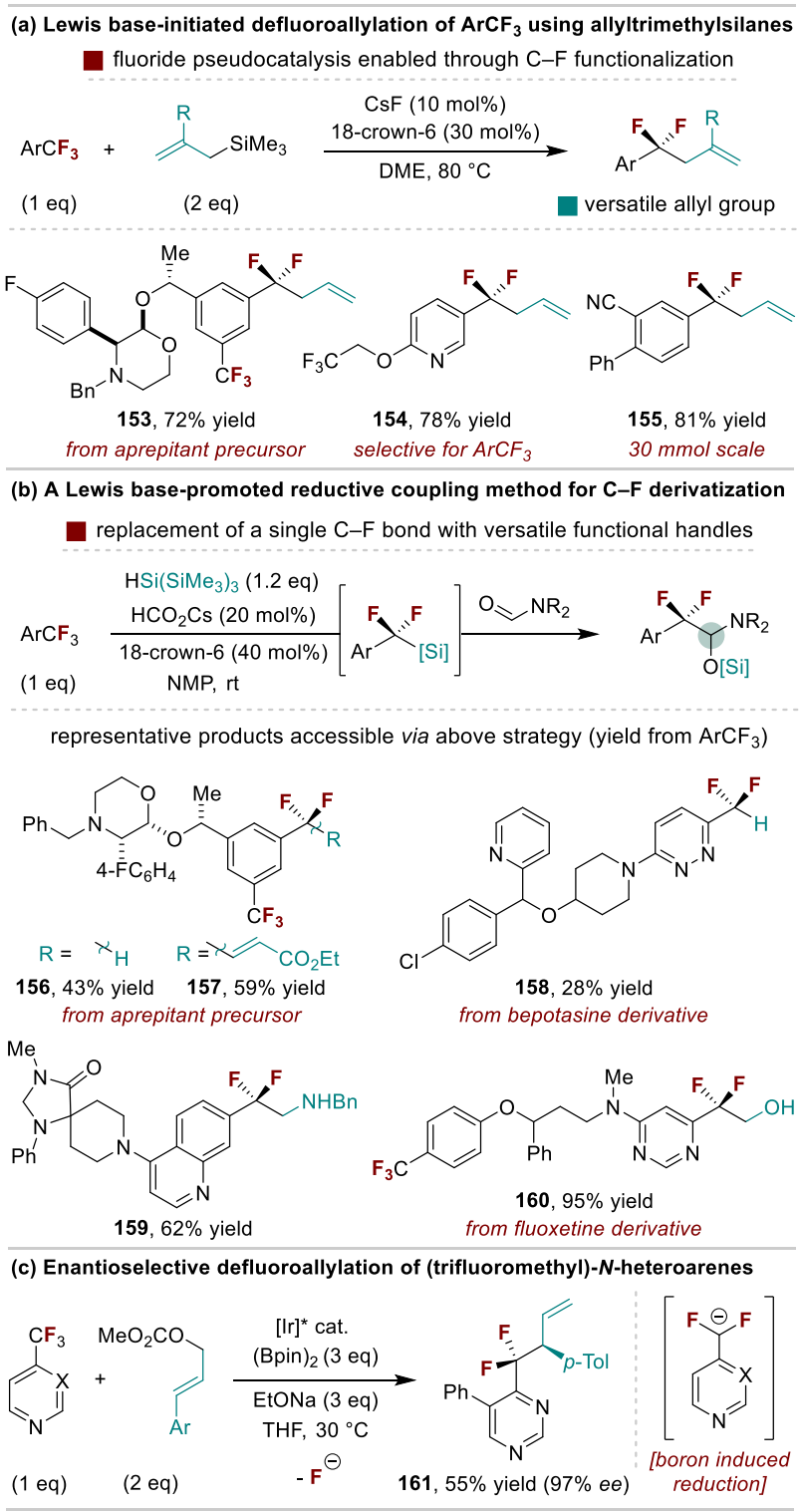

Figure 1-6. (a) Lewis base-promoted defluoroallylation of trifluoroemthylarenes. (b) Lewis base-promoted reductive coupling of trifluoromethylarenes and subsequent derivatizations. (c) enantioselective defluoroallylation of *N*-heteroarenes.

1.5 Trifluoromethylarene Derivatization in the Bandar Group

Our groups initial report in selective functionalization of trifluoromethylarenes was led by a former postdoctoral research in our group, Dr. Choasheng Luo, where he found that Lewis-bases could activate allylsilanes which could then couple with $ArCF_3$s and give monoselective allylated products.[35] Importantly, we hypothesized that this mechanism operated through a single electron transfer (SET) from the activated allylsilane to the $ArCF_3$ substrate resulting in a difluorobenzylic radical and an allyl radical which rapidly couple to give the allylated product (Figure 1-7). Due to the activation of $ArCF_3$ substrates operating through a SET reduction, this method is limited to electron-deficient arenes that have less negative reduction potentials (e.g., bis-trifluoromehtylarenes, $ArCF_3$s with EWGs such as sulfonamides or *N*-heteroarenes). The utility of this method was demonstrated through gram-scale reactions and derivatization of the allyl group into diverse difluoroalkyl substituents (Figure 1-6a). Additionally, a key feature of this approach is the use of pseudo-catalytic fluoride salts to accomplish this reaction, as sub-stoichiometric quantities of fluoride salt can be added to the reaction mix to initiate the reaction, where the loss of fluoride from the $ArCF_3$ can propagate the reaction to completion. We noted that one of the major limitations to our group's initial report was that this reaction can only access difluoroalkyl substituents that map onto the allyl coupling fragment.

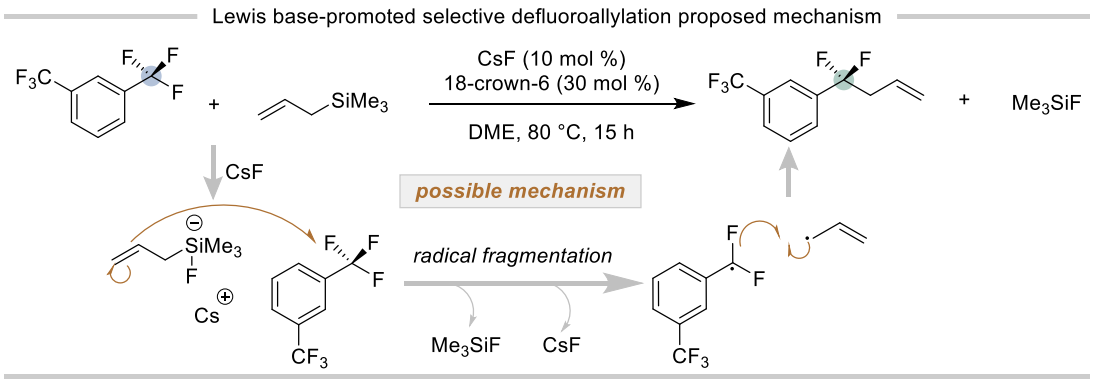

Figure 1-7. Proposed mechanism for Lewis base-promoted defluoroallylation of trifluoromethylarenes.

This limitation was addressed by the development of a generalized base-initiated, silane-mediated, reductive coupling platform of trifluoromethylarenes, spear-headed by Dr. Shawn Wright.[36] This method expands the C−F transformations accessible from trifluoromethylarenes by providing a versatile silylated hemiaminal synthon that possesses the reactivity of both an aldehyde and an iminium ion (Figure 1-6b). Key to this work was the discovery of a general silane reagent that couples with $ArCF_3$s to generate synthetically versatile difluorobenzylic products where commercially available tris(trimethylsilyl)silane (TTMSS) in the presence of Lewis basic salts in formamide solvents (e.g., DMF or 4-formylmorpholine) affords silylated hemiaminal adducts. Notably, omittance of the formamide coupling partner in NMP solvent also resulted in difluorobenzyl silanes which also serve as a readily diversifiable synthetic handle (Figure 1-6b). Derivatization of these benzylsilanes can be done *via* fluoride activation of the benzylsilane to couple with a variety of electrophiles, with an example being a report published by a former post-doctoral researcher in our group, Dr. Tyler Reidl[38] (Figure 1-8), therefore indicating that difluorobenzylic silanes can act as masked carbanions. This reductive coupling platform expands the scope of α,α-difluorobenzylic substructures accessible from $ArCF_3$s to better reflect the structural diversity found in bioactive compounds. The reaction leverages the continuous generation of anionic intermediates to propagate a disilane-mediated defluorosilylation and formamide addition sequence. This ensemble allows a trifluoromethyl C−F bond to formally serve as a masked nucleophile, thus delivering new difluoroalkylarene synthetic linchpins. While this development has significantly expanded the variety of functional groups that can replace one C–F bond of trifluoromethylarenes, a remaining limitation is that this strategy is restricted to electron-deficient arenes, which are prevalent in bioactive motifs.

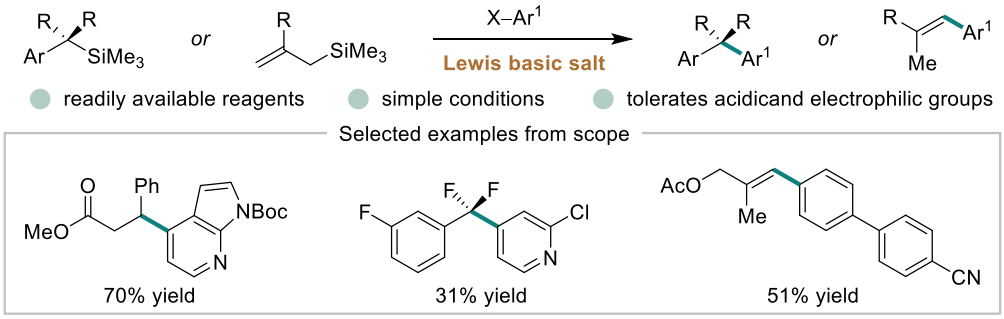

Figure 1-8. Lewis base-promoted coupling of benzyl and allylsilanes with electrophilic arenes.

1.6 Conclusion

The chemistry described in Chapter One is intended to provide background and context for the continued development of monoselective defluorofunctionalization strategies in addition to expressing the importance of organofluorine small molecules for a variety of applications. Organofluorines exist in a range of industries as the incorporation of fluorine has been shown to impart important physiochemical effects and beneficial electronic factors for material applications. The Bandar Group's work has significantly expanded the possibilities of selective defluorinative derivatization of electron-deficient trifluoromethylarenes through the development of Lewis-base promoted strategies. Importantly, electron-neutral to electron-rich trifluoromethylarene derivatization remains an unmet challenge within this platform. Chapter Two will describe my work to address this remaining challenge through the discovery of a Lewis basic salt initiated, silane-mediated reductive coupling reaction that works on unactivated $ArCF_3$s and Chapter Three will detail my expansion into employing our group's halogen-transfer oxidative coupling strategy to access a wider array of difluorobenzylic substructures through C–H functionalization *via* rapid capture of unstable difluorobenzylic anions.

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CHAPTER TWO

LEWIS-BASE PROMOTED MONOSELECTIVE DEFLUOROFUNCTIONALIZATION OF ELECTRON-NEUTRAL TRIFLUOROMETHYLARENES.

2.1 Chapter Overview

Trifluoromethylarenes are an abundantly available motif with over 10,000 compounds commercially available with a variety of reliable methods to install a $–CF_3$ group on arenes.[1] Due to their high availability, trifluoromethylarenes are prevalent in many bioactive compounds as the incorporation of fluorine can impact beneficial properties to a compound such as modulation of lipophilicity, pK_a of nearby functional groups, affinity for binding pockets, and increased permeability through cell membranes.[1] Perfluoroalkyl groups are often considered to be "inert" and therefore can be carried through a multitude of reaction steps while staying intact which greatly contributes to their presence in value-added compounds.[1] However, C–F derivatization of trifluoromethylarenes is largely limited to electron-deficient arenes due to the difficulty of selectively functionalizing one C–F bond of three as these EWGs help to activate the $ArCF_3$ for defluorofunctionalization strategies (Chapter 1.4). This chapter will provide background on the prevalence of trifluoromethylarenes, strategies that selectively functionalize unactivated systems, and my efforts to expand Lewis-base promoted functionalization to this class of arenes.

2.2 Synthesis and Utility of Trifluoromethylarenes

Trifluoromethylarenes can be synthesized through a variety of strategies such as nucleophilic, electrophilic, and radical approaches (Figure 2-1).[1] The traditional synthesis of trifluorormethylarenes was *via* a process developed by Swartz in 1892 wherein trichloromethylbenzene was treated with nucleophilic fluoride (e.g., SbF_2) to generate

trifluoromethylbenzene, however this method is limited to simple trichloromethylbenzene due to the harsh reaction conditions.[2] Since then considerable progress has been made to synthesize $ArCF_3$s from aryl halides,[3] aryl boronic acids,[4] anilines,[5] and through C–H activation of arenes.[6] Commonly these strategies use the Ruppert-Prakash reagent (CF_3SiMe_3) or analogous reagents with Cu or Pd metals as stoichiometric reagents or catalysts, or Ru as a photocatalyst.

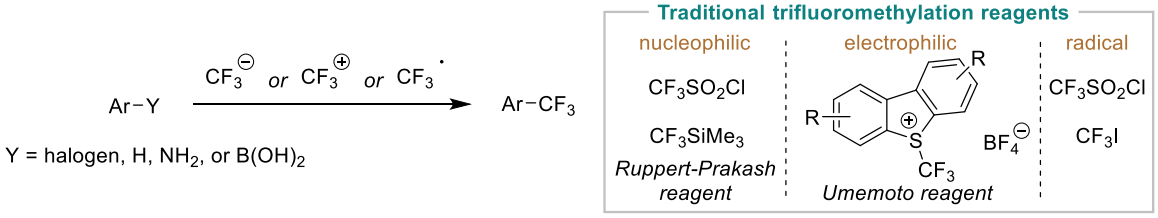

Figure 2-1. Strategies for trifluoromethylation and common trifluoroemthylation reagents.

Electrophilic trifluoromethylation reagents are difficult to synthesize due to the trifluoromethyl group being highly electronegative. The first report of electrophilic reagents was by Yagupolskii and coworkers in 1984,[7] followed by the development of a system of electrophilic reagents from Umemoto and Ishihara in 1993.[8] Since then there have been a variety of electrophilic reagent shave been developed and employed with great success.[9] Incorporation of electrophilic $–CF_3$ groups is commonly done through electrophilic aromatic substitutions (EAS),[10] Cu (can be stoichiometric) or Pd catalyzed reactions.[11, 12]

Radical trifluoromethylation occurs *via* the trifluoromethylation of carbon centered radicals, first reported by Renaud, de Meijere and others in the 1970s, albeit in low yields.[13] Significant improvement for radical trifluoromethylation was reported by Fu and coworkers in 2013 wherein the trifluoromethyl group was installed *via* a copper-promoted Sandmeyer-type protocol through deamination of the amine with the $–CF_3$ group coming from Umemoto's reagent.[14] This strategy has been further expanded by other groups for trifluoromethylation of heteroarenes, functionalization of diazonium salts, and use of other trifluoromethylating reagents

such as Cu(I)–CF_3.[15] Dual photoredox and copper catalysis have been used to achieve radical trifluoromethylation of aryl bromides and aryl thianthrenium salts, which often result in high yields with excellent functional group tolerance.[16]

Trifluoromethylarenes are frequently incorporated into pharmaceuticals, agrochemicals, and materials due their effect on the compound's permeability, lipophilicity, and metabolic stability (Figure 2-2).[1] The $–CF_3$ group has a similar electronegative parameter to a hydroxyl group but has a considerably larger hydrophobic parameter, while sterically resembling isopropyl substituents. Due to the beneficial properties that these functional groups impart to a compound, much effort has been given to derivatize trifluoromethyl groups to difluorobenzylic substructures wherein one fluorine atom is replaced with a different substituent. These various derivatizations have been shown to further increase the potency of the parent compound in pharmaceutical settings and enhance mechanical properties in materials.[17] A withstanding limitation for access to difluorobenzylic substructures is that defluorofunctionalization of electron-neutral to electron-rich trifluoromethylarenes often results in exhaustive defluorination, low functional group tolerance, or the use of complex catalysts systems.

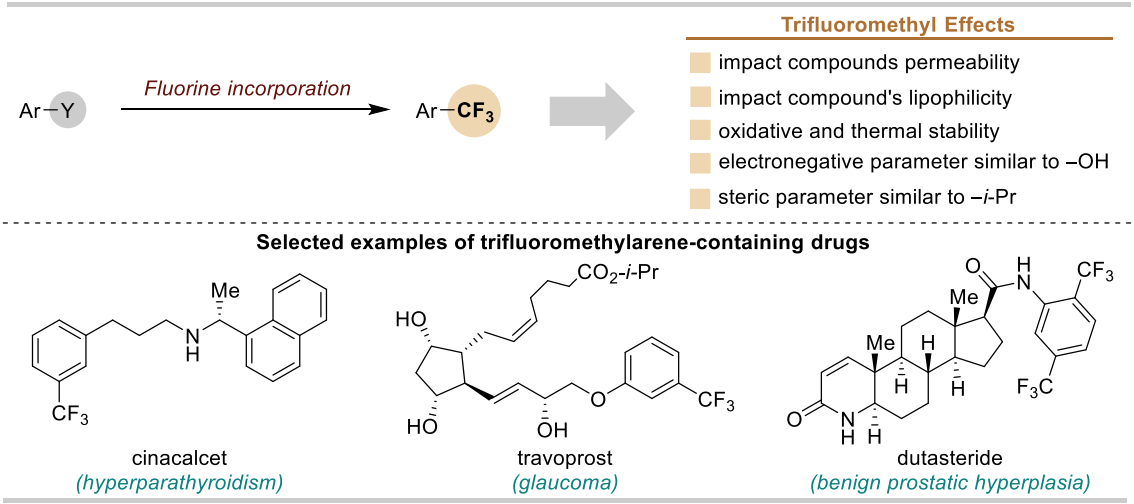

Figure 2-2. Effects of trifluoromethylation on a compound and selected examples of trifluoromethylarenes in drug compounds.

2.3 Derivatization of Electron-Neutral Trifluoromethylarenes

When derivatizing $ArCF_3$s, a fundamental challenge is that the C–F bond of $ArCF_3$ have a high bond strength (~115 kcal/mol for $PhCF_3$) and as substitution of fluoride occurs, the remaining C–F bonds also become weaker (99 kcal/mol for $PhCFH_2$) (Figure 2-3a).[18] This generally means that forcing conditions to activate the first C–F bond, can also activate the remaining C–F bonds in the product often leading to over-functionalization and loss of the desired fluoride substituents. Typical selective defluorination strategies normally rely on a SET to activate the arene to generate a benzylic radical which can couple with Hydrogen-atom-donors (HAD) or alkenes to access difluorobenzylic structures (Figure 2-3b). These processes exploit the fact that $ArCF_3$ starting materials are more easily reduced than the $ArCF_2$–R products, therefore preventing the over-functionalization and loss of fluoride.[19] Importantly, most of these methods require the $ArCF_3$ to be electron-deficient to further exploit the difference in reduction potential between the starting material and the product, meaning that electronically unactivated arenes and electron-rich arenes are largely absent from the current state-of-the-art reports.

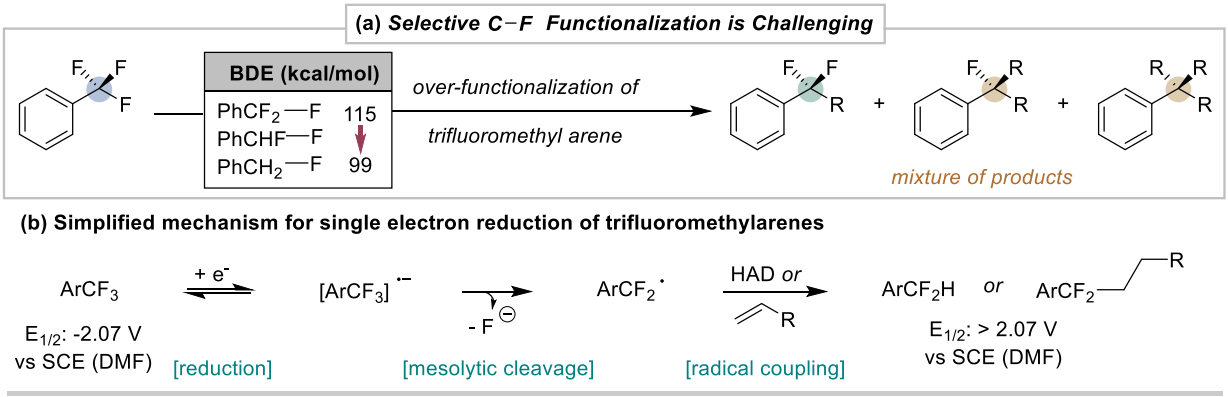

Figure 2-3. (a) Decrease in bond strength upon substitution of fluoride. (b) simplified mechanism for single electron reduction of trifluoromethylarenes with relative reduction protentials.

In a report from Jui and coworkers in 2018 where electron-deficient trifluoromethylarenes are converted *via* defluoroalkylation under photoredox conditions, they show 3 examples of

electron-neutral substrates which were able to undergo mono-selective defluorination when a more highly reducing photocatalyst was employed, albeit in lower yields than electron-deficient arenes (Figure 2-4a).[19a] This work was followed up the following year by the same group to further address this challenge, a range of electron-neutral trifluoromethylarenes were shown to participate in dual organophotoredox catalyzed selective defluoroalkylation and hydrodefluorination processes.[19b] Alternatively, Young's group has reported a frustrated Lewis pair (FLP) approach for selective functionalization of a range of $ArCF_3$s from electron-deficient to electron-rich substrates wherein a Lewis acid is used to activate a C–F bond followed by addition of a bulky Lewis base to generate a cationic salt and prevent further fluoride abstraction by the Lewis acid (Figure 2-4b).[20] Despite these methods addressing this substrate limitations within their own systems, these strategies are not general and either require the use of complex catalysts or unique Lewis acids in addition to them requiring blue LED and cryogenic temperatures, respectively. These factor limit the up-take of these approaches and add extra difficulty for their use on a preparative scale.

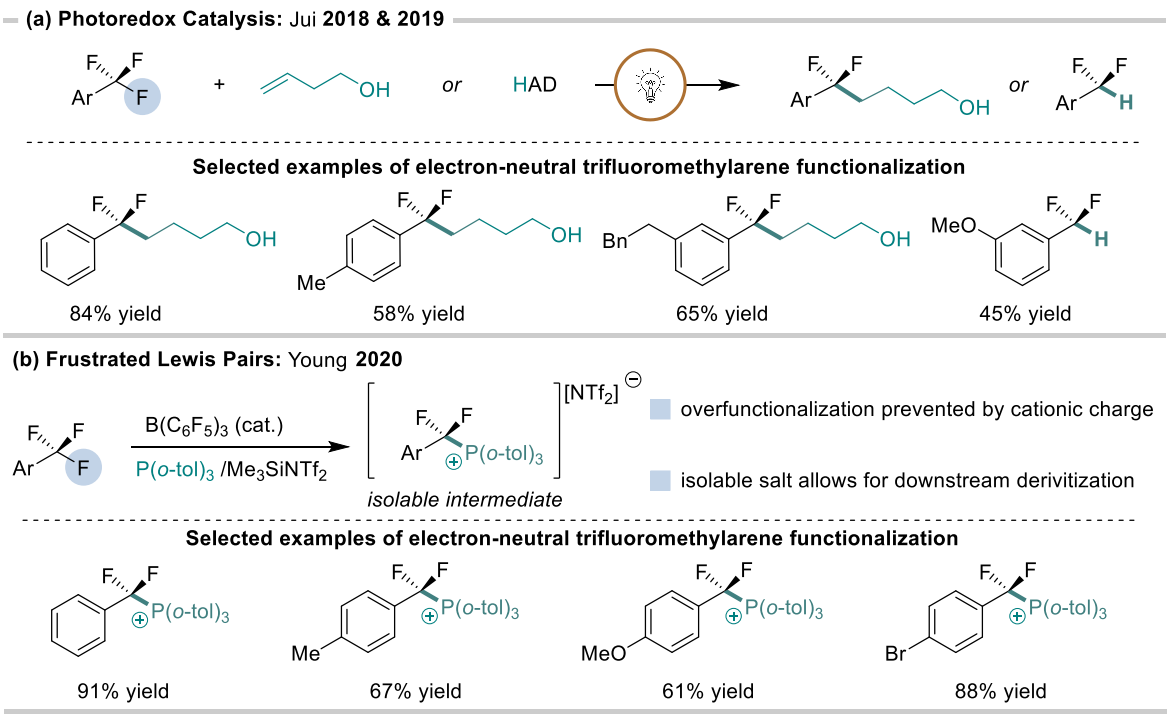

Figure 2-4. (a) Example of electron-neutral trifluoromethylarene defluorofunctionalization *via* photoredox catalysis. (b) Example of electron-neutral trifluoromethylarene defluorofunctionalization *via* Frustrated Lewis Pairs.

2.4 Lewis-base Promoted Monoselective Reduction of Electron-neutral Trifluoromethylarenes

2.4.1 Project Area Overview

In 2019, our group reported a practical strategy that was developed by former postdoc, Dr. Chaosheng Luo, for Lewis base promoted selective defluorofunctionalization of $ArCF_3$s.[21] This initial report used catalytic amounts of Lewis base to activate allyltrimethylsilanes to achieve a defluoroallylation product, where the loss of fluoride from trifluoromethylarenes could serve as the Lewis base to further promote this coupling reaction and allowing it to be pseudocatalytic (Figure 2-5). This report was further expanded upon in 2022 by Dr. Shawn Wright to the use of a general disilane reagent in the presence of formamide electrophile to access the highly derivatizable difluorobenzylic hemiaminal adduct.[22] Importantly, our group's 2022 report

addressed one of the main limitations of our initial report by installing the hemiaminal group which can serve as a masked aldehyde and therefore provides a versatile functional handle, unlike the difluoroallylated products which are limited to olefin derivatization methods (Figure 2-5). A remaining limitation to these reports is that the scope of $ArCF_3$s that participate in the reaction require electron-withdrawing groups to sufficiently activate the $ArCF_3$ for reduction by the silicate or silyl anion intermediate. I aimed to address this withstanding challenge to access difluorobenzylic substructures from electron-neutral trifluoromethylarenes.

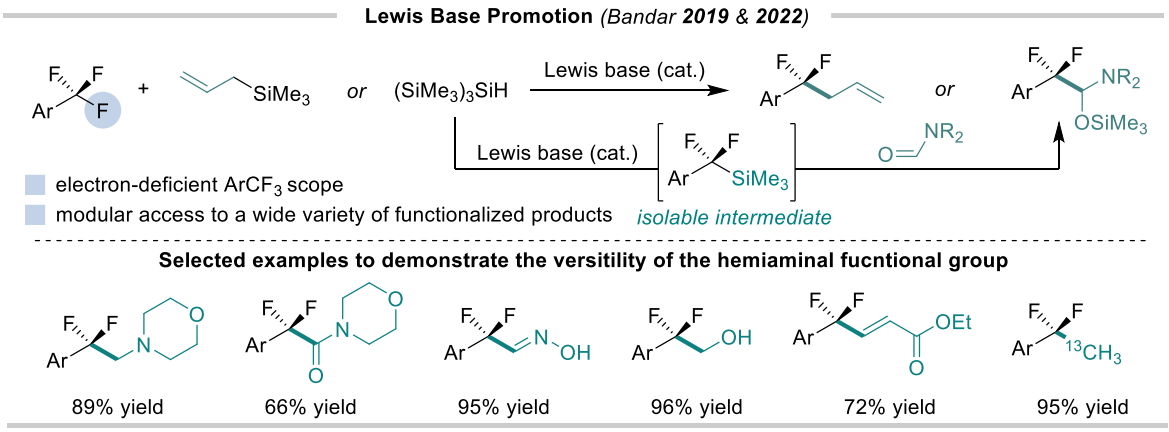

Figure 2-5. Lewis base-promoted selective defluorofunctionalization of trifluoromethylarenes.

From our group's previous reports and other's in the field we had determined that the key step of our transformation was the reduction of the trifluoromethylarene, and in our reports the reducing species was either the allylsilicate or a silyl anion, respectively. Importantly, we were inspired to use silyl anions as they have been reported to have 3 unique modes of reactivity, 1) as a Brønsted base,[23] 2) as a nucleophile,[24] and 3) as a reducing reagent capable of SET (Figure 2-6a).[25] I initially surveyed commercial disilane reagents, specifically hexamethyldisilane, tris(trimethylsilyl)silane, and tetrakis(trimethylsilyl)silane, and considered what silyl anions might be formed upon their activation with a Lewis base. The disilane species used in our 2022 report could produce 3 different silyl anion species, while hexamethyldisilane could only give one,

trimethylsilyl anion. When the basicity of these silyl anions were considered, we found that the trimethylsilane anion is significantly more basic (pK_a, ~45 in DMSO) than the other two silyl anions that TTMSS could generate (pK_a, ~28-30 in DMSO) (Figure 2-6b).[23] Additionally, trimethylsilyl anion is a known strong reductant as it is capable of reducing naphthalene to its radical anion (reduction potential is -2.6 V vs. SCE in DMF), this was an encouraging finding as typical electron-deficient $ArCF_3$s substrates have a reduction potential around -2.07 V vs SCE in DMF, while electron-neutral $PhCF_3$ has one of -2.50 V vs. SCE in DMF (Figure 2-6c).[26] Therefore, I thought that the use of hexamethyldisilane as a precursor to the *in situ* reducing reagent, trimethylsilyl anion, would allow for activation and subsequent functionalization of electron-neutral trifluoromethylarenes. This commercial disilane is also the most cost-effective option being only $130/mol, where TTMSS is $2385/mol and tetrakis(trimethylsilyl)silane is $8795/mol.

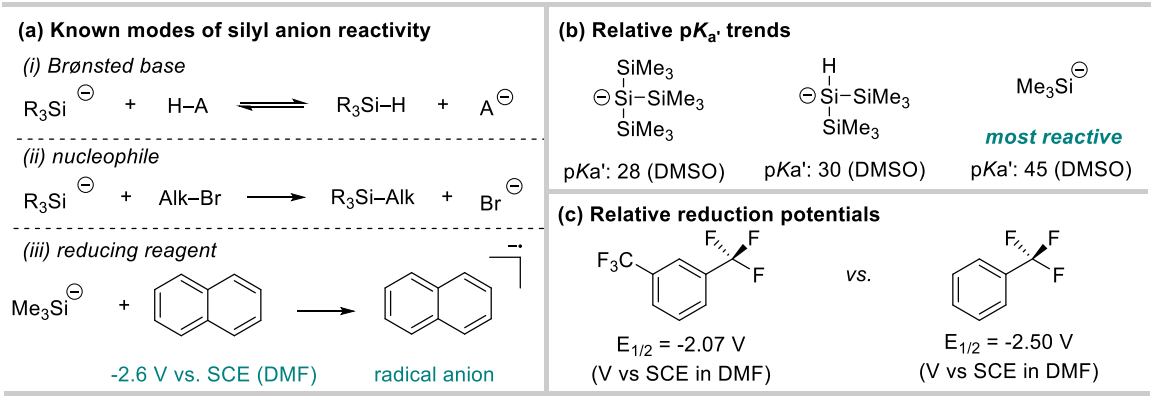

Figure 2-6. (a) Reported and known modes of silyl anion reactivity. (b) Relative pK_a, trends of silyl anion species. (c) Relative reduction potentials of electron-deficient trifluoromethylarenes and electron-neutral trifluoromethylarenes.

2.4.2 Reaction Optimization

To evaluate the efficacy of hexamethyldisilane for activating electron-neutral trifluoromethylarenes, I subjected 3-fluorobenzotrifluoride with a few Lewis bases in DMSO to

achieve selective hydrodefluorination (HDF). This substrate was chosen as it is minimally electron-deficient and works in very slight yield under our group's 2022 reported conditions (28% yield), indicating that we know this substrate can participate in a Lewis base promoted reductive coupling strategy. I found that Cesium carbonate was not a sufficiently strong enough base to generate the necessary trimethylsilyl anion, resulting in no reaction and retention of starting materials. Mildly stronger bases such as hydroxides, alkoxides, and fluorides were all able to promote this reaction to around 50% yields with only catalytic amounts of base (Figure 2-7). Slight modification of the solvent system to a DMPU/DMSO (9:1) increased the yield to 60% for this model substrate (Figure 2-8).

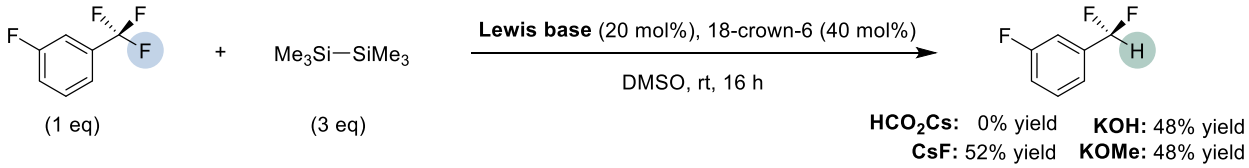

Figure 2-7. Small optimization of 3-fluorobenzotrifluoride with hexamethyldisilane and Lewis bases.

2.4.3 Scope of Selective Hydrodefluorination of Electron-neutral Trifluoromethylarenes

I next evaluated the scope of $ArCF_3$ substrates that would participate in a selective HDF functionalization. A range of electronic-deficient to slightly electron-rich $ArCF_3$s resulted in the selective HDF product, where the electron-neutral compounds gave the best yields, electron-rich arenes had diminished yields and high mass balance of remaining starting material, and electron-deficient systems proved to be too active under these newly found reducing conditions and resulted in low yields but with a loss of starting material. This discovery was consistent with our groups 2022 report which employed TTMSS as the reducing agent precursor for selective functionalization of electron-deficient arenes and is known to not be as strong of a reductant at trimethylsilyl anion. Key substrates that participate in my HDF system include 1-

naphthyltrifluoride (**2-15**), 3-phenylbenzotrifluoride (**2-1**), 3-methylbenzotrifluoride (**2-4**), 4-(trifluoromethyl)pyridine (**2-13**), 2- and 3-imidazolebenzotrifluorides (**2-16, 2-17**), chlorinated (**2-10, 2-11, 2-12**) and fluorinated benzotrifluorides (**2-2, 2-3, 2-4**), and base sensitive amide (**2-14**) functional groups (Figure 2-8a). In the case of iodo- and bromo-substituted arenes, conversion to protodehalogenated trifluoromethylarene or silyldehalogenated trifluoromethylarene were observed without the presence of HDF. Chlorinated trifluoromethylarenes also undergo side-reactions to form minor amounts of proto- (Figure 2-8b, entries **2-10", 2-11", 2-12"**) and silyl-dehalogenated arenes (Figure 2-8b, entries **2-10', 2-11', 2-12'**), in addition to the desired HDF products. Trimethylsilyl anions are known to react with aryl halides to give *ipso*-substituted aryl silanes and protodehalogenated arenes, thus these results are not surprising.[24] Further improvement of this platform can be done to access electron-rich $ArCF_3$s in higher yields by generating more strongly reducing conditions. Isolation of HDF products from the trifluoromethylarene starting materials typically can only be done *via* high-performance liquid chromatography (HPLC) due their similar characteristics on silica gel. A Waters preparatory HPLC was used to successfully isolate some of these compounds, however an isolated yield was not able to be obtained due to the sample size limit of the instrument.

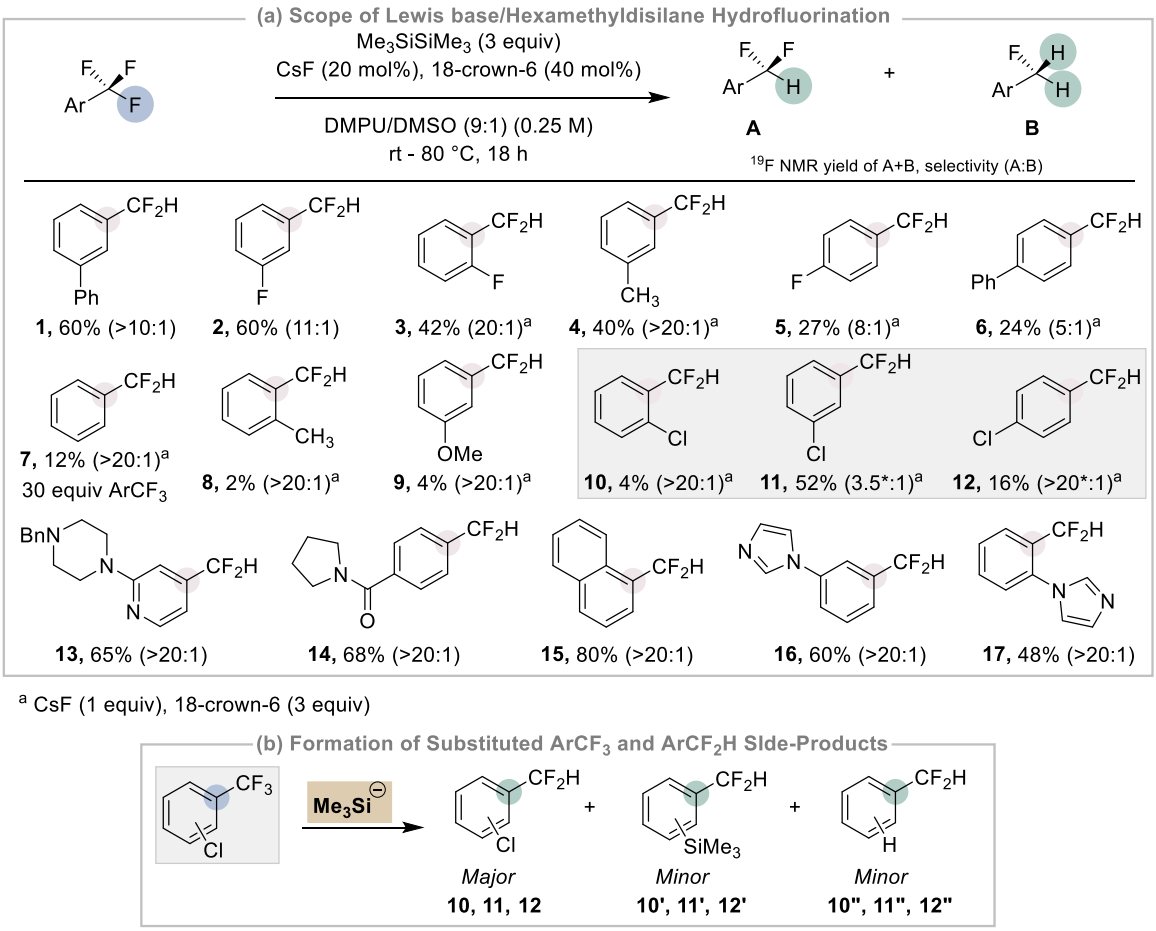

Figure 2-8. (a)Scope of Lewis base-promoted selective reduction of electronically unactivated trifluoromethylarenes. (b) Observation of silyl anion *ipso*-substitution of chloroarenes.

I also evaluated this strategy's efficacy in a late-stage setting by subjecting commercially available Penfluridol (used for treatment of Schizophrenia)[27] to hexamethyldisilane with catalytic cesium fluoride base which resulted in a 7% preliminary yield of the selective hydrodefluorination product (Figure 2-9a). This was a key experiment as Penfluridol contains an electron-neutral trifluoromethylbenzene which cannot be functionalized reliably *via* existing strategies in a late-stage setting. This strategy's impact is highlighted in that if one were in need of a difluorobenzylic derivative of this pharmaceutical, they would have to install the difluoromethyl group in an early step of the synthesis to avoid a variety of functional group intolerances that arise from harsh reaction conditions (Figure 2-9b). This means that libraries and structure-activity-relationships

will be difficult to access due to the time and resource intensive synthesis of these analogues. Additionally, my preliminary 7% yield of the HDF product of Penfluridol was done in the presence of other weak bonds and without protection of the free alcohol, further optimization and protection of this alcohol would likely result in higher yields.

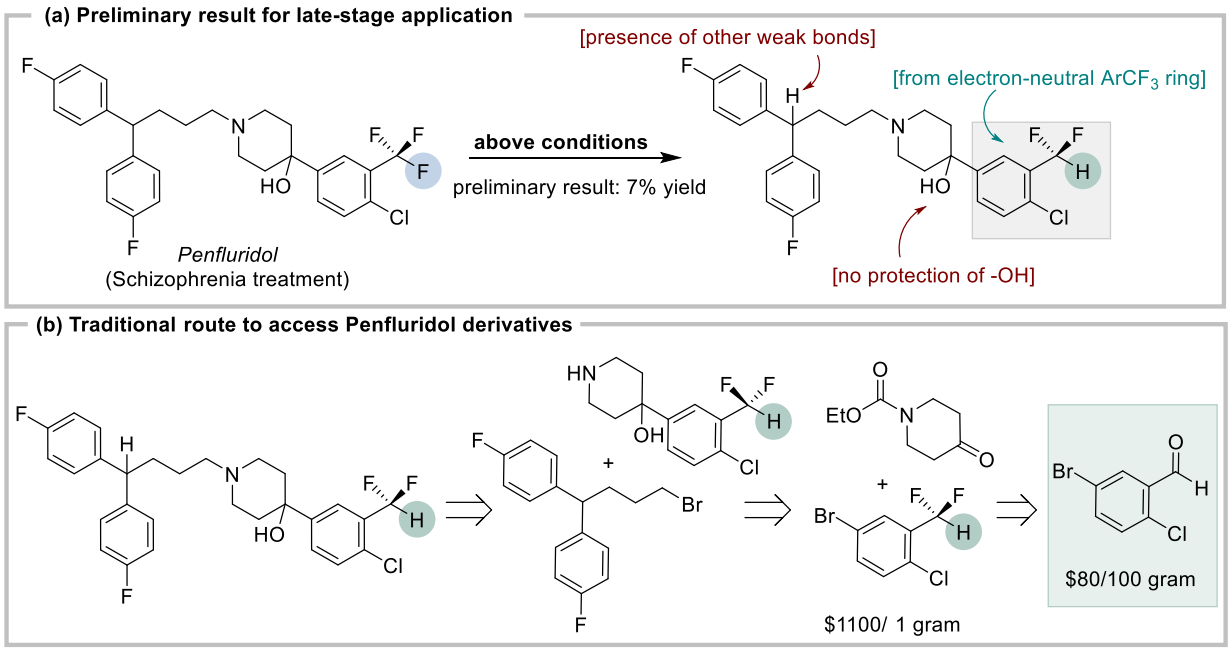

Figure 2-9. (a) Preliminary result of Penfluridol under Lewis base-promoted reductive conditions. (b) Traditional retrosynthetic route for the synthesis of Penfluridol.

In an effort to understand the mechanism for the formation of the HDF product under our reaction conditions, parallel reactions were conducted in protio and deuterated DMSO (Figure 2-10). The results are consistent with the HDF product resulting from a deprotonation rather than a hydrogen atom abstraction as the reaction ran in DMSO-d_6 gave a similar product yield as in DMSO, with trace proton incorporation observed. This is suggestive of formation of a benzylic anion as a key intermediate that deprotonates the DMSO solvent. Having observed product distribution consistent with the presence of a carbanion intermediate, I sought to expand the scope of electrophiles that the anionic intermediate could couple to; while HDF products are useful, access to synthetically versatile products would be even more valuable.

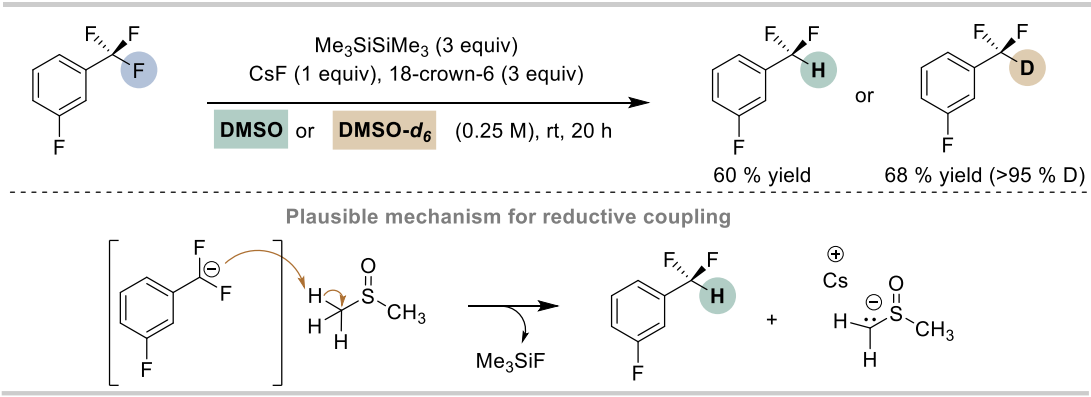

Figure 2-10. Deuteration study for the formation of the reductive product *via* Lewis base-promoted functionalization of electron-neutral trifluoromethylarenes.

2.5 Lewis-base Promoted Reductive Coupling Platform for Rapid Diversification of Electron-neutral Trifluoromethylarenes

2.5.1 Overview of Reaction Expansion to Versatile Groups

My initial efforts to extend electron-neutral trifluoromethylarene defluorofunctionalization were to add formamide electrophiles to the reaction in place of DMSO to access analogues of the difluorohemiaminal adducts that were synthesized in our groups 2022 reductive coupling report. The amplified challenge associated with the formation of cross-coupled products with electron-neutral trifluoromethylarenes is the proper balancing of reactivity for each coupling partner. Specifically, the competition between the silyl anion reacting with the trifluoromethylarene or the formamide electrophile is a key consideration for productive cross-coupling; if one partner is too electrophilic while the other is too unreactive, the reaction results in unproductive cross-coupling.

2.5.2 Optimization of Electrophilic Coupling Partner

I applied my optimized conditions to investigate the reductive coupling of trifluoromethylarenes and formamides to afford hemiaminal (HA) products (Figure 2-11a). With adjustments made to the identity of the formamide coupling partner, HA products can be formed in moderate yields to provide α,α-difluorobenzylic. The observed trends favor formamides with

electron-rich groups attached to nitrogen (*N*-formylpiperidine (**i**) vs. *N*-formylmorpholine (**ii**)), and those that are more sterically accessible (*N*-formylpyrrolidine (**iii**) vs. *N*-formylazapene (**iv**)) (Figure 2-11b). This is consistent with the mechanistic need for both coupling partners to have matched reactivity to achieve cross-coupled products over homo-coupled products. Currently, the optimized conditions provide up to 60% yield using *N*-formylpyrrolidine with electron-neutral trifluoromethylarenes. The afforded hemiaminal products can be diversified further to give a variety of α,α-difluorobenzylic compounds.[22]

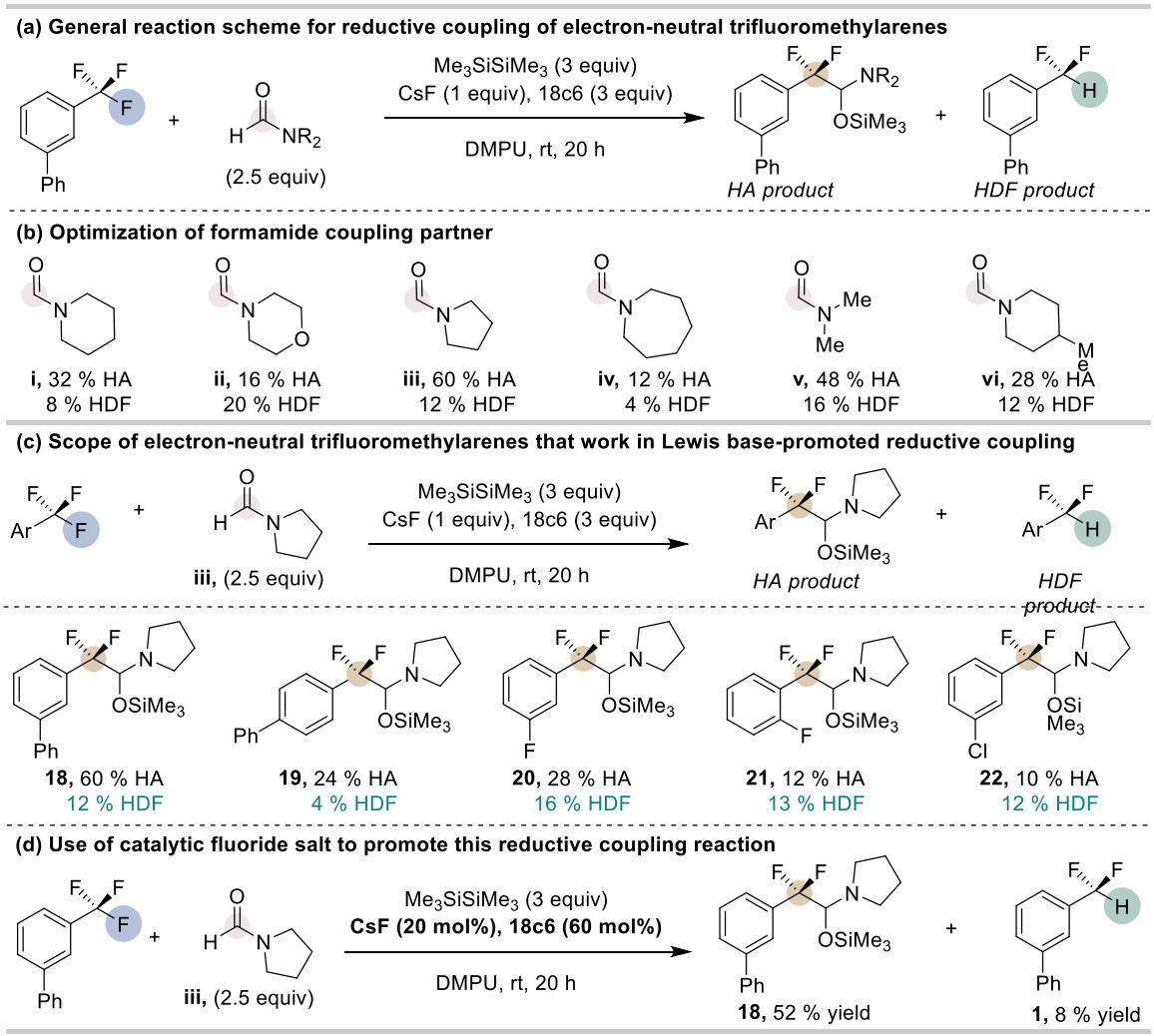

Figure 2-11. (a) General reaction scheme for Lewis base-promoted reductive coupling reaction of electronically unactivated trifluoromethylarenes. (b) Optimization of formamide coupling partner under reductive coupling conditions. (c) Scope of trifluoromethylarenes that participate in this

reaction. (d) Example of electron-neutral trifluoromethylarene under pseudo-catalytic reductive coupling conditions.

2.5.3 Scope of Electron-neutral Trifluoromethylarenes

I then developed a set of reaction conditions with a model substrate, 3-phenylbenzotrifluoride. This mono-selective defluorohemiaminal coupling is compatible with multiple electron-neutral benzotrifluorides. Catalytic amounts of 18-crown-6 ligated fluoride can promote the reaction in comparable yields to stoichiometric quantities (Figure 2-11c). Simple trifluoromethylarenes containing aryl (**2-18, 2-19**) and halogen (**2-20, 2-21, 2-22**) groups are compatible under the reaction conditions. Halogenated trifluoromethylarenes react in varying degrees of success to form the desired HA products such that fluoroarenes provide highest yields followed by chloroarenes, whereas bromo- and iodo-arenes undergo *ipso*-substitution with the trimethylsilyl anion to afford proto- and silyldehalogenatedarene side-products. The trend observed in halogen substitution is consistent with the trends I previously observed in the HDF reaction. I hypothesize that the key to tuning the product selectivity will be to modulate the formamide coupling partner to better complement the electronic properties of the trifluoromethylarene. This process also has the potential to work with catalytic amounts of fluoride salt as demonstrated in Figure 2-11d.

2.5.4 Possible Mechanism for Reductive Coupling of electron-neutral Trifluoromethylarenes

A plausible pathway for this transformation thus involves SET in which the trimethylsilyl anion reduces the trifluoromethylarene. The reduced trifluoromethylarene can undergo mesolytic cleavage to form an α,α-difluorobenzylic radical (and a fluoride anion) which can react with either a trimethylsilyl radical to give α,α-difluorobenzyl(trimethyl)silane or another equivalent of trimethylsilyl anion to propagate a radical nucleophilic substitution ($S_{RN}1$) pathway. The resultant

α,α-difluorobenzyl(trimethyl)silane can be activated by a Lewis base to promote coupling to the formamide partner (Figure 2-12). We note that other pathways are possible, including fluorine atom abstraction, although our observations remain most consistent with a SET step being necessary for this process.

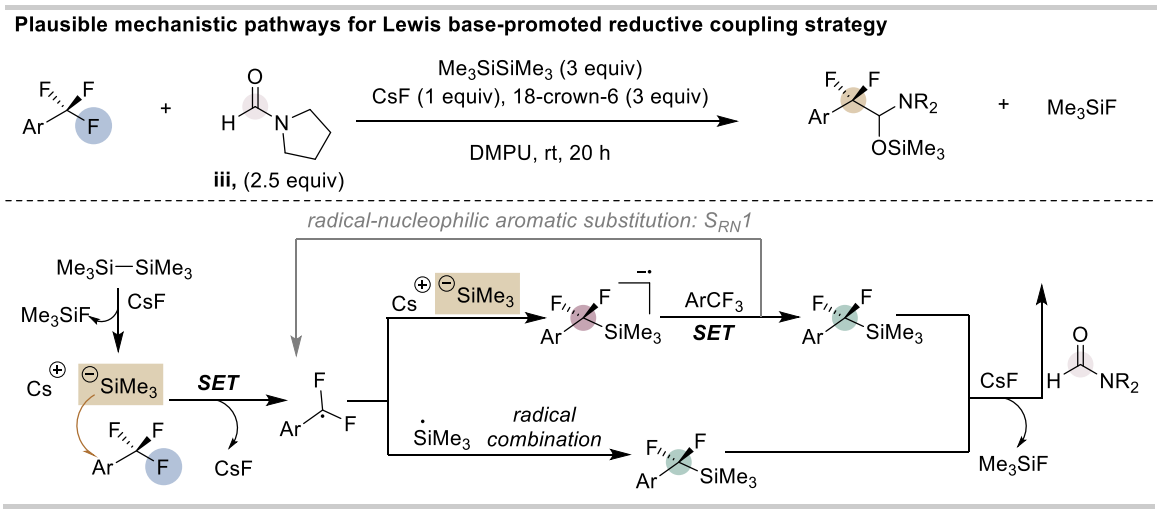

Figure 2-12. Plausible mechanism(s) for the Lewis base-promoted reductive coupling of trifluoromethylarenes.

2.6 Lewis Base-Promoted Reductive Coupling Platform

2.6.1 Generalization of Lewis Base–Promoted, Silane-Mediated Reductive Coupling

Traditionally in organic synthesis, cross-coupling reactions occur between a nucleophile and electrophile which is typical of a polar bond disconnection. In contrast, an emerging strategy to form valuable chemicals is cross-electrophile coupling reactions, which occur between two electrophiles and avoid the need for preformed carbon nucleophiles (Figure 2-13a).[28] A challenge in cross-electrophile coupling is achieving useful selectivity between the electrophiles. Often homocoupling products of one electrophile can form predominately over the desired cross-coupled product, thus establishing control of selective electrophile activation can prove to be difficult.

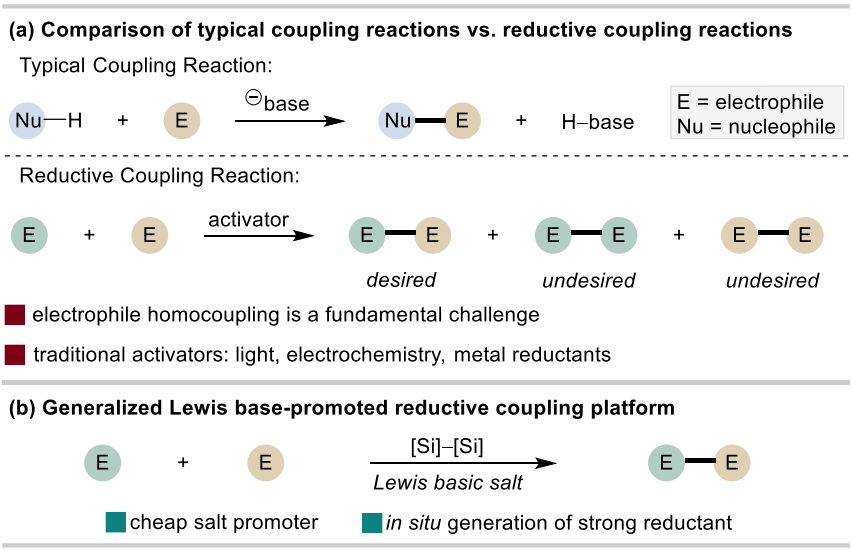

Figure 2-13. (a) Comparison of a typical coupling reaction between pronucleophiles and electrophiles vs. a reductive coupling reaction. (b) Our group's idea for a generalized Lewis base-promoted reductive coupling platform.

We sought to establish a general cross-electrophile coupling platform by leveraging our newly gained insight into the unique reactivity of silyl anions (Figure 2-13b). Our initial hypothesis is that an *in situ* generated silyl anion will facilitate cross-electrophile coupling reactions by serving as an affordable reductant and coupling partner in the reaction where my promising initial results are discussed below.

2.6.2 Cyanoarene Reductive Coupling with Carbonyls

I first targeted the reductive coupling reaction between cyanoarenes and carbonyls using our Lewis base-promoted, silane-mediated platform. This reaction was of interest as a report authored by a former postdoc in our group, Dr. Tyler Reidl, demonstrated that benzyl(trimethyl)silanes will couple with cyanoarenes *via* activation of the silane by Lewis basic salts.[33] This report had me question if other electrophiles, such as carbonyls, could participate in a similar coupling reaction if a general disilane was employed in place of benzylsilanes (Figure 2-14a). A Lewis base-promoted strategy would also add a new approach for the synthesis of

substituted benzyl alcohols as classical methods typically rely on electrochemical, metal, or visible light reduction of the arene to initiate coupling to carbonyl compounds.[34] Therefore, most strategies reduce the cyanoarene to the radical anion followed by reduction of the carbonyl and the sequential radical combination.

Our proposed mechanism for the Lewis base-promoted reductive coupling of cyanoarenes with carbonyls begins with generation of the reactive silyl anion *via* Lewis-base (LB) activation of the disilane (Figure 2-14b). The silyl anion then adds into the carbonyl, followed by 1,2-Brook rearrangement resulting in a reactive carbanion which can rapidly substitute the cyano group on the arene. This proposal is evidenced in that formation of the silyl ether is observed, however I do note that a SET pathway may also be at play under these reaction conditions. Importantly, this strategy works on 4-cyanopyridines with a range of carbonyls including, aliphatic and aromatic aldehydes and ketones (Figure 2-14c). A key challenge in this work is homocoupling of the carbonyl compounds resulting in pinacol products, a process I optimized and discuss in Section 2.6.3 below.

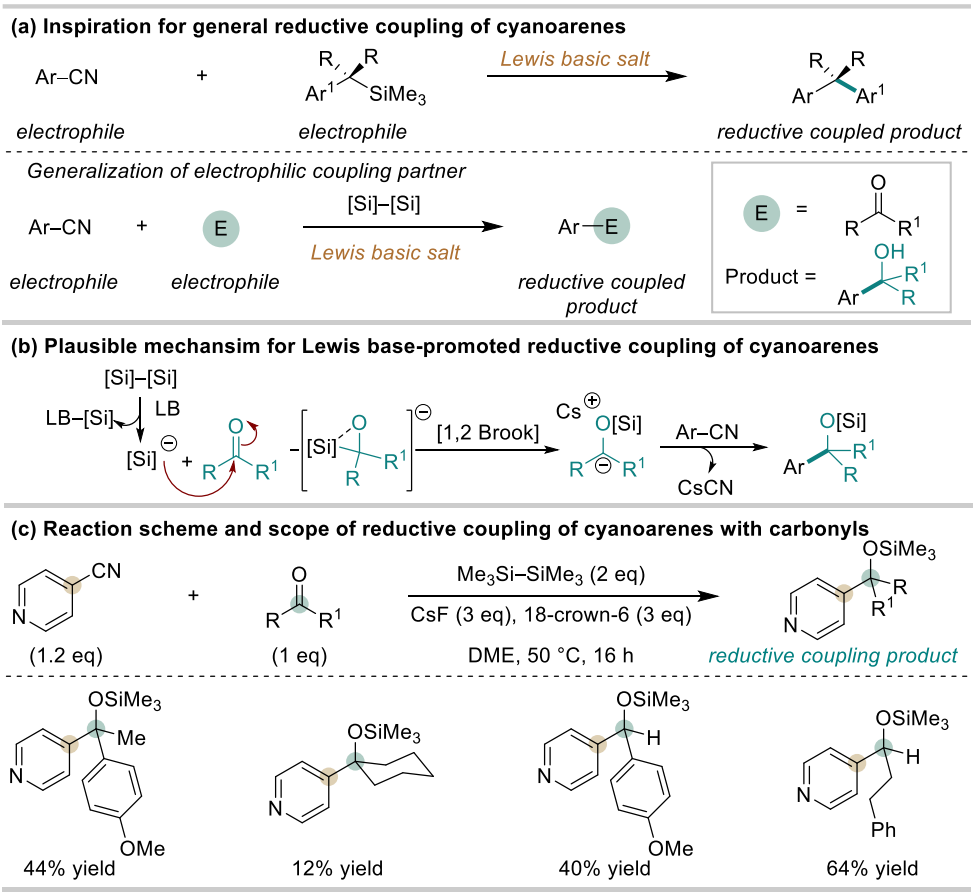

Figure 2-14. (a) Inspiration from previous work to expand electrophilic coupling partners. (b) Plausible mechanism for the reductive coupling of cyanoarenes to carbonyls. (c) Reaction scheme and preliminary scope of cyanoarenes and ketones or aldehyde coupling partners.

2.6.3 Lewis Base-Promoted Pinacol Coupling

I targeted a pinacol coupling reaction with the idea for a new approach *via* Lewis basic salt catalysis which could offer a more practical and scalable strategy since it does not employ a strong reductant (reducing agent formed *in situ*). This approach also offers different ways of controlling selectivity with new types of catalysts, such as using chiral salts for asymmetric catalysis. Pinacol coupling is a widely used transformation to afford 1,2-diols and diamines or 1,2-aminoalcohols, all of which are of great value in natural products, medicines, and as synthetic building blocks, especially when enantiopure.[29] In 2004, Yamamoto reported an asymmetric pinacol homo-

coupling of aryl aldehydes using a chromium catalyst with a bulky bis(8-quinolinolato) (TBOx) ligand.[30] In 2019, Ohmiya reports the racemic pinacol cross-coupling of aryl aldehydes to aryl ketones through a copper catalyzed [1,2]-Brook rearrangement.[31]

Applying our Lewis basic salt promoted reaction conditions to carbonyls and imines yielded pinacol and 1,2-diamine products, respectively (Figure 2-15a). A plausible mechanism of formation for these products is from attack of the trimethylsilyl anion into the π* to form a C–Si bond and generate an oxy- or amino- anion which can then undergo a [1,2]-Brook rearrangement to give the α-oxy or α-amino carbanion intermediate. This highly reactive intermediate can then activate the second electrophile by attack into the π* orbital to give the pinacol coupled product (Figure 2-15b). This method of reductive coupling is an advantageous, one-pot synthesis to access pinacol and 1,2-diamine products.

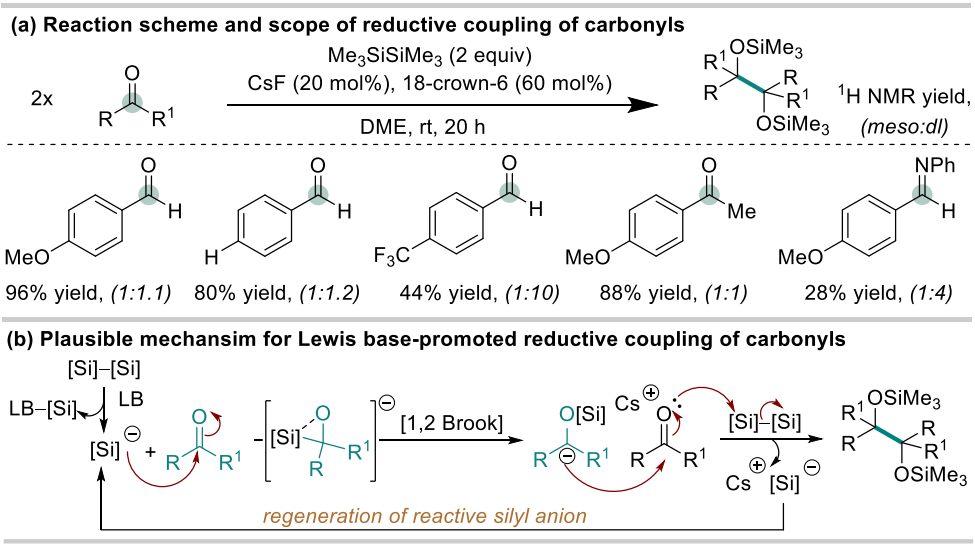

Figure 2-15. (a) Reaction scheme and preliminary scope for Lewis base-promoted reductive pinacol coupling. (b) Plausible mechanism for silyl anion facilitation of reductive pinacol coupling reaction.

Asymmetric pinacol reactions have many of the same challenges as racemic methods with the added task of requiring complex, expensive, or difficult to synthesize chiral ligands in order to

impart chirality in the product. Our group's chemistry allows us to explore chiral salts as a means to impart chirality in pinacol coupling reactions for the first time as opposed to chiral metal-ligand systems or Lewis acids. I screened a multitude of cinchona derived ammonium salts as additives in my coupling reactions, however there was little success for enantioselective or diastereoselective pinacol formation (Figure 2-16). Enantioselelctivity was determined using a Aglient analytical HPLC instrument.

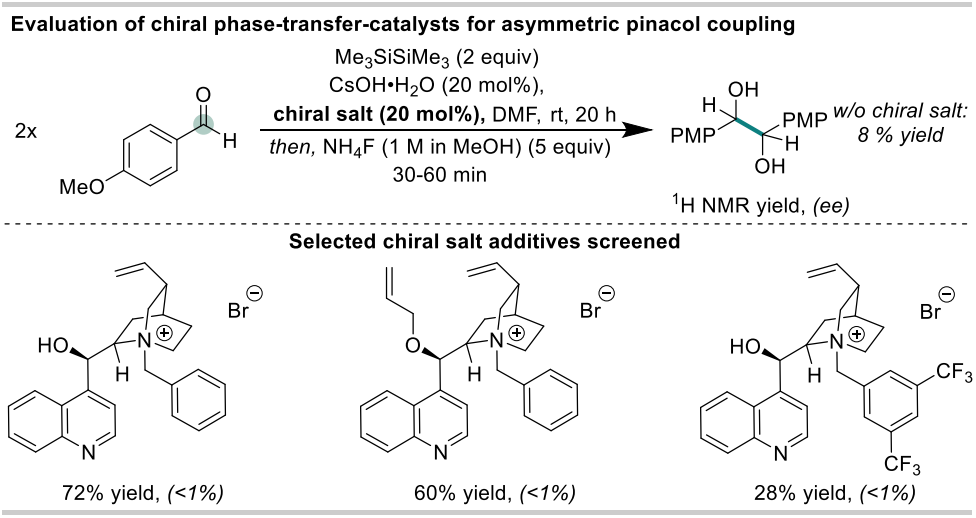

Figure 2-16. Evaluation of chiral phase-transfer-catalysts for asymmetric reductive pinacol coupling process.

2.6.4 Reductive coupling of Aryl Halides with Alkyl Halides

Many aryl-alkyl cross-coupling strategies use photoredox or transition metal catalysis to convert the reactivity of one electrophile to aid in coupling to the second electrophile. For example, MacMillan recently reported a state-of-the-art method for reductive coupling of (hetero)aryl chlorides to alkyl chlorides through a dual photoredox-nickel catalytic cycle.[32] In an analogous reaction I aimed to couple electron-deficient aryl halides and alkyl halides *via* Lewis basic salt-promoted formation of silyl anion species (Figure 2-17a). Preliminary results show promising results with aryl iodides and bromides, while aryl chlorides are less reactive. Primary alkyl halides

react in moderate to good yield, however attempts to couple tertiary halides have been unsuccessful. Reaction efficacy trends that I observed in regard to the aryl halide coupling partner (I, Br > Cl) are consistent with a halophilic attack of the aryl halide by a trimethylsilyl anion. Substitution pattern of compatible alkyl halide coupling partners is suggestive of an S_N2-type attack of the aryl anion intermediate on the alkyl halide.

Given these observations, I hypothesized that the generated trimethylsilyl anion activates the aryl halide *via* C–X attack, generating an aryl anion which then facilitates coupling to the alkyl halide *via* S_N2 attack. Competition between attack of the trimethylsilyl anion on the aryl halide or alkyl halide is evident in crude reaction spectra, as alkylsilane and elimination side-products are observed (Figure 2-17b). My method for Lewis base-promoted reductive coupling of aryl halides to unactivated alkyl halides provides a practical approach to an emerging field of organic transformations.

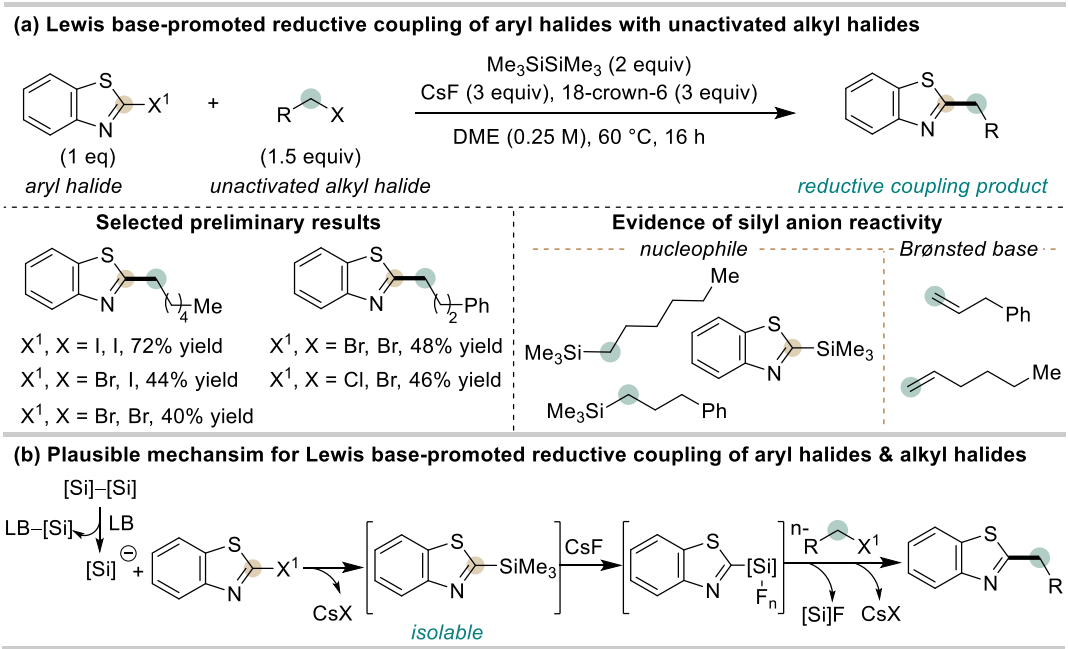

Figure 2-17. (a) Reaction scheme, selected scope examples for Lewis base-promoted reductive coupling of electron-deficient aryl halide with unactivated alkyl halide and evidence for silyl anion formation *via* nucleophilic and Bronsted base byproduct formation. (b) Plausible mechanism for Lewis base-promoted reductive coupling process.

2.7 Conclusion

This work establishes a new, practical approach to accessing difficult modes of reactivity such as selective functionalization of trifluoromethylarenes and cross-electrophile coupling reactions using simple Lewis basic salts under mild reaction conditions. The discovery of the trimethylsilyl anion's ability to promote other reductive coupling reactions offers a one-pot route for accessing valuable products such as α,α-difluoroalkylarenes and reductive coupled products. Through the Lewis base-generation of silyl anions, I have shown near-optimized conditions for mono-selective hydrodefluorination of electron-neutral trifluoromethylarenes and promising yields in other reductive coupling reactions, although more work remains before a full scope can be developed. I have also developed a method for the mono-selective defluorination of electron-neutral trifluoromethylarenes to form C–C coupled adducts with formamides. The hemiaminal products serve as a synthetic handle for further derivatization to access a broad scope of α,α-difluorobenzylic substructures, thereby overcoming the primary limitations from our groups previously reported defluoroallylation work. The next chapter will discuss our discovery and development of a Bronsted base-promoted oxidative coupling strategy to capture unstable anions, specifically from difluoromethylarenes.

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CHAPTER THREE

CAPTURING UNSTABLE CARBANIONS VIA HALOGEN TRANSFER: BASE-PROMOTED OXIDATIVE COUPLING REACTIONS OF α,α-DIFLUOROMETHYLARENES

3.1 Chapter Overview

α,α-difluoromethylarenes are an attractive precursor to valuable difluorobenzylic substructures, however the C–H bond functionalization of α,α-difluoromethylarenes has notoriously been difficult to achieve *via* radical halogenation methods or traditional deprotonative strategies. This chapter will discuss the challenges associated with these strategies and how leveraging our group's halogen transfer platform allows for reliable and general access to difluorobenzylic substructures. The work described in this chapter provides alternative selectivity to traditional nucleophilic fluorination or radical halogenation methods.

3.2 Background and Challenges of Deprotonative Strategies that Produce Unstable Carbanions

Deprotonation is the most fundamental activation strategy of C–H bonds. However, to be effective, the carbanion or metalated intermediate must be stable. Thus, many anions are currently off limits due to inherent instability challenges, such as α- and β-elimination of leaving groups or incompatibility with internal electrophiles. A prototypical example are fluorinated carbanions that are prone to α-fluoride elimination[1]; however, such an approach would be valuable for modular access to valuable fluorinated motifs (Figure 3-1a). Thus far, only Szymczak and coworkers have been successful in developing a deprotonative approach to functionalize difluoromethylarenes ($ArCF_2H$) which they achieve *via* formation of anionic adducts with borazine Lewis acids (Figure

3-1b, i).[2] In additional report by Leroux and coworkers, the deprotonative functionalization of 3-(difluoromethyl) pyridine was shown using LDA base under cryogenic reaction stabilization (Figure 3-1b, ii).[3]

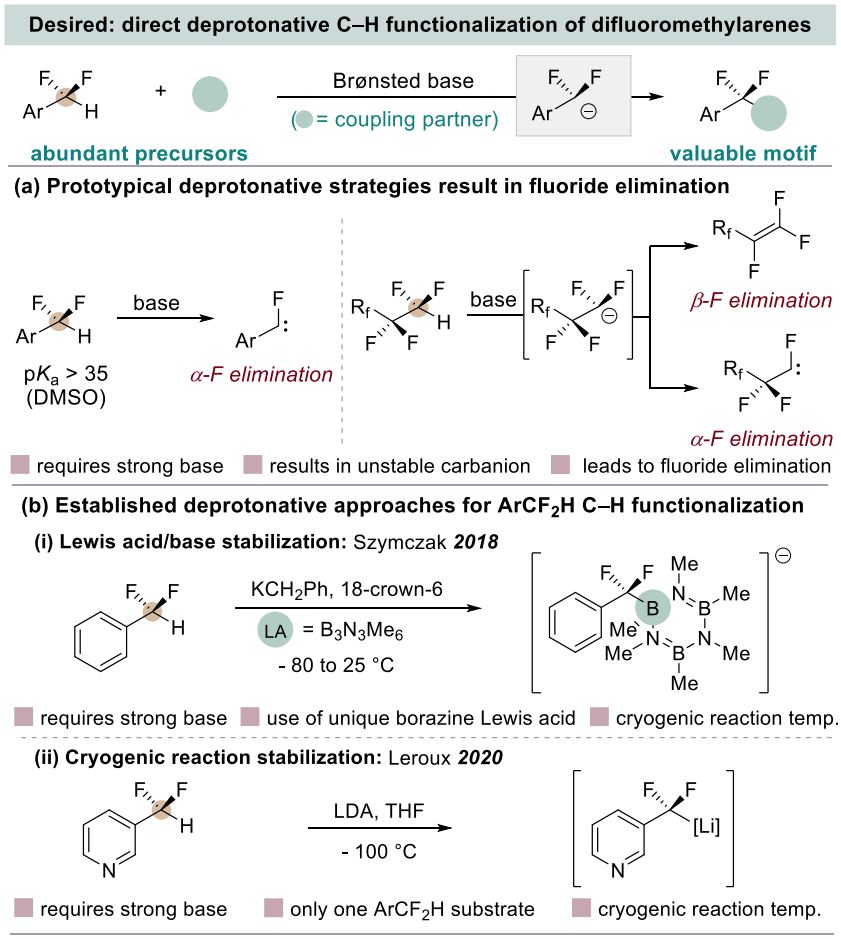


Figure 3-1. (a) Challenges with typical deprotonative strategies of perfluorinated substrates. (b) Productive deprotonative approaches for C–H functionalization of ArCF2H substrates.

Other C–H bonds are also known to result in unstable carbanions under deprotonative conditions, such as haloarenes, 5-membered heteroarenes, 2- or 4-methylbenzotrifluorides, and vinylarenes. Deprotonation of a C–H bond *ortho* to a halide or pseudohalide on an arene can decomposition *via* an aryne pathway.[4] 5-Membered heteroarenes have been reported to undergo decomposition *via* a ring-opening process under basic conditions.[5] Deprotonation of 2- or 4-methylbenzotrifluoride have been reported to undergo fluoride elimination followed by

polymerization of these diene intermediates.[6] Finally, vinylarenes are notorious for undergoing decomposition *via* polymerization under basic conditions.[7] Therefore, the productive functionalization of these carbanions has remained elusive for traditional deprotonation strategies due to the high instability of the resultant anion. We though that our halogen-transfer protocol could serve as a general strategy for the coupling of these substrates with *in situ* pronucleophiles.

3.3 Value of Difluoromethylaryl(thio)ethers and their traditional synthesis

α,α-Difluorobenzyl(thio)ethers are valuable in numerous industries as they possess unique properties that include increased metabolic stability, thermal stability, and dipole moment in bioactive molecules[8]; in material and technological applications, difluoroaryl(thio)ether motifs can enhance the dielectric anisotropy and stability of liquid crystals while broadening the range of the nematic phase range.[9] Traditionally, these compounds are prepared *via* deoxyfluorination methods that require toxic chemicals that react violently with water and are not ideal conditions for a general protocol (Figure 3-2a).[10] Alternatively, access to the halogenated intermediate from α,α-difluoromethylarene would offer a modular approach to difluoromethylaryl(thio)ethers however mechanistic challenges exist for both radical halogenation and deprotonative strategies (Figure 3-2b).[1, 11]

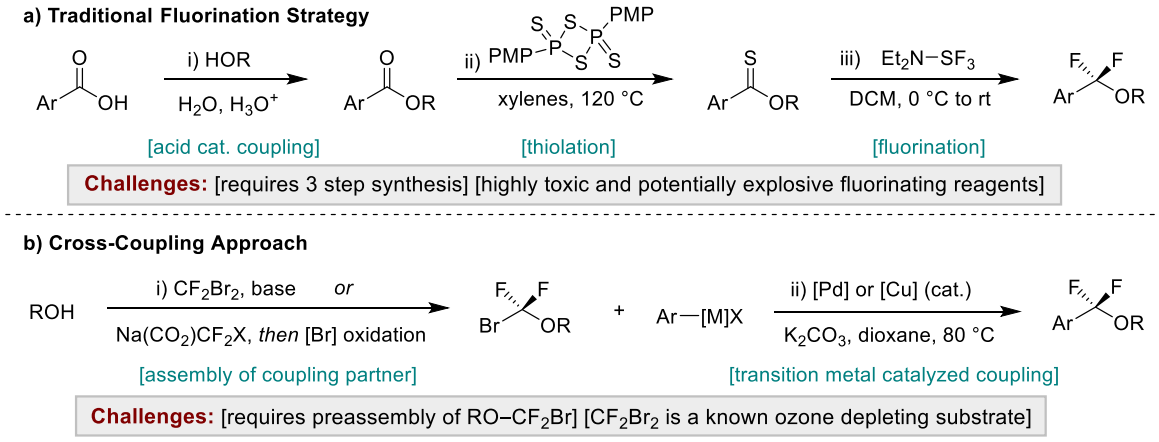


Figure 3-2. (a) Traditional nucleophilic fluorination strategy to access difluorobenzylic ethers. (b) Cross-coupling approach to access difluorobenzylic ethers.

Firstly, derivitization from difluoromethylarenes is attractive as these motifs are abundantly available and can be easily prepared *via* numerous methods. Radical halogenation strategies of difluoromethylarenes are challenging due to the high bond strength of the CF_2–H bond (>88 kcal/mol) which results in long reaction times in addition to competing selectivity with weaker bonds that are present in the molecule[11] (Figure 3-3a). Deprotonation of difluoromethylarenes carries a different challenge such that a strong base is needed to deprotonated these mildly acidic C–H bonds (pK_a >35 in DMSO) and the resultant carbanion is prone to decomposition through a-fluoride elimination (Figure 3-3b).[1] Therefore, a new approach to rapid C-H halogenation could serve as a streamlined and direct strategy for the derivatization of difluoromethylarenes.

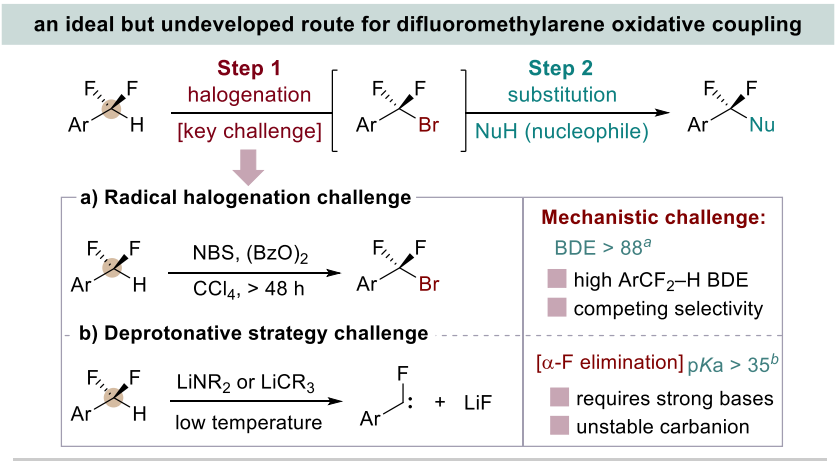


Figure 3-3. (a) traditional challenges with radical halogenation of $ArCF_2H$ C–H bonds. (b) fundamental challenge associated with deprotonative functionalization of difluoromethylarenes.

3.4 Base-Promoted Oxidative Coupling Platform *via* Halogen Transfer, Bandar Group

We recently reported the base-catalyzed, x-transfer to mildly acidic benzylic C–H bonds using KO-*t*-Bu, 2-halothiophene and *in situ* nucleophiles to access benzylic(thio)ethers.[12d] A key mechanistic feature of the X-transfer platform is the compatibility of deprotonation, oxidation and

coupling in a one-pot reaction.[12] We reasoned that our recently disclosed x-transfer platform could address the mechanistic challenges associated with deprotonative approaches and enable the direct oxidative coupling of these C–H bonds. We hypothesize that the use of mild bases can produce a small amount of carbanion in the presence of base-stable halogen oxidants to give the halogenated intermediate before decomposition of the carbanion can occur. The halogenated intermediate formed in this process undergoes coupling with *in situ* nucleophiles to provide a unique synthetic route and utility as compared to the aforementioned routes, thus allowing the direct oxidative coupling of α,α-difluoromethylarenes to heteronucleophiles and showcases the generality of this method to other base-sensitive C–H bonds (Figure 3-4). Importantly, to be effective, the base must only generate low quantities of the unstable anion and the x-transfer must be facile enough to prevent competitive decomposition.

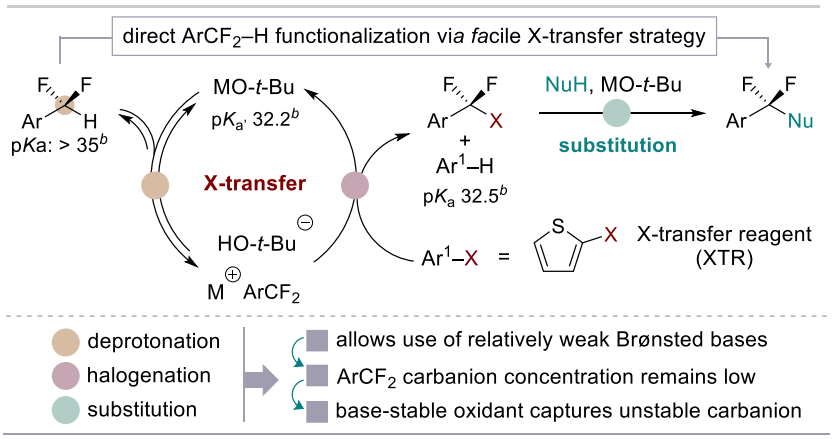


Figure 3-4. Base-promoted halogen-transfer proposed mechanism for direct C–H functionalization of $ArCF_2H$ substrates.

3.5 Reaction Discovery and Optimization

We targeted the coupling of two difluoromethylarenes of differing acidity as model compounds to identify effective conditions for direct oxidative coupling. Optimization of a model reaction between 4-(difluoromethyl)-2-phenylpyridine (**3-1**) or 4-(difluoromethyl) biphenyl (**3-2**) and *para*-methoxyphenol (**3-3**) is shown in Figure 3-5 using KO-*t*-Bu as base. We began by

examining 2-bromothiophenes as potential oxidants, which are inert toward nucleophilic aromatic substitution.[12] Use of inexpensive 2-bromothiophene (**XTR 1**) provides 95% etherification yield with the more acidic model substrate 4-(difluoromethyl)-2-phenylpyridine (**3-1**). While these conditions gave no yield with less acidic substrate, 4-(difluoromethyl) biphenyl (**3-2**). We speculated that due to the higher pK_a of 4-(difluoromethyl) biphenyl (**3-2**) made the initial deprotonation step more difficult resulting in disproportionation of the simple 2-bromothiophenes.

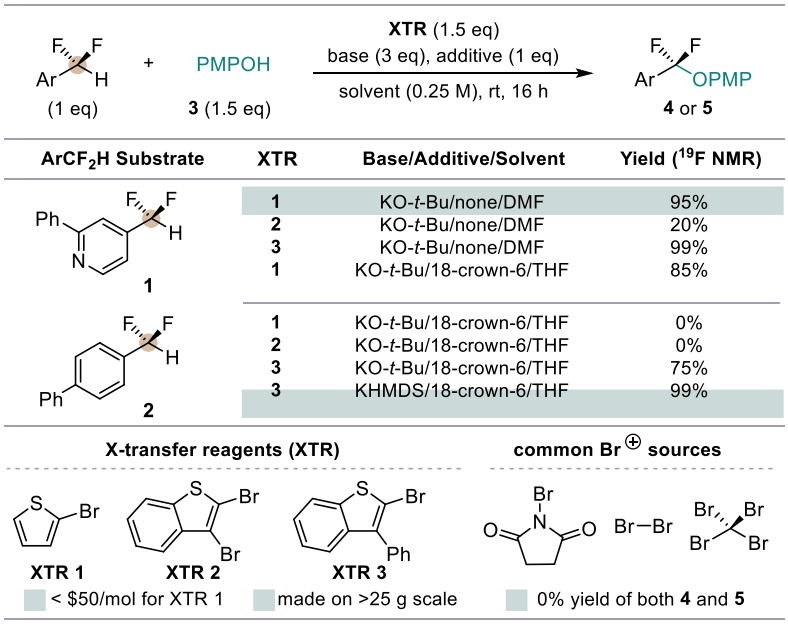


Figure 3-5. Optimization of oxidative coupling condition for direct etherification of ArCF2H C–H bonds.

To address this, we synthesized a X-transfer reagent that is less prone to off-path disproportionation by blocking excess acidic sites as seen in **XTR 2** and **XTR 3**. Use of this more base-stable **XTR 3** (made in 3 steps on a 100 g scale) resulted in a 75% etherification yield with 4-(difluoromethyl) biphenyl (**3-2**), and a switch to KHMDS as a base increases the yield 99% etherified product. Use of common halogenating reagents (e.g., CBr_4, NBS, Br_2) as oxidants results in no product formation, demonstrating the unique efficacy of 2-bromo(benzo[*b*])thiophene reagents under these conditions (Figure 3-5, bottom). We note that with model substrate 4-

(difluoromethyl)-2-phenylpyridine (**3-1**), THF with 18-crown-6 (1 eq) can be used to achieved appreciable yields (85%). 2-Bromo-3-phenylbenzothiophene (**XTR 3**) is accessible in large quantity from thiophenol substitution of bromoacetophenone to produce 1-phenyl-2-(phenylthio)ethan-1-one followed by a cyclization/halogenation sequence (Figure 3-6).

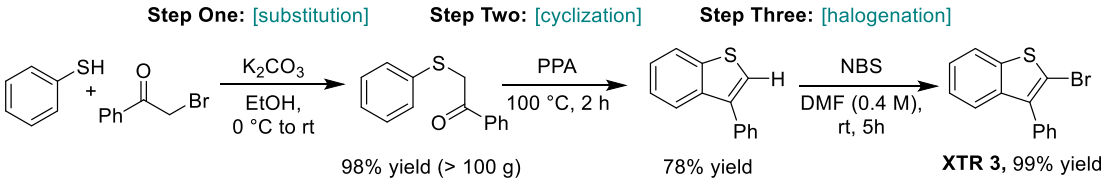


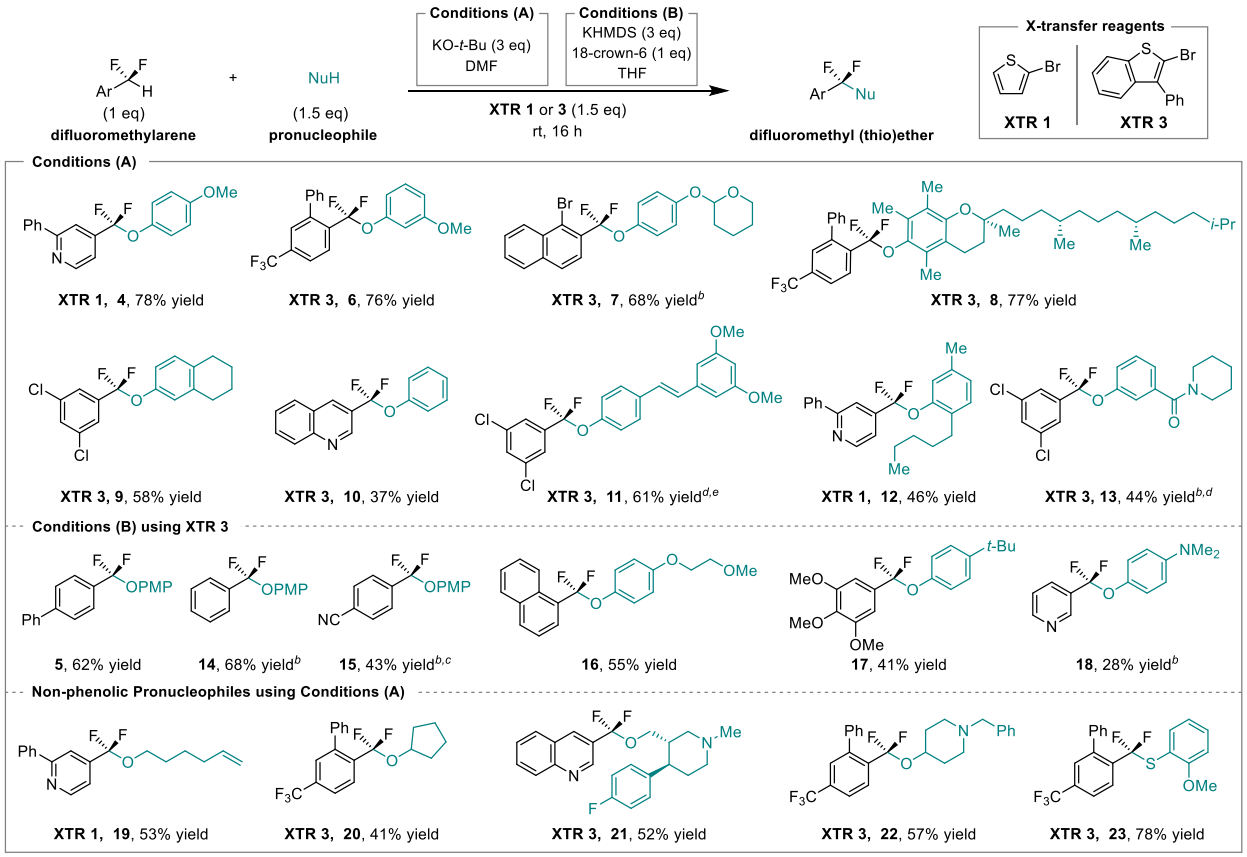
Figure 3-6. Large-scale synthesis of 2-bromo-3-phenylbenzo[*b*]thiophene.

3.6 Substrate Scope

Table 1 provides a scope of difluoromethylaryl(thio)ethers that can be accessed using the two XTRs identified in our optimization studies. A range of electron-deficient to electron-rich α,α-difluoromethylarenes are compatible with this oxidative coupling strategy and give high chemoselectivity. Table 1a shows the use of KO-*t*-Bu in DMF for the etherification of more acidic difluoromethylarenes, including difluoroheteroarenes, haloarenes, and benzotrifluoride variants (**3-4** through **3-13**). Difluoromethylarene with halogen substituents (**3-7, 9, 11, 13**) favor difluoroarylether formation over potential substitution of the aryl halide. Dichloroarene with stilbene (**3-11**) undergoes etherification of the C–H bond over unselective oxidation of olefin or aryl ring. Amides (**3-13**), acetal (**3-7**), and ether linkages (**3-16**) are tolerated and retained under these basic reaction conditions. A variety of steric encumbrance is well tolerated on either coupling partner exemplified by *ortho*-substituents on the difluoromethylarene (**3-6, 7, 8, 20, 22, 23**), *ortho*-substituents on the pronucleophile coupling partner (**3-8, 12, 23**), and *ortho*-substituents on both reagents (**3-8, 23**). As we were inspired by our work of base-catalyzed x-transfer to mildly acidic benzylic C–H, we observed that other acidic benzylic C–H bonds were tolerated in this reaction

such that functionalization of the CF_2H group predominates (**3-7, 3-9, 3-12, 3-22**). This trend is further evaluated below in the unique selectivities section.

Table 3-1. Substrate scope of difluoromethylarene C–H functionalization.



[a]Reaction run at 50 °C. [b]DMPU used as solvent. [c]18-crown-6 (1 equiv) was added. [d]NaO-*t*-Bu used as base. See Supporting Information for full details.

Table 1b shows the use of KHMDS base ligated with 18-crown-6 in THF with **XTR 3** for the etherification of less acidic difluoromethylarenes, including phenyl, naphthyl, tris(methoxy)benzene, and carbonitrilearenes (**3-5, 3-14, 3-15, 3-16, 3-17, 3-18**). 4-cyano(difluoromethyl)benzene favors etherification to the difluoroarylether over oxidation of the cyano group (**3-15**). A range of phenols are compatible with this strategy including those with electron-withdrawing groups (**3-13**) to electron-donating groups (**3-4, 3-17, 3-18**).

Table 1c shows a variety of non-phenolic pronucleophiles that are well-tolerated in this coupling reaction, including primary and secondary alcohols, thiophenols, and amine containing motifs (**3-19** through **3-23**). Pronucleophiles with acidic C–H groups (**3-22**) are tolerated without over-functionalization observed *via* crude NMR spectroscopy. Aniline and amine coupling partners work, but these products are not stable and cannot be isolated. Other nucleophiles (e.g., aliphatic thiols) do not appear to undergo the substitution process, a reaction that is likely to proceed through electron transfer based on prior studies in this area, and may explain the nucleophile scope limitations.

3.7 Recovery and Recyclability of Benzo[b]thiophene Halogen Transfer Reagents

XTR 3 is the most general X-transfer reagent used within this scope and is used in stoichiometric quantities. To demonstrate the recyclability of this reagent, we ran a 11.5 mmol scale reaction for the etherification of difluoromethylbenzene **3-24** with PMPOH, using 5 grams of **XTR 3.** From this reaction, protodehalogenated XTR byproduct **3-25** can be easily recovered the reaction mixture, and regenerate the active **XTR 3** in 88% overall recovery (Figure 3-7).

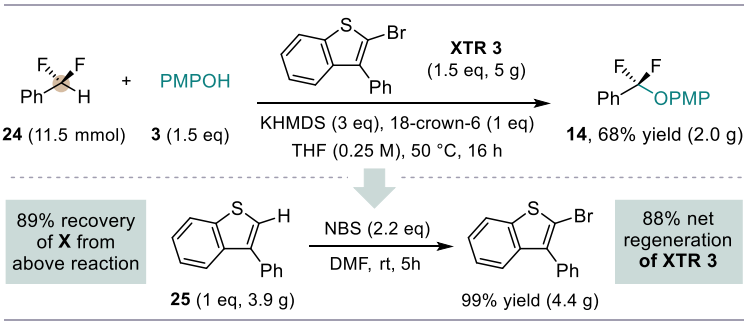


Figure 3-7. Recovery of protodehalogenated XTR and regeneration of the active XTR.

3.8 Novel Access to Difluoromethylaryl(thio)ethers vs. Traditional Nucleophilic Fluorination or Halogenation Strategies

This C–H functionalization approach to α,α-difluorobenzylic compounds offers new synthetic possibilities that complement alternative multistep procedures to gain access to value-

added products. For example, difluoromethylarenes with substituents that contain weak C–H bonds preferentially undergo radical halogenation at the weaker C–H bond making it impossible to prepare the $ArCF_2X$ intermediate if weak bonds are present (Figure 3-8a).[11] This is demonstrated in Figure 3-8a wherein the CH_3 group on both biphenyl substrate (**3-56**) and quinoline substrate (**3-55**) undergo selective bromination over the CF_2–H group. In contrast, base-catalyzed x-transfer selects for functionalization of the difluoromethyl group highlighting the complementary reactivity of X-transfer to radical halogenation.

Figure 3-8b demonstrates the complementary reactivity of X-transfer protocol to traditional fluorination strategies.[10] When two carbonyl groups are present within a molecule, traditional fluorination strategies will selectively fluorinate at the more nucleophilic carbonyl group, such that when an amide and ester both exist, the amide will be fluorinated. Whereas X-transfer strategy provides a new retrosynthetic disconnection by treating the $ArCF_2H$ motif as a synthetic coupling handle and incorporates the fluorine into the molecule in a modular way to access the constitutional isomer **3-33**, which is not accessible *via* traditional fluorination strategies.

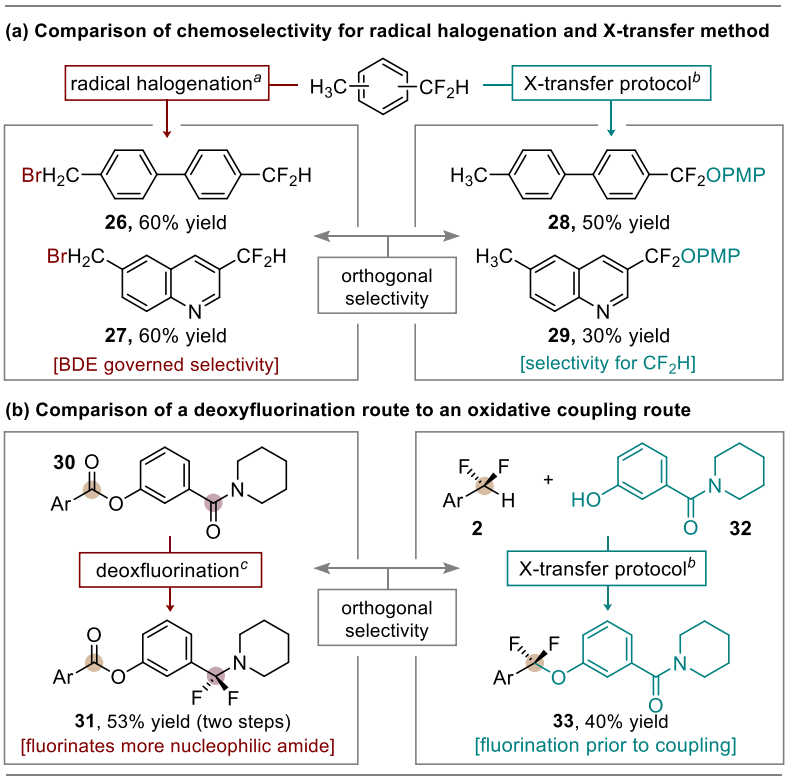


Figure 3-8. (a) Selectivity of radical halogenation methods vs. base-promoted halogen-transfer protocol. (b) Access to isomer of product that would be obtained *via* traditional nucleophilic fluorination methods.

3.9 Mechanistic Studies and Evaluation of Unstable Difluoromethylaryl Anion

To better understand how this process is operating, we studied the reaction profile for the model substrate as shown in Figure 3-9a. A small concentration of $ArCF_2Br$ is observed during the course of this reaction and is functionalized to provide >90% yield of the desired difluorobenzylic ether. The halogenated intermediate was synthesized and isolated using a recently reported base-promoted halogenation method[13] and was subsequently subjected to pseudo-reaction conditions with PMPOH and KO-*t*-Bu to give the desired etherified product, consistent with this halogenated species being an active intermediate in our X-transfer platform (Figure 3-9b). It is noteworthy that under X-transfer conditions the reaction maintains high mass balance. This is in contrast to the behavior of the $ArCF_2H$ substrate in the absence of XTR and

pronucleophile, as shown by the time profiles in Figure 3-9c. Here, KO-*t*-Bu in DMF, THF (with 1 eq of 18-crown-6), and DMPU solvents lead to rapid mass balance loss, showing that the difluorobenzylic anion undergoes decomposition. We also note that mass balance of the difluoromethylarene is lost in the presence of XTR and base when the pronucleophile is omitted, indicating that all three components of the reaction system are needed to effectively functionalize this base-sensitive carbanion.

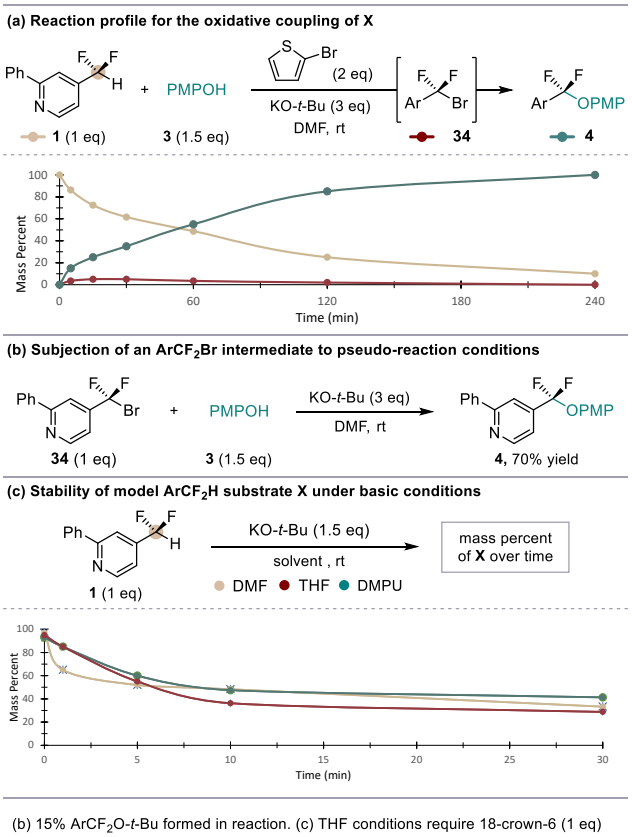


Figure 3-9. (a) reaction profile of difluoromethylarene in XTR conditions. (b) standard reaction conditions without the halogen-transfer reagent to confirm halogenated intermediate is an on-path intermediate. (c) observation of base-sensitity of model $ArCF_2H$ substrate.

3.10 Evaluation of Known Unstable Anions in the Bandar Group's Halogen Transfer Oxidative Coupling Platform

We understand that a critical mechanistic aspect of this work is the rapid capture of the unstable carbanion, we questioned if this principle is at play in our groups previously published

work. To evaluate this, we looked at substrates from our groups previously reported X-transfer functionalization of *N*-heteroarenes, acidic benzenes and methylarenes that could form an unstable carbanion under basic conditions. Specifically, I evaluated: 3-iodopyridine (**3-35**), which can undergo pyridyne formation[4]; thiazole (**3-36**), which can undergo ring opening decomposition[5]; 2-methylbenzotrifluoride (**3-37**), which can undergo fluoride elimination[6]; 4-methylstyrene (**3-38**), which can undergo rapid polymerization.[7] In each case, loss of mass balance of the substrate was observed when stirred with only KO-*t*-Bu, which is consistent with the instability of these carbanions (Figure 3-10). Importantly, we note that the X-transfer platform allows for facile formation of the desired functionalized product *via* rapid X-transfer to the carbanion.[12b] We note that when 1-methylnaphthalene was subjected to the same conditions, full retention of mass balance was observed after 16 h.

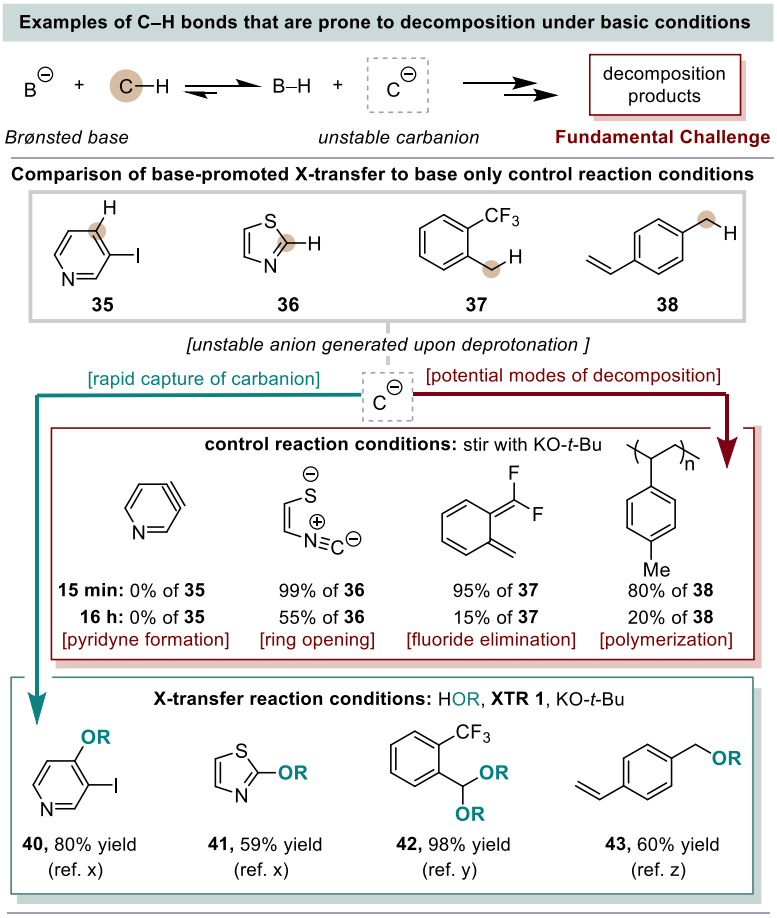


Figure 3-10. Evidence for other unstable carbanions that are formed under basic conditions, and their productive etherification under halogen-transfer conditions.

3.11 Conclusion

Key to the development of this C–H functionalization protocol was the discovery that 2-halo(benzo[*b*])thiophenes can rapidly halogenate unstable carbanions. Thus, deprotonative functionalization of α,α-difluoromethylarenes can be accomplished in a modular fashion using relatively mild bases in the presence of base-tolerant halogen oxidants. The underlying mechanistic steps of this oxidative coupling strategy represent a general platform for deprotonative functionalization of traditionally unstable carbanions that we are currently expanding upon.

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APPENDIX ONE

LEWIS BASE PROMOTED MONOSELECTIVE HYDRODEFLUORINATION OF ELECTRON-NEUTRAL TRIFLUOROMETHYLARENES: EXPERIMENTAL

A1.1 General Information:

All results are preliminary and were analyzed by ^{1}H and ^{19}F NMR spectroscopy. This appendix is intended to provide experimental details and supporting information for the material discussed in Chapter 2.

General Reagent Information: All reactions were performed under a nitrogen (N_2) atmosphere unless otherwise noted. Hexamethyldisilane (Me_6Si_2, CombiBlocks catalog #QB-7675) and 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6, Chem-Impex catalog #03901) were purchased from the indicated vendors and used as received. Cesium fluoride (CsF, Acros Organics catalog # 010019.88) was purchased as a 99.9% pure powder pure solid and used as received. Me_6Si_2, CsF and 18-crown-6 were stored at room temperature (rt) inside a N_2 filled glovebox and used immediately if brought outside the glovebox. 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrmidinone (DMPU, TCI catalog # D2014) and methylsulfoxide (DMSO, Acros Organics catalog # 042780.M1) was purchased and used as received. All other solvents and reagents were purchased from MilliporeSigma, Combi-Blocks, TCI, Acros Organics, Matrix Scientific, Alfa Aesar, or Synthonix and used as received unless otherwise noted. Flash chromatography was performed on 40-63 μm silica gel (SiliaFlash® F60 from Silicycle). Preparative thin-layer chromatography (PTLC) was performed on silica gel 60 Å F254 plates (20 x 20 cm, 1000 μm, SiliaPlate from Silicycle, #TLG-R10011B-341) and visualized with UV light (254 nm). Celite® 545 (Product #CX0574-3) was purchased from Millipore Sigma.

General Analytical Information: All reported compounds were characterized by ^{1}H and ^{19}F NMR spectroscopy. ^{1}H NMR and ^{19}F NMR spectra were obtained on a Bruker NEO400, Bruker US400, or Bruker Ascend 400 spectrometers. ^{1}H NMR data is reported as follows: chemical shift

(δ ppm), multiplicity (s = singlet, br s = broad singlet, d =doublet, t = triplet, q = quartet, quin = quintet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, dq = doublet of quartets, qd = quartet of doublets, m = multiplet), coupling constant (Hz), and integration. All ^{1}H NMR signals are reported as chemical shifts (δ ppm) relative to residual $CHCl_3$ at 7.26 ppm or $(CH_3)_2SO$ at 2.50 ppm.[1] Chemical shifts for ^{19}F NMR are reported in terms of chemical shift in reference to an added internal standard (1,2-difluorobenzene set to δ -138.18 ppm or hexafluorobenzene set to δ -161.64 ppm); reported ^{19}F NMR data are for proton-decoupled spectra. Waters Semi Preparative HPLC-PDA provided by Colorado State University Analytical Resource Core – Molecular and Materials Analysis Center Thin-layer chromatography analysis was performed on silica gel 60 Å F254 plates (250 µm, SiliaPlate from Silicycle, #TLG-R10014B323) and interpreted using UV light (254 nm). Preparatory thin-layer chromatography purification was performed on silica gel 60 Å (1000 µm, Silicycle, #TLG-R10011B-341) and interpreted using UV light (254 nm).

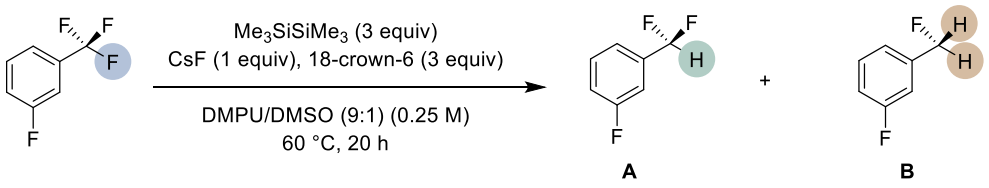
A1.2 Optimization of Selective Reduction of Electron-Neutral Trifluoromethylarenes

(a) Evaluation of changes in optimal base, solvent, disilane species and base additive for selective reduction of 3-fluorobenzotrifluoride.

Preliminary experiments varying base and solvent indicated that CsF in DMPU/DMSO (9:1) could promote the selective reduction of 3-fluorobenzotrifluoride using hexamethyldisilane. The optimized conditions are provided in Table SA1.1 below in comparison to specific changes of reagents or conditions used to inform readers of these effects. These optimization studies were conducted in a N_2 filled glovebox on a 0.25 mmol scale, however a Schlenk line protocol for 1.0 mmol scale reactions is described below.

General procedure for condition variation: Inside a N_2 filled glovebox, an oven-dried 4 mL vial (KIMBLE®, #60910-1) was charged with a magnetic stir bar, 3-fluorobenzotrifluoride (41.0 mg, 0.25 mmol, 1.0 equiv), 18-crown-6 (26.4 mg, 0.75 mmol, 3.0 equiv), base (0.25 mmol, 1.0 equiv), anhydrous solvent (0.25 M, 1 mL), and disilane reagent (0.75 mmol, 3.0 equiv) in successive order. If catalytic base and 18-crown 6 were used: base (0.05 mmol, 0.2 equiv) and 18-crown-6 (0.15 mmol, 0.6 equiv). The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, B7995-13), removed from the glovebox, and placed into an aluminum reaction block preheated to 60 °C. The reaction solution was stirred for 20 h and then 1,3,5-trimethoxybenzene and 1,2-difluorobenzene standards were measured into the reaction solution. For each experiment, the mass of 1,3,5-trimethoxybenzene and 1,2-difluorobenzene standards were measured into the reaction solution. A small aliquot was removed and injected into an NMR tube and constituted in $CDCl_3$ (0.5 mL). ^{1}H NMR spectroscopy (400 MHz, ($CDCl_3$) was used to determine the yield of 1-(difluoromethyl)-3-fluorobenzene (2). The aromatic H signal of 1,3,5-trimethoxybenzene at 6.09 ppm (s, 3H) was integrated against the aromatic H signal of 1-(difluoromethyl)-3-fluorobenzene (2) at 6.58 (t, J = 56.2 Hz, 1H) to determine the yield. Due to frequent overlap of characteristic signals with solvent and/or other byproducts, ^{1}H NMR spectroscopy yields could not always be determined, therefore ^{19}F NMR spectroscopy (376 MHz, $CDCl_3$) was also used to determine yield of 1-(difluoromethyl)-3-fluorobenzene (2). The aromatic F signal of 1,2-difluorobenzene at -138.18 ppm (t, J = 9.0 Hz, 2F) was integrated against the benzylic F signal of 1-(difluoromethyl)-3-fluorobenzene (2) at -111.55 (d, J = 56.2 Hz) to determine the yield. The results are summarized in Table SA1.1 below in addition to representative crude ^{1}H and ^{19}F NMR spectra to demonstrate this analysis.

Table SA1.1. Condition variation for selective reduction of 3-fluorobenzotrifluoride.



Entry	Variation from Standard Conditions	Product **A** (%)	Product **B** (%)	Mass Balance (%)
1	none	60	6	66
2	no 18-crown-6	60	4	92
3	20 mol% CsF/ 60 mol% 18-c-6	60	8	70
4	20 mol% CsF/ no 18-c-6 (48 h)	64	2	90
5	DMSO only	52	2	58
6	THF only	24	0	64
7	TTMSS instead of Me_6Si_2	32	0	32
8	$CsCO_2H$ instead of CsF	0	0	88
9	KOMe instead of CsF	56	8	66
10	20 mol% KOMe/ 60 mol% 18-c-6	48	0	82
11	KOH instead of CsF	64	8	76
12	20 mol% KOH/ 60 mol% 18-c-6	52	0	79

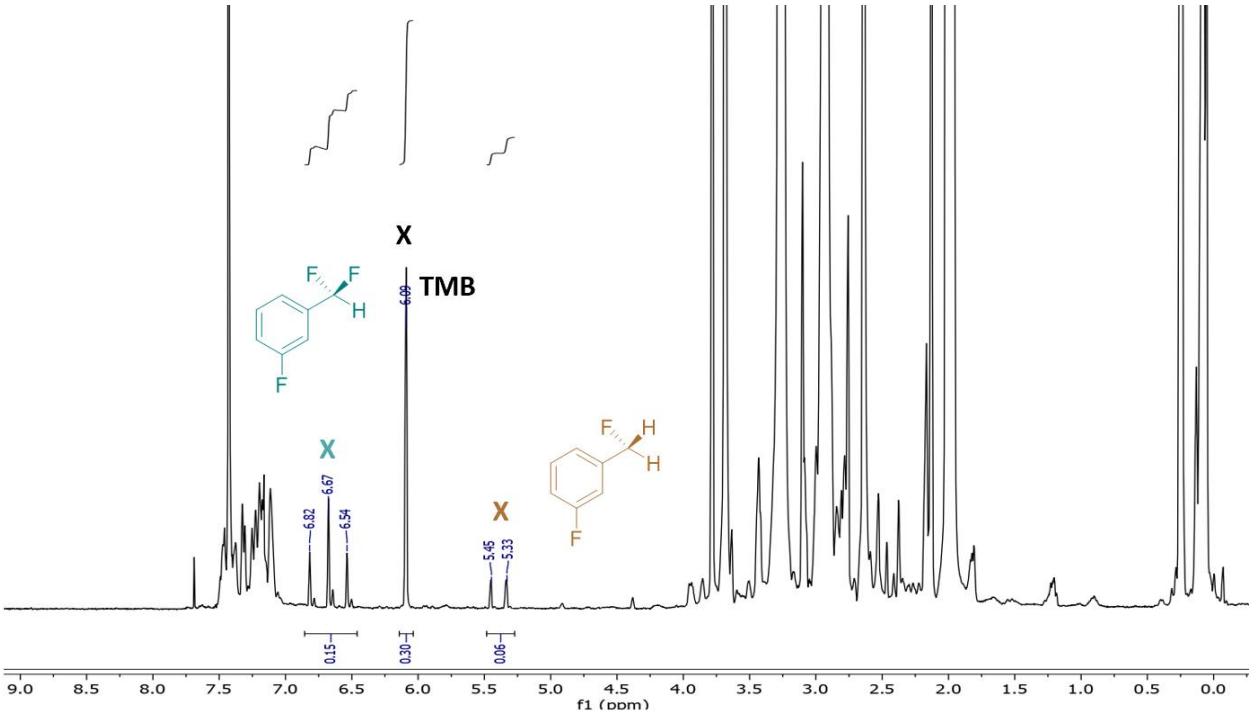


Figure SA1.1. ^{1}H NMR spectral window of the crude reaction solution of reaction from the 20 mol% CsF reaction vial above (entry 3). 1,3,5-Trimethoxybenzene internal standard (16.8 mg, 0.1 mmol, signal at 6.09 ppm calibrated to 0.30 for 0.25 mmol scale reaction) was used to determine the yield of 1-(difluoromethyl)-3-fluorobenzene (**2-2**, 60% yield) and 1-fluoro-3-(fluoromethyl)benzene (12% yield).

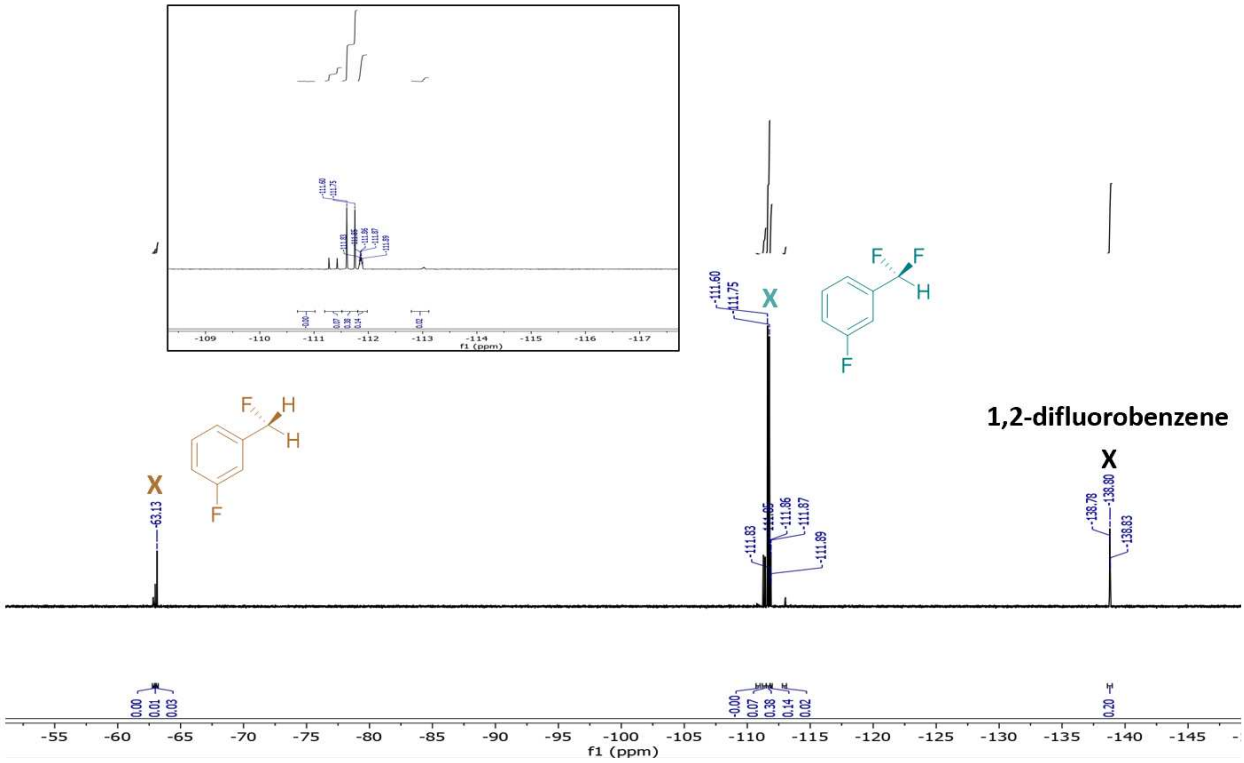


Figure SA1.2. ^{19}F NMR spectral window of the crude reaction solution of reaction from the 20 mol% CsF reaction vial above (entry 3). 1,2-Difluorobenzene internal standard (11.4 mg, 0.10 mmol, signal at -138.18 ppm calibrated to 0.2 for 0.25 mmol scale reaction) was used to determine the yield of of 1-(difluoromethyl)-3-fluorobenzene (**2-2,** 56% yield) and 1-fluoro-3-(fluoromethyl)benzene (overlap).

A1.3 General Procedure for Reduction of Electron-Neutral Trifluoromethylarenes.

Note: The reaction optimization studies were conducted inside a N_2 filled glovebox, while the general procedure for 1.0 mmol scale isolation reactions was developed using a standard manifold Schlenk line. The crude ^{19}F NMR spectroscopy yields observed during optimization are comparable to those for the 1.0 mmol isolation procedure.

General Schlenk line procedure for reduction of electron-neutral trifluoromethylarenes.

Open to air, an 8 mL oven-dried vial was charged with a magnetic stir bar along with trifluoromethylarene (1.0 mmol, 1.0 equiv), CsF (151.9 mg, 1.0 mmol, 1.0 equiv) and 18-crown-6, if indicated (792.6 mg, 3.0 mmol, 3.0 equiv). The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1B) lined with a PTFE septum (Thermo Fisher Scientific, B7995-15), evacuated and backfilled three times with N_2, and left under positive pressure of N_2 using a needle connected to a manifold Schlenk line. Anhydrous DMPU (3.6 mL) and DMSO (0.4 mL) was then added to the 8 mL vial *via* syringe. Hexamethyldisilane (615 μL, 3.0 mmol, 3.0 equiv) was then added to the vial *via* syringe. The reaction vial cap and septum were then wrapped in parafilm (Thermo Fisher Scientific, #C4015-1B) and electrical tape, and an N_2 balloon was inserted through the septum to maintain positive N_2 pressure. The vial was then placed in a preheated heating block at rt or 60 °C for the allotted time with stirring. The reaction solution was allowed to cool to rt and one of the following isolation procedures was followed.

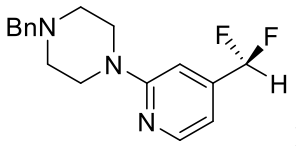
Isolation Procedure I: Upon cooling to room temperature, the mixture was poured into a 250 mL separatory funnel containing water (40 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine (20 mL) and dried with anhydrous Na_2SO_4. The Na_2SO_4 was filtered off and the solution was concentrated *in vacuo* and purified *via* flash chromatography on silica gel.

Isolation Procedure II (PTLC – 0.25 mmol scale): Upon cooling to room temperature, the mixture was poured into a 125 mL separatory funnel containing water (10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried with anhydrous Na_2SO_4. The Na_2SO_4 was filtered off and the solution was concentrated *in vacuo* and purified *via* PTLC.

Isolation Procedure II (Prep-HPLC): Upon cooling to room temperature, the mixture was poured into a 125 mL separatory funnel containing water (10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried with anhydrous Na_2SO_4. The Na_2SO_4 was filtered off and the solution was concentrated *in vacuo* and then redissolved in HPLC-grade MeCN (20 μL). 5-15 μL of this solution was then injected into a prep-HPLC to obtain separation.

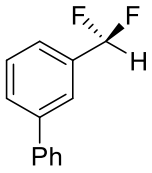
A1.4. Characterization Data of Difluoromethylarene Products

(a) Products isolated using procedure I

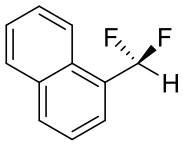


1-benzyl-4-(4-(difluoromethyl)pyridin-2-yl)piperazine (2-13). The title compound was prepared according to the general procedure using 1-benzyl-4-(4-(triifluoromethyl)pyridin-2-yl)piperazine (321.1 mg, 1.0 mmol, 1.0 equiv), CsF (30.4 mg, 0.2 mmol, 0.2 equiv), anhydrous DMPU (3.6 mL) and DMSO (0.4 mL, 0.25M), and hexamethyldisilane (614 μL, 3.0 mmol, 3.0 equiv) at rt. The product was purified *via* Isolation Procedure I ((15:80:5:1) EtOAc/Hexanes/MeOH/TEA eluent) to afford the title compound as a pale yellow solid (146.1 mg, 0.48 mmol, 48% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.26 (d, J = 5.1 Hz, 1H), 7.46 – 7.28 (m, 5H), 6.69 (d, J = 7.3 Hz, 2H), 6.52 (t, J = 56.1 Hz, 1H), 3.60 (t, J = 5.2 Hz, 4H), 3.57 (s, 2H), 2.56 (t, J = 5.1 Hz, 4H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -115.46 (d, J = 56.0 Hz).

(b) Products isolated using procedure II

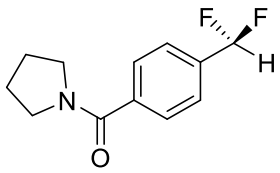


3-(difluoromethyl)-1,1'-biphenyl (2-1). The title compound was prepared according to the general procedure using 3-(trifluoromethyl)-1,1'-biphenyl (55.6 mg, 0.25 mmol, 1.0 equiv), CsF (30.4 mg, 0.05 mmol, 0.2 equiv), anhydrous DMPU (900 μL) and DMSO (100 μL, 0.25M), and hexamethyldisilane (153.5 μL, 0.75 mmol, 3.0 equiv) at rt. The product was purified *via* Isolation Procedure II ((1:99) EtOAc/Hexanes eluent) to afford the title compound as a pale yellow solid .**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 – 7.68 (m, 2H), 7.61 (d, J = 7.5 Hz, 2H), 7.60 – 7.33 (m, 5H), 6.72 (t, J = 56.5 Hz, 1H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -110.65 (d, J = 56.2 Hz).



1-(difluoromethyl)naphthalene (2-15). The title compound was prepared according to the general procedure using 1-(trifluoromethyl)naphthalene (49.0 mg, 0.25 mmol, 1.0 equiv), CsF (30.4 mg, 0.05 mmol, 0.2 equiv), anhydrous DMPU (900 μL) and DMSO (100 μL, 0.25M), and hexamethyldisilane (153.5 μL, 0.75 mmol, 3.0 equiv) at rt. The product was purified *via* Isolation Procedure II ((100:1) Hexanes/TEA eluent) to afford the title compound as a orange oil with some coelution with trimethoxybenzene.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 8.3 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 7.1 Hz, 1H), 7.56 (ddd, J = 27.6, 13.1, 7.9 Hz, 3H), 7.19 (t, J = 54.8, 54.1 Hz, 1H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -110.93 (d, J = 55.2 Hz).

(c) Products isolated using procedure III



(4-(difluoromethyl)phenyl)(pyrrolidin-1-yl)methanone (2-14). The title compound was prepared according to the general procedure using (4-(trifluoromethyl)phenyl)(pyrrolidin-1-yl)methanone (60.8 mg, 0.25 mmol, 1.0 equiv), CsF (30.4 mg, 0.05 mmol, 0.2 equiv), anhydrous DMPU (900 μL) and DMSO (100 μL, 0.25M), and hexamethyldisilane (153.5 μL, 0.75 mmol, 3.0 equiv) at rt. The product was purified *via* Isolation Procedure III ((100:1) Hexanes/TEA eluent) to afford the title compound. **^{1}H NMR** (400 MHz, $CDCl_3$) too dilute with overlap of solvent for 1H NMR spectroscopy **^{19}F NMR** (376 MHz, $CDCl_3$) δ -111.73 (d, J = 55.6 Hz).

A1.5. Deuteration Study in DMSO-d_6

Purpose: We propose that the hydrogen atom was coming from the DMSO solvent, likely through a deprotonative process. To test this hypothesis, I performed comparison reactions in protio-DMSO solvent vs. deutero-DMSO solvent and evaluated the deuterium incorporation into the reduction product.

General Procedure: Inside a N_2 filled glovebox, an oven-dried 4 mL vial (KIMBLE®, #60910-1) was charged with a magnetic stir bar, 3-fluorobenzotrifluoride (41.0 mg, 0.25 mmol, 1.0 equiv), 18-crown-6 (26.4 mg, 0.75 mmol, 3.0 equiv), base (0.25 mmol, 1.0 equiv), anhydrous solvent (0.25 M, 1 mL), and disilane reagent (0.75 mmol, 3.0 equiv) in successive order. The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, #B7995-13), removed from the glovebox, and placed into an aluminum reaction block at rt. The reaction solution was stirred for 20 h and then 1,3,5-trimethoxybenzene and 1,2-difluorobenzene standards were measured into the reaction solution. For each experiment, the mass

of 1,3,5-trimethoxybenzene and 1,2-difluorobenzene standards were measured into the reaction solution. A small aliquot was removed and injected into an NMR tube and constituted in $CDCl_3$ (0.5 mL). ^1H NMR spectroscopy (400 MHz, ($CDCl_3$) was used to determine the yield of 1-(difluoromethyl)-3-fluorobenzene (**2-2**). The aromatic H signal of 1,3,5-trimethoxybenzene at 6.09 ppm (s, 3H) was integrated against the aromatic H signal of 1-(difluoromethyl)-3-fluorobenzene (2) at 6.58 (t, J = 56.2 Hz, 1H) to determine the yield. Due to frequent overlap of characteristic signals with solvent and/or other byproducts, ^1H NMR spectroscopy yields could not always be determined, therefore ^{19}F NMR spectroscopy (376 MHz, CDCl3) was also used to determine yield of 1-(difluoromethyl)-3-fluorobenzene (**2-2**). The aromatic F signal of 1,2-difluorobenzene at -138.18 ppm (t, J = 9.0 Hz, 2F) was integrated against the benzylic F signal of 1-(difluoromethyl)-3-fluorobenzene (**2-2**) at -111.55 (d, J = 56.2 Hz) to determine the yield.

Analysis: ^1H NMR analysis was conducted on a sample of 3-fluorobenzotrifluoride starting material. The spectra of the crude reaction mixture from the deuterium exchange experiment and the corresponding starting material were then overlayed, and each peak was integrated. The percent of deuterium incorporation into 1-(difluoromethyl)-3-fluorobenzene (**2-2**) was calculated based on the reduction of signal integration between the signals in the crude reaction analysis and starting material spectra, in addition to the ^{19}F NMR spectrum providing a calculable yield. The results and stacked spectra assessed are provided below.

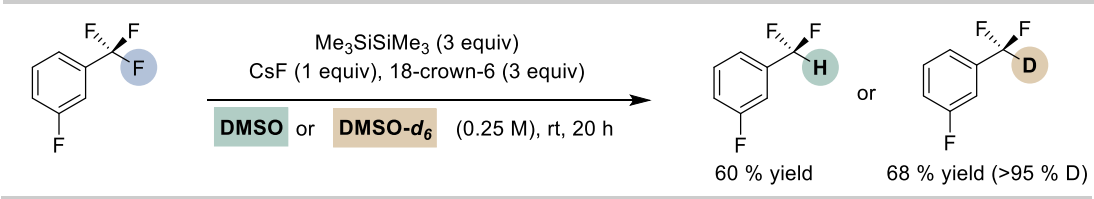


Figure SA1.3. Evaluation of deuterated DMSO as a reaction solvent to determine where hydrogen (or deuterium) comes from.

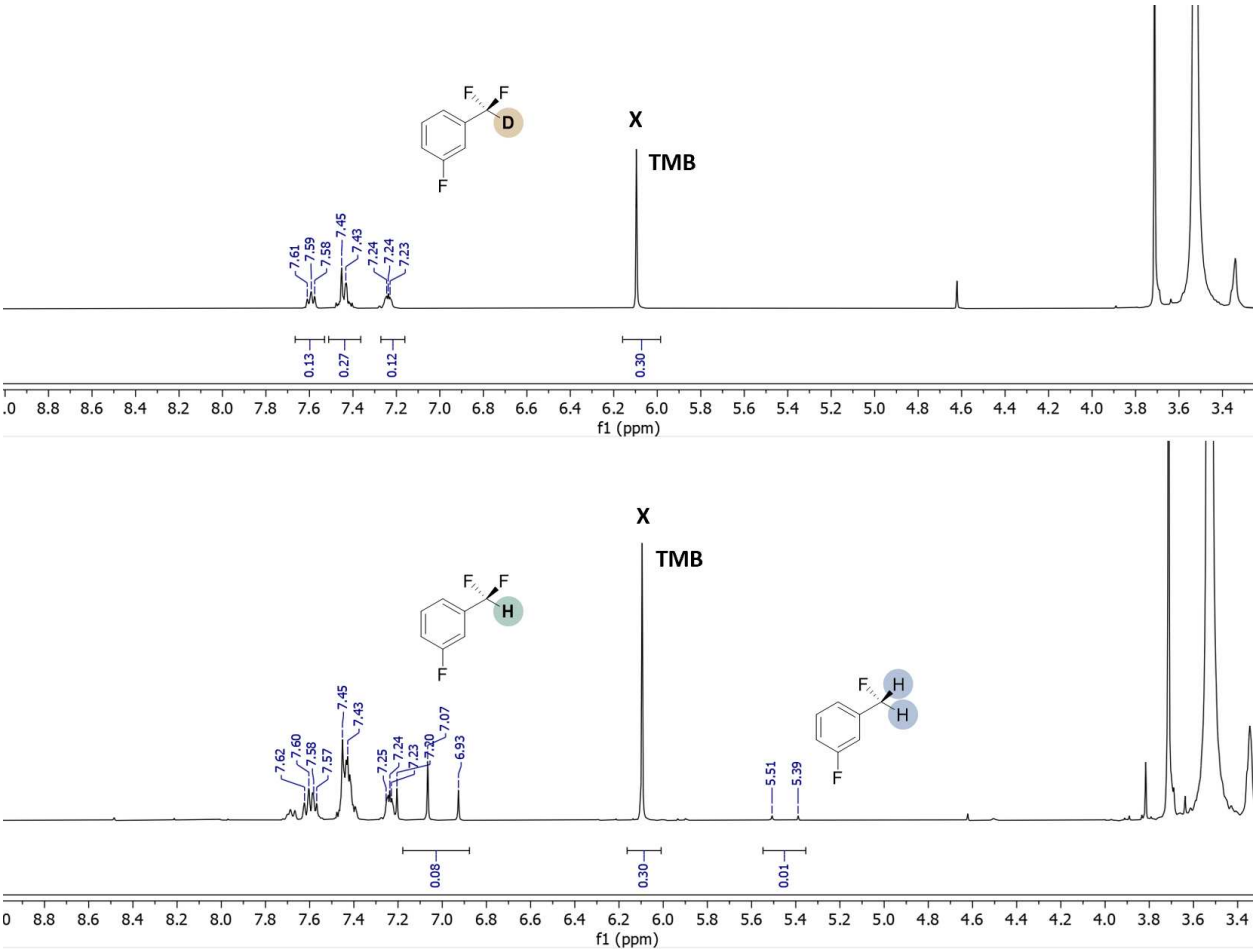


Figure SA1.4. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the crude reaction solution of 1-(difluoromethyl)-3-fluorobenzene (**2-2**) deuteration using $(CD_3)_2SO$, in standard reaction conditions (top). It was determined that full incorporation of deuterium into the reduction product occurred, indicating that the DMSO solvent did serve as the proton/deuterium source. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the crude reaction solution of 1-(difluoromethyl)-3-fluorobenzene (**2-2**) using $(CH_3)_2SO$, in standard reaction conditions (bottom). 1,3,5-Trimethoxybenzene internal standard (16.8 mg, 0.1 mmol, signal at 6.09 ppm calibrated to 0.30 for 0.25 mmol scale reaction) was used to determine the yield of 1-(difluoromethyl)-3-fluorobenzene (**2-2**, overlap, bottom) and 1-fluoro-3-(fluoromethyl)benzene (5% yield, bottom).

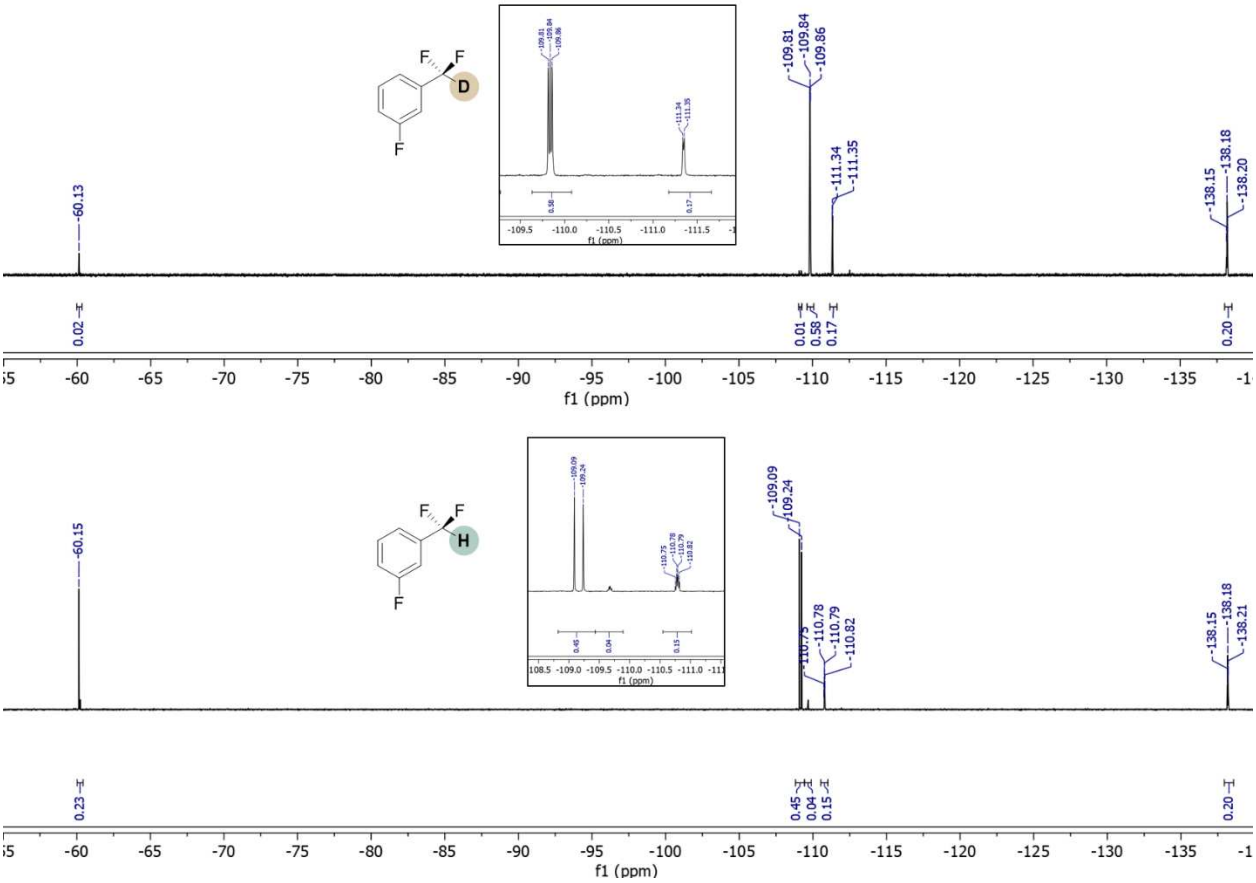
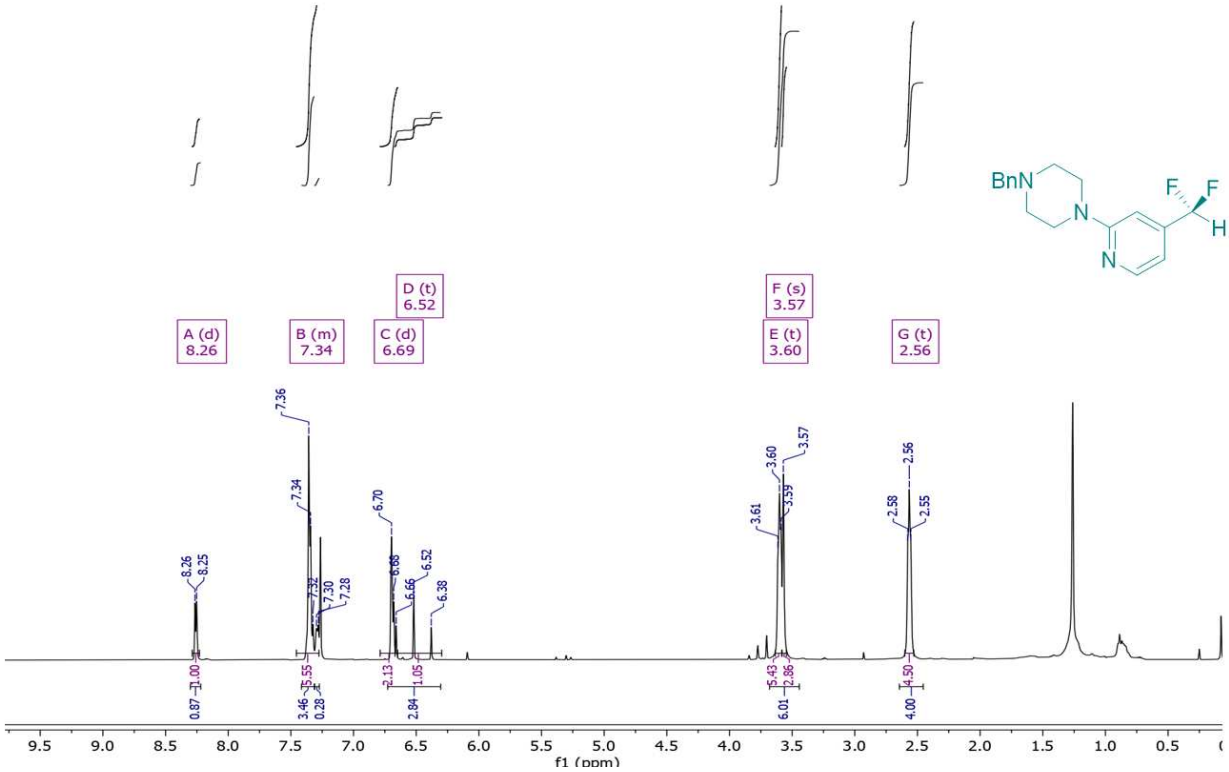


Figure SA1.5. ^{19}F NMR spectrum (376 MHz, $CDCl_3$) of the crude reaction solution of 1-(difluoromethyl)-3-fluorobenzene (**2-2**) deuteration using $(CD_3)_2SO$, in standard reaction conditions (top). It was determined that full incorporation of deuterium into the reduction product occurred, indicating that the DMSO solvent did serve as the proton/deuterium source. ^1H NMR spectrum (400 MHz, $CDCl_3$) of the crude reaction solution of 1-(difluoromethyl)-3-fluorobenzene (**2-2**) using $(CH_3)_2SO$, in standard reaction conditions (bottom). 1,2-Difluorobenzene internal standard (11.4 mg, 0.10 mmol, signal at -138.18 ppm calibrated to 0.2 for 0.25 mmol scale reaction) was used to determine the yield of 1-(difluoromethyl)-3-fluorobenzene (**2-2**, 60% yield, bottom) and 1-(difluoromethyl-*d*)-3-fluorobenzene (68% yield, top).

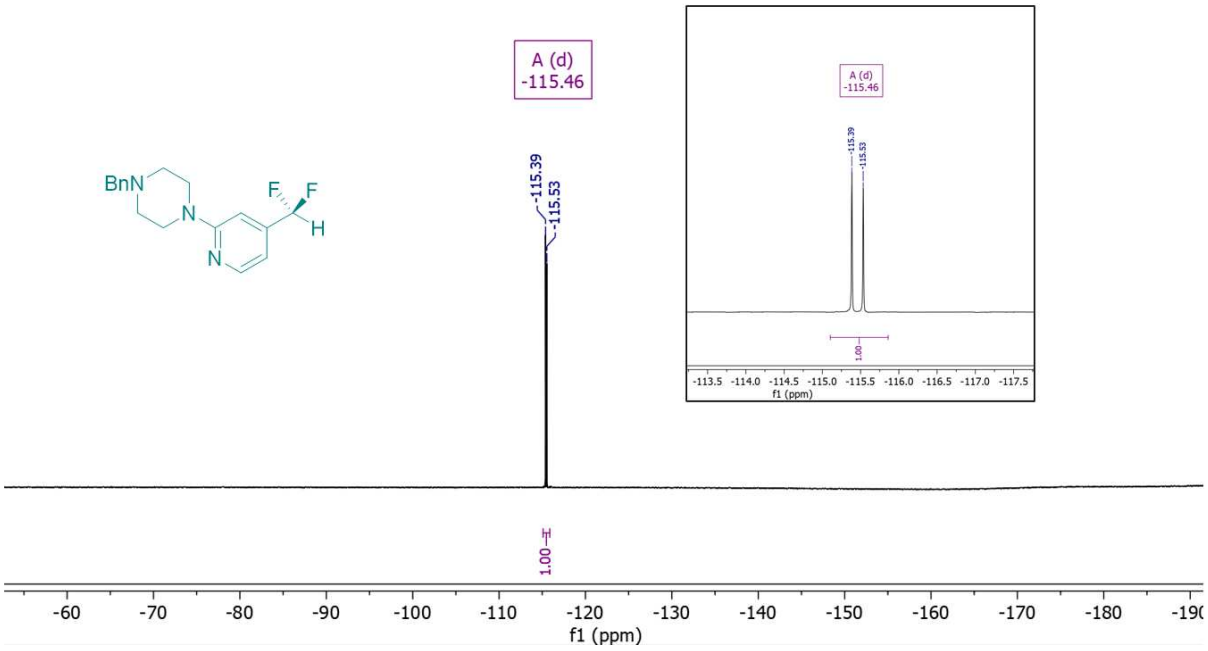
A1.6 References

[1] Fulmer, G. R.; Miller, A. J.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J.; Goldberg, K. I. Organometallics 2010, 29, 2176–2179.

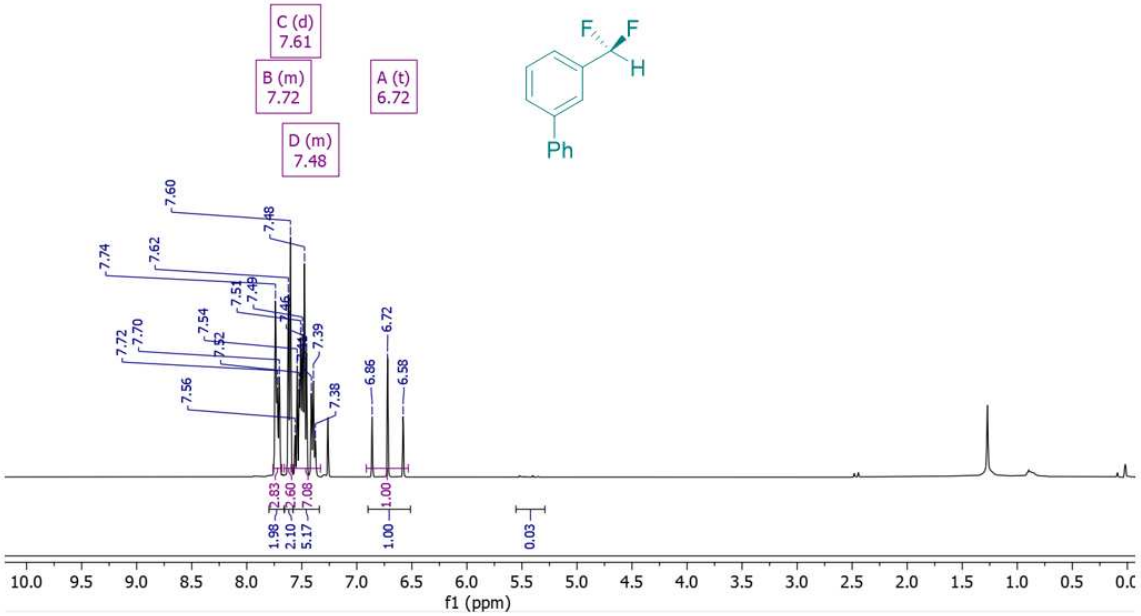
A1.7. NMR spectra of Isolated Substrates



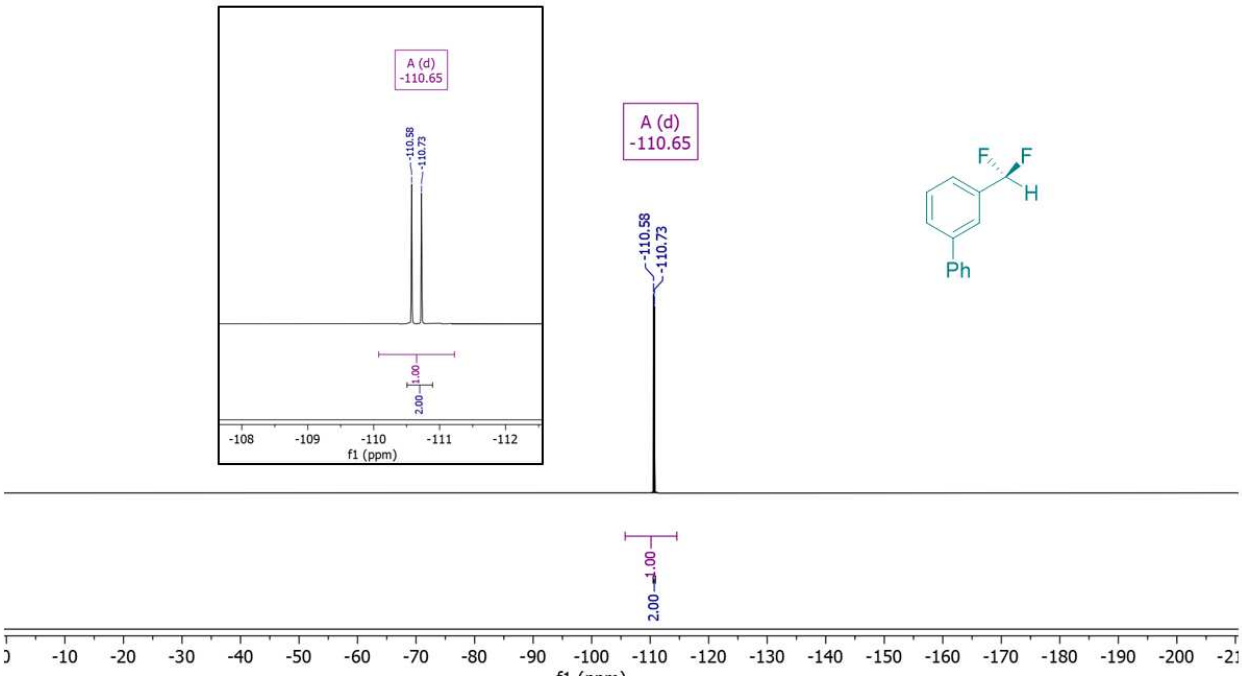
^{1}H NMR spectrum **2-13** (400 MHz, $CDCl_3$)



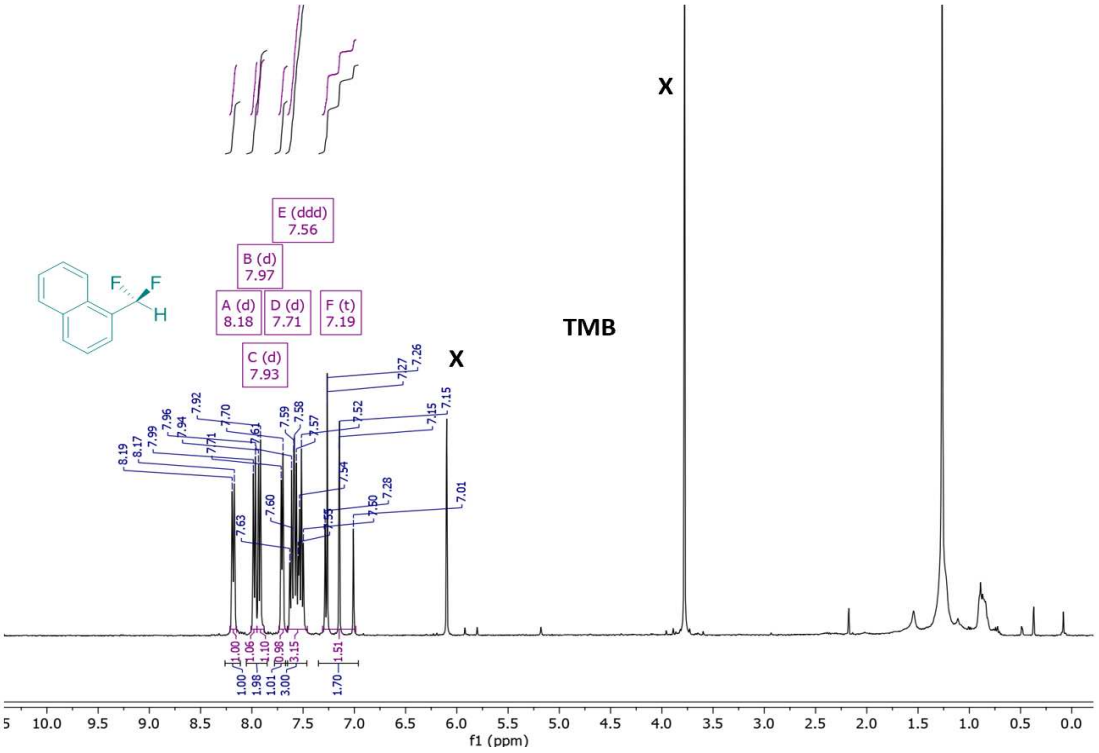
^{19}F NMR spectrum **2-13** (376 MHz, $CDCl_3$)



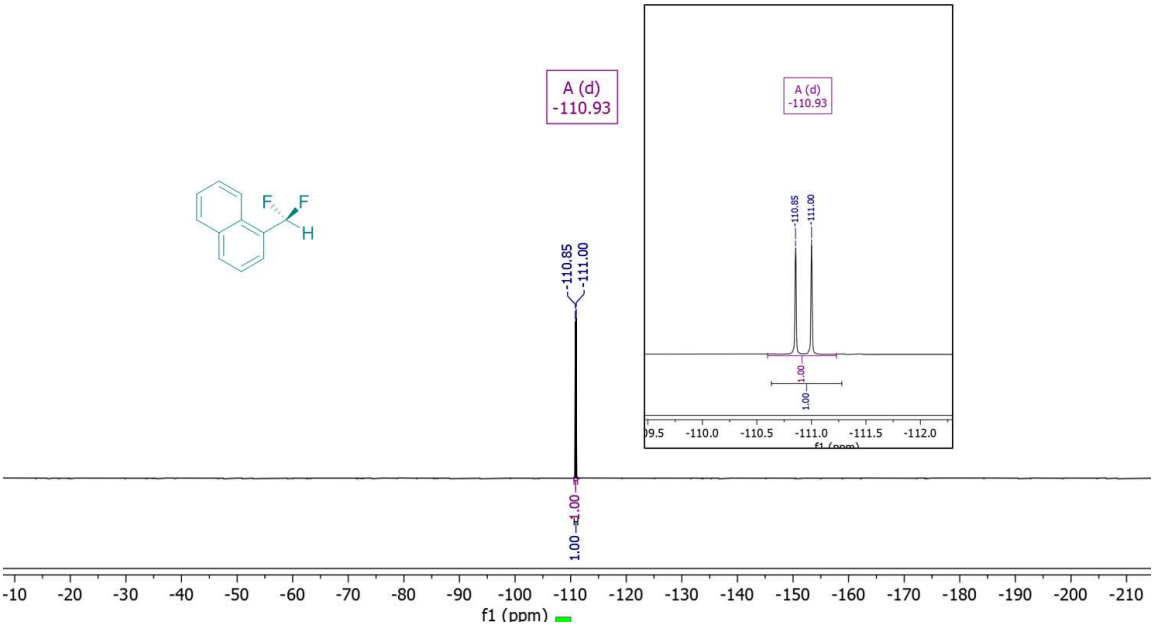
^{1}H NMR spectrum **2-1** (400 MHz, $CDCl_3$)



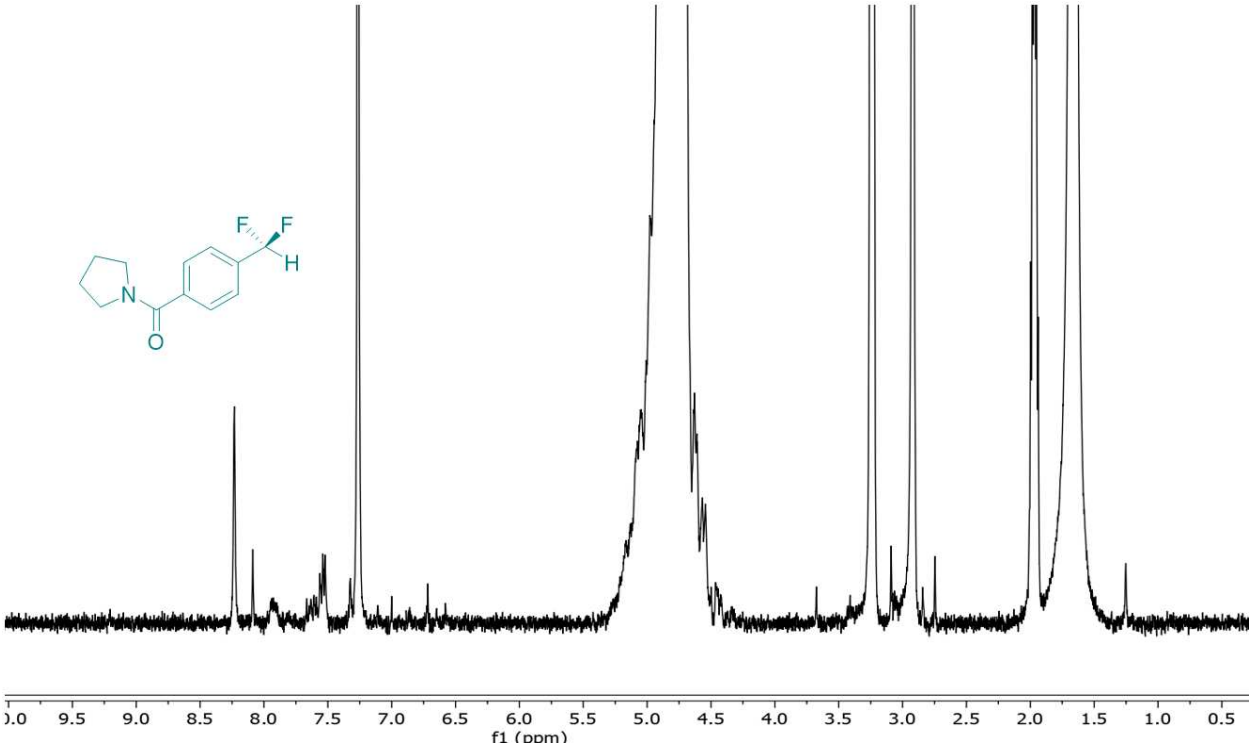
^{19}F NMR spectrum **2-1** (376 MHz, $CDCl_3$)



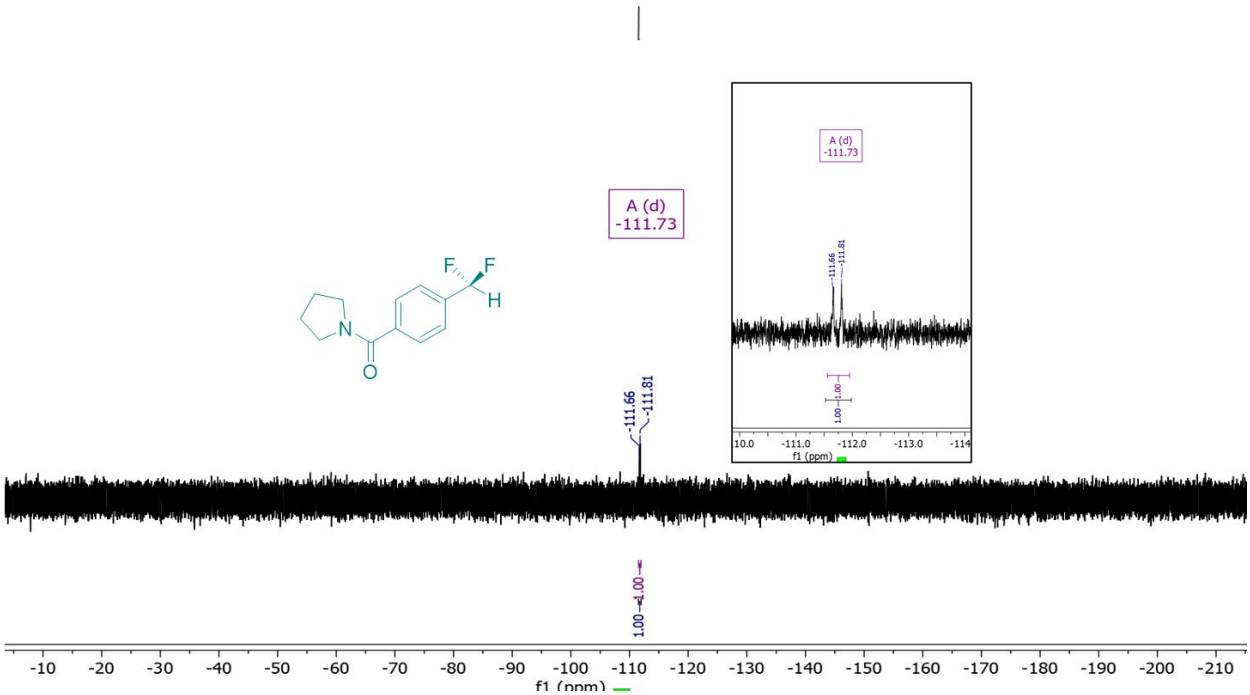
^{1}H NMR spectrum **2-15** (400 MHz, $CDCl_3$)



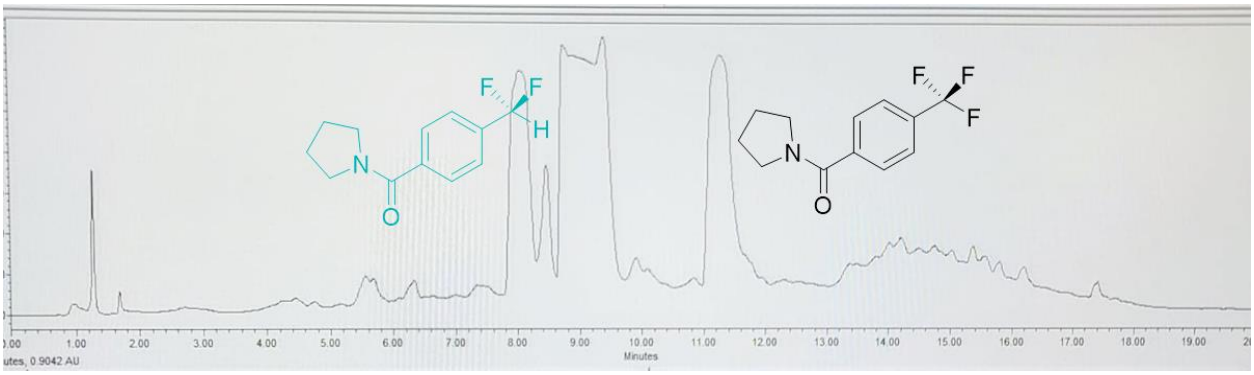
^{19}F NMR spectrum **2-15** (376 MHz, $CDCl_3$)



^{1}H NMR spectrum **2-14** (400 MHz, $CDCl_3$)



^{19}F NMR spectrum **2-14** (376 MHz, $CDCl_3$)



Semi Prep HPLC spectrum of **2-14**

APPENDIX TWO

LEWIS BASE PROMOTED MONOSELECTIVE REDUCTIVE COUPLING OF ELECTRON-NEUTRAL TRIFLUOROMETHYLARENES: EXPERIMENTAL

A2.1 General Information:

All results are preliminary and were analyzed by ^{1}H and ^{19}F NMR spectroscopy. This appendix is intended to provide experimental details and supporting information for the material discussed in Chapter 2.

General Reagent Information: All reactions were performed under a nitrogen (N_2) atmosphere unless otherwise noted. Hexamethyldisilane (Me_6Si_2, CombiBlocks catalog #QB-7675), 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6, Chem-Impex catalog #03901) and 1-Formylpyrrolidine (CombiBlocks, catalog # QH-1295) were purchased from the indicated vendors and used as received. Cesium fluoride (CsF, Acros Organics catalog # 010019.88) was purchased as a 99.9% pure powder pure solid and used as received. Me_6Si_2, CsF and 18-crown-6 were stored at room temperature (rt) inside a N_2 filled glovebox and used immediately if brought outside the glovebox. 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrmidinone (DMPU, TCI catalog # D2014) and methylsulfoxide (DMSO, Acros Organics catalog # 042780.M1) was purchased and used as received. All other solvents and reagents were purchased from MilliporeSigma, Combi-Blocks, TCI, Acros Organics, Matrix Scientific, Alfa Aesar, or Synthonix and used as received unless otherwise noted. Flash chromatography was performed on 40-63 μm silica gel (SiliaFlash® F60 from Silicycle). Preparative thin-layer chromatography (PTLC) was performed on silica gel 60 Å F254 plates (20 x 20 cm, 1000 μm, SiliaPlate from Silicycle, #TLG-R10011B-341) and visualized with UV light (254 nm). Celite® 545 (Product #CX0574-3) was purchased from Millipore Sigma.

General Analytical Information: All reported compounds were characterized by ^{1}H and ^{19}F NMR spectroscopy. ^{1}H NMR and ^{19}F NMR spectra were obtained on a Bruker NEO400, Bruker US400, or Bruker Ascend 400 spectrometers. ^{1}H NMR data is reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, br s = broad singlet, d =doublet, t = triplet, q = quartet, quin = quintet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, dq = doublet of quartets, qd = quartet of doublets, m = multiplet), coupling constant (Hz), and integration. All ^{1}H NMR signals are reported as chemical shifts (δ ppm) relative to residual $CHCl_3$ at 7.26 ppm or $(CH_3)_2SO$ at 2.50 ppm.[1] Chemical shifts for ^{19}F NMR are reported in terms of chemical shift in reference to an added internal standard (1,2-difluorobenzene set to δ -138.18 ppm or hexafluorobenzene set to δ -161.64 ppm); reported ^{19}F NMR data are for proton-decoupled spectra. Thin-layer chromatography analysis was performed on silica gel 60 Å F254 plates (250 µm, SiliaPlate from Silicycle, #TLG-R10014B323) and interpreted using UV light (254 nm) or $KMnO_4$ stain. Preparatory thin-layer chromatography purification was performed on silica gel 60 Å (1000 µm, Silicycle, #TLG-R10011B-341) and interpreted using UV light (254 nm).

A2.2 Optimization of Selective Reduction Coupling of Electron-Neutral Trifluoromethylarenes

(a) Evaluation of changes in optimal base, solvent, disilane species and base additive for selective reductive coupling of 3-phenylbenzotrifluoride.

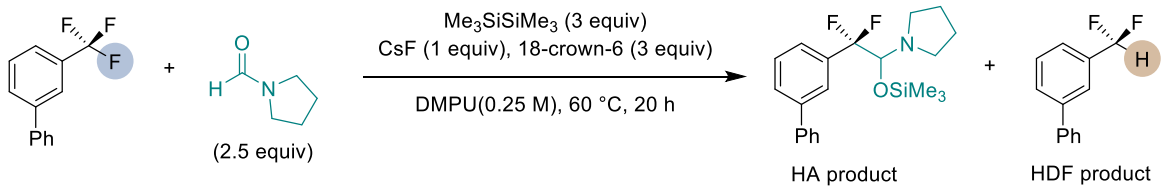
Preliminary experiments varying base and solvent indicated that CsF in DMPU/DMSO (9:1) could promote the selective reductive coupling of 3-phenylbenzotrifluoride using hexamethyldisilane. The optimized conditions are provided in Table SA2.1 below in comparison to specific changes of reagents or conditions used to inform readers of these effects. These

optimization studies were conducted in a N_2 filled glovebox on a 0.25 mmol scale, however a Schlenk line protocol for 1.0 mmol scale reactions is described below.

General procedure for condition variation: Inside a N_2 filled glovebox, an oven-dried 4 mL vial (KIMBLE®, #60910-1) was charged with a magnetic stir bar, 3-phenylbenzotrifluoride (40.0 mg, 0.25 mmol, 1.0 equiv), 18-crown-6 (26.4 mg, 0.75 mmol, 3.0 equiv), base (0.75 mmol, 3.0 equiv), formamide (0.625 mmol, 2.5 equiv), anhydrous solvent (0.25 M, 1 mL), and disilane reagent (0.75 mmol, 3.0 equiv) in successive order. The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, B7995-13), removed from the glovebox, and placed into an aluminum reaction block preheated to rt or 60°C. The reaction solution was stirred for 20 h and then 1,3,5-trimethoxybenzene and 1,2-difluorobenzene standards were measured into the reaction solution. For each experiment, the mass of 1,3,5-trimethoxybenzene and 1,2-difluorobenzene standards were measured into the reaction solution. A small aliquot was removed and injected into an NMR tube and constituted in $CDCl_3$ (0.5 mL). ^{1}H NMR spectroscopy (400 MHz, ($CDCl_3$) was used to determine the yield of 2-([1,1'-biphenyl]-3-yl)-2,2-difluoro-1-(pyrrolidin-1-yl)ethan-1-trimethylsilylnol (**2-16**). The aromatic H signal of 1,3,5-trimethoxybenzene at 6.09 ppm (s, 3H) was integrated against the aromatic H signal of 2-([1,1'-biphenyl]-3-yl)-2,2-difluoro-1-(pyrrolidin-1-yl)ethan-1-trimethylsilylnol (**2-16**) at 4.68 (td, J = 10.4, 4.0 Hz, 1H).determine the yield. Due to frequent overlap of characteristic signals with solvent and/or other byproducts, ^{1}H NMR spectroscopy yields could not always be determined, therefore ^{19}F NMR spectroscopy (376 MHz, $CDCl_3$) was also used to determine yield of 2-([1,1'-biphenyl]-3-yl)-2,2-difluoro-1-(pyrrolidin-1-yl)ethan-1-trimethylsilylnol (**2-16**). The aromatic F signal of 1,2-difluorobenzene at -138.18 ppm (t, J = 9.0 Hz, 2F) was integrated against the benzylic F signal of 2-([1,1'-biphenyl]-3-yl)-2,2-difluoro-1-(pyrrolidin-1-yl)ethan-1-trimethylsilylnol (**2-**

16) at -105.18 (dd, J = 699.6, 248.2 Hz).to determine the yield. The results are summarized in Table SA2.1 below in addition to representative crude ^{1}H and ^{19}F NMR spectra to demonstrate this analysis.

Table SA2.1. Condition variation for selective reductive coupling of 3-phenylbenzotrifluoride.



Entry	Variation from Standard Conditions	HA Product (%)	HDF Product (%)
1	none	60	8
2	no 18-crown-6	x	4
3	20 mol% CsF/ 60 mol% 18-c-6	52	12
4	THF instead of DMPU	48	4
5	DMSO instead of DMPU	0	60
6	rt instead of 60 °C	48	10
7	DMF instead of *N*-formylpyrrolidine	48	16
8	*N*-formylpiperidine instead of *N*-formylpyrrolidine	32	8
9	*N*-formylmorpholine instead of *N*-formylpyrrolidine	16	20
10	TTMSS instead of Me_6Si_2	0	12
11	CsO_2CH instead of CsF	0	0
12	CsO_2CH + TTMSS	48	20

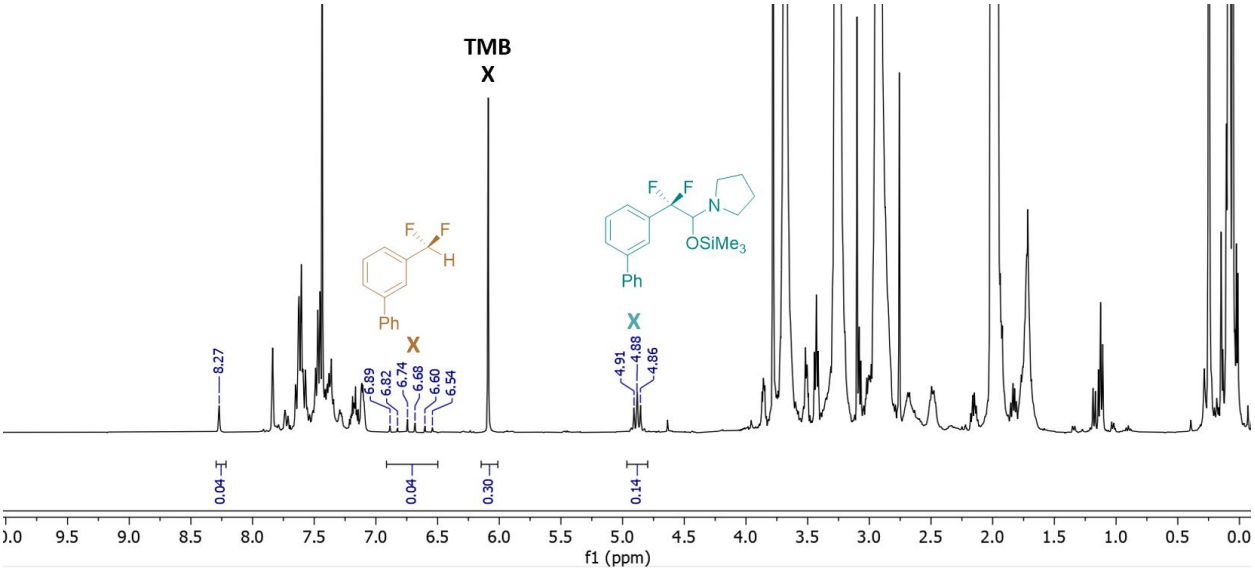


Figure SA2.1. [1]H NMR spectral window of the crude reaction solution of reaction from the 20 mol% CsF reaction time vial above (entry 3). 1,3,5-Trimethoxybenzene internal standard (16.8 mg, 0.1 mmol, signal at 6.09 ppm calibrated to 0.30 for 0.25 mmol scale reaction) was used to determine the yield of 2-([1,1'-biphenyl]-3-yl)-2,2-difluoro-1-(pyrrolidin-1-yl)ethan-1-trimethylsilylnol (**2-16,** 52% yield) and 3-(difluoromethyl)-1,1'-biphenyl (**2-1**, 12% yield).

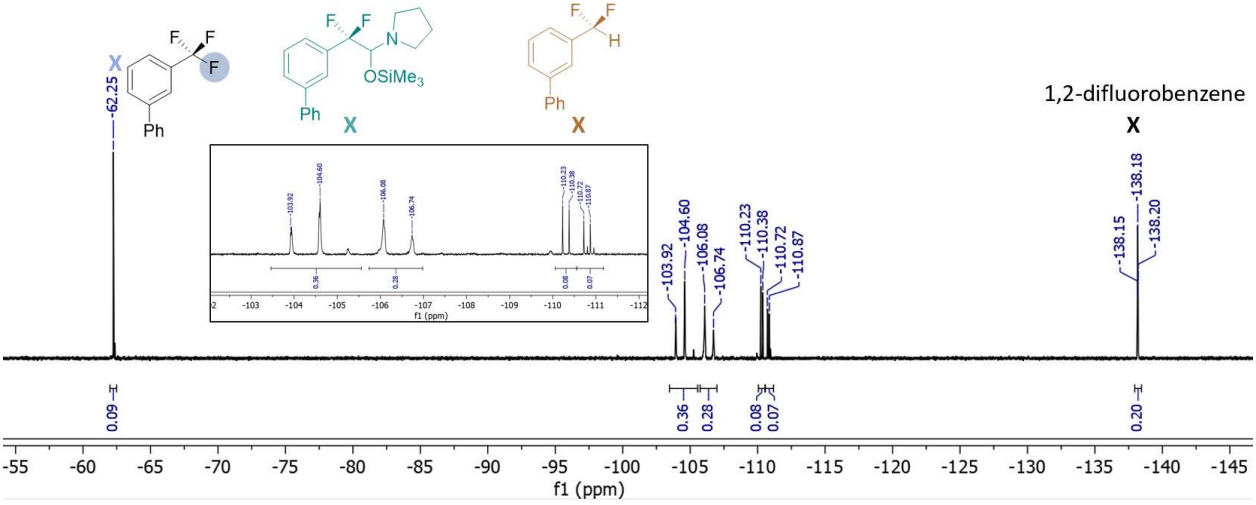


Figure SA2.2. [19]F NMR spectral window of the crude reaction solution of reaction from the 20 mol% CsF reaction time vial above (entry 3). 1,2-Difluorobenzene internal standard (11.4 mg, 0.10 mmol, signal at -138.18 ppm calibrated to 0.2 for 0.25 mmol scale reaction) was used to determine the yield of 2-([1,1'-biphenyl]-3-yl)-2,2-difluoro-1-(pyrrolidin-1-yl)ethan-1-trimethylsilylnol (**2-1**6, 54% yield) and 3-(difluoromethyl)-1,1'-biphenyl (**2-1**, 12% yield) and 3-phenylbenzotrifluoride (40% yield).

A2.3 General Procedure for Reduction of Electron-Neutral Trifluoromethylarenes.

Note: The reaction optimization studies were conducted inside a N_2 filled glovebox, while the general procedure for 1.0 mmol scale isolation reactions was developed using a standard manifold Schlenk line. The crude ^{19}F NMR spectroscopy yields observed during optimization are comparable to those for the 1.0 mmol isolation procedure.

General Schlenk line procedure for reductive coupling of electron-neutral trifluoromethylarenes.

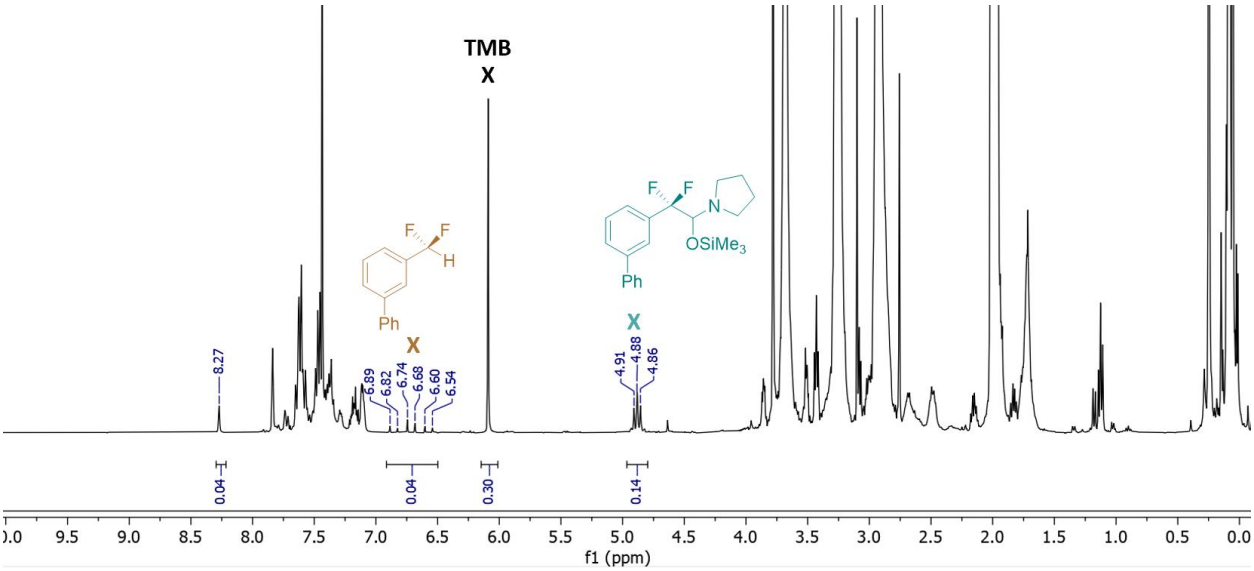
Open to air, an 8 mL oven-dried vial was charged with a magnetic stir bar along with trifluoromethylarene (1.0 mmol, 1.0 equiv), CsF (151.9 mg, 1.0 mmol, 1.0 equiv), 18-crown-6, if indicated (792.6 mg, 3.0 mmol, 3.0 equiv) and *N*-formylpyrrolidine (247.8 mg, 2.5 mmol, 2.5 equiv). The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1B) lined with a PTFE septum (Thermo Fisher Scientific, B7995-15), evacuated and backfilled three times with N_2, and left under positive pressure of N_2 using a needle connected to a manifold Schlenk line. Anhydrous DMPU (4.0 mL, 0.25 M) was then added to the 8 mL vial *via* syringe. Hexamethyldisilane (615 μL, 3.0 equiv, 3.0 mmol) was then added to the vial *via* syringe. The reaction vial cap and septum were then wrapped in parafilm (Thermo Fisher Scientific, #C4015-1B) and electrical tape, and an N_2 balloon was inserted through the septum to maintain positive N_2 pressure. The vial was then placed in a preheated heating block at rt or 60 °C for the allotted time with stirring. The reaction solution was allowed to cool to rt and then was evaluated by NMR spectroscopy.

A2.4 References

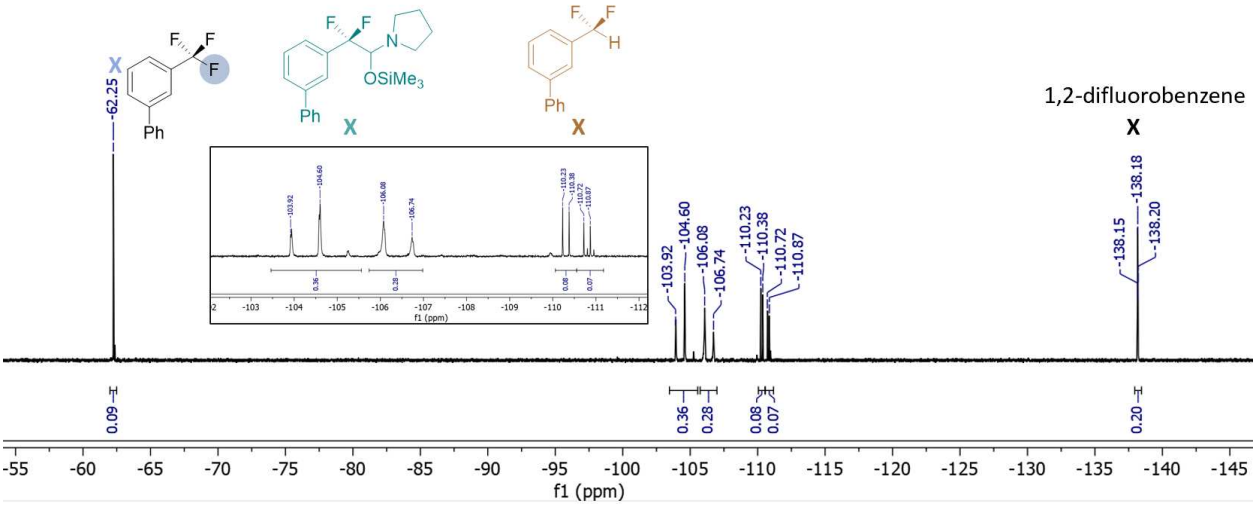
[1] Fulmer, G. R.; Miller, A. J.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J.; Goldberg, K. I. Organometallics 2010, 29, 2176–2179.

A2.5 Crude NMR Spectra of Reductive Coupling of Trifluoromethylarenes in Scope

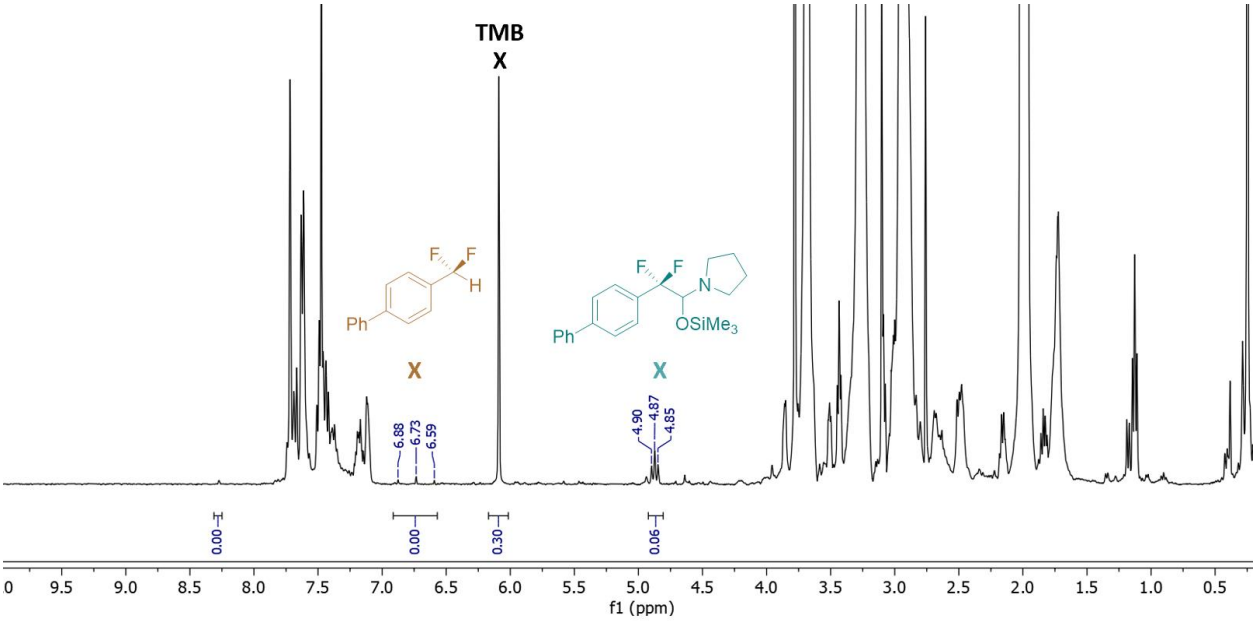
Note: 1,3,5-Trimethoxybenzene internal standard (16.8 mg, 0.1 mmol, signal at 6.09 ppm calibrated to 0.30 for 0.25 mmol scale reaction) was used to determine the yield. 1,2-Difluorobenzene internal standard (11.4 mg, 0.10 mmol, signal at -138.18 ppm calibrated to 0.2 for 0.25 mmol scale reaction) was used to determine the yield



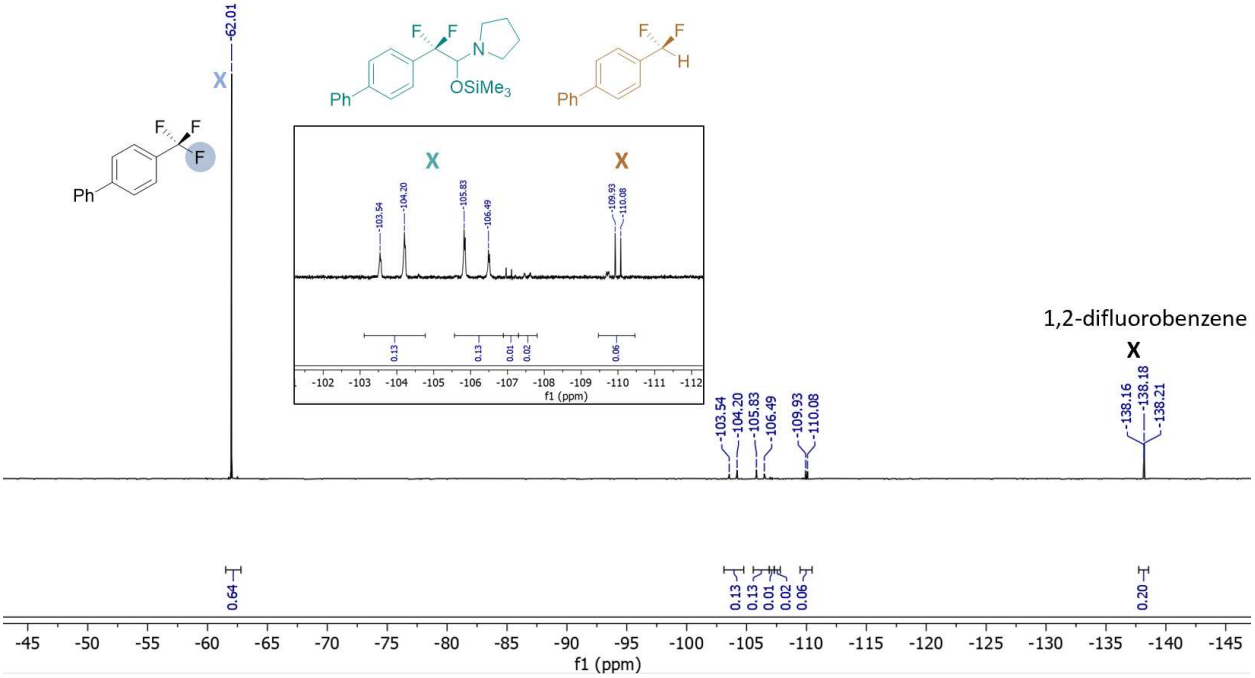
^{1}H NMR spectrum of **2-16** (400 MHz, $CDCl_3$)



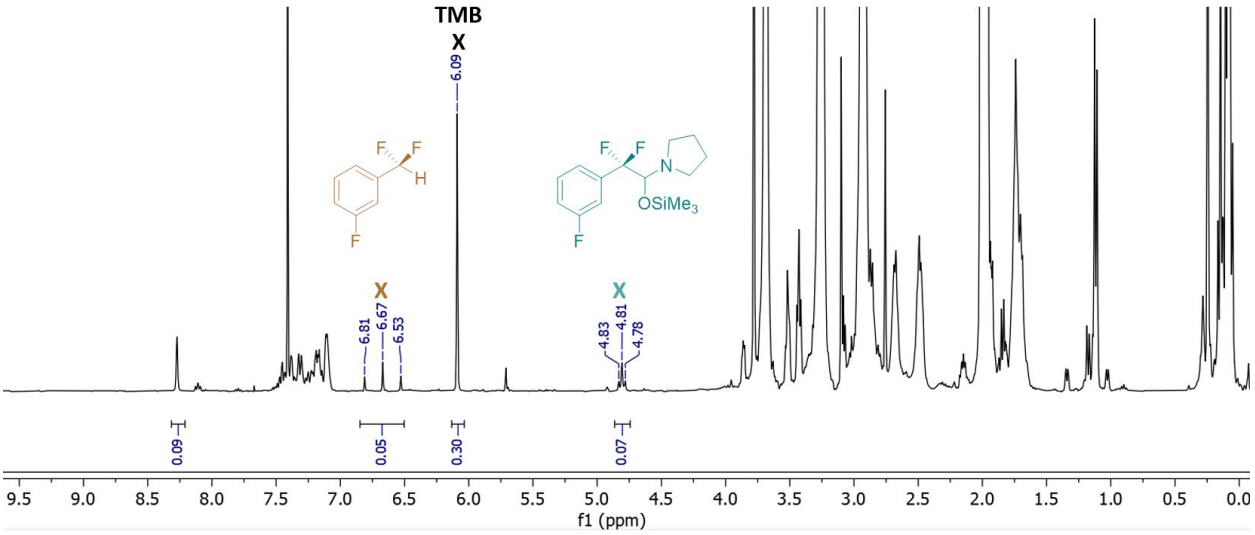
^{19}F NMR spectrum of **2-16** (376 MHz, $CDCl_3$)



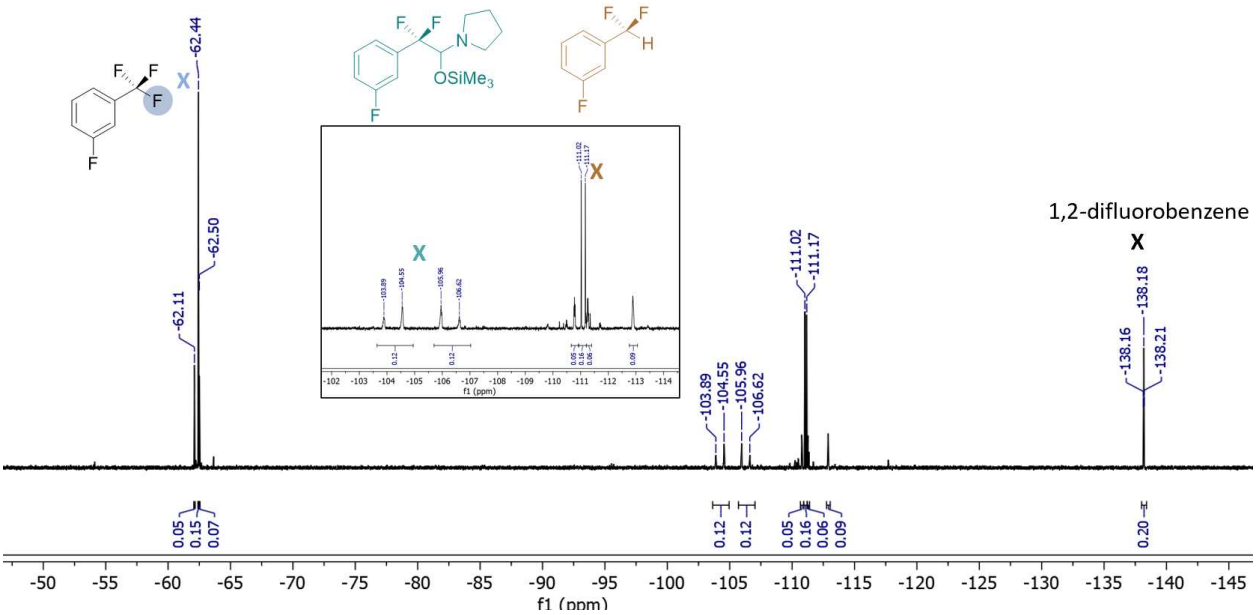
^{1}H NMR spectrum of **2-17** (400 MHz, $CDCl_3$)



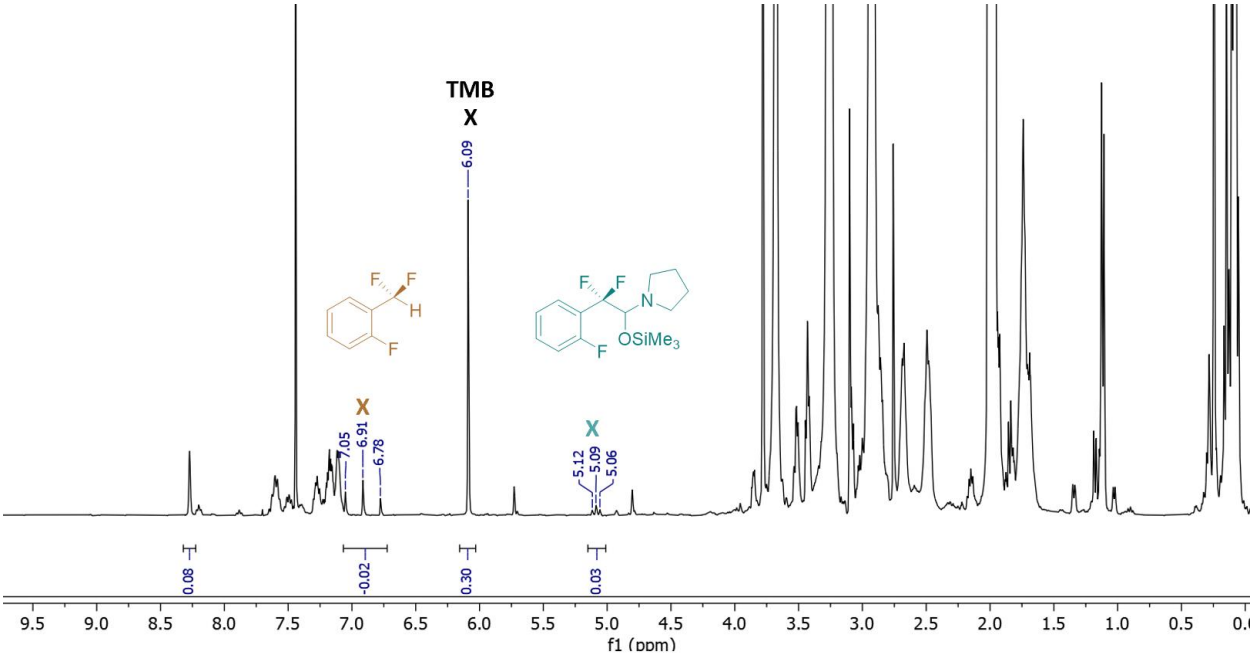
^{19}F NMR spectrum of **2-17** (376 MHz, $CDCl_3$)



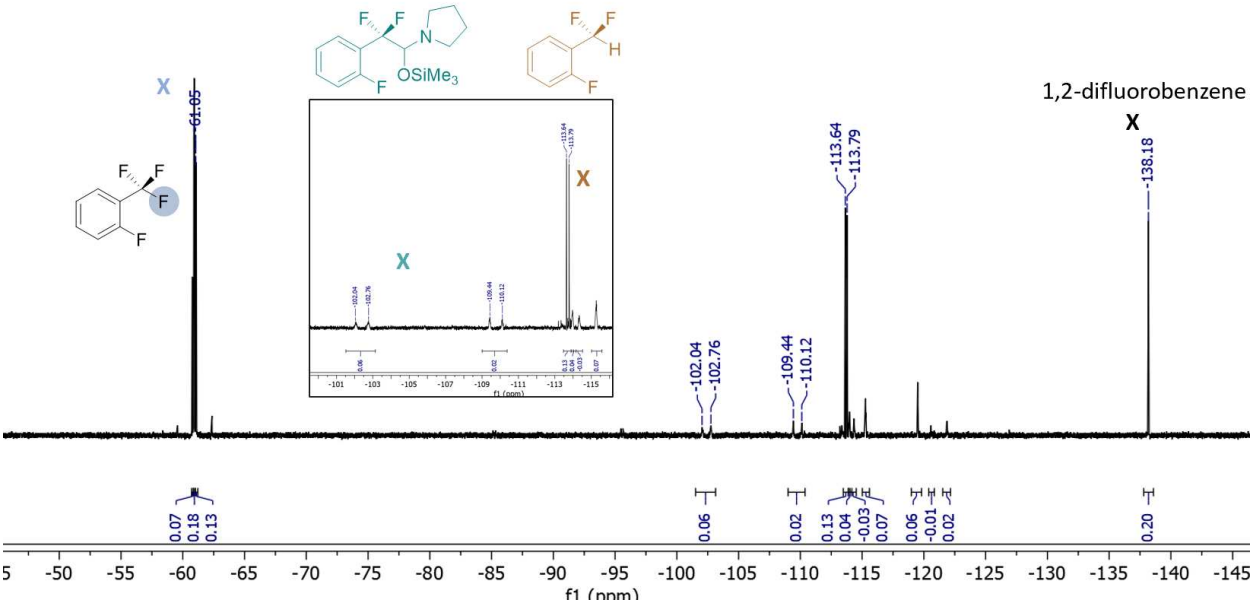
^{1}H NMR spectrum of **2-18** (400 MHz, $CDCl_3$)



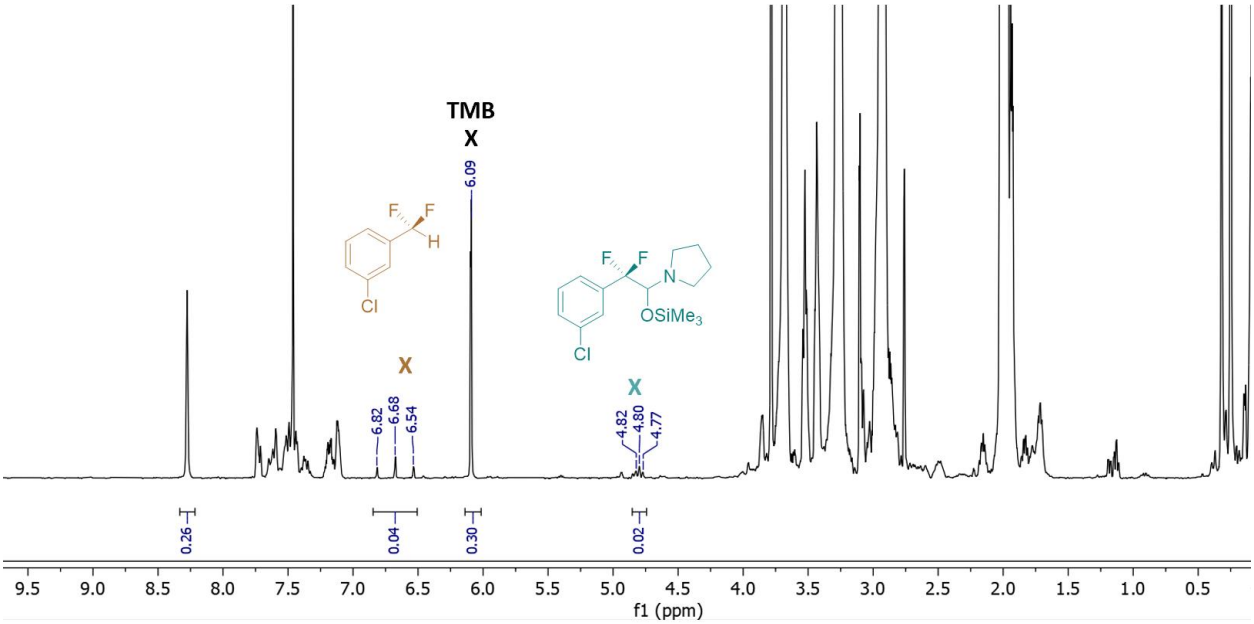
^{19}F NMR spectrum of **2-18** (376 MHz, $CDCl_3$)



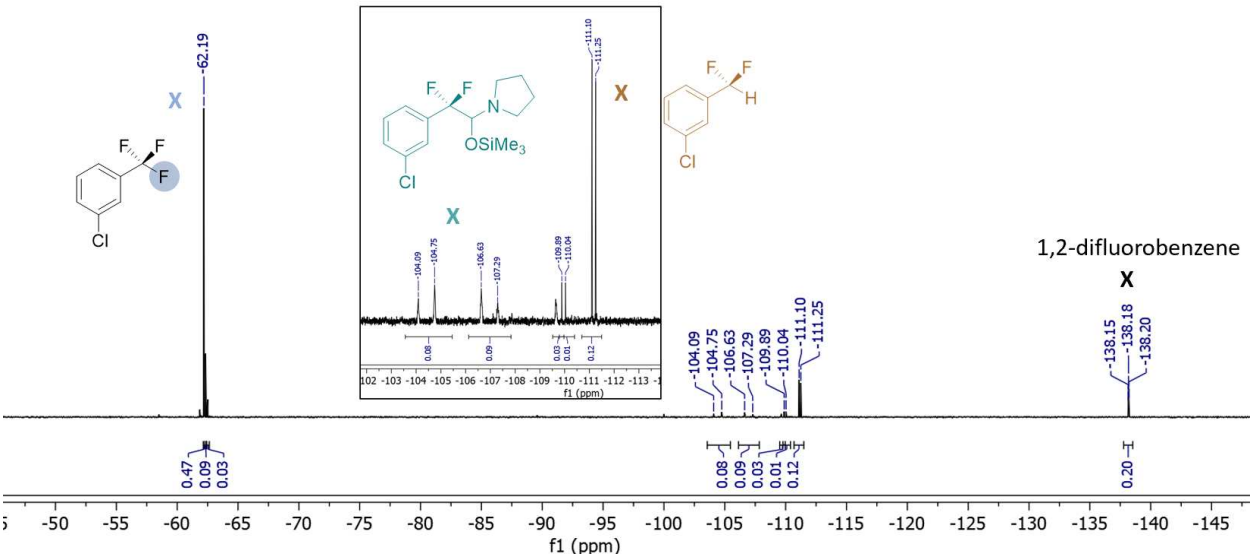
^{1}H NMR spectrum of **2-19** (400 MHz, $CDCl_3$)



^{19}F NMR spectrum of **2-19** (376 MHz, $CDCl_3$)



^{1}H NMR spectrum of **2-20** (400 MHz, $CDCl_3$)



^{19}F NMR spectrum of **2-20** (376 MHz, $CDCl_3$)

APPENDIX THREE

LEWIS BASE PROMOTED MONOSELECTIVE REDUCTIVE COUPLING OF CYANOARENES TO CARBONYLS: EXPERIMENTAL

A3.1 General Information:

All results are preliminary and were analyzed by ^{1}H NMR spectroscopy. This appendix is intended to provide experimental details and supporting information for the material discussed in Chapter 2.

General Reagent Information: All reactions were performed under a nitrogen (N_2) atmosphere unless otherwise noted. Hexamethyldisilane (Me_6Si_2, CombiBlocks catalog #QB-7675), 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6, Chem-Impex catalog #03901) and 1-Formylpyrrolidine (CombiBlocks, catalog # QH-1295) were purchased from the indicated vendors and used as received. Cesium fluoride (CsF, Acros Organics catalog # 010019.88) was purchased as a 99.9% pure powder pure solid and used as received. Me_6Si_2, CsF and 18-crown-6 were stored at room temperature (rt) inside a N_2 filled glovebox and used immediately if brought outside the glovebox. 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrmidinone (DMPU, TCI catalog # D2014) and methylsulfoxide (DMSO, Acros Organics catalog # 042780.M1) was purchased and used as received. All other solvents and reagents were purchased from MilliporeSigma, Combi-Blocks, TCI, Acros Organics, Matrix Scientific, Alfa Aesar, or Synthonix and used as received unless otherwise noted. Flash chromatography was performed on 40-63 μm silica gel (SiliaFlash® F60 from Silicycle). Preparative thin-layer chromatography (PTLC) was performed on silica gel 60 Å F254 plates (20 x 20 cm, 1000 μm, SiliaPlate from Silicycle, #TLG-R10011B-341) and visualized with UV light (254 nm). Celite® 545 (Product #CX0574-3) was purchased from Millipore Sigma.

General Analytical Information: All reported compounds were characterized by ^{1}H NMR spectroscopy. ^{1}H NMR spectra were obtained on a Bruker NEO400, Bruker US400, or Bruker Ascend 400 spectrometers. ^{1}H NMR data is reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, br s = broad singlet, d =doublet, t = triplet, q = quartet, quin = quintet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, dq = doublet of quartets, qd = quartet of doublets, m = multiplet), coupling constant (Hz), and integration. All ^{1}H NMR signals are reported as chemical shifts (δ ppm) relative to residual $CHCl_3$ at 7.26 ppm or $(CH_3)_2SO$ at 2.50 ppm.[1] Thin-layer chromatography analysis was performed on silica gel 60 Å F254 plates (250 µm, SiliaPlate from Silicycle, #TLG-R10014B323) and interpreted using UV light (254 nm) or $KMnO_4$ stain. Preparatory thin-layer chromatography purification was performed on silica gel 60 Å (1000 µm, Silicycle, #TLG-R10011B-341) and interpreted using UV light (254 nm).

A3.2 Optimization of Reductive Coupling of Cyanoarenes to Carbonyls.

(a) Evaluation of changes in optimal base, solvent, and base additive for selective reductive coupling of 4-cyanoarene and 4-methoxybenzaldehyde.

Preliminary experiments varying base and solvent indicated that CsF in DME could promote the selective reductive coupling of 4-cyanoarene and 4-methoxybenzaldehyde using hexamethyldisilane. The optimized conditions are provided in Table SA3.1 below in comparison to specific changes of reagents or conditions used to inform readers of these effects. These optimization studies were conducted in a N_2 filled glovebox on a 0.25 mmol scale, however a Schlenk line protocol for 1.0 mmol scale reactions is described below.

General procedure for condition variation: Inside a N_2 filled glovebox, an oven-dried 4 mL vial (KIMBLE®, #60910-1) was charged with a magnetic stir bar, 4-cyanopyridine (31.2 mg, 0.3 mmol, 1.2 equiv), 4-methoxybenzaldehyde (34 mg, 0.25 mmol, 1.0 equiv), 18-crown-6 (26.4 mg,

0.75 mmol, 3.0 equiv), base (0.75 mmol, 3.0 equiv), anhydrous solvent (0.25 M, 1 mL), and hexamethyldisilane reagent (102.5 μL, 0.5 mmol, 2.0 equiv) in successive order. The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, B7995-13), removed from the glovebox, and placed into an aluminum reaction block preheated to rt or 60°C. The reaction solution was stirred for 20 h and then dibromomethane and 1,2-difluorobenzene standards were measured into the reaction solution. For each experiment, the mass of 1,3,5-trimethoxybenzene and 1,2-difluorobenzene standards were measured into the reaction solution. A small aliquot was removed and injected into an NMR tube and constituted in $CDCl_3$ (0.5 mL). ^1H NMR spectroscopy (400 MHz, ($CDCl_3$) was used to determine the yield of 4-((4-methoxyphenyl)((trimethylsilyl)oxy)methyl)pyridine. The H signal of dibromomethane at 4.92 ppm (s, 2H) was integrated against the aromatic H signal of 4-((4-methoxyphenyl)((trimethylsilyl)oxy)methyl)pyridine at 5.46 (s, 1H) to determine the yield. The results are summarized in Table SA1.1 below in addition to representative crude ^1H spectra to demonstrate this analysis.

Table SA3.1. Condition variation for selective reductive coupling of 4-cyanoarene and 4-methoxybenzaldehyde.

Entry	Variation from Standard Conditions	Product (%)
1	none	40
2	DMSO instead of DME	20
3	DMF instead of DME	28
4	THF instead of DME	16
5	rt instead of 60 °C	12
6	no 18-crown-6	24
7	KF instead of CsF	0
8	KOMe instead of CsF	0

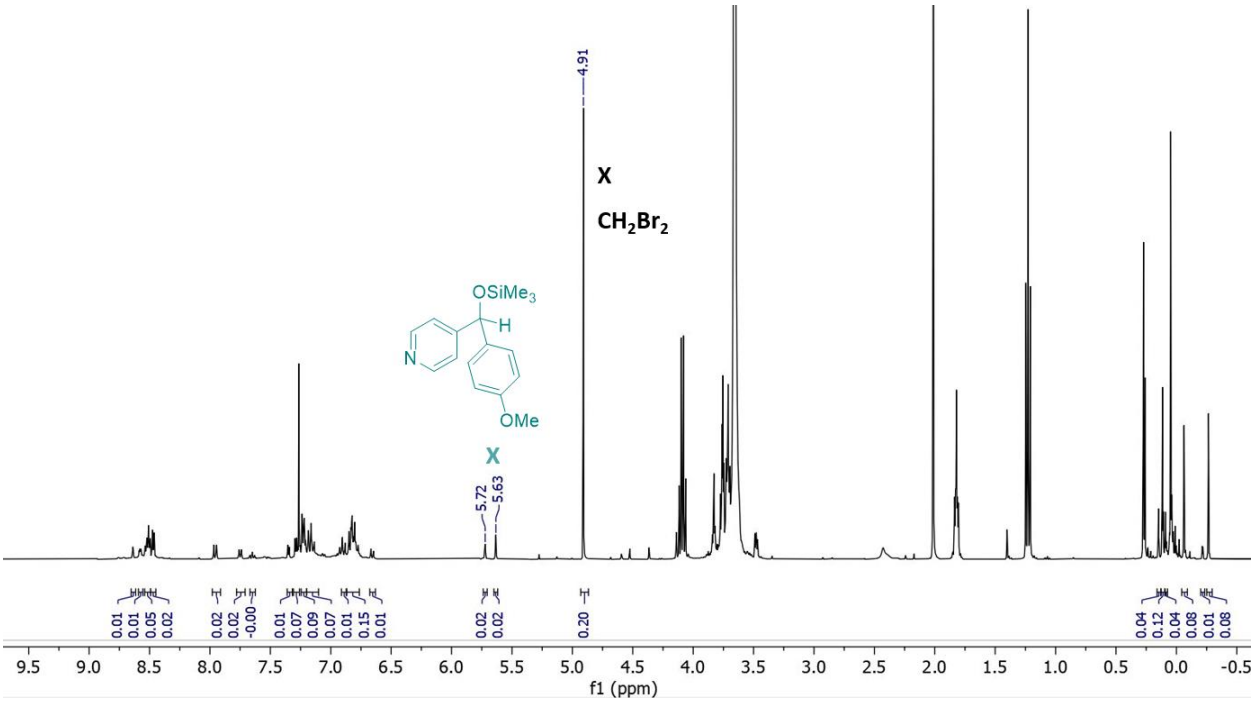


Figure SA3.1. ^{1}H NMR spectral window of the crude reaction solution of reaction from the THF reaction vial above (entry 4). Dibromomethane internal standard (7 µL, 0.1 mmol, signal at 4.92 ppm calibrated to 0.20 for 0.25 mmol scale reaction) was used to determine the yield of 4-((4-methoxyphenyl)((trimethylsilyl)oxy)methyl)pyridine, (16% yield).

A3.3 General Procedure for Reductive Coupling of Cyanoarenes to Carbonyls.

Note: The reaction optimization studies were conducted inside a N_2 filled glovebox, while the general procedure for 1.0 mmol scale isolation reactions was developed using a standard manifold Schlenk line.

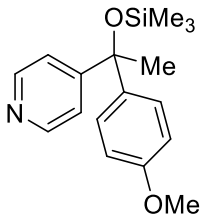
General Schlenk line procedure for Reductive Coupling of Cyanoarenes to Carbonyls.

Open to air, an 8 mL oven-dried vial was charged with a magnetic stir bar along with trifluoromethylarene (1.0 mmol, 1.0 equiv), CsF (151.9 mg, 1.0 mmol, 1.0 equiv), 18-crown-6, if indicated (792.6 mg, 3.0 mmol, 3.0 equiv) and formamide (1.5 mmol, 1.5 equiv). The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1B) lined with a PTFE septum (Thermo Fisher Scientific, B7995-15), evacuated and backfilled three times with N_2, and left under positive pressure of N_2 using a needle connected to a manifold Schlenk line. Anhydrous DMPU (4.0 mL, 0.25 M) was then added to the 8 mL vial *via* syringe. Hexamethyldisilane (615 μL, 3.0 equiv, 3.0 mmol) was then added to the vial *via* syringe. The reaction vial cap and septum were then wrapped in parafilm (Thermo Fisher Scientific, #C4015-1B) and electrical tape, and an N_2 balloon was inserted through the septum to maintain positive N_2 pressure. The vial was then placed in a preheated heating block at rt or 60 °C for the allotted time with stirring. The reaction solution was allowed to cool to rt and one of the following isolation procedures was followed.

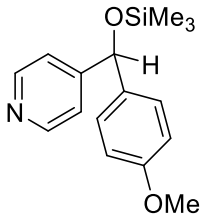
Isolation Procedure I (PTLC – 0.25 mmol scale): Upon cooling to room temperature, the mixture was poured into a 125 mL separatory funnel containing water (10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried with anhydrous Na_2SO_4. The Na_2SO_4 was filtered off and the solution was concentrated *in vacuo* and purified *via* PTLC.

A3.4. Characterization Data of Reductive Coupling of Cyanoarenes to Carbonyl Products

(a) Products isolated using procedure I



4-(1-(4-methoxyphenyl)-1-((trimethylsilyl)oxy)ethyl)pyridine. The title compound was prepared according to the general procedure using 4-cyanopyridine (31.2 mg, 0.3 mmol, 1.2 equiv), 1-(4-methoxyphenyl)ethan-1-one (37.5 mg, 0.25 mmol, 1.0 equiv) CsF (113.9 mg, 0.75 mmol, 3.0 equiv), anhydrous DME (1 mL, 0.25 M) and hexamethyldisilane (102.5 µL, 0.5 mmol, 2.0 equiv) at 60 °C. The product was purified *via* Isolation Procedure I ((50:50) EtOAc/Hexanes eluent) to afford the title compound as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 9.0 Hz, 2H), 7.19 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 3.78 (s, 3H), 1.25 (s, 6H).

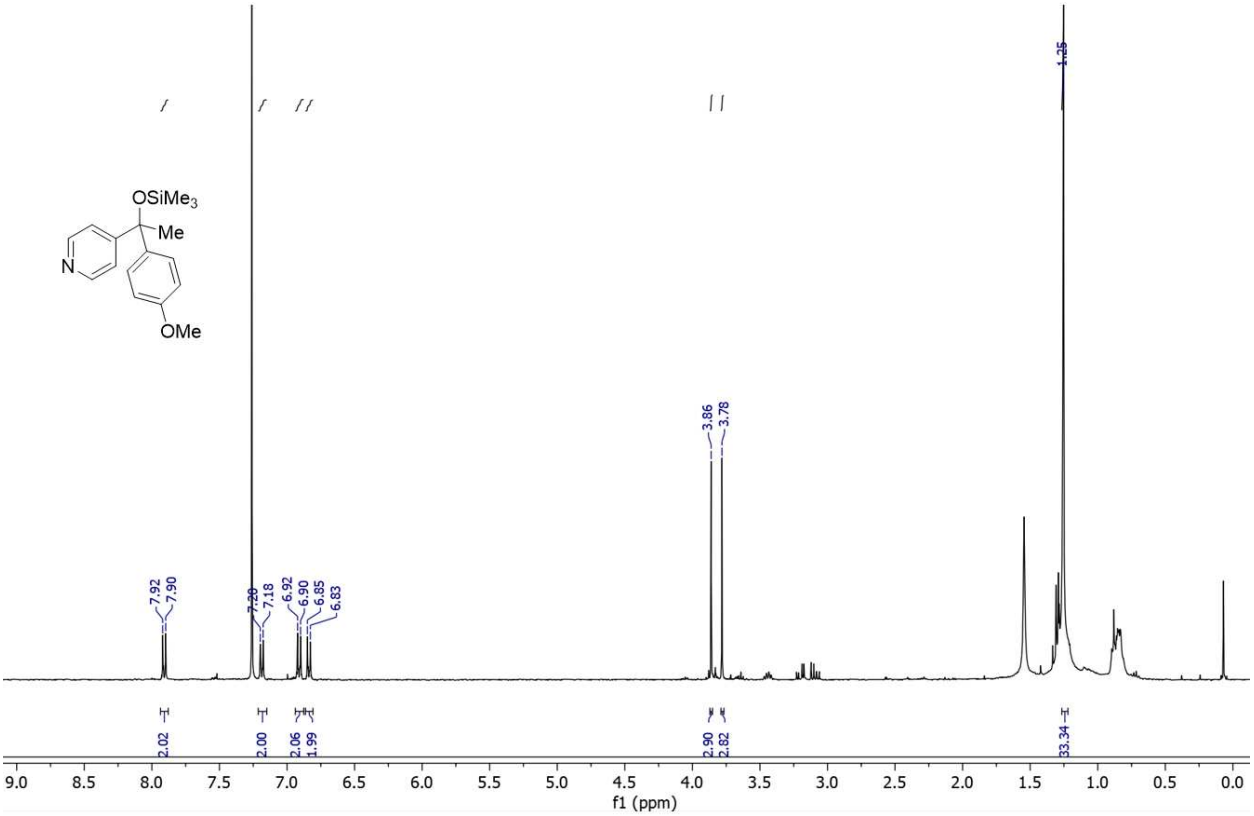


4-((4-methoxyphenyl)((trimethylsilyl)oxy)methyl)pyridine. The title compound was prepared according to the general procedure using 4-cyanopyridine (31.2 mg, 0.3 mmol, 1.2 equiv), 4-methoxybenzaldehyde (34.0 mg, 0.25 mmol, 1.0 equiv) CsF (113.9 mg, 0.75 mmol, 3.0 equiv), anhydrous DME (1 mL, 0.25 M) and hexamethyldisilane (102.5 µL, 0.5 mmol, 2.0 equiv) at 60 °C. The product was purified *via* Isolation Procedure I ((80:20) EtOAc/Hexanes eluent) to afford the title compound as a white solid. **^{1}H NMR** (400 MHz, DMSO) δ 8.46 (d, J = 6.0 Hz, 2H), 7.34 (d, J = 6.1 Hz, 2H), 7.28 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 5.99 (d, J = 4.1 Hz, 1H), 5.66 (d, J = 4.1 Hz, 1H) overlap of –OMe methyl H signals..

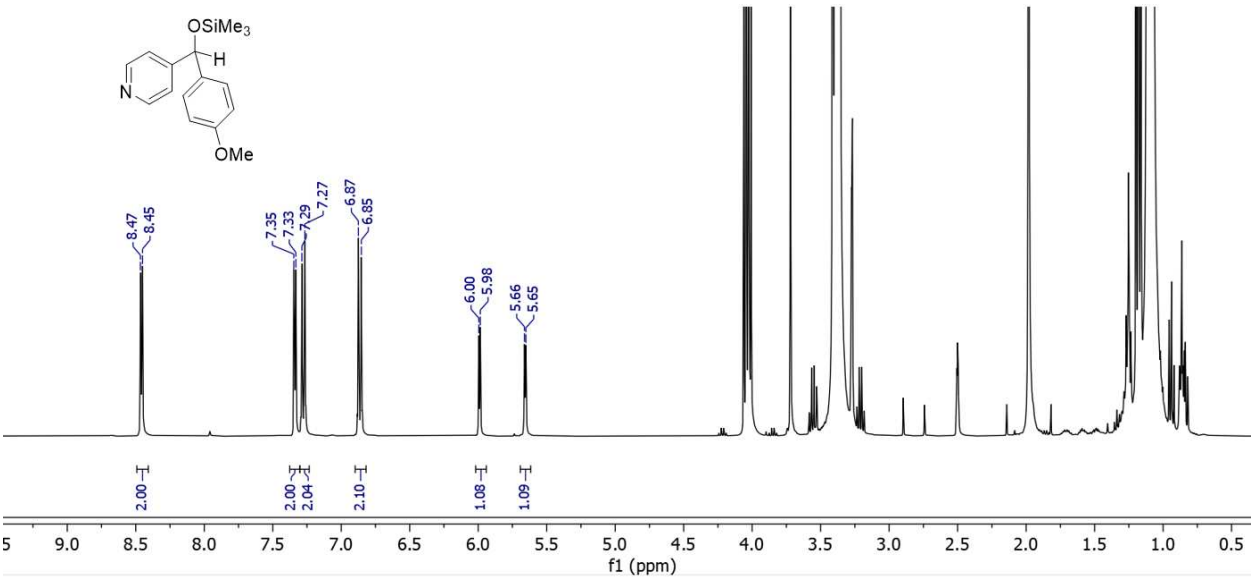
A3.5 References

[1] Fulmer, G. R.; Miller, A. J.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J.; Goldberg, K. I. Organometallics 2010, 29, 2176–2179.

A3.6. NMR spectra of Isolated Substrates

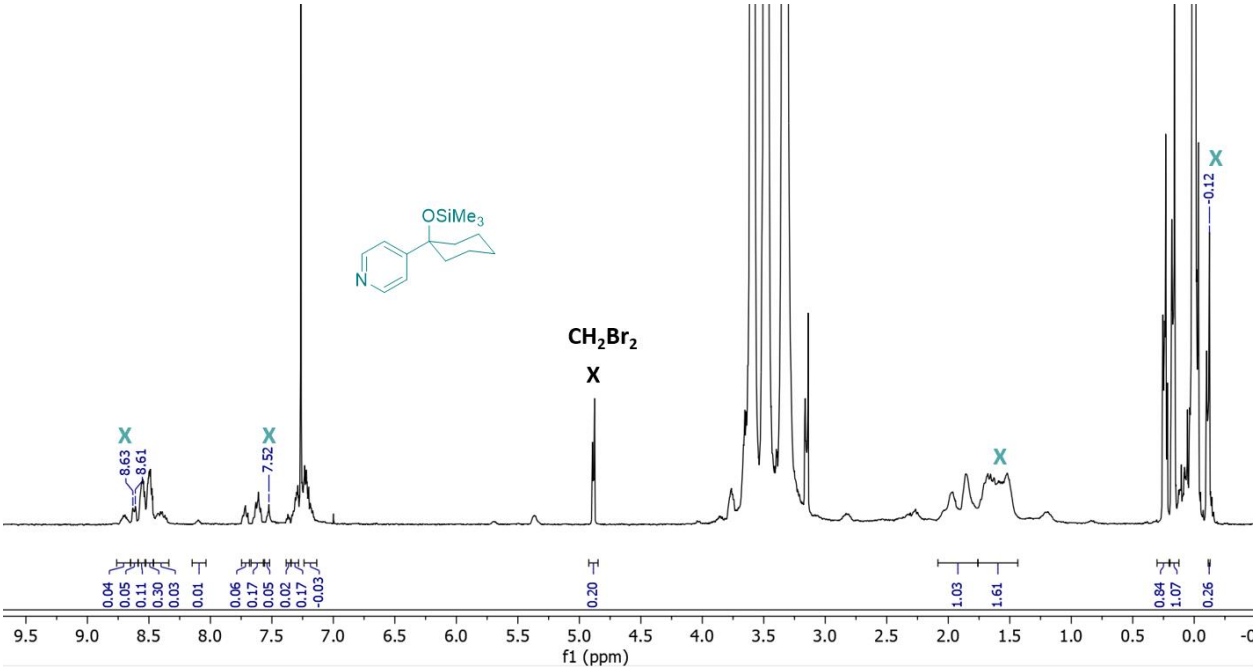


^{1}H NMR spectrum (400 MHz, $CDCl_3$)

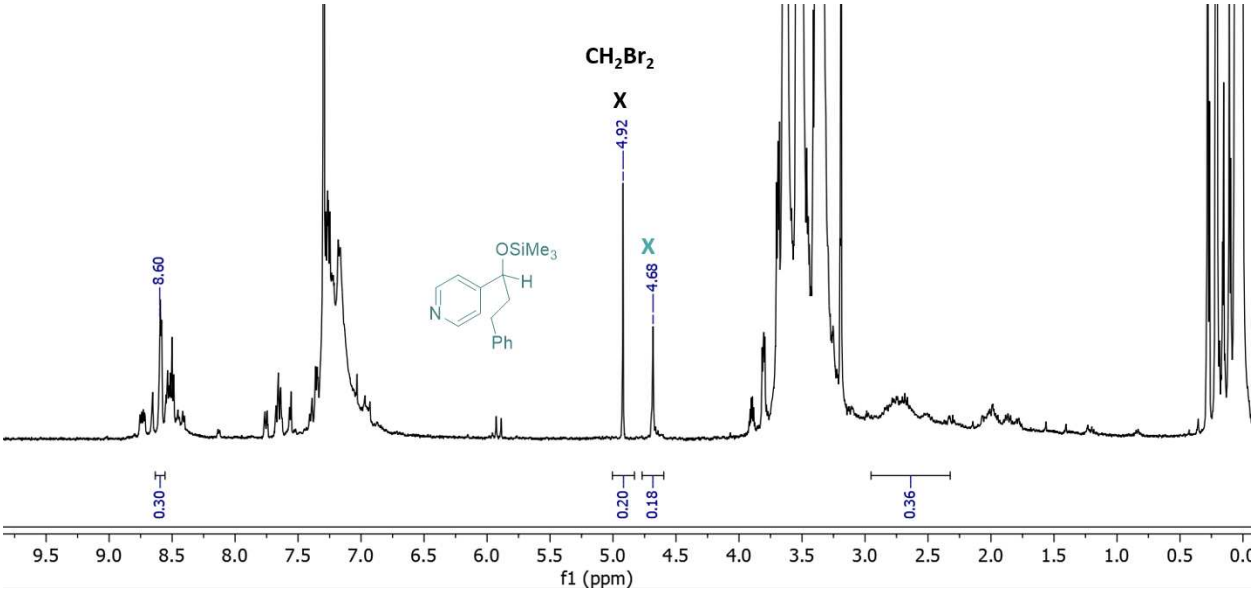


^{1}H NMR spectrum (400 MHz, $CDCl_3$)

A3.7 NMR Spectra of Crude Reaction Mixtures for Unisolated Products



^{1}H NMR spectrum (400 MHz, $CDCl_3$)



^{1}H NMR spectrum (400 MHz, $CDCl_3$)

APPENDIX FOUR

LEWIS BASE PROMOTED MONOSELECTIVE REDUCTIVE COUPLING OF CARBONYLS: EXPERIMENTAL

A4.1 General Information:

All results are preliminary and were analyzed by ^1H spectroscopy. This appendix is intended to provide experimental details and supporting information for the material discussed in Chapter 2.

General Reagent Information: All reactions were performed under a nitrogen (N_2) atmosphere unless otherwise noted. Hexamethyldisilane (Me_6Si_2, CombiBlocks catalog #QB-7675) and 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6, Chem-Impex catalog #03901) were purchased from the indicated vendors and used as received. Cesium fluoride (CsF, Acros Organics catalog # 010019.88) was purchased as a 99.9% pure powder pure solid and used as received. Me_6Si_2, CsF and 18-crown-6 were stored at room temperature (rt) inside a N_2 filled glovebox and used immediately if brought outside the glovebox. 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrmidinone (DMPU, TCI catalog # D2014) and methylsulfoxide (DMSO, Acros Organics catalog # 042780.M1) was purchased and used as received. All other solvents and reagents were purchased from MilliporeSigma, Combi-Blocks, TCI, Acros Organics, Matrix Scientific, Alfa Aesar, or Synthonix and used as received unless otherwise noted. Flash chromatography was performed on 40-63 μm silica gel (SiliaFlash® F60 from Silicycle). Preparative thin-layer chromatography (PTLC) was performed on silica gel 60 Å F254 plates (20 x 20 cm, 1000 μm, SiliaPlate from Silicycle, #TLG-R10011B-341) and visualized with UV light (254 nm). Celite® 545 (Product #CX0574-3) was purchased from Millipore Sigma.

General Analytical Information: All reported compounds were characterized by ^{1}H NMR spectroscopy. ^{1}H NMR spectra were obtained on a Bruker NEO400, Bruker US400, or Bruker Ascend 400 spectrometers. ^{1}H NMR data is reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, br s = broad singlet, d =doublet, t = triplet, q = quartet, quin = quintet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, dq = doublet of quartets, qd = quartet of doublets, m = multiplet), coupling constant (Hz), and integration. All ^{1}H NMR signals are reported as chemical shifts (δ ppm) relative to residual $CHCl_3$ at 7.26 ppm or $(CH_3)_2SO$ at 2.50 ppm.[1] Thin-layer chromatography analysis was performed on silica gel 60 Å F254 plates (250 µm, SiliaPlate from Silicycle, #TLG-R10014B323) and interpreted using UV light (254 nm) or $KMnO_4$ stain. Preparatory thin-layer chromatography purification was performed on silica gel 60 Å (1000 µm, Silicycle, #TLG-R10011B-341) and interpreted using UV light (254 nm).

A4.2 Optimization of Selective Reductive Coupling of Carbonyls

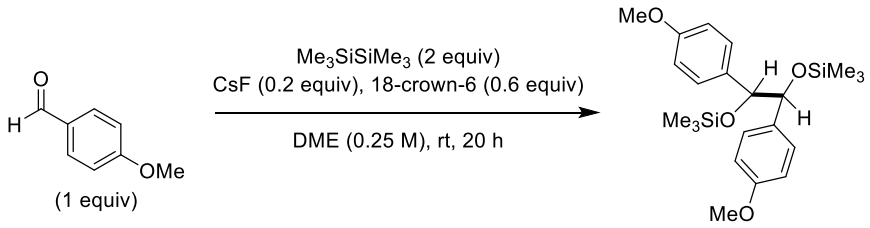
(a) Evaluation of changes in optimal base, solvent, disilane species and base additive for selective reduction of 4-methoxybenzaldehyde.

Preliminary experiments varying base and solvent indicated that CsF in DME could promote the selective reductive coupling of 4-methoxybenzaldehyde using hexamethyldisilane. The optimized conditions are provided in Table SA4.1 below in comparison to specific changes of reagents or conditions used to inform readers of these effects. These optimization studies were conducted in a N_2 filled glovebox on a 0.25 mmol scale, however a Schlenk line protocol for 1.0 mmol scale reactions is described below.

General procedure for condition variation: Inside a N_2 filled glovebox, an oven-dried 4 mL vial (KIMBLE®, #60910-1) was charged with a magnetic stir bar, 4-methoxybenzaldehyde (30.4 µL,

0.25 mmol, 1.0 equiv), 18-crown-6 (39.6 mg, 0.15 mmol, 0.6 equiv), base (0.05 mmol, 0.2 equiv), anhydrous solvent (0.25 M, 1 mL), and hexamethyldisilane (102.5 μL, 0.5 mmol, 2.0 equiv) in successive order. The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, B7995-13), removed from the glovebox, and placed into an aluminum reaction block preheated to rt or 60°C. The reaction solution was stirred for 20 h and then 1,3,5-trimethoxybenzene standard was measured into the reaction solution. For each experiment, the mass of 1,3,5-trimethoxybenzene standard was measured into the reaction solution. A small aliquot was removed and injected into an NMR tube and constituted in $CDCl_3$ (0.5 mL). ^1H NMR spectroscopy (400 MHz, ($CDCl_3$) was used to determine the yield of 4,5-bis(4-methoxyphenyl)-2,2,7,7-tetramethyl-3,6-dioxa-2,7-disilaoctane. The aromatic H signal of 1,3,5-trimethoxybenzene at 6.09 ppm (s, 3H) was integrated against the aromatic H signal of 4,5-bis(4-methoxyphenyl)-2,2,7,7-tetramethyl-3,6-dioxa-2,7-disilaoctane at 4.57 (s, 2H) and 4.41 (s, 2H) to determine the yield. The results are summarized in Table SA4.1 below in addition to representative crude ^1H NMR spectra to demonstrate this analysis.

Table SA4.1. Condition variation for reductive coupling of 4-methoxybenzaldehyde.



Entry	Variation from Standard Conditions	Product (%)
1	none	96
2	DMPU instead of DME	60
3	DMF instead of DME	52
4	THF instead of DME	80
5	60 °C instead of rt	40
6	TBAF instead of CsF	36
7	KF instead of CsF	0
8	no 18-crown-6	0
9	KOMe instead of CsF	60
10	KO-*t*-Bu instead of CsF	20
11	KOH instead of CsF	68
12	TBAB instead of 18-crown-6	12
13	TBAB + KOMe instead of 18-crown-6 + CsF	88

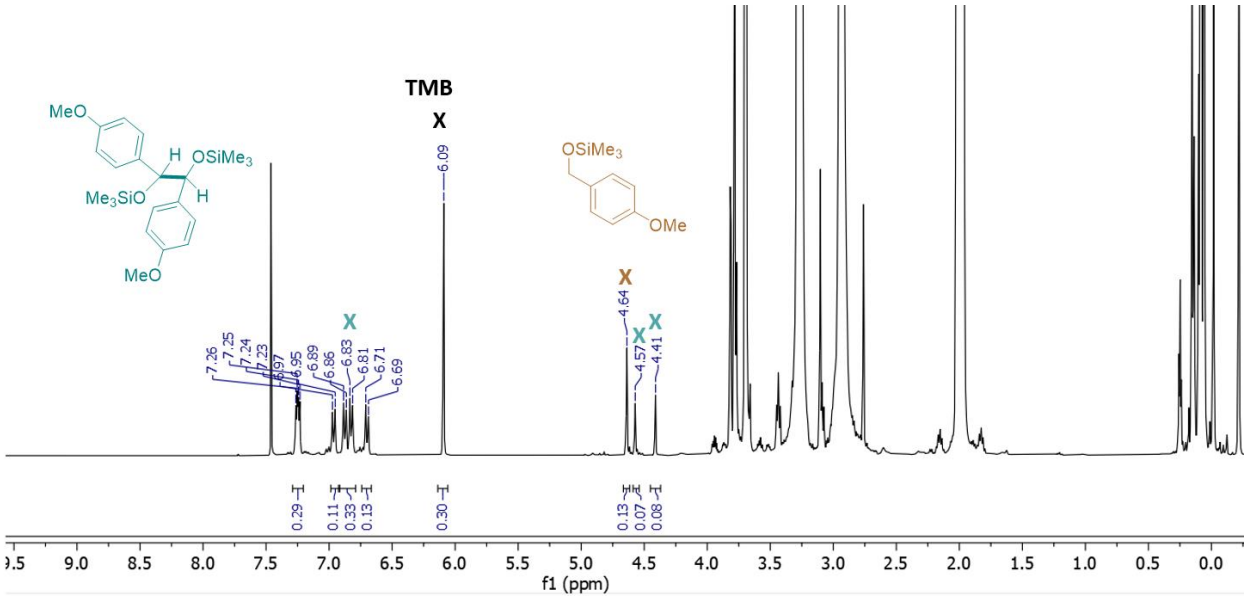


Figure SA4.1. [1]H NMR spectral window of the crude reaction solution of reaction from the 30 min reaction time vial above (entry 3). 1,3,5-Trimethoxybenzene internal standard (16.8 mg, 0.1

mmol, signal at 6.09 ppm calibrated to 0.30 for 0.25 mmol scale reaction) was used to determine the yield of 4,5-bis(4-methoxyphenyl)-2,2,7,7-tetramethyl-3,6-dioxa-2,7-disilaoctane (60% yield) and ((4-methoxybenzyl)oxy)trimethylsilane (26% yield).

A4.3 General Procedure for Reductive Coupling of Carbonyls

Note: The reaction optimization studies were conducted inside a N_2 filled glovebox, while the general procedure for 1.0 mmol scale isolation reactions was developed using a standard manifold Schlenk line. The crude 1H NMR spectroscopy yields observed during optimization are comparable to those for the 1.0 mmol isolation procedure.

General Schlenk line procedure for Reductive Coupling of Carbonyls

Open to air, an 8 mL oven-dried vial was charged with a magnetic stir bar along with carbonyl (1.0 mmol, 1.0 equiv), CsF (30.4 mg, 0.2 mmol, 0.2 equiv), and 18-crown-6, if indicated (158.5 mg, 0.6 mmol, 0.6 equiv). The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1B) lined with a PTFE septum (Thermo Fisher Scientific, B7995-15), evacuated and backfilled three times with N_2, and left under positive pressure of N_2 using a needle connected to a manifold Schlenk line. Anhydrous DMF (4.0 mL, 0.25 M) was then added to the 8 mL vial *via* syringe. Hexamethyldisilane (409.5 μL, 2.0 equiv, 2.0 mmol) was then added to the vial *via* syringe. The reaction vial cap and septum were then wrapped in parafilm (Thermo Fisher Scientific, #C4015-1B) and electrical tape, and an N_2 balloon was inserted through the septum to maintain positive N_2 pressure. The vial was then placed in a preheated heating block at rt and the following isolation procedure was followed.

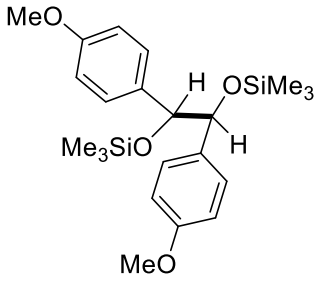
Isolation Procedure I: Upon cooling to room temperature, the mixture was poured into a 250 mL separatory funnel containing water (40 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine (20 mL) and dried

with anhydrous Na_2SO_4. The Na_2SO_4 was filtered off and the solution was concentrated *in vacuo* and purified *via* flash chromatography on silica gel.

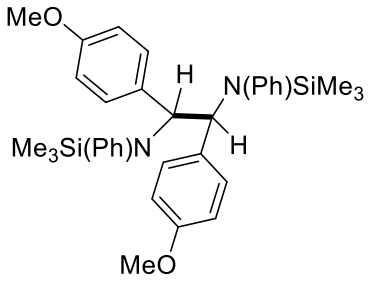
Isolation Procedure II (PTLC – 0.25 mmol scale): Upon cooling to room temperature, the mixture was poured into a 125 mL separatory funnel containing water (10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried with anhydrous Na_2SO_4. The Na_2SO_4 was filtered off and the solution was concentrated *in vacuo* and purified *via* PTLC.

A4.4. Characterization Data of Reductive Coupling of Carbonyls Products

(a) Products isolated using procedure I

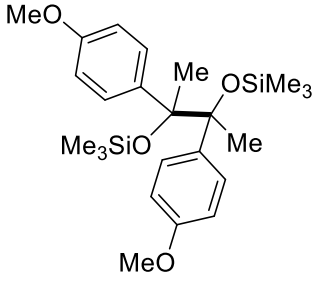


4,5-bis(4-methoxyphenyl)-2,2,7,7-tetramethyl-3,6-dioxa-2,7-disilaoctane. The title compound was prepared according to the general procedure using 4-methoxybenzaldehyde (365 μL, 3.0 mmol, 1.0 equiv), CsF (91.2 mg, 0.6 mmol, 0.2 equiv), 18-crown-6 (475.6 mg, 1.8 mmol, 0.6 equiv), anhydrous DME (12 mL, 0.25 M) and hexamethyldisilane (1.3 mL, 6.0 mmol, 2.0 equiv) at rt. The product was purified *via* Isolation Procedure I ((15:85) EtOAc/Hexanes eluent) to afford the title compound as a white solid (470.8 mg, 2.25 mmol, 75% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (d, J = 8.8 Hz, 4H), 7.21 (d, J = 8.8 Hz, 4H), 7.08 (d, J = 8.8 Hz, 4H), 6.95 (d, J = 8.9 Hz, 4H), 4.82 (s, 2H), 4.66 (s, 2H), 4.07 (s, 6H), 4.02 (s, 6H), 0.23 (s, 18H), 0.03 (s, 18H).



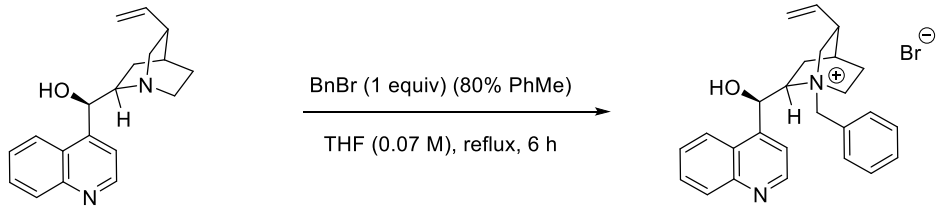
1,2-bis(4-methoxyphenyl)-*N*^{1},*N*^{2}-diphenyl-*N*^{1},*N*^{2}-bis(trimethylsilyl)ethane-1,2-diamine. The title compound was prepared according to the general procedure using (E)-1-(4-methoxyphenyl)-N-phenylmethanimine (211.3 mg, 1.0 mmol, 1.0 equiv), CsF (30.4 mg, 0.2 mmol, 0.2 equiv), anhydrous DME (4 mL, 0.25 M) and hexamethyldisilane (409.5 µL, 2.0 mmol, 2.0 equiv) at rt. The product was purified *via* Isolation Procedure I ((20:80) EtOAc/Hexanes eluent) to afford the title compound. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.04 – 6.88 (m, 12H), 6.80 (d, J = 8.9 Hz, 4H), 6.67 (dd, J = 8.8, 5.1 Hz, 8H), 6.57 (td, J = 7.3, 3.9 Hz, 4H), 6.43 (d, J = 8.8 Hz, 8H), 4.79 (s, 2H), 4.43 (s, 2H), 3.68 (s, 6H), 3.66 (s, 6H).

(b) Products isolated using procedure II

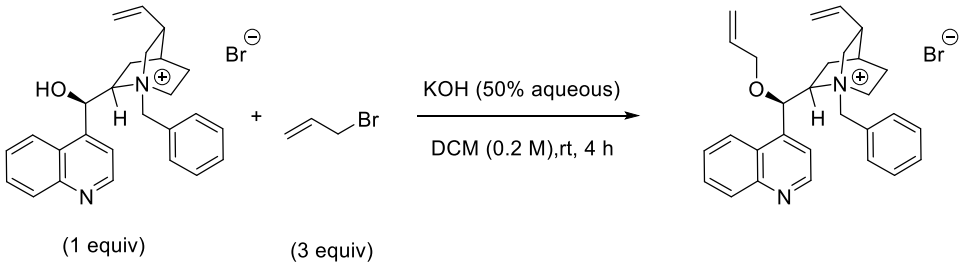


4,5-bis(4-methoxyphenyl)-2,2,4,5,7,7-hexamethyl-3,6-dioxa-2,7-disilaoctane. The title compound was prepared according to the general procedure using 1-(4-methoxyphenyl)ethan-1-one (150.2 mg, 1.0 mmol, 1.0 equiv), CsF (30.4 mg, 0.2 mmol, 0.2 equiv), anhydrous DME (4 mL, 0.25 M) and hexamethyldisilane (409.5 µL, 2.0 mmol, 2.0 equiv) at rt. **^{1}H NMR** (400 MHz, $CDCl_3$) (dl product) δ 7.39 (d, J = 8.8 Hz, 4H), 6.83 (d, J = 8.9 Hz, 4H), 3.82 (s, 6H), 1.35 (s, 6H), -0.12 (s, 18H). **^{1}H NMR** (400 MHz, $CDCl_3$) (meso product) δ 6.77 (d, J = 8.1 Hz, 4H), 6.57 (d, J = 9.1 Hz, 4H), 3.75 (s, 6H),1.68 (s, 6H), 0.04 (s, 18H).

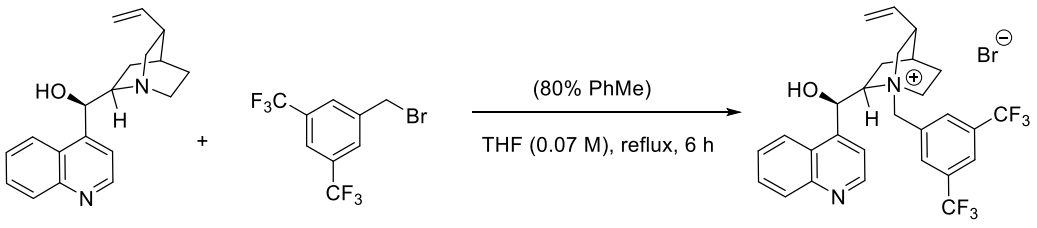
A4.5 Synthesis of cinchonium salts[2,3]



Procedure: An oven-dried round bottom flask (250 mL) was charged with a magnetic stir bar, cinchonine(1.47 g, 5.0 mmol, 1.0 equiv) and anhydrous THF (75 mL, 0.07 M). The flask was sealed with a septum and was sparged with N_2 while stirring vigorously for 10 minutes. Benzyl bromide in PhMe (1 equiv) was then added to the flask *via* syringe and the reaction solution was stirred at reflux for 6 hours. The flask was cooled to rt and then poured over Et_2O (75 mL) and allowed to sitr for an additional 30 minutes. The reaction was then filtered through a frit where the precipitate was washed with Et_2O (50 mL) and dried before use. The title compound was isolated as a white solid (2.08 g, 4.45 mmol, 89% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.85 (d, J = 4.5 Hz, 1H), 8.25 (d, J = 8.1 Hz, 1H), 7.89 (d, J = 4.5 Hz, 1H), 7.62 (t, J = 7.0 Hz, 3H), 7.21 – 7.04 (m, 5H), 6.73 (s, 1H), 6.50 (s, 1H), 6.05 (d, J = 11.8 Hz, 1H), 5.85 (ddd, J = 17.4, 10.5, 7.2 Hz, 1H), 5.44 (d, J = 11.8 Hz, 1H), 5.23 (d, J = 10.4 Hz, 1H), 5.17 (d, J = 17.1 Hz, 1H), 4.47 (t, J = 11.3 Hz, 1H), 4.09 (dt, J = 30.8, 10.7 Hz, 2H), 3.30 (t, J = 11.6 Hz, 1H), 2.76 (q, J = 10.1 Hz, 1H), 2.28 (q, J = 8.9 Hz, 1H), 2.20 – 2.03 (m, 1H), 1.89 – 1.66 (m, 3H), 0.86 – 0.78 (m, 0H), 0.78 – 0.70 (m, 1H).



Procedure: An oven-dried round bottom flask (50 mL) was charged with a magnetic stir bar, (1S,2R,4S,5R)-1-benzyl-2-((R)-hydroxy(quinolin-4-yl)methyl)-5-vinylquinuclidin-1-ium (0.5 g, 1.0 mmol, 1.0 equiv) and anhydrous DCM (5 mL, 0.2 M). The flask was sealed with a septum and was sparged with N_2 while stirring vigorously for 10 minutes. Allyl bromide (0.26 mL, 3 mmol, 3.0 equiv) was then added to the flask *via* syringe followed by KOH (50% aqueous) (0.5 mL) *via* syringe and the reaction solution was stirred at rt for 4 hours. The reaction was extracted with water (10 mL) and then the organic layer was washed with DCM (3 X 5 mL) and then dried over $MgSO_4$, filtered, and concentrated down to 2 mL. This was then added slowly to Et_2O (75 mL) and allowed to sitr for an additional 60 minutes. The reaction was then filtered through a frit where the precipitate was washed with Et_2O (50 mL) and dried before use. The title compound was isolated as an orange solid (273.8 mg, 0.54 mmol, 54% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.99 (d, J = 4.5 Hz, 1H), 8.17 (d, J = 8.5 Hz, 1H), 7.92 (s, 2H), 7.83 (t, J = 7.7 Hz, 1H), 7.52 (q, J = 2.8 Hz, 4H), 6.63 (d, J = 11.6 Hz, 1H), 6.20 (s, 1H), 6.10 (ddt, J = 16.8, 11.5, 5.8 Hz, 1H), 5.91 (ddd, J = 17.2, 10.4, 6.9 Hz, 1H), 5.44 (d, J = 4.7 Hz, 1H), 5.41 (s, 1H), 5.32 (d, J = 10.5 Hz, 1H), 5.23 (d, J = 17.2 Hz, 1H), 4.44 (d, J = 12.1 Hz, 1H), 4.28 (dd, J = 12.4, 5.2 Hz, 1H), 4.20 (t, J = 10.4 Hz, 1H), 3.96 (dd, J = 12.5, 6.6 Hz, 1H), 3.57 (t, J = 11.3 Hz, 1H), 3.48 (q, J = 7.0 Hz, 2H), 2.83 (d, J = 11.0 Hz, 1H), 2.53 – 2.44 (m, 1H), 1.99 (d, J = 13.3 Hz, 2H), 1.79 (s, 1H), 1.56 (s, 3H), 1.21 (t, J = 7.0 Hz, 4H).



Procedure: An oven-dried round bottom flask (250 mL) was charged with a magnetic stir bar, cinchonine (1.47 g, 5.0 mmol, 1.0 equiv) and anhydrous THF (75 mL, 0.07 M). The flask was sealed with a septum and was sparged with N_2 while stirring vigorously for 10 minutes. 1-(bromomethyl)-3,5-bis(trifluoromethyl)benzene in PhMe (1 equiv) was then added to the flask *via* syringe and the reaction solution was stirred at reflux for 6 hours. The flask was cooled to rt and then poured over Et_2O (75 mL) and allowed to sitr for an additional 30 minutes. The reaction was then filtered through a frit where the precipitate was washed with Et_2O (50 mL) and dried before use. The title compound was isolated as a white solid (2.52 g, 4.2 mmol, 84% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.80 (d, J = 4.5 Hz, 1H), 8.21 (d, J = 7.9 Hz, 3H), 7.80 (d, J = 4.5 Hz, 1H), 7.71 (s, 1H), 7.59 (d, J = 8.3 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 7.01 (t, J = 7.6 Hz, 1H), 6.67 (s, 1H), 6.57 – 6.44 (m, 2H), 5.81 (ddd, J = 17.4, 10.4, 7.2 Hz, 1H), 5.65 (dd, J = 23.6, 11.8 Hz, 1H), 5.24 (d, J = 10.4 Hz, 1H), 5.18 (d, J = 17.1 Hz, 2H), 4.56 (t, J = 10.7 Hz, 1H), 4.09 (dd, J = 23.8, 13.8 Hz, 2H), 3.75 – 3.67 (m, 3H), 3.02 (t, J = 11.5 Hz, 1H), 2.54 (q, J = 9.9 Hz, 1H), 2.31 (q, J = 8.9 Hz, 1H), 2.16 – 2.04 (m, 1H), 1.87 – 1.78 (m, 3H), 1.71 (s, 1H).

A4.6 Evaluation of Chiral Ammonium Salts as Phase-Transfer-Catalysts in Asymmetric Pinacol Coupling.

Preliminary experiments varying base and solvent indicated that $CsOH•H_2O$ in DMF could promote the selective reductive coupling of 4-methoxybenzaldehyde using hexamethyldisilane. These studies were conducted in a N_2 filled glovebox on a 0.25 mmol scale described below.

General procedure for asymmetric pinacol coupling: Inside a N_2 filled glovebox, an oven-dried 4 mL vial (KIMBLE®, #60910-1) was charged with a magnetic stir bar, 4-methoxybenzaldehyde (30.4 µL, 0.25 mmol, 1.0 equiv), chiral salt (0.05 mmol, 0.2 equiv), $CsOH•H_2O$ (0.05 mmol, 0.2 equiv), anhydrous DMF (0.25 M, 1 mL), and hexamethyldisilane (102.5 µL, 0.5 mmol, 2.0 equiv)

in successive order. The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, B7995-13), removed from the glovebox, and placed into an aluminum reaction block preheated to rt. The reaction solution was stirred for 20 h and then 1,3,5-trimethoxybenzene standard was measured into the reaction solution. For each experiment, the mass of 1,3,5-trimethoxybenzene standard was measured into the reaction solution. A small aliquot was removed and injected into an NMR tube and constituted in $CDCl_3$ (0.5 mL). ^1H NMR spectroscopy (400 MHz, ($CDCl_3$) was used to determine the yield of 4,5-bis(4-methoxyphenyl)-2,2,7,7-tetramethyl-3,6-dioxa-2,7-disilaoctane. The aromatic H signal of 1,3,5-trimethoxybenzene at 6.09 ppm (s, 3H) was integrated against the aromatic H signal of 4,5-bis(4-methoxyphenyl)-2,2,7,7-tetramethyl-3,6-dioxa-2,7-disilaoctane at 4.57 (s, 2H) and 4.41 (s, 2H) to determine the yield. The reaction was transferred into a 125 mL separatory funnel containing water (10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried with anhydrous $MgSO_4$. The $MgSO_4$ was filtered off and the solution was concentrated *in vacuo* and then NH_4F (1 M in MeOH, 3.0 equiv) was added to the residue and allowed to stir for 60 minutes where is was then concentrated. The resultant residue was washed with *iso*-propyl alcohol (2 mL) and reduced 3 times. The residue was then dissolved in HPLC-grade *iso*-propyl alcohol, then filtered through a celite plug into an HPLC vial for separation on a chiral HPLC column (Daicel Chiralpak OJ-3). Enantiomers were able to be separated using 90:10 Hexanes:IPA eluent with a 1 mL/min, however enantiomeric excess was less than 1% in all reactions screened.

A4.7 References

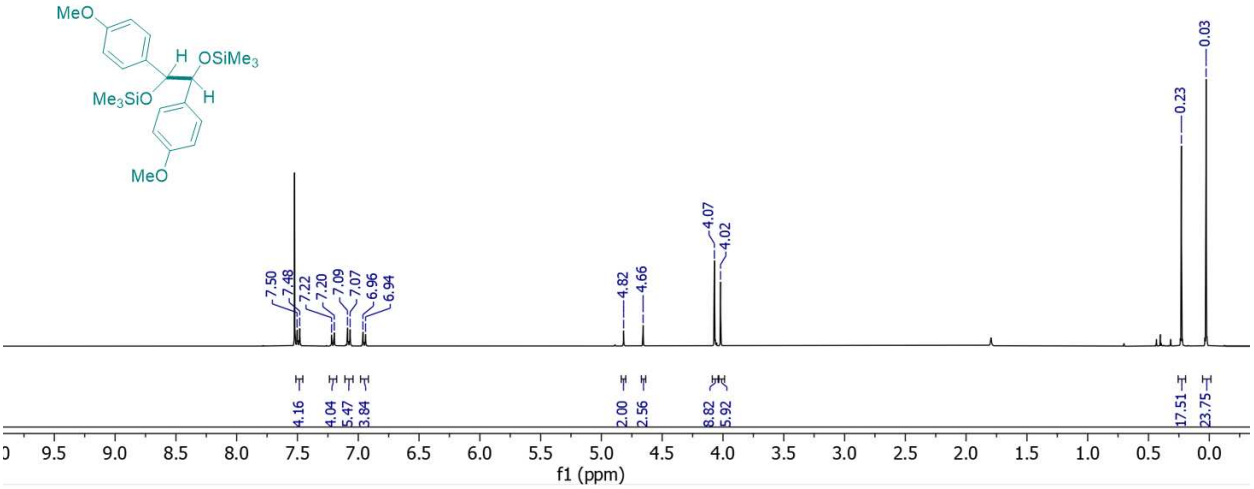
[1] Fulmer, G. R.; Miller, A. J.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.;

Bercaw, J.; Goldberg, K. I. Organometallics 2010, 29, 2176–2179.

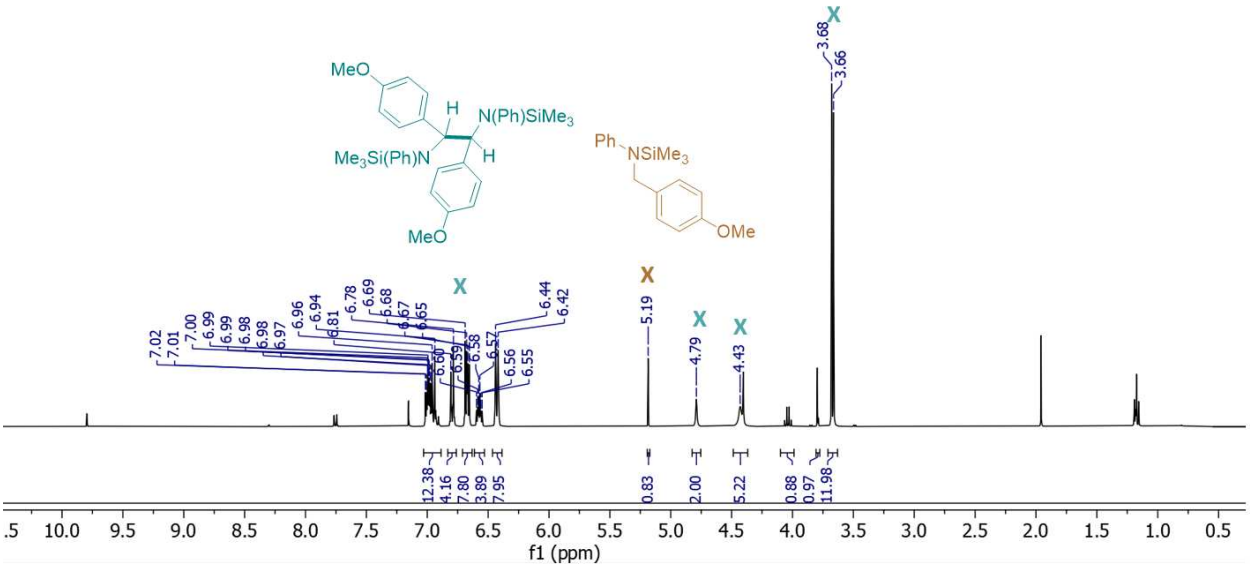
[2] V. A. Solovyeva, K. B. Vu, Z. Merican, R. Sougrat, V. O. Rodionov. *ACS Combinatorial Science* **2014**, *16, 10,* 513-517

[3] M. Lian, Z. Li, J. Du, Q. Meng, Z. Gao. *Eur. J. Org. Chem*. **2010,** *34,* 6525–6530

A4.8 NMR spectra of Isolated Compounds



^{1}H NMR spectrum (400 MHz, $CDCl_3$)



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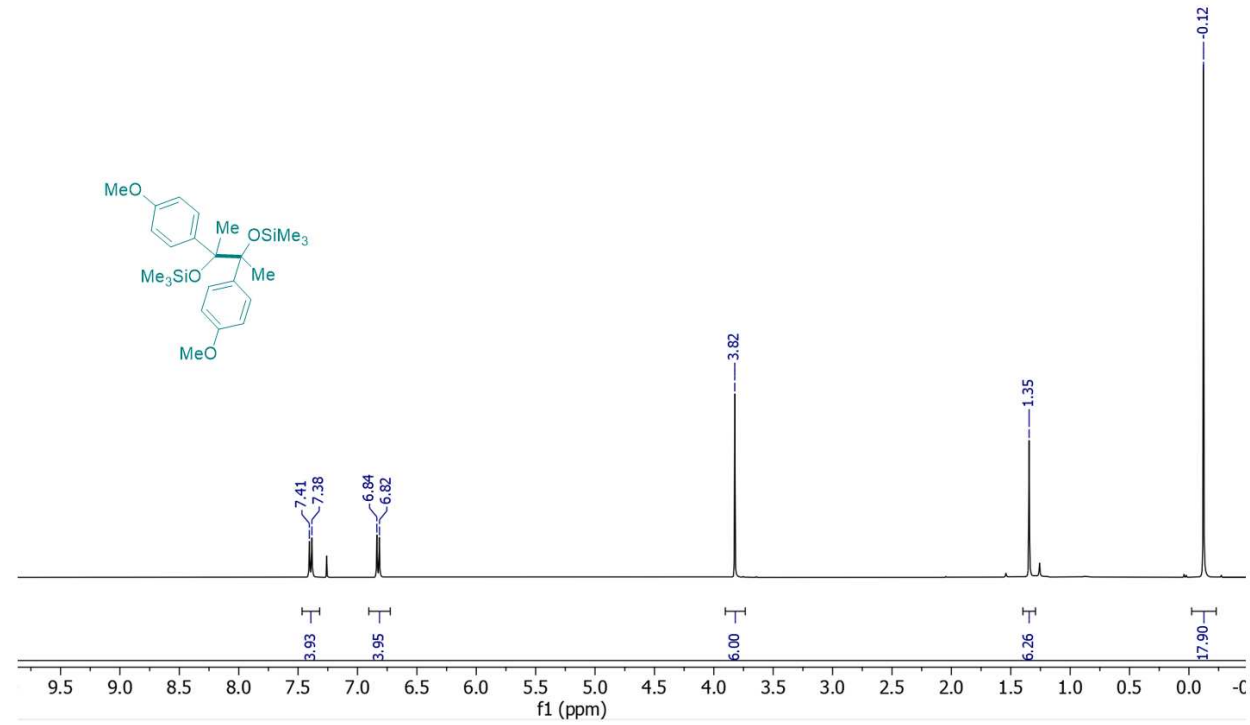

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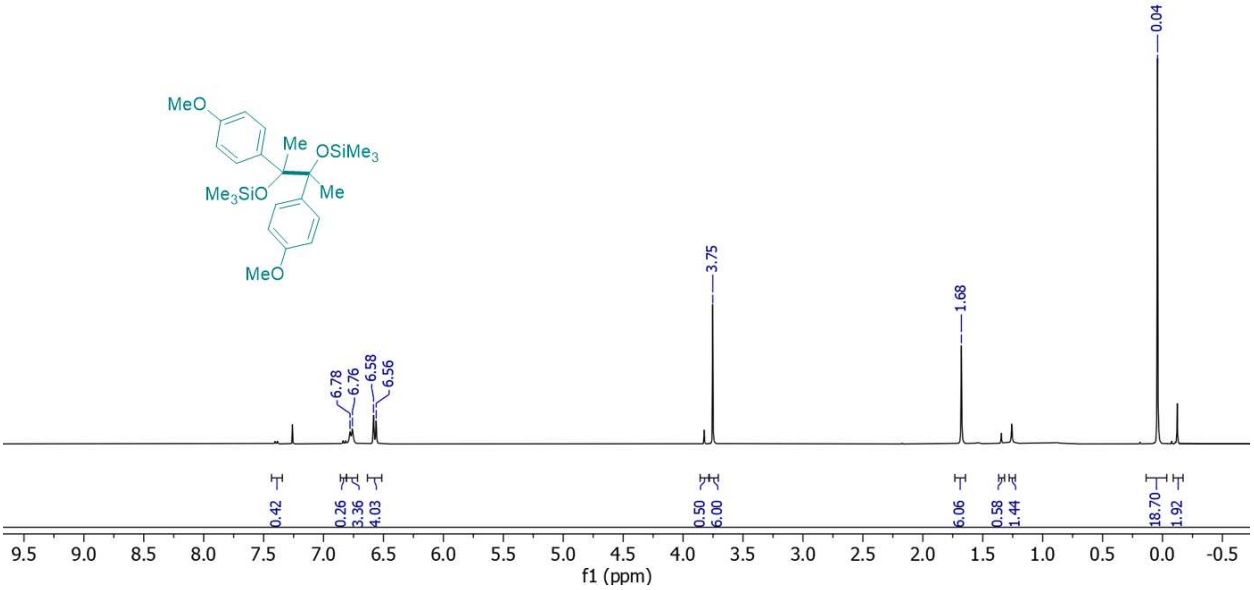
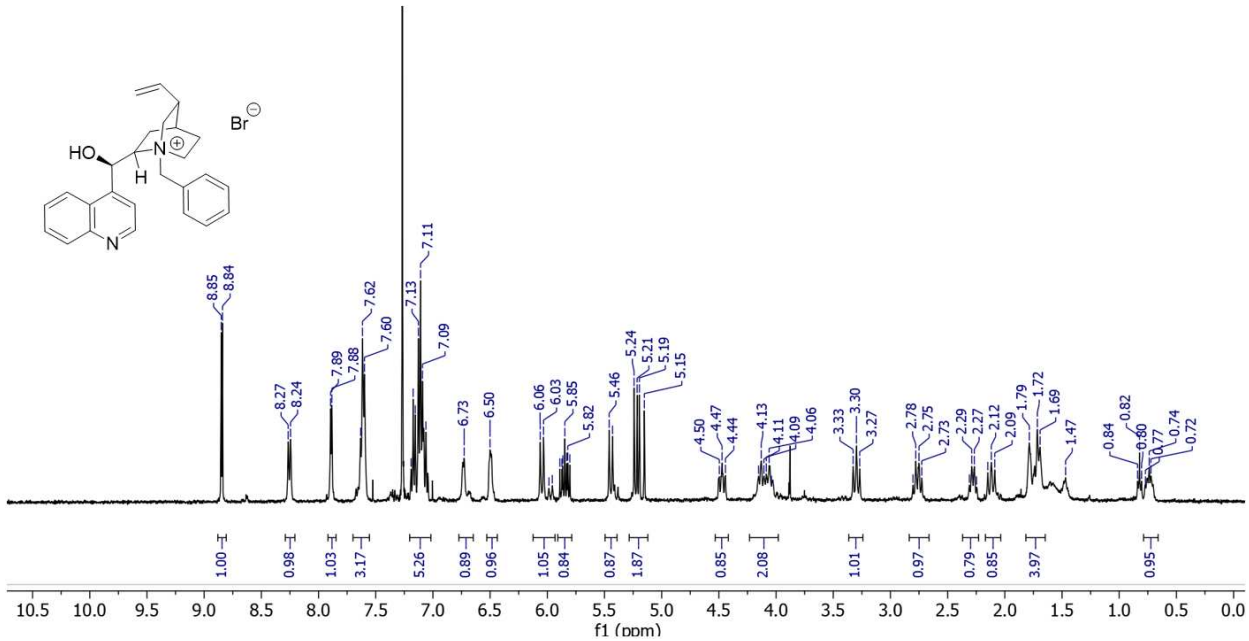
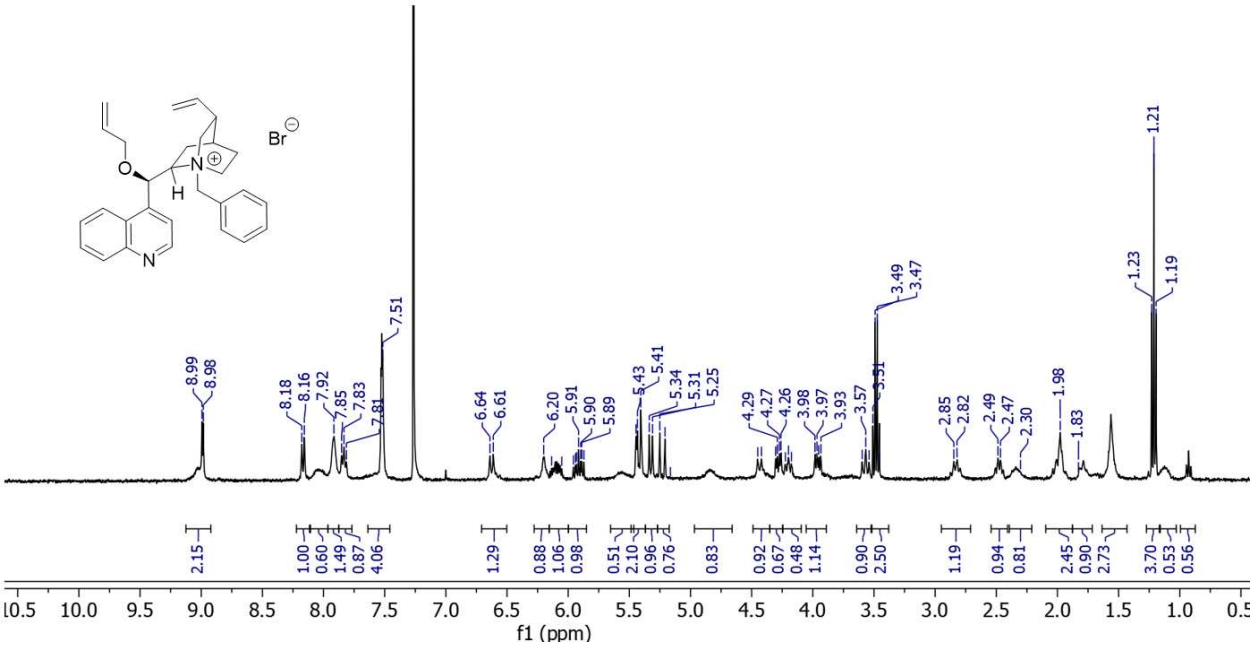


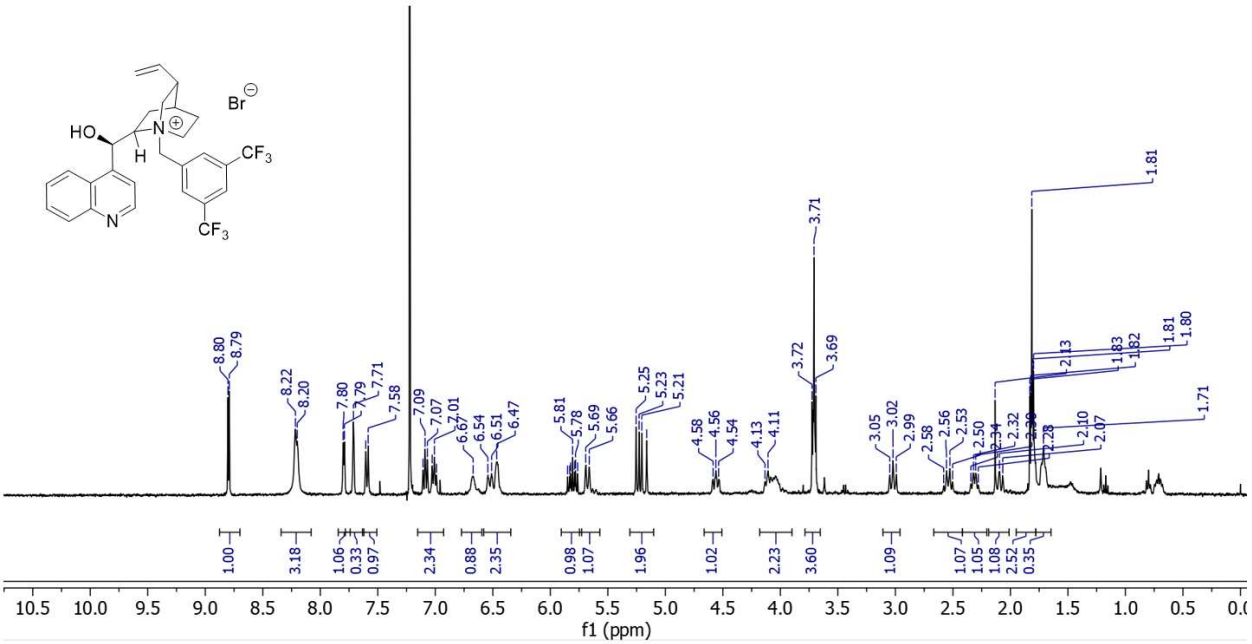
^{1}H NMR spectrum **(meso product)** (400 MHz, $CDCl_3$)



^{1}H NMR spectrum (400 MHz, $CDCl_3$)



^{1}H NMR spectrum (400 MHz, $CDCl_3$)



^{1}H NMR spectrum (400 MHz, $CDCl_3$)

APPENDIX FIVE

LEWIS BASE PROMOTED MONOSELECTIVE REDUCTIVE COUPLING OF HALOARENES TO UNACTIVATEDALKYL HALIDES: EXPERIMENTAL

A5.1 General Information:

All results are preliminary and were analyzed by ^{1}H NMR spectroscopy. This appendix is intended to provide experimental details and supporting information for the material discussed in Chapter 2.

General Reagent Information: All reactions were performed under a nitrogen (N_2) atmosphere unless otherwise noted. Hexamethyldisilane (Me_6Si_2, CombiBlocks catalog #QB-7675) and 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6, Chem-Impex catalog #03901) were purchased from the indicated vendors and used as received. Cesium fluoride (CsF, Acros Organics catalog # 010019.88) was purchased as a 99.9% pure powder pure solid and used as received. Me_6Si_2, CsF and 18-crown-6 were stored at room temperature (rt) inside a N_2 filled glovebox and used immediately if brought outside the glovebox. 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrmidinone (DMPU, TCI catalog # D2014) and methylsulfoxide (DMSO, Acros Organics catalog # 042780.M1) was purchased and used as received. All other solvents and reagents were purchased from MilliporeSigma, Combi-Blocks, TCI, Acros Organics, Matrix Scientific, Alfa Aesar, or Synthonix and used as received unless otherwise noted. Flash chromatography was performed on 40-63 μm silica gel (SiliaFlash® F60 from Silicycle). Preparative thin-layer chromatography (PTLC) was performed on silica gel 60 Å F254 plates (20 x 20 cm, 1000 μm, SiliaPlate from Silicycle, #TLG-R10011B-341) and visualized with UV light (254 nm). Celite® 545 (Product #CX0574-3) was purchased from Millipore Sigma.

General Analytical Information: All reported compounds were characterized by ^{1}H NMR spectroscopy. ^{1}H NMR spectra were obtained on a Bruker NEO400, Bruker US400, or Bruker Ascend 400 spectrometers. ^{1}H NMR data is reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, br s = broad singlet, d =doublet, t = triplet, q = quartet, quin = quintet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, dq = doublet of quartets, qd = quartet of doublets, m = multiplet), coupling constant (Hz), and integration. All ^{1}H NMR signals are reported as chemical shifts (δ ppm) relative to residual $CHCl_3$ at 7.26 ppm or $(CH_3)_2SO$ at 2.50 ppm.[1] Thin-layer chromatography analysis was performed on silica gel 60 Å F254 plates (250 µm, SiliaPlate from Silicycle, #TLG-R10014B323) and interpreted using UV light (254 nm) or $KMnO_4$ stain. Preparatory thin-layer chromatography purification was performed on silica gel 60 Å (1000 µm, Silicycle, #TLG-R10011B-341) and interpreted using UV light (254 nm).

A5.2 Optimization of Reductive coupling of Aryl Halides with Alkyl Halides

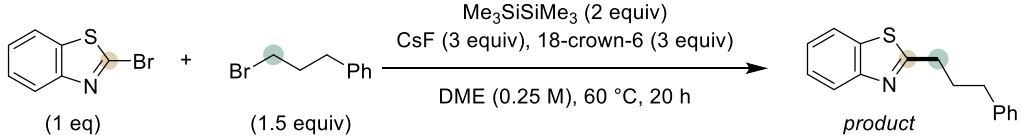
(a) Evaluation of changes in optimal base, solvent and base additive for selective reductive coupling of 2-bromobenzo[*d*]thiazole.

Preliminary experiments varying base and solvent indicated that CsF in DMPU/DMSO (9:1) could promote the selective reductive coupling of 3-phenylbenzotrifluoride using hexamethyldisilane. The optimized conditions are provided in Table SA2.1 below in comparison to specific changes of reagents or conditions used to inform readers of these effects. These optimization studies were conducted in a N_2 filled glovebox on a 0.25 mmol scale, however a Schlenk line protocol for 1.0 mmol scale reactions is described below.

General procedure for condition variation: Inside a N_2 filled glovebox, an oven-dried 4 mL vial (KIMBLE®, #60910-1) was charged with a magnetic stir bar, 2-bromobenzo[*d*]thiazole (53.5 mg, 0.25 mmol, 1.0 equiv), 18-crown-6 (198.2 mg, 0.75 mmol, 3.0 equiv), alkyl halide (0.375 mmol,

1.5 equiv), base (0.75 mmol, 3.0 equiv), anhydrous solvent (0.25 M, 1 mL), and hexamethyldisilane (102.4 μL, 0.5 mmol, 2.0 equiv) in successive order. The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, B7995-13), removed from the glovebox, and placed into an aluminum reaction block preheated to 60°C. The reaction solution was stirred for 20 h and then dibromomethane standard was measured into the reaction solution. For each experiment, the mass of dibromomethane standard was measured into the reaction solution. A small aliquot was removed and injected into an NMR tube and constituted in $CDCl_3$ (0.5 mL). ^1H NMR spectroscopy (400 MHz, ($CDCl_3$) was used to determine the yield of 2-(3-phenylpropyl)benzo[*d*]thiazole. The aromatic H signal of dibromomethane at 4.88 ppm (s, 2H) was integrated against the aromatic H signal of 2-(3-phenylpropyl)benzo[*d*]thiazole at 3.08 (t, J = 7.6 Hz, 2H). to determine the yield. The results are summarized in Table SA1.1 below in addition to representative crude ^1H NMR spectra to demonstrate this analysis.

Table SA5.1. Condition variation for selective reductive coupling of 2-bromobenzo[*d*]thiazole.



Entry	Variation from Standard Conditions	Product (%)
1	none	48
2	KF instead of CsF	0
3	KOMe instead of CsF	0
4	1 equiv of CsF	36
5	0.167 M instead of 0.25 M	44
6	DMSO instead of DME	0
7	DMF instead of DME	0

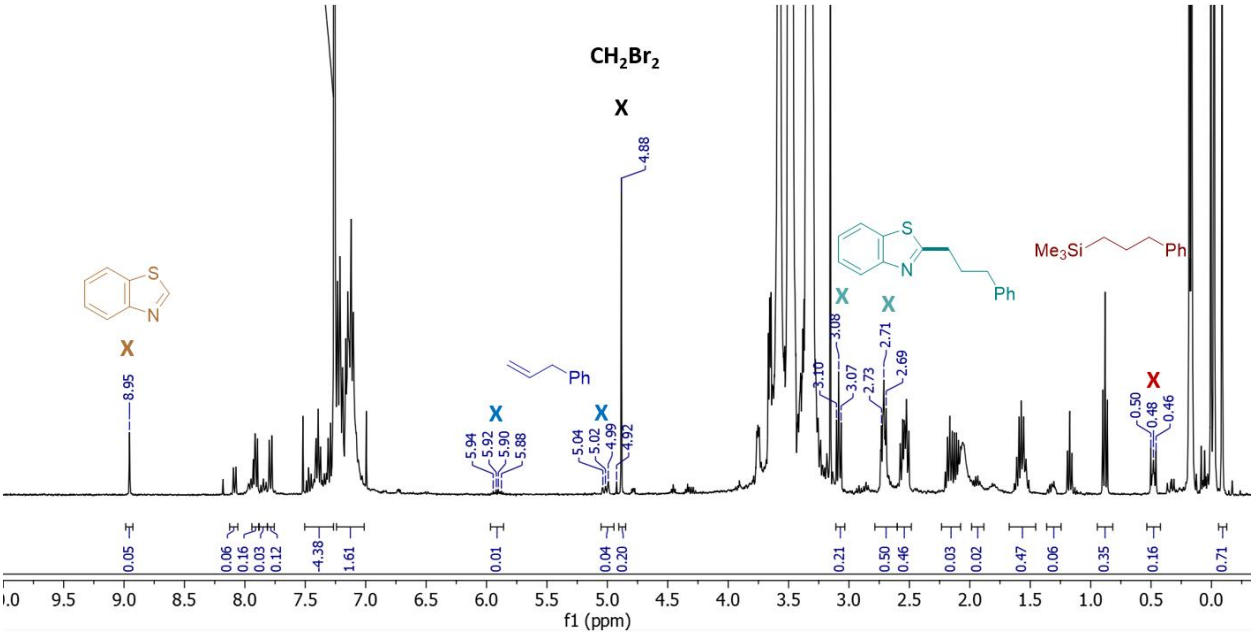


Figure SA5.1. ^{1}H NMR spectral window of the crude reaction solution of reaction from the standard reaction vial above (entry 1). Dibromomethane internal standard (17.4 mg, 0.1 mmol, signal at 4.88 ppm calibrated to 0.20 for 0.25 mmol scale reaction) was used to determine the yield of 2-(3-phenylpropyl)benzo[d]thiazole (48% yield), benzo[*d*]thiazole (20% yield), trimethyl(3-phenylpropyl)silane (20% yield), and allylbenzene (5% yield).

A5.3 General Procedure for Reductive coupling of Aryl Halides with Alkyl Halides.

Note: The reaction optimization studies were conducted inside a N_2 filled glovebox, while the general procedure for 0.25 mmol scale isolation reactions was developed inside a N_2 filled glovebox.

General procedure for reductive coupling of Aryl Halides with Alkyl Halides

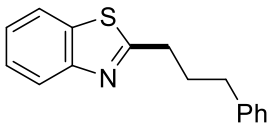
Inside a N_2 filled glovebox, an oven-dried 4 mL vial (KIMBLE®, #60910-1) was charged with a magnetic stir bar, 2-bromobenzo[*d*]thiazole (53.5 mg, 0.25 mmol, 1.0 equiv), 18-crown-6 (198.2 mg, 0.75 mmol, 3.0 equiv), alkyl halide (0.375 mmol, 1.5 equiv), CsF (113.9 mg, 0.75 mmol, 3.0 equiv), anhydrous DME (0.25 M, 1 mL), and hexamethyldisilane (102.4 µL, 0.5 mmol, 2.0 equiv) in successive order. The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, B7995-13), removed from the glovebox, and

placed into an aluminum reaction block preheated to 60°C. The reaction solution was stirred for 20 h and The reaction solution was allowed to cool to rt, then dibromomethane standard was measured into the reaction solution. For each experiment, the mass of dibromomethane standard was measured into the reaction solution. A small aliquot was removed and injected into an NMR tube and constituted in $CDCl_3$ (0.5 mL). ^1H NMR spectroscopy (400 MHz, ($CDCl_3$) was used to determine the yield of 2-(3-phenylpropyl)benzo[*d*]thiazole. The aromatic H signal of dibromomethane at 4.88 ppm (s, 2H) was integrated against the aromatic H signal of 2-(3-phenylpropyl)benzo[*d*]thiazole at 3.08 (t, J = 7.6 Hz, 2H) to determine the crude yield and the following isolation procedure was followed.

Isolation Procedure I (PTLC – 0.25 mmol scale): Upon cooling to room temperature, the mixture was poured into a 125 mL separatory funnel containing water (10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried with anhydrous Na_2SO_4. The Na_2SO_4 was filtered off and the solution was concentrated *in vacuo* and purified *via* PTLC

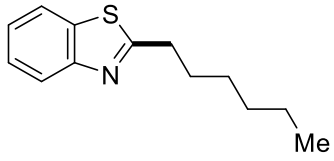
A5.4. Characterization Data of Reductive coupling of Aryl Halides with Alkyl Halides products.

(a) Products isolated using procedure I



2-(3-phenylpropyl)benzo[*d*]thiazole. The title compound was prepared according to the general procedure using 2-bromobenzo[*d*]thiazole (53.5 mg, 0.25 mmol, 1.0 equiv), 18-crown-6 (198.2 mg, 0.75 mmol, 3.0 equiv), (3-bromopropyl)benzene (76 µL, 0.375 mmol, 1.5 equiv), CsF (113.9 mg, 0.75 mmol, 3.0 equiv), DME (1 mL, 0.25M), and

hexamethyldisilane (102.4 μL, 0.5 mmol, 2.0 equiv) at 60 °C. The product was purified *via* Isolation Procedure I ((5:95) EtOAc/Hexanes eluent) to afford the title compound as a pale yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.8 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.47 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.37 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.25 – 7.19 (m, 3H), 3.17 (t, *J* = 7.6 Hz, 2H), 2.78 (t, *J* = 7.9 Hz, 2H), 2.29 – 2.18 (m, 2H).

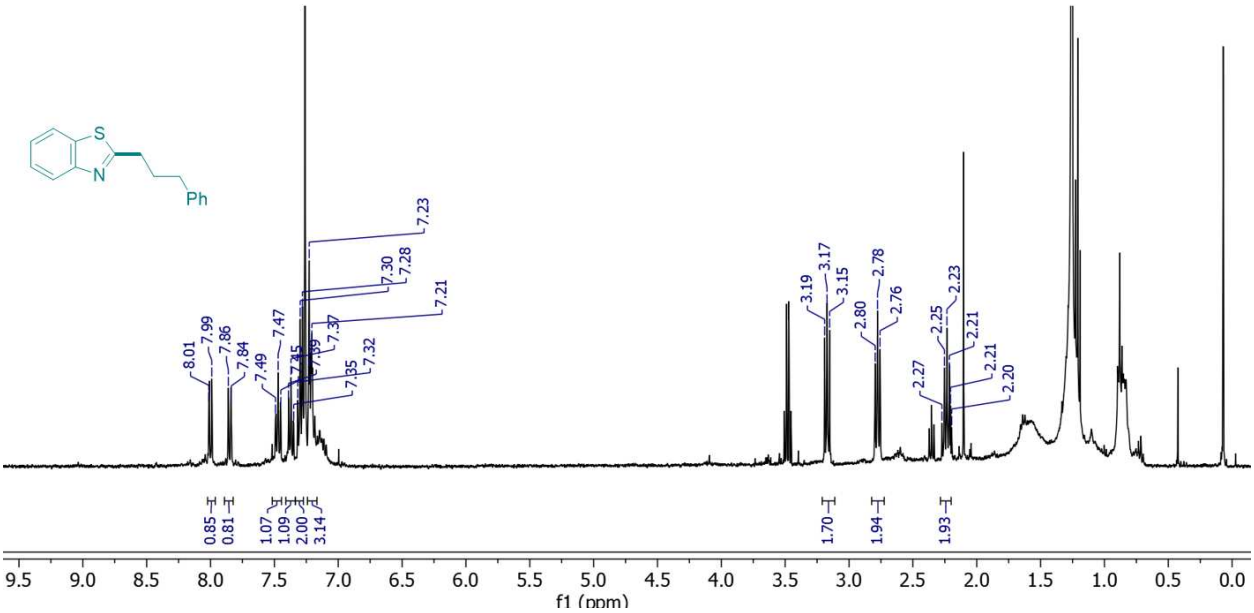


2-hexylbenzo[*d*]thiazole. The title compound was prepared according to the general procedure using 2-bromobenzo[*d*]thiazole (53.5 mg, 0.25 mmol, 1.0 equiv), 18-crown-6 (198.2 mg, 0.75 mmol, 3.0 equiv), 1-bromohexane (52.2 μL, 0.375 mmol, 1.5 equiv), CsF (113.9 mg, 0.75 mmol, 3.0 equiv), DME (1 mL, 0.25M), and hexamethyldisilane (102.4 μL, 0.5 mmol, 2.0 equiv) at 60 °C. The product was purified *via* Isolation Procedure I ((10:90) EtOAc/Hexanes eluent) to afford the title compound as a pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.1 Hz, 1H), 7.84 (d, J = 8.1 Hz, 1H), 7.46 (ddd, J = 8.3, 7.2, 1.3 Hz, 2H), 7.36 (ddd, J = 8.3, 7.3, 1.2 Hz, 1H), 3.13 (t, J = 7.9 Hz, 2H), 1.88 (p, J = 7.8 Hz, 2H), 1.51 – 1.39 (m, 2H), 1.34 (tt, J = 5.9, 2.8 Hz, 4H), 0.88 (t, J = 7.3, 6.6 Hz, 3H).

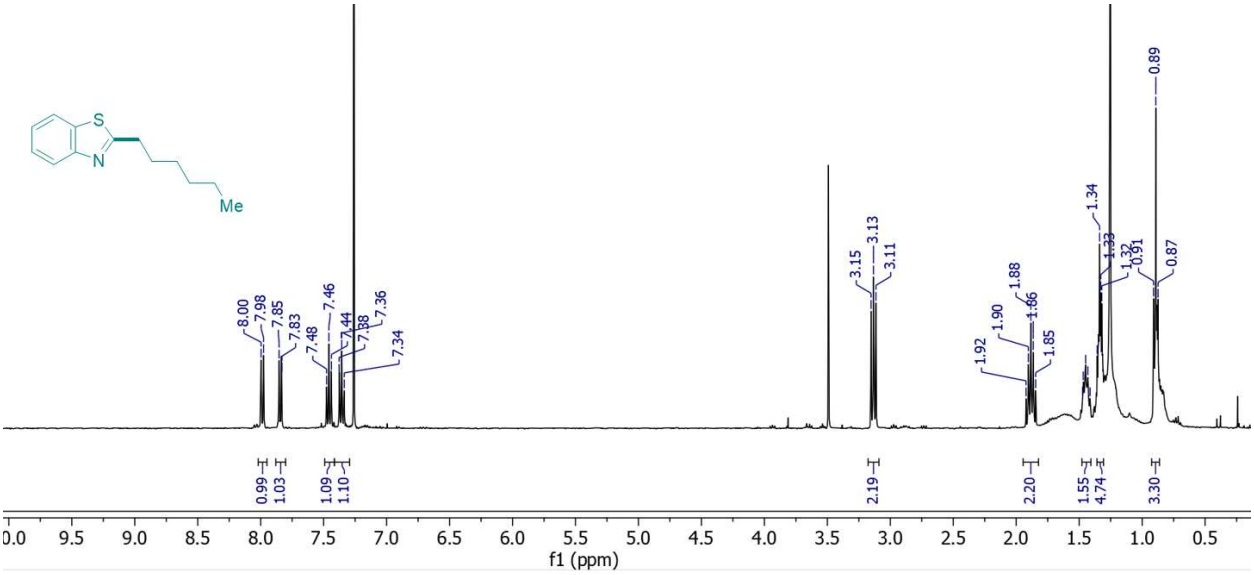
A5.5 References

[1] Fulmer, G. R.; Miller, A. J.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J.; Goldberg, K. I. Organometallics 2010, 29, 2176–2179.

A5.6. NMR spectra of Isolated Substrates



^{1}H NMR spectrum (400 MHz, $CDCl_3$)



^{1}H NMR spectrum (400 MHz, $CDCl_3$)

APPENDIX SIX

CAPTURING UNSTABLE CARBANIONS VIA HALOGEN TRANSFER: BASE-PROMOTED OXIDATIVE COUPLING REACTIONS OF α,α-DIFLUOROMETHYLARENES: EXPERIMENTAL

A6.1 General Information

This appendix is adapted from a manuscript in preparation, Capturing Unstable Carbanions *via* Halogen Transfer: Base-Promoted Oxidative Coupling Reactions of α,α-Difluoromethylarenes. It is intended to provide experimental details and supporting information for the material discussed in Chapter 3.

General Reagent Information: All reactions were performed under a nitrogen (N_2) atmosphere unless otherwise noted. 2-Bromothiophene (Oakwood Chemicals catalog #001055), Diethylaminosulfur trifluoride (DAST, Oakwood Chemicals catalog #002323), *N*-bromosuccinimide (NBS, Oakwood Chemicals catalog #002711), and 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6, Chem-Impex catalog #03901) were purchased from the indicated vendors and used as received. Potassium tert-butoxide (KO-*t*-Bu, Chem-Impex catalog #27317) was purchased as a 99.8% pure powder, and potassium bis(trimethylsilyl)amide (KHMDS, MilliporeSigma catalog #324671) was purchased as a 95% pure solid and used as received. KO-*t*-Bu, KHMDS and 18-crown-6 were stored at room temperature (rt) inside a N_2 filled glovebox and used immediately if brought outside the glovebox. *N,N*-Dimethylformamide (DMF, anhydrous, MilliporeSigma catalog #227056) was purchased and used as received. Tetrahydrofuran (THF) was deoxygenated and dried by passage over packed columns of neutral alumina and copper (II) oxide under positive pressure of N_2. All other solvents and reagents were

purchased from MilliporeSigma, Combi-Blocks, TCI, Acros Organics , Matrix Scientific, Alfa Aesar, or Synthonix and used as received unless otherwise noted. Flash chromatography was performed on 40-63 μm silica gel (SiliaFlash® F60 from Silicycle). Preparative thin-layer chromatography (PTLC) was performed on silica gel 60 Å F254 plates (20 x 20 cm, 1000 μm, SiliaPlate from Silicycle, #TLG-R10011B-341) and visualized with UV light (254 nm). Celite® 545 (Product #CX0574-3) was purchased from Millipore Sigma.

General Analytical Information: All reported compounds were characterized by ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy, FTIR spectroscopy, and mass spectrometry. Melting point analysis was conducted if the compound was solid. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were obtained on a Bruker NEO400, Bruker US400, or Bruker Ascend 400 spectrometers. ^{1}H NMR data is reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, br s = broad singlet, d =doublet, t = triplet, q = quartet, quin = quintet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, dq = doublet of quartets, qd = quartet of doublets, m = multiplet), coupling constant (Hz), and integration. All ^{1}H NMR signals are reported as chemical shifts (δ ppm) relative to residual $CHCl_3$ at 7.26 ppm or $(CH_3)_2SO$ at 2.50 ppm.[1] ^{13}C NMR data is reported as follows: chemical shift (δ ppm), multiplicity (if applicable, d = doublet, quin = quintet, q = quartet, dq = doublet of quartets, qd = quartet of doublets, m = multiplet), and coupling constant (Hz). ^{13}C NMR signals are reported as chemical shifts (δ ppm) relative to $CDCl_3$ at 77.16 ppm, $(CD_3)_2SO$ at 39.52 ppm, $(CD_3)_2CO$ at 206.26 ppm, CH_2Cl_2 at 53.84 ppm or CD_3CN at 1.32 ppm.[1] Chemical shifts for ^{19}F NMR are reported in terms of chemical shift in reference to an added internal standard (1,2-difluorobenzene set to δ -138.18 ppm); reported ^{19}F NMR data are for proton-decoupled spectra. High resolution mass spectra (HRMS) were recorded on an Agilent 6230 LC-MS B-TOF equipped with a dual ESI source, or an Agilent GC coupled to Xevo G2 QTOF *via* APGC ionization

sourceprovided by Colorado State University Analytical Resource Core – Molecular and Materials Analysis Center. IR spectra were recorded using a Thermo Scientific Nicolet iS-50 FTIR Spectrometer and reported as frequency of absorption (cm-1). Melting point analyses were conducted using a MelTemp capillary melting point apparatus. Thin-layer chromatography analysis was performed on silica gel 60 Å F254 plates (250 µm, SiliaPlate from Silicycle, #TLG-R10014B323) and interpreted using UV light (254 nm) or KMnO4 stain. Preparatory thin-layer chromatography purification was performed on silica gel 60 Å (1000 µm, Silicycle, #TLG-R10011B-341) and interpreted using UV light (254 nm).

A6.2 Optimization of C–H Etherification of Difluoromethylarenes

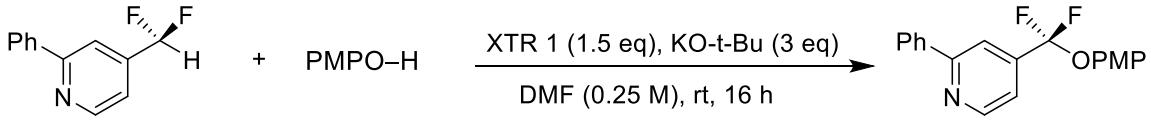
(a) Evaluation of changes in optimal base, halogenating agent, solvent, and base additive for oxidative coupling of 4-(difluoromethyl)-2-phenylpyridine.

Preliminary experiments varying base and solvent indicated that KO-*t*-Bu in DMF could promote coupling of 4-(difluoromethyl)-2-phenylpyridine (**3-1**) with 4-methoxyphenol (PMPOH, **3-3**) using 2-bromothiophene (**XTR 1**) as a sacrificial oxidant. The optimized conditions are provided in Table SA6.1 below in comparison to specific changes of reagents or conditions used to inform readers of these effects. These optimization studies were conducted in a N_2 filled glovebox on a 0.10 mmol scale, however a Schlenk line protocol for 1.0 mmol scale reactions is described below.

General procedure for condition variation: Inside a N_2 filled glovebox, an oven-dried 4 mL vial (KIMBLE®, #60910-1) was charged with a magnetic stir bar, 4-(difluoromethyl)-2-phenylpyridine (20.5 mg, 0.10 mmol, 1.0 equiv), 4-methoxyphenol (18.6 mg, 0.15 mmol, 1.5 equiv), halogenating agent (0.15 mmol, 1.5 equiv), anhydrous solvent (0.25 M, 0.4 mL), 18-crown-6 (26.4 mg, 0.10 mmol, 1.0 equiv) and base (0.30 mmol, 3.0 equiv) in successive order. The vial

was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, B7995-13), removed from the glovebox, and placed into an aluminum reaction block at rt. The reaction solution was stirred for 20 h and then 1,3,5-trimethoxybenzene and 1,2-difluorobenzene standards were measured into the reaction solution. For each experiment, the mass of 1,3,5-trimethoxybenzene and 1,2-difluorobenzene standards were measured into the reaction solution. A small aliquot was removed and injected into an NMR tube and constituted in $CDCl_3$ (0.5 mL). ^1H NMR spectroscopy (400 MHz, ($CDCl_3$) was used to determine the yield of 4-(difluoro(4-methoxyphenoxy)methyl)-2-phenylpyridine (**3-4**). The aromatic H signal of 1,3,5-trimethoxybenzene at 6.09 ppm (s, 3H) was integrated against the aromatic H signal of 4-(difluoro(4-methoxyphenoxy)methyl)-2-phenylpyridine (**3-4**) at 6.90 ppm (d, J = 9.1 Hz, 2H) to determine the yield. Due to frequent overlap of characteristic signals with solvent and/or other byproducts, 1H NMR spectroscopy yields could not always be determined, therefore ^{19}F NMR spectroscopy (376 MHz, $CDCl_3$) was also used to determine yield of 4-(difluoro(4-methoxyphenoxy)methyl)-2-phenylpyridine (**3-4**). The aromatic F signal of 1,2-difluorobenzene at -138.18 ppm (t, J = 9.0 Hz, 2F) was integrated against the benzylic F signal of 4-(difluoro(4-methoxyphenoxy)methyl)-2-phenylpyridine (**3-4**) at -62.63 ppm (s, 2F) to determine the yield. The results are summarized in Table SA6.1 below in addition to representative crude ^1H and ^{19}F NMR spectra to demonstrate this analysis.

Table SA6.1. Condition variation for the C–H etherification of 4-(difluoromethyl)-2-phenylpyridine



1 (1 eq) **3** (1.5 eq) **4**

Entry	change from the "standard conditions"	Yield (^{19}F NMR)
1	none	95%
2	50 °C instead of rt	95%
3	THF used as solvent instead of DMF	0%
4	KHMDS instead of KO-*t*-Bu	5%
5	NaO-*t*-Bu instead of KO-*t*-Bu	5%
6	KOH instead of KO-*t*-Bu	0%
7	2 eq of KO-*t*-Bu instead of 3 eq of KO-*t*-Bu	5%
8	4 eq of KO-*t*-Bu instead of 3 eq of KO-*t*-Bu	30%
9	no XTR 1	0%
10	2-iodothiophene instead of XTR 1	15%
11	XTR 2 instead of XTR 1	20%
12	XTR 3 instead of XTR 1	75%
13	30 min instead of 16 h	30%
14	2 h instead of 16h	65%
15	reaction ran open to air instead of under N_2	50%
16	3 eq 18-crown-6 added	95%
17	0.1 M instead of 0.25 M	40%
18	1 M instead of 0.25 M	70%
19	NBS used instead of XTR 1	0%
20	Br_2 used instead of XTR 1	0%
21	CBr_4 used instead of XTR 1	0%

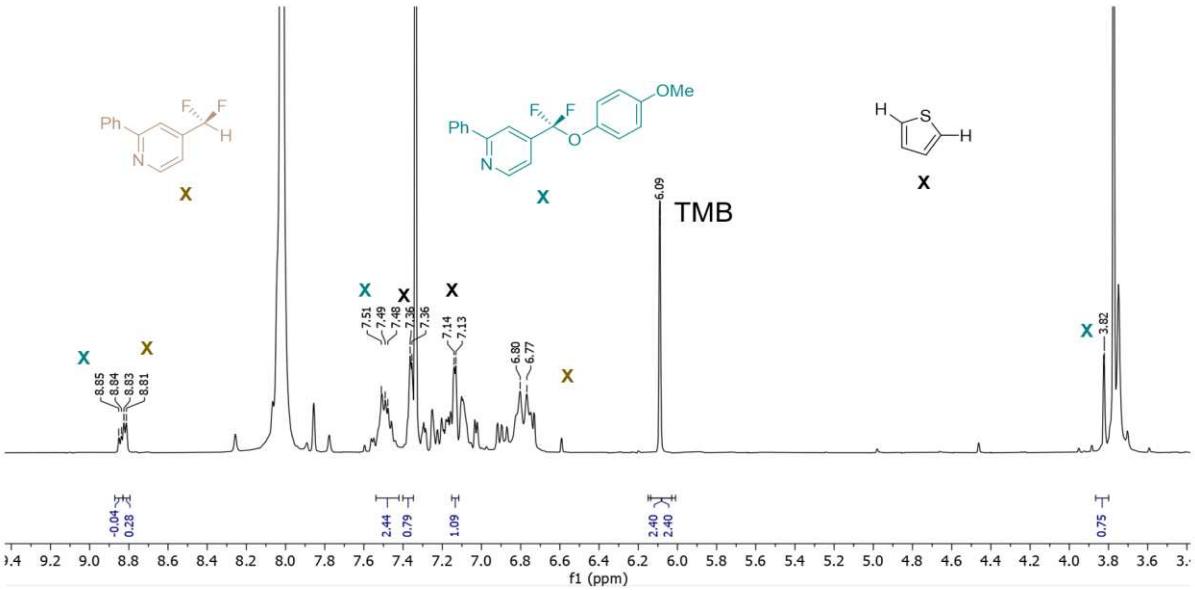


Figure SA6.1: ^{1}H NMR spectral window of the crude reaction solution of reaction from the 30 min reaction time vial above (entry 13). 1,3,5-Trimethoxybenzene internal standard (13.7 mg, 0.08 mmol, signal at 6.09 ppm calibrated to 2.43 for 0.1 mmol scale reaction) was used to determine the yield of 4-(difluoromethyl)-2-phenylpyridine (**3-1**, overlap) and 4-(difluoro(4-methoxyphenoxy)methyl)-2-phenylpyridine (**3-4**, overlap).

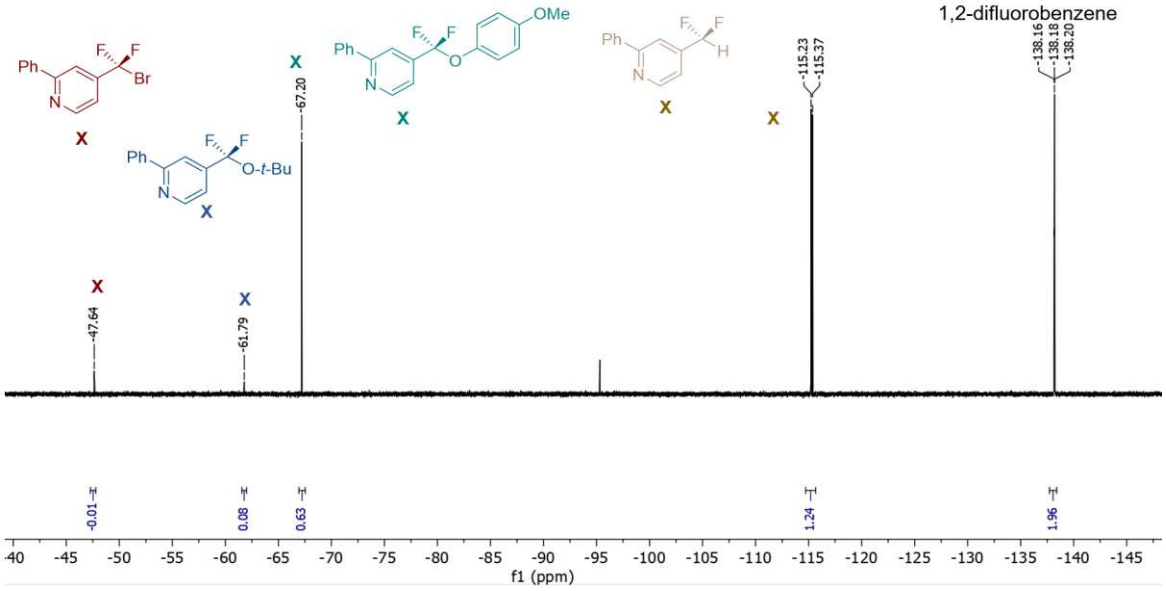


Figure SA6.2: ^{19}F NMR spectral window of the crude reaction solution of reaction from the 30 min reaction time vial above (entry 13). 1,2-Difluorobenzene internal standard (10.8 mg, 0.10 mmol, signal at -138.18 ppm calibrated to 1.95 for 0.1 mmol scale reaction) was used to determine the yield of 4-(difluoromethyl)-2-phenylpyridine (**3-1**, 62% yield), 4-(difluoro(4-methoxyphenoxy)methyl)-2-phenylpyridine (X, 30% yield), 4-(tert-butoxydifluoromethyl)-2-phenylpyridine (**3-4**, 4% yield), 4-(bromodifluoromethyl)-2-phenylpyridine (**3-34**, 2% yield).

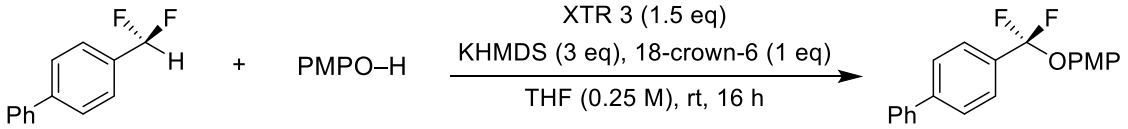
(b) Evaluation of changes in optimal base, halogenating agent, solvent, and base additive for oxidative coupling of 4-(difluoromethyl)biphenyl, a representative neutral difluoromethylarene.

Preliminary experiments varying base and solvent indicated that 18-crown-6 ligated KHMDS in THF could promote coupling of 4-(difluoromethyl)biphenyl (**3-2**) with 4-methoxyphenol (PMPOH, **3**) using 2-bromo-3-phenylbenzo[b]thiophene (**XTR 3**) as a sacrificial oxidant. The optimized conditions are provided in Table SA6.2 below in comparison to specific changes of reagents or conditions used to inform readers of these effects. These optimization studies were conducted in a N_2 filled glovebox on a 0.10 mmol scale, however a Schlenk line protocol for 1.0 mmol scale reactions is described below.

General procedure for condition variation: Inside a N_2 filled glovebox, an oven-dried 4 mL vial (KIMBLE®, #60910-1) was charged with a magnetic stir bar, 4-(difluoromethyl)biphenyl (20.4 mg, 0.10 mmol, 1.0 equiv), 4-methoxyphenol (12.2 mg, 0.10 mmol, 1.0 equiv), halogenating agent (0.15 mmol, 1.5 equiv), anhydrous solvent (0.25 M, 0.4 mL), 18-crown-6 (26.4 mg, 0.10 mmol, 1.0 equiv) and base (0.30 mmol, 3.0 equiv) in successive order. The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, #B7995-13), removed from the glovebox, and placed into a preheated 50 °C aluminum reaction block. The reaction solution was stirred for 20 h at 50 °C and then allowed to cool to rt. 1,3,5-Trimethoxybenzene standard and 1,2-difluorobenzene standard were measured into the reaction solution. A small aliquot was then removed, injected into an NMR tube and constituted in $CDCl_3$ (0.5 mL). ^1H NMR spectroscopy (400 MHz, ($CDCl_3$) was used to determine the yield of 4-(difluoro(4-methoxyphenoxy)methyl)-1,1'-biphenyl (**3-5**). The aromatic H signal of 1,3,5-trimethoxybenzene at 6.09 ppm (s, 3H) was integrated against the aromatic H signal of 4-

(difluoro(4-methoxyphenoxy)methyl)-1,1'-biphenyl (**3-5**) at 6.91 ppm (d, J = 9.1 Hz, 2H), to determine the yield. Due to frequent overlap of characteristic signals with solvent and/or other byproducts, ^{1}H NMR spectroscopy yields could not always be determined, therefore ^{19}F NMR spectroscopy (376 MHz, $CDCl_3$) was also used to determine the yield of 4-(difluoro(4-methoxyphenoxy)methyl)-1,1'-biphenyl (**3-5**). The aromatic F signal of 1,2-difluorobenzene at -138.18 ppm (t, J = 9.0 Hz, 2F) was integrated against the benzylic F signal 4-(difluoro(4-methoxyphenoxy)methyl)-1,1'-biphenyl (**3-5**) at -65.59 ppm (s, 2F) to determine the yield. The results are summarized in Table SA6.2 below in addition to representative crude ^{1}H and ^{19}F NMR spectra to demonstrate this analysis.

Table SA6.2. Condition variation for the C–H etherification of 4-(difluoromethyl)biphenyl. [a]80% $ArCF_2Br$ observed.



2 (1 eq) **3** (1.5 eq) **5**

Entry	change from the "standard conditions"	Yield (^{19}F NMR)
1	none	85%
2	no 18-crown-6	0%[a]
3	50 °C instead of rt	99%
4	DMF used as solvent instead of THF	40%
5	KO-*t*-Bu instead of KHMDS	2%
6	NaHMDS instead of KHMDS	0%[a]
7	KOH instead of KHMDS	0%
8	2 eq of KHMDS instead of 3 eq of KHMDS	0%
9	4 eq of KHMDS instead of 3 eq of KHMDS	65%
10	no XTR 3	0%
11	2-iodo-3-phenylbenzo[*b*]thiophene instead of XTR 3	0%
12	XTR 1 instead of XTR 3	0%
13	XTR 2 instead of XTR 3	0%
14	30 min instead of 16 h	5%
15	2 h instead of 16h	95%
16	reaction ran open to air instead of under N_2	25%
17	3 eq 18-crown-6 added	95%
18	0.1 M instead of 0.25 M	65%
19	1 M instead of 0.25 M	25%
20	KHMDS in THF (1 M)	80%
21	NBS used instead of XTR 3	0%
22	Br_2 used instead of XTR 3	0%
23	CBr_4 used instead of XTR 3	0%

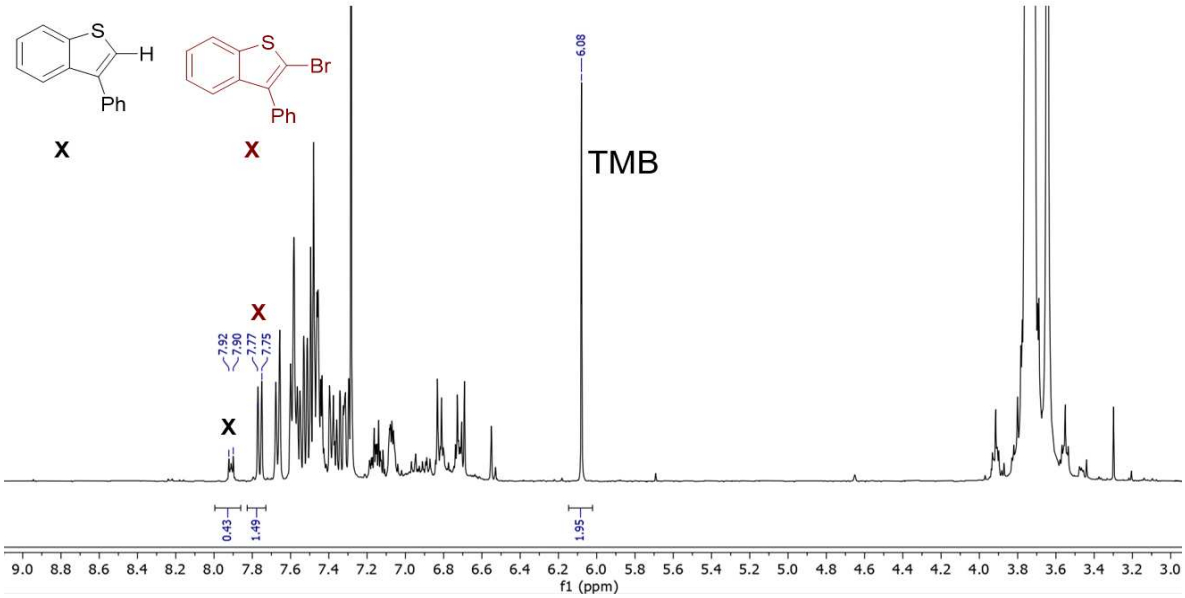


Figure SA6.3: [1]H NMR spectral window of the crude reaction solution of reaction from the KO-*t*-Bu reaction vial above (entry 5). 1,3,5-Trimethoxybenzene internal standard (11.0 mg, 0.065 mmol, signal at 6.09 ppm calibrated to 1.95 for 0.1 mmol scale reaction) was used to determine the yield of 4-(difluoromethyl)biphenyl (**3-2**, overlap), 4-(difluoro(4-methoxyphenoxy)methyl)biphenyl (**3-5**, overlap), 2-bromo-3-phenylbenzo[*b*]thiophene (**XTR 3**, 140% yield) 3-phenylbenzo[*b*]thiophene (**3-25**, 20% yield).

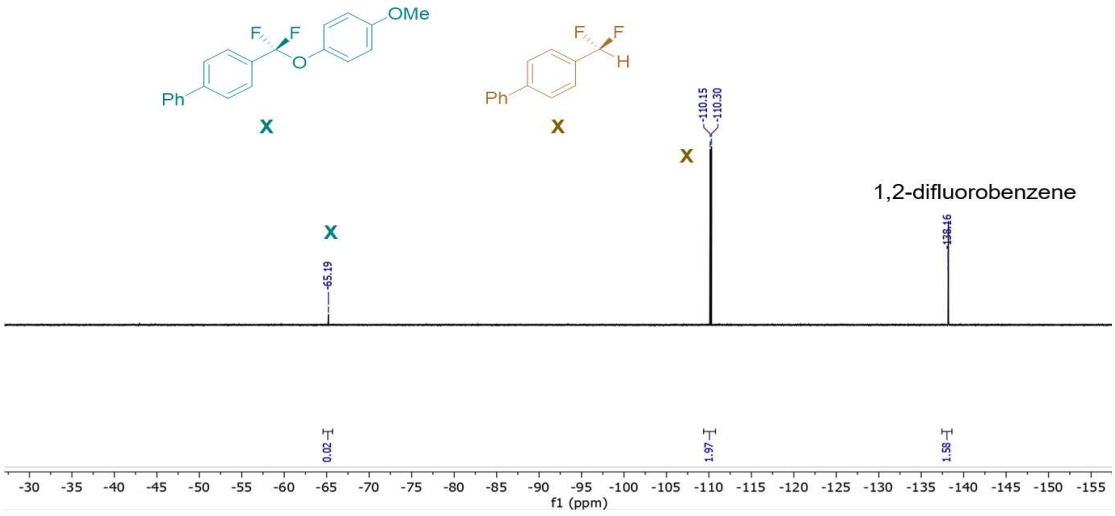


Figure SA6.4: [19]F NMR spectral window of the crude reaction solution of reaction from the KO-*t*-Bu reaction vial above (entry 5). 1,2-Difluorobenzene internal standard (9.0 mg, 0.079 mmol, signal at -138.18 ppm calibrated to 1.58 for 0.1 mmol scale reaction) was used to determine the yield of 4-(difluoromethyl)biphenyl (**3-2**, 96% yield), 4-(difluoro(4-methoxyphenoxy)methyl)biphenyl (**3-5**, 2% yield).

A6.3 Synthesis of 2-Bromo-3-phenylbenzo[*b*]thiophene.

Step 1a: 1-phenyl-2-(phenylthio)ethan-1-one

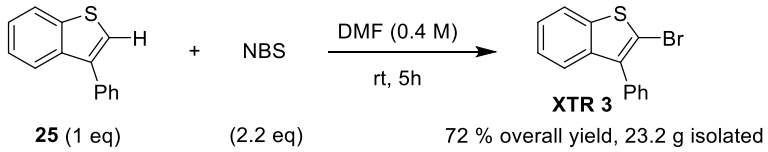
Procedure: An oven-dried 2 L Erlenmeyer flask was charged with a magnetic stir bar, anhydrous K_2CO_3 (75.3 g, 545 mmol, 1.2 equiv), and absolute ethanol (1.5 L, ~0.3 M). The solution was cooled to 0 °C using an ice-water bath and thiophenol (50.0 g, 454 mmol, 1.0 equiv) was added. After stirring for 10 min at 0 °C, 2-bromoacetophenone (90.3 g, 454 mmol, 1.0 equiv) was added portion wise. The reaction mixture was warmed to rt and stirred for 15 h open to air. Next, ice (~ 500 g) was added to the reaction mixture and stirred until the ice melted (30 min). The resulting precipitate was collected *via* filtration and washed with deionized water (300 mL) to provide the title product as a white solid (102.0 g, 447 mmol, 98% yield). ^{1}H NMR (400 MHz, CDCl3) δ 7.97 (d, *J* = 8.2 Hz, 2H), 7.61 (td, *J* = 7.4, 1.6 Hz, 1H), 7.49 (td, *J* = 7.8, 1.6 Hz, 2H), 7.44 – 7.40 (m, 2H), 7.35 – 7.19 (m, 3H), 4.30 (s, 2H). ^{13}C NMR (101 MHz, CDCl3) δ 194.2, 135.6, 135.0, 133.7, 130.7, 129.3, 128.9 (2C), 127.3, 41.4. The spectroscopic data is consistent with a previous report.[2]

Step 2a: 3-phenylbenzo[*b*]thiophene (3-25)

Procedure: An oven-dried 500 mL Erlenmeyer flask was charged with a magnetic stir bar and 84% polyphosphoric acid (PPA, 125 g, 62.5 mL). The flask was inserted into a silicon oil bath preheated to 100 °C and stirring was initiated. Next, 1-phenyl-2-(phenylthio)ethan-1-one (25 g, 110 mmol, 1.0 equiv) was added portion wise and the reaction mixture turned orange. We note that the stir bar must be smoothly stirring PPA before adding 1-phenyl-2-(phenylthio)ethan-1-one to obtain the cleanest reaction. If 1-phenyl-2-(phenylthio)ethan-1-one is added when the stir bar is not thoroughly mixing PPA, decomposition of starting material may be observed. Once all of 1-phenyl-2-(phenylthio)ethan-1-one was added, the reaction mixture was stirred at 100 °C for 2 h.

The reaction mixture was cooled to rt and poured into a 1 L Erlenmeyer flask containing a magnetic stir bar with equal parts ice (~ 300 g) and EtOAc (300 mL). The resulting mixture was stirred vigorously until PPA dissolved and two layers were cleanly formed. The resulting mixture was then poured into a separatory funnel containing H_2O (200 mL) and the aqueous layer was extracted with EtOAc (3 x 200 mL). The organic layers were combined and dried over Na_2SO_4. The Na_2SO_4 was removed by filtration and the organic layer was concentrated *in vacuo*. Silica gel chromatography (100% hexanes) yielded the title compound as a clear oil (18.0 g, 85.6 mmol, 78% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 – 8.04 (m, 1H), 7.80 – 7.72 (m, 1H), 7.69 – 7.61 (m, 1H), 7.59 – 7.46 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.8, 138.2, 138.0, 136.1, 128.8, 128.8, 127.6, 124.5, 124.4, 123.6, 123.0. The spectroscopic data is consistent with a previous report.[3]

Step 3: 2-bromo-3-phenylbenzo[*b*]thiophene (XTR 3)



A round bottom flask (500 mL) was charged with a magnetic stir bar, compound **xx** (22.3 g, 106 mmol, 1.0 equiv) and DMF (300 mL, 0.4 M) and was then cooled to 0 °C in an ice bath. *N*-Bromosuccinimide (23.0 g, 127 mmol, 1.1 equiv) was added to the flask and was warmed to rt with stirring. After 2 h, additional *N*-bromosuccinimide (23.0 g, 127 mmol, 1.1 equiv) was added to the flask and stirred at rt for another 4 h. Upon completion (monitored by TLC), the reaction was added to H_2O (1.7 L) in a clean round bottom flask (2 L), where the desired product precipitated out of solution. The mixture was filtered and the solid was recrystallized from hot hexanes to yield the title compound as a pale yellow solid (23.2 g, 94.5 mmol, 80% yield). **^{1}H**

NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.9, 0.9 Hz, 1H), 7.59 – 7.41 (m, 7H), 7.40 – 7.26 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.8, 138.8, 137.2, 133.9, 130.0, 128.6, 128.1, 124.8, 122.9, 121.7, 113.3. **IR** (neat, cm^{-1}) 3057, 1481, 1455, 1439, 1426, 1332, 1259, 1027, 990, 885, 749, 728, 710, 696, 638, 608. **HRMS** (APGC-TOF) $[M+H]^+$ calcd. for $[C_{14}H_9BrOS]^+$ = 287.9608, 288.9651 found. **Melting Point:** 72-74 ºC.

A6.4 General Procedures for Difluoromethylarene C–H Oxidative Coupling

Note: The reaction optimization studies were conducted inside a N_2 filled glovebox, while the general procedure for 1.0 mmol scale isolation reactions was developed using a standard manifold Schlenk line. The crude ^{19}F NMR spectroscopy yields observed during optimization are comparable to those for the 1.0 mmol isolation procedure.

General Schlenk line procedure for oxidative coupling of difluoromethylarenes.

Protocol A: Open to air, an 8 mL oven-dried vial was charged with a magnetic stir bar along with KO-*t*-Bu (336.6 mg, 3.0 mmol, 3.0 equiv) and 18-crown-6, if indicated (264.2 mg, 1.0 mmol, 1.0 equiv). The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1B) lined with a PTFE septum (Thermo Fisher Scientific, B7995-15), evacuated and backfilled three times with N_2, and left under positive pressure of N_2 using a needle connected to a manifold Schlenk line. Anhydrous DMF (1 mL) was then added to the 8 mL vial *via* syringe. The remaining reagents were then charged into a separate 4 mL oven-dried vial: difluoromethylarene (1.0 mmol, 1.0 equiv), XTR 1 or XTR 3 (1.5 mmol, 1.5 equiv), pronucleophile (1.5 mmol, 1.5 equiv), and anhydrous DMF (2 mL). This vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1B) lined with a PTFE septum (Thermo Fisher Scientific, B7995-13), evacuated and backfilled three times with N_2, and left under positive pressure of N_2 with a needle on a manifold Schlenk

line. The entire contents of the 4 mL vial containing the substrates were promptly transferred to the 8 mL vial containing the base *via* a syringe under N_2. Additional solvent (1 mL) was added to the 4 mL vial and this liquid was transferred to the 8 mL vial *via* syringe. The reaction vial cap and septum were then wrapped in parafilm (Thermo Fisher Scientific, #C4015-1B) and electrical tape, and an N_2 balloon was inserted through the septum to maintain positive N_2 pressure. The vial was then placed in a preheated heating block at rt or 50 °C for the allotted time with stirring. The reaction solution was allowed to cool to rt and one of the following isolation procedures was followed.

Protocol B: Open to air, an 8 mL oven-dried vial was charged with a magnetic stir bar along with KHMDS (598.2 mg, 3.0 mmol, 3.0 equiv) and 18-crown-6 (264.2 mg, 1.0 mmol, 1.0 equiv). The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1B) lined with a PTFE septum (Thermo Fisher Scientific, B7995-15), evacuated and backfilled three times with N_2, and left under positive pressure of N_2 using a needle connected to a manifold Schlenk line. Anhydrous solvent (THF, or DMPU) (1 mL) was then added to the 8 mL vial *via* syringe. The remaining reagents were then charged into a separate 4 mL oven-dried vial: difluoromethylarene (1.0 mmol, 1.0 equiv), XTR 3 (434.1 mg, 1.5 mmol, 1.5 equiv), pronucleophile (1.5 mmol, 1.5 equiv), and solvent (2 mL). This vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1B) lined with a PTFE septum (Thermo Fisher Scientific, B7995-13), evacuated and backfilled three times with N_2, and left under positive pressure of N_2 with a needle on a manifold Schlenk line. The entire contents of the 4 mL vial containing the substrates were promptly transferred to the 8 mL vial containing the base *via* a syringe under N_2. Additional solvent (1 mL) was added to the 4 mL vial and this liquid was transferred to the 8 mL vial *via* syringe. The reaction vial cap and septum were then wrapped in parafilm (Thermo Fisher Scientific, #C4015-1B) and electrical tape, and a N_2

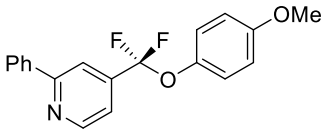
balloon was inserted through the septum to maintain positive N_2 pressure. The vial was then placed in a preheated heating block at rt or 50 °C for the allotted time with stirring. The reaction solution was allowed to cool to rt and one of the following isolation procedures was followed.

Isolation Procedure I: Upon cooling to room temperature, the mixture was poured into a 250 mL separatory funnel containing water (40 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine (20 mL) and dried with anhydrous Na_2SO_4. The Na_2SO_4 was filtered off and the solution was concentrated *in vacuo* and purified *via* flash chromatography on silica gel.

Isolation Procedure II (removal of excess pronucleophile): Upon cooling to room temperature, the mixture was poured into a 250 mL separatory funnel containing NaOH (1 M, 40 mL) and toluene (20 mL). The aqueous layer was extracted with toluene (3 x 40 mL). The combined organic layers were washed with brine (20 mL) and dried with anhydrous Na_2SO_4. The Na_2SO_4 was filtered off and the solution was concentrated *in vacuo* and purified *via* flash chromatography on silica gel.

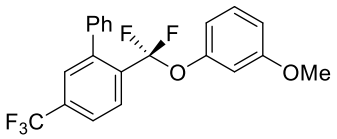
A6.5 Characterization Data of Difluoromethylarene Coupled Products

(a) Products shown in Table 1a.

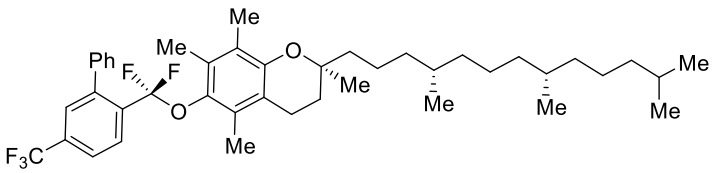


4-(difluoro(4-methoxyphenoxy)methyl)-2-phenylpyridine (3-4). The title compound was prepared according to Protocol A using 2-phenyl-4-(difluoromethyl)pyridine (205.2 mg, 1.0 mmol, 1.0 equiv), *p*-methoxyphenol (186.3 mg, 1.5 mmol, 1.5 equiv), XTR 1 (326.1 mg, 2.0 mmol, 2.0 equiv), KO-*t*-Bu (336.6 mg, 3.0 mmol, 3.0 equiv) and anhydrous DMF (4 mL, 0.25 M) at rt. The product was purified *via* Isolation Procedure I (0 – 10% EtOAc/Hexanes eluent gradient) to afford the title compound as a pale yellow solid (254.9 mg, 0.78 mmol, 78% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.84 (d, *J* = 5.3 Hz, 1H), 8.05 (m, 3H), 7.21 (d, *J* = 9.1 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 3.82 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.63 (s, 2F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.6, 157.8, 150.5, 143.4, 142.7 (t, J =

33.5 Hz), 138.7, 129.7, 129.0, 127.2, 123.5, 121.1 (t, J = 261.6, 261.1 Hz), 118.4 (t, J = 3.3 Hz), 116.9 (t, J = 3.6 Hz), 114.6, 55.7. **IR** (neat, cm^{-1}) 3016, 2956, 2835, 1607, 1502, 1479, 1462, 1402, 1298, 1267, 1240, 1183, 1162, 1102, 1070, 1056, 1036, 1026, 1019, 1009, 891, 840, 807, 774, 733, 689 679, 633. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{19}H_{15}F_2NO_2]^+$ = 328.1071, 328.1162 found. **Melting Point:** 92-94 ºC.

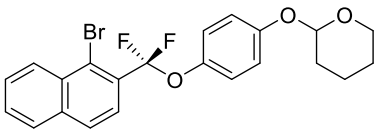


2-(difluoro(3-methoxyphenoxy)methyl)-5-(trifluoromethyl)-1,1'-biphenyl (3-6). The title compound was prepared according to Protocol A using 2-phenyl-4-(trifluoromethyl) difluoromethylbenzene (272.2 mg, 1.0 mmol, 1.0 equiv), *m*-methoxyphenol (186.0 mg, 1.5 mmol, 1.5 equiv), XTR 3 (434.1 mg, 1.5 mmol, 1.5 equiv), KO-*t*-Bu (336.6 mg, 3.0 mmol, 3.0 equiv) and anhydrous DMF (4 mL, 0.25 M) at rt. The product was purified *via* Isolation Procedure I (gradient 100-98:2 Hexanes/EtOAc) to afford the title compound as a pale yellow liquid (298.6 mg, 0.76 mmol, 76% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.3 Hz, 1H), 7.67 (d, *J* = 8.3 Hz, 1H), 7.53 (s, 1H), 7.35 (m, 5H), 7.06 (t, *J* = 8.3 Hz, 1H), 6.64 (d, *J* = 10.9 Hz, 1H), 6.40 (d, *J* = 8.1 Hz, 1H), 6.15 (s, 1H), 3.64 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -56.94 (s, 2F), -58.46 (s, 3F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.3, 142.6, 139.7, 135.0 (t, *J* = 30.8 Hz), 132.6 (q, *J* = 32.8 Hz), 130.1, 129.6, 129.4, 129.0 (q, *J* = 3.8 Hz), 128.8 (d, *J* = 2.0 Hz), 128.6, 128.3, 127.9, 127.8, 127.0 (d, *J* = 5.9 Hz), 125.0, 124.2 (d, *J* = 3.6 Hz), 123.7 – 122.1 (m), 121.4, 114.2, 111.9, 107.9, 55.4, 27.5. **IR** (neat, cm^{-1}) 3052, 2360, 2340, 1608, 1482, 1454, 1439, 1335, 1307, 1257, 1129, 1044, 728, 697. HRMS (ESI) $[M-H]^-$ calcd. for $[C_{21}H_{15}F_5O_2]^-$ = 393.0992, 393.1589 found.



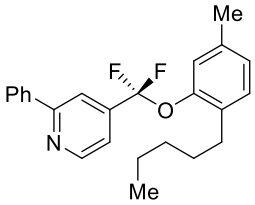
(S)-6-(difluoro(5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)methoxy)-2,5,7,8-tetramethyl-2-((4S,8S)-4,8,12-

trimethyltridecyl)chromane (3-8). The title compound was prepared according to Protocol A using 2-phenyl-4-(trifluoromethyl) difluoromethylbenzene (272.2 mg, 1.0 mmol, 1.0 equiv), vitamin E (645.8 mg, 1.5 mmol, 1.5 equiv), XTR 3 (434.1 mg, 1.5 mmol, 1.5 equiv), KO-*t*-Bu (336.6 mg, 3.0 mmol, 3.0 equiv) and anhydrous DMF (4 mL, 0.25 M) at rt. The product was purified *via* Isolation Procedure I (100-98:2 Hexanes/EtOAc, neutralized silica gel) to afford the title compound as a yellow liquid (509.7 mg, 0.73 mmol, 73% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 7.9 Hz, 1H), 7.77 (d, *J* = 7.0 Hz, 1H), 7.62 (s, 1H), 7.40 (m, 5H), 2.54 (t, *J* = 6.4 Hz, 2H), 2.19 (s, 1H), 2.06 (s, 3H), 1.93– 1.69 (m, 31H), 0.92 – 0.83 (m, 12H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -54.72 (s, 2F), -58.00 (s, 3F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.6, 142.6, 139.8, 139.7, 135.7 (t, J = 32.4, 30.7 Hz), 132.3 (q, J = 32.7 Hz), 129.7, 129.6, 129.2 (d, J = 3.9 Hz), 128.0, 127.9, 127.8, 126.9 (t, J = 5.5 Hz), 125.1 (q, J = 546.1, 255.7 Hz), 124.2 (d, J = 4.0 Hz), 123.2, 122.2 (t, J = 265.3, 264.2 Hz), 117.6, 75.2, 40.2, 40.1, 39.5, 37.8 – 37.3 (m), 33.0, 32.9, 31.3, 31.2, 28.2, 25.0, 24.9, 24.6, 24.0, 22.9, 22.8, 21.2, 20.8, 19.9, 14.3 (t, J = 3.1 Hz), 13.4 (d, J = 3.2 Hz), 11.9. **IR** (neat, cm^{-1}) 2926, 2867, 1461, 1410, 1377, 1337, 1302, 1253, 1173, 1115, 1088, 1046, 1027, 1017, 905, 839, 699. **HRMS** (ESI) $[M-H]^-$ calcd. for $[C_{43}H_{57}F_5O_2]^-$ = 699.4279, 699.4772 found.



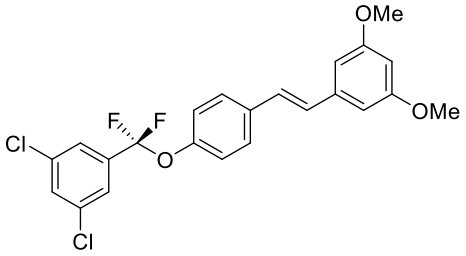
2-(4-((1-bromonaphthalen-2-yl)difluoromethoxy)phenoxy)tetrahydro-2H-pyran (3-7). The title compound was prepared according to Protocol A using 1-bromo-2-(difluoromethyl)napthalene (257.1 mg, 1.0 mmol, 1.0 equiv), 4-((tetrahydro-2H-pyran-2-yl)oxy)phenol (291.4 mg, 1.5 mmol, 1.5 equiv), XTR 3 (434.1 mg, 1.5 mmol, 1.5 equiv), KO-*t*-Bu (336.6 mg, 3.0 mmol, 3.0 equiv) and anhydrous DMF (4 mL, 0.25 M) at 50 °C. The product was purified *via* Isolation Procedure I (90:10 Hexanes/EtOAc) to afford the title compound as a

pale yellow solid (303.7 mg, 0.68 mmol, 68% yield). **^{1}H NMR** (400 MHz, $CDCl_3$ δ 8.57 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 5.5 Hz, 3H), 7.68 – 7.60 (m, 2H), 7.31 (m, 2H), 7.07 (d, *J* = 9.1 Hz, 2H), 5.40 (s, 1H), 3.94 (t, *J* = 9.2 Hz, 1H), 3.65 (s, 1H), 2.03-1.56 (m, 8H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -60.36 (s, 2F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.9, 144.6, 135.1, 132.8, 131.2 (t, *J* = 31.0 Hz), 128.4, 128.2, 128.1 (d, *J* = 1.7 Hz), 127.8, 123.8 (t, *J* = 6.3 Hz), 123.2, 122.6, 120.4 (t, *J* = 263.4, 262.6 Hz), 117.1, 115.8, 96.8, 62.1, 30.4, 27.7, 25.2, 18.8. **IR** (neat, cm^{-1}) 2941, 1503, 1465, 1332, 1290, 1244, 1332, 1290, 1244, 1194, 1181, 1120, 1047, 1033, 1025, 1012, 960, 918, 867, 848, 820, 780, 767, 744. **HRMS** (ESI) $[M-H]^-$ calcd. for $[C_{22}H_{19}BrF_2O_3]^-$ = 447.0486, 447.0623 found. **Melting Point:** 105-110 ºC.

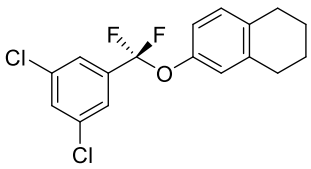


4-(difluoro(5-methyl-2-pentylphenoxy)methyl)-2-phenylpyridine (3-12). The title compound was prepared according to Protocol A using 2-phenyl-4-(difluoromethyl)pyridine (205.2 mg, 1.0 mmol, 1.0 equiv), 5-methyl-2-pentylphenol (267.0 mg, 1.5 mmol, 1.5 equiv), XTR 1 (326.1 mg, 2.0 mmol, 2.0 equiv), KO-*t*-Bu (336.6 mg, 3.0 mmol, 3.0 equiv) and anhydrous DMF (4mL, 0.25 M) at rt. The product was purified *via* Isolation Procedure I (90:10 Hexanes/EtOAc) to afford the title compound as a yellow liquid (181.4 mg, 0.46 mmol, 46% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.86 (d, *J* = 5.1 Hz, 1H), 8.10 – 8.01 (m, 3H), 7.61 – 7.42 (m, 4H), 7.21 (s, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 9.3 Hz, 1H), 2.67 – 2.59 (m, 2H), 2.37 (s, 3H), 1.66 – 1.54 (m, 2H), 1.31 (p, *J* = 3.8 Hz, 4H), 0.89 – 0.79 (m, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -61.33 (s, 2F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.5, 150.4, 148.1, 142.9 (t, *J* = 33.8 Hz), 138.6, 136.9, 132.5, 130.2, 129.6, 128.9, 127.1, 126.8, 123.7, 122.5, 121.1 (t, *J* = 263.4, 262.6 Hz), 118.4, 118.2 (t, *J* = 3.4 Hz), 116.6 (t, *J* = 3.6 Hz), 31.8, 30.0, 22.6, 21.1, 14.0. **IR** (neat, cm^{-1}) 3051, 1455, 1440, 1426, 1331, 1258, 1153, 1070, 990,

749, 728, 710, 695, 638, 608. **HRMS** (APGC-TOF) [M+H]+ calcd. for [C25H29F2NO]+ = 398.2217, 398.1916 found.

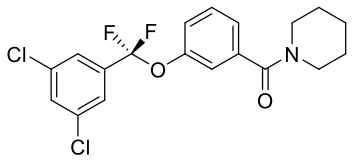


(E)-1,3-dichloro-5-((4-(3,5-dimethoxystyryl)phenoxy)difluoromethyl)benzene (3-11). The title compound was prepared according to Protocol A using (3,5-dichloro)difluoromethylbenzene (197.0 mg, 1.0 mmol, 1.0 equiv), (*E*)-4-(3,5-dimethoxystyryl)phenol (384.6 mg, 1.5 mmol, 1.5 equiv), XTR 3 (434.1 mg, 1.5 mmol, 1.5 equiv), KO-*t*-Bu (336.6 mg, 3.0 mmol, 3.0 equiv), 18-crown-6 (264.2 mg, 1.0 mmol, 1 equiv), NaO-*t*-Bu (288.2 mg, 3.0 mmol, 3.0 equiv) and anhydrous DMF (4 mL, 0.25 M) at rt. The product was purified *via* Isolation Procedure I (100 to 90:10 Hexanes: EtOAc; neutralized silica gel) to afford the title compound as a yellow oil (275.4 mg, 0.61 mmol, 61% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 2.0 Hz, 1H), 7.54 (dt, *J* = 6.6, 1.8 Hz, 2H), 7.27 (d, *J* = 9.3 Hz, 2H), 7.14 – 6.98 (m, 1H), 6.69 (d, *J* = 2.0 Hz, 1H), 6.44 (q, *J* = 2.1 Hz, 1H), 3.86 (d, *J* = 1.7 Hz, 4H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -60.43 (s, 2F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.2, 149.5, 139.2, 136.8 (t), 135.6, 135.3, 131.2, 129.3, 128.1, 127.7, 124.6 (t, J = 3.7 Hz), 122.2, 120.8 (t, J = 263.8, 263.0 Hz), 104.8, 100.3, 55.5. **IR** (neat, cm^{-1}) 3068, 3005, 2952, 2832, 1592, 1508, 1456, 1432, 1201, 1182, 1149, 1121, 1071,1030, 964, 924, 867, 841, 820, 796, 676. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{23}H_{18}Cl_2F_2O_3]^+$ = 451.0601, 451.0790 found.

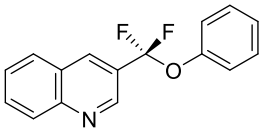


6-((3,5-dichlorophenyl)difluoromethoxy)-1,2,3,4-tetrahydronaphthalene (3-9). The title compound was prepared according to Protocol A using (3,5-dichloro)difluoromethylbenzene (197.0 mg, 1.0 mmol, 1.0 equiv), 5,6,7,8-tetrahydronaphthalen-2-ol (222.3 mg, 1.5 mmol, 1.5 equiv), XTR 3 (434.1 mg, 1.5 mmol, 1.5 equiv), KO-*t*-Bu (336.6 mg, 3.0 mmol, 3.0 equiv) and

anhydrous DMF (4 mL, 0.25 M) at rt. The product was purified *via* Isolation Procedure I (100 Hexanes; neutralized silica gel) to afford the title compound as a clear oil (112.7 mg, 0.33 mmol, 33% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 1.9 Hz, 2H), 7.50 (t, *J* = 2.0 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 8.5 Hz, 2H), 2.76 (m, 4H), 1.80 (p, *J* = 3.3 Hz, 4H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -60.32 (s, 2F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.5, 138.6, 137.0 (t, *J* = 33.4 Hz), 135.4, 135.0, 131.0, 130.0, 124.6 (t, *J* = 3.8 Hz), 122.2, 120.6 (t, *J* = 262.1, 260.9 Hz), 119.1, 29.5, 28.9, 23.1, 22.9. **IR** (neat, cm^{-1}) 3096, 2940, 2925, 2851, 2835, 1576, 1496, 1432, 1415, 1236, 1220, 1148, 1132, 1078, 1062, 862, 821, 799, 762, 720, 674. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{17}H_{14}Cl_2F_2O]^+$ = 343.0390, 343.0261 found.

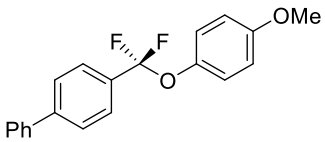


(3-((3,5-dichlorophenyl)difluoromethoxy)phenyl)(piperidin-1-yl)methanone (3-13). The title compound was prepared according to the general procedure (A) using (3,5-dichloro)difluoromethylbenzene (197.0 mg, 1.0 mmol, 1.0 equiv), 3-[(piperidin-1-yl)carbonylphenol (307.9 mg, 1.5 mmol, 1.5 equiv), 2-bromo, 3-phenylbenzo[*b*]thiophene (434.1 mg, 1.5 mmol, 1.5 equiv.), 18-crown-6 (264.2 mg, 1.0 mmol, 1 equiv) at 50 °C. The product was purified *via* isolation procedure I (gradient 100 to 75:25 Hexanes:EtOAc) to afford the title compound as an orange oil (176.1 mg, 0.44 mmol, 44% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 2H), 7.54 (s, 1H), 7.45 (t, *J* = 8.1 Hz, 1H), 7.32 (d, *J* = 7.1 Hz, 3H), 3.73 (s, 2H), 3.36 (s, 2H), 1.80 – 1.48 (m, 6H). 1**^{9}F NMR** (376 MHz, $CDCl_3$) δ -64.81(s, 2F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.9, 149.8, 138.1, 136.4 (t, *J* = 33.1 Hz), 135.5, 131.2, 129.8, 124.5, 124.5, 124.4, 122.8, 120.7 (t, *J* = 263.4 Hz), 120.4, 48.8, 43.2, 26.5, 25.8, 24.6. **IR** (neat, cm^{-1}) 2936, 2855, 1630, 1577, 1487, 1429, 1270, 1205, 1142, 1107, 1049, 1001, 942, 866, 801, 736, 687. HRMS (ESI) $[M+H]^+$ calcd. for $[C_{19}H_{17}Cl_2F_2NO_2]^+$ = 400.0604, 400.0700 found.



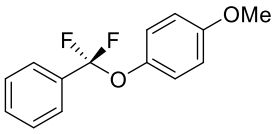
3-(difluoro(phenoxy)methyl)quinoline (3-10). The title compound was prepared according to Protocol A using 3-difluoromethylquinoline (179.2 mg, 1.0 mmol, 1.0 equiv), phenol (141.1 mg, 1.5 mmol, 1.5 equiv), XTR 3 (434.1 mg, 1.5 mmol, 1.5 equiv), KO-*t*-Bu (336.6 mg, 3.0 mmol, 3.0 equiv) and anhydrous DMF (4 mL, 0.25 M) at rt. The product was purified *via* Isolation Procedure I (100 to 90:10 Hexanes:EtOAc) to afford the title compound as a pale yellow oil (101.2 mg, 0.37 mmol, 37% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.5 Hz, 1H), 8.28 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.91 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.87 (d, *J* = 8.6 Hz, 1H), 7.81 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.69 – 7.61 (m, 1H), 7.44 – 7.31 (m, 4H), 7.25 – 7.18 (m, 1H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -65.15 (s, 2F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.0 (t, J = 33.5 Hz), 150.4, 147.2, 137.7, 130.4, 130.2, 129.4, 128.6, 128.1, 127.6, 125.8, 122.1, 120.0 (t, J = 264.7, 264.1 Hz), 117.6 (t, J = 2.4 Hz). The spectroscopic data is consistent with a previous report.[4]

(b) Products shown in Table 1b.

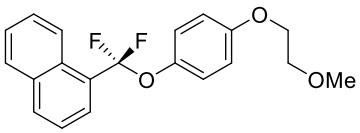


4-(difluoro(4-methoxyphenoxy)methyl)-1,1'-biphenyl (3-5). The title compound was prepared according to Protocol B using 4-(difluoromethyl)biphenyl (204.2 mg, 1.0 mmol, 1.0 equiv), *p*-methoxyphenol (186.0 mg, 1.5 mmol, 1.5 equiv), KHMDS (598.2 mg, 3.0 mmol, 3.0 equiv), 18-crown-6 (264.2 mg, 1.0 mmol, 1.0 equiv), XTR 3 (434.1 mg, 1.5 mmol, 1.5 equiv) and anhydrous THF (4 mL, 0.25 M) at 50 °C. The product was purified *via* Isolation Procedure I (97:3 Hexanes/EtOAc) to afford the title compound as a pale yellow solid (202.8 mg, 0.62 mmol, 62% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.6 Hz, 2H), 7.71 (d, *J* = 8.6 Hz, 2H), 7.64 (d, *J* = 7.0 Hz, 2H), 7.50 (t, *J* = 7.4 Hz,

2H), 7.42 (t, *J* = 7.3 Hz, 1H), 7.24 (d, *J* = 9.1 Hz, 2H), 6.91 (d, *J* = 9.1 Hz, 2H), 3.84 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -60.49 (s, 2F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.3, 143.9, 143.7, 140.2, 132.6 (t, *J* = 32.4 Hz), 128.9, 127.9, 127.3, 127.29, 126.1 (t, *J* = 3.8 Hz), 123.4, 122.3 (t, *J* = 260.0 Hz), 114.4, 55.6. **IR** (neat, cm^{-1}) 2959, 2917, 2835, 2360, 2340, 1594, 1506, 1465, 1404, 1331, 1295, 1249, 1113, 1063, 1047, 1028, 1015, 1006, 952, 845, 833, 738, 723, 705, 688, 592, 552. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{20}H_{16}F_2O_2]^+$ = 327.1118, 327.2027 found. **Melting Point:** 93-96 ºC.

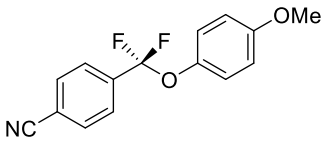


1-(difluoro(phenyl)methoxy)-4-methoxybenzene (3-14). The title compound was prepared according to Protocol B using (difluoromethyl)benzene (128.2 mg, 1.0 mmol, 1.0 equiv), *p*-methoxyphenol (186.3 mg, 1.5 mmol, 1.5 equiv), KHMDS (598.2 mg, 3.0 mmol, 3.0 equiv), 18-crown-6 (264.2 mg, 1.0 mmol, 1.0 equiv), XTR 3 (434.1 mg, 1.5 mmol, 1.5 equiv) anhydrous THF (4 mL, 0.25 M) 50 °C. The product was purified *via* Isolation Procedure I (95:5 Hexanes/EtOAc) to afford the title compound as a pale yellow solid (169.3 mg, 0.68 mmol, 68% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 6.6 Hz, 2H), 7.38 (t, *J* = 7.9 Hz, 3H), 7.09 (d, *J* = 9.0 Hz, 2H), 6.78 (d, *J* = 9.1 Hz, 2H), 3.71 (s, 3H).**^{19}F NMR** (376 MHz, $CDCl_3$) δ -60.83 (s, 2F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.4, 144.0 (t, J = 2.0 Hz), 134.0 (t, J = 32.0 Hz), 130.9, 128.6, 125.7 (t, J = 3.8 Hz), 123.5, 122.3 (t, J = 261.4, 260.7 Hz), 114.4, 55.6. The spectroscopic data is consistent with a previous report. [5]

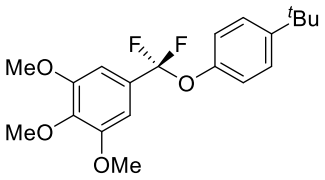


1-(difluoro(4-(2-methoxyethoxy)phenoxy)methyl)naphthalene (3-16). The title compound was prepared according to Protocol B using 1-(difluoromethyl)naphthalene (178.2 mg, 1.0 mmol, 1.0 equiv), 4-(2-methoxy-ethoxy)-phenol (252.1 mg, 1.5 mmol, 1.5 equiv), KHMDS (598.2 mg, 3.0 mmol, 3.0 equiv), 18-crown-6 (264.2 mg, 1.0 mmol, 1.0 equiv), XTR 3 (434.1 mg, 1.5 mmol, 1.5 equiv) and anhydrous THF (4

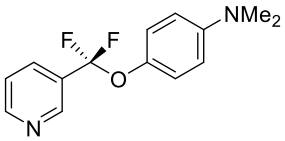
mL, 0.25 M) at rt. The product was purified *via* Isolation Procedure I (80:20 Hexanes/EtOAc) to afford the title compound as a yellow oil (188.9 mg, 0.55 mmol, 55% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.93 – 7.80 (m, 3H), 7.59 – 7.42 (m, 3H), 7.15 (d, *J* = 9.1 Hz, 2H), 6.82 (d, *J* = 9.1 Hz, 2H), 4.07 – 3.97 (m, 2H), 3.71 – 3.63 (m, 2H), 3.38 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -58.84 (s, 2F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.5, 144.2 (t, *J* = 2.2 Hz), 134.1, 131.9, 129.5 (d, *J* = 1.7 Hz), 129.2 (t, *J* = 30.0, 27.8 Hz), 128.7, 127.1, 126.2, 125.2 (t, *J* = 2.6 Hz), 124.9 (t, *J* = 6.3 Hz), 124.3, 123.1, 121.5 (t, *J* = 262.9, 262.1 Hz), 117.9, 115.5, 115.1, 71.0, 67.7, 59.2. **IR** (neat, cm^{-1}) 2925, 1470, 1453, 1308, 1250, 1202, 1115, 1078, 1062, 1034, 1022, 970, 923, 839, 803, 775, 730. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{20}H_{18}F_2O_3]^+$ = 345.1224, 345.1156 found.



4-(difluoro(4-methoxyphenoxy)methyl)benzonitrile (3-15). The title compound was prepared according to Protocol B using 4-carbonitrile-(difluoromethyl)benzene (153.1 mg, 1.0 mmol, 1.0 equiv), *p*-methoxyphenol (186.3 mg, 1.5 mmol, 1.5 equiv), KHMDS (598.2 mg, 3.0 mmol, 3.0 equiv), 18-crown-6 (264.2 mg, 1.0 mmol, 1.0 equiv), XTR 3 (434.1 mg, 1.5 mmol, 1.5 equiv) and anhydrous DMPU (4 mL, 0.25 M) at 50 °C. The product was purified *via* Isolation Procedure I (95:5 Hexanes/EtOAc) to afford the title compound as a white powder (119.2 mg, 0.43 mmol, 43% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 9.1 Hz, 2H), 3.81 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -61.35 (s, 2F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.6, 143.3, 138.1 (t, *J* = 33.0 Hz), 132.4, 126.6 (t, *J* = 3.6 Hz), 123.6, 123.3, 117.9 (t, *J* = 314.5, 303.4 Hz), 114.5, 55.6. **IR** (neat, cm^{-1}) 2960, 2916, 2235, 1502, 1440, 1407, 1309, 1245, 1195, 1165, 1149, 1105, 1060, 1018, 846, 830, 770. **HRMS** (APGC-TOF) [M+H]+ calcd. for [C15H11F2NO2]+ = 276.0758, 276.0838 found. **Melting Point:** 95-97 ºC.



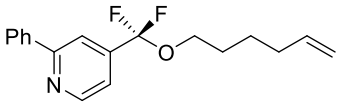
5-((4-(*tert*-butyl)phenoxy)difluoromethyl)-1,2,3-trimethoxybenzene (3-17). The title compound was prepared according to Protocol B using 3,4,5-trimethoxy(difluoromethyl)benzene (218.2 mg, 1.0 mmol, 1.0 equiv), 4-(*tert*-butyl)phenol (225.2 mg, 1.5 mmol, 1.5 equiv), KHMDS (598.2 mg, 3.0 mmol, 3.0 equiv), 18-crown-6 (264.2 mg, 1.0 mmol, 1.0 equiv), XTR 3 (434.1 mg, 1.5 mmol, 1.5 equiv) and anhydrous THF (4 mL, 0.25 M) at rt. The product was purified *via* Isolation Procedure II (100 to 90:10 gradient of Hexanes/EtOAc) to afford the title compound as a pale yellow oil (150.4 mg, 0.41 mmol, 41% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 8.9 Hz, 2H), 6.95 (s, 2H), 3.92 (s, 9H), 1.33 (s, 9H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -59.77 (s, 2F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.2, 148.6, 148.1 (d, *J* = 1.9 Hz), 139.9 (d, *J* = 1.7 Hz), 129.3 (t, *J* = 32.4 Hz), 126.3, 123.3 (t, *J* = 261.4, 260.3 Hz), 121.5, 103.0 (t, *J* = 3.8 Hz), 60.9, 56.3, 34.5, 31.4, 29.7. **IR** (neat, cm^{-1}) 2963, 1597, 1508, 1462, 1417, 1330, 1266, 1228, 1175, 1105, 1039, 1016, 1004, 901, 842, 728. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{20}H_{24}F_2O_4]^+$ = 367.1643, 367.1704 found.



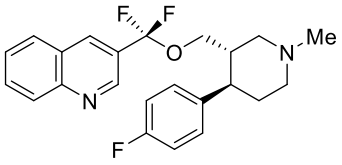
4-(difluoro(pyridin-3-yl)methoxy)-*N*,*N*-dimethylaniline (3-18). The title compound was prepared according to Protocol B using 3-difluoromethylpyridine (129.1 mg, 1.0 mmol, 1.0 equiv), 4-(dimethylamino)phenol (206.4 mg, 1.5 mmol, 1.5 equiv), KHMDS (598.2 mg, 3.0 mmol, 3.0 equiv), 18-crown-6 (264.2 mg, 1.0 mmol, 1.0 equiv), XTR 3 (434.1 mg, 1.5 mmol, 1.5 equiv) and anhydrous THF (4 mL, 0.25 M) 50 °C. The product was purified *via* Isolation Procedure I (80:20 Hexanes/EtOAc, neutralized silica gel) to afford the title compound as a yellow solid (73.6 mg, 0.28 mmol, 28% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.77 (d, *J* = 4.9, 1.6 Hz, 1H), 8.04 (dtd, *J* = 8.1, 1.8, 0.9 Hz, 1H), 7.43 (dd, *J* = 5.7, 5.0 Hz, 1H), 7.15 (d, *J* = 9.1 Hz, 2H), 6.71 (d, *J* = 9.3 Hz, 2H), 2.97 (s, 7H). **^{19}F**

NMR (376 MHz, $CDCl_3$) δ -60.51 (s, 2F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.8, 148.9, 147.3 (t, J = 3.9 Hz), 140.6, 133.5 (t, J = 3.5 Hz), 130.2 (t, J = 34.6, 33.0 Hz), 123.1, 123.0, 121.4 (t, J = 259.5 Hz), 112.9, 40.9. **IR** (neat, cm^{-1}) 2917, 1609, 1511, 1424, 1316, 1211, 1191, 1148, 1120, 1103, 1064, 1012, 967, 946, 823, 812, 787, 713, 698. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{14}H_{14}F_2N_2O]^+$ = 265.1074, 265.1182 found. **Melting Point:** 52-54 ºC.

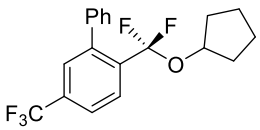
(c) Products shown in Table 1c.



4-(difluoro(hex-5-en-1-yloxy)methyl)-2-phenylpyridine (3-19). The title compound was prepared according to Protocol A using 2-phenyl-4-(difluoromethyl)pyridine (205.2 mg, 1.0 mmol, 1.0 equiv), 5-hexen-1-ol (180 µL, 1.5 mmol, 1.5 equiv), KO-*t*-Bu (336.6 mg, 3.0 mmol, 3.0 equiv), XTR 1 (326.1 mg, 2.0 mmol, 2.0 equiv) and anhydrous DMF (4 mL, 0.25 M) at rt. The product was purified *via* Isolation Procedure I (80:20 Hexanes/EtOAc) to afford the title compound as a yellow oil (160.4 mg, 0.53 mmol, 53% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.81 (d, *J* = 5.1 Hz, 1H), 8.04 (d, *J* = 7.1 Hz, 2H), 7.95 (s, 1H), 7.56 – 7.44 (m, 4H), 5.92 – 5.77 (m, 1H), 5.11 – 4.98 (m, 1H), 4.11 (t, *J* = 6.6 Hz, 2H), 2.15 (q, *J* = 7.3 Hz, 2H), 1.86 – 1.74 (m, 2H), 1.59 – 1.51 (m, 2H). **^{19}F NMR** 376 MHz, $CDCl_3$) δ -66.05 (s, 2F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.3, 150.2, 143.1 (t, *J* = 34.6 Hz), 138.7, 138.3, 129.4, 128.9, 127.0, 121.7 (t, *J* = 259.2, 256.4 Hz), 118.2, 116.6, 115.0, 64.2 (t, *J* = 5.7 Hz), 33.2, 28.6, 25.1. **IR** (neat, cm^{-1}) 2937, 1564, 1476, 1445, 1400, 1367, 1330, 1276, 1258, 1166, 1055, 1021, 911, 893, 842, 773, 692, 635. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{18}H_{19}F_2NO]^+$ = 304.1435, 304.1530 found.

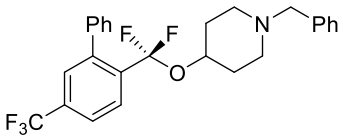


3-(difluoro(((3S,4R)-4-(4-fluorophenyl)-1-methylpiperidin-3-yl)methoxy)methyl)quinoline (3-21). The title compound was prepared according to Protocol A using 3-difluoromethylquinoline (179.2 mg, 1.0 mmol, 1.0 equiv), (3*S*,4*R*)-4-(4-fluorophenyl)-3-hydroxymethyl-1-methylpiperidine (334.9 mg, 1.5 mmol, 1.5 equiv), KO-*t*-Bu (336.6 mg, 3.0 mmol, 3.0 equiv), XTR 3 (434.1 mg, 1.5 mmol, 1.5 equiv) and anhydrous DMF (4 mL, 0.25 M) at rt. The product was purified *via* Isolation Procedure I (50:50 to 100 Hexanes: EtOAc) to afford the title compound as a yellow oil (205.3 mg, 0.52 mmol, 52% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.5 Hz, 1H), 8.23 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.81 (t, *J* = 8.6, 6.9 Hz, 1H), 7.66 (dq, *J* = 8.1, 3.3, 2.8 Hz, 2H), 7.26 – 7.18 (m, 2H), 7.01 (td, *J* = 8.6, 1.7 Hz, 2H), 3.89 (dt, *J* = 10.2, 2.3 Hz, 1H), 3.76 (dd, *J* = 10.0, 6.5 Hz, 1H), 3.29 (d, *J* = 11.5 Hz, 1H), 3.06 (d, *J* = 11.0 Hz, 1H), 2.44 (s, 3H), 2.26 – 1.76 (m, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -69.79 (dd, 2F), -111.39 – -111.87 (m, 1F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.7 (d, J = 244.6 Hz), 151.2 (t, J = 34.1 Hz), 147.1, 138.8 (d, J = 3.2 Hz), 137.6, 130.3, 130.1, 128.9 (d, J = 7.8 Hz), 128.5, 128.0, 127.6, 120.6 (t, J = 261.1 Hz), 117.5 (t, J = 2.2 Hz), 115.5 (d, J = 21.1 Hz), 64.8 (t, J = 5.5 Hz), 59.0, 56.0, 46.1, 43.3, 41.2, 34.0. **IR** (neat, cm^{-1}) 2937, 2847, 2785, 2360, 1601, 1509, 1466, 1448, 1382, 1330, 1298, 1248, 1222, 1171, 1159, 1142, 1061, 1035, 978, 943, 908, 829, 789, 757, 729, 641, 623, 543. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{23}H_{23}F_3N_2O]^+$ = 401.1762, 401.1967 found.



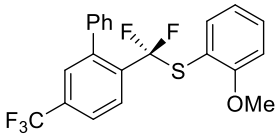
2-((cyclopentyloxy)difluoromethyl)-5-(trifluoromethyl)-1,1'-biphenyl (3-20). The title compound was prepared according to Protocol A using 2-phenyl-4-(trifluoromethyl)difluoromethylbenzene (272.2 mg, 1.0 mmol, 1.0 equiv), cyclopentanol (158.1 μL, 1.5 mmol, 1.5 equiv), KO-*t*-Bu (336.6 mg, 3.0 mmol, 3.0 equiv), XTR 3 (434.1 mg, 1.5 mmol, 1.5 equiv) and anhydrous DMF (4 mL, 0.25 M) at rt. The product was purified *via*

Isolation Procedure I (100 Hexanes; gravity column) to afford the title compound as a clear oil (145.9 mg, 0.41 mmol, 41% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.2 Hz, 1H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.52 (s, 1H), 7.42 – 7.28 (m, 4H), 4.72 (tt, *J* = 6.1, 3.0 Hz, 1H), 1.69 – 1.55 (m, *J* = 4.3 Hz, 2H), 1.55 – 1.35 (m, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -58.35 (s, 2F), -58.79 (s, 3F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.4 (t, J = 2.0 Hz), 140.1, 136.1 (t, J = 31.7 Hz), 132.1 (q, J = 32.7 Hz), 129.3 (d, J = 1.6 Hz), 128.8 (q, J = 3.7 Hz), 127.7, 127.6, 126.9 (t, J = 5.8 Hz), 125.1 (q, J = 273.3, 272.1 Hz), 124.0 (q, J = 3.8 Hz), 119.8 (t, J = 518.7, 259.4 Hz), 77.8 (t, J = 4.8 Hz), 33.2, 23.4. **IR** (neat, cm^{-1}) 2963, 1414, 1338, 1255, 1199, 1171, 1084, 1017, 952, 904, 838, 766, 732, 698. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{19}H_{17}F_5O]^+$ = 357.1200, 357.0747 found.



1-benzyl-4-(difluoro(5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)methoxy)piperidine (3-22). The title compound was prepared according to Protocol A using 2-phenyl-4-(trifluoromethyl)difluoromethylbenzene (272.2 mg, 1.0 mmol, 1.0 equiv), 1-benzyl-4-hydroxypiperidine (287.5 mg, 1.5 mmol, 1.5 equiv), KO-*t*-Bu (336.6 mg, 3.0 mmol, 3.0 equiv), XTR 3 (434.1 mg, 1.5 mmol, 1.5 equiv) and anhydrous DMF (4 mL, 0.25 M) at rt. The product was purified *via* Isolation Procedure I (90:10 Hexanes/EtOAc) to afford the title compound as a pale yellow oil (212.0 mg, 0.46 mmol, 46% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.3 Hz, 1H), 7.69 (d, *J* = 10.3 Hz, 1H), 7.56 (s, 1H), 7.45 – 7.25 (m, 3H), 4.30 (m, 1H), 3.45 (s, 2H), 2.53 (m, 2H), 2.11 (m, 2H), 1.66 (m, 2H), 1.51 (m, 2H).**^{19}F NMR** (376 MHz, $CDCl_3$) δ -57.31 (s, 2F), -58.01 (s, 3F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.2 (d, J = 2.3 Hz), 139.9, 138.4, 135.8 (t, J = 31.4 Hz), 132.0 (q, J = 32.8 Hz), 129.2 (d, J = 2.0 Hz), 129.1, 128.8 (q, J = 3.8 Hz), 128.2, 127.7, 127.6, 127.0, 126.8 (t, J = 5.8 Hz), 123.9 (q, J = 3.8 Hz), 122.5 (t, J = 261.2, 258.8 Hz), 122.3 (q, J = 545.5, 273.9, 273.1 Hz), 71.8, 62.9, 50.7, 32.1. **IR** (neat, cm^{-1})

2953, 2804, 1491, 1414, 1338, 1313, 1254, 1171, 1127, 1100, 1083, 1017, 904, 838, 787, 771, 732, 697, 665. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{26}H_{24}F_5NO]^+$ = 462.1778, 462.1908 found.



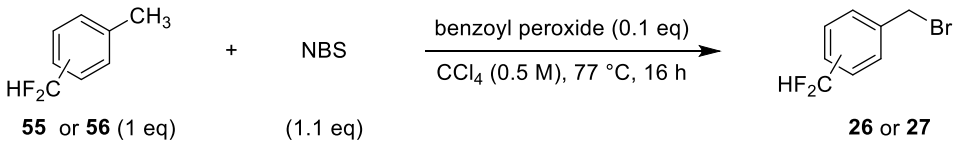
(difluoro(5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)methyl)(2-methoxyphenyl)sulfane (3-23). The title compound was prepared according to Protocol A using 2-phenyl-4-(trifluoromethyl)difluoromethylbenzene (272.2 mg, 1.0 mmol, 1.0 equiv), 2-methoxythiophenol (182.3 μL, 1.5 mmol, 1.5 equiv), KO-*t*-Bu (336.6 mg, 3.0 mmol, 3.0 equiv), XTR 3 (434.1 mg, 1.5 mmol, 1.5 equiv) and anhydrous DMF (4 mL, 0.25 M) at rt. The product was purified *via* Isolation Procedure II (99:1 Hexanes:EtOAc) to afford the title compound as a pale yellow oil (320.1 mg, 0.78 mmol, 78% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 – 7.55 (m, 2H), 7.52 (s, 1H), 7.50 – 7.46 (m, 2H), 7.45 – 7.41 (m, 4H), 7.41 – 7.35 (m, 1H), 6.91 (t, *J* = 8.1 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 3.65 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -58.19 (s, 3F), -62.94 (s, 2F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.7, 141.7, 139.6, 139.3, 137.3 (t, *J* = 23.8 Hz), 132.3, 131.5 (q, *J* = 33.0, 32.5, 31.8 Hz), 129.5, 128.9 (q, *J* = 3.7 Hz), 127.7, 127.5, 127.3 (t, *J* = 6.4 Hz), 126.8, 125.0, 124.0, 123.6 (q, *J* = 3.8 Hz), 122.2, 120.9, 114.8, 111.4, 55.6. **IR** (neat, cm^{-1}) 3063, 2938, 2838, 1584, 1477, 1464, 1445, 1432, 1409, 1335, 1276, 1250, 1172, 1126, 1087, 1072, 1016, 921, 839, 824, 789, 751, 731, 699, 685, 638. **HRMS** (ESI) $[M-H]^-$ calcd. for $[C_{21}H_{15}F_2OS]^-$ = 409.0764, 409.2826 found.

A6.6 Comparison to Radical Halogenation and Deoxyfluorination Protocols

a) Comparison to traditional radical halogenation in the presence of weak C–H bonds

Purpose: We performed studies described below to examine the selectivity of the halogen transfer protocol compared to traditional radical halogenation protocols for molecules that contain both difluoromethyl and methyl aryl substituents.

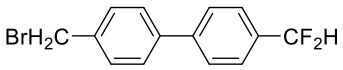
Traditional Radical Halogenation[6]

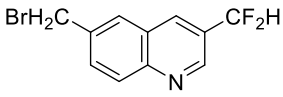


55 or **56** (1 eq) (1.1 eq) **26** or **27**

Procedure: Inside a N_2 filled glovebox, an oven-dried 4 mL vial (KIMBLE®, #60910-1) was charged with a magnetic stir bar, α,α-difluoromethylarene (0.50 mmol, 1.0 equiv), *N*-bromosuccinimide (98.0 mg, 0.55 mmol, 1.1 equiv), CCl_4 (1.0 mL, 0.5 M) and benzoyl peroxide (12.0 mg, 0.05 mmol, 0.01 equiv) in successive order. The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, #B7995-13), removed from the glovebox, and placed into a preheated aluminum reaction block at 77 °C. The reaction solution was stirred for 20 h at 77 °C and was then cooled to rt. Hexanes (2 mL), 1,3,5-trimethoxybenzene standard and 1,2-difluorobenzene standard were then measured into the reaction solution. A small aliquot was then removed, injected into an NMR tube and constituted in $CDCl_3$ (0.5 mL). ^{1}H NMR spectroscopy (400 MHz, $CDCl_3$) was used to determine the yield of 4-(bromomethyl)-4'-(difluoromethyl)-1,1'-biphenyl (**3-26**) and 6-(bromomethyl)-3-(difluoromethyl)quinoline (**3-27**). The aromatic H signal of 1,3,5-trimethoxybenzene at 6.09 ppm (s, 3H) was integrated against the aromatic H signal of **3-26** at 4.55 ppm (s, 2H) and **3-27** at 4.66 ppm (s, 2H) to determine the yield. ^{19}F NMR spectroscopy (376 MHz, $CDCl_3$) was also used to confirm that there was no activation of the CF_2H group.

Analysis: Traditional radical halogenation methods are completely selective for the CH_3 group over the CF_2H group. This is exemplified by the two examples below wherein no substitution of CF_2H group was observed by ^{1}H or ^{19}F NMR spectroscopy.

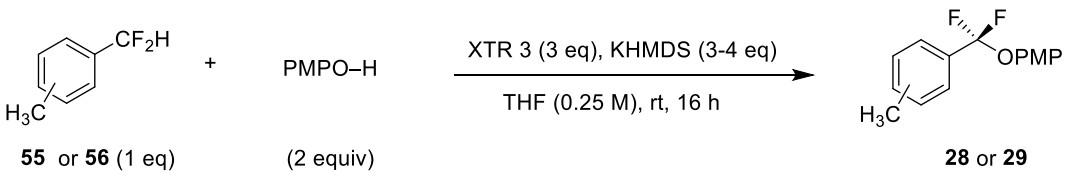
 **4-(bromomethyl)-4'-(difluoromethyl)-1,1'-biphenyl (3-26).** The title compound was prepared according to the procedure using 4-(difluoromethyl)-4'-methyl-1,1'-biphenyl (109.1 mg, 0.50 mmol, 1.0 equiv), *N*-bromosuccinimide (98.0 mg, 0.55 mmol, 1.1 equiv), CCl_4 (1.0 mL, 0.5 M) and benzoyl peroxide (12.0 mg, 0.05 mmol, 0.01 equiv) at 77 °C. The product was purified *via* Isolation Procedure I on a silica prep plate (95: 5 Hexanes: EtOAc) to afford the title compound as a white powder with some contamination with NMR standard: 1,3,5-trimethoxybenzene. No formation of the regioisomer was observed in the reaction. **^{1}H NMR** δ 7.73 – 7.60 (m, 4H), 7.64 – 7.54 (m, 4H), 6.69 (t, *J* = 57.1, 1H), 4.55 (s, 2H).**^{19}F NMR** (376 MHz, $CDCl_3$) δ -110.74 (d, *J* = 53.4 Hz, 2F). **IR** (neat, cm^{-1}) 2962, 2836, 1506, 1466, 1334, 1297, 1201, 1146, 1112, 1063, 1026, 845, 793, 688. **HRMS** (ESI) $[M-H]^-$ calcd. for $[C_{14}H_{11}BrF_2]^-$ = 296.0012, 295.2273 found. **Melting Point:** 69-73 ℃.

 **6-(bromomethyl)-3-(difluoromethyl)quinoline (3-27).** The title compound was prepared according to the procedure using 3-(difluoromethyl)-6-methylquinoline (96.5 mg, 0.5 mmol, 1.0 equiv), *N*-bromosuccinimide (98.0 mg, 0.55 mmol, 1.1 equiv), CCl_4 (1.0 mL, 0.5 M) and benzoyl peroxide (12.0 mg, 0.05 mmol, 0.01 equiv) at 77 °C. The product was purified *via* Isolation Procedure I on a prep plate (85:15 Hexanes:EtOAc) to afford the title compound as a pale yellow powder with some coelution with 3-(difluoromethyl)-6-methylquinoline. No formation of the regioisomer was observed in the reaction. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.31 (s, 1H), 8.18 (d, *J* = 8.7 Hz, 1H), 7.90 (s, 1H), 7.84 (d, *J* = 8.8 Hz, 1H), 6.88 (t, *J* = 56.8, 1H), 4.66 (s, 2H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -111.88 (d, *J* = 56.6 Hz, 2F). **^{13}C NMR** (101 MHz, CDCl3) δ 148.77, 147.69 (t, *J* = 5.3 Hz), 137.26, 133.80 (t, *J* = 6.7 Hz), 132.05, 130.40, 128.08, 126.68, 113.52 (t, *J* = 240.0 Hz), 32.52. **IR** (neat, cm^{-1}) 2962, 2836, 1506, 1466, 1441, 1405, 1334, 1297, 1250, 1201, 1146, 1112, 1062, 1046,

1027, 845, 793, 739. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{11}H_8BrF_2N]^+ = 271.9808$, 271.9898 found.

Melting Point: 78-81 ºC.

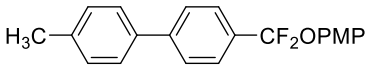
X-Transfer Oxidative Coupling Protocol



Procedure: Open to air, an 8 mL oven-dried vial was charged with a magnetic stir bar along with KHMDS (3.0-4.0 mmol, 3.0-4.0 equiv). The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1B) lined with a PTFE septum (Thermo Fisher Scientific, B7995-15), evacuated and backfilled three times with N_2, and left under positive pressure of N_2 using a needle connected to a manifold Schlenk line. Anhydrous THF (1 mL) was then added to the 8 mL vial *via* syringe. The remaining reagents were then charged into a separate 4 mL oven-dried vial: difluoromethylarene (1.0 mmol, 1.0 equiv), XTR 3 (868.2 mg, 3.0 mmol, 3.0 equiv), 4-methoxyphenol (248.0 mg, 2.0 mmol, 2.0 equiv) and THF (2 mL). This vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1B) lined with a PTFE septum (Thermo Fisher Scientific, B7995-13), evacuated and backfilled three times with N_2, and left under positive pressure of N_2 with a needle on a manifold Schlenk line. The entire contents of the 4 mL vial containing the substrates were promptly transferred to the 8 mL vial containing the base *via* a syringe under N_2. Additional solvent (1 mL) was added to the 4 mL vial and this liquid was transferred to the 8 mL vial *via* syringe. The reaction vial cap and septum were then wrapped in parafilm (Thermo Fisher Scientific, #C4015-1B) and electrical tape, and a N_2 balloon was inserted through the septum to maintain positive N_2 pressure. The vial was then placed in a heating block at rt for the allotted time with stirring. The reaction solution was allowed to cool to rt and one of

the following isolation procedures was followed. ^{1}H NMR spectroscopy (400 MHz, $CDCl_3$) was used to determine the yield of 4-(difluoro(4-methoxyphenoxy)methyl)-4'-methyl-1,1'-biphenyl (**3-28**) and 3-(difluoro(4-methoxyphenoxy)methyl)-6-methylquinoline (**3-29**). The aromatic F signal of 1,2-difluorobenzene at -138.18 ppm (t, J = 9.0 Hz, 2F) was integrated against the benzylic F signal of **x** at -65.51 ppm (s, 2F) and **x** at -64.50 ppm (s, 2F) to determine the yield. ^{19}F NMR spectroscopy (376 MHz, $CDCl_3$) was also used to confirm that there was no activation of the CH_3 group.

Analysis: X-transfer oxidative coupling gives complete selectivity for the CF_2H C–H bond over the CH_3 C–H bond. This is distinct from traditional radical halogenation strategies which are selective for the CH_3 C–H bonds.



4-(difluoro(4-methoxyphenoxy)methyl)-4'-methyl-1,1'-biphenyl (3-28). The title compound was prepared according to the procedure using 4-(difluoromethyl)-4'-methyl-1,1'-biphenyl (218.3 mg, 1.0 mmol, 1.0 equiv), 4-methoxyphenol (248.0 mg, 2.0 mmol, 2.0 equiv), XTR 3 (868.0 mg, 3.0 mmol, 3.0 equiv), anhydrous THF (0.25 M, 4.0 mL) and KHMDS (798.0 mg, 4.0 mmol, 4.0 equiv). The product was only evaluated by ^{1}H NMR and ^{19}F NMR spectroscopy. No formation of the regioisomer was observed in the reaction.

^{19}F NMR (376 MHz, $CDCl_3$) δ -65.51 (s, 2F).

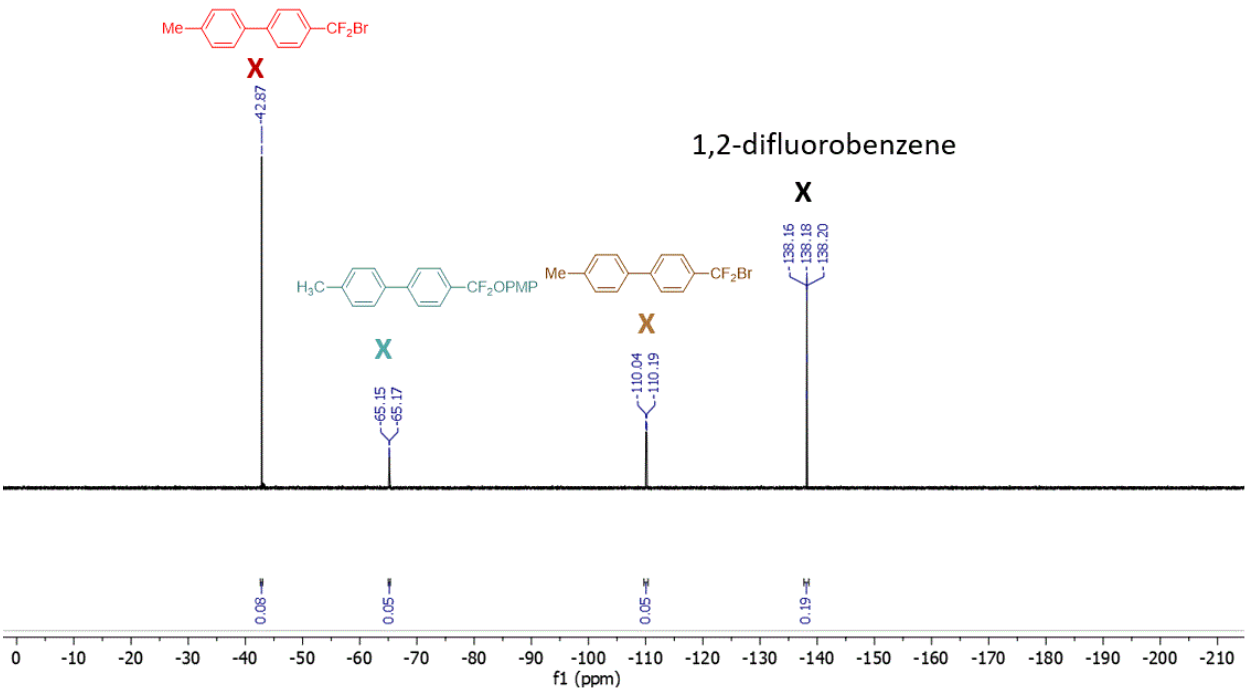
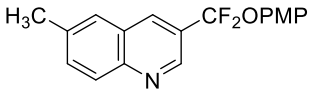


Figure SA6.5. ^{19}F NMR spectral window of the crude reaction solution of reaction above. 1,2-Difluorobenzene internal standard (10.7 mg, 0.095 mmol, signal at -138.18 ppm calibrated to 0.19 for 0.1 mmol scale reaction) was used to determine the yield of 4-(difluoromethyl)-4'-methyl-1,1'-biphenyl (**3-56**, 25% yield), 4-(difluoro(4-methoxyphenoxy)methyl)-4'-methyl-1,1'-biphenyl (**3-28**, 25% yield) and 3-(bromodifluoromethyl)-6-methylquinoline (40% yield).



3-(difluoro(4-methoxyphenoxy)methyl)-6-methylquinoline (3-29). The title compound was prepared according to the procedure using 3-(difluoromethyl)-6-methylquinoline (193.2 mg, 1.0 mmol, 1.0 equiv), 4-methoxyphenol (248.0 mg, 2.0 mmol, 2.0 equiv), XTR 3 (868.0 mg, 3.0 mmol, 3.0 equiv), anhydrous THF (0.25 M, 4.0 mL) and KHMDS (598.4 mg, 3.0 mmol, 3.0 equiv). The product was purified *via* Isolation Procedure I (90:10 Hexanes:EtOAc, neutralized silica gel) to afford the title compound as a pale yellow powder with some 3-(difluoromethyl)-6-methylquinoline coelution. No formation of the regioisomer was observed in the reaction. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.15 (s, 1H), 8.46 (s, 1H), 8.09 (d, *J* = 7.9 Hz, 1H), 7.72 – 7.62 (m, 2H), 7.23 (d, *J* = 8.7 Hz, 2H), 6.94 – 6.85 (m, 2H),

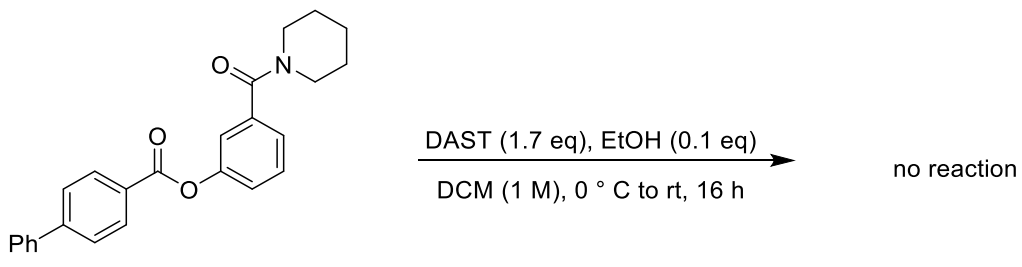
3.82 (s, 3H), 2.58 (s, 3H).**^{19}F NMR** (376 MHz, $CDCl_3$) δ -64.50 (s, 2F). **^{13}C NMR** (101 MHz, CDCl3) δ 157.5, 146.3, 146.2 (d, *J* = 5.1 Hz), 137.6 (d, J = 6.3 Hz), 133.5, 133.4, 133.2 (t, *J* = 6.7 Hz), 129.2, 129.1, 127.3, 127.1, 126.9, 126.7, 123.4, 115.0 (t, *J* = 239.2 Hz), 114.5, 55.6, 21.6. **IR** (neat, cm-1) 2967, 1615, 1571, 1503, 1383, 1292, 1245, 1183, 1138, 1027, 830, 794. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{18}H_{15}F_2NO_2]^+$ = 316.1108, 316.1181 found. **Melting Point:** 34-36 ºC.

b) Comparison to deoxyfluorination methods in presence of multiple carbonyl groups

Purpose: A traditional way to synthesize difluorobenzylic ethers is *via* thiolation followed by fluorination of the thioester motif. However, a challenge in this strategy is selectivity in the presence of other carbonyl groups such that the most nucleophilic carbonyl will be fluorinated. This is demonstrated in the example shown below. We will then demonstrate that X-transfer oxidative coupling can be used to directly access targets with inverted fluorination.

Traditional Deoxyfluorination Protocol[7]

Purpose: We examined a substrate that contains both an amide and an ester functional group under deoxyfluorination strategies. First, we found that the parent compound (**X**) was not active to fluorination. Then, we subjected the parent compound to thiolation conditions to access an intermediate that is more prone for fluorination. Both thiolation and the subsequent fluorination step were selective for the more nucleophilic amide carbonyl.

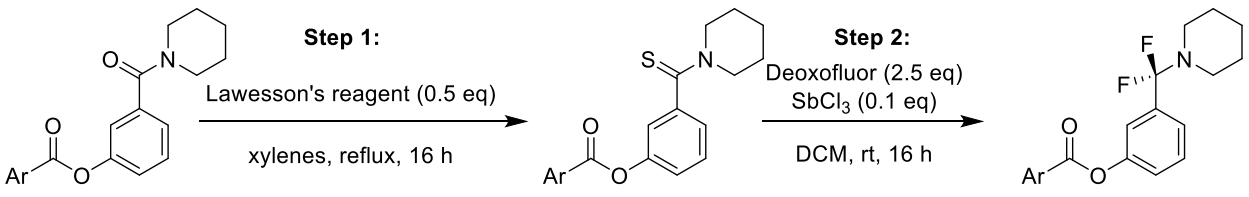


57(1 eq)

Procedure: An oven-dried round bottom flask (10 mL) was charged with a magnetic stir bar, 3-(piperidine-1-carbonyl)phenyl [1,1'-biphenyl]-4-carboxylate **3-57** (770.9 mg, 2.0 mmol, 2.0 equiv) and anhydrous DCM (2 mL, 1 M). The flask was sealed with a septum and was sparged with N_2 while stirring vigorously for 10 minutes at 0 °C. DAST (0.5 mL, 3.4 mmol, 1.7 equiv) was then added to the flask *via* syringe and the reaction as allowed to stir at 0 °C for 5 min. Then EtOH (0.1 equiv) was added dropwise *via* syringe (special care was taken during this addition as it is quite exothermic) at 0 °C. The flask was then allowed to warm to rt as it stirred. After 16 h the reaction mixture was cooled to 0 °C and quenched slowly with $NaHCO_3$ (sat. aq) before it was transferred to a separatory funnel containing H_2O (10 mL) and DCM (5 mL). The aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine (1 x 25 mL) and then dried over Na_2SO_4, filtered, and then concentrated *in vacuo*. 1,2-Difluorobenzene standard was then measured into the reaction solution and the mass of 1,2-difluorobenzene weighed into the vial was recorded separately. A small aliquot was then removed, injected into an NMR tube and constituted in $CDCl_3$ (0.5 mL). ^1H NMR spectroscopy (400 MHz, $CDCl_3$) of the crude reaction indicated that no product was formed and all of the starting material was accounted for.

Analysis: Direct deoxyfluorination of 3-(piperidine-1-carbonyl)phenyl [1,1'-biphenyl]-4-carboxylate **3-57** results in no reaction with 100% starting material remaining.

Purpose: Thiolation of the carbonyl is required to achieve fluorination.



Step 1: Amide Thiolation (3-58) [8]

Procedure: To an oven-dried round bottom flask (100 mL) charged with a Teflon-coated stir bar was added 3-(piperidine-1-carbonyl)phenyl [1,1'-biphenyl]-4-carboxylate **3-57** (1.51 g, 4.0 mmol, 1.0 equiv), Lawesson's reagent (808 mg, 2.0 mmol, 0.5 equiv) and xylenes (12 mL, 0.33 M). A reflux condensor fitted with a rubber septum were then placed onto the flask, and the reaction mixture was placed into a preheated oil bath at 140 °C and stirred under reflux. After 16 h, the flask was removed from the oil bath and the solution was allowed to cool to rt. The reaction mixture was filtered and concentrated *in vacuo*. Silica gel column chromatography (30% ethyl acetate in hexanes) provided the product as a yellow solid (3.55 g, 8.9 mmol, 90% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 9.1 Hz, 2H), 7.76 (d, *J* = 7.8 Hz, 2H), 7.69 (d, *J* = 7.2 Hz, 2H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.26 – 7.24 (m, 1H), 7.24 – 7.19 (m, 2H), 4.46 – 4.30 (m, 2H), 3.67 – 3.59 (m, 2H), 1.89 – 1.73 (m, 4H), 1.70 – 1.58 (m, 2H). **IR** (neat, cm^{-1}) 2940, 1723, 1599, 1492, 1434, 1257, 1243, 1170, 1071, 881, 745, 696. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{25}H_{23}F_2NO_2S]^+$ = 402.5204, 402.1655 found. **Melting Point:** 102-105 ºC.

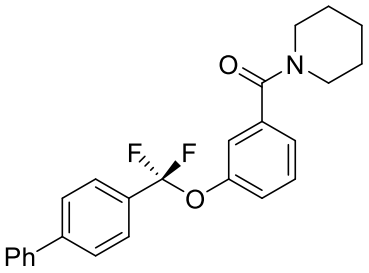
Step 2: Fluorination (3-31)

Procedure: To an oven-dried round bottom flask (25 mL) charged with a Teflon-coated stir bar was added 3-(piperidine-1-carbonothioyl)phenyl [1,1'-biphenyl]-4-carboxylate **3-58** (401.5 mg, 1.0 mmol, 1.0 equiv) and DCM (10 mL, 0.1 M). The flask was sparged with N_2 while stirring vigorously for 5 min. Then bis(2-methoxyethyl)aminosulfur trifluoride (0.46 mL, 2.5 mmol, 2.5 equiv) was added *via* syringe followed by $SbCl_3$ (22.8 mg, 0.1 mmol, 0.1 equiv). The reaction mixture was allowed to stir at rt for 16 h. The reaction mixture was cooled to 0 °C and quenched with $NaHCO_3$ (30 mL) dropwise. The mixture was then transferred to a separtory funnel containing H_2O (20 mL) and DCM (10 mL). The aqueous layer was extracted with DCM (3 x 20 mL) and

then the organic layer was washed with brine (1 x 30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. 1,2-Difluorobenzene standard was then measured into the reaction solution and a small aliquot was then removed, injected into an NMR tube and constituted in $CDCl_3$ (0.5 mL). ^1H NMR spectroscopy (400 MHz, $CDCl_3$) was used to determine the yield of 3-(difluoro(piperidin-1-yl)methyl)phenyl [1,1'-biphenyl]-4-carboxylate (**3-31**). The aromatic F signal of 1,2-difluorobenzene at -138.18 ppm (t, J = 9.0 Hz, 2F) was integrated against the benzylic F signal of **3-31** at -72.91 (d, J = 713.1 Hz) to determine the yield. Product is not stable to silica gel column chromatography. No formation of the regioisomer was observed in the reaction. **^1H NMR** (400 MHz, $CDCl_3$) δ 8.29 (d, J = 8.5 Hz, 2H), 7.77 (d, J = 8.5 Hz, 2H), 7.72 – 7.65 (m, 2H), 7.59 – 7.40 (m, 4H), 7.38 – 7.31 (m, 3H), 4.33 (s, 2H), 3.51 (s, 2H), 1.81 – 1.69 (m, 3H), 1.69 – 1.48 (m, 3H). **^{19}F NMR** (376 MHz, $CDClz_3$) δ -72.91 (d, J = 713.1 Hz). **IR** (neat, cm^{-1}) 2939, 2854, 1725, 1630, 1600, 1583, 1434, 1257, 1242, 1172, 1071, 1000, 742, 696. **Melting Point:** 82-87 ºC.

Analysis: Subjection of the thiolated title compound to fluorination conditions produced a product that did not match X-transfer results, indicating that the other isomer was formed. This is consistent with the thioamide being more nucleophilic and therefore more likely to be fluorinated. This is supported by observation of **3-57** being inactive to fluorination conditions, implying that fluorination must occur at the same site of thiolation.

X-Transfer Oxidative Coupling Protocol to Access (3-((3,5-dichlorophenyl)difluoromethoxy)phenyl)(piperidin-1-yl)methanone (3-33).



Procedure: Open to air, an 8 mL oven-dried vial was charged with a magnetic stir bar along with KHMDS (598.2 mg, 3.0 mmol, 3.0 equiv) and 18-crown-6 (264.2 mg, 1.0 mmol, 1.0 equiv). The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1B) lined with a PTFE septum (Thermo Fisher Scientific, B7995-15), evacuated and backfilled three times with N_2, and left under positive pressure of N_2 using a needle connected to a manifold Schlenk line. Anhydrous THF (1 mL) was then added to the 8 mL vial *via* syringe. The remaining reagents were then charged into a separate 4 mL oven-dried vial: 4-(difluoromethyl)-1,1'-biphenyl (204.2 mg, 1.0 mmol, 1.0 equiv), 3-[(piperidin-1-yl)carbonylphenol (307.9 mg, 1.5 mmol, 1.5 equiv), XTR 3 (434.1 mg, 1.5 mmol, 1.5 equiv), and anhydrous THF (2 mL). This vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1B) lined with a PTFE septum (Thermo Fisher Scientific, B7995-13), evacuated and backfilled three times with N_2, and left under positive pressure of N_2 with a needle on a manifold Schlenk line. The entire contents of the 4 mL vial containing the substrates were promptly transferred to the 8 mL vial containing the base *via* a syringe under N_2. Additional solvent (1 mL) was added to the 4 mL vial and this liquid was transferred to the 8 mL vial *via* syringe. The reaction vial cap and septum were then wrapped in parafilm (Thermo Fisher Scientific, #C4015-1B) and electrical tape, and an N_2 balloon was inserted through the septum to maintain positive N_2 pressure. The vial was then placed in a preheated heating block at 50 °C for the allotted time with stirring. The reaction solution was allowed to cool to rt and the following isolation procedure was followed. Upon cooling to room temperature, the mixture was poured into a 250 mL separatory

funnel containing water (40 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine (20 mL) and dried with anhydrous Na_2SO_4. The Na_2SO_4 was filtered off and the solution was concentrated *in vacuo* and purified *via* flash chromatography on silica gel. The product was purified *via* flash chromatography on silica gel (75:25 Hexanes:EtOAc) to afford the title compound ((3-([1,1'-biphenyl]-4-yldifluoromethoxy)phenyl)(piperidin-1-yl)methanone) as an orange solid (71.2 mg, 0.17 mmol, 17% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 (s, 2H), 7.54 (s, 1H), 7.45 (t, *J* = 8.1 Hz, 1H), 7.32 (d, *J* = 7.1 Hz, 3H), 3.73 (s, 2H), 3.36 (s, 2H), 1.80 – 1.48 (m, 6H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -64.81(s, 2F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.9, 149.8, 138.1, 136.4 (t, *J* = 33.1 Hz), 135.5, 131.2, 129.8, 124.5, 124.5, 124.4, 122.8, 120.7 (t, *J* = 263.4 Hz), 120.4, 48.8, 43.2, 26.5, 25.8, 24.6. **IR** (neat, cm^{-1}) 2939, 2857, 1724, 1924, 1579, 1439, 1320, 1261, 1151, 1107, 1071, 1001, 744, 728, 395. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{25}H_{23}F_2NO_2]^+$ = 408.1697, 408.1800 found. **Melting Point:** 75-79 ºC.

Analysis: Formation of the desired compound is observed and confirmed *via* isolation.

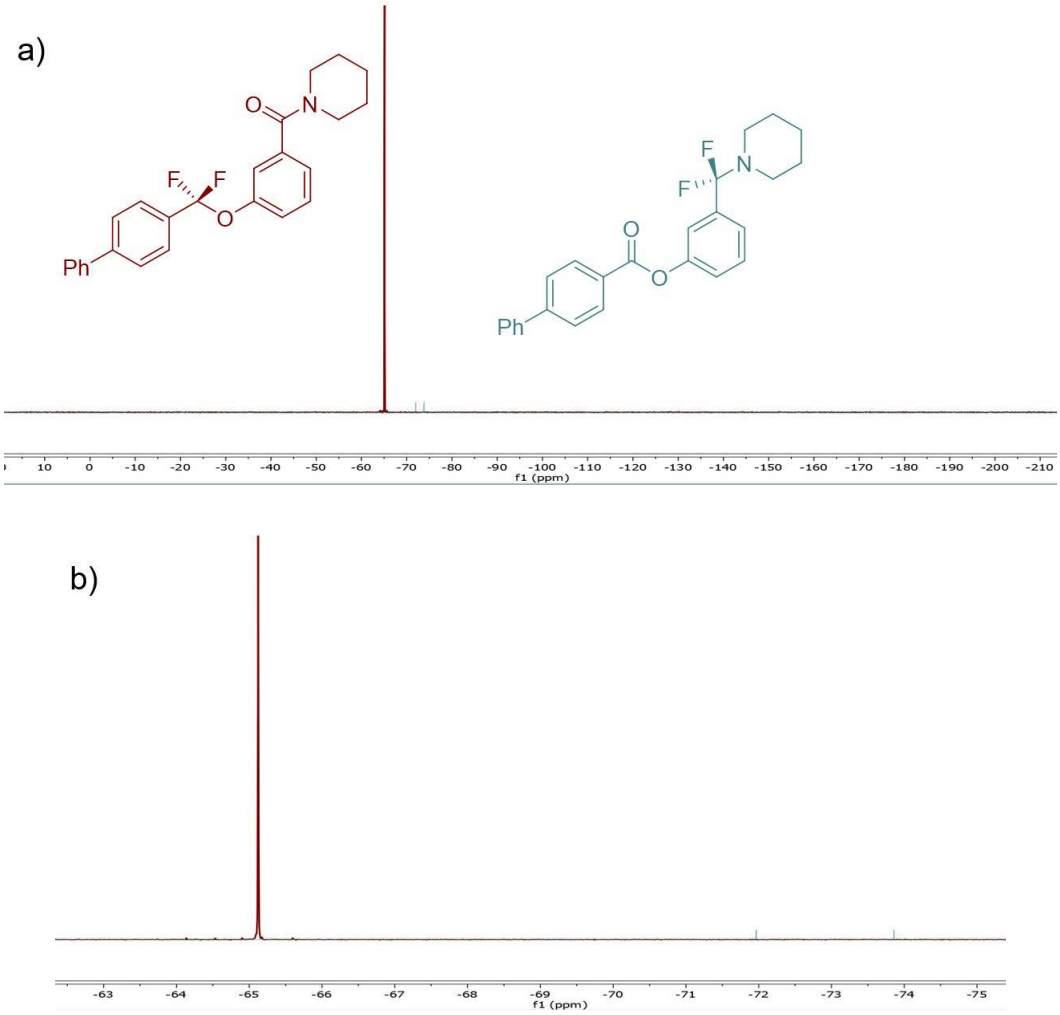


Figure SA6.6: (a) Overlay of ^{19}F NMR spectra of isolated fluorinated product from the difluoromethylarene oxidative coupling protocol (maroon spectrum) and from the nucleophilic fluorination of the thiolated carbonyl protocol (teal spectrum) describe above. (b) Zoomed in ^{19}F NMR spectrum from (a).

A6.7 Mechanistic Studies and Base Stability Tests

(a) Determination of the reaction profile

Purpose: This experiment was performed to analyze components of the reaction solution at different time points to observe the formation and consumption of potential reaction intermediates.

Procedure: Inside a N_2 filled glovebox, eight different oven-dried 4 mL vials (KIMBLE®, #60910-1) were each charged with magnetic stir bars, 4-(difluoromethyl)-2-phenylpyridine (20.5

mg, 0.1 mmol, 1.0 equiv), 4-methoxyphenol (18.6 mg, 0.15 mmol, 1.5 equiv), 2-bromothiophene (24.5 mg, 0.15 mmol, 1.5 equiv), anhydrous DMF (0.4 mL, 0.25 M), and KO-*t*-Bu (33.6 mg, 0.3 mmol, 3.0 equiv) in successive order. The vials were sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, B7995-13), removed from the glovebox, and were stirred at rt. After the time indicated, a reaction vial was quenched with 0.2 mL $CDCl_3$ and an aliquot was analyzed by ^{19}F NMR spectroscopy using 1,2-difluorobenzene as the internal standard (triplet centered at -138.18 ppm) to provide ^{19}F NMR spectroscopy yields of 4-(difluoromethyl)-2-phenylpyridine (**x**, -110.73 ppm (d, J = 59.2 Hz, 2F)), 4-(bromodifluoromethyl)-2-phenylpyridine intermediate (**x**, -47.73 ppm (s, 2F)) (see section 11 e for synthesis), and 4-(difluoro(4-methoxyphenoxy)methyl)-2-phenylpyridine (**x**, -62.63 ppm (s, 2F)). The data points are tabulated below. Vial 0 is an analysis of the reaction solution before addition of base. Note: A 10 second relaxation delay was used to achieve accurate integration (+/- 10%) using the 1,2-difluorobenzene internal standard in ^{19}F NMR spectroscopy.

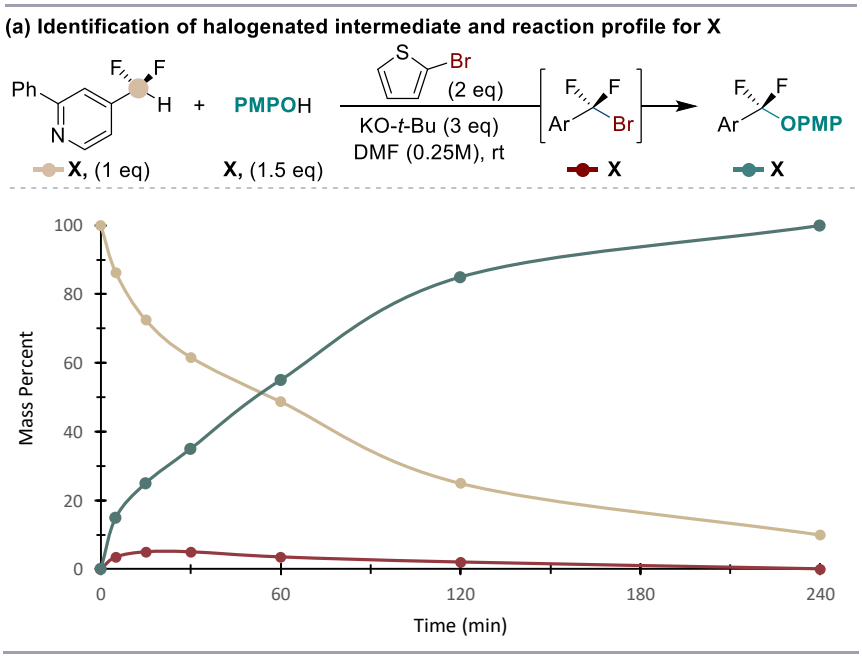


Figure SA6.7. Reaction profile analysis of x with XTR 1, PMPOH, and KO-*t*-Bu.

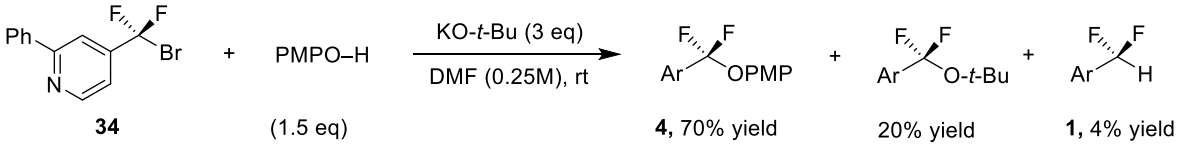
Table SA6.3. Numerical results for the reaction profile analysis of x.

Vial	Time (min)	$ArCF_2H$ (X)	$ArCF_2Br$ (X)	Product (X)
0	0	100%	0%	0%
1	5	86%	4%	15%
2	15	73%	5%	25%
3	30	62%	5%	35%
4	60	49%	4%	55%
5	120	25%	2%	85%
6	240	10%	0%	100%

Result: Upon monitoring the reaction over time, we observed the formation of 4-(bromodifluoromethyl)-2-phenylpyridine that is ultimately consumed by the end of the reaction. A small quantity of 4-(*tert*-butoxydifluoromethyl)-2-phenylpyridine was also observed over the course of the reaction.

b) Subjection of an $ArCF_2Br$ intermediate to pseudoreaction conditions

Discussion: We subjected the independently synthesized 4-(bromodifluoromethyl)-2-phenylpyridine, **3-34,** to pseudo-X-transfer oxidative coupling conditions to validate its role as a reaction intermediate as seen below. Formation of the desired etherified product is consistent with the halogenated compound being a productive reaction intermediate. No starting material (**3-1**) remaining.



Procedure: In a nitrogen-filled glovebox, to an oven-dried 1-dram glass vial charged with a Teflon-coated stir bar was added 4-(bromodifluoromethyl)-2-phenylpyridine (28.4 mg, 0.1 mmol,

1.0 equiv), KO-*t*-Bu (33.6 mg, 0.3 mmol, 3.0 equiv), PMPOH (18.6 mg, 0.15 mmol, 1.5 equiv) and anhydrous DMF (0.4 mL). The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, B7995-13), removed from the glovebox, and placed into an aluminum reaction block at rt with stirring. After 16 h, 1,3,5-trimethoxybenzene and 1,2-difluorobenzene standards were then measured into the reaction solution. A small aliquot was removed and injected into an NMR tube and constituted in $CDCl_3$ (0.5 mL). ^1H NMR spectroscopy (400 MHz, ($CDCl_3$) or ^{19}F NMR spectroscopy (376 MHz, $CDCl_3$) was used to determine the yield of 4-(difluoro(4-methoxyphenoxy)methyl)-2-phenylpyridine (**3-4**). The aromatic H signal of 1,3,5-trimethoxybenzene at 6.09 ppm (s, 3H) was integrated against the aromatic H signal of 4-(difluoro(4-methoxyphenoxy)methyl)-2-phenylpyridine (**3-4**) at 6.90 ppm (d, J = 9.1 Hz, 2H) to determine the yield. The aromatic F signal of 1,2-difluorobenzene at -138.18 ppm (t, J = 9.0 Hz, 2F) was integrated against the benzylic F signal of 4-(difluoro(4-methoxyphenoxy)methyl)-2-phenylpyridine (**3-4**) at -62.63 ppm (s, 2F) to determine the yield to be 70% by spectroscopy.

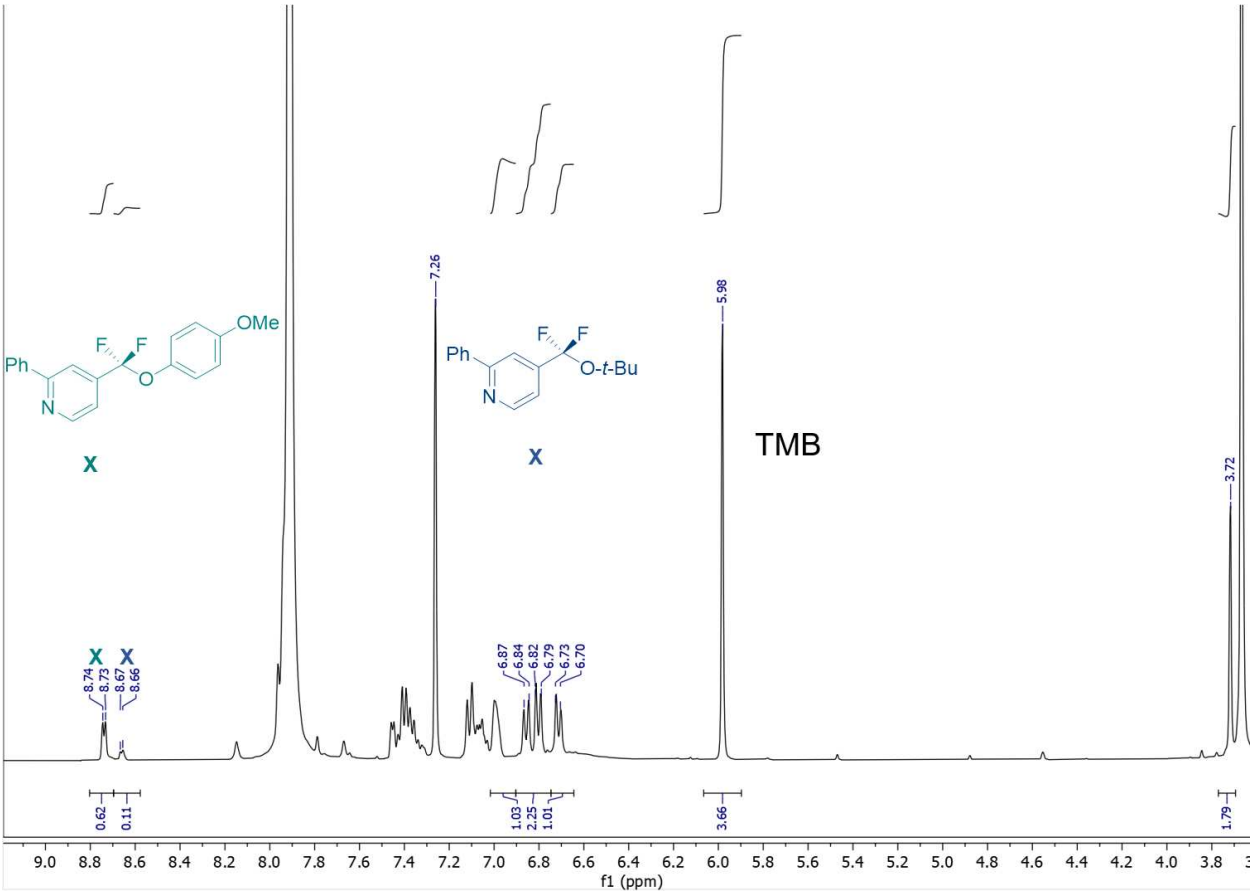


Figure SA6.8. [1]H NMR spectral window of the crude reaction solution of reaction above 1,3,5-Trimethoxybenzene internal standard (20.6 mg, 0.12 mmol, signal at 6.09 ppm calibrated to 3.66 for 0.1 mmol scale reaction) was used to determine the yield of 4-(difluoro(4-methoxyphenoxy)methyl)-2-phenylpyridine (**3-4**, 62% yield).

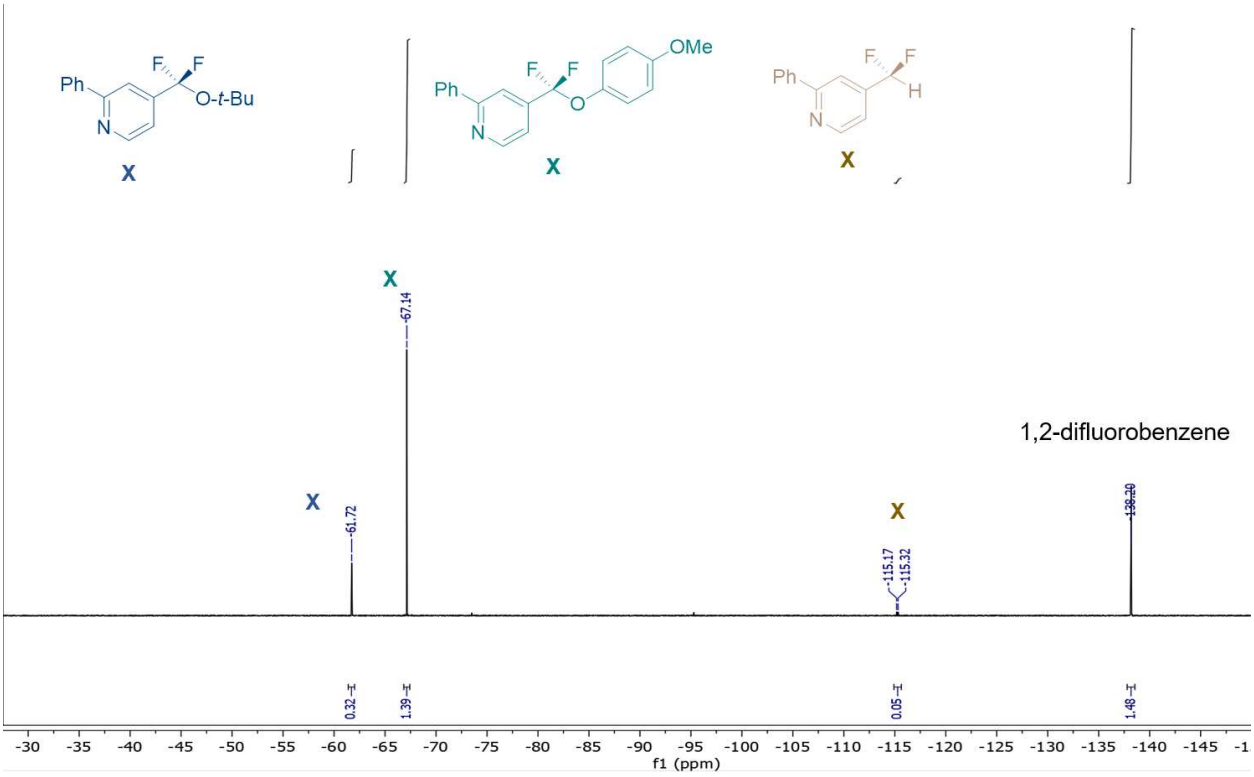


Figure SA6.9. ^{19}F NMR spectral window of the crude reaction solution of reaction above. 1,2-Difluorobenzene internal standard (8.5 mg, 0.07 mmol, signal at -138.18 ppm calibrated to 1.48 for 0.1 mmol scale reaction) was used to determine the yield of 4-(difluoromethyl)-2-phenylpyridine (**3-1**, 2% yield), 4-(difluoro(4-methoxyphenoxy)methyl)-2-phenylpyridine (**3-4**, 69% yield), 4-(tert-butoxydifluoromethyl)-2-phenylpyridine (16% yield), 4-(bromodifluoromethyl)-2-phenylpyridine (**3-34**, 0% yield).

c) Control studies to test the base-stability of $ArCF_2H$ in various solvents

Discussion: We conducted control studies on the base stability of difluoromethylarenes in the absence of X-transfer reagents and coupling partner. Here, KO-*t*-Bu in various solvents lead to rapid mass balance loss, showing that the difluorobenzylic anion undergoes decomposition. Additionally, 3.0 equiv of base in the presence of 1.5 equiv of pronuleophile maintained good mass balance, indicating that deprotonation to give a "stable" anion (e.g., alkoxide) is preferred over formation of unstable anions. We also note that loss of mass balance is observed when the pronucleophile is omitted from the reaction conditions but the XTR is present, indicating that all

three components of the reaction system are needed to effectively functionalize this base-sensitive carbanion.

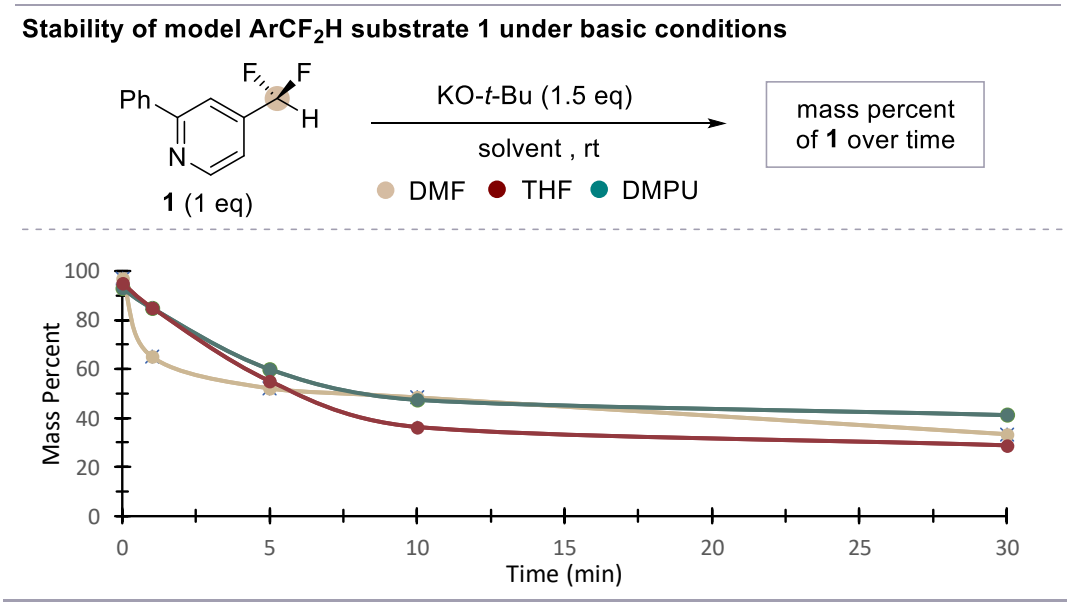


Figure SA6.10. Reaction profile analysis of **3-1** with KO-*t*-Bu in DMF, THF (with 18-crown-6, 1 eq), or DMPU.

Procedure: In a nitrogen-filled glovebox, to an oven-dried 1-dram glass vial charged with a Teflon-coated stir bar was added 4-(difluoromethyl)-2-phenylpyridine (20.5 mg, 0.1 mmol, 1.0 equiv), KO-*t*-Bu (16.8 mg, 0.15 mmol, 1.5 equiv), and anhydrous solvent (0.4 mL, 0.25 M). The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, B7995-13), removed from the glovebox, and placed into an aluminum reaction block at rt with stirring. After the allotted time, $CHCl_3$ (0.2 mL) was added to quench the reaction and then 1,3,5-trimethoxybenzene sand 1,2-difluorobenzene standards were measured into the reaction solution. A small aliquot was removed and injected into an NMR tube and constituted in $CDCl_3$ (0.5 mL). ^1H NMR spectroscopy (400 MHz, ($CDCl_3$) and ^{19}F NMR spectroscopy (376 MHz, $CDCl_3$) was used to determine the mass balance of 4-(difluoromethyl)-2-phenylpyridine (**3-1**). The aromatic H signal of 1,3,5-trimethoxybenzene at 6.09 ppm (s, 3H)

was integrated against the aromatic H signal of 4-(difluoromethyl)-2-phenylpyridine (**3-1**) at 6.90 ppm (d, *J* = 9.1 Hz, 2H) and the aromatic F signal of 1,2-difluorobenzene at -138.18 ppm (t, *J* = 9.0, 2.1 Hz) was integrated against the benzylic F signal of 4-(difluoromethyl)-2-phenylpyridine (**3-1**) at -110.73 ppm (d, *J* = 59.2 Hz, 2F) to determine the remaining mass balance.

Table SA6.4. Numerical results for the reaction profile analysis of **3-1** with only base.

Vial	Time (min)	DMF	THF	DMPU
0	0	100%	100%	100%
1	1	65%	85%	85%
2	5	52%	55%	60%
3	10	48%	36%	48%
4	30	33%	29%	41%

A6.8. Recovery and Regeneration of 2-Bromo-3-phenylbenzo[b]thiophene from a Multigram Scale Difluoromethylarene Etherification Reaction

a) Recovery of 3-phenylbenzo[*b*]thiophene from the multigram scale coupling of 3-14.

Procedure: Open to air, an oven-dried round bottom flask (100 mL) was charged with a magnetic stir bar along with **3-24** (1.47 g, 11.5 mmol, 1.0 equiv), **3-3** (2.14 g, 17.3 mmol, 1.5 equiv), **XTR 3** (5 .00 g, 17.3 mmol, 1.5 equiv), 18-crown-6 (3.00 g, 1.0 mmol, 1.0 equiv) and anhydrous THF (46 mL, 0.25 M). The flask was fitted with a rubber septum , inserted into an oil bath and sparged with N2 while stirring vigorously for 5-10 minutes. Then KHMDS (6.88 g, 34 .5 mmol, 3.0 equiv) was added all at once, the flask was attached to a reflux condenser (under N_2 using a needle attached a Schlenk manifold) and was heated to 50 °C and stirred for 16 h. The reaction solution was allowed to cool to room temperature and the product was purified *via* Isolation Procedure I (Section 3) (100 to 90:10 gradient of Hexanes/EtOAc) to afford the dehalogenated product **3-25**

as a clear oil (3.91 g, 15.4 mmol, 89% yield) and the title compound as a pale yellow oil (1.96 g, 7.82 mmol, 68% yield). These results match those described above for the 1 mmol Schlenk line protocol (**3-14**).

b) Regeneration of 2-bromo-3-phenylbenzo[*b*]thiophene

Procedure: A round bottom flask (100 mL) was charged with a magnetic stir bar, compound **3-25** (3.9 g, 15 mmol, 1 equiv), and DMF (40 mL, 0.4 M) and was cooled to 0 °C. Then *N*-bromosuccinimide (3.00 g, 12.5 mmol, 1.1 equiv) was added to the flask and the solution was warmed to rt while stirring. After 2 h, additional N-bromosuccinimide (3.0 g, 12.5 mmol, 1.1 equiv) was added to the solution and stirred at rt for another 4 h. Upon completion (monitored by TLC), H_2O (60 mL) was added to the reaction flask, where the title compound crashed out of solution. The mixture was filtered and the solid was purified *via* flash chromatography on silica gel (100 to 90:10 Hexanes/EtOAc) to afford the title compound as a pale yellow solid (4.4 g, 14.3 mmol, 95% yield). 1H NMR (400 MHz, CDCl3) δ 7.77 (d, J = 7.9, 0.9 Hz, 1H), 7.59 – 7.41 (m, 7H), 7.40 – 7.26 (m, 2H). 13C NMR (101 MHz, CDCl3) δ 139.8, 138.8, 137.2, 133.9, 130.0, 128.6, 128.1, 124.8, 122.9, 121.7, 113.3.

A6.9. Application of X-transfer Platform to Additional Unstable C–H Bonds

Discussion: Based on the above studies, we questioned if the X-transfer platform was potentially responsible for capturing other types of unstable carbanions in our group's previously published methods. [9] We previously reported conditions for C–H substitution of N-heteroarenes, benzenes and toluenes. Notably, the scope of these methods include substrates that may be considered to be unstable under strongly basic reaction conditions. This includes *ortho*-halo aryl carbanions and substituted methylarenes that are prone to aryne formation, and substrates that contain base-

sensitive functional groups such as 1,3-azoles, haloarenes, styrenes, and -CF_3 groups in conjugation with a carbanion. To test this effect, we subjected these substrates to base control studies to determine if they are unstable to base alone. The choice of base was based off the optimized and published procedures for the X-transfer promoted oxidative coupling reactions.

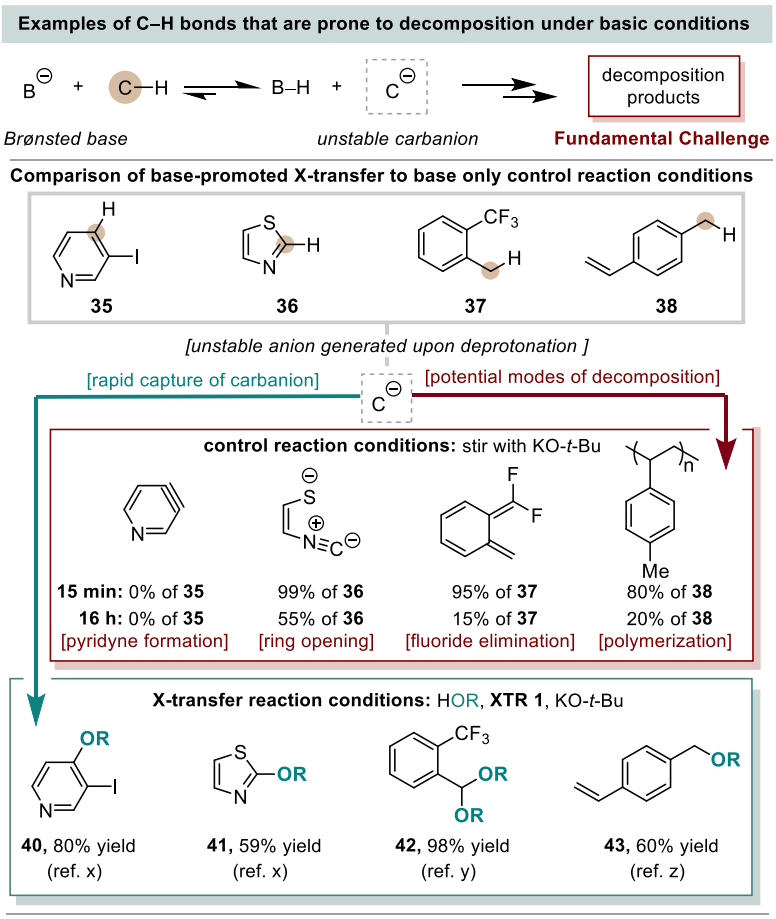


Figure SA6.11. Analysis of other C–H bonds under X-transfer coupling conditions compared to base-only reaction conditions.

Procedure: In a nitrogen-filled glovebox, to an oven-dried 1-dram glass vial charged with a Teflon-coated stir bar was added substrate (0.1 mmol, 1.0 equiv), KO-t¬-Bu (22.4 mg or 44.8 mg, 0.2 mmol or 0.4 mmol, 2 or 4 equiv) and anhydrous solvent (0.4 mL, 0.25 M). The vial was sealed with a screw cap (Thermo Fisher Scientific, #C4015-1A) lined with a PTFE septum (Thermo Fisher Scientific, B7995-13), removed from the glovebox, and placed into an aluminum reaction

block at rt with stirring. After the allotted time, AcOH (0.1 mL) was added to quench the reaction and then 1,3,5-trimethoxybenzene standard was measured into the reaction solution. For thiazole **3-36** and benzotrifluoride **3-37**, an additional 1.0 to 0.5 mL of MeOH was added to solubilize any precipitate that formed. A small aliquot was removed and injected into an NMR tube and constituted in CDCl3 (0.5 mL). 1H NMR spectroscopy (400 MHz, (CDCl3) was used to determine the mass balance of the substrate (**3-35** through **3-38**) remaining. The aromatic H signal of 1,3,5-trimethoxybenzene at 6.09 ppm (s, 3H) was integrated against the characteristic aromatic peaks of the respective substrate to determine the yield.

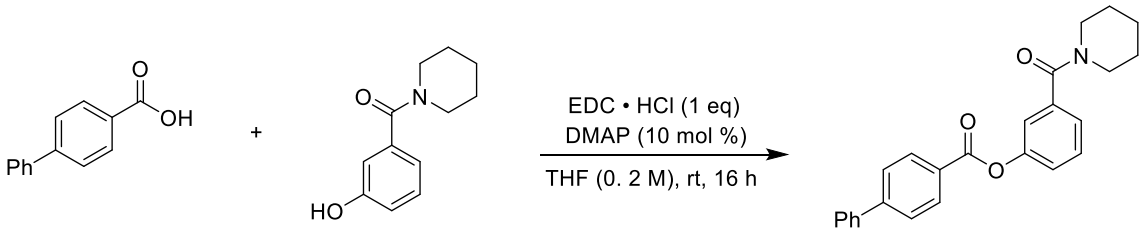
Table SA6.5: ^{1}H NMR spectroscopy analysis for evaluation of mass balance for 3-iodopyridine, thiazole, 2-methylbenzotrifluoride, and 4-methylstyrene.

Substrate	Chemical Shift (δ)	Splitting	Integration
3-iodopyridine (**35**)	8.82 ppm	s	1
thiazole (**36**)	8.87 ppm	s	1
2-methylbenzotrifluoride (**37**)	7.57 ppm	d (*J* = 7.8 Hz)	1
4-methylstyrene (**38**)	5.67 ppm	d (*J* = 17.6 Hz)	1

A6.10 Synthesis and Characterization of Starting Materials

All substrates that are not described below were purchased from commercial suppliers and used as received. All non-commercial substrates and reagents used are described below.

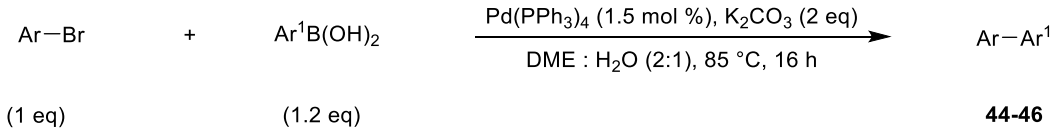
a) Peptide Coupling (x)



x (1 eq) **x** (1 eq) **X**, 94% yield (3.56 g)

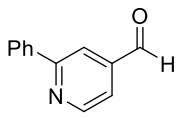
Procedure: To an oven-dried round bottom flask (100 mL) charged with a Teflon-coated stir bar was added [1,1'-biphenyl]-4-carboxylic acid (1.98 g, 10.0 mmol, 1.0 equiv), (3-hydroxyphenyl)(piperidin-1-yl)methanone (2.05 g, 10.0 mmol, 1.0 equiv), THF (50 mL, 0.2 M), DMAP (122.2 mg, 1.0 mmol, 0.1 equiv) and EDC•HCl (1.92 g, 10.0 mmol, 1.0 equiv). The reaction mixture was stirred at rt for 16 h. After 16 h, the reaction mixture was filtered and concentrated *in vacuo*. Silica gel column chromatography (70% ethyl acetate in hexanes) provided the product **xx** as a white solid (3.38 g, 9.9 mmol, 99% yield). **^{1}H NMR** (400 MHz, CDCl3) δ 8.28 (d, *J* = 9.1 Hz, 2H), 7.76 (d, *J* = 8.1 Hz, 2H), 7.69 (d, *J* = 7.6 Hz, 2H), 7.56 – 7.41 (m, 4H), 7.37 – 7.30 (m, 3H), 3.59 (d, *J* = 118.6 Hz, 4H), 1.83 – 1.61 (m, 6H). **IR** (neat, cm^{-1}) 3010, 2962, 2837, 2361, 2235, 1727, 1606, 1594, 1504, 1466, 1321, 1250, 1147, 1111, 1046, 1027, 846, 793, 740, 689, 592. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{25}H_{23}NO_3]^+$ = 386.1678, 386.1795 found. **Melting Point:** 122-124 ºC.

b) Suzuki cross-coupling for synthesis of biaryl compounds

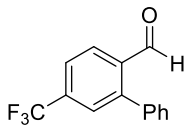


General Procedure: An oven-dried round bottom flask (100 mL) was charged with a magnetic stir bar, bromoarene (20 mmol, 1 equiv), arylboronic acid (24 mmol, 1.2 equiv), K_2CO_3 (5.6 g, 40 mmol, 2 equiv), DME (40 mL) and water (20mL) and was sparged with N_2 while stirring vigorously for 10 minutes. $Pd(PPh_3)_4$ (280 mg, 0.3 mmol, 0.015 equiv) was then added to the flask and the flask was fitted with a reflux condenser and inserted into a preheated 85 °C silicon oil bath and stirred for 16 h. The reaction mixture was cooled to rt and transferred to a separatory funnel containing H_2O (50 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (3 x

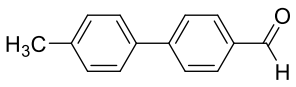
40 mL). The combined organic layers were washed with brine (1 x 50 mL) and then dried over Na_2SO_4, filtered, and then concentrated *in vacuo* before purification by flash chromatography on silica gel to yield the title compound. This material was used directly in the next step for deoxyfluorination.



2-phenylisonicotinaldehyde (3-44). The title compound was prepared according to the general procedure using 2-bromoisonicotinaldehyde (3.72 g, 20.0 mmol, 1.0 equiv), phenylboronic acid (2.92 g, 24 mmol, 1.2 equiv), K_2CO_3 (5.6 g, 40 mmol, 2 equiv), DME (40 mL) and water (20mL), and $Pd(PPh_3)_4$ (280 mg, 0.3 mmol, 0.015 equiv). The product was purified *via* silica gel flash chromatography (100 to 80:20 Hexanes/EtOAc) to afford the title compound as a yellow oil (3.12 g, 17 mmol, 85% yield). **^{1}H NMR** 400 MHz, $CDCl_3$) δ 10.15 (s, 1H), 8.95 (d, *J* = 4.8 Hz, 1H), 8.14 (s, 1H), 8.06 (d, *J* = 7.0 Hz, 2H), 7.64 (d, *J* = 5.0 Hz, 1H), 7.56 – 7.42 (m, 3H). The spectroscopic data is consistent with a previous report. [10] This material was used directly in the next step for deoxyfluorination.



5-(trifluoromethyl)-[1,1'-biphenyl]-2-carbaldehyde (3-45). The title compound was prepared according to the general procedure using 2-bromo-4-(trifluoromethyl)benzaldehyde (5.6 g, 20.0 mmol, 1.0 equiv)), phenylboronic acid (2.92 g, 24 mmol, 1.2 equiv), K_2CO_3 (5.6 g, 40 mmol, 2 equiv), DME (40 mL) and water (20mL), and $Pd(PPh_3)_4$ (280 mg, 0.3 mmol, 0.015 equiv). The product was purified *via* silica gel flash chromatography (100 to 90:10 Hexanes/EtOAc) to afford the title compound as a yellow oil (4.13 g, 16.5 mmol, 82% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.94 (s, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 9.9 Hz, 2H), 7.50 – 7.38 (m, 3H), 7.38 – 7.29 (m, 2H). The spectroscopic data is consistent with a previous report. [11]



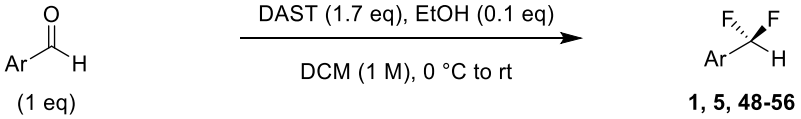
4'-methyl-[1,1'-biphenyl]-4-carbaldehyde (3-46). The title compound was prepared according to the general procedure using 4-bromobenzaldehyde (1.85 g, 10.0 mmol, 1.0 equiv), *p*-tolylboronic acid (1.63 g, 12.0 mmol, 1.2 equiv), K_2CO_3 (5.6 g, 40 mmol, 2 equiv), DME (40 mL) and water (20mL), and $Pd(PPh_3)_4$ (280 mg, 0.3 mmol, 0.015 equiv). The product was purified *via* silica gel flash chromatography (100% DCM) to afford the title compound as a white powder (1.89 g, 9.6 mmol, 96% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.05 (s, 1H), 7.94 (d, J = 9.0 Hz, 2H), 7.74 (d, J = 9.0 Hz, 2H), 7.54 (d, J = 11.1 Hz, 2H), 7.29 (d, J = 9.0 Hz, 6H), 2.42 (s, 3H). The spectroscopic data is consistent with a previous report. [12]

c) Pd-catalyzed hydrodechlorination to synthesize 6-methylquinoline-3-carbaldehyde (3-47).

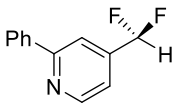
Procedure: An oven-dried round bottom flask (250 mL) was charged with a magnetic stir bar, 2-chloro-6-methylquinoline-3-carbaldehyde (2.05 g, 10 mmol, 1.0 equiv), TEA (8 mL, 60 mmol, 6.0 equiv) and DMF (100 mL, 0.1 M) and was sparged with N_2 while stirring vigorously for 10 minutes. $Pd(PPh_3)_4$ (1.00 g, 1.0 mmol, 0.1 equiv) was then added to the flask followed by formic acid (2.26 mL, 54 mmol, 5.4 equiv) dropwise *via* syringe. The flask was then fitted with a reflux condenser and inserted into a preheated 110 °C silicon oil bath and stirred for 2 h. The reaction mixture was cooled to rt and quenched slowly with H_2O before it was transferred to a separatory funnel containing H_2O (50 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (1 x 50 mL) and then dried

over Na_2SO_4, filtered, and then concentrated *in vacuo* before purification by flash chromatography on silica gel (80:20 Hexanes/EtOAc) to afford the title compound as a yellow solid (942 mg, 5.5 mmol, 55% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.26 (s, 1H), 9.31 (s, 1H), 8.57 (s, 1H), 8.10 (d, *J* = 8.6 Hz, 1H), 7.83 – 7.59 (m, 2H), 2.60 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 190.8, 163.5, 149.0, 148.3, 139.5, 138.2, 135.2, 129.1, 128.7, 128.2, 127.2, 21.6. The spectroscopic data is consistent with a previous report. [13] This material was used directly in the next step for deoxyfluorination.

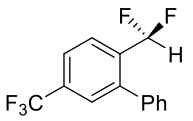
d) Aldehyde deoxyfluorination to prepare difluoromethylarenes



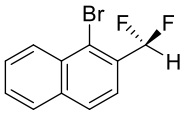
Procedure: An oven-dried round bottom flask (100 – 250 mL) was charged with a magnetic stir bar, benzaldehyde (1.0 equiv) and anhydrous DCM (1 M). The flask was sealed with a septum and was sparged with N_2 while stirring vigorously for 10 minutes at 0 °C in an ice bath. Diethylaminosulfur trifluoride (1.7 equiv) was then added to the flask *via* syringe and the reaction solution was stirred at 0 °C for 5 min. Ethanol (0.1 equiv) was then added dropwise *via* syringe (special care was taken during this addition as it is quite exothermic) at 0 °C. The reaction solution was then allowed to warm to rt as it stirred. After 16 h, the reaction mixture was cooled to 0 °C and quenched slowly with $NaHCO_3$ (sat. aq) before being transferred to a separatory funnel containing H_2O (50 mL) and DCM (20 mL). The aqueous layer was extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine (1 x 50 mL) and then dried over Na_2SO_4, filtered and concentrated *in vacuo* before purification by flash chromatography on silica gel to yield the title compound.



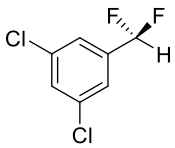
4-(difluoromethyl)-2-phenylpyridine (3-1). The title compound was prepared according to the general procedure using 2-phenylisonicotinaldehyde (3.12 g, 17.0 mmol, 1.0 equiv), diethylaminosulfur trifluoride (4.50 mL, 34.0 mmol, 2.0 equiv), EtOH (0.15 mL, 1.70 mmol, 0.1 equiv), DCM (20 mL, 1 M). The product was purified *via* silica gel flash chromatography (80:20 Hexanes/EtOAc) to afford the title compound as a yellow oil (2.31 g, 0.66 mmol, 66% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.83 (d, *J* = 5.0 Hz, 1H), 8.08 – 8.02 (m, 2H), 7.85 (s, 1H), 7.59 – 7.41 (m, 3H), 7.35 (d, *J* = 5.0 Hz, 1H), 6.70 (t, *J* = 55.8 Hz, 1H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -110.73 (d, *J* = 59.2 Hz, 2F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.4, 150.4, 142.9 (t, *J* = 23.3 Hz), 138.5, 129.6, 128.9, 127.0, 118.2 (t, *J* = 5.7 Hz), 116.6 (t, *J* = 6.0 Hz), 113.2 (t, *J* = 240.9 Hz). The spectroscopic data is consistent with a previous report. [14]



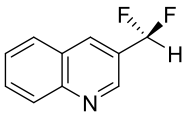
2-phenyl-4-(trifluoromethyl) difluoromethylbenzene (3-48). The title compound was prepared according to the general procedure using 5-(trifluoromethyl)-[1,1'-biphenyl]-2-carbaldehyde (4.13 g, 16.5 mmol, 1.0 equiv), diethylaminosulfur trifluoride (4.50 mL, 34.0 mmol, 2.1 equiv), EtOH (0.15 mL, 1.70 mmol, 0.1 equiv), DCM (20 mL, 1 M). The product was purified *via* silica gel flash chromatography (100% Hexanes) to afford the title compound as a clear oil (3.5 g, 0.78 mmol, 78% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.66 (s, 1H), 7.56 – 7.45 (m, 3H), 7.44 – 7.36 (m, 2H), 6.58 (t, *J* = 54.5 Hz, 1H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -58.09, -103.64 (d, *J* = 54.8 Hz, 2F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.2 (t, *J* = 6.5 Hz), 137.2, 135.1 (t, *J* = 22.6 Hz), 132.6 (q, *J* = 48.2, 33.3, 32.0, 31.5 Hz), 129.4, 128.7, 128.6, 127.2 (q, *J* = 3.8 Hz), 126.5 (t, *J* = 5.3 Hz), 125.0, 124.7 (q, *J* = 3.7 Hz), 122.3, 112.2 (t, *J* = 237.2 Hz). **IR** (neat, cm^{-1}) 3060, 1492, 1447, 1417, 1382, 1335, 1294, 1251, 1206, 1170, 1126, 1064, 1030, 1020, 904, 865, 839, 802, 771, 701, 661, 607. **HRMS** (ESI) $[M-H]^-$ calcd. for $[C_{14}H_9F_5]^-$ = 271.0624, 271.2590 found.



1-bromo-2-(difluoromethyl) napthalene (3-49). The title compound was prepared according to the general procedure using 1-bromo-2-naphthaldehyde (2.35 g, 10.0 mmol, 1.0 equiv), diethylaminosulfur trifluoride (2.30 mL, 17.0 mmol, 1.7 equiv), EtOH (0.1 mL, 1.00 mmol, 0.1 equiv), DCM (10 mL, 1 M). The product was purified *via* silica gel flash chromatography (98:2 Hexanes/EtOAc) to afford the title compound as a white powder (1.72 g, 6.7 mmol, 67% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 8.4 Hz, 1H), 7.93 (dd, *J* = 14.4, 8.2 Hz, 2H), 7.78 – 7.61 (m, 3H), 7.28 (t, 1H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -108.10 (d, *J* = 55.2 Hz, 2F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.4, 131.8, 131.2 (t, *J* = 23.6 Hz), 128.6, 128.4, 128.2, 128.1, 127.7, 123.3 (t, *J* = 7.7 Hz), 122.6 (t, *J* = 5.7 Hz), 114.8 (t, *J* = 238.0 Hz). The spectroscopic data is consistent with a previous report. [15]

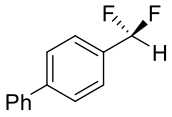


(3,5-dichloro)difluoromethylbenzene (3-50). The title compound was prepared according to the general procedure using 3,5-dichlorobenzaldehyde (3.50 g, 20.0 mmol, 1.0 equiv), diethylaminosulfur trifluoride (4.50 mL, 34.0 mmol, 1.7 equiv), EtOH (0.2 mL, 2.00 mmol, 0.1 equiv), DCM (20 mL, 1 M). The product was purified *via* silica gel flash chromatography (100% Hexanes) to afford the title compound as a clear oil (3.0 g, 0.76 mmol, 76% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.31 (s, 2H), 6.49 (t, *J* = 56.0 Hz, 1H).**^{19}F NMR** (376 MHz, $CDCl_3$) δ -107.45 (d, *J* = 55.9 Hz, 2F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.2 (t, *J* = 23.3 Hz), 135.6, 130.9 (t, *J* = 1.9 Hz), 124.3 (t, *J* = 6.2 Hz), 112.8 (t, *J* = 241.2 Hz). The spectroscopic data is consistent with a previous report. [16]

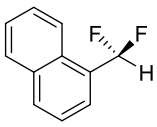


3-difluoromethylquinoline (3-51). The title compound was prepared according to the general procedure using quinoline-3-carbaldehyde (1.57 g, 10.0 mmol, 1.0 equiv), diethylaminosulfur trifluoride (2.30 mL, 17.0 mmol, 1.7 equiv), EtOH (0.1 mL, 1.00 mmol,

0.1 equiv), DCM (10 mL, 1 M). The product was purified *via* silica gel flash chromatography (100 to 90:10 Hexanes/EtOAc) to afford the title compound as a pale yellow oil (1.0 g, 0.56 mmol, 56% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.34 (s, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.84 (t, *J* = 7.7, 6.8 Hz, 1H), 7.66 (t, J = 7.5 Hz, 1H), 6.92 (t, *J* = 55.8 Hz, 1H).**^{19}F NMR** (376 MHz, $CDCl_3$) δ -106.66 (d, J = 55.6 Hz, 2F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.1, 147.1 (t, *J* = 5.3 Hz), 133.9 (t, *J* = 6.7 Hz), 131.1, 129.6, 128.4, 127.6, 126.9, 113.7 (t, *J* = 239.5 Hz). The spectroscopic data is consistent with a previous report. [17]

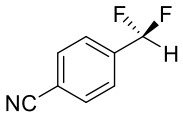


4-(difluoromethyl)-1,1'-biphenyl (3-2). The title compound was prepared according to the general procedure using [1,1'-biphenyl]-4-carbaldehyde (3.64 g, 20.0 mmol, 1.0 equiv), diethylaminosulfur trifluoride (4.50 mL, 34.0 mmol, 1.7 equiv), EtOH (0.15 mL, 2.00 mmol, 0.1 equiv), DCM (20 mL, 1 M). The product was purified *via* silica gel flash chromatography (80:20 Hexanes/EtOAc) to afford the title compound as a white powder (2.25 g, 0.55 mmol, 55% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.67 – 7.56 (m, 4H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 7.3 Hz, 1H), 6.72 (t, *J* = 56.5 Hz, 1H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -105.61 (d, *J* = 56.5 Hz, 2F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.7, 140.2, 133.2, 128.9, 127.9, 127.5, 127.3, 126.0 (t, *J* = 6.0 Hz), 114.8 (t, *J* = 238.4 Hz). The spectroscopic data is consistent with a previous report. [18]

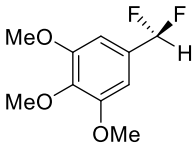


1-(difluoromethyl)naphthalene (3-52). The title compound was prepared according to the general procedure using 1-naphthaldehyde (3.12 g, 20.0 mmol, 1.0 equiv), diethylaminosulfur trifluoride (4.50 mL, 34.0 mmol, 1.7 equiv), EtOH (0.15 mL, 2.00 mmol, 0.1 equiv), DCM (20 mL, 1 M). The product was purified *via* silica gel flash chromatography (90:10 Hexanes/EtOAc) to afford the title compound as a clear oil (2.14 g, 12.0

mmol, 60% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.3 Hz, 1H), 7.93 (dd, *J* = 19.7, 8.1 Hz, 2H), 7.68 (d, *J* = 7.1 Hz, 1H), 7.63 – 7.45 (m, 3H), 7.15 (t, *J* = 55.9, 54.7 Hz, 2H).**^{19}F NMR** (376 MHz, $CDCl_3$) δ -63.50 (s, 2F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 133.8, 131.5 (t, *J* = 1.9 Hz), 129.7, 129.5 (t, *J* = 21.0, 20.0 Hz), 128.8, 127.2, 126.4, 124.8 (t, *J* = 8.6 Hz), 124.7, 123.6 (d, *J* = 1.9 Hz), 115.4 (t, *J* = 238.4 Hz). The spectroscopic data is consistent with a previous report. [19]

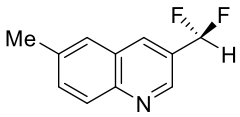


4-carbonitrile-(difluoromethyl)benzene (3-53). The title compound was prepared according to the general procedure using 4-carbonitrile-benzaldehyde (2.62 g, 20.0 mmol, 1.0 equiv), diethylaminosulfur trifluoride (4.50 mL, 34.0 mmol, 1.7 equiv), EtOH (0.15 mL, 2.00 mmol, 0.1 equiv), DCM (20 mL, 1 M). The product was purified *via* silica gel flash chromatography (100 to 70:30 Hexanes/EtOAc) to afford the title compound as a yellow oil (2.56 g, 0.84 mmol, 84% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 6.62 (t, *J* = 55.8 Hz, 1H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -108.48 (d, J = 56.8 Hz, 2F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.6 (t, *J* = 22.8 Hz), 132.6, 126.4 (t, *J* = 6.1 Hz), 117.9, 115.8, 114.8 (t, *J* = 2.2 Hz), 113.4, 111.0. The spectroscopic data is consistent with a previous report. [19]

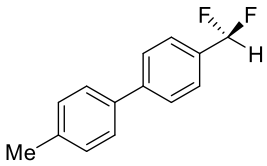


3,4,5-trimethoxy(difluoromethyl)benzene (3-54). The title compound was prepared according to the general procedure using 3,4,5-trimethoxybenzaldehyde (3.92 g, 20.0 mmol, 1.0 equiv), diethylaminosulfur trifluoride (4.50 mL, 34.0 mmol, 1.7 equiv), EtOH (0.15 mL, 2.00 mmol, 0.1 equiv), DCM (20 mL, 1 M). The product was purified *via* silica gel flash chromatography (100 to 80:20 Hexanes/EtOAc) to afford the title compound as a white powder (2.67 g, 12.2 mmol, 61% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.66 (s, 2H), 6.51 (t, *J* = 55.9 Hz, 1H), 3.91 (s, 9H). **^{19}F NMR** (376

MHz, $CDCl_3$) δ -104.66 (d, *J* = 56.6 Hz, 2F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.6, 139.8 (d, *J* = 2.4 Hz), 129.7 (t, *J* = 22.5 Hz), 114.6 (t, *J* = 239.1 Hz), 102.6 (t, *J* = 6.2 Hz), 60.9, 56.2. The spectroscopic data is consistent with a previous report. [20]



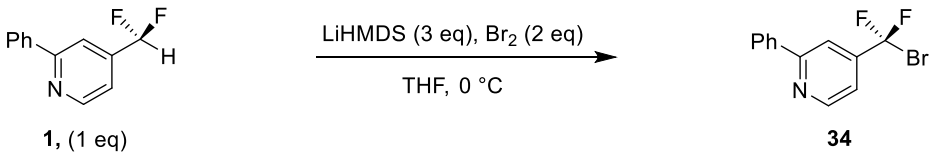
3-(difluoromethyl)-6-methylquinoline (3-55). The title compound was prepared according to the general procedure using 6-methylquinoline-3-carbaldehyde (942 mg, 5.50 mmol, 1.0 equiv), diethylaminosulfur trifluoride (2.30 mL, 17.0 mmol, 3.1 equiv), EtOH (0.1 mL, 1.00 mmol, 0.4 equiv), DCM (10 mL, 0.6 M). The product was purified *via* silica gel flash chromatography (80:20 Hexanes/EtOAc) to afford the title compound as a yellow powder (0.74 mg, 3.8 mmol, 70% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.25 (s, 1H), 8.09 (d, *J* = 8.6 Hz, 1H), 7.68 (d, *J* = 9.2 Hz, 2H), 6.90 (t, *J* = 55.9 Hz, 1H), 2.60 (s, 3H).**^{19}F NMR** (376 MHz, $CDCl_3$) δ -106.59 (d, *J* = 55.7 Hz, 2F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.7, 146.2 (t, *J* = 7.1, 5.2 Hz), 137.7, 133.4, 133.2 (t, *J* = 6.7 Hz), 129.2, 127.1, 126.9, 113.8 (t, *J* = 239.4 Hz), 30.9, 21.6. The spectroscopic data is consistent with a previous report. [21]



4-(difluoromethyl)-4'-methyl-1,1'-biphenyl (3-56). The title compound was prepared according to the general procedure using 4'-methyl-[1,1'-biphenyl]-4-carbaldehyde (1.90 g, 9.60 mmol, 1.0 equiv), diethylaminosulfur trifluoride (2.30 mL, 17.0 mmol, 1.9 equiv), EtOH (0.1 mL, 1.00 mmol, 0.1 equiv), DCM (10 mL, 1 M). The product was purified *via* silica gel flash chromatography (100% Hexanes) to afford the title compound as a white powder (1.4 g, 6.7 mmol, 70% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 8.3, 2.3 Hz, 2H), 7.30 (d, *J* = 6.9 Hz, 2H), 6.72 (t, *J* = 56.5, 1H), 2.44 (s, 3H).**^{19}F NMR** (376 MHz, $CDCl_3$) δ -105.35 (d, *J* = 56.2 Hz, 2F). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.6 (d, J = 2.0 Hz), 137.8, 137.3,

132.9 (t, J = 22.5 Hz), 129.7, 127.2, 127.1, 126.0 (t, J = 6.0 Hz), 114.8 (t, J = 238.4 Hz), 21.2. The spectroscopic data is consistent with a previous report. [22]

e) Bromination of 4-(difluoromethyl)-2-phenylpyridine (3-34).[23]



1, (1 eq) **34**

Procedure: This procedure was inspired by a literature report for 2-chloro-3-(difluoromethyl)quinoxaline base-promoted bromination. An oven-dried round bottom flask (10 mL) was charged with a magnetic stir bar, 4-(difluoromethyl)-2-phenylpyridine (205.2 mg, 1 mmol, 1.0 equiv), THF (4 mL, 0.25 M) and bromine (0.1 mL, 2 mmol, 2.0 equiv), and was cooled to 0 °C in an ice bath. LiHMDS (502 mg, 3.0 mmol, 3.0 equiv) was then added to the flask slowly. The reaction flask was capped with a yellow stopper and allowed to stir at 0 °C for 12 h. $NaSO_3$ (sat. aq. solution, 5 mL) was added to the reaction slowly to quench the remaining bromine before the solution was transferred to a separatory funnel containing H_2O (50 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (1 x 50 mL) and then dried over Na_2SO_4, filtered, and then concentrated *in vacuo* before purification *via* silica gel flash chromatography (100 to 90:10 gradient Hexanes/EtOAc) to afford 4-(bromodifluoromethyl)-2-phenylpyridine (**xx**) as a yellow oil (223.9 mg, 0.79 mmol, 79% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.84 (dd, *J* = 5.1, 0.8 Hz, 1H), 8.07 – 7.99 (m, 2H), 7.89 (dt, *J* = 1.7, 0.8 Hz, 1H), 7.61 – 7.46 (m, 3H), 7.42 (dd, *J* = 5.2, 1.7 Hz, 1H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -47.73 (s, 2F). **NMR** (101 MHz, $CDCl_3$) δ 158.8, 150.6, 146.3 (t, *J* = 25.3 Hz), 138.2, 129.8, 129.0, 127.1, 118.3 (t, *J* = 304.1 Hz), 116.5 (t, *J* = 4.7 Hz), 114.9 (t, *J*

= 4.9 Hz). **IR** (neat, cm^{-1}) 3050, 2360, 1598, 1561, 1473, 1445, 1397, 1306, 1274, 1232, 1129, 1101, 1078, 1053, 1026, 913, 881, 836, 735, 702, 690, 612. **HRMS** (ESI) $[M+H]^+$ calcd. for $[C_{12}H_8BrF_2N]^+$ = 283.9808 283.9979 found.

A6.11 References

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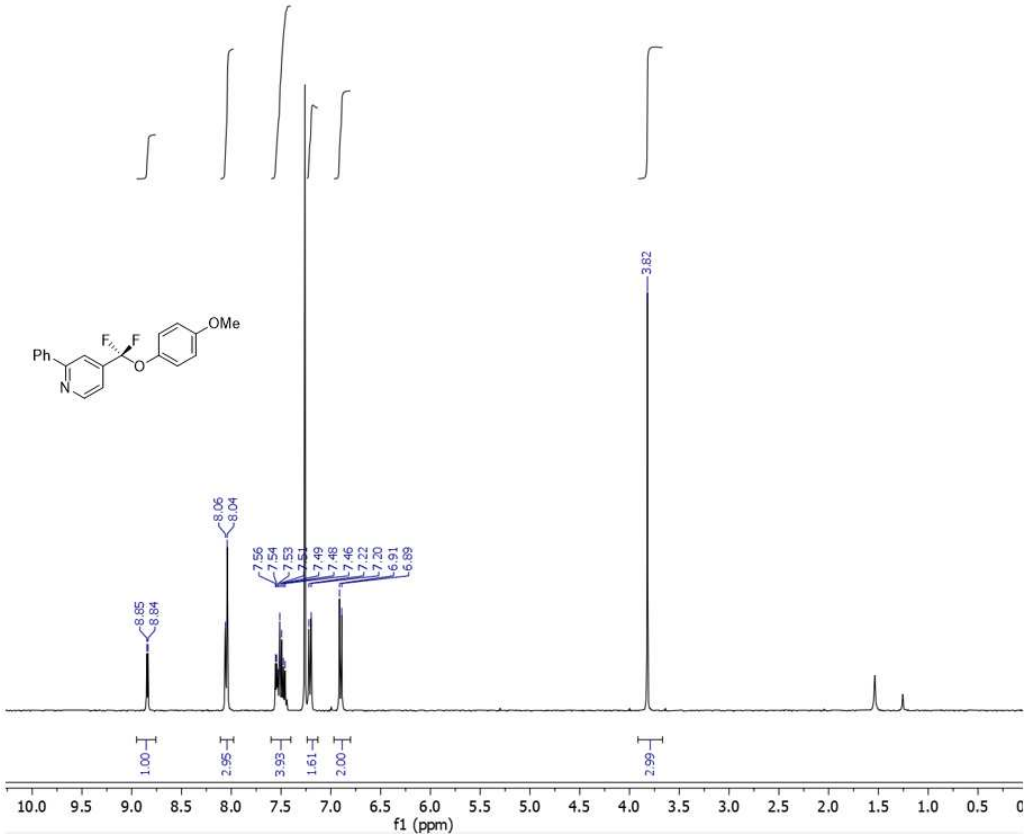
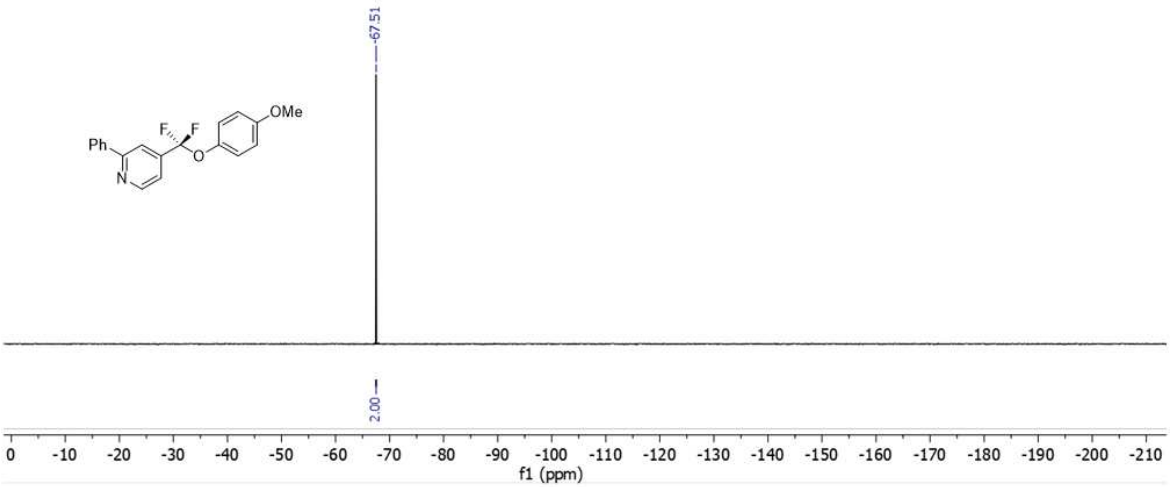
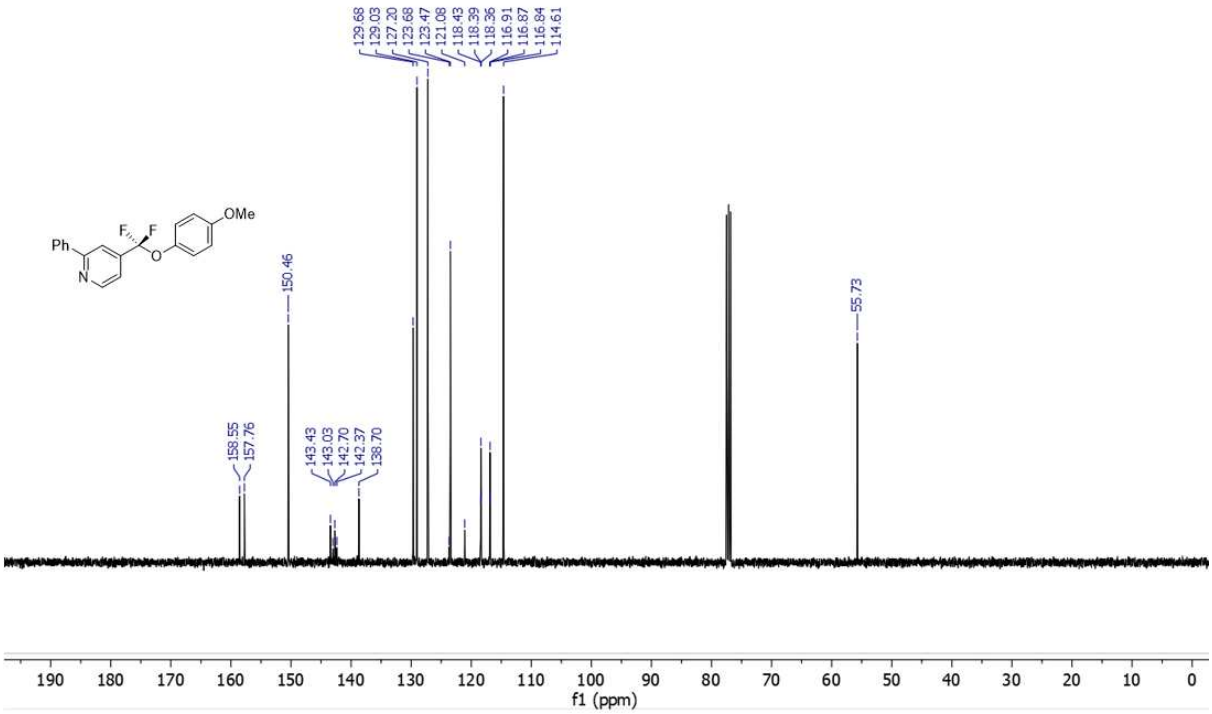


^{1}H NMR spectrum **3-4** (400 MHz, $CDCl_3$)



^{19}F NMR spectrum **3-4** (376 MHz, $CDCl_3$)



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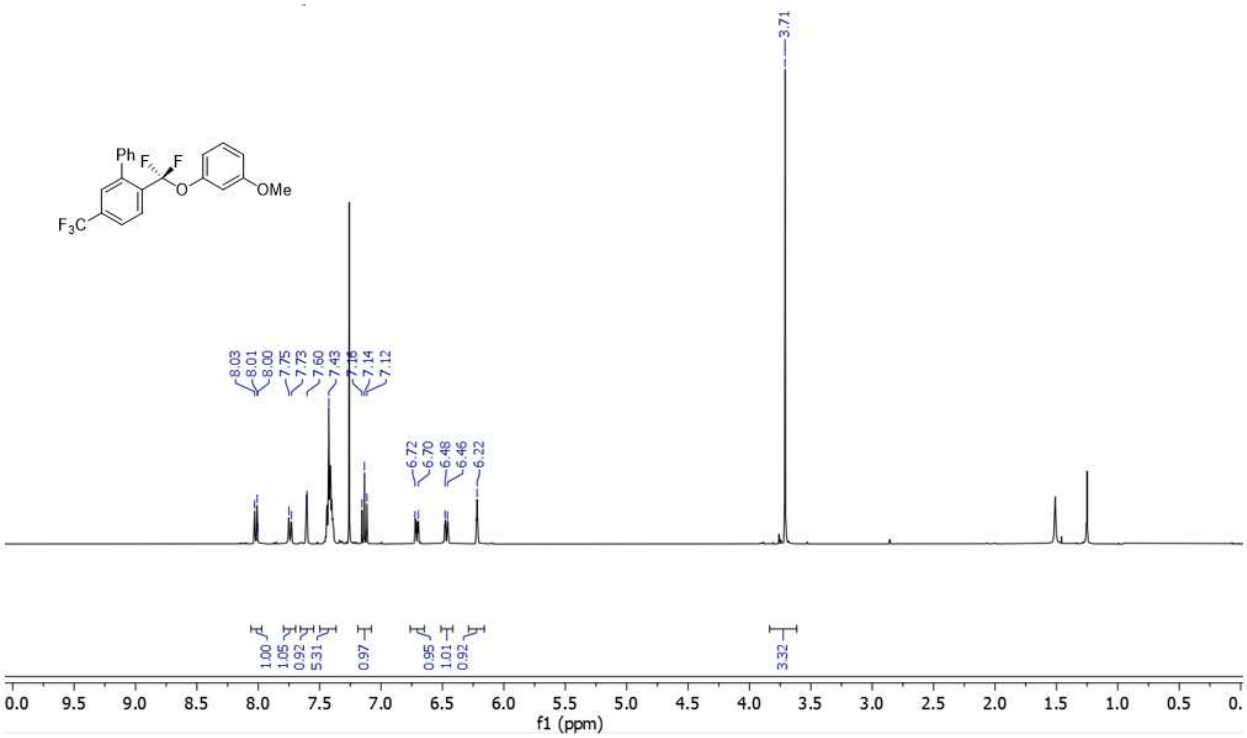
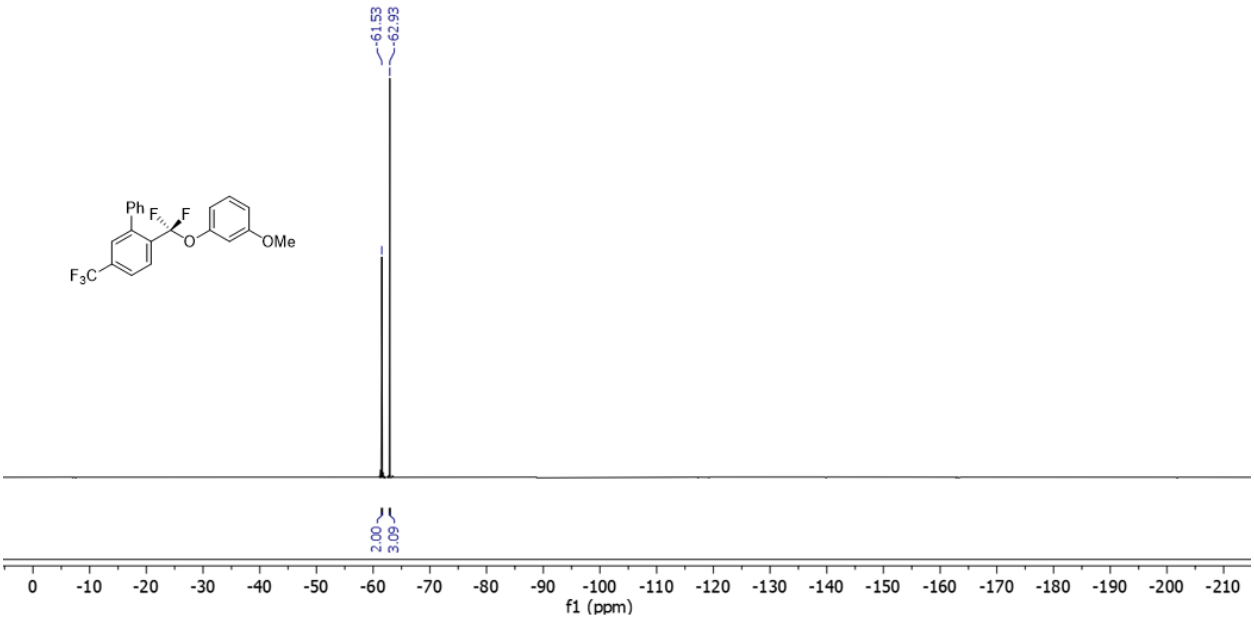


^{1}H NMR spectrum **3-6** (400 MHz, $CDCl_3$)



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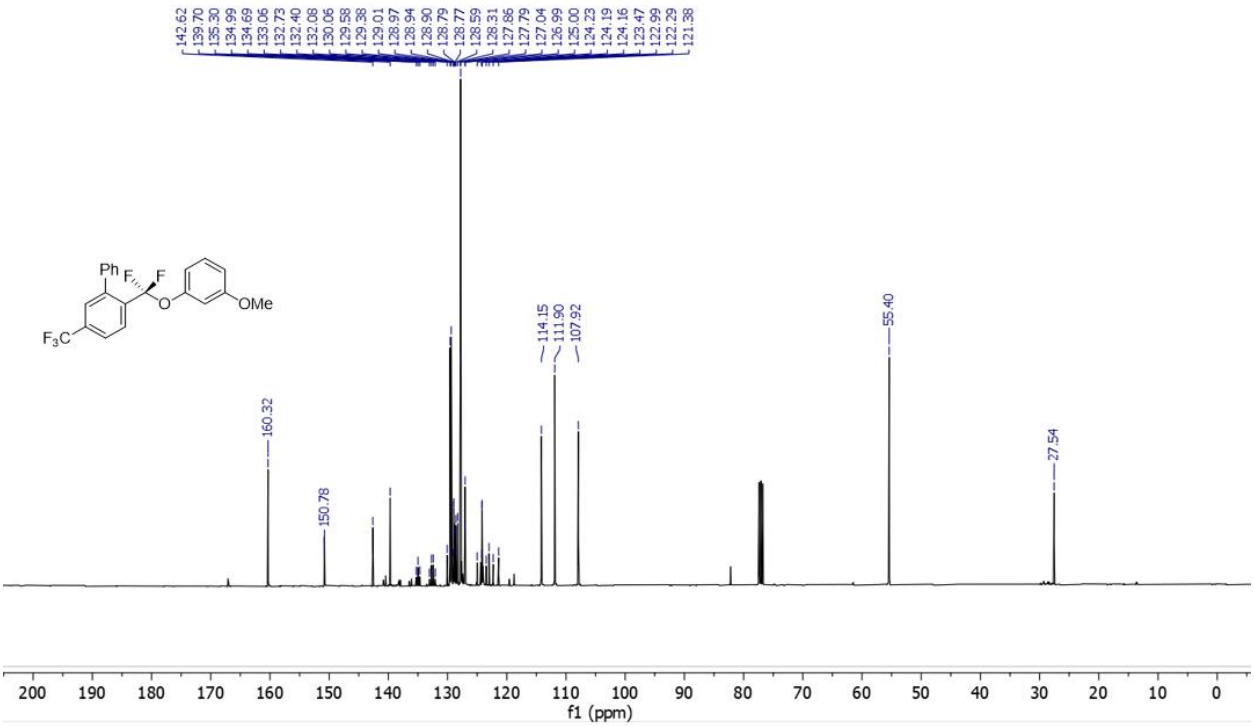

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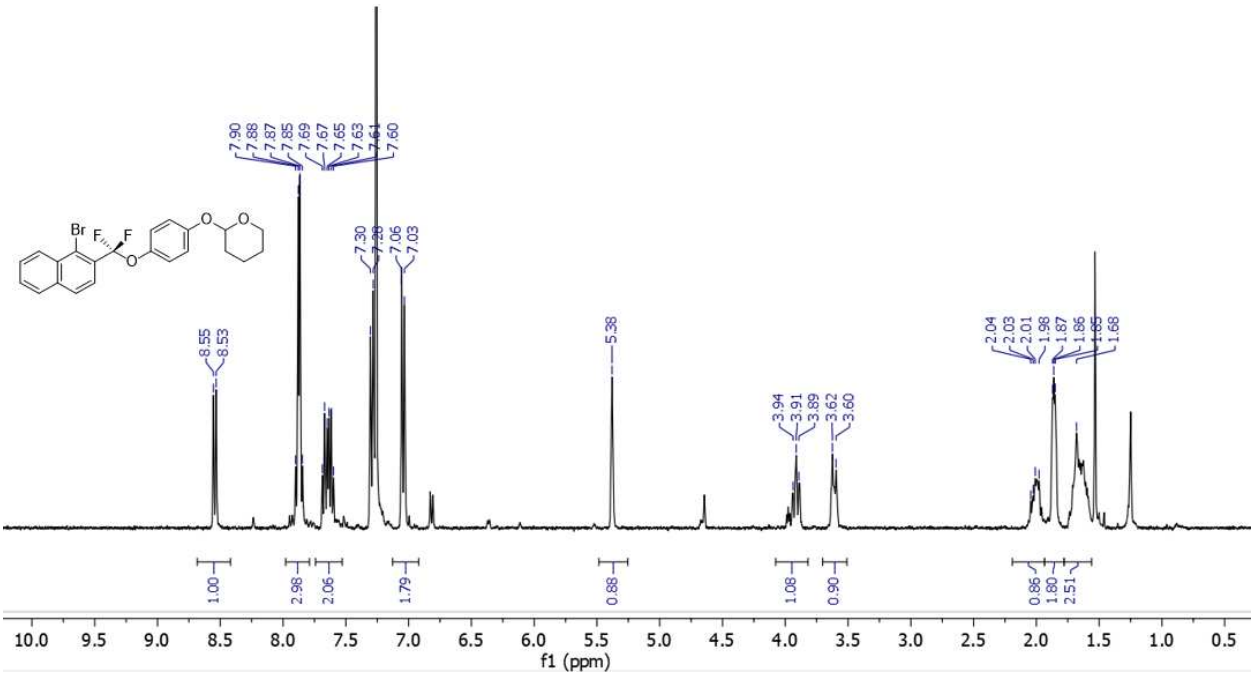

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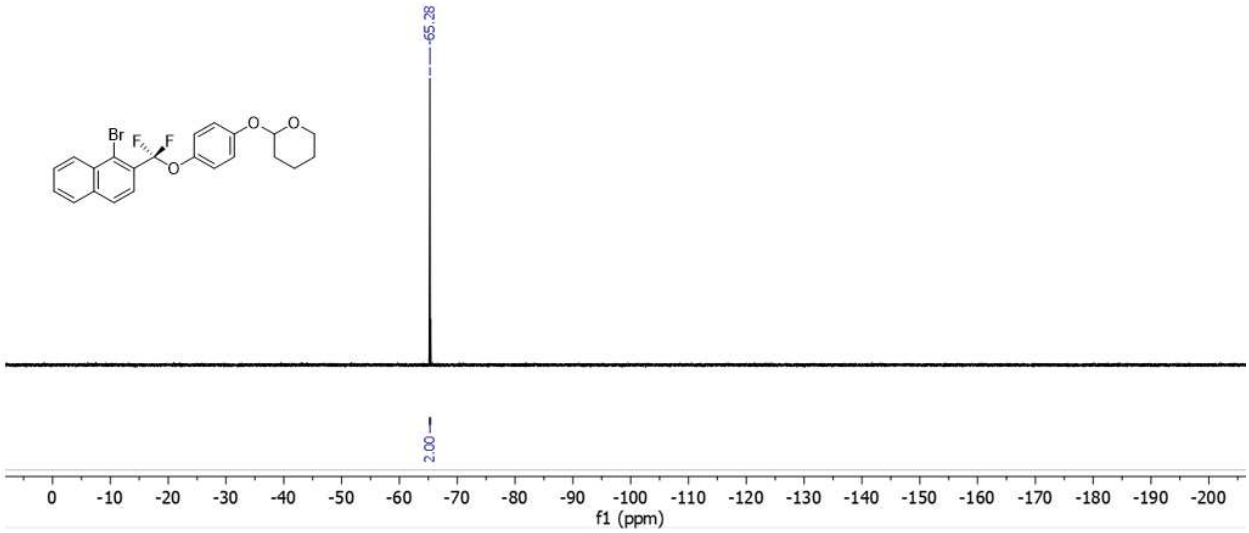

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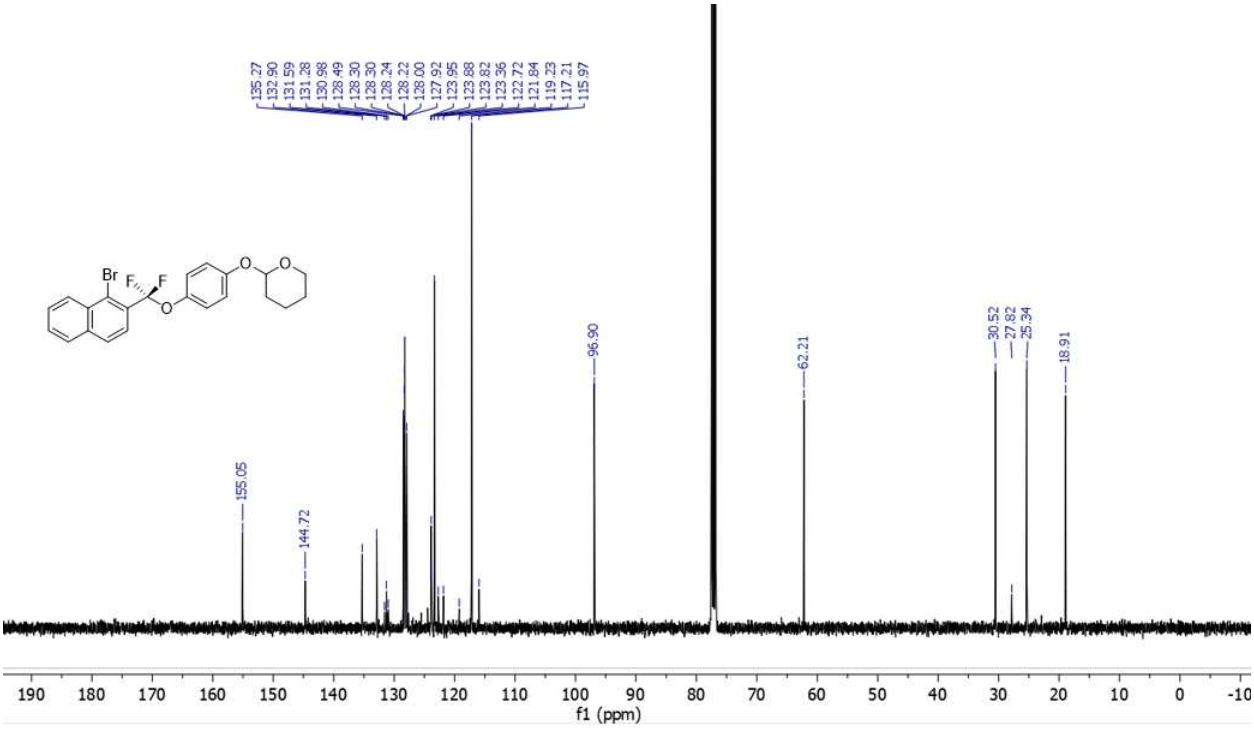

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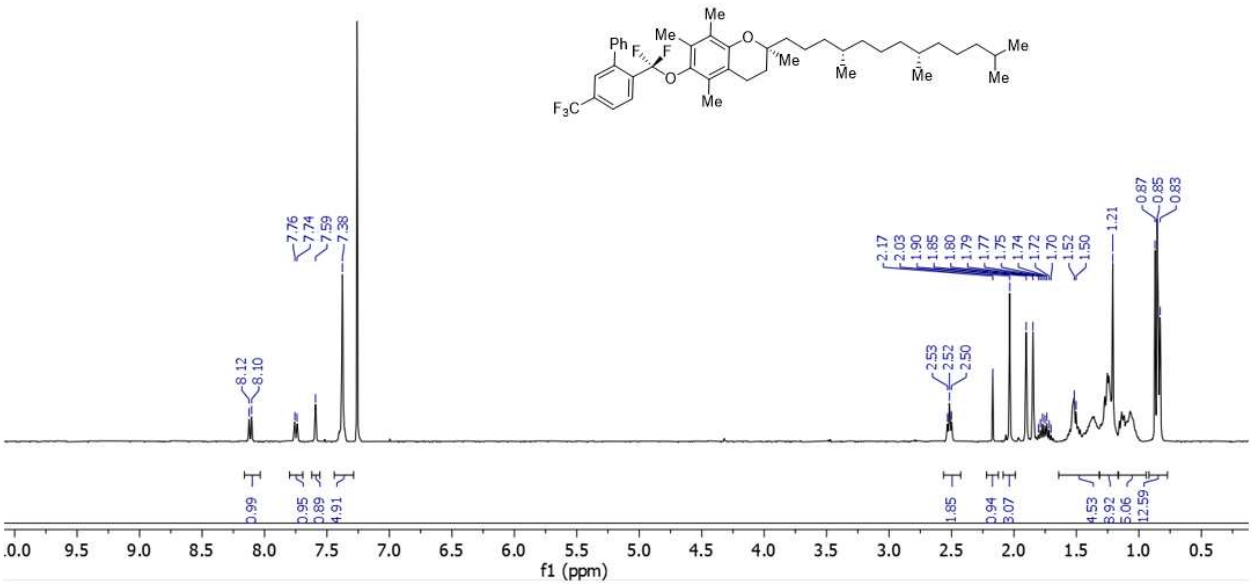

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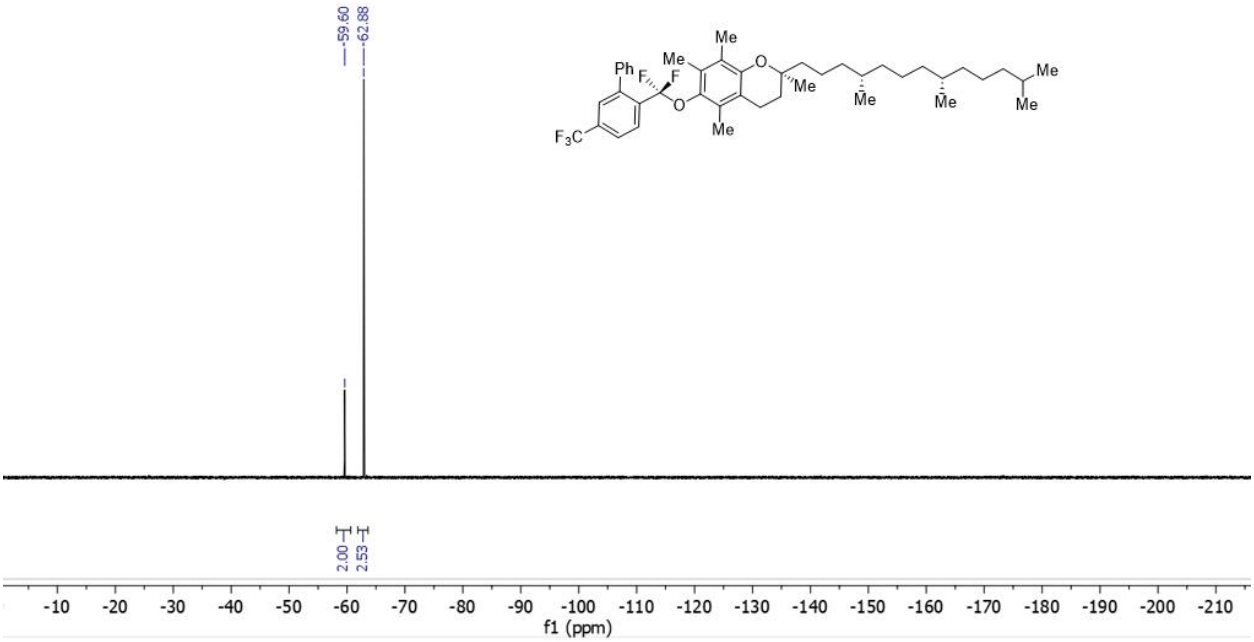

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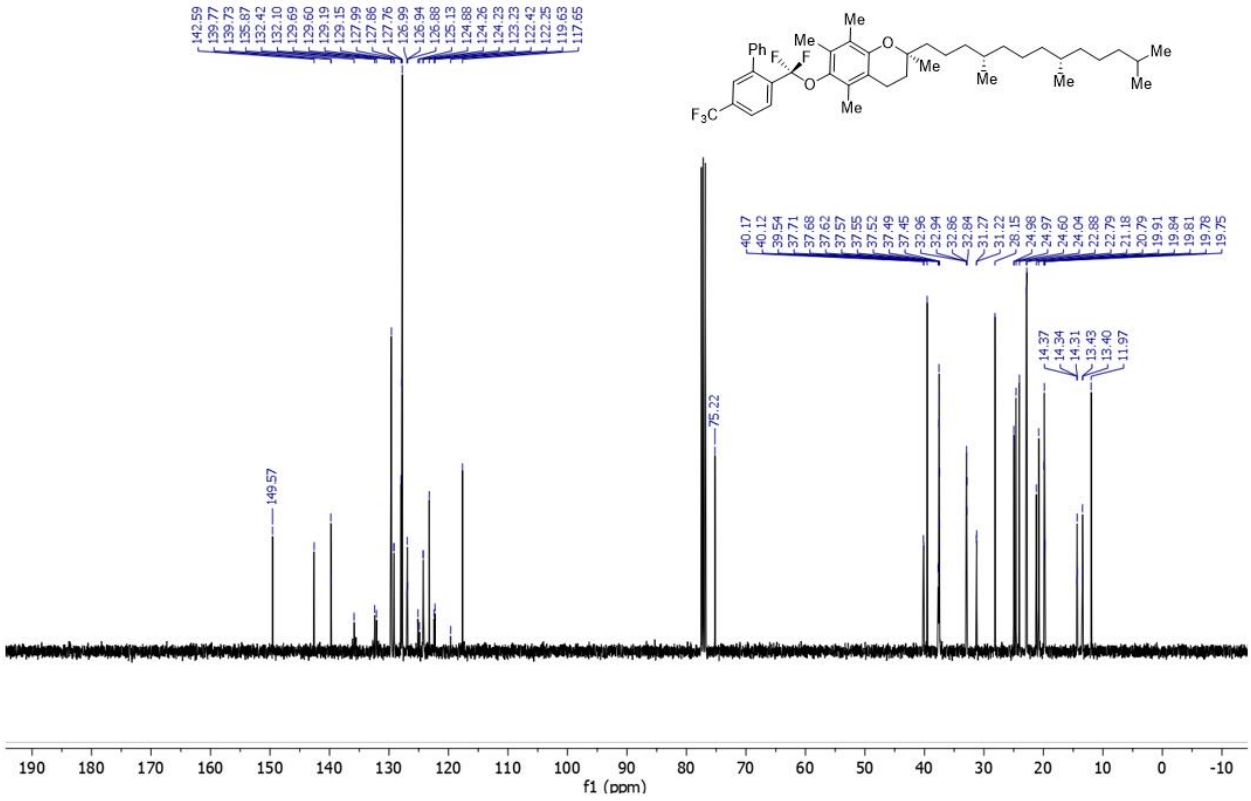

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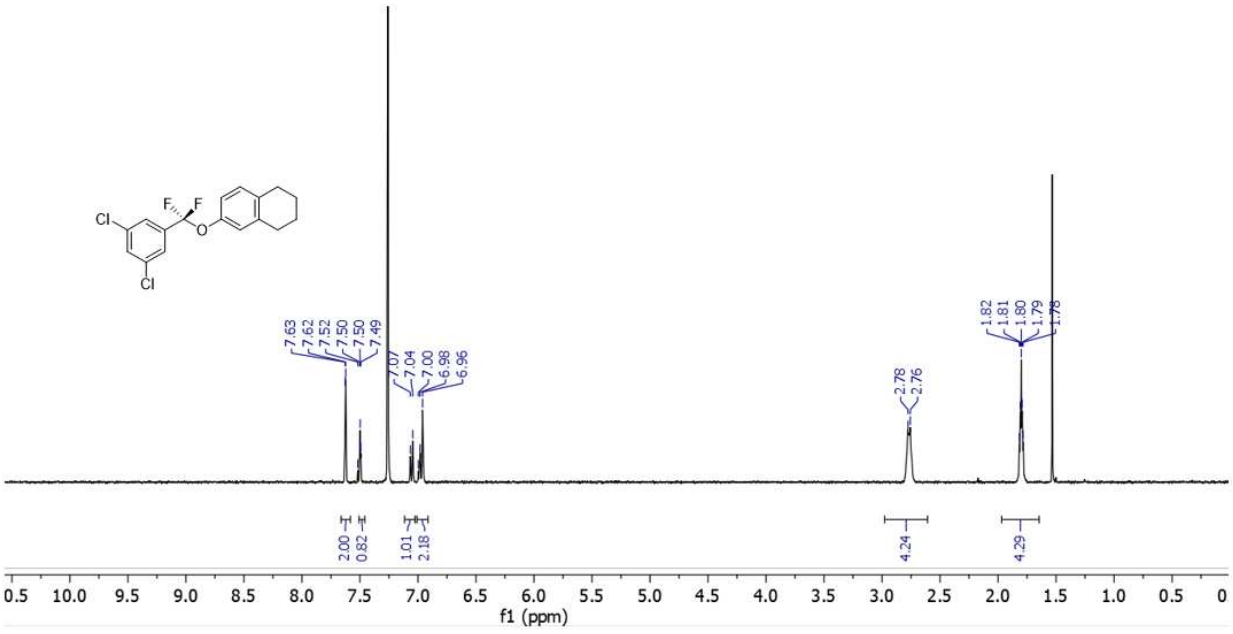

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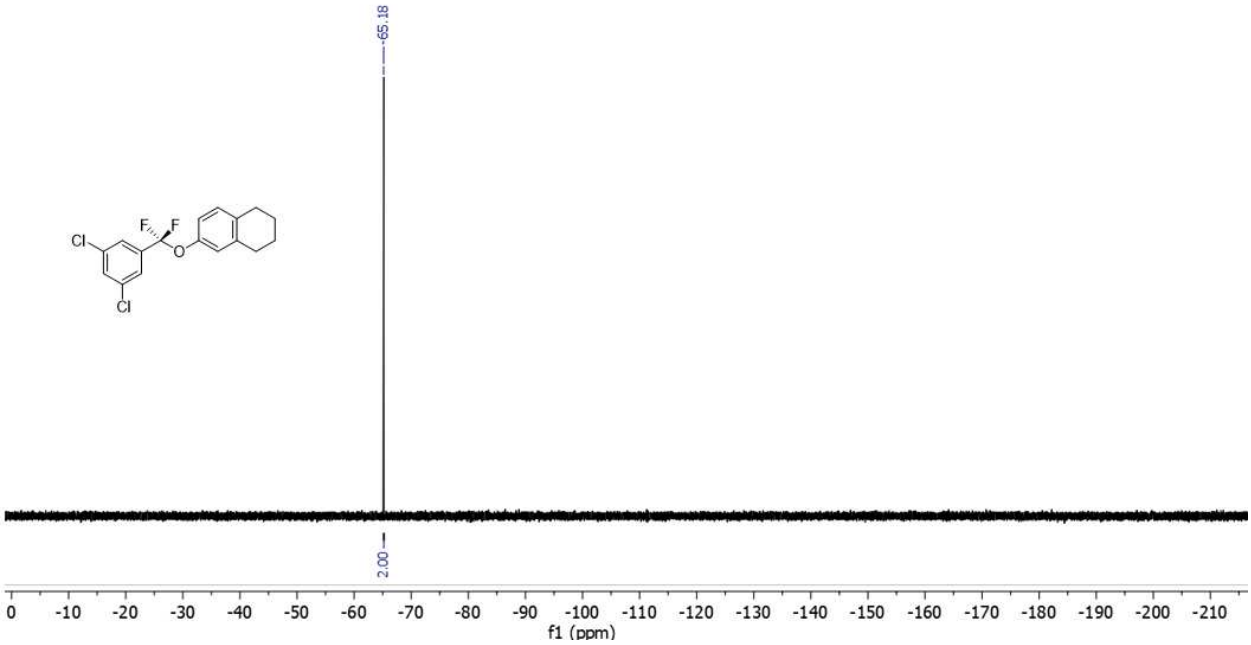

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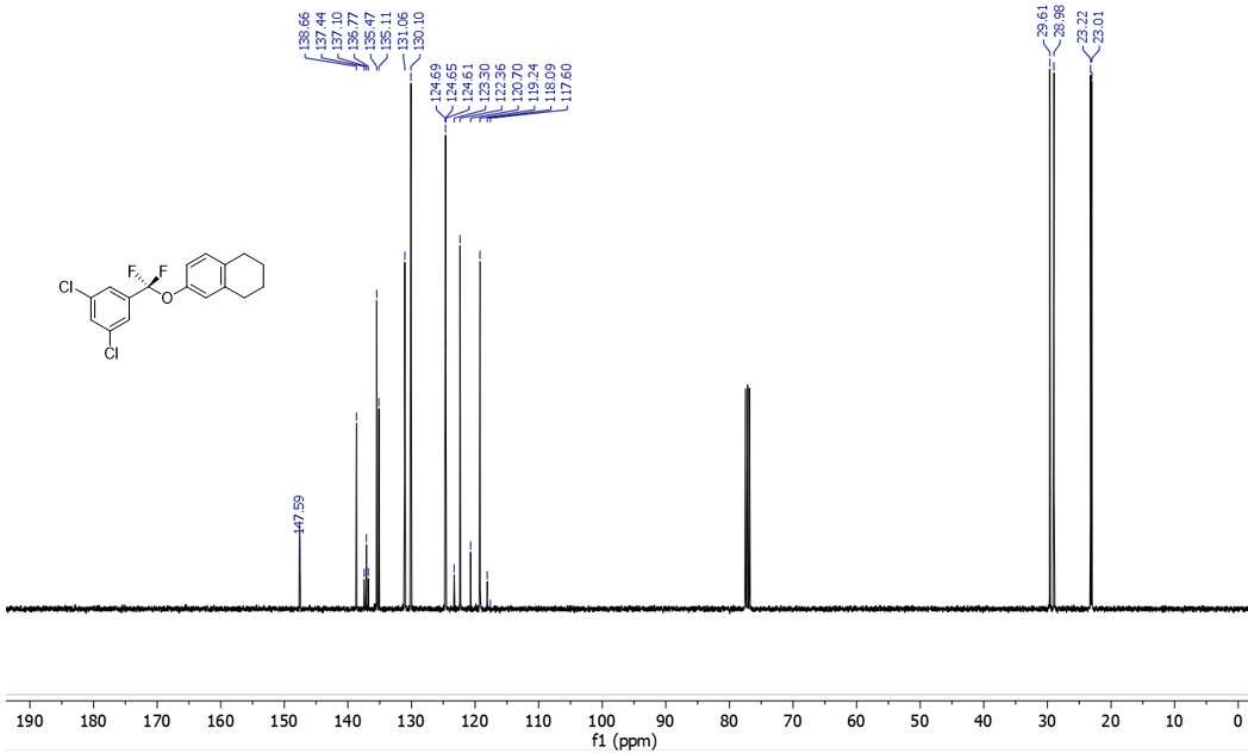

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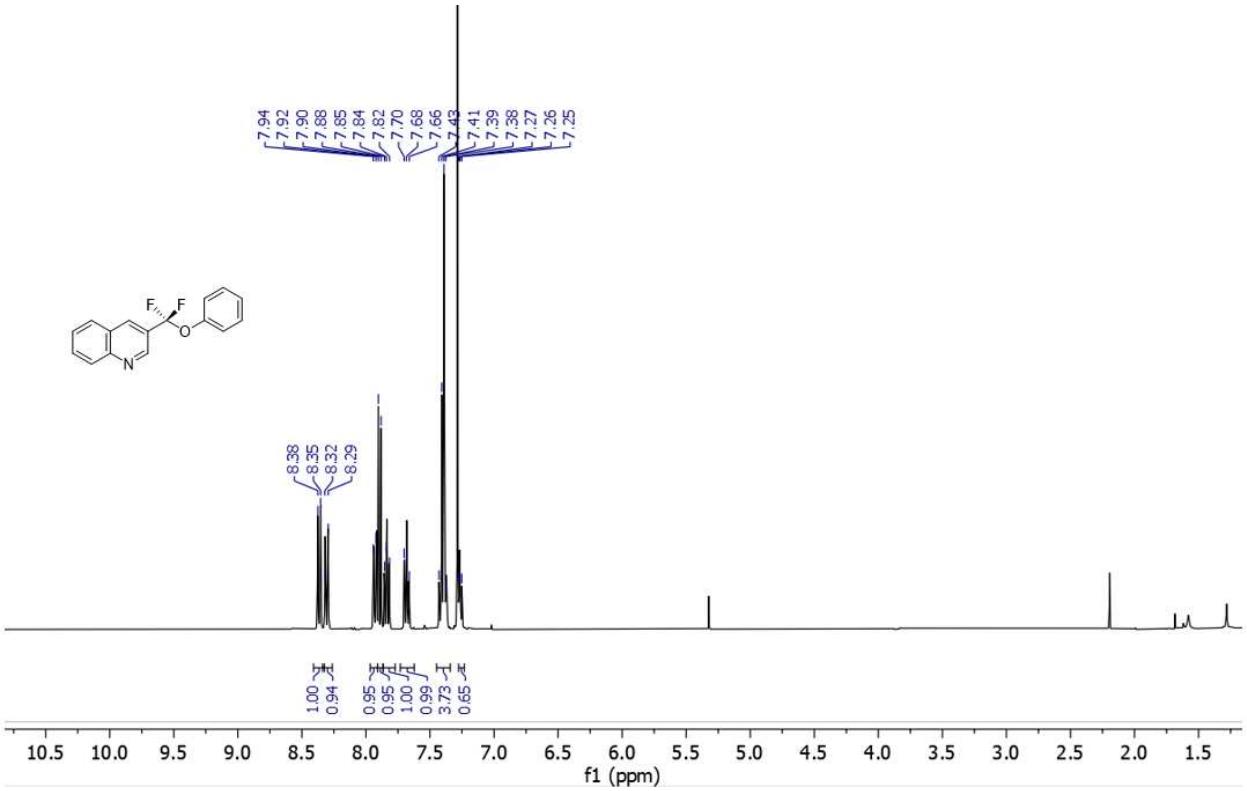

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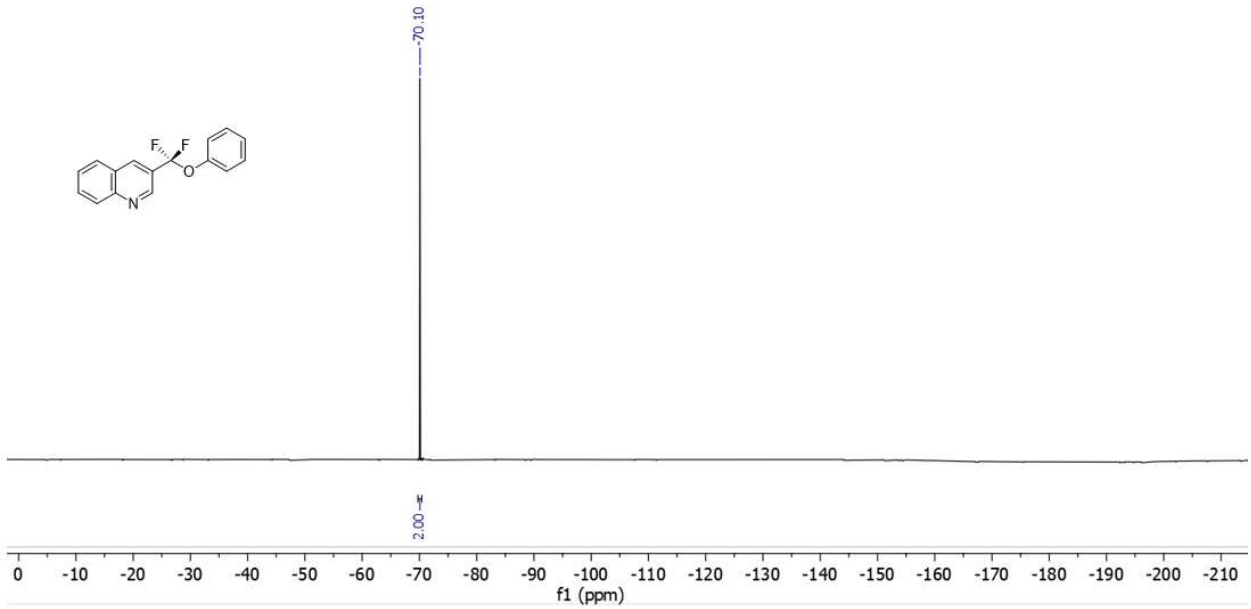

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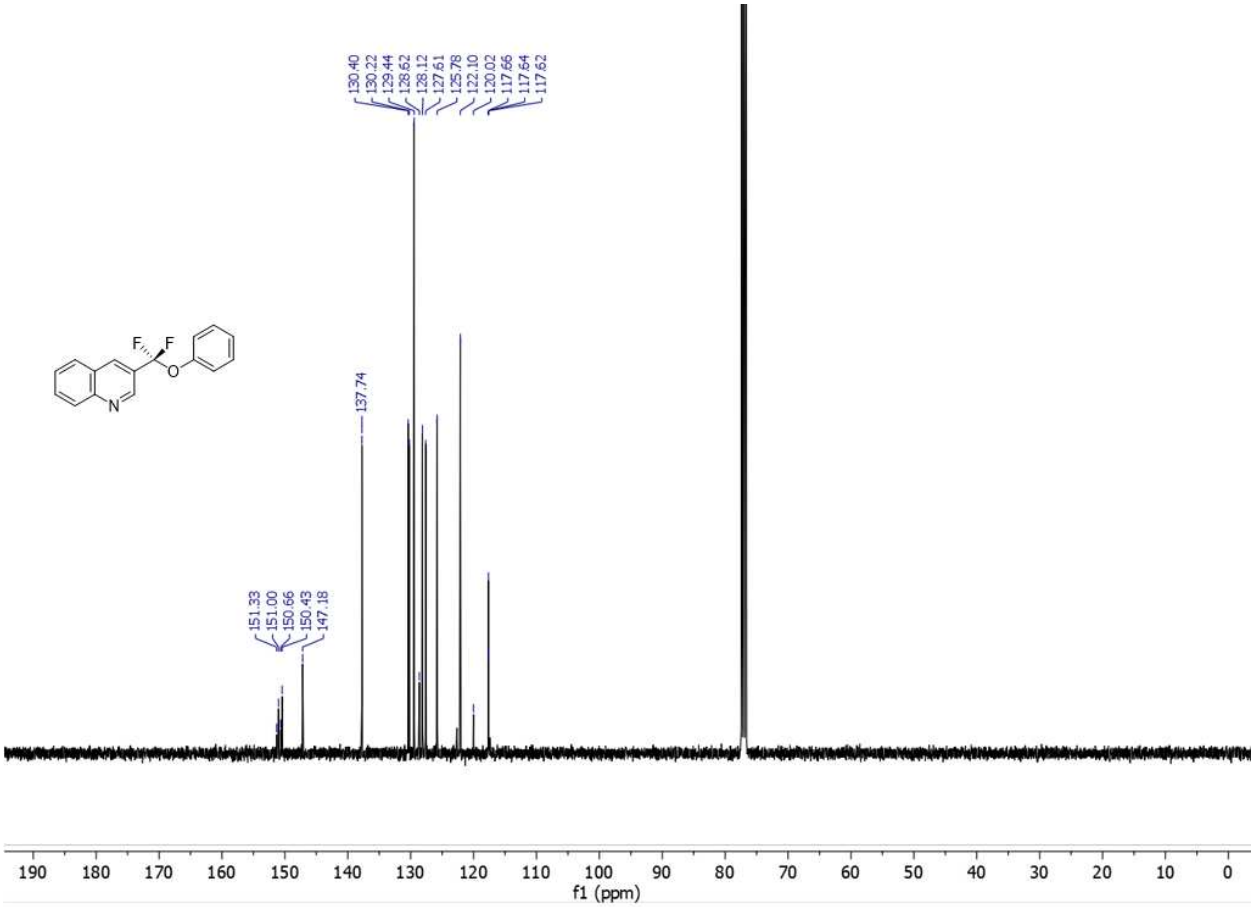

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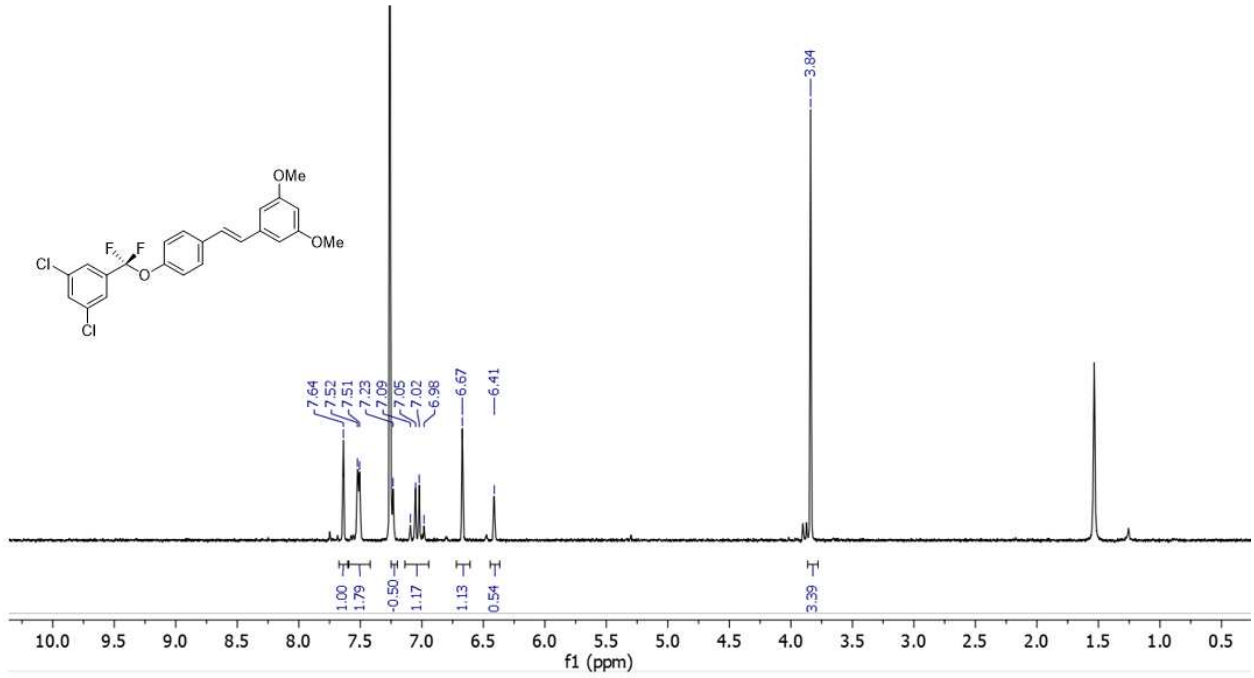

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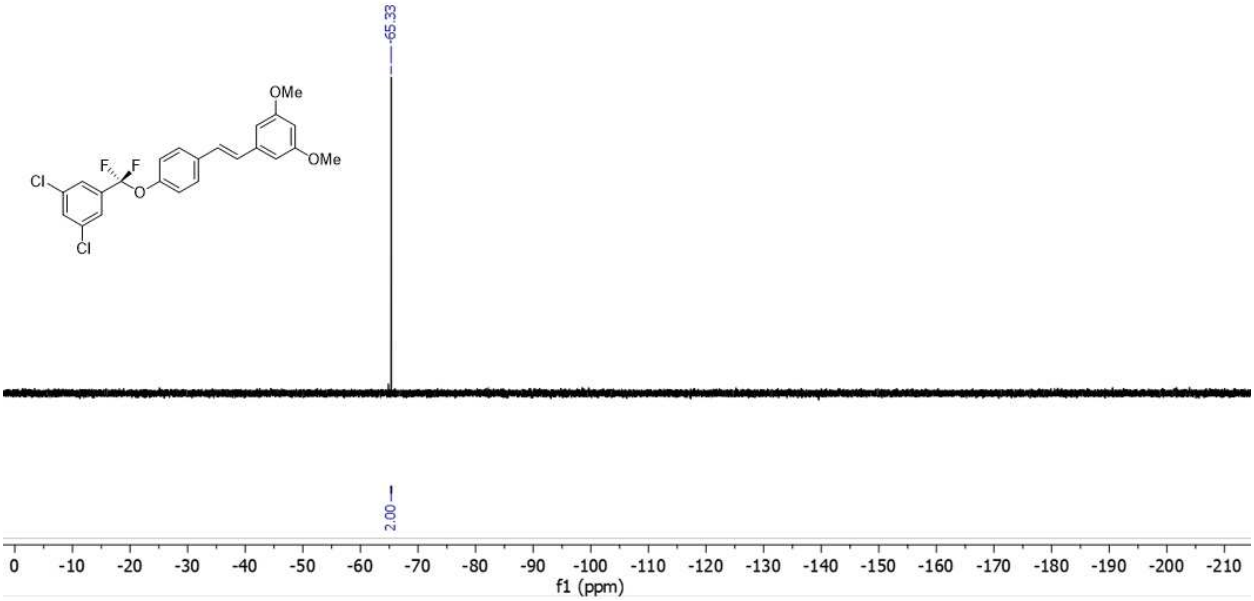

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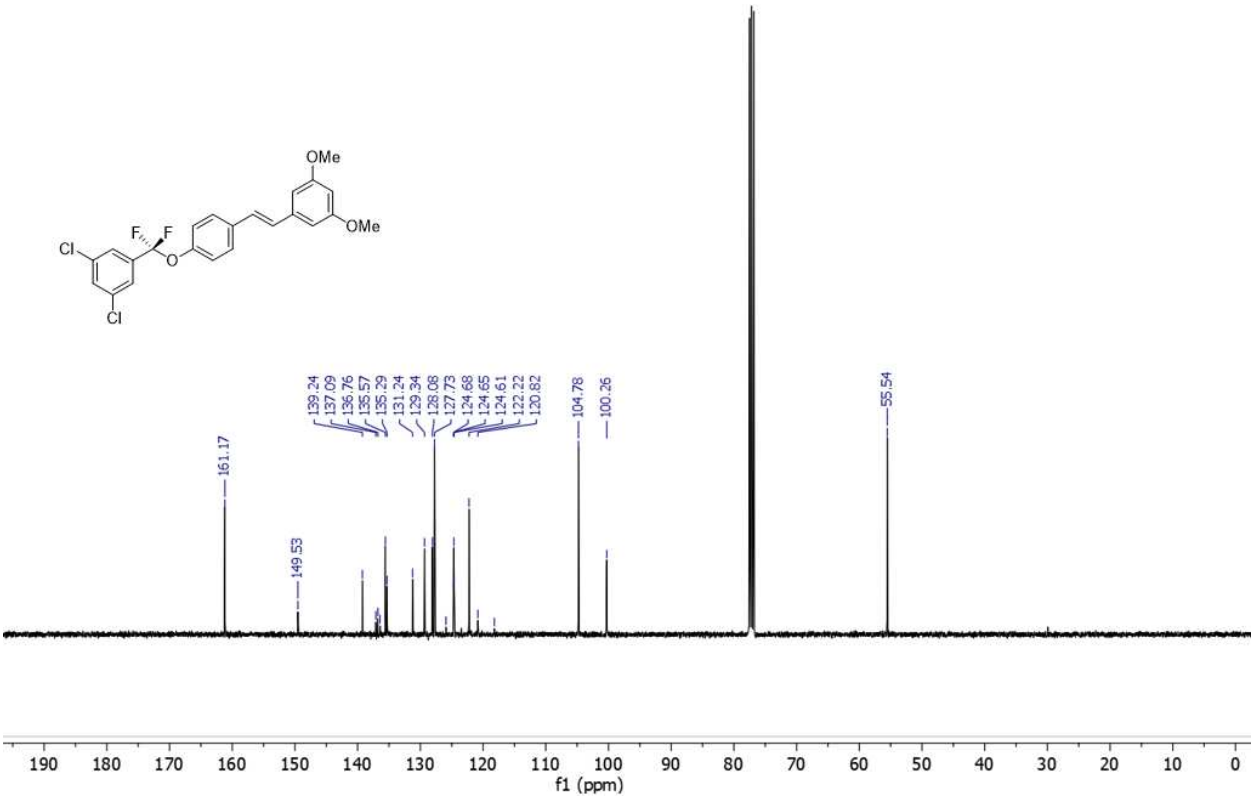

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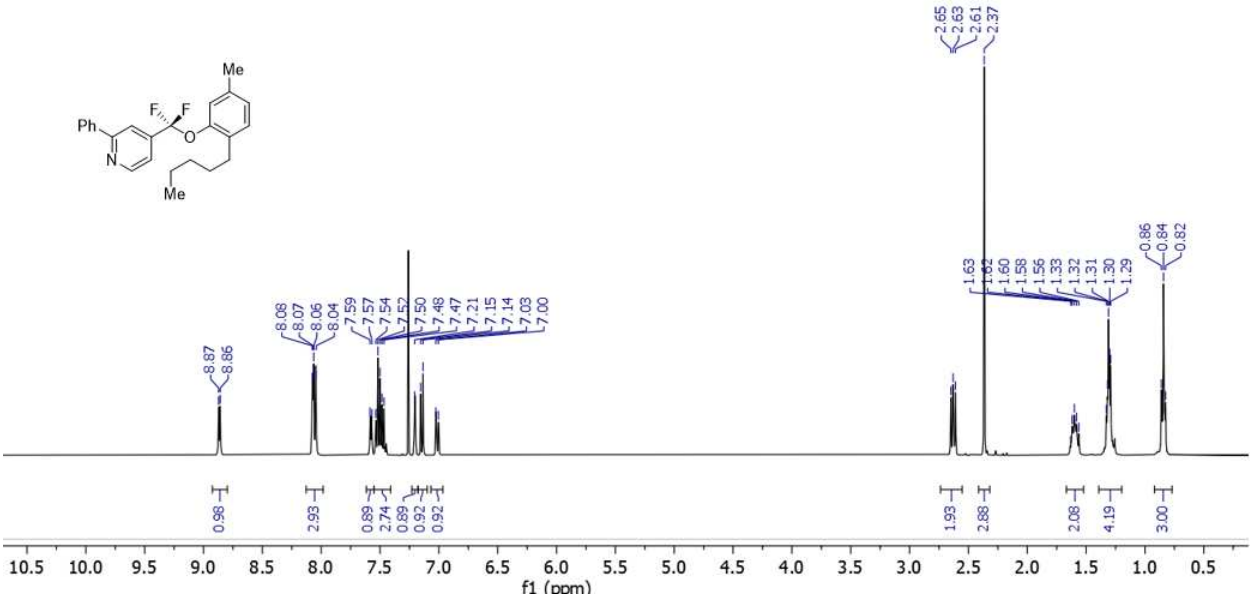

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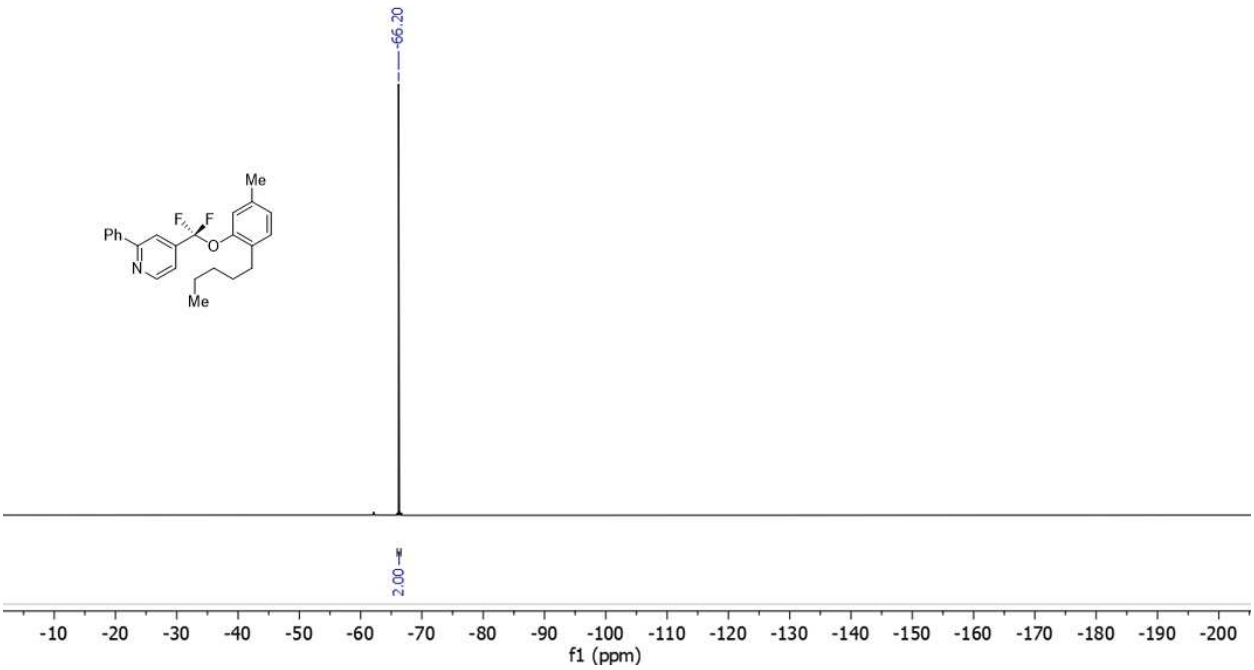

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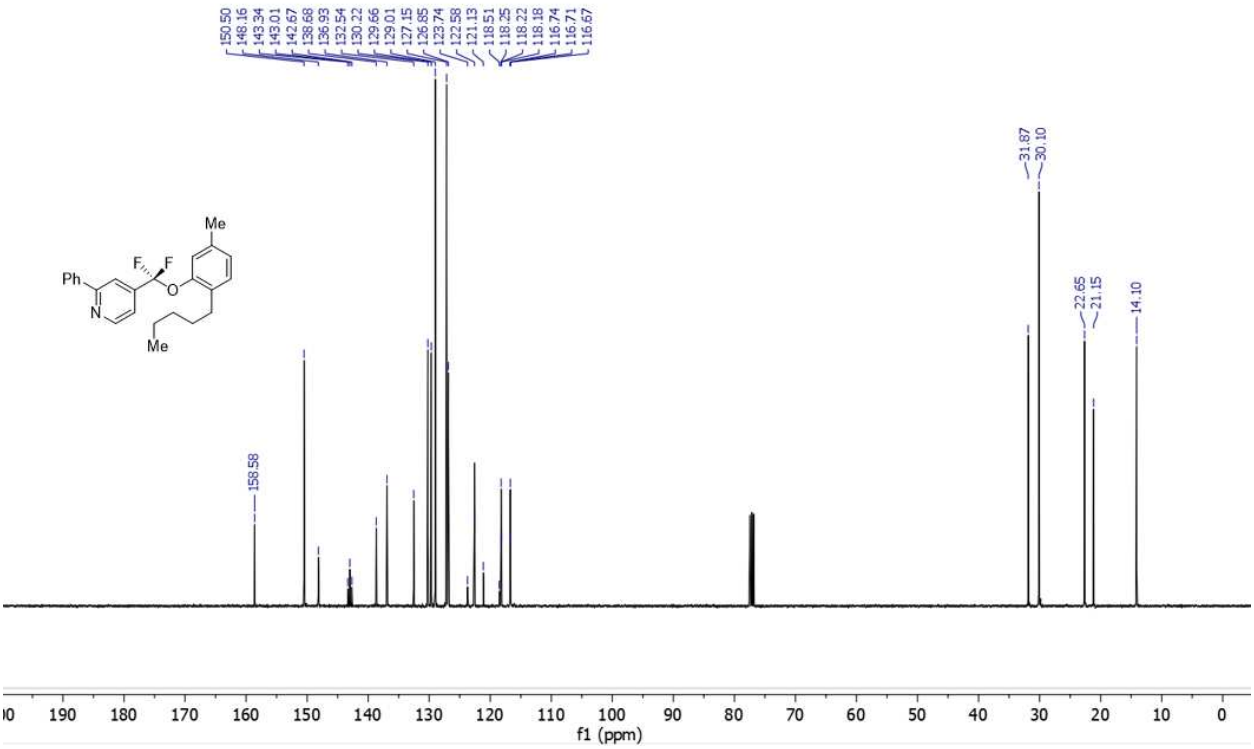

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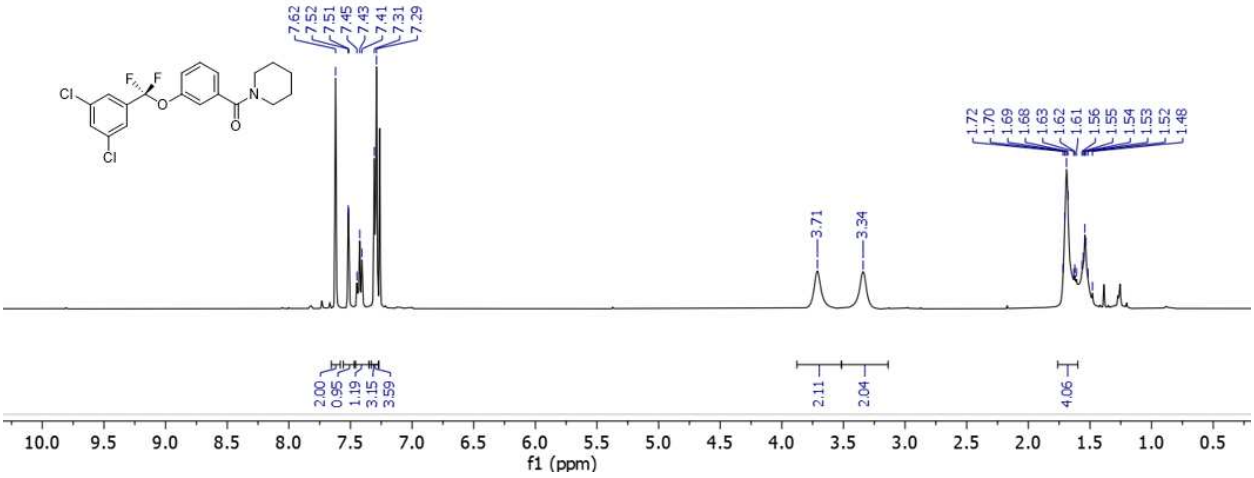

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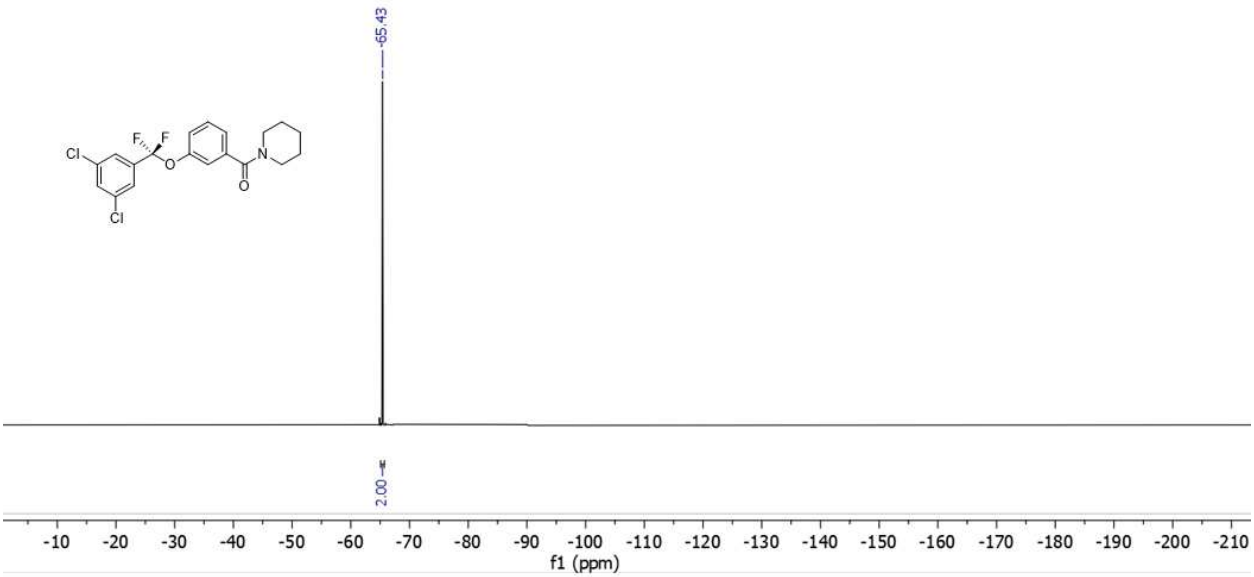

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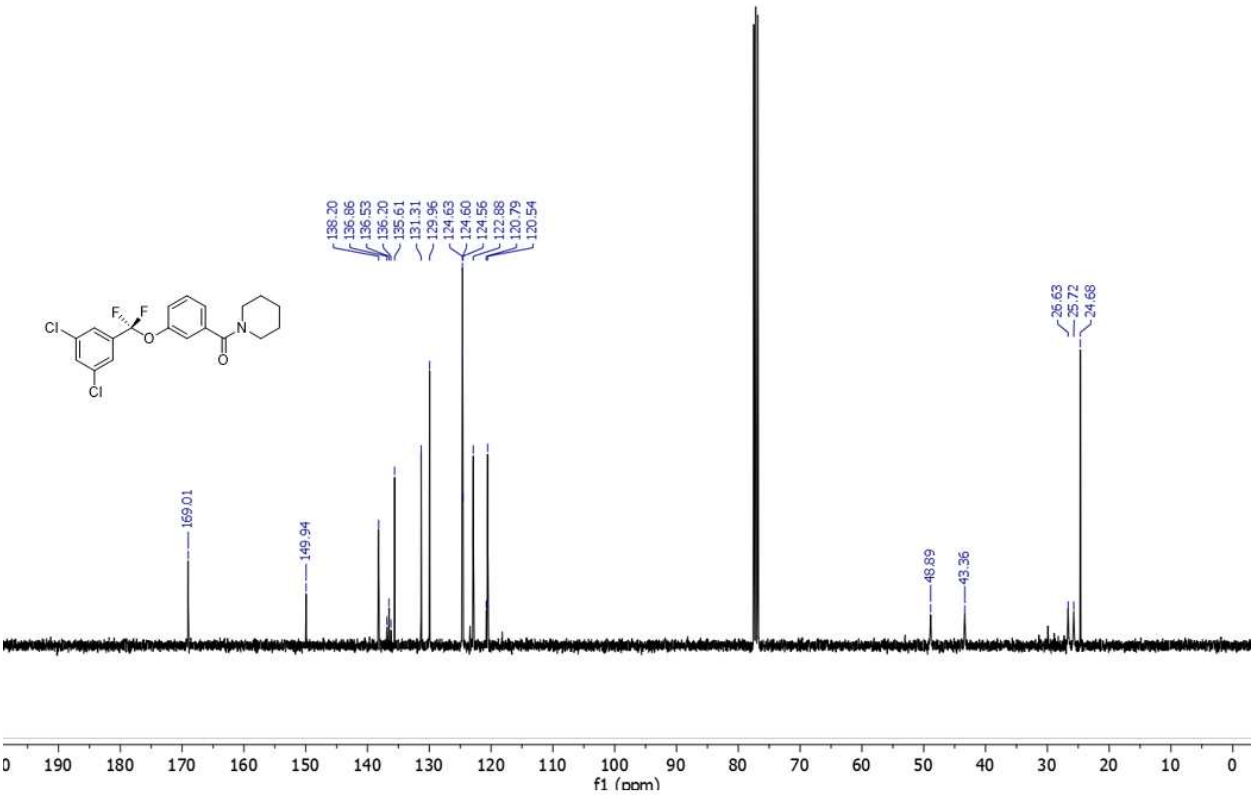

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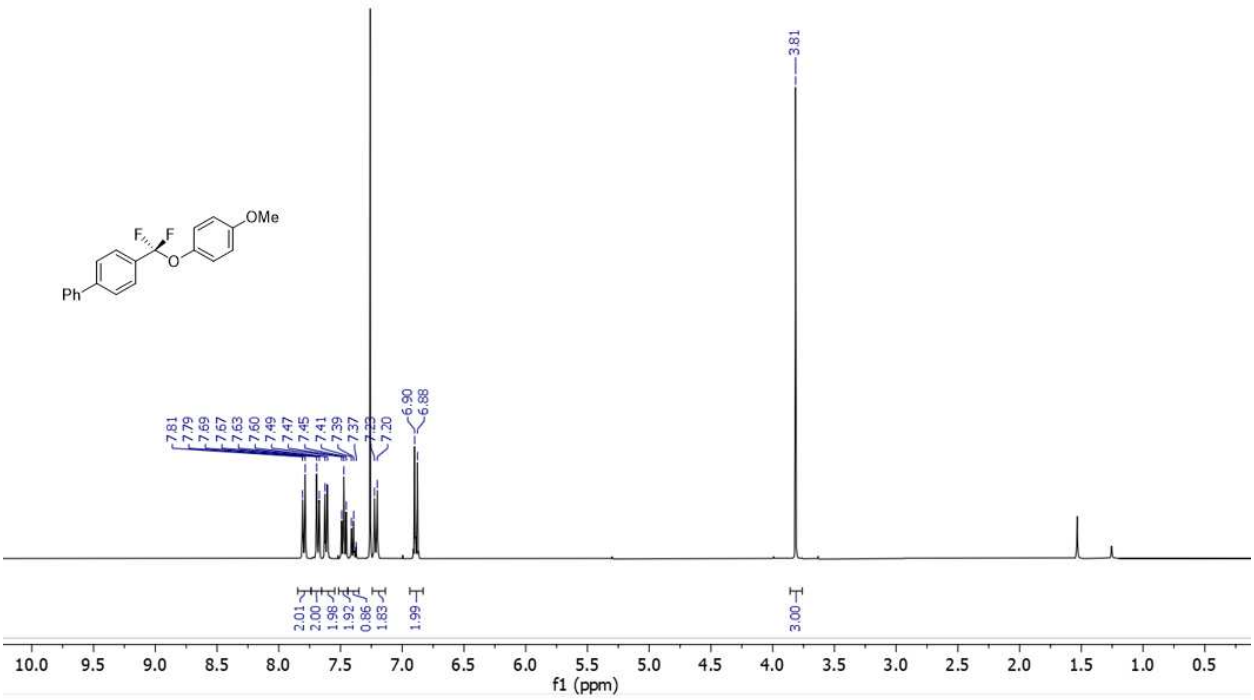

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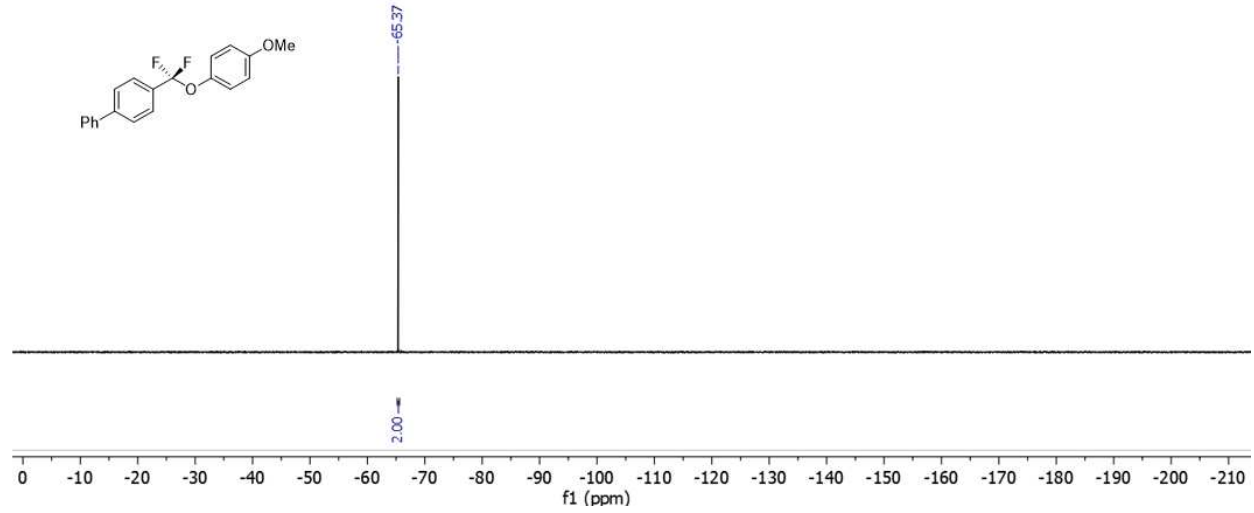

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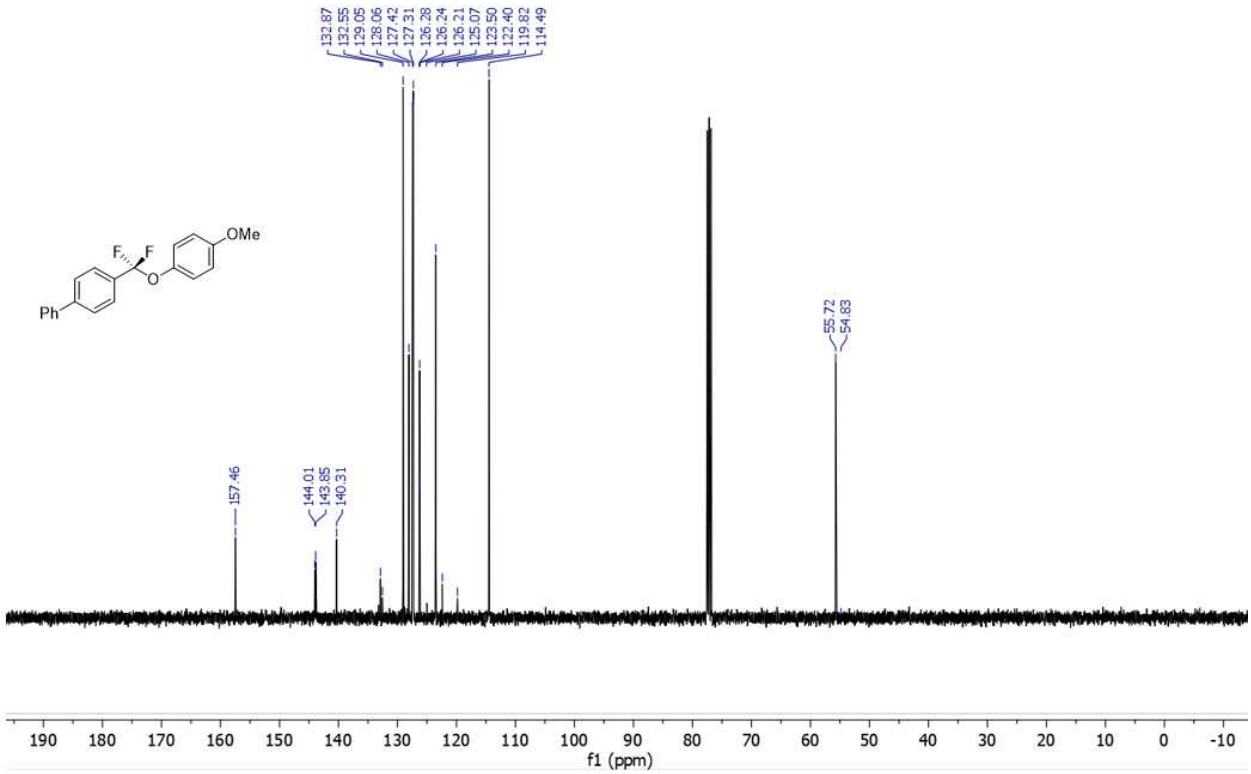

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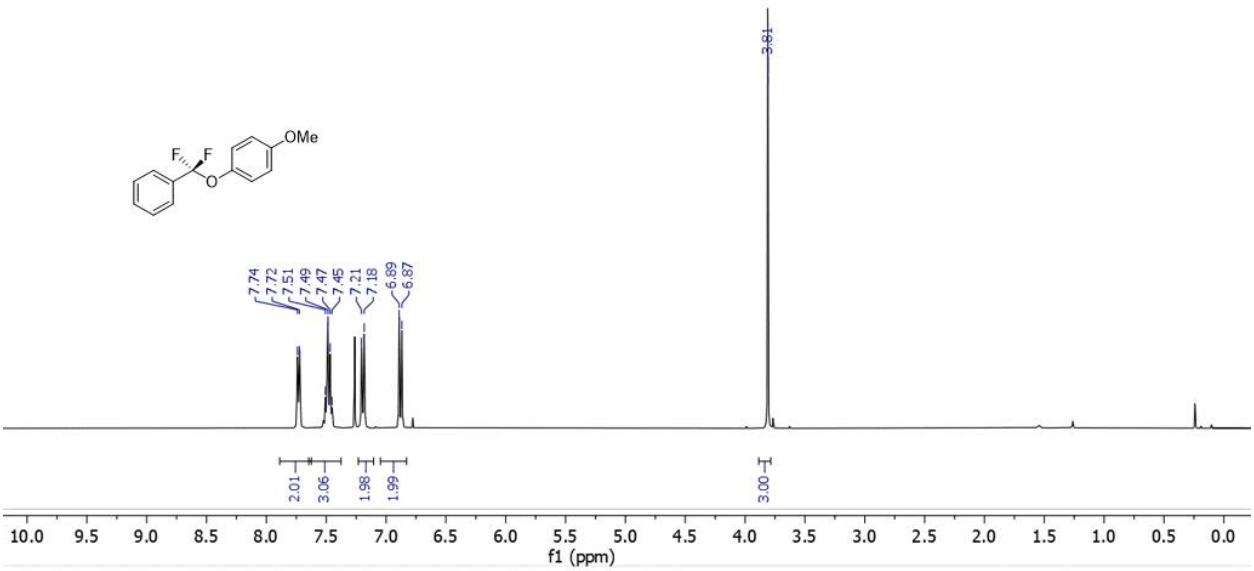

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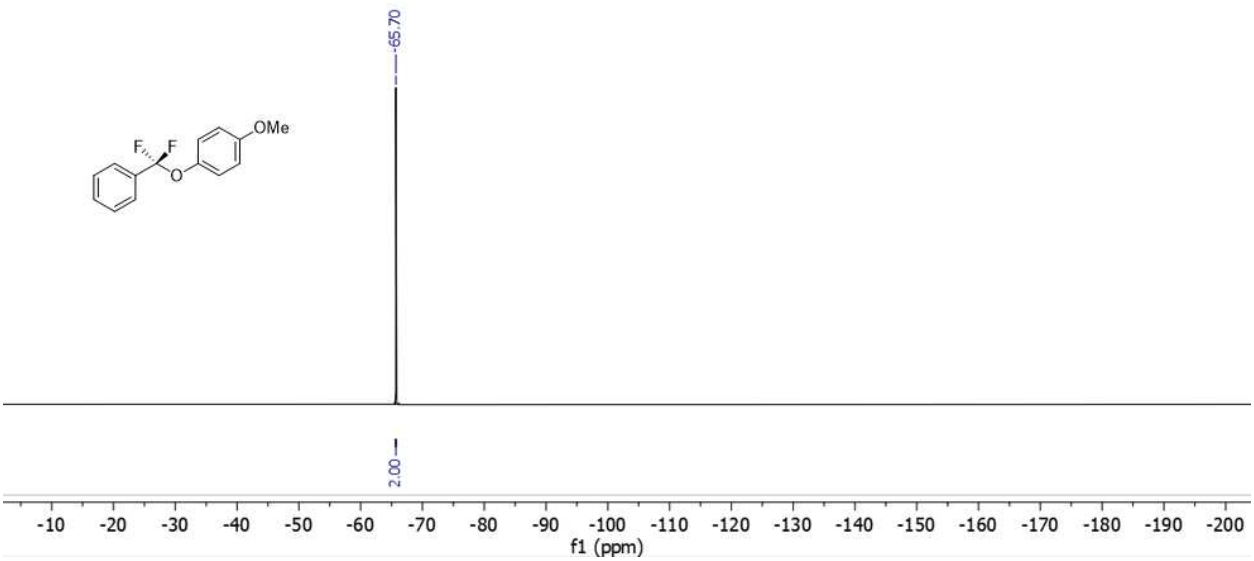

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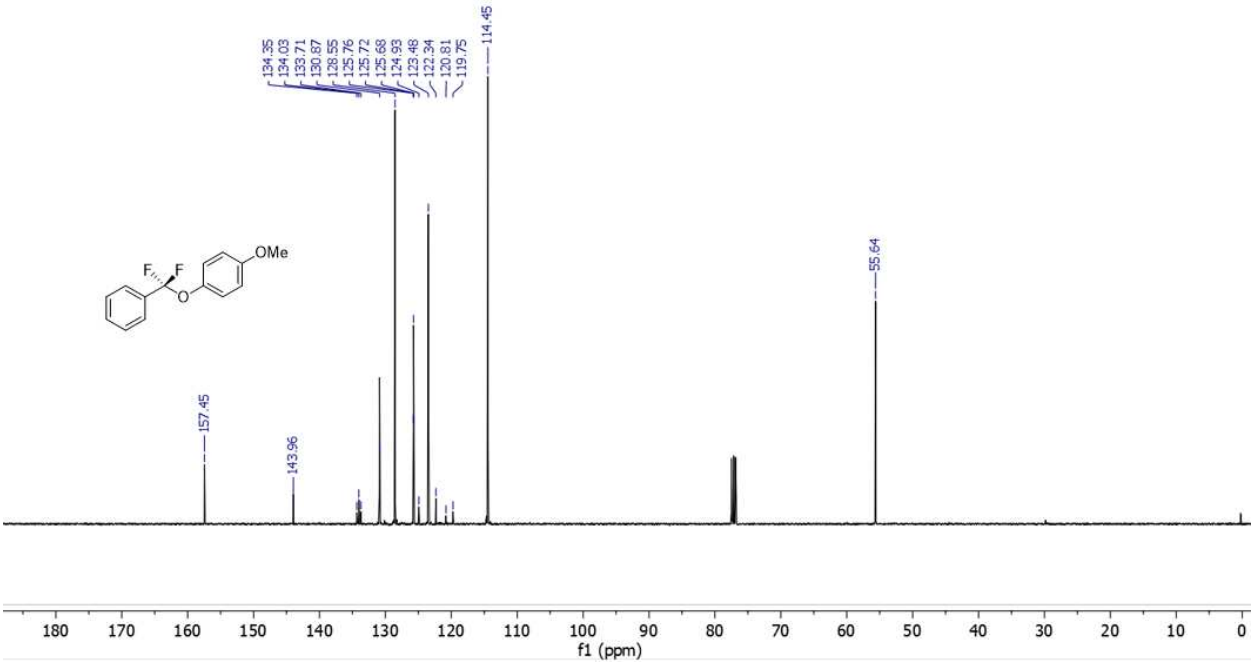

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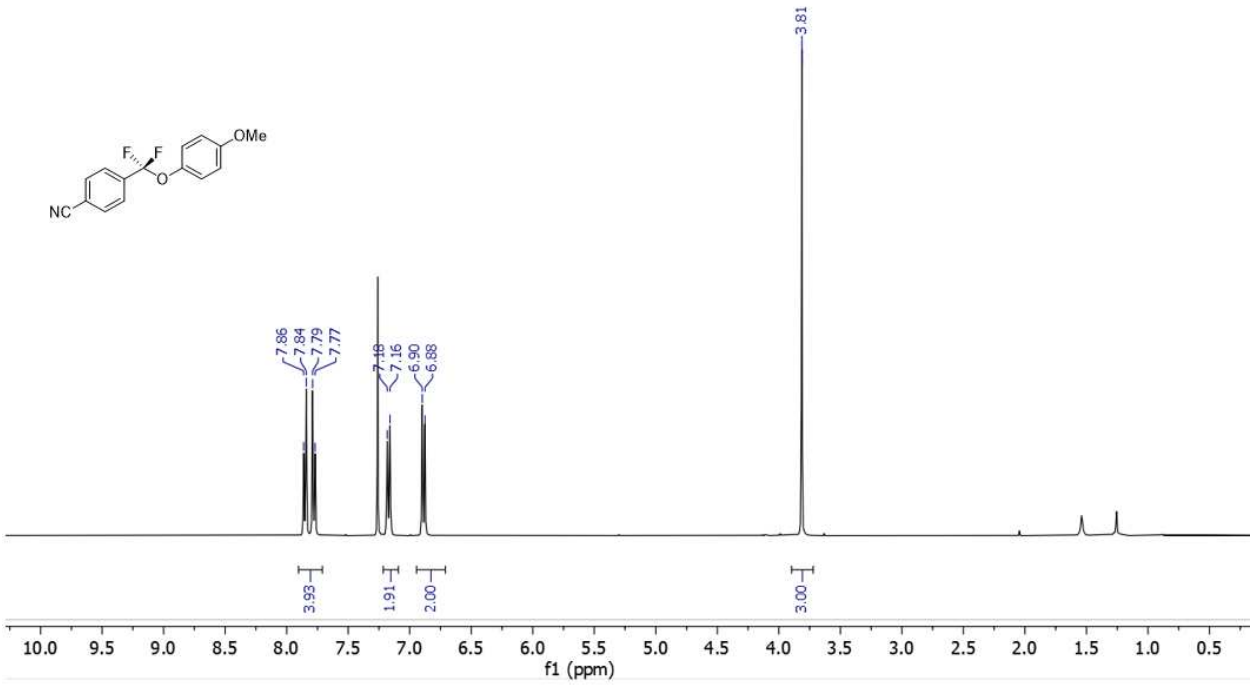

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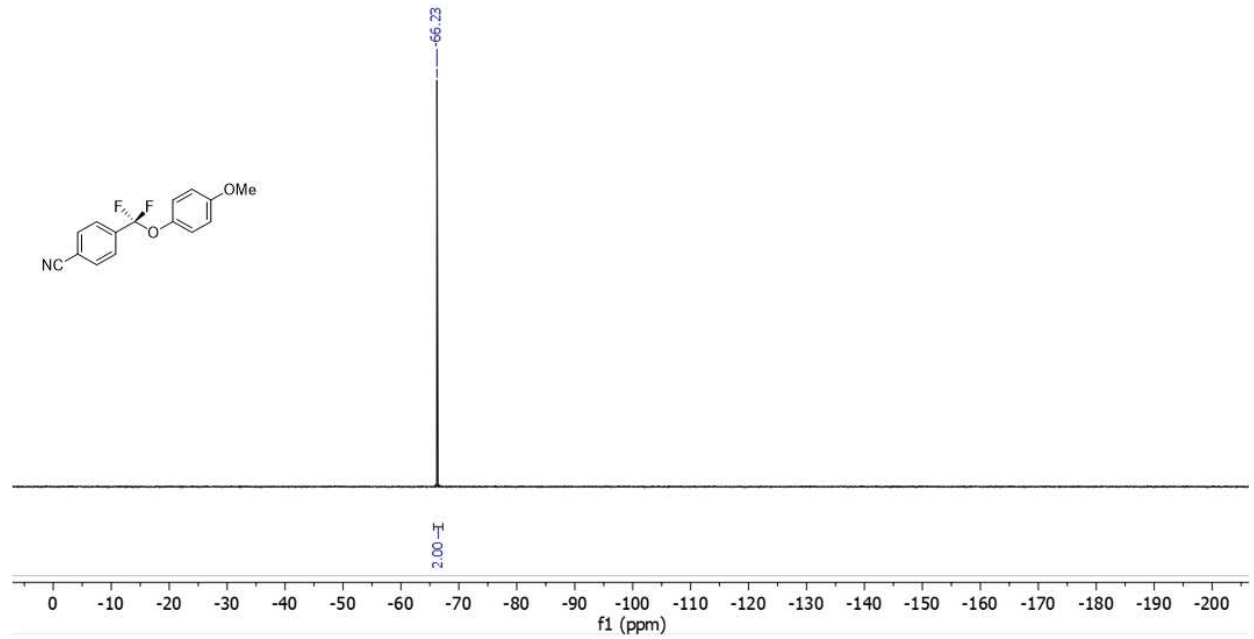

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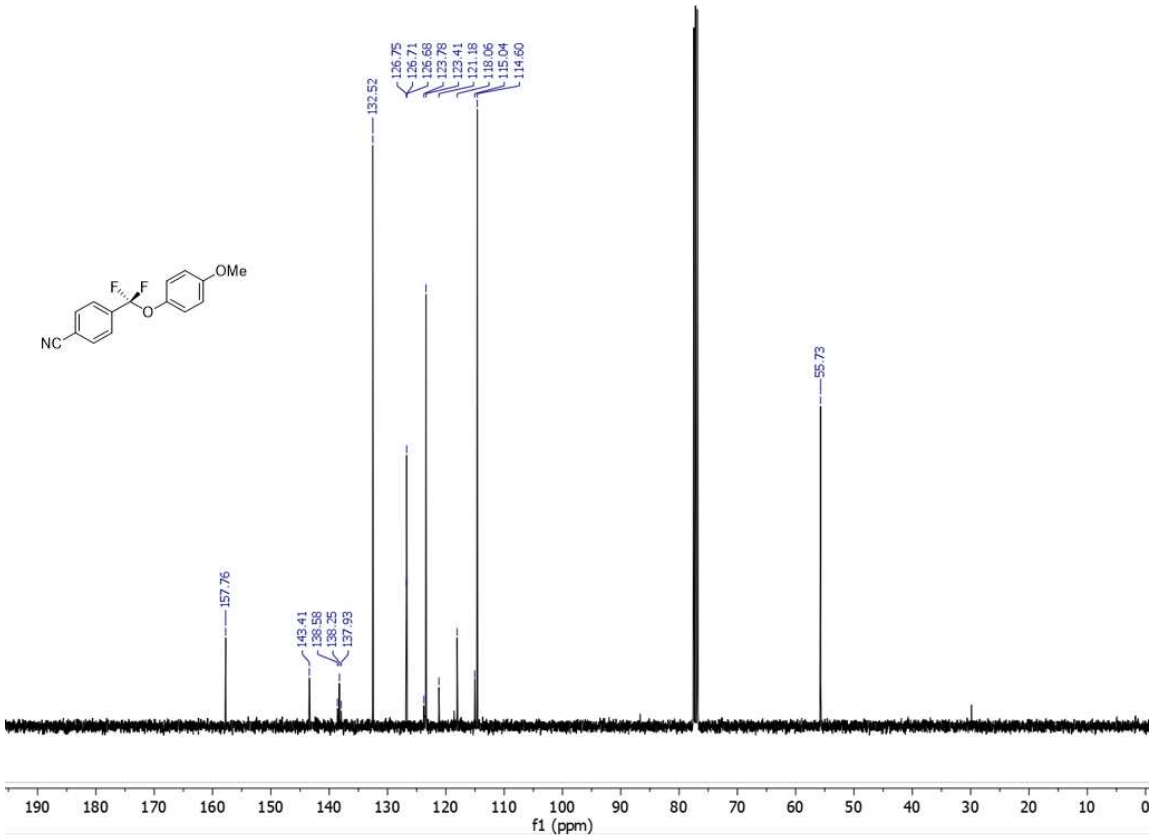

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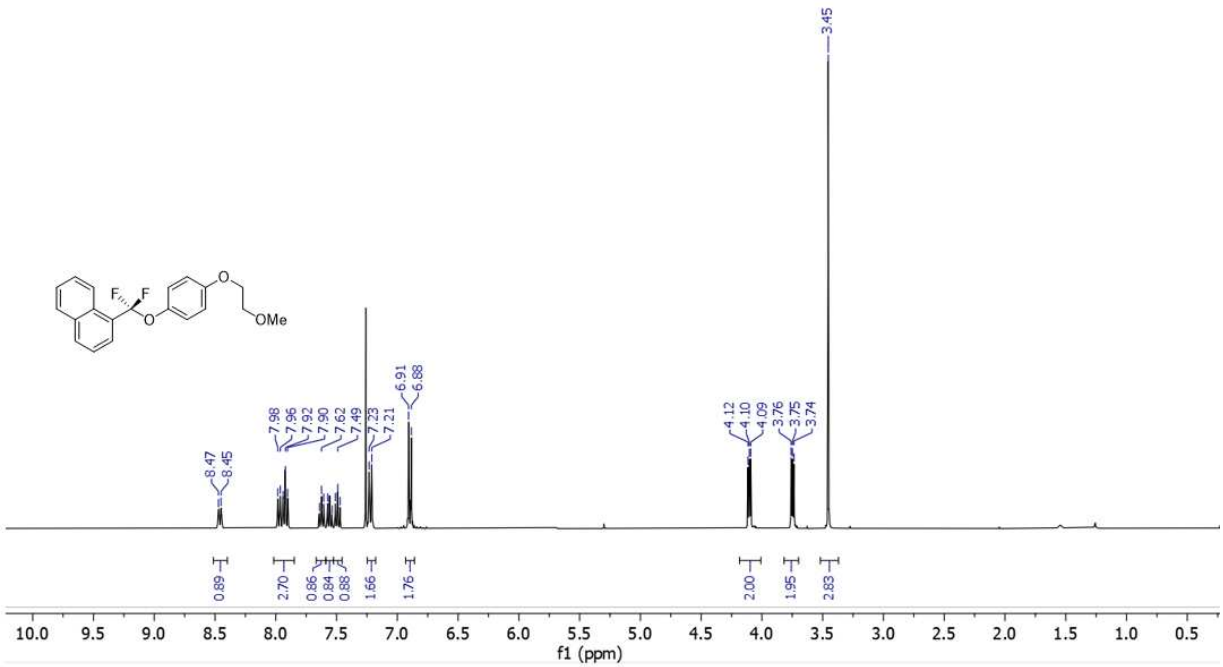

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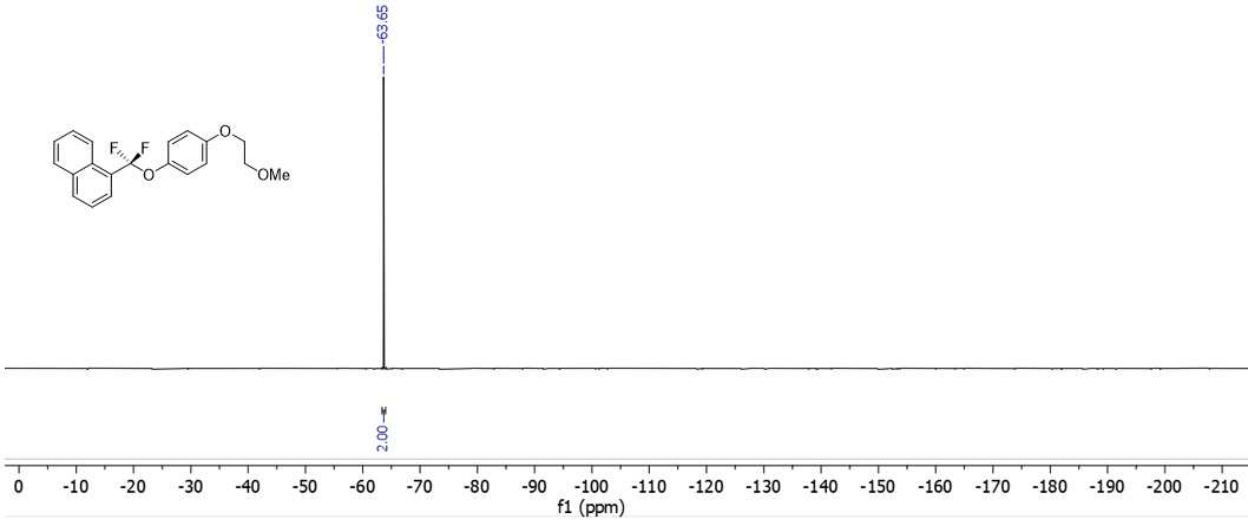

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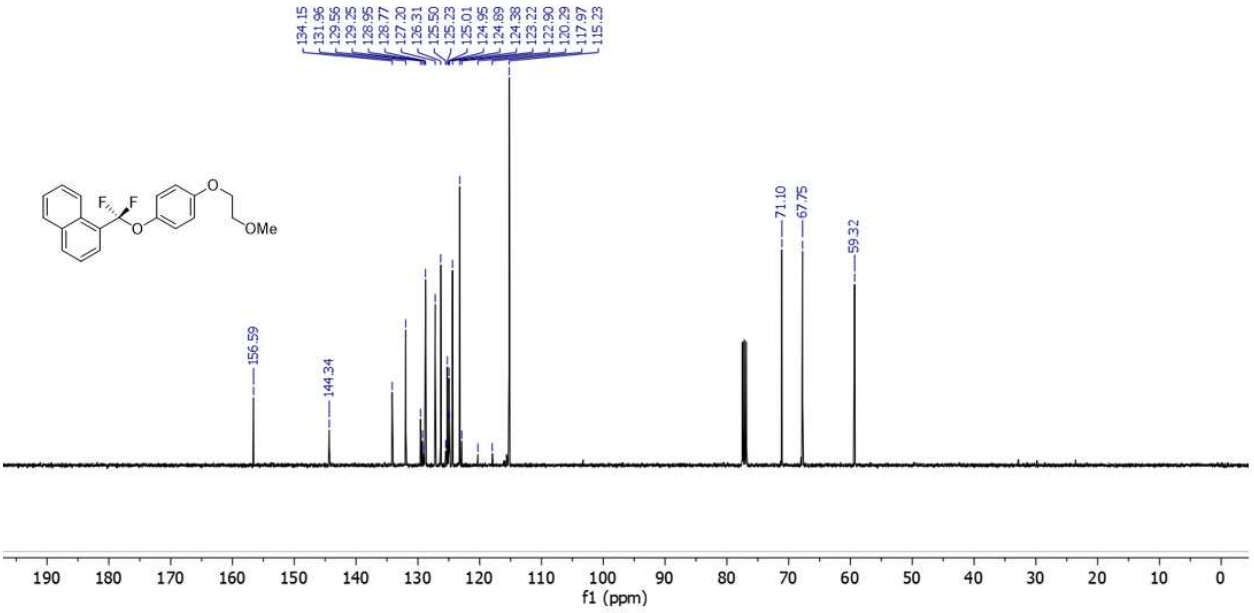

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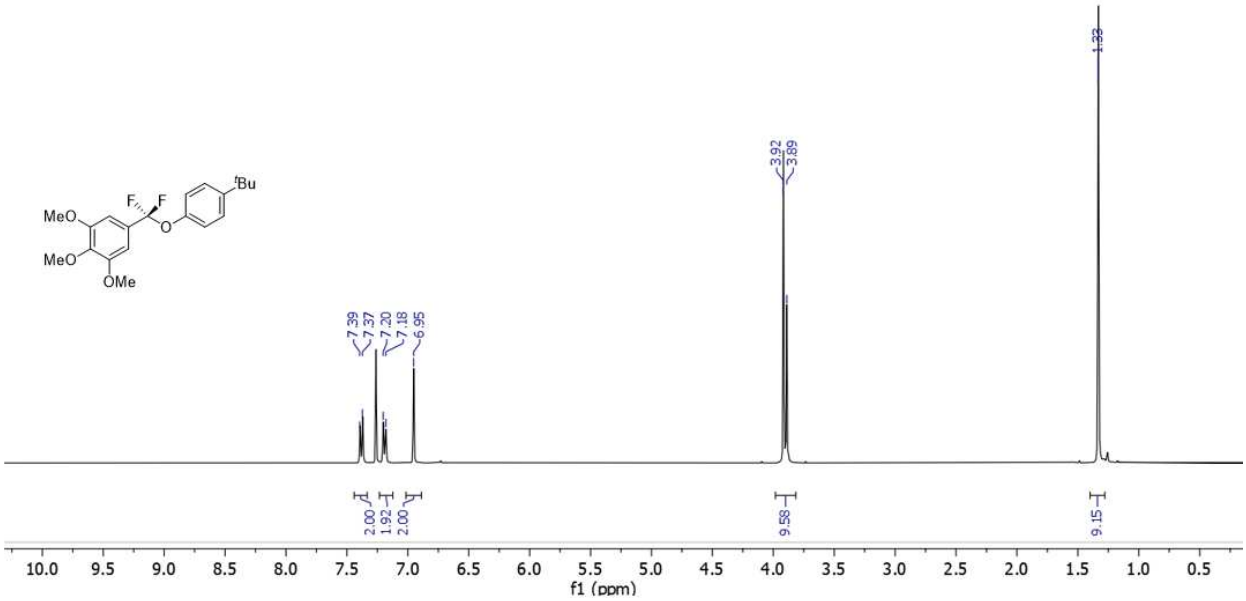

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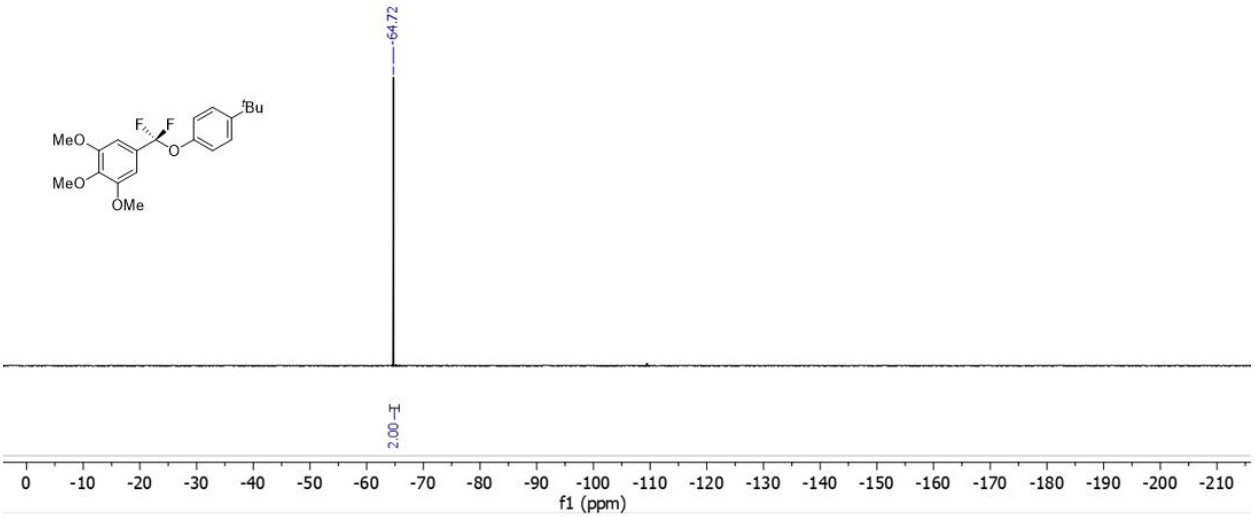

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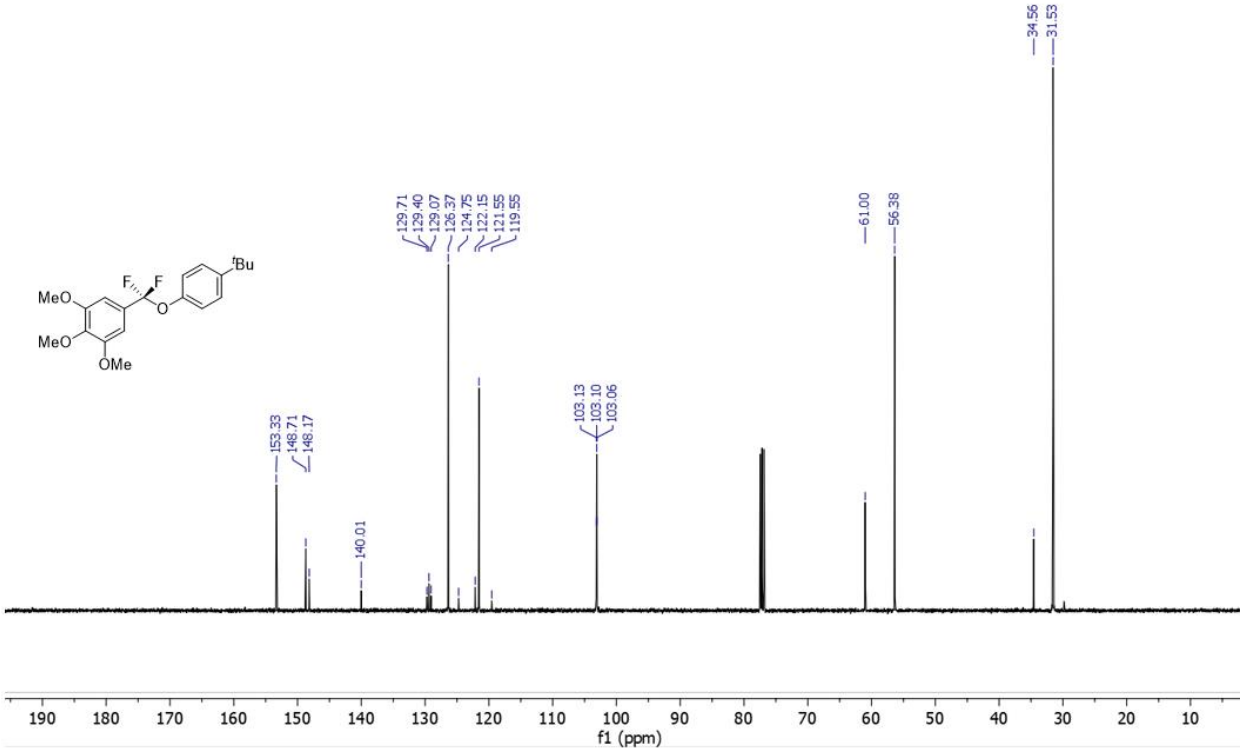

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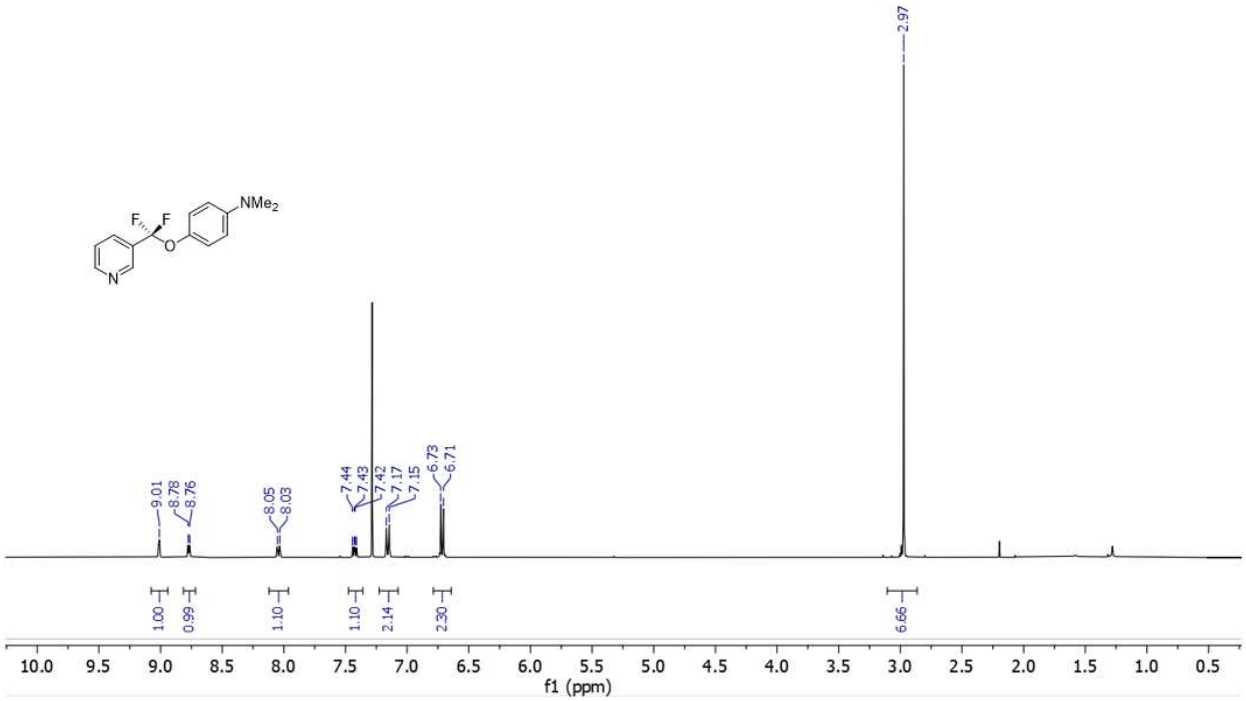

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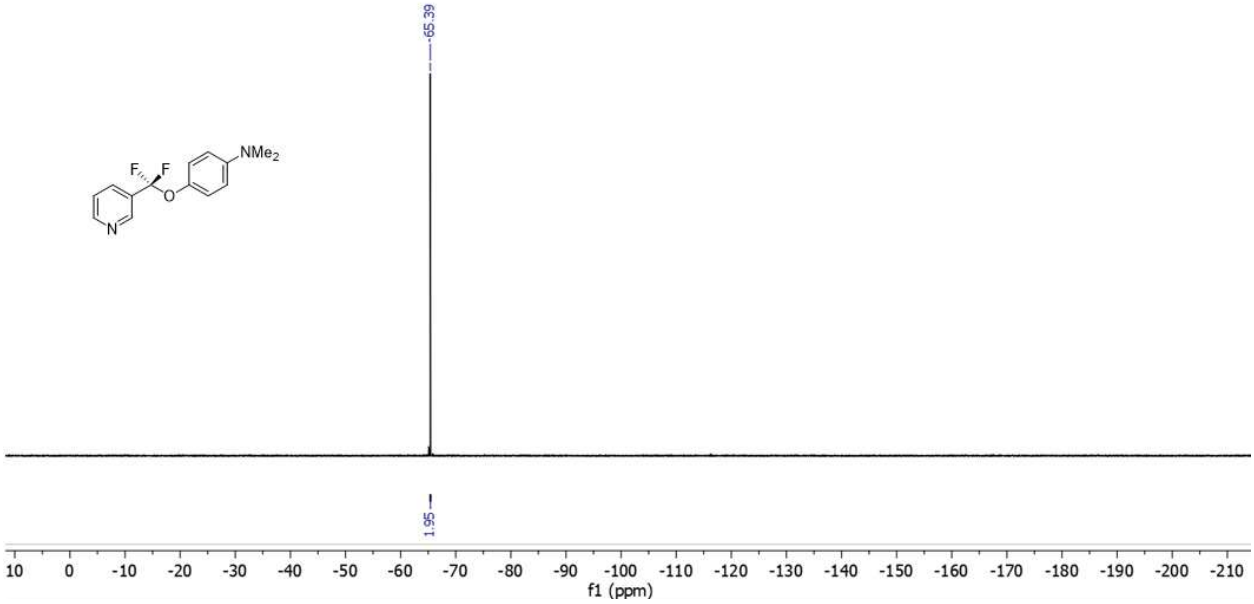

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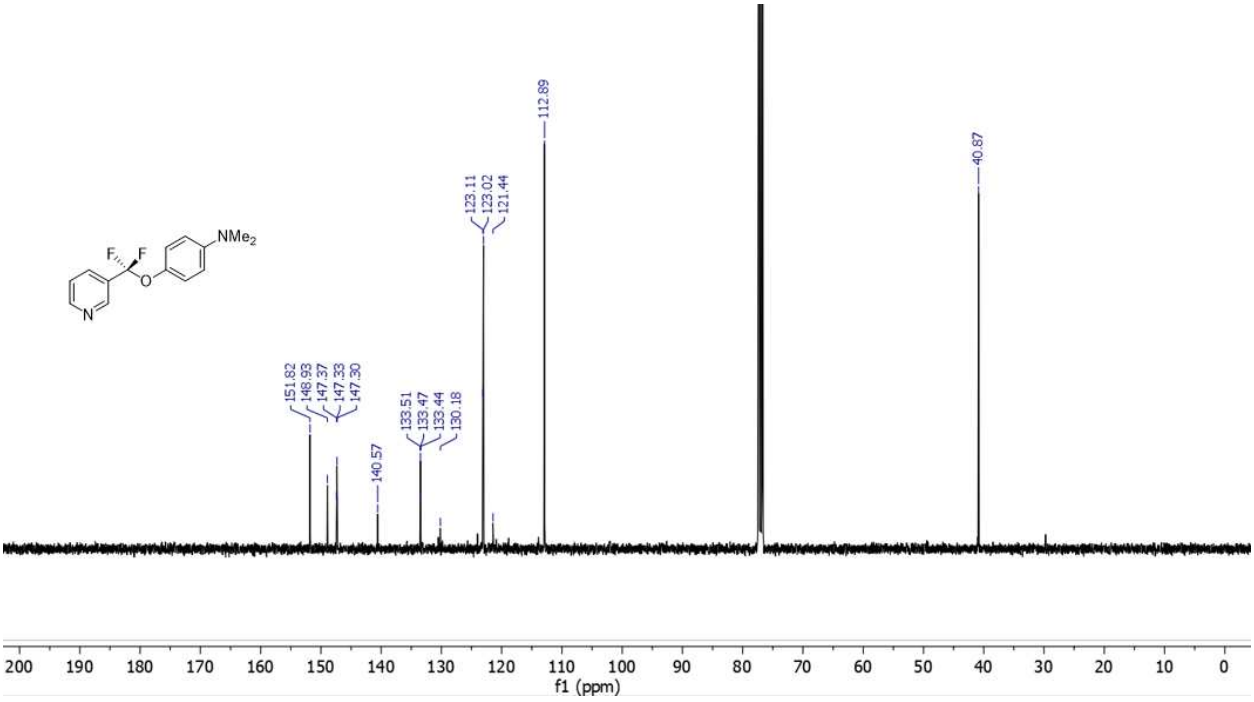

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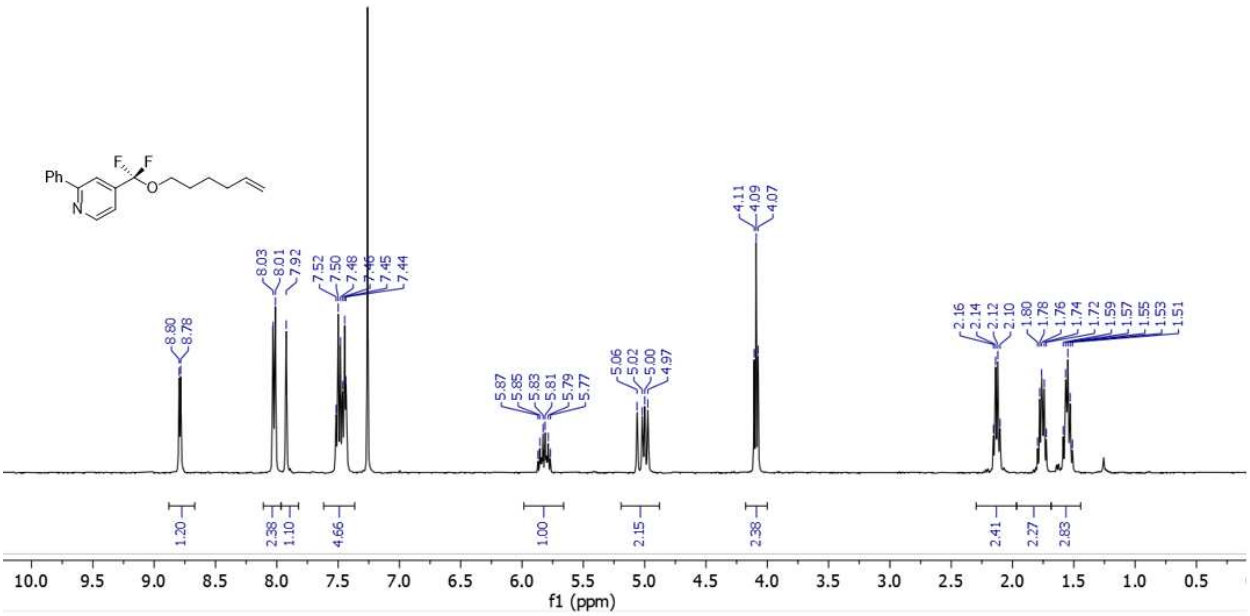

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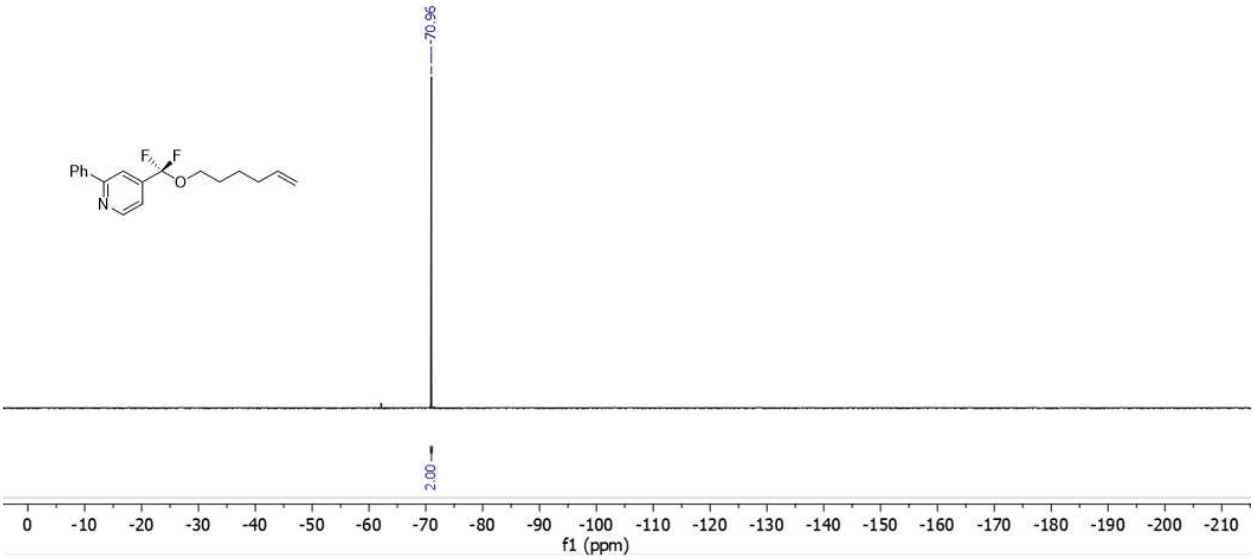

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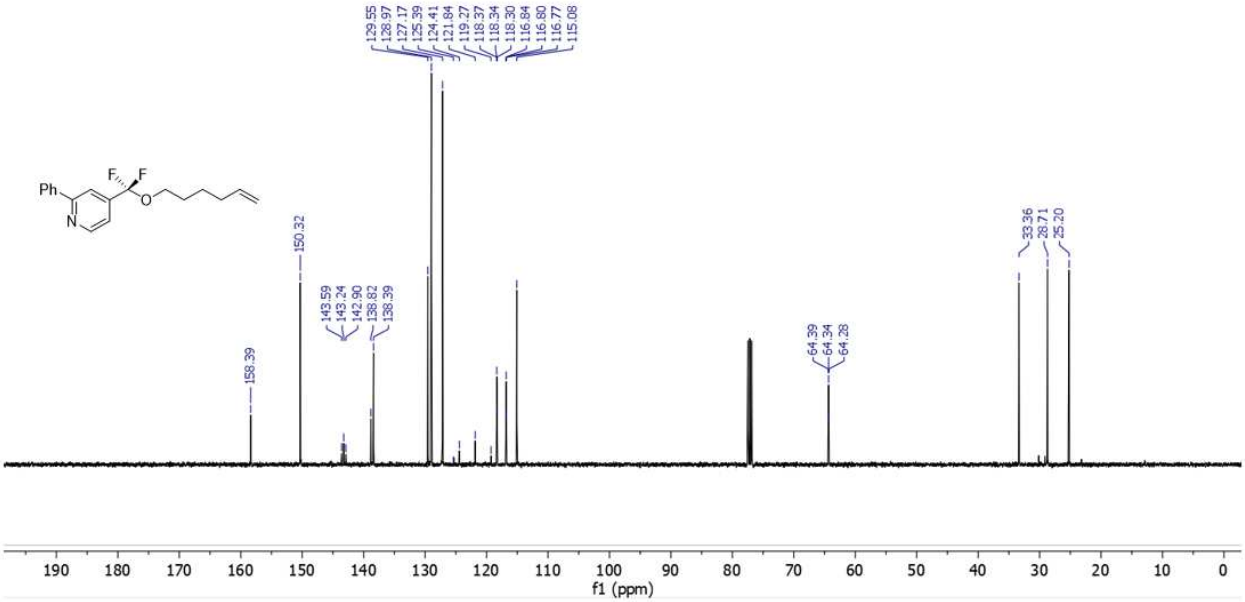
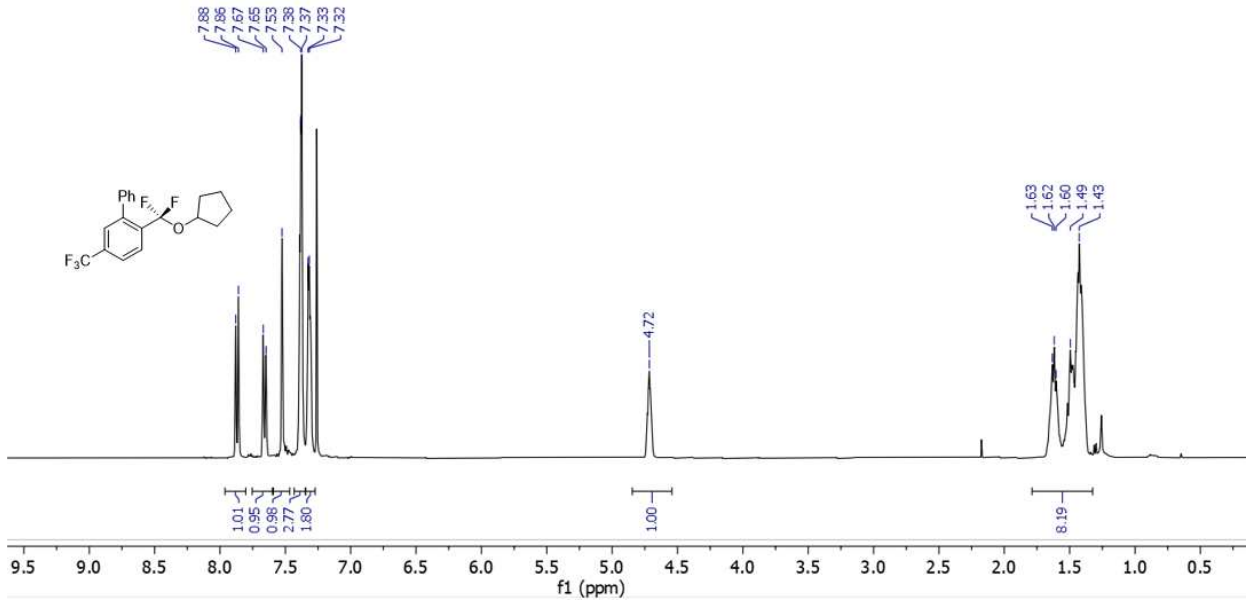
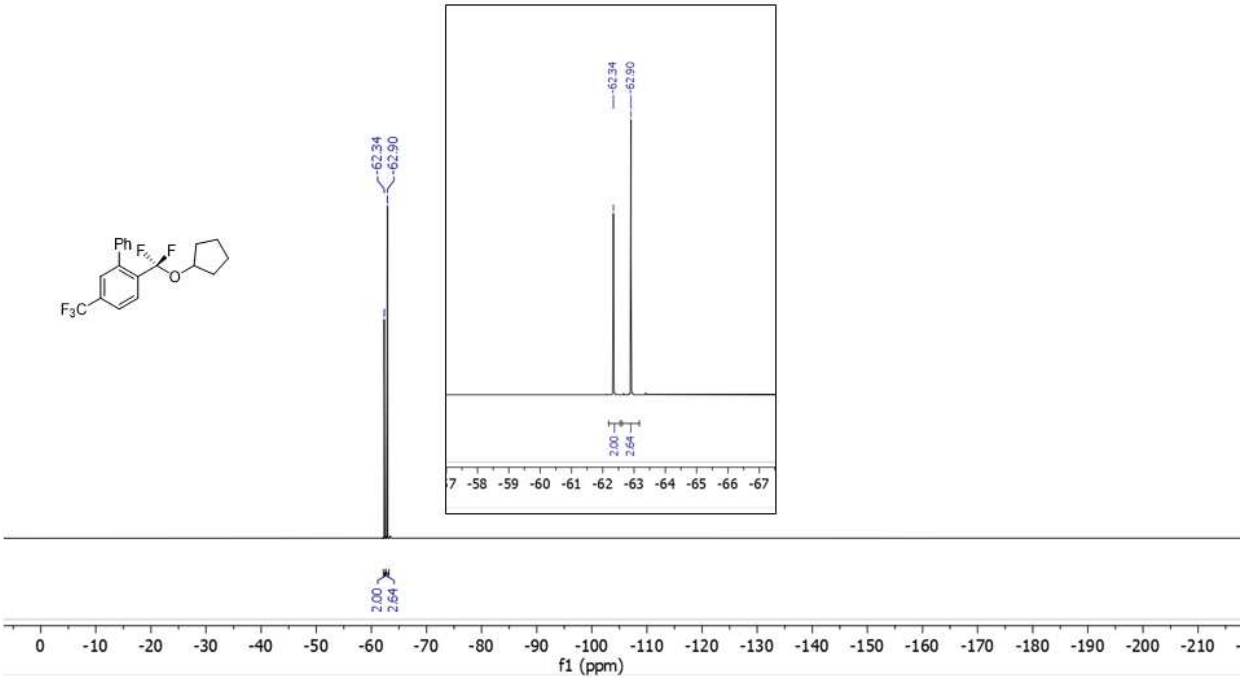


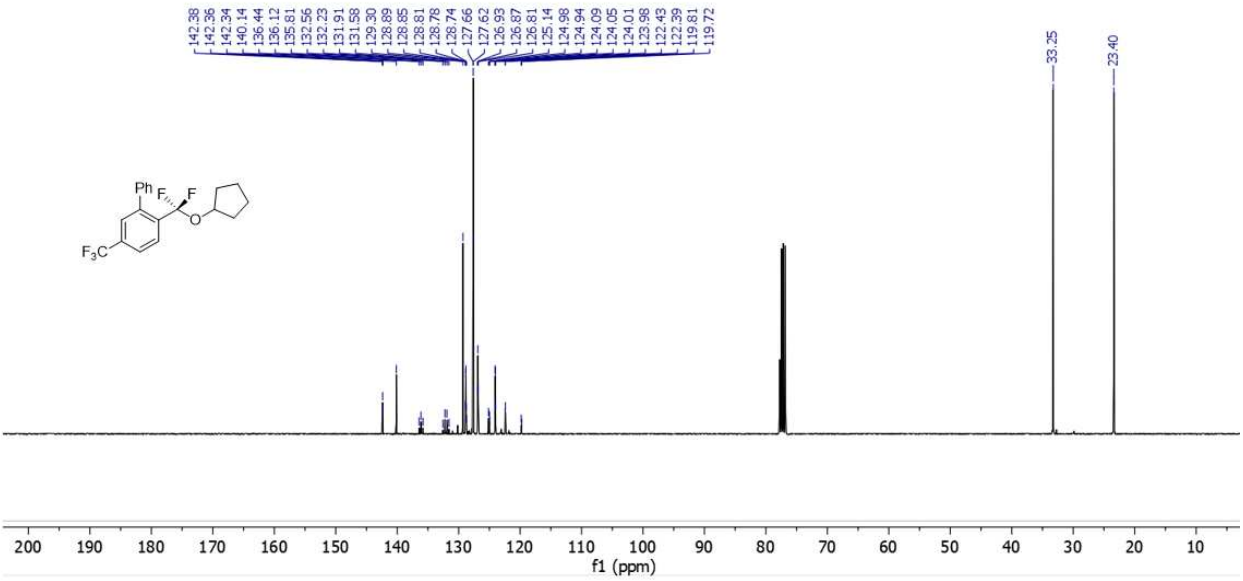
^{13}C NMR spectrum **3-19** (101 MHz, $CDCl_3$)



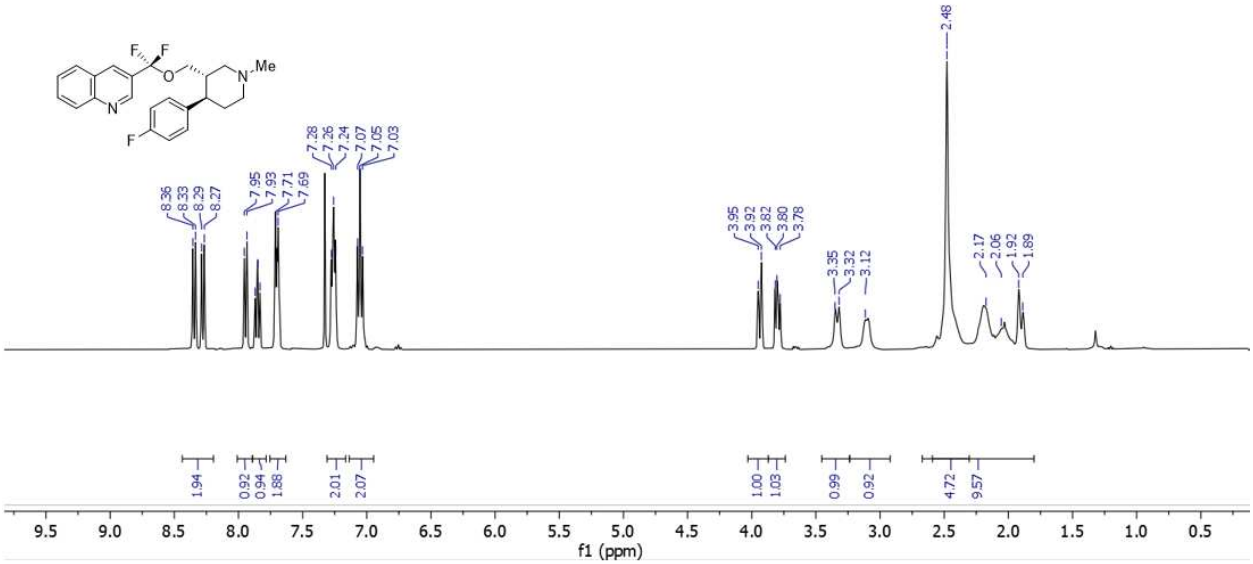
^{1}H NMR spectrum **3-20** (400 MHz, $CDCl_3$)



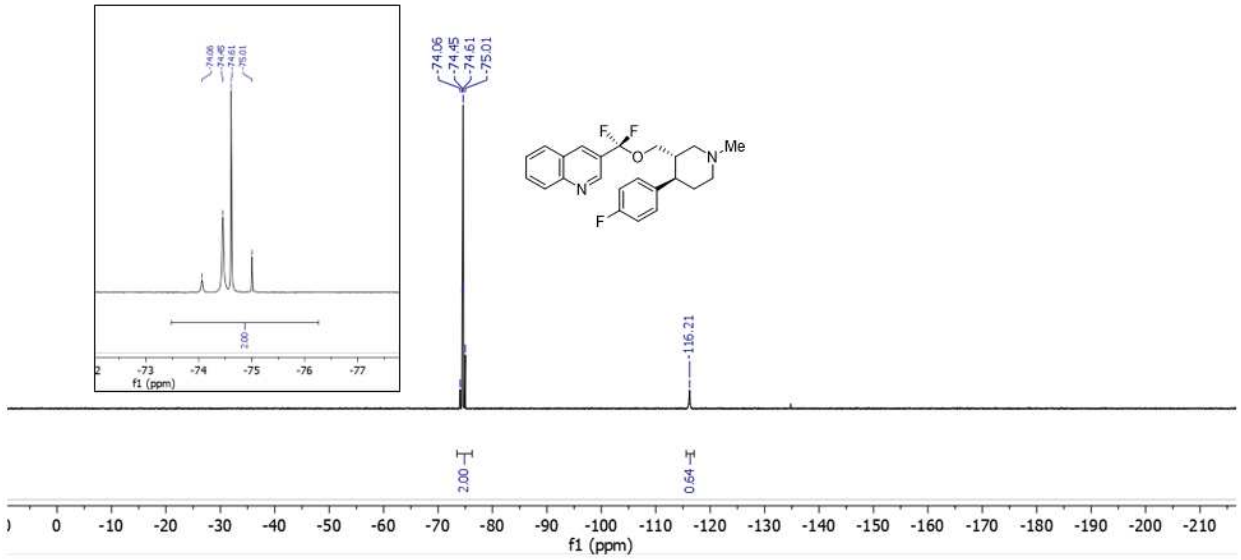
^{19}F NMR spectrum **3-20** (376 MHz, $CDCl_3$)



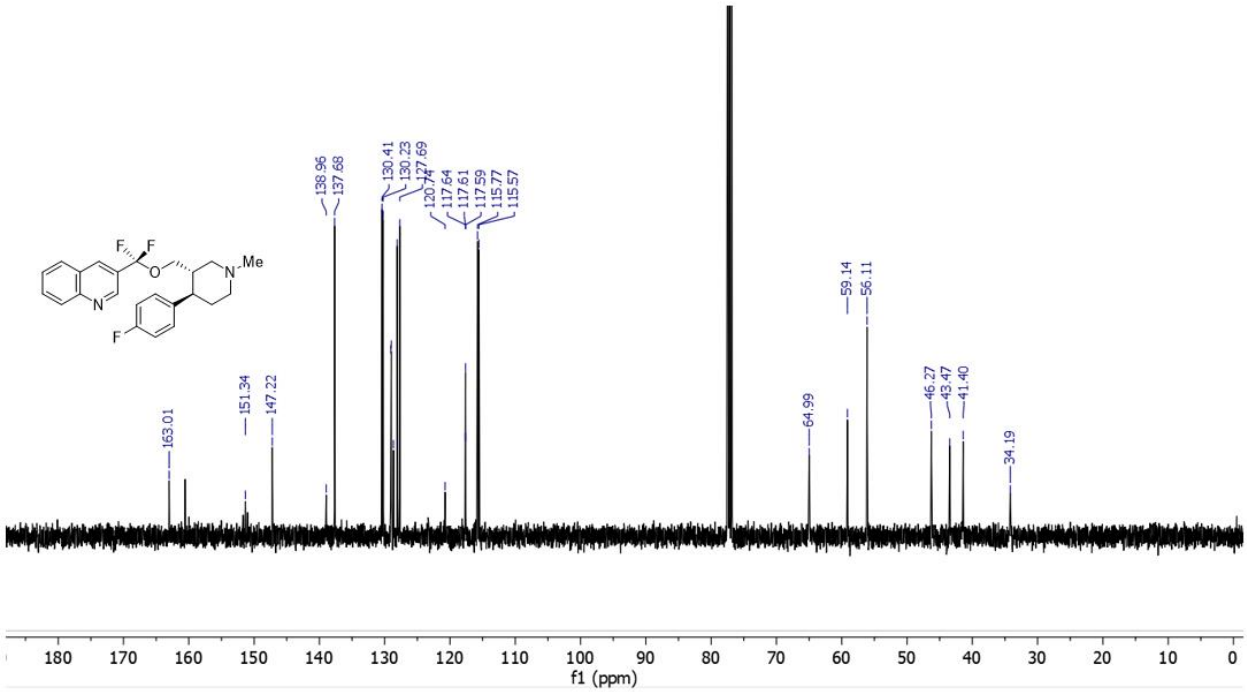
^{13}C NMR spectrum **3-20** (101 MHz, $CDCl_3$)



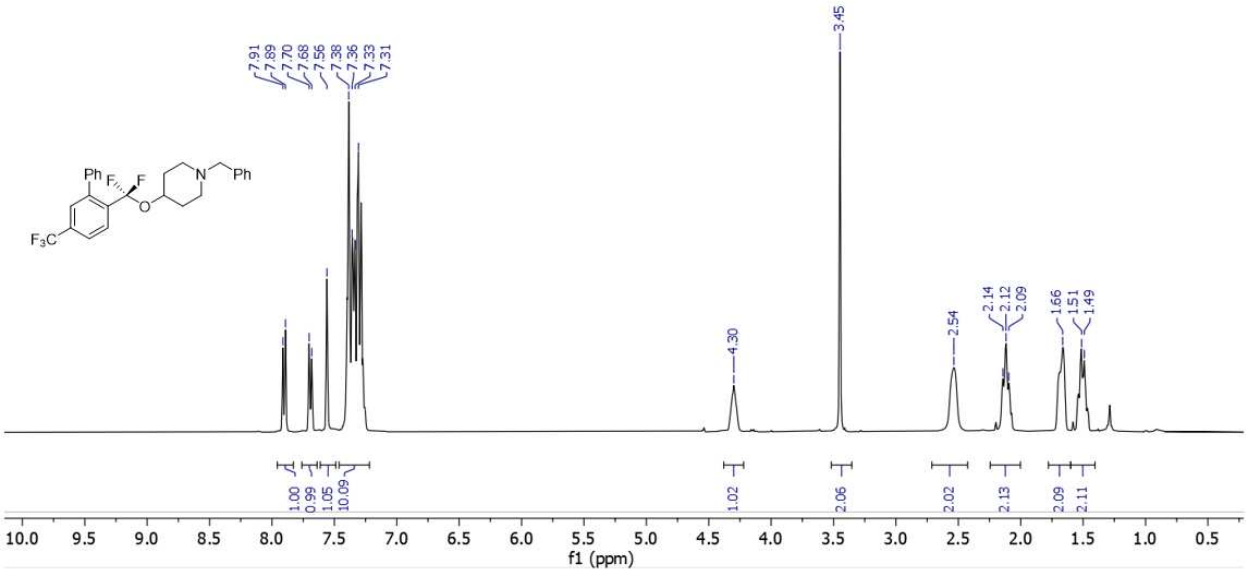
^{1}H NMR spectrum **3-21** (400 MHz, $CDCl_3$)



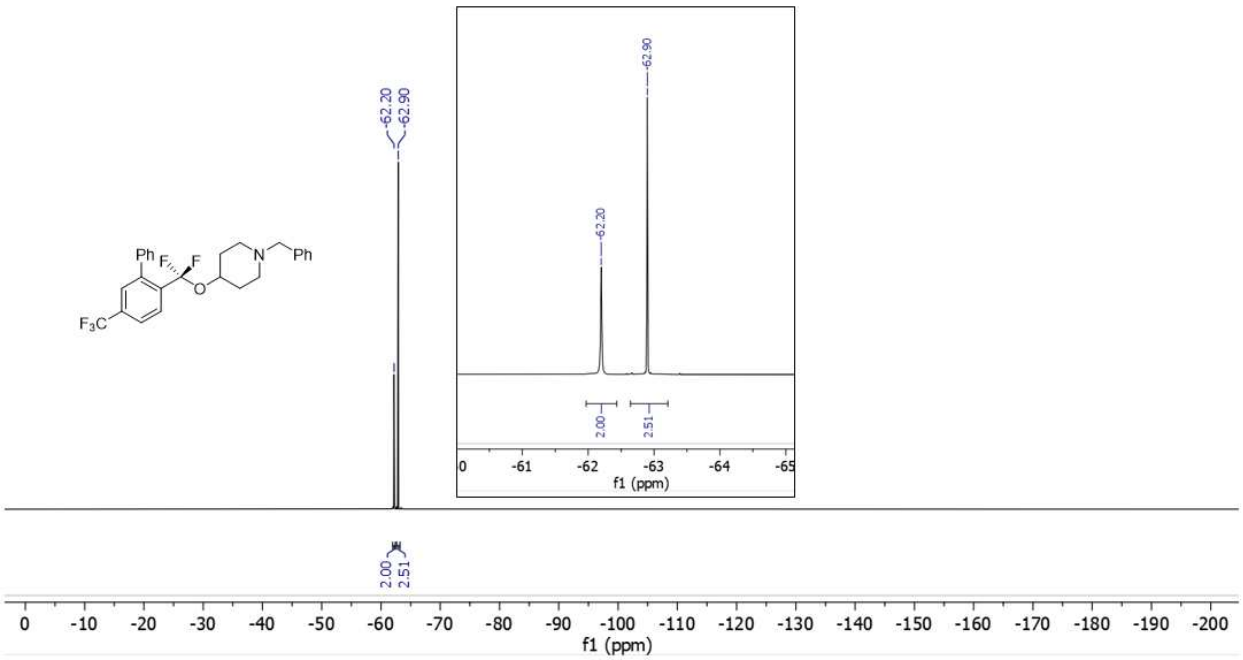
^{19}F NMR spectrum **3-21** (376 MHz, $CDCl_3$)



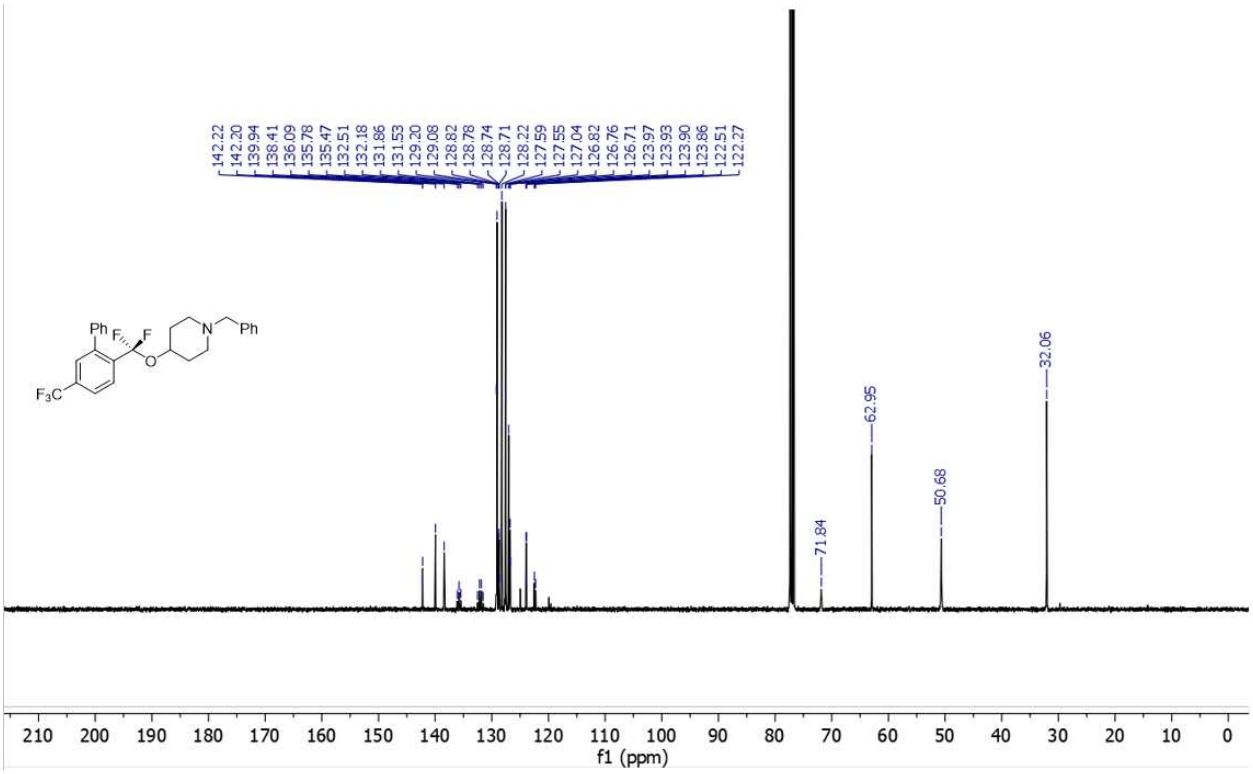
^{13}C NMR spectrum **3-21** (101 MHz, $CDCl_3$)



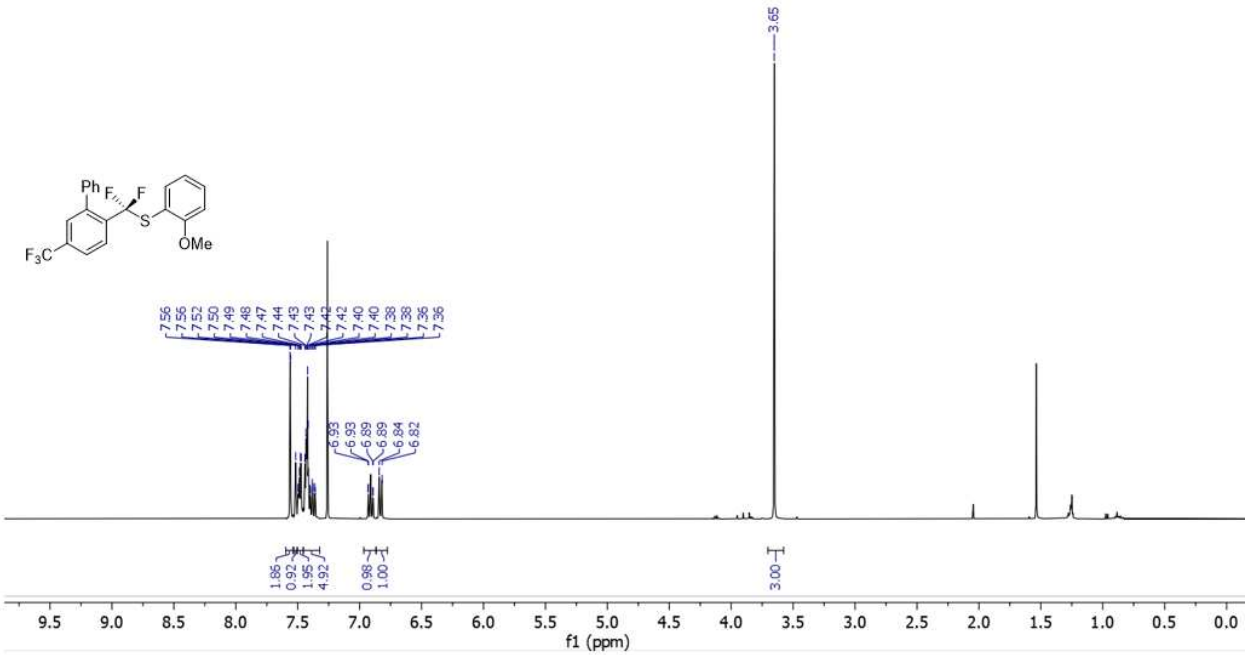
^{1}H NMR spectrum **3-22** (400 MHz, $CDCl_3$)



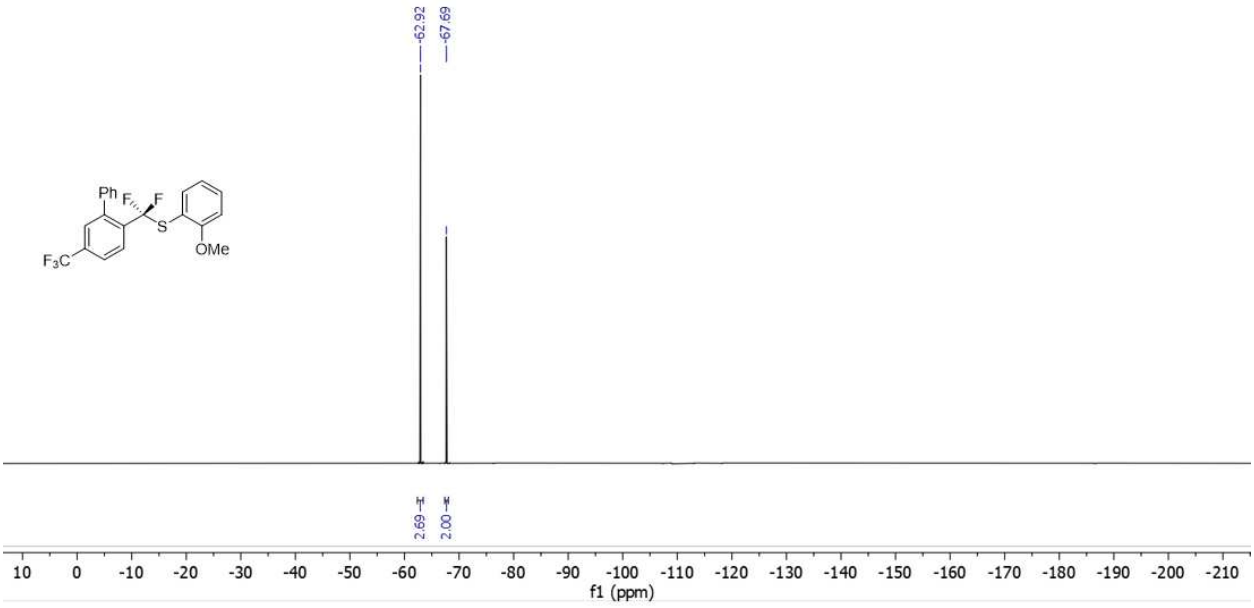
^{19}F NMR spectrum **3-22** (376 MHz, $CDCl_3$)



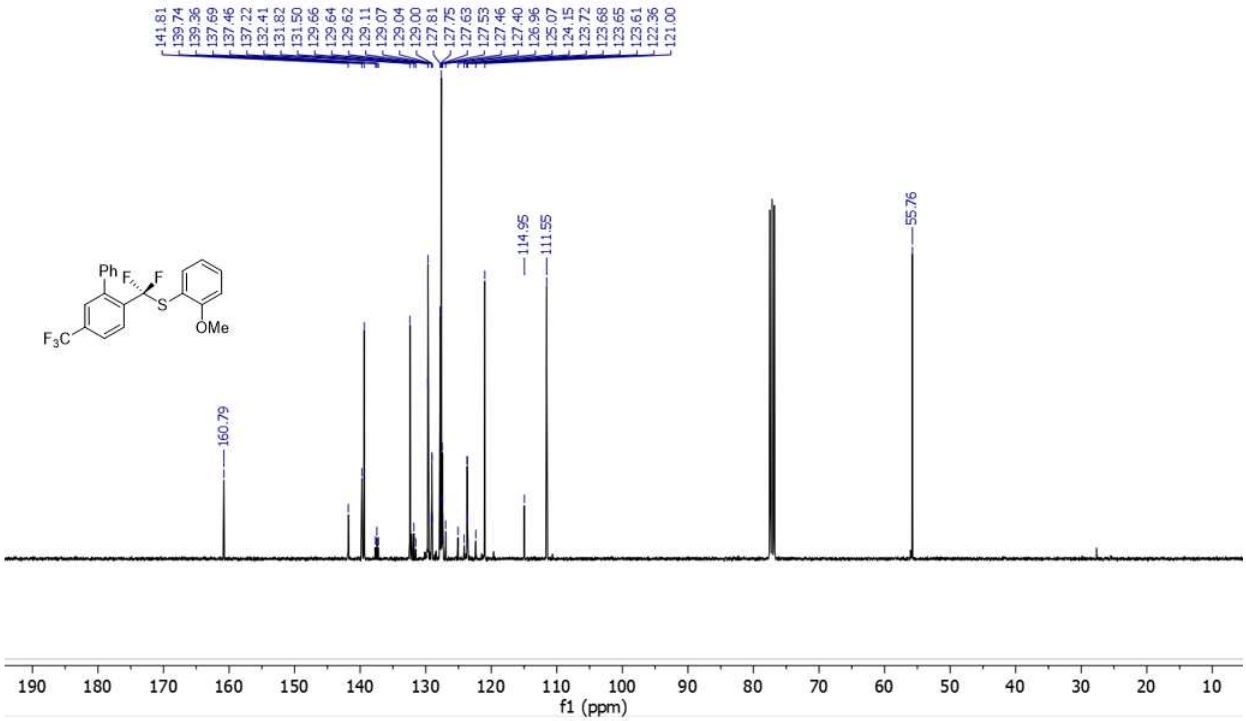
^{13}C NMR spectrum **3-22** (101 MHz, $CDCl_3$)



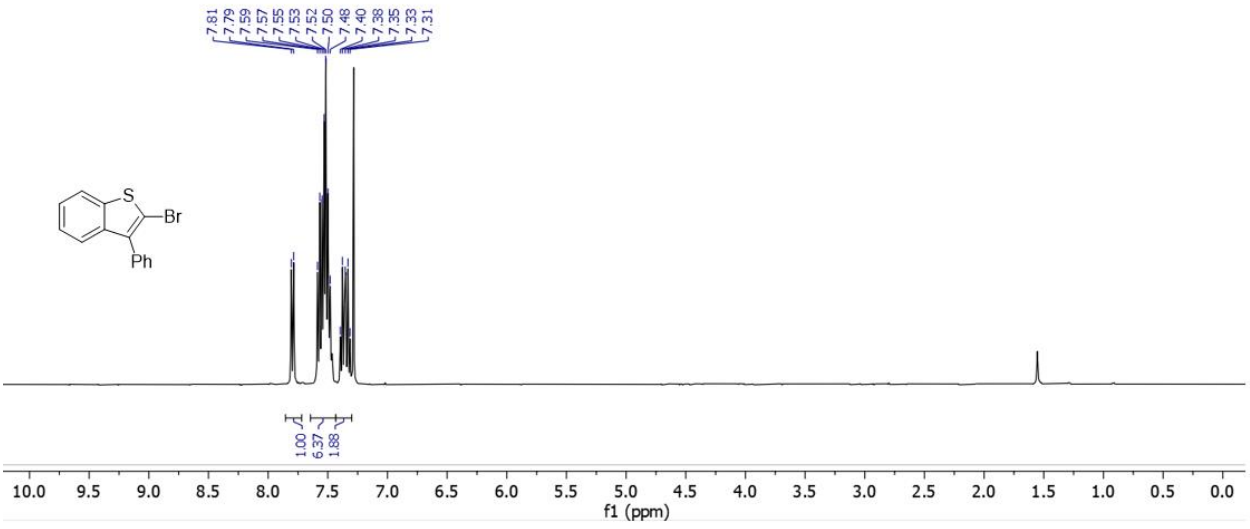
^{1}H NMR spectrum **3-23** (400 MHz, $CDCl_3$)



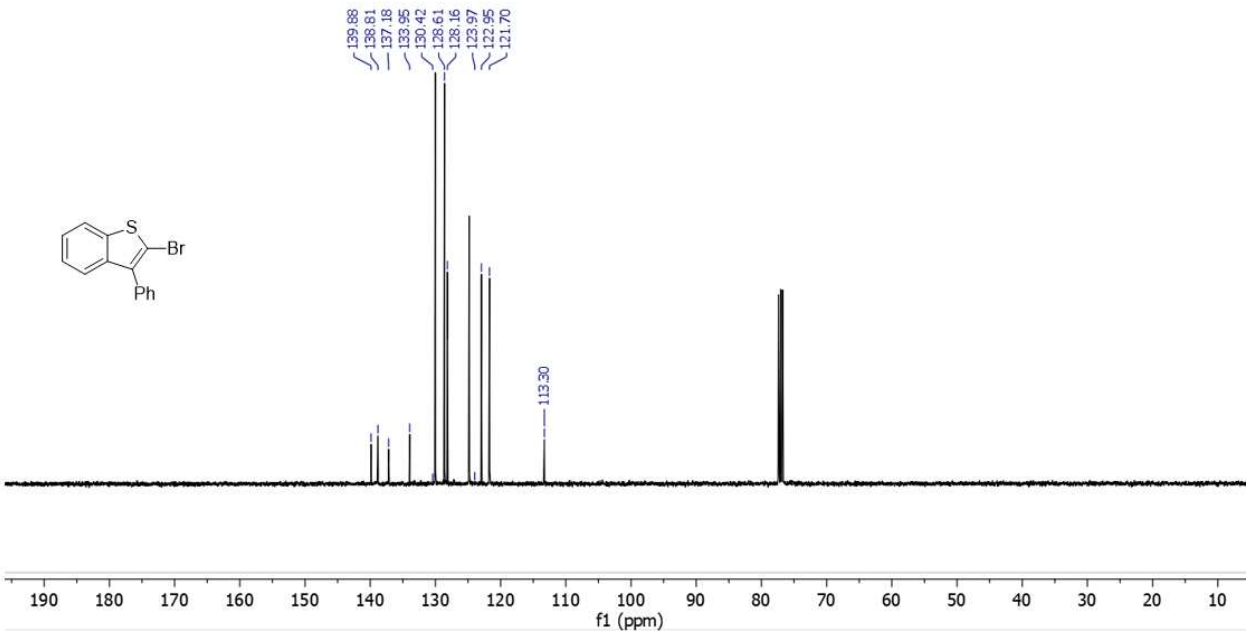
^{19}F NMR spectrum **3-23** (376 MHz, $CDCl_3$)



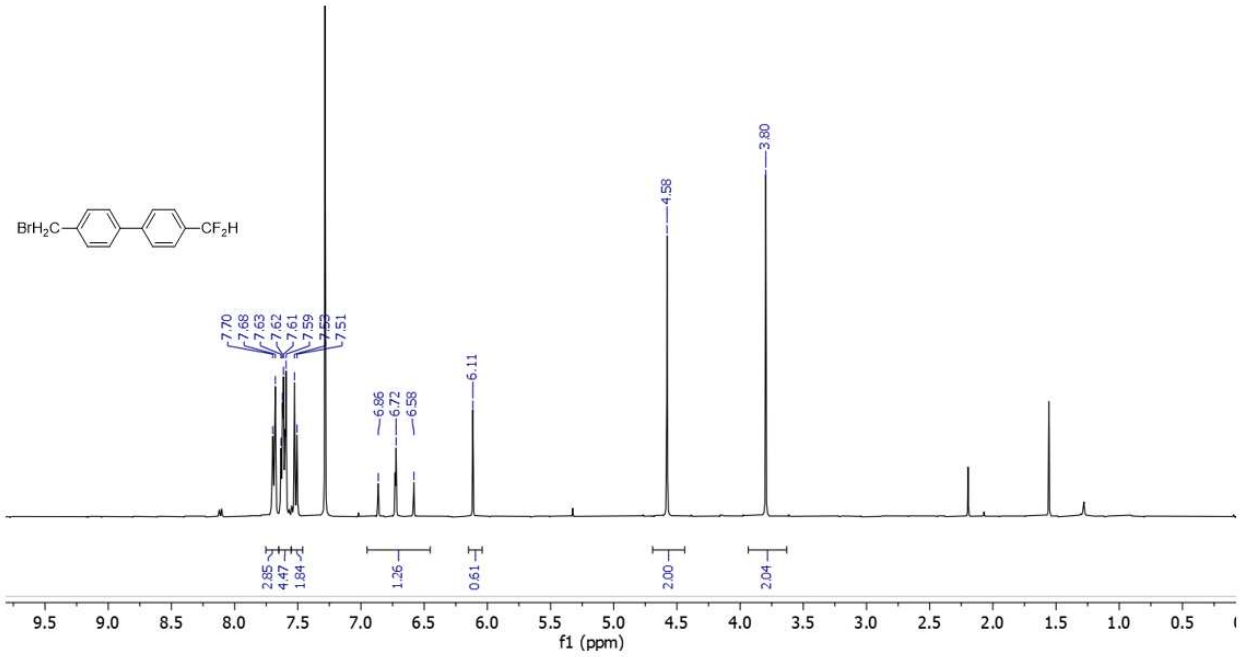
^{13}C NMR spectrum **3-23** (101 MHz, $CDCl_3$)



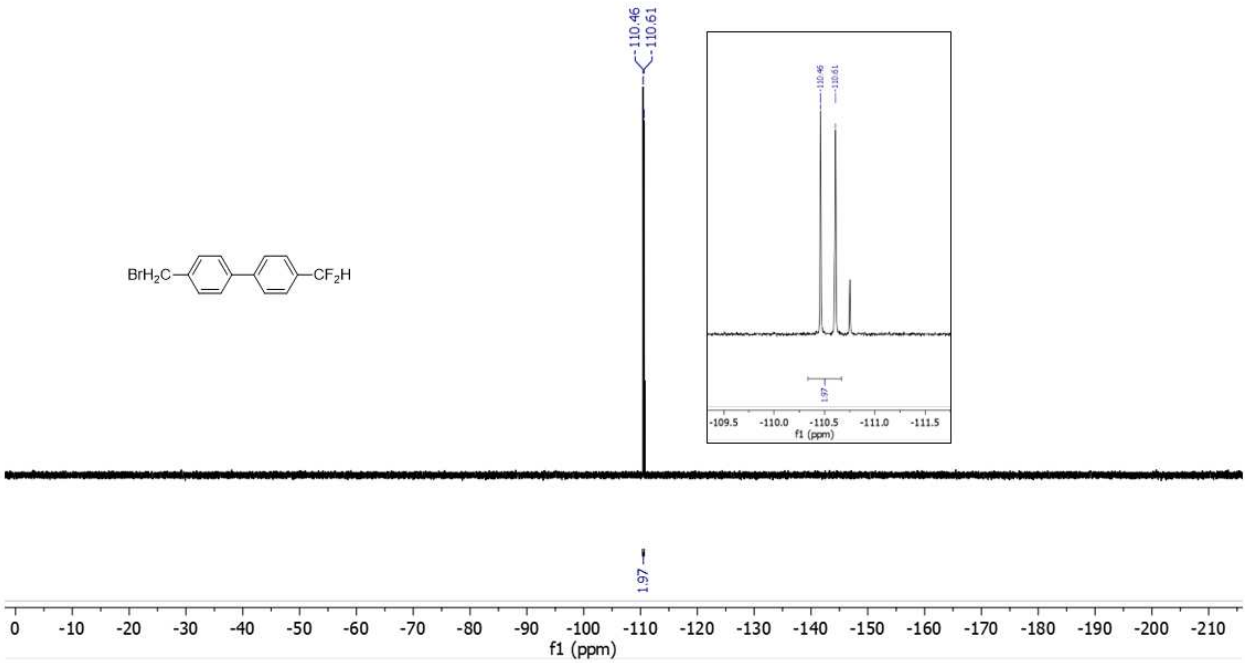
^{1}H NMR spectrum **3-XTR 3** (400 MHz, $CDCl_3$)



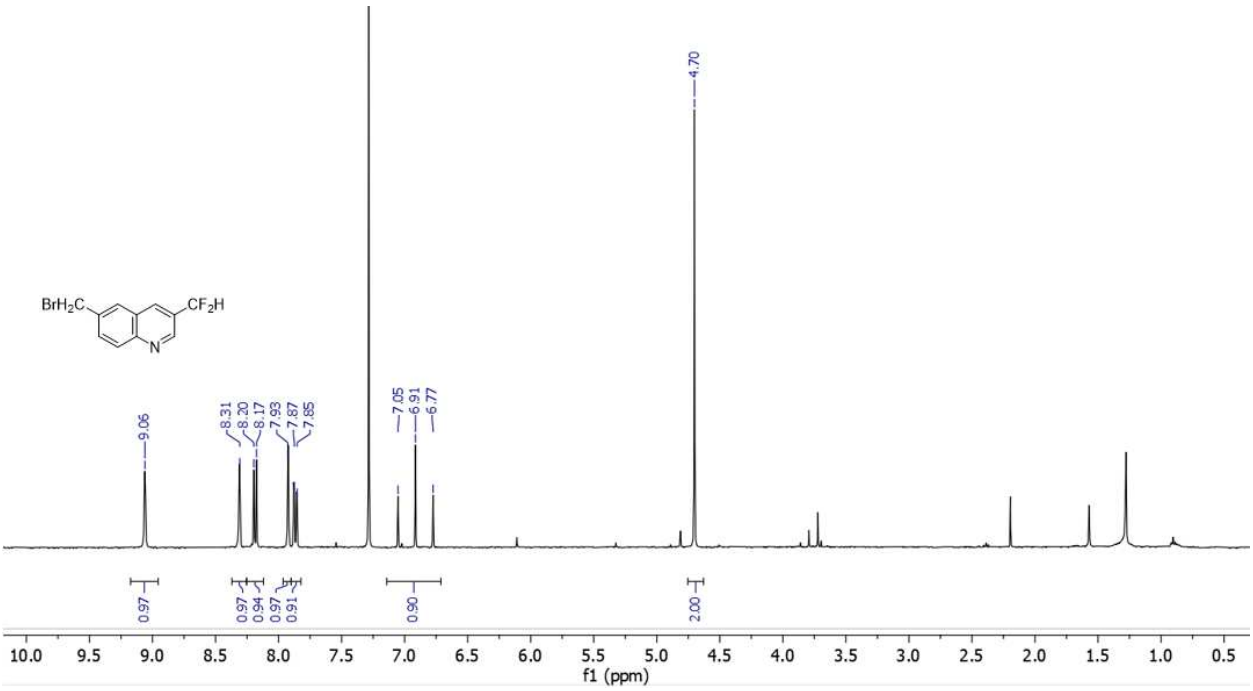
^{13}C NMR spectrum **3-XTR 3** (101 MHz, $CDCl_3$)



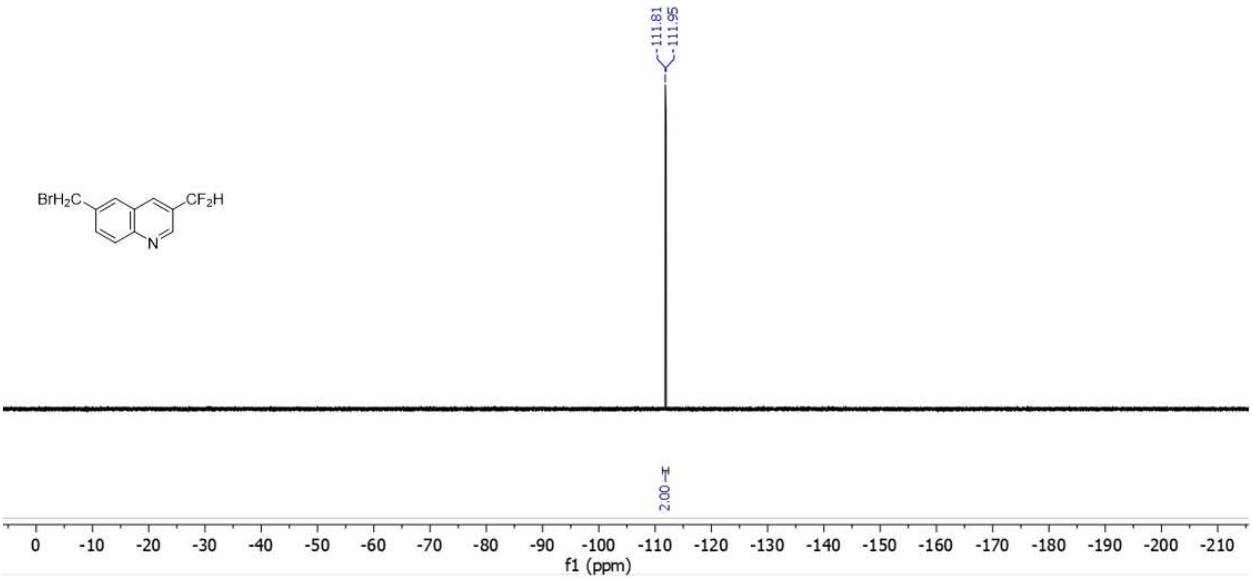
^{1}H NMR spectrum **3-26** and **starting material** (400 MHz, $CDCl_3$)



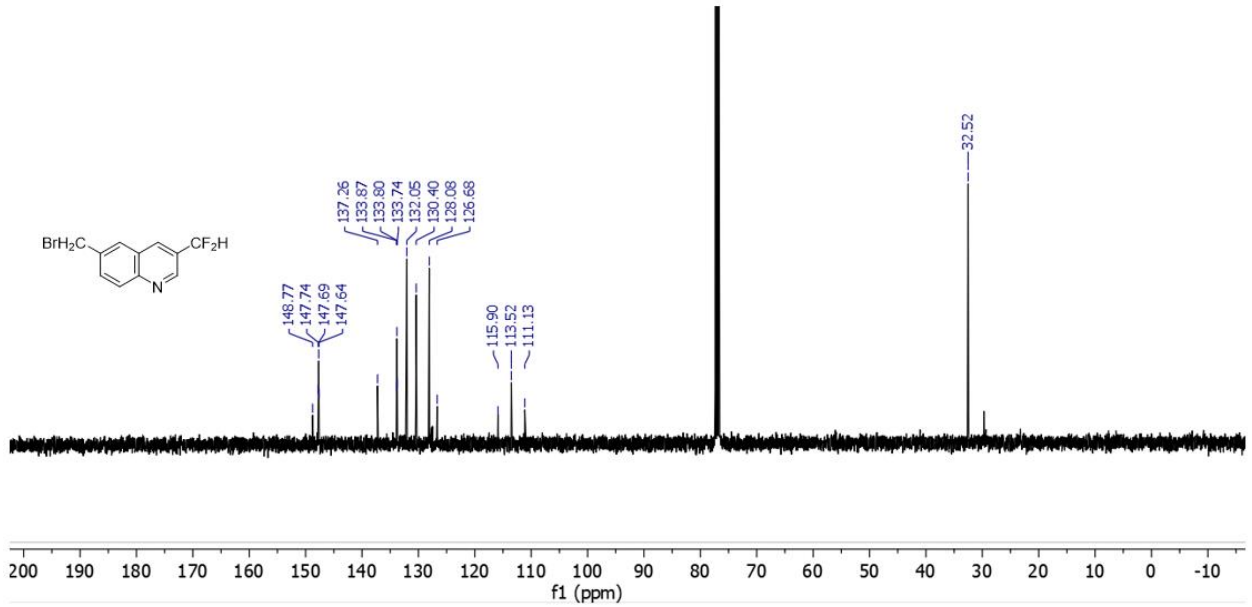
^{19}F NMR spectrum **3-26** and **starting material** (376 MHz, $CDCl_3$)



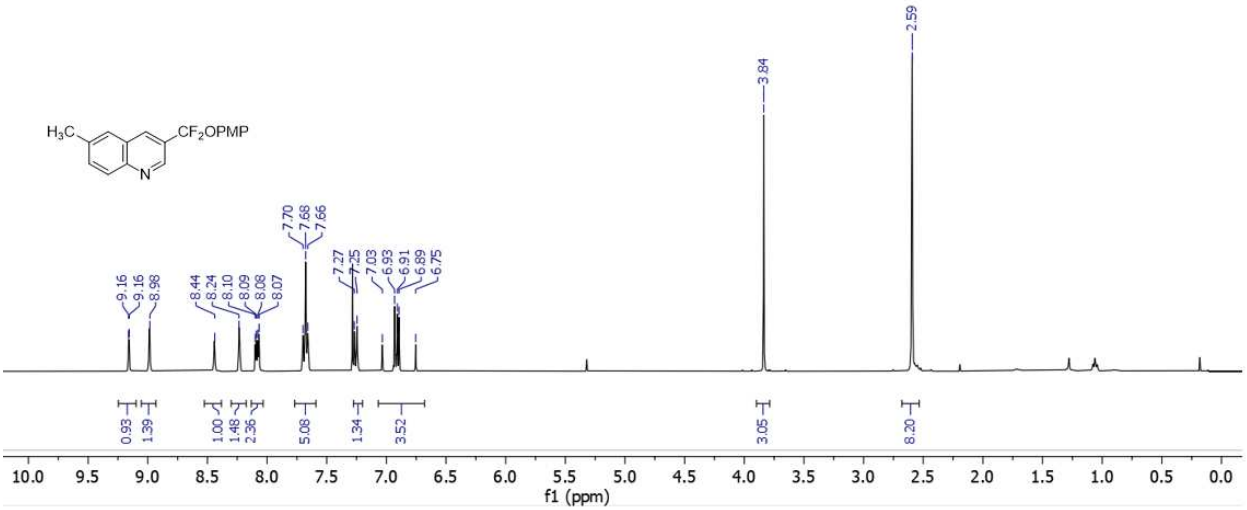
^{1}H NMR spectrum **3-27** (400 MHz, $CDCl_3$)



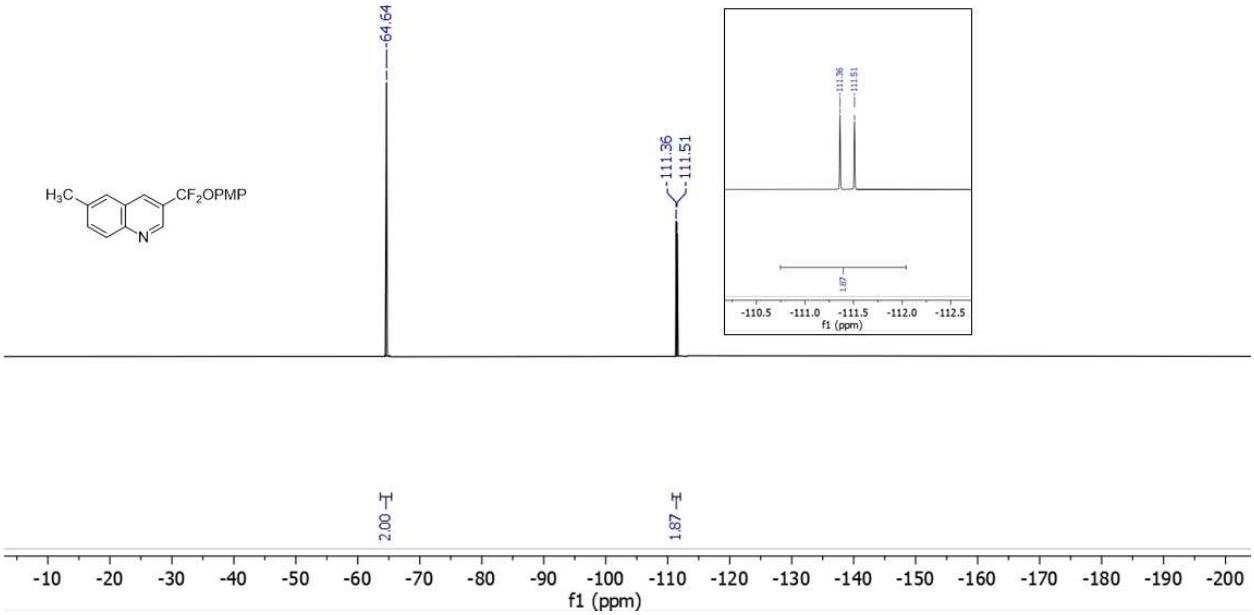
^{19}F NMR spectrum **3-27** (376 MHz, $CDCl_3$)



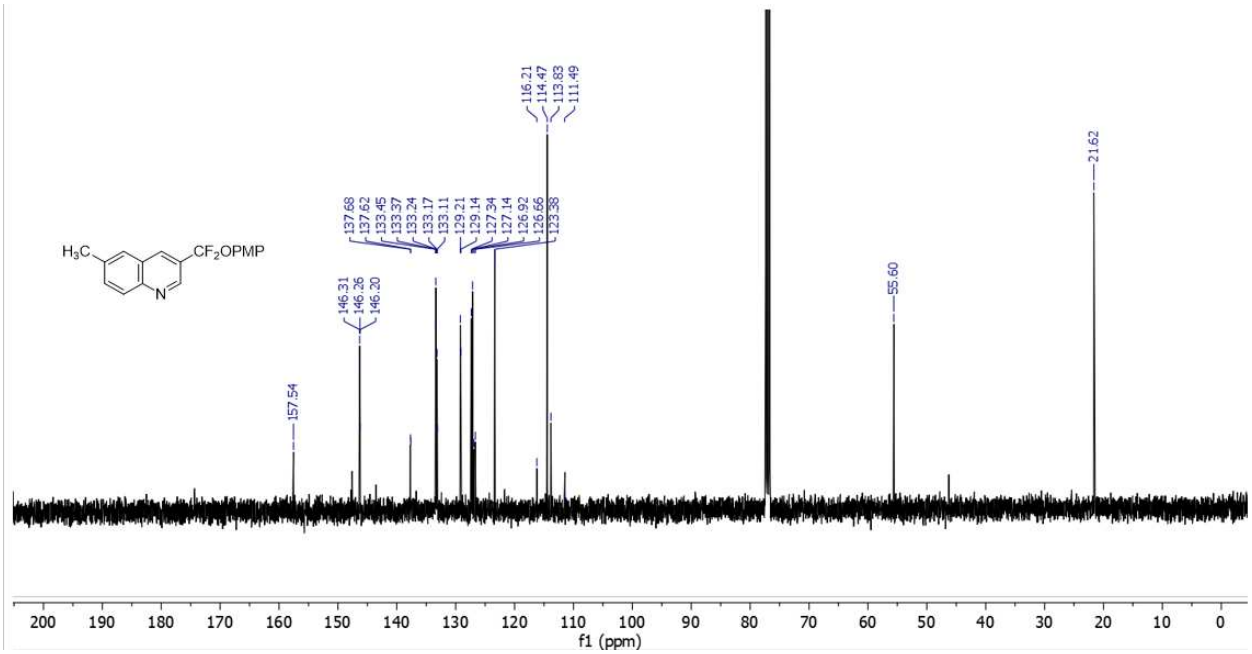
^{13}C NMR spectrum **3-27** (101 MHz, $CDCl_3$)



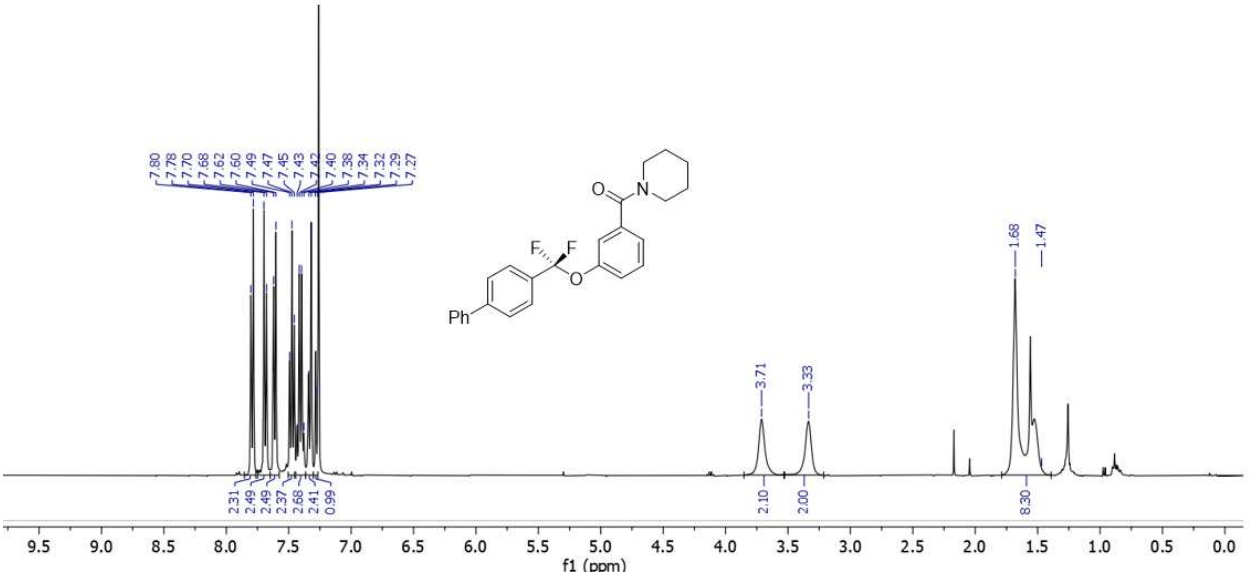
[1]H NMR spectrum **3-29** (400 MHz, $CDCl_3$)



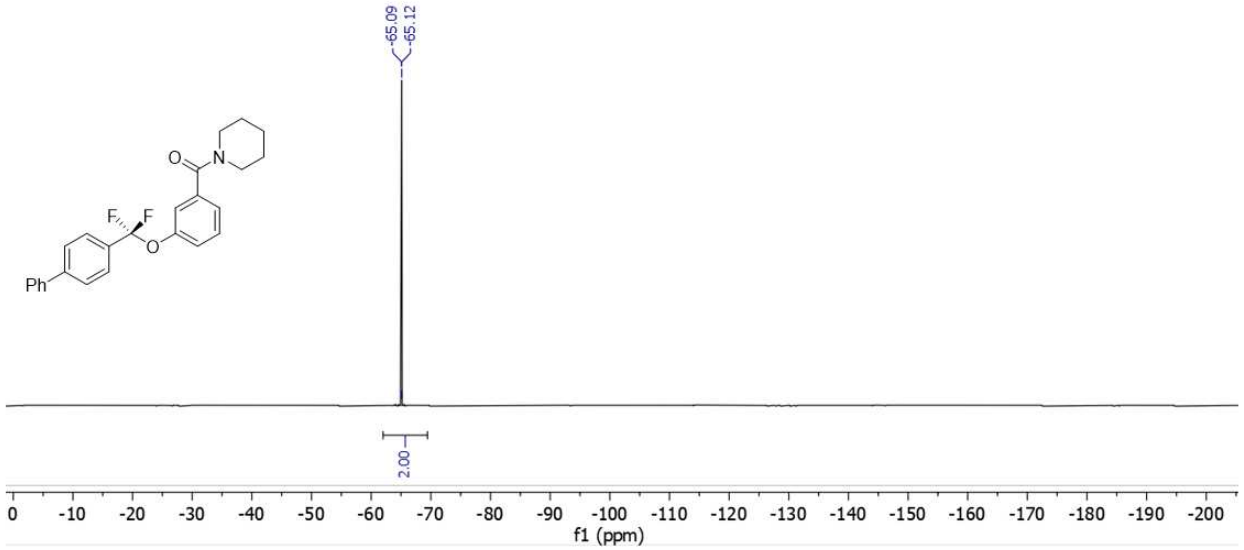
[19]F NMR spectrum **3-29** (376 MHz, $CDCl_3$)



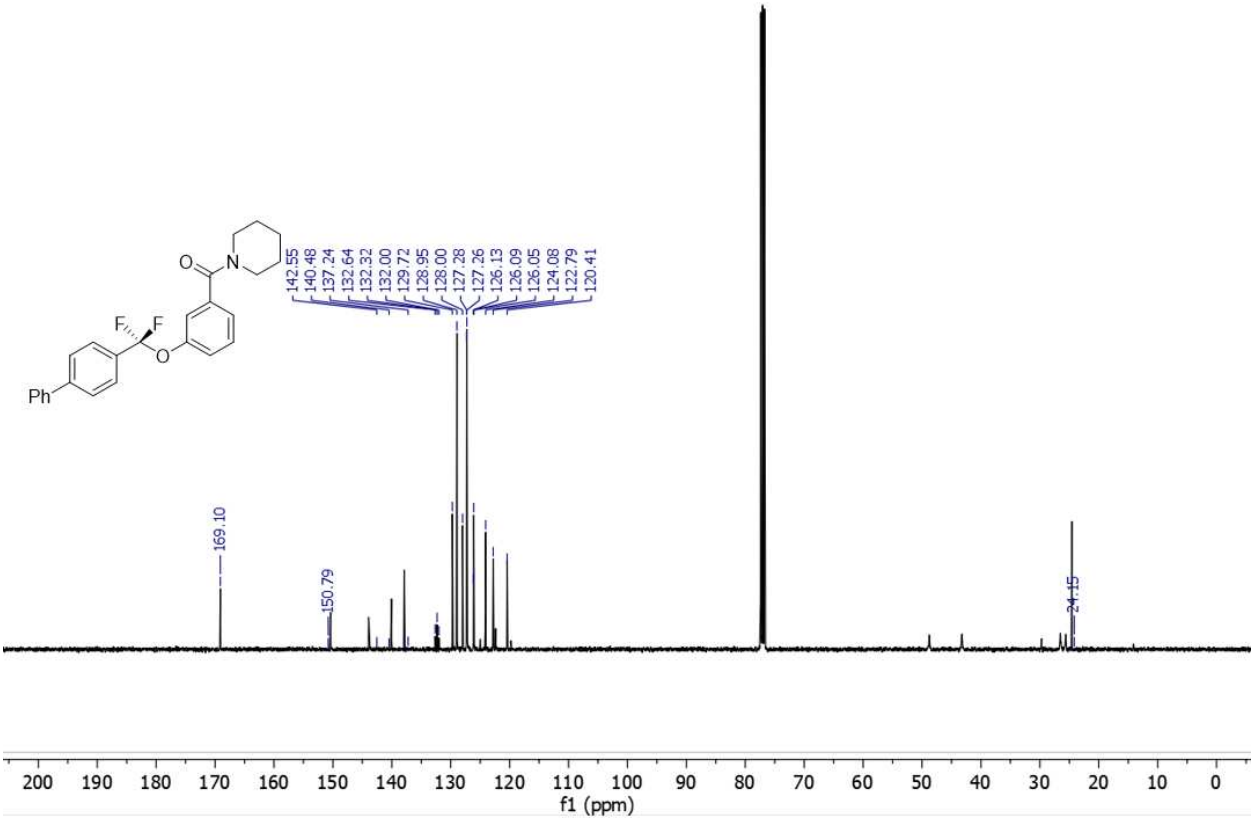
^{13}C NMR spectrum **3-29** (101 MHz, $CDCl_3$)



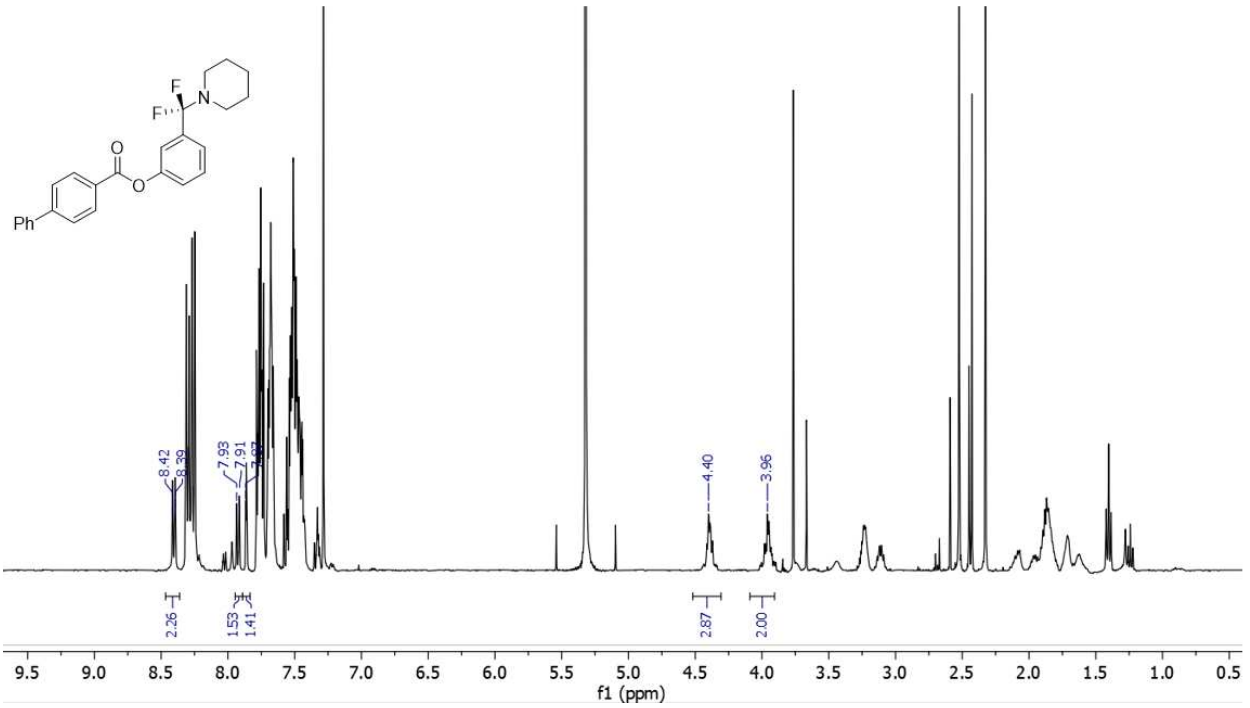
^{1}H NMR spectrum **3-33** (400 MHz, $CDCl_3$)



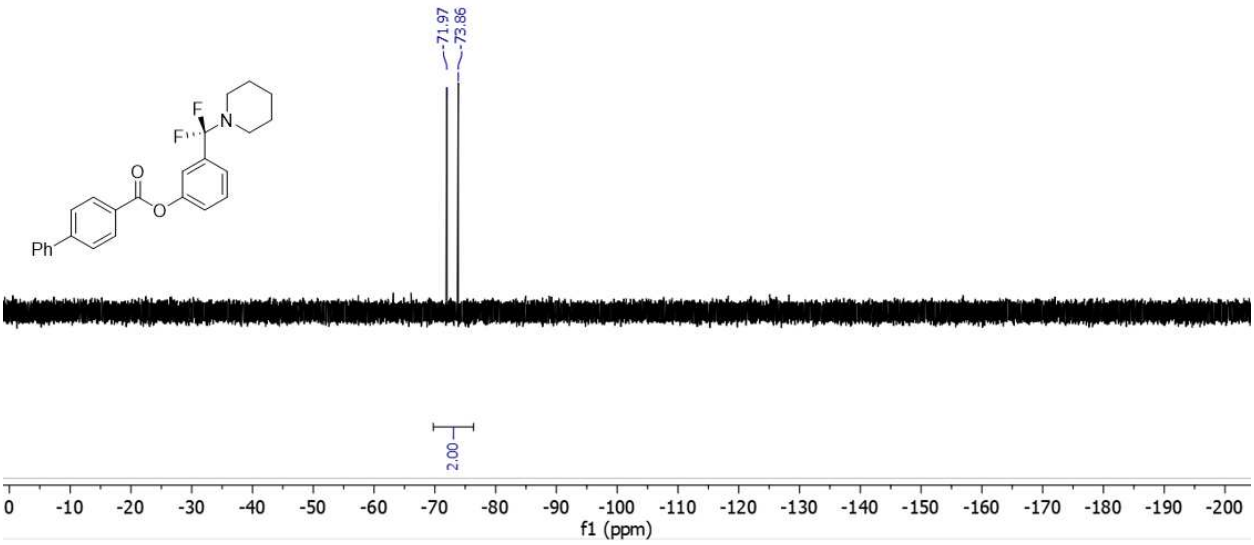
^{19}F NMR spectrum **3-33** (376 MHz, $CDCl_3$)



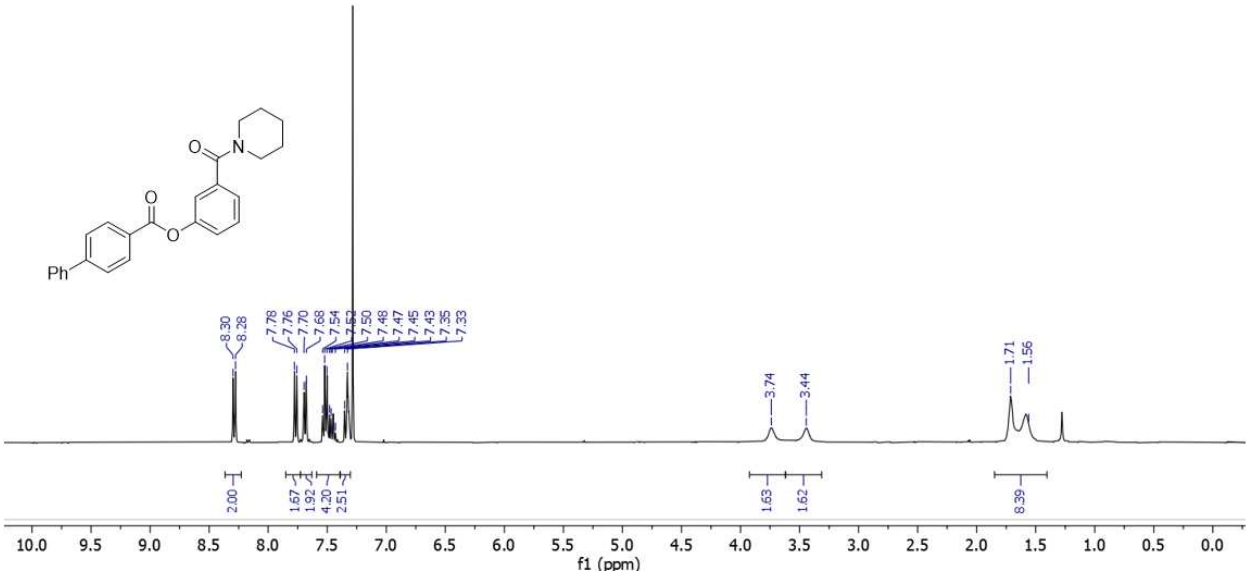
^{13}C NMR spectrum **3-33** (101 MHz, $CDCl_3$)



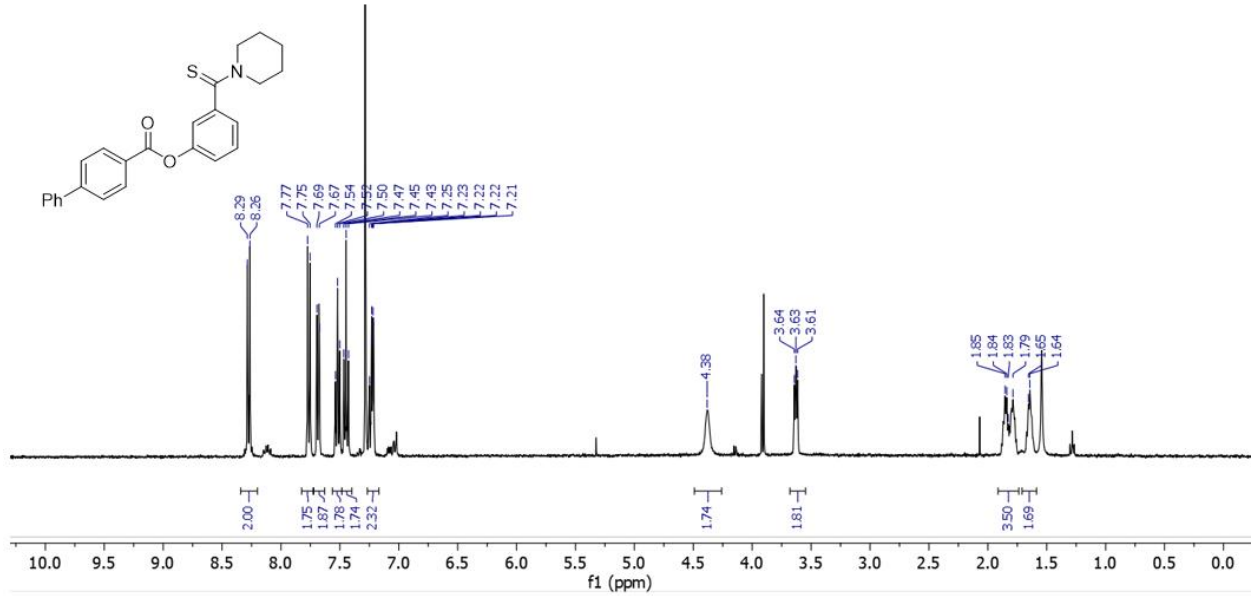
^{1}H NMR crude spectrum **3-31** (400 MHz, $CDCl_3$)



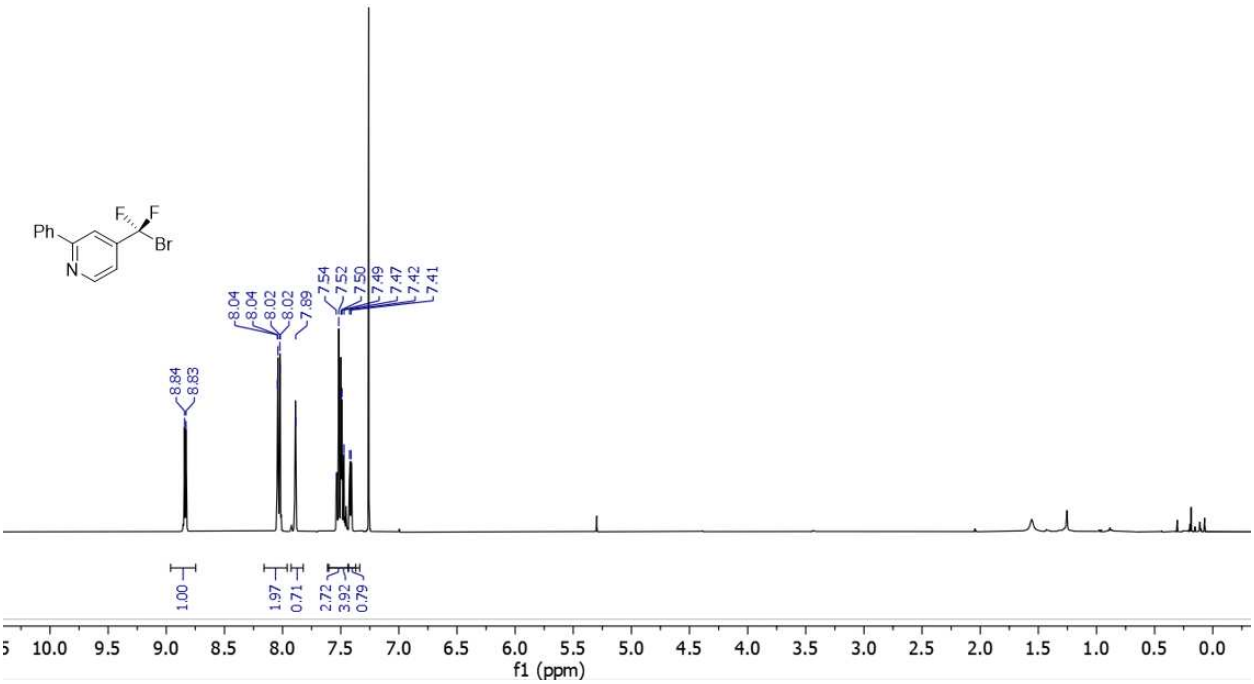
^{19}F NMR spectrum **3-31** (376 MHz, $CDCl_3$)



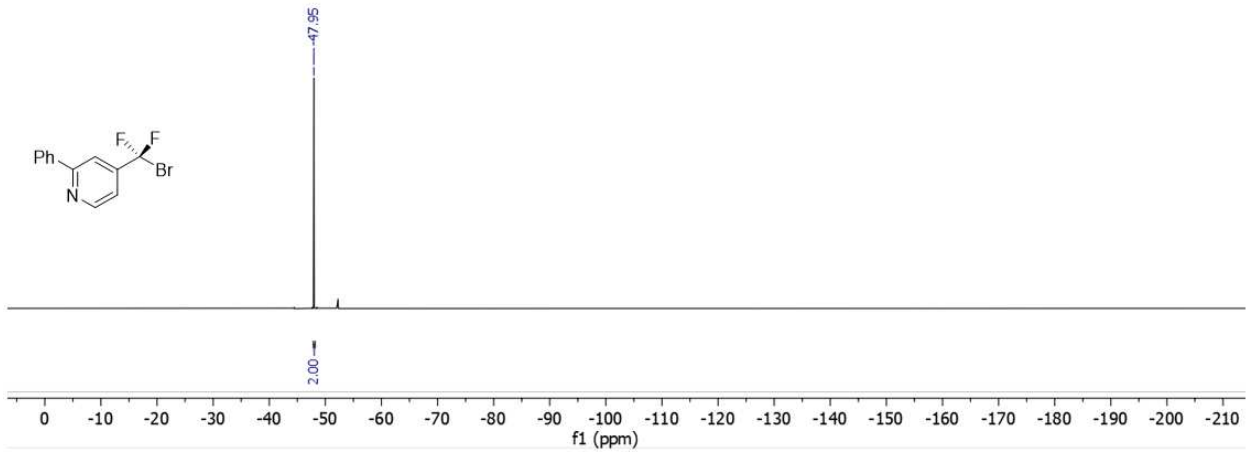
^{1}H NMR spectrum **3-57** (400 MHz, $CDCl_3$)



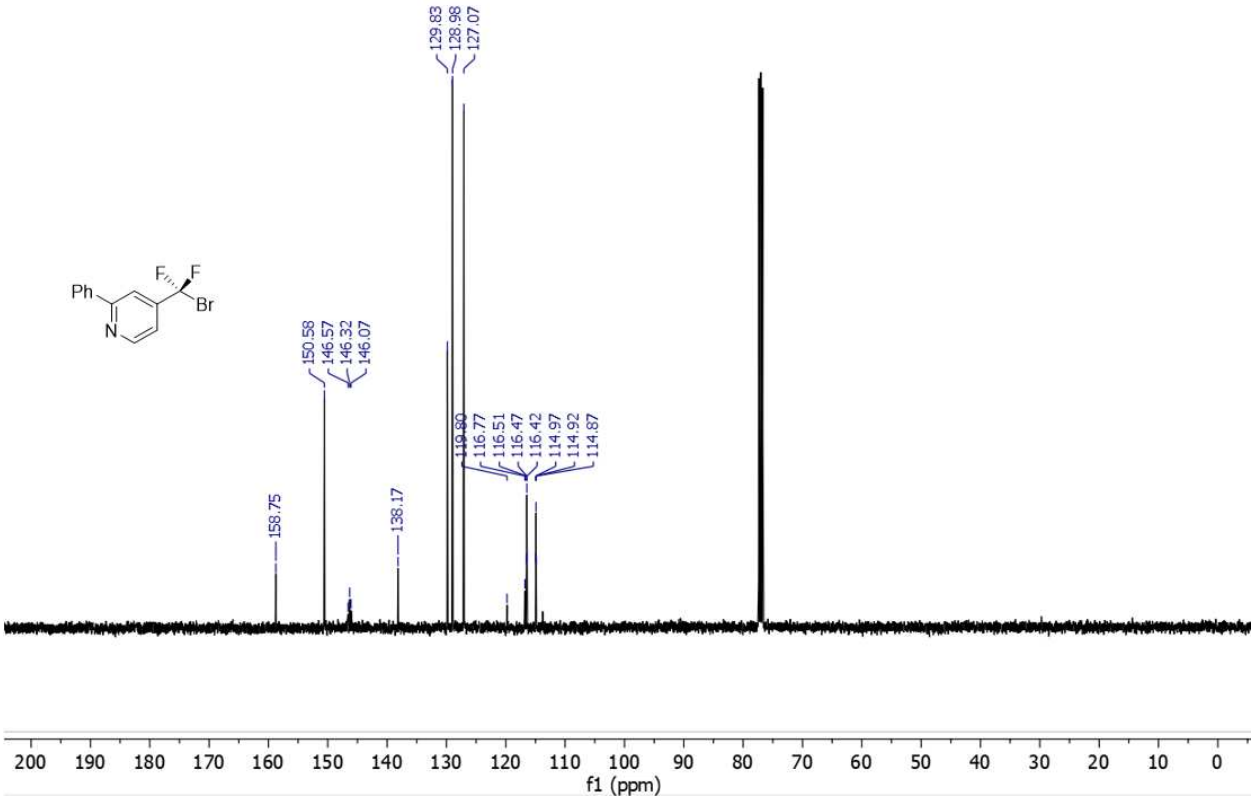
^{1}H NMR spectrum **3-58** (400 MHz, $CDCl_3$)



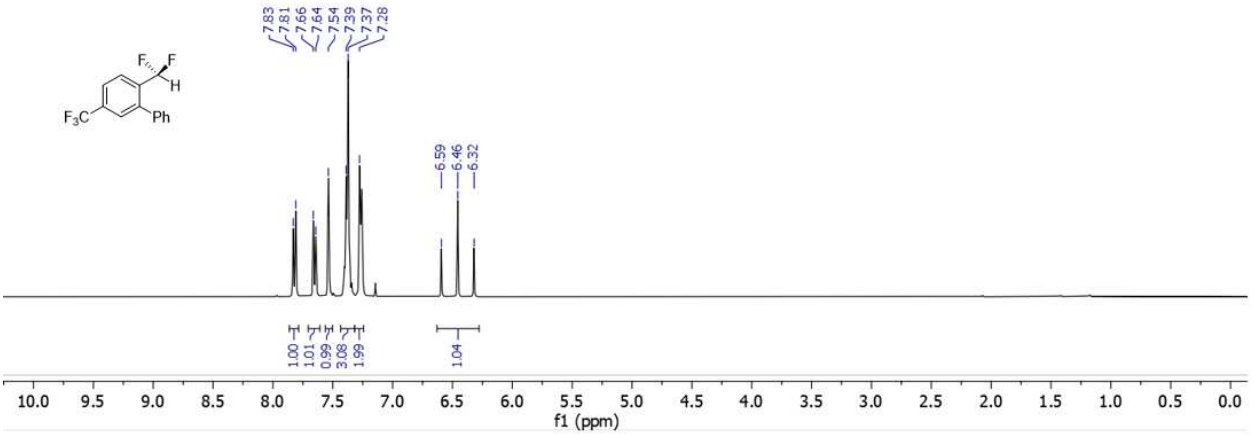
^{1}H NMR spectrum **3-34** (400 MHz, $CDCl_3$)



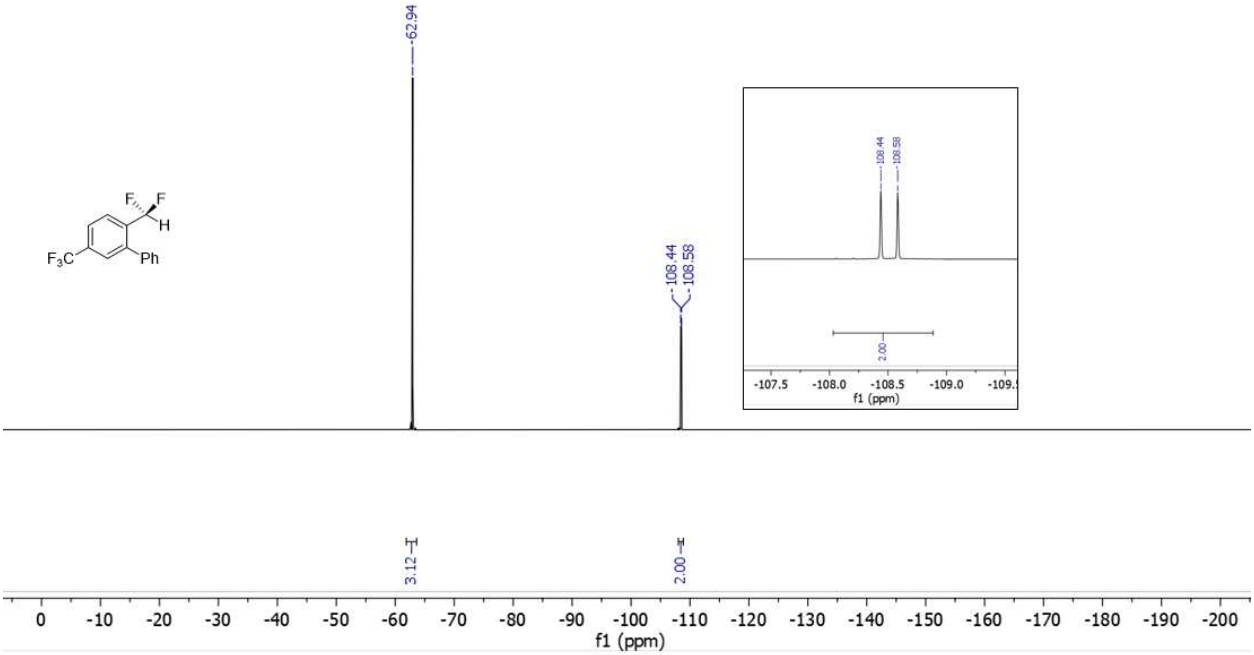
^{19}F NMR spectrum **3-34** (376 MHz, $CDCl_3$)



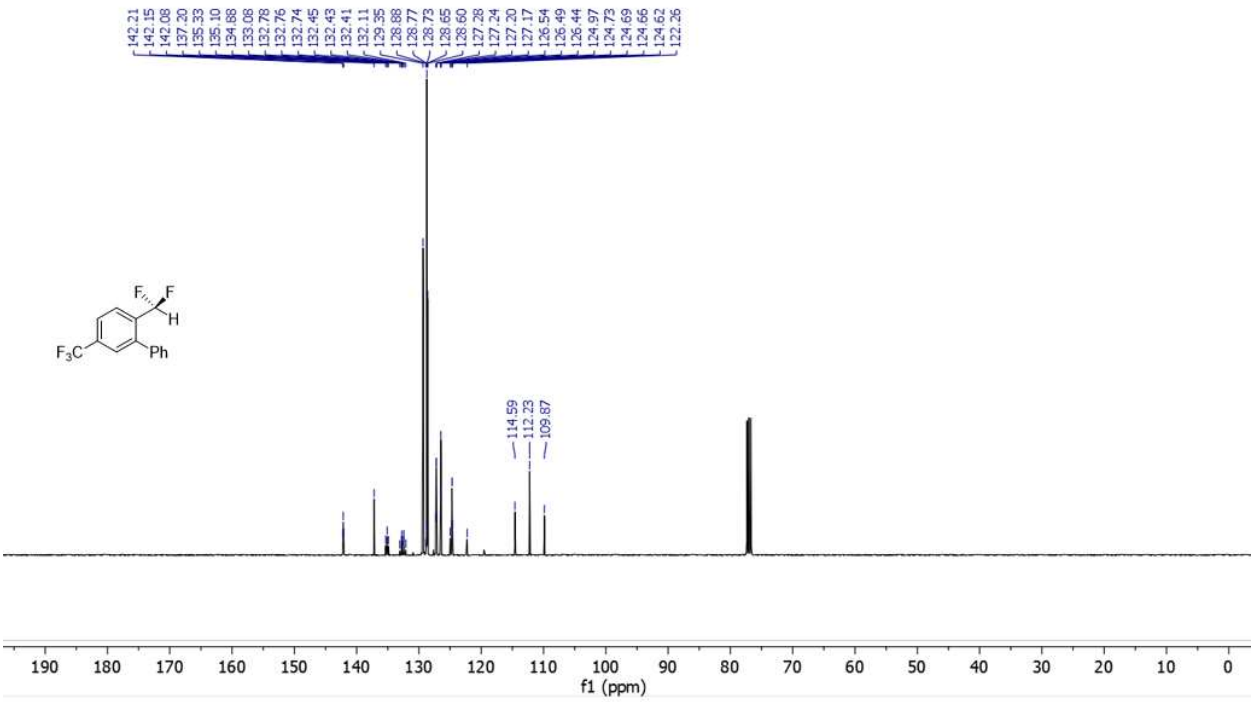
^{13}C NMR spectrum **3-34** (101 MHz, $CDCl_3$)



^{1}H NMR spectrum **3-48** (400 MHz, $CDCl_3$)



^{19}F NMR spectrum **3-48** (376 MHz, $CDCl_3$)



^{13}C NMR spectrum **3-48** (101 MHz, $CDCl_3$)

LIST OF ABBREVIATIONS

$ArCF_3$	trifluoromethylarene
$ArCF_2H$	α,α-difluoromethylarene
TBAB	*tetra*-butyl ammonium bromide
THF	tetrahydrofuran
HMPA	hexamethylphosphoramide
MeCN	acetonitrile
DMSO	dimethylsulfoxide
LED	light emitting diode
HDF	hydrodefluorination
HFIP	hexafluoro-2-propanol
FLP	frustrated Lewis pairs
DME	dimethoxyethane
NMP	*N*-methyl-2-pyrrolidine
EtONa	sodium ethoxide
Bpin	boron(pinacolato)
PhMe	toluene
DCM	dichloromethane
EtOAc	ethyl acetate
DMF	dimethylformamide
EtOH	ethanol
E	electrophile

HNuc	pronucleophile
L.A.	Lewis acid
L.B.	Lewis base
T	temperature
h	hour
min	minute
equiv or eq	equivalent(s)
PCET	proton coupled electron transfer
EWD	electron withdrawing group
EDG	electron donating group
NMR	nuclear magnetic resonance
XTR	halogen transfer reagent
TTMSS	tris(trimethylsilyl)silane
TMS	trimethylsilyl
SET	single electron transfer
HA	hemiaminal
HAD	Hydrogen-atom-donor
HPLC	high-performance liquid chromatography
rt	room temperature
IPA	*iso*-Propyl alcohol