THE USE OF METHYL 2-(FLUOROSULFONYL)-2,2-DIFLUOROACETATE AS THE DIFLUOROCARBENE SOURCE TO GENERATE AN IN-SITU SOURCE OF DIFLUOROMETHYLENE TRIPHENYLPHOSPHONIUM YLIDE

By

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A THESIS PRESENTED TO THE GRADUATE SCHOOL OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT OF REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE

UNIVERSITY OF FLORIDA

2013

To my family and friends for supporting me

ACKNOWLEDGEMENTS

I would like to thank my advisor, Dr. William R. Dolbier Jr., for providing me the opportunity to perform my graduate research in his lab. He has given me great advice, knowledge, direction, and support throughout my graduate research. I would also like to thank my committee members, Dr. Ronald K. Castellano, Dr. Aaron Aponick, Dr. Ben Smith and Dr. Kenneth Sloan, for their support and help as well.

I would also like to thank the many members of Dr. Dolbier's group throughout my research here at the University of Florida. In particular, I would like to thank Dr. Fei Wang for his experience and guidance with reactions as well as being a great mentor. I would like to thank Dr. Zhaoyun Zheng for his knowledge and Henry Martinez for his help with calculations. I would also like to thank Masamune Okamoto, Dr. Xiao-jun-Tang, and Dr. Kanishev Oleksandr for help with research and being good labmates.

Outside of the University of Florida, I would like to thank my family for their support and encouragement during my research. Finally, I would like to thank all of my friends for their support, notably Donovan Thompson for his support and encouragement.

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December 2013

Chair: William R. Dolbier, Jr.
Major: Chemistry

Under moderate conditions in the presence of a demethylating reagent, such as iodide, methyl 2,2,-difluoro-2-(fluorosulfonyl)acetate (MFDA) releases difluorocarbene, which, in the presence of triphenylphosphine, forms difluoromethylene triphenylphosphonium ylide. When the process is carried out also in the presence of aldehydes or activated ketones, the ensuing *in situ* Wittig-type reaction of the ylide with the carbonyl reactants produces 1,1-difluoroalkenes in good yield. Density Functional Theory calculations were used to provide new estimates of the energies and structures of singlet and triplet states of CH_2:, CHF:, and CF_2: carbenes, as well as those of their respective triphenylphosphonium ylides.

CHAPTER 1
BACKGROUND

1.1 Introduction

1.1.1 Fluorine

1.1.1.1 Properties of Fluorine and the C-F Bond

Elemental fluorine was first isolated by Henri Moissan in 1886. He would later be recognized for his effort by being awarded the Nobel Prize in 1906. Since this discovery, incorporation of fluorine into organic molecules has become increasingly important to organic and medicinal chemist because of the ability of fluorine to enhance the physical properties of fluorinated compounds.

Fluorine is the most electronegative element. This characteristic associated with fluorine can be attributed to the element's small atomic radii. In fact, fluorine has the smallest atomic radii of all period 2 elements.[1] Fluorine's small radius makes the removal of electrons to form F^+ extremely difficult. On the other hand, the acceptance of an electron to form F^- is much easier. The electronegativity of fluorine is 4.0 (Pauling, Table 1-1)[1] and 4.44 (Mulliken)[2]. The Van der Waal radii for fluorine is 1.47 Angstroms (Table 1-2), which is smaller than both carbon and oxygen. The effect of radii size on bond length is also shown in Table 1-2, with the C-F bond length (1.35 Å) being shorter than the C-O and C-C bonds both.[1] The C-F bond is also more polarized than other bonds. By subtracting the electronegativity of carbon(2.5) from fluorine(4.0), one can calculate the polarity of the C-F bond. The polarity of the C-F bond is about 1.5, which is more polarized than the C-Cl bond (0.61).[2]

Table 1-1 Electronegativities of Elements according to Pauling scale.[1]

H(2.1)				
Li	C	N	O	F
1.0	2.5	3.0	3.5	4.0
Na	Si	P	S	Cl
0.9	1.8	2.1	2.5	3.0
K				Br
0.8				2.8
Cs				I
0.7				2.5

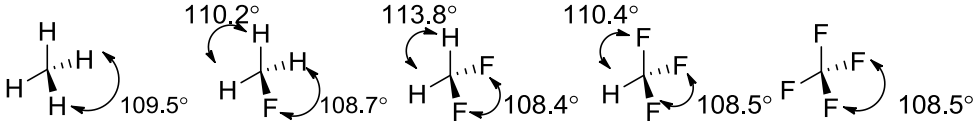
Table 1-2. Van der Waals radii and average C-X bond lengths of common elements[1]

Van der Waals radii (Angstrom)	C(1.70)	O(1.52)	F(1.47)
Bond Lengths (Angstrom)	C-C(1.54)	C-O(1.43)	C-F(1.35)

These attributes make the C-F bond the strongest bond in organic chemistry. The formation to the C-F bond places most of the electron density on fluorine.[1,2] Thus bond strength can be associated with the attraction between $F^{\delta-}$ and $C^{\delta+}$, which is known as the inductive effect. Therefore, as the number of fluorine atoms about a carbon center increases, the carbon becomes increasing positive and the C-F bond is shortened (Table 1-3)[1]. On steric grounds, medicinal chemists often use fluorine to replace hydrogen.[1] The replacement of hydrogen with fluoride can alter a compounds bond angles and pka value.[1,3,4,5] As fluorine pulls electron density toward it, the repulsion between C-H bonds is relaxed and the bond angle widens.[1] These trends can be seen as we go from fluoromethane to tetrafluoromethane (Table1-3)[1]. When

hydrogen is replaced by fluorine on an alkanoic acid, the pKa is lowered and acidity increased (Table 1-4)[3,4,5]. As the fluorine is moved closer to the carboxylic acid the acidity of the molecule will steadily increase

Table 1-3. Bond lengths and bond angles[1]



	CH_4	CH_3F	CH_2F_2	CHF_3	CF_4
C-F bond length/Angstrom	-----	1.39	1.36	1.33	1.32

Table 1-4. Acidity of carboxylic acids[3,4,5]

Carboxylic Acid	pKa
$CH_3CH_2CH_2COOH$	4.8
$CF_3CH_2CH_2COOH$	4.2
CF_3COOH	0.2
CFH_2COOH	2.6
CH_3COOH	4.9

Fluorine addition can also alter the electronegativity of a functional group.[2] By removing a single hydrogen atom from a methyl group and replacing it with a fluorine atom, the electronegativity of the group is increased. For example, the electronegativity of a methyl substituent is 2.3, which is similar to elemental carbon. On the other hand, a trifluoromethyl substituent has an electronegativity around 3.4. This closely resembles that of oxygen. These effects can also be seen with other electronegative elements but are more substantial with fluorine.[2]

The strength of the C-F bond makes it a poor leaving group.[1,2] Therefore, it cannot undergo S_N2 type chemistry. Fluorine can be displaced in $E1_{CB}$ elimination reactions. For example, when 2-fluorobutane is deprotonated at the β position to the

fluorine, inductive withdrawal by fluorine stabilizes the resulting anion produced. The fluoride ion is then eliminated to neutralize the intermediate. The most common case of C-F bond cleavage is in nucleophilic aromatic substitution reactions. Fluorine, like most halogens is electron withdrawing. When fluorine is attached to a benzene ring, the benzene ring is considered electron-poor. This characteristic makes the aromatic ring susceptible to nucleophilic attack. Fluorine then stabilizes the negative charge on the ring before it is eliminated Figure 1-1).[1]

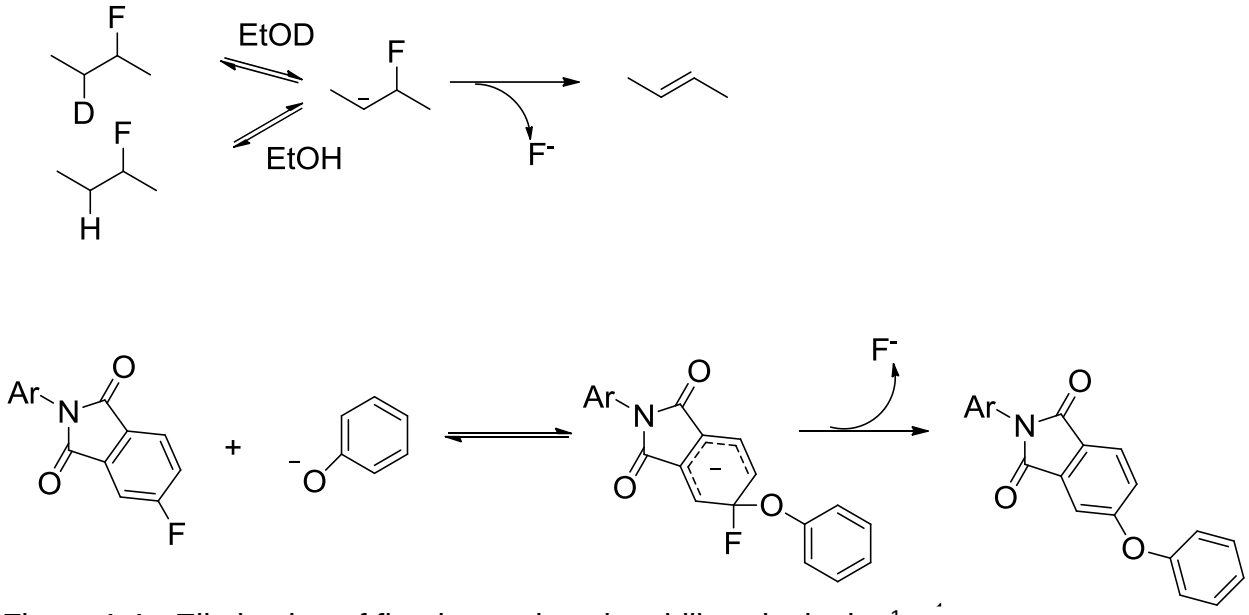


Figure 1-1. Elimination of fluorine and nucleophilic substitution[1]

The electron withdrawing nature of fluorine can also lead to unexpected conformations. The most common example is that of 1,2-difluoroethane (Figure 1-2). In this example the gauche conformation is preferred to the anti by 1.8 kcal/mol.[2,6] In the anti-conformation, fluorine atoms are aligned such that an excellent acceptor (C-F) is placed anti to an excellent donor (C-F). On the other hand, when the fluorine atoms are placed gauche, two good acceptors (C-F) are anti to C-H. Although, C-H is not a strong

donor, it is better the C-F. Orbital interactions stabilize what would be an overall strained structure.[2,6]

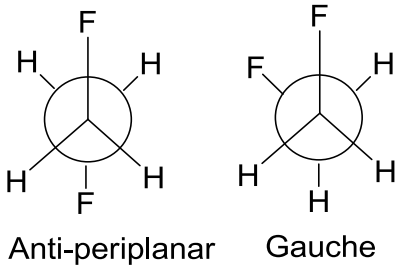


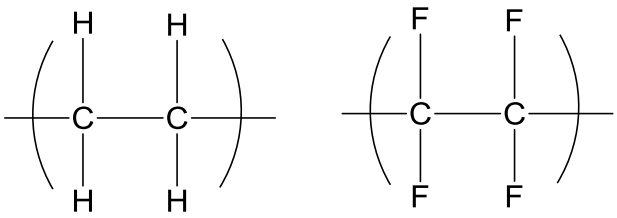
Figure 1-2. Conformation of 1,2 difluoromethane

1.1.1.2. Pharmaceuticals, materials, and agrochemicals

In the developed world, we encounter compounds containing fluorine every day. Naturally occurring fluorinated molecules are scarce; therefore most fluorinated molecules are developed synthetically. Over the last few decades, the interest in these molecules has grown due to the effect that fluorine can have on their physical, chemical, and biological properties.[1,7]

Chlorofluorocarbons (CFC) were the first fluorinated chemical used in the modern world.[7] They were used as refrigerants, but were replaced by hydrofluorocarbons (HFC) because of potential environmental impacts. Chlorofluorocarbons found a new synthetic use in the production of tetrafluoroethylene, which would be responsible for the development of polytetrafluoroethylene (PTFE). This polymer was of great value because it was more chemical and thermal resistant than the hydrocarbon version polyethylene (Figure1- 3). Unlike the hydrogens in polyethylene, fluorine (in PTFE) has three electrons pairs in its outer valence shell. These electron pairs form a “protective sheath” that blocks the backbone from nucleophilic attack, therefore providing the increased chemical and thermal resistance. Since this development, fluorinated materials are now used in waterproof clothing, non-

stick cookware, and artificial veins. Other materials such as perfluoropolyethers are used as lubricants on spacecraft because they remain fluid over a wide temperature range (-90°C to 250°C).[7]



Polyethylene Polytetrafluoroethylene

Figure 1-3. PE vs. PTFE

Organofluorines have also found uses in the medicinal field. Currently, perfluorobutane, a perfluorocarbon (PFC), is used as an ultrasound contrast imaging agent for visualizing heart and liver disease.[7] Other PFCs have been used to fill deflated lungs in premature babies. The synthesis of the first fluorinated steroid showed that a single fluorinated substituent could increase the biological activity of the parent steroid. This discovery led to the development of many fluorinated pharmaceuticals such as Prozac® and Cipro® (Figure1-4). The ability for Prozac® to cross the blood brain barrier is owed to the presence of the trifluormethyl group. Prozac® and Cipro® were two of the top 20 bestselling drugs as of 2009.[7]

The agrochemical industries regularly use some well-known brand-name fluorinated chemicals as herbicides, pesticides, and even fertilizer (Figure 1-4).[7] They are all manufactured and produced in large quantities. The use of fluorinated compounds is still currently being studied, but over half of the current products in field trials are fluorinated.[7] Therefore, fluorinated products will play an increased role in the future.

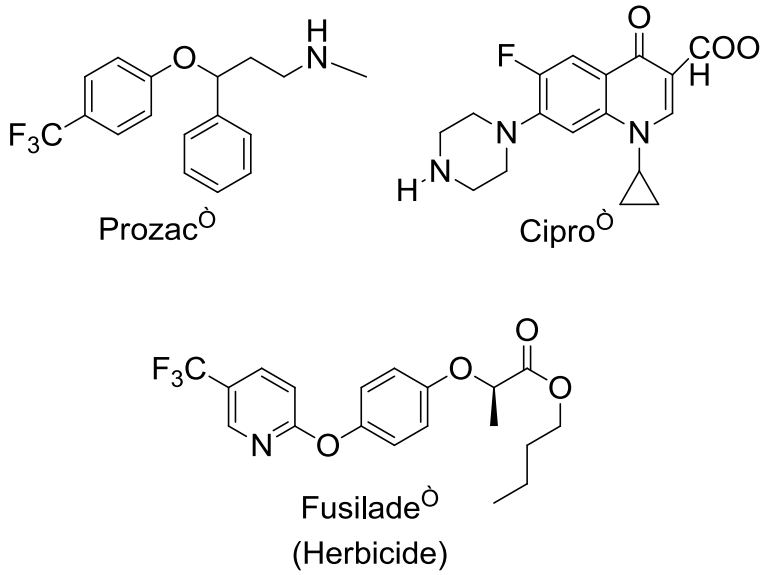


Figure 1-4. Common pharmaceuticals and herbicides

1.1.2 Classical Olefination Reactions Containing Phosphonium Ylides

1.1.2.1 The Wittig reaction

The Wittig reaction is a classical reaction used to prepare alkenes from aldehydes and ketones using an ylide prepared from a phosphonium salt (Scheme 2). The reaction was first discovered in 1954 by Georg Wittig.[8] He would later win the Nobel Prize in Chemistry for his work in 1979. The Wittig reaction produces high yields of di- and tri- substituted alkenes. On the other hand, preparation of tetra substituted alkenes produce lower yields because of steric bulk. The phosphonium ylide (Wittig reagent) is prepared by reacting tri-substituted phosphines with an alkyl halide. This reaction produces a phoshonium salt. Once this salt is treated with base (i.e NaH, NaOMe, BuLi etc.), the Wittig reagent results. Researchers usually observe a color change in the reaction once the ylide is produced. Ylides are resonance stabilized, and can exist in a zwitterionic form with positive and negative charges on adjacent atoms. Wittig reagents are prepared in situ and not isolated because of their relative instability in air. There are two types of ylides, stabilized and non-stabilized. Non-stabilized ylides

are reacted under inert conditions. These ylides have an election donating group adjacent to the negatively charged carbon. They are less stable, react faster and produce (Z)-alkenes. The stabilized ylide has an electron withdrawing group adjacent to the negatively charge carbon. This ylide is stabilized by conjugation and leads to the (E)-alkene.[9]

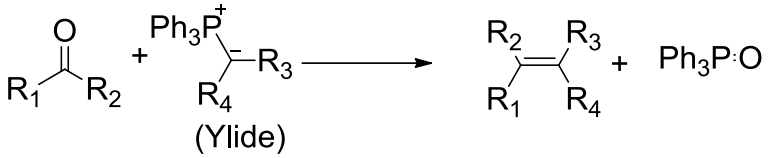


Figure 1-5. Typical Wittig Reaction

The general mechanism for the Wittig reaction is initiated by nucleophilic addition of the negatively charged carbon of the ylide on the carbonyl carbon. This initial step produces a betaine that can cyclize to give an oxaphosphetane intermediate. This intermediate will decompose to give an alkene and a phosphine oxide. The driving force behind the Wittig reaction is the formation of the more stable double bond between the phosphorus and oxygen in phosphine oxide (Figure 1-6).[8,9]

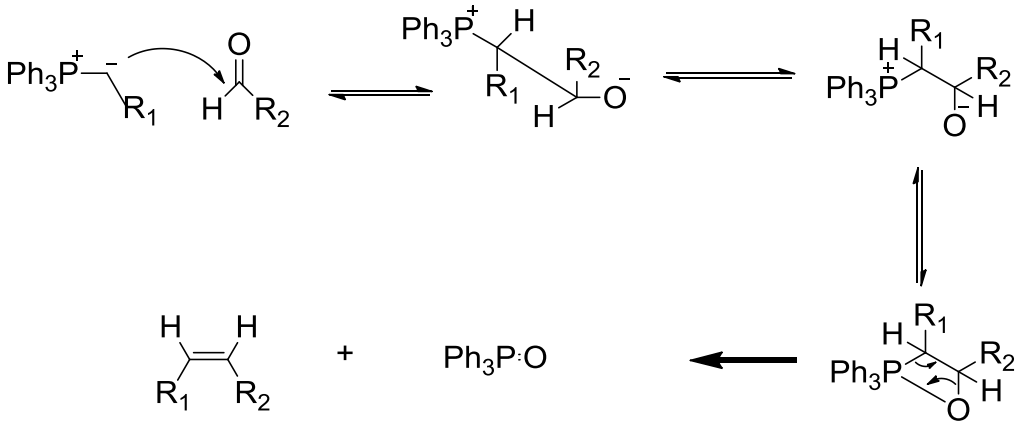


Figure 1-6. Typical Wittig mechanism

The mechanisms for the unstabilized and stabilized ylide can be analyzed from a stereochemical perspective. The unstabilized ylide reacts with the carbonyl compound but they approach each other at right angles to form a puckered four membered oxaphosphetane ring. This syn-oxaphosphetane places large substituents away from each other and is less stable than the anti-form. The instability of the intermediate does not allow time for the more stable conformation to form. Therefore, the kinetically controlled Z-alkene is formed. In the case of stabilized ylides, the opposite is true. This reaction can form both syn- and anti-intermediates. The stabilization of the intermediate gives adequate time for the syn formation to interconvert to form the anti-conformation. Thus, the E-alkene predominates and the final product is thermodynamically controlled.[9]

1.1.2.2. Horner-Wadsworth-Emmons olefination

Another classical reaction that features a phosphonium ylide is the Horner-Wadsworth-Emmons Olefination. In 1958, Horner and coworkers proposed a modified version of the Wittig reaction using phosphonate-stabilized carbanions.[10,11] This discovery was then expanded upon by Wadsworth and Emmons in the early 1960s.[12] Phoshonate-stablized carbanions have some advantages over phosphonium ylides used in the Wittig reaction. For example, phoshonate-stablized carbanions are more nucleophilic and basic. They are susceptible to alkylation unlike phosphonium ylides. The dialkyl phosphate salt, a byproduct of the Horner-Wadsworth-Emmons process, is easier to remove compared to the triphenylphosphine oxide associated with the Wittig.[13]

The overall mechanism for the Horner Wadworth Emmons olefination is similar to that of the Wittig. The first step is deprotonation to form the phosphate carbanion. The rate-limiting step is the addition of the carbanion into the corresponding aldehyde or ketone. The elimination is driven by the formation of the phosphorus oxygen bond and

an electron withdrawing group (EWG) alpha to the phosphonate. If the EWG is not present, the resulting is an alpha-hydroxyphosphonate. This reaction yields E-alkenes and Z-alkenes, but the overall reaction favors the E-alkene, which is determined by the equilibrium of the intermediates.[13]

1.2 Events Leading to This Research

1.2.1 Methyl 2,2-Difluoro-2-(Fluorosulfonyl) Acetate (MDFA)

MDFA has previously been primarily known as an excellent precursor of trifluoromethyl copper (Figure 1-7).[14] The initial step of this reaction involves formation of the copper salt with elimination of methyl halide. The salt then decomposes to release difluorocarbene and a fluoride ion, which are in equilibrium with trifluoromethyl anion. Dimethyl formaldehyde (DMF) is used as a solvent since it stabilizes the anion. In the presence of CuI, the equilibrium shifts to form [CF_3 CuI^-], thus, forming the stable $CuCF_3$. Trifluoromethyl copper then undergoes a reaction with aryl or alkyl halides to produce trifluoromethyl- aryl and alkyl substrates.

Recently we reported that MDFA could be used as an effective source of difluorocarbene to synthesize difluorocyclopropanes from alkenes (Figure 1-7). In the latter reaction, difluorocarbene formation was initiated by demethylation of MDFA by an iodide ion, with trimethylsilyl chloride (TMSCl) being used to trap fluoride ion. Since difluorocarbene is relatively unreactive with alkenes, this reaction required high temperatures to obtain the product in higher yields.[15]

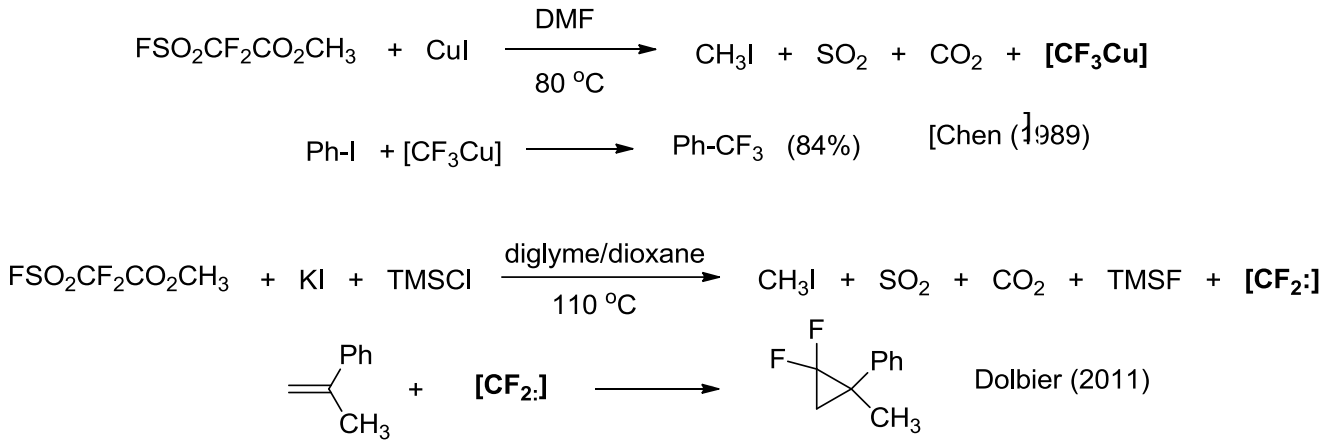


Figure 1-7. Previous work with MFDA

Although commercially available, MFDA can be easily prepared by reacting 3,3,4,4-tetrafluoro[1,2]oxathiethane 2,2-dioxide with sodium methoxide in diethyl ether at 0°C (Figure 1-8).[21] If can also be prepared from difluoro (fluorosulfonyl)acetic acid. This acid is added to silver oxide to from the silver salt in diethyl ether. The silver salt, silver difluoro(fluorosulfonyl) acetate, is then reacted with methyl iodide to produce MFDA.[22] Another convenient way to form MFDA is by adding methanol dropwise to trimethysilyl Fluorosulfonyl difluoroacetae (TFDA) at 0°C, allowing the mixture to warm to room temperature, and then refluxing overnight. MFDA is also commercially available.[23]

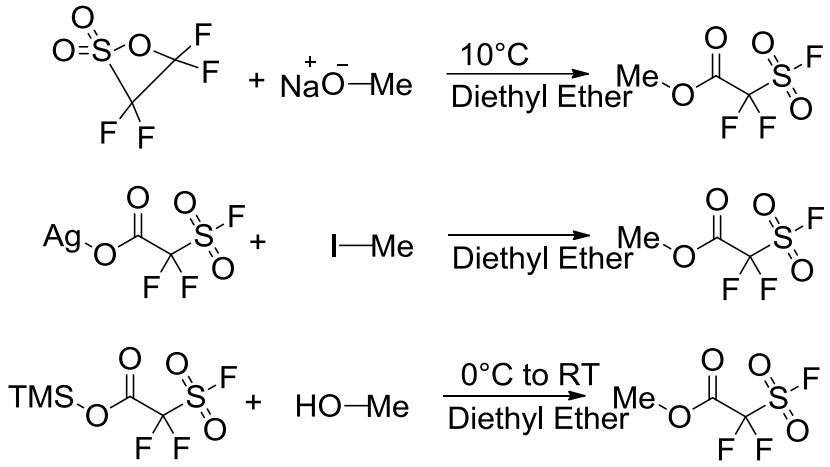


Figure 1-8. MFDA preparation

1.2.2 1,1-Difluoroalkenes

1.2.2.1 Uses of 1,1 difluoroalkenes

1,1-Difluoroalkenes have generated interest as potential enzyme inhibitors,[24-27] but more commonly they have been utilized as fluorinated building blocks (Figure 1-9). Monofluoroalkenes can easily be prepared from difluoroalkenes using a benzene solution of sodium bis(2-methoxyethoxy)aluminum hydride (SBAH). This reaction gives excellent yields of the desired product with no over-reduction detected.[28] Difluoroalkenes can also undergo the addition of fluoride in the presence of a proton source to give 2,2,2-trifluoroethyl groups. Burton and coworkers showed that in the presence of potassium fluoride, a fluoride anion would attack the terminal carbon of the olefin. The subsequent anion could then be protonated by water in DMF.[31] This procedure was later modified by substituting tetrabutylammonium fluoride for KF in THF at room temperature.[30] Nucleophillic attack is not limited to the fluorine anion; other nucleophiles can also be implemented such as lithium alkyl reagents. These reactions were performed using exo-difluorinated vinyloxiranes as the substrates. The addition of the alkyl to the double bond followed an S_N2' type mechanism with the opening of the adjacent epoxide.[32] Difluoroalkenes are precursors of ring fluorinated heterocycles via intramolecular cyclization reactions.[33-35] 1,1-Difluoroalkenes are also precursors of esters and carboxylic acids (Figure 1-9).[16]

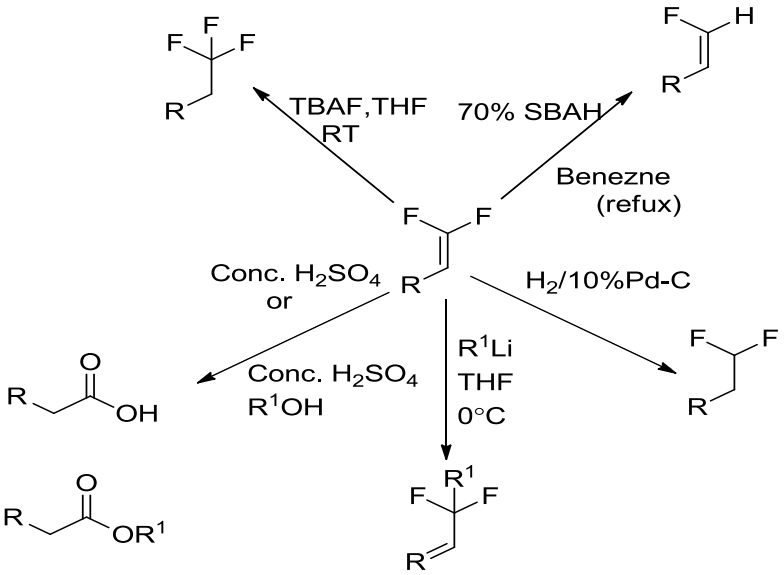


Figure 1-9. Synthetic uses for 1,1 difluoroalkenes

1.2.2.2 Synthesis of 1, 1, difluoroalkenes

The versatility of the chemistry with difluoroalkenes has led to various approaches for their preparation, many of them involving a Wittig reaction involving the presumed, but thus far undetected, difluoromethylene triphenylphosphonium ylide. Fuqua and coworkers were the first to propose the intermediacy of difluoromethylene triphenylphosphonium ylide and to study the reaction of this presumed intermediate with aldehydes to form 1,1-difluoroalkenes.[17,18] In 1964, they reported a process involving a refluxing solution of sodium chlorodifluoroacetate in diglyme at 160 ^{o}C in the presence of Ph_3P and aldehyde substrate. High yields were obtained, as shown in Scheme 7 below. Aliphatic aldehydes were also decent substrates with heptanal yielding 52% of 1,1-difluoro-1-octene.

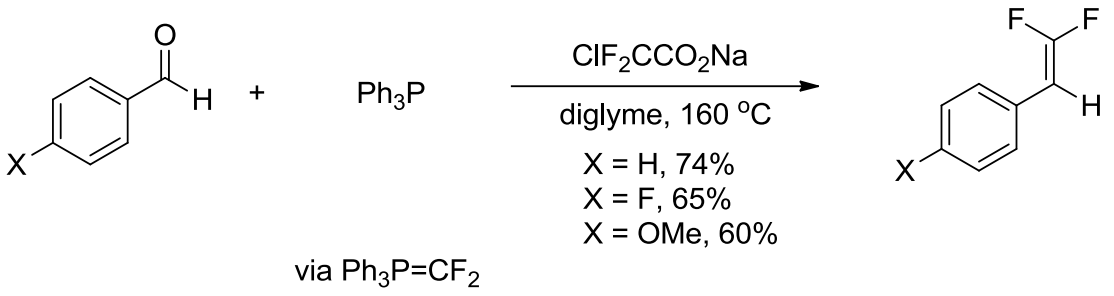


Figure 1-10. Fuqua procedure

Although the mechanism proposed by Fuqua involved initial formation of difluorocarbene by thermal decomposition of chlorodifluoroacetate, followed by trapping of the carbene by triphenylphosphine to form the ylide, Burton has suggested that alternative mechanisms, not involving the intermediacy of CF_2:, are more likely.[19] Their suggestion was based upon the fact that the thermal decomposition of the sodium chlorodifluoroacetate in diglyme was much faster in the presence of Ph_3P, thus requiring involvement of Ph_3P in the rate determining step of the mechanism, as well as to the fact that no cyclopropanation was observed to occur when 2,3-dimethyl-2-butene was added to the reaction mixture.

Herkes and Burton were successful in using essentially the same process with activated ketone substrates, such as trifluoroacetophenone (68% yield).[19] Burton subsequently introduced another approach for preparing this ylide intermediate, via reaction of CF_2Br_2 with triphenylphosphine at room temperature (Figure 1-11), which gave higher yields in reactions with activated ketones, but lower with aldehydes.[36,37] Again, this process did not require the intermediacy of difluorocarbene. In subsequent papers, they found that using $(Me_2N)_3P$ instead of Ph_3P led to high yields in reactions with non-activated ketones.[38,39] Another example of a difluorocarbene/Ph_3P procedure, using $(CF_3)_2Hg$ as the CF_2: source proved effective with non-activated ketones.[20]

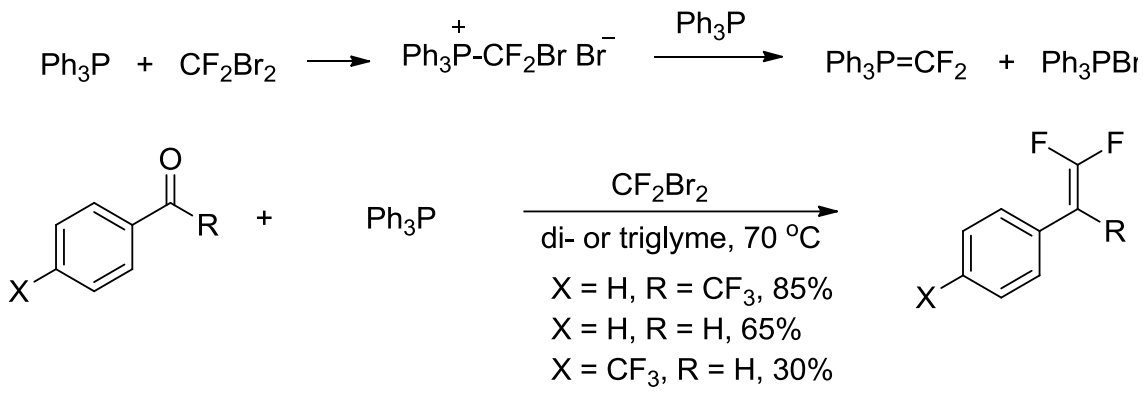


Figure 1-11. Burton procedure

1,1-Difluoroalkenes can also be synthesized from aldehydes and ketones via Horner-Wadsworth-Emmons/Horner-Wittig type[40,42] and Julia[42] or Julia-Kocienski protocols,[43] which require the preparation of fluorinated phosphonate, sulfinate or sulfone precursors, the use of strong bases and low temperatures. The latter reaction is exceptional in that it provides excellent yields from non-activated ketone substrates. These past successes led us to investigate new uses for MFDA. In particular, we wanted to use MFDA to produce 1,1-difluoroalkenes and have comparable yields to previous mentioned procedures.

CHAPTER 2
RESULTS

2.1 Initial Experiments To Prepare 1,1 Difluoroalkenes.

Initially, it was hoped that Ph_3P might be used both to demethylate MDFA and combine with the generated CF_2: to form the ylide. Thus initial experiments involved simply adding Ph_3P to MDFA in THF at 100 ^oC in the presence of benzaldehyde (Figure 2-1). Although about 5% of desired β,β-difluorostyrene was formed, the major product of this reaction, quite unexpectedly, was difluorotriphenylphosporane,[45,46] characterized unambiguously by its ^{19}F NMR signal, a doublet at δ - 41.1 ($^1J_{PF}$ = 664 Hz). This result indicated that the S_N2 nucleophilic demethylation reaction with Ph_3P was not effectively competing with the alternative mechanism that led to Ph_3PF_2 (most probably initiated by Ph_3P attack on the carbonyl oxygen of MDFA). [47]

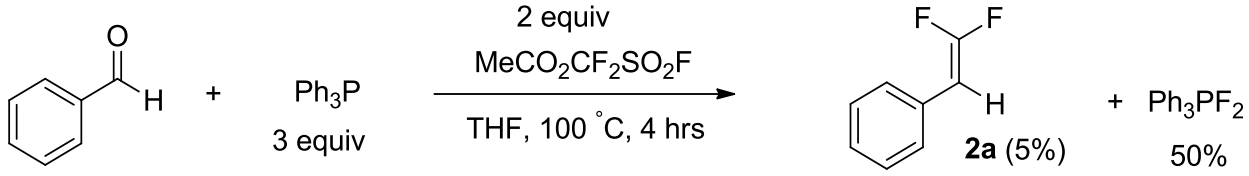


Figure 2-1. Initial Rrsults using Ph3P as both nucleophile and ylide component

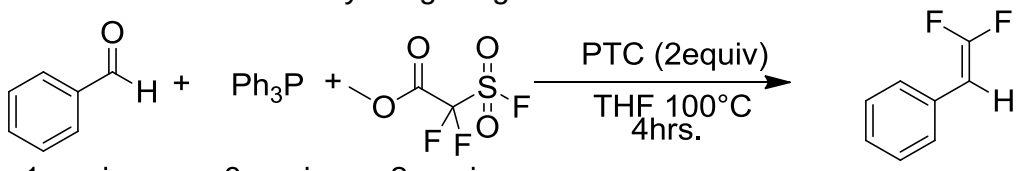
2.2 Demethylating Reagent

After initial attempts, efforts were made to find an appropriate demethylating reagent to initiate this reaction. Various iodide and bromide sources were investigated that hopefully would complete with the non-productive reaction instigated by Ph_3P alone. These experiments would mirror the initial experiment, except 2 equivalence of a demethylating reagent would be added to the reaction (Figure 2-1).

2.2.1 Experiments on the Effect of Phase Transfer Catalysts as Demethylating Reagent

Phase transfer catalysts (PTCs) were first chosen as suitable bromide and iodine sources because they display great solubility in most organic solvents and are commercially available. We investigated two types of PTCs which include phosphonium and ammonium salts. When comparing the phosphonium salts, tetrabutylphosphonium bromide (TBPB, Entry 1,Table 2-1) gave a higher yield than tetrabutylphosphonium iodide (TBPI, Entry 5, Table 2-1). These results were unexpected because previous research suggests iodide sources to be the best reagents to initiate these reactions. Alternatively, ammonium salts gave the opposite result. Tetrabutylammonium bromide (TBAB, Entry 2, Table 2-1) gave a lower yield than tetrabutylammonium iodide (TBAI, Entry 3, Table 2-1). Next, it was proposed that methyltriphenylphosphonium iodide could be formed *in situ* from the reaction of triphenylphosphine and methyiodide produced from iodide attacking the methyl group on MFDA. Therefore, methyltriphenylphosphonium iodide was synthesized and used for the demethylating reagent. This reaction produced a 35% yield of 1,1 difluorostyrene (Entry 4, Table 2-1).

Table 2-1. PTC as Demethylating reagent



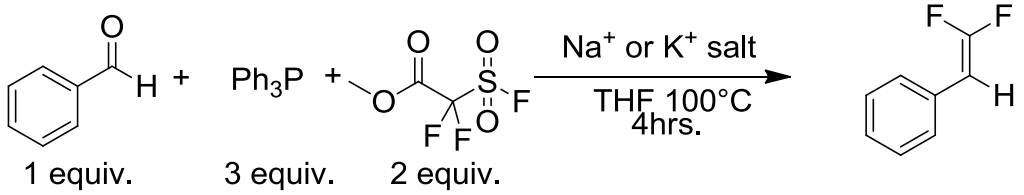
1 equiv. 3 equiv. 2 equiv.

Entry	Phase Transfer Catalyst(PTC)	Yeild
1	Tetrabutylphosphonium bromide (TBPB)	40%
2	Tetrabuylammonium bromide(TBAB)	28%
3	Tetrabutylammonium iodide (TBAI)	38%
4	MethylTriphenylphosphonium Iodide	35%
5	Tetrabutylphosphonium Iodide (TBPI)	27%

2.2.2 Experiments on the Effect of Potassium/Sodium Salts as Demethylating Reagents

After success with PTCs, other iodide and bromide sources such as sodium iodide, potassium iodide, and potassium thiocyanide were all examined as potential demethylating reagents. These salts are relatively inexpensive and commercially available. The same protocol was followed as previous experiments. Under these conditions, these salts did not display great solubility in organic solvents compared to the PTCs. Nevertheless, potassium iodide still gave a moderate yield of desired product (Table 2-2, Entry 1). Sodium iodide was the least soluble. This factor contributed to the lower yield (Table 2-2, Entry 3). Although potassium thiocyanide displayed moderate solubility, it gave the poorest results of these salts (Table 2-2, Entry 2). The thiocyanide anion prefer to attack the carbonyl directly, compared to the demethylation pathway.

Table 2-2. Sodium and potassium salts as demethylating reagents



1 equiv. 3 equiv. 2 equiv.

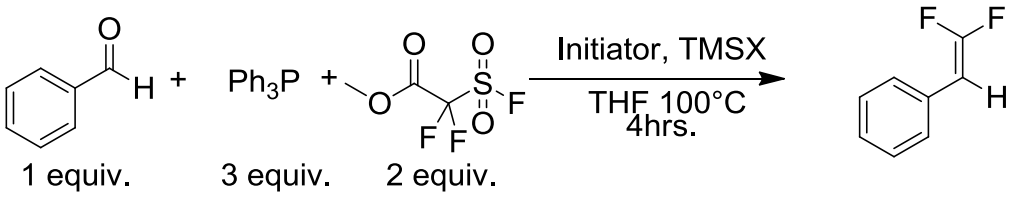
Entry	Na^+ or K^+ salt	Yeild
1	Potassium Iodide (KI)	34%
2	Potassium Thiocyanate (KSCN)	8%
3	Sodium Iodide (NaI)	18%

2.2.3 Other Experiments with Demethylation

Since PTCs and potassium/sodium salts were efficient demethylating reagents, it seemed plausible that catalytic amounts of these reagents could be used to initiate

these reactions. After initiation, free fluorine anion would be trapped by TMSX (X= I or Cl) and release X^- (I^- or Cl^-) that would push the reaction to completion. Reaction conditions were similar to the previous except 10% demethylating reagent and 2 equiv. on TMSX were added to the mixture. If only TMSX was used, no reaction occurred (Entry 1 & 2, Table 2-3). When catalytic amounts of tetrabutylammonium iodide with either TMSI or TMSCl, yields decreased (Entry 3 & 4, Table 2-3). Therefore, these reactions were not pursued further. In another attempt, zinc (II) iodide was used in the place of the demethylating reagents, but no desired product was obtained (Entry 5),

Table 2-3. Other attempt at demethylation of MFDA



1 equiv. 3 equiv. 2 equiv.

Entry	Initiator	TMSX	Yeild
1	none	X=Cl	0%
2	none	X=I	0%
3	Tetrabutylammonium iodide (TBAI)	X=Cl	26%
4	Tetrabutylammonium iodide (TBAI)	X=I	26%
5	ZnI_2	none	0%

2.3 Optimization of Experiments with Selected Demethylating Reagents

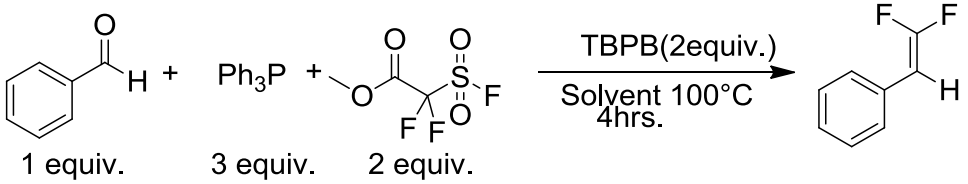
. In examining various sources of these nucleophiles, tetrabutyl phosphonium bromide (TBPB) and potassium iodide (KI) were found to give the best results, and they were chosen to be used in experiments designed to optimize conditions of the reaction.

2.3.1 Tetrabutylphosphonium Bromide (TBPB)

2.3.1.1 TBPB with alternating solvents, concentration and temperature

Since this reaction worked well in 10 mL of the polar aprotic solvent THF (Entry 1, Table 2-4), other solvents with similar characteristics were selected to optimize the reaction. Acetonitrile and 1, 4-dioxane were both tested under similar conditions as previously mentioned (Entry 2 & 3, Table 2-4). The yields decreased in acetonitrile and no reaction occurred in 1, 4-dioxane. Next the concentration of the solution was examined. We hypothesized that with less solvent and thus a more concentrated solution, that yields would increase. Since THF gave the best results, reactions were run with 5 mL and 2 mL of this solvent (Entry 4 & 5, Table 2-4). Initial yields decreased slightly to 37% in 5 mL but significantly in 2 mL (11%). Next, temperatures were lowered to 80˚C for the 10 mL and 5 mL THF reaction. The 10 mL reactions were similar to previous results, but for 5 mL reaction, increased yields of 50% were observed (Entry 1 and 2, Table 2-5). Lowering the temperature was not beneficial to the overall yields of this reaction. This could be due to poor decomposition of MFDA by TBAB at lower temperatures.

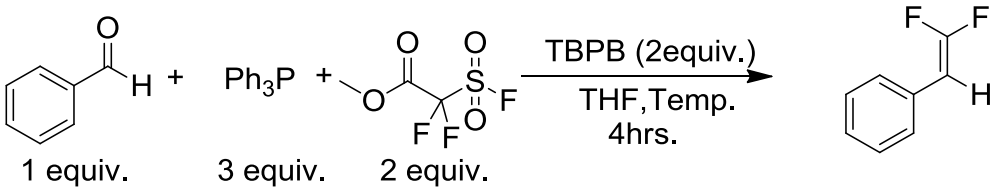
Table 2-4. Effect of solvent and concentration with TBAB



1 equiv. 3 equiv. 2 equiv.

Entry	Solvent	Conc.(mL)	Yield
1	Tetrahydrofuran(THF)	10	40%
2	1,4 Dioxane	10	0%
3	Acetonitrile	10	26%
4	Tetrahydrofuran(THF)	5	37%
5	Tetrahydrofuran(THF)	2	0%

Table 2-5. Effects of temperature and concentration with TBAB



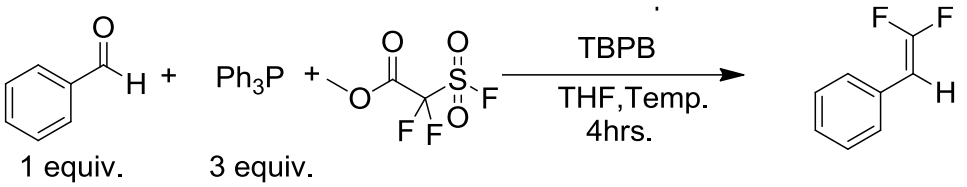
1 equiv. 3 equiv. 2 equiv.

Entry	Temperature	Conc.(mL)	Yield
1	80°C	10	38%
2	80°C	5	50%
3	70°C	5	21%

2.3.1.2 Effect of equiv. MFDA and TBPB

To determine if the amount of MFDA and TBPB added affected the overall yield, experiments were designed to test these factors. First at 100˚C in 5 mL of THF, 3 equiv. of both MFDA and TBPB were added, but yields decreased to 26%. The same observation occurred at 80˚C under the same conditions (Entry 3, Table 2-6). If TBPB was increased to 2.5 equiv. and MFDA left at 2 equiv., the reaction again gave lower yields (Entry 2, Table 2-6). The same was observed when MFDA was decreased but TBPB was constant (Entry 4, Table 2-6). This suggested that the overall reaction conditions with TBPB were optimal at 80˚C in 5 mL THF with the other conditions remaining the same as the initial experiment.

Table 2-6. Effect of concentration of MFDA and temperature



1 equiv. 3 equiv.

Entry	MFDA(equiv.)	TBAB(equiv.)	Temp.(°C)	Yield
1	3	3	100	26%
2	2	2.5	100	18%
3	3	3	80	30%
4	1.75	2	80	45%

2.3.1.3 Expanded substrate scope with TBPB

Due to success with benzaldehyde, we examined aliphatic aldehydes and ketones. Under optimal conditions and hexanal as a substrate, the overall reaction gave a yield of 30%. On the other hand, ketones such as tert-butylketone and 3-pentanone were unreactive under these conditions.

2.3.2 Potassium Iodide (KI)

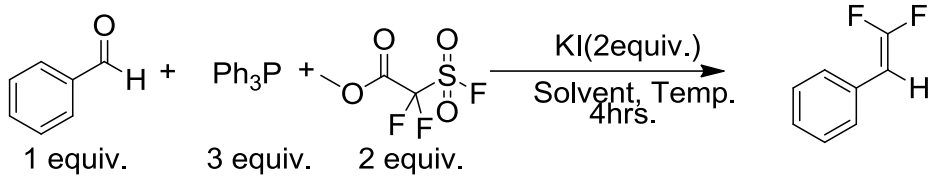
Since potassium iodide gave highest yields of the potassium/sodium salts, efforts were made to optimize these conditions.

2.3.2.1 Potassium iodide with alternating solvents, concentration and temperature

After witnessing the affect solvent, concentration, and temperature had on previous reactions, we decide to vary these conditions to optimize this reaction. Since yields improved when solvent amount was decreased from 10 mL to 5 mL, all experiments were run using the latter. Under initial conditions, the highest yields obtained with KI were 34%. Two experiments were set up at 80˚C using acetonitrile and tetrahydrofuran. The overall yield increased in both cases, the former (45%) and the latter (40%) (Table 2-7). Next, temperatures were lowered to 70˚C, and these reactions

were repeated. Acetonitrile gave the best results, but tetrahydrofuran also showed improvement (Entry 2 & 5, Table 2-7). Temperatures below 70˚C did not increase yields. Toluene was explored as a solvent, but yields obtained were low.

Table 2-7. Effects of solvent and temperature with potassium iodide



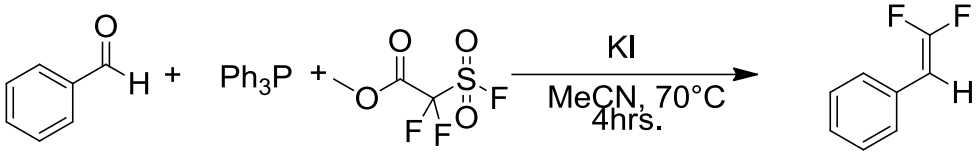
1 equiv. 3 equiv. 2 equiv.

Entry	Solvent	Temp.	Yield
1	Acetonitrile(MeCN)	80°C	45%
2	Toluene	70°C	26%
3	Acetonitrile(MeCN)	70°C	64%
4	Tetrahydrofuran(THF)	80°C	40%
5	Tetrahydrofuran(THF)	70°C	55%

2.3.2.2 Potassium iodide with alternating equiv. of MFDA and KI

In the first set of experiments, KI would be varied using acetonitrile as the solvent at 70˚C. All other variables would remain the same. Increasing the amount of KI had a negative impact on the yield overall (Table 2-8). If the amount of KI was decreased, the amount of MFDA at the end of the reaction increased. The second set of experiments would consist of keeping KI constant, but varying the amount of MFDA(Table 2-8). When MFDA was lowered to 1.75 equiv. the overall yield increased to 75%. However, using less MFDA than this led to a decreased yield.

Table 2-8. Effects of concentration of MFDA and potassium iodide



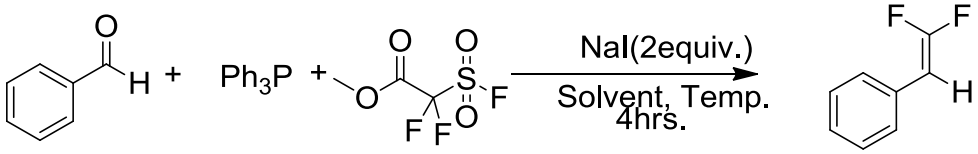
1 equiv. 3 equiv.

Entry	MFDA(equiv.)	KI(equiv.)	Yield
1	2	3	24%,36%
2	2	2.5	56%
3	2	2	64%
4	1.75	2	75%
5	1.5	2	64%
6	1.25	2	64%

2.3.3 Other Optimization Attempts

Due to the lower cost of sodium iodide (NaI) compared to KI, efforts were made to optimize conditions with this demethylating reagent. In an attempt to increase solubility of NaI in organic solvents, experiments were performed in tetrahydrofuran, acentonitrile, and 1,4 dioxane. Solubility increased, but the reaction did not perform well at 100˚C. Therefore temperatures were lowered and the yield increased to 32% in acetonitrile (Table 2-9, Entry 1). Further optimization did not improve results.

Table 2-9. Effect of solvents and temperature with sodium iodide



1 equiv. 3equiv. 1.75 equiv.

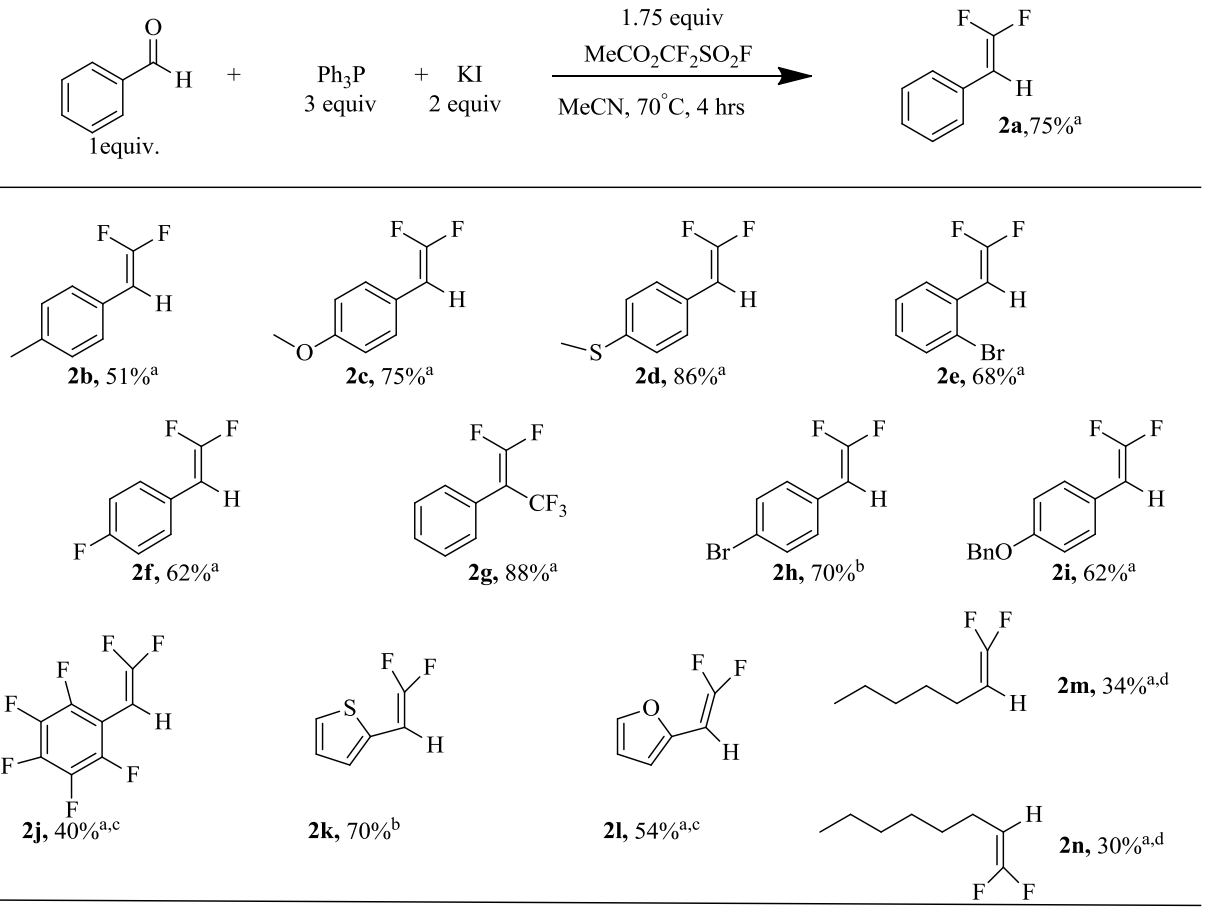
Entry	Solvent	Temp.	Yield
1	Acetonitrile(MeCN)	70°C	32%
2	Tetrahydrofuran (THF)	70°C	<10%
3	1,4 Dioxane	70°C	18%
4	Acetonitrile (MeCN)	80°C	<10%
5	Acetonitrile (MeCN)	50°C	trace

2.4 Optimized Reaction Conditions and Expanded Substrate Scope

Once best conditions were determined, a variety of aldehydes and activated ketones were examined to determine the scope of the reaction. The results of these

reactions are found in Table 2-10. These results indicate that MDFA gives the desired product in high yield for substituted benzaldehydes, activated ketones, and electron-rich heterocyclic aldehydes. Results were less satisfactory for aliphatic aldehydes or highly electron deficient benzaldehydes, or the highly electron deficient 2- or 3-pyridinecarboxaldehyde under standard conditions. 4-(Dimethylamino)-benzaldehyde also failed as a substrate. Small amounts of the above-mentioned difluoromethyl phosphonium co-product always accompanied formation of the desired 1,1-difluoroalkenes.

Figure 2-2. Yields of 1,1 difluoroalkenes from respective subtrates

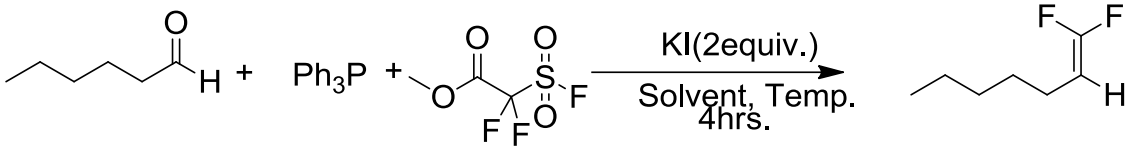


[a]Yield determinde by ^{19}F NMR and Trifluorotoluene as the standard.[b]Isolated Yields. [c] Performed at optimized conditions but with 2 equiv. of MDFA.[d] Performed at optimized conditions but with 2 equiv. of MDFA at 80°C

2.4.1 Alkyl Aldehydes

Alkyl aldehydes gave poor results under optimized conditions. The best results are summarized in Table 2-10. Hexanal, heptanal and octanal were chosen to explore these reactions further because of their higher boiling point compared to shorter chained aldehydes. Overall, the reactions with hexanal, heptanal, and octanal were not dependent on solvent choice. Acetonitrile was the best solvent for these three aldehydes. On the other hand, an increase in temperature and MFDA did increase the yield of both hexanal and heptanal. These results are summarized in Table 2-11, Table 2-12, and Table 2-13.

Table 2-10. Optimization of substrate hexanal



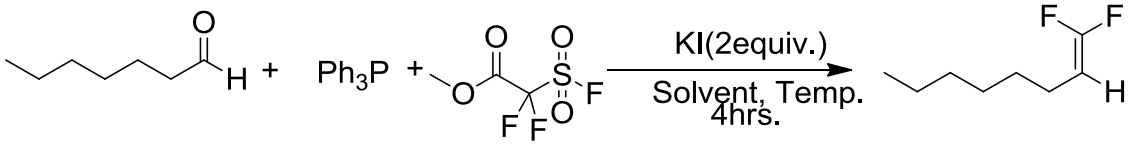
1 equiv. 3 equiv. 1.75 equiv.

2m

Entry	Solvent	Temp.	Yield
1	Acetonitrile(MeCN)	70°C	15%
2	Tetrahydrofuran (THF)	70°C	16%
3	1,4 Dioxane	70°C	13%
4	Acetonitrile (MeCN)	80°C	13%
5	Acetonitrile (MeCN)[a]	80°C	34%

[a] Using 2 equiv. of MFDA

Table 2-11. Optimization of substrate heptanal

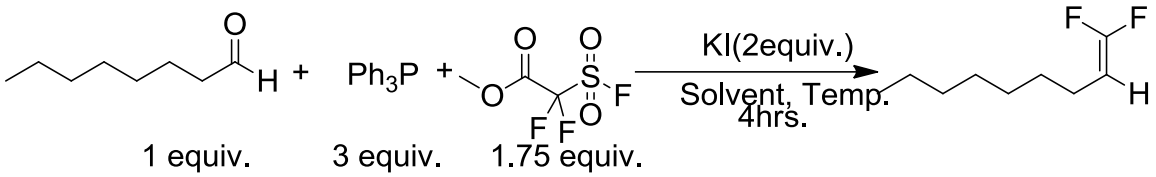


1 equiv. 3 equiv. 2 equiv.

2n

Entry	Solvent	Temp.	Yield
1	Acetonitrile (MeCN)	70°C	30%
2	Tetrahydrofuran (THF)	75°C	trace%
3	Tetrahydrofuran (THF)	80°C	>10%

Table 2-12. Optimization of substrate octanal

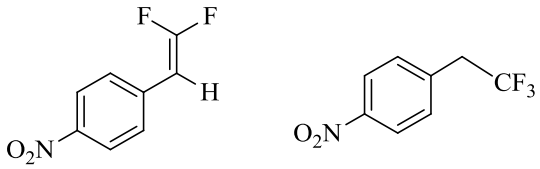


1 equiv. 3 equiv. 1.75 equiv.

Entry	Solvent	Temp.	Yield
1	Acetonitrile (MeCN)	70°C	18%
2	Acetonitrile (MeCN) with NaI	70°C	18%
3	Acetonitrile (MeCN)	80°C	trace

2.4.2 4-Nitrobenzaldehyde

In the reaction with 4-nitrobenzaldehyde, desired product (**3a**) was obtained in low yield. We considered that this might be due to poor solubility of the starting material in CH_3CN. An attempt to increase the yield by changing solvents resulted in the formation of 4-nitro-(2,2,2-trifluoroethyl)benzene (**3b**) (Figure 2-2). Compound **3b** presumably derives from nucleophilic attack by fluoride ion at the terminal CF_2 group of the initial product formed, **3a**. Such a reaction has precedent and indeed has been demonstrated to be a reasonable method for synthesizing 2,2,2-trifluoroethyl aromatics from β,β–difluorostyrenes[29,30]



3a,15%[a] **3b,** 37%[b] 50%[c]

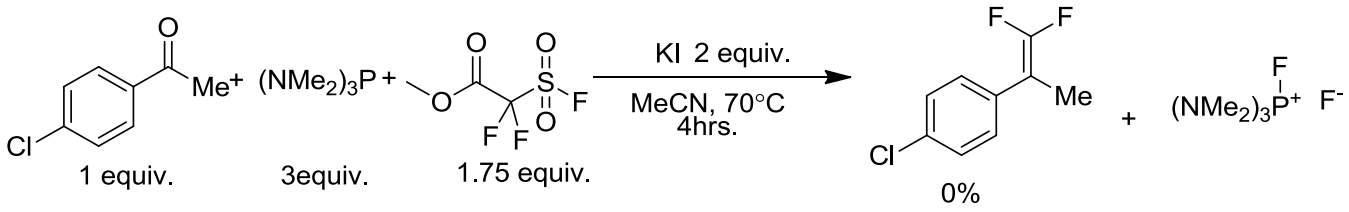
[a]Reaction at optimized conditions. [b]Reaction at optimized conditions in THF. [c]Reaction at optimized condition in 1,4 Dioxane

Figure 2-3. Reaction with 4-Nitro Benzaldehyde

2.4.3 Aromatic and Aliphatic Ketones

Under optimized conditions when triphenylphosphine was used to form the difluoromethyl ylide, no product could be observed by ^{19}FNMR with aromatic or aliphatic

ketones. Previous work suggested the use of tri(dimethyamino)phosphine, which is better suited for Wittig reactions with aliphatic ketones and aromatic ketones. Two substrates, cyclohexanone and 4 chloroacetophenone were used for these experiments. In both cases, only trace amount of product were observed by ^{19}FNMR. The main product appeared to be difluoro, tri(dimethylamino)phoshonium salt $[(NMe_3)PF]^+F^-$. This could be due to the high reactivity of $(NMe_3)P$. This result indicated that the S_N2 nucleophilic demethylation reaction of KI was not effectively competing with the alternative mechanism that led to $(NMe_3)PF_2$ (most probably initiated by $(NMe_3)P$ attack on the carbonyl oxygen of MDFA).[30]



*The same result was observed with cyclohexanone.

Figure 2-4. Reaction using tri(dimethylamino) phosphine under optimized conditions

CHAPTER 3
DISCUSSION

3.1 Mechanism and Calculations

Although the involvement of difluoromethylene triphenylphosphonium ylide, $Ph_3P{=}CF_2$, as the key intermediate in the Wittig-type reactions reported by Fuqua, Burton and many others, as discussed above, has never been questioned, the nature and stability of this intermediate, in particular the strength of binding between the Ph_3P and CF_2: entities has definitely been an issue addressed in a number of papers. Our specific results appear to be unambiguously derived from the generation of difluorocarbene, *followed by its combination with Ph_3P to form the ylide*, $Ph_3P{=}CF_2$, with subsequent Wittig reaction of this ylide with aldehydes and ketones by the usual mechanism to form 1,1-difluoroalkenes. Therefore, we considered that it would be worthwhile to carry out a computational reexamination of the binding and structure of this ylide.

Difluorocarbene has, itself, been subject of several computational studies [49-51] with the large energy difference between its singlet (S) and triplet (T) states (with the singlet being the ground state) creating particular interest in this carbene. When compared with the CH_2 carbene, replacement of hydrogen with fluorine has been shown to contribute significantly to the stabilization of the singlet versus the triplet state.

These three carbenes can be considered to be “starting materials,” which, when combined with triphenylphosphine, form their respective triphenylphosphonium ylides. All three of these ylides have been used as Wittig reagents, but, in contrast to methylene triphenylphosphonium ylide,[52] neither the CHF or the nCF_2 ylides are sufficiently stable to be isolated.[19,53]

In 1986, using *ab-initio* molecular orbital theory (SCF level),[54] Dixon and Smart examined the interaction between the CF_2 (S) and PH_3. At this level of theory, it was found that the bond length between the CF_2 carbon and the phosphorous was 3.54 Å, which is essentially two separate species with little interaction. In addition, the binding energy between the CF_2 and the PH_3 was calculated to be only 1.2 kcal/mol, which was consistent with Burton's evidence for facile dissociation of the CF_2=PPh_3 ylide.[54] However, calculations by Allen and co-workers in 1988 at the HF/3-21G* level reported that the C-P bond length of the same molecule was 1.635 Å[55], which could be interpreted as a double bond considering that their calculations for the C-P bond length of CH_2-PH_3 was 1.646 Å. Unfortunately, the authors did not mention or discuss the discrepancy between their results and those of Dixon and Smart.

Because of the apparent weak interaction between the CF_2(S) and PH_3 reported by Dixon and Smart, we considered that the use of density functionals, and more important those that include medium range attractive interactions such as M06-2X,[56-58] might provide greater insight in calculating the structures and energies of these types of molecules.

3.2 Ground State Calculations of the Single and Triplet State for CH_2, CHF and CF_2 Carbenes

Ground state calculations of the singlet and triplet state for the CH_2, CHF and CF_2 carbenes were carried out and the results were compared with available experimental data. Both structures and S-T energy gaps (Table 3-1) were found to be in good agreement with available experimental and previous computational results.[49-51]

Table 3-1. Geometrical data and energy gaps for various methyl carbenes at the M06-2X/6-311+G(2df,2p) level.[a,b]

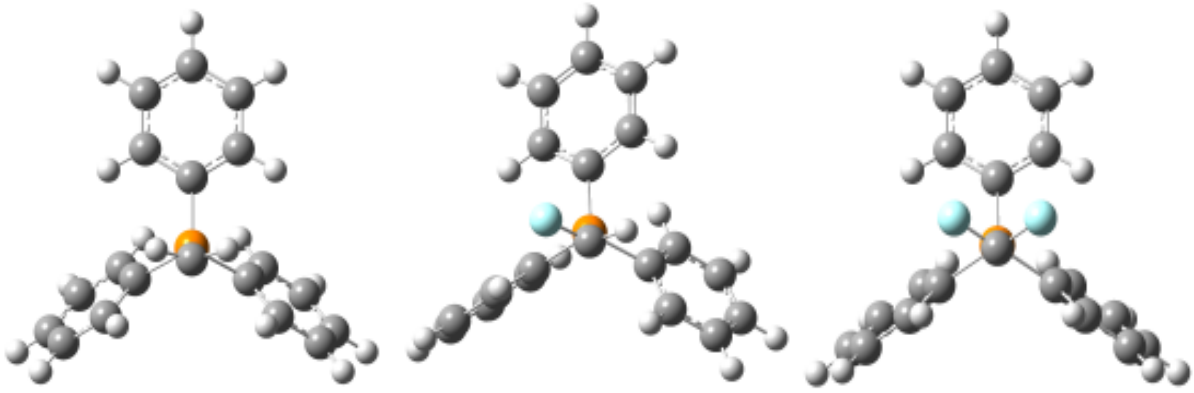
	C-H (Å)	C-F (Å)	X-C-Y (Degrees)	DE (T-S) (kcal/mol)
CH2(S)	1.106 (1.107)	--	102.0 (102.4)	-11.26 (-9.37)
CH2(T)	1.076 (1.075)	--	134.3 (133.9)	
CHF(S)	1.118 (1.138)	1.299 (1.305)	102.3 (103.5)	9.59 (8.0-14.60)
CHF(T)	1.083 (1.088)	1.307 (1.304)	121.9 (121.2)	
CF2(S)	--	1.293 (1.304)	104.5 (104.8)	54.25 (56.60)
CF2(T)	--	1.307 (1.298)	118.9 (118.1)	

[a] In parenthesis are experimental values or difference-dedicated configuration interaction results, available from [32] and references therein; [b] X= H,F ; Y = H,F.

As expected, all singlet carbenes have greater bond lengths and smaller X-C-Y angles than the triplet carbenes, consistent with the presumed sp^2 and sp hybridization, respectively. Although energy gaps have been calculated more precisely with different density functionals and basis sets,[51] our calculated energy gaps between the triplet and singlet carbenes using the M06-2X function are close to earlier reported values. Our structural calculations are also consistent with the experimental data reported for CH_2.[42,43]

3.3 Calculated Ground State Structures of the CH_2-PPh_3, CHF-PPh_3 and CF_2-PPh_3 Ylides

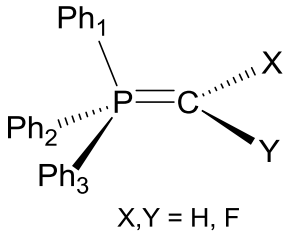
With our calculated ground state structures and energies of the singlet carbenes in excellent agreement with both previous theory and experiment, the ground state structures of the CH_2-PPh_3, CHF-PPh_3 and CF_2-PPh_3 ylides were then calculated. These structures are depicted in Figure 3-1, with the data being provided in Table 3-2.



(a) **(b)** **(c)**

Figure 3-1. Depictions of the calculated structures of (a) CH_2=PPh_3, (b) CHF=PPh_3, and (c) CF_2=PPh_3

Table 3-2. Geometrical data for various phosphonium ylides at the M06-2X/6-311+G(2df,2p) level[a]



	Distance (Å)					Angle (Degrees)		
	P-C	**C-H**	**C-F**	**P-Ph(2, 3)**	**P-Ph1**	**X-C-Y**	**P-C-H**	**P-C-F**
CH_2-PPh_3	1.674 (1.662)	1.082 (0.932)	--	1.821 (1.816)	1.847 (1.839)	116.0 (121.9)	116.2 (118.8)	--
CHF-PPh_3	1.707	1.085	1.391	1.814	1.842	111.8	115.6	115.3
CF_2-PPh_3	1.815	--	1.378	1.808	1.82	105.1	--	109.2

[a] Experimental values in parenthesis when available [33]

In comparing the structures of all three ylides, one can see that the methylene carbon of CH_2-PPh_3 has the greatest sp^2 character, with this carbon taking on

increasing sp^3 character as each H is replaced by F. These changes are reflected in the longer C-P bonds and the greater pyramidalization as one proceeds from the CH_2 to the CHF to the CF_2 ylide. Although our calculated bond length for the C-P bond in CF_2=PPh_3 (1.815 Å) is much shorter than the 3.54 Å calculated by Dixon and Smart for CF_2-PH_3, it is significantly longer than the 1.635 Å calculated by Allen. The X-C-Y angle is observed to decrease as the number of fluorine increases, a trend consistent with the change from sp^2 to sp^3 hybridization at the methylene carbon.

In order to quantify the stability of the CF_2-PPh_3 ylide, the enthalpy and the free energy of the reaction between the singlet carbene and triphenylphosphine to produce the ylide was calculated (Figure 3-2). Both gas phase and solvent were considered and the data is shown in Table 3-3.

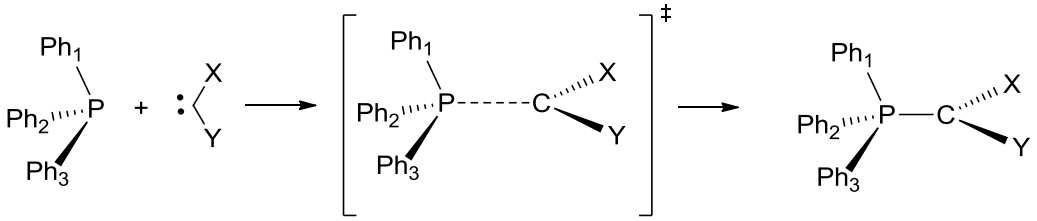


Figure 3-2. Calculated reaction for formation of ylides from carbene and Ph_3P

Table 3-3 Relative 298 K free energies (kcal/mol) for CH_2, CHF and CF_2 triphenylphosphonium ylides [a]

	CH_2-PPh_3	CHF-PPh_3	CF_2-PPh_3	CF_2-PPh_3-TS
ΔH (Gas)	-79.02	-43.57	-6.80	-3.21
ΔG (Gas)	-67.15	-30.85	5.42	8.38
ΔH (Solv)[b]	-79.12	-46.55	-14.42	-4.53
ΔG (Solv)[b]	-69.15	-35.73	-4.10	5.17
Dipole	2.96	4.42	5.78	

[a] Energies in kcal/mol. [b] Solv = Acetonitrile c. Dipole in Debye

In the gas phase, formation of both the CH_2 and the CHF ylide are highly exothermic and exergonic, whereas for the CF_2 ylide the reaction is exothermic, but endergonic. However, since the dipole moment of the CF_2-PPh_3 ylide is much larger than those of the CH_2 and CHF ylides, this suggests that the CF_2 ylide might be more favored than the others in polar solvents. When acetonitrile was included as solvent in the calculation, formation of the CH_2 and CHF ylides remained highly exothermic and exergonic, but the values were not much different from those for the gas phase. On the other hand, in the polar solvent, formation of the CF_2 ylide proved to be not only exothermic, but also exergonic to the extent of -4.1 kcal/mol. These results suggest that formation of the CF_2-PPh_3 ylide would be favored in polar solvents, and it should thus be possible for it to participate in Wittig reactions.

In order to have a better understanding of the stability and behavior of the CF_2-PPh_3 ylide, the transition state for the C-P bond formation/dissociation was calculated (Figure 3-2, Table 3-3), and the reaction was seen to have a relatively flat potential energy surface at 298K, with a calculated activation free energy in acetonitrile of 5.17 kcal/mol, relative to the singlet CF_2 carbene and PPh_3 at infinite separation. Thus the dissociation of the ylide to its carbene and phosphine components would only have to

overcome a 9.27 kcal/mol barrier. This is consistent with the kind of reversibility of ylide formation that was observed by Burton[53].

CHAPTER 4
CONCLUSION

In conclusion, it has been found that under moderate conditions, in the presence of a demethylating reagent such as iodide, methyl 2,2,-difluoro-2-(fluorosulfonyl)acetate releases difluorocarbene, which in the presence of triphenylphosphine forms difluoromethylene triphenylphosphonium ylide. When the process is carried out in the presence of aldehydes or activated ketones, an *in situ* Wittig-type reaction of the ylide with the carbonyl reactants produces 1,1-difluoroalkenes in good yield. Calculations indicated that the ylide intermediate was only weakly bound, but was sufficiently stable to propose its involvement in the kind of usual Wittig reaction expected of phosphonium ylides.

CHAPTER 5
EXPERIMENTAL

5.1 General Information

NMR spectra were obtained in $CDCl_3$ using TMS and $CFCl_3$ as the internal standards for $^{1}H/^{13}C$ NMR and ^{19}F NMR spectra, respectively. The identities of known compounds **2a−2c, 2e-2h, 2j, 2l-2n,** and **3** were initially determined on the basis of their characteristic fluorine NMR spectra, but were also confirmed by examination of their proton spectra. New compounds **2d, 2i,** and **2k** were fully characterized on the basis of their ^{1}H, ^{13}C, and ^{19}F NMR spectra, and by their exact masses as determined by HRMS.

5.2 General Procedure or 1,1-Difluoroalkenes Reactions.

5.2.1. 4-Bromo- (2,2-difluoroethenyl)benzene

A 250 mL, three necked round bottomed flask was equipped with a stir bar. The vessel was then fitted with a condenser topped by a T-tube with slow flow of N_2, and then sealed with septa. The vessel was flamed dried and then allowed to cool to room temperature. Under the inert, nitrogen atmosphere, acetonitrile (75 mL) was added to the vessel, and the temperature was increased to 70 °C. Then triphenylphosphine (34.5 g, 135 mmol, 3 equiv), potassium iodide (15.0 g, 90 mmol, 2 equiv), and 4-bromobenzaldehyde (9.80 g, 45 mmol, 1 equiv) were added and let stir for 30 min. Methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (MDFA) (19.7 g, 78.75 mmol,1.75 equiv) was then added slowly over a period 1 hr. The resulting mixture was stirred for three hours, a nitrogen atmosphere being maintained until the end of the reaction. Then the reaction was quenched with water and extracted with ethyl acetate. Trifluorotoluene (15 mmol) was added as internal standard and the yield of the crude reaction was measured by ^{19}F NMR (72%). The ethyl acetate was then removed by rotary

evaporation to produce a black, semi-solid slurry. Product was isolated from the slurry and separated from residual triphenylphosphine by extraction 5 times with hexane (100 mL) The combined hexane extracts were combined and concentrated. Additional impurities were removed via column chromatography using a 95:5 mixture of hexanes: methylene chloride to obtain pure product: (6.9g (70%), clear liquid); ^{1}H NMR, δ 7.48 (d, *J* = 9.1 Hz , 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 5.25 (dd, *J* = 25 Hz, *J* = 3.1 Hz, 1H); ^{19}F NMR, δ − 81.8 (dd, *J* = 30.1 Hz, *J* = 26.5 Hz, 1F), − 83.7 (dd, *J* = 29.1 Hz, *J* = 3.8 Hz, 1F). The above data is in accord with those reported in the literature.[44]

5.2.2 (2,2-Difluoroethenyl)benzene (2a)

^{1}H NMR δ 5.40 (dd, $^{3}J_{FH}$ = 26.6 & 4.1 Hz, 1H), 7.55 (m, 5H); ^{19}F NMR δ − 82.9 (dd, *J* = 33.6 Hz, 27.4 Hz, 1F), − 84.8 (d, *J* = 31.7 Hz, 1F).[19,61,62]

5.2.3 4-Methyl- (2,2-difluoroethenyl)benzene (2b)

^{1}H NMR d 5.25 ($^{3}J_{FH}$ = 26.4 & 4.2 Hz, 1 H), 7.16 (d, $^{3}J_{HH}$ = 8.4 Hz, 2H), 7.24 (d, $^{3}J_{HH}$ = 8.4 Hz, 2H); ^{19}F NMR δ −84.9 (dd, *J* = 38.1 Hz, 28.2 Hz, 1F), −86.9 (d, *J* = 37.5 Hz, 1F)[61-63]

5.2.4 4-Methoxy-(2,2-difluoroethenyl)benzene (2c)

^{1}H NMR d 3.83 (s, 3H), 5.24 (dd, $^{3}J_{FH}$ = 26.3 & 4.5 Hz, 1H), 6.91 (d, $^{3}J_{HH}$ = 8.6 Hz, 2H), 7.29 (d, $^{3}J_{HH}$ = 8.6 Hz, 2H); ^{19}F NMR δ −87.3 (dd, *J* = 42.3Hz, *J* = 26.8 Hz, 1F), −89.2 (d, *J* = 41.3 Hz,1F)[61-63]

5.2.5 4-Thiomethyl-(2,2-difluoroethenyl)benzene (2d)

^{1}H NMR, δ 2.48 (s, 3H), 5.23 (dd, $^{3}J_{FH}$ = 25.5 & 3.6 Hz, 1H), 7.23 (m, 4H); ^{19}F NMR, δ − 85.3 (dd, *J* = 34.9Hz, *J* = 25.6 Hz, 1F), −87.2 (d, *J* = 35.3 Hz,1F); GC−MS (exact mass, DART-TOF-MS): calcd $C_9H_9F_2S$ $(M)^+$ 187.0393, found 187.0399.

5.2.6 2-Bromo-(2,2-difluoroethenyl)benzene (2e)

^{1}H NMR δ 5.24 (dd, $^{3}J_{FH}$ = 26.1 & 3.9 Hz, 1H), 7.04 (m, 2H), 7.29 (m, 2H); ^{19}F NMR: δ −84.3 (dd, *J* = 25.9Hz, *J* = 3Hz, 1F), −85.3 (dd, *J* = 28 Hz, , *J* = 2 1F).[64]

5.2.7 **4-Fluoro-(2,2-difluoroethenyl)benzene (2f)**

^{1}H NMR δ 5.24 (dd, $^{3}J_{FH}$ = 26.1 & 3.6 Hz, 1H), 7.02 (m, 2H), 7.25 (m, 2H); ^{19}F NMR: δ −85.1 (dd, *J* = 36.6Hz, *J* = 28.2 Hz, 1F), −87.2 (dt, *J* = 33.8 Hz, *J*=3.7,1F).[18,62]

5.2.8 4-Trifluoromethyl-(2,2-difluoroethenyl)benzene (2g)

^{19}F NMR: δ -77.9 (m,1F),-76.8 (qq, J=10.4Hz, J=24.3Hz, J=33.3Hz, J= 46.5Hz, 1F) ,-59.7 (dd, *J* = 10.4 Hz, *J* = 24.3 Hz, 3F)[64]

5.2.9 4-Benzyloxy-(2,2-difluoroethenyl)benzene (2i)

^{1}H NMR, δ 5.21 (dd, $^{3}J_{FH}$ = 26.1 & 3.6 Hz, 1H), 6.07 (s, 3H), 6.95 (m, 2H), 7.33-7.44 (m, 5H); ^{19}F NMR, δ − 87.1 (dd, $^{2}J_{FF}$ = 42.6Hz, $^{3}J_{HF}$ = 25.9 Hz, 1F), − 88.8 (d, $^{2}J_{FF}$ = 40.6 Hz,1F); GC−MS (exact mass, DART-TOF-MS): calcd $C_{15}H_{13}F_{2}O$ $(M)^{+}$ 247.0934, found 247.0933.

5.2.10 2,3,4,5,6-Pentafluoro-(2,2-difluoroethenyl)benzene (2j)

19F NMR δ -77.3 (m, 1F), -81.1 (s, 1F), -141.3(t, J) 17.8 Hz, 2F), -157.4 (t, J) 21Hz, 1F), -164.6 (m, 2F).[30]

5.2.11 1-(2,2-Difluoroethenyl) thiophene (2k)

^{1}H NMR, δ 7.25 (t, *J* = 1 Hz , 1H), 7.24(d, *J* = 1 Hz, 1H), 7.0 (d, *J* = 3 Hz, 1H), 5.55 (dd, $^{3}J_{HF}$ = 24 Hz, $^{3}J_{HF}$ = 2.1 Hz, 1H). ^{19}F NMR, δ − 80.7 (dd, $^{2}J_{FF}$ = 32.4 Hz, *J* = 1 Hz, 1F), −87.9 (dd, $^{2}J_{FF}$ = 32.4 Hz, *J* = 1.7 Hz, 1F). ^{13}C NMR: δ 160.0 (s), 132(s), 127 (s), 126

(s), 125 (s), 77(s); GC−MS (exact mass, DART-TOF-MS): calcd $C_6H_5F_2S$ $(M + H)^+$, 147.0080, found 147.0082.

5.2.12 1-(2,2-Difluoroethenyl)furan (2l)

^{19}F NMR: δ −85.1 (dd, $^3J_{HF}$ = 31.8 Hz, $^2J_{FF}$ = 29.3 Hz, 1F), −86.7 (d, $^2J_{FF}$ = 29.3 Hz,1F)[18]

5.2.13 1,1-Difluoro-1-heptene (2m)

^{19}F NMR: δ-85.1 (dd, , *J* = 35.3Hz, *J* = 28.2 Hz, 1F), −86.8 (d, *J* =32.2Hz,1F) [61]

5.2.14 1,1-Difluoro-1-octene (2n)

^{19}F NMR: δ -91.8 (d , *J* = 51.6 Hz, 1F), −94.5(dd, *J* =28.2 Hz, *J*=26.7Hz 1F)[62]

5.2.15 4-Nitro-(2,2-difluoroethenyl)benzene (3a)

^{19}F NMR: δ -80.1 (dd, *J* =26.2Hz, *J*=18.5Hz 1F) −81.4. (d) , *J* = 18 Hz, 1F) [18,62]

5.2.4 4-Nitro-(2,2,2-trifluoroethyl)benzene (3b)

^{19}F NMR: δ -66.5 (t, *J* = 10.7 Hz, 3F) [18,66]

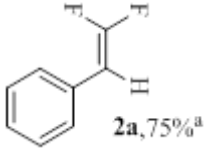
5.3 Computational Method

All quantum chemical calculations were performed using Gaussian 09 Rev. A.02 [65] at the M06-2X/6-311+G(2df,2p) level of theory[56-58], including frequency calculation to identify the structures as either ground state or transition state. All calculated transition states presented one and only one negative frequency.

The influence of acetonitrile as a solvent was evaluated using the SMD continuum solvation model[68]. Free energies in solution were calculated by summing the gas phase thermal contributions with the single point SMD/M06-2X energies. Correction from the

gas to the solution phase was made by adding -1.9 kcal/mol (RT Ln([Sln]/[Gas])) to the free energy of each molecule.

APPENDIX A
NMR Spectra of Corresponding Compounds



2a, 75%[a]

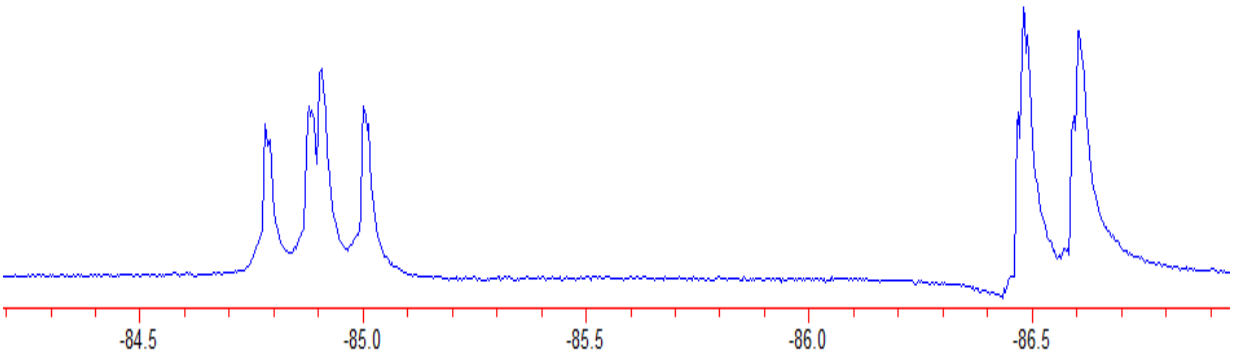


Figure A-1. ^{19}F NMR of (2,2-Difluoroethenyl)benzene (2a)

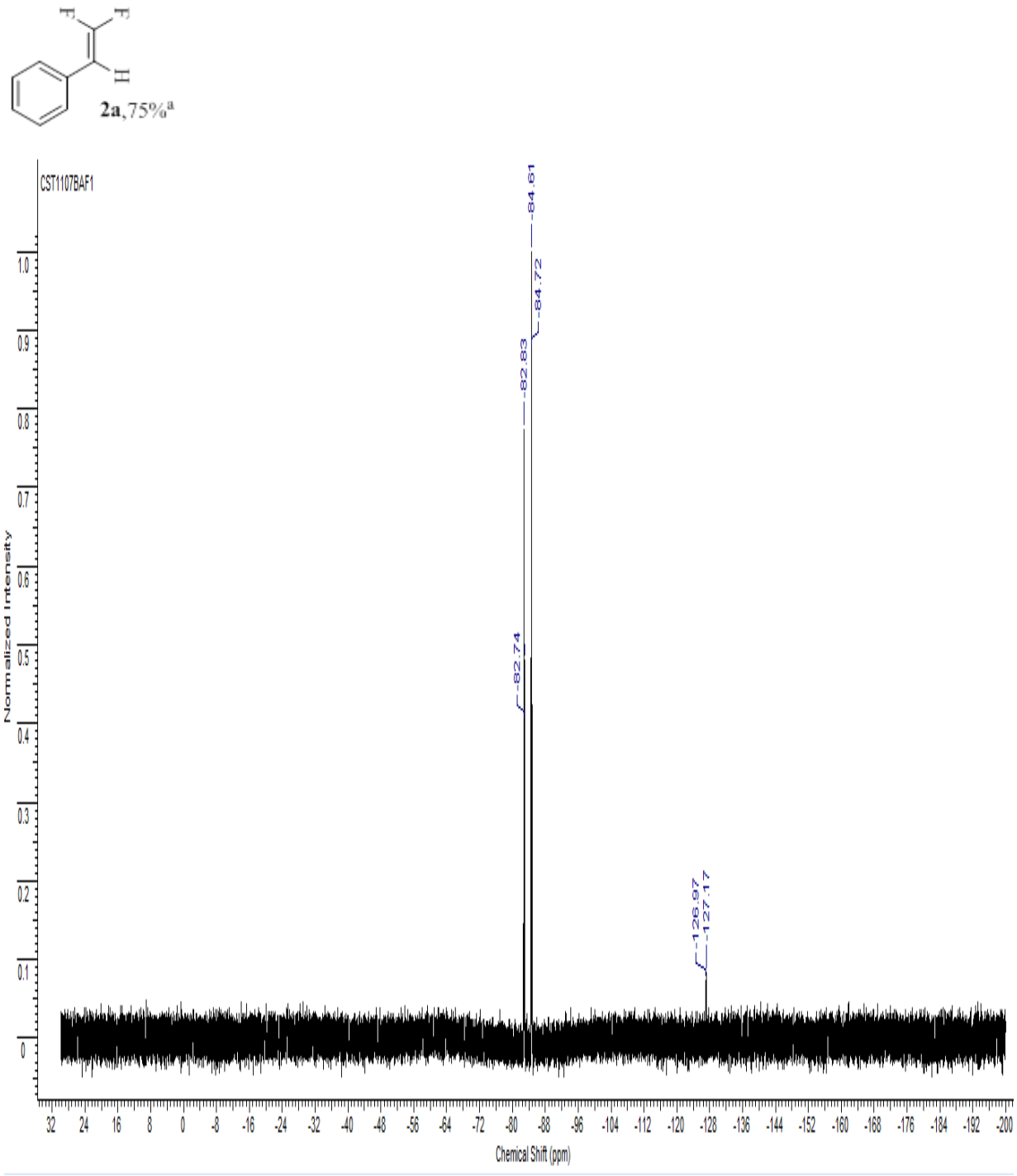
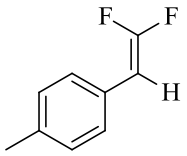


Figure A-2. ^{19}F NMR of (2,2-Difluoroethenyl)benzene (2a)



2b, 51%[a]

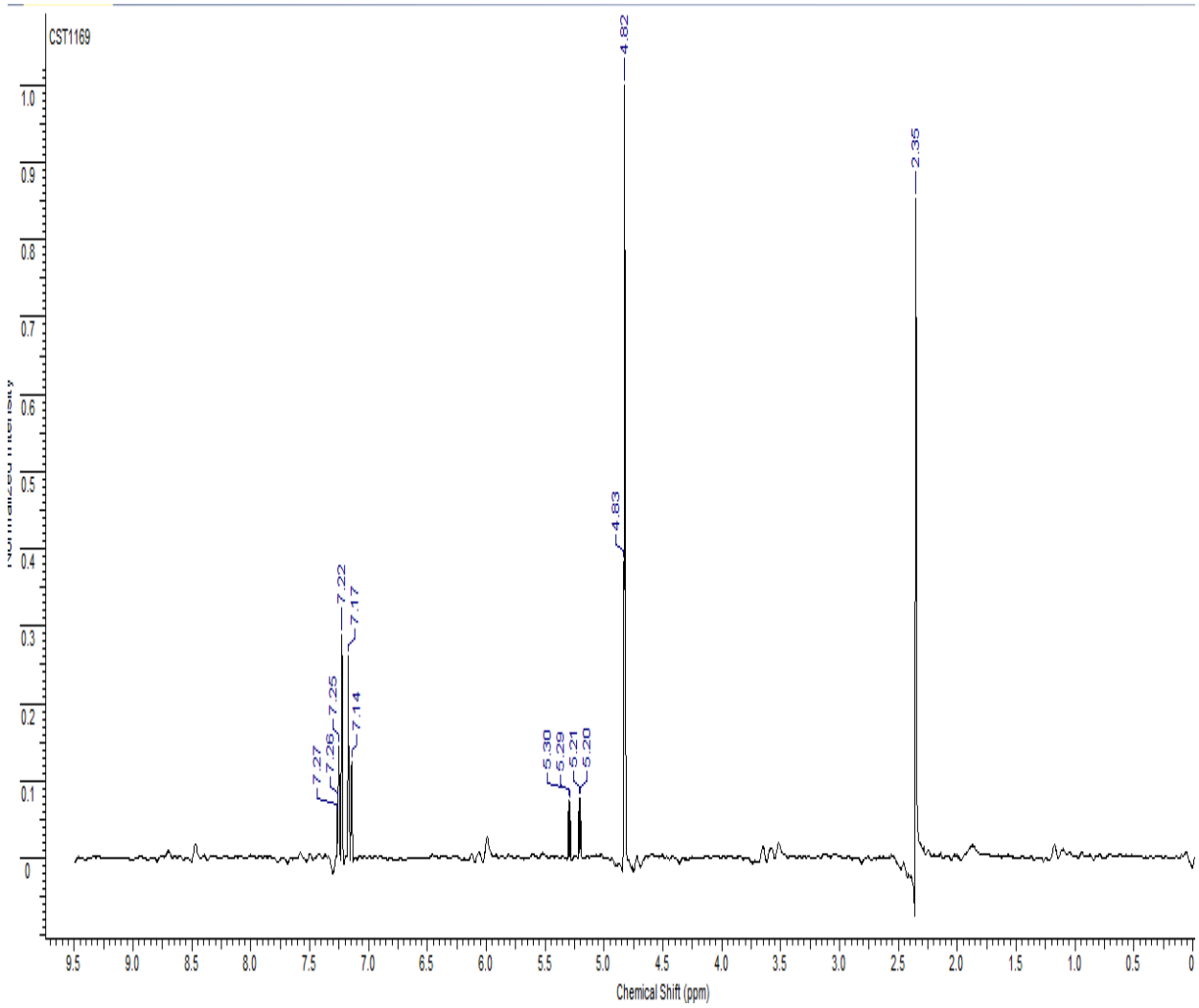
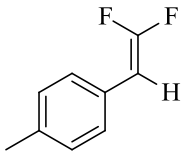


Figure A-3. ^{1}H NMR of (2,2-Difluoroethenyl)benzene (2b)



2b, 51%[a]

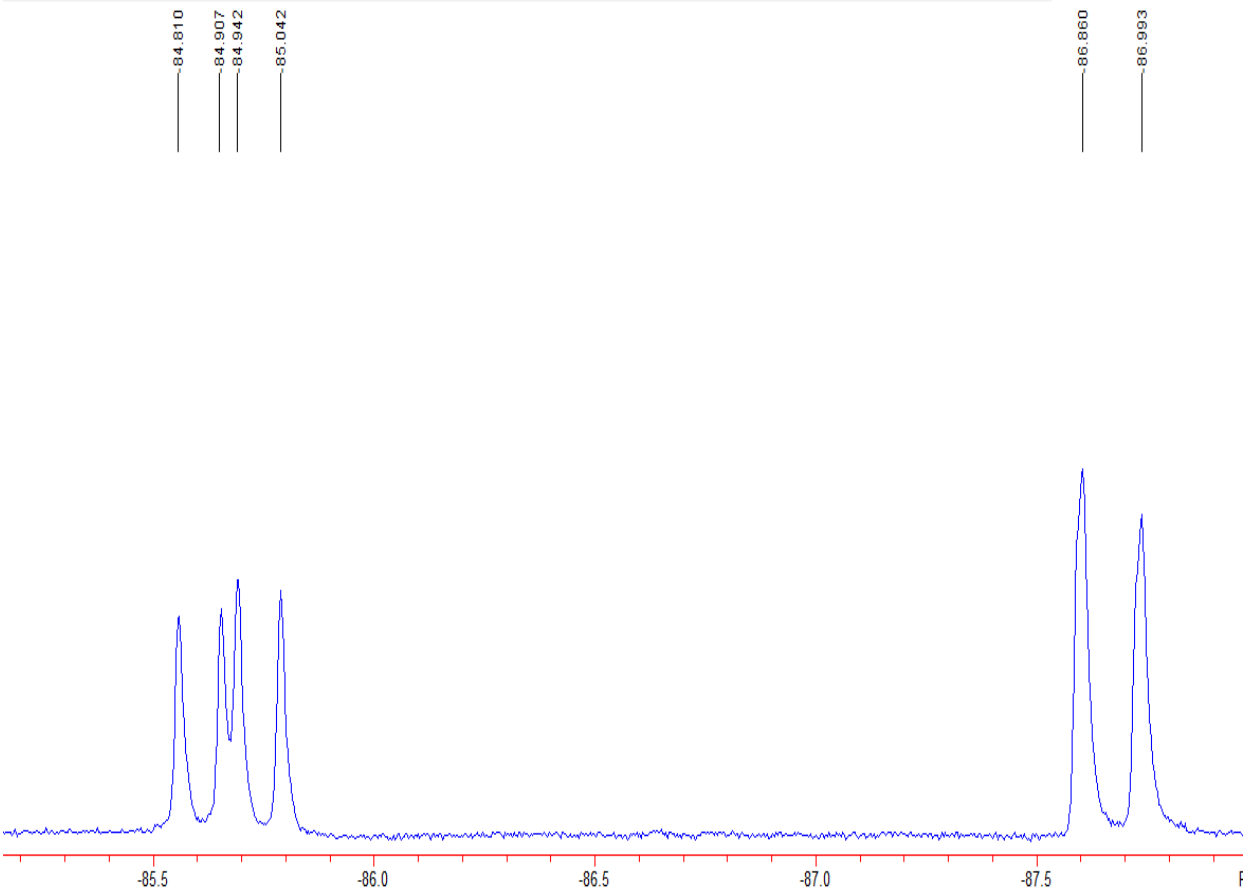
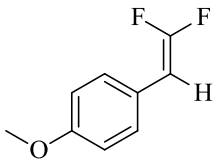


Figure A-4. ^{19}F NMR of 4-Methyl- (2,2-Difluoroethenyl)benzene (2b)



2c, 75%[a]

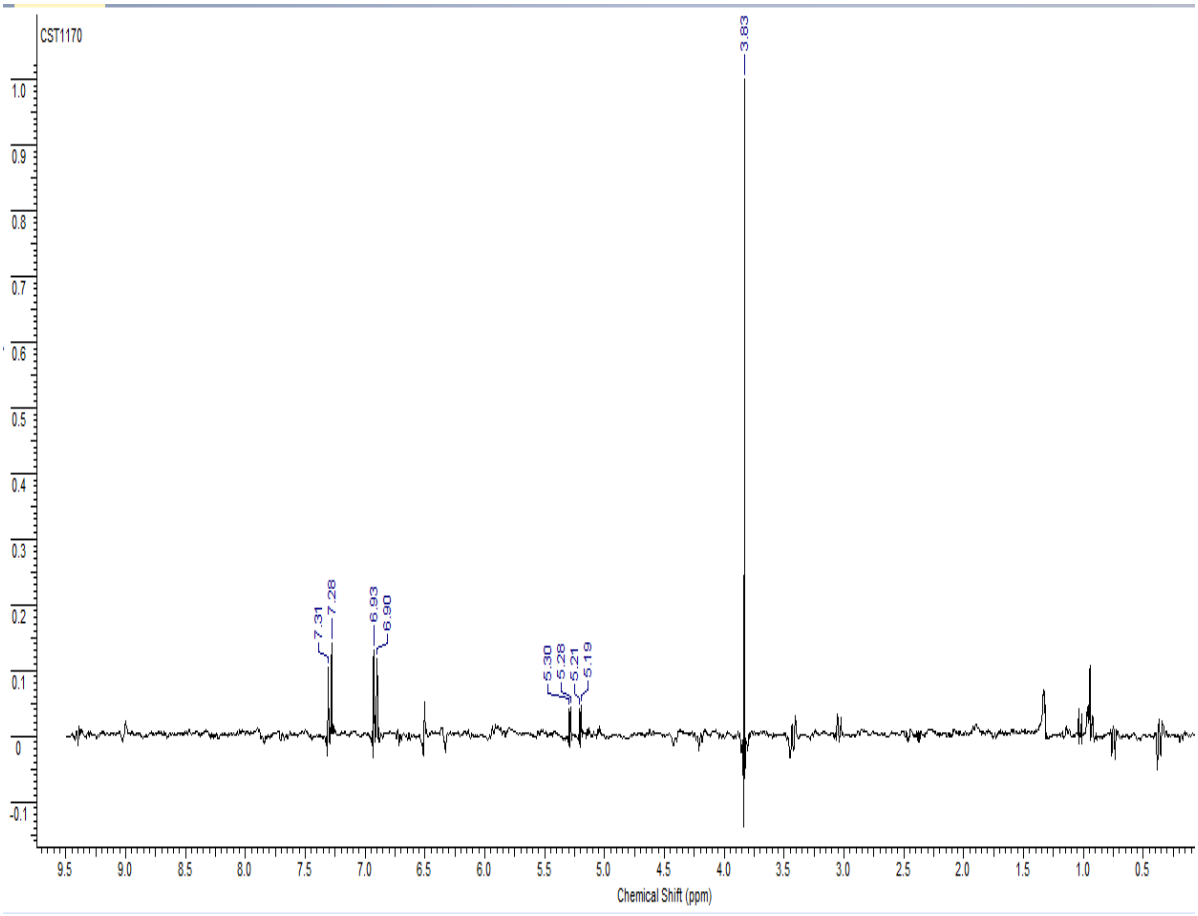
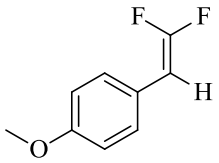


Figure A-5. ^{1}H NMR of 4-Methyl- (2,2-Difluoroethenyl)benzene (2c)



2c, 75%[a]

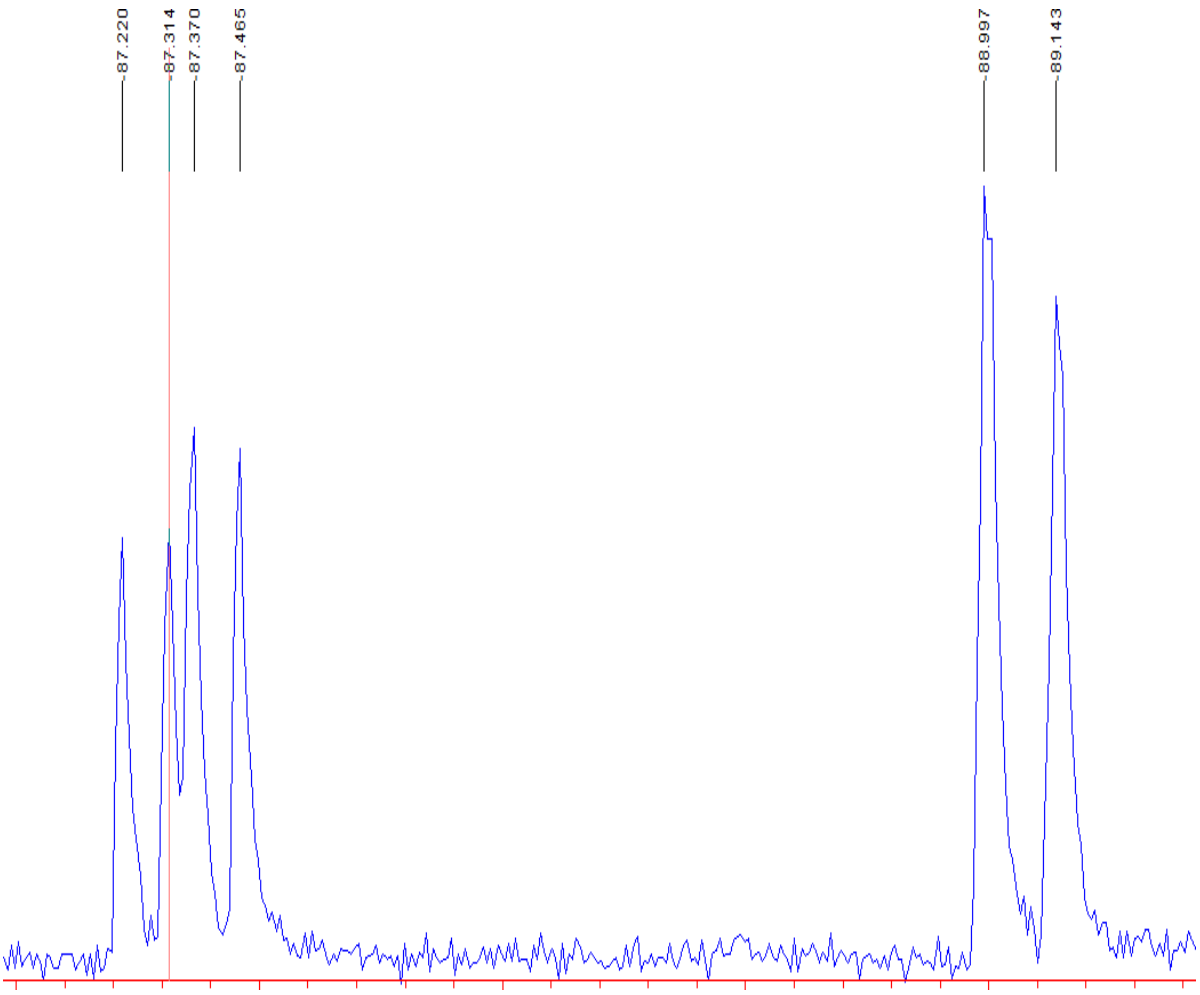
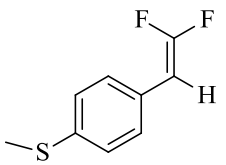


Figure A-6. ^{19}F NMR of 4-Methoxy- (2,2-Difluoroethenyl)benzene (2c)



2d, 86%[a]

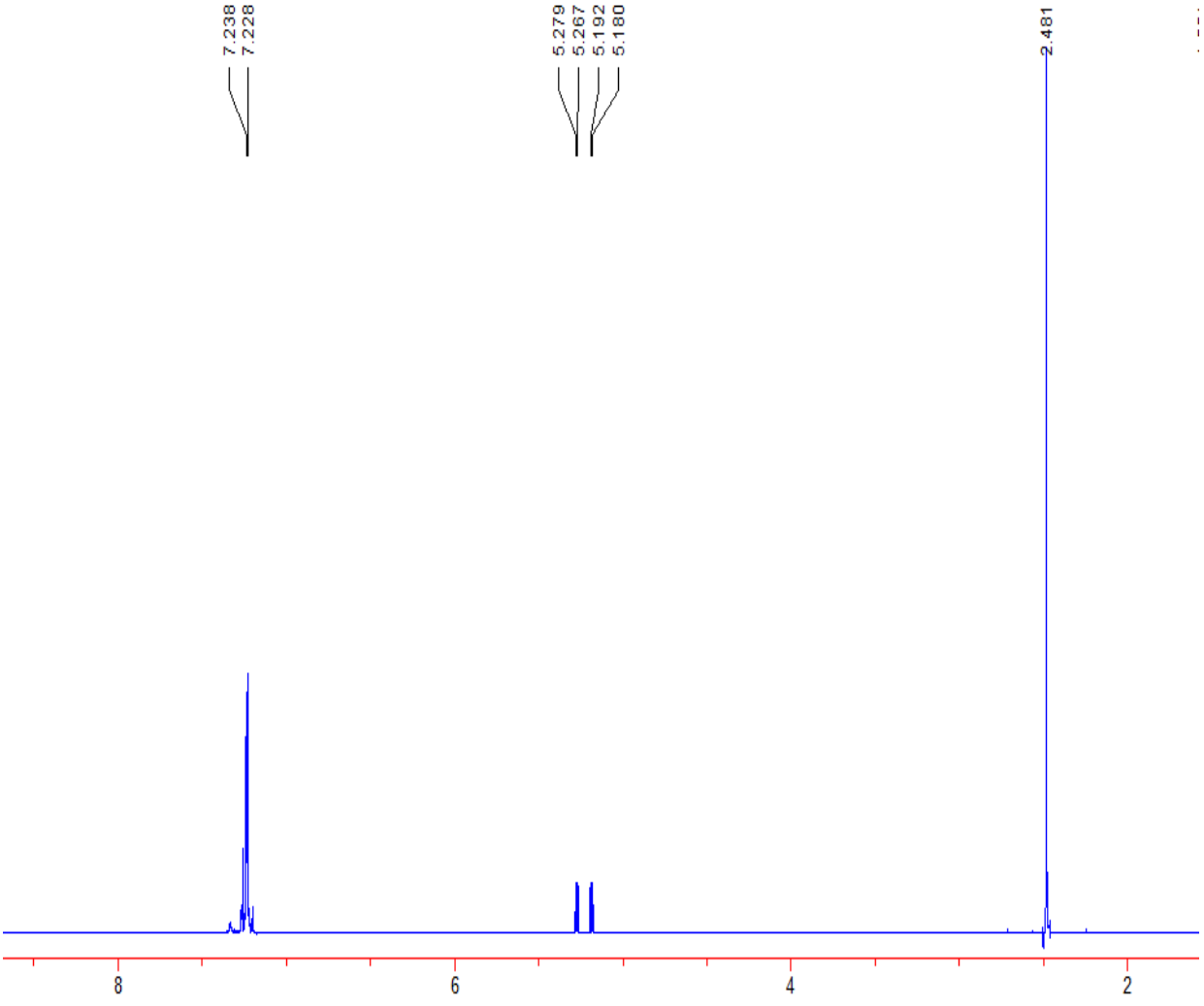
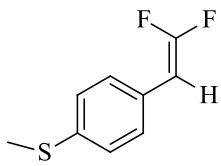


Figure A-7. ^{1}H NMR of 4-Thiomethoxy- (2,2-Difluoroethenyl)benzene (2d)



2d, 86%[a]

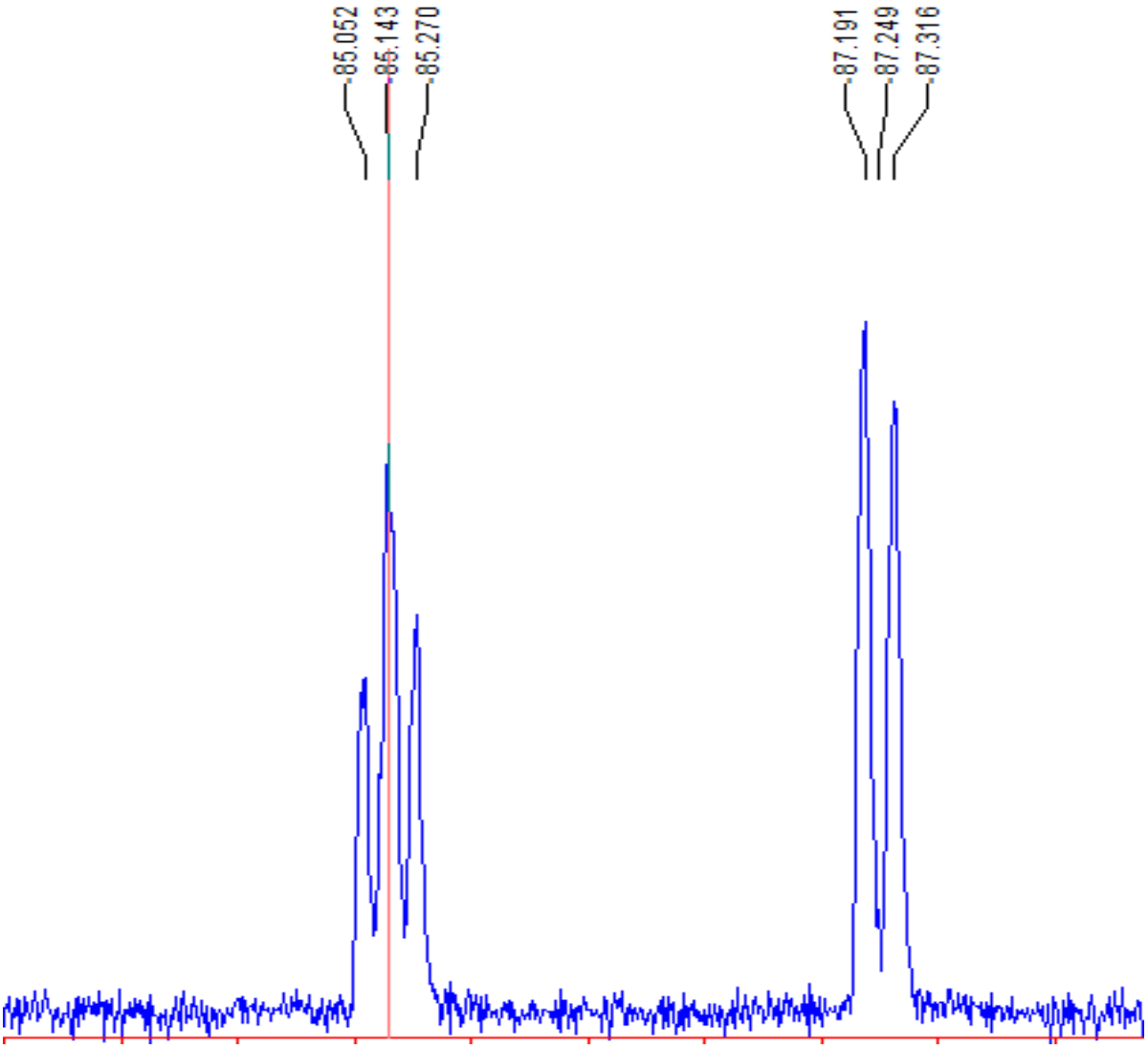
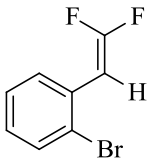


Figure A-8. ^{19}F NMR of 4-Thiomethoxy- (2,2-Difluoroethenyl)benzene (2d)



2e, 68%[a]

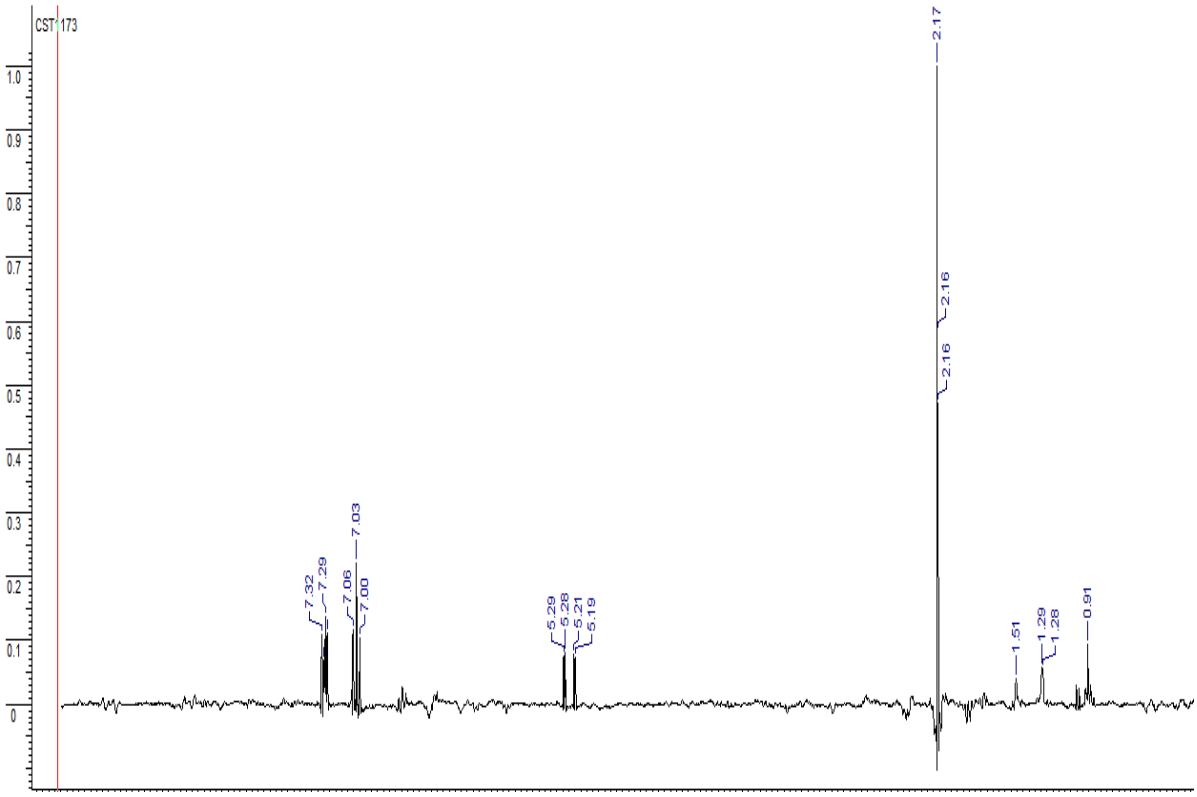


Figure A-9. ^{1}H NMR of 2-Bromo- (2,2-Difluoroethenyl)benzene (2e)

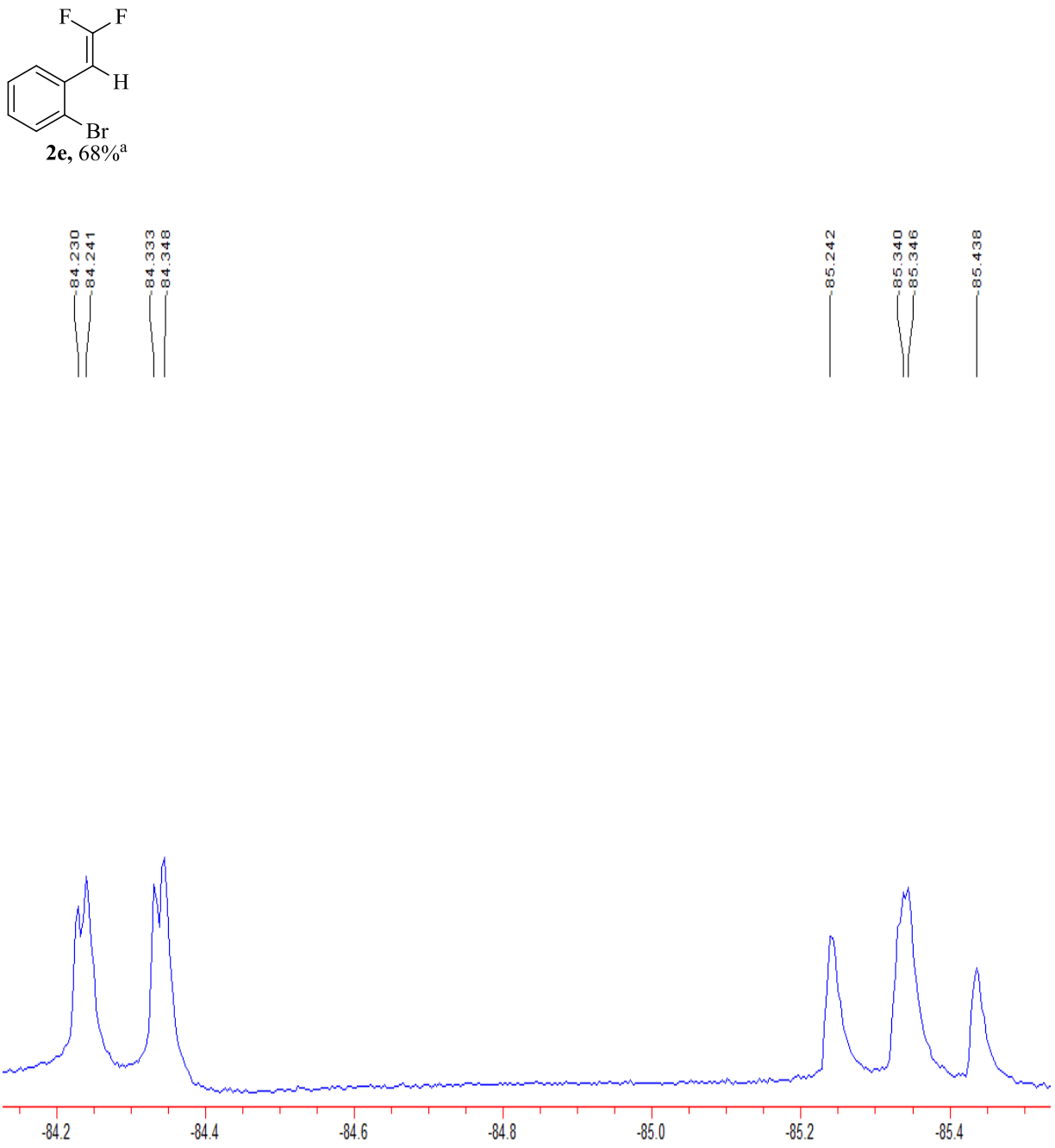


Figure A-10. ^{19}F NMR of 2-Bromo- (2,2-Difluoroethenyl)benzene (2e)

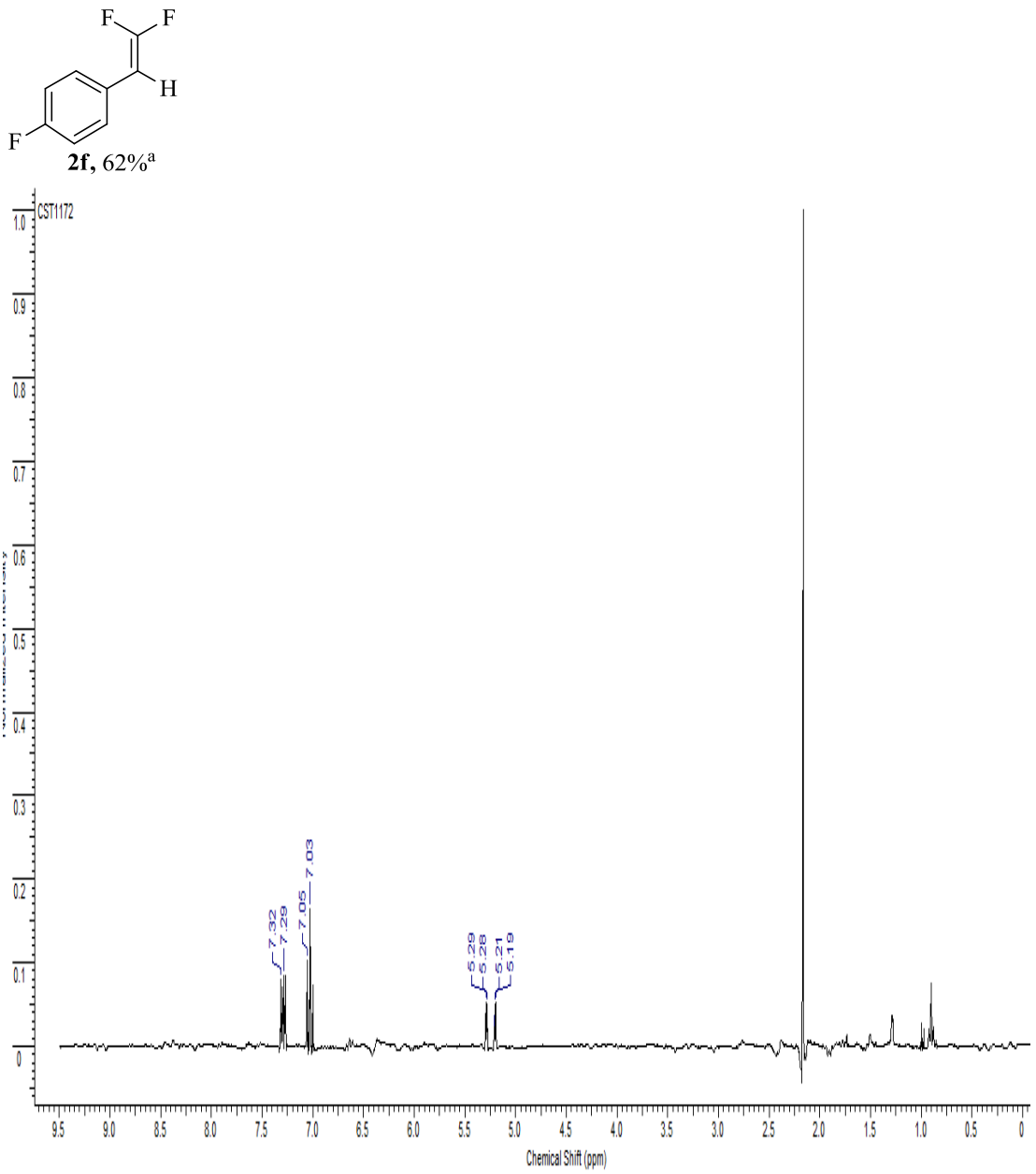
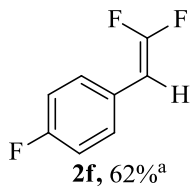


Figure A-11. ^{1}H NMR of 4-Fluoro- (2,2-Difluoroethenyl)benzene (2f)



2f, 62%[a]

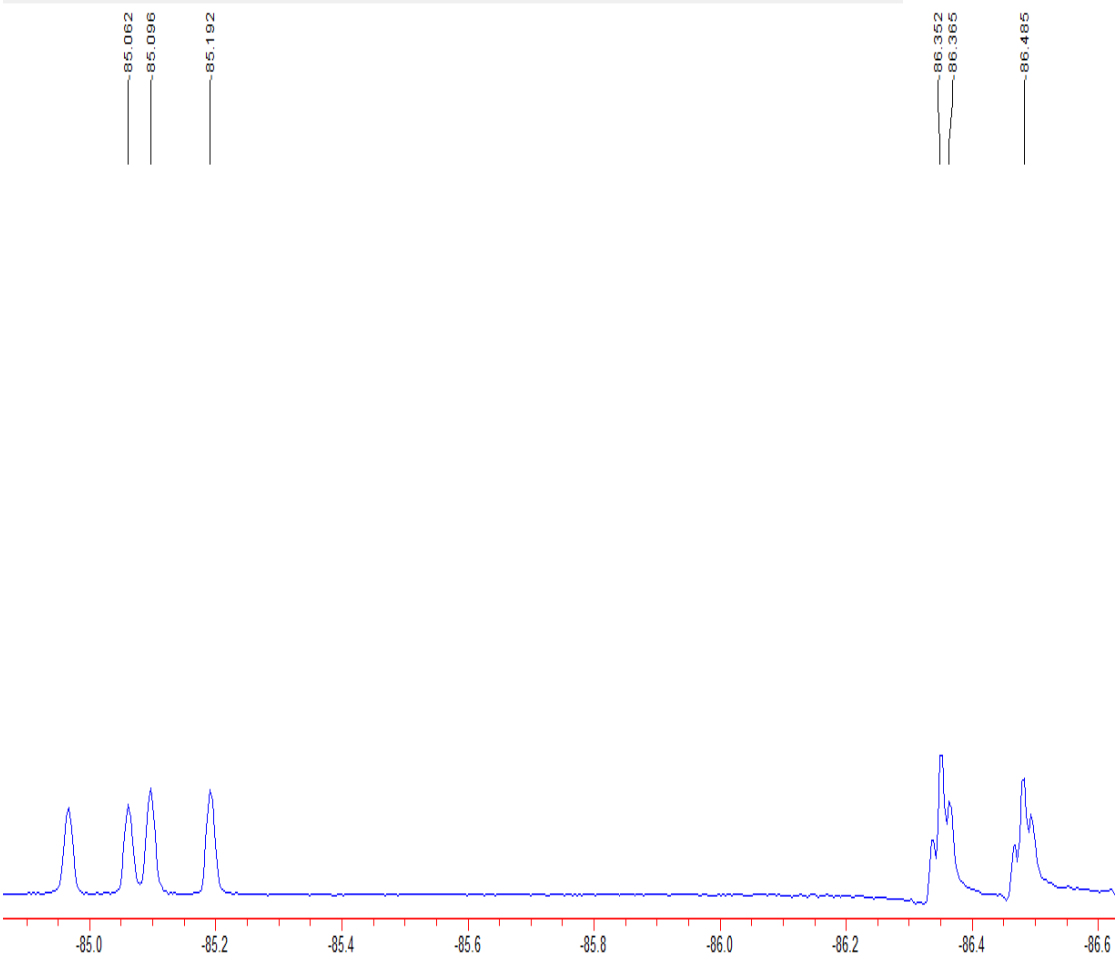
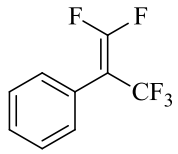


Figure A-12. ^{19}F NMR of 4-Fluoro- (2,2-Difluoroethenyl)benzene (2f)



2g, 88%[a]

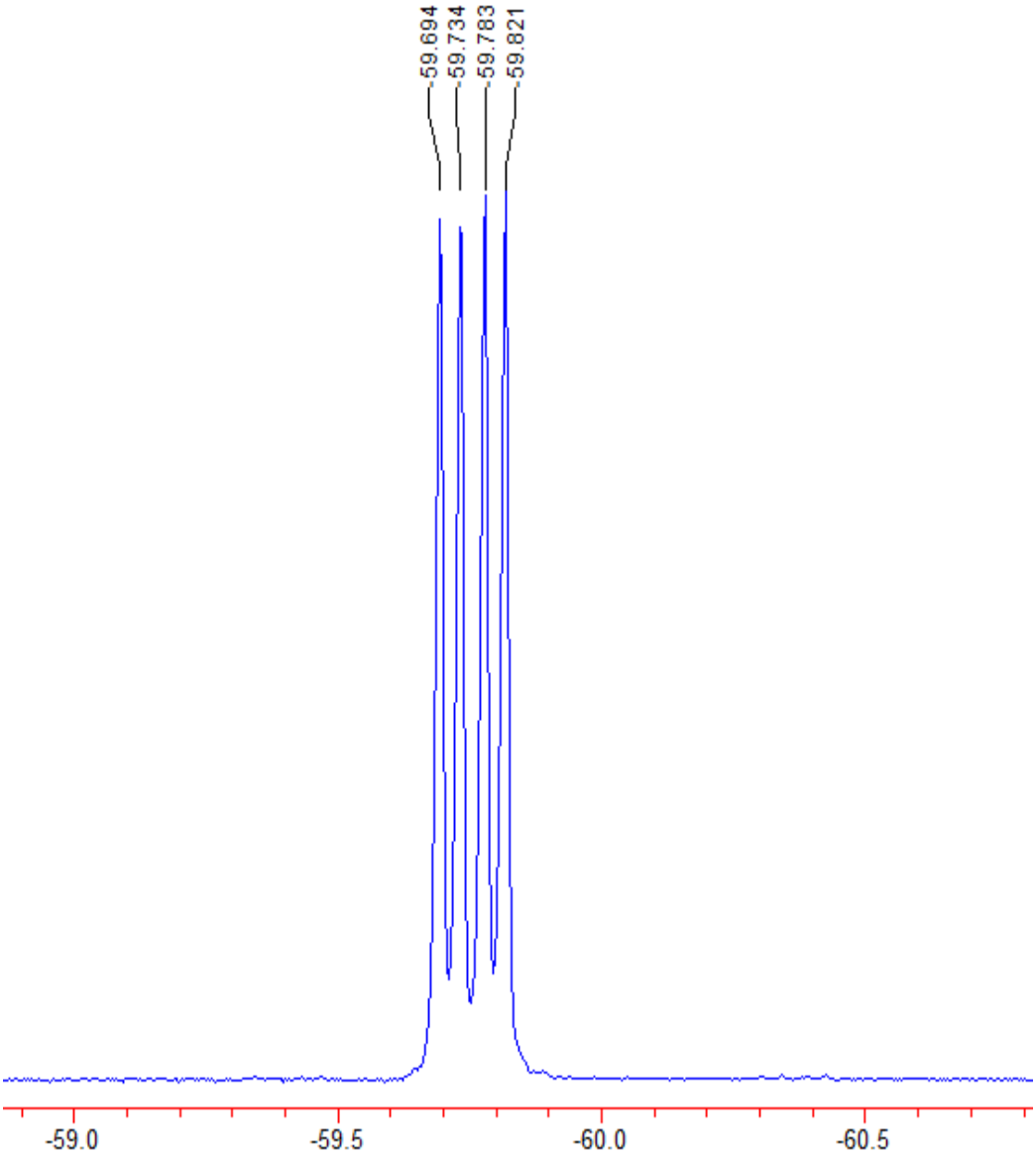


Figure A-13 ^{19}F NMR of 4-Trifluoromethyl-(2,2-difluoroethenyl)benzene (2g)

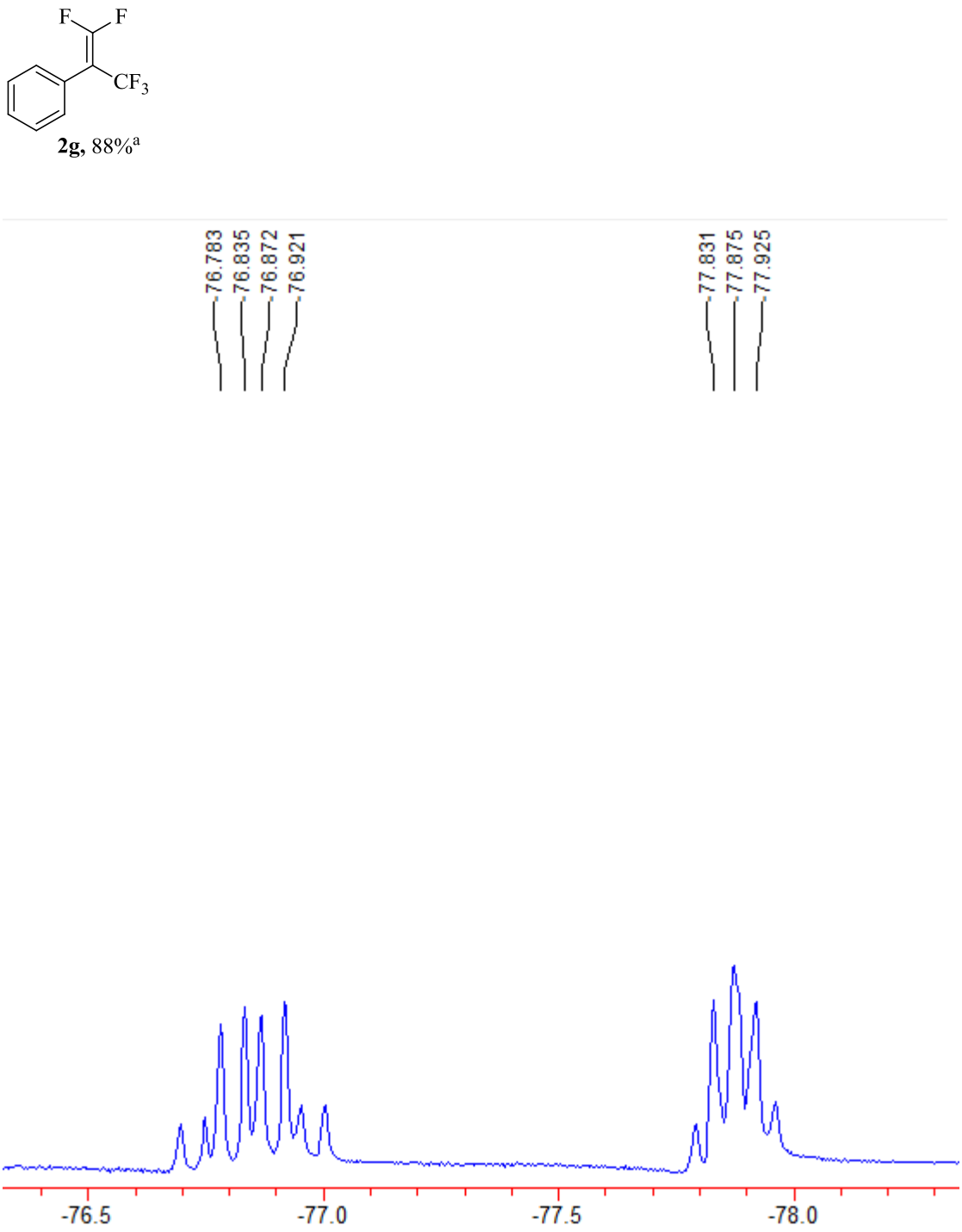
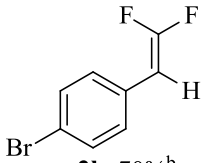


Figure A-14. ^{19}F NMR of 4-Trifluoromethyl-(2,2-difluoroethenyl)benzene (2g)



2h, 70%[b]

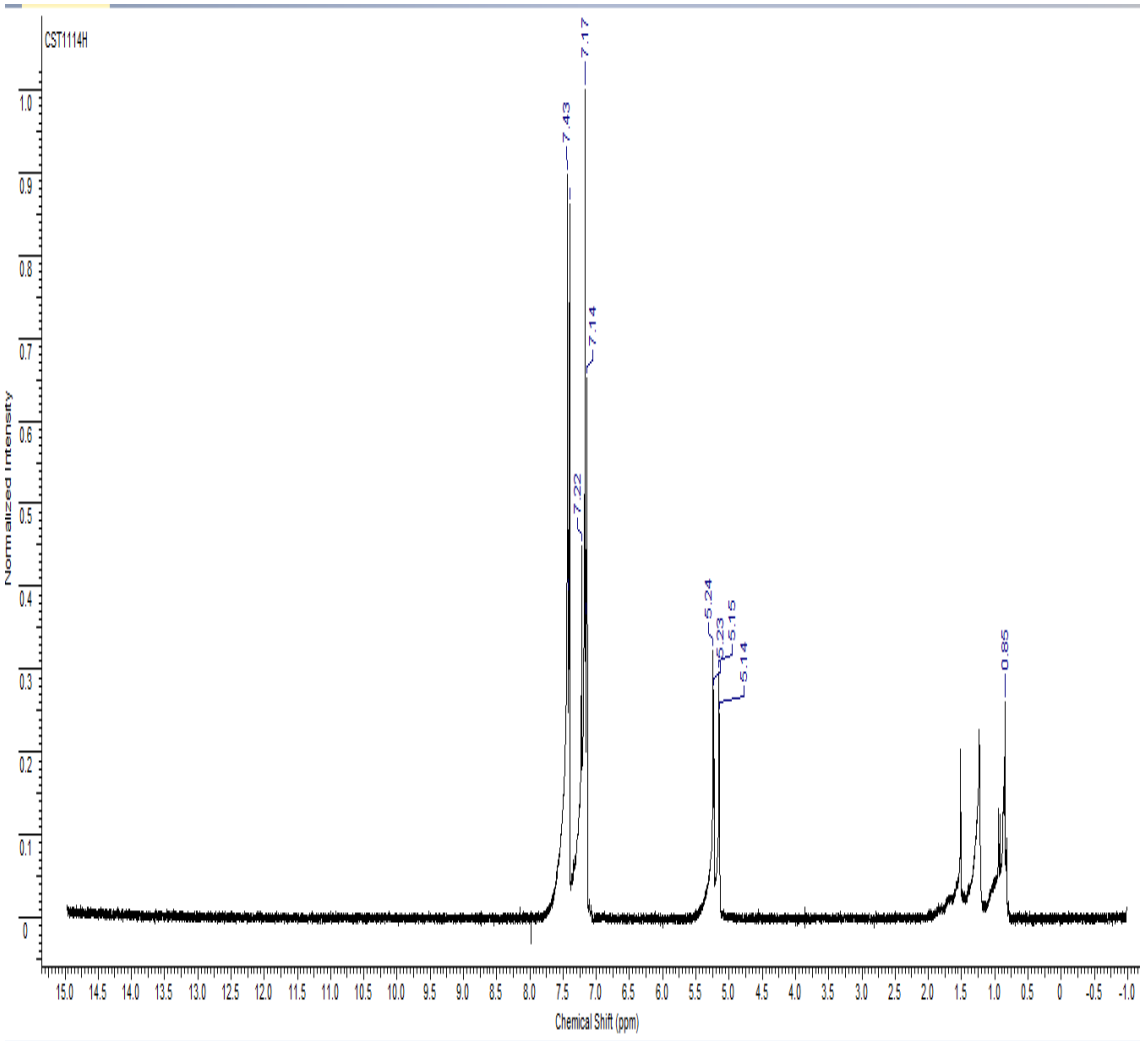
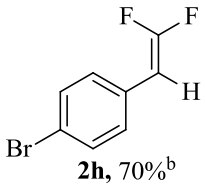


Figure A-15. ^{1}H NMR of 4-Bromo- (2,2-Difluoroethenyl)benzene (2h)



2h, 70%[b]

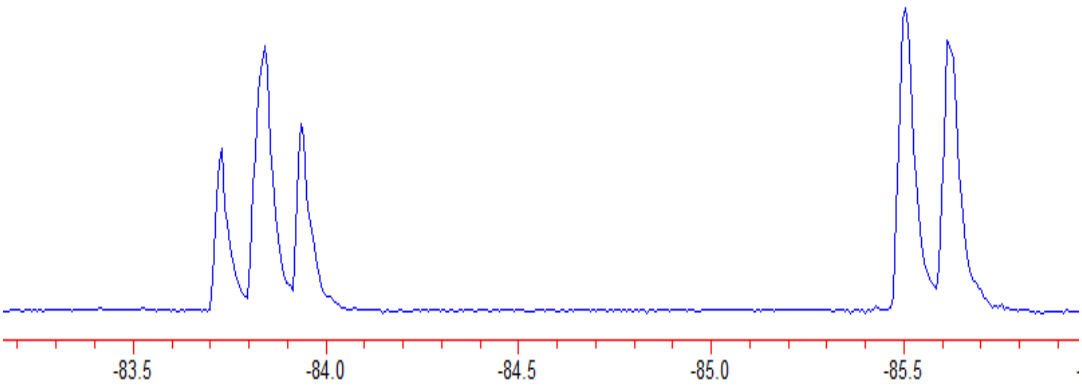


Figure A-16. ^{19}F NMR of 4-Bromo- (2,2-Difluoroethenyl)benzene (2h)

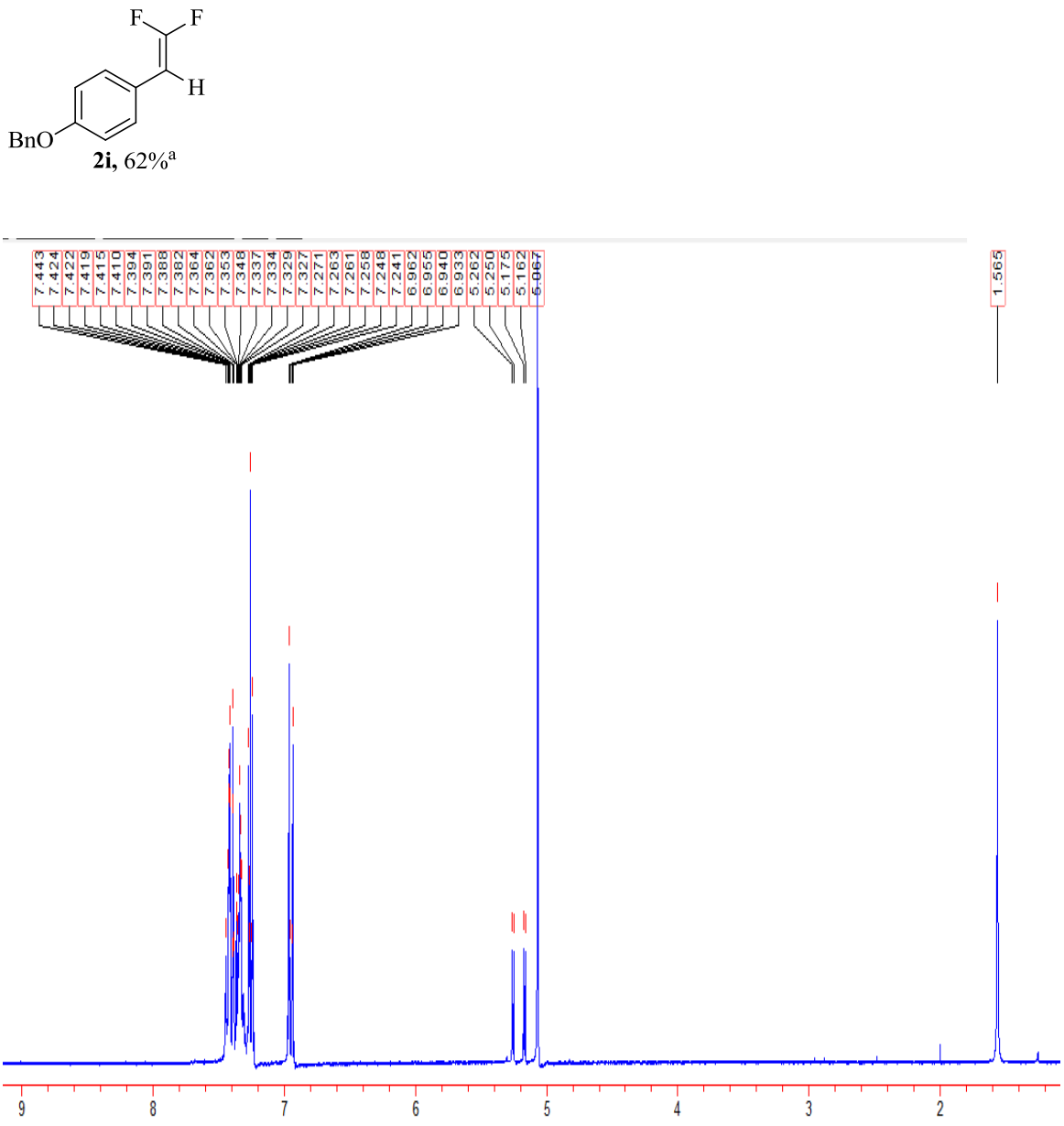


Figure A-17. ^{1}H NMR of 4-Benzyloxy- (2,2-Difluoroethenyl)benzene (2i)

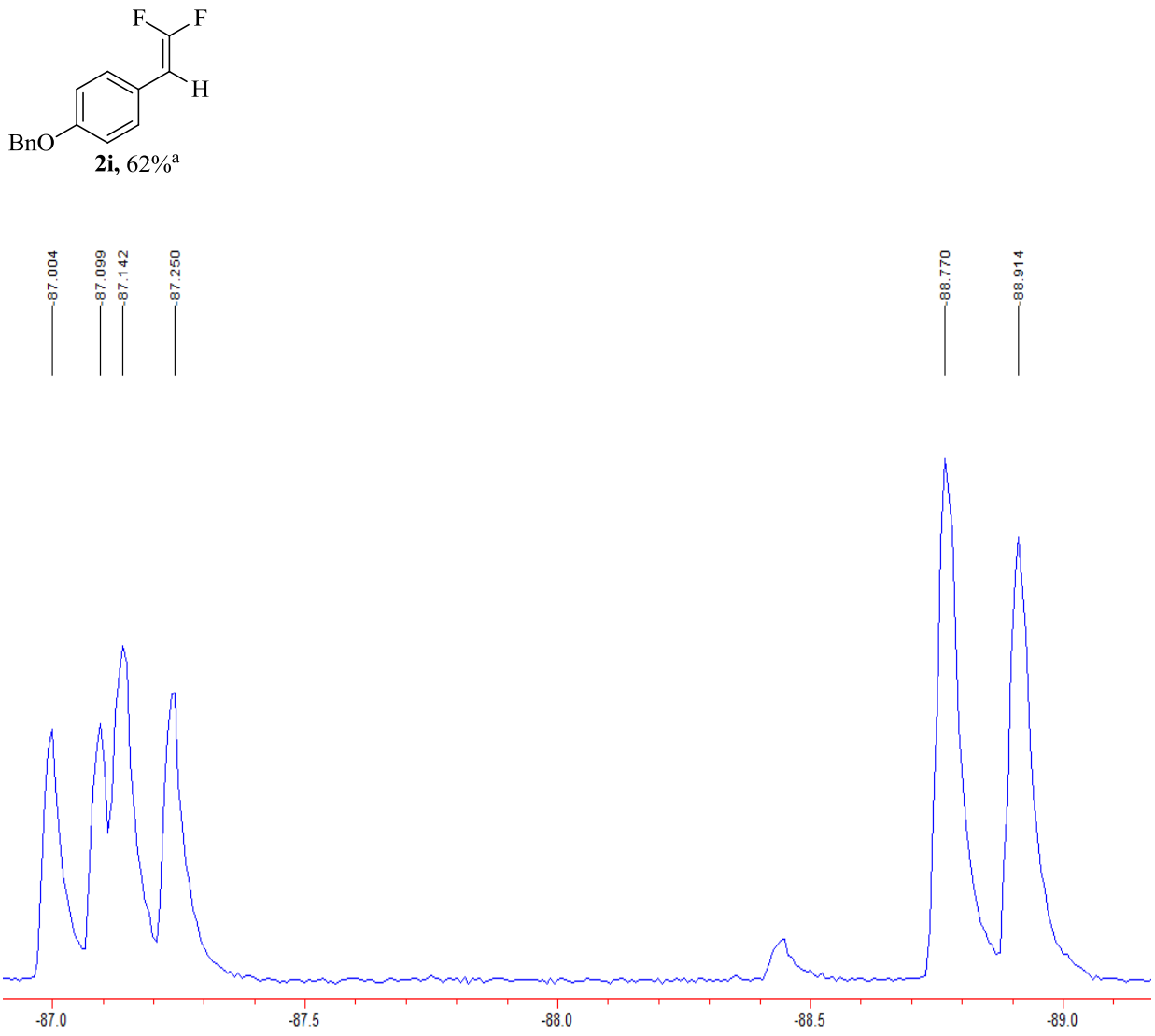
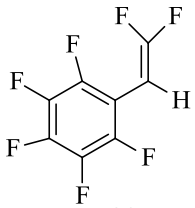


Figure A-18. ^{19}F NMR of 4-Benzyloxy- (2,2-Difluoroethenyl)benzene (2i)



2j, 40%[a,c]

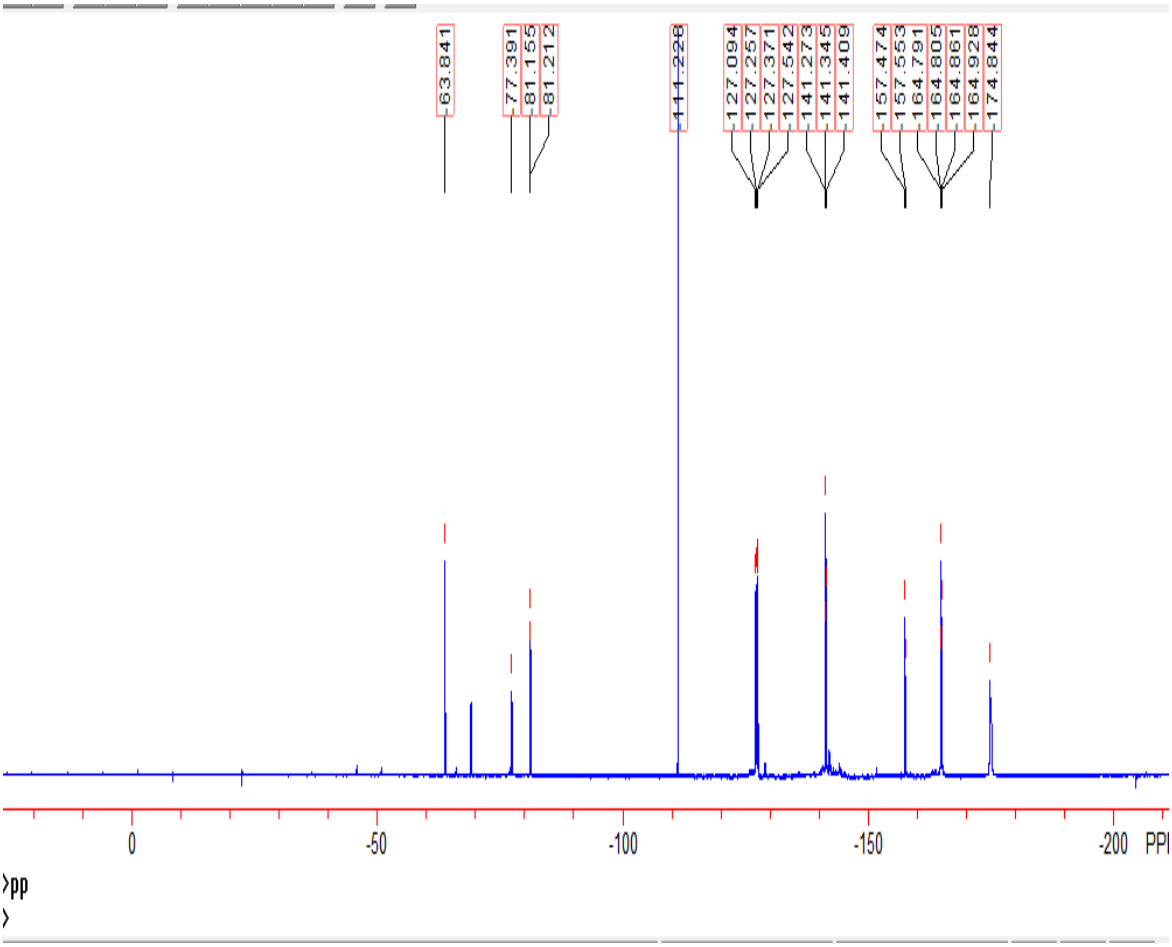
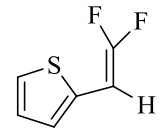


Figure A-19. ^{19}F NMR of 2,3,4,5,6-Pentafluoro-(2,2-difluoroethenyl)benzene (2j)



2k, 70%[b]

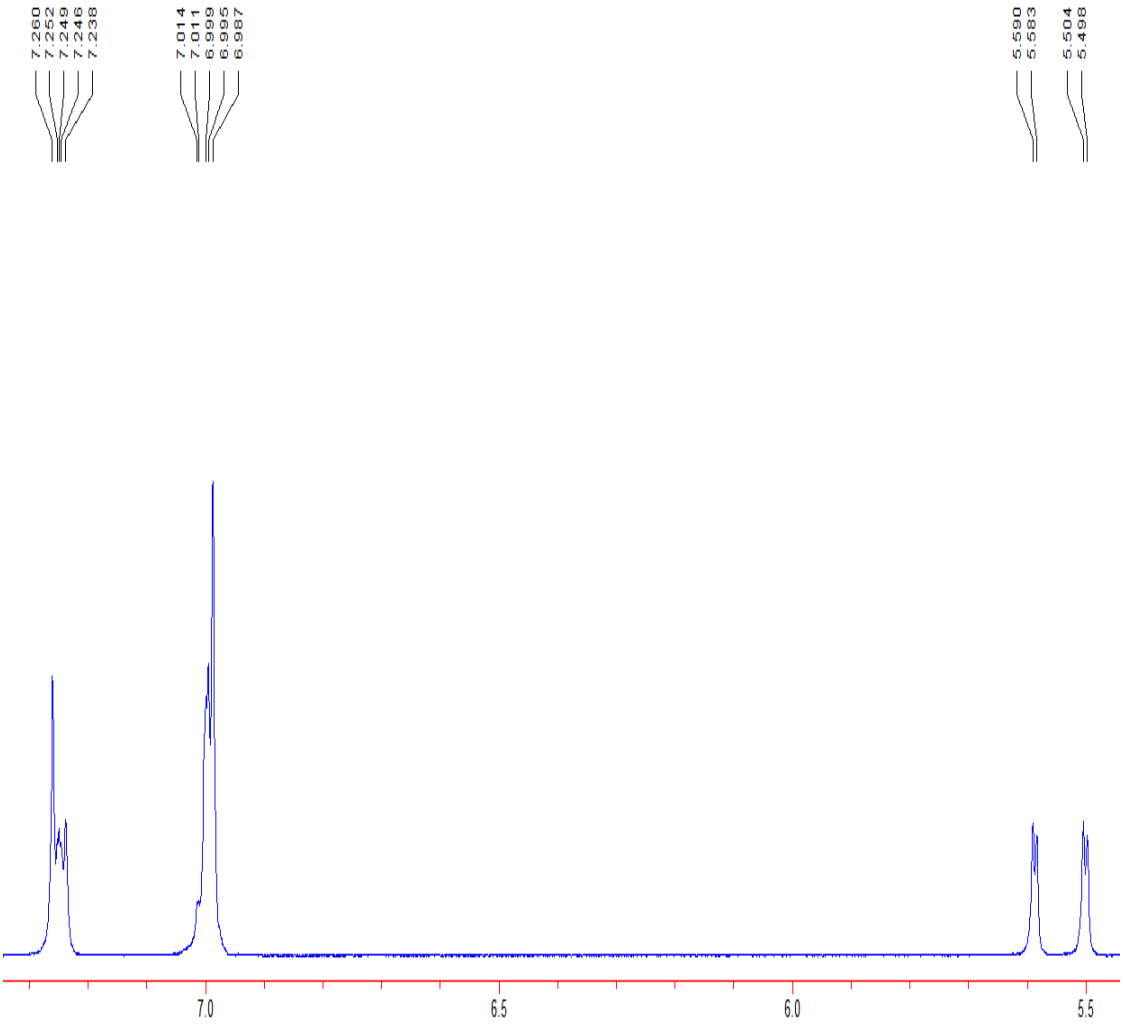
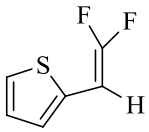


Figure A-20. ^{1}H NMR of 1-(2,2-Difluoroethenyl) thiophene (2k)



2k, 70%[b]

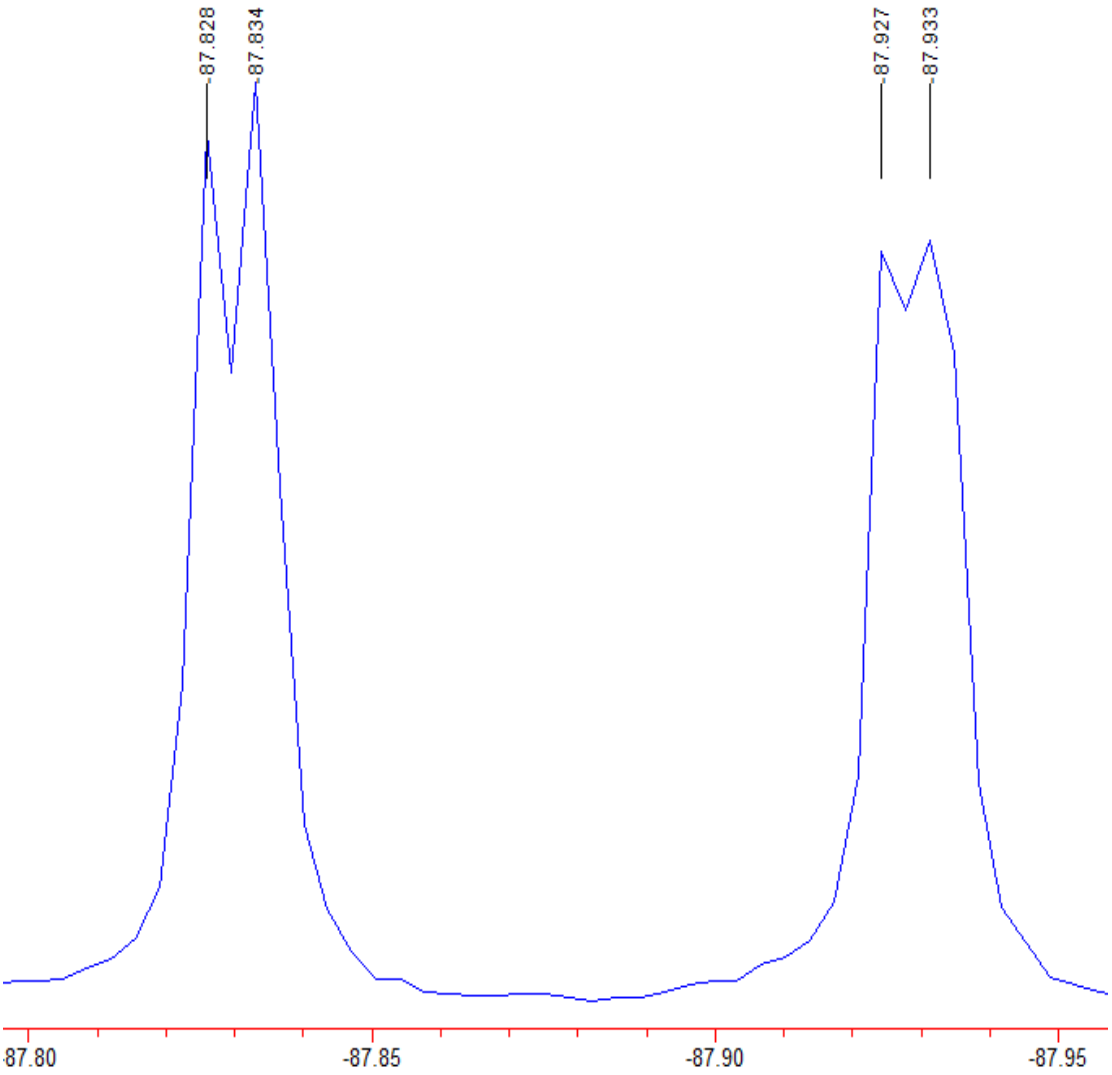
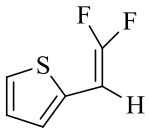


Figure A-21. ^{19}F NMR of 1-(2,2-Difluoroethenyl) thiophene (2k)



2k, 70%[b]

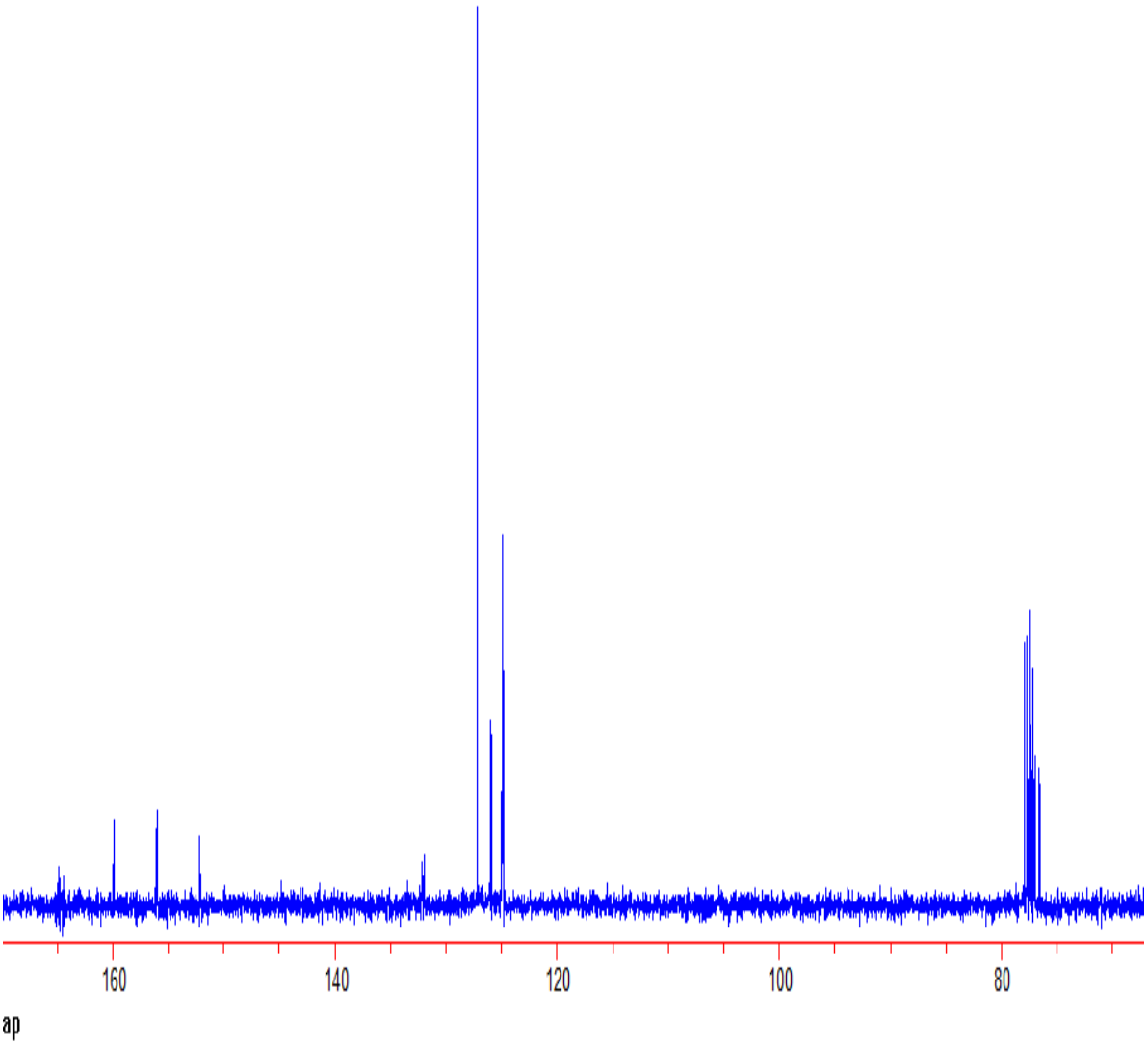
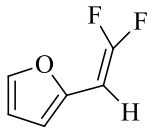


Figure A-22. ^{13}C NMR of 1-(2,2-Difluoroethenyl) thiophene (2k)



2l, 54%[a,c]

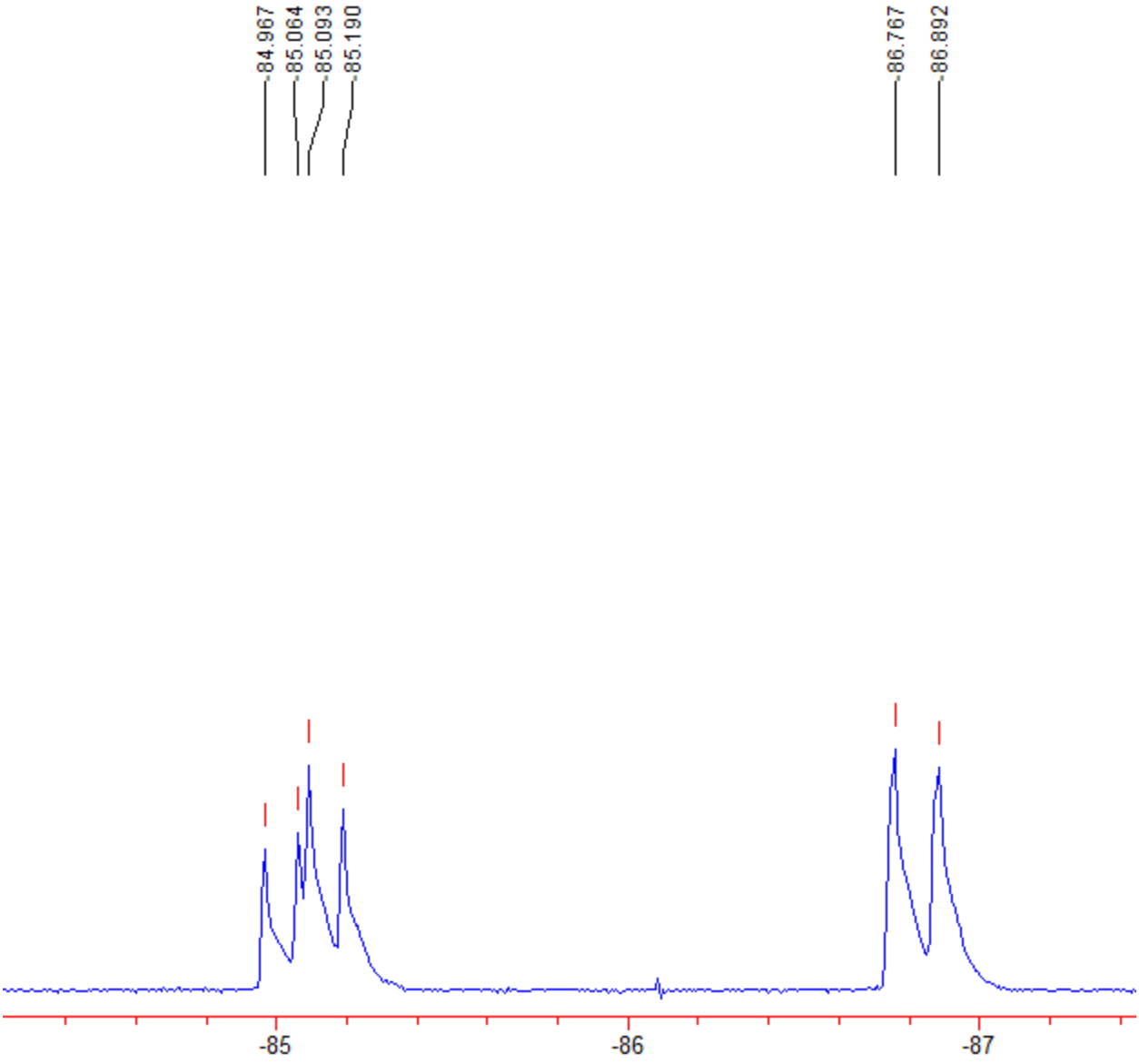


Figure A- 23. ^{19}F NMR of 1-(2,2-Difluoroethenyl) furan (2l)

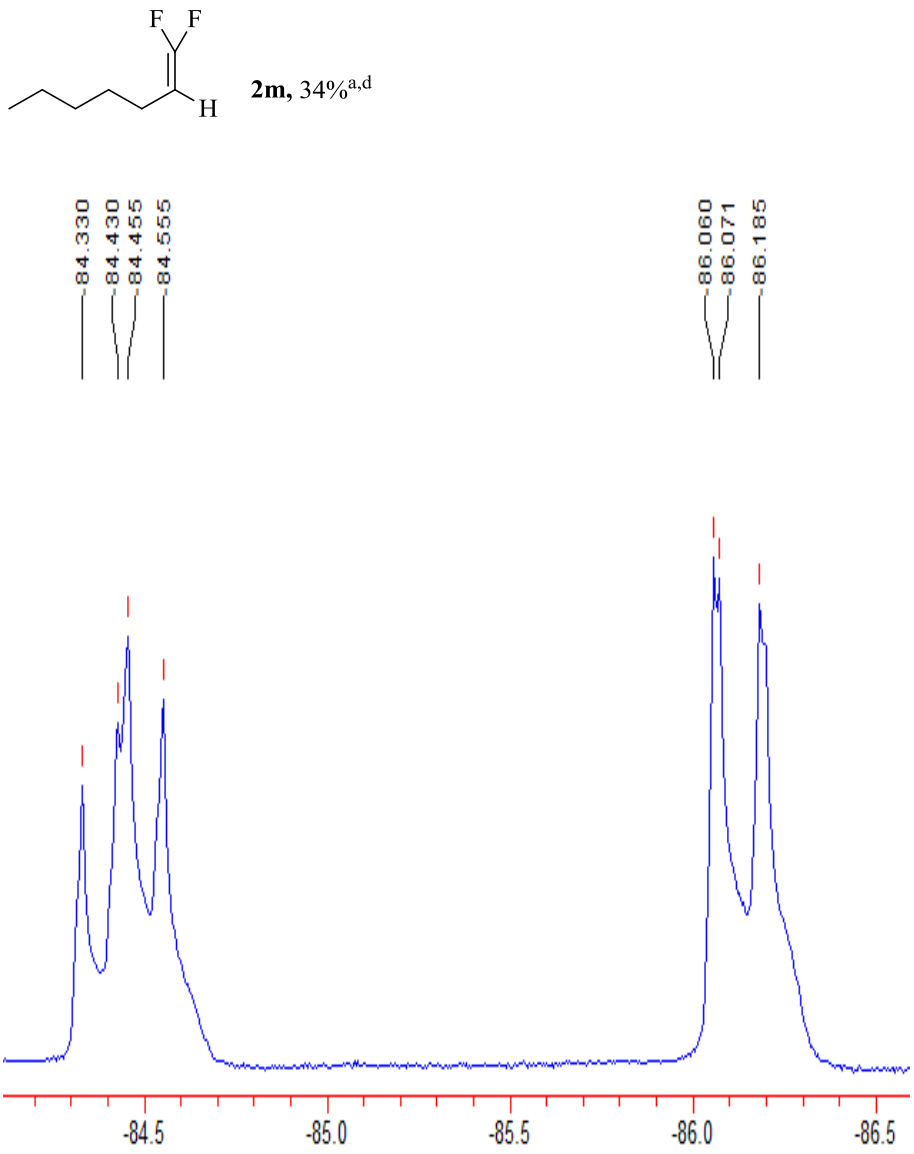
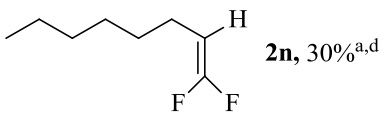


Figure A-24. ^{19}F NMR of 1,1-Difluoro-1-heptene (2m)



2n, 30%[a,d]

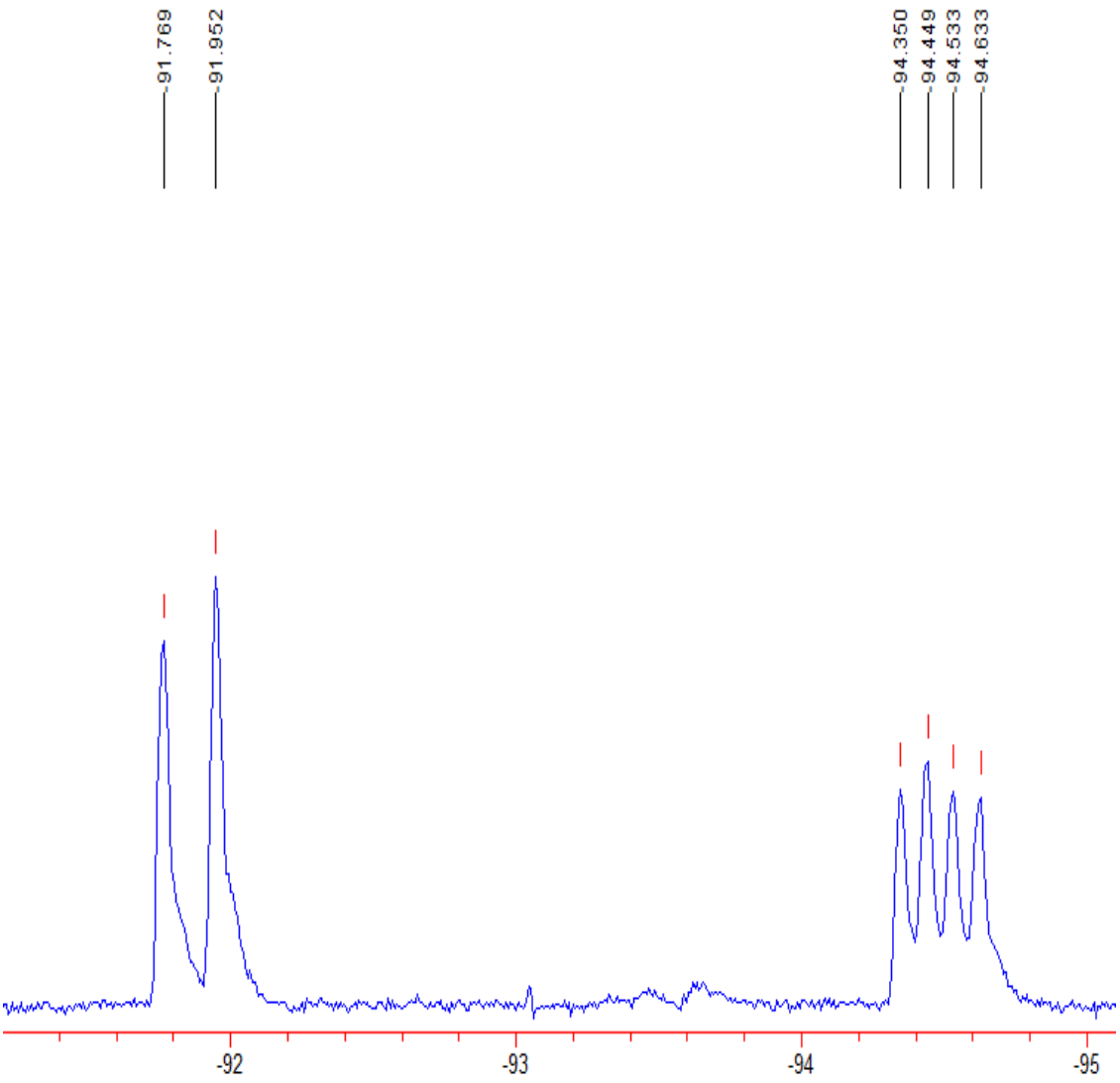
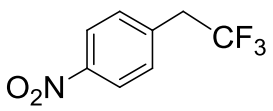


Figure A-25. ^{19}F NMR of 1,1-Difluoro-1-octene (2n)



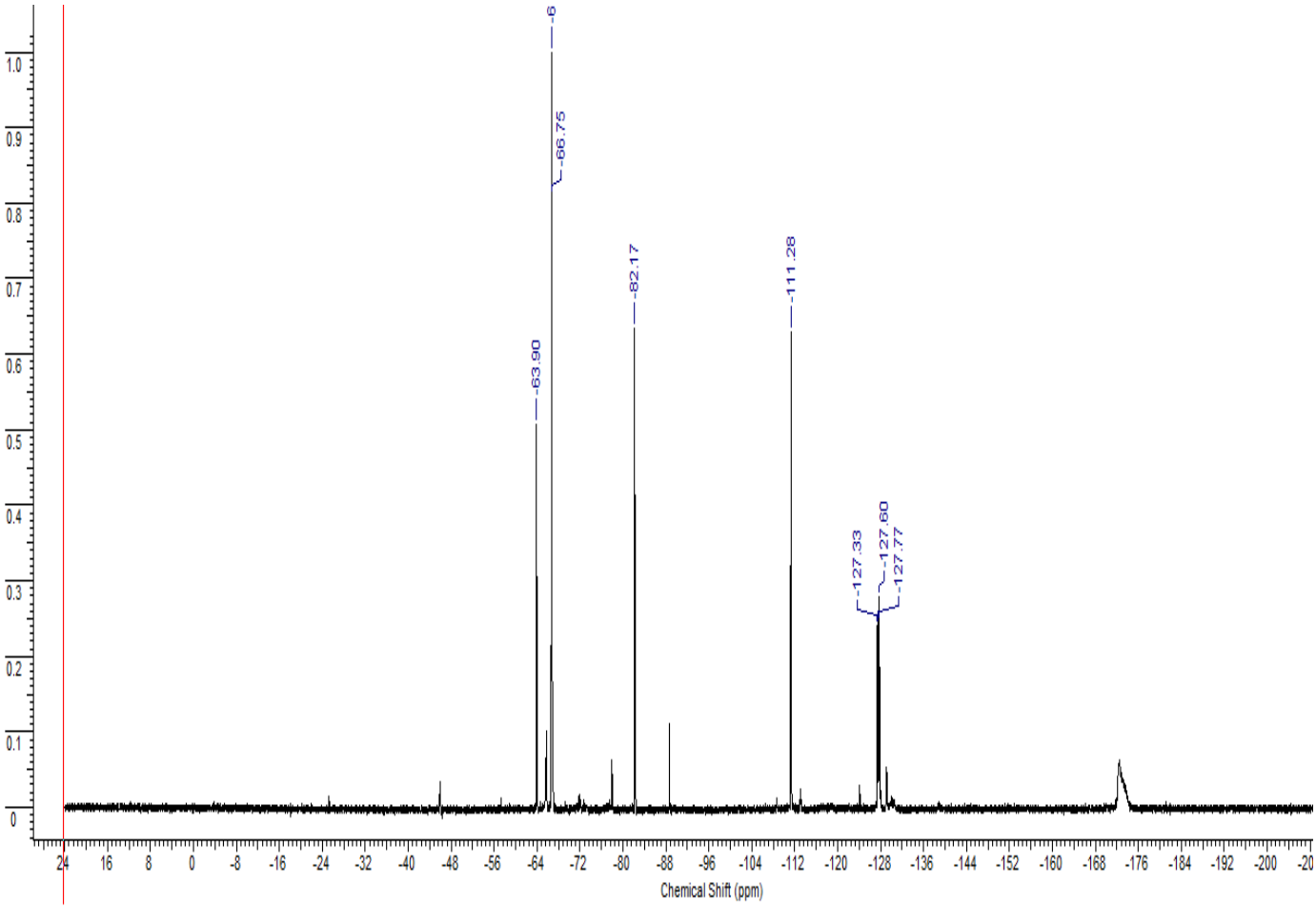


Figure A-26. ^{19}F NMR of 4-Nitro-(2,2,2-trifluoroethyl)benzene (3b)

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BIOGRAPHICAL SKETCH

Charles Seth Thomoson was born in Tifton, Georgia. He graduated with honors from Tift. County High School in 2006. After graduation, he attended Abraham Baldwin Agricultural College for one year before he decided to move to Statesboro, Georgia in 2007. He then attended Georgia Southern University in fall 2007, where he pursued a degree in the field of chemistry. He performed undergraduate research at the University of New Hampshire under the advisement of Dr. Charles Zercher. He graduated in fall 2010 from Georgia Southern University with a B.S in Chemistry. He accepted a job at Imperial Sugar Company in fall 2010 preforming duties to maintain quality control and quality assurance of products. He enrolled into the University of Florida in fall 2011 as a graduate student in organic chemistry under the direction of Dr. William R. Dolbier Jr., where he studied organic chemistry involving fluorine.