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Metal-Based Approaches for the Fluoroalkylation of Aryl Halides

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Metal-Based Approaches for the Fluoroalkylation of Aryl Halides

by

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TFE	Tetrafluoroethylene
THF	Tetrahydrofuran
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
MeCN	Acetonitrile
DMPU	1,3-Dimethyltetrahydropyrimidin-2(1*H*)-one DMI
DMI	1,3-Dimethyl-2-imidazolidinone
bpy	2,2'-Bipyridine
dtbpy	4,4′-Di-tert-butyl-2,2′-dipyridyl
phen	1,10- Phenanthroline
Ph	Phenyl
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxy
Equiv.	Equivalents
TBAB	Tetra-*n*-butyl ammonium bromide
DCM	Dichloromethane
RBF	Round bottom flask
ORTEP	Oak Ridge Thermal-Ellipsoid Plot Program
XPS	X-ray Photoelectron Spectroscopy
Bathophen	4,7-Diphenyl-1,10-phenathroline
TMP	2,2,6,6-Tetramethylpiperidine

ABSTRACT

Fluorine-containing molecules have become increasingly more prevalent in life sciences, agricultural, and materials fields. Difluoromethylene and trifluoromethyl moieties can modify the electronic properties as well as the hydrophobicities of the parent molecules. These groups also are much more resistant to degradation and metabolic decomposition pathways relative to their non-fluorinated counterparts, a feature that is especially important for medicinal applications.

Herein, I report the preparation of novel dinuclear zinc reagents from commercially available α,ω-diiodoperfluoroalkanes and dibromoperfluoroalkanes for the preparation of both fluoroalkyl ring systems and linear fluoroalkyl linked arenes under relatively mild conditions. Additionally, the dizinc reagents are more stable and more versatile than analogous α,ω-dinucleophiles previously developed. The formation of varying (CF_2) linker lengths can be achieved with only minor modifications to the conditions. I also detail my first efforts to develop a catalytic method for polydifluoromethylenation of both aryl iodides and aryl diiodides.

In addition to the protocol described above, I describe a new route to prepare fluoroalkylated chains that are unsymmetrically disubstituted with aryl end groups. My approach involved the use of a novel α-bromo-ω-silyl fluoroalkane. Using the appropriate silver salt and ligand, the isolable silver reagent, [(phen)Ag$(CF_2)_n$Br], could be prepared in good yields. This reagent undergoes cross-coupling with aryl iodides in the presence of a copper catalyst to form the targeted arylated fluoroalkyl bromide building blocks.

Lastly, copper complexes containing fluoroalkyl moieties have been employed in a myriad of protocols, yet I am not aware of any studies comparing their efficacy under

similar conditions for fluoroalkylations. By studying well-known metal catalyzed trifluoromethylations of aryl halides, I benchmarked several copper trifluoromethyl reagents. I believe the findings reported should help others better understand these reactions.

Chapter 1. Introduction

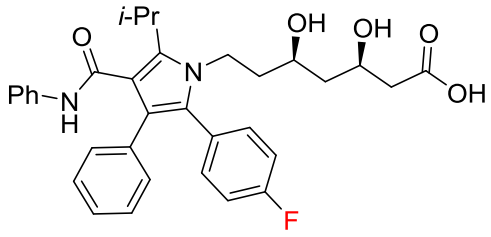
1.1. Advantages of Incorporating Fluorine into Organic Compounds

1.1.1. Widespread Use of Fluorine in Pharmaceutical Drugs

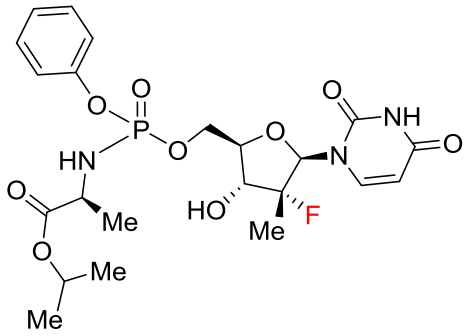
The development of fluoroalkylated organic systems has been of great interest for some time. Fluorine has been incorporated into many organic structures in order to enhance the physical and electronic properties.[1,2] Approximately 20 percent of all new pharmaceutical drugs and 30 percent of the top-selling drugs (in recent years) contain fluorine moieties reported in Figure 1.1.[3,4] Many of these drugs are also the all-time highest grossing pharmaceuticals ever developed.[5,6] Lipitor is the highest grossing drug of all time, with $13 billion in sales in 2006.[7] Some of the highest grossing pharmaceutical drugs are highlighted in Figure 1.2.[8,9]

Rank of organofluorine containing pharmaceuticals (2008)	Trade name	US sales in 2008 ($ x 10^9)
1	Lipitor	5.9
4	Advair Discus	3.6
5	Prevacid	3.3
11	Lexapro	2.4
17	Crestor	1.7
18	Vytorin	1.5
20	Celebrex	1.5
22	Levaquin	1.5
28	Risperdal	1.2
30	Zetia	1.2

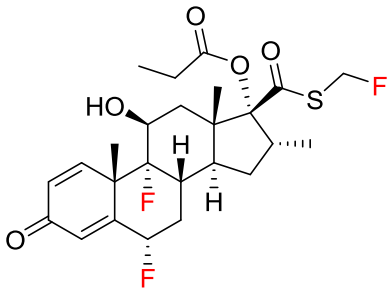
Table 1.1. Top-Selling Fluorine-Containing Drugs from 2008.



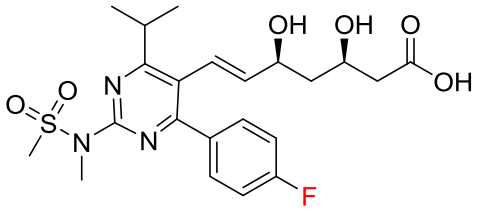
Lipitor (Atorvastatin)
treats high cholesterol
1.9 $ billion (2015)



Sovaldi (Sofosbuvir)
treats hepatitis C
6.6 $ billion (2015)



Seretide (Fluticasone&Salmeterol)
anti-inflammatory, treats constriction of airways
8.0 $ billion (2015)



Crestor (Rosuvastatin)
treats high cholesterol
8.6 $ billion (2015)

Figure 1.1. Highlighted Top-Selling Drugs of All Time.

1.1.2. The Benefits of Fluorine in Pharmaceutical Drugs

Fluorine has many unique properties that make it an attractive moiety to incorporate into pharmaceuticals. Fluorine is only slightly larger than hydrogen and approximately the same size as oxygen and nitrogen (calculating Van der Waals radii for each species), therefore not greatly affecting the size of the molecule (Table 1.1).[10,11] However, the electronegativity of fluorine is far greater than any other functional group.[12] These properties facilitate a highly polarized C-F bond which leads to the alteration of the acidity/ basicity of proximate functionalities.[13] Additionally, molecules modified with

fluorine or trifluoromethyl moieties have demonstrated increased cell permeability and increased hydrophobicity.[1,2,14-21]

Atom	Pauling's Electronegativity (χ_p)	Van der Waals Radii (Å)
H	2.20	1.20
F	3.98	1.47
Cl	3.16	1.74
Br	2.96	1.84
I	2.66	1.98
Cl	2.55	1.70
N	3.04	1.55
O	3.44	1.52

Table 1.2. Properties of Fluorine.

Most importantly, addition of fluorinated groups is integral in preventing metabolic decomposition in the body.[15,16,2,22,23] Such imparted stability is exploited in peptide-derived targets that are being explored for various treatments, such as Odanacatib for osteoporosis and bone metastasis.[24,25] Odanacatib finds 10-20 fold increase in potency as well as increased selectivity when the vulnerable sites are modified (Figure 1.3). Other drugs see similar improvement. For Januvia, drug for the treatment of diabetes mellitus type 2, substitution of the ethyl with the trifluoromethyl group greatly improves its bioavailability (Figure 1.3).[26,27] The clearance of the drug from plasma is lower while the cell permeability is more than seven and a half times greater than the peptide-based precursor.

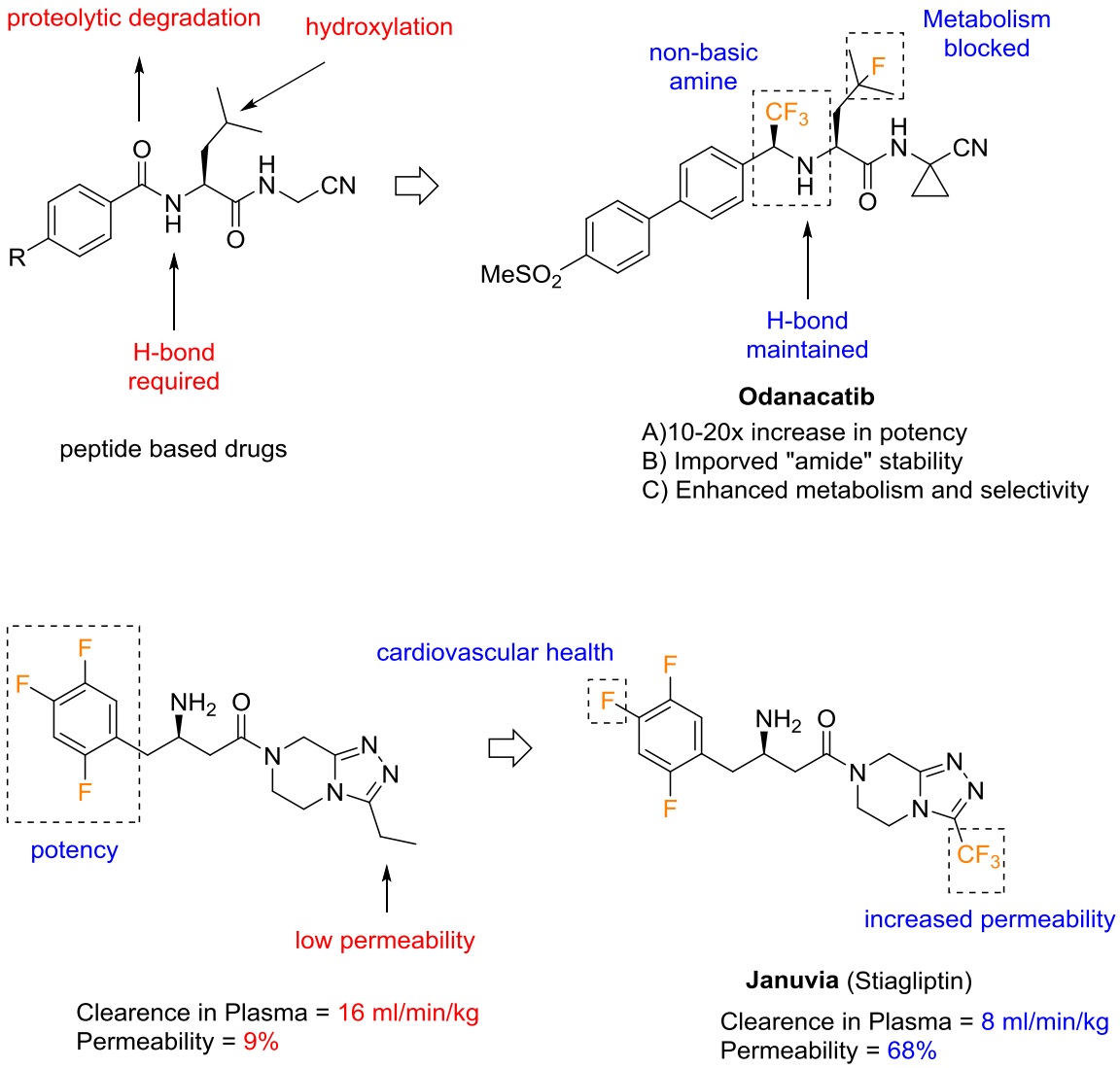


Figure 1.2. Improved Efficacy of Fluorinated Drugs.

1.1.3. Trifluoromethyl and Polydifluoromethylene-Containing Organic Systems

Fluorinated molecules are not only found in the pharmaceutical industry, but also make up about 25% of the agricultural sector.[28] Many of these compounds contain trifluoromethyl or polydifluoromethylene moieties. The fluorinated functional groups are employed, in part, to stabilize the desired compounds, such as **1a** and **1b** in Figure 1.4.

Tetrafluoroalkyl linkers are also present in liquid crystals such as **1c** and **1d**.[29-31] The polydifluoromethylene motif is commonly found in fluoropolymers such as Teflon (**1e**) as well.[32,33] In all of these cases, the incorporation of fluorine bestows properties not inherent to the parent nonfluorinated derivative.

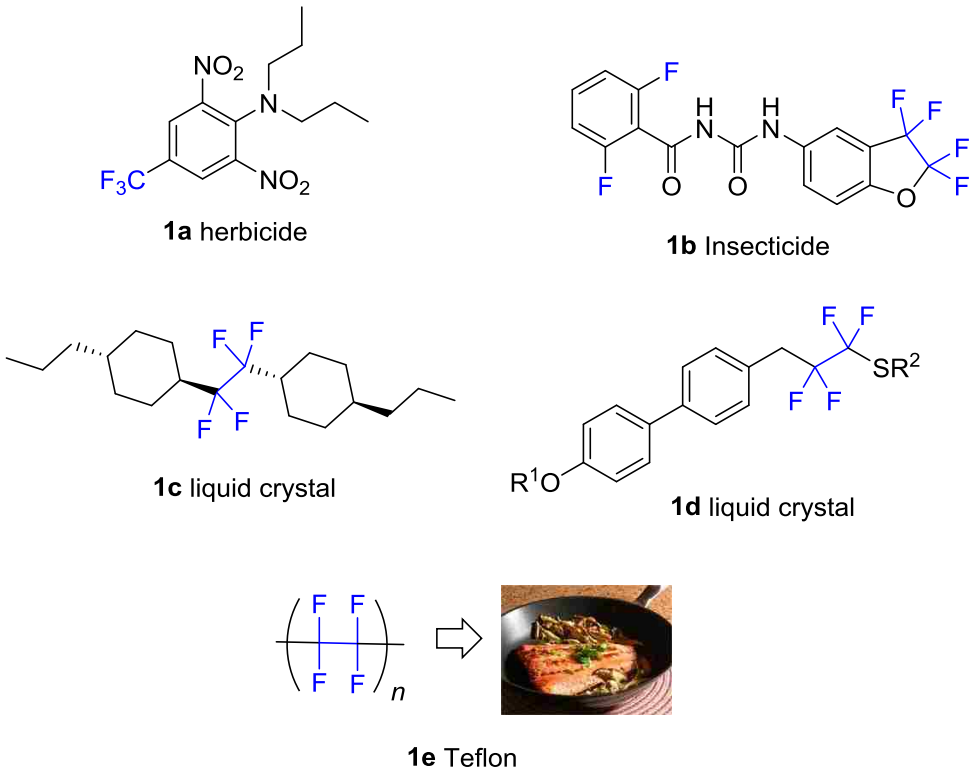


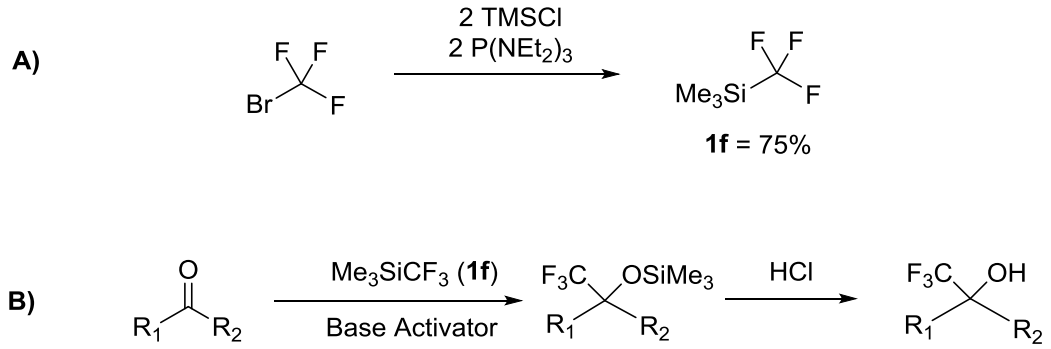
Figure 1.3. More Fluorine-Containing Compounds.

1.2. Protocols for Preparing Fluoroalkylated Molecules Using Metal-Mediated Pathways

1.2.1. Trifluoromethylation

Installation of fluorine-containing moieties are not always so easy. The methods vary, depending on the both the target species and the type of group being installed (F, CF_3, CF_2H, $(CF_2)_{n,...}$ etc). Ruppert and Prakash demonstrated that one of the

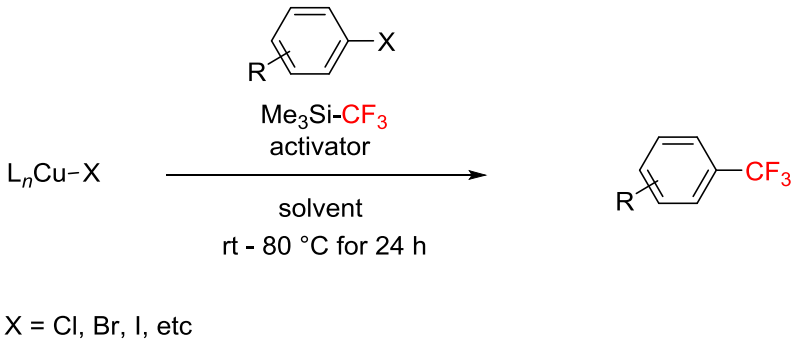
most versatile reagents for trifluoromethylation was a $Me_3Si\text{-}CF_3$.[34] The silane reagent **1f** was first prepared using commercially available trifluoromethyl bromide, trimethylsilyl chloride, and tris(diethylamino)phosphine (Scheme 1.1 A).[35,36] The authors reported that the phosphine reagent activates the trifluoromethyl bromide, facilitating nucleophilic attack onto the silyl center. Ejection of the chloride gives the stable and colorless **1f** in 75% yield. This reagent acts as a nucleophilic equivalent of the CF_3 group. The silane **1f** is activated by base such as CsF or tetrabutyl ammonium fluoride, the anion equivalent undergoes reactions with electrophiles to prepare trifluoromethyl containing products (Scheme 1.1 B).[34,37,38]



Scheme 1.1. Formation of Novel Trifluoromethyl Silyl Reagent A) and Reaction with Electrophiles B).

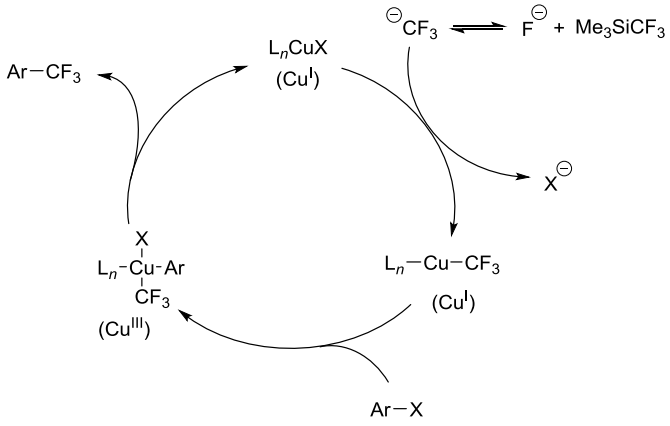
When using copper salts, it was found that Ruppert-Prakash reagent (**1f**) was an excellent trifluoromethyl source for preparing both *in situ* and isolable [L_nCuCF_3] complexes for trifluoromethylation of aryl iodides (Scheme 1.2).[39-46] Copious research has been devoted to the copper(I) mediated trifluoromethylation of aryl halides as late stage trifluoromethyl pathways.[42,47-49] The general scheme for trifluoromethylation of aryl halides is highlighted below (Scheme 1.2). Copper complexes were also prepared by two

alternative methods not needing silyl activation. First, by direct activation of fluoroform (CF_3H) using copper(I) bases or second, by zinc trifluoromethyl complexes.[50-54] Regardless of trifluoromethyl source, the copper trifluoromethyl complex is the crucial species for driving the trifluoromethylations.



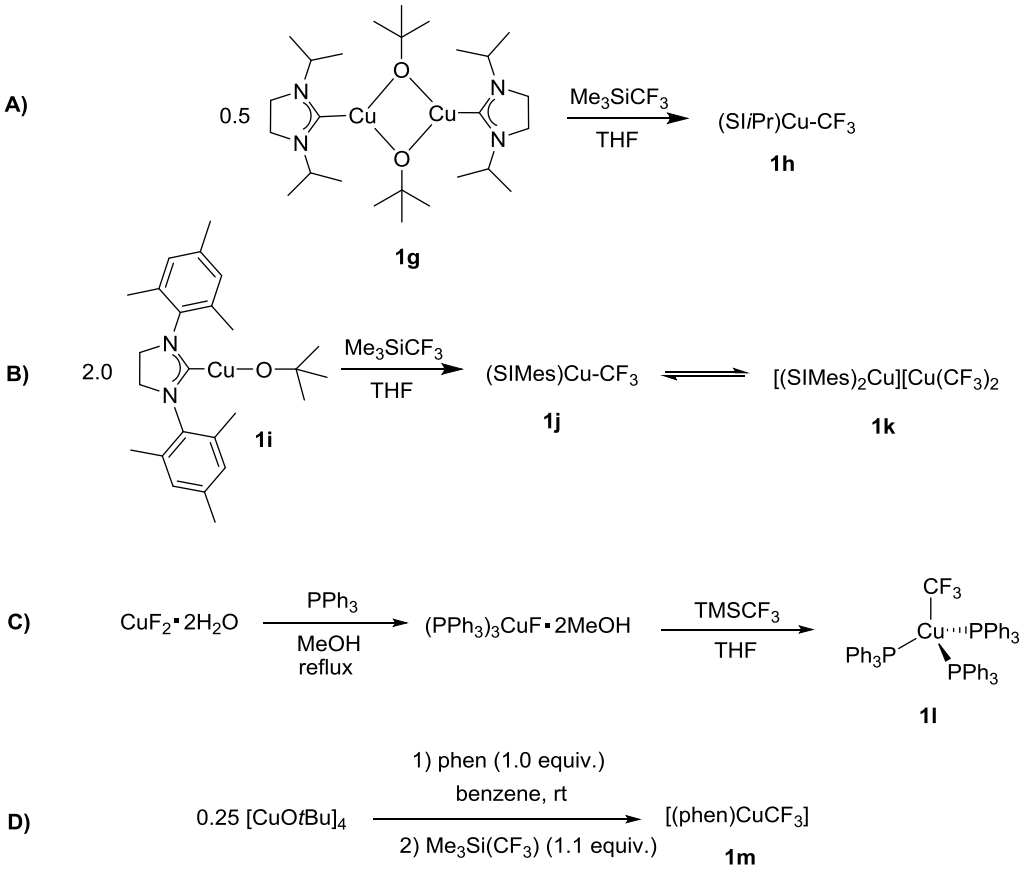
Scheme 1.2. Trifluoromethylation of Aryl Halides.

In the above reaction, trifluoromethyl anion is captured by the copper salt. Oxidative addition to the copper(I) complex [L_nCuCF_3] followed by reductive elimination forms the desired trifluoromethyl product. Catalytic methods for the above reaction are also known.[40] A proposed general reaction cycle is highlighted in Scheme 1.3. Here, the ligand, often a diamine such as phen, is employed to convert aryl halides to trifluoromethyl arenes.[40,55]



Scheme 1.3. Proposed Catalytic Cycle for Trifluoromethylation.

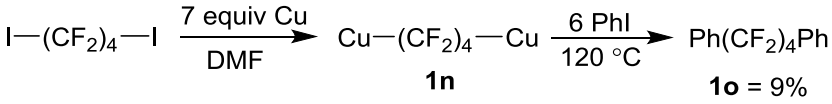
For isolated copper trifluoromethyl systems described in Scheme 1.4, addition of activator is not needed; instead the basic copper reacts directly with the trimethyl(trifluoro)silane.[42-46] The *N*-heterocyclic carbene (NHC) complexes of trifluoromethyl copper, such as **1g** and **1l**, react cleanly with Ruppert-Prakash reagent to form the first well-characterized copper complexes (**1h** and **1j**) for trifluoromethylation (Scheme 1.4, A, B). The phosphine ligated complex **1l** can be simply prepared from the CuF species prepared *in situ* from copper(II) fluoride (Scheme 1.4, C). Lastly, the inexpensive phen ligated complex **1m** can be prepared by copper base activation of Ruppert-Prakash reagent.



Scheme 1.4. Methods for Preparing Isolable Trifluoromethyl Copper Complexes.

1.2.2. Polydifluoromethylenation by Dinucleophile Reagents

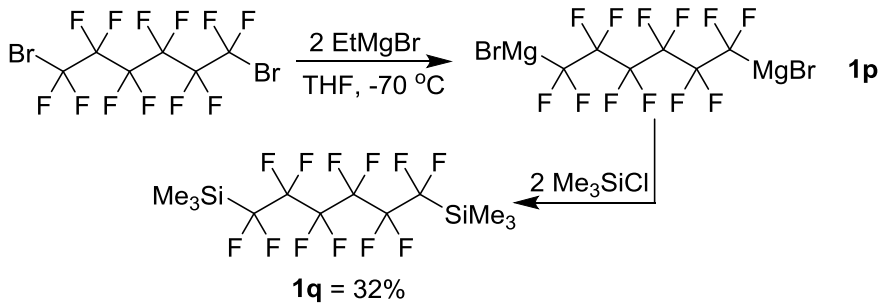
While the previously described reactions are effective means for installing (-CF_3) groups, installation of $(CF_2)_n$ units is far less studied. Starting with the seminal work in 1969, McLoughlin and Thrower described the *in situ* formation of dinucleophiles for the transfer of repeating difluoromethylene synthons.[56] Using α,ω-diiodoperfluoroalkanes, dicopper complexes such as **1n,** could be prepared using super-stoichiometric quantities of copper metal (Scheme 1.5). The dicopper species could be treated with super-stoichiometric quantities of ArI at high temperatures to form the respective bisarylated product . Unfortunately, the yield of the new linear fluoroalkylated molecules such as **1o**, was quite low. For other substrates, the yields were more favorable, however, the need for excessive quantities of metal and electrophile severely limited the practicality of the reaction. An alternative system would need to be developed if installation of fluoroalkylated groups was desired.



Scheme 1.5. Protocol for Disubstituted Perfluoroalkanes.

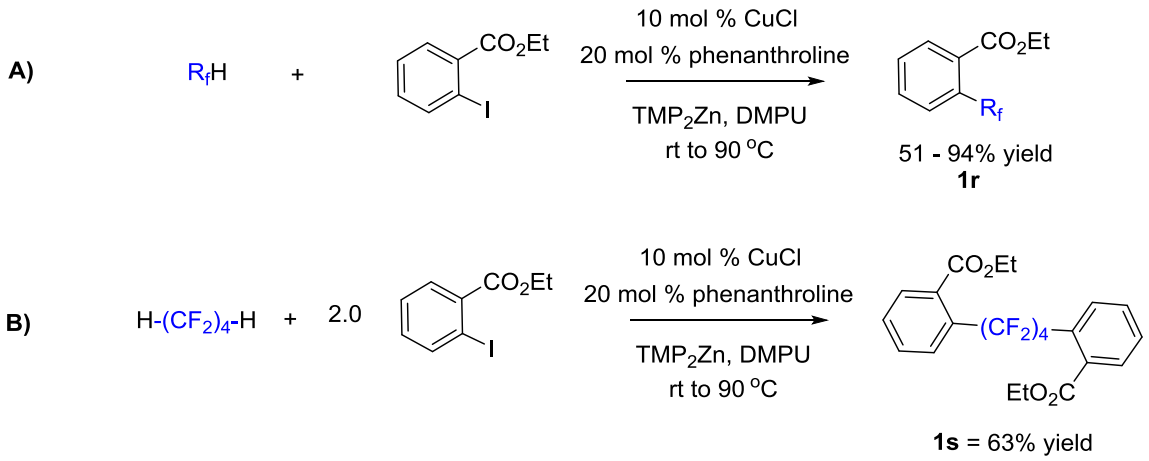
To this end, Tamborski and coworkers reported a method for forming the diGrignard reagent (**1p**) using 1,6-dibromododecafluorohexane at low temperatures.[57] The resulting product could be observed, albeit it was prone to decomposition. Nonetheless, silylation could be achieved for the diGrignard resulting in only 32% yield

of product **1q** (Scheme 1.6).[58] Further chemistry was not heavily explored, which may be due to the diGrignard having a half-life of ~2 hours at –50°C.



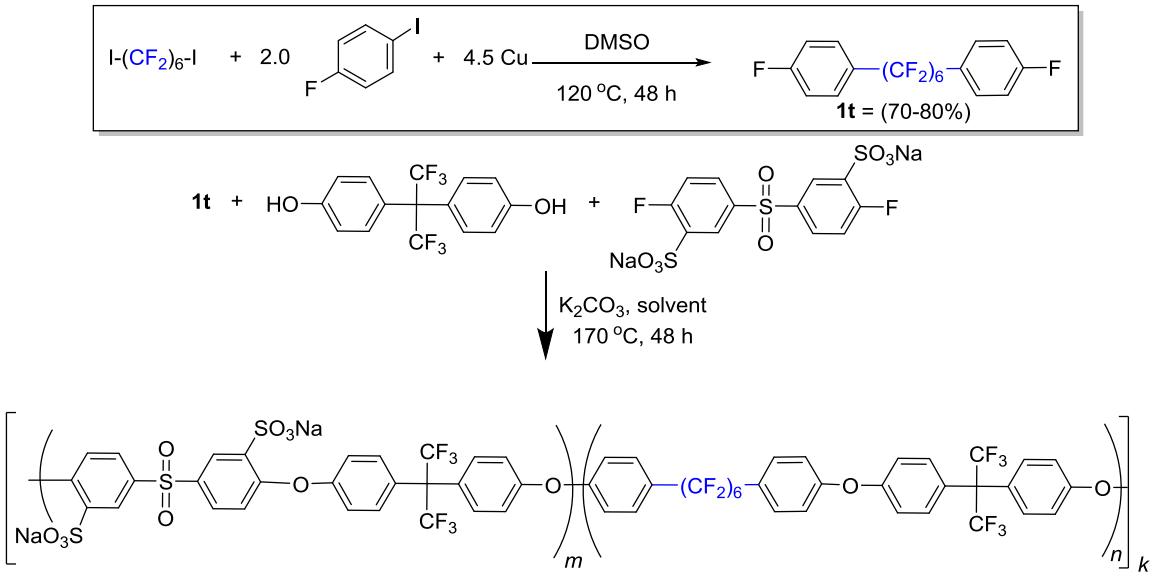
Scheme 1.6. The Preparation of DiGrignard and Dislyl Reagents.

In the 2011, Daugulis *et al.* described an *in situ* preparation for zinc-nucleophile systems.[59] They determined that zinc, being one of the few metals that could make stable reagents, could be used for reactions with 1*H*-perfluoroalkanes. The zinc base chosen, TMP_2Zn, was powerful enough to deprotonate the R_FH reagents and prepare what was preliminarily considered as a ZnR_f synthon. Upon selection of the known copper/1,10-phenanthroline (phen) system, they observed good conversion in the presence of aryl iodides to the respective aryl fluoroalkane **1r** (Scheme 1.7, A).[40,59] Encouragingly, treatment of 1,4-dihydrooctafluorobutane with 2 equivalents of aryl iodide under their conditions gave the fluoroalkyl linked aryl species **1s** in good yield (Scheme 1.7, B). This approach uses catalytic amounts of copper and ligand to achieve the transformation, but is somewhat limited in substrate scope.



Scheme 1.7. *In Situ* Generated Zinc Complexes for Fluoroalkylation of 1*H*-Perfluoroalkanes.

Similar reactions have been employed in the construction of fluorinated analogues of sulfonated poly (arylene ether sulfone) ionomers (SPAES). Polymers containing SPAES represent a class of materials for direct methanol fuel cells, but they can suffer from high methanol permeability and hydration endangering their viability. To combat the disadvantages, fluoroalkylated block copolymers were introduced to increase hydrophobicity and enhance the electronic properties of the membrane.[60] Using I-$(CF_2)_6$-I and 1-fluoro-4-iodobenzene with excess copper metal, the product **1t** (Scheme 1.8) could be prepared in good yield. This building unit was incorporated to prepare fluorinated sulfonated poly (arylene ether sulfone) ionomers (F-SPAES) with better resistance to methanol permeation and hydration while keeping good electron mobility. Ultimately, the new polymers are proving to be very promising membranes.[60]

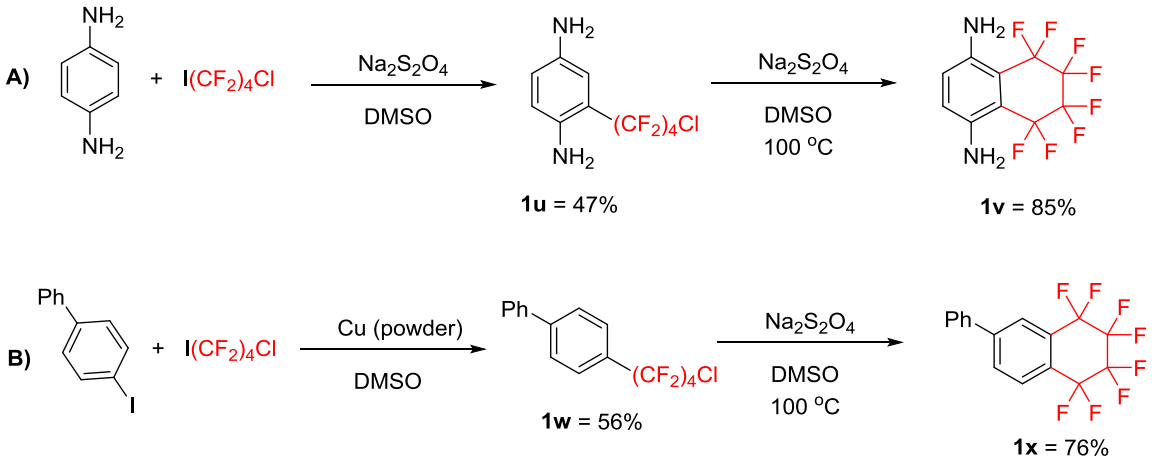


Scheme 1.8. Formation of F-SPAES.

1.2.3. Polydifluoromethylenation by Radical Reagents

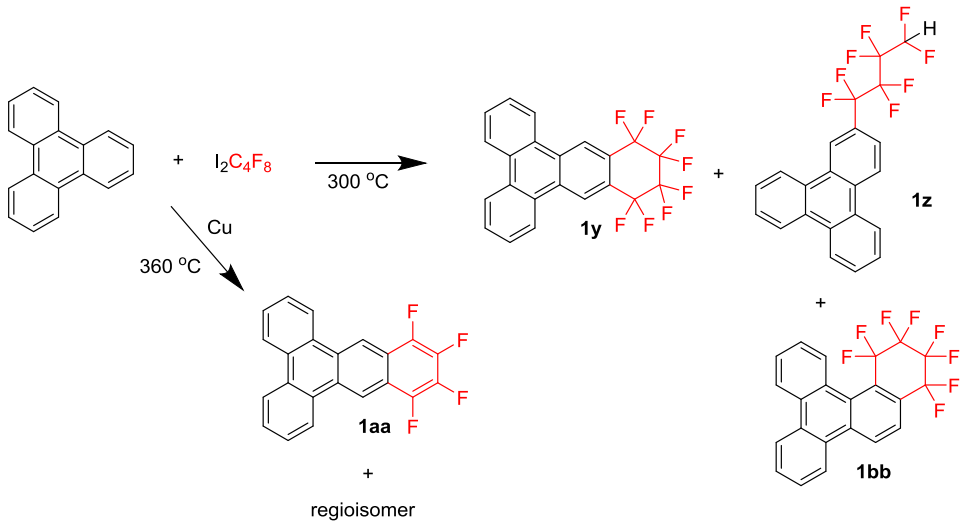
While the dinucleophiles described above present promise for future adaptation, the majority of difluoromethylenations are mediated by radical chemistry. The preparation of fluoroalkylated ring systems was possible using $Na_2S_2O_4$ as a reductant for $I(CF_2)_4Cl$ in the presence of substituted arenes (Scheme 1.9, A).[61] Sodium dithionite is important because it has been shown to selectively reduce the C-I bond in the presence of C-Cl bond.[62] This selectivity allows for synthesis of $Ar(CF_2)_4Cl$ (**1u)** before the cyclization is performed, followed by use of an additional equivalent of sulfur reductant at higher temperatures to form **1v**. It is also possible to install the $–(CF_2)_4Cl$ group using Ullmann coupling of aryl halides. The copper-mediated system benefits from aryl halide substrate choice as opposed to the needed *ortho*- and *meta*-substitutions on the reactive phenyl starting material (Scheme 1.9, B). Intramolecular cyclization could be achieved

from the $Ar(CF_2)_4Cl$ intermediate produced by either method with yields ranging from 10-85%.[61]



Scheme 1.9. Examples of Radical Perfluoroalkylations.

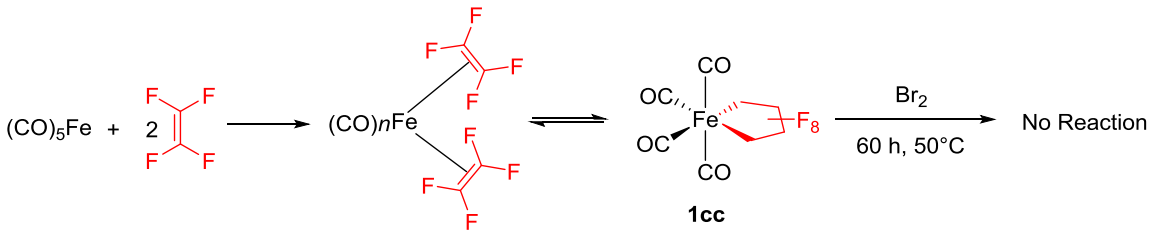
Strauss and Boltalina *et al.* found that optoelectronic properties of polycyclic aromatic hydrocarbons (PAH) could be enhanced by the addition of fluorine-containing moieties.[63] This discovery lead them to prepare not only fluoroalkylated ring structures, but also selectively defluorinated arenes (Scheme 1.10).[64] The 1,4-diiodoperfluorobutane reagent could undergo radical addition to the triphenylene systems, leading to products of interest. The resulting products were largely planar molecules containing fluorinated rings. If copper metal was used at 360 °C the reaction would proceed to form (Scheme 8) the defluorinated compound 1z instead. These molecules are of interest in charge-transfer chemistry as acceptor molecules because of the enhanced electron affinity of the fluorinated PAH.[64]



Scheme 1.10. Radical Perfluoroalkylations for Organofluorine Ring Compounds.

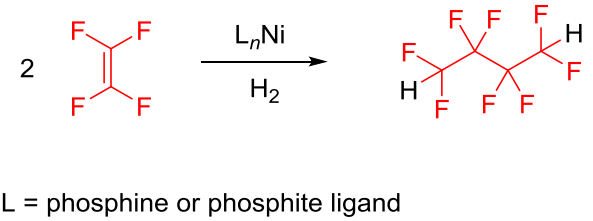
1.2.4. Polydifluoromethylenation via Tetrafluoroethylene

While tetrafluoroethylene (TFE) was used primarily for the preparation of Teflon, many researchers have turned their focus towards exploring its reactivity with base metals for the synthesis of fine chemicals. In 1961, Stone and coworkers found that iron pentacarbonyl and TFE form the air stable solid **1cc**, reported in Scheme 1.11.[65,66] Even upon heating **1cc** in the presence of Br_2, no carbon monoxide or fluorocarbons were released after 60 hours. Heating **1cc** further at 70 °C only afforded perfluorobutane in 70% yield.[65] They noted the reactivity displayed is in stark contrast to that of nonfluorinated analogues, which degrade even at mild temperatures.

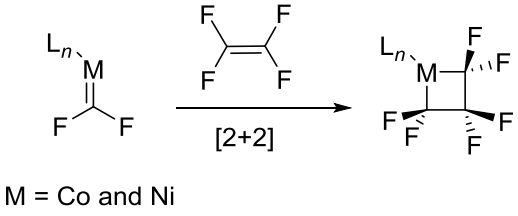


Scheme 1.11. Oxidative Coupling of TFE to Iron Pentacarbonyl.

The metallacyclic motif described above is applicable to a number of metal centers such as nickel and cobalt.[66-69] For example, nickel complexes have been found to be able to catalyze the formation of α,ω-dihydroperfluoroalkanes (Scheme 1.12).[70] Nickel and cobalt perfluorometallacycles still receive a great deal of interest. Two major questions are being explored for these complexes: First, are salt or base able to activate or modify the perfluorometallacyclic rings?[71-73] Second, can metal fluorocarbenes be prepared and tested in cross metathesis chemistry (Scheme 1.13)?[74-77]



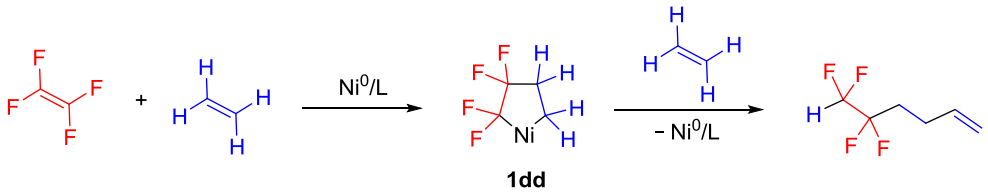
Scheme 1.12. Nickel Catalyzed Preparation of α,ω-Dihydroperfluoroalkanes.



Scheme 1.13. Difluorocarbene Route for Preparation of Perfluorometallacyclobutanes.

Ogoshi and coworkers have made several key discoveries in the use of fluorine-containing nickelacycles. They reported that when treating $Ni(COD)_2$ (bis(1,5-cyclooctadiene)nickel(0)) with TFE and ethylene, the mixed metallacycle **1dd** could be formed (Scheme 1.14).[78,79] The nickel complex **1dd** further reacted to form various

fluorine-containing products. It is clear that many new and exciting ways are being developed to install repeating difluoromethylene groups.



Scheme 1.14. Specialty Chemicals Prepared by Nickel Oxidative Coupling.

1.3. Overview of Thesis

The reports in Chapters 2-5 report my recent contributions to the field of organometallic fluorine chemistry. Chapters 2-3 will highlight my breakthrough with dizinc dinucleophiles for fluoroalkylation. The major issues addressed are versatility, selectivity, and safety in both preparation of the organofluorine systems and the TFE-free perfluoronickelacyclopentanes. Additionally, Chapter 3 displays my findings on difunctionalized systems prepared by copper(I) catalysis. Chapter 4 focuses on the novel preparation of α-bromo-ω-silylfluoroalkane reagents and their ability to prepare arylated fluoroalkyl bromide building blocks. Lastly, Chapter 5 benchmarks copper trifluoromethyl systems. All chapters taken together describe my contributions to better understand metal-mediated fluoroalkylated systems.

1.4. References

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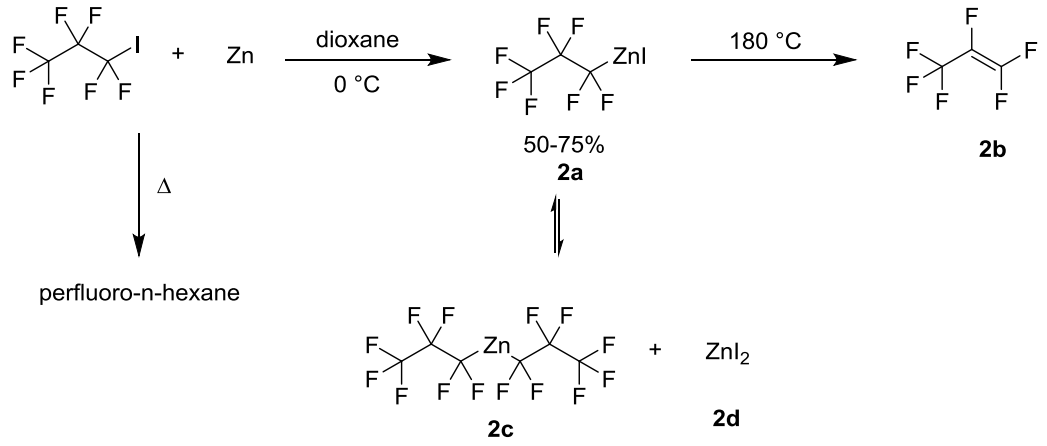
Chapter 2. Discovery and Preparation of a Novel and Stable Dizinc Reagent for Polydifluoromethylenation

2.1. Background and Significance

2.1.1. Monofluoroalkyl Zinc Complexes

Group 12 metals have been shown to support fluoroalkyl ligands. While these fluoroorganometallic species were first prepared from mercury and cadmium precursors, zinc derivatives were sought after as suitable non-toxic alternatives.[1-5] Fluoroalkylated zinc halides were initially prepared in dioxane according to Scheme 2.1.[6,7] The reaction provides the highest yield of product when the temperature is kept below 0 °C. At higher temperatures, radical homocoupling of the fluoroalkyl starting material is observed or dezincation as described in Scheme 2.1. Heating compound **2a** at high temperature causes elimination and formation of the fluoroolefin **2b.** It should also be noted that evidence of Schlenk equilibrium of product **2a** to **2c** and **2d** was not observed (Scheme 2.1).[6] The reactivity of the fluoroalkyl zinc reagents falls between the analogous stable and unreactive compounds of mercury and the very reactive and unstable magnesium species. The stability of the respective zinc complexes can be related to the solvent as ancillary

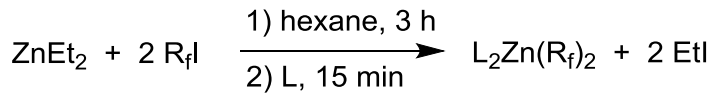
ligands. Isolation of unsolvated species proved extremely difficult and such attempts led to significant decomposition.[7]



Scheme 2.1. Preparation of Perfluoroalkyl Zinc Iodide Complexes.

2.1.2. Bisperfluoroalkyl Zinc Complexes

In 1979, Asprey and coworkers identified halogen-free zinc complexes prepared from mercury bistrifluoromethyl precursors and diethyl zinc.[8] This method yielded mixtures of $Hg(CF_3)(CH_3)$, $Zn(CF_3)(CH_3)$, and $Zn(CF_3)_2$ in various ratios, allowing for the NMR characterization of the species in equilibrium. It was not until Naumann and coworkers prepared bisperfluoroalkyl zinc-solvent complexes directly from the perfluoroalkyl iodides and dialkylzinc that the bisperfluoroalkyl species could be cleanly isolated.[9,10] The bisperfluoroalkyl species was prepared in alkane solvent at –20 °C, followed by addition of coordinating solvent at room temperature to achieve the stable zinc complex as shown in Scheme 2.2. Although this route does not require ligand exchange from trifluoromethyl mercury, it does demand the costly dialkyl zinc starting material.

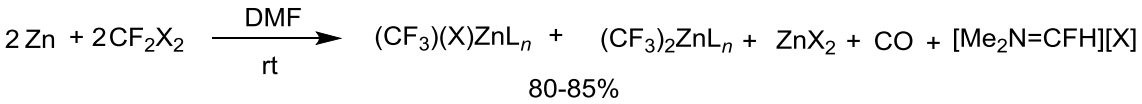


L = CH_3CN, THF, DMSO

R_f = *i*-C_3F_7, $(CF_2)_nCF_3$; *n* = 1-3, 6-8

2.2. Synthesis of Bisperfluoroalkyl Zinc Complexes.

An alternative route to bistrifluoromethyl zinc and cadmium complexes, described in Scheme 2.3, has also been reported. Zinc dust could be employed instead of dialkyl zinc to prepare the trifluoromethylated zinc product.[11] The DMF solvent also acts as a reactant, sequestering some of the difluorocarbene produced *in situ*. The resulting species, Me_2NCF_2H, acts as a source of fluoride. Fluoride and difluorocarbene are presumably in equilibrium with the trifluoromethyl anion which is captured by the metal. The equilibrium is driven towards the formation of more trifluoromethyl anion, subsequently producing a high yield of the CF_3ZnX and $(CF_3)_2Zn$ mixture (80-85%).



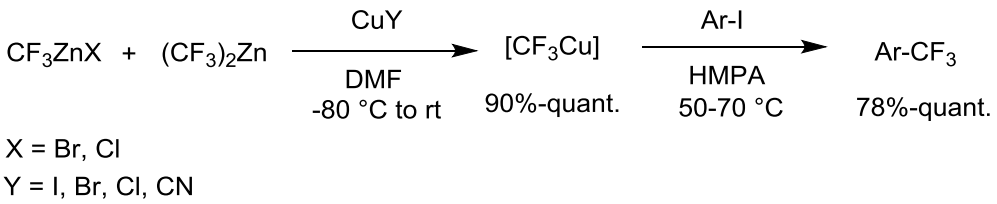
Scheme 2.3. Alternative Preparation of $Zn(CF_3)_2$.

2.1.3. Zinc Complexes as Nucleophiles for Copper-Mediated Catalysis

Copper trifluoromethyl complexes are often employed as catalysts for the trifluoromethylation of organic halides. The most popular method for their preparation involves use of the Ruppert-Prakash reagent, $(CH_3)_3SiCF_3$, and base activator such as such as CsF or KO*t*Bu.[12-15] However, this trifluoromethyl anion equivalent can also react

with other electrophiles, such as a carbonyl moiety in the substrate, leading to undesired side products. To avoid off-cycle reactions, pre-isolated $CuCF_3$ compounds are often employed.

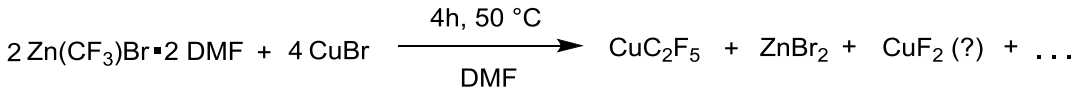
Zinc complexes represent alternative reagents for fluoroalkylation chemistry. Burton and coworkers explored protocols to activate fluoroalkyl halides with zinc for the addition to copper.[11,16-18] The reported synthesis takes advantage of the zinc and cadmium reagents' stability against decomposition and reactivity toward transmetalation with the copper(I) salts.[18] The formation of trifluoromethyl copper species took place cleanly at low temperature with excellent yield, as shown in Scheme 2.4.[18] If HMPA was added, the copper species could be warmed to room temperature without decomposition. Addition of aryl iodide to the resulting copper solution followed by heating to 50-70 °C, afforded good to excellent yields of the respective trifluoromethyl arenes (yields calculated by NMR spectroscopy with respect to $PhCF_3$). While the reaction described in Scheme 2.4 was only a preliminary study with a small scope of aryl iodides, this was, as Burton described, "the *first unequivocal* pre-generative route to $[CF_3Cu]$."[18]



Scheme 2.4. Trifluoromethylation Using *In Situ* Generated Zinc Complex.

The isolated $Zn(CF_3)Br \cdot 2$ DMF complex can be used in place of the *in situ* generated $L_2[ZnCF_3]X$ or $L_2Zn(CF_3)_2$. The active species, $CuCF_3$, could be generated from the zinc reagents and CuBr in order to trifluoromethylate aryl iodides.[19]

Pentafluoroethylation was also achievable with the same [$CuCF_3$] starting material. Trifluoromethyl copper was observed by NMR to form pentafluoroethyl copper if left to stir at room temperature.[18] Therefore, pentafluoroethyl copper could be obtained as the sole species if temperature was increased to 50 °C after four hours (Scheme 2.5).[18] The decomposition of the trifluoromethyl copper to difluorocarbene and CuF facilitates the difluorocarbene insertion into the copper trifluoromethyl species. Both CuC_2F_5 and $CuCF_3$ could convert aryl iodides to their respective fluoroorganic products in decent to good yield.



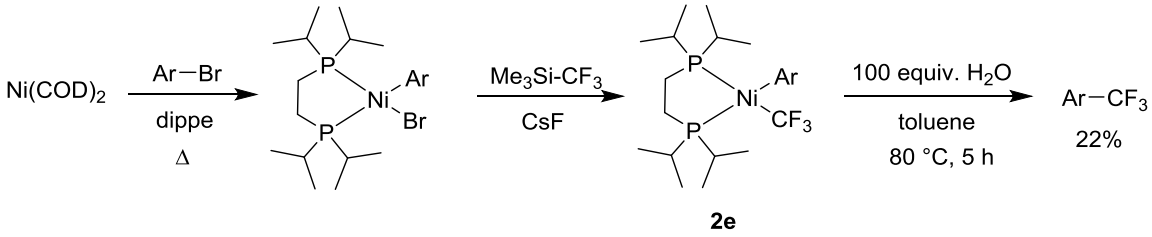
Scheme 2.5. Formation of [CuC_2F_5].

2.1.4. Other Fluoroalkyl Containing Metal Complexes

While copper is invaluable in trifluoromethylations chemistry, its use does have its drawbacks.[20-26] Both palladium and nickel generally have a larger substrate scope and often require less energy to perform analogous cross-couplings.[27] Unfortunately, there were few known palladium and nickel complexes containing trifluoromethyl ligands. The compound (xantphos)Pd(CF_3)(Ar) was explored as a possible intermediate in trifluoromethylation of aryl iodide.[28] The species was found to be extremely resistant to reductive elimination to give Ar-CF_3, only forming it at temperatures of 80 °C and requiring the bulky phosphine ligand (Xantphos). This reactivity contrasts with the very facile reductive elimination of Ar-Me from the respective L_nPd(Me)(Ar).[28-36] The need of special conditions, preligation, harsh conditions, and cost make palladium a less attractive

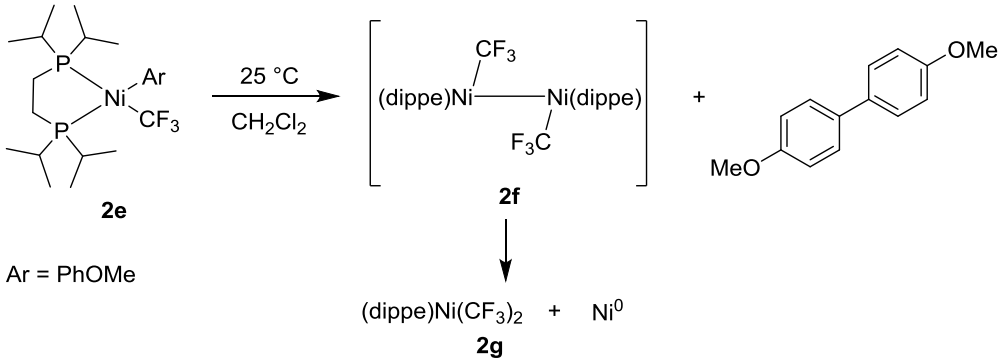
catalyst for trifluoromethylation. Therefore, nickel has received increased investigation as a cheaper and more reactive metal for these transformations.

In 2008, the nickel complex **2e** was reported (Scheme 2.6).[37] Species **2e** was seen as an analogous intermediate of the (Xantphos)Pd(CF_3)(Ar) species produced in trifluoromethylation reactions. Frustratingly, **2e** was only able to achieve reductive elimination of Ar-CF_3 in low yield. The reaction required 100 equivalents of water and heating at 80 °C, shown in Scheme 2.6.



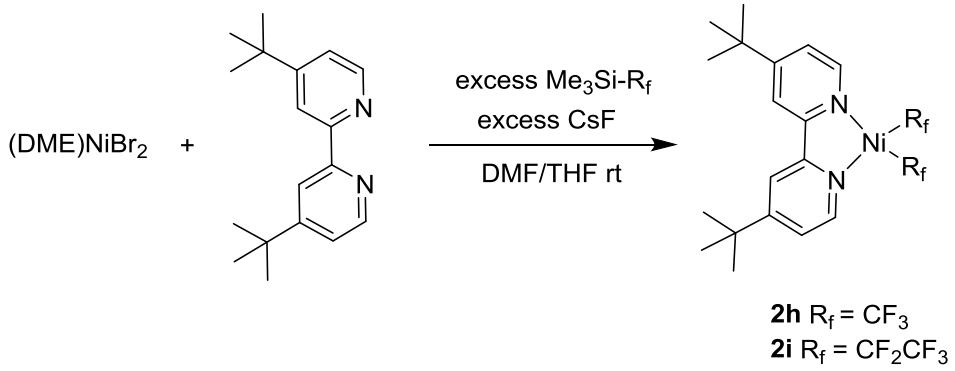
Scheme 2.6. Preparation of $L_nNi(Ar)(CF_3)$ from Ni^0 Precursor.

The air-stable compound **2e** instead favored exchange of ligands and homocoupling to form of biaryl compound and bis(trifluoromethyl) nickel **2g** (Scheme 2.7). This reactivity is in contrast with the nonfluorinated congeners which cleanly affords Ar-CH_3 at room temperature upon exposure to air.



Scheme 2.7. Decomposition Pathway of Complex **2e.**

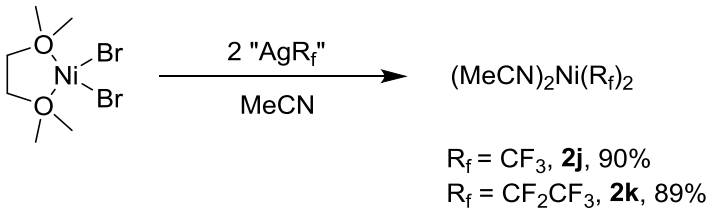
Vicic and coworkers sought to study the chemistry of nickel bipyridine complexes bearing fluoroalkyl functional groups. As highlighted in Chapter 1.2.4, the only known bipyridyl nickel species were perfluoronickelacyclopentanes prepared from tetrafluoroethylene (TFE).[38-40] The Vicic group prepared the perfluoroalkyl derivative, (bpy)Ni(R_f)$_2$, using an excess of perfluoroalkyl silyl reagents and cesium fluoride as an activator (Scheme 2.8).[41] The activated perfluoroalkyl moiety could be captured by nickel dibromide and dtbpy to form the desired product **2h** and **2i** shown in Scheme 2.8. One of the intriguing differences between the (bpy)NiMe$_2$ and (bpy)Ni(CF_3)$_2$ is the latter's stability. The air sensitive nonfluorinated complex liberates ethane at 30 °C, whereas the air stable fluoroalkylated derivative **2h** does not expel perfluoroethane even at temperatures up to 130 °C.



Scheme 2.8. Synthetic Route to Linear Bis(perfluoroalkyl) Complexes.

A high-yield preparation for the nickel complex **2j**, a precursor to **2h**, was reported in 2013 (Scheme 2.9).[42] By switching base activator from CsF to AgF, the fluoroalkylation of the nickel dibromide was achieved in excellent yields (Scheme 2.9).

The previous protocol (Scheme 2.8) using CsF only gave 11% of the desired nickel complex **2h**. All of the aforementioned protocols provided insight into how a zinc perfluoroalkyl reagent could best be used to generate perfluoroalkyl complexes of nickel. Such transmetalative methods with zinc are desired if more sophisticated reactions involving perfluoroalkyl nucleophiles are to be developed.

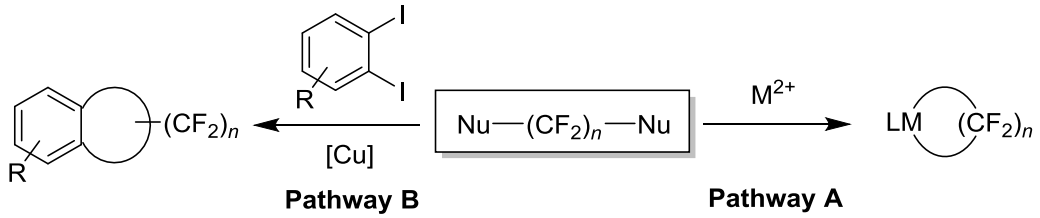


Scheme 2.9. High-Yield Synthesis of Bis(perfluoroalkyl) Nickel Precursor.

2.1.5. Project Goals

While the preparation of nucleophiles for trifluoromethylation reactions represents a significant advancement in synthetic chemistry, advances in difluoromethylenation were still lacking. In addition, stable difunctional reagents for either cross coupling or preparation of organometallic complexes containing perfluoroalkyl ligands, such as those prepared by the proposed Scheme 2.10, were unknown. Thus, I began work toward a dinucleophile reagent made using zinc as a stable source for difluoromethylenation chemistry. First, the dizinc reagent would need to be relatively simple to produce and not need reagents such as tetrafluoroethylene (TFE). Second, the reagent would be stable towards decomposition pathways but reactive enough to achieve the desired transformations. Third, the dinucleophile should be able applicable to different chain lengths.

Scheme 2.10 illustrates two possible applications in which the proposed dizinc reagent could find use. In pathway **A**, perfluorometallacycles could be prepared without the need for TFE. The resulting metallacyclic species can also be used to prepare higher valent nickel complexes with the stabilizing fluoroalkyl ligands.[42] In addition, pathway **B** gives access to a catalog of unexplored organofluorine ring systems.

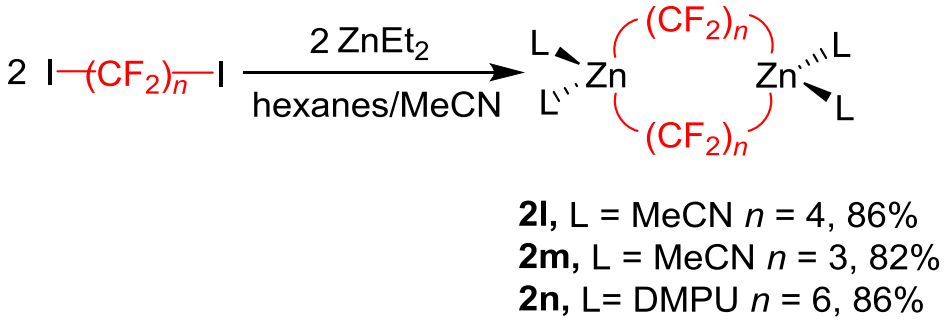


Scheme 2.10. Proposed Uses of a Dinucleophile for Fluoroalkylation.

2.2. Results and Discussions

2.2.1. Novel Perfluoroalkylated Dizinc Reagent

Revisiting Naumann and coworkers' original findings,[9,10] I tested the reactivity of α,ω-diiodoperfluoroalkanes with diethyl zinc at various conditions. The respective dizinc reagents could be made and isolated as free-flowing white solids in good yields (Scheme 2.11).[43] Compounds **2m** and **2n** both were collected, and then their identities and purities were confirmed by ^{1}H and ^{19}F NMR spectroscopies, as well as elemental analysis. However, impurities in **2l** were observed even after careful recrystallization.



Scheme 2.11. Discovery of Novel Cyclic Perfluoroalkyl Dizinc Complexes.

Unexpectedly, the new zinc species described in Scheme 2.11 contained two zinc centers, each linked by two perfluoroalkyl synthons. The species **2l** and **2m** were confirmed by X-ray crystallography (Figure 2.1 and Figure 2.2, respectively) and indeed exist as solvent-ligated dizinc complexes. This dinuclearity is in contrast to other known metal complexes bearing $(CF_2)_n$ linkages, such as perfluoronickelacyclopentane, which display a square planar mononuclear and metallacyclic structure.

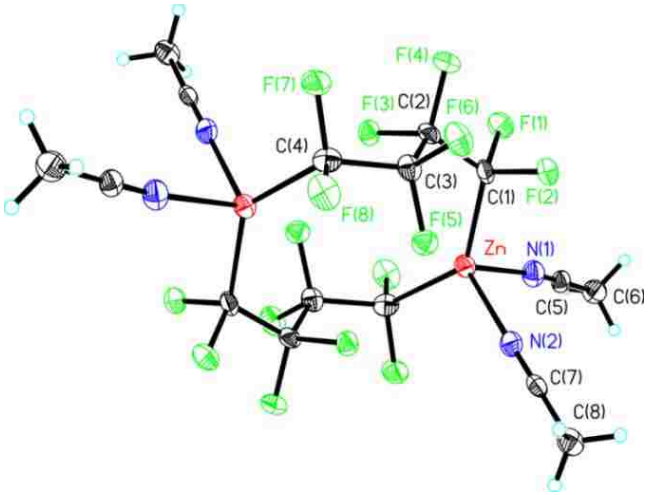


Figure 2.1. ORTEP Diagram of Ligated Dizinc Complex **2l**. Selected bond lengths (Å): Zn− C1 2.032(4); Zn−C4 2.036(5); Zn−N2 2.077(4); Zn−N1 2.102(4). Selected bond

angles (deg): C1−Zn−C4 134.44(17); C1−Zn−N2 106.98(15); C4−Zn−N2 110.04(16); C1−Zn−N1 105.24(16); C4− Zn−N1 96.14(17); N2−Zn−N1 96.37(14).

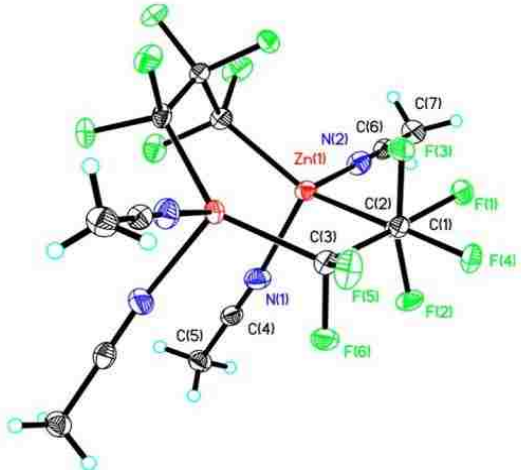


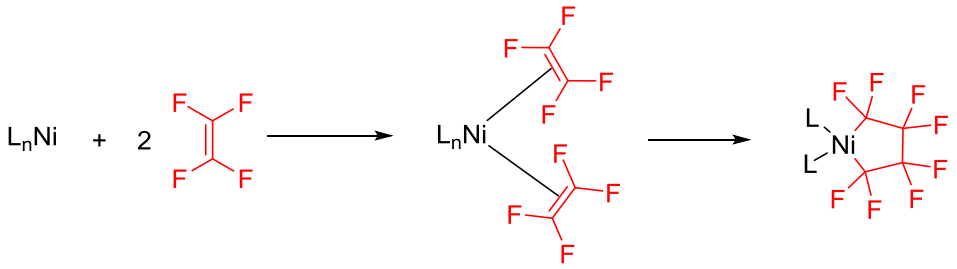
Figure 2.2. ORTEP Diagram of Ligated Dizinc Complex **2m**. Co-crystallized benzene has been omitted for clarity. Selected bond lengths (Å): Zn1−C1 2.0248 (17); Zn1−N1 2.0835(16); Z1− N2 2.1161(15). Selected bond angles (deg): C1−Zn1−N1 105.63(6); C1−Zn1−N2 100.74(6); N1−Zn1−N2 93.86(6).

Non-fluorinated congeners of the dizinc reagents are known, such as 1,3-dizinc compounds.[44] These compounds exhibit the same dinuclearity observed for the fluorine-containing analogues. However, the nuclearity of such species depends on the nature of the metal. Zinc prefers a tetrahedral geometry, as opposed to that of nickel(II), which prefers square planarity. This preference in bond angles should influence the nuclearity of the species, depending on the length of the fluoroalkyl linker. Bickelhaupt, reported that cycloalkylated zinc metallacycles existed exclusively in the dimeric form. However, for

similar magnesium compounds, it was found they undergo interconversion between the monomer and dimer.[45,46] According to Bent's rule, they stated, the decrease in *p* character of zinc orbitals causes the respective angles to be larger, illustrated by the stable dimeric species.[45,47]

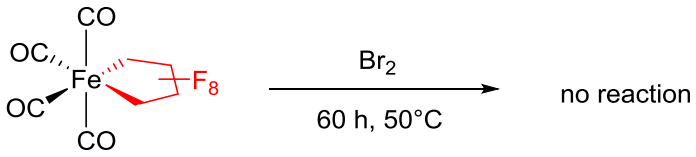
2.2.2. Novel Route to Perfluoronickelacyclopentanes

With the dizinc species prepared, I then demonstrated its ability to prepare cyclic fluoroalkylated ring structures of other metals. Although, only a few perfluorometallacycles had been reported, cobalt and nickel have continued to demonstrate promising chemistry.[48,49] The scarcity of these fluoroorganometallic compounds primarily arises from difficulties in their preparation. All known methods use tetrafluoroethylene (TFE) gas to produce the metallacycle through oxidative coupling at a low valent base metal (Scheme 2.12).[38-40] The TFE reagent itself is increasingly difficult chemical to obtain and is dangerous to work with.[50] Often, TFE is obtained through the pyrolysis of waste Teflon at high temperatures. Unfortunately, this route neither removes the flammable or explosive hazards in handling the gas, nor the toxic side-products that can be produced, such as perfluoroisobutylene.[51]



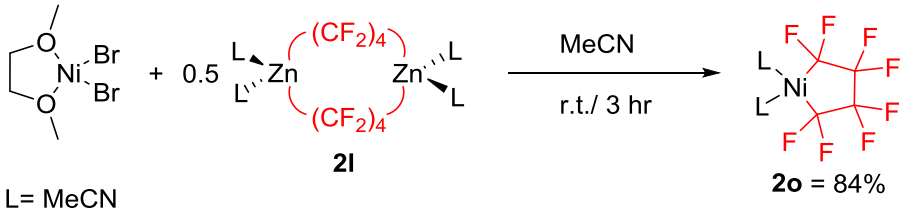
Scheme 2.12. Oxidative Coupling of Tetrafluoroethylene.

Despite these complications, the synthetic chemistry involving metallacyclic intermediates is of ongoing interest in organometallic chemistry. Difluoromethylene synthons have been shown to stabilize late-metal complexes. Stone *et al*. found that the fluorinated iron metallacycle, described in Scheme 2.13, was very stable and did not release carbon monoxide or fluorocarbon even with treatment of bromine for 60 h at 50 °C.[52] It should be noted the nonfluorinated analogue does not exhibit such thermal stability.[53,54] Computational analysis points to stabilization of the *d*-orbitals through π-backbonding, resulting in a shorter bond for M-R_f vs M-R.[42,55]



Scheme 2.13. Robustness of Metal Complexes Containing Fluoroalkyl Ligand.

A TFE-free pathway to prepare perfluorometallacycles would be both advantageous and safer for laboratories. The dizinc reagent (**2l**) cleanly reacts at room temperature with (DME)$NiBr_2$ at room temperature to produce the desired metallacycle product in 84% yield (Scheme 2.14).[43] This reaction represents the first facile TFE-free route to a perfluoronickelacyclopentane.



Scheme 2.14. TFE-Free Synthesis of Perfluoronickelacyclopentane.

A crystal structure confirmed that the product of the reaction described in Scheme 2.14 was the monomeric species **2o**.The reaction is analogous to that used to prepare the non-cyclic $(MeCN)_2Ni(R_f)_2$, where the *in situ* $[AgR_f]$ species is replaced by the zinc reagent **2l**.[42] The Vicic group is continuing research into the synthesis of other metallacycles as well as further exploring the chemistry of this nickel species.[56] The octafluorobutyl synthons have allowed for the study of higher valent nickel complexes.[57] These intermediates are important for understanding and elucidating how Ni^{III}/Ni^{IV} mechanisms may operate during catalysis.[58-63]

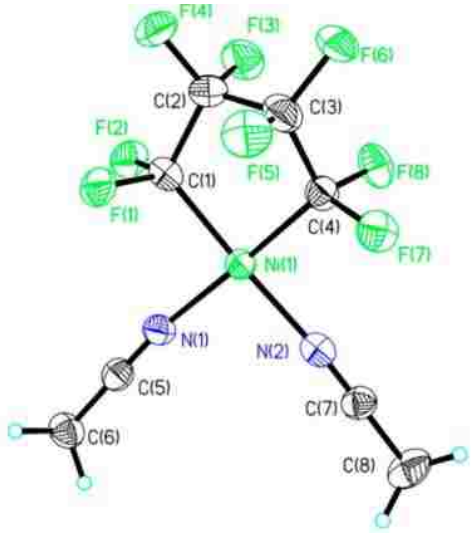
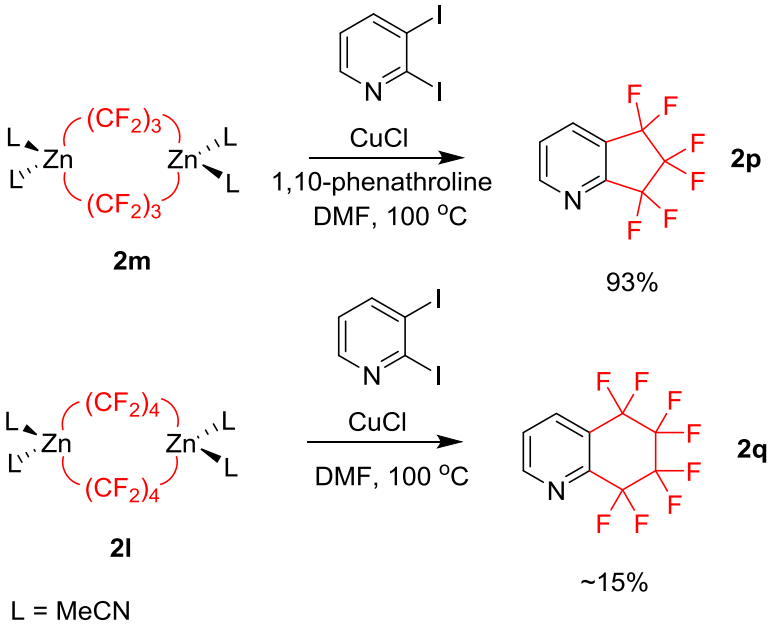


Figure 2.3. ORTEP Diagram of Nickel Complex **2o**. Selected bond lengths (Å): Ni1−C1 1.893(5); Ni1−C4 1.887(5); Ni1−N1 1.903(5); Ni1−N2 1.898(5). Selected bond angles (deg): C4−Ni1−C1 86.7(2); C4− Ni1−N2 91.5(2); C1−Ni1−N2 176.8(2); C4−Ni1−N1 177.7(2); C1−Ni1−N1 91.3(2).

2.2.3. Perfluoroalkylated Dizinc Complex for Polydifluoromethylenation

Copper had also been shown to be an active metal for trifluoromethylations with

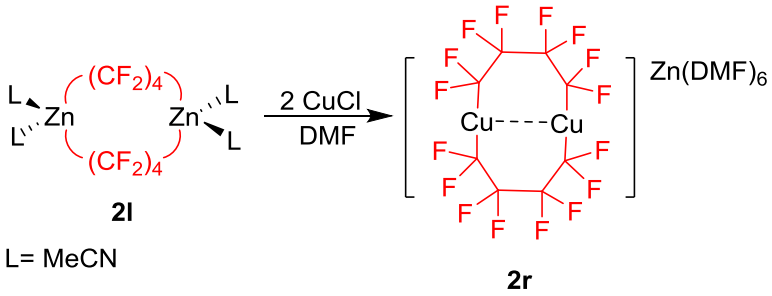
zinc reagents. This compound could also be used to could couple aryl diiodides with the dizinc reagents to form organofluorine ring systems. Using a 1,10- phenanthroline (phen) copper chloride system, good yields of **2p** (Scheme 2.15) were observed, though very low yields of **2q** (Scheme 2.15) under similar reaction conditions were observed.[43] Addition of ligand, such as phen, did not show any significant increase in yields of **2q**.



Scheme 2.15. Copper-Mediated Process to Organofluorine Ring Systems.

An inactive dicuprate **2r,** only observed for the C_4 dizinc derivative (**2l**), was formed competitively in solution when **2l** was mixed with copper salts (Scheme 2.16). The formation of this new species **2r** was nearly instantaneous, with resonances observed by ^{19}F NMR spectroscopy at δ −115.8 and −139.5. This novel dicuprate was initially thought to be the active transmetalating reagent. It was not until it could be isolated from the reaction and tested against aryl dihalides that it was discovered to be an inactive species. Furthermore, it is inert at even high temperature (100 °C) for several days,

opened to oxygen. The bis(trifluoromethyl) cuprate was also inactive towards the reaction with aryl halides.[26] However, $[(SIMes)_2Cu][(CF_3)_2]$ was shown to be in equilibrium with the active neutral species $(SIMes)Cu(CF_3)$.[26]



Scheme 2.16. Formation of the Inactive Dicuprate **2r**.

The crystal structure was obtained for **2r** (Figure 2.4), identifying it as only the second well-characterized bisperfluoroalkyl cuprate.[26,43] The structure displays a very close Cu-Cu interaction of 2.5481(4) Å. X-ray Photoelectron Spectroscopy (XPS) data was collected for **2r** comparing it to known standards of Cu_2O and CuO (Cu^I and Cu^{II}). Examination of the spectra in Figure 2.5 confirms distinctive copper(I) character, not copper(II). The spectra were referenced to the C(1s) peak at 284.6 eV.

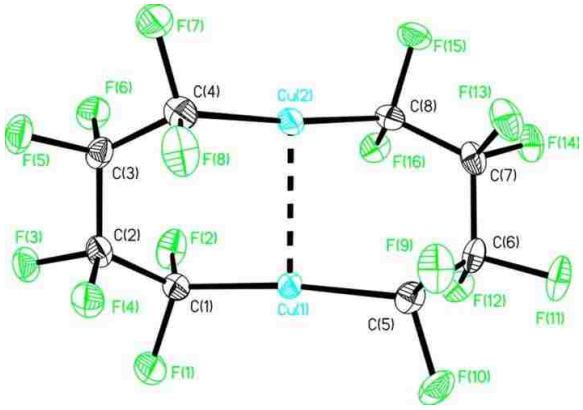


Figure 2.4. ORTEP Diagram of Dicuprate **2r**. The $[Zn(DMF)_6]$ dication has been

removed for clarity. Selected bond lengths (Å): Cu1−C1 1.925(2); Cu1−C5 1.925(2); Cu1−Cu2 2.5481(4); Cu2− C8 1.927(2); Cu2−C4 1.934(2). Selected bond angles (deg): C1− Cu1−C5 173.67(9); C8−Cu2−C4 174.21(9).

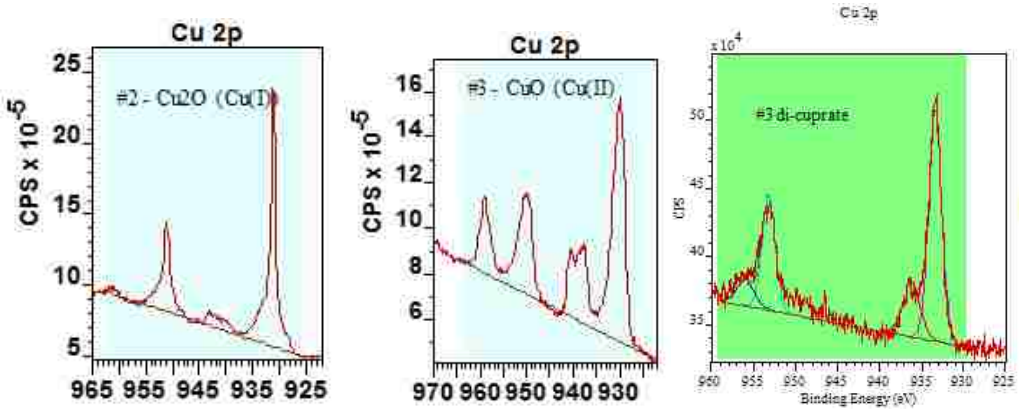
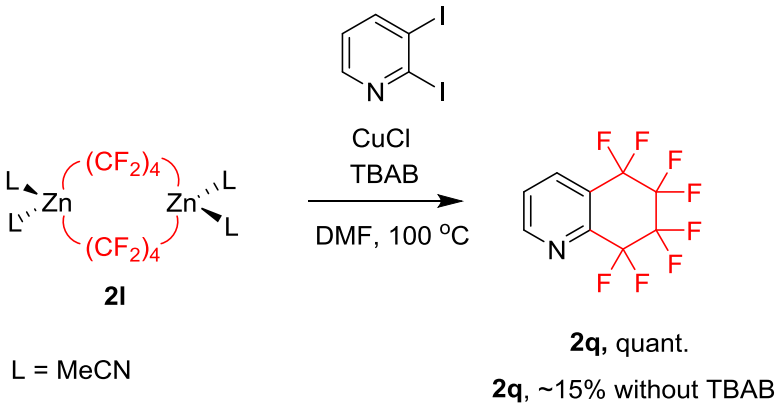


Figure 2.5. XPS Spectra for the Cu (2p) Region of Cu_2O, CuO, and **2r**.

2.2.4. Suppression of the Inactive Dicuprate

Additives and solvents were explored as a way to suppress the formation of inactive dicuprate **2r**. Organ and coworkers postulated that bromide or other halide sources can increase the activity of organozinc reagents. They noted that addition of tetrabutyl ammonium bromide enhances the reactivity of the respective zinc reagents in Negishi couplings by forming higher order zincates.[64,65] For the C_3 and C_6 dizinc reagents (**2m, 2n)** there seemed to be little to no change upon addition of $[(Bu)_4N]Br$ (TBAB), but the C_4 reagent (**2l**) gave a drastic increase in product formation despite lingering impurities in the dizinc starting material (Scheme 2.17). Addition of 1.10-Phenanthroline was found to be unnecessary for the C_4 dizinc species. The source of the copper did not seem to make a significant difference in yield, yet CuCl had a nominal increase in yield. With the main deleterious species suppressed, the reaction with the octafluorobutyl dizinc

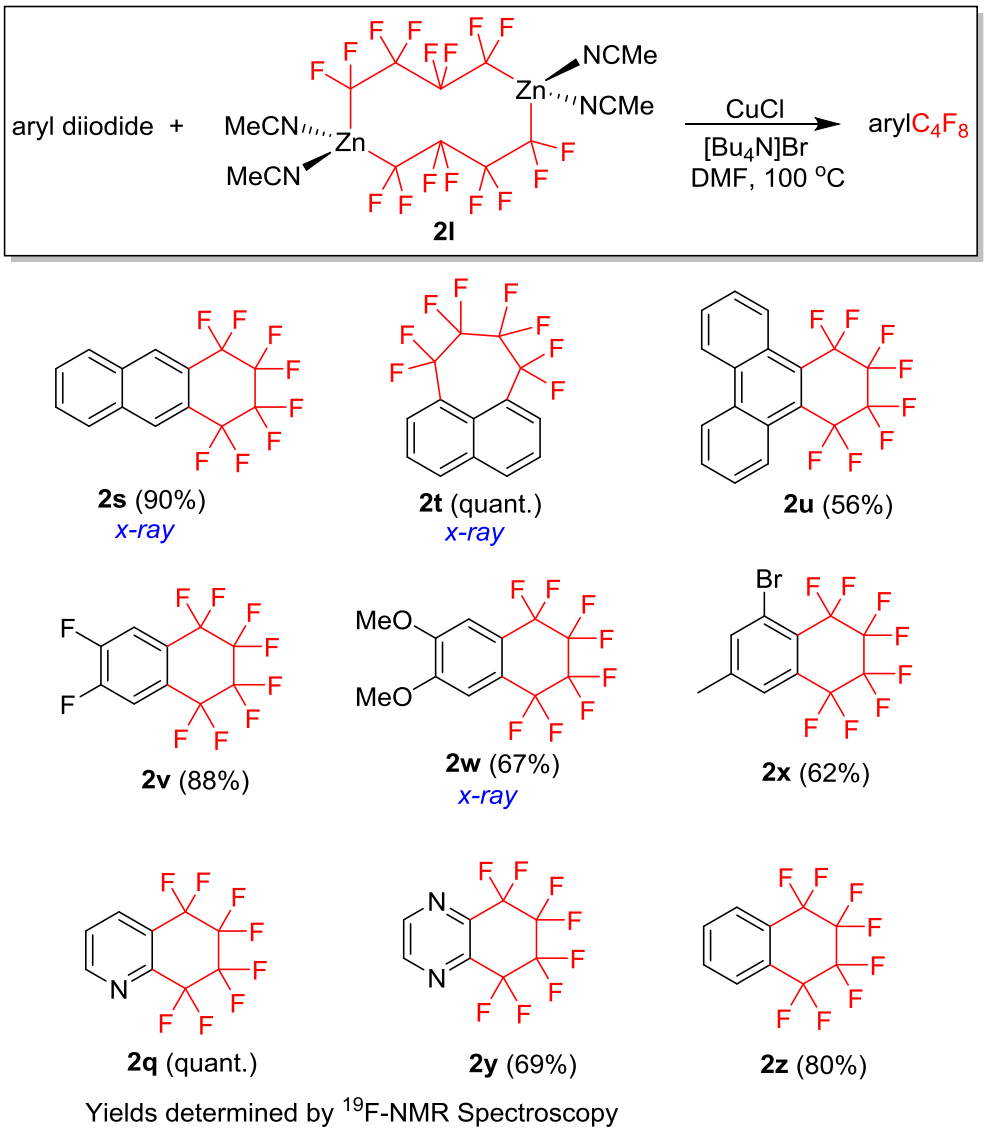
reagent (**2l**) could be optimized. A 50 mol % catalyst loading of CuCl was optimal.[43]



Scheme 2.17. Optimized Copper-Mediated Process to Organofluorine Ring Systems.

Furthermore, if an excess of diethyl zinc (2 equivalents) was used for the construction of the C_4 dizinc reagent (revised synthesis of **2l** reported in the Experimental Section), the mono- or di- hydrodezincation of the product was not observed by ^{19}F NMR spectroscopy (observed impurities in original synthesis).[66] This result may be due to the high reactivity of this dizinc along with the fast decomposition being in non-ligating solvent.

For the C_4 reagent (**2l**), good yields were obtained for the conversions of aryl diiodides to fluoroalkyl ring systems (Scheme 2.18).[66] The reactions proceeded cleanly to afford product within 3 hours at 100 °C. Crystal structures were also obtained for some of the novel isolated fluorocyclic organic compounds in Scheme 2.18. Product **2t** is especially interesting, considering the 7-membered ring is formed in quantitative yields under the reaction conditions. The work-up involved hexane/water extractions to collect the organic fraction. However, all products were nearly impossible to separate from aryl diiodide, owing mainly to their very similar retention factors or difficulty in distillation.

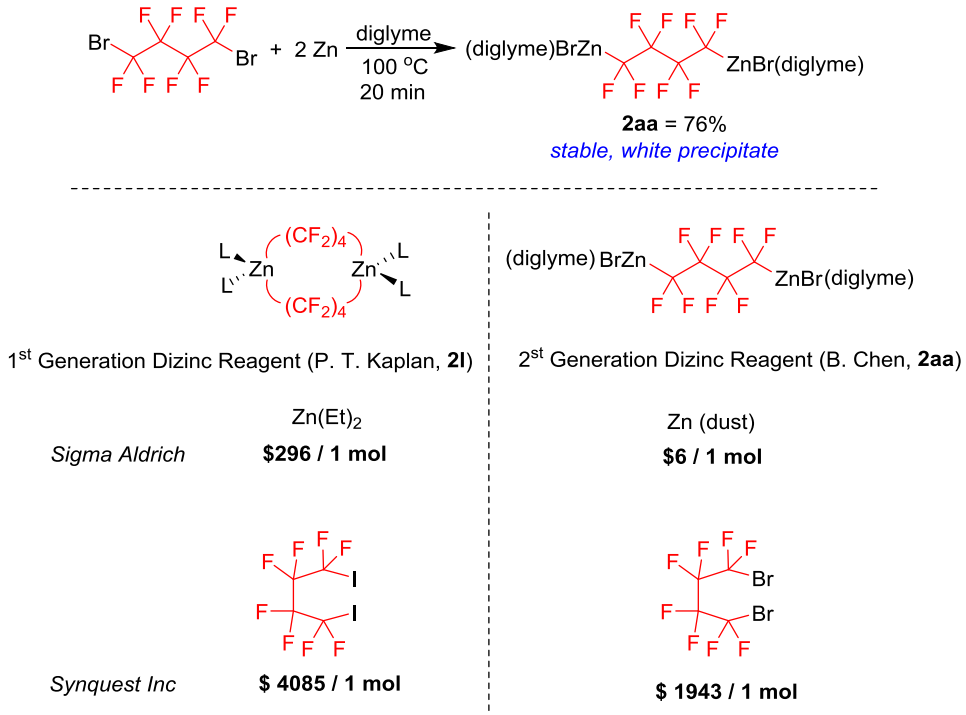


Scheme 2.18. Protocol and Yields for the Construction of Organofluorine Ring Systems.

2.2.5. A Second Generation of Dizinc Reagents

Further examination of the chemistry of zinc reagents revealed a cheaper alternative for producing good yields of active species for polydifluoromethylation. Using zinc dust (which is three orders of magnitude less expensive than diethyl zinc) and

α,ω-dibromooctafluorobutane (which is half the cost of α,ω-diiodooctafluorobutane), a new dizinc species could be synthesized in good yield in just 20 minutes at 100 °C. The cost analysis and reaction conditions are described in Scheme 2.19.[66] Solvent is key in preparation of new species; diglyme prevented decomposition and precipitated the white solid product from the soluble monozinc reagents in solution. This dizinc reagent is very similar to those prepared previously, where the Schlenk equilibrium favors R_fZnX as the active species.[19,67]



Scheme 2.19. Route to 2nd Generation Dizinc Reagent and Cost Comparison to 1st Generation Dizinc Reagent.

Complex **2aa** could be recrystallized from THF/pentane to give a cyclic dizinc species, which has been structurally characterized (Figure 2.5).[66] No cyclic perfluoroalkyl dizinc complexes were observed in solution by ^{19}F NMR spectroscopy or isolated from

the reaction. Overall, this new route provides an inexpensive means to generate (Scheme 2.19) these difunctionalized octafluorobutyl reagents in less than a half hour using air-stable reagents.

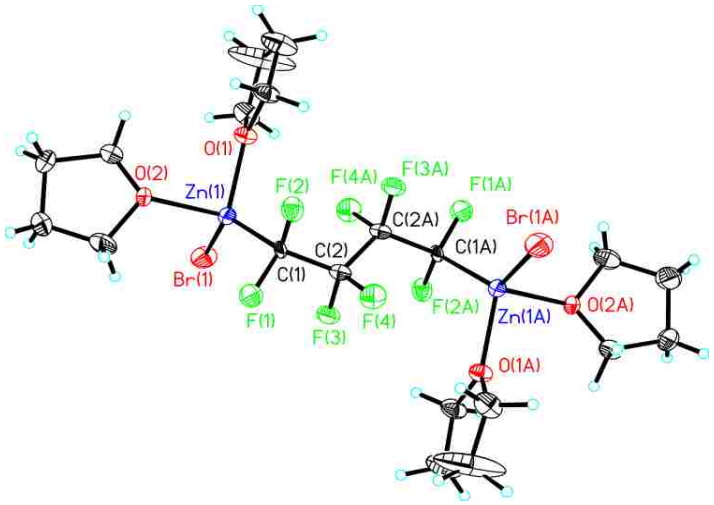
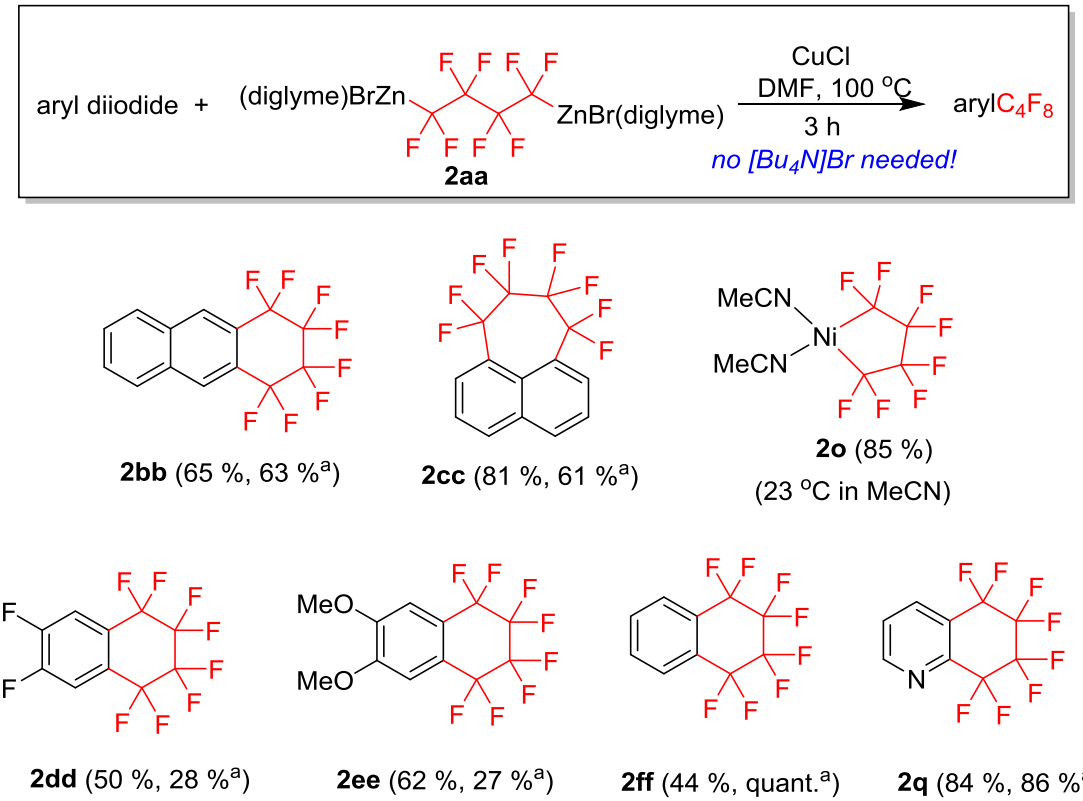


Figure 2.5. ORTEP Diagram of 2nd Generation Dizinc Complex **2aa** Solvated with THF. Selected bond lengths (Å): Zn1-O1 2.034(10); Zn1-C1 2.058(16); Zn1-O2 2.073(10); Zn1-Br1 2.338(2); C1-C2 1.517(19). Selected bond angles (deg): O1-Zn1-C1 112.3(5); O1-Zn1-O2 93.1(4); C1-Zn1-O2 107.9(5); O1- Zn1-Br1 108.5(3); C1-Zn1-Br1 126.6(4); O2-Zn1-Br1 102.6(3); C2-C1-Zn1 116.1(11).

A similar reactivity study was examined for this second generation zinc reagent, and is shown in Scheme 2.20. Use of **2aa** produced the desired fluoroalkylated ring systems in slightly lower but still respectable yields.[66] Most interestingly, the reactions did not need the addition of bromide salt or stabilizing ligand to enhance the reactivity. In most cases, additive simply did not affect the yields of the product. The solvent mixture of 1:1 DMF to 1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone, (DMPU), a cyclic urea, was tested. It has been reported that DMPU enhances the reactivity of the copper species

in cross-coupling chemistry.[67] While this held true for formation of product **2ff**, use of DMPU solvent was detrimental in almost all other cases for Scheme 2.20. Lastly, **2aa** was able to mediate the formation of the respective nickel metallacycle **2o** in 85% under the identical conditions. The dicuprate species **2r** was also not observed by ^{19}F NMR spectroscopy for the reaction described in Scheme 2.20 and did not quench the reaction.



Yields determined by ^{19}F-NMR except for **2o**

[a]for 1:1 DMF/DMPU used as solvent

Scheme 2.20. Protocol and Yields for the Construction of Organofluorine Ring Systems Using the 2nd Generation Dizinc Reagent **2aa**.

Comparison of the two dizinc reagents identifies several differences. For the first

generation dizinc species **2l**, the highest reactivity is observed with the lowest number of equivalents (two equivalents of reagent or two octafluorobutyl synthons). On the other hand, the second generation species **2aa** is nearly half the cost using air-stable starting material and can still effectively transform aryl diiodides and nickel dihalides. Additionally, **2aa** does not need addition of $[Bu_4N]Br$ or other additives to avoid the cuprate **2r**. No cuprate species was observed by ^{19}F NMR spectroscopy. However, it should be noted, that five equivalents of **2aa** are needed to perform the desired conversion aryl diiodides in Scheme 2.20. This result indicates that during the reaction of 1st generation dizinc reagent, **2l**, with CuCl and aryl diiodides, that the less reactive 2nd generation species, **2aa**, is formed *in situ* and while this species does react the reaction is less efficient than that of the original dizinc species **2l**.

2.2.6. Stability of Dizinc Reagents Containing Octafluorobutyl Synthons

Regardless of dizinc species used, the overall stability of these compounds was found to be excellent, marking them the first stable and isolable dinucleophiles for this kind of chemistry. The reagents are stable under inert atmosphere for months and even in acetonitrile only show minor decomposition after 300 hours as monitored by ^{19}F NMR spectroscopy (Figure 2.6).[66] The major decomposition product is the α,ω-dihydroperfluoroalkane through hydrodezincation pathway. Analogous dinucleophiles, such as the Grignard species $BrMg(CF_2)_6MgBr$, decompose even at –50°C with half-lives less than two hours.[68,69]

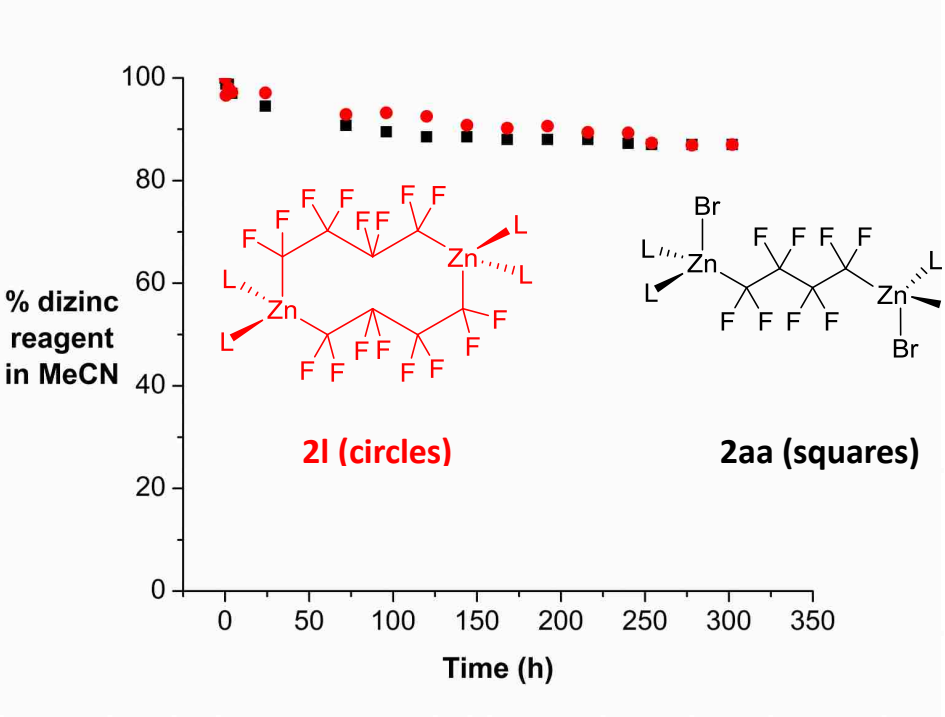
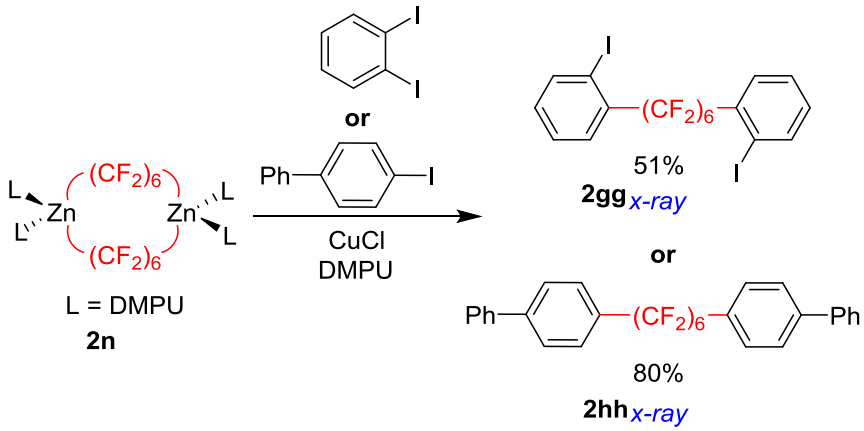


Figure 2.6. Stability of Dizinc Complexes **2l** and **2aa**.

2.2.7. Reactivity of Dizinc Reagent 2n

The cross coupling of aryl diiodides with the C_6 dizinc reagent **2n** in Scheme 2.21 did not produce the desired cyclic product. Instead 1,2-diiodobenzene yielded 51% of a linear bis(2-iodobenzene) linked with the perfluorohexyl unit (**2gg**).[43] This result is not too surprising when one accounts for both the kinetic energy needed to bend the fluoroalkyl chain and thermodynamic ring strain involved in the formation of the organofluorine ring. To further demonstrate its ability to prepare acyclic compounds, the 4-iodobiphenyl substrate was tested (Scheme 2.21) and found the respective product **2hh** could be obtained in 80% isolated yield. There are two notable differences for the C_6 derivative **2n** versus **2m**, **2l**, and **2aa**: the need to use DMPU as both solvent and ligand, and the ability to separate the products in Scheme 2.21 by column chromatography.



Scheme 2.21. Reactivity of C_6 Reagent **2n** with Iodo-Containing Substrates.

2.3. Conclusions

The novel dizinc complexes reported here represent a stable yet reactive scaffold for preparing fluoroalkylated compounds. Unlike the previous reported dinucleophiles, such as $BrMg(CF_2)_6MgBr$, **2l-2n** and **2aa** do not decompose significantly even at room temperature for several months under inert atmosphere.[68,69] Although **2l** can easily decompose to 1,4-dihydrooctafluorobutane, both **2l** and **2aa** were quite stable at room temperature in acetonitrile (less than 10% decomposition after 300 hours).

The C_4 dizinc species, **2l**, is the first effective reagent for the preparation of perfluoronickelacyclopentanes from a tetrafluoroethylene-free protocol. The nickel complex, $[(MeCN)_2Ni(C_4F_8)]$ (**2o**), is also an excellent precursor to a variety of substituted species. The labile acetonitrile ligands allow for a great degree of modularity on the nickel center, ultimately, granting access to higher valent nickel complexes.[57] Most importantly, this delivers small laboratories, lacking methods for obtaining or preparing TFE, an alternative synthesis to **2o** and its derivatives.

Finally, preliminary studies using the dizinc reagents with copper catalysts and organic iodides established new facile routes to prepare cyclic and acyclic fluoroalkylated products. Many of the cyclic products had not yet been reported. The few reports required superstoichiometric quantities of copper and multiple steps under radical conditions.[70,71] In contrast, my method demonstrates a mild, non-radical protocol with potential for further more complicated transformations. However, high catalyst loading of copper, need for additives and inert atmosphere, and arduous isolation of organofluorine-ring compounds hamper the overall efficiency in organic transformations. Future research should focus on both the metal catalyst system and the elucidation and collection methods of organofluorine-containing compounds.

2.4. Experimental Details

2.4.1. Materials

Diethyl zinc was purchased from Sigma Aldrich as a 1.0 M solution in hexanes. 1,4-diiodooctafluorobutane (98% purity) and 1,4-dibromooctafluorobutane (98% purity) were obtained from Synquest Labs Inc. All other chemical were verified by ^{1}H-NMR for purity and used without further purification. All solvents were purified by passing through activated alumina and/or copper in a solvent purification system supplied by Pure Process Technology or purchased anhydrous from Fisher Scientific (toluene, acetonitrile, and DMF).

2.4.2. Instrumentation and Equipment

All manipulations were performed using standard Schlenk and high-vacuum techniques or in a nitrogen filled glovebox. Solution ^{1}H-NMR spectra were recorded at ambient temperature on a Bruker DRX 500 MHz spectrometer and referenced to residual

proton solvent signals. Solution ^{13}C-NMR spectra were recorded on a Bruker NMR spectrometer operating at 125 MHz and referenced to solvent signals. All ^{19}F-NMR spectra were recorded on the Bruker NMR spectrometer operating at 470 MHz and referenced to trifluorotoluene set at δ −63.7. Yields determined by ^{19}F NMR have an estimated error of 10%. A Bruker D8 Quest diffractometer was used for X-ray crystal structure determinations. Elemental Analyses were performed at Midwest Microlab, LLC. Mass spectral data (low res) were recorded on a HP 5890 Series II Plus GC/MS.High Resolution Mass Spectroscopy was performed by University of Notre Dame's Mass Spectrometry and Proteomics Facility. The XPS analysis was performed by Dr. Henry Luftman at Lehigh University's Center for Advanced Materials and Nanotechnology using a Scienta ESCA-300.

2.4.3. Methods

2.4.3.1. Procedure for the Synthesis of Perfluoroalkyl Metal Complexes

2.4.3.1.1. Initial Preparation of $[(MeCN)_2Zn((CF_2)_4)_2Zn(MeCN)_2]$ (2l)

An 8-mL portion of a 1.0 M diethyl zinc solution in hexanes was prechilled in a vial to –78 °C under a nitrogen atmosphere. 1,4-Diiodooctafluorobutane (3.64 g, 8.02 mmol) was diluted with 8 mL of pentane and was also prechilled to –78 °C. The zinc solution was added dropwise to the 1,4-diiodooctafluorobutane solution at –78 °C. The reaction vial was then stirred for 3 h at –20 °C. After 3 h, 4 mL of MeCN was then added, and the mixture was stirred vigorously for 1 h and then warmed to room temperature. The pentane layer was decanted away, and benzene was added to precipitate an off-white solid. The mixture was stirred overnight, and then the solid was pumped dry on a high vacuum line. The product **2l** was obtained in 86% yield as a white solid. ^{19}F NMR

(CD_3CN, 470 MHz): δ −124.33 (br s), −124.86 (br s). Anal. Calcd (found) for $C_{16}H_{12}F_{16}N_4Zn_2$: C, 27.65 (27.76); H, 1.74 (1.88).

2.4.3.1.2. Revised Preparation of $[(MeCN)_2Zn((CF_2)_4)_2Zn(MeCN)_2]$ (2l)

An 8-mL portion of a 1.0 M diethyl zinc solution in hexanes was prechilled in a vial to –78 °C under a nitrogen atmosphere. 1,4-Diiodooctafluorobutane (1.82 g, 4.05 mmol) was diluted with 8 mL of pentane and was also prechilled to –78 °C. The zinc solution was then added dropwise to the 1,4-diiodooctafluorobutane solution at –78 °C. The reaction vial was then stirred for 3 h at –20 °C. After 3 h, 4 mL of MeCN was then added, and the mixture was stirred vigorously for 15 mins and warmed to room temperature. The pentane layer was decanted away and the solution dried down. The sticky solid was washed with benzene and dried down overnight on a high-vacuum line. The product **2l** was obtained in 91.2% yield as a white solid.

2.4.3.1.3. Preparation of (Diglyme)$BrZn(CF_2)_4ZnBr$(diglyme) (2aa)

To a resealable pressure tube was added Zn dust (0.392 g, 6.00 mmol) and a solution of $Br(CF_2)_4Br$ (1.260 g, 3.502 mmol) in diglyme (4 mL) under N_2 atmosphere at room temperature. The resulting mixture was sealed and quickly submerged in an oil bath preheated to 80 °C. After 20 min, the mixture was cooled to room temperature and filtered. The product was rinsed with diglyme followed by pentane to afford dizincbromide diglyme complex **2aa** (1.72 g, 76%): white/grey solid. ^{19}F NMR (471 MHz, THF-d_8) δ –122.52 (s, 4F), –124.27 (s, 4F). Anal. Calcd (found) for $C_{16}H_{28}Br_2F_8O_6Zn_2$: C, 25.32 (23.50); H, 3.72 (3.60). Recrystallization from THF/Pentane afforded X-ray quality crystals of **2aa**.

2.4.3.1.4. Preparation of $[(MeCN)_2Ni(C_4F_8)]$ (2o) from Dizinc Complex 2l

A (251 mg, 0.361 mmol) portion of **2l** freshly crystallized from benzene, was dissolved in 8 mL of MeCN and was then immediately added dropwise to a stirred mixture of [(DME)$NiBr_2$] (202 mg, 0.654 mmol) in 4 mL of acetonitrile. The mixture was stirred for 3 h at room temperature, and then the volatiles were removed under vacuum. The nickel complex was extracted from the residue with benzene, and this benzene solution was filtered and then dried under vacuum to yield an orange solid. Yield of **2o**: 84%. X-ray quality crystals were grown from THF/ether. ^{19}F NMR (CD_3CN, 470 MHz): δ −106.0 (s), −139.4 (s). Anal. Calcd (found) for $C_8H_6F_8N_2Ni$: C, 28.19 (27.85); H, 1.77 (1.88).

2.4.3.1.5. Preparation of [$(MeCN)_2Ni(C_4F_8)$] (2o) from Dizinc Complex 2aa

A (31 mg, 0.10 mmol) portion of [(DME)$NiBr_2$], and complex **2aa** (152 mg, 0.200 mmol) was dissolved in 2 mL of MeCN and stirred for 3 h at room temperature in a glovebox, and then the volatiles were removed under vacuum. The nickel complex was extracted from the residue with benzene, and this benzene solution was filtered then dried under vacuum to yield a yellow solid (290 mg, 85%). Analytical data matched previously reported literature values for **2o**.

2.4.3.1.6. Isolation of Dicuprate Complex for Structural Characterization (2r)

The zinc complex **2l** (1.05 g, 1.51 mmol) and copper chloride (300 mg, 3.03 mmol) were dissolved in 4 mL of DMF and stirred for 3 h at room temperature. The mixture was checked by ^{19}F NMR, and it was determined that 63.3% conversion to the cuprate species occurred. The mixture was filtered through a 0.2 μm PTFE filter, and the yellow solution was placed in a vial. Ether was layered on top of the yellow solution and placed in a −35 °C freezer overnight to form colorless crystals. ^{19}F NMR (DMF-d_7, 470

MHz): δ −115.75 (br s, 4F), −139.48 (br s, 4f). Crystals decompose upon extended time under vacuum. Anal. Calcd (found) for $C_{26}H_{42}Cu_2F_{16}N_6O_6Zn$: C, 30.29 (29.72); H, 4.11 (4.01). (29.72); H, 4.11 (4.01).

2.4.3.2. Initial Procedure for Fluoroalkylated Organic Compounds Using 2l

2.4.3.2.1. Preparation of 1,1,2,2,3,3,4,4-Octafluoro-1,2,3,4-tetrahydronaphthalene (2z)

The zinc complex **2l** (35 mg, 0.050 mmol) was dissolved in 0.8 mL of DMF and 0.4 mL of DMPU. Tetra-*n*-butylammonium bromide (32 mg, 0.099 mmol) was then added, followed by sequential addition of copper chloride (10. mg, 0.10 mmol) and 1,2 diiodobenzene (33 mg, 0.10 mmol). A 0.012 mL portion of trifluorotoluene (0.098 mmol) was syringed into the vial as the internal standard. The solution was then transferred to a J-Young NMR tube, sealed, and heated for 3 h at 100 °C. The NMR yield of **2z** was 28%. ^{19}F NMR (ethyl ether, 470 MHz): δ −103.6 (br s, 4F), −135.7 (br s, 4F). EI^+ MS: m/z = 276.

2.4.3.2.2. Preparation of 5,5,6,6,7,7,8,8-Octafluoro-5,6,7,8-tetrahydroquinoline (2q)

The zinc complex **2l** (35 mg, 0.050 mmol) was weighed into in a 20 mL vial and dissolved in 0.8 mL of DMF. Tetra-*n*-butylammonium bromide (32 mg, 0.099 mmol) was added, followed by the addition of copper chloride (10. mg, 0.10 mmol) and 2,3-diiodopyridine (33 mg, 0.10 mmol). A 0.012 mL portion of trifluorotoluene (0.098 mmol) was syringed into the vial as the internal standard. The solution was transferred to a J-Young NMR tube, sealed, and then heated for 3 h at 100 °C. The NMR yield of **2q** was 90%. 1H NMR ($CDCl_3$, 500 MHz): δ 9.05 (d, J = 4.7 Hz, 1H), 8.23 (d, J = 8.2 Hz, 1H), 7.76 (dd, J = 8.2, 4.7 Hz, 1H). ^{19}F NMR ($CDCl_3$, 470 MHz): δ −105.9 (s, 2F),

−111.6 (s, 2F), −135.6 (s, 2F), −136.0 (s, 2F). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.05 (d, J_{HH} = 4.7 Hz, 1H), 8.23 (d, J_{HH} = 8.2 Hz, 1H), 7.76 (dd, J_{HH} = 8.2, 4.7 Hz, 1H). EI^+ MS: m/z = 277.

2.4.3.3. General Procedure for the Preparation of Organofluorines

2.4.3.3.1. Using Zinc Reagent 2l revised Synthesis

The dizinc reagent **2l** (69 mg, 0.10 mmol) was dissolved in 1.0 mL of DMF in a 20 mL reaction vial. Tetra-*n*-butylammonium bromide (TBAB) was added (64 mg, 0.20 mmol) to the solution and the resulting mixture was stirred. Then 0.10 mmol of the diiodoarene and CuCl (10. mg, 0.10 mmol) were added to the stirred solution. 0.012 mL of α,α,α-trifluorotoluene (0.098 mmol) syringed into the solution as the internal standard. The solution was transferred to a J. Young NMR tube fitted with a Teflon screw cap and was heated for 3 h at 100 °C. After analysis of NMR yields, the solution in the NMR tube was diluted with hexanes and washed with water. The hexane layer was dried over anhydrous Na_2SO_4, and all volatiles were removed under vacuum.

2.4.3.2.2. Using Zinc Reagent 2aa

To a resealable pressure tube was added the zinc complex **2aa** (380. mg, 0.501 mmol), copper chloride (20. mg, 0.20 mmol), and 0.1 mmol of diiodoarene in 1 mL of DMF under N2 atmosphere at room temperature. The resulting mixture was sealed and quickly submerged in an oil bath preheated to 100 °C. After 3 h, the mixture was cooled to room temperature and 0.012 mL of α,α,α-trifluorotoluene (0.098 mmol) was syringed into the tube as the reference standard. After analysis of NMR yields, the solution was diluted with hexanes and washed with water. The hexane layer was dried over anhydrous Na_2SO_4, and all volatiles were removed under vacuum.

2.4.3.2.3. Using Zinc Reagent 2aa and DMF/DMPU Solvent

To a resealable NMR tube was added the zinc complex (190. mg, 0.250 mmol), copper chloride (10. mg, 0.10 mmol), diiodoarene (0.050 mmol), 0.5 mL of DMF and 0.5 mL of DMPU under N_2 atmosphere at room temperature. Lastly, 0.012 mL of α,α,α-trifluorotoluene (0.098 mmol) was syringed into the tube as the internal standard. The resulting mixture was sealed and quickly submerged in an oil bath and heated at 100 °C for 3 h. After analysis of NMR yields, the product was collected from a hexane/ water separation where the hexane layer was taken and dried over anhydrous Na_2SO_4. The residue was concentrated under vacuum.

2.4.3.2.4. Analytical data for 1,1,2,2,3,3,4,4-octafluoro-1,2,3,4-tetrahydoanthracene (2s)

^{19}F NMR ($CDCl_3$, 470 MHz): δ –102.02 (s, 4F), –135.09 (s, 4F). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.43 (s, 2H), 8.05 (dd, J_{HH} = 6.2, 3.3 Hz, 2H), 7.76 (dd, J_{HH} = 6.3, 3.2 Hz, 2H). Exact mass (EI^+) calcd for $C_{14}H_6F_8$ 326.0345, found 326.0342.

2.4.3.2.5. Analytical data for 7,7,8,8,9,9,10,10-octafluoro-7,8,9,10-tetrahydrocyclohepta[de] naphthalene (2t)

^{19}F NMR ($CDCl_3$, 470 MHz): δ –103.88 (s, 4F), –128.16 (s, 4F). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.17 (d, J_{HH} = 7.4 Hz, 2H), 8.12 (d, J_{HH} = 8.2 Hz, 2H), 7.69 (t, J_{HH} = 7.8 Hz, 2H). Exact mass (EI^+) calcd for $C_{14}H_6F_8$ 326.0345, found 326.0342.

2.4.3.2.6. Analytical data for 1,1,2,2,3,3,4,4-octafluoro-1,2,3,4-tetrahydrotriphenylene (2u)

^{19}F NMR ($CDCl_3$, 470 MHz): δ –102.42 (s, 4F), –136.11 (s, 4F). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.79 (d, J_{HH} = 8.5Hz, 2H), 8.56 (dt, J_{HH} = 7.3, 3.1 Hz, 2H), 7.87 (t,

J_{HH} = 8.2 Hz, 2H), 7.77 (t, J_{HH} = 7.2 Hz, 2H). Exact mass (EI^+) calcd for $C_{18}H_8F_8$ 376.0498, found 376.0471.

2.4.3.2.7. Analytical data for 1,1,2,2,3,3,4,4,6,7-decafluoro-1,2,3,4-tetrahydronaphthalene (2v)

^{19}F NMR (DMF, 470 MHz): δ –103.17 (s, 4F), –135.11 (s, 2F), –136.70 (s, 4F). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.72 (dd, J_{HF} = 8.2 Hz, 2.0 H). Exact mass (EI^+) calcd for $C_{10}H_2F_{10}$ 312.0122, found 311.9997.

2.4.3.2.8. Analytical data for 1,1,2,2,3,3,4,4-octafluoro-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene (2w)

^{19}F NMR ($CDCl_3$, 470 MHz): δ –102.61 (s, 4F), –134.97 (s, 2F). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.19 (s, 2H), 4.01 (s, 6H). Exact mass (EI^+) calcd for $C_{12}H_8F_8O_2$: 336.0374, found 336.0397.

2.4.3.2.9. Analytical data for 5-bromo-1,1,2,2,3,3,4,4-octafluoro-1,2,3,4-tetrahydro-7-methyl-naphthalene (2x)

^{19}F NMR ($CDCl_3$, 470 MHz): δ –103.78 (s, 2F), –106.07 (s, 2F), –134.37 (s, 2F), –136.58 (s, 2F). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.83 (s, 1H), 7.62 (s, 1H), 2.49 (s, 3H).

2.4.3.2.10. Analytical data for 5,5,6,6,7,7,8,8-octafluoro-5,6,7,8-tetrahydroquinoxaline (2y)

^{19}F NMR ($CDCl_3$, 470 MHz): δ –112.17 (s, 4F), –134.91 (s, 4F). ^1H NMR ($CDCl_3$, 300 MHz): δ 9.09 (s, 2H).

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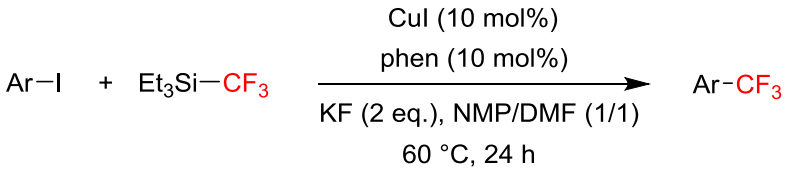
Chapter 3. Copper Catalyzed Cross-Coupling of Aryl Iodides with Dizinc Reagents

3.1. Background and Significance

3.1.1. Catalytic Trifluoromethylation of Aryl Iodides using Copper and Monofluoroalkyl Zinc Reagents

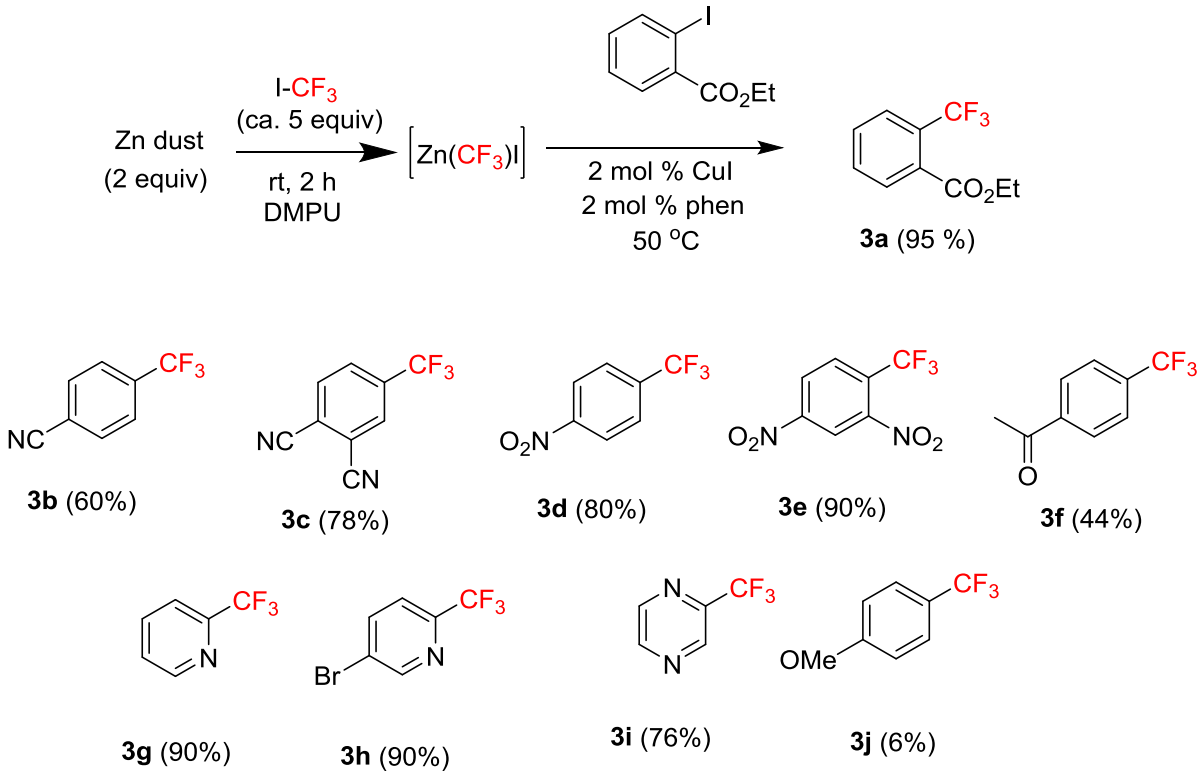
Although initial results reported by others verified the trifluoromethyl zinc reagent's ability to participate in trifluoromethylations of aryl iodides, cross-couplings were limited by scope and high catalyst loading.[1,2] The species[$CuCF_3$], prepared *in situ*, had already been shown to achieve transformation of aryl iodides in with as little as 10 mol% catalyst loading of copper salt.[3,4] One reported reaction (Scheme 3.1) required triethyl(trifluoromethyl) silane, potassium fluoride to activate the silane, and phen ligand to stabilize the active copper species, [$CuCF_3$]. Good yields were only obtained for electron deficient aryl iodides while electron rich substrates exhibited greatly diminished formation.



Scheme 3.1. Preparation of Trifluoromethyl Arenes.

The copper protocol was adopted by Mikami and coworkers in late 2013 for use with zinc.[5] Using Zn dust to insert into I-CF_3, [$Zn(CF_3)I$] was prepared *in situ* in DMPU solvent. The zinc complex (prepared in excess) reacted with catalytic amounts of CuI and phen (2 mol% each) to form the active species [$Cu(CF_3)I]^-$ which reacted with aryl iodides (Scheme 3.2).[5] The reaction cleanly transformed ethyl 2-iodobenzoate into ethyl

2-trfluoromethylbenzoate (trifluoromethylated product **3a**) in 95% yield, as well as other electron deficient arenes (**3b-3i**), but did not afford good yields of electron rich substrates **3j**. The reaction can be achieved without the addition of phen, but phenanthroline demonstrated a greatly reduced reaction time.

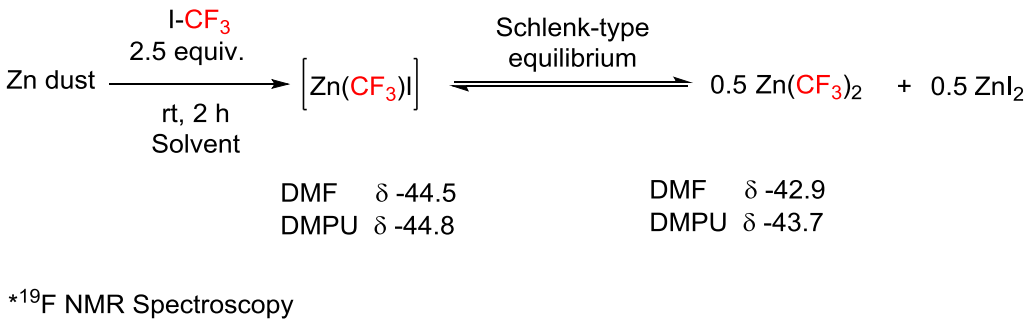


Yields determined by ^{19}F-NMR Spectroscopy

Scheme 3.2. Trifluormethylation Using a Monofluoroalkyl Zinc Reagent and Copper Catalyst.

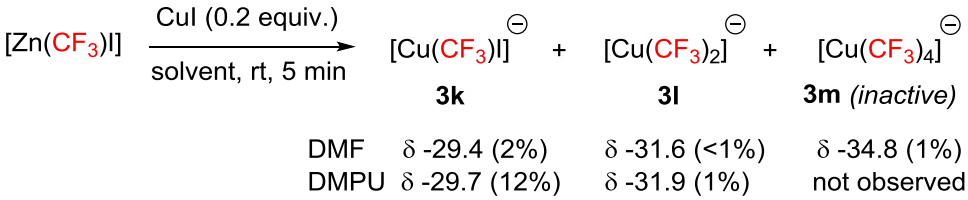
Solvent is important for the formation of the desired species in the above scheme. If non-polar solvent is employed, formation of zinc complex [Zn(CF_3)I] was completely suppressed. Some polar solvents even failed to produce the desired zinc species in adequate yields. Only DMF and DMPU proceeded to form [Zn(CF_3)I]. Unlike the

previous zinc complex [Zn(*i*-(C_3F_7)I], [Zn(CF_3)I] was observed by ^{19}F NMR spectroscopy to be in Schlenk equilibrium with [Zn(CF_3)$_2$] and ZnI_2 (Scheme 3.3).[5,6]



Scheme 3.3. Schlenk-Type Equilibrium of Monofluoroalkyl Zinc Species.

Solvent also plays an important role in the formation of the active copper species for the reaction shown in Scheme 3.4. DMF disfavors the active copper species **3k** compared with the use of DMPU as solvent. Furthermore, DMF favors formation of the inactive copper (III) species **3m**.[5,7,8] Although the paper does not mention activity of **3l**, previous reports indicate it is probably an inactive species.[9] However, formation of the neutral copper species [$CuCF_3$], known to be reactive with even electron rich aryl halides, was not observed by ^{19}F NMR spectroscopy.[5,10]

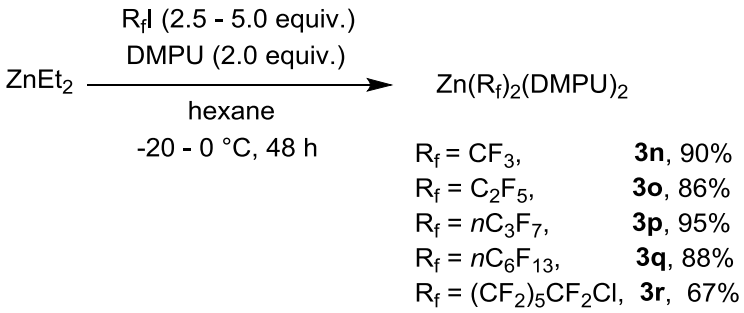


*Yields calculated with respect to the CuI by ^{19}F NMR Spectroscopy

Scheme 3.4. Formation of Cuprates from [Zn(CF_3)I] Complex at Room Temperature.

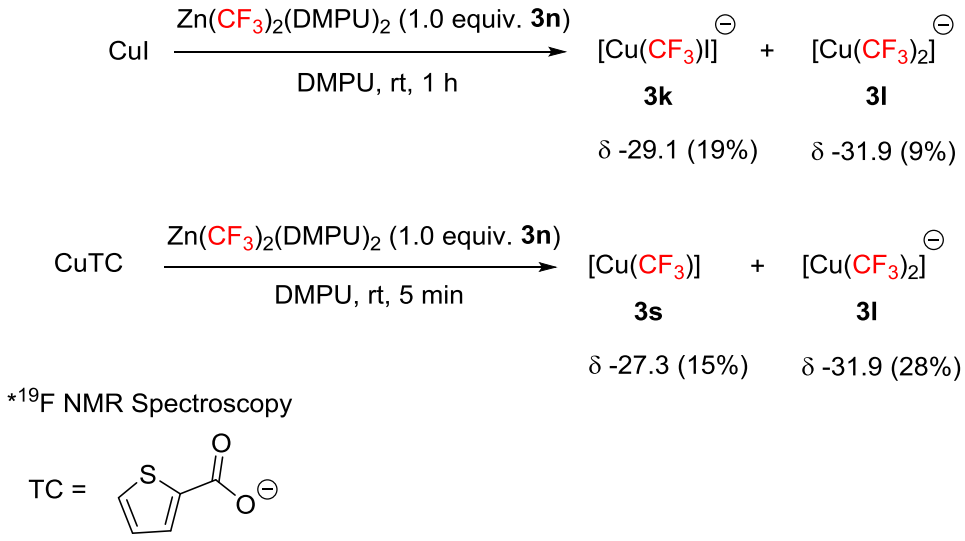
3.1.2. Bis(fluoroalkyl) Zinc Reagents in Copper Catalyzed Transformations of Aryl Iodides

In 2015, Mikami and coworkers prepared bis(fluoroalkylated) zinc complexes from diethyl zinc and 1-iodoperfluoroalkanes according to reported protocols.[11-13] The DMPU was again key in isolating the zinc complexes as stable solids (Scheme 3.5). With the exception of $L_nZn(CF_3)_2$ (**3n)**, which was moisture sensitive, **3o**-**3r** did not exhibit substantial decomposition in air at room temperature.



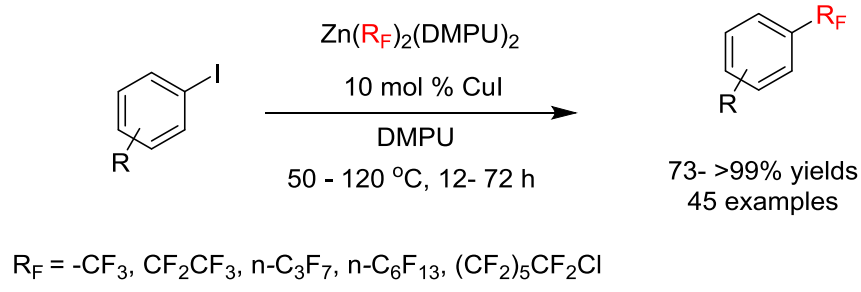
Scheme 3.5. Protocol to Isolated Bis(fluoroalkylated) Zinc Complexes.

The zinc reagent **3n** could transmetalate copper iodide to the active copper complex **3k** (Scheme 3.6). Interestingly, the neutral species $CuCF_3$ was not produced, but instead the cuprate species, **3k** and **3l**, were observed by ^{19}F NMR spectroscopy in solution.[14] On the other hand, copper(I)-thiophene-2-carboxylate (CuTC) afforded a mixture of the neutral species **3s** and the cuprate **3l**.



Scheme 3.6. Transmetalation of the CF_3 Group to Copper.

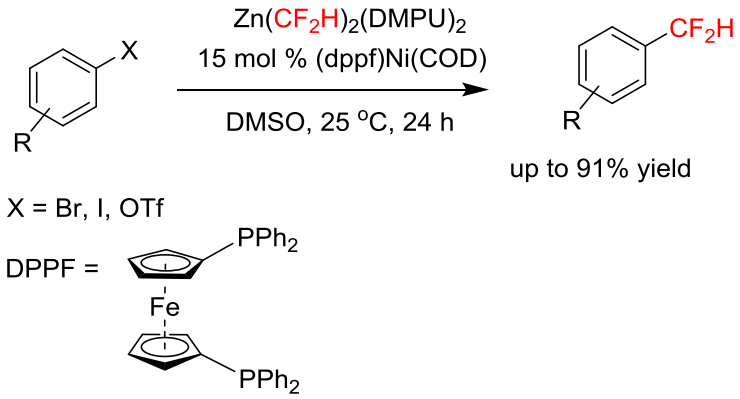
More importantly, CuTC was a capable precursor in transformation of even electron rich aryl iodides (such as those containing methoxy moieties) to the trifluoromethylated products. Despite this finding, copper (I) iodide was employed the aryl halides giving good to excellent yields of fluoroalkylated product (Scheme 3.7). The reaction worked best under ligand free conditions with 10 mol% of copper catalyst and tolerated some functional groups: Br, esters, aldehydes, and methoxy. This protocol represents fairly mild reaction conditions for the synthesis of valuable fluoroalkylated products.



Scheme 3.7. Formation of Fluoroalkylated Arenes and Heteroarenes.

3.1.3. Negishi-like Systems for Fluoroalkylation

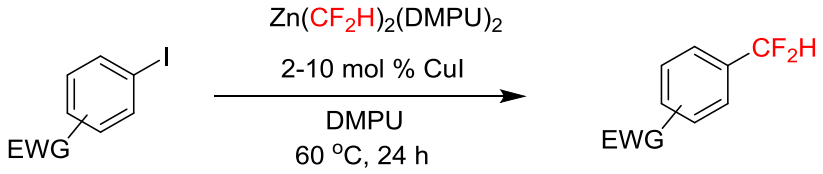
Unfortunately, there are only a handful of other Negishi-like protocols for perfluoroalkylation of aryl halides. The difluoromethylation protocol outlined in Scheme 3.8 represents the first nickel catalyzed system reported.[15] Using 15 mol % (dppf)Ni(COD), Vicic and coworkers, reported difluoromethylation of aryl iodides, bromides, and triflates in good to excellent yields at room temperature. The synthesis of $(DMPU)_2Zn(CF_2H)_2$ took place at room temperature using $ZnEt_2$ and ICF_2H.[13,15] They cite both the ligand and the solvent, DMSO, as the key components in suppression of the very stable, inactive complex, $L_nNi(CF_2H)_2$.[15,16] However, activation of electron rich species were less facile. It should be mentioned that DMSO is also able to suppress the hydrodezincation commonly seen for copper systems.[13,17]



Scheme 3.8. Difluoromethylation using Novel Bis(difluoromethyl) Zinc Reagent and Nickel Catalyst.

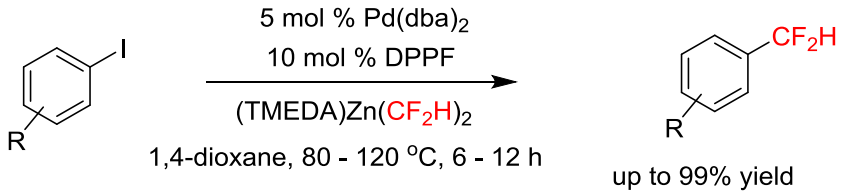
Mikami and coworkers modified the nickel catalyzed protocol (described above in Scheme 3.8, for two different difluoromethylation pathways (Scheme 3.9 - 3.10).[18,19]

Here, they reported that CuI was able to difluoromethylate aryl iodides in moderate to good yields. While both a small scope of substrates and only moderate yield were reported, the reaction neither needs activator nor ligand to prepare the respective difluoromethylated arenes (Scheme 3.9).[19]



Scheme 3.9. Difluoromethylation by Copper Catalyzed System.

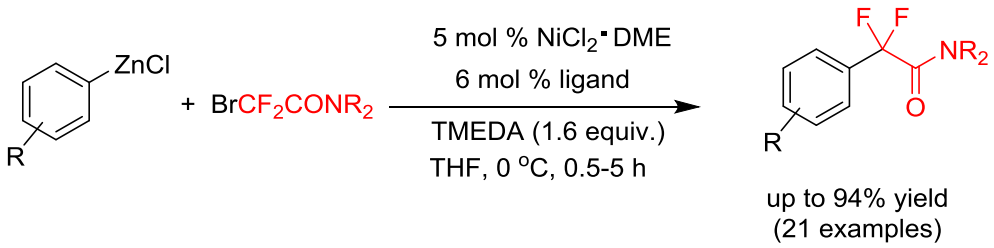
On the other hand, the palladium catalyzed system was far more robust than that of copper.[18] Only 5 mol% palladium catalyst loading was needed to prepare good to excellent yields of the difluoromethyl arenes (Scheme 3.10). Both electron rich and electron poor aryl iodides were converted in excellent yields. The catalyst was also able to transform electron poor aryl bromides, although at diminished yields.



Scheme 3.10. Difluoromethylation by Palladium Catalyzed System.

Ando and coworkers demonstrated nickel-catalyzed negishi cross-coupling of bromodifluoroacetamides, reported in Scheme 3.11. As little as 5-6% of nickel catalyst and ligand loading was needed to perform the desired conversion.[20] It represents the

reverse of previous systems explored, where the nucleophile is the aryl substrate and the electrophile is the fluorine containing species.



Scheme 3.11. Another Protocol for Catalytic Fluoroalkyl Incorporation.

3.1.4. Project Goals

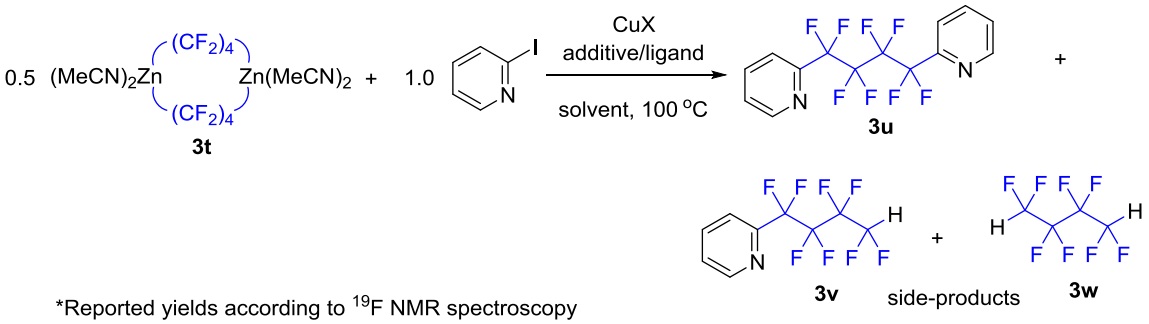
Ultimately, the aforementioned results with fluoroalkyl zinc reagents encouraged me to explore a catalytic method for fluoroalkylation with my dinucleophile reagents (highlighted in Chapter 2.3.1). I identified three major factors that would need to be addressed. First, what is the best catalyst for these fluoroalkylations and what is its optimum loading? Second, what is best combination of solvents and additives to suppress decomposition pathways or inactive metal complexes? Third, can the protocol be used to prepare a catalog of cyclic or acyclic fluoroalkylated compounds? To address these questions, I focused on a copper catalyzed system because of the similarities to published protocols.

3.2. Results and Discussions

3.2.1. Investigation of Perfluoroalkylated Dizinc Reagents for Polydifluoromethylenation Reactions

The substrate 2-iodopyridine was selected as a model reagent because of its high reactivity. The dinucleophile complex (1st generation C_4 dizinc reagent **3t**) was also

selected because of my initial findings that it could react with 2-iodopyridine quickly to achieve 70% of the desired fluoroalkyl linked product **3u**, reported in Table 3.1. After testing various salts, additives, and ligands, CuCl and CuOAc were found to be the most promising copper precatalysts. All other copper salts suffered from lower yields even if addition of tetrabutyl ammonium bromide (TBAB) was employed. Therefore, both were explored further in the new catalytic protocol (Table 3.1). Using stoichiometric loadings of all reagents (Table 3.1, entry 1), a mixture of product **3u** and the hydrogen terminated product **3v** were observed by ^{19}F NMR spectroscopy. If I used the published protocol (2 equivalents of dizinc reagent),[17] the product yield was increased to 79%. Decreasing the loading of copper chloride further is deleterious. DMPU solvent was reported to enhance the cross-coupling power of fluoroalkylated zinc complexes.[5] In this work (see Table 3.1, entry 4) it effectively suppressed the desired product **3u** and formed the undesired byproducts **3v** and **3w**. The use of copper(I) acetate showed a much more favorable trend (Table 3.1, entries 5-8). When just 10 mol% of CuOAc was added, the reaction displayed nearly complete transformation of substrate, although only 65% of **3u** to the 35% of **3v** (Table 3.1, entry 6). Surprisingly, addition of TBAB slightly lowered the yield of **3u** and was unnecessary for the suppressing the inactive dicuprate.[13] Actually, only at higher loadings (50%-100%) of copper(I) acetate was the dicuprate once again observed. Addition of bidentate coordinating ligands, such as bpy or phen did not significantly impact the reaction. DMSO had been reported as an optimal solvent to suppress the hydrodezincation of bis(fluoroalkylated) zinc reagents.[15] Upon replacing DMF with DMSO, near complete suppression of **3v** and 87% of **3u** was found (Table 3.1, entry 7). Decreasing the catalyst loading further did not improve the results.



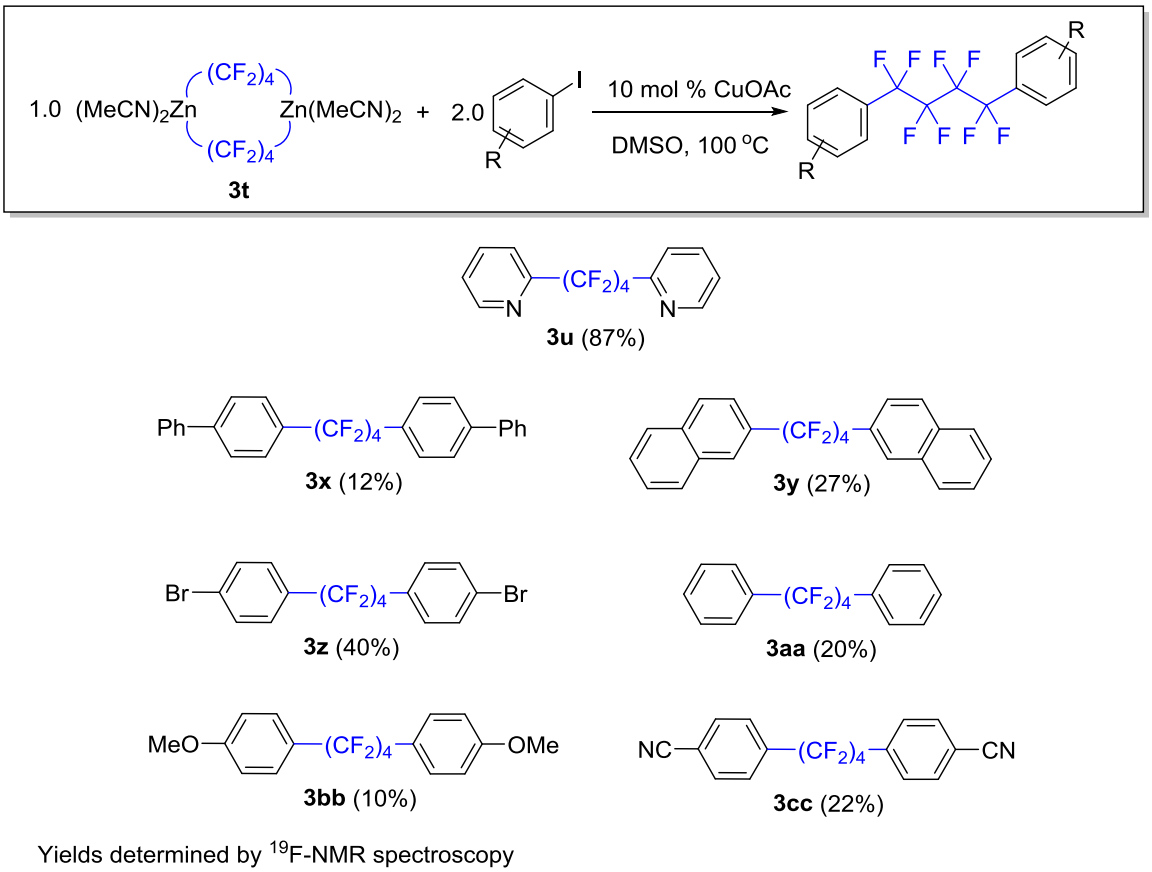
*Reported yields according to ^{19}F NMR spectroscopy vs trifluorotoluene internal standard

Entry	Dizinc	CuX	Additive/ligand	Solvent	3u	Other
1	1 equiv.	100% CuCl	2 equiv. of TBAB	DMF	48%	20% **3v**
2	2 equiv.	50% CuCl	2 equiv. of TBAB	DMF	79%	n/a
3	2 equiv.	10% CuCl	2 equiv. of TBAB	DMF	53%	n/a
4	2 equiv.	10% CuCl	2 equiv. of TBAB	DMPU	0%	30% **3v** + 62% **3w**
5	2 equiv.	10% CuOAc	2 equiv. of TBAB	DMF	51%	15% **3v**
6	2 equiv.	10 % CuOAc	none	DMF	65%	35% **3v**
7	2 equiv.	10% CuOAc	none	DMSO	87%	n/a
8	2 equiv.	1% CuOAc	none	DMSO	51%	n/a

Table 3.1. Catalytic Parameters for Fluoroalkylation Using **3t**.

3.2.2. Scope of Fluoroalkylation of Aryl Iodides

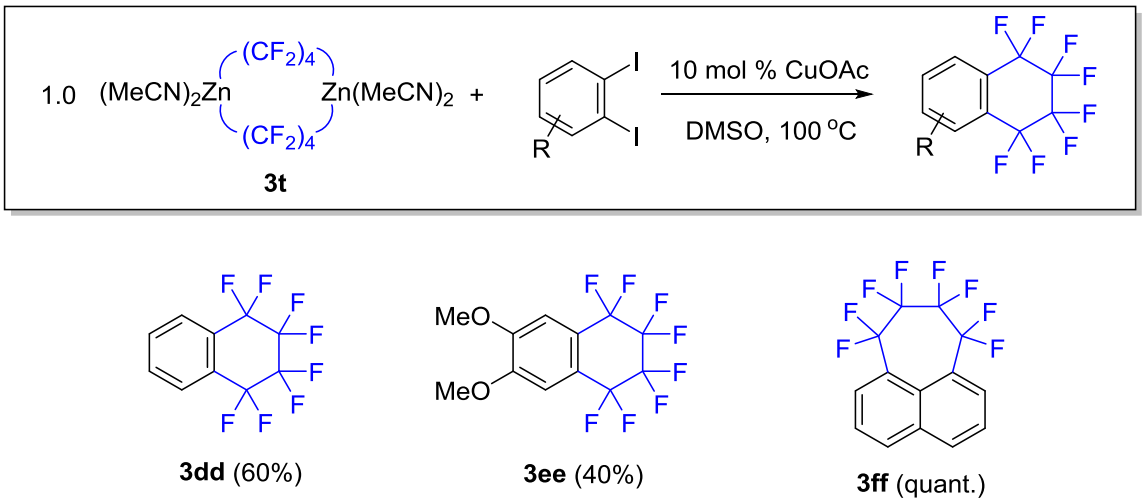
Attempts to develop a library of acyclic fluoroalkyl linked products by copper catalysis only resulted in poor yields (Scheme 3.12). The formation of **3u** occurred in good yield whereas, **3x-3cc** were produced in poor to very low yields. The side-products varied from hydrodezincated, 1,4-dihydrooctafluorobutane (**3w**), hydrogen terminated products (like **3v**), or uncharacterized fluorine containing compounds.



Scheme 3.12. Acyclic Linked Fluoroalkylated Arenes Using **3t**.

3.2.3. Preparation of Organofluorine Containing Ring Compounds

Catalysis involving diiodoaryl substrates gave much more promising results. Reported in Scheme 3.13, near quantitative yields of **3ff** were achieved after 12 hours. While **3dd** and **3ee** displayed slightly diminished yields compared to the past protocol.[17] Although a full exploration of the scope of the reactivity of **3t** would be fruitful, I focused instead on the C_6 dizinc species (**3gg**) which had already displayed more favorable reactivity towards desired products.

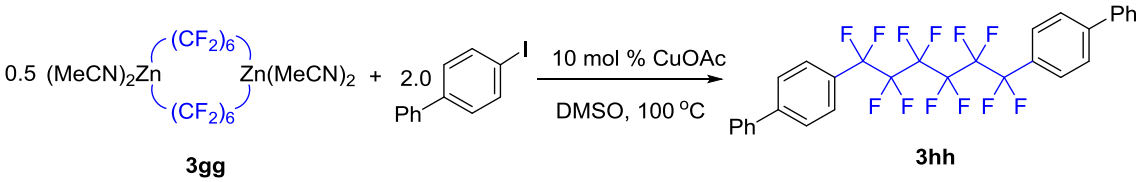


Yields determined by ^{19}F-NMR spectroscopy

Scheme 3.13. Protocol for the Preparation of Fluorine-Containing Ring Compounds.

3.2.4. Catalytic Protocol and Optimization Using C_6 Dizinc Reagent (3hh)

Turning my attention towards C_6 derivative **3gg**, I decided to optimize my system against the less reactive 4-iodobiphenyl (Table 3.2). The reactivity of this substrate could be compared to reported stoichiometric protocol and the initial catalytic findings, reported in Scheme 3.12.[13] Once again, the copper (I) acetate concentration was inversely proportional to product formation (Table 3.2, entries 1-3), albeit when concentrations lower than 10 mol% were used, a diminished yield of **3hh** was observed. Increasing the loading of **3gg** was extremely beneficial, with a quantitative yield of **3hh** observed when dizinc reagent was increased from stoichiometric quantities (0.05 mmol) to 4 equivalents (0.20 mmol reported in Table 3.2, entry 7). Moreover, increasing the number of equivalents of 4-iodobiphenyl to 4 equivalents (0.80 mmol) also increases the yield of product **3ii**, albeit only 72% (Table 3.2, entry 8).



3gg

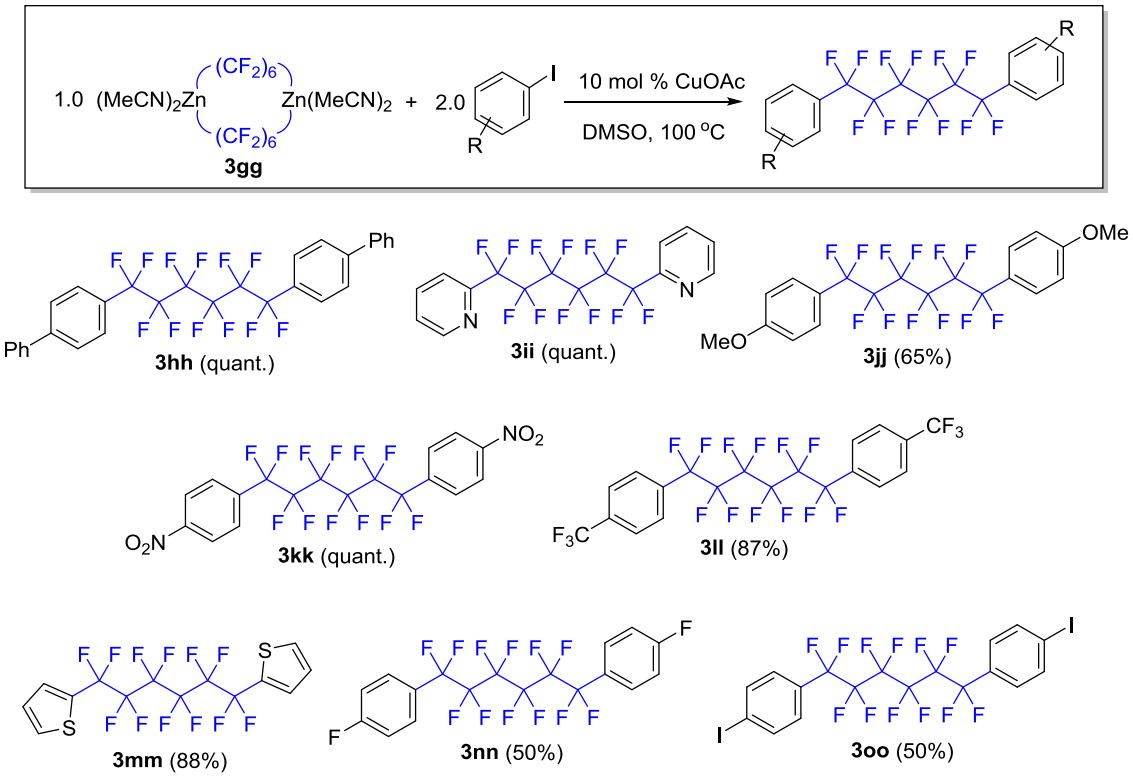
3hh

Entry	C_6 dizinc	4-iodobiphenyl	CuOAc	Temp. (°C)	Product % Yield
1	0.05 mmol	0.20 mmol	0.20 mmol	100 °C	17
2	0.05 mmol	0.20 mmol	0.10 mmol	100 °C	27
3	0.05 mmol	0.20 mmol	10 mol %	100 °C	46
4	0.10 mmol	0.20 mmol	10 mol %	100 °C	67
5	0.10 mmol	0.20 mmol	10 mol %	50 °C	31
6	0.10 mmol	0.20 mmol	5 mol %	100 °C	40
7	0.20 mmol	0.20 mmol	10 mol %	100 °C	>99
8	0.05 mmol	0.80 mmol	10 mol %	100 °C	72

Table 3.2. Reaction Parameters for Fluoroalkylation Using **3gg**.

3.2.5. Scope of Bis(aryl) Perfluorohexane Compounds

The reaction parameters in Table 3.2, entry 7 were used to examine an array of aryl iodides. Encouragingly, yields of products **3hh-3oo** were moderate to excellent (Scheme 3.14). Even electron-rich substrates (such as those containing methoxy moieties) achieved a good yield of 65% by ^{19}F NMR spectroscopy (Scheme 3.14). Heterocycles **3ii** and **3mm** also possess the capability to be used as specialty ligands as pyridine or thiophene surrogates. Compound **3nn** has been used in polymer synthesis as a key block copolymer.[21] Although compound **3oo** could potentially be used to prepare dimer, oligomer, and polymeric systems with 1,4-diidophenyl substrates for preparation of specialty materials.[21,22] Ultimately, future research should elucidate the properties of the compounds described in Scheme 3.14, as well as expanding the scope to more complex systems.



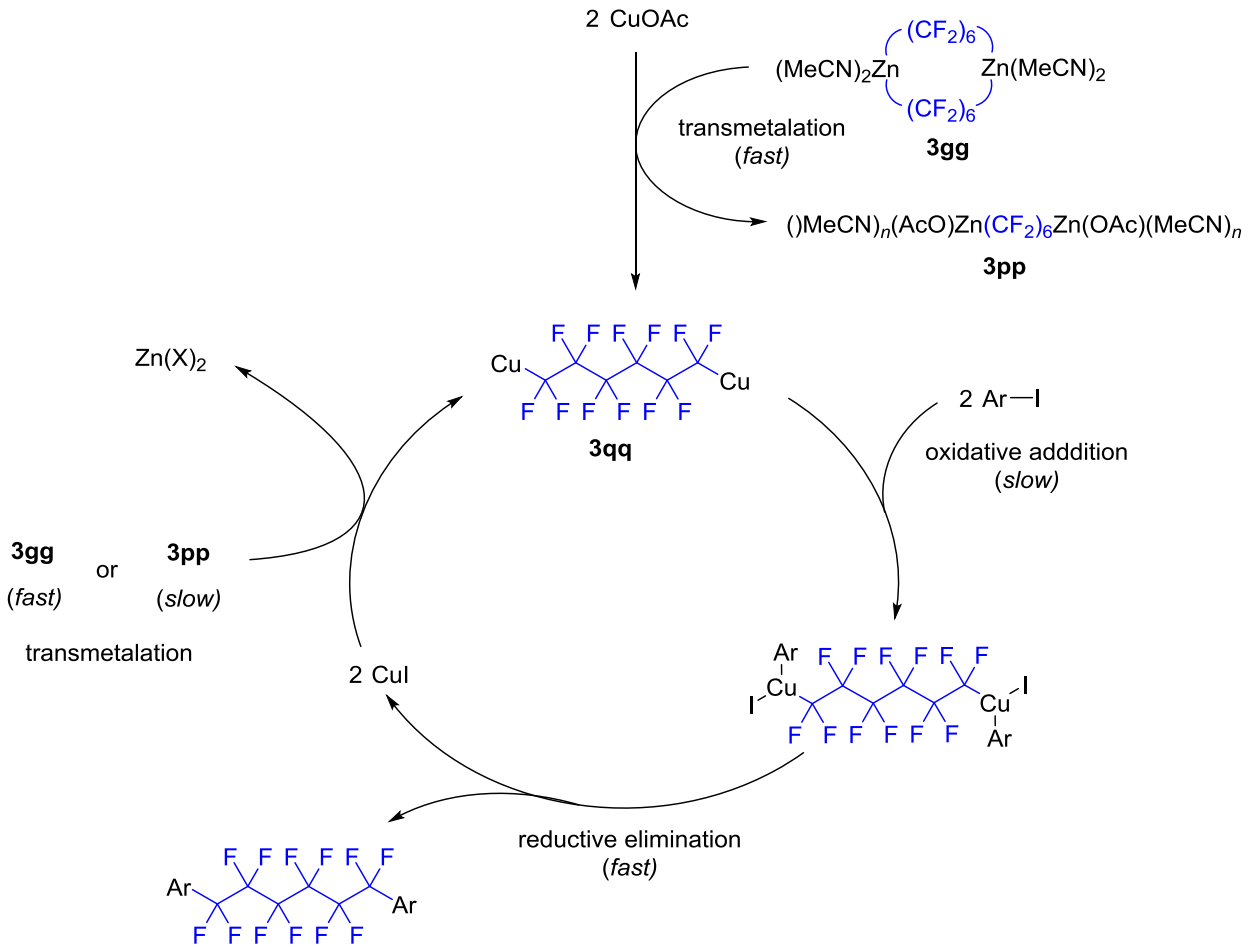
Yields determined by ^{19}F-NMR spectroscopy

Scheme 3.14. Acyclic Linked Fluoroalkylated Arenes Using **3gg**.

3.2.6. Preliminary Mechanism

Having demonstrated good reactivity of the dizinc complex **3gg**, I investigated other factors that could affect the reaction. Based on reported proposed catalytic cycles, Scheme 3.15 was proposed.[3-5,10,14,19] The transmetalation of **3gg** to the CuOAc appears fast, based on both the color change upon addition of copper salt and the formation of bis(aryl) perfluorohexane product when an electron-deficient aryl iodide is used. Although the active species **3qq** is proposed to be formed *in situ*, it was not definitely detected in solution, mainly due to the myriad of peaks in ^{19}F NMR spectrum. The reaction efficiency seems to depend on the substrates themselves. When 4-iodopyridine is

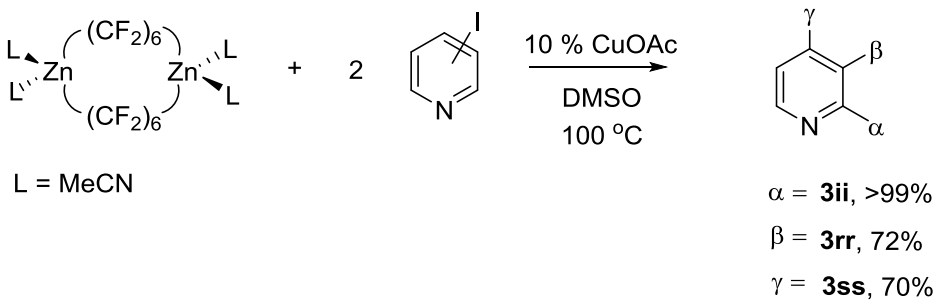
employed as the substrate, only about 30% yield is formed after several hours. On the other hand, 2-iodopyridine achieves near quantitative yield after an hour. The variation of yields suggests that more investigations are needed to understand the mechanism.



Scheme 3.15. Proposed Catalytic Cycle.

I then investigated how the reaction was influenced by regioisomers of iodopyridine. Classic organic chemistry and resonance dictates the following order γ > α >> β for nucleophilic attack. However, reaction with copper (I) acetate and dinucleophile **3gg** favored α > β ≈ γ (Scheme 3.16). Not only was the reaction with 2-iodopyridine the

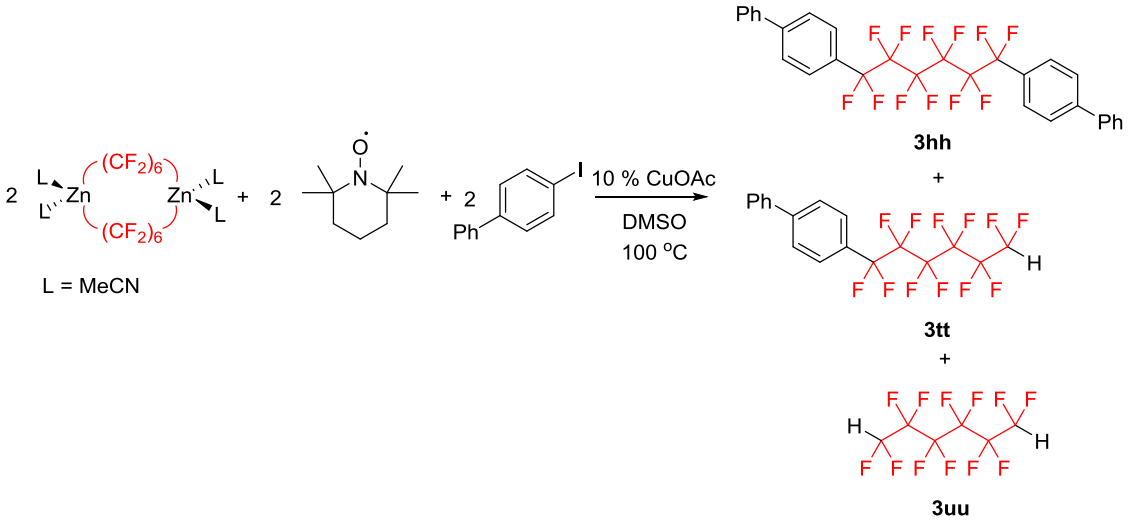
fastest of the three regioisomers, the yield was also the highest (quantitative after just an hour). The formation of **3rr** and **3ss** was slower, only achieving approximately 70% yield. It is most likely coordination of the 2-iodopyridine to the copper complex the greatly facilitates insertion into the α position.



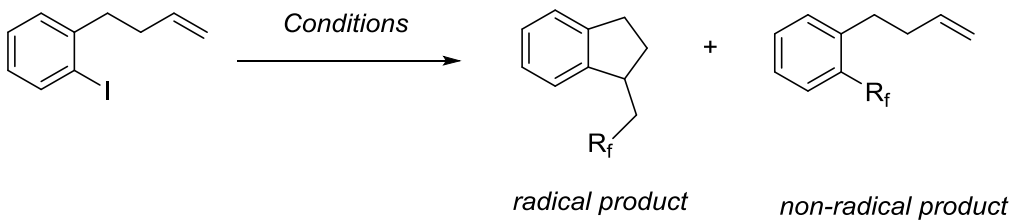
Scheme 3.16. Reactivity of Iodopyridines.

However, when a less reactive substrate (such as 4-iodoanisole) was used, significant byproduct formation was observed. One of the major byproducts is 1,6-dihydrododecafluorohexane. It is unclear whether it forms by a radical or two electron method. It has been proposed that the trifluoromethylation of aryl halides using [$CuCF_3$] is a non-radical process.[23,24] Interestingly, the dizinc complex **3gg** decomposes quantitatively to H-$(CF_2)_6$-H when heated at 100 ºC in only acetonitrile, but minimal formation of H-$(CF_2)_6$-H under the same conditions in DMSO. Knowing this, the model reaction from Table 3.2 was compared with and without radical source. Addition of TEMPO, according to Scheme 3.17, heavily suppressed the formation of **3hh**. No TEMPO adduct was observed; instead the major byproducts were **3tt** and **3uu.** In the future, a better radical clock experiment could be used for the elucidation of possible single-electron-transfer mechanism (SET). A good radical probe would be 2-(2-propen-1-

yloxy)iodobenzene or o-(3- butenyl)iodobenzene, which have been used in copper trifluoromethyl systems to identify radical vs. non-radical pathways (Scheme 3.18).[24-26]



Scheme 3.17. Suppression of Catalysis Using TEMPO.



Scheme 3.18. Radical Trap Probe Mechanism.

3.3. Conclusions

Although all of the project goals have been addressed, they have not been answered to complete satisfaction. The C_4 dizinc complex **3t** still requires significant research to optimize for future catalytic fluoroalkylations. Determination of the active copper species is still desired for the elucidation of the mechanism. Most importantly, the role of the solvent should be investigated. Is DMSO really crucial, how does it bind to the

copper catalysis, and can ligand be developed that mimics its beneficial effects? Lastly, the role of radical chemistry should be explored further, hopefully determining why TEMPO is so deleterious.

Despite the shortcomings, this work represents a fertile research project for further examination of dinucleophiles for fluoroalkylation. The catalyst system can use as little as 10 mol% of copper acetate without need for additional ligand. While high concentrations of dizinc complex **3gg** are required, the formation of bis(aryl) perfluorohexane is achieved in good to excellent yield.

3.4. Experimental Details

3.4.1. Materials

Diethyl zinc was purchased from Sigma Aldrich as a 1.0 M solution in hexanes. 1,4-diiodooctafluorobutane (98% purity) was obtained from Synquest Labs Inc. All other chemical were verified by ^{1}H-NMR for purity and used without further purification. All solvents were purified by passing through activated alumina and/or copper in a solvent purification system supplied by Pure Process Technology or purchased anhydrous from Fisher Scientific (toluene, acetonitrile, DMF, and DMSO).

3.4.2. Instrumentation and Equipment

All manipulations were performed using standard Schlenk and high vacuum techniques or in a nitrogen filled glovebox. Solution ^{1}H-NMR spectra were recorded at ambient temperature on a Bruker DRX 500 MHz or Bruker Ascend 400 MHz spectrometer and referenced to residual proton solvent signals. Solution ^{13}C-NMR spectra were recorded on a Bruker DRX NMR spectrometer operating at 125 MHz or Bruker Ascend NMR operating at 101 MHz and referenced to solvent signals. All ^{19}F-NMR

spectra were recorded on the Bruker NMR spectrometer operating at 470 MHz or Bruker Ascend NMR operating at 376 MHz and referenced to trifluorotoluene set at δ −63.7. Yields determined by ^{19}F NMR have an estimated error of 10%. A Bruker D8 Quest diffractometer was used for X-ray crystal structure determinations.

3.4.3. Methods

3.4.3.1. Synthesis of Dizinc Complexes

3.4.3.1.1. $[(MeCN)_2Zn((CF_2)_4)_2Zn(MeCN)_2]$ (3t)

An 8 mL portion of a 1.0 M diethyl zinc solution in hexanes was prechilled in a vial to −78 °C under a nitrogen atmosphere. 1,4-Diiodooctafluorobutane (1.82 g, 4.01 mmol) was diluted with 8 mL of pentane and was also prechilled to −78 °C. The zinc solution was then added dropwise to the 1,4-diiodooctafluorobutane solution at −78 °C. The reaction vial was then stirred for 3 h at −20 °C. After 3 h, 4 mL of MeCN was then added and the mixture was stirred vigorously for 15 mins and warmed to room temperature. The pentane layer was decanted away and the solution dried down. The sticky solid was washed with benzene and dried down overnight on a high-vacuum line. The product **3t** was obtained in 91.2% yield as a white solid.

3.4.3.1.2. $[(MeCN)_2Zn((CF_2)_6)_2Zn(MeCN)_2]$ (3gg)

Same as reported procedure except ligating solvent is acetonitrile.[13]

3.4.3.2. General Procedure for the Synthesis of Acyclic Fluoroorganic Compounds (C_4 Chain length)

The zinc complex **3t** (69 mg, 1.0 mmol) was massed in a 20 mL vial and dissolved in 1.00 mL of dimethyl sulfoxide (DMSO). Sequential addition of aryl iodide (0.200 mmol) and finally 10 mol% of copper acetate (2.5 mg, 0.020 mmol) were mixed

into the vial. 0.012 mL of α,α,α-trifluorotoluene (TFT, 0.098 mmol) was syringed into the vial as the internal standard. The solution was transferred to a J Young NMR tube with a Teflon screw cap and heated overnight (12 hours) at 100 °C.

3.4.3.2.1. Analytical data for 1,4-bis(2-pyridyl)perfluorobutane (3u)

^{19}F NMR ($CDCl_3$, 470 MHz): δ –115.10 (s, 4F), –122.52 (s, 4F). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.76 (d, J_{HH} = 3.8 Hz, 1H), 7.87 (t, J_{HH} = 7.5 Hz, 1H), 7.70 (d, J_{HH} = 7.7 Hz, 1H), 7.48 (m, J_{HH} = 3.8 Hz, 1H).

3.4.3.2.2. Analytical data for 1,4-bis(4-biphenyl)perfluorobutane (3x)

^{19}F NMR (DMSO, 470 MHz): δ –102.28 (s, 4F), –121.81 (s, 4F).

3.4.3.2.3. Analytical data for 1,4-bis(2-naphthyl)perfluorobutane (3y)

^{19}F NMR (DMSO, 470 MHz): δ –111.46 (s, 4F), –123.31 (s, 4F).

3.4.3.2.4. Analytical data for 1,4-bis(2-bromophenyl)perfluorobutane (3z)

^{19}F NMR (DMSO, 470 MHz): δ –112.36 (s, 4F), –123.63 (s, 4F).

3.4.3.2.5. Analytical data for 1,4-bis(phenyl)perfluorobutane (3aa)

^{19}F NMR (DMSO, 470 MHz): δ –112.14 (s, 4F), –123.62 (s, 4F).

3.4.3.2.6. Analytical data for 1,4-bis(4-methoxyphenyl)perfluorobutane (3bb)

^{19}F NMR (DMSO, 470 MHz): δ –111.05 (s, 4F), –123.70 (s, 4F).

3.4.3.2.7. Analytical data for 1,4-bis(4-cyanophenyl)perfluorobutane (3cc)

^{19}F NMR (DMSO, 470 MHz): δ –113.05 (s, 4F), –123.44 (s, 4F).

3.4.3.3. General Procedure for the Synthesis of Cyclic Fluoroorganic Compounds

The zinc complex **3t** (69 mg, 1.0 mmol) was massed in a 20 mL vial and dissolved in 1.00 mL of dimethyl sulfoxide . Sequential addition of diiodoarene (0.100 mmol) and finally 10 mol% of copper acetate (2.5 mg, 0.020 mmol) were mixed into the

vial. 0.012 mL of α,α,α-trifluorotoluene (TFT, 0.098 mmol) was syringed into the vial as the internal standard. The solution was transferred to a J Young NMR tube with a Teflon screw cap and heated overnight (12 hours) at 100 °C. Products **3dd-3ff** matched previous reported analytical valules.[13,17]

3.4.3.4. General Procedure for the Synthesis of Acyclic Fluoroorganic Compounds (C_6 Chain length)

The zinc complex **3gg** (179 mg, 2.00 mmol) was massed in a 20 mL vial and dissolved in 1.00 mL of Dimethyl sulfoxide (DMSO). Sequential addition of aryl iodide (0.200 mmol) and finally 10 mol% of copper acetate (2.5 mg, 0.020 mmol) were mixed into the vial. 0.012 mL of α,α,α-trifluorotoluene (TFT, 0.098 mmol) syringed into the vial as the internal standard. The solution was transferred to a J Young NMR tube and Teflon screw cap and heated overnight (12 hours) at 100°C.

3.4.3.4.1. Analytical data for 1,6-bis(4-biphenyl)perfluorohexane (3hh)

Same as previously reported analytical values.[13]

3.4.3.4.2. Analytical data for 1,6-bis(2-pyridyl)perfluorohexane (3ii)

^{19}F NMR (DMSO, 376 MHz): δ –115.18 (s, 4F), –123.75 (s, 4F), –124.16 (s, 4F).

3.4.3.4.3. Analytical data for 1,6-bis(4-methoxyphenyl)perfluorohexane (3jj)

^{19}F NMR (DMSO, 470 MHz): δ –110.92 (s, 4F), –123.62 (s, 4F), –124.20 (s, 4F).

3.4.3.4.5. Analytical data for 1,6-bis(4-nitrophenyl)perfluorohexane (3kk)

^{19}F NMR (DMSO, 376 MHz): δ –112.61 (s, 4F), –123.48 (s, 4F), –123.86 (s, 4F).

3.4.3.4.6. Analytical data for 1,6-bis(4-(trifluoromethyl)phenyl)perfluorohexane (3ll)

^{19}F NMR (DMSO, 376 MHz): δ –64.54 (s, 6F), –112.82 (s, 4F), –123.58 (s, 4F), –124.06 (s, 4F).

3.4.3.4.7. Analytical data for 1,6-bis(2-thiophenyl)perfluorohexane (3mm)

^{19}F NMR (DMSO, 376 MHz): δ –102.19 (s, 4F), –123.63 (s, 4F), –123.89 (s, 4F).

3.4.3.4.8. Analytical data for 1,6-bis(4-fluorophenyl)perfluorohexane (3nn)

^{19}F NMR (DMSO, 376 MHz): δ –109.36 (s, 2F), –111.49 (s, 4F), –123.57 (s, 4F), –124.16 (s, 4F).

3.4.3.4.9. Analytical data for 1,6-bis(4-iododophenyl)perfluorohexane (3oo)

^{19}F NMR ($CDCl_3$, 376 MHz): δ –112.19 (s, 4F), –122.34 (s, 4F), –123.00 (s, 4F).

3.4.3.4.10. Analytical data for 1,6-bis(3-pyridyl)perfluorohexane (3rr)

^{19}F NMR (DMSO, 376 MHz): δ –114.64 (s, 4F), –123.59 (s, 4F), –124.27 (s, 4F).

3.4.3.4.11. Analytical data for 1,6-bis(4-pyridyl)perfluorohexane (3ss)

^{19}F NMR (DMSO, 376 MHz): δ –113.02 (s, 4F), –123.49 (s, 4F), –124.17 (s, 4F).

3.4.3.5. TEMPO Suppression of Acyclic Fluoroorganic Compounds (C_6 Chain length)

The zinc complex **3gg** (179 mg, 2.00 mmol) was massed in a 20 mL vial and dissolved in 1.00 mL of dimethyl sulfoxide. Sequential addition of aryl iodide (0.200 mmol), TEMPO ((2,2,6,6-Tetramethyl-piperidin-1-yl)oxyl, 0.200 mmol) and finally 10 mol% of copper acetate (2.5 mg, 0.020 mmol) were mixed into the vial. 0.012 mL of α,α,α-trifluorotoluene (0.098 mmol) syringed into the vial as the internal standard. The solution was transferred to a J Young NMR tube with a Teflon screw cap and heated overnight (12 hours) at 100 °C.

3.5. References

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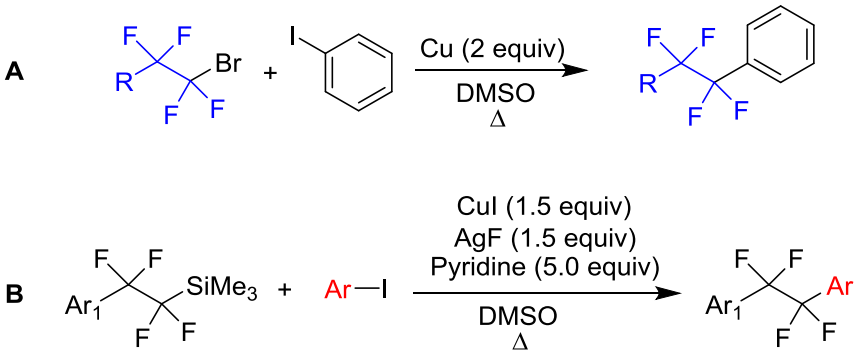
Chapter 4. Novel and Versatile Route to Arylated Fluoroalkyl Bromide Building Blocks

4.1. Background and Significance

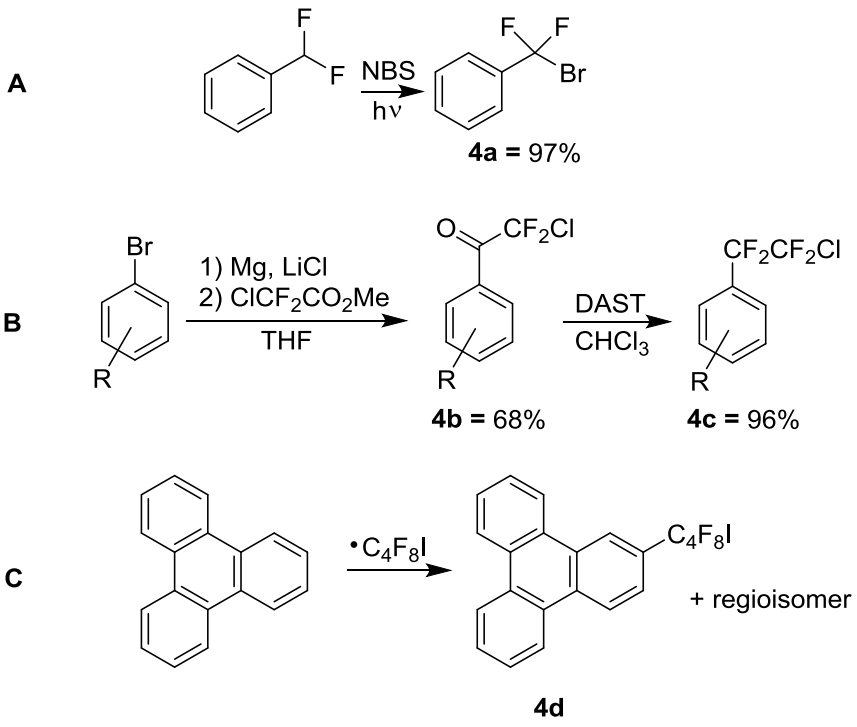
4.1.1. Protocols for Synthesis of Arylated Fluoroalkyl Halides

As discussed in Chapters 2 and 3, the preparation of symmetrically disubstituted fluoroalkanes are now better understood. However, facile synthetic routes to unsymmetrical derivatives are still scant. Arylated fluoroalkyl halides could be important building blocks for the preparation of unsymmetrically disubstituted fluoroalkanes, as described in Scheme 4.1, A.[1-5] Alternatively, aryl fluoroalkyl silyl species can also be used in routes for preparing unsymmetrical disubstituted derivatives (Scheme 4.1, B).[6] Despite the value of these difunctionalized species, versatile yet mild methods for their synthesis are lacking.



Scheme 4.1. Preparation of Unsymmetrically Disubstituted Tetrafluoroethanes.

Simple aryl difluoromethyl bromides **4a** can be prepared by subjecting difluoromethyl phenyl to *N*-bromosuccinimide (NBS) under sunlight/sunlamp in excellent yields, as highlighted in Scheme 4.2A.[7] Unfortunately, only simply building blocks can be formed in this manner. Gouverneur and coworkers presented a very elegant pathway to prepare aryltetrafluoroalkyl chlorides (Scheme 4.2 B).[6] First, the Grignard reagents were formed from aryl bromides, then the Grignard intermediate, were treated with chlorodifluoroacetate in the presence of LiCl to form product, like **4b**. Second, the ketone in **4b** was converted into a difluoromethylene group to afford **4c** using *N*,*N*-diethylaminosuflur trifluoride (DAST). The harsh conditions prevent this this methodology from being extended to other functionalized aryl groups. Alcohols, aldehydes, and ketones are not well tolerated and the chain length is restricted to tetrafluoroethyl linkers.[6] Strauss and Boltalina et al. demonstrated the ability to prepare fluoroalkyliodide radicals from α,ω-diiodoperfluorobutanes which combine with triphenylene to achieve the aryloctafluorobutyl iodide (Scheme 4.2 C).[5] Although this synthesis would be amenable to other chain lengths, the formation of an isomer makes obtaining high quantities of pure material more difficult. Ultimately, if a facile difunctionalized reagent could be prepared for controlled arylation (monosubstitution), then a milder route to the anticipated product could be accessed.

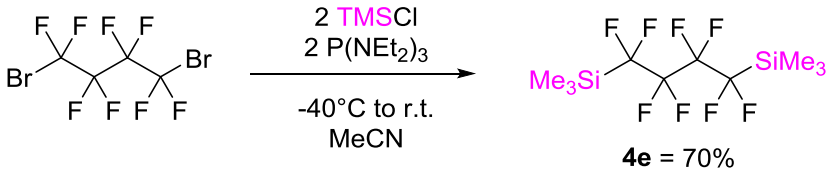


Scheme 4.2. Synthesis of Arylated Fluoroalkyl Halides.

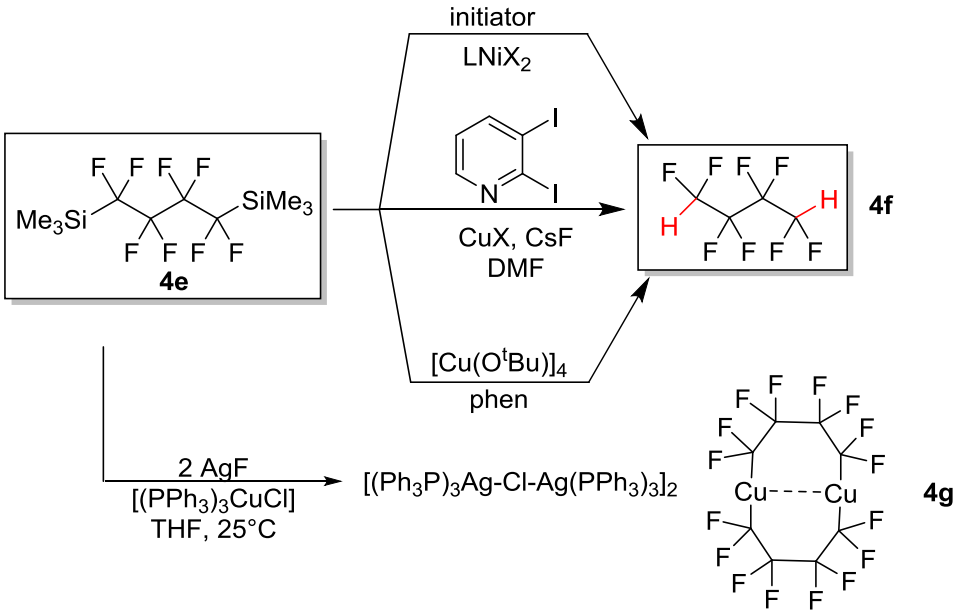
4.1.2. Difunctionalized Silyl Reagents for Polydifluoromethylenation

Vicic and coworkers hoped to find an improved method for installing repeating difluoromethylene groups of variable size. Using the original preparations reported by Ruppert and Prakash, they synthesized gram quantities of bench-top stable 1,4-(disilyl)octafluorobutane in 75% yield (Scheme 4.3).[8-10] X-ray crystallography of the low melting point solid confirmed the product to indeed be **4e**. Activation of the silane with various bases, such as MF or MO^tBu, in the presence of substrate (such as nickel dihalide, copper and aryl dihalide, or $[Cu(O^tBu)]_4$ and phen), however, only lead to high yields of the hydrodesilylated product (Scheme 4.4).[10] Transformation of **4e** was achieved when AgF and $[(Ph_3P)_3CuCl]$ was employed (Scheme 4.4). The new complex **4g** formed was found to have an identical ^{19}F NMR spectrum (δ -115.7 and -139.4) with

previously reported dicuprate, which is inactive in coupling reactions.[11] X-ray crystallography confirmed the identity of **4g**.[10]



Scheme 4.3. Synthesis of (Disilyl)octafluorobutane.

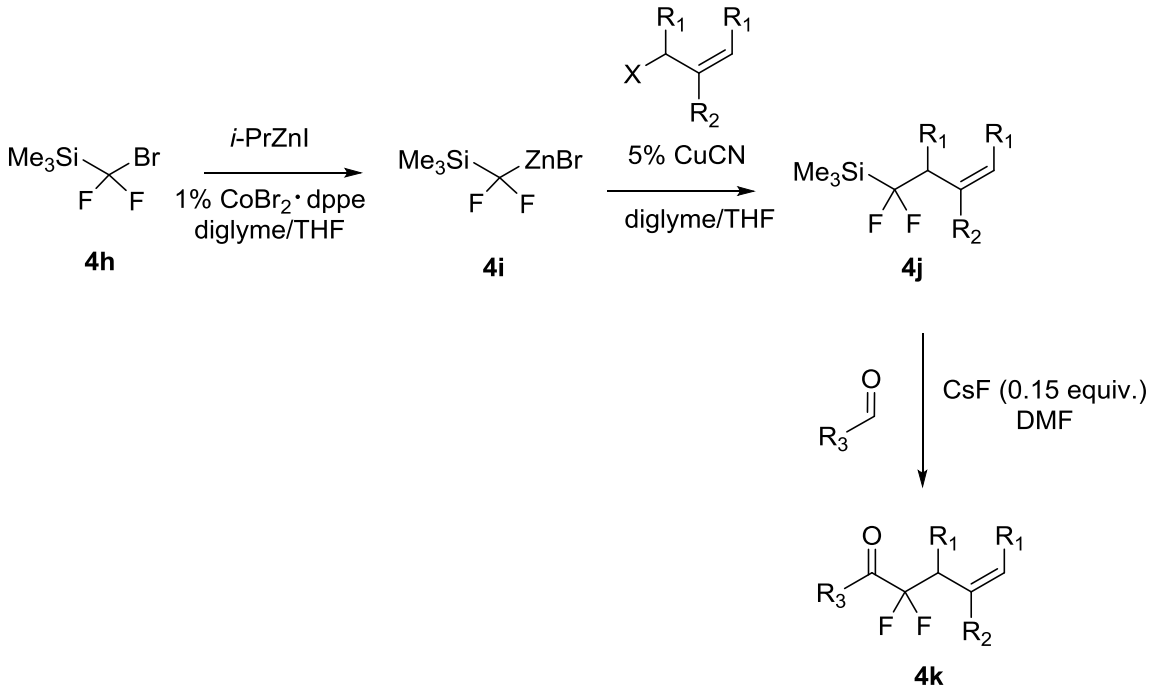


Scheme 4.4. Reactivity of Disilane Reagent.

4.1.3. Bifunctionalized Reagents for Difluoromethylenation

Although the bis(silyl) reagents such as **4e** may not effective precursors for fluoroalkylation reactions, Dilman *et al*. discovered that using the commercially available silane, $Me_3Si(CF_2)Br$, they could prepare a variety of unsymmetrically disubstituted products as highlighted in Scheme 4.5.[12-14] The two distinct functionalities of **4h** permit

for the selective transformation of either the electrophilic or nucleophilic site. Dilman found that treating **4h** with isopropyl zinc iodide forms the nucleophile **4i**, which reacts with electrophiles under copper-catalytic conditions. The resulting species **4j** was activated by catalytic amounts of fluoride in the presence of aldehyde to achieve the desired disubstituted compound **4k**. However, more complex bifunctionalized reagents analogous to **4h** are unavailable, preventing exploration of longer fluorocarbon chain containing compounds.

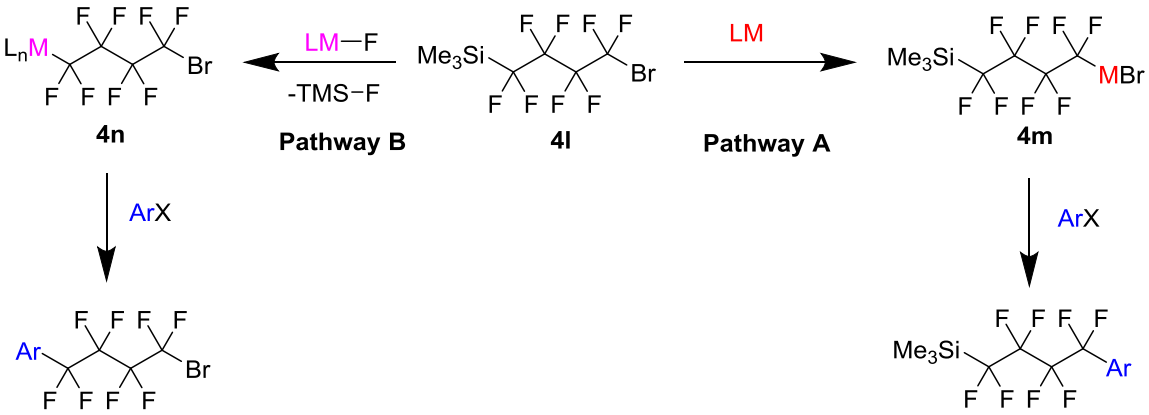


Scheme 4.5. Reactivity of Geminal Silyl/Bromo Reagent **4h**.

4.1.4. Project Goals

The aim of this project was to discover a more versatile method for the preparation of bifunctionalized reagents. Inspired by Dilman and coworkers, an α-bromo-ω-silyl fluoroalkane reagents appeared to be promising targets for this investigation.

Compound **4l,** reported in Scheme 4.6, was chosen as a novel reagent for perfluorobutylation. If **4l** were successfully synthesized, two synthetic routes would be made available. Pathway A in Scheme 4.6 could use previously published protocols to achieve **4m** as an reactant in copper-mediated cross-couplings.[11,15] Alternatively, Pathway B in Scheme 4.6 could be explored using metal fluorides to prepare arylated fluoroalkylated bromides through species **4n**.[16-18]



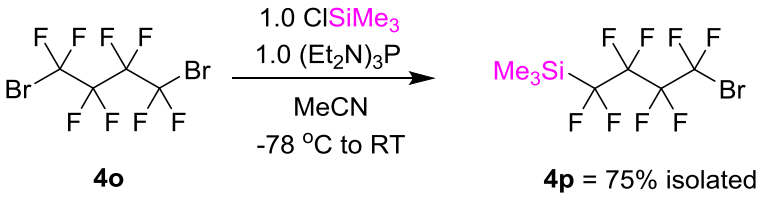
Scheme 4.5. Proposed Protocols for Fluoroalkylations Made Available by **4l**.

4.2. Results and Discussion

4.2.1. Novel Bifunctionalized Silyl/Bromo Reagents for Fluoroalkylation

Revisiting the reaction from Scheme 4.3, I attempted to partially silylate dibromofluoroalkane **4o** with 0.5 equivalents of trimethylsilyl chloride and tris(diethylamino)phosphine in Scheme 4.6.[8-10] Fortunately, the α-bromo-ω-silyl fluoroalkane **4p** was formed in good yield as a colorless oil.[19] Monosilylation of the α-,ω-dibromofluoroalkane could be only achieved selectively at low temperatures. If temperature was allowed to warm too quickly or the reaction stirred for more than three

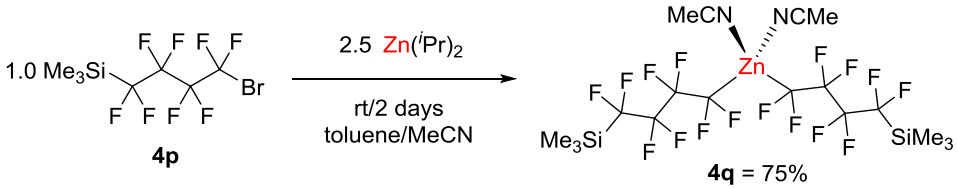
and a half hours, the disilyl species **4e** was observed. The reagent **4p** could be prepared in gram quantities and stored under dry conditions on the benchtop.



Scheme 4.6. Synthesis of Bisfunctionalized Silyl/Bromo Reagent.

4.2.2. Activation of the Carbon-Bromide Bond Using Dialkyl Zinc

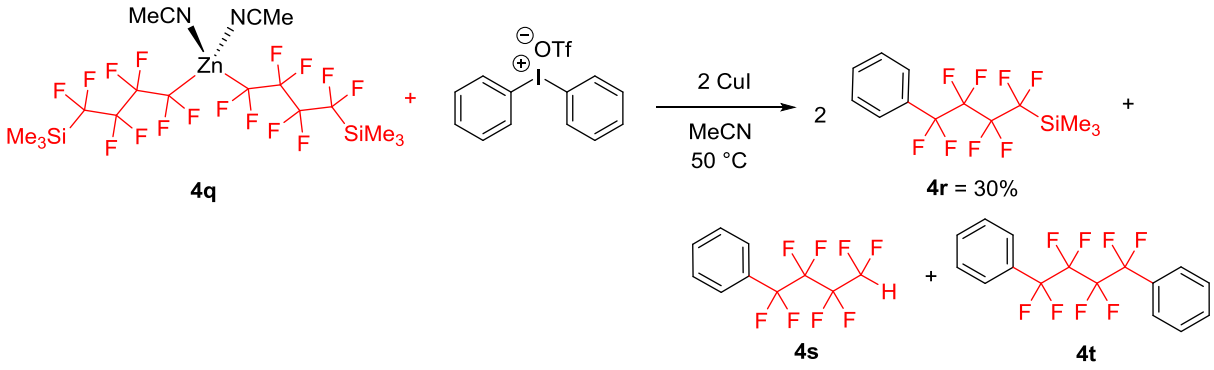
To probe Br-C bond activation, **4p** was allowed to react with a variety of dialkyl zinc reagents in attempt to prepare bis(fluoroalkyl)zinc complexes. Preparation of a bis(fluoroalkylsilane) zinc species was observed, characterized and confirmed by X-ray crystallography (Scheme 4.7). The yield of the reaction was 75% of white solid. Unlike previous dinucleophiles prepared by our lab with diethyl zinc, diisopropyl zinc was required as more active halogen exchange reagent.[11] The reaction needs both superstoichiometric amounts of $Zn(^{i}Pr)_2$, an expensive reagent, and long reaction times (about 2 days) to reach completion.



Scheme 4.7. Formation of the Bis(octafluorobutyl(trimethylsilyl)) Zinc Complex **4q**.

With species **4q** in hand, I explored its reactivity towards arylated perfluorobutylsilane formation. When reacted with aryl iodides under copper-mediated

coupling conditions, consumption of zinc reagent was rapid, but the product formation was prevented by the decomposition of the silane through protodesilylation which occurred even after just a few hours (product **4s**, Scheme 4.8). This decomposition arose even with very reactive electrophiles, such as aryl iodonium salts, which only led to 30% of the desired product 4**r** detected by ^{19}F NMR spectroscopy (Scheme 4.8.) Formation of bis(arylated) product **4t** was also observed under those reported conditions. This result indicates that the activation of the silane by copper halide further complicates the reaction. Recognizing the inherent difficulty in tuning the system and the reactivity of the silane, I turned to researching activation of the more facile carbon-silane bond.

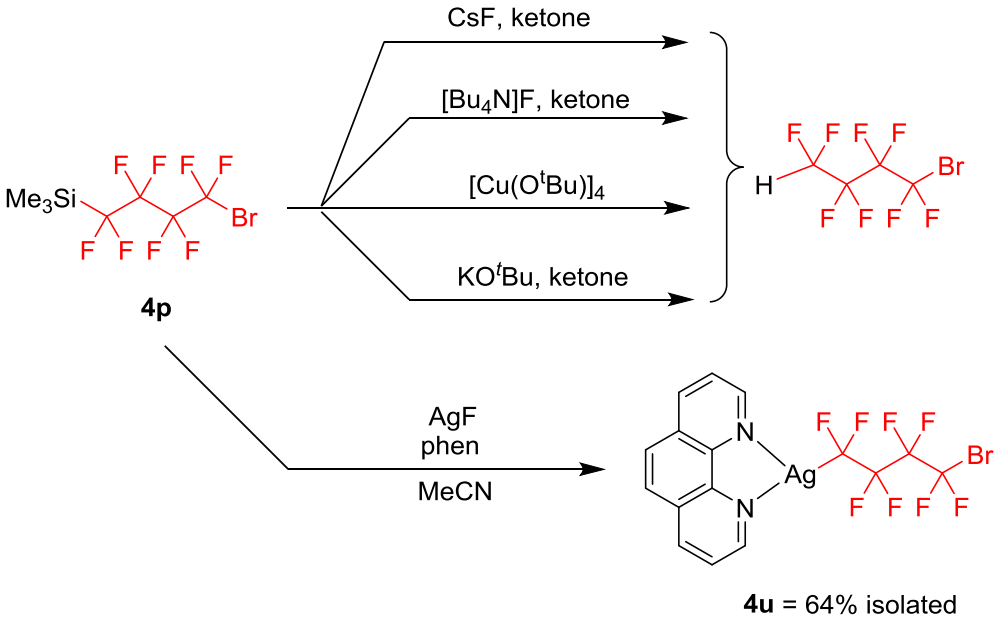


Scheme 4.8. Reactivity of Zinc Complex **4q** with Aryl Iodonium Salts.

4.2.3. Discovery of a Novel Silver Octafluoroalkyl Bromide Complex

Given that the carbon-silyl bond was quite reactive in reagent **4p**, it might be possible to exploit that reactivity for the preparation of arylated fluoroalkyl bromides. All initial reagents, however, promoted only protodesilylation (Scheme 4.9). Silver fluoride was the one exception. After its addition, four new peaks in MeCN at δ –64.18, –112.58 (d, J = 40 Hz), –117.69, and –119.78 were observed by ^{19}F NMR spectroscopy. Given

that silver reagents can be used as nucleophiles for transmetalation, I opted to synthesize an isolable silver reagent.[17,20-24] Ligation with phen facilitated clean precipitation of free flowing white solid **4u** in moderate yield (Scheme 4.9).[19] X-ray crystallography confirmed that **4u** was the first isolable, well characterized, bifunctionalized silver reagent (Figure 4.1).



Scheme 4.9. Activation of Silyl Moiety in **4p** and Formation of Novel Silver Complex **4u**.

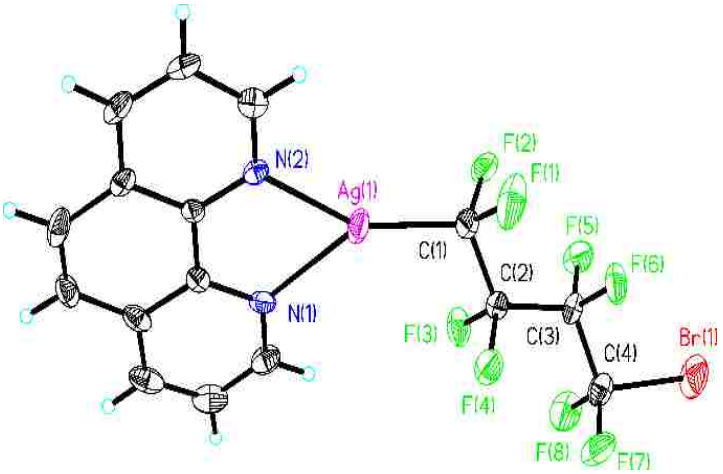
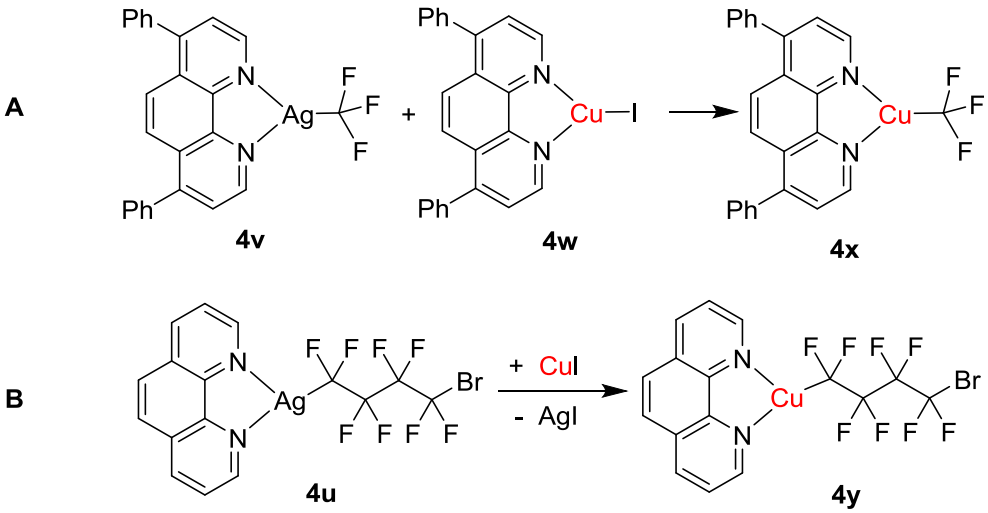


Figure 4.1. ORTEP Diagram of **4u**. Selected bond lengths (Å): Ag1−C1 2.096(10); Ag1−N2 2.281(7); Ag1−N1 2.353(8). Selected bond angles (deg): C1−Ag1−N2 150.5(3); C1−Ag1−N1 137.6(3); N2−Ag1−N1 71.9(3).

4.2.3. Formation of Active Fluoroalkyl Bromide Copper Complex

Haung and coworkers reported the synthesis of ligated silver trifluoromethylations using a copper iodide system (Scheme 4.10, A).[23] They detail that [(bathophen)$AgCF_3$] (**4v)** reacted with [(bathophen)CuI] (**4w**) to yield 80% of **4x** (Scheme 4.10, A). The trifluoromethyl copper species **4x** is active for trifluoromethylations of aryl iodides. Testing the bifunctionalized silver complex **4u** under similar conditions, I found it readily undergoes transmetalation to the copper species **4y** (highlighted in Scheme 4.10, B). Additionally, both the active octafluorobutyl bromide ligand and the ancillary phen ligand were transferred yielding quantitative (^{19}F NMR) yields after just 5 minutes and 67% isolated blood orange needles. The copper species is shock-sensitive and difficult to isolate, slow precipitation at low temperatures

allowed for the preparation of X-ray quality crystals. An ORTEP diagram of **4y** is shown in Figure 4.2.



Scheme 4.10. Transmetalation of Silver Fluoroalkyl Reagents

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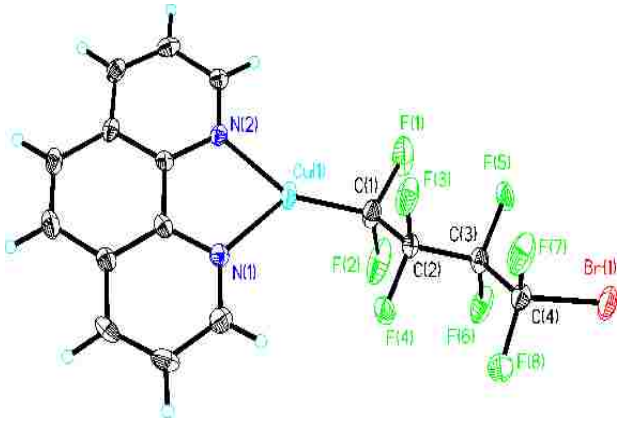
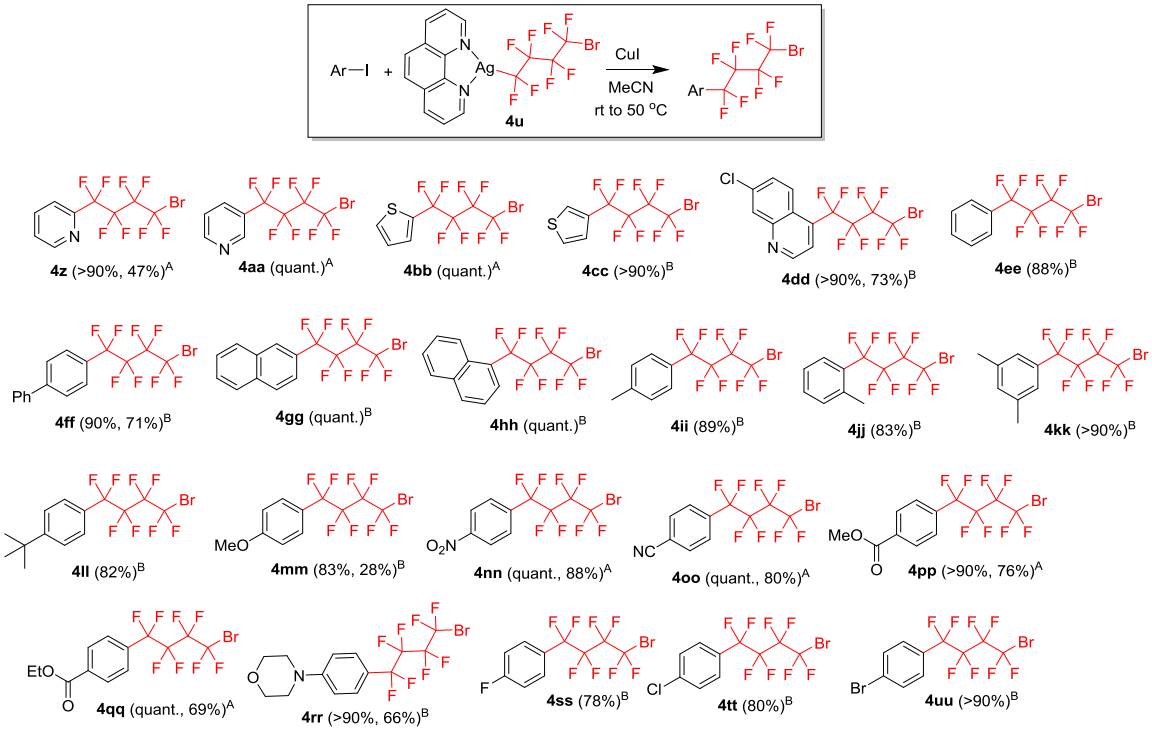


Figure 4.2. ORTEP Diagram of **4y**. Selected bond lengths (Å): Cu1−C1 1.928(7); Cu1−N2 2.022(4); Cu1−N1 2.091(5). Selected bond angles (deg): C1−Cu1−N2 145.5(3); C1− Cu1−N1 133.1(2); N2−Cu1−N1 80.78(19).

4.2.4. Synthetic Protocol for Arylated Octafluorobutyl Bromide Compounds

Having demonstrated that **4u** was an effective reagent for transmetalation, I hoped to explore its ability to prepare arylated fluoroalkyl bromide building blocks. Encouragingly, not only was the protocol reported in Scheme 4.11 achieved under mild conditions, but complete retention of bromide moiety was also found.[19] The preparation of heterocycles **4z-4dd** proceeded to give excellent yields, electron rich arenes **4ff-4mm** achieved good to excellent yields, and electron poor arenes **4nn-4rr** gave excellent yields. The transformation of aryl iodides in the presence of -F, -Cl, and -Br was also well tolerated (**4ss-4uu**).[19] Electron-deficient or sufficiently active aryl iodides ran at room temperature. Electron rich arenes needed an additional heating at 50°C overnight to achieve good yields of arylated fluoroalkyl bromide building blocks.

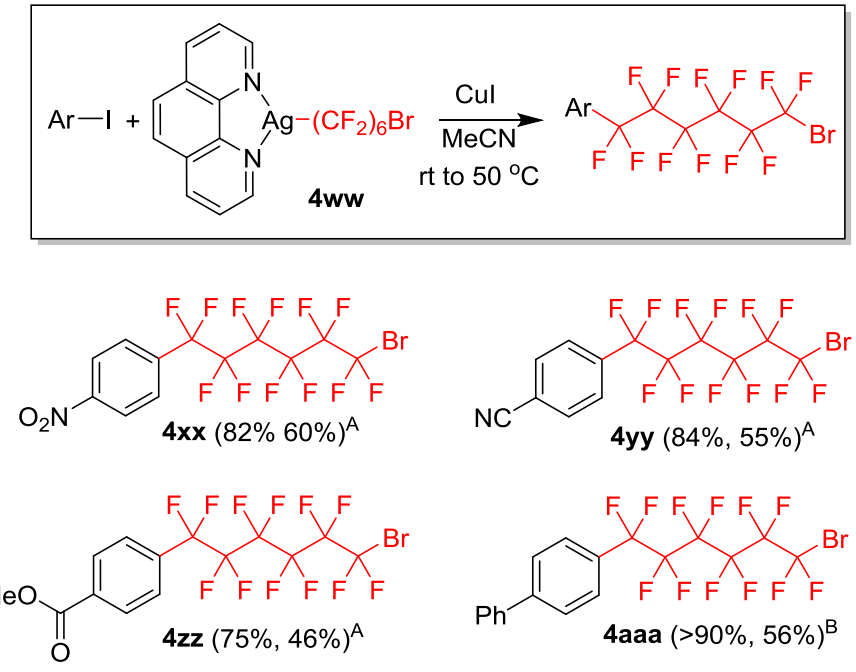


Scheme 4.11. Arylated Fluoroalkyl Bromide Building Blocks. The yields of $Ar(CF_2)_4Br$ were determined by ^{19}F NMR spectroscopy using α,α,α-trifluorotoluene as internal

standard. Isolated yields of nonvolatile products are the second number in parentheses. [A]Reactions run at room temperature for 24 h. [B]Reactions run at room temperature for 20h followed by an additional 24 h at 50 °C.

4.2.5. Expanding to Longer Chain Lengths

The methodology highlighted in Scheme 4.11, should also be applicable to not just the $(CF_2)_4$ synthon, but also to longer-chain derivatives. Preparing the respective silyl reagent TMS-$(CF_2)_6$-Br (**4vv**) and silver reagent **4ww** under identical conditions (see methods), transformation of the selected aryl iodides was possible under mild conditions (Scheme 4.12).[19] Yields of **4xx-4aaa** were respectable compared with their octafluorobutyl analogues reported in Scheme 4.11.



Scheme 4.12. Protocol Involving Longer Fluoroalkyl Chain Lengths Arylated Fluoroalkyl Bromide Building Blocks. The yields of Ar$(CF_2)_4$Br were determined by ^{19}F

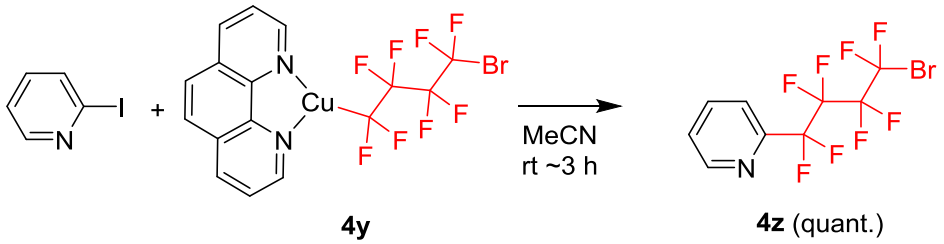
NMR spectroscopy using α,α,α-trifluorotoluene as internal standard. Isolated yields of nonvolatile products are the second number in parentheses. [A]Reactions run at room temperature for 24 h. [B]Reactions run at room temperature for 20 h followed by an additional 24 h at 50 °C.

Isolated yields and those determined by ^{19}F NMR spectroscopy vary for some products. This variation is due to several reasons: products and reactants have similar boiling points making distillation difficult, products and reactants have similar retention times on silica gel causing some product to be contaminated (therefore not collected in final mass), and some products are sensitive to the silica gel separation and exhibit decomposition. **2pp** exhibited significant loss (55% recovery) when pure product was test on column. However, arylated fluoroalkyl bromide compounds do not decompose in water.

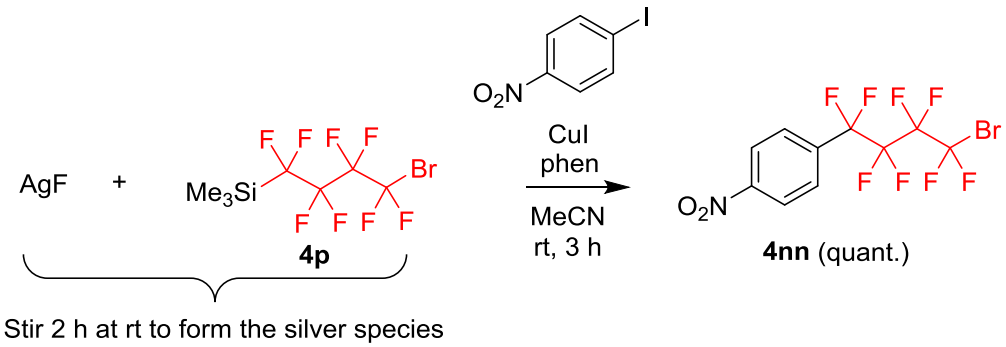
4.2.6. Active Complex and *In Situ* Reaction

Reactions can also be mediated by the isolated copper species **4y** (Scheme 4.13). Complex **4y** shows excellent reactivity, and quantitative product formation (**4z**) can be observed by ^{19}F NMR spectroscopy in about three hours. The copper complex, (phen)CuI, was recovered as a precipitate from the reaction (it also can be recovered from reactions described in Scheme 4.11-4.12). It should be noted, attempts to prepare the copper species directly failed when AgF was not used as the activator of the silyl reagent. Investigation into the mechanism found that addition of copper(I) iodide, 1,10-phenanthroline, and aryl iodide to a solution of silver(I) fluoride and α-bromo-ω-silyl octafluorobutane (**4p**) consumed the *in situ* silver species (Scheme 4.14). Quantitative

formation of the product **4nn** was observed after three hours. In electron rich systems, the (phen)Cu(CF_2)$_n$Br was observed indicating oxidative addition of the aryl halide is most likely the rate limiting step.



Scheme 4.13. Fluoroalkylation Using the Copper Intermediate **4y**.



Scheme 4.14. *In Situ* Preparation of **4u** for the Synthesis of Arylated Fluoroalkyl Bromide Building Blocks.

4.3. Conclusions

The goal of the work in this chapter was to discover new bifunctionalized reagents that would be versatile, easy to use, and tolerant of functional groups. The novel unsymmetrically difunctionalized silyl reagent is a convenient precursor that can be prepared in gram scale and used for the preparation of arylated fluoroalkyl bromide buildings blocks. Most encouragingly, the motif is applicable to different fluorocarbon

chain lengths under very mild conditions. Therefore, both functional group tolerance and versatility are achieved which allows for a large library of building blocks from commercially available aryl iodides. Lastly, the observation that the copper fluoroalkyl complexes can be prepared from preligated silver analogues sans preligated copper salt is an important discovery for future fluoroalkylation methodologies.

4.4. Experimental Details

4.4.1. Materials

All metal reagents were purchased from Sigma Aldrich. 1,4-dibromooctafluorobutane (98% purity) and 1,6-dibromododecafluorohexane (98% purity) were purchased from SynQuest Labs, Inc. and used without further purification. All other chemical were verified by ^{1}H-NMR for purity and used without further purification. All solvents were purified by passing through activated alumina and/or copper in a solvent purification system supplied by Pure Process Technology or purchased anhydrous from Fisher Scientific (toluene, acetonitrile, and DMF).

4.4.2. Instrumentation and Equipment

All manipulations were performed using standard Schlenk and high vacuum techniques or in a nitrogen filled glovebox. Solution ^{1}H-NMR spectra were recorded at ambient temperature on a Bruker DRX 500 MHz spectrometer and referenced to residual proton solvent signals. Solution ^{13}C-NMR spectra were recorded on a Bruker NMR spectrometer operating at 125 MHz and referenced to solvent signals. All ^{19}F-NMR spectra were recorded on the Bruker NMR spectrometer operating at 470 MHz and referenced to α,α,α-trifluorotoluene set at δ −63.7. Yields determined by ^{19}F NMR have an estimated error of 10%. A Bruker D8 Quest diffractometer was used for X-ray crystal

structure determinations. Elemental Analyses were performed at Midwest Microlab, LLC. Mass spectral data (low res) was recorded on a HP 5890 Series II Plus GC/MS. High Resolution Mass Spectroscopy was performed by University of Notre Dame's Mass Spectrometry and Proteomics Facility.

4.4.3. Methods

4.4.3.1. Procedure for the Synthesis of α-Bromo-ω-silyl Perfluoroalkanes

4.4.3.1.1. Synthesis of 1-Bromo-4-(trimethylsilyl)perfluorobutane (4p)

To a 100 mL round bottom flask 14.286 g (39.701 mmol) of 1,4-dibromoperfluorobutane was added under N_2 atmosphere followed by addition of 5.20 mL (41.0 mmol) of chlorotrimethylsilane and 34 mL of acetonitrile (MeCN). Chilled solution at –78 ^{o}C for 30 minutes, and then slowly add 11.2 mL (40.9 mmol) of tris(diethylamino)phosphine and stir for 3.5 h at –78 ^{o}C and allow it to warm to room temperature. The mixture was evaporated under vacuum while heating the round bottom flask to 50 ^{o}C and collecting all volatile material in the cooled trap after about 1-2 h. The solution from the trap was collected and organic layer was extracted using pentane/water mixture in a separator funnel and dried over Na_2SO_4. Reactants/by-products and solvent were removed under vacuum (30-34 ^{o}C, 500 Torr for 15-30 min). Finally, the product was vacuum transferred over on the high vacuum line. The isolated yield of the colorless oil **4p** was 75% (11 g). ^{19}F NMR ($CDCl_3$, 470 MHz): δ –64.00 (t, J = 13.7 Hz, 2F), –118.13 (t, J = 14.4 Hz, 2F), –119.13 (t, J = 13.6 Hz, 2F), –129.25 (t, J = 13.9 Hz, 2F). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.31 (s, 9H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ 125.48 (tt, J = 274.1, 44.7 Hz), 116.08 (tt, J = 314.4, 38.2 Hz), 109.98 (t quin, J = 267.4, 34.0 Hz), 113.33 (t quin, J = 260.1, 31.2 Hz). Anal. Calcd for $C_7H_9BrF_8Si$: C, 23.81; H, 2.57.

4.4.3.1.2. Synthesis of 1-Bromo-6-(trimethylsilyl)perfluorohexane (4vv)

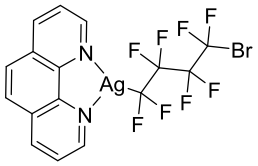
To a 20 mL vial 4.599 g (10.00 mmol) of 1,6-dibromoperfluorohexane was added under N_2 atmosphere followed by addition of 1.40 mL (11.0 mmol) of chlorotrimethylsilane and 10.0 mL of acetonitrile (MeCN). Chilled solution at –78 ^{o}C for 30 minutes, and then slowly add 2.80 mL (10.1 mmol) of tris(diethylamino)phosphine and stir for 3.5 h at –78 ^{o}C and allow it to warm to room temperature. The mixture was evaporated under vacuum while heating the round bottom flask to 50 ^{o}C and collecting all volatile material in the cooled trap after about 1-2 h. The solution from the trap was collected and organic layer was extracted using pentane/water mixture in a separator funnel and dried over Na_2SO_4. By-products and solvent were removed under vacuum (rt, 500 Torr for 5 min). Vacuum distillation of solution at 50-60 ^{o}C (about 30 minutes of heating) produced colorless liquid **4vv** in 31% yield (1.40 g). ^{19}F NMR ($CDCl_3$, 470 MHz): δ –64.25 (t, *J* = 14.4 Hz, 2F), –118.25 (s, 2F), –119.89 (s, 2F), –122.19 (s, 2F), –122.80 (s, 2F), –129.31 (t, *J* = 14.4 Hz, 2F). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.30 (s, 9H). Anal. Calcd for $C_9H_9BrF_{12}Si$: C, 23.86; H, 2.00. Found: C 22.86; H 1.61. Found: C 24.09; H 2.64

4.4.3.2. Procedure for the Synthesis of Bifunctionalized Fluoroalkyl Containing Metal Complexes

4.4.3.2.1. Preparation of Bis(acetonitrile)bis(perfluorobutyl-4-trimethylsilyl)zinc (4q)

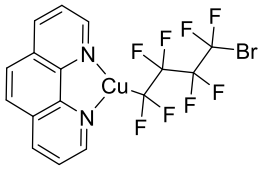
To a 20 mL vial 0.999 g (2.83 mmol) of 1-bromo-4-(trimethylsilyl)perfluorobutane was added under N_2 atmosphere followed by addition of 4 mL of toluene and 1.5 mL of acetonitrile. The solution was chilled for 10 min at –37°C

before the addition of 4.25 mL (1.00 M solution in toluene) of diisopropyl zinc. The solution stirred for 2 days at RT. The yellowish solution was dried down by high vacuum line for 1.5 h. The residue was dissolved in toluene and precipitated using ether in the freezer at –37°C. Precipitate was dried yielding **4q** in 75 % yield as a white solid. ^{19}F NMR (Toluene-d_8, 470 MHz): δ –121.00 (s, 2F), –123.43 (s, 2F), –124.86 (s, 2F), –128.48 (t, J = 12.2 Hz, 2F). ^{1}H NMR (Toluene-d_8, 300 MHz): δ 0.52 (s, 6H), 0.20 (s, 18H) Anal. Calcd for $C_{18}H_{24}F_{16}N_2Si_2Zn$: C, 31.16; H, 3.49. Found: C 30.84; H 3.75.



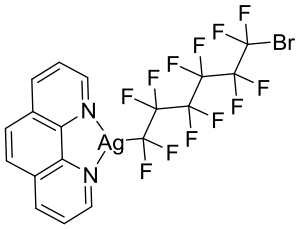
4.4.3.2.2. Preparation of Complex 4u

Addition of 0.389 g (3.07 mmol) of AgF was stirred in 5 mL of acetonitrile followed by 1.052 g (2.979 mmol) of 1-bromo-4-(trimethylsilyl)perfluorobutane. The mixture was stirred for 3.5 h and filtered through 0.2 μm PTFE syringe filter giving a yellow solution. 0.515 g (2.86 mmol) 1,10-phenanthroline (phen) was dissolved into 1.00 mL of acetonitrile before being added to the stirring silver solution. After 10 minutes of stirring, a white solid precipitate was visible. The off-white solid was collected on a filter funnel and washed 3x with 6 mL of ether. The white crystalline product **4u** was obtained in 64% yield, (1.04 g). Recrystallization of solid was possible using MeCN/ether to obtain colorless needles. ^{19}F NMR (THF-d_8, 470 MHz): δ –63.11 (t, J = 11.7 Hz, 2F), –106.77 (d, J = 53.8 Hz, 2F), –116.98 (t, J = 12.4 Hz, 2F), –118.40 (s, 2F). ^{1}H NMR (THF-d_8, 300 MHz): δ 9.07 (d, J = 4.3 Hz, 2H), 8.57 (d, J = 8.2 Hz, 2H), 8.01 (s, 2H), 7.90 (dd, J = 8.1, 4.6 Hz, 2H). Anal. Calcd for $C_{16}H_8F_8N_2AgBr$: C, 33.83; H, 1.42. Found: C 33.90; H 1.39.



4.4.3.2.3. Preparation of Complex 4y

In a 20 mL vial 64 mg (0.11 mmol) of (1,1,2,2,3,3,4,4-octafluoro-5-bromobutyl)(1,10-phenanthroline-κN^1,κN^{10})silver reagent and 3 mL of MeCN were stirred for 1 min. 31 mg (0.16 mmol) CuI was added to the stirring mixture forming a red solution. The reaction was stirred for 20 h at rt, followed by filtration of silver salt on a 0.2 μm PTFE filter. 16 mL of ether was added to the dark red-orange solution and it was placed in the freezer for 7 days at –37°C. Orange needles formed in 67% yield (39 mg) and confirmed to be **4y**. ^{19}F NMR (THF-d_8, 470 MHz): δ –62.32 (s, 2F), –110.38 (s, 2F), –116.73 (t, J_{FF} = 12.1 Hz, 2F), –119.94 (t, J_{FF} = 13.0 Hz 2F). ^{1}H NMR (MeCN-d_3, 300 MHz): δ 9.04 (s, 2H), 8.69 (s, 2H), 8.10 (s, 2H), 7.79 (s, 2H). Anal. Calcd for $C_{16}H_8F_8N_2Cu$: C, 36.70; H, 1.54. Found: C 36.59; H 1.47.



4.4.3.2.4. Preparation of Complex 4ww

Addition of 195 mg (1.42 mmol) of AgF was stirred with 4 mL of acetonitrile followed 646 mg (1.42 mmol) of 1-bromo-6-(trimethylsilyl)perfluorohexane. The mixture was stirred for 3.5 h and filtered through 0.2 μm PTFE syringe filter, giving a yellow solution. 0.255 g (1.42 mmol) 1,10-phenanthroline (phen) was dissolved into 1.00 mL of acetonitrile before being added to the stirring silver solution. After 10 minutes of stirring, a white solid precipitate was visible. The off-white solid was collected on a filter

funnel and washed 3x with 4 mL of ether. The off-white crystalline product **4ww** was obtained in 46% yield (438 mg). ^{19}F NMR (THF-d_8, 470 MHz): δ –65.38 (t, J = 14.3 Hz 4F), –108.86 (d, J = 52.4 Hz 2F), –118.10 (s, 2F), –118.90 (s, 2F), –121.62 (s, 2F), –121.84 (s, 2F). ^{1}H NMR (THF-d_8, 300 MHz): δ 9.02 (d, J = 3.4 Hz, 2H), 8.51 (dd, J = 8.1, 1.6 Hz, 2H), 7.97 (s, 2H), 7.84 (dd, J = 8.1, 4.5 Hz, 2H). Anal. Calcd for $C_{18}H_8AgBrF_{12}N_2$: C, 37.32; H, 1.57. Found: C 36.15; H 2.66.

4.4.3.3. General Synthesis of ArC_4F_8Br from Scheme 4.11

To a 20 mL vial, 60. mg (0.11 mmol) of $PhenAg(CF_2)_4Br$ was mixed in 1.0 mL of MeCN. Sequential addition of 0.10 mmol of Ar-I and 20. mg (0.11 mmol) of CuI were added to the vial. The solution changed from a white mixture to a reddish solution as solid precipitated to the bottom of the vial. After 1 day of stirring at room temperature, the solution was filtered through a 0.2 μm PTFE filter and washed with an additional 0.5 mL of MeCN into a re-sealable Air tight NMR tube. Yields were calculated against 0.012 mL of α,α,α-trifluorotoluene (0.098 mmol) internal standard. Reactions not complete were heated at 50 °C overnight to give full conversion.

For isolated products, 0.50 mmol (0.10 mmol excess of silver reagent and copper salt) reactions ran in 6.0 mL of MeCN with 5.0 mL of MeCN to transfer into re-sealable air tight ampules. Filtration was accomplished using fine frit glass filter funnels.

For gram scale reaction, (5.0 mmol, 0.10 mmol excess of silver reagent and copper salt) reaction ran in 33.0 mL of MeCN in a 100 mL RBF with 5.0 mL of MeCN to transfer. Filtration was accomplished using fine frit glass filter funnels. 58% of product was collected. Isolation was accomplished by removing solvent under reduced pressure followed by column chromatography using hexanes, hexanes/DCM 50%, or DCM.

4.4.3.3.1. Procedure for 2-(4-Bromo-1,1,2,2,3,3,4,4-octafluorobutyl)pyridine (4z)

Synthesised following general procedure 4.4.3.3. from 2-iodopyridine (0.50 mmol scale). Purification by flash silica column chromatography (eluent: 50% dichloromethane in hexanes) to yield >90% by internal standard, (84 mg, 47% yield isolated yield) as a light yellow oil. Analytical data for 2-(4-bromo-1,1,2,2,3,3,4,4-octafluorobutyl)pyridine (**4z**) ^{19}F NMR ($CDCl_3$, 470 MHz): δ –64.08 (t, *J* = 13.7 Hz, 2F), –115.12 (t, *J* = 13.1 Hz, 2F), –117.73 (t, *J* = 12.8 Hz, 2F), –122.09 (t, *J* = 12.9 Hz, 2F). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.78 (d, *J* = 4.7 Hz, 1H), 7.89 (td, *J* = 7.8, 1.7 Hz, 1H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.75 (dd, *J* = 7.7, 5.2 Hz, 1H). Exact mass (EI^+) calcd for $C_9H_4NF_8Br$ 356.9399, found 356.9427.

4.4.3.3.2. Procedure for 3-(4-Bromo-1,1,2,2,3,3,4,4-octafluorobutyl)pyridine (4aa)

Synthesised following general procedure 4.4.3.3. from 3-iodopyridine (0.10 mmol scale) and formed quantitative yield by internal standard, as a light yellow oil. Analytical data for 3-(4-bromo-1,1,2,2,3,3,4,4-octafluorobutyl)pyridine (**4aa**) ^{19}F NMR (MeCN-d_3, 470 MHz): δ –65.88 (s, 2F), –112.38 (s, 2F), –117.82 (s, 2F), –122.17 (s, 2F). ^{1}H NMR (MeCN-d_3, 300 MHz): δ 8.70-8.35 (m, 2H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.57 (dd, J = 6.0, 1.6 Hz, 1H). Exact mass (EI^+) calcd for $C_9H_4NF_8Br$ 356.9399, found 356.9400.

4.4.3.3.3. Procedure for 2-(4-Bromo-1,1,2,2,3,3,4,4-octafluorobutyl)thiophene (4bb)

Synthesised following general procedure 4.4.3.3. from 2-iodothiophene (0.10 mmol scale) and formed quantitative yield by internal standard, as a colorless oil. Analytical data for 2-(4-bromo-1,1,2,2,3,3,4,4-octafluorobutyl)thiophene (**4bb**) ^{19}F NMR (MeCN-d_3, 470 MHz): δ –65.82 (t, *J* = 14.3 Hz, 2F), –101.57 (t, *J* = 14.0 Hz, 2F), –117.86 (s, 2F), –121.90 (s, 2F). ^{1}H NMR (MeCN-d_3, 300 MHz): δ 7.80 (dd, *J* = 5.0, 1.3

Hz, 1H), 7.57 (d, *J* = 3.7 Hz, 1H), 7.26-7.20 (m, 1H). Exact mass (EI^+) calcd for $C_8H_3SF_8Br$ 361.9011, found 361.9008.

4.4.3.3.4. Procedure for 3-(4-Bromo-1,1,2,2,3,3,4,4-octafluorobutyl)thiophene (4cc)

Synthesised following general procedure 4.4.3.3. from 3-iodothiophene (0.10 mmol scale) to yield >90% by internal standard, as a colorless oil. Analytical data for 3-(4-bromo-1,1,2,2,3,3,4,4-octafluorobutyl)thiophene (**4cc**) ^{19}F NMR (MeCN-d_3, 470 MHz): δ –65.76 (t, *J* = 13.7 Hz, 2F), –106.81 (t, *J* =13.3 Hz, 2F), –117.99 (t, *J* = 13.8 Hz, 2F), –122.47 (s, 2F). ^1H NMR (MeCN-d_3, 300 MHz): δ 7.55 (dd, *J* = 3.0, 1.1 Hz, 1H), 7.35 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.14 (dd, *J* = 5.0, 1.1 Hz, 1H). Exact mass (EI^+) calcd for $C_8H_3SF_8Br$ 361.9011, found 361.9007.

4.4.3.3.5. Procedure for 7-Chloro-4-(4-bromo-1,1,2,2,3,3,4,4-octafluorobutyl)quinoline (4dd)

Synthesised following general procedure 4.4.3.3. from 7-chloro-4-iodoquinoline (0.10 mmol scale). Purification by flash silica column chromatography (eluent: dichloromethane) to yield >90% by internal standard, (32 mg, 73% yield isolated yield) as a white solid. Analytical data for 7-chloro-4-(4-bromo-1,1,2,2,3,3,4,4-octafluorobutyl)quinoline (**4dd**) ^{19}F NMR ($CDCl_3$, 470 MHz): δ –64.24 (t, *J* = 14.9 Hz, 2F), –107.86 (t, *J* = 14.3 Hz, 2F), –117.61 (t, *J* = 14.2 Hz, 2F), –112.17 (t, *J* = 14.2 Hz, 2F). ^1H NMR ($CDCl_3$, 300 MHz): δ 9.08 (s, 1H), 8.23 (s, 1H), 8.13 (s, 1H), 7.66 (s, 2H). Exact mass (EI^+) calcd for $C_{13}H_5NF_8ClBr$ 440.9166, found 440.9166

4.4.3.3.6. Procedure for 1-(4-Bromo-1,1,2,2,3,3,4,4-octafluorobutyl)benzene (4ee)

Synthesised following general procedure 4.4.3.3. from iodobenzene (0.10 mmol scale) to yield 88% by internal standard, as a colorless oil. Analytical data for 1-(4-bromo-1,1,2,2,3,3,4,4-octafluorobutyl)benzene (**4ee**) ^{19}F NMR ((MeCN-d_3, 470 MHz): δ –65.73 (s, 2F), –111.54 (s, 2F), –117.84 (s, 2F), –122.14 (s, 2F). ^{1}H NMR (MeCN-d_3, 300 MHz): δ 7.66 (d, J = 8.1 Hz, 2H), 7.59 (d, J = 8.1 Hz, 2H). Exact mass (EI$^+$) calcd for $C_{10}H_5F_8Br$ 355.9447, found 355.9465.

4.4.3.3.7. Procedure for 4-(4-Bromo-1,1,2,2,3,3,4,4-octafluorobutyl)biphenyl (4ff)

Synthesised following general procedure 4.4.3.3. from 4-iodobiphenyl (0.50 mmol scale). Purification by flash silica column chromatography (eluent: hexanes) to yield 90% by internal standard, (153.8 mg, 71% yield isolated yield) as a white solid. Analytical data for 4-(4-bromo-1,1,2,2,3,3,4,4-octafluorobutyl)biphenyl (**4ff**) ^{19}F NMR ($CDCl_3$, 470 MHz): δ –64.03 (t, J = 14.2 Hz, 2F), –111.59 (t, J = 14.6 Hz, 2F), –117.59 (t, J = 15.0 Hz, 2F), –121.98 (t, J = 12.9 Hz, 2F). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.71 (d, J = 8.6 Hz, 2H), 7.67 (d, J = 7.9 Hz, 2H), 7.63 (d, J = 8.6 Hz, 2H), 7.48 (t, J = 7.8 Hz, 2H), 7.42 (tt, J = 8.4, 1.0 Hz, 1H). Exact mass (EI$^+$) calcd for $C_{16}H_9F_8Br$ 431.9760, found 431.9767.

4.4.3.3.8. Procedure for 2-(4-Bromo-1,1,2,2,3,3,4,4-octafluorobutyl)naphthalene (4gg)

Synthesised following general procedure 4.4.3.3. from 2-iodonaphthalene (0.10 mmol scale) and formed quantitative yield by internal standard, as a white solid. Analytical data for 2-(4-bromo-1,1,2,2,3,3,4,4-octafluorobutyl)naphthalene (**4gg**) ^{19}F NMR ($CDCl_3$, 470 MHz): δ –64.03 (t, J = 13.3 Hz, 2F), –111.18 (t, J = 13.3 Hz, 2F), –

117.55 (t, J = 16.0 Hz, 2F), –121.80 (t, J = 13.3 Hz, 2F). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.13 (s, 1H), 7.97-7.91 (m, 3H), 7.64-7.58 (m, 3H). Exact mass (EI^+) calcd for $C_{14}H_7F_8Br$ 405.9603, found 431.9727.

4.4.3.3.9. Procedure for 1-(4-Bromo-1,1,2,2,3,3,4,4-octafluorobutyl)naphthalene (4hh)

Synthesised following general procedure 4.4.3.3. from 1-iodonaphthalene (0.10 mmol scale) and formed quantitative yield by internal standard, as a white solid. Analytical data for 2-(4-bromo-1,1,2,2,3,3,4,4-octafluorobutyl)naphthalene (**4hh**) ^{19}F NMR ($CDCl_3$, 470 MHz): δ –63.90 (t, J = 13.8 Hz, 2F), –105.46 (t, J = 13.8 Hz, 2F), –117.67 (t, J = 16.0 Hz, 2F), –120.40 (t, J = 13.8 Hz, 2F). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.24 (d, J = 8.7 Hz, 1H), 8.06 (d, J = 8.2 Hz, 1H), 7.92 (d, J = 8.3 Hz, 1H), 7.83 (d, J = 7.3 Hz, 1H), 7.61 (t, J = 7.7 Hz, 1H), 7.56 (t, J = 7.9 Hz, 2H). Exact mass (EI^+) calcd for $C_{14}H_7F_8Br$ 405.9603, found 405.9581.

4.4.3.3.10. Procedure for 4-(4-Bromo-1,1,2,2,3,3,4,4-octafluorobutyl)toluene (4ii)

Synthesised following general procedure 4.4.3.3. from 4-iodotoluene (0.10 mmol scale) to yield 89% by internal standard, as a colorless oil. Analytical data for 4-(4-bromo-1,1,2,2,3,3,4,4-octafluorobutyl)toluene (**4ii**) ^{19}F NMR (MeCN-d_3, 470 MHz): δ –65.69 (t, J = 13.7 Hz, 2F), –111.12 (t, J = 13.8 Hz, 2F), –117.82 (s, 2F), –122.16 (s, 2F). ^{1}H NMR (MeCN-d_3, 300 MHz): δ 7.58 (d, J = 8.2 Hz, 2H), 6.97 (d, J = 7.9 Hz, 2H), 2.27 (s, 3H). Exact mass (EI^+) calcd for $C_{11}H_7F_8Br$ 369.9603, found 369.9606.

4.4.3.3.11. Procedure for 2-(4-Bromo-1,1,2,2,3,3,4,4-octafluorobutyl)toluene (4jj)

Synthesised following general procedure 4.4.3.3. from 2-iodotoluene (0.10 mmol scale) to yield 83% by internal standard, as a colorless oil. Analytical data for 2-(4-

bromo-1,1,2,2,3,3,4,4-octafluorobutyl)toluene (**4jj**) ^{19}F NMR (MeCN-d_3, 470 MHz): δ –65.57 (t, J = 13.9 Hz, 2F), –106.87 (t, J = 15.2 Hz, 2F), –118.04 (t, J = 16.6 Hz, 2F), –121.00 (s, 2F). ^{1}H NMR (MeCN-d_3, 300 MHz): δ 7.53 (dd, J = 22.1, 7.8 Hz, 2H), 7.38 (d, J = 3.9 Hz, 2H), 2.47 (s, 3H). Exact mass (EI$^+$) calcd for $C_{11}H_7F_8Br$ 369.9603, found 369.9579.

4.4.3.3.12. Procedure for 1-(4-Bromo-1,1,2,2,3,3,4,4-octafluorobutyl)-3,5-dimethylbenzene (4kk)

Synthesised following general procedure 4.4.3.3. from 1-iodo-3,5-dimethylbenzene (0.10 mmol scale) to yield 91% by internal standard, as a colorless oil. Analytical data for 1-(4-bromo-1,1,2,2,3,3,4,4-octafluorobutyl)-3,5-dimethylbenzene (**4kk**) ^{19}F NMR (MeCN-d_3, 470 MHz): δ –65.66 (t, J = 14.1 Hz, 2F), –111.18 (t, J = 14.3 Hz, 2F), –117.86 (t, J = 14.1 Hz, 2F), –121.99 (t, J = 11.4 Hz, 2F). ^{1}H NMR (MeCN-d_3, 300 MHz): δ 7.30 (s, 1H), 7.26 (s, 2H), 2.36 (s, 6H). Exact mass (EI$^+$) calcd for $C_{12}H_9F_8Br$ 383.9760, found 383.9786.

4.4.3.3.13. Procedure for 1-(4-Bromo-1,1,2,2,3,3,4,4-octafluorobutyl)-4-tertbutylbenzene (4ll)

Synthesised following general procedure 4.4.3.3. from 1-iodo-4-tertbutylbenzene (0.10 mmol scale) to yield 82% by internal standard, as a colorless oil. Analytical data for 1-(4-bromo-1,1,2,2,3,3,4,4-octafluorobutyl)-4-tertbutylbenzene (**4ll**) ^{19}F NMR (MeCN-d_3, 470 MHz): δ –65.68 (s, 2F), –111.12 (s, 2F), –117.82 (s, 2F), –122.08 (s, 2F). ^{1}H NMR (MeCN-d_3, 300 MHz): δ 7.63 (d, J = 8.6 Hz, 2H), 7.21 (d, J = 8.6 Hz, 2H), 1.27 (s, 9H). Exact mass (EI$^+$) calcd for $C_{14}H_{13}F_8Br$ 412.0073, found 412.0063.

4.4.3.3.14. Procedure for 1-(4-Bromo-1,1,2,2,3,3,4,4-octafluorobutyl)anisole (4mm)

Synthesised following general procedure 4.4.3.3. from 4-iodoanisole (0.50 mmol scale). Purification by flash silica column chromatography (eluent: 50% dichloromethane in hexanes) to yield 83% by internal standard, (54 mg, 28% yield isolated yield) as a colorless oil. Analytical data for 1-(4-bromo-1,1,2,2,3,3,4,4-octafluorobutyl)anisole (**4mm**) ^{19}F NMR ($CDCl_3$, 470 MHz): δ –64.01 (t, *J* = 13.8 Hz, 2F), –110.74 (t, *J* = 13.8 Hz, 2F), –117.61 (t, *J* = 13.7 Hz, 2F), –122.16 (t, *J* = 13.7 Hz, 2F). ^{1}H NMR (MeCN-d_3, 300 MHz): δ 7.51 (d, *J* = 8.8 Hz, 2H), 6.99 (d, *J* = 8.9 Hz, 2H), 3.86 (s, 3H). Exact mass (EI^+) calcd for $C_{11}H_7OF_8Br$ 385.9553, found 385.9557.

4.4.3.3.15. Procedure for 4-(4-Bromo-1,1,2,2,3,3,4,4-octafluorobutyl)nitrobenzene (4nn)

Synthesised following general procedure 4.4.3.3. from 4-iodonitrobenzene (0.50 mmol scale). Purification by flash silica column chromatography (eluent: 50% dichloromethane in hexanes) and formed quantitative yield by internal standard, (180 mg, 88% yield isolated yield) as a white solid. Analytical data for 4-(4-bromo-1,1,2,2,3,3,4,4-octafluorobutyl)nitrobenzene (**4nn**) ^{19}F NMR ($CDCl_3$, 470 MHz): δ –64.35 (t, *J* = 13.9 Hz, 2F), –112.17 (t, *J* = 14.3 Hz, 2F), –117.50 (t, *J* = 16.0 Hz, 2F), –121.83 (t, *J* = 14.1 Hz, 2F). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.38 (d, *J* 8.5 Hz, 2H), 7.82 (d, *J* = 8.6 Hz, 2H). Exact mass (EI^+) calcd for $C_{10}H_4NO_2F_8Br$ 402.9328, found 402.9317.

4.4.3.3.16. Procedure for 4-(4-Bromo-1,1,2,2,3,3,4,4-octafluorobutyl)benzonitrile (4oo)

Synthesised following general procedure 4.4.3.3. from 4-iodobenzonitrile (0.50 mmol scale). Purification by flash silica column chromatography (eluent: 50% dichloromethane

in hexanes) and formed quantitative yield by internal standard, (150 mg, 80% yield isolated yield) as a white solid. Analytical data for 4-(4-bromo-1,1,2,2,3,3,4,4-octafluorobutyl)benzonitrile (**4oo**) ^{19}F NMR ($CDCl_3$, 470 MHz): –64.33 (t, *J* = 14.3 Hz, 2F), –112.64 (t, *J* = 14.3 Hz, 2F), –117.54 (t, *J* = 15.5 Hz, 2F), –121.92 (t, *J* = 14.0 Hz, 2F). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.83 (s, *J* = 8.1 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 2H). Exact mass (EI^+) calcd for $C_{11}H_4NF_8Br$ 380.9399, found 380.9427.

4.4.3.3.17. Procedure for Methyl 4-(4-bromo-1,1,2,2,3,3,4,4-octafluorobutyl)benzoate (4pp)

Synthesised following general procedure 4.4.3.3. from methyl 4-iodobenzoate (0.50 mmol scale). Purification by flash silica column chromatography (eluent: 50% dichloromethane in hexanes) to yield >90% by internal standard, (160 mg, 76% yield isolated yield) as a white solid. Analytical data for methyl 4-(4-bromo-1,1,2,2,3,3,4,4-octafluorobutyl)benzoate (**4pp**) ^{19}F NMR ($CDCl_3$, 470 MHz): δ –64.18 (t, *J* = 14.4 Hz, 2F), –112.22 (t, *J* = 14.3 Hz, 2F), –117.56 (t, *J* = 15.1 Hz, 2F), –122.02 (t, *J* = 13.2 Hz, 2F). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.17 (d, *J* = 8.7 Hz, 2H), 7.68 (d, *J* = 8.3 Hz, 2H), 3.96 (s, 3H). Exact mass (EI^+) calcd for $C_{12}H_7O_2F_8Br$ 413.9502, found 413.9530.

4.4.3.3.18. Procedure for Ethyl 4-(4-bromo-1,1,2,2,3,3,4,4-octafluorobutyl)benzoate (4qq)

Synthesised following general procedure 4.4.3.3. from ethyl 4-iodobenzoate (0.50 mmol scale). Purification by flash silica column chromatography (eluent: 50% dichloromethane in hexanes) and formed quantitative yield by internal standard, (140 mg, 69% yield isolated yield) as a white solid. Analytical data for ethyl 4-(4-bromo-1,1,2,2,3,3,4,4-octafluorobutyl)benzoate (**4qq**) ^{19}F NMR ($CDCl_3$, 470 MHz): –64.18 (t, *J* = 14.2 Hz, 2F),

–112.20 (t, *J* = 14.1 Hz, 2F), –117.55 (t, *J* = 14.0 Hz, 2F), –122.04 (t, *J* = 13.7 Hz, 2F). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.17 (d, *J* = 8.1 Hz, 2H), 7.68 (d, *J* = 8.2 Hz, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 1.42 (d, *J* = 7.1 Hz, 3H). Exact mass (EI^+) calcd for $C_{13}H_9O_2F_8Br$ 427.9658, found 427.9655.

4.4.3.3.19. Procedure for 1-(4-Bromo-1,1,2,2,3,3,4,4-octafluorobutyl)-4-(4-morpholinyl)benzene (4rr)

Synthesised following general procedure 4.4.3.3. from 4-(4-iodophenyl)morpholine (0.50 mmol scale). Purification by flash silica column chromatography (eluent: dichloromethane) to yield >90% by internal standard, (150 mg, 66% yield isolated yield) as a white solid. Analytical data for 1-(4-bromo-1,1,2,2,3,3,4,4-octafluorobutyl)-4-(4-morpholinyl)benzene (**4rr**) ^{19}F NMR ($CDCl_3$, 470 MHz): δ –63.96 (t, *J* = 14.0 Hz, 2F), –110.78 (t, *J* = 13.9 Hz, 2F), –117.61 (t, *J* = 13.8 Hz, 2F), –122.18 (t, *J* = 11.7 Hz, 2F). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.45 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 3.87 (t, *J* = 3.0 Hz, 4H), 3.26 (t, *J* = 3.1 Hz, 4H). Exact mass (EI^+) calcd for $C_{14}H_{12}NOF_8Br$ 440.9975, found 440.9985.

4.4.3.3.20. Procedure for 4-(4-Bromo-1,1,2,2,3,3,4,4-octafluorobutyl)-1-fluorobenzene (4ss)

Synthesised following general procedure 4.4.3.3. from 1-fluoro-4-iodobenzene (0.10 mmol scale) to yield 78% by internal standard, as a colorless oil. Analytical data for 4-(4-bromo-1,1,2,2,3,3,4,4-octafluorobutyl)-1-fluorobenzene (**4ss**) ^{19}F NMR (MeCN-d_3, 470 MHz): δ –65.76 (s, 2F), –109.28 (s, 1F), –110.78 (s, 2F), –117.83 (s, 2F), –112.10 (s, 2F). ^{1}H NMR (MeCN-d_3, 300 MHz): δ 8 7.70 (t, *J* = 8.6 Hz, 2H), 7.32 (t, *J* = 8.8 Hz, 2H). Exact mass (EI^+) calcd for $C_{10}H_4F_9Br$ 373.9353, found 373.9349.

4.4.3.3.21. Procedure for 4-(4-Bromo-1,1,2,2,3,3,4,4-octafluorobutyl)-1-chlorobenzene (4tt)

Synthesised following general procedure 4.4.3.3. from 1-chloro-4-iodobenzene (0.10 mmol scale) to yield 80% by internal standard, as a colorless oil. Analytical data for 4-(4-bromo-1,1,2,2,3,3,4,4-octafluorobutyl)-1-chlorobenzene (**4tt**) ^{19}F NMR (MeCN-d_3, 470 MHz): δ –65.80 (t, J = 12.9 Hz, 2F), –111.49 (t, J = 13.3 Hz, 2F), –117.82 (s, 2F), –122.13 (s, 2F). ^{1}H NMR (MeCN-d_3, 300 MHz): δ 7.62 (q, J = 8.6 Hz, 4H). Exact mass (EI^+) calcd for $C_{10}H_4F_8ClBr$ 389.9057, found 389.9076.

4.4.3.3.22. Procedure for 4-(4-Bromo-1,1,2,2,3,3,4,4-octafluorobutyl)-1-bromobenzene (4uu)

Synthesised following general procedure 4.4.3.3. from 1-bromo-4-iodobenzene (0.10 mmol scale) to yield >90% by internal standard, as a colorless oil. Analytical data for 4-(4-bromo-1,1,2,2,3,3,4,4-octafluorobutyl)-1-bromobenzene (**4uu**) ^{19}F NMR (MeCN-d_3, 470 MHz): δ –65.81 (t, J = 12.5 Hz, 2F), –111.67 (t, J = 12.9 Hz, 2F), –117.82 (s, 2F), –122.14 (s, 2F). ^{1}H NMR (MeCN-d_3, 300 MHz): δ 7.76 (d, J = 8.5 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H). Exact mass (EI^+) calcd for $C_{10}H_4F_8Br_2$ 433.8552, found 433.8578.

4.4.3.4. General Synthesis of $ArC_6F_{12}Br$ from Scheme 4.12

To a 20 mL vial, 60.0 mg (0.106 mmol) of $PhenAg(CF_2)_6Br$ was mixed in 1.0 mL of MeCN. Sequential addition of 0.100 mmol of Ar-I and 20.0 mg (0.105 mmol) of CuI were added to the vial. The solution changed from a white mixture to a reddish solution as solid precipitated to the bottom of the vial. After 1 day of stirring at room temperature, the solution was filtered through a 0.2 μm PTFE filter and washed with an additional 0.5 mL of MeCN into a re-sealable Air tight NMR tube. Yields were calculated against 0.012

mL of (0.098 mmol) internal standard. Reactions not complete were heated at 50 °C overnight to give full conversion Isolation was accomplished by removing solvent under reduced pressure followed by column chromatography using hexanes, hexanes/DCM 50%, or DCM.

4.4.3.4.1. Procedure for 4-(4-Bromo-1,1,2,2,3,3,4,4,5,5,6,6-dodecafluorohexyl)nitrobenzene (4xx)

Synthesised following general procedure 4.4.3.4. from 4-iodonitrobenzene (0.10 mmol scale). Purification by flash silica column chromatography (eluent: 50% dichloromethane in hexanes) to yield 82% by internal standard (30. mg, 60% yield isolated yield) as a white solid. Analytical data for 4-(4-bromo-1,1,2,2,3,3,4,4,5,5,6,6-dodecafluorohexyl)nitrobenzene (**4xx**) ^{19}F NMR ($CDCl_3$, 470 MHz): δ –64.45 (t, *J* = 13.2 Hz, 2F), –112.12 (t, *J* = 13.1 Hz, 2F), –118.25 (s, 2F), –122.09 (s, 4F), –122.54 (s, 2F). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.38 (d, *J* = 8.5 Hz, 2H), 7.82 (d, *J* = 8.6 Hz, 2H). Exact mass (EI^+) calcd for $C_{12}H_4NO_2F_{12}Br$ 500.9234, found 500.9220.

4.4.3.4.2. Procedure for 4-(4-Bromo-1,1,2,2,3,3,4,4,5,5,6,6-dodecafluorohexyl)benzonitrile (4yy)

Synthesised following general procedure 4.4.3.4. from 4-iodobenzonitrile (0.10 mmol scale). Purification by flash silica column chromatography (eluent: 50% dichloromethane in hexanes) to yield 84% by internal standard, (26 mg, 55% yield isolated yield) as a white solid. Analytical data for 4-(4-bromo-1,1,2,2,3,3,4,4,5,5,6,6-dodecafluorohexyl)benzonitirle (**4yy**) ^{19}F NMR ($CDCl_3$, 470 MHz): δ –64.45 (t, *J* = 13.3 Hz, 2F), –112.58 (t, *J* = 13.1 Hz, 2F), –118.24 (s, 2F), –122.11 (s, 4F), –122.61 (s, 2F).

^{1}H NMR ($CDCl_3$, 300 MHz): 7.83 (d, *J* = 8.3 Hz, 2H), 7.74 (d, *J* = 8.3 Hz, 2H). Exact mass (EI^+) calcd for $C_{13}H_4NF_{12}Br$ 480.9335, found 480.9328.

4.4.3.4.3. Procedure for Methyl 4-(4-bromo-1,1,2,2,3,3,4,4,5,5,6,6-dodecafluorohexyl)benzoate (4zz)

Synthesised following general procedure 4.4.3.4. from methyl 4-iodobenzoate (0.10 mmol scale). Purification by flash silica column chromatography (eluent: 50% dichloromethane in hexanes) to yield 75% by internal standard, (24 mg, 46% yield isolated yield) as a white solid. Analytical data for methyl 4-(4-bromo-1,1,2,2,3,3,4,4,5,5,6,6-dodecafluorohexyl)benzoate (**4zz**) ^{19}F NMR ($CDCl_3$, 470 MHz): δ –64.39 (t, *J* = 13.7 Hz, 2F), –112.16 (t, *J* = 13.4 Hz, 2F), –118.25 (s, 2F), –122.15 (s, 4F), –122.75 (s, 2F). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.17 (d, *J* = 8.6 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 2H), 3.96 (s, 3H). Exact mass (EI^+) calcd for $C_{14}H_7O_2F_{12}Br$ 513.9438, found 513.9443.

4.4.3.4.4. Procedure for 4-(4-Bromo-1,1,2,2,3,3,4,4,5,5,6,6-dodecafluorohexyl)biphenyl (4aaa)

Synthesised following general procedure 4.4.3.4. from 4-iodobiphenyl (0.10 mmol scale). Purification by flash silica column chromatography (eluent: hexanes) to yield >90% by internal standard, (30 mg, 56% yield isolated yield) as a white solid. Analytical data for 4-(4-bromo-1,1,2,2,3,3,4,4,5,5,6,6-dodecafluorohexyl)biphenyl (**4aaa**) ^{19}F NMR ($CDCl_3$, 470 MHz): δ –64.32 (t, *J* = 13.7 Hz, 2F), –111.53 (t, *J* = 13.3 Hz, 2F), –118.23 (s, 2F), –122.08 (s, 2F), –122.22 (s, 2F), –122.73 (s, 2F). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.48 (t, *J* = 8.0 Hz, 2H),

7.42 (tt, J = 8.4, 1.0 Hz, 1H). Exact mass (EI^+) calcd for $C_{18}H_9F_{12}Br$ 531.9696, found 531.9697.

4.5. References

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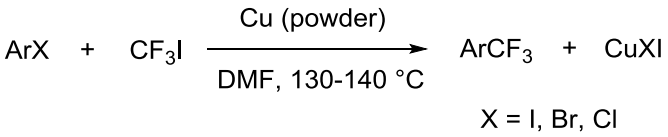
Chapter 5. Benchmarking Experiment of Well-Defined Copper Catalysts for the Trifluoromethylation of Aryl Halides

5.1. Background and Significance

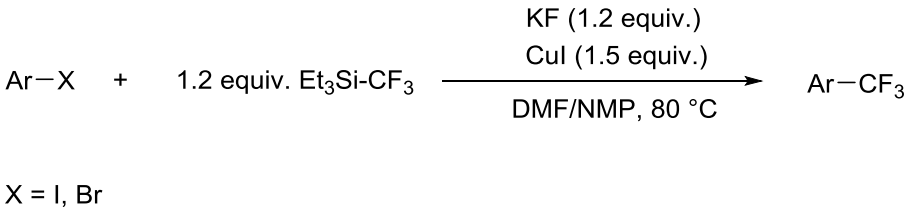
5.1.1. *In situ* Copper Mediated Trifluoromethylations of Aryl Halides

Revisiting the observations involving copper salt precatalysts discussed in Chapters 2-4, I became increasingly interested in benchmarking the reactivity of well-defined fluorocarbon containing copper complexes. Trifluoromethyl copper reagents [L_nCuCF_3] were chosen as the benchmarking platform because of the extensive research and methods developed around this fully characterized class of copper reagents. One of the earliest examples of copper trifluoromethylation came from Kobayashi and Kumadaki. Herein, they reported (Scheme 5.1) that copper metal powder could cross-couple aryl halides with trifluoromethyl iodide to achieve the desired trifluoromethyl arene.[1]



Scheme 5.1. Trifluoromethylation Using Copper Powder.

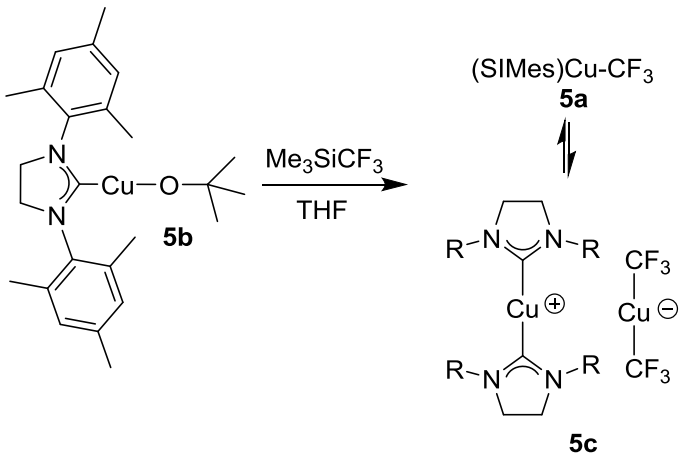
Unfortunately, conditions described in Scheme 5.1 required high temperatures and 15 mole equivalents of trifluoromethyl iodide. Milder conditions for the transformation were discovered in 1991.[2] That work involved mixing potassium fluoride and triethyl(trifluoromethyl)silane to *in situ* generate the [L_nCuCF_3] species form copper(I) iodide (Scheme 5.2). This new protocol not only invoked more moderate temperatures of 80 °C, but also required far less trifluoromethyl reactant.



Scheme 5.2. Copper Mediated Trifluoromethylation by KF/Et_3SiCF_3 System.

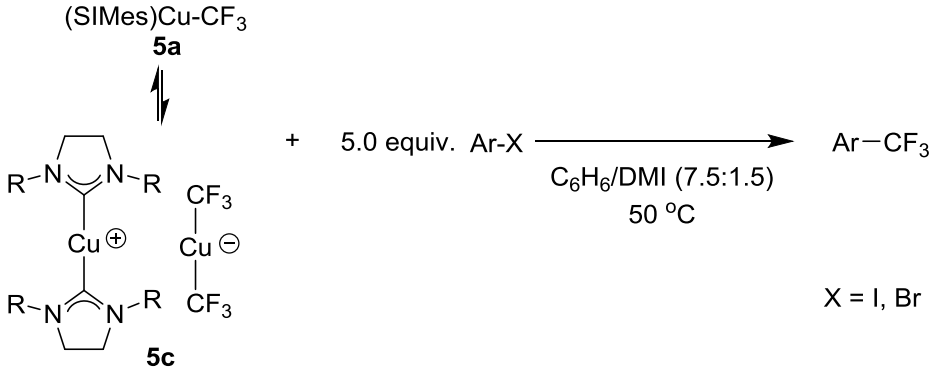
5.1.2. First Isolated [L_nCuCF_3] Complex for Trifluoromethylation of Aryl Halides

It was not until 2008 that novel well-defined (structurally characterized) *N*-heterocyclic carbene (NHC) complexes of trifluoromethyl copper, such as **5a**, were discovered to be active for the trifluoromethylation of aryl halides.[3,4] [(SIMes)$CuCF_3$] (**5a**, SIMes = 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene) was prepared from the reaction of [(SIMes)Cu(O^tBu)] (**5b**) and Me_3SiCF_3 (Scheme 5.3). Curiously, Vicic and coworkers found that the neutral species **5a** underwent an unusual ligand redistribution to the cuprate complex, [$(SIMes)_2Cu$][$Cu(CF_3)_2$] (**5c**) in solution.[4] Dissolution of complex **5c** demonstrated equilibrium in THF at 25 °C, slightly favoring the formation of **5c** by an estimated $K_{eq} \sim 1.2$ (Scheme 5.3.).



Scheme 5.3. Preparation of Isolable Copper Complexes **5a** and **5c**.

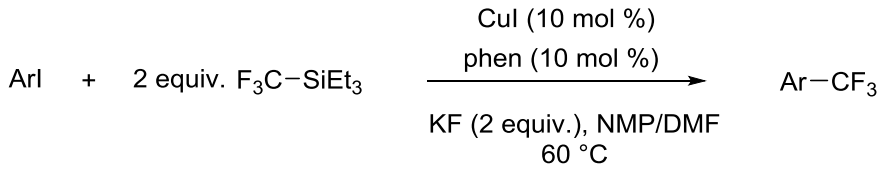
Despite the equilibrium shown in Scheme 5.3, **5c** was able to trifluoromethylate aryl iodides in good to excellent yields (up to 93%), albeit requiring the unique solvent mixture of (7.5/1.5) benzene/DMI (1,3-dimethyl-2-imidazolidinone), reported in Scheme 5.4. Kinetic studies of $[(SIMes)_2Cu][Cu(CF_3)_2]$ (**5c**) in neat aryl iodide determined an inverse relationship between concentration of **5c** and the rate of trifluoromethylation.[4,5] Vicic and coworkers proposed that **5c** was not the active species in Scheme 5.4, assuming concentration-dependent equilibrium.



Scheme 5.4. Trifluoromethylation of Aryl Halides with **5a** and **5c** Mixture.

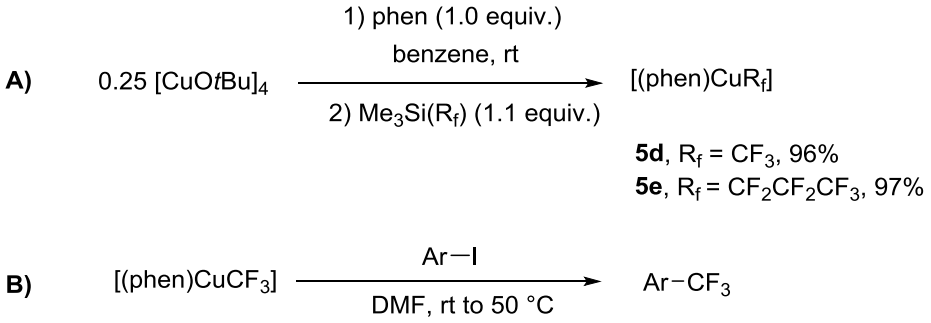
5.1.3. Synthesis and Reactivity of Isolable (Phen)$CuCF_3$ Complex (5d) for Transformation of Aryl Halides

Shortly after the discovery of the NHC copper complexes described above, Amii and coworkers reported the *in situ* preparation of phenanthroline complexes of copper for transformation of aryl iodides (in Scheme 5.5).[6] Although the reaction was quite effective at trifluoromethylating electron poor aryl iodides (63-99%), electron-rich substrates suffered from diminished yields (44%).



Scheme 5.5. Catalytic Trifluoromethylation of Aryl Iodides Using *In Situ* (Phen)$CuCF_3$ (**5d**).

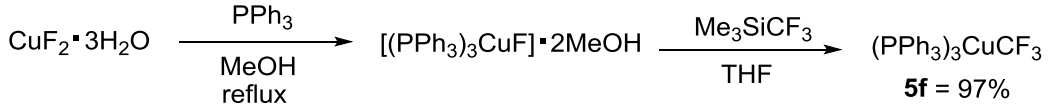
However, in 2011, Hartwig and coworkers developed a protocol for preparing the first isolated (phen)$CuCF_3$] reagent (**5d**, Scheme 5.6, A).[7] An unprecedented scope of aryl halide substrates was reported in their trifluoromethylation studies. Excellent yields and tolerance of functional groups in the formation or trifluoromethyl products was observed (Scheme 5.6, B). The reaction was amenable for the preparation of many n-heptylfluoropropane containg arenes using **5e** under Scheme 5.6, B-like conditions. The use of [(phen)$CuCF_3$] (**5d**) has been very successful in trifluoromethylation reactions, both due to the simple preparation with inexpensive ancillary ligand (phenanthroline) and breadth of chemical reactivity.[7-9] It can now be purchased commercially, or prepared *in situ* by a variety of methods, including reaction of $[Cu(O^tBu)]_4$ with Me_3SiCF_3 and phen[7] or by reaction of $[(MeO)_3BCF_3]$ with CuI and phen.[10]



Scheme 5.6. Protocol for Fluoroalkyl Copper Complexes **5d** and **5e** for Fluoroalkylations.

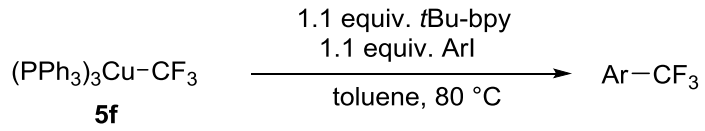
5.1.4. Characterization and Reactivity of $[(PPh_3)_3CuCF_3]$ (5f) for the Trifluoromethylation of Aryl Iodides

Grushin and coworkers published an alternative method in 2011 for the formation of the compound $[(PPh_3)_3CuCF_3]$ (**5f**) (Scheme 5.7).[11] While **5f** had been known since 2000 and, to my knowledge, was the first isolated copper trifluoromethyl complex, there were no reports on its trifluoromethylating ability nor on its structural data.[12] The Grushin protocol (Scheme 5.7) represented a simple, efficient, and inexpensive method to prepare the air stable complex **5f**.



Scheme 5.7. Novel Method for (Trifluoromethyl)tris(triphenylphosphine) Copper(I) (**5f**).

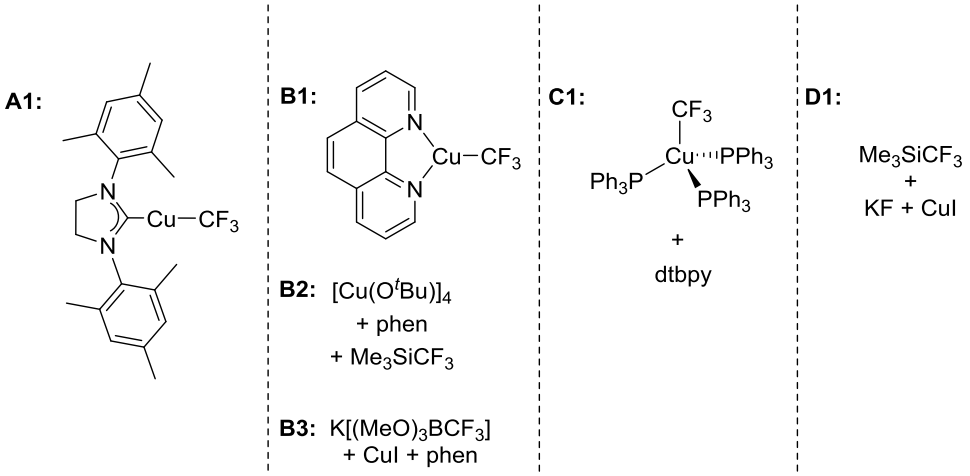
Initial studies found that **5f** was only capable of trifluoromethylating neat iodobenzene, reaching a yield of 91% after 24 hours at 70 °C.[11] In order to minimize side-products and enhance the yields of the desired products, dtbpy (dtbpy = 4,4′-di-*tert*-butylbipyridine) was added to reaction mixtures of $[(PPh_3)_3CuCF_3]$ and aryl iodides, reported in Scheme 5.8. The addition dtbpy to $[(PPh_3)_3CuCF_3]$ resulted in dramatic color change to an orange-red solution, suggesting coordination of bipyridine to the copper complex. Reactions with the bipyridine ligand displayed a greatly improved formation of product when compared to **5f** without ligand.



Scheme 5.8. Trifluoromethylation of Aryl Iodides by Bipyridine Assisted (**5f**).

5.1.5. Project Goals

Although copper catalysts described above are now commonly used ubiquitously as trifluoromethylating reagents of aryl halides, there lacks research data for comparing the various compounds under similar reaction conditions. Each catalyst operates under unique reaction parameters in literature reports, with only a single time point yields reported for most systems. Having benchmarked conditions to compare the various protocols and would not only help us better understand the reactions, but also standardize this research moving forward.[13] To this effort, I pursued a standard reaction (identical reaction conditions) to track product formation over time for systems described in Scheme 5.9, **A-D**. Furthermore, I set out to compare the well-defined [L_nCuCF_3] reagents employed directly with their *in situ* generated complexes described by published reports.

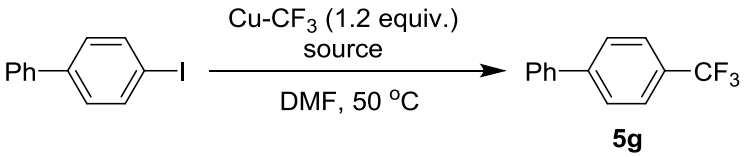


Scheme 5.9. Catalysts and Pre-Catalysts Systems Used for Trifluoromethylation Reactions.

5.2. Results and Discussion

5.2.1. Standard Reaction for Copper Catalyst Systems

In order to compare copper catalysts described in Scheme 5.9 qualitatively, a standard protocol was needed. Noting the prolific use of the phenanthroline-based catalyst system, this "standard" system was modeled on conditions similar to Hartwig's parameters published in 2011.[7] These conditions involve reacting 4-iodo-1,1'-biphenyl with a [L_nCuCF_3] source at 50 °C in DMF solvent (Scheme 5.10). However, 'standard' conditions were slightly diluted compared to published protocols to ensure homogeneity of all the respective copper catalysts. The formation of 4-(trifluoromethyl)-1,1'-biphenyl (**5g**) was monitored by gas chromatography against calibrated standard of undecane (see methods).



Scheme 5.10. Standard Conditions for Trifluoromethylation.

All experiments were performed in triplicate, with average yields reported graphically versus time (Figure 5.1). Hartwig's reagent, either generated *in situ* (**B2**) or from commercially purchased reagent (**B1**), gave the highest yields of 4-(trifluoromethyl)-1,1'-biphenyl product after 22 hours. Although **B1** and **B2** were very competitive up to the 5 hour mark, the *in situ* reagent (**B2**) achieved approximately 15% higher yields at longer reaction times. Surprisingly, the related phen system **B3**, that employs the trifluoromethyl source $K[(MeO)_3BCF_3]$, (**5h**) only achieved a yield of 31%. The discrepancy among **B1**, **B2**, and **B3** is curious, and suggests that the subtle differences in trifluoromethyl source affect the overall reactivities. Lastly, for the trifluoromethyl systems **A1**, **C1**, and **D1**, poor initial and overall performance (<10% yield) was observed in DMF solution at 50 °C (Figure 5.1).

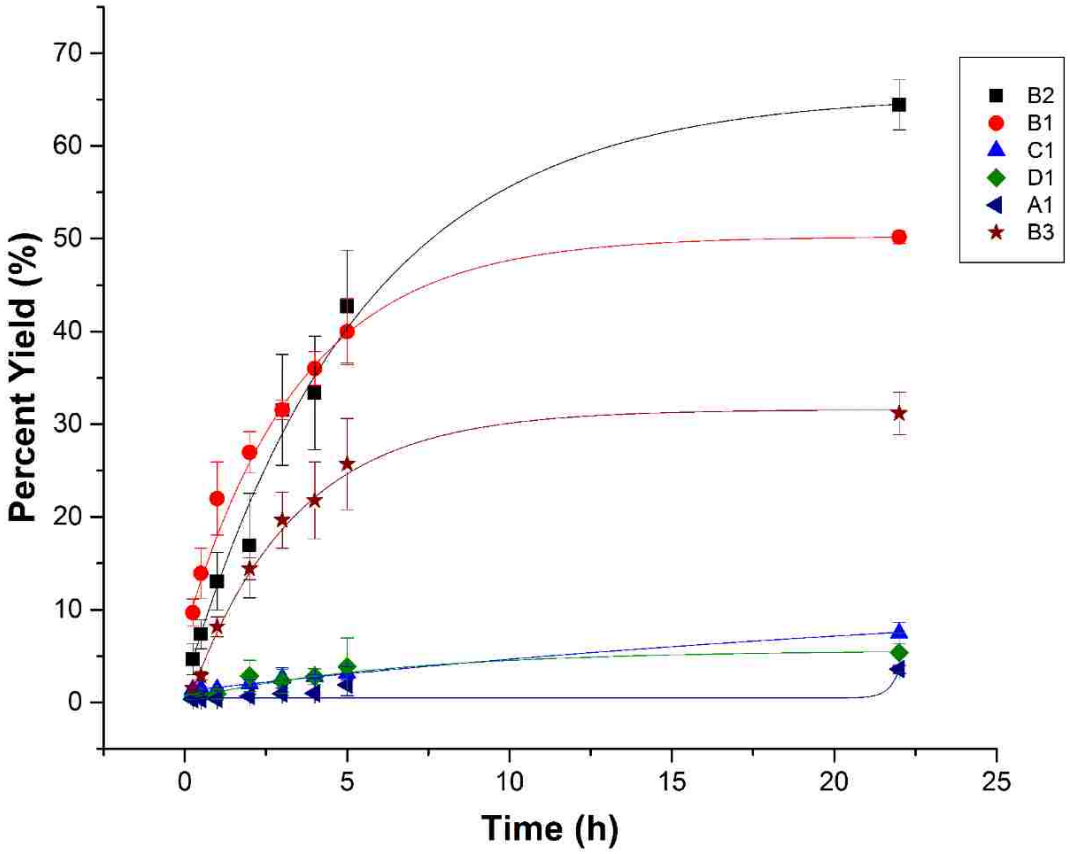


Figure 5.1. Yields of 4-(Trifluoromethyl)-1,1'-biphenyl Over Time for the Catalyst Systems Described in Scheme 5.9 Under 'Standard' Conditions (See Experimental for Full Details).

5.2.2. Optimized Reaction for Copper Catalyst Systems

Although [(SIMes)$CuCF_3$] (**A1**) and the [$(PPh_3)_3CuCF_3$ + dtbpy] combination (**C1**) systems did not perform well at 'standard' conditions, I wanted to accurately assess their reactivity by comparing each system using the published procedures to that of the highest performing catalyst, [(phen)$CuCF_3$] (**B1**).[4,11] The results of this study are shown in Figure 5.2. Both systems (**A1**) and (**C1**) showed higher reactivity than the standard conditions described in Figure 5.1, citing the importance of solvent in facilitating the

desired trifluoromethylation. The **C1** system displays significant increase in the initial rate of the reaction, but plateaus after about 5 hours at ~38% yield. System **A1** displays the opposite trend. Initially, very little product formation is observed by GC-FID, but after 22 hours ~42% yield is achieved. When system **A1** is monitored by ^{19}F NMR spectroscopy, both the neutral species, [(SIMes)Cu(CF_3)] (**5a**) and the ionic species [$(SIMes)_2Cu$][$Cu(CF_3)_2$] (**5c**) are observed. The data suggest that consumption of **5a** slowly shifts the equilibrium from **5c** to **5a** in order to trifluoromethylate the aryl halide. The sluggish reactivity of system **A1** further indicates that **5c** is not the active complex in trifluoromethylation, agreeing with the findings of Vicic and coworkers.[4,5] Nevertheless, **A1** was found to steadily produce 4-(trifluoromethyl)-1,1'-biphenyl after 22 hours (49% after 21 hours), demonstrating good, yet slow reactivity. Now, comparing all three systems **A1**, **B2**, and **C1** operating at optimized conditions, still established **B2** as the most effective trifluoromethylating system for 4-iodo-1,1'-biphenyl.

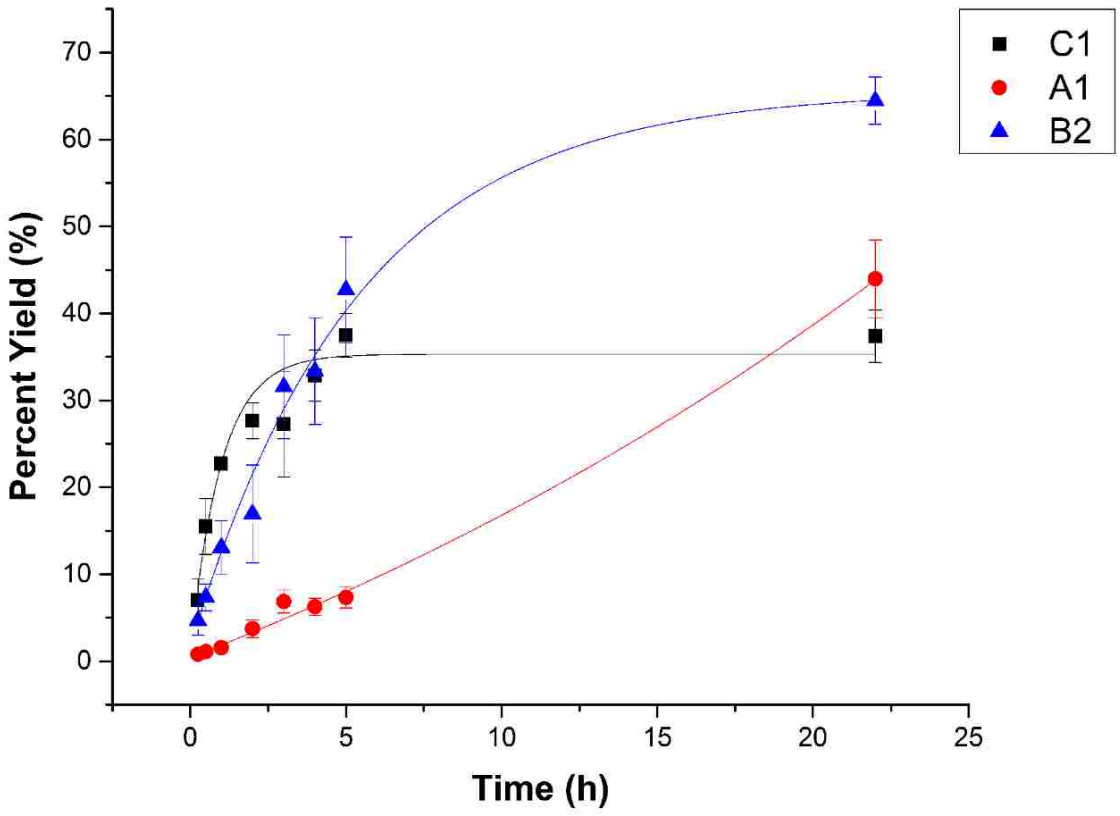
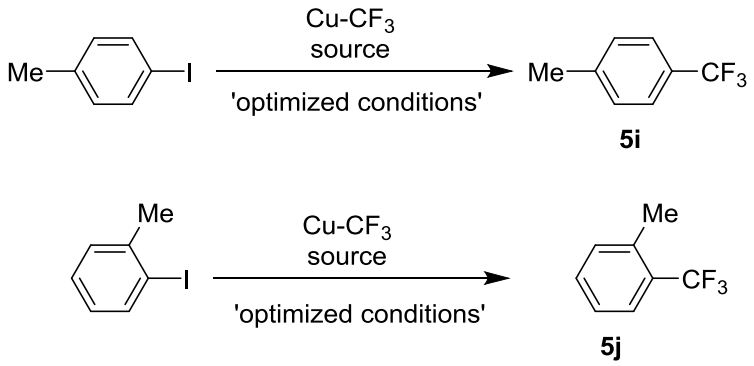


Figure 5.2. Yields of 4-(Trifluoromethyl)-1,1'-biphenyl Over Time for the Catalyst Systems Described in Scheme 5.9. Conditions for **C1**: toluene solvent, 80 °C, **A1**: DMI/Benzene solvent (1.5:7.5), 50 °C (See Experimental for Full Details).

5.2.3. Iodotoluene Reactions with Copper Catalyst Systems A1 and B1

Having demonstrated [(SIMes)$CuCF_3$] (**A1**) and Hartwig's reagent generated *in situ* (**B2**) as the most active for the trifluoromethylation of 4-iodo-1,1'-biphenyl in Scheme 5.10, I compared their reactivity against other substrates. The iodotoluene system was chosen as way to probe the steric effects of the methyl substituent on the formation of product. For this study, I used 2-iodotoluene and 4-iodotoulene were used with systems **A1** and **B2** described in Scheme 5.11.



Scheme 5.11. Trifluoromethylation of Iodotoluene Substrates with System **A1** and **B2**.

Reactions with iodotoluenes were analyzed by ^{19}F NMR spectroscopy and referenced against fluorobenzene internal standard. Data were plotted graphically in Figure 5.3 for 4-iodotoluene and Figure 5.4 for 2-iodotoluene using systems **A1** and **B2**. Surprisingly, both iodotoluene reagents were found to be well converted after 22 hours by **A1** or **B2**. The **B2** system displays very similar reactivity profile to that of Figure 5.1, albeit with >90% yield for the products **5i** and **5j**. An induction period is present for the **A1** system, with no product observed until after 3 hours. After the induction period, the rate of formation of products **5i** and **5j** was very fast. The [(SIMes)$CuCF_3$] complex (**5a**) was even found to be more effective at trifluoromethylations of 2-iodotoluene. The induction period may be related to the equilibrium between the neutral copper species (active) and the cuprate complex (inactive). Further investigation is needed to determine whether the induction period is real or a lack of sensitivity in NMR spectroscopy versus GC-FID.

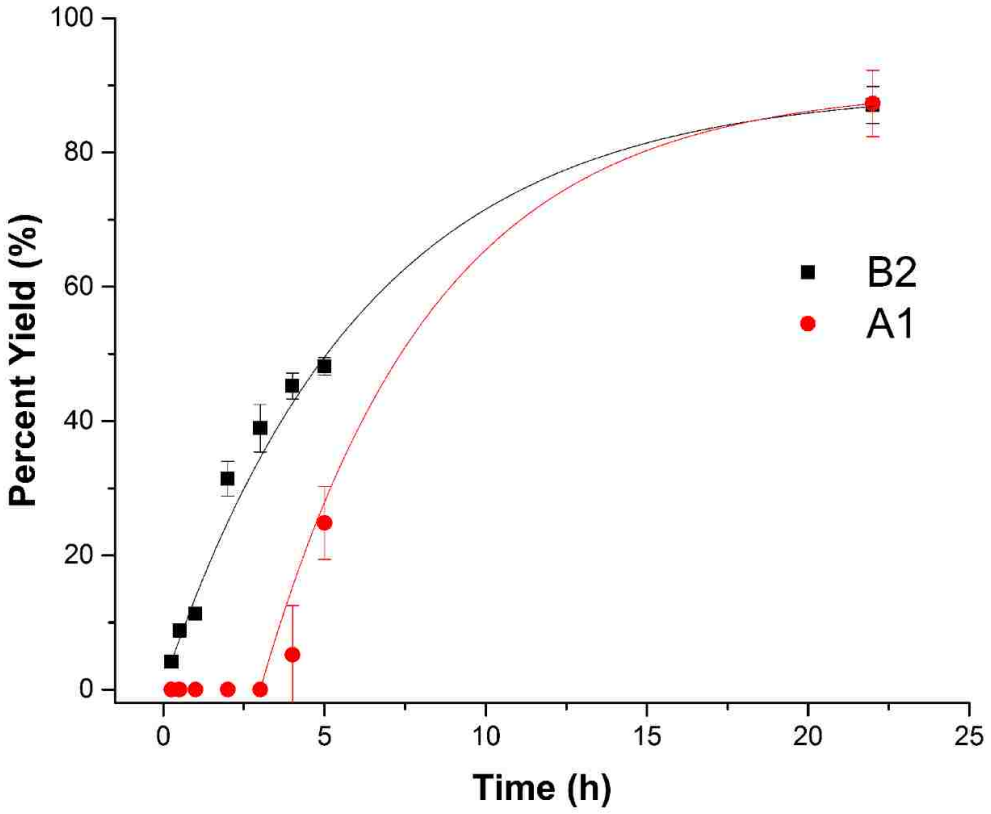


Figure 5.3. Yields of 4-(Trifluoromethyl)toluene Over Time for the Catalyst Systems Described in Scheme 5.9. **A1**: DMI/Benzene solvent (1.5:7.5), 50 °C (See Experimental for full details).

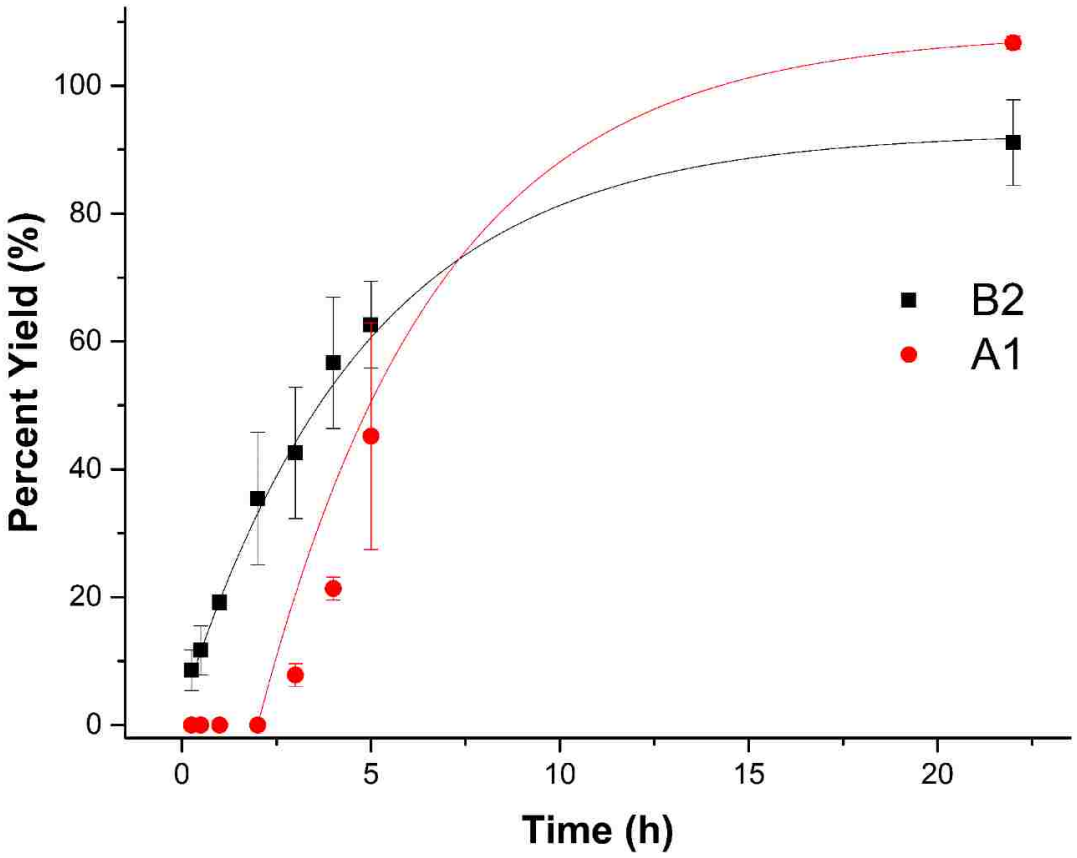


Figure 5.4. Yields of 2-(Trifluoromethyl)toluene Over Time for the Catalyst Systems Described in Scheme 5.9. **A1**: DMI/Benzene solvent (1.5:7.5), 50 °C (See Experimental for full details).

5.3. Conclusions

Although there are still variables to be explored, this research represents some of my important findings toward benchmarking of copper catalyzed trifluoromethylation systems. This chapter reports two major results that could not have been elucidated under traditional single time point yields. First, that some catalysts have induction periods over which formation of product is very slow. Second, that the initial rates of phen-type copper catalysts are similar but achieve vastly different total yields. Solvent is another

key factor. For systems **A1** and **C1** yields are vastly different when comparing optimized to 'standard' conditions. The solvent mixture for system **A1** is likely needed to drive the equilibrium from the more polar cuprate **5c** to the less polar neutral copper catalyst **5a**. Both NHC copper complex system and Hartwig's phen copper system were exceedingly effective at trifluoromethylation. Ultimately, not only does Hartwig's *in situ* catalyst prove to be the most potent under the conditions described, but also one of the simplest to prepare and use.

5.4. Experimental Details

5.4.1. Materials

[(Phen)$CuCF_3$] was purchased from Aspira Scientific (Lot #40C906) and used without further purification. All other copper reagents were prepared according to reported procedures and were verified by ^{1}H-NMR and ^{19}F-NMR for purity. Copper salt precursors were purchased from Sigma Aldrich. Trimethyl(trifluoromethyl)silane was purchased from SynQuest Labs, Inc. and used without further purification. All other chemical were verified by ^{1}H-NMR for purity and used without further purification. All solvents were purified by passing through activated alumina and/or copper in a solvent purification system supplied by Pure Process Technology or purchased anhydrous from Fisher Scientific (toluene, acetonitrile, DMF, and DMI).

5.4.2. Instrumentation and Equipment

The quantitative analyses for Figures 5.1 and 5.2 were accomplished using a Shimadzu GC-2010 Plus Gas Chromatograph and flame ionization detector (FID). A Rxi-5ms (fused silica), low-polarity phase, crossbond diphenyl dimethyl polysiloxane, 15.0 m length column was used. Parameters were: injection volume of 4.0µL, 25:1 split ratio,

linear velocity of 57.0 cm/sec, total flow of 65.3 mL/min, and temperature program starting at 40 °C held for one minute, followed by temperature ramp of 20.00 °C a minute to the final temperature of 250 °C which was held for 4 minutes. All peaks were well separated. Mass spectral data was recorded on a HP 5890 Series II Plus GC/MS. All manipulations were performed using standard Schlenk and high vacuum techniques or in a nitrogen filled glovebox. The quantitative analyses for Figures 5.3 and 5.4 were accomplished using a Bruker Ascend 400 MHz spectrometer by ^{19}F-NMR spectra referenced to internal standard of fluorobenzene. Solution ^{1}H-NMR spectra were recorded at ambient temperature on a Bruker Ascend 400 MHz spectrometer and referenced to residual proton solvent signals. ^{13}C-NMR spectra were recorded on a Bruker Ascend NMR operating at 101 MHz and referenced to solvent signals. ^{19}F-NMR spectra were recorded on the Bruker Ascend NMR operating at 376 MHz and referenced to trifluorotoluene set at δ −63.7.

5.4.3. Methods

5.4.3.1. Procedure for NHC Copper Complexes

5.4.3.1.1. Preparation of [(SIMes)Cu(O^{t}Bu)] (5b)

A suspension of [(SIMes)CuCl] (prepared by reported literature)[14,15] (330 mg, 0.814 mmol) and *t*-BuONa (78 mg, 0.81 mmol) in 6.0 mL THF was stirred for 2 h at room temperature and then filtered through a pad of Celite. The Celite was washed two times with 4 mL of THF. The filtrate was evaporated on a high vacuum line. The resulting light yellow residue was dissolved in benzene and then filtered through a pad of Celite. The Celite was washed two times with 4 mL of benzene. The filtrate was evaporated on a high vacuum line and the resulting white solid was washed with pentane

and filtered. Yield 92%. The spectroscopic data matched literature values. ^{1}H NMR (C_6D_6): δ 1.31 (s, 9H), 2.12 (s, 6H), 2.14 (s, 12H), 3.01 (s, 4H), 6.73 (s, 4H).

5.4.3.1.2. Preparation of [(SIMes)$_2$Cu][Cu(CF$_3$)$_2$] (5c)

A solution of [(SIMes)Cu(O^{t}Bu)] (220 mg, 0.500 mmol) and $CF_3Si(CH_3)_3$ (0.110 mL, 0.740 mmol) in 6.0 mL THF was stirred at room temperature. The conversion to product was monitored by ^{19}F NMR spectroscopy, and after 1.5 h the volatiles were evaporated on a high vacuum line. The white residue was filtered and washed twice with 5 mL toluene and then twice with 5 mL of pentane. Yield of $[(SIMes)_2Cu][Cu(CF_3)_2]$ was 81%. The spectroscopic data matched literature values. ^{1}H NMR (25 °C, CD_2Cl_2): δ 1.84 (s, 12H), 2.39 (s, 6H), 3.80 (s, 4H), 6.89 (s, 4H). ^{19}F NMR (25 °C, CD_2Cl_2):δ –31.33 (s, 3F).

5.4.3.2. Trifluoromethylation of 4-Iodobiphenyl at Standard Conditions

5.4.3.2.1. General Procedure for the Standard Conditions of Trifluoromethylation of 4-Iodobiphenyl (Systems A1, B1, and C1)

To a 20 mL vial, (0.279 mmol, 1.20 equiv.) of copper trifluoromethyl reagent was stirred in 5.40 mL of DMF. To the solution, 67.1 mg (0.232 mmol) of 4-iodobiphenyl and 60.50 µL (0.2851 mmol) of undecane, as internal standard, were added to the vial. After the solution was allowed to stir for five minutes, 0.60 mL aliquots were taken and transferred into 5 mL air-tight ampules. The ampules were sealed and placed in an oil bath at 50 °C. The reactions were removed and quenched with 0.60 mL of methanol in air. Each solution was run on GC-FID for formation of the respective 4-trifluoromethylbiphenyl product. Trifluoromethyl reagents used were (phen)$CuCF_3$ and $[(SIMes)_2Cu][Cu(CF_3)_2]$ (0.140 mmol).

5.4.3.2.2. Grushin's Reagent $(PPh_3)_3CuCF_3$ (5f, System C1):

A vial was charged with (0.232 mmol) of 4-iodobiphenyl, 264 mg (0.288 mmol) of $(PPh_3)_3CuCF_3$, and 77.2 mg (0.288 mmol) of 4,4′-di-tert-butyl-2,2′-dipyridyl in 5.4 mL of DMF as solvent. Grushin's reagent **5f** was prepared according to reported literature.[11]

5.4.3.2.3. General procedure for the Standard Conditions of Trifluoromethylation of 4-Iodobiphenyl Using *In Situ* Reagents (Systems B2, B3, and D1)

Preparation of each reagent (**B2, B3, and D1**) is described below followed by addition of 60.50 µL (0.2851 mmol) of undecane, as internal standard. After the solution was allowed to stir for five minutes, 0.60 mL aliquots were taken and transferred into 5 mL air-tight ampules. The ampules were sealed and placed in an oil bath at 50 °C. The reactions were removed and quenched with 0.60 mL of methanol in air. Each solution was run on GC-FID for formation of the respective 4-trifluoromethylbiphenyl product.

5.4.3.2.4. Hartwig's Reagent (5d, System B2):

For the preparation of *in situ* (phen)$CuCF_3$, a vial was charged with 28.4 mg (0.279 mmol) of CuCl, 32.3 mg (0.279 mmol) of KO*t*Bu, and 51.5 mg (0.279 mmol) of 1,10-phenanthroline. To the vial, 5.4 mL of DMF was added. The solution was stirred for 0.5 h before the addition of 0.0423 mL (0.407 mmol) of $(Me)_3SiCF_3$. The solution was stirred for an additional hour before the introduction of 0.232 mmol of 4-iodobiphenyl.

5.4.3.2.5. Borate Reagent (5h, System B3):

A vial was charged with (0.232 mmol) of 4-iodobiphenyl, 53.6 mg (0.279 mmol) of CuI, 60.5 mg (0.279 mmol) of $[K][B(OMe_3)(CF_3)]$, and 51.5 mg (0.279 mmol) of 1,10-phenanthroline in 5.4 mL of DMF as solvent. The borate reagent **5h** was prepared according to reported procedure.[10,16,17]

5.4.3.2.6. Fuchikami L_nCuCF_3 (System D1):

A vial was charged with (0.232 mmol) of 4-iodobiphenyl, 53.6 mg (0.279 mmol) of CuI, 16.7 mg (0.279 mmol) of KF, and 0.0423 mL (0.279 mmol) of $(Me)_3SiCF_3$ in 5.4 mL of DMF as solvent.

5.4.3.3. General Procedure for the 'Best' Conditions of Trifluoromethylation of 4-Iodobiphenyl (System A1 and C1)

5.4.3.3.1. Vicic's $[(SIMes)_2Cu][Cu(CF_3)_2]$ (5c, System A1):

A vial was charged with 1.150 mmol of 4-iodobiphenyl and 105 mg (0.240 mmol) of $[(SIMes)_2Cu][Cu(CF_3)_2]$ in 5.4 mL of DMI/benzene (1.5:7.5) with 60.50 µL (0.2851 mmol) of undecane, as internal standard. After the solution was allowed to stir for five minutes, 0.60 mL aliquots were taken and transferred into 5 mL air-tight ampules. The ampules were sealed and placed in an oil bath at 50 °C. The reactions were removed and quenched with 0.60 mL of methanol in air. Each solution was run on GC-FID for formation of the respective 4-trifluoromethylbiphenyl product.

5.4.3.3.2. Grushin's Reagent $(PPh_3)_3CuCF_3$ (5f, System C1):

A vial was charged with 0.307 mmol of 4-iodobiphenyl, 264 mg (0.288 mmol) of $(PPh_3)_3CuCF_3$, and 85.0 mg (0.316 mmol) of 4,4′-di-tert-butyl-2,2′-dipyridyl in 5.4 mL of toluene with 60.50 µL (0.2851 mmol)) of undecane, as internal standard. After the solution was allowed to stir for five minutes, 0.60 mL aliquots were taken and transferred into 5 mL air-tight ampules. The ampules were sealed and placed in an oil bath at 80 °C. The reactions were removed and quenched with 0.60 mL of methanol in air. Each solution was run on GC-FID for formation of the respective 4-trifluoromethylbiphenyl

product. All data were treated with a best fit curve generated by Origin 9.0.0 program. The exponential fit with function ExpGro1 was selected for the data.

5.4.3.4. General Procedure for the trifluoromethylation of 2-iodotoluene and 4-iodotoluene (System A1 and B2)

5.4.3.4.1. Vicic's $[(SIMes)_2Cu][Cu(CF_3)_2]$ (5c, System A1):

A vial was charged with 270 mg (1.20 mmol) of 2-iodotoluene or 4-iodotoluene and 105 mg (0.240 mmol) of $[(SIMes)_2Cu][Cu(CF_3)_2]$ in 5.4 mL of DMI/benzene (1.5:7.5) with 90.0 µL (0.949 mmol) of fluorobenzene, as internal standard. After the solution was allowed to stir for five minutes, 0.60 mL aliquots were taken and transferred into 5 mL air-tight ampules. The ampules were sealed and placed in an oil bath at 50 °C. The reactions were removed and quenched with 0.60 mL of methanol in air. Each solution was run by ^{19}F-NMR spectroscopy for formation of the respective 2-trifluoromethyltoluene or 4-trifluoromethyltoluene product.

5.4.3.4.2. *In Situ* Hartwig's Reagent (5d, System B2):

For the preparation of *in situ* (phen)$CuCF_3$, a vial was charged with 28.4 mg (0.279 mmol) of CuCl, 32.3 mg (0.279 mmol) of KO*t*Bu, and 51.5 mg (0.279 mmol) of 1,10-phenanthroline. To the vial, 5.4 mL of DMF was added. The solution was stirred for 0.5 h before the addition of 0.0423 mL (0.279 mmol) of $(Me_3)SiCF_3$. The solution was stirred for an additional hour before the introduction of 52.1 mg (0.232 mmol) of 2-iodotoluene or 4-iodotoluene and 90.0 µL (0.949 mmol) of fluorobenzene, as internal standard. After the solution was allowed to stir for five minutes, 0.60 mL aliquots were taken and transferred into 5 mL air-tight ampules. The ampules were sealed and placed in an oil bath at 50 °C. The reactions were removed and quenched with 0.60 mL of

methanol in air. Each solution was run by ^{19}F-NMR spectroscopy for formation of the respective 2-trifluoromethyltoluene or 4-trifluoromethyltoluene product.

5.5. References

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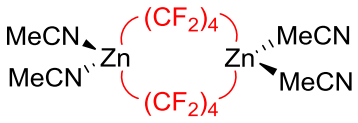
Chapter 6. Appendix

6.1. Data and Spectra for Chapter 2

Figure 6.1a: ^{19}F NMR spectrum of **2l**  in CD_3CN:

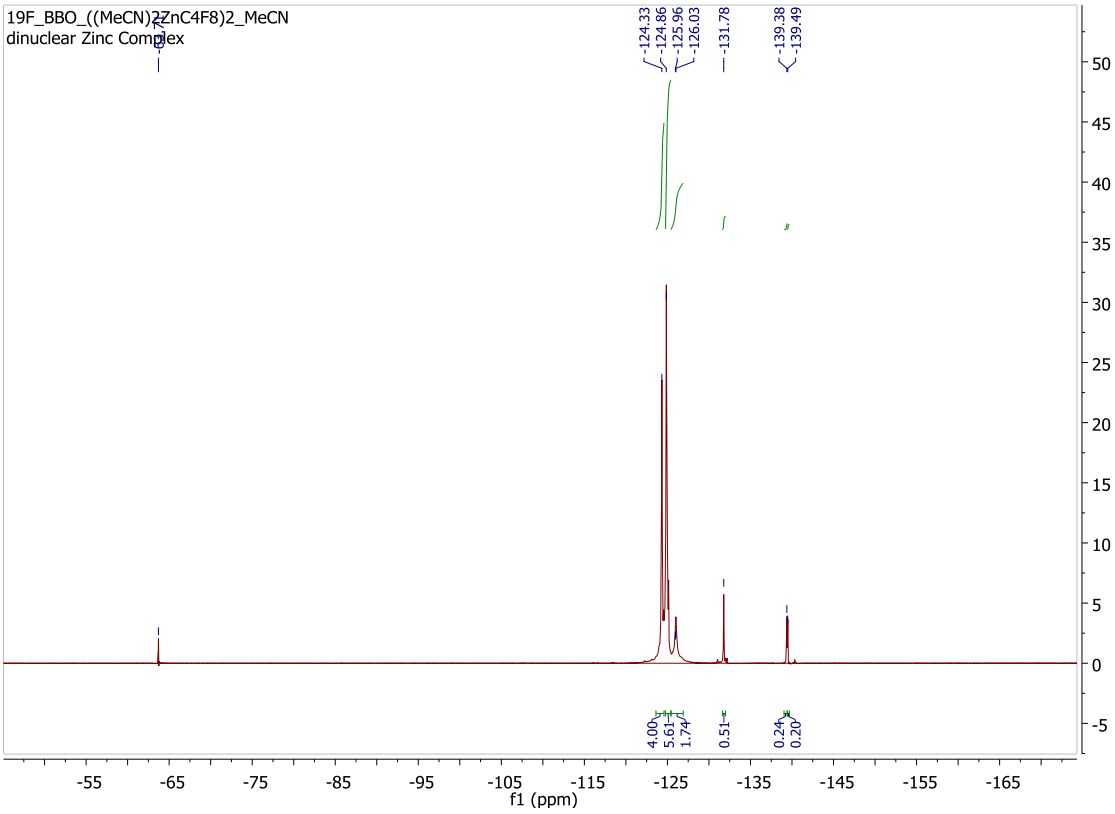
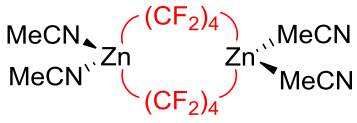


Figure 6.1b: ^{1}H NMR spectrum of **2l** 

in CD_3CN: Fluorine internal standard and benzene (for crystallization) show up at 7.37 to7.75 ppm.

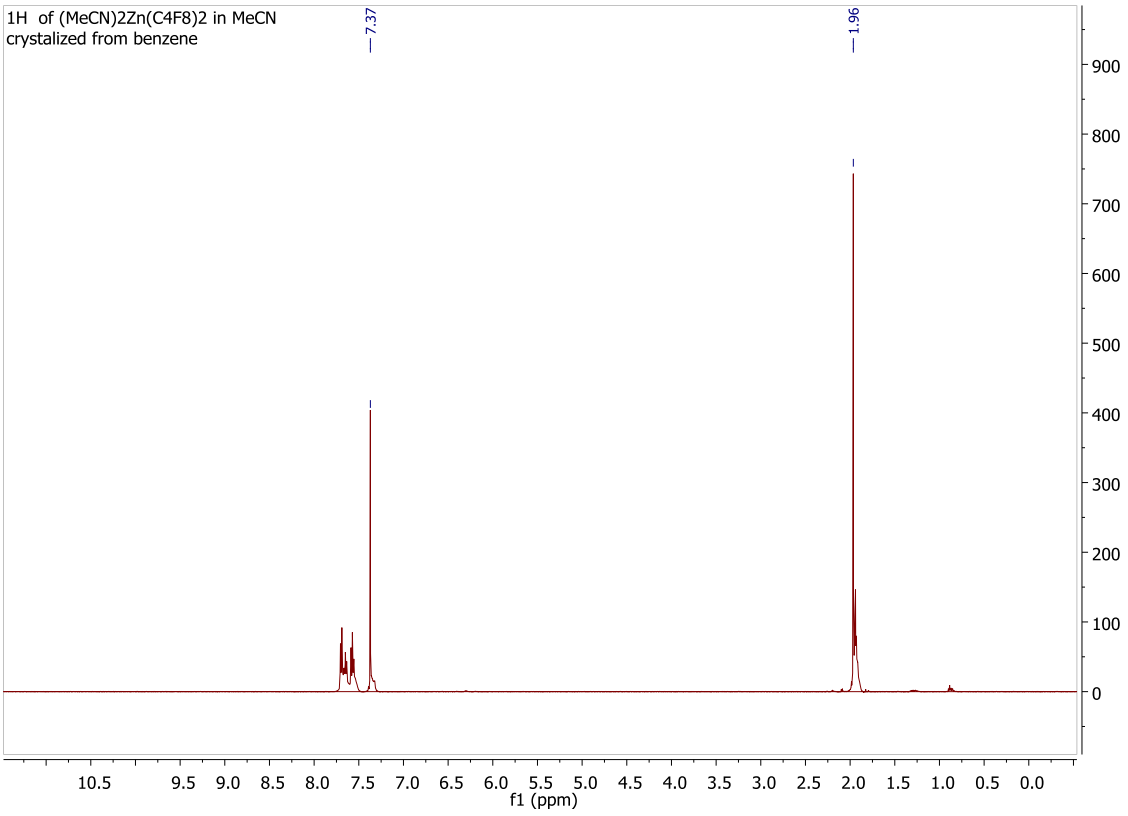
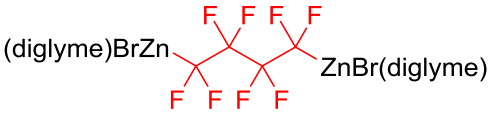


Figure 6.1c: ^{19}F NMR spectrum of **2aa** 

in THF–*d*8 :

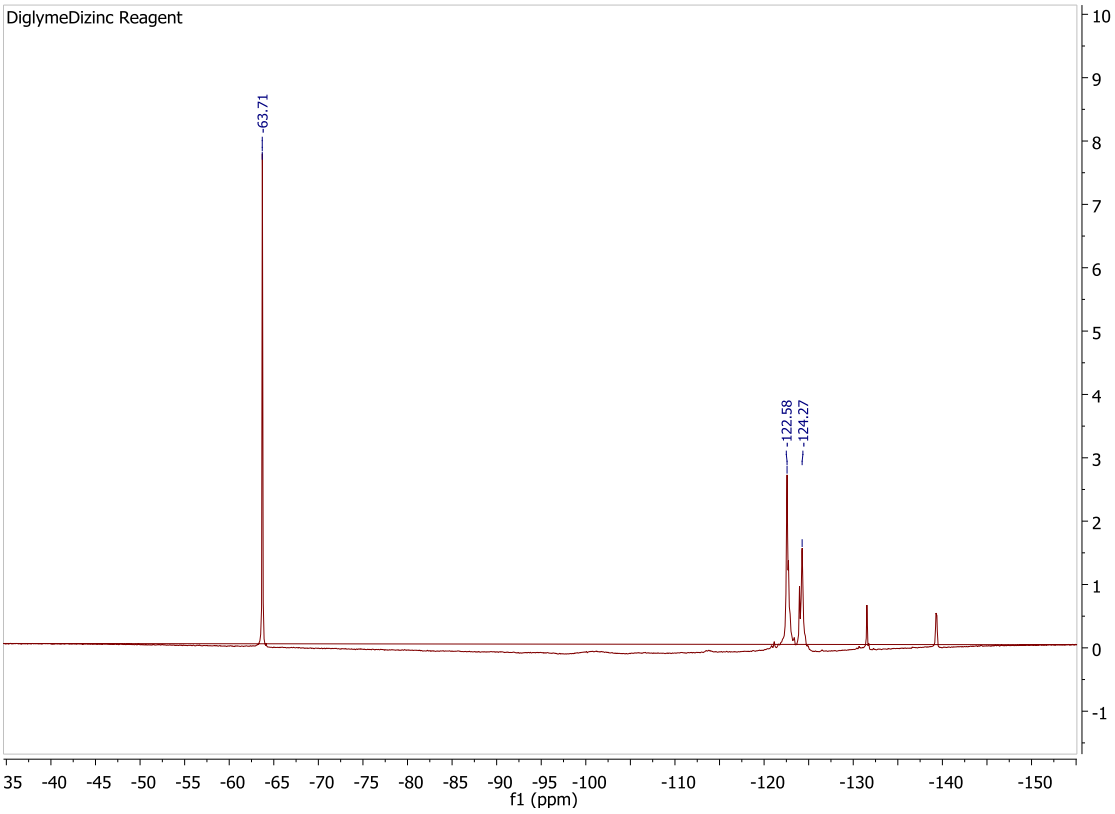
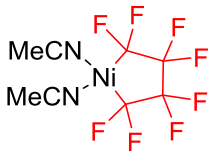
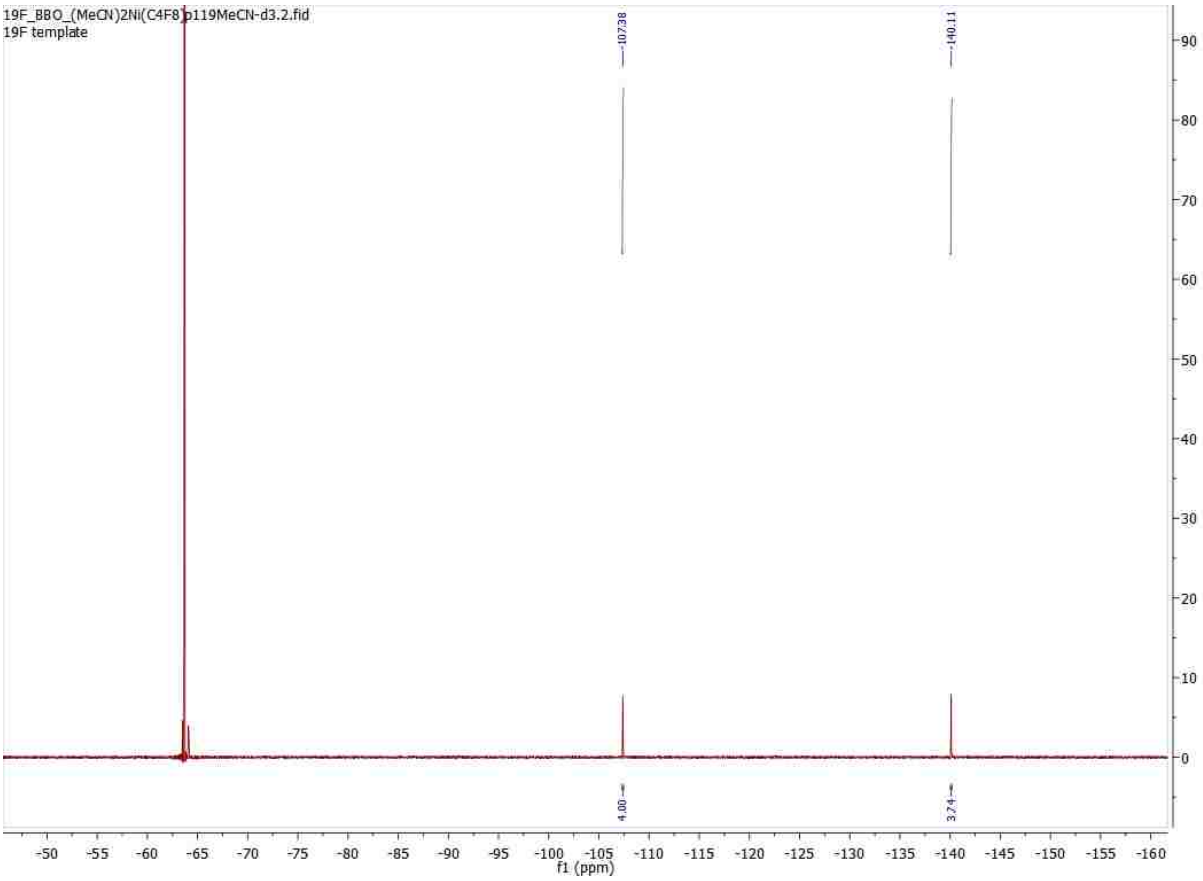


Figure 6.1d: ^{19}F NMR spectrum of **2o** 

in CD_3CN:



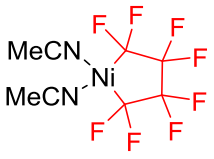
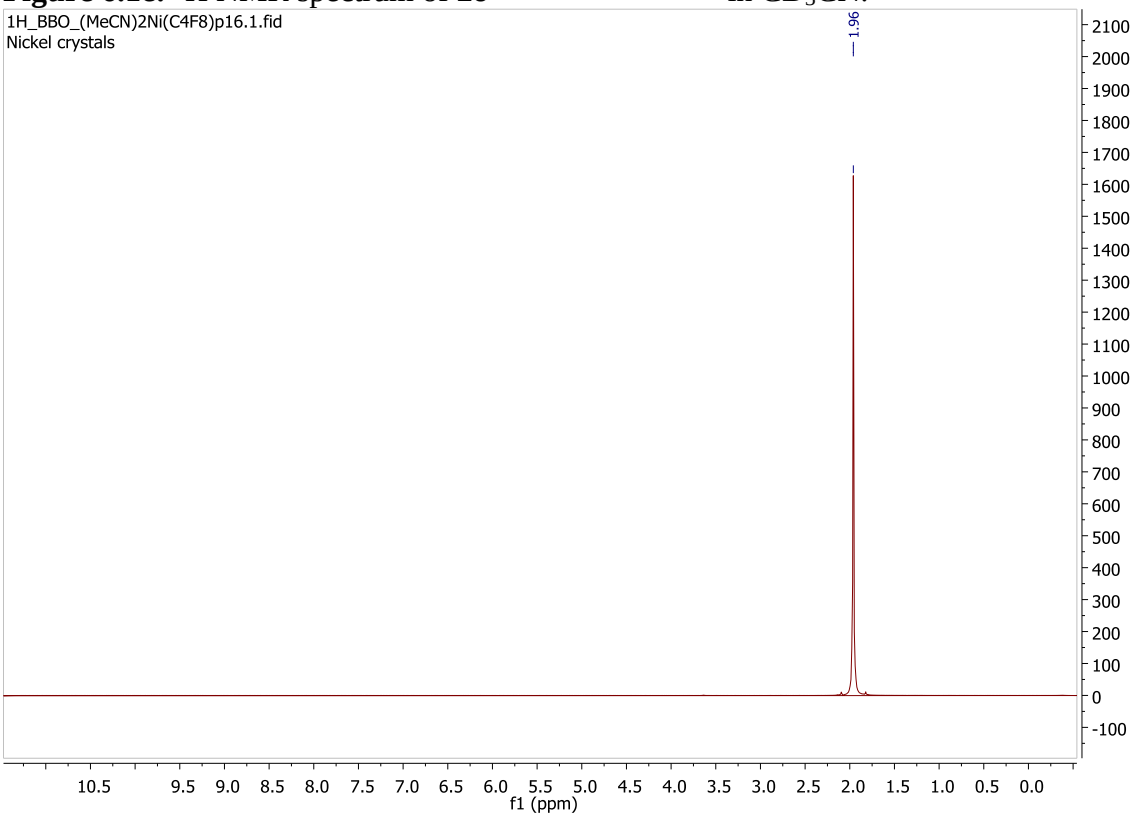


Figure 6.1e: ^{1}H NMR spectrum of **2o** in CD_3CN:



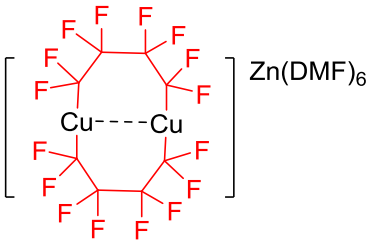
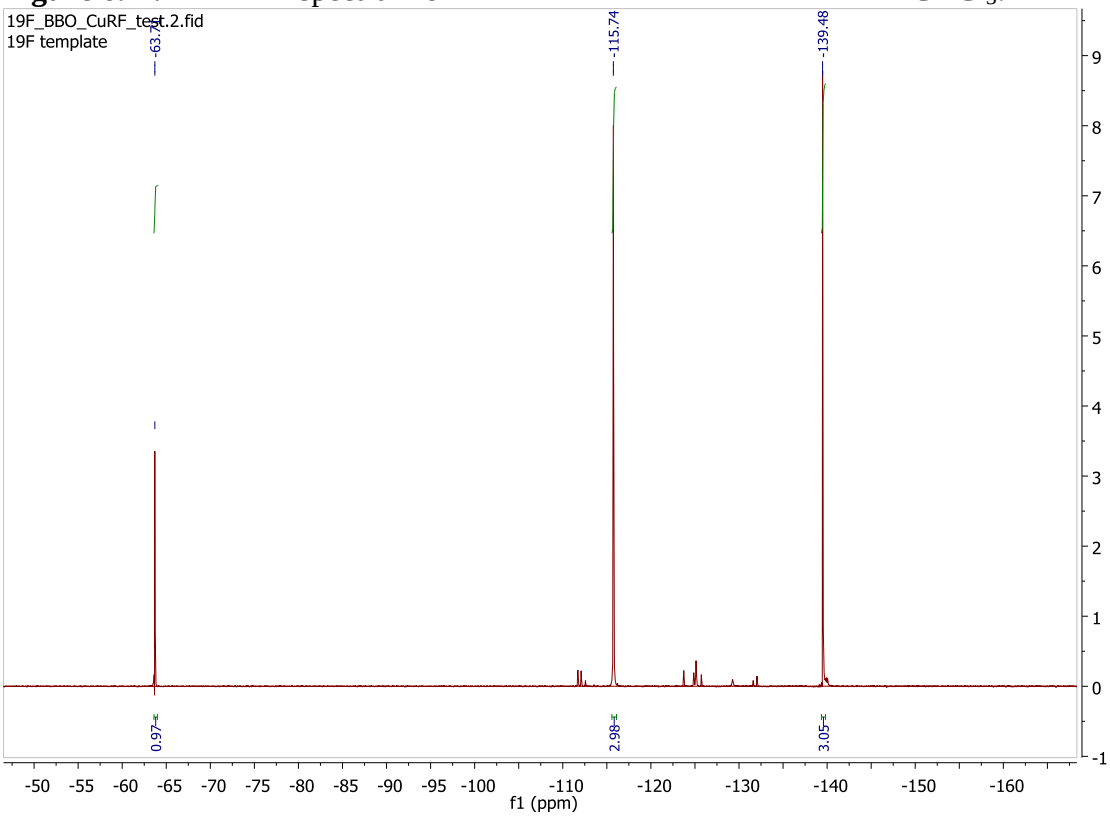


Figure 6.1f: ^{19}F NMR spectrum of **2r** in $CDCl_3$:



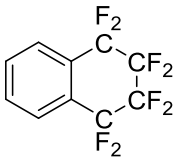


Figure 6.1g: ^{19}F NMR spectrum of **2z** in ethyl ether:

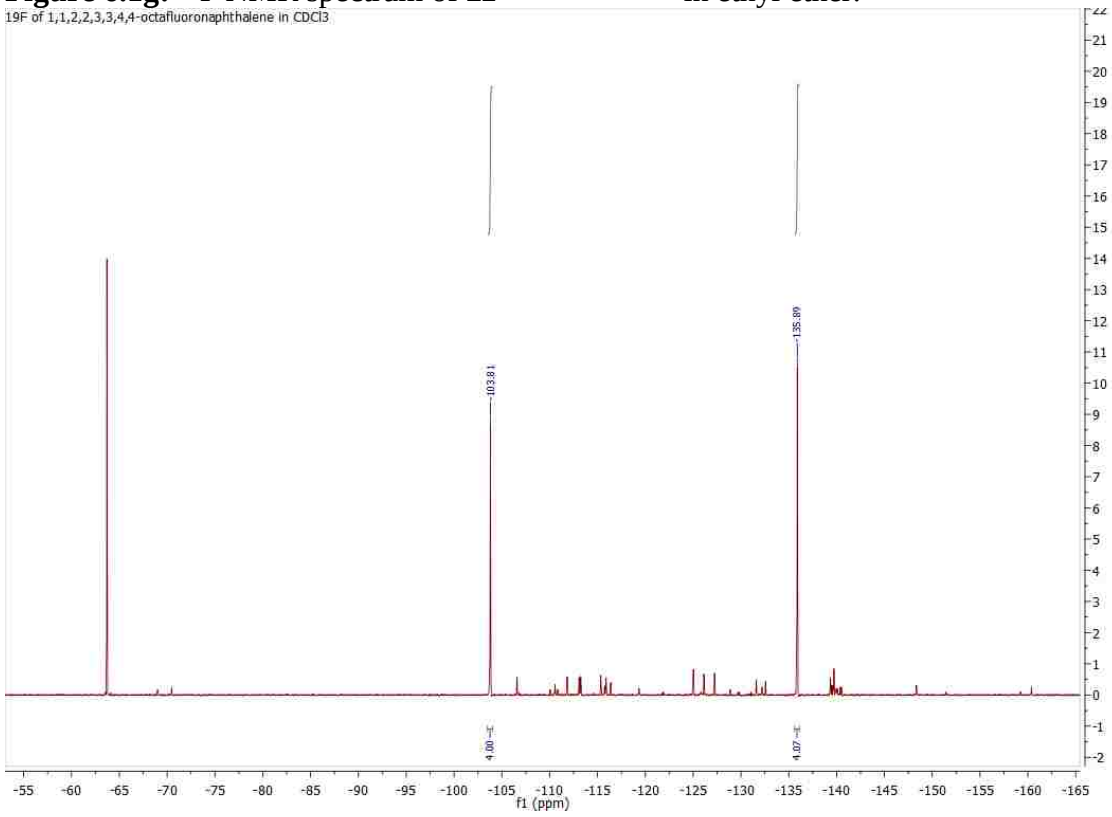
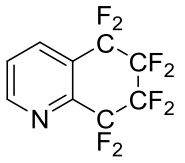
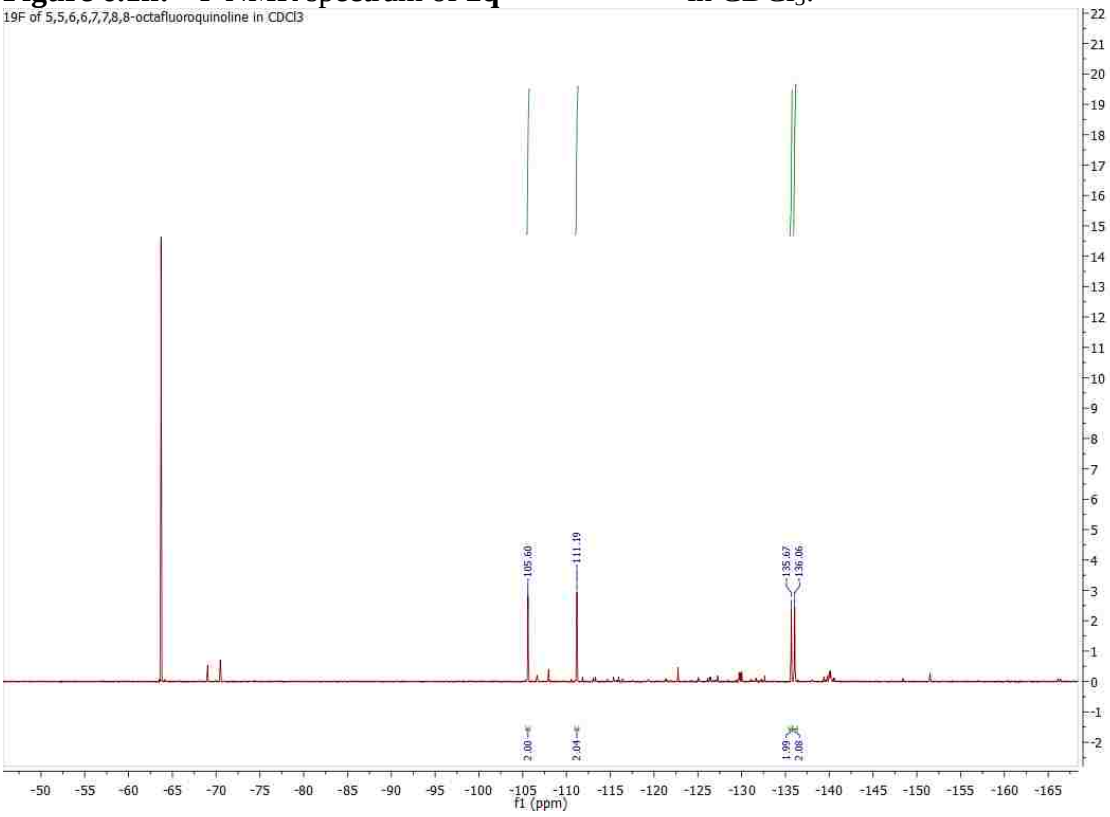


Figure 6.1h: ^{19}F NMR spectrum of **2q**  in $CDCl_3$:



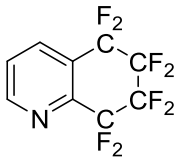
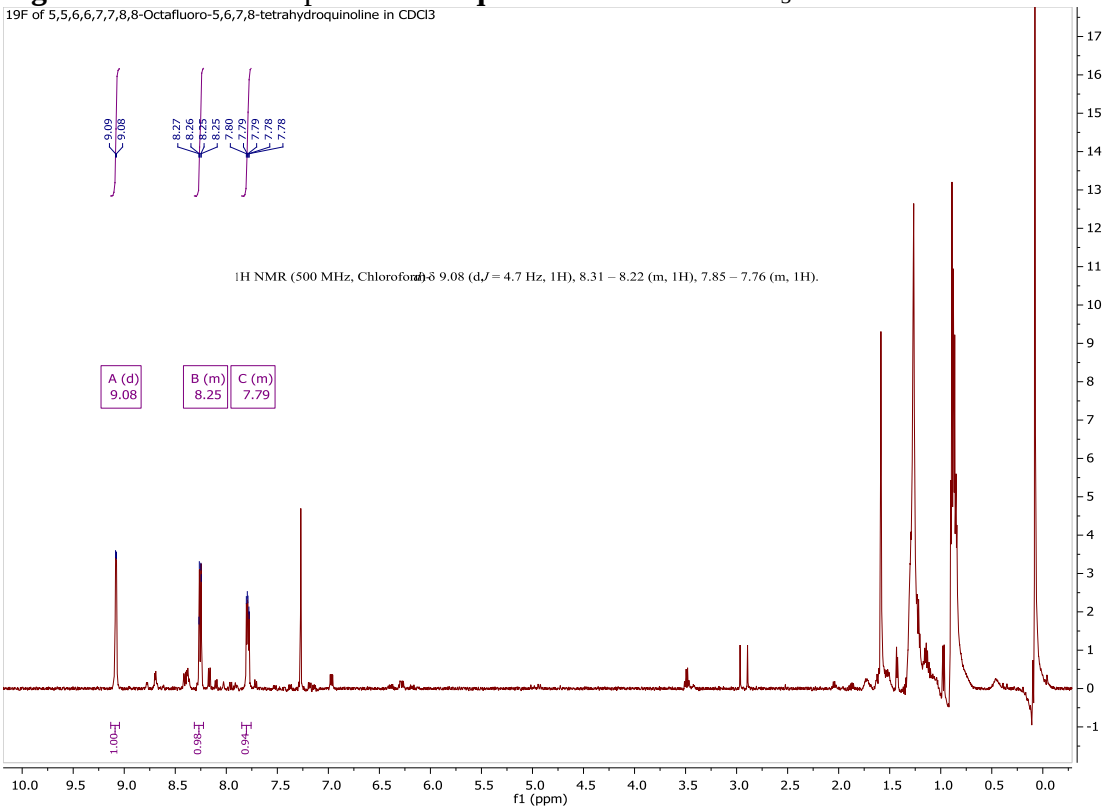


Figure 6.1i: ^{1}H NMR spectrum of **2q** in $CDCl_3$:



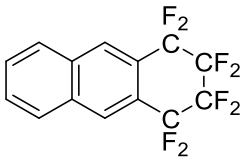
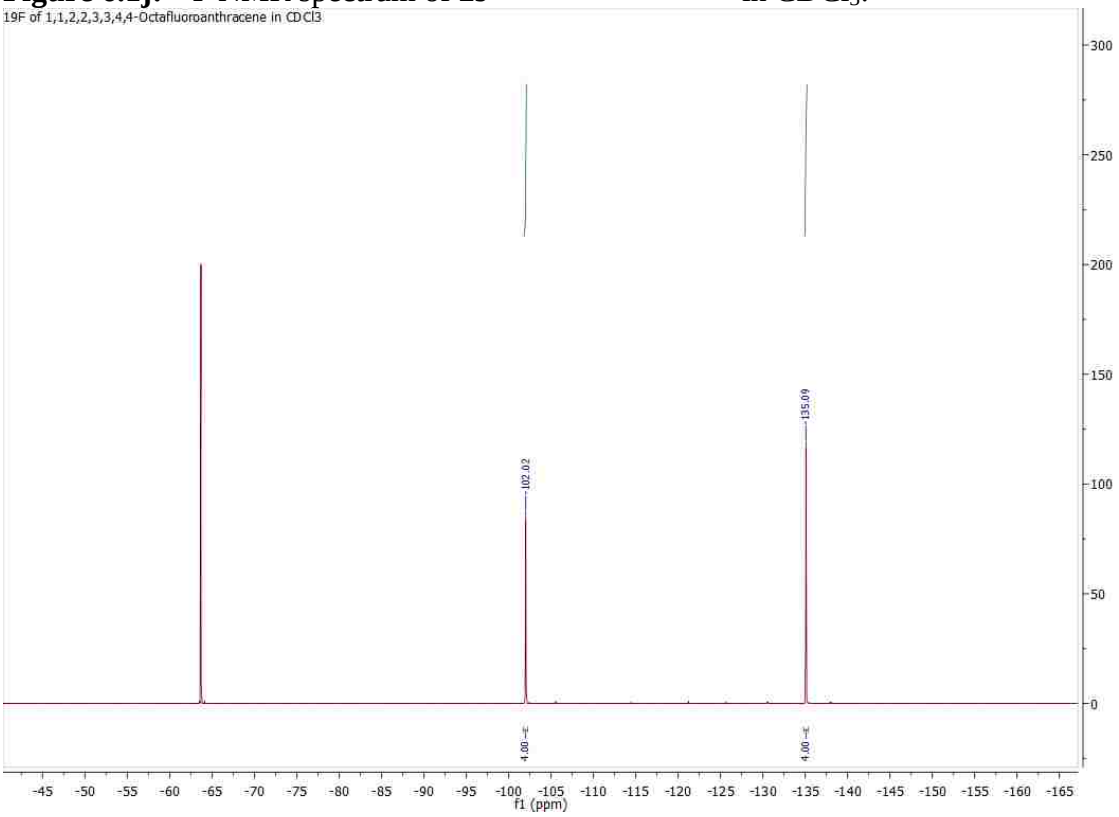


Figure 6.1j: ^{19}F NMR spectrum of **2s** in $CDCl_3$:



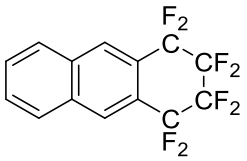


Figure 6.1k: ^{1}H NMR spectrum of **2s** in $CDCl_3$:

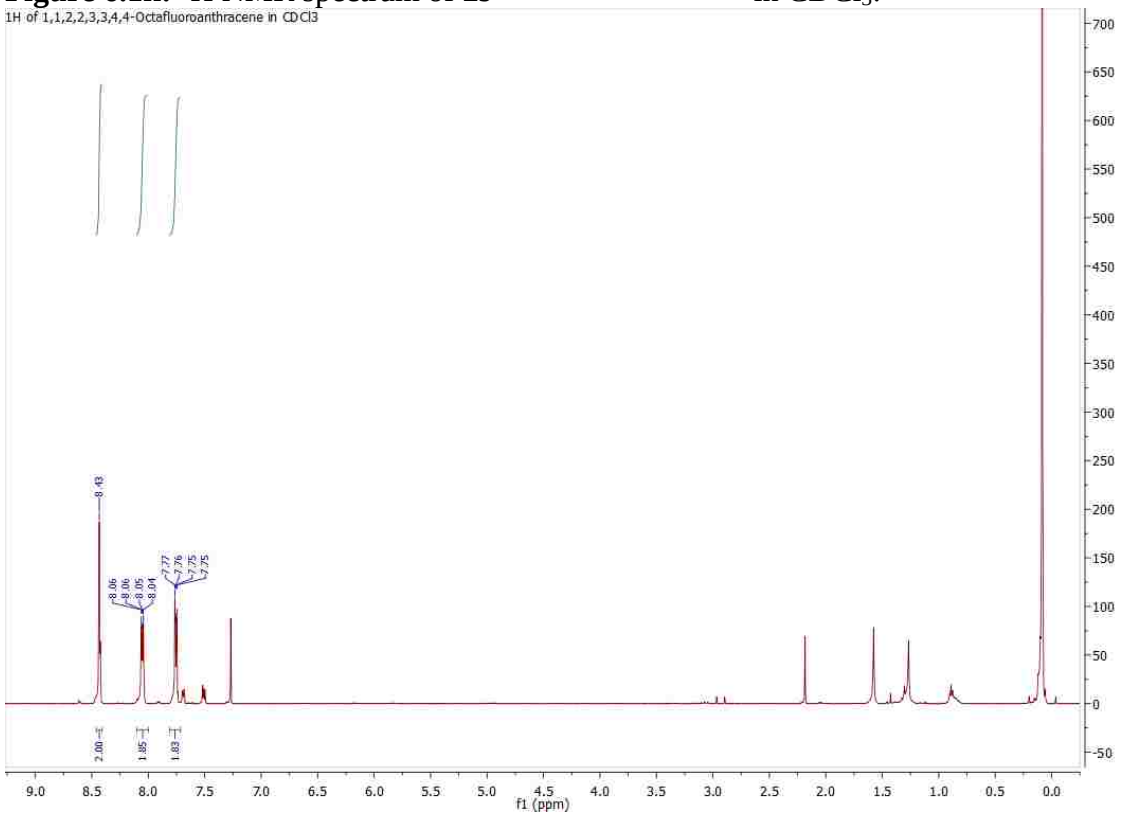
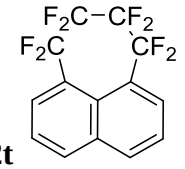


Figure 6.1l: ^{19}F NMR spectrum of **2t**  in $CDCl_3$:

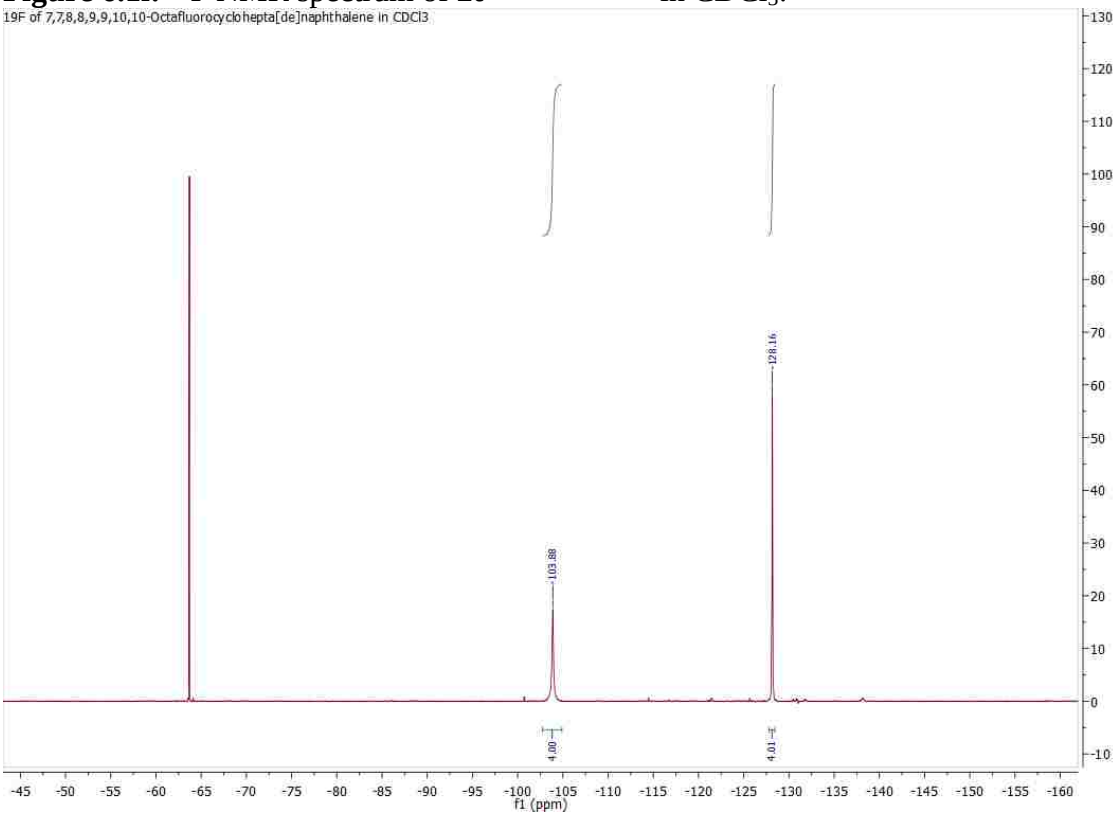
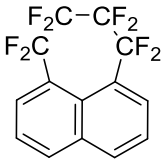


Figure 6.1m: ^{1}H NMR spectrum of **2t**  in $CDCl_3$:

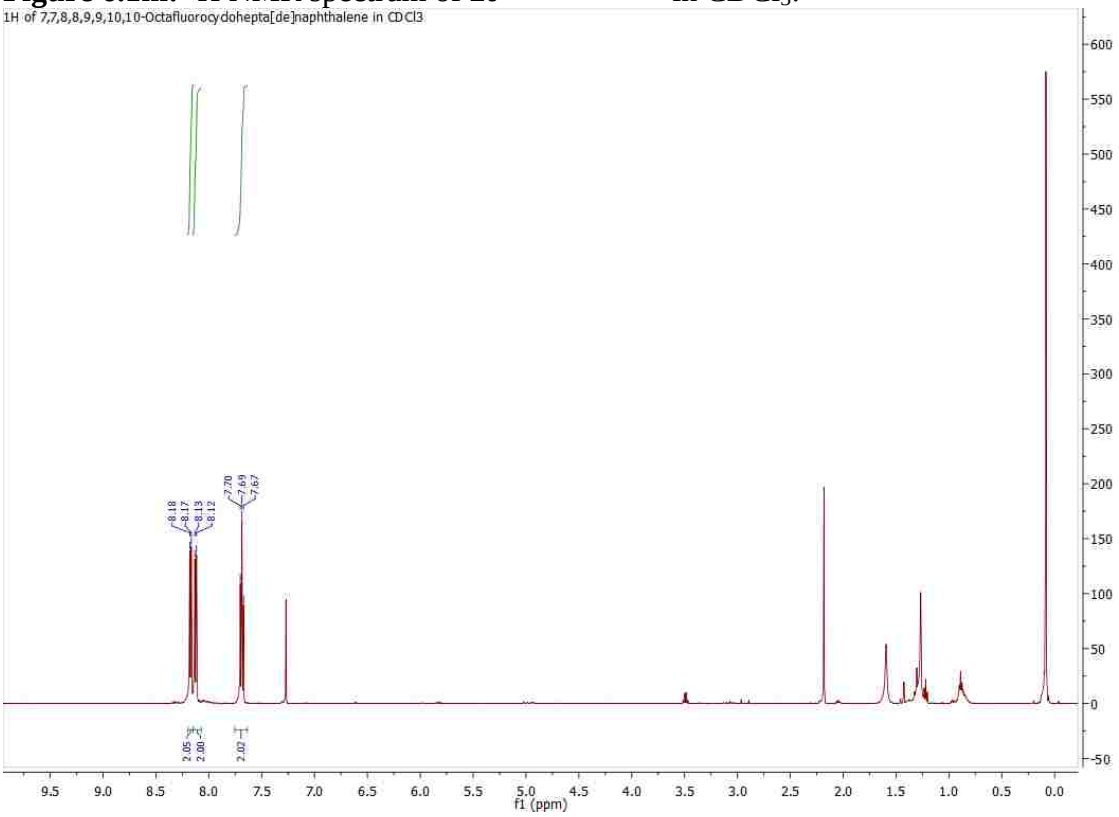
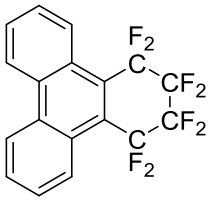


Figure 6.1n: ^{19}F NMR spectrum of **2u**  in $CDCl_3$:

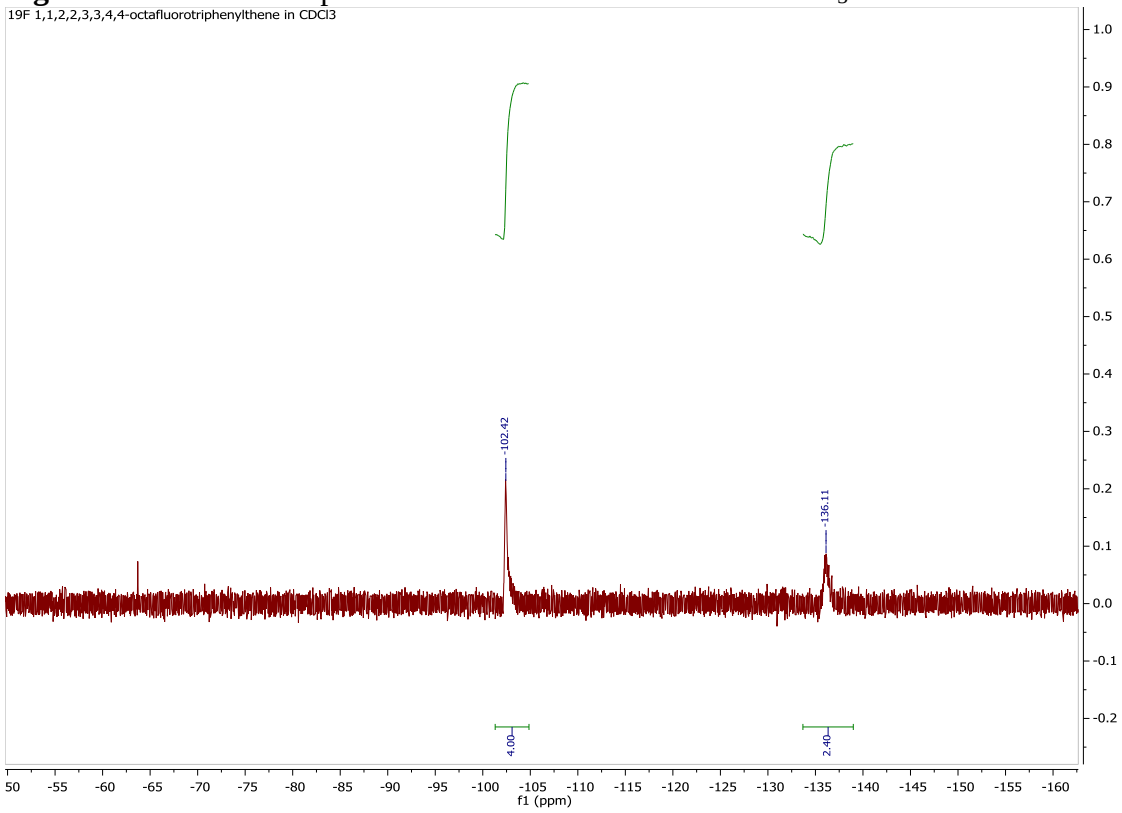
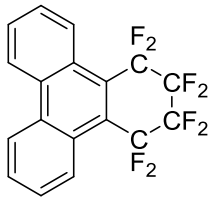
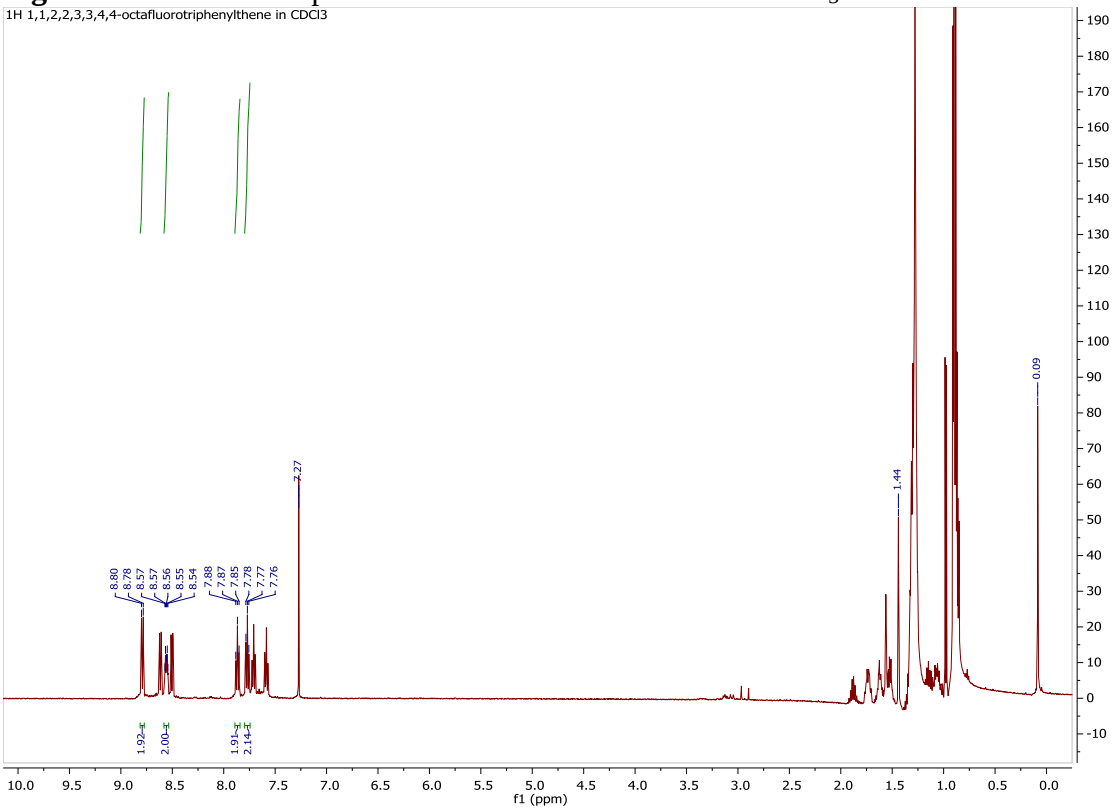


Figure 6.1o: ^{1}H NMR spectrum of **2u**  in $CDCl_3$:



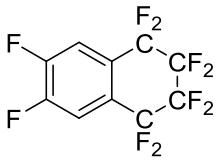


Figure 6.1p: ^{19}F NMR spectrum of **2v** in $CDCl_3$: Residual starting material also still observed.

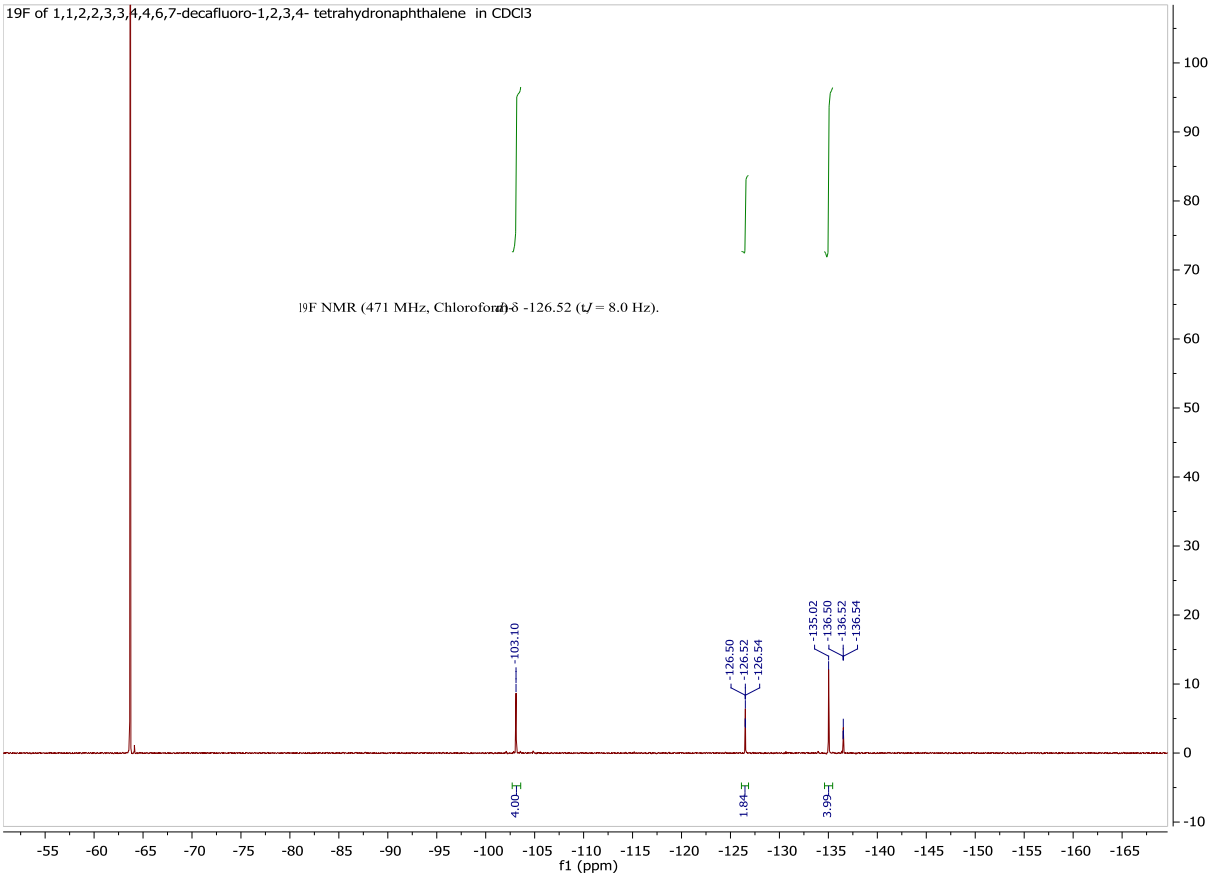
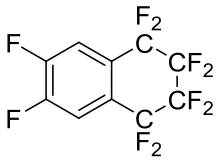


Figure 6.1q: ^{1}H NMR spectrum of **2v**  in $CDCl_3$: Residual starting material also still observed.

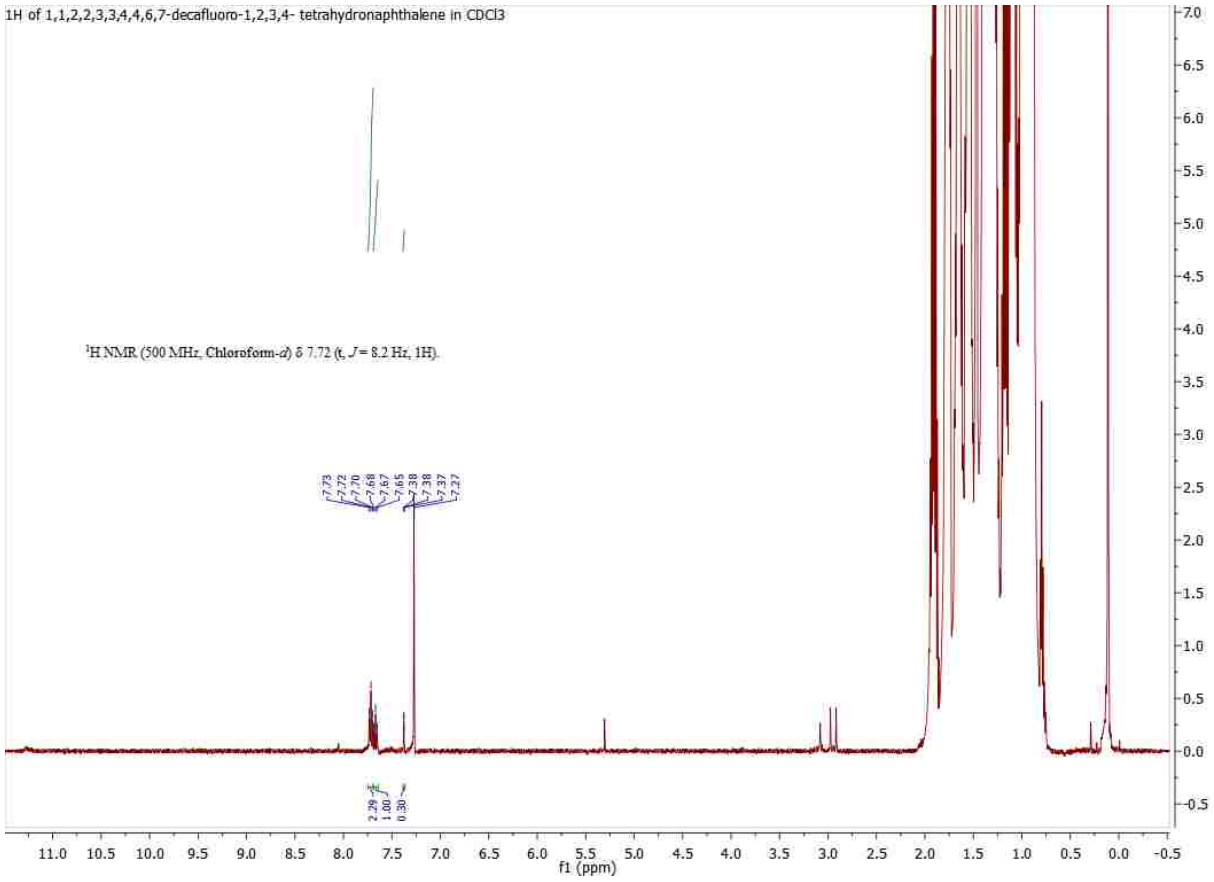
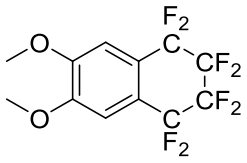
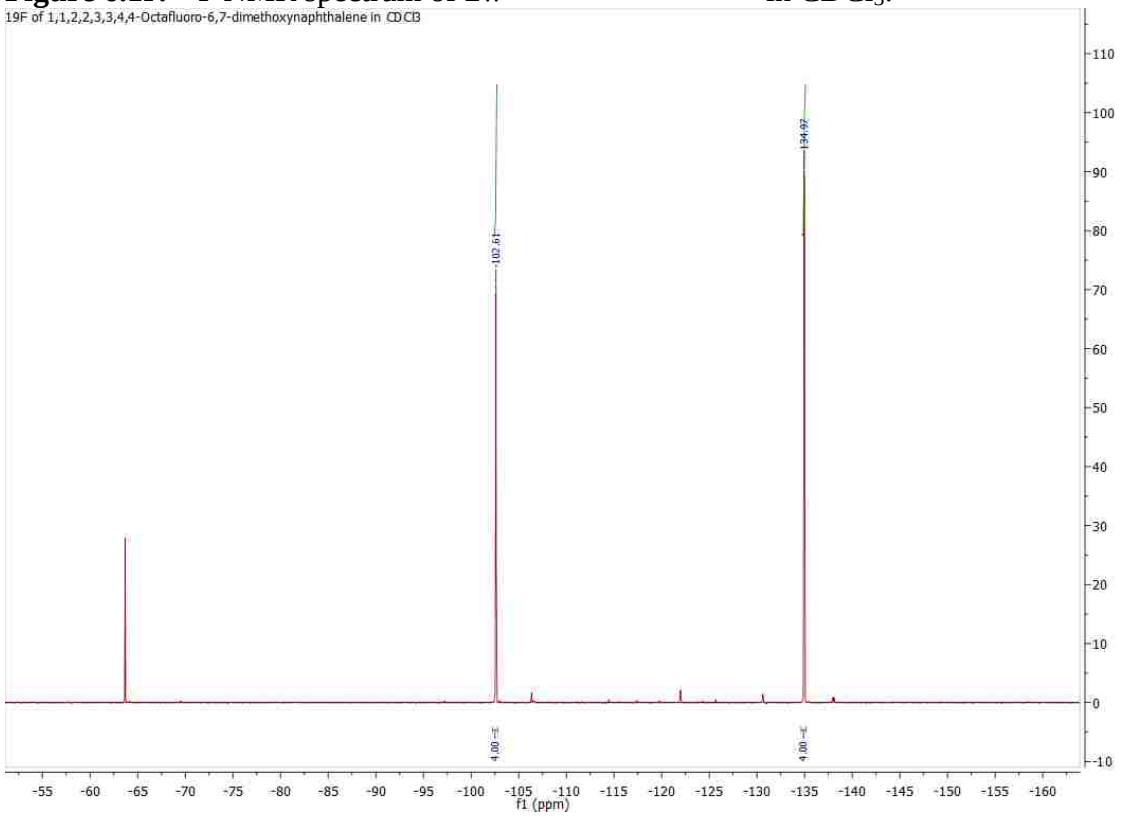


Figure 6.1r: ^{19}F NMR spectrum of **2w**  in $CDCl_3$:



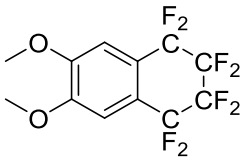


Figure 6.1s: ^{1}H NMR spectrum of **2w** in $CDCl_3$: Residual starting material also still observed.

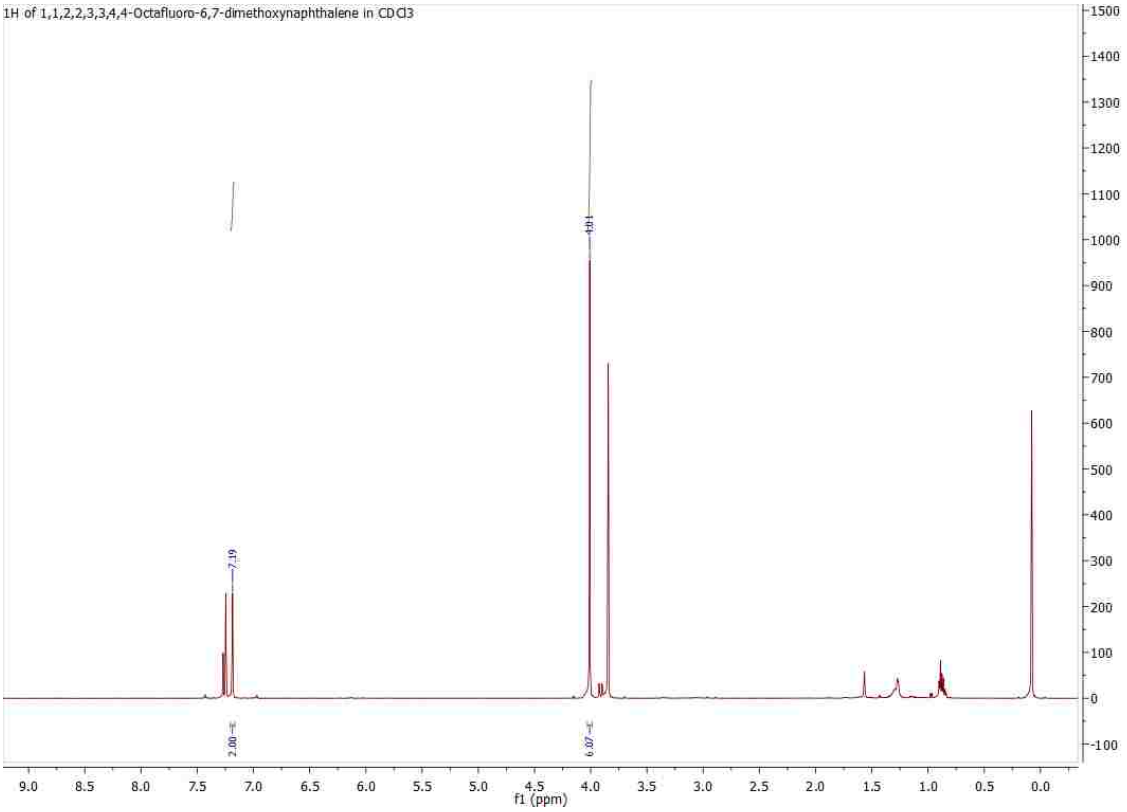
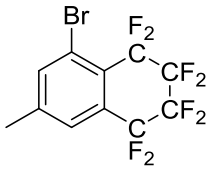


Figure 6.1t: ^{19}F NMR spectrum of **2x**  in $CDCl_3$:

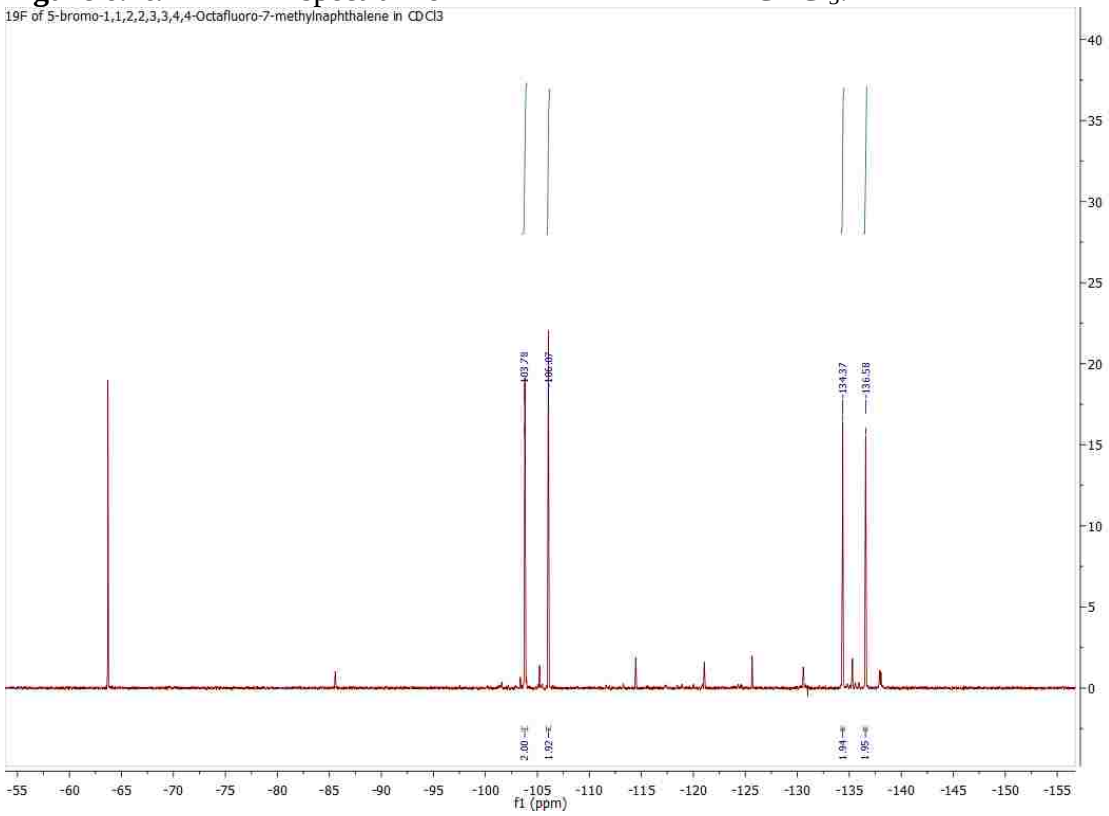
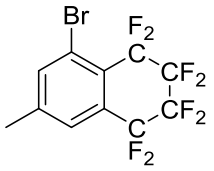
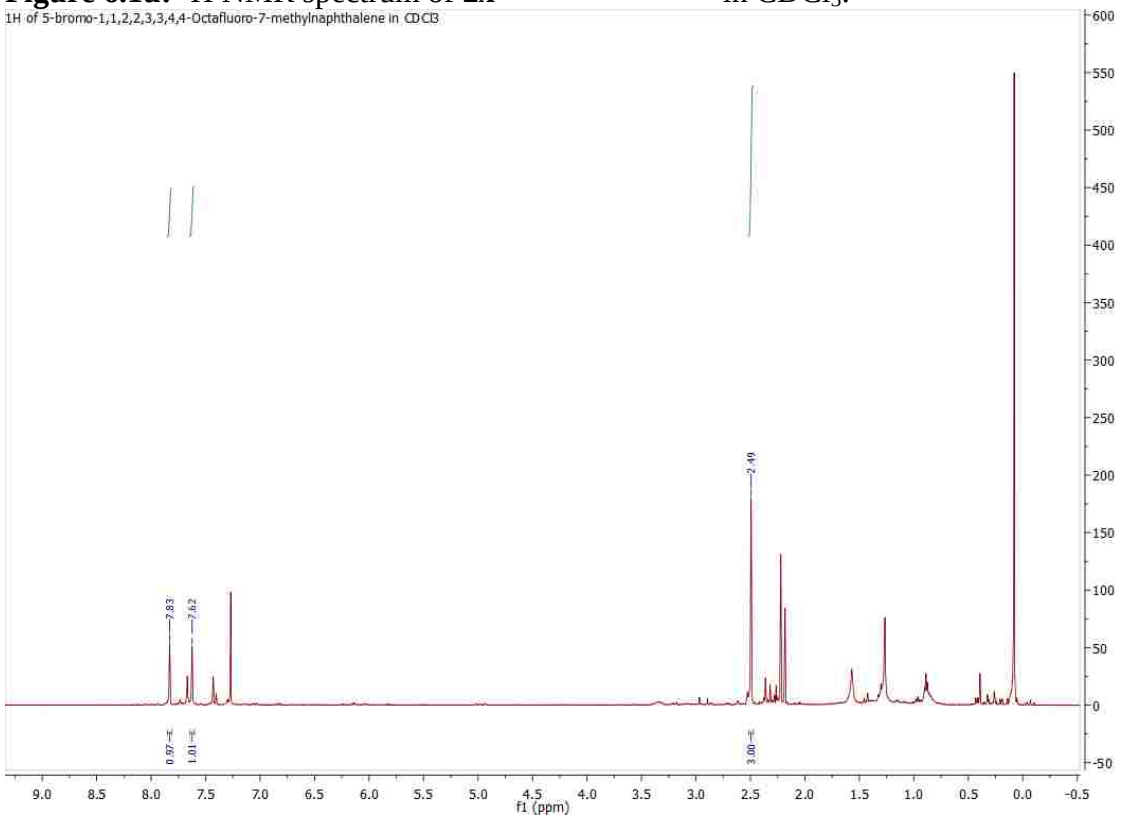


Figure 6.1u: ^{1}H NMR spectrum of **2x** 

in $CDCl_3$:



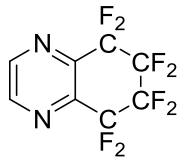
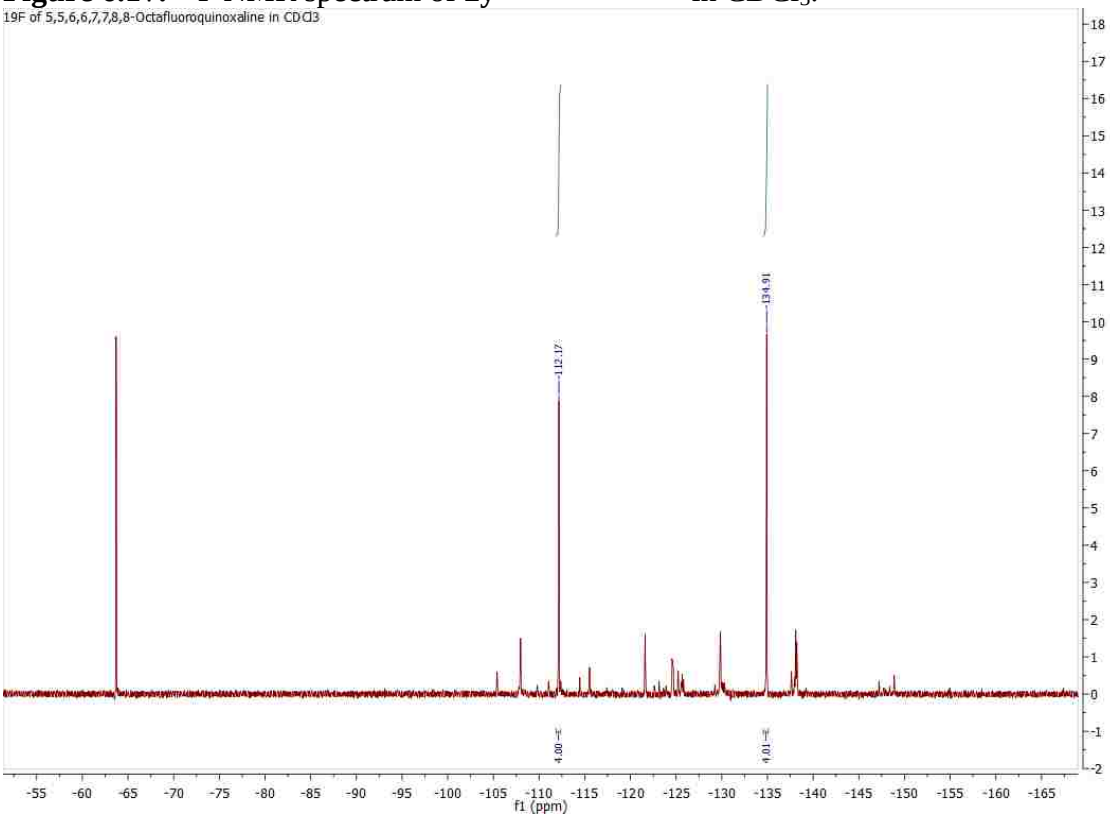


Figure 6.1v: ^{19}F NMR spectrum of **2y** in $CDCl_3$:



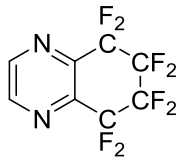
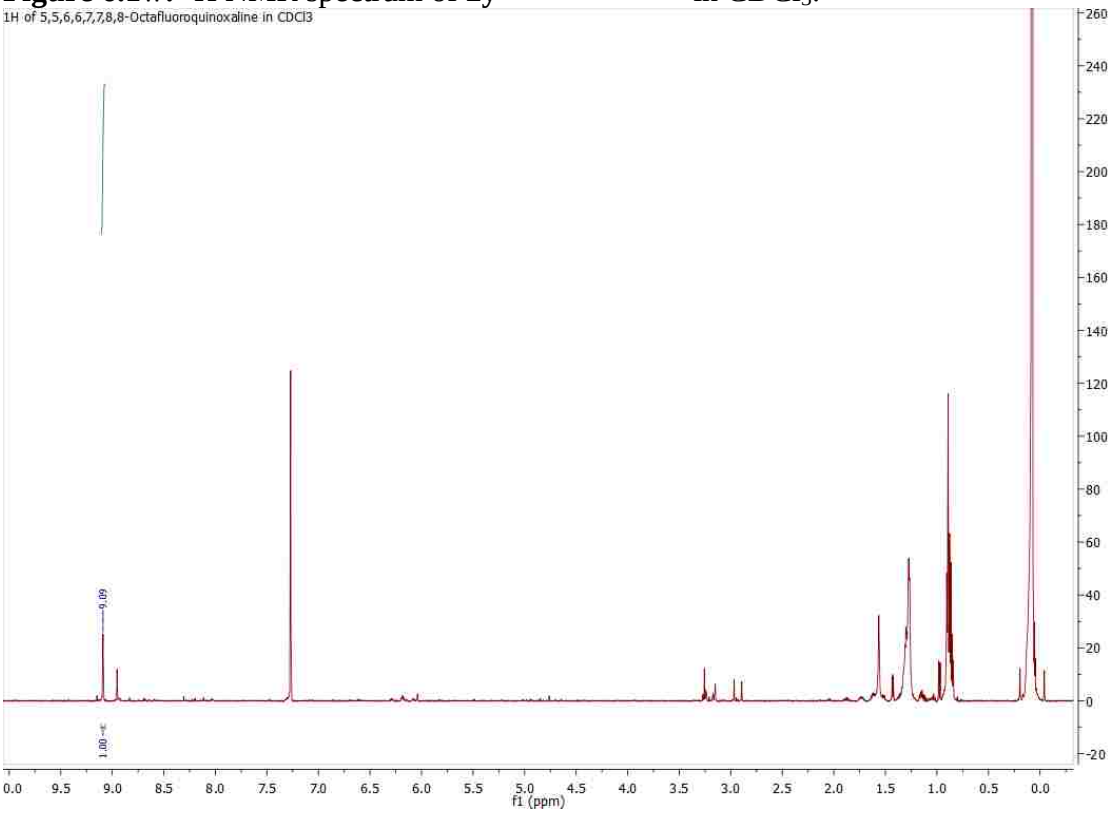
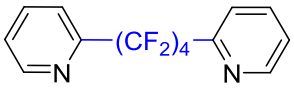


Figure 6.1w: ^{1}H NMR spectrum of **2y** in $CDCl_3$:



6.2. Data and Spectra for Chapter 3

Figure 6.2a: ^{19}F NMR spectrum of **3u**  in DMSO:

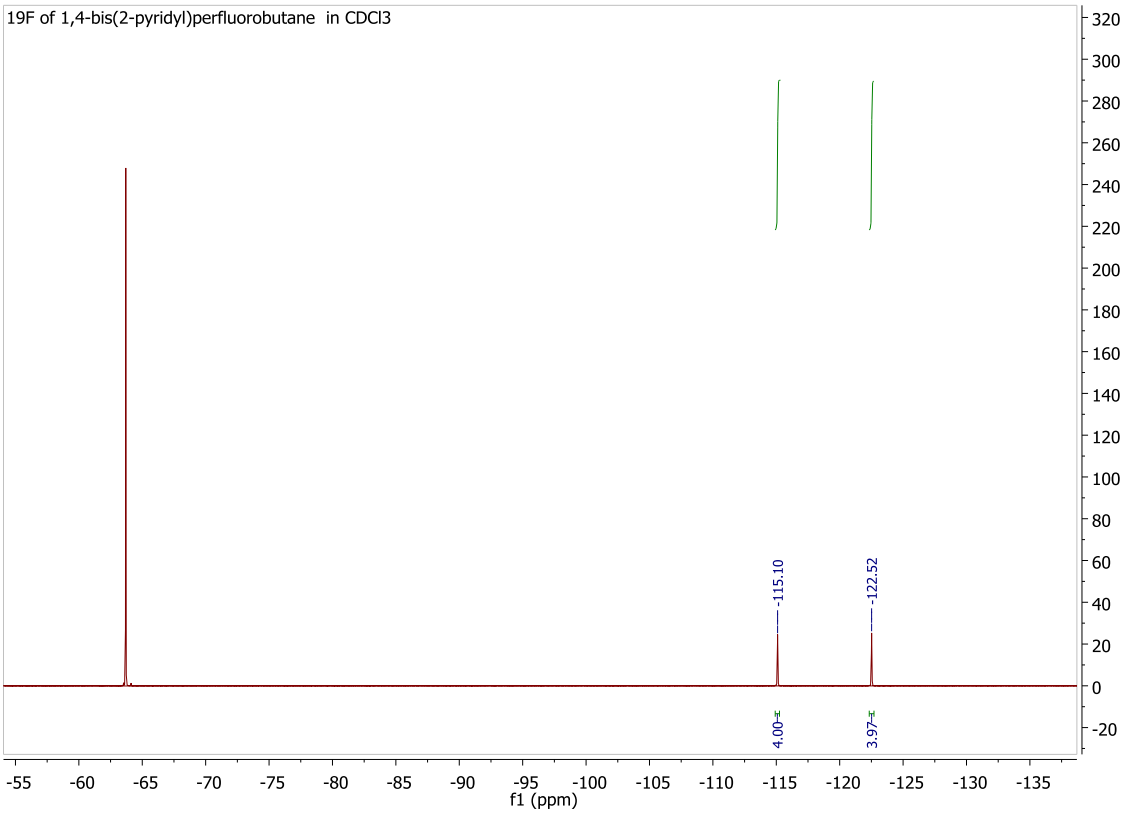
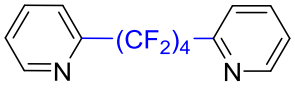


Figure 6.2b: ^{1}H NMR spectrum of **3u**  in DMSO:

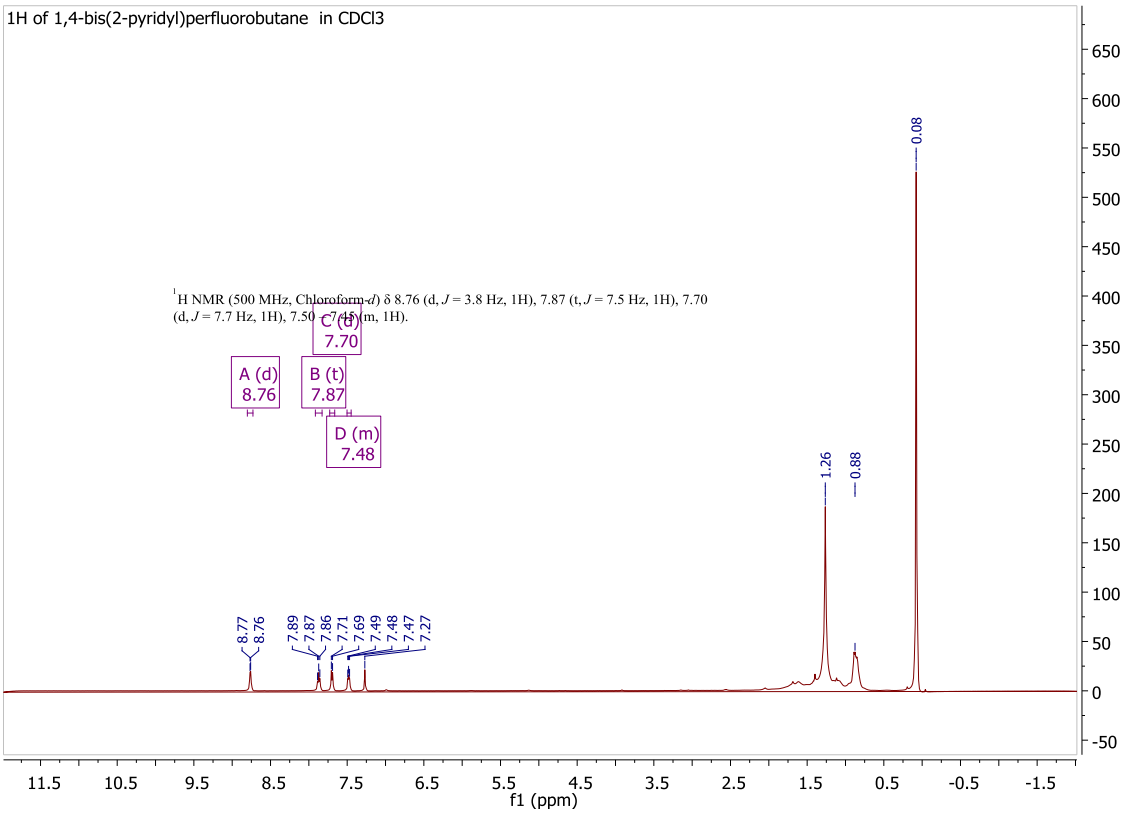
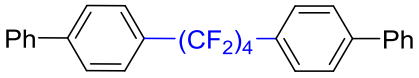


Figure 6.2c: ^{19}F NMR spectrum of **3x**  in DMSO:

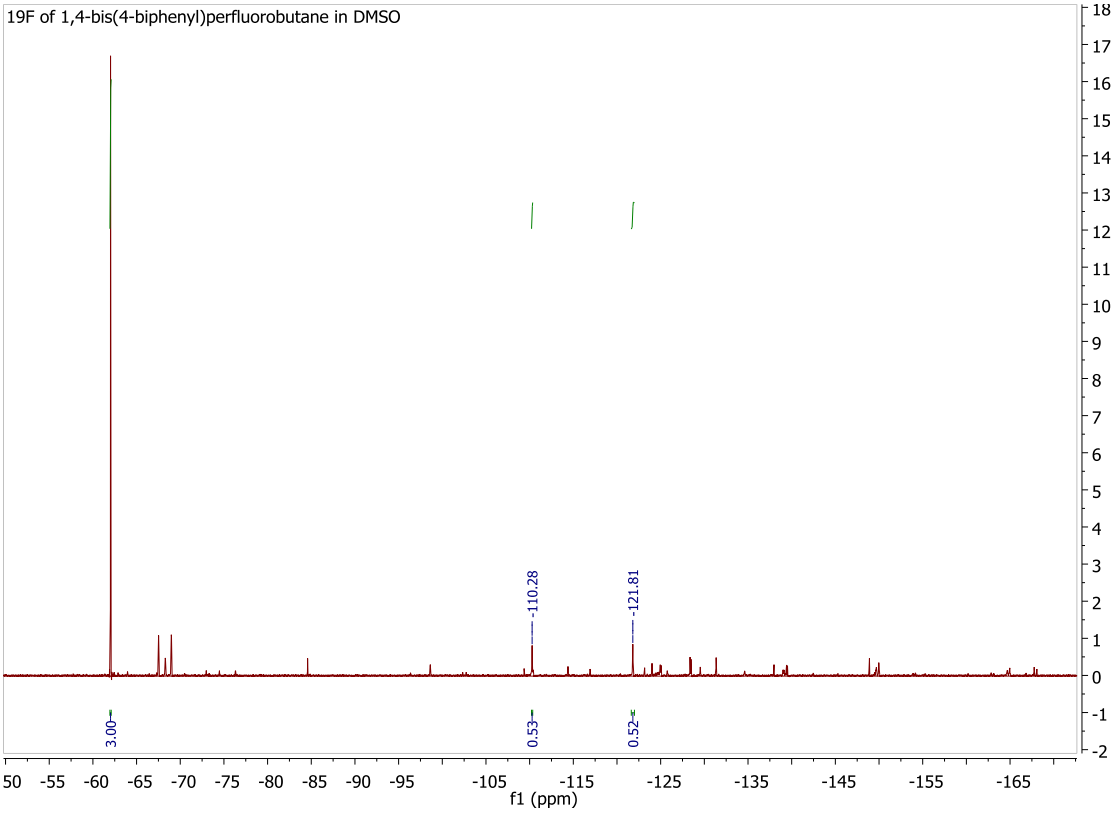
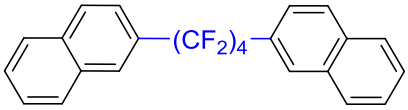


Figure 6.2d: ^{19}F NMR spectrum of **3y**  in DMSO:

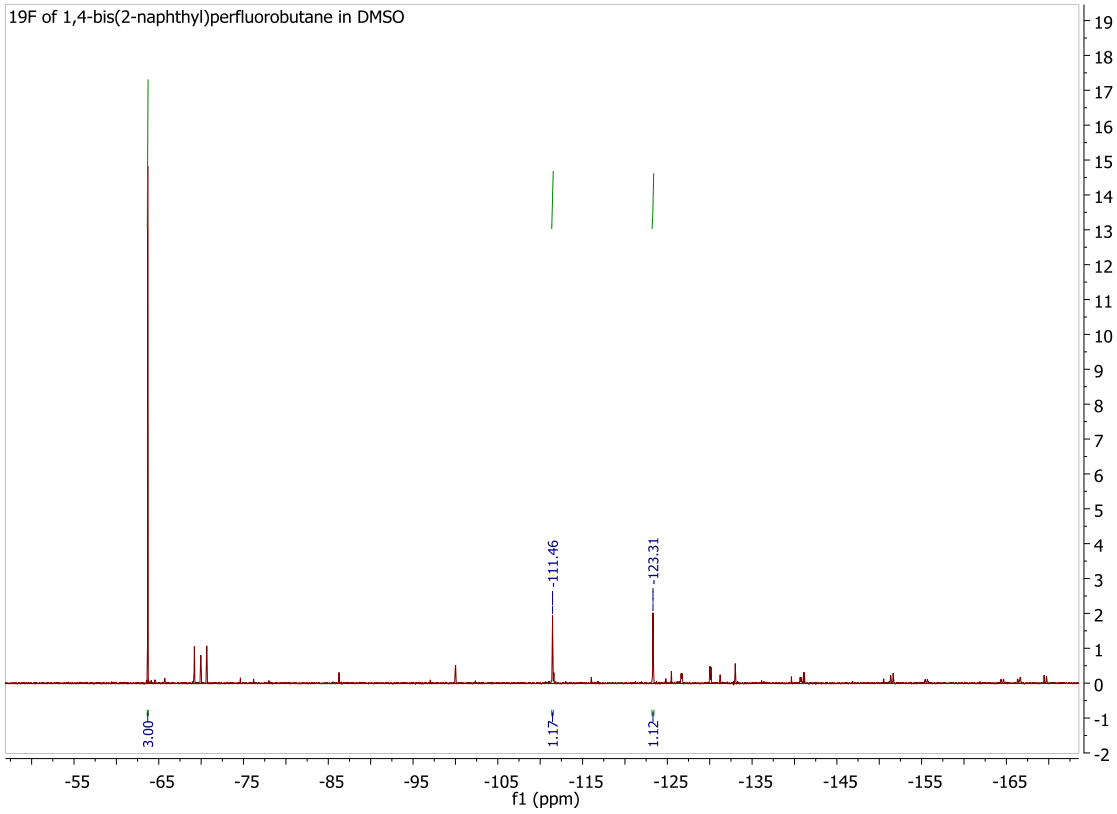
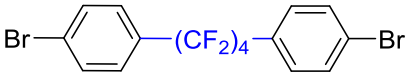


Figure 6.2e: ^{19}F NMR spectrum of **3z**  in DMSO:

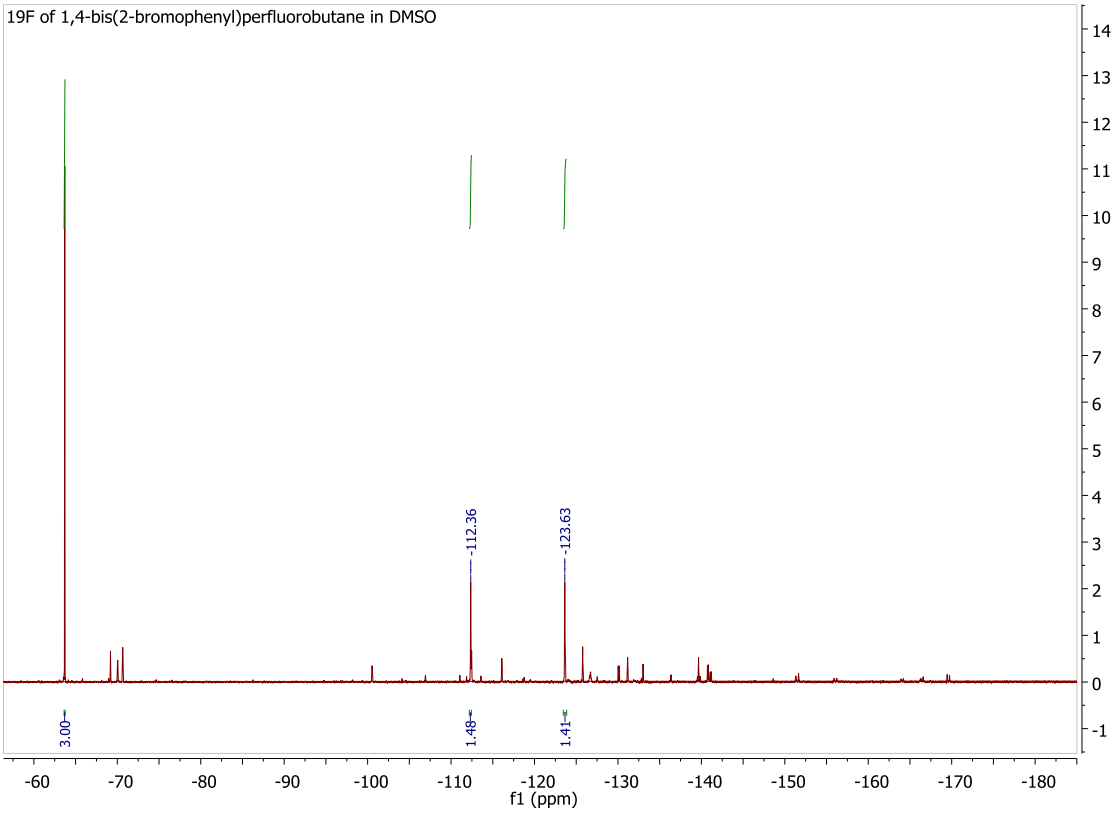
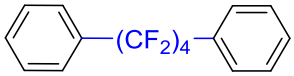


Figure 6.2f: ^{19}F NMR spectrum of **3aa**  in DMSO:

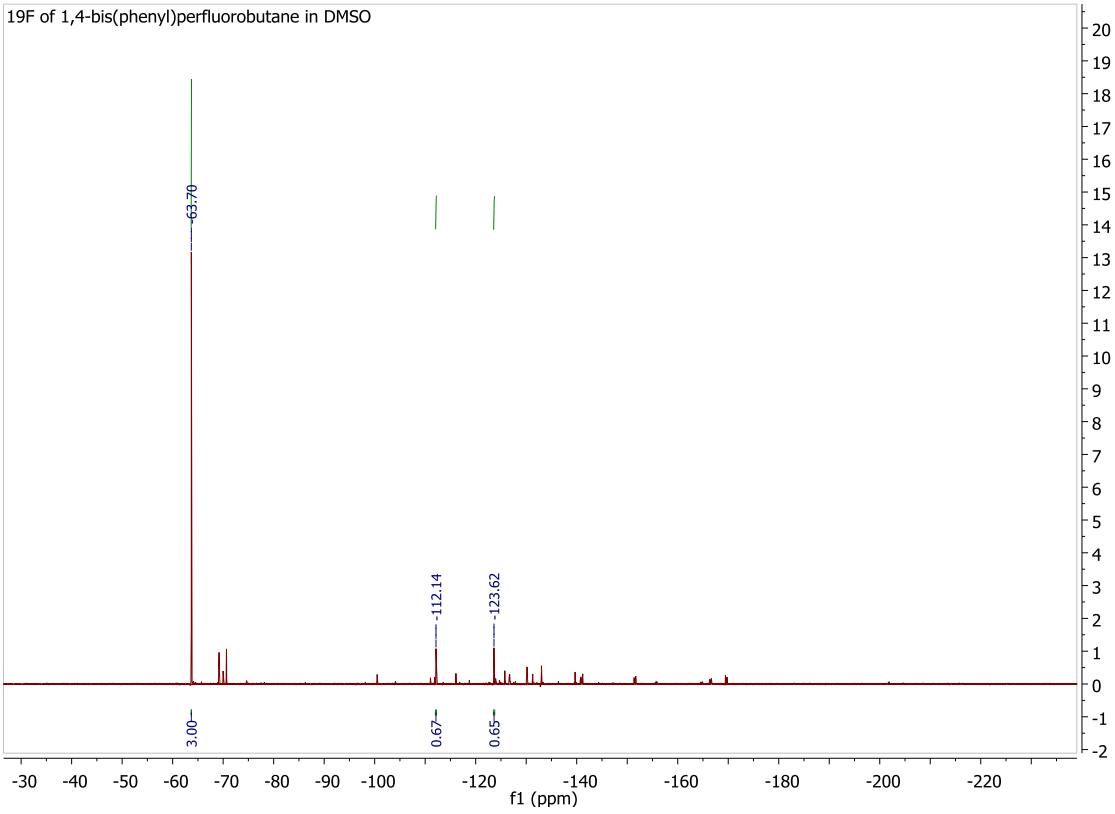
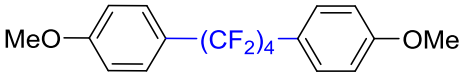


Figure 6.2g: ^{19}F NMR spectrum of **3bb**  in DMSO:

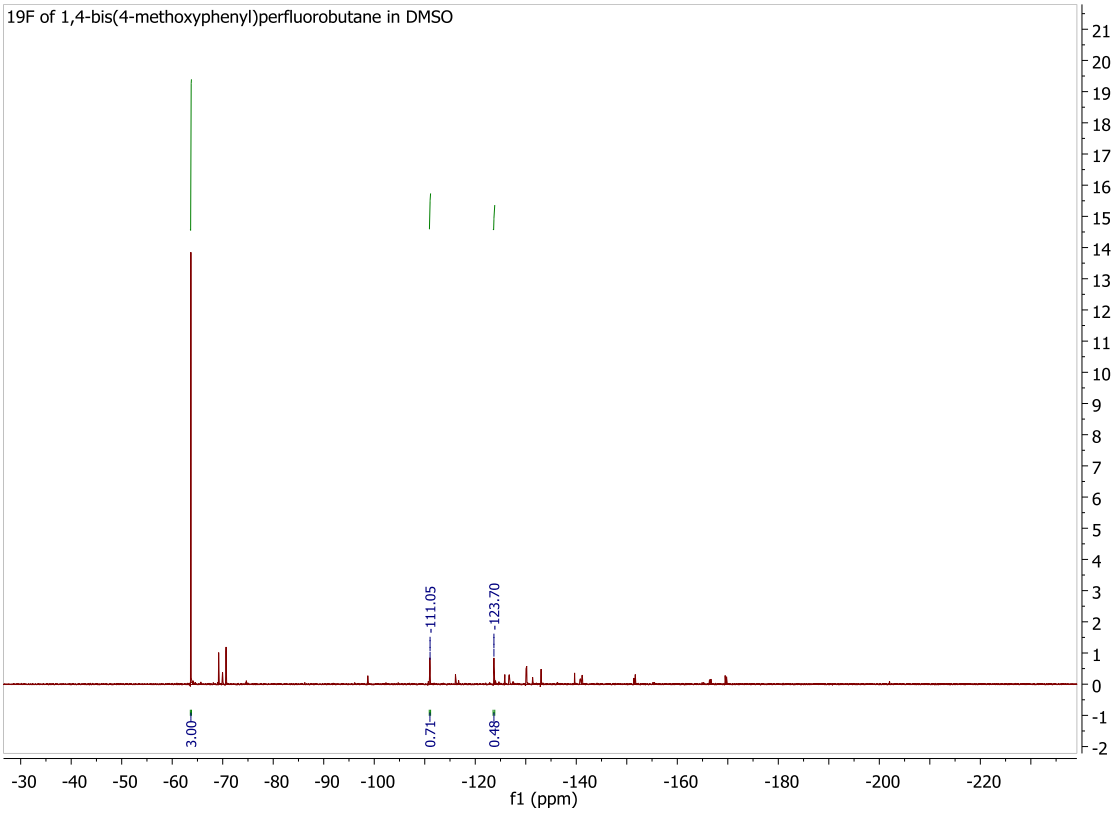
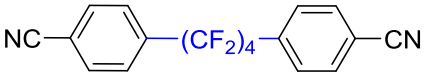


Figure 6.2h: ^{19}F NMR spectrum of **3cc**  in DMSO:

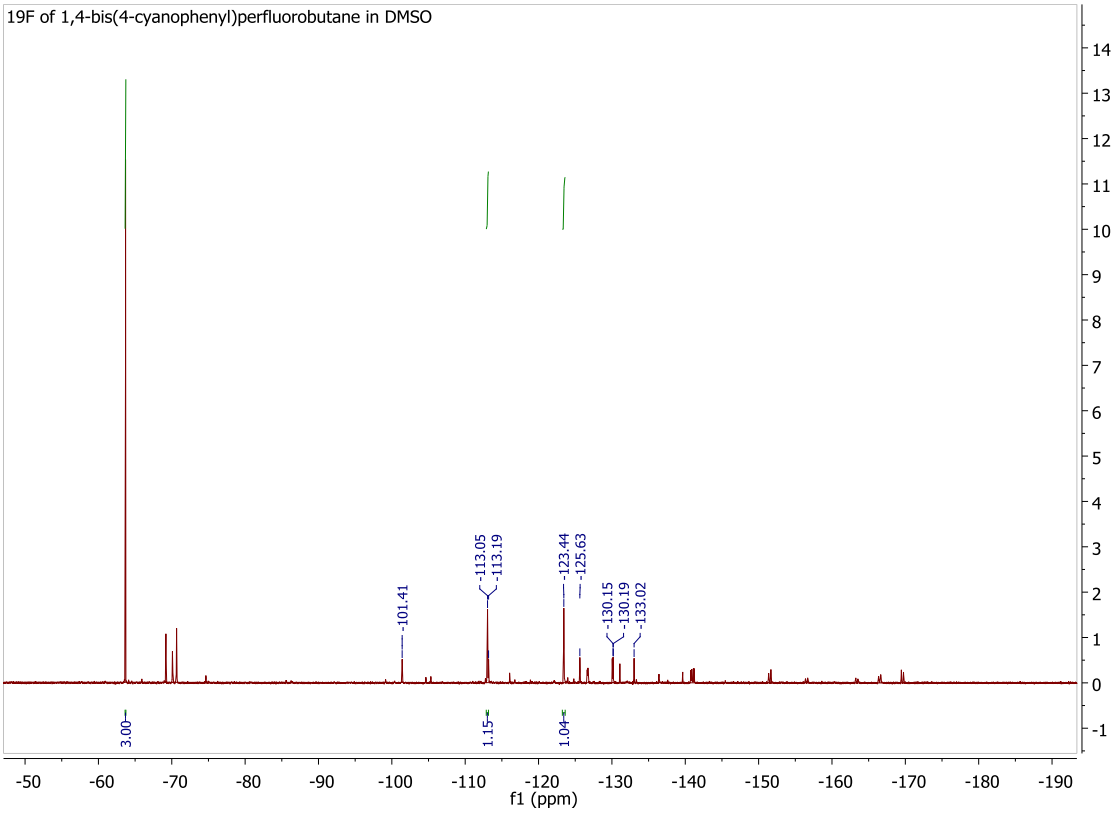
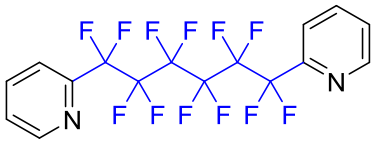


Figure 6.2i: ^{19}F NMR spectrum of **3ii**  in DMSO:

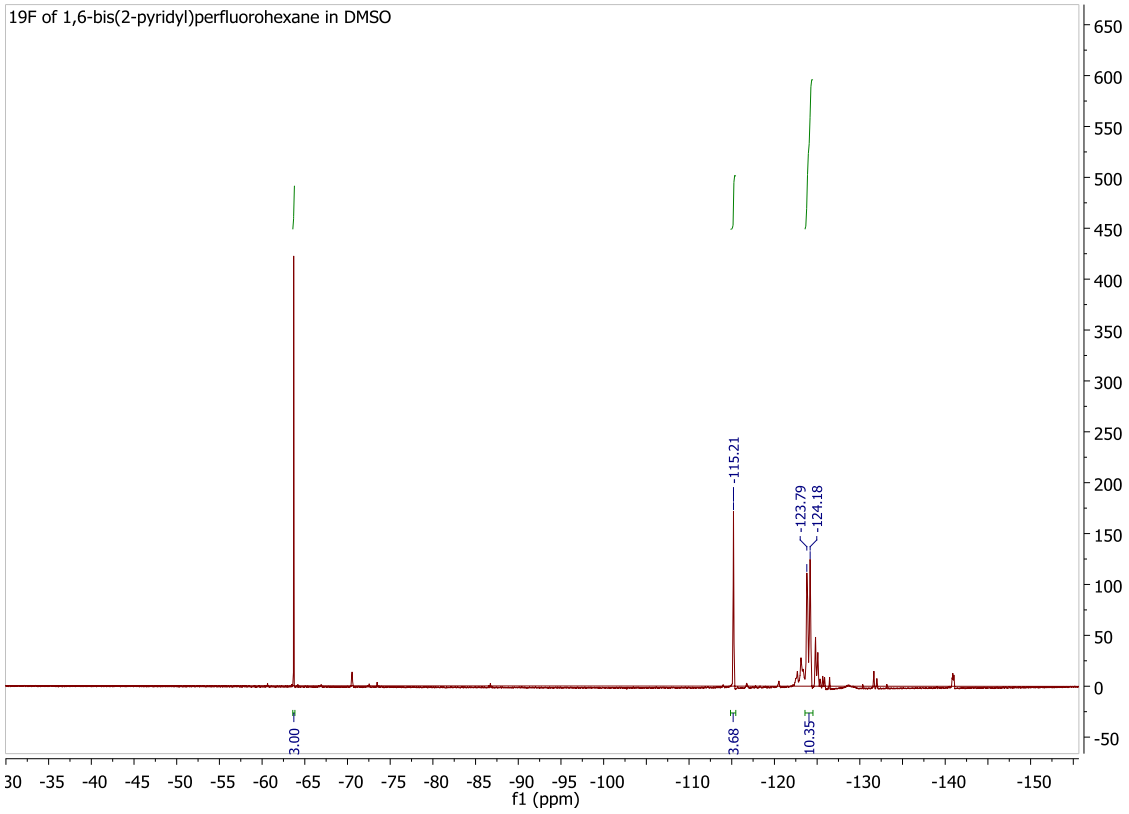
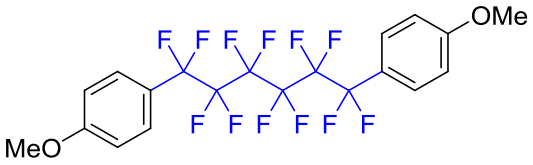


Figure 6.2j: ^{19}F NMR spectrum of **3jj**  in DMSO:

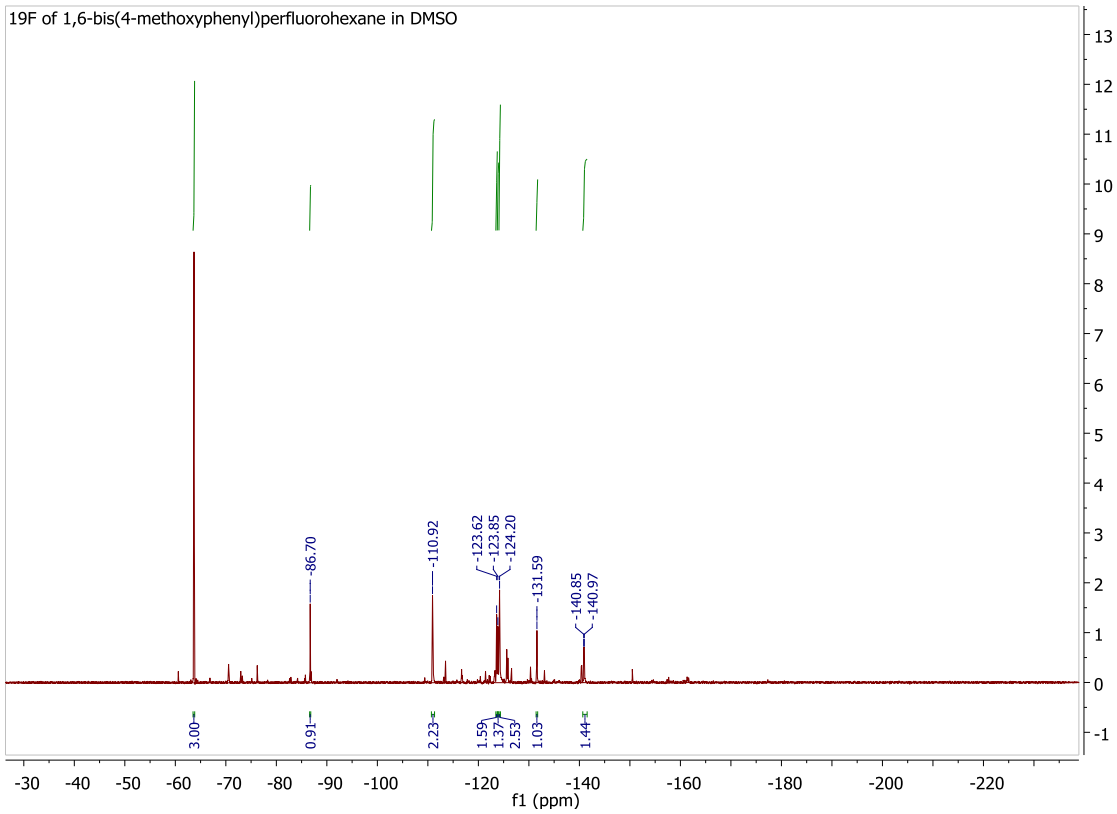
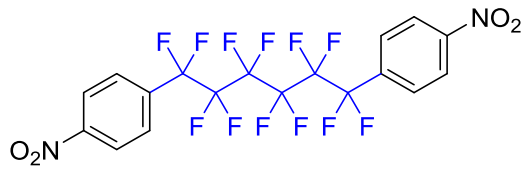


Figure 6.2k: ^{19}F NMR spectrum of **3kk**  in

DMSO:

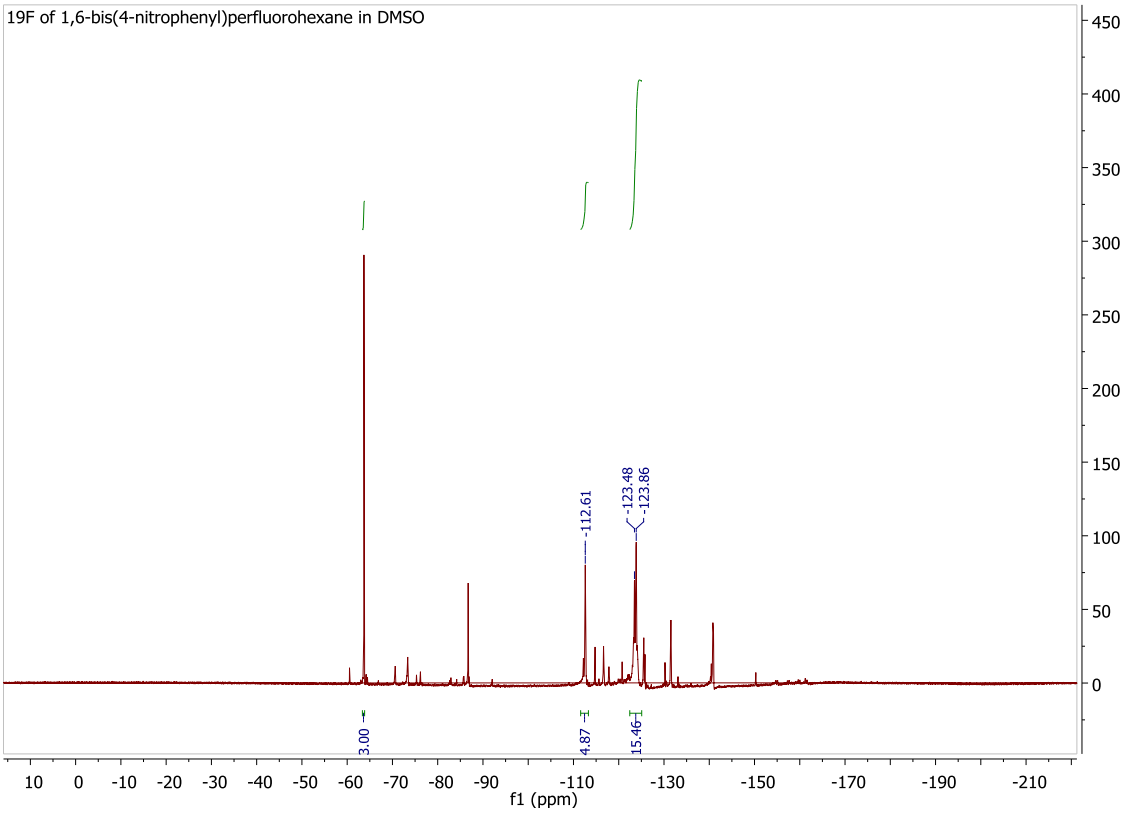
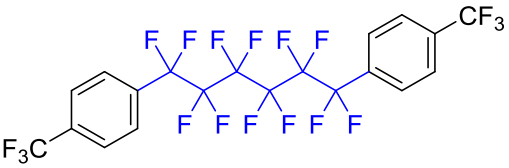


Figure 6.2l: ^{19}F NMR spectrum of **3ll**  in DMSO:

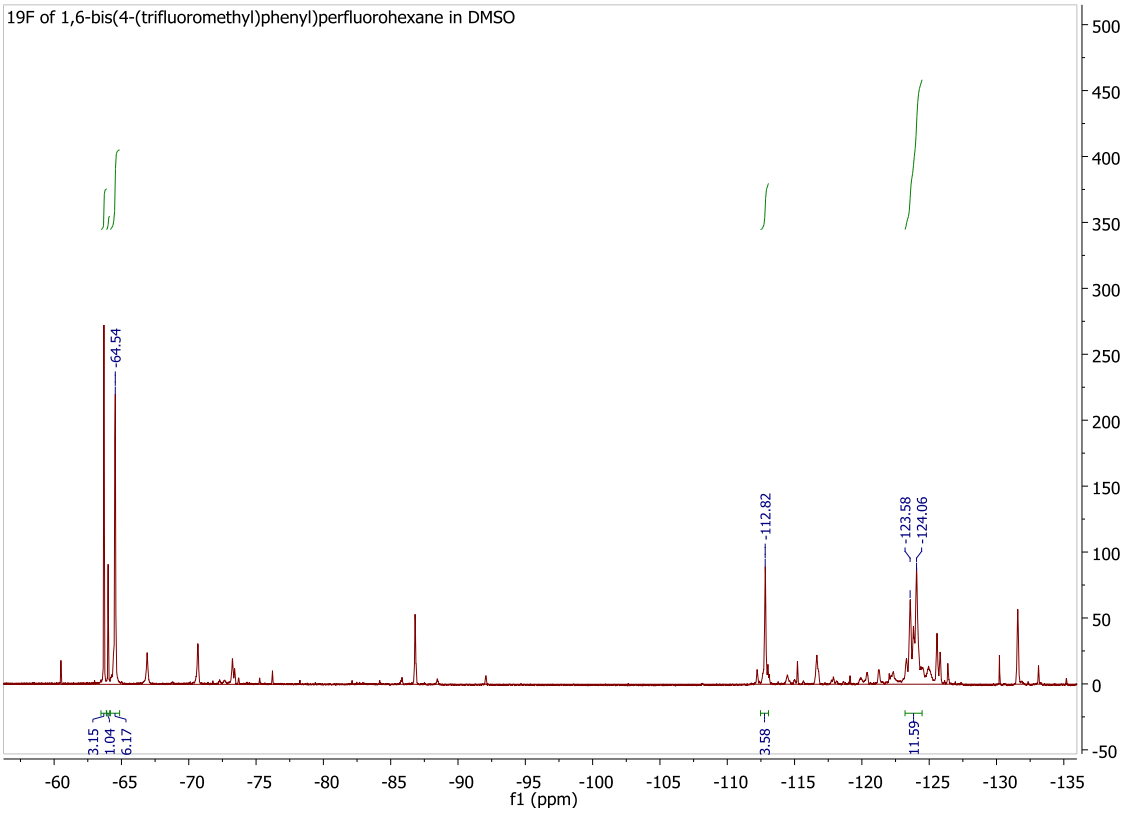
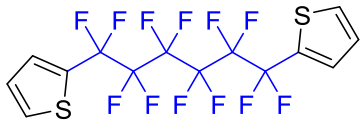


Figure 6.2m: ^{19}F NMR spectrum of **3mm**  in DMSO:

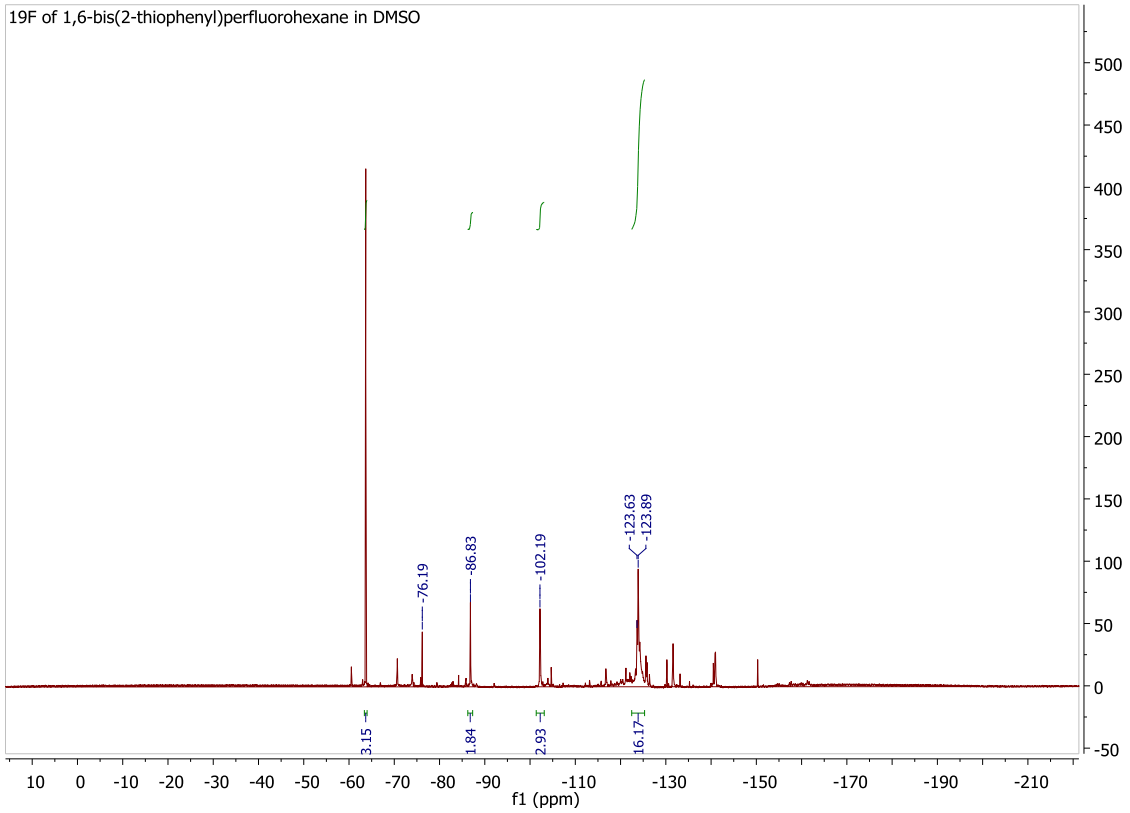
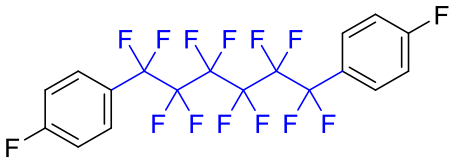


Figure 6.2n: ^{19}F NMR spectrum of **3nn**  in DMSO:

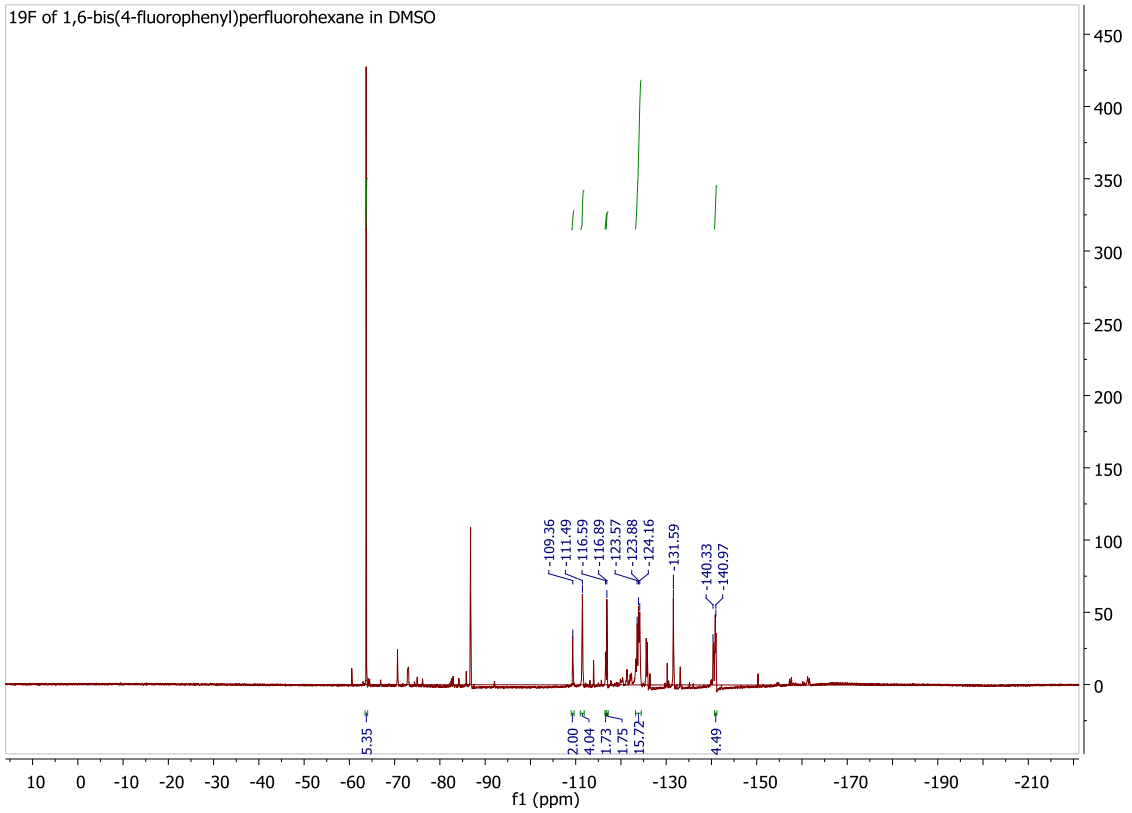
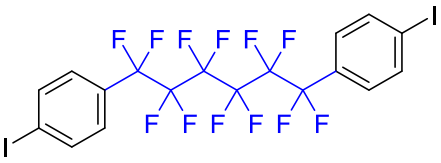


Figure 6.2o: ^{19}F NMR spectrum of **3oo**  in DMSO:

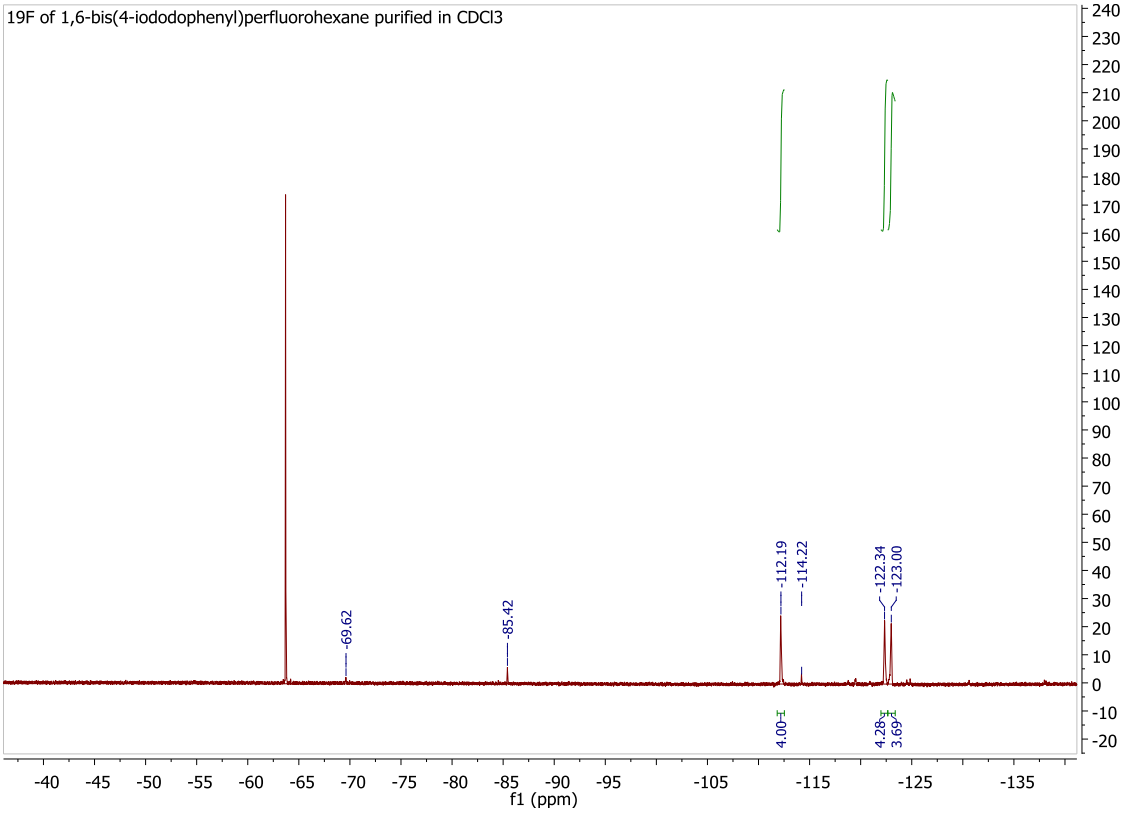
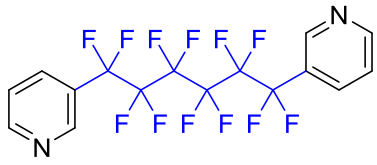


Figure 6.2p: ^{19}F NMR spectrum of **3rr**  in DMSO:

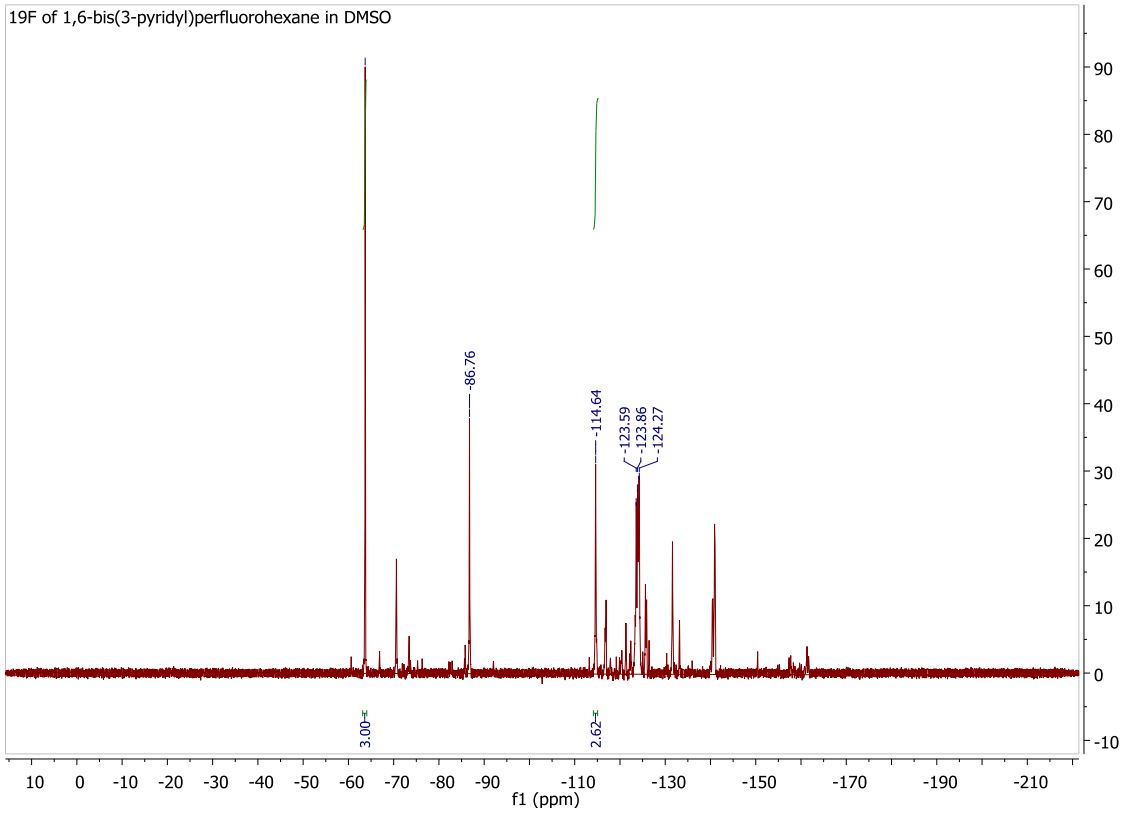
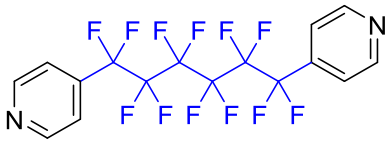


Figure 6.2q: ^{19}F NMR spectrum of **3ss**  in DMSO:

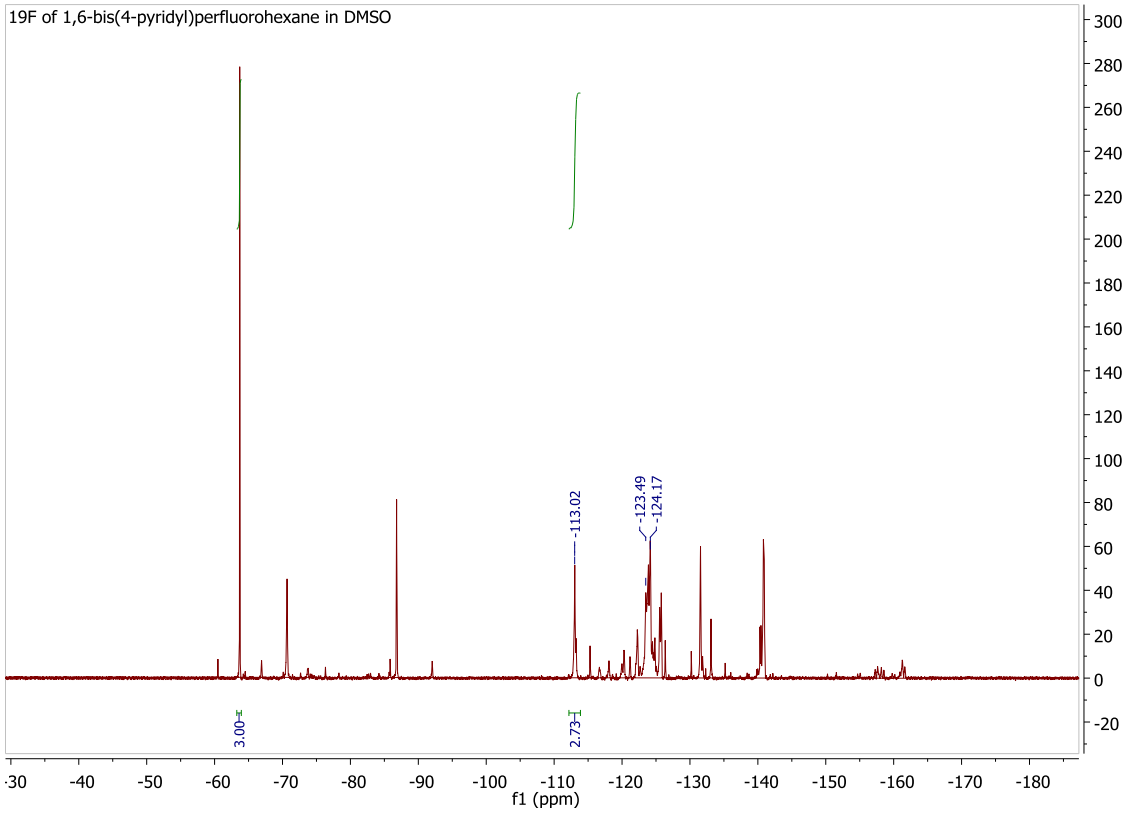
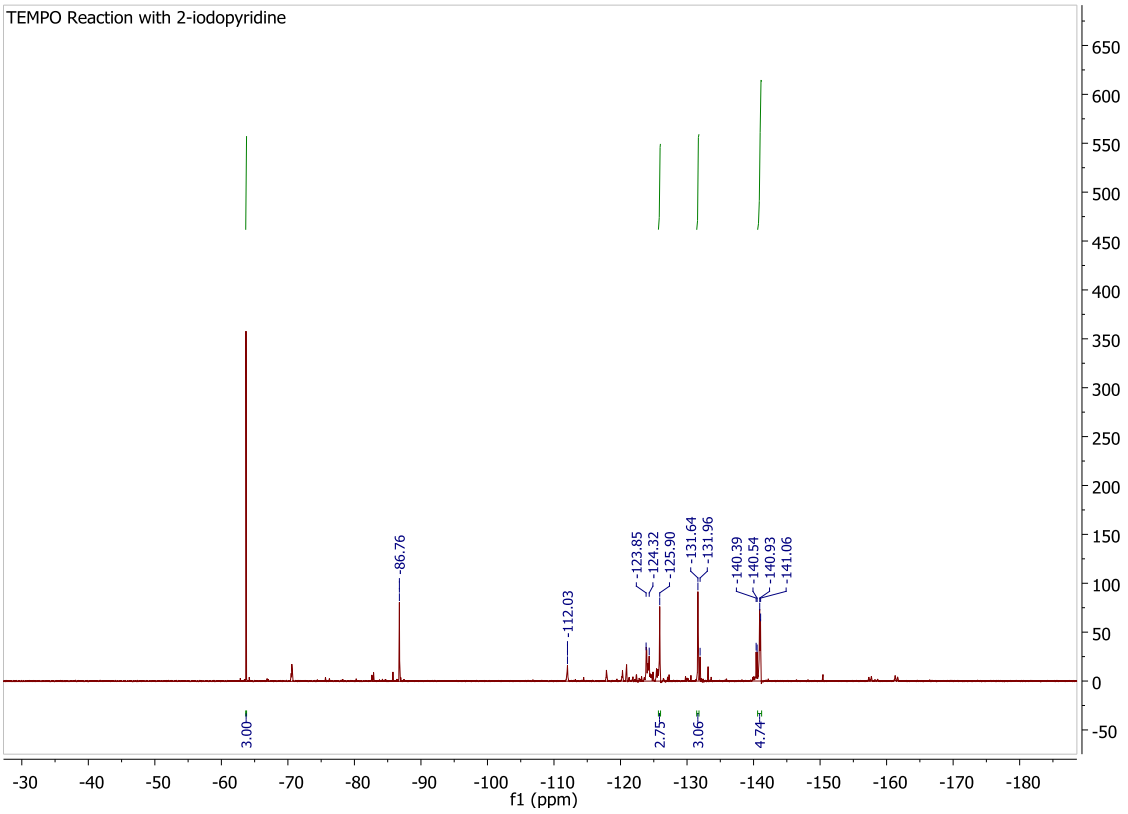
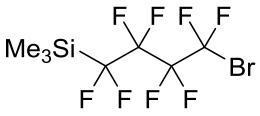


Figure 6.2r: ^{19}F NMR spectrum for TEMPO reaction in DMSO:



6.3. Data and Spectra for Chapter 4

Figure 6.3a: ^{19}F NMR spectrum of **4p**  in $CDCl_3$:

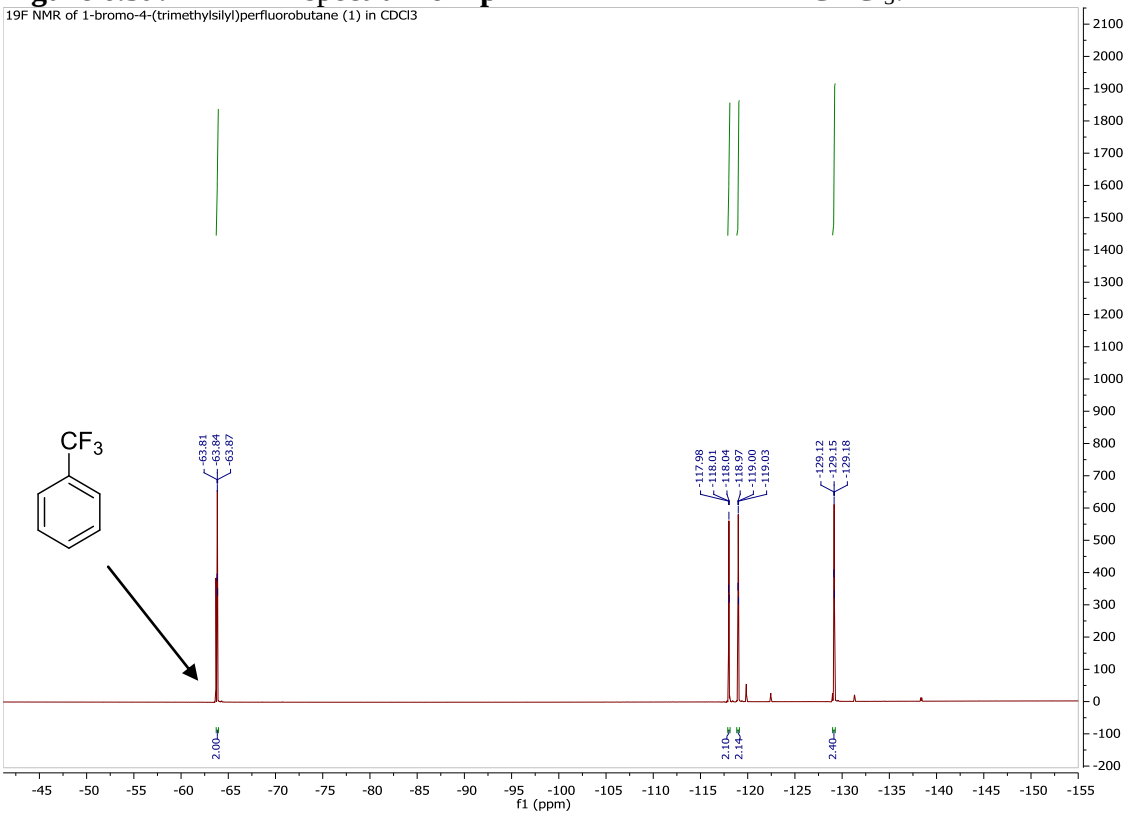
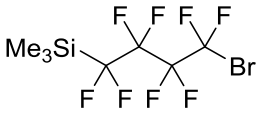


Figure 6.3b: ^{1}H NMR spectrum of **4p** 

(**1**) in $CDCl_3$:

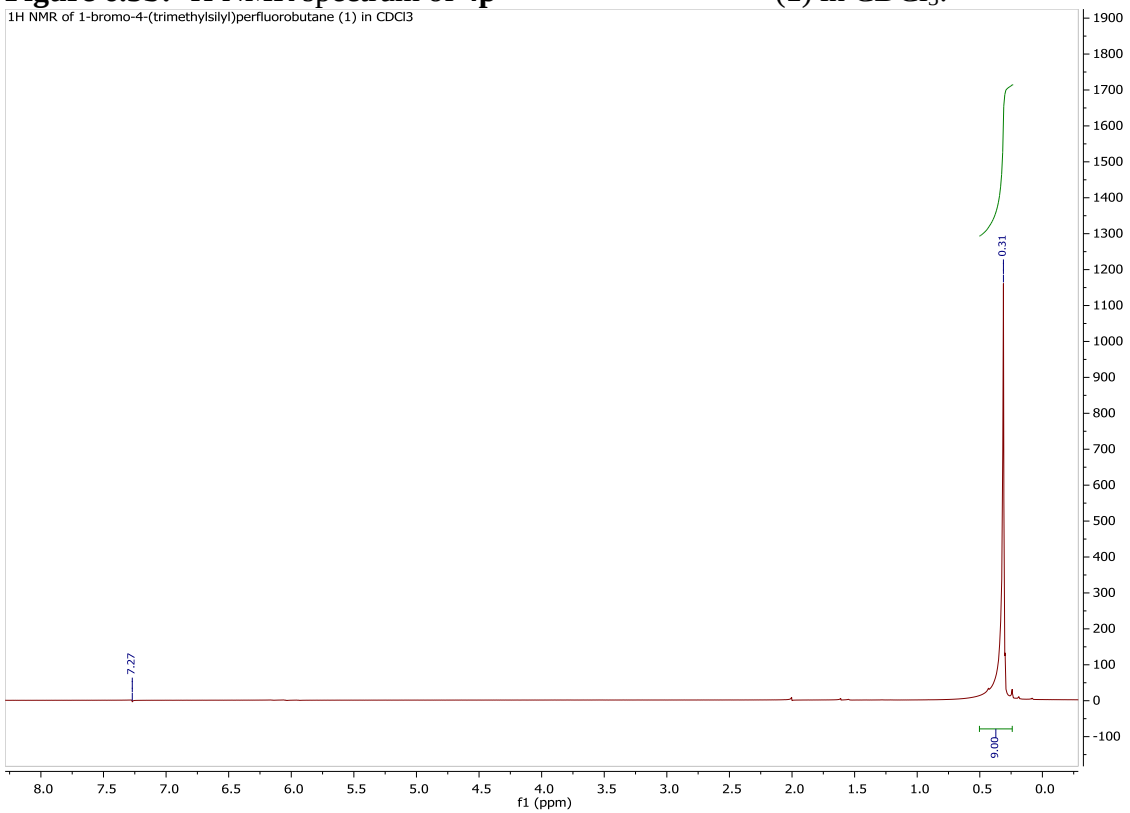
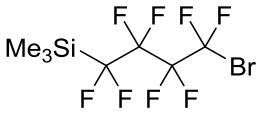


Figure 6.3c: ^{13}C NMR spectrum of **4p**  in $CDCl_3$:

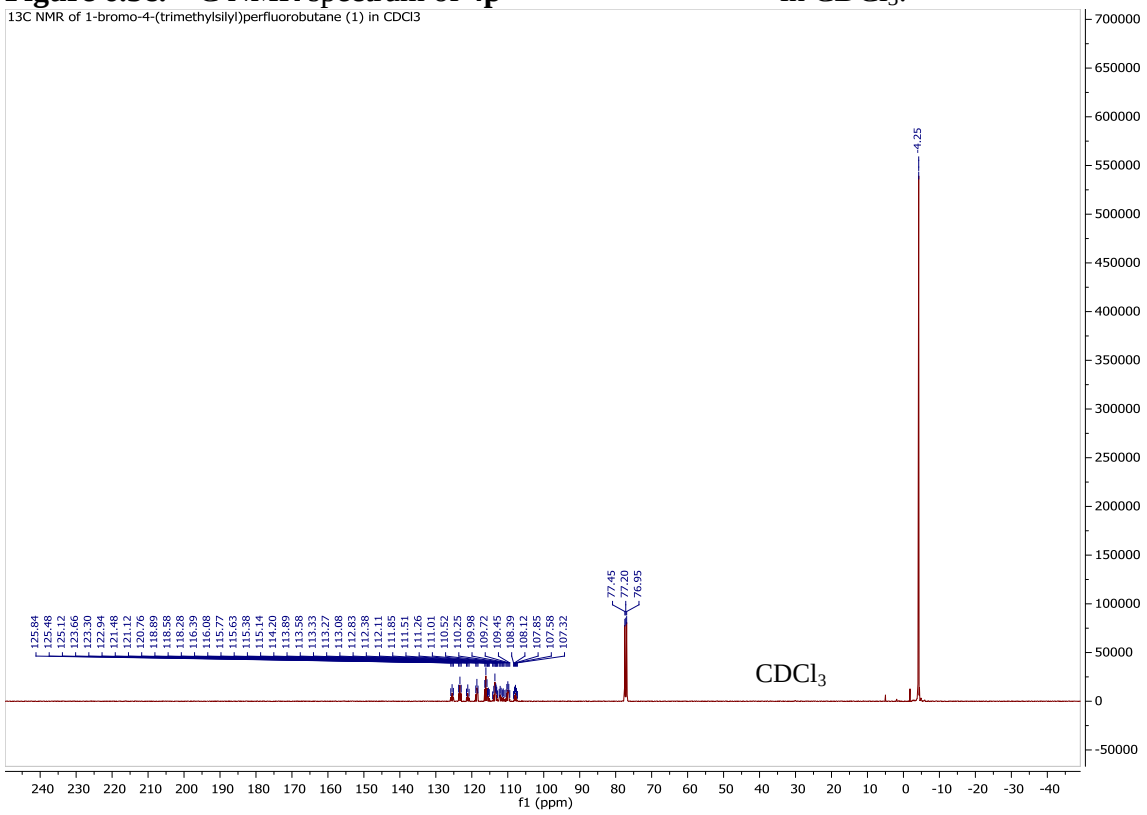
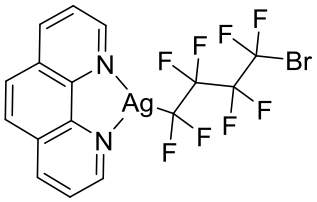
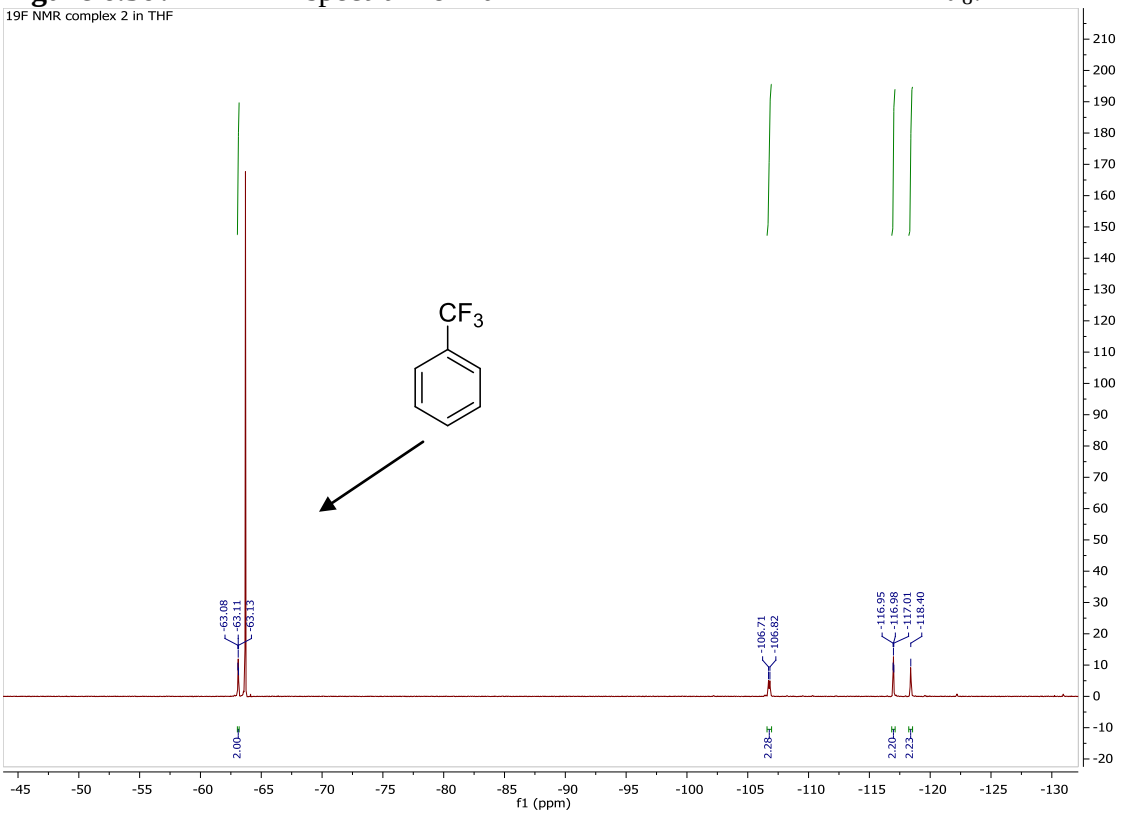


Figure 6.3d: ^{19}F NMR spectrum of **4u**  in THF-d_8:



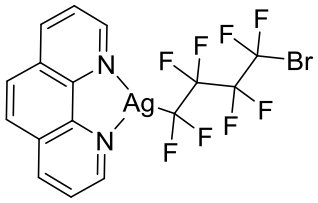
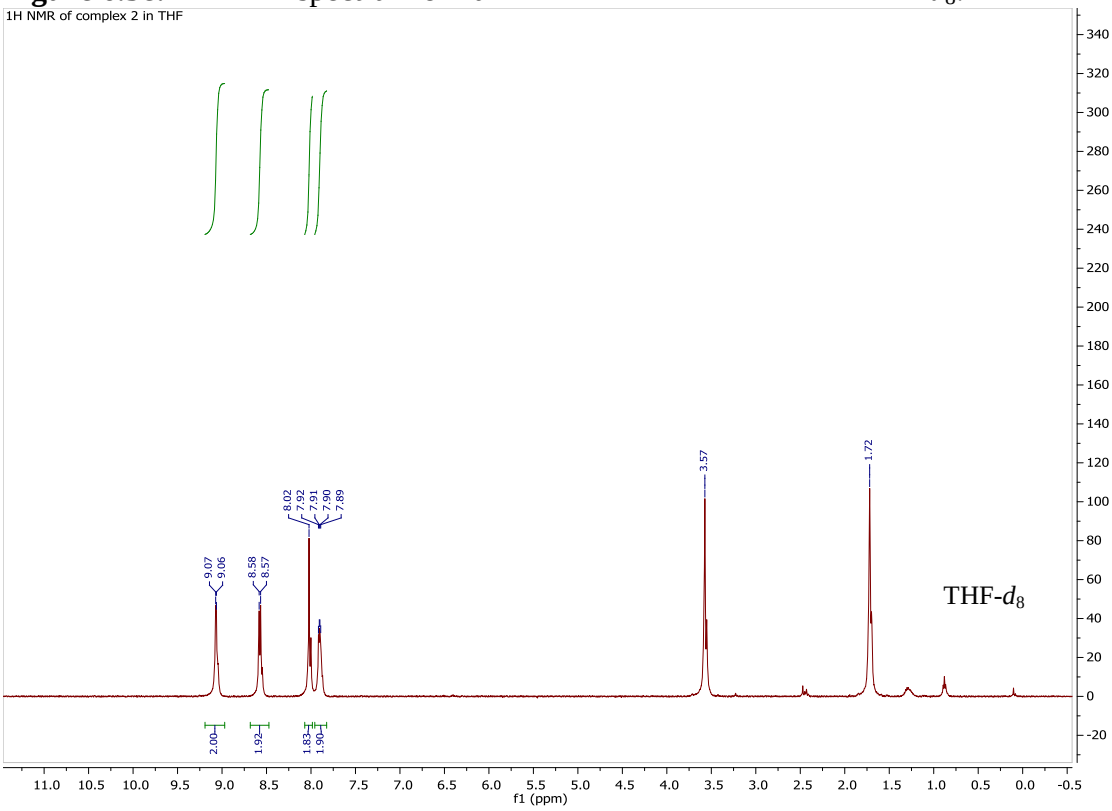


Figure 6.3e: ^{1}H NMR spectrum of **4u** in THF-d_8:



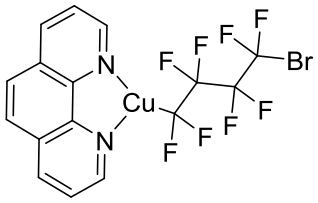


Figure 6.3f: ^{19}F NMR spectrum of **4y** in: THF-d_8

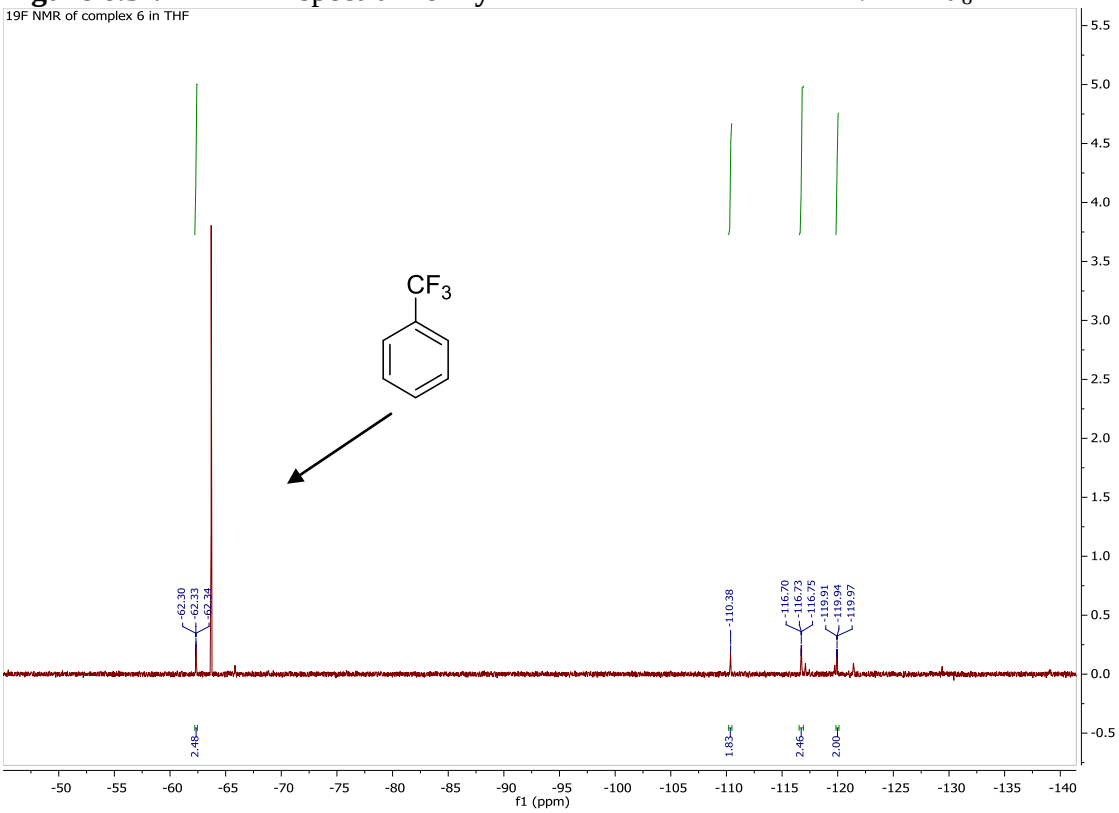
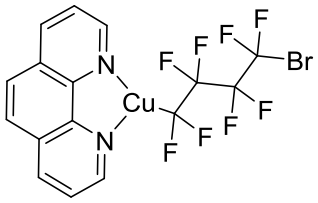


Figure 6.3g: ^{1}H NMR spectrum of **4y**  in: MeCN-d_3

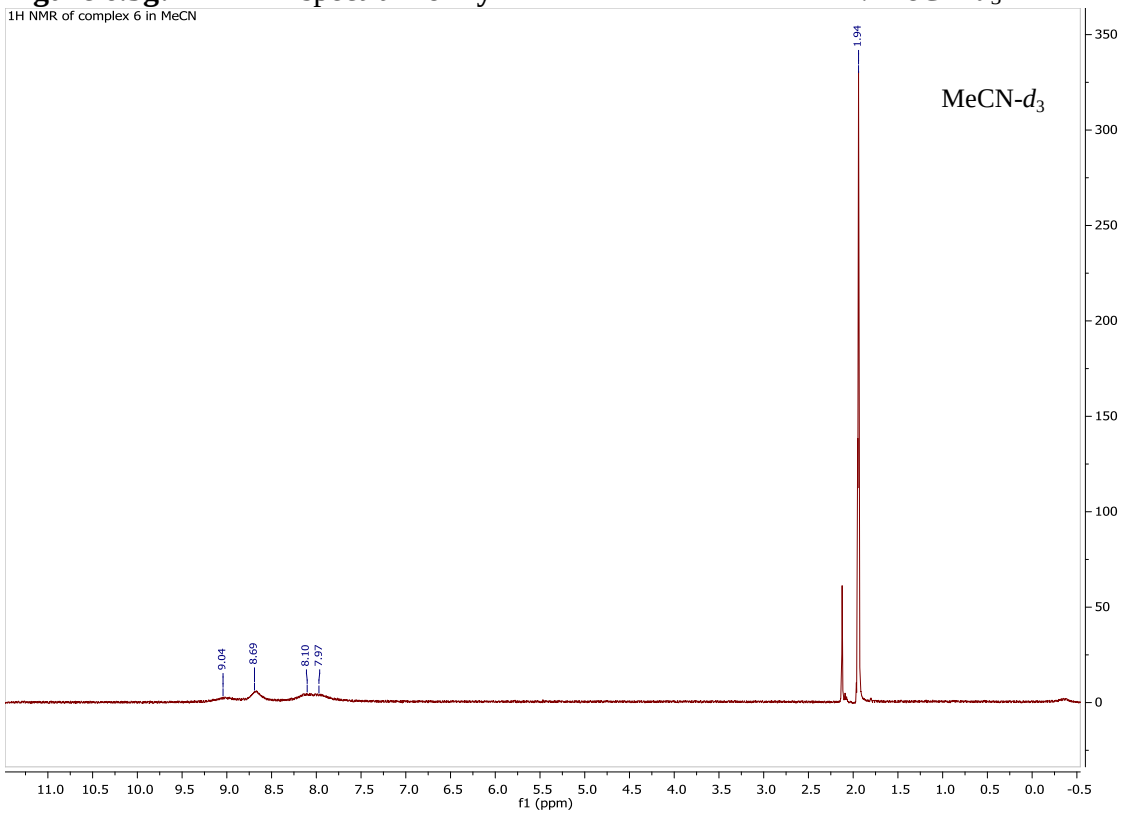


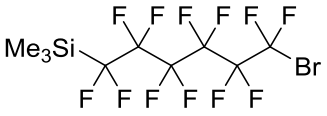
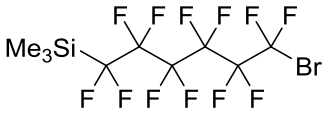
Figure 6.3h: ^{19}F NMR spectrum of **4vv**  in $CDCl_3$:

Figure 6.3i: ^{1}H NMR spectrum of **4vv**  in $CDCl_3$:

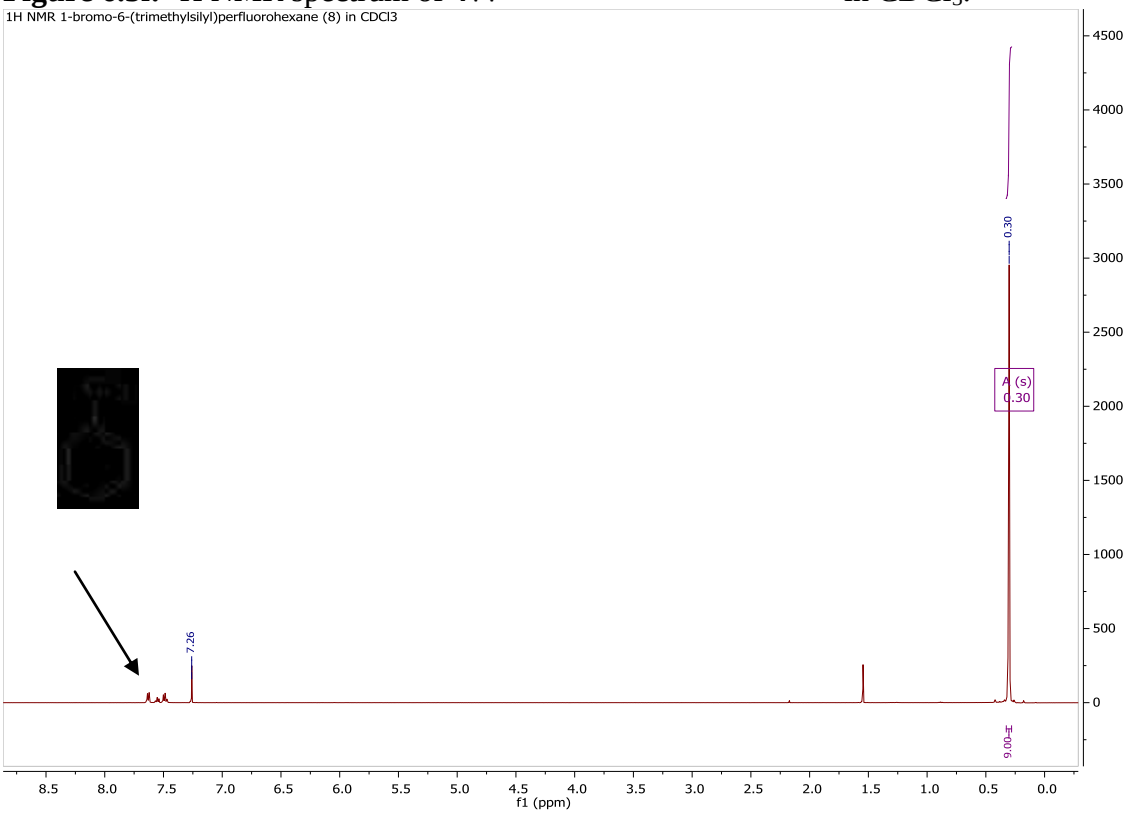
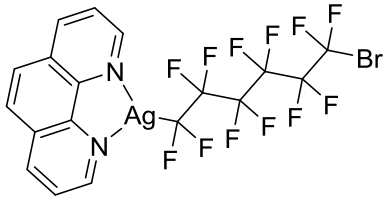
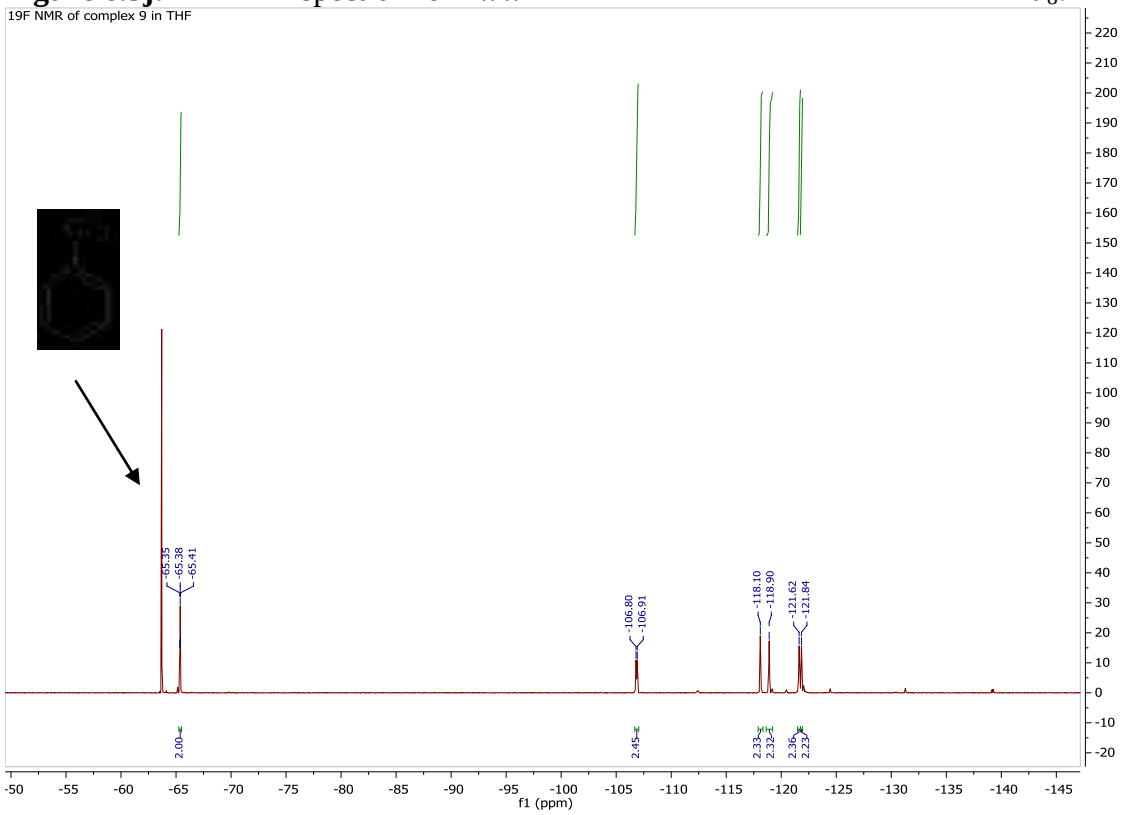


Figure 6.3j: ^{19}F NMR spectrum of **4ww**  in THF-d_8:



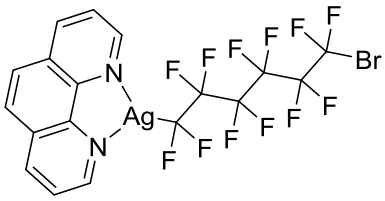


Figure 6.3k: ^{1}H NMR spectrum –d_8 of **4ww** in THF-*d*:

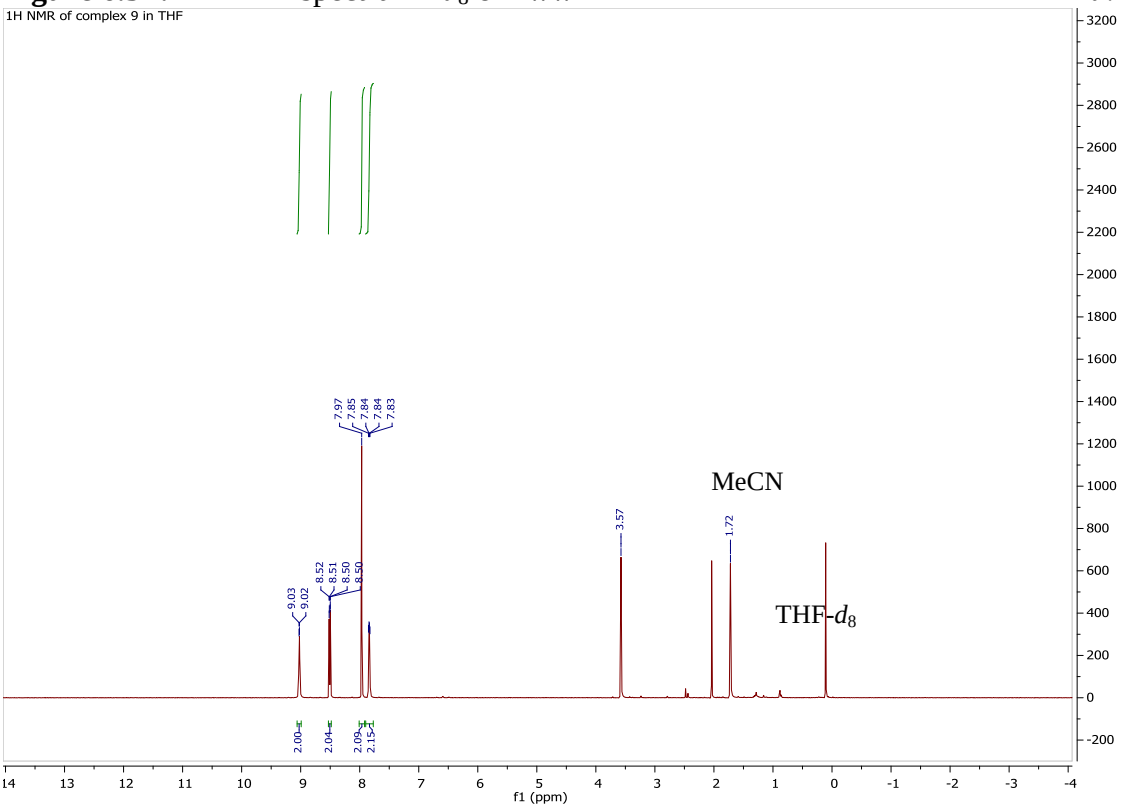
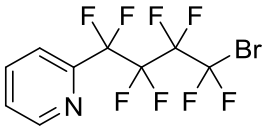


Figure 6.3l: ^{19}F NMR spectrum of **4z**  in $CDCl_3$:

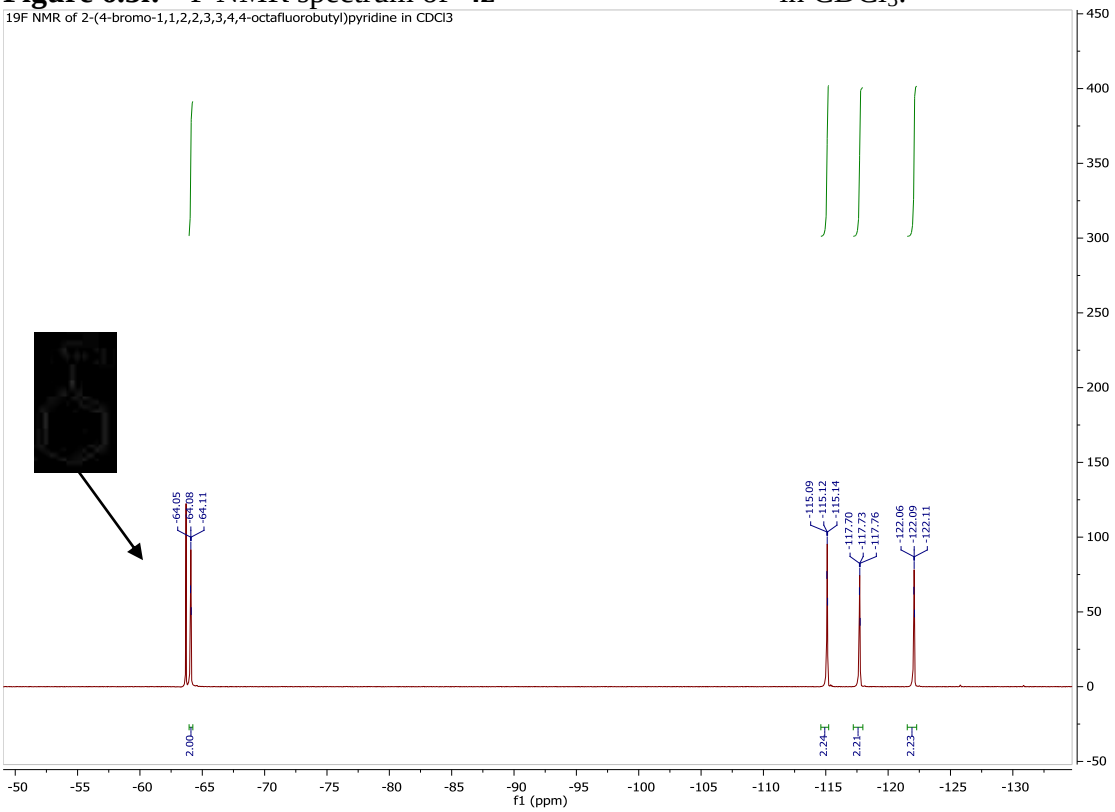
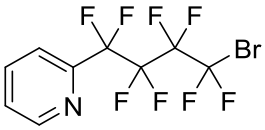


Figure 6.3m: ^{1}H NMR spectrum of **4z**  in $CDCl_3$:

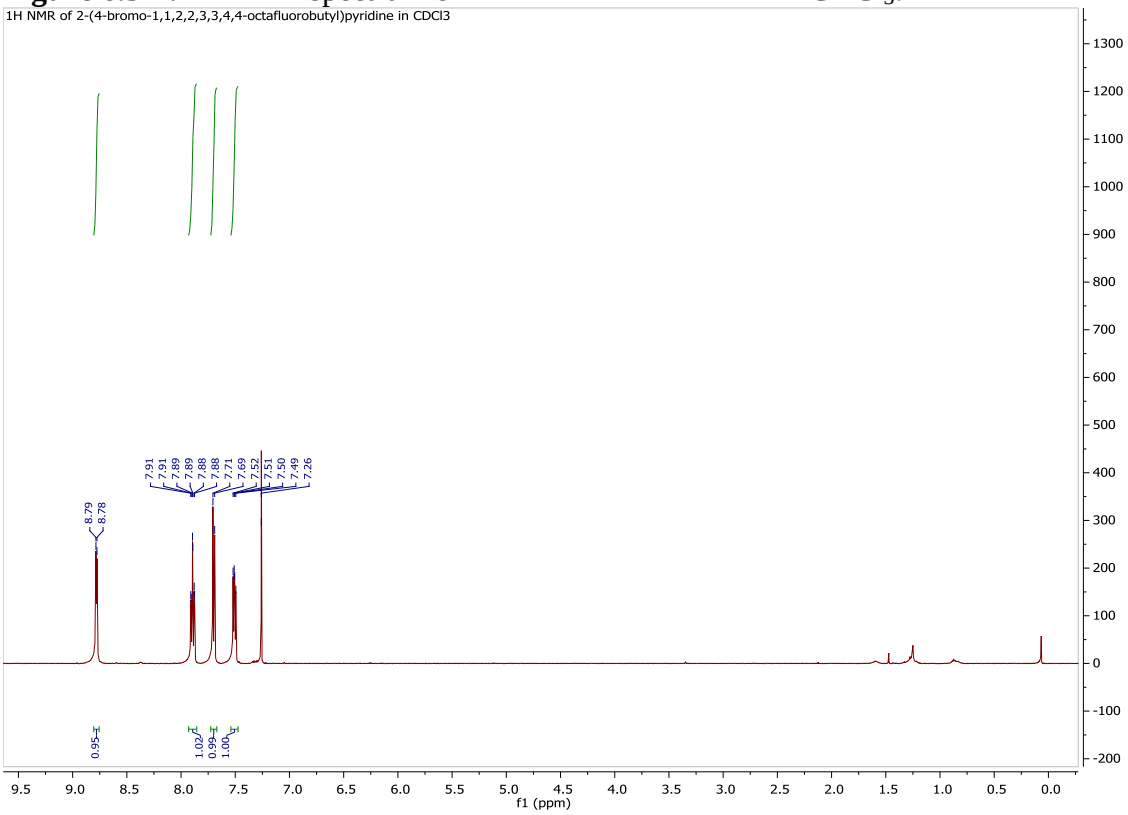
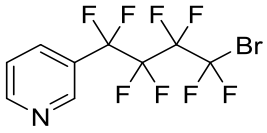


Figure 6.3n: ^{19}F NMR spectrum of **4aa**  in MeCN-d_3:

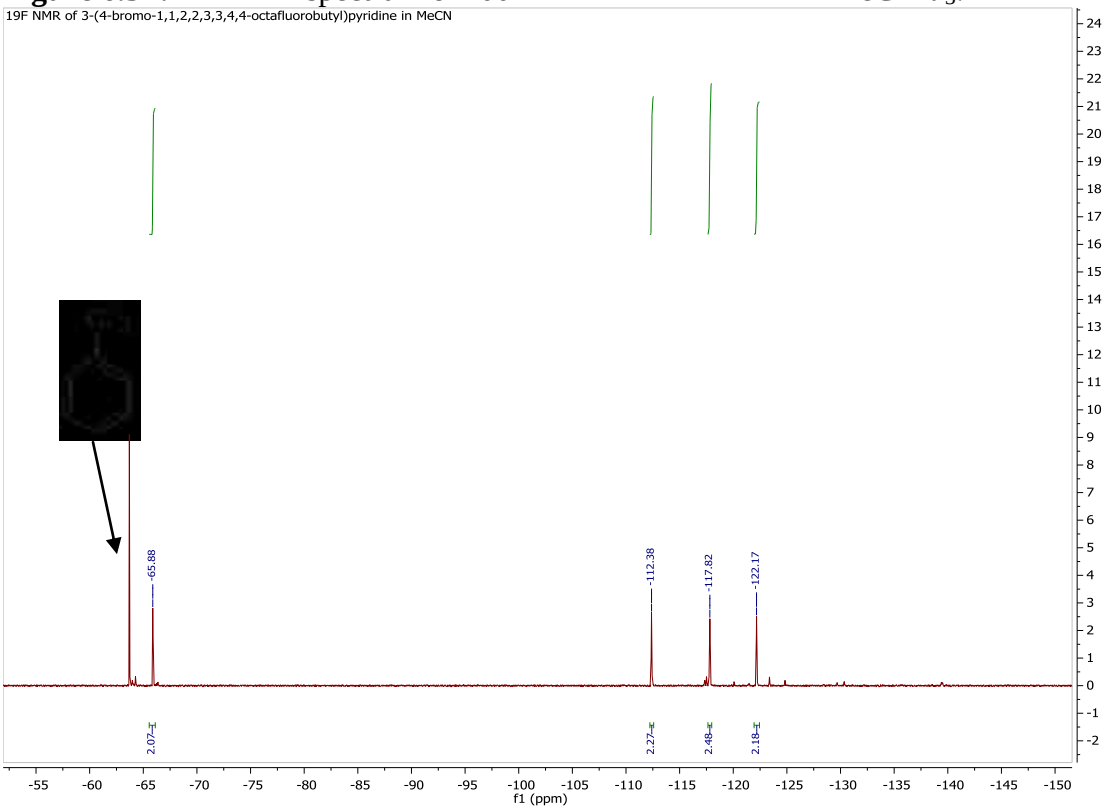
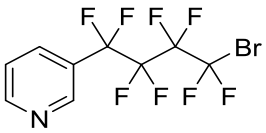


Figure 6.3o: ^{1}H NMR spectrum of **4aa** 

in MeCN-d_3:

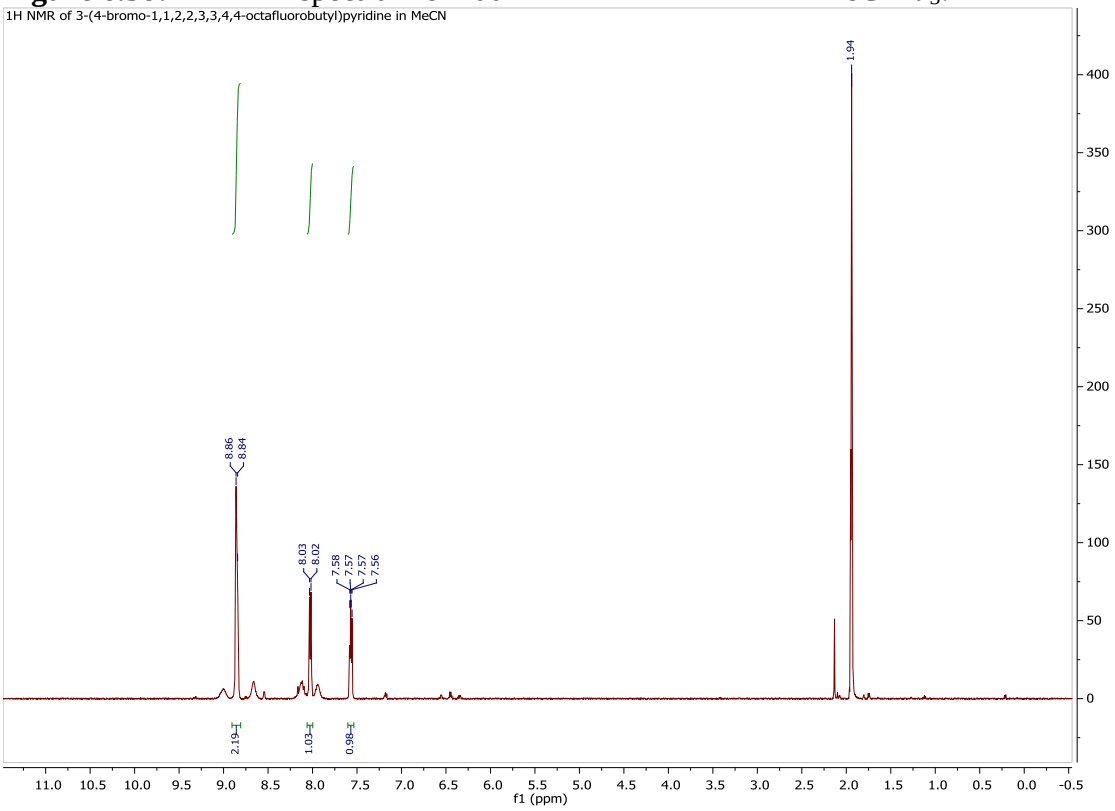
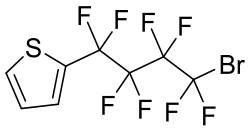


Figure 6.3p: ^{19}F NMR spectrum of **4bb**  in MeCN-d_3:

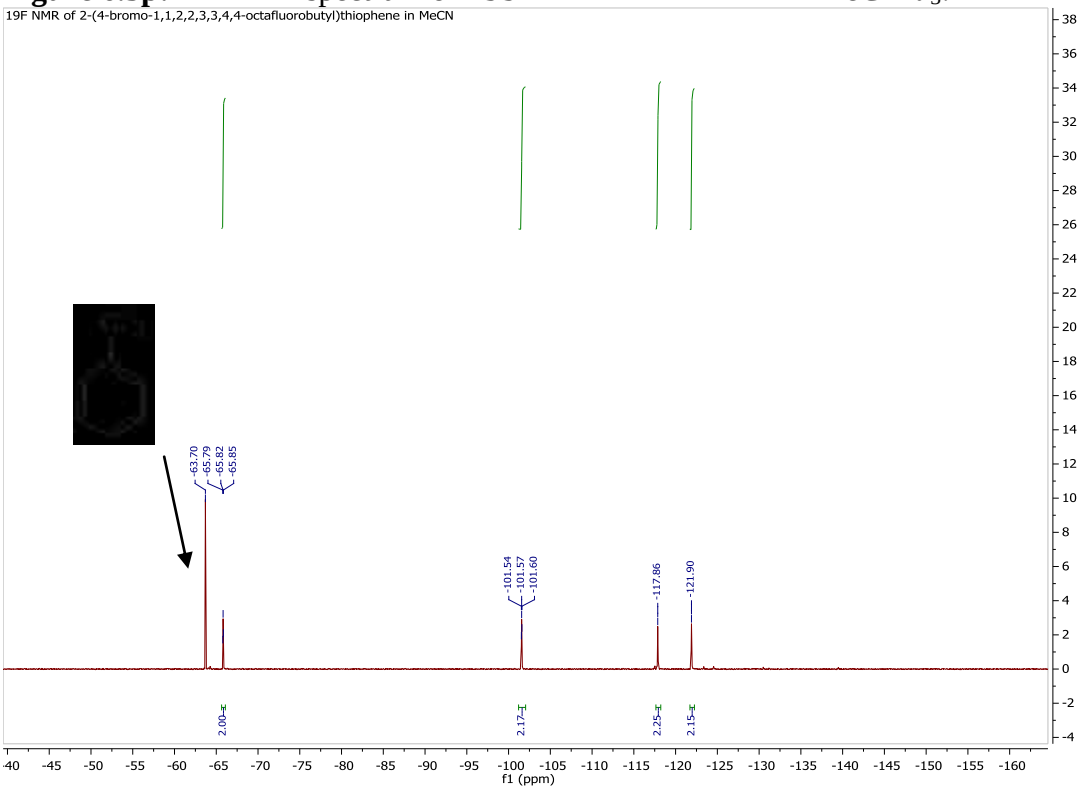
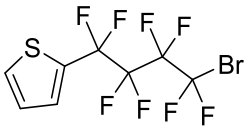


Figure 6.3q: ^{1}H NMR spectrum of **4bb**  in MeCN-d_3:

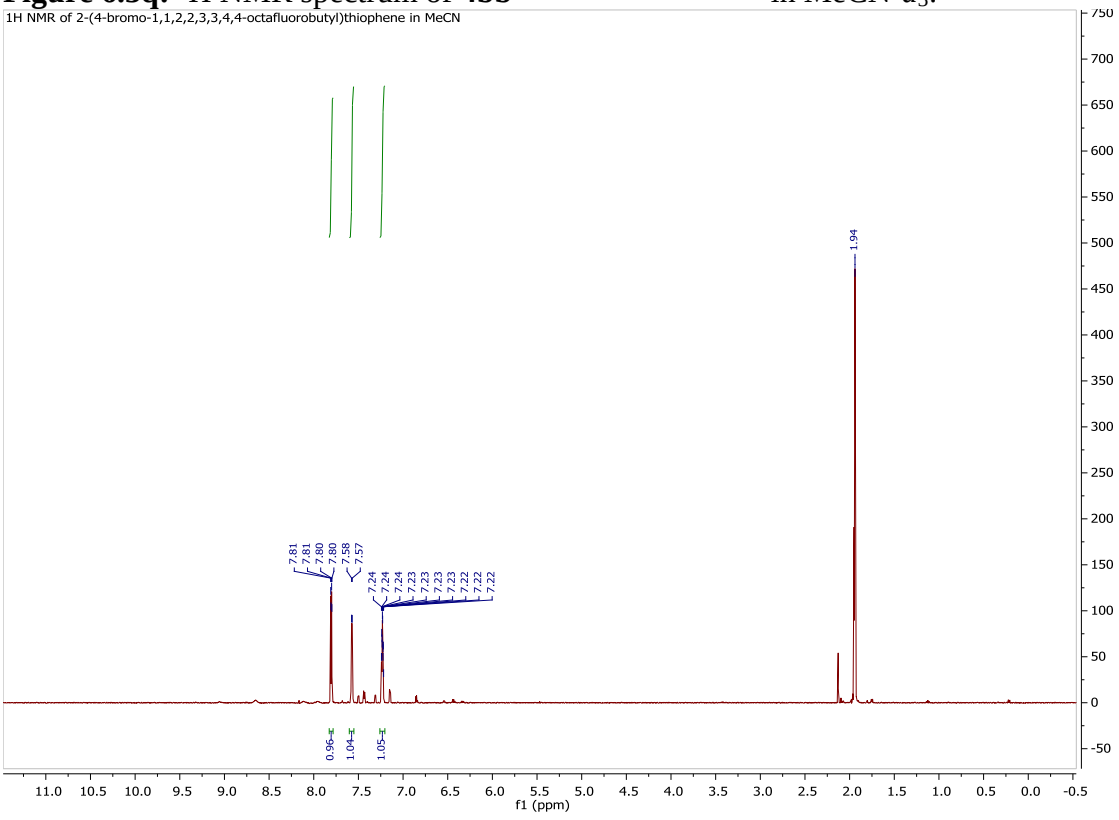
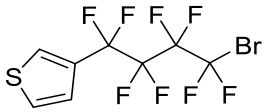


Figure 6.3r: ^{19}F NMR spectrum of **4cc**  in MeCN-d_3:

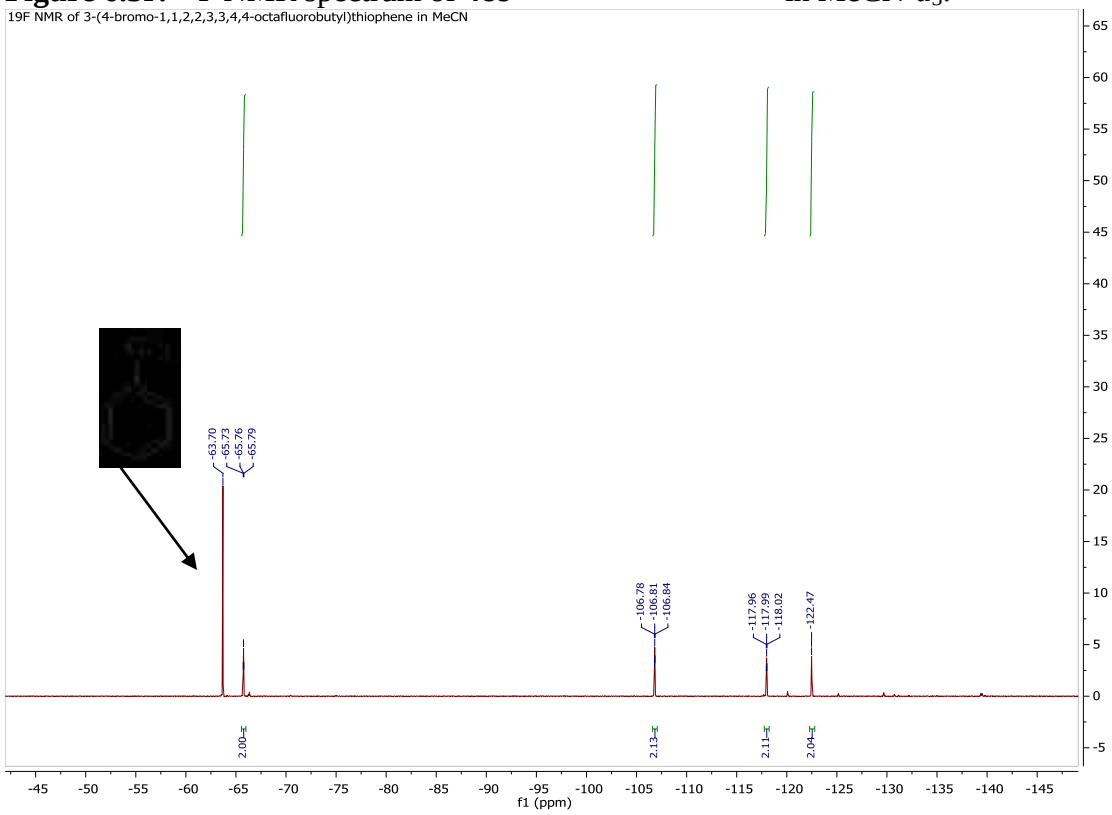
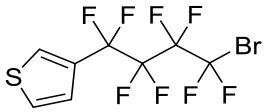


Figure 6.3s: ^{1}H NMR spectrum of **4cc**  in MeCN-d_3:

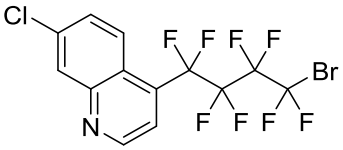
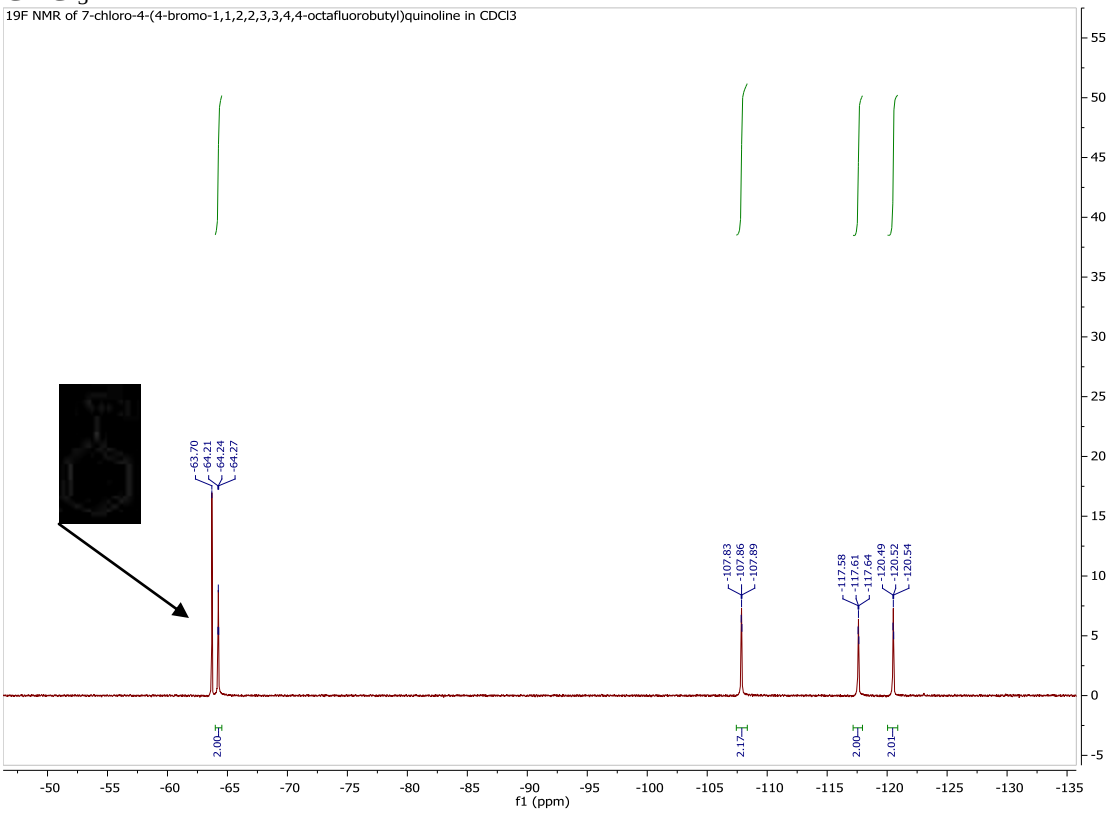


Figure 6.3t: ^{19}F NMR spectrum of **4dd** in $CDCl_3$



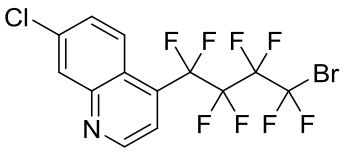


Figure 6.3u: ^{1}H NMR spectrum of **4dd** in $CDCl_3$:

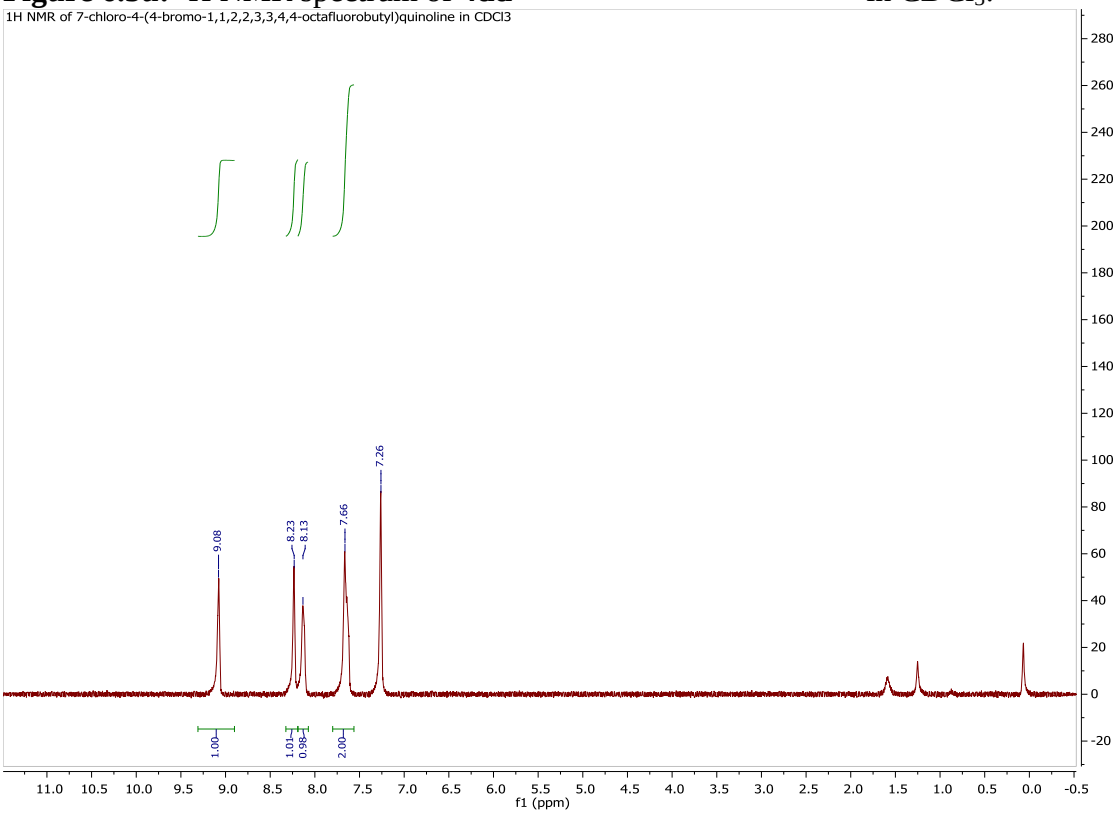
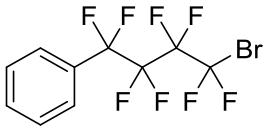


Figure 6.3v: ^{19}F NMR spectrum of **4ee** 

in MeCN-d_3:

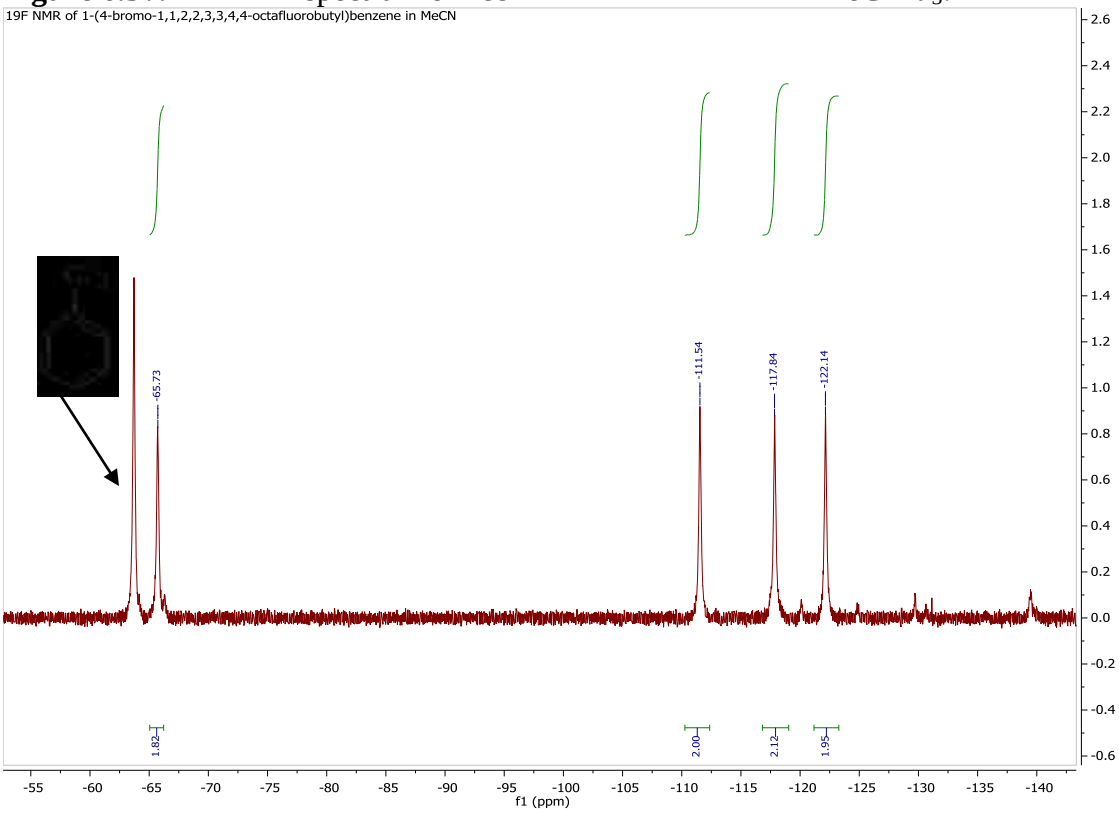
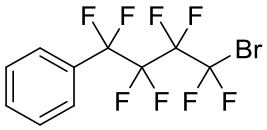
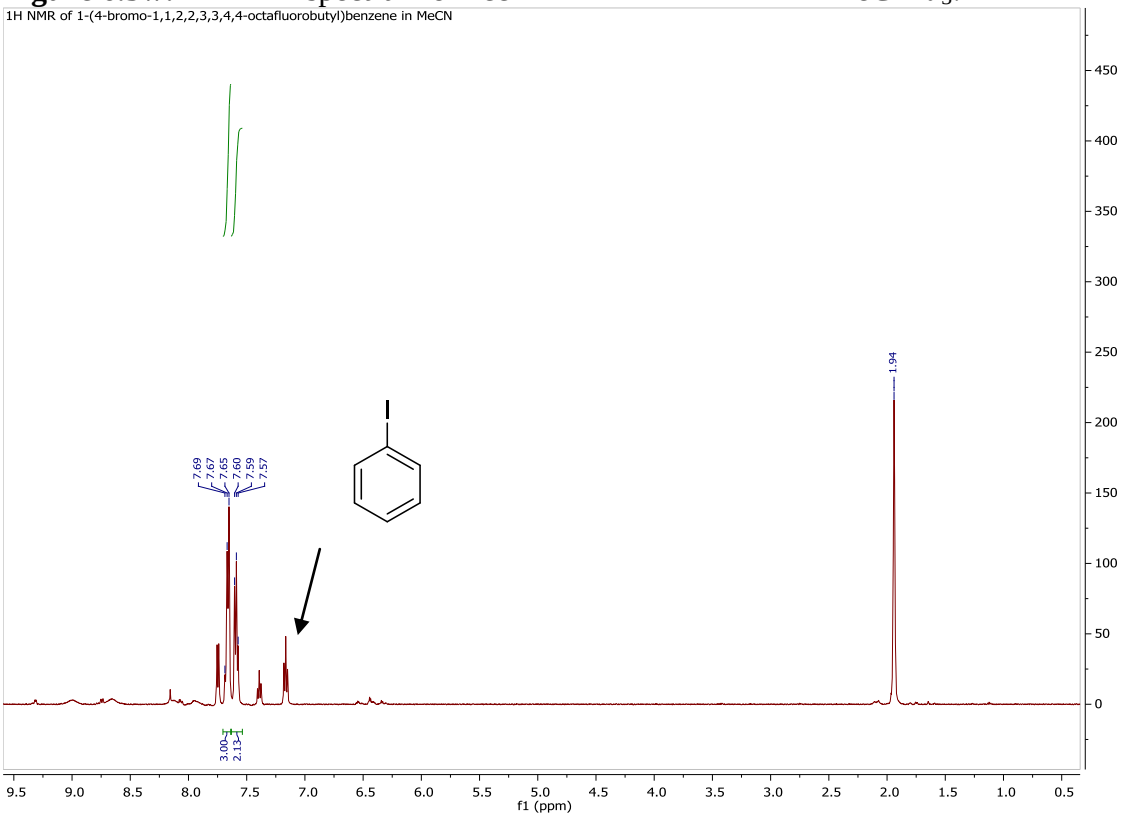


Figure 6.3w: ^{1}H NMR spectrum of **4ee**  in MeCN-d_3:



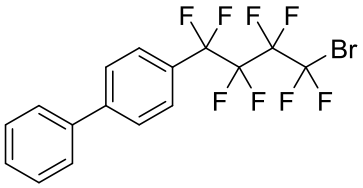
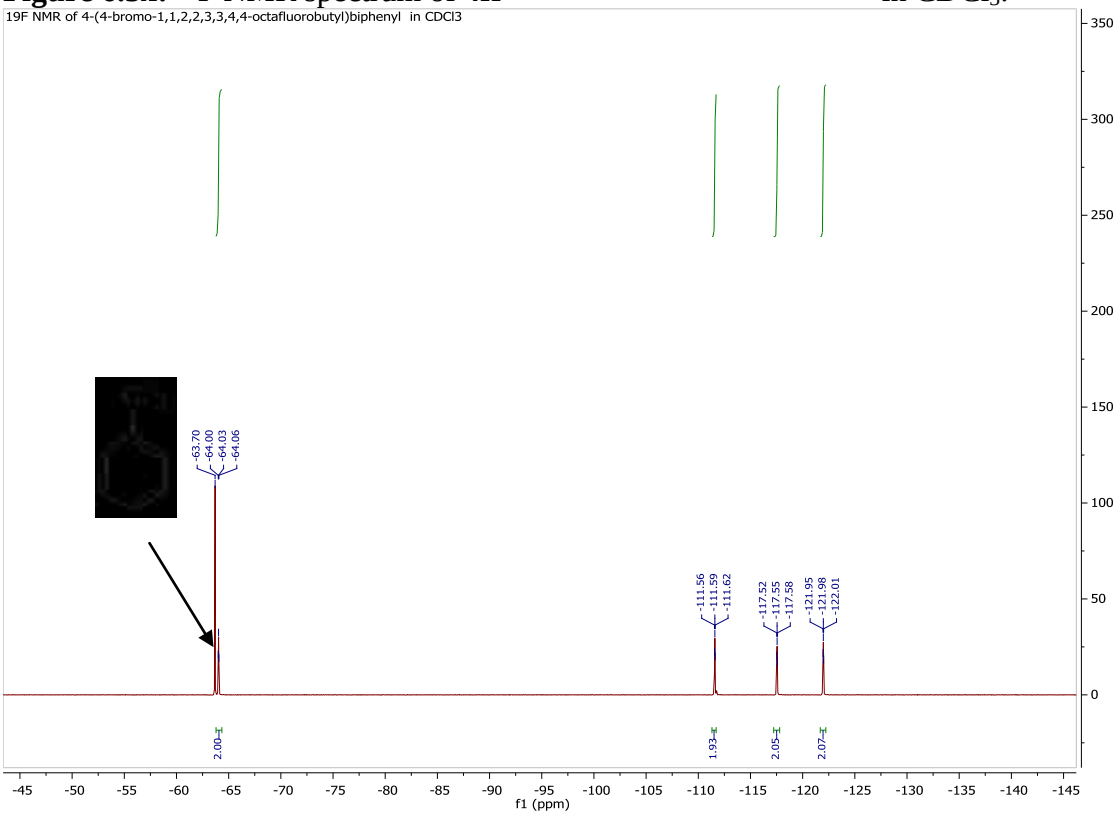


Figure 6.3x: ^{19}F NMR spectrum of **4ff** in $CDCl_3$:



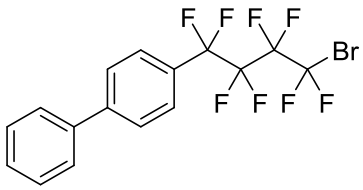


Figure 6.3y: ^{1}H NMR spectrum of **4ff** in $CDCl_3$:

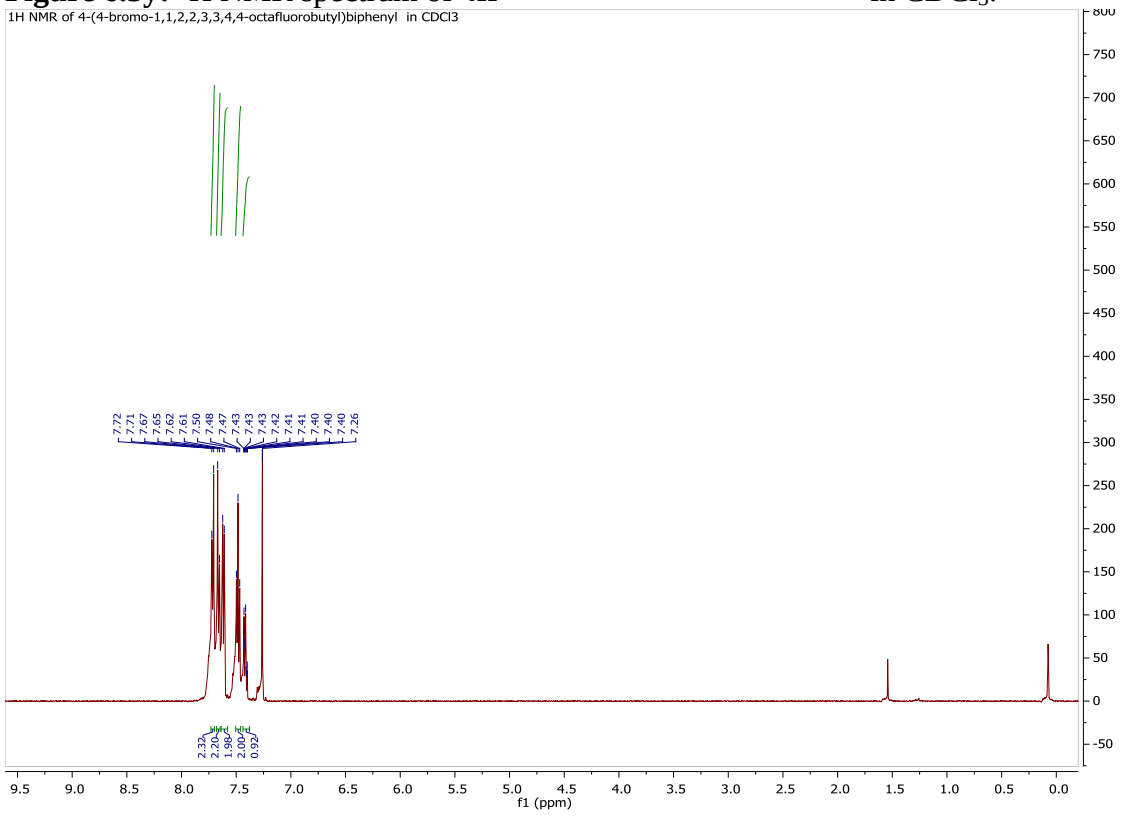
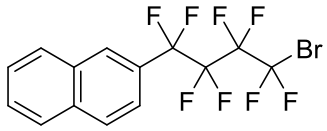


Figure 6.3z: ^{19}F NMR spectrum of **4gg** 

in $CDCl_3$:

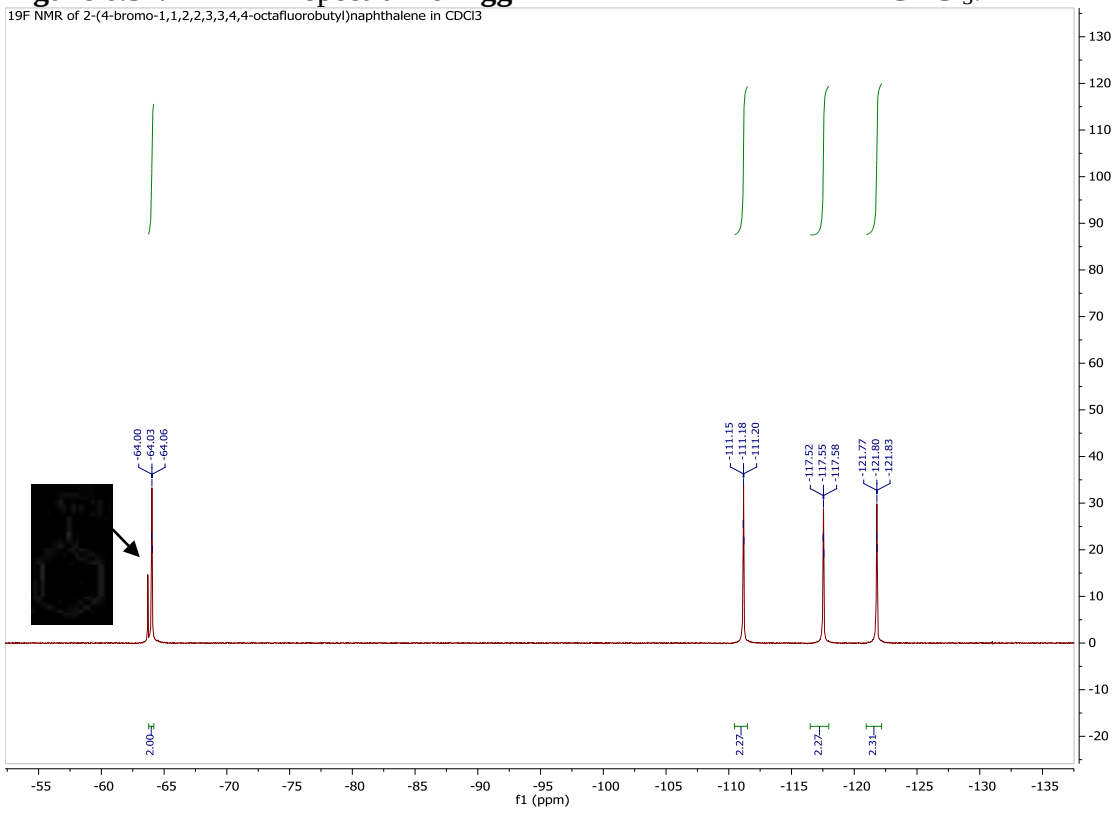
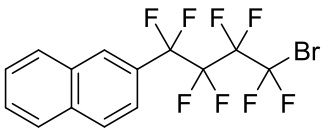


Figure 6.3aa: ^{1}H NMR spectrum of **4gg**  in $CDCl_3$:

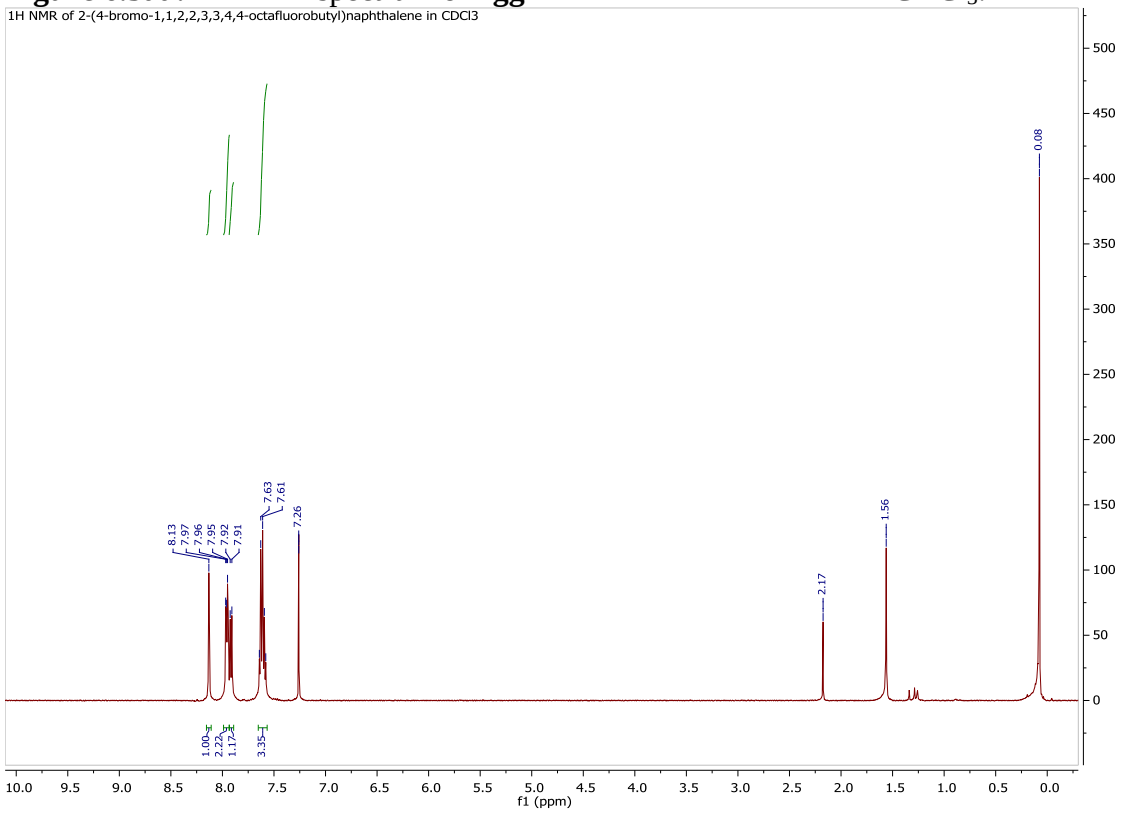
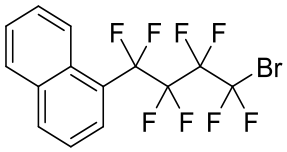


Figure 6.3bb: ^{19}F NMR spectrum of **4hh** 

in $CDCl_3$:

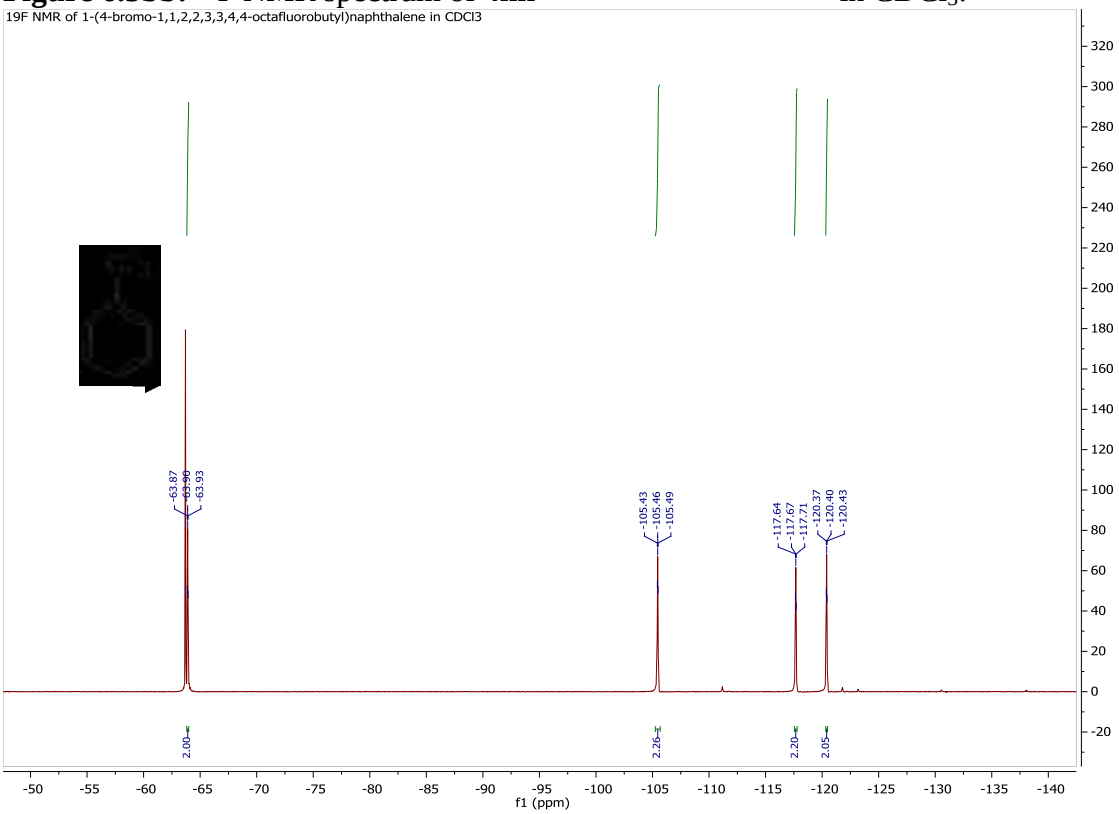
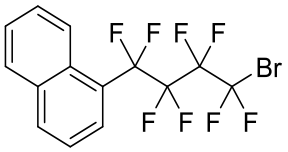


Figure 6.3cc: ^{1}H NMR spectrum of **4hh** 

in $CDCl_3$:

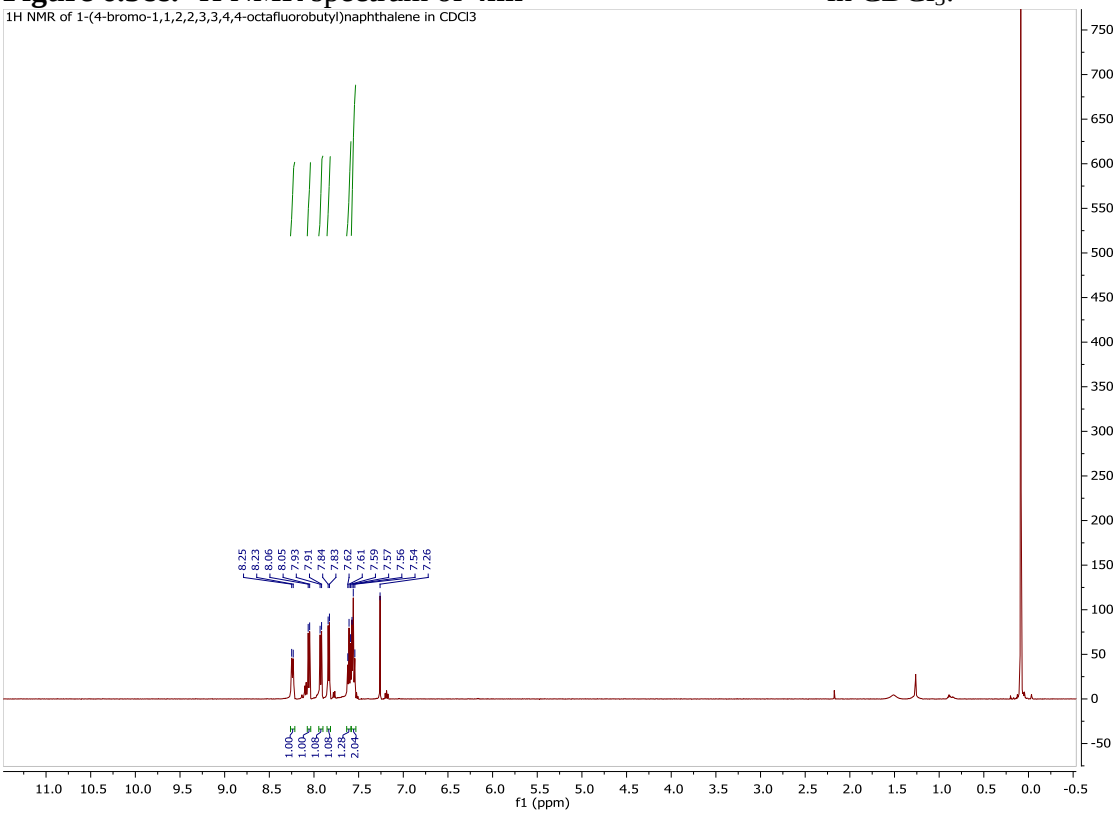


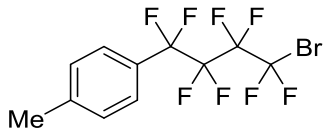
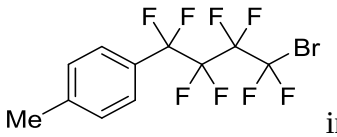
Figure 6.3dd: ^{19}F NMR spectrum of **4ii**  in MeCN-d_3:

Figure 6.3ee: ^{1}H NMR spectrum of **4ii**  in MeCN-d_3:

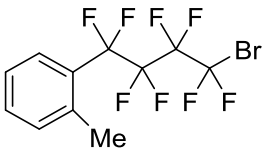


Figure 6.3ff: ^{19}F NMR spectrum of **4jj** in MeCN-d_3:

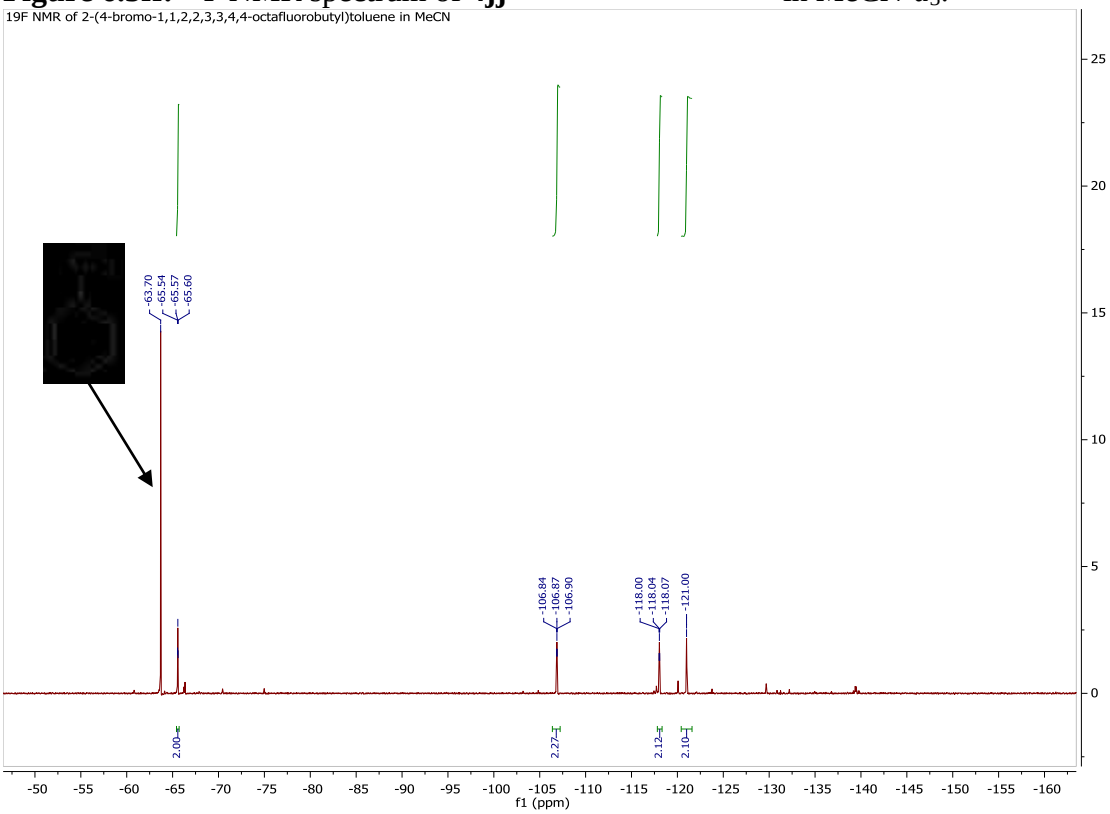
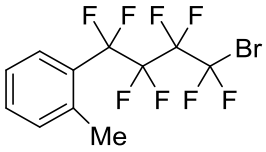
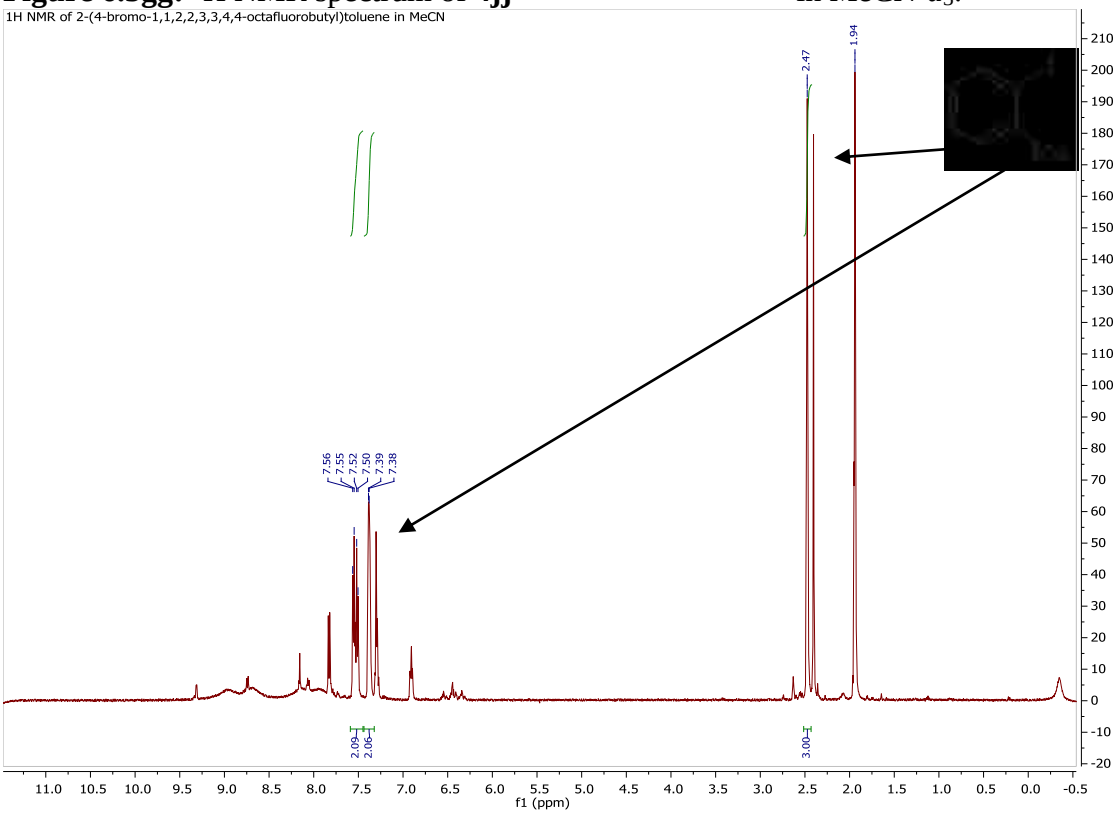


Figure 6.3gg: ^{1}H NMR spectrum of **4jj**  in MeCN-d_3:



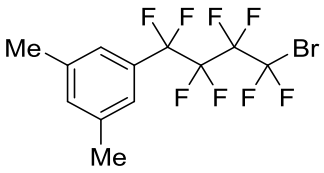
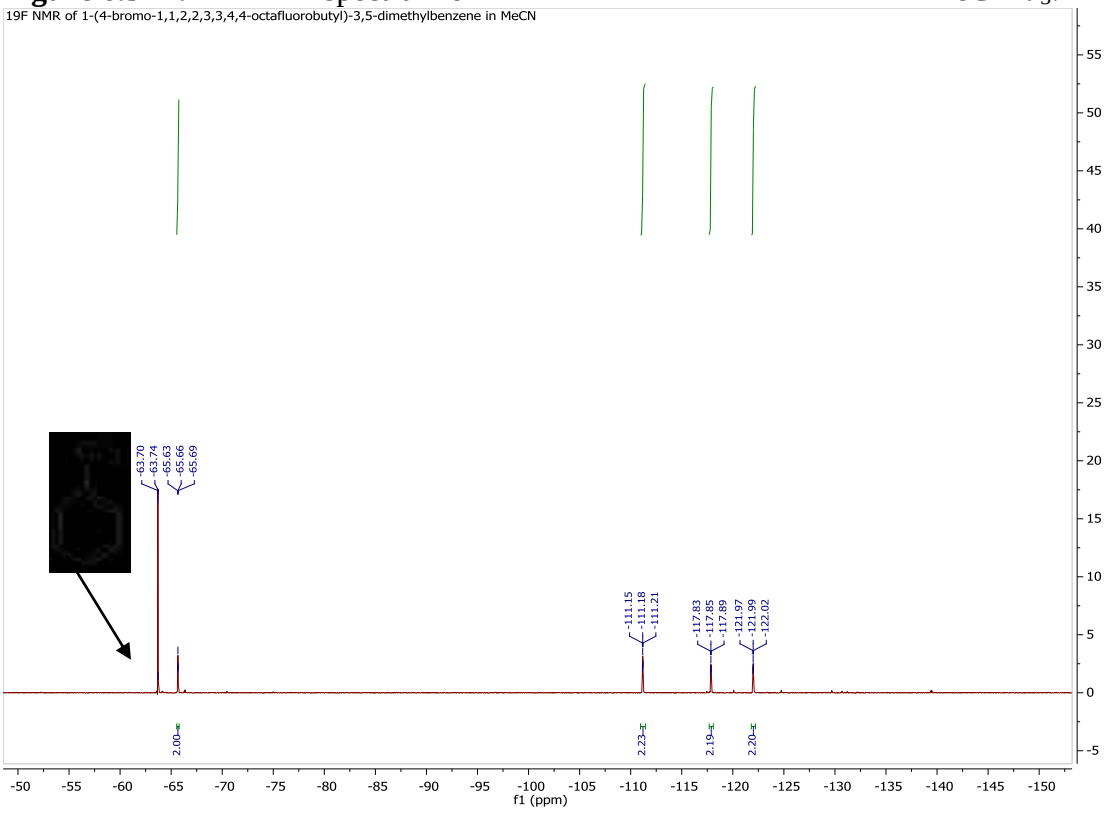


Figure 6.3hh: ^{19}F NMR spectrum of **4kk** in MeCN-d_3:



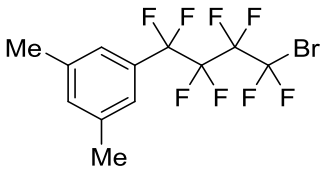


Figure 6.3ii: ^{1}H NMR spectrum of **4kk** in MeCN-d_3:

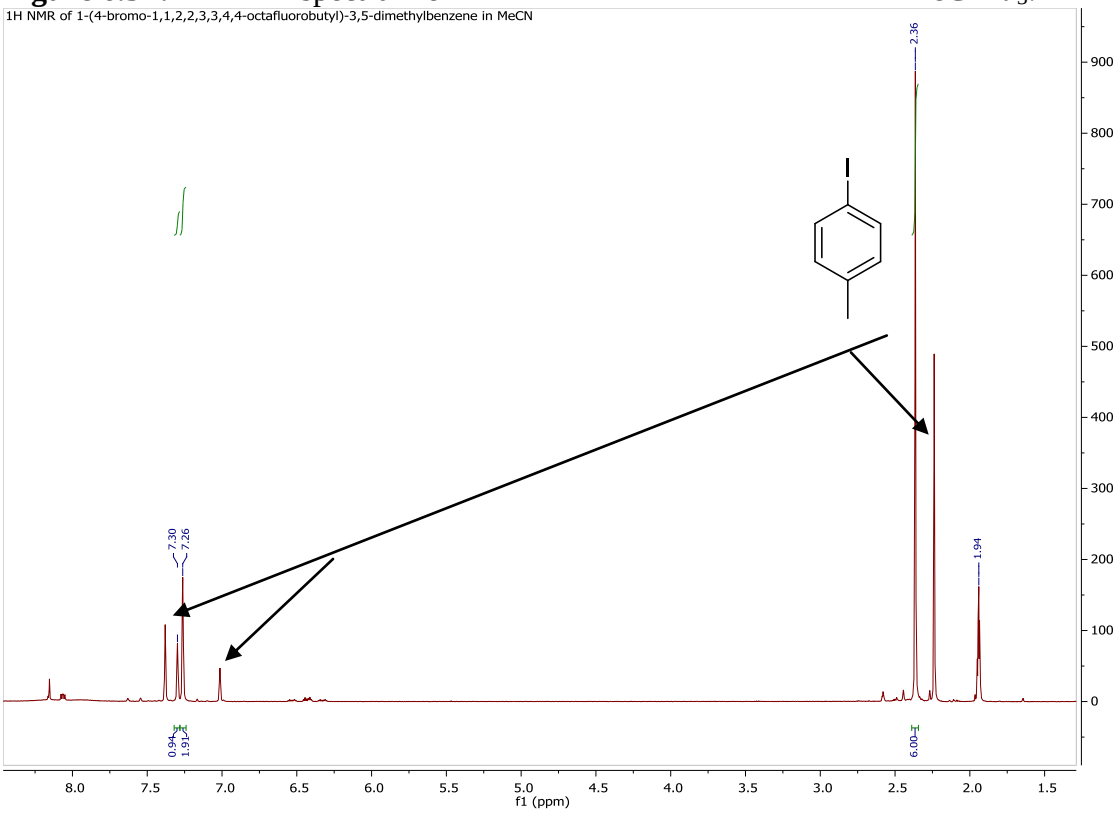
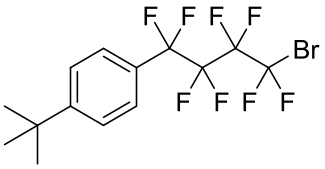


Figure 6.3jj: ^{19}F NMR spectrum of **4ll** 

in MeCN-d_3:

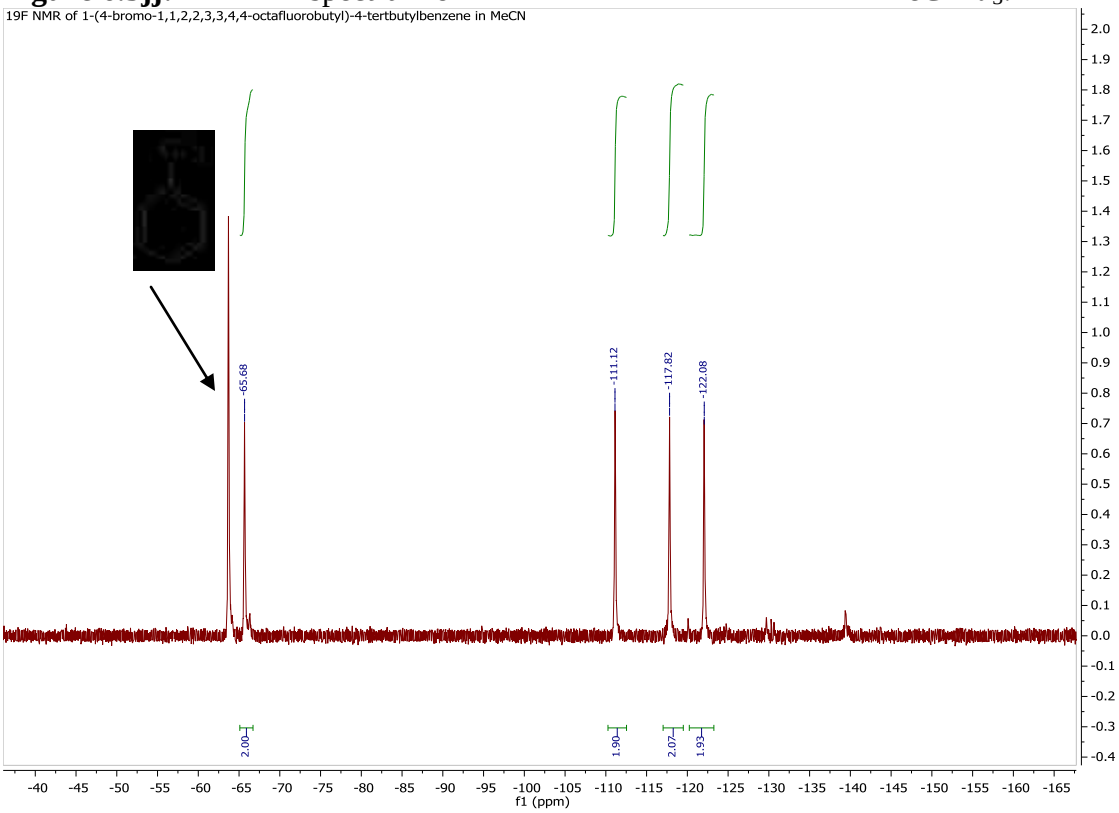
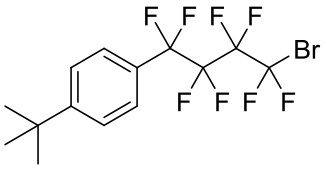


Figure 6.3kk: ^{1}H NMR spectrum of **4ll**  in MeCN-d_3:

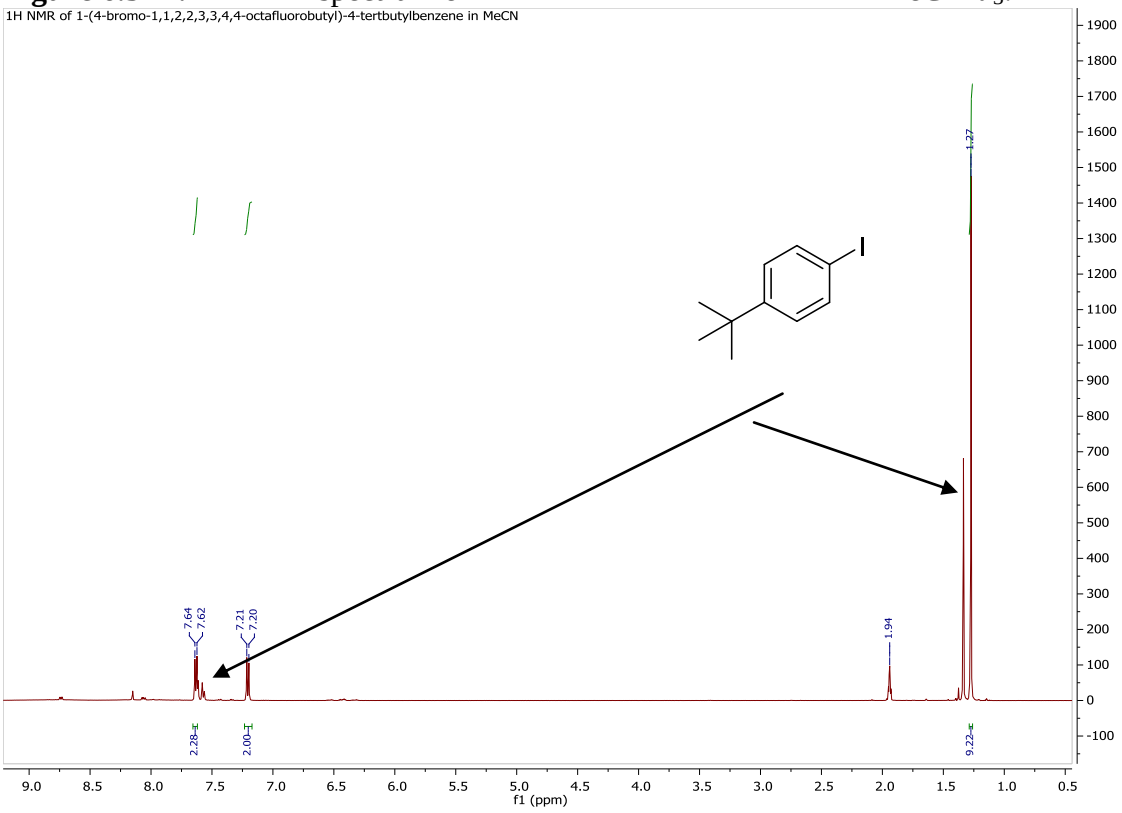


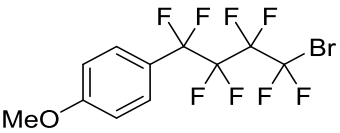
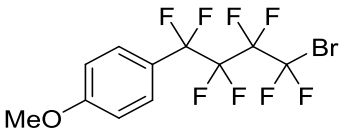
Figure 6.3ll: ^{19}F NMR spectrum of **4mm**  in $CDCl_3$:

Figure 6.3mm: ^{1}H NMR spectrum of **4mm** 

in $CDCl_3$:

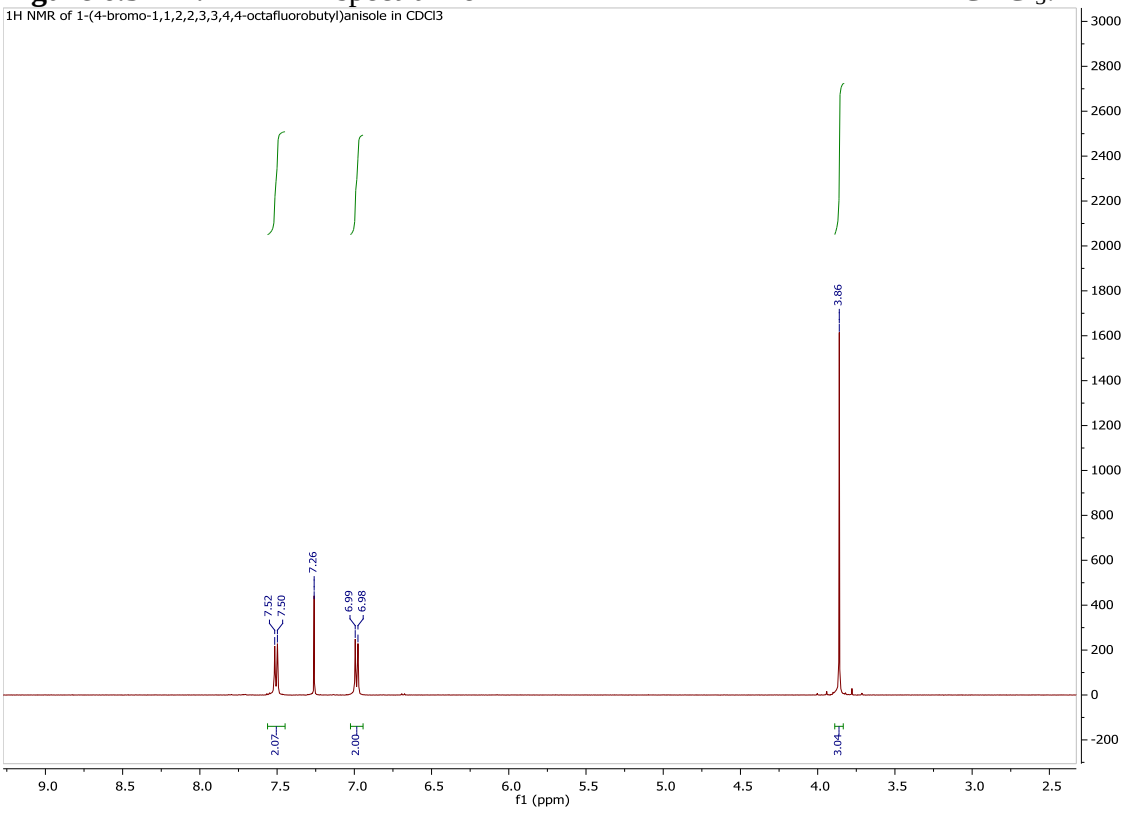
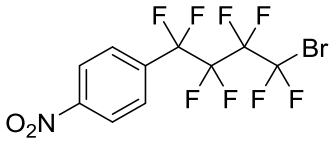


Figure 6.3nn: ^{19}F NMR spectrum of **4nn**  in $CDCl_3$:

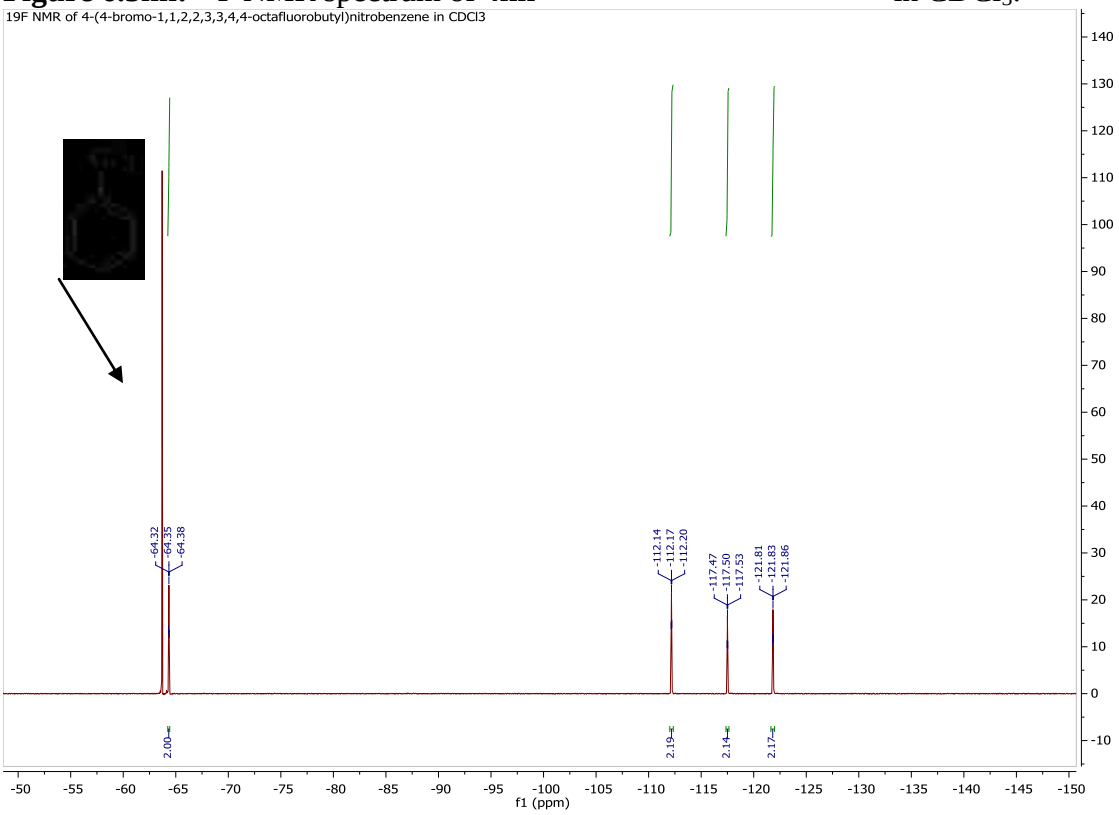


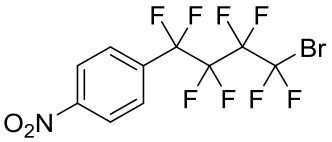
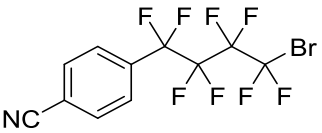
Figure 6.3oo: ^{1}H NMR spectrum of **4nn**  in $CDCl_3$:

Figure 6.3pp: ^{19}F NMR spectrum of **4oo**  in $CDCl_3$:

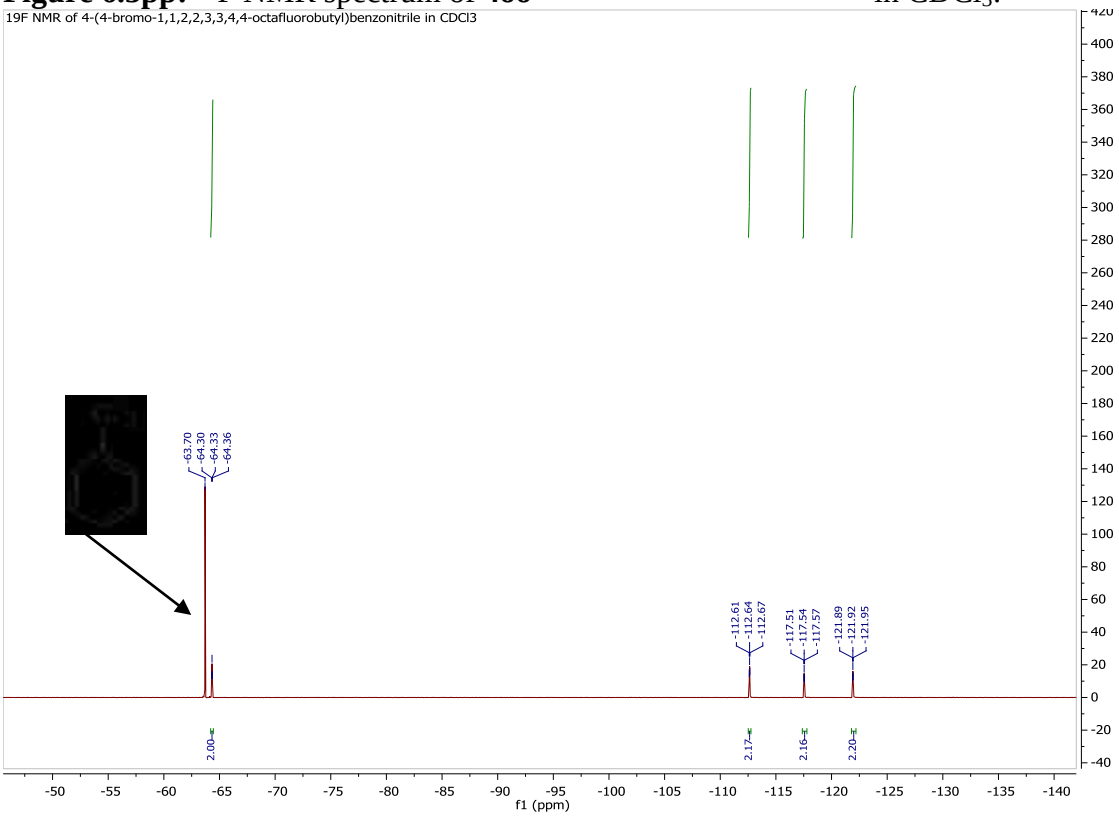
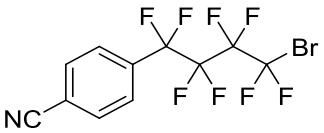
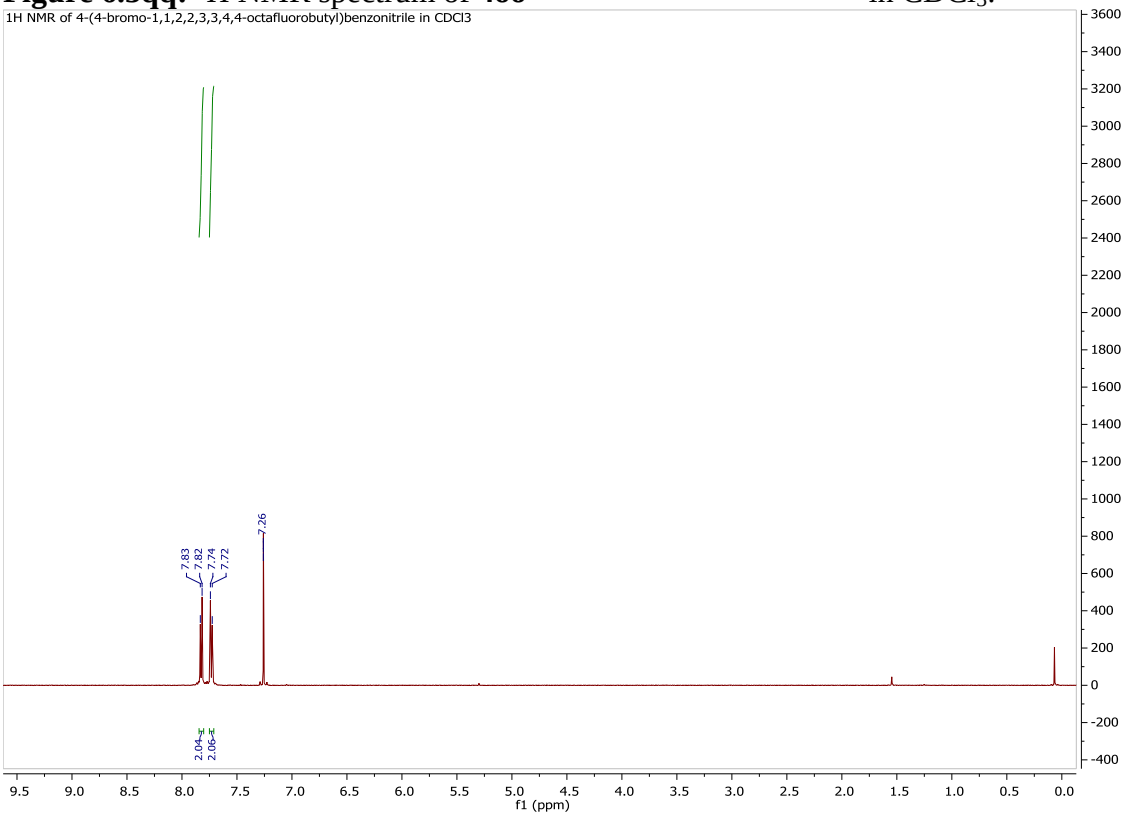


Figure 6.3qq: ^{1}H NMR spectrum of **4oo**  in $CDCl_3$:



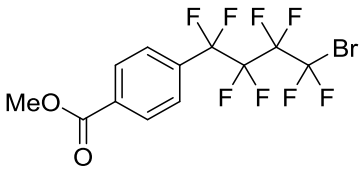
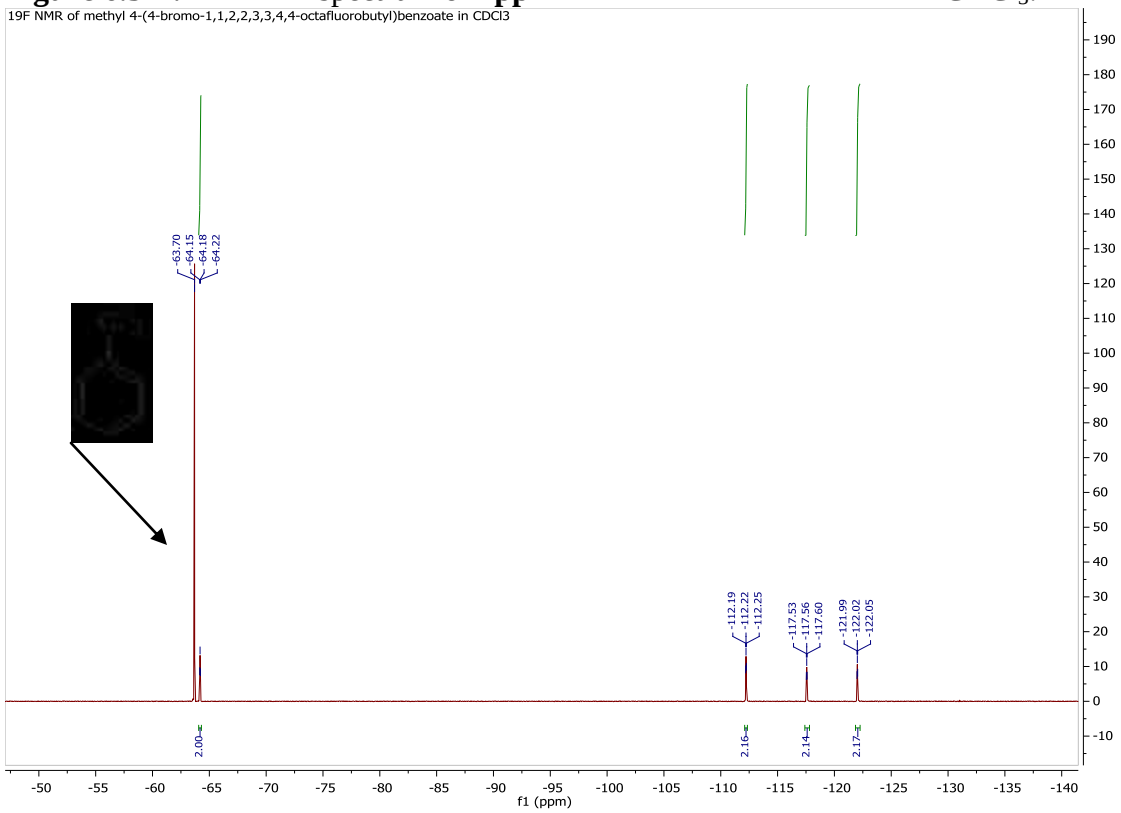


Figure 6.3rr: ^{19}F NMR spectrum of **4pp** in $CDCl_3$:



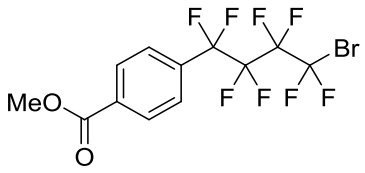
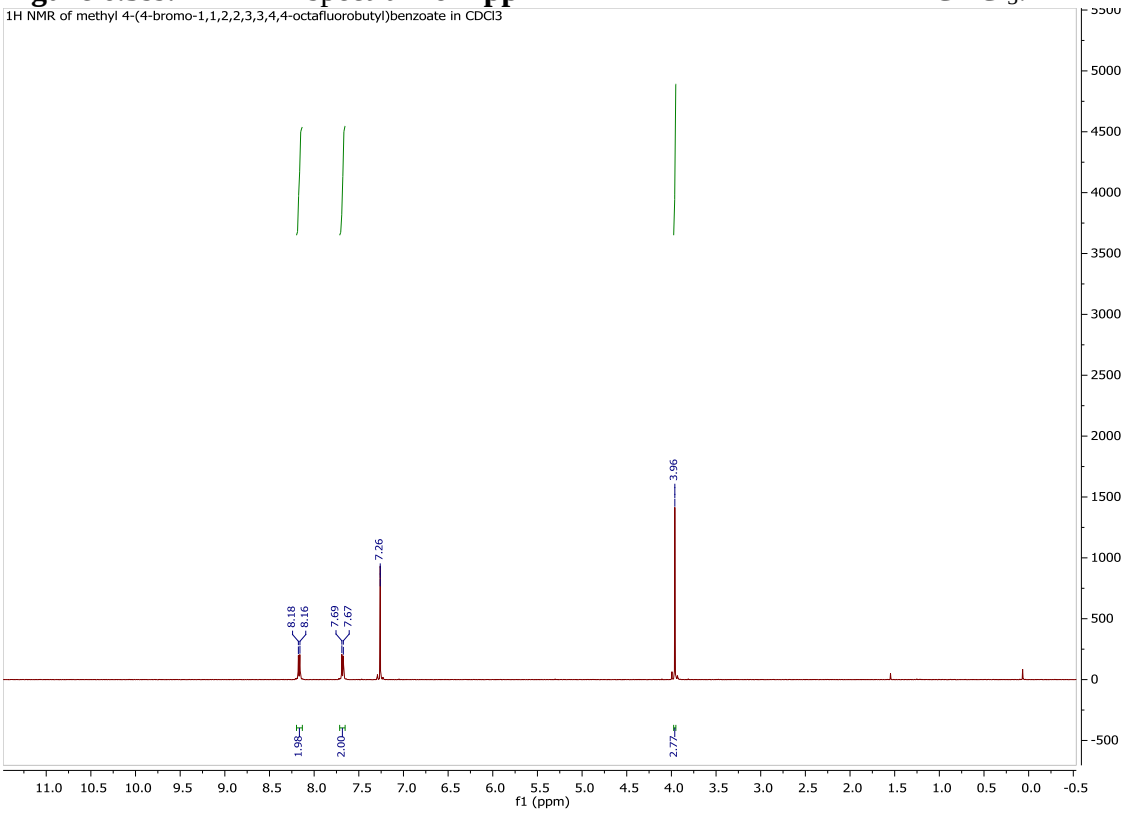


Figure 6.3ss: ^{1}H NMR spectrum of **4pp** in $CDCl_3$:



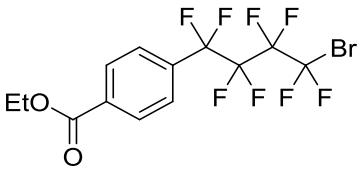
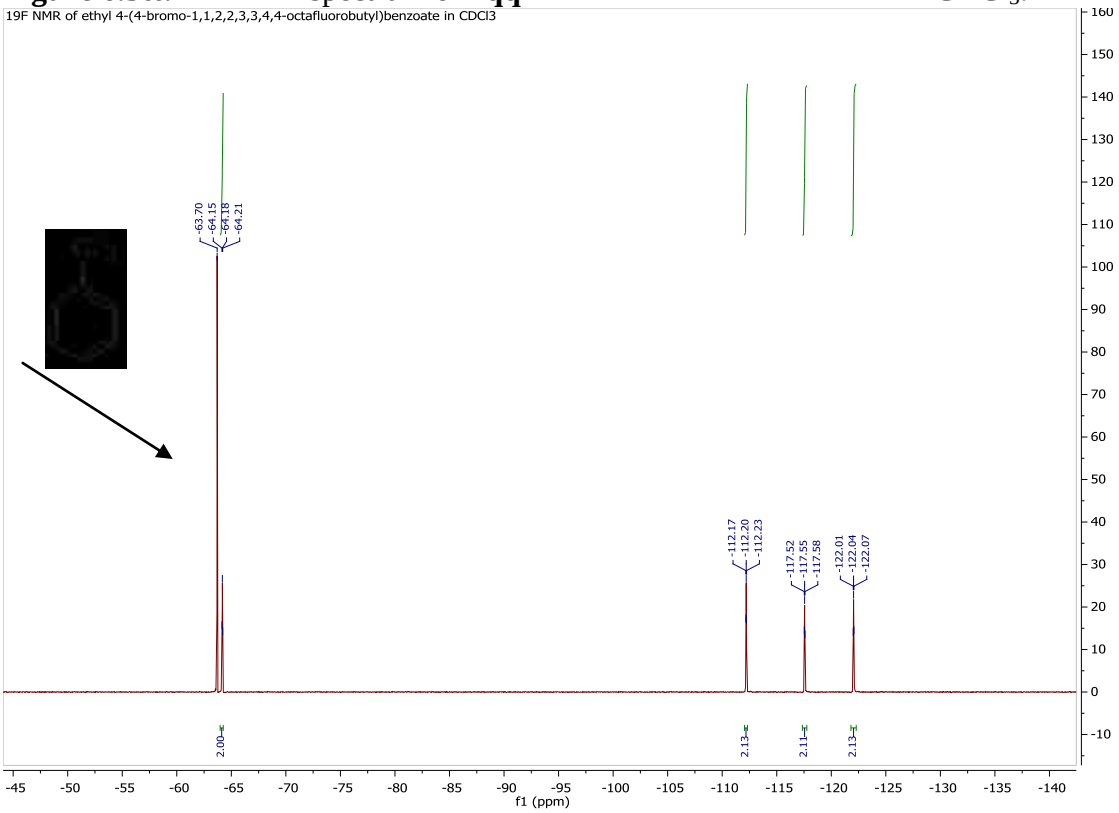


Figure 6.3tt: ^{19}F NMR spectrum of **4qq** in $CDCl_3$:



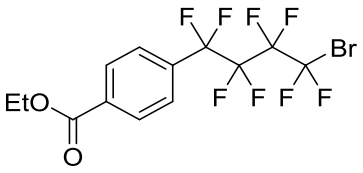


Figure 6.3uu: ^{1}H NMR spectrum of **4qq** in $CDCl_3$:

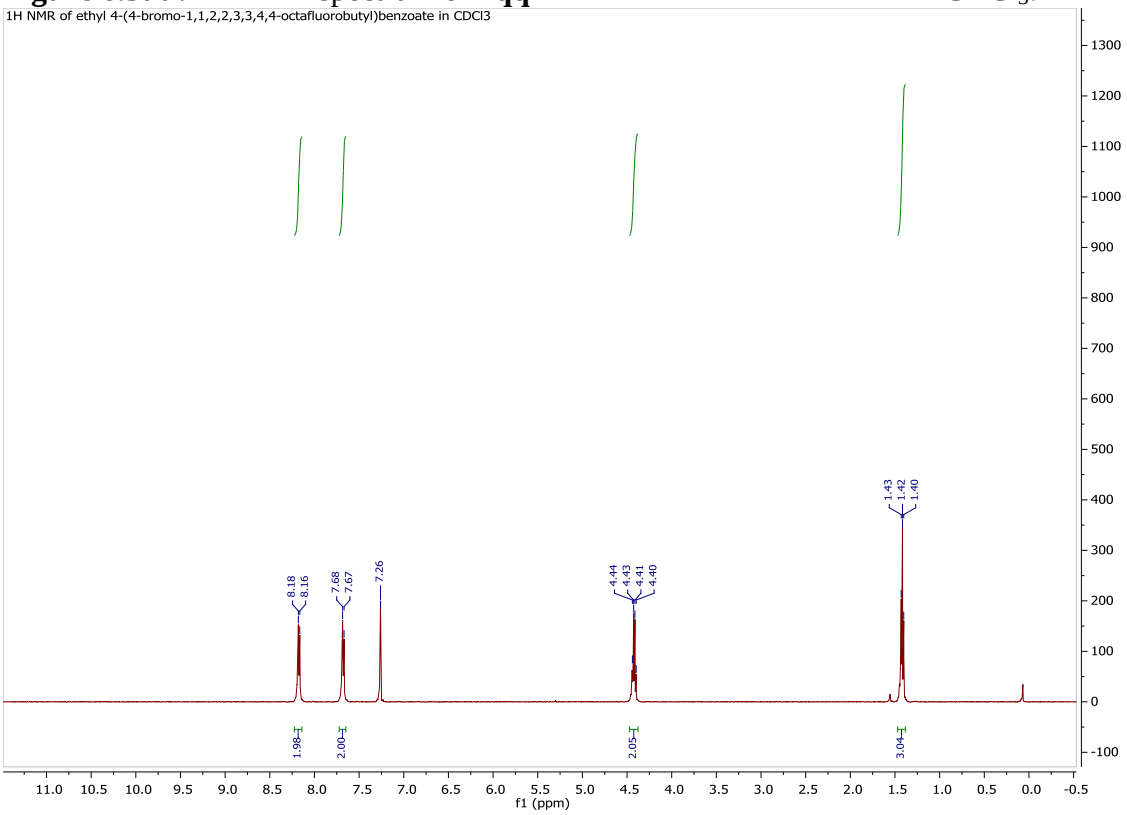
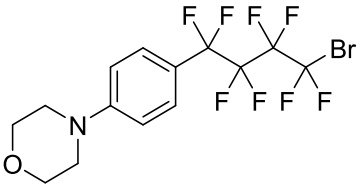


Figure 6.3vv: ^{19}F NMR spectrum of **4rr** 

in $CDCl_3$:

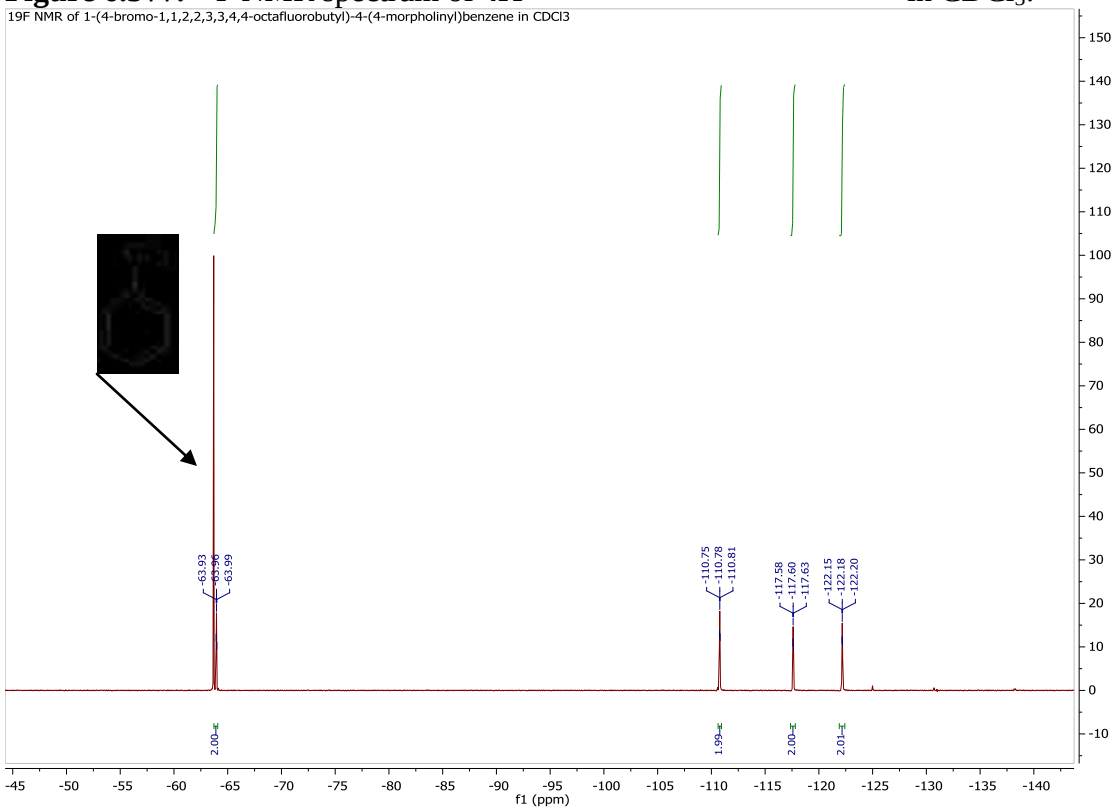
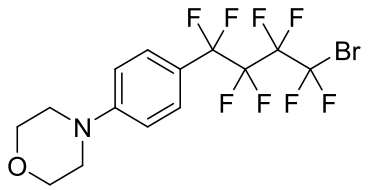


Figure 6.3ww: ^{1}H NMR spectrum of **4rr**  in $CDCl_3$:

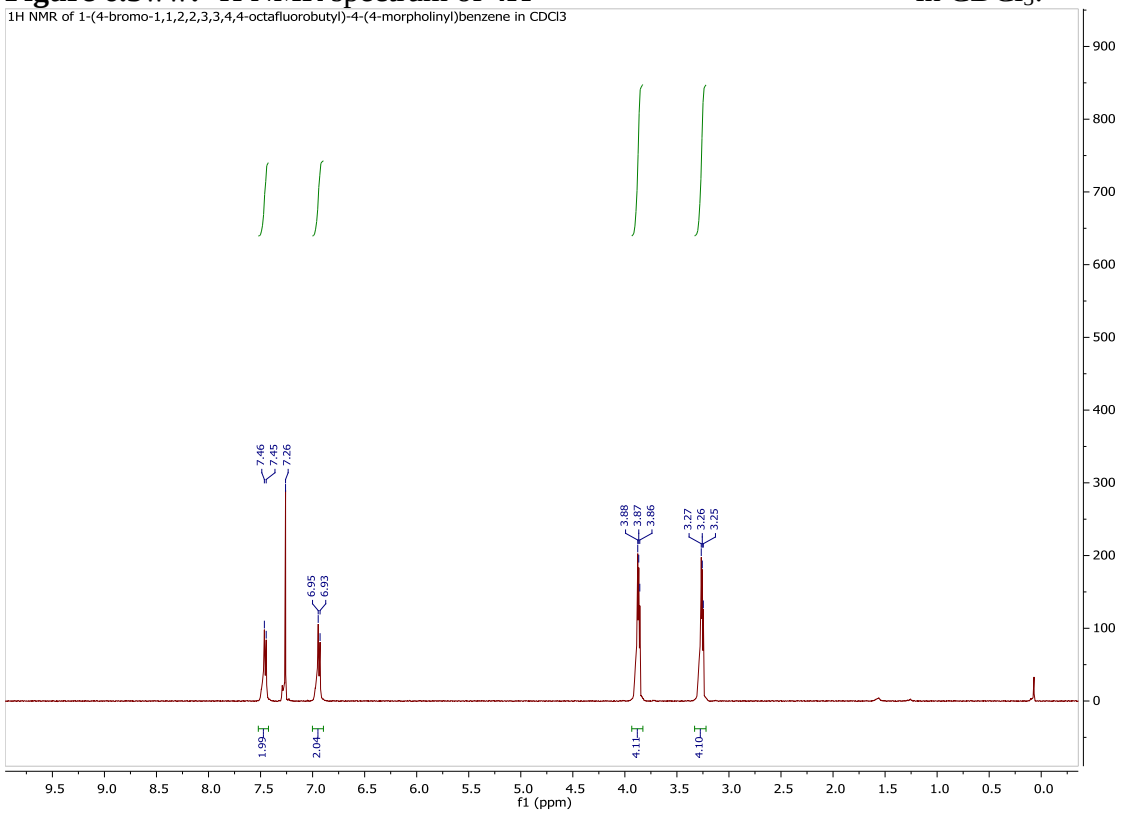
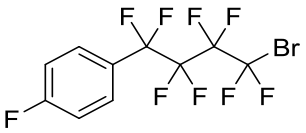


Figure 6.3xx: ^{19}F NMR spectrum of **4ss**  in MeCN-d_3:

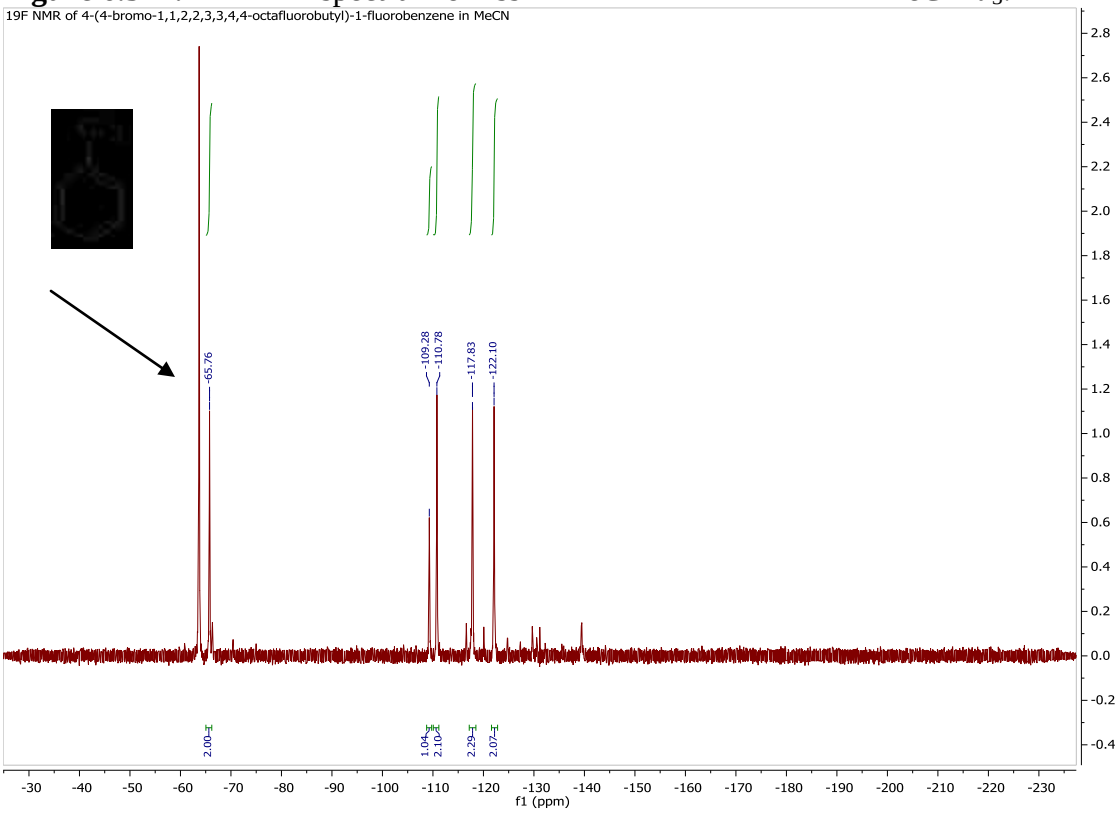
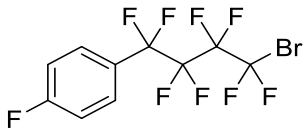


Figure 6.3yy: ^{1}H NMR spectrum of **4ss**  in MeCN-d_3:

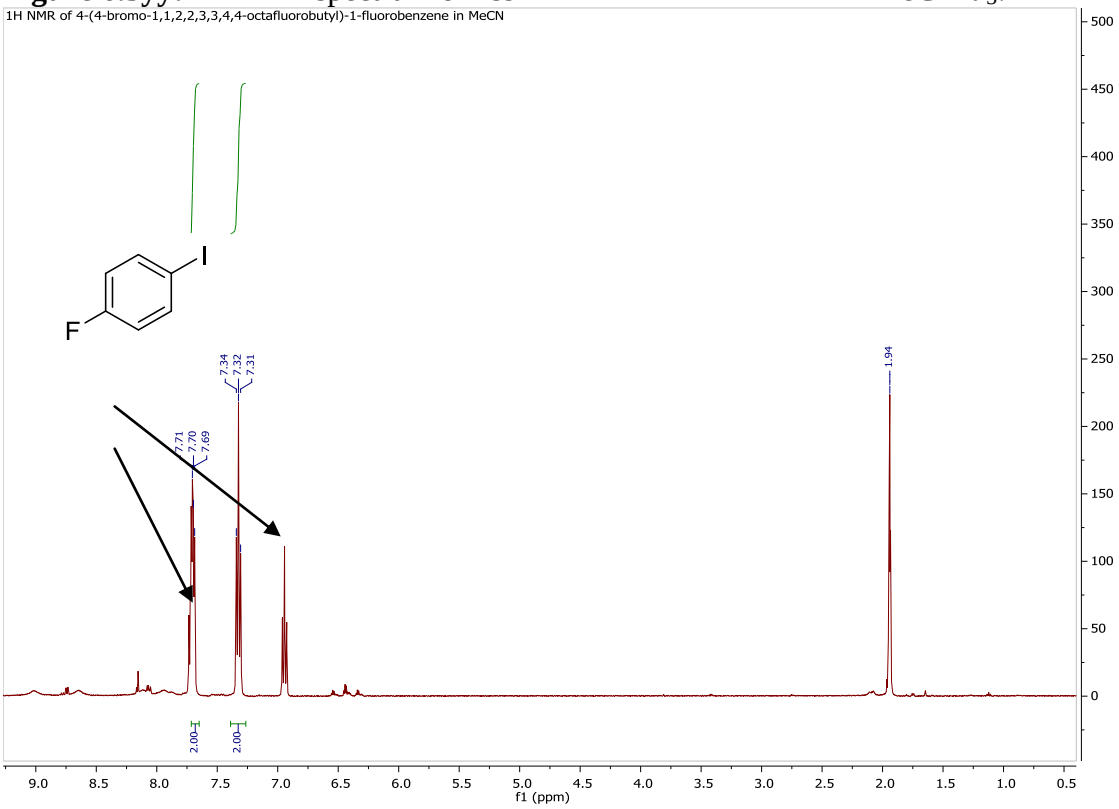
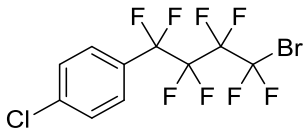


Figure 6.3zz: ^{19}F NMR spectrum of **4tt**  in MeCN-d_3:

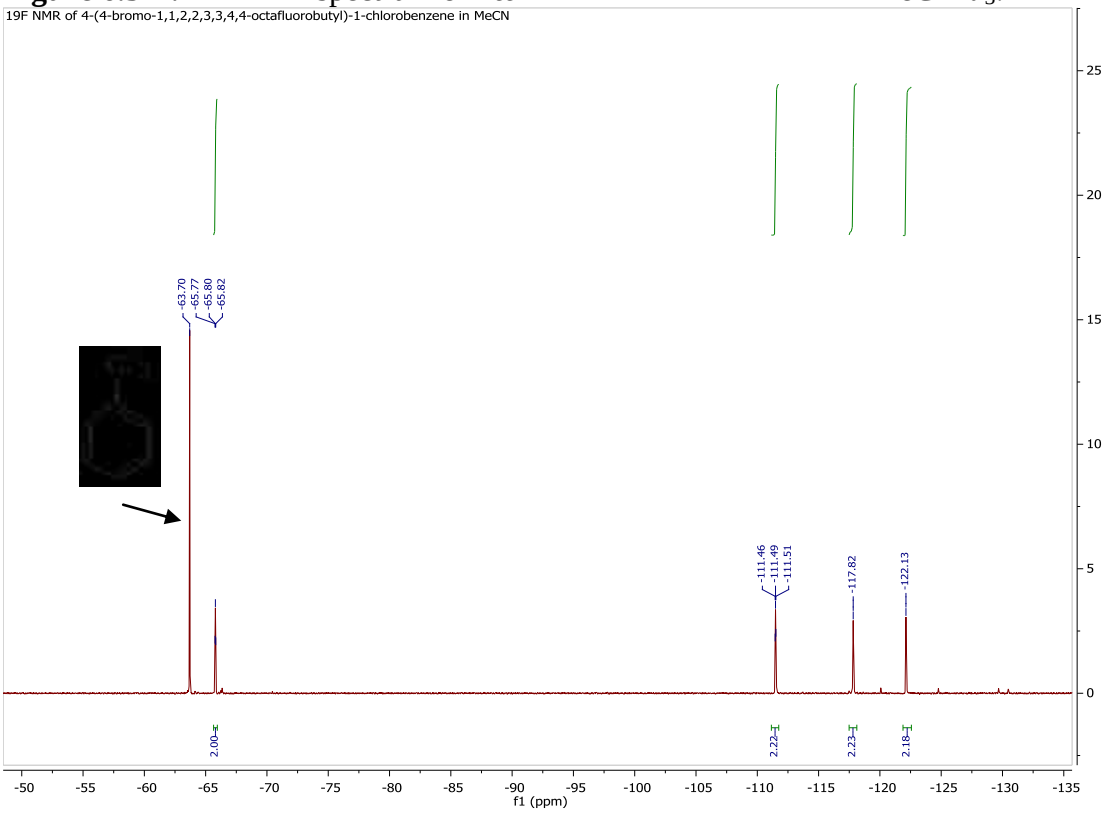


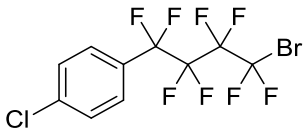
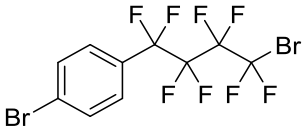
Figure 6.3aaa: ^{1}H NMR spectrum of **4tt**  in MeCN-d_3:

Figure 6.3bbb: ^{19}F NMR spectrum of **4uu**  in MeCN-d_3:

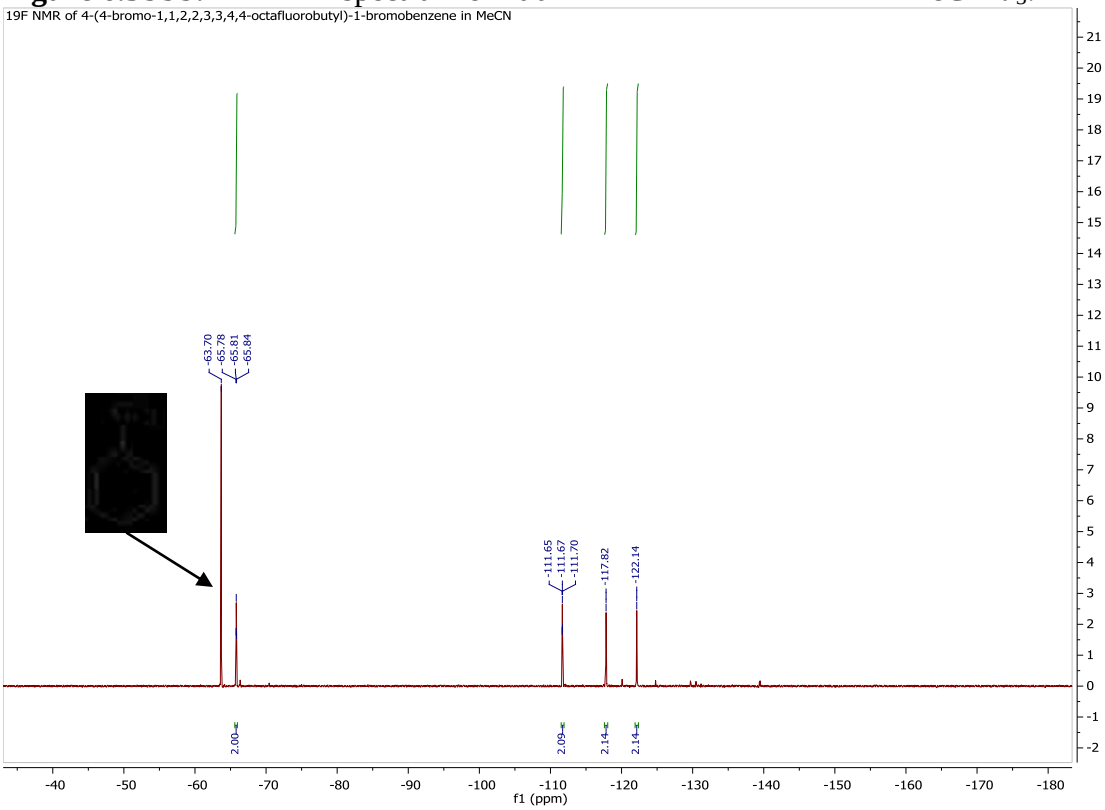


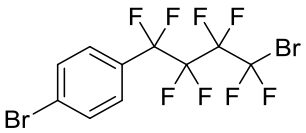
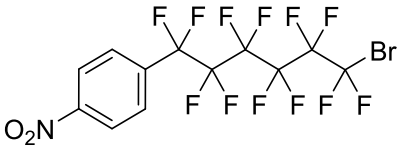
Figure 6.3ccc: ^{1}H NMR spectrum of **4uu**  in MeCN-d_3:

Figure 6.3ddd: ^{19}F NMR spectrum of **4xx**  in $CDCl_3$:

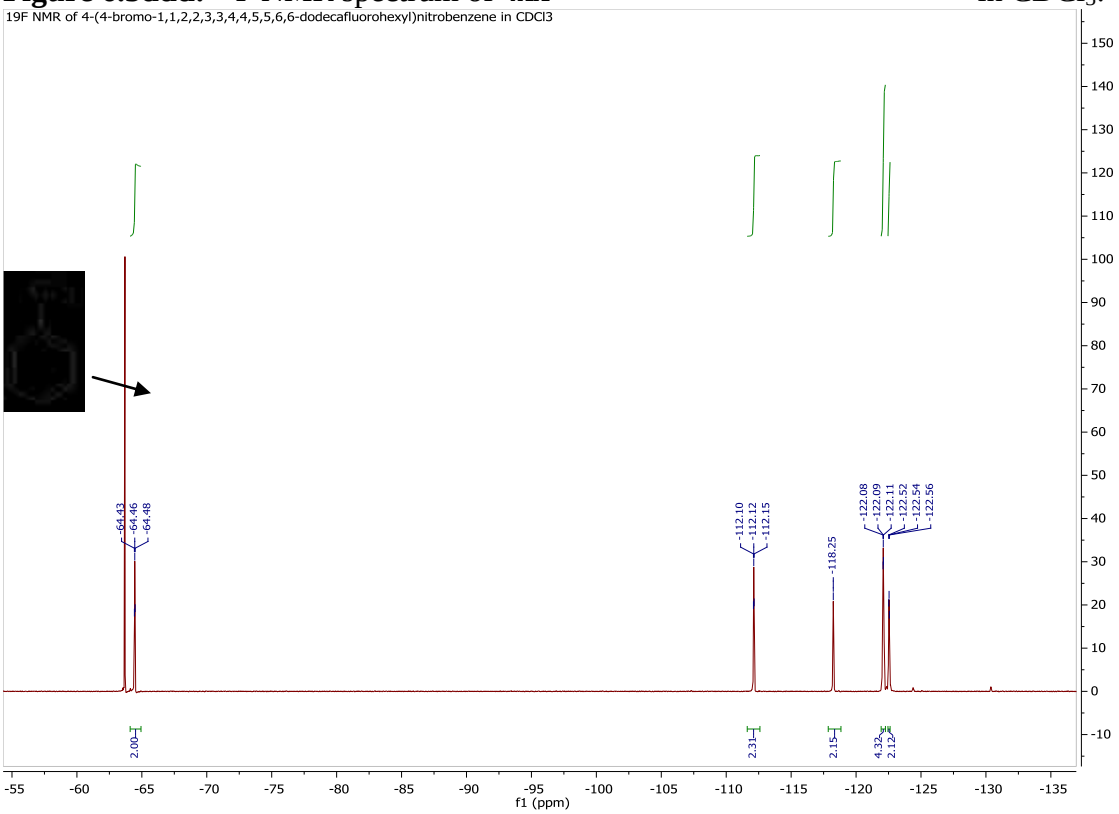
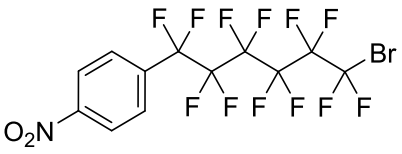


Figure 6.3eee: ^{1}H NMR spectrum of **4xx**  in $CDCl_3$:

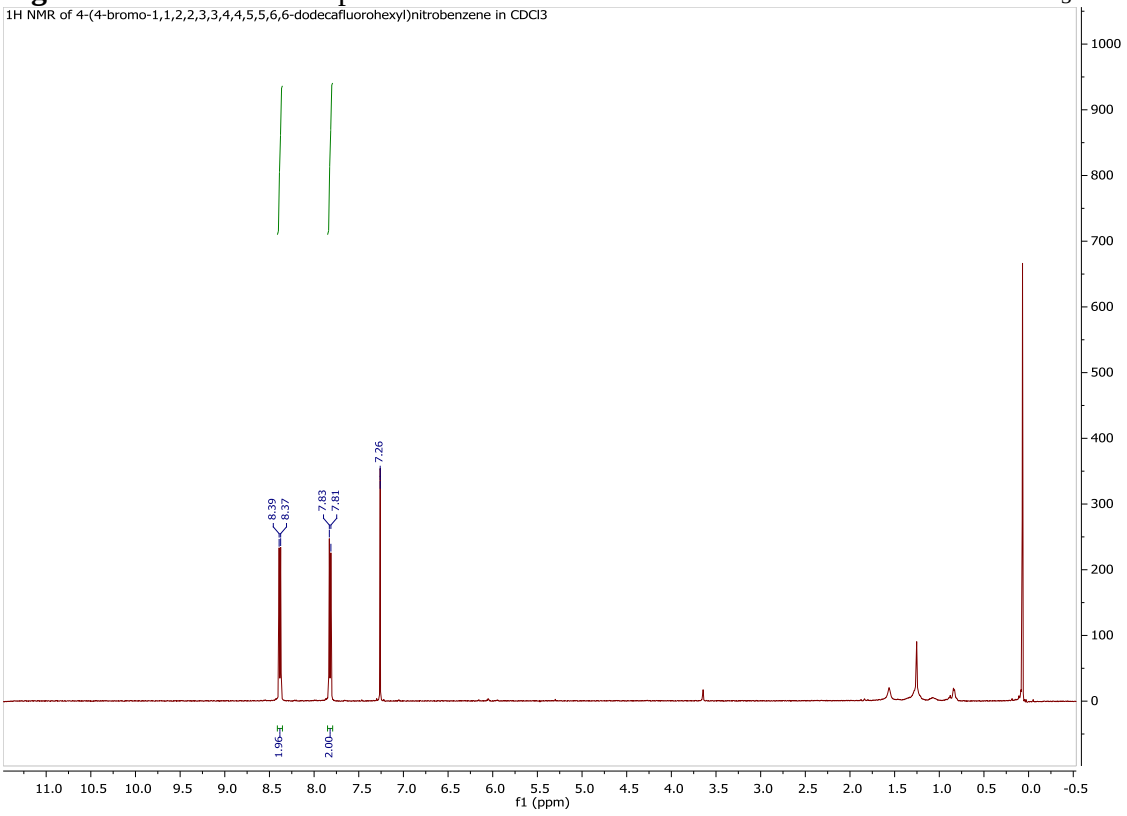
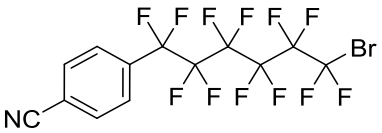


Figure 6.3fff: ^{19}F NMR spectrum of **4yy**  in $CDCl_3$:

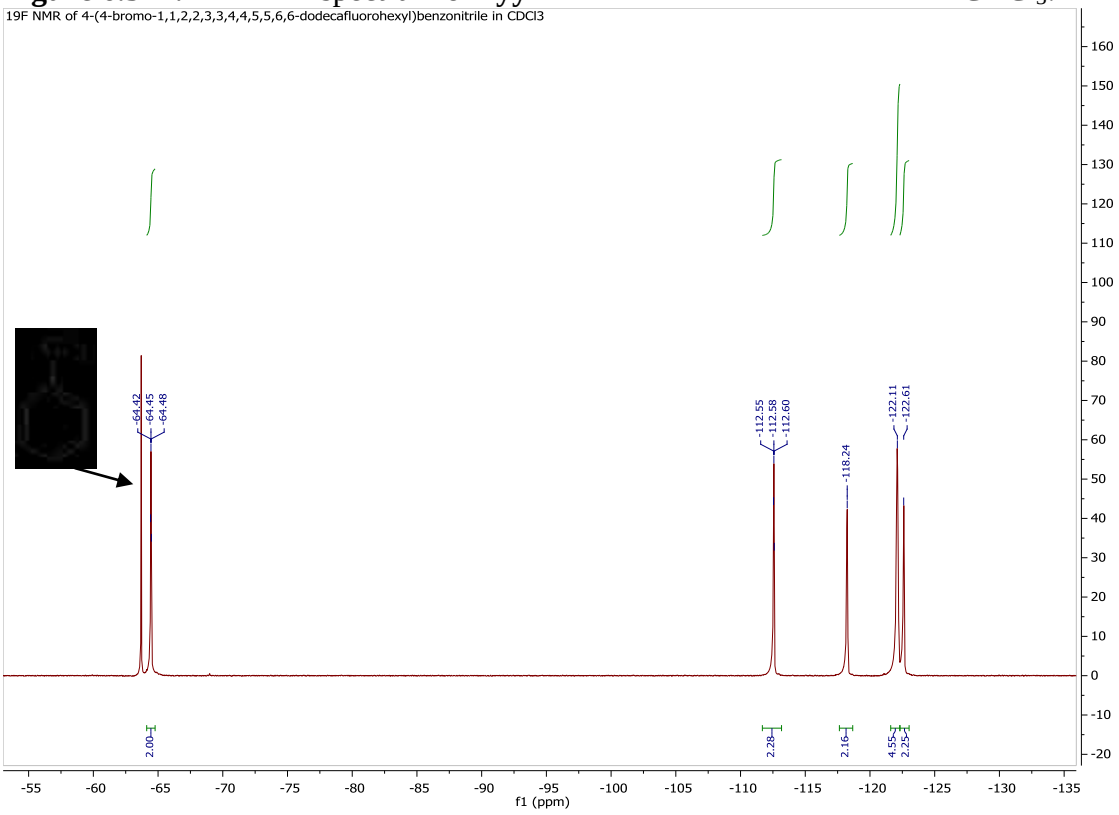
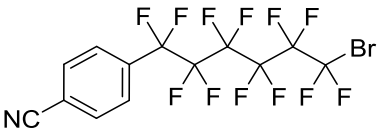
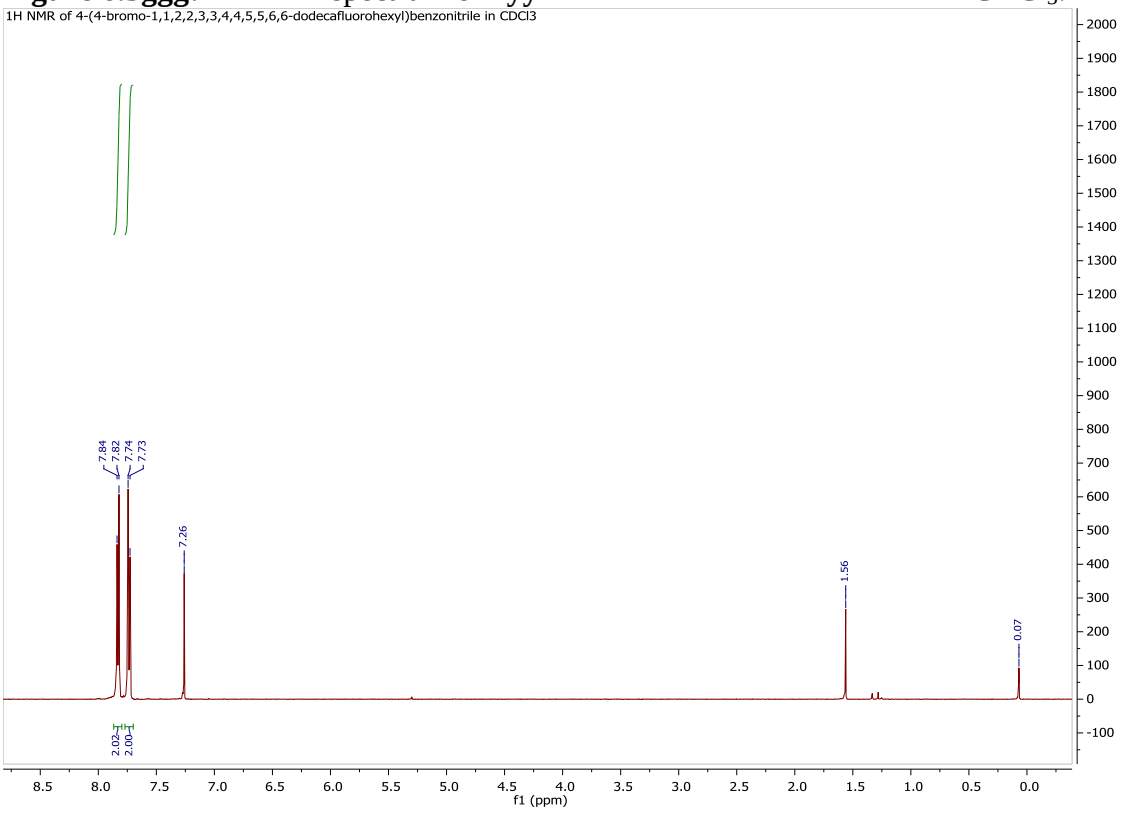


Figure 6.3ggg: ^{1}H NMR spectrum of **4yy** 

in $CDCl_3$:



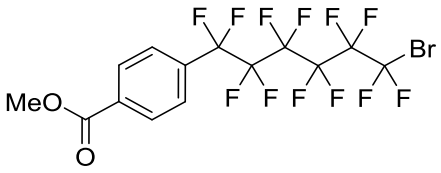
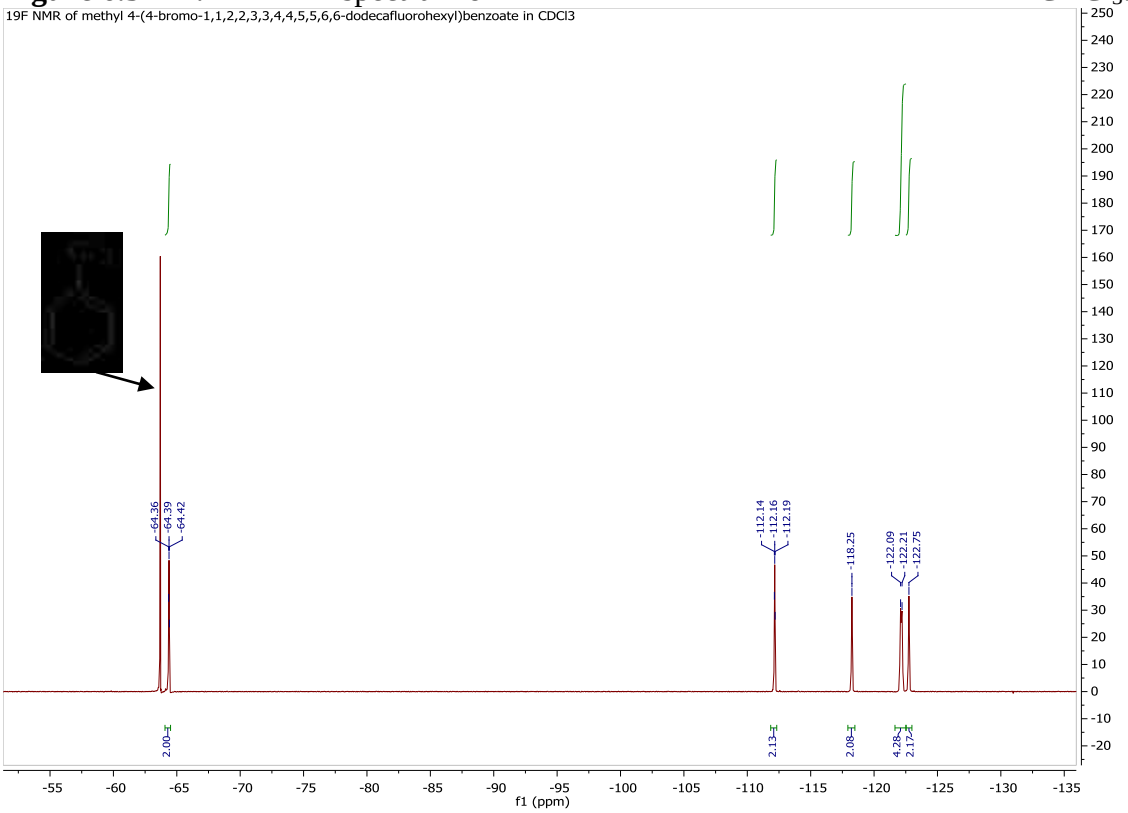


Figure 6.3hhh: ^{19}F NMR spectrum of **4zz** in $CDCl_3$:



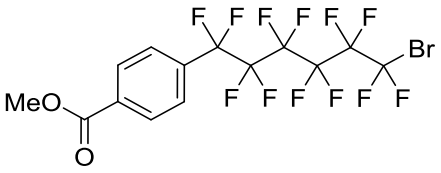
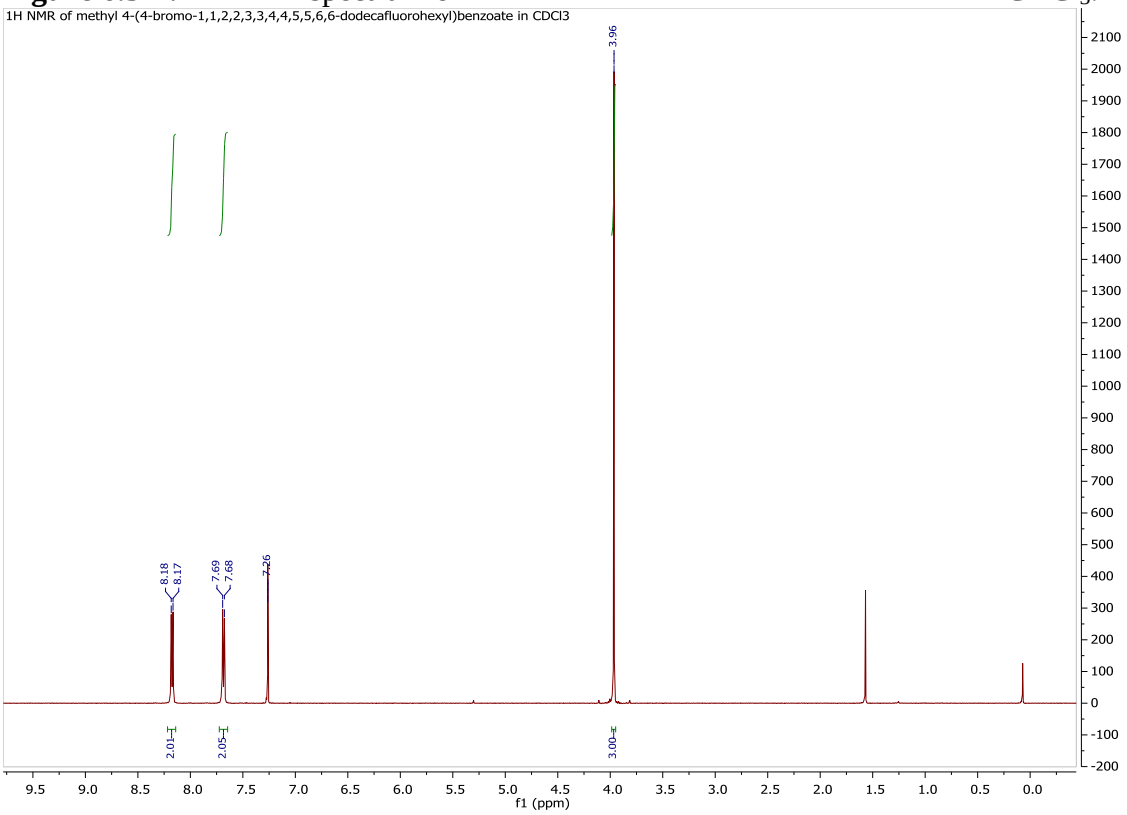


Figure 6.3iii: ^{1}H NMR spectrum of **4zz** in $CDCl_3$:



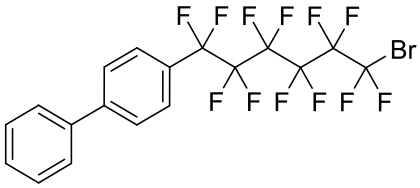
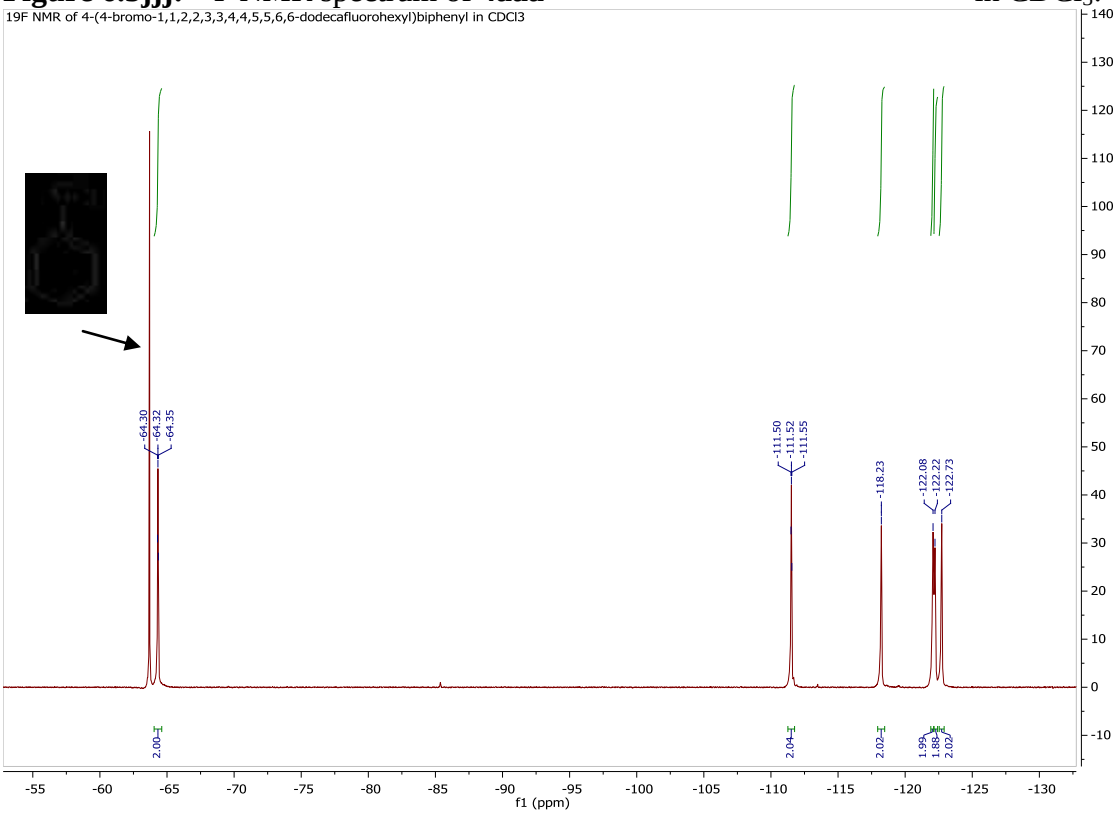


Figure 6.3jjj: ^{19}F NMR spectrum of **4aaa** in $CDCl_3$:



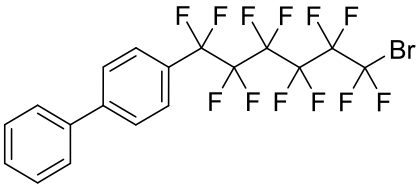
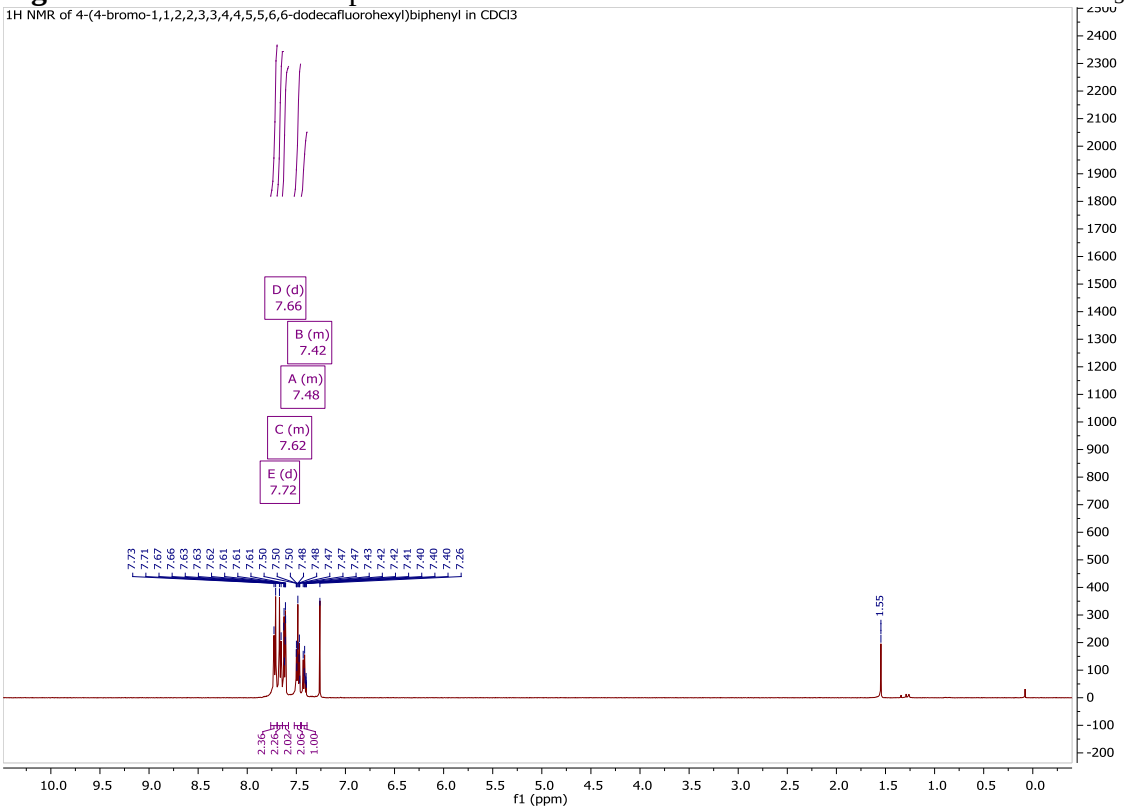


Figure 6.3kkk: ^{1}H NMR spectrum of **4aaa** in $CDCl_3$:



6.4. Data and Spectra for Chapter 5

Figure 6.4a: ^{19}F NMR spectrum of **5c** in CH_2Cl_2:

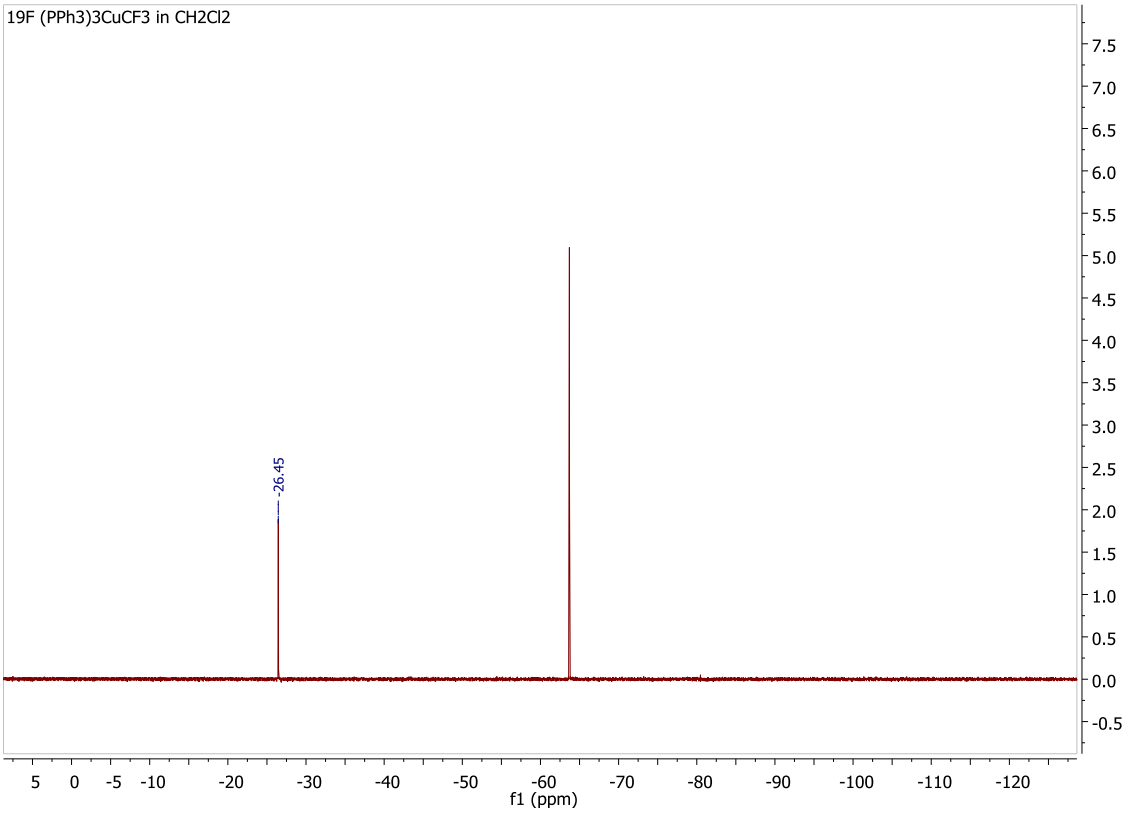


Figure 6.4b: ^{31}P NMR spectrum of **5c** in CH_2Cl_2: Referenced to PPh_3 before being taken.

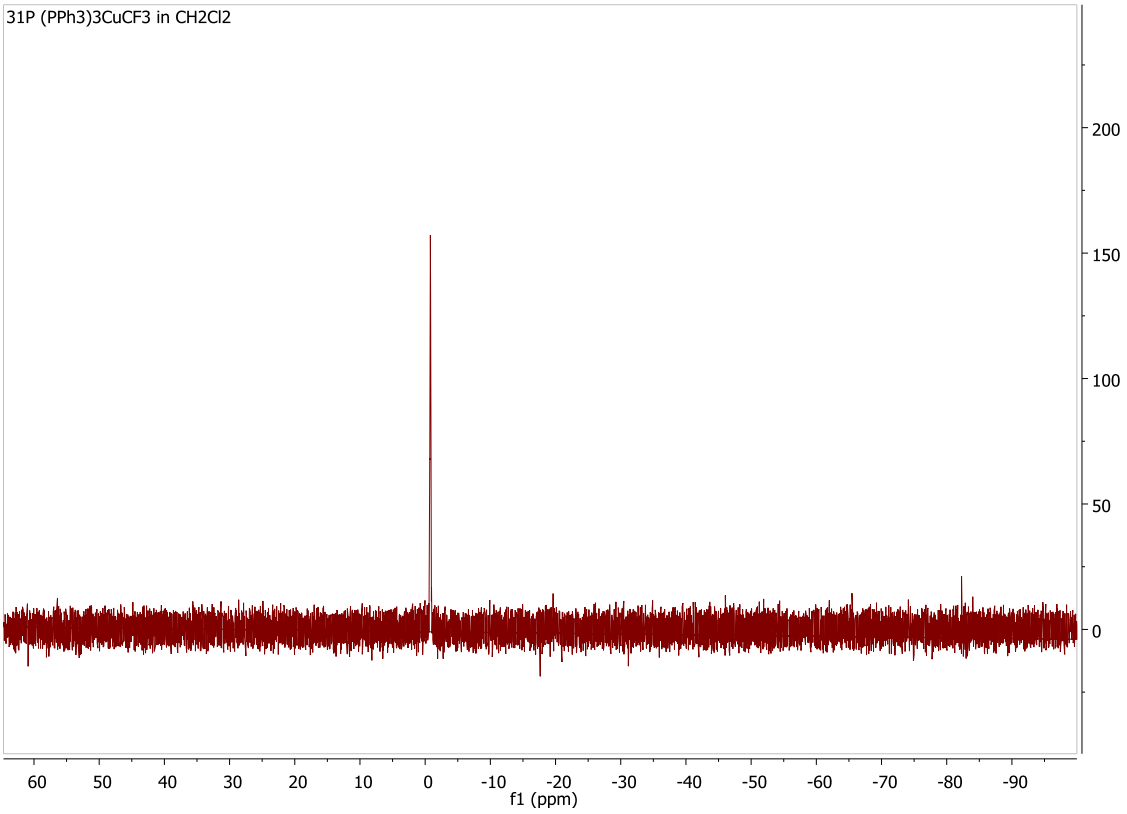


Figure 6.4c: ^{1}H NMR spectrum of **5b** in C_6D_6:

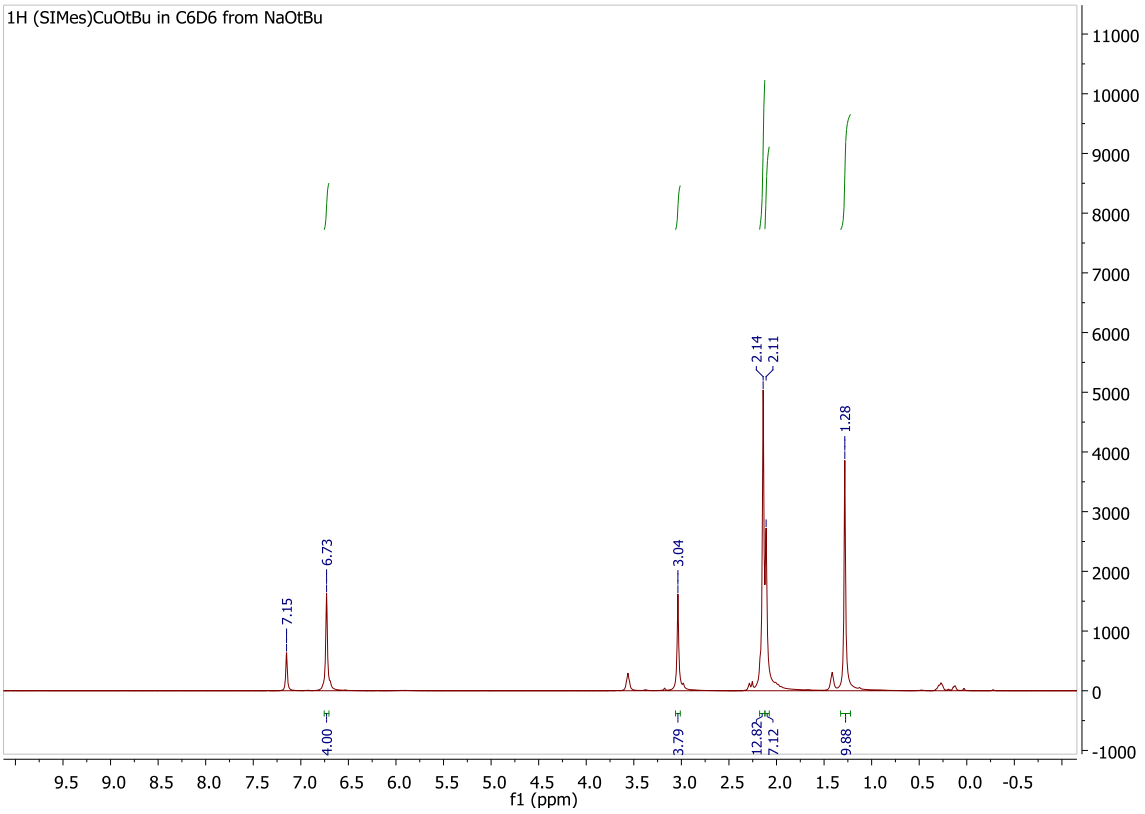


Figure 6.4d: ^{19}F NMR spectrum of **5c** in CD_2Cl_2: Referenced to $ArCF_3$ before being taken. Equilibrium observed

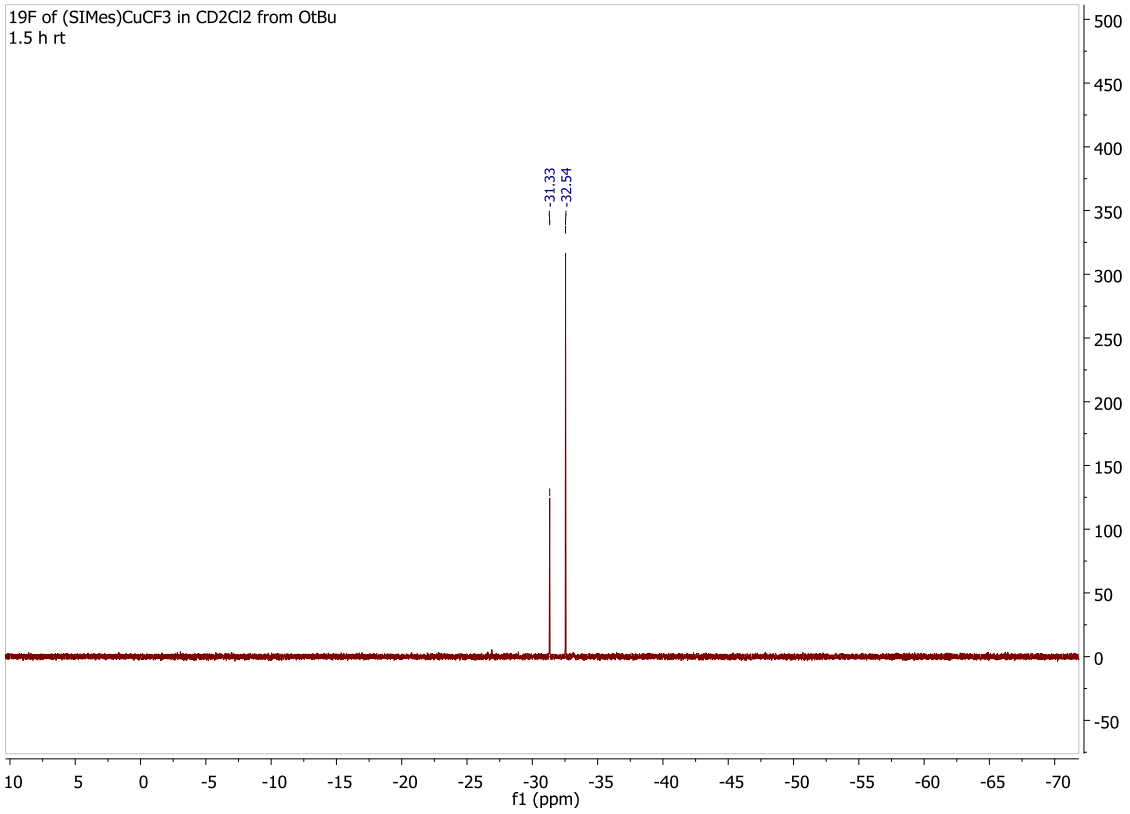


Figure 6.4e: ^{1}H NMR spectrum of **5c** in CD_2Cl_2: Equilibrium observed

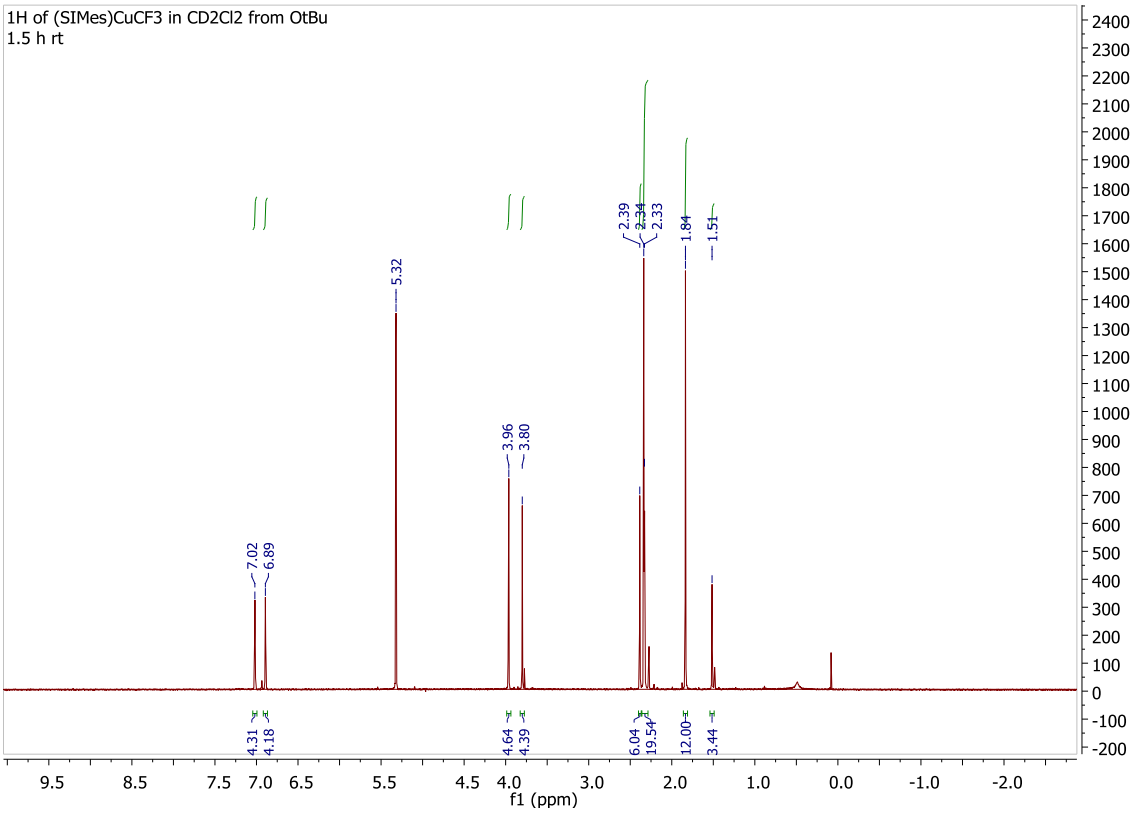


Figure 6.4f: ^{19}F NMR spectrum of **5h** in DMSO-d_6:

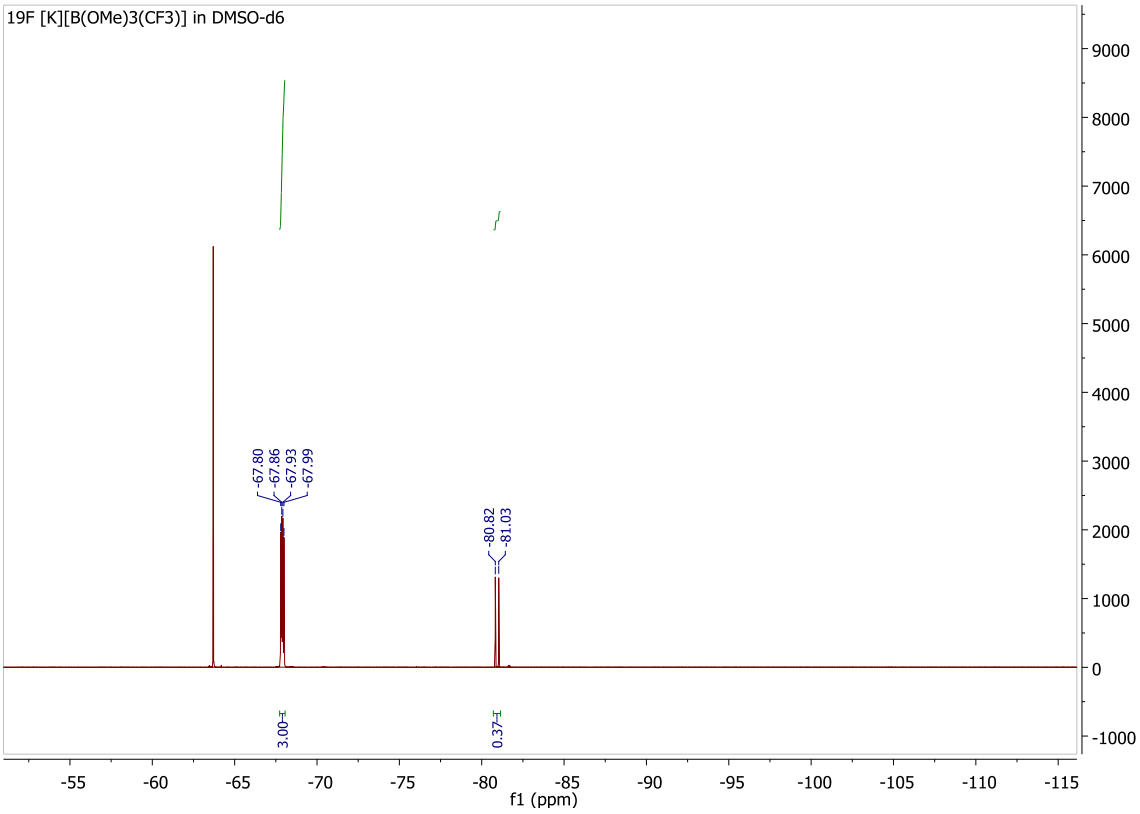
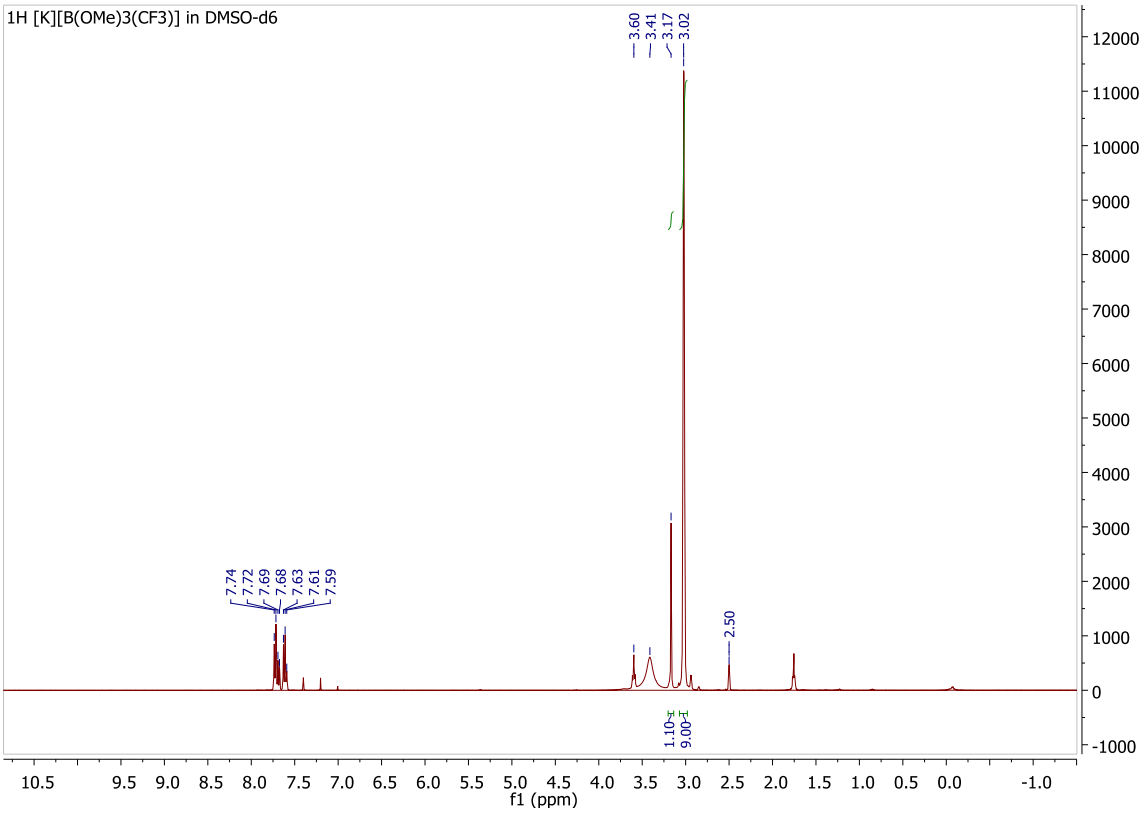


Figure 6.4g: ^{1}H NMR spectrum of **5h** in DMSO-d_6:



Curriculum Vitae

Peter T. Kaplan

PROFESSIONAL SUMMARY

- Doctoral level chemist with an expertise in organometallic synthesis and catalysis
- Substantial exposure to air-free techniques: glove box and Schlenck line; experience in operating a variety of analytical tools, including multinuclear NMR spectroscopy, X-ray crystallography, GC-(MS and FID)
- Strong communication, critical thinking, method development and active collaborations with other groups

EDUCATION

Expected May 2017	**Lehigh University, Department of Chemistry** Doctor of Philosophy in Chemistry
2012	**DeSales University, Department of Chemistry** B.S. in Chemistry, minor in mathematics

PROFESSIONAL DEVELOPMENT

Fellowship, Lehigh University (2015-2016)

Research Assistant, Lehigh University (Spring 2013-Fall 2014)

- Synthesis and development of new dizinc reagents for polyfluoromethylenation chemistry
- Development of a tetrafluoroethylene-free preparation of perfluoronickelacycles
- Explore pathways to arylated fluoroalkyl bromide building blocks
- Experience with ^{1}H, ^{19}F, and ^{13}C-NMR, GC-MS, Flash separation instrumentation and air free techniques

Teaching Assistant, Lehigh University (2012-present)

- Undergraduate level General Chemistry Laboratory
- Graded assignments and enforced proper laboratory safety protocols
- Prepared stock solutions and laboratory stations
- Presented briefing on chemical principles

Analytical Internship, BASF (summer and winter of 2011-2012)

- Sample and standard preparation for trace metal analysis
- Experience running GC-MS, ^{1}H-NMR, ICP, UV-VIS, and AA-graphite furnace
- Conducted migration studies on polymer samples
- Wrote and updated ISO qualified SOPs for instrumentation

Chemistry Demonstrations, DeSales University (2009-2012)

- Prepared and presented chemical reactions or physical changes
- Exposed local elementary, middle, and high school students to general chemistry
- Served in a leadership role both as a Junior and Senior (vice-president and president)
- Interviewed potential presenters and oversaw demonstrations

Peer Tutor, DeSales University (2009-2012)

- Tutor for general chemistry, analytical chemistry, instrumental analysis, organic chemistry, and inorganic chemistry courses
- Experience with one-on-one and group tutoring

Undergraduate Research Experience (Fall 2011-Spring 2012)

- Research Advisor: Professor Francis C. Mayville
- Project: Synthesis of Spermidine Analogues as Possible Growth Inhibitors of Breast Cancer Cells
- Experience with organic synthesis and Infrared Spectroscopy of samples

Job Shadowing Experience, Ciba Chemicals (Spring 2008)

- Observed analytical techniques and process of investigation
- Introduced to Gas Chromatography and Liquid Chromatography

AWARDS & HONORS

- Newton W. & Constance B. Buch Fellowship (2015-2016)*
- Student Poster Competition Award Winner, 22nd Winter Fluorine Conference (2015)
- DeSales Excellence in Chemistry Demonstrations (2012)
- DeSales Excellence in Research (2012)
- Senior Chemistry Demonstration Leader (2011-2012)
- Junior Chemistry Demonstration Leader (2010-2011)

- Dean's List DeSales University (2010-2012)
- DeSales Chemistry Scholarship (2008-2012)

PUBLICATIONS

1. "Mild, Safe, and Versatile Reagents for $(CF_2)_n$ Transfer and the Construction of Fluoroalkyl-Containing Rings." **Kaplan, P. T**.; Xu, L.; Chen, B.; McGarry, K. R.; Yu, S.; Wang, H.; Vicic, D. A. *Organometallics* **2013**, *32*, 7552.

   Highlighted in: * *C&E News* **2014**, *92*, 28-29.

2. "Synthetic Utility of Dizinc Reagents Derived from 1,4-Diiodo- and 1,4-Dibromooctafluorobutane." **Kaplan, P. T**.; Chen, B.; Vicic, D. A. ***J. Fluorine Chem.* 2014, *168*, 158–162**

3. "A Versatile Route to Arylated Fluoroalkyl Bromide Building Blocks." **Kaplan, P. T**.; Vicic, D. A. *Org. Lett.* **2016**, *18* (4), 884–886

   Highlighted in: * *Synfacts* **2016**, *12*, 0467.

PRESENTATIONS

252nd ACS National Meeting & Exposition

- *"Versatile Route to Arylated Fluoroalkyl Bromide Building Blocks."* ***Kaplan, P. T.****; Vicic, D. A. Abstracts of the 252nd ACS National Meeting, Philadelphia, PA 19107, August 21-25, 2016*

6th Biennial Mid-Atlantic Seaboard Inorganic Symposium

- "Versatile Route to Arylated Fluoroalkyl Bromide Building Blocks." **Kaplan P. T.**; Vicic, D. A. Abstracts of the 6th Biennial Mid-Atlantic Seaboard Inorganic Symposium, Philadelphia, PA, 20 July 2016

10th Annual NIH CounterACT Network Research Symposium

- "Thermal Stress Stability Studies on a Unique Class of Anti-Inflammatory Triazoleimines Reveals a New Thermal Rearrangement." **Heindel N. D.**; Guillon C. D.; Rapp R. D.; Kaplan P. T.; Fianu-Velgus C.; Saxena J.; Heck D. E.; Laskin J. D. Abstracts of the 10th Annual CounterACT Conference, Davis, CA, 16 June 2016, Poster # V11

251st ACS National Meeting & Exposition

- "New Metal-mediated Fluoroalkylation Reactions." **Vicic, D. A.**; Kaplan, P.; Xu, L.; Yu, S. San Diego, CA, United States, March 13-17, 2016

22nd Winter Fluorine Conference

- "New Reagents for $(CF_2)_n$ Transfer and the Construction of Fluoroalkyl-containing Rings." **Kaplan, P. T**.; Chen, B.; Yu, S.; Xu, L.; McGarry, K.; Vicic, D. A. Abstracts of the 22nd Winter Fluorine Conference, St Pete Beach, FL 33706, January 11-16, 2015

**Winner of Student Poster Competition Award Winner*

248th ACS National Meeting & Exposition

- *"New Reagents for $(CF_2)_n$ Transfer and the Construction of Fluoroalkyl-containing Rings."* ***Vicic, D. A****.; Kaplan, P. T.; Chen, B. San Francisco, CA, United States, August 10-14, 2014*

247th ACS National Meeting & Exposition

- *"Revisiting the use of zinc in perfluoroalkylation reactions."* ***Vicic, D. A****.; Kaplan, P. T.; Xu, Long; Chen, B.; Yu, S.; McGarry, K. R. Dallas, TX, United States, March 16-20, 2014*

16th Annual Green Chemistry and Engineering Conference

- "The Synthesis of Several Spermidine Analogs in a Series of Alcohols as Possible Growth Inhibitors of Breast Cancer Cells." Mayville, F C. Jr.; **Bauer, T. M**.; **Kaplan, P. T.** Abstracts of the 16th Annual Green Chemistry and Engineering Conference, Washington DC, June 18-20, 2012

DeSales Oral Presentation of Research (May 2012)

VOLUNTEER SERVICE

Chemistry Lab Experience Assistant (March 2015)

- Provided incentive and motivation for talented students towards college careers and advanced study
- Established closer ties with Lehigh University and the surrounding high schools
- Facilitated an opportunity for Lehigh University faculty and staff to become better acquainted with the needs and interests of high school students

STEM Panelist (October 2015)

- Participated in a graduate student information session for science career direction