5-2016

Development and applications of novel HF-based fluorination reagents : DMPU-HF.

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DEVELOPMENT AND APPLICATIONS OF NOVEL HF-BASED FLUORINATION REAGENTS—DMPU-HF

By

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A Dissertation
Submitted to the Faculty of the
College of Arts and Science of the University of Louisville
in Partial Fulfillment of the Requirements
for the Degree of

Doctor of Philosophy in Chemistry

Department of Chemistry
University of Louisville
Louisville, Kentucky

May 2016.

DEVELOPMENT AND APPLICATIONS OF NOVEL HF-BASED FLUORINATION REAGENT-DMPU-HF

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A Dissertation Approved on

April 8th, 2016

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ACKNOWLEDGEMENTS

I am grateful to God who has been gracious to me all these years and through these times and period of my entire life.

I am especially grateful to Professor G.B. Hammond for serving as my research advisor, acting as counselor as well as being, in many instances, a father. I am extremely grateful to Professor Bo Xu (DongHua University, Shanghai, China) for his constant support, scientific acumen and advising skills.

I would also like to thank the following faculty members for reading this thesis and sitting on my defense committee: Dr. Michael H. Nantz, Dr. Muriel C. Maurer, and Dr Jorge G. Gomez-Gutierrez Many thanks to Dr. Nantz for his kindness and patience with me, despite my many lapses. Many thanks to Dr. Neal Stolowich who offered me numerous help tips on how to run NMR experiments. Dr. William Richmond has been very helpful in solving many problems on our HPLC, and GC-MS apparatus. I also want to thank Dr. Luzzio for his guidance during my short stay in his laboratory and Dr. Mark Mashuta for helping me with all the X-ray experiments. My profound gratitude to Dr. Wittebort for his support and for allowing me to use his HF apparatus as well as to do my HF complex reactions in his laboratory.

Also, I feel fortunate to have been a member of a terrific group of highly dedicated scientists in the Hammond Lab. I am grateful to the past and present group members of the Hammond research group over the years: Dr. Leping Liu, Dr. Zhuang Jin, Dr. Manish

Kumar, Dr. Deepika Malhotra and current members: Rene Ebule, Shengzong Liang, Zichao Lu, Nicole Robertson and Zofia Hetman. I want to acknowledge the help provided by Dr. Zhou Li, currently a postdoc in the group, and for allowing me to incorporate in my thesis his analysis of hydrogen bonding acceptors and donors (Figure 4). People come and go, but their cooperation and friendship remain etched in my memory.

I have a deep appreciation to my parents and siblings for their unconditional love and support. My beloved wife Ugoeze in whose eyes the sun rises and sets, has been a major fulcrum to me throughout these years. Words are not enough to express my profound gratitude for the love, patience, support and care that she has bestowed upon me during my graduate studies.

ABSTRACT

DEVELOPMENT AND APPLICATIONS OF NOVEL HF-BASED FLUORINATION REAGENT—DMPU-HF

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The utility of fluorine in medicinal and manufacturing chemistry is undisputed. Despite its usefulness, the incorporation of fluorine in organic molecules is not without challenges. Regardless of their electrophilic or nucleophilic nature, most, if not all, fluorinating reagents derive from HF. Nucleophilic reagents are less expensive compared with their counterparts, and many are not commercially available. The Hammond laboratory is interested in developing and applying HF-based fluorination reagents that are cost effective and capable of enhancing both classical and metal based transformations. The following chapters describe some of the applications of our HF-based reagent.

Chapter 2 discusses the preparation and role of DMPU-HF in the fluorination of alkynes in the presence of a metal catalyst. This reaction employs the imidogold precatalyst, which is activated by DMPU-HF to enhance both mono- and di-fluorination of alkynes. Approaches to induce monofluorination and difluorination of terminal alkynes by an HF-based reagent, unprecedented in the literature, are also discussed.

In Chapter 3, we describe further the application of DMPU-HF to the diastereoselective synthesis of fluorinated tetrahydropyrans and the N-tosylpiperidine analogues. We also showed that the acidic behavior of DMPU-HF makes it a better fluorinating reagent when compared to existing HF-based reagents in these types of transformations.

Further extension of DMPU-HF to the ring opening of aziridines is discussed in Chapter 4. A wide variety of N-tosyl aziridines undergo efficient ring opening in the presence of DMPU-HF at room temperature. The methodology was also extended to some N-substituted aziridines including unactivated substrates, all of which were efficiently fluorinated under these conditions.

Chapter 5 gives an overview of some of the applications of DMPU-HF to other known C-F bond formations. Examples of such transformations include but are not limited to the ring opening of epoxides, fluorobromination of unsaturated compounds and the metal free synthesis of fluoroamines.

Finally, Chapter 6 provides spectroscopic data for all the new compounds prepared in chapters 2 to 5.

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1 INTRODUCTION

This chapter provides a brief overview of fluorine containing compounds and also surveys some existing methods for nucleophilic fluorination. Also, in this chapter, a literature precedent for the use of common HF-based reagents like pyridine-HF (Olah's) and trimethylamine trishydrogen fluoride will be discussed. More importantly, the hydrogen bond basicity concept and the introduction of DMPU-HF will be examined.

1.1 The History and Importance of Organofluorine Chemistry

Fluorine is the 13th most abundant element on earth, yet despite this fact, naturally existing organofluorine compounds are scarce, with just about 21 fluorinated secondary metabolites identified to date. Eight out of these metabolites are isolated from the plant *Dichapetalum toxicatium* and they are ω-fluorinated fatty acids (Figure 1).[1] Compared to other halogens like chlorine, iodine or bromine, which in many instances occur in natural products (ca. 3000), we see a huge disparity with that of fluorine containing natural products. This disparity can be attributed to two major factors: first, fluorspar (CaF_2), which is the most abundant form of natural occurring fluorine, has a very low solubility in water. Secondly, hydrated fluoride ion has low nucleophilicity.[2]

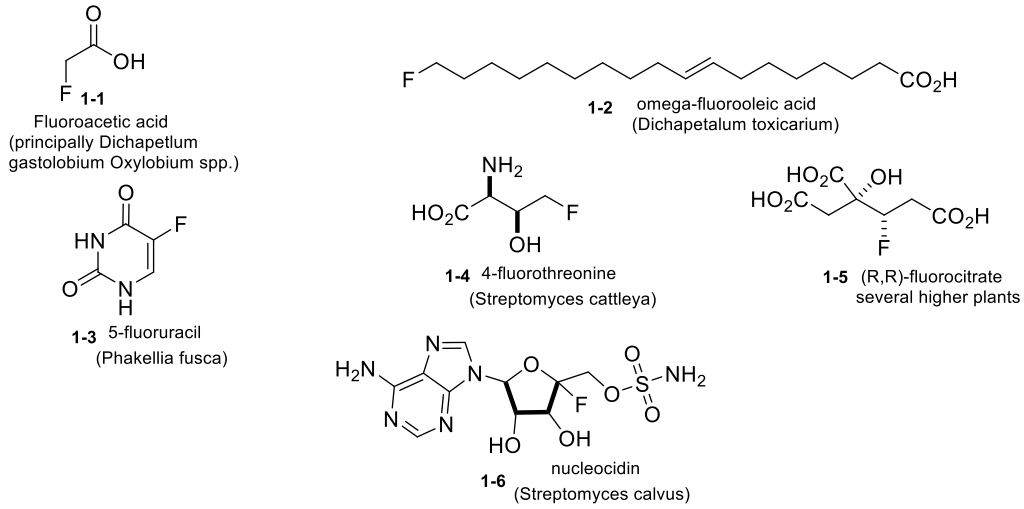


Figure 1. Some fluorinated metabolite products and their sources.

Fluorine element, since its discovery in 1886 by Henri Moissan, has played a prominent role in the scientific community because of its peculiar properties.[3] The presence of one or more fluorine atom(s) in an organic compound endows reactivity and properties, which are significantly different from those of its non-fluorinated analogue without enormous modification of sterics.[4] Today, fluorine containing compounds have been applied in various fields such as medicine,[5] agrochemicals,[6] electronics and organic materials.[7] It is not surprising therefore that the study of fluorinated organic materials currently constitutes a field of research, which has seen tremendous progress in recent years, as demonstrated by the increase in publications of fluorine containing compounds.[8] This significant growth can be attributed to the unique reactivity observed in compounds, which have the fluorine atom.

1.2 Properties of fluorine

As earlier posited, one or more fluorine atoms in an organic molecule confers significant changes to its properties. These significant changes are due to the unique properties of the fluorine atom and some of these properties are discussed as follows.

1.2.1 Electronic effect of fluorine

Fluorine element has a value of 4.0 in the Pauling electronegativity scale,[9] thus making it the most electronegative element known. The strong electronegativity of the fluorine element gives it a powerful negative inductive (*–I*) ability, which usually has dramatic effects on the acidity or basicity of neighboring functional groups[10] (Table 1). This fact has been exploited to enhance the bioavailability or binding affinity of pharmaceutical drugs.[5b]

For instance, the p*K*a as reported in Table 1[3] of a series of organic acid decreases when fluorine is substituted for hydrogen due to its strong inductive effect. Also the basicity of organic bases decreases after fluorination as illustrated in Table 2.[3]

Table 1. pK_a of organic acids in comparison to their fluorinated analogue.

Acid	**p*K*a**	**Acid (F)**	**p*K*a**
CH_3COOH	4.76	CF_3COOH	0.52
C_6H_5COOH	4.21	C_6F_5COOH	1.75
CH_3CH_2OH	15.9	CF_3CH_2OH	12.4
C_6H_5OH	10.0	C_6F_5OH	5.5

Table 2. pK_b of organic bases in comparison to their fluorinated analogue.

Base	**pK_b**	**Bases (F)**	**pK_b**
$CH_3CH_2NH_2$	3.3	$CF_3CH_2NH_2$	8.1
$C_6H_5NH_2$	9.4	$C_6F_5NH_2$	14.4

1.2.2 Bond energy and bond length

The carbon-fluorine (C-F) bond is the strongest of the carbon/other element bonds. This bond strength plays a huge role in determining much of the chemistry of organofluorine compounds. For instance, the C-F bond strength is much greater than that of the other halogen atoms (Table 3). The implication of this is that while alkyl bromides or iodides readily undergo S_N1 and/or S_N2 reactions, alkyl fluorides are much less reactive.[3] As a matter of fact, the reactions of alkyl fluorides with strong nucleophiles proceed via elimination (E2) rather than via nucleophilic substitution.

Table 3. Bond strength of R-X (Kcal/mol).

R	**H**	**F**	**Cl**	**Br**	**I**
CH_3	105	113	84	70	57
CH_3CH_2	101	111	85	71	56

1.2.3 Size of fluorine

The Van der Waals radius of fluorine is 1.47 Å, in contrast to hydrogen, which is 1.20 Å, making fluorine the smallest element after hydrogen. Fluorine though closer in size to oxygen (1.57 Å),[11] has been found to be a good substitute for hydrogen, which in most

cases results to a useful steric bias.[12] Fluorine, due to its steric resemblance with hydrogen, has been successfully employed to mimic hydrogen in bioactive molecules.[13] It should be noted however, that despite this steric resemblance, the high electronegativity of fluorine relative to hydrogen renders both the reactivity and polarity of the C-F bond orthogonal to that of the C-H bond. This fact has also been thoroughly explored in the design of fluorinated drugs like the fluorinated thalidomide or fluorouracil (Figure 2).

1-7 (S)-fluorothalidomide **1-8** 5-fluorouracil

Figure 2. Fluorine as a mimic for hydrogen in bioactive molecules.

More so, due to the similarity in size between fluorine and oxygen as well as their similar electronegativity (3.98 and 3.44 on the Pauline scale), fluorine, when replaced with oxygen, has been employed in probing the importance of hydrogen bonding versus bond polarity in biological systems.[14] The replacement of a C-OH to a C-F bond though accompanied by the loss of the acidic hydrogen has helped in understanding the role of the C-OH bond in biological systems, especially with respect to its polar nature and its hydrogen bonding properties. Unlike the C-OH bond, replacement of a C=O group with a C-F or a CF_2 group is not ideal requiring significant changes to the geometry at carbon (from sp^2 to sp^3), which also involves an unsatisfactory change in molecular shape.

1.3 Fluorination in organic chemistry

The role of fluorine is not limited to the modification of the molecular properties of organic molecules or pharmaceutical compounds. The ^{19}F nucleus, for instance, has an excellent NMR profile and has become a popular choice with chemical biologists, for the investigation of macromolecules as well as the study of metabolic processes. More so, ^{19}F NMR has also been applied in the growing field of *positron emission topography* (PET)), which is an imaging technique used in clinical diagnosis. PET utilizes the short lived ^{18}F fluorine isotope.[15] Fluorination in organic chemistry can therefore be achieved either by electrophilic or nucleophilic fluorinating reagents.

Electrophilic fluorination involves the utilization of an "F^+" reagent that is attacked by electron rich centers. Thus, reagents that are able to transfer "F^+" to an electron rich site are considered electrophilic reagents. Elemental fluorine is such a reagent, but due to its high reactivity, low selectivity and toxicity, its use is limited.[16] Over the years, a large number of "F^+" reagents have been developed, which have been used extensively for the fluorination and discovery of organic molecules. Such reagents include but are not limited to RO-F (e.g, fluoroxytrifluoromethane),[17] N-F (e.g, *N*-fluoropyridinium triflates, Selectfluor and their derivatives).[18]

Nucleophilic fluorination is another useful strategy in achieving fluorination of organic compounds. This primarily involves the use of fluoride ion, such as fluoride salts like KF or reagents that are capable of releasing fluoride ion. One big challenge to the use of the fluoride ion as a fluorinating source is its ability to be strongly solvated in protic solvents, which makes it a poor nucleophile. Also, it forms a tight ion pair in most aprotic solvents, limiting its nucleophilic profile. In order to increase its nucleophilic properties,

these barriers need to be overcome. Considerable efforts have been made in developing nucleophilic fluorinating reagents in the last decades. For example, in 1975, Middleton[19] reported the preparation of diethylaminosulfur trifluoride (DAST), which could substitute a hydroxyl and/or carbonyl oxygen with fluorine to generate the mono and/or *gem*-difluoronated products respectively.[20] One drawback of DAST is that it undergoes explosive degradation at temperatures above 90 °C. Several other dialkyaminosulfur trifluoride analogues have since been developed with similar reaction mechanism. Among these reagents are perfluoro-1-butanesulfonyl chloride **1-9** (PBSF),[21] the commercially available tetrafluoroethyldimethylamine **1-10** (TFEDMA),[22] the Ishikawa reagent[23] **1-11** and Fluolead[24] **1-12**, which was introduced in 2009 by Umemoto (Figure 3).

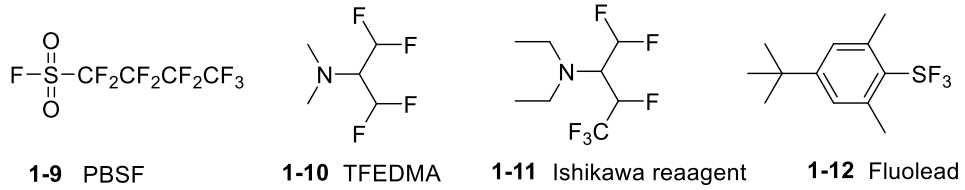


Figure 3. Alternatives to dialkyaminosulfur trifluorides.

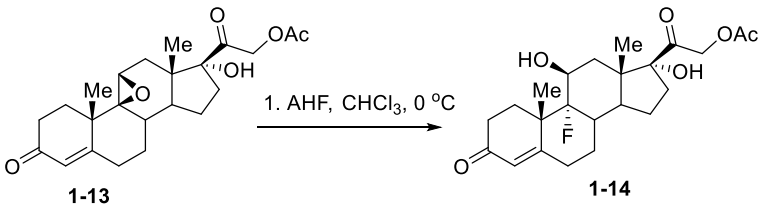
HF-based reagents

In 1771, Wilhelm Scheele liberated hydrogen fluoride from the mineral fluorspar (CaF_2) using sulfuric acid and noted that the acid so formed, destroyed glass.[25] Later in the 19th century, Sir Humphrey Davy determined that this acid did not contain oxygen. While trying to understand hydrogen fluoride, many scientists were badly injured or died. For example, Sir Davy lost his eyes, Gay-Lussac and Henri Moissan and many others died during the course of their work with hydrogen fluoride.[26] Hydrogen fluoride is one of the most inexpensive sources of fluoride but its use is very limited because of its corrosiveness,

toxicity and low boiling point (b.p 19 ˚C). Its handling requires special apparatus. Anhydrous hydrogen fluoride is used as an alkylation catalyst in gasoline production and has also been applied in aluminum production, steel treatment, glass etching, and refrigeration manufacture of fluorocarbons as well as semiconductors.[27]

Although HF is diatomic, the HF molecules in anhydrous hydrogen fluoride (AHF) form relatively strong intermolecular H···F hydrogen bonds. It is noteworthy that AHF is more commonly used than the aqueous hydrogen fluoride. This is because AHF is miscible with water in any proportion due to the high solvation properties of fluoride ion.[28] Aqueous hydrogen fluoride is a very weak acid, as well as a weak nucleophile. Turrell and co-workers using vibrational spectroscopy described the apparent weakness of aqueous HF as due to a strong ion pair or proton transfer between water molecules and the fluoride ion.[29] Aqueous HF is much easy to handle than AHF, but too weak to induce fluorination as compared to AHF. Anhydrous fluoride has been applied in halogen exchange reactions,[30] and has been applied as a solvent and catalyst in Friedel-Craft reactions. In this case, it usually promotes unselective reactivity, such as acid mediated rearrangements and polymerization.[31]

Despite the unwanted side reactions and toxicity of AHF, Fried and Sabo in 1954, demonstrated a major reactivity of AHF when the fluorinated derivative of cortisone was prepared. Their studies spurred a revolution in the study of synthetic steroids and essentially medicinal chemistry.[32] As an example, 9α-fluorocortisol (brand name Florinef) is found to possess ten times the biological activity of cortisol, which according to Fried is due to the β-alcohol and the small size of fluorine (Scheme 1).



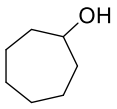
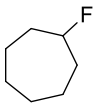
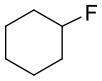
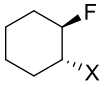
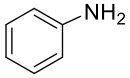
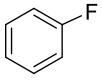
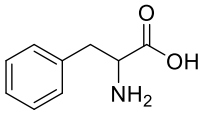
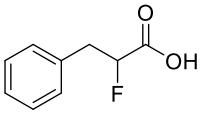
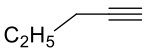
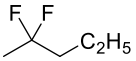
Scheme 1. Preparation of 9α-fluorocortisol.

Another revolution was observed when Hirschmann and coworkers reported that under the same conditions they were unable to reproduce the result of Fried and Sabo in the preparation of fluorocortisol. However, they reported that the addition of a base like pyridine, tetrahydrofuran or ammonia to the AHF/chloroform mixture led to an appreciable yield of the fluoricortisol acetate.[33] They anticipated that by controlling the amount of pyridine or any other organic bases in the AHF/base mixture, they could influence the reactivity of AHF in the synthesis of fluorocortisol.

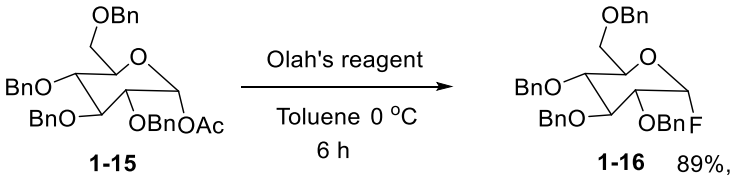
Bergstrom and coworkers, following the lead from the results of Hirschmann on the synthesis of 9α-fluorocortisol, prepared a 70% solution of HF in Pyridine (Pyridine**.**9HF) for the hydrofluorination of dehydrosteroids to form 9α-fluoro-11-deoxysteroids.[34] Few years later, Olah and co-workers explored the synthetic utility of Pyridine/HF mixture and came up with interesting findings of its applicability. No wonder the reagent is being regarded today as *Olah's reagent* or pyridinium poly(hydrogenfluoride) (PPHF).[35]

The laboratory of Olah demonstrated the reactivity of PPHF on a wide range of organic substrates and reactions, which include but are not limited to alkynes, alcohols, alkenes and the ring opening of epoxides. Representative examples of the reactivity of PPHF as demonstrated by Olah's laboratory are highlighted in Table 4.

Table 4. Selected reactions with Olah's reagent.

entry	substrate	reagent	product	yield (%0
1		PPHF		84
2		PPHF		80
3		PPHF,NXS		85 (X=Cl) 90 (X=Br) 85 (X=I)
4		PPHF,$NaNO_2$		84
5		PPHF,$NaNO_2$		98
6		PPHF		70

Perhaps one of the more notable applications of PPHF is the fluorination of the anomeric position in carbohydrates[36] described by Noyori and coworkers in the preparation of glycosyl fluorides Scheme 2. The authors concluded that amidst the available fluorination reagents and methods for the synthesis of fluorinated carbohydrates, the attractiveness of PPHF (Olah's reagent) is characterized by its wider applicability, high yield, operational simplicity and the low cost.



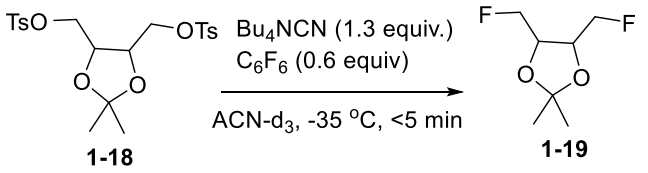
1-15 **1-16** 89%,

Scheme 2. Synthesis of 1-fluoro-2,3,4,6-tetra-O-benzyl-1-deoxy-α-D-glucose using Olah's reagent.

From these results, PPHF is believed to have superior chemoselectivity to AHF in many cases and before now, it was considered to be highly acidic for which all reactions must be carried out in plastic vessels. So, by varying the nature of the Lewis base and the stoichiometry of HF relative to the base, chemists essentially developed a variety of HF-base reagents with a range of properties.[37] The more common base being used other than pyridine is triethylamine, which has since led to the much milder nucleophilic fluorinating source TREAT-HF or triethylamine trifluoride ($Et_3N.3HF$). One very important advantage of TREAT-HF, is the fact that it can be used in standard glass vessels and distilled in *vacuo* without the release of HF, albeit the use of TREAT-HF requires more forcing conditions.[38]

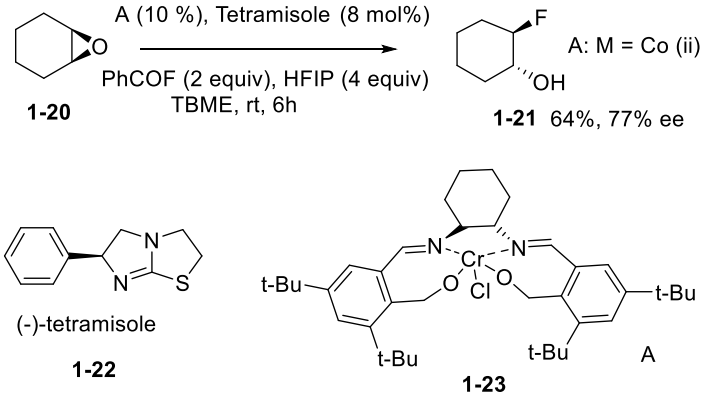
Latent hydrogen fluoride source

In situ generated fluoride ion for nucleophilic reactions was introduced recently as a useful strategy to combat the many problems associated with fluoride ions, which ranges from the ease of solvation in protic solvents, insolubility in organic solvents (e.g fluoride salts like CsF), toxicity and handling difficulties (e.g, AHF). In 2005, DiMagno and Sun reported that anhydrous tetrabutylammonium fluoride (TBAF) can be generated *in situ* by the low temperature reaction of hexafluorobenzene and tetrabutylammonium cyanide, and that the resulting reagent is stable at room temperature.[39] TBAF prepared from this *in situ* protocol was efficiently applied in the fluorination of simple alkyl halides and sulfonates at room temperature without forming the hydrolysis byproducts, which are typical of hydrated TBAF (Scheme 3).[39]



Scheme 3. Fluorination by TBAF generated *in situ*.

Inspired by this work, the Doyle group envisioned that they could enhance asymmetric fluorination by using latent HF source. Such latent HF would comprise a source of fluoride and a source of proton. They believed that this strategy will circumvent the handling issues associated with HF-containing reagents. So in 2010, the Doyle group demonstrated the dual cooperative catalytic enantioselective ring opening of epoxide by latent HF. The latent HF was formed *in situ* by the catalytic action of 1,5-diazobiclo[4.3.0]non-5-ene (DBN) or tetramisole on benzoylfluoride and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP).[40]

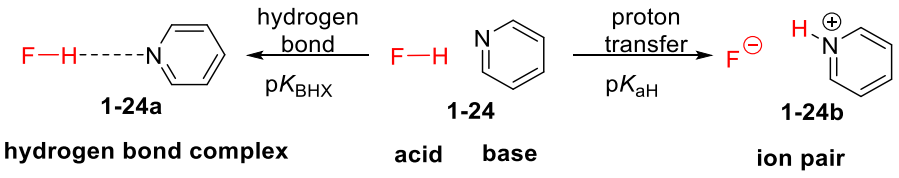


Scheme 4. Enantioselective synthesis of fluorohydrins by HF generated *in situ*.

A follow up of their protocol demonstrated its effectiveness in the ring opening of aziridines[41] as well as the enantioselective catalytic ring opening of aziridines.[42] While this method is attractive, it is neither cost effective nor atom economical, which could limit its general applicability especially for scale-up processes.

1.4 The hydrogen bonding concept and the development of new HF-based reagent-DMPU-HF.

Most, if not all, fluorinating reagents (electrophilic or nucleophilic) are made from hydrogen fluoride (HF). Therefore, an HF-based fluorinating reagent would be ideal in terms of cost and atom economy, but HF itself is a hazardous gas at room temperature and is very difficult to handle without special equipment as stated earlier. The only existing complexes of HF with organic bases are: pyridine-HF (Olah's reagent)[37, 43] and triethylamine-HF.[44] These are liquids at room temperature and have been explored extensively as nucleophilic sources of fluorine,[37] but their use is hampered by the fact that the organic bases (pyridine and trimethylamine) reduce the acidity of the system and may interfere with many metal catalysts. For example, pyridine can complex strongly with many transition metals and therefore reduce their activities. In general, pyridine-HF and triethylamine-HF are not ideal reagents for acids or metal catalyzed reactions. If HF-based nucleophilic fluorination reagents could be made compatible with acid or transition metal catalysts, it could open the door for reactivities and selectivities hitherto unknown. Our primary goal is to develop a new generation of HF-based nucleophilic fluorination reagents to overcome the existing drawbacks with pyridine-HF and triethylamine-HF, namely incompatibility with acids or transition metal catalysts.



Scheme 5. Comparing hydrogen bond dissociation and a Brønsted acid-base reaction.

When an organic base (e.g., pyridine) interacts with HF (an acid), it serves simultaneously as a hydrogen bond acceptor (HBA) and a Brønsted base (Scheme 5)

Hydrogen bonding, rather than an ionic interaction, has been identified to be the major type of interaction between HF and an organic base in complexes like pyridine-HF.[37] In order to reduce the volatility of an HF complex (make it a liquid or solid at room temperature), we have to use a relatively good hydrogen bonding acceptor (HBA) to complex with HF. Our hypothesis is that *a strong (good) hydrogen bonding acceptor is not necessarily a strong base (Brønsted or Lewis base***)**. Thus, a compound that serves as good hydrogen bonding acceptor (better than pyridine or triethylamine), while being less basic (e.g., less basic than pyridine) is expected to form a less volatile complex. And due to the low basicity of this HBA, the HBA-HF complex will be compatible with acid catalysts or mediators. By doing this, we may achieve unprecedented reactivity and selectivity in HF-participating reactions. In order to accomplish this goal, it is foremost necessary to investigate a quantitative descriptor of hydrogen bond basicity and Brønsted basicity. Because there is no unified Lewis basicity scale, we focused on Brønsted basicity first.

It is commonly assumed that the relative hydrogen-bond basicity of an organic compound bears a simple correlation with its Brønsted basicity (pK_{aH^+}, pK_a of its conjugate acid); however, this assumption holds true only for structurally close related compounds (Figure 4). In 2009, Laurence and co-workers reported a comprehensive database of hydrogen-bond basicity (measured by pK_{BHX}).[45] The pK_{BHX} of most compounds ranges from 1 to 5, where a bigger number indicates a more stable hydrogen bond complex.[45] Based on analytical results of 232 typical nitrogen, oxygen, sulfur and carbon bases, there was no general relationship between pK_{BHX} and pK_{aH^+} (Figure 4).[45] In other words, *a weak base is not necessarily a weak hydrogen bond acceptor*. This finding will allow us to

discover new good hydrogen bonding acceptors, which are weak bases themselves but capable of complexing with HF.

From figure 4, we see that both pyridine and triethylamine are considered as 'ordinary bases', since they are close to the trend (solid yellow line in Figure 4). We seek 'anomaly' HBAs, that is, good hydrogen bond acceptors that are also weak Brønsted bases. Among many 'anomaly' hydrogen bond acceptors in the Laurence's database, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) is one we thought of as a potential candidate. DMPU (pK_{BHX} = 2.82) is a much better hydrogen bond acceptor than pyridine (pK_{BHX} = 1.86) and Et_3N (pK_{BHX} = 1.98),[45] and at same time it is significantly less basic than pyridine and Et_3N (Figure 5). Thus, a DMPU-HF solution should have a higher complex ratio compared to pyridine-HF or triethylamine-HF complexes. In addition, DMPU only weakly coordinates to most transition metal catalysts, so DMPU is less likely to interfere with most transition metal catalysts. Moreover, DMPU is a very weak nucleophile, so it will not compete with HF in nucleophilic reactions. In addition, it has other advantages such as low cost, wide availability, environmental friendliness, and chemical inertness, compared to several competitors, such as hexamethylphosphoramide (HMPA) and tris(pyrrolidinophosphine) oxide. Therefore, the DMPU-HF complex would be an ideal new fluorination reagent,[46] especially in transformations mediated by acids or transition metal catalysts.[47]

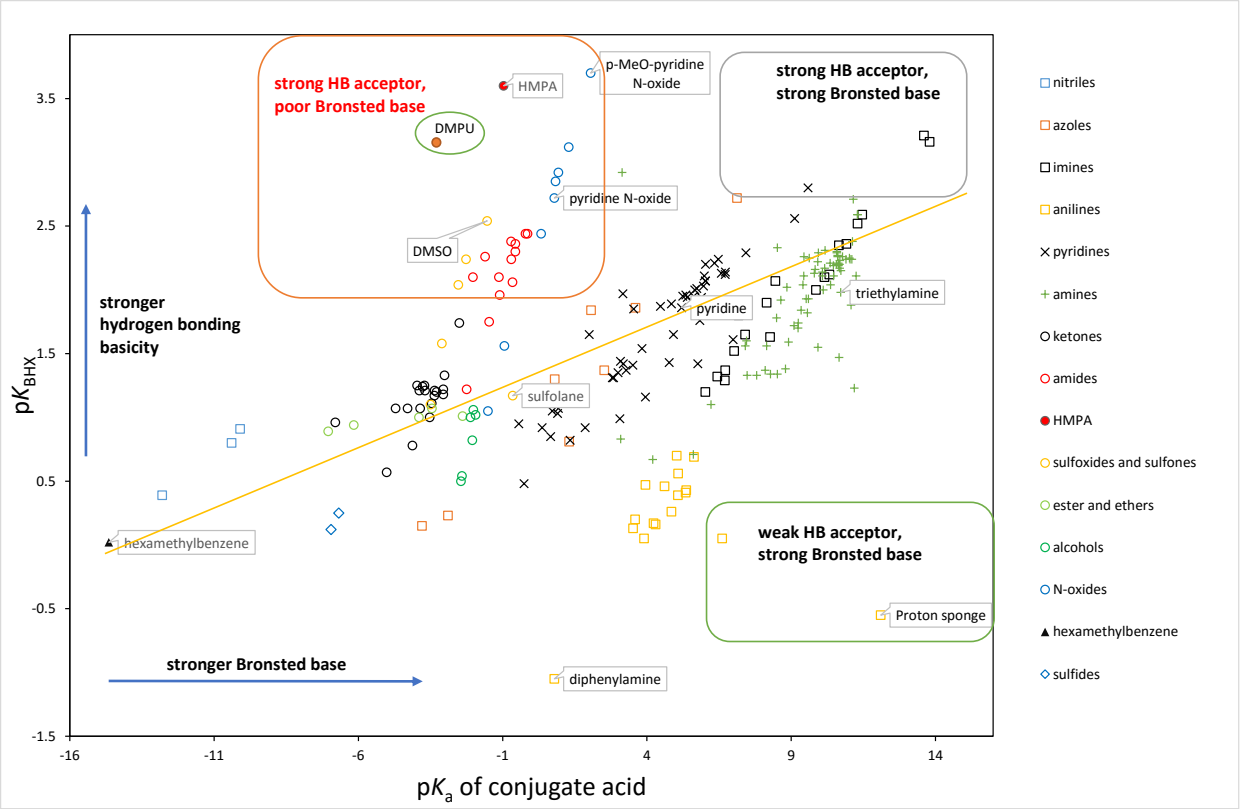


Figure 4. Lack of general relationship between pK_{BHX} and pK_{BH+}

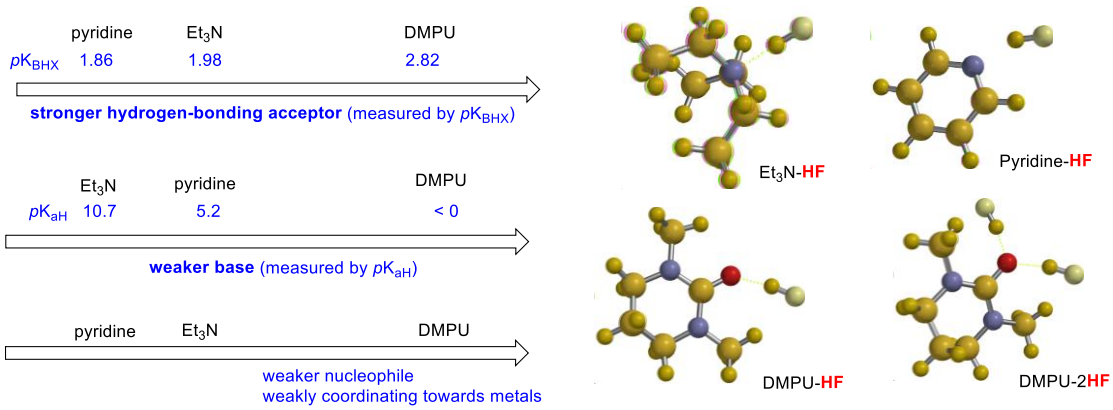


Figure 5. Comparison of DMPU-HF with pyridine-HF and Et_3N-HF

1.5 Summary of thesis research

The Hammond laboratory is interested in developing an HF-based nucleophilic fluorination reagent that are cost effective and are capable of enhancing both classical and metal based synthetic transformations. The following chapters describe some of the applications of DMPU-HF our first HF-based fluorination reagent.

2 DESIGNER HF-BASED NUCLEOPHILIC REAGENTS: HIGHLY REGIOSELECTIVE SYNTHESIS OF FLUOROALKENES AND *GEM*-DIFLUOROMETHYLENE COMPOUNDS FROM ALKYNES

2.1 Preparation of designer HF-based nucleophilic reagents

We have established from Figure 4 that a higher pK_{BHX} implies a high tendency of a substance to form strong hydrogen bond. The reported comprehensive database of the hydrogen-bond basicity of over a thousand compounds (*hydrogen bond acceptors* Figure 6) by Laurence and co-workers[45] assisted us as a guide in the preparation of suitable bases or solvents for use in our designer HF-based reagents. Among the many hydrogen bonding acceptors in Laurence's database, we considered 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) as an ideal hydrogen bonding acceptor to form a complex with HF. DMPU is inexpensive and is readily available. What is even more important, as illustrated in Figure 5, DMPU (pK_{BHX} = 2.82) is a better hydrogen bonding acceptor than pyridine (pK_{BHX} = 1.86) and Et_3N (pK_{BHX} = 1.98),[45] and at same time DMPU is much less basic than pyridine and Et_3N). So, a DMPU-HF complex should have higher acidity compared to pyridine-HF and triethylamine-HF complexes. Also, DMPU is weakly coordinating to most metal catalysts, so DMPU is unlikely to interfere strongly with most transition metal catalysts. Moreover, DMPU is a very weak nucleophile, so it will not compete with HF in

nucleophilic reactions. Therefore, HF/DMPU complex can be an ideal new fluorination reagent, especially in transition metal catalyzed reactions.

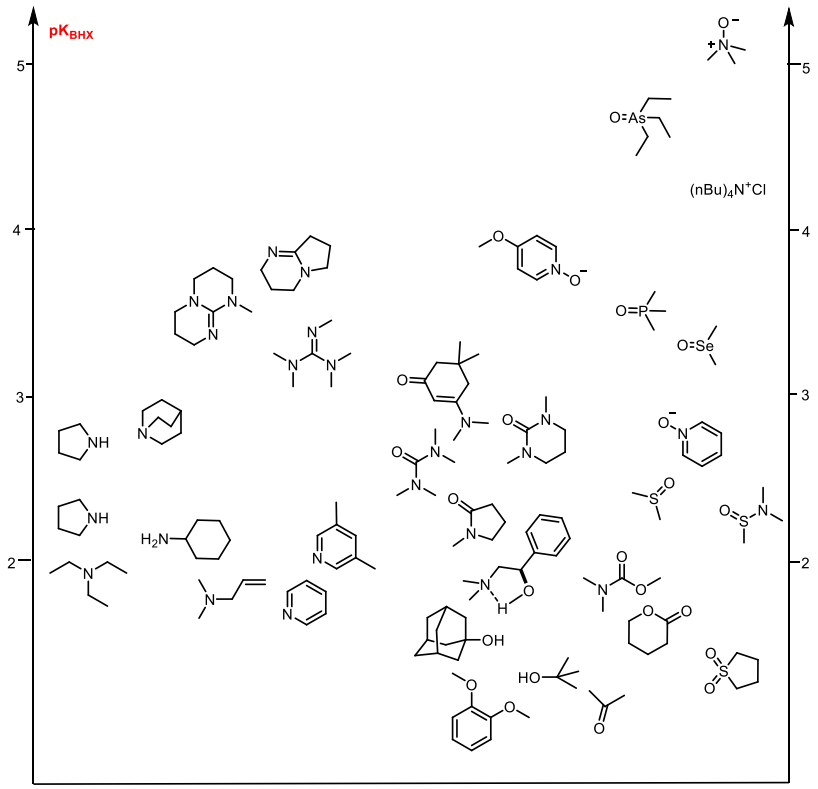


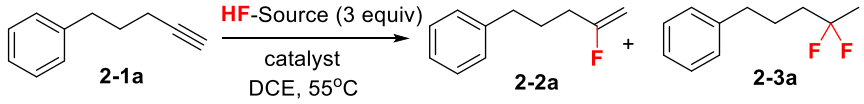
Figure 6. Schematic representation of the pK_{BHX} scale of common organic compounds.

2.2 Monofluorination of alkynes using DMPU-HF

Fluoroalkenes are important synthetic building blocks and targets,[48] but they are made from a shallow pool of fluoro-alkene synthons,[49] or their preparation requires lengthy procedures that are not functional group friendly.[50] Typical synthetic methods of fluoroalkenes include tandem addition-reduction,[50a] tandem addition-elimination,[51] Shapiro reaction,[48b] Julia-Kocienski olefination,[52] or Peterson olefination.[53] Sadighi and coworkers have reported a SIPr-Au catalyzed mono-hydrofluorination of alkynes using Et_3N/HF complex,[54] _ENREF_58 but due to the low acidity of the Et_3N/HF system

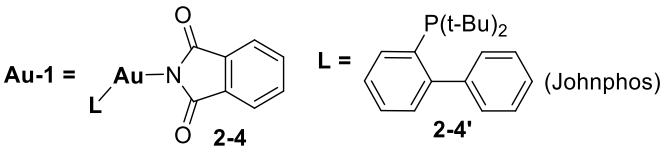
stoichiometric amounts of acid and acidic co-catalyst have to be used. Also, this method only works for internal alkynes, where there is no reliable way to control regioselectivity. By taking advantage of the unique properties of our DMPU-HF reagent, we were able to mono- and di-hydrofluorinate both, terminal and internal alkynes in highly regioselective fashion.

Table 5. Reaction condition optimization of mono-hydrofluorination of alkyne.



Entry	HF source[a]	catalyst	time / h	2a / %[b]	3a / %
1	Pyridine/HF	-	24	0	0
2	$Bu_4N^+OTf^-$/HF	-	48	0	0
3	DMPU-HF	-	48	0	0
4	Pyridine/HF	TfOH (100%)	24	0	0
5	DMPU-HF	TfOH (100%)	24	0	0
6	Pyridine/HF	**Au-1** (5%)	5	13	3
7	DMPU-HF	**Au-1** (5%)	5	48	52
8	DMPU-HF	**Au-1** (5%)	24	32	68
9	DMPU-HF (1.2 equiv)	**Au-1** (5%)	3	99	<1
10	DMPU-HF (1.2 equiv)	**Au-1** (2%)	3	99	<1
11	DMPU-HF (1.2 equiv)	**Au-1** (1%)	5	83	0

a) Concentration of HF sources: pyridine/HF (70%), DMPU-HF (65 w/w %), b) determined by GC-MS.

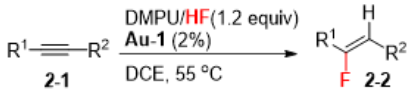


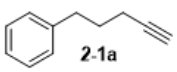
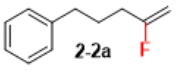
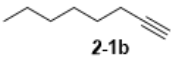
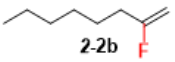
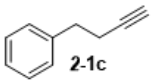
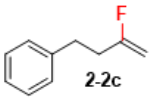
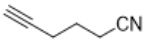
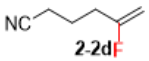
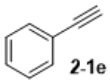
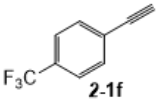
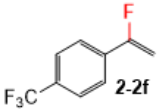
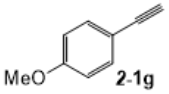
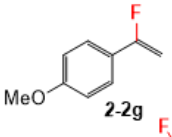
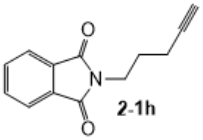
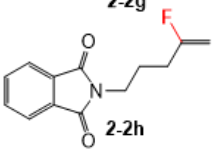
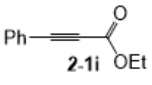
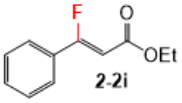
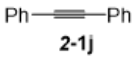
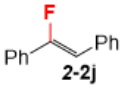
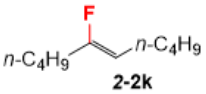
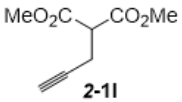
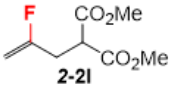
We used the mono-hydrofluorination of **2-1a** as our model reaction. The fluorination agents alone were not able to fluorinate alkyne **2-1a** (Table 5, entries 1-3) and

a strong acid (TfOH) was not an effective mediator either (Table 5, entries 4-5). The HF/DMPU complex we prepared has 65 w/w% HF content, mole ratio of HF:DMPU is around 11.8:1. Recently, we reported an acid-assisted activation of an imidogold precatalyst as a superior way to generate cationic gold compared to the common silver based methodology.[55] We found that our DMPU-HF system is acidic enough to activate the imidogold precatalyst (**Au-1**). Indeed, the DMPU-HF system is much more efficient in the fluorination of **2-1a** (Table 5, entries 6-7) than the commonly used pyridine/HF. DMPU-HF/Au-1 system is highly reactive but it gave a mixture of mono-fluorinated product **2-2a** and di-fluorinated product **2-3a** (Table 5, entry 8). We were able to achieve a selective mono-fluorination by reducing the amount of fluorination reagent from 3 equiv to 1.2 equiv (Table 5, entry 9). We were able to maintain the good yield and selectivity of product **2-2a** even at lower gold pre-catalyst loading (2% and 1%) (Table 5, entries 10-11, respectively).

With optimized conditions in hand, we investigated the scope of the mono-hydrofluorination of alkynes (Table 6). Clean and regioselective transformations were observed for all the terminal alkynes tested (Table 6, entries 1-8). The reaction also worked well for internal alkynes though longer reaction times and higher loadings of gold catalyst were needed (Table 6, entries 9-11). This reaction also has good functional group tolerance: an alkyne with a strong electron withdrawing group (Table 6, entry 9) and an alkyne with an acidic C-H and ester groups (Table 6, entry 12) gave the corresponding fluoro-alkenes in good yields and selectivity.

Table 6. Substrate scope for monofluorination of alkyne.

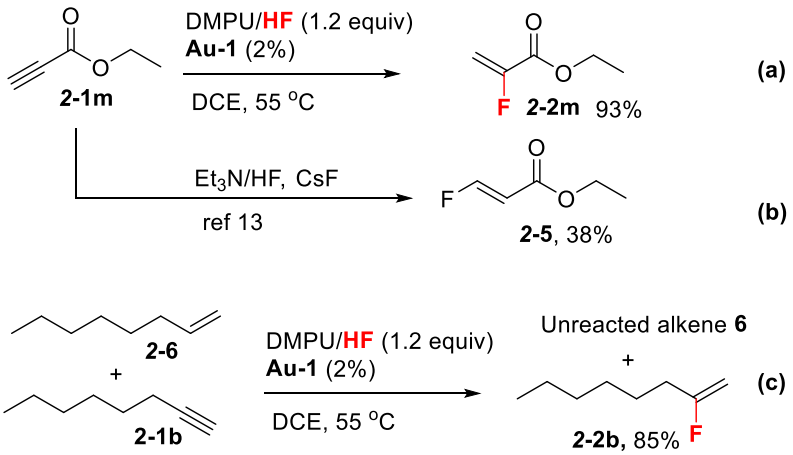


entry	1	2	yield %
1	 2-1a	 2-2a	92 (79)[b]
2	 2-1b	 2-2b	89
3	 2-1c	 2-2c	96 (81)[b]
4	 2-1d	 2-2d	89[b]
5	 2-1e	 2-2e	71
6	 2-1f	 2-2f	88
7	 2-1g	 2-2g	67
8	 2-1h	 2-2h	89
9	 2-1i	 2-2i	84[b]
10	 2-1j	 2-2j	85
11	 2-1k	 2-2k	84[b]
12	 2-1l	 2-2l	87[b]

a) Alkyne 1 (0.5 mmol), (DMPU/HF (65 w/w%) (1.2 equiv), DCE as solvent, 55 °C, 3 h. b) isolated yields, other yields are ^{19}F-NMR yields using benzotrifluoride as internal standard

We found that in the mono-hydrofluorination of an acceptor substituted terminal alkyne **2-1m**, the DMPU-HF/Au-1 system yielded a completely different regioisomer compared to the literature, when no catalyst was used. Thus, the uncatalyzed HF addition to **2-1m** gave the Michael addition product **2-5**),[56] whereas our DMPU-HF/Au-1 system reversed the tendency towards Michael addition to give **2-2m** instead as the only isomer (Scheme 6a).

The DMPU-HF/Au-1 system is highly effective for alkyne hydrofluorination, but it is not a good catalyst for hydrofluorination of alkenes (Scheme 6c). In other words, alkene groups are well tolerated. For example, a 1:1 mixture of 1-octene (**2-6**) and 1-octyne (**2-1b**) gives only alkyne hydrofluorination product **2-2b** under the same conditions of our model reaction.

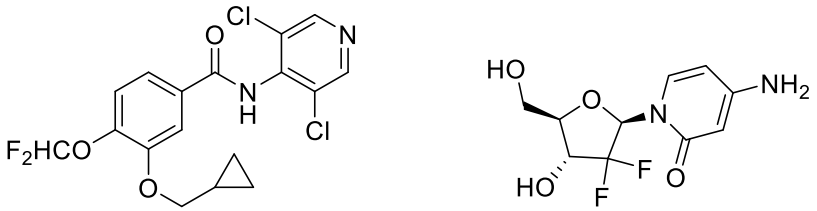


Scheme 6. Selectivity of DMPU-HF/Au-1 fluorination system.

2.3 *Gem*-difluorination of alkynes using DMPU-HF

Organic compounds containing a *gem*-difluoromethylene group are useful for a variety of applications in biological, pharmaceutical and materials chemistry. In this regard, *gem*-difluoromethylene-containing compounds have been sought after due to their

HIV protease,[57] and protein tyrosine phosphatase inhibitions, phosphate,[58] carbonyl[59] and retropeptide[60] mimicries. In addition, the anomeric effects of heteroatom substituents such as δ-fluorinated ethers, -thioethers and -amines have sparked a flurry of new applications.[61] For example, there are a good number of successful applications of CF_2 containing compounds in medicine and advanced materials. Examples of the former are shown in Figure 7.



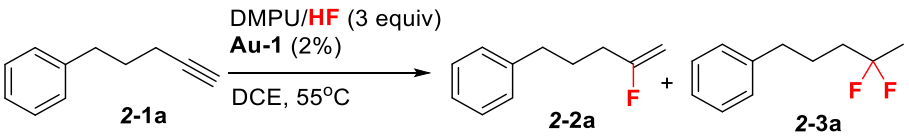
2-7 Roflumilast **2-8** Gemcitabine

Figure 7. Examples of medicines containing difluoromethylene (CF_2).

Over the years a variety of synthetic protocols for this class of compounds have been developed. They can be prepared from their corresponding carbonyl compounds or through various derivatives such as oximes and dithiolanes,[62] electrophilic fluorinations of unsaturated compounds and enolates,[63] free-radical additions of halodifluoroalkanes to olefins,[64] and nucleophilic difluoromethylations of aldehydes and ketones.[65] Other approaches involve methods that utilize fluorinated compounds as synthons.[66] Enantioselective *gem*-difluorination reactions have emerged employing chiral auxiliaries such as sulfinimines, and chiral Lewis acid catalysts.[67] In this regard, the di-hydrofluorination of an alkyne is a straightforward and atom economic way to synthesize CF_2 containing compound **2-3**. Olah and coworkers have reported the synthesis of the difluorinated alkane in limited scope and selectivity.[43] As shown above in Table 5, we observed the formation of **2-3a** during our search for optimal conditions for the synthesis

of **2-2a** (entry 8). We believed that further hydrofluorination of fluoroalkene **2-2** would give di-hydrofluorination product **2-3**, but, as we saw in Scheme 6c, our DMPU-HF/Au-1 system is not a good catalytic system for the hydrofluorination of alkene, so a complete conversion of **2-2** to **2-3** is difficult. We then explored the possibility of using a co-catalyst or additive that could catalyze further the hydrofluorination of **2-2** to give the desired product **2-3** (Table 7). Additional nucleophilic fluorine sources (CsF and AgF, Table 7, entries 1-2) were moderately effective, but could not convert all the **2-2a** to **2-3a**. A weak Lewis acid ($KCTf_3$, Table 7, entry 3) was not effective either but stronger acids ($Ga(OTf)_3$ and $KHSO_4$, Table 7, entries 4-5) helped to produce **2-3a** with very good selectivity. Because $KHSO_4$ is relatively inexpensive and readily available, we selected $KHSO_4$ as our co-catalyst for the synthesis of **2-3**.

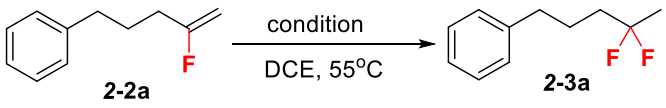
Table 7. Optimization for di-hydrofluorination of alkyne 1.



entry	Additive	time / h	**2-2a / %**	**2-3a / %**
1	CsF (100%)	24	15	85
2	AgF (100%)	24	96	4
3	$KCTf_3$ (10%)	24	67	33
4	$Ga(OTf)_3$ (10%)	24	<0.5	99
5	$KHSO_4$ (150%)	24	<1	99

We conducted a control experiment to get a clearer understanding of the role of a Lewis acid like $Ga(OTf)_3$ in the formation of *gem*-difluoromethylene compound **2-3**

(Equation 1). DMPU-HF alone can convert **2-2a** to **2-3a** without any catalyst, but this reaction is sluggish (Equation 1, condition 1). However, a Lewis acid like $Ga(OTf)_3$ can significantly speed up this conversion (Equation 1, condition 2).

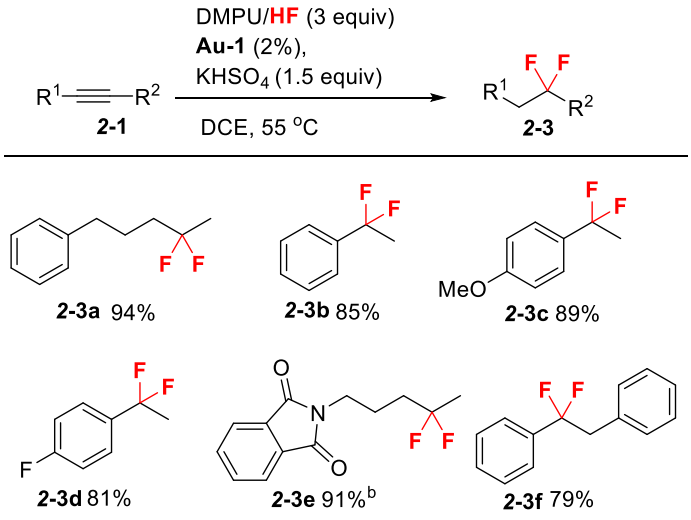


		time	conversion
condition 1	DMPU/**HF** (1 equiv)	1 h 2 h	16% 18%
condition 2	DMPU/**HF** (1 equiv), $Ga(OTf)_3$ (10%)	1 h 2 h	47% 56%

Equation 1. Control experiment on the role of Lewis acid on *gem*-difluoro synthesis.

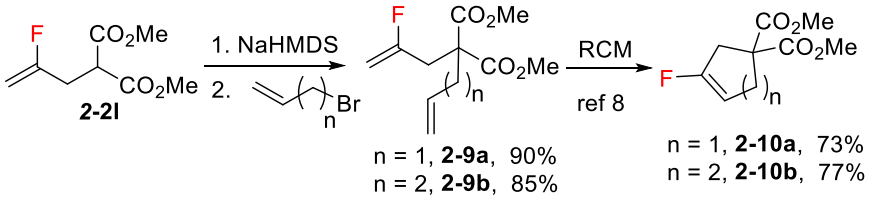
With the optimized condition for dihydrofluorination of an alkyne in hand, we investigated the substrate scope of this transformation (Table 8). This reaction worked very well for both terminal and internal alkynes.

Table 8. Substrate scope for di-hydrofluorination of alkyne **2-1**.



a) Alkyne 1 (0.5 mmol), (DMPU/HF (65 w/w%) (3.0 equiv), DCE as solvent, KHSO4 (1.5 equiv), 55°C, 12 h; b) isolated yield, other yields are ^{19}F-NMR yields using benzotrifluoride (trifluoromethylbenzene) as internal standard

The usefulness of our method was further validated by the synthesis of fluorocarbocycles via ring-closing metathesis (RCM) reactions (Scheme 7).[49] Because fluoroalkenes can be prepared efficiently using our new method and alkene groups are well tolerated, we can envision a diverse set of fluorocycles made by the combination of alkyne mono-hydrofluorination and RCM reactions.



Scheme 7. Synthesis of fluorocarbocycles.

2.4 Conclusion

In conclusion, our new fluorination reagent DMPU-HF not only is easily handled but also is an efficient fluorination system for the regioselective mono- and di-hydrofluorination of alkynes. Further applications of this new fluorination reagent are currently being conducted in our laboratory.

2.5 Experimental section

General experimental information

^{1}H and ^{13}C NMR spectra were recorded at 500 and 126 (or 400 and 101) MHz respectively, while ^{19}F was recorded at 376 MHz using $CDCl_3$ as a solvent. The chemical shifts are reported in δ (ppm) values (^{1}H and ^{13}C NMR relative to $CHCl_3$, δ 7.26 ppm for ^{1}H NMR and δ 77.0 ppm for ^{13}C NMR, multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), m (multiplet) and br (broad). Coupling constants, *J*, are reported in Hertz (Hz). All air and/or moisture sensitive reactions

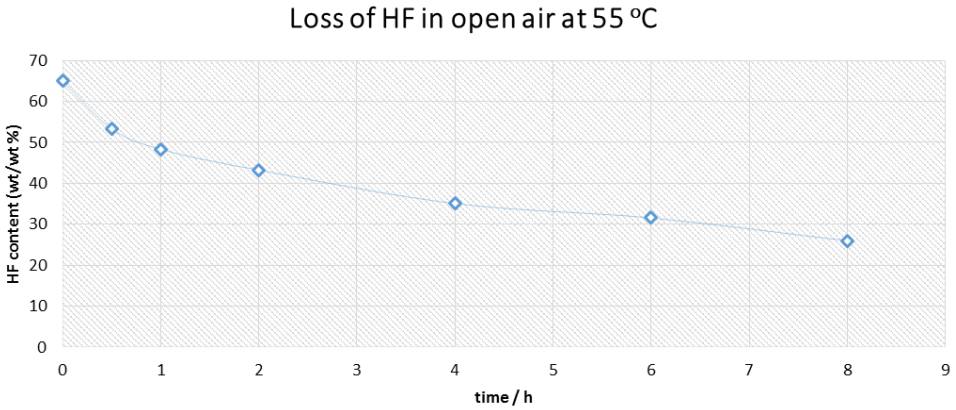
were carried out under argon atmosphere. Solvents (1,2-dichloroethane and dichloromethane) were chemically dried using a commercial solvent purification system. All other reagents and solvents were employed without further purification. The products were purified using a commercial flash chromatography system or a regular glass column. TLC was developed on Merck silica gel 60 F254 aluminum sheets.

Gold pre-catalyst (**Au-1**) was prepared using our published procedure.[68]

Preparation of DMPU-HF complex (HF 65% w/w)

DMPU (5 g) was added into a long Teflon tube, the Teflon tube was cooled to 0°C, and 9.3g of HF gas was condensed into the Teflon tube under stirring. The obtained liquid was stored in a 25 mL Teflon vial with a screw cap at room temperature.

The boiling point of DMPU-HF complex (HF 65% w/w) is around 50-120 °C. The boiling point is not well defined (HF evaporates continuously in the range of 50-120 °C).



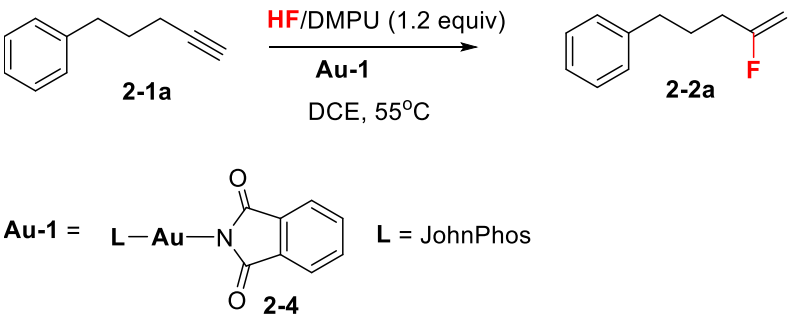
We also conducted HF loss experiment in open air at 55°C (the reaction temperature we used in our synthetic applications). In a well-vented fume hood, 1 gram of DMPU-HF complex (HF 65% w/w) was added to 5 mL polypropylene vial, the vial was heated to 55°C

in open air (without cap), and we measured the weight of polypropylene vial periodically. We calculated the percent of HF left over time (we assumed evaporation of DMPU was negligible).

General procedure for synthesis of fluoroalkene 2-2

Reactions were performed in 5 mL polypropylene vials with cone-lined caps. GC-MS and ^{19}F NMR analysis were used to monitor the progress of reactions.

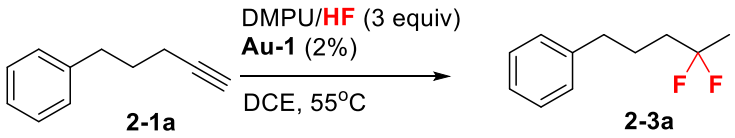
Using synthesis of **2-2a** as an example:



To a solution of 5-phenyl-1-pentyne **2-1a** (14.4 mg, 0.10 mmol) in DCE (0.5 mL) in a polypropylene vial, imidogold precatalyst **Au-1** (2 mol%, 0.01 M stock solution in DCE) was added at room temperature. The reaction mixture was stirred for 3 h at 55°C. Upon completion, the reaction was quenched with saturated sodium bicarbonate. The mixture was extracted with hexane and washed with brine; the organic layer was collected, dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography purification (eluent: hexane) to give fluoroalkene **2-2a** as a colorless oil.

General procedure for synthesis of gem-difluoromethylene compounds 3

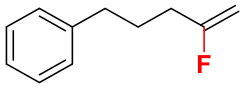
Using synthesis of **2-3a** as an example:



To a solution of 5-phenyl-1-pentyne (14.4 mg, 0.10 mmol) in DCE (0.5 mL), imidogold precatalyst **Au-1** (2 mol% from a 0.01 M solution in DCE), $KHSO_4$ (1.5 equiv) were added at room temperature. The mixture was stirred for 24 h at 55 °C. Upon completion, the reaction was quenched with saturated sodium bicarbonate. The mixture was separated with hexane and washed with brine; the organic layer was collected, dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography purification (eluent: hexane) to give **3a** as a colorless oil.

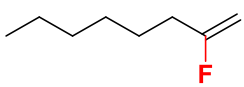
Spectroscopic data of 2-2 and 2-3

(4-Fluoropent-4-en-1-yl) benzene (2-2a)



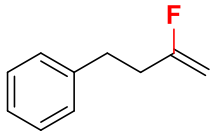
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.18 (m, 5H), 4.52 (dd, *J* = 17.6, 2.6 Hz, 1H), 4.31 – 4.12 (m, 1H), 2.66 (t, *J* = 7.7 Hz, 2H), 2.27 – 2.13 (m, 2H), 1.92 – 1.78 (m, 2H).^{19}F NMR (376 MHz, $CDCl_3$) δ -94.91 (ddd, *J* = 50.0, 33.4, 16.4 Hz, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 141.62, 128.41, 128.34, 125.89, 89.80, 89.60, 34.89, 31.56, 31.38, 31.11, 27.60, 22.63. HRMS (EI$^+$) for $C_{11}H_{13}F$ Cald = 164.1001, found 164.1001.

2-Fluorooct-1-ene (2-2b)



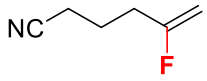
^{19}F NMR (CCl_4) -93.5 ppm ($CFCl_3$) (m). Its spectroscopic data is consistent with a literature report.[69]

(3-Fluorobut-3-en-1-yl) benzene (2-2c)



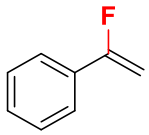
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.46-2.62 (m, 2H), 2.48-2.92 (m, 2H), 4.45 (dd, $^{2}J_{H\text{-}F}$ = 50.0 Hz, *J* = 2.5 Hz, 1H), 4.61 (dd, $^{2}J_{H\text{-}F}$ = 18.0 Hz, *J* = 2.5 Hz, 1H), 7.22-7.33 (m, 3H), 7.47-7.55 ppm (m, 2H); ^{19}F NMR (470 MHz, $CDCl_3$): d = -95.5 ppm (dq, $^{3}J_{F\text{-}H(olefin)}$=49.8 Hz, $^{3}J_{F\text{-}H}$ = $^{3}J_{F\text{-}Hcis(olefin)}$ =17.4 Hz, 1F,). Its spectroscopic data is consistent with a literature report.[50a]

5-Fluorohex-5-enenitrile (2-2d)



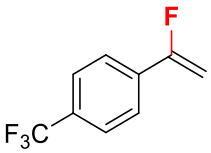
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.59 (dd, *J* = 17.2, 3.0 Hz, 1H), 4.31 (dd, *J* = 49.7, 2.9 Hz, 1H), 2.48 – 2.28 (m, 4H), 1.87 (m, 2H).^{19}F NMR (376 MHz, $CDCl_3$) δ -97.09 (m, 1F).^{13}C NMR (100 MHz, $CDCl_3$) δ 165.25, 162.69, 118.95, 91.68, 91.48, 30.71, 30.43, 21.83, 16.16. HRMS (ESI^+) Calcd. for C_6H_9FN 114. 0719, found 114.0720.

(1-Fluorovinyl) benzene (2-2e)



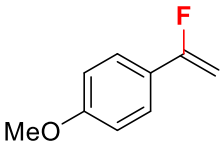
Following general procedure for synthesis of **2** except ratio of phenylacetylene and DMPU-HF is 2:1. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57-7.55 (m, 2H), 7.38-7.37 (m, 3H), 5.04 (dd, 1H, *J* = 49.7; 3.4 Hz), 4.85 (dd, 1H, *J* = 17.7, 3.4 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ –108.47 (dd, $^{3}J_{HF}$ = 51.9; 18.3 Hz). Its spectroscopic data is consistent with a literature report.[50a]

1-(1-Fluorovinyl)-4-(trifluoromethyl)benzene (2-2f)



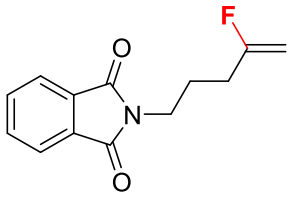
^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.98 (dd, 1 H, *J* = 17.5, 3.7 Hz), 5.14 (dd, 1H, *J* = 48.9, 3.7 Hz, H_B), 7.58–7.70 (m, 4H). ^{19}F NMR ($CDCl_3$, 282 MHz): d 63.42 (s, 3F, CF_3), -108.72 (dd, 1F, *J* = 50.8, 17.7 Hz, 1-CF). Its spectroscopic data is consistent with a literature report.[70]

1-(1-Fluorovinyl)-4-methoxybenzene (2-2g)



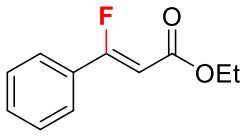
Following general procedure for synthesis of **2** except ratio of phenylacetylene and DMPU-HF is 2:1. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50 (d, *J* = 8.8 Hz, 2 H), 6.90 (d, *J* = 8.7 Hz, 2 H), 4.89 (dd, *J* = 3.4, 50.2 Hz, 1 H), 4.74 (dd, *J* = 3.4, 18.1 Hz, 1 H), 3.84 (s, 3 H) ppm. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –107.2 (dd, $^{3}J_{F–H}$ = 18.1, 50.0 Hz, 1F). Its spectroscopic data is consistent with a literature report.[71]

2-(4-Fluoropent-4-en-1-yl)isoindoline-1,3-dione (2-2h)



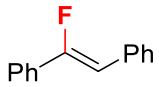
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.80 (m, 2H), 7.72 (dt, *J* = 4.5, 3.6 Hz, 2H), 4.52 (dd, *J* = 17.5, 2.2 Hz, 1H),4.28 (dd, *J* = 50.2, 2.1 Hz, 1H), 3.73 (t, *J* = 7.1 Hz, 2H), 2.25 (dt, *J* = 15.3, 7.6 Hz, 2H), 1.99 – 1.83 (m, 2H).^{19}F NMR (376 MHz, $CDCl_3$) δ -95.15 (m, 1F).^{13}C NMR (101 MHz,$CDCl_3$) δ 168.31, 166.63, 164.08, 133.96, 132.02, 123.23, 90.28, 90.08, 77.32,77.00, 76.68, 37.16, 29.45, 29.17, 25.04. HRMS (CI^+) calcd. for $C_{13}H_{13}FNO_2$ 234. 0930, found 234. 0930.

(Z)-Ethyl 3-fluoro-3-phenylacrylate (2-2i)



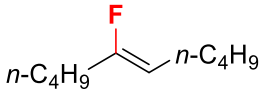
^{1}H NMR (400 MHz, $CDCl_3$), δ 7.62 (d, *J* = 7.6 Hz, 2H), 7.38-7.47 (m, 3H), 5.88 (d, *J* = 33.4 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1 (d, *J* = 275.9 Hz), 163.90 (d, *J* = 2.3 Hz), 125.5 (d, *J* = 8.0 Hz), 97.1 (d, *J* = 6.8 Hz), 60.3, 14.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ -96.16 (d, *J* = 33 Hz, 1F). Its spectroscopic data is consistent with a literature report.[72]

(Z)- (1-Fluoroethene-1,2-diyl)dibenzene (2-2j)



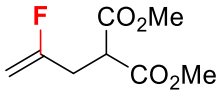
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67–7.69 (m, 4 H), 7.37–7.46 (m, 5 H), 7.27–7.31 (m, 1 H), 6.34 (d, *J* = 39.5 Hz, 1 H) ppm. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –114.2 (d, $^{3}J_{F–H}$ = 39.9 Hz). Its spectroscopic data is consistent with a literature report.[73]

(Z)-5-Fluorodec-5-ene (2-2k)



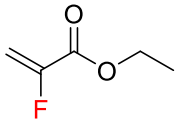
^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.46 (dt, *J* = 38.4, 7.2 Hz, 1H), 2.14 (dt, *J* = 17.2, 7.2 Hz, 2H), 2.08-2.03 (m, 2 H), 1.51-1.43 (m, 2H), 1.39-1.28 (m, 6H),0.95-0.88 (m, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) δ–110.7 (dt, *J* = 38.4, 16.9 Hz). Its spectroscopic data is consistent with a literature report.[74]

Dimethyl 2-(2-fluoroallyl)malonate (2-2l)



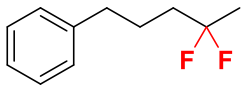
^{1}H NMR (700 MHz, $CDCl_3$) δ 4.59 (dd, *J* = 17.0, 2.6 Hz, 1H), 4.33 (dd, *J* = 49.4, 2.8 Hz, 1H), 3.73 (s, 3H), 3.65 (s, 3H), 2.81 (dd, *J* = 17.0, 7.6 Hz, 2H).^{19}F NMR (470 MHz, $CDCl_3$) δ -97.34 (m, 1F).^{13}C NMR (176 MHz, $CDCl_3$) δ 168.58, 166.89, 92.34, 92.23, 52.78, 52.53, 48.80, 41.10, 31.47, 31.31. EI-HR MS (ESI +) Calcd for $C_8H_{11}FO_4$ = 190.0641, found: 190.0639.

Ethyl-2-fluoroacrylate (2-2m)



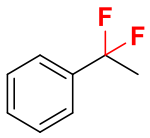
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.67 (dd, 1H, *J* = 43.5; 3.4 Hz), 5.31 (dd, 1H, *J* = 13.2; 3.4 Hz), 4.30 (q, 2H, *J* = 7.2 Hz), 1.34 (t, 3H, *J* = 7.1 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ –117.72 (d, $^{3}J_{HF}$ = 42.7 Hz). Its spectroscopic data is consistent with a literature report.[75] Pure **2m** was not isolated due to its volatility.

(4, 4-Difluoropentyl)benzene (2-3a)



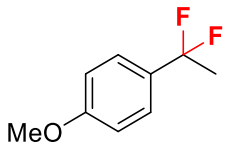
^{19}F NMR (376 MHz, $CDCl_3$) δ -90.529 (m, 1F). HRMS (EI +) calcd. for $C_{11}H_{14}F_2$ 184.1064; found 184.1064. Note: The product **2-3a** is very volatile and usually cyclizes on silica gel chromatography to an unidentifiable product, so analytically pure **2-3a** couldn't be obtained.

(1,1-Difluoroethyl)benzene (2-3b)



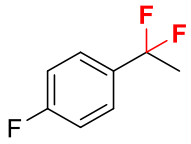
^{19}F NMR (376 MHz, $CDCl_3$) δ -87.16 (q, *J* =18.6 Hz). Its spectroscopic data is consistent with a literature report.[76]

1-(1,1-Difluoroethyl)-4-methoxybenzene (2-3c)



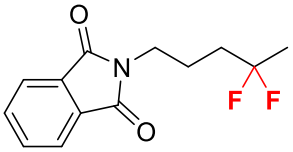
^{19}F NMR (376 MHz, $CDCl_3$) δ -86.4 (q, *J* =18.6 Hz). Its spectroscopic data is consistent with a literature report.[77]

1-(1,1-difluoroethyl)-4-fluorobenzene (2-3d)



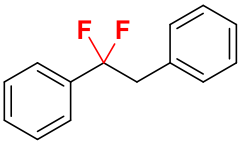
^{19}F NMR (376 MHz, $CDCl_3$) δ -86.08 (q, *J* = 19.0 Hz, 2F), -113.17 (m, 1F). Its spectroscopic data is consistent with a literature report.[78]

2-(4,4-Difluoropentyl)isoindoline-1,3-dione (2-3e)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.83 (m, 2H), 7.76-7.70 (m, 2H), 3.74 (t, *J* = 6.6 Hz, 2H), 1.93-1.87 (m, 4H), 1.59 (t, J_{HF} = 18.4 Hz, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -91.4 (m). Its spectroscopic data is consistent with a literature report.[79]

(1,1-difluoroethane-1,2-diyl)dibenzene (2-3f)

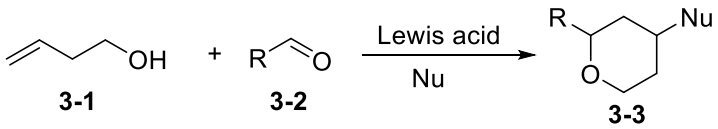


^{1}H NMR δ: 3.46 (t, 2H, *J* = 15.8 Hz), 7.13-7.16 (m, 2H), 7.28-7.30 (m, 3H), 7.37-7.42 (m, 5H), ^{19}F NMR δ: -94.7 (t, 2F, *J* = 15.8 Hz). Its spectroscopic data is consistent with a literature report.[80]

3 PREPARATION OF FLUORINATED TETRAHYDROPYRANS AND PIPERIDINES USING A NEW NUCLEOPHILIC FLUORINATION REAGENT–DMPU-HF

3.1 Background

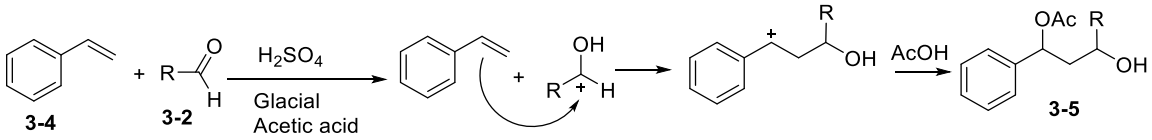
The Prins cyclisation reaction is a reaction leading to a tetrahydropyran from a homoallylic alcohol and an aldehyde in the presence of a Lewis or Brønsted acid and a nucleophile. Common nucleophiles used for this reaction are bromide,[81] chloride,[82] iodide,[81a] acetate[81b, 83] _ENREF_92 and tosylate.[83a]



Scheme 8: General case for the Prins reaction.

Though Ballard reported the first synthesis of pyran via the Prins cyclization reaction[84] the Prins reaction was first reported by Kriewitz in 1899, described as the condensation of an olefin and an aldehyde to give rise to unsaturated alcohols.[85] However, it was not until 1919 that a comprehensive study was carried out by H. J. Prins.[86] He performed reactions with styrene, α-pinene and camphene with formaldehyde using water or glacial acetic acid as solvent. From his study (Scheme 9), it was reported that with water as solvent, unsaturated alcohols or 1,3-butanediols were obtained while with glacial acetic acid, esters from acetic acid were usually obtained. Today these types of reaction that

involve the condensation of an olefin with an aldehyde in the presence of an acid is often called the Prins reaction.

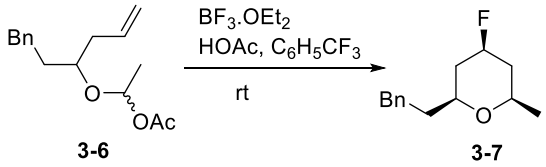


Scheme 9. Example of the condensation reaction carried out by H.J Prins in 1919.

The tetrahydropyran motif is quite common in many natural products and this has led to the development of a vast array of synthetic methodologies to access the tetrahydro pyran rings effectively.

3.2 Fluoro-Prins cyclization reaction

Investigation of the literature reveals very few examples of the Prins fluorinaton reaction. Reported cases of 4-fluorotetrahydropyran synthesis appeared as an unexpected by-product of the Prins cyclization reaction. This observation was first made by Rychnovsky[81b, 87] *et al*. in 1996 when $BF_3.OEt_2$ was used as Lewis acid to promote oxygen substitution at the 4-position of the tetrahydropyran moiety Scheme 10.



Scheme 10. Prins cyclizattion leading to the fluorinated pyran.

They, however, observed an accidental deviation from their synthetic target with the substitution of the fluorine atom instead. Ever since, few other cases of the fluoro-Prins reaction have been reported.[88]

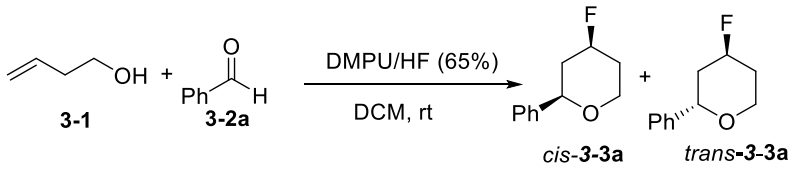
3.3 Fluoro-Prins reaction with DMPU-HF

As earlier stated, the Prins reaction[81a, 89] of a homoallylic alcohol and an aldehyde in the presence of an acid is a well-established synthetic methodology for the preparation of tetrahydropyrans.[86, 90] However, there are only few reports on the Prins reaction for the synthesis of fluorinated tetrahydropyrans.[88a, 88c, 91] Most of the reported syntheses of fluorinated tetrahydropyrans utilize a strong Lewis acid, $BF_3 \cdot OEt_2$, as the fluorine source. Hence, they suffer from low yields and especially low diastereoselectivity[88c]. Fuchigami and coworkers reported the synthesis of 4-fluoro-tetrahydropyrans with HF salts in liquid form, but a large excess of HF was needed (HF as solvent).[88a] Because the Prins reaction requires an acidic medium, the more acidic HF/DMPU system should improve the efficiency of Prins cyclization. Since DMPU-HF reagent is more acidic than Olah's reagent (pyridine·9HF) or triethylamine HF ($Et_3N \cdot 3HF$). We propose that its use could be advantageous in fluorination reactions that require a highly acidic medium.

We began our study on the fluoro-Prins reaction by first reacting the homoallylic alcohol **3-1** and benzaldehyde **3-2a** in the presence of DMPU-HF in different solvents. We were pleased to find that the reaction of homoallylic alcohol **3-1** and benzaldehyde **3-2a** in the presence of DMPU-HF produced the expected 4-fluorotetrahydropyran **3-3a** (Table 9). Reactions in a number of nonpolar solvents (hexane, toluene, and DCM) provided high efficiency and excellent diastereoselectivity (Table 9, entries 1-3). A lower concentration of HF in the reaction medium (34% HF/DMPU wt/wt, DMPU:HF = 1: 3.3) slowed down the reaction, but the diastereoselectivity was maintained (Table 9, entry 4). A complete replacement of solvent by DMPU resulted in a much slower conversion and eroded the

diastereomeric ratio (Table 9, entry 5). Reactions were completely shut down in Lewis basic solvents, including THF and DMF (Table 8, entry 6, 7).

Table 9. Optimization of the fluoro-Prins reaction.

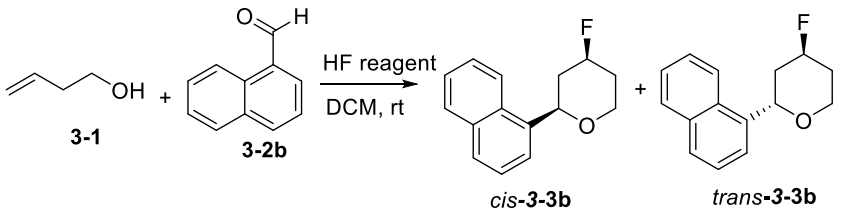


3-1 **3-2a** *cis*-**3**-**3a** *trans*-**3**-**3a**

Entry	Solvent	time / h	conversion / %	*cis/trans*[b]
1	Hexane	3	100	17:1
2	Toluene	3	100	17:1
3	DCM	3	96	17:1
4[c]	DCM	9	90	17:1
5	DMPU	3	42	10:1
6	THF	9	0	-
7	DMF	9	0	-

a)**1** (0.2 mmol), **2** (0.2 mmol), DMPU-HF (2.1 mmol of HF) and solvent (0.5 mL) was mixed in a polyethylene vial, then stirred for 3-9 h at rt; b) determined by ^{19}F NMR. [c]34 % DMPU-HF.

We also compared the reactivity and selectivity of Olah's reagent and HF/DMPU in the Prins reaction of 2-naphthaldehyde (Scheme 11). The more acidic DMPU-HF reagent enabled a faster conversion and much better diastereoselectivity than Olah's reagent. The origin of this diastereoselectivity is still not clear to us, however, we think that the steric imposition from the structure of DMPU may be playing an important role in enhancing the selectivity observed in this reaction.

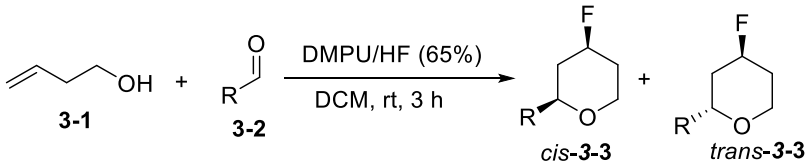


HF reagent	time	conversion	*cis/trans*
Pyridine/HF (70%)	48 h	95%	4:1
DMPU/HF (65%)	3 h	97%	17:1

Scheme 11. Reactivity and selectivity of Olah's reagent and DMPU-HF on fluoro-Prins reaction.

To explore the general applicability of our methodology, several aldehydes were subjected to our optimized reaction conditions (Table 10). Aromatic and aliphatic aldehydes gave the corresponding fluorinated tetrahydropyrans in good yields and good diastereoselectivity. A more electron-rich aldehyde, such as 4-hydroxy-3,5-dimethoxybenzaldehyde, did not react under these conditions. The same phenomenon was also observed in the $BF_3 \cdot OEt_2$-mediated Prins cyclization[88c] (Table 10, entry 10).

Table 10. Scope of the fluoro-Prins reaction.

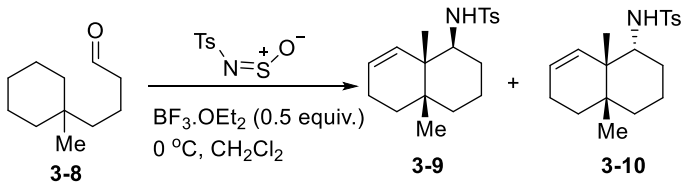


Entry	R	3	yield (%)	*cis*-3/*trans*-3[b]
1	C_6H_5-	**3-3a**	75	17:1
2	2-naphtyl	**3-3b**	74	> 20:1
3	4-Cl-C_6H_4-	**3-3c**	87	> 20:1
4	4-Br-C_6H_4-	**3-3d**	91	> 20:1
5	4-NO_2-C_6H_4-	**3-3e**	81	> 20:1
6	4-CF_3-C_6H_4-	**3-3f**	92	> 20:1
7	4-*i*-Pr-C_6H_4-	**3-3g**	78	> 20:1
8	4-Me-C_6H_4-	**3-3h**	72	> 20:1
9	2-NO_2-C_6H_4-	**3-3i**	76	> 20:1
10	4-OH-3,5-dimethoxy-C_6H_2	**3-3j**	No rxn	-
11	6-Br-2-OH-3-MeO-C_6H_2	**3-3k**	56	> 20:1
12	cyclohexyl-	**3-3l**	88	20:1

a)1 (0.2 mmol), 2 0.2 mmol, DMPU-HF (2.1 mmol HF) in DCM 0.5 mL was mixed in a plastic vial, and was stirred for 3 h at rt. b) determined by ^{19}F NMR.

3.4 Aza-Prins fluorination reaction

In the case of the aza-Prins reaction, the alcohol is replaced by an amine and this type of reaction has been widely explored. Weinreb[92] in 1988 reported the intramolecular aza-Prins cyclization where an aldehyde was converted to the tosyl iminium intermediate (Scheme 12) and in the presence of $BF_3.OEt_2$, the Prins cyclization occurred.

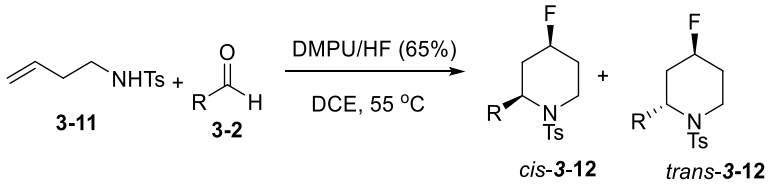


Scheme 12. Weinreb's example of aza-Prins cyclization reaction.

Several natural products like (+)-cortisatin A (an anti-angiogenic steroidal alkaloid) have been synthesized via this methodology.[93] More recently, the aza Prins cyclization reaction has gained increased interest and there have been several report to the formation of piperidines from the homoallylic amines and aldehydes in the presence of a variety of Lewis acids such as FeX_3 (X = Br, Cl),[94] PMA,[95] GaI_3,[96] I_2[97] and/or $InCI_3$,[98] which has led to the incorporation of various nucleophiles such as Cl^-, Br^-, I^- and more recently F^- where $BF_3.OEt_2$[88c] and $Et_4NF/5HF$[88a] were the acids used.

We investigated the aza-Prins cyclization of aldehyde and *N*-tosyl homoallyl amine in the presence of our DMPU-HF reagent. As shown in Table 11, the reaction of *N*-tosyl homoallyl amine **3-11** with aliphatic aldehydes furnished the corresponding fluoropiperidines **3-12** in excellent yields and good diastereoselectivity after a few hours. Similar to previous literature reports,[99] this reaction did not proceed well with aryl aldehydes (Table 11, entries 3-5), and longer reaction times were needed in order to achieve a full conversion. The reaction became very sluggish with an electron rich aromatic aldehyde (e.g. anisaldehyde) and only trace amount of product was obtained even after an extended reaction time (Table 11, entry 6).

Table 11. Scope of the aza-Prins fluorocyclization.



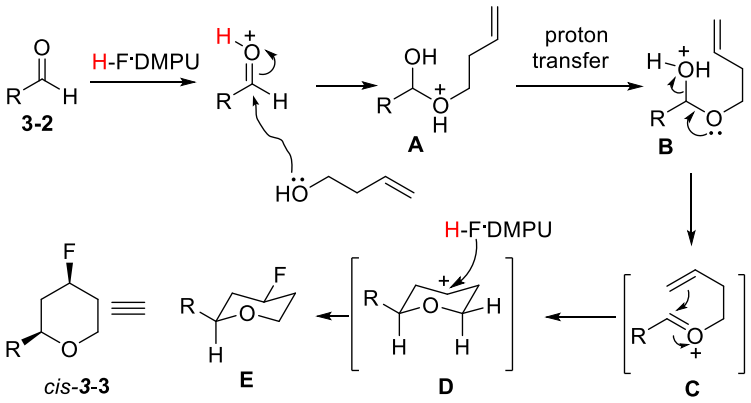
3-11 3-2 *cis*-**3**-12 *trans*-**3**-12

Entry	R	time (h)	3-11	yield (%)	*cis-5/trans-3-12*[b]
1	Cyclohexyl-	4	**3-11a**	100	10:1
2	n-C_5H_{11}-	4	**3-11b**	100	8.5:1
3	Ph	24	**3-11c**	96	2:1
4	4-Br-C_6H_4-	24	**3-11d**	90	2.5:1
5	4-NO_2-C_6H_4-	24	**3-11e**	42	2:1
6	4-MeO-C_6H_4-	48	**3-11f**	0	-

a)**4** (0.2 mmol), 2 (0.2 mmol), DMPU-HF (2.1 mmol of HF) in DCE 0.5 mL was mixed in a polyethylene vial, then stirred at 55 °C; b) determined by ^{19}F NMR. c) room temperature; d) determined by ^{19}F NMR using $PhCF_3$ as internal standard.

3.5 Mechanism and stereochemistry of fluoro-Prins cyclization reaction

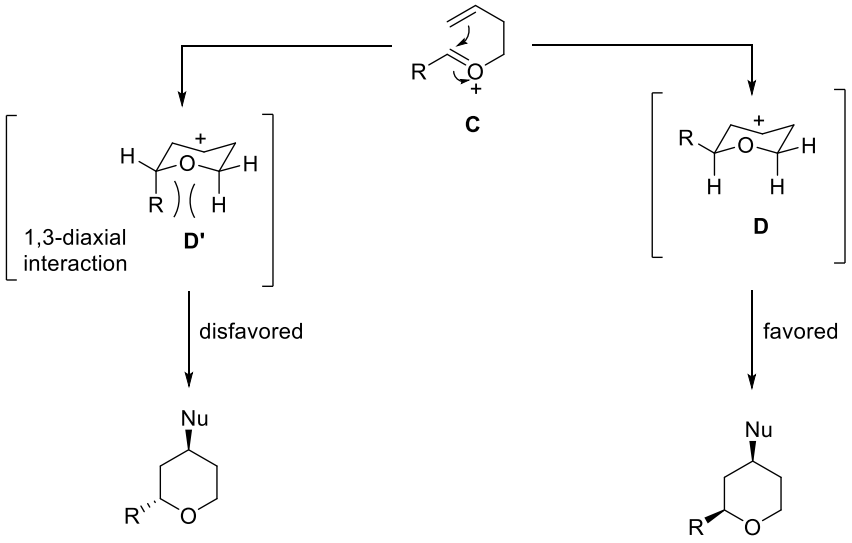
The mechanism of the Prins cyclization reaction has been investigated by several research groups.[83a, 100] and our proposed mechanism for this project with DMPU-HF follows the general consensus.



Scheme 13. Proposed mechanism for the fluoro-Prins cyclization.

The proposed mechanism of the fluoro-Prins cyclization reaction is shown in Scheme 13. First, DMPU-HF activates the aldehyde **3-2**, which then reacts with the homoallylic alcohol. Subsequent elimination of water results in the formation of the intermediate oxonium ion **C** that then cyclizes into carbocation **D**. The nucleophilic fluorine in DMPU-HF quenches intermediate **D** to give the fluorinated product **3-3**.[81b, 82, 101]

Theoretical calculations by Alder and co-workers showed *syn*-diastereoselective preference for the Prins cyclization reaction.[90] Going by the general mechanism of the Prins reaction, Alder et al observed that the oxonium ion **C** forms the more favorable chair-like transition state **D** to avoid 1,3-diaxial interaction seen in **D'** Scheme 14.



Scheme 14. Plausible stereochemical outcome for the Prins cyclization

Using the B3LYP/6-31G computer model, Alder reported further that the C^{+}-H bond of **D** was semiaxial in the chair 4-tetrahydropyranyl cation and it is the most stable conformation. Hence, the nucleophilic attack occurred from the equatorial position given rise to the *syn* products. The work of David O'Hagan et al[88c] on the synthesis of 4-fluoro substituted tetrahydropyrans via the Prins reaction lend support to the *syn* diasteroselectivity observed in the products. They obtained **3-3e** from the reaction of the corresponding homoallylic alcohol and 4-nitrobenzaldehyde in the presence $BF_3.OEt_2$ in a 10:1 diastereomeric ratio and unambiguously confirmed its *syn* stereochemical outcome via X-ray crystallography. Using the spectroscopic data (^{1}H, ^{19}F, and ^{13}C) of **3-3e**, they were able to characterize the *syn* products of other substrates.

We were able to determine the diastereoselectivity of our products by comparing the spectroscopic data of our results with the data given by Fuchigami and David O'Hagan.[88a, 88c] Most of the substrates we experimented in this reaction were similar to the substrates reported by these authors and our results agree well with the data in literature.

3.6 Summary

In summary, DMPU-HF is a suitable nucleophilic fluorination reagent for the diastereoselective synthesis of substituted 4-fluorotetrahydropyrans and 4-fluoropiperidines via the Prins reaction. When compared to other commonly used nucleophilic fluorination reagents like pyridine/HF, DMPU-HF gives both higher yields and better *cis/trans* selectivity. Aside the fact that DMPU-HF is more acidic than the common HF-based reagents like $Et_3N.3HF$ and Py/HF, which we believe is important in facilitating the success of the fluoro-Prins cyclization reaction, we are yet to be sure of its role in enhancing better *cis/trans* selectivity when compared with these other reagents. We hope that the on-going computational analysis will help us understand the role of DMPU-HF better. The experimental procedure is simple and is amenable to scale-up.

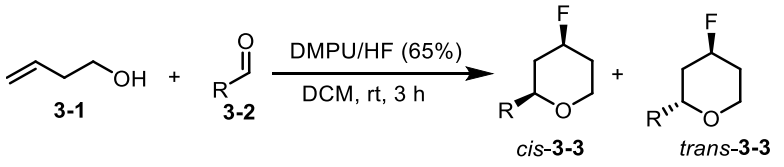
3.7 Experimental section

1. General Information

NMR spectra were recorded on a 400 MHz or a 500 MHz spectrometer. Chemical shifts are given in ppm. The spectra are calibrated to the residual ^{1}H and ^{13}C and ^{19}F signals of the solvents. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), doublet-doublet (dd), quintet (quint), septet (sept), multiplet (m), and broad (br).

Unless otherwise stated, starting materials were purchased from Aldrich and/or Fluka. Solvents were used as purchased. Conversion was monitored by thin layer chromatography (TLC) using Merck TLC silica gel 60 F254. Compounds were visualized by UV-light at 254 nm and by dipping the plates in an polymoybdenic acid (PMA), *p*-anisaldehyde, solutions or an aqueous potassium permanganate solution followed by heating, depending on the compounds formed.

2. General method for the oxa-Prins fluorocyclization reaction

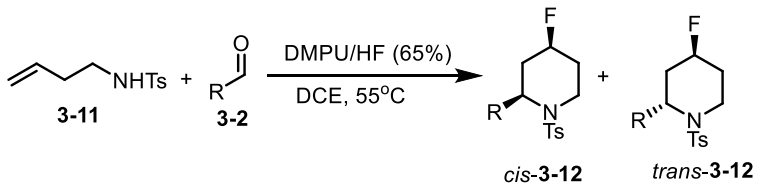


yield up to 92%, *cis/trans up to 20:1*

In a polyethylene vial charged with a magnetic stirring bar, homoallylic alcohol **3-1** (0.2 mmol) and aldehyde **3-2** (0.2 mmol) were dissolved in 0.5 mL dichloromethane, then DMPU-HF (HF content 65 % wt/wt, 58 µL, 2.1 mmol) was added to the mixture and was stirred for 3 h at room temperature. The progress of reaction can be monitored by TLC

(green or dark brown dots on anisaldehyde stain). After completion of the reaction the mixture was quenched with cold water, and the organic phase was extracted with chloroform (5 mL). The organic phase was washed with aqueous sodium bicarbonate, a 2 M solution of sodium bisulfite and brine. Finally the organic phase was dried over sodium sulfate and was concentrated to dryness in vacuum. The crude product was chromatographed with a 10:1 mixture of hexanes and EtOAc to afford the corresponding fluoro-tetrahydropyrans **3-3**.

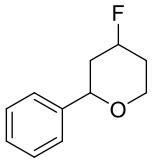
3. General method for the aza-Prins fluorocyclization reaction



In a polyethylene vial charged with a magnetic stirrer, homoallylic tosylamine (0.2 mmol) and aldehyde **3-2** (0.2 mmol) were dissolved in 0.5 mL dichloroethane, then DMPU-HF (HF content 65 % wt/wt, 58 µL, 2.1 mmol) was added to the mixture and was stirred for 3 h at 55 °C. The progress of reaction can be monitored by TLC (green or dark brown dots on anisaldehyde stain). After completion of the reaction, the mixture was quenched with cold water, and the organic phase was extracted with chloroform (2 mL). The organic phase was washed with aqueous sodium bicarbonate, a 2M solution of sodium bisulfite and brine. Finally the organic phase was dried over sodium sulfate and was concentrated to dryness in vacuum. The crude product was chromatographed with a 10:1 mixture of hexanes and EtOAc to afford the corresponding fluoro-piperidine **3-12**.

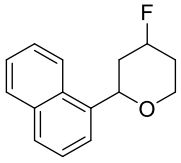
Spectroscopic data for compounds

4-Fluoro-2-phenyltetrahydro-2H-pyran (3-3a)



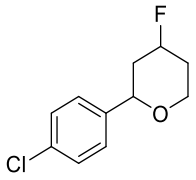
Colorless oil, (24.7 mg)^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.22 (m, 5 H), 4.95–4.65 (m, $J_{H,F}$ = 49.1 Hz, 1 H), 4.33–4.27 (m, 1 H), 4.24–4.15 (m, 1 H), 3.60–3.49 (m, 1 H), 2.38–2.28 (m, 1 H), 2.15–2.06 (m, 1 H), 1.94–1.68 (m, 2H). Its spectroscopic data is consistent with a literature report.[88a, 91a]

4-Fluoro-2-(naphthalen-1-yl)tetrahydro-2H-pyran(3-3b)



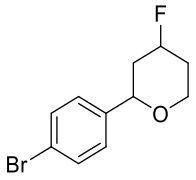
Brown solid, (34 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.73 (m, 4H), 7.59 – 7.34 (m, 3H), 5.01 – 4.72 (dtt, J= 49.0 Hz, 10.7 Hz, 5.1 Hz. 1H), 4.50 (d, *J* = 11.3 Hz, 1H), 4.27 (dd, *J* = 11.6, 5.6 Hz, 1H), 3.63 (t, *J* = 12.3 Hz, 1H), 2.62 – 2.34 (m, 1H), 2.25 – 2.06 (m, 1H), 2.01 – 1.72 (m, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ 138.67, 133.26, 133.01, 128.26, 128.00, 127.65, 126.17, 125.94, 124.57, 123.95, 109.99, 89.39 (d, *J* = 177.2 Hz), 77.88 (d, *J* = 11.4 Hz), 65.54 (d, *J* = 11.9 Hz), 40.57 (d, *J* = 17.1 Hz), 33.01 (d, *J* = 17.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -169.74 (d, *J* = 49.0 Hz, 1F). MS: m/z= 230.11 ([M] $^{+}$). ESI HRMS: calcd. for $C_{15}H_{15}FONa^{+}$ ($[M+Na]^{+}$) 253.0999; found 253.0999.

2-(4-Chlorophenyl)-4-fluorotetrahydro-2H-pyran (3-3c)



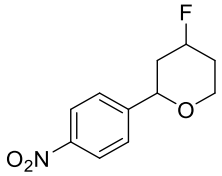
Semisolid, (36.4 mg). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27–7.35 (4 H, m) 4.72–4.92 (1 H, m), 4.30 (1 H, dd, *J* = 11.6, 2.0 Hz), 4.18–4.24 (1 H, m), 3.56 (1 H, tt, *J* = 12.4, 1.6 Hz), 2.28–2.37 (1 H, m), 2.10–2.17 (1 H, m), 1.85 (1 H, dp, *J* = 11.2, 4.8 Hz), 1.71 (1 H, p, *J* = 10.0 Hz). Its spectroscopic data is consistent with a literature report.[91a]

2-(4-Bromophenyl)-4-fluorotetrahydro-2H-pyran (3-3d)



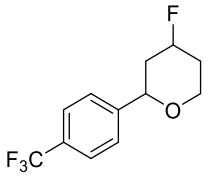
Brown solid, (46.4 mg) Cis isomer**:** ^{19}F NMR ($CDCl_3$, 376 MHz): δ - 171.1 (m); *trans* isomer: ^{19}F NMR ($CDCl_3$, 376 MHz) δ -186.3 (m). Its spectroscopic data is consistent with a literature report.[88c]

4-Fluoro-2-(4-nitrophenyl)tetrahydro-2H-pyran (3-3e)



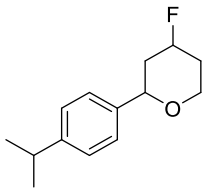
Yellow solid (36.1mg) Cis isomer**:** ^{19}F NMR ($CDCl_3$, 376 MHz): δ - 170.5 (m); *trans* isomer ^{19}F NMR ($CDCl_3$, 376 MHz) δ -185.3 (m). Its spectroscopic data is consistent with a literature report.[88c]

4-Fluoro-2-(4-(trifluoromethyl)phenyl)tetrahydro-2H-pyran (3-3f)



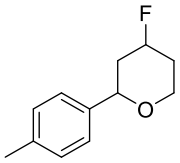
Yellow solid, (45.3 mg). This compound is known:^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 (2 H, d, J = 8.0 Hz), 7.46 (2 H, d, *J* = 8.0 Hz), 7.46 (2 H, d, J = 8.0 Hz), 4.73–4.93 (1 H, m), 4.37 (1 H, dd, *J* = 11.2, 2.0 Hz), 4.20–4.26 (1 H, m), 3.57 (1 H, tt, *J* = 14.0, 2.0 Hz), 2.32–2.39 (1 H, m), 2.10–2.20 (1 H, m), 1.80–1.92 (1 H, m), d 1.63–1.75 (m, 1 H). Its spectroscopic data is consistent with a literature report.[91a]

4-Fluoro-2-(4-isopropylphenyl)tetrahydro-2H-pyran (3-3g)



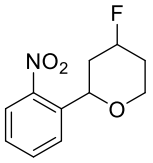
Yellow solid, (33.9 mg)**:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 6.84 (m, 5H), 5.04 – 4.56 (m, 1H), 4.37 – 4.26 (m, 1H), 4.20 (dt, *J* = 11.6, 5.7 Hz, 1H), 3.56 (td, *J* = 12.4, 1.5 Hz, 1H), 2.97 – 2.81 (m, 1H), 2.45 – 2.28 (m, 1H), 2.18 – 2.06 (m, 1H), 1.93 – 1.72 (m, 2H), 1.25 (dd, *J* = 6.9, 1.5 Hz, 6H).^{13}C NMR (100 MHz, $CDCl_3$) δ 148.61, 138.51, 130.37, 126.60, 126.53, 125.97, 89.47 (d, *J* = 176.8 Hz), 77.76 (d, *J* = 11.4 Hz), 65.44 (d, *J* = 11.9 Hz), 40.27 (d, *J* = 16.9 Hz), 34.34 (s, 4H), 33.84 (s, 13 H), 33.00 (d, *J* = 17.5 Hz), 23.9823.67. ^{19}F NMR (376 MHz, $CDCl_3$) δ -169.65 (dd, *J* = 49.2, 4.5 Hz, 1F). MS: m/z 222.1 $[M]^+$. ESI HRMS: calcd. for $C_{14}H_{20}FO^+$ ($[M+H]^+$) 223.1493; found 223.1492.

4-Fluoro-2-(p-tolyl)tetrahydro-2H-pyran (3-3h)



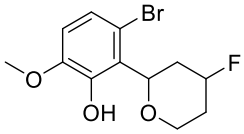
Colorless oil, (28 mg). 1H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, J = 8.1 Hz, 2 H), 7.14 (d, J = 8.1 Hz, 2 H), 4.92–4.62 (m, $J_{H,F}$ = 49.1 Hz, 1 H), 4.28–4.12 (m, 2H), 3.57–3.47 (m, 1 H), 2.32 (s, 3 H), 2.30–2.24 (m, 1 H), 2.12–2.04 (m, 1 H), 1.92–1.66 (m, 2 H). Its spectroscopic data is consistent with a literature report.[88a]

4-Fluoro-2-(2-nitrophenyl)tetrahydro-2H-pyran (3-3i)



Yellow oil, (33.6 mg). ^{1}H NMR (CDCl3, 400 MHz): d 1.57–1.67 (1 H, m), 1.81–1.93 (1 H, m), 2.12–2.18 (1 H, m), 2.58–2.65 (1 H, m), 3.58 (1 H, tt, J = 12.4, 1.6 Hz), 4.17–4.24 (1 H, m), 4.70 (1 H, dd, J = 11.2, 2.0 Hz), 4.78–4.98 (1 H, m), 4.90 (1 H, dd, J = 12.8, 1.6 Hz), 7.42–7.47 (1 H, m), 7.64–7.68 (1 H, m), 7.81 (1 H, d, J = 8.0 Hz), 7.94 (1 H, d, J = 8.0 Hz). Its spectroscopic data is consistent with a literature report.[91a]

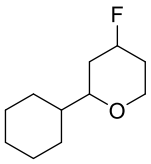
3-Bromo-2-(4-fluorotetrahydro-2H-pyran-2-yl)-6-methoxyphenol (3-3k)



Dark brown solid (33.7 mg):^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, J = 8.7 Hz, 1H), 6.68 (d, J = 8.7 Hz, 1H), 4.94 (d, J = 11.8 Hz, 1H), 4.91 – 4.70 (m, 1H), 4.37 – 4.25 (m, 1H), 3.85 (s, 3H), 3.62 (t, J = 12.5 Hz, 1H), 2.48 – 2.36 (m, 1H), 2.22 – 2.10 (m, 1H), 1.99 –

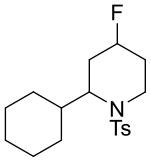
1.82 (m, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ 148.35, 146.36, 123.48, 112.37, 111.69, 87.84 (d, *J* = 178.8 Hz), 79.71 (d, *J* = 12.4 Hz), 66.11 (d, *J* = 12.1 Hz), 56.16, 36.72 (d, *J* = 18.1 Hz), 32.78 (d, *J* = 18.6 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -171.10 (d, *J* = 46.8 Hz, 1F). MS: m/z = 304.01 $[M]^+$. ESI HRMS: calcd. for $C_{12}H_{15}FO_3Na^+$ 327.0003; found 327.0003, cald. For $C_{12}H_{16}FO_3^+$ ($[M+H]^+$) 305.0183; found 305.0183.

2-Cyclohexyl-4-fluorotetrahydro-2H-pyran (3-3l)



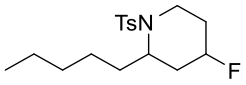
Light yellow Oil, (33 mg).Cis isomer: ^{19}F ($CDCl_3$, 376 MHz): δ - 168.8 (m); *trans* isomer: ^{19}F NMR ($CDCl_3$, 376 MHz) δ -184.8 (m). Its spectroscopic data is consistent with a literature report.[88b]

2-Cyclohexyl-4-fluoro-1-tosylpiperidine (3-12a)



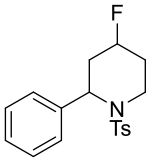
Colorless oil, (63.4 mg). Cis isomer: ^{19}F NMR ($CDCl_3$, 376 MHz): δ - 175.2 (m); *trans* isomer: ^{19}F NMR ($CDCl_3$, 376 MHz) δ -178.9(m). Its spectroscopic data is consistent with a literature report.[88a]

4-Fluoro-2-pentyl-1-tosylpiperidine (3-12b)



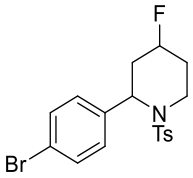
Colorless oil, (60.2 mg) Cis isomer: ^{19}F NMR ($CDCl_3$, 376 MHz): δ - 176.1 (m); *trans* isomer: ^{19}F NMR ($CDCl_3$, 376 MHz) δ -179 (m). Its spectroscopic data is consistent with a literature report.[88c]

4-Fluoro-2-phenyl-1-tosylpiperidine (3-12c)



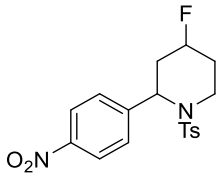
Colorless oil, (27 mg). Cis isomer: ^{19}F NMR ($CDCl_3$, 376 MHz): δ - 177.2 (m); *trans* isomer: ^{19}F NMR ($CDCl_3$, 376 MHz) δ -179.8 (m). Its spectroscopic data is consistent with a literature report.[88a]

2-(4-Bromophenyl)-4-fluoro-1-tosylpiperidine (3-12d)



Brown solid, (40 mg) Cis isomer: ^{19}F NMR ($CDCl_3$, 376 MHz): δ - 175.6 (m); *trans* isomer: ^{19}F NMR ($CDCl_3$, 376 MHz) δ -181.3 (m). Its spectroscopic data is consistent with a literature report.[88c]

4-Fluoro-2-(4-nitrophenyl)-1-tosylpiperidine (3-12e)



Light yellow solid, (23.1 mg). Cis isomer: ^{19}F NMR ($CDCl_3$, 376 MHz): δ - 176 (m); *trans* isomer: ^{19}F NMR ($CDCl_3$, 376 MHz) δ -180.1 (m). Its spectroscopic data is consistent with a literature report.[88c]

4 REGIOSELECTIVE RING OPENING OF AZIRIDINES BY DMPU-HF

4.1 Background

Among fluorinated compounds, β-fluoroamines are important building blocks and motifs in medicinal chemistry (Figure 8),[102] thus, efficient synthetic approaches toward β-fluoroamine motif are in high demand.

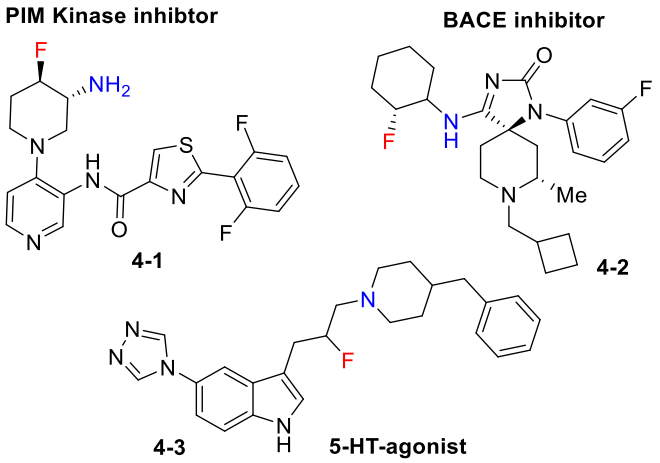
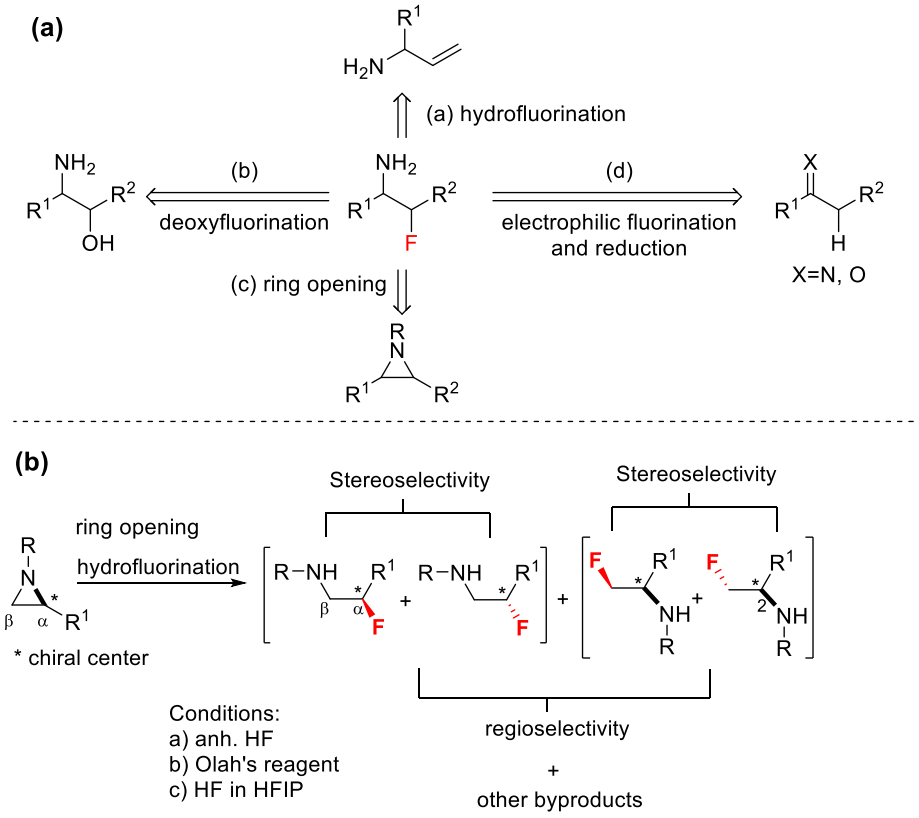


Figure 8. β-Fluoroamines in medicinal chemistry.

In addition to the improved metabolic stability as well as the binding affinity offered by drugs containing C-F bonds, β-fluoro substitution lowers the pKa of amines (Table 2), which in turn improves bioavailability and increases the blood-brain barrier penetration. The past decade has witnessed the development of new and improved methods for the synthesis of β-fluoroamines due to their utility in medicinal chemistry.[95]



Scheme 15. Synthetic routes toward β-fluoroamines.

Reported synthetic routes toward β-fluoroamines could be categorized into several classes (Scheme 15a): (a) hydrofluorination of *N*-allylic amines by fluoroantimonic acid,[103] (b) deoxyfluorination of β-aminoalcohols and their derivatives,[104] (c) nucleophilic ring opening of aziridines by metal fluorides or hydrogen fluoride,[105] and (d) electrophilic fluorination of imines or other synthetic equivalents and subsequent reduction.[106] Among these methods, the nucleophilic ring opening of aziridines (Scheme 15a, route c) is ideal because of the low cost of reagents, mild reaction conditions, and general accessibility of substrates,[107] while the production of regioisomers and stereoisomers makes it problematic (Scheme 15b).[108] Hydrogen fluoride (HF) is one of the most straightforward, and economic reagents for this type of transformation. The pioneering work of Wade[109] and Laurent[110] demonstrated the use of anhydrous hydrogen fluoride as well as HF-amine reagents[34-35, 44,

[111] to open aziridines (Scheme 15b). However, besides the inconvenient operation of anhydrous hydrogen fluoride, these reaction conditions suffer from moderate to low yields, production of isomeric mixtures, and side products. In addition, bicyclic aziridines usually gave rise to the formation of a mixture of diastereomers. Coutts and co-workers also reported the ring-opening of *N*-tosylaziridines employing pyridine-HF-KF system.[112] However, the yield was not significantly improved under these conditions, and the scope of reactive substrates was limited. Recently, Doyle and co-workers reported opening aziridines with hydrogen fluoride generated from acyl fluoride, but this method only worked well with symmetrical *cis*-2,3-disubsituted aziridines, also required expensive hexafluoroisopropanol as reaction medium.[41-42] Considering all these limitations, there is a keen need of developing a regioselective and stereospecific method to convert aziridines into β-fluoroamines.

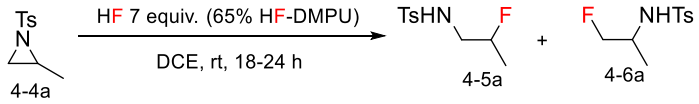
Our previous work with DMPU-HF[113] demonstrated to be an efficient nucleophilic fluorination reagent in gold-catalyzed hydrofluorination of alkynes[114] and fluoro-Prins cyclization reactions.[115] DMPU-HF exhibited high reactivity and less interference to metal catalyst compared to Olah's reagent (pyridine-HF) and triethylamine-HF. The improved reactivity of DMPU-HF drove us to see if it could solve the long-term existing selectivity and efficiency problems in the hydrofluorination of aziridines.

4.2 Results and discussions

Reaction design and optimization

We chose the hydrofluorination of 2-methyl *N*-tosylaziridine **4-1a** as model reaction (Table 12). We found that by treating **4-1a** with 65% DMPU-HF in DCE under room temperature, **4-1a** was regioselectively converted into the desired 2-fluoropropyl-*N*-tosylamine **4-2a** with high yield and conservation of tosyl protective group[116] (Table 11, entry 1). The reaction did not take place in tetrahydrofuran (entry 2), and the addition of scandium triflate significantly reduced the yield (entry 3). No substantial effect was observed when the amount of DMPU-HF was doubled (Table 11, entry 4). Shorter reaction time caused an incomplete conversion, but the material balance remained good (Table 1, entry 5). Elevating the reaction temperature did not reduce yield (Table 11, entry 6). On the other hand, Olah's reagent (65% HF in pyridine) provided an incomplete conversion within the same time frame, and the material balance and regioselectivity were deteriorated (Table 11, entry 7). Another common HF-based reagent, triethylamine trihydrofluoride, gave no reaction at all (Table 11, entry 8). The regioselectivity of aziridine ring opening by DMPU-HF indicated that this process favored an S_N1-like pathway, in which the positive charge was developed on a more substituted carbon. On the contrary, reaction drifted toward an S_N2-like pathway when the less acidic Olah's reagent was used.

Table 12. Development of reaction conditions.

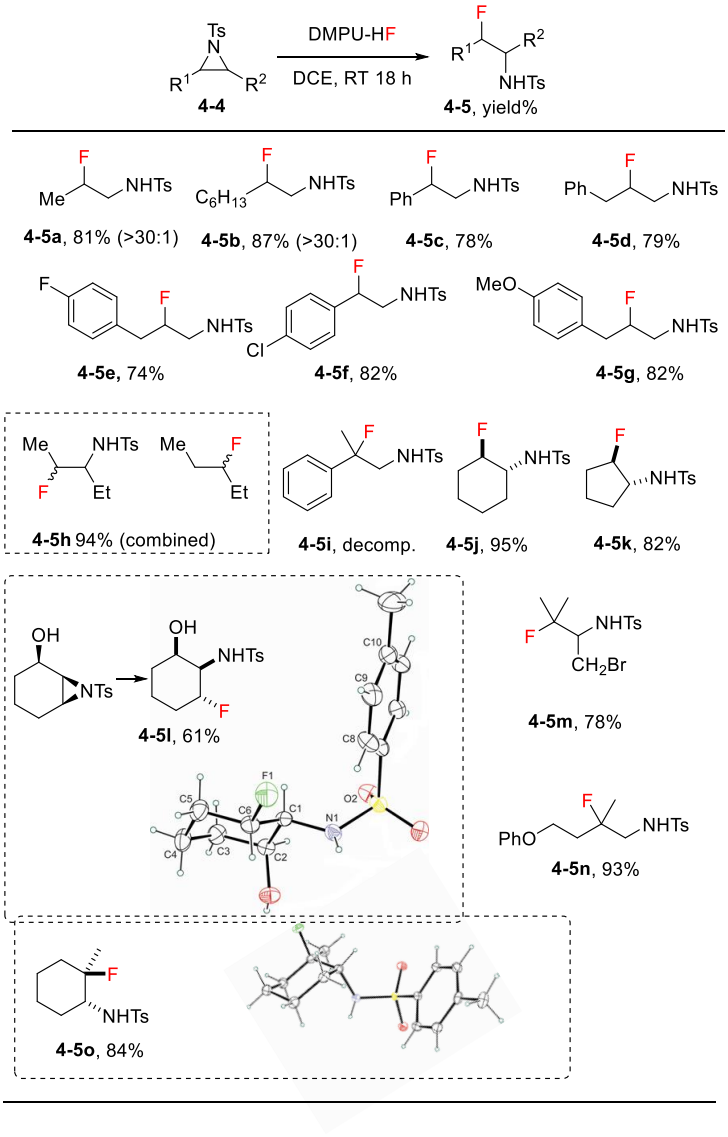


Entry	Variation on standard conditions	Conversion (%)	Yield (%)[b]	Ratio of **4-5a**:**4-6a**[c]
1	None	> 99	93 (87[d])	>30:1
2	THF as solvent	0	N/A	N/A
3	Add 10 mol% of $Sc(OTf)_3$	97	69	>30:1
4	15 equiv of HF	99	86	>30:1
5	9 h	54	43	>30:1
6	55 ℃	> 99[e]	88	>30:1
7	65% HF-Pyridine	85	78	7:1
8	$3HF{\cdot}NEt_3$	0	N/A	N/A

a) Standard reaction conditions: 1 (0.2 mmol), HF 7.5 equiv (65% in DMPU) (1.5 mmol HF) in 0.5 mL of dichloroethane (DCE) at room temperature in a sealed polypropylene vial over for 18 h. b) Determined by ^{19}F NMR using benzotrifluoride as an internal standard. c) Determined by ^{19}F NMR. d) Isolated yield. e) Reaction time was shorten to12 h.

The effectiveness of this method was confirmed by ring opening of various *N*-tosyl aziridines (Scheme 16). Hydrofluorination of the mono alkyl-, aryl-, and benzyl-substituted *N*-tosylaziridines **4-4a**-**4g** occurred at the most substituted carbon, providing primary alkyl amines **4-5a**-**5g** in good yields (Scheme 16). 2-Ethyl-3-methyl-1-tosylaziridine **1h** yielded an inseparable mixture of regioisomers and diastereomers under these conditions (Scheme 16, **4-5h**). *Gem*-disubstituted aziridine **4-4i** decomposed significantly under these conditions, without yielding isolable amounts of product **4-5i**. Cyclic aiziridines **4-4j** and **4-4k** were converted into *trans*-β-fluoroamines **4-5j** and **4-5k** in good yields and diastereoselectivity. Reaction of β-hydroxyl cyclic aziridine **4-4l** took place at less hindered side with the retention of hydroxyl group, and X-ray crystallography confirmed the

configuration of **4-5l**. Trisubstituted aziridines **4-4m** and **4-4n** were fluorinated also at the more substituted carbon in moderate to good efficiency (Scheme 16, **4-5m** and **4-5n**). Bicyclic α-substituted aziridine **4-4o** yielded *trans*-substituted product **4-5o** with the same regioselectivity.

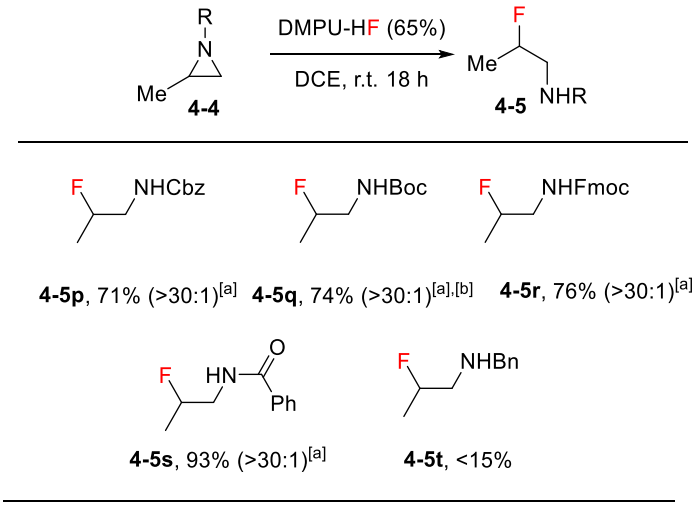


Only major regioisomers are presented. Numbers are isolated yields. Numbers in parenthesis are regioisomeric ratio determined by ^{19}F NMR. Reaction conditions: aziridine 1 (0.5 mmol), 65% DMPU-HF (98 µL, 3.6 mmol HF), DCE (1 mL), room temperature for 18 h.

Scheme 16. Scope of N-tosylaziridines

Next, we tested aziridines with various *N*-protecting groups, see Table 13. Aziridines protected by Fmoc (**44p**), Cbz (**4-4r**) and benzoyl (**4-4s**) groups were well tolerated under reaction conditions, affording the corresponding β-fluoroamines **4-5p**, **4-5r** and **4-5s** in excellent yields and regioselectivity under standard reaction conditions. It should be noted that, in the reaction of **4-4s**, the re-cyclized Heine product,[117] which was the major side product in Laurent's report[110], was not observed at all under our reaction conditions. The acid-sensitive Boc protecting group could be well conserved by limiting reaction time to 20 minutes, while the yield was not reduced (Table 13, **4-5q**).[41] On the contrary, benzyl-protected aziridine **4-4t** was only partially converted into **4-5t** even after extended reaction times Table 13.

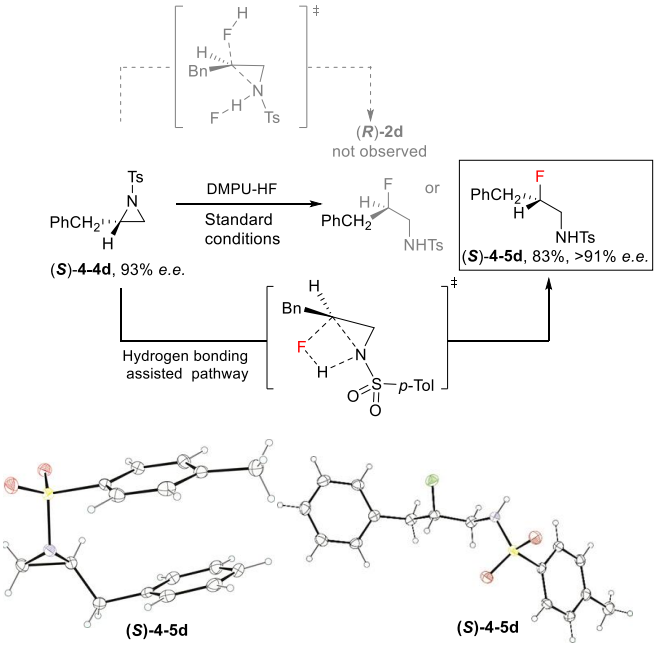
Table 13. Scope of N-protected groups.



Only major regioisomers are presented. Reaction conditions: aziridine 1 (0.5 mmol), 65% DMPU-HF (98 µL, 3.6 mmol HF), DCE (1 mL), room temperature for 18 h, all yields are isolated yields. a) Numbers in parenthesis are regioisomeric ratios as determined by ^{19}F NMR. b) Reaction was quenched after 20 minutes**.**

We also wanted to explore the stereochemical behavior of aziridine ring opening by DMPU-HF.[118] Despite its importance, the absolute stereochemistry of products derived from the acid-catalyzed ring-opening of epoxides or aziridines have not been vigorously

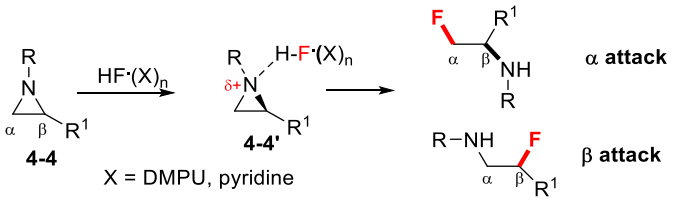
pursued in the literature.[105,108b] We planned to study the stereochemistry of this reaction using optically pure aziridines and determine the product stereochemistry by X-ray crystallography. We subjected enantiomerically pure aziridine **(*S*)-4-4d** to standard reaction conditions, which produced **(*S*)-4-5d** with almost perfect retention of stereoconfiguration (Scheme 17). The retention of stereoconfiguration was further confirmed by the X-ray crystallography of both starting material and product (Scheme 17).



Scheme 17. Stereospecific ring opening of aziridine **(*S*)-4-4d** by HF**.**

The textbook mechanism for acid-catalyzed ring-opening of small ring heterocycles (epoxides and aziridines) is a pathway between the idealized S_N2 and S_N1 mechanisms (eq-2).[119] In the corresponding transition state, part of the S_N1 bond-breaking has already happened, that is, there is significant δ+ character on the carbon being attacked by HF. So the regioselectivity will be determined by carbocation stability (even though a free carbocation does not actually form). The nucleophile (HF) will preferentially attack the more substituted carbon of aziridine. Because a free carbocation does not actually form,

the outcome of nucleophilic displacement will be exclusive inversion of configuration just like with an S_N2 process.[119] Our regioselectivity can be well explained by this mechanism: the nucleophile (HF) always attacks at the more substituted carbon of aziridines (Scheme 16).



Equation 2. Mode of attack of HF on aziridine.

This mechanism can also explain the poor results when pyridine-HF and Et_3N-HF were used. In the case of Et_3N-HF, the acidity of system is low due to the high basicity of Et_3N, so only S_N2 pathway is possible, but HF is a weak nucleophile, which led to no reaction at all (Table 12, entry 7). Pyridine-HF has higher acidity than Et_3N-HF, but still has lower acidity than DMPU-HF. Due to higher acidity of DMPU-HF system, a larger positive charge appears at nitrogen and β-carbon of aziridine at an earlier stage of reaction coordinate (Equation 2). Pyridine-HF based nucleophilic substitution has more tendency for an S_N2 attack on α-carbon of aziridines (Equation 2). This could explain why pyridine-HF system gives a higher ratio of α-attack product (Table 12, entry 8). Of course, the steric factor may also influence the regioselectivity; in our case, HF is a small nucleophile, so the influence of steric factor is relatively small.

For the stereochemical behavior of aziridine ring opening by DMPU-HF, in order to explain the experimental results (Scheme 17), we proposed a different mechanism than the classic mechanism: hydrogen bond-assisted S_N1-like pathway. This mechanism could be rationalized by the fact that HF itself is a very strong hydrogen bonding donor.

But this mechanism failed to explain the reactions of bicyclic aziridines (Scheme 16, **4-5j**, **4-5k**, **4-5e**, **4-5o**). In these cases, *trans* ring opening products were obtained, which indicates inversions of stereoconfiguration. We are not sure about the detailed mechanism yet. The inversions of stereoconfiguration maybe be explained by special conformation of bicyclic aziridines or the cis-products, but more research is needed.[110]

4.3 Regiochemistry of products

The relative chemical shift of ^{19}F NMR spectroscopy is a powerful tool that can be easily used to probe the regioselectivity of products much more than ^{1}H NMR spectroscopy.[120] The wide difference in the chemical shift of the ^{19}F NMR of regioisomers makes it a more reliable tool than the ^{1}H NMR spectra in the determination of regioisomers for similar compounds. For example, the typical ^{19}F NMR chemical shift for primary alkyl fluoride is within the range of -212 to -226 ppm and the chemical shift of the secondary alkyl fluoride for the same compounds have a downfield shift of about +35 ppm from their primary analogue, absorbing at about -177 to -191 ppm. On the other hand the difference in the chemical shift value of the ^{1}H NMR for a primary alkyl fluoride and its secondary analogue is about 0.3 to 0.5 ppm.[120] From these values, the regioselectivity of our products can be easily determined using the ^{19}F NMR spectroscopy.

Aside from comparing our data, which agrees well with literature for most of our compounds, the regioselectivity was reliably determined by a careful analysis of the ^{19}F NMR spectroscopy. As a representative example, the ^{19}F NMR spectrum of the crude **4-2a** is given below.

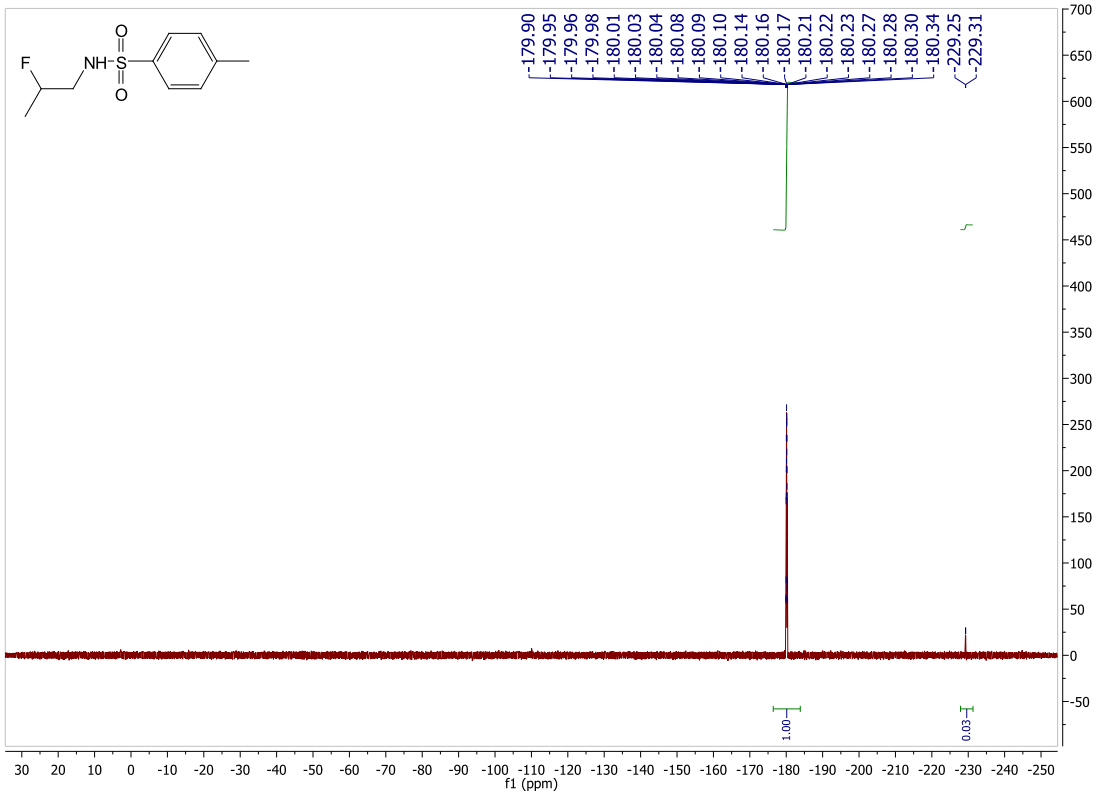


Figure 9. Representative spectrum of the regioisomeric distribution of **4-2a** using ^{19}F NMR

From Figure 9 above, the regioisomeric distribution of the fluorotosyl amine can be easily determined. The major product (secondary alkyl fluoride) has its ^{19}F NMR chemical shift at about -180 ppm and the minor product (primary alkyl fluoride) is -229 ppm respectively. These values compare well with the data earlier discussed as well as what is reported in literature. More so, the ratio of the chemical shifts is an indication of the regioisomeric distribution of the compounds, which in this case is greater than 20:1in favor of the major product for compound **4-2a.**

4.4 Experimental

General Information

NMR spectra were recorded on AV2 400 or AV2 500 MHz Bruker spectrometers. Chemical shifts are given in ppm. The spectra are calibrated to the residual ^{1}H and ^{13}C signals of the solvents. Multiplicities are abbreviated as follows: singlet (s), doublet (d). triplet (t), quartet (q), doublet-doublet (dd), quintet (quint), septet (sept), multiplet (m), and broad (br).

Materials and Methods: Unless otherwise stated, starting materials were purchased from Aldrich and/or Fluka. Substrates **4-1a** through **4-1k** were already reported in the literature. Solvents were purchased in HPLC quality, degassed by purging thoroughly with nitrogen and dried over activated molecular sieves of appropriate size. Alternatively, they were purged with argon and passed through alumina columns in a solvent purification system (Innovative Technology). Conversion was monitored by thin layer chromatography (TLC) using Merck TLC silica gel 60 F254. Compounds were visualized by UV-light at 254 nm and by dipping the plates in a polymoybdenic acid (PMA), p-anisaldehyde, ninhydrinsolutions or an aqueous potassium permanganate solution followed by heating depending on the compounds formed. Chloramine-T trihydrate (98%), phenyltrimethylammonium tribromide, (97%) and *S*-benzyltosyl aziridine (93%) were purchased from Sigma-Aldrich and used without further purification (unless otherwise stated).

Synthesis and Characterization of Aziridines:

2-Methyl-1-tosylaziridine (4-1a)

2-methylaziridine (790µL, 10mmole) was added to a biphasic mixture of EtOAc (15mL) and 1M k_2CO_3 (15mL) at 0˚C. Under vigorous stirring, the solution of 4-methylbenzenesulfonyl chloride (1.91g, 10mmol) in EtOAc (15mL) was added dropwise. After 1 h the reaction was allowed to reach ambient temperature and stirred for another 12 h. The phases were separated and the organic phase was washed with water, dried over Na_2SO_4 and concentrated. The crude white solid need no further purification and gave 98% yield. This compound is known[107a] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.80 (m, 2H), 7.36-7.31 (m, 2H), 2.83 (dqd, J = 6.9, 5.6, 4.6 Hz, 1H), 2.61 (d, J = 7.0 Hz, 1H), 2.44 (s, 3H), 2.02 (d, J = 4.6 Hz, 1H), 1.25 (d, J= 5.6 Hz, 3H)

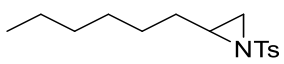
Aziridines **4-1b** through **4-1o** were made from a modified procedure by Sharpless:

The product was synthesized following the method described by Jamison below [107a]:

To a mixture of Chloramine-T trihydrate (1.55 g, 5.5 mmol) and alkene (5.0 mmol) in CH_3CN (25 mL) at ambient temperature was added $PhNMe_3Br_3$ (188.0 mg, 0.50 mmol). The reaction was stirred vigorously for 15 h and then concentrated in vacuo. The resulting residue was dissolved in CH_2Cl_2 (5-10 mL) and filtered through a short column (silica gel, 3 x 4 cm) eluting with (150 mL of a 1:9 EtOAc/hexane mixture). After evaporation of the solvent, the residue was dissolved in CH_3CN (10 mL). K_2CO_3 (2.77 g, 20.0 mmol) was added and the mixture was stirred vigorously at 45 °C for 2 h. After cooling to ambient temperature, the mixture was diluted with Et_2O (20 mL), filtered of Celite (washing with

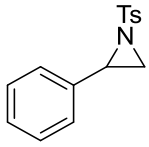
Et_2O) and concentrated. The crude product was subjected to column chromatography on silica gel (7:1 Hex:EtOAc).

2-Hexyl-1-tosylaziridine (4-4b)



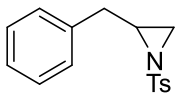
Following the general procedure starting from 1-octene (5.0 mmol, 785µL), **4-4b** was isolated by column chromatography on silica gel (Hex/EtOAc, 7:1) in 76% yield as a colorless gel to white solid. This compound is known.[121] ^{1}H NMR ($CDCl_3$, 400 MHz), δ 0.85 (t, 3H, J = 6.8 Hz), 1.18-1.37 (m, 9H), 1.51-1.58 (m, 1H), 2.06 (d, 1H,J= 4.6 Hz),2.44 (s, 3H), 2.64(d, 1H,J= 7.0 Hz), 2.66-2.71 (m, 1H), 7.33 (d, 2H,J=8.4 Hz), 7.82 (d, 2H, J= 8.4 Hz).

2-Phenyl-1-tosylaziridine (4-4c)



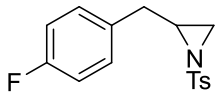
Following the general procedure starting from styrene (5.0 mmol, 573µL), **4-4c** was isolated by column chromatography on silica gel (Hex/EtOAc, 7:1) in 62% yield faint yellow powder. This compound is known.[121] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.38 (d, 1H, J = 4.6 Hz), 2.43 (s, 3H,), 2.98 (d, 1H, J = 7.3 Hz), 3.77 (dd, 1H, J = 4.6, 7.3 Hz), 7.19-7.36 (m, 7H), 7.86 (d, 2H, J = 8.2 Hz).

2-Benzyl-1-tosylaziridine (4-4d)



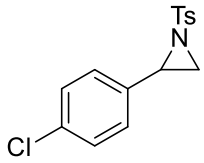
Following the general procedure starting from allylbenzene (5.0 mmol, 591µL), **4-4d** was isolated by column chromatography on silica gel (Hex/EtOAc, 7:1) in 58% yellow solid. This compound is known.[107a] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.66 (m,2H), 7.24–.19 (m,2H), 7.18–7.12 (m,3H),7.07–7.02 (m,2H), 2.95(tdd,J= 7.0, 5.2, 4.6 Hz, 1H), 2.81 (dd,J= 14.5, 5.2Hz,1H), 2.71 (d,J= 6.9 Hz, 1H),2.69 (dd,J= 14.6, 7.2 Hz,1H),2.42 (s,3H), 2.16 (d,J= 4.5 Hz, 1H)

2-(4-Fluorobenzyl)-1-tosylaziridine (4-4e)



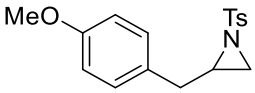
Following the general procedure starting from 1-allyl-4-fluorobenzene (5.0 mmol, 591µL), **4-4e** was isolated by column chromatography on silica gel (Hex/EtOAc, 7:1) in 58% yellow solid. This compound is known.[107a] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.61 (m,2H), 7.20 (app d, J= 8.2 Hz,2H), 7.00–6.93(m,2H), 6.82–6.76 (m ,2H), 2.92–2.82 (m, 2H), 2.74 (d, J= 6.6 Hz, 1H), 2.56–2.48 (m, 1H), 2.43 (s, 3H), 2.16 (d, J = 4.3 Hz,1H)

2-(4-Chlorophenyl)-1-tosylaziridine (4-4f)

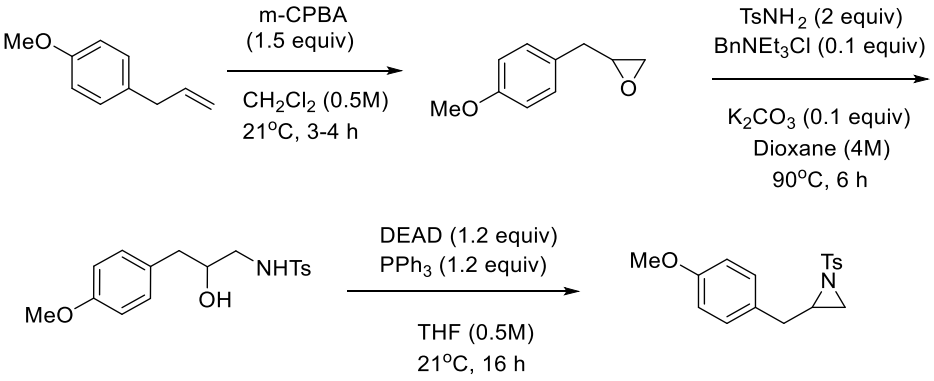


Following the general procedure starting from 1-chloro-4-vinylbenzene (5.0 mmol, 637µL), **4-4f** was isolated by column chromatography on silica gel (Hex/EtOAc, 7:1) in 58% yellow solid. This compound is known.[122] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86 (d, 2H, J = 8.3 Hz), 7.34 (2H, J = 8.0 Hz), 7.26 (d, 2H, J = 8.2), 7.14 (d, 2H, J = 7.8), 3.73 (m, 1H), 2.98 (m, 1H, J = 7.2), 2.44 (s, 3H, Ar-CH3), 2.35 (s, J = 4.3 Hz).

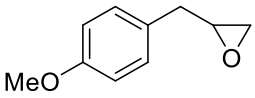
2-(4-Methoxybenzyl)-1-tosylaziridine (4-4g)



The general procedure failed in this case so an alternate procedure according to literature[107a] was employed as follows



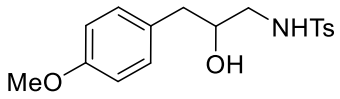
2-(4-Methoxybenzyl)oxirane (4-4ga)



A solution of 1-allyl-4-methoxybenzene (50.0 mmol, 7.41 g) in CH_2Cl_2 (75 mL) in a 250 mL round bottom flask was cooled to 0oC with an ice bath, m-chloroperbenzoic acid (12.1 g, 50 mmol) was added portion wise over 10 minutes. The mixture was allowed to warm to ambient temperature and then stirred until TLC indicated complete consumption of the starting material (*ca* 4 h). If complete conversion is not obtained within 2 h, an additional portion of m-CPBA (*ca* 3 g) may be added and the mixture stirred an additional 2 h. After completion, saturated aqueous $NaHCO_3$ (75 mL) was slowly added and the mixture was stirred vigorously until gas evolution had ceased, after which the mixture was poured into a separatory funnel. The organic layer was separated and washed with 1M aq. Sodium

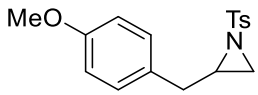
sulfite, once with brine and then dried over Na_2SO_4. After removal of the solvent by rotary evaporation, the crude product was purified by chromatography on silica gel (hex/EtOAc 7:1) to afford the desired product **4-4ga** in 92 % as a colorless liquid.

N-(2-Hydroxy-3-(4-methoxyphenyl)propyl)-4-methylbenzenesulfonamide (4-4gb)



An oven-dried round bottom flask equipped with a magnetic stir bar was charged with epoxide **4-4ga** (24.4 mmol, 4 g), 4-methylbenzenesulfonamide (48.8 mmol, 8.36 g), K_2CO_3 (2.4 mmol, 0.337 g), $BnNEt_3Cl$ (2.4 mmol, 0.556 g), and anhydrous dioxane (5.0 mL). The flask was fitted with a reflux condenser and the mixture was heated to 90 °C.When complete consumption of the starting material was indicated by TLC after approximately 5 hours, the mixture was cooled to ambient temperature, diluted with CH_2Cl_2 (30 mL) and then filtered through a 2 cm pad of Celite, which was thoroughly washed with CH_2Cl_2 (100 mL). Purification by flash chromatography on silica gel (EtOAc/hexane, gradient, 100 to 4:1) yielded the product **4-4gb** as a white solid quantitavely. The product contains small amount of the $TsNH_2$ from ^1H NMR.

2-(4-Methoxybenzyl)-1-tosylaziridine (4-4g)

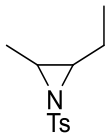


To a dry 250 mL round bottom flask containing a magnetic stir bar was added **4-4gb** (25 mmol, 2.0 g) and PPh_3 (29.5 mmol, 7.74 g). The flask was fitted with a rubber septum, purged with argon and then THF (50.0 mL) was added. The flask was cooled to 0°C with an ice bath and diethyl azodicarboxylate (DEAD) (29.5 mmol, 5.137 g, 4.65 mL) was

added drop-wise over a period of 10 minutes, after which the ice bath was removed and the mixture was allowed to stir at ambient temperature for 16 h. The reaction mixture was evaporated under reduced pressure. Et_2O (200 mL) was added and the reaction was stirred for 20 minutes. The solids were removed by filtration through a 3cm pad of Celite, washing with Et_2O, and the filtrate was concentrated by rotary evaporation. This crude oil so obtained was chromatographed on silica gel (EtOAc/hexane, gradient 20:80 to 45:55), which yielded the desired aziridine as a white solid 57 %. If necessary, recrystallization from hexanes/ethanol can also be carried out.

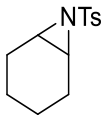
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 –7.66 (m, 2H), 7.25–7.19 (m, 2H), 6.98–6.92 (m, 2H), 6.71–6.65 (m, 2H), 3.77 (s, 3H), 2.91 (tt, J = 7.1, 4.8 Hz, 1H), 2.77 (dd, J = 14.5, 5.1 Hz, 1H), 2.70 (d, J= 6.9 Hz, 1H,), 2.61 (dd, J = 14.5, 7.2 Hz, 1H), 2.43 (s, 3H), 2.14 (d, J= 4.6 Hz, 1H,).

2-Ethyl-3-methyl-1-tosylaziridine (4-4h)



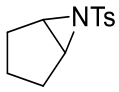
Following the general procedure starting from (5.0 mmol, 547 µL), **4-4h** was isolated by column chromatography on silica gel (Hex/EtOAc, 7:1) in 84% yield as a white solid. This compound is known.[123] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81 (t, *J*=7.7, 2H), 7.28 (dd, *J*=17.2, 9.1, 1H), 2.98 – 2.81 (m, 2H), 2.81 – 2.52 (m, 1H), 2.41 (d, *J*=3.3, 1H), 1.18 (d, *J*=5.9, 3H), 0.83 (t, *J*=7.4, 3H).

7-Tosyl-7-azabicyclo[4.1.0]heptane (4-4i)



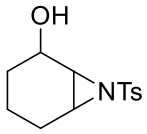
Following the general procedure starting from cyclohexene (5.0 mmol, 507 µL), **4-4i** was isolated by column chromatography on silica gel (Hex/EtOAc, 7:1) in 84% yield as a white solid. This compound is known.[121] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.14-1.21 (m, 2H), 1.25-1.47 (m, 2H), 1.79 (dt, 4H, J = 1.4, 5.8 Hz), 2.44 (s, 3H), 2.97 (t, 2H, J = 1.4 Hz), 7.32 (d, 2H, J = 8.1 Hz), 7.81(d, 2H, J = 8.1 Hz).

6-Tosyl-6-azabicyclo[3.1.0]hexane (4-4j)



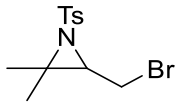
Following the general procedure starting from cyclohexene (5.0 mmol, 442 µL), **4-4j** was isolated by column chromatography on silica gel (Hex/EtOAc, 7:1) in 84% yield as a white solid. This compound is known.[121] ^{1}HNMR ($CDCl_3$, 400MHz) δ 7.80 (d, J =8.3Hz, 2H), 7.31(d, J =8.0Hz, 2H), 3.32 (s, 2H), 2.59 (s, 3H), 1.89-1.96 (m, 2H), 1.52-1.65 (m,3H), 1.33-1.43 (m,1H)

***Syn*-7-Tosyl-7-azabicyclo[4.1.0]heptan-2-ol (4-4k)**



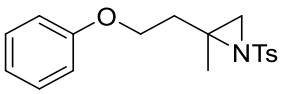
Following the general procedure starting from cyclohex-2-enol (5.0 mmol, 491µL), **4-4k** was isolated by column chromatography on silica gel (Hex/EtOAc, 7:1) in 31% yield colorless oil. This compound is known.[107b] ^{1}H NMR ($CDCl_3$, 400MHz) δ 7.82 (d, J = 8.4Hz, 2H), 7.33 (d, J = 8.1Hz, 2H), 3.93 (brs, 1H), 3.18 (m, 2H), 2.43 (s, 3H) 1.80-1.15 (m, 7H)

3-(Bromomethyl)-2,2-dimethyl-1-tosylaziridine (4-4l)

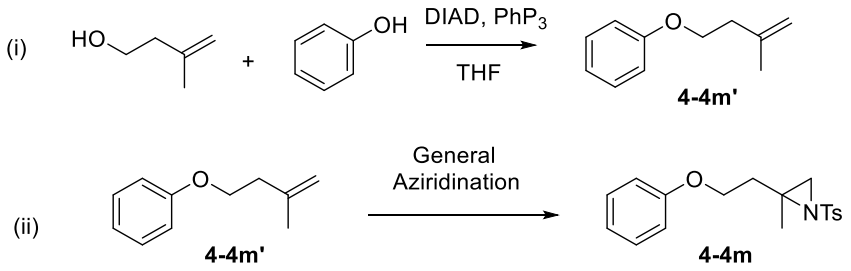


Following the general procedure starting from 1-bromo-3-mthyl-2-butene (5.0 mmol, 578 µL), **4-4l** was isolated by column chromatography on silica gel (Hex/EtOAc, 7:1) in 76% yield as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81 (d, *J*=8.2, 2H), 7.32 (d, *J*=8.0, 2H), 3.09 (dd, *J*=7.0, 4.5, 1H), 2.67 (d, *J*=6.9, 3H), 2.41 (d, *J*=7.0, 1H), 2.35 (d, *J*=4.4, 1H), 1.59 – 1.49 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 144.89, 134.37, 129.77, 129.69, 128.37, 128.29, 59.75, 48.50, 31.76, 31.56, 28.85, 21.67. m/z = 318.22 ($[M]^+$). ESI HRMS: calcd. for $C_{18}H_{22}NO_3S^+$ ($[M+H]^+$) 318.0158; found 318.0157.

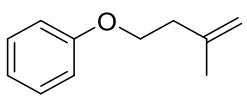
2-Methyl-2-(2-phenoxyethyl)-1-tosylaziridine (4-4m)



4m was prepared following the general aziridination procedure of the corresponding alkene **4m'**



((3-Methylbut-3-en-1-yl)oxy)benzene (4-4m')

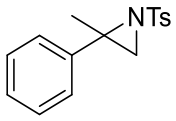


To a stirred solution of 3-methyl-3-buten-1-ol (5.8mmol) in tetrahydrofuran (15 ml) were added sequentially phenol (0.66 g), triphenylphosphine (1.92 g) and diisopropyl

azodicarboxylate (1.45 g). The mixture was heated at 70° C. overnight and then was concentrated in vacuo. The residue was purified by column chromatography (SiO_2; gradient: hexane/EtOAc100:0->70:30) to give (3-methyl-but-3-enyloxy)-benzene in 53 %, which agrees well with the literature.[124] ^{1}H NMR ($CDCl_3$, 400MHz) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 – 7.16 (m, 2H), 7.03 – 6.83 (m, 3H), 4.83 (dd, *J*=16.0, 0.7, 2H), 4.20 – 3.97 (m, 2H), 2.51 (t, *J*=6.9, 2H), 1.81 (d, *J*=0.4, 3H).

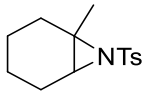
2-Methyl-2-(2-phenoxyethyl)-1-tosylaziridine (4-4m): Following the general procedure for tosyl aziridination starting from the corresponding phenoxy alkene (4-4m', 498 mg), 4-4m was isolated in 85% yield as a colorless liquid. ^{1}H NMR ($CDCl_3$, 400MHz) ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81 (t, *J*=16.3, 2H), 7.36 – 7.14 (m, 4H), 7.00 – 6.90 (m, 1H), 6.90 – 6.79 (m, 1H), 4.13 – 3.97 (m, 2H), 2.65 (d, *J*=13.5, 1H), 2.45 (s, 1H), 2.41 (s, 3H), 2.29 – 2.17 (m, 1H), 2.06 (dt, *J*=14.3, 5.8, 1H), 1.73 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.48, 143.92, 137.75, 129.52, 129.46, 127.35, 120.84, 114.43, 77.43, 77.11, 76.79, 64.48, 48.74, 41.38, 37.03, 21.59, 21.57, 19.12. m/z= 332.1315 ($[M]^+$). ESI HRMS: calcd. for $C_{18}H_{22}NO_3S^+$ ($[M+H]^+$) 280.1338; found 332.1312

2-Methyl-2-phenyl-1-tosylaziridine (4-4n)



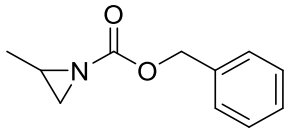
Following the general procedure starting with alpha-methylstyrene (5 mmol, 655 µL), the corresponding aziridine was isolated in 77% yield as a white solid. This compound is known[125] (Unstable, decomposes over the bench after 24h. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.29 – 8.98 (m, 2H), 7.86 (d, J=8.3, 2H), 7.36 (d, J=8.0, 2H), 7.33 – 7.26 (m, 3H), 2.95 (s, 1H), 2.51 (s, 1H), 2.42 (s, 3H), 2.04 (s, 3H).

1-Methyl-7-tosyl-7-azabicyclo[4.1.0]heptane (4-4o)



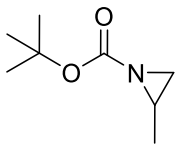
Following the general procedure starting with methylcyclohexene (5 mmol, 600 µL), the corresponding aziridine was isolated in 65% yield as a white solid. This compound is known.[121] ^{1}H NMR (400 MHz, CDCl3):δ 7.81 (2H, d, J = 8.0Hz), 7.29 (2H, d, J = 8.0Hz), 3.04 (1H, d, J = 5.6Hz), 2.41(3H, s), 2.01 – 2.07(1H, m), 1.77 – 1.86 (1H, m), 1.70(3H, s), 1.48 – 1.59(2H, m), 1.29 – 1.44 (3H, m), 1.12 – 1.27(1H, m).

Benzyl 2-methylaziridine-1-carboxylate (4-4p)



2-Methyl aziridine is dissolved in CH_2Cl_2 and triethylamine under argon at 0° C. Benzylchloroformate is added and the contents of the flask are at room temperature overnight. The mixture is poured into 10% citric acid and is extracted with $CHCl_3$. The organic layer is washed with dilute aqueous $NaHCO_3$ and dried over Na_2SO_4. The solution is evaporated to yield N-Cbz-2-methyl aziridine (71% colorless oil).[126] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.27 (m, 5H), 5.12 (s, 2H), 2.59 – 2.46 (m, 1H), 2.33 (d, *J* = 5.8 Hz, 1H),1.99–1.92(m,1H),1.27(d,*J*=5.5Hz,3H).

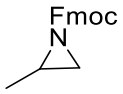
tert-Butyl 2-methylaziridine-1-carboxylate (4-4q)



2-methylaziridine (353µL, 5mmole) was added to a biphasic mixture of dioxane (10mL) and 2 equivalent of $NaHCO_3$ (252 mg) in water (10mL). Under vigorous stirring, the

solution of Boc anhydride (1.148µL, 5mmol) in dioxane (10mL) was added dropwise. The reaction was stirred for 18 h, after which the phases were separated and the organic phase was washed with water, dried over Na_2SO_4 and concentrated. The crude product was chromatographed on silica gel using Hexane: ethylacetate mixture (5:1) to afford the pure colorless oil in 89% yield. This compound is known.[127] ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.45-2.35 (m, 1H), 2.20 (d, J=5.9 Hz, 1H), 1.84 (d, J=3.7 Hz, 1H), 1.42 (s, 9H), 1.23 (d, J=5.9 Hz, 3H).

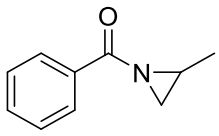
(9H-Fluoren-9-yl) methyl 2-methylaziridine-1-carboxylate (4-4r)



2-methylaziridine (353µL, 5mmole) was added to a biphasic mixture of EtOAc (10mL) and 4 equivalent of K_2CO_3 (2.764g) in water (10mL). Under vigorous stirring, the solution of fluorenylmethyloxycarbonyl chloride (1.293g, 5mmol) in EtOAc (10mL) was added dropwise. The reaction was stirred for 18 h, after which the phases were separated and the organic phase was washed with water and dried over Na_2SO_4, filtered and concentrated. The product a yellow oil (94%) needed no further purification.

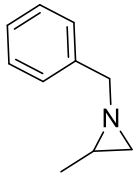
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.5 Hz, 2H), 7.62 (d, *J* = 7.3 Hz, 2H), 7.40 (t, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 4.42 (d, *J* = 7.0 Hz, 2H), 4.24 (t, *J* = 6.7 Hz, 1H), 2.45 (s, 1H), 2.28 (d, *J* = 5.7 Hz, 1H), 1.95 (s, 1H), 1.57 (s, 1H), 1.27 (d, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.64, 141.32, 137.33, 127.76, 127.06, 125.08, 119.96, 67.97, 60.37, 46.99, 33.84, 32.59, 21.04, 17.37, 14.18. : m/z= 279.13 ($[M]^+$). ESI HRMS: calcd. for $C_{18}H_{18}NO_2H^+$ ($[M+H]^+$) 280.1338; found 280.1336

(2-Methylaziridin-1-yl)(phenyl)methanone (4-4s)



2-Methyl aziridine (10mmol) is dissolved in CH_2Cl_2 and trimethylamine (2 equiv.) under argon at 0° C. Benzoylchloride (10.5mmol) is added and the contents of the flask are at room temperature overnight. The mixture is poured into 10% citric acid and is extracted with $CHCl_3$. The organic layer is washed with dilute aqueous $NaHCO_3$ and dried over Na_2SO_4. The solution is evaporated to yield N-Bn-2-methyl aziridine. (59 % colorless oil) This compound is known[117] ^{1}H NMR ($CDCl_3$, 400MHz): δ 8.03 (m, 2H), 7.55 (m, 1H), 7.46 (m, 2H), 2.58 (m, 1H), 2.55 (d, J = 5.6 Hz, 1H), 2.15 (d, J = 3.6 Hz, 1H), 1.40 (d, J = 5.6 Hz, 3H).

1-Benzyl-2-methylaziridine (4-4t)



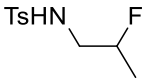
2-Methyl aziridine (10mmol) is dissolved in CH_2Cl_2 and trimethylamine (2 equiv) under argon at 0° C. Benzylchloride (10.5mmol) is added and the contents of the flask are at room temperature overnight. The mixture is poured into 10% citric acid and is extracted with $CHCl_3$. The organic layer is washed with dilute aqueous $NaHCO_3$ and dried over Na_2SO_4. The solution is evaporated to yield N-Bn-2-methyl aziridine. (41% yellow oil). This compound is known[128] ^{1}H NMR ($CDC1_3$) δ 1.20 (d, J = 5.4Hz, 3H), 1.37 (d, J = 6.3Hz,

1H), 1.49-.54(m, 1H), 1.57 (d, J = 3.6Hz, 1H), 3.39 (d, J = 13.8Hz, 1H), 3.46 (d, J = 13.5Hz, 1H), 7.24-7.36 (m, 5H)

General procedure for the hydrofluorination of aziridines

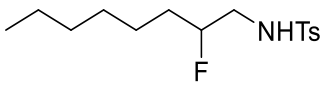
In a 20 mL polyethylene vial charged with a magnetic stirrer 0.5 mmole of the aziridine is dissolved in 1.5 mL of dichloroethane. 98 µL of DMPU-HF (65%) was then pipetted into the mixture and the reaction was heated at 55 °C for 18 h. The reaction was quenched with $NaHCO_3$ and the mixture was separated with DCM, washed with brine and the organic layer was dried over Na_2SO_4, concentrated under reduced pressure and chromatographed with silica gel using a mixture of Hexane:EtOAc (7:1) to afford the corresponding fluorinated product.

N-(2-Fluoropropyl)-4-methylbenzenesulfonamide (4-5a)



The product was prepared from 2-methyl-1-tosylaziridine according to the general procedure to afford the title compound in 81% yield, as yellow oil. The major product was isolated in a 47:1 ratio as judged by ^{19}F NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.0 Hz, 2H), 7.31 (d, *J* = 7.8 Hz, 2H), 4.83 (s, 1H), 4.79 – 4.56 (m, 1H), 3.35 (d, *J* = 1.2 Hz, 1H), 3.29 – 2.90 (m, 1H), 2.42 (s, 3H), 1.28 (ddd, *J* = 24.0, 6.4, 1.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.61, 136.89, 129.77, 126.98, 89.15 (d, *J* = 167.5), 60.34, 48.14 (d, *J* = 21.3 Hz), 21.48, 20.98, 18.06 (d, *J* = 21.8 Hz), 14.16. ^{19}F NMR (376 MHz, $CDCl_3$) δ -155.24 – -192.00 (m, 1F), -229.28 (d, *J* = 21.9 Hz, 1F). MS: m/z = 231.1[M] $^{+}$. HRMS: calcd. For $C_{10}H_{15}FNO_2SH^{+}$ = 232.0808; found 232.0806.

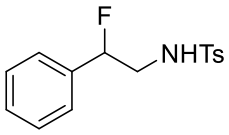
N-(2-Fluorooctyl)-4-methylbenzenesulfonamide (4-5b)



Major isomer isolated

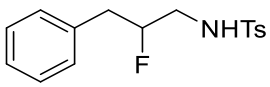
This compound is known.[129] The major product was prepared from the 1-octene-tosylaziridine according to the general procedure to afford the title compound over 30:1 ratio as determined by ^{19}F NMR, 87%, white solid. Major isomer, ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C) δ 186.3 (m, 1F) Minor ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C) δ 230.9 (m, 1F).

N-(2-Fluoro-2-phenylethyl)-4-methylbenzenesulfonamide (4-5c)



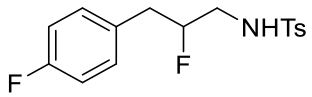
This compound is known.[130] The product was prepared from 2-phenyl-1-tosylaziridine according to the general procedure to afford the title compound in 79% yield, as yellow oil and the only product. ^1H NMR (400MHz, $CDCl_3$) δ 7 65 (d, J = 8.0 Hz, 2H), 7.29–7.14 (m, 7H), 5.38 (ddd, J = 48.1, 8.3, 3.4 Hz, 1H), 5.16 (dd, J = 7.8, 4.8 Hz, 1H), 3.32–3.17 (m, 2H), 2.31 (s, 3H).

N-(2-Fluoro-3-phenylpropyl)-4-methylbenzenesulfonamide (4-5d)



This compound is known.[129] The product was prepared from 2-benzyl-1-tosylaziridine according to the general procedure to afford the title compound in 79% yield, as a light yellow solid. ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C) δ 184.6 (m, 1F).

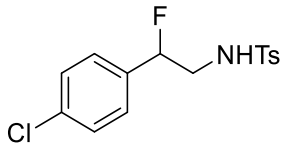
N-(2-Fluoro-3-(4-fluorophenyl)propyl)-4-methylbenzenesulfonamide (4-5e)



The product was prepared from 2-(4-fluorobenzyl)-1-tosylaziridine according to the general procedure to afford the title compound in 74% yield, as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.11 (dd, *J* = 8.5, 5.4 Hz, 2H), 6.98 (t, *J* = 8.7 Hz, 2H), 4.79 – 4.69 (m, 1H), 4.62 (ddd, *J* = 12.6, 7.1, 3.3 Hz, 1H), 3.29 – 3.13 (m, 1H), 3.13 – 2.98 (m, 1H), 2.98 – 2.79 (m, 2H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.78, 136.59, 130.76 (d, *J* = 8.0Hz) 129.84, 127.01, 115.49 (d, *J* = 21.4 Hz, 92.58 (d, *J* = 174.1 Hz, 46.02 (d, *J* = 21.3 Hz), 37.64 (d, *J* = 21.0 Hz) 21.53. ^{19}F NMR (376 MHz, $CDCl_3$) δ -103.56 – -125.42 (m, 1F), -185.09 (ddd, *J* = 43.4, 31.9, 12.6 Hz, 1F). MS: m/z = 325.09 $[M]^+$. HRMS: calcd. For $C_{16}H_{17}F_2NSO_2Na^+$= 348.0840; found 348.0840, cald. For $C_{16}H_{18}F_2NSO_2^+$= 326.1021; found 326.1021.

N-(2-(4-Chlorophenyl)-2-fluoroethyl)-4-methylbenzenesulfonamide (4-5f)

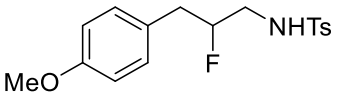


The product was prepared from 2-(4-chlorophenyl)-1-tosylaziridine according to the general procedure to afford the title compound in 82% yield, as a light yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.1 Hz, 2H), 7.31 (t, *J* = 8.1 Hz, 4H), 7.18 (d, *J* = 8.2 Hz, 2H), 5.48 (ddd, *J* = 47.5, 8.1, 3.4 Hz, 1H), 4.83 (s, 1H), 3.54 – 3.01 (m, 1H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.82, 134.98, 134.92, 134.72, 129.83, 129.72, 128.91, 128.81, 128.05, 127.13, 126.97, 126.89, 126.82, 92.06 (d, *J* = 174.6 Hz), 48.42 (d,

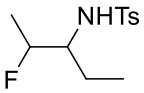
J = 25.0 Hz, 2H). 47.37, 21.53 ^{19}F NMR (376 MHz, $CDCl_3$) δ -183.4 (m, 1F). MS: m/z = 327.05 $[M]^+$. HRMS: calcd. For $C_{15}H_{15}ClNNaSO_2Na^+$= 350.0388; found 350.0390, cald. For $C_{16}H_{16}ClNSO_2^+$= 328.0569; found 328.0571.

N-(2-Fluoro-3-(4-methoxyphenyl)propyl)-4-methylbenzenesulfonamide (4-5g)



The product was prepared from 2-(4-methoxybenzyl)-1-tosylaziridine according to the general procedure to afford the title compound in 82% yield, as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.06 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 4.77 – 4.64 (m, 1H), 4.59 (dd, *J* = 6.8, 2.8 Hz, 1H), 3.79 (s, 3H), 3.30 – 3.13 (m, 1H), 3.12 – 2.99 (m, 1H), 2.97 – 2.74 (m, 2H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.70, 125.29, 92.82 (d, *J* = 173.3) 55.24, 46.06 (d, *J* = 21.0 H), 37.64 (d, *J* = 21.0 Hz), 21.53 ^{19}F NMR (376 MHz, $CDCl_3$) δ -170.97 – -206.82 (m, 1F). MS: m/z = 337.1$[M]^+$. HRMS: calcd. For $C_{17}H_{20}FNSO_3Na^+$ = 360.1040; found 360.1040, cald. For $C_{17}H_{21}FNSO_3^+$ = 338.1221; found 337.1220.

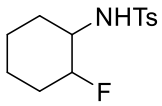
N-(2-Fluoropentan-3-yl)-4-methylbenzenesulfonamide (4-5h)



The product was prepared from 2-ethyl-3-methyl-1-tosylaziridine according to the general procedure to afford mixtures of the title compound in 94% yield, as a yellow oil.^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 (d, J=8.2, 2H), 7.28 (dd, J=14.2, 6.3, 2H), 4.86 (dd, J=17.6, 9.3, 1H), 4.74 – 4.08 (m, 1H), 3.52 – 3.09 (m, 1H), 2.41 (s, 3H), 1.68 – 1.49 (m, 1H), 1.40 (ddd, J=21.8, 10.7, 5.9, 1H), 1.28 – 0.98 (m, 3H), 0.96 – 0.72 (m, 3H). ^{13}C NMR (100

MHz, $CDCl_3$) δ = 143.45, 143.33, 138.25, 138.11, 129.73, 129.67, 129.60, 126.95, 126.92, 98.06, 96.32, 92.33, 90.62, 58.96, 58.75, 52.03, 51.81, 24.77, 24.61, 24.40, 21.86, 21.81, 21.50, 17.32, 17.13, 16.91, 14.76, 14.71, 10.15, 9.94, 9.54, 9.49. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -185.12 – -188.99 (m, 1F), -193.86 – -198.22 (m, 1F) MS: m/z = 259.1$[M]^+$. HRMS: calcd. For $C_{12}H_{18}FNSO_2Na^+$ = 282.0934; found 282.093, cald. For $C_{17}H_{19}FNSO_2^+$= 260.1115; found 260.1111.

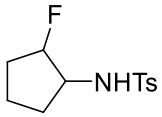
N-(2-Fluorocyclohexyl)-4-methylbenzenesulfonamide (4-5i)



This compound is known.[130] The product was prepared from the cyclohexyl-tosylaziridine according to the general procedure to afford the title compound, 95% yield, white solid.

^1H NMR (400 MHz, $CDCl_3$) δ 1.13-1.29 (m, 4H), 1.32-1.52 (m, 1H), 1.71-1.76(m, 1H), 2.04-2.15 (m, 2H),3.20-3.28 (m, 1H), 4.21 (dddd $^2J_{H-F}$ 50.1 Hz, $^3J_{H-H}$ 9.9, 9.0, 4.5 Hz, 1H), 4.90 (d, J)5.7Hz, 1H), 7.51-7.60 (m, 3H),7.90-7.93 (m, 2H).

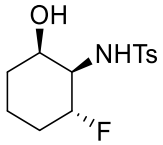
N-(2-Fluorocyclopentyl)-4-methylbenzenesulfonamide (4-5j)



This compound is known.[130] The product was prepared from the cyclopentyl-tosylaziridine according to the general procedure to afford the title compound, 83% yield, white powder.

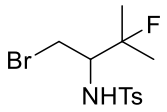
^1H NMR (400 MHz, $CDCl_3$) δ 1.35-1.42 (m, 1H), 1.61-2.09 (m, 5H), 2.41 (s, 3H), 3.56-3.68 (m, 1H), 4.71(d, J) 6.1 Hz, 1H), 4.78 and 4.96 (double multiplet, $^2J_{H-F}$) 51.9 Hz, 1H), 7.32 (d, J) 7.5 Hz, 2H), 7.78 (d, J)7.6 Hz, 2H

N-((1S, 2R, 3R)-2-Fluoro-3-hydroxycyclohexyl)-4-methylbenzenesulfonamide (4-5k)



The product was prepared from syn-7-tosyl-7-azabicyclo[4.1.0]heptan-2-ol according to the general procedure to afford the title compound in 61% yield, as a white solid. The structure of this compound is also confirmed by X-Ray crystallography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 5.08 (d, *J* = 5.4 Hz, 1H), 4.57 (dtd, *J* = 50.0, 9.5, 4.6 Hz, 1H), 4.22 (s, 1H), 3.17 (tdd, *J* = 8.9, 5.6, 3.2 Hz, 1H), 2.43 (s, 3H), 2.20 – 1.96 (m, 2H), 1.85 – 1.33 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.63, 136.72, 129.65, 127.21, 90.58 (d, *J* = 176.1 Hz,) 69.12 (d, *J* = 6.5 Hz), 59.68 (d, *J* = 18.1 Hz), 36.44, 26.29, 21.55, 17.44 (d, *J* = 9.8 Hz), 14.17. ^{19}F NMR (376 MHz, $CDCl_3$) δ -186.52 (d, *J* = 48.9 Hz, 1F). MS: m/z = 287.1 $[M]^+$. HRMS: calcd. For $C_{13}H_{18}FNSO_3Na^+$= 310.0884; found 310.0884, cald. For $C_{13}H_{19}FNSO_3^+$= 288.1064; found 288.1064.

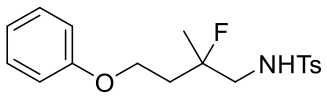
N-(1-Bromo-3-fluoro-3-methylbutan-2-yl)-4-methylbenzenesulfonamide (4-5l)



The product was prepared from 3-(bromomethyl)-2,2-dimethyl-1-tosylaziridine according to the general procedure to afford the title compound in 78% yield, as a viscous colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 (d, J=8.3, 2H), 7.47 – 7.31 (m, 2H), 4.99 (dd, J=7.9, 4.0, 1H), 3.95 (td, J=9.7, 3.5, 1H), 3.61 (ddd, J=14.2, 8.3, 3.5, 1H), 3.18 (ddd, J=14.1, 9.4, 4.6, 1H), 2.43 (s, 3H), 1.46 (dd, J=21.7, 18.7, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 143.83, 136.75, 129.87, 129.80, 129.67, 127.05, 96.24, 94.52, 77.34, 77.02,

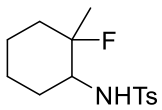
76.70, 58.96, 58.69, 45.66, 29.68, 26.06, 25.82, 23.57, 23.33, 21.54.^{19}F NMR (376 MHz, $CDCl_3$) δ = -138.17 (dtd, J=43.4, 21.7, 10.0, 1F). MS: m/z = 337.0 $[M]^+$. HRMS: calcd. For $C_{12}H_{17}FBrNSO_2Na^+$ = 360.0040; found 360.0037, cald. For $C_{12}H_{18}FBrNSO_2^+$= 338.0220; found 338.0217.

N-(2-Fluoro-2-methyl-4-phenoxybutyl)-4-methylbenzenesulfonamide (4-5m)



The product was prepared from 2-methyl-2-(2-phenoxyethyl)-1-tosylaziridine according to the general procedure to afford the title compound in 93% yield, as a viscous colorless oil. 1H NMR (400 MHz, $CDCl_3$) δ = 7.73 (d, J=8.2, 2H), 7.36 – 7.20 (m, 4H), 6.96 (t, J=7.4, 1H), 6.81 (d, J=8.6, 2H), 4.87 (t, J=6.8, 2H), 4.15 – 3.92 (m, 2H), 3.15 (ttd, J=19.9, 13.3, 6.9, 2H), 2.41 (s, 3H), 2.17 (dqd, J=11.4, 9.0, 4.8, 2H), 1.44 (d, J=22.2, 3H). 13C NMR (100 MHz, $CDCl_3$) δ = 158.09, 143.58, 136.77, 129.78, 129.51, 126.97, 121.12, 114.34, 96.33, 94.64, 62.75, 50.48, 50.23, 36.68, 36.46, 23.17, 22.94, 21.50 ^{19}F NMR (376 MHz, $CDCl_3$) δ = -142.72 – -158.79 (m, 1F). MS: m/z = 351.13 $[M]^+$. HRMS: calcd. For $C_{18}H_{23}FNSO_3^+$= 352.1377; found 352.1375

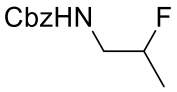
N-(2-Fluoro-2-methylcyclohexyl)-4-methylbenzenesulfonamide (4-5o)



The product was prepared from 1-methyl-7-tosyl-7-azabicyclo[4.1.0]heptane according to the general procedure to afford the title compound in 84% yield, as a white solid. H NMR (400 MHz, $CDCl_3$) δ = 7.77 (d, *J*=8.0, 2H), 7.27 (d, *J*=8.6, 2H), 5.14 (d, *J*=8.2, 1H), 3.45

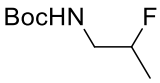
– 3.20 (m, 1H), 2.41 (s, 3H), 1.95 – 1.74 (m, 1H), 1.74 – 1.51 (m, 4H), 1.43 (d, *J*=18.9, 2H), 1.26 (dd, *J*=26.4, 12.1, 3H), 0.85 (dd, *J*=15.9, 9.0, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 143.30, 137.71, 129.55, 127.10, 96.22, 94.49, 57.72, 35.71, 35.51, 31.55, 29.38, 22.62, 22.01, 21.94, 21.53, 20.67, 14.09. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -141.11. d, 1F.MS: m/z = 285.12 $[M]^+$. HRMS: calcd. For $C_{18}H_{23}FNSO_3^+$= 285.1272; found 285.1270.

Benzyl (2-fluoropropyl)carbamate (4-5p)



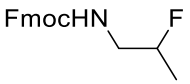
This compound is known.[131] The major product (90:1 as obtained by ^{19}F NMR) was prepared from benzyl 2-methylaziridine-1-carboxylate according to the general procedure to afford the title compound in 66% yield as a yellow. ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C) δ -179.9 (m, 1F).

tert-Butyl (2-fluoropropyl)carbamate (4-5q)



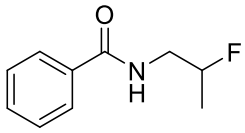
This compound is known.[132] The major product was prepared from tert-butyl 2-methylaziridine-1-carboxylate (> 30:1) according to the general procedure to afford the title compound as a colorless oil. ^{19}F NMR ($CDCl_3$, 376 MHz) δ -180.8 (m, 1F). ^{1}HNMR ($CDCl_3$, 500 MHz) δ 4.88 (br s, 1H), 4.79–4.63 (m, 1H), 3.49–3.38 (m, 1H), 3.19–3.09 (m, 1H), 1.44 (s, 9H), 1.30 (dd, *J* = 23.7, 6.3 Hz, 1H).

(9H-Fluoren-9-yl)methyl (2-fluoropropyl)carbamate (4-5r)



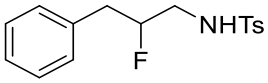
The product was prepared from (9H-fluoren-9-yl)methyl-2-methylaziridine-1-carboxylate according to the general procedure to afford the title compound quantitatively as a white solid 76%. The major product was isolated almost exclusively with trace amount of the minor product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.5 Hz, 2H), 7.61 (d, *J* = 7.2 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 2H), 5.22 (brs, 1H), 4.75 (d, *J* = 49.3 Hz, 1H), 4.43 (d, *J* = 6.7 Hz, 2H), 4.23 (t, *J* = 6.5 Hz, 1H), 3.66 – 3.10 (m, 1H), 1.33 (dd, *J* = 23.8, 6.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.52, 143.87, 141.32, 127.72, 127.06, 124.91 (d, *J* = 27.2 Hz), 120.01, 89.79 (d, *J* = 166.6 Hz), 82.40, 74.06, 66.85, 47.2, 46.19 (d, *J* = 20.6 Hz), 18.05 (d, *J* = 21.9 Hz). Major product ^{19}F NMR (376 MHz, $CDCl_3$) δ -179.71 (dddd, *J* = 49.1, 29.2, 24.3, 20.1 Hz, 1F), Minor product: -231.17 (d, *J* = 25.2 Hz, 1F). (major:minor 57:1) MS: m/z = 299.1[M] $^{+}$. HRMS: calcd. For $C_{18}H_{17}FNSO_2Na^{+}$ = 322.1219; found 322.1218, cald. For $C_{18}H_{18}FNSO_2^{+}$= 300.1400; found 300.1399.

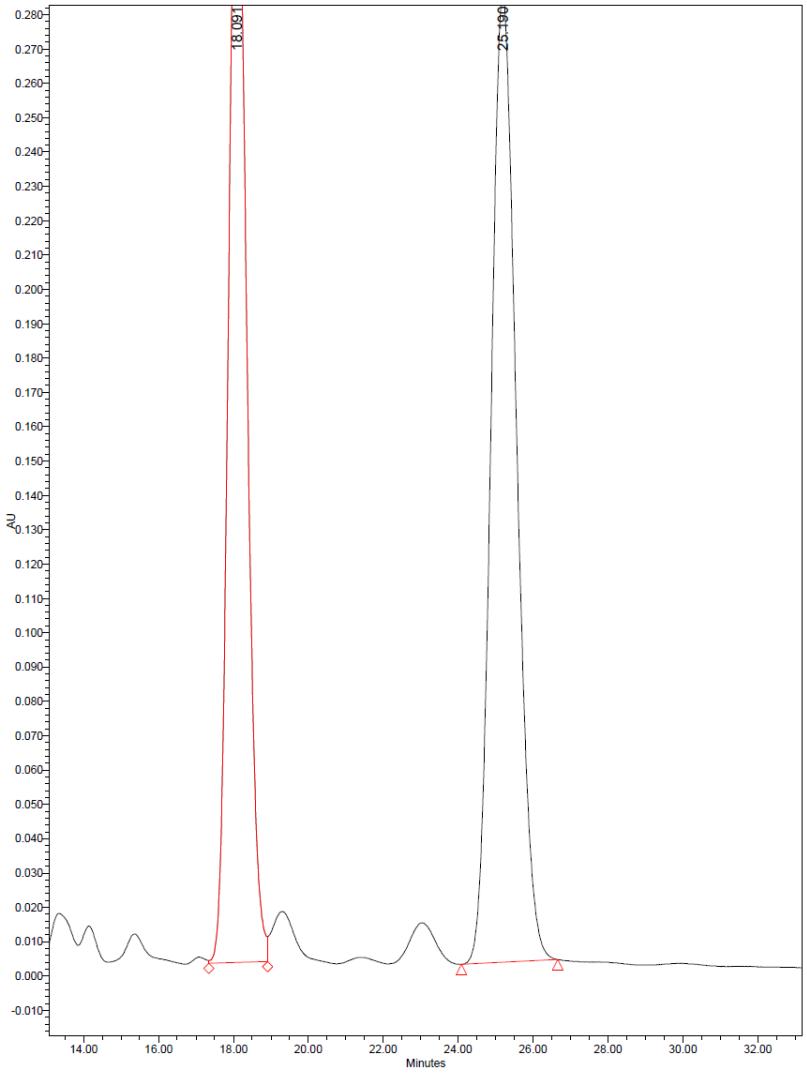
N-(2-Fluoropropyl)benzamide (4-5s)



The product was prepared from (2-methylaziridin-1-yl)(phenyl)methanone according to the general procedure to afford the title compound quantitatively as a yellow oil 58%. The major product was isolated in >30:1 regioselectivity though contaminated a little with the Heine product. This compound is known.[132] ^{19}F NMR ($CDCl_3$, 376 MHz) δ -168.1 (m, 1F). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.82–7.77 (m, 2H), 7.55–7.48 (m, 1H), 7.47–7.42 (m, 1H), 6.48 (br s, 1H), 4.92–4.79 (m, 1H), 3.95–3.84 (m, 1H), 3.47–3.38 (m, 1H), 1.40 (dd, *J* = 23.9, 6.3 Hz, 3H).

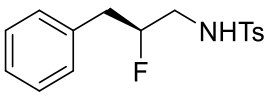
HPLC Traces for *rac*-2d

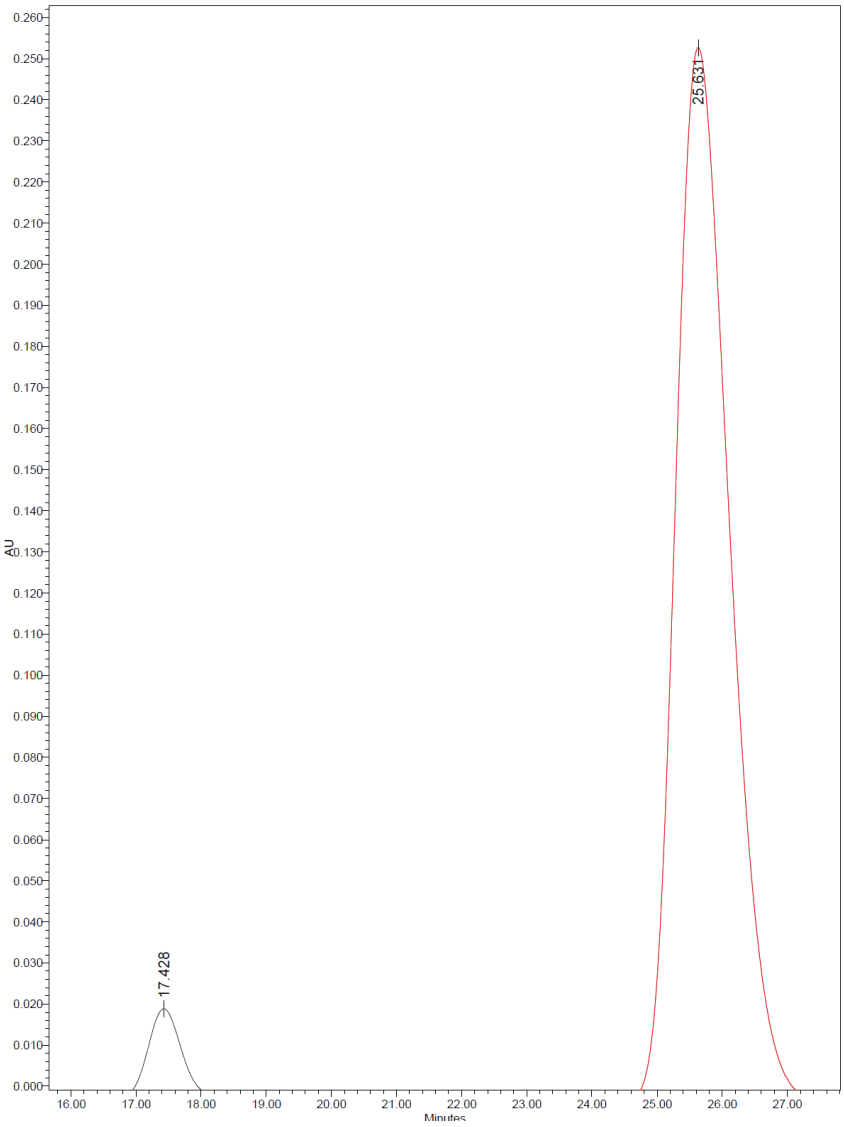




	Name	Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA Match1 Spect. Name	PDA Match1 Angle	PDA Match1 Threshold	PDA Match1 Lib. Name	Area (μV*sec)	% Area	Height (μV)	Int Type
1		18.091							11620840	46.45	345529	VV
2		25.190							13397610	53.55	282032	BB

HPLC Traces for (S)-2d





	Name	Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA Match1 Spect. Name	PDA Match1 Angle	PDA Match1 Threshold	PDA Match1 Lib. Name	Area (μV*sec)	% Area	Height (μV)	Int Type
1		17.428							1864327	4.78	53068	BB
2		25.632							37100041	95.22	634254	BB

Chromatography conditions: Waters 600 HPLC pump, Waters 2996 PDA detector, Diacel OD-H column (5 μm, 4.6 mm I.D. × 250 mm L), 10% isopropanol/90% hexane, 1m L/min, λ=227nm

4.5 Conclusion

In conclusion, our DMPU-HF reagent usually gives high both high regioselectivity and high stereoselectivity in ring opening hydrofluorination of aziridines, and wide scope of β-fluoro-amines can be accessed conveniently. These improved reaction conditions should have further implications on developing other ring opening reactions.

4.5.1 Crystal data and structure refinement for (*S*)-4-1d.

Identification code	**(*S*)-4-1d**	
Empirical formula	C16 H17 N O2 S	
Formula weight	287.37	
Temperature	100.5(6) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 2_1	
Unit cell dimensions	a = 7.3082(2) Å	α= 90°.
	b = 12.6670(4) Å	β= 102.802(3)°.
	c = 7.9739(3) Å	γ = 90°.
Volume	719.82(4) $Å^3$	
Z	2	
Density (calculated)	1.326 Mg/m^3	
Absorption coefficient	0.225 mm^{-1}	
F(000)	304	
Crystal color, habit	colorless plate	
Crystal size	0.38 x 0.28 x 0.10 mm^3	
Theta range for data collection	3.28 to 28.16°.	
Index ranges	-9<=h<=9, -16<=k<=16, -10<=l<=10	
Reflections collected	17424	
Independent reflections	3518 [R(int) = 0.034]	
Completeness to theta = 28.16°	99.8 %	
Absorption correction	multi-scan	
Max. and min. transmission	1.000 and 0.928	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3518 / 1 / 238	
Goodness-of-fit on F^2	1.019	
Final R indices [I>2σ(I)]	R1 = 0.025, wR2 = 0.058	
R indices (all data)	R1 = 0.026, wR2 = 0.058	
Absolute structure parameter	-0.03(4)	
Largest diff. peak and hole	0.291 and -0.195 $e.Å^{-3}$	

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for (*S*)-4-1d.

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	X	Y	Z	U(eq)
S(1)	11061(1)	3397(1)	3463(1)	19(1)
O(1)	11424(2)	2535(1)	4661(1)	29(1)
O(2)	12605(1)	4069(1)	3308(1)	25(1)
N(1)	9300(2)	4075(1)	3949(1)	18(1)
C(1)	9981(2)	2935(1)	1406(2)	17(1)
C(2)	8764(2)	2079(1)	1242(2)	21(1)
C(3)	7874(2)	1746(1)	-386(2)	22(1)
C(4)	8166(2)	2257(1)	-1853(2)	20(1)
C(5)	9432(2)	3096(1)	-1645(2)	20(1)
C(6)	10337(2)	3445(1)	-23(2)	18(1)
C(7)	7100(2)	1951(1)	-3623(2)	27(1)
C(8)	9856(2)	5001(1)	5117(2)	22(1)
C(9)	9055(2)	5177(1)	3275(2)	18(1)
C(10)	7047(2)	5512(1)	2622(2)	22(1)
C(11)	6351(2)	5249(1)	741(2)	19(1)
C(12)	6710(2)	5936(1)	-509(2)	23(1)
C(13)	6107(2)	5702(1)	-2247(2)	26(1)
C(14)	5135(2)	4774(1)	-2748(2)	26(1)
C(15)	4775(2)	4086(1)	-1510(2)	26(1)
C(16)	5385(2)	4315(1)	226(2)	22(1)

Bond lengths [Å] and angles [°] for (*S*)-4-1d.

S(1)-O(1)	1.4361(11)
S(1)-O(2)	1.4409(11)
S(1)-N(1)	1.6633(11)
S(1)-C(1)	1.7552(13)
N(1)-C(9)	1.4917(17)
N(1)-C(8)	1.4968(18)
C(1)-C(6)	1.3840(18)
C(1)-C(2)	1.3897(18)
C(2)-C(3)	1.383(2)
C(2)-H(2)	0.989(18)
C(3)-C(4)	1.395(2)
C(3)-H(3)	0.924(19)
C(4)-C(5)	1.3940(18)
C(4)-C(7)	1.5044(19)
C(5)-C(6)	1.3882(17)
C(5)-H(5)	0.930(17)
C(6)-H(6)	0.946(16)
C(7)-H(7A)	0.9600
C(7)-H(7B)	0.9600
C(7)-H(7C)	0.9600
C(8)-C(9)	1.4724(19)
C(8)-H(8A)	0.930(18)
C(8)-H(8B)	0.921(17)
C(9)-C(10)	1.5056(18)
C(9)-H(9)	0.923(15)
C(10)-C(11)	1.5103(18)
C(10)-H(10A)	0.963(17)
C(10)-H(10B)	0.958(18)
C(11)-C(12)	1.391(2)
C(11)-C(16)	1.3924(19)
C(12)-C(13)	1.390(2)
C(12)-H(12)	0.968(18)
C(13)-C(14)	1.385(2)
C(13)-H(13)	0.98(2)
C(14)-C(15)	1.386(2)
C(14)-H(14)	0.926(17)
C(15)-C(16)	1.387(2)
C(15)-H(15)	0.97(2)
C(16)-H(16)	0.970(18)

O(1)-S(1)-O(2)	118.27(7)
O(1)-S(1)-N(1)	106.04(6)
O(2)-S(1)-N(1)	112.07(6)
O(1)-S(1)-C(1)	110.29(7)

O(2)-S(1)-C(1)	108.37(6)
N(1)-S(1)-C(1)	100.32(6)
C(9)-N(1)-C(8)	59.03(8)
C(9)-N(1)-S(1)	115.89(9)
C(8)-N(1)-S(1)	115.62(9)
C(6)-C(1)-C(2)	121.31(12)
C(6)-C(1)-S(1)	119.09(10)
C(2)-C(1)-S(1)	119.59(10)
C(3)-C(2)-C(1)	118.99(12)
C(3)-C(2)-H(2)	120.5(10)
C(1)-C(2)-H(2)	120.4(10)
C(2)-C(3)-C(4)	121.19(13)
C(2)-C(3)-H(3)	118.9(11)
C(4)-C(3)-H(3)	119.9(11)
C(5)-C(4)-C(3)	118.39(12)
C(5)-C(4)-C(7)	120.03(13)
C(3)-C(4)-C(7)	121.54(13)
C(6)-C(5)-C(4)	121.31(13)
C(6)-C(5)-H(5)	119.7(11)
C(4)-C(5)-H(5)	119.0(11)
C(1)-C(6)-C(5)	118.77(13)
C(1)-C(6)-H(6)	119.7(9)
C(5)-C(6)-H(6)	121.5(9)
C(4)-C(7)-H(7A)	109.5
C(4)-C(7)-H(7B)	109.5
H(7A)-C(7)-H(7B)	109.5
C(4)-C(7)-H(7C)	109.5
H(7A)-C(7)-H(7C)	109.5
H(7B)-C(7)-H(7C)	109.5
C(9)-C(8)-N(1)	60.31(8)
C(9)-C(8)-H(8A)	119.8(11)
N(1)-C(8)-H(8A)	114.0(11)
C(9)-C(8)-H(8B)	119.5(11)
N(1)-C(8)-H(8B)	117.0(11)
H(8A)-C(8)-H(8B)	114.7(15)
C(8)-C(9)-N(1)	60.66(9)
C(8)-C(9)-C(10)	121.96(12)
N(1)-C(9)-C(10)	114.73(11)
C(8)-C(9)-H(9)	117.6(9)
N(1)-C(9)-H(9)	115.6(10)
C(10)-C(9)-H(9)	114.8(9)
C(9)-C(10)-C(11)	111.67(11)
C(9)-C(10)-H(10A)	107.6(9)
C(11)-C(10)-H(10A)	111.6(9)
C(9)-C(10)-H(10B)	109.1(10)
C(11)-C(10)-H(10B)	108.6(10)

H(10A)-C(10)-H(10B)	108.1(14)
C(12)-C(11)-C(16)	118.90(13)
C(12)-C(11)-C(10)	119.93(13)
C(16)-C(11)-C(10)	121.15(12)
C(13)-C(12)-C(11)	120.89(13)
C(13)-C(12)-H(12)	119.8(10)
C(11)-C(12)-H(12)	119.2(10)
C(14)-C(13)-C(12)	119.83(14)
C(14)-C(13)-H(13)	119.7(12)
C(12)-C(13)-H(13)	120.5(12)
C(13)-C(14)-C(15)	119.60(14)
C(13)-C(14)-H(14)	119.7(11)
C(15)-C(14)-H(14)	120.7(11)
C(14)-C(15)-C(16)	120.65(14)
C(14)-C(15)-H(15)	120.6(11)
C(16)-C(15)-H(15)	118.8(11)
C(15)-C(16)-C(11)	120.12(13)
C(15)-C(16)-H(16)	121.5(10)
C(11)-C(16)-H(16)	118.4(10)

Symmetry transformations used to generate equivalent atoms:

Anisotropic displacement parameters ($Å^2$x 10^3) for (*S*)-4-1d.

The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

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

C(13)	23(1)	32(1)	23(1)	8(1)	5(1)	3(1)
C(14)	18(1)	39(1)	20(1)	-2(1)	-1(1)	4(1)
C(15)	16(1)	27(1)	32(1)	-7(1)	3(1)	-2(1)
C(16)	18(1)	22(1)	29(1)	3(1)	8(1)	2(1)

Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for (*S*)-4-1d.

	X	Y	Z	U(eq)
H(2)	8490(20)	1738(15)	2270(20)	24(4)
H(3)	7060(20)	1181(15)	-490(20)	25(5)
H(5)	9690(20)	3414(15)	-2620(20)	25(4)
H(6)	11200(20)	4013(13)	122(19)	17(4)
H(7A)	6807	1211	-3641	40
H(7B)	7853	2094	-4442	40
H(7C)	5958	2351	-3916	40
H(8A)	9110(30)	5097(14)	5910(20)	26(4)
H(8B)	11120(20)	5105(13)	5550(20)	24(4)
H(9)	9860(20)	5381(12)	2596(19)	11(3)
H(10A)	6310(20)	5170(13)	3320(20)	18(4)
H(10B)	6950(20)	6259(14)	2770(20)	23(4)
H(12)	7330(20)	6601(14)	-160(20)	27(4)
H(13)	6340(30)	6196(16)	-3120(30)	38(5)
H(14)	4780(20)	4607(13)	-3910(20)	23(4)
H(15)	4090(30)	3439(18)	-1840(20)	40(5)
H(16)	5150(20)	3838(14)	1110(20)	28(4)

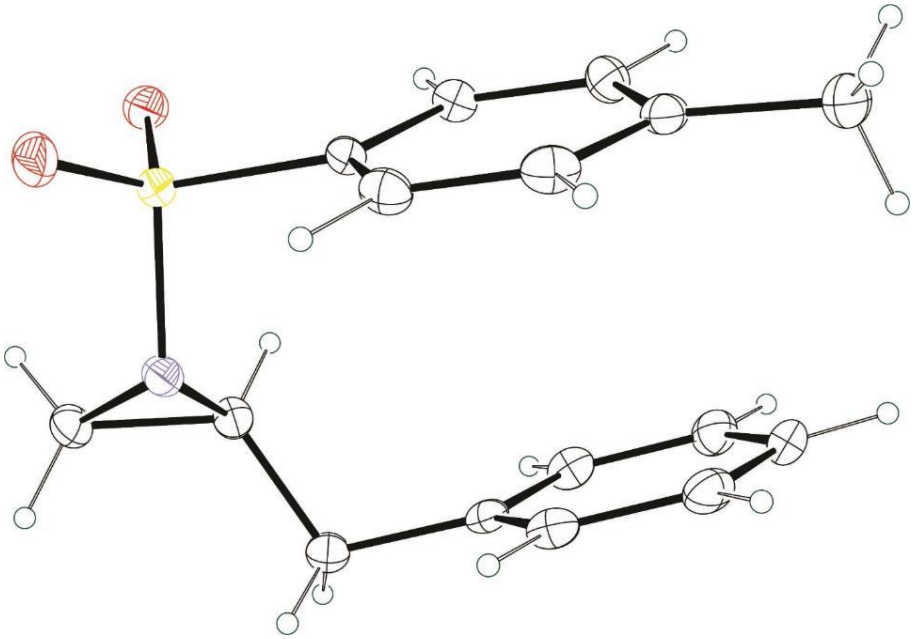
Torsion angles [°] for (*S*)-4-1d.

O(1)-S(1)-N(1)-C(9)	161.44(9)
O(2)-S(1)-N(1)-C(9)	31.03(11)
C(1)-S(1)-N(1)-C(9)	-83.77(10)
O(1)-S(1)-N(1)-C(8)	95.12(10)
O(2)-S(1)-N(1)-C(8)	-35.30(11)
C(1)-S(1)-N(1)-C(8)	-150.10(10)
O(1)-S(1)-C(1)-C(6)	-147.78(10)
O(2)-S(1)-C(1)-C(6)	-16.87(12)
N(1)-S(1)-C(1)-C(6)	100.70(11)
O(1)-S(1)-C(1)-C(2)	33.38(12)
O(2)-S(1)-C(1)-C(2)	164.29(10)
N(1)-S(1)-C(1)-C(2)	-78.14(11)
C(6)-C(1)-C(2)-C(3)	-1.01(19)
S(1)-C(1)-C(2)-C(3)	177.81(11)
C(1)-C(2)-C(3)-C(4)	-0.5(2)
C(2)-C(3)-C(4)-C(5)	2.1(2)
C(2)-C(3)-C(4)-C(7)	-175.53(13)
C(3)-C(4)-C(5)-C(6)	-2.31(19)
C(7)-C(4)-C(5)-C(6)	175.37(13)
C(2)-C(1)-C(6)-C(5)	0.82(19)
S(1)-C(1)-C(6)-C(5)	-178.01(10)
C(4)-C(5)-C(6)-C(1)	0.88(19)
S(1)-N(1)-C(8)-C(9)	106.08(10)
N(1)-C(8)-C(9)-C(10)	102.41(14)
S(1)-N(1)-C(9)-C(8)	-105.62(11)
C(8)-N(1)-C(9)-C(10)	-114.18(13)
S(1)-N(1)-C(9)-C(10)	140.20(10)
C(8)-C(9)-C(10)-C(11)	-158.53(13)
N(1)-C(9)-C(10)-C(11)	-88.93(14)
C(9)-C(10)-C(11)-C(12)	-84.00(16)
C(9)-C(10)-C(11)-C(16)	94.55(15)
C(16)-C(11)-C(12)-C(13)	0.5(2)
C(10)-C(11)-C(12)-C(13)	179.04(13)
C(11)-C(12)-C(13)-C(14)	0.0(2)
C(12)-C(13)-C(14)-C(15)	-0.1(2)
C(13)-C(14)-C(15)-C(16)	-0.3(2)
C(14)-C(15)-C(16)-C(11)	0.8(2)
C(12)-C(11)-C(16)-C(15)	-0.82(19)
C(10)-C(11)-C(16)-C(15)	-179.39(12)

Symmetry transformations used to generate equivalent atoms:

Intra-molecular Hydrogen bonds for (*S*)-4-1d [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)



X-ray crystallography of **(*S*)-1d**. Thermal ellipsoids are shown at 50% probability

4.5.2 Crystal data and structure refinement for *(S)*-4-2d.

Identification code	***(S)*-4-2d**	
Empirical formula	C16 H18 F N O2 S	
Formula weight	307.37	
Temperature	99.9(1) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 2_1 2_1 2_1	
Unit cell dimensions	a = 8.2947(3) Å	α= 90°.
	b = 9.5293(2) Å	β= 90°.
	c = 18.8749(4) Å	γ = 90°.
Volume	1491.92(7) $Å^3$	
Z	4	
Density (calculated)	1.368 Mg/m^3	
Absorption coefficient	0.231 mm^{-1}	
F(000)	648	
Crystal color, habit	colorless prism	
Crystal size	0.30 x 0.18 x 0.15 mm^3	
Theta range for data collection	3.26 to 28.06°.	
Index ranges	-10<=h<=10, -12<=k<=12, -24<=l<=24	
Reflections collected	16718	
Independent reflections	3614 [R(int) = 0.046]	
Completeness to theta = 28.06°	99.8 %	
Absorption correction	multi-scan	
Max. and min. transmission	1.000 and 0.845	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3614 / 0 / 248	
Goodness-of-fit on F^2	1.032	
Final R indices [I>2sigma(I)]	R1 = 0.0341, wR2 = 0.0733	
R indices (all data)	R1 = 0.0379, wR2 = 0.0752	
Absolute structure parameter	-0.04(6)	
Largest diff. peak and hole	0.376 and -0.320 $e.Å^{-3}$	

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for *(S)*-4-2d.

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	4248(1)	5944(1)	2400(1)	17(1)
F(1)	8675(1)	5418(1)	3467(1)	25(1)
O(1)	4153(2)	7312(1)	2720(1)	22(1)
O(2)	3118(2)	4889(1)	2618(1)	22(1)
N(1)	6013(2)	5327(2)	2545(1)	19(1)
C(1)	4047(2)	6189(2)	1476(1)	16(1)
C(2)	3096(2)	7292(2)	1234(1)	19(1)
C(3)	2836(3)	7433(2)	509(1)	22(1)
C(4)	3522(2)	6500(2)	28(1)	21(1)
C(5)	4477(2)	5416(2)	283(1)	20(1)
C(6)	4741(2)	5248(2)	1007(1)	20(1)
C(7)	3214(3)	6680(2)	-756(1)	29(1)
C(8)	7444(2)	6184(2)	2411(1)	19(1)
C(9)	8236(2)	6643(2)	3092(1)	18(1)
C(10)	9741(2)	7518(2)	2981(1)	21(1)
C(11)	10404(2)	8068(2)	3675(1)	19(1)
C(12)	11608(2)	7355(2)	4036(1)	22(1)
C(13)	12140(3)	7816(2)	4694(1)	25(1)
C(14)	11471(2)	9000(2)	4997(1)	25(1)
C(15)	10293(2)	9737(2)	4637(1)	24(1)
C(16)	9764(2)	9276(2)	3980(1)	22(1)

Bond lengths [Å] and angles [°] for *(S)*-4-2d.

S(1)-O(2)	1.4345(13)
S(1)-O(1)	1.4388(12)
S(1)-N(1)	1.6012(15)
S(1)-C(1)	1.7683(16)
F(1)-C(9)	1.413(2)
N(1)-C(8)	1.463(2)
N(1)-H(1N)	0.815(19)
C(1)-C(6)	1.386(2)
C(1)-C(2)	1.391(2)
C(2)-C(3)	1.392(2)
C(2)-H(2)	0.94(2)
C(3)-C(4)	1.392(3)
C(3)-H(3)	0.94(2)
C(4)-C(5)	1.388(3)
C(4)-C(7)	1.513(3)
C(5)-C(6)	1.392(3)
C(5)-H(5)	0.96(2)
C(6)-H(6)	0.95(2)
C(7)-H(7C)	0.9600
C(7)-H(7A)	0.9600
C(7)-H(7B)	0.9600
C(8)-C(9)	1.508(2)
C(8)-H(8A)	0.97(2)
C(8)-H(8B)	0.94(2)
C(9)-C(10)	1.516(3)
C(9)-H(9)	1.03(2)
C(10)-C(11)	1.515(2)
rC(10)-H(10A)	0.94(2)
C(10)-H(10B)	0.95(2)
C(11)-C(12)	1.386(3)
C(11)-C(16)	1.392(3)
C(12)-C(13)	1.391(3)
C(12)-H(12)	0.93(2)
C(13)-C(14)	1.381(3)
C(13)-H(13)	0.95(2)
C(14)-C(15)	1.383(3)
C(14)-H(14)	0.98(2)
C(15)-C(16)	1.387(3)
C(15)-H(15)	0.92(2)
C(16)-H(16)	0.93(2)
O(2)-S(1)-O(1)	118.60(8)
O(2)-S(1)-N(1)	106.96(8)
O(1)-S(1)-N(1)	108.12(8)

O(2)-S(1)-C(1)	108.31(8)
O(1)-S(1)-C(1)	106.75(7)
N(1)-S(1)-C(1)	107.67(8)
C(8)-N(1)-S(1)	120.50(12)
C(8)-N(1)-H(1N)	119.8(14)
S(1)-N(1)-H(1N)	112.7(14)
C(6)-C(1)-C(2)	120.97(15)
C(6)-C(1)-S(1)	120.39(13)
C(2)-C(1)-S(1)	118.51(13)
C(1)-C(2)-C(3)	118.91(17)
C(1)-C(2)-H(2)	119.2(12)
C(3)-C(2)-H(2)	121.9(12)
C(4)-C(3)-C(2)	121.05(18)
C(4)-C(3)-H(3)	121.3(12)
C(2)-C(3)-H(3)	117.6(12)
C(5)-C(4)-C(3)	118.88(17)
C(5)-C(4)-C(7)	121.34(17)
C(3)-C(4)-C(7)	119.78(17)
C(4)-C(5)-C(6)	121.01(17)
C(4)-C(5)-H(5)	122.0(13)
C(6)-C(5)-H(5)	117.0(13)
C(1)-C(6)-C(5)	119.17(17)
C(1)-C(6)-H(6)	121.6(12)
C(5)-C(6)-H(6)	119.1(12)
C(4)-C(7)-H(7C)	109.5
C(4)-C(7)-H(7A)	109.5
H(7C)-C(7)-H(7A)	109.5
C(4)-C(7)-H(7B)	109.5
H(7C)-C(7)-H(7B)	109.5
H(7A)-C(7)-H(7B)	109.5
N(1)-C(8)-C(9)	111.60(15)
N(1)-C(8)-H(8A)	109.4(13)
C(9)-C(8)-H(8A)	107.3(12)
N(1)-C(8)-H(8B)	108.0(13)
C(9)-C(8)-H(8B)	112.2(13)
H(8A)-C(8)-H(8B)	108.4(18)
F(1)-C(9)-C(8)	107.36(14)
F(1)-C(9)-C(10)	108.17(14)
C(8)-C(9)-C(10)	113.60(15)
F(1)-C(9)-H(9)	106.2(11)
C(8)-C(9)-H(9)	109.9(12)
C(10)-C(9)-H(9)	111.3(12)
C(11)-C(10)-C(9)	111.67(15)
C(11)-C(10)-H(10A)	110.8(12)
C(9)-C(10)-H(10A)	106.4(13)
C(11)-C(10)-H(10B)	111.1(12)

C(9)-C(10)-H(10B)	106.8(12)
H(10A)-C(10)-H(10B)	109.9(17)
C(12)-C(11)-C(16)	118.54(17)
C(12)-C(11)-C(10)	121.11(17)
C(16)-C(11)-C(10)	120.29(17)
C(11)-C(12)-C(13)	120.82(18)
C(11)-C(12)-H(12)	120.1(14)
C(13)-C(12)-H(12)	119.0(14)
C(14)-C(13)-C(12)	120.06(19)
C(14)-C(13)-H(13)	123.0(14)
C(12)-C(13)-H(13)	116.9(14)
C(13)-C(14)-C(15)	119.70(18)
C(13)-C(14)-H(14)	119.3(13)
C(15)-C(14)-H(14)	121.0(13)
C(14)-C(15)-C(16)	120.17(19)
C(14)-C(15)-H(15)	120.0(14)
C(16)-C(15)-H(15)	119.8(14)
C(15)-C(16)-C(11)	120.68(18)
C(15)-C(16)-H(16)	119.1(14)
C(11)-C(16)-H(16)	120.1(14)

Symmetry transformations used to generate equivalent atoms:

Anisotropic displacement parameters ($Å^2$x 10^3) for *(S)*-4-2d.

The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	18(1)	15(1)	17(1)	0(1)	0(1)	-1(1)
F(1)	26(1)	24(1)	26(1)	8(1)	-5(1)	-2(1)
O(1)	26(1)	18(1)	21(1)	0(1)	1(1)	0(1)
O(2)	23(1)	21(1)	24(1)	1(1)	2(1)	-4(1)
N(1)	19(1)	15(1)	22(1)	0(1)	-4(1)	0(1)
C(1)	14(1)	17(1)	17(1)	1(1)	-2(1)	-4(1)
C(2)	20(1)	14(1)	23(1)	-1(1)	0(1)	0(1)
C(3)	22(1)	18(1)	25(1)	4(1)	-5(1)	0(1)
C(4)	19(1)	22(1)	21(1)	2(1)	-2(1)	-6(1)
C(5)	18(1)	22(1)	22(1)	-6(1)	2(1)	-1(1)
C(6)	17(1)	18(1)	24(1)	0(1)	-3(1)	0(1)
C(7)	35(1)	29(1)	22(1)	1(1)	-6(1)	-1(1)
C(8)	18(1)	22(1)	18(1)	2(1)	1(1)	0(1)
C(9)	17(1)	18(1)	20(1)	2(1)	0(1)	0(1)
C(10)	18(1)	24(1)	21(1)	3(1)	1(1)	0(1)
C(11)	14(1)	20(1)	23(1)	4(1)	2(1)	-5(1)
C(12)	20(1)	18(1)	28(1)	4(1)	0(1)	0(1)
C(13)	22(1)	23(1)	31(1)	8(1)	-5(1)	-2(1)
C(14)	24(1)	25(1)	25(1)	2(1)	-4(1)	-9(1)
C(15)	20(1)	21(1)	31(1)	-3(1)	2(1)	-2(1)
C(16)	15(1)	22(1)	30(1)	3(1)	-2(1)	0(1)

Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10 ^{3}) for *(S)*-4-2d.

	x	y	z	U(eq)
H(1N)	6060(20)	4480(20)	2495(10)	16(5)
H(2)	2660(20)	7920(20)	1562(10)	15(5)
H(3)	2200(30)	8190(20)	356(10)	16(5)
H(5)	4980(30)	4740(20)	-28(12)	26(6)
H(6)	5360(20)	4480(20)	1166(10)	19(5)
H(7C)	4030	6193	-1020	43
H(7A)	3241	7660	-874	43
H(7B)	2174	6302	-873	43
H(8A)	7130(30)	7020(20)	2157(11)	23
H(8B)	8140(30)	5660(20)	2124(11)	23
H(9)	7410(30)	7160(20)	3406(11)	22
H(10A)	9440(20)	8260(20)	2682(11)	21(5)
H(10B)	10510(30)	6930(20)	2747(11)	21(5)
H(12)	12050(30)	6540(20)	3846(12)	32(6)
H(13)	12980(30)	7290(20)	4911(12)	30(6)
H(14)	11870(30)	9320(20)	5461(11)	22(5)
H(15)	9830(30)	10510(20)	4841(12)	30(6)
H(16)	8940(30)	9760(20)	3753(12)	30(6)

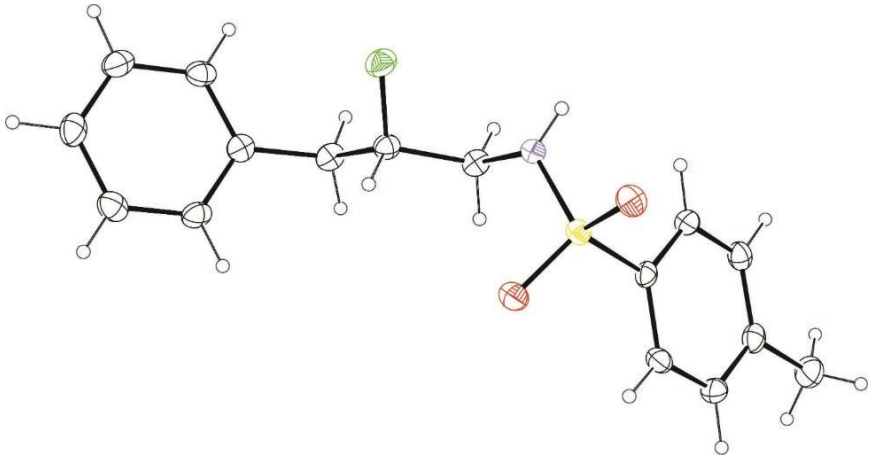
Table 6. Torsion angles [°] for *(S)*-2d.

O(2)-S(1)-N(1)-C(8)	-176.88(13)
O(1)-S(1)-N(1)-C(8)	-48.10(15)
C(1)-S(1)-N(1)-C(8)	66.90(14)
O(2)-S(1)-C(1)-C(6)	-78.93(16)
O(1)-S(1)-C(1)-C(6)	152.30(15)
N(1)-S(1)-C(1)-C(6)	36.41(16)
O(2)-S(1)-C(1)-C(2)	97.04(15)
O(1)-S(1)-C(1)-C(2)	-31.74(16)
N(1)-S(1)-C(1)-C(2)	-147.63(14)
C(6)-C(1)-C(2)-C(3)	0.5(3)
S(1)-C(1)-C(2)-C(3)	-175.41(15)
C(1)-C(2)-C(3)-C(4)	-0.6(3)
C(2)-C(3)-C(4)-C(5)	0.1(3)
C(2)-C(3)-C(4)-C(7)	179.89(18)
C(3)-C(4)-C(5)-C(6)	0.5(3)
C(7)-C(4)-C(5)-C(6)	-179.32(18)
C(2)-C(1)-C(6)-C(5)	0.0(3)
S(1)-C(1)-C(6)-C(5)	175.89(14)
C(4)-C(5)-C(6)-C(1)	-0.5(3)
S(1)-N(1)-C(8)-C(9)	108.21(15)
N(1)-C(8)-C(9)-F(1)	59.62(18)
N(1)-C(8)-C(9)-C(10)	179.17(15)
F(1)-C(9)-C(10)-C(11)	-66.22(19)
C(8)-C(9)-C(10)-C(11)	174.69(15)
C(9)-C(10)-C(11)-C(12)	94.7(2)
C(9)-C(10)-C(11)-C(16)	-82.6(2)
C(16)-C(11)-C(12)-C(13)	1.5(3)
C(10)-C(11)-C(12)-C(13)	-175.91(18)
C(11)-C(12)-C(13)-C(14)	-0.1(3)
C(12)-C(13)-C(14)-C(15)	-1.2(3)
C(13)-C(14)-C(15)-C(16)	1.2(3)
C(14)-C(15)-C(16)-C(11)	0.2(3)
C(12)-C(11)-C(16)-C(15)	-1.5(3)
C(10)-C(11)-C(16)-C(15)	175.90(17)

Symmetry transformations used to generate equivalent atoms:

Intermolecular Hydrogen bonds for *(S)*-4-2d [Å and °].

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	A
N1-H1N	0.815	2.111	171.41	2.920	O1 [-x+1, y-1/2, -z+1/2]



X-ray crystallography of **(*S*)-2d**. Thermal ellipsoids are shown at 50% probability

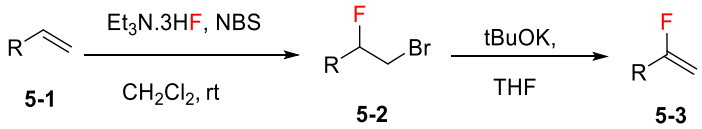
5 OTHER NUCLEOPHILIC REACTIONS BY DMPU-HF

5.1 Introduction

We have successfully applied DMPU-HF to such nucleophilic fluorination as the hydrofluorination of alkynes,[114] fluoro-Prins cyclization reaction,[133] and the regioselective ring opening of aziridines; making it a useful if not a better addition to the HF-based fluorination reagents. DMPU-HF as has been established here, forms a more stable complex with HF in that it can handle up to 12 moles of HF per mole of DMPU in contrast to pyridine, which handles only 9 moles of HF per mole of pyridine. Moreover, because of its less basic nature, the acidic property of HF is retained in most reactions (Figure 5). Perhaps its non-coordinating or less nucleophilic properties make it quite useful in fluorination reactions utilizing metal catalysis.[114] We intend to use this chapter to showcase some of our efforts to other applications of DMPU-HF in fluorination reactions.

5.2 Bromofluorination of unsaturated compounds

Bromofluorination of alkenes involves the mixture of an electrophilic brominating reagent and a fluoride to form the 1,2-bromofluoro alkane. Not until recently, this reaction has been a major source of building blocks to many fluorine containing compounds[134]. Earlier synthetic strategies toward the synthesis of vinyl fluorides, which in turn have been employed to polymer synthesis stem from bromofluorination reactions[51] (Scheme 18)

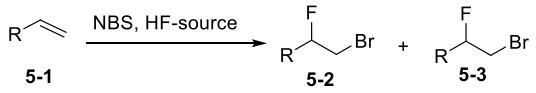


Scheme 18. Bromofluorination of alkenes.

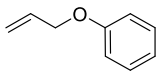
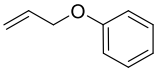
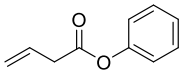
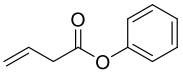
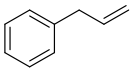
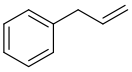
The usefulness of the bromofluorination protocol has ultimately led to the employment of several fluorinating and brominating reagents and conditions for the development of this methodology.[35, 134-135] Despite this fact, the challenge of obtaining good yield and a high regioselective product is yet to be unraveled, most especially for substituted allylic and/or homoallylic alkenes. For instance, Haufe and co-workers[38, 134] conducted a study of the bromofluorination of substituted allylic and the homoallylic alkenes (Table 14). The authors concluded that the nature of the amine/HF does not strongly influence the regioselectivity of bromofluorination, but influence the extent of side reactions like the formation of dibromides, which is usually observed with the less acidic $Et_3N.3HF$. From their results, as seen in Table 14, we can see that the regioselectivity of the bromofluorination of terminal alkenes is essentially 2:1in most cases favoring the fluorine at the internal position.

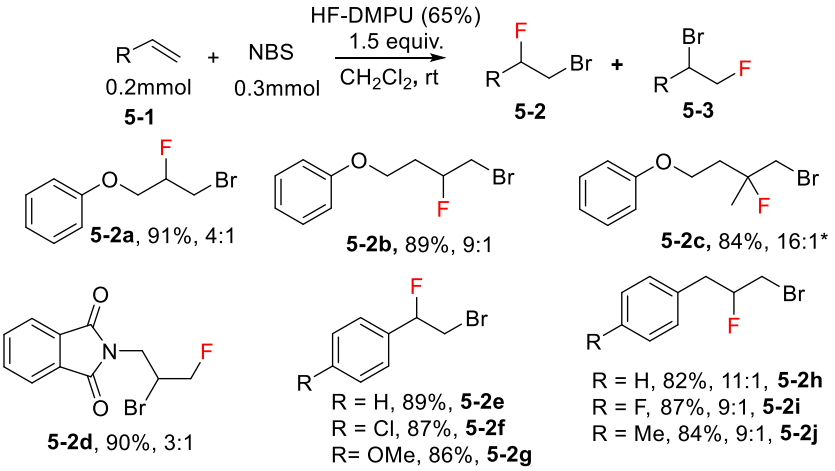
With this in mind, we decided to replicate the conditions of this reaction using N-bromosuccinimide as the brominating source and DMPU-HF as the fluoride source respectively with the hope of improving the yield and regioselectivity of the bromofluorination especially with terminal alkenes. The results obtained from the NMR of the crude products showed moderate to good regioselectivity and high yields as illustrated in Scheme 19.

Table 14. Bromofluorination of allylic alkenes.



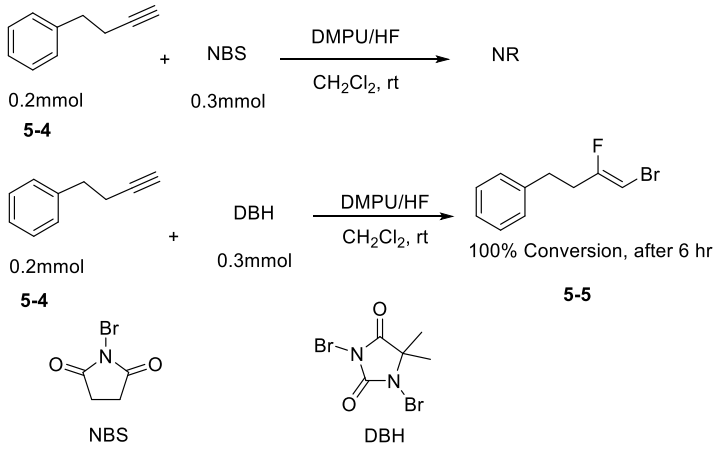
5-1 5-2 5-3

entry	substrate	HF-source	yield (%)	5-3a:5-3b (%)
1		$Et_3N.3HF$	42	63:37
2		Py.9HF	57	66:34
3		$Et_3N.3HF$	22	78:22
4		Py.9HF	51	74:26
5		$Et_3N.3HF$	74	4.5:1
6		Py.9HF	80	6:1



Scheme 19. Preliminary results of bromofluorination of alkenes with DMPU-HF.

Recently the development of efficient and sustainable methods for the synthesis of halo-fluorinated alkenes has increased due to the central role of this class of compounds in biological systems and pharmaceutical applications.[72] Difunctionalization of carbon triple bonds portends an easier route to the synthesis of these group of compounds. In this project, we will also explore the effect of DMPU-HF and a brominating reagent on both terminal and internal alkynes. In our preliminary study, (Scheme 20) we found that NBS was rather too weak to affect the needed bromofluorination on the corresponding alkyne. However, the alkyne was easily converted to the corresponding bromofluoroalkene in the presence of DMPU-HF when it was reacted with the stronger electrophilic brominating source 1,3-dibromo-5,5-dimethylhydantoin (DBH).



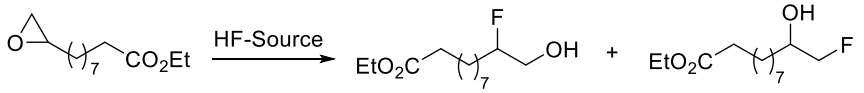
Scheme 20. Bromofluorination of phenylbutyne with DMPU-HF and a brominating source.

5.3 Ring opening of epoxides

Ring opening fluorination of epoxide has been a convenient method for the preparation of fluorohydrin.[136] Due to complications with the handling of anhydrous hydrogen fluoride (AHF), the direct treatment of epoxides with AHF has found limited use.

Alternative fluorine sources have over the years been employed in the synthesis of fluorohydrin. Other fluoride sources like HF-amine complex,[35, 38] potassium hydrogen difluoride,[137] silicon tetrafluoride,[138] and tetrabutylammonium dihydrogen trifluoride[139] have all been applied to fluorohydrin synthesis via epoxide opening. Many of these methodologies suffer from limited scope and low regioselectivity. Haufe and Sattler for instance, systematically studied the effect of the identity of the amine and the HF/amine ratio on the outcome of epoxide ring-opening reactions.[140] (Table 15)

Table 15. Regioselectivity of epoxide ring opening by amine—HF reagents.



5-6 **5-7** **5-8**

entry	HF-source	solvent	temperature	conv (%)	yield (%)	rr[a]
1	70% HF/Py	DCM	rt	>99	83	92:8
2	60% HF/Py	DCM	rt	>98	79	83:17
3	50% HF/Py	DCM	rt	>98	74	74:26
4	40% HF/Py	DCM	rt	5	nd	55:45
5	30% HF/Py	DCM	rt	2	nd	50:50
6	$Et_3N{\cdot}3HF$	toluene	100 °C	82	77	45:55
7	$Et_3N{\cdot}HF$ [b]	neat	100 °C	82	44	24:76
8	$Et_3N{\cdot}DBU{\cdot}2HF$ [c]	neat	100 °C	99	40	20:80

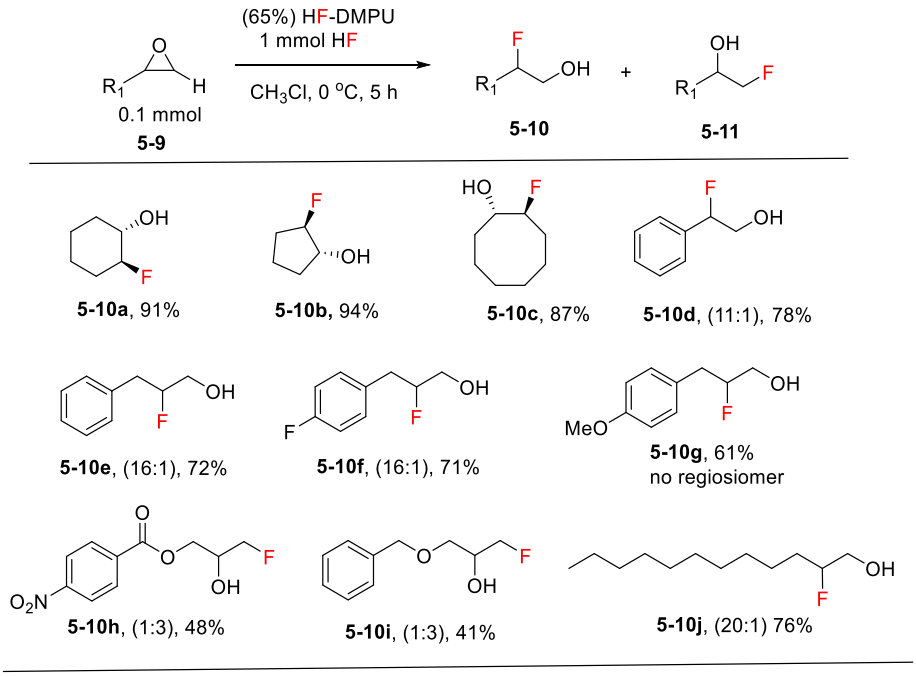
a) Regiosomeric ratio, b) prepared by addinng 2 equiv Et_3N to $Et_3N.3HF$. c) prepared by adding 1 equiv DBU to Et3N.3HF

The authors stated that a 70% Pyridine-HF solution provided the fluorohydrin in good yield and at room temperature favoring the internal fluorinated regiosiomer. Upon increasing the amount of pyridine in PPHF however, there was a decrease in reactivity providing a mixture of the internal and terminal fluorohydrins (entries 2-5, Table 15). More

so, the use of $Et_3N.3HF$ required forced reaction conditions and the terminal fluorohydrin is generated by adding external amine (entries 7-8).

From these results we envisaged that since DMPU-HF is more acidic than 70% Pyridine-HF, we could obtain a more regioselective result under the same reaction conditions than what has been reported. So as part of our ongoing work, we tested DMPU-HF on the ring opening of epoxides and our preliminary results are summarized in Table 16. This project will explore a larger substrate scope that will include compounds that are acid and/or base sensitive and the effect of DMPU-HF on chiral epoxides will as well be considered.

Table 16. Ring opening of epoxides using DMPU-HF.



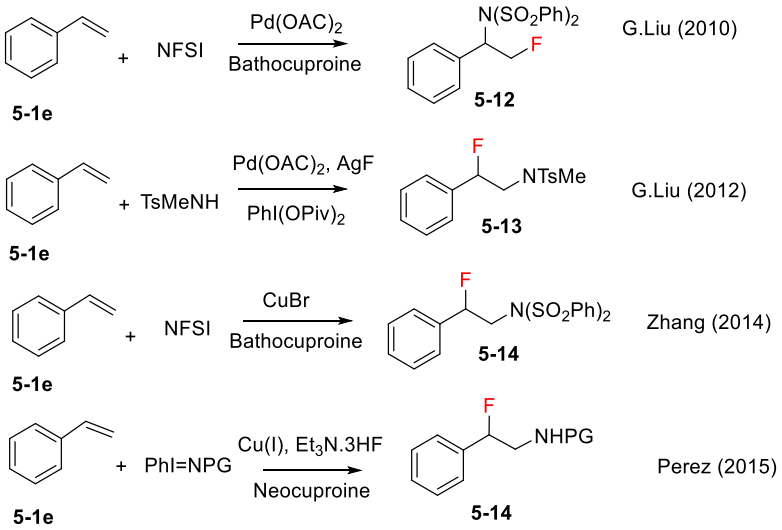
Yields and regioisomeric ratio are given by ^{19}F NMR using benzotrifluoride as internal standard

Though we are still exploring more substrates for the regioselective synthesis of fluorohydrins, our results showed good yield and good regioselectivities especially for the

non-symmetric epoxides. The electronic effects of compounds **5-10h** and **5-10i**, resulted in the favorability of the terminal fluorohydrin.

5.4 Metal free dual functionalization of alkenes

Dual functionalization of an alkene especially toward the synthesis of 1,2-fluoroamines is a useful and novel strategy that has gained a lot of attention in the last few years. Compounds containing the 1,2-aminofluoro moiety are valuable as building blocks because they can be elaborated toward the synthesis of many medicinal drugs that have diverse pharmaceutical properties. 1,2-Fluoroamines are not usually obtained directly, but rather through multiple step protocol like the ring opening of aziridines, which usually proceed in *anti*-fashion thus forming predominantly the *trans* fluoroamine products. Though the last six years has witnessed a surge in this dual functionalization methodology toward aminofluorination, the use of metal catalysts and styrene substrates has limited its applicability.[141] (Scheme 21)



Scheme 21. Catalytic aminofluorination of styrenes.

Inspired by the work of Barry Sharpless[142] in the synthesis of 1,2-aminoalcohol via the reaction of an alkene and chloramine-T in the presence of chromium tetraoxide. We investigated the effect of DMPU-HF and chloramine-T on cyclohexene and allylbenzene and found promising results, which when optimized will give rise to a direct procedure of obtaining the cis-fluoroamines from alkenes (Table 17).

Table 17 illustrates our effort in trying to optimize the fluoroamination of alkenes using allyl benzene, DMPU-HF and chloramine-T. Initial studies without molecular sieves (MS) resulted in more of the products being converted to the fluorohydrin (entries 1 and 2) and no significant conversion to the fluoroamine even after prolonged reaction time. The addition of MS suppressed completely the formation of the fluorohydrin and gave promising conversion to the fluoroamine (entries 23). Several Lewis acids were added to boost the reaction for optimal conversion but failed to optimize the yield of the fluoroamine. The addition of potassium hydrogen difluoride (KHF_2) resulted in moderate conversion to the fluoroamine (entries 13-14). We then hypothesized that a dehydrated chloramine-T may suppress significantly the production of the fluorohydrin (**5-10e**), which may ultimately influence the successful conversion to the fluoroamine (**5-15h**).

With the help of an Abderhalden pistol Figure 10, we obtained dry chloramine-T and conducted similar reactions with allybenzene and cyclohexene.

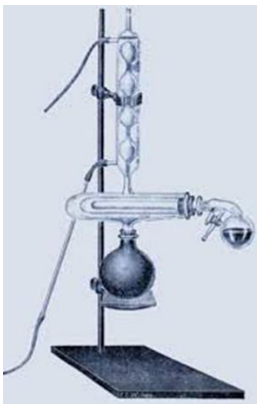
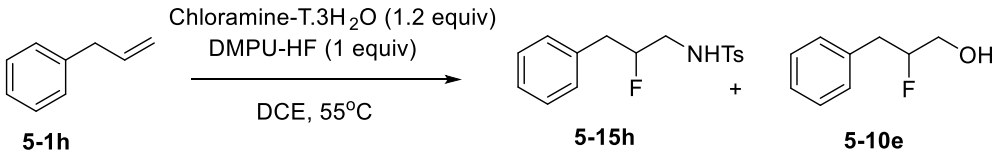


Figure 10. Abderhalden pistol

Gratifyingly, under the given conditions and without the aid of any additive or Lewis acid, the reaction proceeded smoothly to give a complete conversion to the fluoroamine (Table 18). Interestingly, when we compared the crude NMR spectra of the cyclohexyl tosylfluoroamines obtained from the ring opening of aziridine and the direct dual functionalization of the alkene (cyclohexene), we observed a slight shift in the ^{19}F NMR. That is, *ca* 86 ppm for the ^{19}F of 1,2-fluorotosylamine from cyclohexyl azirdine to *ca* 72 ppm for the 1,2-fluorotosylamine from the direct reaction of cyclohexene and chloramine-T. We believed this shift may be the result of the different stereochemistry of the products obtained due to their different pathways of formation.

Table 17. Optimization studies on the direct aminofluorination of alkenes.

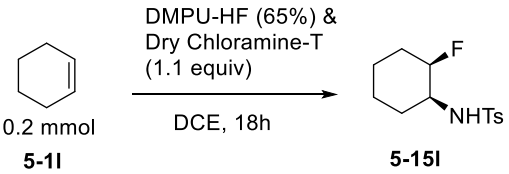


5-1h **5-15h** **5-10e**

Entry	MS	Additive	Time	Conversion (%) (A:B)
1	No	-	24	11/48
2	No	-	48	11/65
3	Yes	-	24	23:0
4	Yes	-	48	24:0
5	Yes	$KHSO_4$ (1 equiv)	24	31:0
6	Yes	$KHSO_4$ (3 Equiv)	24 + 24	36:0
7	Yes	CoF_2 (10 mol%)	24	41
8	Yes	CoF_2 (20 mol%)	24 + 24	39
9	Yes	CuCl (10 mol%)	24	Trace
10	Yes	$CuCl_2$ (10 mol%)	24	Trace
11	Yes	$FeCl_3$ (10 mol%)	24	Trace
12	Yes	Ga-triflate 10 mol%	24	44
13	Yes	KHF_2 (0.5 equiv)	24	51
14	Yes	KHF_2 (3 equiv)	24	51
15	Yes	BF_3.OEt (10 mol%)	24	<11
16	Yes	In_3Br 10 mole%	24	31
17	Yes	$FeCl_3$ (1 Equiv)	24	NR
18	Yes	AgF_2 (10 mol%)	24	NR

At the time of writing this thesis, our major challenge is the isolation of the products obtained from this reaction. So far we have obtained the crude product cyclohexyl fluorotosylamine, which will help us to confirm unambiguously the stereochemistry of the product via X-ray crystallography and also give us plausible insights into the mechanism of this reaction.

Table 18. Fluoroamine from dry chloramine-T and DMPU-HF.



0.2 mmol
5-1l

5-15l

Substrate	MS	HF (equiv)	Conversion %	Temp (^{o}C)
Cyclohexene	None	7 equiv	85	55
Cyclohexene	Yes	7 equiv	100	55
Cyclohexene	Yes	7 equiv	100	RT, 48 h
Cyclohexene	Yes	10 equiv	100	55
Allybenzene	Yes	7 equiv	67	55
Allybenzene	Yes	10 equiv	83	55
Allybenzene	Yes	10 equiv	>99	65

5.5 Summary and conclusions

We have shown that DMPU-HF is a useful fluorination reagent, which can effectively rival existing HF-based fluorination reagents. Aside from the successful application to the bromofluorination of alkenes, ring opening of epoxides and the dual fluoroamino functionalization of an alkene, the Hammond laboratory is exploring other useful applications of DMPU-HF. As an offshoot of this work, the Hammond laboratory is also exploring hydrohalogenation protocols and reagents using DMPU.

5.6 Experimental

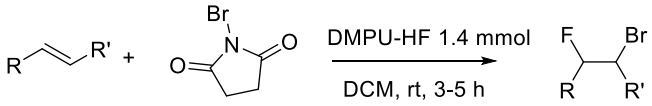
General Information

NMR spectra were recorded on AV2 400 or AV2 500 MHz Bruker spectrometers. Chemical shifts are given in ppm. The spectra are calibrated to the residual ^{1}H and ^{13}C signals of the solvents. Multiplicities are abbreviated as follows: singlet (s), doublet (d).

triplet (t), quartet (q), doublet-doublet (dd), quintet (quint), septet (sept), multiplet (m), and broad (br).

Materials and Methods: Unless otherwise stated, starting materials were purchased from Aldrich and/or Fluka. Substrates were already reported in the literature. Solvents were purchased in HPLC quality, degassed by purging thoroughly with nitrogen and dried over activated molecular sieves of appropriate size. Alternatively, they were purged with argon and passed through alumina columns in a solvent purification system (Innovative Technology). Conversion was monitored by thin layer chromatography (TLC) using Merck TLC silica gel 60 F254. Compounds were visualized by UV-light at 254 nm and by dipping the plates in a polymoybdenic acid (PMA), p-anisaldehyde, ninhydrinsolutions or an aqueous potassium permanganate solution followed by heating depending on the compounds formed. Unless otherwise stated, starting materials were purchased from commercial sources.

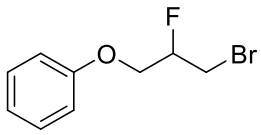
Synthesis and characterization of bromofluoro alkanes



General method: In a polyethylene vial charged with a magnetic stirring bar, the alkene (0.2 mmol) and *N*-bromosuccinimide (0.3 mmol) were dissolved in 0.7 mL of dichloromethane, then DMPU-HF (HF content 65 % wt/wt, 41 µL, 1.4 mmol) was added to the mixture and was stirred for 3 h at room temperature. The progress of reaction was monitored by TLC (green or dark brown dots on anisaldehyde stain). After completion of the reaction the mixture was quenched with cold water, and the organic phase was extracted with chloroform (5 mL). The organic phase was washed with aqueous sodium bicarbonate

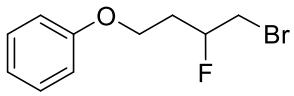
and brine. Finally the organic phase was dried over sodium sulfate and was concentrated to dryness in vacuum. The crude product was chromatographed with a 10:1 mixture of hexanes and EtOAc to afford the corresponding bromofluoro alkanes. Unless otherwise stated, the crude ^{19}F NMR data is given for unknown compounds only.

(3-Bromo-2-fluoropropoxy)benzene (5-2a)



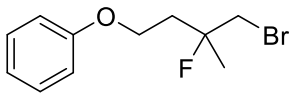
Yellow oil, 91% ^{19}F NMR yield of mixture of regioisomers. This compound is known[134] ^{19}F NMR (376 MHz, $CDCl_3$) δ -183.7 (m, 1F major), -217.1 (m, 1F minor)

(4-Bromo-3-fluorobutoxy)benzene (5-2b)



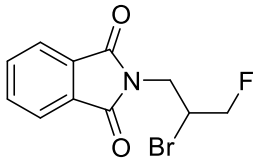
Crude ^{19}F NMR yield of mixture of compounds 87%. ^{19}F NMR (376 MHz, $CDCl_3$) δ -181.0 (m, 1F major), -211.2 (m, 1F minor)

(4-Bromo-3-fluoro-3-methylbutoxy)benzene (5-2c)



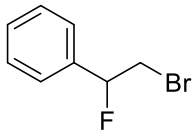
Dark brown oil, 84% ^{19}F NMR yield, messy ^{1}H spectrum ^{19}F NMR (376 MHz, $CDCl_3$) δ -144.7 (m, 1F)

2-(4-Bromo-3-fluorobutyl)isoindoline-1,3-dione (5-2d)



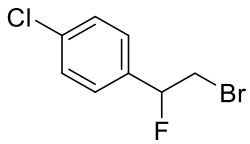
This compound is known[134] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82-7.90 (m, 2H), 7.70-7.75 (m, 2H), 4.45-4.82 (m, 3H), 4.07-4.26 (m, 2H), ^{19}F NMR (376 MHz, $CDCl_3$) δ -213.7 (m, 1F)

(2-Bromo-1-fluoroethyl)benzene (5-2e)



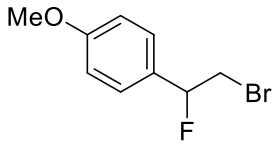
Colorless oil, 89%. This compound is known[51] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.5 (m, *5*H), 5.60 (dd, *J* = 47.1, 7.8, 4.1 Hz, 1H), 3.66 (ddd, *J* = 15.3, 11.3, 7.8 Hz,1H), 3.58 (ddd, *J* = 26.0, 11.3, 4.2Hz, 1H), ^{19}F NMR (376 MHz, $CDCl_3$) δ -175.0 (m, 1F)

1-(2-Bromo-1-fluoroethyl)-4-chlorobenzene (5-2f)



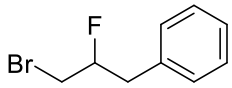
Yellow oil, 87%. This compound is known[51] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dm, 7.3Hz, 2H), 7.32 (dm, 7.3Hz, 2H), 5.62 (ddd, *J* = 46.6, 7.3, 4.5 Hz, 1H), 3.68 (ddd, *J* = 16.3, 11.3, 7.3 Hz,1H), 3.61 (ddd, *J* = 24.4, 11.3, 4.4Hz, 1H), ^{19}F NMR (376 MHz, $CDCl_3$) δ -174.5 (m, 1F)

1-(2-bromo-1-fluoroethyl)-4-methoxybenzene (5-2g)



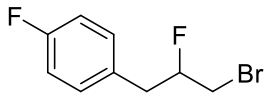
Yellow oil, 86% (NMR). Unstable compound, decompose on silica chromatography. ^{19}F NMR (376 MHz, $CDCl_3$) δ -171.2 (m, 1F): compound decompose on chromatography

(3-Bromo-2-fluoropropyl)benzene (5-2h)



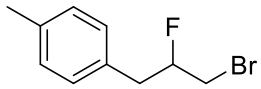
Colorless oil, 82% ^{19}F NMR yield. This compound is known ^{19}F NMR (376 MHz, $CDCl_3$) δ -170.9 (m, 1F)

1-(3-Bromo-2-fluoropropyl)-4-fluorobenzene (5-2i)



Brown oil, 87% (NMR). ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.8 (m, 1F), 175.7 (m, 1F major)

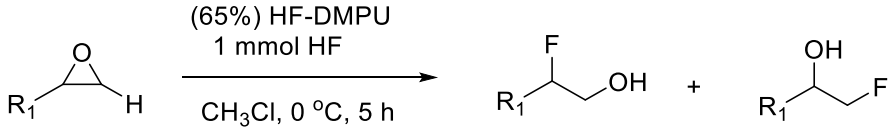
1-(3-Bromo-2-fluoropropyl)-4-methylbenzene (5-2j)



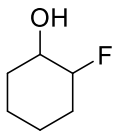
Colorless oil, 84% yield (minor unknown fluorinated product). ^{19}F NMR (376 MHz, $CDCl_3$) δ -175.3 (m, 1F)

Synthesis and characterization of fluorohydrins

General method: In a polyethylene vial charged with a magnetic stirring bar, the epoxide (0.2 mmol) was dissolved in 1 mL of dichloromethane maintained at 0 °C, then DMPU-HF (HF content 65 % wt/wt, 41 µL, 1.4 mmol) was added slowly. The mixture was stirred for 1 to 2 h at this temperature and then warmed to room temperature for another 3 h. The progress of reaction was monitored by TLC (green or dark brown dots on anisaldehyde stain). After completion of the reaction, the mixture was quenched with cold water, and the organic phase was extracted with chloroform (5 mL). The organic phase was washed with aqueous sodium bicarbonate, a 2 M solution of sodium bisulfite and brine. Finally the organic phase was dried over sodium sulfate and was concentrated to dryness in vacuum. The crude product was chromatographed with a 10:1 mixture of hexanes and EtOAc to afford the corresponding bromofluoro alkanes. Unless otherwise stated, the crude ^{19}F NMR data is given for unknown compounds only.

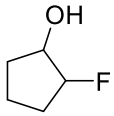


2-Fluorocyclohexan-1-ol (5-10a)



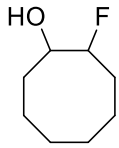
Colorless oil, 91% NMR yield. This compound is known.[143] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.69-1.77 (m, 2H), 1.20-1.51 (m, 4H), 1.99-2.13 (m, 2H), 2.45 (br s, 1H), 3.57-3.67 (m, 2H), 4.21 (dm, *J* = 51.3Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -181.4 (d, *J* = 51.3Hz)

2-Fluorocyclopentan-1-ol (5-10b)



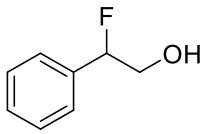
Colorless oil, 94% NMR yield. This compound is known ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.70-2.18 (m), 2.28 (br s, 1H), 4.42-4.44 (m, 1H), 4.91-5.03 (ddt, *J* = 48.4, 8.1, 2.4 Hz, 1H)

2-Fluorocyclooctan-1-ol (5-10c)



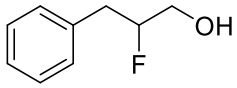
Colorless oil, 87% NMR yield. This compound is known.[144] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32-2.09 (m), 2.25 (br s, 1H), 3.78-3.89 (m, 1H), 4.46 (ddt, *J* = 48.6, 8.6, 2.7 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -182.1 (m);

2-Fluoro-2-phenylethan-1-ol (5-10)



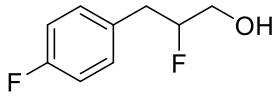
Colorless oil, 78% NMR yield. This compound is known.[143] ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02 (bs, 1H), 3.76-4.01 (m, 2H), 5.57 (ddd, J = 3.0, 7.5, 48.3 Hz, 1H), 7.34-7.41 (m, 5H) ^{19}F NMR (376 MHz, $CDCl_3$) δ -186.8 (m)

2-Fluoro-3-phenylpropan-1-ol (5-10e)



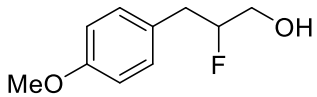
Colorless oil, 78% NMR yield. This compound is known.[143] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.20 (m, 5H); 4.78 (dm, *J* = 49.0 Hz) 3.84-3.63 (m, 2H); 3.10-2.89 (m, 2H); 1.92 (s, br, 1H) ^{19}F NMR (376 MHz, $CDCl_3$) δ: –187.6 (m).

2-Fluoro-3-(4-fluorophenyl)propan-1-ol (5-10f)



Colorless oil, 78% NMR yield. This compound is known.[145] ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.87-3.01 (m, 2 H,) 3.63-3.83 (m, 2 H,), 4.74 (ddq, *J* = 48.4 Hz, 3.2 Hz and 6.0 Hz, 1H), 6.98-7.02 (m, 2H,), 7.12-7.18 (m, 2H,); ^{19}F NMR (376 MHz, $CDCl_3$) δ: –116. 2 (m, 1F), -188.3 (m, 1F)

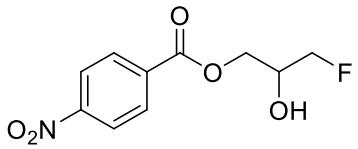
2-Fluoro-3-(4-methoxyphenyl)propan-1-ol (5-10g)



White solid 56% NMR yield. This compound is known.[145] ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.02 (br, 1H), 2.68-2.98 (m, 2H), 3.62-3.79 (m, 2 H), 3.81(s, 3H), 4.73(ddq, *J* =

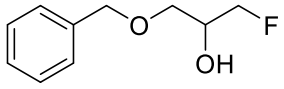
48.8 Hz, 2.4 Hz and 6.0 Hz, 1H), 6.85 (d, J = 8.8 Hz, 2H,), 7.15 (d, J = 8.8 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$): δ -187.6 (m).

3-Fluoro-2-hydroxypropyl 4-nitrobenzoate (5-10h)



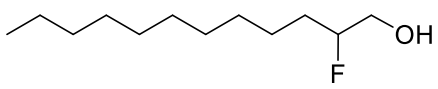
Brown solid, 48% yield ^{19}F NMR (376 MHz, $CDCl_3$) δ: –233.4 (m, 1F).

1-(Benzyloxy)-3-fluoropropan-2-ol (5-10i)



Colorless oil, 41% yield. This compound is known.[146] ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.56 (bs, 1H), 3.54 (d, J = 5.1Hz, 2H), 3.69- 4.09 (m, 1H), 4.32 (dd, J = 48.0Hz, 2H), 4.53 (s, 2H), 7.31(m, 5H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: –234.85 (m, 1F)

2-Fluorododecan-1-ol (5-10j)

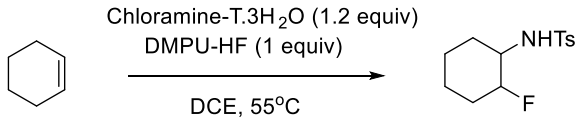


Waxy solid, 78% NMR yield. This compound is known.[143] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.524 (dm, J = 51.3 Hz, 1H); 3.77-3.50 (m, 3H); 1.71-1.16 (m, 18H); 0.85 (t, J = 6.6 Hz, 3H) ^{19}F NMR (376 MHz, $CDCl_3$) δ: –189.6 (m)

Synthesis of fluorotosyl amine via metal free protocol

In a polyethylene vial charged with a magnetic stirring bar, the alkene (0.2 mmol), dry chloramine-T (1.1 equiv) was dissolved in 1 mL of dichloroethane maintained at room temperature. DMPU-HF (HF content 65 % wt/wt, 41 µL, 1.4 mmol) was added slowly and

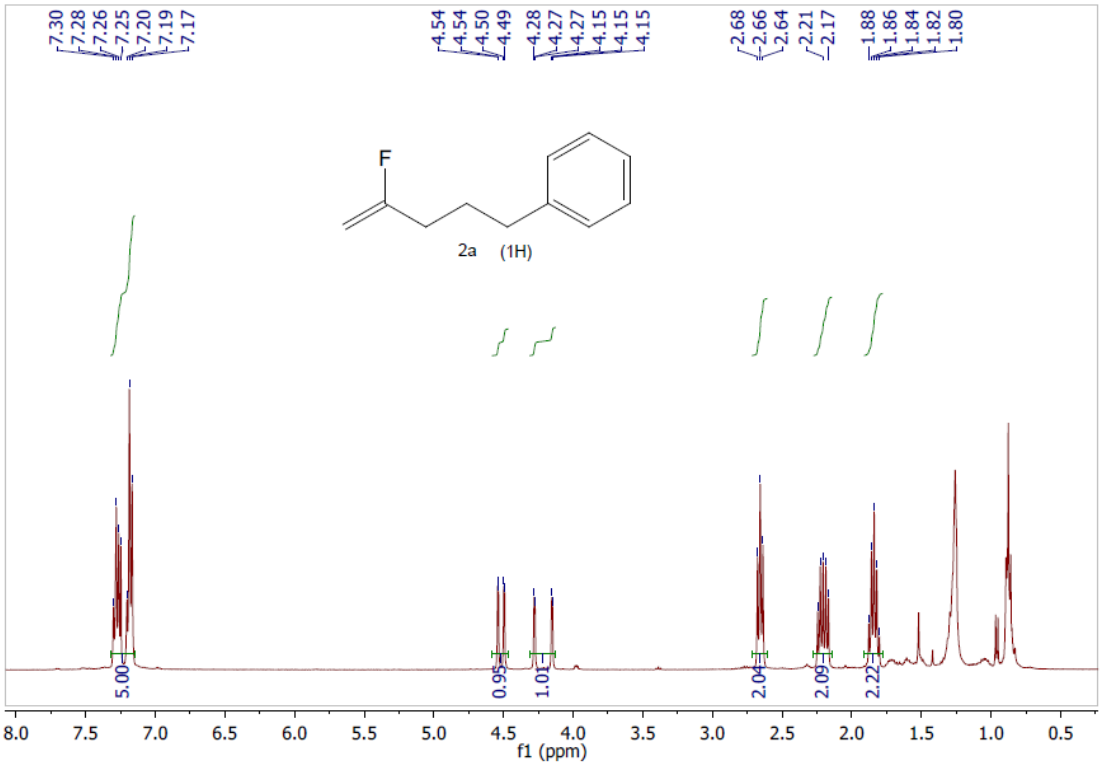
the mixture was stirred slowly maintained at 65 ^{o}C for 18 h. The progress of reaction can be monitored by TLC (green or dark brown dots on anisaldehyde stain). After completion of the reaction the crude product was analyzed with NMR spectroscopy. The products are quite unstable during work-up and efforts are still ongoing to obtain analytical pure products.



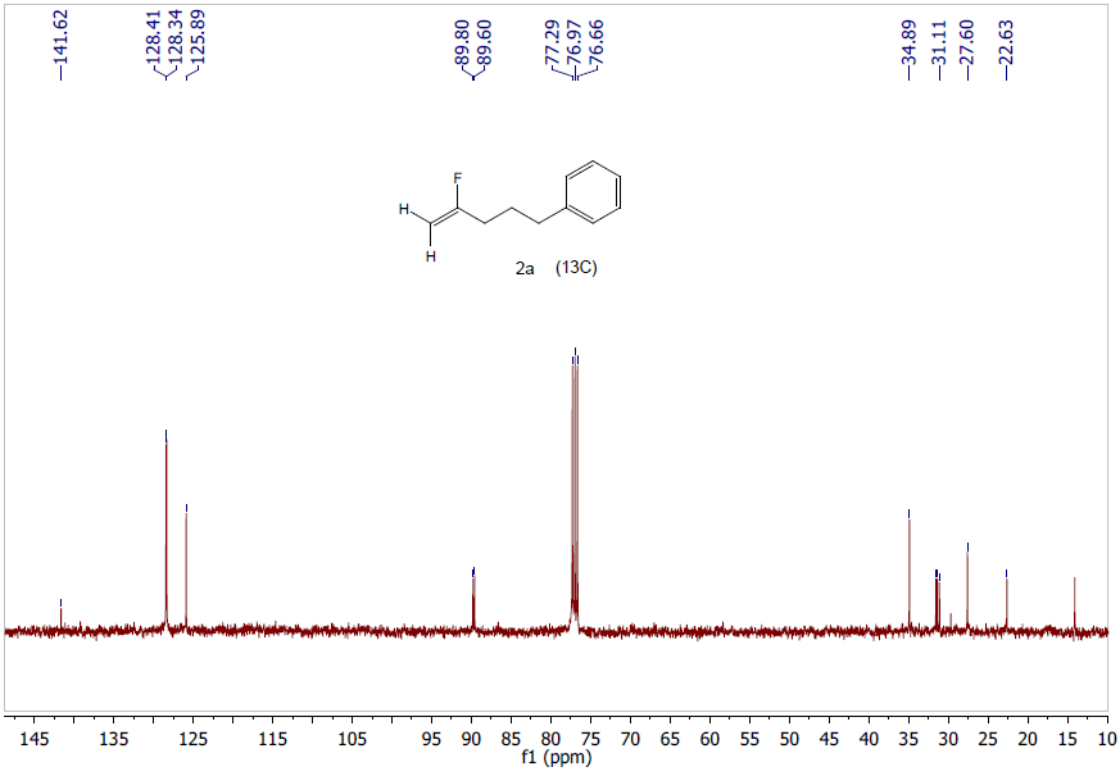
6 SPECTROSCOPIC DATA

NMR FILES FOR MONO- AND DI-FLUORINATION OF ALKYNES

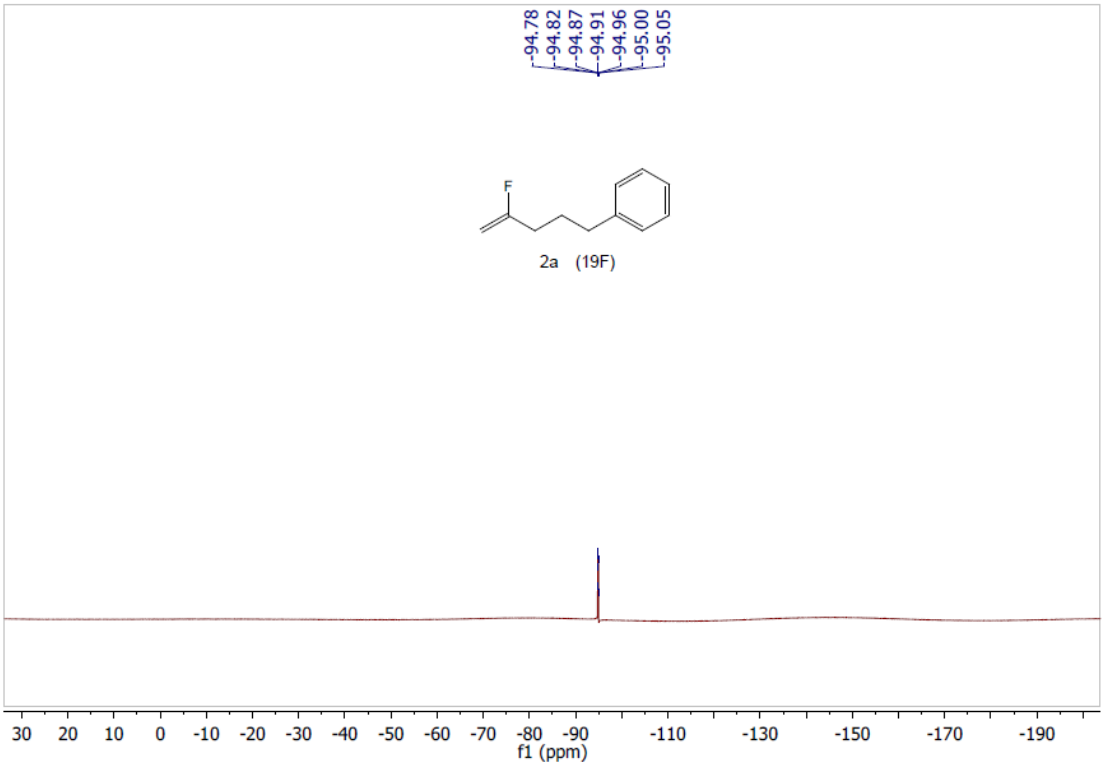
^{1}H NMR Spectrum 2-2a



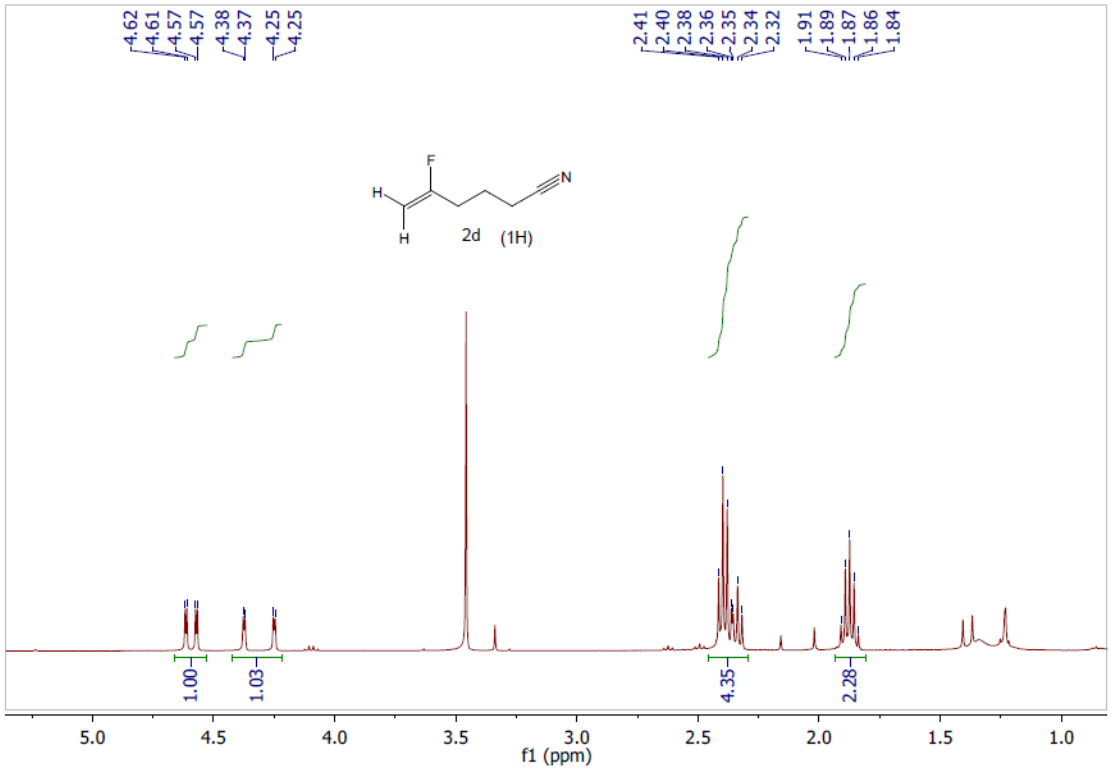
^{13}C NMR Spectrum 2-2a



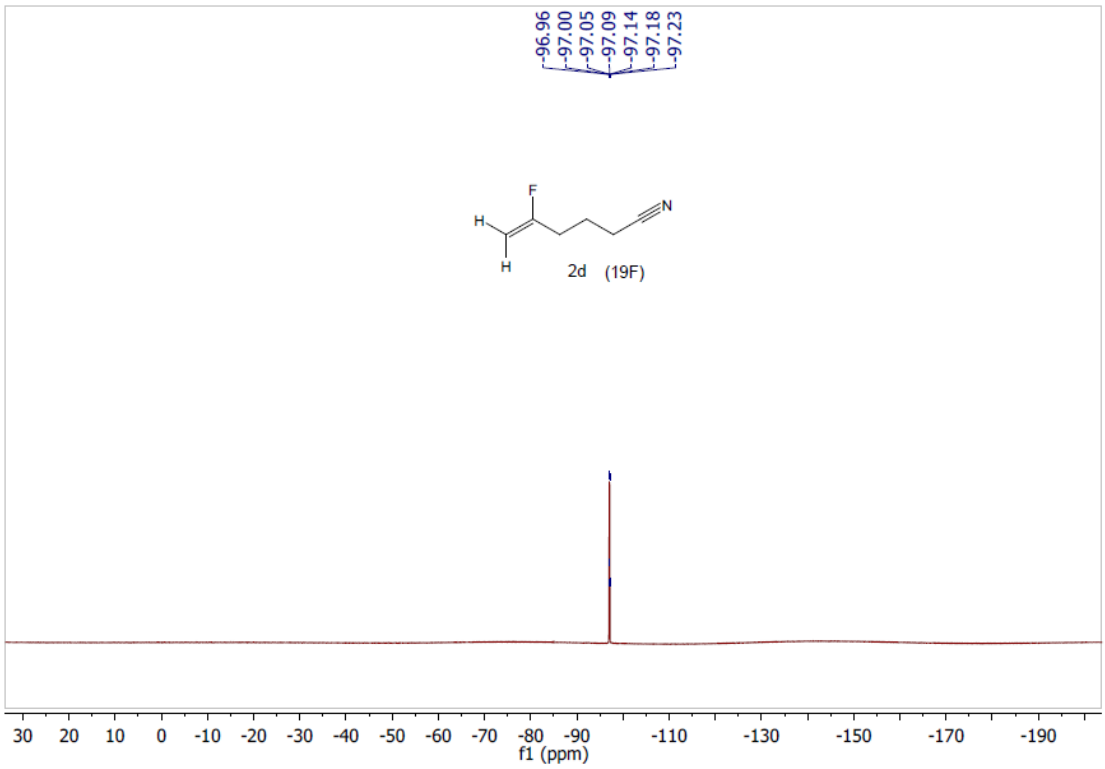
^{19}F NMR Spectrum 2-2a



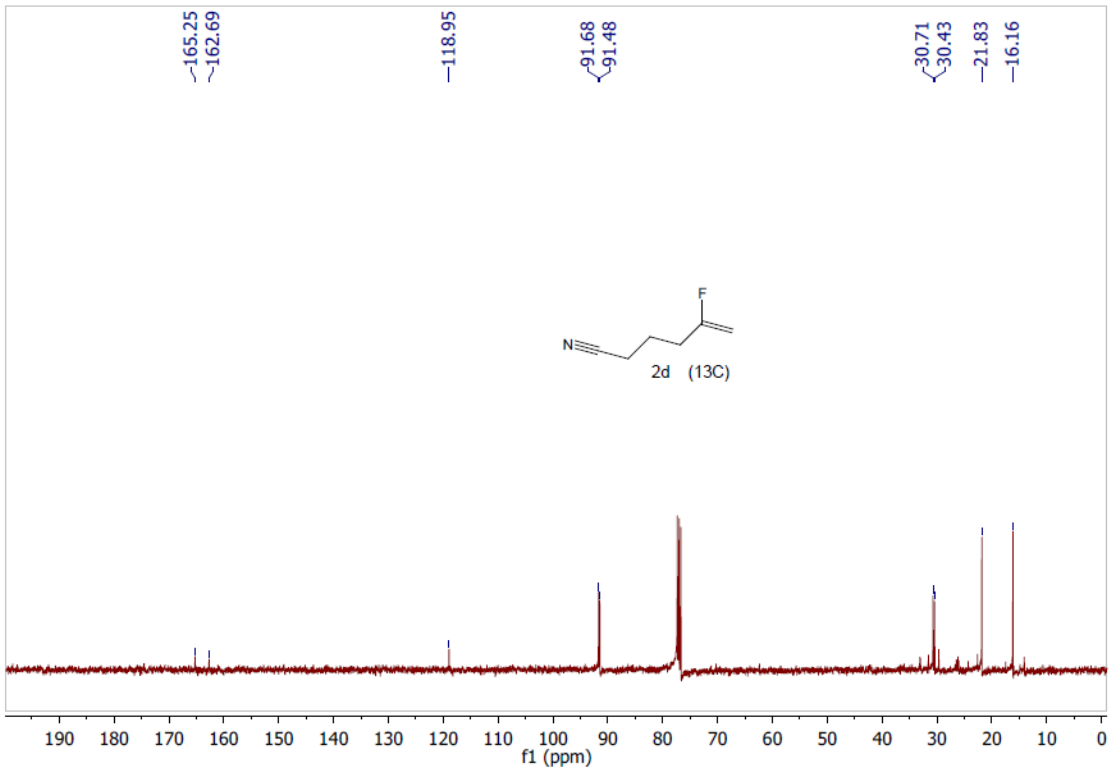
^{1}H NMR Spectrum 2-2d



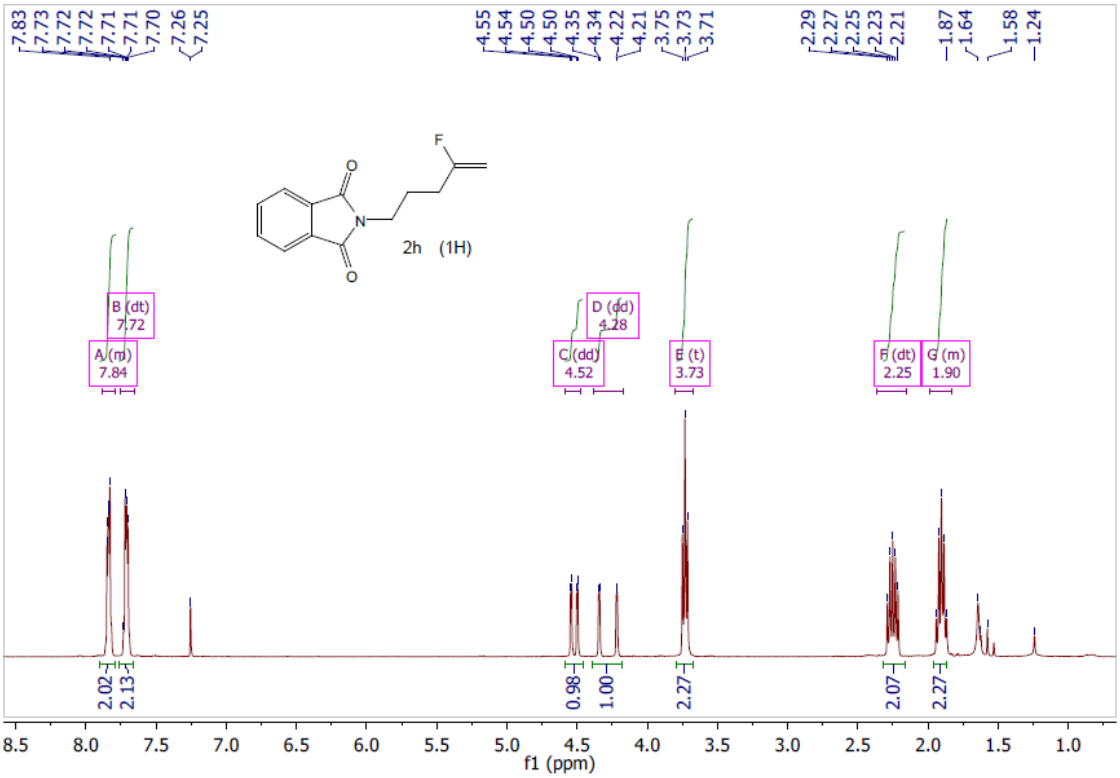
^{19}F NMR Spectrum 2-2d



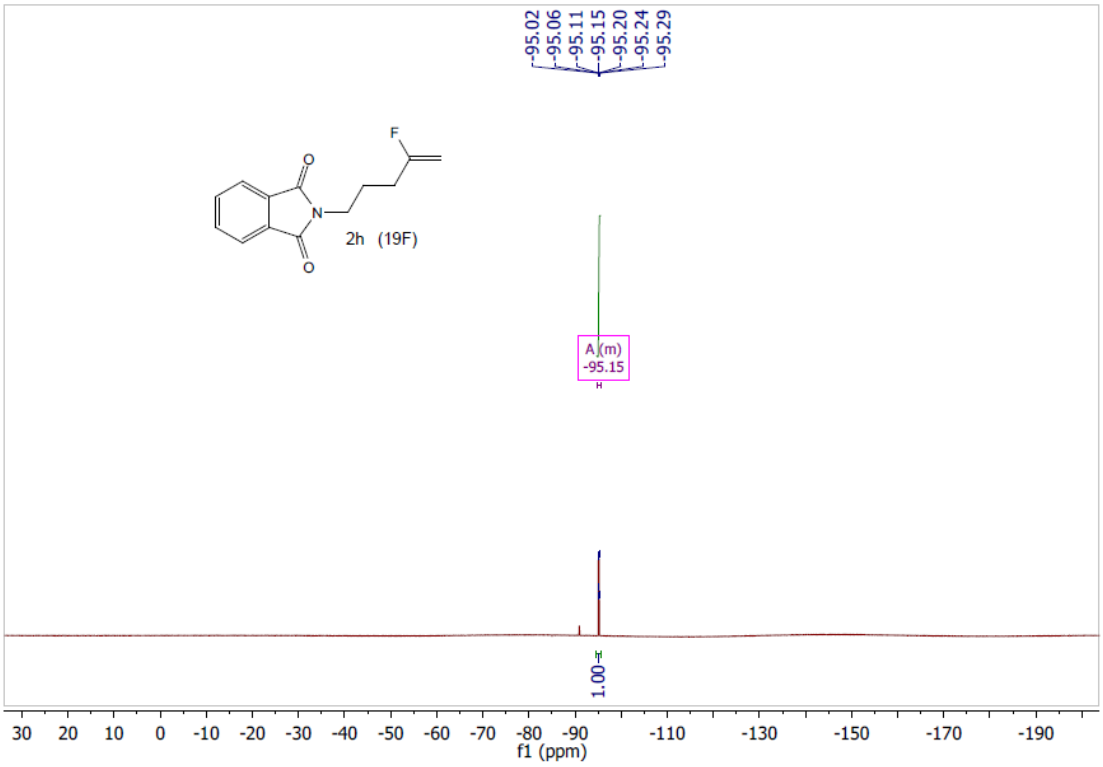
^{13}C NMR Spectrum 2-2d



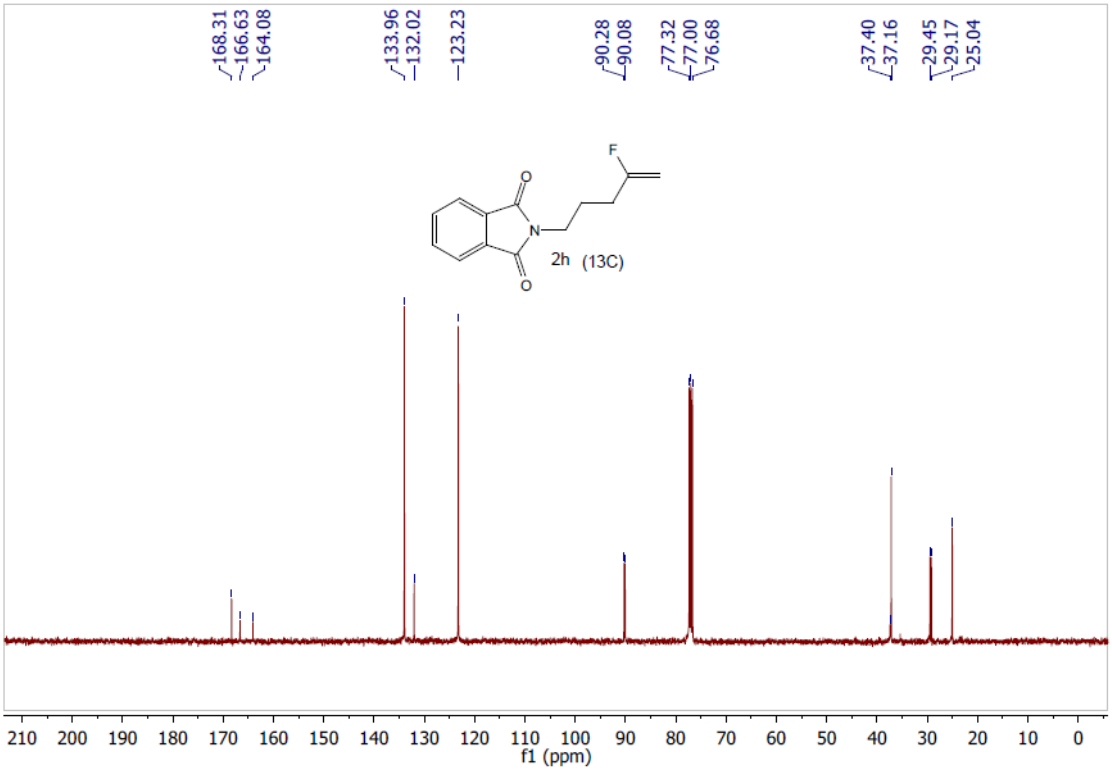
^{1}H NMR Spectrum 2-2h



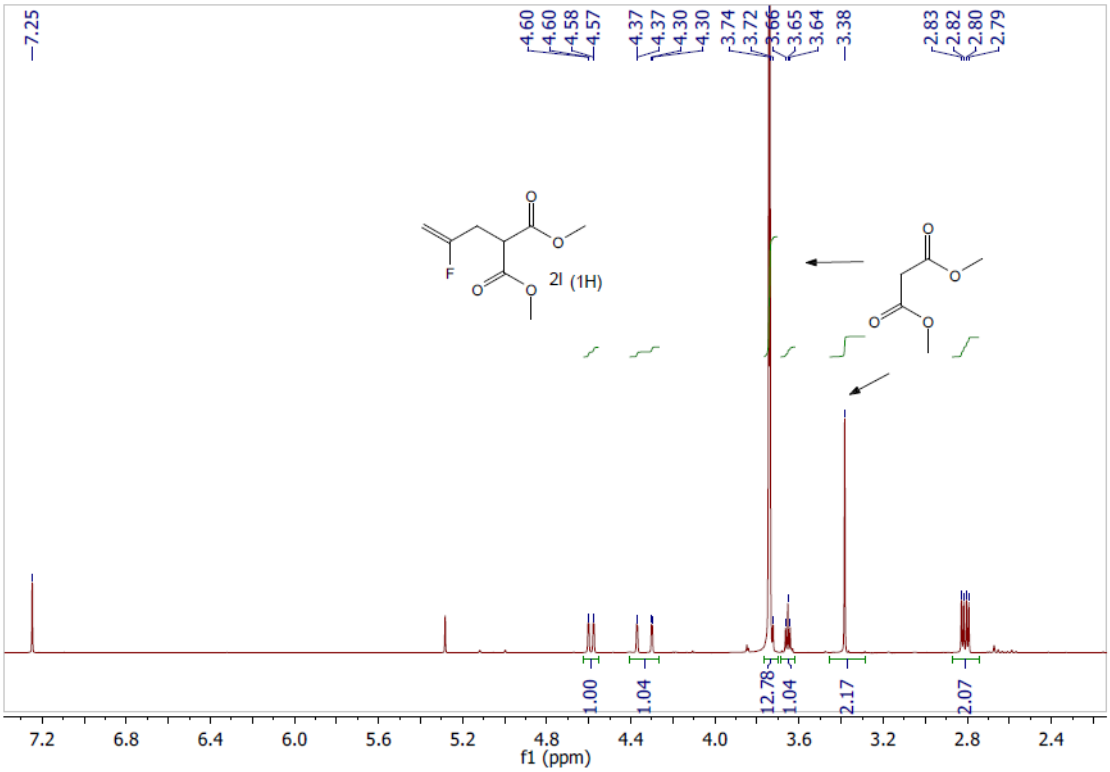
^{19}F NMR Spectrum 2-2h



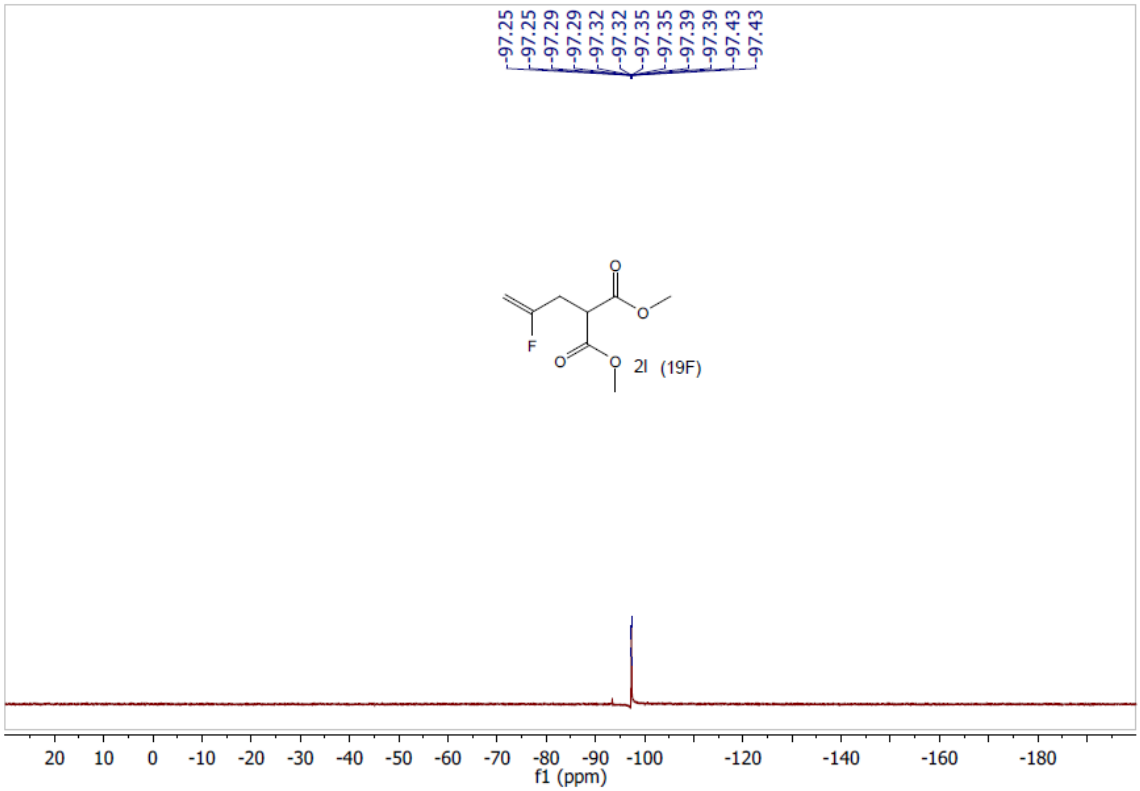
^{13}C NMR Spectrum 2-2h



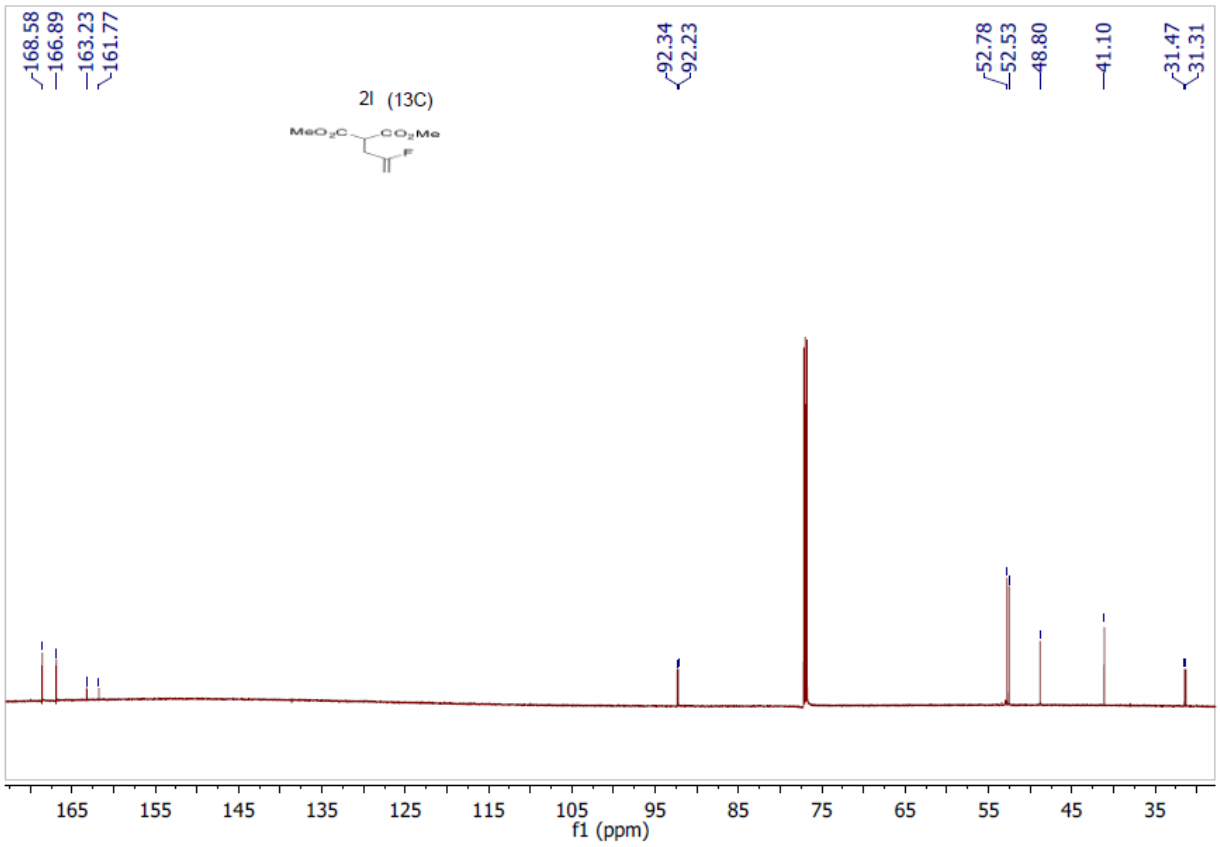
^{1}H NMR Spectrum 2-2l



^{19}F NMR Spectrum 2-2l

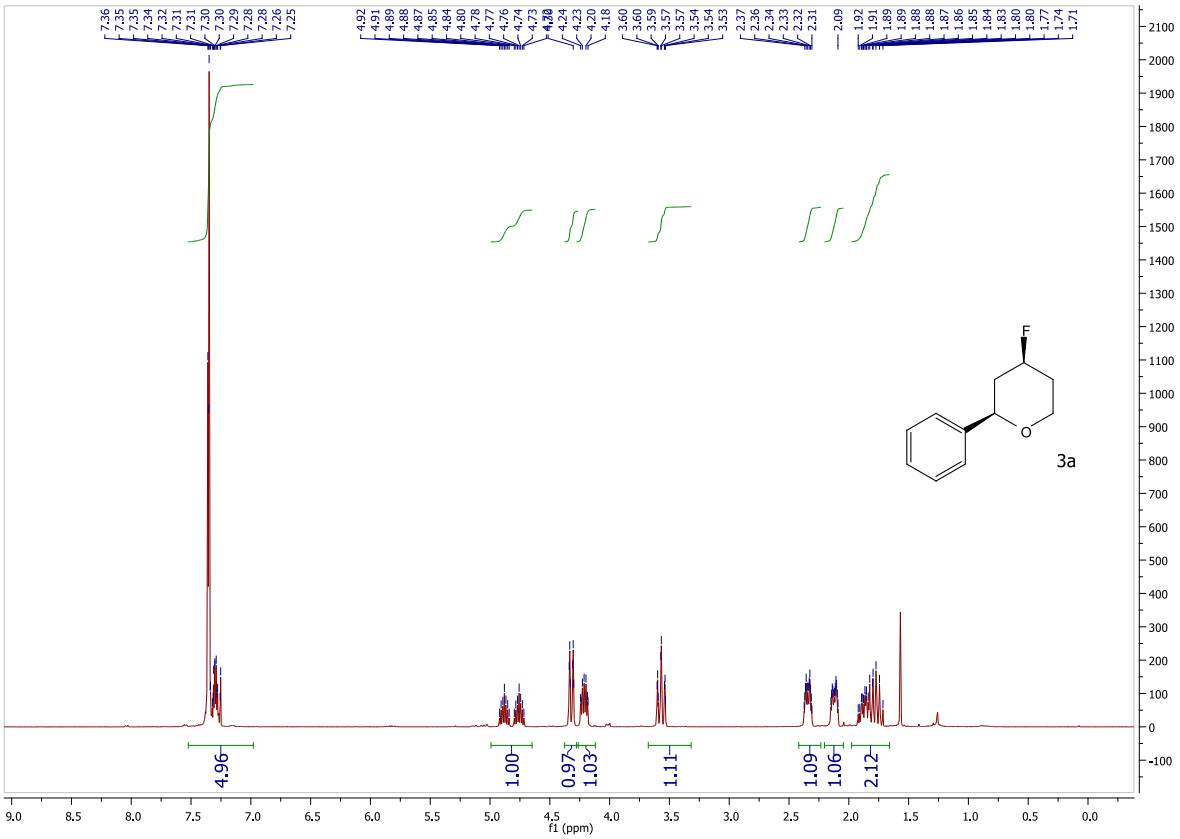


^{13}C NMR Spectrum 2-2l

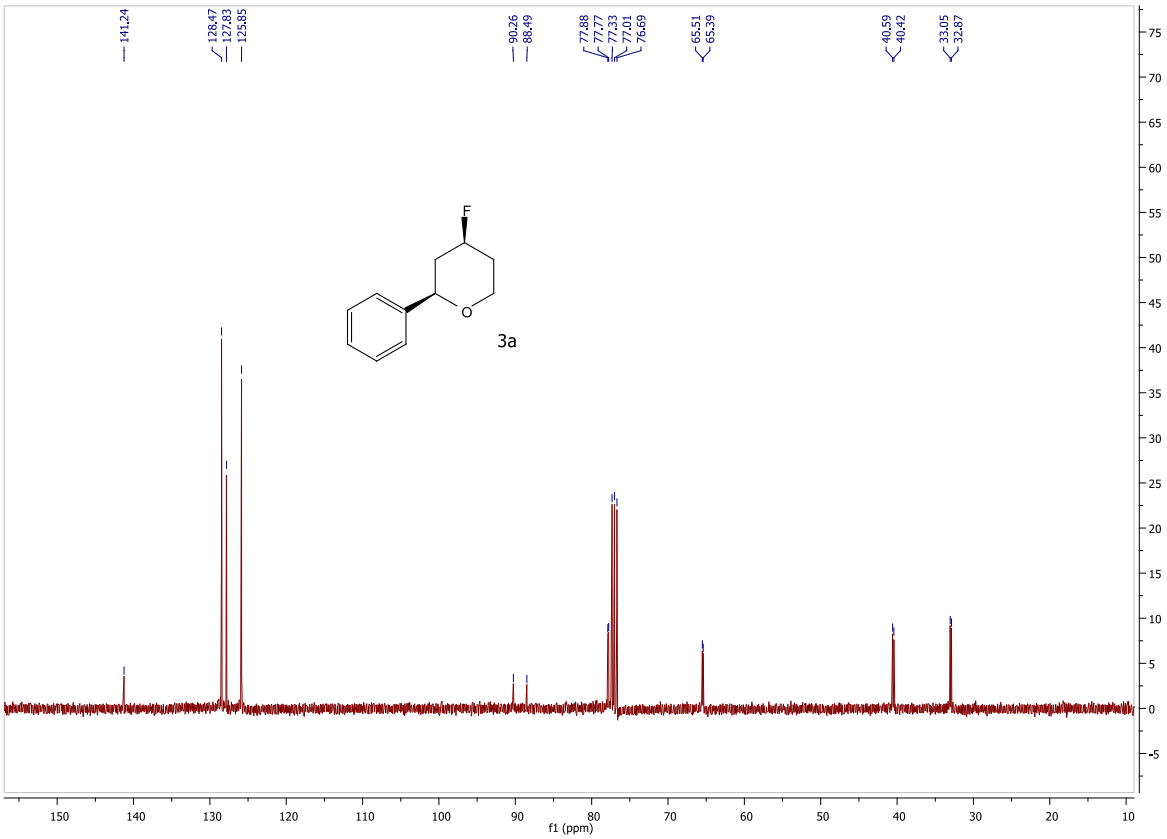


NMR FILES FOR PRINS-CYCLIZATION

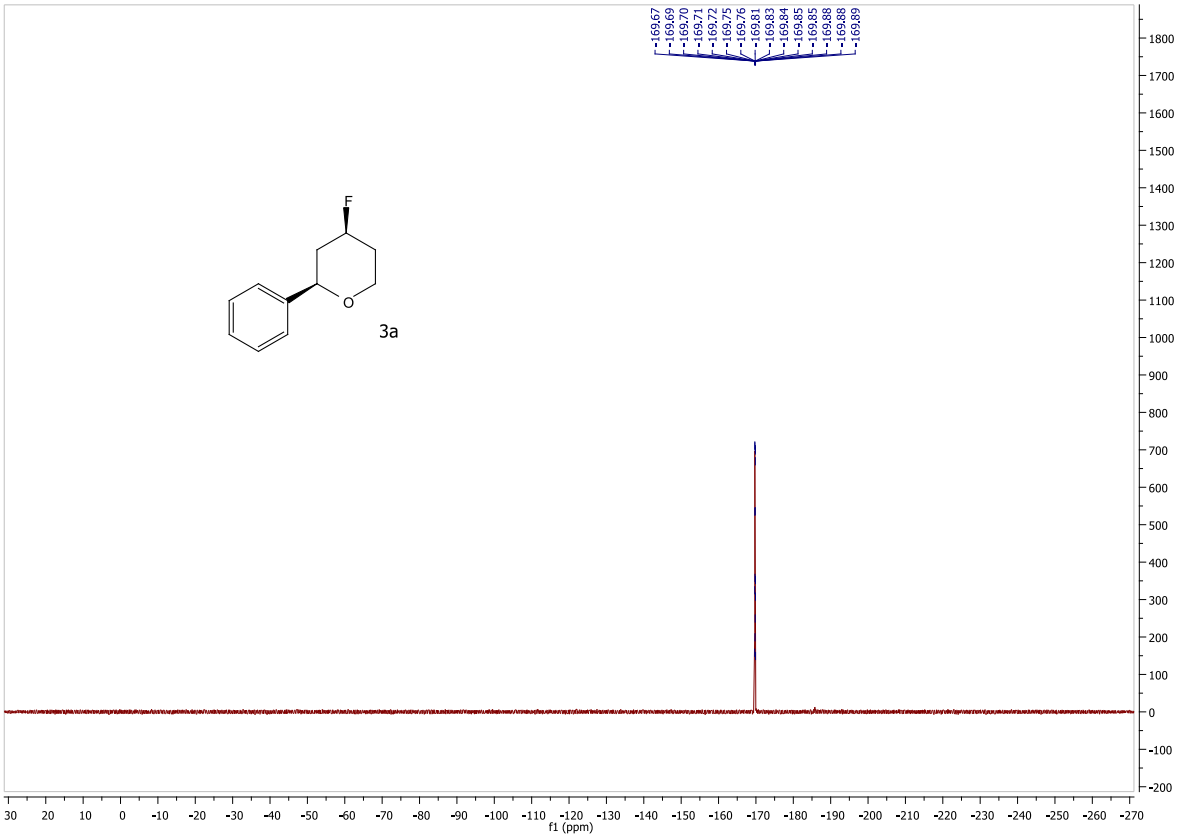
^{1}H NMR Spectrum 3-3a



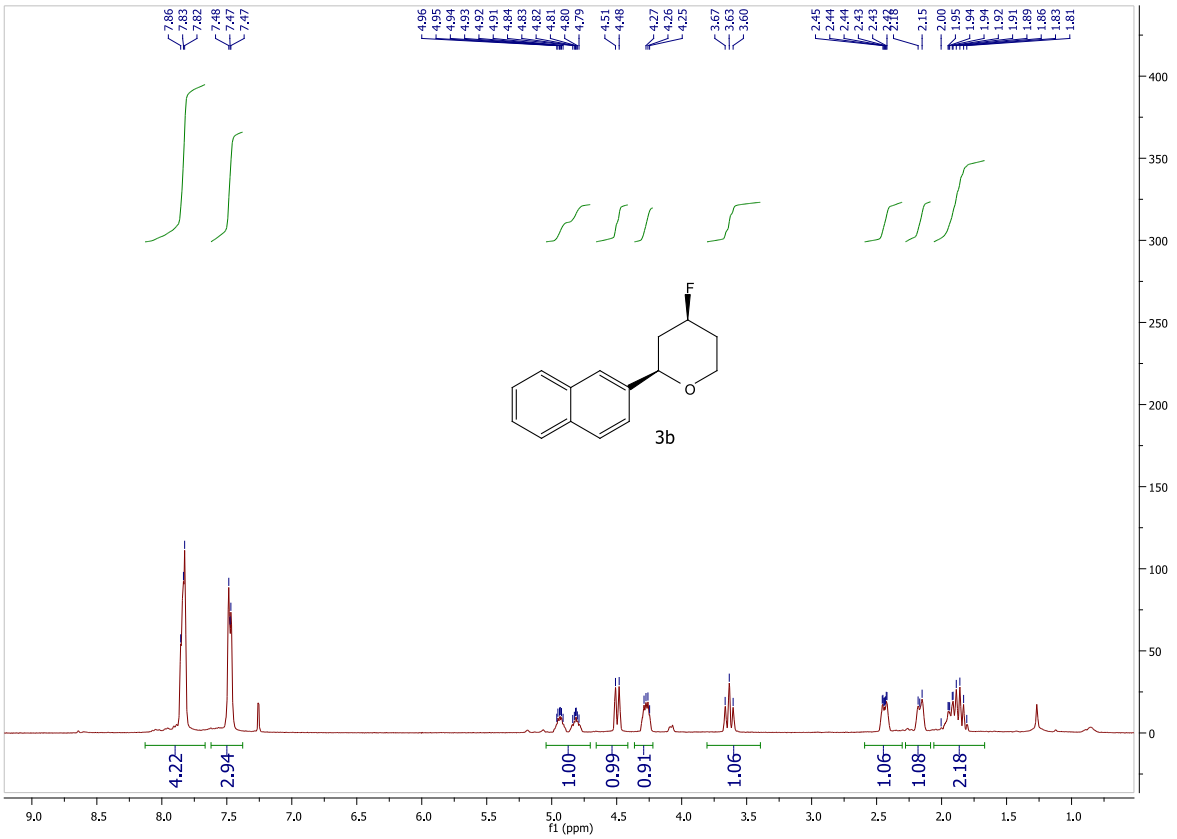
^{13}C NMR Spectrum 3-3a



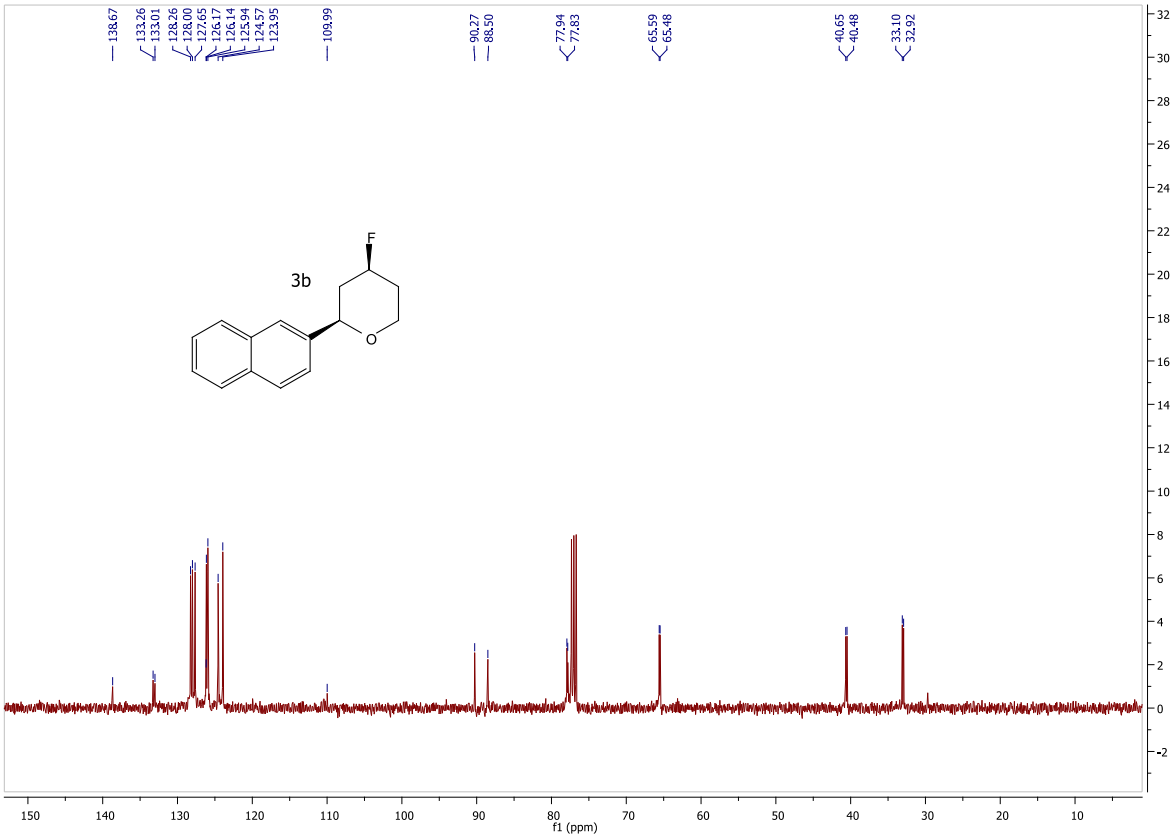
^{19}F NMR Spectrum 3-3a



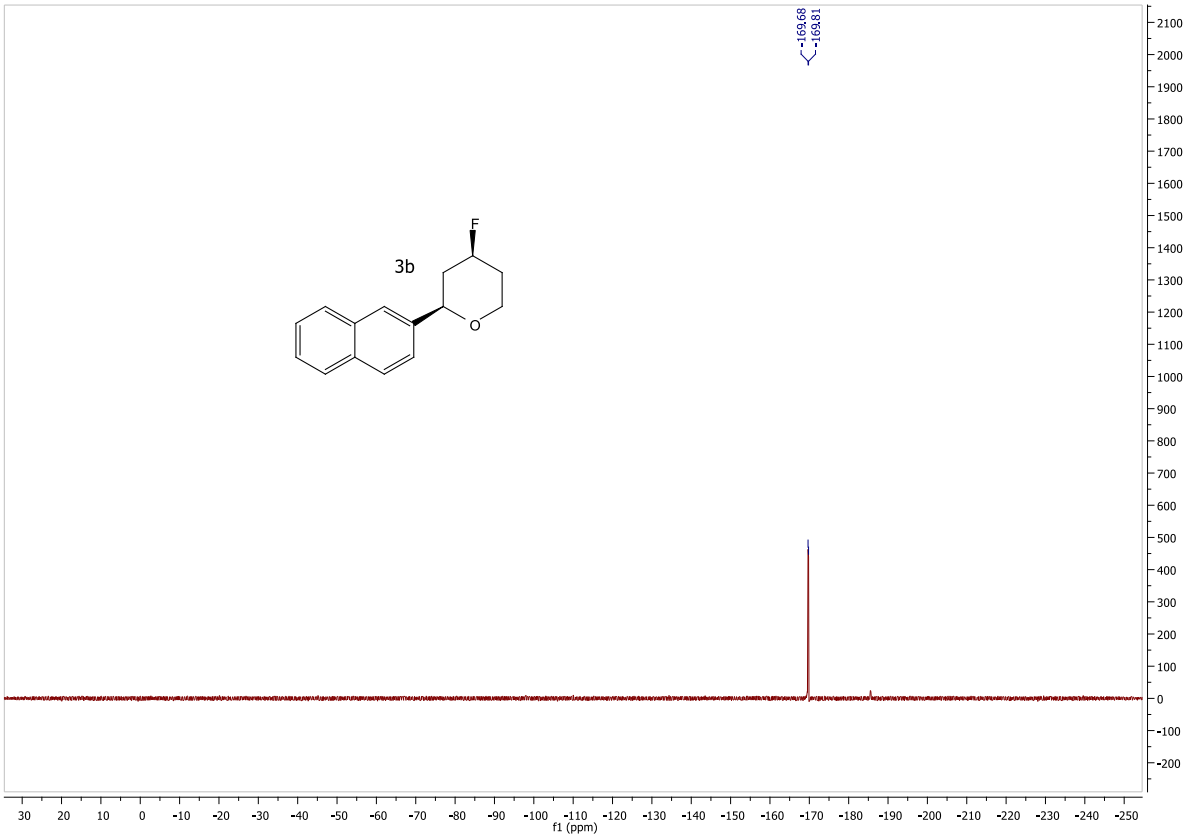
^{1}H NMR Spectrum 3-3b



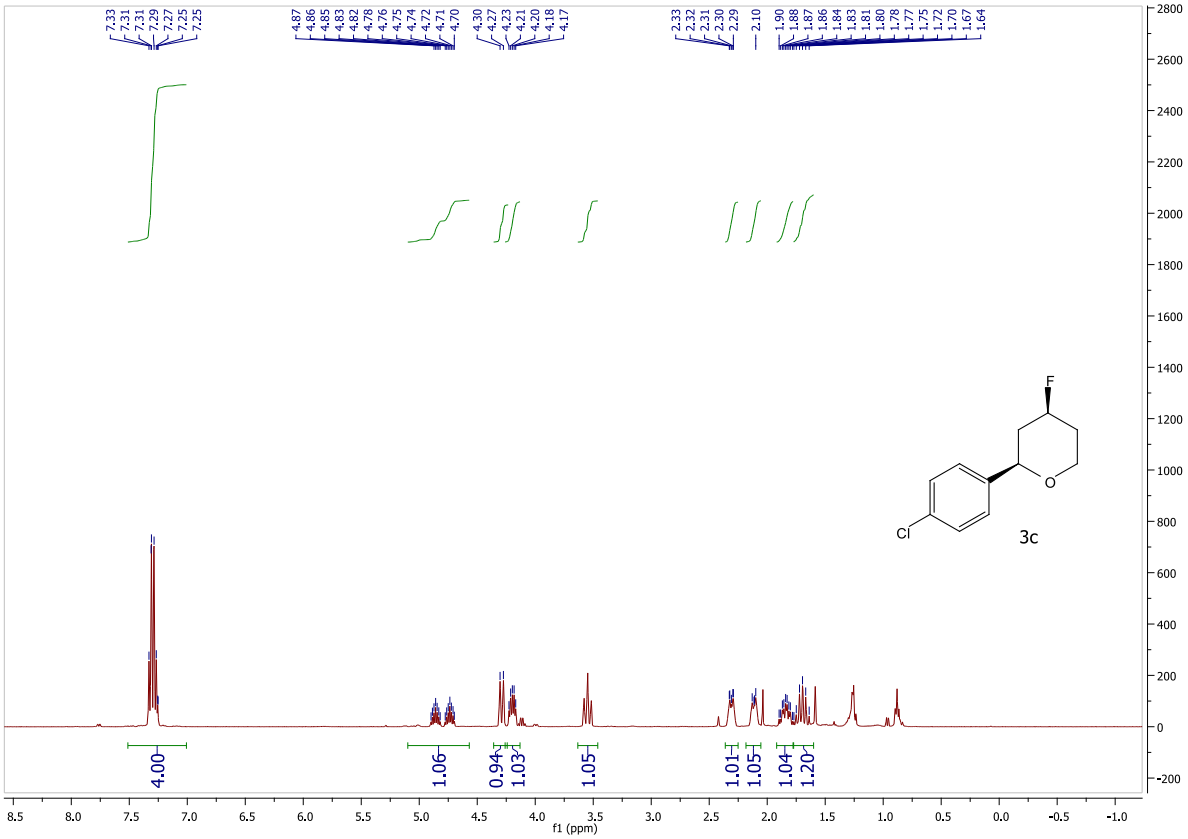
^{13}C NMR Spectrum 3-3b



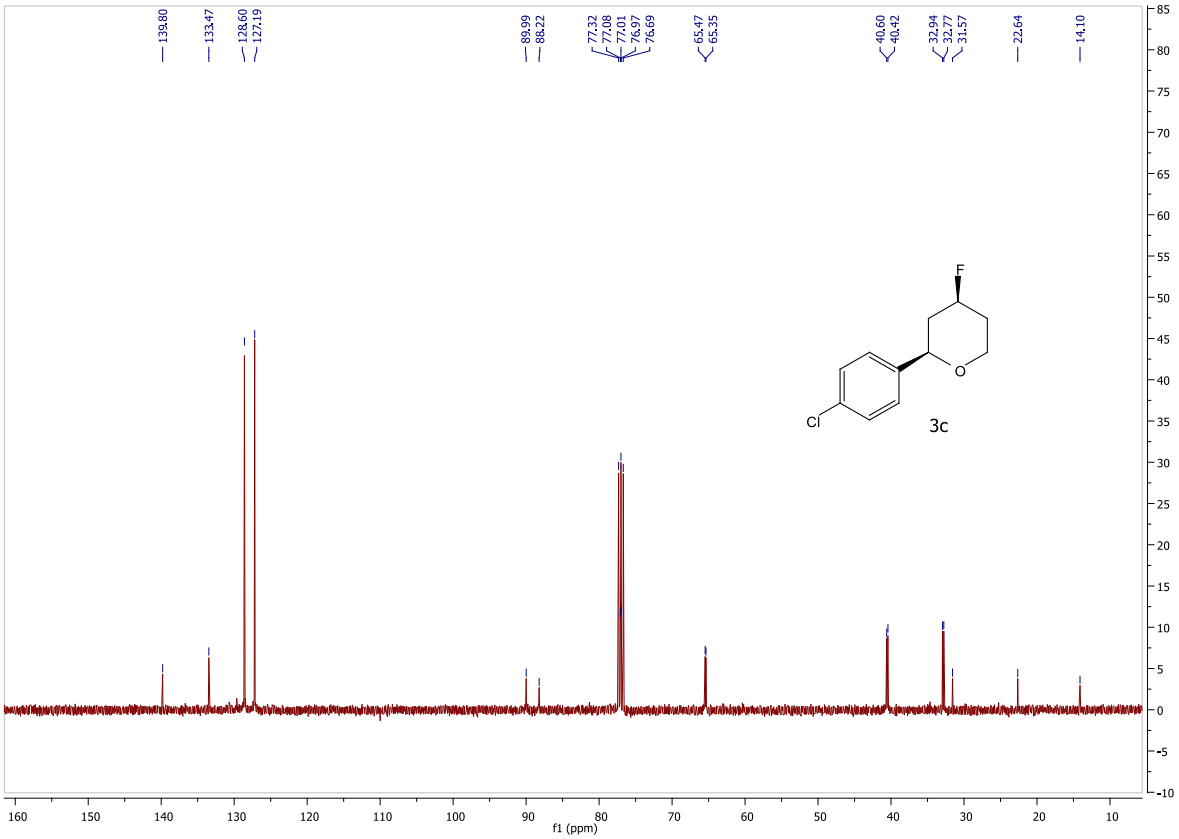
^{19}F NMR Spectrum 3-3b



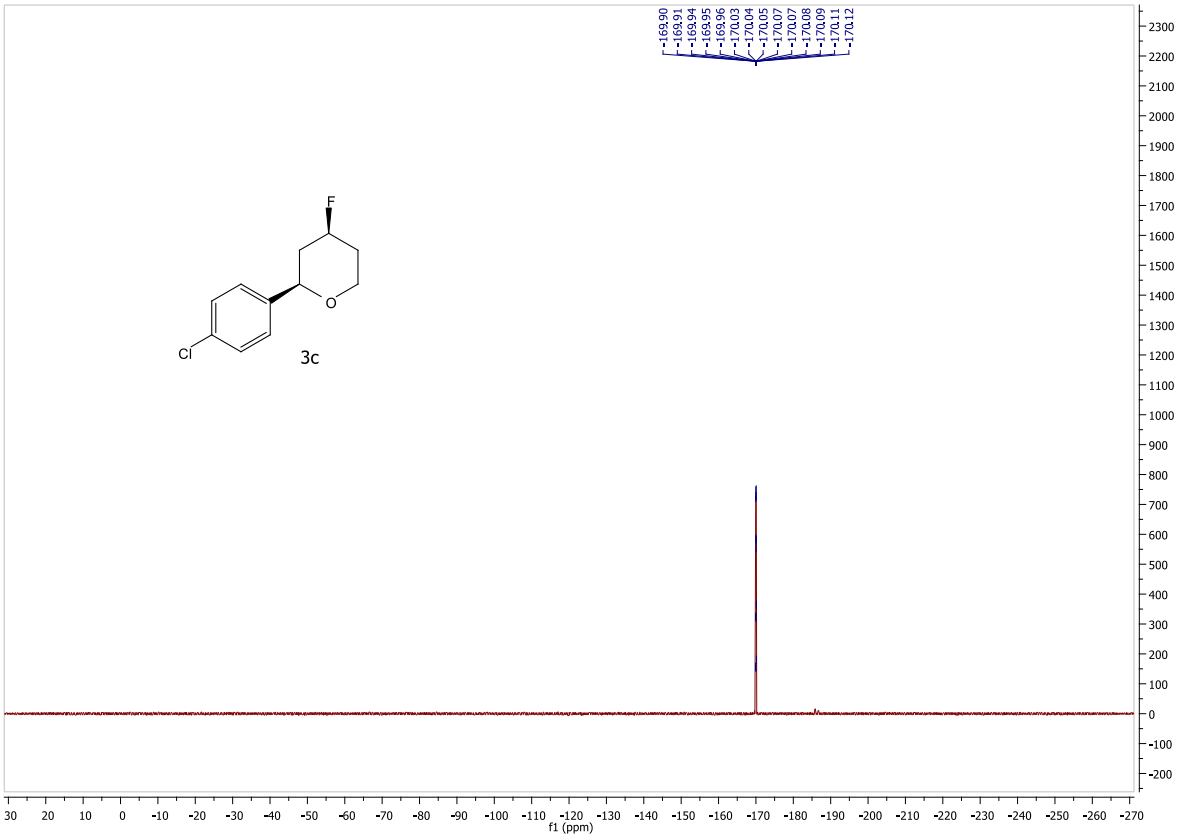
^{1}H NMR Spectrum 3-3c



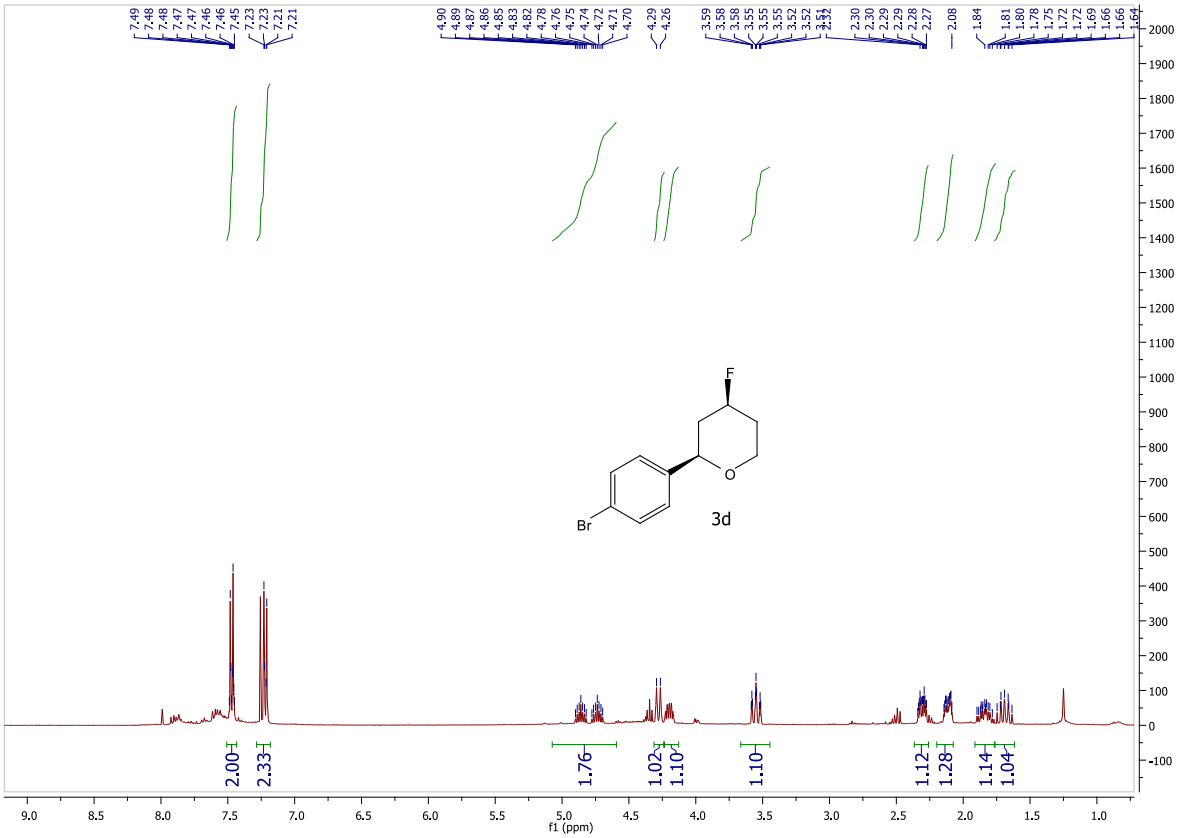
NMR Spectrum 3-3c



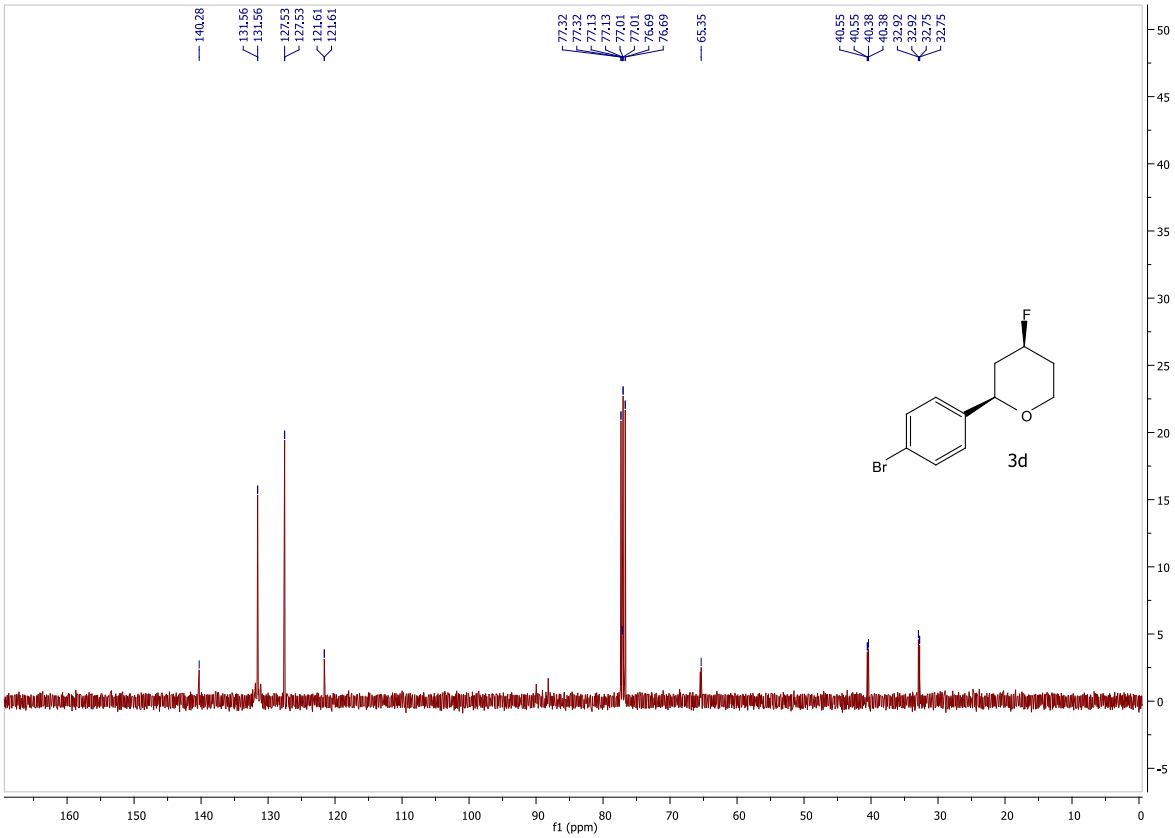
^{19}F NMR Spectrum 3-3c



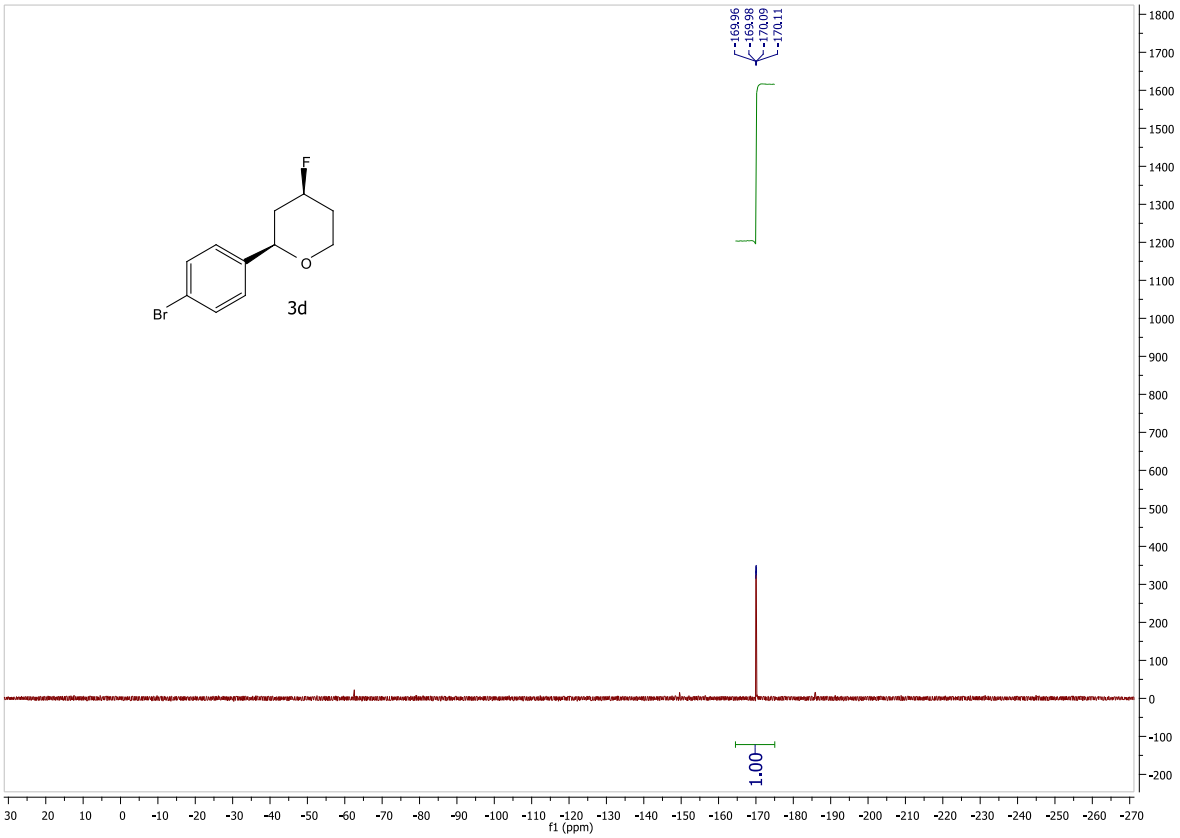
^{1}H NMR Spectrum 3-3d



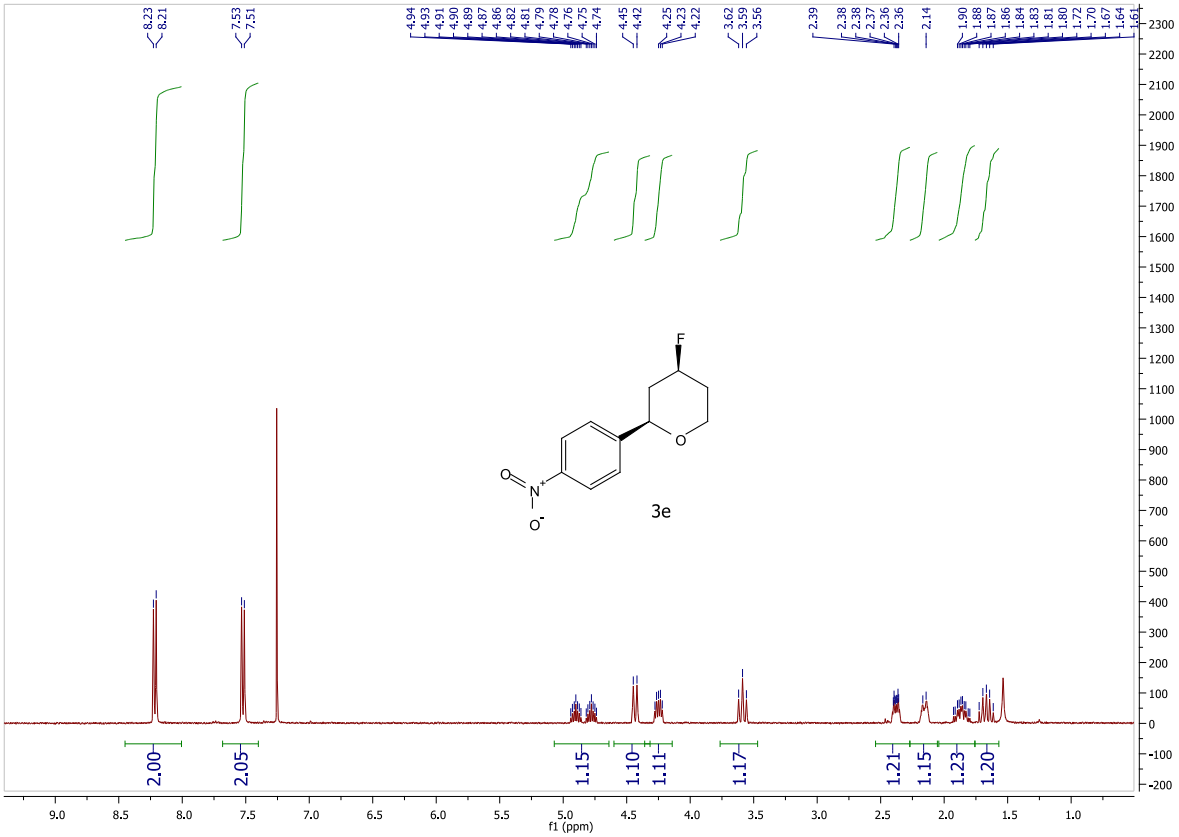
^{13}C NMR Spectrum 3-3d



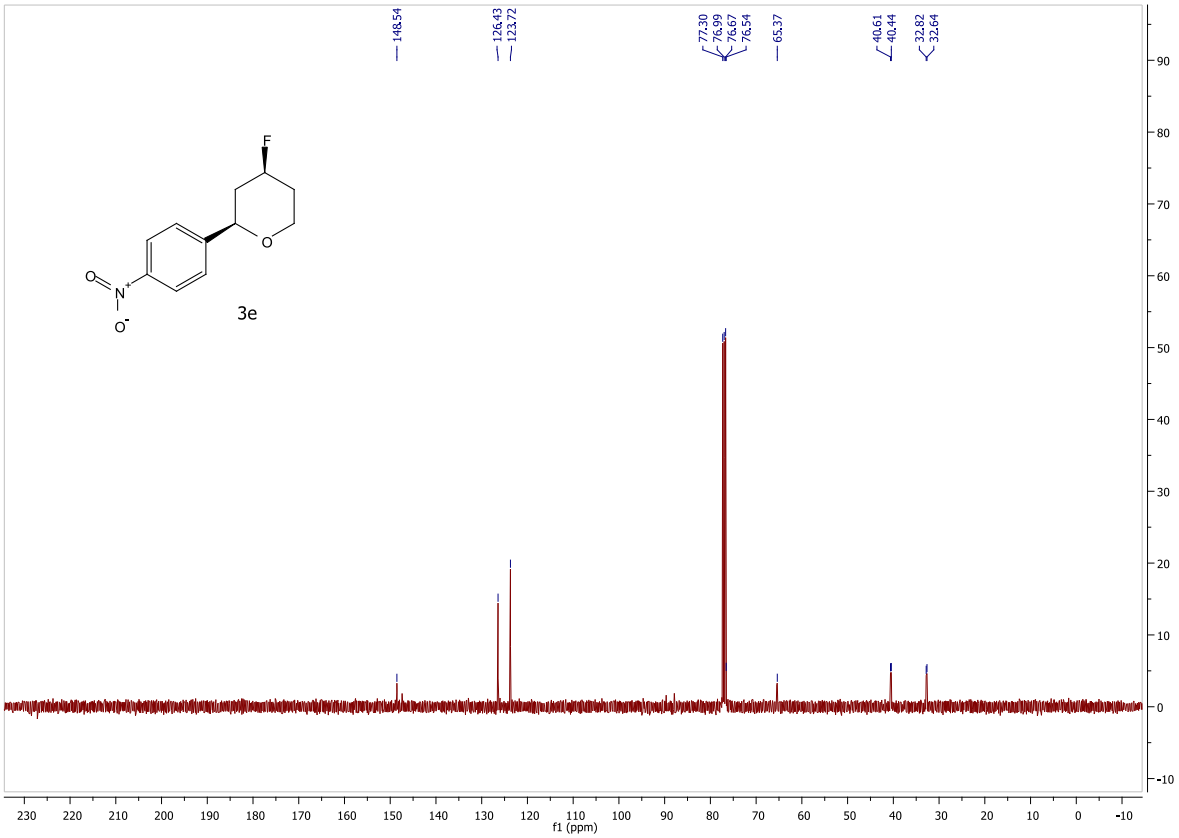
^{19}F NMR Spectrum 3-3d



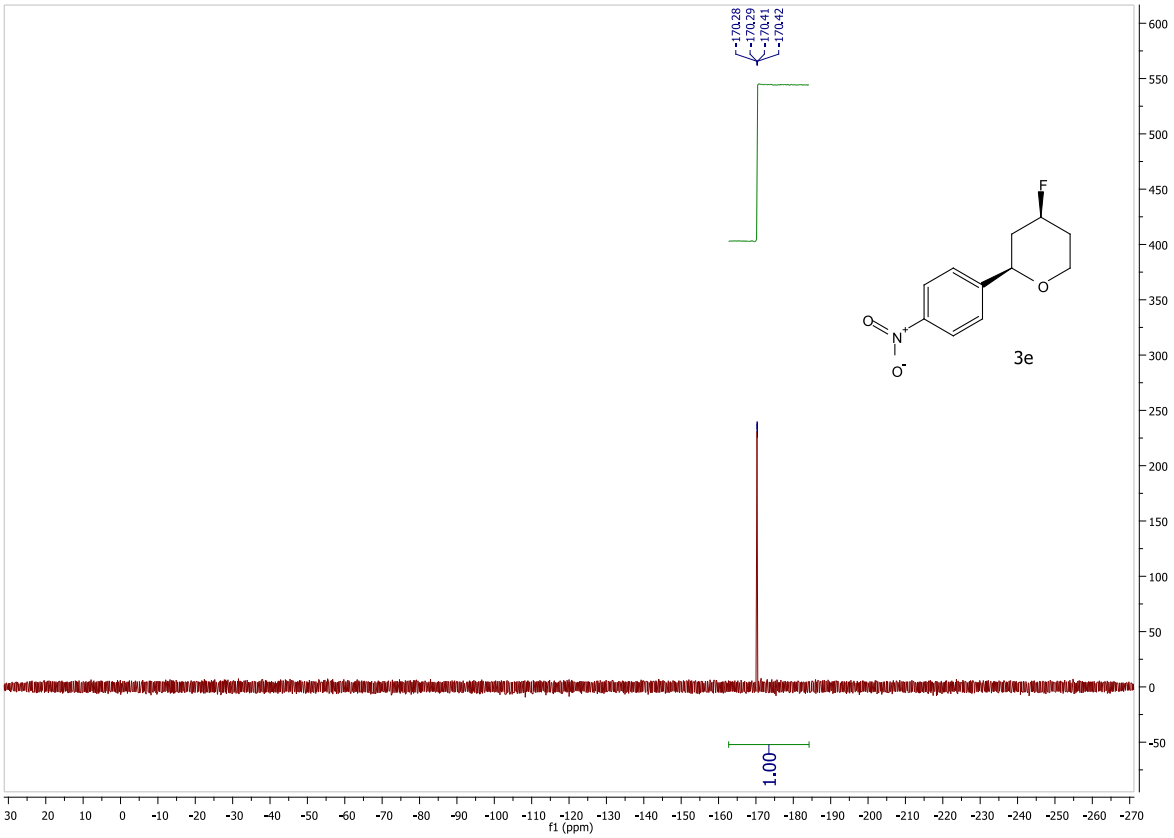
^{1}H NMR Spectrum 3-3e



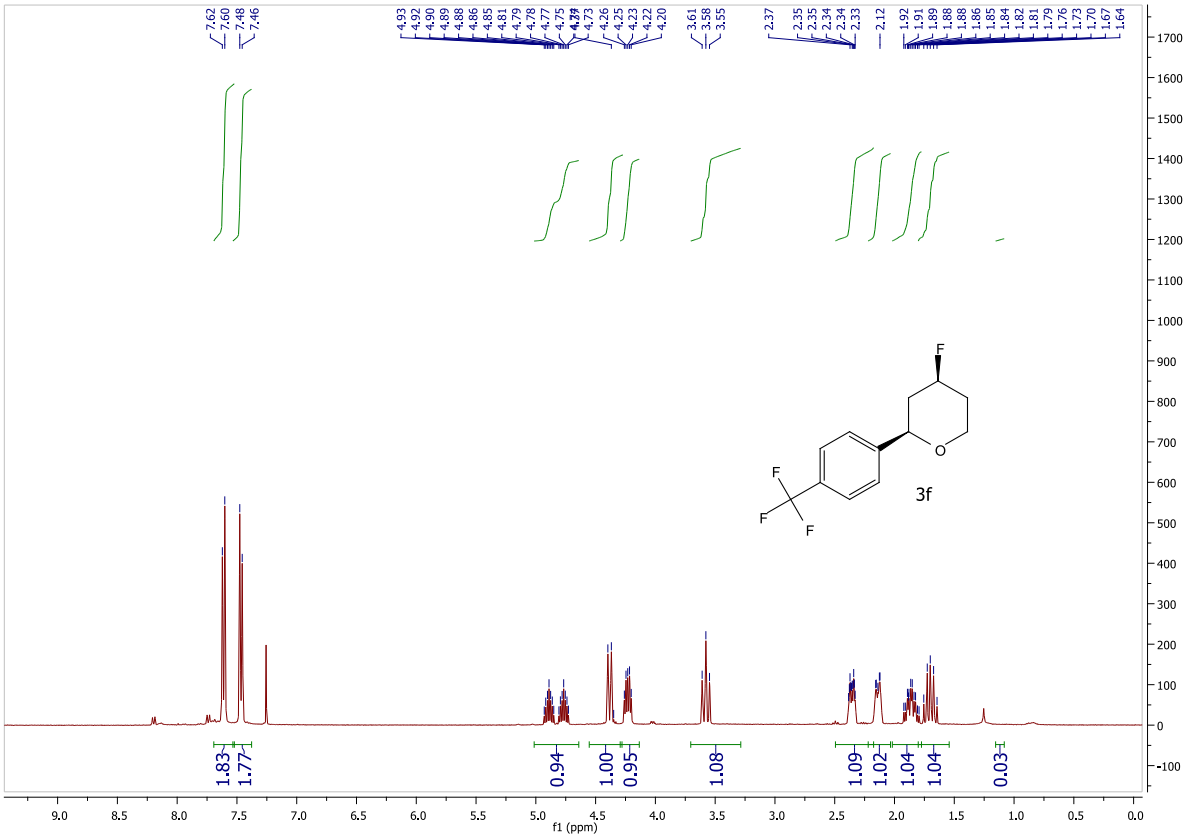
^{13}C NMR Spectrum 3-3e



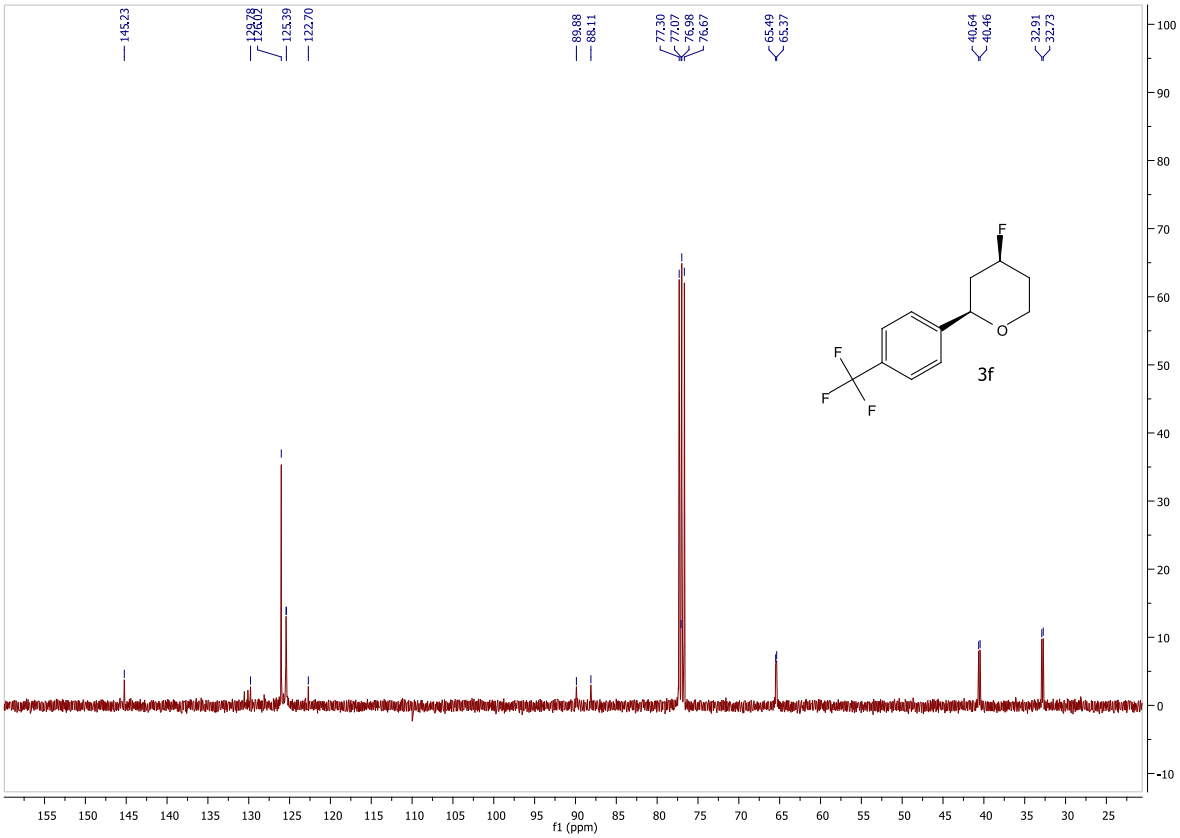
^{19}F NMR Spectrum 3-3e



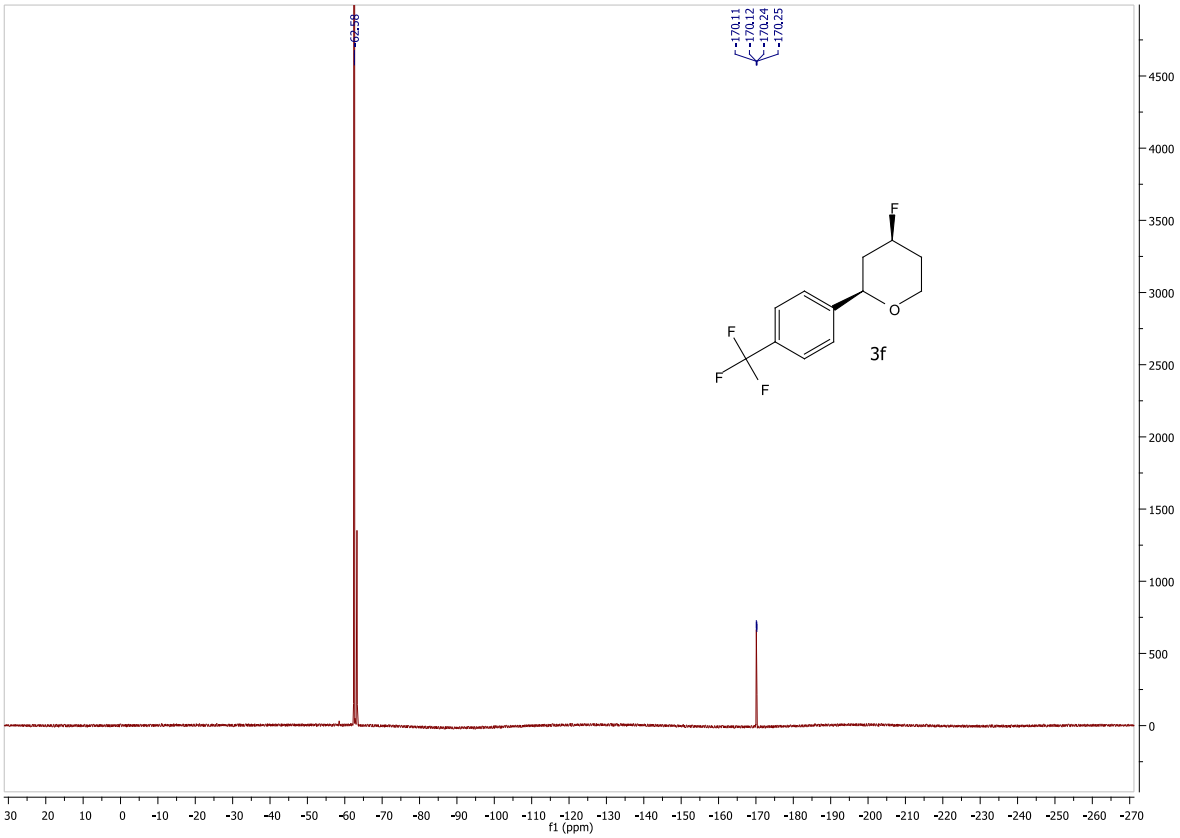
^{1}H NMR Spectrum 3-3f



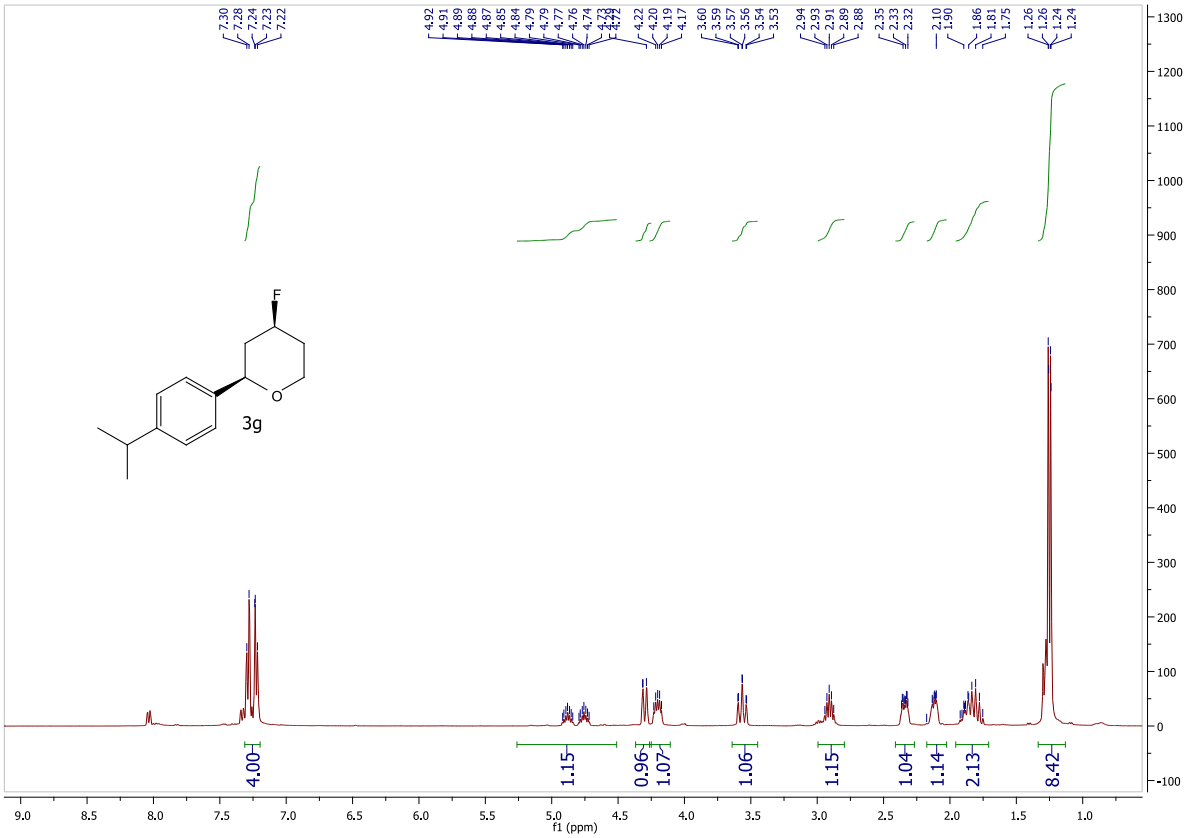
NMR Spectrum 3-3f



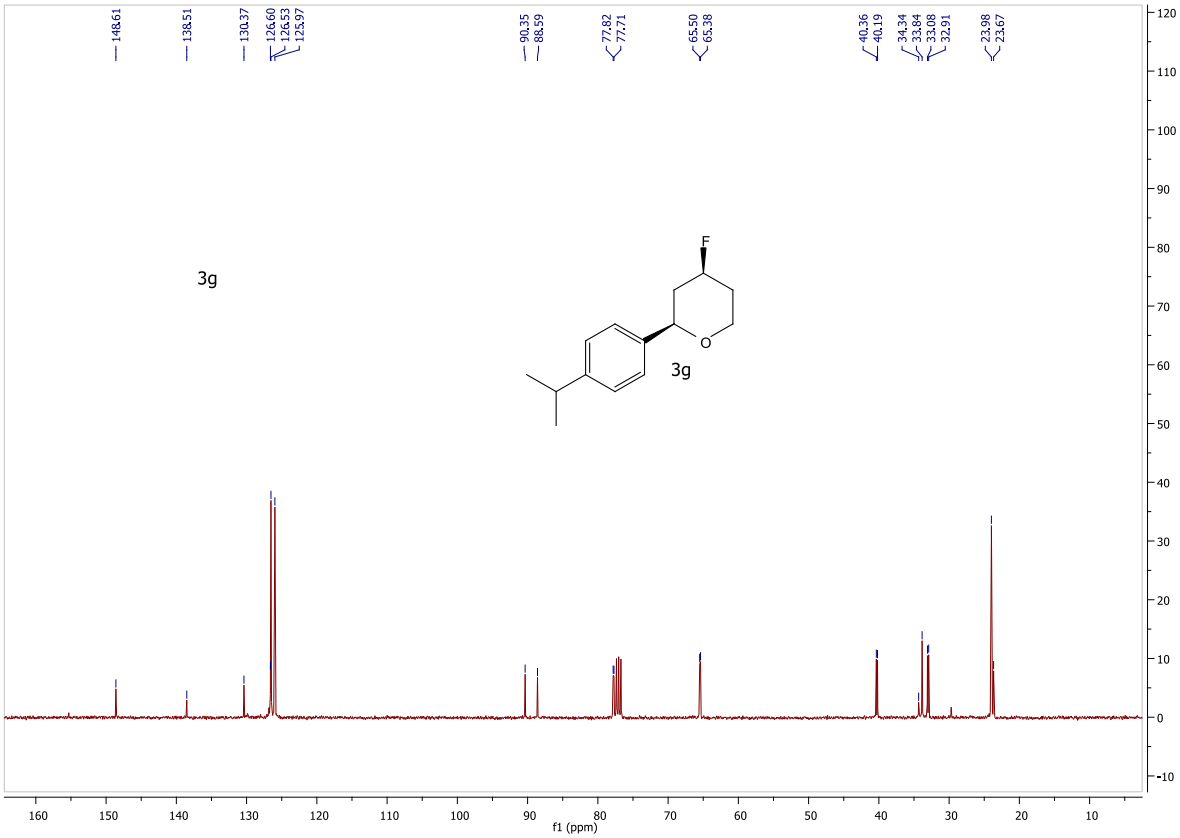
^{19}F NMR Spectrum 3-3f



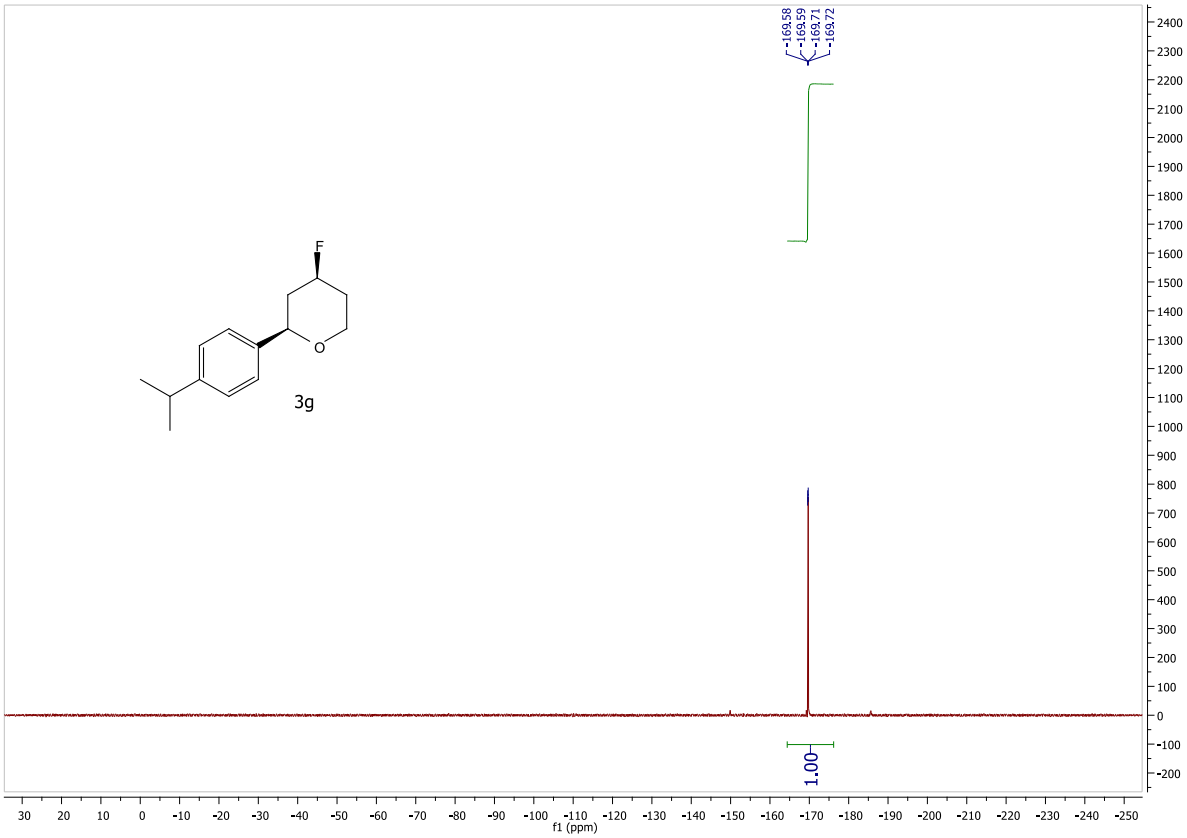
^{1}H NMR Spectrum 3-3g



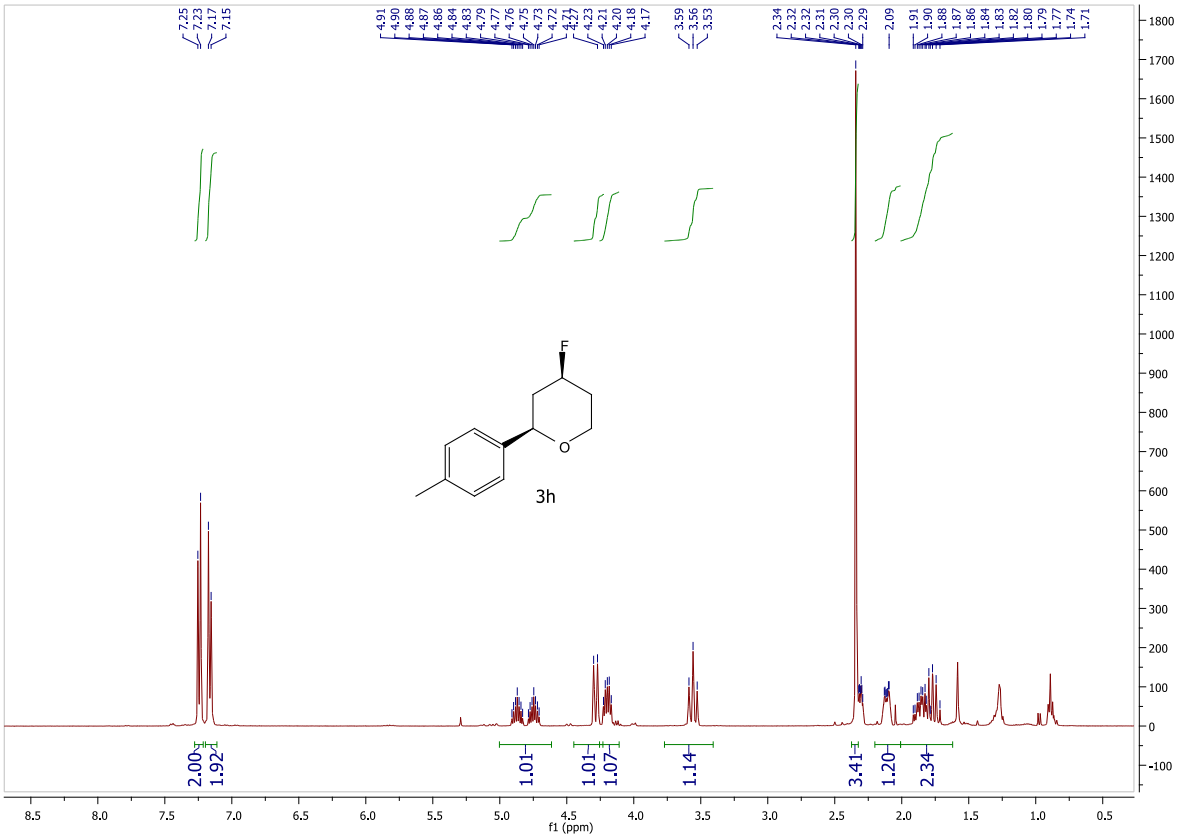
^{13}C NMR Spectrum 3-3g



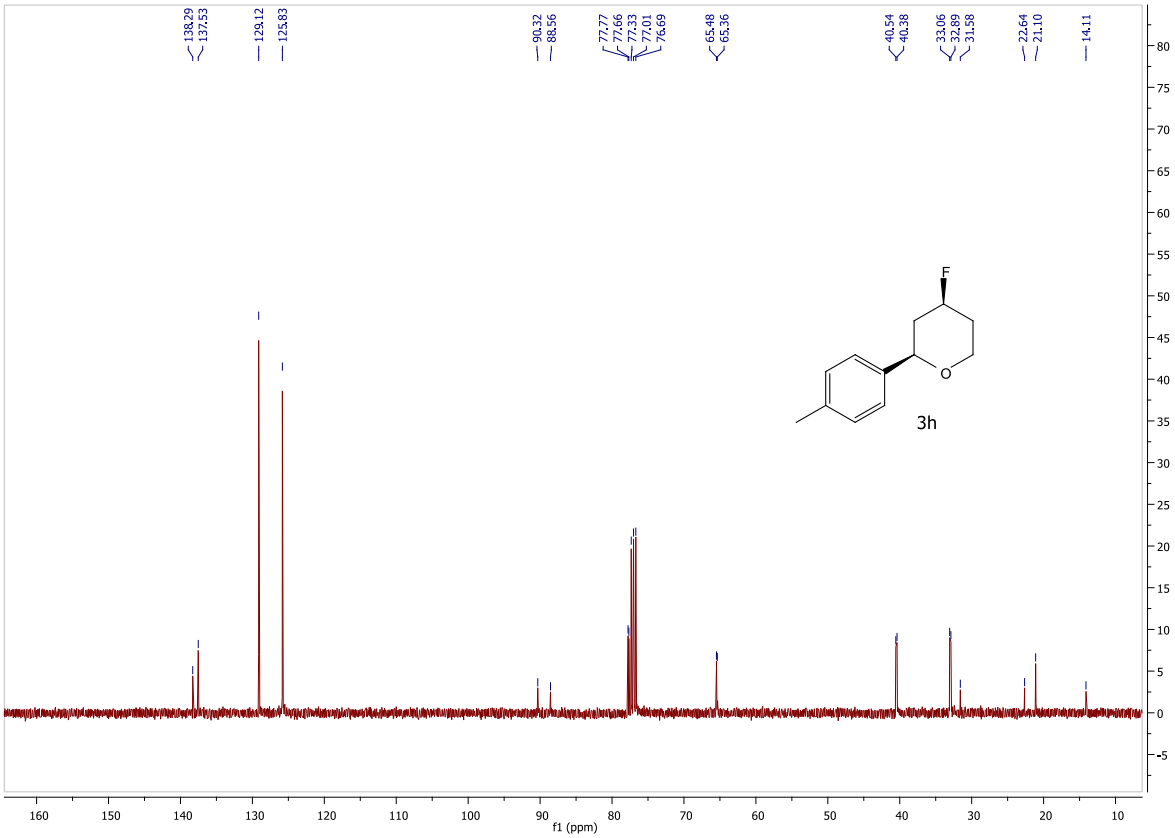
^{19}F NMR Spectrum 3-3g



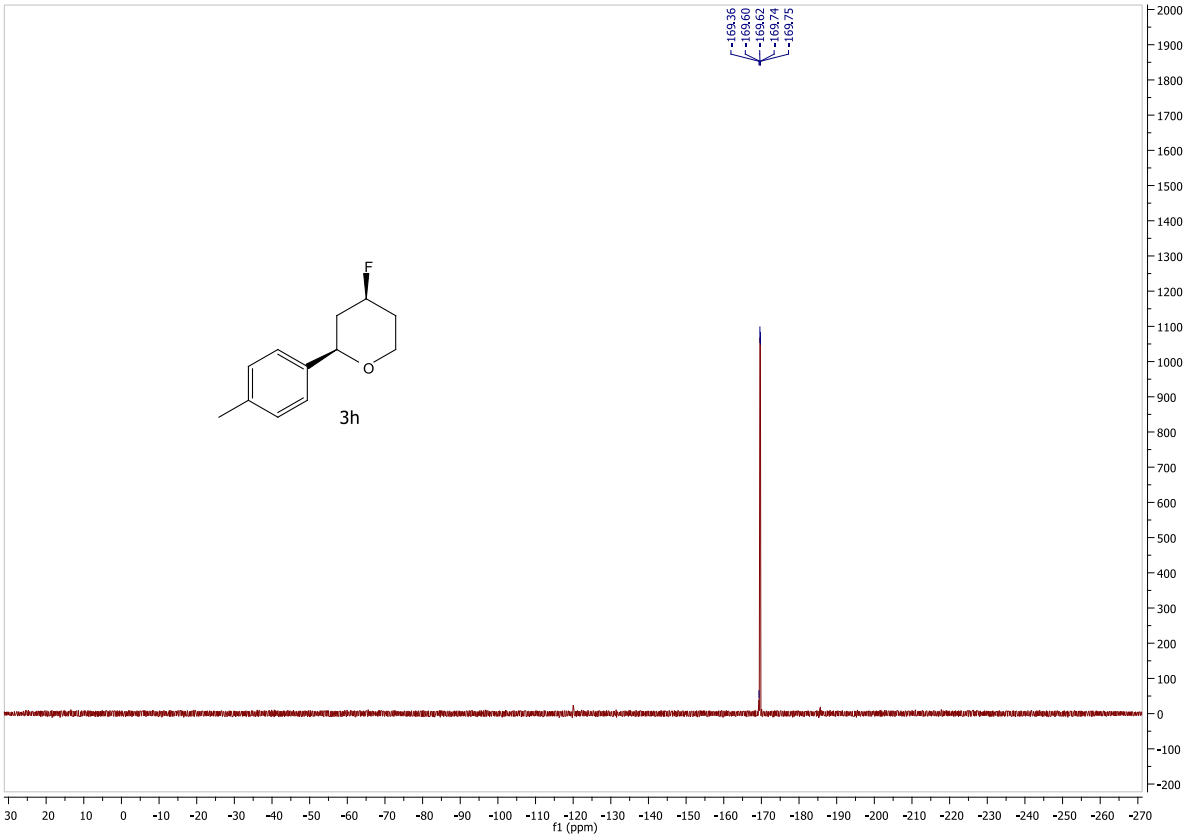
^{1}H NMR Spectrum 3-3h



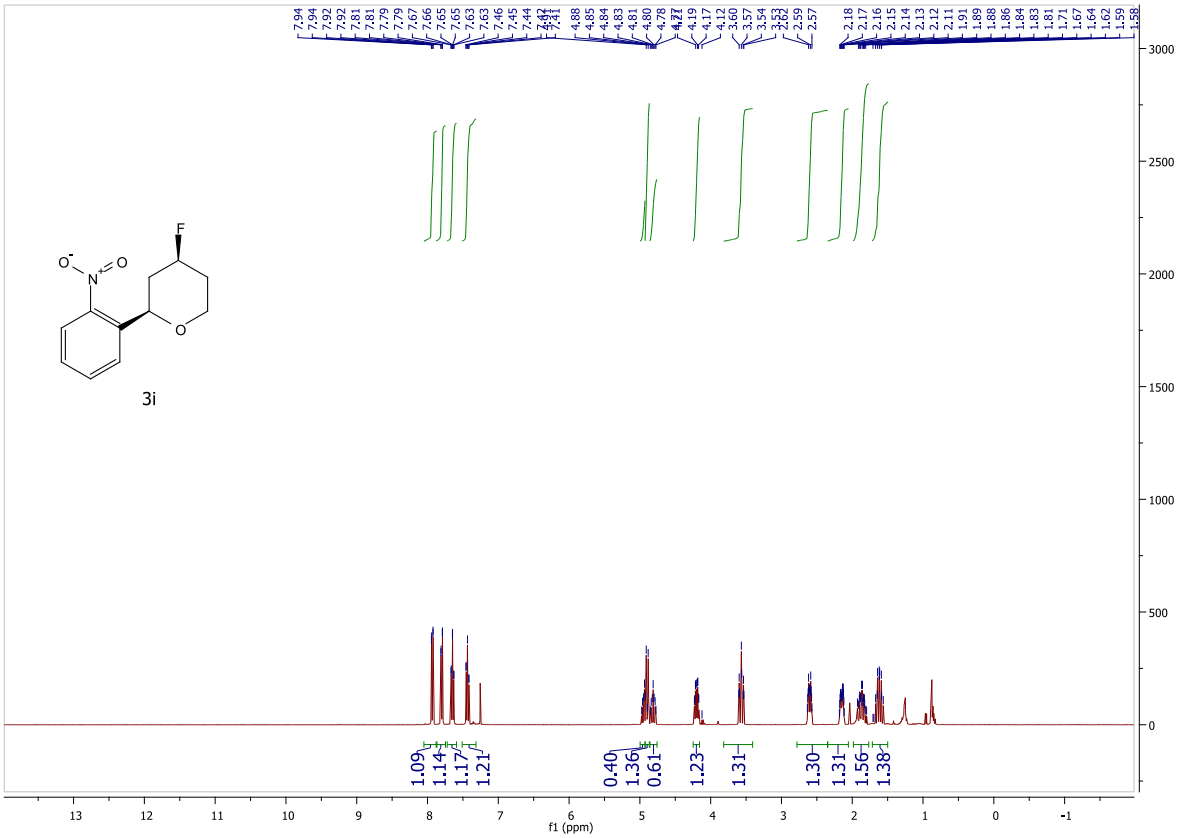
^{13}C NMR Spectrum 3-3h



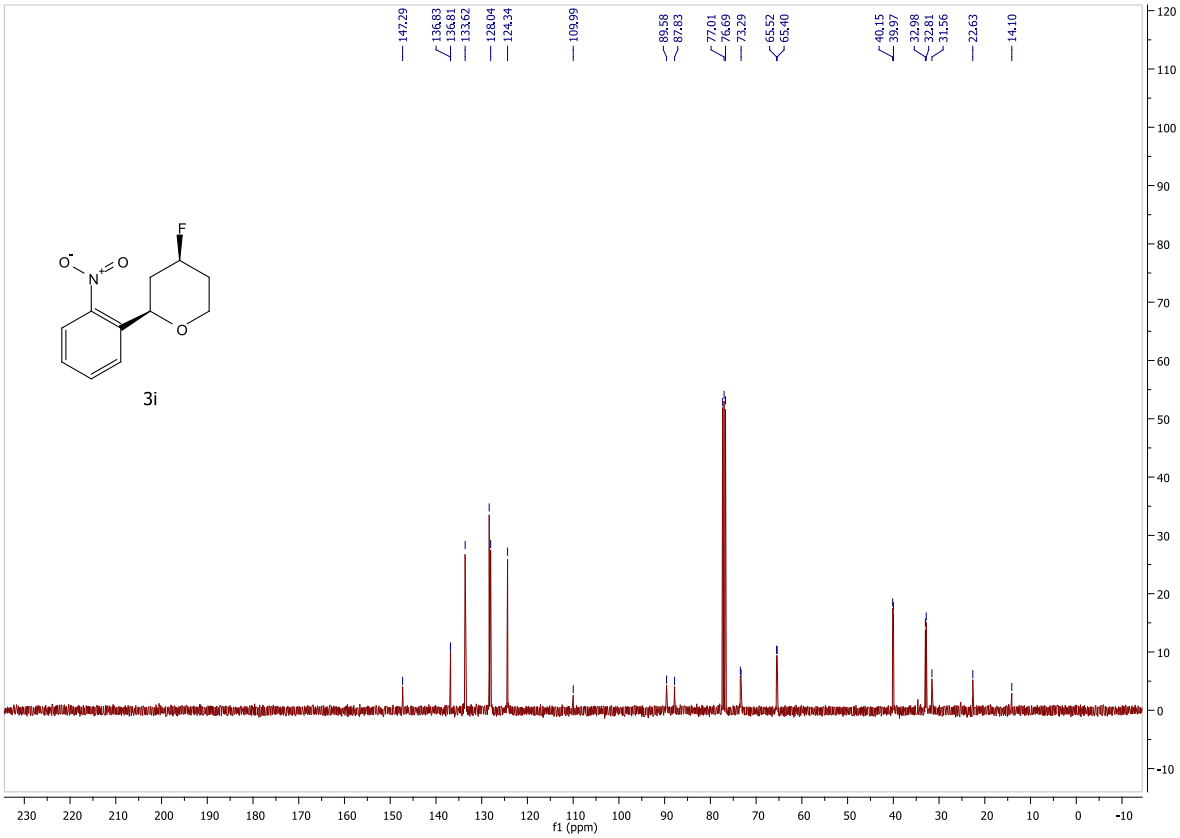
^{19}F NMR Spectrum 3-3h



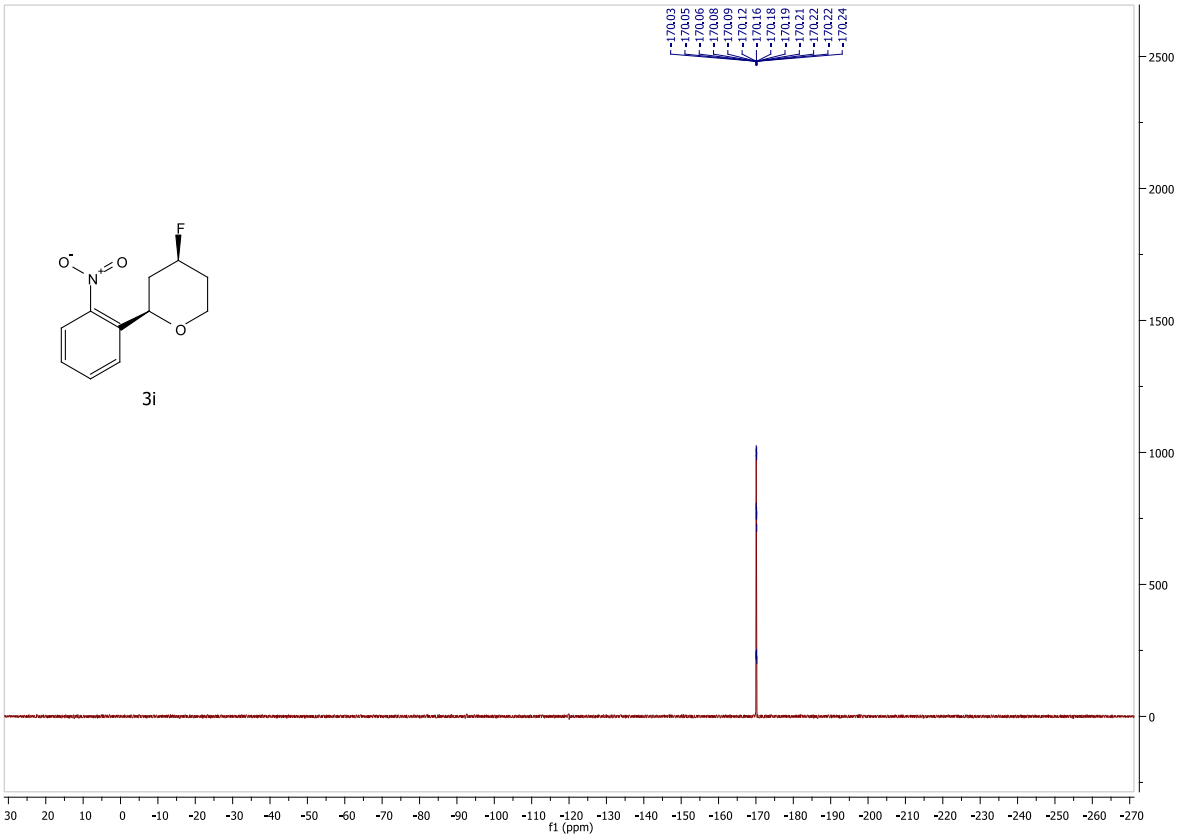
^{1}H NMR Spectrum 3-3i



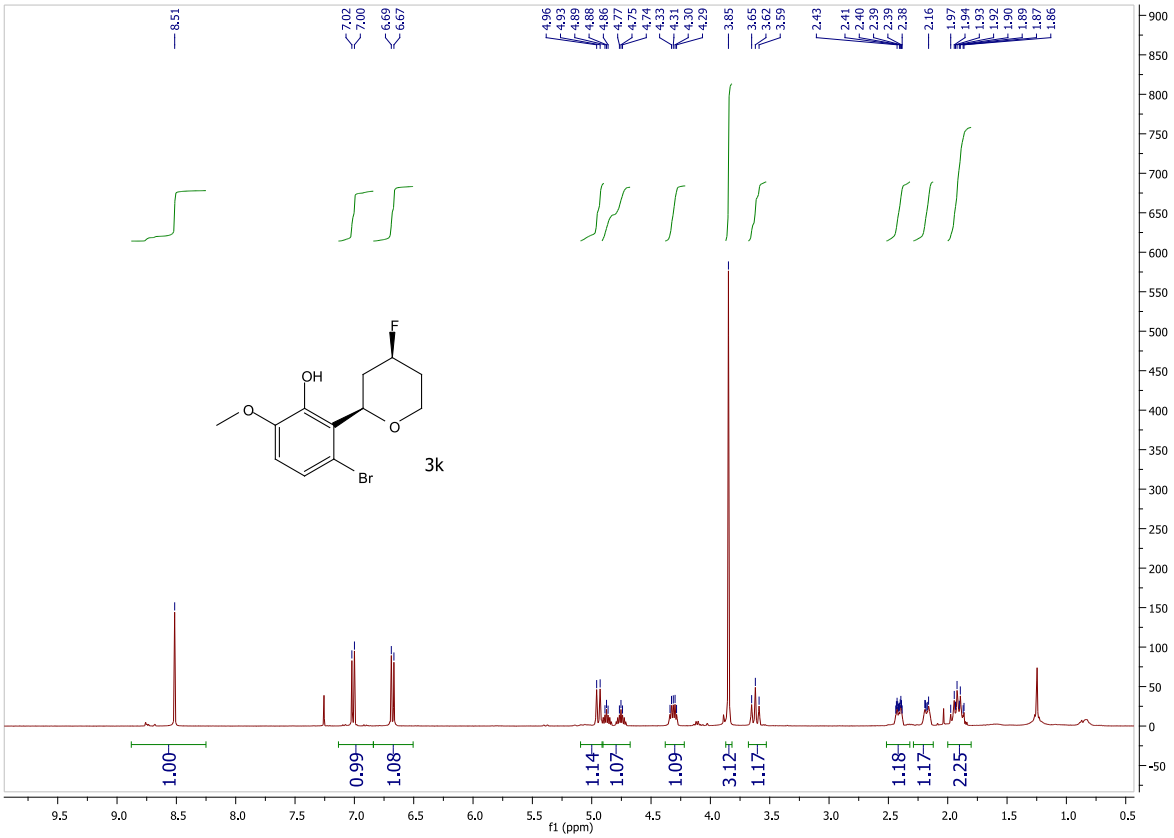
^{13}C NMR Spectrum 3-3i



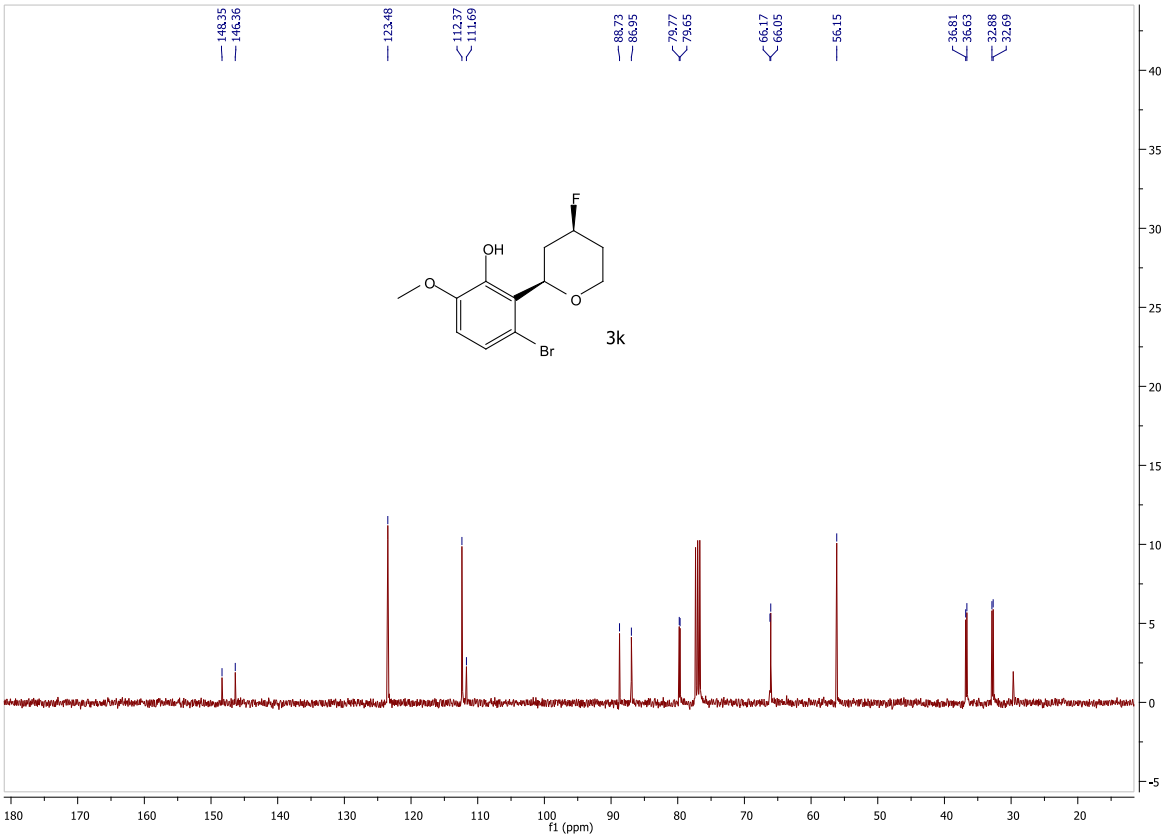
^{19}F NMR Spectrum 3-3i



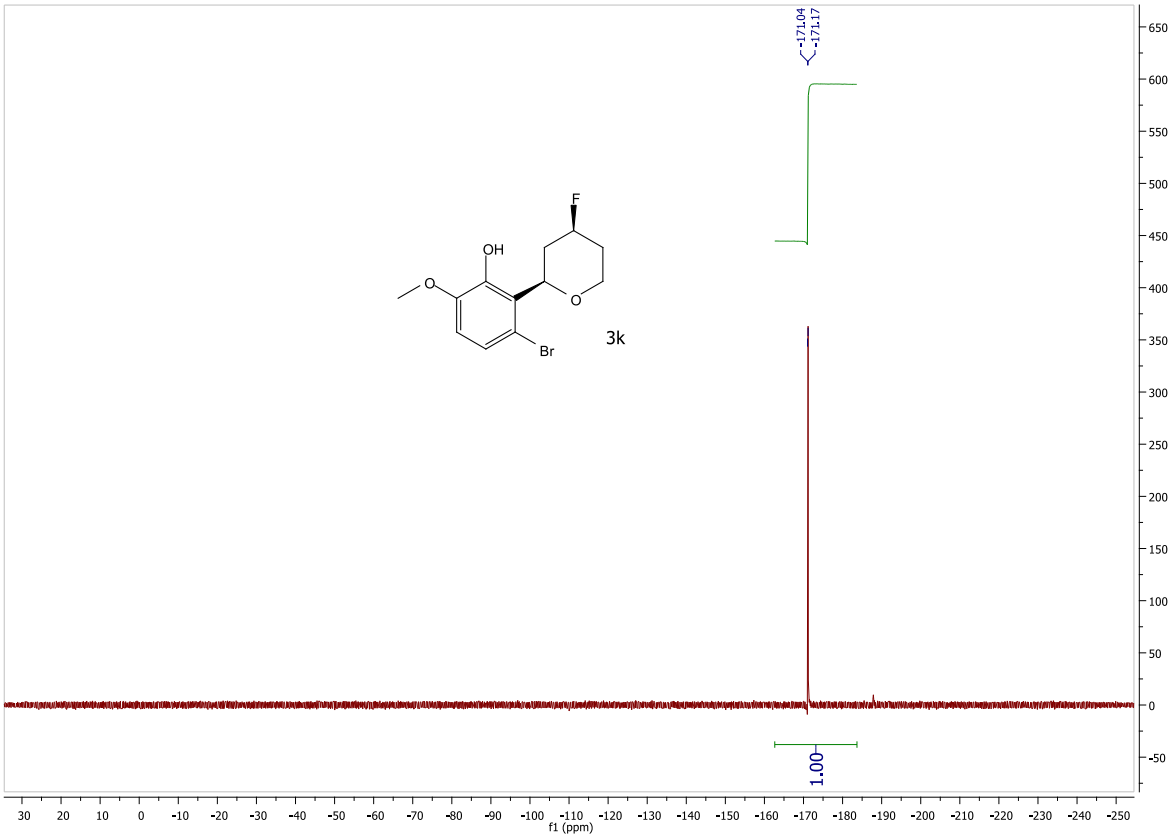
^{1}H NMR Spectrum 3-3k



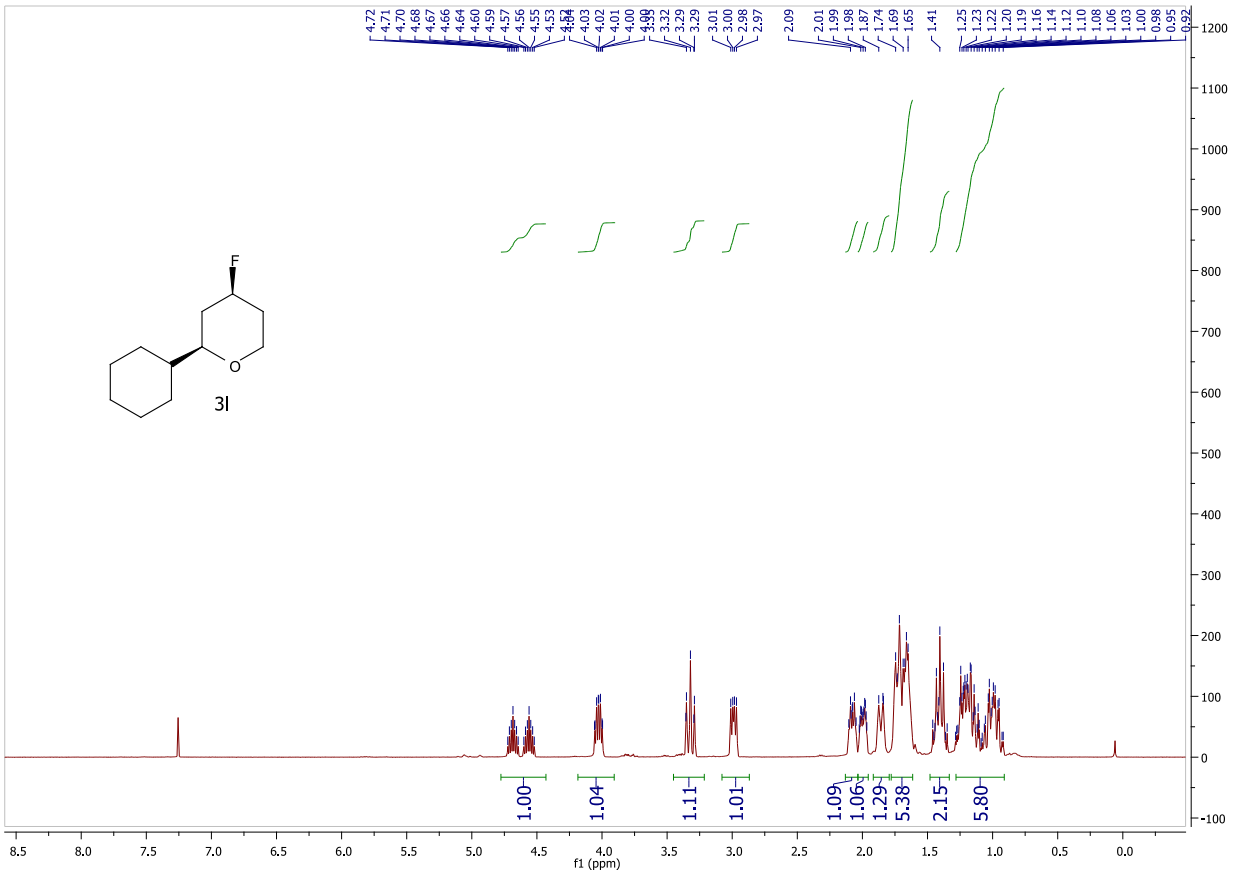
^{13}C NMR Spectrum 3-3k



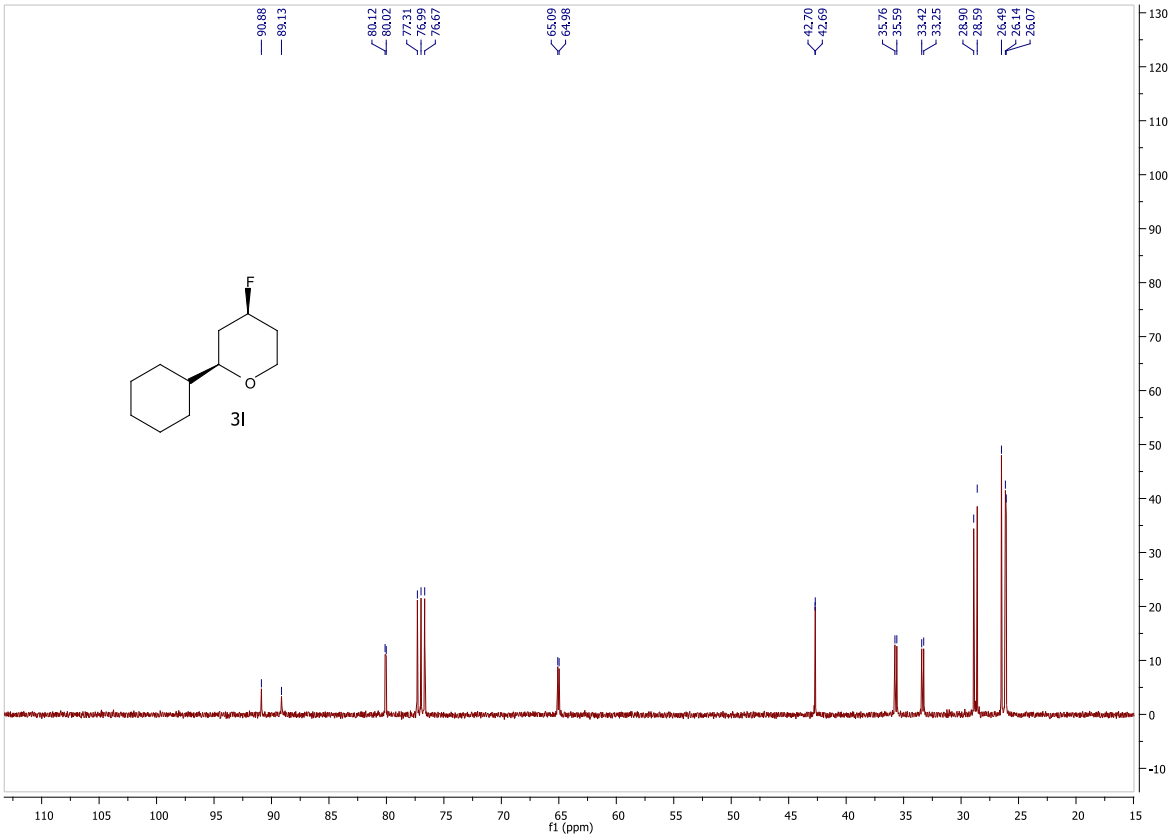
^{19}F NMR Spectrum 3-3k



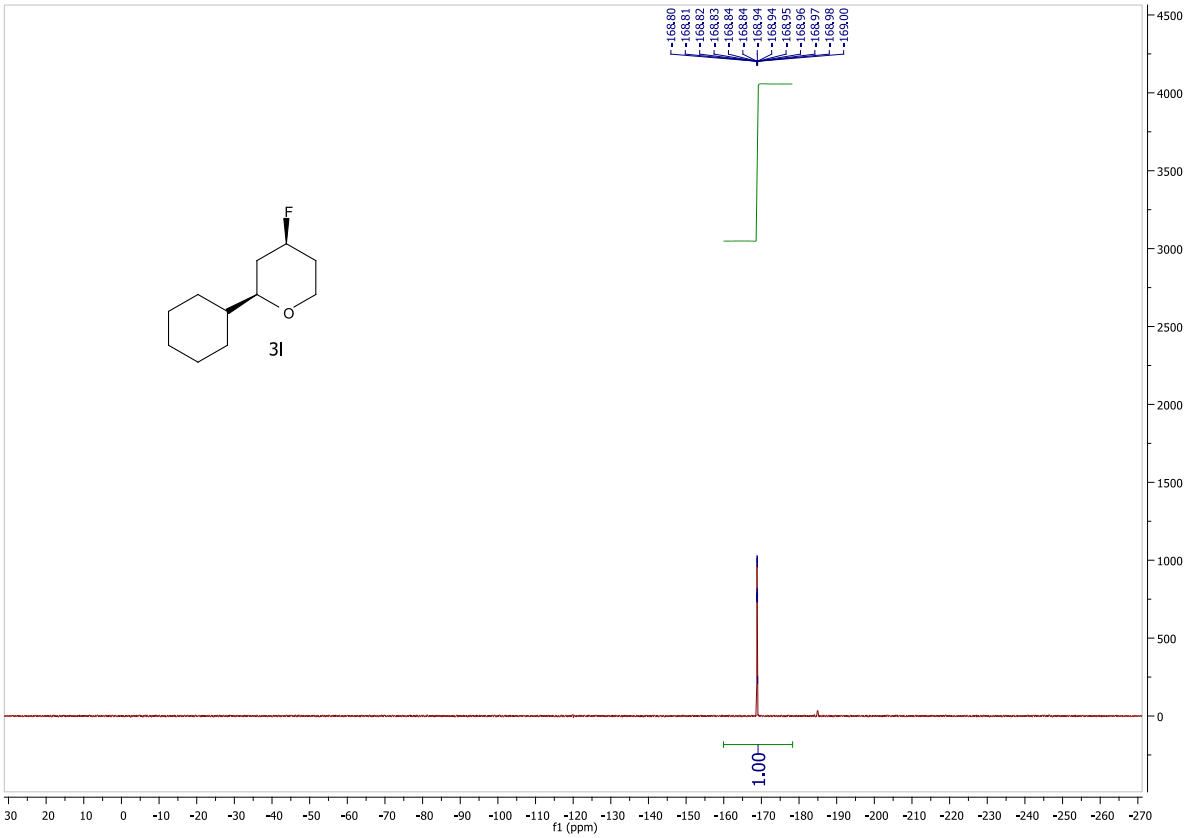
^{1}H NMR Spectrum 3-3l



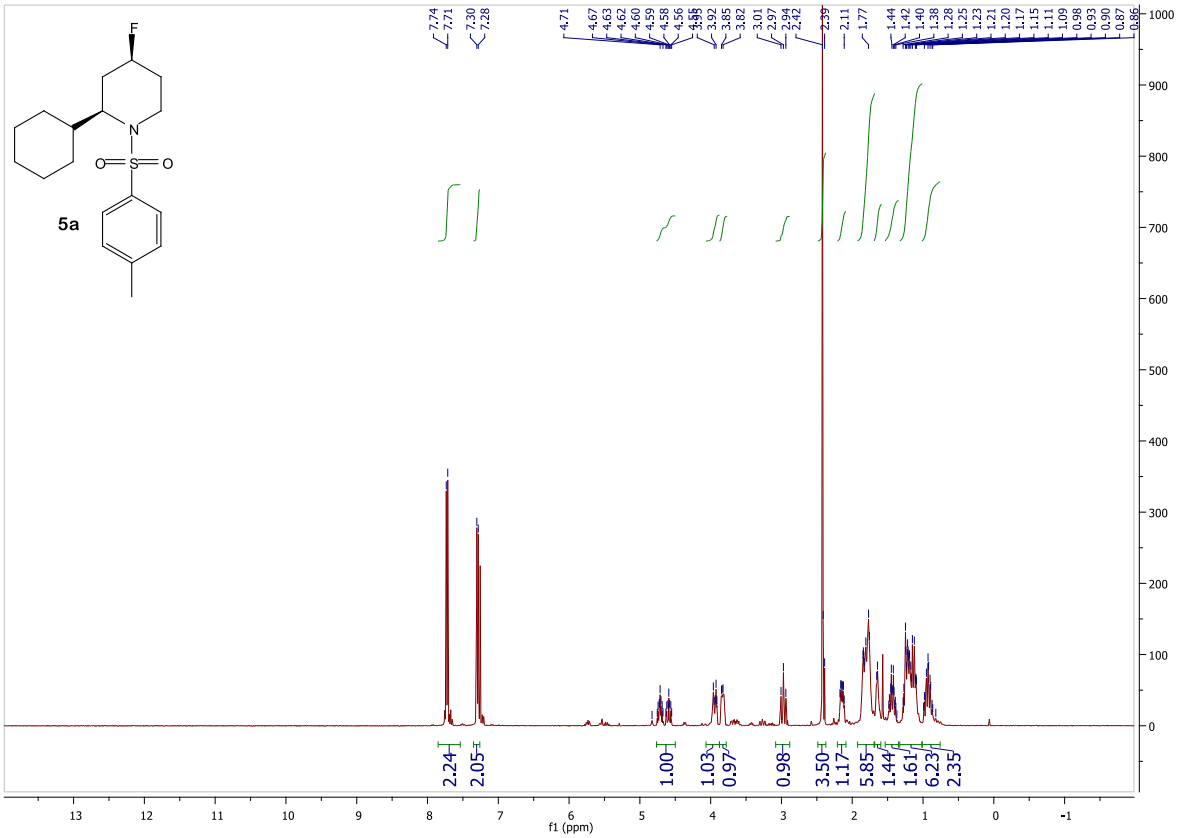
^{13}C NMR Spectrum 3-3l



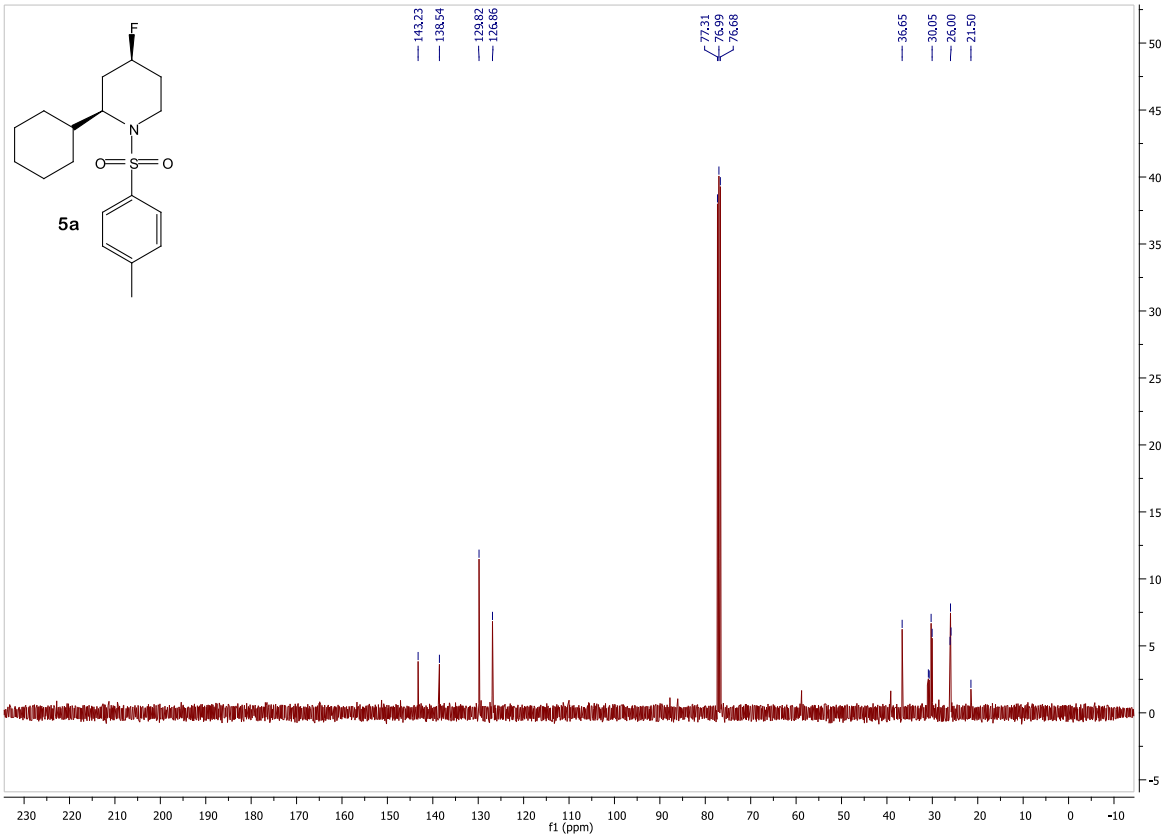
^{19}F NMR Spectrum 3-3l



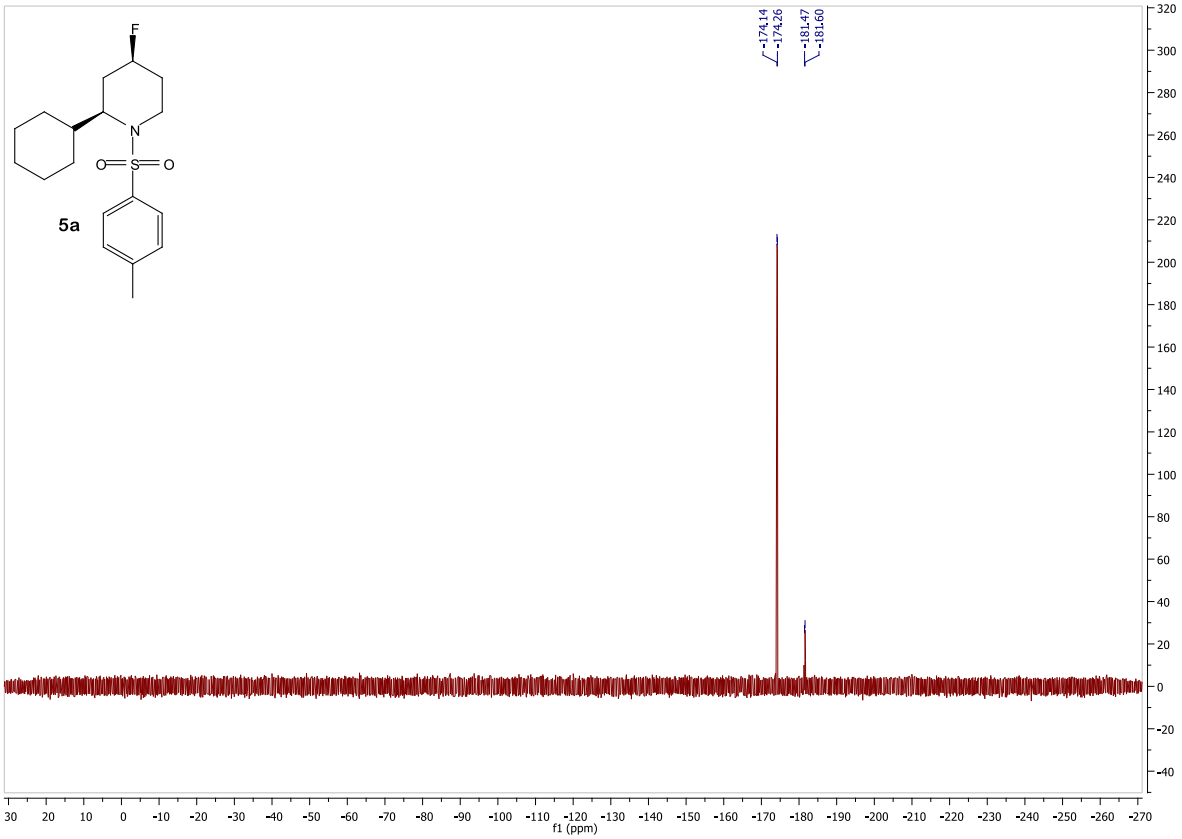
NMR Spectrum 3-12a



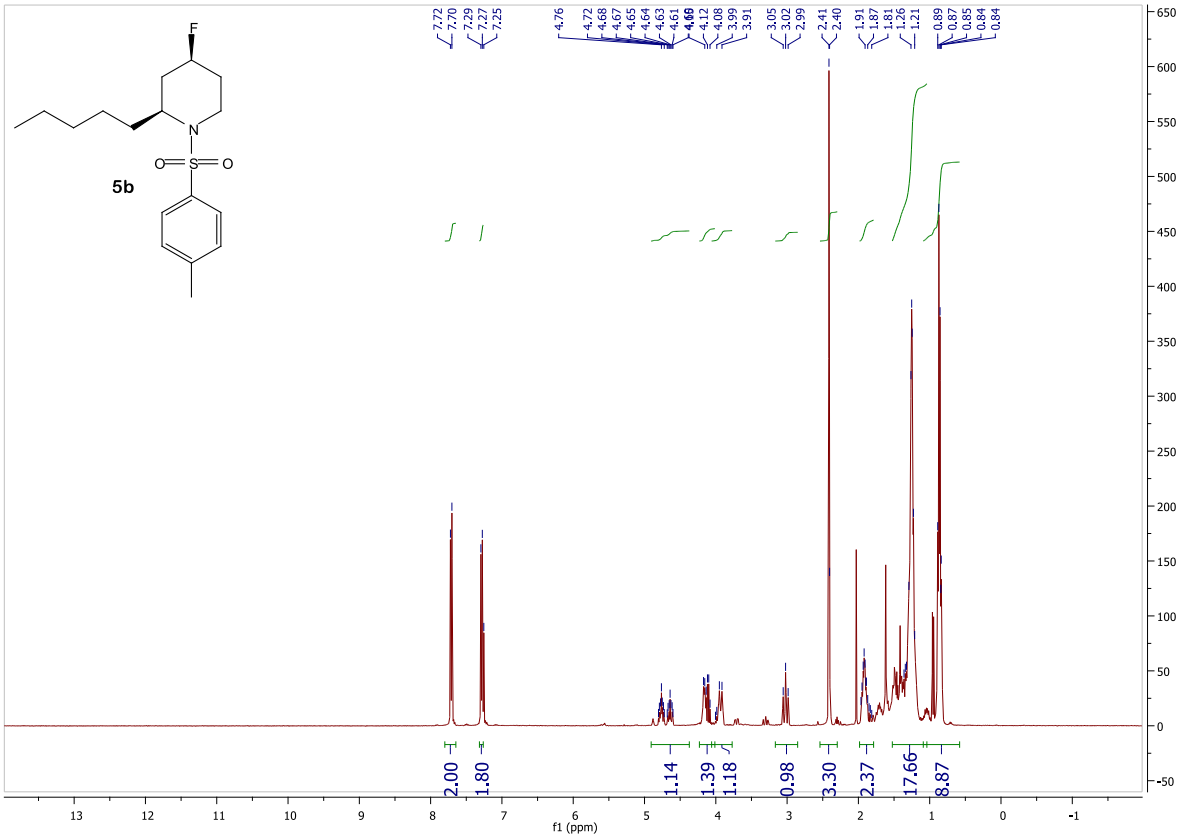
^{13}C NMR Spectrum 3-12a



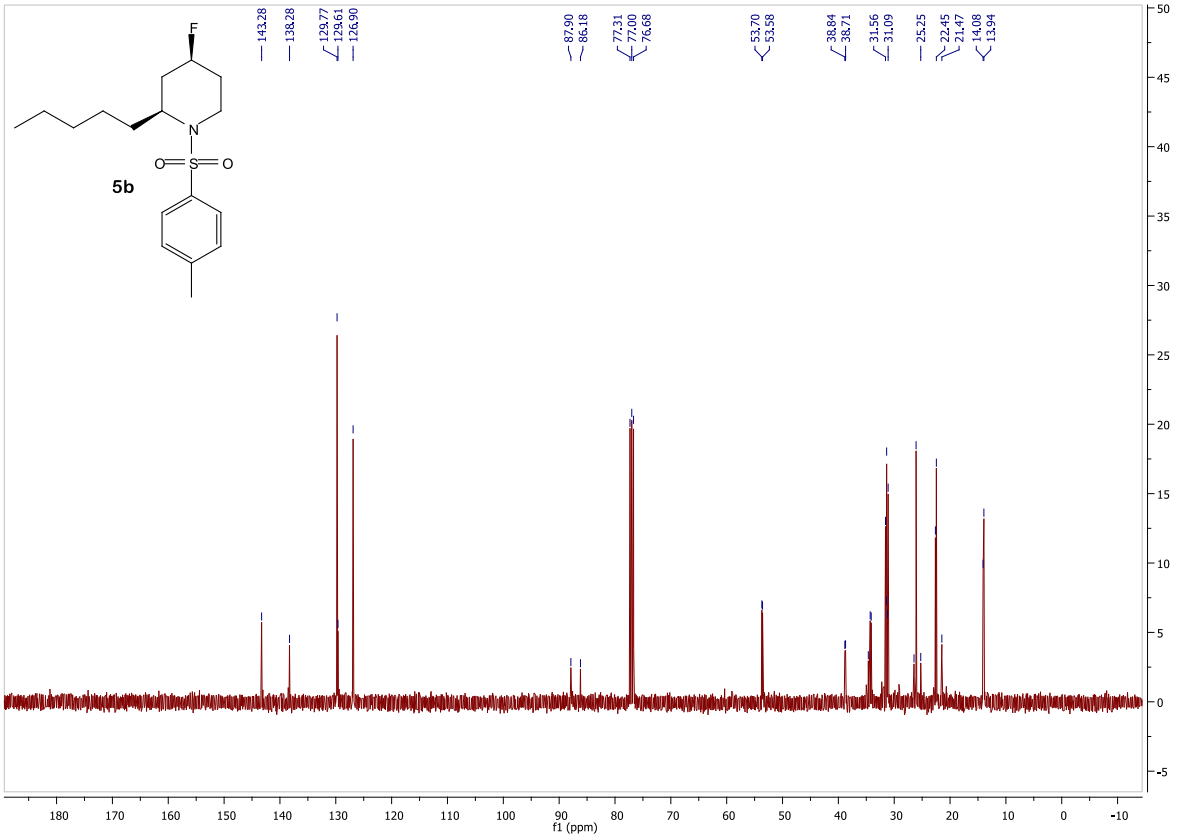
^{19}F NMR Spectrum 3-12a



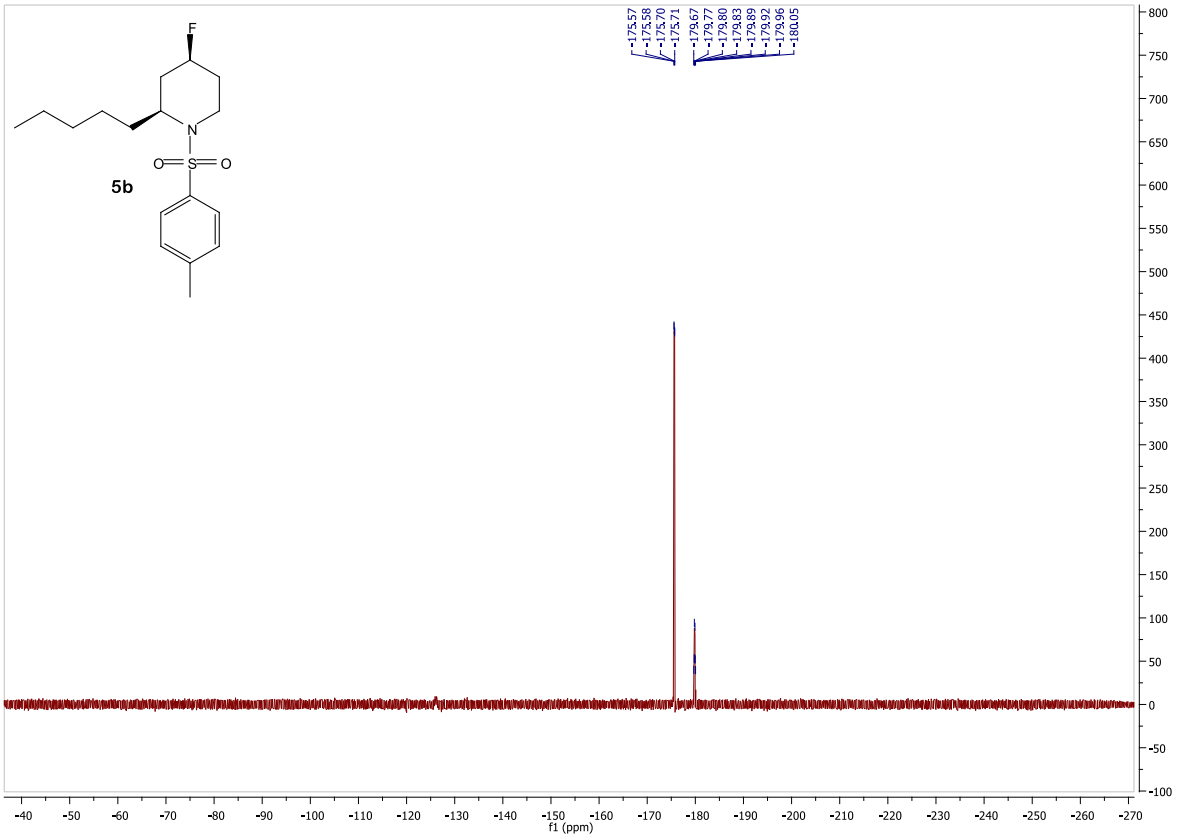
^{1}H NMR Spectrum 3-12b



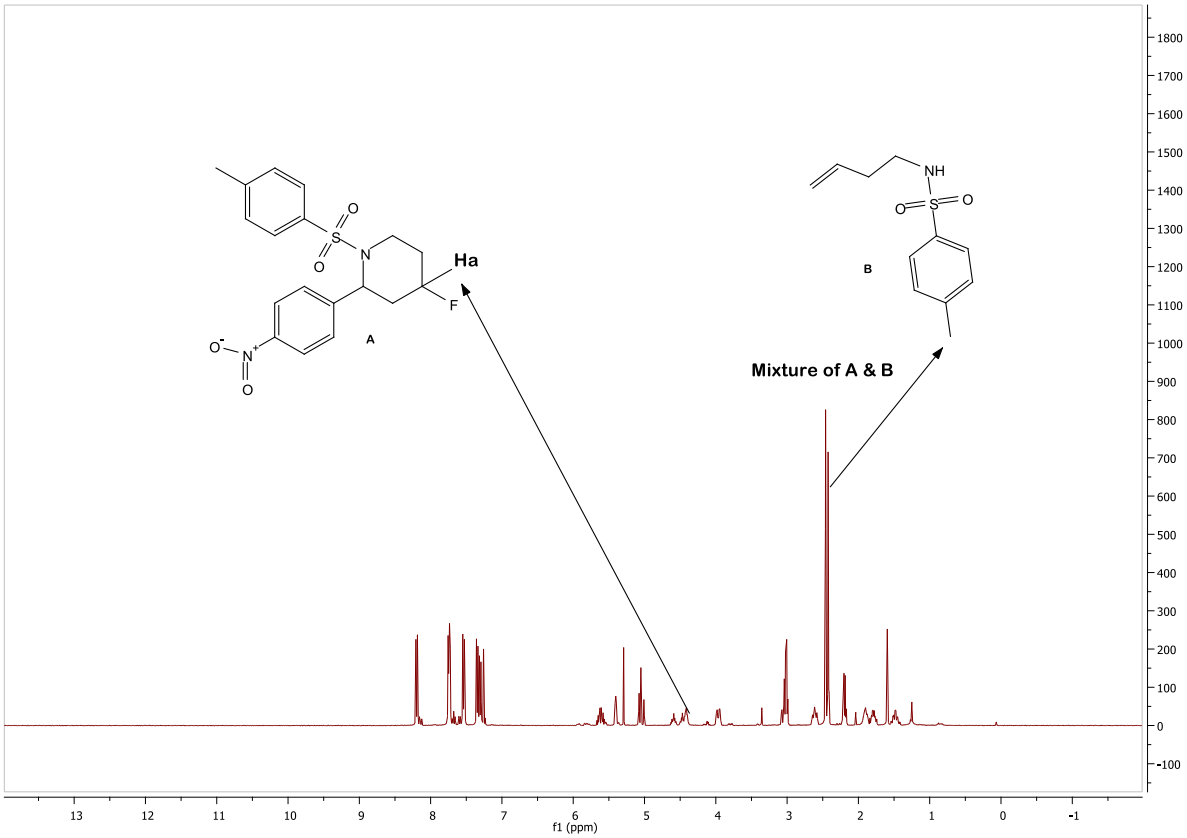
^{13}C NMR Spectrum 3-12b



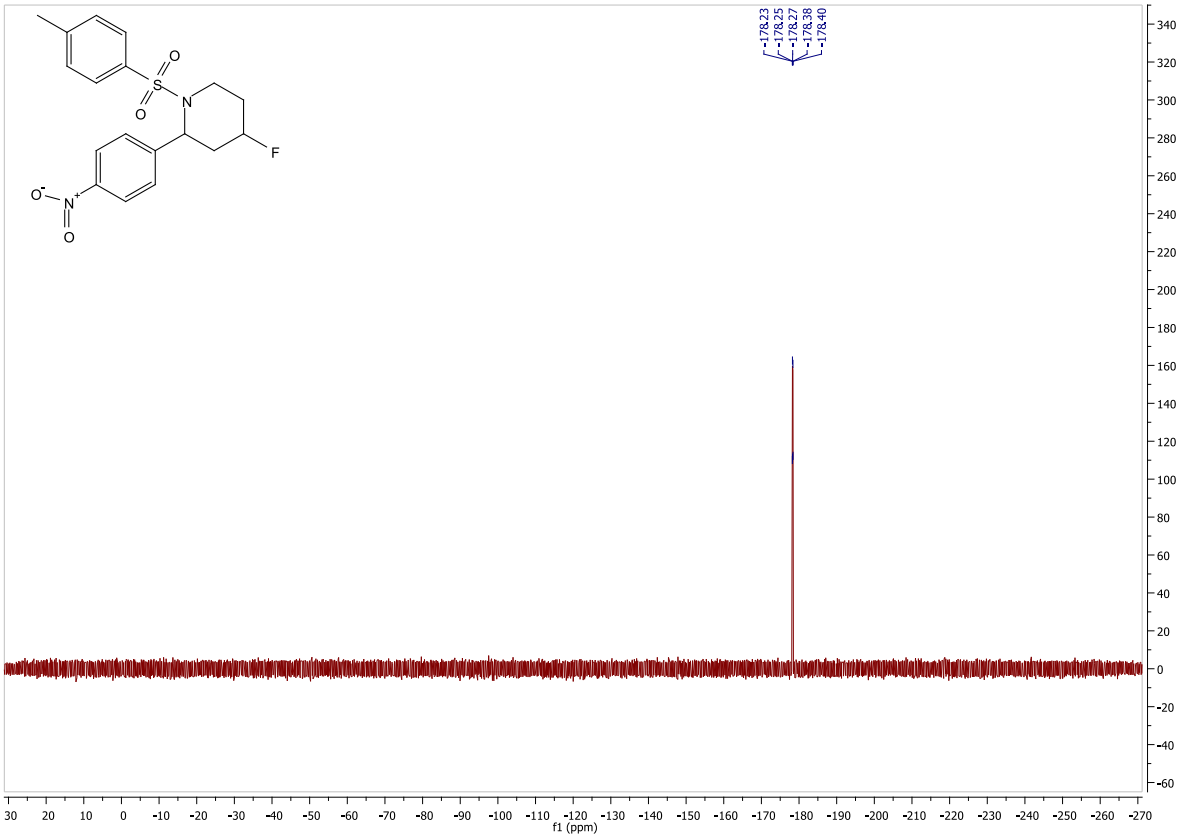
^{19}F NMR Spectrum 3-12b



^{1}H NMR Spectrum 3-12e: Representative spectra for aromatic aza-prins

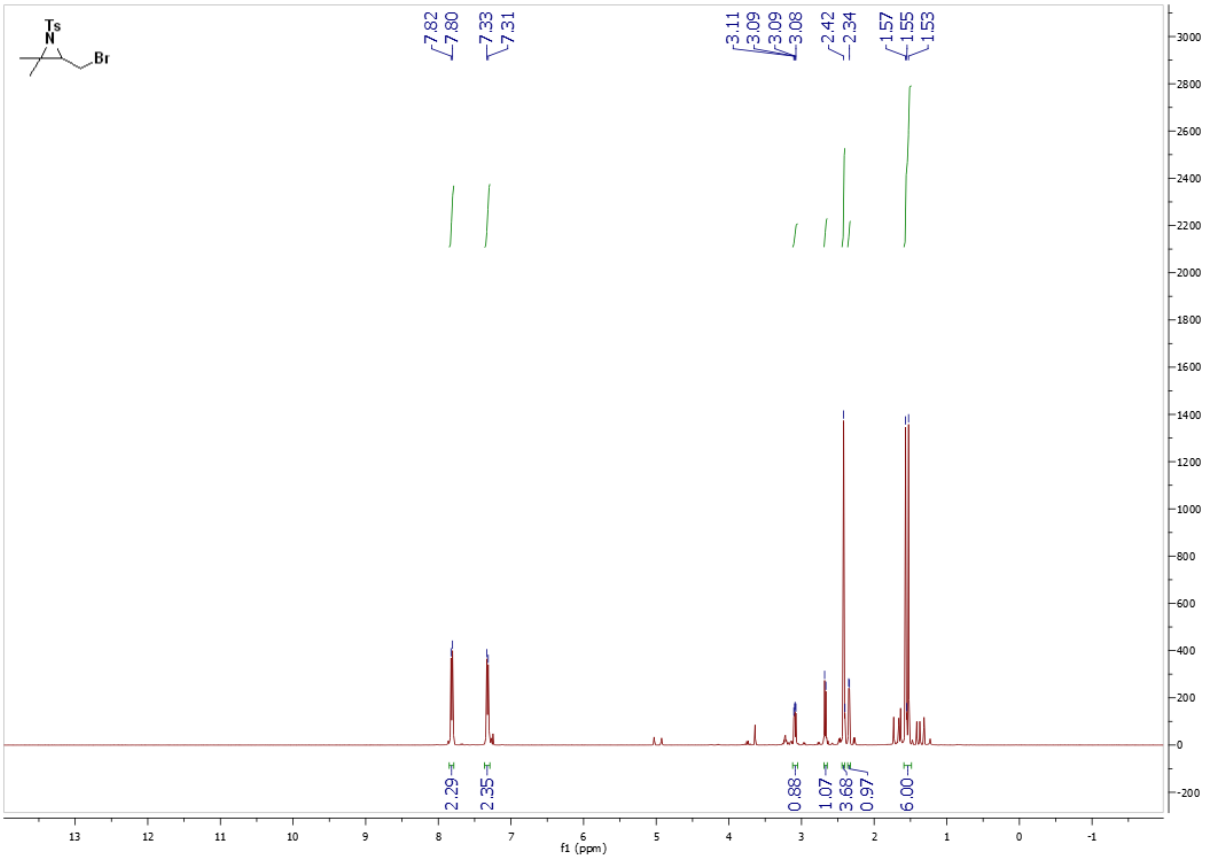


^{19}F NMR Spectrum 3-12e: Representative spectra for aromatic aza-prins

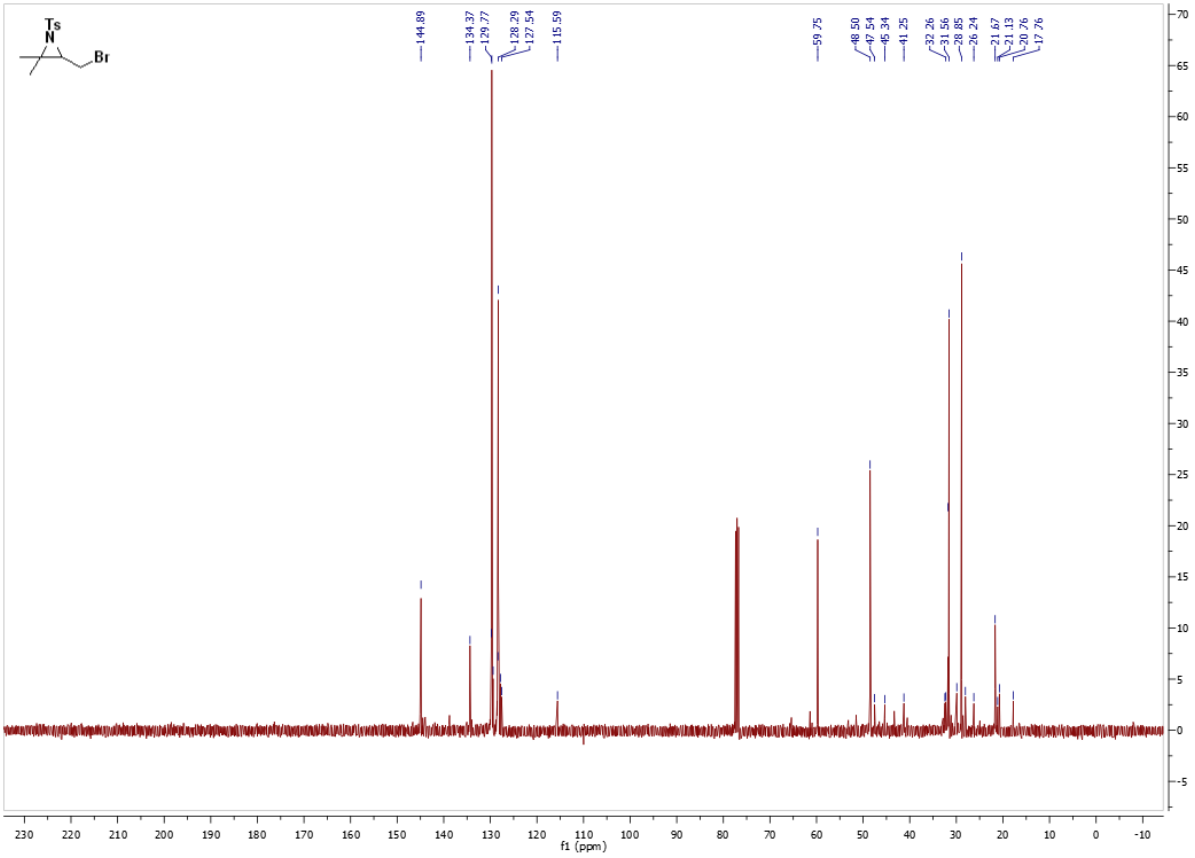


NMR FILES FOR AZIRIDINE RING OPENING

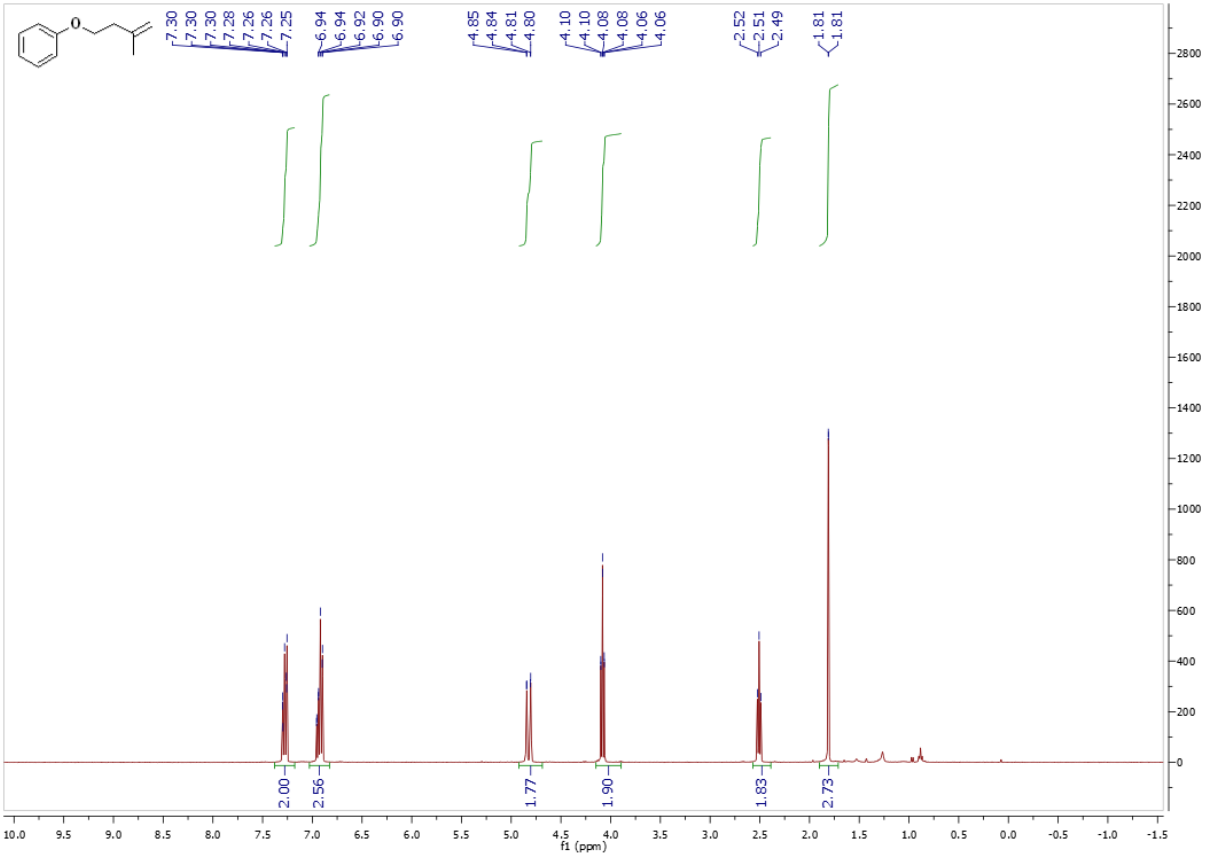
^{1}H NMR for 4-1l



^{13}C NMR for 4-1l



^{1}H NMR for 4-1m'



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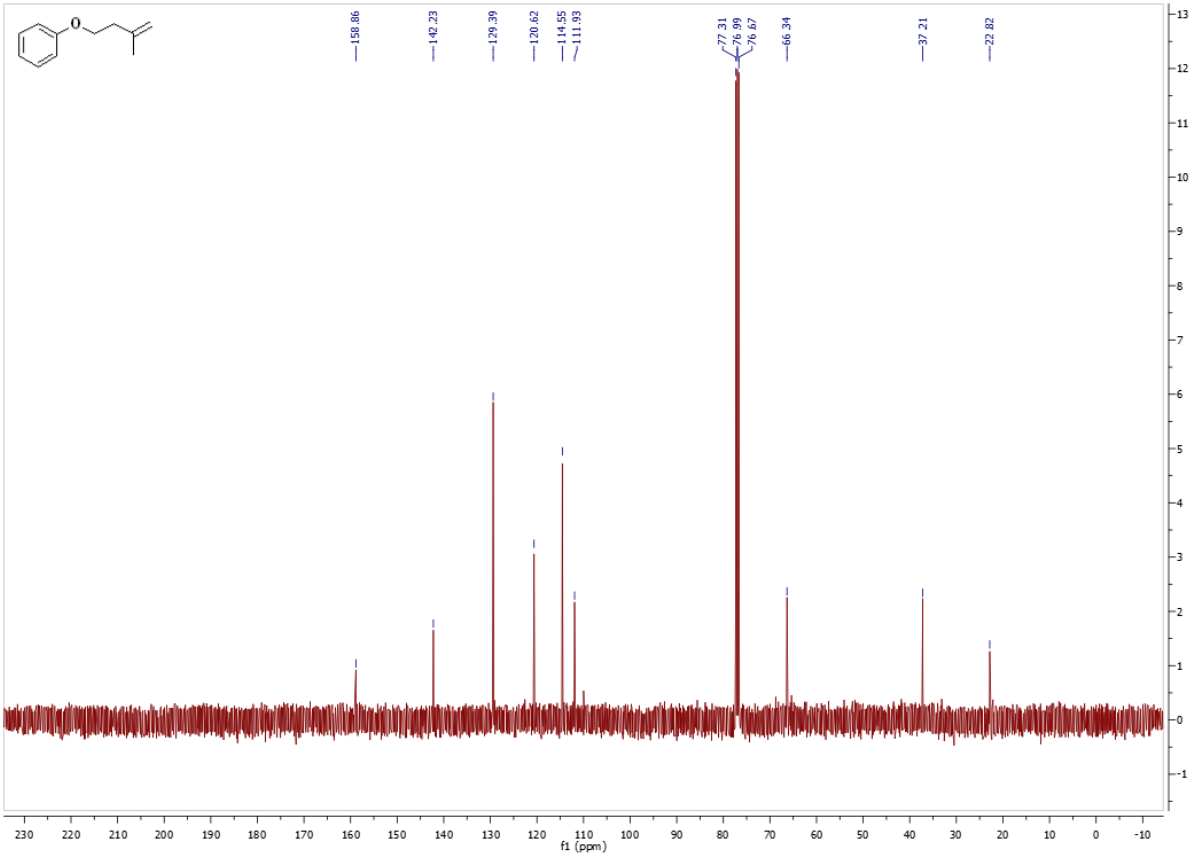

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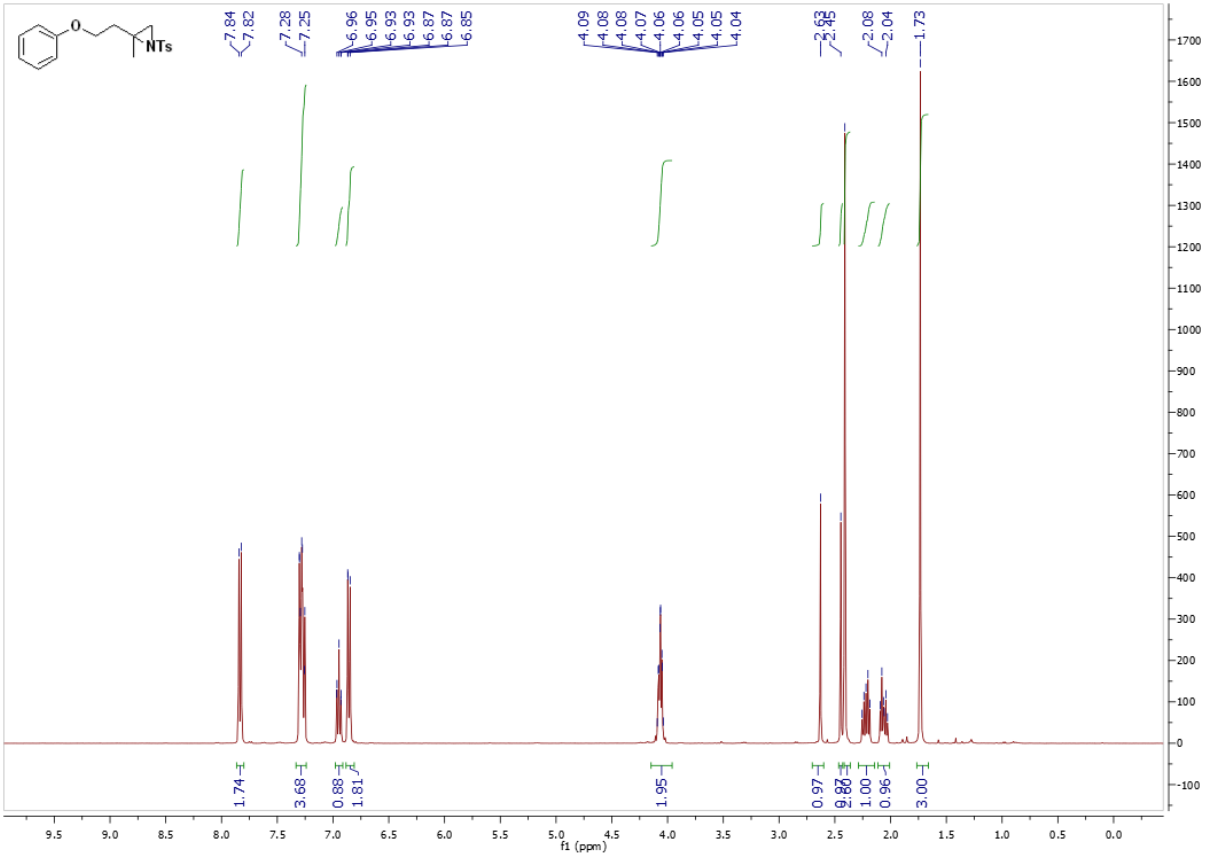
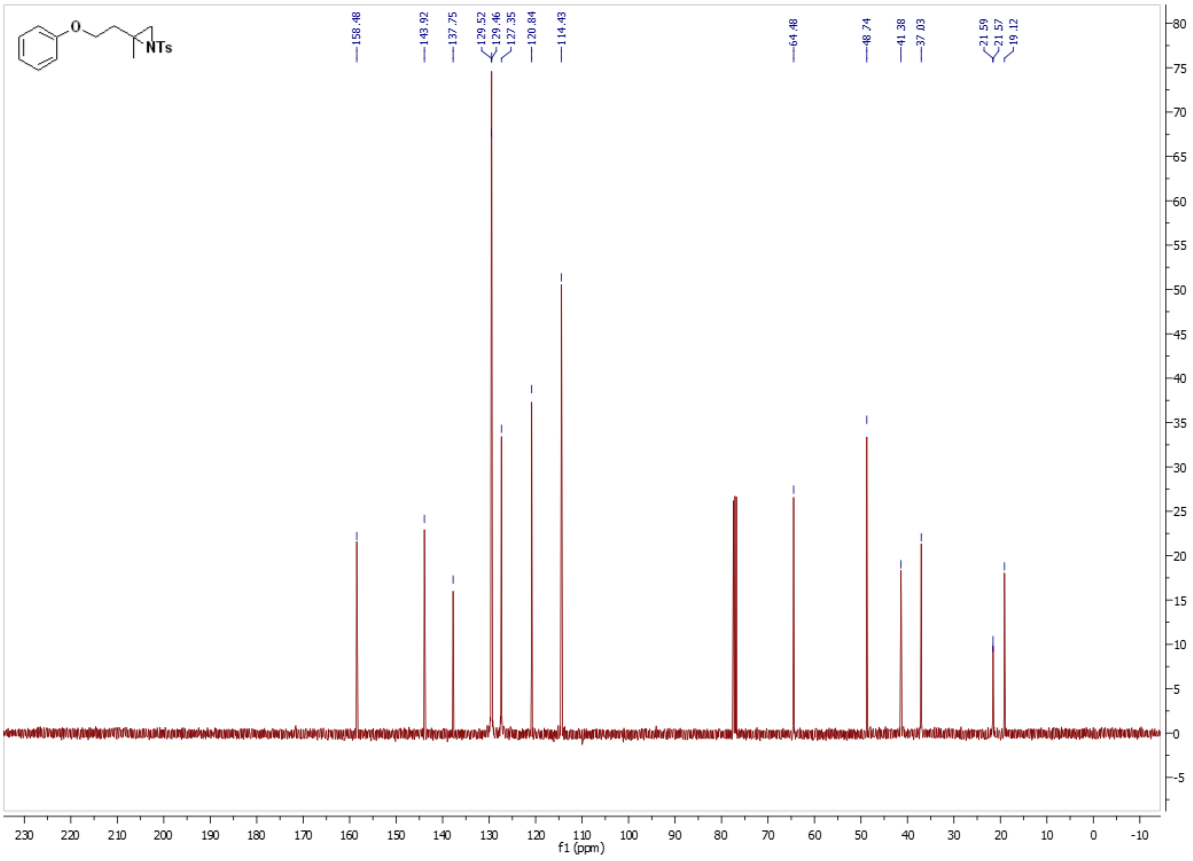
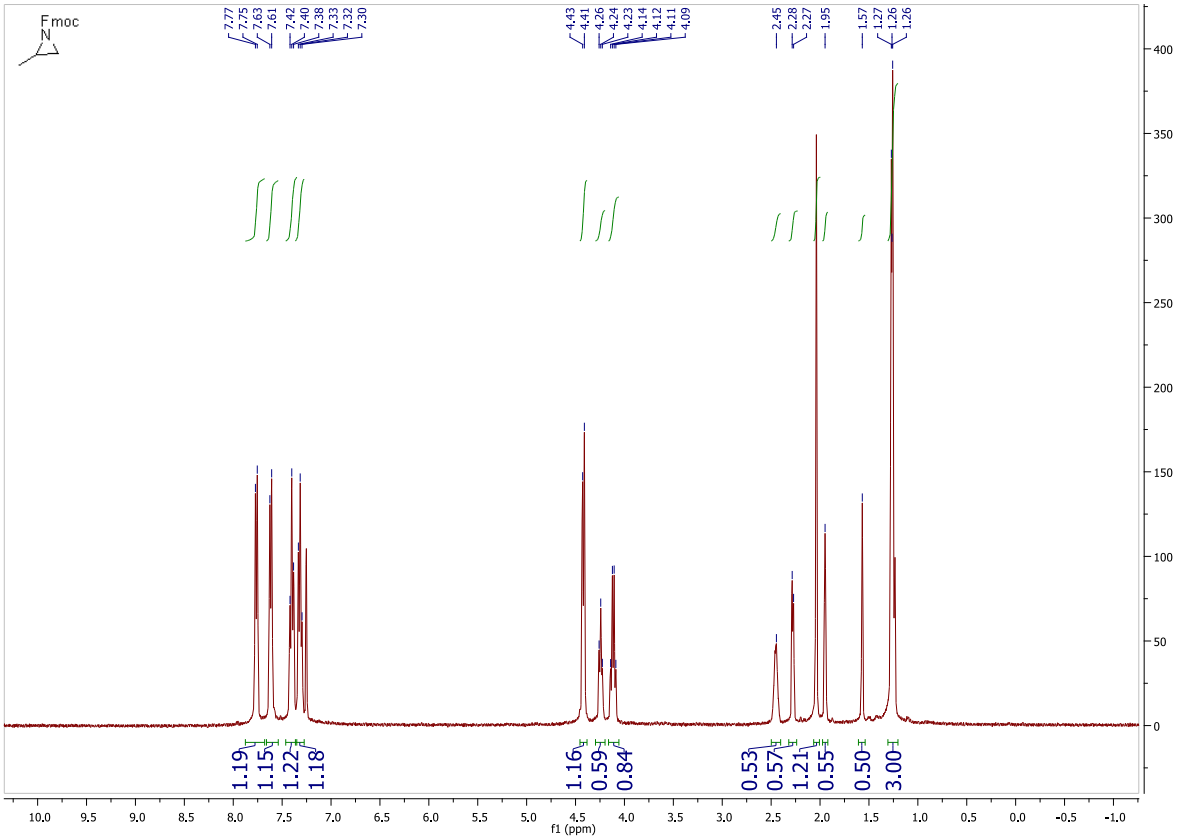


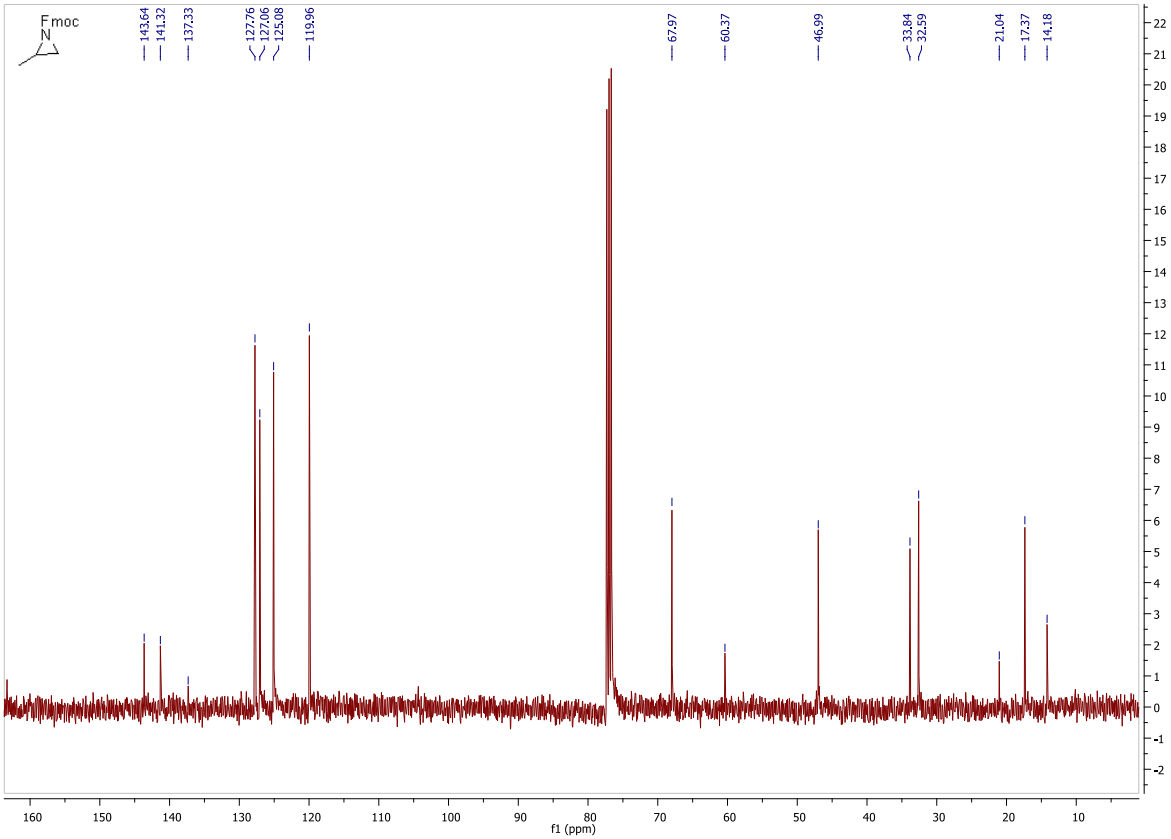
^{13}C NMR for 4-1m



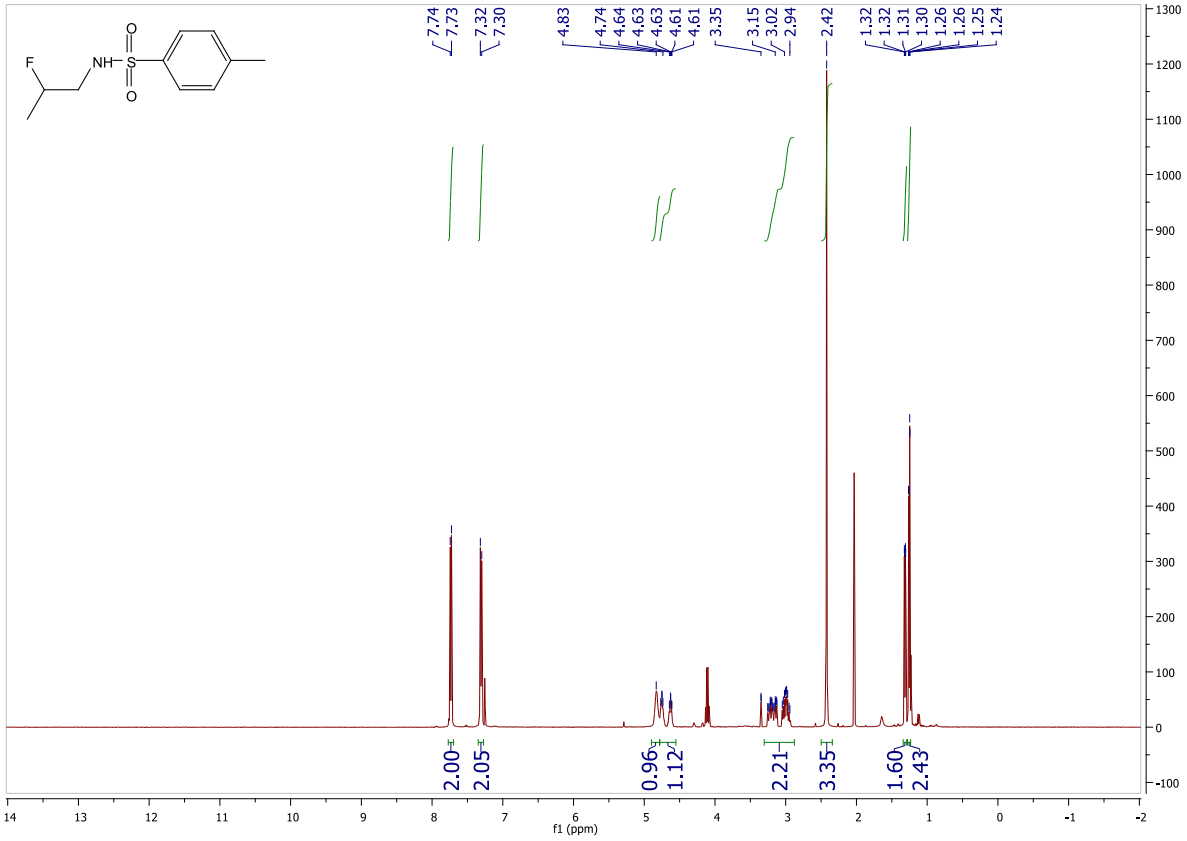
^{1}H NMR for 4-1r



^{13}C NMR for 4-1r



^{1}H NMR for 4-2a



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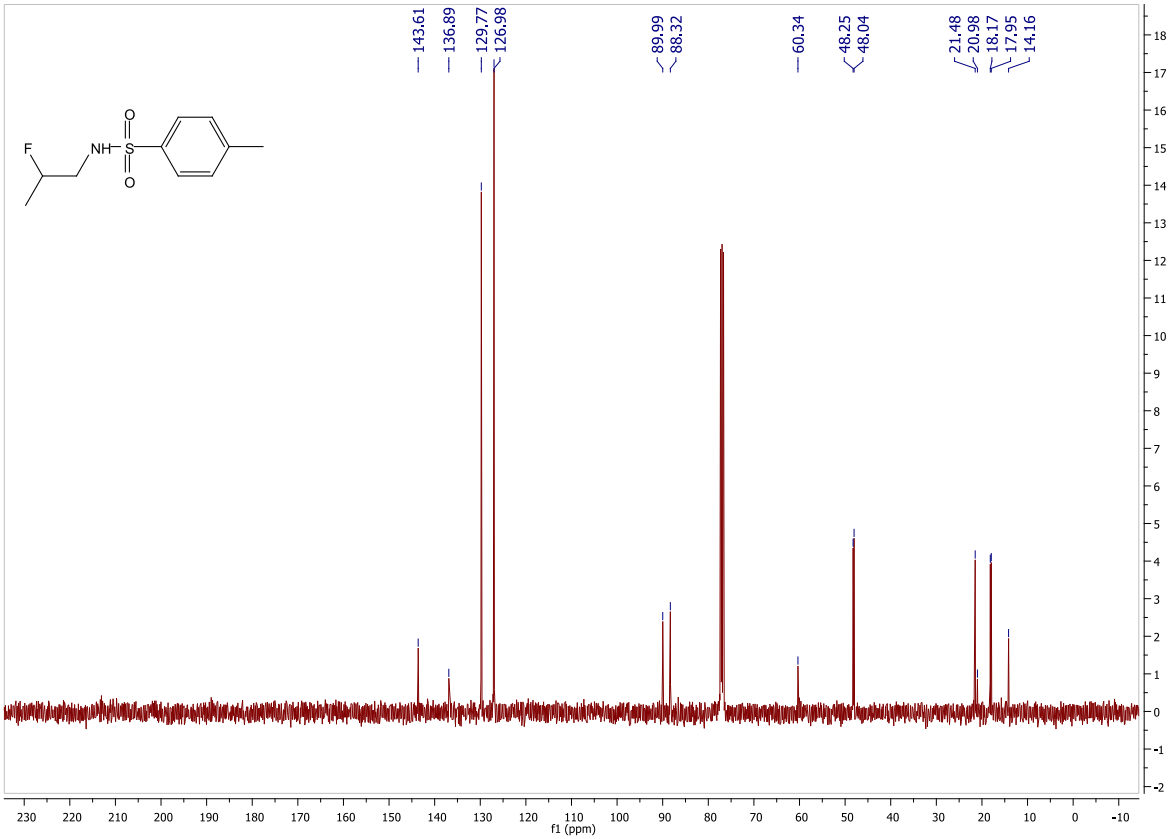
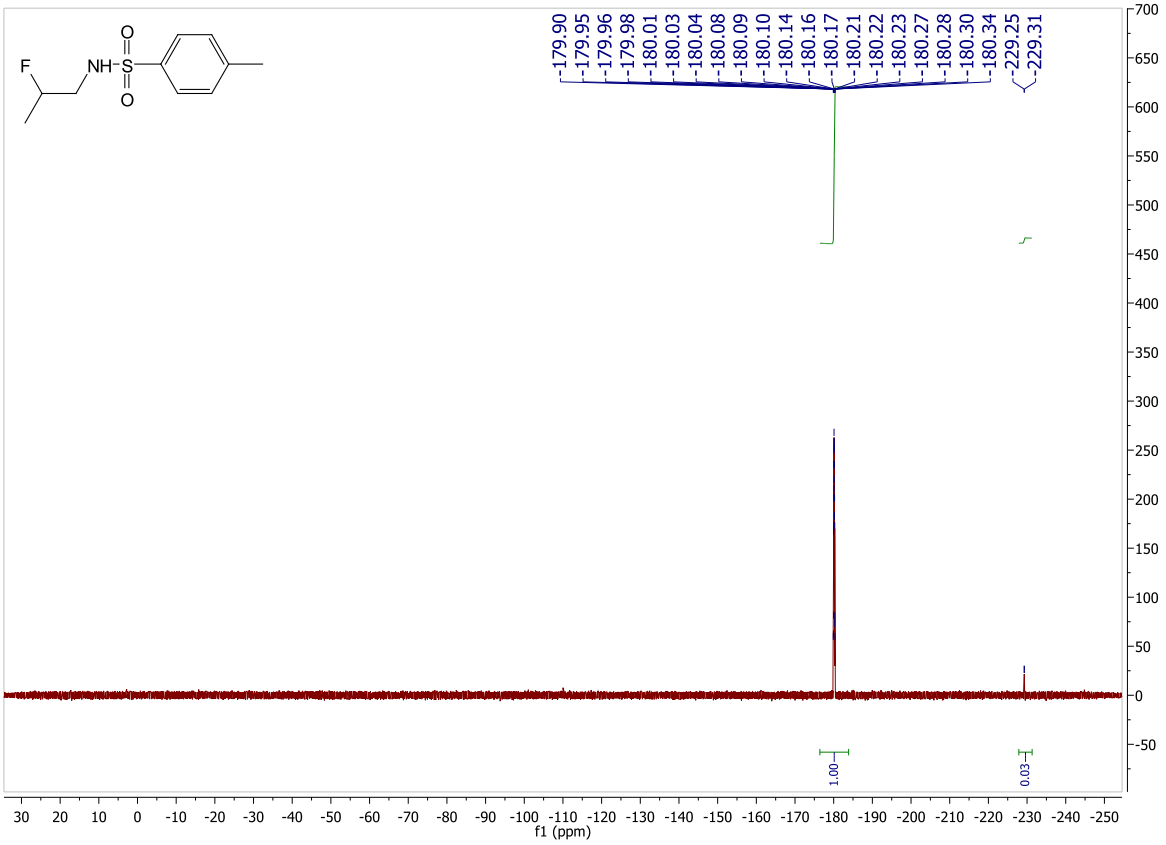
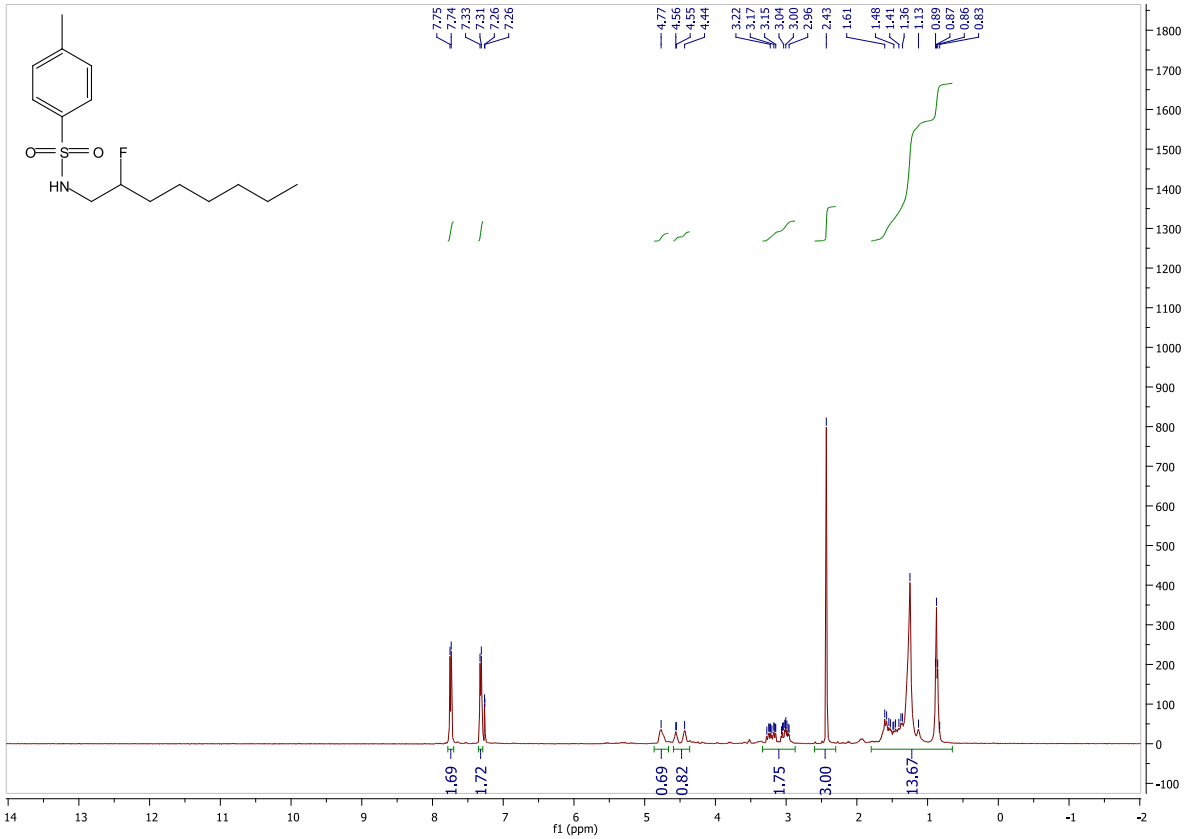


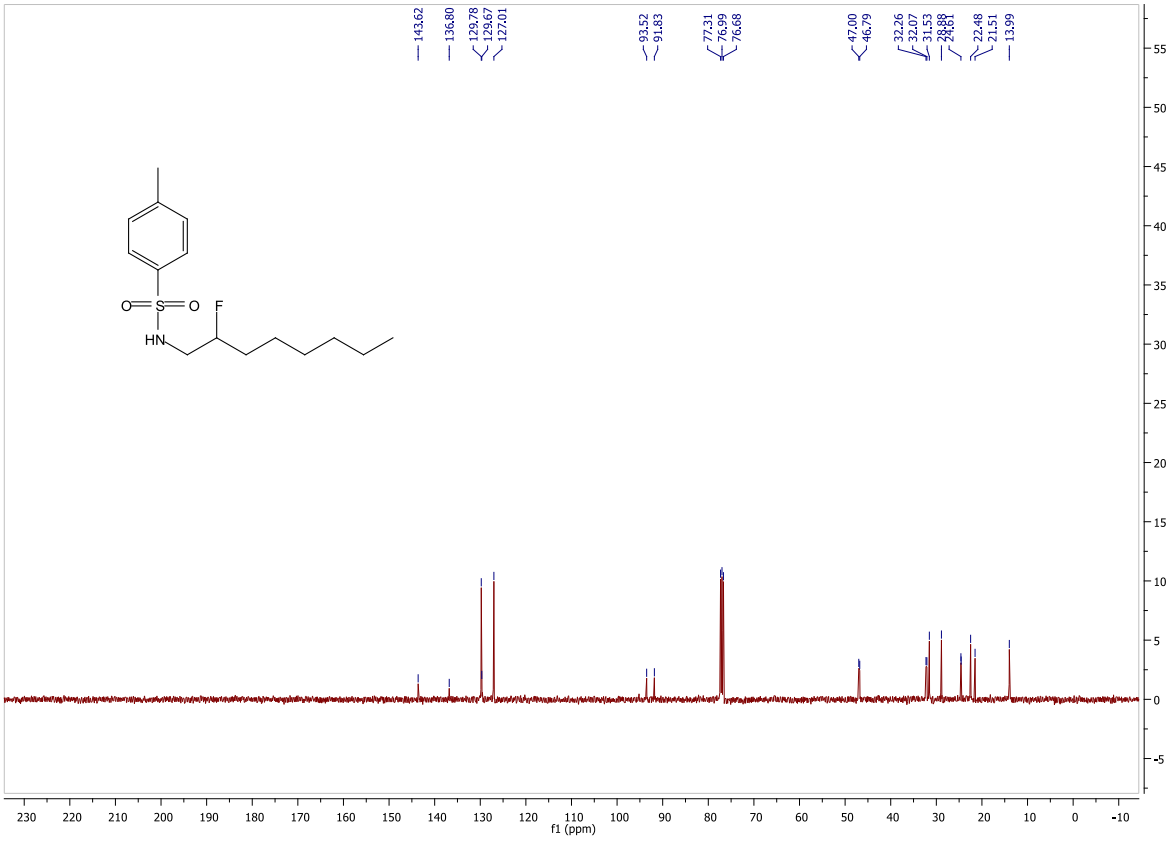
^{19}F NMR for 4-2a



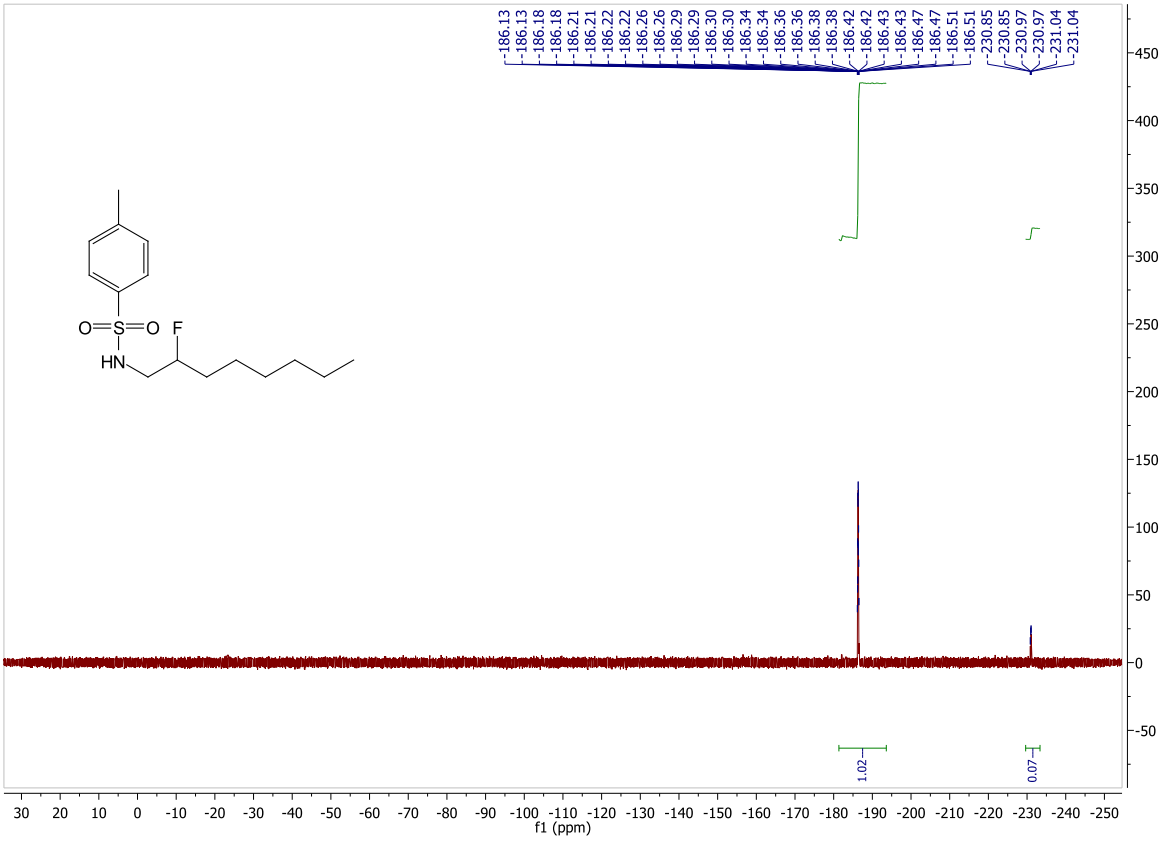
^{1}H NMR for 4-2b



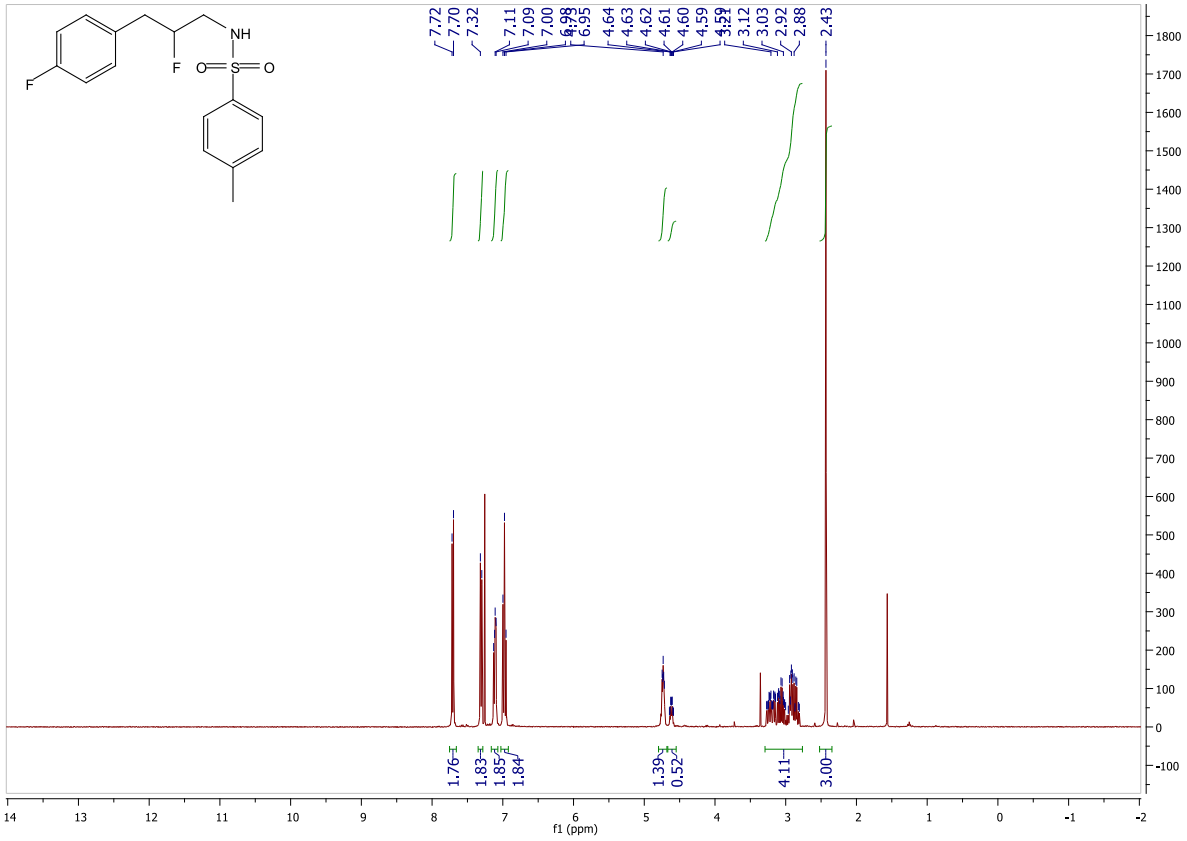
^{13}C NMR for 4-2b



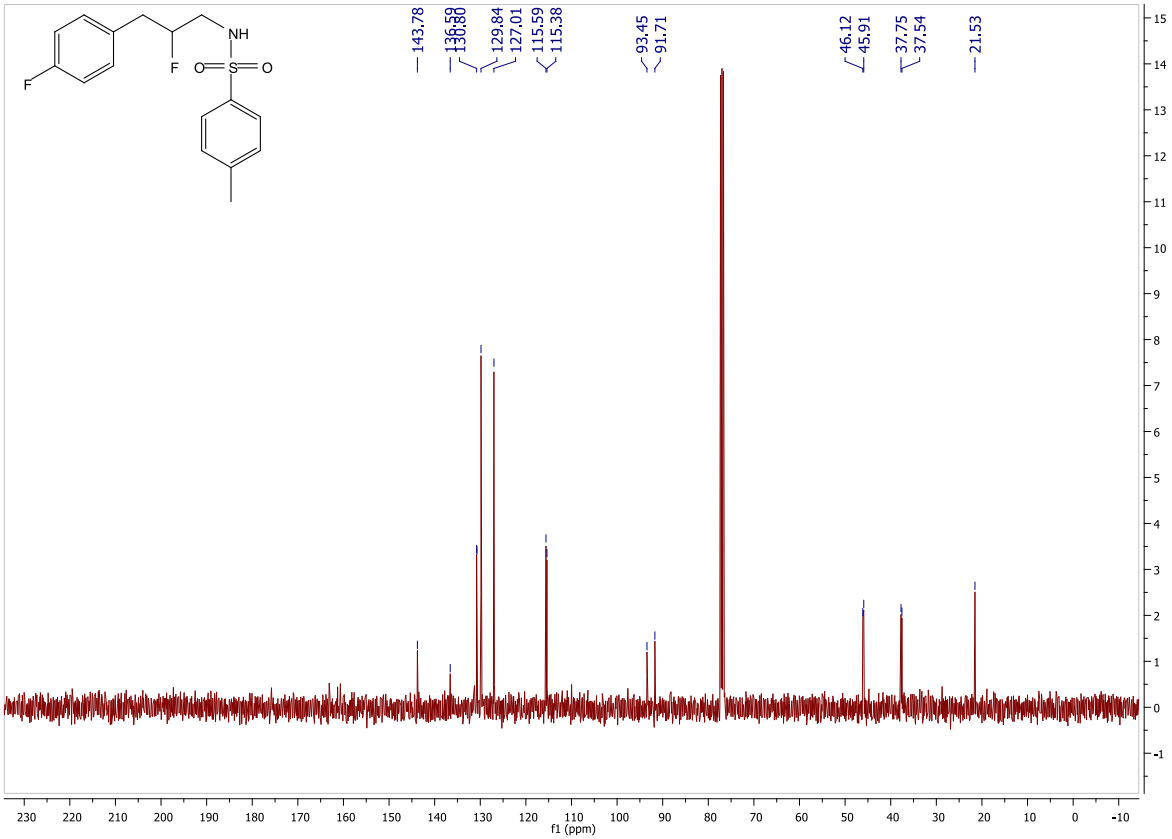
^{19}F NMR for 4-2b



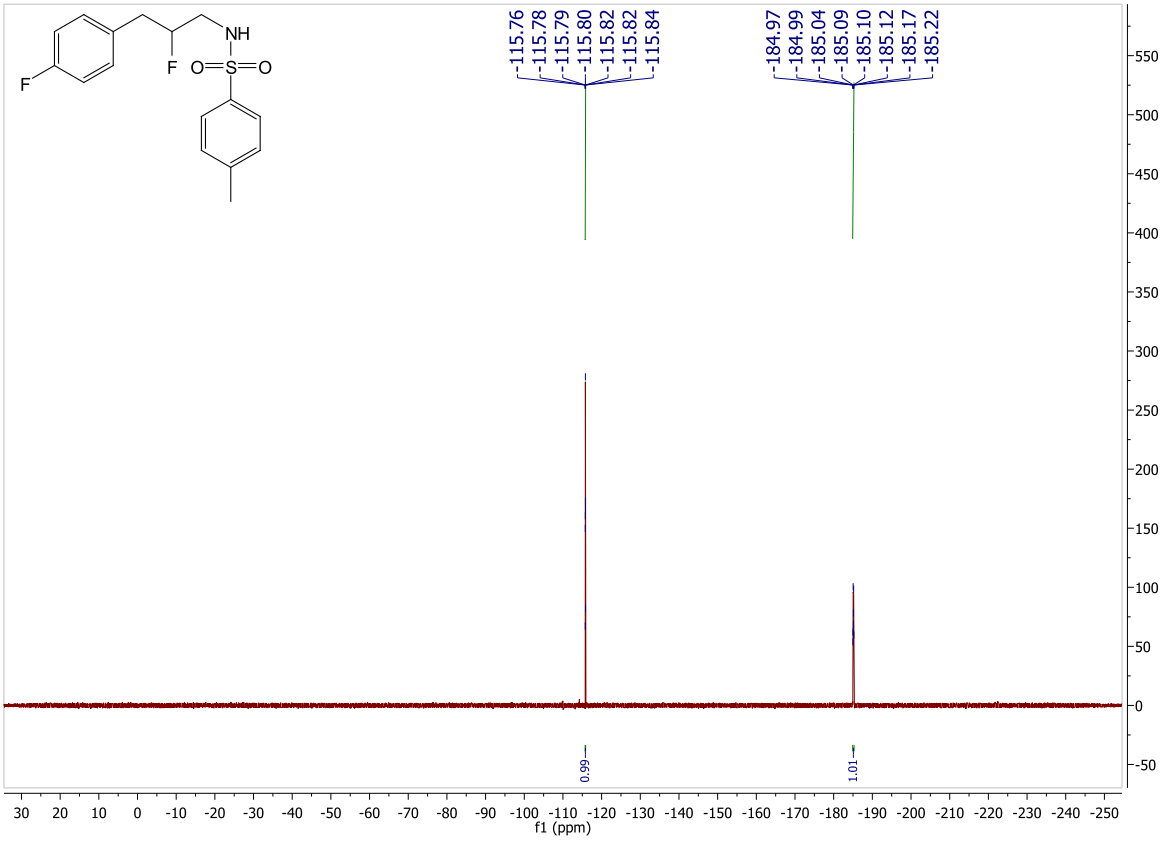
^{1}H NMR for 4-2e



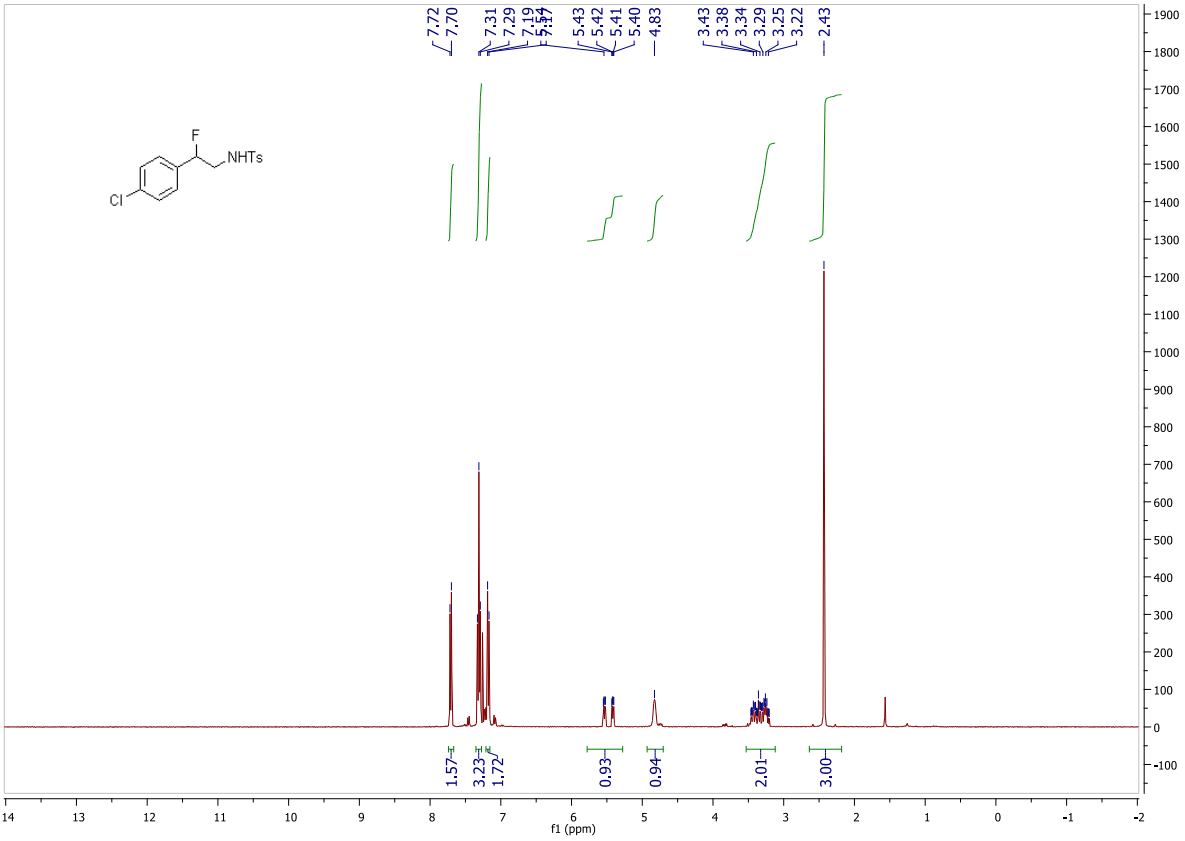
^{13}C NMR for 4-2e



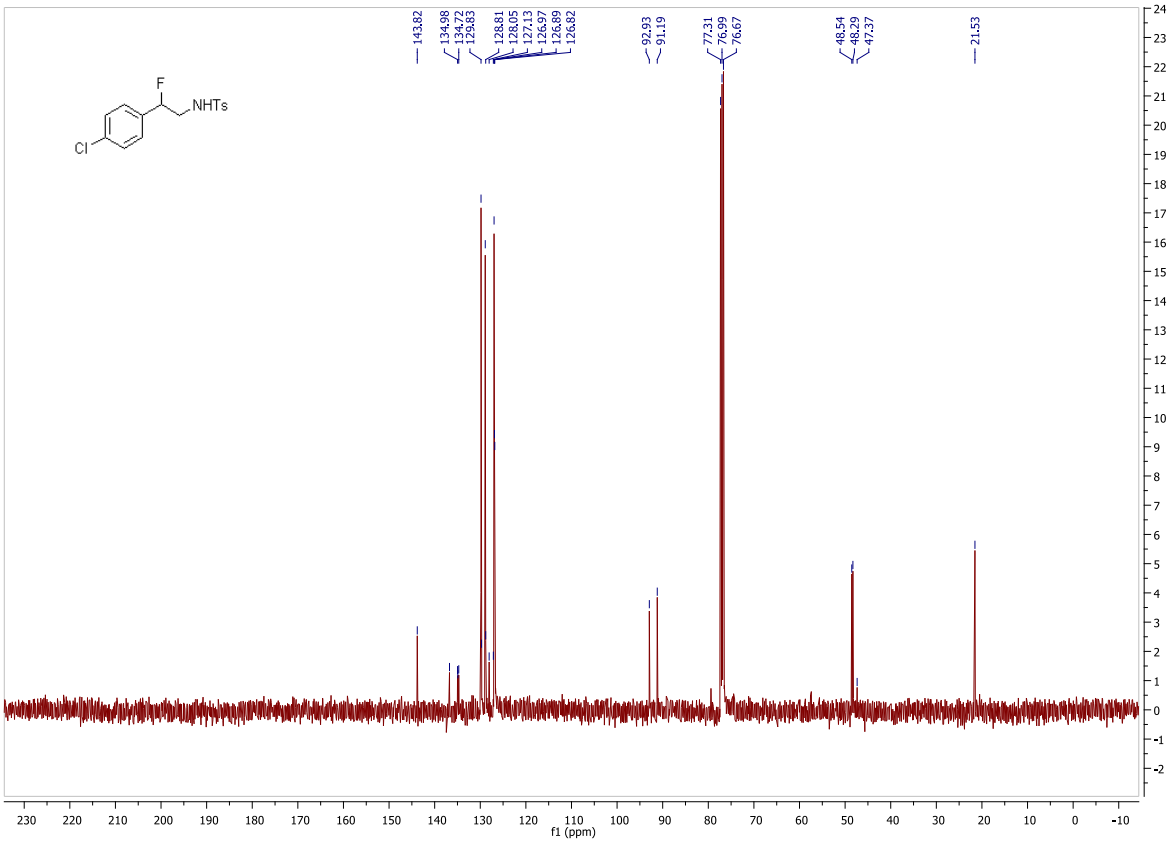
^{19}F NMR for 4-2e



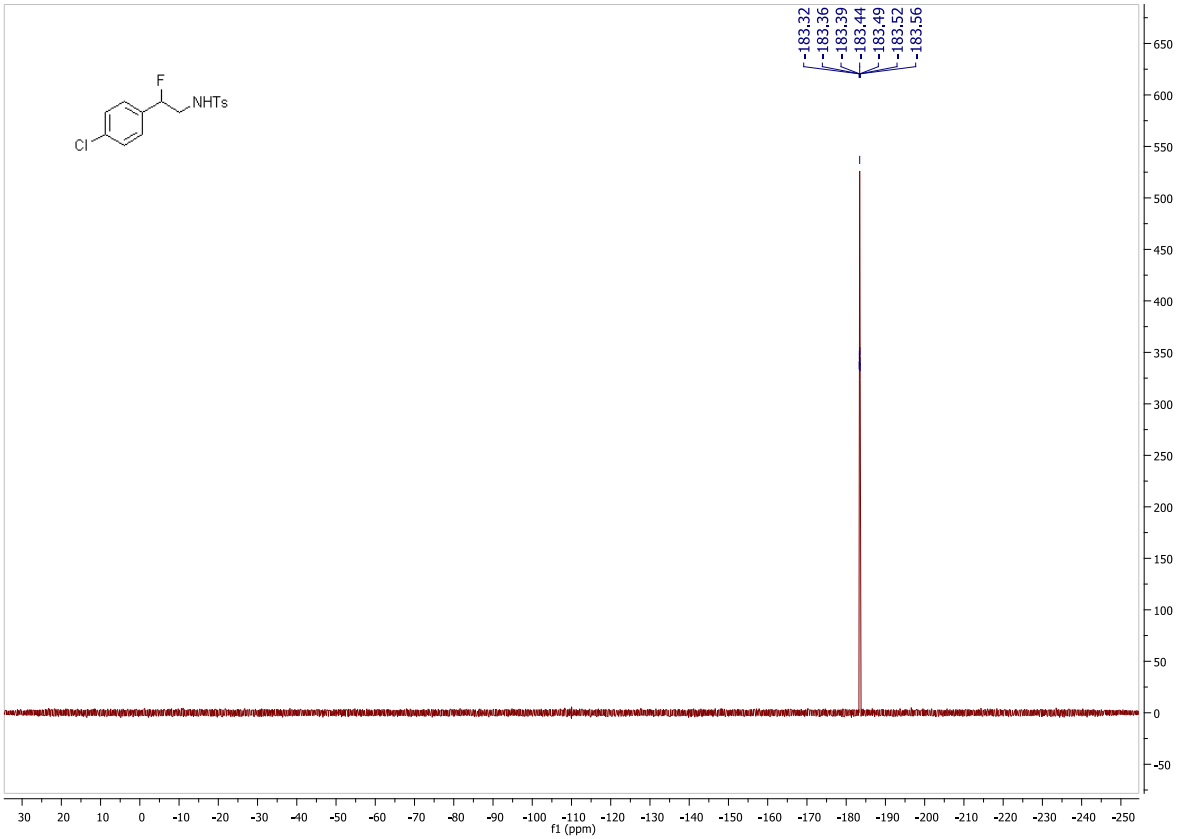
^{1}H NMR for 4-2f



^{13}C NMR for 4-2f



^{19}F NMR for 4-2f



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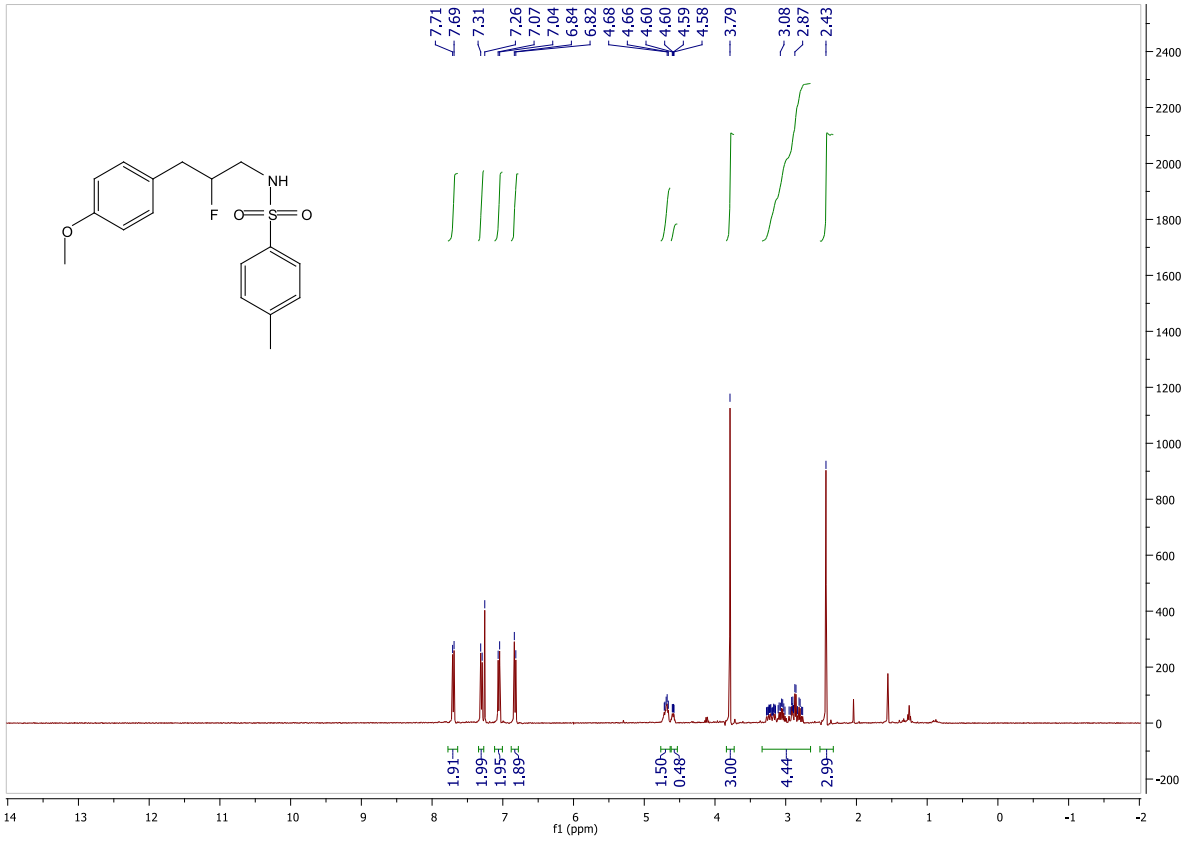
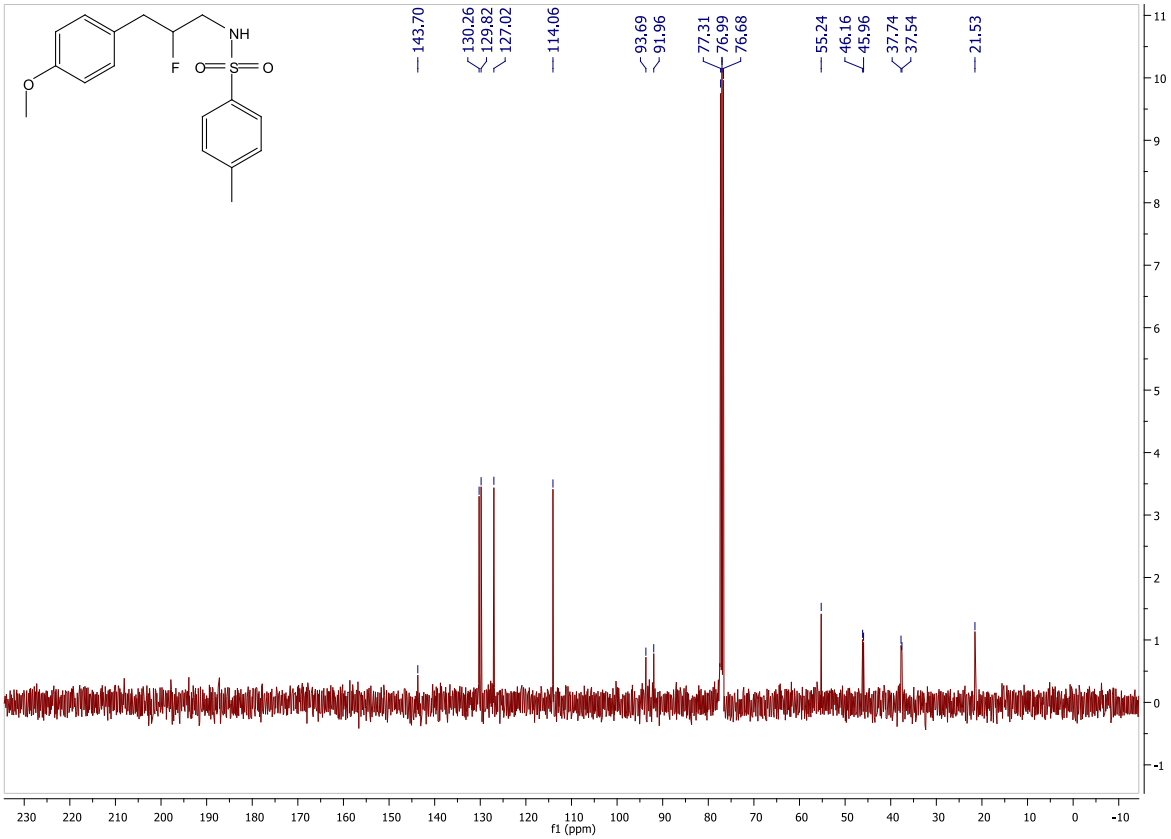
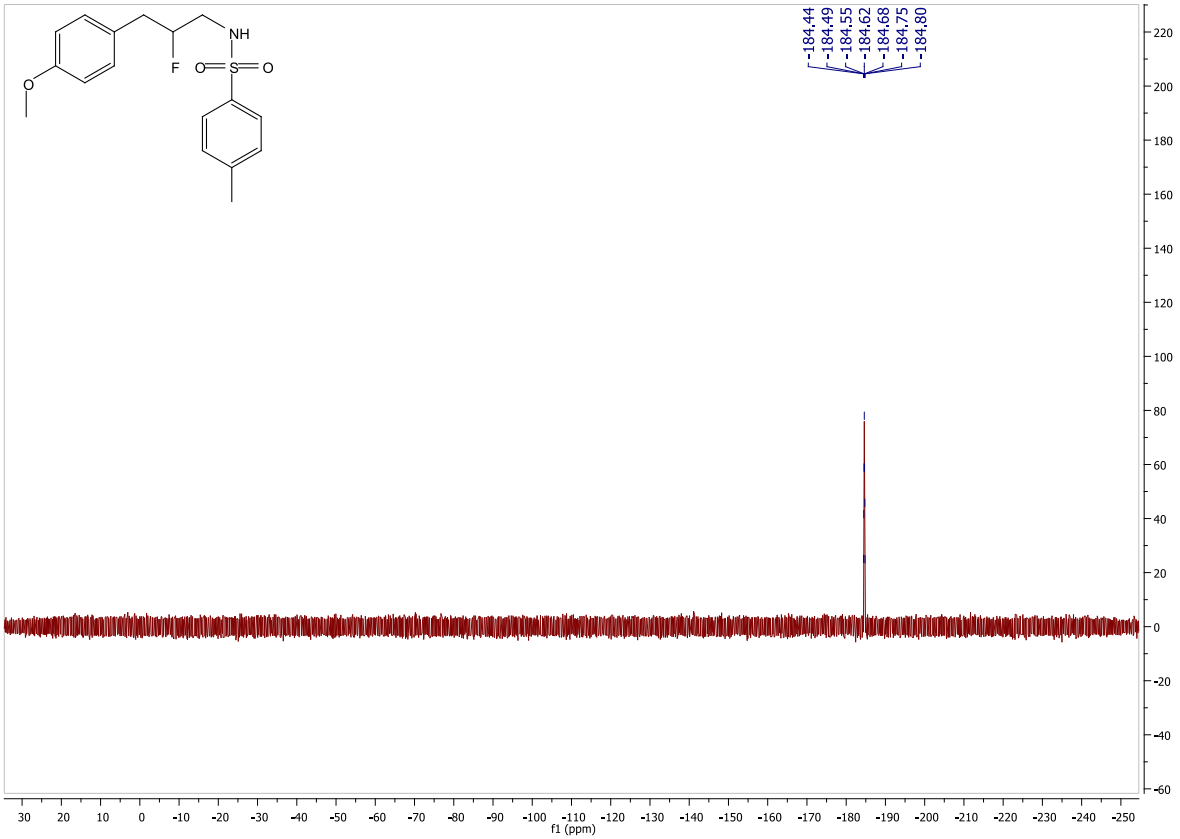


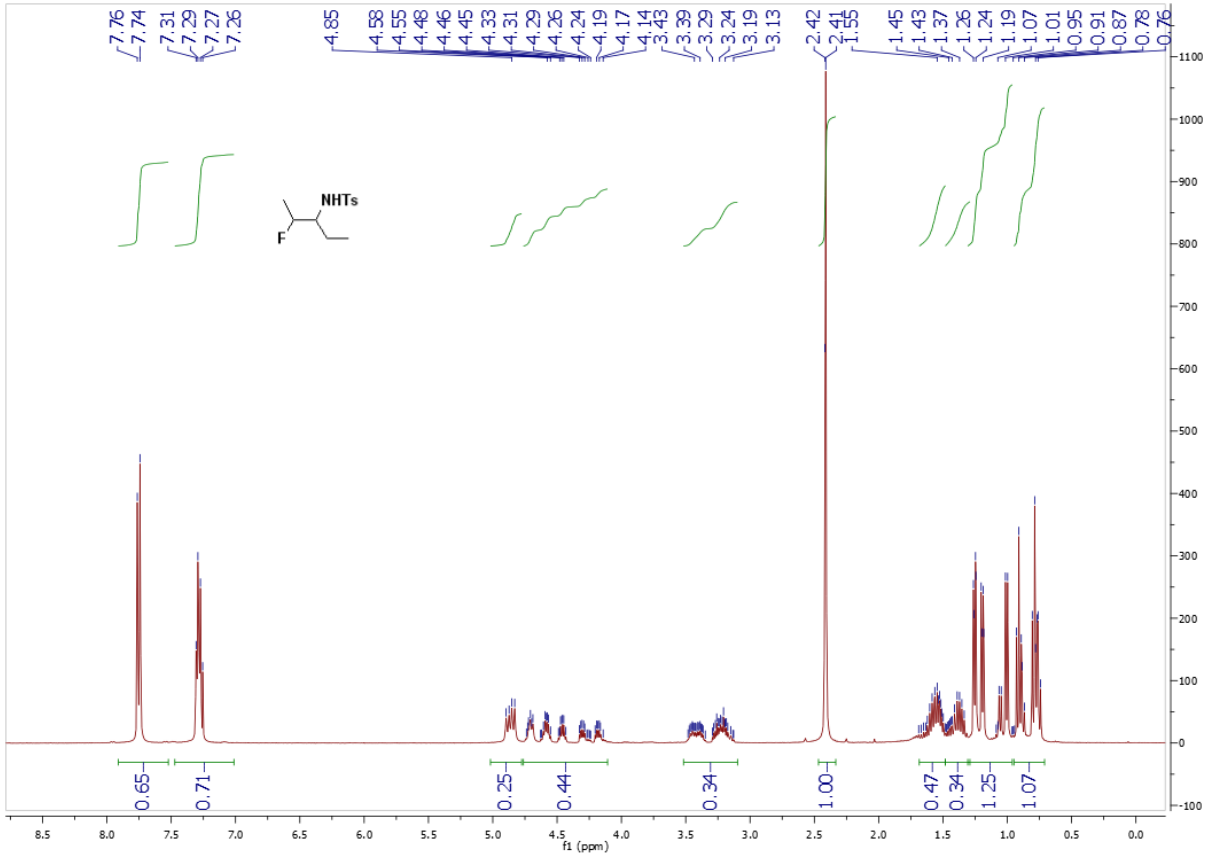
^{13}C NMR for 4-2g



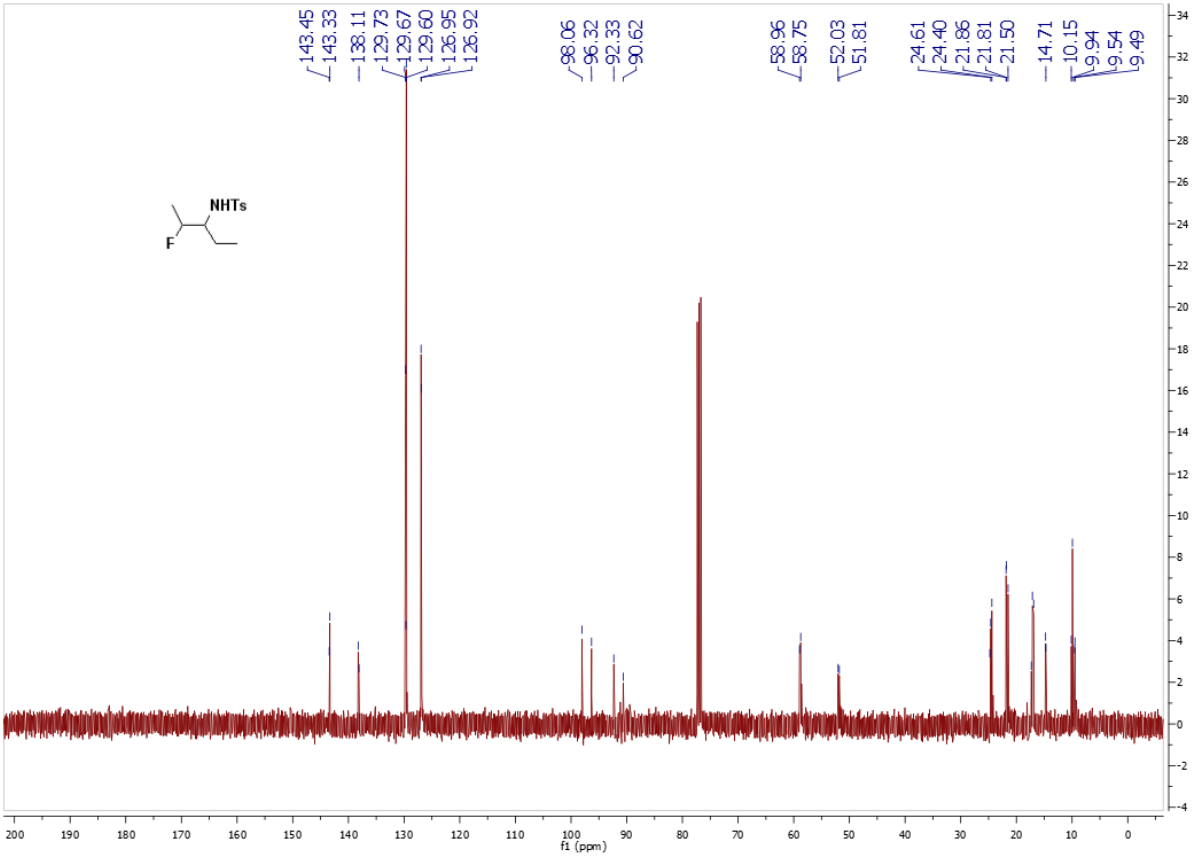
^{19}F NMR for 4-2g



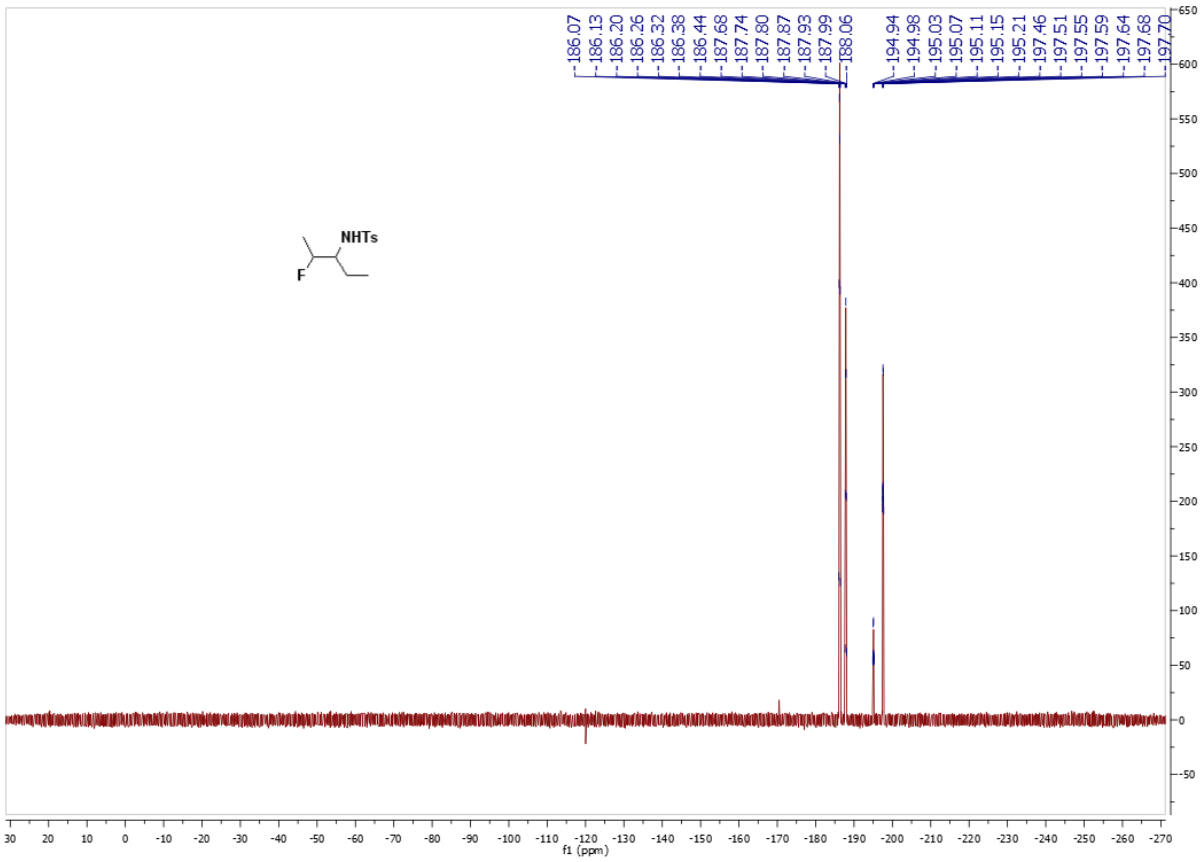
^{1}H NMR for 4-2h



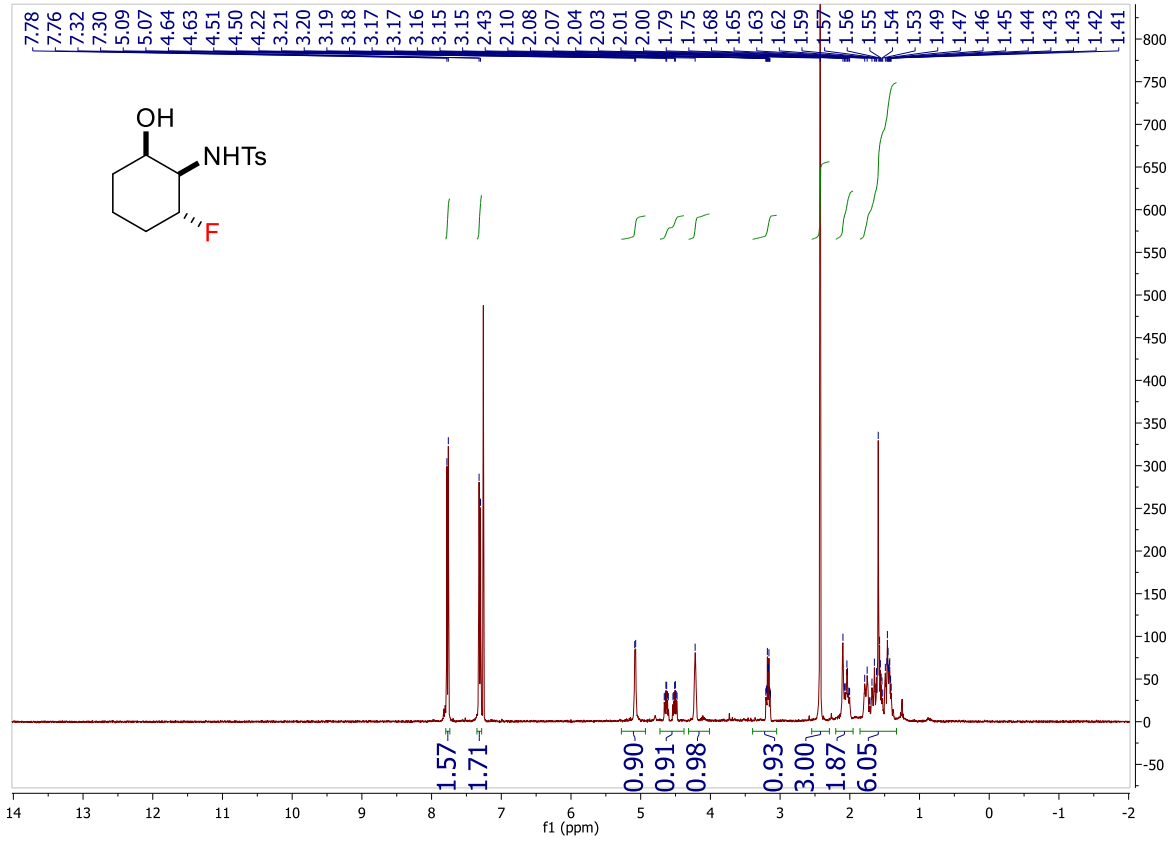
^{13}C NMR for 4-2h



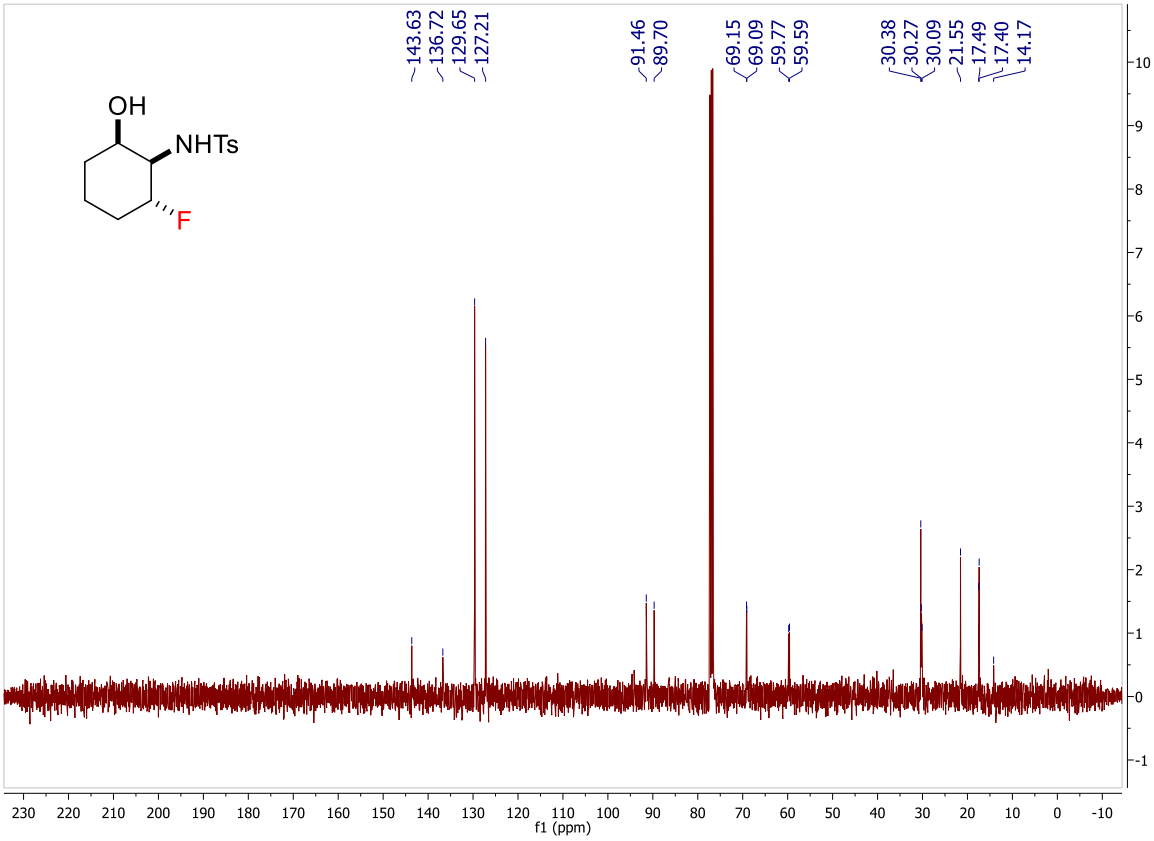
^{19}F NMR for 4-2h



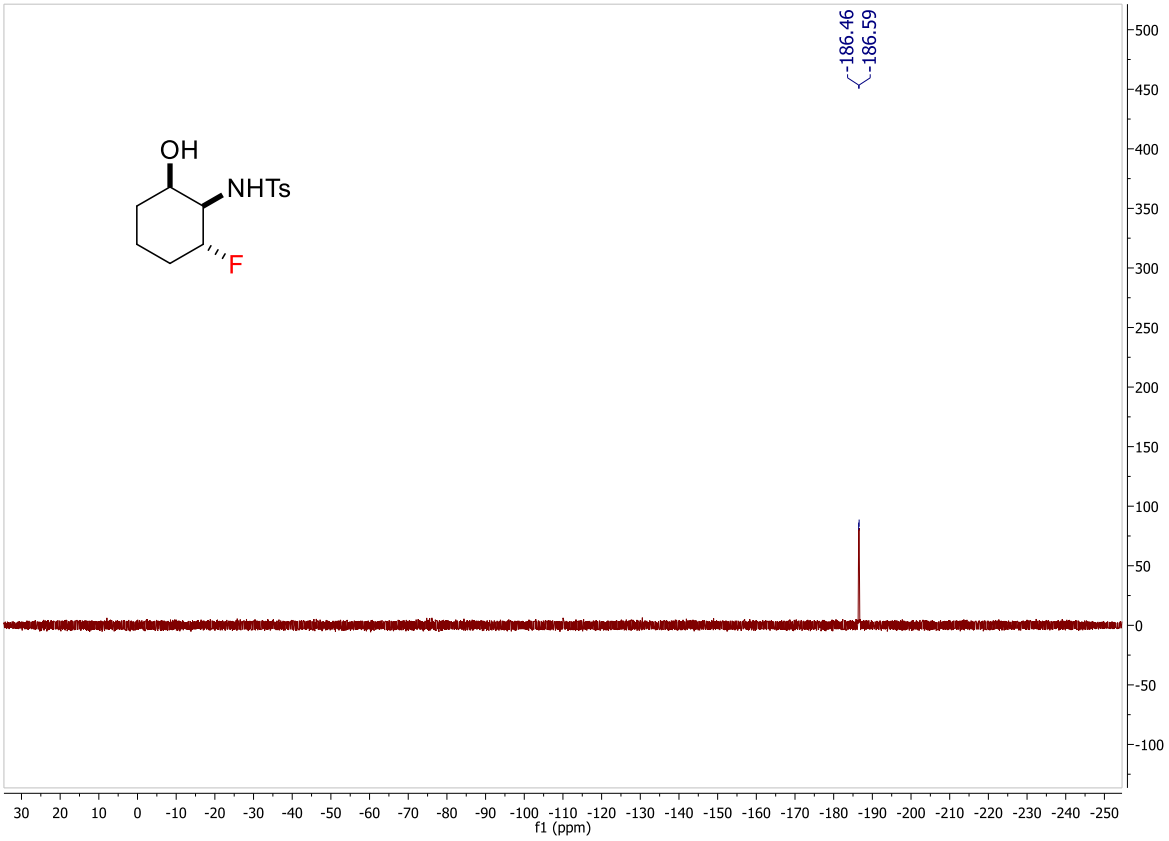
^{1}H NMR for 4-2l



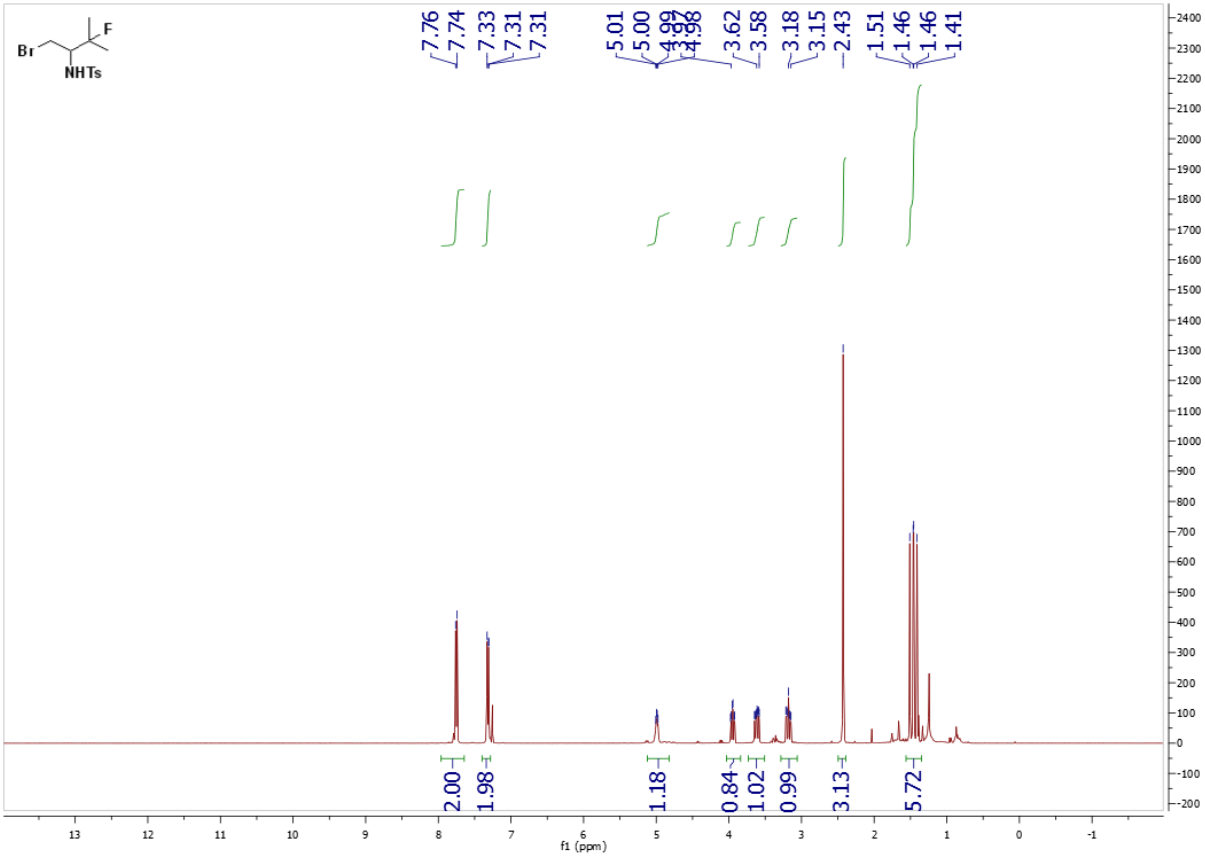
^{13}C NMR for 4-2l



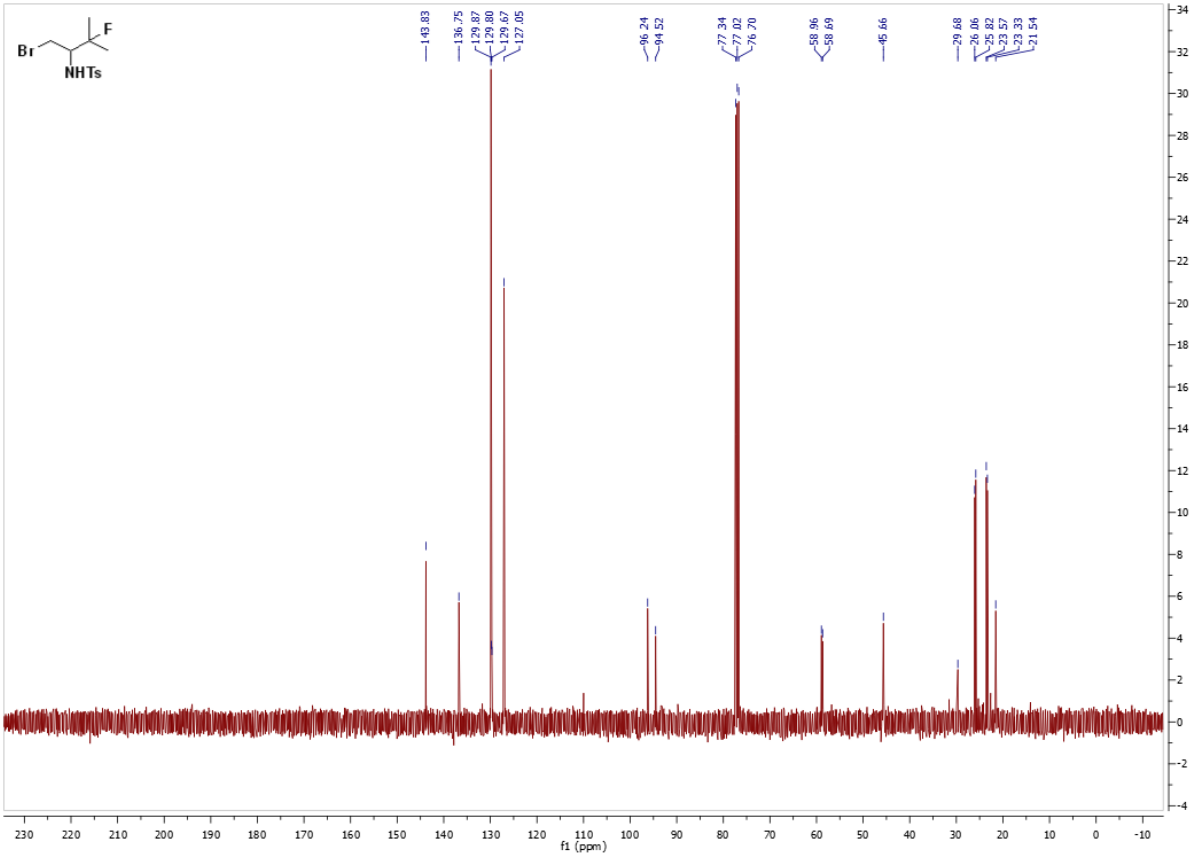
^{19}F NMR for 4-2l



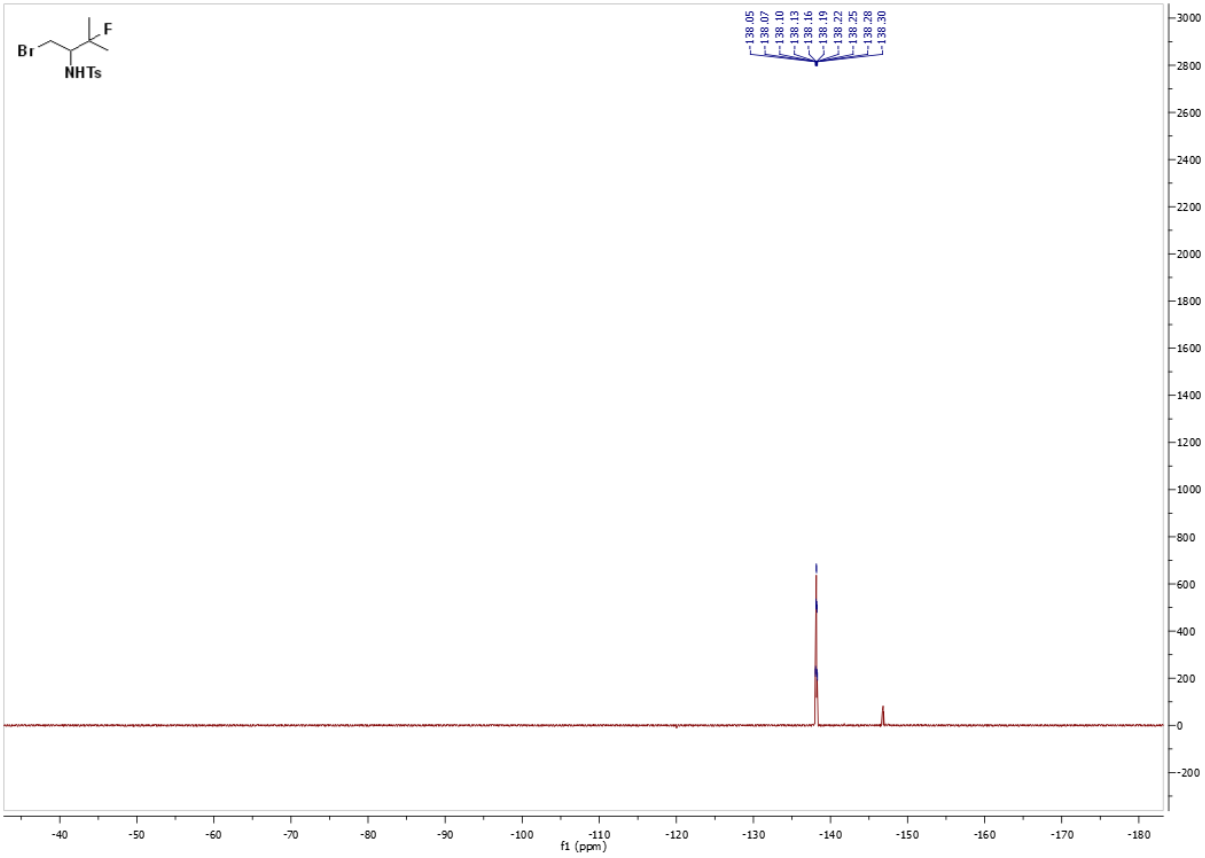
^{1}H NMR for 4-2m



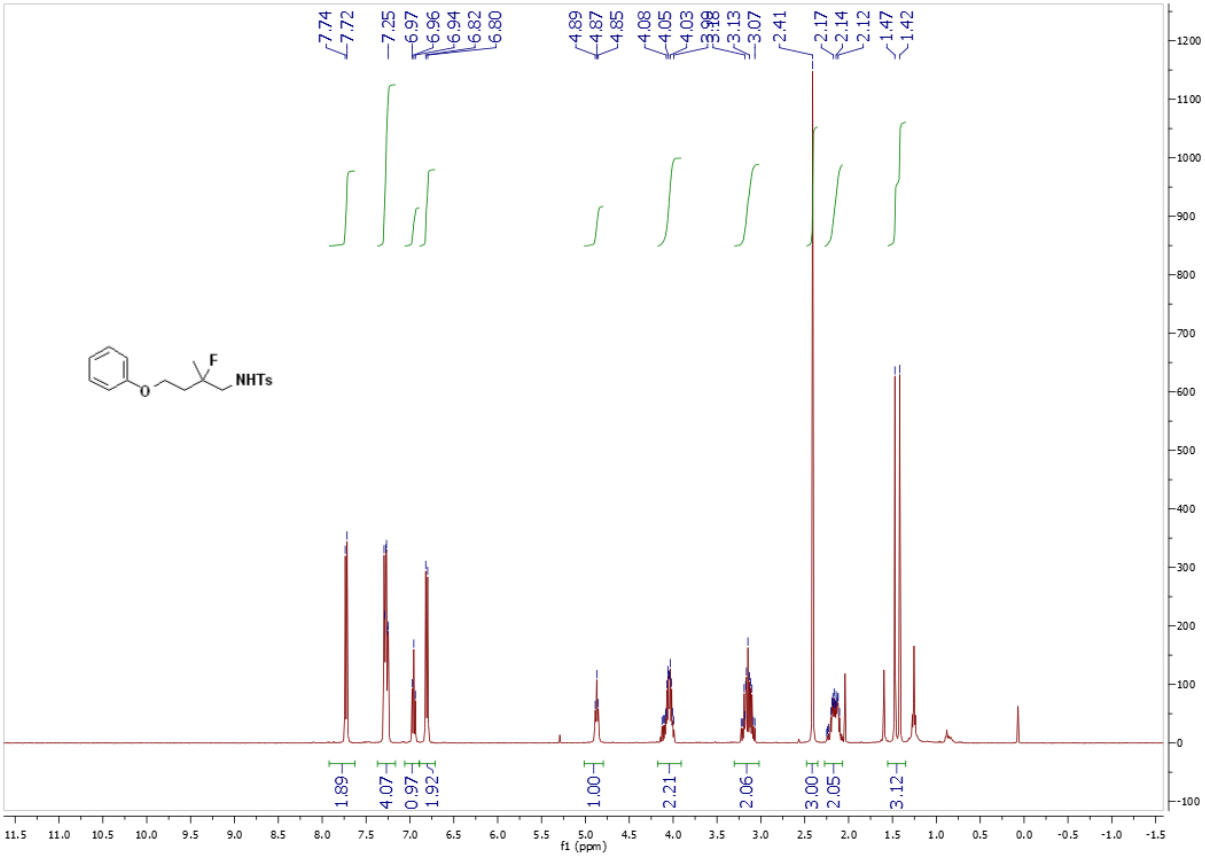
^{13}C NMR for 4-2m



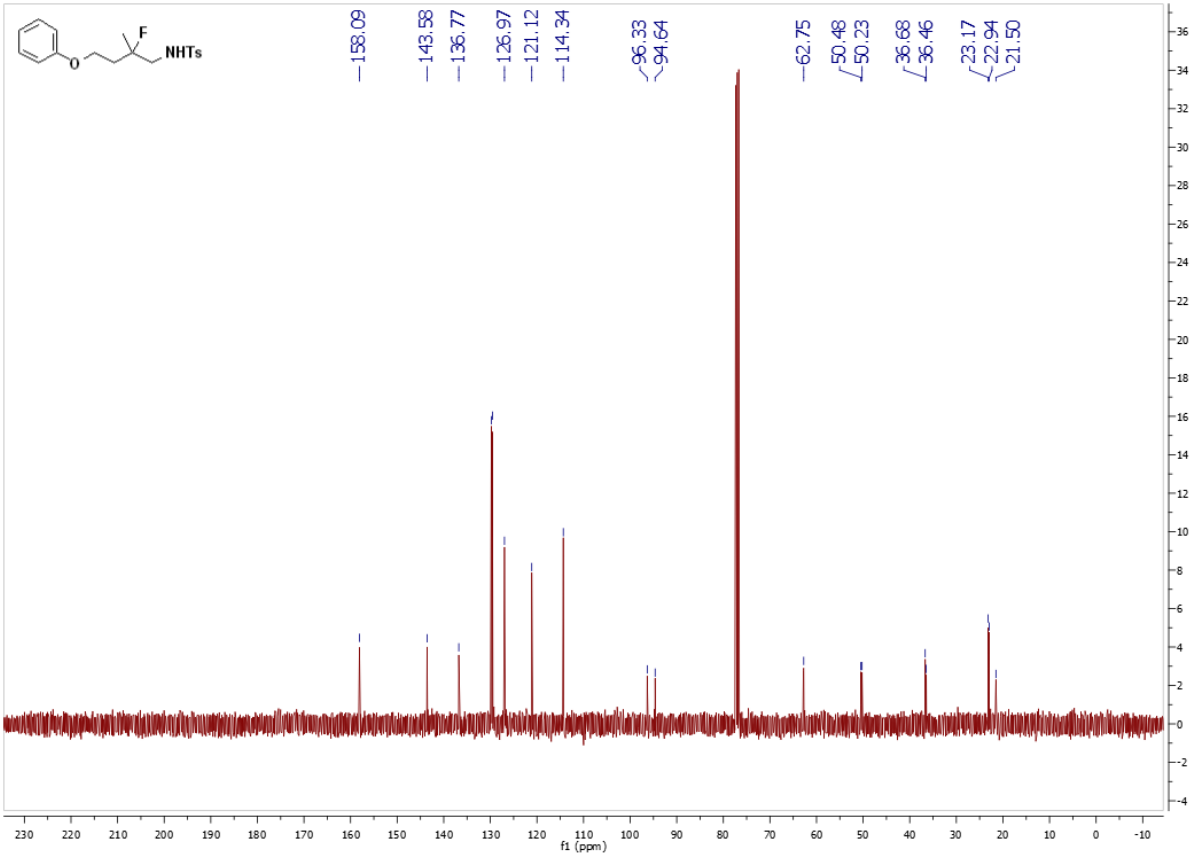
^{19}F NMR for 4-2m



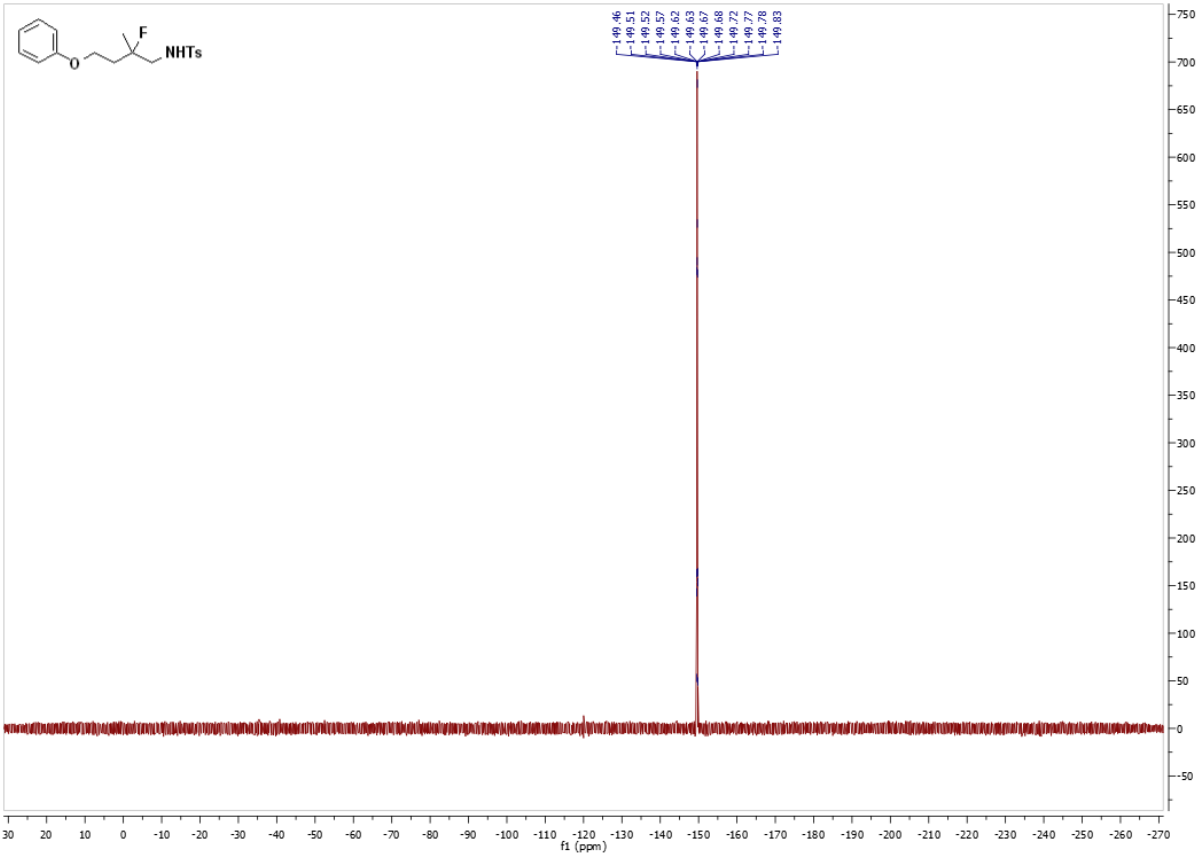
^{1}H NMR for 4-2n



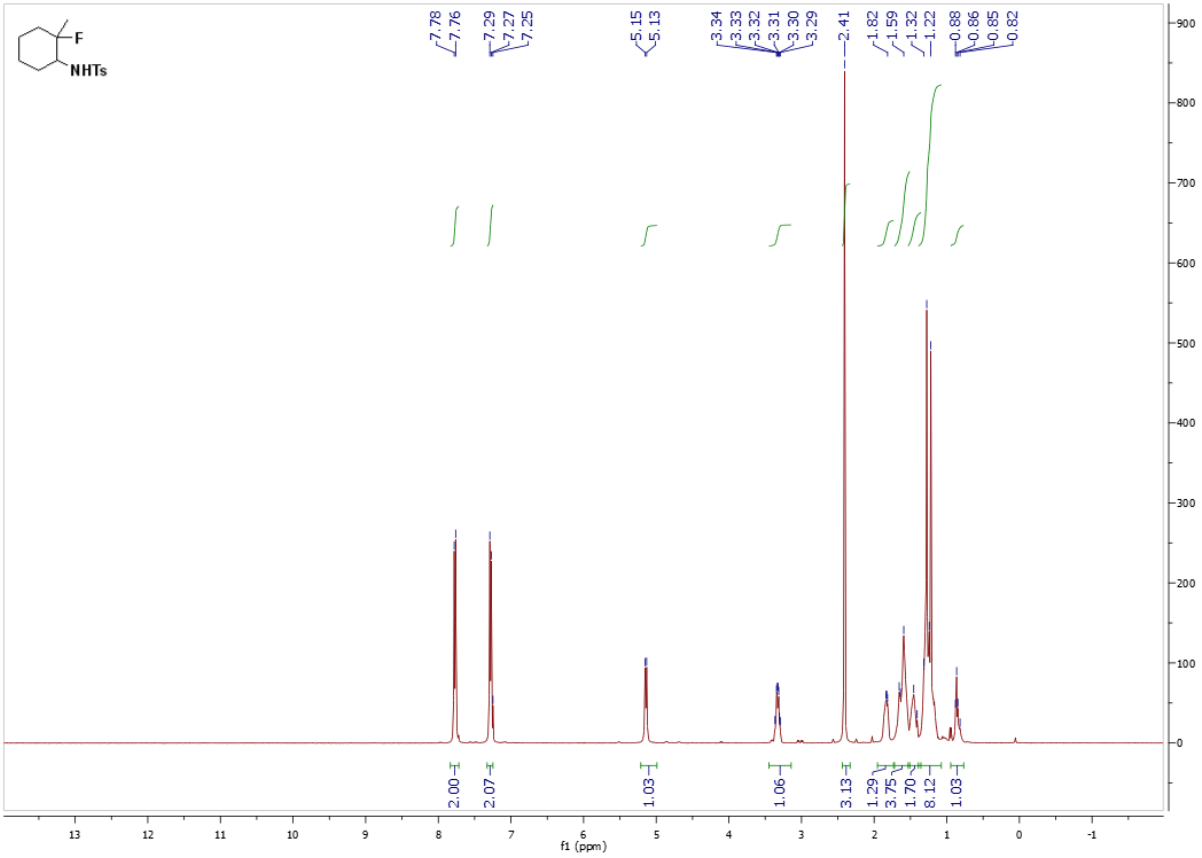
^{13}C NMR for 4-2n



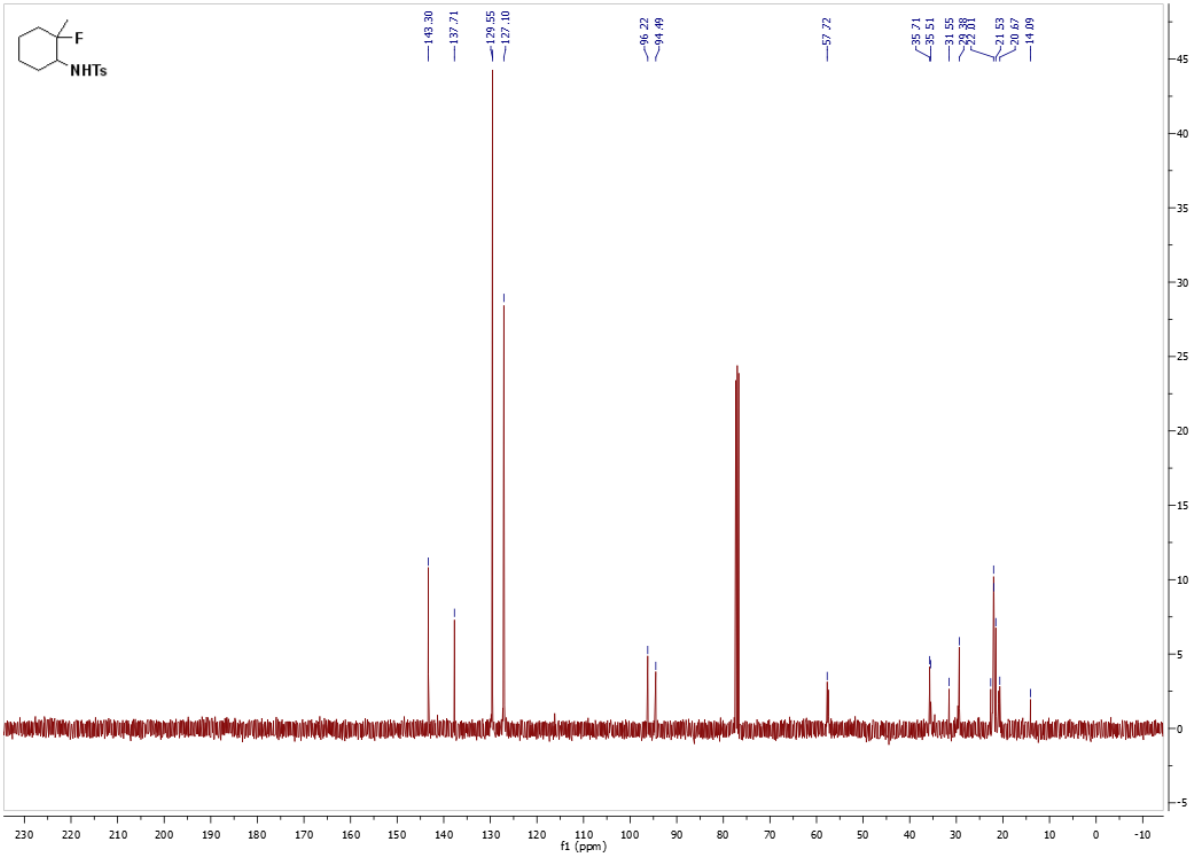
^{19}F NMR for 4-2m



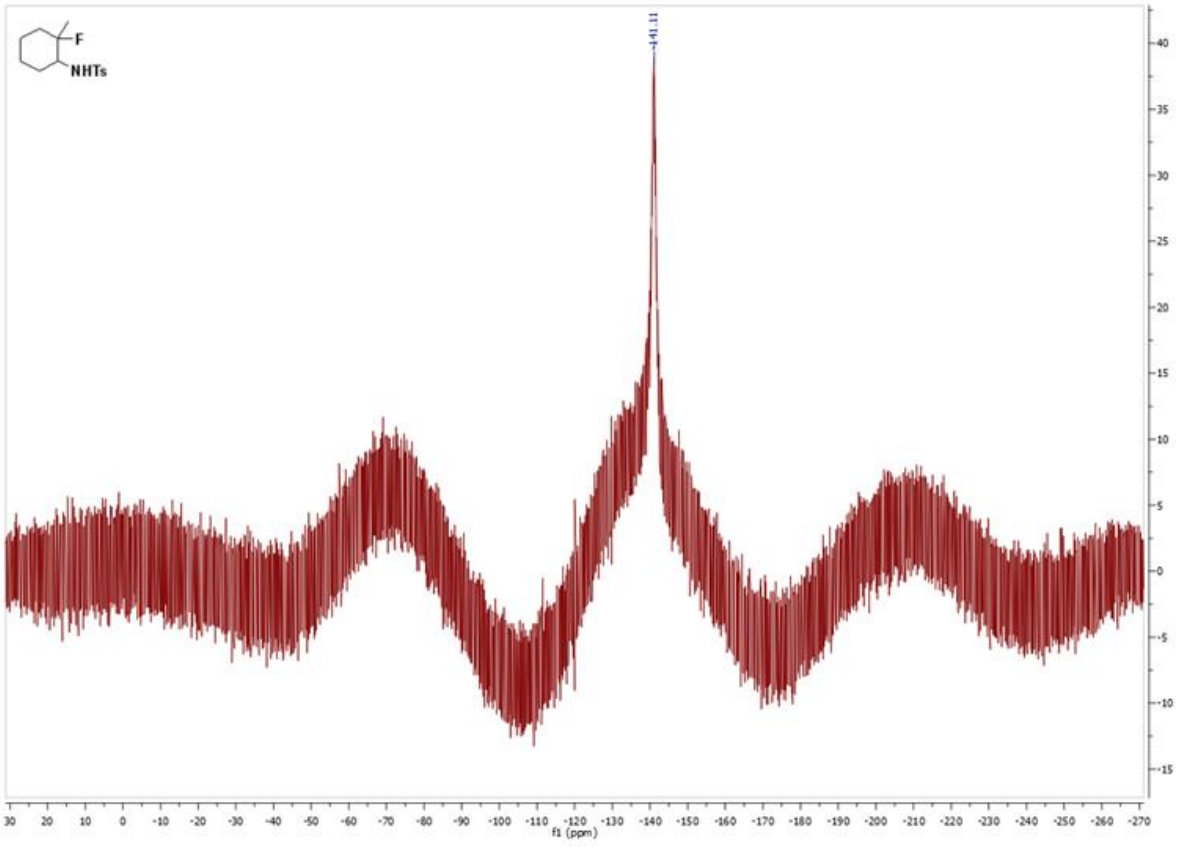
^{1}H NMR for 4-2o



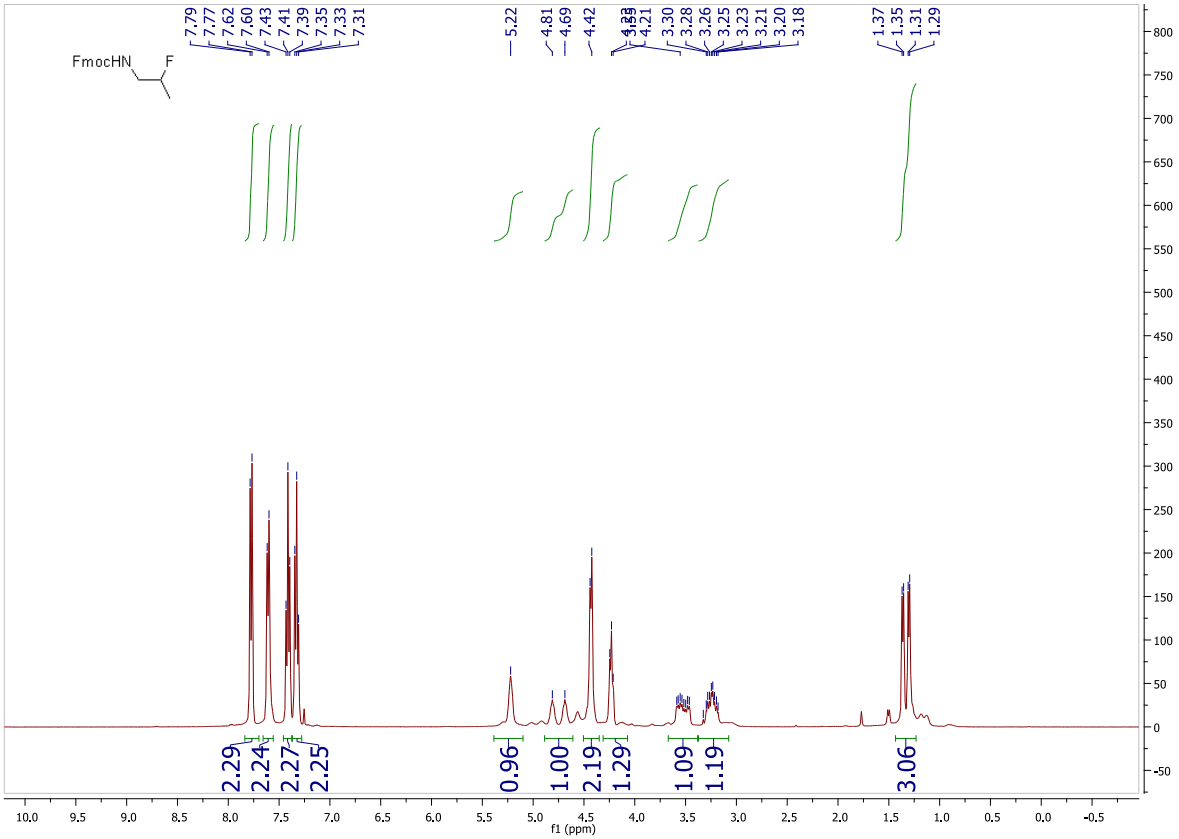
^{13}C NMR for 4-2o



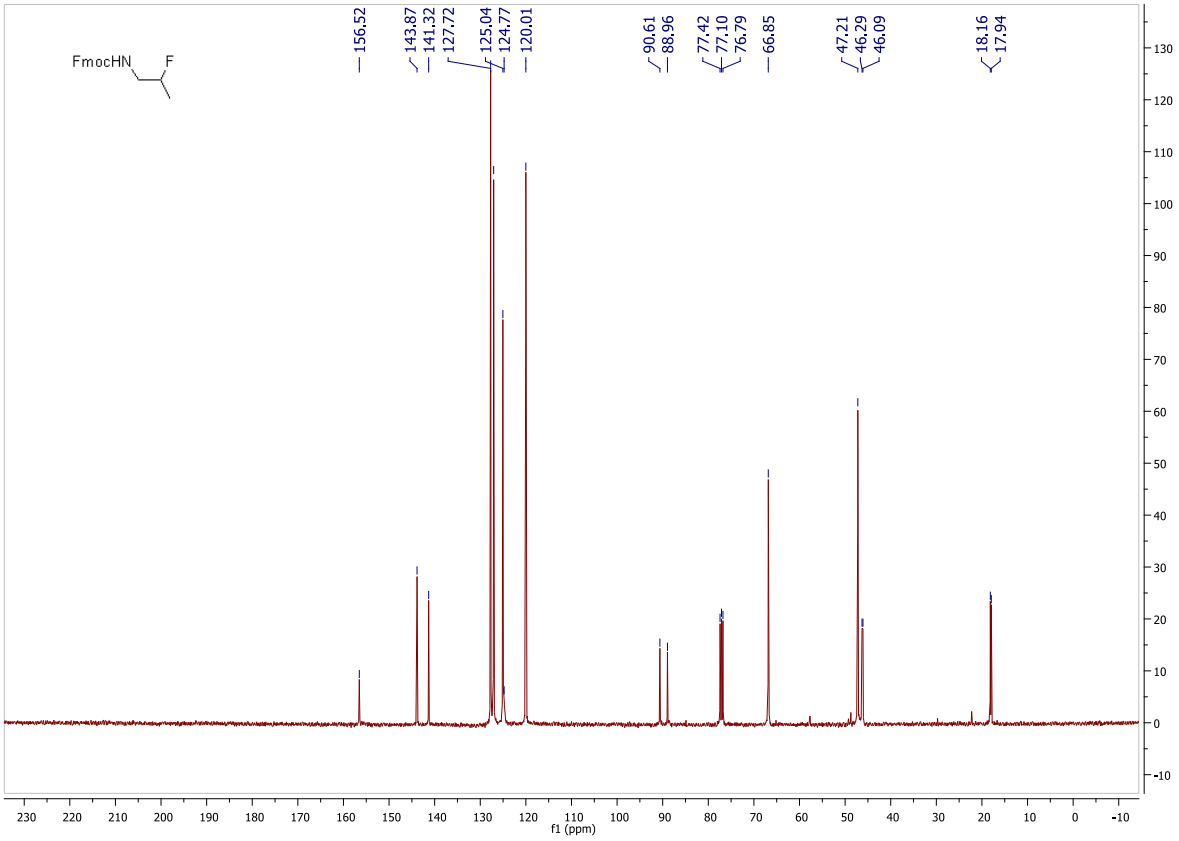
^{19}F NMR for 4-2o



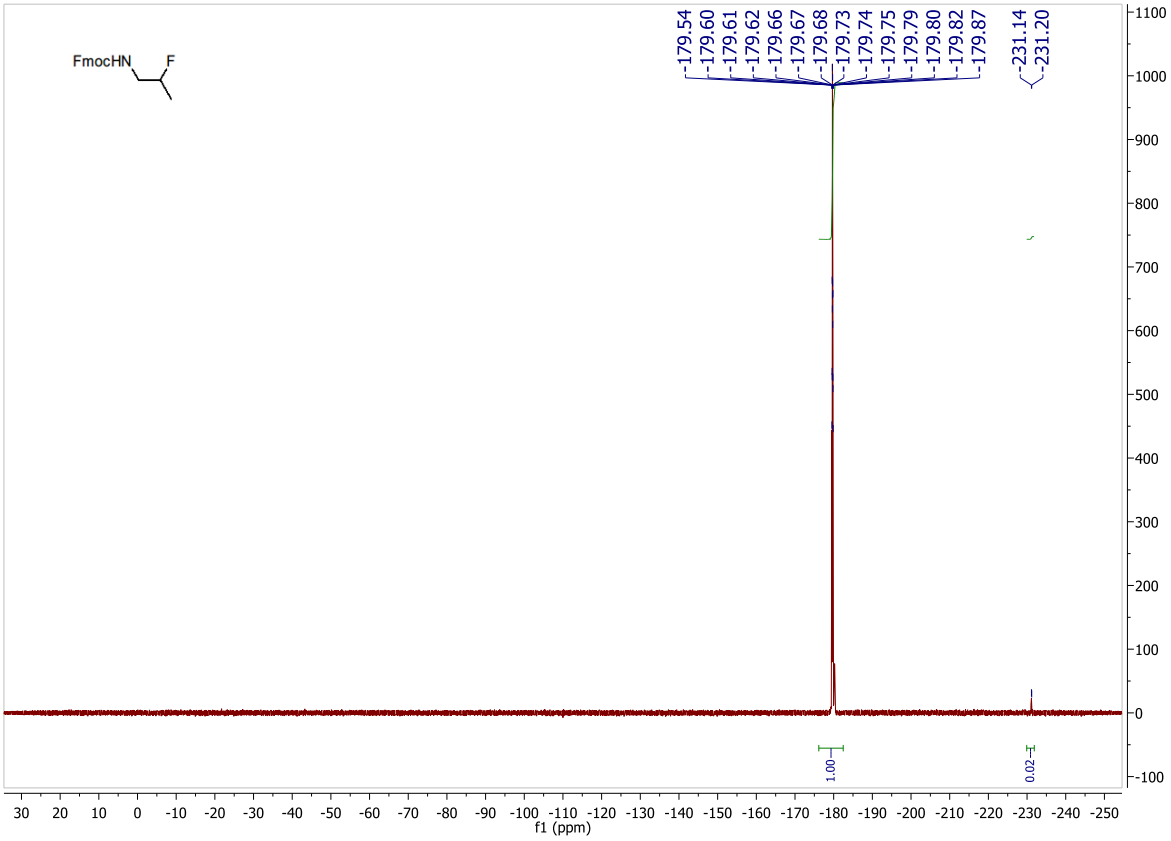
^{1}H NMR for 4-2r



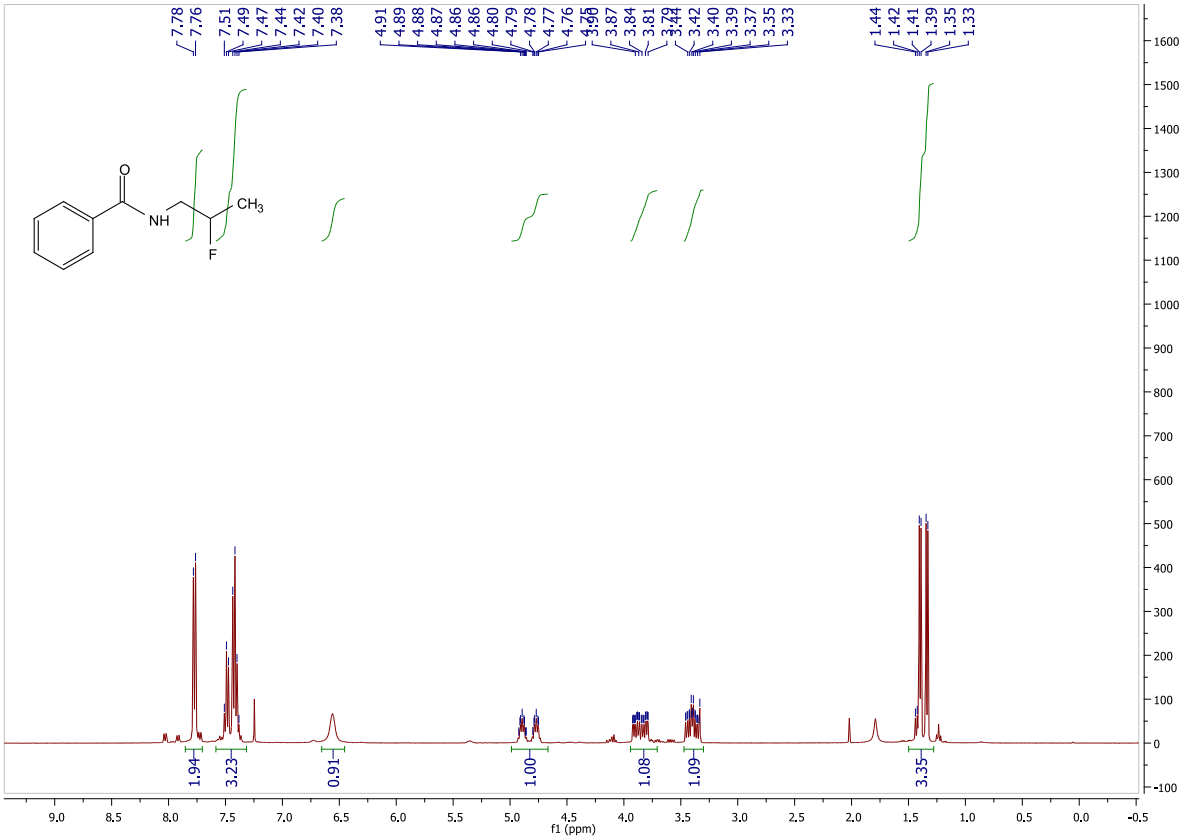
^{13}C NMR for 4-2r



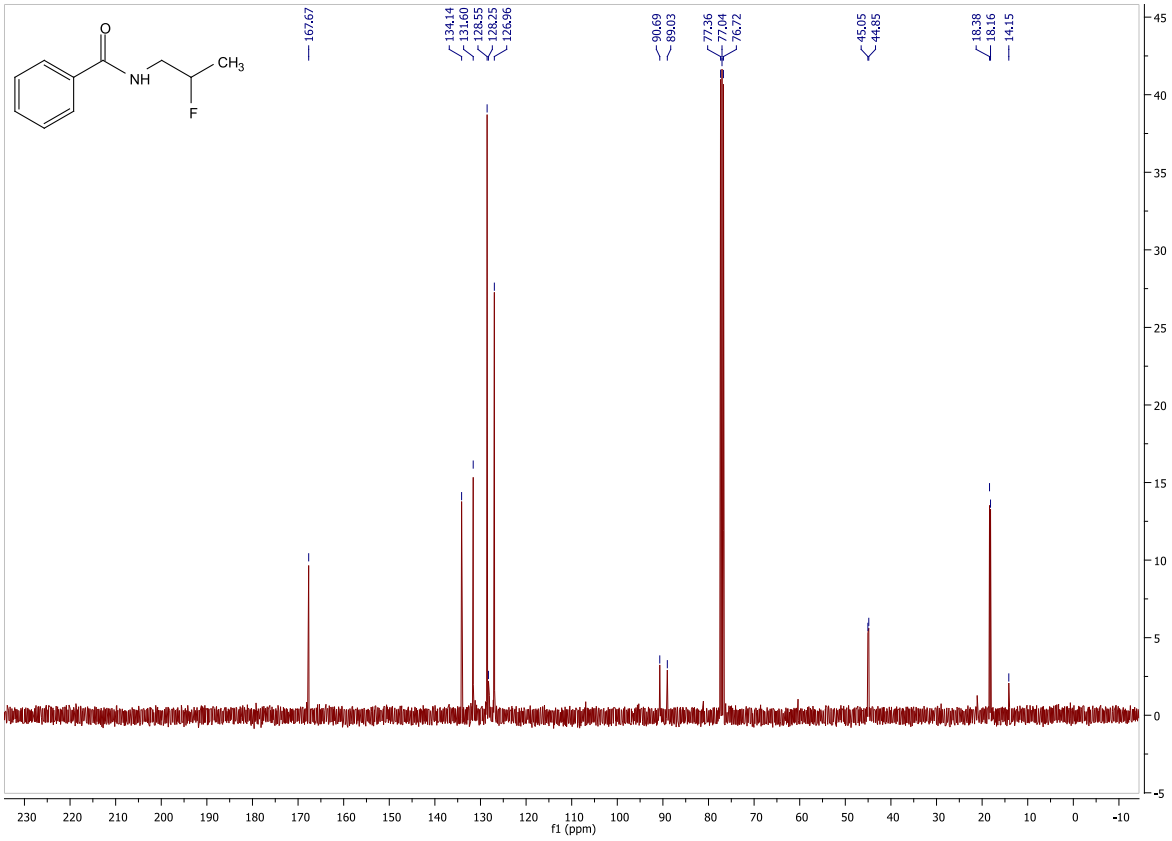
^{19}F NMR for 4-2r



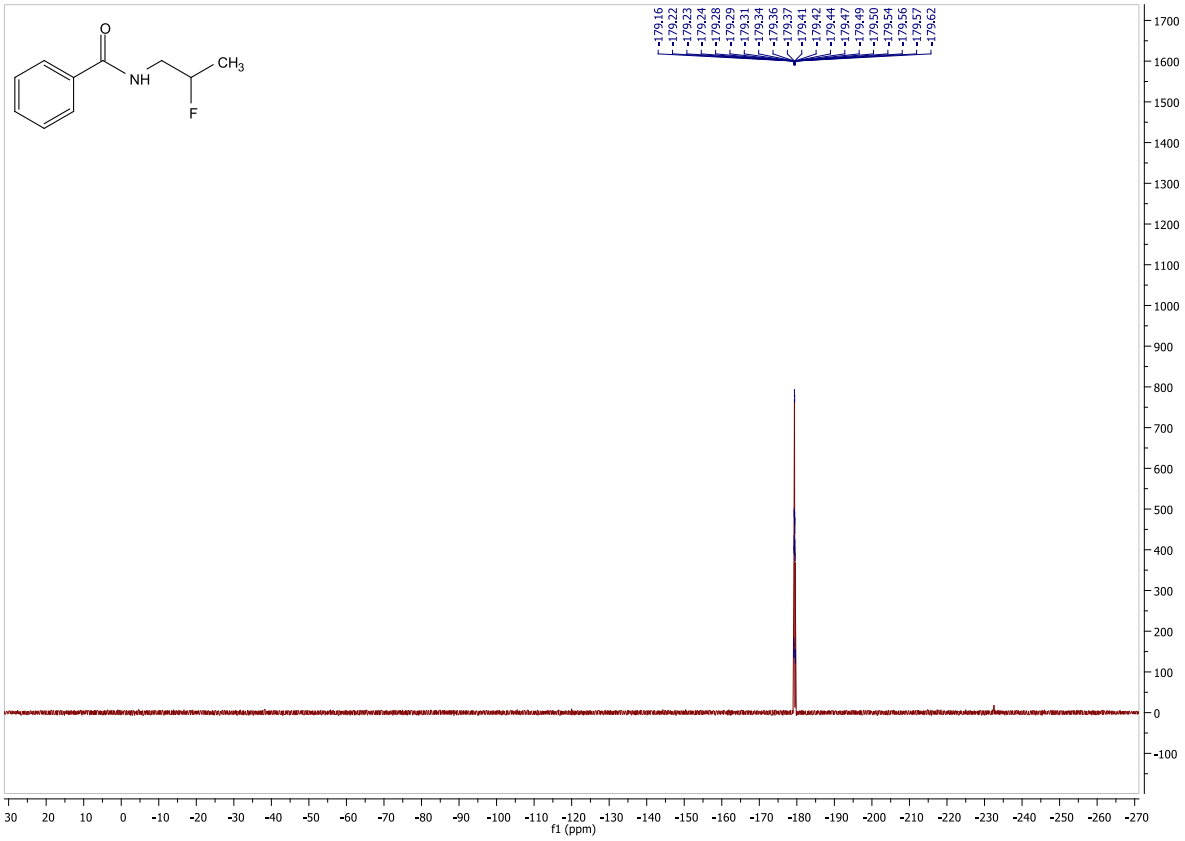
^{1}H NMR for 4-2s



^{13}C NMR for 4-2s

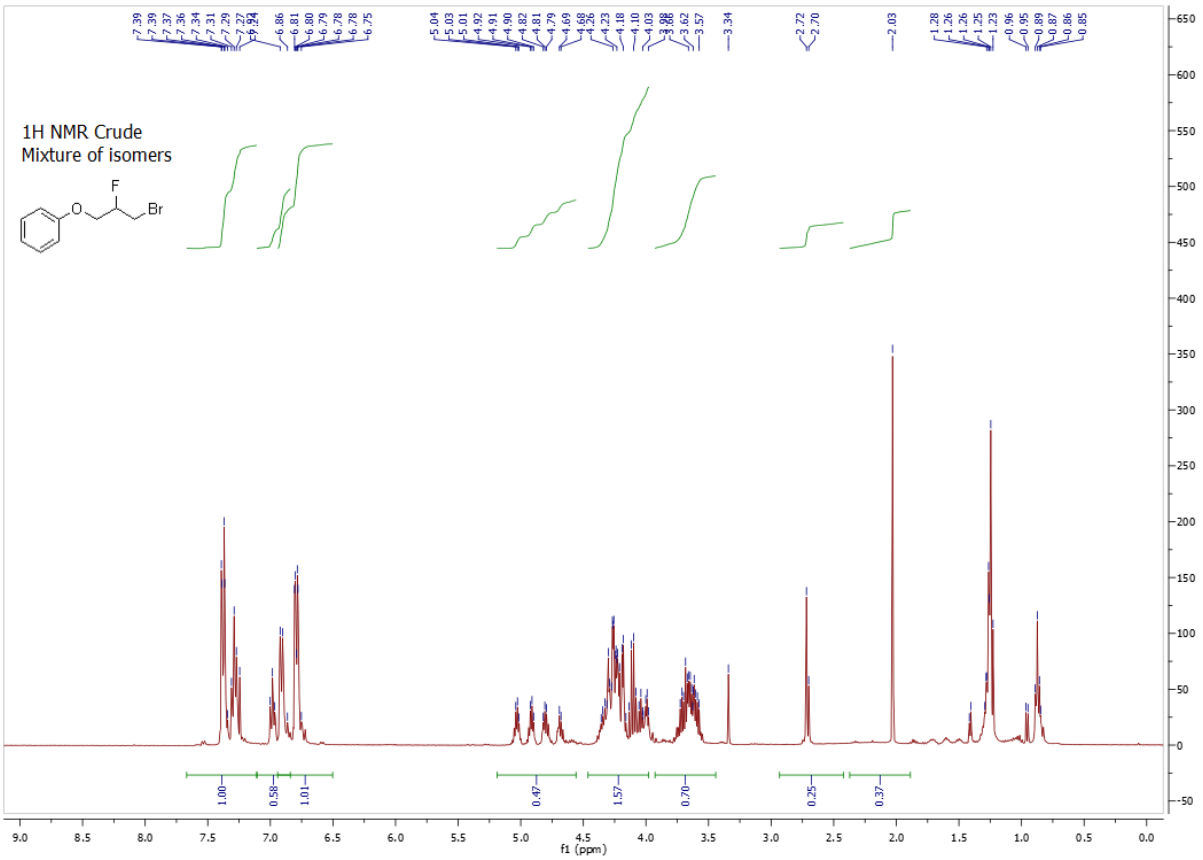


^{19}F NMR for 4-2s

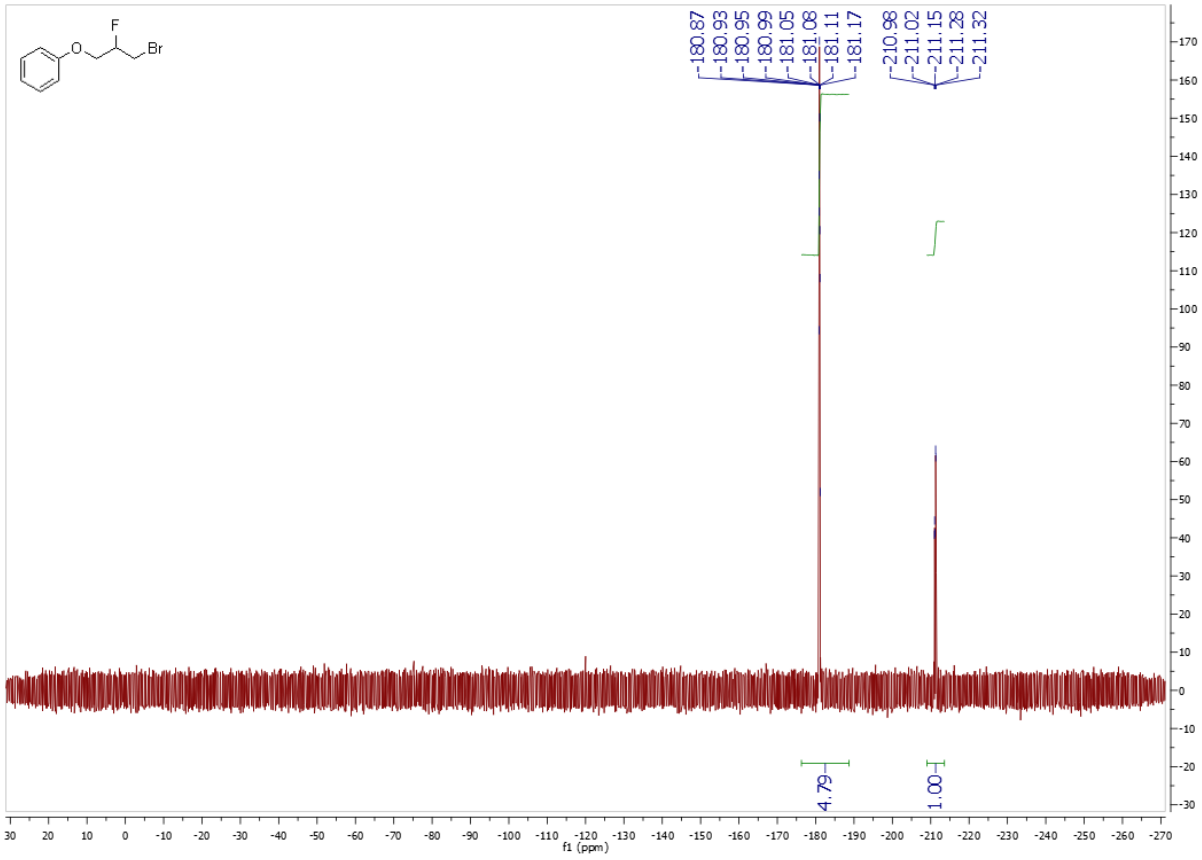


NMR FILES FOR AZIRIDINE BOMOFLUORINATION OF ALKENES

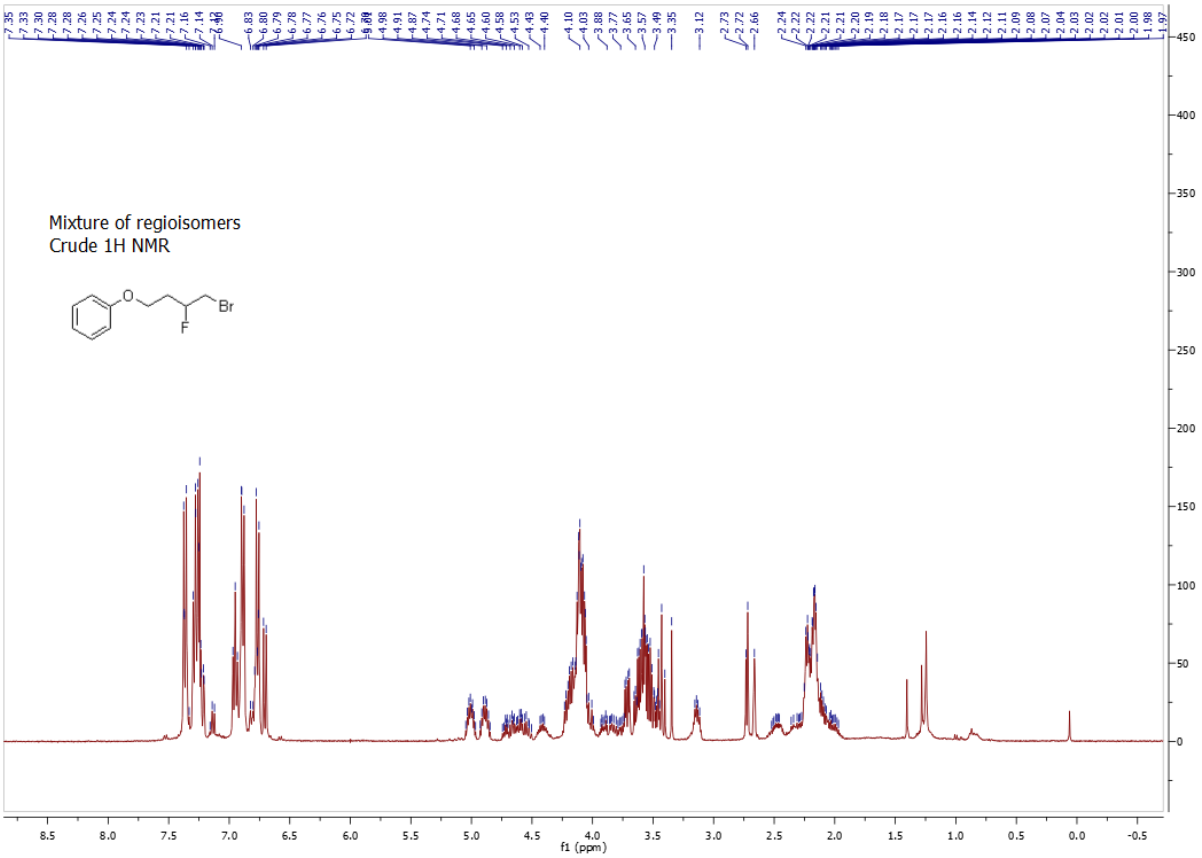
^{1}H NMR spectrum 5-2a



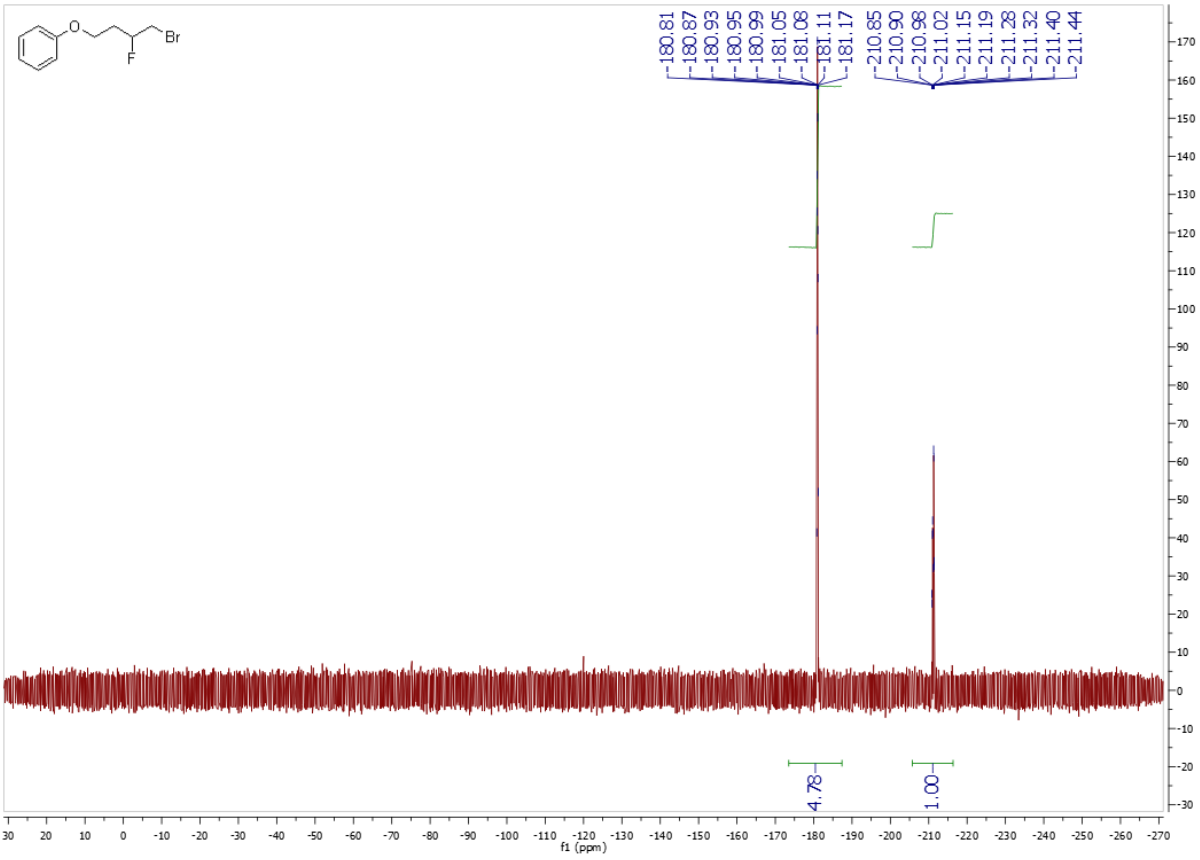
^{19}F NMR spectrum 5-2a



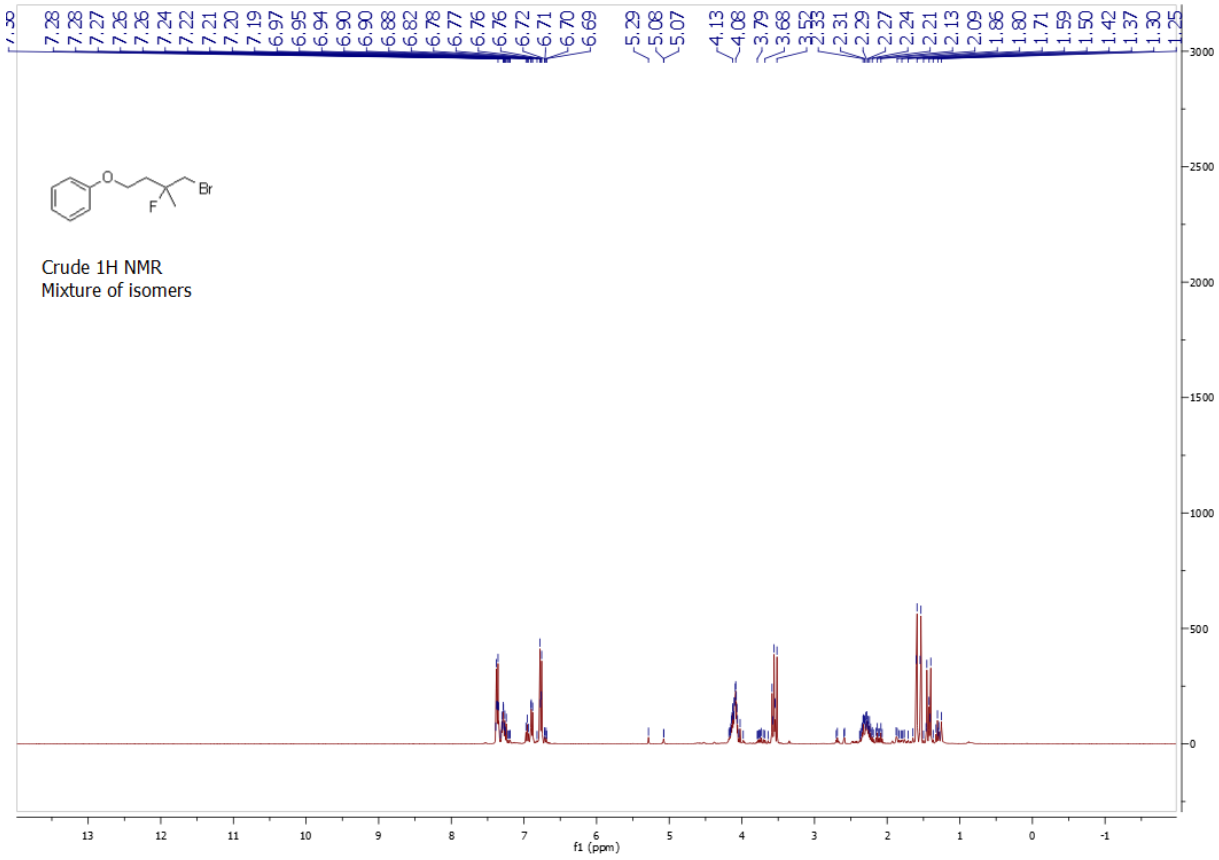
^{1}H NMR spectrum 5-2b



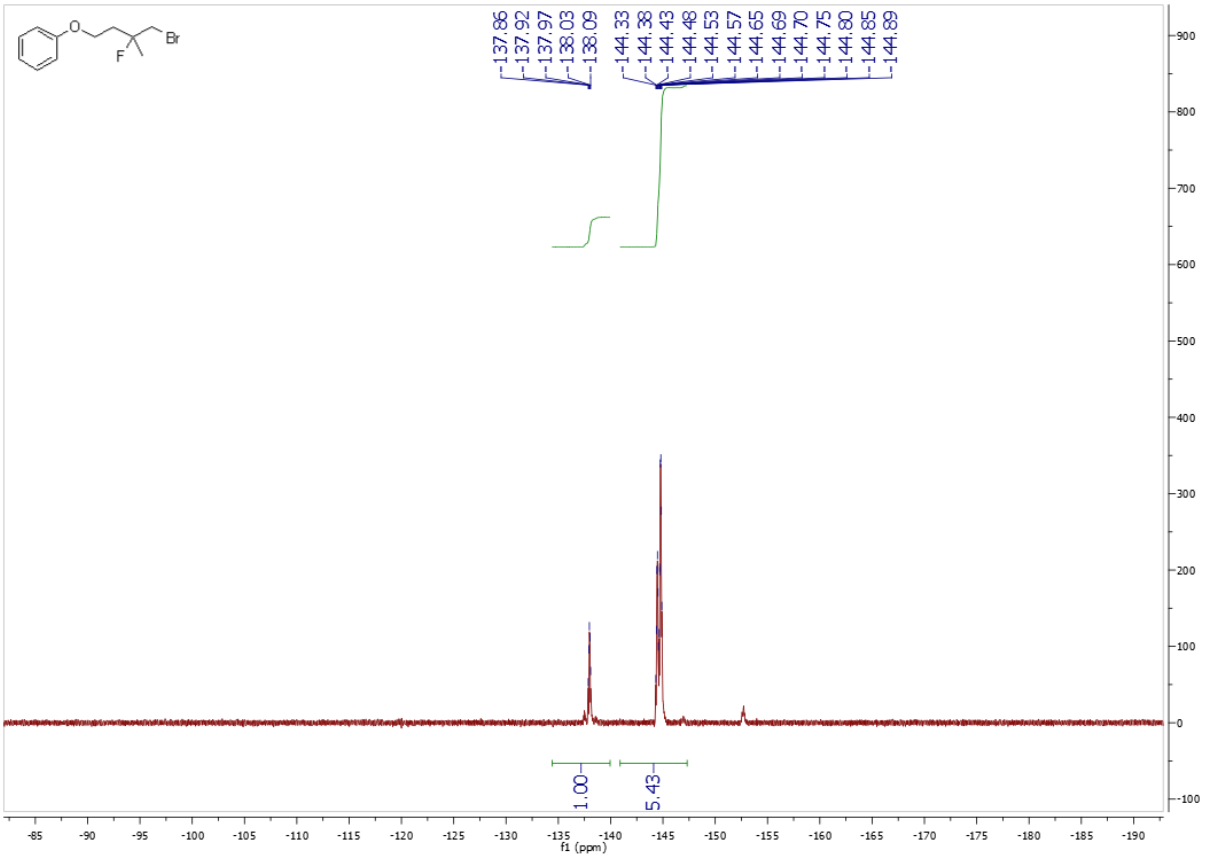
^{19}F NMR spectrum 5-2a



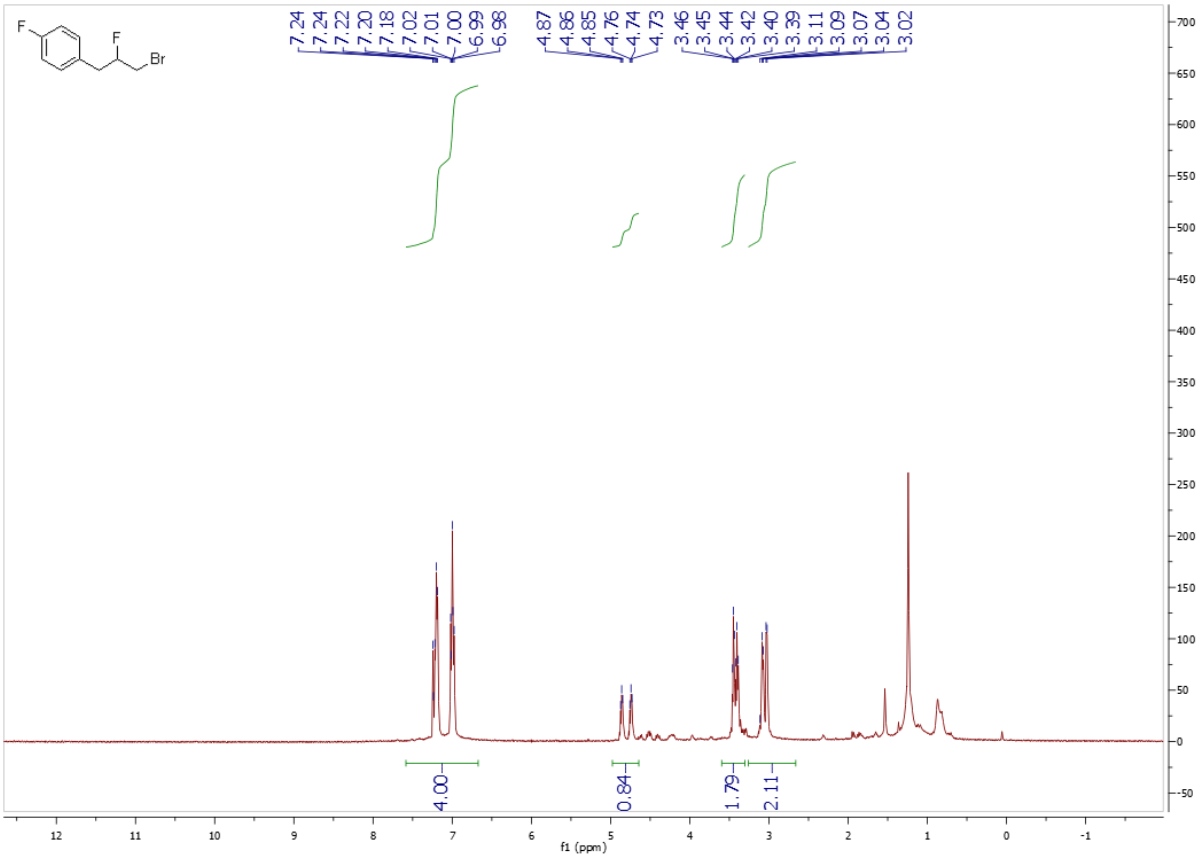
^{1}H NMR spectrum 5-2c



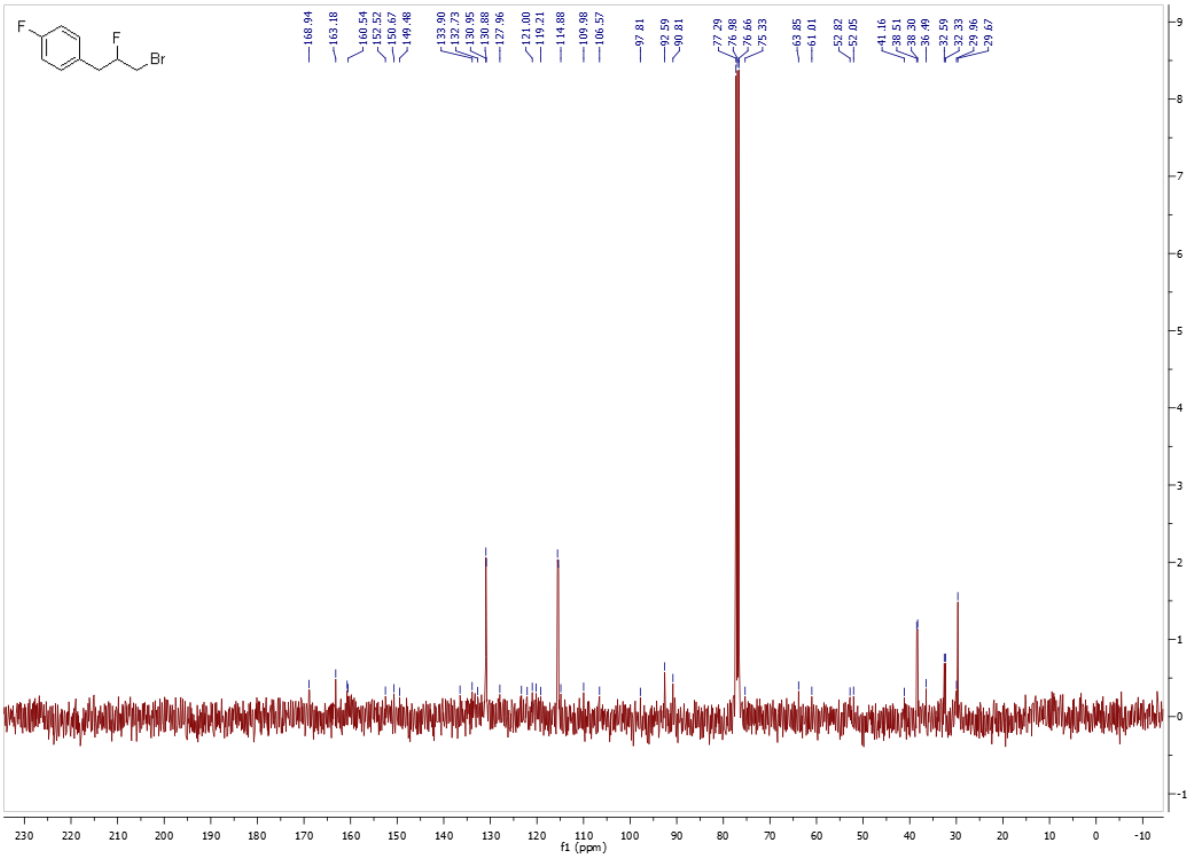
^{19}F NMR spectrum 5-2c



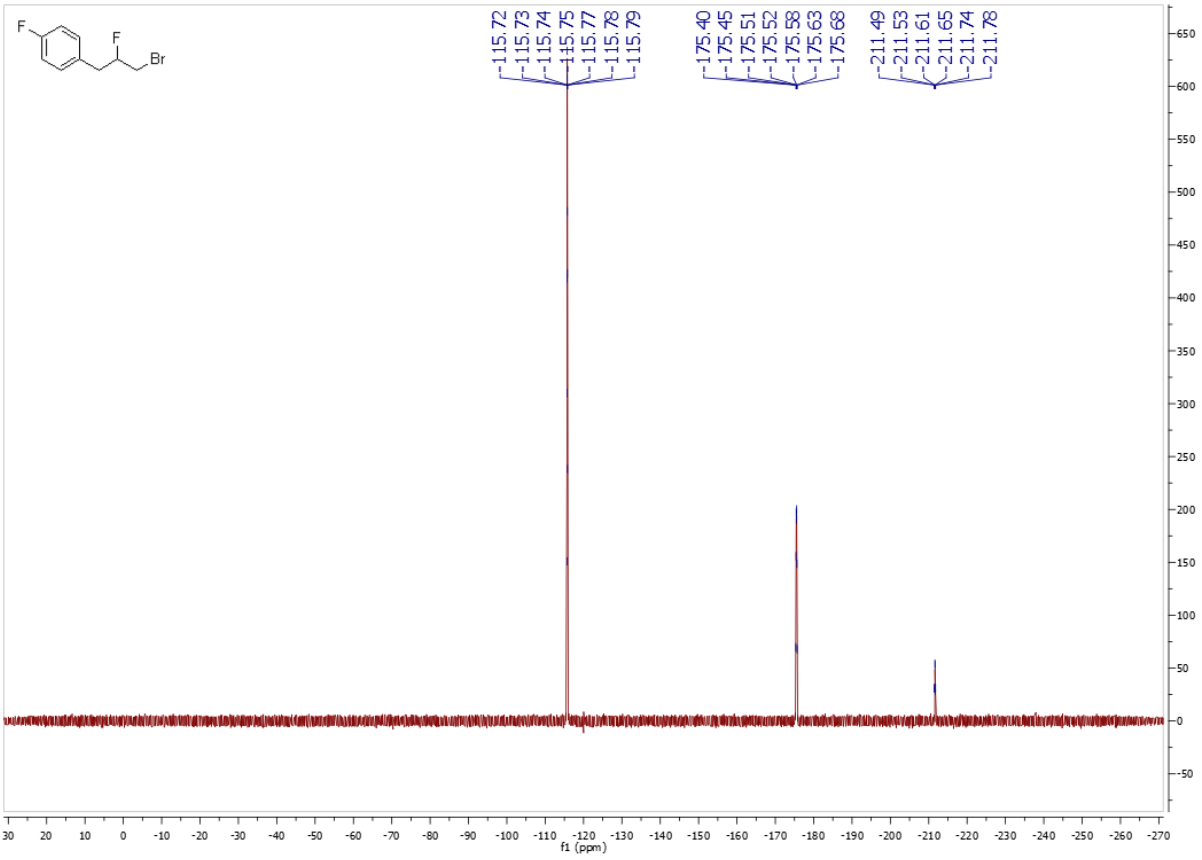
^{1}H NMR spectrum 5-2h



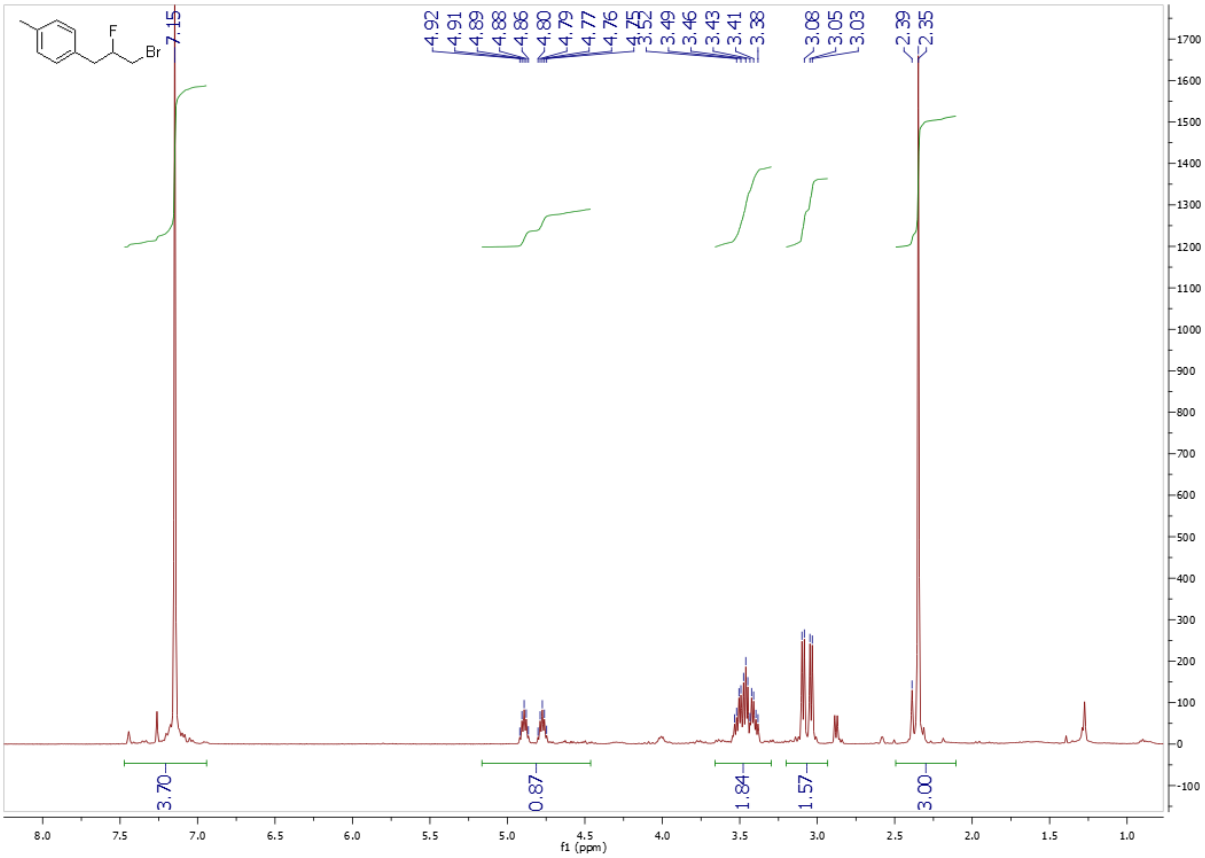
^{13}C NMR spectrum 5-2h



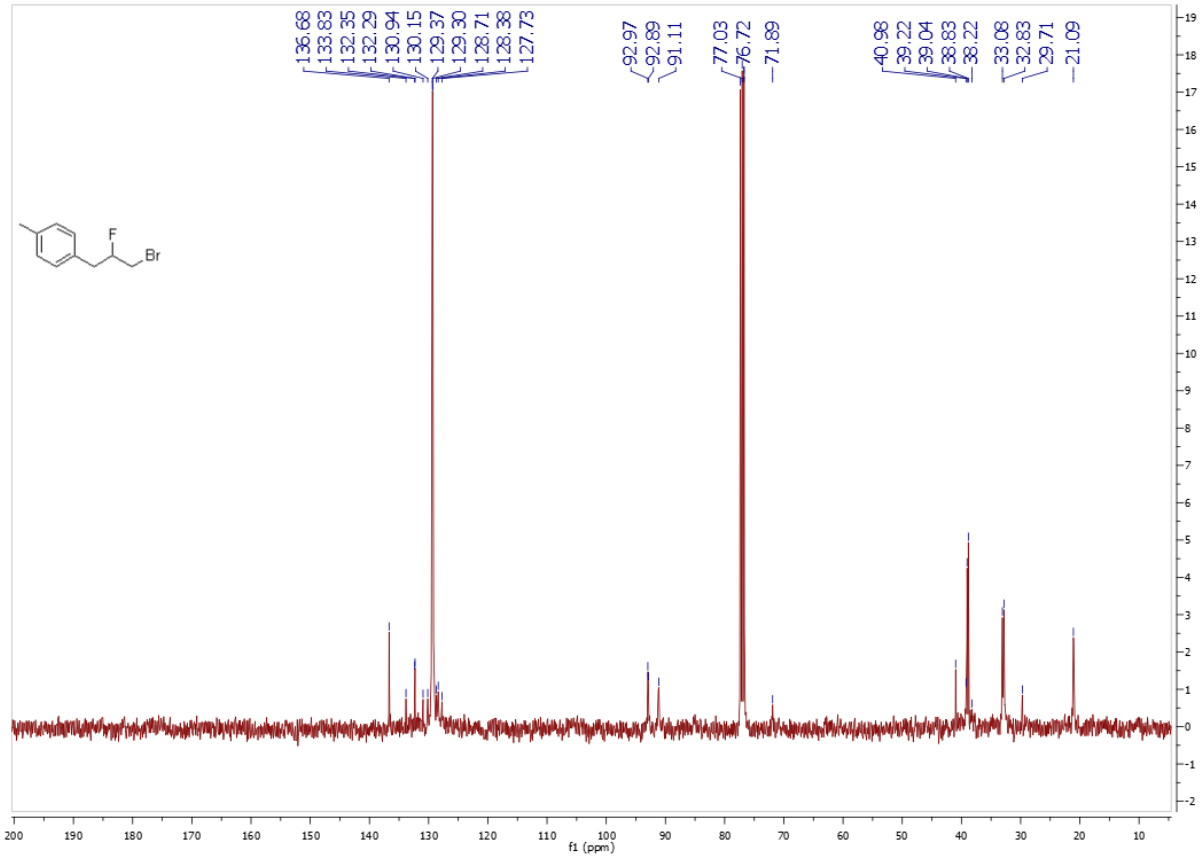
^{19}F NMR spectrum 5-2h



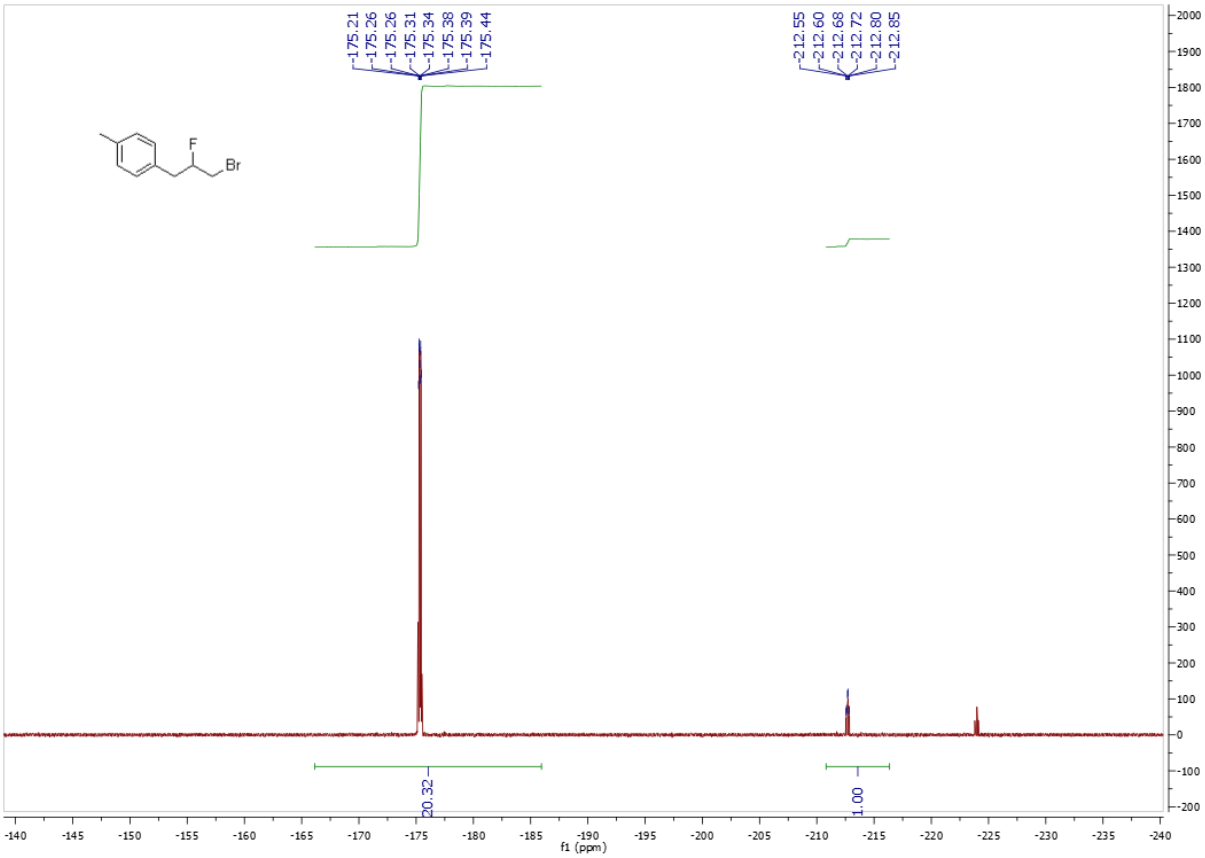
^{1}H NMR spectrum 5-2j



^{13}C NMR spectrum 5-2j

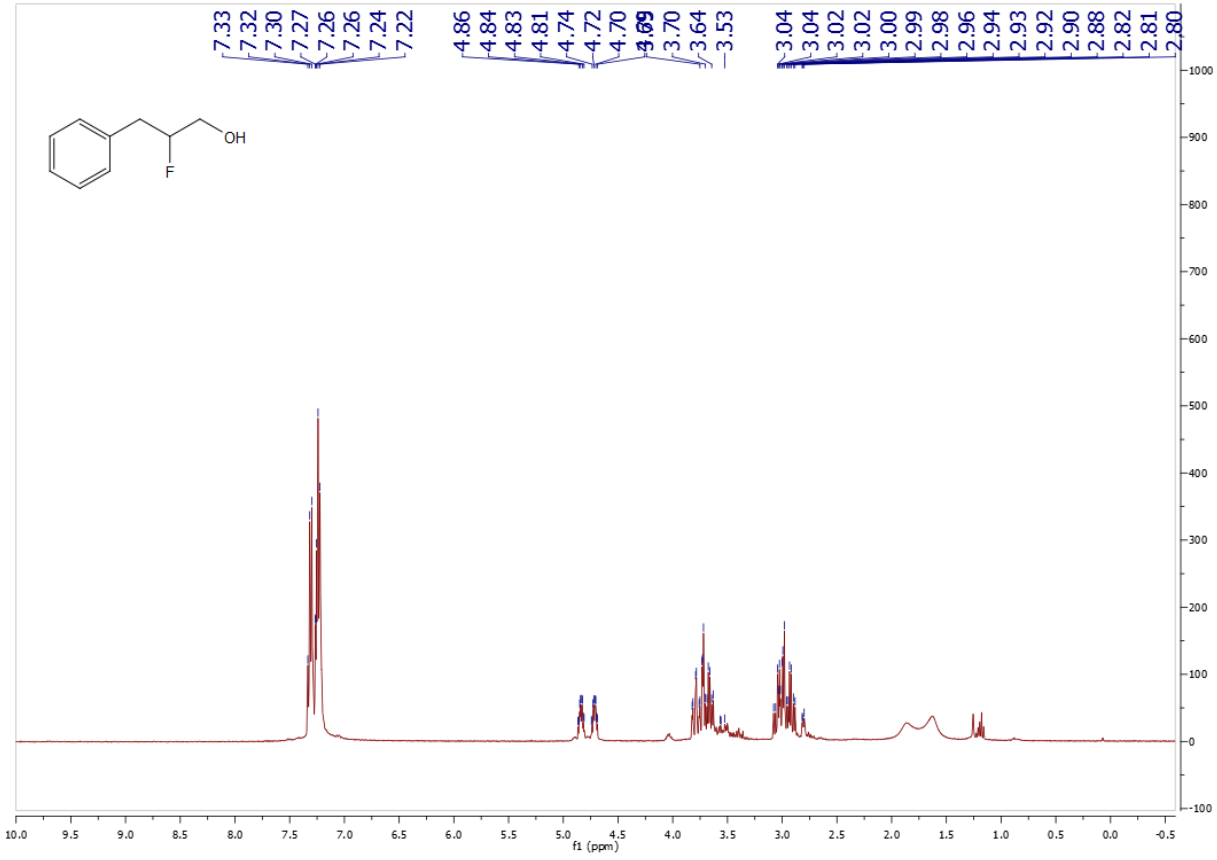


^{19}F NMR spectrum 5-2j

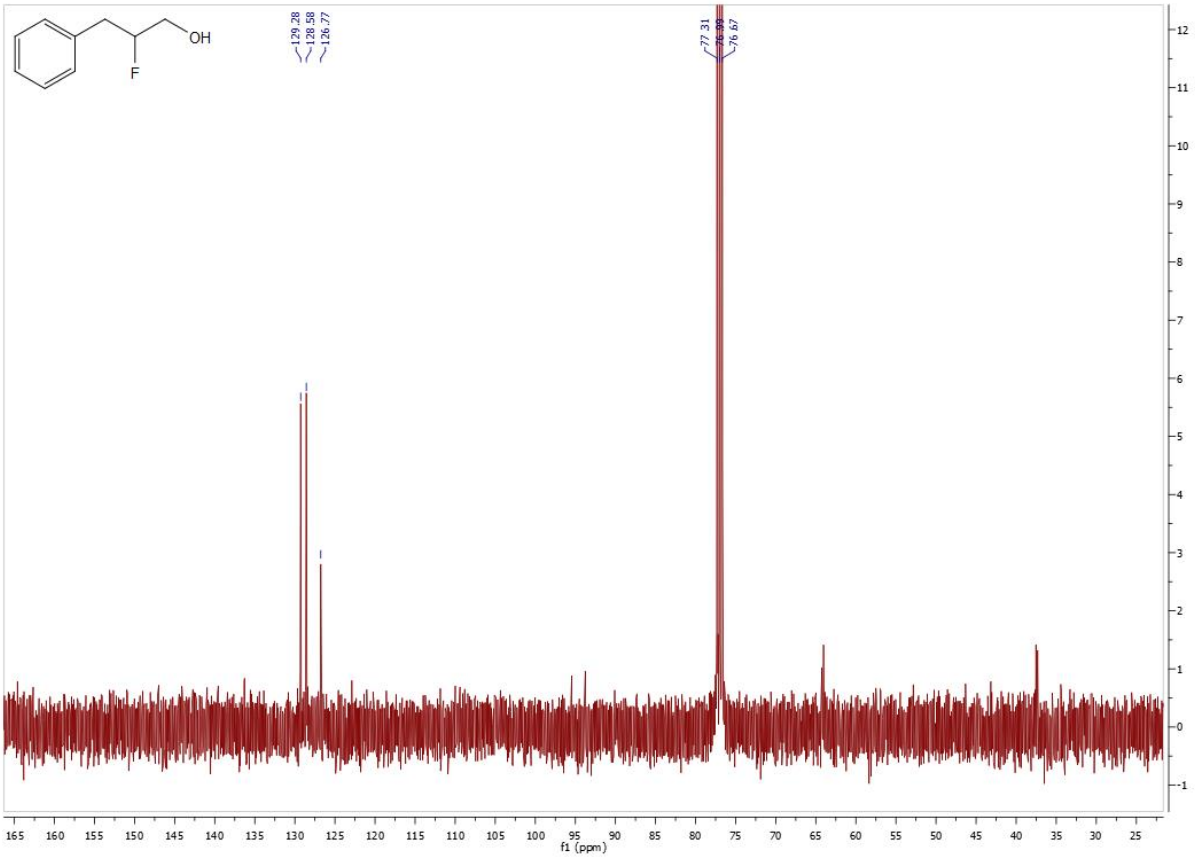


NMR FILES FOR FLUOROHYDRIN SYNTHESIS

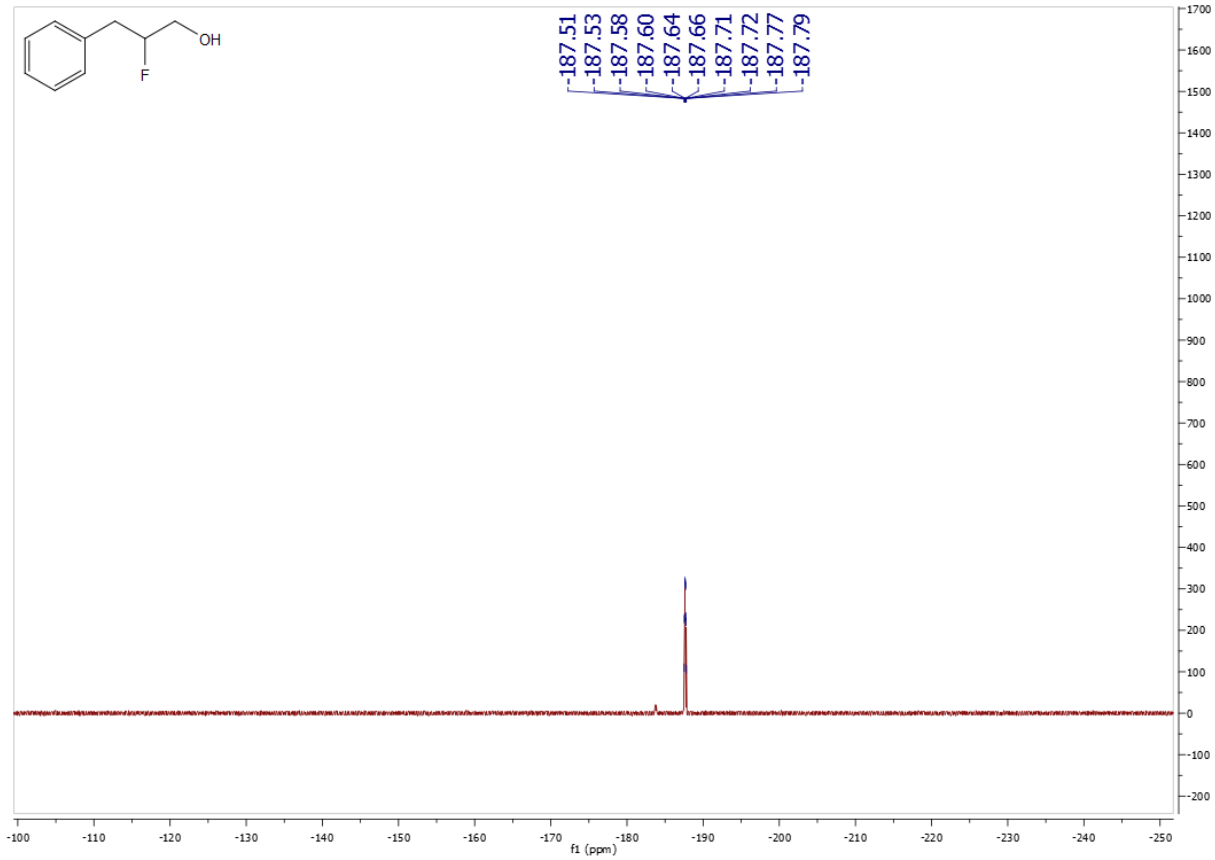
^{1}H NMR spectrum 5-10e



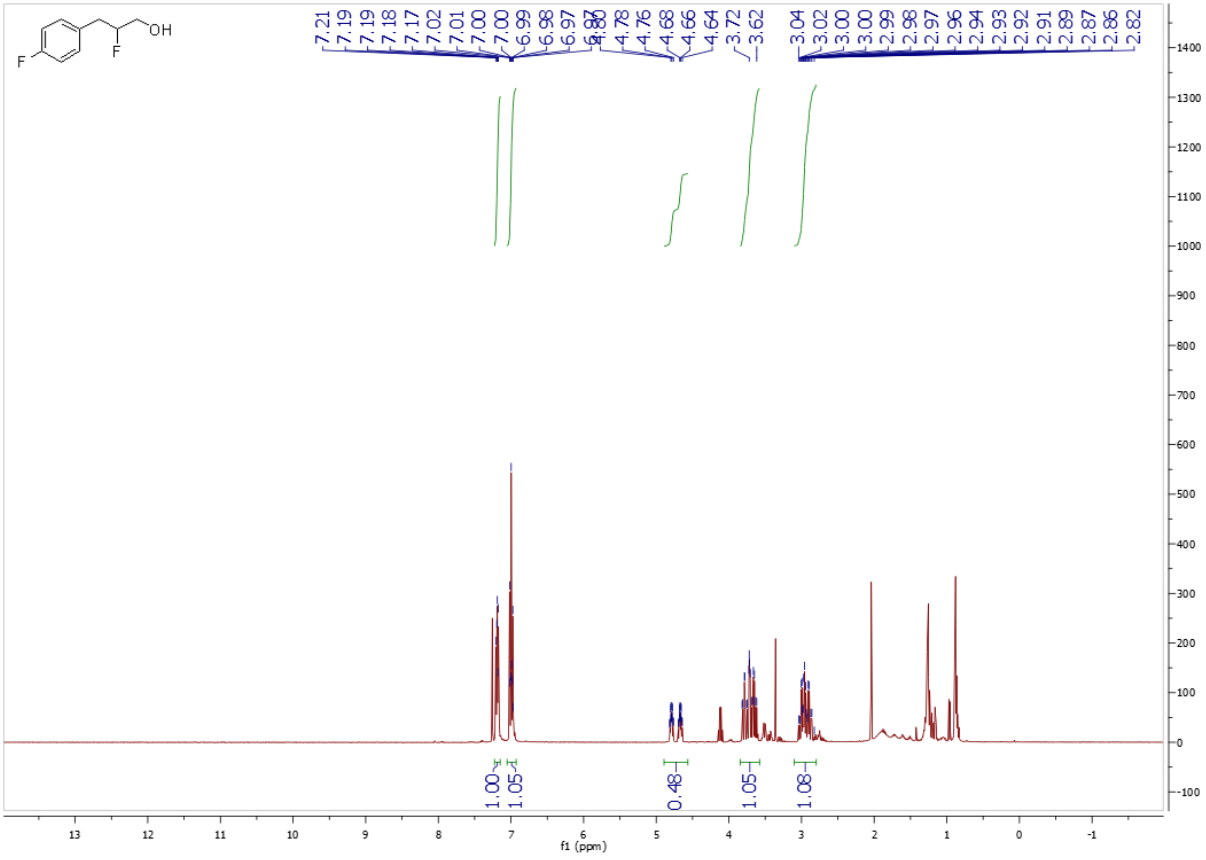
^{13}C NMR spectrum 5-10e



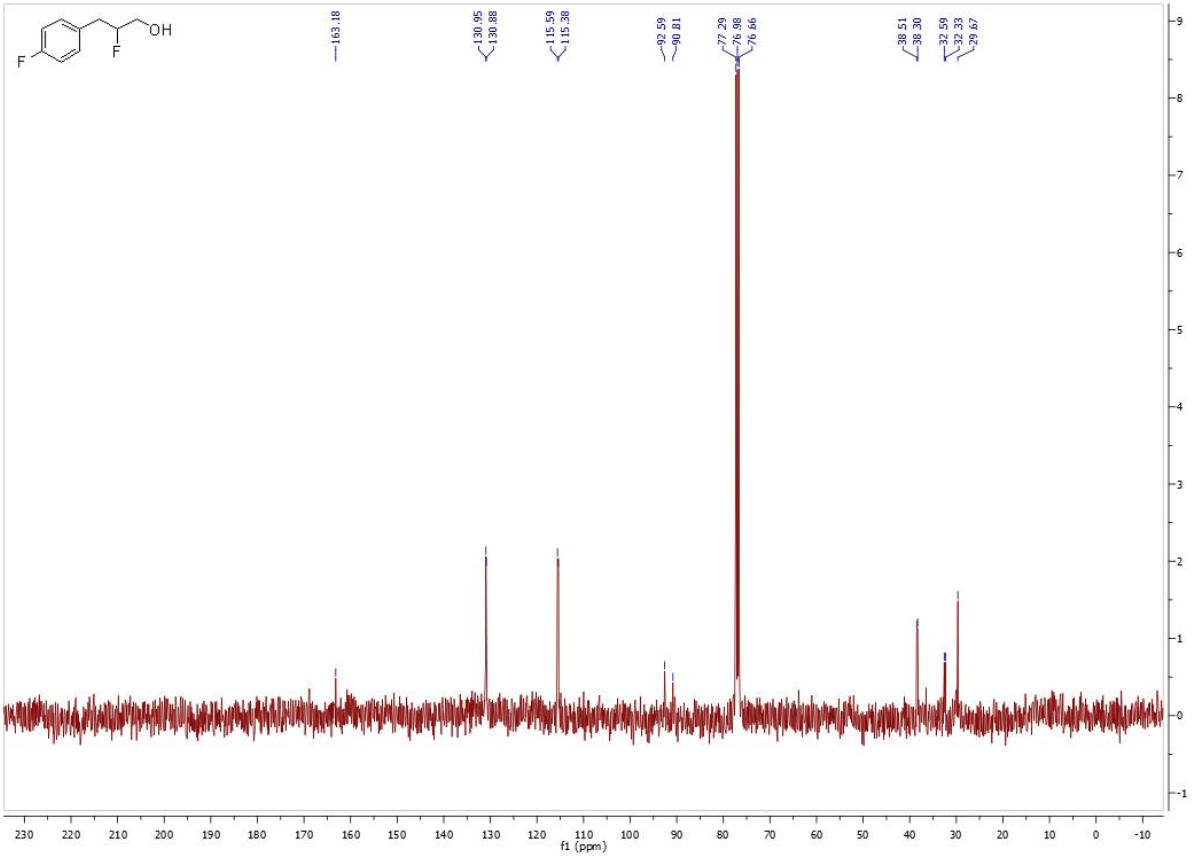
^{19}F NMR spectrum 5-10e



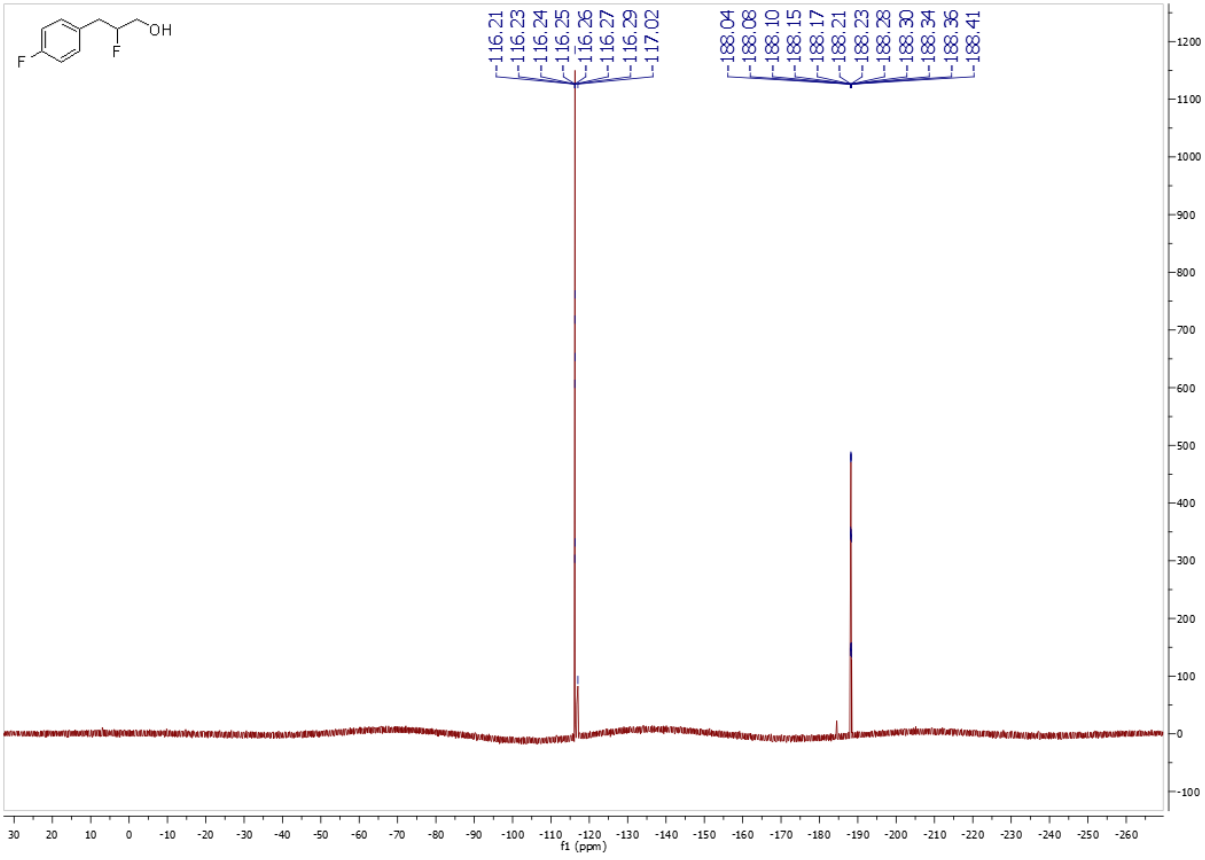
^{1}H NMR spectrum 5-10f



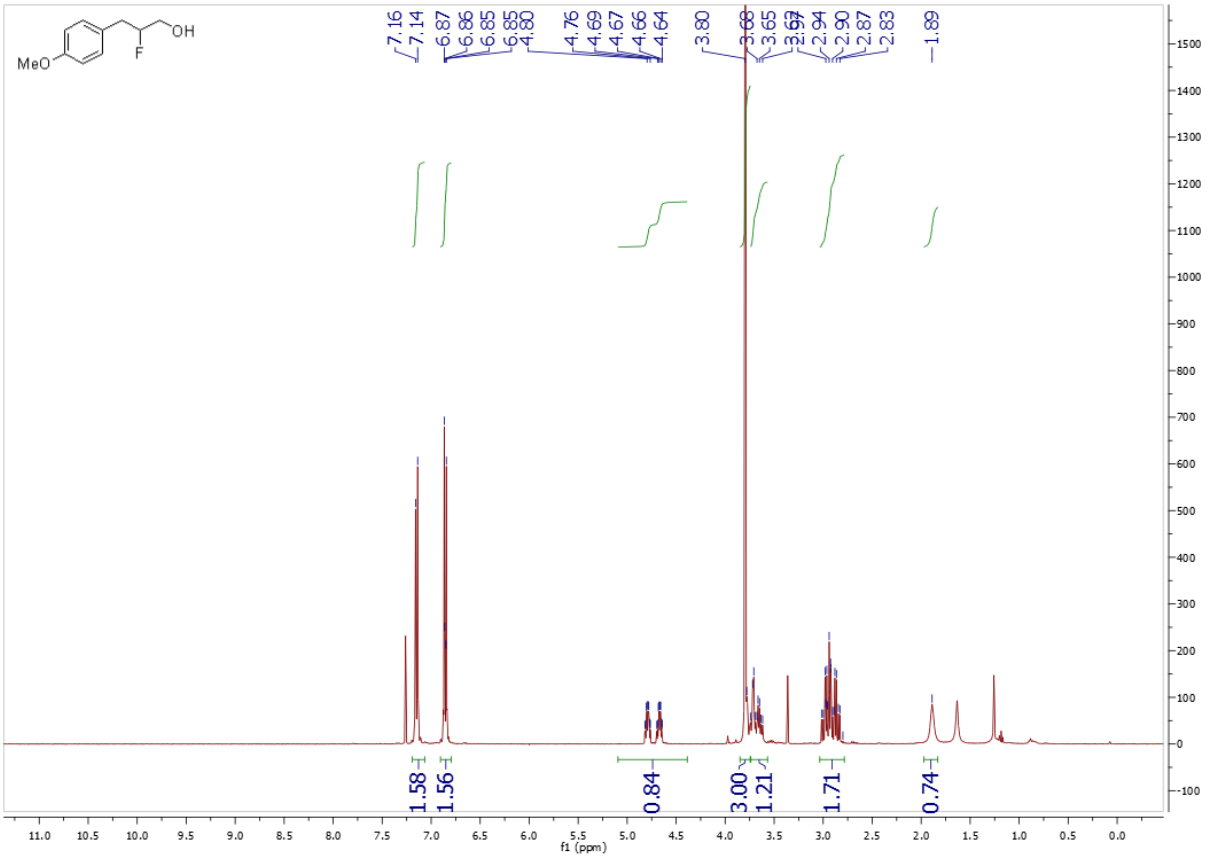
^{13}C NMR spectrum 5-10f



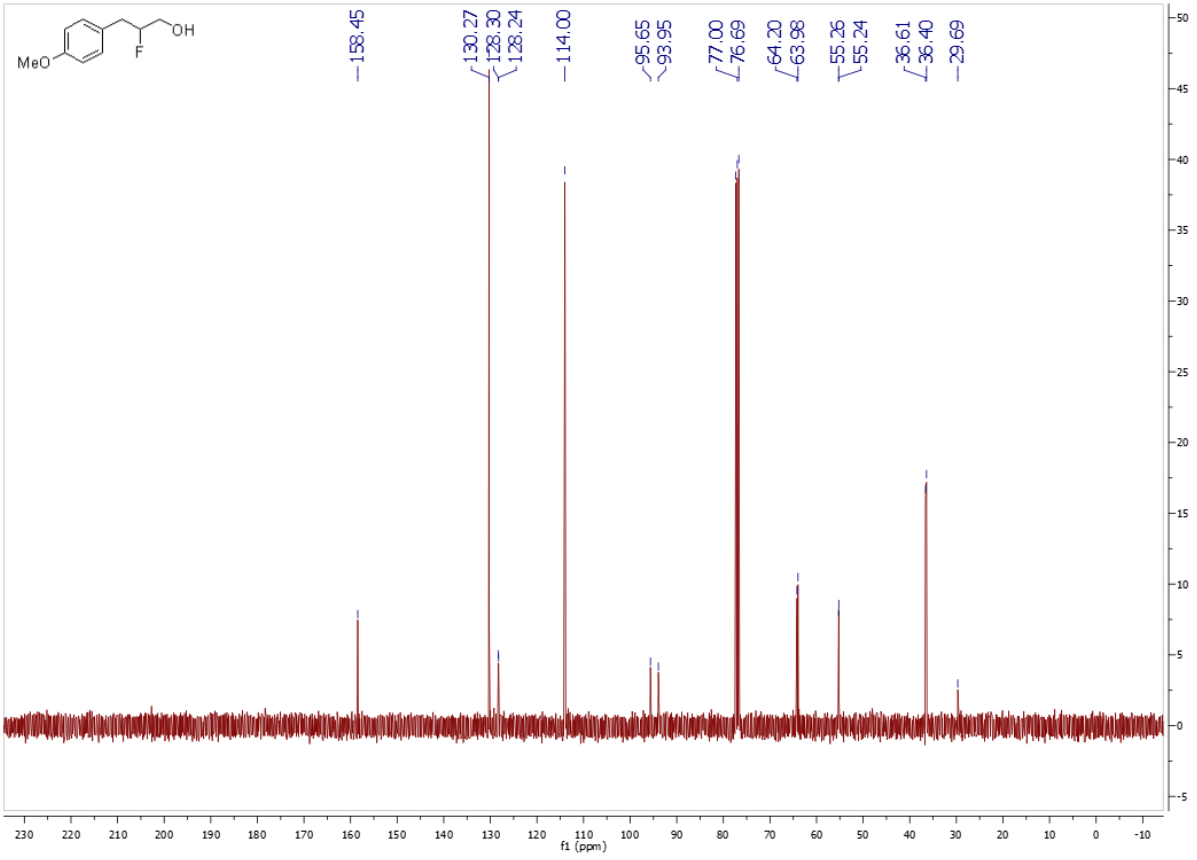
^{19}F NMR spectrum 5-10e



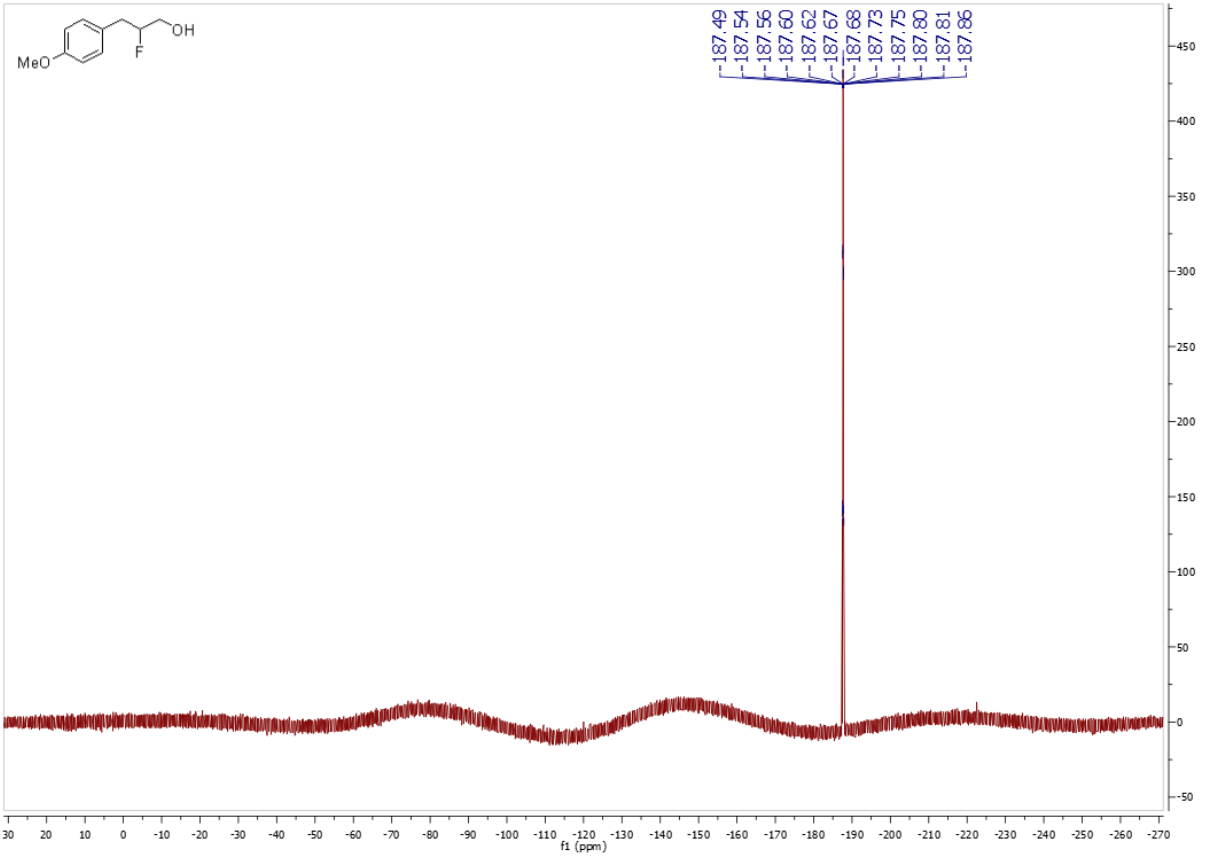
^{1}H NMR spectrum 5-10g



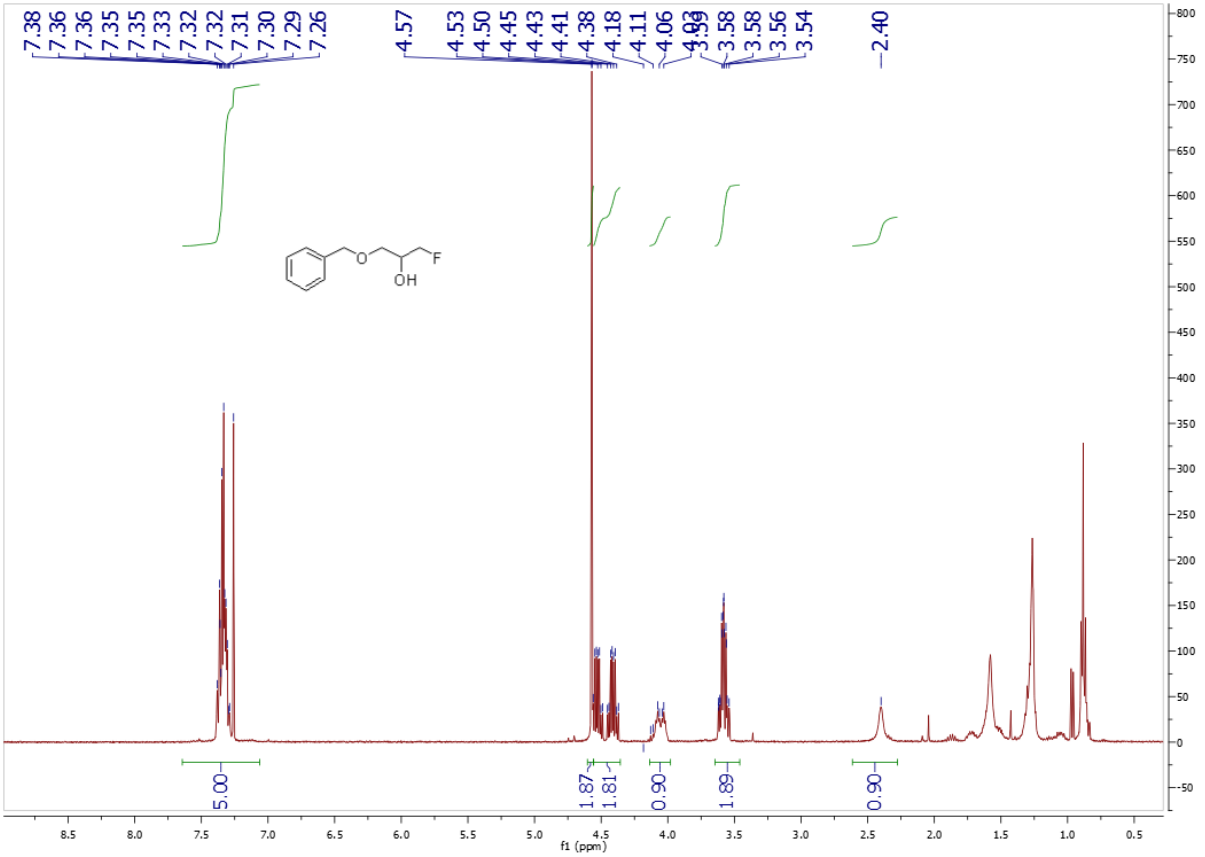
^{13}C NMR spectrum 5-10g



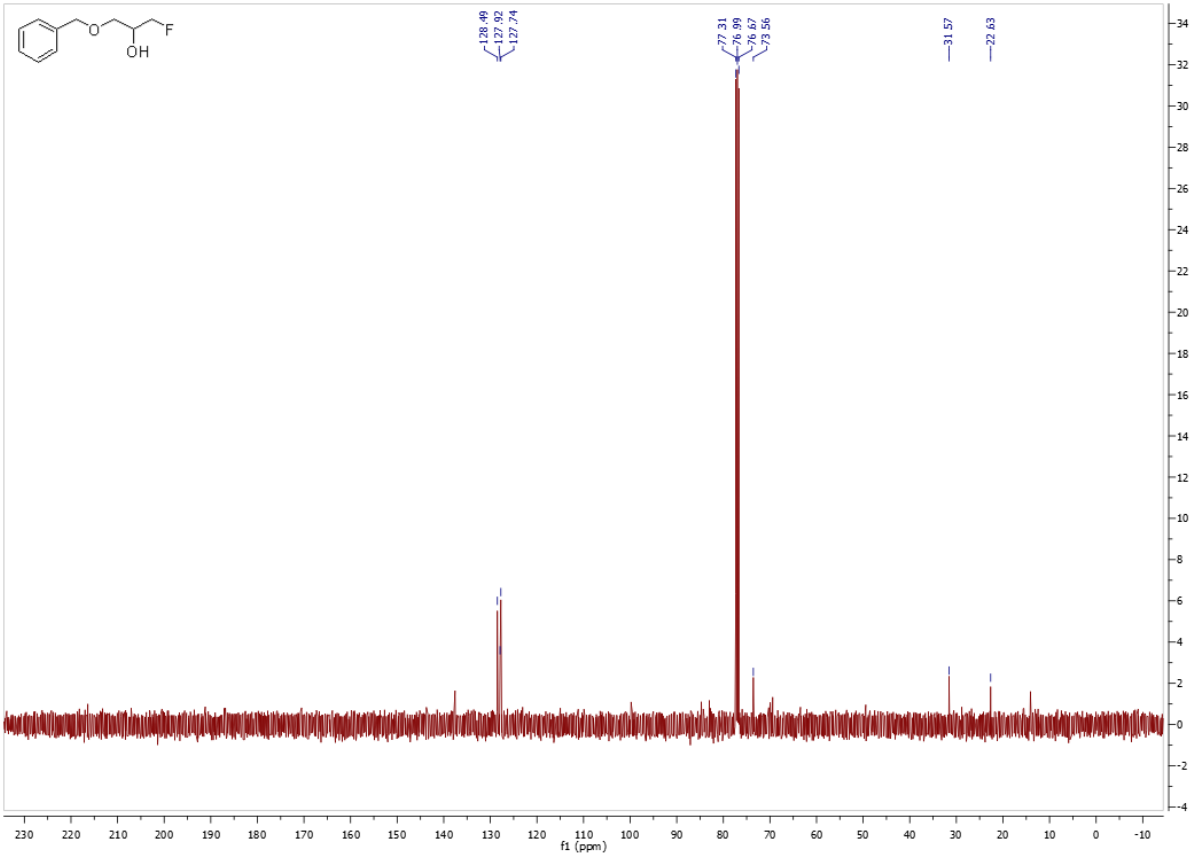
^{19}F NMR spectrum 5-10g



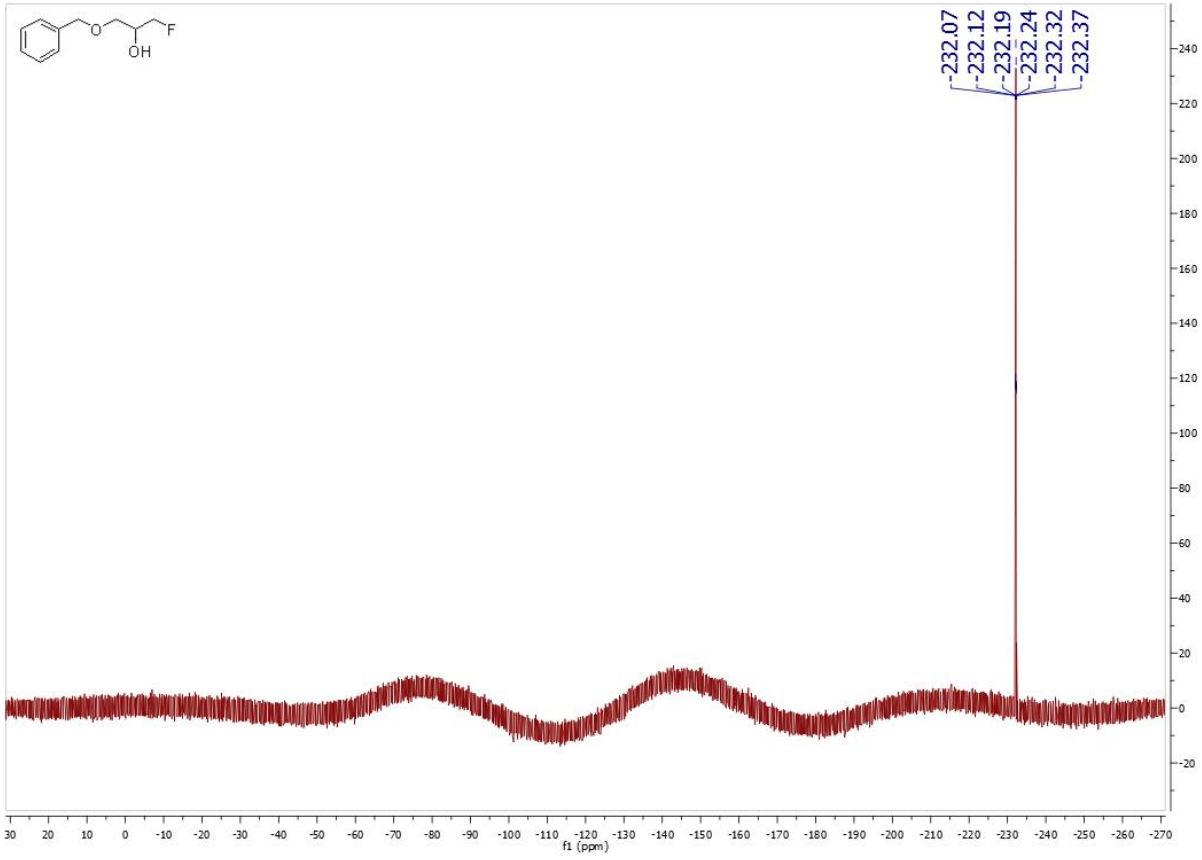
^{1}H NMR spectrum 5-10i



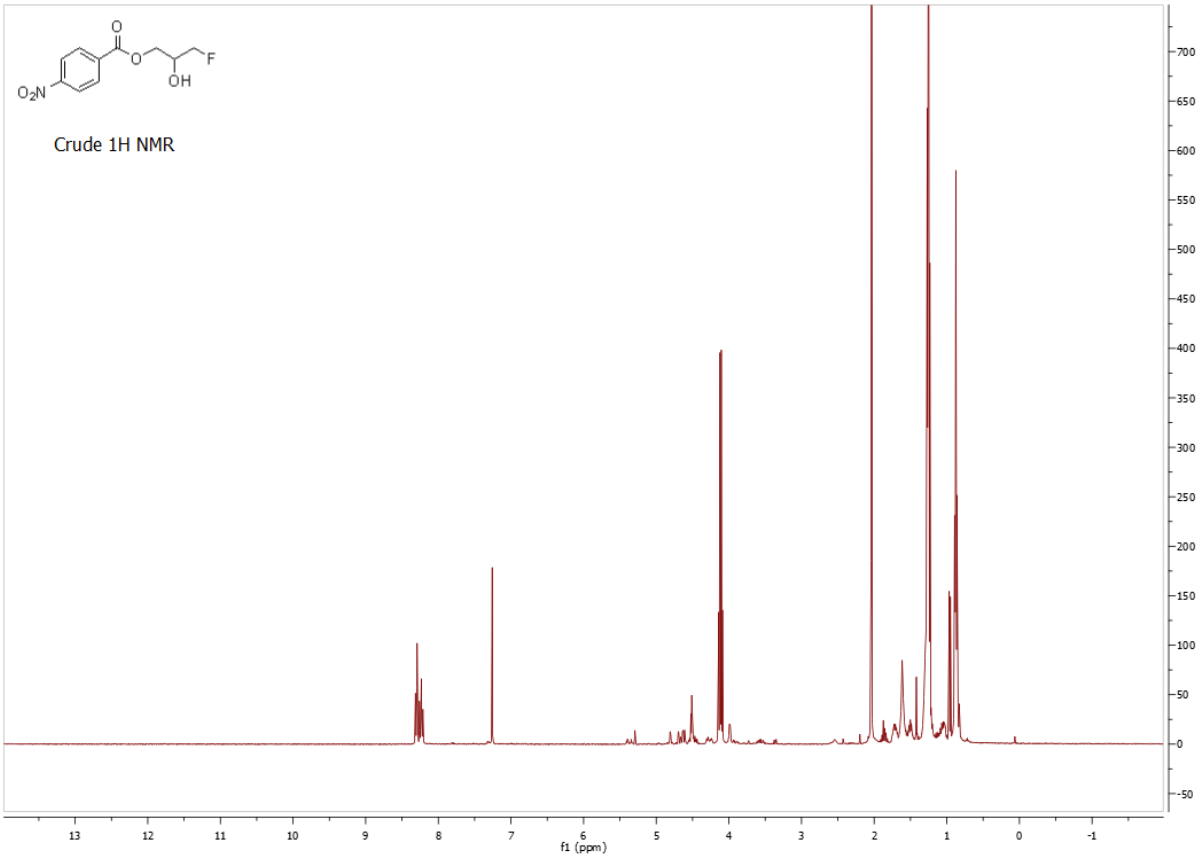
^{13}C NMR spectrum 5-10i



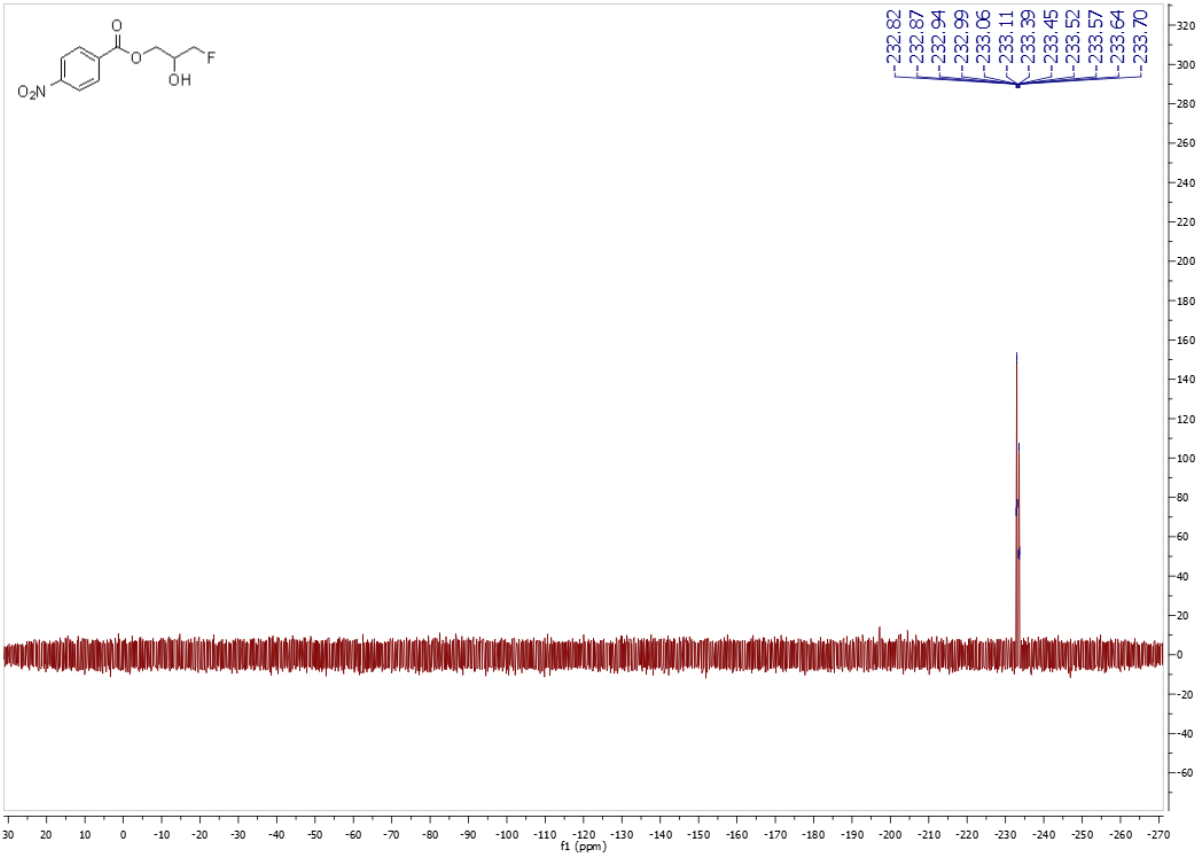
^{19}F NMR spectrum 5-10i



^{1}H NMR spectrum 5-10h

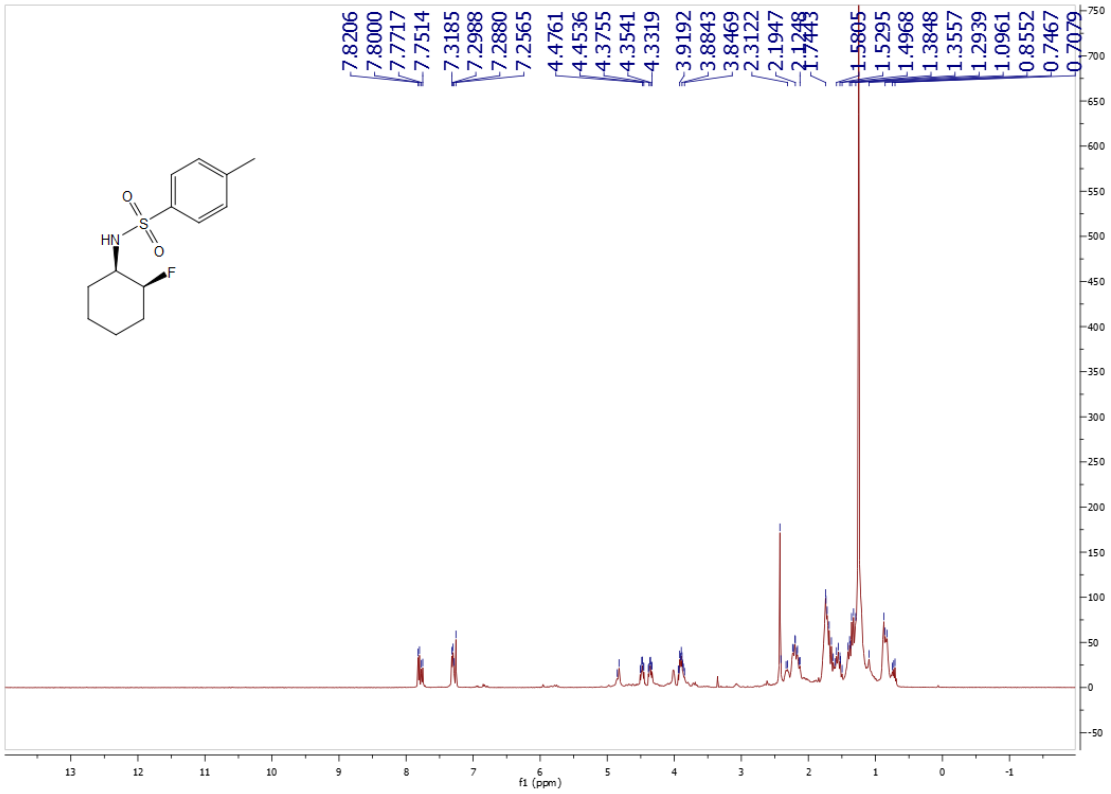


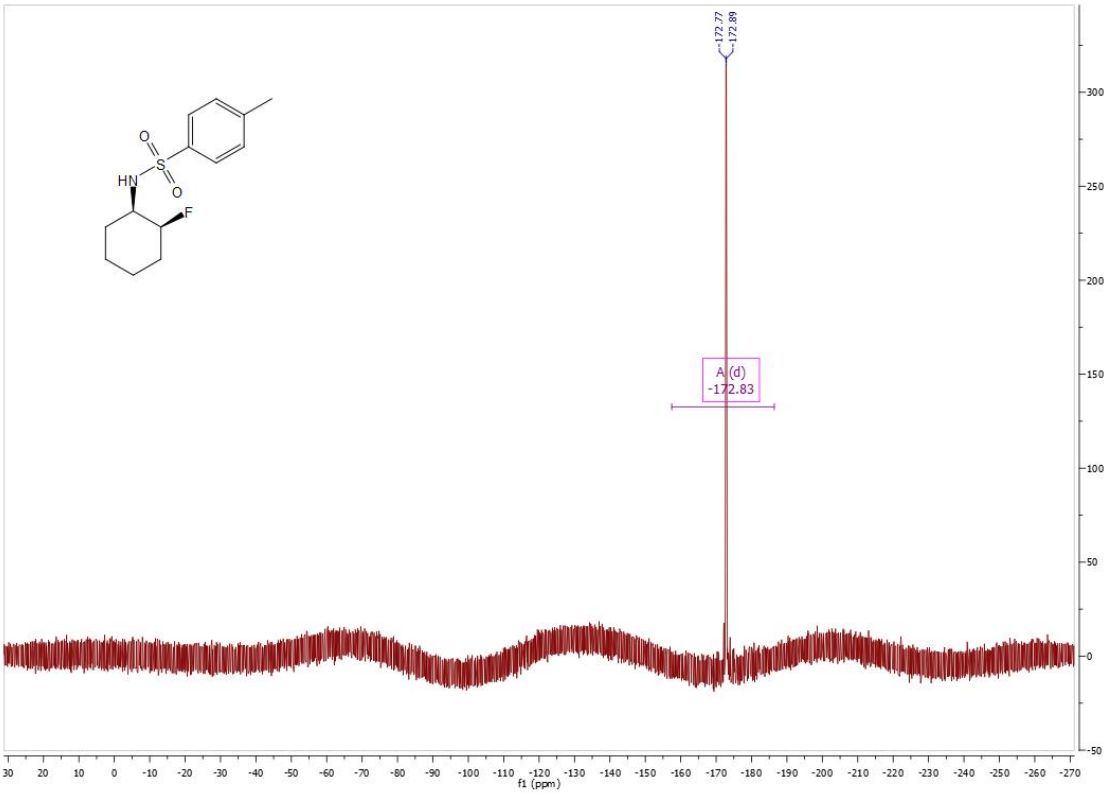
^{19}F NMR spectrum 5-10h



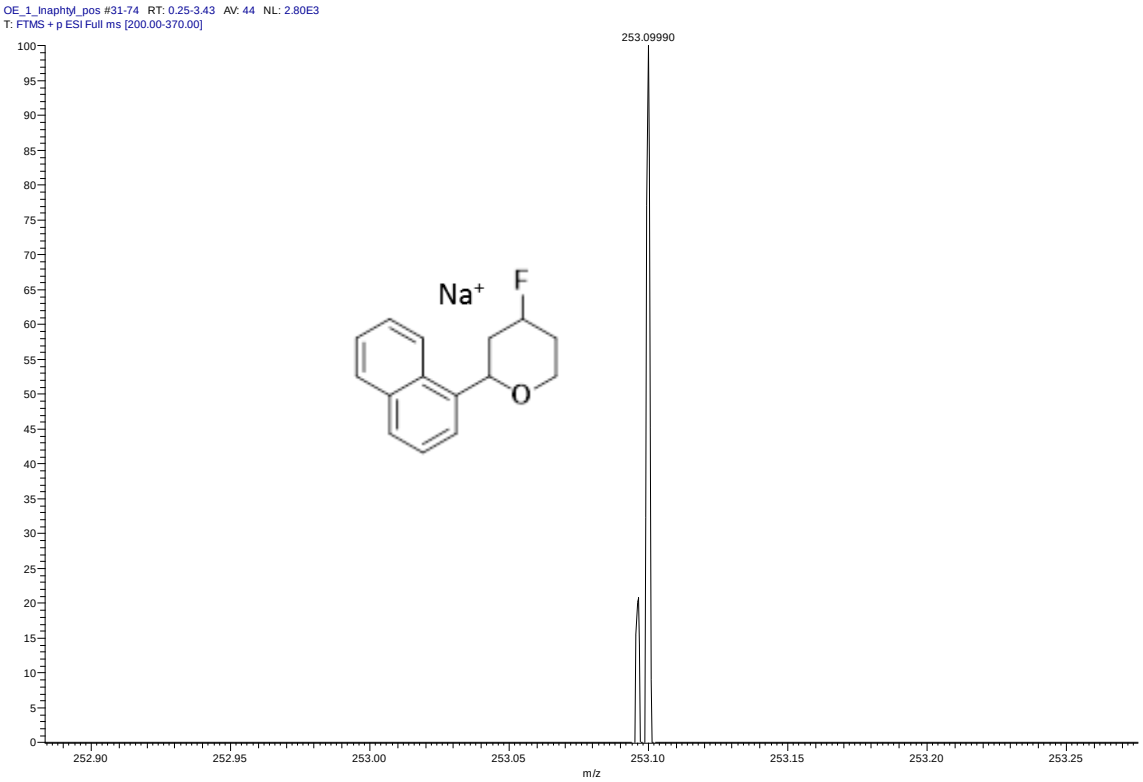
NMR FILES FOR CRUDE 1,2-FLUOROCYCLOHEXYLTOSYL AMINE

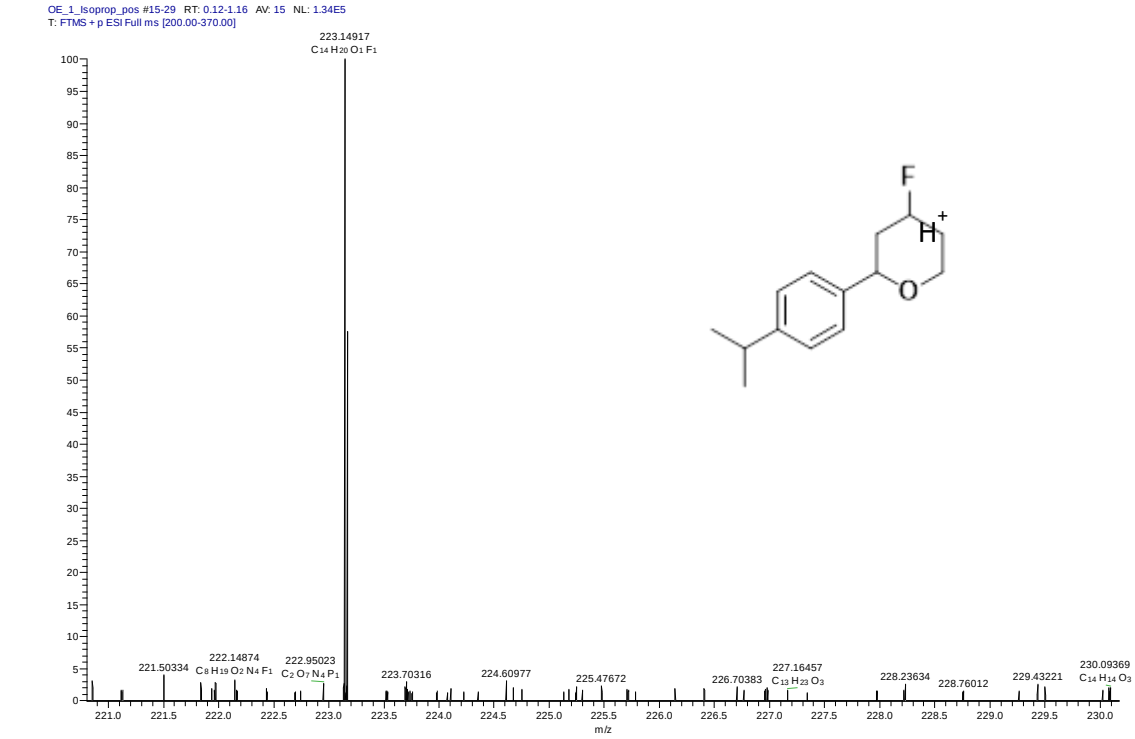
Crude ^{1}H and ^{19}F NMR





HRMS copies of unknown compounds (Prins reaction)

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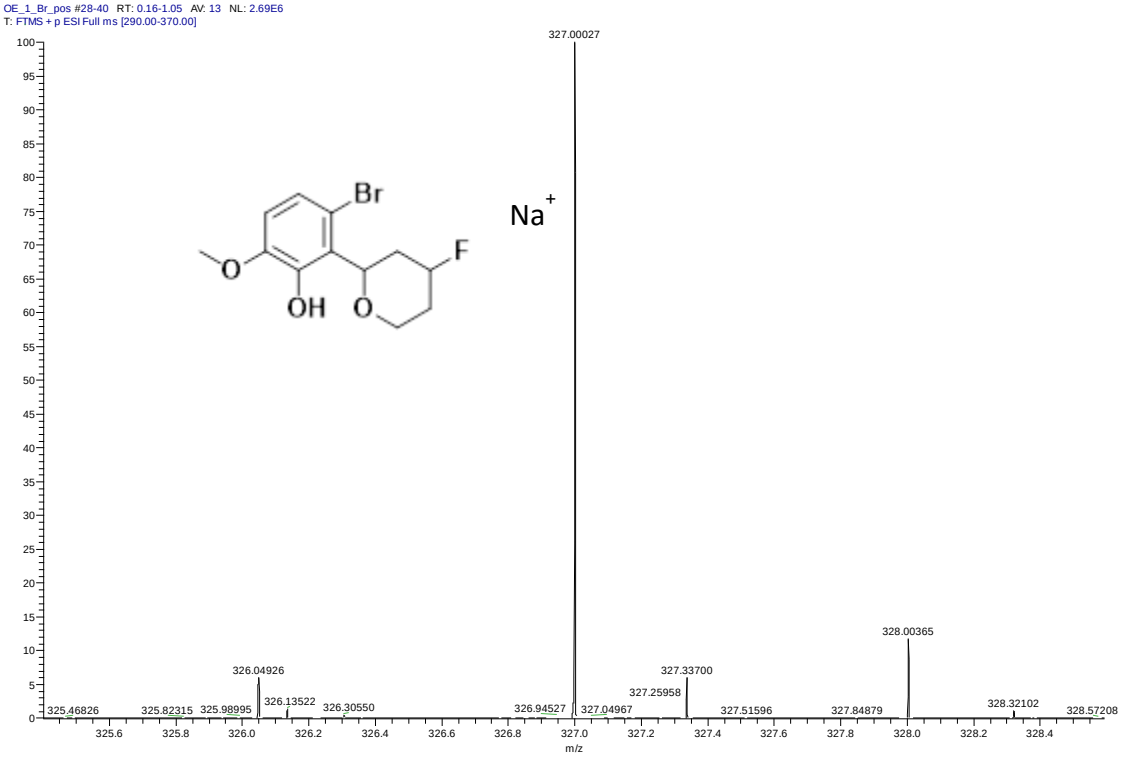
T: FTMS + p ESI Full ms [200.00-370.00]
223.14917
C14 H20 O1 F1
221.50334
222.14874
C8 H19 O2 N4 F1
222.95023
C2 O7 N4 P1
223.70316
224.60977
225.47672
226.70383
227.16457
C13 H23 O3
228.23634
228.76012
229.43221
230.09369
C14 H14 O3
F
H+
O
m/z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T: FTMS + p ESI Full ms [290.00-370.00]
327.00027
Br
Na+
O
F
OH
O
325.46826
325.82315
325.98995
326.04926
326.13522
326.30550
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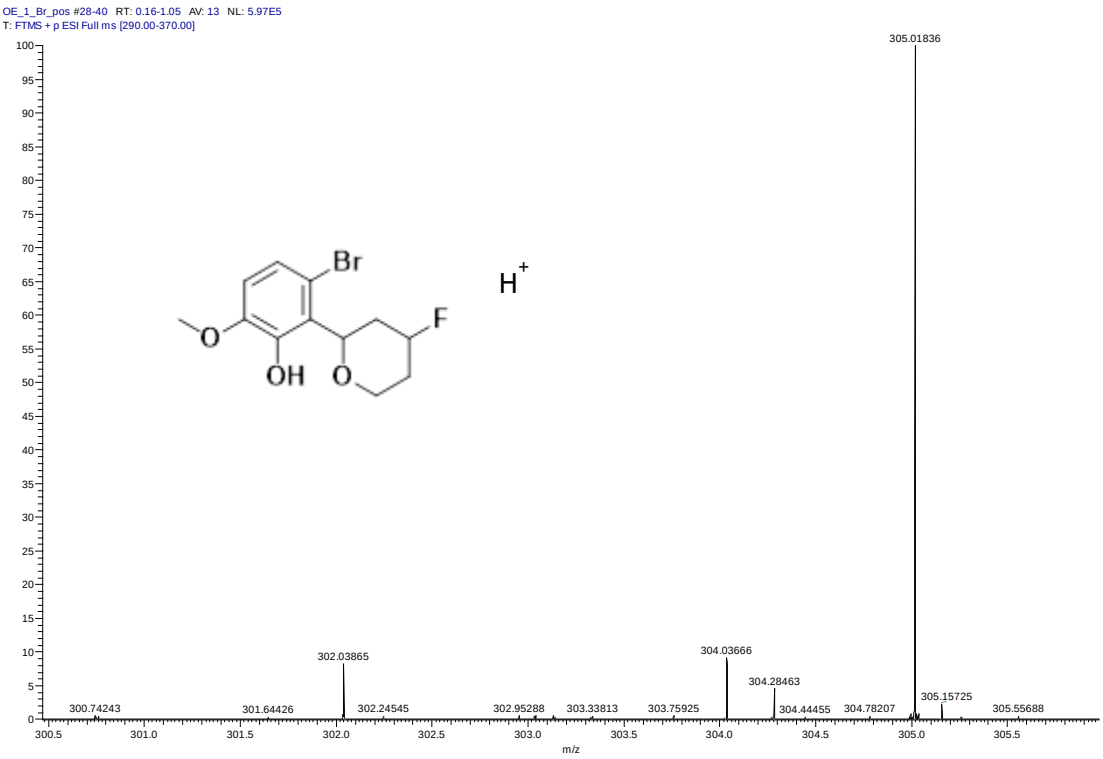
328.00365
328.32102
328.57208
m/z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T: FTMS + p ESI Full ms [290.00-370.00]
Br
F
O
OH
O
H+
305.01836
304.03666
302.03865
304.28463
305.15725
300.74243
301.64426
302.24545
302.95288
303.33813
303.75925
304.44455
304.78207
305.55688
m/z

REFERENCES

1. (a) O'Hagan, D.; B. Harper, D. *J. Fluorine Chem.* **1999,** *100* (1–2), 127-133; (b) Murphy, C. D.; Schaffrath, C.; O'Hagan, D. *Chemosphere* **2003,** *52* (2), 455-461; (c) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014,** *114* (4), 2432-2506.

2. Harper, D. B.; O'Hagan, D. *Natural Product Reports* **1994,** *11* (0), 123-133.

3. Uneyama, K., *Organofluorine Chemistry*. Blackwell publishing: Oxford, 2006.

4. O'Hagan, D. *Chem. Soc. Rev.* **2008,** *37* (2), 308-319.

5. (a) Ismail, F. M. D. *J. Fluorine Chem.* **2002,** *118* (1–2), 27-33; (b) Isanbor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006,** *127* (3), 303-319; (c) O'Hagan, D. *J. Fluorine Chem.* **2010,** *131* (11), 1071-1081; (d) Kirk, K. L. *J. Fluorine Chem.* **2006,** *127* (8), 1013-1029.

6. Jeschke, P. *ChemBioChem* **2004,** *5* (5), 570-589.

7. Kirsch, P.; Bremer, M. *Angew. Chem. Int. Ed.* **2000,** *39* (23), 4216-4235.

8. Schofield, H. *J. Fluorine Chem.* **1999,** *100* (1–2), 7-11.

9. (a) Pauling, L. *J. Am. Chem. Soc.* **1932,** *54* (9), 3570-3582; (b) Pauling, L., *The nature of the chemical bond and the structure of molecules and crystals: an introduction to modern structural chemistry*. Cornell university press: 1960; Vol. 18.

10. (a) Smart, B. E. *J. Fluorine Chem.* **2001,** *109* (1), 3-11; (b) Schlosser, M. *Angew. Chem. Int. Ed.* **1998,** *37* (11), 1496-1513.

11. Bondi, A. *J. Phys. Chem.* **1964,** *68* (3), 441-451.

12. Stabel, A.; Dasaradhi, L.; O'Hagan, D.; Rabe, J. P. *Langmuir* **1995,** *11* (5), 1427-1430.

13. Heidelberger, C.; Chaudhuri, N. K.; Danneberg, P.; Mooren, D.; Griesbach, L.; Duschinsky, R.; Schnitzer, R. J.; Pleven, E.; Scheiner, J. *Nature* **1957,** *179* (4561), 663-666.

14. (a) Jenkins, C. L.; Lin, G.; Duo, J.; Rapolu, D.; Guzei, I. A.; Raines, R. T.; Krow, G. R. *J. Org. Chem.* **2004,** *69* (25), 8565-8573; (b) Holmgren, S. K.; Taylor, K. M.; Bretscher, L. E.; Raines, R. T. *Nature* **1998,** *392* (6677), 666-666.

15. Cobb, S. L.; Murphy, C. D. *J. Fluorine Chem.* **2009,** *130* (2), 132-143.

16. (a) Merritt, R. F. *J. Org. Chem.* **1966,** *31* (11), 3871-3873; (b) Purrington, S. T.; Kagen, B. S.; Patrick, T. B. *Chem. Rev.* **1986,** *86* (6), 997-1018.

17. (a) Hesse, R. *Isr. J. Chem.* **1978,** *17* (1-2), 60-70; (b) Lerman, O.; Tor, Y.; Rozen, S. *J. Org. Chem.* **1981,** *46* (22), 4629-4631.

18. (a) Umemoto, T.; Tomizawa, G. *J. Org. Chem.* **1995,** *60* (20), 6563-6570; (b) Umemoto, T.; Fukami, S.; Tomizawa, G.; Harasawa, K.; Kawada, K.; Tomita, K. *J. Am. Chem. Soc.* **1990,** *112* (23), 8563-8575; (c) Banks, R. *J. Chem. Soc. Perkin. Trans* **1988,** *1*, 2805; (d) Lal, G. S.; Pastore, W.; Pesaresi, R. *J. Org. Chem.* **1995,** *60* (22), 7340-7342; (e) Barnette, W. E. *J. Am. Chem. Soc.* **1984,** *106* (2), 452-454.

19. Middleton, W. J. *J. Org. Chem.* **1975,** *40* (5), 574-578.

20. Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. *J. Org. Chem.* **1999,** *64* (19), 7048-7054.

21. Yin, J.; Zarkowsky, D. S.; Thomas, D. W.; Zhao, M. M.; Huffman, M. A. *Org. Lett.* **2004,** *6* (9), 1465-1468.

22. Petrov, V. A.; Swearingen, S.; Hong, W.; Chris Petersen, W. *J. Fluorine Chem.* **2001,** *109* (1), 25-31.

23. Takaoka, A.; Iwakiri, H.; Ishikawa, N. *Bull. Chem. Soc. Jpn.* **1979,** *52* (11), 3377-3380.

24. (a) Bresciani, S.; Slawin, A. M. Z.; O'Hagan, D. *J. Fluorine Chem.* **2009,** *130* (6), 537-543; (b) Umemoto, T.; Singh, R. P.; Xu, Y.; Saito, N. *J. Am. Chem. Soc.* **2010,** *132* (51), 18199-18205.

25. Okazoe, T. *Proceedings of the Japan Academy, Series B* **2009,** *85* (8), 276-289.

26. Weeks, M. E. *J. Chem. Educ.* **1932,** *9* (11), 1915.

27. Segal, E. B. *Chemical Health and Safety* **2000,** *7* (1), 18-23.

28. Chambers, C.; Holliday, A. *Group* **1975,** *4*, 160.

29. Giguere, P. A.; Turrell, S. *J. Am. Chem. Soc.* **1980,** *102* (17), 5473-5477.

30. Rogers, M. T.; Katz, J. J. *J. Am. Chem. Soc.* **1952,** *74* (6), 1375-1377.

31. Baasner, B.; Klauke, E. *J. Fluorine Chem.* **1982,** *19* (3-6), 553-564.

32. Fried, J.; Sabo, E. F. *J. Am. Chem. Soc.* **1954,** *76* (5), 1455-1456.

33. Hirschmann, R. F.; Miller, R.; Wood, J.; Jones, R. *J. Am. Chem. Soc.* **1956,** *78* (19), 4956-4959.

34. Bergstrom, C. G.; Nicholson, R. T.; Dodson, R. M. *J. Org. Chem.* **1963,** *28* (10), 2633-2640.

35. Olah, G. A.; Welch, J. T.; Vankar, Y. D.; Nojima, M.; Kerekes, I.; Olah, J. A. *J. Org. Chem.* **1979,** *44* (22), 3872-3881.

36. Hayashi, M.; Hashimoto, S.-i.; Noyori, R. *Chem. Lett.* **1984,** (10), 1747-1750.

37. Yoneda, N. *Tetrahedron* **1991,** *47* (29), 5329-5365.

38. Haufe, G. *J. Prakt. Chem.* **1996,** *338* (1), 99-113.

39. Sun, H.; DiMagno, S. G. *J. Am. Chem. Soc.* **2005,** *127* (7), 2050-2051.

40. Kalow, J. A.; Doyle, A. G. *J. Am. Chem. Soc.* **2010,** *132* (10), 3268-3269.

41. Kalow, J. A.; Schmitt, D. E.; Doyle, A. G. *J. Org. Chem.* **2012,** *77* (8), 4177-4183.

42. Kalow, J. A.; Doyle, A. G. *Tetrahedron* **2013,** *69* (27–28), 5702-5709.

43. Olah, G. A.; Welch, J. T.; Vankar, Y. D.; Nojima, M.; Kerekes, I.; Olah, J. A. *J. Org. Chem.* **1979,** *44* (22), 3872-3881.

44. Haufe, G. *Journal für Praktische Chemie/Chemiker-Zeitung* **1996,** *338* (1), 99-113.

45. Laurence, C.; Brameld, K. A.; Graton, J. r. m.; Le Questel, J.-Y.; Renault, E. *J. Med. Chem.* **2009,** *52* (14), 4073-4086.

46. Many HF/urea or HF/amide complexes have been used for fluorination of benzotrichlorides. see Hayashi, H.; Sonoda, H.; Goto, K.; Fukumura, K.; Naruse, J.; Oikawa, H.; Nagata, T.; Shimaoka, T.; Yasutake, T.; Umetani, H. US US 6,417,361.

47. Gouverneur, V. *Science* **2009,** *325*, 1630-1631.

48. (a) Jin, Z.; Hammond, G. B.; Xu, B. *Aldrichimica Acta* **2012,** *45* (3), 67-83; (b) Yang, M.-H.; Matikonda, S. S.; Altman, R. A. *Org. Lett.* **2013,** *15* (15), 3894-3897; (c) Patrick, T. B.; Nadji, S. *J. Fluorine Chem.* **1990,** *49* (1), 147-50; (d) Yamaki, Y.; Shigenaga, A.; Tomita, K.; Narumi, T.; Fujii, N.; Otaka, A. *J. Org. Chem.* **2009,** *74* (9), 3272-3277; (e) Watanabe, D.; Koura, M.; Saito, A.; Yanai, H.; Nakamura, Y.; Okada, M.; Sato, A.; Taguchi, T. *J. Fluorine Chem.* **2011,** *132* (5), 327-338; (f) Narumi, T.; Tomita, K.; Inokuchi, E.; Kobayashi, K.; Oishi, S.; Ohno, H.; Fujii, N. *Org. Lett.* **2007,** *9* (17), 3465-3468; (g) Nakamura, Y.; Okada, M.; Sato, A.; Horikawa, H.; Koura, M.; Saito, A.; Taguchi, T. *Tetrahedron* **2005,** *61* (24), 5741-5753; (h) Zhang, H.; Zhou, C.-B.; Chen, Q.-

Y.; Xiao, J.-C.; Hong, R. *Org. Lett.* **2010,** *13* (4), 560-563; (i) Lemonnier, G.; Van Hijfte, N.; Sebban, M.; Poisson, T.; Couve-Bonnaire, S.; Pannecoucke, X. *Tetrahedron* **2014,** *70* (19), 3123-3133; (j) Prakash, G. K. S.; Chacko, S.; Vaghoo, H.; Shao, N.; Gurung, L.; Mathew, T.; Olah, G. A. *Org. Lett.* **2009,** *11* (5), 1127-1130; (k) Han, S. Y.; Jeong, I. H. *Org. Lett.* **2010,** *12* (23), 5518-5521; (l) Zajc, B.; Kake, S. *Org. Lett.* **2006,** *8* (20), 4457-4460; (m) Burton, D. J.; Yang, Z.-Y.; Qiu, W. *Chem. Rev. (Washington, D. C.)* **1996,** *96* (5), 1641-1715; (n) Furuya, T.; Ritter, T. *Org. Lett.* **2009,** *11* (13), 2860-2863; (o) Pfund, E.; Lebargy, C.; Rouden, J.; Lequeux, T. *J. Org. Chem.* **2007,** *72* (21), 7871-7877; (p) Kerr, W. J.; Morrison, A. J.; Pazicky, M.; Weber, T. *Org. Lett.* **2012,** *14* (9), 2250-2253; (q) Nguyen, T.-H.; Abarbri, M.; Guilloteau, D.; Mavel, S.; Emond, P. *Tetrahedron* **2011,** *67* (19), 3434-3439; (r) Van Steenis, J. H.; Van der Gen, A. *Eur. J. Org. Chem.* **2001,** (5), 897-910; (s) van Steenis, J. H.; van der Gen, A. *J. Chem. Soc., Perkin Trans. 1* **2002,** (19), 2117-2133; (t) Ghosh, A. K.; Banerjee, S.; Sinha, S.; Kang, S. B.; Zajc, B. *J. Org. Chem.* **2009,** *74* (10), 3689-3697.

49. Salim, S. S.; Bellingham, R. K.; Satcharoen, V.; Brown, R. C. D. *Org. Lett.* **2003,** *5* (19), 3403-3406.

50. (a) Thi-Huu, N.; Abarbri, M.; Guilloteau, D.; Mavel, S.; Emond, P. *Tetrahedron* **2011,** *67* (19), 3434-3439; (b) La Combe, E. M.; Stewart, B. *J. Am. Chem. Soc.* **1961,** *83* (16), 3457-3461.

51. Schlosser, M.; Brügger, N.; Schmidt, W.; Amrhein, N. *Tetrahedron* **2004,** *60* (35), 7731-7742.

52. Zhu, L.; Ni, C.; Zhao, Y.; Hu, J. *Tetrahedron* **2010,** *66* (27–28), 5089-5100.

53. Asakura, N.; Usuki, Y.; Iio, H. *J. Fluorine Chem.* **2003,** *124* (1), 81-88.

54. (a) Akana, J. A.; Bhattacharyya, K. X.; Mueller, P.; Sadighi, J. P. *J. Am. Chem. Soc.* **2007,** *129* (25), 7736-7737; (b) Gorske, B. C.; Mbofana, C. T.; Miller, S. J. *Org. Lett.* **2009,** *11*, 4318-4321.

55. Han, J.; Shimizu, N.; Lu, Z.; Amii, H.; Hammond, G. B.; Xu, B. *Org. Lett.* **2014,** *16*, 3500–3503.

56. Patrick, T. B.; Neumann, J.; Tatro, A. *J. Fluorine Chem.* **2011,** *132* (10), 779-782.

57. (a) Specker, E.; Bottcher, J.; Lilie, H.; Heine, A.; Schoop, A.; Muller, G.; Griebenow, N.; Klebe, G. *Angewandte Chemie-International Edition* **2005,** *44* (20), 3140-3144; (b) Myers, A. G.; Barbay, J. K.; Zhong, B. Y. *J. Am. Chem. Soc.* **2001,** *123* (30), 7207-7219.

58. Ohagan, D.; Rzepa, H. S. *Chem. Commun.* **1997,** (7), 645-652.

59. Leriche, C.; He, X. M.; Chang, C. W. T.; Liu, H. W. *J. Am. Chem. Soc.* **2003,** *125* (21), 6348-6349.

60. Sani, M.; Bruche, L.; Chiva, G.; Fustero, S.; Piera, J.; Volonterio, A.; Zanda, M. *Ange. Chem. Int. Ed.* **2003,** *42* (18), 2060-2063.

61. Leroux, F.; Jeschke, P.; Schlosser, M. *Chem. Rev.* **2005,** *105*, 827-856.

62. Sondej, S. C.; Katzenellenbogen, J. A. *J. Org. Chem.* **1986,** *51* (18), 3508-3513.

63. Baudoux, J.; Cahard, D. *Organic Reactions* **2007**.

64. Yue, X.; Zhang, X.; Qing, F.-L. *Org. Lett.* **2008,** *11* (1), 73-76.

65. (a) Ni, C.; Hu, J. *Tetrahedron Lett.* **2005,** *46* (48), 8273-8277; (b) Hu, J.; Zhang, W.; Wang, F. *Chem. Commun.* **2009,** (48), 7465-7478.

66. (a) Qing, F.-L.; Zheng, F. *Synlett* **2011,** (8), 1052-1072; (b) Wang, Z.; Hammond, G. B. *J. Org. Chem.* **2000,** *65* (20), 6547-6552.

67. (a) Soloshonok, V. A., *Fluorine-containing synthons, ACS symposium series 911*. Oxford University Press,Washington, D.C: 2005; (b) Kirsch, P., *Modern fluoroorganic chemistry*. Wiley-VCH, Weinheim: 2004.

68. Kumar, M.; Scobie, M.; Mashuta, M. S.; Hammond, G. B.; Xu, B. *Org. Lett.* **2013,** *15* (4), 724-727.

69. (a) Tanner, D. D.; Bostelen, P. V. *Can. J. Chem.* **1976,** *54* (15), 2417-2425; (b) Rothenberg, G.; Royz, M.; Arrad, O.; Sasson, Y. *J. Chem. Soc., Perkin Trans. 1* **1999,** (11), 1491-1494.

70. Hruschka, S.; Rosen, T. C.; Yoshida, S.; Kirk, K. L.; Fröhlich, R.; Wibbeling, B.; Haufe, G. *Biorg. Med. Chem.* **2008,** *16* (15), 7148-7166.

71. Yang, M.-H.; Matikonda, S. S.; Altman, R. A. *Organic Letters* **2013,** *15* (15), 3894-3897.

72. Li, Y.; Liu, X.; Ma, D.; Liu, B.; Jiang, H. *Adv. Synth. Catal.* **2012,** *354* (14-15), 2683-2688.

73. Akana, J. A.; Bhattacharyya, K. X.; Müller, P.; Sadighi, J. P. *J. Am. Chem. Soc.* **2007,** *129* (25), 7736-7737.

74. Wong, O. A.; Shi, Y. *J. Org. Chem.* **2009,** *74* (21), 8377-8380.

75. Mandal, S. K.; Ghosh, A. K.; Kumar, R.; Zajc, B. *Org. & Bio. Chem.* **2012,** *10* (16), 3164-3167.

76. (a) Reddy, V. P.; Alleti, R.; Perambuduru, M. K.; Welz-Biermann, U.; Buchholz, H.; Prakash, G. K. S. *Chem. Commun.* **2005,** (5), 654-656; (b) Suga, H.; Hamatani, T.; Guggisberg, Y.; Schlosser, M. *Tetrahedron* **1990,** *46* (12), 4255-4260; (c) Rozen, S.; Brand, M.; Zamir, D. *J. Am. Chem. Soc.* **1987,** *109* (3), 896-897.

77. Gustafsson, T.; Gilmour, R.; Seeberger, P. H. *Chem. Commun.* **2008,** (26), 3022-3024.

78. Xia, J.-B.; Zhu, C.; Chen, C. *J. Am. Chem. Soc.* **2013,** *135* (46), 17494-17500.

79. Cantet, A.-C.; Carreyre, H.; Gesson, J.-P.; Jouannetaud, M.-P.; Renoux, B. *J. Org. Chem.* **2008,** *73* (7), 2875-2878.

80. Ye, C.; Twamley, B.; Shreeve, J. M. *Org. Lett.* **2005,** *7* (18), 3961-3964.

81. (a) Zhao, X.-L.; Liu, L.; Chen, Y.-J.; Wang, D. *Tetrahedron* **2006,** *62* (29), 7113-7120; (b) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001,** *66* (13), 4679-4686.

82. Al-Mutairi, E. H.; Crosby, S. R.; Darzi, J.; Harding, J. R.; Hughes, R. A.; King, C. D.; Simpson, T. J.; Smith, R. W.; Willis, C. L. *Chem. Commun.* **2001,** (9), 835-836.

83. (a) Kataoka, K.; Ode, Y.; Matsumoto, M.; Nokami, J. *Tetrahedron* **2006,** *62* (11), 2471-2483; (b) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002,** *4* (4), 577-580.

84. Williams, P. H.; Ecke, G. G.; Ballard, S. A. *J. Am. Chem. Soc.* **1950,** *72* (12), 5738-5743.

85. Kriewitz, O. *Berichte der deutschen chemischen Gesellschaft* **1899,** *32* (1), 57-60.

86. Arundale, E.; Mikeska, L. A. *Chem. Rev.* **1952,** *51* (3), 505-555.

87. Hu, Y.; Skalitzky, D. J.; Rychnovsky, S. D. *Tetrahedron Lett.* **1996,** *37* (48), 8679-8682.

88. (a) Kishi, Y.; Inagi, S.; Fuchigami, T. *Eur. J. Org. Chem.* **2009,** *2009* (1), 103-109; (b) Kishi, Y.; Nagura, H.; Inagi, S.; Fuchigami, T. *Chem. Commun.* **2008,** (33), 3876-

3878; (c) Launay, G. G.; Slawin, A. M. Z.; O'Hagan, D. *Beilstein J. Org. Chem.* **2010,** *6*, 10.3762/bjoc.6.41.

89. (a) Yadav, Jhillu S.; Reddy, Basi V. S.; Reddy, Maddi S.; Niranjan, N.; Prasad, Attaluri R. *Eur. J. Org. Chem.* **2003,** *2003* (9), 1779-1783; (b) Yadav, J. S.; Reddy, B. V. S.; Reddy, M. S.; Niranjan, N. *J. Mol. Catal. A: Chem.* **2004,** *210* (1–2), 99-103; (c) White, J. D.; Blakemore, P. R.; Browder, C. C.; Hong, J.; Lincoln, C. M.; Nagornyy, P. A.; Robarge, L. A.; Wardrop, D. J. *J. Am. Chem. Soc.* **2001,** *123* (35), 8593-8595; (d) Tian, X.; Jaber, J. J.; Rychnovsky, S. D. *J. Org. Chem.* **2006,** *71* (8), 3176-3183; (e) Nannei, R.; Dallavalle, S.; Merlini, L.; Bava, A.; Nasini, G. *J. Org. Chem.* **2006,** *71* (16), 6277-6280.

90. Alder, R. W.; Harvey, J. N.; Oakley, M. T. *J. Am. Chem. Soc.* **2002,** *124* (18), 4960-4961.

91. (a) Bondalapati, S.; Reddy, U. C.; Kundu, D. S.; Saikia, A. K. *J. Fluorine Chem.* **2010,** *131* (3), 320-324; (b) Yadav, J. S.; Subba Reddy, B. V.; Anusha, B.; Subba Reddy, U. V.; Bhadra Reddy, V. V. *Tetrahedron Lett.* **2010,** *51* (21), 2872-2874.

92. Melnick, M. J.; Freyer, A. J.; Weinreb, S. M. *Tetrahedron Lett.* **1988,** *29* (32), 3891-3894.

93. (a) Lee, H. M.; Nieto-Oberhuber, C.; Shair, M. D. *J. Am. Chem. Soc.* **2008,** *130* (50), 16864-16866; (b) Aoki, S.; Watanabe, Y.; Sanagawa, M.; Setiawan, A.; Kotoku, N.; Kobayashi, M. *J. Am. Chem. Soc.* **2006,** *128* (10), 3148-3149.

94. Carballo, R. M.; Ramírez, M. A.; Rodríguez, M. L.; Martín, V. S.; Padrón, J. I. *Org. Lett.* **2006,** *8* (17), 3837-3840.

95. Yadav, J. S.; Reddy, B. V. S.; Chaya, D. N.; Kumar, G. G. K. S. N.; Naresh, P.; Jagadeesh, B. *Tetrahedron Lett.* **2009,** *50* (16), 1799-1802.

96. Yadav, J. S.; Subba Reddy, B. V.; Chaya, D. N.; Narayana Kumar, G. G. K. S.; Aravind, S.; Kunwar, A. C.; Madavi, C. *Tetrahedron Lett.* **2008,** *49* (20), 3330-3334.

97. Silva Jr, L. F.; Quintiliano, S. A. *Tetrahedron Lett.* **2009,** *50* (19), 2256-2260.

98. Dobbs, A. P.; Guesné, S. J. J.; Martinović, S.; Coles, S. J.; Hursthouse, M. B. *J. Org. Chem.* **2003,** *68* (20), 7880-7883.

99. (a) Yoshida, J.-i.; Sugawara, M.; Tatsumi, M.; Kise, N. *J. Org. Chem.* **1998,** *63* (17), 5950-5961; (b) Yoshida, J.; Ishichi, Y.; Isoe, S. *J. Am. Chem. Soc.* **1992,** *114* (19), 7594-7595.

100. Barry, C. S.; Bushby, N.; Harding, J. R.; Hughes, R. A.; Parker, G. D.; Roe, R.; Willis, C. L. *Chem. Commun.* **2005,** (29), 3727-3729.

101. Damera, K.; Yu, B.; Wang, B. *J. Org. Chem.* **2015,** *80* (11), 5457-5463.

102. (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008,** *37* (2), 320-330; (b) Gharbaoui, T.; Sengupta, D.; Krishnan, A. M.; Shah, N.; Macias, M.; Hart, R. M.; Lally, E. A. Crystalline forms and processes for the preparation of phenyl-pyrazoles useful as modulators of the 5-ht2a serotonin receptor. WO2007136689, 2007; (c) Barrow, J. C.; Coburn, C. A.; Egbertson, M. S.; McGaughey, G. B.; McWherter, M. A.; Neilson, L. A.; Selnick, H. G.; Stauffer, S. R.; Yang, Z.-Q.; Yang, W.; Lu, W.; Fahr, B.; Rittle, K. E. Preparation of spiropiperidine compounds as β-secretase inhibitors for the treatment of Alzheimer's disease. WO2006044497A2, 2006; (d) Burger, M.; Lan, J.; Lindvall, M.; Nishiguchi, G.; Tetalman, M. Preparation of thiazole carboxamides as PIM kinase inhibitors and their use in treating cancer. US20100216839A1, 2010; (e) Castro Pineiro, J. L.; Macleod, A. M.; Rowley, M.; Van Niel, M. B. Piperazine, piperidine and tetrahydropyridine derivatives useful as selective 5-HT agonists. WO9718203A1, 1997.

103. (a) Berrier, C.; Jacquesy, J. C.; Jouannetaud, M. P.; Vidal, Y. *Tetrahedron* **1990,** *46* (3), 815-26; (b) Liu, F.; Martin-Mingot, A.; Jouannetaud, M.-P.; Zunino, F.; Thibaudeau, S. *Org. Lett.* **2010,** *12* (4), 868-871; (c) Liu, F.; Martin-Mingot, A.; Lecornue, F.; Jouannetaud, M.-P.; Maresca, A.; Thibaudeau, S.; Supuran, C. T. *J. Enzyme Inhib. Med. Chem.* **2012,** *27* (6), 886-891; (d) Moine, A.; Thibaudeau, S.; Martin, A.; Jouannetaud, M.-P.; Jacquesy, J.-C. *Tetrahedron Lett.* **2002,** *43* (22), 4119-4122; (e) Zunino, F.; Liu, F.; Berrier, C.; Martin-Mingot, A.; Thibaudeau, S.; Jouannetaud, M.-P.; Jacquesy, J.-C.; Bachmann, C. *J. Fluorine Chem.* **2008,** *129* (9), 775-780; (f) Thibaudeau, S.; Martin-Mingot, A.; Jouannetaud, M.-P.; Karam, O.; Zunino, F. *Chem. Commun.* **2007,** (30), 3198-3200.

104. (a) Al-Maharik, N.; O'Hagan, D. *Aldrichimica Acta* **2011,** *44* (3), 65-75; (b) L'Heureux, A.; Beaulieu, F.; Bennett, C.; Bill, D. R.; Clayton, S.; LaFlamme, F.; Mirmehrabi, M.; Tadayon, S.; Tovell, D.; Couturier, M. *J. Org. Chem.* **2010,** *75* (10), 3401-3411; (c) Kim, D. W.; Ahn, D.-S.; Oh, Y.-H.; Lee, S.; Kil, H. S.; Oh, S. J.; Lee, S. J.; Kim, J. S.; Ryu, J. S.; Moon, D. H.; Chi, D. Y. *J. Am. Chem. Soc.* **2006,** *128* (50), 16394-16397; (d) Marquez, V. E.; Tseng, C. K. H.; Mitsuya, H.; Aoki, S.; Kelley, J. A.; Ford, H., Jr.; Roth, J. S.; Broder, S.; Johns, D. G.; Driscoll, J. S. *J. Med. Chem.* **1990,** *33* (3), 978-85.

105. (a) Hu, X. E. *Tetrahedron* **2004,** *60* (12), 2701-2743; (b) McNally, A.; Haffemayer, B.; Collins, B. S. L.; Gaunt, M. J. *Nature (London, U. K.)* **2014,** *510* (7503), 129-133.

106. (a) Andrews, P. C.; Bhaskar, V.; Bromfield, K. M.; Dodd, A. M.; Duggan, P. J.; Duggan, S. A. M.; McCarthy, T. D. *Synlett* **2004,** *2004* (05), 0791-0794; (b) Malamakal, R. M.; Hess, W. R.; Davis, T. A. *Org. Lett.* **2010,** *12* (10), 2186-2189; (c) Appayee, C.; Brenner-Moyer, S. E. *Org. Lett.* **2010,** *12* (15), 3356-3359; (d) Schulte, M. L.; Lindsley,

C. W. *Org. Lett.* **2011,** *13* (20), 5684-5687; (e) Shirakami, S.; Inoue, T.; Mukoyoshi, K.; Nakajima, Y.; Usuda, H.; Hamaguchi, H.; Higashi, Y.; Hatanaka, K. Preparation of fused pyridine derivatives as JAK3 inhibitors for treatment of autoimmune disease, leukemia, etc. WO2008084861A1, 2008.

107. (a) Jensen, K. L.; Standley, E. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2014,** *136* (31), 11145-11152; (b) Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998,** *120* (27), 6844-6845.

108. (a) van Oosten, E. M.; Gerken, M.; Hazendonk, P.; Shank, R.; Houle, S.; Wilson, A. A.; Vasdev, N. *Tetrahedron Lett.* **2011,** *52* (32), 4114-4116; (b) Ding, C.-H.; Dai, L.-X.; Hou, X.-L. *Synlett* **2004,** *2004* (12), 2218-2220; (c) Zhang, W. X.; Su, L.; Hu, W. G.; Zhou, J. *Synlett* **2012,** *23* (16), 2413-2415.

109. Wade, T. N. *J. Org. Chem.* **1980,** *45* (26), 5328-5333.

110. Alvernhe, G. M.; Ennakoua, C. M.; Lacombe, S. M.; Laurent, A. J. *J. Org. Chem.* **1981,** *46* (24), 4938-4948.

111. (a) Franz, R. *J. Fluorine Chem.* **1980,** *15* (5), 423-434; (b) Olah, G. A.; Nojima, M.; Kerekes, I. *Synthesis* **1973,** *1973* (12), 779-780.

112. Coutts, R. T.; Benderly, A.; Mak, A. L. C. *J. Fluorine Chem.* **1980,** *16* (3), 277-283.

113. DMPU-HF is available from Sigma-Aldrich (Cat. No. 802794).

114. Okoromoba, O. E.; Han, J.; Hammond, G. B.; Xu, B. *J. Am. Chem. Soc.* **2014,** *136* (41), 14381-14384.

115. Okoromoba, O. E.; Hammond, G. B.; Xu, B. *Org. Lett.* **2015,** *17* (16), 3975-3977.

116. DMPU-HF was found to be an efficient detosylation reagent toward N-tosyl triazoles and indoles.

117. Martin, A.; Casto, K.; Morris, W.; Morgan, J. B. *Org. Lett.* **2011,** *13* (20), 5444-5447.

118. Tanner, D. *Angew. Chem., Int. Ed. Eng.* **1994,** *33* (6), 599-619.

119. (a) Smith, J. G., *Organic chemistry*. 4th ed.; McGraw-Hill: New York, NY, 2014; (b) Brown, W. H.; Iverson, B. L.; Anslyn, E. V.; Foote, C. S., *Organic chemistry*. 7th edition. ed.; Wadsworth Cengage Learning: Australia ; Belmont, CA, 2014; p xxx, 1216, 21, 10, 35 pages.

120. Dolbier, W. R., *Guide to fluorine NMR for organic chemists*. John Wiley & Sons: 2009.

121. Minakata, S.; Morino, Y.; Oderaotoshi, Y.; Komatsu, M. *Chem. Commun.* **2006,** (31), 3337-3339.

122. Cui, Y.; He, C. *J. Am. Chem. Soc.* **2003,** *125* (52), 16202-16203.

123. Maestre, L.; Sameera, W. M. C.; Díaz-Requejo, M. M.; Maseras, F.; Pérez, P. J. *J. Am. Chem. Soc.* **2013,** *135* (4), 1338-1348.

124. Badet, B.; Julia, M.; Mallet, J.; Schmitz, C. *Tetrahedron* **1988,** *44* (10), 2913-2924.

125. Gao, G.-Y.; Harden, J. D.; Zhang, X. P. *Org. Lett.* **2005,** *7* (15), 3191-3193.

126. McGhee, A.; Cochran, B. M.; Stenmark, T. A.; Michael, F. E. *Chem. Commun.* **2013,** *49* (60), 6800-6802.

127. Hodgson, D. M.; Humphreys, P. G.; Xu, Z.; Ward, J. G. *Angew. Chem. Int. Ed.* **2007,** *46* (13), 2245-2248.

128. Chamchaang, W.; Pinhas, A. R. *J. Org. Chem.* **1990,** *55* (9), 2943-2950.

129. Ding, C.-H.; Dai, L.-X.; Hou, X.-L. *Synlett* **2004,** (12), 2218-2220.

130. Fan, R.-H.; Zhou, Y.-G.; Zhang, W.-X.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem.* **2004,** *69* (2), 335-338.

131. Vasdev, N.; van Oosten, E. M.; Stephenson, K. A.; Zadikian, N.; Yudin, A. K.; Lough, A. J.; Houle, S.; Wilson, A. A. *Tetrahedron Lett.* **2009,** *50* (5), 544-547.

132. Barker, T. J.; Boger, D. L. *J. Am. Chem. Soc.* **2012,** *134* (33), 13588-13591.

133. Okoromoba, O. E.; Hammond, G. B.; Xu, B. *Org. Lett.* **2015,** *17* (16), 3975-3977.

134. Lübke, M.; Skupin, R.; Haufe, G. *J. Fluorine Chem.* **2000,** *102* (1–2), 125-133.

135. Camps, F.; Chamorro, E.; Gasol, V.; Guerrero, A. *J. Org. Chem.* **1989,** *54* (18), 4294-4298.

136. Hiyama, T., *Organofluorine compounds: chemistry and applications*. Springer Science & Business Media: 2013.

137. (a) Tamura, M.; Shibakami, M.; Arimura, T.; Kurosawa, S.; Sekiya, A. *J. Fluorine Chem.* **1995,** *70* (1), 1-3; (b) Oshida, J.-i.; Morisaki, M.; Ikekawa, N. *Tetrahedron Lett.* **1980,** *21* (18), 1755-1756.

138. Shimizu, M.; Yoshioka, H. *Tetrahedron Lett.* **1988,** *29* (33), 4101-4104.

139. Landini, D.; Penso, M. *Tetrahedron Lett.* **1990,** *31* (49), 7209-7212.

140. Sattler, A.; Haufe, G. *J. Fluorine Chem.* **1994,** *69* (2), 185-190.

141. (a) Saavedra-Olavarria, J.; Arteaga, G. C.; Lopez, J. J.; Perez, E. G. *Chem. Commun.* **2015,** *51* (16), 3379-3382; (b) Qiu, S.; Xu, T.; Zhou, J.; Guo, Y.; Liu, G. *J. Am. Chem. Soc.* **2010,** *132* (9), 2856-2857; (c) Zhang, H.; Song, Y.; Zhao, J.; Zhang, J.; Zhang, Q. *Angew. Chem. Int. Ed.* **2014,** *53* (41), 11079-11083.

142. Sharpless, K. B.; Chong, A. O.; Oshima, K. *J. Org. Chem.* **1976,** *41* (1), 177-179.

143. Yoshino, H.; Nomura, K.; Matsubara, S.; Oshima, K.; Matsumoto, K.; Hagiwara, R.; Ito, Y. *J. Fluorine Chem.* **2004,** *125* (7), 1127-1129.

144. Wölker, D.; Haufe, G. *J. Org. Chem.* **2002,** *67* (9), 3015-3021.

145. Luo, F.; Wang, P.; Gong, Y. *Tetrahedron Lett.* **2010,** *51* (13), 1693-1695.

146. Muehlbacher, M.; Poulter, C. D. *J. Org. Chem.* **1988,** *53* (5), 1026-1030.

APPENDIX

LIST OF ABBREVIATIONS USED

AHF: Anhydrous hydrogen fluride
CI: Chemical Ionization
DAST: (Diethylamino)sulfur trifluoride
DCM: Dichloromethane
DCE: 1,2-Dichlorethane
DMSO: Dimethylsulfonyl Oxide
DMPU: 1,3-dimethyltetrahydropyrimidin-2(1H)-one
DBH:1,3-dimethyl hydantoin
dr: diastereomeric ratio
ee: Enantiomeric excess
EI: Electrospray Ionization
EtOAc: Ethyl Acetate
GC: Gas Liquid Chromatography
h: Hour
HBA: Hydrogen bond acceptor
HBD: Hydrogen bond donor
HF: Hydrogen fluoride
HPLC: High performance liquid chromatography
HRMS: High resolution mass spectroscopy
Hz: Hertz
m: meta
mg: milligram
min: minute
mL: milliliter
mmol: millimole
MsOH: Methanesulfonic acid
NBS: N-Bromosuccinimide
NMR: Nuclear magnetic resonance spectroscopy
o: ortho
p: para
ppm: Parts per million
PPHF: Pyridinium poly(hydrogen fluoride)
Py: Pyridine
PBSF: perfluoro-1-butanesulfonyl chloride
TBS: *tert*-Butyldimethylsilyl
tert: tertiary
TMS: Trimethylsilyl
TFEDMA: tetrafluoroethyldimethylamine
TfOH: Trifluoromethanesulfonic acid

THF: Tetrahydrofuran
TLC: Thin layer chromatography
TREAT-HF: Triethylamine tris-hydrogen fluoride

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University of Louisville, Louisville, KY
Dissertation: Development and applications of HF-based reagents—DMPU-HF
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Master of Science, Chemistry December 2010 (Advisor: C. Okoro)
Thesis: Synthesis and structural activity relationship of fluorinated acridones as potential anticancer agents
Tennessee State University, Nashville, TN

Bachelor of Science, Chemistry, December 2005
Obafemi Awolowo University, Ile–Ife, Nigeria
Honors thesis: Comparative study on the proximate analysis of human milk and baby formula, under the supervision of Dr. E.A. Oluyemi

Research Experience

Graduate Research

University of Louisville, Kentucky (PhD Candidate) August, 2012 – Present

- Developed a novel DMPU-HF reagent for selective fluorination reactions
- Synthesized a variety of fluorinated medium sized rings using mild and efficient fluorinating reagent
- Developing chiral DMPU-HF analogues for asymmetric fluorination reactions under the supervision of G.B Hammond

University of Louisville, Kentucky (PhD Candidate) May, 2011 – May, 2012

- Tandem Henry/oxa-Michael Route to the disubstituted 1, 3-dihydrobenzo[c]furan System under the supervision of F.A Luzzio

Tennessee State University, Nashville, Tennessee (M.S.) 2008 – 2010

- Synthesis and structure activity relationship of small to medium sized trifluoromethylated enaminones and acridones under the supervision of C. Okoro

Undergraduate Research Assistant 2004-2005
Obafemi Awolowo University, Ile–Ife, Nigeria

- Comparative study on the proximate analysis of human milk and baby formula,

under the supervision of Dr.E. Oluyemi

Publication

- Regioselective synthesis of fluorohydrins from alkenes and epoxides by DMPU-HF: Okoromoba O.E.: Zhou L.; Bo, X.; Hammond
  (Manuscript in preparation)
- Regioselective ring opening of aziridines by DMPU-HF: Okoromoba O.E.; Robertson, N.; Zhou L.; Xu, B.; Hammond, G. B
  (Manuscript in preparation)
- Preparation of Fluorinated Tetrahydropyrans and Piperidines using a New Nucleophilic Fluorination Reagent DMPU-HF: Okoromoba, O.E.; Hammond, G.B.; Xu, B.; *Org. Lett.* **2015,** *17(16),* 3975
- Designer HF-Based Fluorination Reagent: Highly Regioselective Synthesis of Fluoroalkenes and gem-Difluoromethylene Compounds from Alkynes. Okoromoba, O.E.; Han, J.; Hammond, G.B.; Xu, B., *J. Am. Chem. Soc.*, **2014***, 136 (41),* 14381
- Synthesis and anticonvulsant activity of fluorinated cyclic enaminones: Apraku, J. O., Okoromoba, O.E., Faadeyi, F. Okoro, C.*; Lett. Drug Des. Discov. **2013**, 10,* 1024
- Tandem Henry/oxa-Michael Route to the 1, 3-Disubstituted-1, 3-Dihydrobenzo[c]furan System Luzzio F. A and Okoromoba O.E., *Tetrahedron Lett.* **2011**, *52,* 6530.

Presentations

- Okoromoba O.E.; Xu. B.; Hammond, G.B., Modulating the reactivity of HF through Laurence's hydrogen bond basicity scale, *ACS national meeting,* August **2015 ORG 606**
- Okoromoba O.E,; Xu, B.; Hammond, G.B., "Modulating HF reactivity through Laurence's hydrogen bond basicity scale" *NOBChCE national meeting,* September, **2015 Technical session 9**
- Okoromoba O.E,; Xu, B.; Hammond, G. B.,"Taming of the shrew: modulating the properties of hydrogen fluoride" *NOBChCE national meeting, New Orleans, Louisiana,* September, **2014 Technical session 11**
- Okoromoba O.E.; Luzzio. F. A.; "Tandem Henry/oxa-Michael Route to the 1, 3-disubstituted-benzoiso furans"*ACS National Conference, San Diego, CA,* March, **2012 ORG 672**

Honors/Awards/Grants

- McSweeney Fellowship Award 2011 – 2015
- Two time recipient of NOBChCE Travel Grant Award September 2014, 2015
- Recipient of Bursary Award to attend the 21st International Symposium of fluorine Chemistry and the 6th International Symposium of Fluorous Technologies August 2015

Leadership and Activities

- Vice President, Chemistry Graduate Student, University of Louisville
  2012 – 2014
- Chemistry Ambassador to the Graduate School, University of Louisville
  2011– 2015
- President, Students Chemical Society of Nigeria Obafemi Awolowo University
  2004 – 2005

Professional Memberships/Affiliations

- American Chemical Society (ACS) 2010 – Present
- The National organization for Black Chemists And Chemical Engineers (NOBChCE) 2013 – Present