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Development and applications of novel and practical fluorination reagents.

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University of Louisville

DEVELOPMENT AND APPLICATIONS OF NOVEL AND PRACTICAL FLUORINATION REAGENTS

By

Yuhao Yang
B.S., Donghua University, 2018
M.S., University of Louisville, 2020

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A Dissertation Approved on

April 28, 2023

by the following Dissertation Committee:

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Dissertation Director Dr. Gerald B. Hammond

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Dr. Michael H. Nantz

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Dr. Farshid Ramezanipour

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Dr. Xiao-An Fu

DEDICATION

This dissertation is dedicated to my parents
Mr. Jianxun Yang and Mrs. Chunhong Rao
who have given me life and education.

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ABSTRACT

DEVELOPMENT AND APPLICATIONS OF NOVEL AND PRACTICAL FLUORINATION REAGENTS

Yuhao Yang

April 28th, 2023

The fluorine (F) atom has distinctive properties such as the highest electronegativity, small size, low polarizability, and strong C–F bond strength. Not surprisingly, fluorinated organic compounds have garnered significant attention in the pharmaceutical, agrochemical, and material fields. Since organofluorides are very rare in nature, we need fluorination reagents to help us transfer fluorine into the organic molecules. In past decades, a vast number of fluorination reagents have been developed and many of them are commercially available now. However, there is still much room for the improvement of these reagents. Our target is to develop novel and practical fluorination reagents to make up for the shortcomings of the currently popular ones.

We have developed a novel fluorinating agent, *N*-fluoro-*N*-(*tert*-butyl)-*tert*-butanesulfonamide (NFBB), which was prepared in excellent yield using *N*-fluorobenzenesulfonimide (NFSI) or F_2/N_2 and was purified by simple distillation. Its easy preparation and purification made NFBB a reagent suitable for large scale production. NFBB provided unprecedented high-yielding fluorination of highly basic organolithium species, which has been an unsolved problem for a long time. With NFBB, a conceptually new base-catalyzed, self-sustaining fluorination of active methylene compounds was discovered. NFBB also fluorinated other carbanions such as Grignard reagents and enolates in good yields. NFBB is expected to play an important role in the preparation of many useful fluorinated compounds and it is now commercialized by Tokyo Chemical Industry Co., Ltd. (TCI).

The trifluoromethylthio (CF_3S) group has the highest lipophilicity among the common fluorine-containing moieties. Therefore, introducing a fluorine atom or a CF_3S group into a bioactive molecule could produce dramatic effects on its physical, chemical, and biological properties. We have developed a novel trifluoromethylthiolating reagent, *S*-trifluoromethyl trifluoromethanesulfonothioate (TTST). Unlike conventional CF_3S reagents, TTST can be easily prepared in one step from commercially inexpensive sodium trifluoromethanesulfinate and triflic anhydride. TTST is a highly reactive, versatile, and atom-efficient reagent that can generate CF_3S^+, CF_3S^-, and $CF_3S^{\bullet}/CF_3^{\bullet}$ reactive species. Many kinds of *C*, *O*, *S*, and *N*-nucleophiles were trifluoromethylthiolated by TTST in high yields. Notably, TTST reacted with sodium phenoxides to provide a new series of hitherto difficult to prepare aryl trifluoromethanesulfenates that were found to undergo a novel acid-catalyzed CF_3S(II)-rearrangement reaction. By means of Cu or TDAE/Ph_3P combination, TTST generated two CF_3S anion species that are useful to prepare trifluoromethylthio compounds in high atom-economy fashion. Photocatalytic radical trifluoromethyl-trifluoromethylthiolation of alkenes with only one equivalent of TTST was achieved in high yield as well as in high atom-efficiency. TTST is expected to be a compelling alternative to the current CF_3S reagents in terms of preparation, reactivity, and practicality.

We also found a novel application of the fluorinated solvent, 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), which assisted the hydrohalogenation of alkenes with inactive aqueous hydrogen halide solutions via hydrogen bonding. Dynamic studies showed this reaction is hydrogen bond acidity-dominated and dilution-accelerated. Both aqueous HCl, HBr, and HI provided good yields of the hydrohalogenated products in this system.

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CHAPTER 1

INTRODUCTION TO ORGANOFLUORINE CHEMISTRY

1.1 Where are organofluorides from?

Fluorine is the 24th most abundant element in the universe and the 13th most abundant element on Earth. However, only three classes of the numerous fluorine-containing minerals are allowed to be exploited economically.[1] They are: Fluorite (CaF_2), fluoraptite ($Ca_5(PO_4)_3F$), and natural cryolite (Na_3AlF_6). Fluorite, also known as fluorspar, is the main source of fluorocarbons. (Figure 1) The majority of traded and consumed fluorspar is classified as either acid grade (acidspar), with a CaF_2 content of over 97%, which is used for the manufacture of HF, or subacid grade (includes ceramic and metallurgical grade, metspar), with a CaF_2 content of 97% or less, which is used for the metal smelting. All fluorinated organic compounds are synthesized using HF as a starting material. This can be done directly by using HF as a fluorinating agent or indirectly by using it to synthesize a fluorinating agent, includes the fluorine gas, which can then react with an appropriate organic substrate.[2]

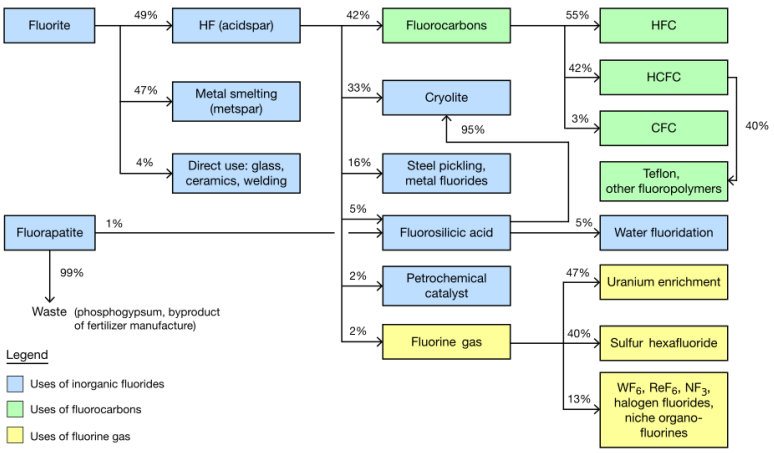
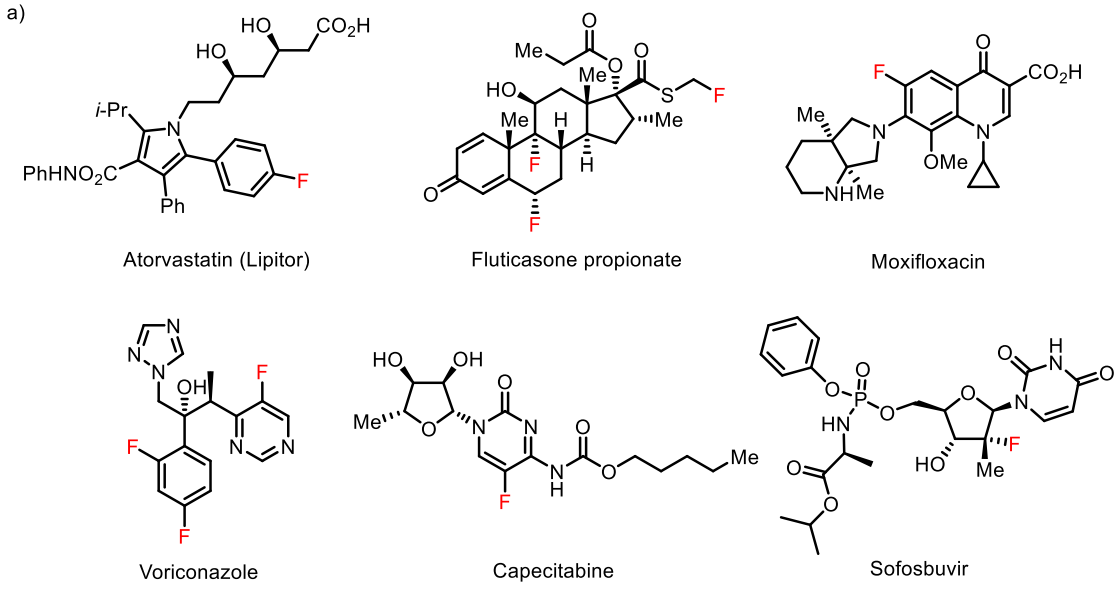


Figure 1. Fluorine industry supply chain: major sources, intermediates and applications. Copyright (C) 2000,2001,2002 Free Software Foundation, Inc.

1.2 Organofluorides in pharmaceuticals and agrochemicals

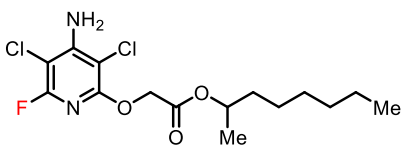
Fluorinated organic compounds occupy an important position in pharmaceuticals[3], agrochemicals[4], and materials[2]. Especially, in the first two areas, the presence of fluorine has attracted attention during the last decades. Fluorine atom has a comparable size (van der Waals radius: 1.47 Å) with hydrogen atom (1.20 Å) and hydroxyl group (1.40 Å) which makes it a good bioisostere of them in a bioactive compound with respect to steric requirements at receptor sites.[5] Due to the high electronegativity (4.0 on Pauling scale) of fluorine atom, the C-F bond is highly polarized. It can interact with a protein backbone to identify the fluorophilic environments of protein which can be targeted to enhance protein-ligand recognition.[6-8] Other properties such as motabolic stability, lipophilicity, and acidity or basicity of the bioactive compounds can be affected by fluorine atom in a favorable way.[9] Fluorine-scan/fluorine editing of a lead molecule is now a routine step in the drug discovery.[10]

About 60% of top-selling and 20% of all pharmaceuticals contain fluorine.[3, 11] In 2020, Lipitor (Atorvastatin) was the most commonly prescribed medication in the United States to lower

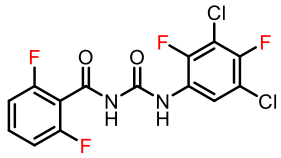


Scheme 1. a) Fluorine-containing pharmaceuticals. b) Fluorine-containing agrochemicals

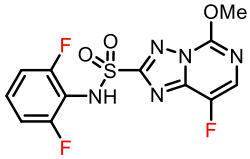
b)



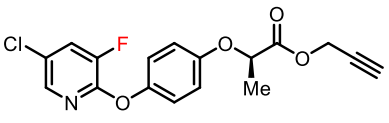
Fluroxypyr methylheptyl



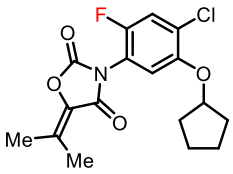
Teflubenzuron



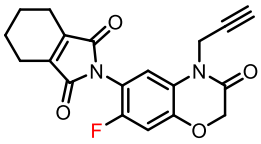
Florasulam



Clodinafop propargyl



Pentoxazone

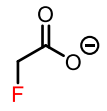


Flumioxazin

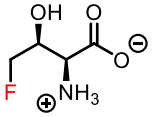
cholesterol and to reduce the risk of heart disease, with more than 114 million prescriptions as reported on ClinCalc. And about 30% of agrochemicals contain at least one fluorine atom (Scheme 1).[4, 11] In addition, ^{18}F labeled molecules play a important role in positron emission tomography (PET) as the radiotracer. For example, positron emission tomography with 2-deoxy-2-[^{18}F]fluoroglucose integrated with computed tomography (^{18}F-FDG PET/CT) has emerged as a powerful imaging tool for the detection of various cancers.[12]

1.3 Fluorine-containing natural products

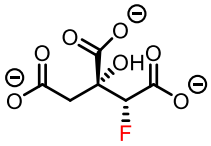
Natural products (NPs) are a rich source of novel compound classes and new drugs.[13] Although fluorine is the 13th most abundant element in the Earth's crust and the most abundant halogen on the Earth, it is a rarely bound to carbon in natural products.[14] Organofluorine compounds



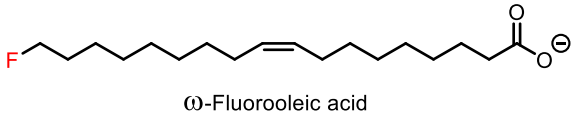
Fluoroacetate



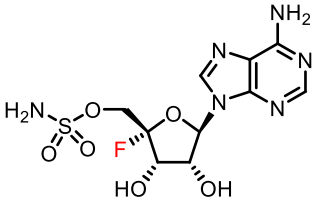
4-Fluoro-L-threonine



(2R,3R)-2-Fluorocitrate



ω-Fluorooleic acid



Nucleocidin

Scheme 2. Fluorine-containing natural products

were only found in a limited number of plants in tropical and subtropical regions, as well as in two types of microorganisms called actinomycetes. No organic compounds containing fluorine have been discovered in animals or marine organisms. The lack of fluorine-containing natural products, compared to other halogenated metabolites, is due to the unique chemical properties of fluorine, which distinguish it as a "superhalogen".[15] Only 5 fluorine-containing natural products have been structurally characterized (Scheme 2).[16]

1.4 Fluorinating agents

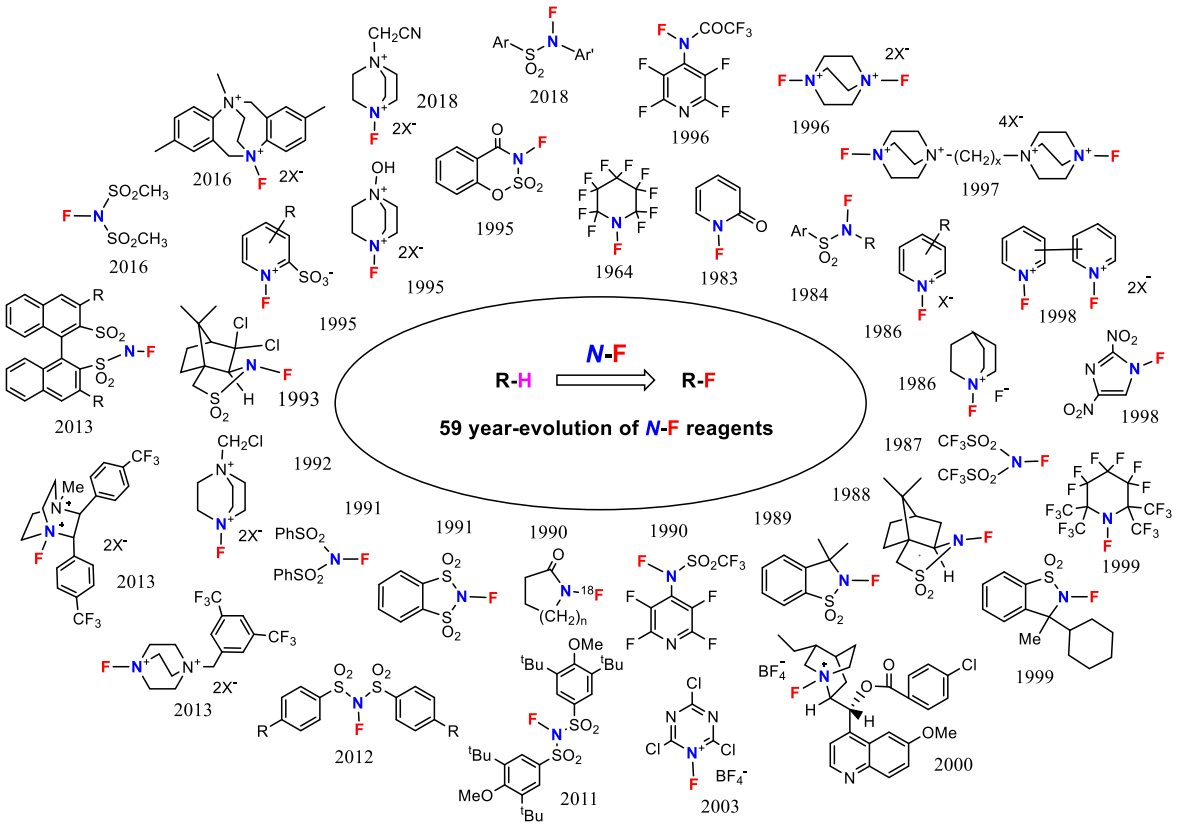
1.4.1 History of fluorinating agents

Since we cannot get enough organofluorine compounds from nature, there has been a great demand for the development of fluorinating agents and fluorination methodologies to transfer a fluorine atom to organic compounds. Fluorinating agents can be categorized as nucleophilic and electrophilic. Both nucleophilic and electrophilic reagents can be used for radical fluorination by means of reaction conditions.[17]

The history of electrophilic fluorinating agents can be traced back to 1886 when Henri Moissan first isolated molecular fluorine (F_2).[18] Although F_2 gas diluted with N_2 can be used at very low temperature for organic synthesis,[19] F_2 is extremely reactive and toxic unlike other halogens. The use of F_2 gas requires special skills and equipment and has significant safety risk. Therefore, easy-to-handle and selective fluorinating agents are essential for the wide-spread advancement of organofluorine chemistry to many non-fluorine chemists. Alternatives to F_2, such as perchloryl fluoride ($FClO_3$)[20] and the *O*-F reagents such as CF_3OF[21], $CsSO_4F$[22], and CF_3COOF[23] had been used as fluorinating agents for many years. However, these reagents still have high risks for safe handling. Although XeF_2[24] was considered as a safer alternative, it is very expensive because of the scarcity of Xe in nature.

In late 20th century, *N*-F fluorinating agents appeared as safe and easy-to-handle electrophilic fluorine source.[25-26] This breakthrough enabled an increasing number of researchers to engage in organofluorine chemistry. The *N*-F electrophilic fluorinating agents have made

significant contribution to the current “golden age” of fluorine chemistry, by virtue of their easy-to-handle nature, high reactivity and selectivity, and wide applications.



Scheme 3. Development of electrophilic *N*-F fluorinating agents

We summarized this 59 year-evolution of *N*-F reagents in a chronological order as a review paper.[25] (Scheme 3) Banks reported the groundbreaking research on perfluoro-*N*-fluoropiperidine[27] in 1964. However, the compound was not feasible for two decades due to the low yields in production and fluorination reactions. The initial interest in *N*-F compounds was sparked in the 1980s with the publication of the first report on an *N*-F fluorinating agent, *N*-fluoro-2-pyridone[28], by Purrington in 1983. The following year, Barnette described *N*-fluoro-*N*-alkylarenesulfonamides[29] as stable crystalline compounds that were easy to work with and useful for the fluorination of carbanions. Soon after, in 1986, Umemoto reported a range of *N*-fluoropyridinium triflates[30-31] that were reactive, easy to handle, and broadly applicable. Following Umemoto's discovery, several *N*-F fluorinating agents were reported, including the powerful *N*-

fluorotrifluoromethanesulfonimide[32] by DesMarteau in 1987, mild *N*-fluorosultams, including the first chiral *N*-fluorosultams by Lang in 1988[33] and 1989[34], less reactive *N*-fluorolactams by Sathyamurthy in 1990[35], and moderate *N*-fluoro-*o*-benzenedisulfonimide (NFOBS)[36] and *N*-fluorobenzenesulfonimide (NFSI)[37] by Davis and Differding in 1991, and powerful 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bistetrafluoroborate (Selectfluor™)[38] by Banks in 1992. Currently popular *N*-F fluorinating agents such as N-fluoropyridinium salts, NFSI, and Selectfluor were developed within a decade from Purrington's first report in 1983.

Following this initial development, other noteworthy *N*-F reagents were developed, including a series of zwitterionic *N*-fluoropyridinium salts by Umemoto in 1995[39], another Selectfluor-type reagent, 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bistetrafluoroborate (NFTh/Accufluor™) by Poss and Shia in 1995, a more powerful reagent, 1,4-difluoro-1,4-diazoniabicyclo[2.2.2]octane bistetrafluoroborate by Umemoto in 1996[40], and a high-fluorine content and powerful reagent, *N*,*N*'-difluoro-2,2'-bipyridinium bistetrafluoroborate (Synfluor™) by Umemoto in 1998[41].

In 2000, practical chiral reagents, *N*-fluorinated chiral cinchona alkaloids, were reported by Shibata and Takeuchi[42] and by Cahard[43]. In 2003, Cahard showed that chiral *N*-fluorocinchona alkaloids could be prepared quantitatively with not only Selectfluor but also with other powerful *N*-F fluorinating agents, such as NFTh, NFSI, and *N*-fluoro-2,6-dichloropyridinium tetrafluoroborate[44]. After a ten-year hiatus, in 2013, chiral dicationic DABCO-based *N*-F reagents and chiral *N*-fluorobinaphthyldisulfonimides were reported by Gouverneur[45] and by Shibata, Ma, and Cahard[46]. In 2016, Shibata reported *N*-fluoromethanesulfonimide (Me-NFSI) as a high atom-economy reagent[47], and Gouverneur and Cvingroš reported a novel *N*-F reagent derived from the ethylene-bridged Tröger base[48]. More recently, in 2018, Zipse and Renaud disclosed *N*-fluoro-*N*-aryl-arenesulfonamides (NFAS)[49] as radical fluorinating agents.

1.4.2 Existing problems of the popular fluorinating agents

Although a large number of *N*-F fluorinating agents have been developed so far and many of them have been commercialized. NFSI,[37] Selectfluor,[38] and *N*-fluoropyridinium salts[50]

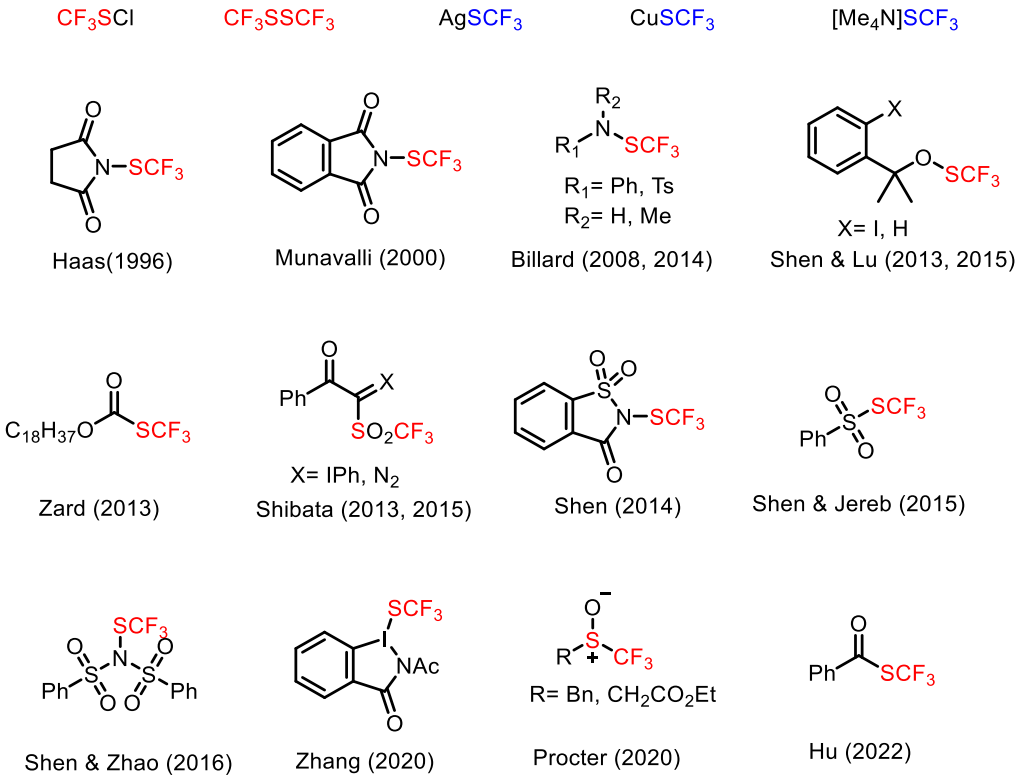
represent the most popular fluorinating agents which are widely used and produced in factories on a large scale. However, they have very low fluorine content. Comparing with their over 300 g/mol molecular weight, only a fluorine atom (19 g/mol) is useful. The ionic nature of Selectfluor and *N*-fluoropyridinium salts makes them difficult to dissolve in non-polar organic solvents, which limits their applications in many situations. Although these reagents are very reactive and powerful, none of them are suitable for the fluorination of highly basic and nucleophilic compounds such as organo lithium and magnesium species. For example, NFSI provided only 37% yield for the fluorination of phenyllithium, Selectfluor and NFPY unable to produce any desired phenyl fluoride. Thus, a more selective and practical fluorinating agent is needed to be developed.

1.5 Trifluoromethylthiolating reagents

1.5.1 History of trifluoromethylthiolating reagents

Besides the excellent electronic and metabolic properties granted by the fluorine atom, trifluromethylthio (CF_3S) group possesses the highest lipophilicity (Hansch's hydrophobic parameter $\pi = 1.44$)[51] among the common fluorine-containing moieties, which greatly enhances the cell membrane permeability of the drug candidates.[52] Thus, the synthesis of CF_3S-incorporated molecules is of great importance, and numerous trifluoromethylthiolation methodologies[53-56] have been developed. Trifluoromethylthiolating reagents, as the cornerstone, play a pivotal role in the development of the field.[57-60] The first generation of CF_3S reagents are CF_3SCl[61-63] and CF_3SSCF_3.[64-66] However, their toxicity and gaseousness make them impractical reagents for general use. Nucleophilic CF_3S reagents such as $AgSCF_3$[67], $CuSCF_3$[68], $[Me_4N]SCF_3$,[69] *etc*. are expensive and/or sensitive to air. In the past two decades, many shelf-stable and easy-to-handle electrophilic CF_3S reagents have been developed as useful CF_3S-transfer tools. For example (Scheme 4), Haas's *N*-[(trifluoromethyl)thio]succinimide,[70] Munavalli's *N*-[(trifluoromethyl)thio]phthalimide,[71] Billard's trifluoromethanesulfanylamides and sulfonamides,[72-73] Shen and Lu's trifluoromethyl-substituted thioperoxide reagents,[74-76] Zard's trifluoromethylthiocarbonate,[77] Shibata's trifluoromethanesulfonyl hypervalent iodonium ylide,[78-79] Shen's *N*-trifluoromethylthiosaccharin,[80] Shen and Jereb's thifluoromethylthiosulfonate,[81-82] Shen

and Zhao's *N*-trifluoromethylthio-dibenzenesulfonimide,[83-84] Zhang's hypervalent trifluoromethylthio-iodine(III) reagent,[85] Procter's trifluoromethyl sulfoxides,[86] and Hu's trifluoromethylthioate.[87]



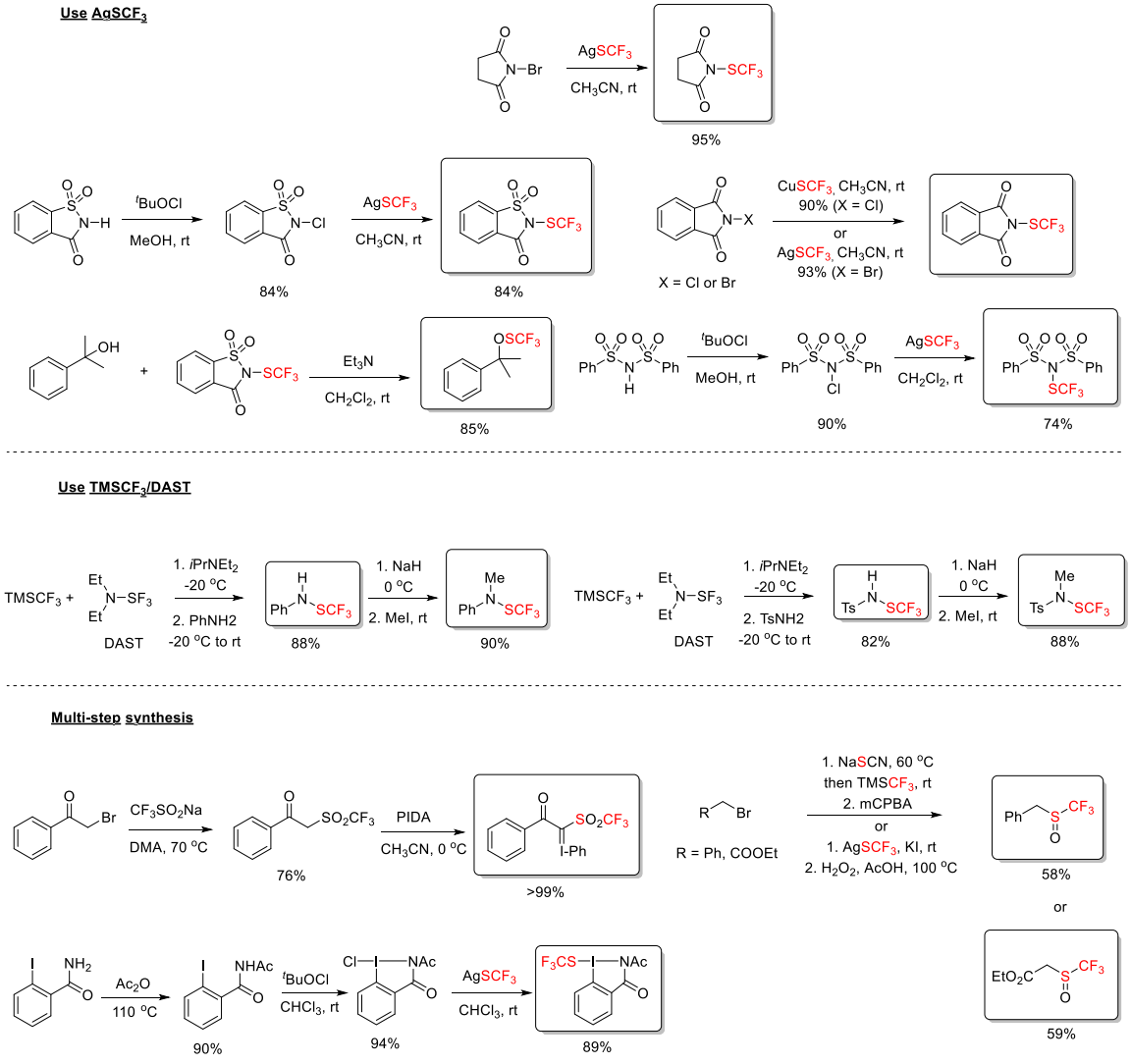
Scheme 4. Conventional trifluoromethylthiolating reagents

1.5.2 Common problems of the conventional fluorinating agents

Although many CF_3S reagents are currently available, they have common significant drawbacks: the use of expensive $AgSCF_3$ or $TMSCF_3$/DAST as CF_3S source in their preparation, and/or multi-step synthesis as well as low atom-economy. (Scheme 5) These disadvantages will be magnified when the CF_3S reagents are prepared on a large scale.

Moreover, these reagents cannot consider both reactivity and stability at the same time. For example, the reactive *N*-trifluoromethylthio-dibenzenesulfonimide[83-84] is moisture sensitive, *N*-trifluoromethylthiosaccharin[80] is unstable toward the column chromatography; whereas stable *N*-[(trifluoromethyl)thio]phthalimide[71] and trifluoromethanesulfanylamides[52] need an acid-activation for many reactions.

An easy-to-handle, easy-to-prepare, and reactive CF_3S reagent with high atom-economy is urgently needed.



Scheme 5. Selected examples of the preparation of CF_3S reagents

1.6 1,1,1,3,3,3-Hexafluoroisopropanol (HFIP) in organic synthesis

1,1,1,3,3,3-Hexafluoroisopropanol (HFIP) is a highly polar solvent with strong hydrogen bond-donating (HBD) properties. This unique solvent has been utilized in various organic synthesis applications due to its capability of stabilizing ionic species, transferring protons, and participating in many intermolecular interactions.[88] Over the course of the last decade, the use of HFIP as a solvent has transitioned from a relatively uncommon choice to a mainstream option in

many areas of organic synthesis. This is primarily due to the observation that reactions conducted in HFIP often exhibit superior performance compared to other solvents. As a result, HFIP is now more frequently considered as a viable solvent choice, which has catalyzed an increase in its usage and citations. (Figure 2)

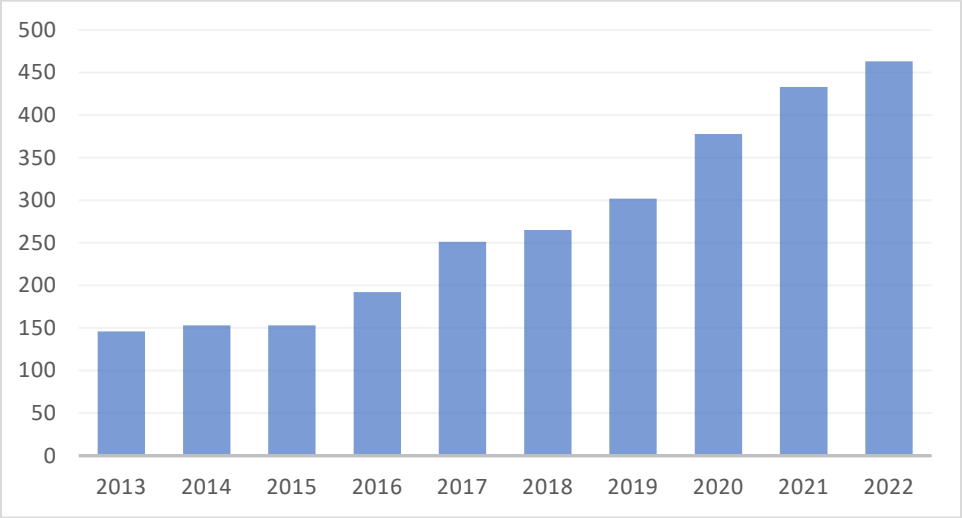


Figure 2. Number of publications related to HFIP in past decade (source: SciFinder)

Legros and coworkers investigated the impact of polyfluorinated alcohols on Brønsted acidity and hydrogen-bond donor ability, as well as their ability to promote selected reactions.[89] The study found that the hydrogen-bond donor ability was affected by the steric bulk around the hydroxyl group of different fluorinated alcohols, while the Brønsted acidity was mainly influenced by the number of CF_3 groups in the molecule rather than its overall structure. The evaluation of various polyfluorinated alcohol solvents as promoters in sulfoxide oxidation and imino Diels−Alder reactions demonstrated that the hydrogen-bond donor ability played a crucial role in promoting these reactions, whereas the Brønsted acidity had minimal effect. In these reactions, HFIP outperformed other fluorinated solvents such as TFE.

The extraordinary hydrogen-bond donor ability and high ionizing power of HFIP often enhance the reaction rate or provide activating effect.[90-91] The perceived benefits of HFIP, such as its ease of removal and recyclability, have also led to researchers re-evaluating the cost/benefit ratio of using this solvent.

CHAPTER 2

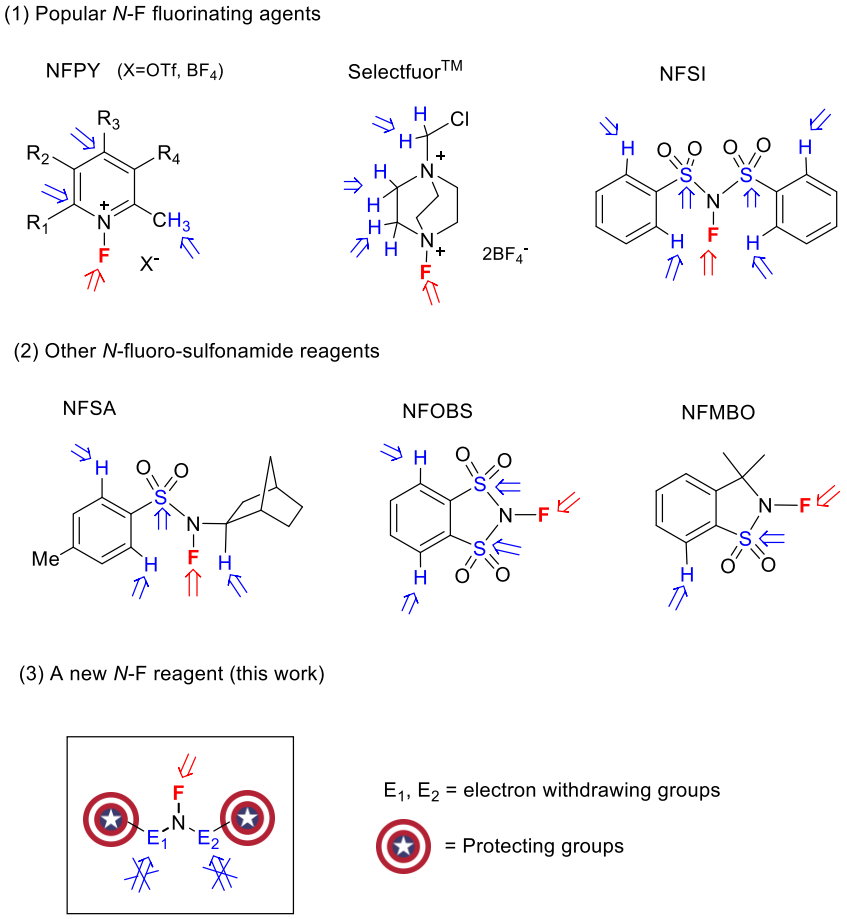
DEVELOPMENT OF *N*-FLUORO-*N*-(*TERT*-BUTYL)-*TERT*-BUTANESULFONAMIDE

(Warning: Fluorine gas is highly toxic and reactive; organolithium reagents like tert-butyllithium are pyrophoric. The use of these reagents requires special skills trained by professionals.)

2.1 Background

Ever since organofluorine compounds garnered widespread attention because of the unique properties of fluorine,[11] there has been a demand for synthetic methods that can introduce fluorine atom(s) into organic compounds in an efficient manner.[92] A case in point are (hetero)aryl and alkenyl fluorides whose widespread applications include the fields of medicines[3], agrochemicals[4], and novel functional materials[2]. (Hetero)aryl- and alkenyl lithiums and Grignard reagents can be regarded as the obvious starting materials for the synthesis of (hetero)aryl and alkenyl fluorides because vast number of those compounds are available.[93-96] Recently, two methods for the fluorination of LiCl-mediated Grignard reagents have been reported.[97-98] Yet, methods for the fluorination of highly basic organolithiums are very inefficient. The first fluorination of phenyl lithium was conducted using dangerous $FClO_3$ in 1969 and produced fluorobenzene in only 42% yield.[20] Afterward, safe and easy-to-handle *N*–F fluorinating agents emerged, such as the currently popular *N*-fluoropyridinium salts (NFPY)[50], fluorobenzenesulfonimide (NFSI)[37], and *N*-chloromethyl-*N*-fluoro-1,4-diazoniabicyclo[2,2,2]octane bistetrafluoroborate (Selectfluor™)[38] (Scheme 6, top). Other easy-to-handle *N*-F reagents such as *N*-fluoro-*N*-exo-norbornyl-*p*-toluenesulfonamide (NFSA),[29] *N*-fluoro-*o*-benzenedisulfonimide (NFOBS),[99] and *N*-fluoro-3,3-dimethyl-2,3-dihydro-1,2-benzothiazole-1,1-dioxide (NFMBO)[34] were also developed (Scheme 6, middle). These electrophilic *N*-F reagents fluorinated nucleophilic substrates such as enolate anions but the fluorination of strongly basic (hetero)aryl and alkenyl lithiums failed or,

at best, was unsatisfactory. For example, NFPY and Selectfluor failed to fluorinate aryl and alkenyl lithiums;[38, 50, 100] NFSA fluorinated 2-lithioanisole and a 2-lithio-*p*-toluenesulfonamide derivative, but the yields were low (24% and 55%, respectively);[29] whereas NFSI[37, 99, 101], NFOBS[99], or NFMBO[101-102] afforded less than desirable results in many cases.



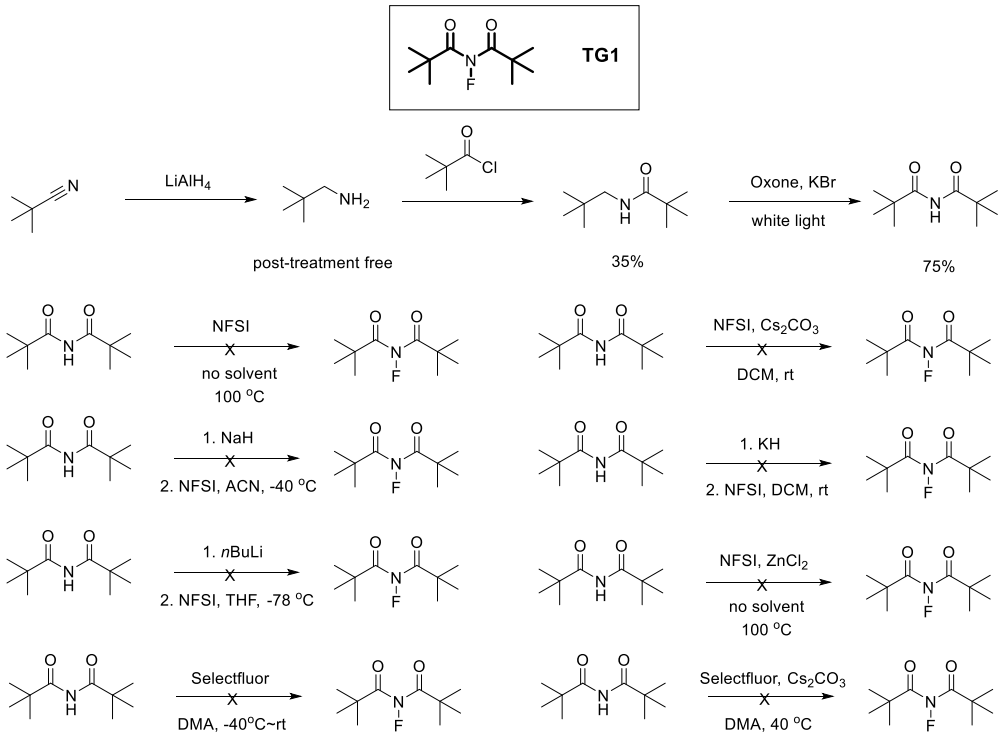
Scheme 6. Reactive sites on the electrophilic *N*-F fluorinating agents

We speculated that the failures observed with the existing fluorinating reagents were caused by many reactive sites susceptible to deprotonation or nucleophilic attack by strong bases (see => in Scheme 6), so we designed a molecule consisting of the fluorine core, -E_1NFE_2-, sandwiched between two protecting groups (Scheme 6, bottom). E_1 and E_2 are electron withdrawing groups such as carbonyl and sulfonyl groups which increase the electrophilicity of the fluorine atom. This ensures that the reagent has substantial reactivity. We expected that the protecting groups could prevent the side reactions happening on the undesired E_1 and E_2 site so that only fluorine atom would participate

the reaction. Therefore, the reagent has a very high selectivity that is excellent for the fluorination of strongly basic and nucleophilic substances.

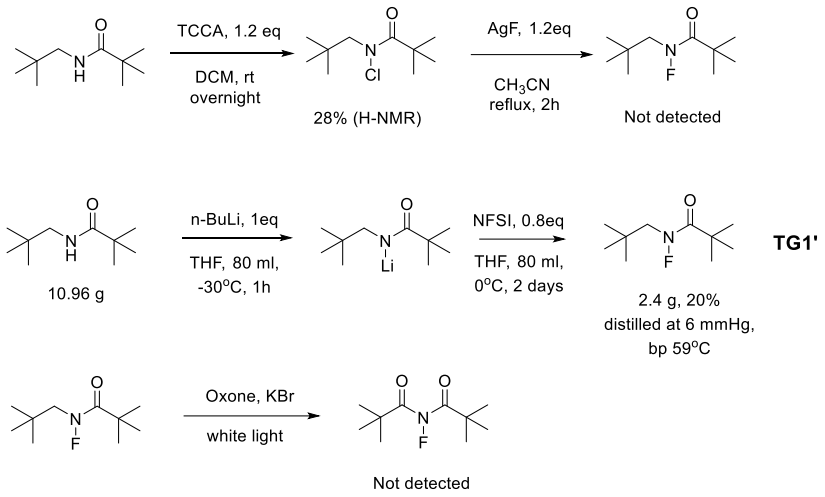
2.2 Results and discussion

First, we needed to choose the protecting group and steric effects were first considered. Steric effects play a vital role in organic chemistry, they have a nearly ubiquitous presence and can influence the activation energies and rates of a wide range of chemical reactions to varying degrees.[103] In our case, we believed that a protecting group with significant steric hindrance would have a significant effect on the nucleophilic attack of E_1 and E_2. Tertiary butyl group has the largest A-value (>4) among the common substituents and could be the best choice.[104] In addition, unlike benzene ring, the tertiary butyl group itself is chemically inert and cannot be deprotonated by strong bases. The good lipophilicity of tertiary butyl group would make this reagent easily soluble in organic solvents.



Scheme 7. Attempt of preparing TG1

Initially we focused on the preparation of target reagent 1 (TG1) because we noticed the lack of *N*-fluoro imide type of fluorinating agents in the market.[25] We started with the commercially inexpensive *tert*-butyl nitrile which we reduced to the neopentyl amine. After reacting with pivaloyl chloride, an amide was formed which was oxidized to *tert*-butyl imide using Oxone/KBr under the visible light.[105] However, could not convert the *tert*-butyl imide to the desired reagent TG1 even though we tried various conditions. (Scheme 7)



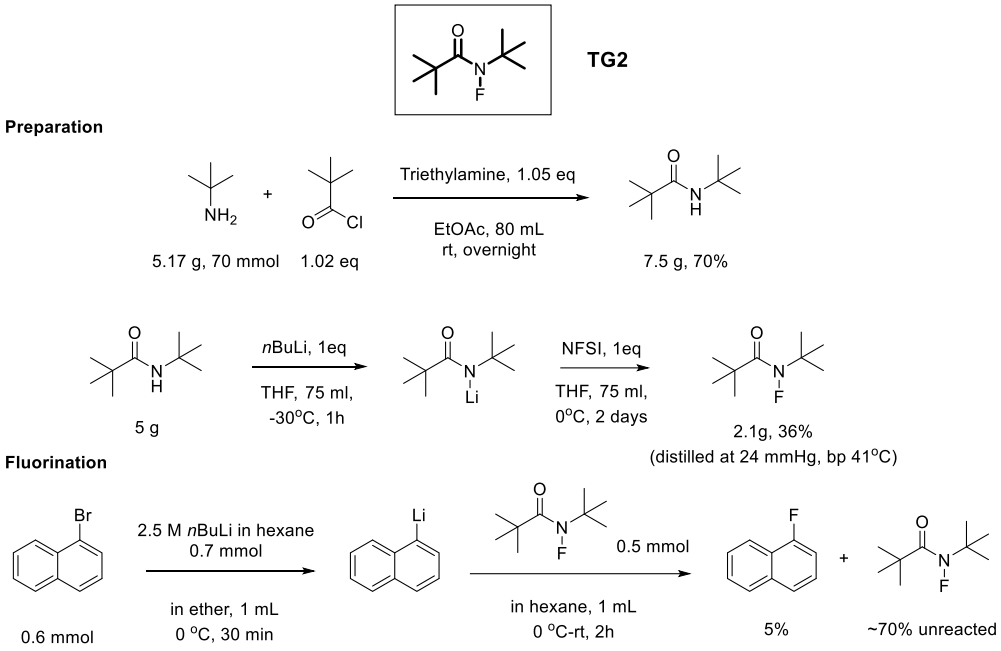
Scheme 8. Alternative routes to prepare TG1

Instead of preparing the TG1 from the corresponding imide, we sought to prepare the *N*-fluoro amide TG1' and then oxidize it to the *N*-fluoro imide TG1 (Scheme 8). Although TG1' could not be obtained by replacing the chlorine using silver fluoride, it was successfully prepared by deprotonation with *n*-BuLi and fluorination with NFSI. TG1' was distilled in 20% yield with a bp of 59 °C / 6 mmHg. However, the oxidation of TG1' did not produce any TG1. It should be mentioned that even if TG1' could be a fluorinating agent, the alpha-proton next to the *N*-F moiety could easily react with a strong base to eliminate HF. Obviously, it is not a reagent that fits our philosophy.

Given that the *N*-fluoro amide can be easily prepared, why not try to prepare an *N*-fluoro amide which has no alpha-proton? Then we turned our attention to the target reagent 2 (TG2).

The preparation of TG2 was much simpler. We started with *tert*-butyl amine and pivaloyl chloride, which are both commercially inexpensive. The *tert*-butyl amide was obtained in 70%

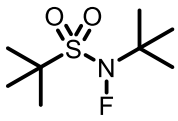
yield after recrystallization from hexane in one step. With the same deprotonation and fluorination methods used in preparing TG1', the TG2 was obtained in 36% yield after distillation as a colorless oil (bp 41 ^{o}C / 24 mmHg). We could not wait to apply this reagent for the fluorination of highly basic and nucheophilic species. (Scheme 9)



Scheme 9. Preparation of TG2 and its fluorination

We chose naphthyllithium as a substrate, which was generated *in situ* by reacting the corresponding naphthyl bromide with *n*-BuLi. However, the desired product naphthyl fluoride was formed in only 5% yield. But we found that about 70% of TG2 remained unreacted. This indicated that the TG2 has a low reactivity, but indeed, the bulky *tert*-butyl group can protect the carbonyl site from being attacked by the strong nucleophile, lithium naphthalene. Now we just needed a reagent with higher reactivity.

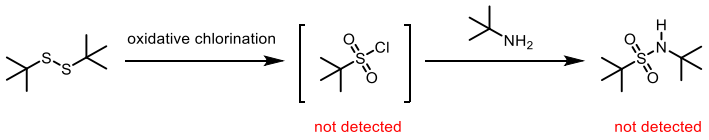
The reactivities of *N*-F fluorinating agents are closely related to the acidity of their corresponding *N*-H compounds.[106] The more acidic the *N*-H compounds, the higher reactivity of the *N*-F reagents. Since sulfonamide (pKa = ~17.5) is much more acid than the amide (pKa = ~25.5), we speculated that the target reagent 3, *N*-fluoro-*N*-(*tert*-butyl)-*tert*-butanesulfonamide (**NFBB, 1**), should have higher reactivity than TG2, and the protecting effect of *tert*-butyl group would be preserved. (Scheme 10)



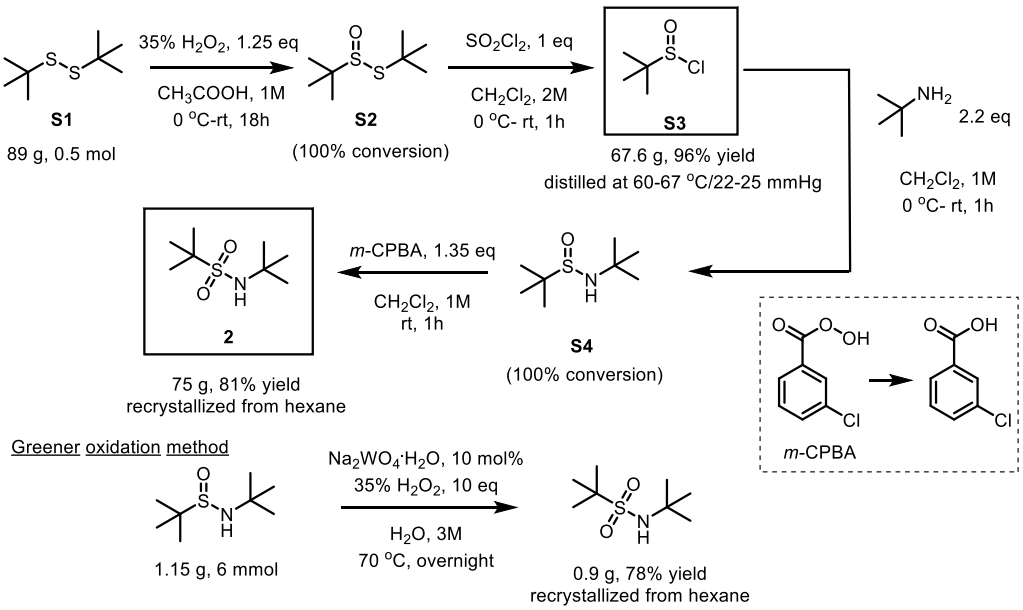
1, NFBB

Scheme 10. Structure of NFBB

To prepare NFBB we needed to tackle two challenges. The first one was the thermal instability of the C(^{t}Bu)-S bond, likely caused by C-S bond cleavage promoted by the electron-withdrawing groups. For example, it is known that ^{t}BuSO$_2$Cl decomposes at room temperature with a half-life ca. 34 h at 35 ^{o}C.[107] Therefore, the sulfonamide precursor of NFBB cannot be simply prepared from the ^{t}BuSO$_2$Cl and ^{t}BuNH$_2$. The *in-situ* generation of ^{t}BuSO$_2$Cl from *tert*-butyl disulfide, followed by addition of ^{t}BuNH$_2$ did not yield any *tert*-butyl sulfonamide. (Scheme 11) Also, even if we prepared the sulfonamide, NFBB might be an unstable reagent because of the electron-withdrawing effect of *N*-F moiety.



Scheme 11. Preparation of *tert*-butyl sulfonamide via ^{t}BuSO$_2$Cl

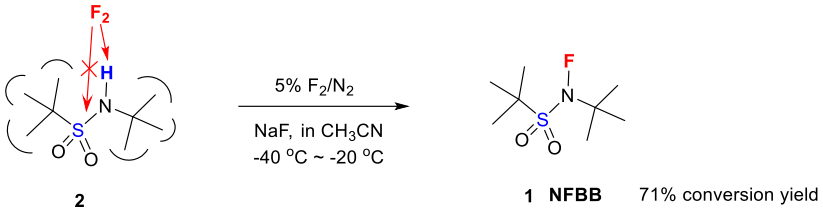


Scheme 12. Preparation of *tert*-butyl sulfonamide via ^{t}BuSOCl

But we did not give up on this reagent. We finally found another route to prepare the *tert*-butyl sulfonamide **2**. Oxidation of *tert*-butyl disulfide **S1** by hydrogen peroxide in acetic acid gave *tert*-butylthiosulfinate **S2** in 100% conversion. After work-up and solvent evaporation, the crude **S2** reacted with sulfuryl chloride efficiently to produce ^{t}BuSOCl **S3** which was obtained by distillation in excellent yield (bp 60-67 ^{o}C / 22-25 mmHg). Different from $^{t}BuSO_2Cl$, **S3** is a stable compound and it reacted with $^{t}BuNH_2$ to provide *tert*-butyl sulfinamide **S4** in full conversion. Next, **S4** was oxidized by *m*-CPBA to generated desired sulfonimide **2** in 81% yield after recrystallization from hexane. (Scheme 12) Although this process required multiple steps, all the reactions were highly efficient. For example, short reaction time, excellent yield, and no need of column chromatography. It can also be easily scaled up to hundred-gram-scale. The only flaw was the use of relatively expensive *m*-CPBA as an oxidant, which always generated *m*-chlorobenzoic acid as side-product. To solve this problem, we also developed a greener oxidation method. In this green method, hydrogen peroxide was used as an oxidant and sodium tungstate was used as a catalyst of this reaction. The reaction proceeded in water solution and the only side-product was water! The desired sulfonamide **2** was obtained in similar yield after recrystallization from hexane.

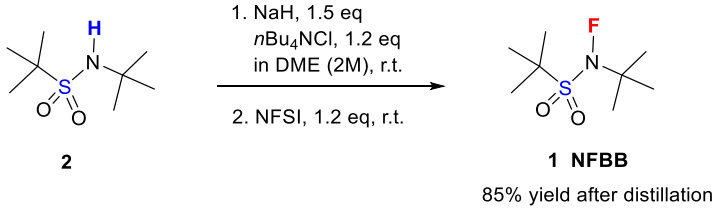
With the NFBB precursor **2** in hand, the second challenge was how to overcome an anticipated low chemical yield in the fluorination of sulfonamide **2**. Although many *N*-fluorosulfonamides have been synthesized by fluorination of the corresponding sulfonamides with molecular fluorine (F_2) diluted with N_2,[25] the sulfonamide of an amine possessing a tertiary butyl group gave a very low yield (14%) of the *N*-F product because the S-N bond of $RSO_2NH^{t}Bu$ was easily cleaved during the fluorination.[29]

To our delight, we found that the readily available precursor, *N*-(*tert*-butyl)-*tert*-butanesulfonamide[108] (**2**), was fluorinated with 5% F_2/N_2 in acetonitrile in the presence of NaF to produce NFBB **1** in a good conversion yield (Scheme 13). This result can be justified by claiming that the strong steric hindrance in the two bulky *tert*-butyl groups permits F_2 to react with NH but blocks attack to the S-N bond.



Scheme 13. Synthesis of NFBB with molecular fluorine

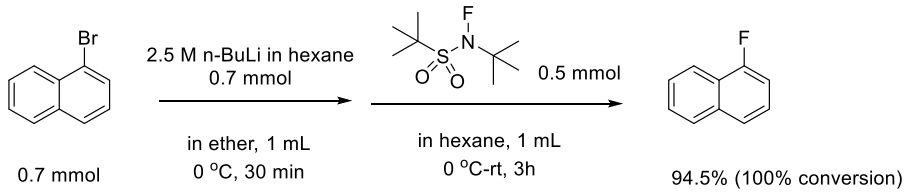
Although F_2 is readily generated through electrolysis and current safety measure makes its use appropriate in industrial environments, the use of F_2 is rare in standard research laboratories because of its high explosiveness and toxicity.[19] Accordingly, we investigated the synthesis of NFBB using safe alternative fluorine sources. In 2000, it was reported that *N*-fluoro sulfonamides could be prepared from sulfonamides using the safe and readily available NFSI.[109] However, in addition to the low yields obtained, the reported method required large excess of NFSI (3 eq) and KH (6 eq) and dilute condition (0.1 M). Despite a plethora of optimization efforts, this reaction was hitherto considered impractical.



Scheme 14. Preparation of NFBB with NFSI

After many trials (see **Experimental** section for detail), we found a breakthrough methodology using a quaternary ammonium chloride as a key additive. Thus, **2** reacted with significantly lesser amounts of cheap NaH in 1,2-dimethoxyethane (DME) in the presence of tetrabutylammonium chloride, followed by fluorination with an almost equimolar amount of NFSI (Scheme 14). This reaction proceeded to completion in a high concentrated DME solution (2 M to **2**) at rt and produced pure NFBB in a high isolated yield (85%) after distillation (96% NMR yield before isolation). This surprising facile distillation of NFBB, its high chemical yield and trouble-free preparation make our method suitable for scalable production.

We first thought NFBB would be unstable because the electron withdrawing *N*F moiety might make the C(*t*Bu)-S bond easy to break. But we were happy to find that NFBB is air and thermally stable, and was an easily distillable liquid (bp 61.5-62 ^{o}C/9.5-10.1 mmHg). No decomposition was observed by ^{1}H-NMR after heating neat NFBB at 120 ^{o}C for 12 h, and only minute decomposition was observed at 150 ^{o}C for 12 h. NFBB exhibited high chemical stability against acid and alkali. Any decomposition did not occur for a week in 1M HCl and 1M KOH. In addition, NFBB has very low oxidation power. NFBB decomposed very slowly with iodide anion, 0.75M KI in acetonitrile, half-life *ca.* 8 h. NFBB did not decompose with 0.75M triethylamine in acetonitrile for a week (see **Experimental** section for detail). These properties are in sharp contrast to the current *N*-F reagents such as NFSI and Selectfluor, which decomposed immediately with KI and Et_3N. NFBB is exceedingly soluble in non-polar and polar organic solvents. These features are the result of its special structure: an SO_2NF moiety flanked by two very bulky, lipophilic, and σ-electron-donating *tert*-butyl groups.

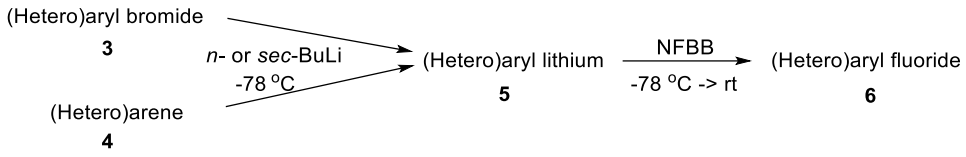


Scheme 15. Fluorination of naphthyllithium with NFBB

We wanted to compare the reactivity between TG2 and NFBB to prove our previous assumption that NFBB is more reactive and have the same protecting effect on the sulfone site. We applied NFBB to the fluorination of the same substrate naphthyllithium. (Scheme 15) Excitingly, the fluorinated product was obtained in 94.5% yield based on all-consumed NFBB which clearly suggested that NFBB was a perfect reagent for the fluorination of highly basic organo lithium species.

To explore the substrate scope, we examined NFBB in the fluorination of various (hetero)aryl lithiums. We found that the best results were obtained when NFBB, dissolved in twice the volume of dry hexane, was added dropwise to a solution of (hetero)aryl lithium **5**—prepared in situ from the corresponding aryl bromide **3** or arene **4**, dissolved in dry THF or diethyl ether, using

n- or *sec*-butyllithium at -78 °C—and the reaction mixture was allowed to warm to room temperature (Scheme 16).

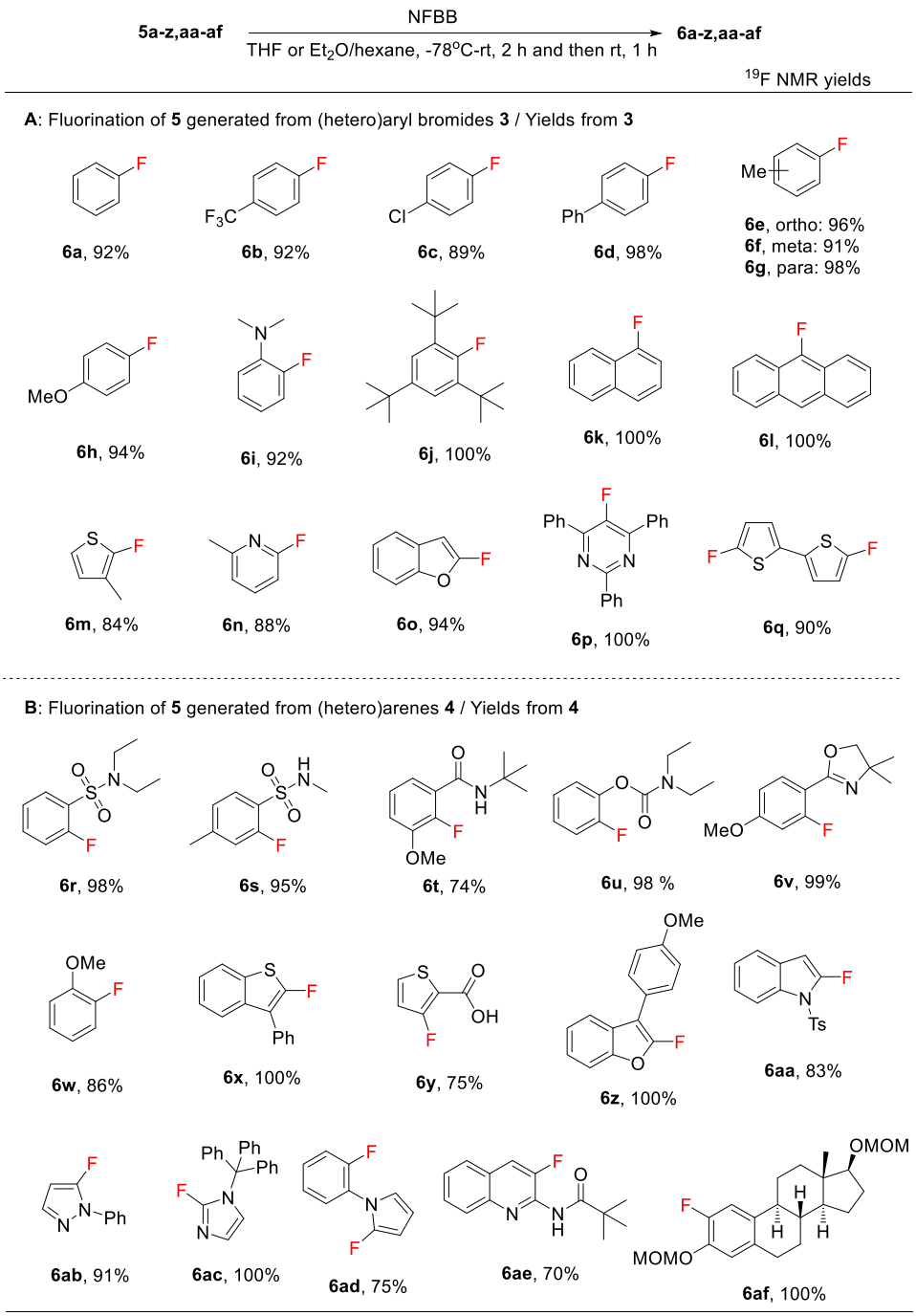


Scheme 16. Fluorination with NFBB following preparation of (hetero)aryl lithiums

Table 1**A** illustrates the fluorination of many (hetero)aryl lithiums **5**, prepared *in situ* from (hetero)aryl bromides **3**, producing (hetero)aryl fluorides **6a**-**q** in extremely high overall yields. Quantitative yield (100%) or close to it (>90%) were obtained in most cases. Electron-withdrawing (**6b**, **c**) and donating (**6e**-**j**) substituents were well tolerated. It should be noted that NFBB was able to fluorinate a site that was hindered by bulky *tert*-butyl groups in quantitative fashion (**6j**). Difluorination of dilithio bithiophene proceeded in an excellent 90% yield (**6q**). The lower yields observed with **6c**, **m**, and **n** were likely due to the difficulty in generating (hetero)aryl lithiums **5** from bromoarenes **3**.

Table 1**B** shows the fluorination of the organo lithiums **5** generated by the regioselective deprotonation of (hetero)arenes **4**. Many fluoro(hetero)arenes were obtained in quantitative yield or close to it. We attributed the lesser yields obtained for **6t**, **y**, **aa**, **ad**, and **ae** to the difficulty in generating the organo lithiums **5** from the substrates **4**. The fluorination of (hetero)aryl and alkenyl lithiums with NFBB was outstanding compared to any of the other reported fluorinating agents mentioned in the introduction. It is worth noting that **6af**, a precursor readily derived to bioactive 2-fluoro estradiol, was obtained in quantitative yield by the NFBB-fluorination using the MOM-protected estradiol. This method is simple and much better than the two recently reported multi-step methods for the preparation of 2-fluoro estradiol using Selectfluor/$Et_3N{\cdot}3HF$[110] and CsF under photo activation[111].

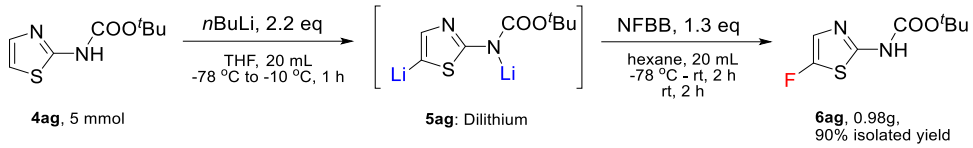
Table 1. Fluorination of (hetero)aryl lithiums 5 with NFBB.



See **Experimental** section for detail for detailed procedures.

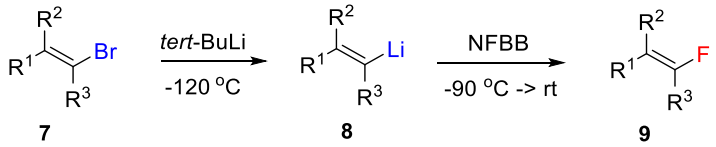
We demonstrated the practicability of NFBB by conducting the gram-scale preparation of Boc-protected 2-amino-5-fluorothiazole **6ag** (Scheme 17), an important building block for glucokinase activators that are potential medicaments for Type 2 Diabetes.[112] 2-(*N*-Boc-amino)thiazole **4ag** was treated with 2.2 eq of *n*-BuLi to yield dilithium **5ag**, followed by reaction

with NFBB to give the desired 5-fluorinated 2-aminothiazole **6ag** in a 90% isolated yield. In contrast, the fluorination of the dilithium **5ag** with NFSI gave a mixture of **6ag** (70%), 5-phenylsulfonyl-2-(*N*-Boc-amino)thiazole (15%), and the starting **4ag** (10%), from which fluoro product **6ag** was isolated in 36% yield by repeated crystallization.[113]



Scheme 17. Gram-scale fluorination with NFBB

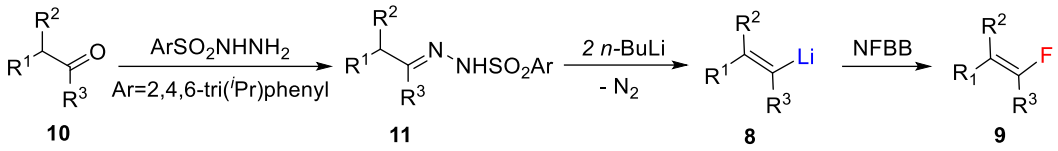
In 1986, Schwartz reported the first fluorination of alkenyl lithiums—formed *in situ* from alkenyl iodides and *tert*-BuLi—with *N*-fluoro-*N*-(*tert*-butyl)benzenesulfonamide at -120 °C.[114] However, a considerable amount of the protonated products formed in this reaction, and protonation became the major reaction when the temperature rose above -120 °C. Since NFSI was developed in 1991, NFSI has been used extensively for the preparation of many biologically attractive alkenyl fluorides.[115-116] However, NFSI-led fluorinations suffered from protonated byproducts or low yields. Although it has been known that alkenyl bromides **7** can undergo Br/Li exchange with *tert*-BuLi at -120 °C to generate alkenyl lithiums **8**,[117] the conversion of easily available alkenyl bromides to alkenyl fluorides via lithiation has only been reported in a few cases, and only in low yields.[118-120] We have successfully carried out the fluorination of alkenyl lithiums **8** from bromides **7** with NFBB at -90 °C to room temperature to give the corresponding fluoroalkenes (**9a-j**) in a stereo- and regiospecific manner (Scheme 18) (Table 2**A**).



Scheme 18. NFBB-fluorination of alkenyl lithiums 8 prepared from bromides 7

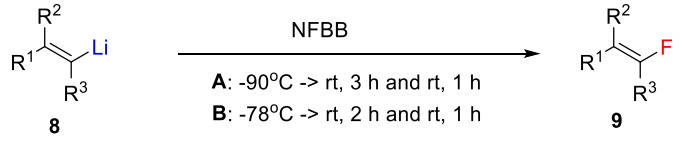
Arylvinyl fluorides **9a**, **c**, **d**, **f**-**h** were obtained in excellent overall yields (81-100%) from bromides **7**. The main cause for the lesser yield of **9b** and **e** was ascribed to the difficulty in generating alkenyl lithiums **8** from **7**. Alkylvinyl fluoride **9i** was also obtained in excellent yield.

Moreover, the fluorinated steroid derivative **9j** was obtained in excellent 90% yield, indicating the high potential of this method in the medicinal field.

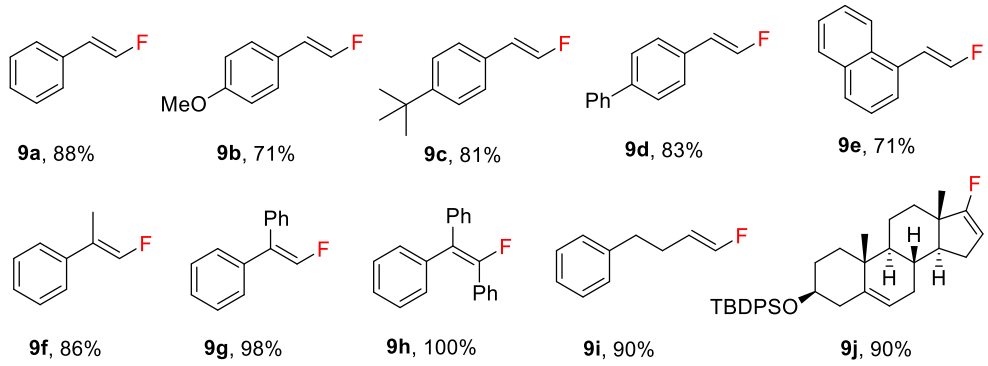


Scheme 19. NFBB-fluorination of alkenyl lithiums 8 prepared by Shapiro reaction

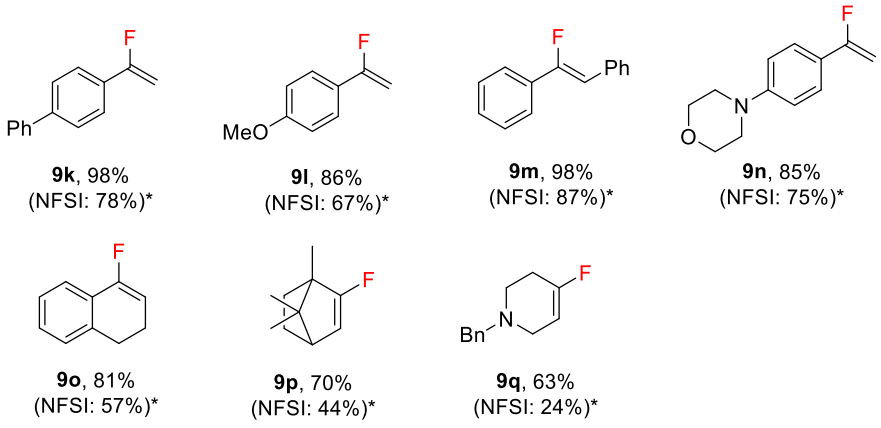
Table 2. Fluorination of alkenyl lithiums 8 with NFBB.



A: Fluorination of **8** generated from alkenyl bromides **7** /Yields from **7**



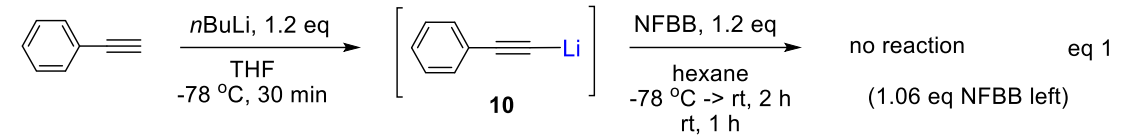
B: Fluorination of **8** generated from hydrazone **11** by Shapiro reaction /Yields from hydrazone **11**

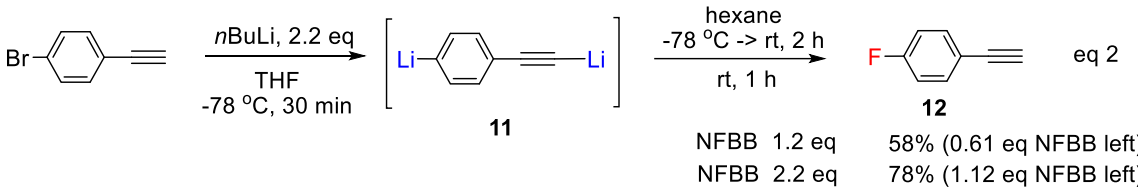


*The data are ^{19}F NMR yields with NFSI reported in ref. 77. See **Experimental** section for detailed procedures.

In 2013, Altman and coworkers reported the NSFI fluorination of alkenyl lithium **8**—generated *in situ* by treatment of 2,4,6-triisopropylbenzenesulfonyl hydrazone **11** derived from ketone **10** with *n*-BuLi (Shapiro reaction).[100] We treated the alkenyl lithium **8**—prepared in the same way as Altman's—with NFBB (Scheme 19). As shown in Table 2**B**, NFBB produced aryl fluoroalkenes (**9k**-**o**) and alkyl fluoroalkenes (**9p**-**q**) in remarkably higher yields compared to NFSI, demonstrating the viability of NFBB for preparing fluoroalkenes.

In addition to the fluorination of (sp^2)C-Li species, we were interested in the fluorination of (sp)C-Li species. As shown in Scheme 20, we found that NFBB did not react with alkynyl lithium **10** and remained intact (eq 1). This unexpected chemoselectivity was clearly proved by the reaction of dilithium **11**, which gave only product **12** fluorinated at the aryl lithium part (eq 2).





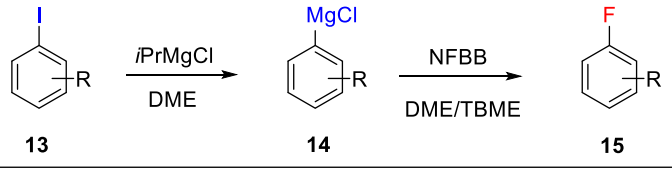
Scheme 20. Reactivity of NFBB to alkynyl lithiums

This unexpected chemoselectivity cannot be explained by the steric factor of NFBB alone, because alkynyl lithiums are sterically smaller than aryl lithiums and NFBB can fluorinate sterically hindered sites as seen in the fluorination of **5j**. The chemoselectivity could be attributed to the mildness in reactivity of NFBB and the unusual *N*-F fluorination mechanism that is still unsolved.[25] Thus, NFBB has the extraordinary selectivity which is useful for the selective fluorination.

In addition to organolithium compounds, Grignard reagents are also important precursors to (hetero)aryl fluorides. The advantage of using organomagnesium compounds hinges in their better functional group tolerance.[121] In early reports, simple phenylmagnesium halide alone was fluorinated with *N*-F reagents such as *N*-fluoro-*N*-*tert*-butyl-*p*-toluenesulfonamide

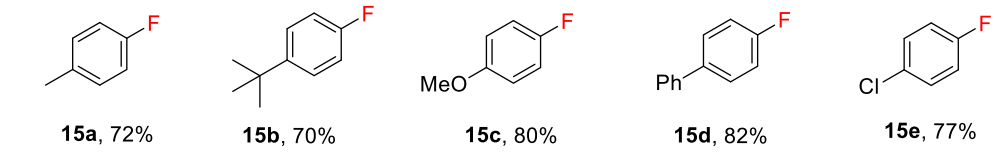
(fluorobenzene's yield 50%)[29], NFPY (58%)[50], Selectfluor (TfO salt) (66%)[38], and NFOBS (80%)[99]. One exception was that 1-naphthylmagnesium bromide was fluorinated with NFMBO, giving 1-fluoronaphthalene in only 17% yield[102]. Afterward, Knochel and coworkers developed a LiCl-mediated preparation of Grignard reagents[122] and applied it for the preparation of various (hetero)aryl fluorides using NFSI as an electrophilic fluorinating agent; 43-94% yields were obtained.[97] But this process included a complete solvent replacement step from THF to a CH_2Cl_2/perfluorodecaline (4/1) solvent, which is not easy to be reproduced as the Grignard reagent is quite sensitive to the air, and is costly in a large scale. In the same year, Beller and coworkers reported a similar LiCl-mediated process using NFPY as a fluorinating agent. Solvent replacement was not needed in this case but the yields (33-83%) were lower.[98] Since there is no systematic report on the fluorination of traditional standard Grignard reagents (without LiCl), we developed a convenient pathway to serve this purpose. Standard aryl magnesium chlorides were generated via I/Mg exchange in dimethoxyethane (DME) with *i*PrMgCl from the aryl iodides at room temperature or low temperature for the electron rich or electron deficient aromatic derivatives, respectively. Then NFBB, dissolved in twice the volume of *tert*-butyl methyl ether (TBME), was added and the reaction mixture was stirred at room temperature to give the fluorinated products in moderate to high yields (Table 3).

Table 3. Fluorination of Grignard reagents 14 with NFBB.

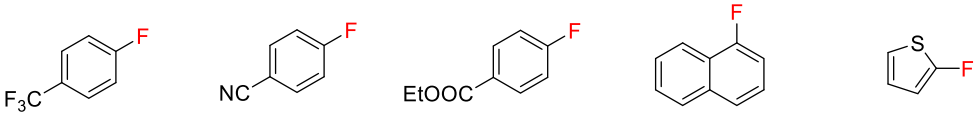


13 **14** **15** ^{19}F NMR yields

Fluorination of **11** generated from aryl iodides **10** / Yields from **10**



15a, 72% **15b**, 70% **15c**, 80% **15d**, 82% **15e**, 77%



15f, 68% **15g**, 64% **15h**, 48% **15i**, 83% **15j**, 45%

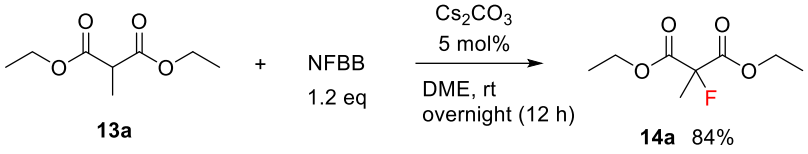
See **Experimental** section for detail for detailed procedures.

Phenyl derivatives bearing electron-donating groups **14a-c** were fluorinated in 70-80% yields, while electron-withdrawing groups **14d-h** afforded the respective products in 48-82% yields. 4-Me (**14a**) and 4-MeO (**14c**) furnished the same range of yields as Beller's (73-83%) using the LiCl-mediated Grignard reagents, while 4-Cl (**14e**) was better than Beller's (48-66%). Naphthyl **14i** was obtained in 83% yield, which was much better than the 17% yield obtained with the same standard Grignard reagent with NFMBO mentioned above.[102] Thiophenyl **14j** gave a low yield (45%). It is worth noting that sensitive functional groups such as cyano (**14g**) and ethoxycarbonyl (**14h**) were well tolerated. No such examples were given, or only very low yields (30-33% for *p*-CN) were obtained in the Beller's case.[98] In this way, NFBB demonstrated the usefulness of the standard Grignard reagents. However, the fluorination yields of the Grignard reagents were relatively lower than those of the aryl lithium reagents. This might be attributed to the different reactivity between the Grignard and lithium reagents and thus, the different fluorination mechanism with NFBB, which might result from the unusual, unsolved *N*-F fluorination mechanism.[25] The Grignard method is less reactive than the lithium method, because the carbon-magnesium bond has less ionic character than the carbon-lithium bond.

Fluorinated active methylene compounds are also important because organic molecules bearing fluorine atoms attached to aliphatic sp^3 carbon rather than aromatic sp^2 carbon are regarded as hit-to-lead compounds in life-science programs[123] and active methylene compounds are versatile building blocks for the synthesis of valuable natural and pharmaceutical products.[124] The fluorination of active methylene compounds is typically carried out by treating their corresponding metal salts with *N*-F fluorinating agents. With NFBB, we found an absolutely new methodology for the fluorination of active methylene compounds.

The conventional method for fluorination of active methylene compounds is the fluorination of their metal salts or direct or Lewis acid-catalyzed fluorination of the active methylene compounds with a strong *N*-F fluorinating agent such as NFSI[37], Selectfluor[38], NFPy[50], and Me-NFSI (*N*-fluoromethanesulfonimide)[47]. During the examination of fluorination of active methylene compounds with NFBB we realized that the yields did not change regardless of the

amount of the base used, rather they increased with less amount of the base. Then we noticed an effective deprotonating ability of the bulky sulfonamido anion, $[^tBuSO_2N^tBu]^-$ that was formed from NFBB after the fluorination. This was a completely different behavior when it was compared to a strong *N*-F reagent such as NFSI, which gives a very stable anion, $[PhSO_2NSO_2Ph]^-$, after the fluorination. This observation led us to conceive a base-catalyzed "*self-sustaining fluorination*" of NFBB for active methylene compounds, because NFBB could act as both fluorinating and deprotonating agent. We found Cs_2CO_3 as the best catalytic base because of its better solubility in organic solvents and the expected enhanced reactivity of carbanions.[125] In the test reaction, NFBB and malonate **16a** were dissolved in 1,2-dimethoxyethane (DME), followed by addition of 20 mol% Cs_2CO_3, and the reaction mixture was stirred overnight at room temperature. Encouragingly, the fluorinated product **17a** was obtained in 83% yield. DME proved to be better for this reaction than other solvents such as acetonitrile, dichloromethane, diethyl ether, and toluene. Next, we tried the reaction with reduced amount of Cs_2CO_3, 10 mol% and 5 mol% loading, which gave the desired product in 85% and 84% (Scheme 21), respectively. We did not reduce the amount of Cs_2CO_3 further to maintain the reproducibility.

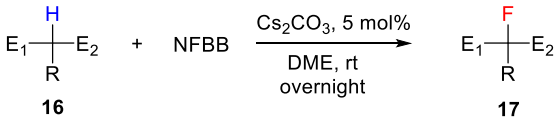


Scheme 21. Cs_2CO_3-catalyzed Fluorination of diethyl malonate

With the optimal 5 mol% condition in hand, we studied a broad range of malonate derivatives 16b-p and other active methylene compounds 16q-z, aa. (Table 4) Diethyl 2-phenylmalonate (**16c**) was fluorinated in excellent 90% yield. A variety of functional groups on the benzene ring of **16c** were tolerated. Acetyl (**16e**), ethoxycarbonyl (**16f**), cyano (**16g**), nitro (**16h**), methoxy (**16j**), and acetamido (**16k**) functional groups on the benzene ring did not affect the result; 89-94% yields were obtained. It is worth noting that the amino group (**16i**), which is prone to be oxidized or strongly activates the aromatic ring also worked well with mild NFBB, giving the fluoro product in 71% yield. The powerful NFSI or Selectfluor decompose with easily oxidizable amino compounds. Other 2-substituents of malonates such as benzyl (**16d**), phenoxy (**16l**),

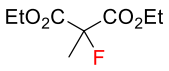
pyridyl (**16m**), allyl (**16n**), and propynyl (**16o**) were tolerated and efficiently converted to the fluoro products in high to excellent yields. The success of **16n** and **16o** allows for further derivatization to other fluorine-containing products. Keto esters (**16q-u**), diketones (**16y, z**) and other types of active methylene compounds (**16v-x**) were also suitable for this fluorination reaction. The low fluorination yield (13%) of diketone **16aa** could be ascribed to the low reactivity of its salt, where the anionic species is stabilized by the neighboring benzoyl groups possessing considerably strong electron-withdrawing properties. Cyclic malonate (**16p**), cyclic keto esters (**16q, r**), and thienyl keto ester (**16s**) produced the desired products in very good yields. The nipecotic acid derivative (**16u**), a potent inhibitor of γ-aminobutyric acid (GABA) uptake[126-127], was selectively fluorinated by our method in 63% yield, though it has an easily oxidizable amine moiety. Difluorination of 2,2-unsubstituted malonate (**16b**) and keto ester (**16t**) were also realized in high yields when 2.2 eq of NFBB was used, demonstrating the high applicability of this method. This new method needs only a catalytic amount of a mild and safe base and hence, is highly economical and environment friendly.

Table 4. Base-catalyzed fluorination of active methylene compounds with NFBB.

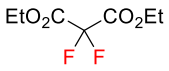


E_1, E_2 = a functional group that withdraws electrons by resonance

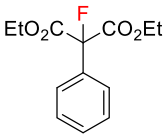
^{19}F NMR yields



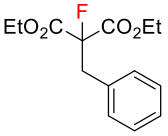
17a, 84%



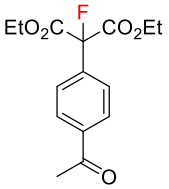
17b, 83%[a]



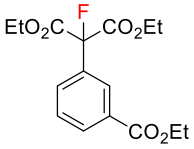
17c, 90%



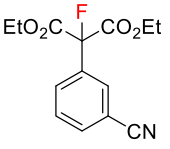
17d, 96%



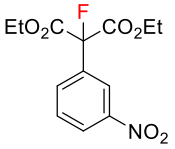
17e, 91%



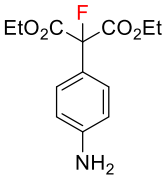
17f, 94%



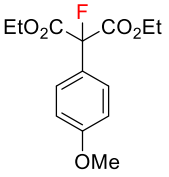
17g, 89%



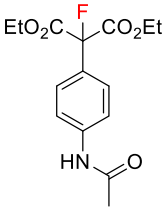
17h, 90%



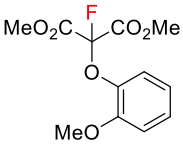
17i, 71%



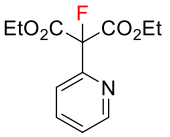
17j, 90%



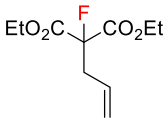
17k, 89%



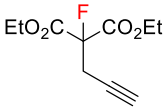
17l, 73%



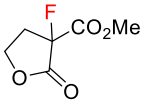
17m, 84%



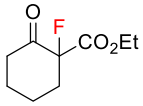
17n, 89%



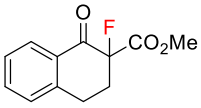
17o, 86%



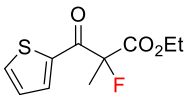
17p, 87%



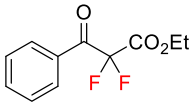
17q, 80%[a]



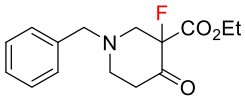
17r, 92%[a]



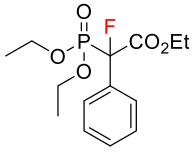
17s, 89%[a]



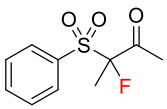
17t, 83%[a]



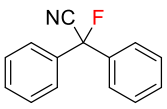
17u, 63%[a]



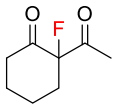
17v, 62%[a]



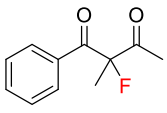
17w, 86%[a]



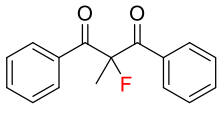
17x, 60%[a]



17y, 52%



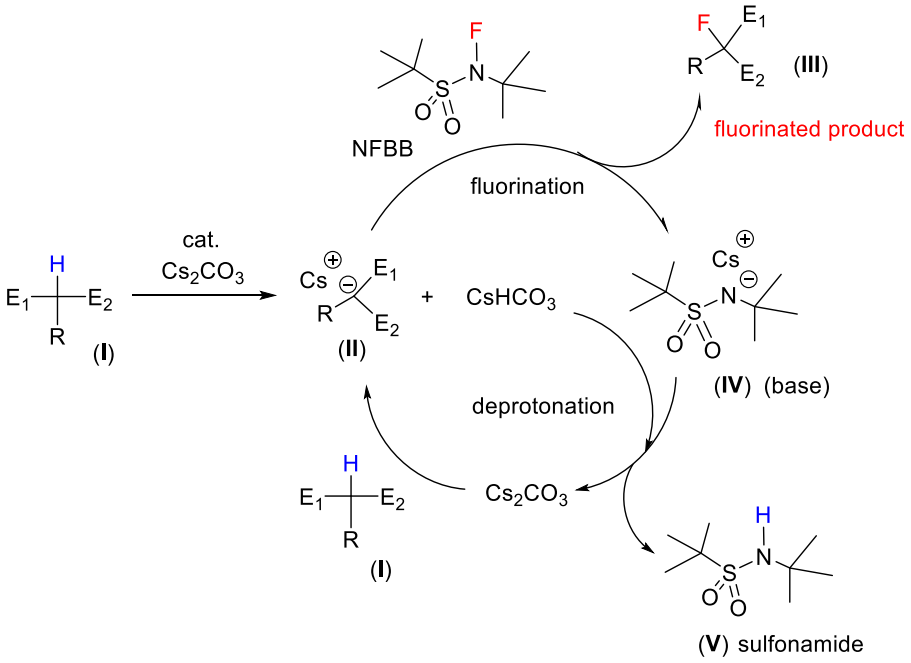
17z, 49%



17aa, 13%

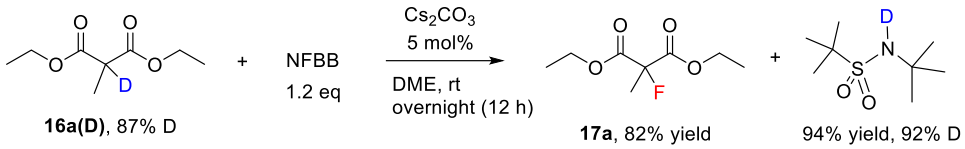
a.10 mol% Cs_2CO_3 was used.

The proposed reaction mechanism for the Cs_2CO_3-catalyzed fluorination with NFBB is shown in Scheme 22. A catalytic amount of Cs_2CO_3 deprotonates the active methylene compound **I**, giving the anionic species **II** and $CsHCO_3$. Species **II** then reacts with NFBB to produce the fluoro product **III** and sulfonamido anion species **IV**. Since $CsHCO_3$ (pKa = ~10 in H_2O) is more acidic than the active methylene compounds (dimethyl malonate pKa = 13 in H_2O), the species **IV** could then deprotonate $CsHCO_3$ to regenerate Cs_2CO_3 together with the formation of sulfonamide **V**. This regenerated Cs_2CO_3 starts the fluorination and deprotonation cycle to produce the fluoro product **III**.



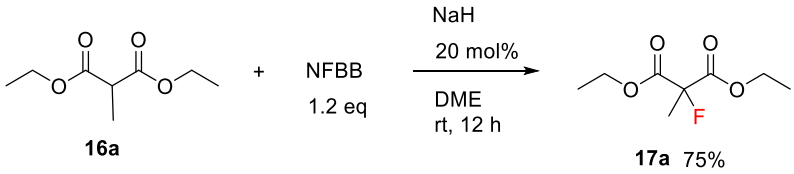
Scheme 22. Proposed reaction mechanism for Cs_2CO_3-catalyzed fluorination of active methylene compounds with NFBB

To confirm this mechanism, we carried out the reaction of 2-deuterated malonate **16a(D)** with 87% D purity. As seen in Scheme 23, we found that the obtained sulfonamide **V(D)** had 92% D purity by integral analysis of ^1H NMR. Thus, the 2-D atom was completely transferred to the sulfonamide within experimental error. This clearly supported the fluorination-deprotonation cycle mechanism.



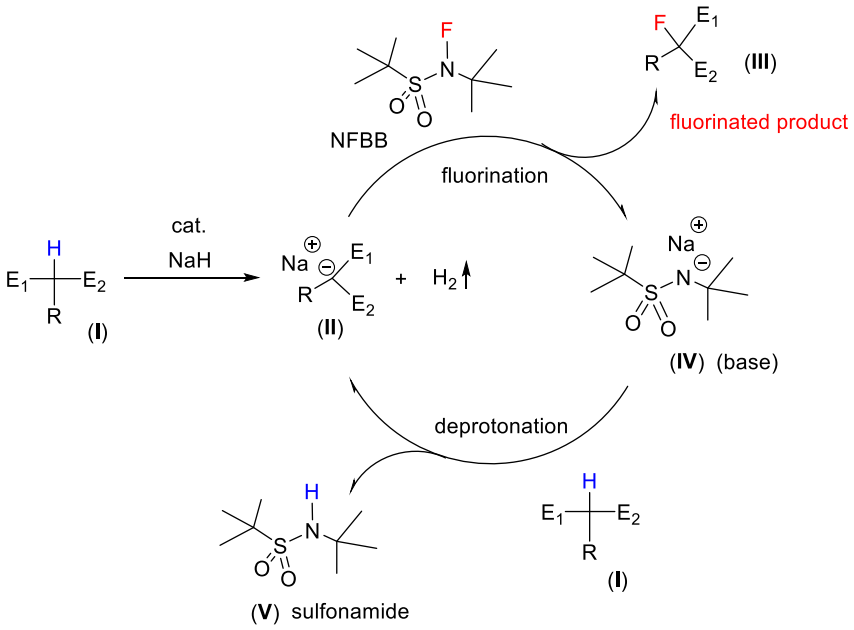
Scheme 23. Cs_2CO_3-catalyzed fluorination of 2- deuterated malonate 16a(D) with NFBB

Since cesium carbonate (Cs_2CO_3) is a dibasic substance, the second base, $CsHCO_3$, can participate in the catalytic cycle. We investigated whether the presence of $CsHCO_3$ was crucial or not for the base-catalyzed self-sustaining fluorination process by conducting the reaction using NaH as a mono-basic substance. It was found that the malonate was fluorinated in good yield (75%) using a catalytic account of NaH under the same conditions (Scheme 24). NaH does not form a second base, but only anionic species **II** by the reaction of active methylene compound **I**. Accordingly, in the mono-base case, another reaction mechanism is proposed as seen in Scheme 25: the resulting anionic species **II** reacts with NFBB to product the fluoro product **III** and the sulfonamido anion species **IV**, which then reacts with **I** to recover the anionic species **II**, which starts the fluorination-deprotonation cycle.



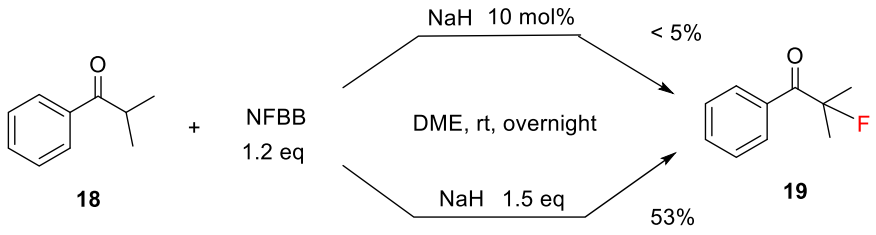
Scheme 24. NaH-catalyzed fluorination of diethyl malonate 16a with NFBB

The actual mechanism depends on the acidity of the active methylene compounds. When the acidity is close to that of $CsHCO_3$, both base-catalyzed mechanisms of Scheme 22 and Scheme 25 occur. Anyway, in the Cs_2CO_3-catalyzed reaction, $CsHCO_3$ does mediate the fluorination-deprotonation cycle.



Scheme 25. Proposed reaction mechanism for mono-base-catalyzed fluorination with NFBB

The base-catalyzed fluorination and deprotonation cycle mechanism can clearly explain the results of fluorination of less acidic isobutyrophenone (**18**) with NFBB (Scheme 26). The use of a catalytic amount of base (NaH) almost did not provide fluoro product **19** (< 5%) while an excess amount of the base produced **19** in 53% yield. As the acidity (pKa 26.3 in DMSO) of α-proton of **18** is much lower than that (pKa ~18 in DMSO) of NH of the sulfonamide (^{t}BuSO$_2$NH^{t}Bu), the cyclic fluorination/deprotonation mechanism with NFBB cannot happen, because the sulfonamide anion base (**IV**) cannot deprotonate isobutyrophenone. Thus, the fluorination methodology by the fluorination-deprotonation cycle of NFBB is dependent on the acidity/basicity relationship of the substrates and the sulfonamide base **IV**.



Scheme 26. Fluorination of isobutyrophenone 18 with NFBB

2.3 Conclusion

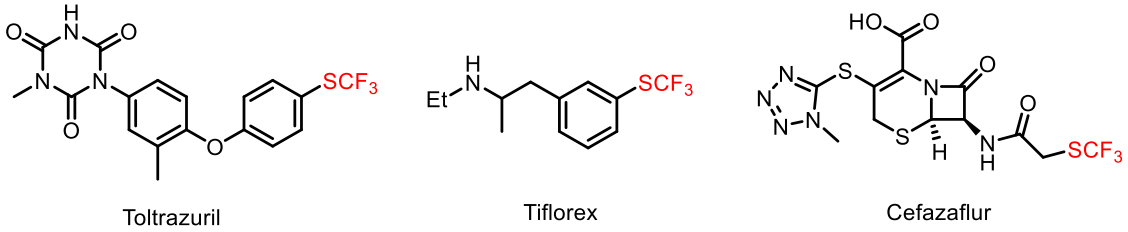
In summary, to tackle the unsolved problem of fluorination of highly basic organo lithium species we designed a series of sterically hindered fluorinating agents. We put effort into preparing *N*-fluoro imide (TG1) but failed to get the desired reagent. We successfully prepared *N*-fluoro amide (TG2). However, low reactivity of this reagent limited its application. After overcoming two challenges—stability and preparation yield—we succeeded in developing the novel *N*-fluoro-*N*-(*tert*-butyl)-*tert*-butanesulfonamide (NFBB), a mild and highly selective reagent for fluorination of carbanions. NFBB fluorinated many highly basic (hetero)aryl and alkenyl lithiums in unprecedented high or quantitative yields. The mild NFBB showed extraordinary chemoselectivity against alkynyl lithiums. The standard Grignard reagents were also fluorinated by NFBB in good yields, in which sensitive functional groups were well tolerated. Significantly, NFBB created a conceptionally new and widely applicable base-catalyzed fluorination-deprotonation cycle reaction, namely the “self-sustaining” fluorination reaction of active methylene compounds, which is highly economical and environmentally friendly. It was clearly evidenced by a deuterium-tracing experiment. Many useful fluorinations were shown to be achieved by means of NFBB. Since our tailor designed NFBB has high fluorine content and high air and heat stability and can be prepared in high yield via standard distillation it will be suitable for large scale preparation. For these reasons, it is expected that NFBB will offer unparalleled usefulness for the practical preparation of many kinds of useful organofluorine compounds in academic and industrial research and applications. NFBB is now commercialized by Tokyo Chemical Industry Co., Ltd. (TCI).

CHAPTER 3

DEVELOPMENT OF S-TRIFLUOROMETHYL TRIFLUOROMETHANESULFONOTHIOATE

3.1 Background

Trifluoromethylthio (CF_3S) group is the most lipophilic (π = 1.44)[51] fluorine-containing group. Introducing the CF_3S group to a drug candidate can dramatically improve its membrane permeability and metabolic stability helping to improve the overall efficiency of a drug candidate. CF_3S-incorporated compounds are found in many pharmaceuticals and agrochemicals such as Toltrazuril[128], Tiflorex[129], and Cefazaflur[130.53] (Scheme 27). In addition, the CF_3S group could be easily and selectively oxidized to trifluoromethylsulfinyl (CF_3SO) or trifluoromethysulfonyl (CF_3SO_2) compounds, two important structural motifs in drug candidates.[131] As discussed in Chapter 1, the currently available trifluoromethylthiolating reagents have significant disadvantages such as the use of expensive materials and/or multi-steps for their preparation, low atom-economy, and narrow applicability. Hence, easily preparable, atom-economical, bench-stable, yet reactive CF_3S reagents are needed.

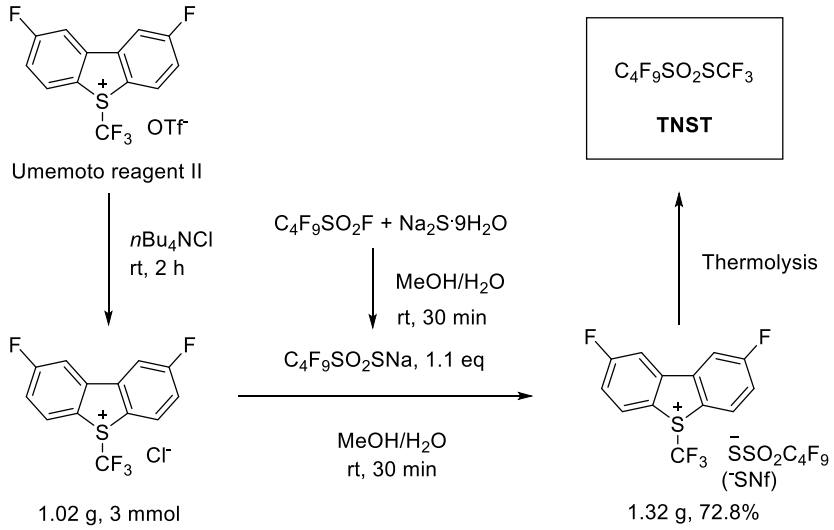


Scheme 27. CF_3S-Containing pharmaceuticals and agrochemicals

3.2 Results and discussion

Inspired by the success of a novel CF_3O reagent trifluoromethyl nonaflate ($C_4F_9SO_2OCF_3$, TFNf) that was reported by our group recently[132], we decided to synthesize a CF_3S reagent with a similar structure: *S*-trifluoromethyl nonafluorobutanesulfonothioate, $C_4F_9SO_2SCF_3$, TNST.

Since TFNf was prepared by thermolysis of the ONf salt of Umemoto reagent II[133], it is reasonable to imagine that if we have the SNf salt of Umemoto reagent II, we could prepare the TNST through its thermolysis. (Scheme 28)



Scheme 28. Attempt of preparing TNST

We began with commercially available Umemoto reagent II, which exchanged anion with *n*Bu_4NCl smoothly to give the Cl salt of Umemoto reagent II. This Cl salt was insoluable in acetonitrile and was collected by filtration in excellent yield. Next, we needed to replace the Cl anion with the SNf anion. However, neither the sodium nor the potassium SNf salt was commercially available. We thought the NaSNf could be prepared *in-situ* by reacting the nonafluorobutanesulfonyl fluoride with sodium sulfide in the mixed solvents of methanol and water. Then the Cl salt of Umemoto reagent II, dissolved in water, was added to the reaction mixture of NaSNf. After stirring at room temperature for half an hour and evaporating the solvents, we obtained a crude mixture of SNf salt of Umemoto reagent II. Subsequently, the thermolysis of

this crude mixture produced a colorless oil, although the boiling point of this oil was lower than we expected for TNST. Frustratingly, the NMR data of this oil matched TFNf.

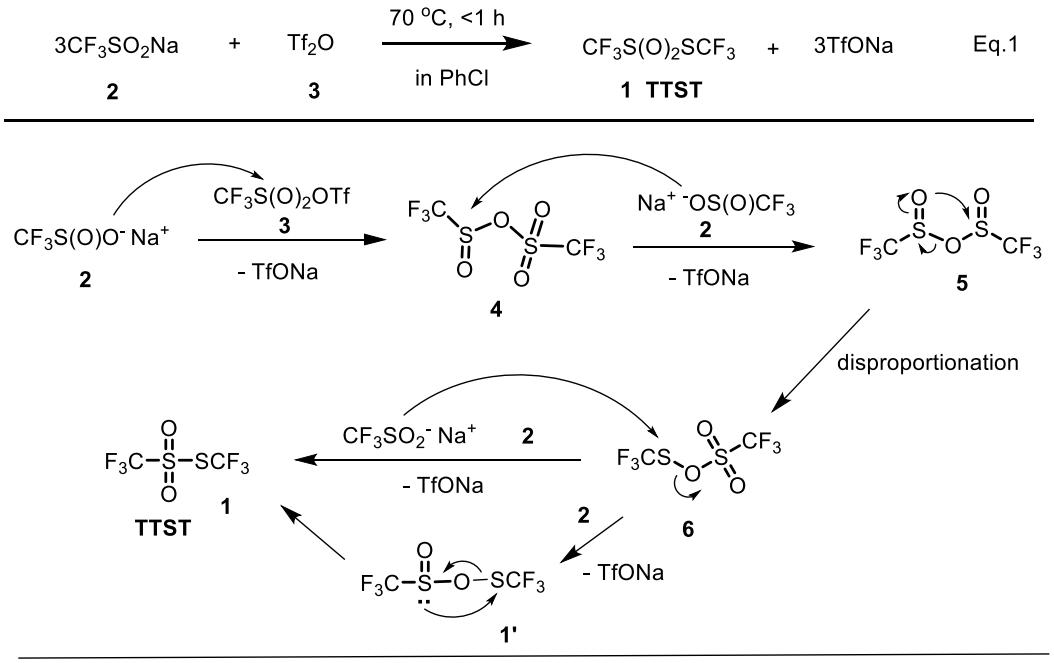
We sought to find the reason for the failure of preparing TNST. After carefully checking of the ^{1}H- and ^{19}F-NMR data of the SNf salt of Umemoto reagent II we had prepared, we found that what we thought as SNf salt was acturally the ONf salt. The sodium sulfide probably hydrolyzed to sodium hydroxide in a solution of water and methanol and we obtained NaONf instead of NaSNf.

Although this problem could be solved by using anhydrous sodium sulfide, the commercial source of anhydrous sodium sulfide was very expensive while *in-situ* preparation of anhydrous sodium sulfide required sodium metal which was highly reactive and dangerous to work with. In addition, sodium metal could not react with elemental sulfur perfectly in organic solvents. The presense of unreacted sodium metal and elemental sulfur made the reaction of *in-situ* generated sodium sulfide with nonafluorobutanesulfonyl fluoride very complicated. We believed even if we could obtain the TNST, the use of expensive starting materials and the lengthy process of preparation would make it an impractical reagent.

S-Trifluoromethyl trifluoromethanesulfonothioate ($CF_3SO_2SCF_3$, TTST, **1**) is an simplified analogue of TNST. Although TTST was first synthesized in 1955,[134] it was never used as a CF_3S reagent. The preparative process for TTST involved three steps from CS_2 and required the handling of toxic chemicals (IF_5, CF_3SSCF_3, CF_3SCl) and a long reaction time. Recently, it was reported that **1** was prepared from CF_3SO_2Cl and KXCN (X=S, Se).[135] However, this report was inaccurate because their obtained product's NMR data did not match TTST.

Inspired by our recent studies on reactions of CF_3SO_2Na/TfOH/Tf_2O to prepare the Umemoto reagent IV,[136] we tried to prepare TTST using commercially inexpensive CF_3SO_2Na and Tf_2O in one step. We were excited to find that **1** can be obtained in good yield by simply mixing CF_3SO_2Na (**2**) and Tf_2O (**3**) in nonpolar chlorobenzene (Eq.1, Scheme 29, see **Experimental** for detailed procedure of preparation). The reaction is fast and its exothermicity can be regulated by a controlled addition of **3**. We proposed a plausible mechanism for this transformation (Scheme 29). Trifluoromethanesulfinyl triflate (**4**)[133, 137] resulting from the reaction

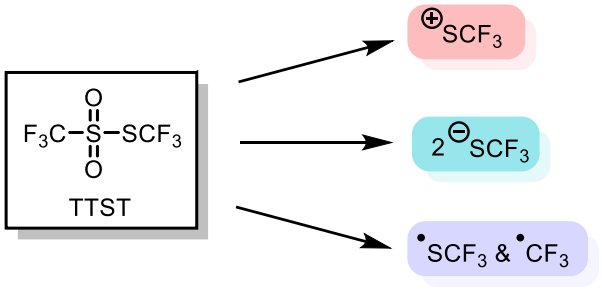
of **2** and **3** reacted with another molecule of **2** to form trifluoromethanesulfinic anhydride (**5**). Disproportionation of **5** generates trifluoromethanesulfenyl triflate (**6**),[136-138] which then reacts with a third molecule of **2** to produce **1** directly or through its isomer **1'**; in total, three molecules of TfONa are byproducts of this reaction. An additional key advantage is that this reaction is easily scalable because **1** can be simply isolated by direct distillation from the reaction mixture.



Scheme 29. Proposed mechanism for the preparation of TTST (1)

TTST (**1**) is a colorless liquid with a b.p. of 66-69 °C. It is bench-stable and easy-to-handle in air. No obvious decomposition was observed (<1%) after heating in toluene-d_8 at 130 °C for 15 hours. The high thermal stability of **1** was supported by the fact that **1** could be fractionally distilled from the reaction mixture that was heated to 172 °C (see **Experimental** section for detail).

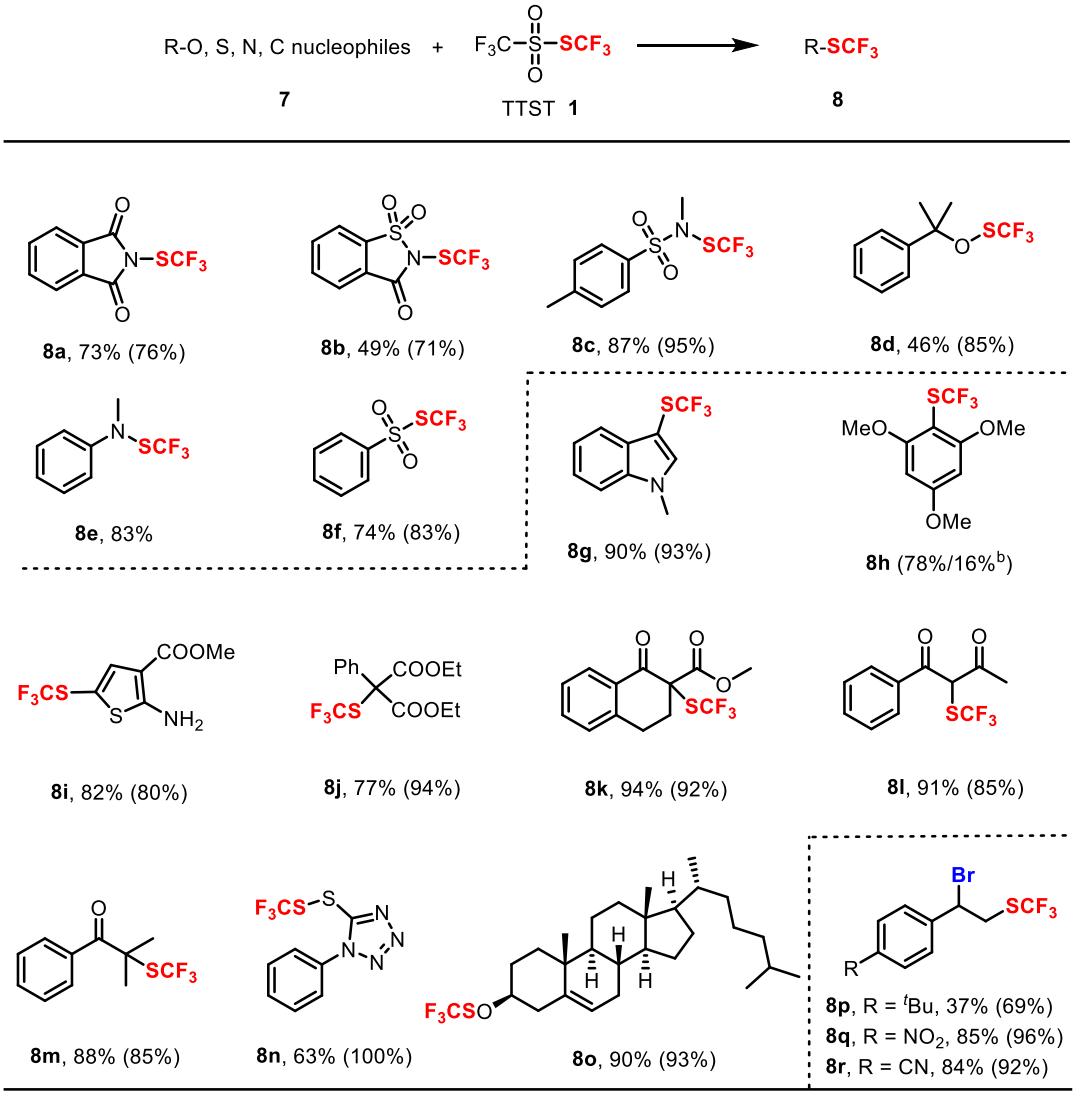
We found TTST (**1**) to be a widely applicable and atom-efficient trifluoromethylthiolating reagent which could generate both electrophilic, nucleophilic, and radical CF_3S species as well as the radical CF_3 species. (Scheme 30)



Scheme 30. Structure and transformations of TTST

As an electrophilic trifluoromethylthiolating reagent, TTST reacted with various O, S, N, and C nucleophiles effectively (Table 5). It should be noted that TTST provided a simple-step preparation for many of the literature reported CF_3S reagents and in high yields. For example, Munavalli's (**8a**) [71] and Shen's (**8b**) [80] reagents could be prepared without using the expensive $AgSCF_3$, and Billard's (**8c**)[73], Shen and Lu's (**8d**)[74-76], Billard's (**8e**)[72], Shen and Jereb's (**8f**)[81-82] reagents could be prepared without using expensive CF_3S reagents. Thus, the higher reactivity of TTST compared with those conventional reagents was confirmed. In addition, TTST reacted well with electron rich (hetero)aromatics (**8g**-**i**). Carbanions generated from malonate (**8j**), β-keto ester (**8k**), β-diketone (**8l**) and ketone (**8m**) were trifluoromethylthiolated with TTST in excellent yields. TTST also reacted with heterocyclic thiol (**8n**) and bioactive alcohol (**8o**) efficiently to produce the corresponding CF_3S products. In the presence of lithium bromide, TTST gave difunctionalized products (**8p**-**r**) of alkenes in very good yields.

Table 5. Electrophilic reactions with TTST[a]

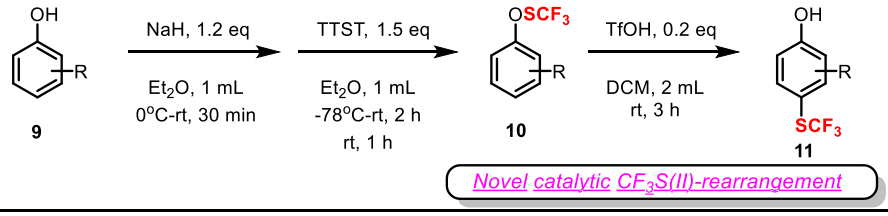


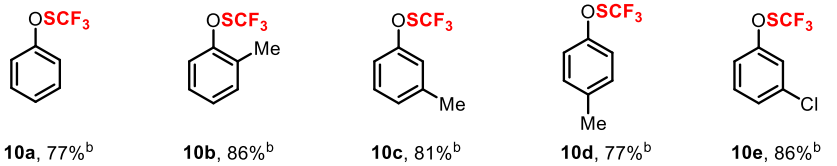
[a]Yields are isolated yields of pure compounds. Yields in parentheses are ^{19}F-NMR yields using an internal standard. [b]Di-SCF_3 product.

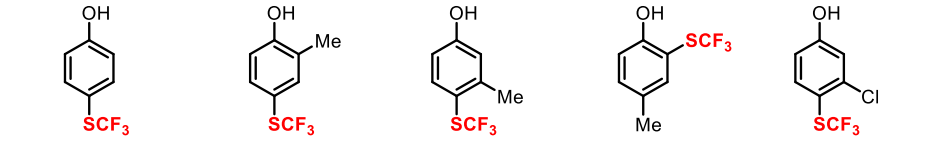
Although there were many reports of trifluoromethylthiolation of diverse nucleophiles, the trifluoromethylthiolation of a very common type of nucleophile, phenoxides, which can be easily generated from phenols has been neglected. To our best knowledge, aryl trifluoromethanesulfenates ($ArOSCF_3$) have never been characterized or studied except for a short preparative description of $PhOSCF_3$ that appeared in 1986, but without experimental data.

We were pleased to find that $ArOSCF_3$ can be easily obtained by reacting TTST with the corresponding phenoxides in high yields and that $ArOSCF_3$ underwent a novel triflic acid-

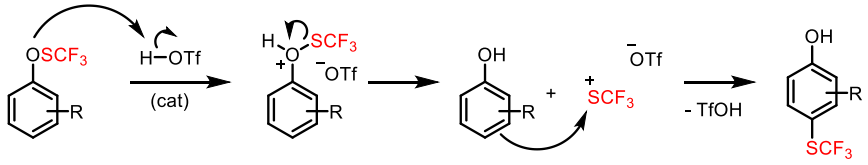
Table 6. Preparation of $ArOSCF_3$ and the novel catalytic $CF_3S(II)$-rearrangement[a]



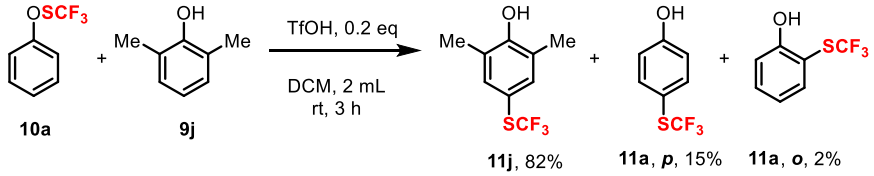


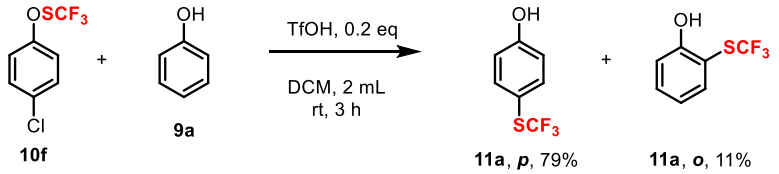


Proposed mechanism



Mechanistic study



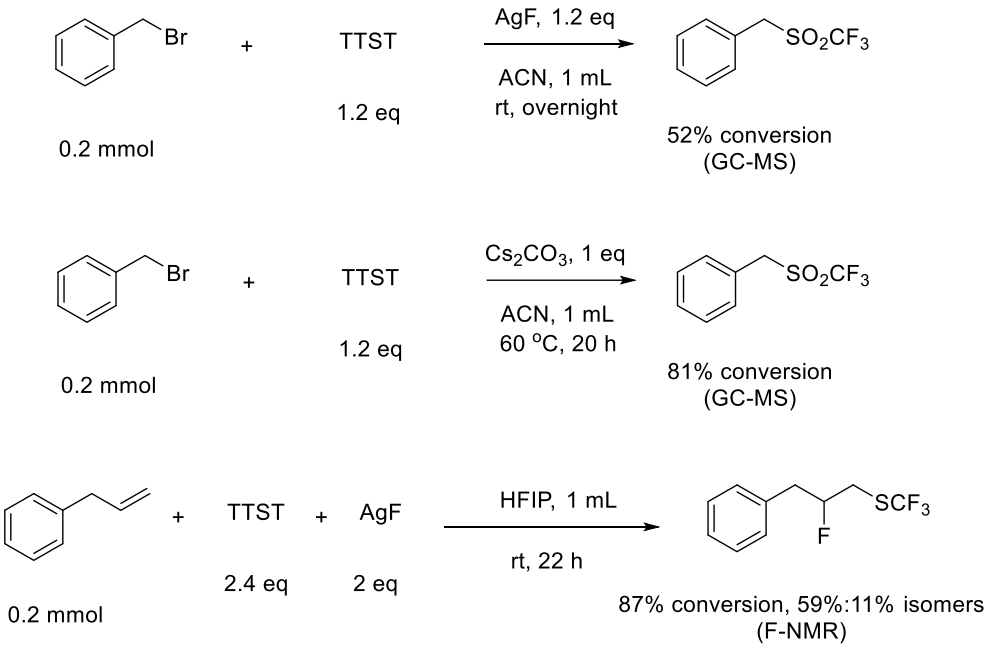


[a]Yields are NMR yields using 4-chlorobenzotrifluoride or 4-bromobenzotrifluoride as an internal standard. [b]Isolated yields of pure compounds after distillation. [c] Crude **10** were used, yields are based on phenol **9**.

catalyzed CF_3S^{II}-rearrangement to produce *p*/*o*-CF_3S-substituted phenols in which the *p*-isomer predominated. $ArOSCF_3$ are thermally stable and the derivatives with lower boiling point were isolated by distillation (**10a**-**f**). Although they could not be isolated and purified by SiO_2 column chromatography because of their decomposition on silica gel, we found that by simply filtering the reaction mixture using Celite, followed by the evaporation of the solvent allowed us to obtain the crude products with >95% purity in most cases. Even though this rearrangement may be formally like the Fries rearrangement,[139] the mechanism should be different because the reaction started by protonation of the oxygen atom of the phenol moiety in our rearrangement (see Proposed mechanism in Table 6). The traditional Fries rearrangement of $PhOC(O)R$[139] starts with the activation of the functional group (-C(O)-) connecting to the oxygen of the phenol moiety with an acid such as a Lewis acid. A similar $CF_3S^{IV}(O)$-rearrangement of $ArOS^{IV}(O)CF_3$ has been reported.[140] The favored rearrangement to the *para* position (**11a**-**c**,**e**,**g**-**i**) in the CF_3S^{II}-rearrangement is similar to the Fries rearrangement. However, low yields were observed for the *para*-blocked compounds (**11d**, **f**). We proposed a reaction mechanism involving the intra and inter molecular reactions of the resulting reactive CF_3S cationic species (*see* Proposed mechanism in Table 6) on the basis that, when a more electron rich phenol (**9j** or **9a**) coparticipated, the CF_3S product (**11j** or **11a**) from the electron-rich phenol was formed by the intermolecular reaction (*see* Mechanistic study experiment in Table 6).

As nucleophilic CF_3S reagents such as $AgSCF_3$ are usually expensive and sensitive, we wanted to investigate if TTST could be a good nucleophilic CF_3S anion source. $C_4F_9SO_2OCF_3$, TFNf, was reported to be activated by AgF to generate CF_3O anion,[132] we applied the same methodology to TTST. Nevertheless, the reaction of benzyl bromide and TTST in the presence of AgF only provided the CF_3SO_2 substituted product in 52% yield based on GC-MS and ^{19}F-NMR analyses. We also tried using Cs_2CO_3 as an activating reagent with heat but the main product

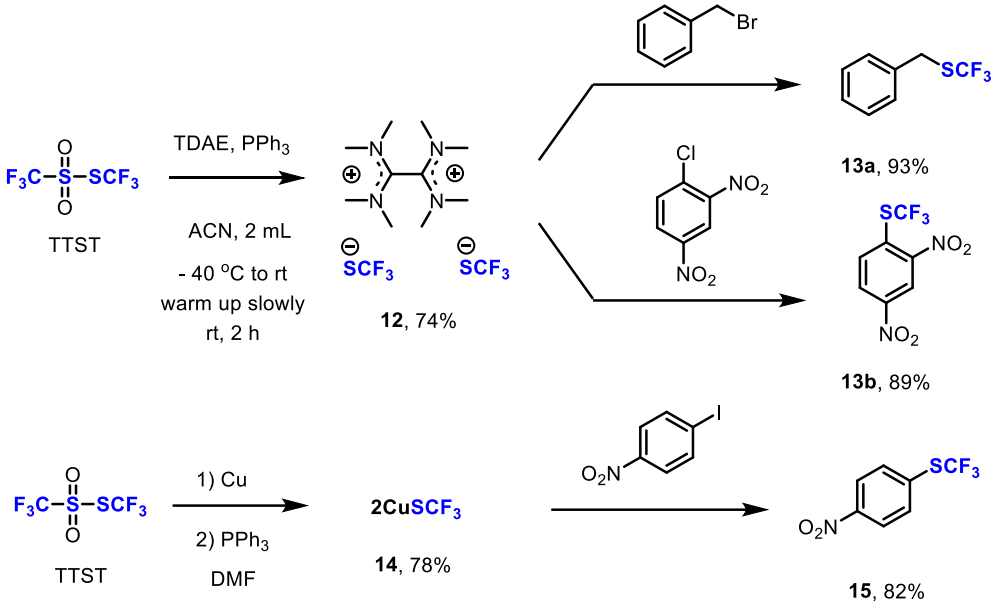
was the CF_3SO_2 substituted one instead of CF_3S substituted product. These results suggested that the CF_3S part of TTST was highly electrophilic and the F anion of AgF or CO_3 anion of Cs_2CO_3 only attacked the CF_3S site to produce $Ag/CsSO_2CF_3$. On the other hand, a CF_3SF species would have been formally produced. Although it was not detected in the reaction mixture of AgF and TTST in acetonitrile as solvent, the CF_3SF species was successfully trapped by an alkene using HFIP as solvent. (Scheme 31)



Scheme 31. Activation of TTST by AgF and Cs_2CO_3

Tetrakis(dimethylamino)ethylene (TDAE) is a two-electron donor. To our delight, we found that it reacted with TTST in the presence of Ph_3P (2 eq) to produce $TDAE^{2+}2SCF_3^-$ (**12**),[141] which substituted the bromine in benzyl bromide and the chlorine in 2,4-dinitrochlorobenzene with CF_3S in excellent yields (Table 7). We also found another example in which TTST reacted with copper powder and Ph_3P to deliver 2 equivalents of $CuSCF_3$ (**14**), which was then treated with 4-iodobenzene to produce CF_3S product **15** in high yield.[142-143] It should be noted that TTST exhibited a high atom economy performance because two CF_3S^- equivalents were generated from one equivalent of TTST.

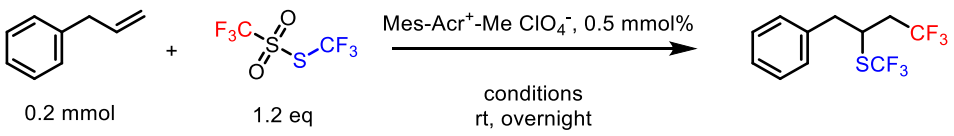
Table 7. Nucleophilic reactions using TTST as CF_3S anion source[a]



[a]Yields are NMR yields using 4-chlorobenzotrifluoride as an internal standard.

The high atom economy and broad application of TTST (**1**) was further established by the radical trifluoromethylthio-trifluoromethylation of alkenes using a photo organo catalyst, 9-mesityl-10-methylacridinium perchlorate (Mes-Acr^{+}-Me ClO_4^{-}). The reported methods for this transformation required both CF_3S and CF_3 reagents[144-145] or multiple transition metal catalysts with an equimolar oxidizer ($K_2S_2O_8$), and a ligand (Ph_3P).[146] Instead, we hoped this reaction could be achieved by using TTST alone, acting as a source of CF_3S and CF_3. We chose allylbenzene as a model substrate to optimize the reaction condition.

Table 8. Reaction condition optimization for the trifluoromethylthio-trifluoromethylation of alkenes



Entry	Conditions	Yield
1	In 1 mL of dimethyl carbonate, 450-455 nm LED, under air	45%
2	In 1 mL of dimethyl carbonate, 450-455 nm LED, no photocatalyst, under air	0%
3	In 1 mL of dimethyl carbonate, white LED, under air	45%

4	In 1 mL of dimethyl carbonate, white LED, 5 mol% photocatalyst, under air	42%
5	In 1 mL of dimethyl carbonate, 365 nm LED, under air	42%
6	In 1 mL of dimethyl carbonate, 405 nm LED, under air	50%
7	In 1 mL of dimethyl carbonate, 405 nm LED, under argon	57%
8	In 1 mL of dimethyl carbonate, 450-455 nm LED, under argon	55%
9	In 1 mL of dimethyl carbonate, 425 nm LED, under argon	59%
10	In 1 mL of dichloroethane, 425 nm LED, under argon	44%
11	In 1 mL of dimethoxyethane, 425 nm LED, under argon	62%
12	In 1 mL of toluene, 425 nm LED, under argon	18%
13	In 1 mL of acetonitrile, 425 nm LED, under argon	49%
14	In 1 mL of tetrahydrofuran, 425 nm LED, under argon	40%
15	In 1 mL of diethyl ether, 425 nm LED, under argon	50%
16	In 1 mL of *tert*-butyl methyl ether, 425 nm LED, under argon	59%
17	In 1 mL of dimethylformamide, 425 nm LED, under argon	64%
18	In 1 mL of dimethyl sulfoxide, 425 nm LED, under argon	0%
19	In 1 mL of acetone, 425 nm LED, under argon	56%
20	In 1 mL of dimethylformamide, 425 nm LED, under argon, 1.5 eq TTST	67%

[a]Yields are NMR yields using 4-chlorobenzotrifluoride as an internal standard.

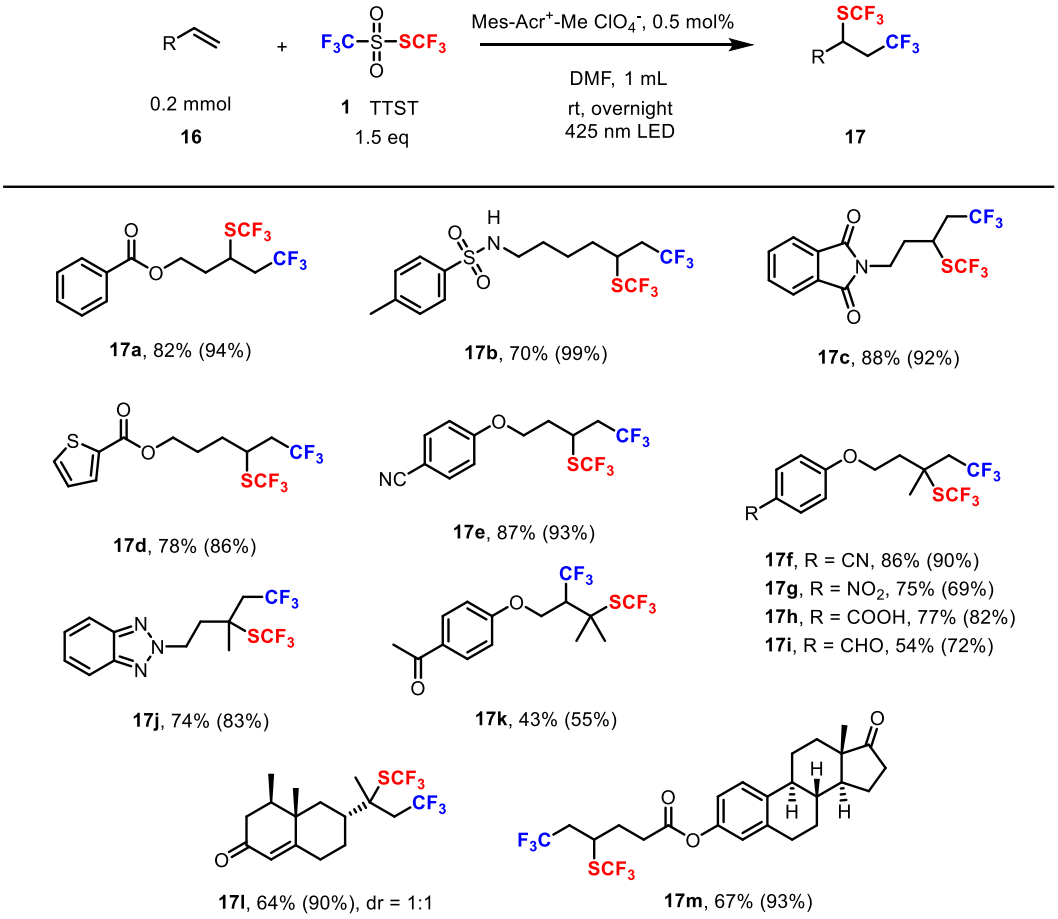
As we can see from Table 8, the reaction produced 45% of desired product in dimethyl carbonate (DMC) under 450-455 nm LED irridiation under air (entry 1). No desired product was formed without photocatalyst (entry 2), but increasing the amount of photocatalyst to 5 mol% did not increase the yield (entry 3-4). The wavelength of LED light slighly affected the yields and the best choice of LED light was 425 nm (entry 3, 5-9). Changing the reaction atomosphere from air to argon increased the yield by 7% (entry 6-7). We tried the reaction in different organic solvents such as dimethyl carbonate (DMC), dichloroethane (DCE), dimethoxyethane (DME), toluene, acetonitrile (ACN), tetrahydrofuran (THF), diethyl ether, *tert*-butyl methyl ether (TBME), dimethylformamide (DMF), dimethyl sulfoxide (DMSO), and acetone (entry 9-19). DMF proved to be the best choice of solvent and DMSO gave 0% yield of desired product, probably because

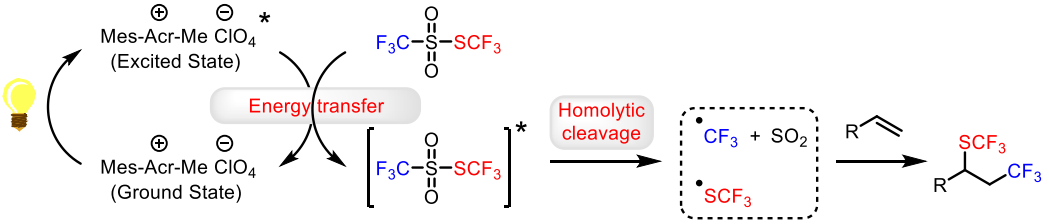
TTST reacted with DMSO. Finally, increasing the amount of TTST to 1.5 equivalents increased the yield from 64% to 67% (entry 17, 20). It's worth noting that we did not need extra additives for this transformation and that both CF_3S and CF_3 radicals were generated from one equivalent of TTST!

With the optimal condition in hand, we explored the substrate scope of this new metal-free photocatalytic trifluoromethylthio-trifluoromethylation reaction. To our delight, this reaction worked with a broad range of substrates (Table 9). Mono-, di-, and tri-substituted alkenes with a variety of functional groups such as ester (**17a**), sulfonamide (**17b**), imide (**17c**), nitriles (**17e**, **f**), nitro (**17g**), ether (**17e-i**), carboxylic acid (**17h**), aldehyde (**17i**), and ketone (**17k**) were all tolerated and the products were obtained in very good yields. Heterocycles like thiophene (**17d**) and benzotriazole (**17j**) as well as bioactive molecules (**17l, m**) also worked in excellent yields.

Maes and co-workers have conducted a thorough study on the photo arylthio-arylsulfonylation of alkenes with $ArSO_2SAr'$ and Mes-Acr^+-Me ClO_4^- catalyst, and they proposed a novel energy transfer (EnT) mechanism of the activated catalyst to $ArSO_2SAr'$.[147] Given that TTST is much more electron deficient than $ArSO_2SAr'$, it is much less likely that TTST will release an electron to the photocatalyst. Therefore, the same EnT mechanism can be proposed for our radical trifluoromethyl-trifluoromethylthiolation (*see* the bottom of Table 9). First, the photocatalyst Mes-Acr^+-Me ClO_4^- reaches the excited state under the irradiation of 425 nm LED light. After EnT from the excited state of the photocatalyst to TTST, it gets excited and the excited TTST undergoes homolytic cleavage to generate both CF_3S and CF_3 radicals and SO_2. The two radicals are trapped regioselectively by the double bond in a sequential manner based on their respective reactivities. The radical inhibition and cyclization experiments supported a radical pathway of this reaction (*see* **Experimental** section).

Table 9. Photocatalytic radical trifluoromethyl-trifluoromethylthiolation of alkenes using TTST (1)[a]





[a]Yields are isolated yields of pure compounds. Yields in parentheses are ^{19}F-NMR yields using an internal standard.

3.3 Conclusion

In summary, although we failed to prepare the $C_4F_9SO_2SCF_3$ (TNST) through the anion exchange of Umemoto reagent II followed by thermolysis, we successfully developed a better analogue: $CF_3SO_2SCF_3$ (TTST), which turned out to be a new practical and atom-efficient trifluoromethylthiolating reagent. TTST was simply prepared in one step using commercially

inexpensive Langlois reagent (CF_3SO_2Na) and Tf_2O. TTST is an easy-to-handle, thermally stable, yet highly reactive and versatile reagent that can be used for both electrophilic and nucleophilic CF_3S transfer reactions, as well as for the radical-based CF_3S and CF_3 incorporation to alkenes. In addition, we synthesized and studied a new type of molecule, phenyl trifluoromethanesulfenates, which revealed a novel catalytic CF_3S(II)-rearrangement. TTST is expected to be a attractive alternative to the current SCF_3 reagents in terms of preparation, reactivity, and practicability.

CHAPTER 4

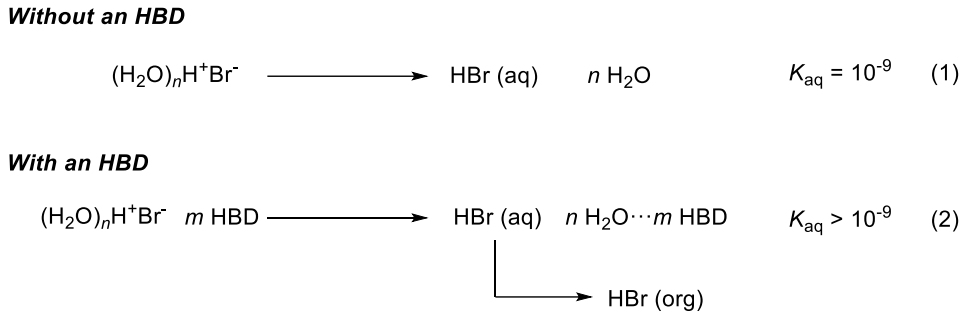
HFIP PROMOTED HYDROHALOGENATION USING AQUEOUS HX SOLUTION

4.1 Background

Markovnikov hydrobromination of alkenes is an important transformation toward synthetically important secondary and tertiary alkyl bromides.[148] This transformation is usually expected to start with the protonation of the double bond of an alkene to produce a stabilized carbocation, which subsequently reacts with a bromide to provide the alkyl bromide. Despite its simple mechanism, which is usually taught at the very beginning of college organic chemistry, in practice, this transformation cannot be conveniently carried out under mild conditions. Representative conditions for alkene hydrobromination include 1) dispensing gaseous HBr gas into a solution of alkene,[149] 2) treating alkenes with a mixture of metal bromides and strong acids[150], and 3) refluxing hydrobromic acid and alkene together in the presence of a phase transfer catalyst.[151] The demanding special instruments, restricted moisture exclusion operation, or a high temperature account for the difficulty of carrying out a hydrobromination of an alkene in the presence of water. Indeed, aqueous hydrobromic acid is not regarded as an efficient hydrobrominating reagent.

The poor reactivity of hydrobromic acid could be attributed to the high ionization potential of HBr in water, which significantly reduces concentration of HBr in the organic phase, hence retarding the reaction (Scheme 32, 1). To turn hydrobromic acid into an efficient hydrobrominating reagent, the basic component, water, should be suppressed. Mayr reported that the nucleophilicity of water could be largely inhibited by adding 1,1,1,3,3,3-hexafluoroisopropanol (HFIP).[152] Since HFIP is a well-known hydrogen bond donor (HBD) and found to accelerate a

wide scope of acid-mediated transformations,[88] we thought that introducing a strong HBD like HFIP would suppress the basicity of water, hence liberating HBr from the aqueous phase (Scheme 32, 2).[153] In this regard, a quantitative descriptor of hydrogen bond donor ability (acidity) is needed.



Scheme 32. Liberation of HBr from water by adding a hydrogen bond donor

In a series of papers of 1980s, Abraham and co-workers analyzed the equilibrium constant of a series of hydrogen bond complexes in carbon tetrachloride, and found that, the equilibrium constant K of a hydrogen bond complexation reaction in equation 3 could be expressed by equation 4, in which log K_A^H is considered the hydrogen bond acidity of donor, and L_B and D_B describe the properties of acceptor.[154] It shared great resemblance to Mayr's correlation equation of chemical kinetics.[155] This equation provides a direct quantitative approach toward comparing the thermal stability of hydrogen bond complexes and donor ability of hydrogen bond donor.[156] These data are a valuable supplement to Laurence's pK_{BHX} data.[157]

$$HBD + HBA \rightarrow HBD\cdot HBA \qquad (3)$$

$$\log K = L_B \times \log K_A^H + D_B \qquad (4)$$

By carefully looking into log K_A^H of different compounds, we found that the hydrogen bond donor studies by Abraham could be categorized into three groups according to the relationship between their log K_A^H and Brønsted acidity pKa (Figure 3). Most compounds (○ in Figure 3), including trifluoroacetic acid (TFA), a variety of phenols, alcohols, water, have a good linear relationship between their log K_A^H and Brønsted acidity pKa (⋯⋯ in Figure 3), and hence are considered "normal". Many carboxylic acids gather in an area lower than the linear fitting of the first group (▲ in Figure 3), which means they have poor hydrogen bond donor ability compared

with their moderate strong Brønsted acidity. In contrast, perfluoro-*tert*-butanol (PFTBA), HFIP and phenols bearing electron withdrawing group[158] occupy the region above the linear fitting of the first group, thus these weak O-H acids are good hydrogen bond donors (■ in Figure 3). These classification does not only help screening desired hydrogen bond donors, but also helps to elucidate whether Brønsted acidity or hydrogen bond acidity is the dominating factor in transformations.

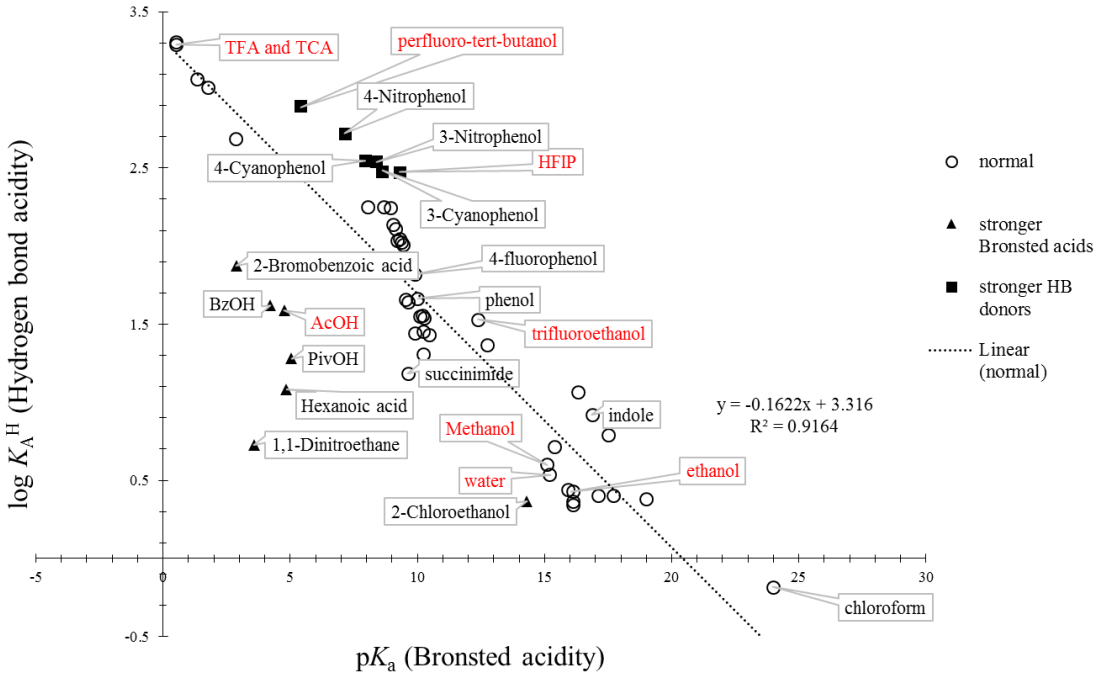
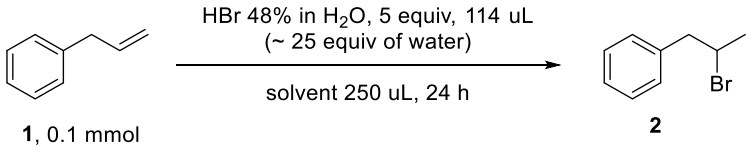


Figure 3. Relationship between Brønsted Acidity and Hydrogen Bond Acidity

4.2 Results and discussion

Table 10. Hydrogen Bond Acidity-Dominated Hydrobromination



1, 0.1 mmol

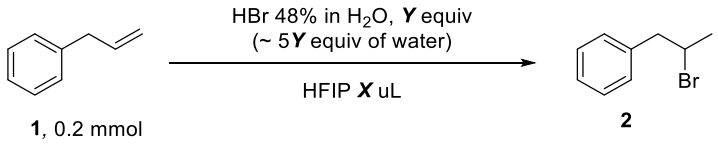
2

Entry	Solvent	pK_a	logK_A^H	Conversion (%)
1	CF_3CO_2H	0.52	3.31	> 95
2	$(CF_3)_3COH$	5.4	2.9	70
3	$(CF_3)_2CHOH$	9.3	2.47	> 95
4	AcOH	4.8	1.59	0

5	CF_3CH_2OH	12.4	1.53	0
6	MeOH	15.1	0.6	0
7	MeCN, THF	-	-	0
8	DCE, toluene	-	-	0
9	neat	-	-	0

We examined the reaction of allylbenzene **1** with 5 equivalents of hydrobromic acid in different solvents. As we had anticipated, hydrobromination only took place in trifluoroacetic acid, PFTBA and HFIP, which possess high hydrogen bond acidity (Table 10, entry 1, 2, 3). In contrast, acetic acid, albeit being more Brønsted acidic than PFTBA and HFIP, could not carry out any observable conversion because of its low hydrogen bond acidity, further proving that hydrogen bond acidity is the dominating factor in this transformation (entry 4). Weak hydrogen bond donor 2,2,2-trifluoroethanol failed to promote this reaction, although its hydrogen bond acidity was used to promote other types of reactions (entry 5).[159] Methanol also failed to provide any conversion due to its higher hydrogen bond basicity than water (entry 6). Other Lewis basic or neutral solvents (entry 7, 8) also failed to carry out this transformation. Finally, a control experiment of mixing hydrobromic acid and **1** did not yield any product (entry 9).[160]

Table 11. Dilution-Accelerated Hydrobromination



1, 0.2 mmol

2

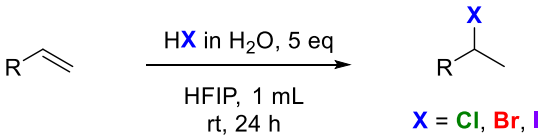
Entry	***X*** **(μL)**	***Y*** **(equiv)**	**[1] (mol/L)***	***n*(HFIP):*n*(H_2O)**	**$\tau_{1/2}$ of 1 (min)**
1	250	5	0.80	0.48	588
2	500	5	0.40	0.95	168
3	750	5	0.27	1.42	75.4
4	1000	5	0.20	1.90	60.0
5	1500	5	0.13	2.85	24.9
6	2000	5	0.10	3.80	16.6

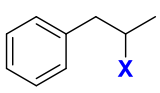
7	500	3	0.30	1.58	138
8	500	1.5	0.30	3.16	106
9	500	1	0.30	4.47	100

* Only the volume of HFIP was considered.

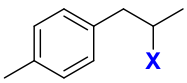
More interestingly, in a subsequent study, we observed a counter intuitive phenomenon: that the reaction was accelerated upon dilution (Table 11)! For example, when the loading of HBr is fixed, halving the loading of HFIP extended half-life of **1** from 168 minutes to 588 minutes (entry 1, 2). On the contrary, increasing the loading of HFIP significantly shortened the reaction time (entry 3-6). In an extremely diluted condition (entry 6), the reaction reached 50% completion in only 16.6 minutes! By comparison, reducing the loading of HBr (water) also accelerated the reaction (entry 2, 7-9), but the effect was not as obvious as with HFIP.

Table 12. Hydrohalogenation of Alkenes Using Aqueous HX

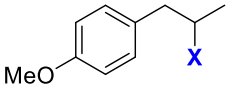




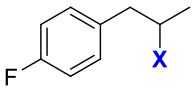
2a-Cl, 65%
2a-Br, 63%
2a-I, 58%



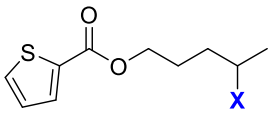
2b-Cl, 42%
2b-Br, 98%[a]
2b-I, 90%



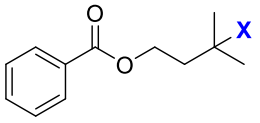
2c-Cl, 70%
2c-Br, 81%
2c-I, 77%



2d-Cl, 57%[b]
2d-Br, 73%
2d-I, 79%



2e-Cl, 70%
2e-Br, 80%
2e-I, 50%



2f-Cl, 75%[c]
2f-Br, 89%[d]
2f-I, 55%

Reaction conditions: alkene (0.4 mmol), 37% HCl or 48%HBr or 57% HI solution (5 eq) in HFIP (1 mL) at room temperature for 24 h, isolated yields. a. ^{1}H-NMR yield using dibromomethane as an internal standard. b. ^{19}F-NMR yield using 4-fluorobenzonitrile as an internal standard. c. 37% HCl solution (10 eq) and 50 ^{o}C were used. d. 48% HBr solution (7eq) and 50 ^{o}C were used.

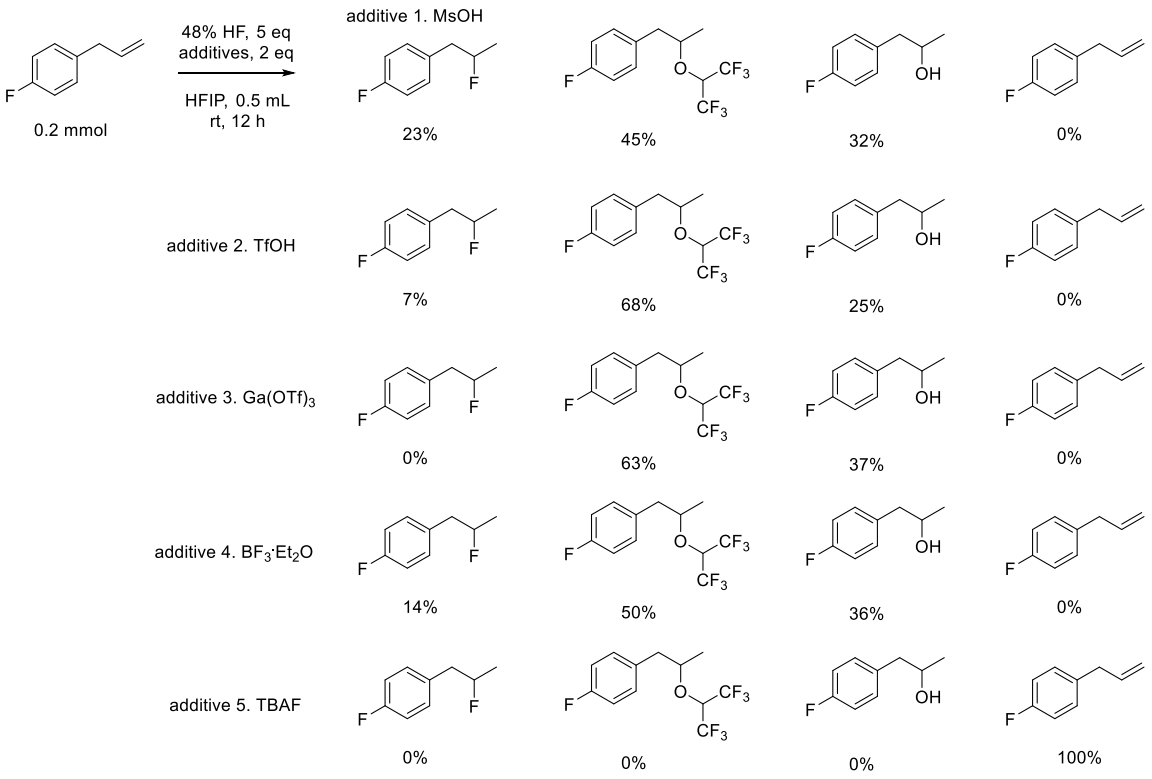
We applied the optimal conditions to the hydrohalogenation of different alkenes. (Table 12) To our delight, our system worked for both HCl, HBr, and HI aqueous solutions. The hydrohalogenation products were obtained in moderate to good yields. Benzene rings bearing an electron donating (**2b, c**) or withdrawing group (**2d**) did not show a difference in the yield of the products. An alkene with a heterocyclic ring (**2e**) was also hydrohalogenated in good yields. The hydrohalogenation of tri-substituted alkene (**2f**) succeeded when gentle heat was applied.

4.3 Limitation

Our protocol had some limitations. First, it did not work for styrene derivatives. Dimerization or polymerization happened once the acid was added to the HFIP solution of the styrene derivatives as we observed a white emulsion appeared immediately. Dimers of the styrene derivatives were detected by GC-MS.

Also, it did not work for the aqueous HF solution (48%) which was a much more important transformation because of the significance of fluorine. We attributed the failure to the low acidity and nucleophilicity of HF in this system. We tried to add acid additive such as methanesulfonic acid (MsOH), triflic acid (TfOH), and Lewis acids such as $Ga(OTf)_3$ or $BF_3{\cdot}Et_2O$, and though the desired hydrofluorinated products were formed in some cases, the yields were very low. The major side-products of the reaction were the HFIP adducts and the water adducts, which further indicated a lower nucleophilicity of the fluorine anion than HFIP and water under the reaction conditions. The addition of a more reactive fluoride, tetrabutylammonium fluoride (TBAF) did not help solve this problem either. (Scheme 33)

Substrate scope was another limitation of this protocol. For some amide and sulfonamide substrates, the hydrohalogenation did not happen at all even with heating and using more equivalents of acid.



Scheme 33. Hydrofluorination of alkene using aqueous HF

4.4 Conclusion

We have developed a novel hydrogen-bonding assisted hydrohalogenation of unactivated alkenes using HFIP. Dynamic studies indicate this reaction is hydrogen bond acidity-dominated and dilution-accelerated. The unreactive aqueous 37% HCl, 48% HBr, and 57% HI all provide good yields of the hydrohalogenated products in this system. Although some limitations have been observed, this method still represents an efficient and convenient option for the hydrohalogenation of many alkenes.

CHAPTER 5

EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA OF SYNTHESIZED COMPOUNDS

5.1 General information

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded at 400, 100, and 376 MHz, respectively, using $CDCl_3$ as the solvent, unless otherwise noted. The chemical shifts are reported in δ (ppm) values relative to $CHCl_3$ (δ 7.26 ppm for ^{1}H NMR, δ 77.0 ppm for ^{13}C NMR) and $CFCl_3$ (δ 0.00 ppm for ^{19}F NMR), and multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), h (hextet), hept (heptet), m (multiplet) and br (broad). Coupling constants, *J*, are reported in Hertz.

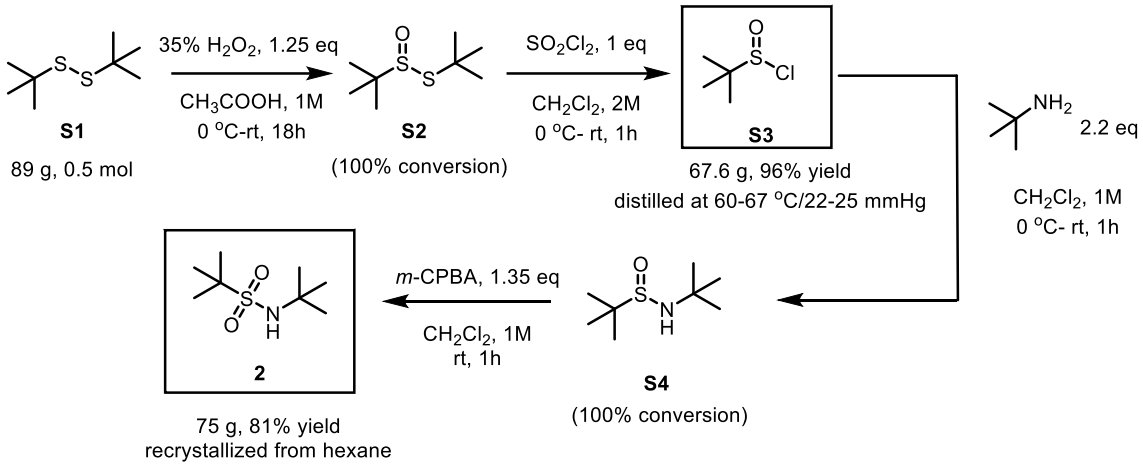
Unless otherwise noted, all reactions were carried out under anhydrous conditions and nitrogen or argon atmosphere. Photocatalyzed reactions were performed using an EvoluChem 8-position PhotoRedOx Box™ equipped with an EvoluChem™ LED spotlight and a built-in fan manufactured by HepatoChem Inc. Yields refer to purified and spectroscopically pure compounds using a Teledyne ISCO Combi*Flash* EZ prep system, which is a dual function purification system that enables the user to perform both flash and preparative (Prep) purifications on the same instrument. Preparative (Prep) purifications were performed with a 150 mm × 20 mm HPLC column (packing material: RediSep Prep C18, 100 Å, 5 μm), eluted with a H_2O/ACN gradient (100:0 to 0:100) for 40 min at a flow rate of 19 mL/min. ^{19}F-NMR yields were determined by ^{19}F-NMR spectroscopic analysis of the reaction mixture using an internal standard. Unless otherwise noted, all reagents were purchased from commercial sources and used directly without further purification. Solvents such as dichloromethane (DCM), diethyl ether (Et_2O), dimethylformamide (DMF), and acetonitrile (ACN) were dried using a commercial solvent purification system. Tetrahydrofuran (THF) was dried just before use by distillation from sodium benzophenone ketyl

(deep blue color). Chlorobenzene was dried by distillation, followed by addition of 4Å molecular sieves. All NMR solvents were purchased from Cambridge Isotope Laboratories, Inc. HRMS data were obtained from Indiana University Bloomington Mass Spectral Facility using Thermo LTQ-Orbitrap XL mass spectrometer with ESI or APCI ionization and 7250 QTOF high resolution GC/MS with EI ionization.

5.2 Experimental section of Chapter 2

5.2.1. Preparation of the designed *N*-F fluorinating agent

5.2.1.1 Preparation of *N*-(*tert*-butyl)-*tert*-butanesulfonamide (2)



N-(*tert*-Butyl)-*N*-*tert*-butanesulfonamide (**2**) was prepared according to the reported method[108] as follows:

Step 1: To a stirred solution of *tert*-butyl disulfide (**S1**) (89 g, 0.5 mol, 1 eq) in glacial acetic acid (500 mL) was added 35% H_2O_2 (60.7 g, 0.625 mmol, 1.25 eq) dropwise at 0 °C. The reaction mixture was allowed to warm up to room temperature gradually. The stirring was continued until all the disulfide was consumed. It took 18 h. The reaction was monitored by ^1H NMR measurement of the reaction mixture [**S1**, δ=1.30 (s); **S2**, δ=1.39 (s) and 1.54 (s)]. The mixture was then poured onto ice water (500 mL), extracted with CH_2Cl_2 (2 x 300 mL), and washed in turn with saturated aqueous solutions of Na_2SO_3 (200 mL), Na_2CO_3 (200 mL), and water (200 mL). The organic layer was dried with $MgSO_4$, filtered, and evaporated to dryness.

The resulting crude *tert*-butyl *tert*-butanethiosulfinate (**S2**) was used for the subsequent step without further purification.

Step 2: The crude **S2** (~0.5 mol, 1 eq) was dissolved in CH_2Cl_2 (250 mL) and a solution of sulfuryl chloride (67.5 g, 0.5 mol, 1 eq) in CH_2Cl_2 (50 mL) was slowly added to the solution of **S2** at 0 ^oC. The resulting yellow solution was stirred for 1 h and allowed to gradually reach room temperature. At this point, NMR analysis revealed no starting material remaining. The solvent and volatile byproducts were removed by an evaporator (aspirator) at room temperature (*Note*: stench) and the resulting oily residue was distilled under reduced pressure to give 67.6 g (96%) of *tert*-butylsulfinyl chloride (**S3**) as a pale-yellow oil (boiling point; 60-67 °C at 22-25 mmHg).

Step 3: To a stirred solution of *tert*-butylamine (77.2 g, 1.056 mol, 2.2 eq) in CH_2Cl_2 (480 mL) cooled at 0 ^oC, was added **S3** prepared above (67.6 g, 0.48 mol, 1 eq) dropwise over a period of 30 mins. The reaction mixture was stirred for 1 h and allowed to gradually reach room temperature. The *tert*-butylammonium chloride formed was filtered off through a pad of Celite. The organic solvent and excess of *tert*-butylamine were evaporated by an evaporator and finally by a vacuum pump. The resulting *N*-(*tert*-butyl)-*tert*-butanesulfinamide (**S4**) was essentially pure and wasused for the next step without further purification. **S4**: ^1H NMR (500 MHz, $CDCl_3$) δ 2.88 (s, 1H), 1.13 (s, 9H), 1.02 (s, 9H);^{13}C NMR (126 MHz, $CDCl_3$) δ 54.77, 52.82, 30.71, 22.15.

Step 4: To a stirred solution of **S4** (~0.48 mol, 1 eq) in CH_2Cl_2 (480 mL) was added *m*-chloroperbenzoic acid (purity 75%/H_2O 25%; 138 g, 0.6 mol, 1.25 eq) slowly at room temperature over a period of 40 mins. The reaction mixture was stirred at room temperature for 1 h. The completion of this reaction was checked by GC-MS. The precipitates formed were filtered off through a pad of Celite. The filtrate was washed in turn with saturated aqueous solutions of Na_2SO_3 (200 mL), Na_2CO_3 (until neutral), and water (200 mL). The organic layer was dried with $MgSO_4$ and evaporated to give crude *N*-(*tert*-butyl)-*tert*-butanesulfonamide (**2**) as a solid, which was then recrystallized from hexane to give 75 g (81%) of pure **2** as white needles. **2**: ^1H NMR (400 MHz, $CDCl_3$) δ 3.62 (s, 1H), 1.38 (s, 9H), 1.37 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 59.43, 55.77, 30.68, 24.31.

5.2.1.2 Preparation of *N*-fluoro-*N*-(*tert*-butyl)-*tert*-butanesulfonamide (1, NFBB)

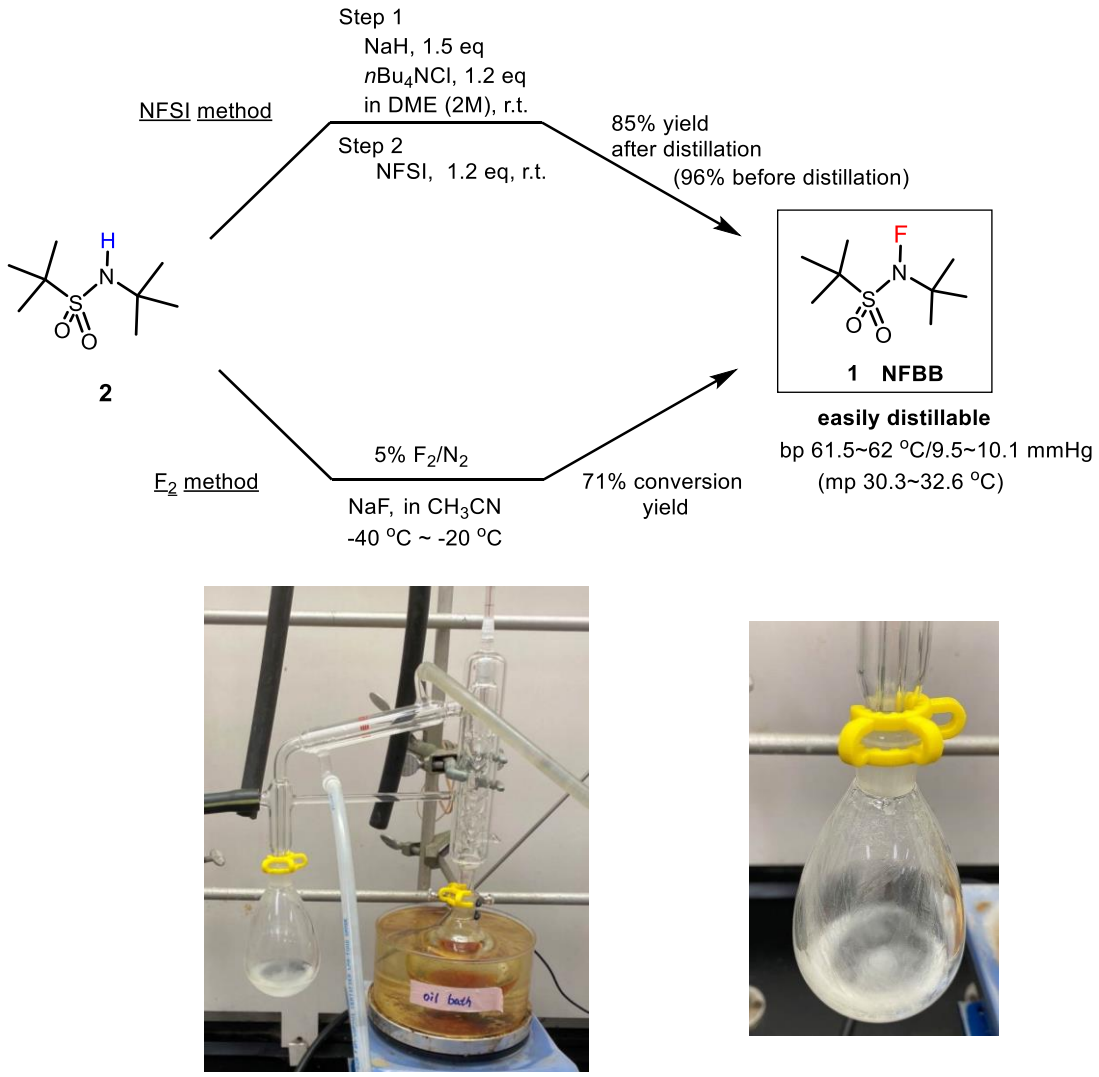


Figure S1. Distillation of NFBB (1) under reduced pressure; ~20 g scale production

5.2.1.3 NFSI method

To a flame-dried 250 mL three-neck round bottom flask, equipped with a stir bar and argon flow, was added NaH (60% in mineral oil, 6.21 g, 155 mmol, 1.5 eq). The oil in the NaH was removed by washing with dry hexane three times (18 mL each) and the NaH was dried under vacuum. In another flask, tetrabutylammonium chloride (TBAC) (35.2 g, 124 mmol, 1.2 eq) was

put and dried under vacuum at 90 ^{o}C for 3 h, and then *N*-(*tert*-butyl)-*N*-*tert*-butanesulfonamide (**2**) (20.0 g, 104 mmol, 1 eq) was added. The mixture of **2** and TBAC was dissolved in 50 mL of 1,2-dimethoxyethane (DME) [*Note*: A sonicator was used to help dissolve TBAC]. At room temperature, the solution of **2**/TBAC in DME was added to the flask containing NaH via a syringe. DME (2 mL) was used to complete the transfer. The resulting mixture was stirred overnight at room temperature (13 h, 800 rpm). *N*-Fluorobenzenesulfonimide (NFSI) (39.9 g, 124 mmol, 1.2 eq) was added as a solid slowly to the mixture over a period of 1 h, maintaining the inside temperature at 33-36 ^{o}C, and the reaction mixture was stirred for another 1 h at room temperature. After that, 20 mL of 1M KOH/MeOH solution (KOH, 0.2 eq) was slowly added and the reaction mixture was stirred for 30 min at room temperature (this process was to quench the reaction and to destroy small amounts of $PhSO_2F$ and others (not identified) as side products). Then the reaction mixture was diluted with Et_2O (400 mL) and was cooled in a cooling bath at -10 ^{o}C for a short time to form precipitates from the lower viscous layer. The resulting mixture was stirred at room temperature for an additional 30 min to complete the precipitation. The precipitates were removed by filtration through a pad of Celite and washed with another 400 mL of Et_2O. The filtrate was filtered again to give a clear solution. The solvents were evaporated by an evaporator and the resulting crude product was distilled under reduced pressure by standard distillation technique (*see* the photos above), giving 18.6 g (85%) of pure NFBB (**1**): bp 61.5~62 ^{o}C/9.5~10.1 mmHg; mp 30.3~32.6 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (d, J = 2.2 Hz, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 66.64 (d, J = 12.5 Hz), 62.49, 27.17 (d, J = 6.9 Hz), 24.31 (d, J = 2.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -56.99 (s); IR (neat, cm^{-1}) 2986.5, 2940.3, 1479.5, 1369.3, 1332.2, 1190.9, 1133.4, 894.5, 794.5, 665.8; HRMS: (EI) m/z: $[M\text{-}CH_2F]^+$ Calcd. for $C_7H_{16}NO_2S$ 178.0902, Found: 178.0895.

5.2.1.4 Reaction optimization for the fluorination of 2 with NFSI

General procedure: To a flame-dried reaction flask equipped with a magnetic stir bar and an argon balloon, was added *N*-(*tert*-butyl)-*N*-*tert*-butanesulfonamide (**2**) (1 eq), a base, a dry solvent (Solvent 1 in Table S1), and an ammonium salt (as an additive for entries 12-14), and the

reaction mixture was stirred at room temperature for the time (Time 1 in Table S1). After the deprotonation of step 1, a solution of NFSI in a dry solvent (Solvent 2 in Table S1) or NFSI as a solid (Entries 12-14) was added at room temperature and stirred at the same temperature for the time (Time 2). After the reaction was quenched by adding a minimum amount of sat. aq. solution of NH_4Cl, an internal standard was then added, and its weight was recorded. An 80 µL aliquot of the solution was transferred to an NMR tube and the ^{19}F-NMR was measured to determine its ^{19}F-NMR yield based on the internal standard.

Table S1. Reaction condition optimization for the fluorination of 1 with NFSI

Entry	**2** (mmol)	Base	Additive	Solvent 1[a]	Time 1	"F" source	Solvent 2[a]	Time 2	Yield[b] of **1**
1	60	KH, 6 eq	-	DCM	5 h	NFSI, 3 eq	DCM	13 h	70% (58%)
2	2	NaH, 3 eq	-	DCM	6 h	NFSI, 3 eq	DCM	13 h	7%
3	5	KH, 1.2 eq	-	DCM	13 h	NFSI, 1.2 eq	DCM	48 h	60%
4	5	NaH, 1.2 eq	-	THF	13 h	NFSI, 1.3 eq	DCM[c]	48 h	41%
5	2	NaH, 1.2 eq	-	ACN[d]	1 h	Selectfluor™ 1.3 eq	ACN	13 h	0%
6	2	*n*-BuLi, 1.2 eq	-	THF	1 h[e]	NFSI, 1.3 eq	DCM	13 h[f]	7%
7	2	*t*-BuOK, 1.2 eq	-	THF	1 h[g]	NFSI, 1.3 eq	DCM	13 h[g]	0%
8	2	NaH, 1.5 eq	-	Et_2O	13 h	NFSI, 1.5 eq	Et_2O	24 h	29%
9	2	NaH, 1.5 eq	-	Dioxane	13 h	NFSI, 1.5 eq	Dioxane	24 h	12%
10	2	NaH, 1.5 eq	-	DME	13 h	NFSI, 1.5 eq	DME	24 h	40%
11	2	NaH, 1.5 eq	Bu_4NCl, 0.2 eq	DME[h]	13 h	NFSI, 1.2 eq	-	24 h	51%
12	**104**	**NaH, 1.5 eq**	**Bu_4NCl, 1.2 eq**	**DME[i]**	**13 h**	**NFSI, 1.2 eq**	**-**	**1 h**	**96% (85%)**
13	310	NaH, 1.5 eq	$BnEt_3NCl$, 1.2 eq	THF[j]	13 h	NFSI, 1.2 eq	-	1 h	63% (50%)

a) In order to stir smoothly, reactions were conducted in a total amount solvent of ~0.12 M concentration (to **2**), except for entries 11, 12, and 13. *b*) ^{19}F NMR yields; the values in parentheses were isolated yields after distillation. *c*) THF was evaporated under the vacuum before the addition of DCM. *d*) ACN = acetonitrile. *e*) -78 ^{o}C. *f*) -78 ^{o}C to rt. *g*) reflux. *h*) 1 M concentration (to **2**). *i*) 2 M concentration (to **2**). *j*) 0.5 M concentration (to **2**).

As seen in Table S1, the reaction with NFSI was examined using many conditions. Finally, we found that around an equimolar amount of tetrabutylammonium chloride as an additive and DME as a solvent dramatically improved the reaction. In conclusion, Entry 12 was the best conditions, which gave 96% ^{19}F NMR yield and 85% isolated yield after the distillation. The detailed procedure of Entry 12 is described above.

5.2.1.5 F_2 method

F_2 reaction apparatus: We used a F_2 reaction apparatus modified based on the reported aparatus[161], in which a cylinder of 5% F_2/95% N_2 was used and the amount of flowed gas of 5%F_2/95%N_2 was measured by total volume.

Procedure: 5% F_2/95% N_2 (F_2: ~3.75 mmol, ~2.5 eq) was passed through a stirred mixture of *N*-(*tert*-butyl)-*tert*-butanesulfonamide (**2**) (1.5 mmol, 1 eq) and NaF (powder, 15 mmol, 10 eq) in acetonitrile (15 mL) during a period of 4 h, maintaining the reaction temperature at -40 ~ -20 ^{o}C. ^{1}H- and ^{19}F NMR analysis of the reaction mixture showed that NFBB (**1**) was produced in 71% yield based on the consumed **2** [56% of **2** was consumed (44% of **2** left unreacted) and **1** was produced in 40% yield] and that *N,N*-difluoro-*tert*-butylamine ($^{t}BuNF_2$) as a side product was formed in 16% yield.

5.2.2 NFBB stability tests

5.2.2.1 Thermal stability test

Two sealed NMR tubes, each charged with 10 µL of neat NFBB, were heated at 120 ^{o}C and 150 ^{o}C for 12 h, respectively. After that, 500 µL of $CDCl_3$ was added to each of the NMR tubes. The two samples were analyzed by ^{1}H NMR and ^{19}F NMR. As seen in Figure S2, no decomposition was observed on both ^{1}H and ^{19}F NMR spectra after heating neat NFBB at 120 ^{o}C for 12 h, and a tiny decomposition (red arrows) was observed on the ^{1}H-NMR spectrum after

heating neat NFBB at 150 °C for 12 h. NFBB: ^{1}H NMR 1.44 ppm; ^{19}F NMR -56.99 ppm. *Note*: three tiny peaks around the big peak (1.44 ppm) of NFBB on the ^{1}H NMR are two satellite peaks and **2** (1.37 and 1.38 ppm) as a very small amount of a contaminant.

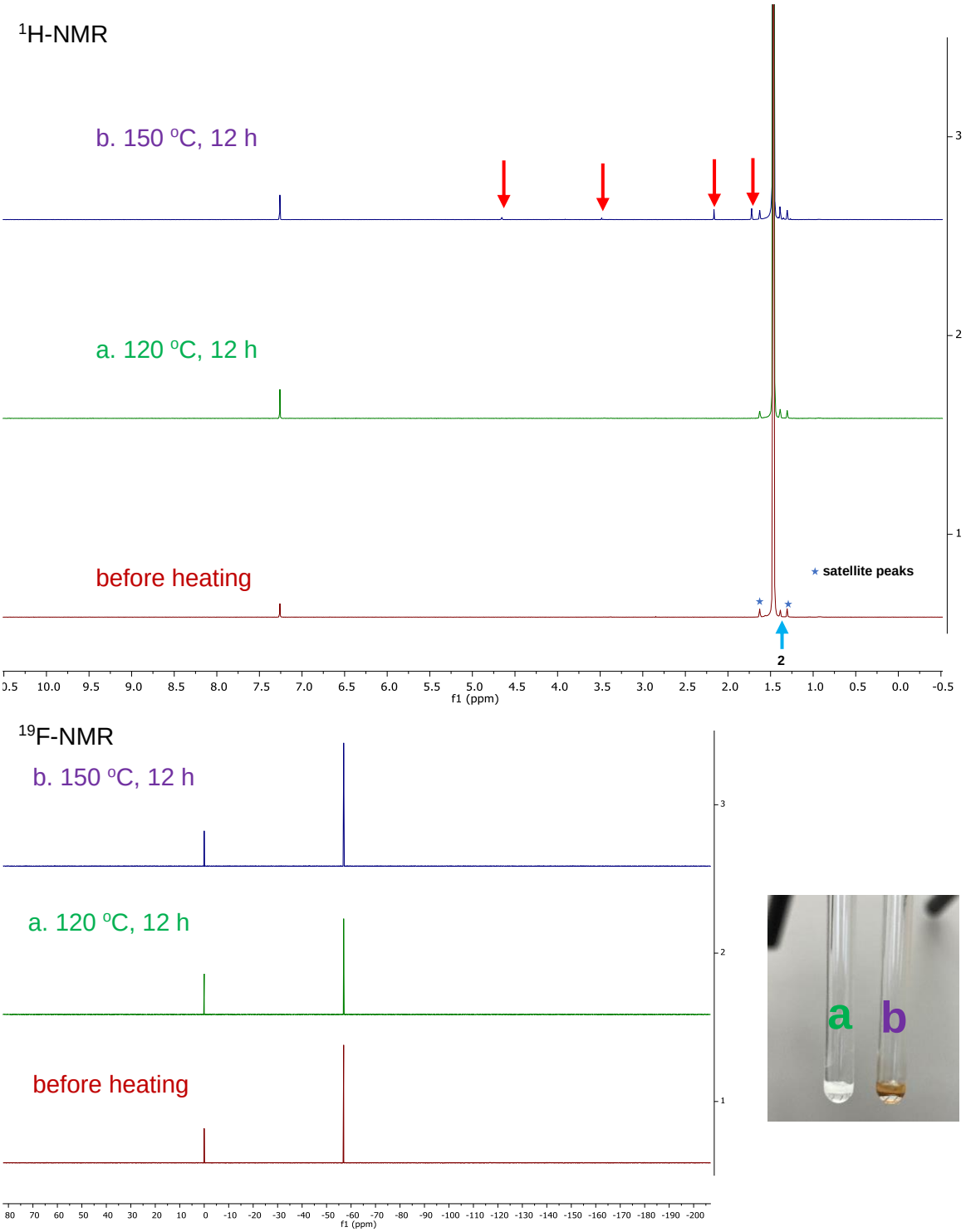


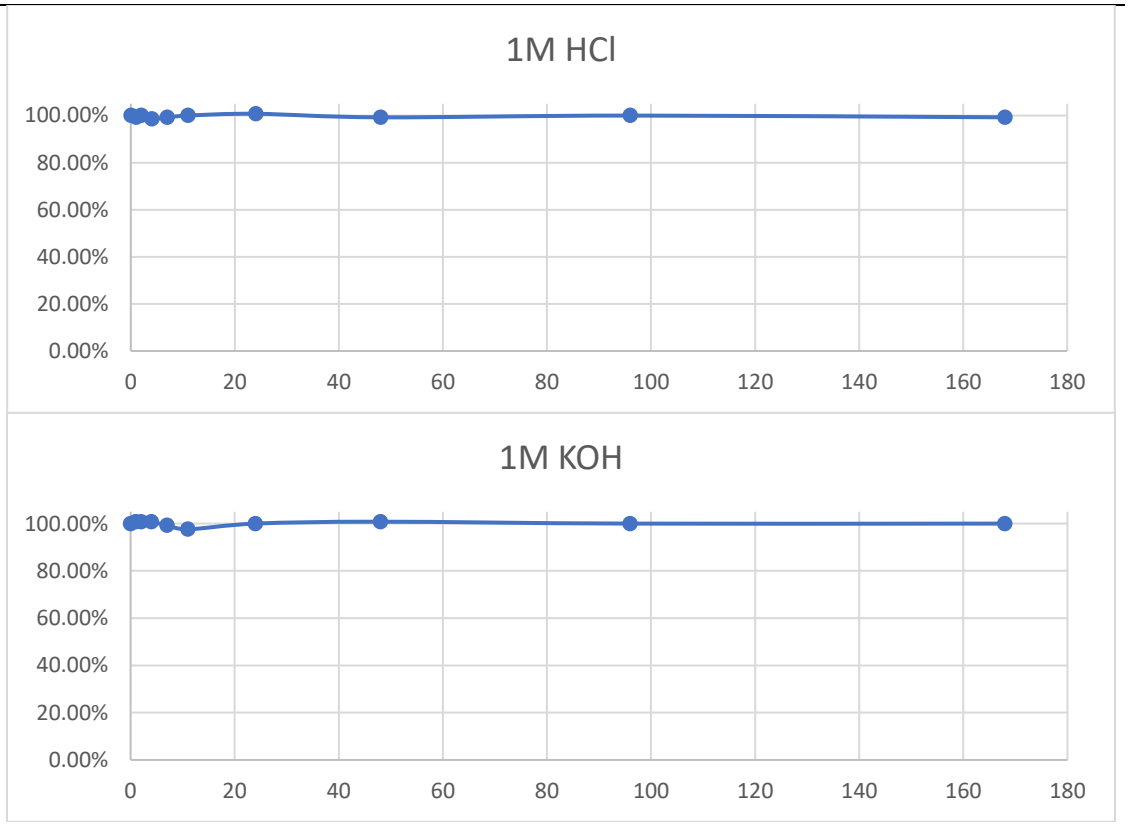
Figure S2. Thermal stability test of NFBB

5.2.2.2 Chemical stability test

About 0.5 mmol of NFBB was stirred (800 rpm) in a 2 mL solution or suspension of 1M HCl in methanol, 1M KOH in methanol, 0.75M Et_3N in acetonitrile and 0.75M KI in acetonitrile (suspension), respectively. 4-Fluorobiphenyl (~0.4 mmol) was added at the beginning as an internal standard (integrated as 1 in ^{19}F NMR spectra). 30 µL of each reaction mixture was taken out for ^{19}F NMR analysis every time. Table S2 shows the change of integration values of the NFBB over time. The changes of remaining NFBB percentages over time (in hours) are shown in the figures. In conclusion, the NFBB was stable in HCl, KOH and Et_3N solutions, but reacted with KI solution slowly.

Table S2. Chemical stability test

	0h	1h	2h	4h	7h	11h	24h	48h	96h	168h (1 week)
HCl	1.33	1.32	1.33	1.31	1.32	1.33	1.34	1.32	1.33	1.32
KOH	1.24	1.25	1.25	1.25	1.23	1.21	1.24	1.25	1.24	1.24
Et_3N	1.22	1.22	1.22	1.23	1.22	1.24	1.23	1.23	1.22	1.21
KI	1.22	1.12	1.02	0.86	0.67	0.49	0.18	0.02	0	0



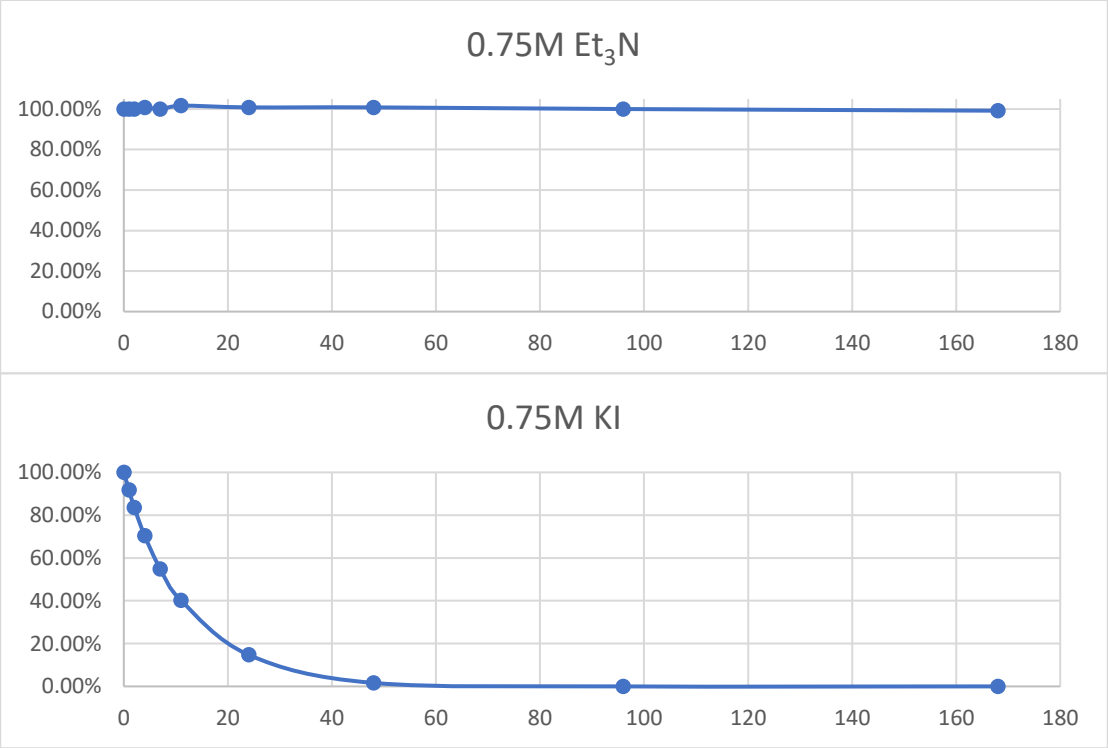
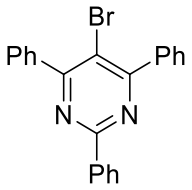


Figure S3. Chemical stability test of NFBB

5.2.3. Fluorination of (hetero)aryl lithiums with NFBB

5.2.3.1 Preparation of (hetero)aryl bromides and (hetero)arenes

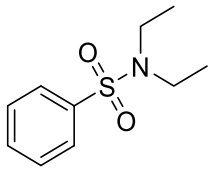
5-bromo-2,4,6-triphenylpyrimidine (3p)



This compound was prepared in 90% yield according to the reported method[162]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57-8.53 (m, 2H), 7.90-7.85 (m, 4H), 7.55-7.51 (m, 6H), 7.50-7.44 (m, 3H).

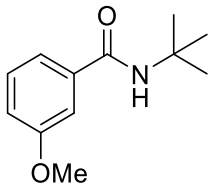
***N*,*N*-diethyl-benzenesulfonamide (4r)**



This compound was prepared in 96% yield according to the reported method[163]. The NMR data agree with the reported data.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 7.2 Hz, 2H), 7.58-7.52 (m, 1H), 7.51-7.46 (m, 2H), 3.25 (q, J = 7.2 Hz, 4H), 1.13 (t, J = 7.2 Hz, 6H).

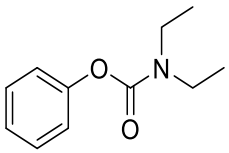
_N_-(_tert_-butyl)-3-methoxybenzamide (4t)



This compound was prepared in 92% yield according to the reported method[164]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 1H), 7.31 (t, J = 7.9 Hz, 1H), 7.22 (dt, J = 7.7, 1.3 Hz, 1H), 7.01 (ddd, J = 8.2, 2.7, 1.0 Hz, 1H), 5.94 (br.s, 1H), 3.85 (s, 3H), 1.48 (s, 9H).

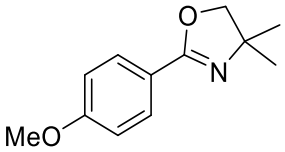
phenyl diethylcarbamate (4u)



This compound was prepared in 95% yield according to the reported method[165]. The NMR data agree with the reported data.

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.38-7.32 (m, 2H), 7.19-7.17 (m, 1H), 7.13-7.11 (m, 2H), 3.45-3.38 (m, 4H), 1.27-1.19 (m, 6H).

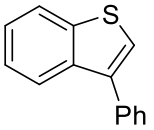
2-(4-methoxyphenyl)-4,4-dimethyl-4,5-dihydrooxazole (4v)



This compound was prepared in 82% yield according to the reported method[166]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.85 (m, 2H), 6.92-6.88 (m, 2H), 4.08 (s, 2H), 3.84 (s, 3H), 1.37 (s, 6H).

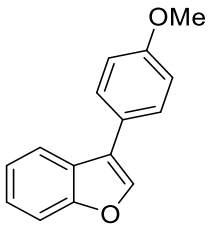
3-phenylbenzo[b]thiophene (4x)



This compound was prepared in 99% yield according to the reported method[167]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-7.90 (m, 2H), 7.62-7.58 (m, 2H), 7.52-7.47 (m, 2H), 7.44-7.38 (m, 4H).

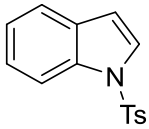
3-(4-methoxyphenyl)benzofuran (4z)



This compound was prepared in 98% yield according to the reported method[168]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83-7.79 (m, 1H), 7.73 (s, 1H), 7.60-7.52 (m, 3H), 7.37-7.28 (m, 2H), 7.05-7.00 (m, 2H), 3.87 (s, 3H).

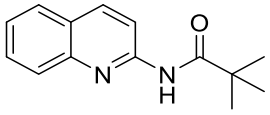
***5*- tosyl-1H-indole (4aa)**



This compound was prepared in 94% yield according to the reported method[169]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.3 Hz, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 3.7 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.33-7.28 (m, 1H), 7.24-7.19 (m, 3H), 6.65 (d, J = 3.7 Hz, 1H), 2.33 (s, 3H).

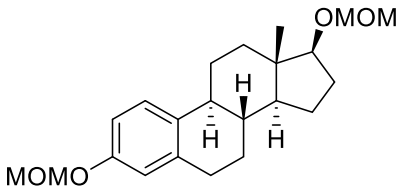
_N_-(quinolin-2-yl)pivalamide (4ae)



This compound was prepared in quantitative yield according to the reported method[170]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, J = 9.0 Hz, 1H), 8.30 (br.s, 1H), 8.17 (d, J = 9.0 Hz, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.69-7.63 (m, 1H), 7.48-7.42 (m, 1H), 1.38 (s, 9H).

(8R,9S,13S,14S,17S)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene (4af)

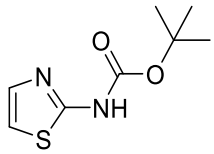


This compound was prepared in 96% yield according to the reported method[171]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 8.6 Hz, 1H), 6.83 (dd, J = 8.5, 2.7 Hz, 1H), 6.77 (d, J = 2.7 Hz, 1H), 5.14 (s, 2H), 4.69-4.64 (m, 2H), 3.62 (t, J = 8.5 Hz, 1H), 3.47 (s, 3H), 3.38 (s, 3H),

2.88-2.82 (m, 2H), 2.33-2.24 (m, 1H), 2.24-2.14 (m, 1H), 2.13-2.04 (m, 1H), 2.03-1.96 (m, 1H), 1.91-1.84 (m, 1H), 1.77-1.65 (m, 1H), 1.64-1.15 (m, 7H), 0.81 (s, 3H).

***tert*-butyl thiazol-2-ylcarbamate (4ag)**

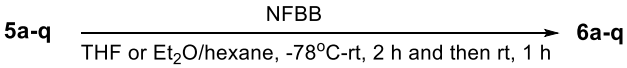


This compound was prepared in 78% yield according to the reported method[172]. The NMR data agree with the reported data.

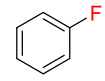
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.66 (s, 1H), 7.38 (d, J = 3.6 Hz, 1H), 6.87 (d, J = 3.6 Hz, 1H), 1.58 (s, 9H).

5.2.3.2 Fluorination of (hetero)aryl lithiums 5, generated from (hetero)aryl bromides, with NFBB

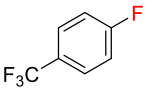
Table S3A. Fluorination of (Hetero)aryl lithiums 5 with NFBB



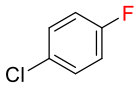
A: Fluorination of **5** generated from (hetero)aryl bromides **3** / Yields from **3**



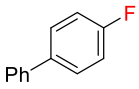
6a, 92%



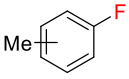
6b, 92%



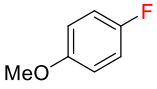
6c, 89%



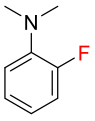
6d, 98%



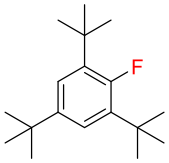
6e, ortho: 96%
6f, meta: 91%
6g, para: 98%



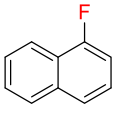
6h, 94%[a]



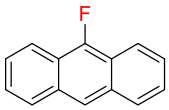
6i, 92%[a]



6j, 100%[a]

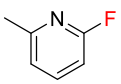


6k, 100%

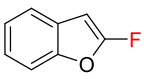


6l, 100%[a]

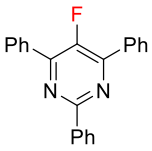
6m, 84%[a]



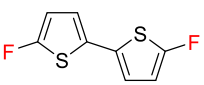
6n, 88%[a]



6o, 94%[a]



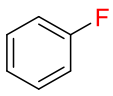
6p, 100%[b]



6q, 90%[c]

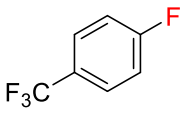
***Table S3A*.** Fluorination of (hetero)aryl lithiums **5** generated from (hetero)aryl bromides with NFBB. The reactions were carried out according to the general procedure **A** (below), unless otherwise noted: [a] *n*-BuLi (1.1 eq) was used for lithiation. [b] THF (2 mL) and *n*-BuLi (1.1 eq) were used for lithiation. [c] THF (2 mL), *n*-BuLi (2.4 eq), 1 h at -78 °C and 1 h at rt were used for lithiation. NFBB (2.5 eq) was used for fluorination.

General procedure A: To a flame-dried 8 mL reaction vial equipped with a magnetic stir bar and an argon balloon, was added a (hetero)aryl bromide substrate (0.5 mmol) and dry THF (1 mL). The solution was cooled down to -78°C and 0.24 mL of *n*-BuLi (2.5 M in hexane, 0.6 mmol, 1.2 eq) was added via syringe through its open-top cap with TFE septum. After stirring at -78°C for 1 h, a solution of 127 mg of NFBB (0.6 mmol, 1.2 eq) in dry hexane (2 mL) was added dropwise via syringe. The reaction mixture was warmed up to room temperature over a period of 2 h and stirred at room temperature for 1 h. After quenching the reaction with a few drops of sat. aq. solution of NH_4Cl, the reaction mixture was stirred until clear (EtOAc was added if necessary). An internal standard was then added, and its weight was recorded. An 80 µL aliquot of the solution was transferred to an NMR tube and analyzed by ^{19}F NMR. The yield of the product was determined by comparing the integration values of the product peak and the internal standard peak. Products were identified by spectral comparison with authentic samples except for **6j**, **6**l, **6p**, and **6q** for which pure products were isolated for identification by preparative HPLC chromatography using a 150 mm × 20 mm column (packing material: RediSep Prep C18, 100 Å, 5 µm) with a H_2O/MeCN gradient elution (100:0 to 0:100) for 40 min at a flow rate of 19 mL/min.



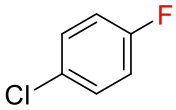
6a: The general procedure A was followed using bromobenzene (0.5 mmol) as a substrate and 4-fluoroanisole (60.6 mg, 0.481 mmol) as an internal standard. Yield: 92% (^{19}F NMR). The ^{19}F NMR spectral data matched those of an authentic sample (TCI). The identity of the product was further confirmed by GC/MS analysis.

^{19}F NMR (376 MHz, $CDCl_3$): δ -113.28 (ddd, J = 14.8, 9.2, 5.6 Hz).



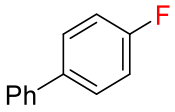
6b: The general procedure A was followed using 4-bromobenzotrifluoride (0.5 mmol) as a substrate and 4-fluoroanisole (61.0 mg, 0.484 mmol) as an internal standard. Yield: 92% (^{19}F NMR). The ^{19}F NMR spectral data matched those of an authentic sample (Matrix). The identity of the product was further confirmed by GC/MS analysis.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.57 (s, 3F), -108.04 (m, 1F).



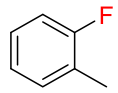
6c: The general procedure A was followed using 1-bromo-4-chlorobenzene (0.5 mmol) as a substrate and 4-fluoroanisole (61.5 mg, 0.488 mmol) as an internal standard. Yield: 89% (^{19}F NMR). The ^{19}F NMR spectral data matched those of an authentic sample (Acros). The identity of the product was further confirmed by GC/MS analysis.

^{19}F NMR (376 MHz, $CDCl_3$) δ -116.42 (tt, J = 8.5, 4.5 Hz).



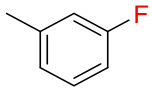
6d: The general procedure A was followed using 4-bromobiphenyl (0.5 mmol) as a substrate and 4-fluoroanisole (62.6 mg, 0.497 mmol) as an internal standard. Yield: 98% (^{19}F NMR). The ^{19}F NMR spectral data matched those of an authentic sample (TCI). The identity of the product was further confirmed by GC/MS analysis.

^{19}F NMR (376 MHz, $CDCl_3$) δ -116.34 (m).



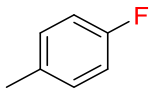
6e: The general procedure A was followed using 2-bromotoluene (0.5 mmol) as a substrate and 4-fluoroanisole (61.6 mg, 0.489 mmol) as an internal standard. Yield: 96% (^{19}F NMR). The ^{19}F NMR spectral data matched those of an authentic sample (Alfa Aesar). The identity of the product was further confirmed by GC/MS analysis.

^{19}F NMR (376 MHz, $CDCl_3$) δ -118.08 (m).



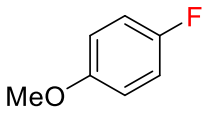
6f: The general procedure A was followed using 3-bromotoluene (0.5 mmol) as a substrate and 4-fluoroanisole (60.9 mg, 0.483 mmol) as an internal standard. Yield: 91% (^{19}F NMR). The ^{19}F NMR spectral data matched those of an authentic sample (TCI). The identity of the product was further confirmed by GC/MS analysis.

^{19}F NMR (376 MHz, $CDCl_3$) δ -114.74 (td, J = 9.3, 6.0 Hz).



6g: The general procedure A was followed using 4-bromotoluene (0.5 mmol) as a substrate and 4-fluoroanisole (62.4mg, 0.495 mmol) as an internal standard. Yield: 98% (^{19}F NMR). The ^{19}F NMR spectral data matched those of an authentic sample (TCI). The identity of the product was further confirmed by GC/MS analysis.

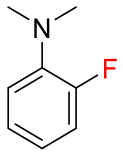
^{19}F NMR (376 MHz, $CDCl_3$) δ -119.09 (m).



6h: The general procedure A was followed using 4-bromoanisole (0.5 mmol) as a substrate and 4-fluorobiphenyl (85.4 mg, 0.497 mmol) as an internal standard. Instead of 1.2 eq, 1.1 eq of *n*-BuLi was used for lithiation. Yield: 94% (^{19}F NMR). The ^{19}F NMR spectral data matched those of

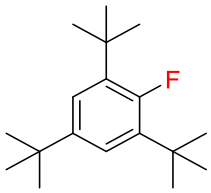
an authentic sample (Oakwood). The identity of the product was further confirmed by GC/MS analysis.

^{19}F NMR (376 MHz, $CDCl_3$) δ -124.90 (tt, J = 8.3, 4.2 Hz).



6i: The general procedure A was followed using 2-bromo-*N*,*N*-dimethylaniline (0.5 mmol) as a substrate and 4-fluorobiphenyl (86.3 mg, 0.502 mmol) as an internal standard. Instead of 1.2 eq, 1.1 eq of *n*-BuLi was used for lithiation. Yield: 92% (^{19}F NMR). The ^{19}F NMR spectral data matched those of an authentic sample (Ambeed). The identity of the product was further confirmed by GC/MS analysis.

^{19}F NMR (376 MHz, $CDCl_3$) δ -123.07 (m).

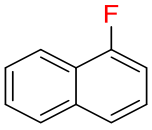


6j[173]: The general procedure A was followed using 1-bromo-2,4,6-tri-*tert*-butylbenzene (0.5 mmol) as a substrate and 4-fluorobiphenyl (86.5 mg, 0.503 mmol) as an internal standard. Instead of 1.2 eq, 1.1 eq of *n*-BuLi was used for lithiation. Yield: 100% (^{19}F NMR).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.18 (d, J = 7.2 Hz, 2H), 1.39 (s, 18H), 1.31 (s, 9H).

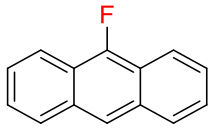
^{13}C NMR (176 MHz, $CDCl_3$) δ 159.33 (d, J = 249.2 Hz), 144.74 (d, J = 3.5 Hz), 136.24 (d, J = 13.6 Hz), 121.93 (d, J = 6.3 Hz), 34.72, 34.72, 31.70, 30.26 (d, J = 3.7 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -112.03 (s).



6k: The general procedure A was followed using 1-bromonaphthalene (0.5 mmol) as a substrate and 4-fluoroanisole (61.3 mg, 0.487 mmol) as an internal standard. Yield: 100% (^{19}F NMR). The ^{19}F NMR spectral data matched those of an authentic sample (Chem-Impex). The identity of the product was further confirmed by GC/MS analysis.

^{19}F NMR (376 MHz, $CDCl_3$) δ -123.90 (dd, J = 10.7, 5.3 Hz).

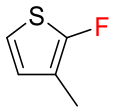


6l[174]: The general procedure A was followed using 9-bromoanthracene (0.5 mmol) as a substrate and 4-fluorobiphenyl (86.3 mg, 0.502 mmol) as an internal standard. Instead of 1.2 eq, 1.1 eq of *n*-BuLi was used for lithiation. Yield: 100% (^{19}F NMR).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, J = 8.3 Hz, 2H), 8.20 (s, 1H), 7.98 (d, J = 7.6 Hz, 2H), 7.57 – 7.47 (m, 4H).

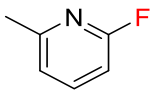
^{13}C NMR (126 MHz, $CDCl_3$) δ 153.96 (d, J = 257.6 Hz), 131.90 (d, J = 4.6 Hz), 127.70 (d, J = 3.7 Hz), 125.80, 125.43 (d, J = 3.2 Hz), 121.20 (d, J = 6.7 Hz), 120.50 (d, J = 5.1 Hz), 119.03 (d, J = 14.9 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -131.70 (s).



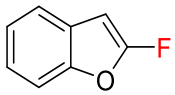
6m: The general procedure A was followed using 2-bromo-3-methylthiophene (0.5 mmol) as a substrate and 4-fluoroanisole (60.3 mg, 0.479 mmol) as an internal standard. Instead of 1.2 eq, 1.1 eq of *n*-BuLi as used for lithiation. Yield: 84% (^{19}F NMR). The ^{19}F NMR spectral data matched the reported data[175]. The identity of the product was further confirmed by GC/MS analysis.

^{19}F NMR (376 MHz, $CDCl_3$) δ -141.79 (m).



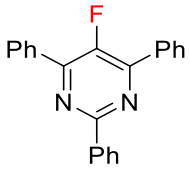
6n: The general procedure A was followed using 2-bromo-6-methylpyridine (0.5 mmol) as a substrate and 4-fluoroanisole (63.2 mg, 0.502 mmol) as an internal standard. Instead of 1.2 eq, 1.1 eq of *n*-BuLi was used for lithiation. Yield: 88% (^{19}F NMR). The ^{19}F NMR spectral data matched those of an authentic sample (Oakwood). The identity of the product was further confirmed by GC/MS analysis.

^{19}F NMR (376 MHz, $CDCl_3$) δ -68.48 (s).



6o: The general procedure A was followed using 2-bromobenzothiophene (0.5 mmol) as a substrate and 4-fluoroanisole (62.7 mg, 0.498 mmol) as an internal standard. Instead of 1.2 eq, 1.1 eq of *n*-BuLi was used for lithiation. Yield: 94% (^{19}F NMR). The ^{19}F NMR spectral data matched the reported data[175]. The identity of the product was further confirmed by GC/MS analysis.

^{19}F NMR (376 MHz, $CDCl_3$) δ -112.97 (d, *J* = 6.7 Hz).



6p: The general procedure A was followed using 5-bromo-2,4,6-triphenylpyrimidine (0.5 mmol) as a substrate and 4-fluorobiphenyl (85.7 mg, 0.498 mmol) as an internal standard. THF (2 mL) and *n*-BuLi (1.1 eq) were used for lithiation. Yield: 100% (^{19}F NMR). White solid, mp 152.3-152.9 ^{o}C.

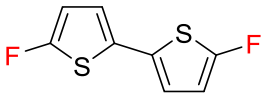
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64-8.60 (m, 2H), 8.28-8.23 (m, 4H), 7.60 – 7.49 (m, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.50 (d, J = 8.7 Hz), 152.96 (d, J = 11.5 Hz), 152.87 (d, J = 269.6 Hz), 137.27, 133.97 (d, J = 4.3 Hz), 130.73, 130.39, 129.45 (d, J = 6.5 Hz), 128.61, 128.49, 128.30.

^{19}F NMR (376 MHz, $CDCl_3$) δ -140.68 (s).

IR (neat, cm^{-1}): v = 3062.0, 1567.4, 1533.4, 1494.5, 1445.0, 1393.0, 1378.1, 1313.9, 736.8, 684.9.

HRMS: (ESI) m/z: $[M + H]^+$ Calcd. for $C_{22}H_{16}N_2F$ 327.1292, Found: 327.1293.



6q: The general procedure A was followed using 5,5'-dibromo-2,2'-bithiophene (0.5 mmol) as a substrate and 4-fluorobiphenyl (85.6 mg, 0.498 mmol) as an internal standard. THF (2 mL), *n*-BuLi (2.4 eq), 1 h at -78 °C and 1 h at rt were used for lithiation. NFBB (2.5 eq) was used for fluorination. Yield: 90% (^{19}F NMR). Brown yellow solid, mp 39.5-40.6 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (dd, J = 4.0, 2.6 Hz, 2H), 6.38 (dd, J = 4.1, 1.5 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.18 (d, J = 291.8 Hz), 125.43, 119.73, 107.77 (d, J = 10.1 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -130.38 (m).

IR (neat, cm^{-1}): v = 3101.3, 3072.9, 1714.8, 1548.3, 1454.4, 1189.9, 1036.7, 868.1, 777.8, 701.2.

HRMS: (EI) m/z: $[M]^+$ Calcd. for $C_8H_4F_2S_2$ 201.9722, Found: 201.9716.

5.2.3.3 Fluorination of (hetero)aryl lithiums 5, generated from (hetero)arenes, with NFBB

Table S3B. Fluorination of (Hetero)aryl lithiums 5 with NFBB

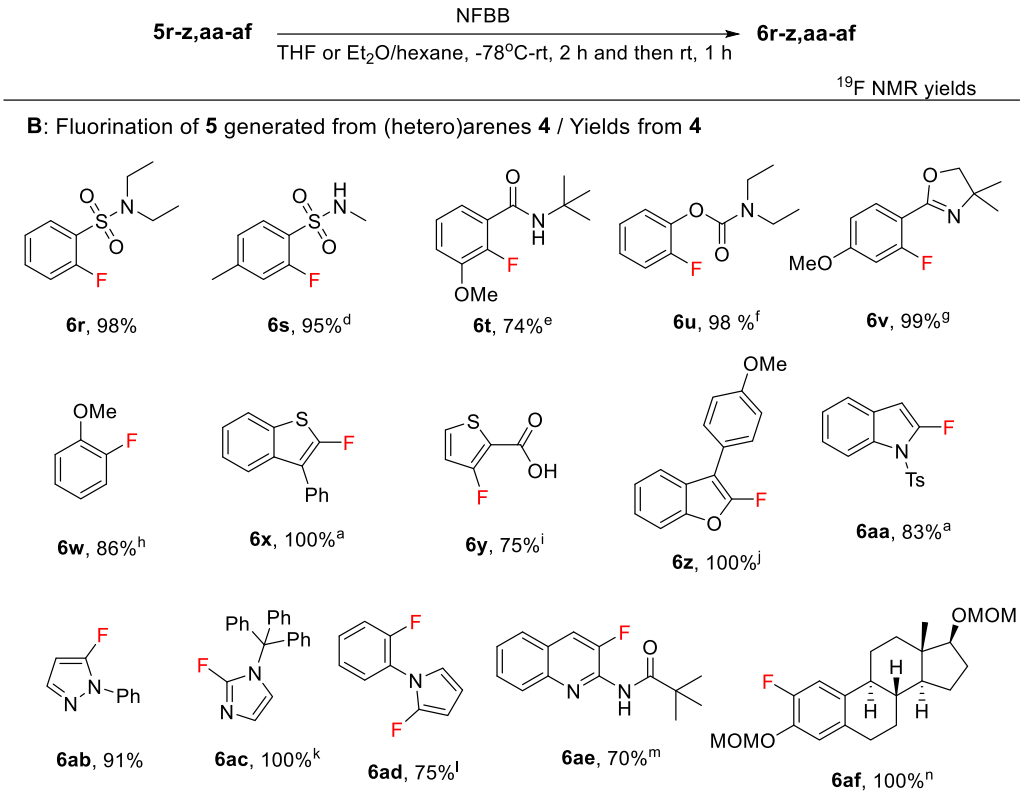
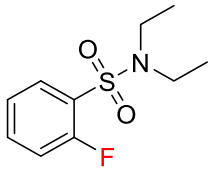


***Table S3B*.** Fluorination of (hetero)aryl lithiums **5**, generated from (hetero)arenes, with NFBB. The reactions were carried out according to the general procedure **B** (below), unless otherwise noted: [a] *n*-BuLi (1.1 eq) was used for lithiation. [d] *n*-BuLi (2.4 eq), addition at -78 °C and 1 h at 0 °C were used for lithiation. NFBB (1.5 eq) was used for fluorination. [e] *n*-BuLi (2.2 eq), addition at -78 °C and 1 h at 0 °C were used for lithiation. NFBB (1.3 eq) was used for fluorination. [f] *sec*-BuLi (1.1 eq) in cyclohexane (1.4 M) and TMEDA (1.1 eq) were used for lithiation. [g] *sec*-BuLi (1.2 eq) in cyclohexane (1.4 M), TMEDA (1.2 eq), addition at -78 °C and 1 h at -20 °C were used for lithiation. [h] *n*-BuLi (2.0 eq), TMEDA (2.0 eq), 1 h at rt were used for lithiation. [i] *n*-BuLi (2.2 eq) was used for lithiation. [j] *n*-BuLi (1.1 eq) and 1 h at 0 °C were used for lithiation. [k] THF (2 mL), addition at 0 °C and 1.5 h at rt were used for lithiation. [l] For lithiation step, Et_2O (2 mL) was used, *n*-BuLi (2.0 eq) was added at 0 °C and stirred for 15 min, TMEDA (2.0 eq) was then added at 0 °C and stirred for 15 min. NFBB (2.2 eq) was used for fluorination. [m] Et_2O (1 mL), *n*-BuLi (2.4 eq), addition at -70 °C and 3 h at 0 °C were used for lithiation. NFBB (1.5 eq) was used for

fluorination. [n] *sec*-BuLi (1.8 eq) in cyclohexane (1.4 M) and 2 h at -72 ^{o}C were used for lithiation. NFBB (2.0 eq) was used for fluorination.

General procedure B: To a flame-dried 8 mL reaction vial equipped with a magnetic stir bar and an argon balloon, was added a (hetero)arene substrate (0.5 mmol) and dry THF (1 mL). The solution was cooled down to -78^{o}C and 0.24 mL of *n*-BuLi (2.5 M in hexane, 0.6 mmol, 1.2 eq) was added via syringe through its open-top cap with TFE septum. After stirring at -78^{o}C for 1 h, a solution of 127 mg of NFBB (0.6 mmol, 1.2 eq) in dry hexane (2 mL) was added dropwise via syringe. The reaction mixture was warmed up to room temperature over a period of 2 h and stirred at room temperature for 1 h. After quenching the reaction with a few drops of sat. aq. solution of NH_4Cl, the reaction mixture was stirred until clear (EtOAc was added if necessary). An internal standard was then added, and its weight was recorded. An 80 µL aliquot of the solution was transferred to an NMR tube and analyzed by ^{19}F NMR. The yield of the product was determined by comparing the integration values of the product peak and the internal standard peak. Pure products were isolated for identification by preparative HPLC chromatography using a 150 mm × 20 mm column (packing material: RediSep Prep C18, 100 Å, 5 µm) with a H_2O/MeCN gradient elution (100:0 to 0:100) for 40 min at a flow rate of 19 mL/min except for the cases of **6w** and **6y** in which the products were identified by the spectral comparison with the authentic samples.

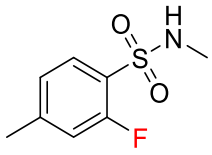


6r[176]: The general procedure B was followed using *N,N*-diethyl-benzenesulfonamide (0.5 mmol) as a substrate and 4-fluorotoluene (57.5 mg, 0.523 mmol) as an internal standard. Yield: 94% (^{19}F NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.87 (m, 1H), 7.56-7.49 (m, 1H), 7.27-7.13 (m, 2H), 3.35 (q, J = 7.2 Hz, 4H), 1.13 (t, J = 7.2 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.74 (d, J = 254.8 Hz), 134.40 (d, J = 8.3 Hz), 130.81, 128.86 (d, J = 14.9 Hz), 124.23 (d, J = 4.0 Hz), 117.06 (d, J = 22.1 Hz), 41.71 (d, J = 2.7 Hz), 14.08.

^{19}F NMR (376 MHz, $CDCl_3$) δ -108.80 (m).

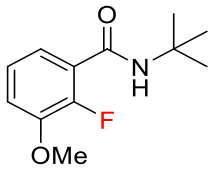


6s[99]: The general procedure B was followed using *N*-methyl-*p*-toluenesulfonamide (0.5 mmol) as a substrate and 4-fluorotoluene (41.9 mg, 0.381 mmol) as an internal standard. *n*-BuLi (2.4 eq), addition at -78 °C and then stirring for 1 h at 0 °C were used for lithiation. NFBB (1.5 eq) was used for fluorination. Yield: 95% (^{19}F NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (t, J = 7.8 Hz, 1H), 7.10-6.98 (m, 2H), 4.66 (br.q, J = 4.6 Hz, 1H), 2.67 (d, J = 5.3 Hz, 3H), 2.42 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.63 (d, J = 253.0 Hz), 146.71 (d, J = 8.5 Hz), 130.54, 125.13 (d, J = 3.3 Hz), 123.61 (d, J = 13.8 Hz), 117.29 (d, J = 20.9 Hz), 29.25, 21.46.

^{19}F NMR (376 MHz, $CDCl_3$) δ -112.46 (dd, J = 11.2, 7.7 Hz).



6t: The general procedure B was followed using *N*-(*tert*-butyl)-3-methoxybenzamide (0.5 mmol) as a substrate and 4-fluorobiphenyl (86.0 mg, 0.500 mmol) as an internal standard. *n*-BuLi (2.2 eq), addition at -78 °C and then stirring for 1 h at 0 °C were used for lithiation. NFBB (1.3 eq) was used for fluorination. Yield: 74% (^{19}F NMR). White solid, mp 73.2-74.2 °C.

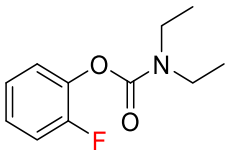
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (t, J = 7.2 Hz, 1H), 7.08 (t, J = 8.0 Hz, 1H), 7.00 (t, J = 8.1 Hz, 1H), 6.48 (br.d, J = 11.7 Hz, 1H), 3.84 (s, 3H), 1.42 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.22, 150.36 (d, J = 246.4 Hz), 147.67 (d, J = 12.6 Hz), 124.03 (d, J = 4.6 Hz), 123.42 (d, J = 9.8 Hz), 122.08, 115.61 (d, J = 2.6 Hz), 56.41, 51.66, 28.72.

^{19}F NMR (376 MHz, $CDCl_3$) δ -137.62 (m).

IR (neat, cm^{-1}): v = 3302.3, 3084.3, 2984.2, 2960.3, 2926.8, 1643.7, 1552.9, 1483.9, 1330.4, 1270.8, 1064.8, 930.0, 750.3, 663.9.

HRMS: (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{12}H_{16}O_2NFNa$ 248.1057, Found: 248.1058.

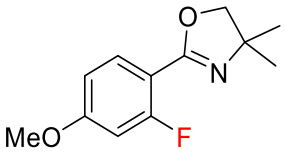


6u[177]: The general procedure B was followed using phenyl diethylcarbamate (0.5 mmol) as a substrate and 4-fluorobiphenyl (86.4 mg, 0.502 mmol) as an internal standard. *sec*-BuLi (1.1 eq) in cyclohexane (1.4 M) and TMEDA (1.1 eq) were used for lithiation. Yield: 98% (^{19}F NMR).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.19 (t, J = 7.9 Hz, 1H), 7.17-7.08 (m, 3H), 3.46 (q, J = 7.3 Hz, 2H), 3.39 (q, J = 7.4 Hz, 2H), 1.27 (t, J = 7.4 Hz, 3H), 1.21 (t, J = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.55 (d, J = 248.2 Hz), 153.17, 138.98 (d, J = 12.2 Hz), 126.15 (d, J = 7.1 Hz), 124.18, 124.08 (d, J = 3.9 Hz), 116.34 (d, J = 18.6 Hz), 42.38, 41.99, 13.91, 13.18.

^{19}F NMR (376 MHz, $CDCl_3$) δ -130.32 (m).



6v[99]: The general procedure B was followed using 2-(4-methoxyphenyl)-4,4-dimethyl-4,5-dihydrooxazole (0.5 mmol) as a substrate and 4-fluorobiphenyl (86.6 mg, 0.503 mmol) as an internal standard. *sec*-BuLi (1.2 eq) in cyclohexane (1.4M), TMEDA (1.2 eq), addition at -78 ^{o}C and then stirring for 1 h at -20 ^{o}C were used for lithiation. Yield: 99% (^{19}F NMR). Yellow oil.

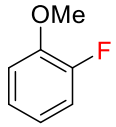
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (t, J = 8.6 Hz, 1H), 6.67-6.56 (m, 2H), 4.01 (s, 2H), 3.76 (s, 3H), 1.33 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.95 (d, J = 11.2 Hz), 162.06 (d, J = 257.1 Hz), 158.68 (d, J = 5.4 Hz), 131.84 (d, J = 3.8 Hz), 109.90 (d, J = 3.1 Hz), 108.57 (d, J = 10.8 Hz), 101.98 (d, J = 25.7 Hz), 78.46, 67.34, 55.49, 28.22.

^{19}F NMR (376 MHz, $CDCl_3$) δ -107.15 (dd, J = 12.4, 8.5 Hz).

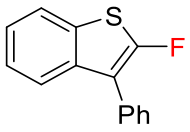
IR (neat, cm^{-1}): v = 2966.7, 2931.5, 2897.0, 2842.2, 1645.7, 1620.2, 1509.6, 1290.0, 1123.2, 1024.7, 953.0, 837.0.

HRMS: (ESI) m/z: $[M + H]^+$ Calcd. for $C_{12}H_{15}O_2NF$ 224.1081, Found: 224.1081.



6w: The general procedure B was followed using anisole (0.5 mmol) as a substrate and 4-fluorotoluene (57.0 mg, 0.518 mmol) as an internal standard. *n*-BuLi (2.0 eq), TMEDA (2.0 eq), and addition and then stirring for 1 h at rt were used for lithiation. Yield: 86% (^{19}F NMR). The ^{19}F NMR spectral data matched those of an authentic sample (Oakwood). The identity of the product was further confirmed by GC/MS analysis.

^{19}F NMR (376 MHz, $CDCl_3$) δ -136.10 (m).

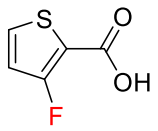


6x[178]: The general procedure B was followed using 3-phenylbenzo[b]thiophene (0.5 mmol) as a substrate and 4-fluorobiphenyl (85.8 mg, 0.499 mmol) as an internal standard. *n*-BuLi (1.1 eq) was used for lithiation. Yield: 100% (^{19}F NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77-7.72 (m, 2H), 7.63-7.57 (m, 2H), 7.57-7.51 (m, 2H), 7.48-7.35 (m, 3H).

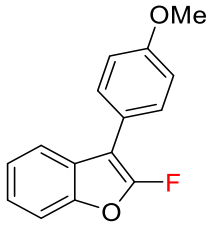
^{13}C NMR (100 MHz, $CDCl_3$) δ 159.70 (d, J = 292.0 Hz), 136.00 (d, J = 3.8 Hz), 131.14, 130.80, 129.37, 128.74, 127.83, 125.12, 124.57 (d, J = 4.4 Hz), 122.59, 122.54, 116.91 (d, J = 7.2 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -131.37 (s).



6y: The general procedure B was followed using 2-thiophenecarboxylic acid (0.5 mmol) as a substrate and 4-fluoroanisole (59.0 mg, 0.468 mmol) as an internal standard. *n*-BuLi (2.2 eq) was used for lithiation. Yield: 75% (^{19}F NMR). The ^{19}F NMR spectral data matched those of an authentic sample (AmBeed). The identity of the product was further confirmed by GC/MS analysis.

^{19}F NMR (376 MHz, $CDCl_3$) δ -115.97 (d, J = 3.5 Hz).

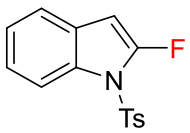


6z[179]: The general procedure B was followed using 3-(4-methoxyphenyl)benzofuran (0.5 mmol) as a substrate and 4-fluorobiphenyl (85.8 mg, 0.499 mmol) as an internal standard. *n*-BuLi (1.1 eq), addition at 0 ^{o}C and then stirring for 1 h at 0 ^{o}C were used for lithiation. Yield: 100% (^{19}F NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76-7.71 (m, 1H), 7.63-7.58 (m, 2H), 7.48-7.42 (m, 1H), 7.35-7.29 (m, 2H), 7.07-7.02 (m, 2H), 3.88 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.76, 156.17 (d, J = 281.9 Hz), 147.05, 128.89 (d, J = 2.7 Hz), 127.59, 123.74, 123.66 (d, J = 3.8 Hz), 121.78 (d, J = 4.4 Hz), 119.86 (d, J = 5.6 Hz), 114.40, 111.09, 92.78 (d, J = 8.8 Hz), 55.29.

^{19}F NMR (376 MHz, $CDCl_3$) δ -117.40 (s).

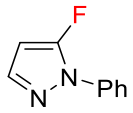


6aa[180]: The general procedure B was followed using 1-tosyl-1H-indole (0.5 mmol) as a substrate and 4-fluorobiphenyl (85.5 mg, 0.497 mmol) as an internal standard. *n*-BuLi (1.1 eq) was used for lithiation. Yield: 83% (^{19}F NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 8.3 Hz, 1H), 7.81 (d, J = 8.3 Hz, 2H), 7.39 (d, J = 7.1 Hz, 1H), 7.34-7.29 (m, 1H), 7.28-7.20 (m, 3H), 5.94 (d, J = 3.2 Hz, 1H), 2.36 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.80 (d, J = 279.0 Hz), 145.55, 134.90, 130.81, 129.93, 126.81, 126.52 (d, J = 5.9 Hz), 124.12, 124.03 (d, J = 4.1 Hz), 120.68 (d, J = 6.6 Hz), 114.04, 86.60 (d, J = 12.0 Hz), 21.52.

^{19}F NMR (376 MHz, $CDCl_3$) δ -126.53 (d, J = 3.1 Hz).

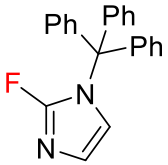


6ab[181]: The general procedure B was followed using 1-phenylpyrazole (0.5 mmol) as a substrate and 4-fluorobiphenyl (86.2 mg, 0.501 mmol) as an internal standard. Yield: 91% (^{19}F NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.61 (m, 2H), 7.53 (dd, J = 3.2, 2.0 Hz, 1H), 7.51-7.43 (m, 2H), 7.37-7.31 (m, 1H), 5.91 (dd, J = 5.4, 2.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.39 (d, J = 280.2 Hz), 139.59 (d, J = 11.0 Hz), 137.18, 129.22, 127.24, 121.44 (d, J = 4.2 Hz), 88.15 (d, J = 15.3 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -133.42 (m).



6ac: The general procedure B was followed using 1-tritylimidazole (0.5 mmol) as a substrate and 4-fluorotoluene (59.2 mg, 0.538 mmol) as an internal standard. THF (2 mL), addition at 0 °C and then stirring for 1.5 h at rt were used for lithiation. Yield: 100% (^{19}F NMR). White solid, mp 186.5-187.8 °C.

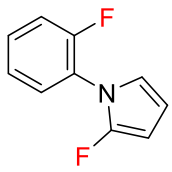
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.30 (m, 9H), 7.19-7.14 (m, 6H), 6.65 (s, 1H), 6.53 (d, J = 2.0 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.16 (d, J = 246.1 Hz), 141.55, 129.26, 128.09, 127.93, 121.59 (d, J = 11.3 Hz), 117.90 (d, J = 5.3 Hz), 74.79.

^{19}F NMR (376 MHz, $CDCl_3$) δ -97.87 (s).

IR (neat, cm^{-1}): v = 3176.8, 3060.1, 1966.7, 1563.0, 1547.9, 1493.9, 1440.3, 1318.3, 1231.5, 1120.4, 762.1, 700.0, 672.6.

HRMS: (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{22}H_{17}N_2FNa$ 351.1268, Found: 351.1268; $[M - C_3H_2N_2F]^+$ Calcd. for $C_{19}H_{15}$ 243.1168, Found: 243.1170.



6ad: The general procedure B was followed using 1-phenylpyrrole (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.1 mg, 0.501 mmol) as an internal standard. For the lithiation step: 2 mL of Et_2O was used, 2.0 eq of *n*-BuLi was added at 0 °C and stirred for 15 min, then 2.0 eq of TMEDA was added at 0 °C and stirred for 15 min. NFBB (2.2 eq) was used for fluorination. Yield: 75% (^{19}F NMR). Colorless oil.

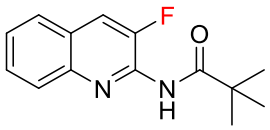
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.35 (m, 2H), 7.30-7.23 (m, 2H), 6.47-6.41 (m, 1H), 6.17 (dt, J = 4.8, 3.7 Hz, 1H), 5.68 (td, J = 3.9, 2.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.38 (d, J = 251.6 Hz), 146.47 (d, J = 262.7 Hz), 129.03 (d, J = 7.6 Hz), 127.51, 124.75 (d, J = 12.2 Hz), 124.53 (d, J = 3.7 Hz), 116.74 (d, J = 20.0 Hz), 113.96, 106.73 (d, J = 4.7 Hz), 86.10 (d, J = 10.8 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -123.46 (m, 1F), -140.55 (dt, J = 13.3, 4.4 Hz, 1F).

IR (neat, cm^{-1}): v = 3132.1, 3073.4, 1582.2, 1513.5, 1491.2, 1440.0, 1330.5, 1267.5, 1221.9, 1173.5, 755.2, 689.1.

HRMS: (EI) m/z: $[M]^+$ Calcd. for $C_{10}H_7F_2N$ 179.0547, Found: 179.0539.



6ae: The general procedure B was followed using *N*-(quinolin-2-yl)pivalamide (0.5 mmol) as a substrate and 4-fluorobiphenyl (86.0 mg, 0.500 mmol) as an internal standard. Et_2O (1 mL), *n*-BuLi (2.4 eq), addition at -70 °C and then stirring for 3 h at 0 °C were used for lithiation. NFBB (1.5 eq) was used for fluorination. Yield: 70% (^{19}F NMR). White solid, mp 134.9-136.5 °C.

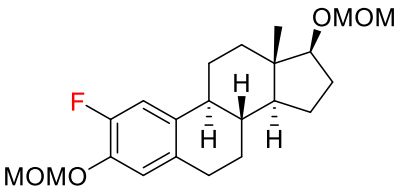
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (br, 1H), 7.98 (d, J = 8.5 Hz, 1H), 7.79 (d, J = 10.2 Hz, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.64 (t, J = 7.7 Hz, 1H), 7.49 (t, J = 7.5 Hz, 1H), 1.39 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.69, 149.63 (d, J = 261.7 Hz), 143.58, 141.64 (d, J = 14.6 Hz), 128.91, 128.23, 127.24 (d, J = 3.9 Hz), 126.86 (d, J = 4.9 Hz), 126.64, 120.07 (d, J = 17.0 Hz), 39.86, 27.51.

^{19}F NMR (376 MHz, $CDCl_3$) δ -128.07 (d, J = 10.2 Hz).

IR (neat, cm^{-1}): v = 3163.7, 2964.8, 2932.2, 2870.7, 1682.9, 1494.4, 1435.4, 1355.2, 1321.3, 1155.5, 891.8, 757.0.

HRMS: (ESI) m/z: $[M + Na]^+$ Calcd. for $C_{14}H_{15}ON_2FNa$ 269.1061, Found: 269.1063.



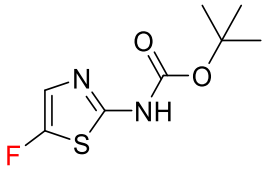
6af[111]: The general procedure B was followed using (8R,9S,13S,14S,17S)-3,17-bis(methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene (0.5 mmol) as a substrate and 4-fluorobiphenyl (86.3 mg, 0.502 mmol) as an internal standard. *sec*-BuLi (1.8 eq) in cyclohexane (1.4 M) and addition at -72 °C and then stirring for 2 h at -72 °C were used for lithiation. NFBB (2.0 eq) was used for fluorination. Yield: 100% (^{19}F NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, J = 13.0 Hz, 1H), 6.87 (d, J = 8.6 Hz, 1H), 5.16 (s, 2H), 4.65 (d, J = 2.8 Hz, 2H), 3.60 (t, J = 8.5 Hz, 1H), 3.51 (s, 3H), 3.37 (s, 3H), 2.79 (dd, J = 9.1, 4.0 Hz,

2H), 2.22-2.13 (m, 2H), 2.08 (dddd, J = 12.8, 9.2, 6.5, 3.4 Hz, 1H), 1.99 (dt, J = 12.4, 3.2 Hz, 1H), 1.87 (ddt, J = 12.5, 5.5, 2.5 Hz, 1H), 1.69 (dddd, J = 12.1, 9.4, 7.0, 3.3 Hz, 1H), 1.58 (dddd, J = 13.5, 11.7, 8.0, 3.4 Hz, 1H), 1.48 (dd, J = 12.9, 3.0 Hz, 1H), 1.43-1.38 (m, 1H), 1.37-1.25 (m, 3H), 1.16 (ddd, J = 12.3, 10.7, 7.1 Hz, 1H), 0.81 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 151.26 (d, J = 242.8 Hz), 142.17 (d, J = 11.1 Hz), 134.93 (d, J = 5.3 Hz), 132.31 (d, J = 3.4 Hz), 118.13, 113.00 (d, J = 18.7 Hz), 95.83, 95.64, 86.34, 56.04, 54.91, 49.79, 43.80, 42.79, 38.06, 37.00, 28.91, 27.93, 26.99, 26.11, 22.89, 11.55.

^{19}F NMR (376 MHz, $CDCl_3$) δ -138.22 (dd, J = 13.0, 8.5 Hz).



6ag[113]: *Gram-scale procedure*: To a flame-dried 250 mL round bottom flask equipped with a magnetic stir bar and an argon balloon, was added a solution of *tert*-butyl thiazol-2-ylcarbamate (5 mmol) and dry THF (20 mL). The flask was cooled down to -78 ^{o}C and 4.4 mL of *n*-BuLi (2.5 M in hexane, 11 mmol, 2.2 eq) was added via syringe and the reaction mixture was allowed to warm up from -78 ^{o}C to – 10 ^{o}C over a period of 1h. After cooling the resulting mixture back to -78 ^{o}C, a solution of NFBB (1.3 eq) in 20 mL of dry hexane was added dropwise via syringe. The reaction mixture was warmed up to room temperature over a period of 2h and stirred at room temperature for 1h. After quenching the reaction with several drops of saturated aqueous solution of NH_4Cl, the reaction mixture was dried with $MgSO_4$, filtered through a pad of Celite, and evaporated in a rotary evaporator. The resulting residue was column chromatographed on silica gel to give pure product **6ag**. Yield: 0.98 g, 90% (isolated).

^{1}H NMR (399 MHz, $CDCl_3$) δ 12.03 (br.s, 1H), 6.89 (d, J = 2.6 Hz, 1H), 1.56 (s, 9H).

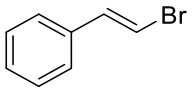
^{13}C NMR (100 MHz, $CDCl_3$) δ 157.70 (d, J = 291.3 Hz), 152.70, 151.69 (d, J = 9.7 Hz), 116.46 (d, J = 13.1 Hz), 82.17, 28.20.

^{19}F NMR (376 MHz, $CDCl_3$) δ -159.00 (s).

5.2.4 Fluorination of alkenyl lithiums with NFBB

5.2.4.1 Preparation of vinyl bromides

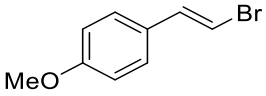
(*E*)-(2-bromovinyl)benzene (7a)



This compound was prepared in 31% yield according to the reported method[182]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 5H), 7.11 (d, J = 13.8 Hz, 1H), 6.77 (d, J = 14.0 Hz, 1H).

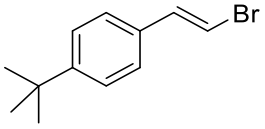
(*E*)-1-(2-bromovinyl)-4-methoxybenzene (7b)



This compound was prepared in 77% yield according to the reported method[182]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 7.6 Hz, 2H), 7.04 (d, J = 14.0 Hz, 1H), 6.85 (d, J = 7.3 Hz, 2H), 6.61 (d, J = 13.9 Hz, 1H), 3.81 (s, 3H).

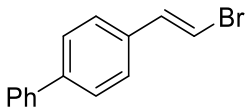
(*E*)-1-(2-bromovinyl)-4-(tert-butyl)benzene (7c)



This compound was prepared in 55% yield according to the reported method[182]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 8.3 Hz, 2H), 7.09 (d, J = 13.9 Hz, 1H), 6.72 (d, J = 14.0 Hz, 1H), 1.31 (s, 9H).

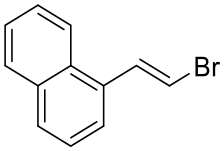
(*E*)-4-(2-bromovinyl)-1,1'-biphenyl (7d)



This compound was prepared in 72% yield according to the reported method[182]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.54 (m, 4H), 7.47-7.41 (m, 2H), 7.40-7.35 (m, 3H), 7.15 (d, J = 14.0 Hz, 1H), 6.82 (d, J = 14.0 Hz, 1H).

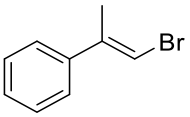
(*E*)-1-(2-bromovinyl)naphthalene (7e)



This compound was prepared in 32% yield according to the reported method[182]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.3 Hz, 1H), 7.88-7.80 (m, 3H), 7.59-7.47 (m, 3H), 7.44 (t, J = 7.8 Hz, 1H), 6.78 (d, J = 13.7 Hz, 1H).

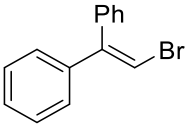
(*E*)-(1-bromoprop-1-en-2-yl)benzene (7f)



This compound was prepared in 69% yield according to the reported method[183]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.29 (m, 5H), 6.45 (s, 1H), 2.23 (s, 3H).

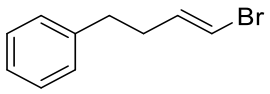
(2-bromoethene-1,1-diyl)dibenzene (7g)



This compound was prepared in 77% yield according to the reported method[184]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.35 (m, 3H), 7.33-7.27 (m, 5H), 7.24-7.18 (m, 2H), 6.78 (s, 1H).

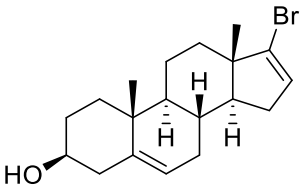
(*E*)-(4-bromobut-3-en-1-yl)benzene (7i)



This compound was prepared in 50% yield according to the reported method[185]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, J = 7.5 Hz, 2H), 7.24-7.15 (m, 3H), 6.23 (dt, J = 14.1, 7.2 Hz, 1H), 6.06 (d, J = 13.5 Hz, 1H), 2.73 (t, J = 7.7 Hz, 2H), 2.38 (q, J = 7.5 Hz, 2H).

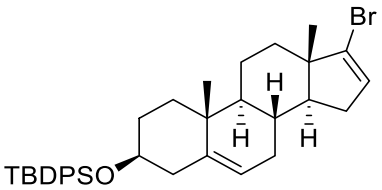
(3S,8R,9S,10R,13S,14S)-17-bromo-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol



This compound was prepared in 60% yield according to the reported method[186]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87-5.81 (m, 1H), 5.38-5.34 (m, 1H), 3.58-3.48 (m, 1H), 2.35-2.23 (m, 2H), 2.14 (ddd, J = 14.8, 6.4, 3.2 Hz, 1H), 2.06-1.98 (m, 1H), 1.93-1.81 (m, 3H), 1.79-1.47 (m, 9H), 1.29-1.02 (m, 5H), 0.86 (s, 3H).

3S,8R,9S,10R,13S,14S)-17-bromo-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl)oxy)(*tert*-butyl)diphenylsilane (7j)



The alcohol (1.2 mmol, 1 eq) prepared above and imidazole (2.5 eq) were dissolved in dry DMF (0.25 M). To this mixture was added *tert*-butyldiphenylsilyl chloride (1.2 eq) dropwise at 0 ^{o}C. The reaction mixture was warmed up and stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane and washed with 10% LiCl aq. solution. The organic layer was dried with $MgSO_4$, filtered, and evaporated. The resulting residue was purified by silica gel chromatography to give the product in 54% yield. White foamy solid, mp 122.9-123.7 ^{o}C.

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.69-7.66 (m, 4H), 7.43-7.39 (m, 2H), 7.38-7.34 (m, 4H), 5.81 (dd, J = 3.3, 1.7 Hz, 1H), 5.14-5.11 (m, 1H), 3.53 (tt, J = 10.9, 4.5 Hz, 1H), 2.34 (tt, J = 10.9, 2.7 Hz, 1H), 2.14 (ddd, J = 13.4, 4.8, 2.3 Hz, 1H), 2.10 (ddd, J = 14.8, 6.4, 3.3 Hz, 1H), 1.93 (dtd, J = 17.4, 5.2, 2.7 Hz, 1H), 1.90-1.86 (m, 1H), 1.73-1.66 (m, 3H), 1.65-1.56 (m, 3H), 1.53-1.40 (m, 3H), 1.24 (td, J = 12.7, 4.7 Hz, 1H), 1.06 (s, 9H), 1.02 (s, 3H), 0.94-0.84 (m, 2H), 0.83 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.71, 135.75, 135.69, 134.77, 129.44, 128.97, 127.45, 120.53, 77.32, 77.00, 76.68, 73.14, 55.57, 50.40, 48.51, 42.47, 37.10, 36.72, 34.49, 31.81, 31.02, 30.69, 27.00, 20.57, 19.30, 19.13, 15.01.

IR (neat, cm^{-1}): v = 3068.6, 2932.4, 2857.6, 1591.6, 1461.4, 1427.9, 1371.9, 1249.1, 1106.2, 1088.1, 800.2, 700.4.

HRMS: (APCI) m/z: $[M - H]^+$ Calcd. for $C_{35}H_{44}OBrSi$ 587.2339, Found: 587.2334.

5.2.4.2 Fluorination of alkenyl lithiums 8, generated from alkenyl bromides, with NFBB

Table S4A. Fluorination of alkenyl lithiums **8** with NFBB

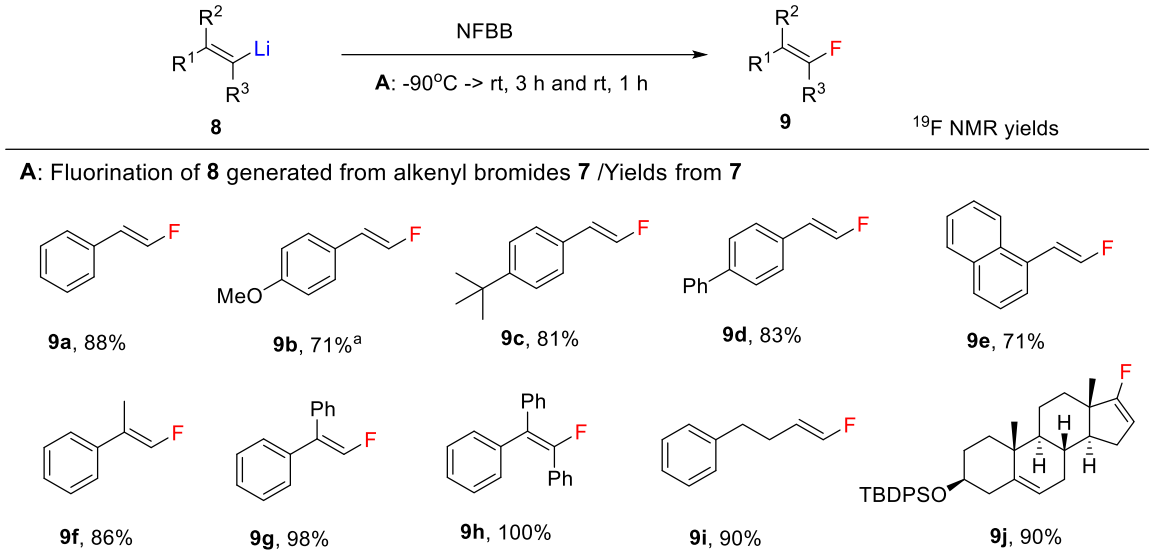
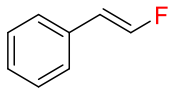


***Table S4A*.** Fluorination of alkenyl lithiums **8**, generated from alkenyl bromides **7**, with NFBB. The reactions were carried out according to the general procedure **C** (below), unless otherwise noted: (a) *tert*-BuLi in pentane (1.6 M) was added at -78 °C and stirred for 30 min at -78 °C.

General procedure C: To a flame-dried 8 mL reaction vial equipped with a magnetic stir bar and an argon balloon, was added an alkenyl bromide substrate (0.5 mmol) and 2.25 mL of dry THF/Et_2O/pentane (4/1/1). The vial was cooled down to -120°C (cooling bath: pentane/liquid N_2 bath) and 0.625 mL of *t*-BuLi (1.6 M in pentane, 1.0 mmol, 2 eq) was added via syringe through its open-top cap with TFE septum. After stirring at -120°C ~ -110°C for 1 h, the reaction mixture was warmed up naturally to -90°C over a period of 30 mins. NFBB (1.2 eq) in dry hexane (2 mL) was added dropwise via syringe. The reaction mixture was warmed up naturally to room temperature over a period of 3 h and stirred at room temperature for 1 h. After quenching the reaction with a few drops of sat. aq. solution of NH_4Cl, the reaction mixture was stirred until clear (EtOAc was added if necessary). An internal standard was then added, and its weight was recorded. An 80 μL aliquot of the solution was transferred to an NMR tube and analyzed by ^{19}F NMR. The yield of the product was determined by comparing the integration values of the product

peak and the internal standard peak. For identification, pure products were isolated by silica gel chromatography.

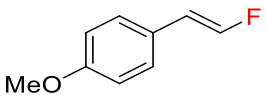


9a[187]: The general procedure C was followed using (*E*)-(2-bromovinyl)benzene (0.5 mmol) as a substrate and 4-fluoroanisole (62.5 mg, 0.496 mmol) as an internal standard. Yield: 88% (^{19}F NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.24 (m, 5H), 7.22 (dd, J = 83.3, 11.4 Hz, 1H), 6.41 (dd, J = 19.3, 11.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.12 (d, J = 259.0 Hz), 132.66 (d, J = 11.5 Hz), 128.76, 127.47, 126.15, 113.86 (d, J = 15.9 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -130.40 (dd, J = 83.3, 19.3 Hz).

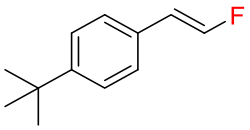


9b[187]: The general procedure C was followed using (*E*)-1-(2-bromovinyl)-4-methoxybenzene (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.4 mg, 0.502 mmol) as an internal standard. *t*-BuLi was added at -78 ^{o}C and the reaction mixture was stirred for 30 mins at -78 ^{o}C instead of -120^{o}C ~ -110^{o}C for 1 h.Yield: 71% (^{19}F NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, J = 7.9 Hz, 2H), 7.09 (dd, J = 83.8, 11.4 Hz, 1H), 6.85 (d, J = 8.3 Hz, 2H), 6.35 (dd, J = 19.6, 11.3 Hz, 1H), 3.81 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.09, 148.98 (d, J = 256.5 Hz), 127.28 (d, J = 3.1 Hz), 125.05 (d, J = 11.7 Hz), 114.24, 113.27 (d, J = 16.0 Hz), 55.27.

^{19}F NMR (376 MHz, $CDCl_3$) δ -133.16 (dd, J = 83.8, 19.7 Hz).

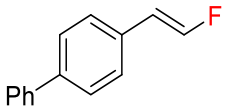


9c[188]: The general procedure C was followed using (*E*)-1-(2-bromovinyl)-4-(*tert*-butyl)benzene (0.5 mmol) as a substrate and 4-fluoroanisole (62.7 mg, 0.498 mmol) as an internal standard. Yield: 81% (^{19}F NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 8.3 Hz, 2H), 7.20 (d, J = 8.1 Hz, 2H), 7.16 (dd, J = 83.7, 11.4 Hz, 1H), 6.39 (dd, J = 19.5, 11.4 Hz, 1H), 1.32 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.63, 149.79 (d, J = 258.1 Hz), 129.75 (d, J = 11.6 Hz), 125.90 (d, J = 3.0 Hz), 125.70, 113.56 (d, J = 15.6 Hz), 34.57, 31.26.

^{19}F NMR (376 MHz, $CDCl_3$) δ -131.50 (dd, J = 83.7, 19.6 Hz).

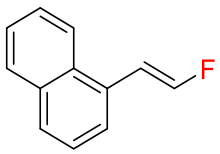


9d[188]: The general procedure C was followed using (*E*)-4-(2-bromovinyl)-1,1'-biphenyl (0.5 mmol) as a substrate and 4-fluoroanisole (62.5 mg, 0.496 mmol) as an internal standard. Yield: 83% (^{19}F NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 7.6 Hz, 2H), 7.61 (d, J = 8.1 Hz, 2H), 7.51 (t, J = 7.5 Hz, 2H), 7.45 – 7.34 (m, 3H), 7.29 (dd, J = 83.1, 11.4 Hz, 1H), 6.50 (dd, J = 19.3, 11.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.16 (d, J = 259.4 Hz), 140.48, 140.27, 131.63 (d, J = 11.8 Hz), 128.79, 127.39, 127.36, 126.85, 126.51 (d, J = 2.2 Hz), 113.49 (d, J = 16.0 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -130.02 (dd, J = 83.1, 19.2 Hz).

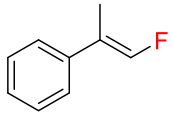


9e[187]: The general procedure C was followed using (*E*)-1-(2-bromovinyl)naphthalene (0.5 mmol) as a substrate and 4-fluoroanisole (62.1 mg, 0.493 mmol) as an internal standard. Yield: 71% (^{19}F NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06-8.00 (m, 1H), 7.92-7.87 (m, 1H), 7.86-7.81 (m, 1H), 7.60-7.52 (m, 2H), 7.48-7.42 (m, 2H), 7.25-6.98 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.71 (d, J = 262.2 Hz), 133.65, 131.54 (d, J = 2.7 Hz), 129.51 (d, J = 11.6 Hz), 128.52, 128.24, 126.27, 126.04, 125.49, 124.35, 124.02, 111.39 (d, J = 15.3 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -124.15 (dd, J = 86.1, 16.0 Hz).

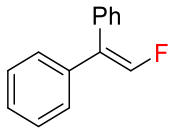


9f[189]: The general procedure C was followed using (*E*)-(1-bromoprop-1-en-2-yl)benzene (0.5 mmol) as a substrate and 4-fluoroanisole (62.4 mg, 0.495 mmol) as an internal standard. Yield: 86% (^{19}F NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H), 6.93 (d, J = 85.1 Hz, 1H), 2.08 (d, J = 3.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.97 (d, J = 257.8 Hz), 137.56 (d, J = 9.3 Hz), 128.53, 127.37, 125.88 (d, J = 3.4 Hz), 120.03 (d, J = 9.9 Hz), 12.19 (d, J = 6.0 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -131.65 (dq, J = 85.1, 3.7 Hz).

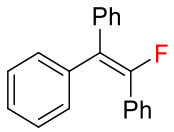


9g[188]: The general procedure C was followed using (2-bromoethene-1,1-diyl)dibenzene (0.5 mmol) as a substrate and 4-fluoroanisole (62.8 mg, 0.498 mmol) as an internal standard. Yield: 98% (^{19}F NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.34 (m, 8H), 7.32-7.28 (m, 2H), 7.02 (d, J = 83.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.76 (d, J = 268.7 Hz), 136.99 (d, J = 8.1 Hz), 135.14, 129.74 (d, J = 4.2 Hz), 128.65 (d, J = 2.7 Hz), 128.48, 128.19, 127.77, 127.73, 126.23 (d, J = 5.5 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -128.56 (d, J = 83.5 Hz).

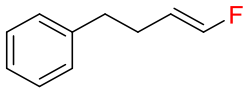


9h[190]: The general procedure C was followed using 1-bromo-1,2,2-triphenylethene (0.5 mmol) as a substrate and 4-fluoroanisole (62.2 mg, 0.494 mmol) as an internal standard. Yield: 100% (^{19}F NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.35 (m, 4H), 7.34-7.26 (m, 6H), 7.26-7.18 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.96 (d, J = 252.5 Hz), 139.01 (d, J = 6.8 Hz), 138.40, 133.05 (d, J = 28.7 Hz), 131.04 (d, J = 3.2 Hz), 129.90 (d, J = 4.6 Hz), 128.61, 128.52, 128.49, 128.45, 128.01, 127.83, 127.33 (d, J = 8.2 Hz), 122.27 (d, J = 18.4 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -103.32 (s).

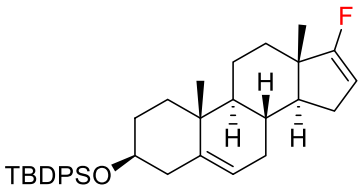


9i[191]: The general procedure C was followed using (*E*)-(4-bromobut-3-en-1-yl)benzene (0.5 mmol) as a substrate and 4-fluoroanisole (62.6 mg, 0.497 mmol) as an internal standard. Yield: 90% (^{19}F NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (t, J = 7.4 Hz, 2H), 7.26-7.17 (m, 3H), 6.52 (dd, J = 85.6, 11.1 Hz, 1H), 5.41 (ddt, J = 18.8, 11.1, 7.7 Hz, 1H), 2.71 (t, J = 7.6 Hz, 2H), 2.26 (q, J = 7.6 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.93 (d, J = 254.0 Hz), 141.13, 128.43, 128.37, 126.03, 110.72 (d, J = 9.6 Hz), 36.06 (d, J = 2.8 Hz), 26.95 (d, J = 9.3 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -130.28 (dd, J = 85.7, 18.9 Hz).



9j[100]: The general procedure C was followed using (((3S,8R,9S,10R,13S,14S)-17-bromo-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl)oxy)(*tert*-butyl)diphenylsilane (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.5 mg, 0.503 mmol) as an internal standard. Yield: 90% (^{19}F NMR).

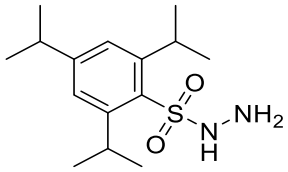
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81-7.73 (m, 4H), 7.51-7.38 (m, 6H), 5.25-5.19 (m, 1H), 4.95-4.90 (m, 1H), 3.63 (tt, J = 10.4, 4.5 Hz, 1H), 2.44 (ddd, J = 13.7, 10.8, 2.9 Hz, 1H), 2.25 (ddd, J = 13.3, 5.0, 2.0 Hz, 1H), 2.08 (ddd, J = 13.0, 6.2, 3.1 Hz, 1H), 2.04-1.95 (m, 1H), 1.93-1.72 (m, 4H), 1.72-1.40 (m, 7H), 1.16 (s, 9H), 1.10 (s, 3H), 1.04 (s, 3H), 1.02-0.93 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.78 (d, J = 289.1 Hz), 141.64, 135.74, 134.75, 129.45, 127.46 (d, J = 2.3 Hz), 120.56, 100.48 (d, J = 10.3 Hz), 73.16, 54.57 (d, J = 5.7 Hz), 50.66, 42.54, 42.27, 37.11, 36.71, 32.76, 31.85, 30.54, 29.85, 27.02, 26.88 (d, J = 7.0 Hz), 20.15, 19.29, 19.12, 15.04 (d, J = 4.1 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -132.40 (d, J = 5.4 Hz).

5.2.4.3 Preparation of trisylhydrazones

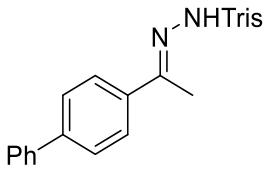
2, 4, 6-triisopropylbenzenesulfonohydrazide



This compound was prepared in 97% yield according to the reported method[100]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (s, 2H), 5.43 (t, J = 4.0 Hz, 1H), 4.16 (hept, J = 6.8 Hz, 2H), 3.65 (d, J = 4.7 Hz, 2H), 2.92 (hept, J = 6.9 Hz, 1H), 1.28 (d, J = 6.8 Hz, 12H), 1.26 (d, J = 6.9 Hz, 6H).

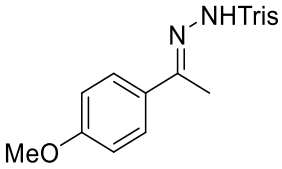
***N*'-(1-([1,1'-biphenyl]-4-yl)ethylidene)-2,4,6-triisopropylbenzenesulfonohydrazide (11k)**



This compound was prepared in 92% yield according to the reported method[100]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.2 Hz, 2H), 7.60-7.52 (m, 5H), 7.43 (t, J = 7.5 Hz, 2H), 7.35 (t, J = 7.2 Hz, 1H), 7.17 (s, 2H), 4.32 (hept, J = 6.7 Hz, 2H), 2.89 (hept, J = 7.1 Hz, 1H), 2.20 (s, 3H), 1.31 (d, J = 6.8 Hz, 12H), 1.24 (d, J = 6.9 Hz, 6H).

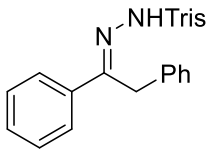
2,4,6-triisopropyl-*N*'-(1-(4-methoxyphenyl)ethylidene)benzenesulfonohydrazide (11l)



This compound was prepared in 90% yield according to the reported method[100]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.9 Hz, 2H), 7.45 (br.s, 1H), 7.16 (s, 2H), 6.81 (d, J = 8.8 Hz, 2H), 4.29 (hept, J = 6.9 Hz, 2H), 3.79 (s, 3H), 2.88 (hept, J = 6.9 Hz, 1H), 2.13 (s, 3H), 1.28 (d, J = 6.9 Hz, 12H), 1.23 (d, J = 6.9 Hz, 6H).

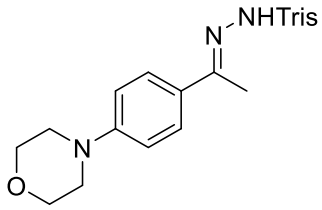
***N*'-(1,2-diphenylethylidene)-2,4,6-triisopropylbenzenesulfonohydrazide (11m)**



This compound was prepared in 48% yield according to the reported method[100]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72-7.68 (m, 2H), 7.57 (br.s, 1H), 7.36- 7.24 (m, 6H), 7.18-7.14 (m, 4H), 4.13 (hept, J = 6.7 Hz, 2H), 4.05 (s, 2H), 2.89 (hept, J = 7.3 Hz, 1H), 1.24 (d, J = 6.9 Hz, 6H), 1.22 (d, J = 6.8 Hz, 12H).

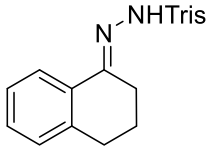
2,4,6-triisopropyl-*N*'-(1-(4-morpholinophenyl)ethylidene)benzenesulfonohydrazide (11n)



This compound was prepared in 60% yield according to the reported method[100]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.7 Hz, 2H), 7.43 (br.s, 1H), 7.15 (s, 2H), 6.88 (d, J = 8.5 Hz, 2H), 4.30 (hept, J = 6.7 Hz, 2H), 3.88 (t, J = 4.7 Hz, 4H), 3.20 (t, J = 4.8 Hz, 4H), 2.88 (hept, J = 6.9 Hz, 1H), 2.12 (s, 3H), 1.29 (d, J = 6.7 Hz, 12H), 1.24 (d, J = 6.9 Hz, 6H).

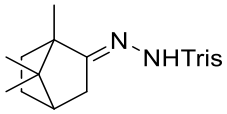
***N*'-(3,4-dihydronaphthalen-1(2H)-ylidene)-2,4,6-triisopropylbenzenesulfonohydrazide (11o)**



This compound was prepared in 48% yield according to the reported method[100]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 7.9 Hz, 1H), 7.54 (br.s, 1H), 7.22 (t, J = 7.5 Hz, 1H), 7.16 (s, 2H), 7.15-7.06 (m, 2H), 4.31 (hept, J = 6.7 Hz, 2H), 2.88 (hept, J = 6.8 Hz, 1H), 2.73 (t, J = 6.0 Hz, 2H), 2.45 (t, J = 6.6 Hz, 2H), 1.92 (p, J = 6.3 Hz, 2H), 1.31 (d, J = 6.7 Hz, 12H), 1.24 (d, J = 6.9 Hz, 6H).

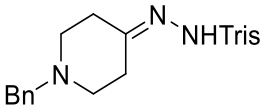
2,4,6-triisopropyl-*N*'-((1S,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)benzenesulfonohydrazide (11p)



This compound was prepared in 30% yield according to the reported method[100]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (s, 2H), 6.91 (br.s, 1H), 4.21 (hept, J = 6.7 Hz, 2H), 2.90 (hept, J = 7.0 Hz, 1H), 2.23 (d, J = 16.7 Hz, 1H), 1.95 (t, J = 4.6 Hz, 1H), 1.87-1.76 (m, 1H), 1.71 (d, J = 16.7 Hz, 1H), 1.63 (td, J = 12.2, 4.1 Hz, 1H), 1.26 (t, J = 6.3 Hz, 19H), 1.17-1.08 (m, 1H), 0.87 (d, J = 2.2 Hz, 6H), 0.61 (s, 3H).

***N*'-(1-benzylpiperidin-4-ylidene)-2,4,6-triisopropylbenzenesulfonohydrazide (11q)**

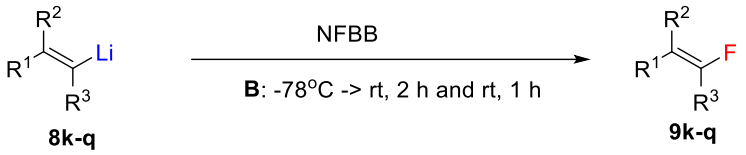


This compound was prepared in 65% yield according to the reported method[100]. The NMR data agree with the reported data.

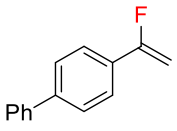
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.22 (m, 5H), 7.18 (br.s, 1H), 7.15 (s, 2H), 4.20 (hept, J = 7.1 Hz, 2H), 3.50 (s, 2H), 2.89 (hept, J = 6.6 Hz, 1H), 2.55-2.45 (m, 4H), 2.37-2.28 (m, 4H), 1.24 (d, J = 7.1 Hz, 18H).

5.2.4.4 Fluorination of alkenyl lithiums 8, generated from trisylhydrazones 11 (Shapiro reaction), with NFBB

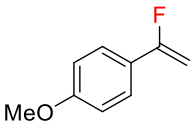
Table S4B. Fluorination of alkenyl lithiums **8** with NFBB



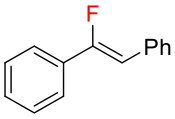
B: Fluorination of **8** generated from hydrazone **11** via Shapiro reaction /Yields from hydrazone **11**



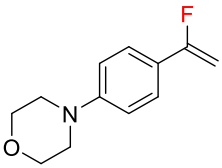
9k, 98%
(NFSI: 78%)[d]



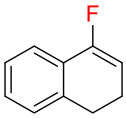
9l, 86%
(NFSI: 67%)[d]



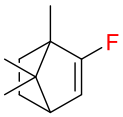
9m, 98%[b]
(NFSI: 87%[c])[d]



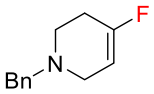
9n, 85%
(NFSI: 75%)[d]



9o, 81%
(NFSI: 57%)[d]



9p, 70%
(NFSI: 44%[c])[d]

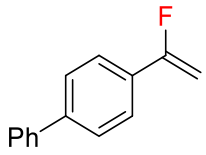


9q, 63%
(NFSI: 24%)[d]

***Table S4B*.** Fluorination of alkenyl lithiums **8**, generated from hydrazones **11**, with NFBB. The reactions were carried out according to the general procedure D (below), unless otherwise noted: (b) *sec*-BuLi in cyclohexane (1.4 M) was used. (c) *sec*-BuLi was used (see ref. [100]). (d) The data in parentheses were the ^{19}F NMR yields with NFSI, which were cited from ref. [100].

General procedure D: To a flame-dried 8 mL reaction vial equipped with a magnetic stir bar and an argon balloon, was add a trisylhydrazone substrate (0.5 mmol) and dry THF (1 mL). The vial was cooled down to -78 °C and 0.44 mL of *n*-BuLi (2.5 M in hexane, 1.1 mmol, 2.2 eq) was added via syringe through its open-top cap with TFE septum. After stirring at -78 °C for 30 mins to generate the dianion and 0 °C for 20 mins to release N_2, the reaction mixture was again cooled down to -78 °C. NFBB (1.3 eq) in dry hexane (2 mL) was added dropwise via syringe. The reaction mixture was warmed up to room temperature over a period of 2 h and stirred at room temperature for 1 h. After quenching the reaction with a few drops of sat. aq. solution of NH_4Cl, the reaction mixture was stirred until clear (EtOAc was added if necessary). An internal standard was then added and its weight was recorded. An 80 µL aliquot of the solution was transferred to an NMR tube and analyzed by ^{19}F NMR. The yield of the product was determined by comparing

the integration values of the product peak and the internal standard peak. Pure products were isolated by silica gel chromatography except for the case of **9p** in which **9p** was identified by spectral analysis of ^{19}F NMR and GC/Mass of the reaction mixture in comparison with the reported data.

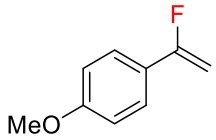


9k[100]: The general procedure D was followed using *N*'-(1-([1,1'-biphenyl]-4-yl)ethylidene)-2,4,6-triisopropylbenzenesulfonohydrazide (0.5 mmol) as a substrate and 4-fluoroanisole (58.9 mg, 0.467 mmol) as an internal standard. Yield: 98% (^{19}F NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.58 (m, 6H), 7.52-7.43 (m, 2H), 7.41-7.33 (m, 1H), 5.09 (dd, J = 49.7, 2.5 Hz, 1H), 4.89 (dd, J = 17.8, 2.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.76 (d, J = 249.8 Hz), 142.12, 140.27, 130.88 (d, J = 29.5 Hz), 128.86, 127.69, 127.14 (d, J = 1.4 Hz), 127.04, 125.04 (d, J = 7.0 Hz), 89.55 (d, J = 22.6 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -108.35 (dd, J = 49.7, 17.8 Hz).

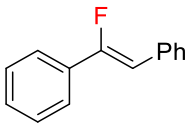


9l[100]: The general procedure D was followed using 2,4,6-triisopropyl-*N*'-(1-(4-methoxyphenyl)ethylidene)benzenesulfonohydrazide (0.5 mmol) as a substrate and 2-fluorobiphenyl (80.8 mg, 0.470 mmol) as an internal standard. Yield: 86% (^{19}F NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 8.3 Hz, 2H), 4.89 (dd, J = 50.1, 2.9 Hz, 1H), 4.74 (dd, J = 18.3, 2.9 Hz, 1H), 3.83 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.92 (d, J = 248.8 Hz), 160.47, 126.09 (d, J = 7.1 Hz), 124.66 (d, J = 29.8 Hz), 113.83, 87.53 (d, J = 22.9 Hz), 55.28.

^{19}F NMR (376 MHz, $CDCl_3$) δ -107.56 (dd, J = 50.1, 18.1 Hz).

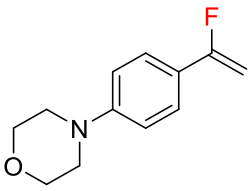


9m[100]: The general procedure D was followed using *N*'-(1,2-diphenylethylidene)-2,4,6-triisopropylbenzenesulfonohydrazide (0.5 mmol) as a substrate and 4-fluoroanisole (58.7 mg, 0.466 mmol) as an internal standard. *sec*-BuLi was used instead of *n*-BuLi. Yield: 98% (^{19}F NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83-7.76 (m, 4H), 7.60-7.48 (m, 5H), 7.45-7.37 (m, 1H), 6.46 (d, J = 39.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.20 (d, J = 258.4 Hz), 133.67 (d, J = 2.0 Hz), 132.89 (d, J = 28.0 Hz), 128.98, 128.90, 128.66, 128.57, 127.31 (d, J = 1.2 Hz), 124.29 (d, J = 7.6 Hz), 105.85 (d, J = 10.5 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -114.69 (d, J = 39.5 Hz).

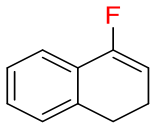


9n[100]: The general procedure D was followed using 2,4,6-triisopropyl-*N*'-(1-(4-morpholinophenyl)ethylidene)benzenesulfonohydrazide (0.5 mmol) as a substrate and 4-fluoroanisole (52.7 mg, 0.418 mmol) as an internal standard. Yield: 85% (^{19}F NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 4.85 (dd, J = 50.3, 3.0 Hz, 1H), 4.70 (dd, J = 18.2, 3.0 Hz, 1H), 3.86 (s, 4H), 3.21 (s, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.04 (d, J = 248.5 Hz), 151.74, 125.68 (d, J = 7.1 Hz), 123.12 (d, J = 29.9 Hz), 114.66, 86.86 (d, J = 23.1 Hz), 66.65, 48.49.

^{19}F NMR (376 MHz, $CDCl_3$) δ -108.07 (dd, J = 50.3, 18.2 Hz).

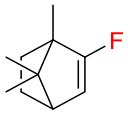


9o[100]: The general procedure D was followed using *N*'-(3,4-dihydronaphthalen-1(2H)-ylidene)-2,4,6-triisopropylbenzenesulfonohydrazide (0.5 mmol) as a substrate and 4-fluoroanisole (59.1 mg, 0.469 mmol) as an internal standard. Yield: 81% (^{19}F NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.37 (m, 1H), 7.27-7.20 (m, 2H), 7.19-7.13 (m, 1H), 5.49 (dt, J = 14.0, 4.6 Hz, 1H), 2.84 (t, J = 8.1 Hz, 2H), 2.40 (ddd, J = 12.7, 8.5, 4.7 Hz, 2H).

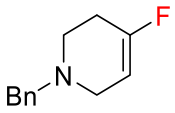
^{13}C NMR (100 MHz, $CDCl_3$) δ 156.88 (d, J = 249.6 Hz), 136.64 (d, J = 6.5 Hz), 129.07 (d, J = 25.6 Hz), 128.25, 127.27 (d, J = 4.2 Hz), 126.41, 120.47 (d, J = 4.6 Hz), 102.74 (d, J = 15.7 Hz), 27.47, 21.18 (d, J = 7.3 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -127.41 (dtd, J = 13.9, 4.8, 2.0 Hz).



9p[100]: The general procedure D was followed using 2,4,6-triisopropyl-*N*'-((1S,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)benzenesulfonohydrazide (0.5 mmol) as a substrate and 4-fluoroanisole (61.2 mg, 0.486 mmol) as an internal standard. Yield: 70% (^{19}F NMR). The ^{19}F NMR spectral data matched that of an reported literature[100]. The identity of the product was further confirmed by GCMS analysis.

^{19}F NMR (376 MHz, $CDCl_3$) δ -132.1 (s).



9q[100]: The general procedure D was followed using 2,4,6-triisopropyl-*N*'-((1S,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)benzenesulfonohydrazide (0.5 mmol) as a substrate and 2-fluorobiphenyl (82.0 mg, 0.477 mmol) as an internal standard. Yield: 63% (^{19}F NMR).

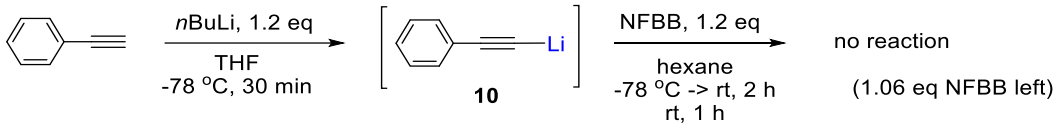
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.24 (m, 5H), 5.16 (dtt, J = 15.0, 3.5, 1.3 Hz, 1H), 3.61 (s, 2H), 3.01 (dq, J = 5.9, 2.8 Hz, 2H), 2.68 (td, J = 5.8, 2.1 Hz, 2H), 2.34-2.28 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.17 (d, J = 257.4 Hz), 138.21, 128.97, 128.29, 127.17, 100.29 (d, J = 14.8 Hz), 61.71, 50.05 (d, J = 9.0 Hz), 49.29 (d, J = 10.0 Hz), 26.45 (d, J = 22.5 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -104.85 (d, J = 15.0 Hz).

5.2.5 Attempts at reaction of alkynyl lithiums with NFBB

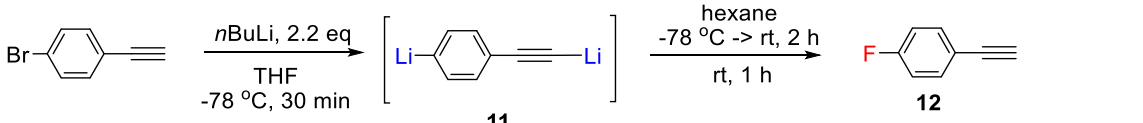
5.2.5.1 Reaction of lithium phenylacetylide (10)



Procedure: To a flame-dried 8 mL reaction vial equipped with a magnetic stir bar and an argon balloon, was added phenylacetylene (0.5 mmol) and dry THF (1 mL). The solution was cooled down to -78°C and 0.24 mL of *n*-BuLi (2.5 M in hexane, 0.6 mmol, 1.2 eq) was added via syringe through its open-top cap with TFE septum. After stirring at -78°C for 30 min, 127 mg of NFBB (0.6 mmol, 1.2 eq) in dry hexane (2 mL) was added dropwise via syringe. The reaction mixture was warmed up to room temperature over a period of 2 h and stirred at room temperature for 1 h. After quenching the reaction with a few drops of sat. aq. solution of NH_4Cl, 2-fluorobiphenyl was added as an internal standard and its weight was recorded. An 80 µL aliquot of the solution was transferred to an NMR tube and analyzed by ^{19}F NMR. The remaining NFBB was determined by comparing the integration values of their peaks and the internal standard peak.

Result: NFBB (1.06 eq) remained intact. No fluorine peak was detected except for NFBB and a lot of phenylacetylene recovered was detected by GC/MS of the reaction mixture.

5.2.5.2 Reaction of dilithiophenylethyne (11)



Procedure: To a flame-dried 8 mL reaction vial equipped with a magnetic stir bar and an argon balloon, was added 4-bromo phenylacetylene (0.5 mmol) and dry THF (1 mL). The solution was cooled down to -78^{o}C and 0.44 mL of *n*-BuLi (2.5 M in hexane, 0.6 mmol, 1.2 eq) was added via syringe through its open-top cap with TFE septum. After stirring at -78^{o}C for 30 min, 127 mg (0.6 mmol, 1.2 eq) or 233 mg (1.1 mmol, 2.2 eq) of NFBB in dry hexane (2 mL) was added dropwise via syringe. The reaction mixture was warmed up to room temperature over a period of 2 h and stirred at room temperature for 1 h. After quenching the reaction with a few drops of sat. aq. solution of NH_4Cl, 2-fluorobiphenyl was added as an internal standard and its weight was recorded. An 80 µL aliquot of the solution was transferred to an NMR tube and analyzed by ^{19}F NMR. The yield of the product and the remaining NFBB were determined by comparing the integration values of their peaks and the internal standard peak. Product **12** was identified by spectral comparison with an authentic sample (Sigma-Aldrich).

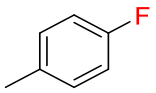
Result for the case of 1.2 eq of NFBB: 4-Fluorophenylacetylene (**12**) was obtained in 58% yield. NFBB (0.61 eq) remained intact. No fluorine peak was detected except for **12** and NFBB.

Result for the case of 2.2 eq of NFBB: 4-Fluorophenylacetylene (**12**) was obtained in 78% yield. NFBB (1.12 eq) remained intact. No fluorine peak was detected except for **12** and NFBB.

5.2.6. Fluorination of Grignard Reagents with NFBB

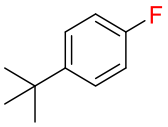
General procedure E: To a flame-dried 8 mL reaction vial equipped with a magnetic stir bar and an argon balloon, was add an aryl iodide substrate (0.5 mmol) and dry DME (1 mL). At room temperature or low temperature for electron rich or electron deficient aryl iodide, respectively, 0.275 mL of *i*PrMgCl (2.0 M in THF, 0.55 mmol, 1.1 eq) was added via syringe through its open-top cap with TFE septum. After stirring at room temperature for 1.5 h or low temperature for 1 h, a solution of NFBB (1.2 eq) in dry TBME (2 mL) was added dropwise via syringe. The reaction mixture was then stirred at room temperature for 6 h. After quenching the reaction with a few drops of sat. aq. solution of NH_4Cl, the reaction mixture was stirred until clear (EtOAc was added if necessary). An internal standard was then added, and its weight was recorded. An 80 µL

aliquot of the solution was transferred to an NMR tube and analyzed by ^{19}F NMR. The yield of the product was determined by comparing the integration values of the product peak and the internal standard peak. Products were identified by spectral comparison with authentic samples.



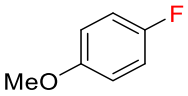
15a (6g): The general procedure E was followed using 4-iodotoluene (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.4 mg, 0.502 mmol) as an internal standard. Room temperature was used for I/Mg exchange. Yield: 72% (^{19}F NMR). The ^{19}F NMR spectral data matched those of an authentic sample (TCI). The identity of the product was further confirmed by GC/MS analysis.

^{19}F NMR (376 MHz, $CDCl_3$) δ -119.16 (m).



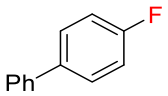
15b: The general procedure E was followed using 1-*tert*-butyl-4-iodobenzene (0.5 mmol) as a substrate and 2-fluorobiphenyl (85.7 mg, 0.498 mmol) as an internal standard. Room temperature was used for I/Mg exchange. Yield: 70% (^{19}F NMR). The ^{19}F NMR spectral data matched the reported data[192]. The identity of the product was further confirmed by GC/MS analysis.

^{19}F NMR (376 MHz, $CDCl_3$) δ -119.22 (m).



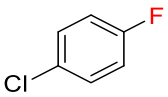
15c (6h): The general procedure E was followed using 4-iodoanisole (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.6 mg, 0.503 mmol) as an internal standard. Room temperature was used for I/Mg exchange. Yield: 80% (^{19}F NMR). The ^{19}F NMR spectral data matched those of an authentic sample (Oakwood). The identity of the product was further confirmed by GC/MS analysis.

^{19}F NMR (376 MHz, $CDCl_3$) δ -124.92 (m).



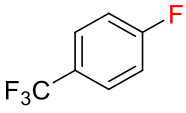
15d (6d): The general procedure E was followed using 4-iodobiphenyl (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.5 mg, 0.503 mmol) as an internal standard. Room temperature was used for I/Mg exchange. Yield: 82% (^{19}F NMR). The ^{19}F NMR spectral data matched those of an authentic sample (TCI). The identity of the product was further confirmed by GC/MS analysis.

^{19}F NMR (376 MHz, $CDCl_3$) δ -116.39 (m).



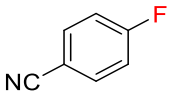
15e (6c): The general procedure E was followed using 1-chloro-4-iodobenzene (0.5 mmol) as a substrate and 2-fluorobiphenyl (85.9 mg, 0.499 mmol) as an internal standard. Room temperature was used for I/Mg exchange. Yield: 77% (^{19}F NMR). The ^{19}F NMR spectral data matched those of an authentic sample (Acros). The identity of the product was further confirmed by GC/MS analysis.

^{19}F NMR (376 MHz, $CDCl_3$) δ -116.45 (m).



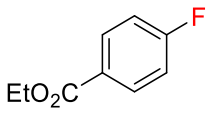
15f (6b): The general procedure E was followed using 4-iodobenzotrifluoride (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.6 mg, 0.503 mmol) as an internal standard. -40°C was used for I/Mg exchange. Yield: 68% (^{19}F NMR). The ^{19}F NMR spectral data matched those of an authentic sample (Matrix). The identity of the product was further confirmed by GC/MS analysis.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.52 (s, 3F), -108.06 (m, 1F).



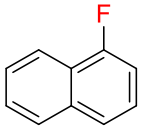
15g: The general procedure E was followed using 4-iodobenzonitrile (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.4 mg, 0.502 mmol) as an internal standard. -40^{o}C for 0.5 h and -30 ^{o}C for another 0.5 h was used for I/Mg exchange. Yield: 64% (^{19}F NMR). The ^{19}F NMR spectral data matched those of an authentic sample (Oakwood). The identity of the product was further confirmed by GC/MS analysis.

^{19}F NMR (376 MHz, $CDCl_3$) δ -102.96 (m).



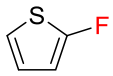
15h: The general procedure E was followed using ethyl 4-iodobenzoate (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.1 mg, 0.500 mmol) as an internal standard. -20^{o}C was used for I/Mg exchange.Yield: 48% (^{19}F NMR). The ^{19}F NMR spectral data matched those of an authentic sample (Ambeed). The identity of the product was further confirmed by GC/MS analysis.

^{19}F NMR (376 MHz, $CDCl_3$) δ -106.60 (m).



15i (6k): The general procedure E was followed using ethyl 1-iodonaphthalene (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.5 mg, 0.503 mmol) as an internal standard. Room temperature for 1h was used for I/Mg exchange. Yield: 83% (^{19}F NMR). The ^{19}F NMR spectral data matched those of an authentic sample (Chem-Impex). The identity of the product was further confirmed by GC/MS analysis.

^{19}F NMR (376 MHz, $CDCl_3$) δ -123.96 (m).



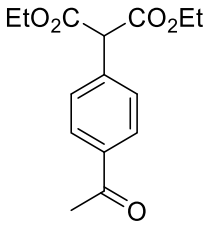
15j: The general procedure E was followed using 2-iodothiophene (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.1 mg, 0.500 mmol) as an internal standard. Room temperature for 1h was used for I/Mg exchange. Yield: 45% (^{19}F NMR). The ^{19}F NMR spectral data matched the reported data[193].

^{19}F NMR (376 MHz, $CDCl_3$) δ -134.63 (m).

5.2.7 Fluorination of active methylene compounds with NFBB

5.2.7.1 Preparation of active methylene compounds

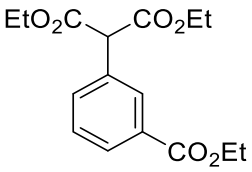
diethyl 2-(4-acetylphenyl)malonate (16e)



This compound was prepared in 86% yield according to the reported method[194]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.3 Hz, 2H), 7.51 (d, J = 8.5 Hz, 2H), 4.41-4.07 (m, 4H), 2.60 (s, 3H), 1.27 (t, J = 7.1 Hz, 6H).

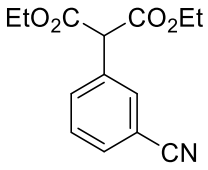
diethyl 2-(3-(ethoxycarbonyl)phenyl)malonate (16f)



This compound was prepared in 86% yield according to the reported method[194]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08-7.96 (m, 2H), 7.65 (d, J = 7.8 Hz, 1H), 7.45 (t, J = 7.7 Hz, 1H), 4.67 (s, 1H), 4.38 (q, J = 7.1 Hz, 2H), 4.29-4.15 (m, 4H), 1.39 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 6H).

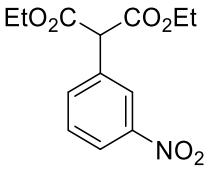
diethyl 2-(3-cyanophenyl)malonate (16g)



This compound was prepared in 61% yield according to the reported method[194]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.69-7.61 (m, 2H), 7.48 (t, J = 7.8 Hz, 1H), 4.63 (s, 1H), 4.31-4.17 (m, 4H), 1.28 (t, J = 7.1 Hz, 6H).

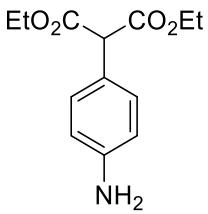
diethyl 2-(3-nitrophenyl)malonate (16h)



This compound was prepared in 84% yield according to the reported method[194]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.24-8.20 (m, 1H), 7.89-7.72 (m, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 4.72 (s, 1H), 4.52-4.08 (m, 4H), 1.29 (t, *J* = 7.1 Hz, 6H).

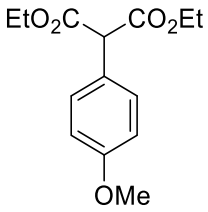
diethyl 2-(4-aminophenyl)malonate (16i)



This compound was prepared in 70% yield according to the reported method[194]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 4.57 (s, 1H), 4.34-4.07 (m, 4H), 2.17 (s, 2H), 1.26 (t, *J* = 7.1 Hz, 6H).

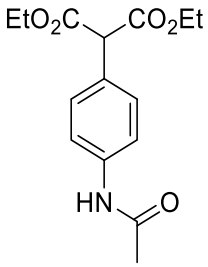
diethyl 2-(4-methoxyphenyl)malonate (16j)



This compound was prepared in 80% yield according to the reported method[195]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.30 (m, 2H), 6.92-6.87 (m, 2H), 4.55 (s, 1H), 4.31-4.13 (m, 4H), 3.80 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 6H).

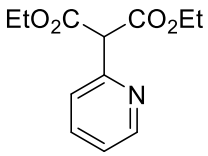
diethyl 2-(4-acetamidophenyl)malonate (16k)



This compound was prepared in 75% yield according to the reported method[194]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.15 (brs, 1H), 4.57 (s, 1H), 4.30-4.09 (m, 4H), 2.17 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 6H).

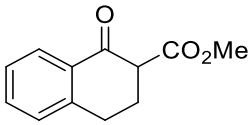
diethyl 2-(pyridin-2-yl)malonate (16m)



This compound was prepared in 90% yield according to the reported method[195]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 4.4 Hz, 1H), 7.71 (td, *J* = 7.7, 1.9 Hz, 1H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.27-7.23 (m, 1H), 4.93 (s, 1H), 4.33-4.17 (m, 4H), 1.27 (t, *J* = 7.1 Hz, 6H).

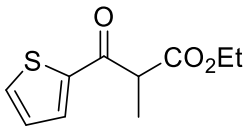
methyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (16r)



This compound was prepared in 69% yield according to the reported method[196]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.40 (s, 1H, enol), 8.05 (dd, *J* = 7.9, 1.4 Hz, 1H, ketone), 7.81 (dd, *J* = 7.4, 1.7 Hz, 1H, enol), 7.50 (td, *J* = 7.5, 1.5 Hz, 1H, ketone), 7.36-7.23 (m, 4H, enol and ketone), 7.21-7.15 (m, 1H, enol), 3.83 (s, 3H, enol), 3.78 (s, 3H, ketone), 3.63 (dd, *J* = 10.3, 4.7 Hz, 1H, ketone), 3.14-2.93 (m, 2H, ketone), 2.84-2.79 (m, 2H, enol), 2.63-2.31 (m, 4H, enol and ketone).

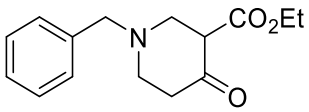
ethyl 2-methyl-3-oxo-3-(thiophen-2-yl)propanoate (16s)



This compound was prepared in 100% yield according to the reported method[197]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 3.8 Hz, 1H), 7.68 (d, *J* = 5.0 Hz, 1H), 7.15 (dd, *J* = 4.9, 3.9 Hz, 1H), 4.26-4.10 (m, 3H), 1.51 (d, *J* = 7.1 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H).

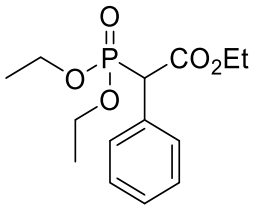
ethyl 1-benzyl-4-oxopiperidine-3-carboxylate (16u)



This compound was prepared in 100% yield according to the reported method[198]. The NMR data agree with the reported data.

^{1}H NMR of enol tautomer (400 MHz, $CDCl_3$) δ 12.02 (s, 1H), 7.37-7.32 (m, 5H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.64 (s, 2H), 3.21 (t, *J* = 1.8 Hz, 2H), 2.60 (t, *J* = 5.8 Hz, 2H), 2.39 (tt, *J* = 5.9, 1.8 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H).

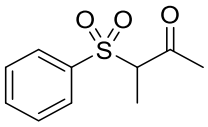
ethyl 2-(diethoxyphosphoryl)-2-phenylacetate (16v)



This compound was prepared in 96% yield according to the reported method[199]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.47 (m, 2H), 7.40-7.29 (m, 3H), 4.35-3.91 (m, 7H), 1.32-1.22 (m, 6H), 1.20 (t, *J* = 7.1 Hz, 3H).

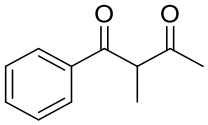
3-(phenylsulfonyl)butan-2-one (16w)



This compound was prepared in 85% yield according to the reported method[200]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.78 (m, 2H), 7.73-7.66 (m, 1H), 7.61-7.54 (m, 2H), 4.16 (q, *J* = 7.1 Hz, 1H), 2.45 (s, 3H), 1.42 (d, *J* = 7.0 Hz, 3H).

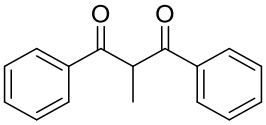
2-methyl-1-phenylbutane-1,3-dione (16z)



This compound was prepared in 80% yield according to the reported method[201]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01-7.92 (m, 2H), 7.65-7.55 (m, 1H), 7.54-7.45 (m, 2H), 4.48 (q, *J* = 7.0 Hz, 1H), 2.16 (s, 3H), 1.46 (d, *J* = 7.0 Hz, 3H).

2-methyl-1,3-diphenylpropane-1,3-dione (16aa)



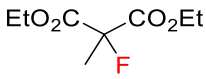
This compound was prepared in 80% yield according to the reported method[201]. The NMR data agree with the reported data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02-7.86 (m, 4H), 7.61-7.51 (m, 2H), 7.51-7.40 (m, 4H), 5.26 (q, *J* = 7.0 Hz, 1H), 1.61 (d, *J* = 7.0 Hz, 3H).

5.2.7.2 Fluorination of active methylene compounds with NFBB

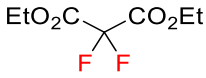
General procedure F: To a flame-dried 8 mL reaction vial equipped with a magnetic stir bar, was add an active methylene compound substrate (0.5 mmol) and NFBB (0.6 mmol, 1.2 eq). Dry Cs_2CO_3 (0.0025 mmol, 5 mol%) and dry DME (2 mL), stored in a glovebox, were then added. The reaction mixture was stirred at room temperature overnight (around 12 h). After that, an internal standard was added, and its weight was recorded. An 80 μL aliquot of the solution was transferred to an NMR tube and analyzed by ^{19}F NMR. The yield of the product was determined by comparing the integration values of the product peak and the internal standard peak. Pure products were isolated by silica gel chromatography except for the case of **17a, 17b, 17i, 17q, 17y, 17aa.** Products **17a, 17b, 17q, 17y, 17aa** were identified by spectral analysis of ^{19}F NMR

and GC/Mass of the reaction mixture in comparison with the reported data. Product **17i** was identified by acetylating to compound **17k**.



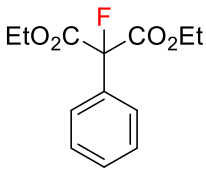
17a: The general procedure F was followed using diethyl methylmalonate (0.5 mmol) as a substrate and 2-fluorobiphenyl (85.9 mg, 0.499 mmol) as an internal standard. Yield: 84% (^{19}F NMR). The ^{19}F NMR spectral data matched those of an authentic sample (Ambeed). The identity of the product was further confirmed by GC/MS analysis.

^{19}F NMR (376 MHz, $CDCl_3$) δ -157.93 (q, *J* = 22.0 Hz).



17b: The general procedure F was followed using diethyl malonate (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.6 mg, 0.503 mmol) as an internal standard. For this case, 2.2 eq of NFBB and 10 mol% of Cs_2CO_3 were used. Yield: 83% (^{19}F NMR). The ^{19}F NMR spectral data matched those of an authentic sample (Ambeed). The identity of the product was further confirmed by GC/MS analysis.

^{19}F NMR (376 MHz, $CDCl_3$) δ -112.70 (s).

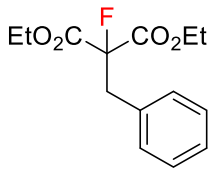


17c[47]: The general procedure F was followed using diethyl phenylmalonate (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.3 mg, 0.501 mmol) as an internal standard. Yield: 90% (^{19}F NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.50 (m, 2H), 7.48-7.32 (m, 3H), 4.33 (q, *J* = 7.1 Hz, 4H), 1.31 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.48 (d, *J* = 26.0 Hz), 133.12 (d, *J* = 22.1 Hz), 129.29, 128.17, 125.56 (d, *J* = 9.0 Hz), 93.97 (d, *J* = 200.3 Hz), 62.85, 13.77.

^{19}F NMR (376 MHz, $CDCl_3$) δ -161.29 (s).

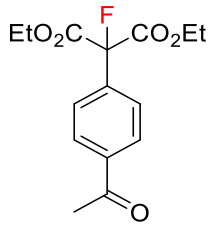


17d[47]: The general procedure F was followed using diethyl benzylmalonate (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.4 mg, 0.502 mmol) as an internal standard. Yield: 96% (^{19}F NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.00 (m, 5H), 4.11 (q, *J* = 7.1 Hz, 4H), 3.35 (d, *J* = 25.6 Hz, 2H), 1.11 (t, *J* = 7.2 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.68 (d, *J* = 25.4 Hz), 132.94, 130.22, 128.25, 127.41, 94.56 (d, *J* = 201.3 Hz), 62.50, 40.09 (d, *J* = 20.8 Hz), 13.80.

^{19}F NMR (376 MHz, $CDCl_3$) δ -165.03 (t, *J* = 25.6 Hz).

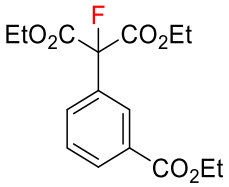


17e[202]: The general procedure F was followed using diethyl 2-(4-acetylphenyl)malonate (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.6 mg, 0.503 mmol) as an internal standard. Yield: 91% (^{19}F NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 8.5 Hz, 2H), 4.33 (q, *J* = 7.1 Hz, 4H), 2.62 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 197.25, 164.89 (d, *J* = 25.3 Hz), 137.63, 137.59 (d, *J* = 22.1 Hz), 128.03, 125.89 (d, *J* = 9.1 Hz), 93.70 (d, *J* = 201.8 Hz), 63.15, 26.54, 13.76.

^{19}F NMR (376 MHz, $CDCl_3$) δ -163.01 (s).



17f: The general procedure F was followed using diethyl 2-(3-(ethoxycarbonyl)phenyl)malonate (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.4 mg, 0.502 mmol) as an internal standard. Yield: 94% (^{19}F NMR). Colorless oil.

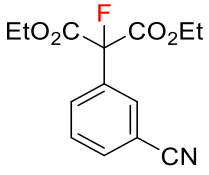
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (t, *J* = 1.9 Hz, 1H), 8.08 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.78 (ddd, *J* = 8.0, 2.1, 1.2 Hz, 1H), 7.48 (ddd, *J* = 8.6, 7.5, 0.7 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 4.32 (q, *J* = 7.1 Hz, 4H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.79, 165.16 (d, *J* = 25.8 Hz), 133.54 (d, *J* = 22.4 Hz), 130.70, 130.47, 130.04 (d, *J* = 8.6 Hz), 128.33, 126.74, 93.62 (d, *J* = 201.2 Hz), 63.10, 61.14, 14.21, 13.81.

^{19}F NMR (376 MHz, $CDCl_3$) δ -161.97 (s).

IR (neat, cm^{-1}): v = 2984.6, 1754.2, 1718.8, 1445.3, 1368.1, 1281.5, 1206.6, 1080.7, 1020.5, 745.6.

HRMS: (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{16}H_{19}O_6FNa$ 349.1058, Found: 349.1060.



17g: The general procedure F was followed using diethyl 2-(3-cyanophenyl)malonate (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.8 mg, 0.504 mmol) as an internal standard. Yield: 89% (^{19}F NMR). Colorless oil.

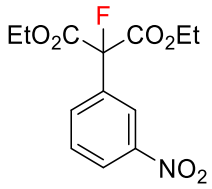
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (t, *J* = 1.6 Hz, 1H), 7.88 (ddd, *J* = 8.1, 2.0, 1.2 Hz, 1H), 7.71 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.60-7.50 (m, 1H), 4.34 (q, *J* = 7.1 Hz, 4H), 1.33 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.59 (d, *J* = 25.4 Hz), 134.48 (d, *J* = 22.8 Hz), 132.85, 129.99 (d, *J* = 9.3 Hz), 129.44 (d, *J* = 9.9 Hz), 129.09, 118.04, 112.61, 92.89 (d, *J* = 203.3 Hz), 63.41, 13.76.

^{19}F NMR (376 MHz, $CDCl_3$) δ -163.99 (s).

IR (neat, cm^{-1}): v = 2986.8, 2232.9, 1751.5, 1446.9, 1369.0, 1225.5, 1091.3, 1043.7, 856.6, 686.3.

HRMS: (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{14}H_{14}O_4NFNa$ 302.0799, Found: 302.0800.



17h: The general procedure F was followed using diethyl 2-(3-nitrophenyl)malonate (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.1 mg, 0.500 mmol) as an internal standard. Yield: 90% (^{19}F NMR). White solid, mp 38.2-41.0 ^{o}C.

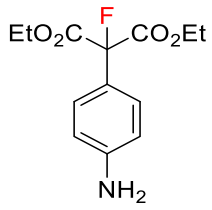
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (t, *J* = 2.0 Hz, 1H), 8.29 (ddd, *J* = 8.2, 2.3, 1.0 Hz, 1H), 7.98 (ddd, *J* = 8.0, 1.9, 1.1 Hz, 1H), 7.62 (t, *J* = 8.1 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 4H), 1.33 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.57 (d, *J* = 25.7 Hz), 148.04, 134.96 (d, *J* = 22.9 Hz), 131.75 (d, *J* = 9.0 Hz), 129.32, 124.26, 121.15 (d, *J* = 10.4 Hz), 92.97 (d, *J* = 203.4 Hz), 63.51, 13.80.

^{19}F NMR (376 MHz, $CDCl_3$) δ -163.21 (s).

IR (neat, cm^{-1}): v = 3000.8, 2971.0, 1737.1, 1537.8, 1435.0, 1368.8, 1227.7, 1097.9, 1039.8, 685.9.

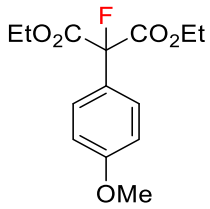
HRMS: (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{13}H_{14}O_6NFNa$ 322.0697, Found: 322.0698.



17i: The general procedure F was followed using diethyl 2-(4-aminophenyl)malonate (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.6 mg, 0.503 mmol) as an internal standard. Yield: 71%

(^{19}F NMR). ^{19}F NMR (376 MHz, $CDCl_3$) δ -156.47 (s). This compound was identified by acetylating to compound **17k** reported below,

^{19}F NMR (376 MHz, $CDCl_3$) δ -160.08 (s).

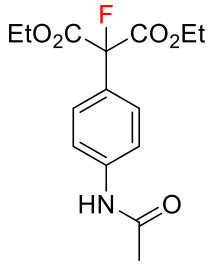


17j[203]: The general procedure F was followed using diethyl 2-(4-methoxyphenyl)malonate (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.2 mg, 0.501 mmol) as an internal standard. Yield: 90% (^{19}F NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.44 (m, 2H), 6.97-6.81 (m, 2H), 4.31 (q, *J* = 7.1 Hz, 4H), 3.80 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.76 (d, *J* = 26.3 Hz), 160.34, 127.19 (d, *J* = 8.4 Hz), 125.20 (d, *J* = 22.5 Hz), 113.64, 93.94 (d, *J* = 199.3 Hz), 62.80, 55.20, 13.84.

^{19}F NMR (376 MHz, $CDCl_3$) δ -158.65 (s).



17k: The general procedure F was followed using diethyl 2-(4-acetamidophenyl)malonate (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.4 mg, 0.502 mmol) as an internal standard. Yield: 89% (^{19}F NMR). White solid, mp 114.0-115.7 ^{o}C.

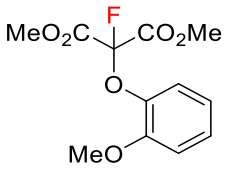
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.43 (m, 5H), 4.32 (q, *J* = 7.1 Hz, 4H), 2.16 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.05, 165.59 (d, *J* = 26.0 Hz), 139.28, 128.25 (d, *J* = 22.1 Hz), 126.33 (d, *J* = 8.7 Hz), 119.36, 93.85 (d, *J* = 199.3 Hz), 62.97, 24.22, 13.75.

^{19}F NMR (376 MHz, $CDCl_3$) δ -160.08 (s).

IR (neat, cm^{-1}): v = 3255.6, 3126.0, 2992.1, 1753.6, 1665.0, 1606.7, 1551.7, 1248.3, 1044.7, 855.1.

HRMS: (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{15}H_{18}O_5NFNa$ 334.1061, Found: 334.1065.



17l: The general procedure F was followed using dimethyl 2-(2-methoxyphenoxy)malonate (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.6 mg, 0.503 mmol) as an internal standard. Yield: 73% (^{19}F NMR). Colorless oil.

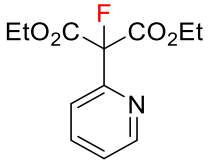
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17-7.03 (m, 2H), 6.91 (dd, *J* = 8.2, 1.5 Hz, 1H), 6.83 (td, *J* = 7.8, 1.5 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.76 (d, *J* = 34.1 Hz), 151.00, 141.75, 126.13, 120.87, 120.57, 112.81, 103.90 (d, *J* = 244.9 Hz), 56.02, 53.60.

^{19}F NMR (376 MHz, $CDCl_3$) δ -113.00 (s).

IR (neat, cm^{-1}): v = 2921.9, 2851.3, 1770.3, 1601.3, 1501.4, 1438.9, 1258.2, 1138.0, 1063.6, 751.2.

HRMS: (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{12}H_{13}O_6FNa$ 295.0588, Found: 295.0590.



17m: The general procedure F was followed using diethyl 2-(pyridin-2-yl)malonate (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.1 mg, 0.500 mmol) as an internal standard. Yield: 84% (^{19}F NMR). Colorless oil.

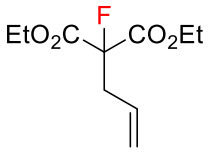
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (ddt, *J* = 4.8, 1.7, 0.8 Hz, 1H), 7.76 (td, *J* = 7.7, 1.6 Hz, 1H), 7.52 (dq, *J* = 8.0, 1.0 Hz, 1H), 7.31 (ddt, *J* = 7.6, 4.8, 1.0 Hz, 1H), 4.47-4.24 (m, 4H), 1.29 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.98 (d, *J* = 25.8 Hz), 153.34 (d, *J* = 24.7 Hz), 149.00, 136.91, 124.25, 121.26 (d, *J* = 4.9 Hz), 95.01 (d, *J* = 198.2 Hz), 62.90, 13.83.

^{19}F NMR (376 MHz, $CDCl_3$) δ -156.08 (s).

IR (neat, cm^{-1}): v = 2986.4, 1747.5, 1588.6, 1436.9, 1369.3, 1231.8, 1085.8, 1046.5, 858.5, 749.4.

HRMS: (EI) m/z: $[M]^+$ Calcd. for $C_{12}H_{14}FNO_4$ 255.0907, Found: 255.0905.

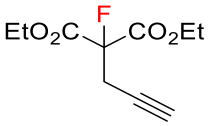


17n[204]: The general procedure F was followed using diethyl allylmalonate (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.3 mg, 0.501 mmol) as an internal standard. Yield: 89% (^{19}F NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.30-5.04 (m, 2H), 4.26 (q, *J* = 7.1 Hz, 4H), 2.87 (ddt, *J* = 23.7, 7.1, 1.2 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.71 (d, *J* = 25.2 Hz), 129.09 (d, *J* = 2.5 Hz), 120.67, 94.00 (d, *J* = 198.9 Hz), 62.48, 38.52 (d, *J* = 21.4 Hz), 13.88.

^{19}F NMR (376 MHz, $CDCl_3$) δ -166.55 (t, *J* = 23.7 Hz).

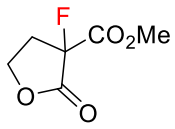


17o[203]: The general procedure F was followed using diethyl 2-(prop-2-yn-1-yl)malonate (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.2 mg, 0.501 mmol) as an internal standard. Yield: 86% (^{19}F NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29 (q, *J* = 7.1 Hz, 4H), 3.06 (dd, *J* = 22.4, 2.6 Hz, 2H), 2.08 (t, *J* = 2.6 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.80 (d, *J* = 25.1 Hz), 92.53 (d, *J* = 203.8 Hz), 75.60, 72.24, 62.93, 25.21 (d, *J* = 22.5 Hz), 13.85.

^{19}F NMR (376 MHz, $CDCl_3$) δ -165.05 (t, *J* = 22.4 Hz).



17p: The general procedure F was followed using methyl 2-oxotetrahydrofuran-3-carboxylate (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.3 mg, 0.501 mmol) as an internal standard. Yield: 87% (^{19}F NMR). Colorless oil.

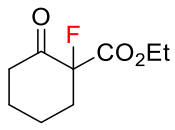
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.57-4.43 (m, 2H), 3.87 (s, 3H), 2.87 (tdd, *J* = 14.1, 7.1, 4.6 Hz, 1H), 2.67 (dddd, *J* = 22.7, 14.1, 8.4, 7.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.48 (d, *J* = 23.8 Hz), 165.88 (d, *J* = 28.1 Hz), 90.92 (d, *J* = 203.5 Hz), 65.57 (d, *J* = 3.2 Hz), 53.60, 33.17 (d, *J* = 21.7 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -165.51 (m).

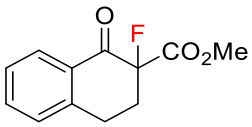
IR (neat, cm^{-1}): v = 2963.7, 1788.3, 1764.6, 1737.8, 1438.8, 1383.0 ,1277.4, 1196.9, 1125.6, 1018.8.

HRMS: (ESI) m/z: $[M+Na]^+$ Calcd. for $C_6H_7O_4FNa$ 185.0221, Found: 185.0220.



17q: The general procedure F was followed using ethyl 2-oxocyclohexanecarboxylate (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.8 mg, 0.504 mmol) as an internal standard. For this case, 10 mol% of Cs_2CO_3 was used. Yield: 80% (^{19}F NMR). The ^{19}F NMR spectral data matched the reported data[205]. The identity of the product was further confirmed by GC/MS analysis.

^{19}F NMR (376 MHz, $CDCl_3$) δ -161.28 (m).

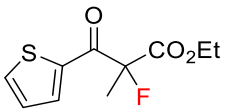


17r[47]: The general procedure F was followed using methyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.1 mg, 0.500 mmol) as an internal standard. For this case, 10 mol% of Cs_2CO_3 was used. Yield: 92% (^{19}F NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17-7.99 (m, 1H), 7.57 (td, *J* = 7.5, 1.4 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 7.7 Hz, 1H), 3.84 (s, 3H), 3.27-3.03 (m, 2H), 2.75 (dddd, *J* = 22.7, 13.9, 7.4, 5.1 Hz, 1H), 2.56 (dddd, *J* = 13.9, 11.3, 7.7, 5.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 188.38 (d, *J* = 18.4 Hz), 167.71 (d, *J* = 25.8 Hz), 143.08, 134.53, 130.34, 128.71, 128.30, 127.17, 93.20 (d, *J* = 193.9 Hz), 52.90, 31.76 (d, *J* = 22.1 Hz), 24.71 (d, *J* = 7.3 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -164.66 (m).



17s: The general procedure F was followed using ethyl 2-methyl-3-oxo-3-(thiophen-2-yl)propanoate (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.2 mg, 0.501 mmol) as an internal standard. For this case, 10 mol% of Cs_2CO_3 was used. Yield: 89% (^{19}F NMR). Colorless oil.

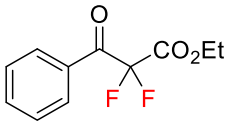
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07-7.88 (m, 1H), 7.72 (d, *J* = 4.9 Hz, 1H), 7.13 (t, *J* = 4.4 Hz, 1H), 4.33-4.11 (m, 2H), 1.84 (d, *J* = 22.6 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 185.13 (d, *J* = 26.3 Hz), 167.59 (d, *J* = 25.9 Hz), 139.20 (d, *J* = 4.0 Hz), 135.58 (d, *J* = 2.3 Hz), 135.21 (d, *J* = 9.9 Hz), 128.49, 97.29 (d, *J* = 195.3 Hz), 62.55, 20.64 (d, *J* = 22.9 Hz), 13.79.

^{19}F NMR (376 MHz, $CDCl_3$) δ -152.66 (q, *J* = 22.6 Hz).

IR (neat, cm^{-1}): v = 3105.1, 2986.0, 1753.9, 1671.3, 1410.5, 1283.3, 1243.6, 1125.5, 1060.6, 727.5.

HRMS: (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{10}H_{11}O_3FNaS$ 253.0305, Found: 253.0306.

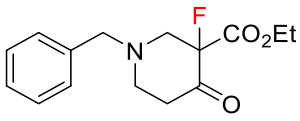


17t[206]: The general procedure F was followed using ethyl benzoylacetate (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.6 mg, 0.503 mmol) as an internal standard. 2.2 eq of NFBB and 10 mol% of Cs_2CO_3 were used. Yield: 83% (^{19}F NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.1 Hz, 2H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 185.42 (t, *J* = 27.5 Hz), 161.77 (t, *J* = 30.5 Hz), 135.05, 131.03, 129.86, 128.93, 109.74 (t, *J* = 264.5 Hz), 63.71, 13.74.

^{19}F NMR (376 MHz, $CDCl_3$) δ -108.13 (s).



17u: The general procedure F was followed using ethyl 1-benzyl-4-oxopiperidine-3-carboxylate (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.7 mg, 0.503 mmol) as an internal standard. For this case, 10 mol% of Cs_2CO_3 was used. Yield: 63% (^{19}F NMR). Colorless oil.

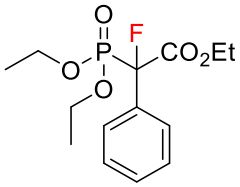
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (m, 5H), 4.38-4.16 (m, 2H), 3.75-3.61 (m, 2H), 3.51 (ddd, *J* = 11.5, 9.0, 2.3 Hz, 1H), 3.09-2.99 (m, 1H), 2.97-2.84 (m, 1H), 2.76-2.56 (m, 3H), 1.29 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 199.91 (d, *J* = 17.0 Hz), 166.15 (d, *J* = 23.7 Hz), 137.17, 128.71, 128.43, 127.60, 93.66 (d, *J* = 198.0 Hz), 62.52, 61.20, 59.13 (d, *J* = 26.2 Hz), 52.48, 40.10, 13.91.

^{19}F NMR (376 MHz, $CDCl_3$) δ -168.23 (m).

IR (neat, cm^{-1}): v = 2981.9, 2814.6, 1734.3, 1454.5, 1369.4, 1241.9, 1105.3, 900.8, 740.8, 698.7.

HRMS: (ESI) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{19}O_3NF$ 280.1343, Found: 280.1346.



17v: The general procedure F was followed using ethyl 2-(diethoxyphosphoryl)-2-phenylacetate (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.2 mg, 0.501 mmol) as an internal standard. For this case, 10 mol% of Cs_2CO_3 was used. Yield: 62% (^{19}F NMR). Colorless oil.

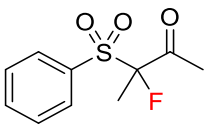
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74-7.67 (m, 2H), 7.40-7.30 (m, 3H), 4.36-4.26 (m, 2H), 4.22-3.92 (m, 4H), 1.32-1.26 (m, 6H), 1.17 (td, *J* = 7.1, 0.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.07 (dd, *J* = 22.7, 4.3 Hz), 132.16 (d, *J* = 20.5 Hz), 128.96, 128.17, 125.25 (dd, *J* = 9.7, 4.2 Hz), 94.55 (dd, *J* = 200.3, 165.9 Hz), 64.57 (dd, *J* = 23.8, 7.1 Hz), 62.66, 16.14 (dd, *J* = 9.2, 5.7 Hz), 13.83.

^{19}F NMR (376 MHz, $CDCl_3$) δ -175.36 (d, *J* = 81.5 Hz).

IR (neat, cm^{-1}): v = 2985.0, 1756.6, 1739.4, 1449.8, 1369.4, 1260.1, 1015.2, 975.4, 736.2, 696.2.

HRMS: (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{14}H_{20}O_5FNaP$ 341.0925, Found: 341.0928.



17w: The general procedure F was followed using 3-(phenylsulfonyl)butan-2-one (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.1 mg, 0.500 mmol) as an internal standard. For this case, 10 mol% of Cs_2CO_3 was used. Yield: 86% (^{19}F NMR). White solid, mp 50.7-52.7 ^{o}C.

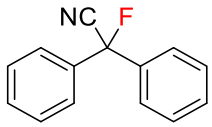
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94-7.85 (m, 2H), 7.79-7.68 (m, 1H), 7.65-7.54 (m, 2H), 2.24 (d, *J* = 4.8 Hz, 3H), 1.77 (d, *J* = 21.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 199.91 (d, *J* = 26.7 Hz), 135.13, 133.95, 130.43, 129.28, 108.59 (d, *J* = 229.7 Hz), 26.74, 17.48 (d, *J* = 20.8 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -150.68 (m).

IR (neat, cm^{-1}): v = 3098.1, 2970.9, 1728.1, 1449.2, 1324.1, 1229.6, 1144.6, 1070.7, 788.6, 688.0.

HRMS: (ESI) m/z: $[M+Na]^+$ Calcd. for $C_{10}H_{11}O_3FNaS$ 253.0305, Found: 253.0307.



17x: The general procedure F was followed using diphenylacetonitrile (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.4 mg, 0.502 mmol) as an internal standard. For this case, 10 mol% of Cs_2CO_3 was used. Yield: 60% (^{19}F NMR). Colorless oil.

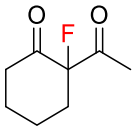
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.49 (m, 4H), 7.49-7.43 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.59 (d, *J* = 24.3 Hz), 130.17, 128.89, 126.15 (d, *J* = 5.1 Hz), 117.24 (d, *J* = 36.1 Hz), 91.64 (d, *J* = 184.0 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -132.48 (s).

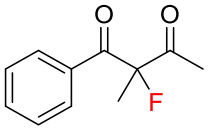
IR (neat, cm^{-1}): v = 3016.6, 2970.9, 1745.1, 1729.2, 1451.1, 1367.2, 1216.7, 985.1, 755.8, 692.3.

HRMS: (EI) m/z: $[M]^+$ Calcd. for $C_{14}H_{10}FN$ 211.0797, Found: 211.0796.



17y: The general procedure F was followed using 2-acetyl-1-cyclohexanone (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.6 mg, 0.503 mmol) as an internal standard. Yield: 52% (^{19}F NMR). The ^{19}F NMR spectral data matched the reported data[207]. The identity of the product was further confirmed by GC/MS analysis.

^{19}F NMR (376 MHz, $CDCl_3$) δ -157.73 (m).

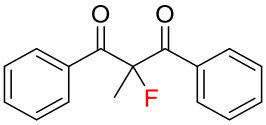


17z[208]: The general procedure F was followed using 2-methyl-1-phenylbutane-1,3-dione (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.3 mg, 0.501 mmol) as an internal standard. Yield: 49% (^{19}F NMR).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01-7.91 (m, 2H), 7.63-7.53 (m, 1H), 7.49-7.39 (m, 2H), 2.32 (d, *J* = 3.4 Hz, 3H), 1.80 (d, *J* = 22.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 202.44 (d, *J* = 24.9 Hz), 193.82 (d, *J* = 25.2 Hz), 133.98, 133.64 (d, *J* = 3.1 Hz), 129.78 (d, *J* = 5.8 Hz), 128.70, 103.36 (d, *J* = 195.3 Hz), 24.90, 20.72 (d, *J* = 23.6 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -152.20 (q, *J* = 22.5 Hz).

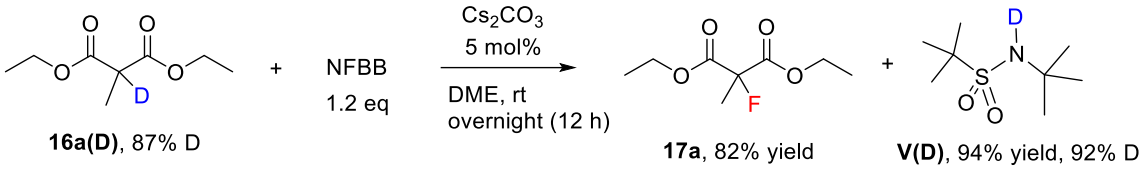


17aa: The general procedure F was followed using 2-methyl-1,3-diphenylpropane-1,3-dione (0.5 mmol) as a substrate and 2-fluorobiphenyl (86.0 mg, 0.499 mmol) as an internal standard. Yield: 13% (^{19}F NMR). The ^{19}F NMR spectral data matched the reported data[209]. The identity of the product was further confirmed by GC/MS analysis.

^{19}F NMR (376 MHz, $CDCl_3$) δ -145.43 (m).

5.2.7.3 Mechanism exploration

Fluorination of 2-deuterated malonate 16a(D) with NFBB



Diethyl 2-methylmalonate-*d* **16a(D)** was prepared according to a reported method[210] in 87% D purity (Figure S4A). The general procedure F was followed using diethyl 2-methylmalonate-*d* (0.5 mmol) as a substrate to give the fluorinated malonate **17a** in 82% yield (^{19}F NMR) and deuterated sulfonamide **V(D)** in 94% yield with 92% D purity (^{1}H NMR) (Figure S4B).

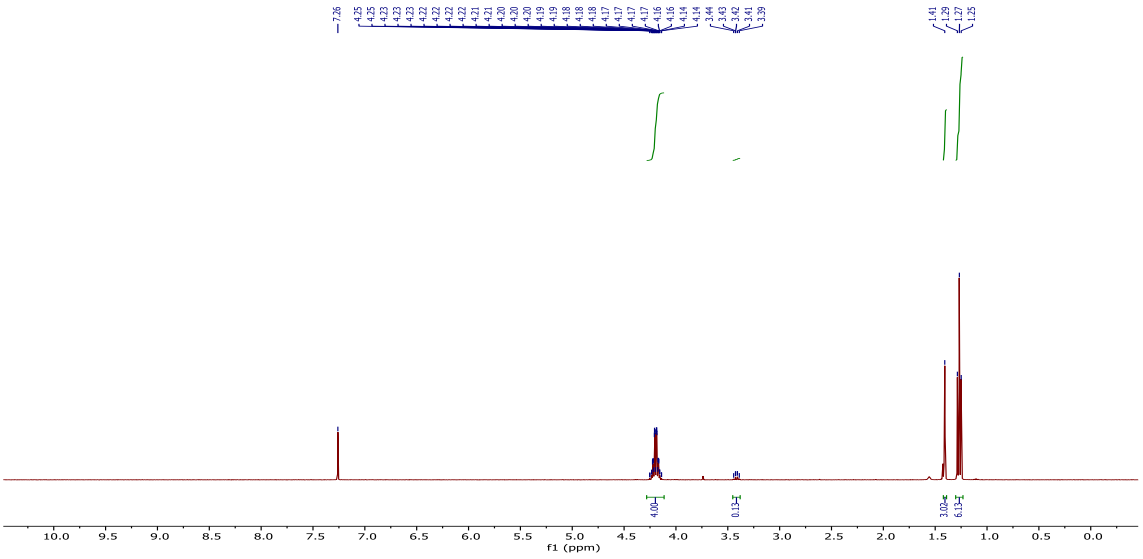


Figure S4A. ^{1}H NMR spectrum of **16a(D)**

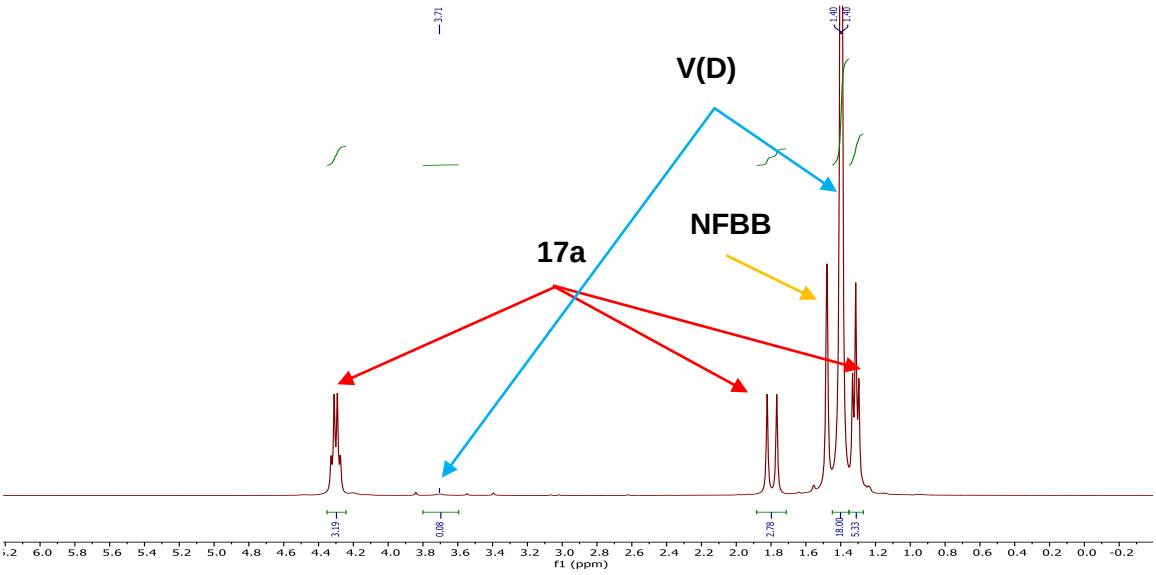
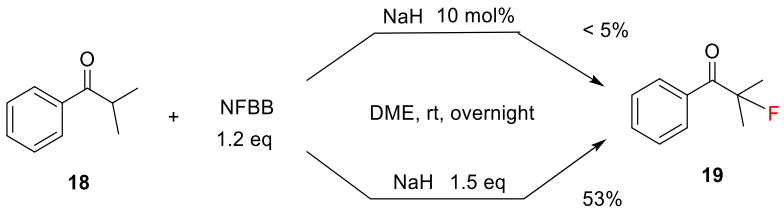


Figure S4B. ^{1}H NMR spectrum of the reaction mixture of **16a(D)** fluorination

Fluorination of isobutyrophenone 18 with NFBB



The general procedure F was followed using isobutyrophenone **18** (0.5 mmol) as a substrate and NaH as a base. The fluorinated ketone **19** was obtained in 53% yield (^{19}F NMR) when 1.5 eq of

NaH was used (Figure S5A). Trace amount of **19** was obtained when 10 mol% NaH was used (Figure S5B). The ^{19}F NMR spectral data of **19** matched the reported data[57]. The identity of **19** was further confirmed by GC/MS analysis. ^{19}F NMR (376 MHz, $CDCl_3$) δ -143.96 (hept, J = 22.3 Hz).

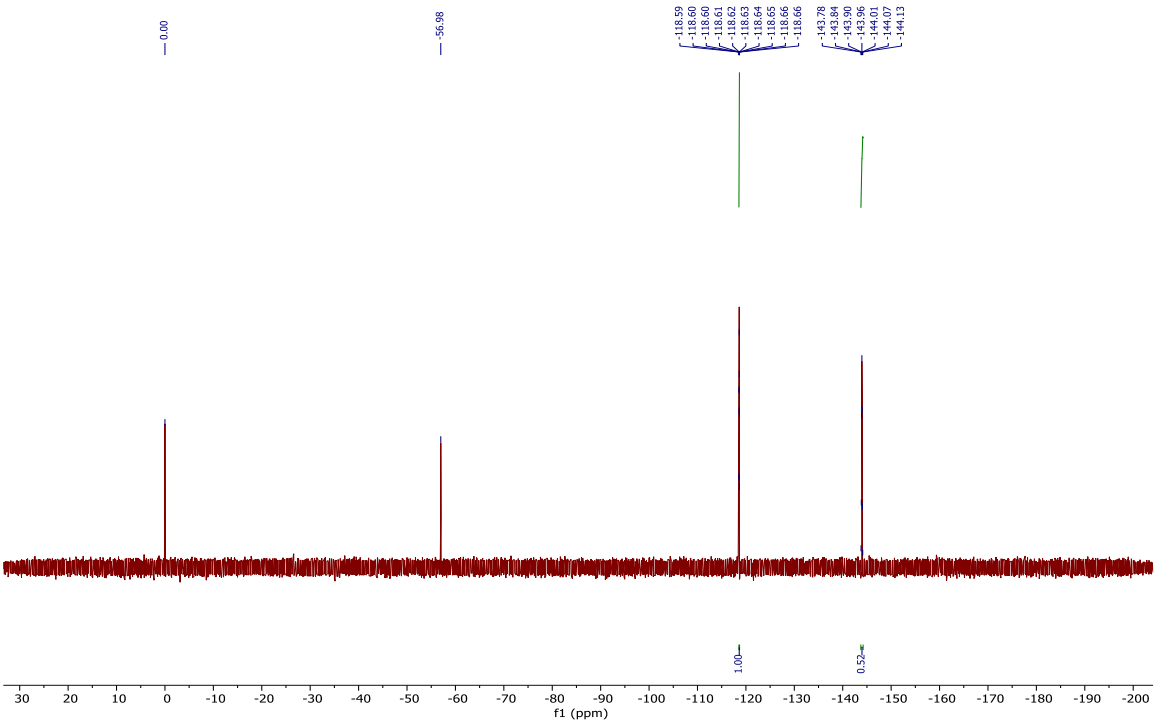


Figure S5A. ^{19}F NMR spectrum with 1.5 eq of NaH

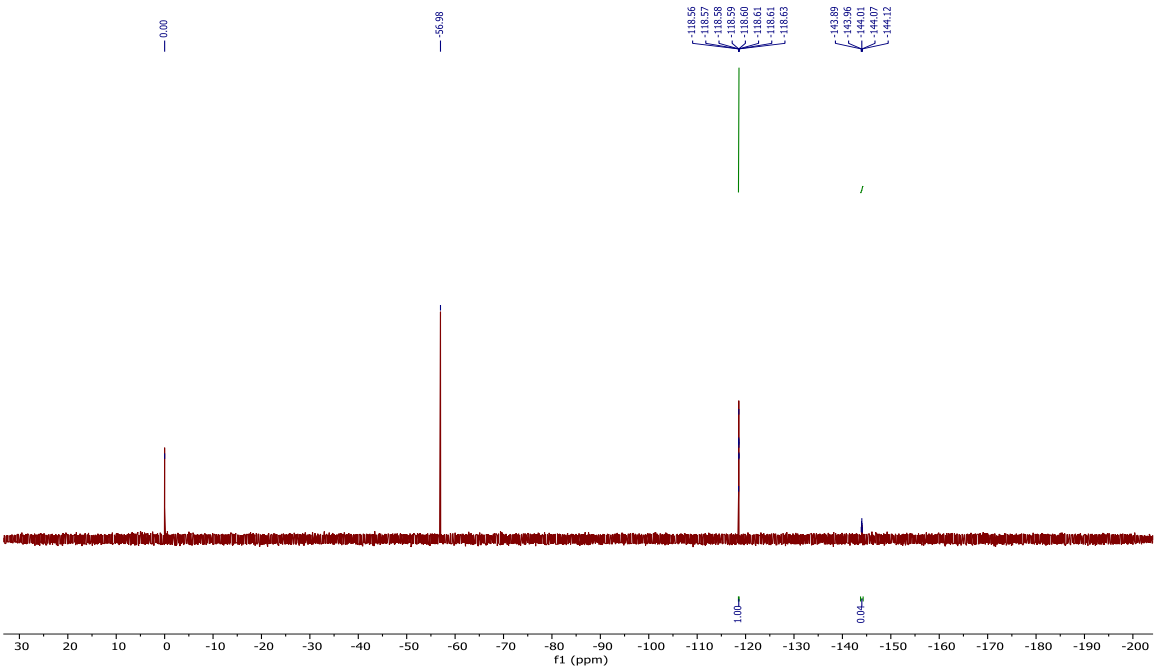
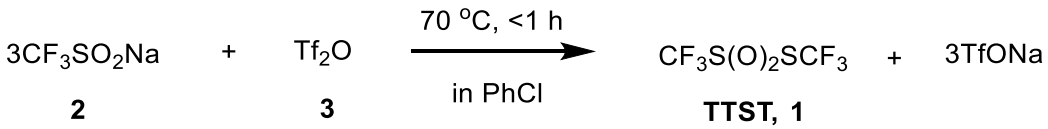


Figure S5A. ^{19}F NMR spectrum with 10 mol% of NaH

5.3 Experimental section of Chapter 3

5.3.1 Preparation of *S*-trifluoromethyl trifluoromethanesulfonothioate (TTST, 1)



Procedure:

In a 500 mL three-necked flask (reactor) equipped with an overhead stirrer, a thermometer, and a 25 mL dropping funnel connecting a $CaCl_2$ drying tube, were placed 40.9 g (262 mmol) of dry, powdered sodium trifluoromethanesulfinate of high purity and 153 mL of dry chlorobenzene. Triflic anhydride (20.3 ml, 122 mmol) was put in the dropping funnel. The reactor was heated on an oil bath of 70 °C and then triflic anhydride was added dropwise to the reactor over a period of 33 minutes with stirring. During the addition, the temperature of the reaction mixture rose to a maximum of 82 °C. The reaction mixture became very viscous as sodium triflate was formed. After the addition, the reaction mixture was stirred for additional 1 hour on the oil bath of 70 °C. Next, the dropping funnel was changed to a distillation set with a distillation column (Snyder distillation column, height 30 cm), a condenser, and a receiver. The oil bath was gradually heated up to 172 °C to collect the distillate (15.8 g; crude product 77%) of less than bp 90 °C, which was redistilled to give 12.7 g (bp 66-69 °C; 62% yield) of pure *S*-trifluoromethyl trifluoromethanesulfonothioate. The precipitate in the reactor was filtered and washed with toluene to give 51.2 g of sodium triflate.

NMR data of TTST:

^{19}F NMR (376 MHz, $CDCl_3$) δ -36.13 (q, J = 4.9 Hz, 3F), -76.80 (q, J = 4.9 Hz, 3F).

^{13}C NMR (100 MHz, $CDCl_3$) δ 126.05 (q, J = 316.6 Hz), 119.13 (q, J = 328.3 Hz).

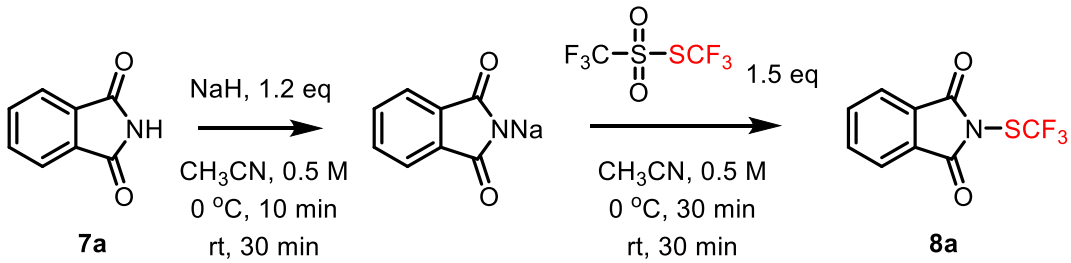
The NMR data agreed with the reference.[211-212]

HRMS: (EI) m/z: $[M]^+$ Calcd. for $C_2F_6O_2S_2$ 233.9244, Found: 233.9232.

Figure S6. Preparation and distillation of TTST

5.3.2 Electrophilic reactions with TTST

2-((Trifluoromethyl)thio)isoindoline-1,3-dione (**8a**)



To a 25 mL Schlenk-type round bottom flask equipped with a magnetic stir bar and connected to an argon cylinder, was added NaH (60% in mineral oil, 8.5 mmol, 1.2 eq). The mineral oil of NaH was removed by washing with dry hexane 4 times (3 mL each). After evaporation of hexane, dry ACN (14 mL) was added, and the reaction mixture was cooled down to 0 °C. **7a** (7.07 mmol, 1 eq) was then added. After stirring for 10 min at 0 °C and then for 30 min at room temperature, the reaction mixture of the resulting sodium salt of **7a** was cooled down to 0 °C again. Subsequently, TTST (10.6 mmol, 1.5 eq) was added dropwise during a period of 3 min, and the reaction mixture was stirred for 30 min at 0 °C and then for another 30 min at room temperature. ^{19}F-NMR yield (76%) was determined by using $PhCF_3$ (1.024g, 7.01 mmol) as an internal standard. The solvent

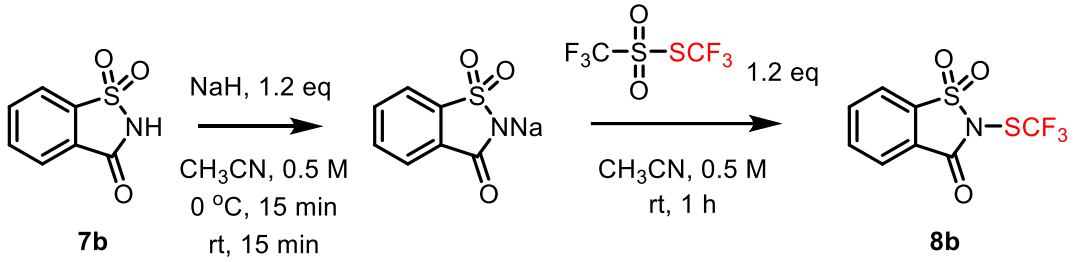
was evaporated, and the residue was purified by silica gel column chromatography (Eluent: DCM) to give **8a** (1.28 g, 73%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, J = 5.5, 3.1 Hz, 2H), 7.87 (dd, J = 5.5, 3.1 Hz, 2H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -49.39.

The NMR data agreed with the reference.[213]

2-((Trifluoromethyl)thio)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (**8b**)



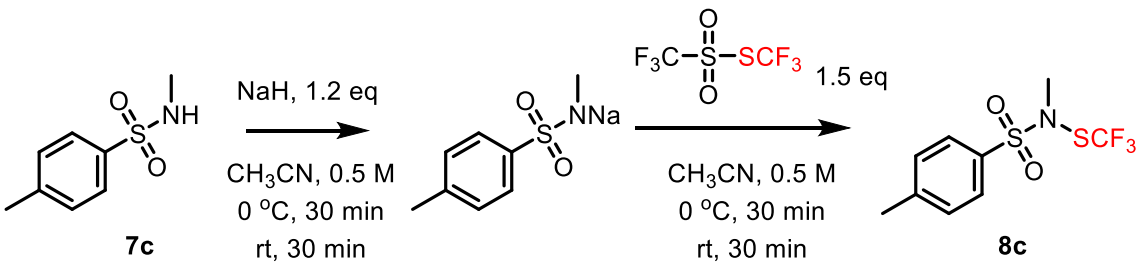
To a 25 mL Schlenk-type round bottom flask equipped with a magnetic stir bar and connected to an argon cylinder, were added NaH (60% in mineral oil, 3.45 mmol, 1.2 eq) and **7b** (2.87 mmol, 1 eq) under a flow of argon. Dry ACN (5.8 mL) was added at 0 °C. After stirring for 15 min at 0 °C and then for 15 min at room temperature, TTST (3.45 mmol, 1.2 eq) was added dropwise to the reaction mixture of the resulting sodium salt of **7b** and the reaction mixture was stirred for 1 h at room temperature. ^{19}F-NMR yield (71%) was determined by using $PhCF_3$ (421 mg, 2.88 mmol) as an internal standard. After evaporation of the solvent, the product **8b** (398 mg, 49%) was isolated by extraction with methylene chloride followed by filtration through Celite.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 – 8.18 (m, 1H), 8.06 – 7.97 (m, 2H), 7.96 – 7.90 (m, 1H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -47.81.

The NMR data agreed with the reference.[80]

N,4-Dimethyl-*N*-((trifluoromethyl)thio)benzenesulfonamide (**8c**)



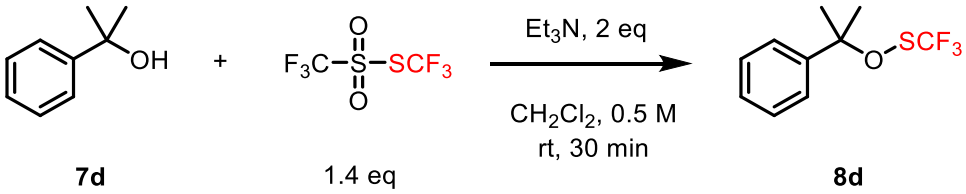
To a 25 mL Schlenk-type round bottom flask equipped with a magnetic stir bar and connected to an argon cylinder, was added NaH (60% in mineral oil, 6.49 mmol, 1.2 eq) under a flow of argon. The mineral oil of NaH was removed by washing with dry pentane 4 times (2 mL each). After evaporation of pentane, dry ACN (11 mL) was added, and the reaction mixture was cooled down to 0 ^{o}C. **7c** (5.41 mmol, 1 eq) was then added. After stirring for 30 min at 0 ^{o}C and then for 30 min at room temperature, the reaction mixture of the resulting sodium salt of **7c** was cooled down to 0 ^{o}C again. Subsequently, TTST (8.12 mmol, 1.5 eq) was added dropwise over a period of 8 min, and the reaction mixture was stirred for 30 min at 0 ^{o}C and another 30 min at room temperature. ^{19}F-NMR yield (95%) was determined by using $PhCF_3$ (791 mg, 5.42 mmol) as an internal standard. The reaction mixture was evaporated to dryness and the residue was extracted with DCM. The extracted product was purified by silica gel column chromatography (eluent: a mixture of DCM and hexane) to give **8c** (1.34 g, 87%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.60 (m, 2H), 7.44 – 7.24 (m, 2H), 3.32 (s, 2H), 2.45 (s, 2H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -50.76.

The NMR data agreed with the reference.[214]

((2-Phenylpropan-2-yl)oxy)(trifluoromethyl)sulfane (**8d**)



7d 1.4 eq **8d**

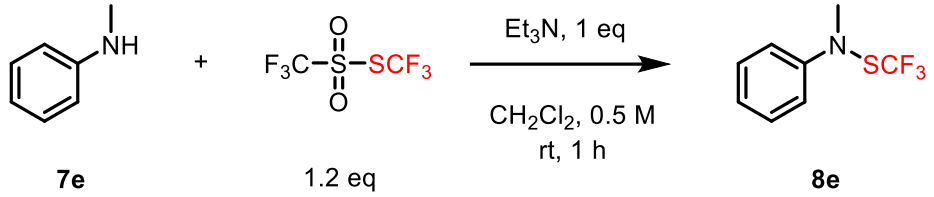
To a 25 mL round bottom flask equipped with a magnetic stir bar and an argon balloon, were added **7d** (5 mmol, 1 eq), dry DCM (10 mL), and Et_3N (10 mmol, 2 eq). TTST (7 mmol, 1.4 eq) was added dropwise over a period of 3 min at room temperature, and the reaction mixture was stirred for 30 min at room temperature. ^{19}F-NMR yield (85%) was determined by using CF_3COOEt (710 mg, 5 mmol) as an internal standard. The solvent was evaporated, and the residue was purified by silica gel column chromatography (eluent: pentane) to give **8d** (542 mg, 46%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.29 (m, 5H), 1.72 (s, 6H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -52.57.

The NMR data agreed with the reference.[80]

N-Methyl-*N*-phenyl-*S*-(trifluoromethyl)thiohydroxylamine (**8e**)



7e 1.2 eq **8e**

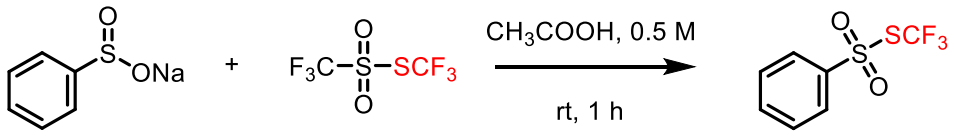
To a 50 mL Schlenk-type round bottom flask equipped with a magnetic stir bar and connected to an argon cylinder, were added **7e** (10.2 mmol, 1 eq) and dry DCM (20 mL) under a flow of argon. TTST (12.2 mmol, 1.2 eq) was added dropwise over a period of 8 min at room temperature, and the reaction mixture was stirred for 24 h. (*Note*: at this point, only half of **7e** reacted.) Then Et_3N (10.2 mmol, 1 eq) was added dropwise over a period of 3 min, and the reaction mixture was stirred for 1 h at room temperature. The solvent was evaporated, and the residue was purified by silica gel column chromatography (eluent: pentane) to give **8e** (1.75 g, 83%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 2H), 7.31 – 7.26 (m, 2H), 7.05 – 6.98 (m, 1H), 3.54 (s, 3H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -50.87.

The NMR data agreed with the reference.[80]

S-Trifluoromethyl benzenesulfonothioate (**8f**)



7f 1.3 eq **8f**

To a 10 mL round bottom flask equipped with a magnetic stir bar and an argon balloon, were added **7f** (2.05 mmol, 1 eq) and CH_3COOH (4 mL). TTST (2.67 mmol, 1.3 eq) was added dropwise over a period of 5 min at room temperature, and the reaction mixture was stirred for 1 h at room temperature. ^{19}F-NMR yield (83%) was determined by using $PhCF_3$ (299 mg, 2.05 mmol) as an internal standard. Diethyl ether was added to the reaction mixture, which was then washed

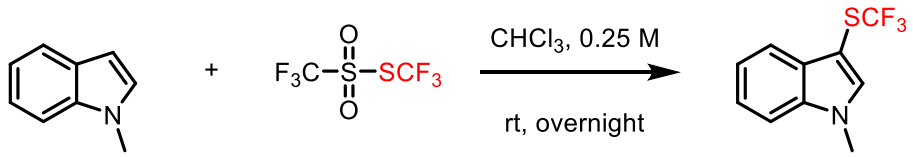
with water, aqueous Na_2CO_3, and then water. The organic layer was separated and dried with $MgSO_4$. After filtration and solvent evaporation, the residue was purified by silica gel column chromatography (eluent: a mixture of pentane and diethyl ether) to give **8f** (368 mg, 74%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.1 Hz, 2H), 7.74 (t, J = 7.7 Hz, 1H), 7.62 (t, J = 7.9 Hz, 2H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -38.88.

The NMR data agreed with the reference.[82]

1-Methyl-3-((trifluoromethyl)thio)-1H-indole (**8g**)



7g 1.2 eq **8g**

To a flame-dried 8 mL reaction vial equipped with a magnetic stir bar, were added **7g** (0.5 mmol, 1 eq) and chloroform (2 mL). TTST (0.6 mmol, 1.2 eq) was added at room temperature, and the reaction mixture was stirred overnight at room temperature. ^{19}F-NMR yield (93%) was determined by using 4-chlorobenzotrifluoride (88.4 mg, 0.491 mmol) as an internal standard. The solvent was evaporated, and the residue was purified by silica gel column chromatography (eluent: a mixture of hexane and ethyl acetate) to give **8g** (104.3 mg, 90%) as a colorless oil.

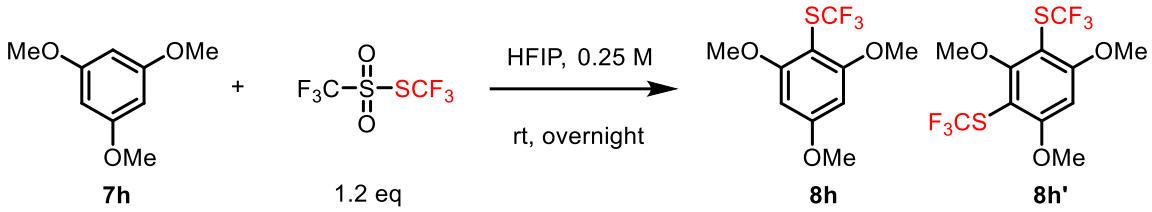
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.80 (m, 1H), 7.46 – 7.12 (m, 4H), 3.77 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 137.16, 136.92, 130.17, 129.47 (q, J = 310.1 Hz), 122.88, 121.24, 119.29, 109.86, 92.82, 33.04.

^{19}F NMR (376 MHz, $CDCl_3$) δ -45.47.

The NMR data agreed with the reference.[80]

(Trifluoromethyl)(2,4,6-trimethoxyphenyl)sulfane (**8h**)

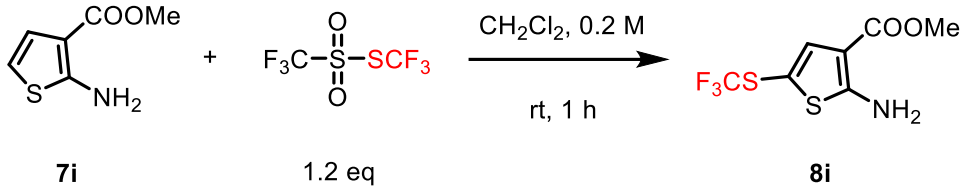


To a flame-dried 8 mL reaction vial equipped with a magnetic stir bar, were added **7h** (0.5 mmol, 1 eq) and HFIP (1,1,1,3,3,3-hexafluoroisopropanol, 2 mL). TTST (0.6 mmol, 1.2 eq) was added at room temperature, and the reaction mixture was stirred overnight at room temperature. ^{19}F-NMR yield (78% for **8h**, 16% for **8h'**) were determined by using 4-chlorobenzotrifluoride (88.9 mg, 0.494 mmol) as an internal standard.

^{19}F NMR (376 MHz, $CDCl_3$) δ -42.93 (**8h'**), -44.09 (**8h**).

The NMR data agreed with the reference.[86, 137] The identities of **8h** and **8h'** were further confirmed by GC-MS analysis.

Methyl 2-amino-5-((trifluoromethyl)thio)thiophene-3-carboxylate (**8i**)



To a flame-dried 8 mL reaction vial equipped with a magnetic stir bar, were added **7i** (0.5 mmol, 1 eq) and DCM (2.5 mL). TTST (0.6 mmol, 1.2 eq) was added at room temperature, and the reaction mixture was stirred for 1 h at room temperature. ^{19}F-NMR yield (80%) was determined by using 4-chlorobenzotrifluoride (90.4 mg, 0.502 mmol) as an internal standard. Et_3N (1.15 mmol, 2.3 eq) was added to the reaction mixture, which was then stirred for 10 min. Then the solvent was evaporated, and the residue was purified by silica gel column chromatography (eluent: a mixture of hexane and ethyl acetate) to give **8i** (105.5 mg, 82%) as a dark solid. Mp 111-114 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (s, 1H), 6.25 (br, 2H), 3.71 (s, 3H).

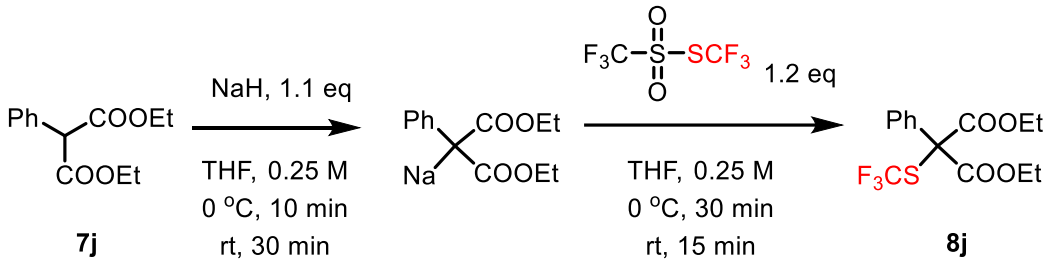
^{13}C NMR (100 MHz, $CDCl_3$) δ 167.87, 165.05, 140.16, 128.41 (q, J = 311.6 Hz), 107.77, 100.83, 51.24.

^{19}F NMR (376 MHz, $CDCl_3$) δ -46.46.

IR (neat, cm^{-1}): v = 775.3, 872.2, 980.3, 1095.8, 1271.0, 1379.1, 1438.8, 1483.5, 1524.5, 1654.9, 2952.0, 3164.5, 3295.0, 3410.5.

HRMS: (EI) m/z: $[M]^+$ Calcd. for $C_7H_6F_3NO_2S_2$ 256.9792, Found: 256.9783.

Diethyl 2-phenyl-2-((trifluoromethyl)thio)malonate (**8j**)



To a flame-dried 8 mL reaction vial equipped with a magnetic stir bar and an argon balloon, were added **7j** (0.5 mmol, 1 eq) and dry THF (2 mL). NaH (60% in mineral oil, 0.55 mmol, 1.1 eq) was added at 0 °C. After stirring at 0 °C for 10 min and then at room temperature for 30 min, the reaction mixture of the resulting sodium salt of **7j** was cooled down to 0 °C. Subsequently, TTST (0.6 mmol, 1.2 eq) was added dropwise, and the reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 15 min. ^{19}F-NMR yield (94%) was determined by using 4-chlorobenzotrifluoride (88.0 mg, 0.489 mmol) as an internal standard. The solvent was evaporated, and the residue was purified by silica gel column chromatography (eluent: a mixture of hexane and ethyl acetate) to give **8j** (128.8 mg, 77%) as a colorless oil.

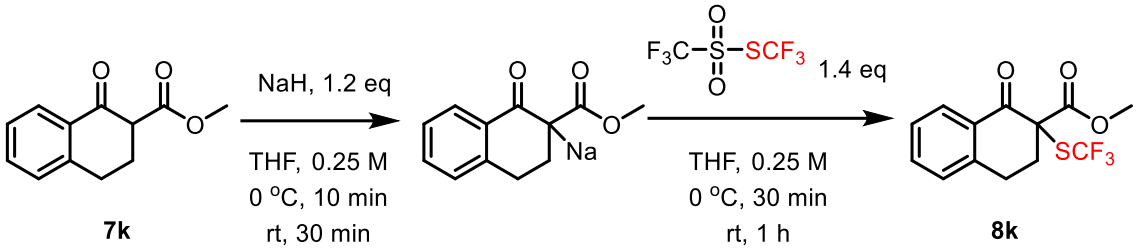
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 – 7.64 (m, 2H), 7.42 – 7.29 (m, 3H), 4.39 – 4.22 (m, 4H), 1.27 (t, J = 7.1 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.43, 133.29, 128.86, 128.81 (q, J = 310.2 Hz), 128.54, 128.23, 67.06, 63.24, 13.57.

^{19}F NMR (376 MHz, $CDCl_3$) δ -38.33.

The NMR data agreed with the reference.[80]

Methyl 1-oxo-2-((trifluoromethyl)thio)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (**8k**)



7k **8k**

To a flame-dried 8 mL reaction vial equipped with a magnetic stir bar and an argon balloon, were added **7k** (0.5 mmol, 1 eq) and dry THF (2 mL). NaH (60% in mineral oil, 0.6 mmol, 1.2 eq) was added at 0 °C. After stirring at 0 °C for 10 min and then at room temperature for 30 min, the reaction mixture of the resulting sodium salt of **7k** was cooled down to 0 °C. Subsequently, TTST (0.7 mmol, 1.4 eq) was added dropwise, and the reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 1 h. ^{19}F-NMR yield (92%) was determined by using 4-chlorobenzotrifluoride (89.5 mg, 0.497 mmol) as an internal standard. The solvent was evaporated, and the residue was purified by silica gel column chromatography (Eluent: a mixture of hexane and ethyl acetate) to give **8k** (142.9 mg, 94%) as a white solid.

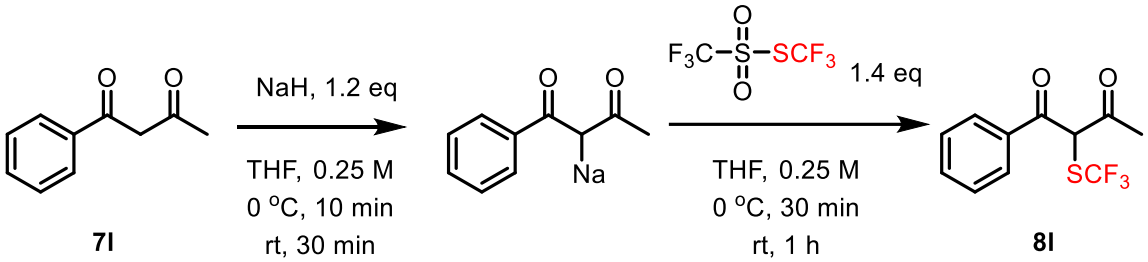
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 7.8 Hz, 1H), 7.54 (t, J = 7.5 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.26 (d, J = 7.7 Hz, 1H), 3.77 (s, 3H), 3.34 – 3.21 (m, 1H), 3.18 – 3.04 (m, 2H), 2.60 – 2.51 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 188.84, 167.34, 142.55, 134.62, 130.23, 129.74 (q, J = 309.4 Hz), 128.80, 128.52, 127.12, 64.31, 53.66, 32.75, 26.13.

^{19}F NMR (376 MHz, $CDCl_3$) δ -36.66.

The NMR data agreed with the reference.[73]

1-Phenyl-2-((trifluoromethyl)thio)butane-1,3-dione (**8l**)



7l **8l**

To a flame-dried 8 mL reaction vial equipped with a magnetic stir bar and an argon balloon, were added **7l** (0.5 mmol, 1 eq) and dry THF (2 mL). NaH (60% in mineral oil, 0.6 mmol, 1.2 eq) was added at 0 °C. After stirring at 0 °C for 10 min and then at room temperature for 30 min, the reaction mixture of the resulting sodium salt of **7l** was cooled down to 0 °C. Subsequently, TTST (0.7 mmol, 1.4 eq) was added dropwise, and the reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 1 h. ^{19}F-NMR yield (85%) was determined by using 4-chlorobenzotrifluoride (88.5 mg, 0.492 mmol) as an internal standard. The solvent was evaporated, and the residue was purified by silica gel column chromatography (eluent: a mixture of hexane and ethyl acetate) to give **8l** (119.5 mg, 91%, a mixture of ketone(minor)/enol(major) forms, and di-SCF_3 of **8l**) as a yellow oil.

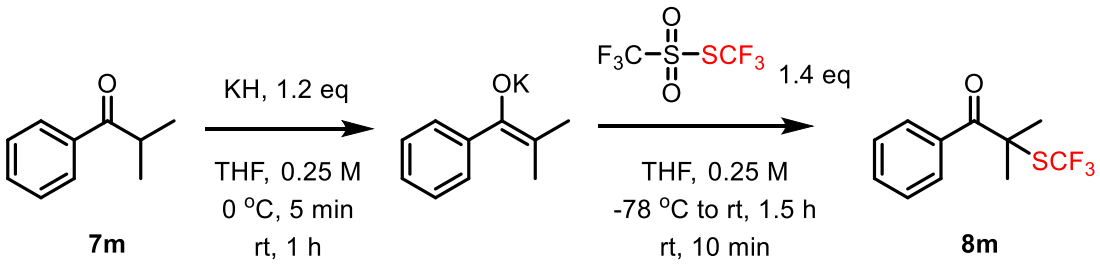
^{1}H NMR (400 MHz, $CDCl_3$, enol) δ 7.65 – 7.58 (m, 2H), 7.52 – 7.47 (m, 1H), 7.47 – 7.41 (m, 2H), 2.58 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 201.66, 194.99, 135.62, 131.26, 129.09 (q, J = 310.9 Hz), 128.66, 127.86, 95.32, 25.20.

^{19}F NMR (376 MHz, $CDCl_3$) δ -37.40 (di-SCF_3 of **8l**), -40.66 (ketone), -46.38 (enol).

The NMR data agreed with the reference.[215]

2-Methyl-1-phenyl-2-((trifluoromethyl)thio)propan-1-one (**8m**)



7m **8m**

To a flame-dried 8 mL reaction vial equipped with a magnetic stir bar and an argon balloon, were added KH (30% in mineral oil, 0.6 mmol, 1.2 eq) and dry THF (1 mL). **7m** (0.5 mmol, 1 eq) dissolved in dry THF (1 mL) was added at 0 °C. After stirring at 0 °C for 5 min and then at room temperature for 1 h, the reaction mixture of the resulting potassium salt of **7m** was cooled down to -78 °C. Subsequently, TTST (0.7 mmol, 1.4 eq) was added dropwise, and the reaction mixture was warmed up slowly to room temperature over a period of 1.5 h and was stirred for another 10

min at room temperature. ^{19}F-NMR yield (85%) was determined by using 4-chlorobenzotrifluoride (90.1 mg, 0.501 mmol) as an internal standard. After some water was added to the reaction mixture, the reaction mixture was extracted with DCM and the organic layers were combined and dried with Na_2SO_4. The solvent was evaporated, and the residue was purified by silica gel column chromatography (Eluent: a mixture of hexane and ethyl acetate) to give **8m** (109.4 mg, 88%) as a yellow oil.

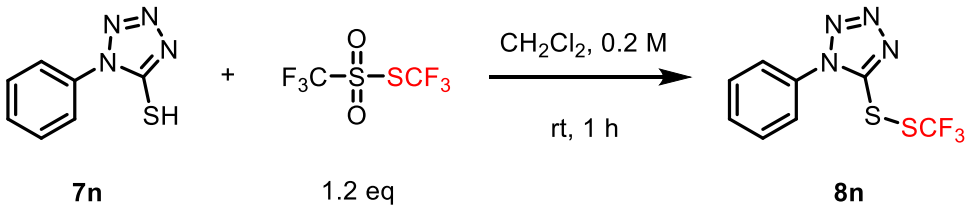
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 – 7.99 (m, 2H), 7.57 – 7.48 (m, 1H), 7.47 – 7.33 (m, 2H), 1.76 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.80, 135.51, 132.24, 129.64 (q, J = 308.8 Hz), 129.41, 128.16, 54.91, 27.53.

^{19}F NMR (376 MHz, $CDCl_3$) δ -37.11.

The NMR data agreed with the reference.[73]

1-Phenyl-5-((trifluoromethyl)disulfaneyl)-1H-tetrazole (**8n**)



7n 1.2 eq **8n**

To a flame-dried 8 mL reaction vial equipped with a magnetic stir bar, were added **7n** (0.5 mmol, 1 eq) and DCM (2.5 mL). TTST (0.6 mmol, 1.2 eq) was added at room temperature, and the reaction mixture was stirred for 1 h at room temperature. ^{19}F-NMR yield (100%) was determined by using 4-chlorobenzotrifluoride (90.5 mg, 0.503 mmol) as an internal standard. The solvent was evaporated, and the residue was purified by silica gel column chromatography (Eluent: a mixture of hexane and ethyl acetate) to give **8n** (88.2 mg, 63%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.55 (m, 3H), 7.55 – 7.49 (m, 2H).

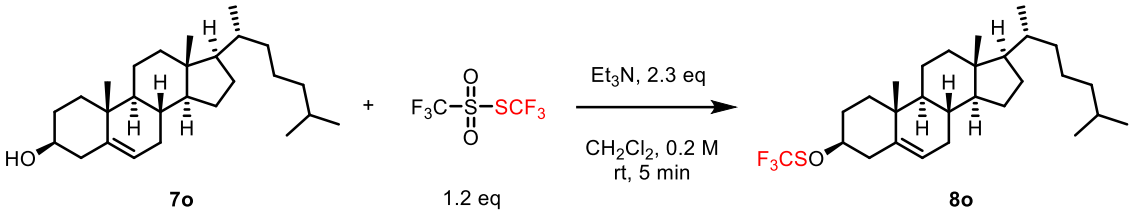
^{13}C NMR (100 MHz, $CDCl_3$) δ 151.02, 132.79, 131.05, 130.03, 127.85 (q, J = 315.3 Hz), 124.44.

^{19}F NMR (376 MHz, $CDCl_3$) δ -45.58.

IR (neat, cm^{-1}): v = 685.8, 756.6, 976.6, 1013.8, 1092.1, 1148.0, 1386.6, 1461.1, 1498.4, 1595.3, 1736.9, 2922.2, 3063.9.

HRMS: (ESI) m/z: $[M+H]^+$ Calcd. for $C_8H_6N_4F_3S_2$ 278.9980, Found: 278.9980.

(1S,2S,4S)-2-((R)-(6-methoxyquinolin-4-yl)(((trifluoromethyl)thio)oxy)methyl)-5-vinylquinuclidine (**8o**)



7o **8o**

To a flame-dried 8 mL reaction vial equipped with a magnetic stir bar, were added **7o** (0.5 mmol, 1 eq) and DCM (2.5 mL). Et_3N (1.15 mmol, 2.3 eq) and TTST (0.6 mmol, 1.2 eq) were added at room temperature, and the reaction mixture was stirred for 5 min at room temperature. ^{19}F-NMR yield (93%) was determined by using 4-chlorobenzotrifluoride (86.5 mg, 0.481 mmol) as an internal standard. The solvent was evaporated, and the residue was purified by silica gel column chromatography (Eluent: hexane) to give **8o** (218.6 mg, 90%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 (dd, J = 5.0, 2.3 Hz, 1H), 3.66 (tt, J = 10.9, 4.7 Hz, 1H), 2.50 (ddd, J = 13.0, 5.1, 2.5 Hz, 1H), 2.33 – 2.19 (m, 1H), 2.10 – 1.94 (m, 3H), 1.93 – 1.77 (m, 2H), 1.62 – 1.01 (m, 21H), 0.99 (s, 3H), 0.92 (d, J = 6.5 Hz, 3H), 0.87 (dd, J = 6.6, 1.7 Hz, 6H), 0.68 (s, 3H).

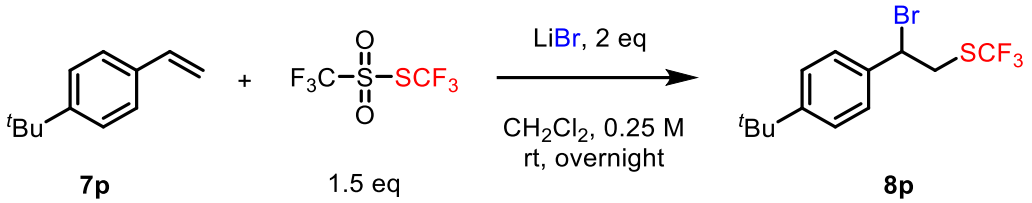
^{13}C NMR (100 MHz, $CDCl_3$) δ 139.36, 131.00 (q, J = 313.4 Hz), 123.03, 90.68, 56.69, 56.17, 49.99, 42.30, 39.72, 39.54, 38.97, 37.10, 36.46, 36.21, 35.82, 31.91, 31.83, 28.51, 28.24, 28.02, 24.28, 23.88, 22.82, 22.56, 21.11, 19.21, 18.71, 11.83.

^{19}F NMR (376 MHz, $CDCl_3$) δ -53.61.

IR (neat, cm^{-1}): v = 738.0, 797.7, 857.3, 939.3, 1025.0, 1125.7, 1159.2, 1364.2, 1464.8, 1736.9, 2866.3, 2937.1.

HRMS: (APCI) m/z: $[M+H]^+$ Calcd. for $C_{28}H_{46}OF_3S$ 487.3216, Found: 487.3216.

(2-Bromo-2-(4-(tert-butyl)phenyl)ethyl)(trifluoromethyl)sulfane (**8p**)



7p 1.5 eq **8p**

To a flame-dried 8 mL reaction vial equipped with a magnetic stir bar, were added **7p** (0.5 mmol, 1 eq), LiBr (1 mmol, 2 eq), and DCM (2 mL). TTST (0.75 mmol, 1.5 eq) was added at room temperature, and the reaction mixture was stirred overnight at room temperature. ^{19}F-NMR yield (69%) was determined by using 4-chlorobenzotrifluoride (80.4 mg, 0.447 mmol) as an internal standard. The reaction mixture was filtered through a pad of Celite and washed with DCM. The filtrate was evaporated, and the residue was purified by preparative HPLC (Eluent: a mixture of water and acetonitrile) to give the **8p** (63.7 mg, 37%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.3 Hz, 2H), 7.70 (d, J = 8.3 Hz, 2H), 5.49 (t, J = 7.9 Hz, 1H), 4.13 (dd, J = 14.2, 6.8 Hz, 1H), 4.00 (dd, J = 13.9, 9.3 Hz, 1H), 1.70 (s, 9H).

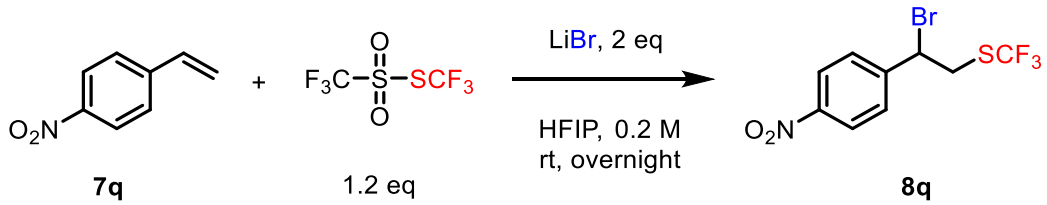
^{13}C NMR (100 MHz, $CDCl_3$) δ 152.45, 135.89, 130.62 (q, J = 306.8 Hz), 127.18, 125.95, 50.96, 38.17, 34.70, 31.18.

^{19}F NMR (376 MHz, $CDCl_3$) δ -41.40.

IR (neat, cm^{-1}): v = 756.6, 834.9, 909.5, 1099.6, 1267.3, 1364.2, 1416.4, 1513.3, 1610.2, 2870.1, 2963.2.

HRMS: (EI) m/z: $[M-Br]^+$ Calcd. for $C_{13}H_{16}F_3S$ 261.0925, Found: 261.0922.

(2-Bromo-2-(4-nitrophenyl)ethyl)(trifluoromethyl)sulfane (**8q**)



7q 1.2 eq **8q**

To a flame-dried 8 mL reaction vial equipped with a magnetic stir bar, were added **7q** (0.2 mmol, 1 eq), LiBr (0.4 mmol, 2 eq), and HFIP (1,1,1,3,3,3-hexafluoroisopropanol, 1 mL). TTST (0.24 mmol, 1.2 eq) was added at room temperature, and the reaction mixture was stirred overnight at room temperature. ^{19}F-NMR yield (96%) was determined by using 4-chlorobenzotrifluoride (36.6

mg, 0.203 mmol) as an internal standard. After some water was added to the reaction mixture, the reaction mixture was extracted with DCM, and the organic layers were combined and dried with Na_2SO_4. The solvent was evaporated, and the residue was purified by silica gel column chromatography (Eluent: a mixture of hexane and ethyl acetate) to give **8q** (56.1 mg, 85%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 7.1 Hz, 2H), 7.58 (d, J = 7.2 Hz, 2H), 5.13 (dd, J = 9.4, 6.4 Hz, 1H), 3.79 (dd, J = 14.5, 6.1 Hz, 1H), 3.58 (dd, J = 14.1, 10.2 Hz, 1H).

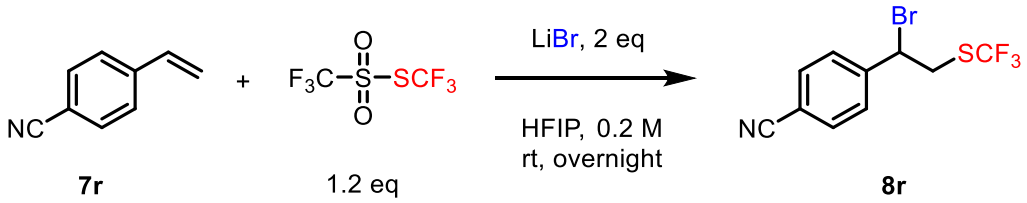
^{13}C NMR (100 MHz, $CDCl_3$) δ 148.08, 145.64, 130.28 (q, J = 307.2 Hz), 128.78, 124.21, 47.96, 37.63.

^{19}F NMR (376 MHz, $CDCl_3$) δ -41.24.

IR (neat, cm^{-1}): v = 693.3, 756.6, 853.6, 909.5, 1095.8, 1345.6, 1520.8, 1606.5, 2862.6, 2944.6, 3004.2, 3082.5.

HRMS: (EI) m/z: $[M-Br]^+$ Calcd. for $C_9H_7F_3NO_2S$ 250.0150, Found: 250.0149.

4-(1-Bromo-2-((trifluoromethyl)thio)ethyl)benzonitrile (**8r**)



7r 1.2 eq **8r**

To a flame-dried 8 mL reaction vial equipped with a magnetic stir bar, were added **7q** (0.2 mmol, 1 eq), LiBr (0.4 mmol, 2 eq), and HFIP (1,1,1,3,3,3-hexafluoroisopropanol, 1 mL). TTST (0.24 mmol, 1.2 eq) was added at room temperature, and the reaction mixture was stirred overnight at room temperature. ^{19}F-NMR yield (92%) was determined by using 4-chlorobenzotrifluoride (36.6 mg, 0.202 mmol) as an internal standard. After some water was added to the reaction mixture, the reaction mixture was extracted with DCM, and the organic layers were combined and dried with Na_2SO_4. The solvent was evaporated, and the residue was purified by silica gel column chromatography (Eluent: a mixture of hexane and ethyl acetate) to give **8q** (52.2 mg, 84%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.6 Hz, 2H), 7.51 (d, J = 8.5 Hz, 2H), 5.07 (dd, J = 9.7, 6.2 Hz, 1H), 3.76 (dd, J = 14.5, 6.2 Hz, 1H), 3.56 (dd, J = 14.5, 9.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.75, 132.73, 130.27 (q, J = 307.3 Hz), 128.49, 118.00, 113.03, 48.47, 37.57.

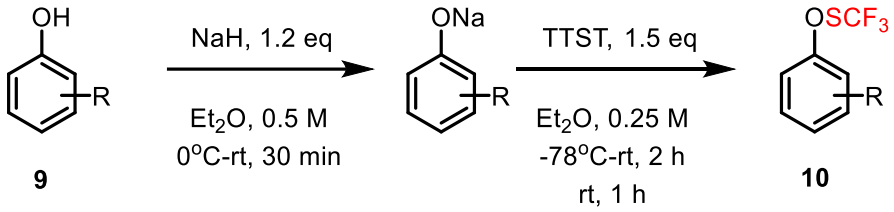
^{19}F NMR (376 MHz, $CDCl_3$) δ -41.25.

IR (neat, cm^{-1}): v = 678.4, 756.6, 834.9, 909.5, 1095.8, 1371.7, 1416.4, 1505.8, 1610.2, 1736.9, 2232.7, 3004.3, 3063.9.

HRMS: (EI) m/z: $[M-Br]^+$ Calcd. for $C_{10}H_7F_3NS$ 230.0251, Found: 230.0247.

5.3.3. Preparation of phenyl-$OSCF_3$ compounds and the novel catalytic CF_3S(II)-rearrangement

5.3.3.1 Preparation of phenyl-$OSCF_3$ compounds

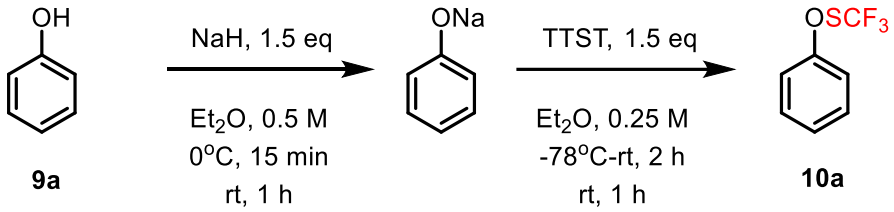


General procedure A (10 mmol scale): To a Schlenk-type 50 mL round bottom flask equipped with a magnetic stir bar and connected to an argon cylinder, was added NaH (60% in mineral oil, 15 mmol, 1.5 eq) under a flow of argon. The mineral oil of NaH was removed by 3 times wash of dry pentane (4 mL each). After evaporation of pentane, dry Et_2O (10 mL) was added, and the flask was cooled down to 0 °C. A solution of **9** (10 mmol, 1 eq) in dry Et_2O (10 mL) was then added over a period of 10 min. After stirring for 15 min at 0 °C and then for 1 h at room temperature, the reaction mixture of the resulting sodium salt of **9** was cooled down to -78 °C. Subsequently, a solution of TTST (15 mmol, 1.5 eq) in dry Et_2O (20 mL) was added dropwise over a period of 20 min, and the reaction mixture was stirred for 40 min at the same temperature and then warmed up slowly to room temperature over a period of 2 h and stirred for another 1 h at room temperature. Then the reaction mixture was filtered through a pad of Celite and washed

with dry pentane. The solvent was evaporated on an oil bath (55 °C) under atmospheric pressure, and the residue was purified by distillation under reduced pressure to give **10a-f** as a colorless oil.

General procedure B (0.5 mmol scale): To a flame-dried 8 mL reaction vial equipped with a magnetic stir bar and an argon balloon, were added **9** (0.5 mmol, 1 eq) and dry Et_2O (1 mL). NaH (60% in mineral oil, 0.6 mmol, 1.2 eq) was added at 0 °C. After stirring for 5 min at 0 °C and then for 30 min at room temperature, the reaction mixture of the resulting sodium salt of **9** was cooled down to -78 °C. Subsequently, a solution of TTST (0.75 mmol, 1.5 eq) in dry Et_2O (1 mL) was added dropwise, and the reaction mixture was warmed up slowly to room temperature over a period of 2 h and was stirred for another 1 h at room temperature. ^{19}F-NMR yield was determined by using 4-chlorobenzotrifluoride as an internal standard. Then the reaction mixture was filtered through a pad of Celite and washed with DCM. The solvent was evaporated to give the crude **10g-i** which was used for the CF_3S(II)-rearrangement without further purification.

Phenoxy(trifluoromethyl)sulfane (**10a**)



9a **10a**

The **general procedure A** was followed using **9a** (10 mmol) as a substrate to give **10a** (1.49 g, 77%) as a colorless oil. Bp 73-76 °C/70 mmHg.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 2H), 7.24 (d, J = 7.9 Hz, 2H), 7.14 (t, J = 7.3 Hz, 1H).

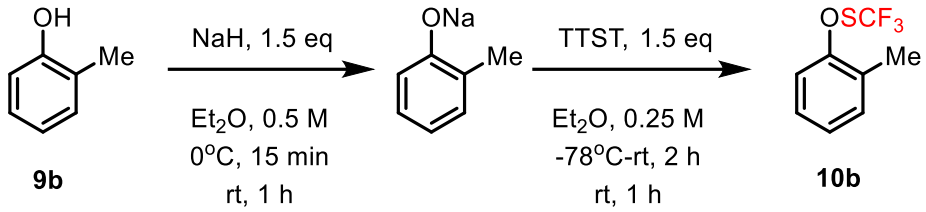
^{13}C NMR (100 MHz, $CDCl_3$) δ 159.84, 130.32 (q, J = 314.7 Hz), 129.64, 124.67, 116.75.

^{19}F NMR (376 MHz, $CDCl_3$) δ -52.86.

IR (neat, cm^{-1}): v = 685.8, 752.9, 853.6, 894.6, 1021.3, 1107.0, 1140.6, 1185.3, 1487.2, 1591.6, 3063.9.

HRMS: (EI) m/z: $[M]^+$ Calcd. for $C_7H_5F_3OS$ 194.0013, Found: 194.0007.

(*o*-Tolyloxy)(trifluoromethyl)sulfane (**10b**)



9b **10b**

The **general procedure A** was followed using **9b** (10 mmol) as a substrate to give **10b** (1.78 g, 86%) as a colorless oil. Bp 61-64.5 °C/48 mmHg.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 8.2 Hz, 1H), 7.20 (t, J = 7.8 Hz, 1H), 7.14 (d, J = 6.8 Hz, 1H), 7.03 (t, J = 7.4 Hz, 1H), 2.28 (s, 3H).

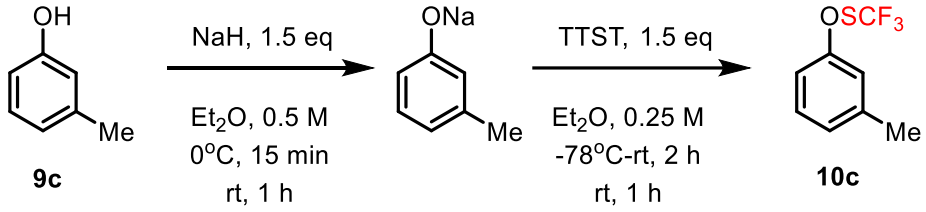
^{13}C NMR (100 MHz, $CDCl_3$) δ 158.31, 131.19, 130.39 (q, J = 313.5 Hz), 127.98, 127.16, 124.59, 115.67, 15.70.

^{19}F NMR (376 MHz, $CDCl_3$) δ -53.10.

IR (neat, cm^{-1}): v = 752.9, 782.7, 864.7, 931.8, 987.7, 1118.2, 1215.1, 1487.2, 1587.8, 2933.4, 3030.3, 3063.9.

HRMS: (EI) m/z: $[M]^+$ Calcd. for $C_8H_7F_3OS$ 208.0170, Found: 208.0164.

(*m*-Tolyloxy)(trifluoromethyl)sulfane (**10c**)



9c **10c**

The **general procedure A** was followed using **9c** (10 mmol) as a substrate to give **10c** (1.68 g, 81%) as a colorless oil. Bp 72.5-74 °C/41 mmHg.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.18 (m, 1H), 7.05 (s, 2H), 6.95 (d, J = 7.5 Hz, 1H), 2.35 (s, 3H).

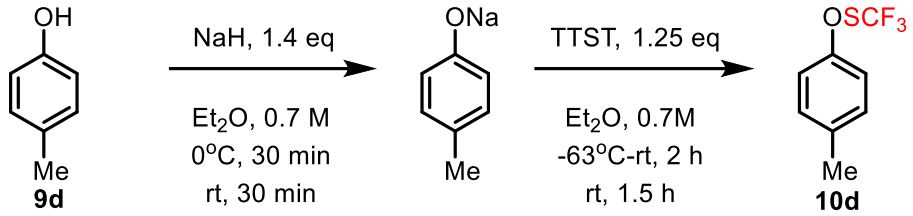
^{13}C NMR (100 MHz, $CDCl_3$) δ 159.80, 140.00, 130.31 (q, J = 313.7 Hz), 129.31, 125.45, 117.38, 113.61, 21.24.

^{19}F NMR (376 MHz, $CDCl_3$) δ -52.90.

IR (neat, cm^{-1}): v = 752.9, 808.8, 857.3, 946.7, 1095.8, 1241.2, 1293.4, 1453.7, 1483.5, 1595.3, 2929.7, 3026.6, 3410.5.

HRMS: (EI) m/z: $[M]^+$ Calcd. for $C_8H_7F_3OS$ 208.0170, Found: 208.0164.

(*p*-Tolyloxy)(trifluoromethyl)sulfane (**10d**)



To a Schlenk-type 50 mL round bottom flask equipped with a magnetic stir bar and connected to an argon cylinder, was added NaH (60% in mineral oil, 33.6 mmol, 1.4 eq) under a flow of argon. The mineral oil of NaH was removed by 4 times wash of dry pentane (4 mL each). After evaporation of pentane, dry Et_2O (14 mL) was added, and the flask was cooled down to 0 °C. A solution of **9d** (24.3 mmol, 1 eq) in dry Et_2O (20 mL) was then added over a period of 8 min. After stirring for 25 min at 0 °C and then for 30 min at room temperature, the reaction mixture of the resulting sodium salt of **9d** was cooled down to -63 °C ($CHCl_3$/liquid N_2 bath). Subsequently, TTST (30 mmol, 1.25 eq) was added dropwise over a period of 13 min, and the reaction mixture was warmed up slowly to room temperature over a period of 2 h and was stirred for another 2 h at room temperature. Then the reaction mixture was filtered through a pad of Celite and washed with dry pentane. The solvent was evaporated at 35 °C under reduced pressure (700 mbar), and the residue was purified by distillation under reduce pressure to give **10d** (3.90 g, 77%) as a colorless oil. Bp 81-82 °C/49-48 mmHg.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (s, 4H), 2.33 (s, 3H).

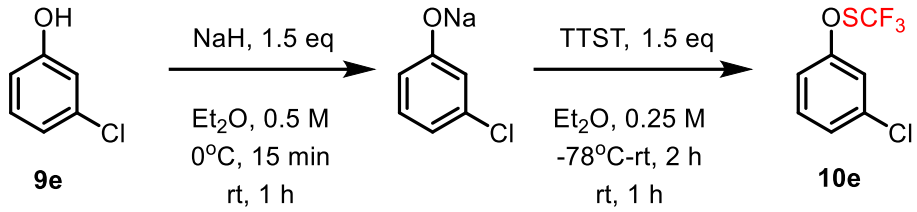
^{13}C NMR (100 MHz, $CDCl_3$) δ 157.99, 134.33, 130.37 (q, J = 313.6 Hz), 130.02, 116.63, 20.47.

^{19}F NMR (376 MHz, $CDCl_3$) δ -52.88.

IR (neat, cm^{-1}): v = 689.6, 756.6, 812.6, 857.3, 1013.8, 1107.0, 1189.0, 1457.4, 1498.4, 1595.3, 2870.1, 2926.0, 3034.1.

HRMS: (EI) m/z: $[M]^+$ Calcd. for $C_8H_7F_3OS$ 208.0170, Found: 208.0163.

(3-Chlorophenoxy)(trifluoromethyl)sulfane (**10e**)



The **general procedure A** was followed using **9e** (10 mmol) as a substrate to give **10e** (1.96 g, 86%) as a colorless oil. Bp 56-59 °C/12 mmHg.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.23 (m, 2H), 7.17 – 7.10 (m, 2H).

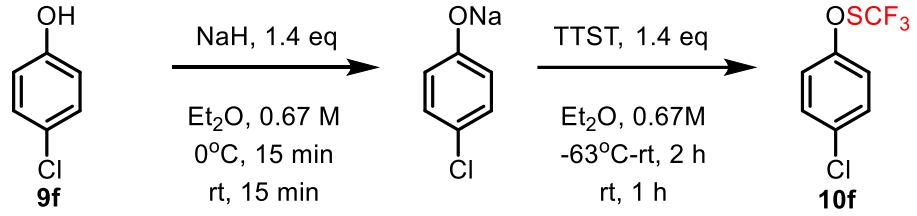
^{13}C NMR (100 MHz, $CDCl_3$) δ 160.14, 135.12, 130.40, 130.02 (q, J = 313.8 Hz), 124.95, 117.35, 114.96.

^{19}F NMR (376 MHz, $CDCl_3$) δ -52.71.

IR (neat, cm^{-1}): v = 674.6, 771.6, 890.8, 998.9, 1110.7, 1185.3, 1263.6, 1431.3, 1468.6, 1584.1, 3071.3.

HRMS: (EI) m/z: $[M]^+$ Calcd. for $C_7H_4ClF_3OS$ 227.9623, Found: 227.9619.

(4-Chlorophenoxy)(trifluoromethyl)sulfane (**10f**)



To a Schlenk-type100 mL round bottom flask equipped with a magnetic stir bar and connected with an argon cylinder, was added NaH (60% in mineral oil, 42 mmol, 1.4 eq) under a low of argon. The mineral oil of NaH was removed by 4 times wash of dry pentane (4 mL each). After evaporation of pentane, dry Et_2O (20 mL) was added, and the flask was cooled down to 0 °C. A solution of **9f** (30 mmol, 1 eq) in dry Et_2O (25 mL) was then added over a period of 5 min. After stirring for 15 min at 0 °C and then for 15 min at room temperature, the reaction mixture of the resulting sodium salt of **9f** was cooled down to -63 °C ($CHCl_3$/liquid N_2 bath). Subsequently, TTST (42 mmol, 1.4 eq) was added dropwise over a period of 10 min, and the reaction mixture was warmed up slowly to room temperature over a period of 2 h and was stirred for another 1 h at room temperature. Then the reaction mixture was filtered through a pad of Celite and washed

with dry pentane. The solvent was evaporated at 35 °C under reduced pressure (600 to 400 mbar), and the residue was purified by distillation under reduced pressure to give **10f** (5.61 g, 82%) as a colorless oil. Bp 60-63 °C/26 mmHg.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 9.0 Hz, 2H), 7.19 (d, J = 9.0 Hz, 2H).

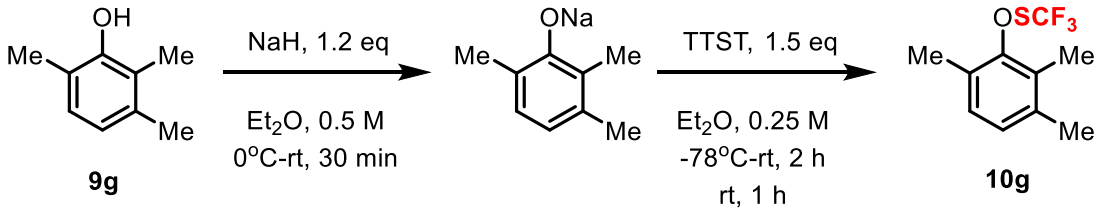
^{13}C NMR (100 MHz, $CDCl_3$) δ 158.31, 130.08 (q, J = 313.8 Hz), 129.88, 129.55, 118.08.

^{19}F NMR (376 MHz, $CDCl_3$) δ -52.75.

IR (neat, cm^{-1}): v = 700.7, 756.6, 823.7, 857.3, 1010.1, 1107.0, 1189.0, 1401.5, 1483.5, 1587.8, 3097.4.

HRMS: (EI) m/z: $[M]^+$ Calcd. for $C_7H_4ClF_3OS$ 227.9623, Found: 227.9616.

(Trifluoromethyl)(2,3,6-trimethylphenoxy)sulfane (**10g**)

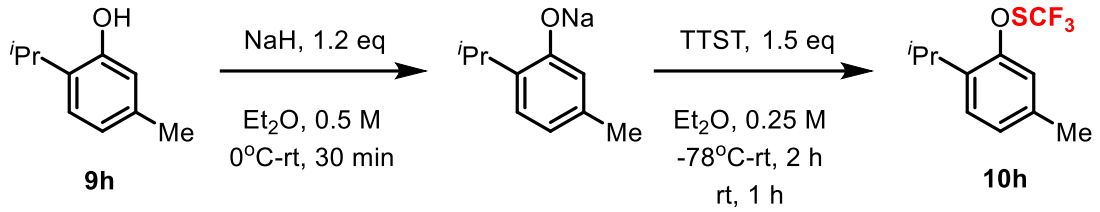


9g **10g**

The general procedure B was followed using **9g** (0.5 mmol) as a substrate and 4-chlorobenzotrifluoride (88.4 mg, 0.491 mmol) as an internal standard to give **10g** (^{19}F-NMR yield: 74%). The reaction mixture was filtered through a pad of Celite and washed with DCM. The solvent was evaporated to give the crude **10g** which was used for the CF_3S(II)-rearrangement without further purification.

^{19}F NMR (376 MHz, $CDCl_3$) δ -52.59.

(2-Isopropyl-5-methylphenoxy)(trifluoromethyl)sulfane (**10h**)



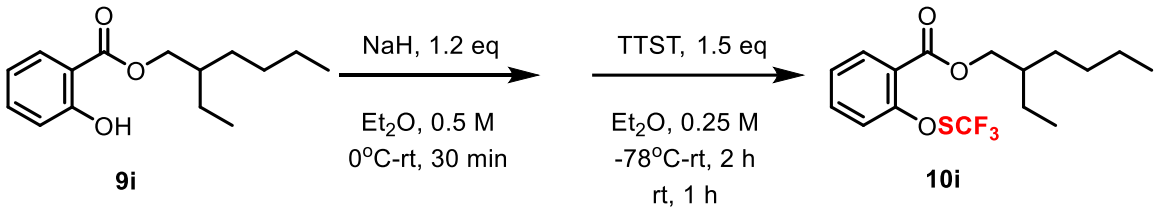
9h **10h**

The general procedure B was followed using **9h** (0.5 mmol) as a substrate and 4-chlorobenzotrifluoride (90.7 mg, 0.504 mmol) as an internal standard to give **10h** (^{19}F-NMR yield:

71%). The reaction mixture was filtered through a pad of Celite and washed with DCM. The solvent was evaporated to give the crude **10h** which was used for the CF_3S(II)-rearrangement without further purification.

^{19}F NMR (376 MHz, $CDCl_3$) δ -52.90.

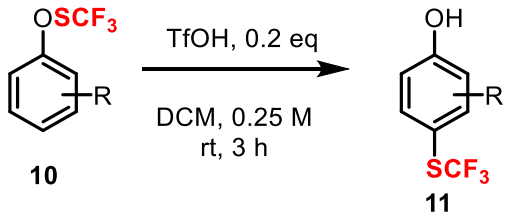
2-Ethylhexyl 2-(((trifluoromethyl)thio)oxy)benzoate (**10i**)



The general procedure B was followed using **9i** (0.5 mmol) as a substrate and 4-chlorobenzotrifluoride (88.5 mg, 0.492 mmol) as an internal standard to give **10i** (^{19}F-NMR yield: 57%). The reaction mixture was filtered through a pad of Celite and washed with DCM. The solvent was evaporated to give the crude **10i** which was used for the CF_3S(II)-rearrangement without further purification.

^{19}F NMR (376 MHz, $CDCl_3$) δ -53.29.

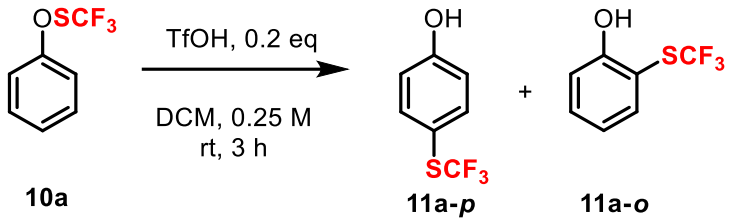
5.3.3.2 The novel catalytic CF_3S(II)-rearrangement



General procedure C: To a flame-dried 8 mL reaction vial equipped with a magnetic stir bar, were added **10** (0.5 mmol, 1 eq) and dry DCM (2 mL). TfOH (0.1 mmol, 0.2 eq) was added at room temperature, and the reaction mixture was stirred for 3 h at room temperature. ^{19}F-NMR yield was determined by using an internal standard. Known compounds **11a**, **11b**, **11c**, **11d**, **11e**, **11g**, **11h** and **11j** were identified by comparing the ^{19}F-NMR data with the reported data.[80, 216-217] Their identities were further confirmed by GC-MS analysis. Unknown compound **11i** was isolated

by preparative HPLC (eluent: a mixture of water and acetonitrile) and characterized. Unknown compound **11f** was assigned by ^{19}F NMR and GC-Mass analysis because the formation of **11f** was a very small amount.

4 and 2-((Trifluoromethyl)thio)phenol (**11a-*p,o***)



10a **11a-*p*** **11a-*o***

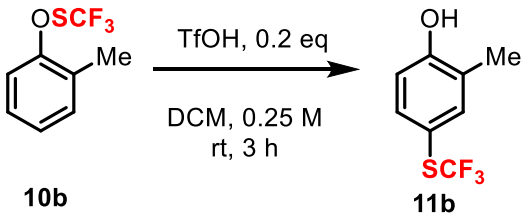
The general procedure C was followed using **10a** (0.25 mmol) as a substrate and 4-chlorobenzotrifluoride (45.4 mg, 0.252 mmol) as an internal standard to give **11a** (^{19}F-NMR yield: *p*/*o* = 73%/10%).

^{19}F NMR (376 MHz, $CDCl_3$) δ -44.41 (*p*), -43.40 (*o*).

The NMR data of **11a-*p*/*o*** agreed with the reference.[216-217]

The identity of **11a-*p*/*o*** was further confirmed by GC-MS analysis.

2-Methyl-4-((trifluoromethyl)thio)phenol (**11b**)



10b **11b**

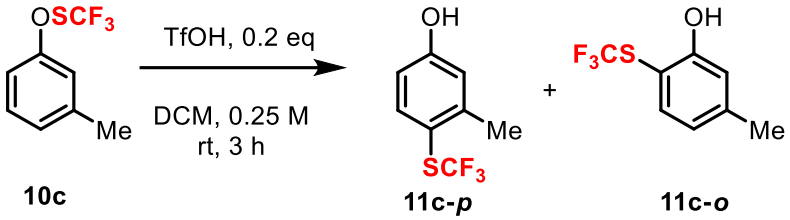
The general procedure C was followed using **10b** (0.5 mmol) as a substrate and 4-chlorobenzotrifluoride (88.2 mg, 0.490 mmol) as an internal standard to give **11b** (^{19}F-NMR yield: 72%).

^{19}F NMR (376 MHz, $CDCl_3$) δ -44.40.

The NMR data agreed with the reference.[216]

The identity of **11b** was further confirmed by GC-MS analysis.

3-Methyl-4 and 6-((trifluoromethyl)thio)phenol (**11c-*p*,*o***)



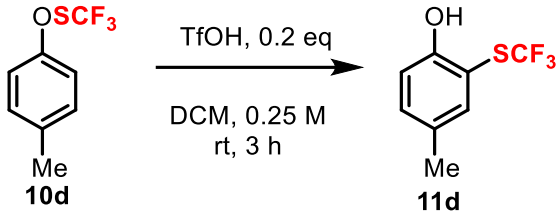
The general procedure C was followed using **10c** (0.5 mmol) as a substrate and 4-chlorobenzotrifluoride (88.2 mg, 0.490 mmol) as an internal standard to give **11c** (^{19}F-NMR yield: *p*/*o* = 74%/11%).

^{19}F NMR (376 MHz, $CDCl_3$) δ -43.98 (*p*), -43.82 (*o*).

The NMR data of **11c-*p*** agreed with the reference.[216]

The identity of **11c-*p*/*o*** was further confirmed by GC-MS analysis. *Note:* the structural assignment of 6-*ortho*-position of **11c-*o*** was tentative.

4-Methyl-2-((trifluoromethyl)thio)phenol (**11d**)



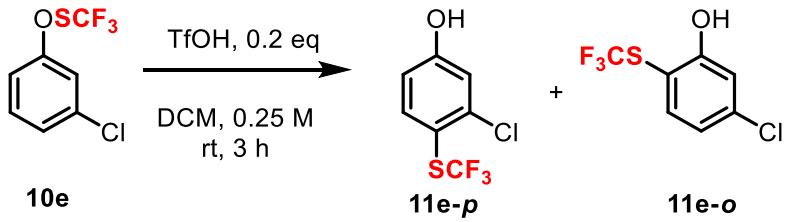
The general procedure C was followed using **10d** (0.5 mmol) as a substrate and 4-bromobenzotrifluoride (113.4 mg, 0.504 mmol) as an internal standard to give **11d** (^{19}F-NMR yield: 17%).

^{19}F NMR (376 MHz, $CDCl_3$) δ -43.41.

The NMR data agreed with the reference.[216]

The identity of **11d** was further confirmed by GC-MS analysis.

3-Chloro-4 and 6-((trifluoromethyl)thio)phenol (**11e-*p*,*o***)



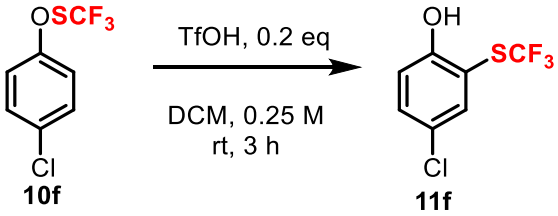
The general procedure C was followed using **10e** (0.5 mmol) as a substrate and 4-chlorobenzotrifluoride (88.6 mg, 0.492 mmol) as an internal standard to give **11e** (^{19}F-NMR yield: *p*/*o* = 60%/16%).

^{19}F NMR (376 MHz, $CDCl_3$) δ -43.68 (*p*), -43.43 (*o*).

The NMR data of **11e-*p*** agreed with the reference.[80]

The identity of **11e-*p*/*o*** was further confirmed by GC-MS analysis. *Note:* the structural assignment of 6-*ortho*-position of **11e-*o*** was tentative.

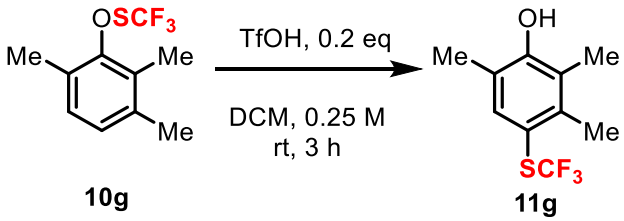
4-Chloro-2-((trifluoromethyl)thio)phenol (**11f**)



The general procedure C was followed using **10f** (0.5 mmol) as a substrate and 4-bromobenzotrifluoride (113.4 mg, 0.504 mmol) as an internal standard to give a trace amount of **11f** (^{19}F-NMR yield: 1%).

^{19}F NMR (376 MHz, $CDCl_3$) δ -43.03. The GC-Mass analysis supported **11f**.

2,3,6-Trimethyl-4-((trifluoromethyl)thio)phenol (**11g**)



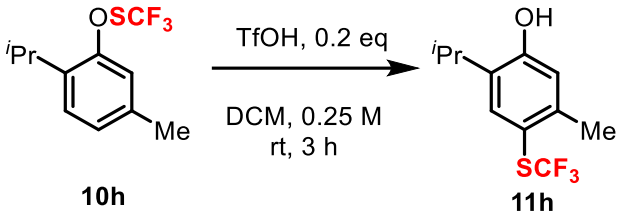
The general procedure C was followed using crude **10g** (0.5 mmol) as a substrate and 4-bromobenzotrifluoride (113.2 mg, 0.503 mmol) as an internal standard to give **11g** (^{19}F-NMR yield: 69%).

^{19}F NMR (376 MHz, $CDCl_3$) δ -44.32.

The NMR data agreed with the reference.[216]

The identity of **11g** was further confirmed by GC-MS analysis.

2-Isopropyl-5-methyl-4-((trifluoromethyl)thio)phenol (**11h**)



10h **11h**

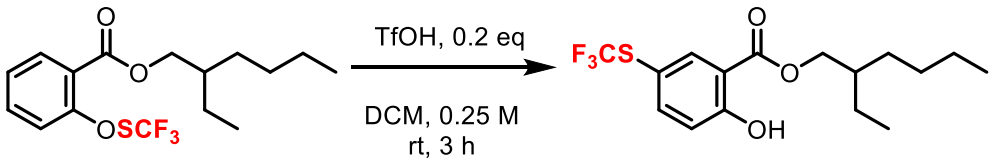
The general procedure C was followed using crude **10h** (0.5 mmol) as a substrate and 4-bromobenzotrifluoride (113.9 mg, 0.506 mmol) as an internal standard to give **11h** (^{19}F-NMR yield: 71%).

^{19}F NMR (376 MHz, $CDCl_3$) δ -44.02.

The NMR data agreed with the reference.[216]

The identity of **11h** was further confirmed by GC-MS analysis.

2-Ethylhexyl 2-hydroxy-5-((trifluoromethyl)thio)benzoate (**11i**)



10i **11i**

The general procedure C was followed using crude **10i** (0.5 mmol) as a substrate and 4-bromobenzotrifluoride (113.9 mg, 0.506 mmol) as an internal standard to give **11i** (^{19}F-NMR yield: 51%). The solvent was evaporated, and the residue was purified by preparative HPLC (eluent: a mixture of water and acetonitrile) to give **11h** (90.5 mg, 52%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.19 (s, 1H), 8.12 (s, 1H), 7.70 (d, J = 8.7 Hz, 1H), 7.03 (d, J = 8.7 Hz, 1H), 4.30 (d, J = 5.8 Hz, 2H), 1.83 – 1.67 (m, 1H), 1.53 – 1.28 (m, 8H), 1.02 – 0.82 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.33, 163.78, 143.32, 138.73, 129.41 (q, J = 308.3 Hz), 119.20, 113.72, 113.67, 68.40, 38.74, 30.48, 28.92, 23.90, 22.91, 13.96, 10.99.

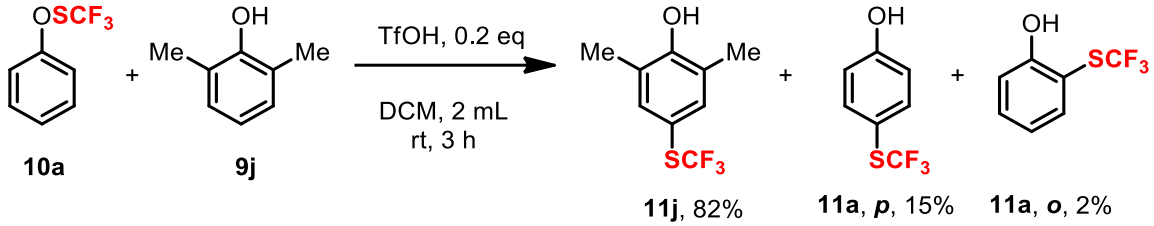
^{19}F NMR (376 MHz, $CDCl_3$) δ -44.30.

IR (neat, cm^{-1}): v = 734.3, 797.7, 834.9, 1095.8, 1207.7, 1244.9, 1293.4, 1323.2, 1472.3, 1677.3, 2929.7, 2959.5.

HRMS: (ESI) m/z: $[M-H]^-$ Calcd. for $C_{16}H_{20}O_3F_3S$ 349.1091, Found: 349.1085.

5.3.3.3 Mechanistic study

The rearrangement reaction of **10a** in the present of **9j**



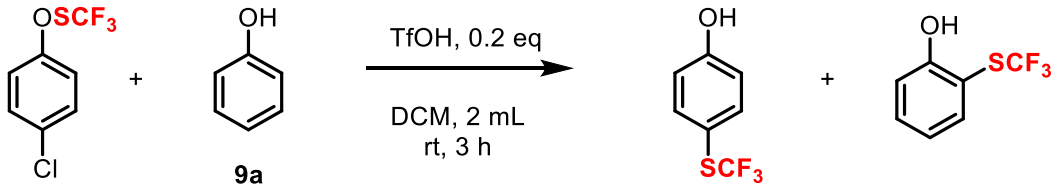
10a **9j** **11j**, 82% **11a**, ***p***, 15% **11a**, ***o***, 2%

To a flame-dried 8 mL reaction vial equipped with a magnetic stir bar, were added **10a** (0.5 mmol, 1 eq), **9j** (0.5 mmol, 1 eq) and dry DCM (2 mL). TfOH (0.1 mmol, 0.2 eq) was added at room temperature, and the reaction mixture was stirred for 3 h at room temperature. ^{19}F-NMR yields (**11j**: 82%, **11a**: *p*/*o* = 15%/2%) were determined by using 4-chlorobenzotrifluoride (91.1 mg, 0.506 mmol) as an internal standard. Known compounds **11a-*p*/*o*** and **11j** were identified by comparing the ^{19}F-NMR data with the references[216-217].

^{19}F NMR (376 MHz, $CDCl_3$) δ -44.41 (**11a-*p***), -44.37 (**11j**), -43.40 (**11a-*o***).

Their identities were further confirmed by GC-MS analysis.

The rearrangement reaction of **10f** in the presence of **9a**



10f **9a** **11a-*p***, 79% **11a-*o***, 11%

To a flame-dried 8 mL reaction vial equipped with a magnetic stir bar, were added **10f** (0.5 mmol, 1 eq), **9a** (0.5 mmol, 1 eq) and dry DCM (2 mL). TfOH (0.1 mmol, 0.2 eq) was added at room temperature, and the reaction mixture was stirred for 3 h at room temperature. ^{19}F-NMR yield (*p*/*o* = 79%/11%) was determined by using 4-chlorobenzotrifluoride (90.4 mg, 0.502 mmol) as an internal standard. Known compound **11a-*p*/*o*** was identified by comparing the ^{19}F-NMR data with the references[216-217].

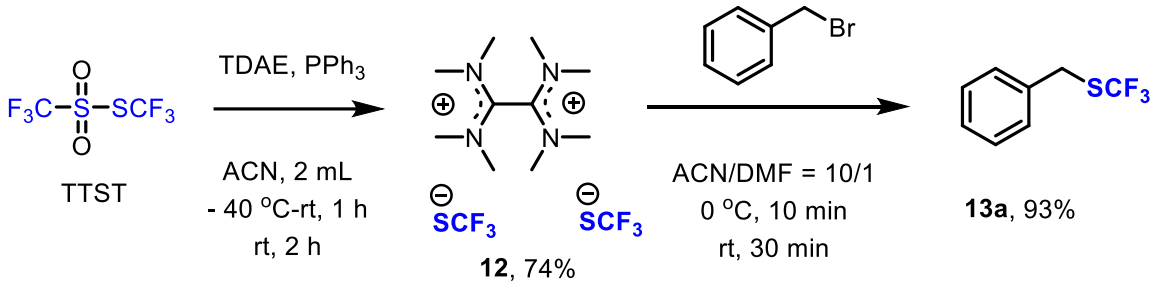
^{19}F NMR (376 MHz, $CDCl_3$) δ -44.40 (**11a-*p***), -43.40 (**11a-*o***).

Their identities were further confirmed by GC-MS analysis.

5.3.4 Nucleophilic reactions using TTST as CF_3S anion source

5.3.4.1 Reaction with TDAE

Benzyl(trifluoromethyl)sulfane (**13a**)



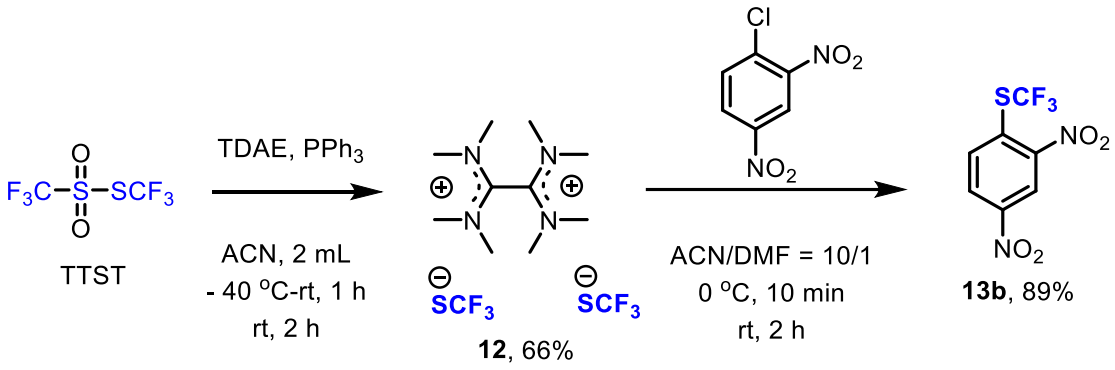
To a flame-dried 8 mL reaction vial equipped with a magnetic stir bar and an argon balloon, were added TDAE (0.24 mmol, 1 eq), PPh_3 (0.48 mmol, 2 eq), and dry ACN (1 mL). The reaction mixture was cooled down to -40 °C and a solution of TTST (0.24 mmol, 1 eq) in dry ACN (1 mL) was added dropwise. Then the reaction mixture was warmed up slowly to room temperature over a period of 1 h and was stirred for another 2 h at room temperature to produce **12** which has 2 SCF_3^-: ^{19}F NMR (376 MHz, CD_3CN) δ -6.45. ^{19}F-NMR yield of **12** (74%, 0.356 mmol SCF_3^-) was determined by using 4-chlorobenzotrifluoride (36.0 mg, 0.2 mmol) as an internal standard. Subsequently, a solution of benzyl bromide (0.3 mmol) in dry DMF (0.2 mL) was added at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and then at room temperature for 30 min to give **13a** (^{19}F-NMR yield: 93%).

^{19}F NMR (376 MHz, CD_3CN) δ -40.86.

The ^{19}F-NMR data of **12** and **13a** agreed with the reference[141].

The identity of **13a** was further confirmed by GC-MS analysis.

(2,4-Dinitrophenyl)(trifluoromethyl)sulfane (**13b**)



To a flame-dried 8 mL reaction vial equipped with a magnetic stir bar and an argon balloon, were added TDAE (0.24 mmol, 1 eq), PPh_3 (0.48 mmol, 2 eq), and dry ACN (1 mL). The reaction mixture was cooled down to -40 °C and a solution of TTST (0.24 mmol, 1 eq) in dry ACN (1 mL) was added dropwise. Then the reaction mixture was warmed up slowly to room temperature over a period of 1 h and was stirred for another 2 h at room temperature to produce **12** which has 2 SCF_3^-: ^{19}F NMR (376 MHz, CD_3CN) δ -6.37. ^{19}F-NMR yield of **12** (66%, 0.318 mmol SCF_3^-) was determined by using 4-chlorobenzotrifluoride (36.0 mg, 0.2 mmol) as an internal standard. Subsequently, a solution of 1-chloro-2,4-dinitrobenzene (0.289 mmol) in dry DMF (0.2 mL) was added at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and then at room temperature for 2 h to give **13b** (^{19}F-NMR yield: 89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (d, J = 2.5 Hz, 1H), 8.51 (dd, J = 9.0, 2.5 Hz, 1H), 8.03 (d, J = 8.9 Hz, 2H).

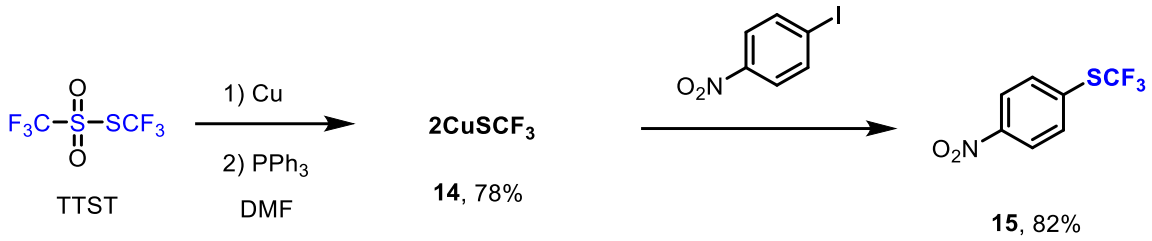
^{13}C NMR (100 MHz, $CDCl_3$) δ 146.92, 146.69, 134.44, 130.69, 128.18 (q, J = 312.1 Hz), 127.87, 121.33.

^{19}F NMR (376 MHz, $CDCl_3$) δ -41.20.

The NMR data of **12** and **13b** agreed with the reference[141].

5.3.4.2 Reaction with Cu

4-Nitro-1-(trifluoromethylthio)benzene (**15**)



To a 25 mL Schlenk flask equipped with a magnetic stir bar and connected to an argon cyclinder, were added Cu powder (4 mmol, 2 eq), dry DMF (5 mL), and *p*-chlorobenzotrifluoride (2 mmol) as an NMR reference under a flow of argon. The flask was placed in a water bath and TTST (2 mmol, 1 eq) was added dropwise over a period of 5 min. The reaction mixture was stirred in the water bath for 10 min and then, at room temperature for 50 min. PPh_3 (4.4 mmol, 2.2 eq) was added for about 1 min. As mild exothermic reaction occurred, the reaction mixture was stirred in a water bath for 10 min and then, at room temperature for 3 h. Two equivalents of $CuSCF_3$ (**14**) formed. ^{19}F-NMR analysis of the reaction mixture containing the NMR reference showed that **14** formed in 78% yield (3.12 mmol). Subsequently, 1-iodo-4-nitrobenzene (2.4 mmol) was added. The reaction mixture was stirred at 120 ^{o}C for 12 h to give **15** (^{19}F-NMR yield: 82% based on the iodide).

^{19}F NMR (376 MHz, CD_3CN) of **14**; δ -25.38.

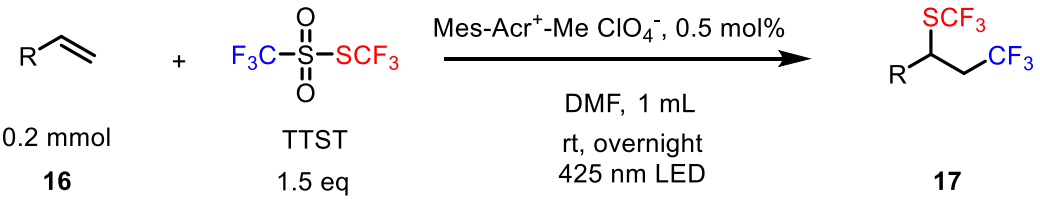
^{19}F NMR (376 MHz, CD_3CN) of **15**; δ -41.35.

The NMR data of **14** and **15** agreed with the reference[142].

The identity of **15** was further confirmed by GC-MS analysis.

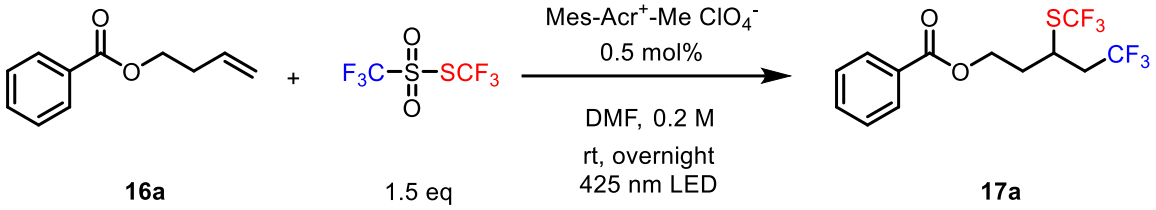
5.3.5 Radical reactions with TTST

5.3.5.1 Photocatalytic radical trifluoromethyl-trifluoromethylthiolation of alkenes



General procedure D: To a flame-dried 8 mL reaction vial equipped with a magnetic stir bar, were added **16** (0.2 mmol, 1 eq) and 9-mesityl-10-methylacridinium perchlorate (0.001 mmol, 0.5 mol%). Then the reaction vial was transferred into a glovebox filled with N_2. DMF (1 mL) was added and the N_2 was blowing into the reaction mixture to remove the O_2 for 2 min using a pipette. Subsequently, TTST (0.3 mmol, 1.5 eq) was added, and the reaction mixture was stirred in the EvoluChem 8-position PhotoRedOx Box™ with a built-in fan on at room temperature overnight (~12 h) under the irradiation of 425 nm LED. ^{19}F-NMR yield was determined by using 4-chlorobenzotrifluoride as an internal standard. The reaction mixture was diluted with EtOAc (20 mL) and washed with 10% LiCl aqueous solution for 3 times (10 mL each). The organic layer was dried with Na_2SO_4. Then the solvent was evaporated, and the residue was purified by silica gel column chromatography (eluent: a mixture of hexane and ethyl acetate) to give pure **17**.

5,5,5-Trifluoro-3-((trifluoromethyl)thio)pentyl benzoate (**17a**)



16a 1.5 eq **17a**

The general procedure D was followed using **16a** (0.2 mmol) as a substrate and 4-chlorobenzotrifluoride (36.9 mg, 0.205 mmol) as an internal standard to give **17a** (56.9 mg) as a colorless oil (^{19}F-NMR yield: 94%, isolated yield: 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.7 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.7 Hz, 2H), 4.60 – 4.45 (m, 2H), 3.66 (tt, J = 9.3, 4.7 Hz, 1H), 2.86 – 2.57 (m, 2H), 2.42 (ddt, J = 14.1, 9.4, 5.1 Hz, 1H), 2.10 (ddt, J = 14.8, 9.7, 5.0 Hz, 1H).

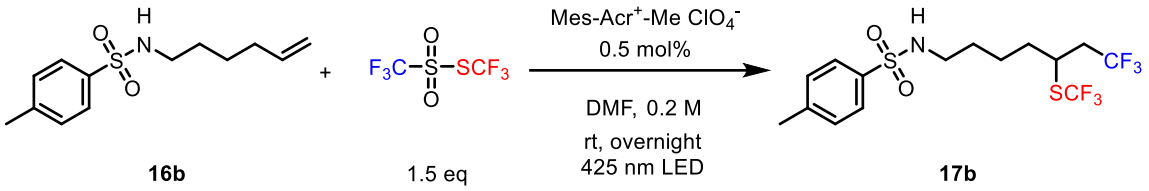
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.19, 133.21, 130.41 (q, J = 307.0 Hz), 129.69, 129.52, 128.47, 125.31 (q, J = 278.1 Hz), 61.13, 40.41 (q, J = 28.5 Hz), 36.37, 33.27.

^{19}F NMR (376 MHz, $CDCl_3$) δ -40.18 (s, 3F), -63.98 (t, J = 10.3 Hz, 3F).

IR (neat, cm^{-1}): v = 708.2, 756.6, 931.8, 1092.1, 1267.3, 1315.8, 1379.1, 1453.7, 1718.3, 2967.0, 3063.9.

HRMS: (EI) m/z: $[M]^+$ Calcd. for $C_{13}H_{12}F_6O_2S$ 346.0462, Found: 346.0463.

4-Methyl-N-(7,7,7-trifluoro-5-((trifluoromethyl)thio)heptyl)benzenesulfonamide (**17b**)



The general procedure D was followed using **16b** (0.2 mmol) as a substrate and 4-chlorobenzotrifluoride (37.0 mg, 0.206 mmol) as an internal standard to give **17b** (59.0 mg) as a white solid. Mp 59.8-51.2 ^{o}C (^{19}F-NMR yield: 99%, isolated yield: 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 4.97 (t, J = 6.2 Hz, 1H), 3.33 (tt, J = 8.3, 4.9 Hz, 1H), 2.94 (q, J = 6.4 Hz, 2H), 2.66 – 2.44 (m, 2H), 2.42 (s, 3H), 1.76 (tq, J = 10.2, 5.1 Hz, 1H), 1.65 – 1.31 (m, 5H).

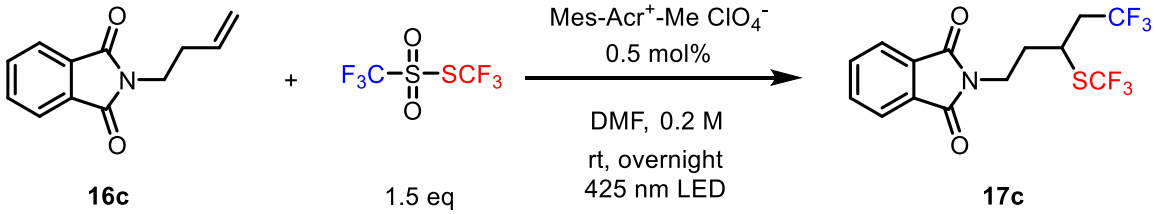
^{13}C NMR (100 MHz, $CDCl_3$) δ 143.49, 136.84, 130.53 (q, J = 306.8 Hz), 129.71, 127.03, 125.34 (q, J = 278.0 Hz), 42.71, 39.98 (q, J = 28.3 Hz), 39.26, 33.72, 28.91, 23.15, 21.41.

^{19}F NMR (376 MHz, $CDCl_3$) δ -40.13 (s, 3F), -64.20 (t, J = 10.1 Hz, 3F).

IR (neat, cm^{-1}): v = 700.7, 816.3, 838.7, 872.2, 1110.7, 1267.3, 1319.5, 1382.8, 1431.3, 2870.1, 2929.7, 3276.3.

HRMS: (APCI) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{20}O_2NF_6S_2$ 424.0834, Found: 424.0835.

2-(5,5,5-Trifluoro-3-((trifluoromethyl)thio)pentyl)isoindoline-1,3-dione (**17c**)



The general procedure D was followed using **16c** (0.2 mmol) as a substrate and 4-chlorobenzotrifluoride (37.0 mg, 0.206 mmol) as an internal standard to give **17c** (65.5 mg) as a colorless oil (^{19}F-NMR yield: 92%, isolated yield: 88%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.80 (m, 2H), 7.75 – 7.69 (m, 2H), 3.97 – 3.78 (m, 2H), 3.46 (tt, J = 9.0, 5.0 Hz, 1H), 2.81 – 2.54 (m, 2H), 2.27 (dq, J = 13.7, 6.7 Hz, 1H), 2.05 (dq, J = 14.8, 7.6 Hz, 1H).

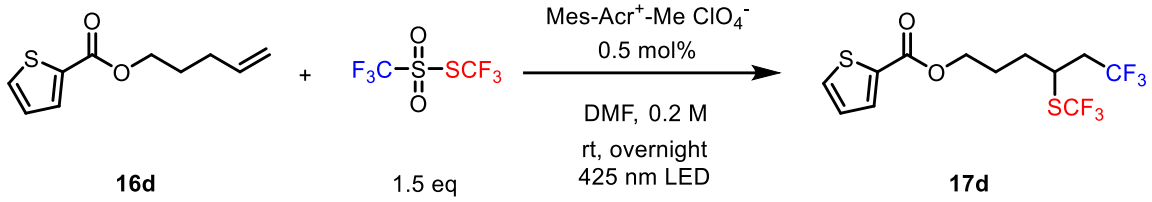
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.02, 134.12, 131.84, 130.31 (q, *J* = 307.2 Hz), 125.23 (q, J = 278.0 Hz), 123.35, 39.93 (q, J = 28.6 Hz), 37.15, 35.09, 32.84.

^{19}F NMR (376 MHz, $CDCl_3$) δ -39.93 (s, 3F), -63.95 (t, J = 10.2 Hz, 3F).

IR (neat, cm^{-1}): v = 715.6, 756.6, 793.9, 834.9, 868.5, 1010.1, 1095.8, 1263.6, 1379.1, 1707.1, 1774.2, 2948.3.

HRMS: (EI) m/z: $[M]^+$ Calcd. for $C_{14}H_{11}F_6NO_2S$ 371.0415, Found: 371.0411.

6,6,6-Trifluoro-4-((trifluoromethyl)thio)hexyl thiophene-2-carboxylate (**17d**)



16d 1.5 eq **17d**

The general procedure D was followed using **16d** (0.2 mmol) as a substrate and 4-chlorobenzotrifluoride (36.8 mg, 0.204 mmol) as an internal standard to give **17d** (57.2 mg) as a colorless oil (^{19}F-NMR yield: 86%, isolated yield: 78%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 3.7 Hz, 1H), 7.56 (d, J = 5.0 Hz, 1H), 7.10 (t, J = 4.4 Hz, 1H), 4.33 (t, J = 5.7 Hz, 2H), 3.48 (tt, J = 8.6, 4.3 Hz, 1H), 2.68 (dqt, J = 15.0, 9.3, 4.6 Hz, 1H), 2.54 (ddd, J = 15.4, 10.1, 7.7 Hz, 1H), 2.05 (ddt, J = 9.9, 6.4, 4.1 Hz, 2H), 1.96 – 1.72 (m, 2H).

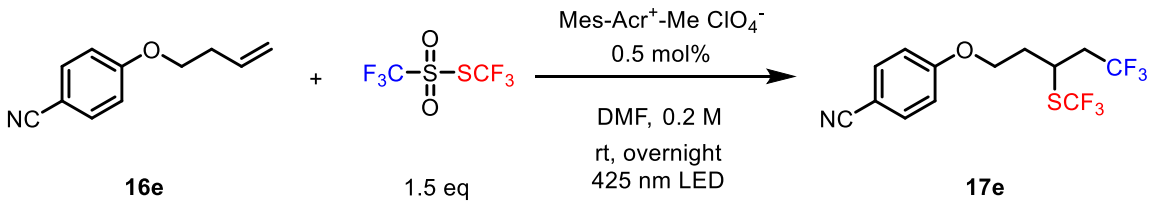
^{13}C NMR (100 MHz, $CDCl_3$) δ 162.05, 133.47, 132.51, 130.50 (q, J = 306.8 Hz), 127.78, 125.32 (q, J = 278.2 Hz), 63.85, 40.24 (q, J = 28.3 Hz), 39.21, 30.82, 25.60.

^{19}F NMR (376 MHz, $CDCl_3$) δ -39.96 (s, 3F), -64.15 (t, J = 10.4 Hz, 3F).

IR (neat, cm^{-1}): v = 719.4, 749.2, 861.0, 913.2, 1088.4, 1259.8, 1379.1, 1420.1, 1524.5, 1707.1, 2959.5, 3108.6.

HRMS: (EI) m/z: $[M]^+$ Calcd. for $C_{12}H_{12}F_6O_2S_2$ 366.0183, Found: 366.0181.

4-((5,5,5-Trifluoro-3-((trifluoromethyl)thio)pentyl)oxy)benzonitrile (**17e**)



16e 1.5 eq **17e**

The general procedure D was followed using **16e** (0.2 mmol) as a substrate and 4-chlorobenzotrifluoride (36.8 mg, 0.204 mmol) as an internal standard to give **17e** (59.9 mg) as a colorless oil (^{19}F-NMR yield: 93%, isolated yield: 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 4.22 (dhept, J = 14.6, 4.6 Hz, 2H), 3.71 (ddd, J = 13.0, 7.1, 4.2 Hz, 1H), 2.86 – 2.55 (m, 2H), 2.44 (ddt, J = 14.0, 9.2, 4.8 Hz, 1H), 2.10 (ddt, J = 14.7, 9.4, 4.5 Hz, 1H).

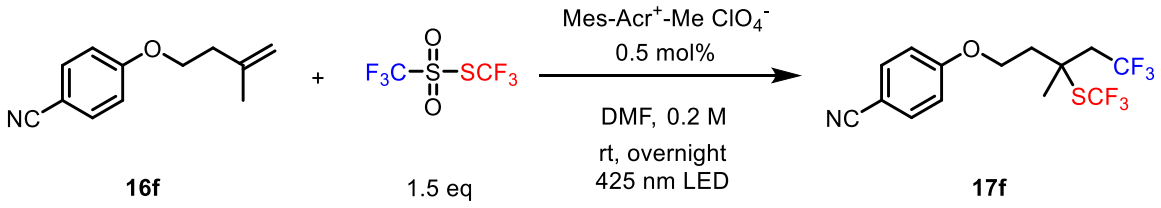
^{13}C NMR (100 MHz, $CDCl_3$) δ 161.53, 134.03, 130.38 (q, J = 307.2 Hz), 125.32 (q, J = 278.0 Hz), 119.00, 115.16, 104.58, 64.32, 40.50 (q, J = 28.6 Hz), 36.22, 33.50.

^{19}F NMR (376 MHz, $CDCl_3$) δ -40.06 (s, 3F), -64.01 (t, J = 10.3 Hz, 3F).

IR (neat, cm^{-1}): v = 697.0, 756.6, 834.9, 905.7, 943.0, 1095.8, 1252.4, 1382.8, 1472.3, 1509.6, 1606.5, 2225.2, 2888.7, 2944.6.

HRMS: (EI) m/z: $[M]^+$ Calcd. for $C_{14}H_{13}F_6NOS$ 357.0622, Found: 357.0624.

4-((5,5,5-Trifluoro-3-methyl-3-((trifluoromethyl)thio)pentyl)oxy)benzonitrile (**17f**)



16f 1.5 eq **17f**

The general procedure D was followed using **16f** (0.2 mmol) as a substrate and 4-chlorobenzotrifluoride (36.9 mg, 0.205 mmol) as an internal standard to give **17f** (61.5 mg) as a colorless oil (^{19}F-NMR yield: 90%, isolated yield: 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.9 Hz, 2H), 6.95 (d, J = 8.5 Hz, 2H), 4.25 (t, J = 6.2 Hz, 2H), 2.76 (qd, J = 10.8, 2.3 Hz, 2H), 2.38 (q, J = 5.7 Hz, 2H), 1.67 (s, 3H).

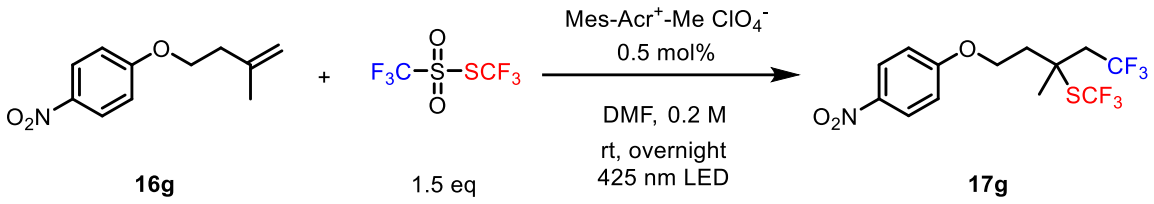
^{13}C NMR (100 MHz, $CDCl_3$) δ 161.41, 134.01, 130.09 (q, J = 308.5 Hz), 125.11 (d, J = 279.2 Hz), 118.97, 115.12, 104.48, 64.35, 50.19, 44.82 (q, J = 27.6 Hz), 39.19, 26.08.

^{19}F NMR (376 MHz, $CDCl_3$) δ -35.83 (s, 3F), -59.76 (t, J = 10.7 Hz, 3F).

IR (neat, cm^{-1}): v = 708.2, 756.6, 834.9, 1095.8, 1200.2, 1256.1, 1300.8, 1371.7, 1509.6, 1606.5, 2225.2, 2944.6.

HRMS: (APCI) m/z: $[M\text{-}CH_2+H]^+$ Calcd. for $C_{13}H_{12}ONF_6S$ 344.0538, Found: 344.0539.

(1,1,1-Trifluoro-3-methyl-5-(4-nitrophenoxy)pentan-3-yl)(trifluoromethyl)sulfane (**17g**)



The general procedure D was followed using **16g** (0.2 mmol) as a substrate and 4-chlorobenzotrifluoride (35.8 mg, 0.199 mmol) as an internal standard to give **17g** (56.7 mg) as a colorless oil (^{19}F-NMR yield: 69%, isolated yield: 75%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.16 (m, 2H), 7.01 – 6.92 (m, 2H), 4.31 (t, J = 6.2 Hz, 2H), 2.78 (qd, J = 10.8, 1.8 Hz, 2H), 2.41 (q, J = 5.9 Hz, 2H), 1.68 (s, 3H).

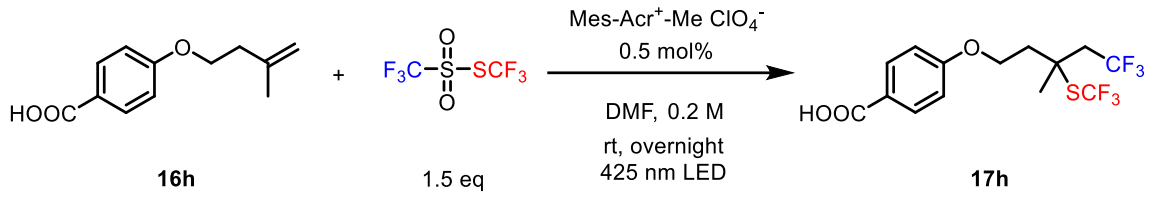
^{13}C NMR (100 MHz, $CDCl_3$) δ 163.14, 141.85, 130.09 (q, J = 309.2 Hz), 125.95, 125.12 (q, J = 279.3 Hz), 114.42, 64.83, 50.19, 44.92 (q, J = 28.1 Hz), 39.18, 26.11.

^{19}F NMR (376 MHz, $CDCl_3$) δ -35.82 (s, 3F), -59.76 (t, J = 10.6 Hz, 3F).

IR (neat, cm^{-1}): v = 689.6, 752.9, 842.4, 1095.8, 1256.1, 1341.8, 1513.3, 1595.3, 2847.7, 2944.6, 3086.2.

HRMS: (EI) m/z: $[M]^+$ Calcd. for $C_{13}H_{13}F_6NO_3S$ 377.0520, Found: 377.0514.

4-((5,5,5-Trifluoro-3-methyl-3-((trifluoromethyl)thio)pentyl)oxy)benzoic acid (**17h**)



The general procedure D was followed using **16h** (0.2 mmol) as a substrate and 4-chlorobenzotrifluoride (35.6 mg, 0.198 mmol) as an internal standard to give **17h** (57.7 mg) as a white solid. Mp 110.4-113.1 °C (^{19}F-NMR yield: 82%, isolated yield: 77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.7 Hz, 2H), 6.95 (d, J = 8.6 Hz, 2H), 4.28 (t, J = 6.2 Hz, 2H), 2.78 (qd, J = 10.8, 3.6 Hz, 2H), 2.40 (q, J = 5.8 Hz, 2H), 1.69 (s, 3H).

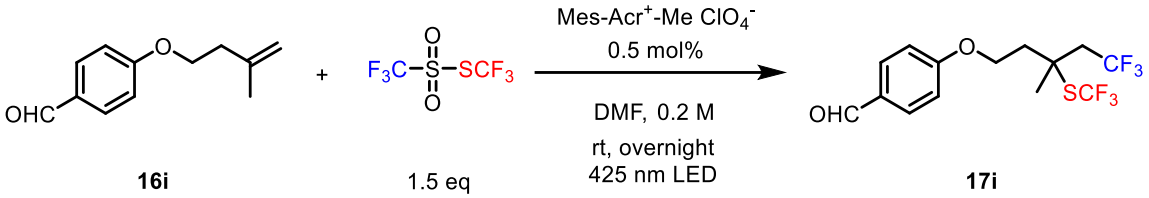
^{13}C NMR (100 MHz, $CDCl_3$) δ 171.89, 162.66, 132.44, 130.18 (q, J = 308.4 Hz), 125.18 (q, J = 279.1 Hz), 122.17, 114.17, 64.24, 50.32, 44.89 (q, J = 27.0 Hz), 39.39, 26.19.

^{19}F NMR (376 MHz, $CDCl_3$) δ -35.83 (s, 3F), -59.78 (t, J = 10.7 Hz, 3F).

IR (neat, cm^{-1}): v = 775.3, 849.8, 954.2, 1021.3, 1095.8, 1252.4, 1297.1, 1427.6, 1602.8, 1669.8, 2557.0, 2661.3, 2944.6.

HRMS: (ESI) m/z: $[M-H]^-$ Calcd. for $C_{14}H_{13}O_3F_6S$ 375.0495, Found: 375.0488.

4-((5,5,5-Trifluoro-3-methyl-3-((trifluoromethyl)thio)pentyl)oxy)benzaldehyde (**17i**)



16i 1.5 eq **17i**

The general procedure D was followed using **16i** (0.2 mmol) as a substrate and 4-chlorobenzotrifluoride (35.8 mg, 0.199 mmol) as an internal standard to give **17i** (39.2 mg) as a white solid (^{19}F-NMR yield: 72%, isolated yield: 54%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.84 (d, J = 8.5 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H), 4.29 (t, J = 6.1 Hz, 2H), 2.78 (qd, J = 10.8, 3.3 Hz, 2H), 2.40 (q, J = 5.8 Hz, 2H), 1.68 (s, 3H).

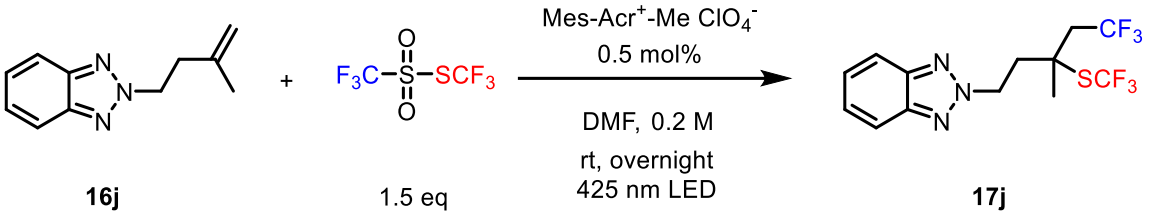
^{13}C NMR (100 MHz, $CDCl_3$) δ 190.69, 163.15, 132.01, 130.33, 130.15 (q, J = 308.5 Hz), 125.16 (q, J = 279.3 Hz), 114.71, 64.36, 50.28, 44.87 (q, J = 27.8 Hz), 39.32, 26.15.

^{19}F NMR (376 MHz, $CDCl_3$) δ -35.82 (s, 3F), -59.76 (t, J = 10.2 Hz, 3F).

IR (neat, cm^{-1}): v = 756.6, 831.2, 1095.8, 1200.2, 1252.4, 1312.0, 1371.7, 1509.6, 1599.0, 1692.2, 2739.6, 2832.8, 2944.6.

HRMS: (ESI) m/z: $[M+H]^+$ Calcd. for $C_{14}H_{15}O_2F_6S$ 361.0691, Found: 361.0693.

2-(5,5,5-Trifluoro-3-methyl-3-((trifluoromethyl)thio)pentyl)-2H-benzo[d][1,2,3]triazole (**17j**)



16j 1.5 eq **17j**

The general procedure D was followed using **16j** (0.2 mmol) as a substrate and 4-chlorobenzotrifluoride (36.0 mg, 0.200 mmol) as an internal standard to give **17j** (53.0 mg) as a colorless oil (^{19}F-NMR yield: 83%, isolated yield: 74%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.82 (m, 2H), 7.44 – 7.35 (m, 2H), 5.10 – 4.88 (m, 2H), 2.83 – 2.67 (m, 4H), 1.60 (s, 3H).

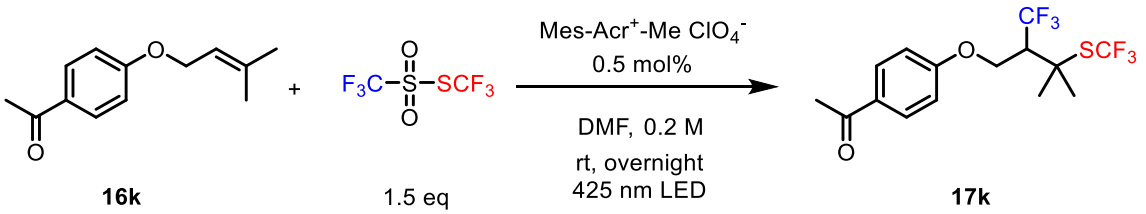
^{13}C NMR (100 MHz, $CDCl_3$) δ 144.44, 130.01 (q, J = 308.8 Hz), 126.58, 125.00 (q, J = 279.2 Hz), 117.96, 52.31, 49.77, 44.98 (q, J = 27.9 Hz), 39.86, 25.19.

^{19}F NMR (376 MHz, $CDCl_3$) δ -35.93 (s, 3F), -59.87 (t, J = 10.1 Hz, 3F).

IR (neat, cm^{-1}): v = 700.7, 745.5, 849.8, 913.2, 1099.6, 1259.8, 1326.9, 1371.7, 1457.4, 1565.5, 2970.7, 3067.6.

HRMS: (ESI) m/z: $[M+H]^+$ Calcd. for $C_{13}H_{14}N_3F_6S$ 358.0807, Found: 358.0808.

1-(4-(4,4,4-Trifluoro-3,3-dimethyl-2-((trifluoromethyl)thio)butoxy)phenyl)ethan-1-one (**17k**)



16k 1.5 eq **17k**

The general procedure D was followed using **16j** (0.2 mmol) as a substrate and 4-chlorobenzotrifluoride (36.0 mg, 0.200 mmol) as an internal standard to give **17j** (32.3 mg) as a colorless oil (^{19}F-NMR yield: 55%, isolated yield: 43%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 4.45 (qd, J = 10.5, 3.8 Hz, 2H), 3.01 (qt, J = 9.6, 3.8 Hz, 1H), 2.56 (s, 3H), 1.82 (s, 3H), 1.59 (s, 3H).

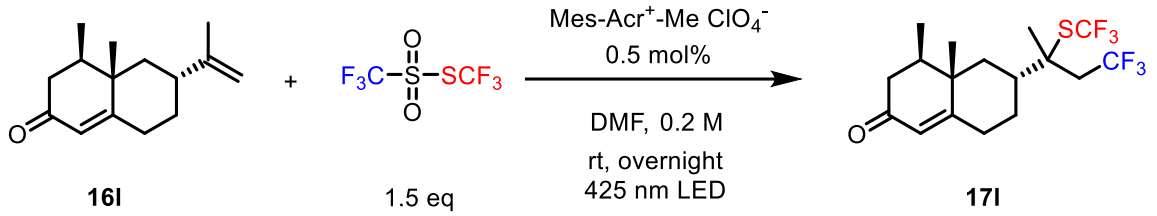
^{13}C NMR (100 MHz, $CDCl_3$) δ 196.64, 161.57, 131.09, 130.60, 130.22 (q, J = 308.5 Hz), 126.23 (q, J = 283.8 Hz), 114.26, 64.59 (d, J = 2.1 Hz), 51.76, 51.64 (q, J = 24.1 Hz), 29.43, 26.33.

^{19}F NMR (376 MHz, $CDCl_3$) δ -35.92 (s, 3F), -61.90 (d, J = 9.5 Hz, 3F).

IR (neat, cm^{-1}): v = 734.3, 834.9, 954.2, 1088.4, 1237.5, 1356.8, 1420.1, 1472.3, 1509.6, 1599.0, 1677.3, 2996.8.

HRMS: (APCI) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{17}O_2F_6S$ 375.0848, Found: 375.0851.

(4R,4aS,6R)-4,4a-Dimethyl-6-(4,4,4-trifluoro-2-((trifluoromethyl)thio)butan-2-yl)-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one (**17l**)



16l 1.5 eq **17l**

The general procedure D was followed using **16l** (0.2 mmol) as a substrate and 4-chlorobenzotrifluoride (36.6 mg, 0.203 mmol) as an internal standard to give **17l** (49.4 mg, **dr = 1:1**) as a colorless oil (^{19}F-NMR yield: 90%, isolated yield: 64%).

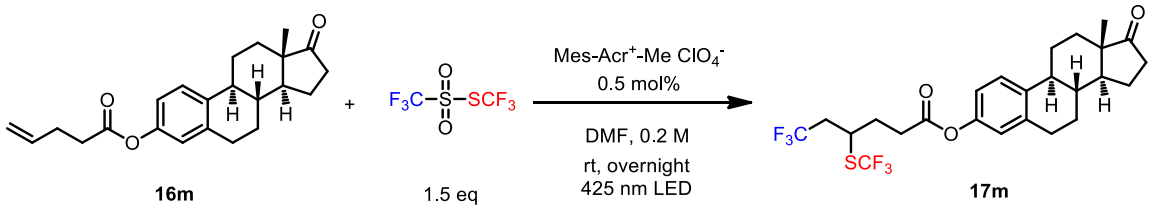
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (s, 1H), 2.94 – 2.57 (m, 2H), 2.51 – 2.37 (m, 2H), 2.30 – 2.24 (m, 2H), 2.22 – 2.07 (m, 3H), 2.07 – 1.95 (m, 1H), 1.66 (s, 3H), 1.48 – 1.25 (m, 1H), 1.24 – 1.10 (m, 1H), 1.07 (d, J = 8.1 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 199.06, 168.32 (d, J = 8.4 Hz), 130.59 (q, J = 308.1 Hz), 125.31 (qd, J = 279.4, 3.5 Hz), 124.82 (d, J = 7.7 Hz), 54.74 (d, J = 12.0 Hz), 43.23 – 42.07 (m), 41.88 (d, J = 2.2 Hz), 41.58, 41.32, 40.43 (d, J = 4.0 Hz), 39.37, 39.29, 39.19 (d, J = 2.5 Hz), 32.46 (d, J = 2.6 Hz), 27.76, 27.45, 24.81 (d, J = 6.6 Hz), 16.75, 16.25, 14.91.

^{19}F NMR (376 MHz, $CDCl_3$) δ -34.51 (d, 3F), -59.48 (t, J = 11.8 Hz, 3F).

The NMR data agreed with the reference.[146]

(8R,9S,13S,14S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl 6,6,6-trifluoro-4-((trifluoromethyl)thio)hexanoate (**17m**)



16m 1.5 eq **17m**

The general procedure D was followed using **16m** (0.2 mmol) as a substrate and 4-chlorobenzotrifluoride (36.3 mg, 0.202 mmol) as an internal standard to give **17m** (70.3 mg) as a colorless oil (^{19}F-NMR yield: 93%, isolated yield: 67%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 8.5 Hz, 1H), 6.84 (dd, J = 8.5, 2.6 Hz, 1H), 6.80 (d, J = 2.5 Hz, 1H), 3.58 (ddd, J = 12.7, 9.7, 4.6 Hz, 1H), 2.94 – 2.88 (m, 2H), 2.82 (t, J = 7.1 Hz, 2H), 2.72 (ddt, J = 16.0, 10.6, 5.2 Hz, 1H), 2.64 – 2.54 (m, 1H), 2.50 (dd, J = 18.6, 8.5 Hz, 1H), 2.45 –

2.32 (m, 2H), 2.28 (td, J = 10.9, 10.5, 3.8 Hz, 1H), 2.20 – 2.05 (m, 2H), 2.05 – 2.01 (m, 1H), 2.00 – 1.93 (m, 2H), 1.70 – 1.37 (m, 6H), 0.90 (s, 3H).

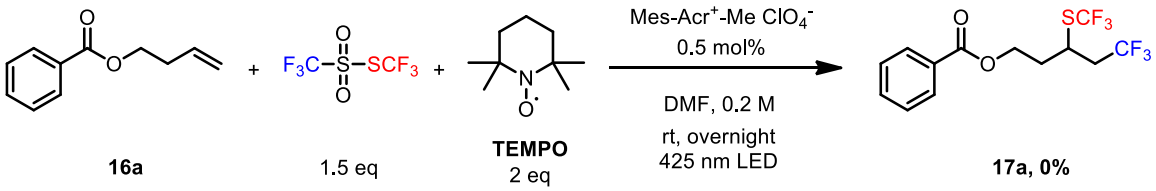
^{13}C NMR (100 MHz, $CDCl_3$) δ 220.58, 170.92, 148.27, 138.07, 137.57, 130.39 (q, J = 307.1 Hz), 126.40, 125.24 (q, J = 278.3 Hz), 121.33, 118.50, 50.36, 47.85, 44.08, 40.71 (q, J = 28.6 Hz), 38.78, 37.92, 35.75, 31.48, 30.96, 29.32, 29.19, 26.23, 25.67, 21.50, 13.73.

^{19}F NMR (376 MHz, $CDCl_3$) δ -39.96 (s, 3F), -64.03 (td, J = 10.7, 4.2 Hz, 3F).

IR (neat, cm^{-1}): v = 730.6, 820.0, 909.5, 1006.4, 1103.3, 1244.9, 1379.1, 1490.9, 1684.8, 1736.9, 2862.6, 2929.7.

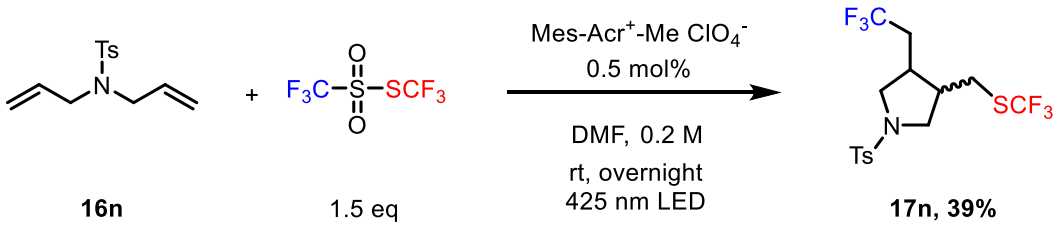
5.3.5.2 Mechanistic study

Radical inhibition experiment



The general procedure D was followed using **16a** (0.2 mmol) as a substrate and TEMPO (0.4 mmol, 2 eq) as a radical scavenger. No **17a** was detected.

Radical cyclization experiment



The general procedure D was followed using **16n** (0.2 mmol) as a substrate and 4-chlorobenzotrifluoride (36.1 mg, 0.201 mmol) as an internal standard to give **17n** (^{19}F-NMR yield: 38%).

^{19}F NMR (376 MHz, $CDCl_3$) δ -41.45 (s, 3F), -65.34 (t, J = 10.8 Hz, 3F).

The NMR data agreed with the reference.[146]

The identity of **17n** was further confirmed by GC-MS analysis.

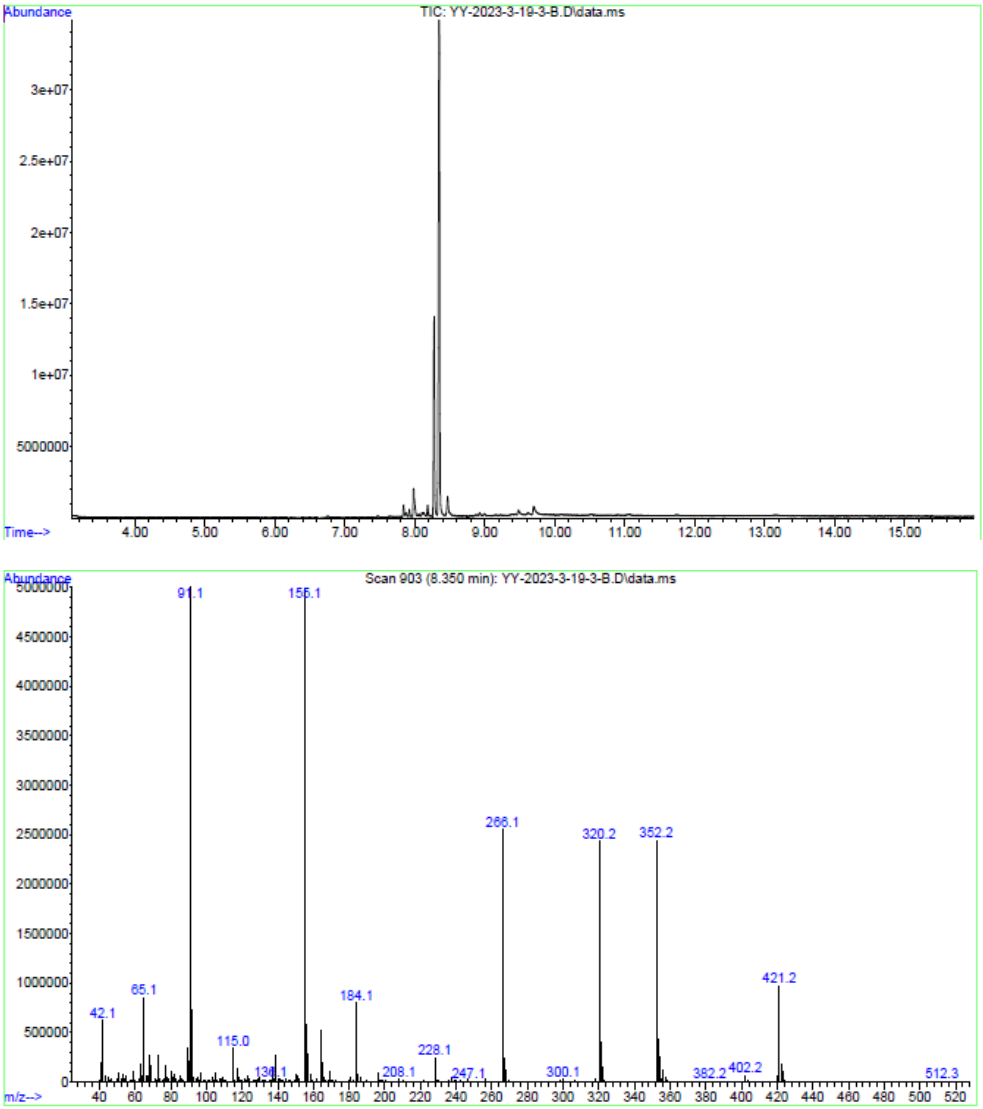
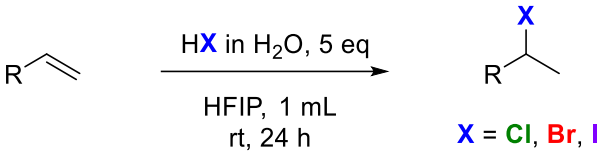
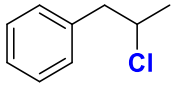


Figure S7. GC-MS of **17n**

5.4 Experimental section of Chapter 4



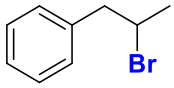
General procedure: To an 8 mL reaction vial equipped with a magnetic stir bar, were added an alkene (0.4 mmol, 1 eq) and HFIP (1 mL). Then aqueous HX solution (37% HCl, or 48% HBr, or 57% HI, 2 mmol, 5 eq) was added and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with EtOAc (20 mL) and washed with saturated $NaHCO_3$ solution for 3 times (10 mL each). The organic layer was dried with Na_2SO_4. Then the solvent was evaporated, and the residue was purified by silica gel column chromatography (eluent: a mixture of hexane and ethyl acetate) to give pure halogenated product.



2a-Cl

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.3 Hz, 2H), 7.29 (d, *J* = 7.3 Hz, 1H), 7.25 (t, *J* = 8.8 Hz, 2H), 4.25 (h, *J* = 6.7 Hz, 1H), 3.12 (dd, *J* = 13.9, 7.0 Hz, 1H), 2.99 (dd, *J* = 13.9, 6.9 Hz, 1H), 1.54 (d, *J* = 6.6 Hz, 3H).

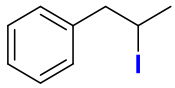
^{13}C NMR (100 MHz, $CDCl_3$) δ 137.94, 129.31, 128.38, 126.76, 58.47, 46.65, 24.63.



2a-Br

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 2H), 7.31 – 7.26 (m, 1H), 7.25 – 7.20 (m, 2H), 4.33 (h, *J* = 6.8 Hz, 1H), 3.25 (dd, *J* = 14.0, 7.0 Hz, 1H), 3.09 (dd, *J* = 14.0, 7.3 Hz, 1H), 1.72 (d, *J* = 6.6 Hz, 3H).

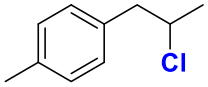
^{13}C NMR (100 MHz, $CDCl_3$) δ 138.50, 129.19, 128.44, 126.83, 50.49, 47.51, 25.66.



2a-I

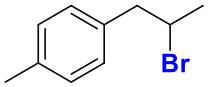
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 2H), 7.31 – 7.27 (m, 1H), 7.23 – 7.18 (m, 2H), 4.37 (h, *J* = 7.0 Hz, 1H), 3.32 (dd, *J* = 14.0, 7.2 Hz, 1H), 3.09 (dd, *J* = 14.1, 7.6 Hz, 1H), 1.92 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.62, 128.92, 128.43, 126.79, 49.46, 28.35, 28.04.



2b-Cl

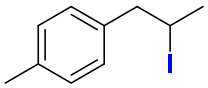
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 – 7.08 (m, 4H), 4.22 (h, *J* = 6.7 Hz, 1H), 3.07 (dd, *J* = 13.9, 7.0 Hz, 1H), 2.94 (dd, *J* = 13.9, 6.9 Hz, 1H), 2.35 (s, 3H), 1.52 (d, *J* = 6.5 Hz, 3H).



2b-Br

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (q, *J* = 7.8 Hz, 4H), 4.29 (h, *J* = 6.9 Hz, 1H), 3.20 (dd, *J* = 14.0, 7.0 Hz, 1H), 3.04 (dd, *J* = 14.1, 7.3 Hz, 1H), 2.34 (s, 3H), 1.70 (d, *J* = 6.6 Hz, 3H).

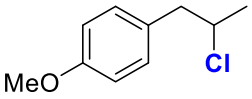
^{13}C NMR (100 MHz, $CDCl_3$) δ 136.40, 135.47, 129.12, 129.06, 50.81, 47.11, 25.61, 21.07.



2b-I

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.05 (m, 4H), 4.51 – 4.26 (m, 1H), 3.27 (dd, *J* = 14.2, 7.0 Hz, 1H), 3.04 (dd, *J* = 14.0, 7.7 Hz, 1H), 2.34 (s, 4H), 1.91 (d, *J* = 6.7 Hz, 3H).

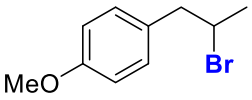
^{13}C NMR (100 MHz, $CDCl_3$) δ 136.62, 136.35, 129.12, 128.81, 49.08, 28.91, 28.00, 21.11.



2c-Cl

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.19 (h, *J* = 6.7 Hz, 1H), 3.80 (s, 3H), 3.04 (dd, *J* = 14.0, 7.0 Hz, 1H), 2.92 (dd, *J* = 14.0, 6.8 Hz, 1H), 1.50 (d, *J* = 6.5 Hz, 3H).

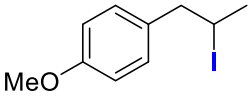
^{13}C NMR (100 MHz, $CDCl_3$) δ 158.45, 130.30, 130.05, 113.78, 58.81, 55.19, 45.77, 24.51.



2c-Br

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.26 (h, *J* = 6.8 Hz, 1H), 3.80 (s, 3H), 3.17 (dd, *J* = 14.1, 6.9 Hz, 1H), 3.01 (dd, *J* = 14.1, 7.2 Hz, 1H), 1.69 (d, *J* = 6.6 Hz, 3H).

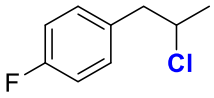
^{13}C NMR (100 MHz, $CDCl_3$) δ 158.48, 130.63, 130.19, 113.81, 55.22, 51.04, 46.63, 25.52.



2c-I

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.3 Hz, 2H), 4.31 (h, *J* = 7.1 Hz, 1H), 3.80 (s, 3H), 3.24 (dd, *J* = 14.2, 7.1 Hz, 1H), 3.01 (dd, *J* = 14.2, 7.5 Hz, 1H), 1.90 (d, *J* = 6.8 Hz, 3H).

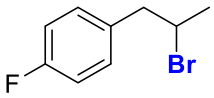
^{13}C NMR (100 MHz, $CDCl_3$) δ 158.50, 131.91, 130.02, 113.87, 55.29, 48.68, 29.39, 27.98.



2d-Cl

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (dd, J = 8.6, 5.4 Hz, 2H), 7.00 (t, J = 8.7 Hz, 2H), 4.26 – 4.11 (m, 1H), 3.03 (dd, J = 14.1, 7.3 Hz, 1H), 2.95 (dd, J = 14.0, 6.4 Hz, 1H), 1.51 (d, J = 6.6 Hz, 3H).

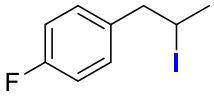
^{13}C NMR (100 MHz, $CDCl_3$) δ 161.81 (d, J = 245.0 Hz), 133.59 (d, J = 2.8 Hz), 130.79 (d, J = 8.0 Hz), 115.20 (d, J = 21.1 Hz), 58.45, 45.69, 24.61.



2d-Br

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (dd, J = 8.5, 5.5 Hz, 2H), 7.00 (t, J = 8.7 Hz, 2H), 4.26 (h, J = 6.8 Hz, 1H), 3.17 (dd, J = 14.2, 7.2 Hz, 1H), 3.05 (dd, J = 14.2, 6.8 Hz, 1H), 1.70 (d, J = 6.6 Hz, 3H).

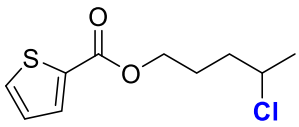
^{13}C NMR (100 MHz, $CDCl_3$) δ 161.84 (d, J = 245.1 Hz), 134.16 (d, J = 2.7 Hz), 130.67 (d, J = 7.8 Hz), 115.24 (d, J = 21.3 Hz), 50.44, 46.53, 25.62.



2d-I

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (dd, J = 8.5, 5.5 Hz, 2H), 7.00 (t, J = 8.7 Hz, 2H), 4.29 (h, J = 7.0 Hz, 1H), 3.23 (dd, J = 14.2, 7.5 Hz, 1H), 3.03 (dd, J = 14.2, 7.1 Hz, 1H), 1.90 (d, J = 6.8 Hz, 3H).

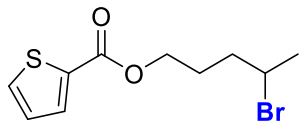
^{13}C NMR (100 MHz, $CDCl_3$) δ 161.76 (d, J = 245.3 Hz), 135.33 (d, J = 2.7 Hz), 130.42 (d, J = 7.8 Hz), 115.26 (d, J = 21.1 Hz), 48.46, 28.45, 28.02.



2e-Cl

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 3.7 Hz, 1H), 7.55 (d, J = 4.9 Hz, 1H), 7.10 (t, J = 4.3 Hz, 1H), 4.33 (td, J = 6.0, 2.8 Hz, 2H), 4.10 (ddd, J = 11.6, 8.9, 5.9 Hz, 1H), 2.00 (tdt, J = 10.6, 7.0, 4.1 Hz, 1H), 1.95 – 1.77 (m, 3H), 1.54 (d, J = 6.6 Hz, 3H).

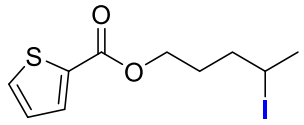
^{13}C NMR (100 MHz, $CDCl_3$) δ 162.18, 133.79, 133.39, 132.33, 127.74, 64.47, 58.06, 36.76, 26.00, 25.38.



2e-Br

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 3.7 Hz, 1H), 7.55 (d, J = 5.0 Hz, 1H), 7.12 – 7.04 (m, 1H), 4.32 (td, J = 5.8, 2.2 Hz, 2H), 4.18 (h, J = 6.5 Hz, 1H), 2.07 – 1.85 (m, 4H), 1.73 (d, J = 6.6 Hz, 3H).

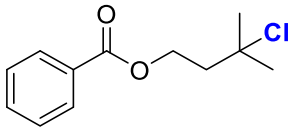
^{13}C NMR (100 MHz, $CDCl_3$) δ 162.11, 133.72, 133.35, 132.32, 127.71, 64.27, 50.67, 37.50, 27.08, 26.44.



2e-I

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, J = 3.8, 1.3 Hz, 1H), 7.55 (dd, J = 5.0, 1.3 Hz, 1H), 7.10 (dd, J = 5.0, 3.8 Hz, 1H), 4.31 (td, J = 6.1, 1.4 Hz, 2H), 4.23 (dddd, J = 13.6, 11.8, 6.1, 4.1 Hz, 1H), 2.03 – 1.72 (m, 7H).

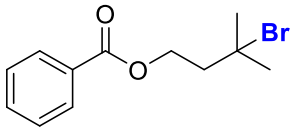
^{13}C NMR (100 MHz, $CDCl_3$) δ 162.10, 133.70, 133.36, 132.33, 127.71, 64.05, 39.23, 29.02, 28.96, 28.91.



2f-Cl

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.9 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.5 Hz, 2H), 4.57 (t, J = 6.7 Hz, 2H), 2.31 – 2.20 (m, 2H), 1.68 (s, 6H).

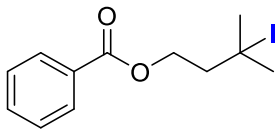
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.42, 132.95, 130.11, 129.51, 128.35, 68.41, 62.01, 44.04, 32.89.



2f-Br

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.9 Hz, 2H), 7.56 (t, J = 7.3 Hz, 1H), 7.44 (t, J = 7.4 Hz, 2H), 4.59 (t, J = 6.7 Hz, 2H), 2.31 (t, J = 6.7 Hz, 2H), 1.86 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.45, 132.99, 130.12, 129.55, 128.38, 64.22, 63.08, 45.46, 34.73.



2f-I

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 7.9 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.7 Hz, 2H), 4.56 (t, J = 6.7 Hz, 2H), 2.18 (t, J = 6.8 Hz, 2H), 2.03 (s, 7H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.40, 132.98, 130.05, 129.54, 128.36, 65.04, 48.16, 46.21, 38.50.

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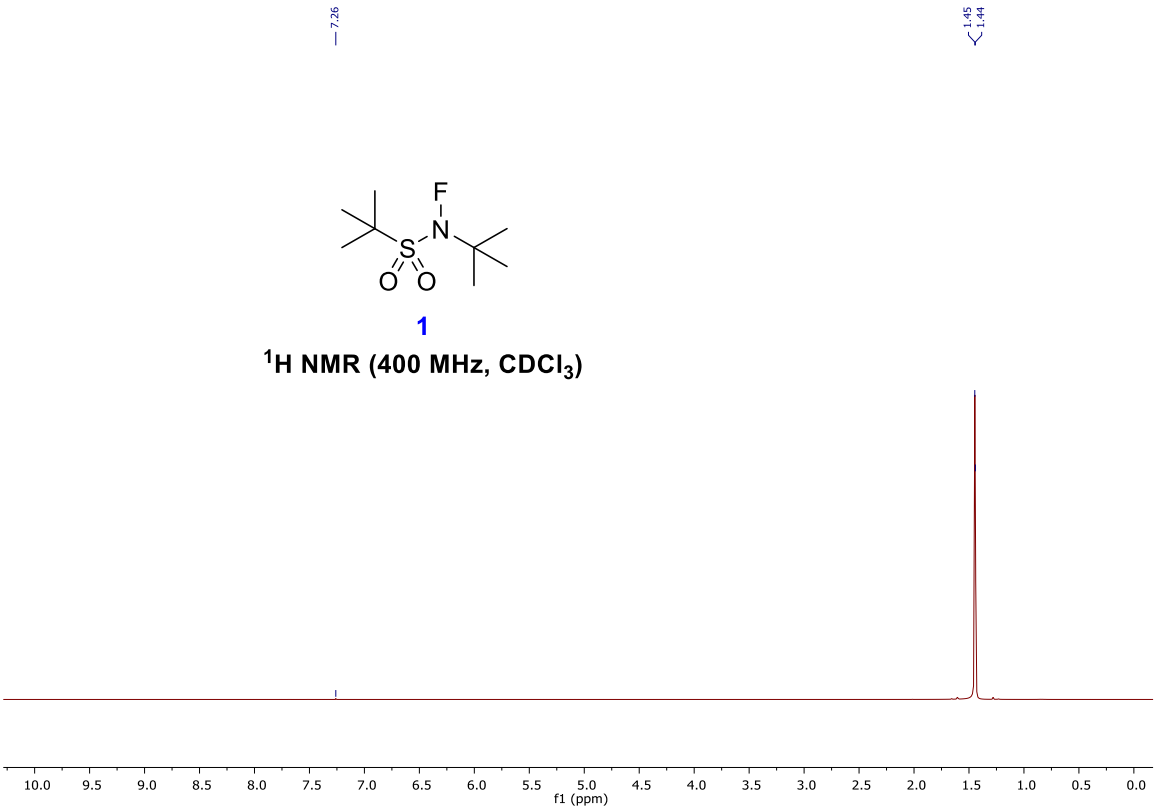
APPENDIX A

NMR SPECTRA OF COMPOUNDS PREPARED IN CHAPTER 2

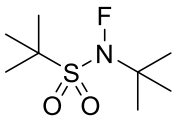
A.1 Spectral data of NFBB



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

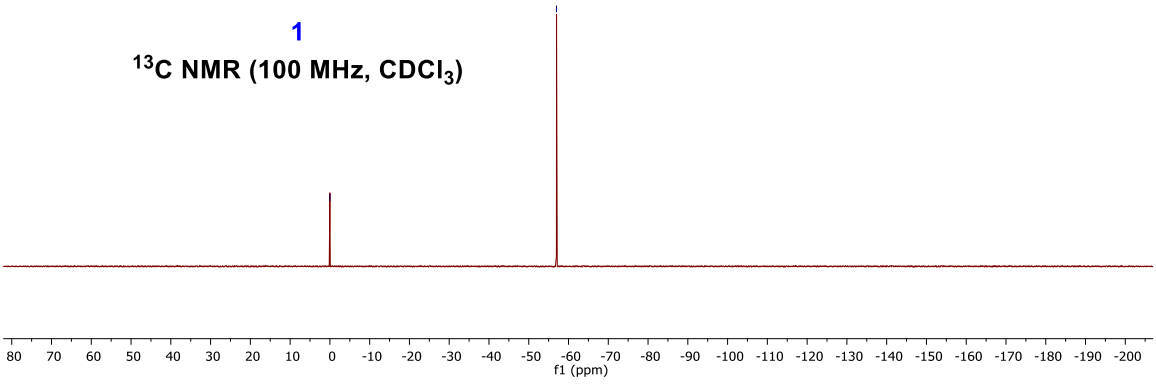
1

^{19}F NMR (376 MHz, $CDCl_3$)

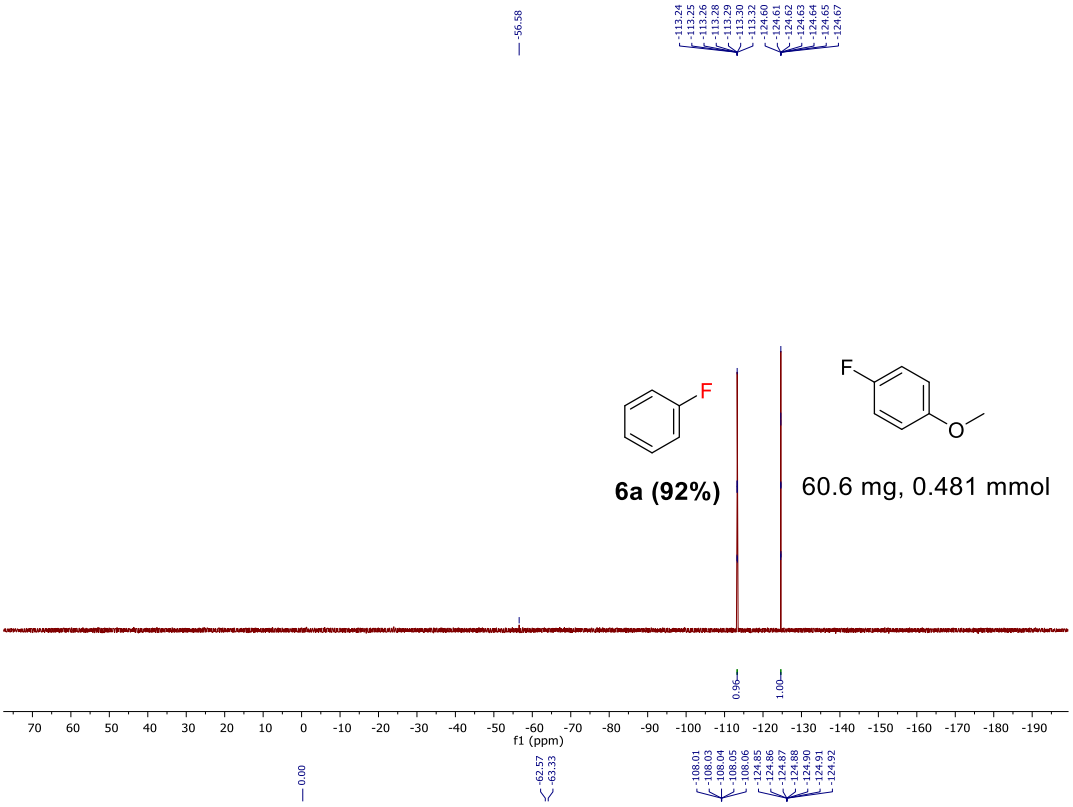


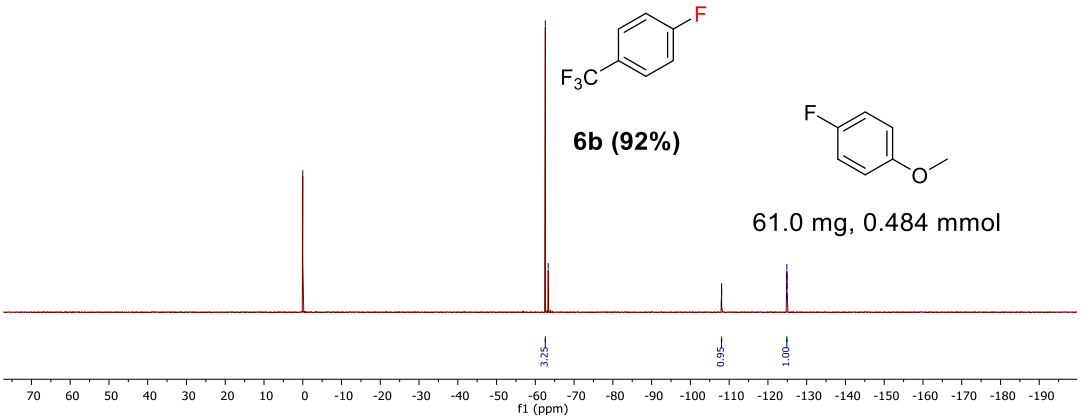
1

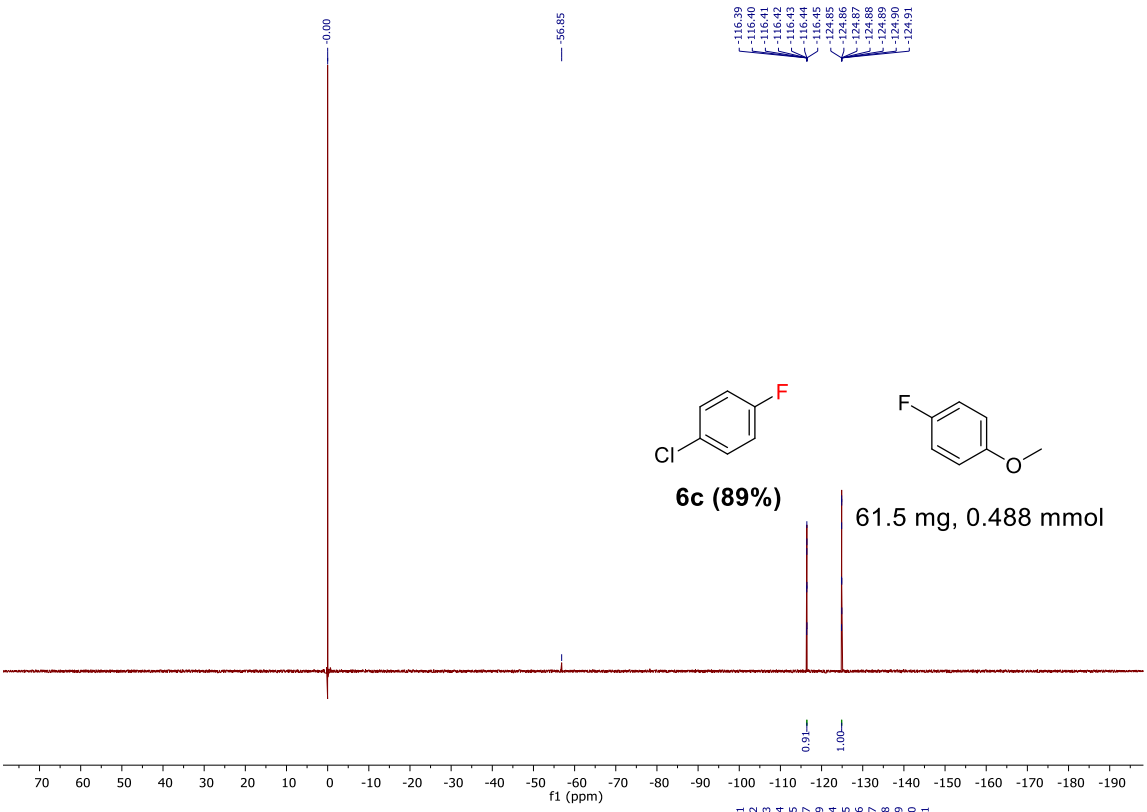
^{13}C NMR (100 MHz, $CDCl_3$)

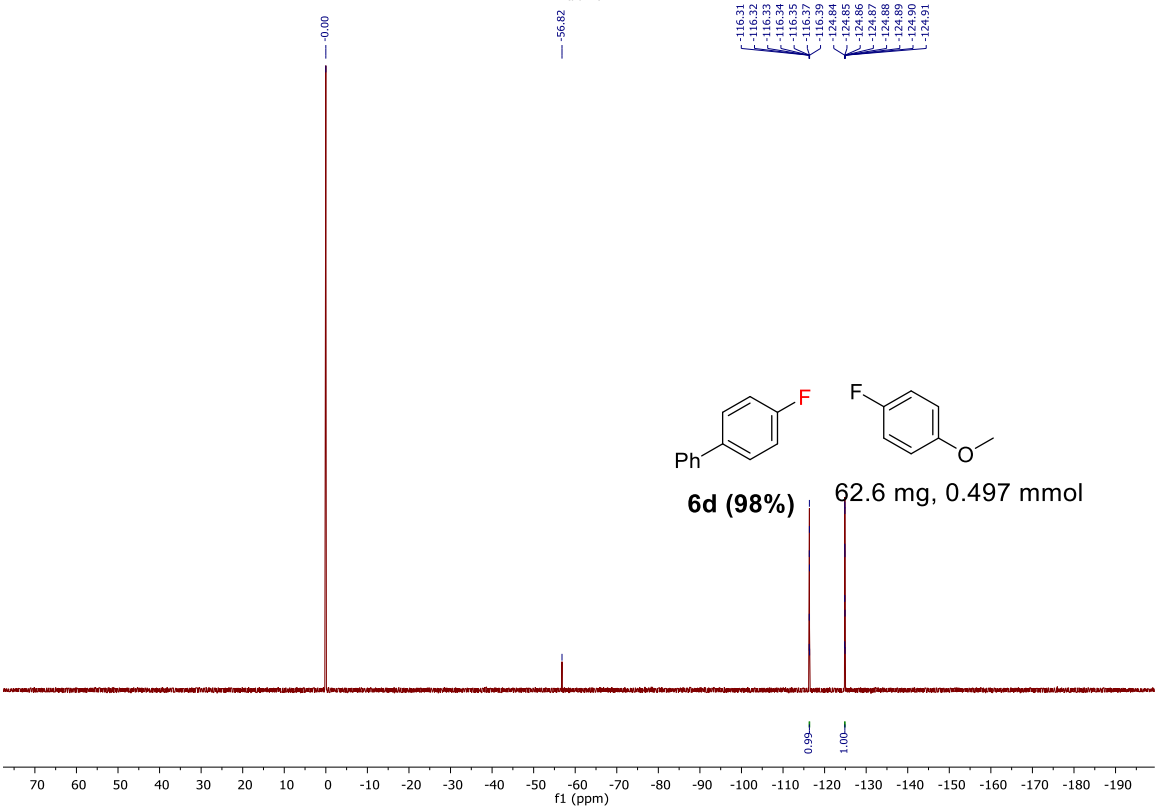


A.2 ^{19}F NMR spectra for determination of fluorination yield with NFBB






-0.00
-56.85
-116.39
-116.40
-116.41
-116.42
-116.43
-116.44
-116.45
-124.85
-124.86
-124.87
-124.88
-124.89
-124.90
-124.91
F
Cl
F
O
6c (89%)
61.5 mg, 0.488 mmol
0.91
1.00
70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)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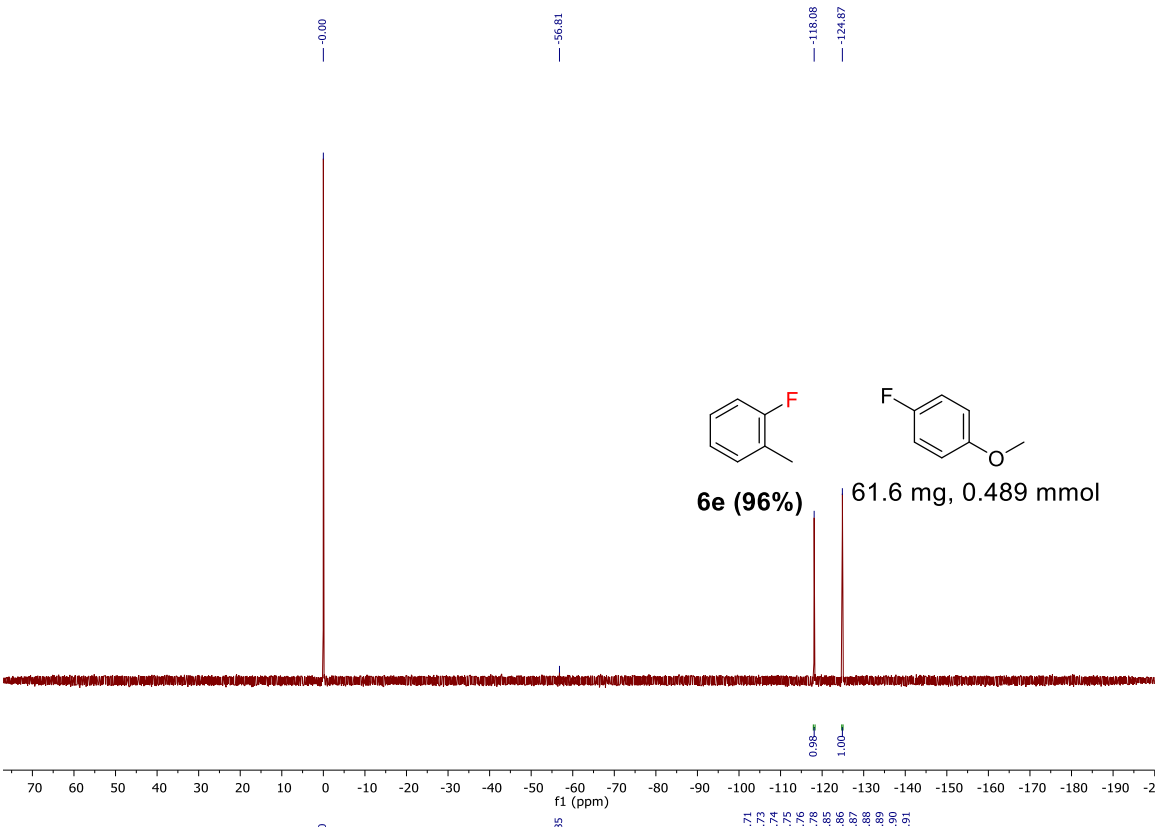
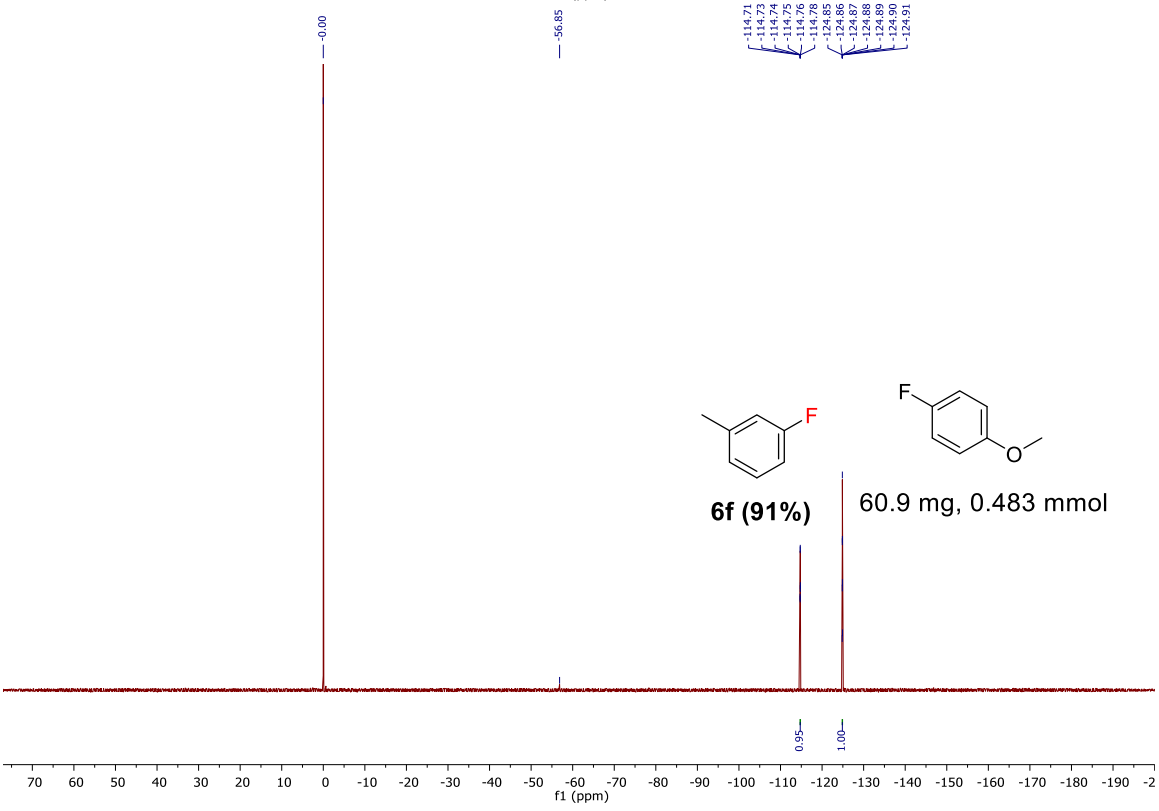
-56.82
-116.31
-116.32
-116.33
-116.34
-116.35
-116.37
-116.39
-124.84
-124.85
-124.86
-124.87
-124.88
-124.89
-124.90
-124.91
F
Ph
F
O
6d (98%)
62.6 mg, 0.497 mmol
0.99
1.00
70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)


-0.00
-56.81
-118.08
-124.87
F
F
O
6e (96%)
61.6 mg, 0.489 mmol
0.98
1.00
f1 (ppm)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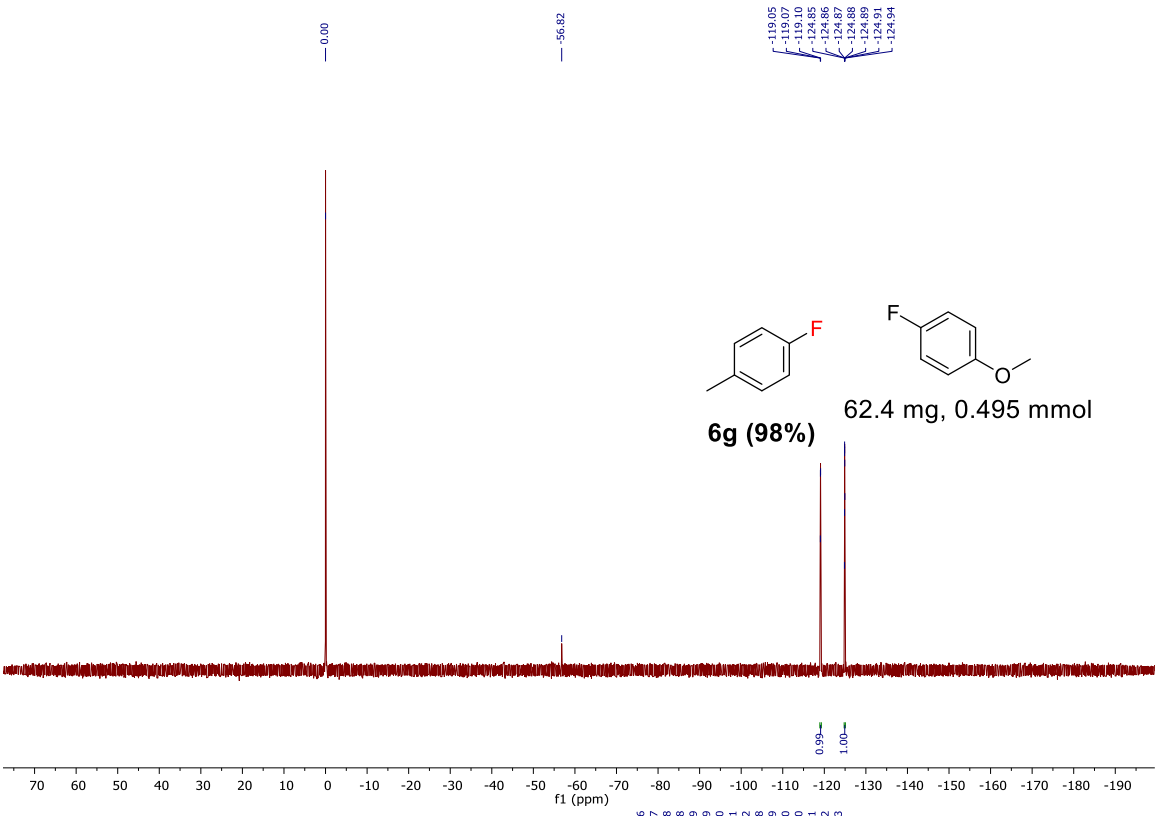
-56.85
-114.71
-114.73
-114.74
-114.75
-114.76
-114.78
-124.85
-124.86
-124.87
-124.88
-124.89
-124.90
-124.91
F
F
O
6f (91%)
60.9 mg, 0.483 mmol
0.95
1.00
f1 (ppm)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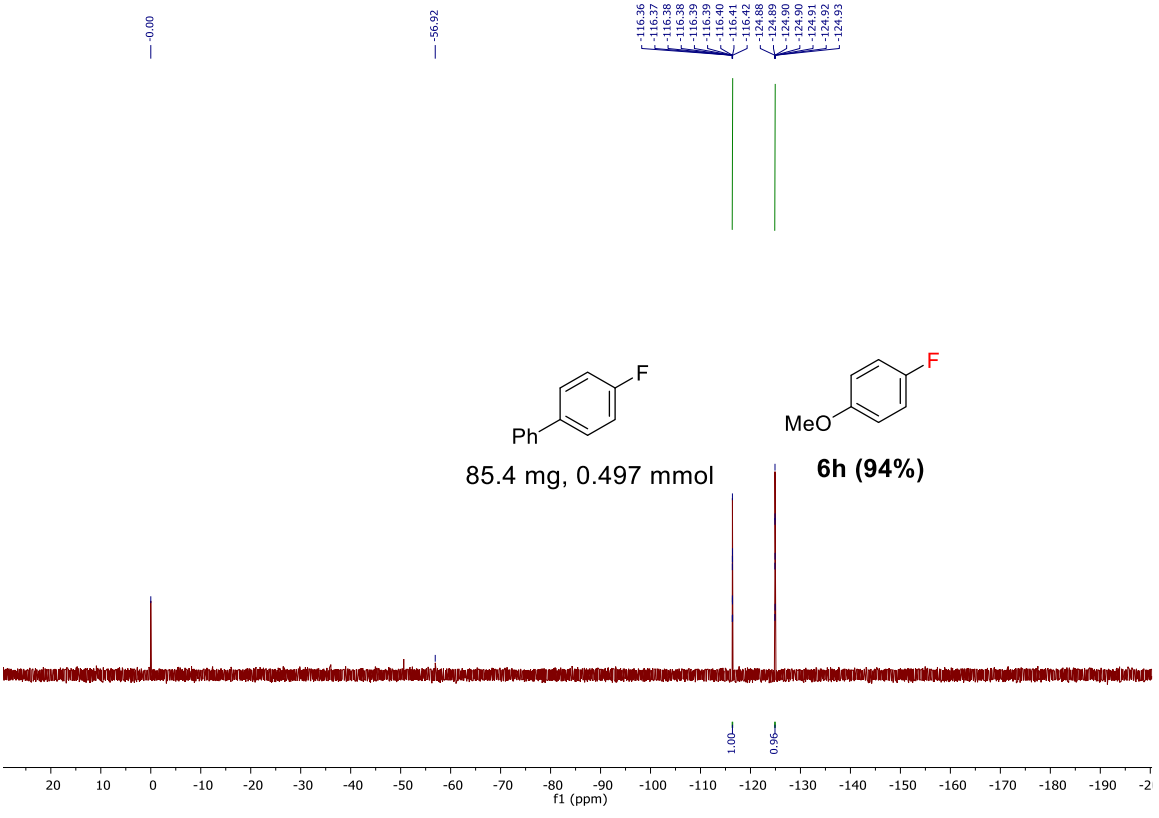
-56.82
-119.05
-119.07
-119.10
-124.85
-124.86
-124.87
-124.88
-124.89
-124.91
-124.94
F
F
O
62.4 mg, 0.495 mmol
6g (98%)
0.99
1.00
70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)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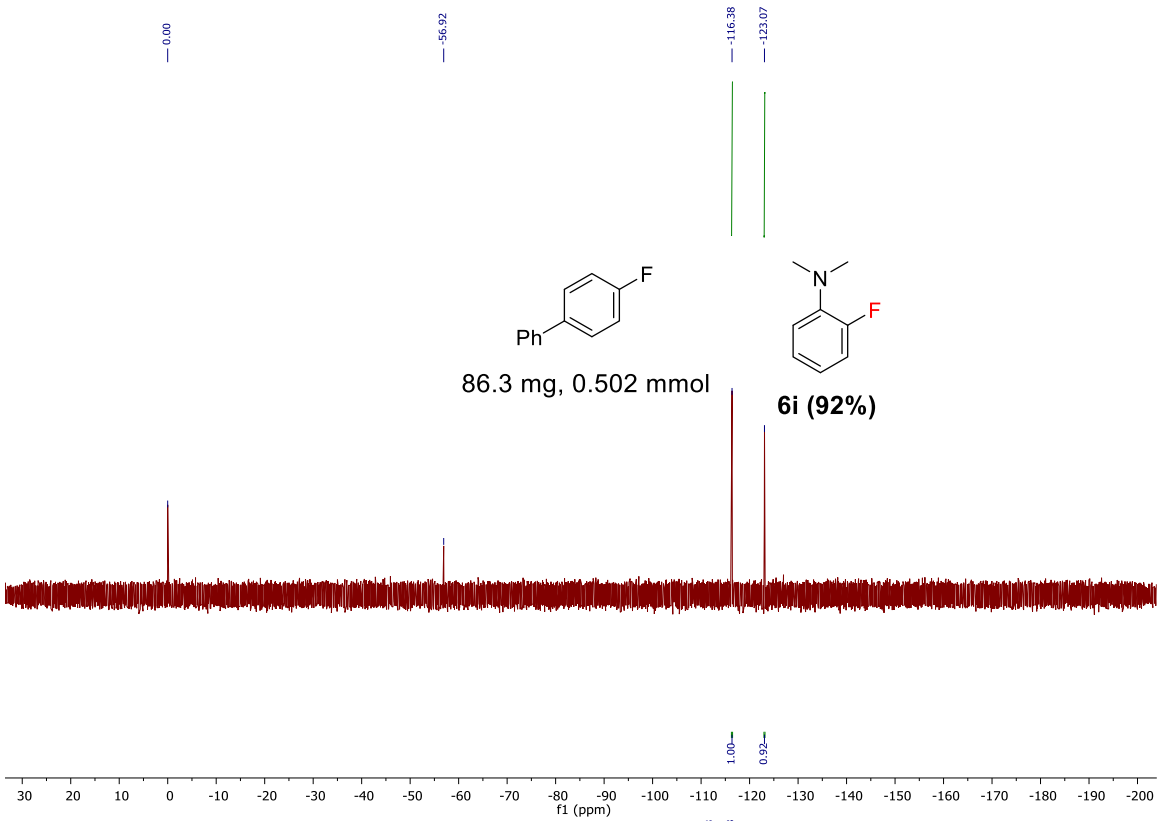
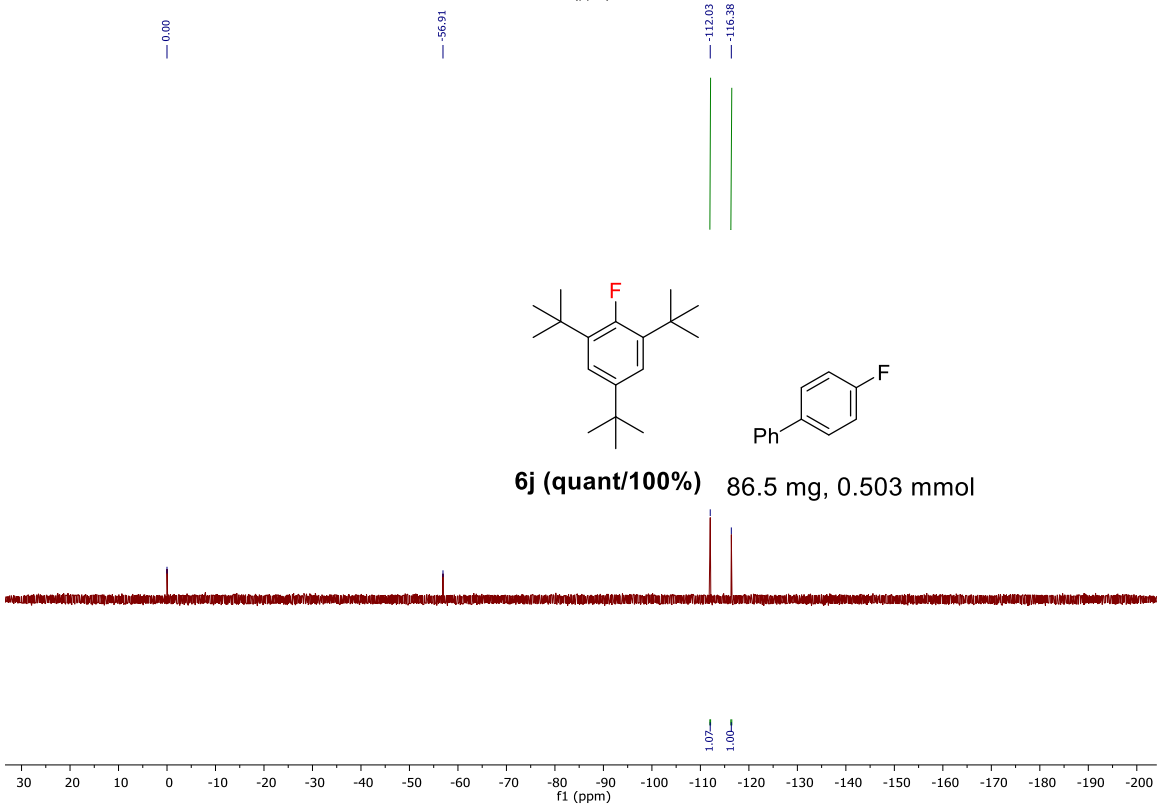
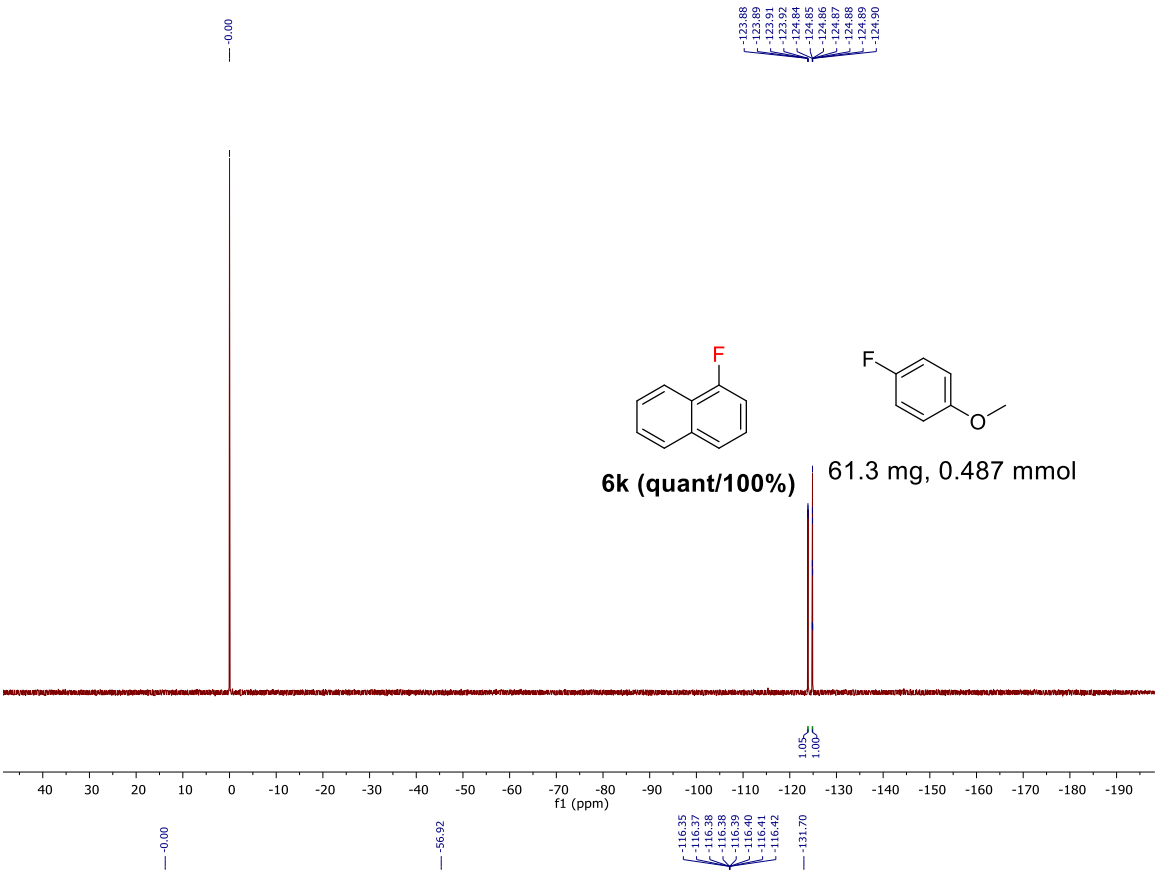
-116.38
-116.39
-116.39
-116.40
-116.41
-116.42
-124.88
-124.89
-124.90
-124.90
-124.91
-124.92
-124.93
F
Ph
MeO
F
85.4 mg, 0.497 mmol
6h (94%)
1.00
0.96
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)


0.00
-56.92
-116.38
-123.07
F
Ph
N
F
86.3 mg, 0.502 mmol
6i (92%)
1.00
0.92
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)


0.00
-56.91
-112.03
-116.38
F
F
Ph
6j (quant/100%)
86.5 mg, 0.503 mmol
1.07
1.00
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)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-123.92
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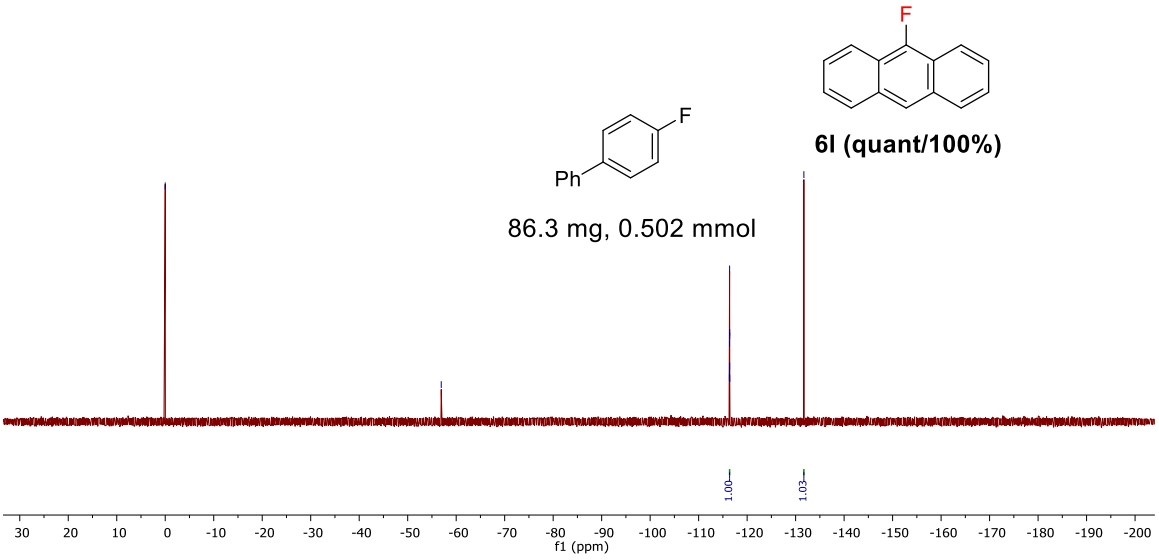
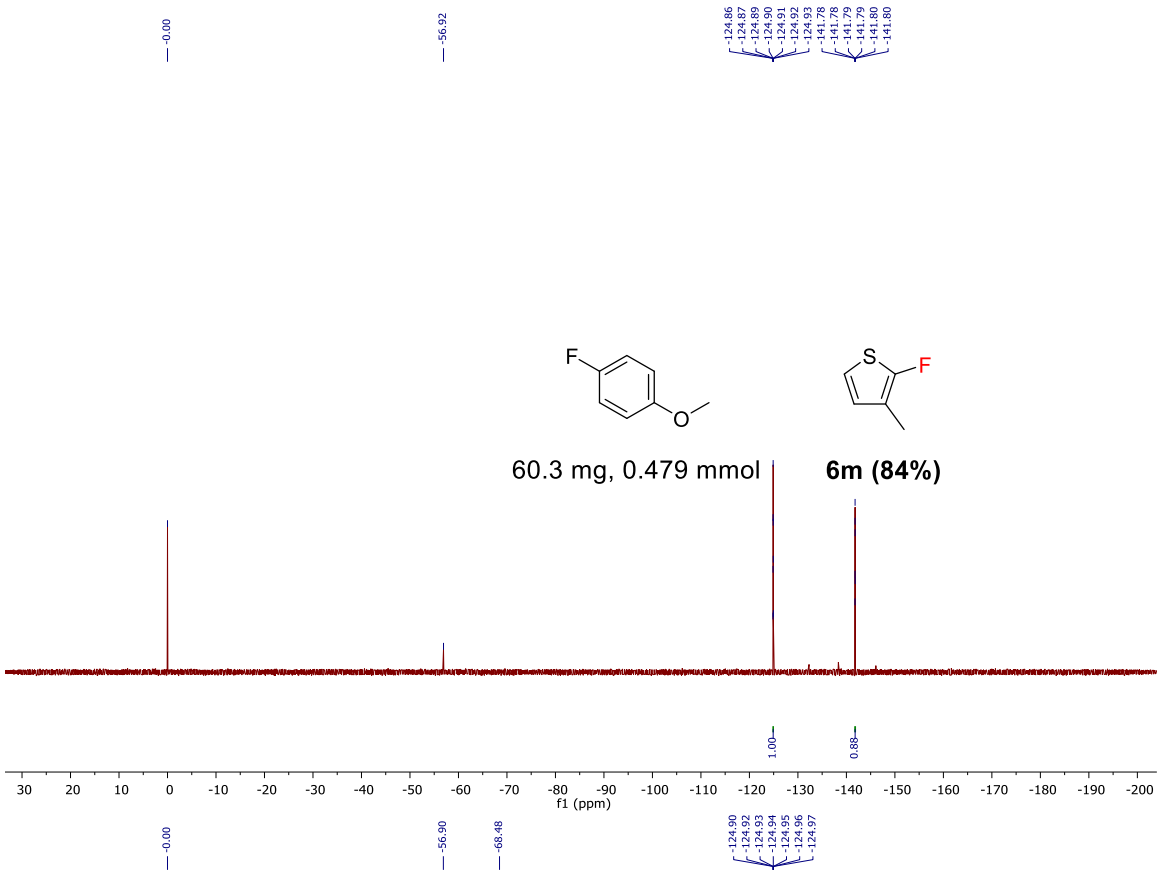
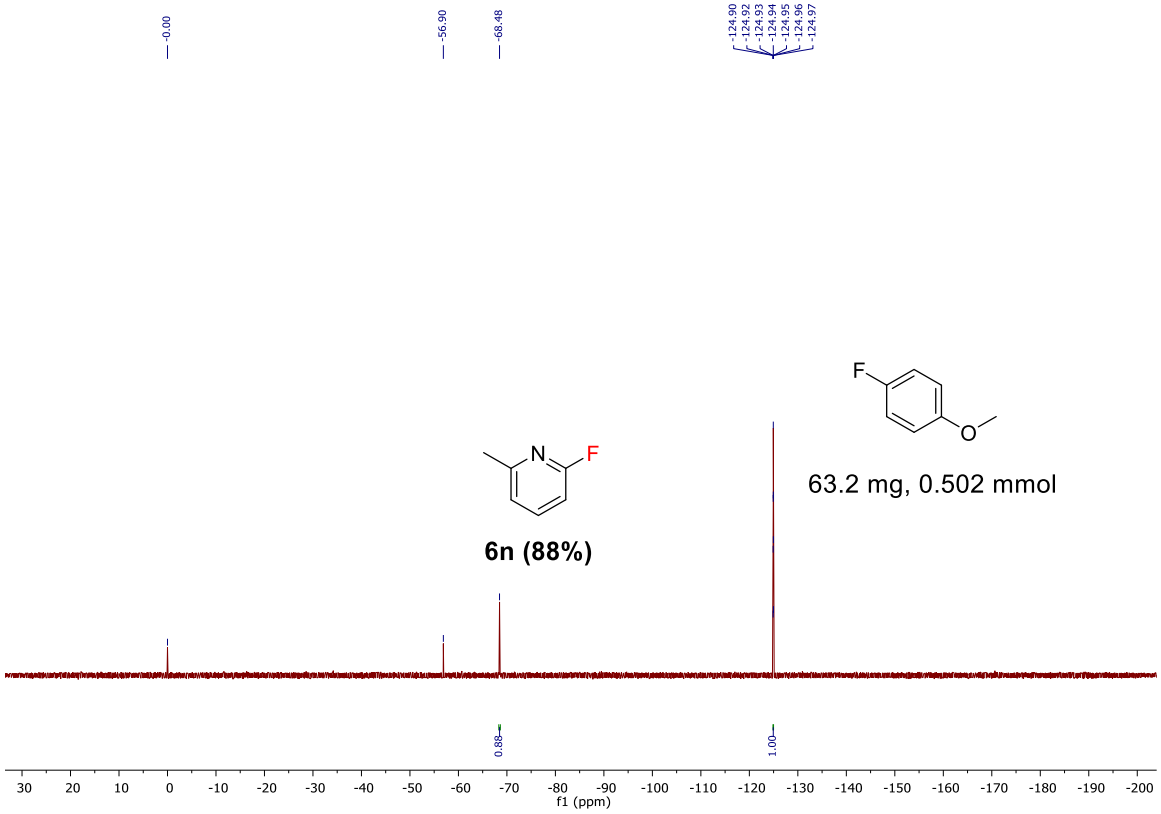
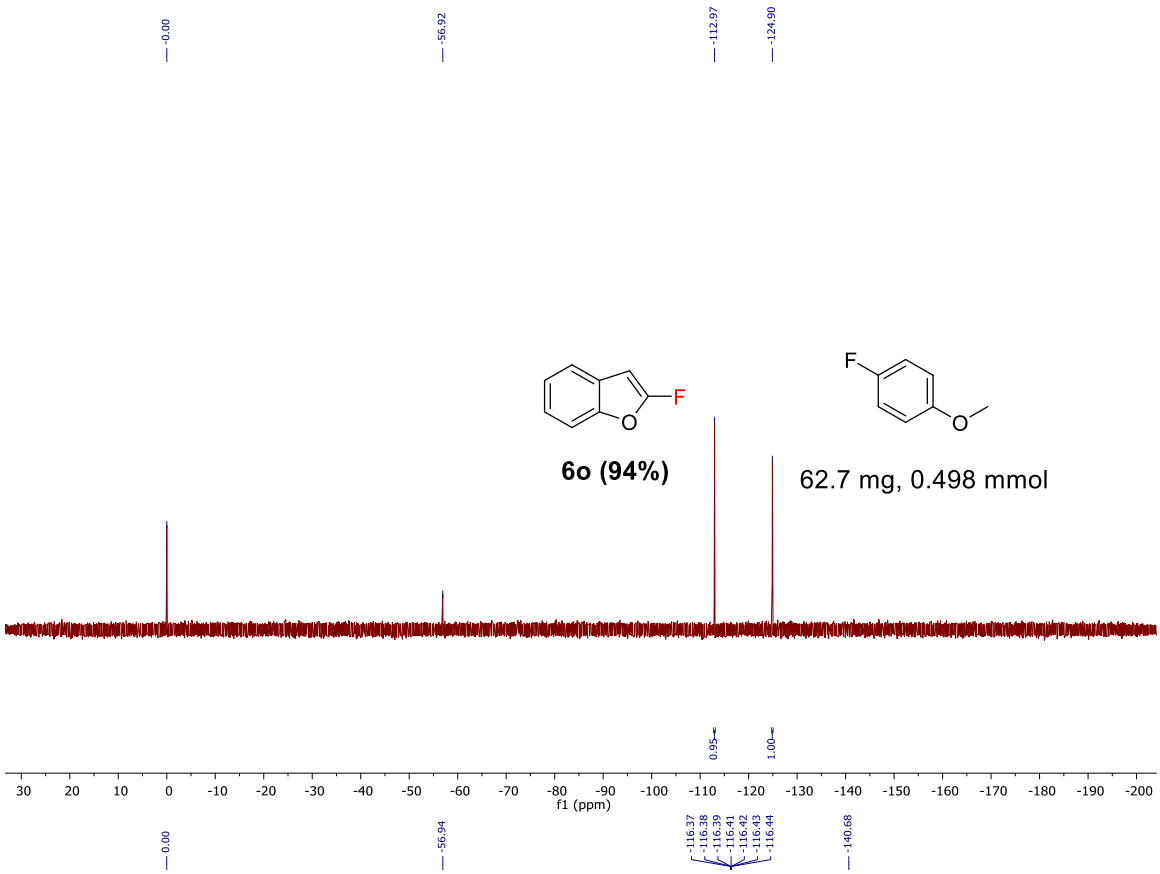
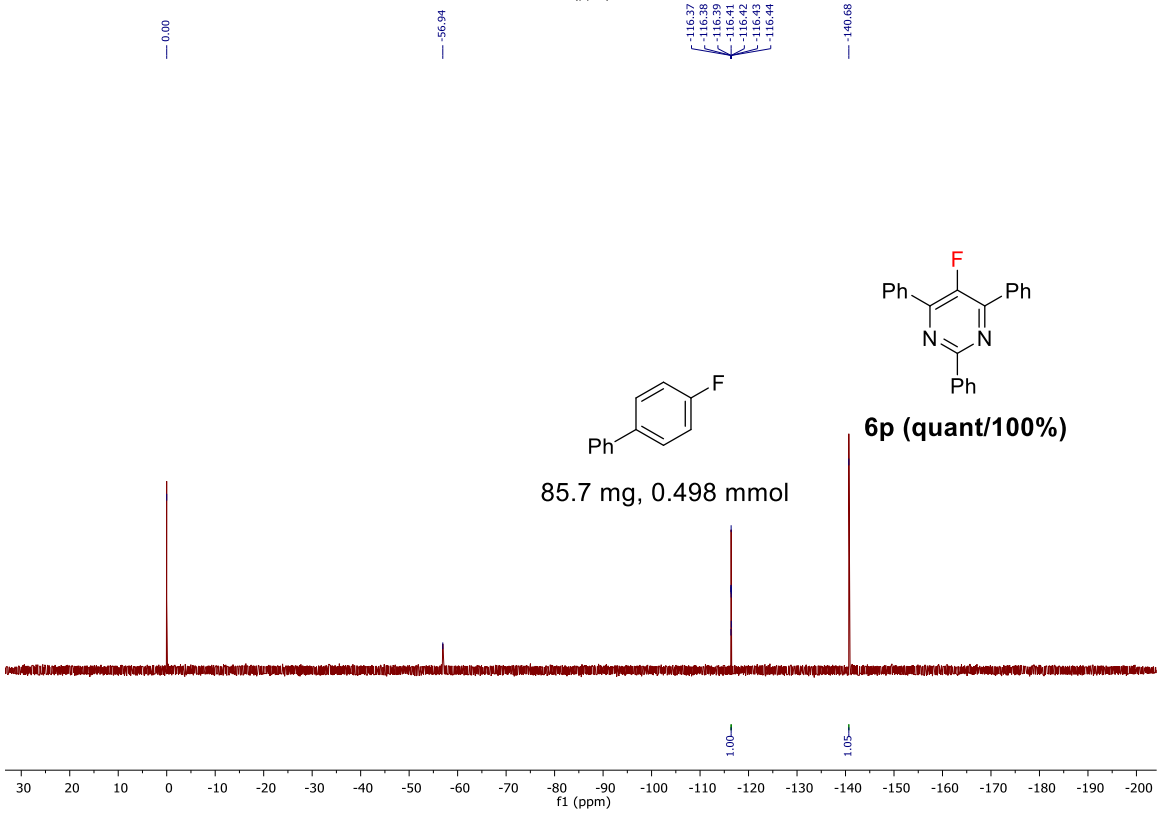
-124.85
-124.86
-124.87
-124.88
-124.89
-124.90
F
F
O
6k (quant/100%)
61.3 mg, 0.487 mmol
1.05
1.00
f1 (ppm)
-0.00
-56.92
-116.35
-116.37
-116.38
-116.39
-116.40
-116.41
-116.42
-131.70

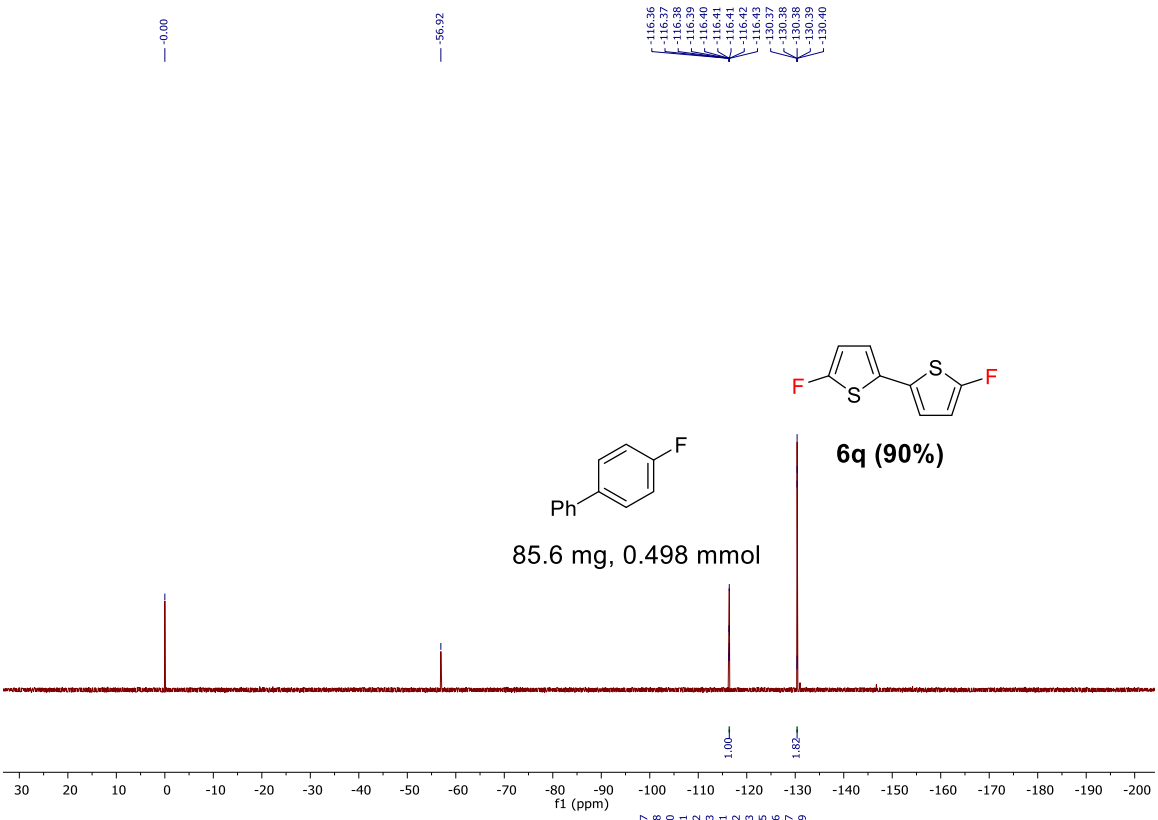

F
F
Ph
6l (quant/100%)
86.3 mg, 0.502 mmol
1.00
1.03
f1 (ppm)

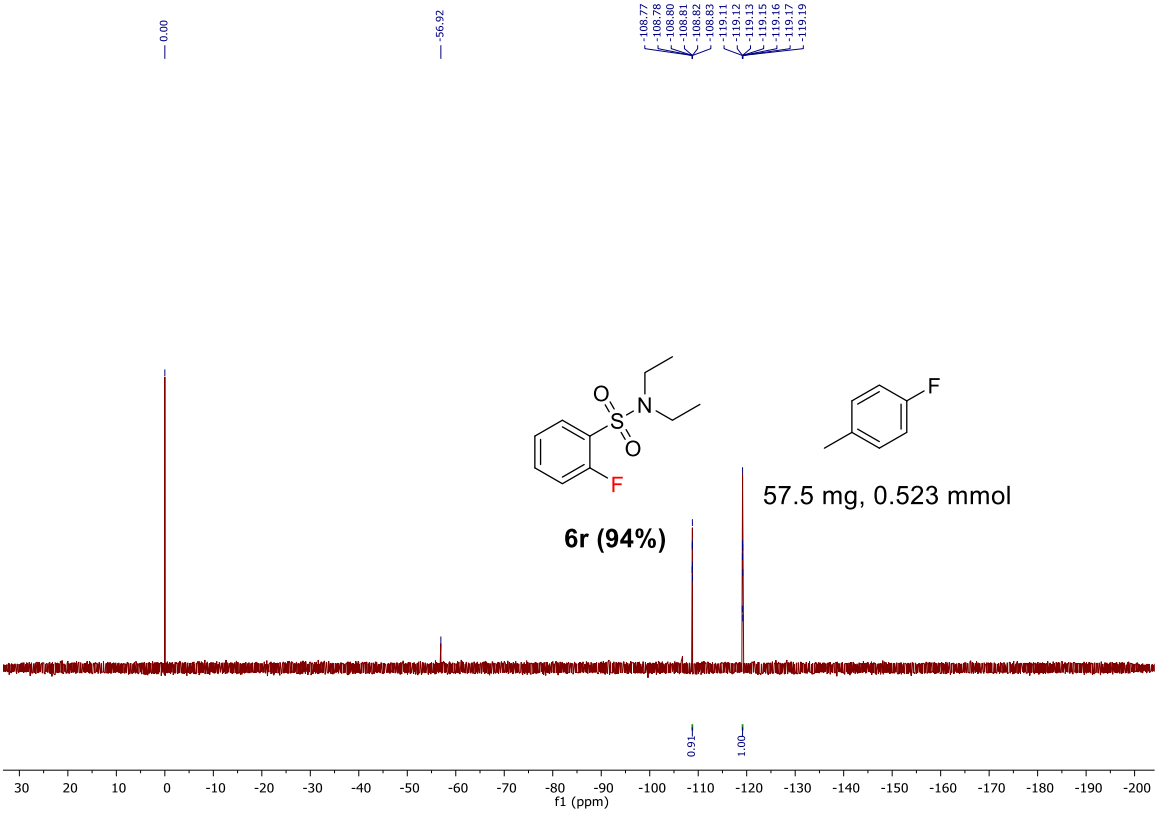

-0.00
-56.92
-124.86
-124.87
-124.89
-124.90
-124.91
-124.92
-124.93
-141.78
-141.78
-141.79
-141.79
-141.80
-141.80
F
O
S
F
60.3 mg, 0.479 mmol
6m (84%)
1.00
0.88
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

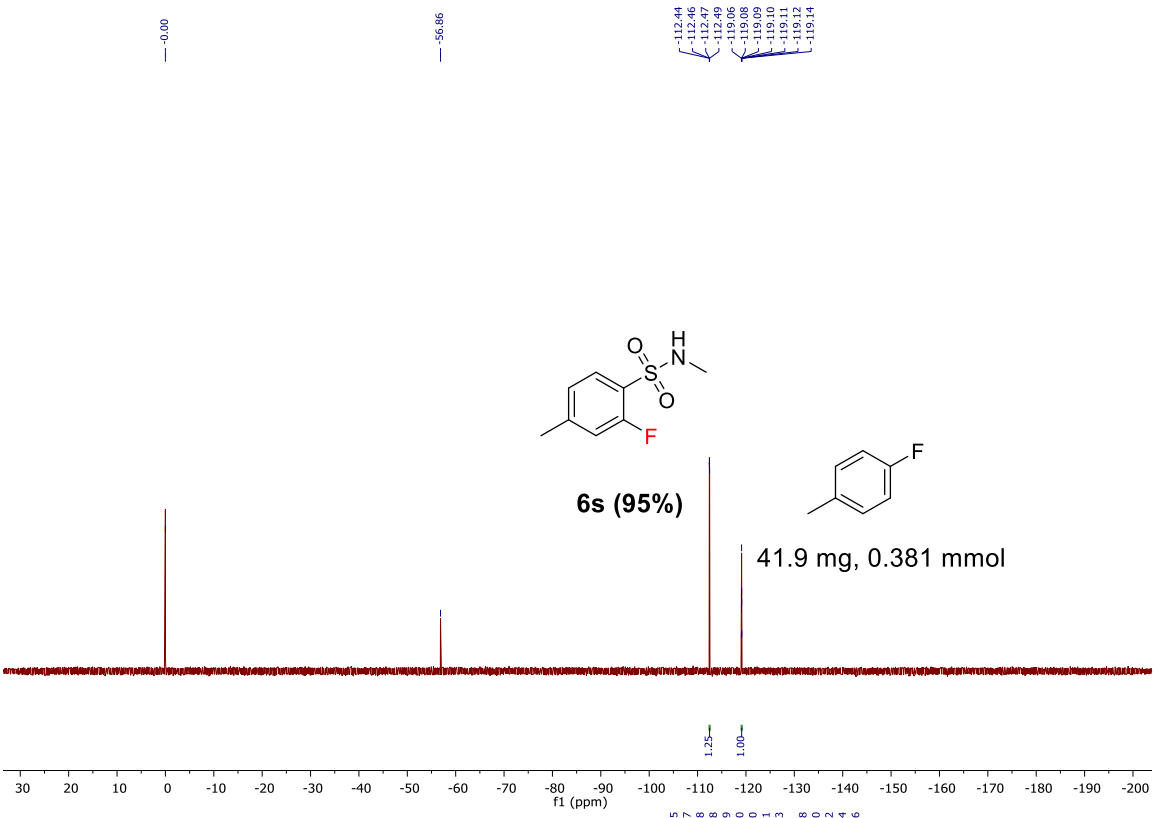

-0.00
-56.90
-68.48
-124.90
-124.92
-124.93
-124.94
-124.95
-124.96
-124.97
F
N
F
O
63.2 mg, 0.502 mmol
6n (88%)
0.88
1.00
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

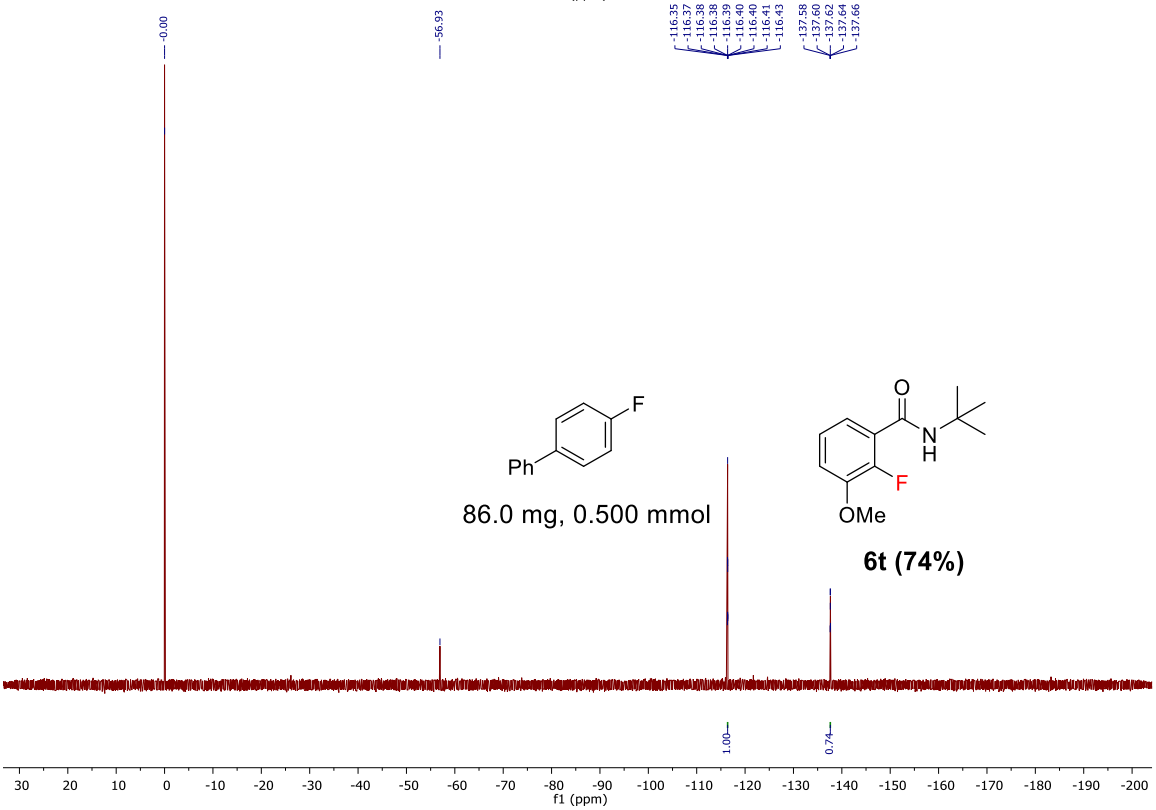

-0.00
-56.92
-112.97
-124.90
F
O
6o (94%)
F
O
62.7 mg, 0.498 mmol
0.95
1.00
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

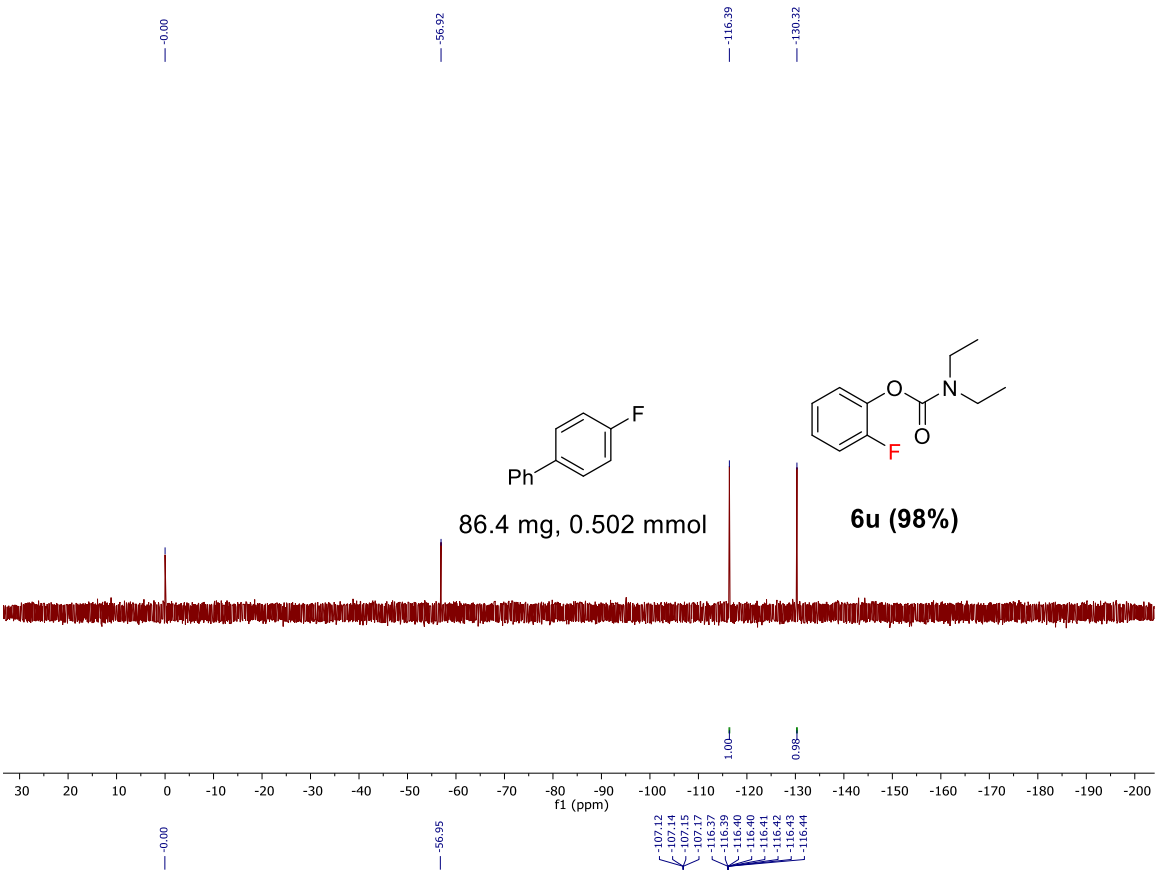

0.00
-56.94
-116.37
-116.38
-116.39
-116.41
-116.42
-116.43
-116.44
-140.68
F
Ph
Ph
N
N
Ph
6p (quant/100%)
F
Ph
85.7 mg, 0.498 mmol
1.00
1.05
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

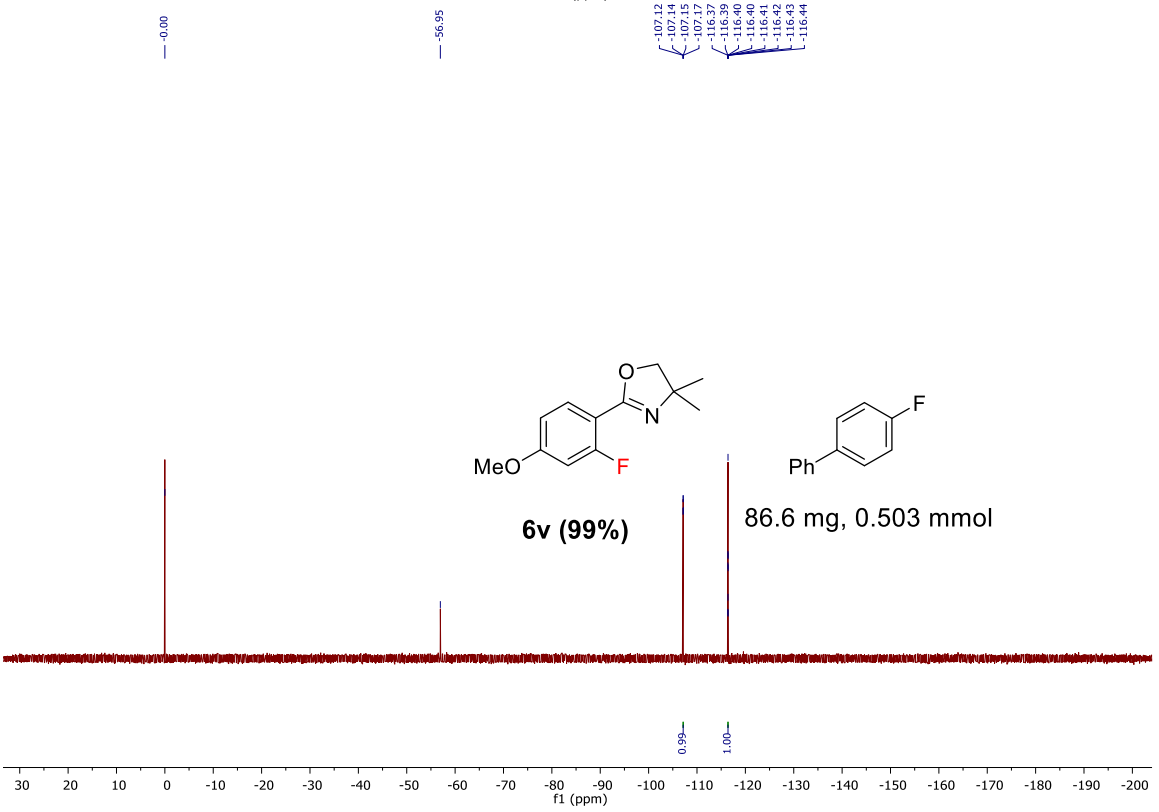

-0.00
-56.92
-116.36
-116.37
-116.38
-116.39
-116.40
-116.41
-116.41
-116.42
-116.43
-130.37
-130.38
-130.38
-130.39
-130.40
F
S
S
F
F
Ph
6q (90%)
85.6 mg, 0.498 mmol
1.00
1.82
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

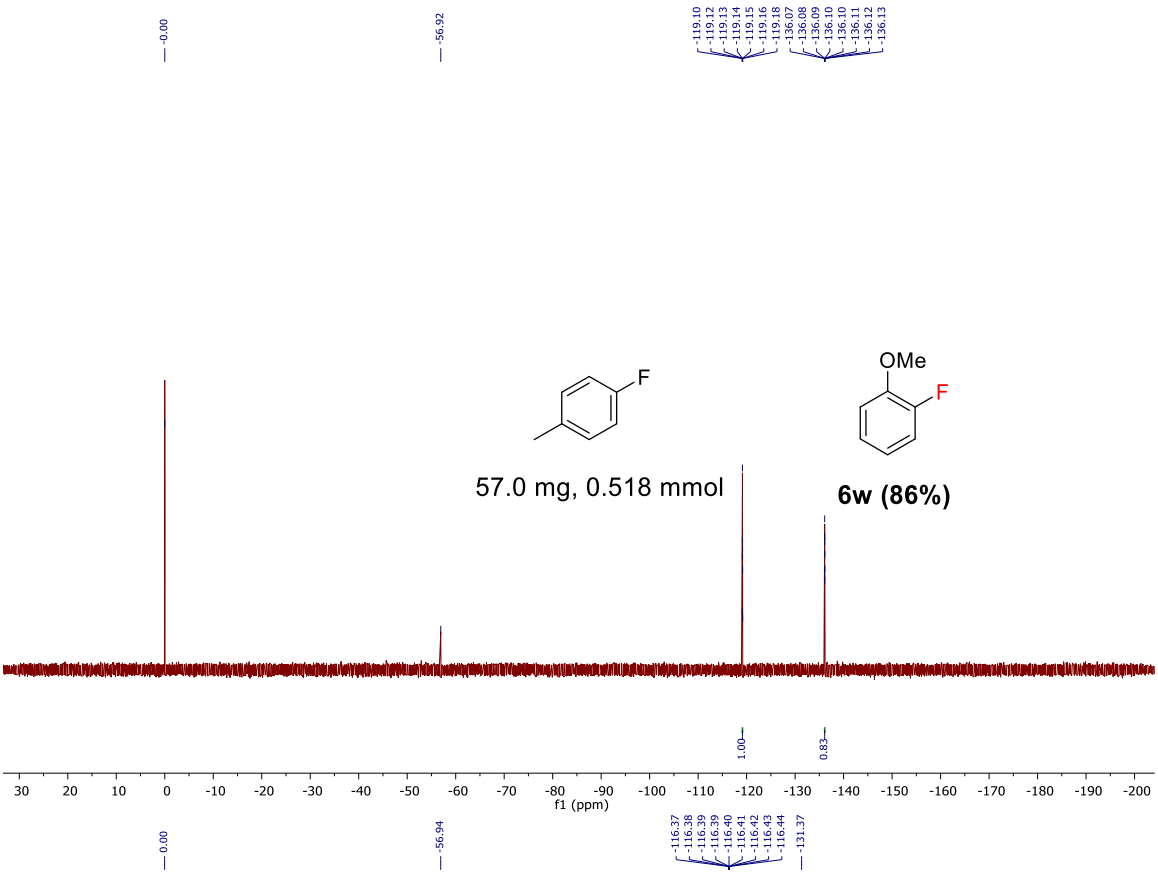

-0.00
-56.92
-108.77
-108.78
-108.80
-108.81
-108.82
-108.83
-119.11
-119.13
-119.15
-119.16
-119.17
-119.19
O
S
N
O
F
F
57.5 mg, 0.523 mmol
6r (94%)
0.91
1.00
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

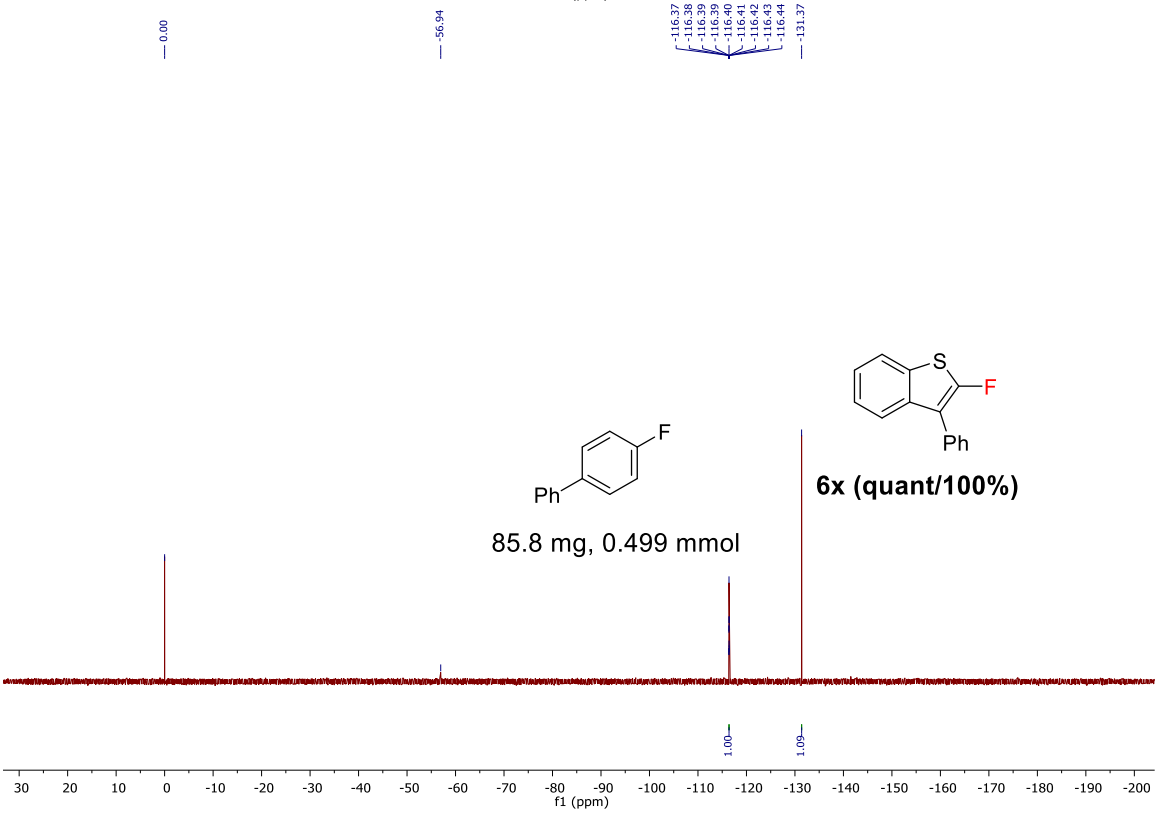

-0.00
-56.86
-112.44
-112.46
-112.47
-112.49
-119.06
-119.08
-119.09
-119.10
-119.11
-119.12
-119.14
6s (95%)
41.9 mg, 0.381 mmol
1.25
1.00
f1 (ppm)

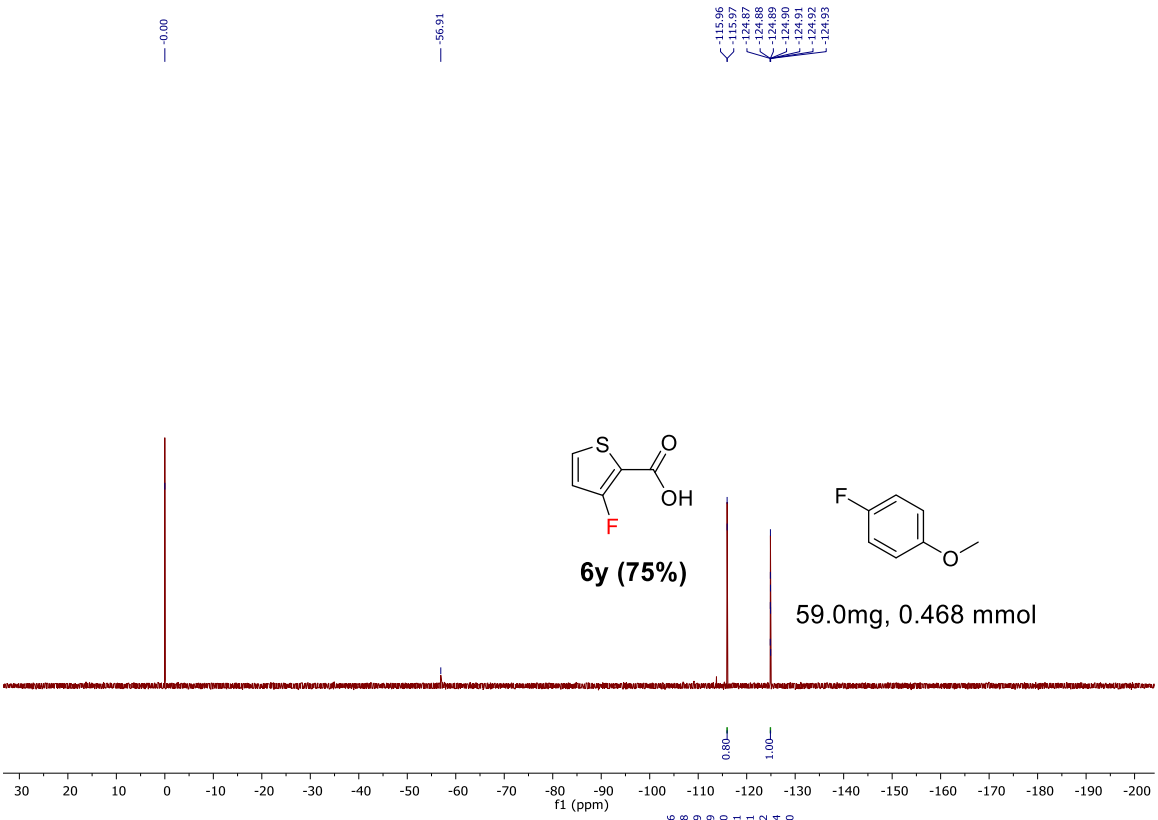

-0.00
-56.93
-116.35
-116.37
-116.38
-116.38
-116.39
-116.40
-116.40
-116.41
-116.43
-137.58
-137.60
-137.62
-137.64
-137.66
Ph
86.0 mg, 0.500 mmol
OMe
6t (74%)
1.00
0.74
f1 (ppm)

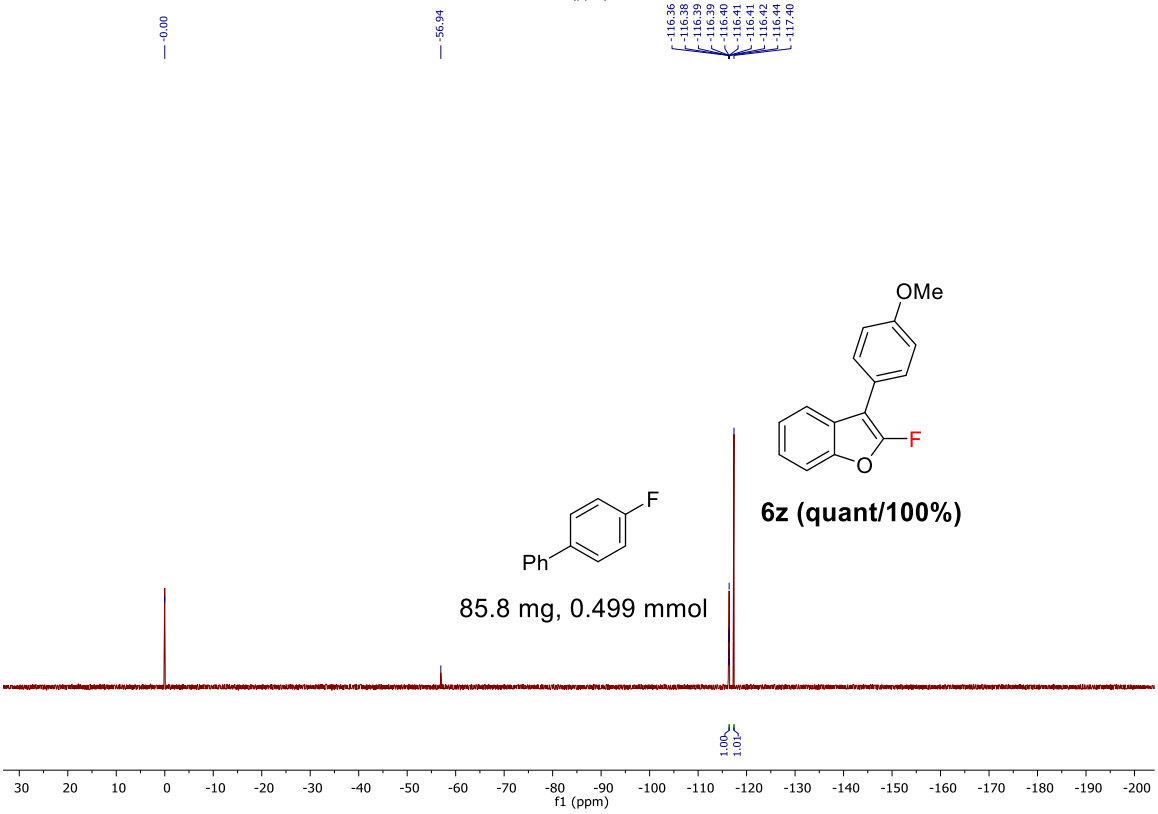

-0.00
-56.92
-116.39
-130.32
F
Ph
86.4 mg, 0.502 mmol
O
N
O
F
6u (98%)
1.00
0.98
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

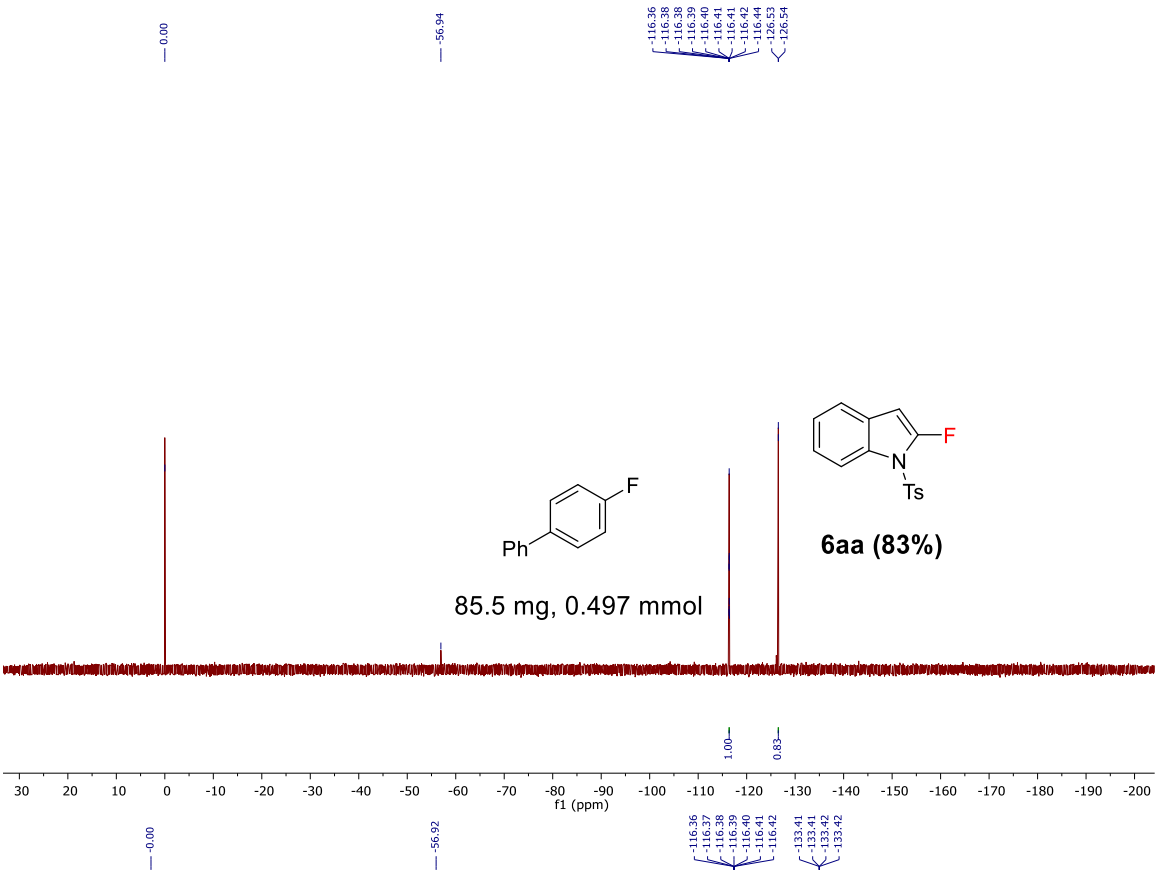

-0.00
-56.95
-107.12
-107.14
-107.15
-107.17
-116.37
-116.39
-116.40
-116.41
-116.42
-116.43
-116.44
O
N
MeO
F
6v (99%)
Ph
F
86.6 mg, 0.503 mmol
0.99
1.00
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

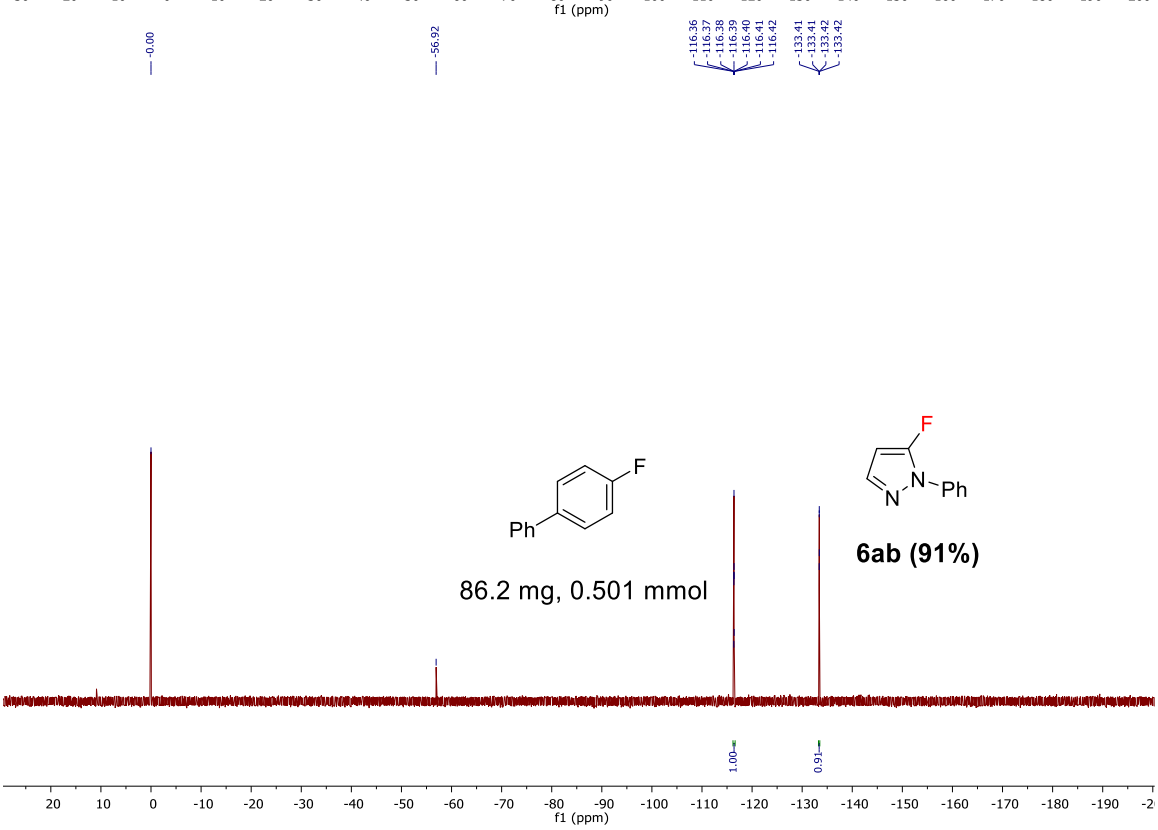

-0.00
-56.92
-119.10
-119.12
-119.13
-119.14
-119.15
-119.16
-119.18
-136.07
-136.08
-136.09
-136.10
-136.10
-136.11
-136.12
-136.13
F
OMe
F
57.0 mg, 0.518 mmol
6w (86%)
1.00
0.83
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

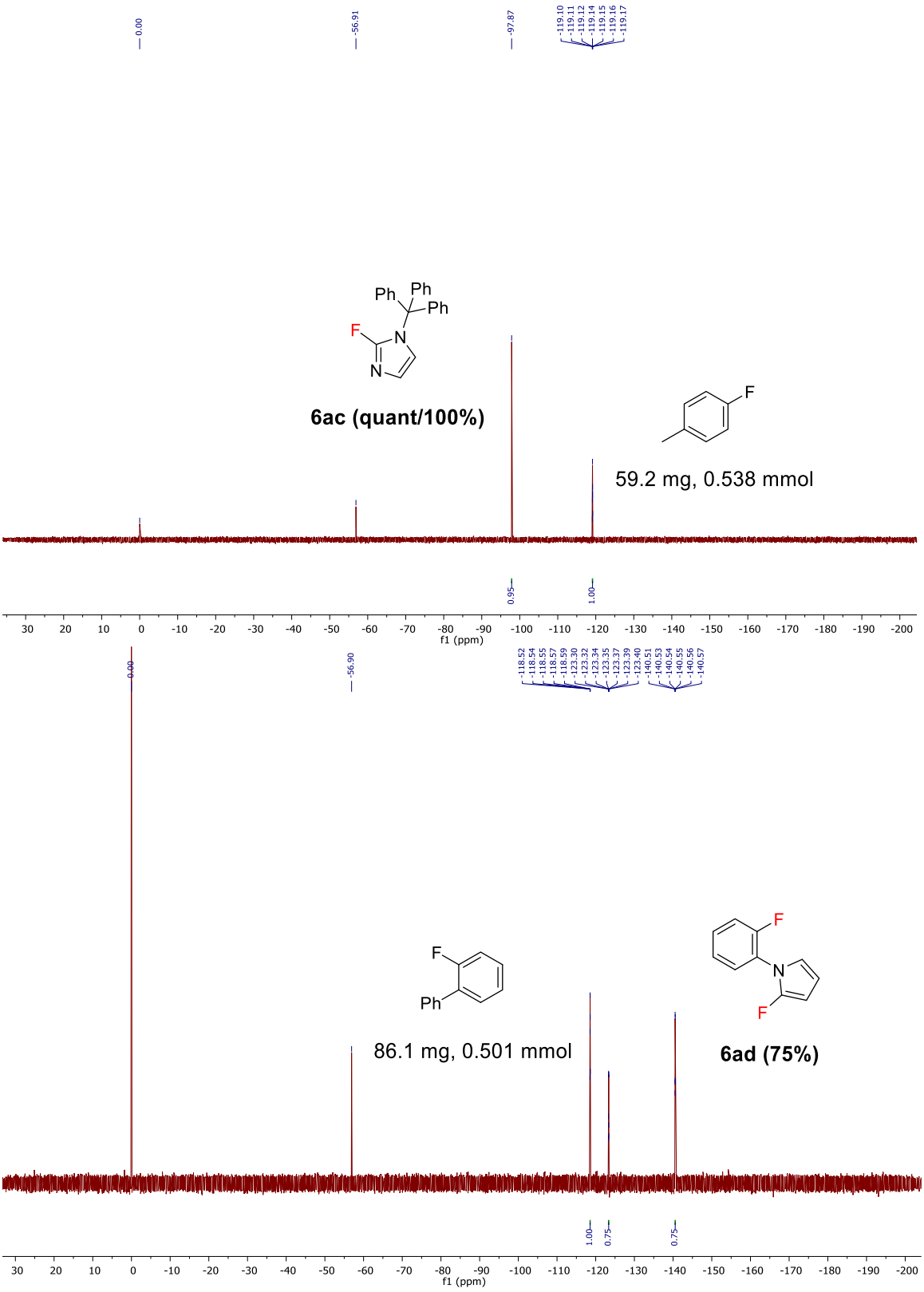

-0.00
-56.94
-116.37
-116.38
-116.39
-116.39
-116.40
-116.41
-116.42
-116.43
-116.44
-131.37
S
F
Ph
F
Ph
6x (quant/100%)
85.8 mg, 0.499 mmol
1.00
1.09
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

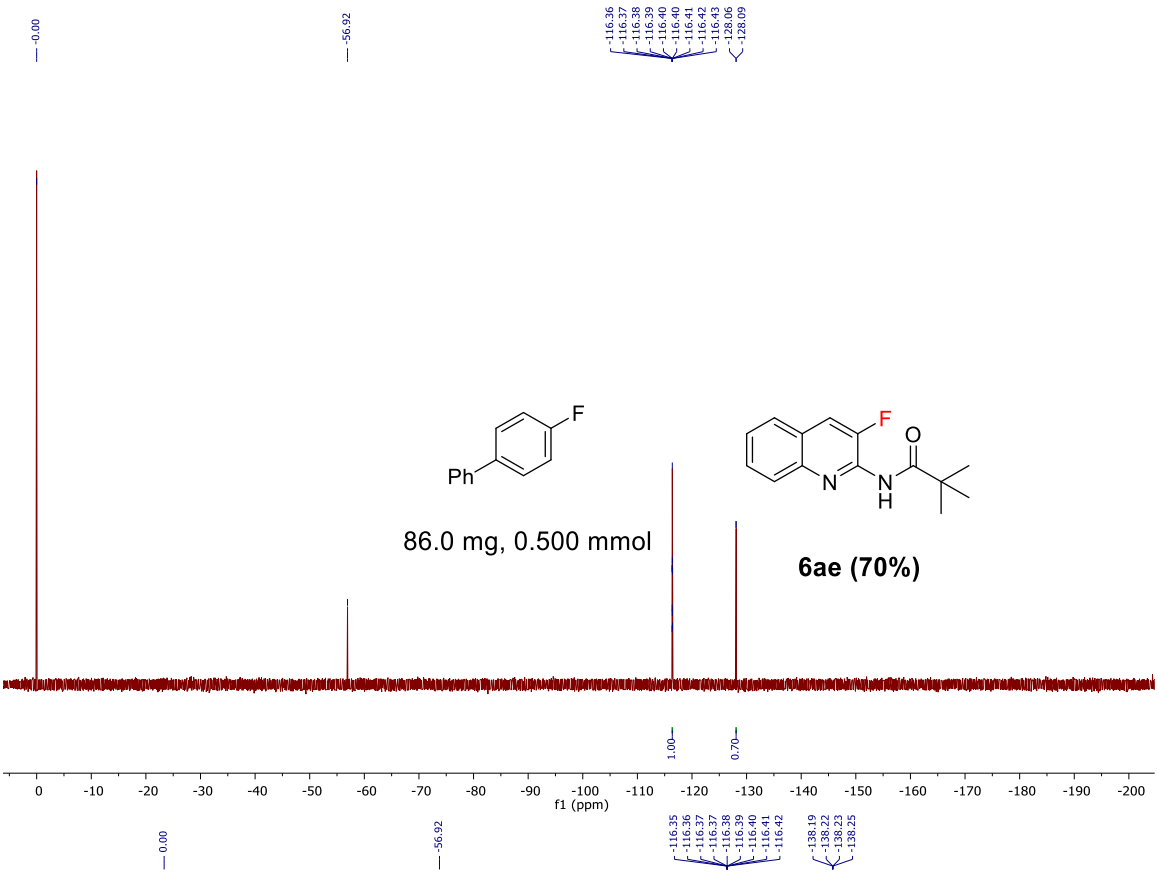

-0.00
-56.91
-115.96
-115.97
-124.87
-124.88
-124.89
-124.90
-124.91
-124.92
-124.93
S
O
OH
F
6y (75%)
F
O
59.0mg, 0.468 mmol
0.80
1.00
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

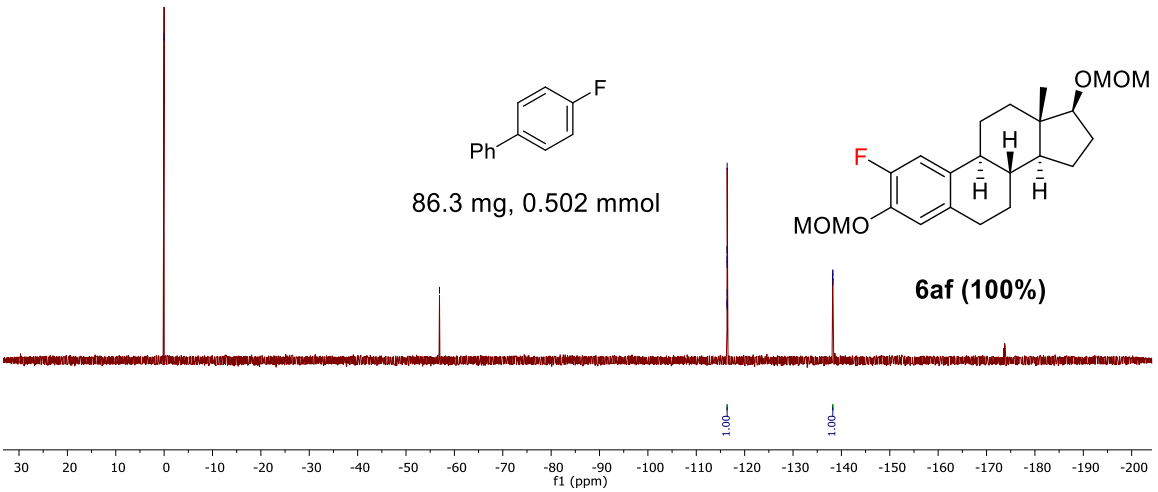

-0.00
-56.94
-116.36
-116.38
-116.39
-116.39
-116.40
-116.41
-116.42
-116.44
-117.40
OMe
F
O
6z (quant/100%)
F
Ph
85.8 mg, 0.499 mmol
1.00
1.01
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

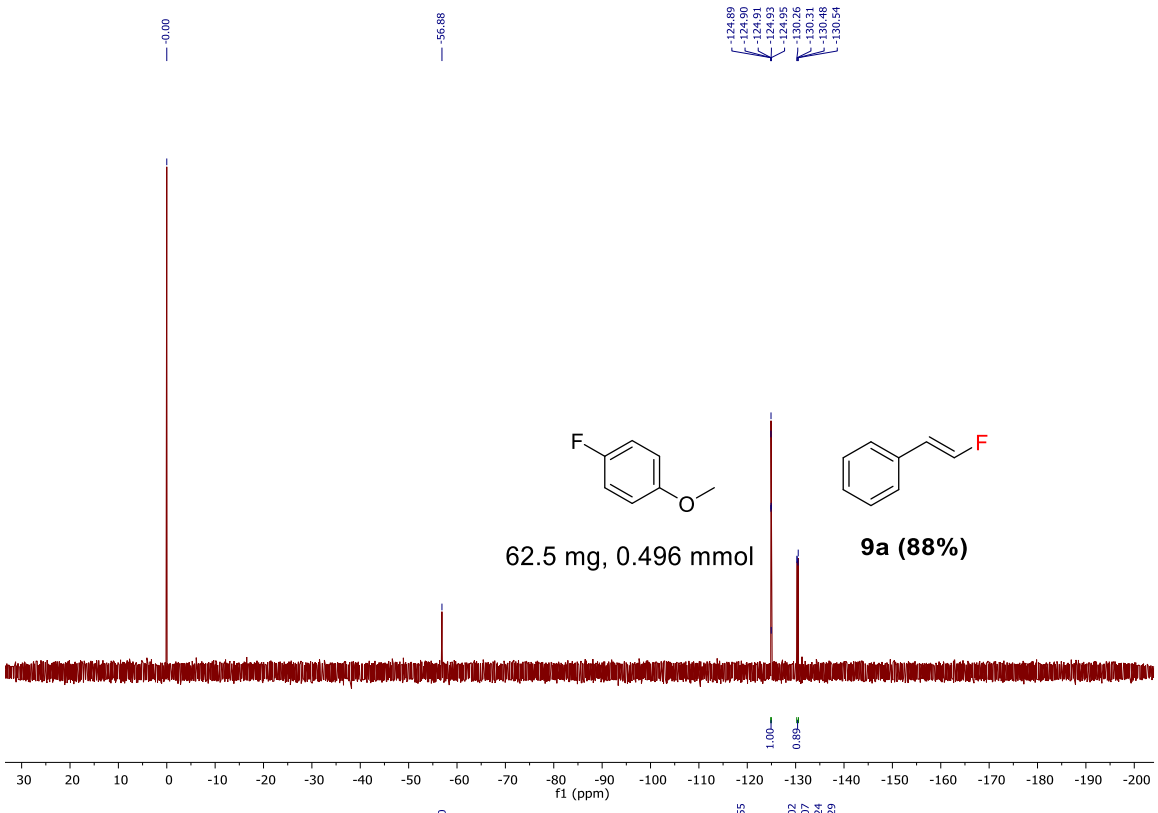

0.00
-56.94
-116.36
-116.38
-116.38
-116.39
-116.40
-116.41
-116.41
-116.42
-116.44
-126.53
-126.54
F
Ph
85.5 mg, 0.497 mmol
F
N
Ts
6aa (83%)
1.00
0.83
f1 (ppm)

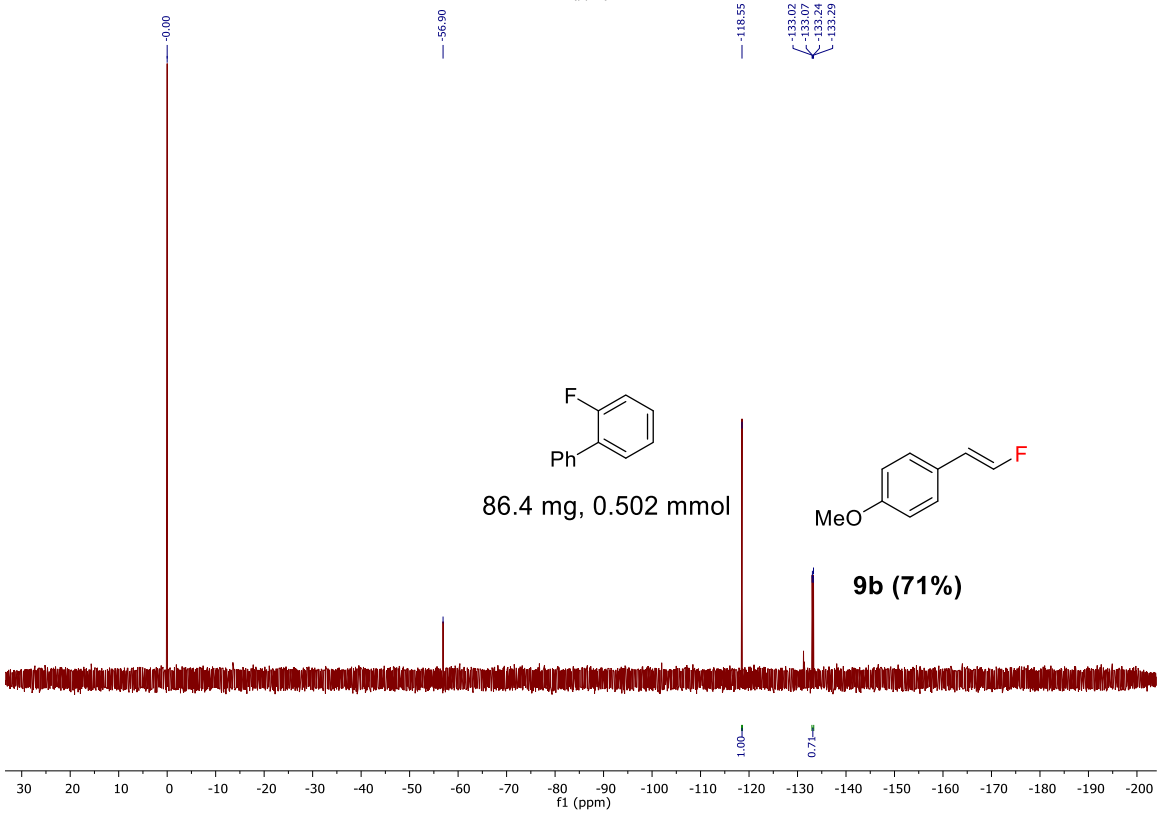

-0.00
-56.92
-116.36
-116.37
-116.38
-116.39
-116.40
-116.41
-116.42
-133.41
-133.41
-133.42
-133.42
F
Ph
86.2 mg, 0.501 mmol
F
N
N
Ph
6ab (91%)
1.00
0.91
f1 (ppm)

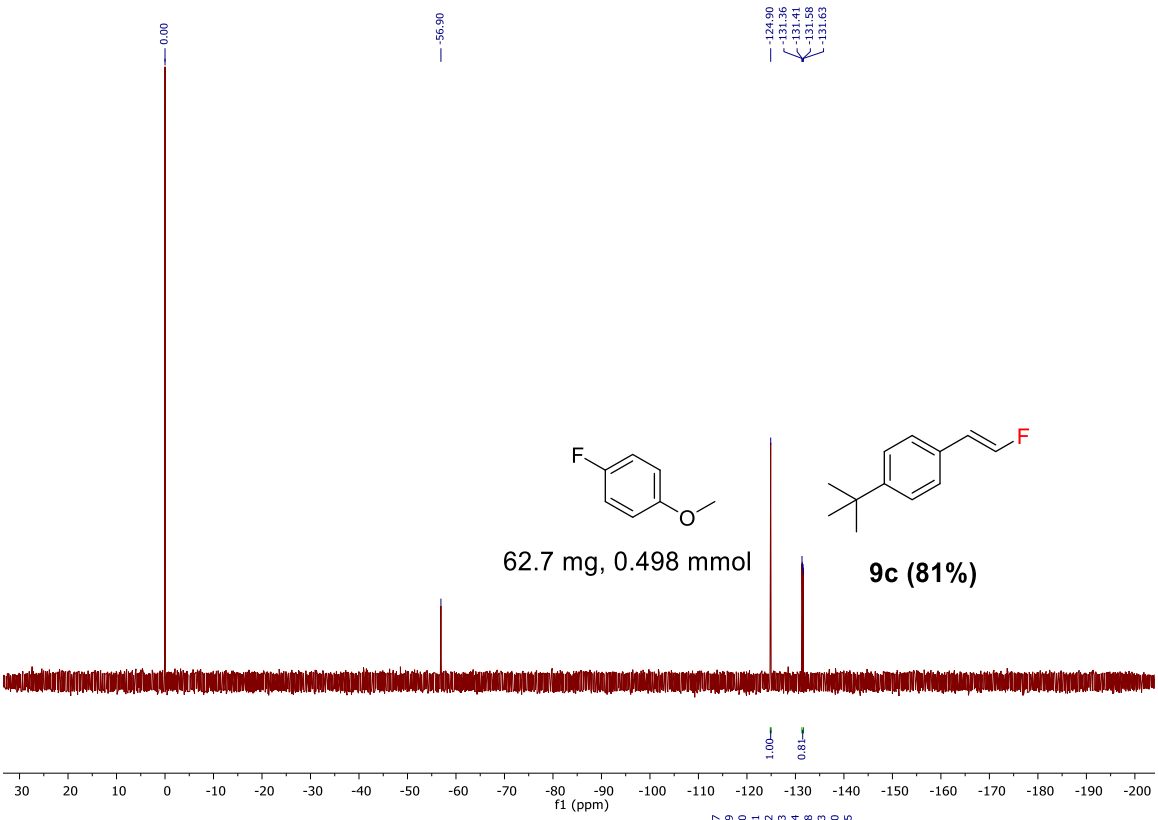

0.00
-56.91
-97.87
-119.10
-119.11
-119.12
-119.14
-119.15
-119.16
-119.17
Ph
Ph
Ph
F
N
N
6ac (quant/100%)
F
59.2 mg, 0.538 mmol
0.95
1.00
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)
0.00
-56.90
-118.52
-118.54
-118.55
-118.57
-118.59
-123.30
-123.32
-123.34
-123.35
-123.37
-123.39
-123.40
-140.51
-140.53
-140.54
-140.55
-140.56
-140.57
F
Ph
86.1 mg, 0.501 mmol
F
N
F
6ad (75%)
1.00
0.75
0.75
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

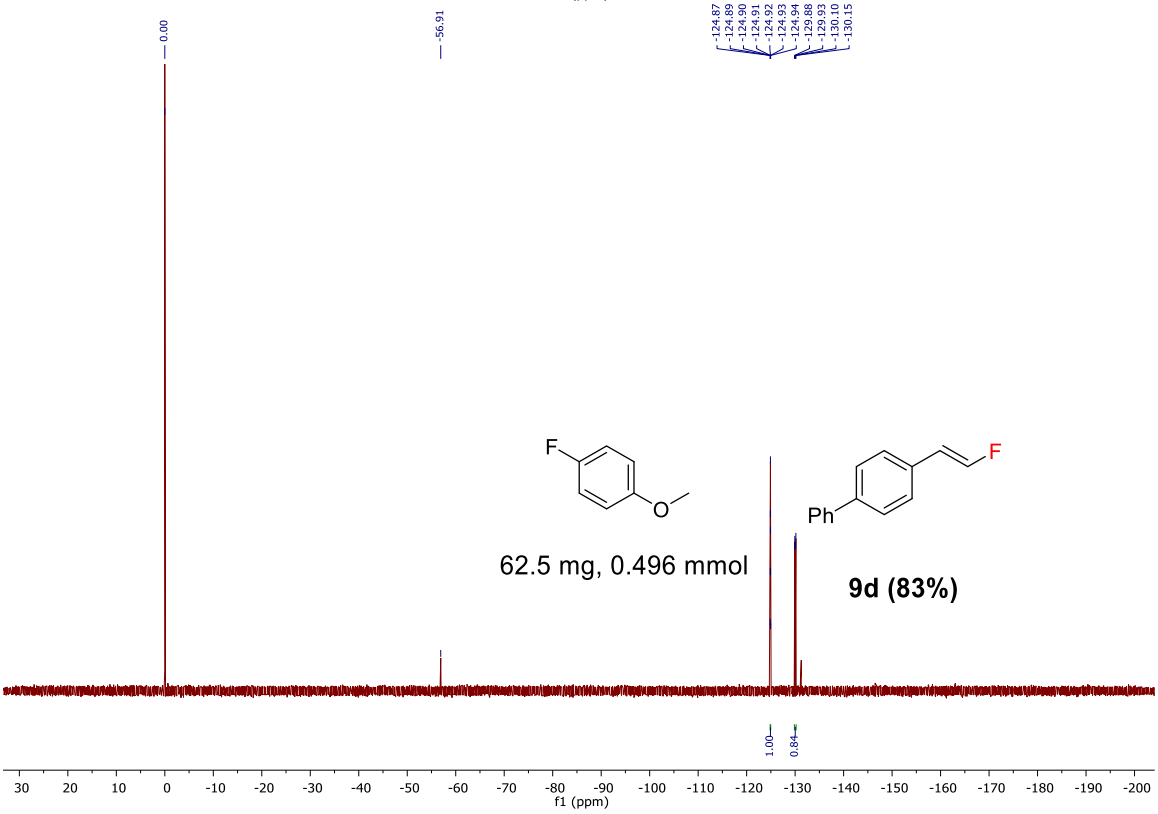

-0.00
-56.92
-116.36
-116.37
-116.38
-116.39
-116.40
-116.40
-116.41
-116.42
-116.43
-128.06
-128.09
F
Ph
86.0 mg, 0.500 mmol
F
O
N
N
H
6ae (70%)
1.00
0.70
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)
-0.00
-56.92
-116.35
-116.36
-116.37
-116.37
-116.38
-116.39
-116.40
-116.41
-116.42
-138.19
-138.22
-138.23
-138.25

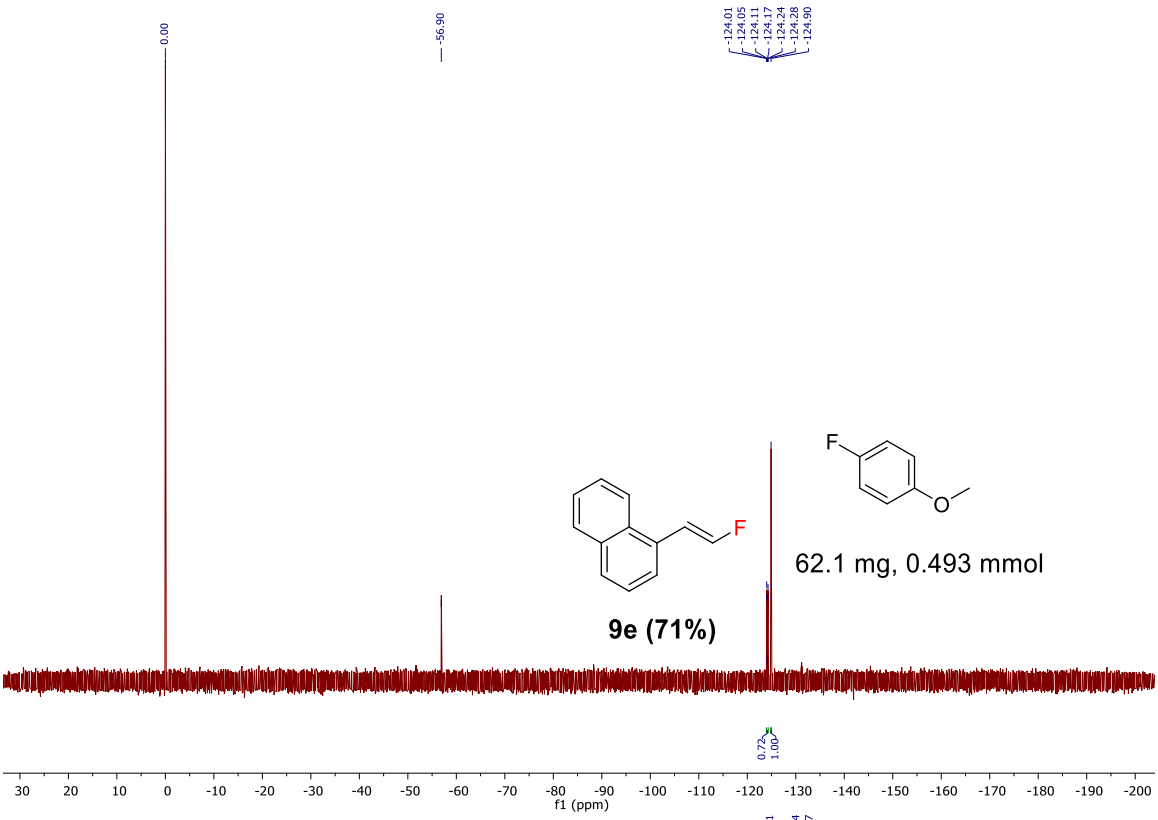

F
Ph
86.3 mg, 0.502 mmol
OMOM
H
F
H
H
MOMO
6af (100%)
1.00
1.00
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

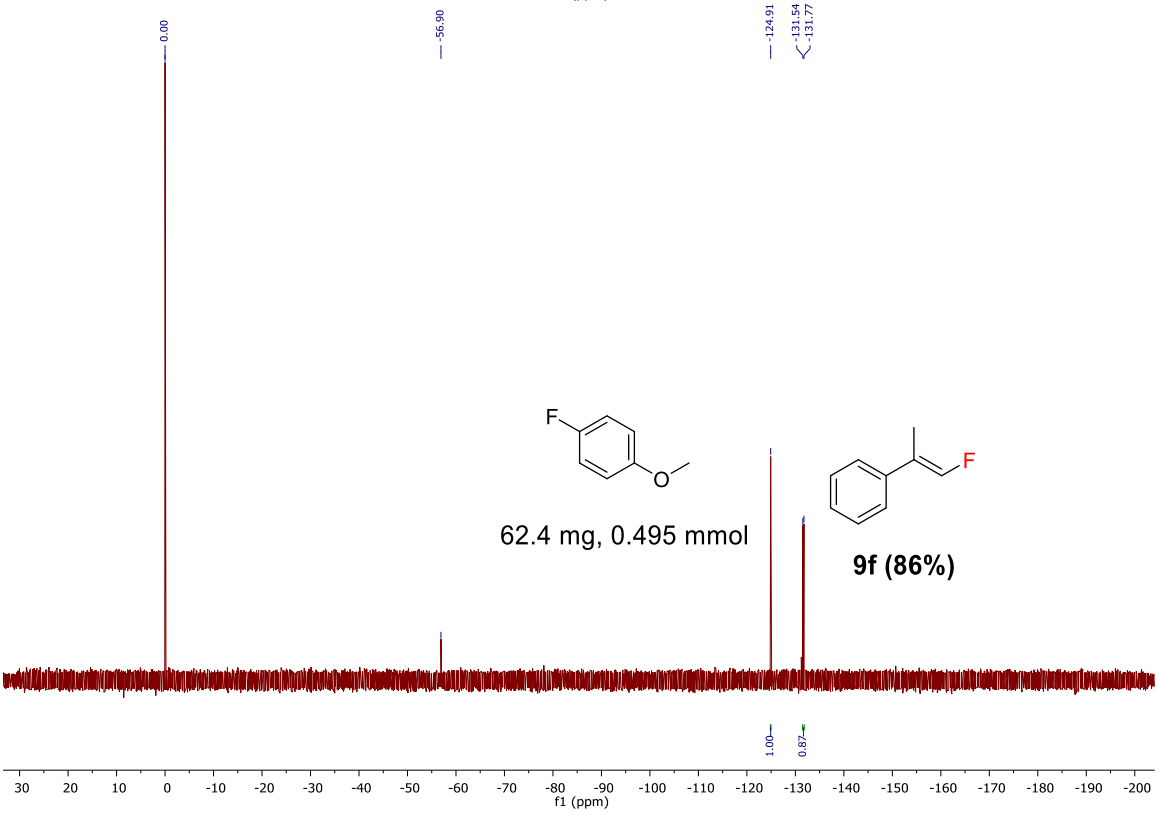

-0.00
-56.88
-124.89
-124.90
-124.91
-124.93
-124.95
-130.26
-130.31
-130.48
-130.54
F
O
F
62.5 mg, 0.496 mmol
9a (88%)
1.00
0.89
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

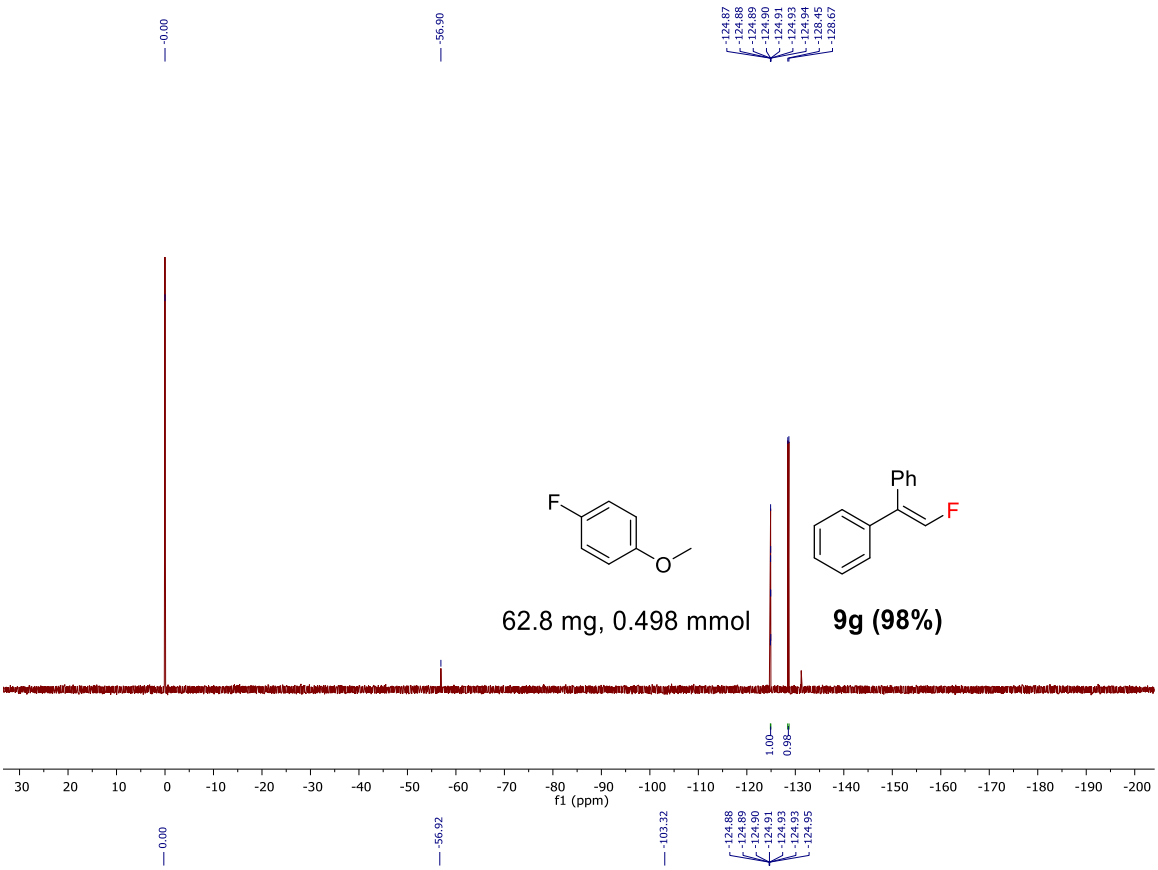

-0.00
-56.90
-118.55
-133.02
-133.07
-133.24
-133.29
F
Ph
86.4 mg, 0.502 mmol
MeO
F
9b (71%)
1.00
0.71
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

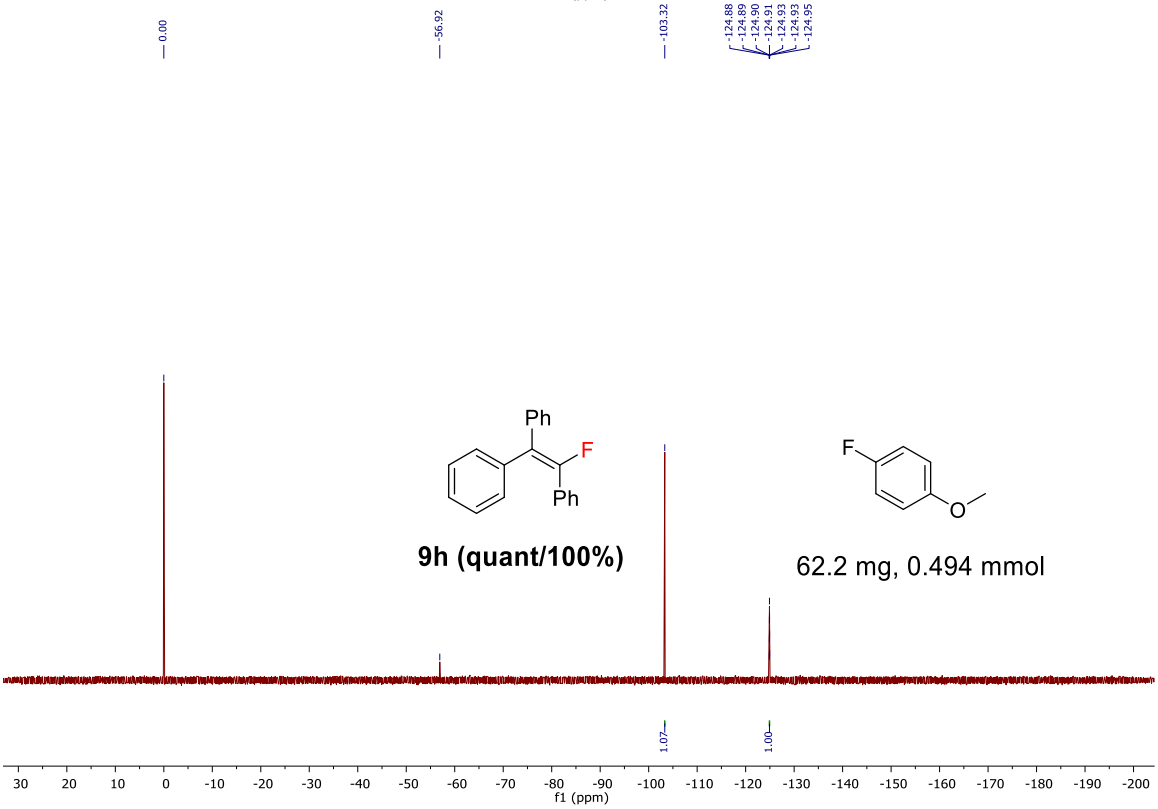

0.00
-56.90
-124.90
-131.36
-131.41
-131.58
-131.63
F
O
62.7 mg, 0.498 mmol
F
9c (81%)
1.00
0.81
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

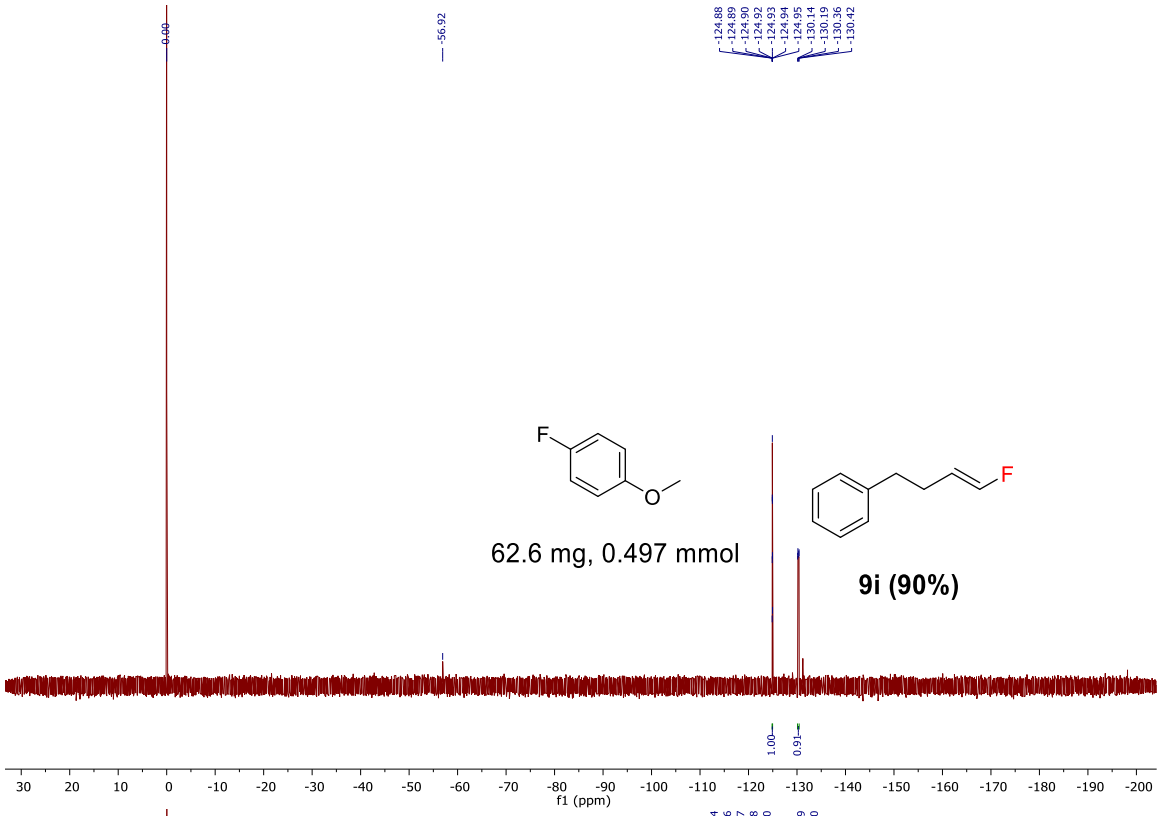

0.00
-56.91
-124.87
-124.89
-124.90
-124.91
-124.92
-124.93
-124.94
-129.88
-129.93
-130.10
-130.15
F
O
62.5 mg, 0.496 mmol
Ph
F
9d (83%)
1.00
0.84
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

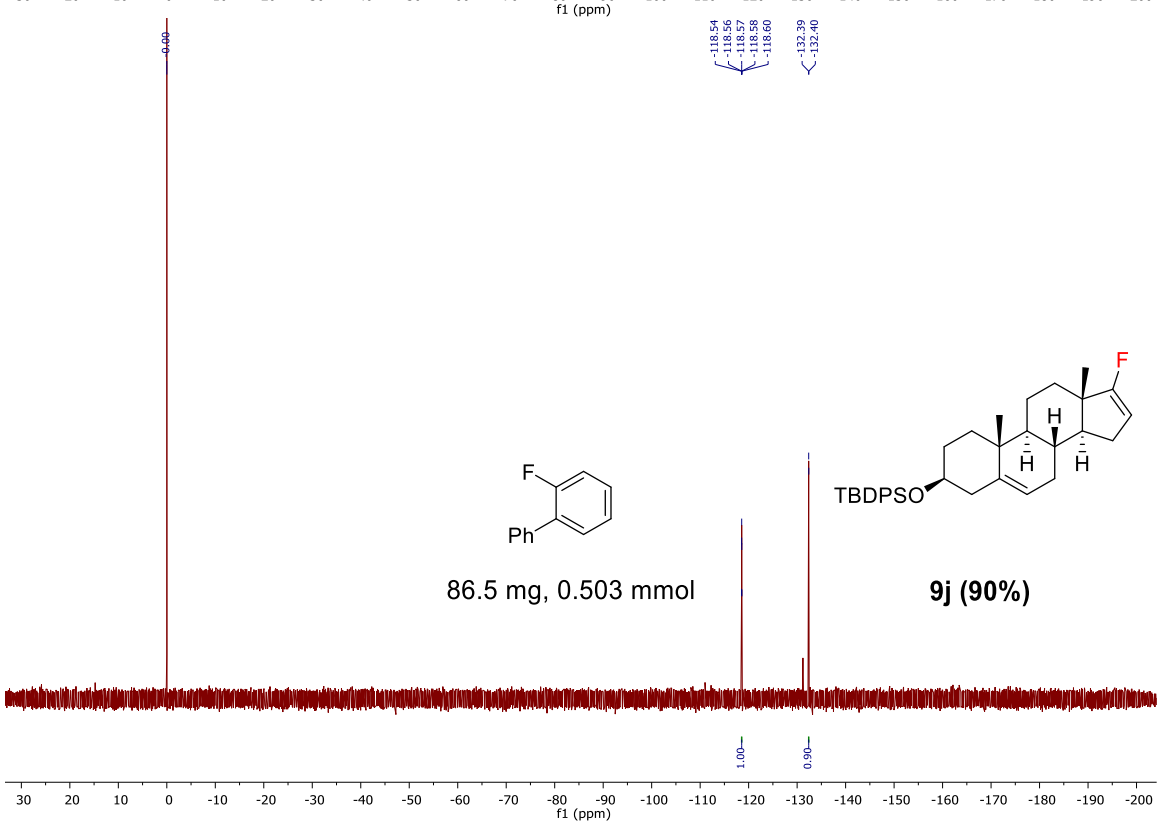

0.00
-56.90
-124.01
-124.05
-124.11
-124.17
-124.24
-124.28
-124.90
F
O
F
62.1 mg, 0.493 mmol
9e (71%)
0.72
1.00
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

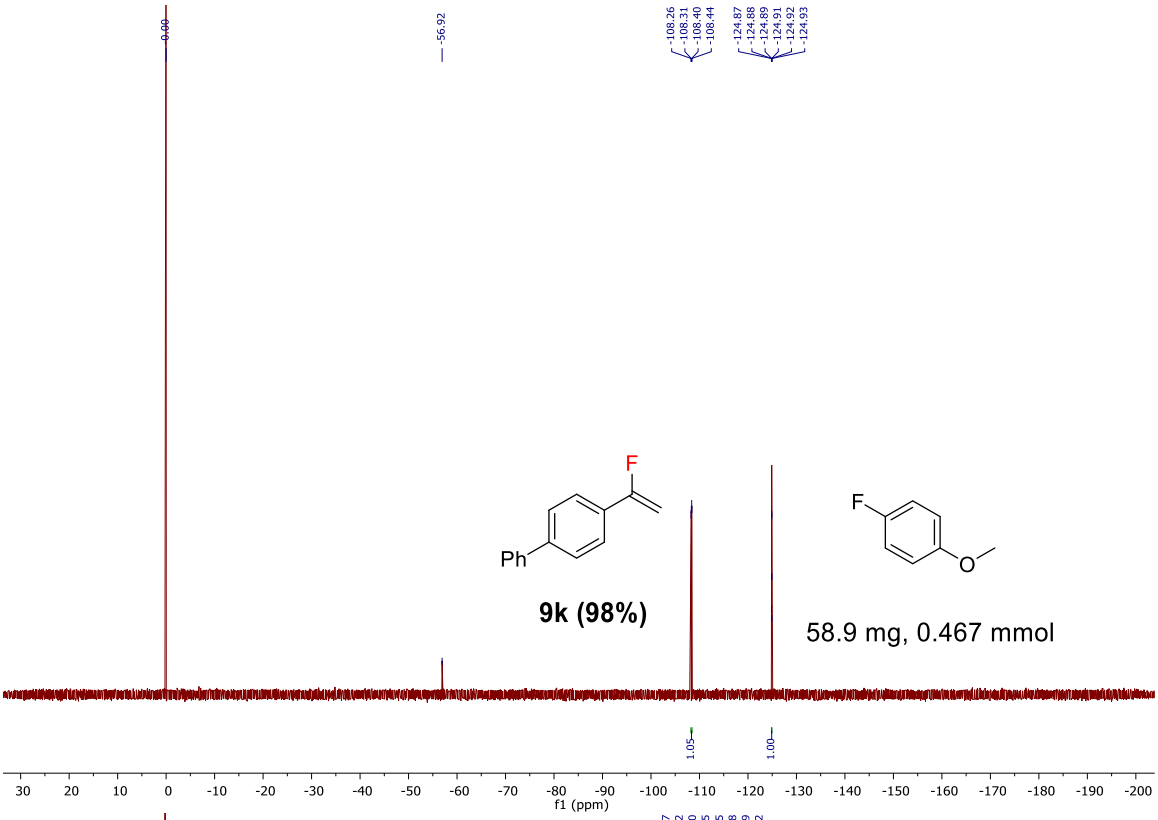

0.00
-56.90
-124.91
-131.54
-131.77
F
O
62.4 mg, 0.495 mmol
F
9f (86%)
1.00
0.87
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

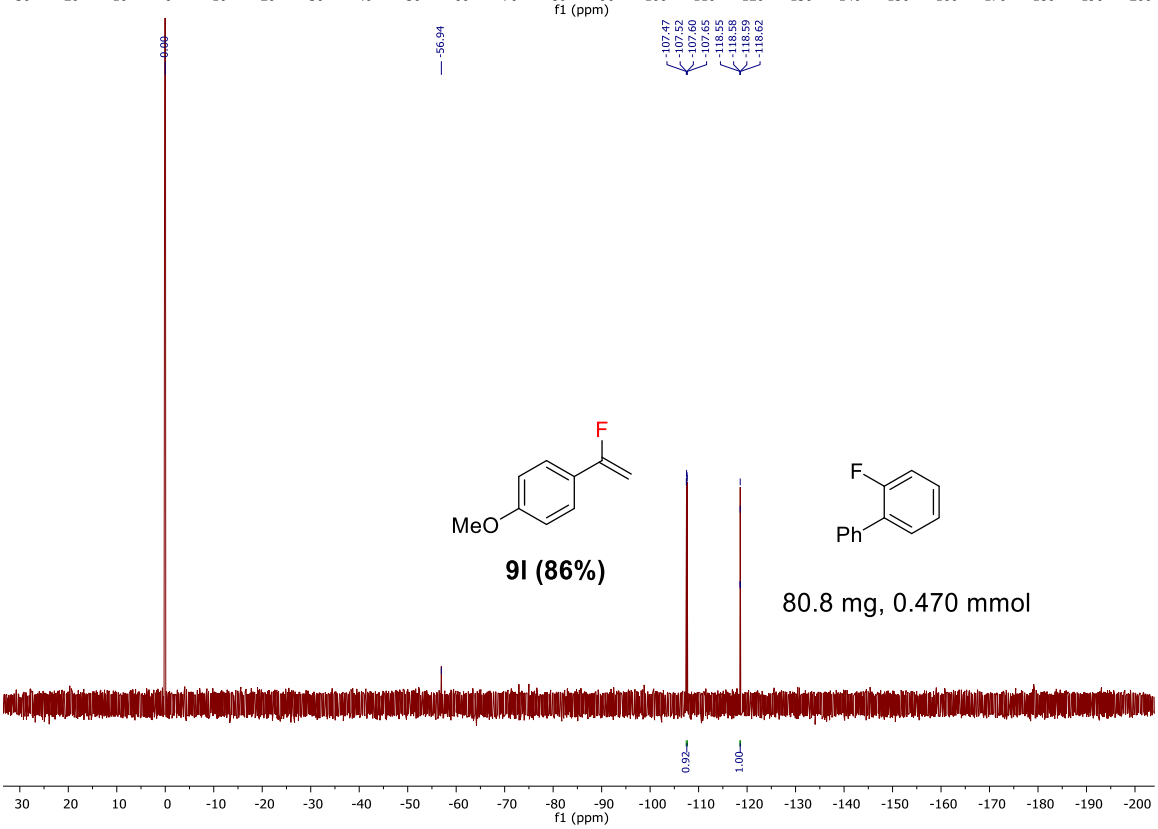

-0.00
-56.90
-124.87
-124.88
-124.89
-124.90
-124.91
-124.93
-124.94
-128.45
-128.67
F
O
62.8 mg, 0.498 mmol
Ph
F
9g (98%)
1.00
0.98
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

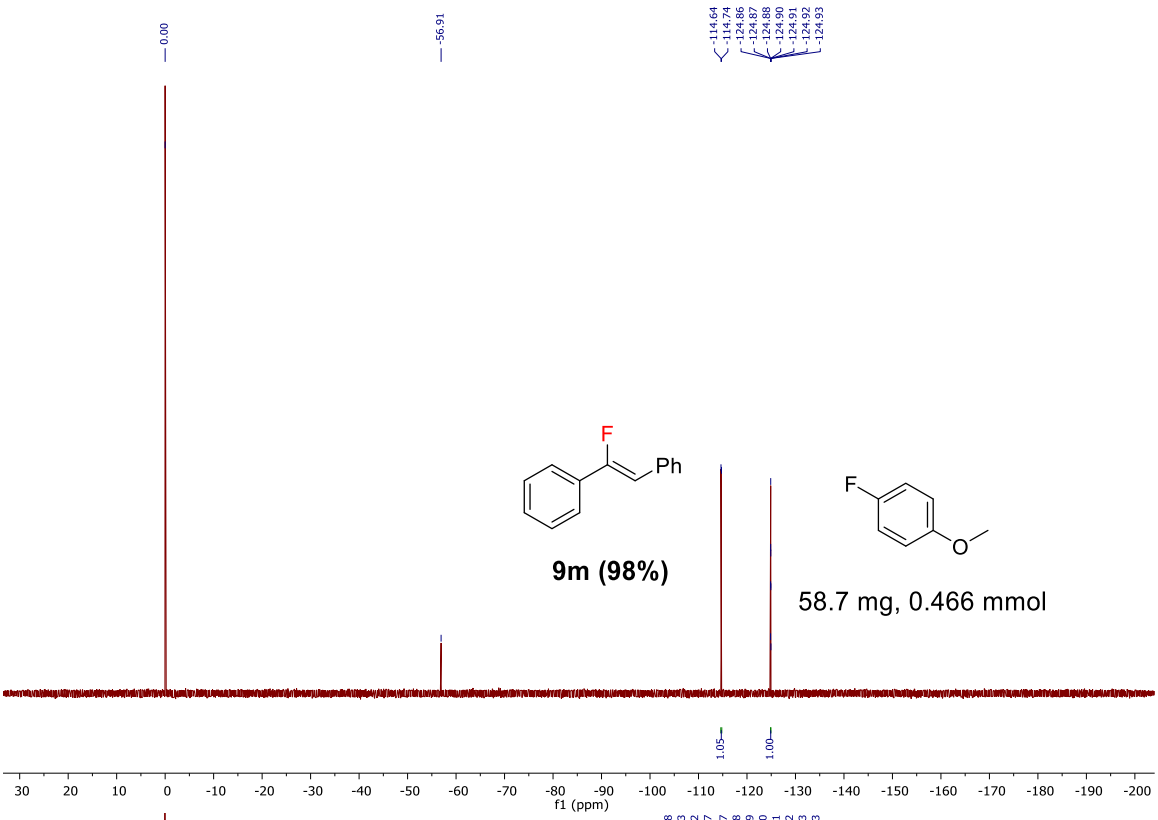

0.00
-56.92
-103.32
-124.88
-124.89
-124.90
-124.91
-124.93
-124.93
-124.95
Ph
F
Ph
9h (quant/100%)
F
O
62.2 mg, 0.494 mmol
1.07
1.00
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

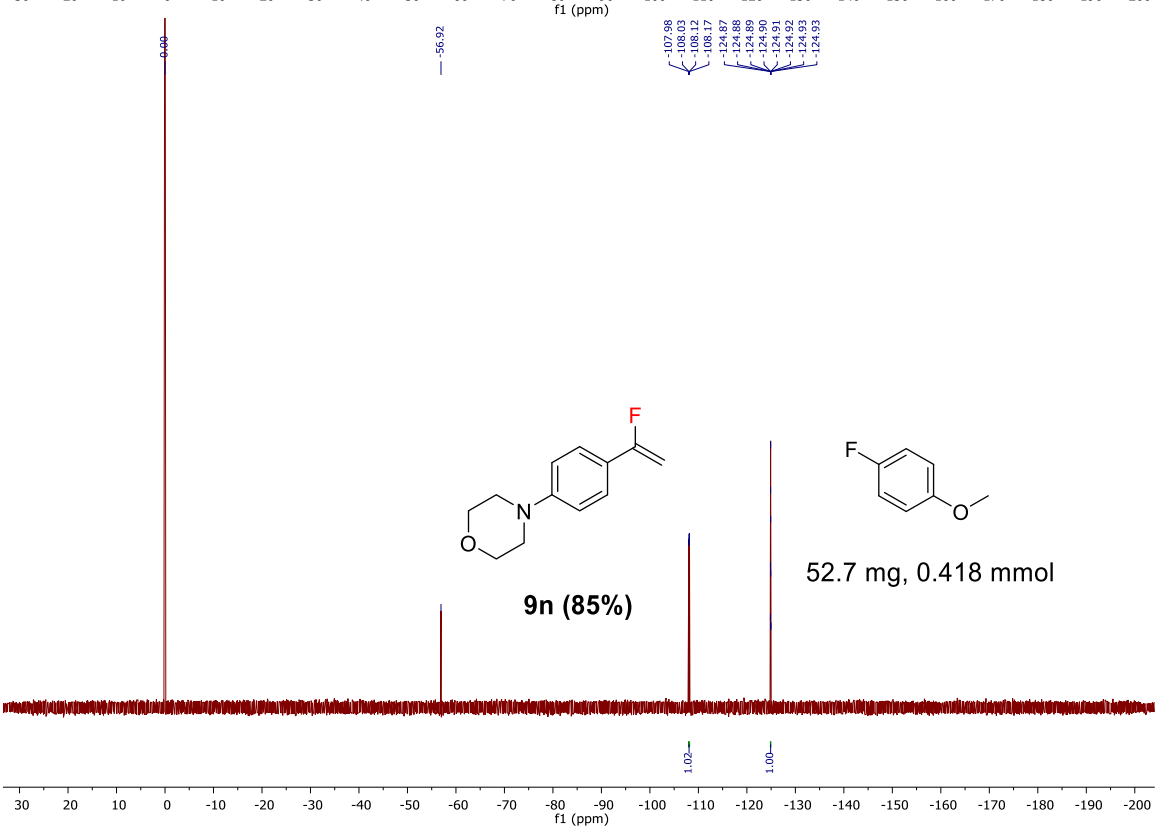

0.00
-56.92
-124.88
-124.89
-124.90
-124.92
-124.93
-124.94
-124.95
-130.14
-130.19
-130.36
-130.42
F
O
62.6 mg, 0.497 mmol
F
9i (90%)
1.00
0.91
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

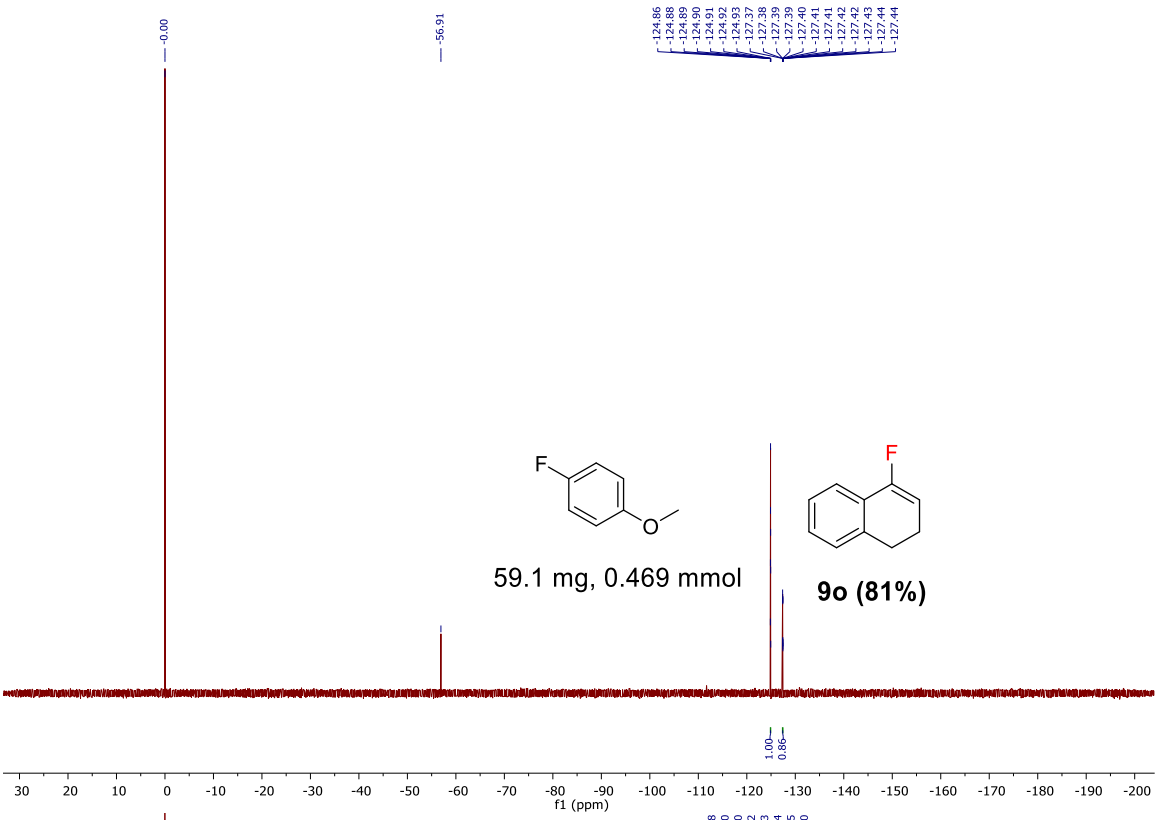

0.00
-118.54
-118.56
-118.57
-118.58
-118.60
-132.39
-132.40
F
Ph
86.5 mg, 0.503 mmol
F
H
H
H
TBDPSO
9j (90%)
1.00
0.90
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

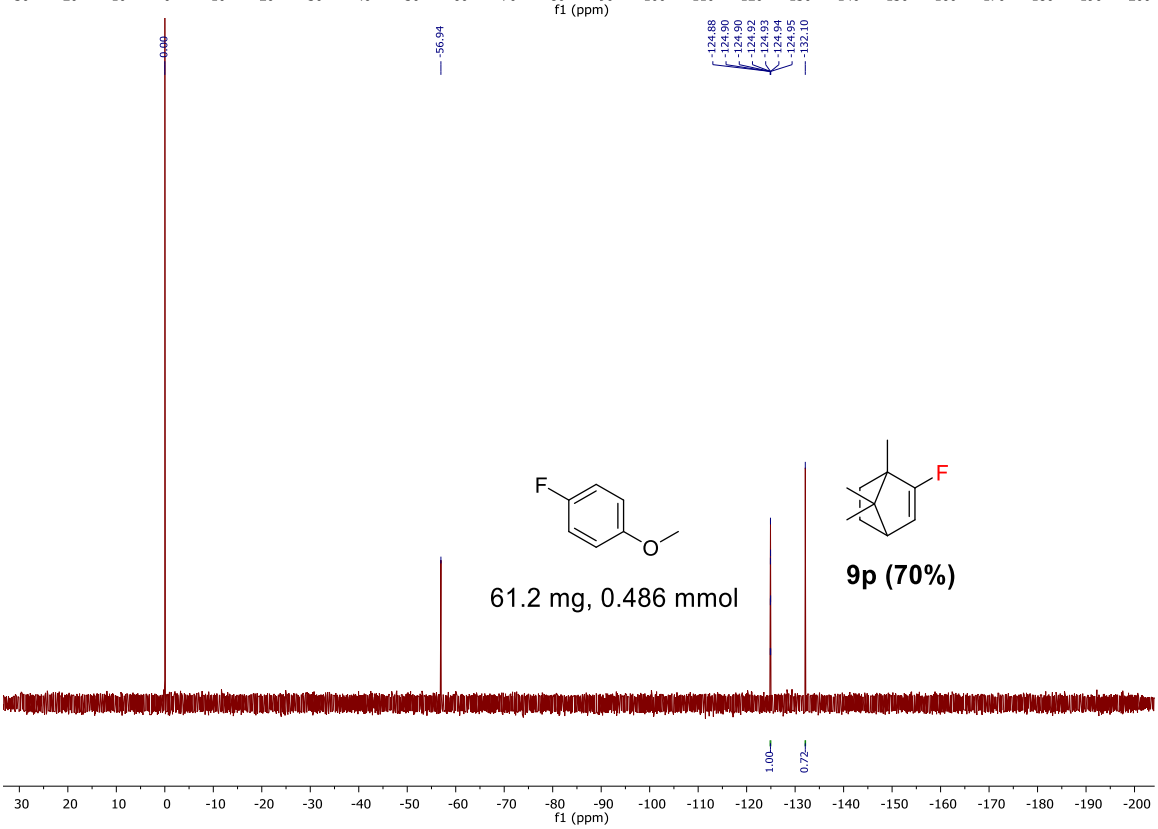

0.00
-56.92
-108.26
-108.31
-108.40
-108.44
-124.87
-124.88
-124.89
-124.91
-124.92
-124.93
F
Ph
9k (98%)
F
O
58.9 mg, 0.467 mmol
1.05
1.00
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

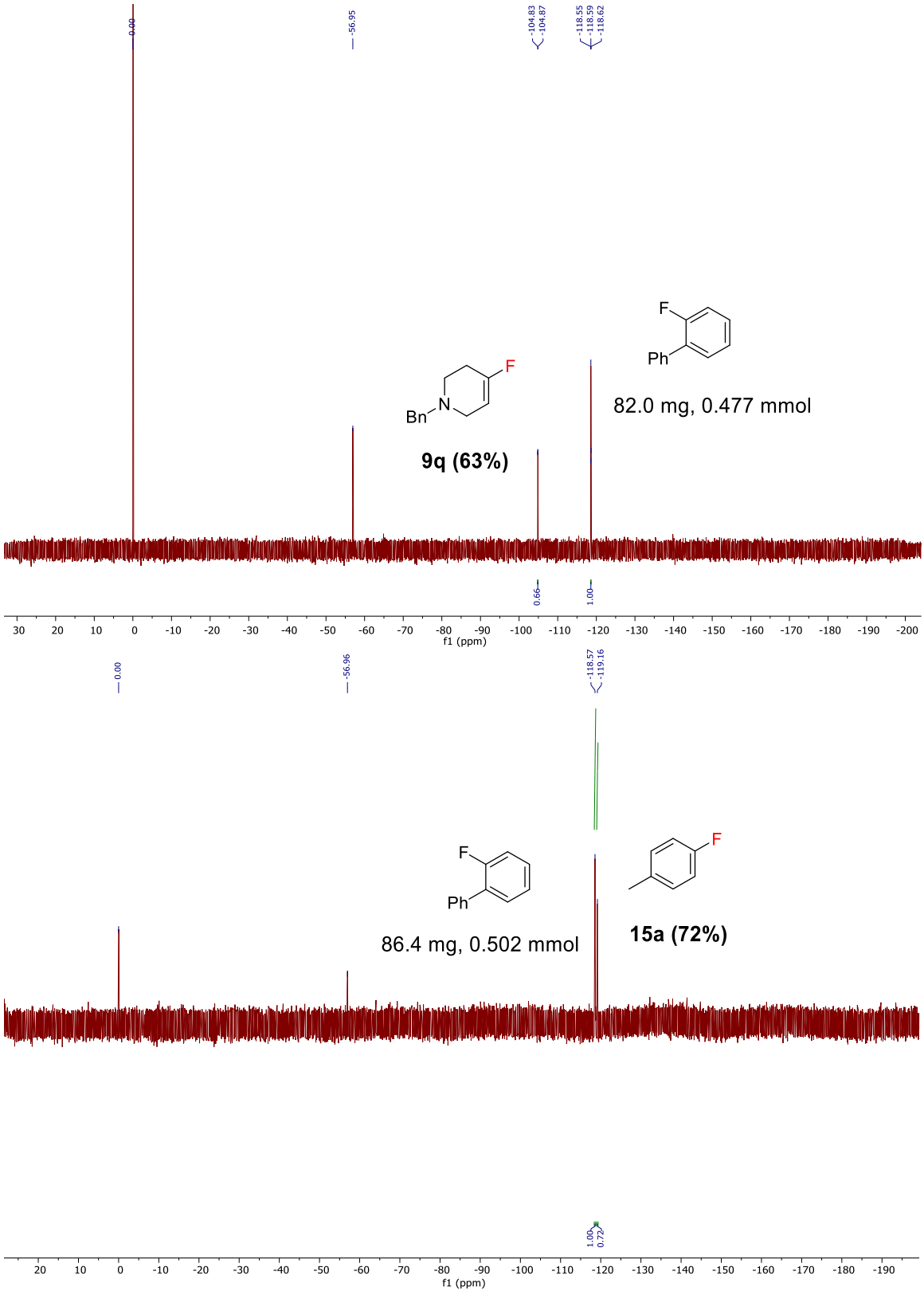

0.00
-56.94
-107.47
-107.52
-107.60
-107.65
-118.55
-118.58
-118.59
-118.62
F
MeO
9l (86%)
F
Ph
80.8 mg, 0.470 mmol
0.92
1.00
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

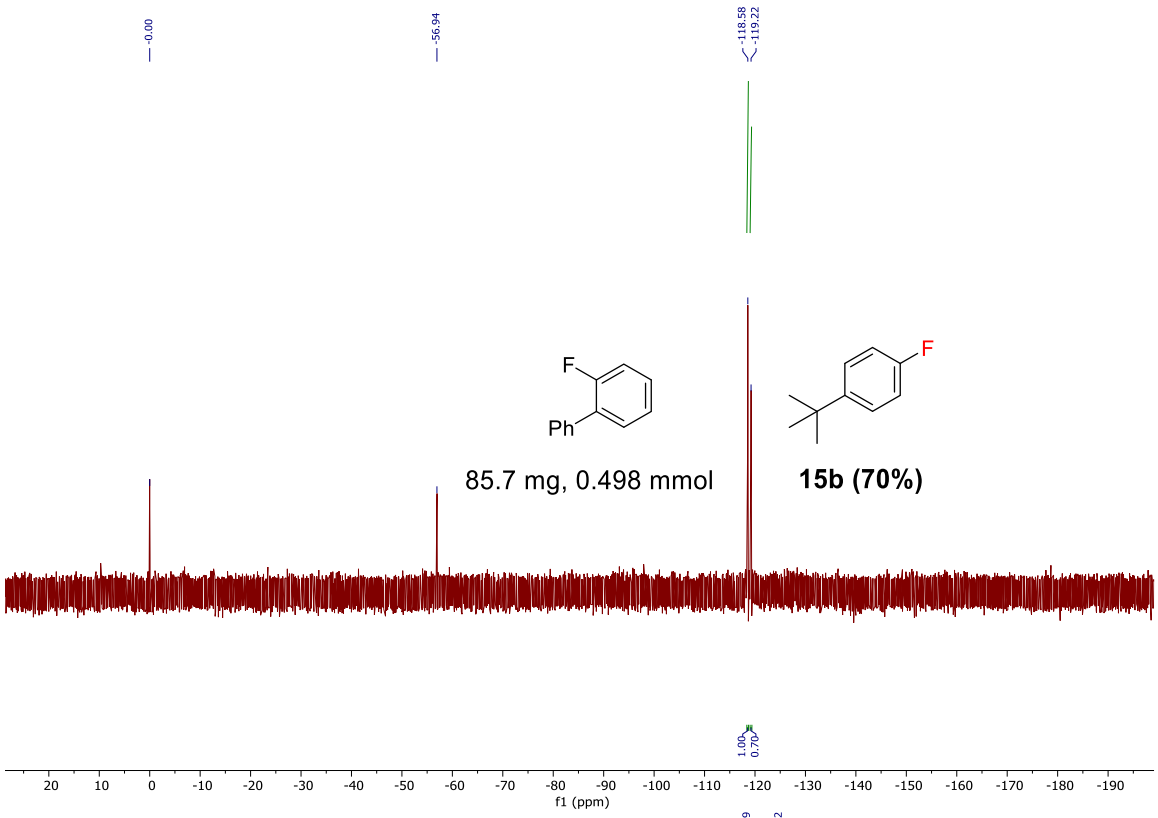

0.00
-56.91
-114.64
-114.74
-124.86
-124.87
-124.88
-124.90
-124.91
-124.92
-124.93
F
Ph
9m (98%)
F
O
58.7 mg, 0.466 mmol
1.05
1.00
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

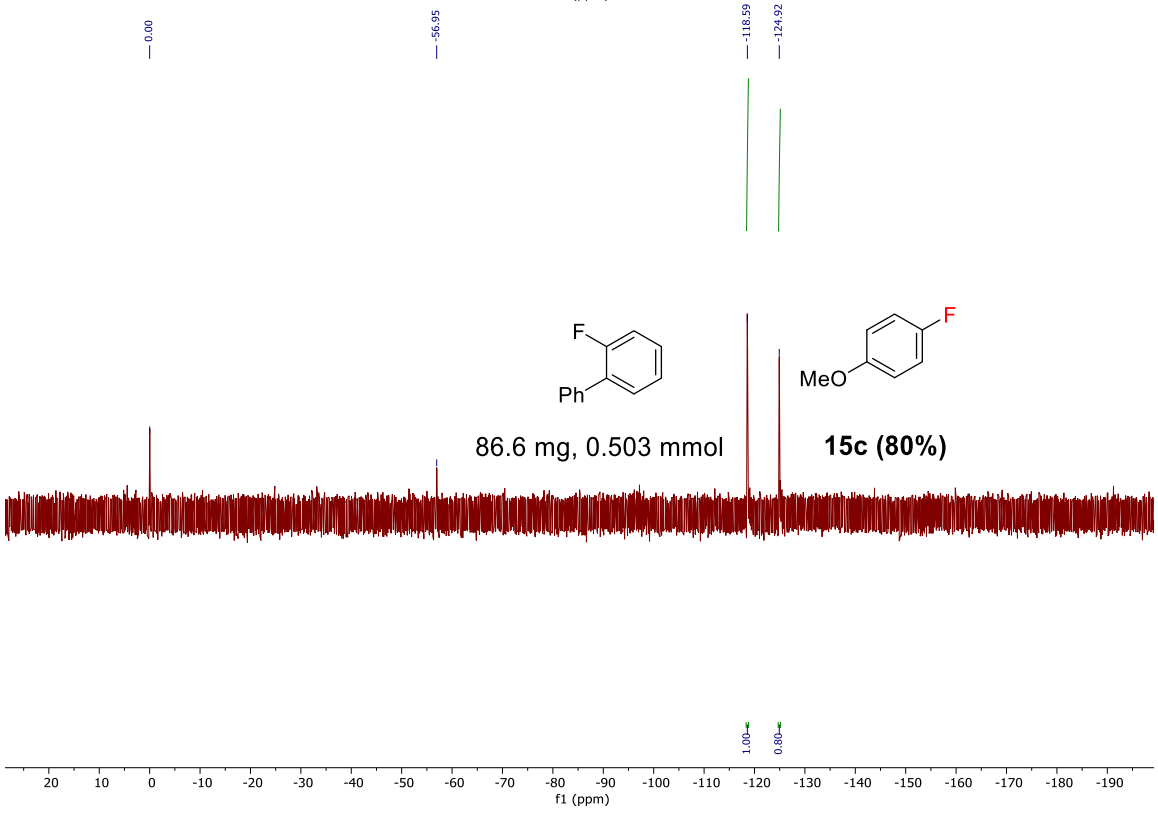

0.00
-56.92
-107.98
-108.03
-108.12
-108.17
-124.87
-124.88
-124.90
-124.91
-124.92
-124.93
-124.93
F
N
O
9n (85%)
F
O
52.7 mg, 0.418 mmol
1.02
1.00
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

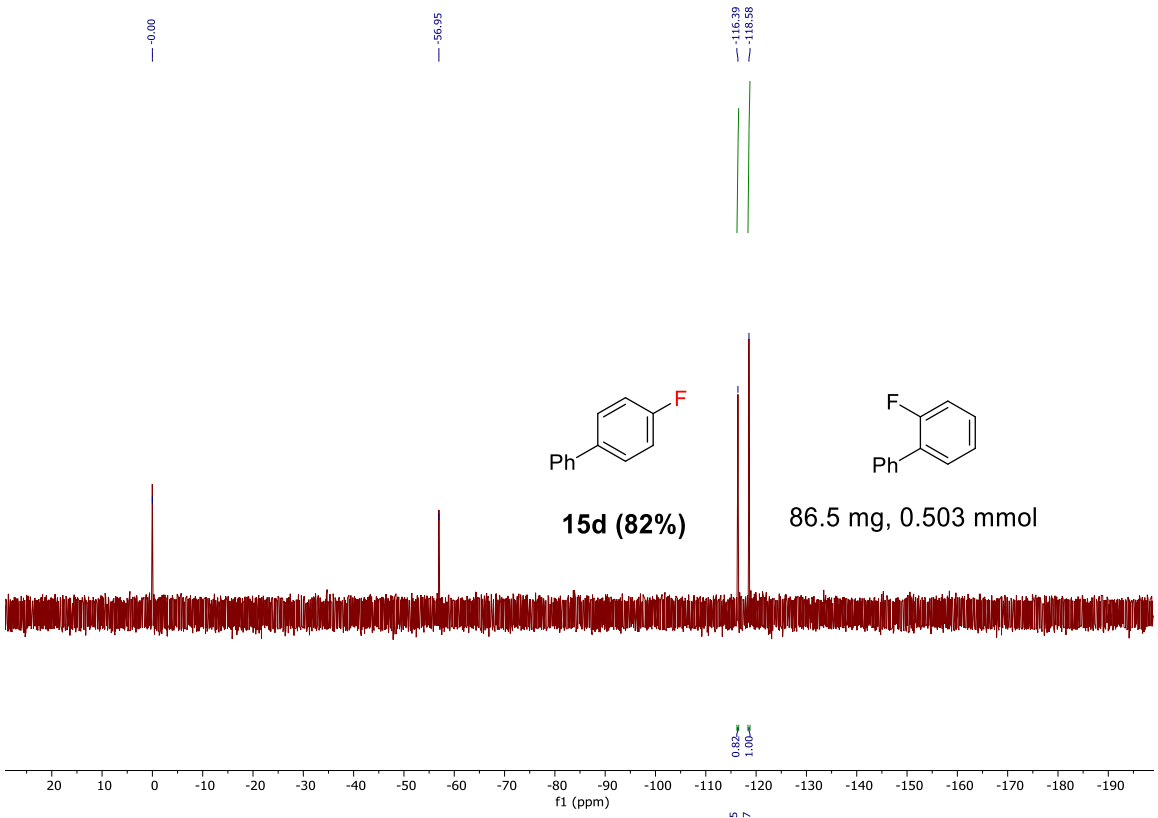

0.00
-56.91
-124.86
-124.88
-124.89
-124.90
-124.91
-124.92
-124.93
-127.37
-127.38
-127.39
-127.39
-127.40
-127.41
-127.41
-127.42
-127.42
-127.43
-127.44
-127.44
F
O
59.1 mg, 0.469 mmol
F
9o (81%)
1.00
0.86
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

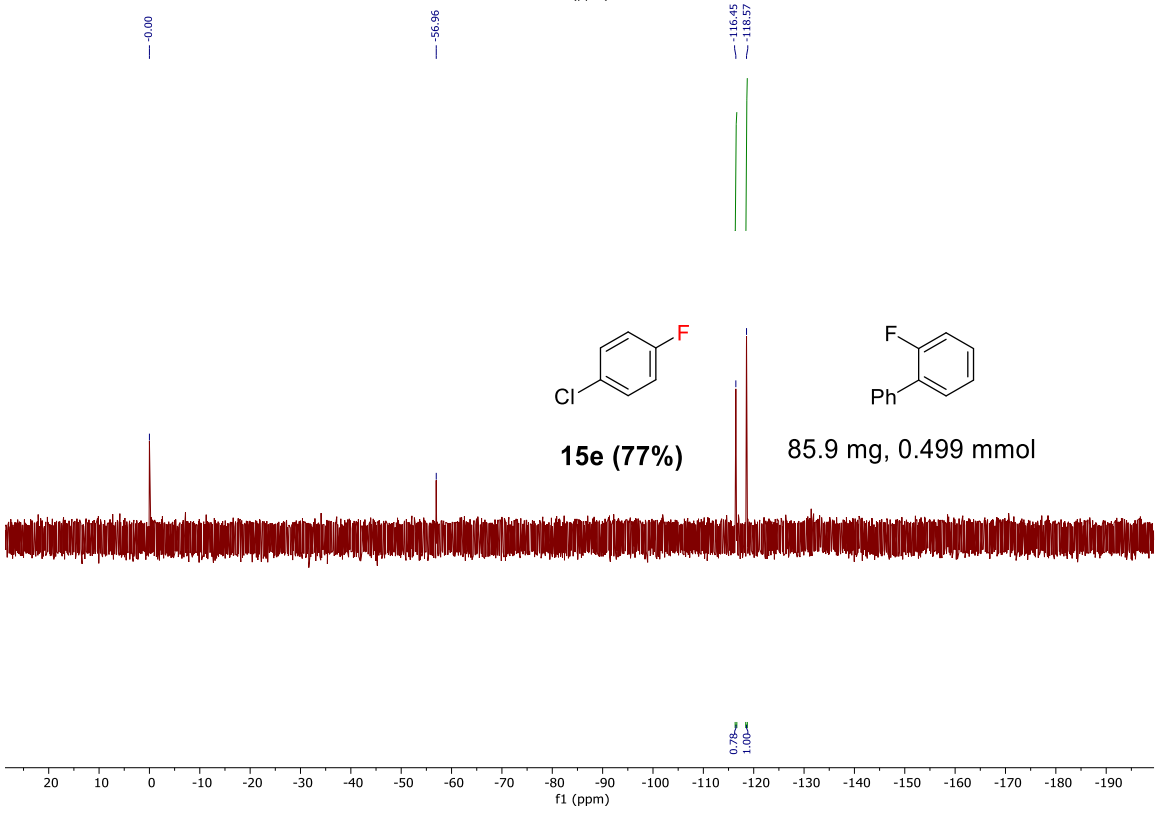

0.00
-56.94
-124.88
-124.90
-124.90
-124.92
-124.93
-124.94
-124.95
-132.10
F
O
61.2 mg, 0.486 mmol
F
9p (70%)
1.00
0.72
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

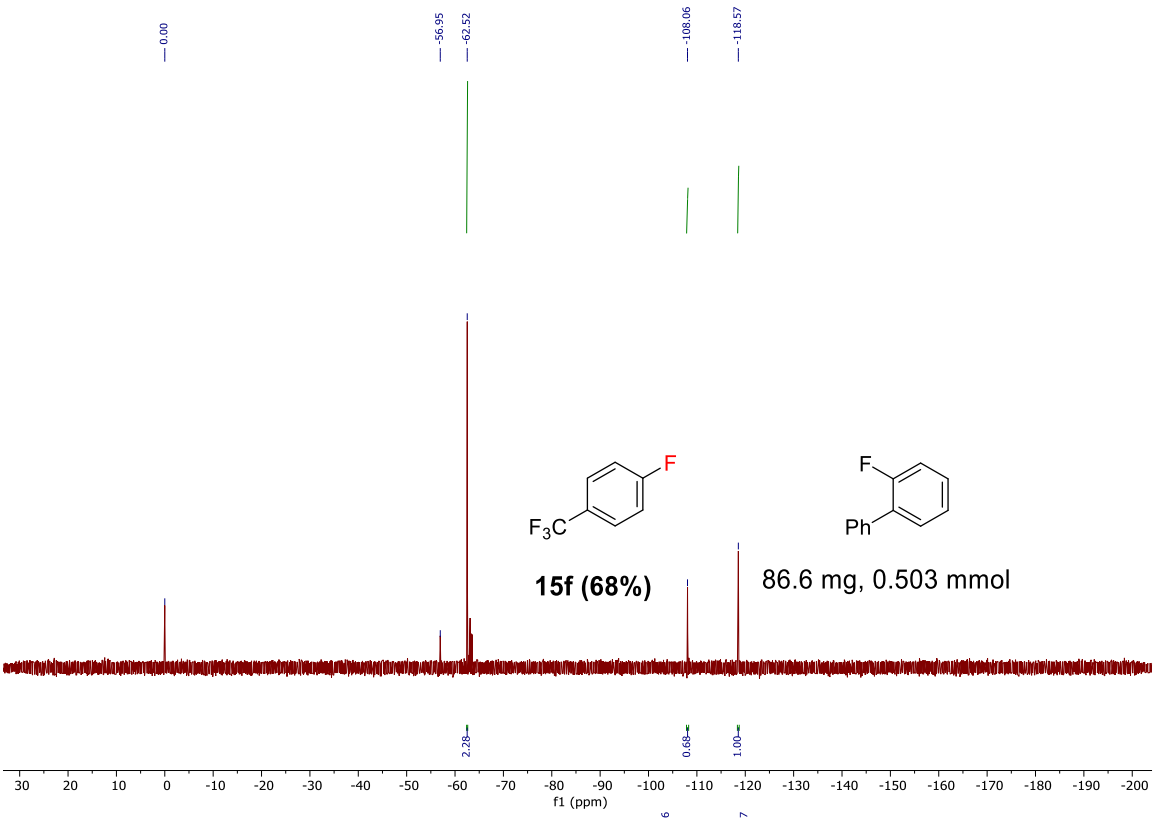

0.00
-56.95
-104.83
-104.87
-118.55
-118.59
-118.62
F
Ph
Bn
N
F
82.0 mg, 0.477 mmol
9q (63%)
0.66
1.00
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)
0.00
-56.96
-118.57
-119.16
F
Ph
F
86.4 mg, 0.502 mmol
15a (72%)
1.00
0.72
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

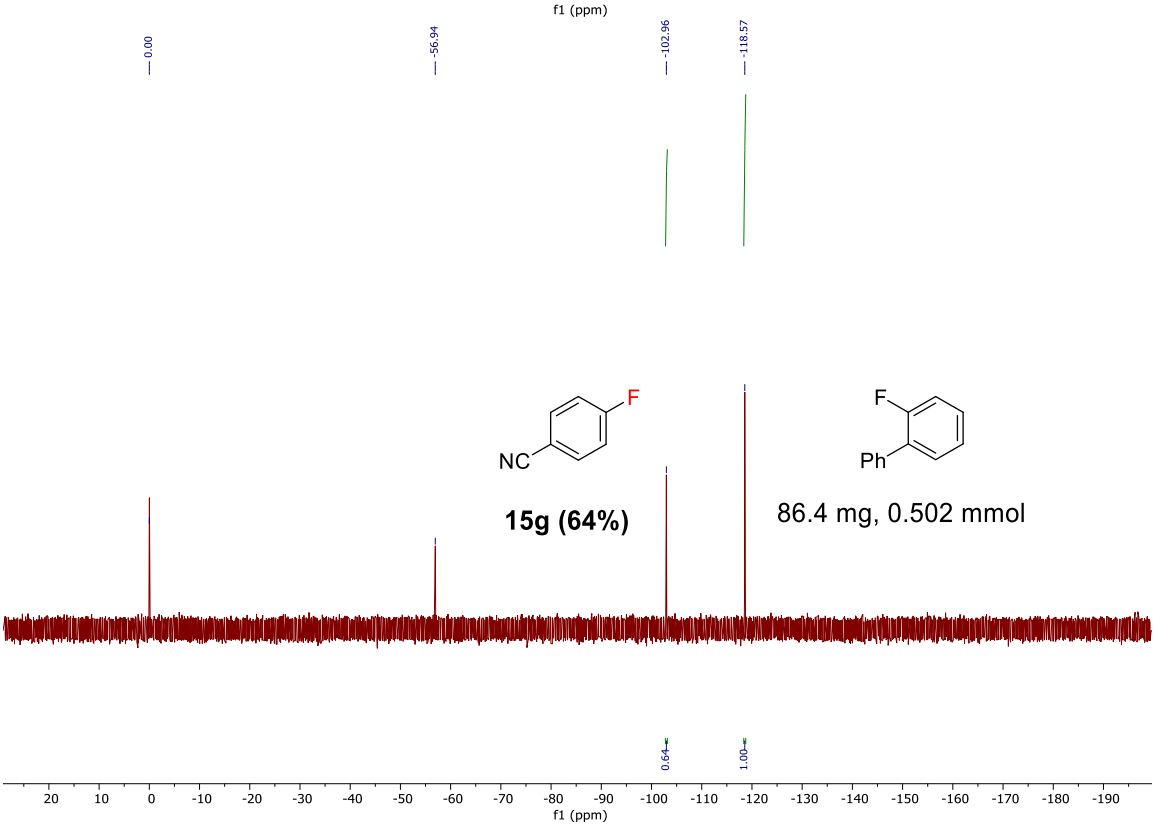

-0.00
-56.94
-118.58
-119.22
F
Ph
85.7 mg, 0.498 mmol
F
15b (70%)
1.00
0.70
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

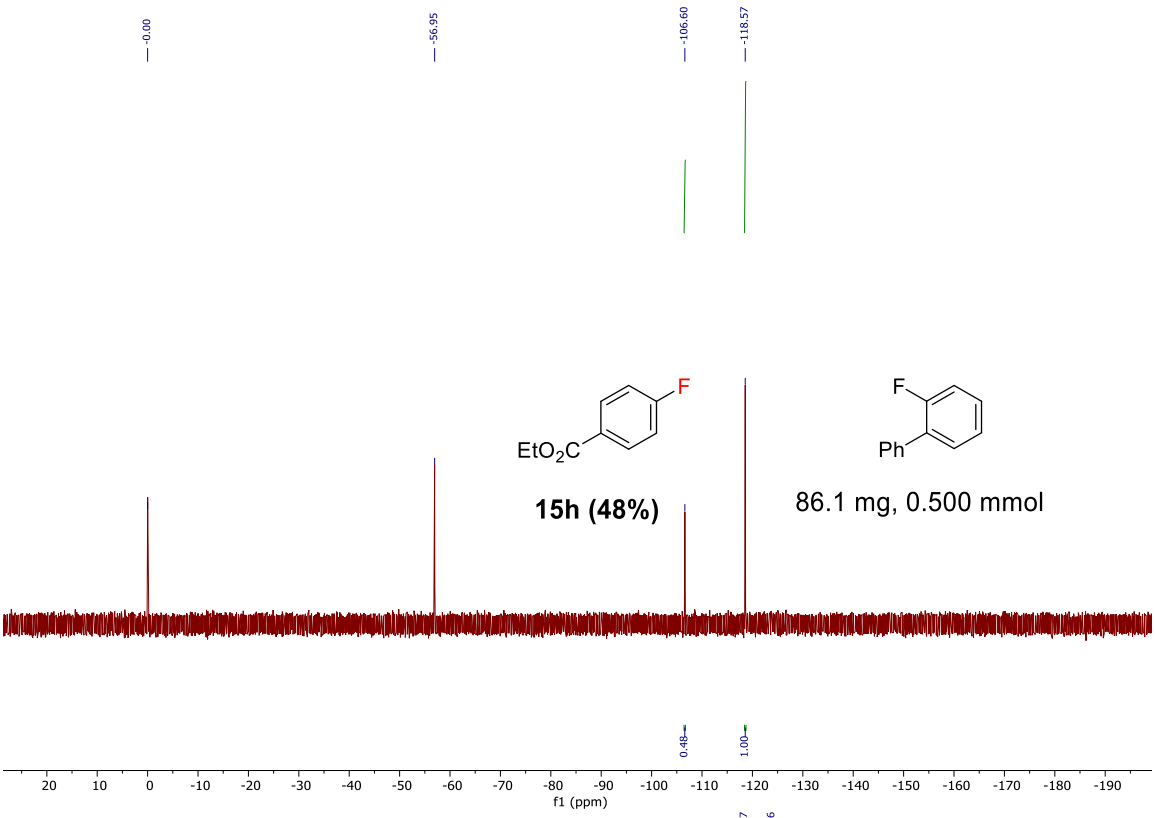

-0.00
-56.95
-118.59
-124.92
F
Ph
86.6 mg, 0.503 mmol
F
MeO
15c (80%)
1.00
0.80
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

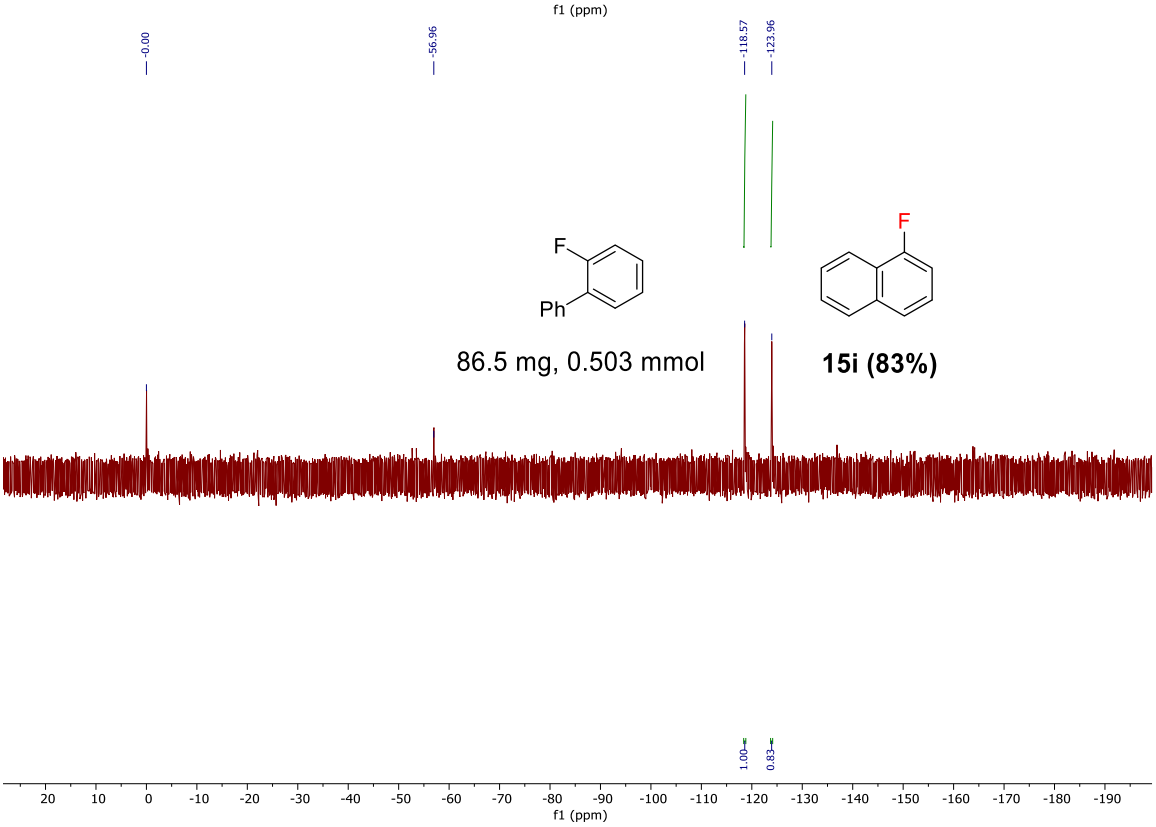

-0.00
-56.95
-116.39
-118.58
F
Ph
F
Ph
15d (82%)
86.5 mg, 0.503 mmol
0.82
1.00
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

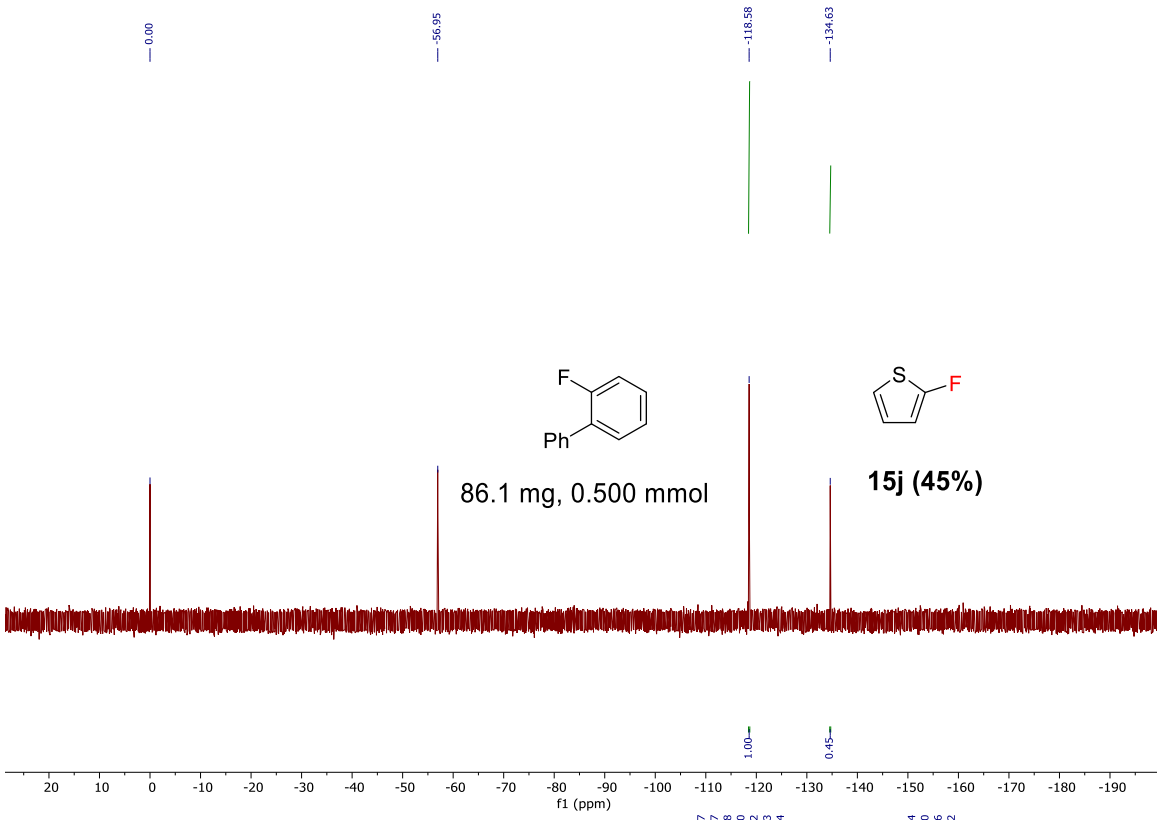

-0.00
-56.96
-116.45
-118.57
F
Cl
F
Ph
15e (77%)
85.9 mg, 0.499 mmol
0.78
1.00
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

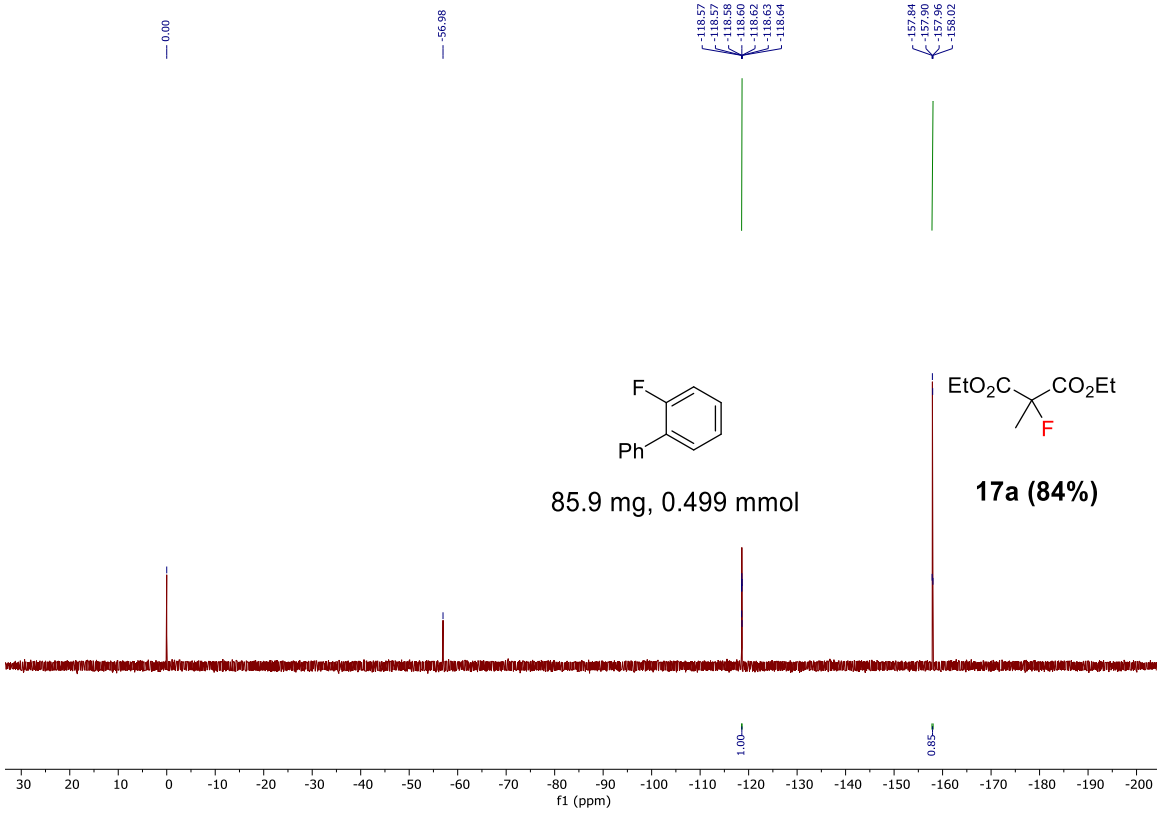

0.00
-56.95
-62.52
-108.06
-118.57
F
F3C
F
Ph
15f (68%)
86.6 mg, 0.503 mmol
2.28
0.68
1.00
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

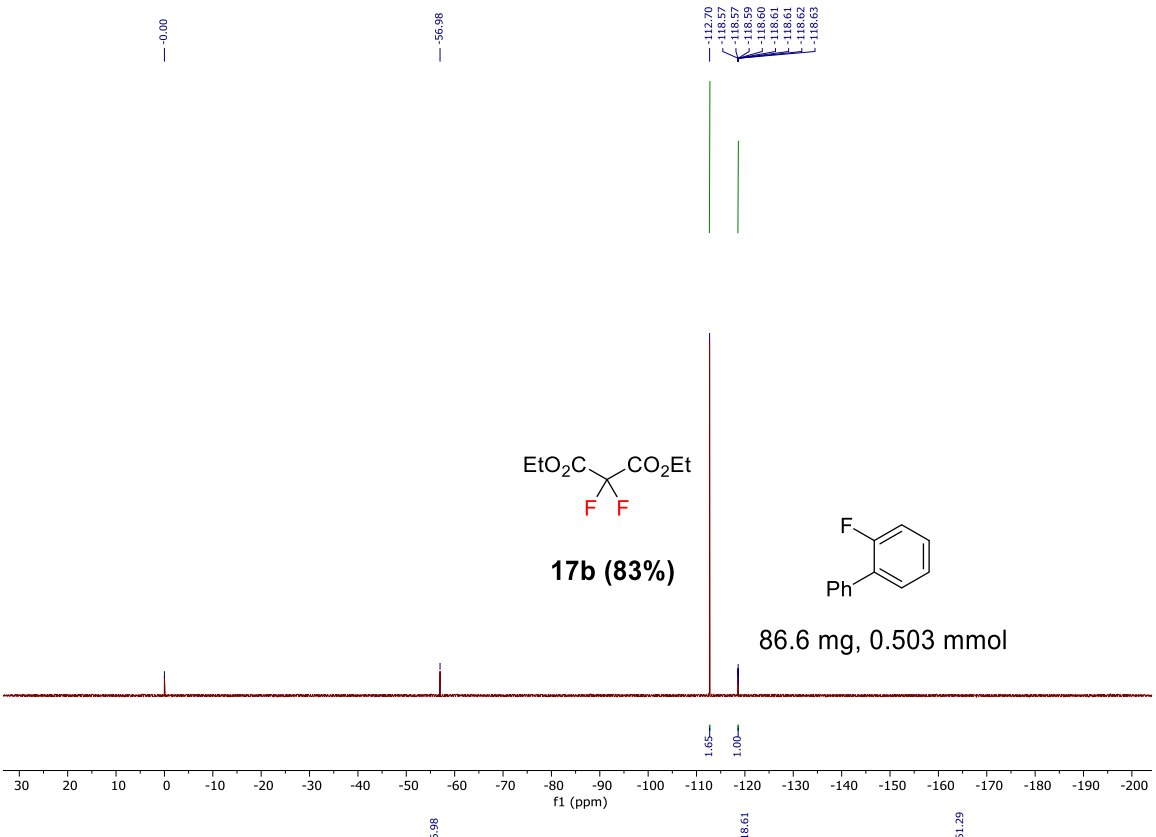

0.00
-56.94
-102.96
-118.57
F
NC
F
Ph
15g (64%)
86.4 mg, 0.502 mmol
0.64
1.00
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

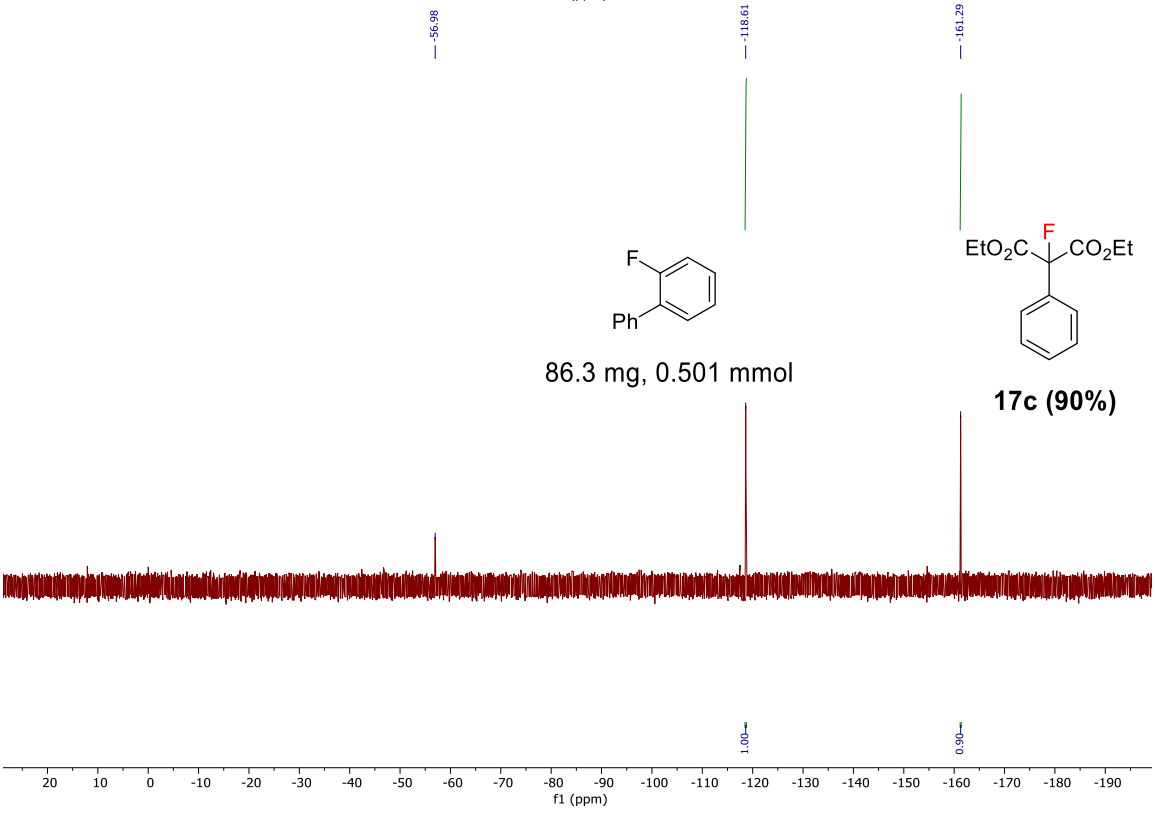

-0.00
-56.95
-106.60
-118.57
F
EtO2C
15h (48%)
F
Ph
86.1 mg, 0.500 mmol
0.48
1.00
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

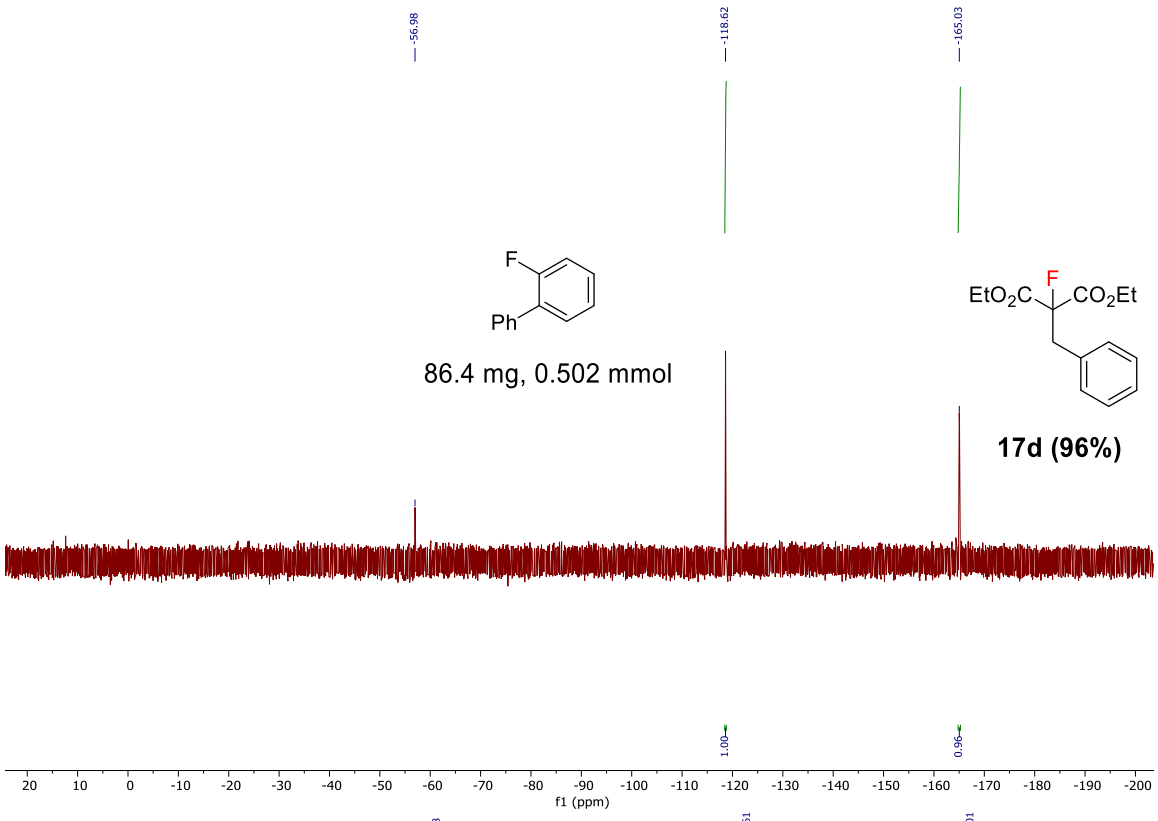

-0.00
-56.96
-118.57
-123.96
F
Ph
86.5 mg, 0.503 mmol
F
15i (83%)
1.00
0.83
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

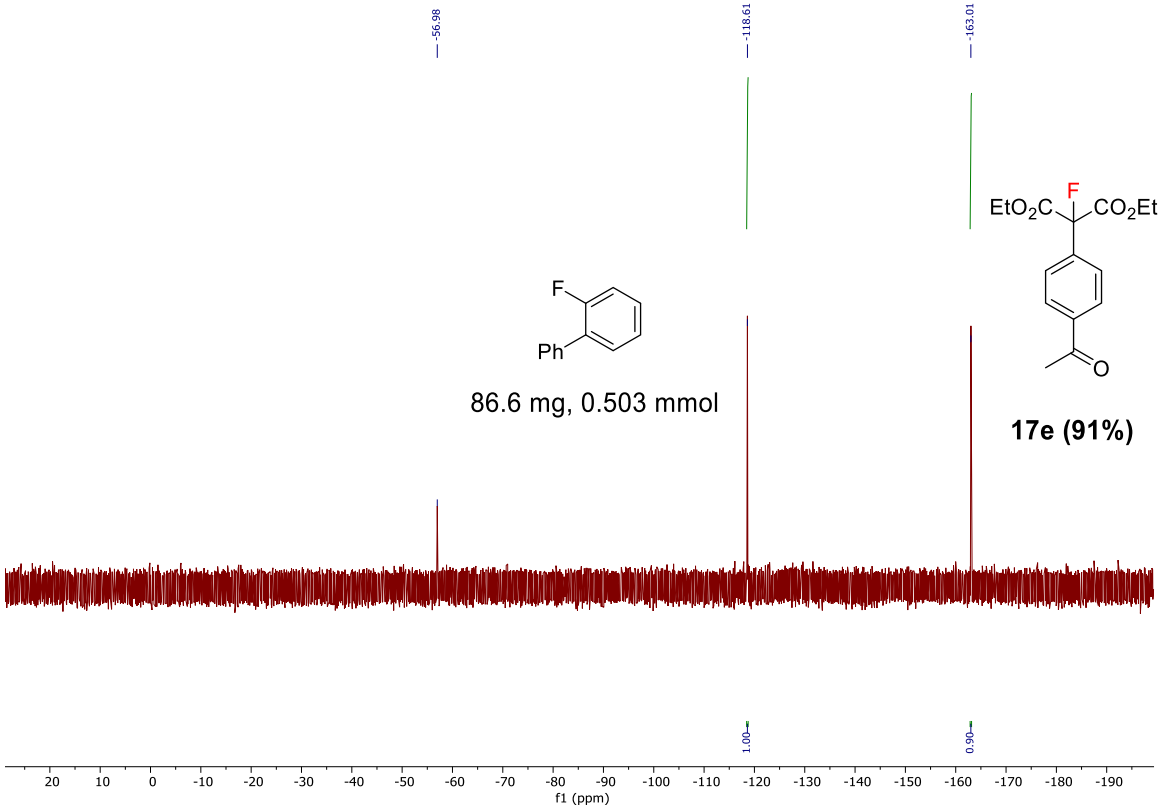

0.00
-56.95
-118.58
-134.63
F
Ph
86.1 mg, 0.500 mmol
S
F
15j (45%)
1.00
0.45
f1 (ppm)

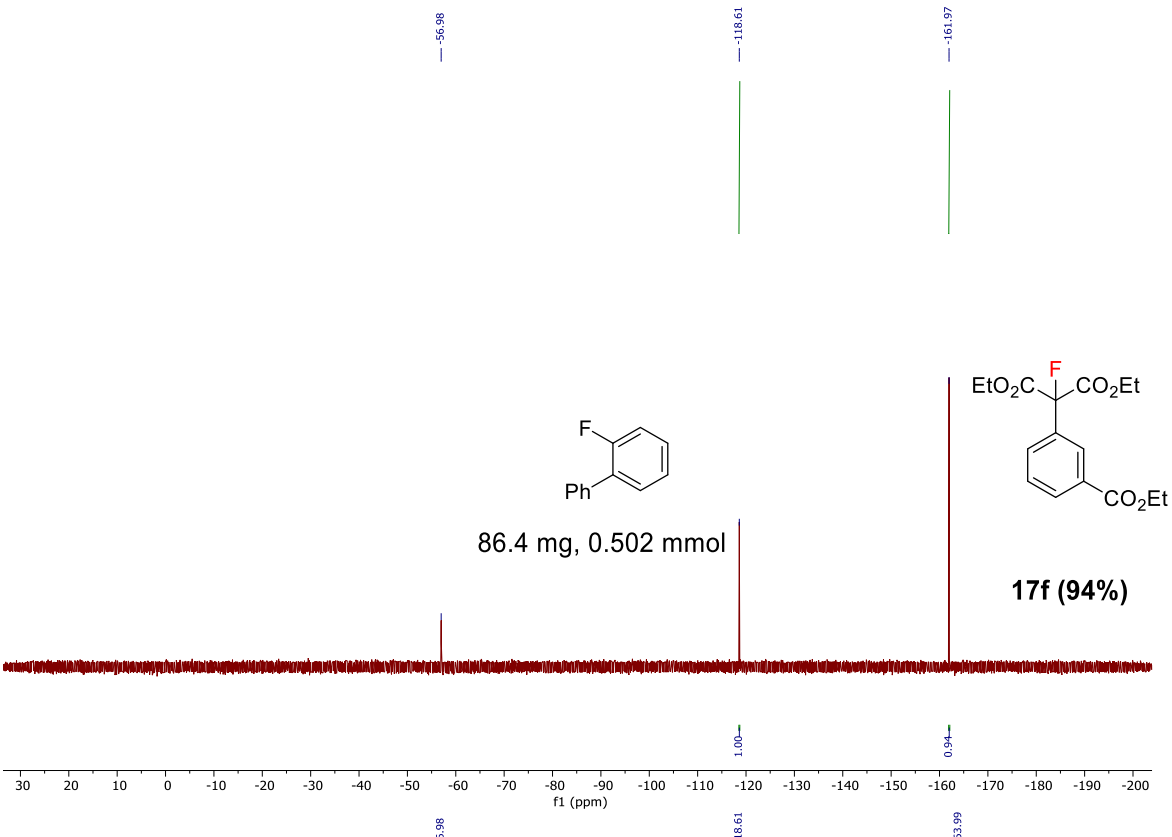

0.00
-56.98
-118.57
-118.57
-118.58
-118.60
-118.62
-118.63
-118.64
-157.84
-157.90
-157.96
-158.02
F
Ph
85.9 mg, 0.499 mmol
EtO2C
CO2Et
F
17a (84%)
1.00
0.85
f1 (ppm)

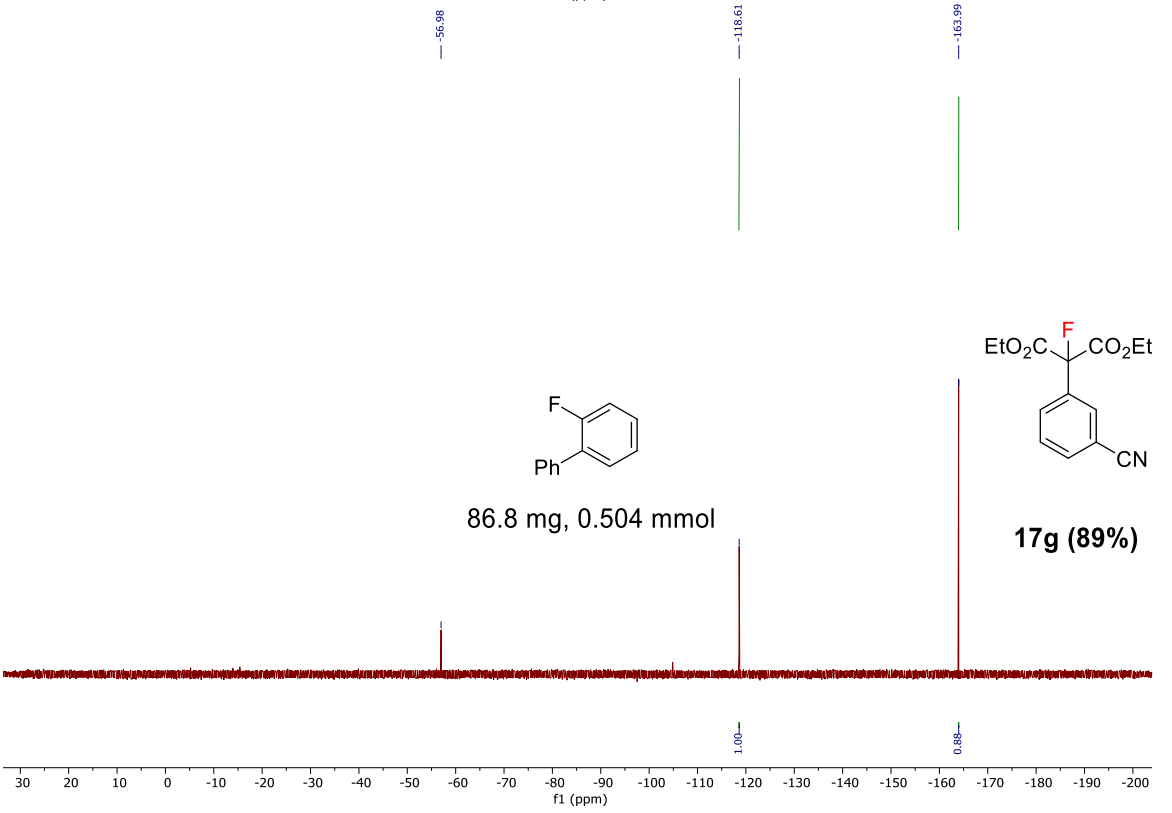

-0.00
-56.98
-112.70
-118.57
-118.57
-118.59
-118.60
-118.61
-118.61
-118.62
-118.63
EtO2C
CO2Et
F F
17b (83%)
F
Ph
86.6 mg, 0.503 mmol
1.65
1.00
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

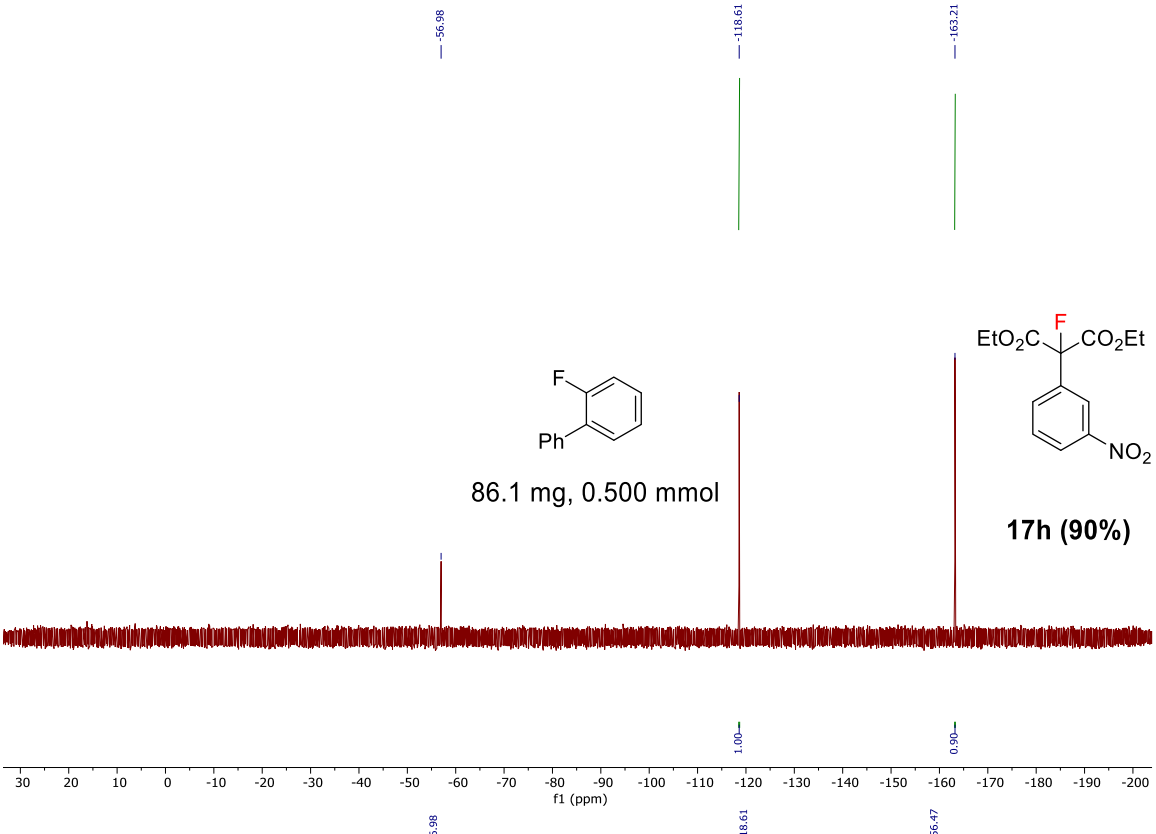

-56.98
-118.61
-161.29
F
Ph
86.3 mg, 0.501 mmol
EtO2C
F
CO2Et
17c (90%)
1.00
0.90
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

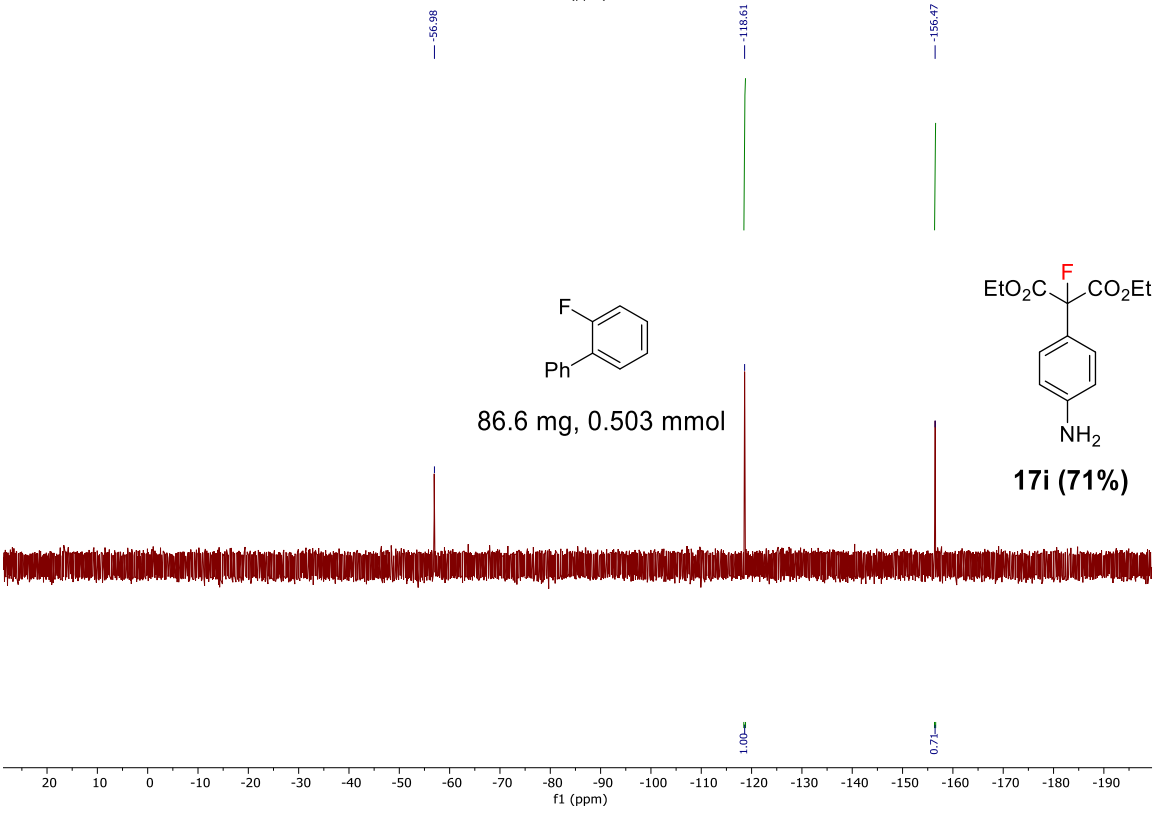

-56.98
-118.62
-165.03
F
Ph
86.4 mg, 0.502 mmol
EtO2C
F
CO2Et
17d (96%)
1.00
0.96
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

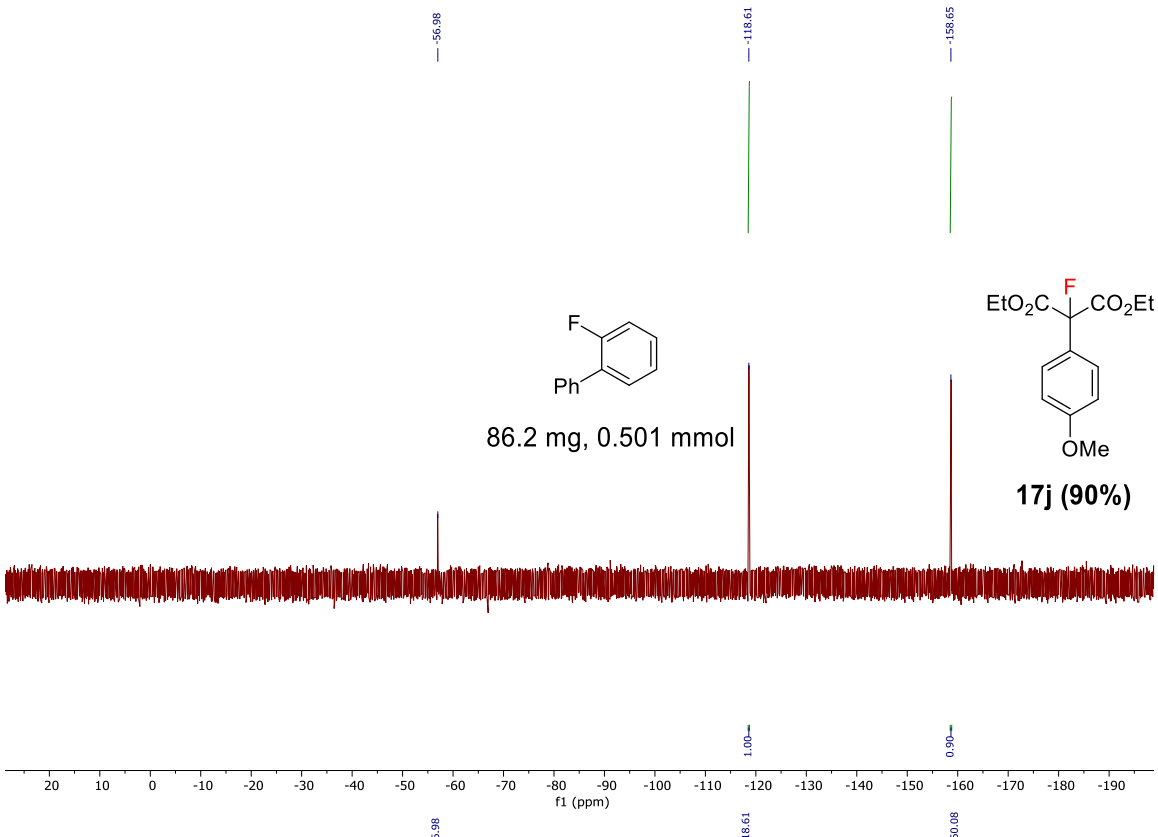

-56.98
-118.61
-163.01
F
Ph
86.6 mg, 0.503 mmol
EtO2C
F
CO2Et
O
17e (91%)
1.00
0.90
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

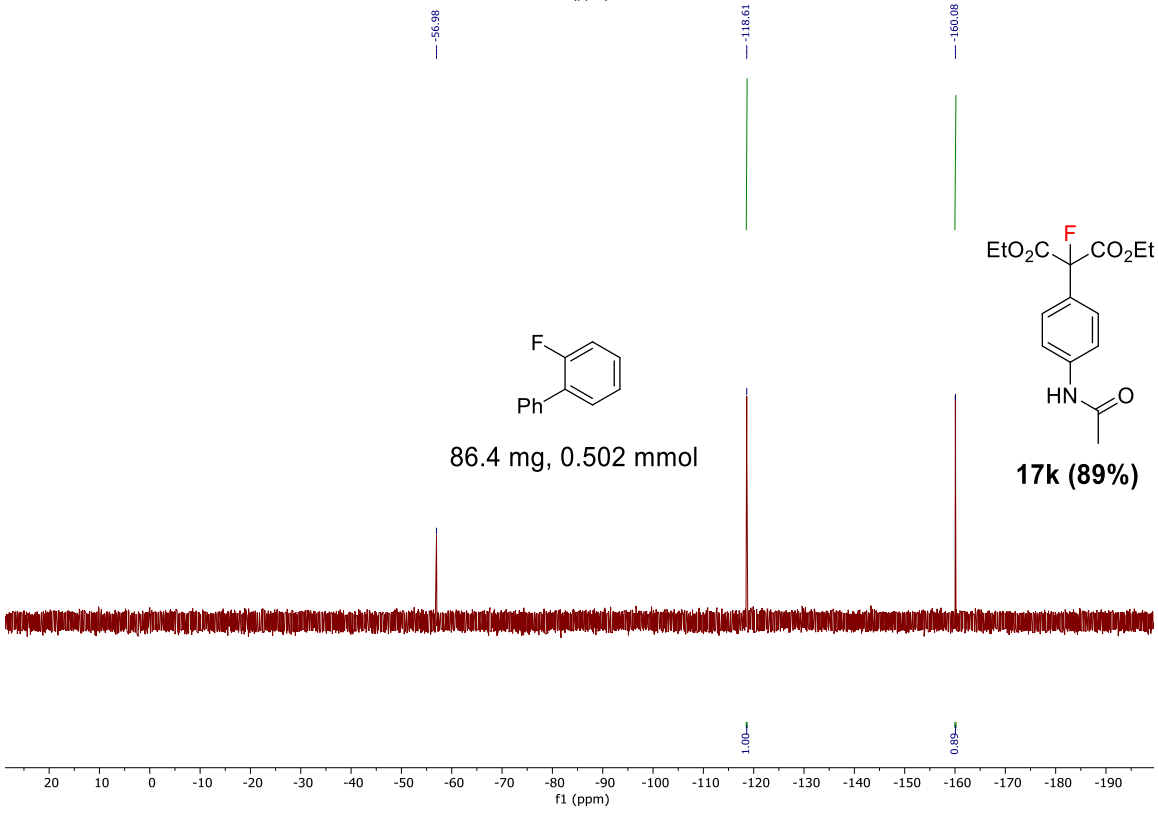

-56.98
-118.61
-161.97
F
Ph
86.4 mg, 0.502 mmol
EtO2C
F
CO2Et
CO2Et
17f (94%)
1.00
0.94
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

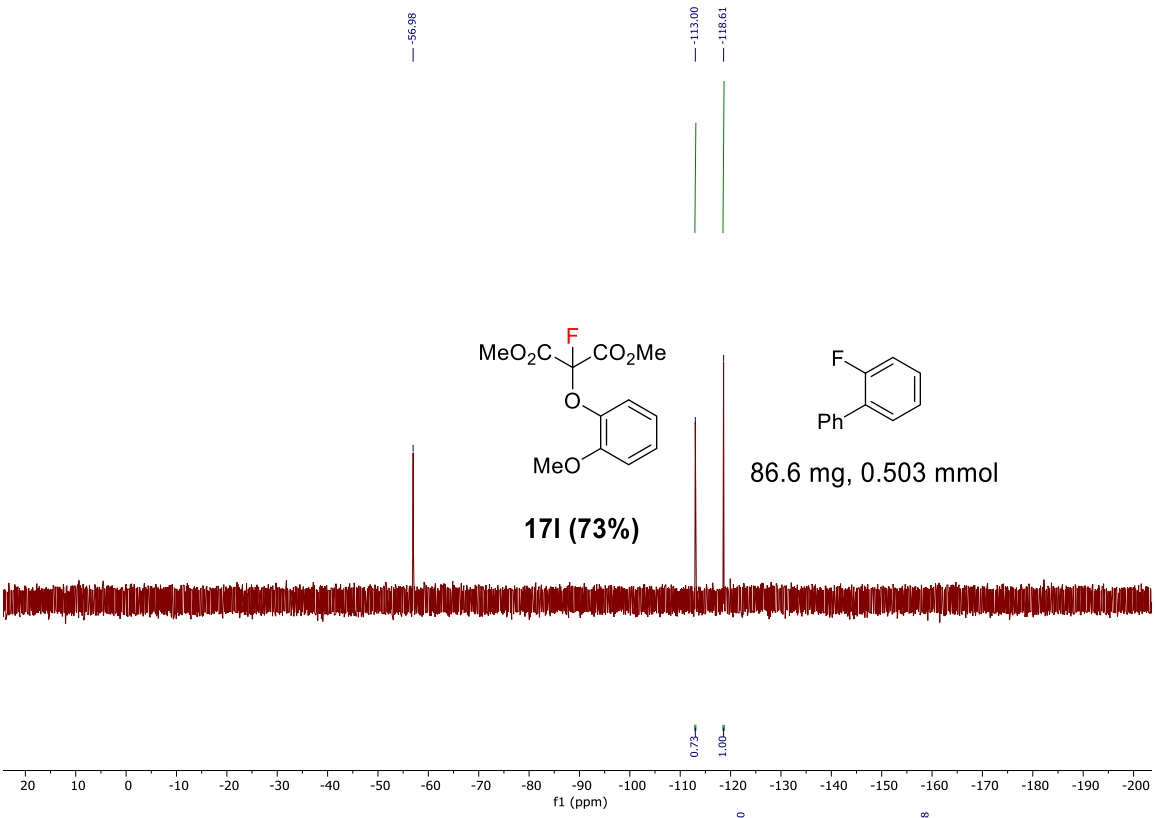

-56.98
-118.61
-163.99
F
Ph
86.8 mg, 0.504 mmol
EtO2C
F
CO2Et
CN
17g (89%)
1.00
0.88
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

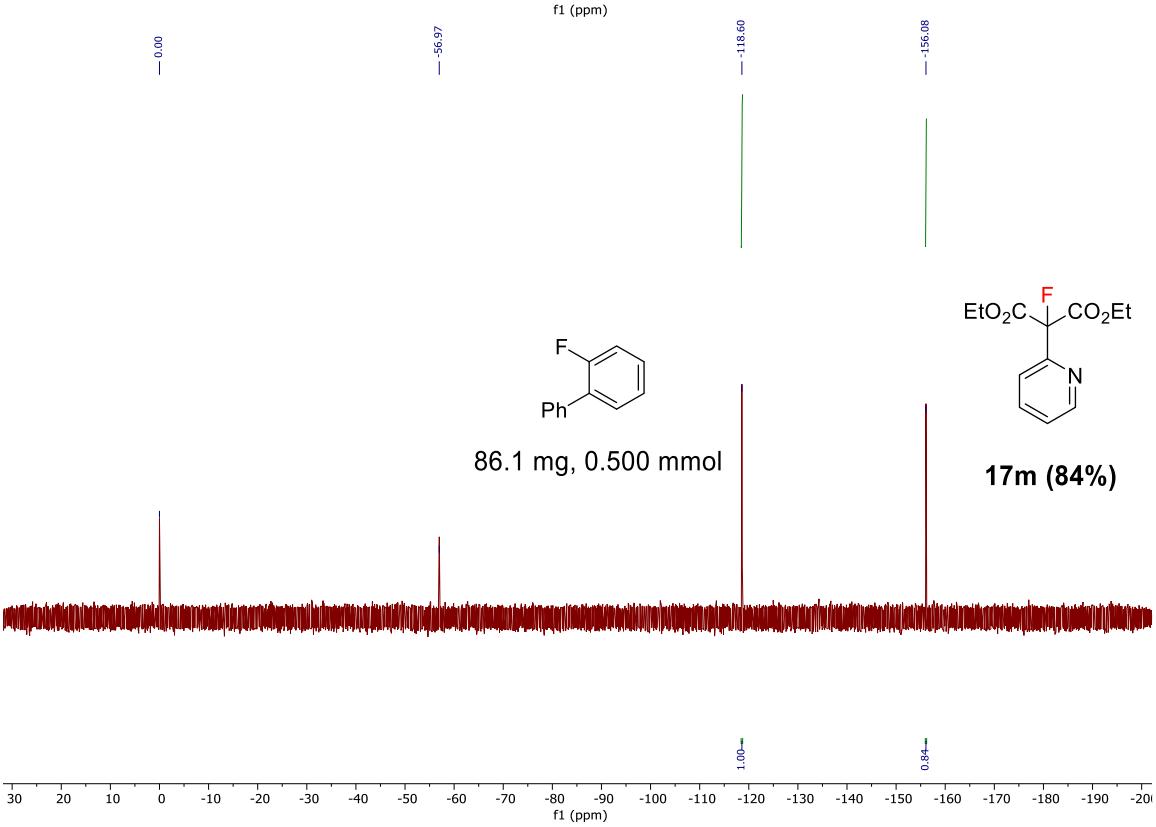

-56.98
-118.61
-163.21
F
Ph
86.1 mg, 0.500 mmol
EtO2C
F
CO2Et
NO2
17h (90%)
1.00
0.90
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

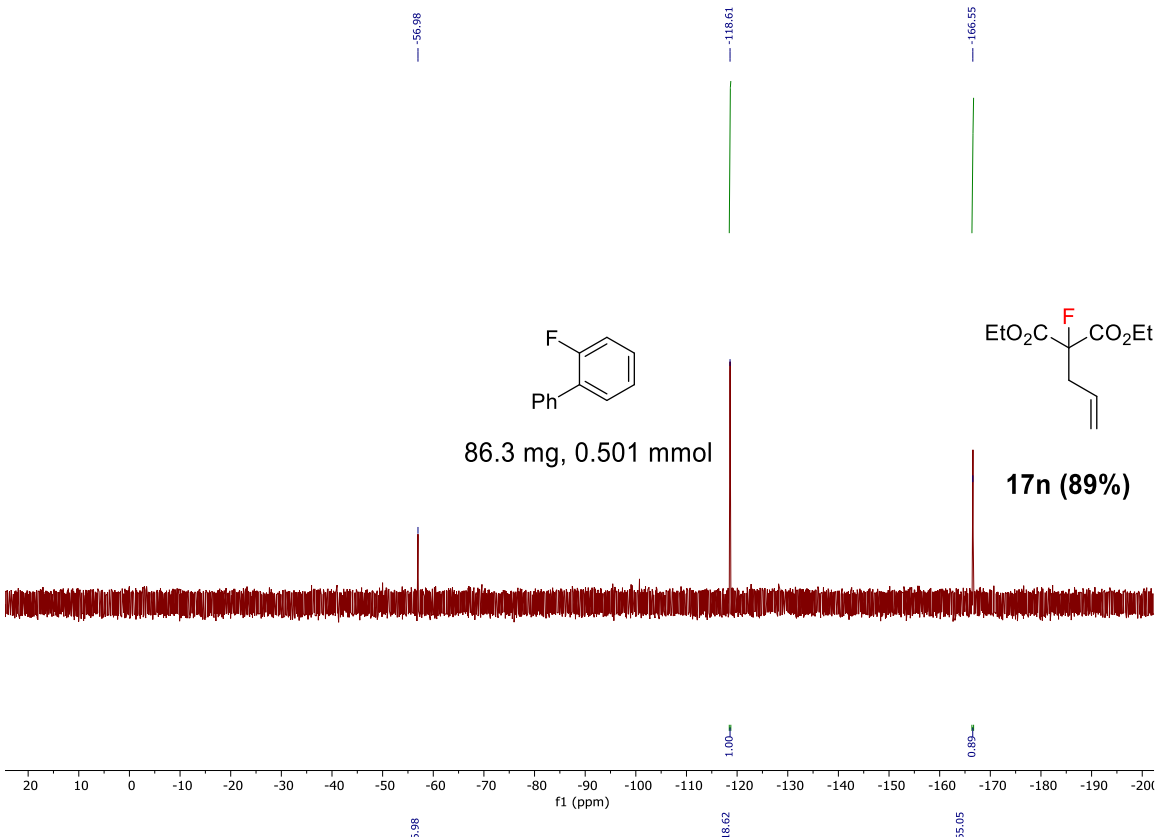

-56.98
-118.61
-156.47
F
Ph
86.6 mg, 0.503 mmol
EtO2C
F
CO2Et
NH2
17i (71%)
1.00
0.71
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

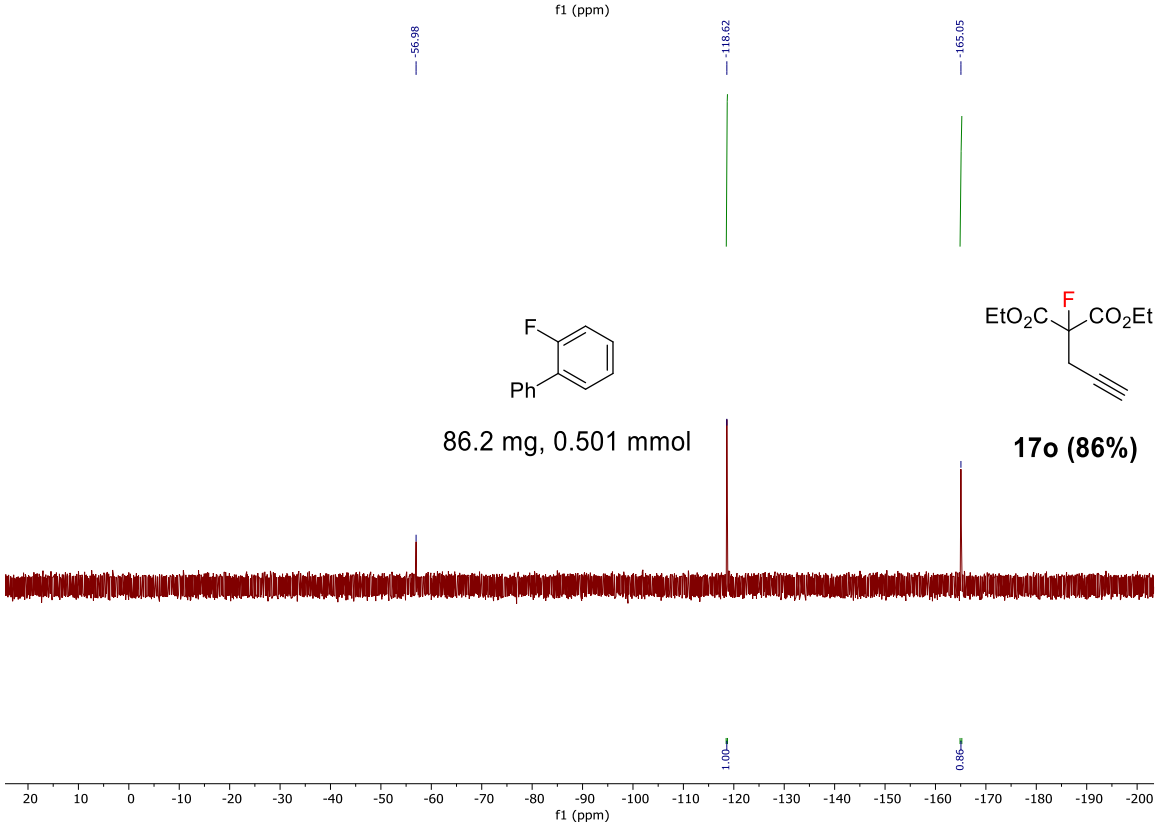

-56.98
-118.61
-158.65
F
Ph
86.2 mg, 0.501 mmol
EtO2C
F
CO2Et
OMe
17j (90%)
1.00
0.90
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

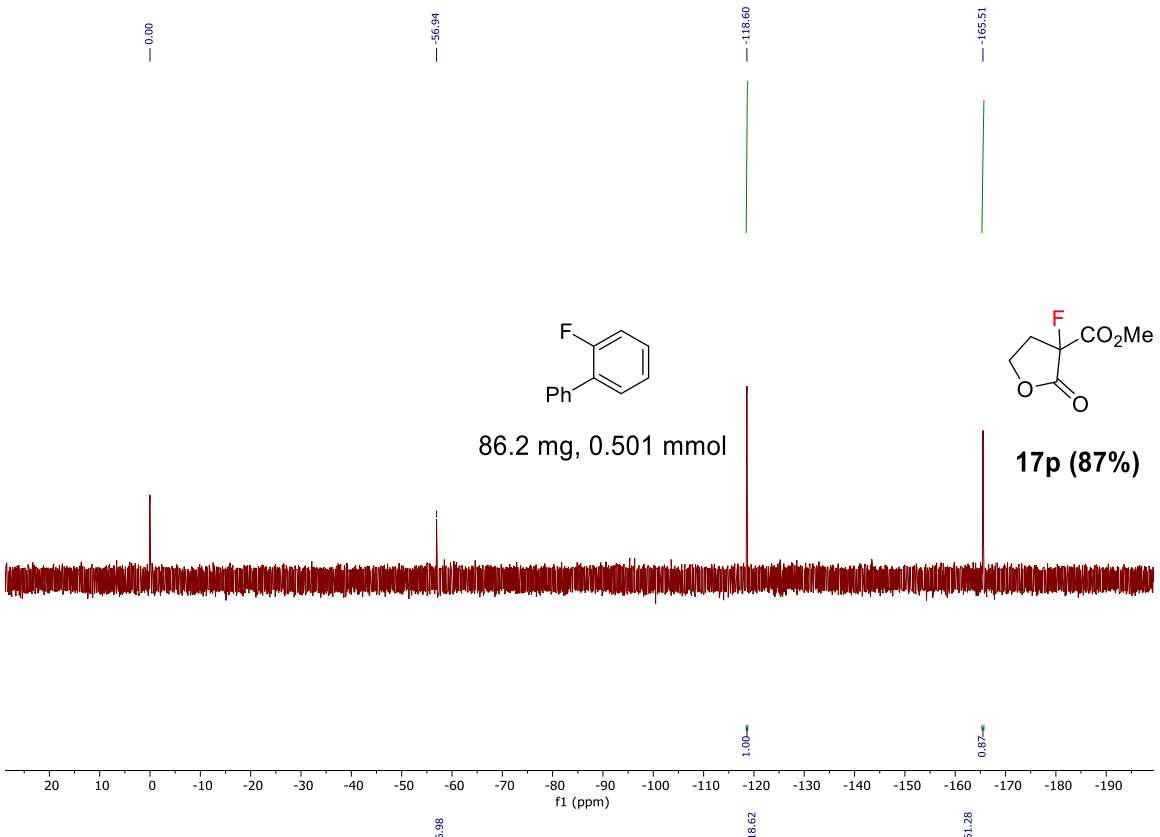

-56.98
-118.61
-160.08
F
Ph
86.4 mg, 0.502 mmol
EtO2C
F
CO2Et
HN
O
17k (89%)
1.00
0.89
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

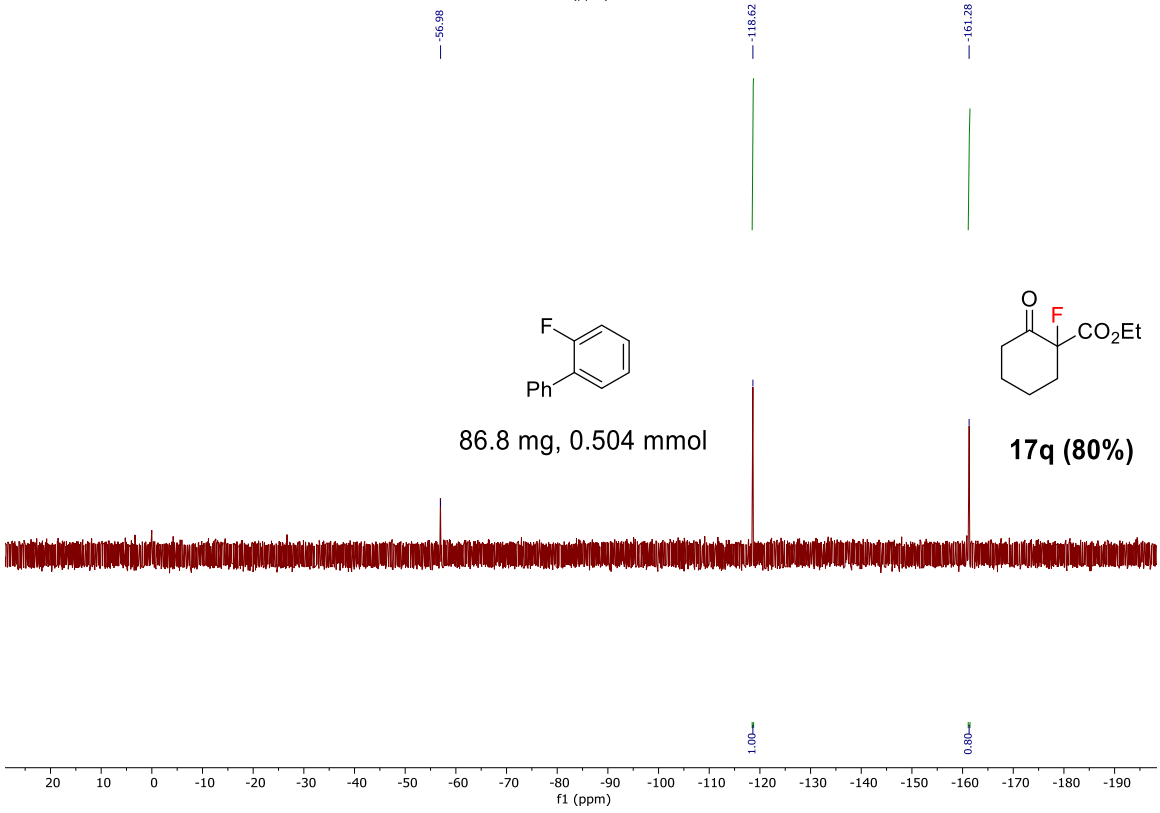

-56.98
-113.00
-118.61
F
MeO2C
CO2Me
O
MeO
17l (73%)
F
Ph
86.6 mg, 0.503 mmol
0.73
1.00
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

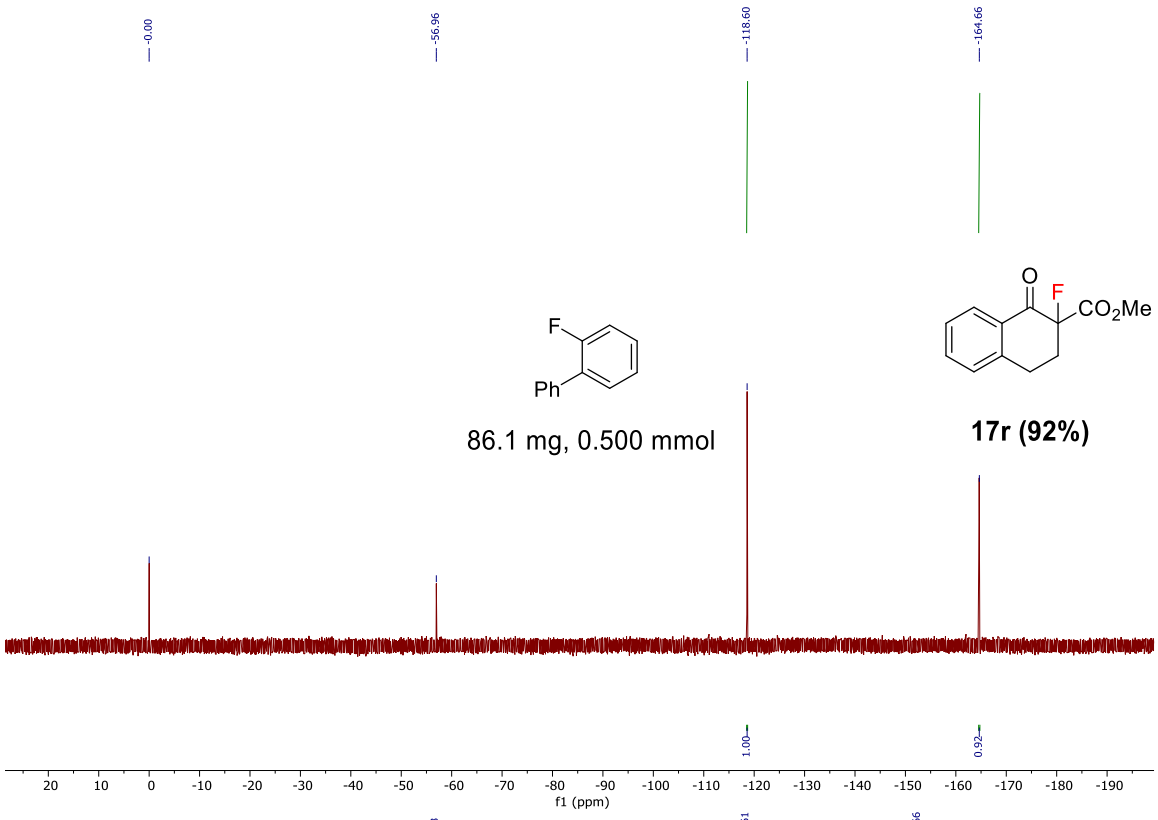

0.00
-56.97
-118.60
-156.08
F
Ph
86.1 mg, 0.500 mmol
F
EtO2C
CO2Et
N
17m (84%)
1.00
0.84
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

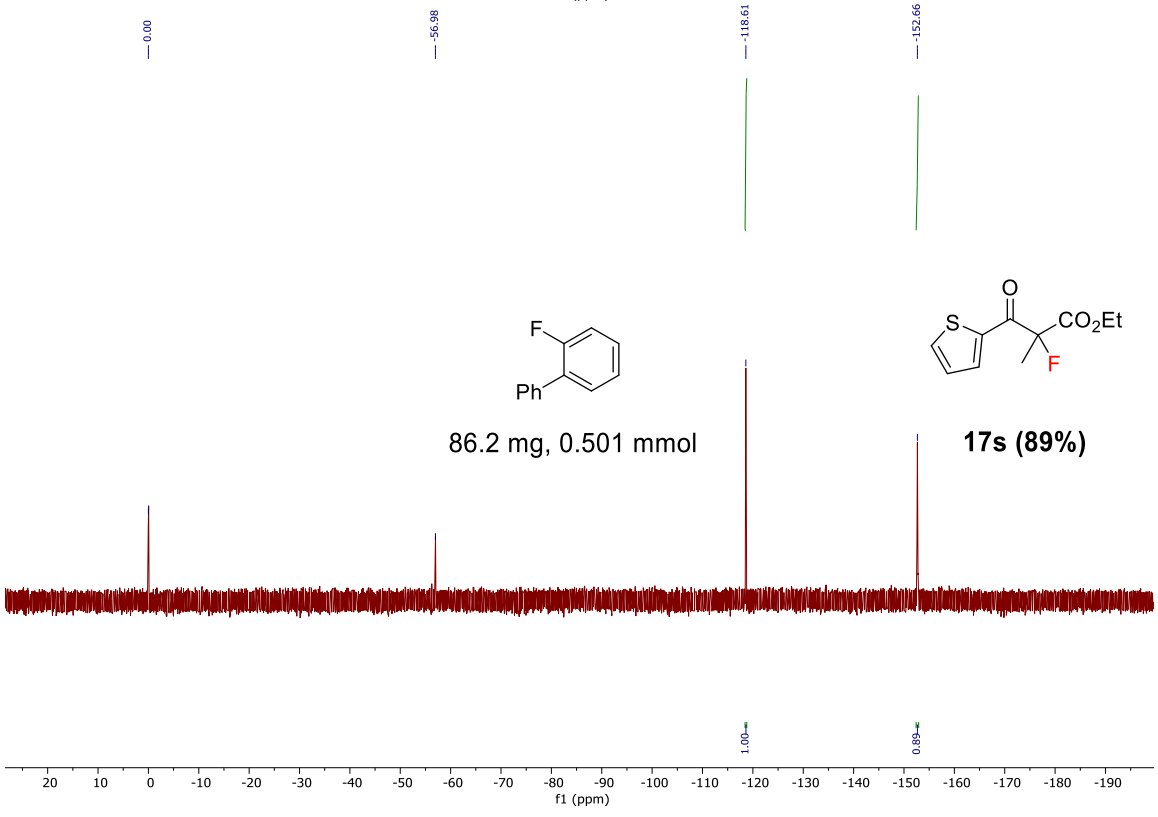

-56.98
-118.61
-166.55
F
Ph
86.3 mg, 0.501 mmol
EtO2C
F
CO2Et
17n (89%)
1.00
0.89
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

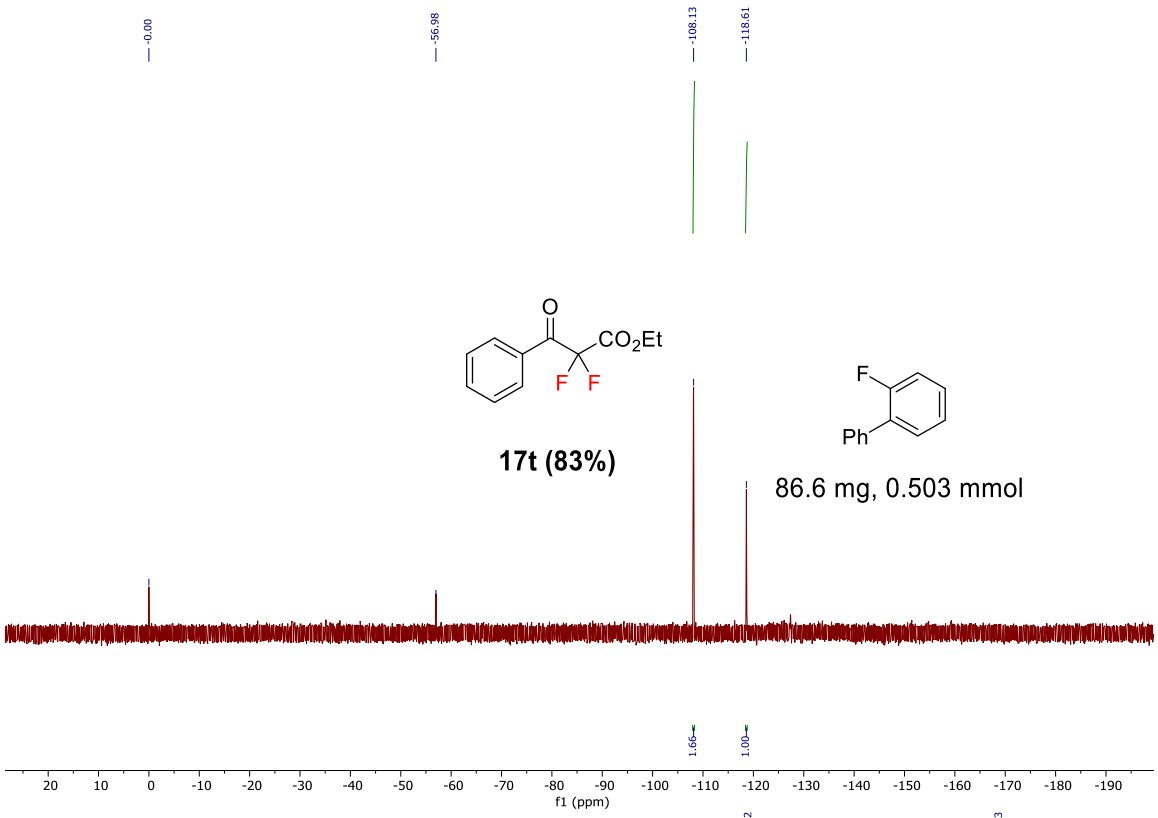

-56.98
-118.62
-165.05
F
Ph
86.2 mg, 0.501 mmol
EtO2C
F
CO2Et
17o (86%)
1.00
0.86
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

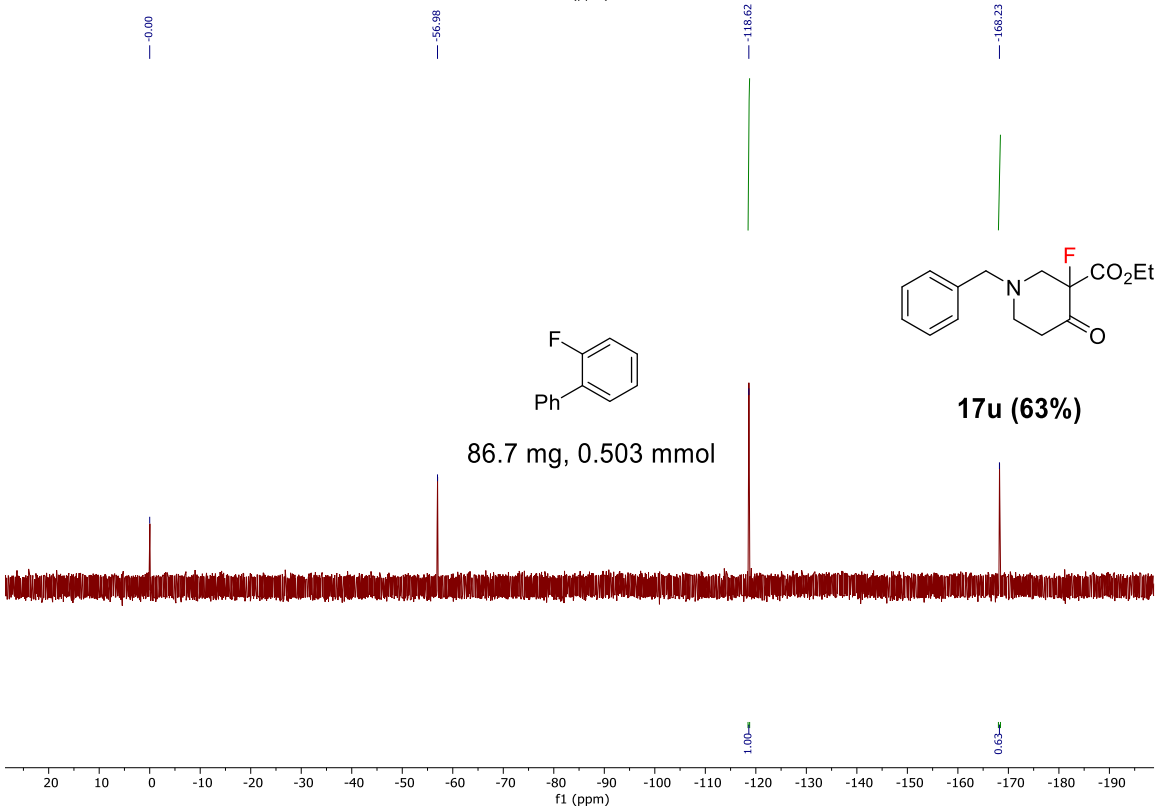

0.00
-56.94
-118.60
-165.51
F
Ph
86.2 mg, 0.501 mmol
F
CO2Me
O
O
17p (87%)
1.00
0.87
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

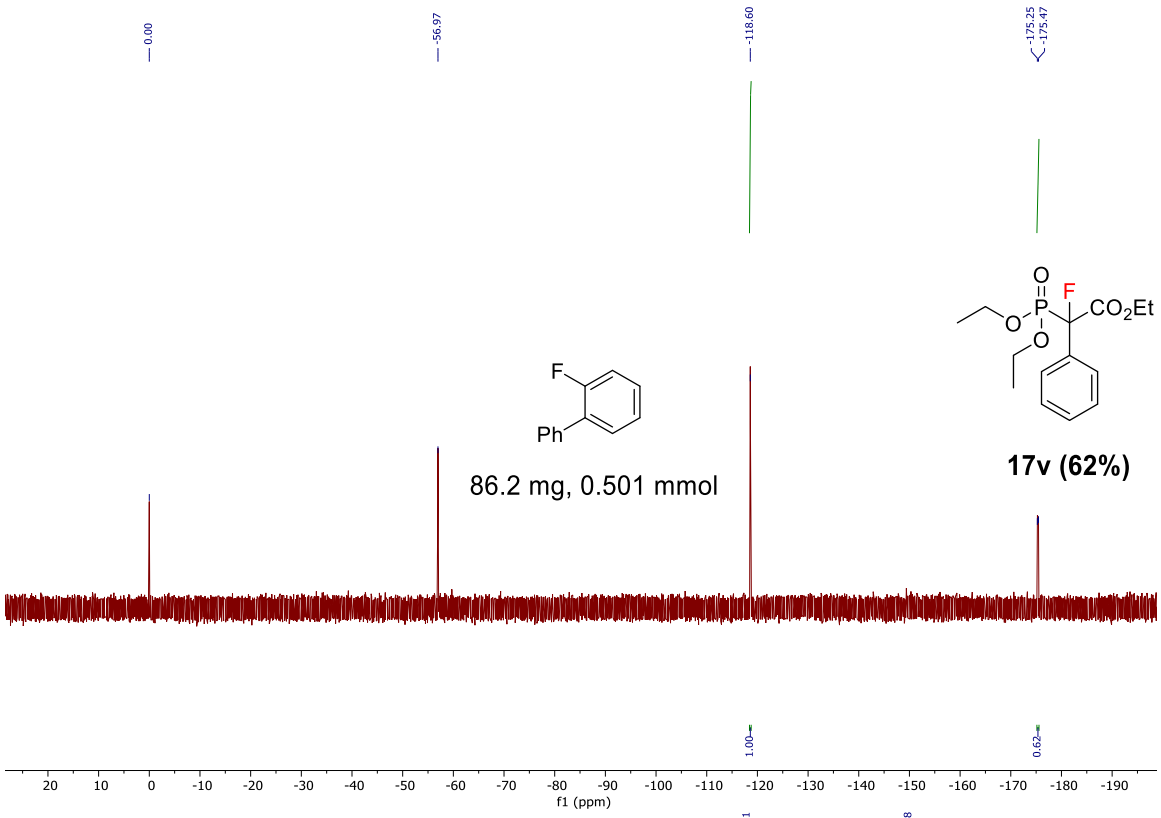

-56.98
-118.62
-161.28
F
Ph
86.8 mg, 0.504 mmol
O
F
CO2Et
17q (80%)
1.00
0.80
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

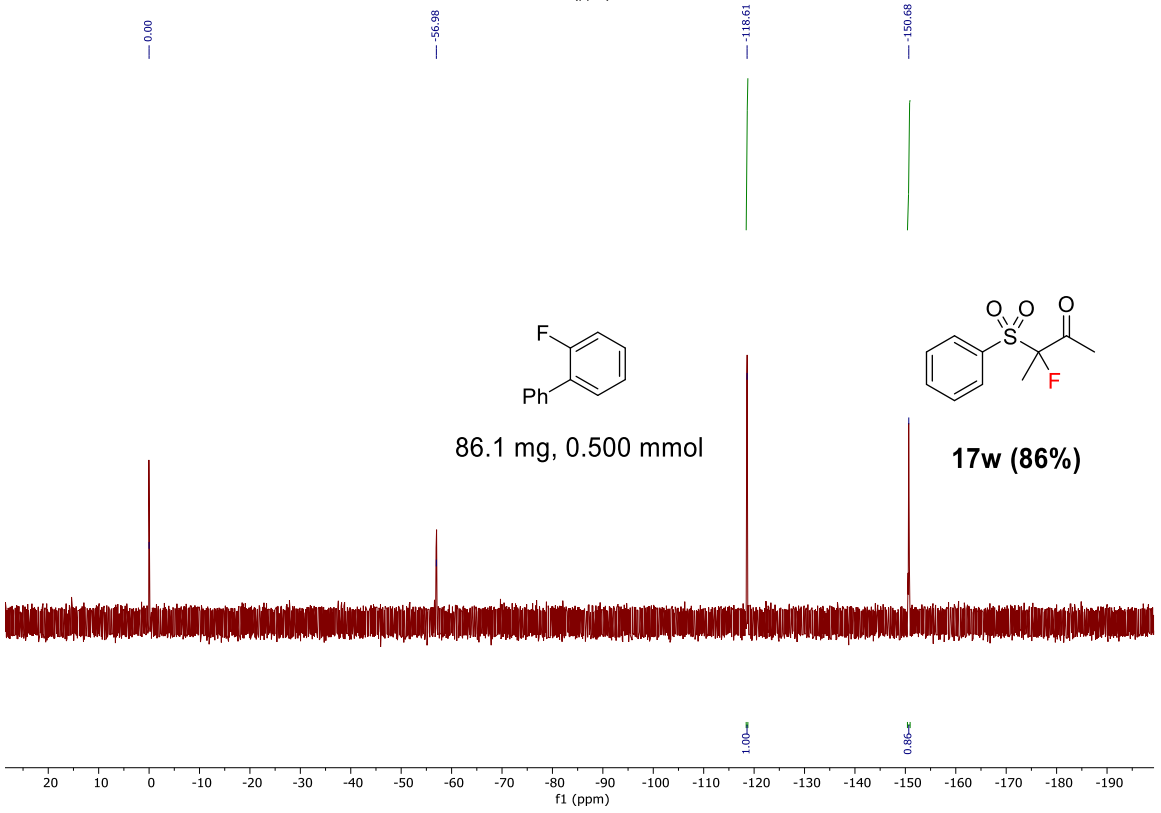

-0.00
-56.96
-118.60
-164.66
F
Ph
86.1 mg, 0.500 mmol
O
F
CO2Me
17r (92%)
1.00
0.92
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

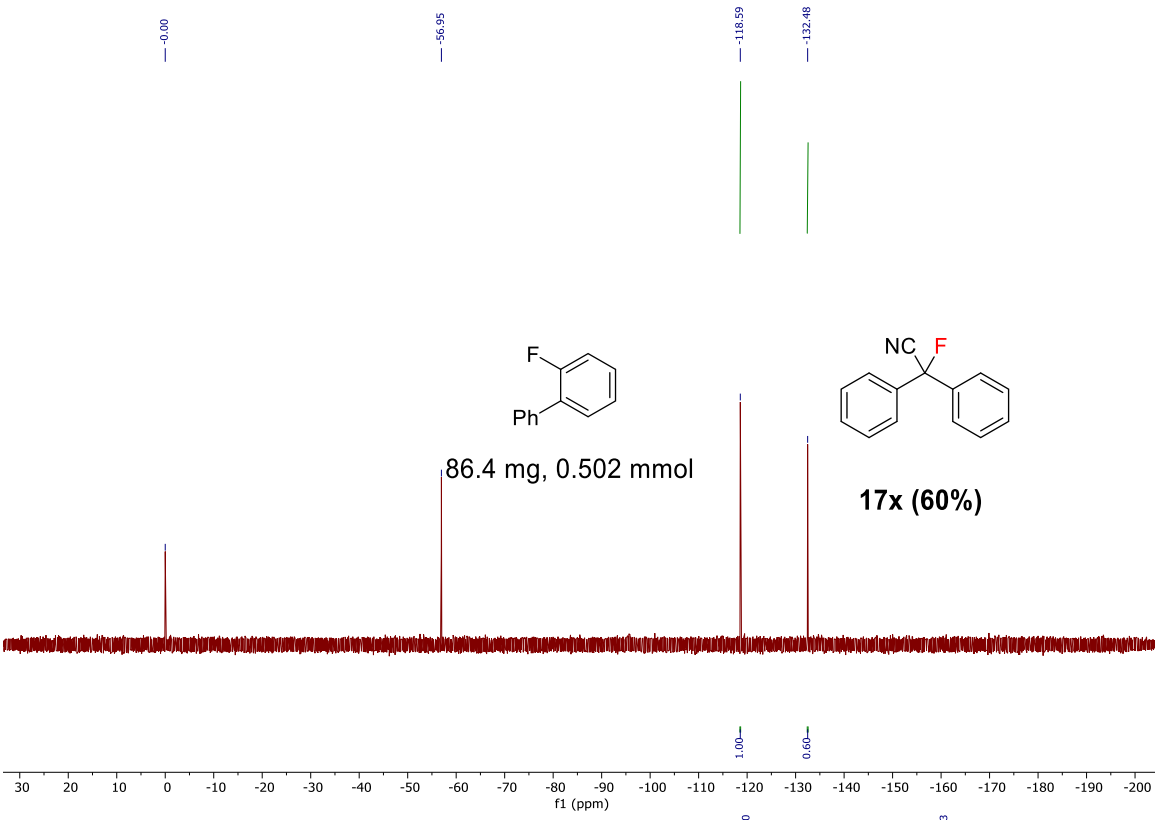

0.00
-56.98
-118.61
-152.66
F
Ph
86.2 mg, 0.501 mmol
O
S
CO2Et
F
17s (89%)
1.00
0.89
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

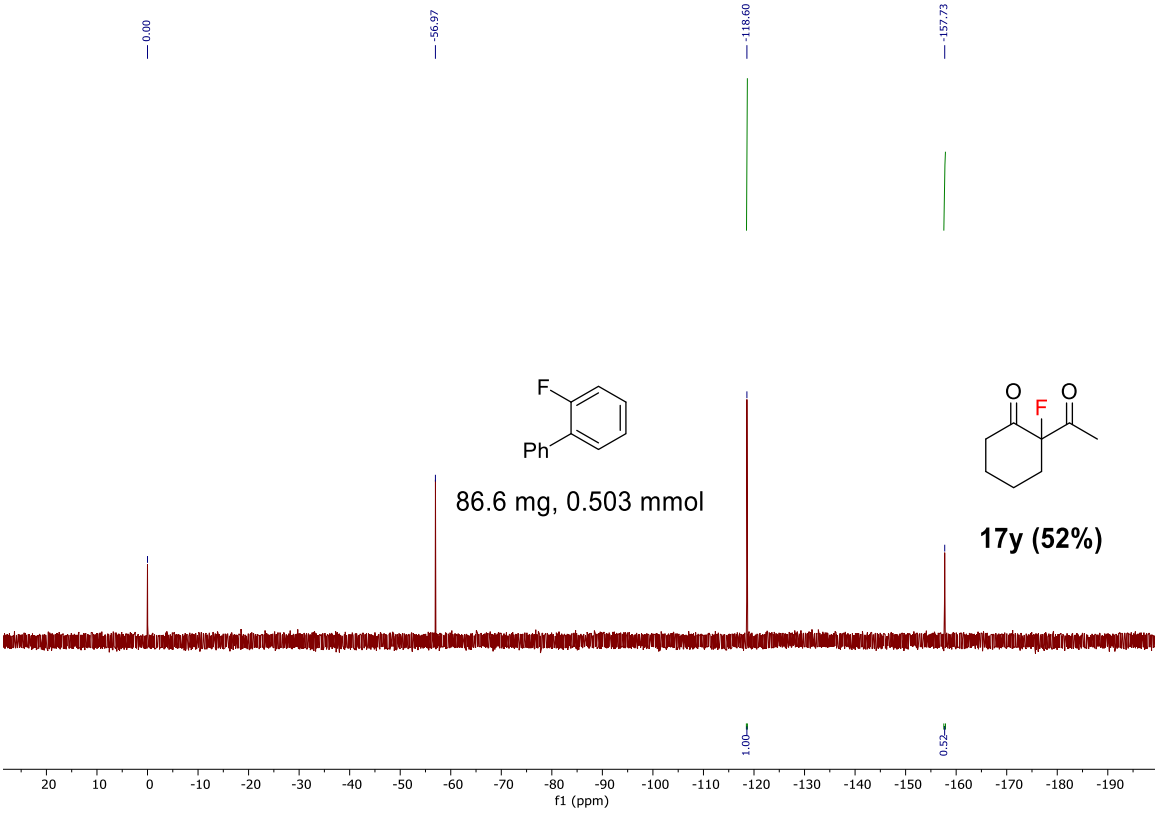

-0.00
-56.98
-108.13
-118.61
O
CO2Et
F F
17t (83%)
F
Ph
86.6 mg, 0.503 mmol
1.66
1.00
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

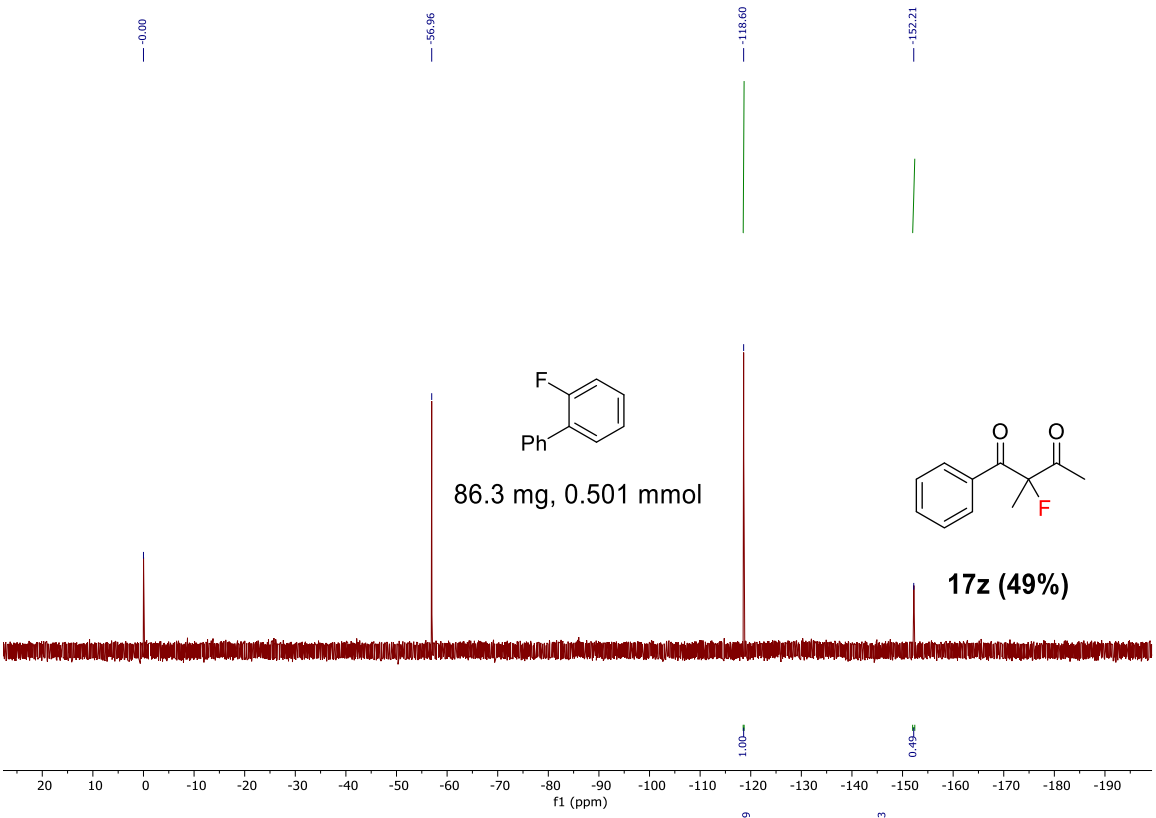

-0.00
-56.98
-118.62
-168.23
F
CO2Et
N
O
F
Ph
86.7 mg, 0.503 mmol
17u (63%)
1.00
0.63
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

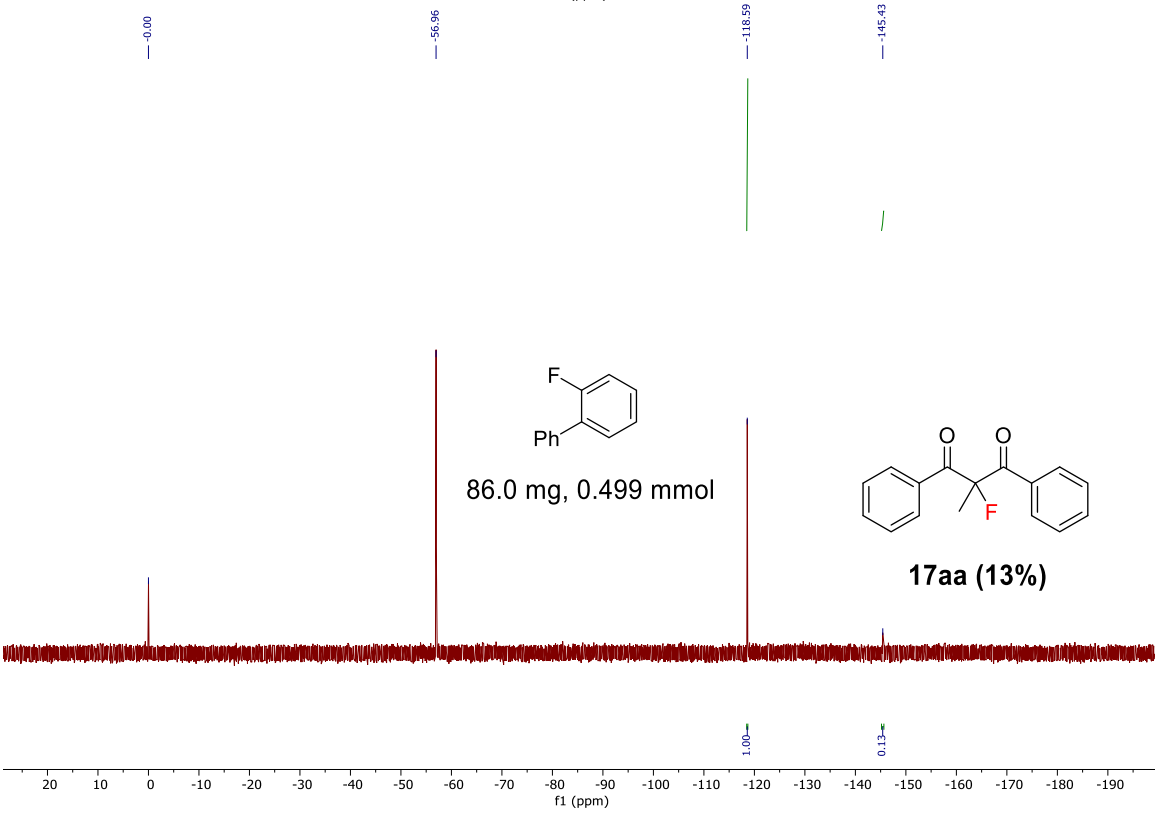

0.00
-56.97
-118.60
-175.25
-175.47
F
Ph
86.2 mg, 0.501 mmol
O
P
F
CO2Et
O
O
17v (62%)
1.00
0.62
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

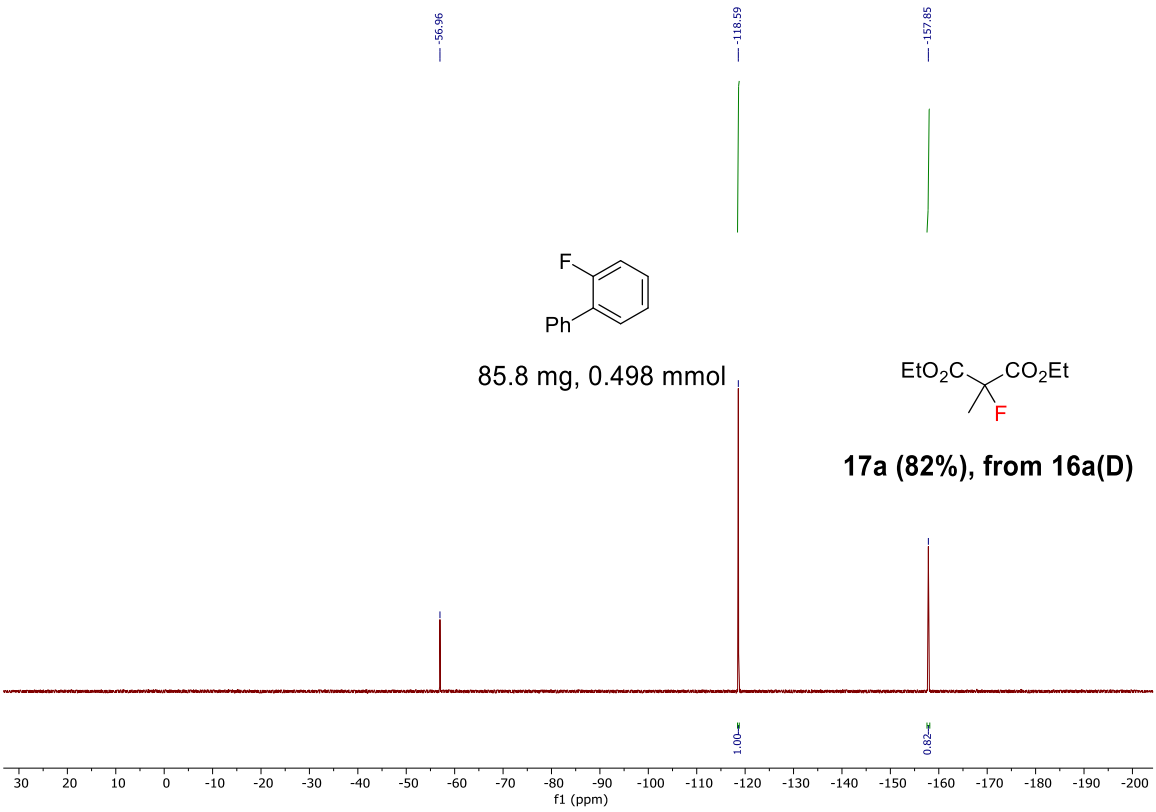

0.00
-56.98
-118.61
-150.68
F
Ph
86.1 mg, 0.500 mmol
O
O
S
O
F
17w (86%)
1.00
0.86
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)


-0.00
-56.95
-118.59
-132.48
F
Ph
86.4 mg, 0.502 mmol
NC
F
17x (60%)
1.00
0.60
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

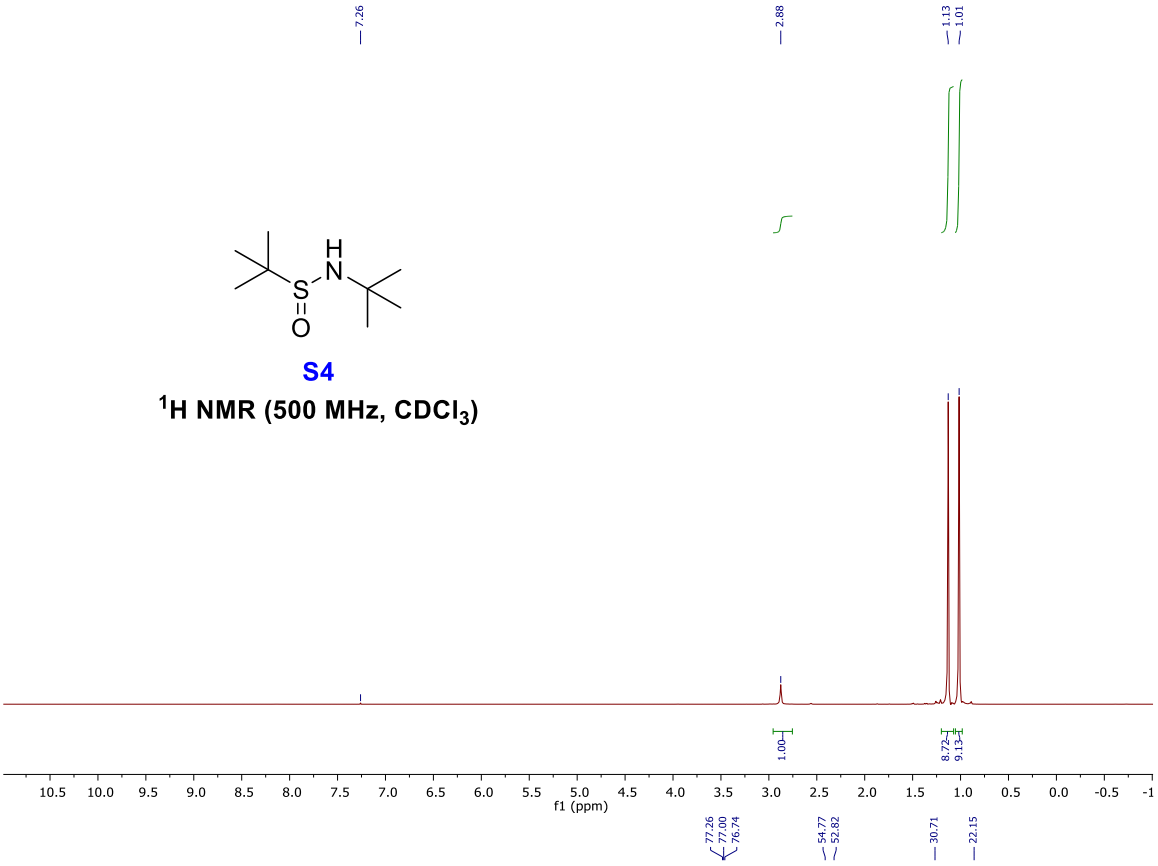

0.00
-56.97
-118.60
-157.73
F
Ph
86.6 mg, 0.503 mmol
O
F
O
17y (52%)
1.00
0.52
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)


-0.00
-56.96
-118.60
-152.21
F
Ph
86.3 mg, 0.501 mmol
O
O
F
17z (49%)
1.00
0.49
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)


-0.00
-56.96
-118.59
-145.43
F
Ph
86.0 mg, 0.499 mmol
O
O
F
17aa (13%)
1.00
0.13
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

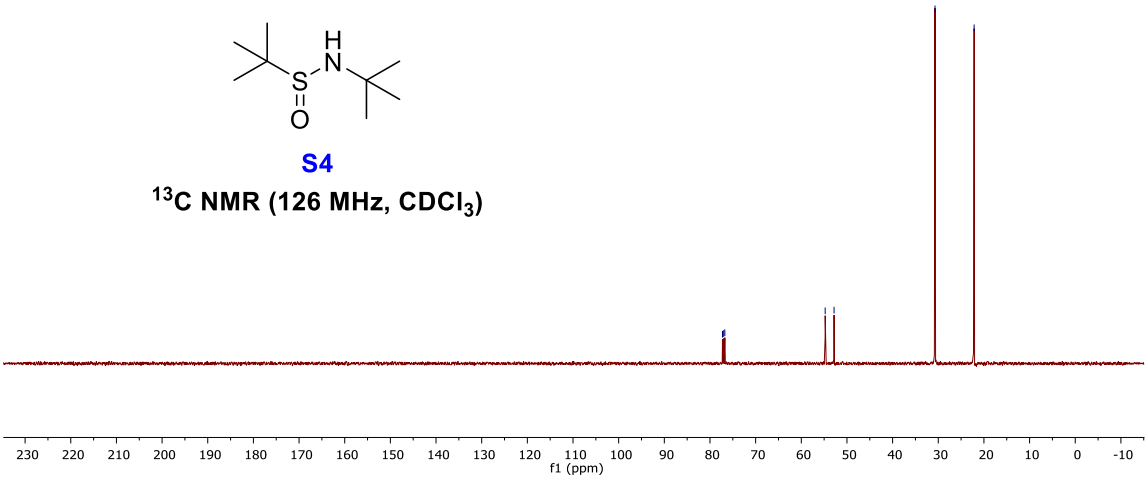

-56.96
-118.59
-157.85
F
Ph
85.8 mg, 0.498 mmol
EtO2C
CO2Et
F
17a (82%), from 16a(D)
1.00
0.82
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

A.3 ^{1}H, ^{13}C, and ^{19}F NMR spectra of isolated products



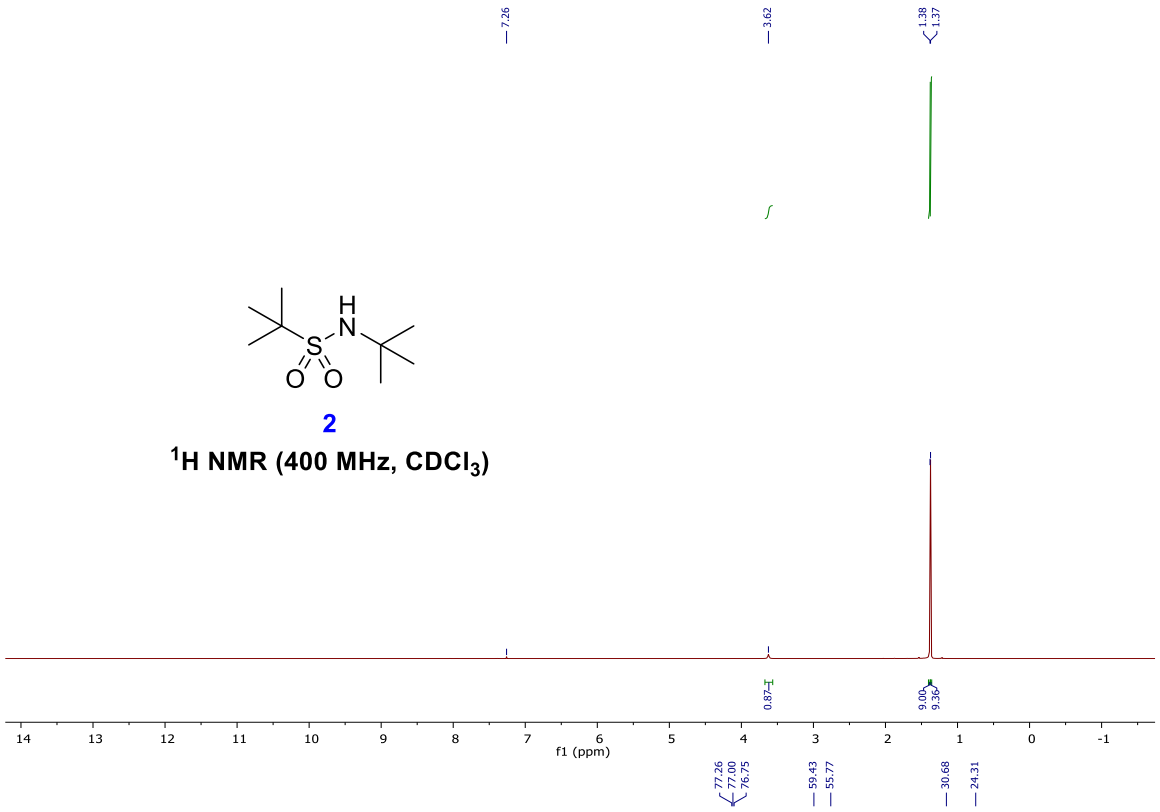
S4

^{1}H NMR (500 MHz, $CDCl_3$)



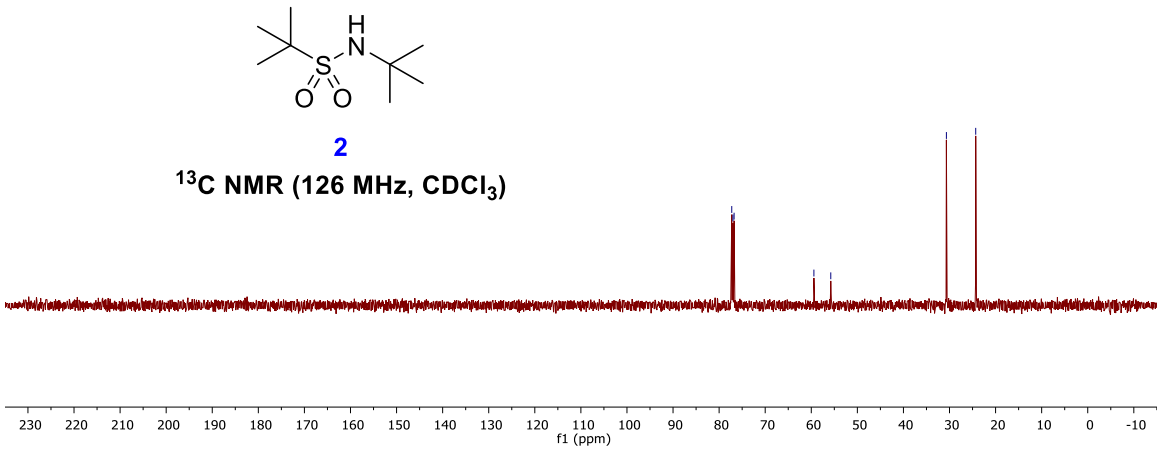
S4

^{13}C NMR (126 MHz, $CDCl_3$)



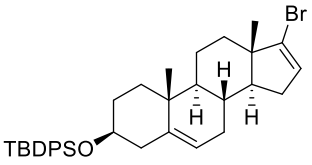
2

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



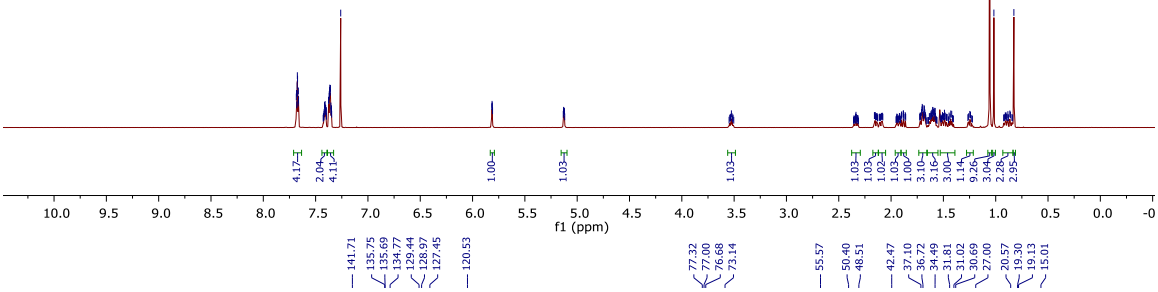
2

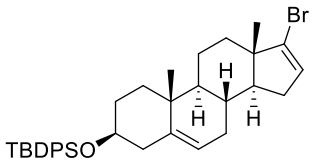
^{13}C NMR (126 MHz, $CDCl_3$)



7j

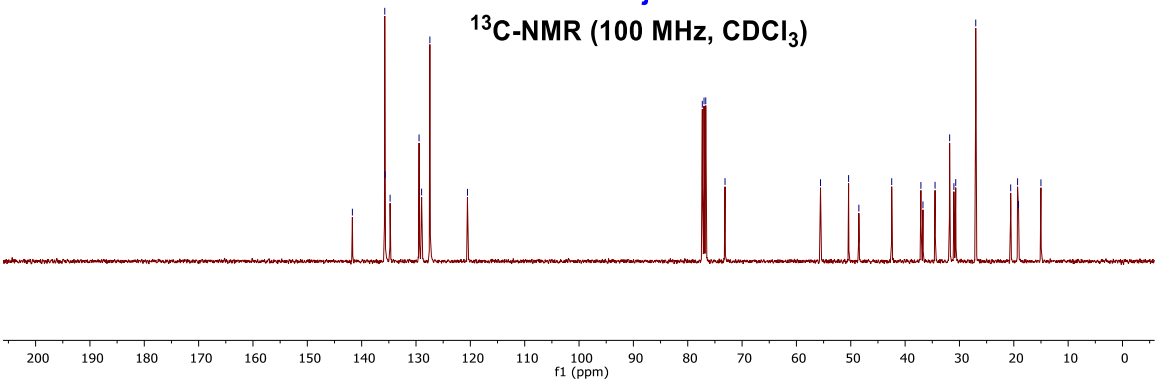
^{1}H-NMR (700 MHz, $CDCl_3$)

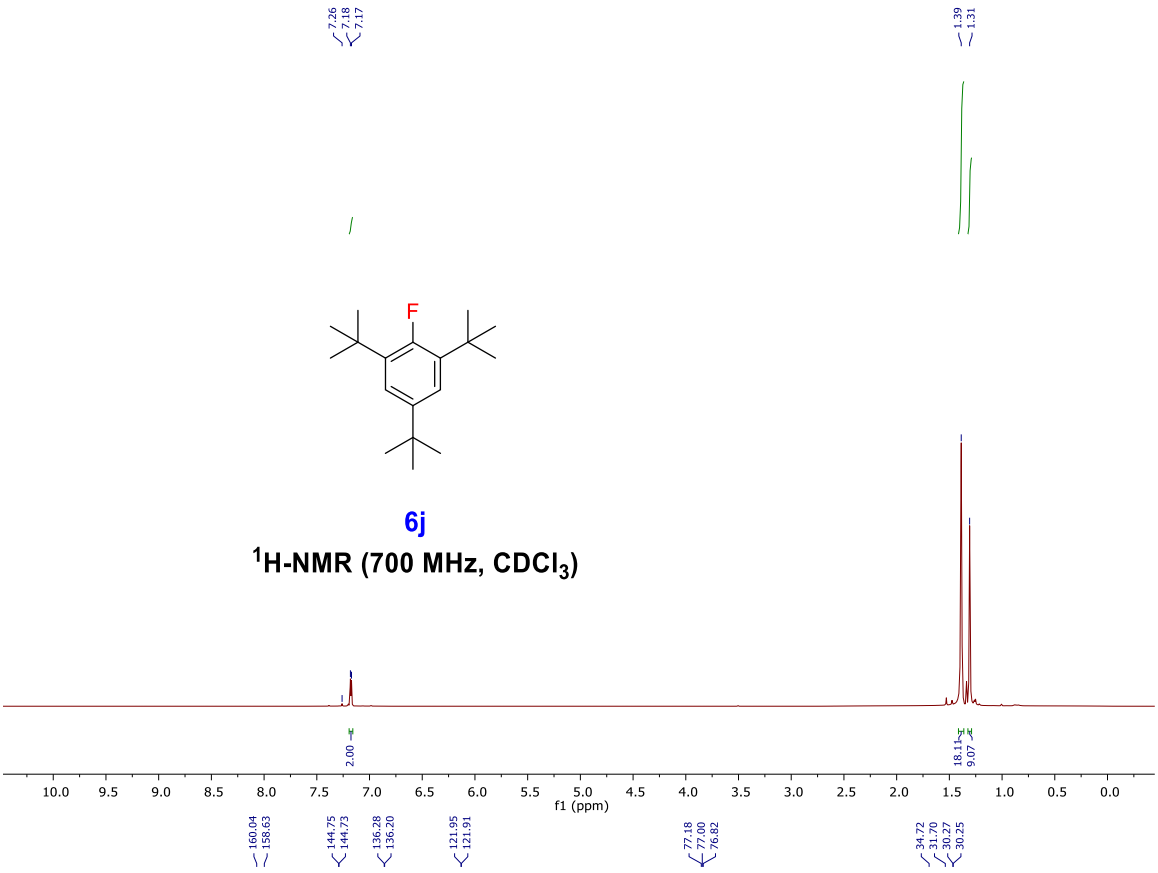




7j

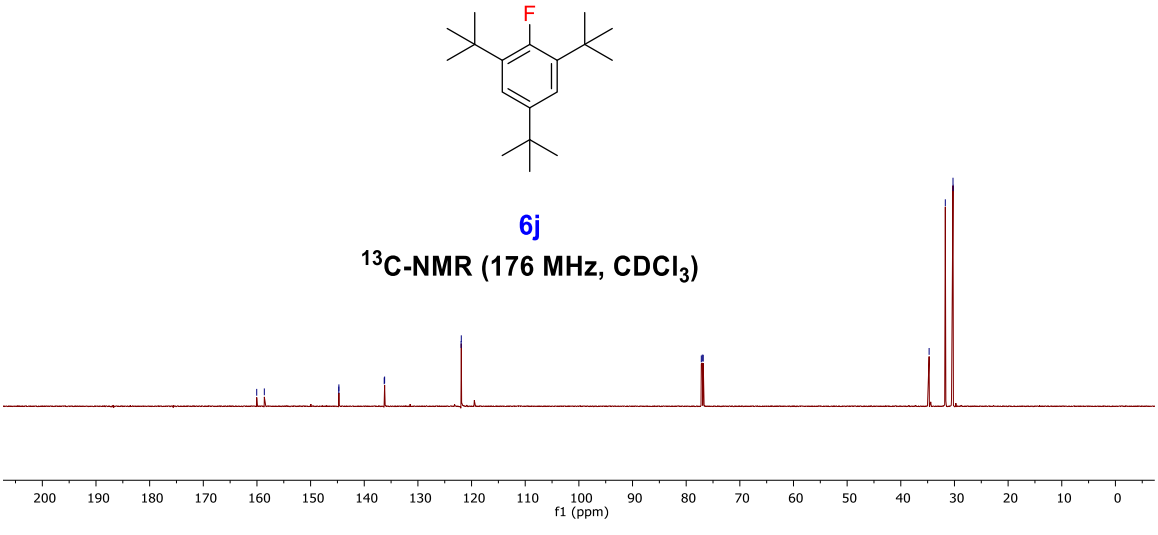
^{13}C-NMR (100 MHz, $CDCl_3$)





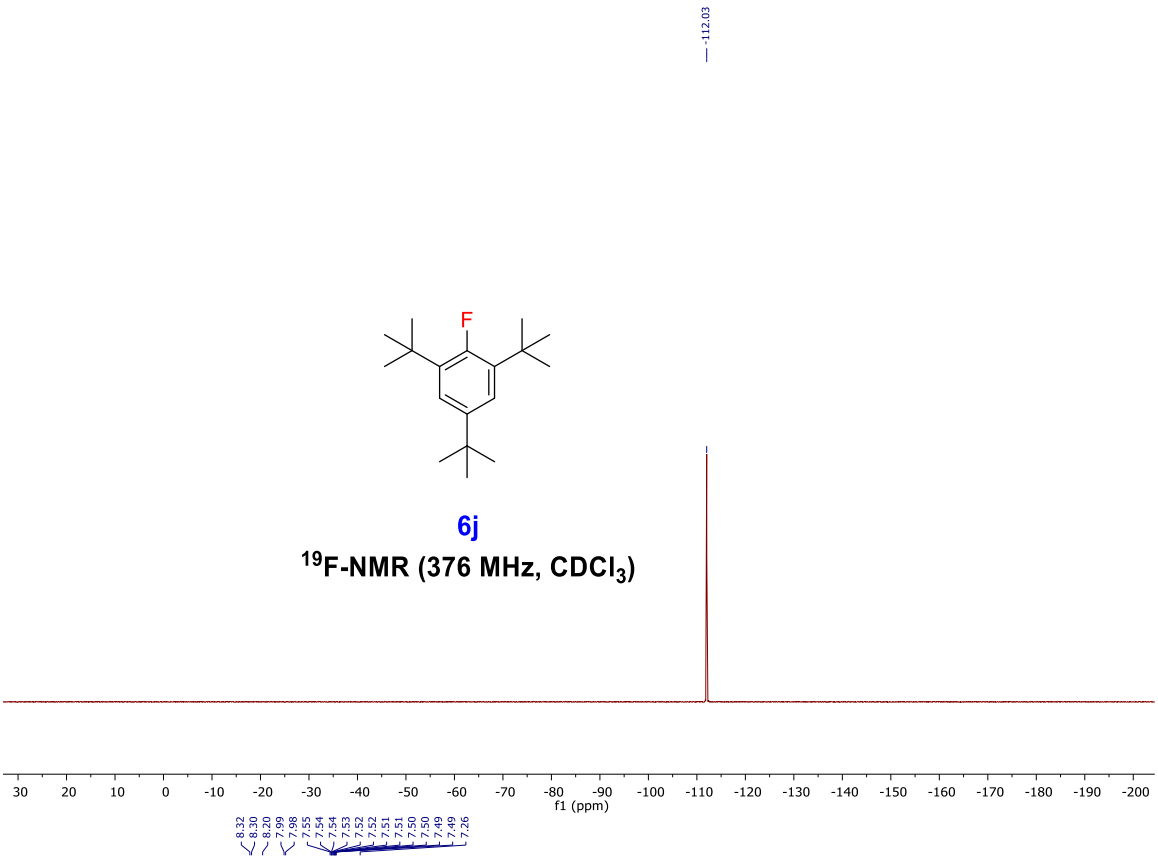
6j

^{1}H-NMR (700 MHz, $CDCl_3$)



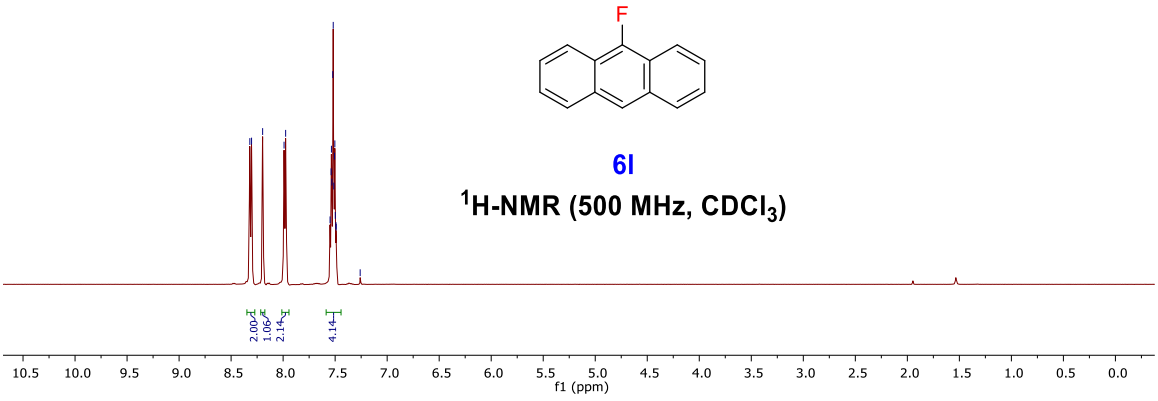
6j

^{13}C-NMR (176 MHz, $CDCl_3$)



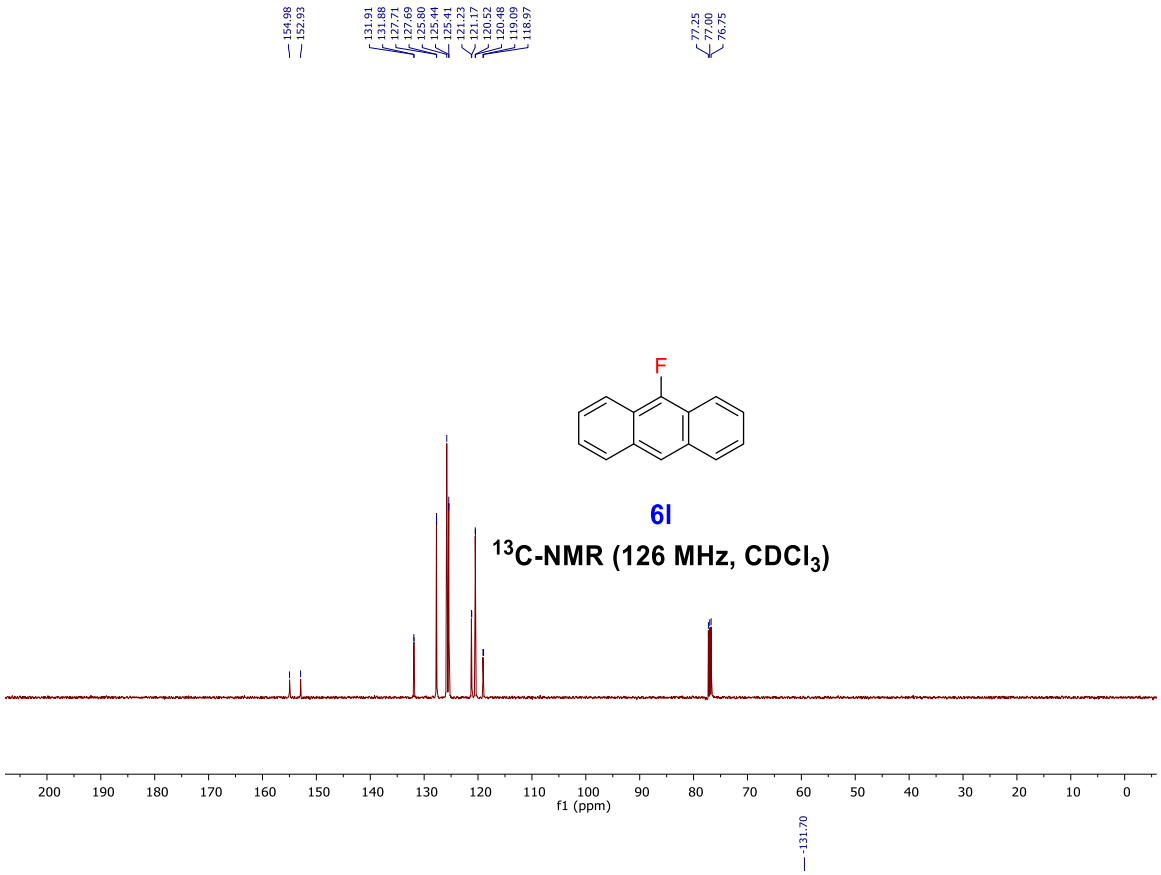
6j

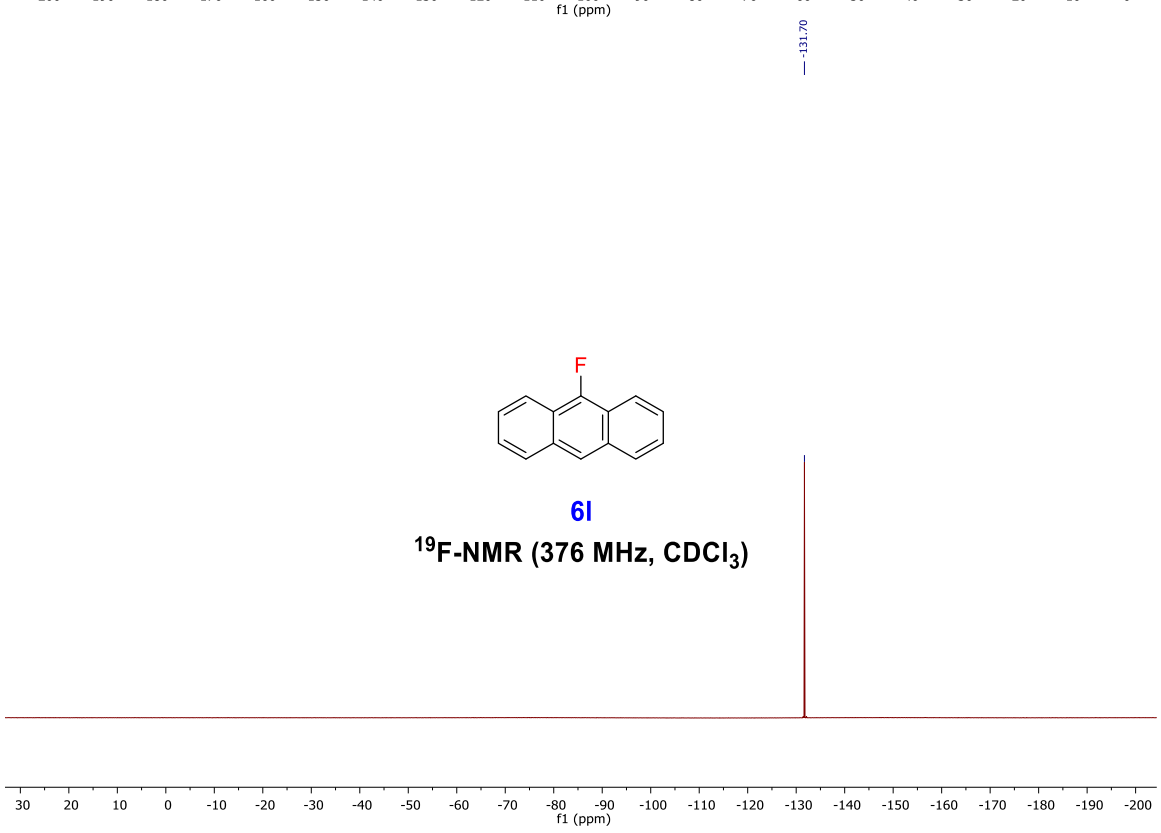
^{19}F-NMR (376 MHz, $CDCl_3$)

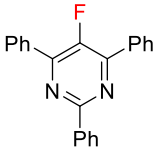


6l

^{1}H-NMR (500 MHz, $CDCl_3$)

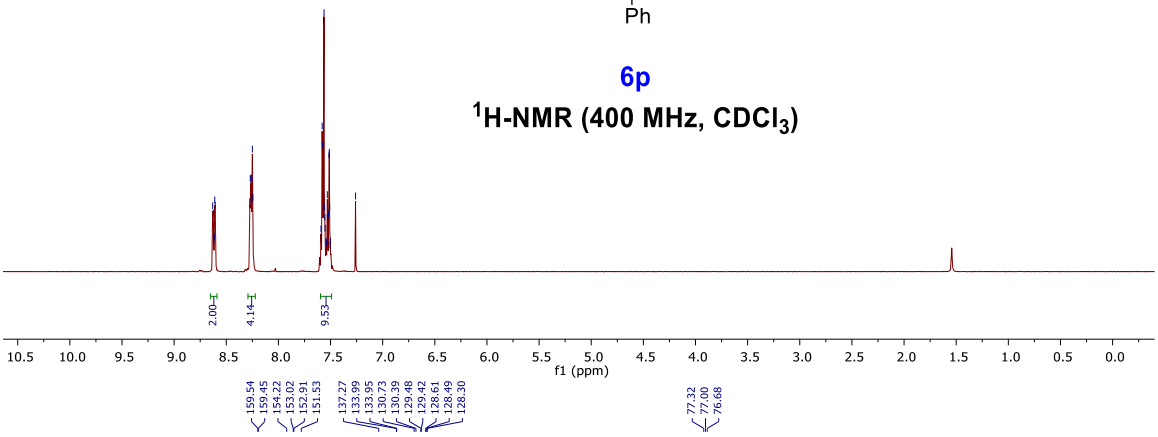

154.98
152.93
131.91
131.88
127.71
127.69
125.80
125.44
125.41
121.23
121.17
120.52
120.48
119.09
118.97
77.25
77.00
76.75
F
6l
13C-NMR (126 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

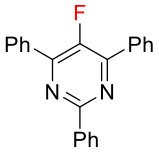

-131.70
F
6l
19F-NMR (376 MHz, CDCl3)
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)



6p

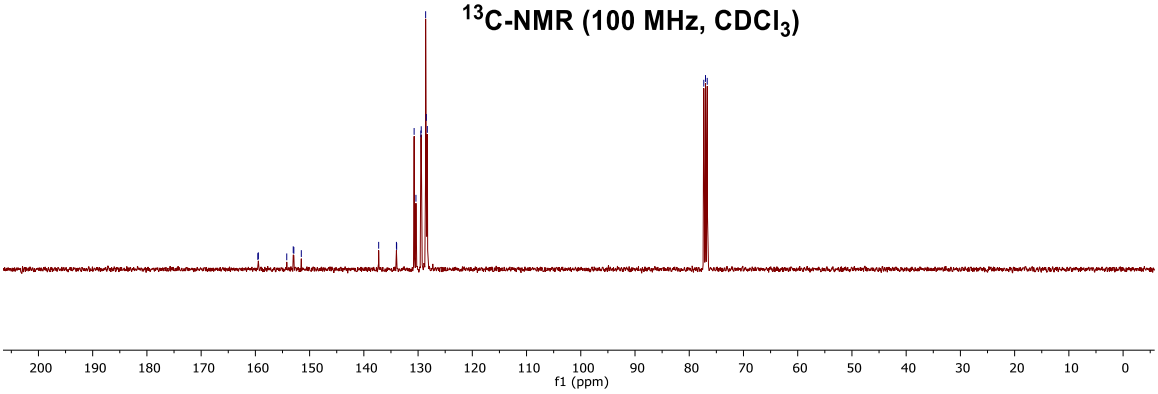
^{1}H-NMR (400 MHz, $CDCl_3$)

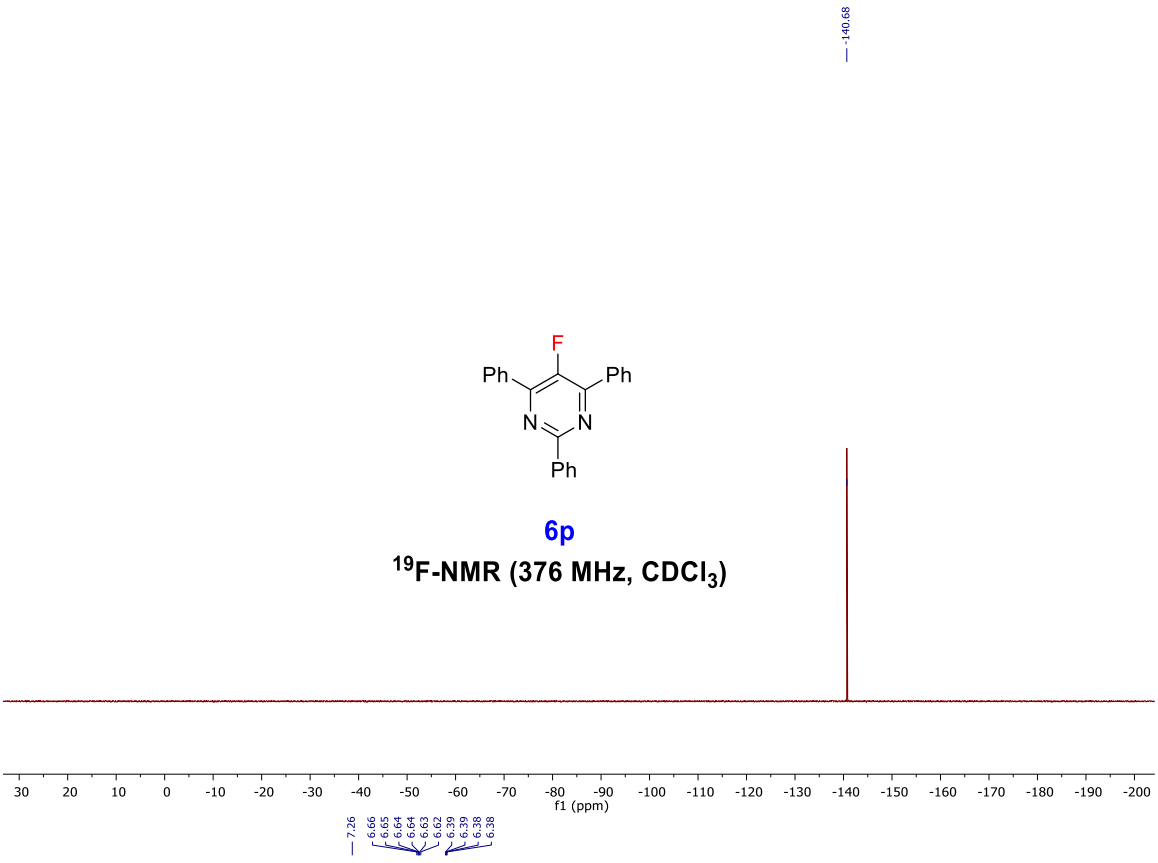




6p

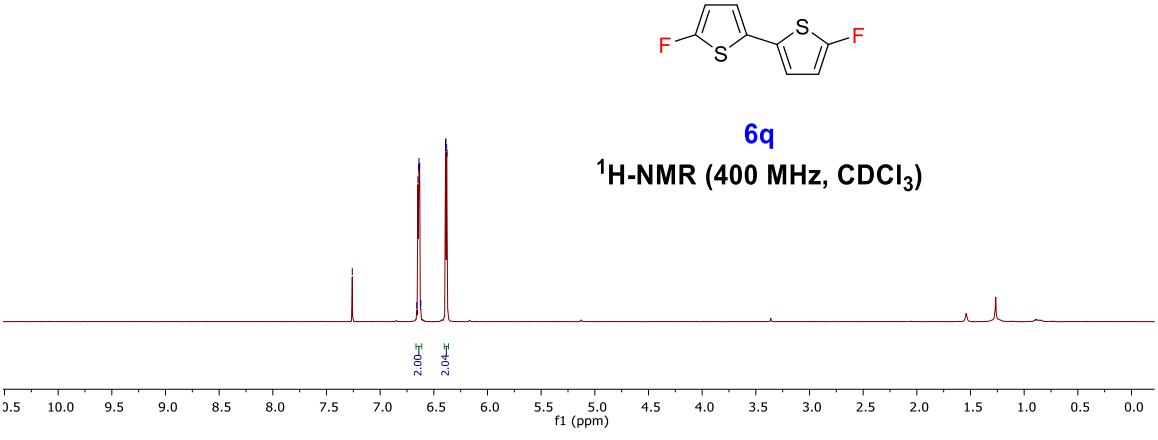
^{13}C-NMR (100 MHz, $CDCl_3$)





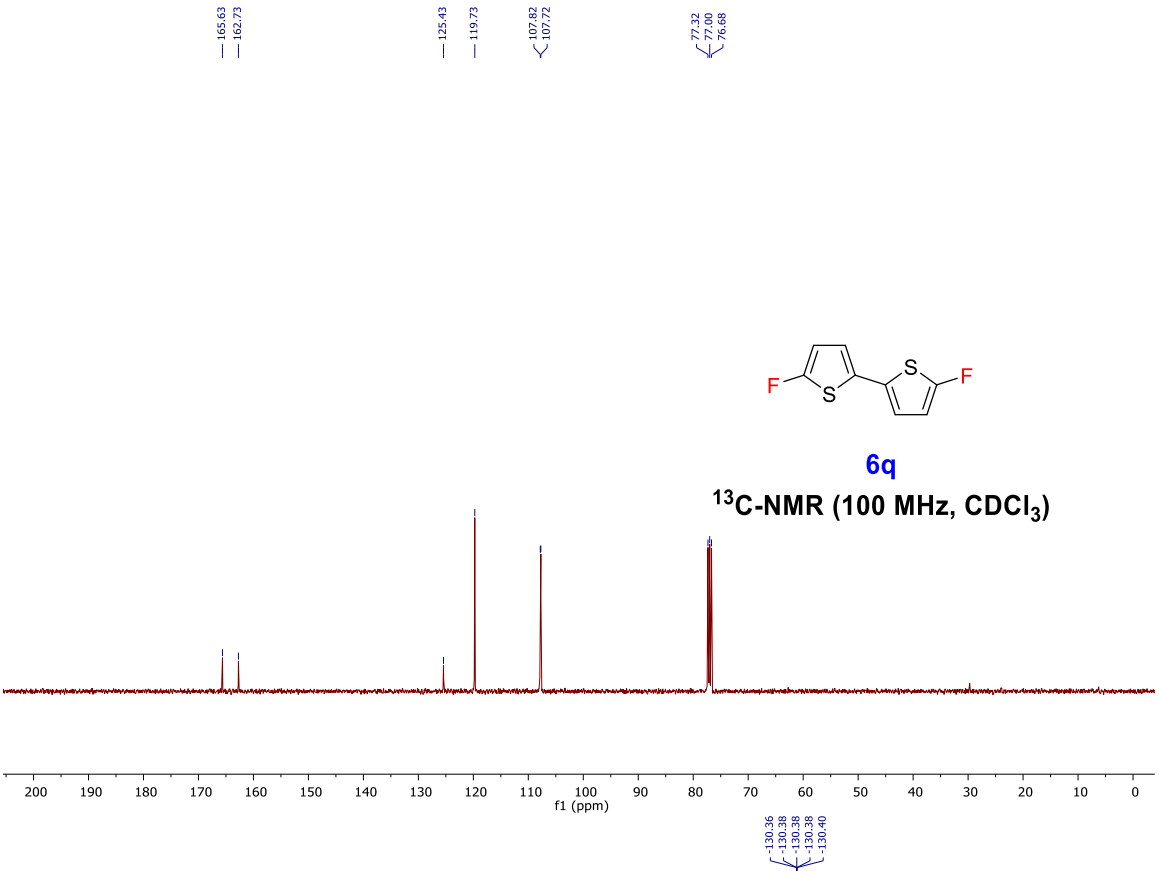
6p

^{19}F-NMR (376 MHz, $CDCl_3$)



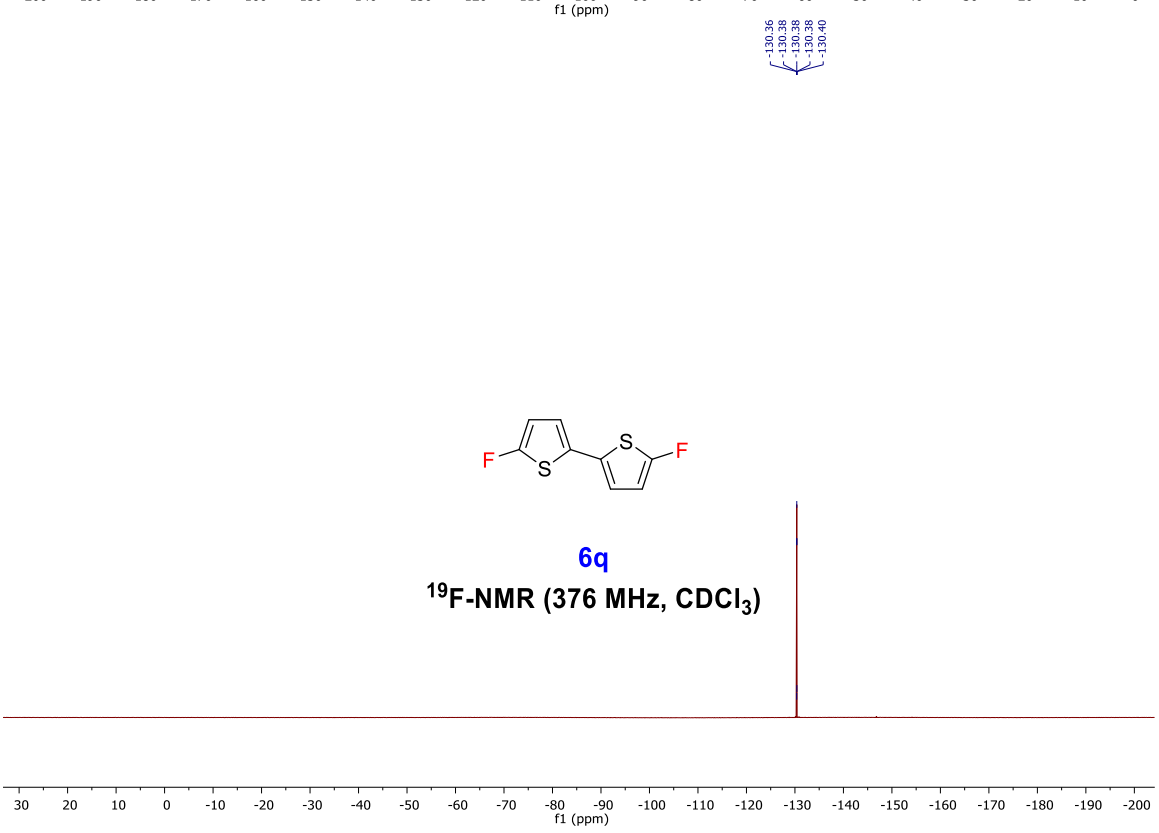
6q

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



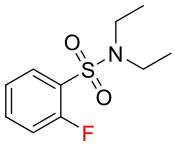
6q

^{13}C-NMR (100 MHz, $CDCl_3$)



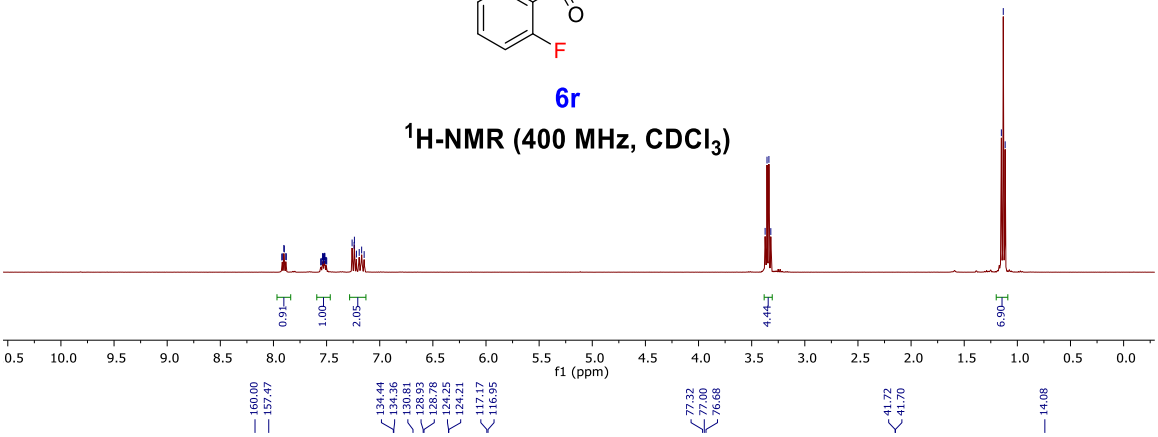
6q

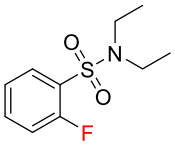
^{19}F-NMR (376 MHz, $CDCl_3$)



6r

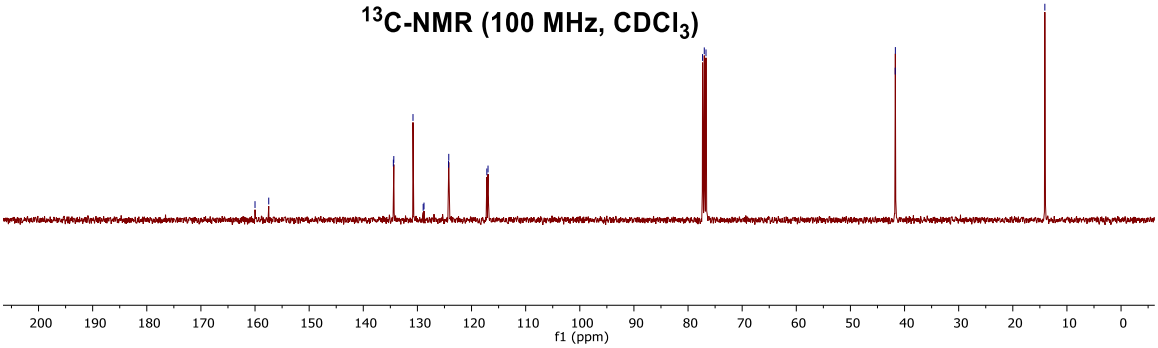
^{1}H-NMR (400 MHz, $CDCl_3$)

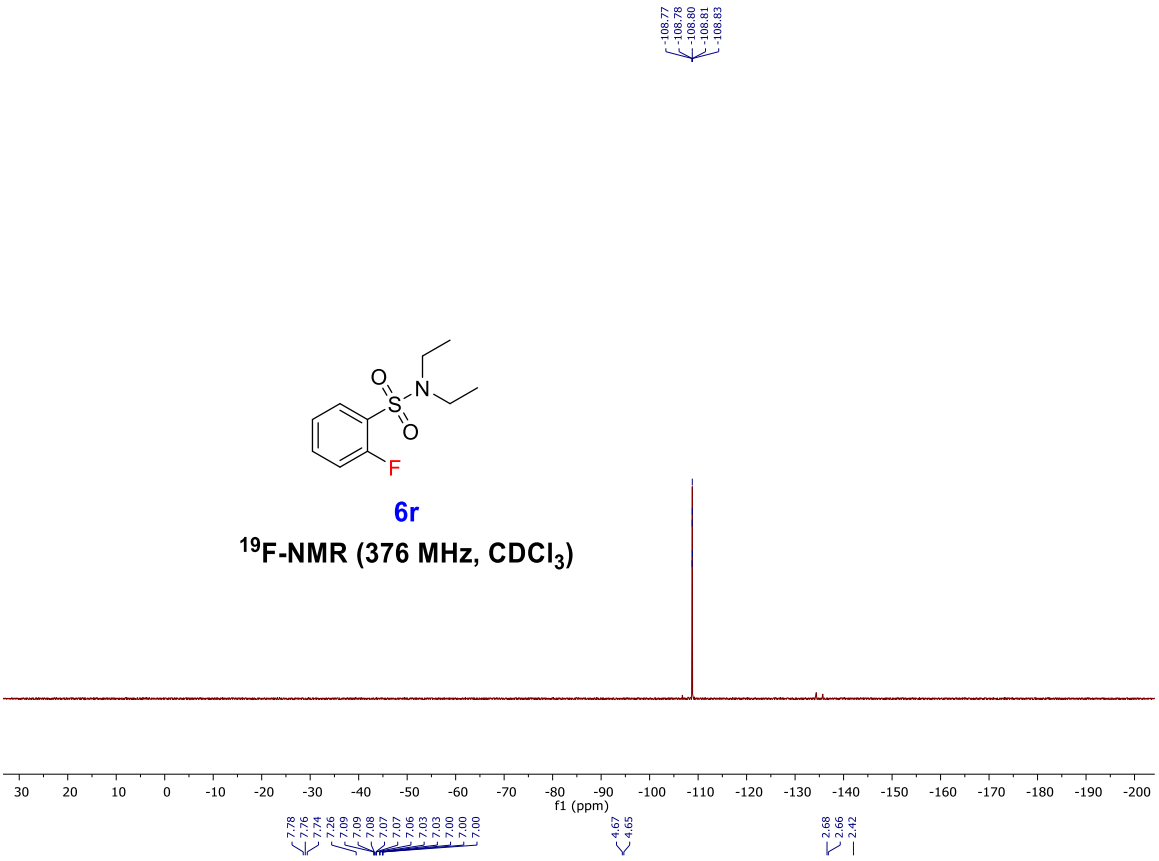




6r

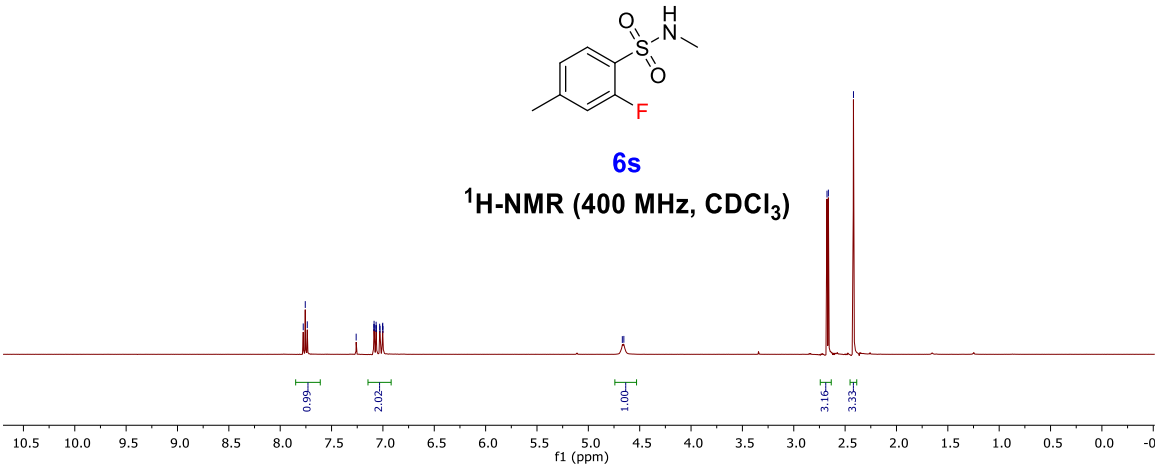
^{13}C-NMR (100 MHz, $CDCl_3$)





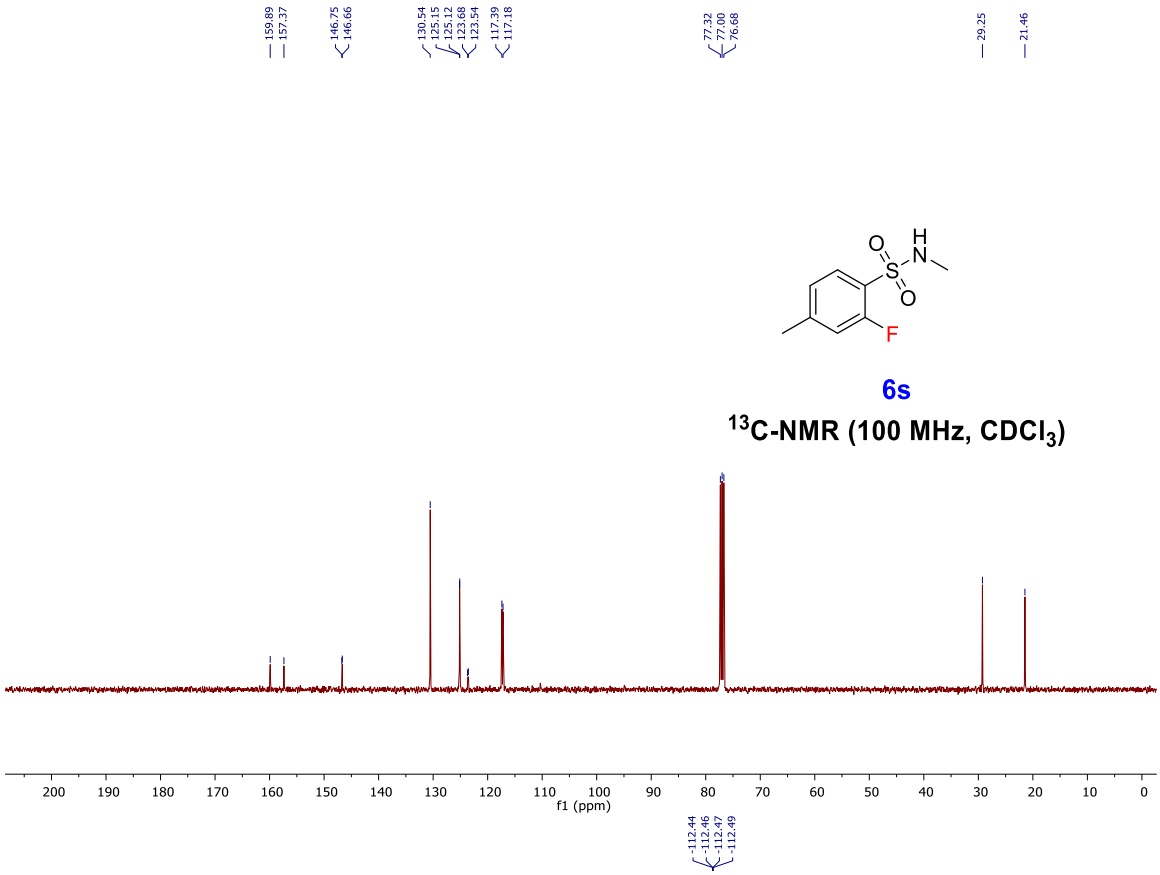
6r

^{19}F-NMR (376 MHz, $CDCl_3$)



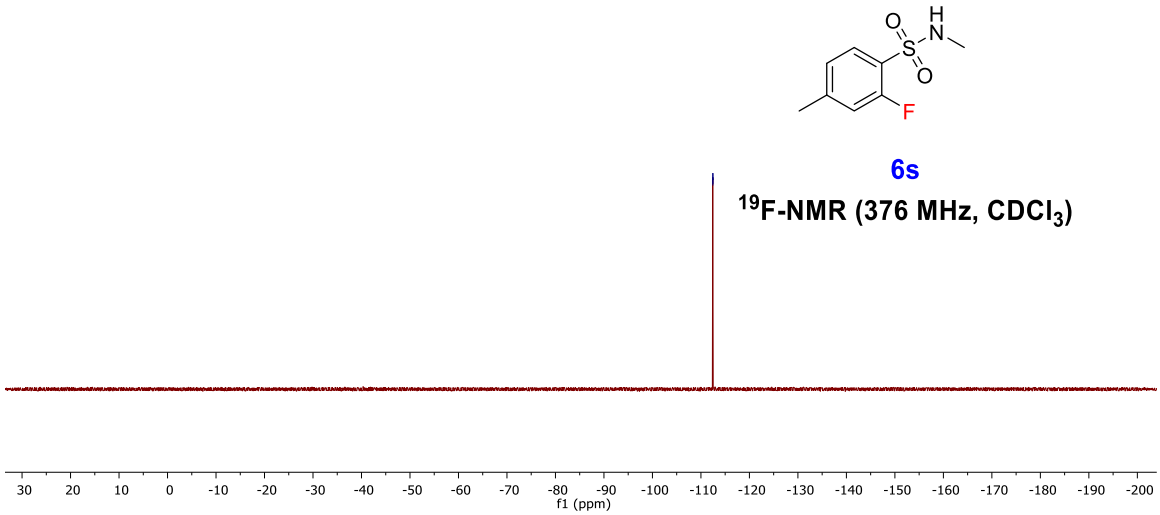
6s

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



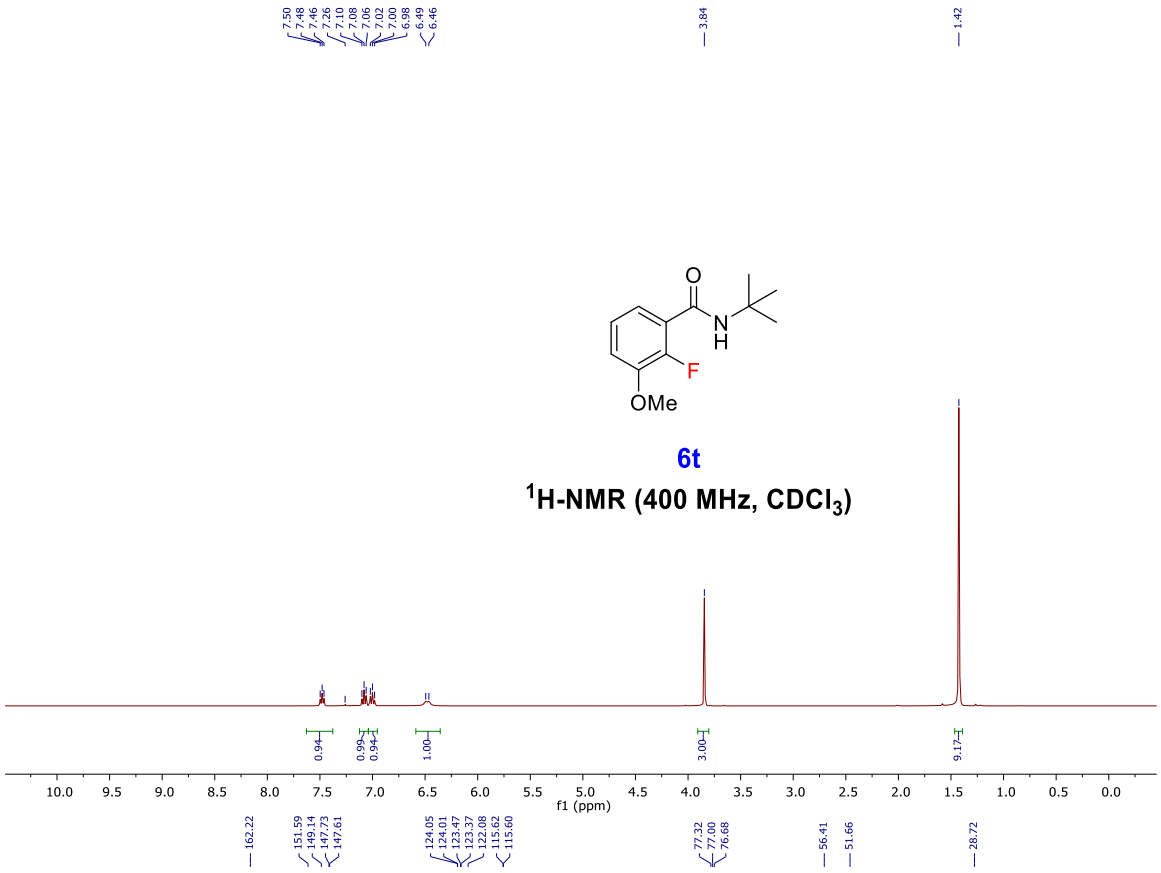
6s

^{13}C-NMR (100 MHz, $CDCl_3$)



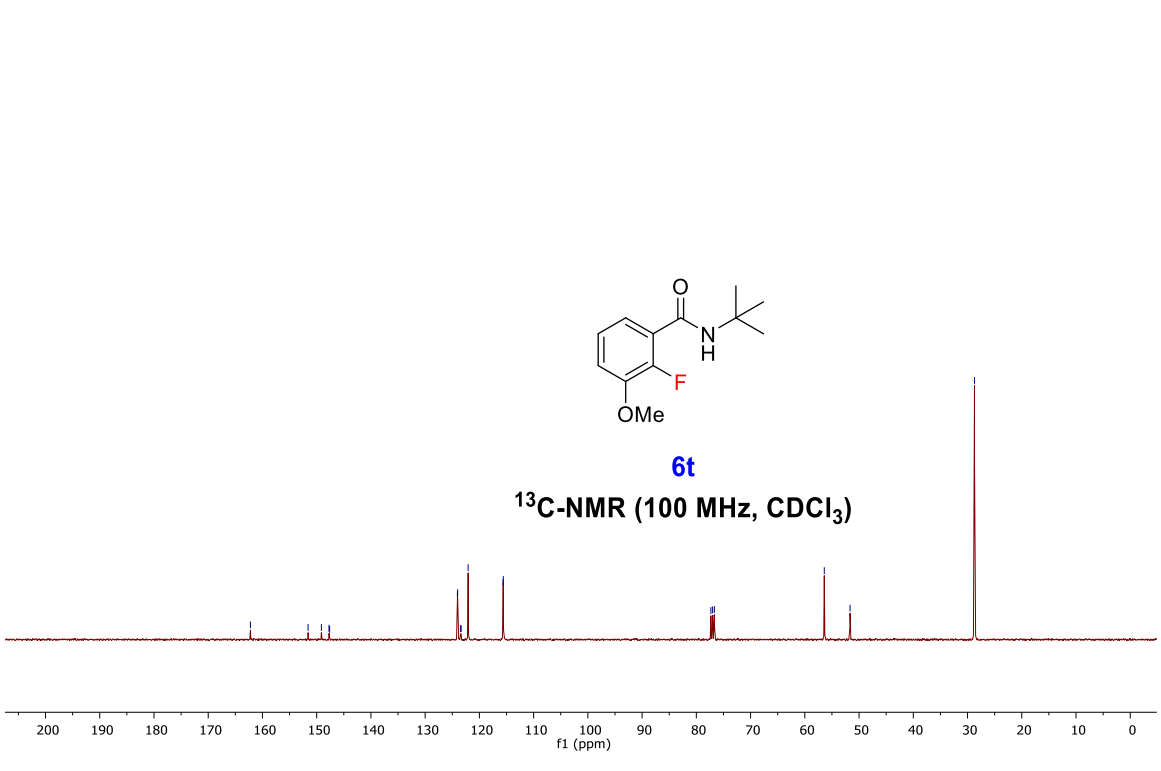
6s

^{19}F-NMR (376 MHz, $CDCl_3$)



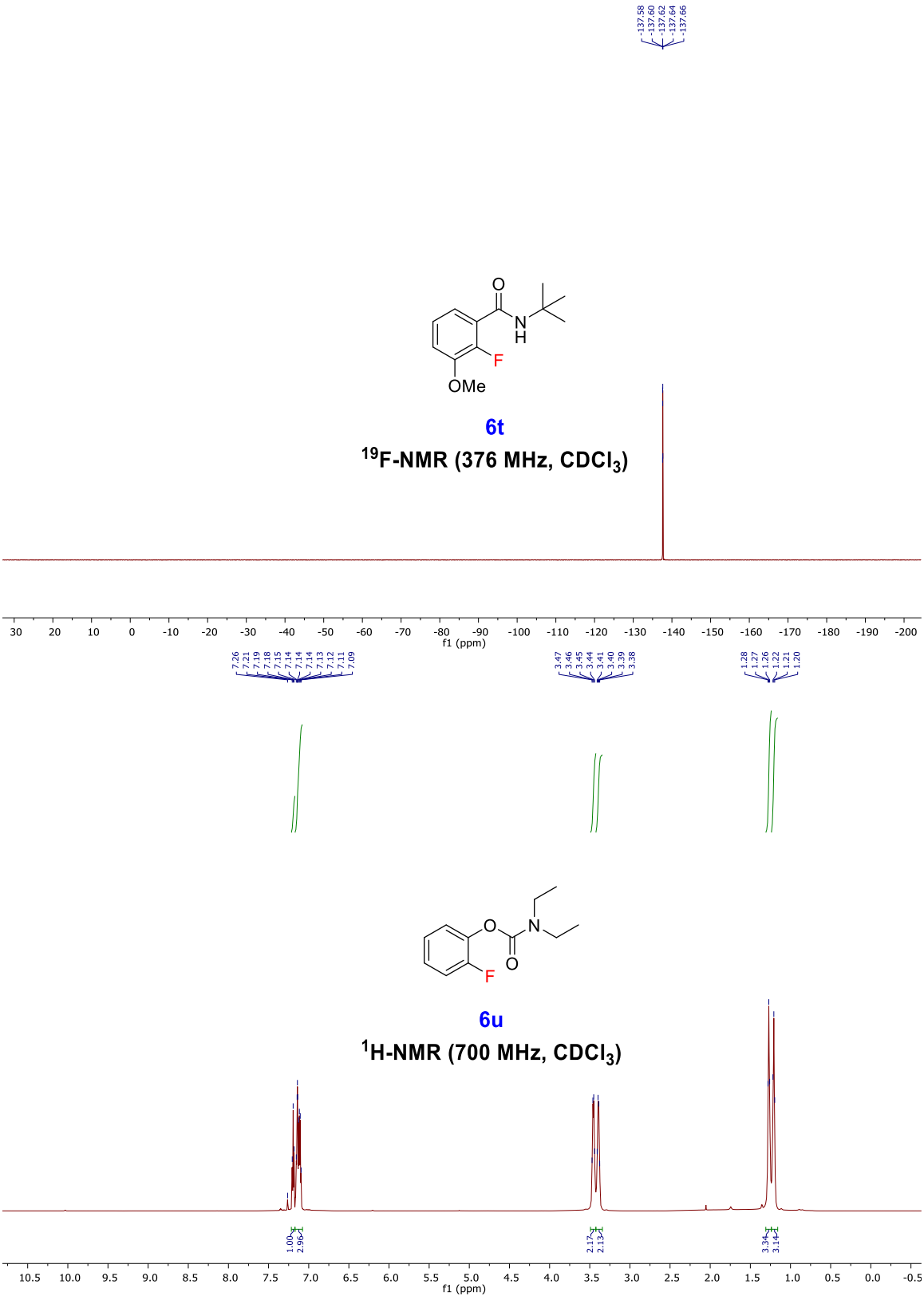
6t

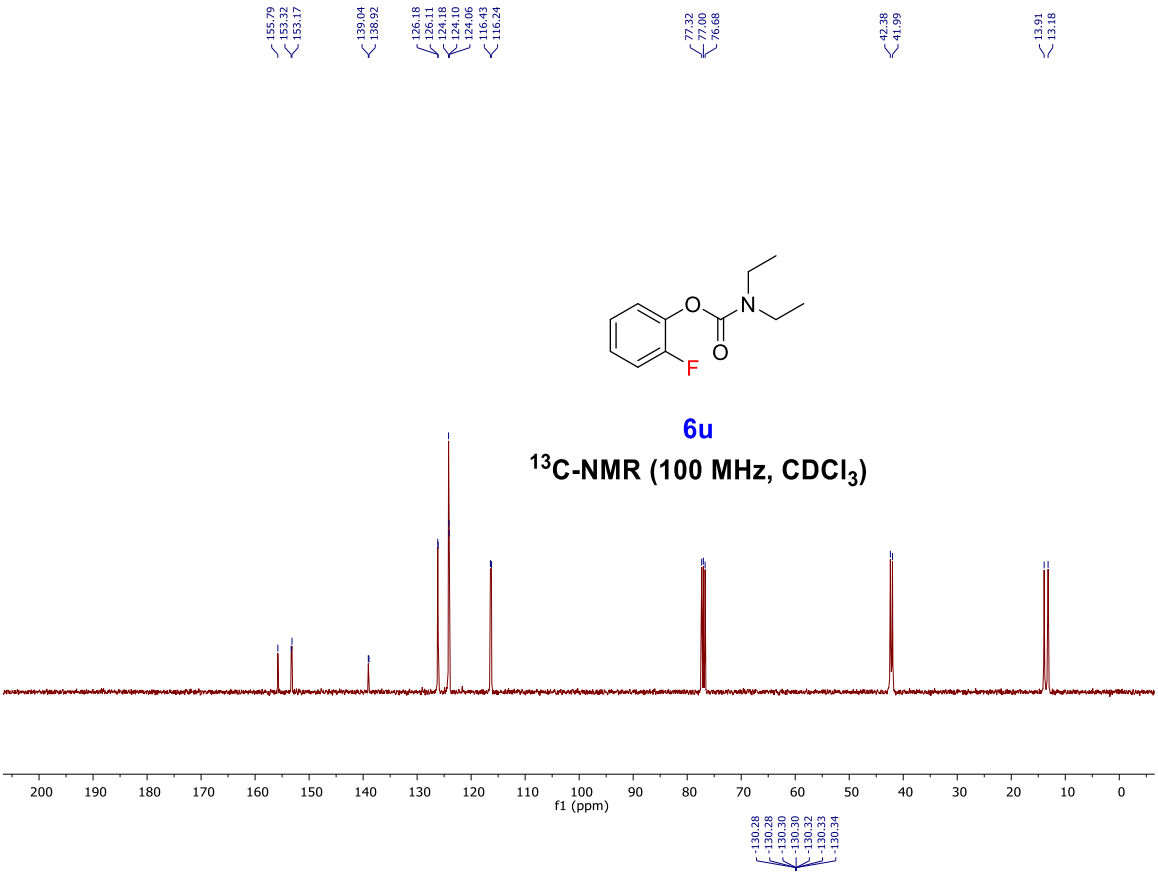
^{1}H-NMR (400 MHz, $CDCl_3$)



6t

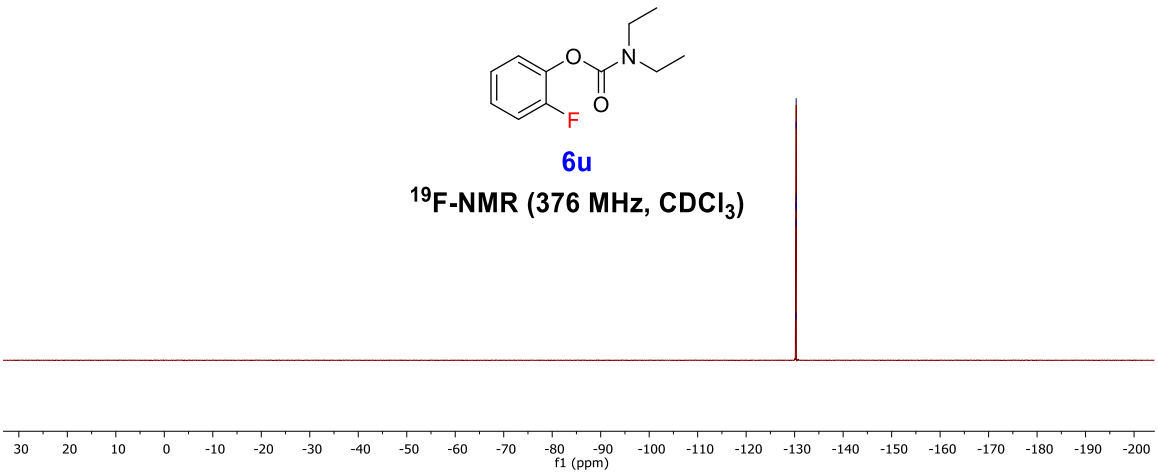
^{13}C-NMR (100 MHz, $CDCl_3$)


-137.58
-137.60
-137.62
-137.64
-137.66
O
N
H
F
OMe
6t
19F-NMR (376 MHz, CDCl3)
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)
7.26
7.21
7.19
7.18
7.15
7.14
7.14
7.14
7.13
7.12
7.11
7.09
3.47
3.46
3.45
3.44
3.41
3.40
3.39
3.38
1.28
1.27
1.26
1.22
1.21
1.20
O
N
O
F
6u
1H-NMR (700 MHz, CDCl3)
1.00
2.96
2.17
2.13
3.34
3.14
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)



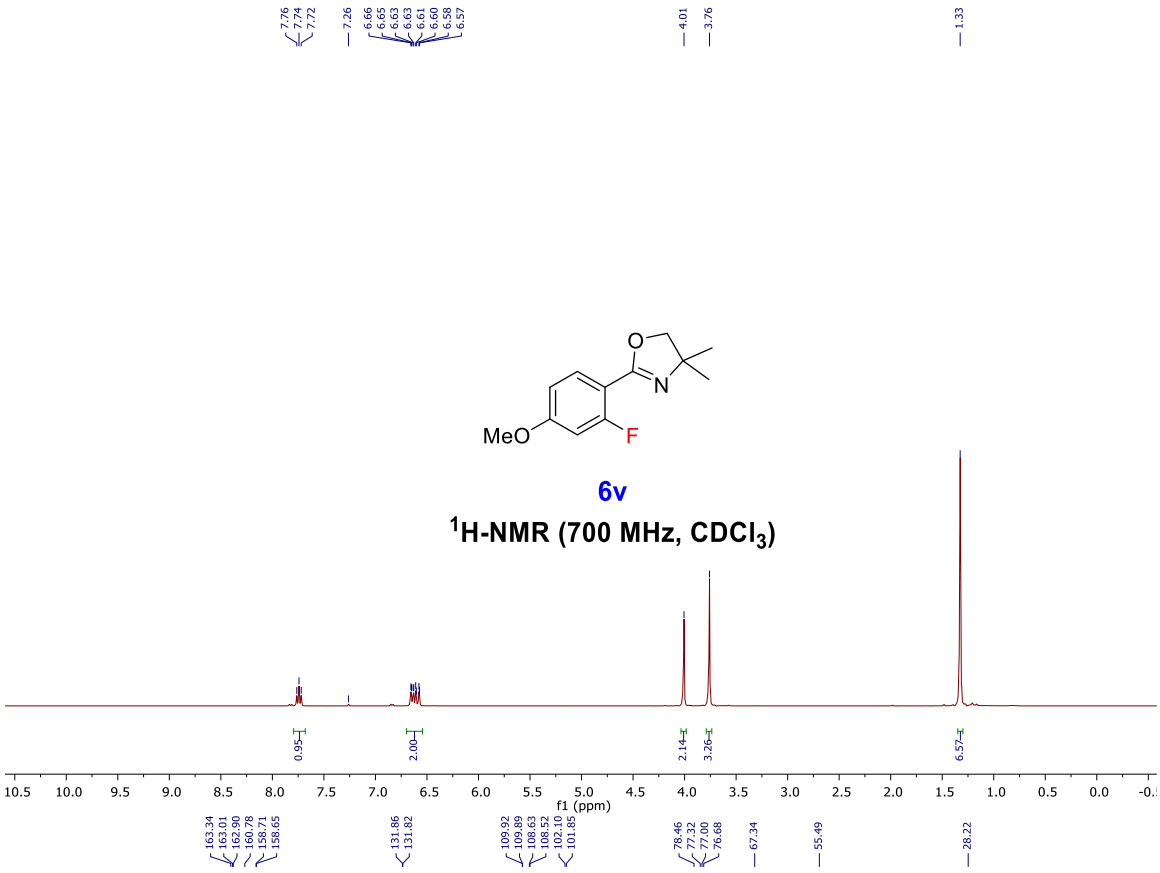
6u

^{13}C-NMR (100 MHz, $CDCl_3$)



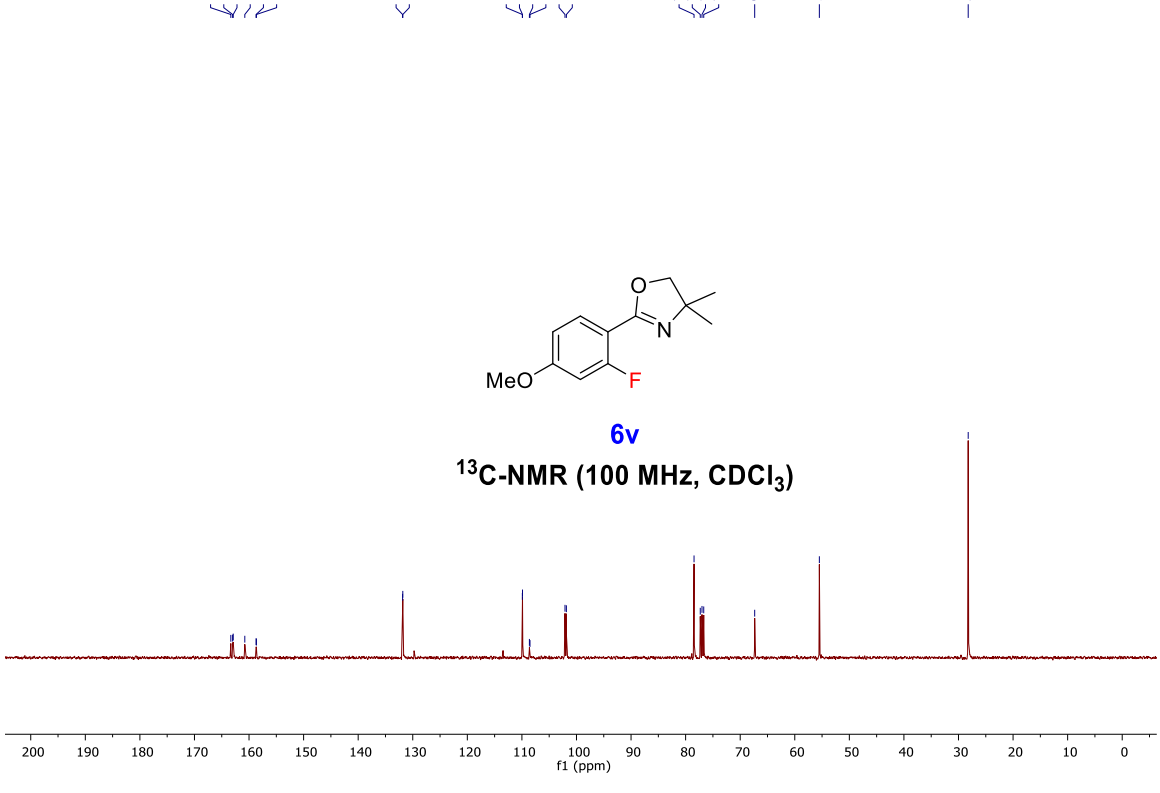
6u

^{19}F-NMR (376 MHz, $CDCl_3$)



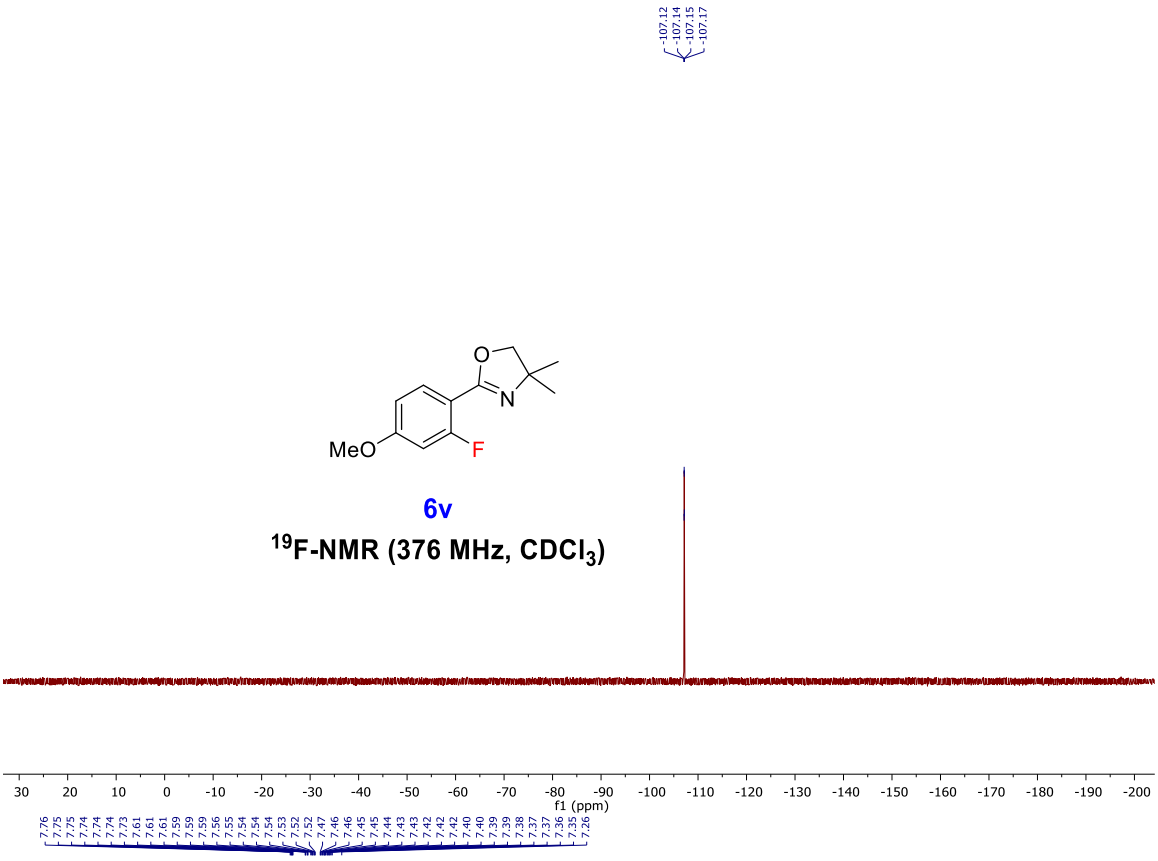
6v

^{1}H-NMR (700 MHz, $CDCl_3$)



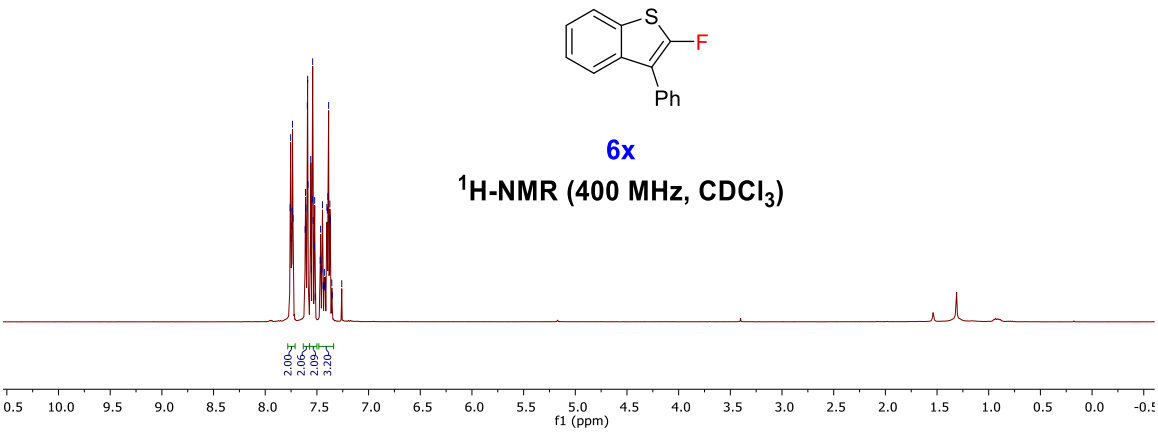
6v

^{13}C-NMR (100 MHz, $CDCl_3$)



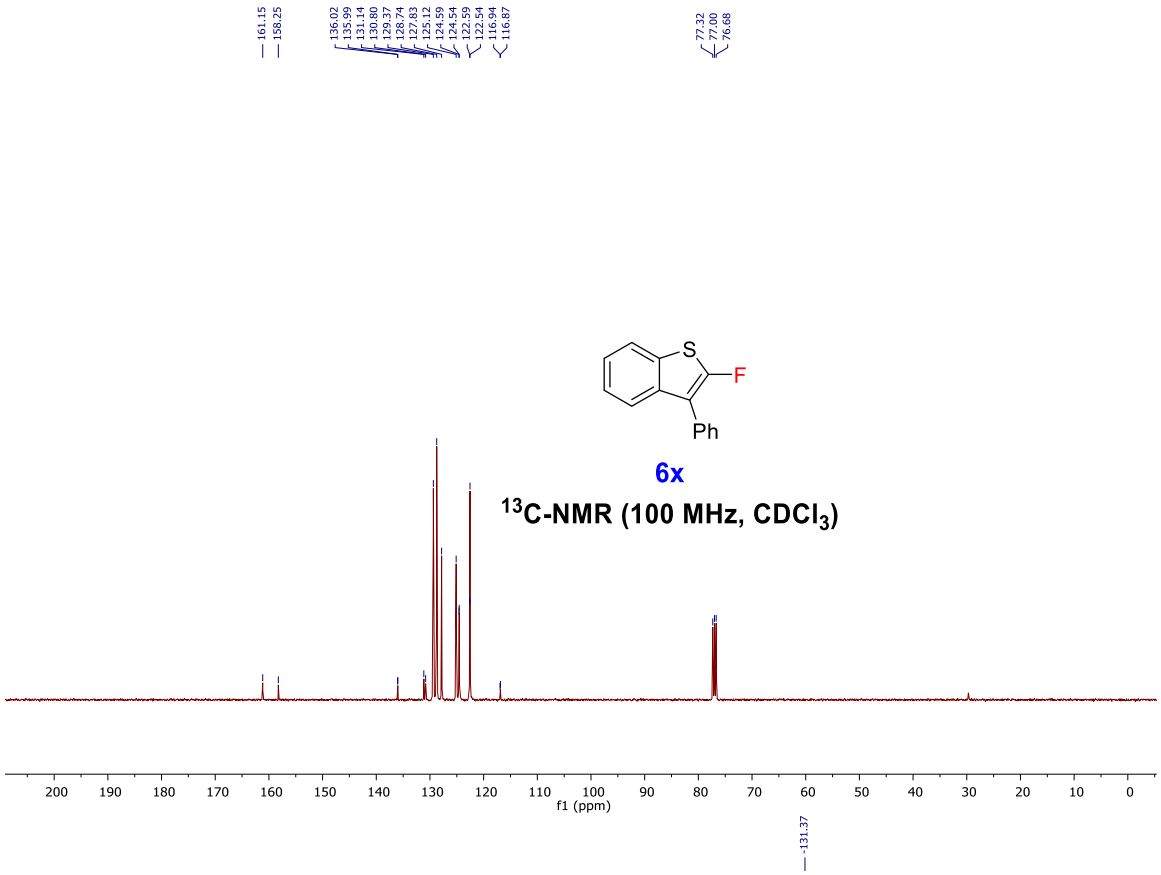
6v

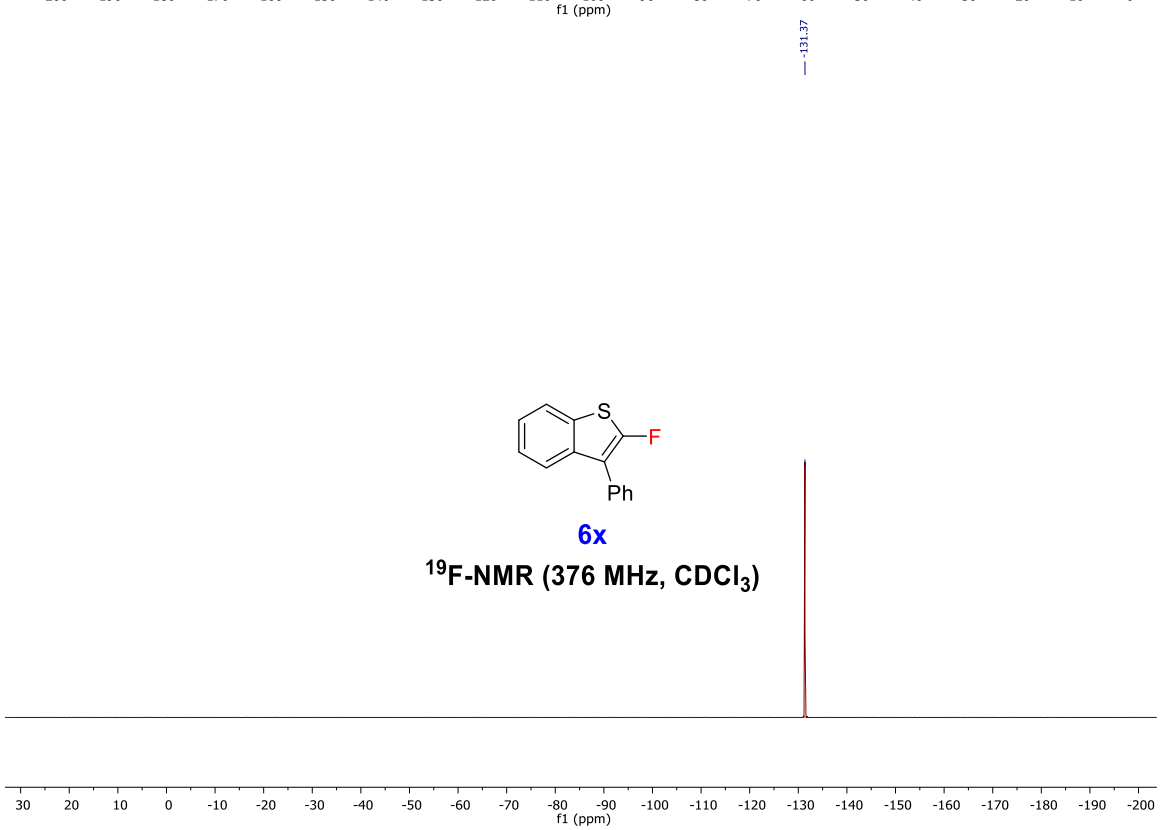
^{19}F-NMR (376 MHz, $CDCl_3$)

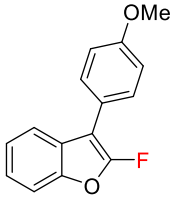


6x

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

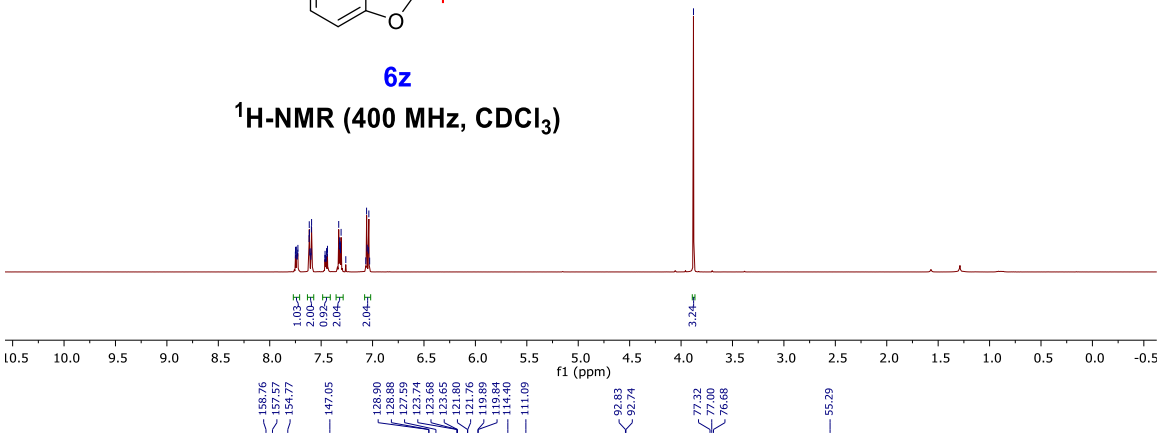

161.15
158.25
136.02
135.99
131.14
130.80
129.37
128.74
127.83
125.12
124.59
124.54
122.59
122.54
116.94
116.87
77.32
77.00
76.68
S
F
Ph
6x
13C-NMR (100 MHz, CDCl3)
f1 (ppm)

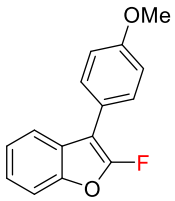

-131.37
S
F
Ph
6x
19F-NMR (376 MHz, CDCl3)
f1 (ppm)



6z

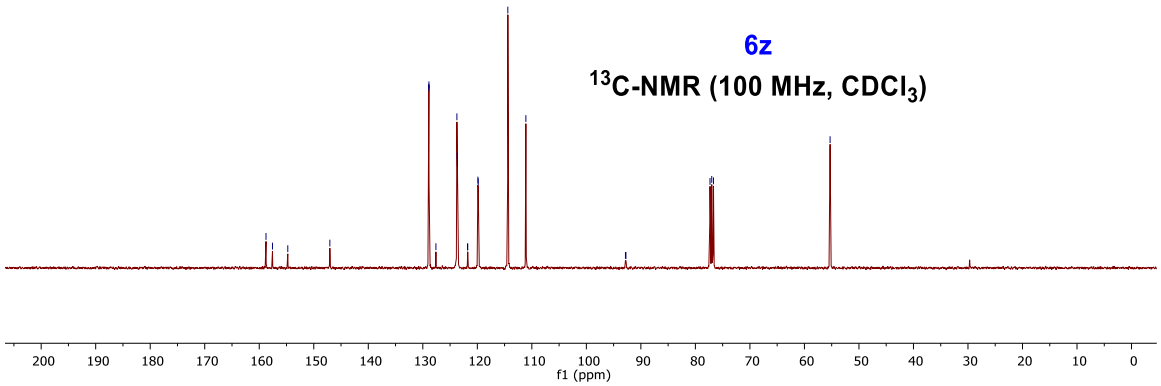
^{1}H-NMR (400 MHz, $CDCl_3$)

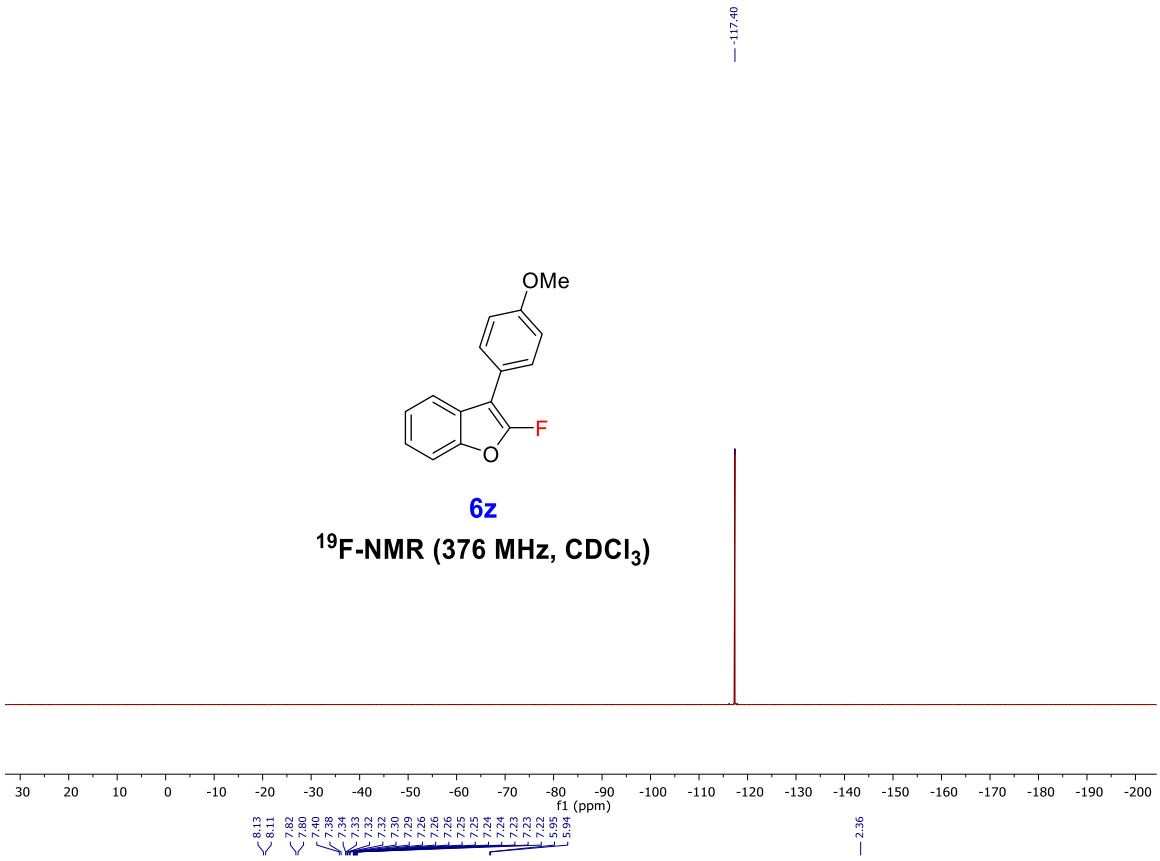




6z

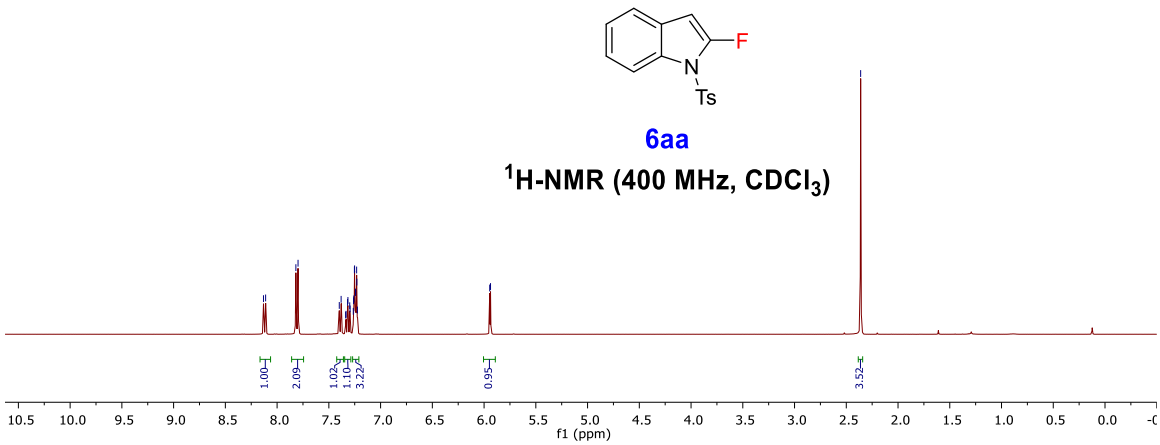
^{13}C-NMR (100 MHz, $CDCl_3$)





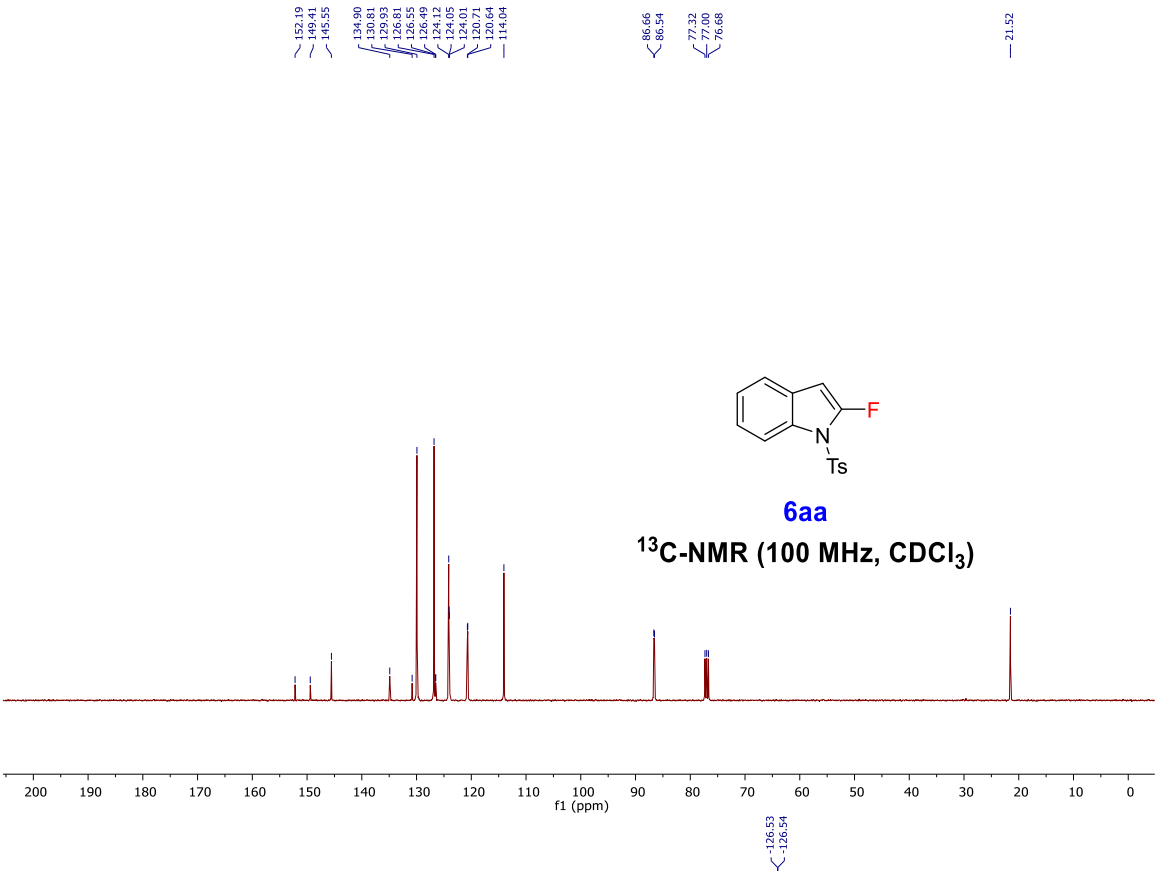
6z

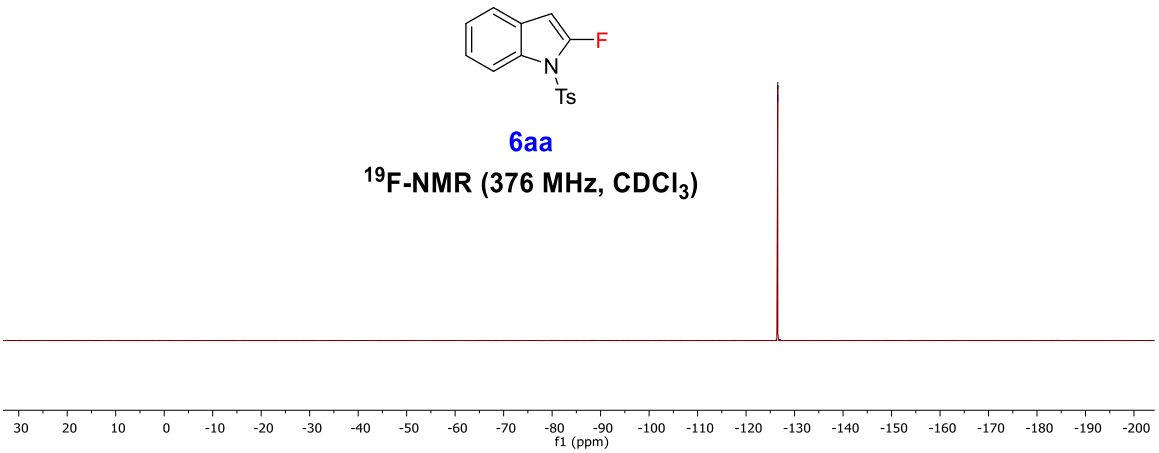
^{19}F-NMR (376 MHz, $CDCl_3$)

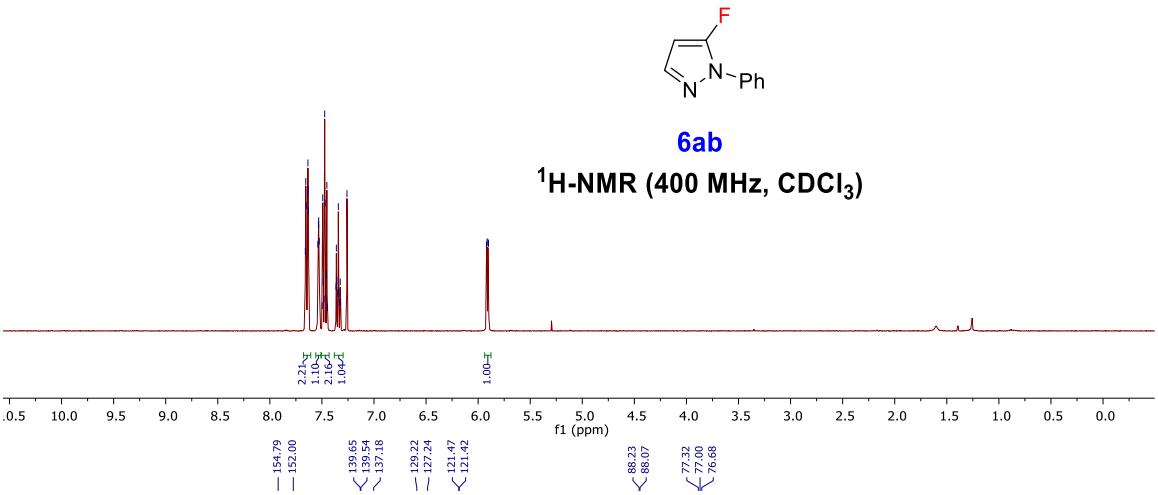


6aa

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

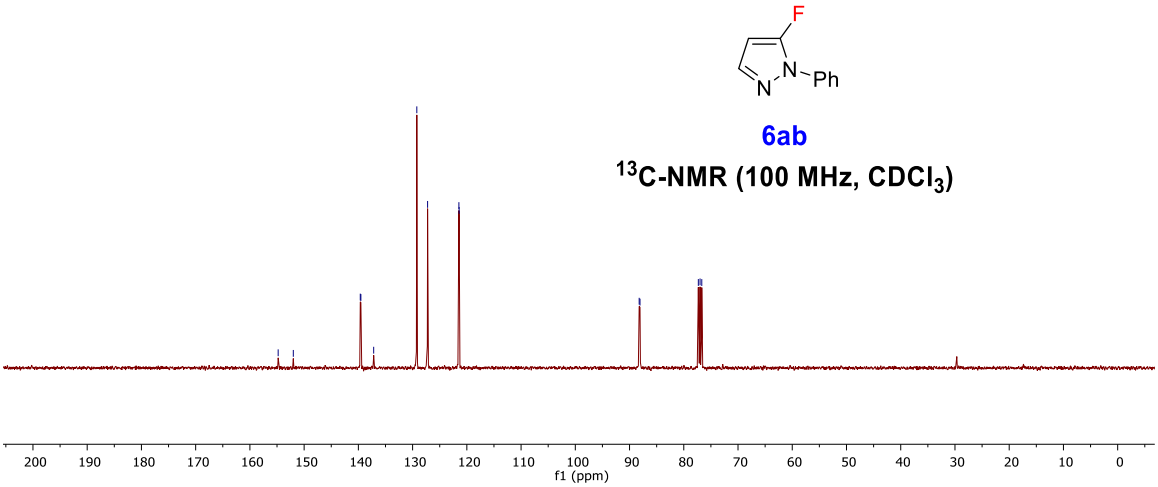

152.19
149.41
145.55
134.90
130.81
129.93
126.81
126.55
126.49
124.12
124.05
124.01
120.71
120.64
114.04
86.66
86.54
77.32
77.00
76.68
21.52
F
N
Ts
6aa
13C-NMR (100 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)
-126.53
-126.54


F
N
Ts
6aa
19F-NMR (376 MHz, CDCl3)
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)



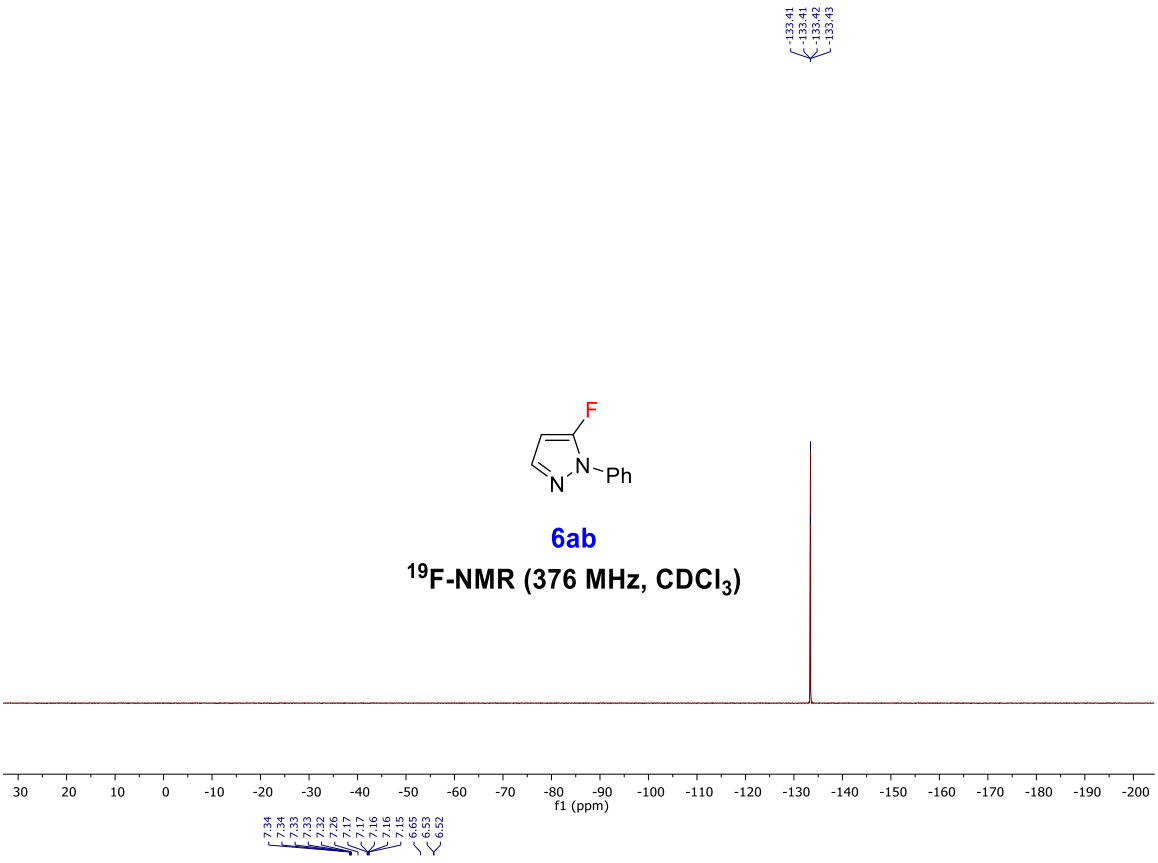
6ab

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



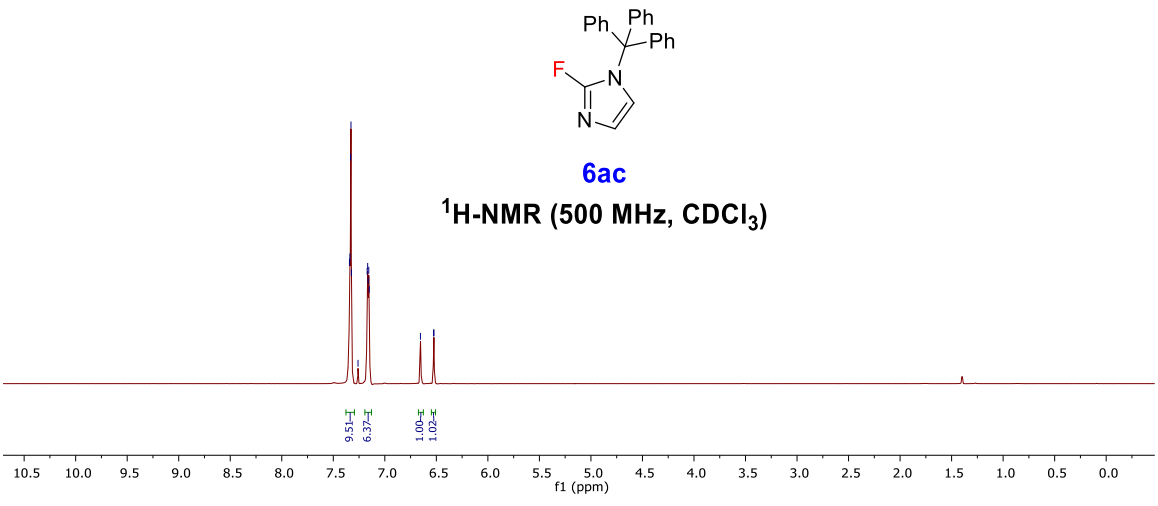
6ab

^{13}C-NMR (100 MHz, $CDCl_3$)



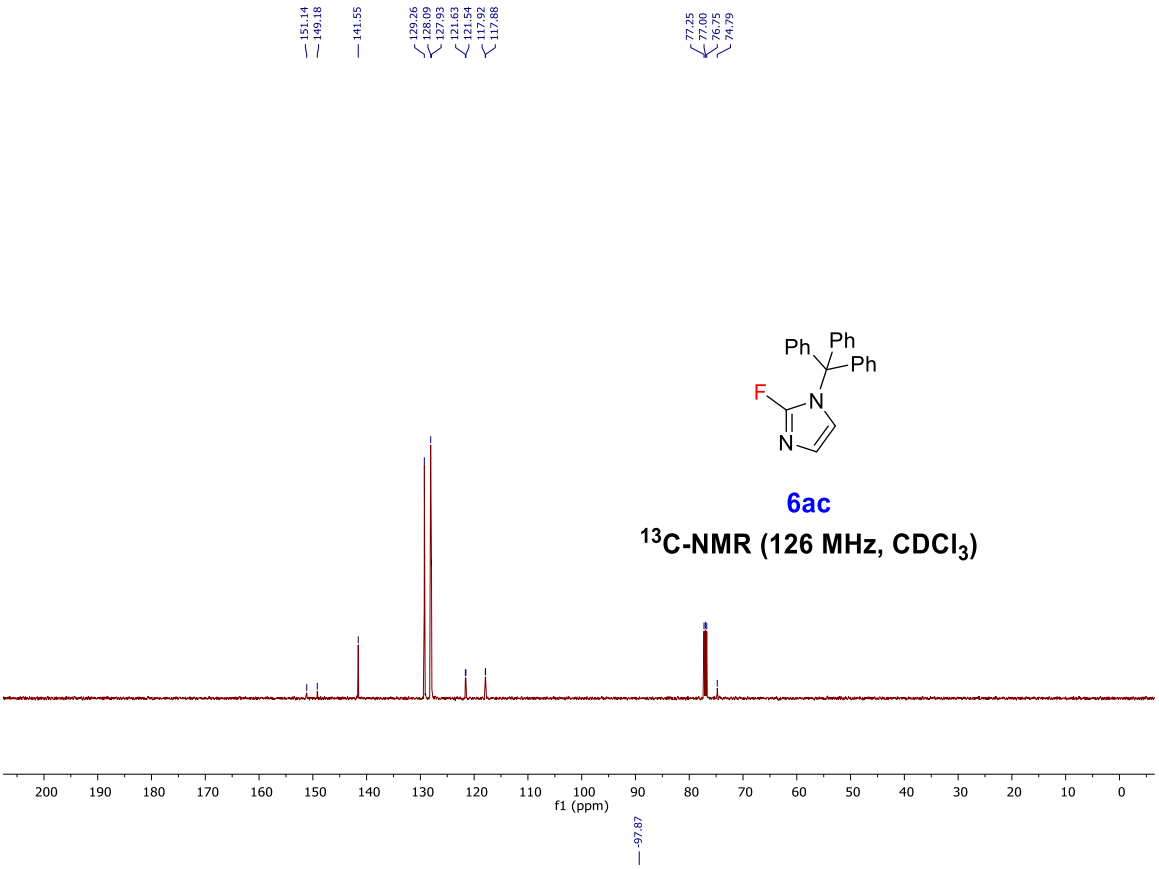
6ab

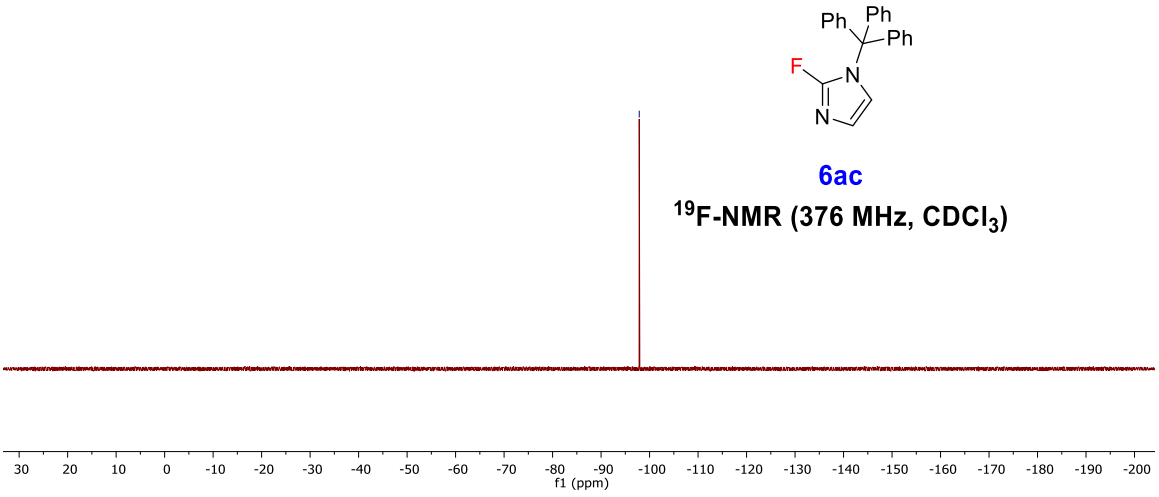
^{19}F-NMR (376 MHz, $CDCl_3$)

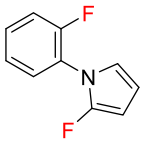


6ac

^{1}H-NMR (500 MHz, $CDCl_3$)

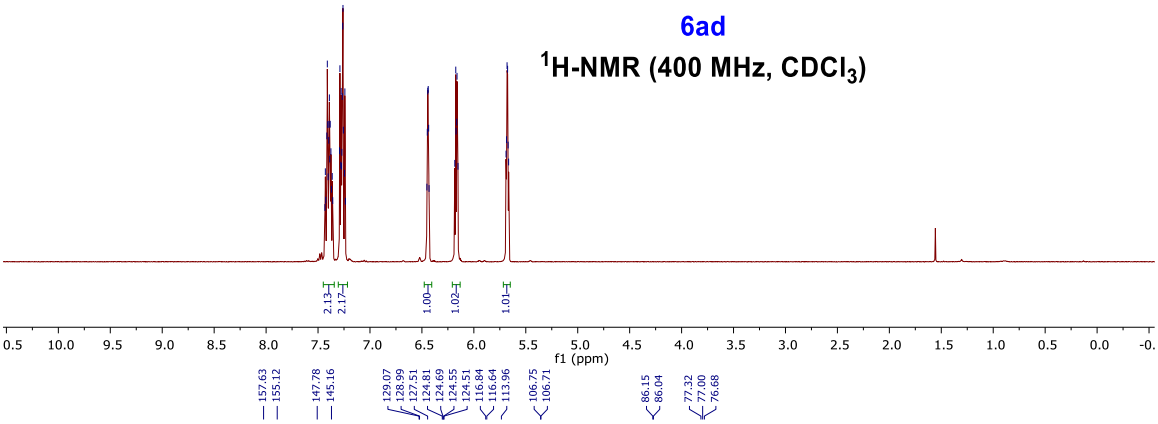

151.14
149.18
141.55
129.26
128.09
127.93
121.63
121.54
117.92
117.88
77.25
77.00
76.75
74.79
Ph
Ph
Ph
F
N
N
6ac
13C-NMR (126 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

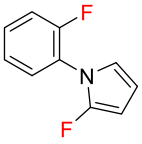

-97.87
Ph
Ph
Ph
F
N
N
6ac
19F-NMR (376 MHz, CDCl3)
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)



6ad

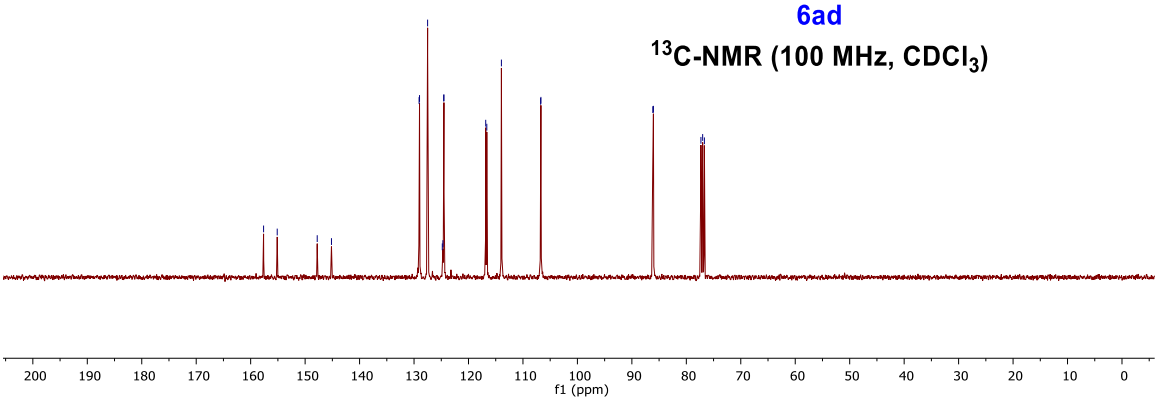
^{1}H-NMR (400 MHz, $CDCl_3$)

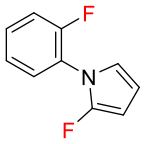




6ad

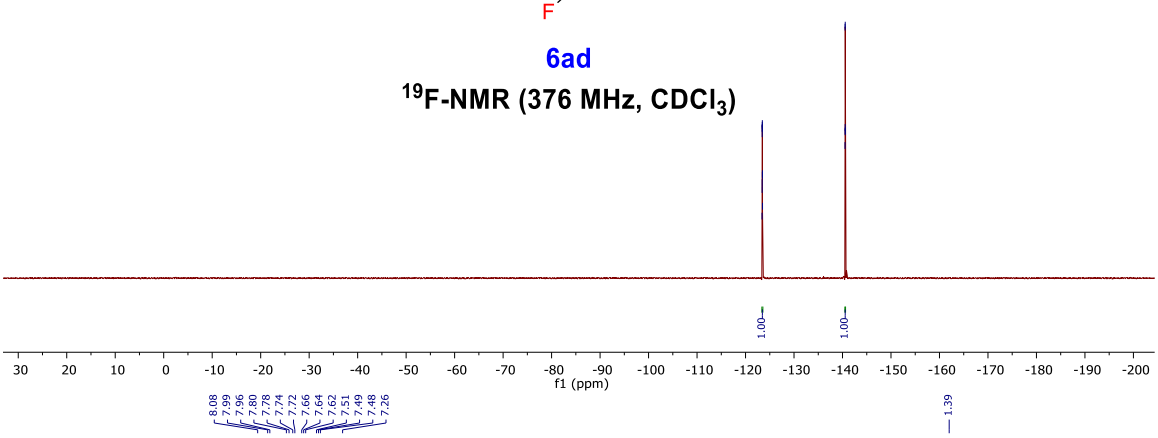
^{13}C-NMR (100 MHz, $CDCl_3$)

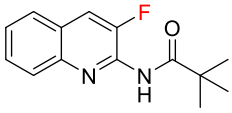




6ad

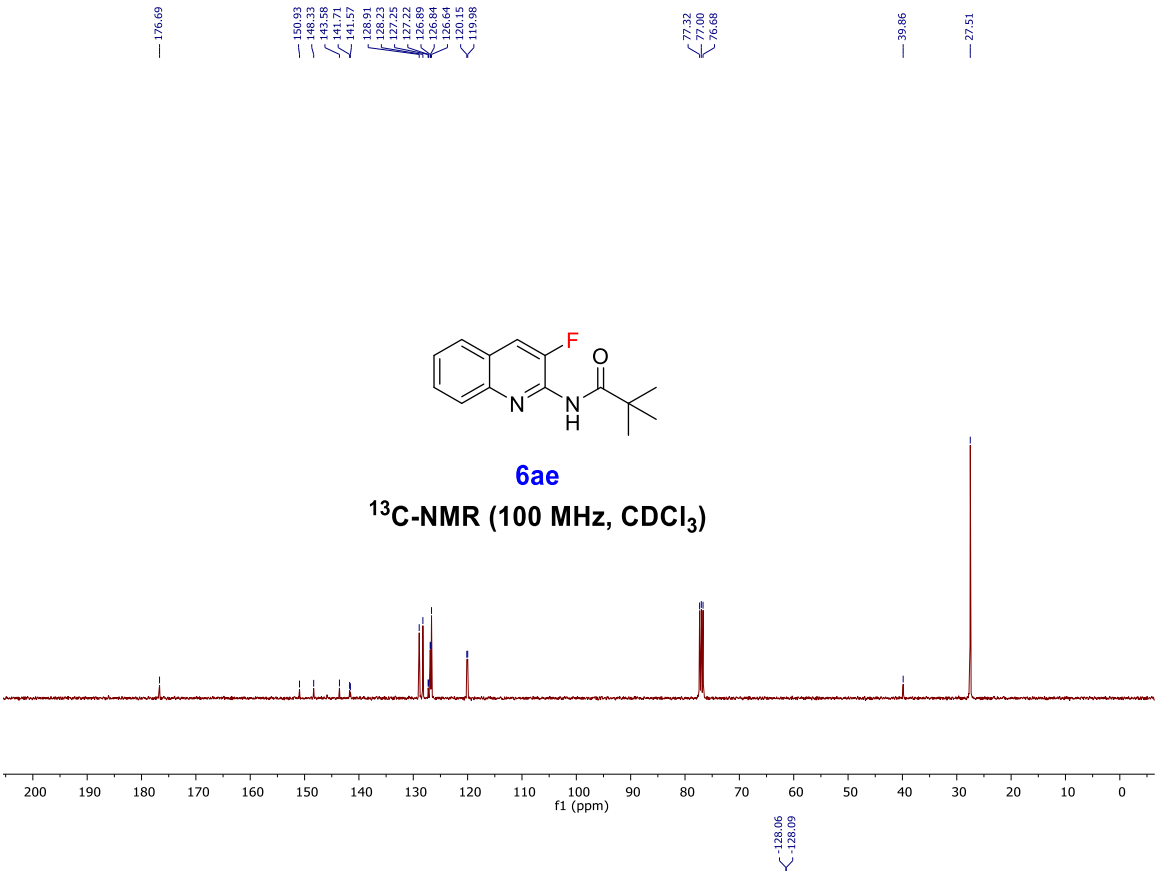
^{19}F-NMR (376 MHz, $CDCl_3$)





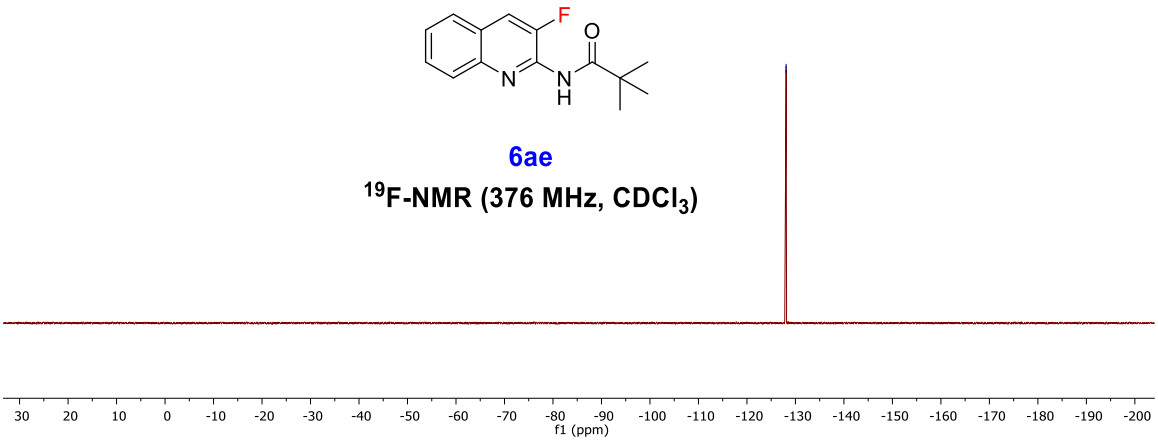
6ae

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



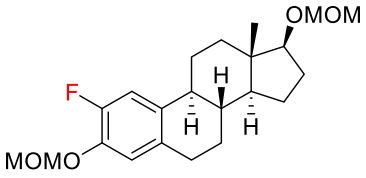
6ae

^{13}C-NMR (100 MHz, $CDCl_3$)



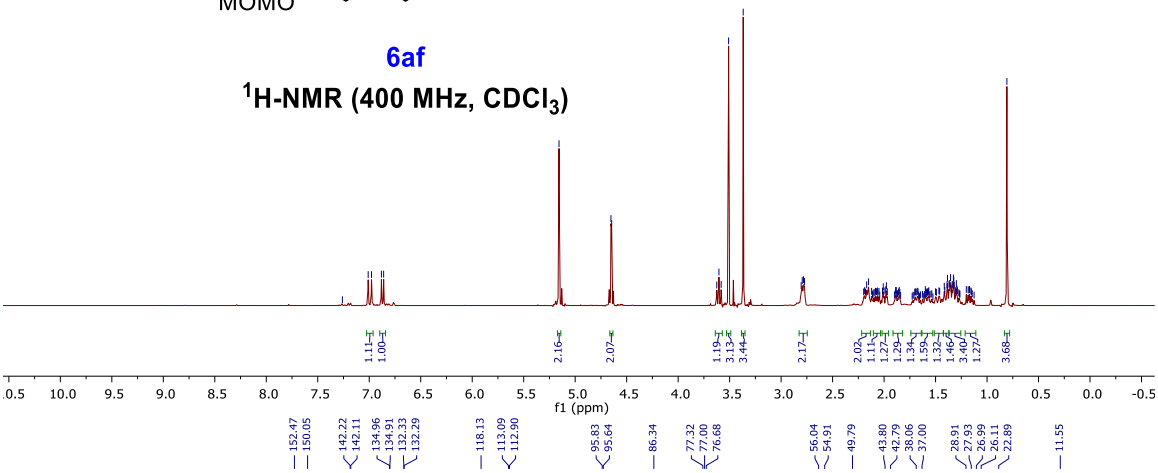
6ae

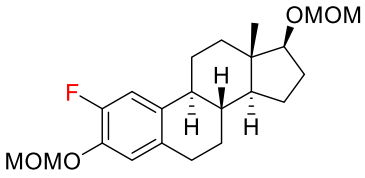
^{19}F-NMR (376 MHz, $CDCl_3$)



6af

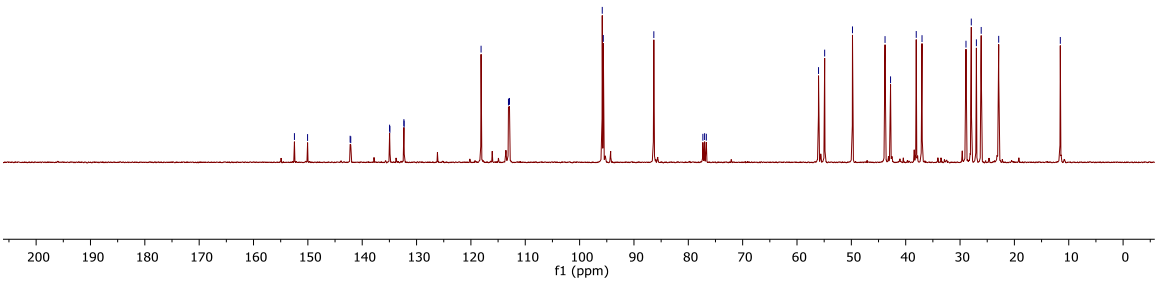
^{1}H-NMR (400 MHz, $CDCl_3$)

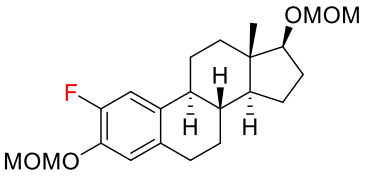




6af

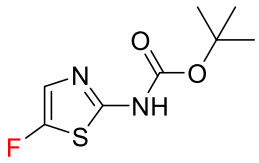
^{13}C-NMR (100 MHz, $CDCl_3$)





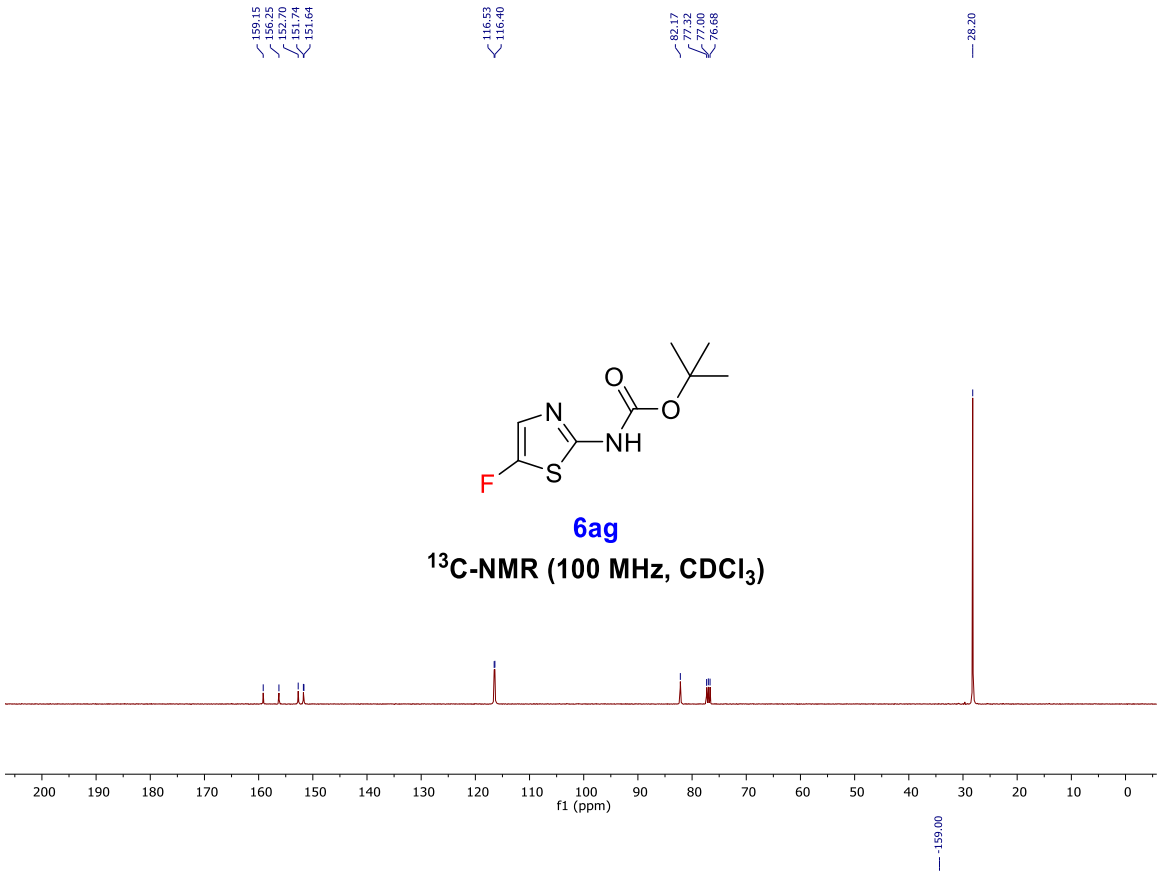
6af

^{19}F-NMR (376 MHz, $CDCl_3$)



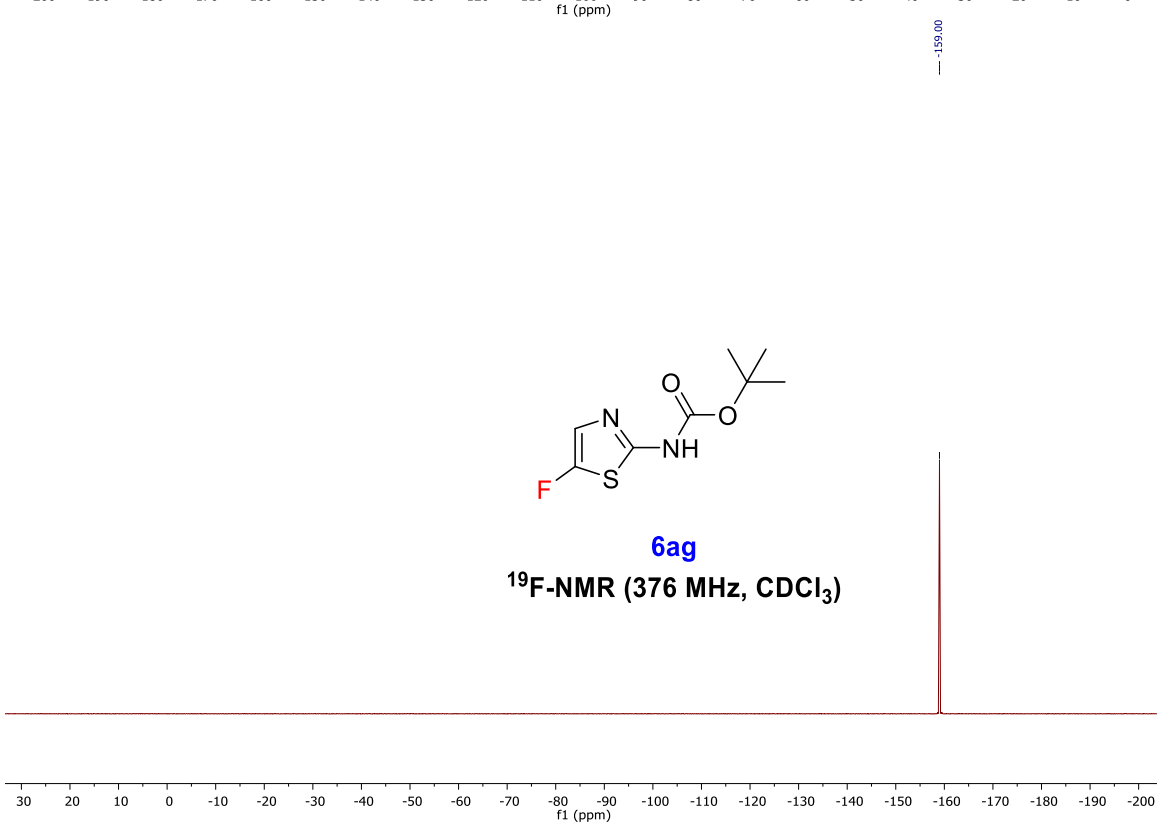
6ag

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



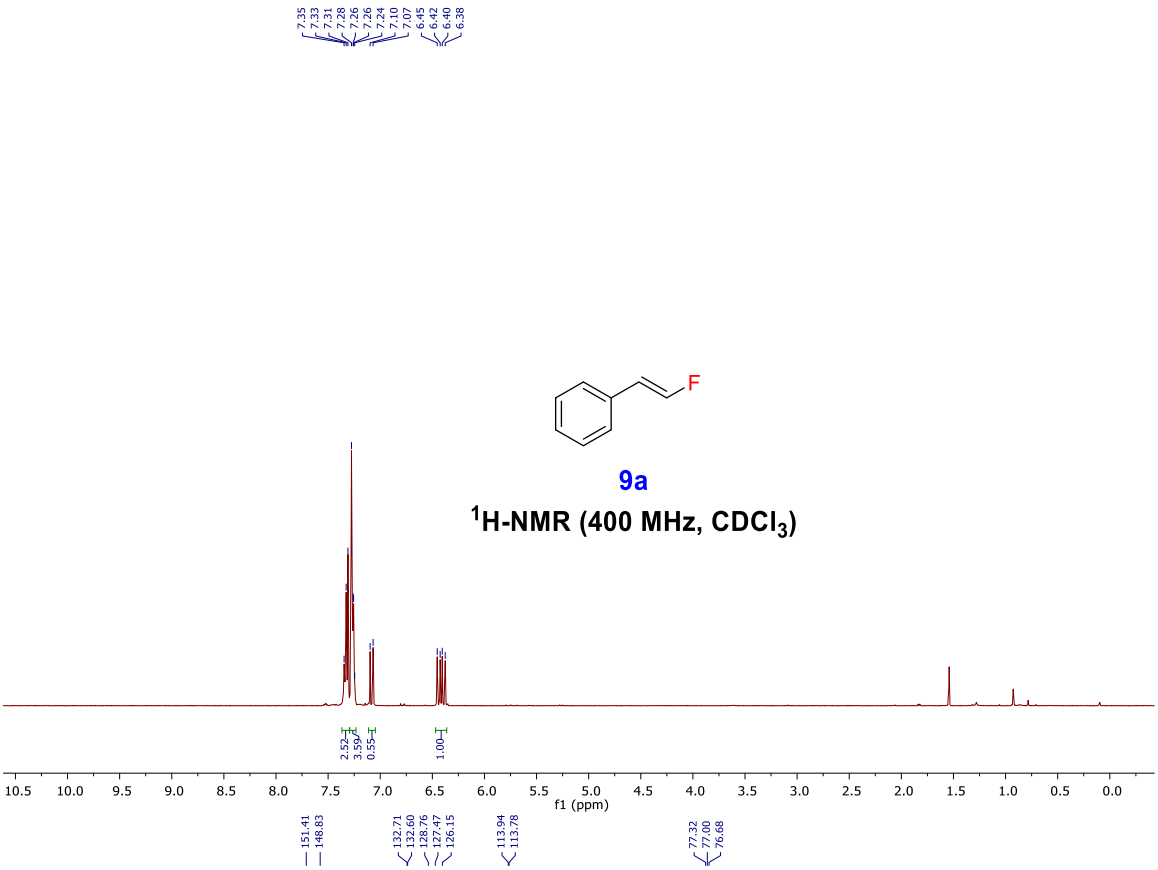
6ag

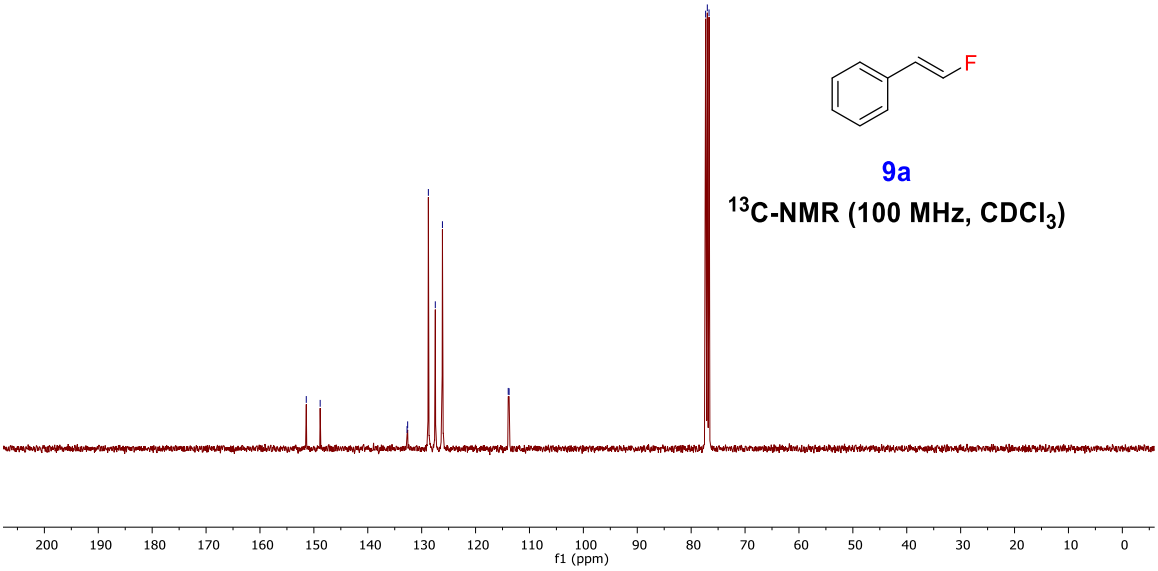
^{13}C-NMR (100 MHz, $CDCl_3$)

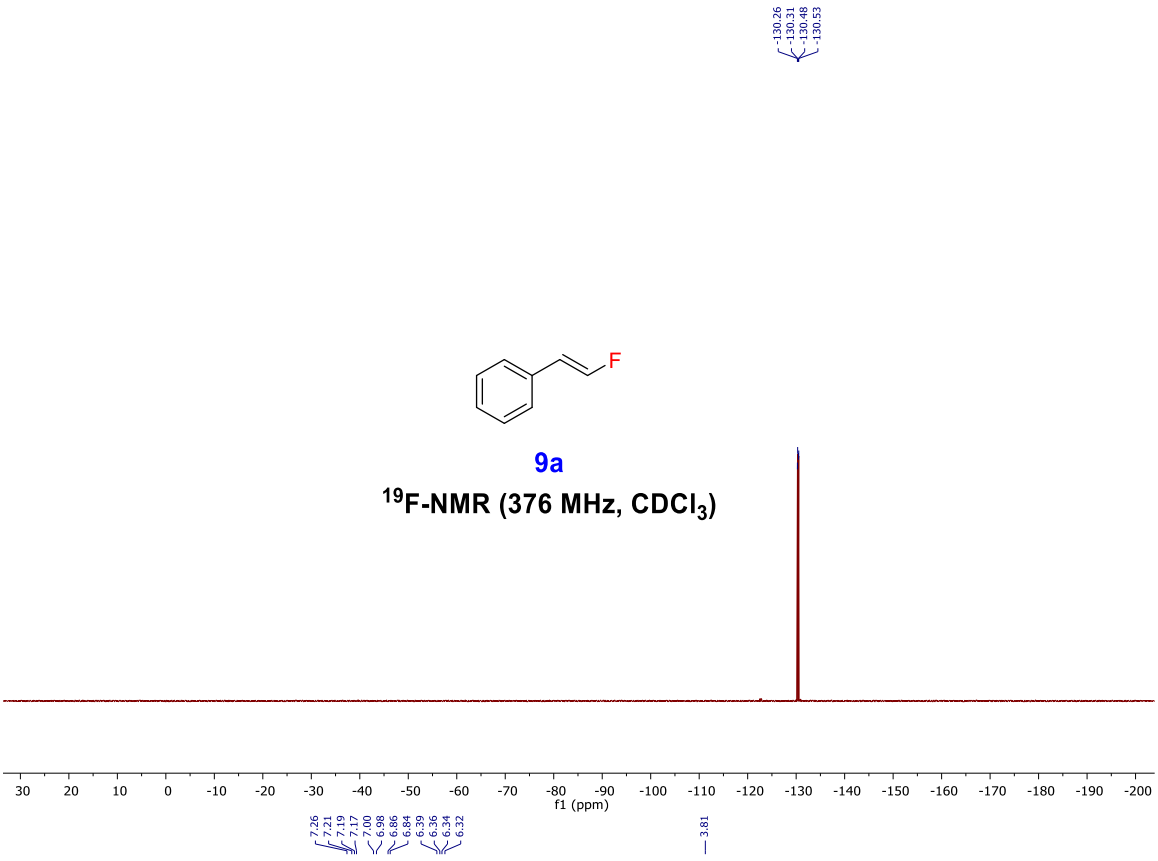


6ag

^{19}F-NMR (376 MHz, $CDCl_3$)

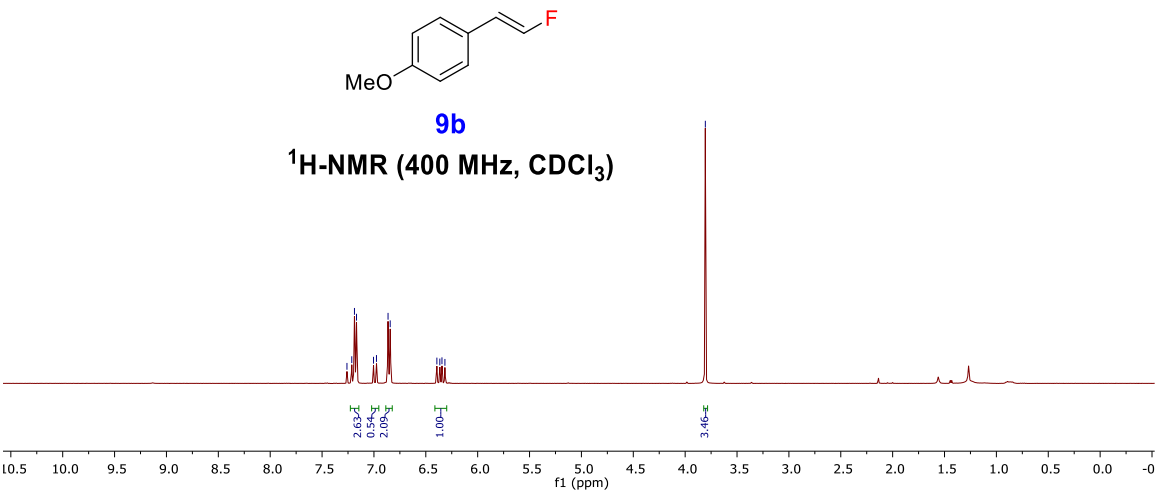

7.35
7.33
7.31
7.28
7.26
7.26
7.24
7.10
7.07
6.45
6.42
6.40
6.38
F
9a
1H-NMR (400 MHz, CDCl3)
2.52
3.59
0.55
1.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
151.41
148.83
132.71
132.60
128.76
127.47
126.15
113.94
113.78
77.32
77.00
76.68


F
9a
13C-NMR (100 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



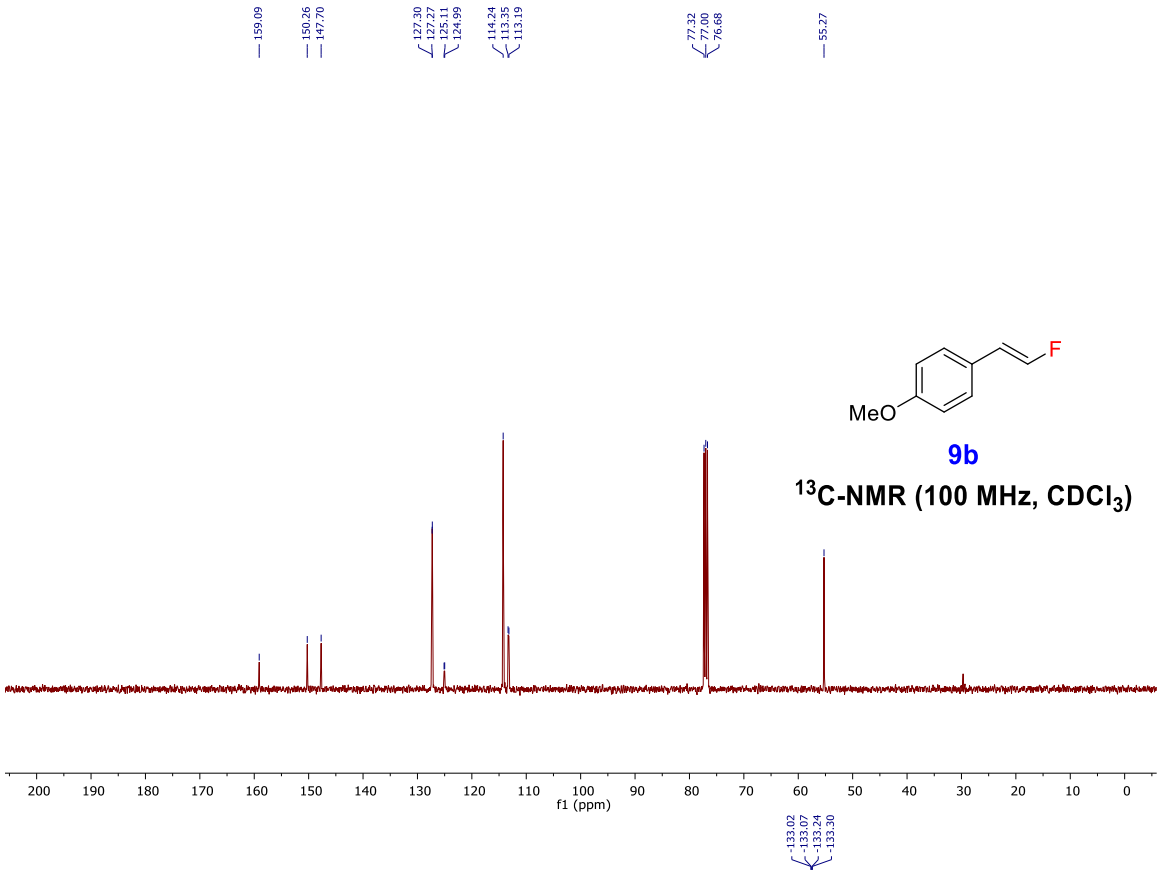
9a

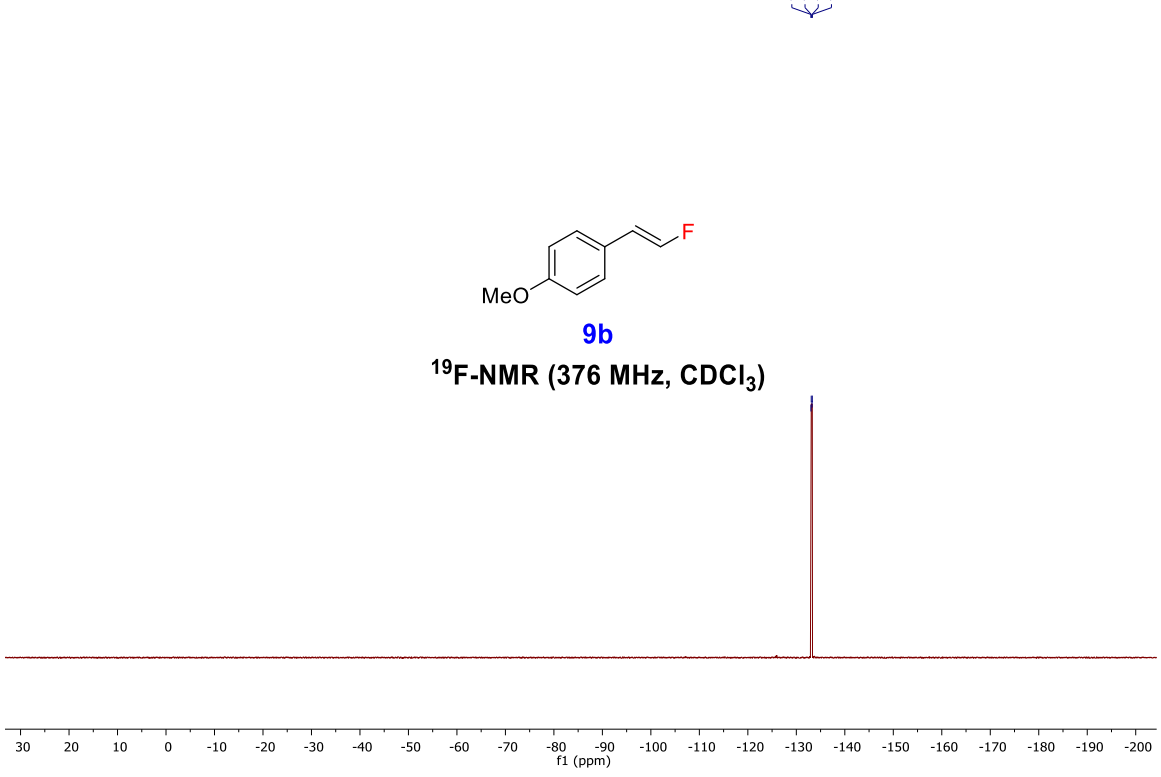
^{19}F-NMR (376 MHz, $CDCl_3$)

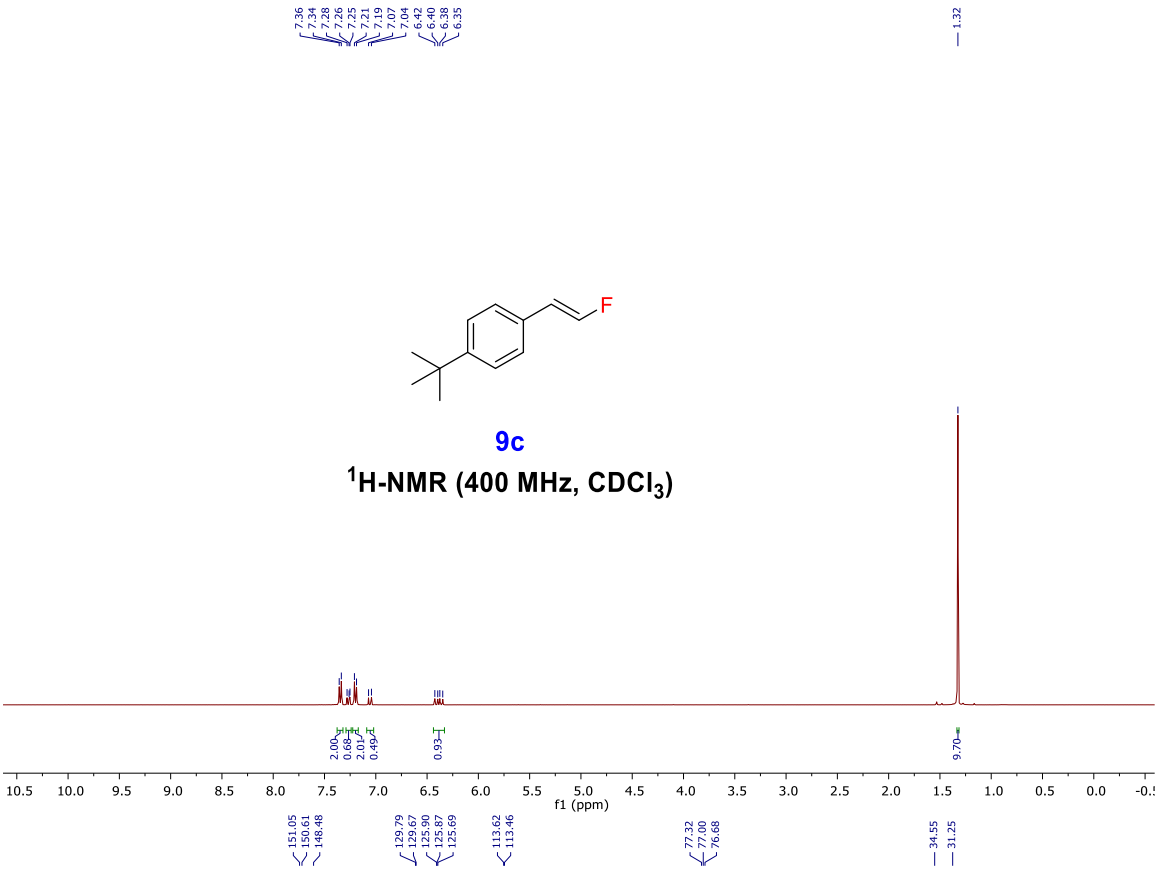


9b

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

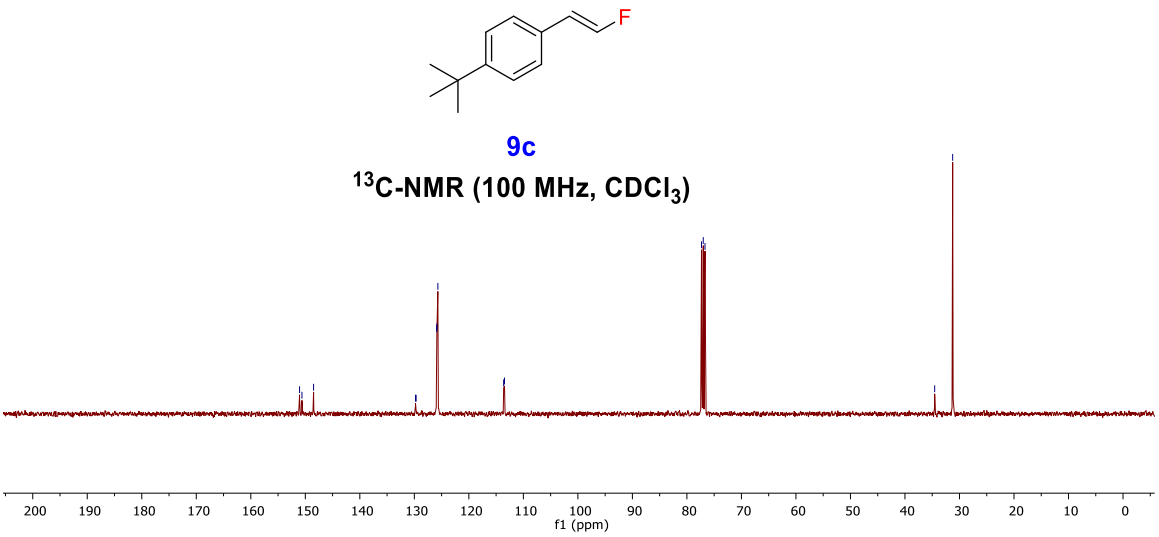

159.09
150.26
147.70
127.30
127.27
125.11
124.99
114.24
113.35
113.19
77.32
77.00
76.68
55.27
F
MeO
9b
13C-NMR (100 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


-133.02
-133.07
-133.24
-133.30
F
MeO
9b
19F-NMR (376 MHz, CDCl3)
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)



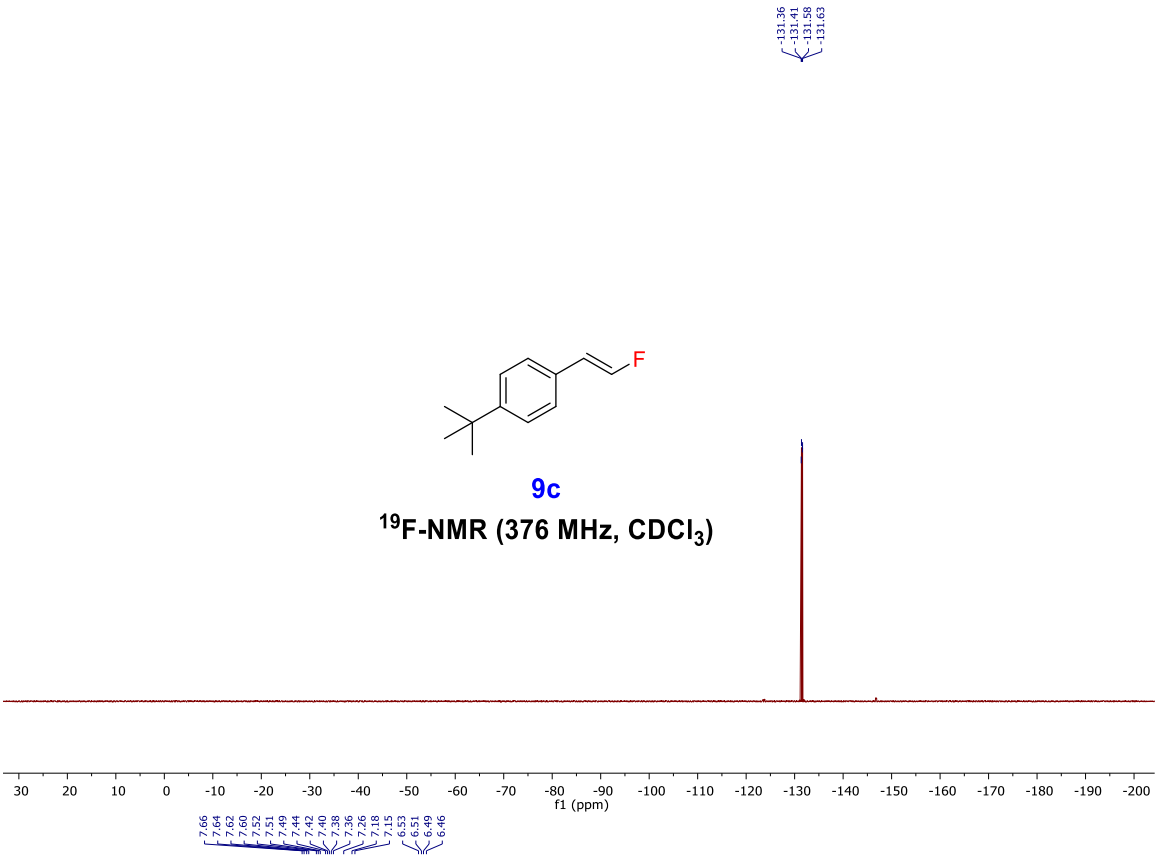
9c

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



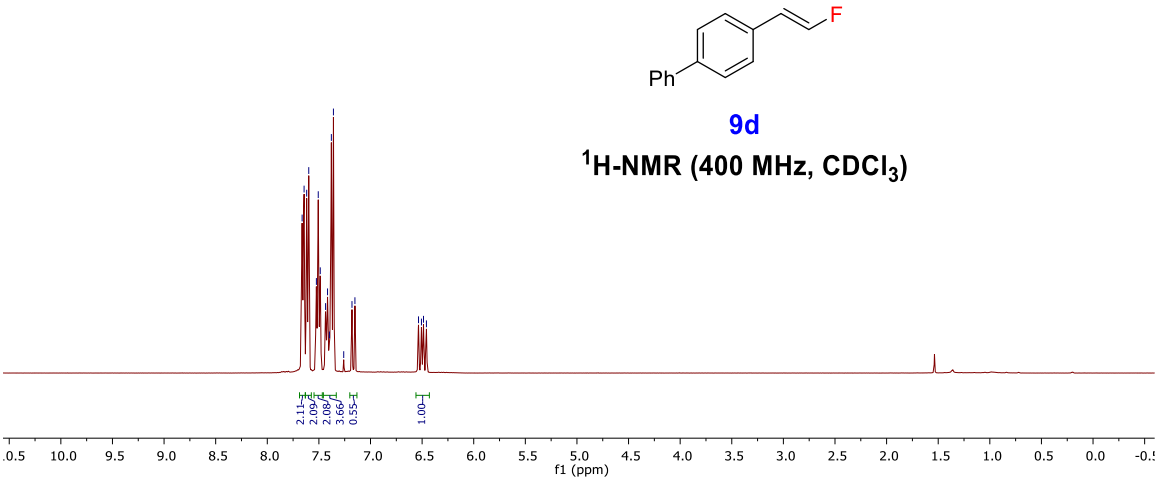
9c

^{13}C-NMR (100 MHz, $CDCl_3$)



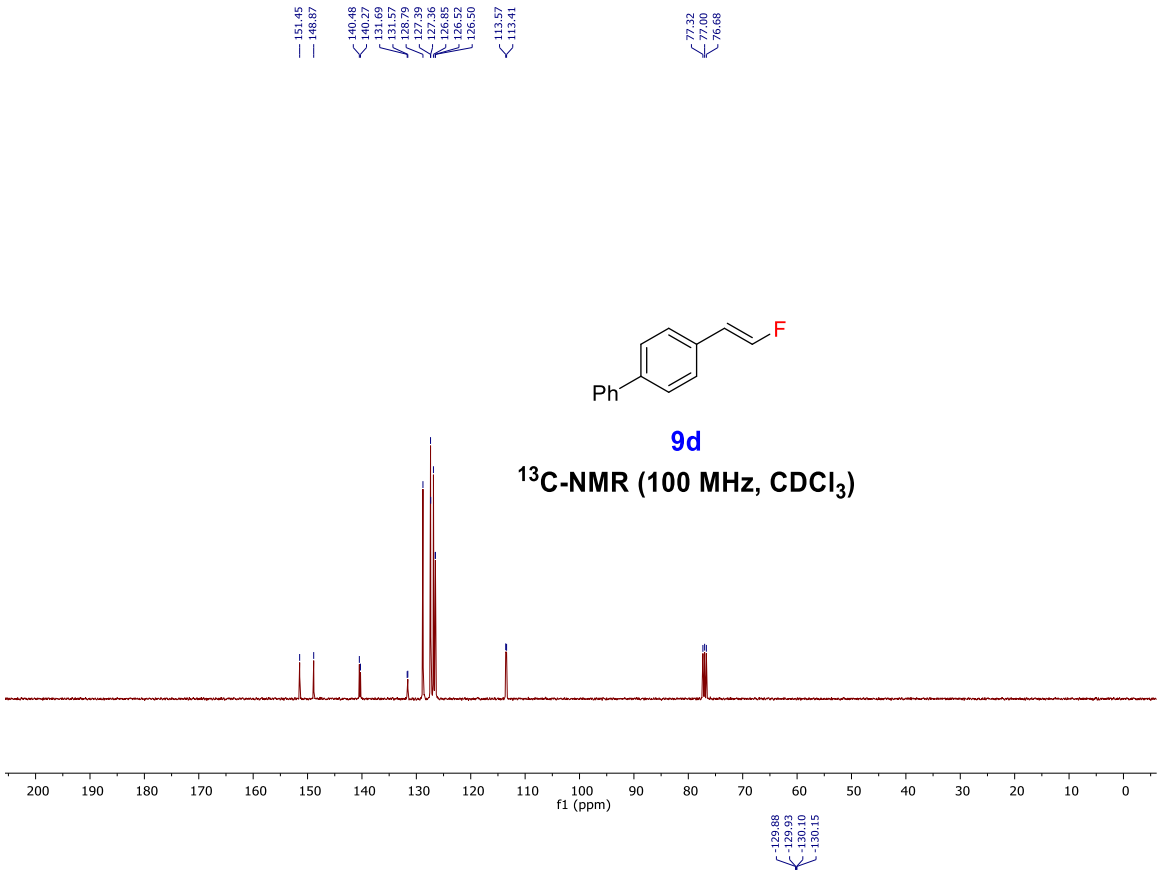
9c

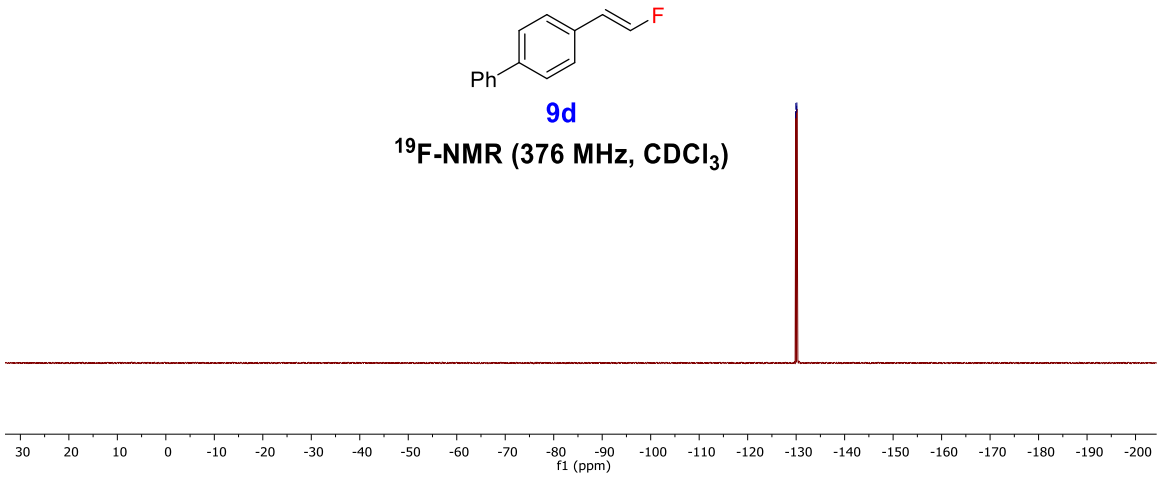
^{19}F-NMR (376 MHz, $CDCl_3$)

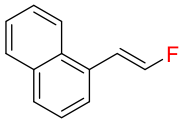


9d

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

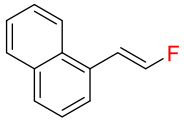

151.45
148.87
140.48
140.27
131.69
131.57
128.79
127.39
127.36
126.85
126.52
126.50
113.57
113.41
77.32
77.00
76.68
F
Ph
9d
13C-NMR (100 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)
129.88
129.93
130.10
130.15


F
Ph
9d
19F-NMR (376 MHz, CDCl3)
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)



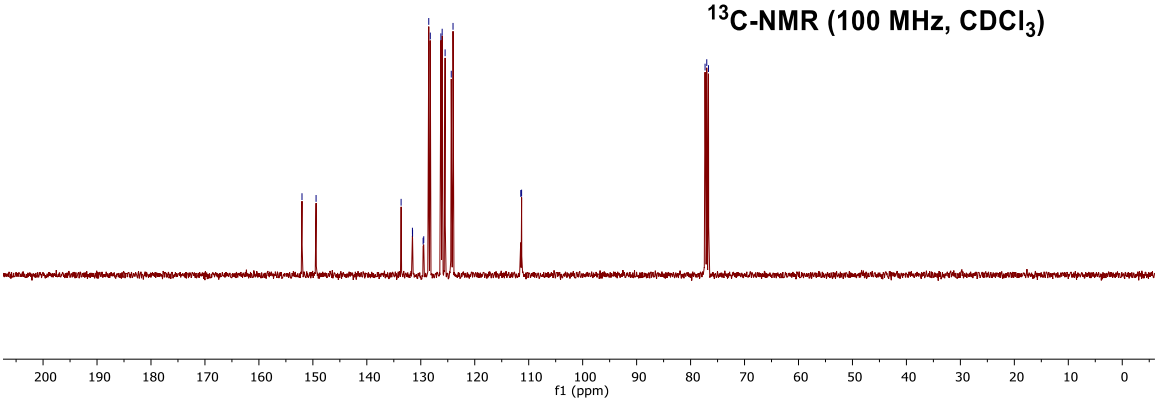
9e

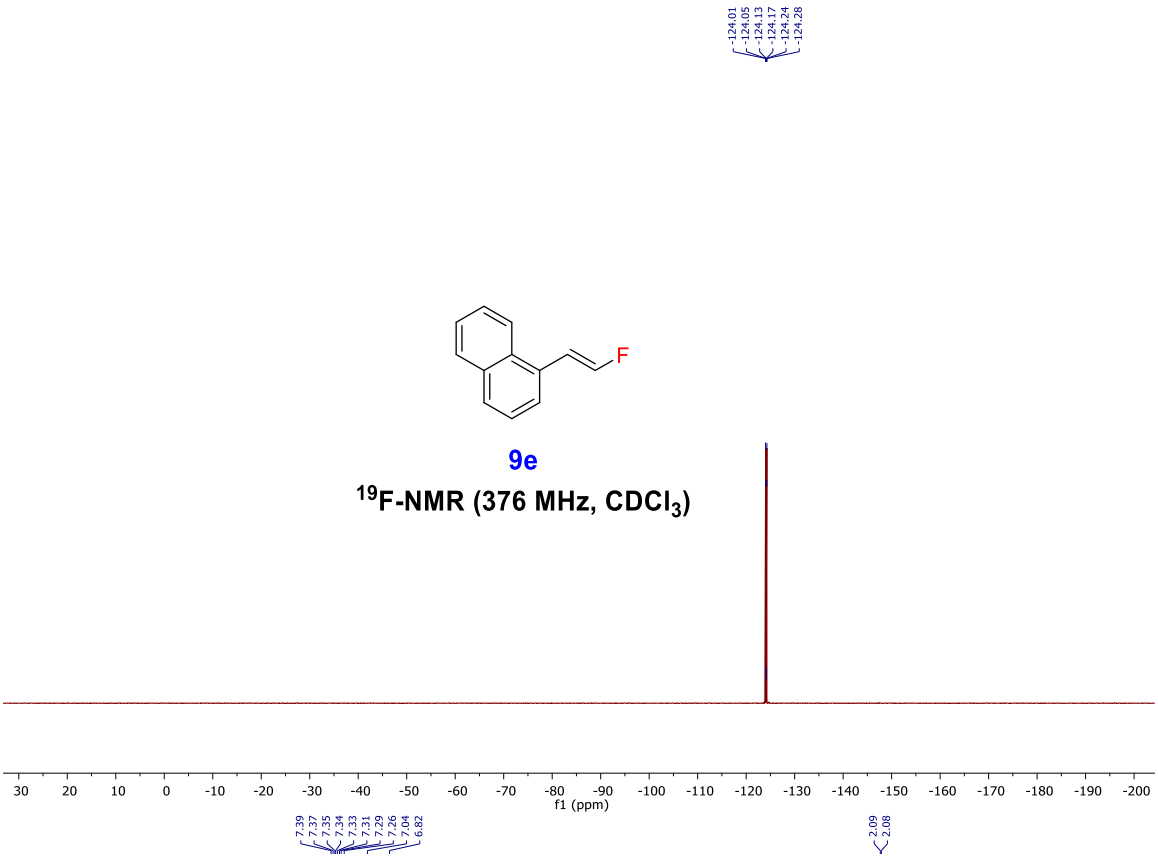
^{1}H-NMR (400 MHz, $CDCl_3$)

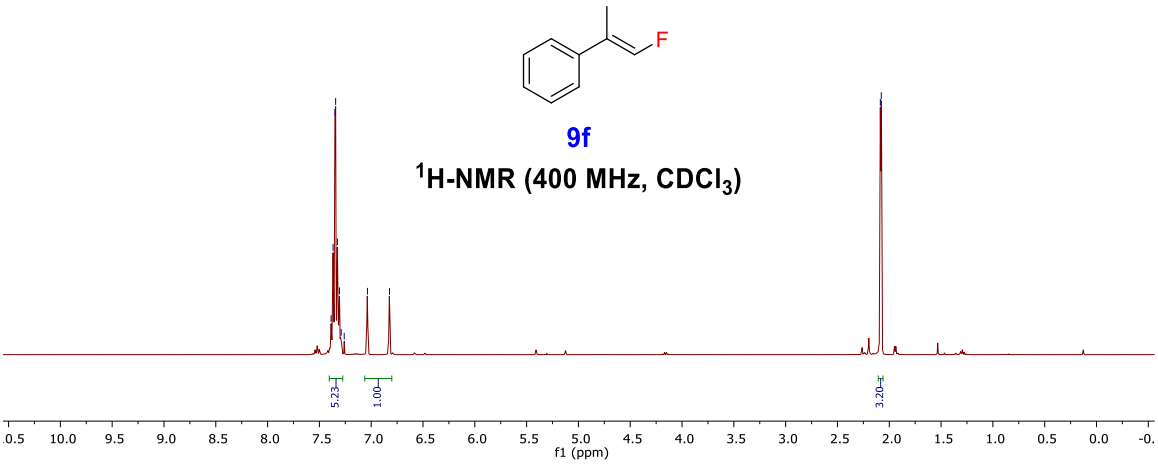


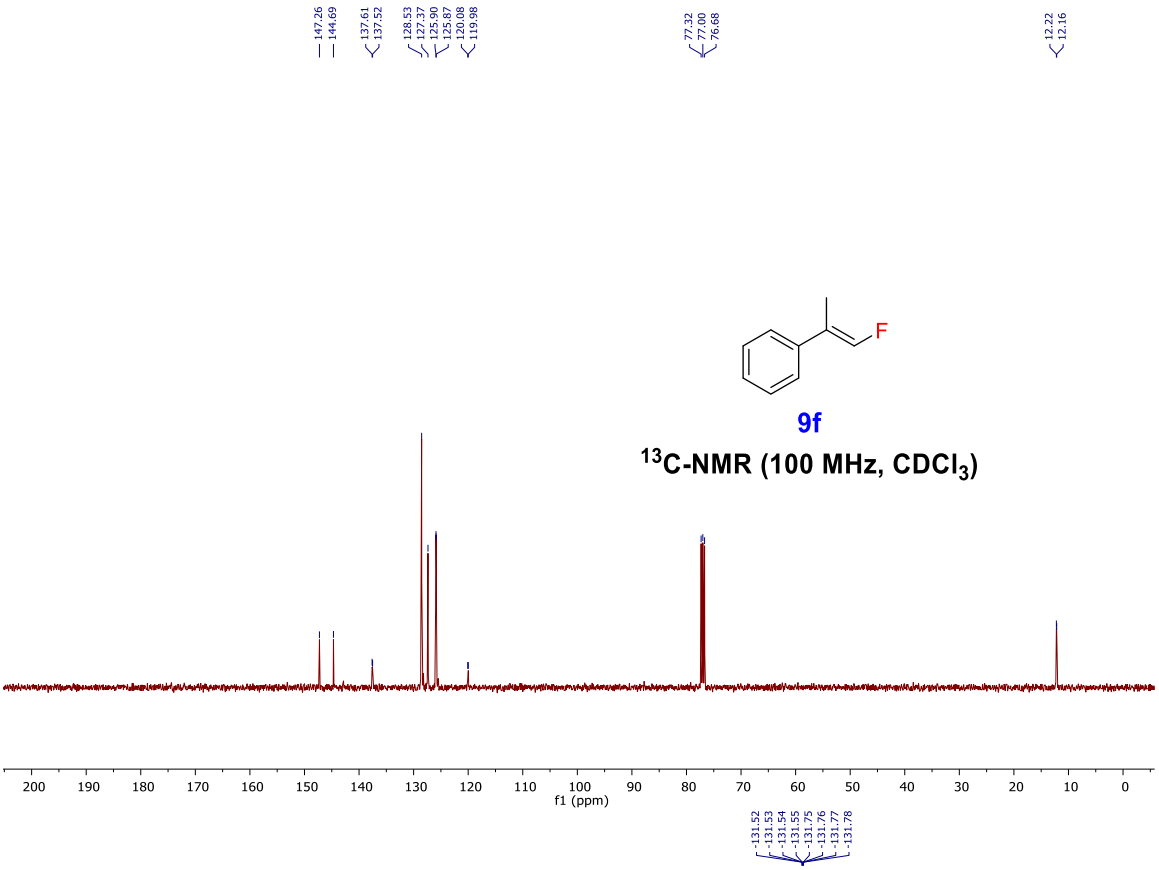
9e

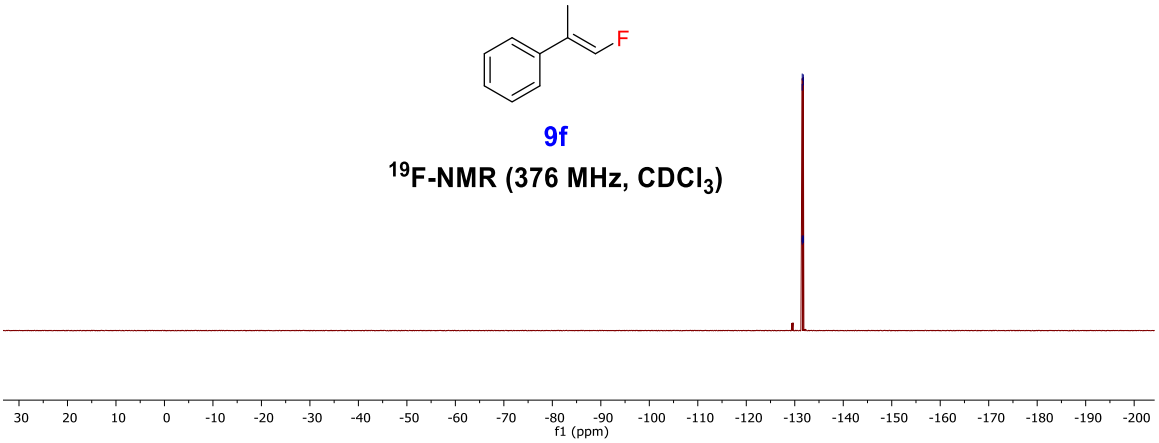
^{13}C-NMR (100 MHz, $CDCl_3$)

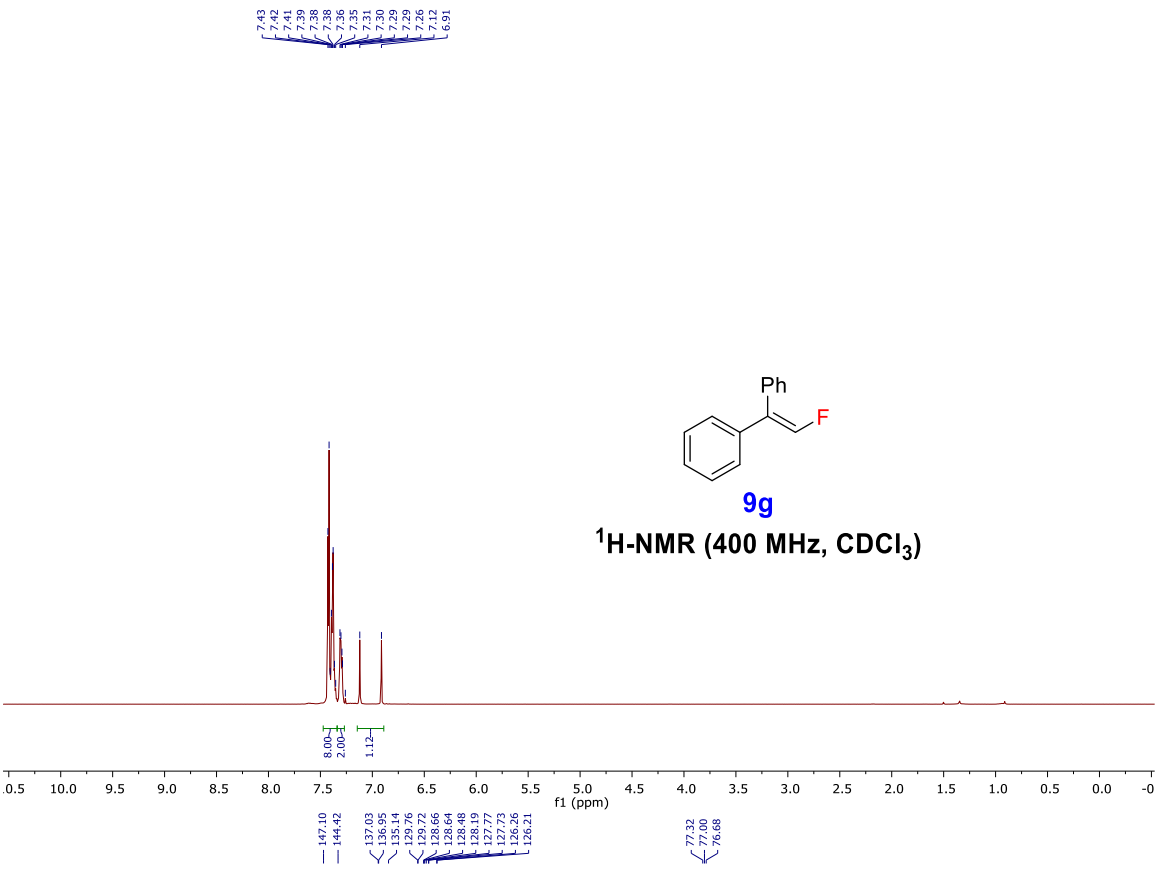



-124.01
-124.05
-124.13
-124.17
-124.24
-124.28
F
9e
19F-NMR (376 MHz, CDCl3)
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)
7.39
7.37
7.35
7.34
7.33
7.31
7.29
7.26
7.04
6.82
2.09
2.08


F
9f
1H-NMR (400 MHz, CDCl3)
5.23
1.00
3.20
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

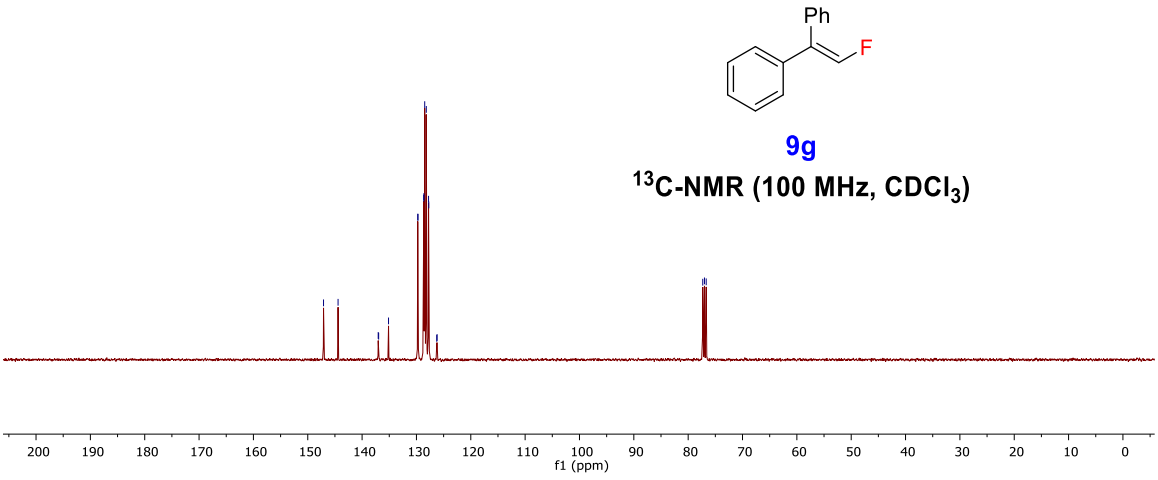

147.26
144.69
137.61
137.52
128.53
127.37
125.90
125.87
120.08
119.98
77.32
77.00
76.68
12.22
12.16
F
9f
13C-NMR (100 MHz, CDCl3)
f1 (ppm)
-131.52
-131.53
-131.54
-131.55
-131.75
-131.76
-131.77
-131.78


F
9f
19F-NMR (376 MHz, CDCl3)
f1 (ppm)



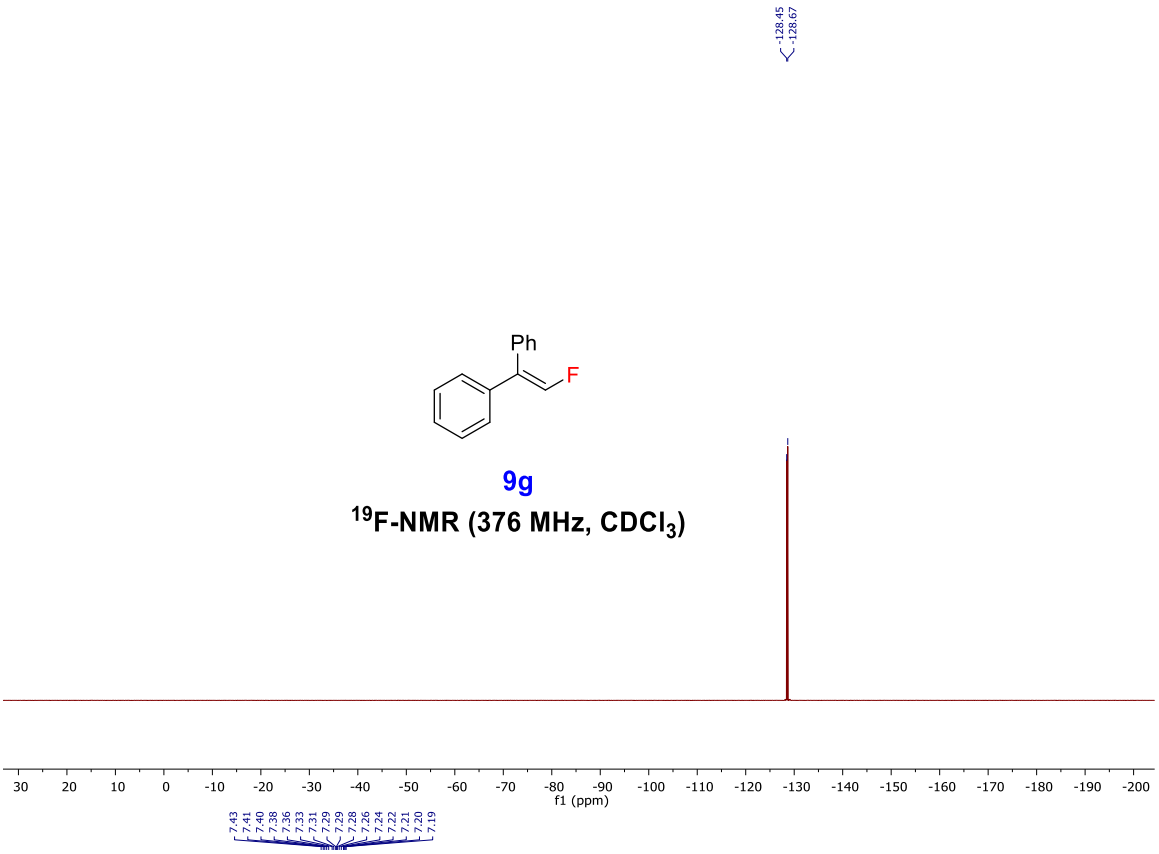
9g

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



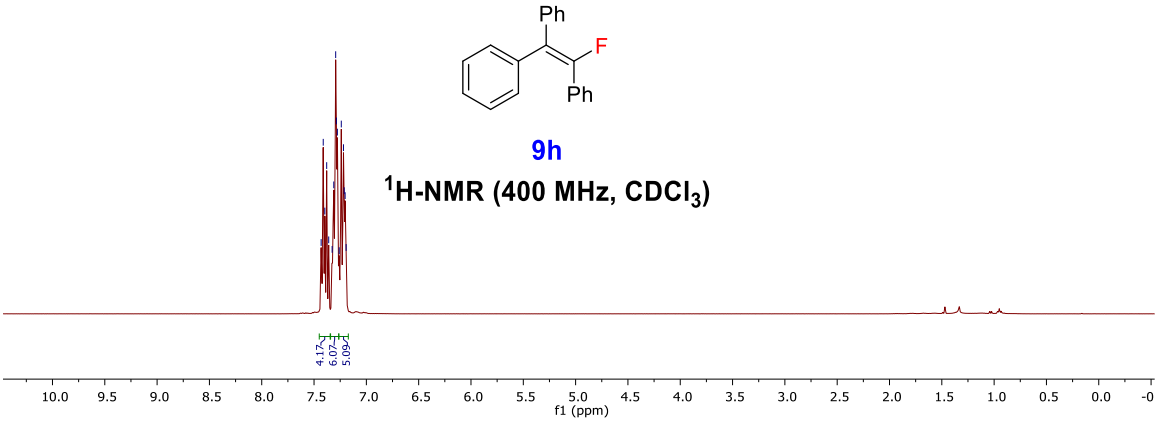
9g

^{13}C-NMR (100 MHz, $CDCl_3$)



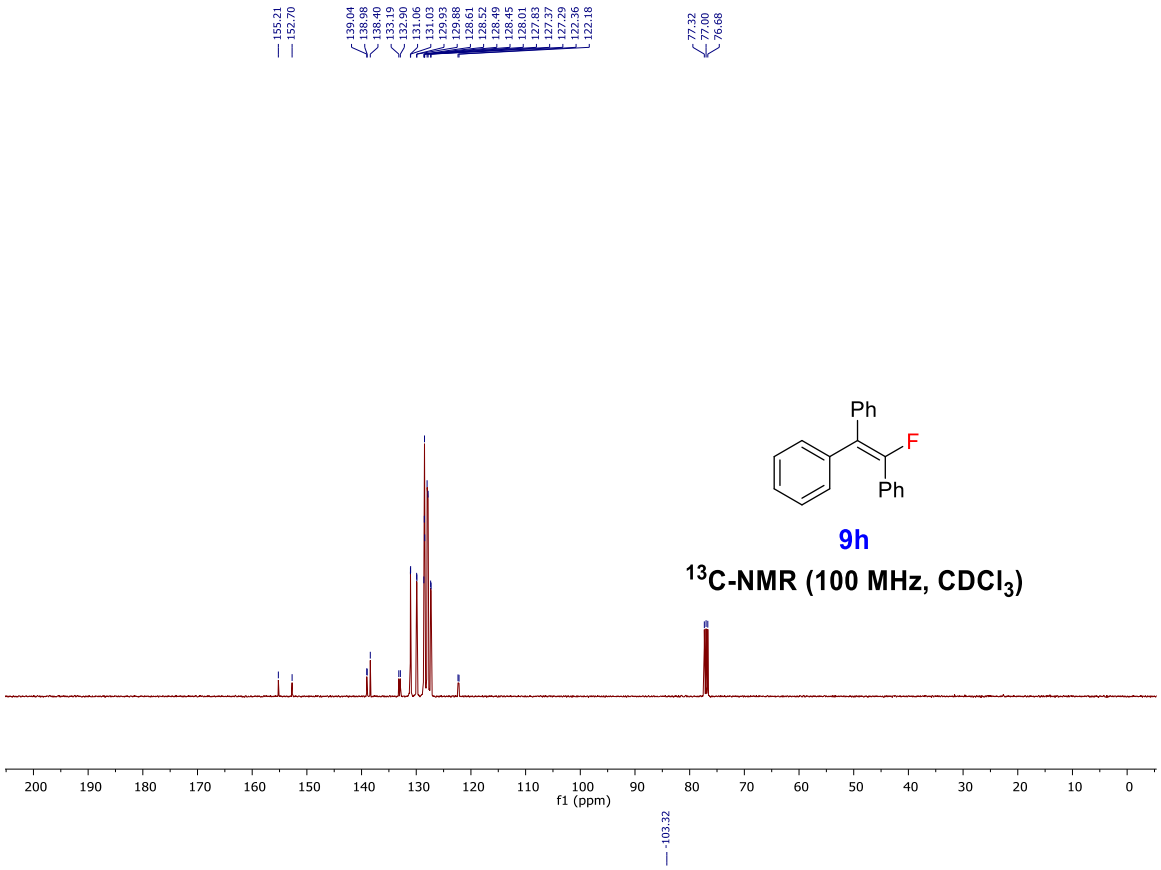
9g

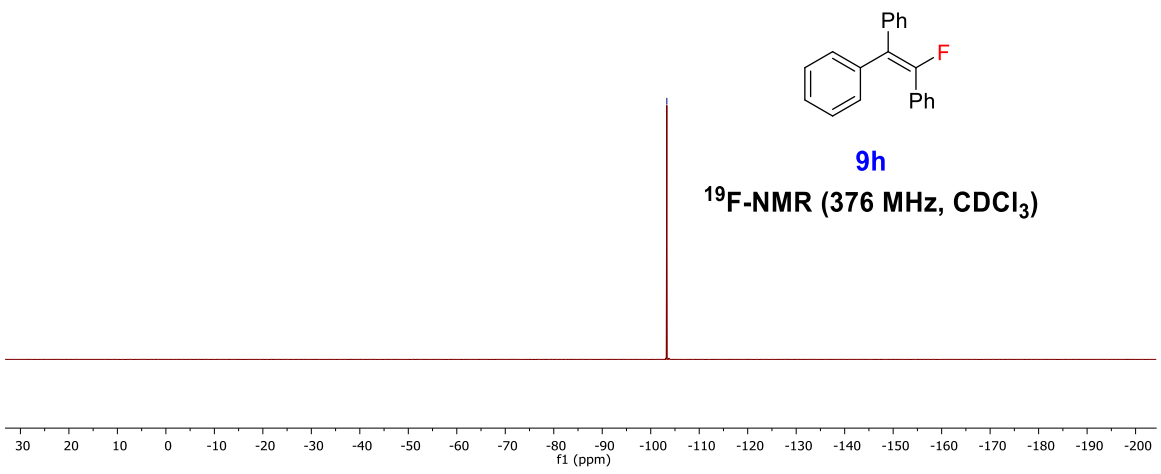
^{19}F-NMR (376 MHz, $CDCl_3$)

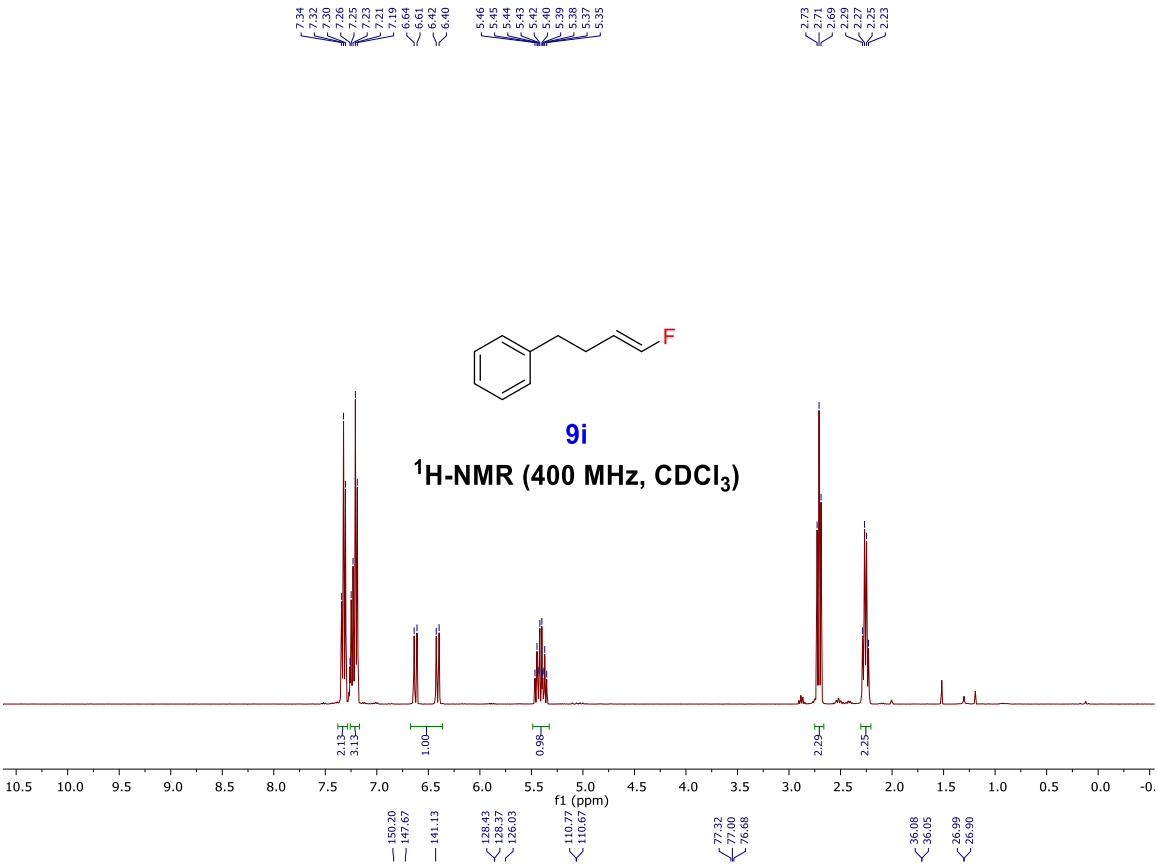


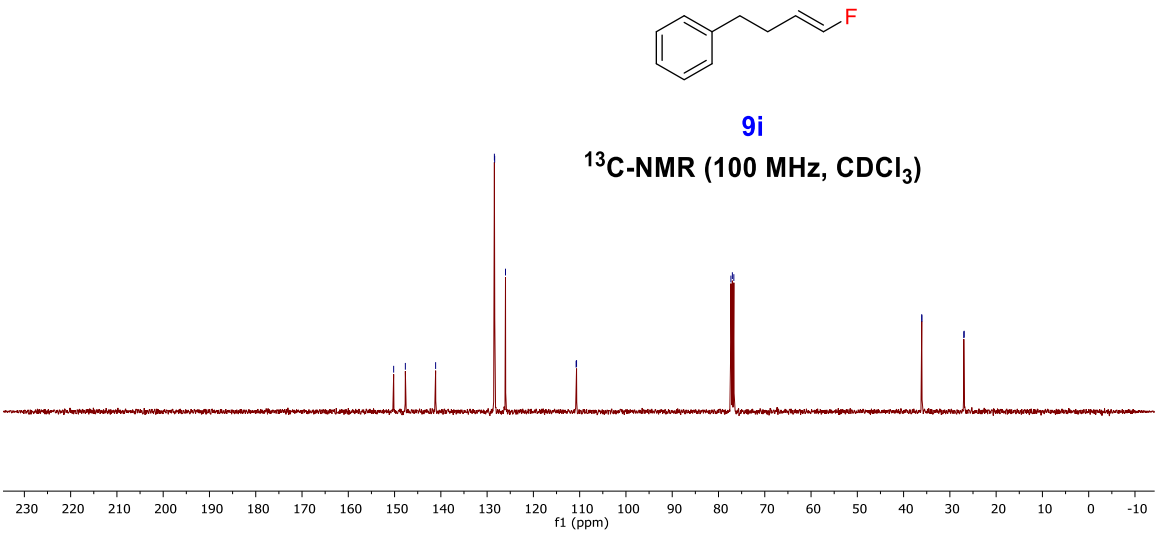
9h

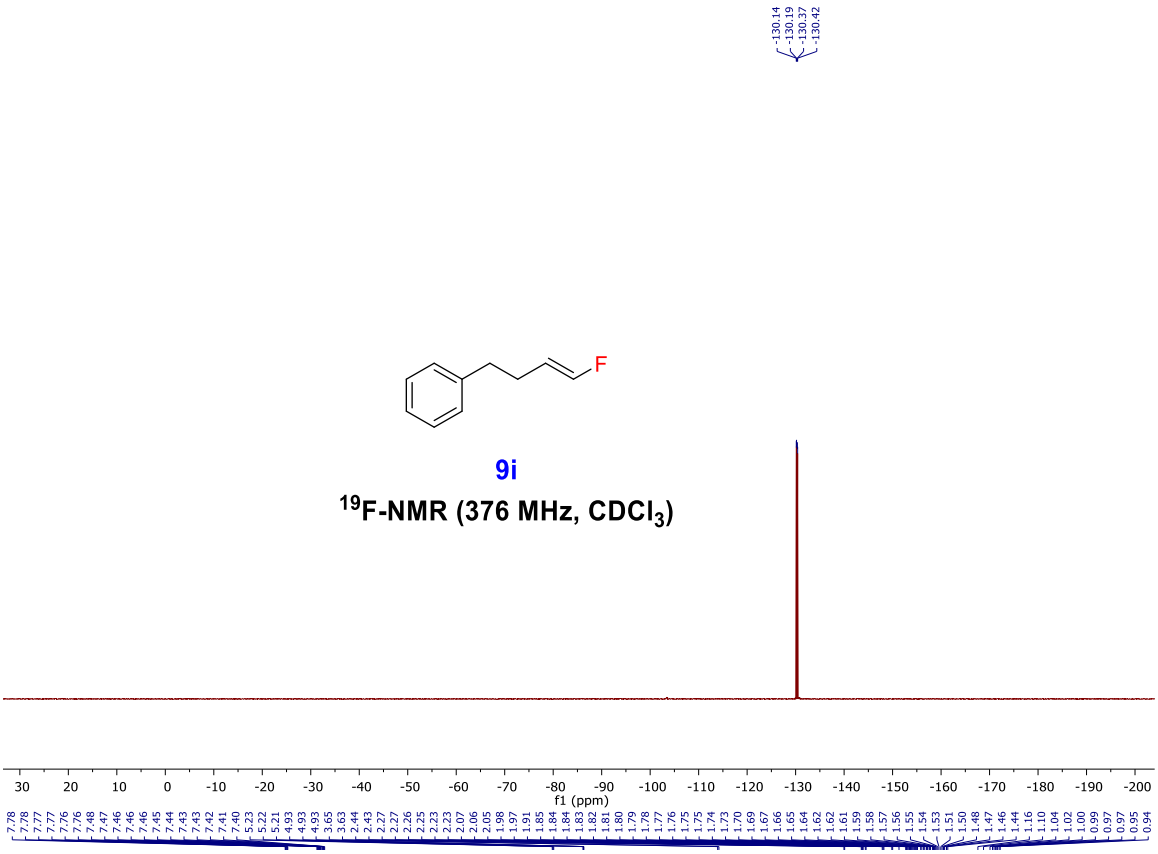
^{1}H-NMR (400 MHz, $CDCl_3$)


155.21
152.70
139.04
138.98
138.40
133.19
132.90
131.06
131.03
129.93
129.88
128.61
128.52
128.49
128.45
128.01
127.83
127.37
127.29
122.36
122.18
77.32
77.00
76.68
Ph
F
Ph
9h
13C-NMR (100 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


-103.32
Ph
F
Ph
9h
19F-NMR (376 MHz, CDCl3)
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

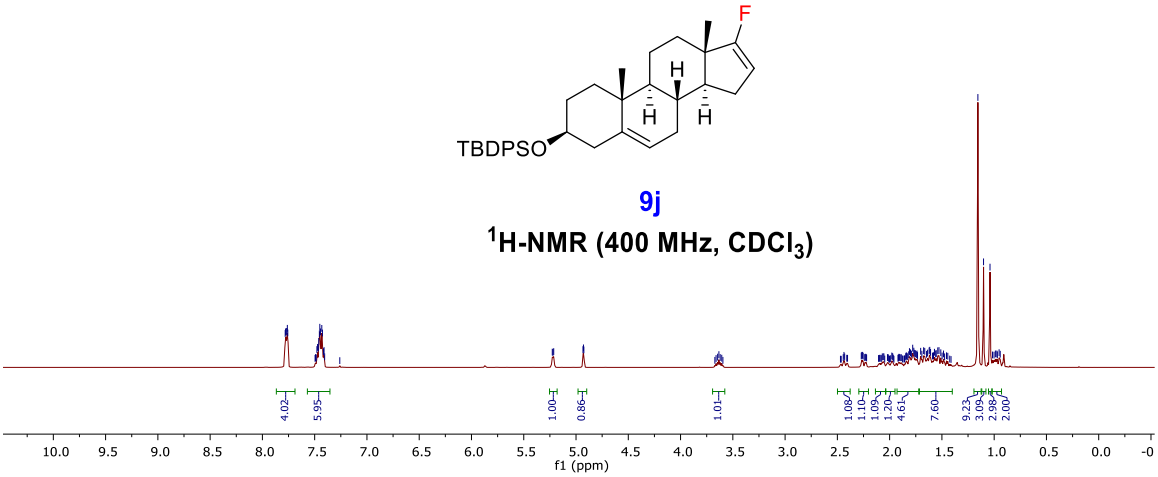

F
9i
1H-NMR (400 MHz, CDCl3)
f1 (ppm)


F
9i
13C-NMR (100 MHz, CDCl3)
f1 (ppm)



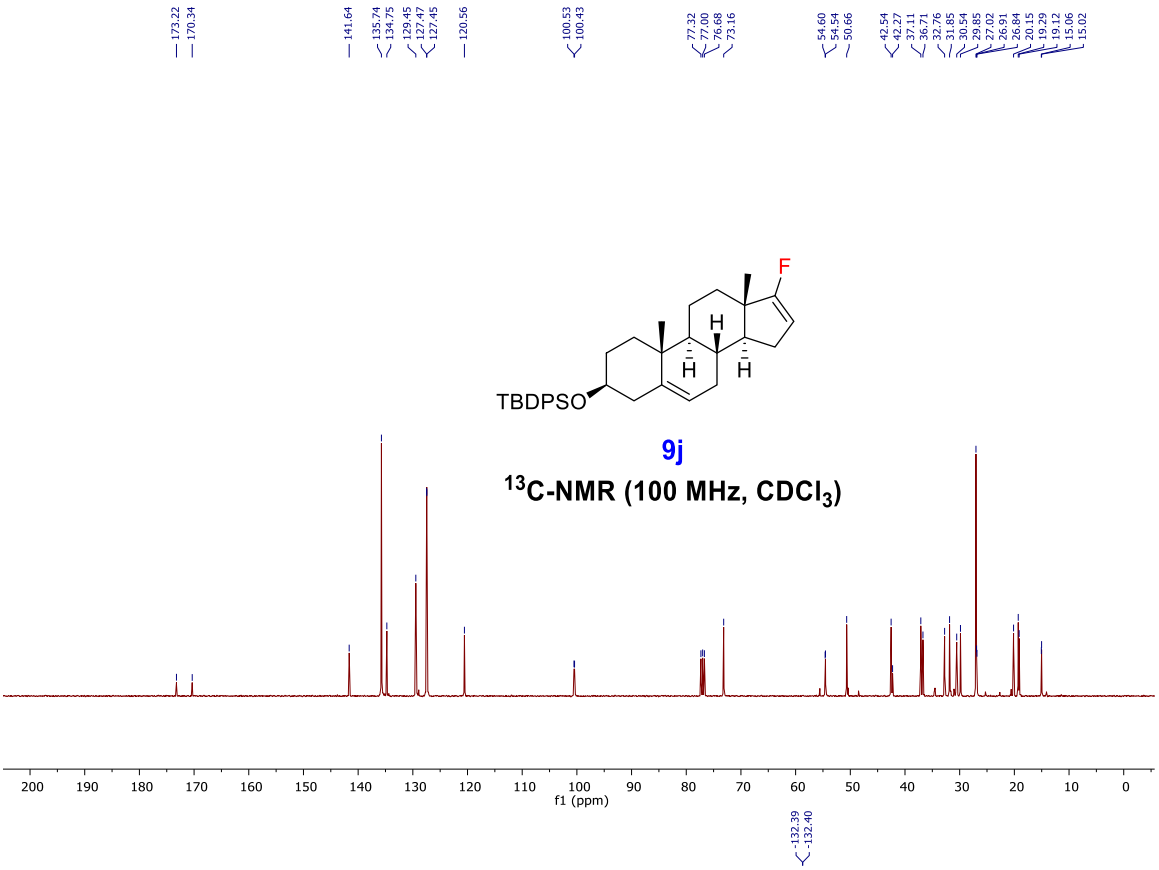
9i

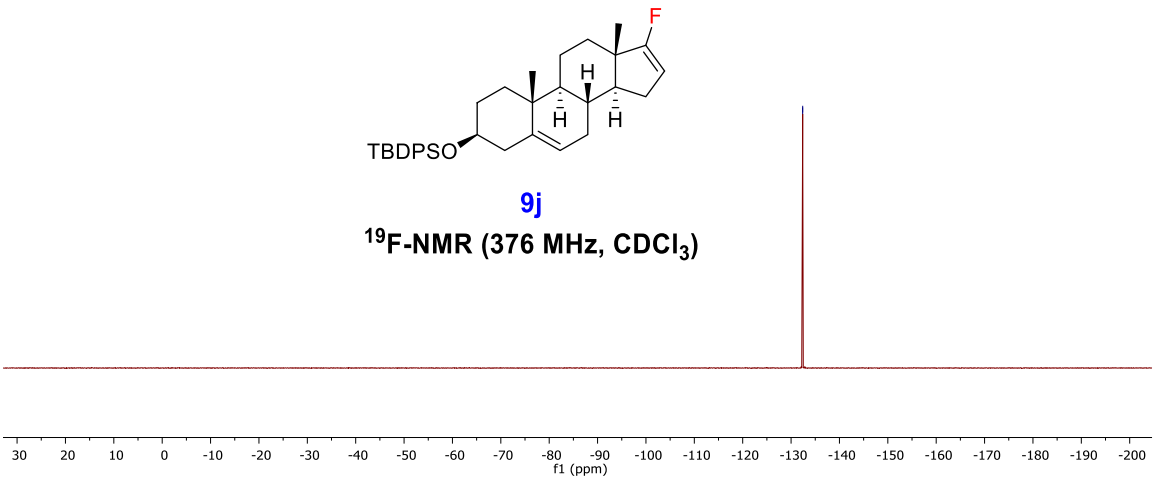
^{19}F-NMR (376 MHz, $CDCl_3$)

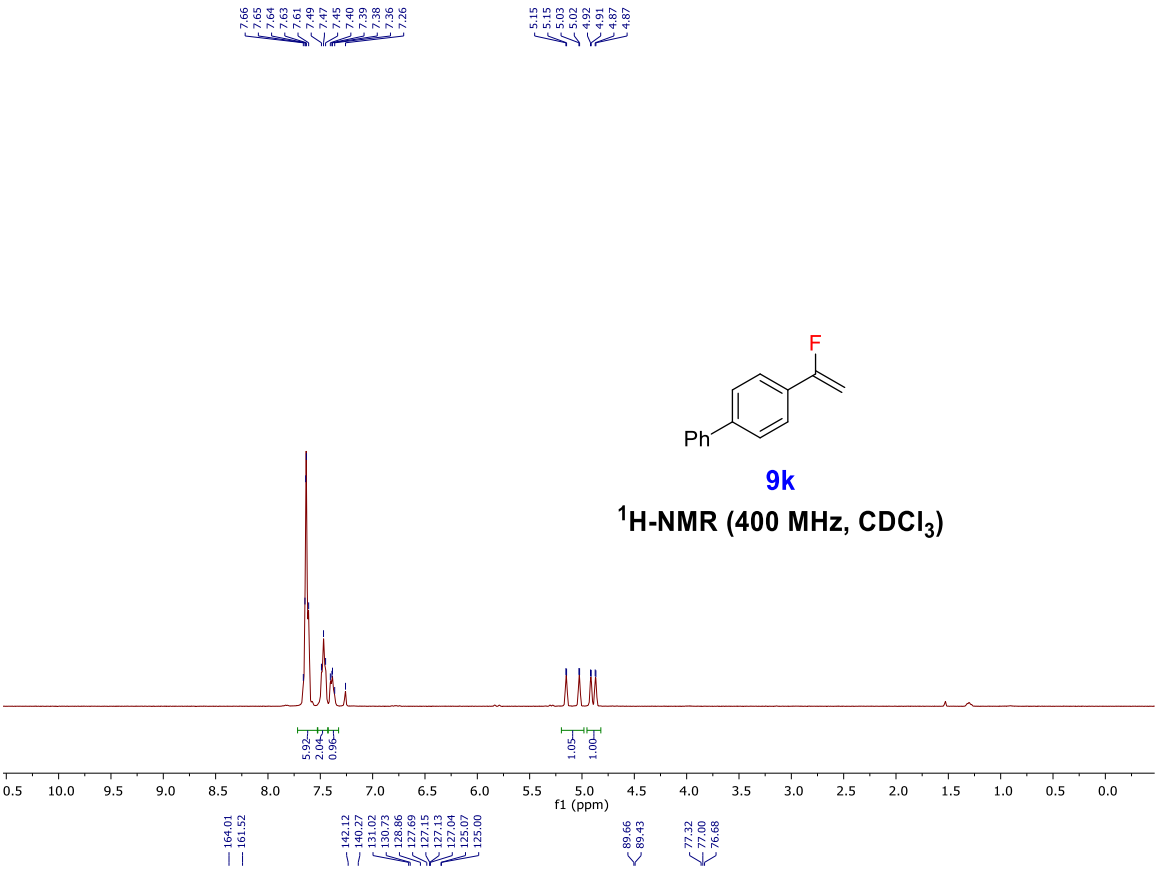


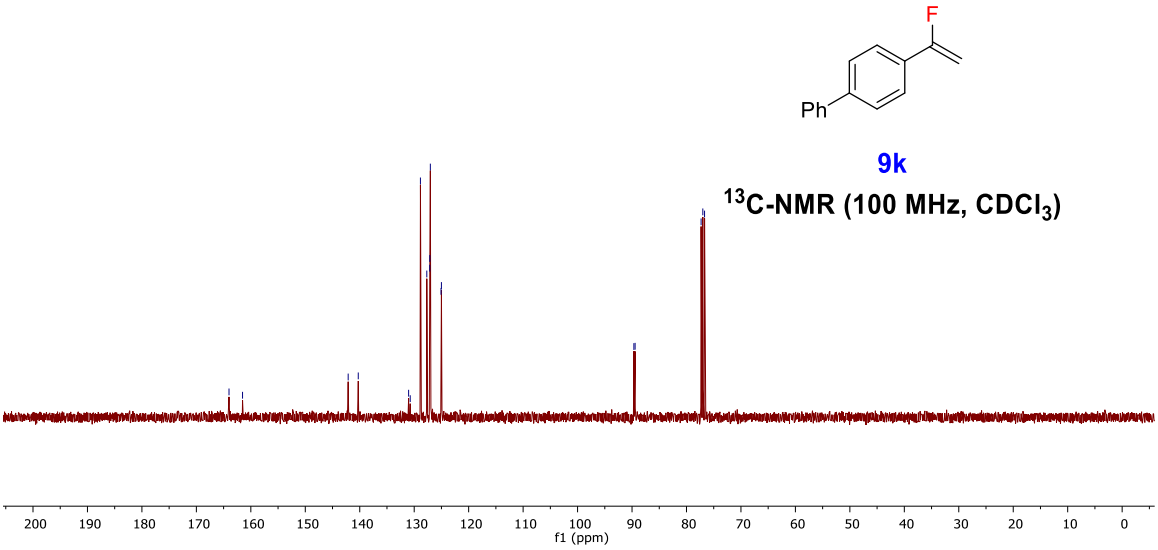
9j

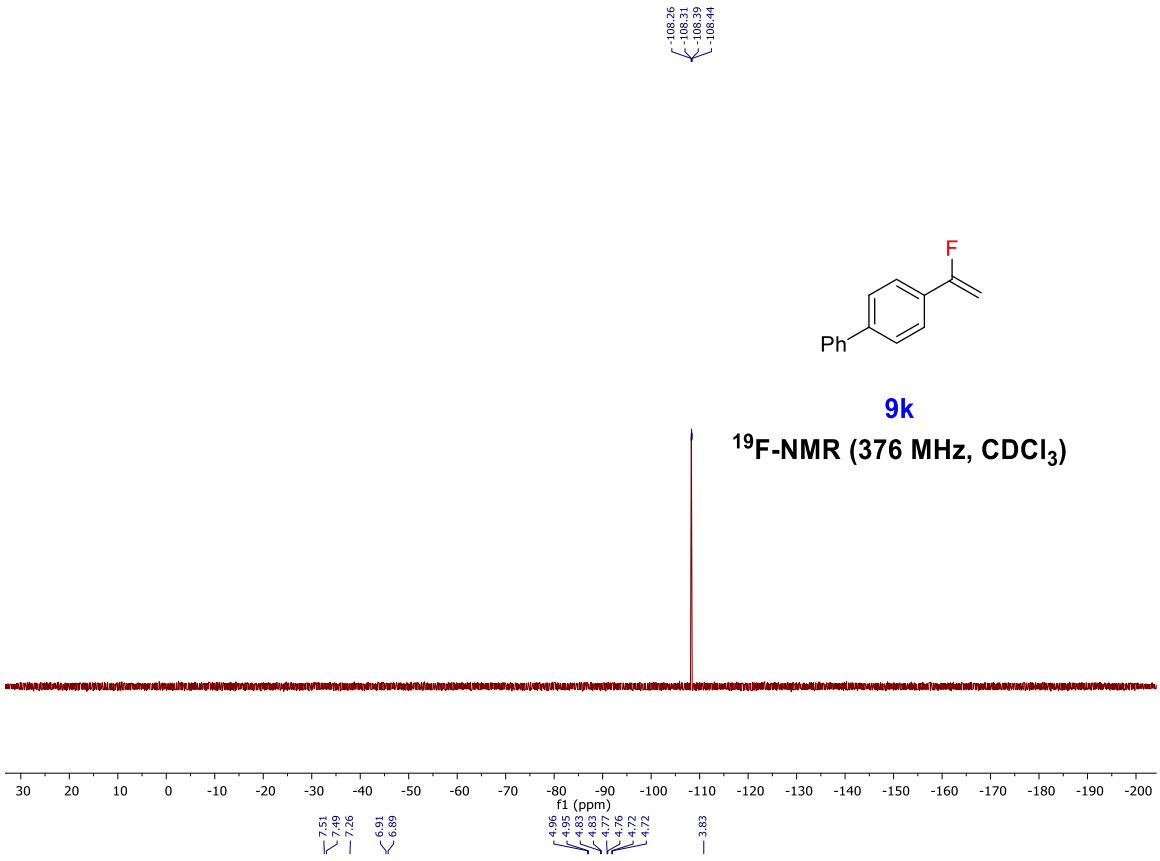
^{1}H-NMR (400 MHz, $CDCl_3$)


173.22
170.34
141.64
135.74
134.75
129.45
127.47
127.45
120.56
100.53
100.43
77.32
77.00
76.68
73.16
54.60
54.54
50.66
42.54
42.27
37.11
36.71
32.76
31.85
30.54
29.85
27.02
26.91
26.84
20.15
19.29
19.12
15.06
15.02
F
H
H
H
TBDPSO
9j
13C-NMR (100 MHz, CDCl3)
f1 (ppm)


-132.39
-132.40
F
H
H
H
TBDPSO
9j
19F-NMR (376 MHz, CDCl3)
f1 (ppm)

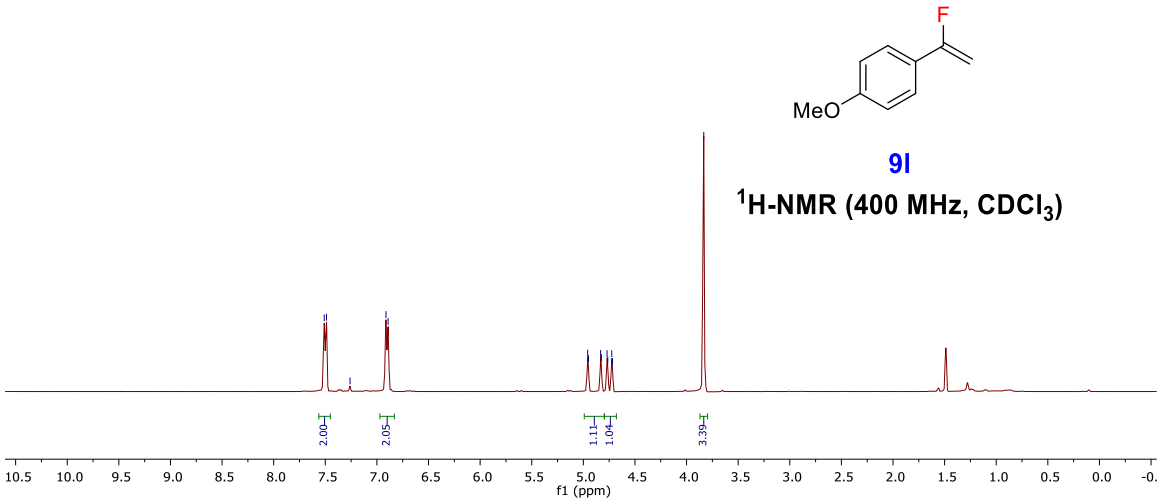

7.66
7.65
7.64
7.63
7.61
7.49
7.47
7.45
7.40
7.39
7.38
7.36
7.26
5.15
5.15
5.03
5.02
4.92
4.91
4.87
4.87
F
Ph
9k
1H-NMR (400 MHz, CDCl3)
5.92
2.04
0.96
1.05
1.00
f1 (ppm)
164.01
161.52
142.12
140.27
131.07
130.73
128.86
127.69
127.15
127.13
127.04
125.07
125.00
89.66
89.43
77.32
77.00
76.68


F
Ph
9k
13C-NMR (100 MHz, CDCl3)
f1 (ppm)



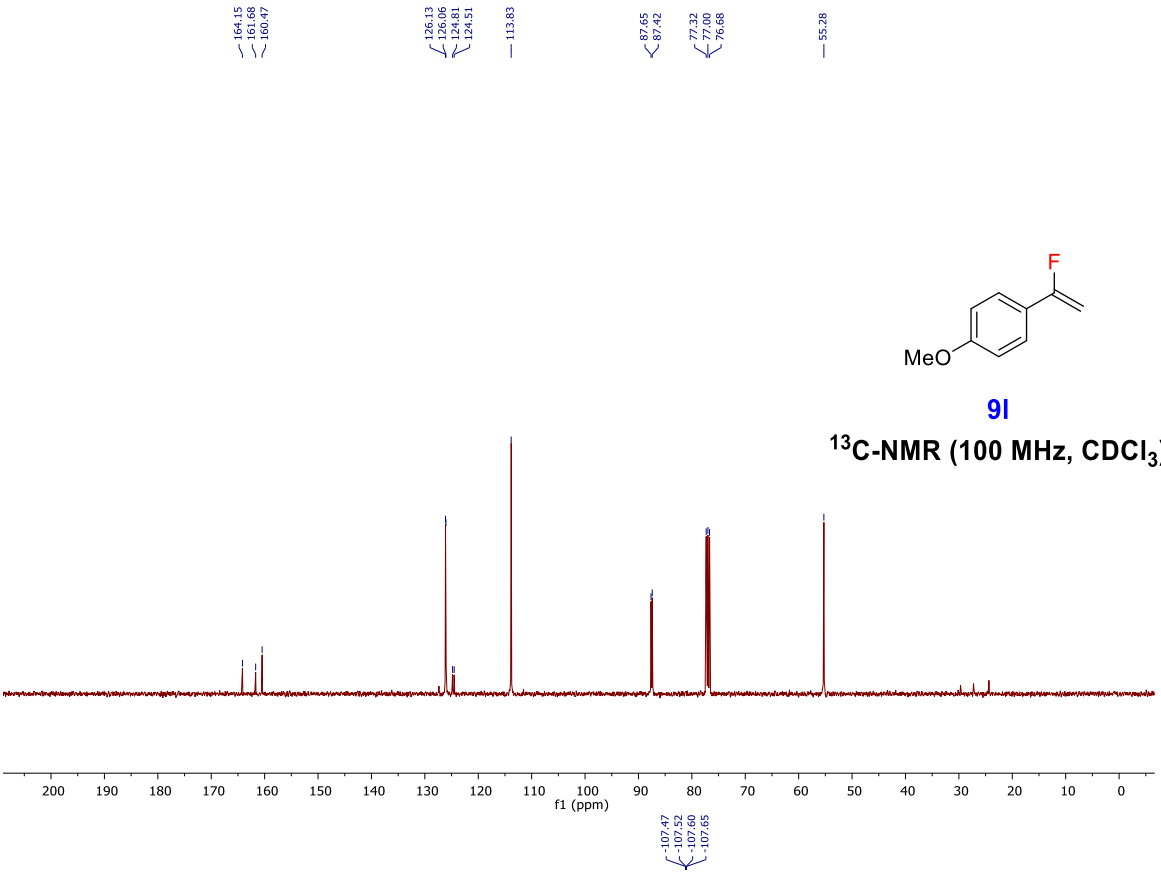
9k

^{19}F-NMR (376 MHz, $CDCl_3$)



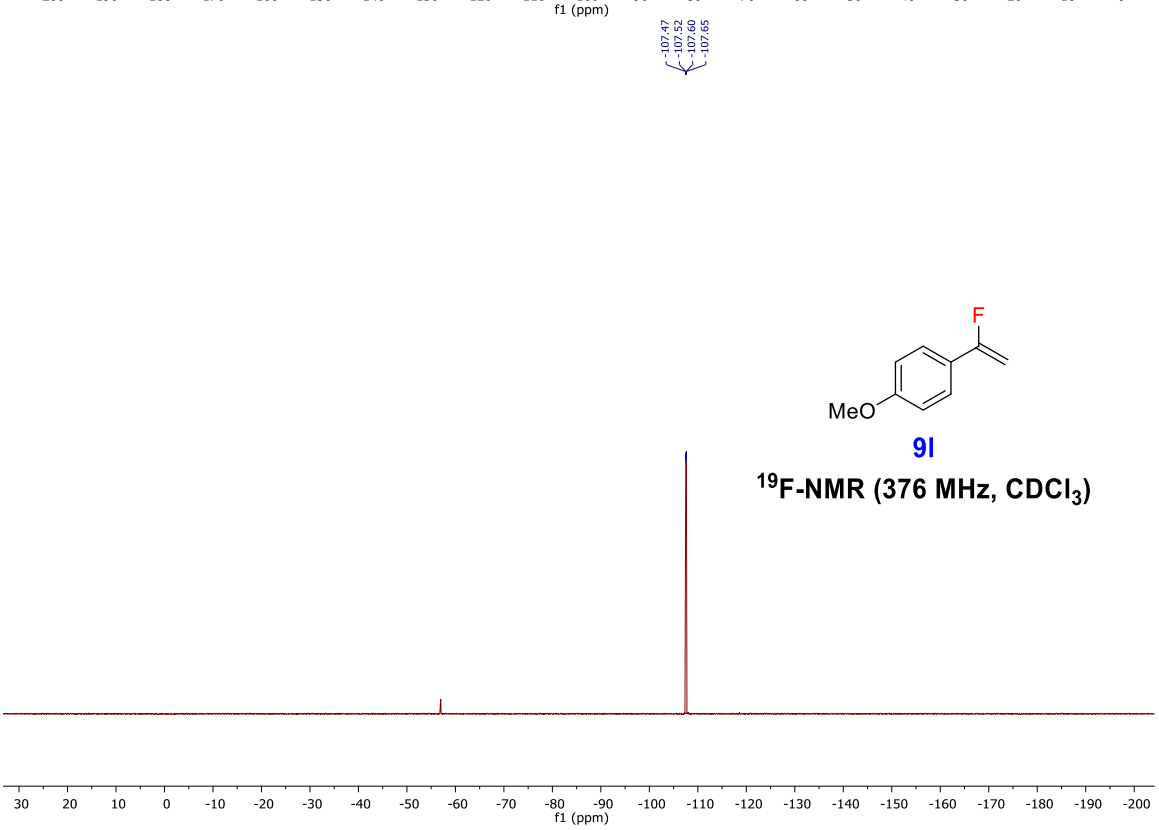
9l

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



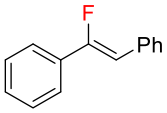
9l

^{13}C-NMR (100 MHz, $CDCl_3$)



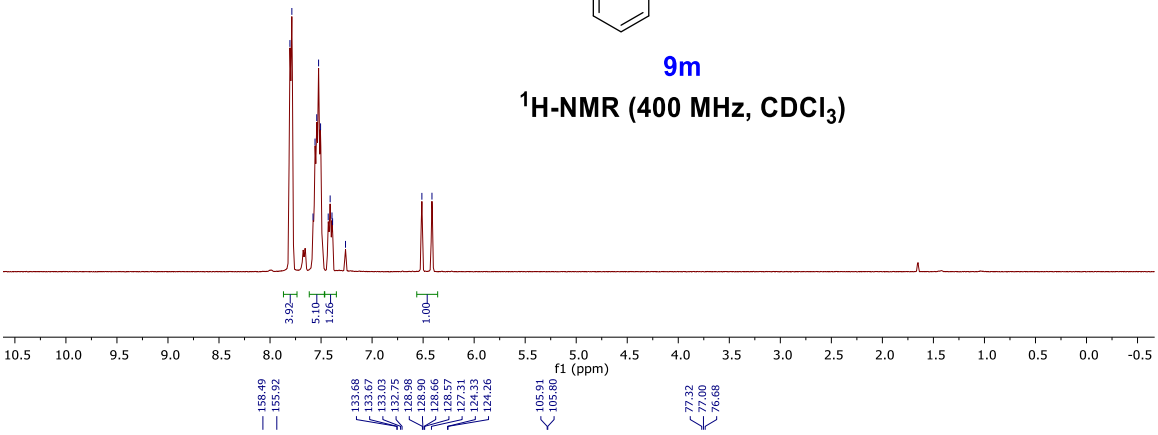
9l

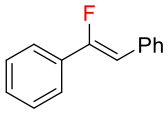
^{19}F-NMR (376 MHz, $CDCl_3$)



9m

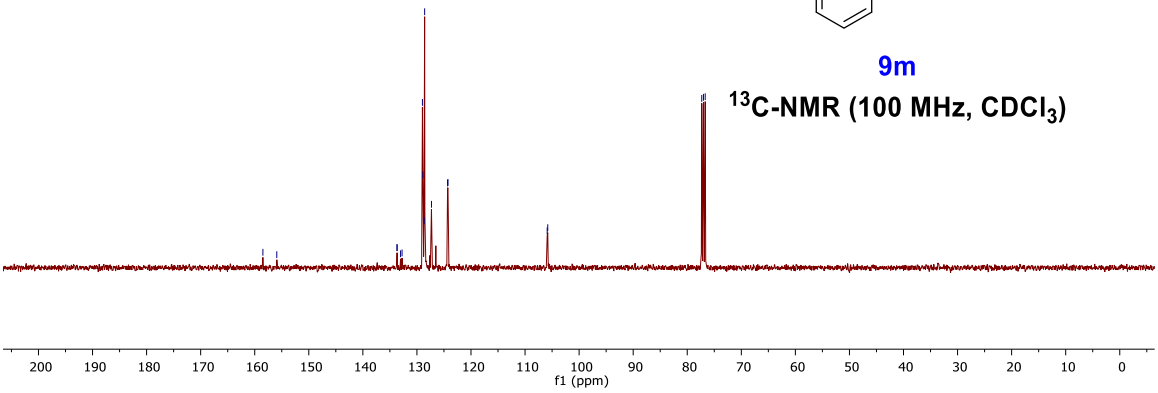
^{1}H-NMR (400 MHz, $CDCl_3$)

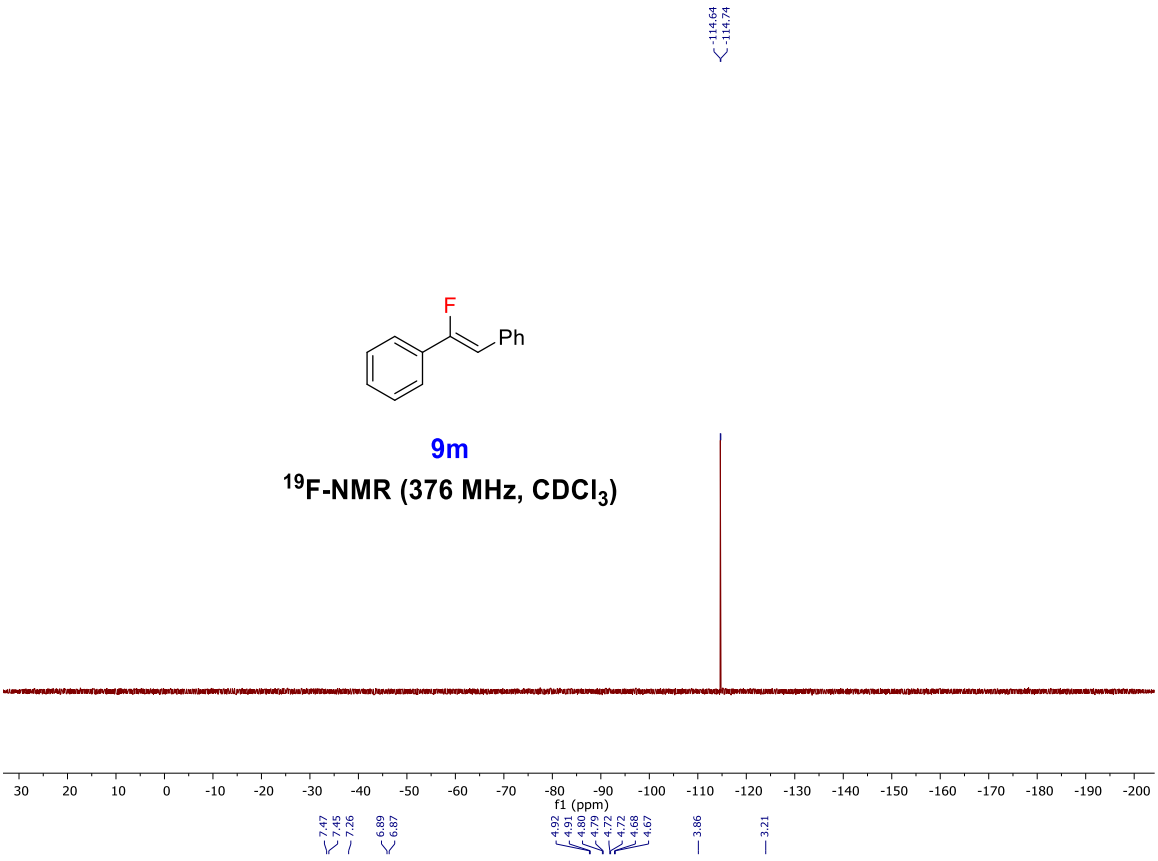




9m

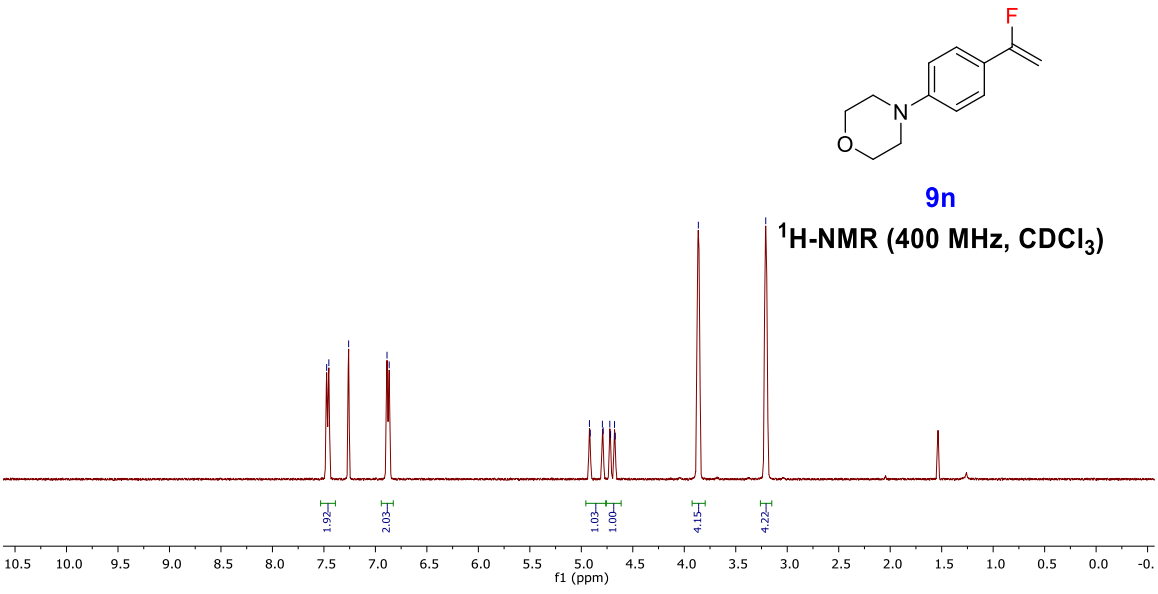
^{13}C-NMR (100 MHz, $CDCl_3$)





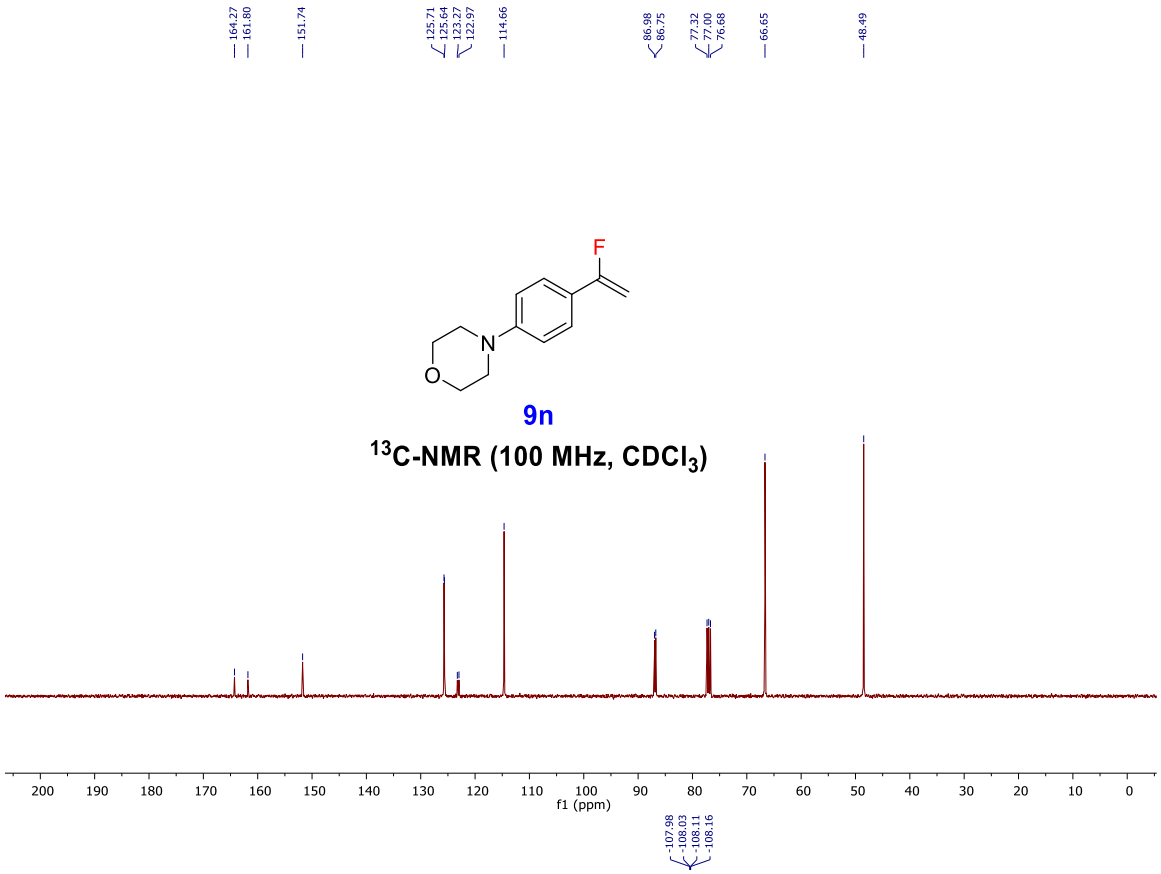
9m

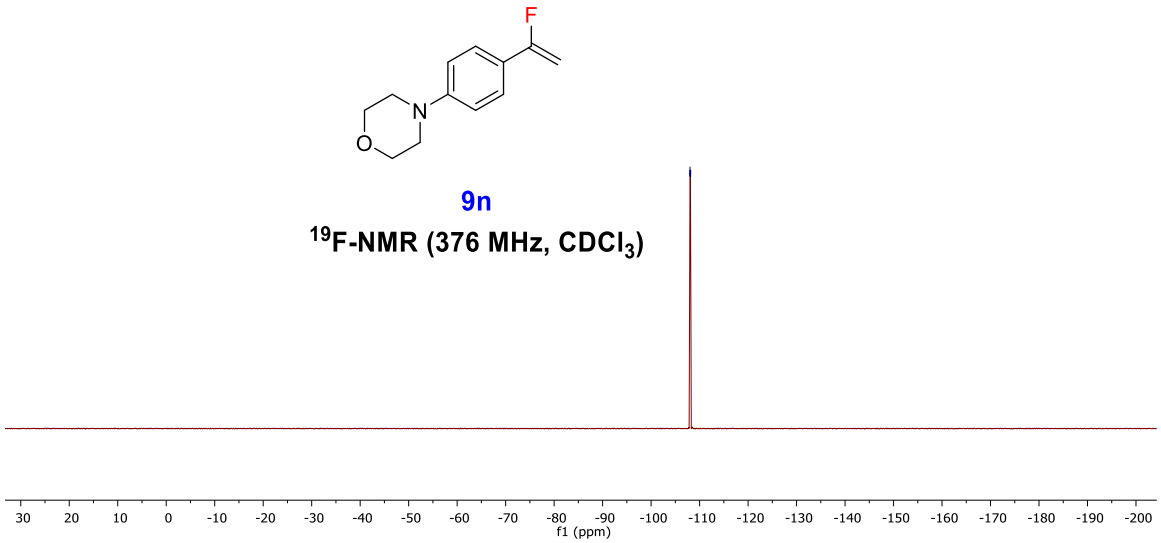
^{19}F-NMR (376 MHz, $CDCl_3$)

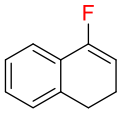


9n

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

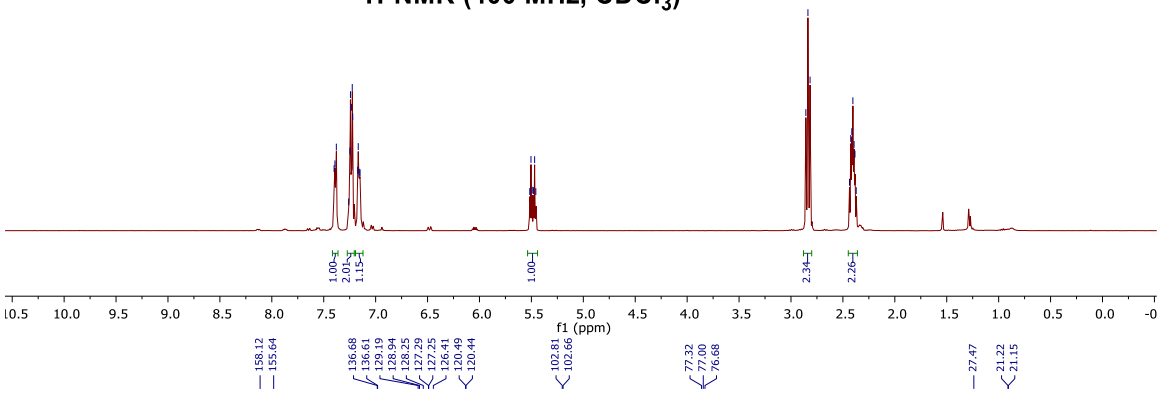

164.27
161.80
151.74
125.71
125.64
123.27
122.97
114.66
86.98
86.75
77.32
77.00
76.68
66.65
48.49
F
N
O
9n
13C-NMR (100 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)
107.98
106.03
108.11
108.16

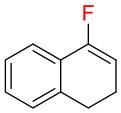

F
N
O
9n
19F-NMR (376 MHz, CDCl3)
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)



9o

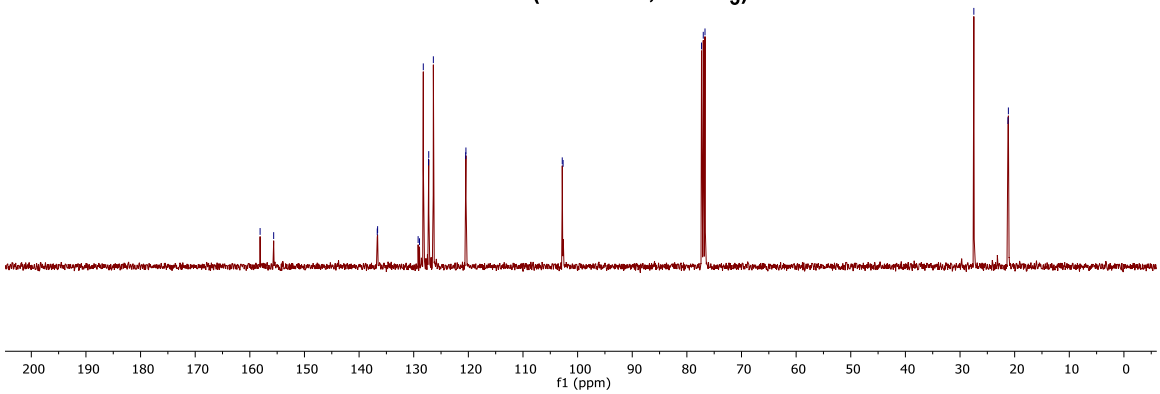
^{1}H-NMR (400 MHz, $CDCl_3$)

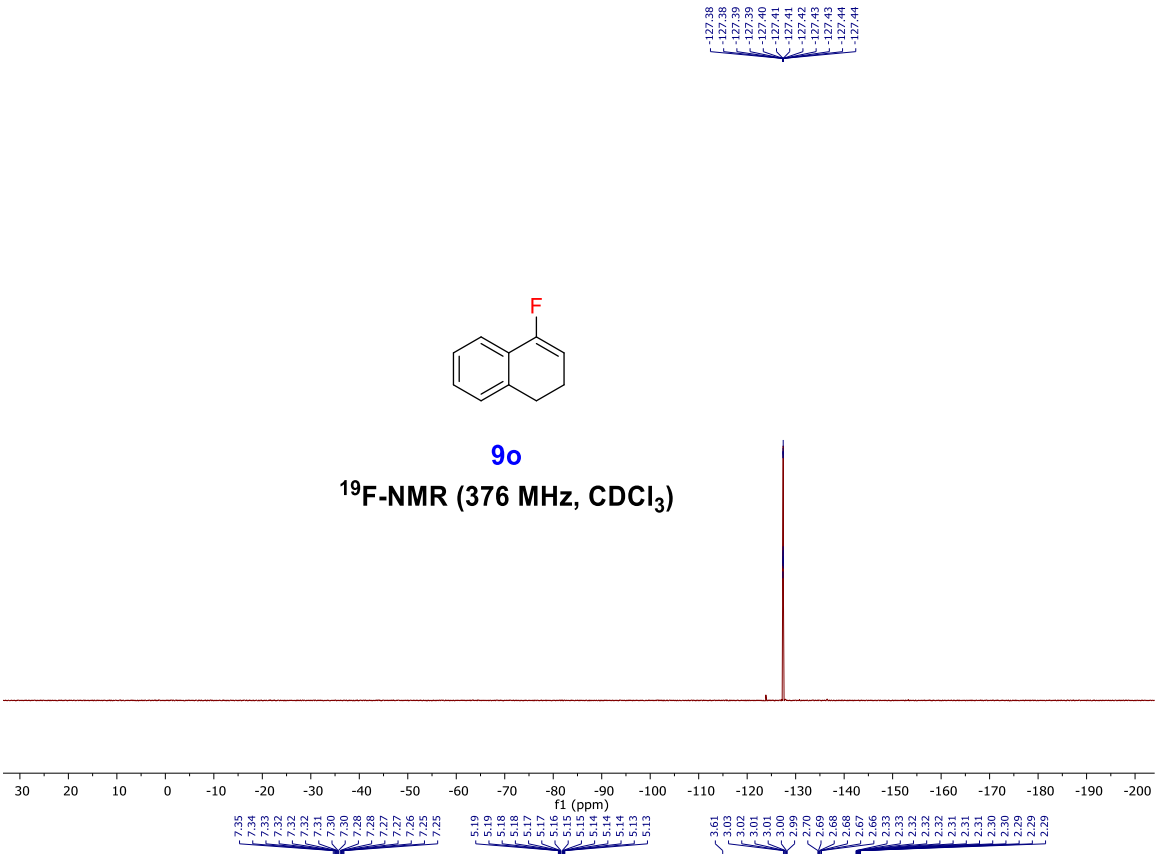


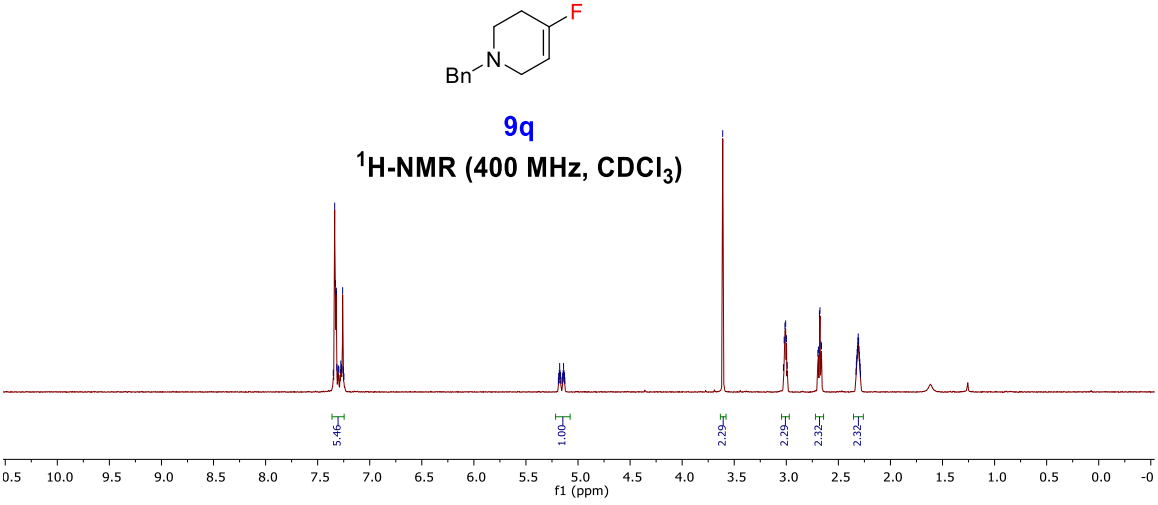


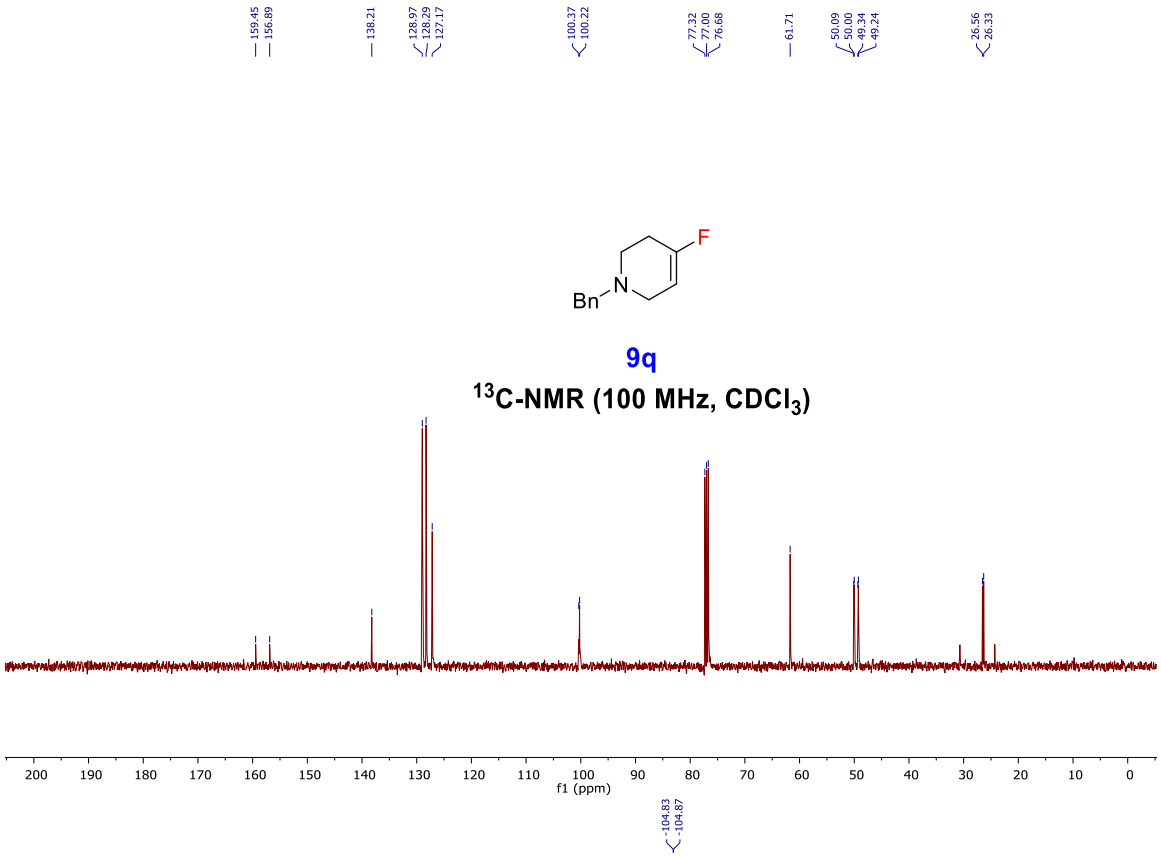
9o

^{13}C-NMR (100 MHz, $CDCl_3$)



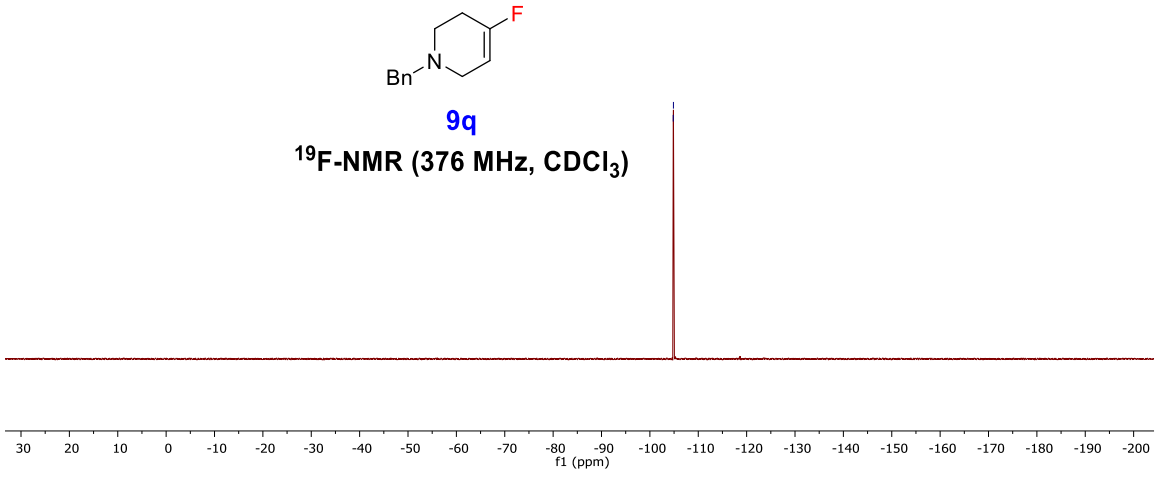

F
9o
19F-NMR (376 MHz, CDCl3)
f1 (ppm)


F
N
Bn
9q
1H-NMR (400 MHz, CDCl3)
f1 (ppm)



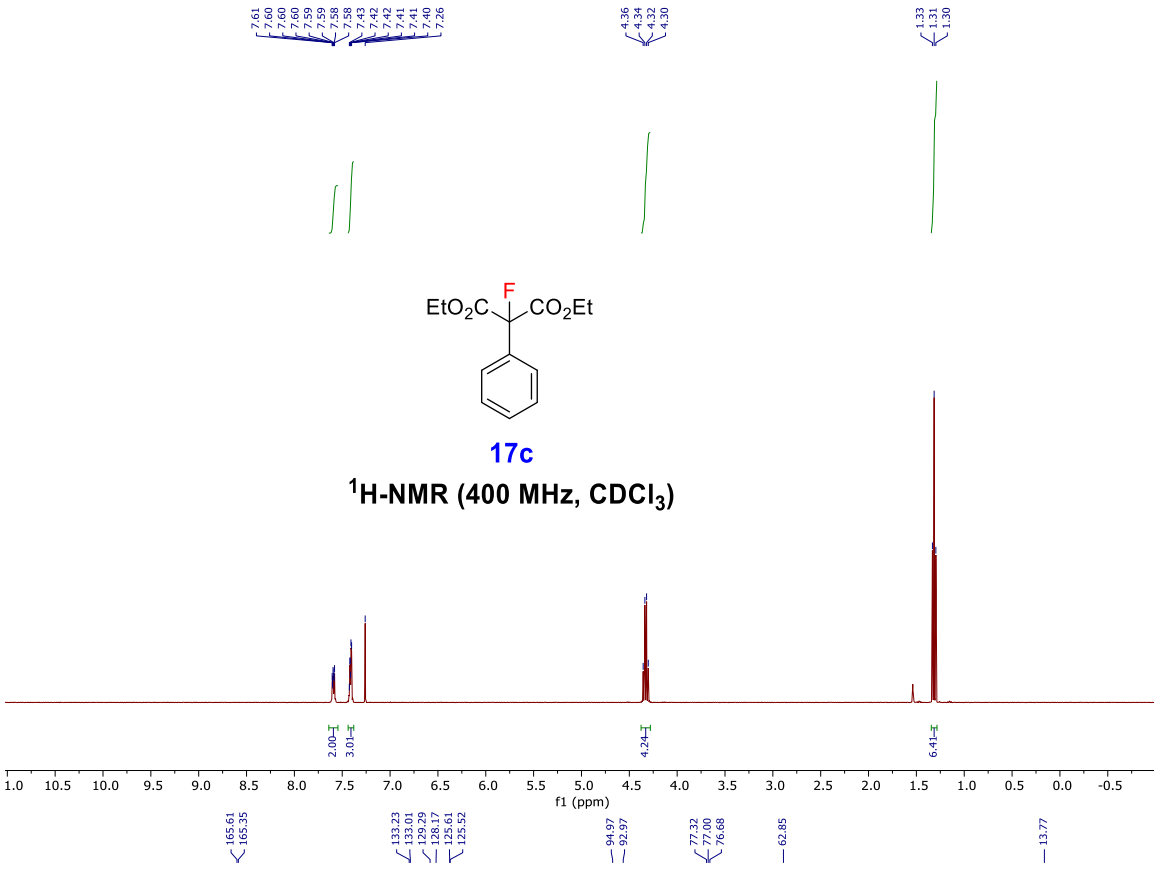
9q

^{13}C-NMR (100 MHz, $CDCl_3$)



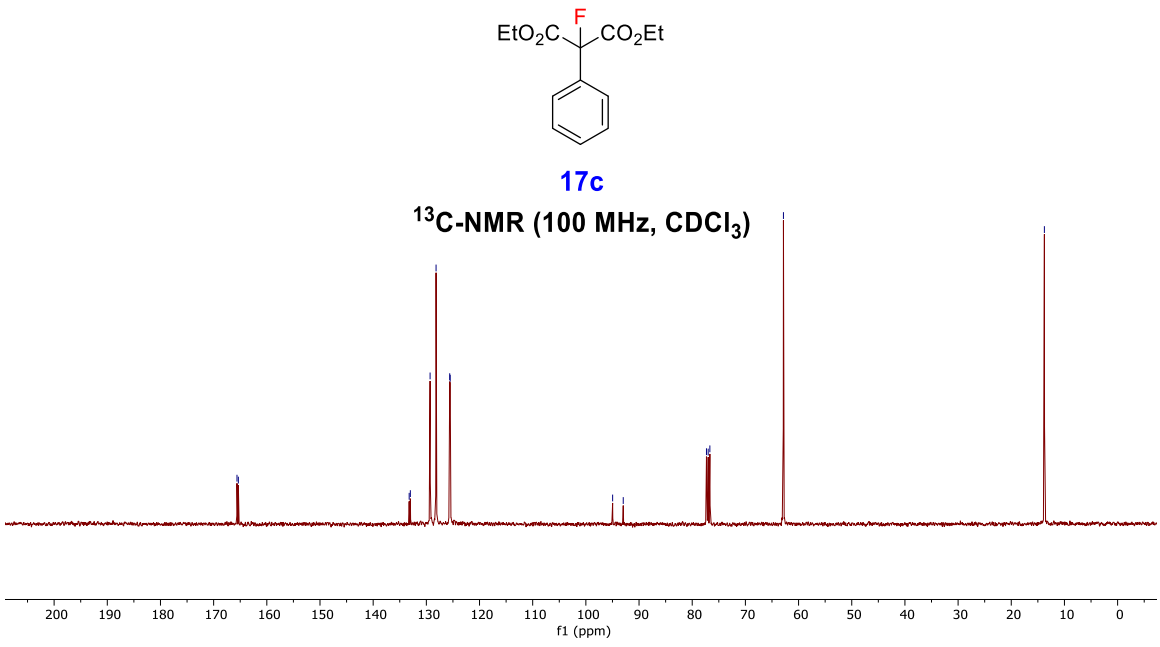
9q

^{19}F-NMR (376 MHz, $CDCl_3$)



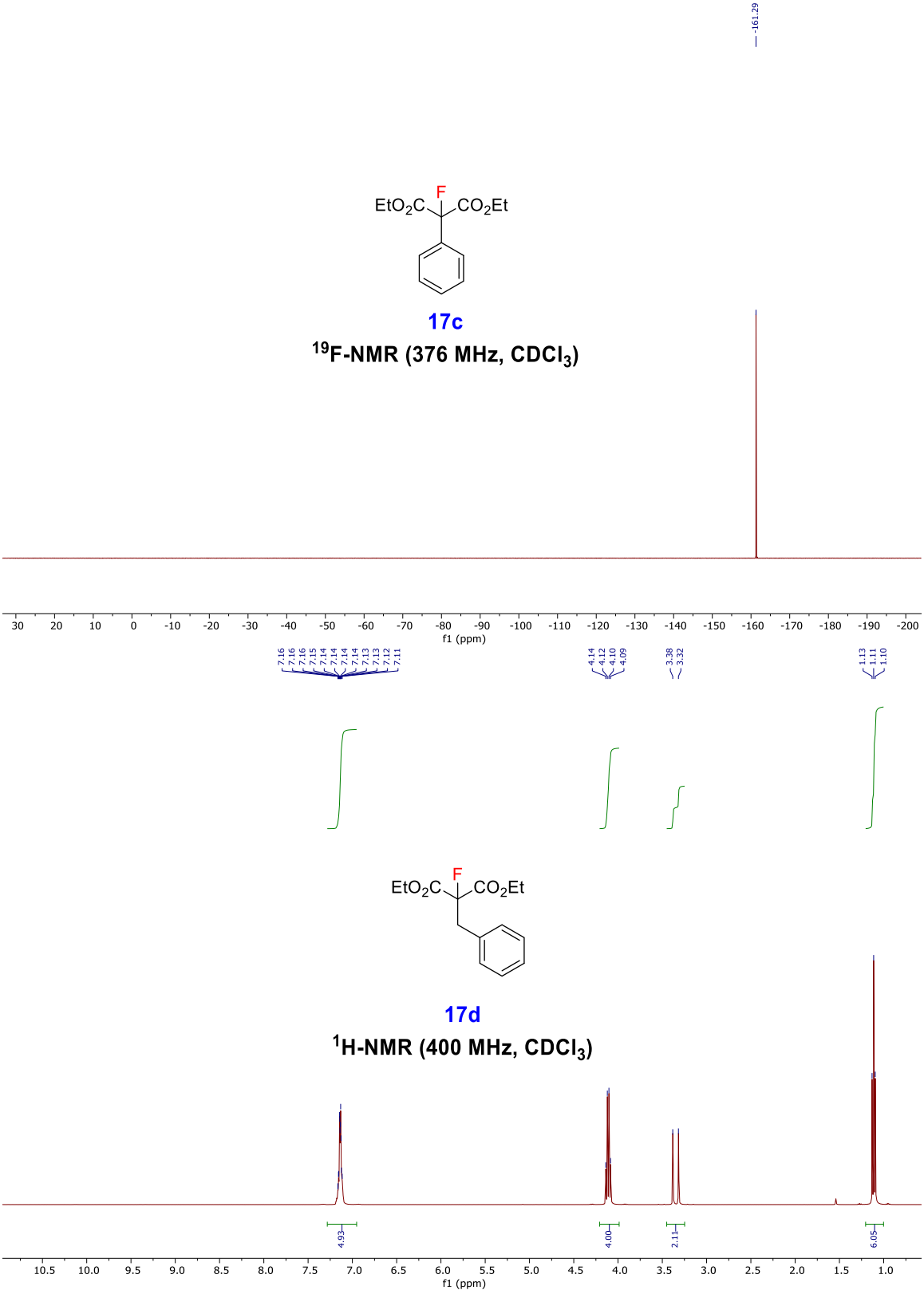
17c

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



17c

^{13}C-NMR (100 MHz, $CDCl_3$)

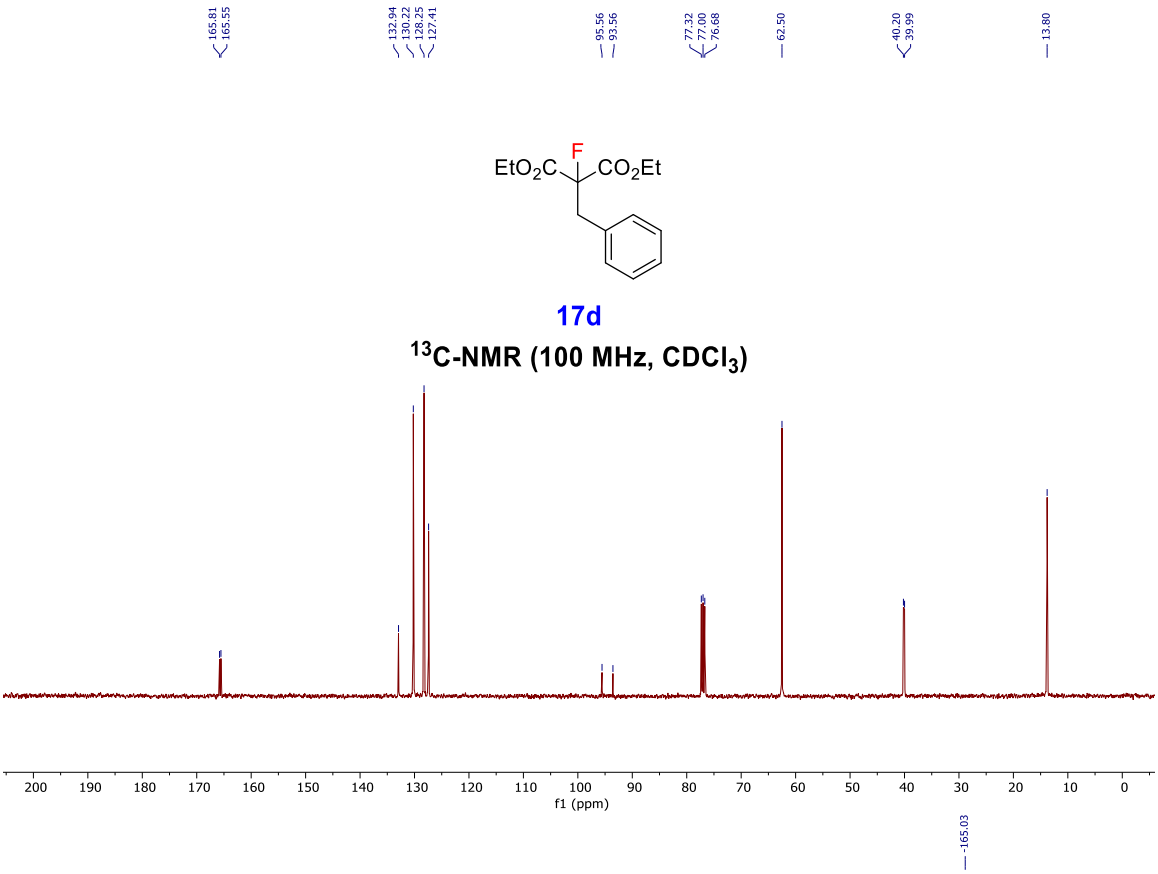


17c

^{19}F-NMR (376 MHz, $CDCl_3$)

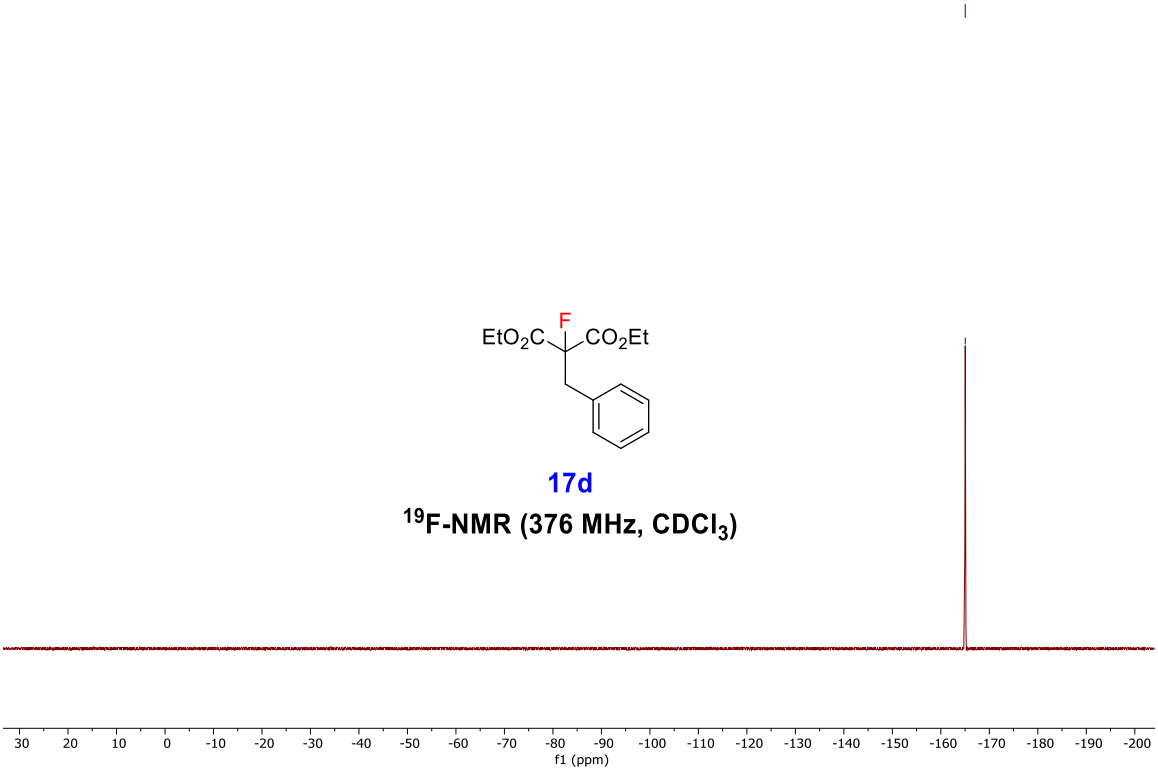
17d

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



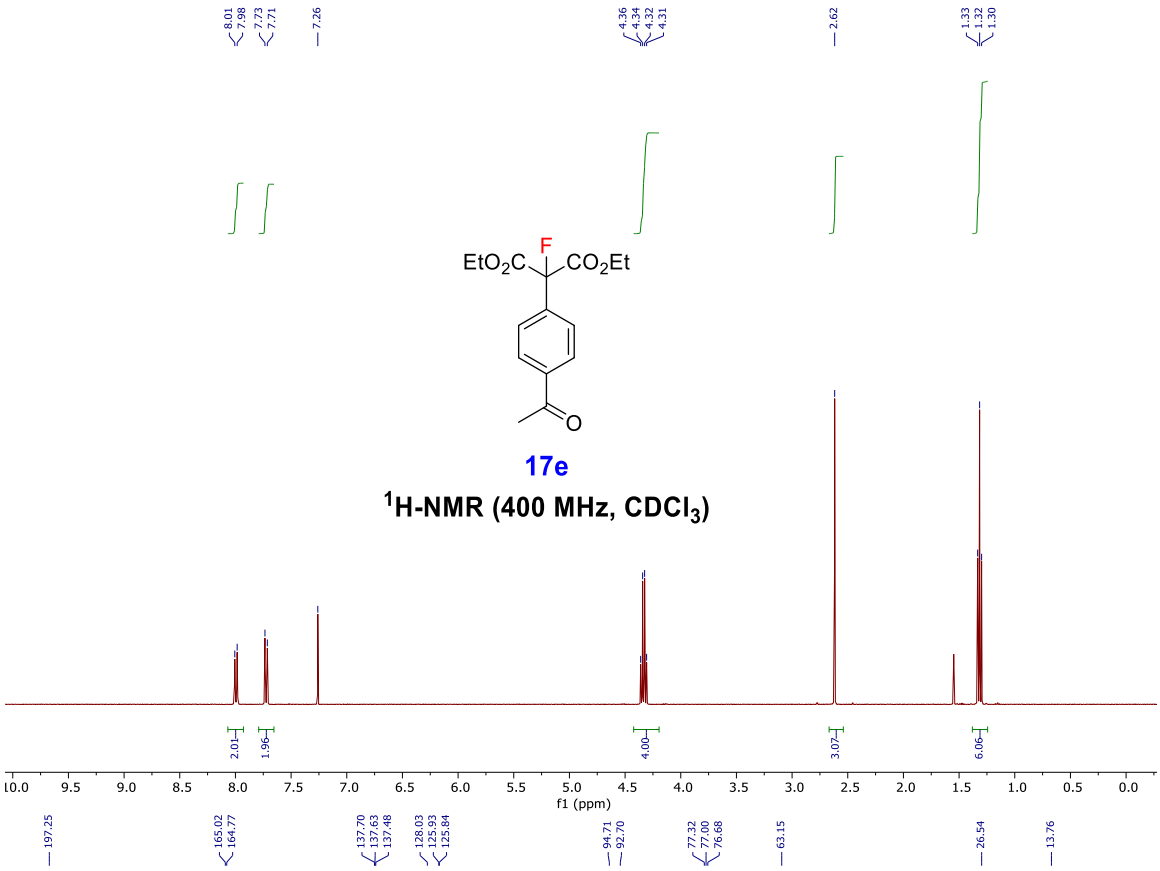
17d

^{13}C-NMR (100 MHz, $CDCl_3$)



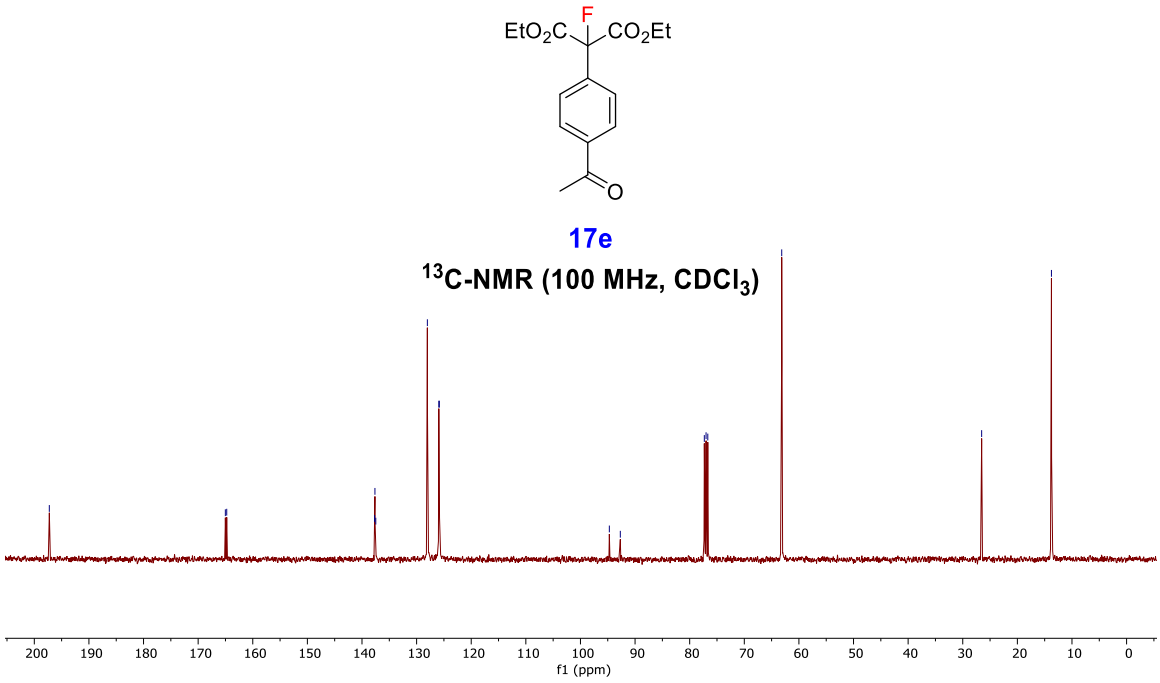
17d

^{19}F-NMR (376 MHz, $CDCl_3$)



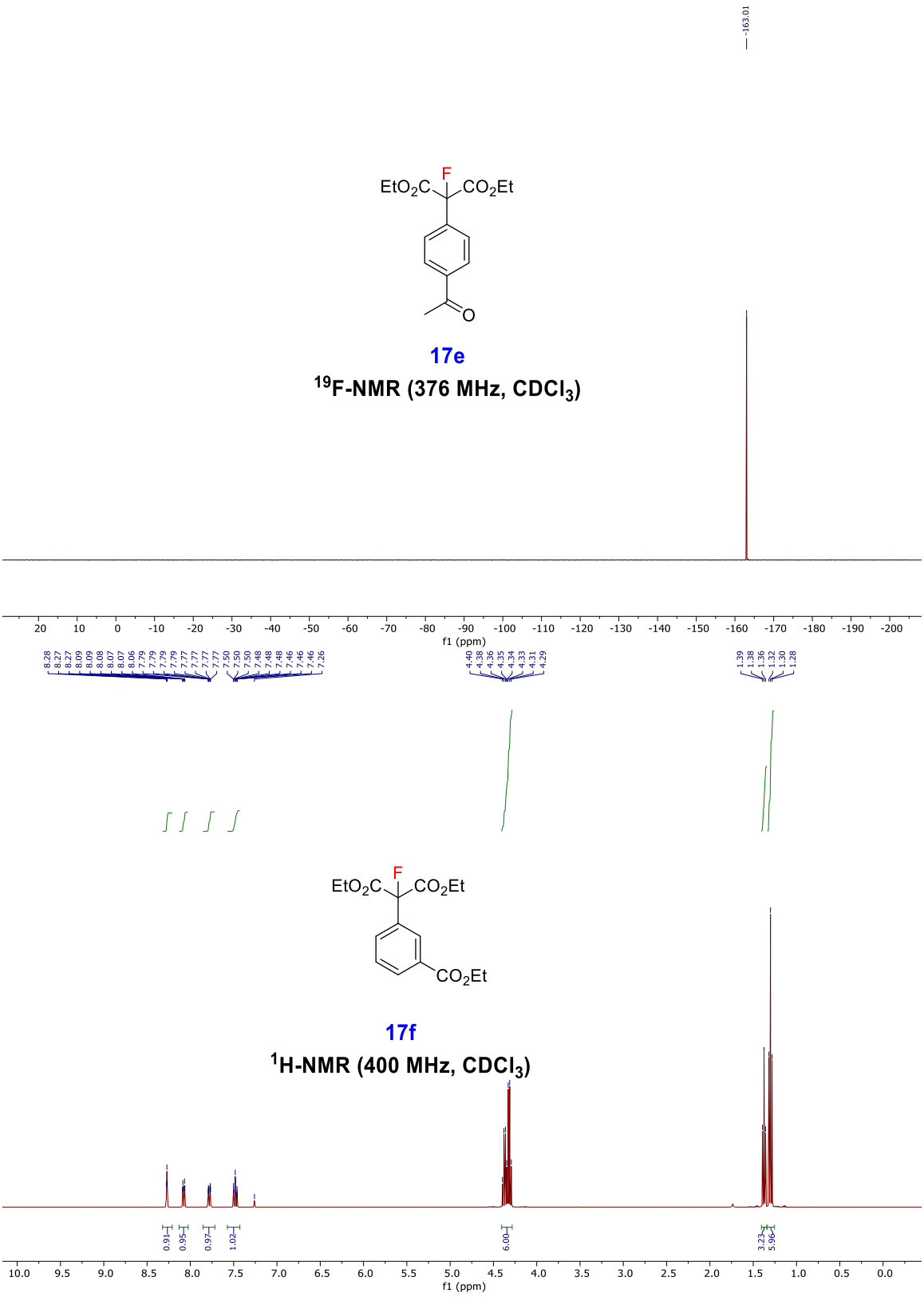
17e

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



17e

^{13}C-NMR (100 MHz, $CDCl_3$)

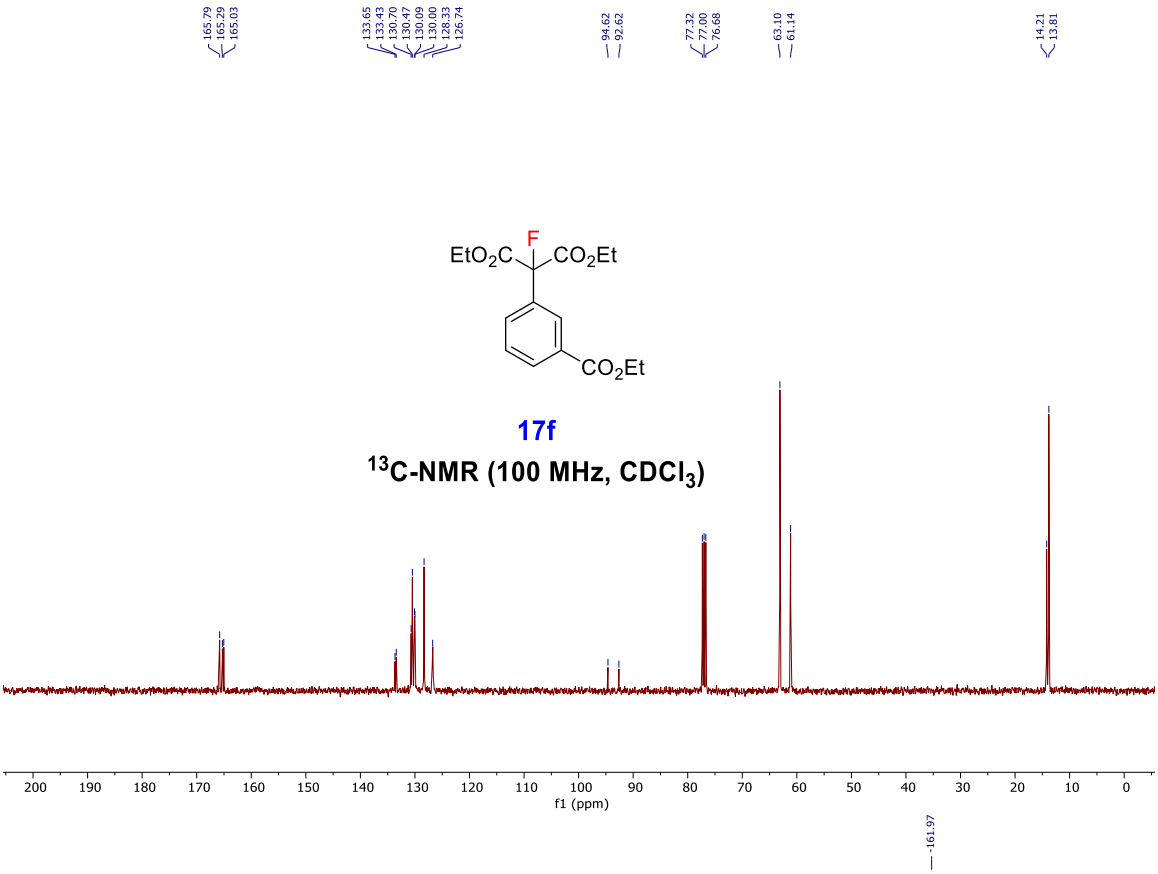


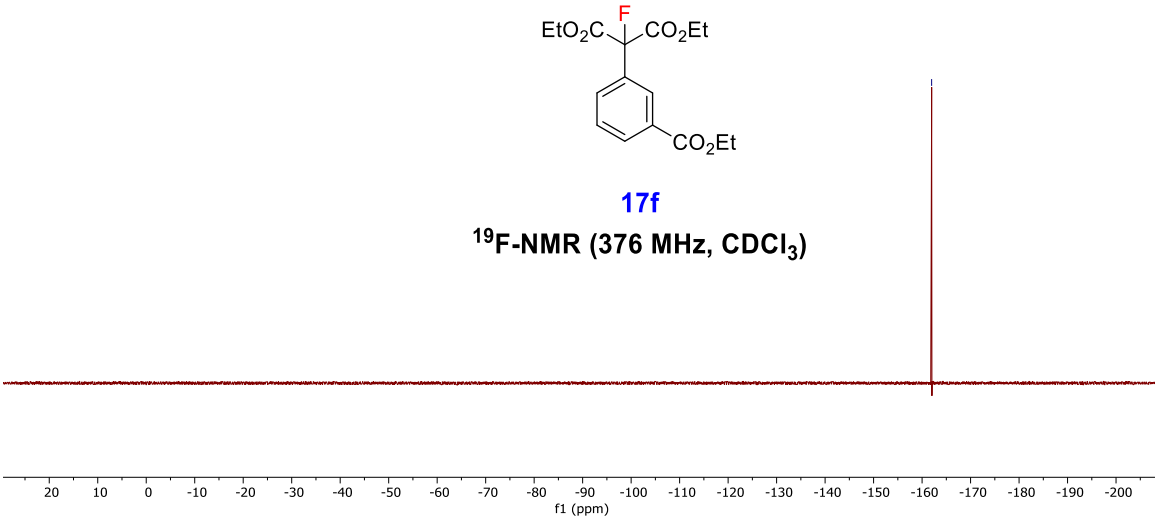
17e

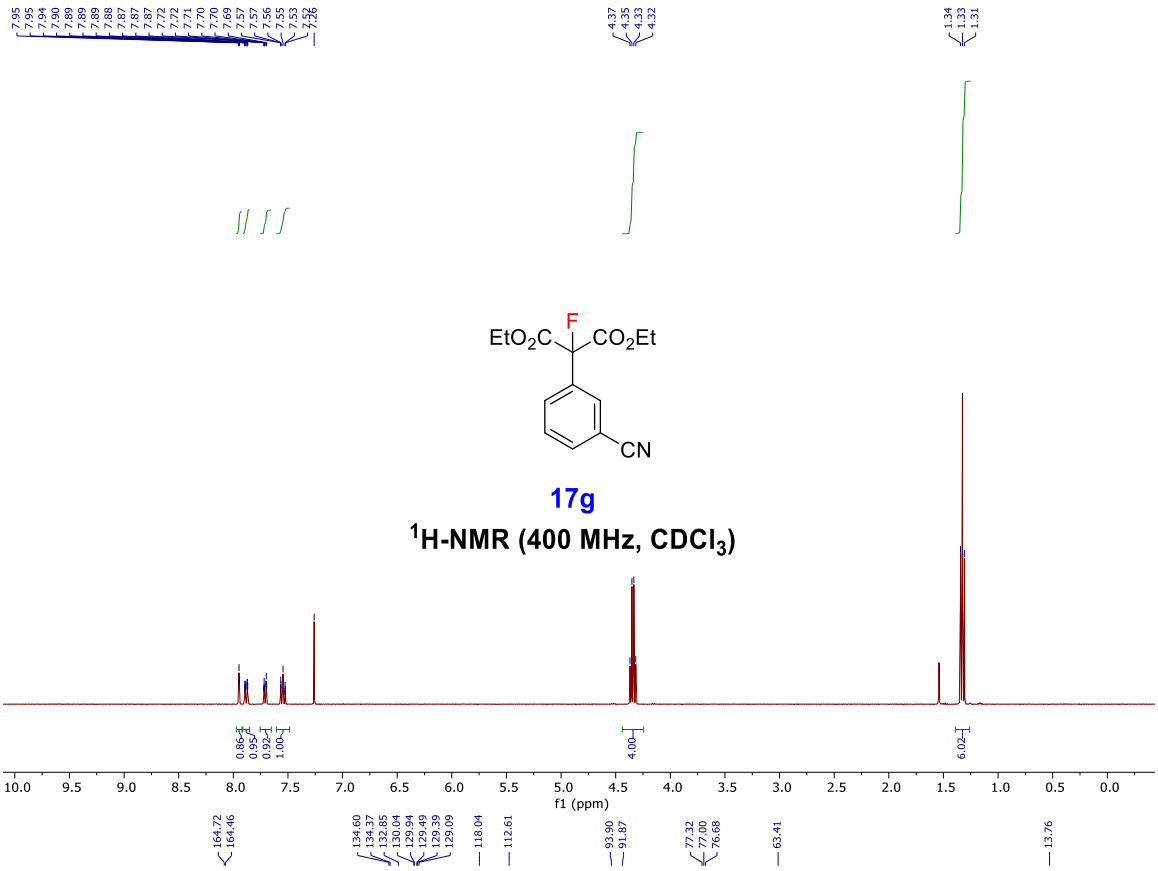
^{19}F-NMR (376 MHz, $CDCl_3$)

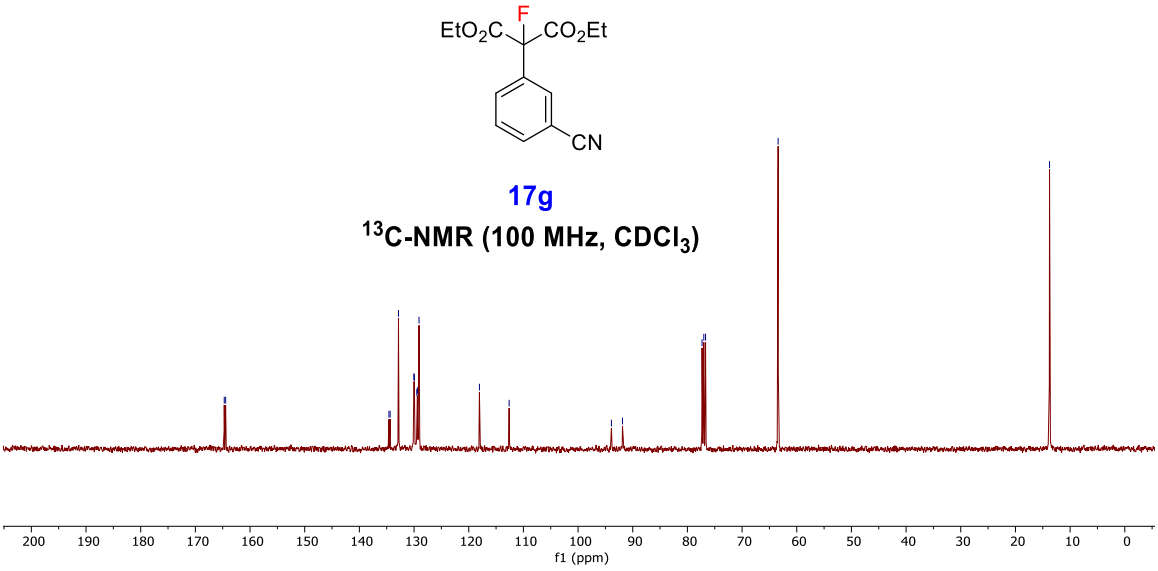
17f

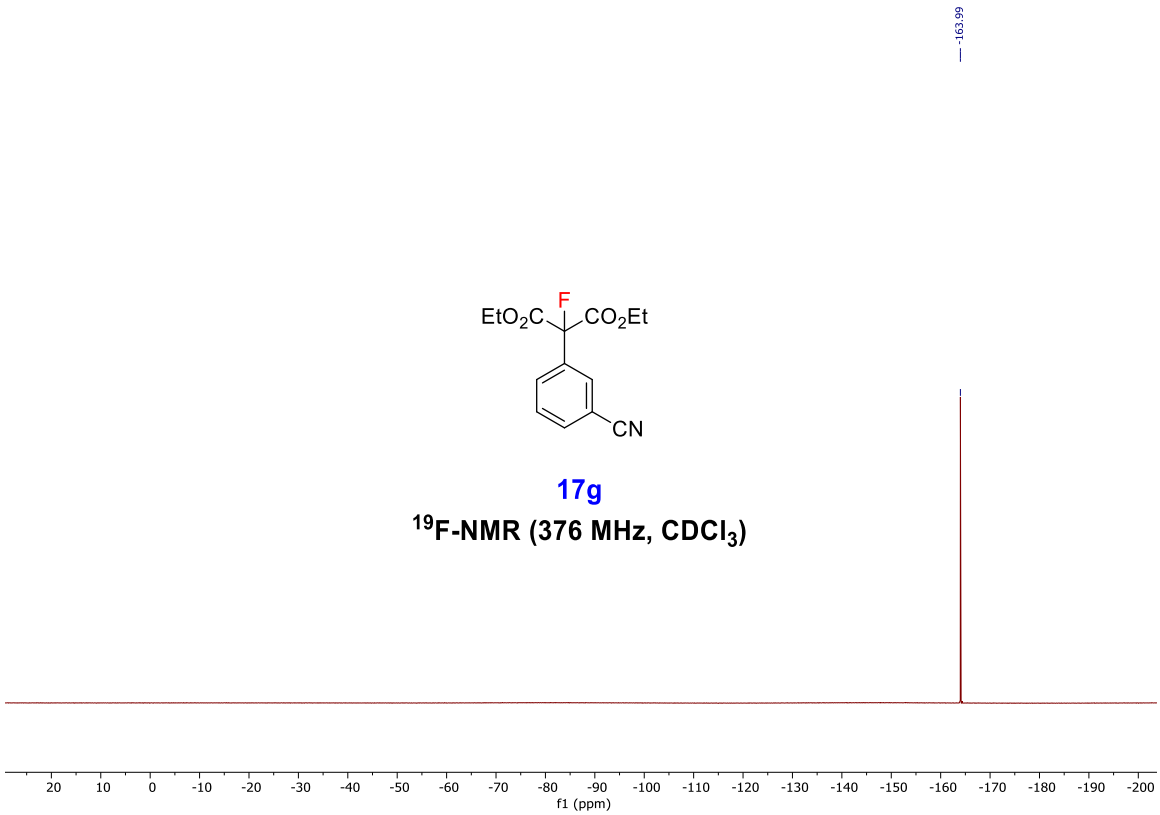
^{1}H-NMR (400 MHz, $CDCl_3$)


165.79
165.29
165.03
133.65
133.43
130.70
130.47
130.09
130.00
128.33
126.74
94.62
92.62
77.32
77.00
76.68
63.10
61.14
14.21
13.81
F
EtO2C
CO2Et
CO2Et
17f
13C-NMR (100 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


-161.97
F
EtO2C
CO2Et
CO2Et
17f
19F-NMR (376 MHz, CDCl3)
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

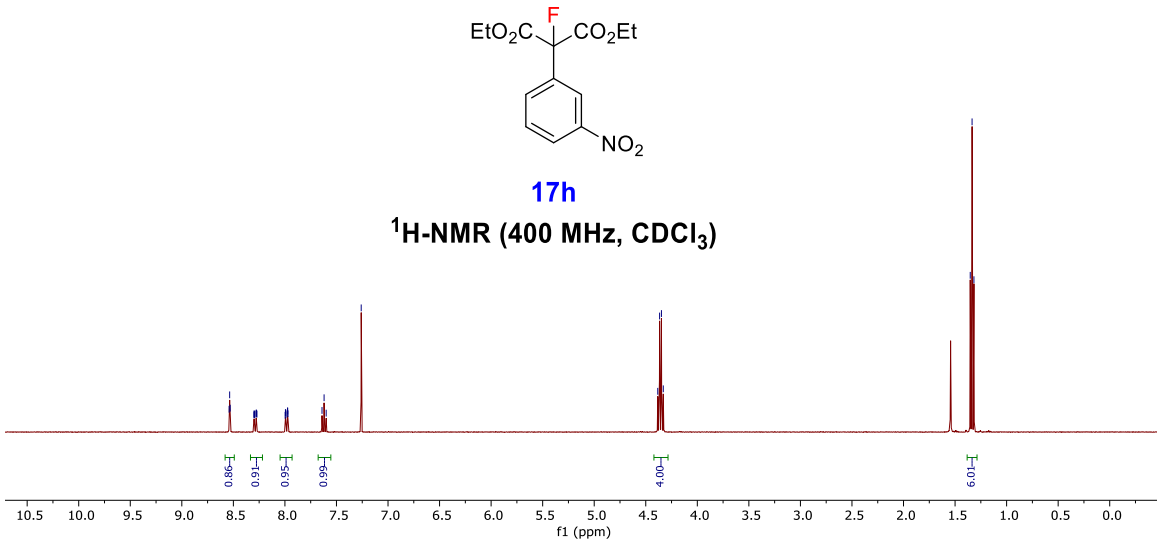

F
EtO2C
CO2Et
CN
17g
1H-NMR (400 MHz, CDCl3)
f1 (ppm)


F
EtO2C
CO2Et
CN
17g
13C-NMR (100 MHz, CDCl3)
f1 (ppm)



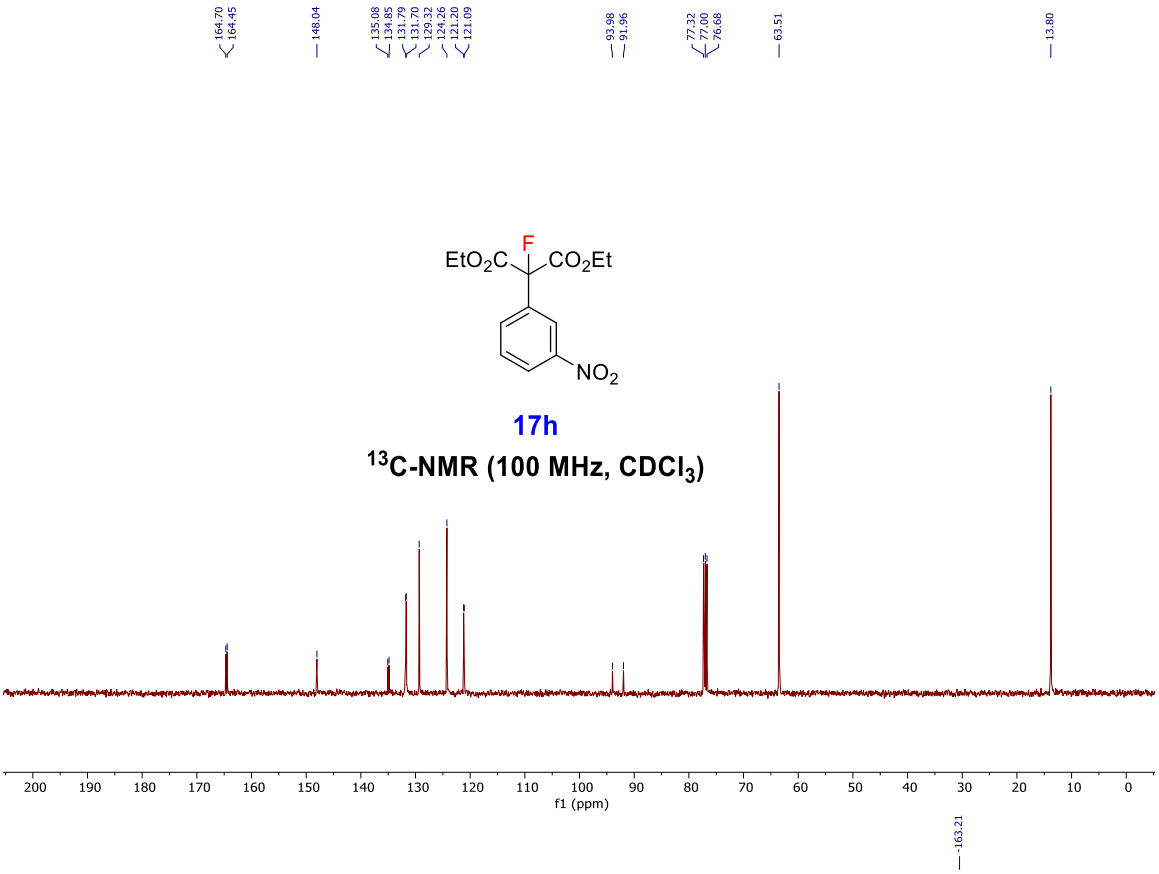
17g

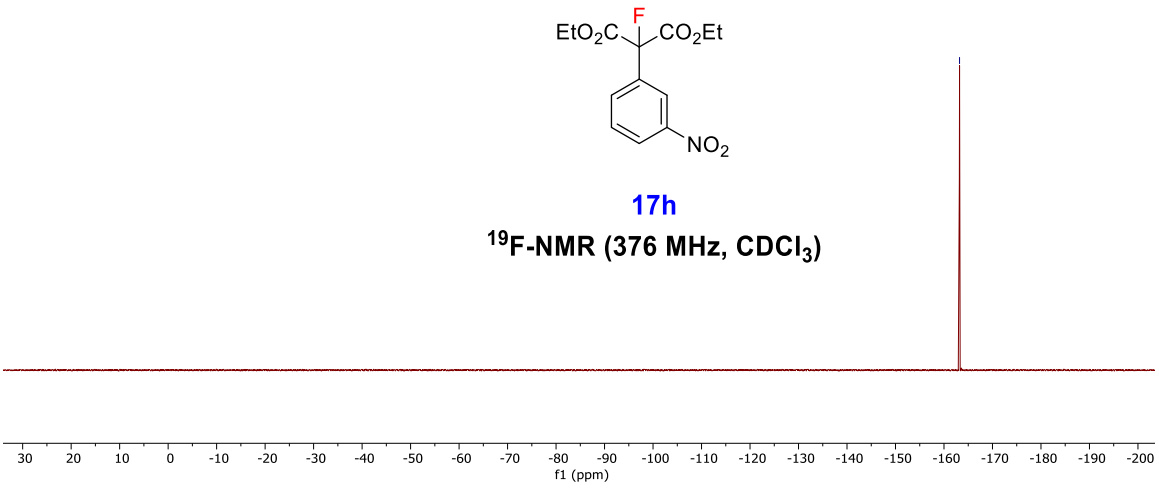
^{19}F-NMR (376 MHz, $CDCl_3$)

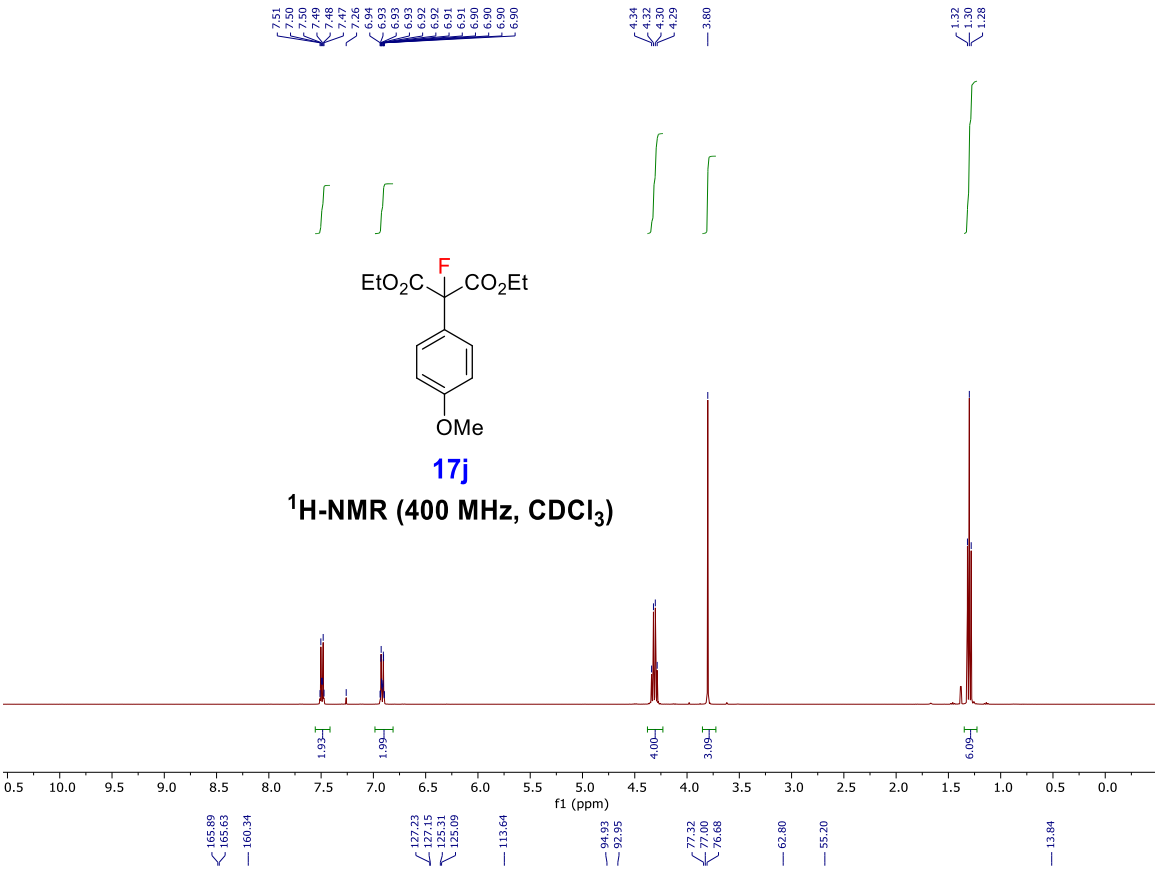


17h

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

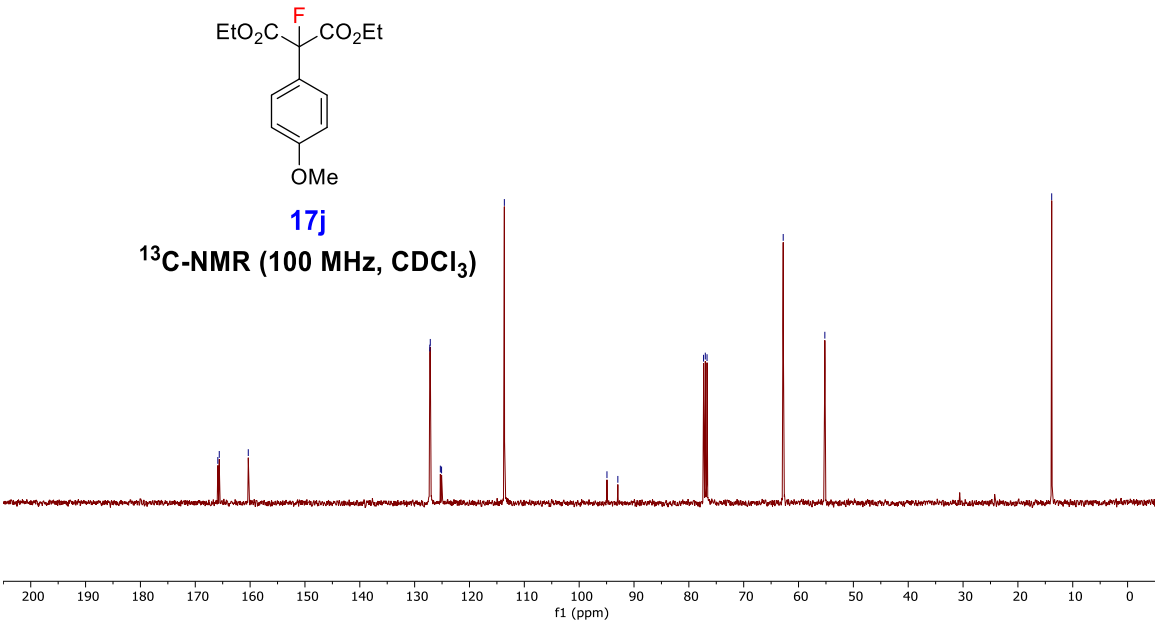

164.70
164.45
148.04
135.08
134.85
131.79
131.70
129.32
124.26
121.20
121.09
93.98
91.96
77.32
77.00
76.68
63.51
13.80
F
EtO2C
CO2Et
NO2
17h
13C-NMR (100 MHz, CDCl3)
f1 (ppm)


-163.21
F
EtO2C
CO2Et
NO2
17h
19F-NMR (376 MHz, CDCl3)
f1 (ppm)



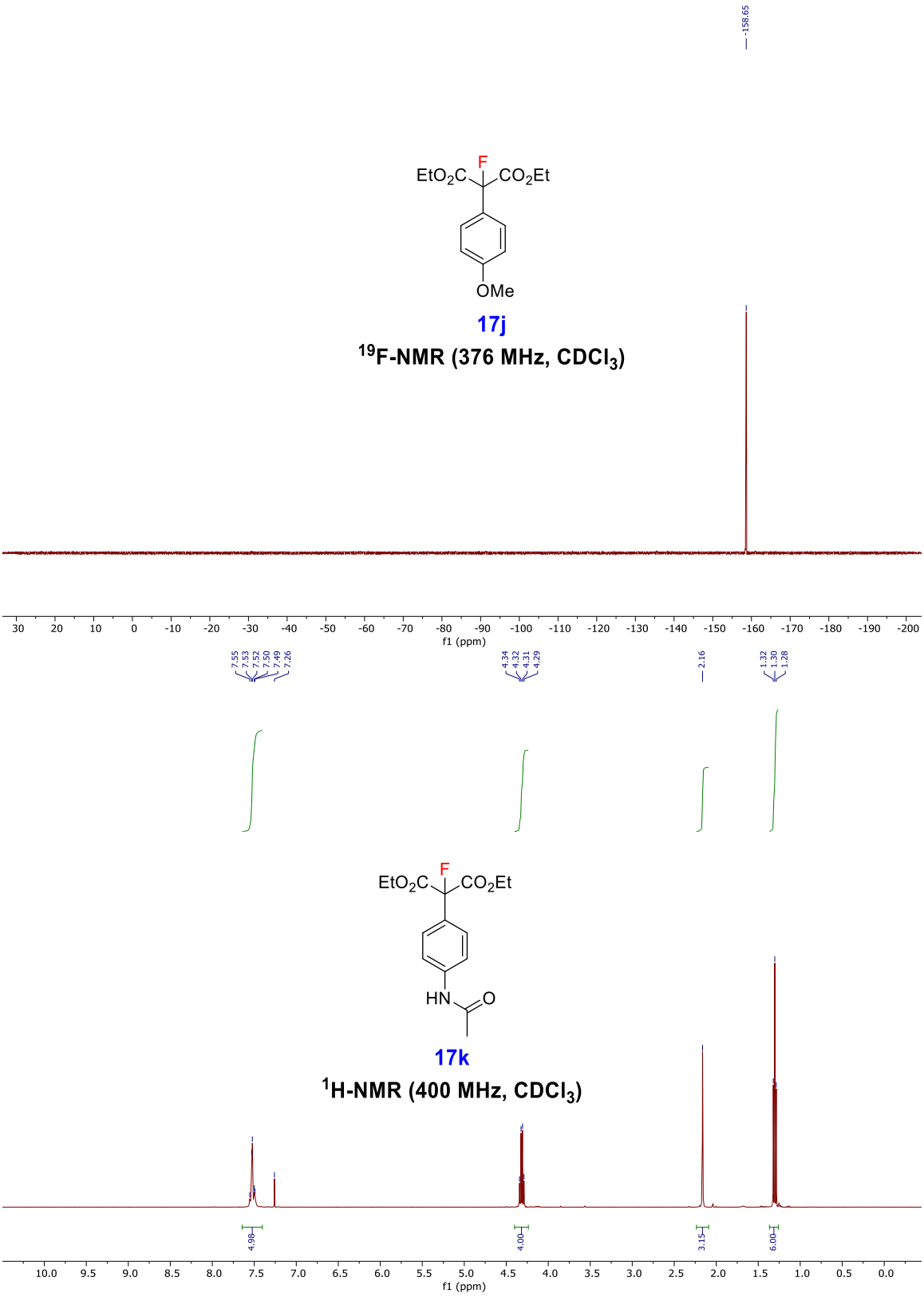
17j

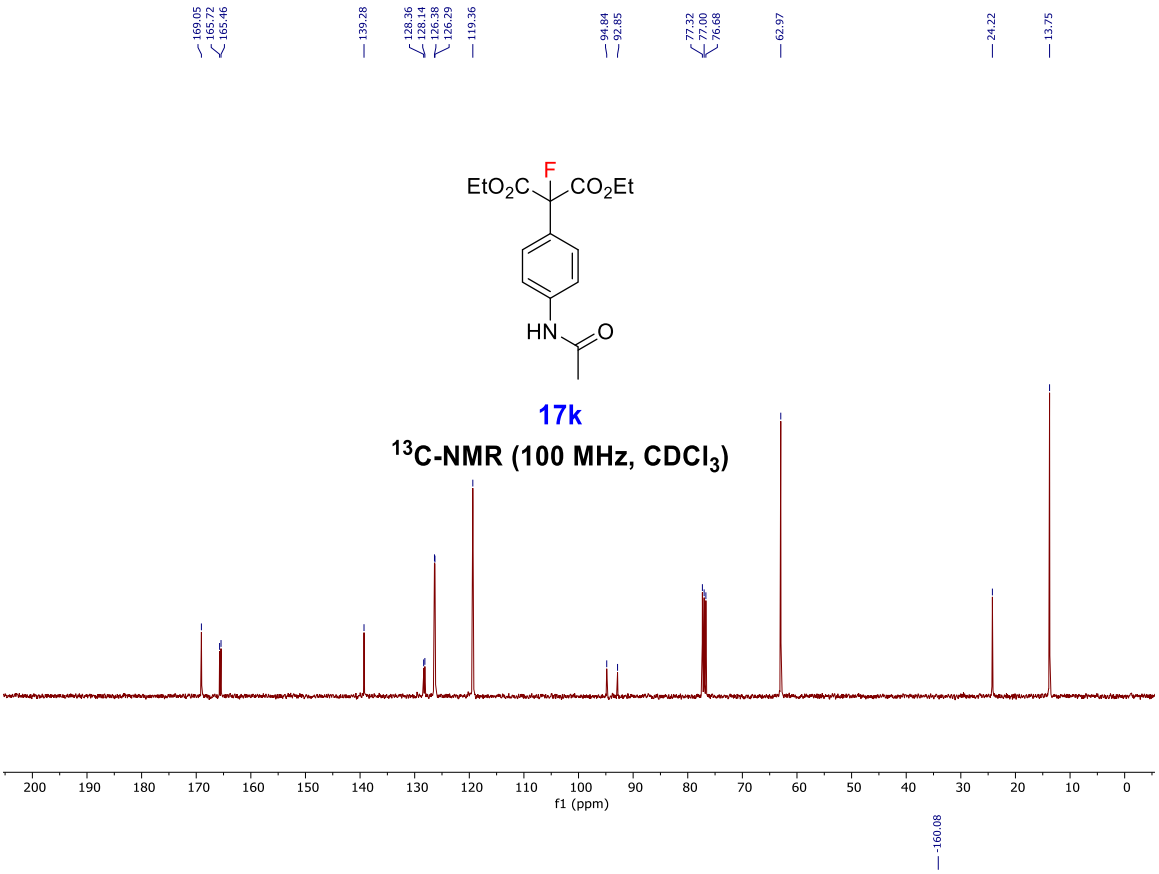
^{1}H-NMR (400 MHz, $CDCl_3$)

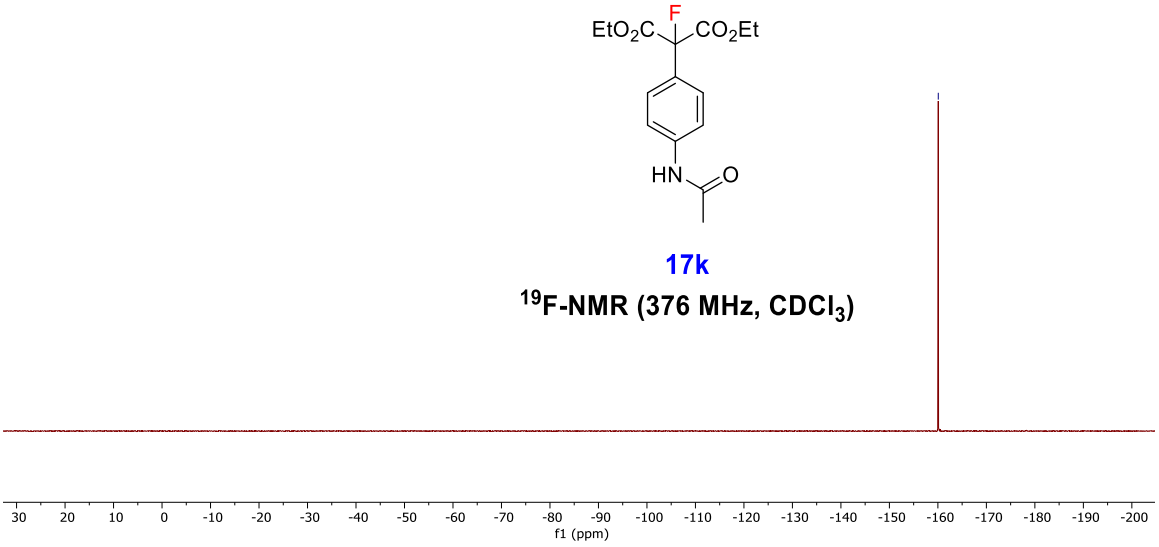


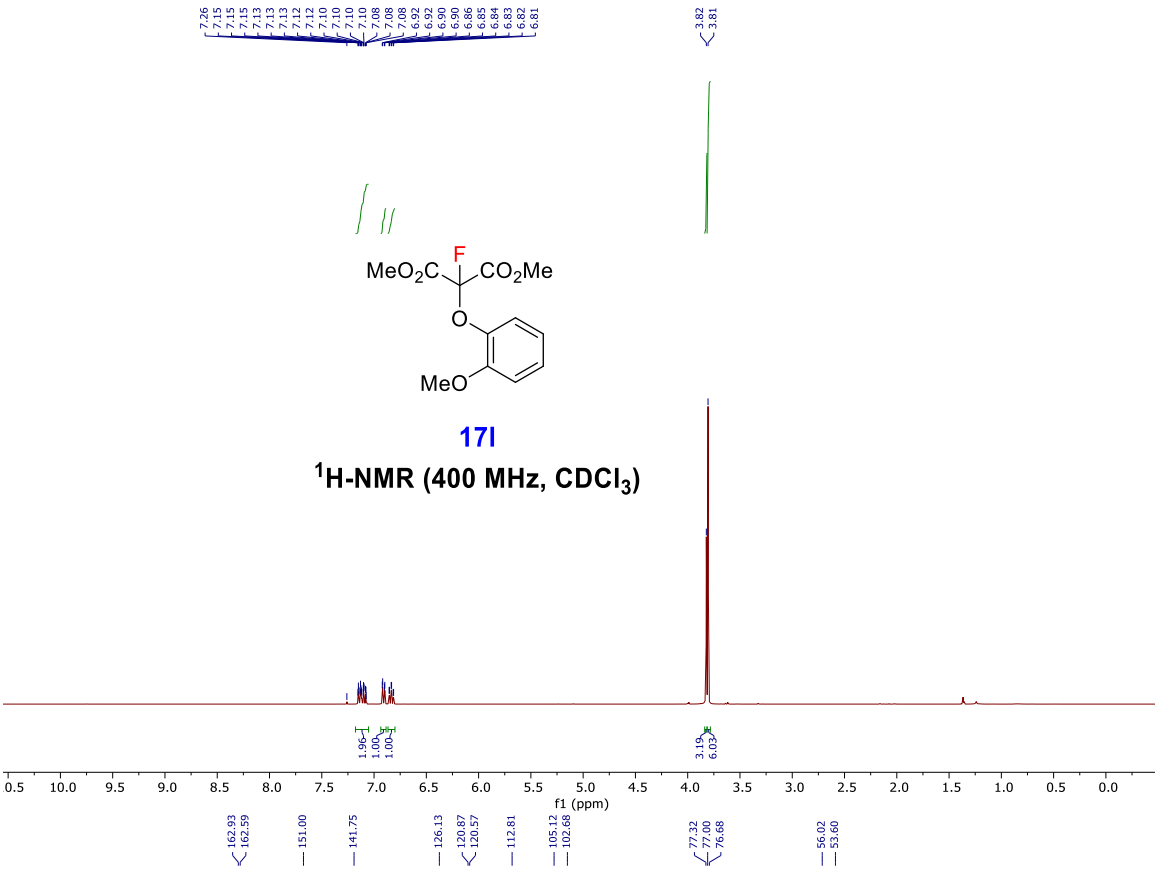
17j

^{13}C-NMR (100 MHz, $CDCl_3$)


-158.65
F
EtO2C
CO2Et
OMe
17j
19F-NMR (376 MHz, CDCl3)
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)
7.55
7.53
7.52
7.50
7.49
7.26
4.34
4.32
4.31
4.29
2.16
1.32
1.30
1.28
F
EtO2C
CO2Et
HN
O
17k
1H-NMR (400 MHz, CDCl3)
4.98
4.00
3.15
6.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

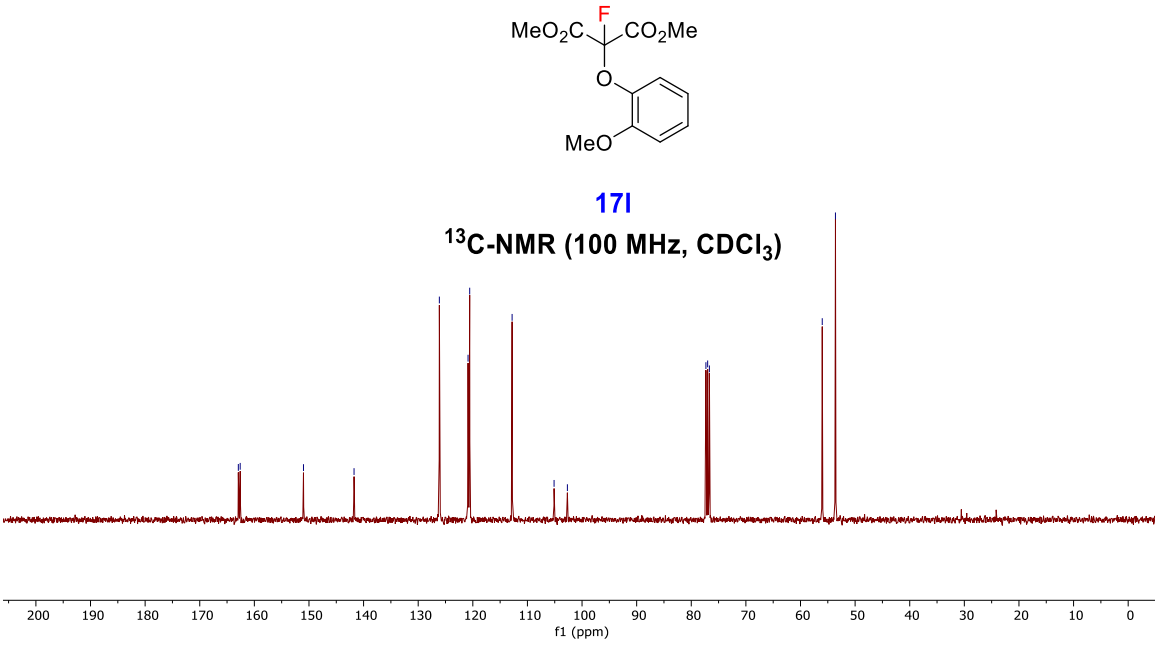

169.05
165.72
165.46
139.28
128.36
128.14
126.38
126.29
119.36
94.84
92.85
77.32
77.00
76.68
62.97
24.22
13.75
F
EtO2C
CO2Et
HN
O
17k
13C-NMR (100 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


-160.08
F
EtO2C
CO2Et
HN
O
17k
19F-NMR (376 MHz, CDCl3)
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)



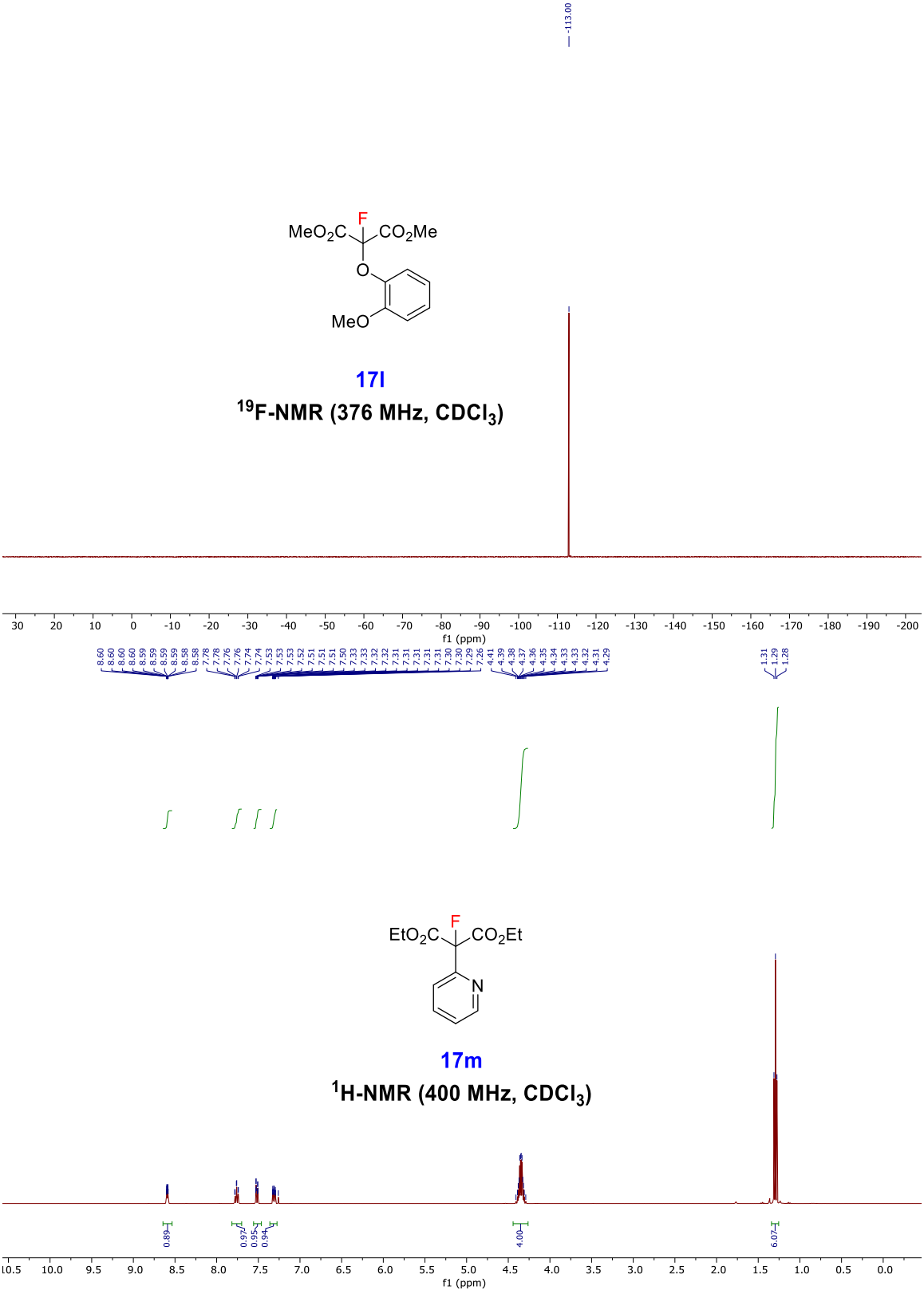
17l

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



17l

^{13}C-NMR (100 MHz, $CDCl_3$)

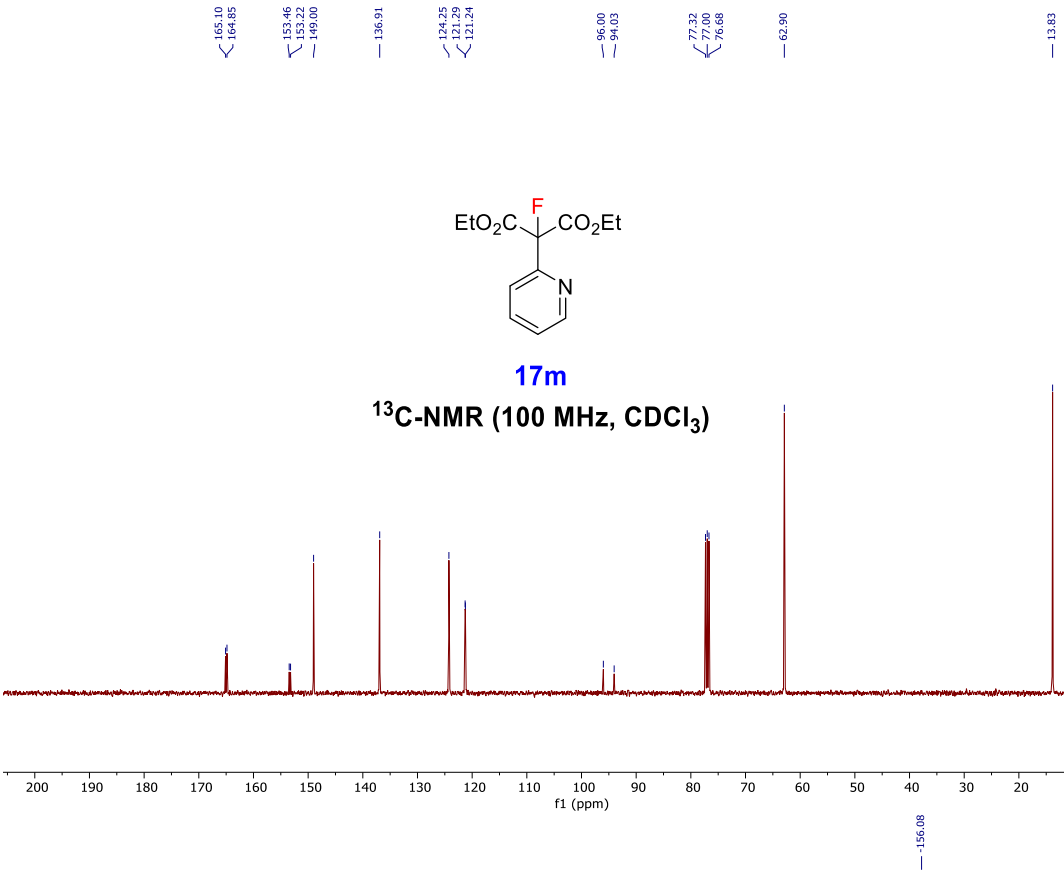


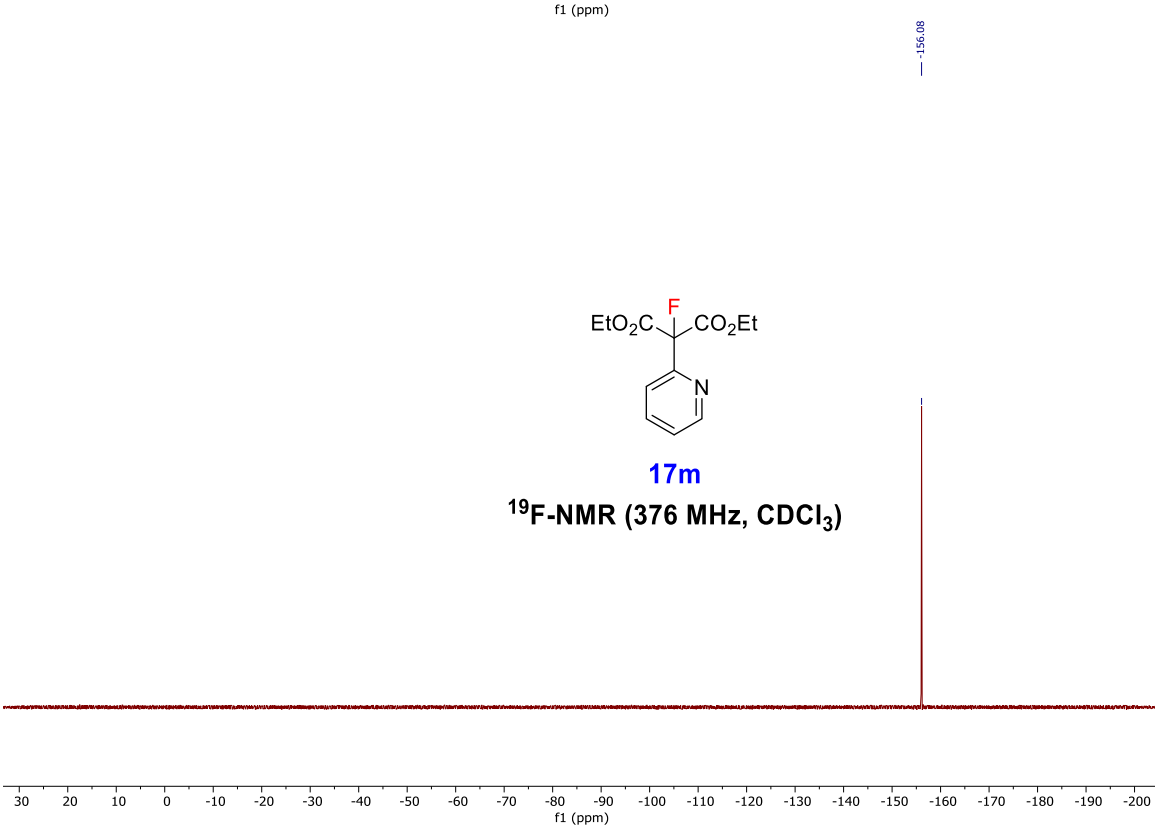
17l

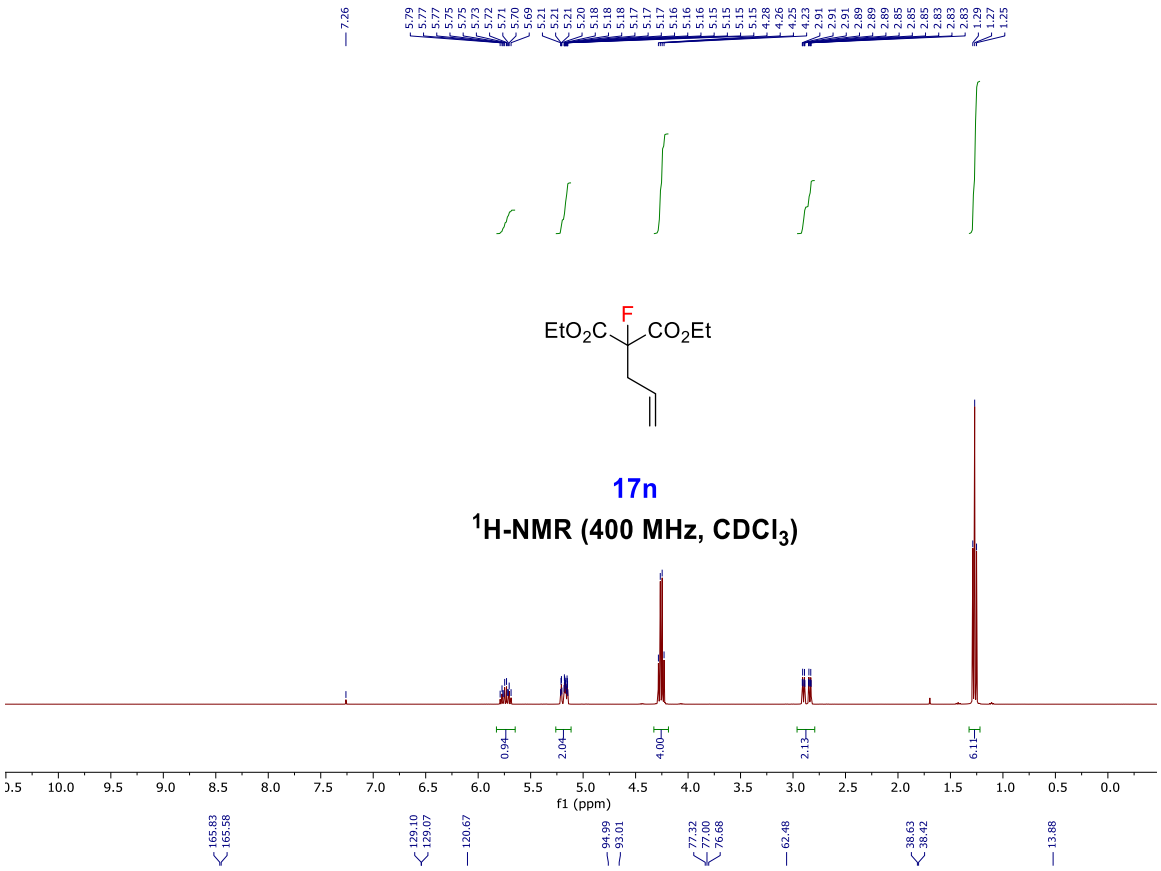
^{19}F-NMR (376 MHz, $CDCl_3$)

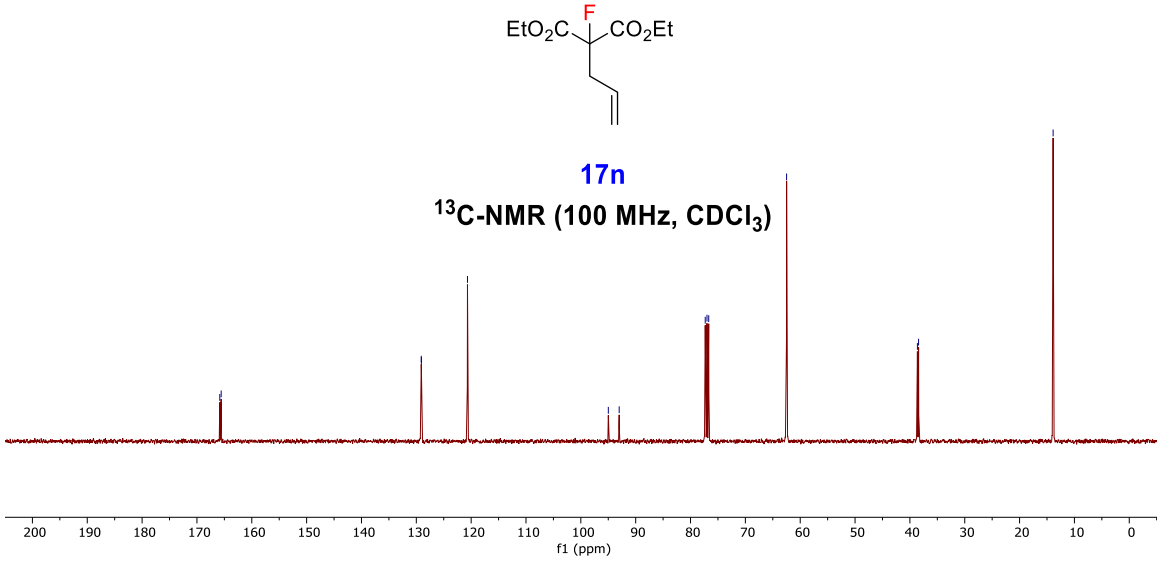
17m

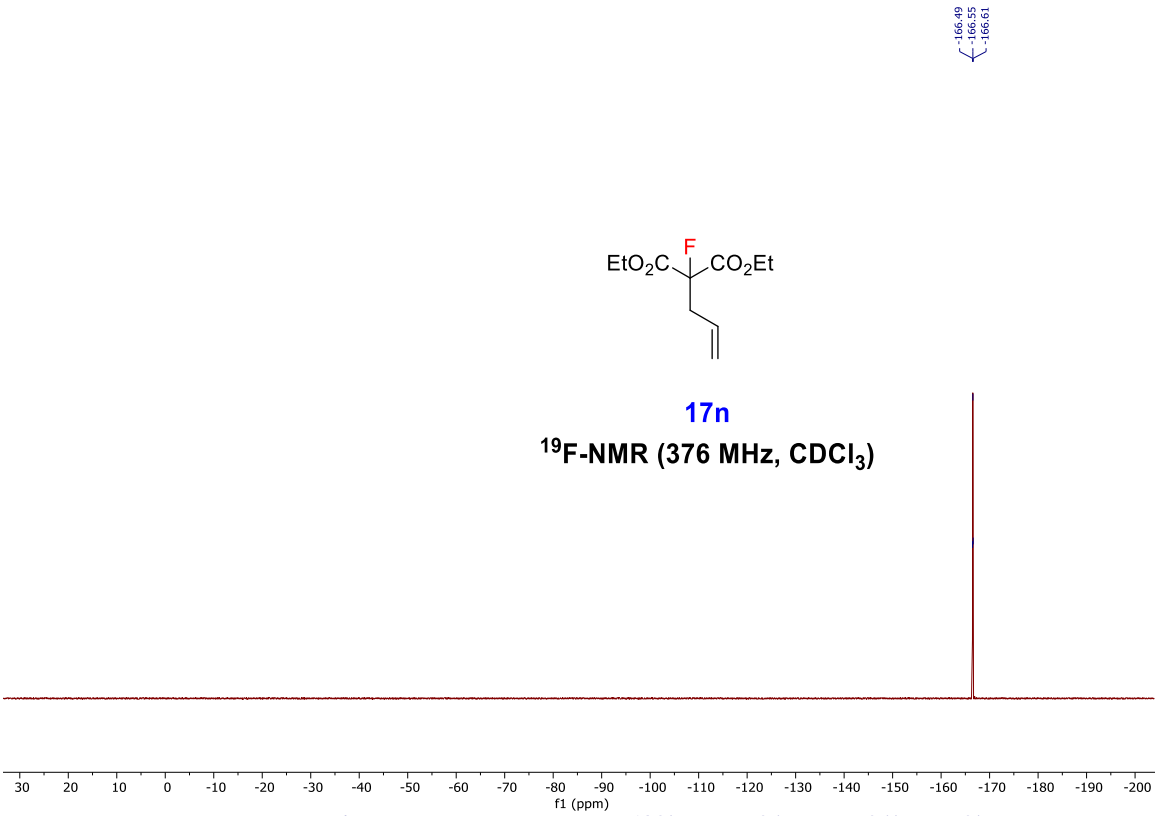
^{1}H-NMR (400 MHz, $CDCl_3$)


165.10
164.85
153.46
153.22
149.00
136.91
124.25
121.29
121.24
96.00
94.03
77.32
77.00
76.68
62.90
13.83
F
EtO2C
CO2Et
N
17m
13C-NMR (100 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


-156.08
F
EtO2C
CO2Et
N
17m
19F-NMR (376 MHz, CDCl3)
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

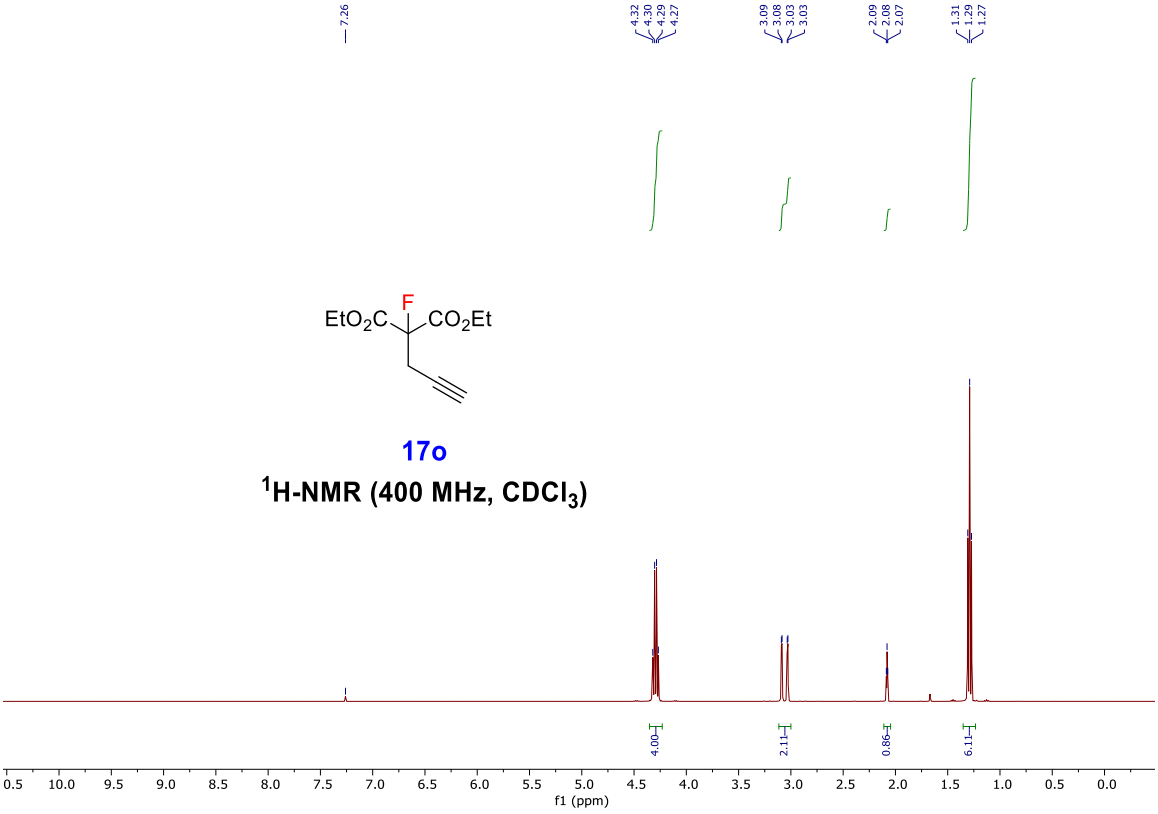

EtO2C
F
CO2Et
17n
1H-NMR (400 MHz, CDCl3)
f1 (ppm)


EtO2C
F
CO2Et
17n
13C-NMR (100 MHz, CDCl3)
f1 (ppm)



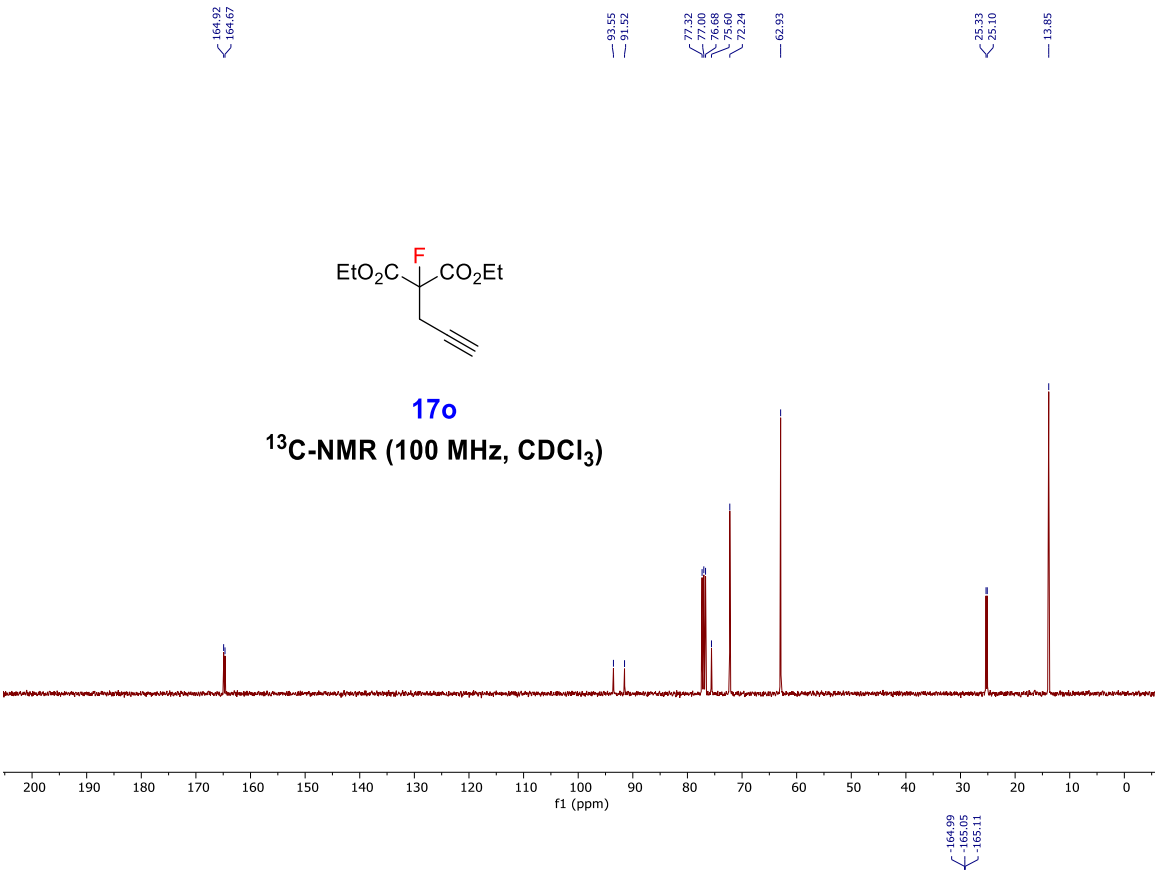
17n

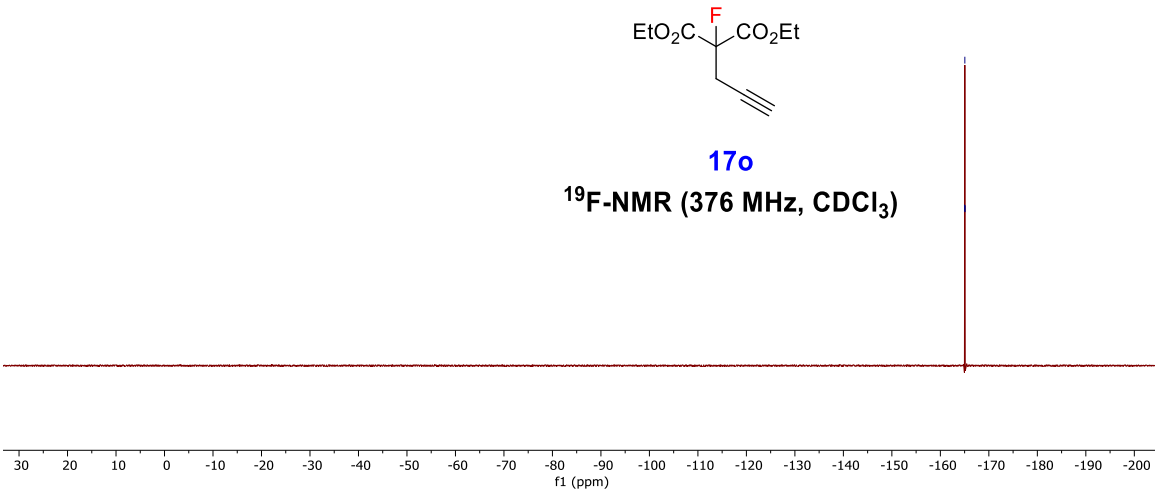
^{19}F-NMR (376 MHz, $CDCl_3$)

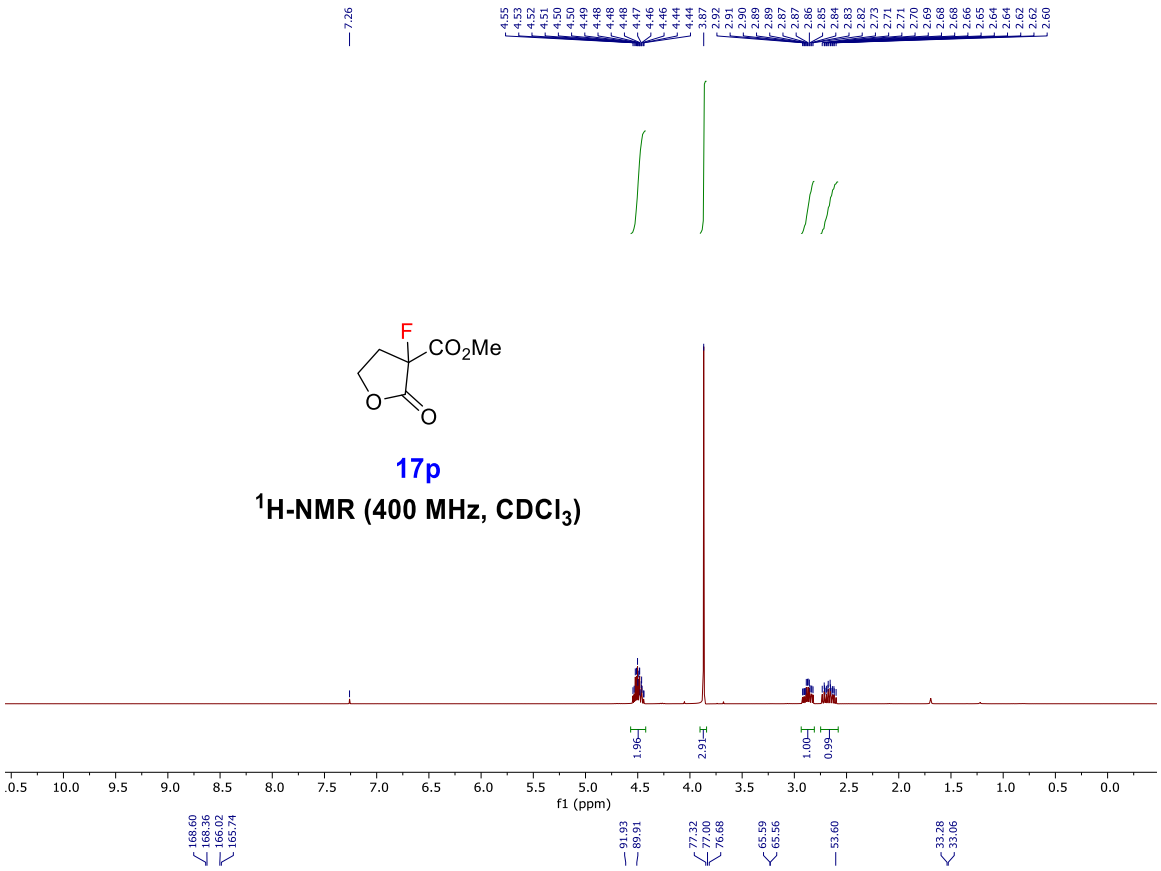


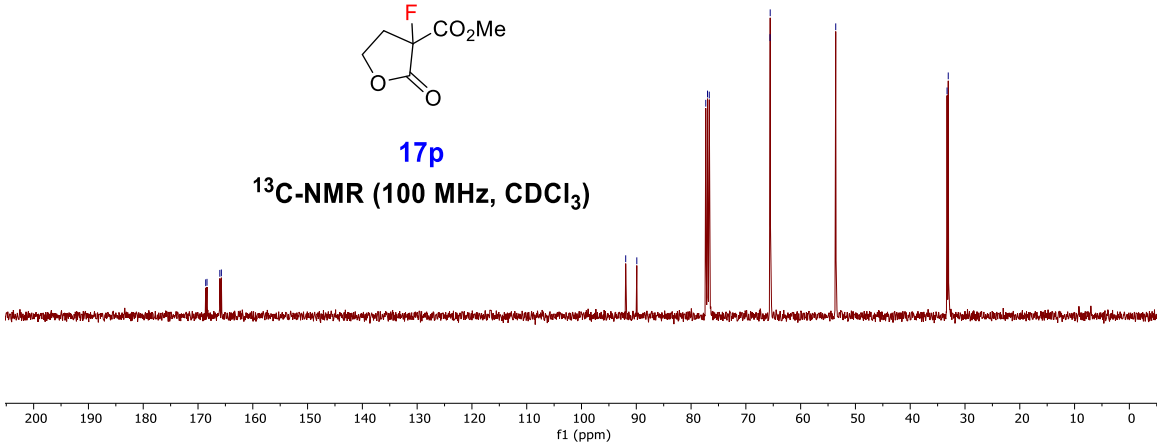
17o

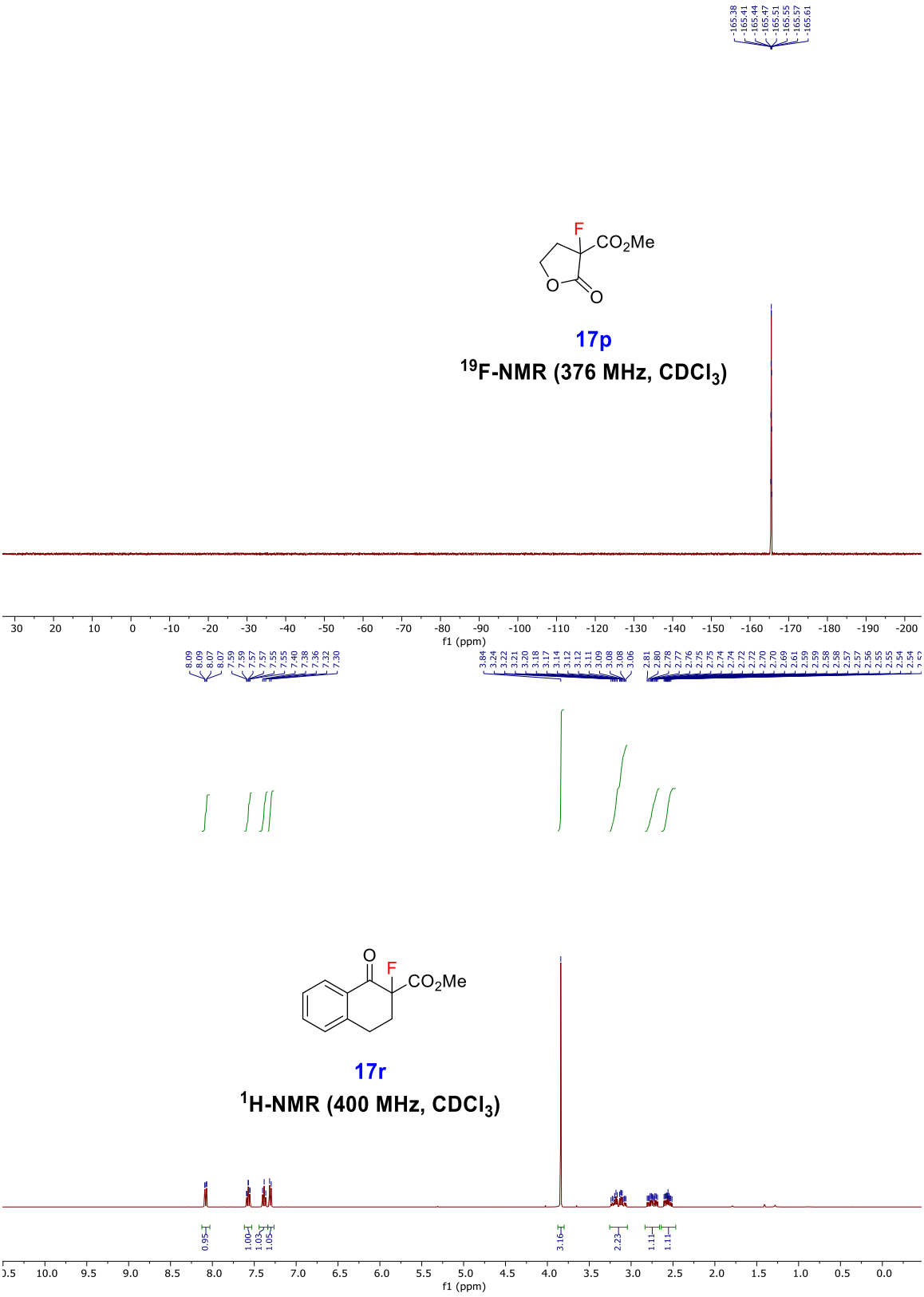
^{1}H-NMR (400 MHz, $CDCl_3$)

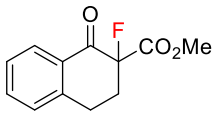

164.92
164.67
93.55
91.52
77.32
77.00
76.68
75.60
72.24
62.93
25.33
25.10
13.85
F
EtO2C
CO2Et
17o
13C-NMR (100 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


-164.99
-165.05
-165.11
F
EtO2C
CO2Et
17o
19F-NMR (376 MHz, CDCl3)
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)


F
CO2Me
O
O
17p
1H-NMR (400 MHz, CDCl3)
f1 (ppm)

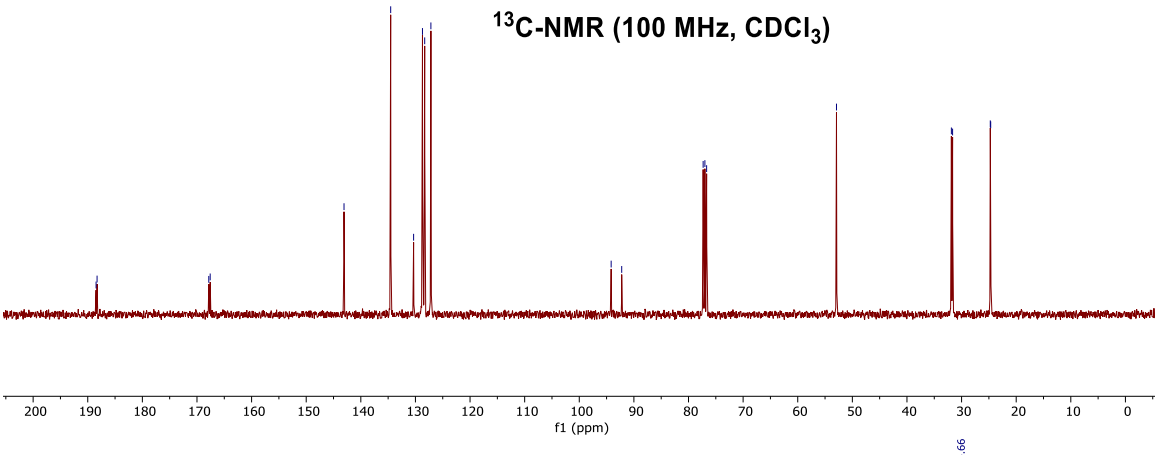

F
CO2Me
O
O
17p
13C-NMR (100 MHz, CDCl3)
f1 (ppm)

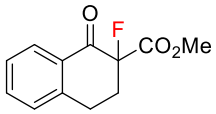

F
CO2Me
O
O
17p
19F-NMR (376 MHz, CDCl3)
f1 (ppm)
O
F
CO2Me
17r
1H-NMR (400 MHz, CDCl3)
f1 (ppm)



17r

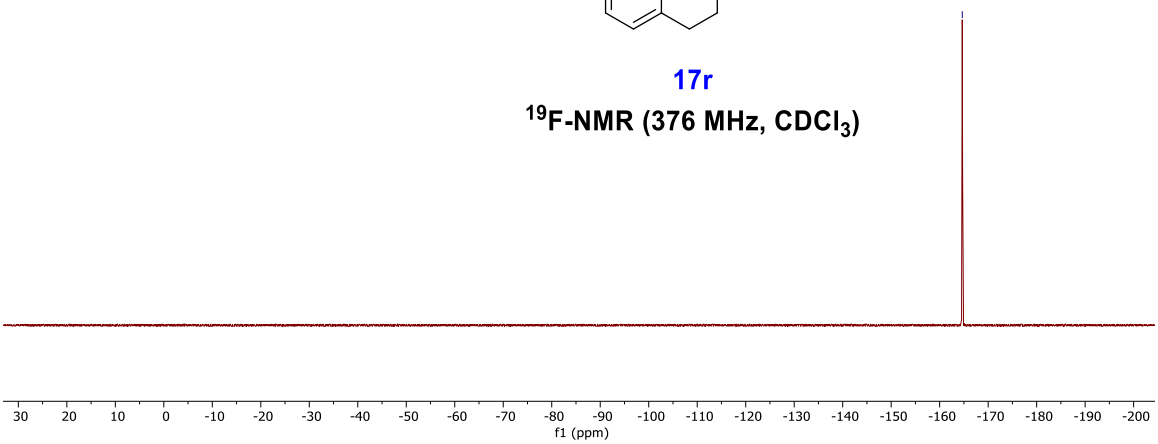
^{13}C-NMR (100 MHz, $CDCl_3$)

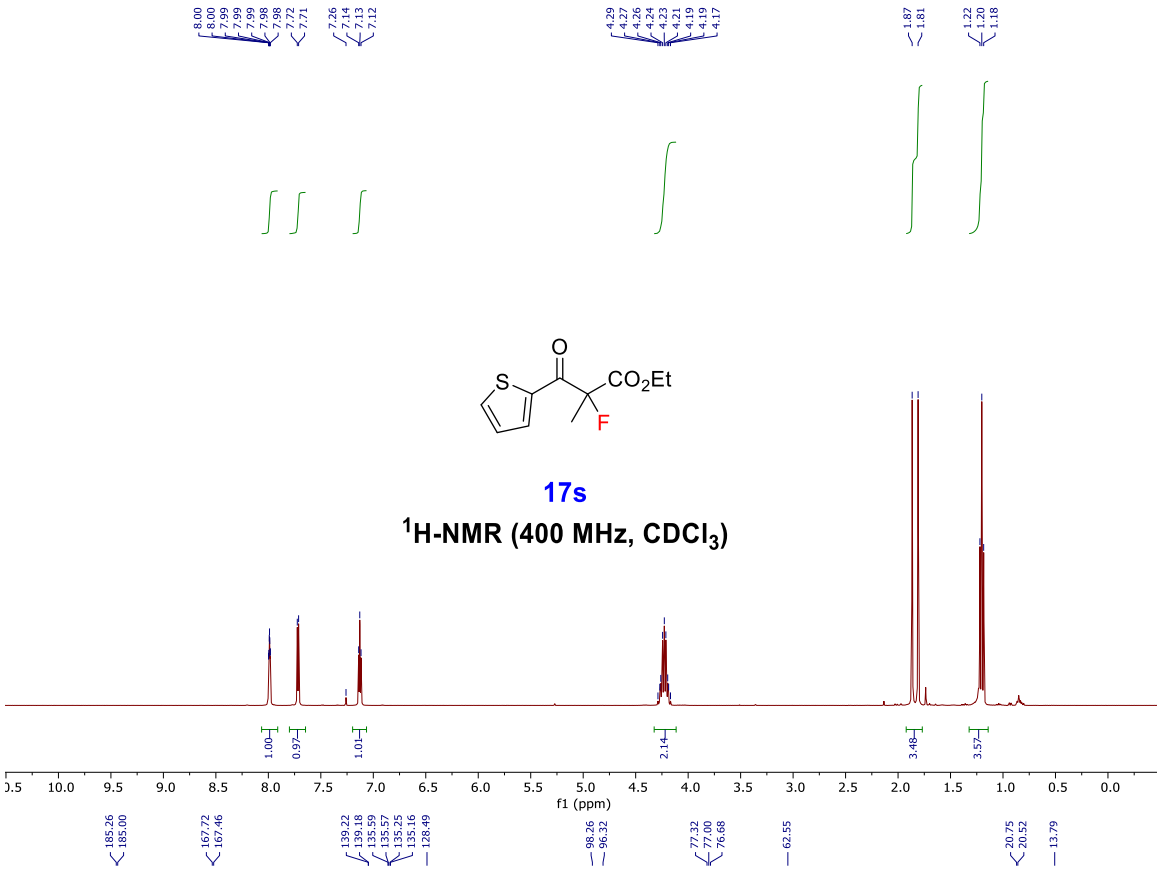




17r

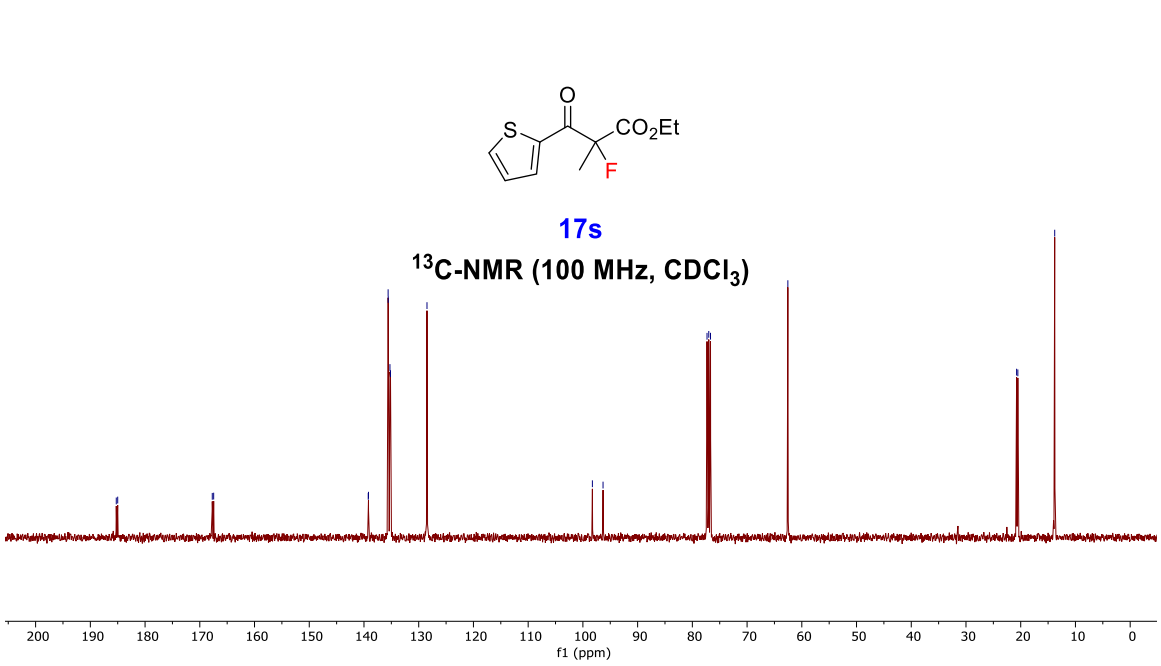
^{19}F-NMR (376 MHz, $CDCl_3$)





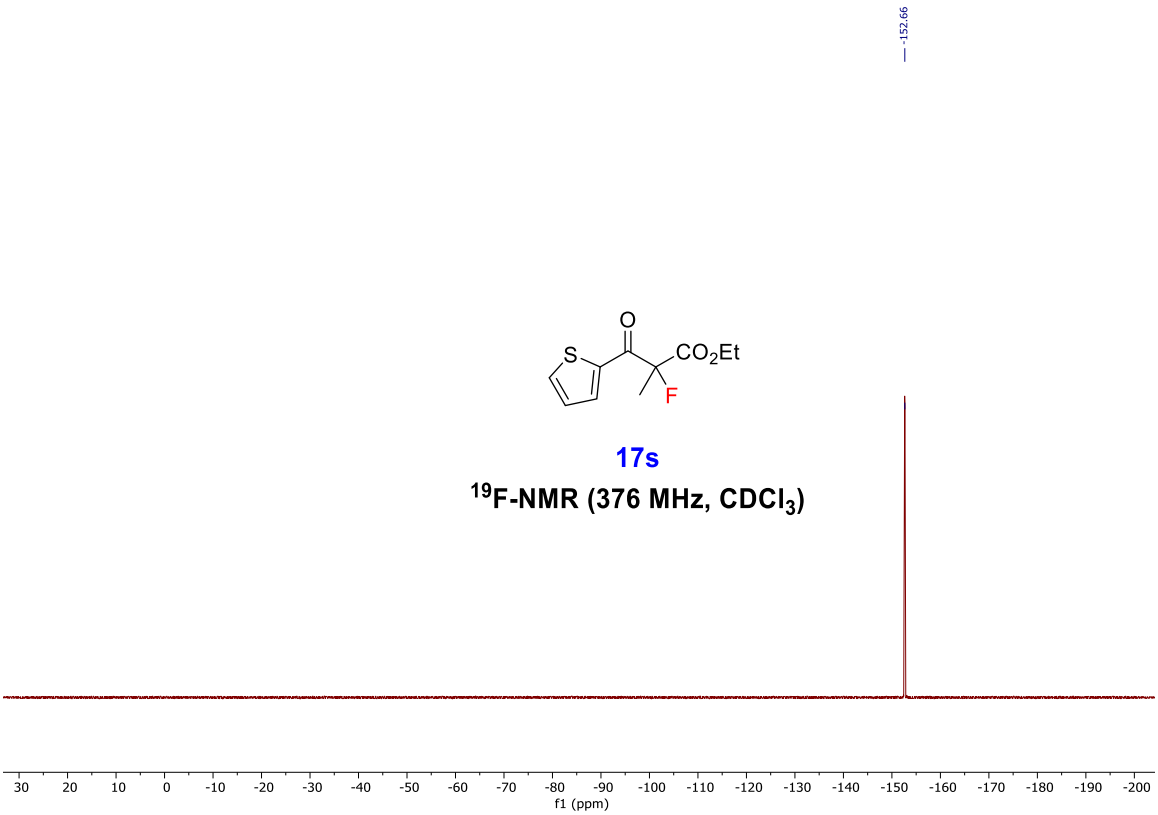
17s

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



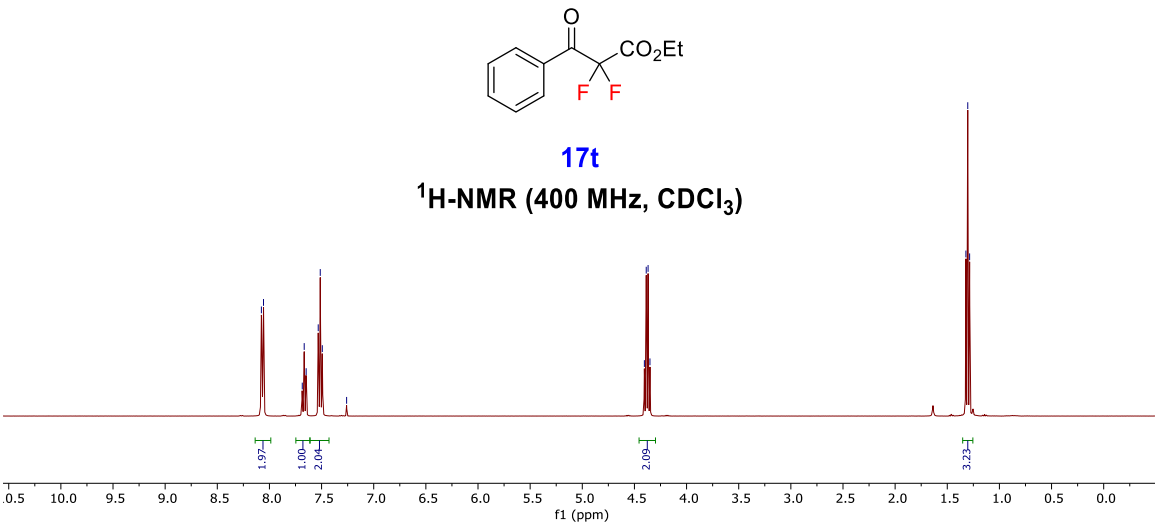
17s

^{13}C-NMR (100 MHz, $CDCl_3$)



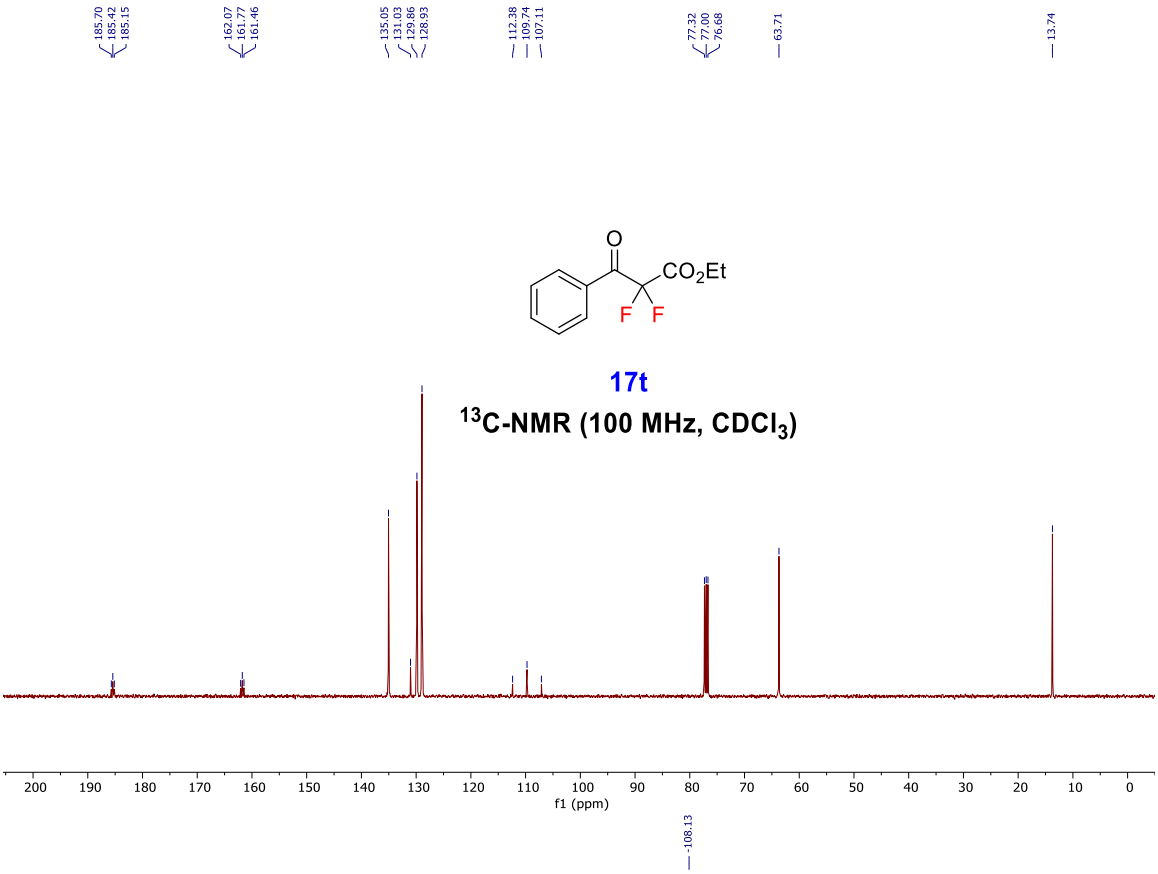
17s

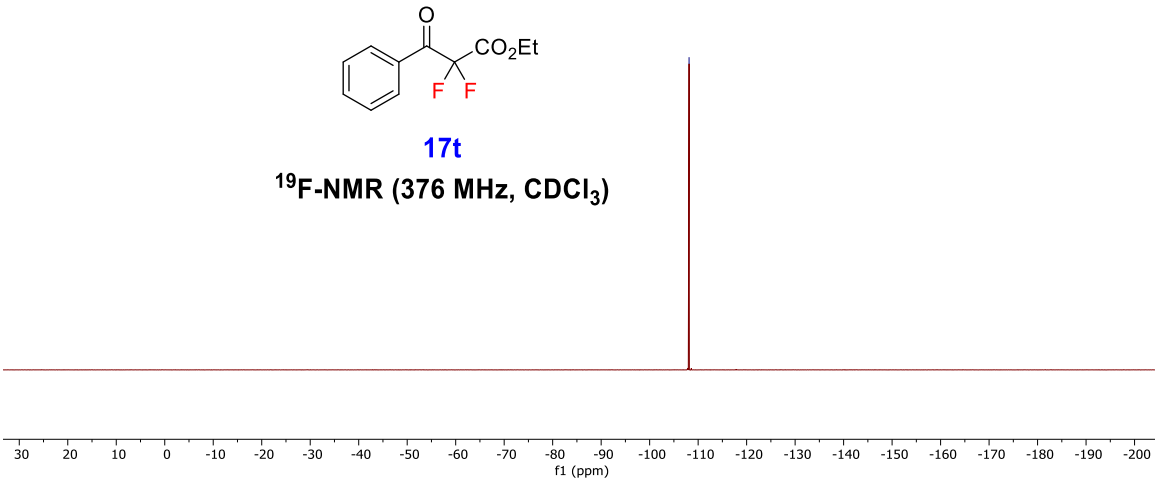
^{19}F-NMR (376 MHz, $CDCl_3$)

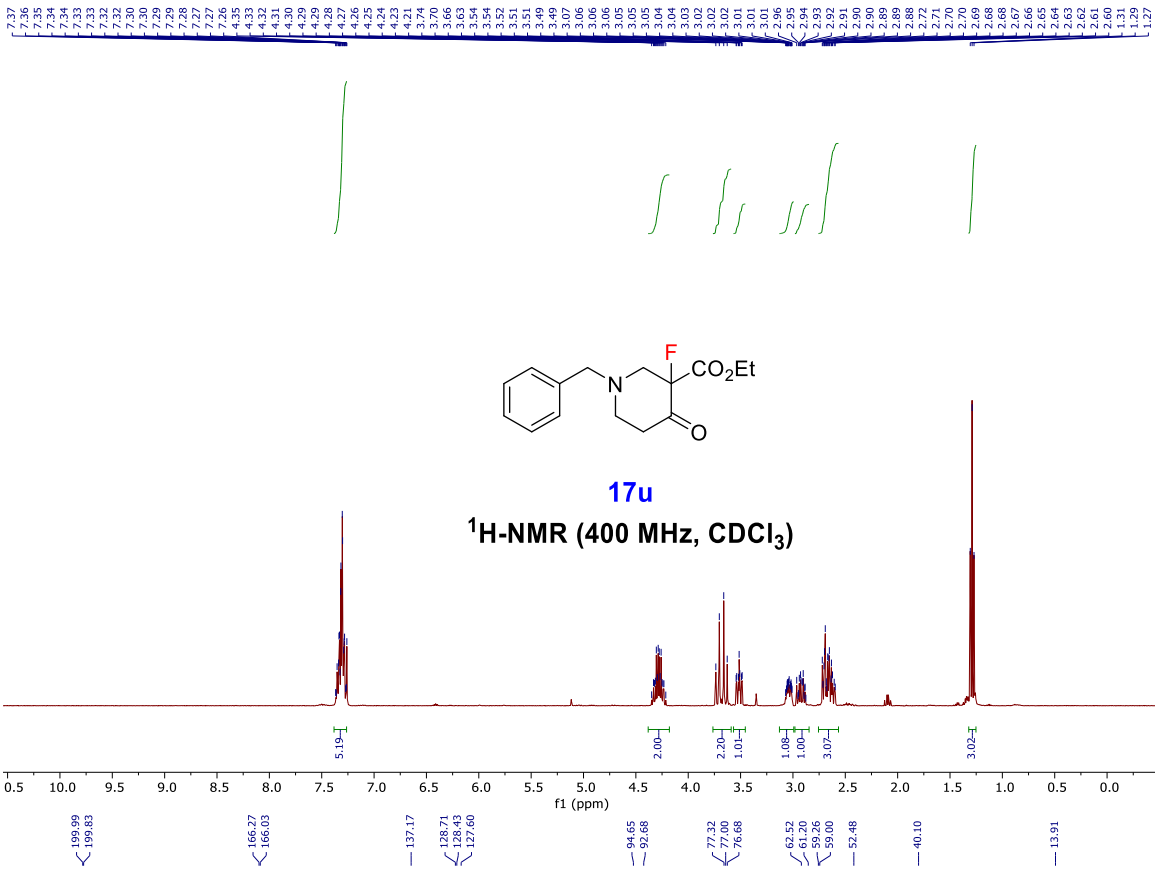


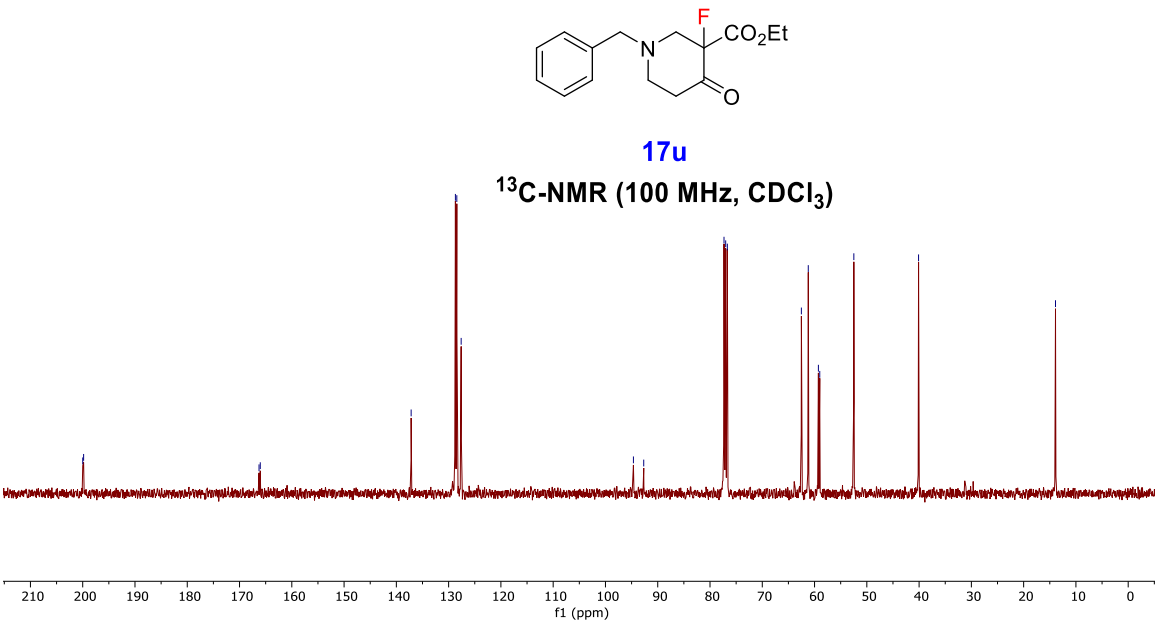
17t

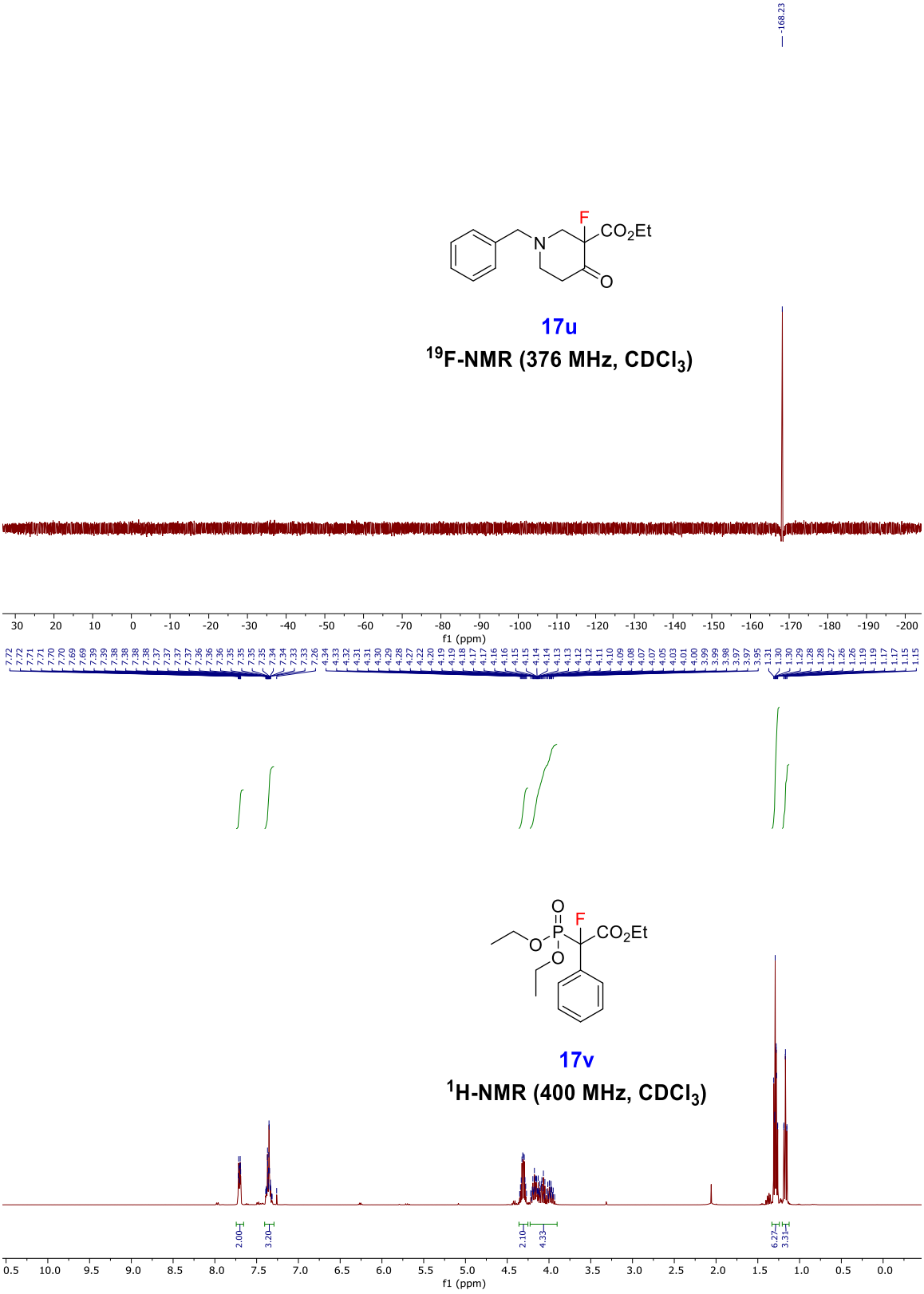
^{1}H-NMR (400 MHz, $CDCl_3$)

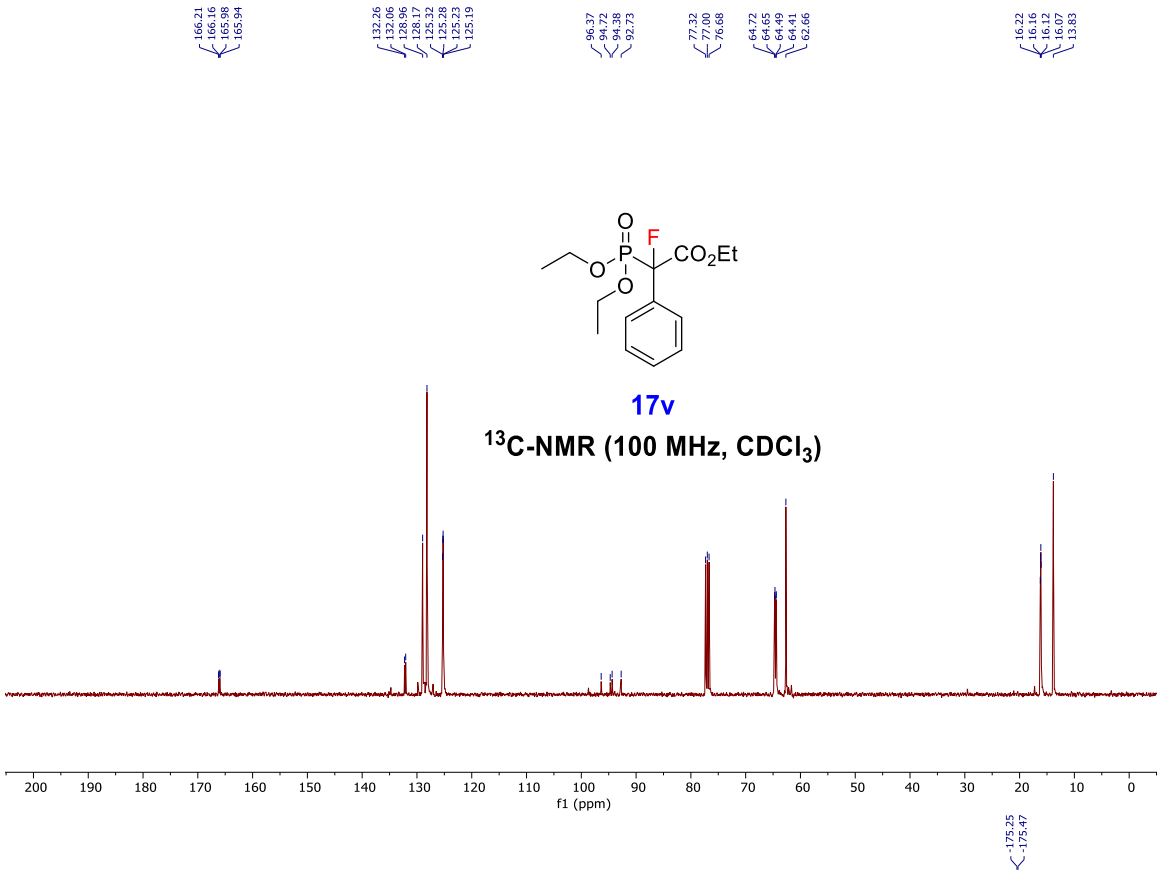

185.70
185.42
185.15
162.07
161.77
161.46
135.05
131.03
129.86
128.93
112.38
109.74
107.11
77.32
77.00
76.68
63.71
13.74
O
CO2Et
F F
17t
13C-NMR (100 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


-108.13
O
CO2Et
F F
17t
19F-NMR (376 MHz, CDCl3)
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)


F
CO2Et
N
O
17u
1H-NMR (400 MHz, CDCl3)
f1 (ppm)

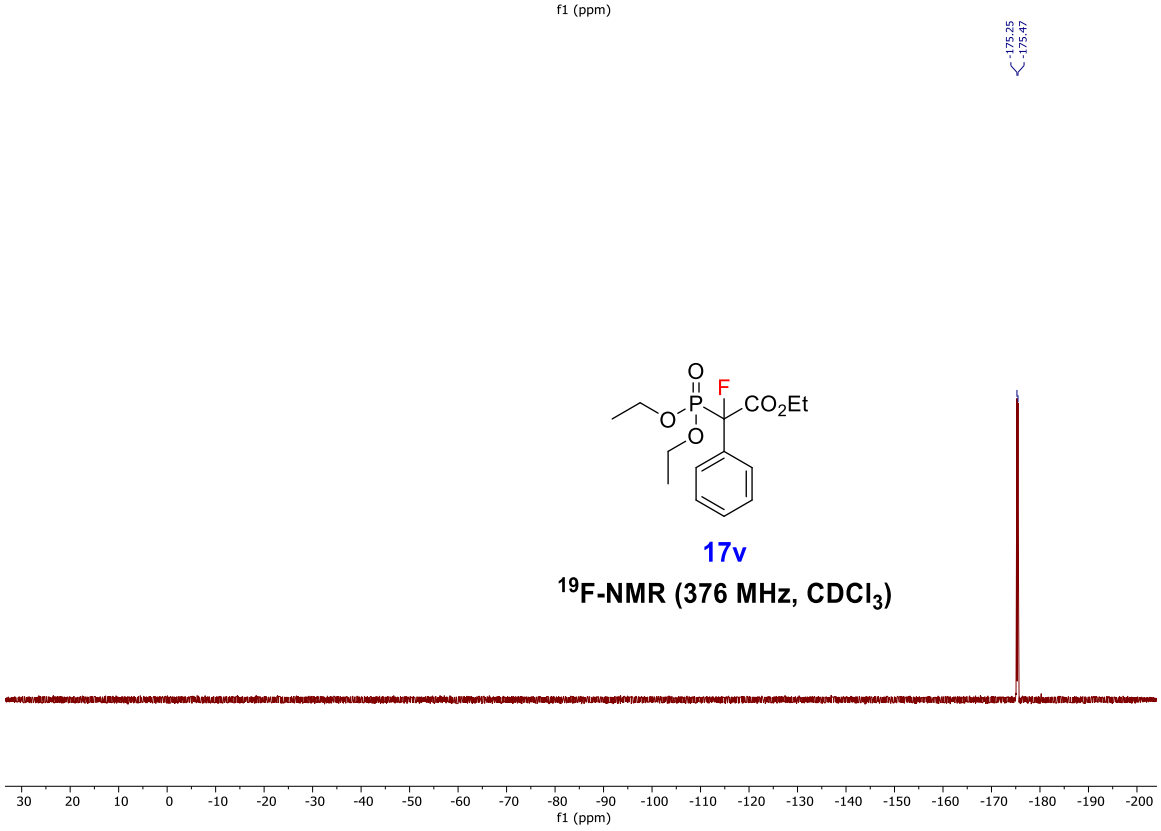

F
CO2Et
N
O
17u
13C-NMR (100 MHz, CDCl3)
f1 (ppm)


-168.23
F
CO2Et
N
O
17u
19F-NMR (376 MHz, CDCl3)
f1 (ppm)
O
P
F
CO2Et
O
O
O
17v
1H-NMR (400 MHz, CDCl3)
2.00
3.20
2.10
4.33
6.27
3.31
f1 (ppm)



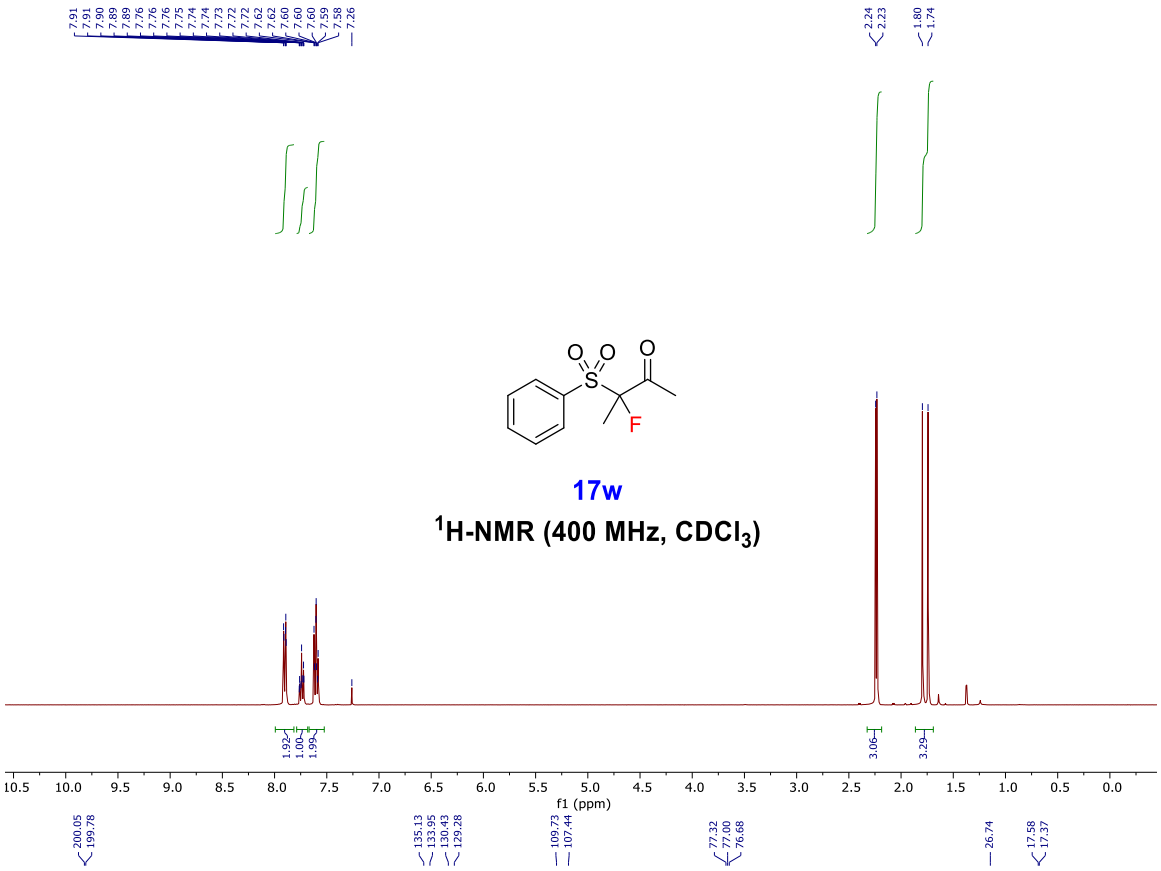
17v

^{13}C-NMR (100 MHz, $CDCl_3$)



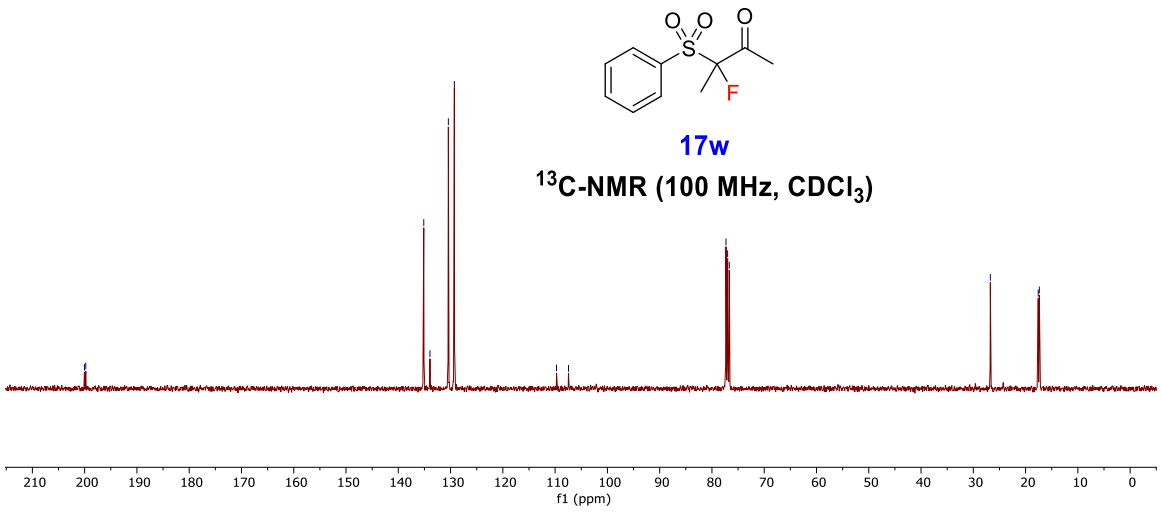
17v

^{19}F-NMR (376 MHz, $CDCl_3$)



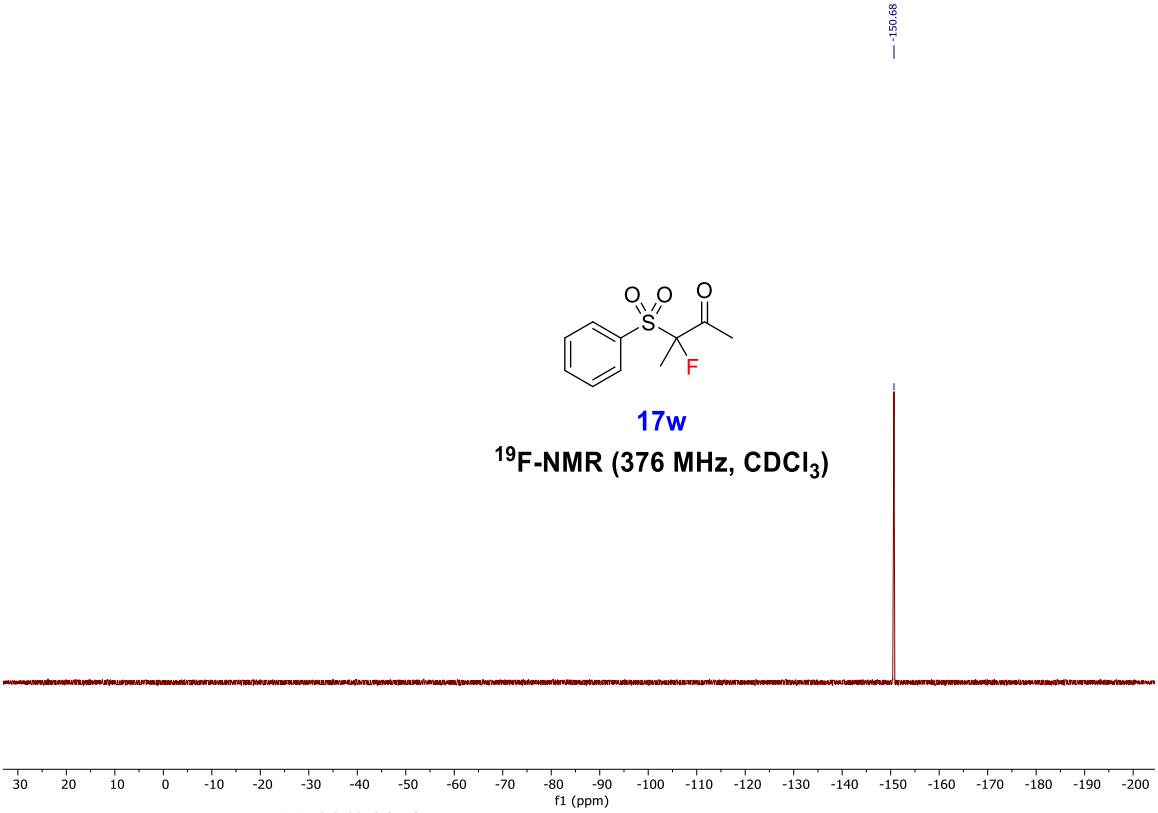
17w

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



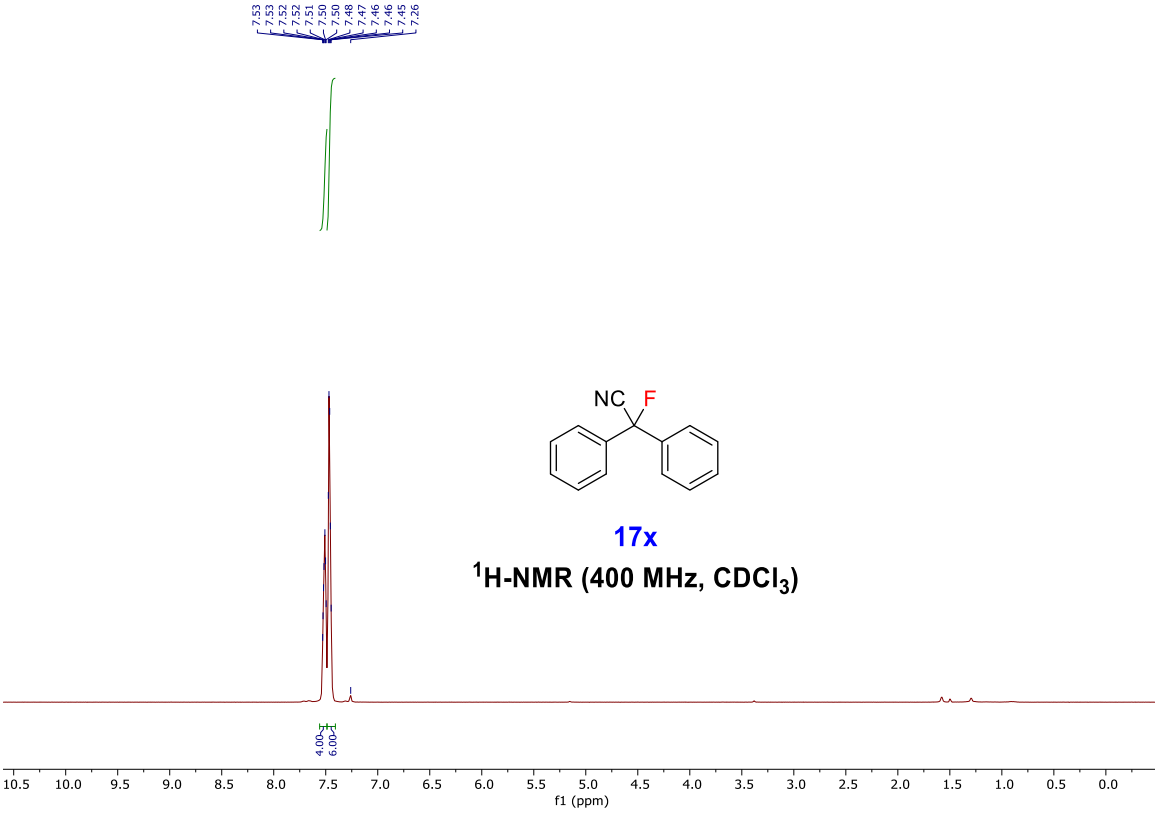
17w

^{13}C-NMR (100 MHz, $CDCl_3$)



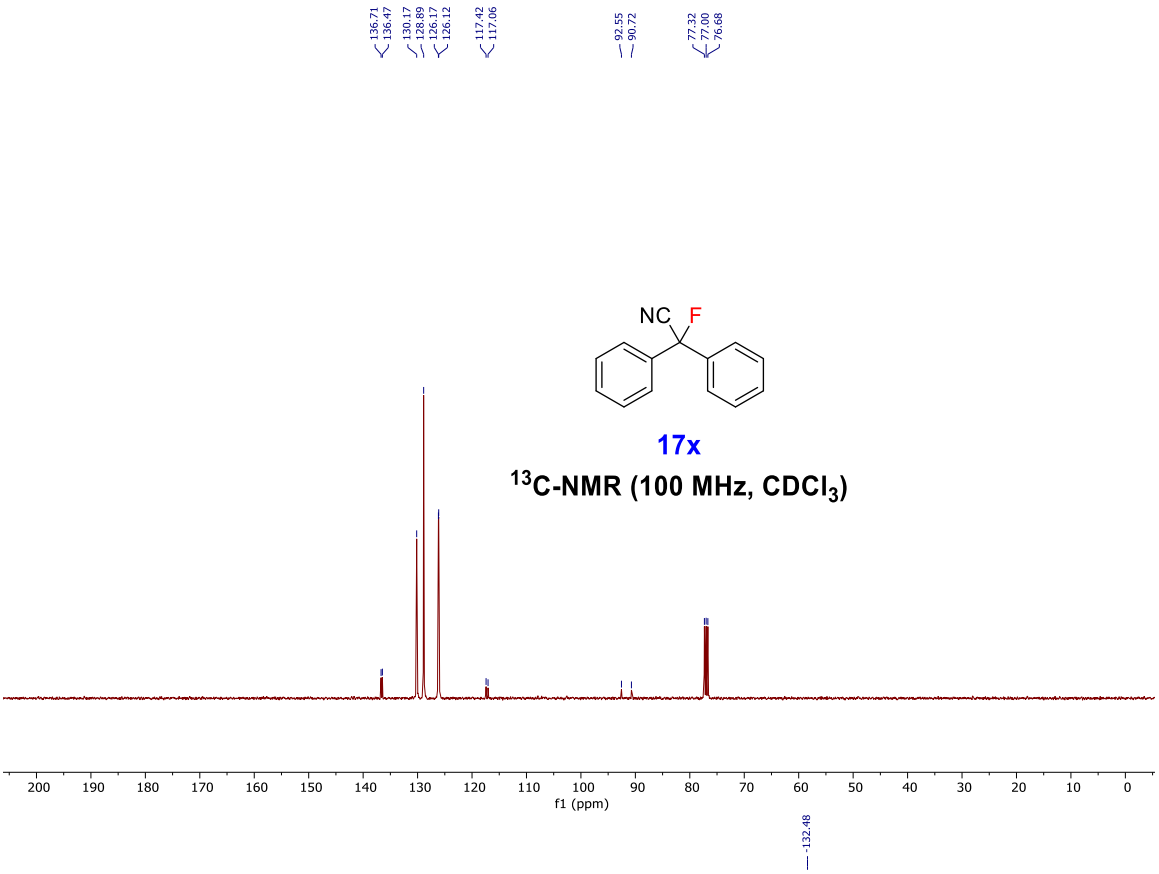
17w

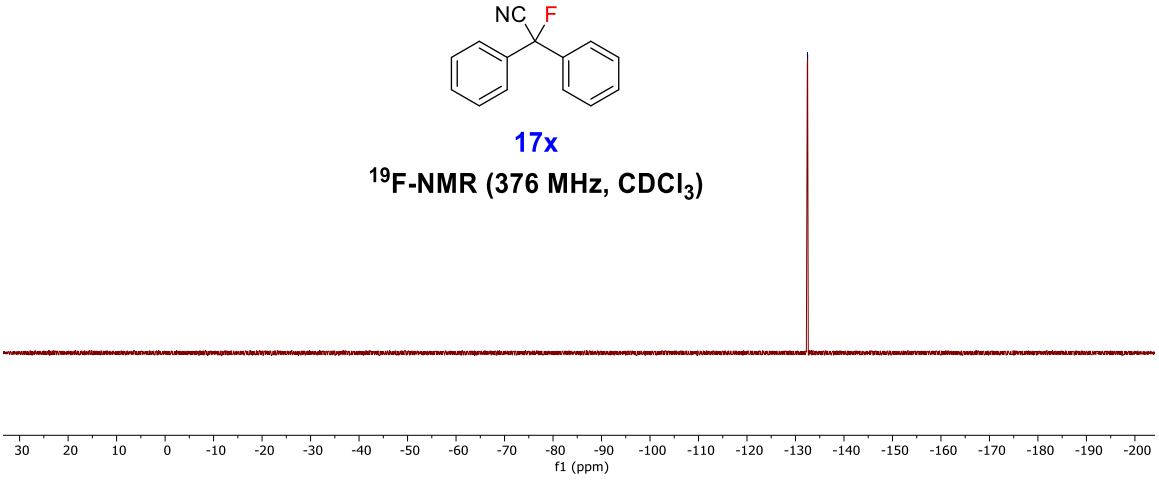
^{19}F-NMR (376 MHz, $CDCl_3$)

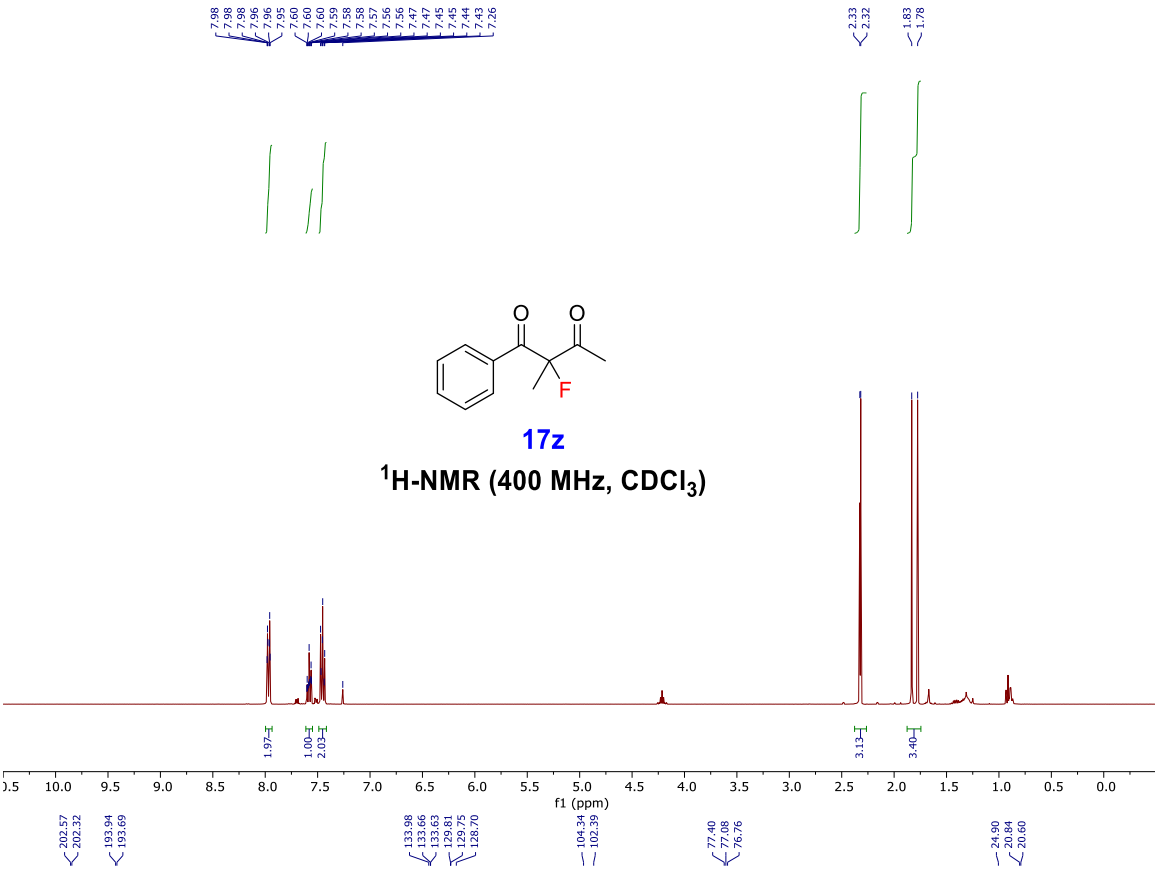


17x

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

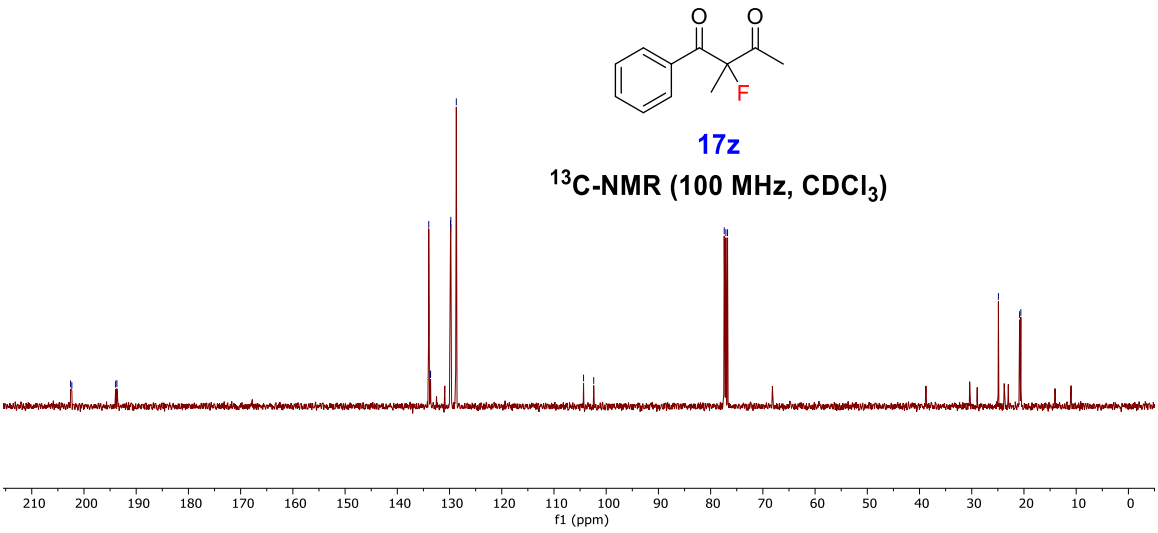

136.71
136.47
130.17
128.89
126.17
126.12
117.42
117.06
92.55
90.72
77.32
77.00
76.68
NC
F
17x
13C-NMR (100 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


-132.48
NC
F
17x
19F-NMR (376 MHz, CDCl3)
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)



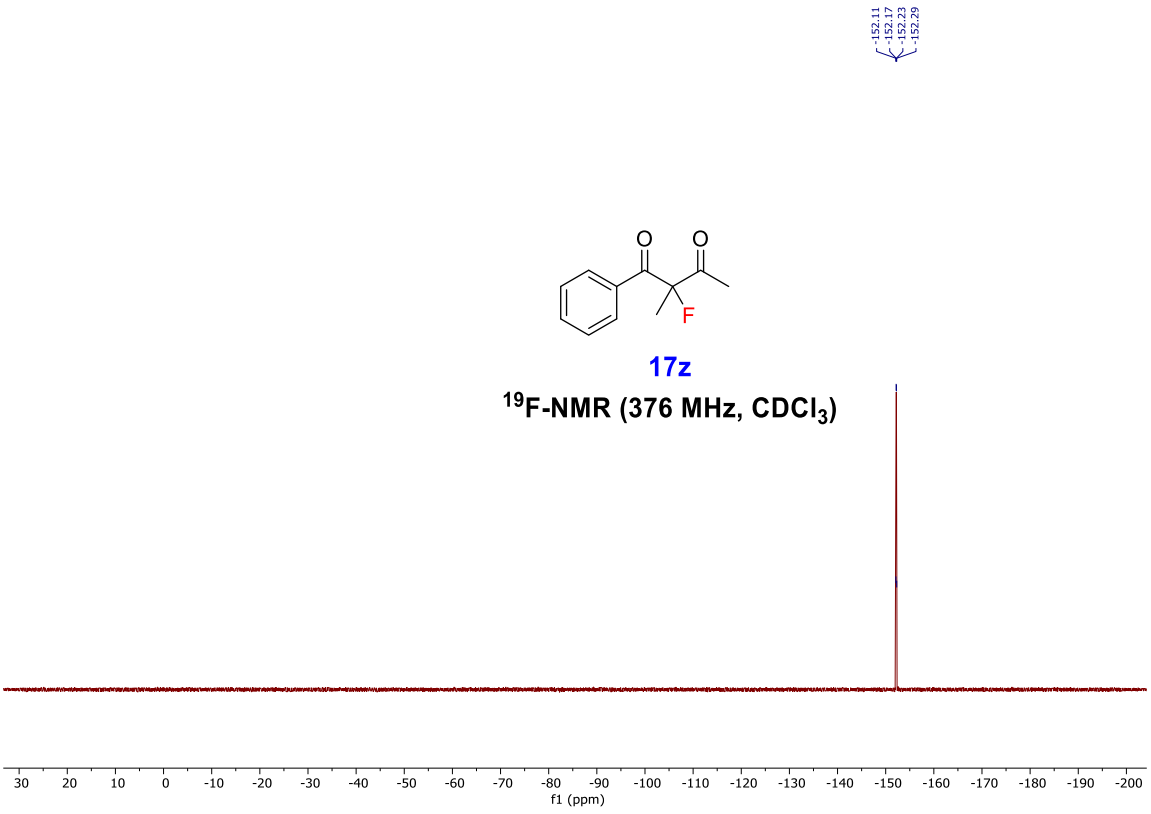
17z

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



17z

^{13}C-NMR (100 MHz, $CDCl_3$)



17z

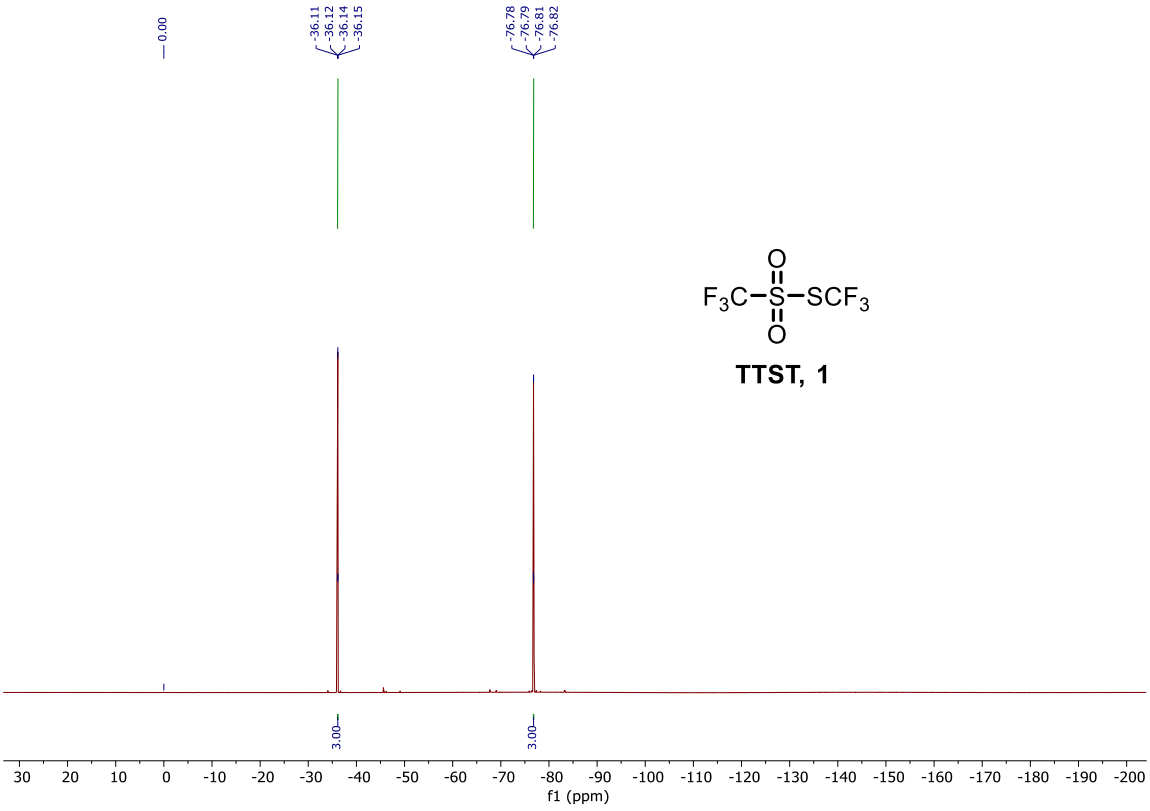
^{19}F-NMR (376 MHz, $CDCl_3$)

APPENDIX B

NMR SPECTRA OF COMPOUNDS PREPARED IN CHAPTER 3

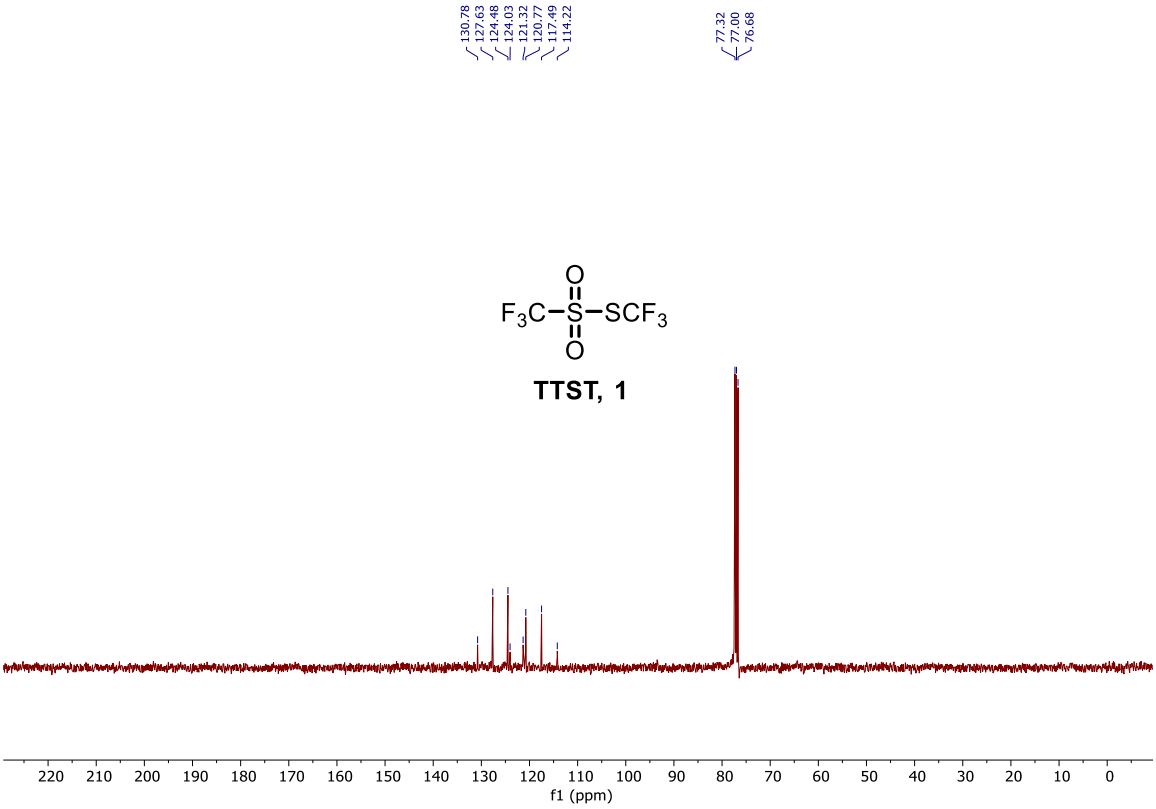
B.1 ^{19}F, ^{1}H, and ^{13}C NMR spectral data

^{19}F NMR (376 MHz, $CDCl_3$) of TTST (1)

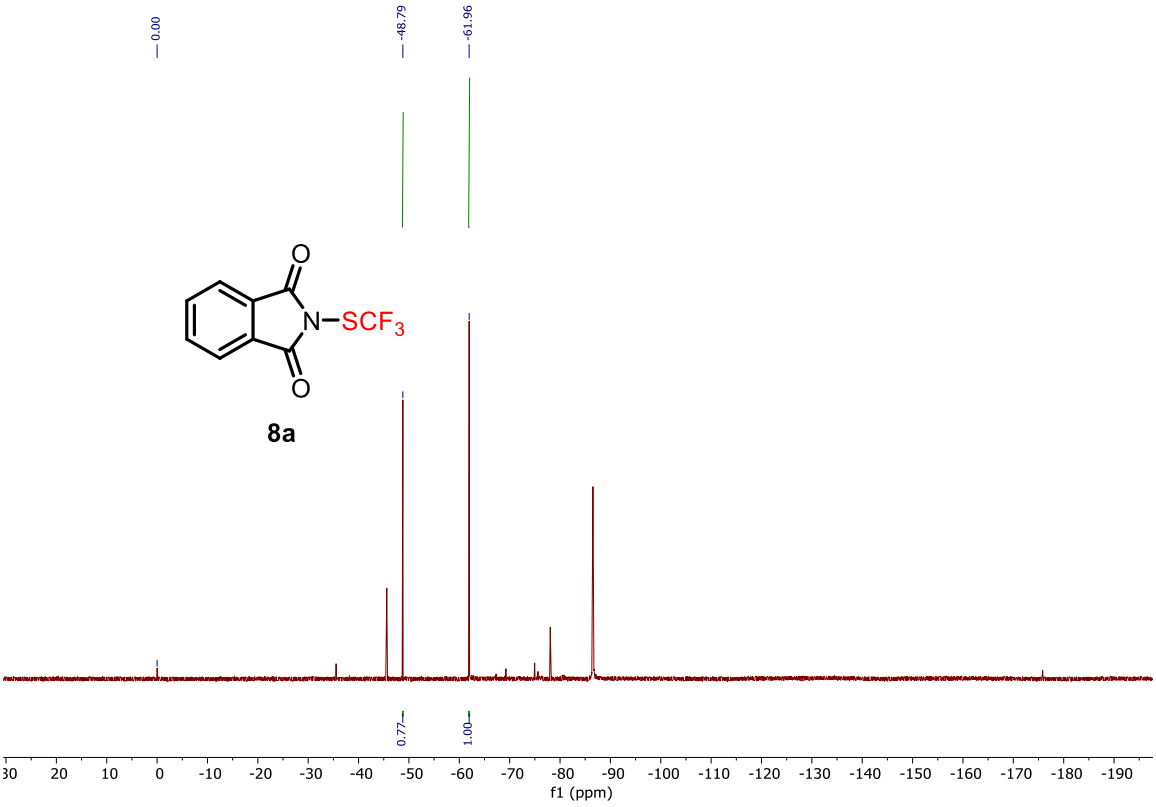


TTST, 1

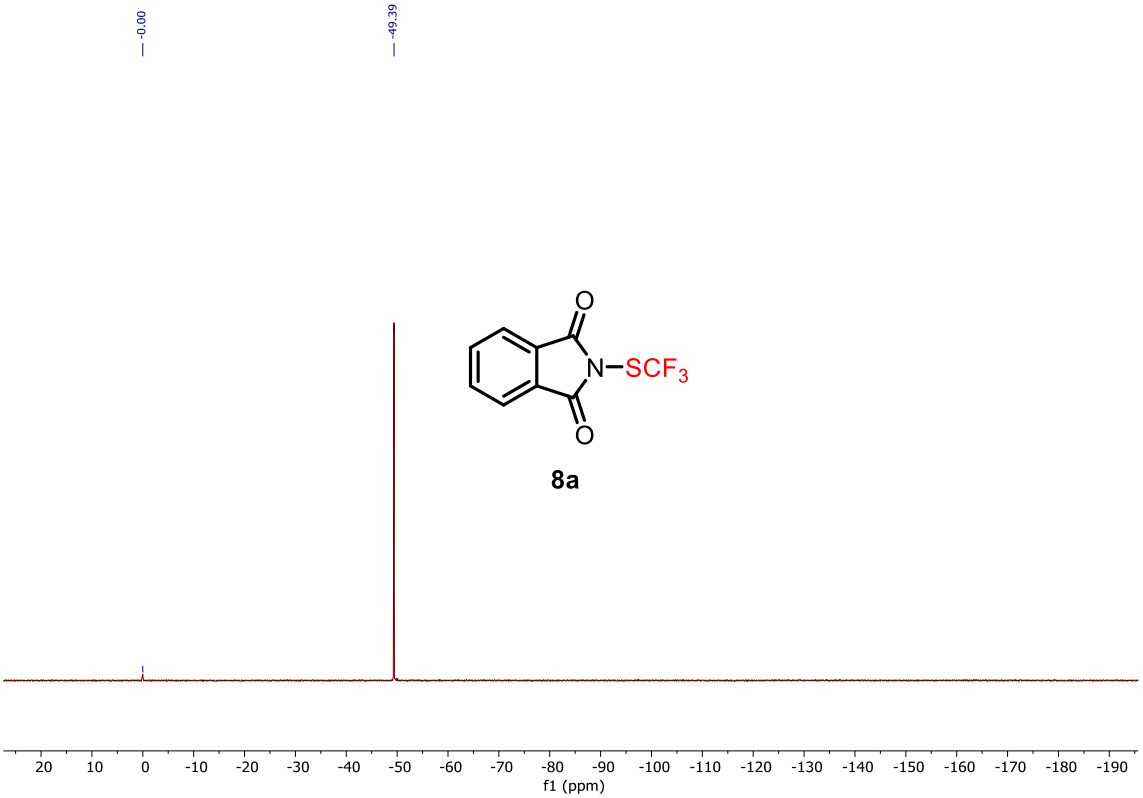
^{13}C NMR (100 MHz, $CDCl_3$) of TTST (1)



^{19}F NMR (376 MHz, CD_3CN) yield of 8a

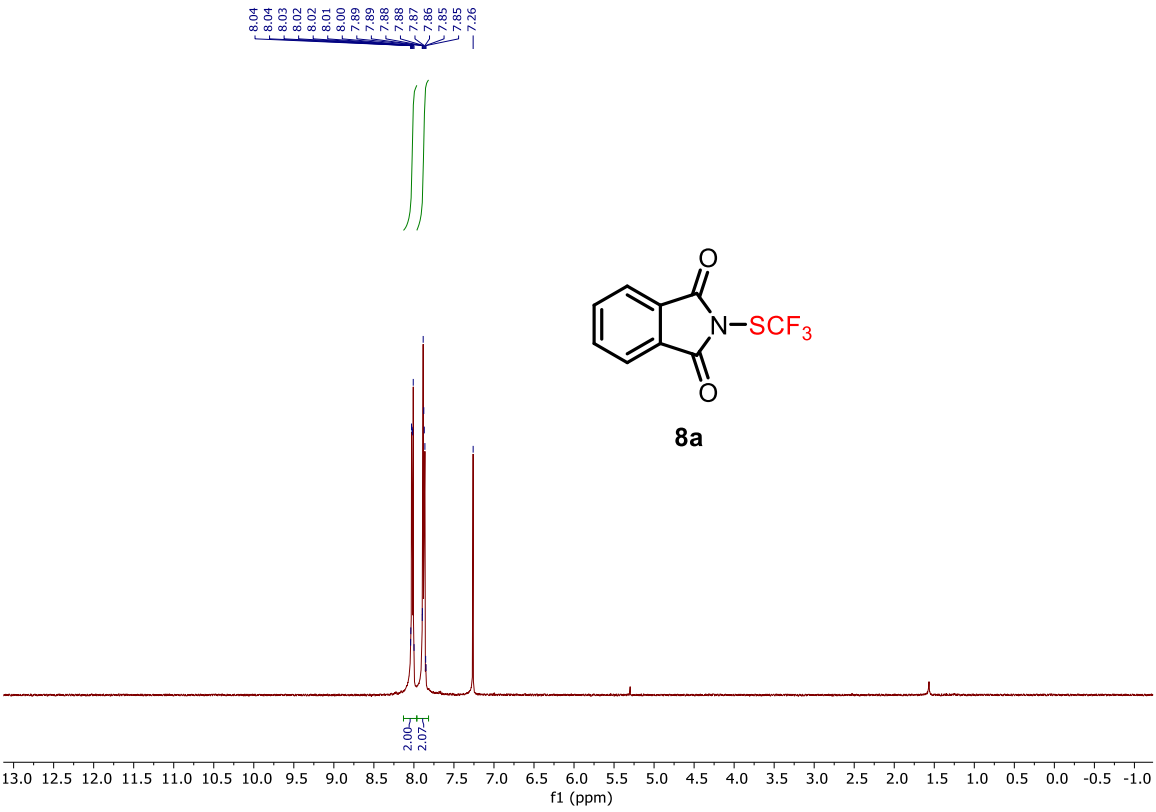


^{19}F NMR (376 MHz, $CDCl_3$) of 8a



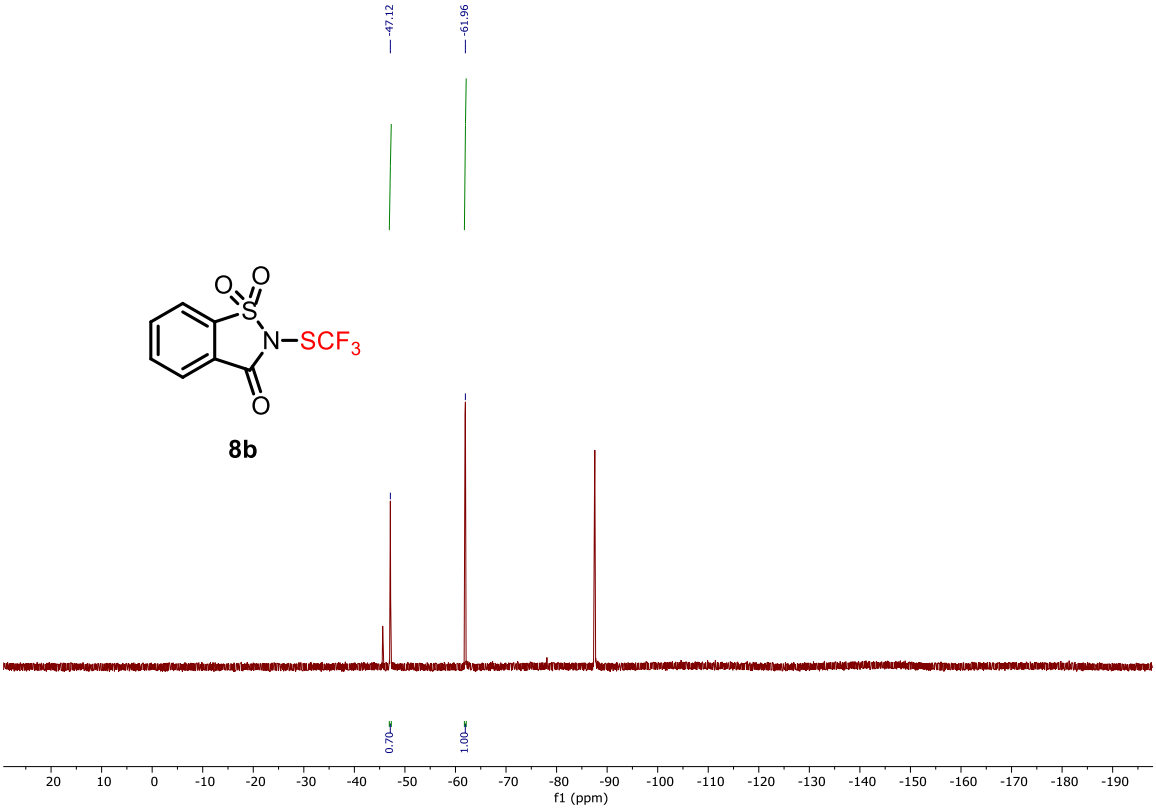
8a

^{1}H NMR (400 MHz, $CDCl_3$) of 8a

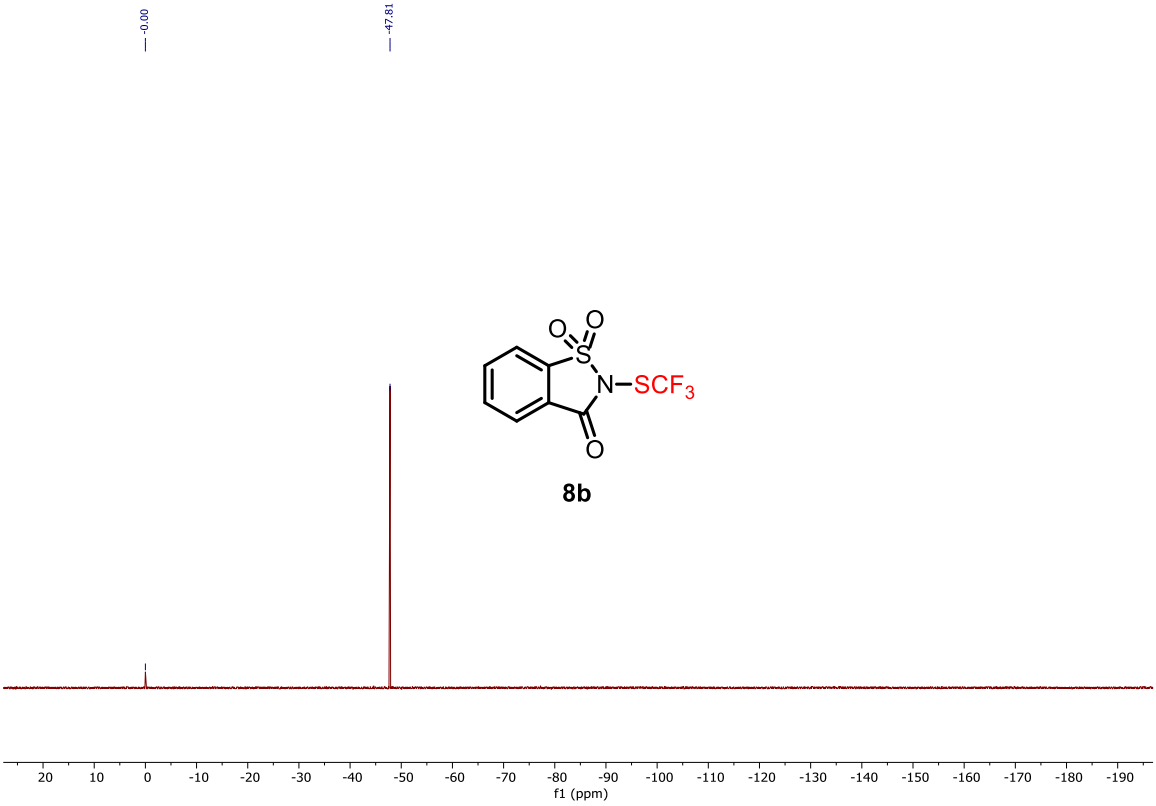


8a

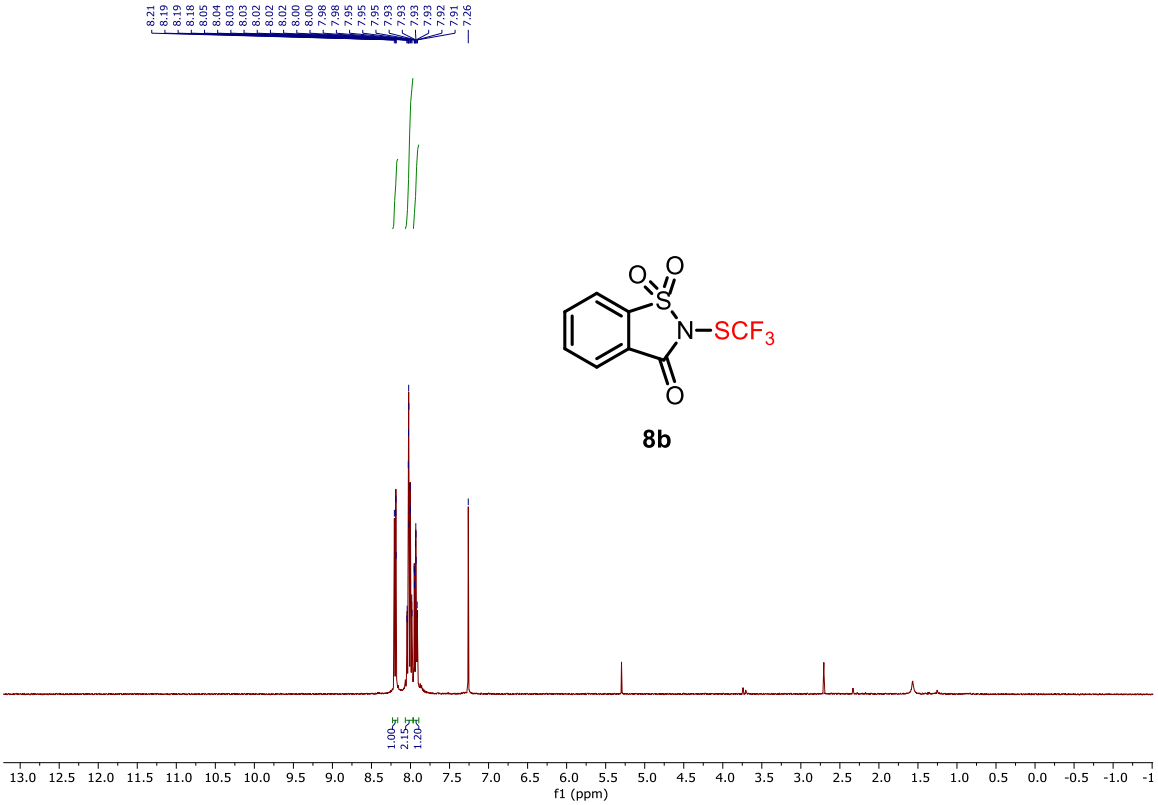
^{19}F NMR (376 MHz, CD_3CN) yield of 8b



^{19}F NMR (376 MHz, CD_3CN) 8b

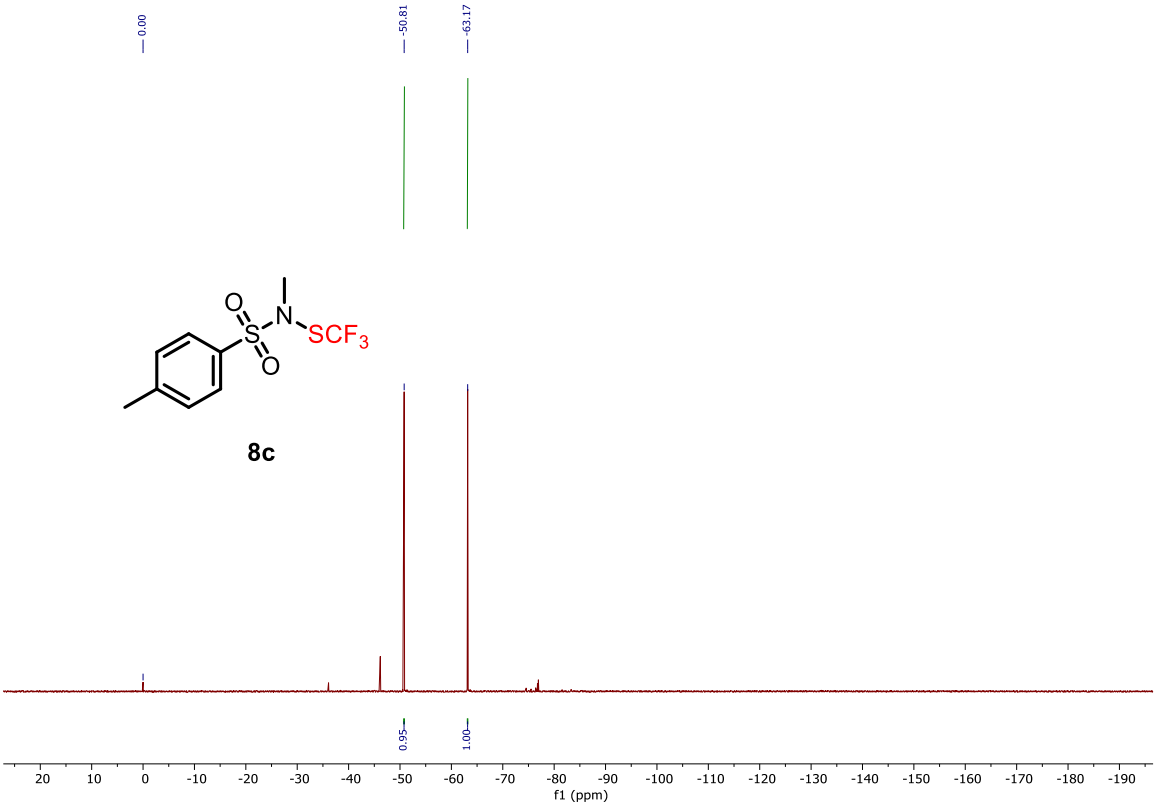


^{1}H NMR (400 MHz, CD_3CN) 8b



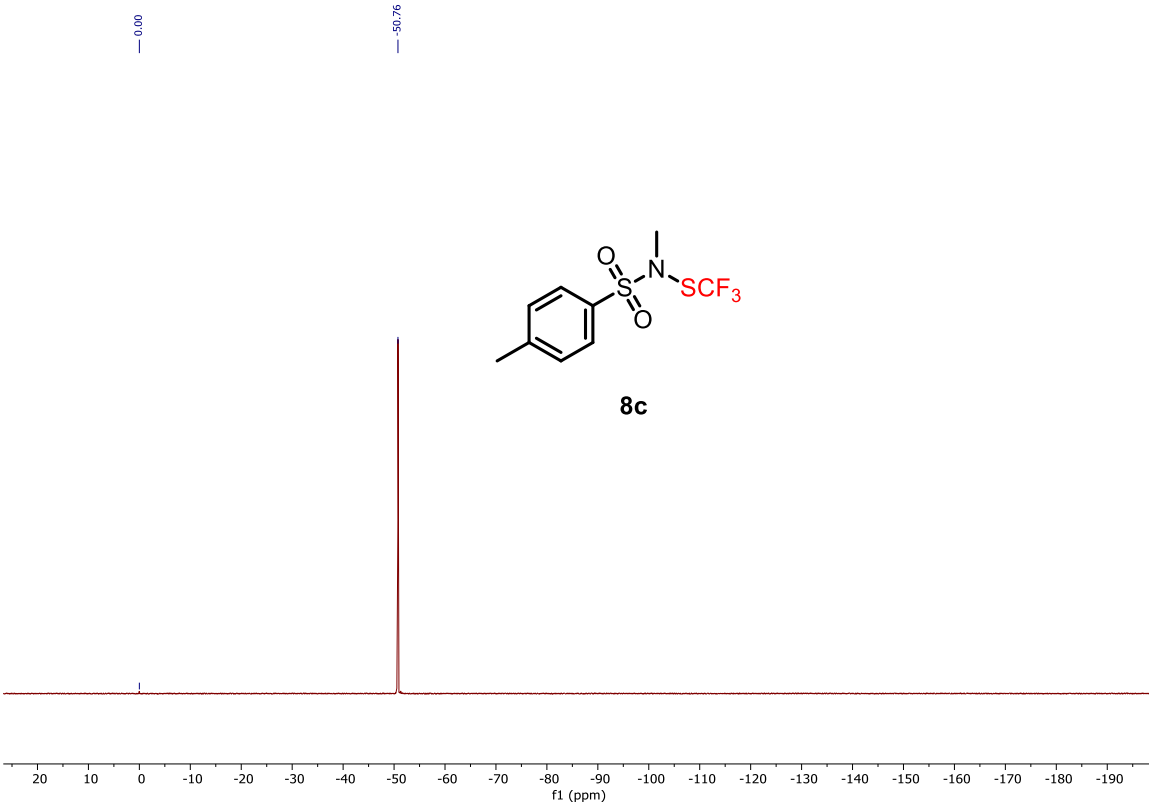
8b

^{19}F NMR (376 MHz, $CDCl_3$) yield of 8c



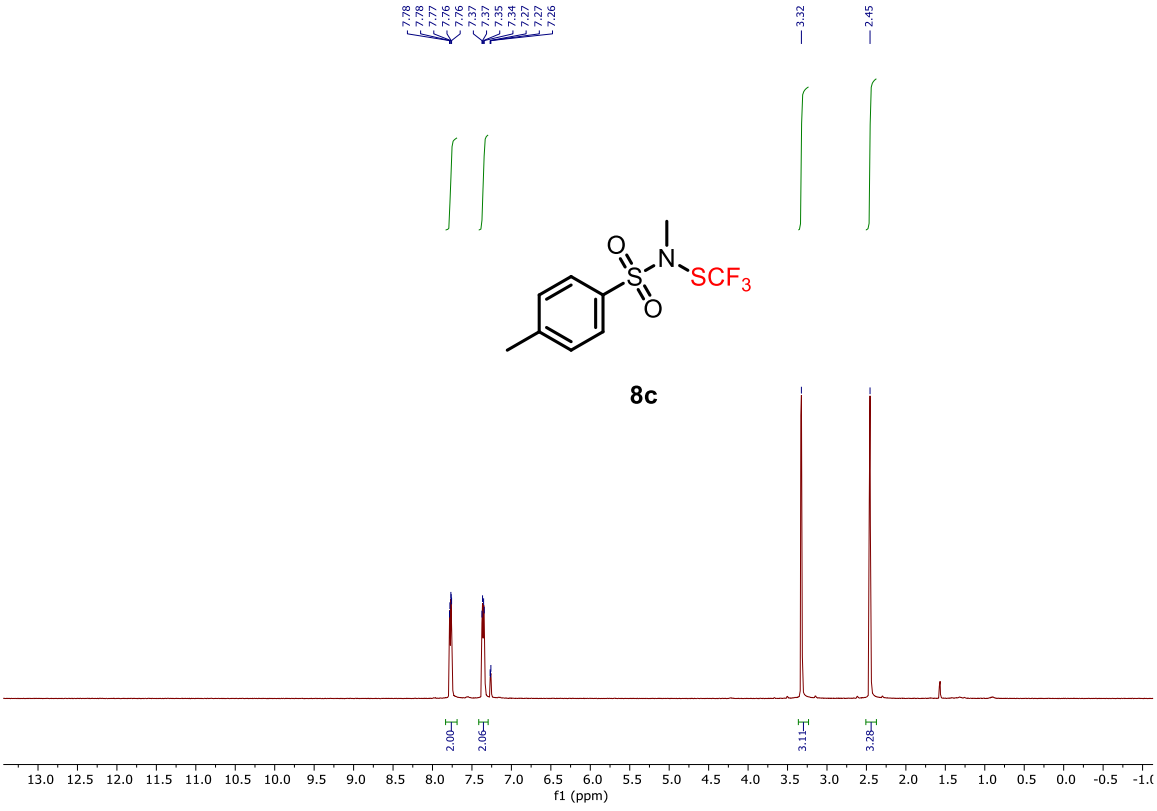
8c

^{19}F NMR (376 MHz, $CDCl_3$) 8c



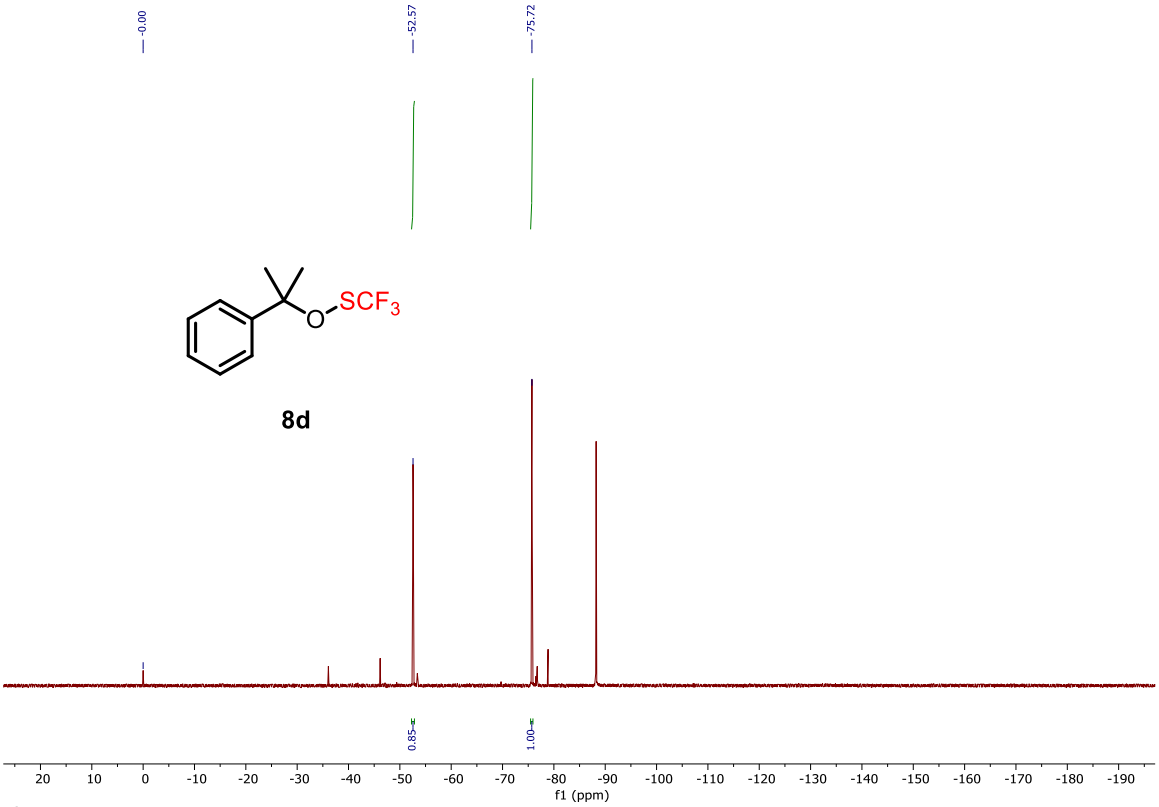
8c

^{1}H NMR (376 MHz, $CDCl_3$) 8c

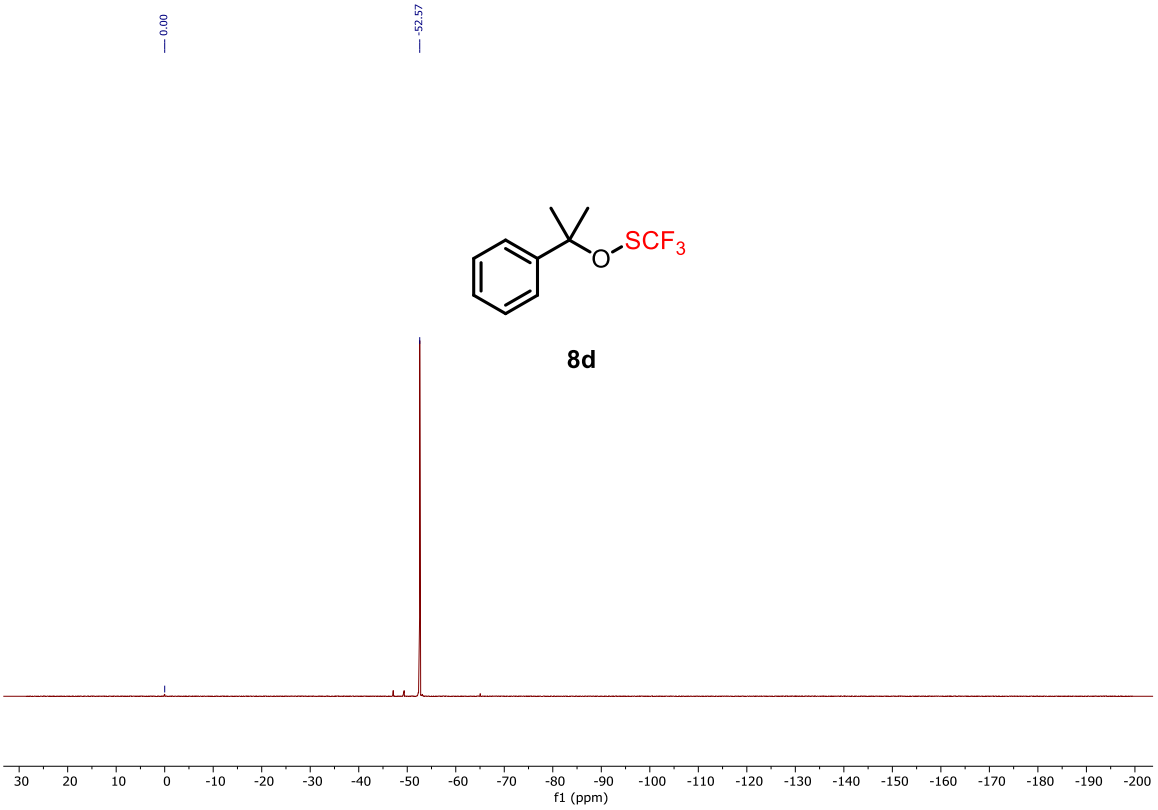


8c

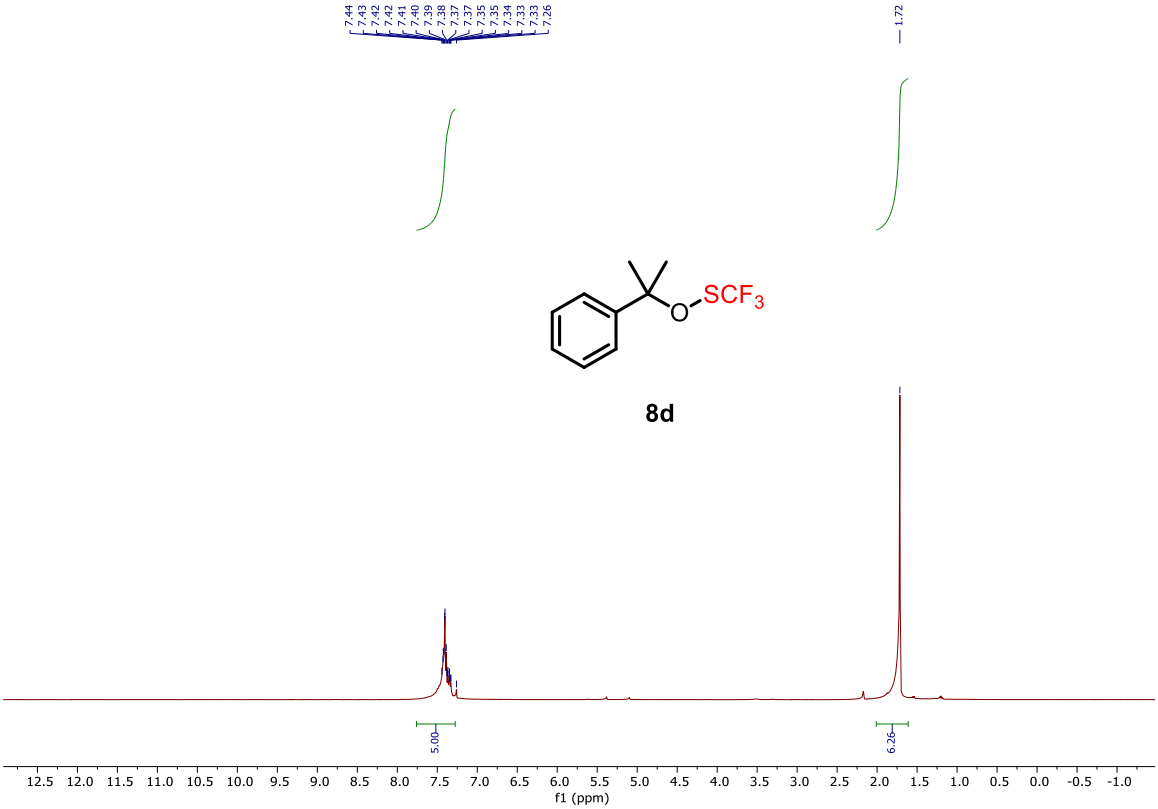
^{19}F NMR (376 MHz, $CDCl_3$) yield of 8d



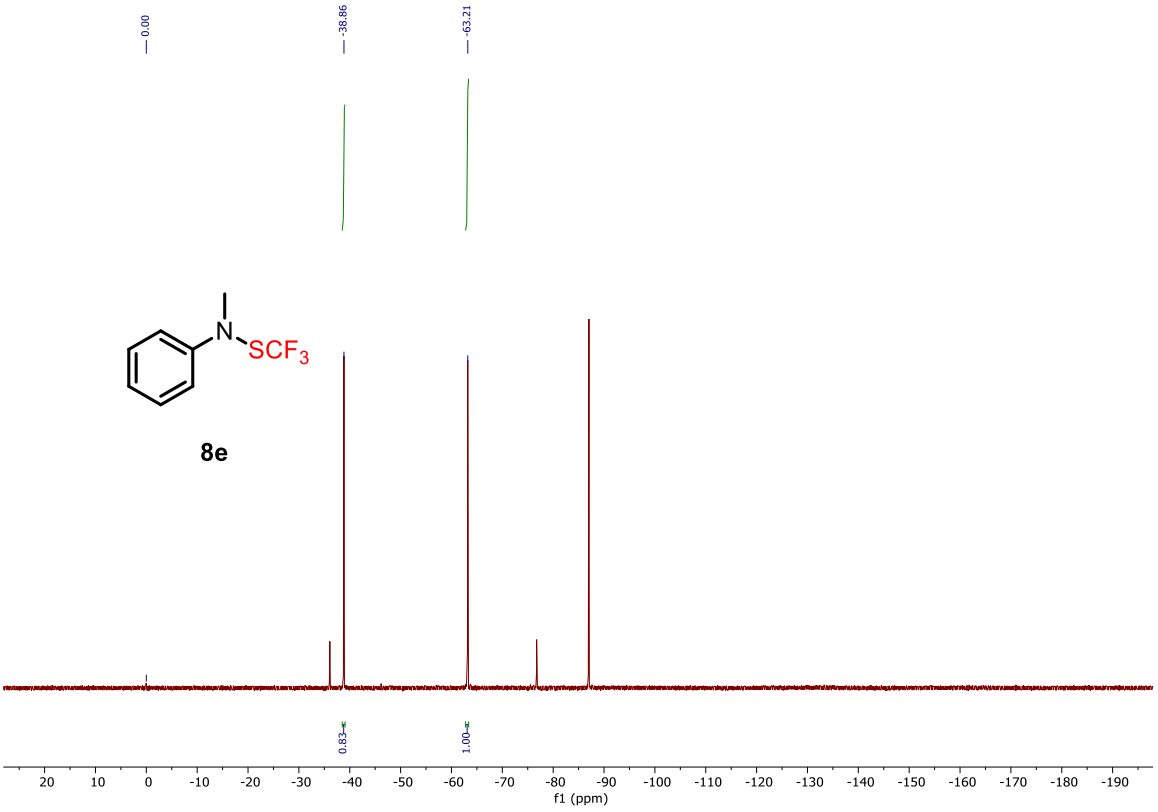
^{19}F NMR (376 MHz, $CDCl_3$) 8d



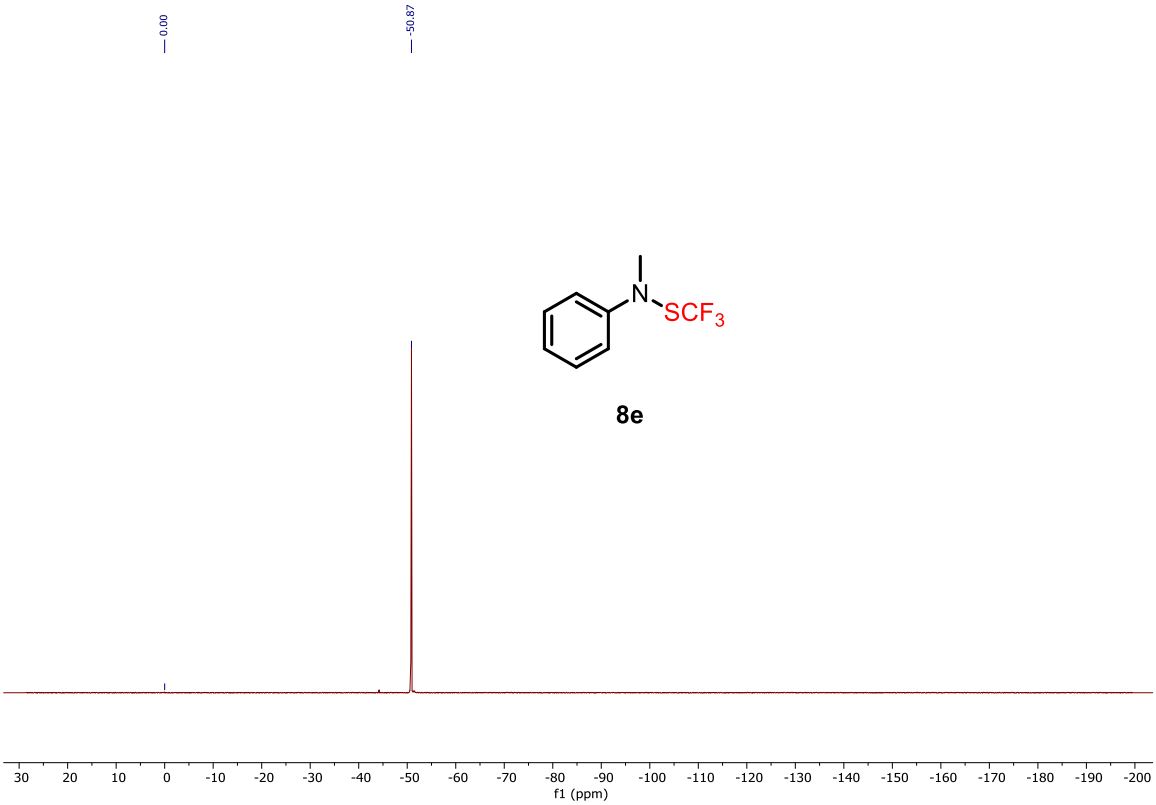
^{1}H NMR (400 MHz, $CDCl_3$) 8d



^{19}F NMR (376 MHz, $CDCl_3$) yield of 8e

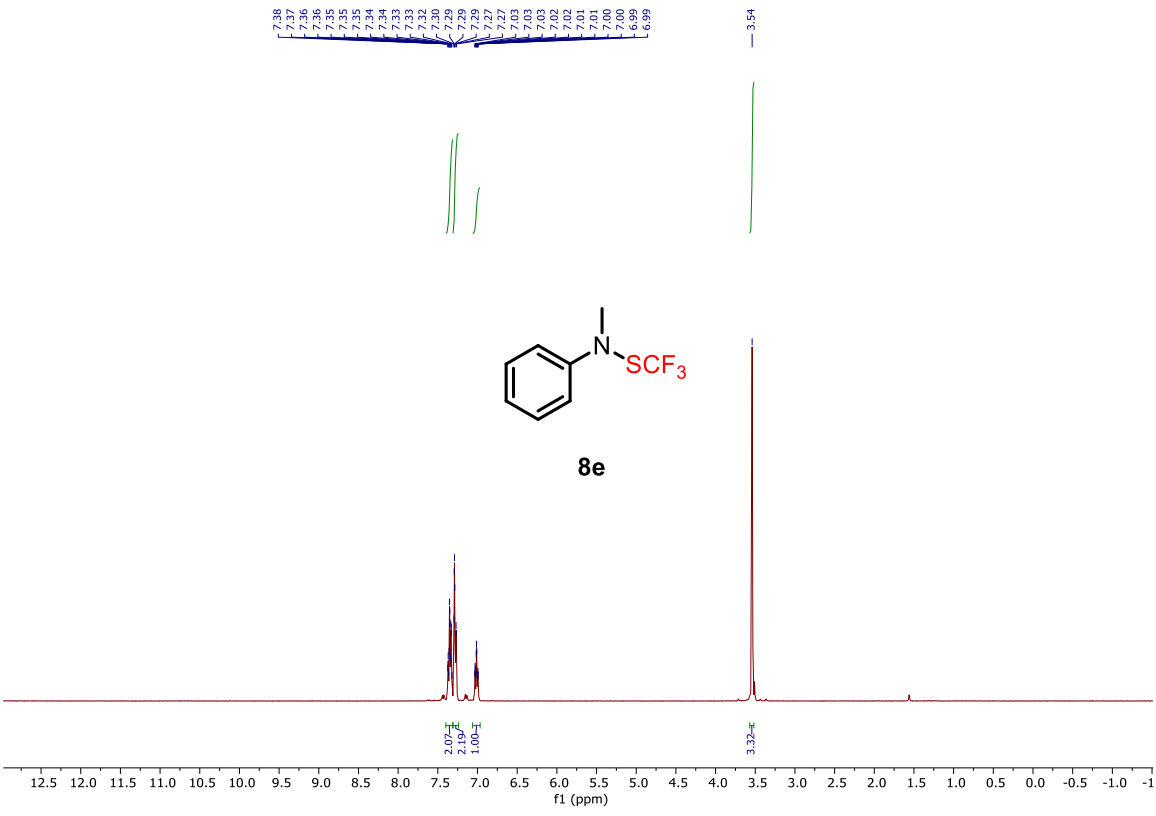


^{19}F NMR (376 MHz, $CDCl_3$) 8e



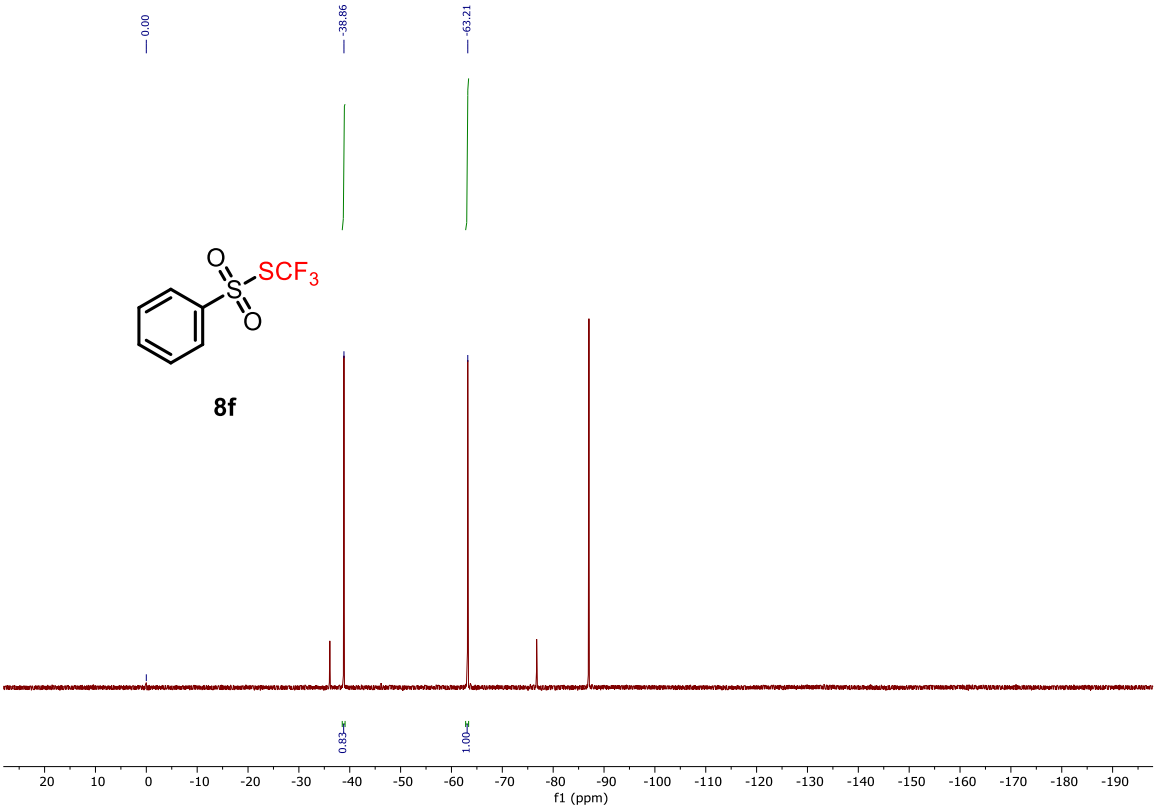
8e

^{1}H NMR (400 MHz, $CDCl_3$) 8e

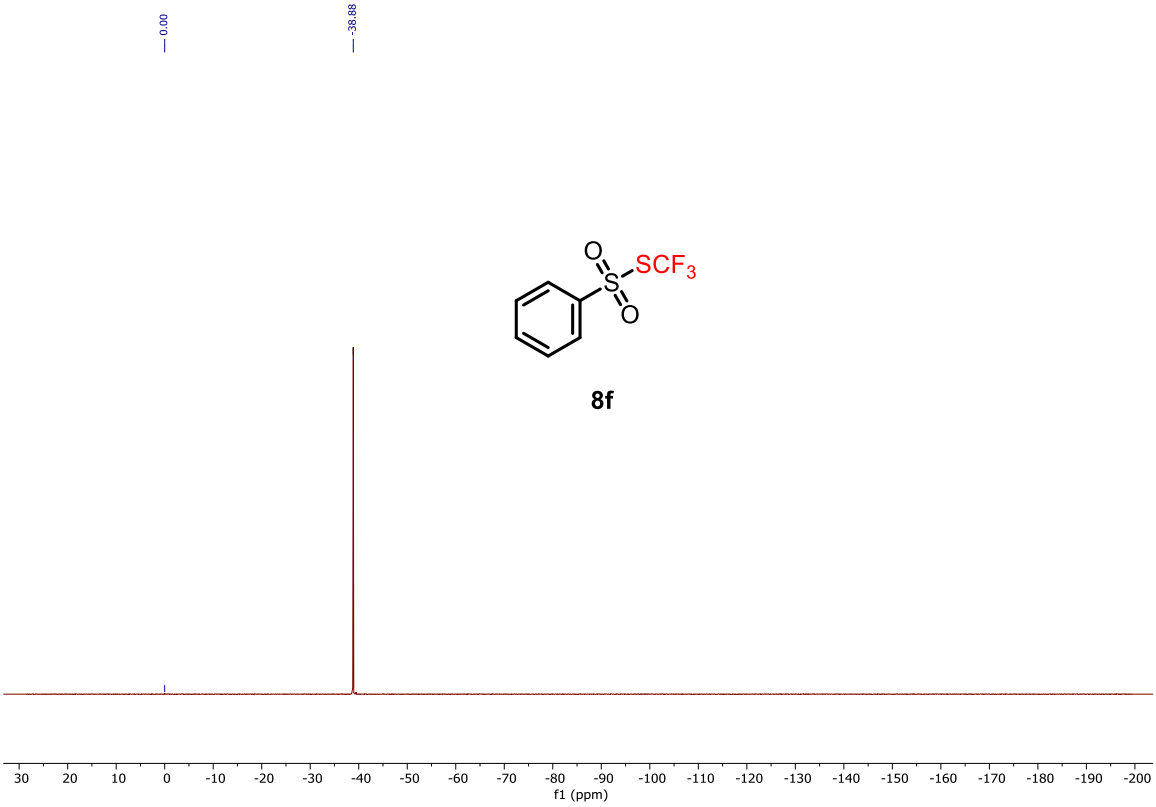


8e

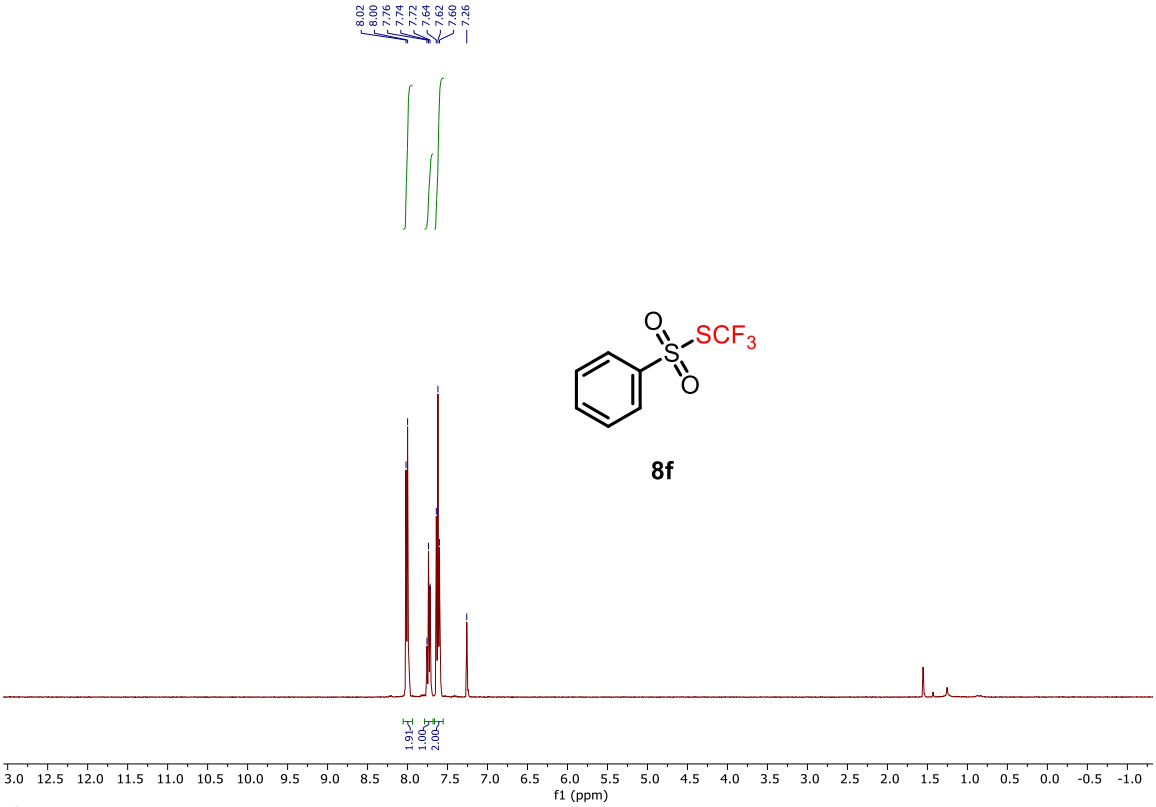
^{19}F NMR (376 MHz, $CDCl_3$) yield of 8f



^{19}F NMR (376 MHz, $CDCl_3$) 8f

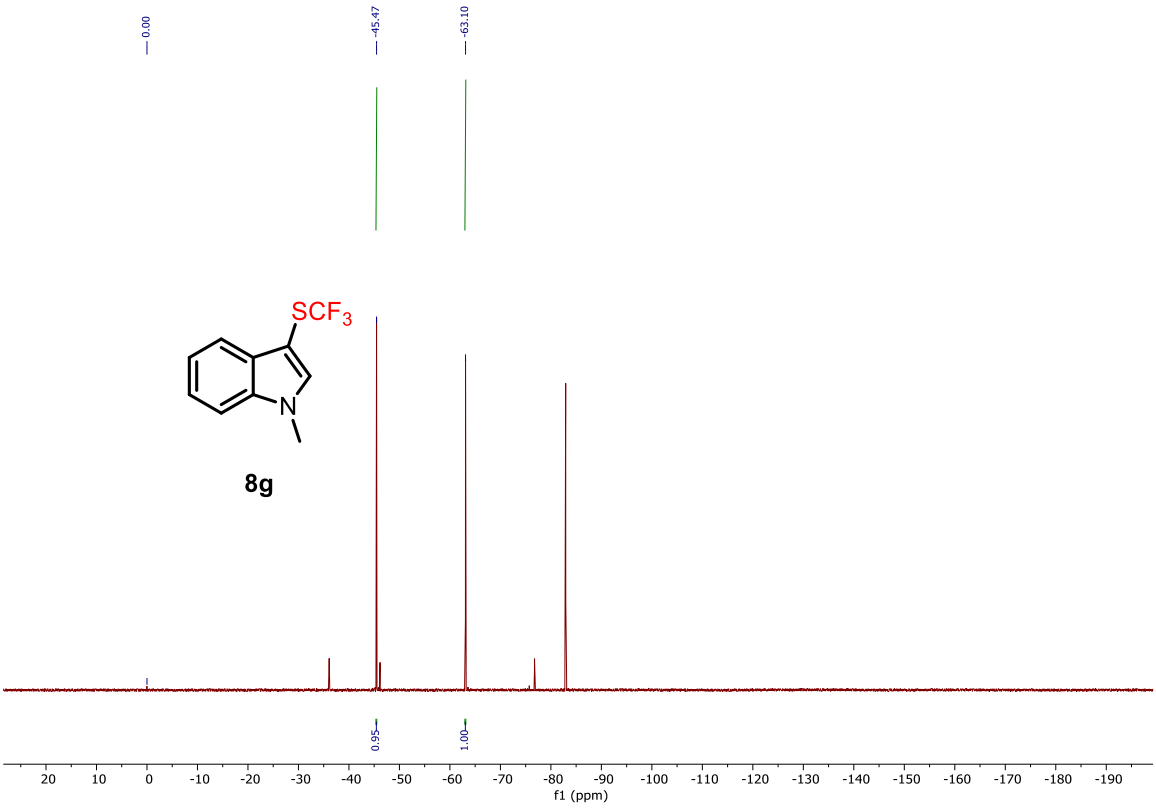


^{1}H NMR (400 MHz, $CDCl_3$) 8f



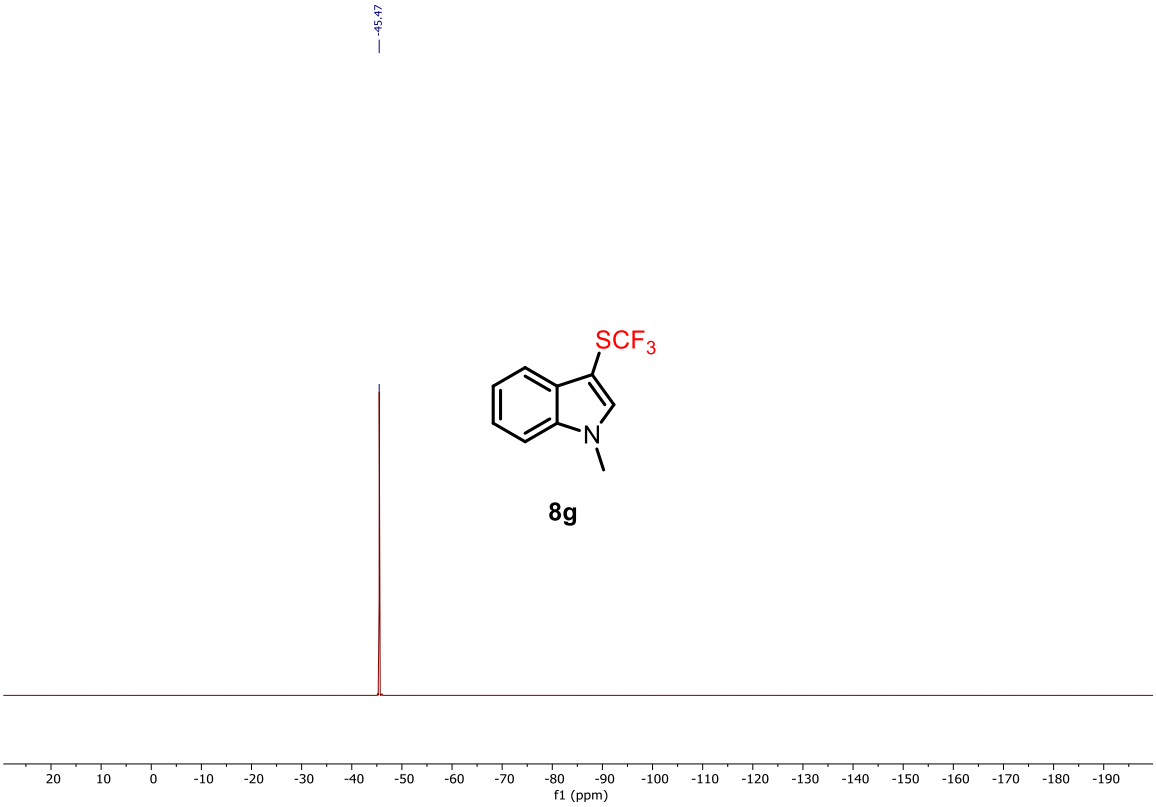
8f

^{19}F NMR (376 MHz, $CDCl_3$) yield of 8g



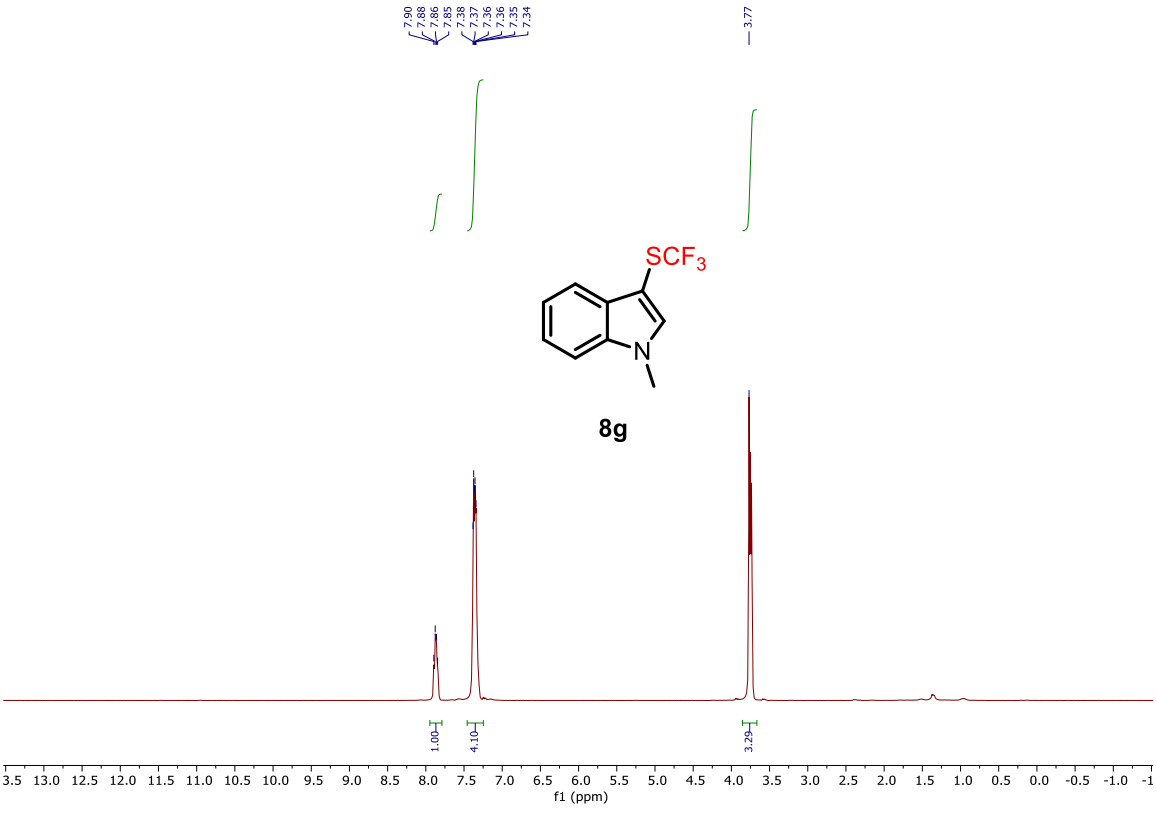
8g

^{19}F NMR (376 MHz, $CDCl_3$) 8g



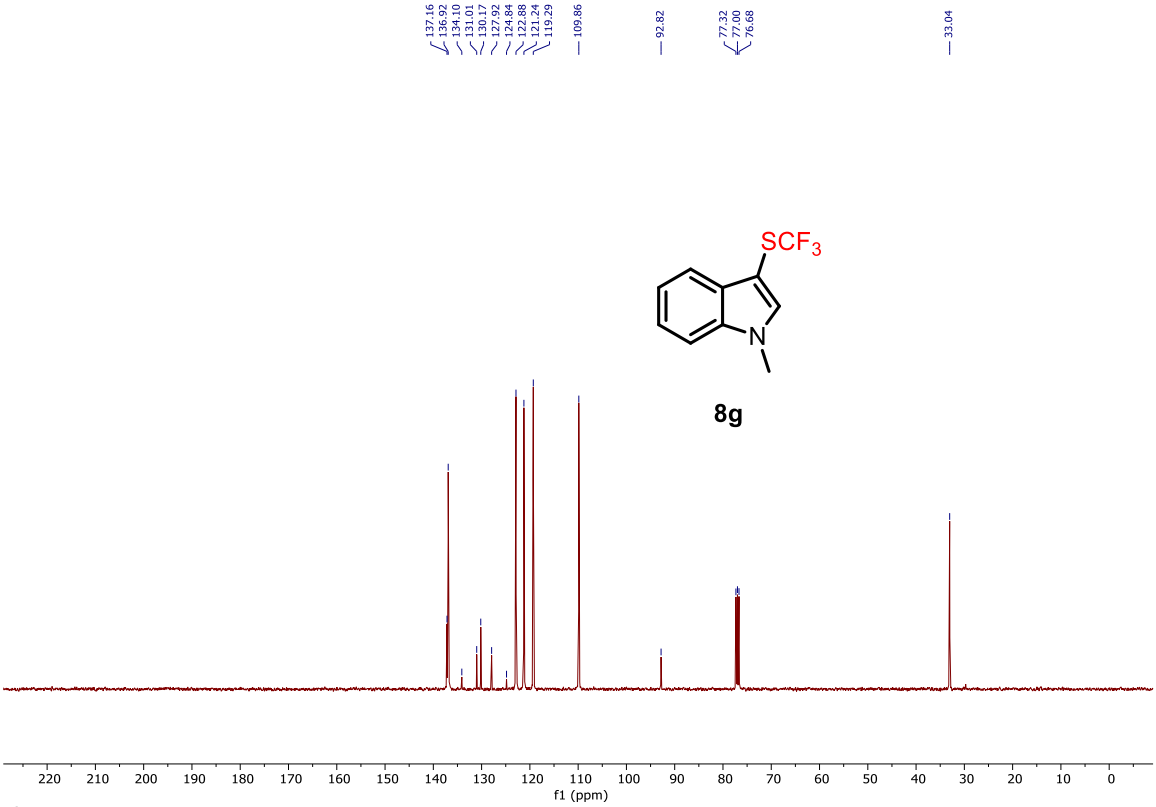
8g

^{1}H NMR (400 MHz, $CDCl_3$) 8g

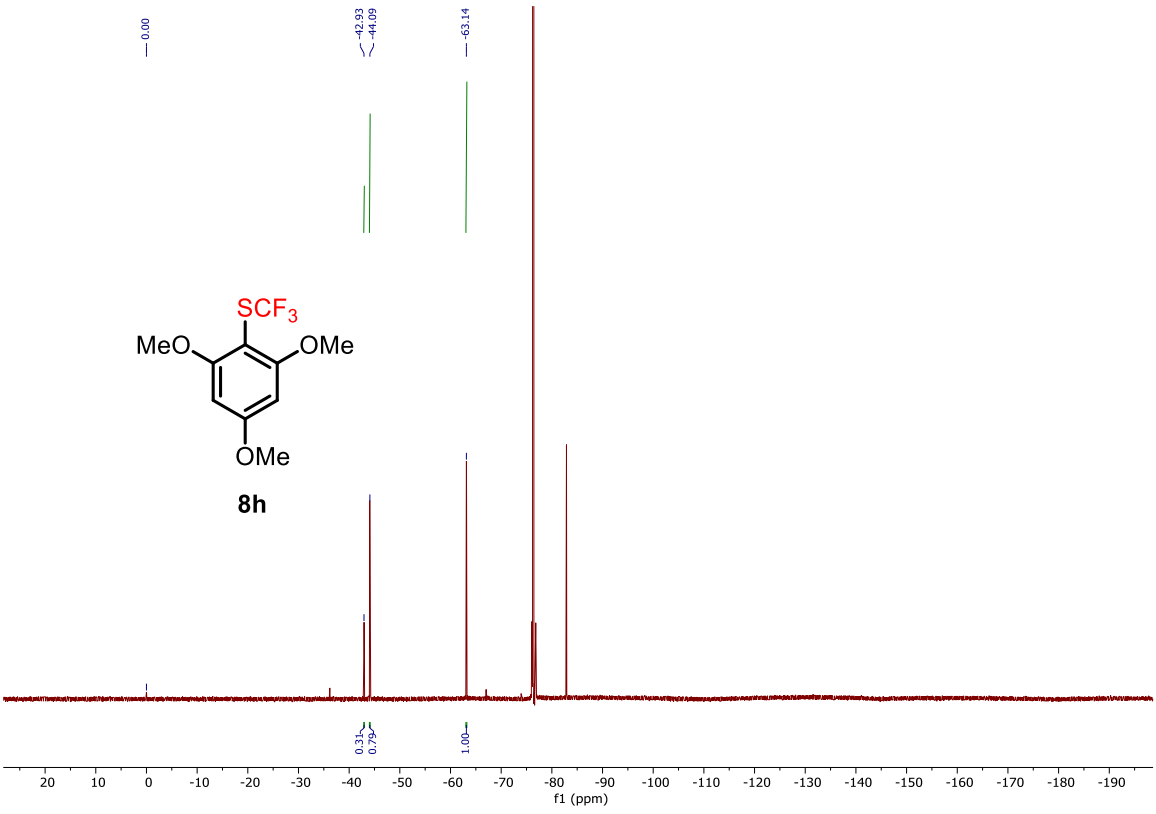


8g

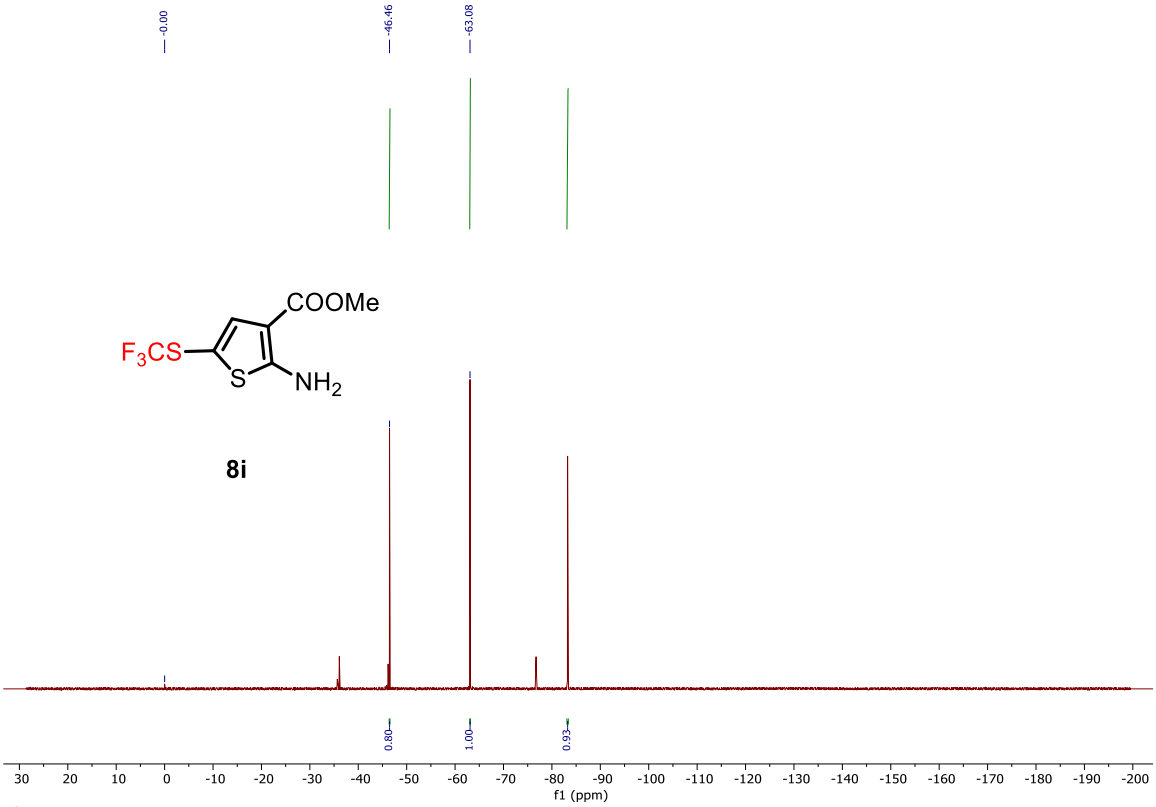
^{13}C NMR (100 MHz, $CDCl_3$) 8g



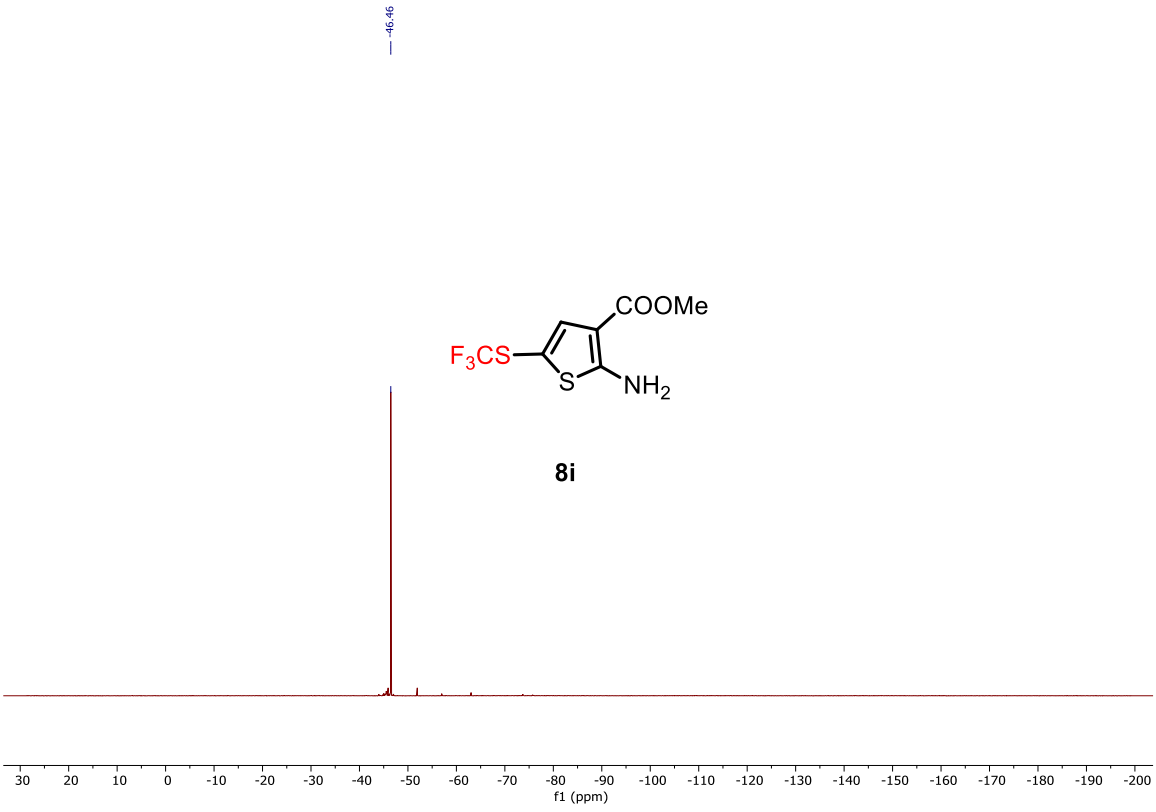
^{19}F NMR (376 MHz, $CDCl_3$) yield of 8h



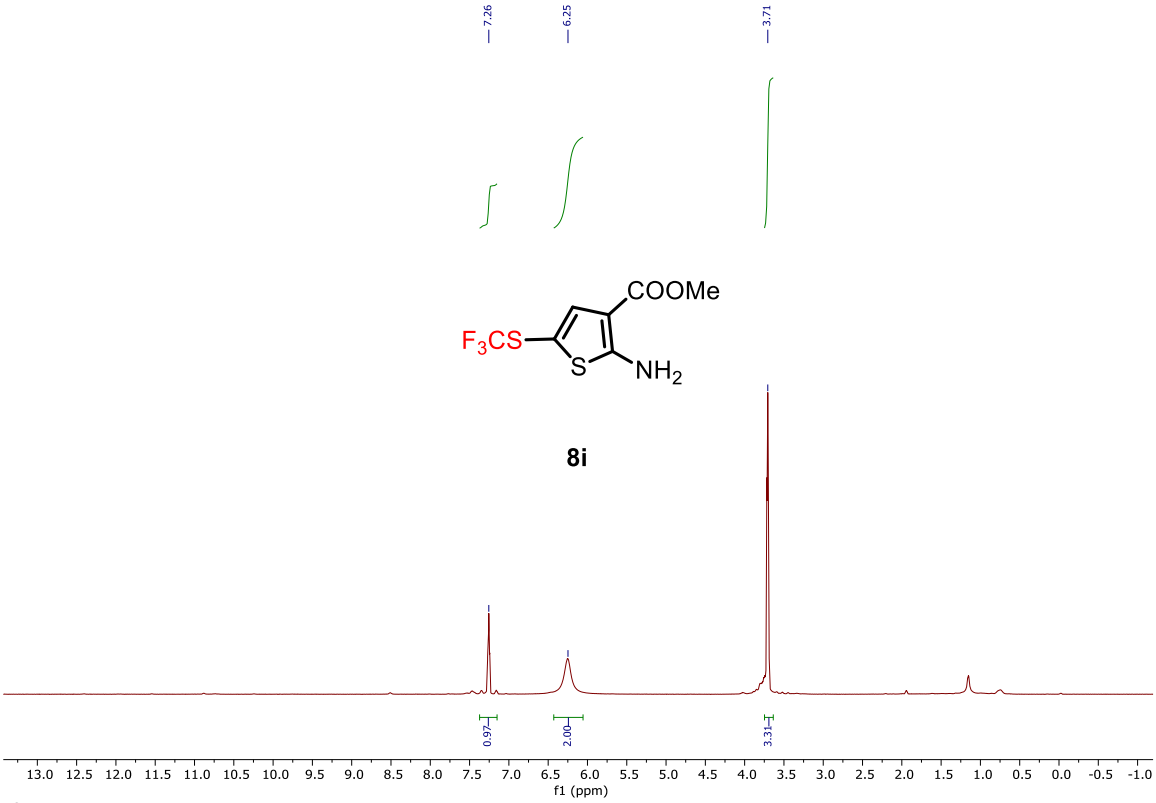
^{19}F NMR (376 MHz, $CDCl_3$) yield of 8i



^{19}F NMR (376 MHz, $CDCl_3$) 8i

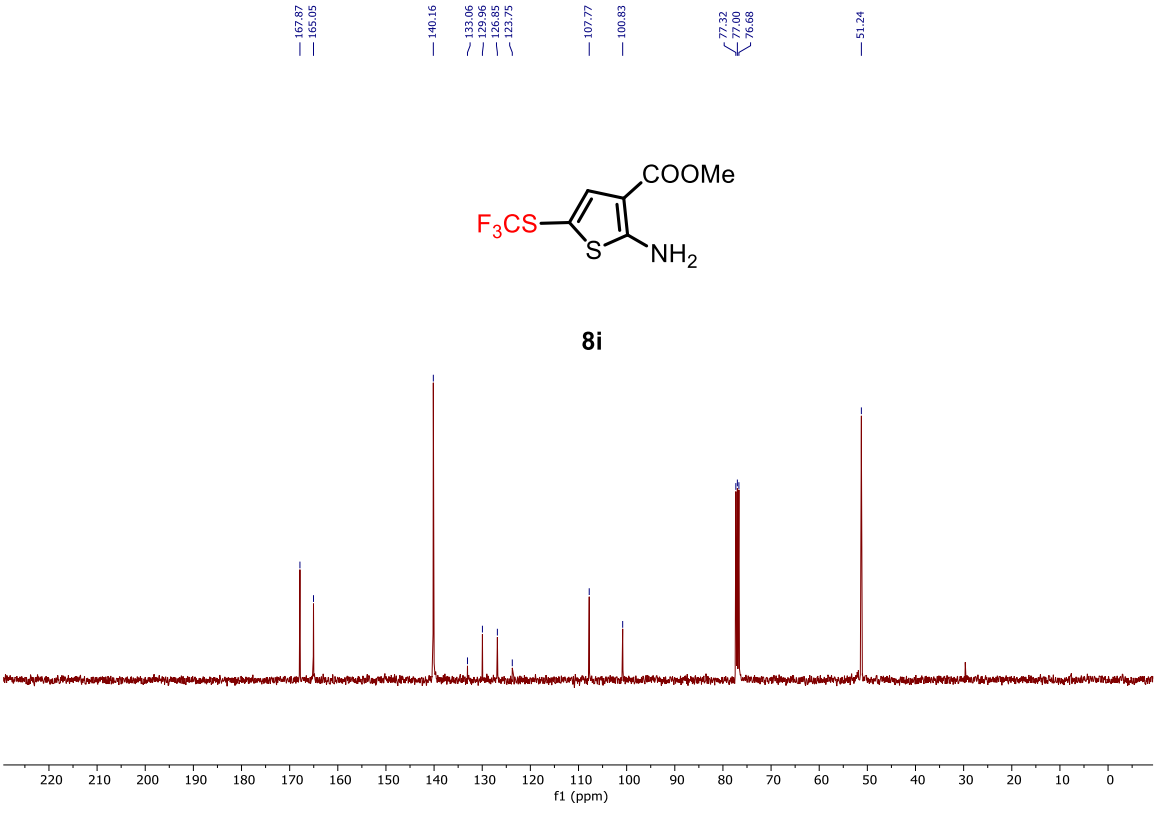


^{1}H NMR (400 MHz, $CDCl_3$) 8i



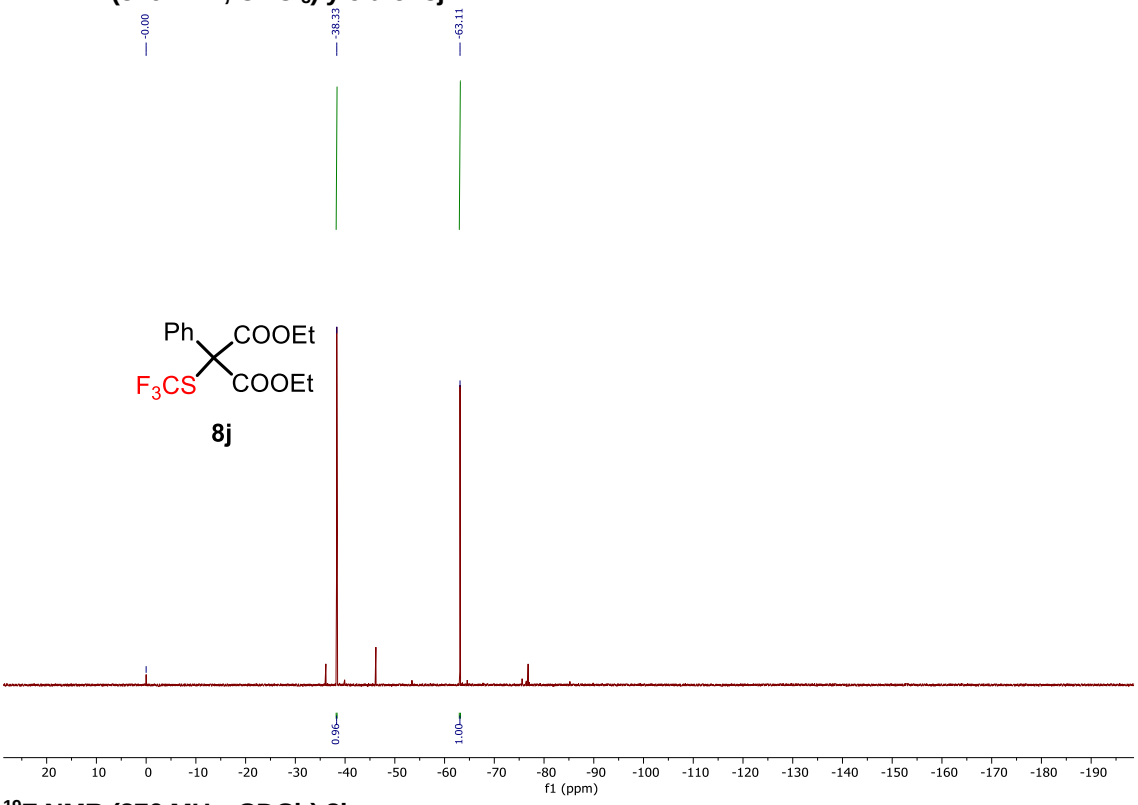
8i

^{13}C NMR (100 MHz, $CDCl_3$) 8i

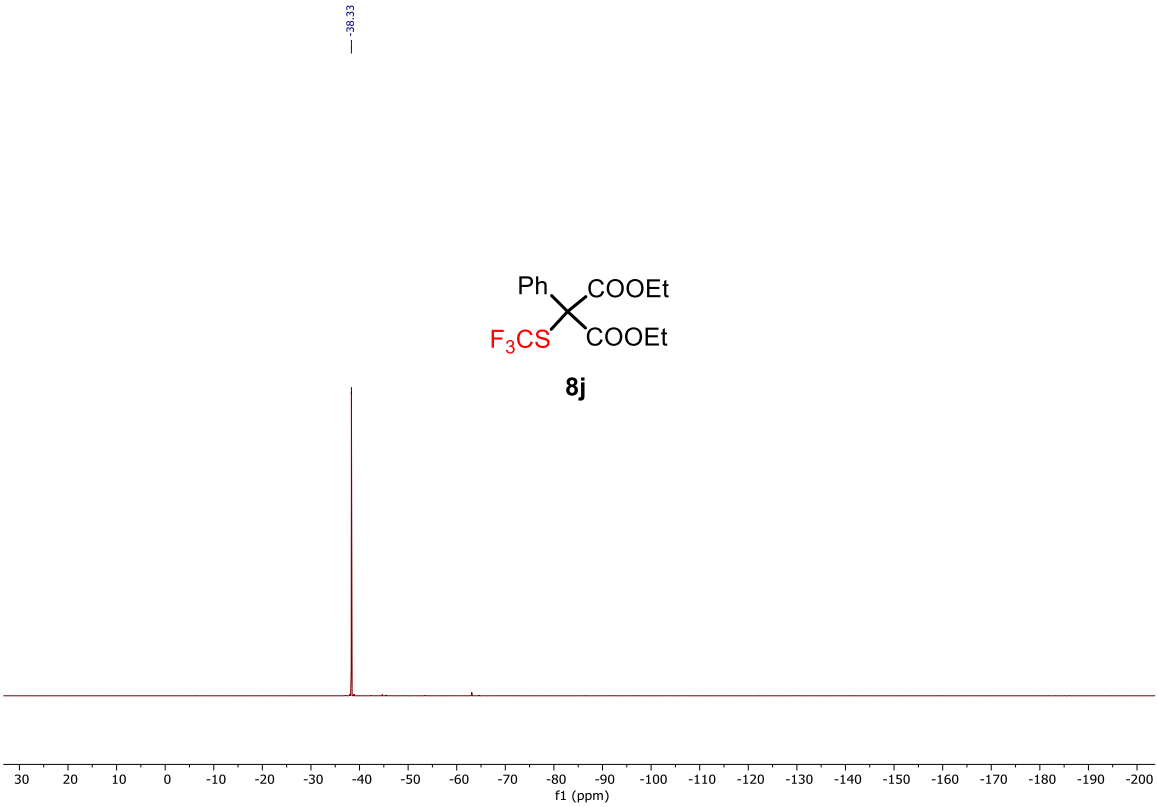


8i

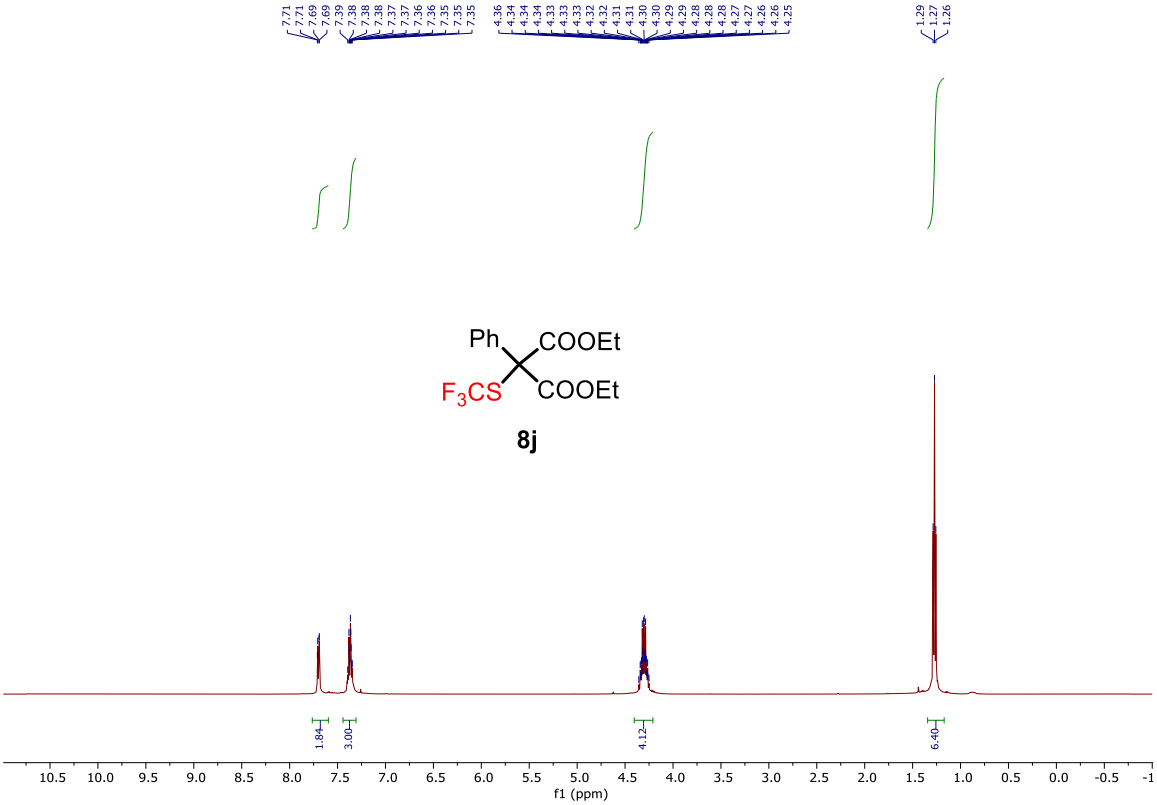
^{19}F NMR (376 MHz, $CDCl_3$) yield of 8j



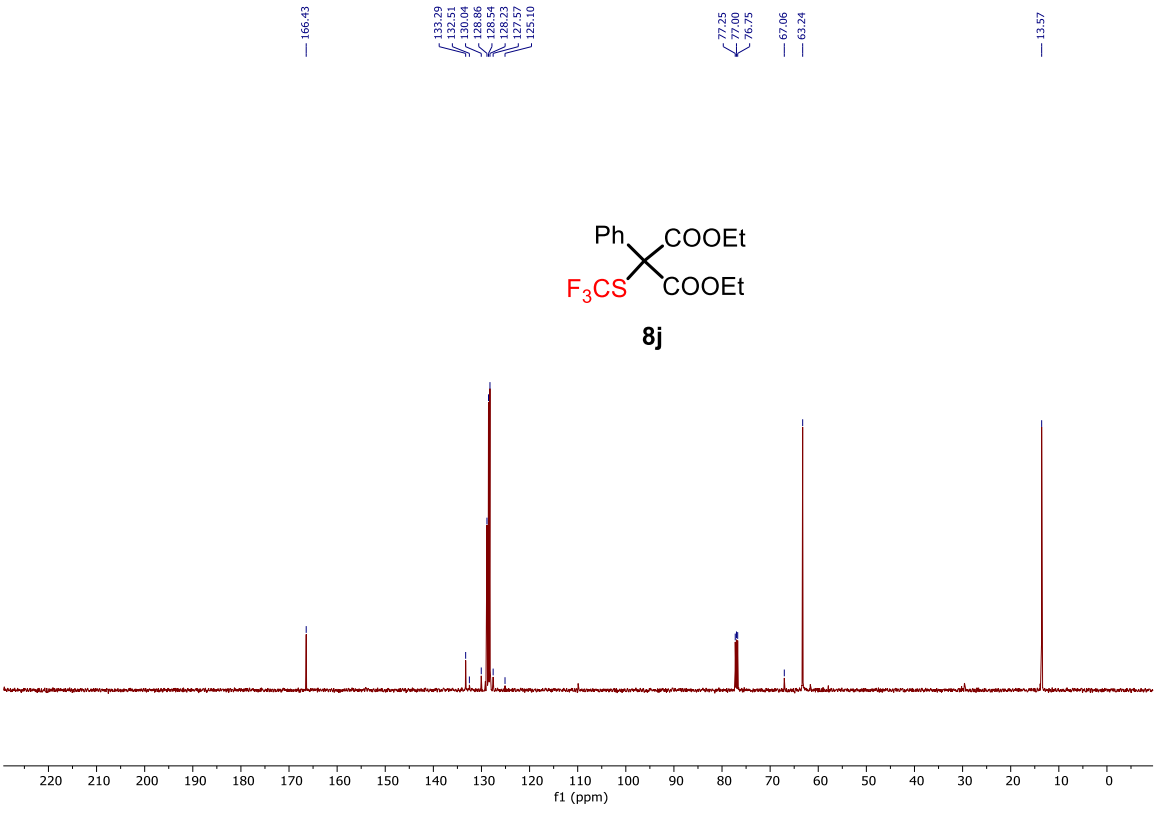
^{19}F NMR (376 MHz, $CDCl_3$) 8j



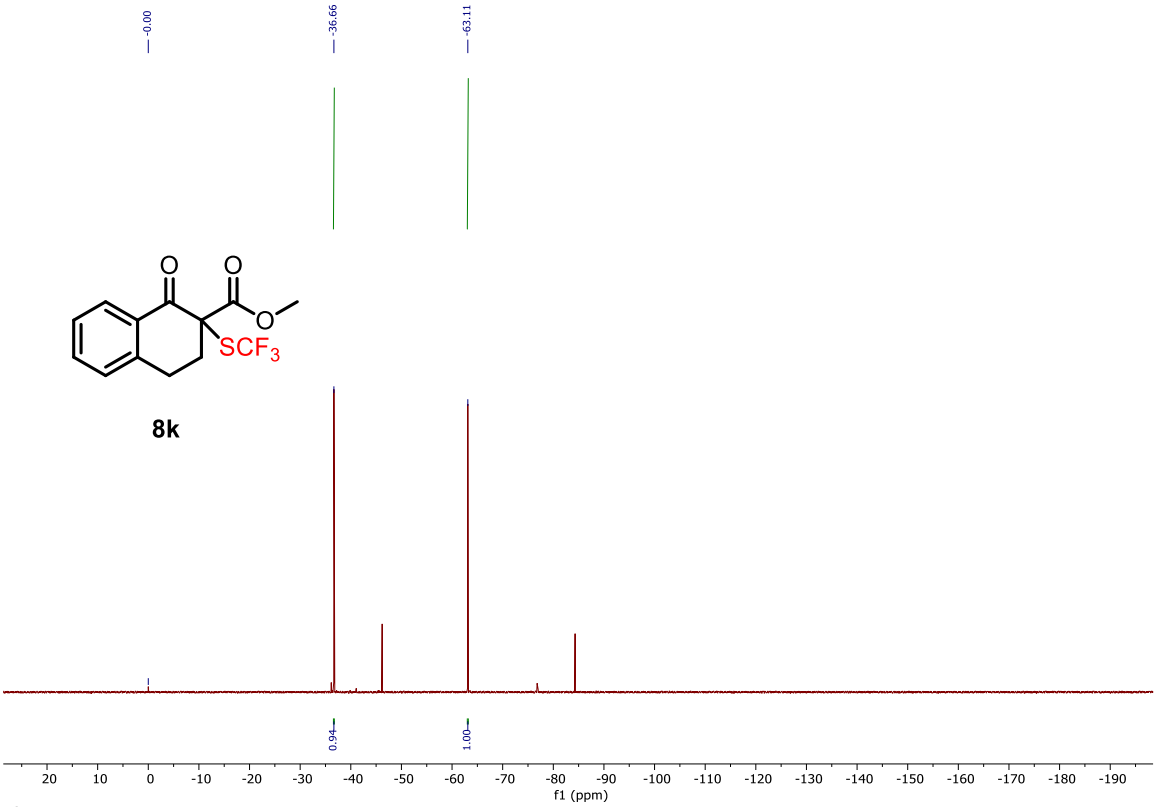
^{1}H NMR (500 MHz, $CDCl_3$) 8j



^{13}C NMR (126 MHz, $CDCl_3$) 8j

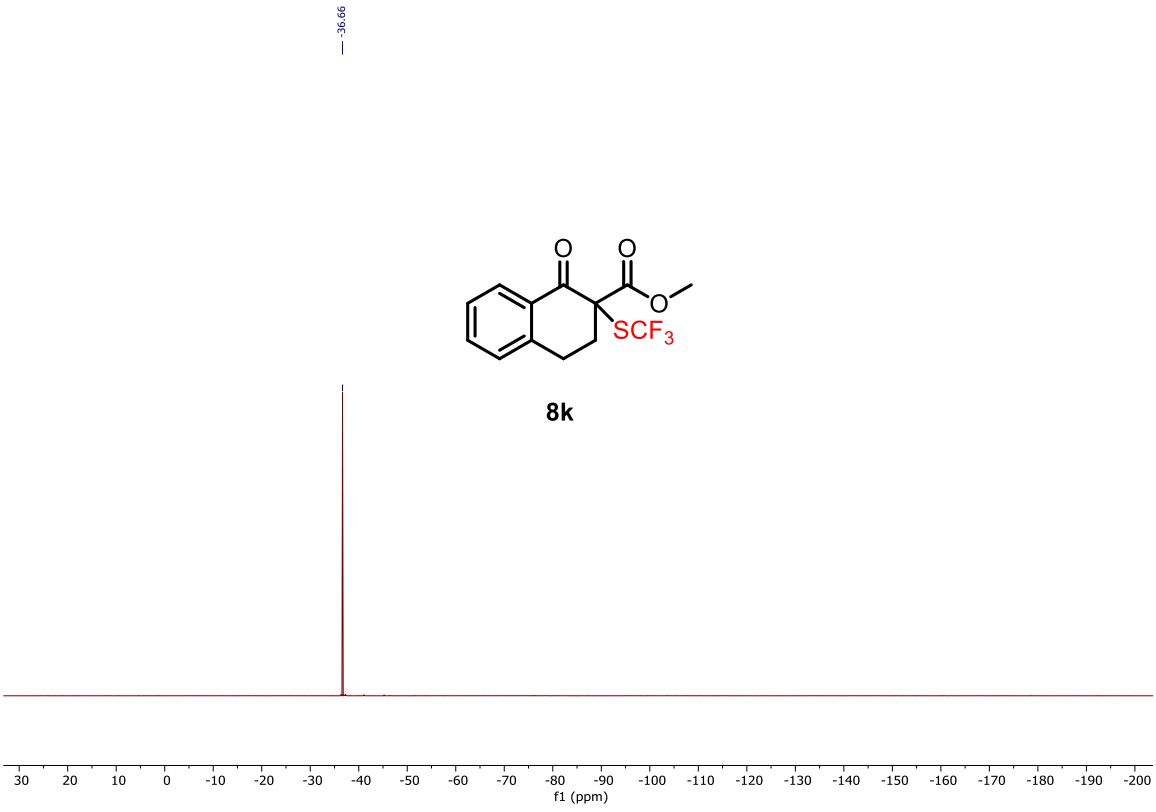


^{19}F NMR (376 MHz, $CDCl_3$) yield of 8k



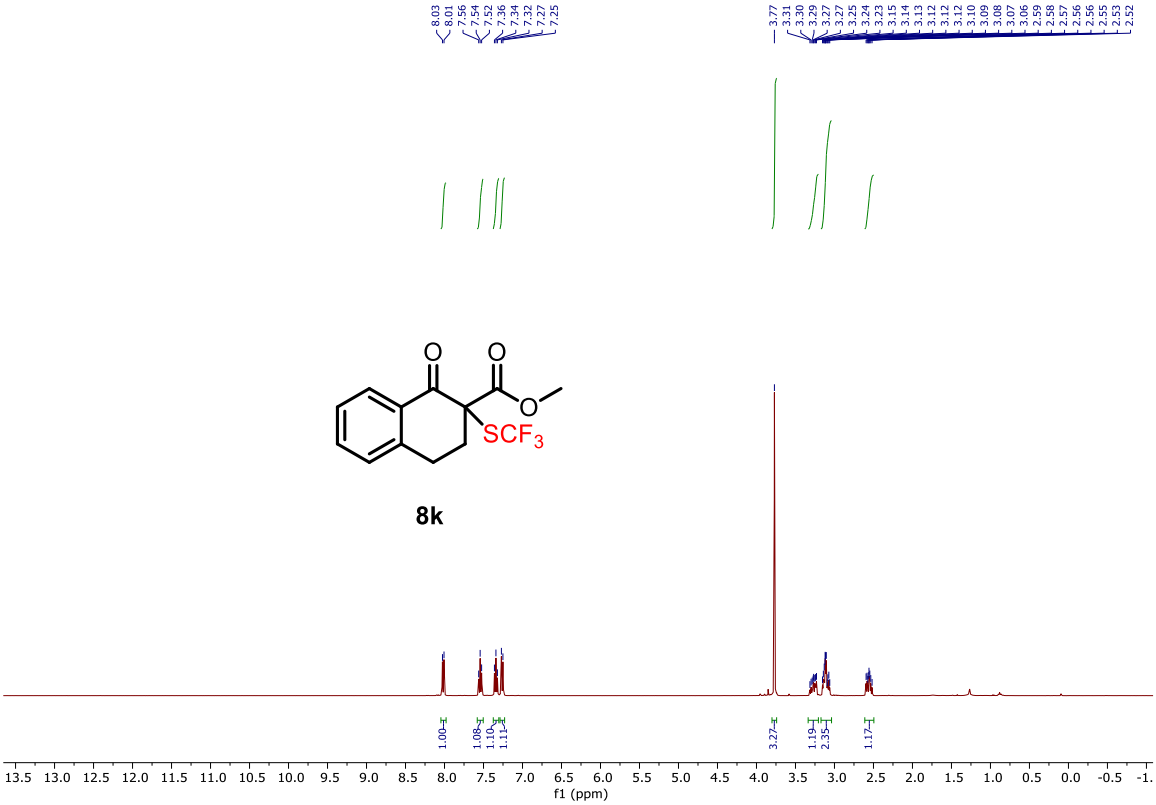
8k

^{19}F NMR (376 MHz, $CDCl_3$) 8k



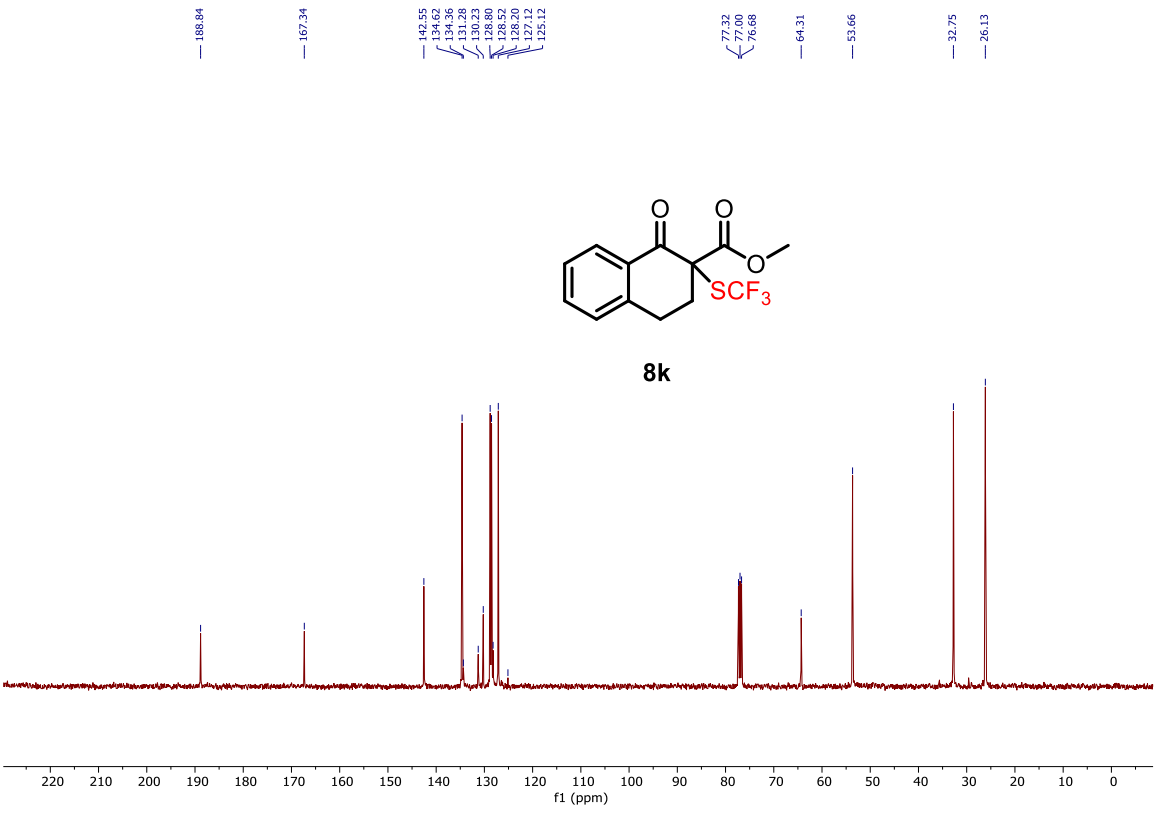
8k

^{1}H NMR (400 MHz, $CDCl_3$) 8k



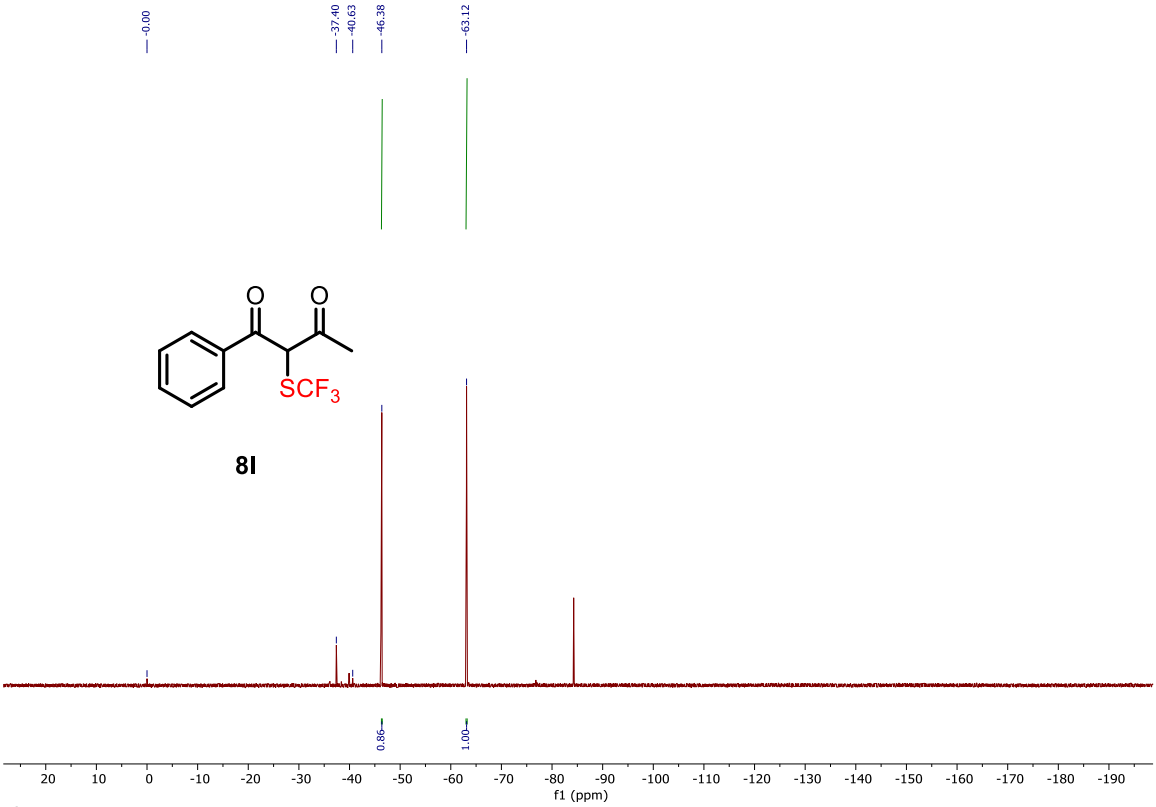
8k

^{13}C NMR (400 MHz, $CDCl_3$) 8k



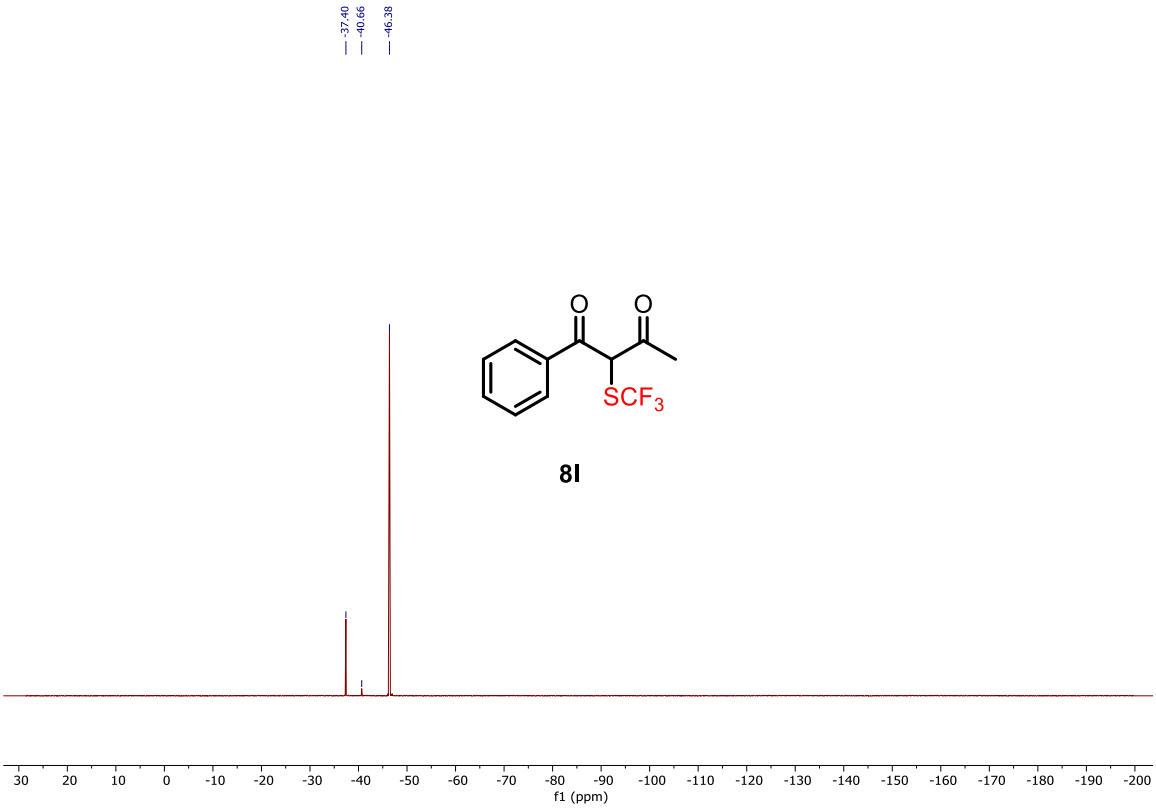
8k

^{19}F NMR (376 MHz, $CDCl_3$) yield of 8l



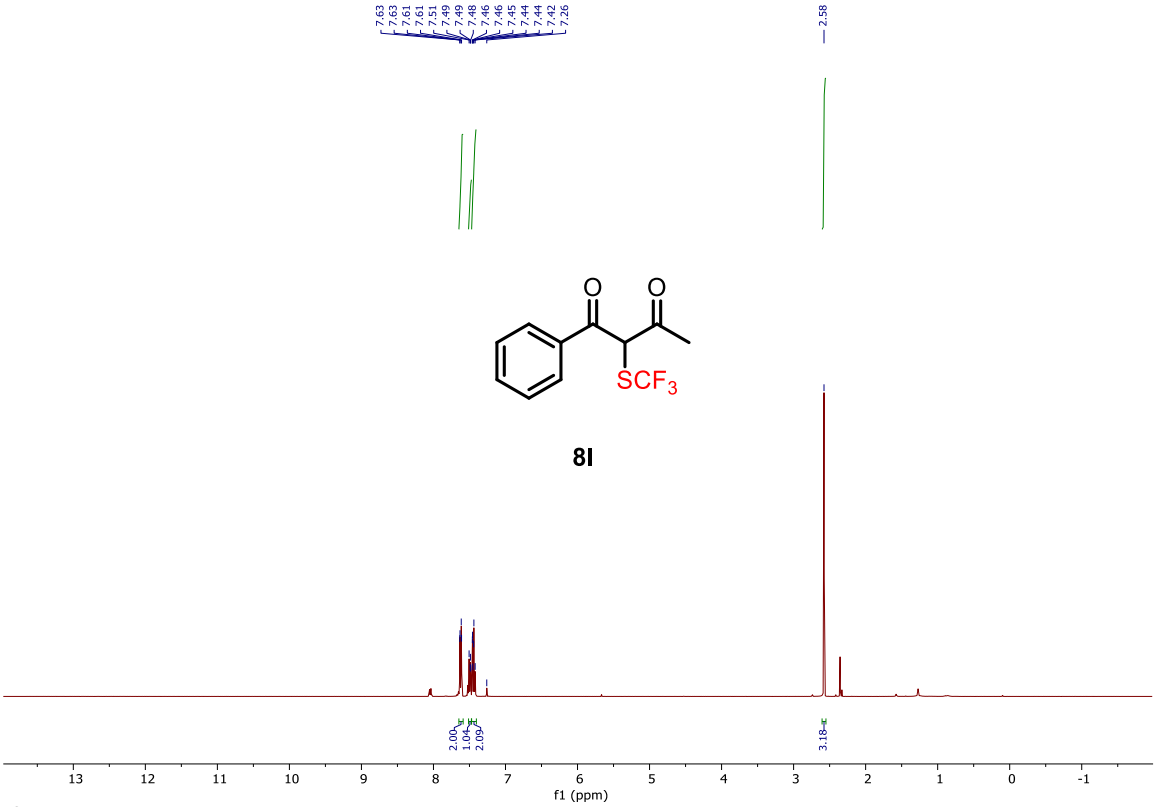
8l

^{19}F NMR (376 MHz, $CDCl_3$) 8l



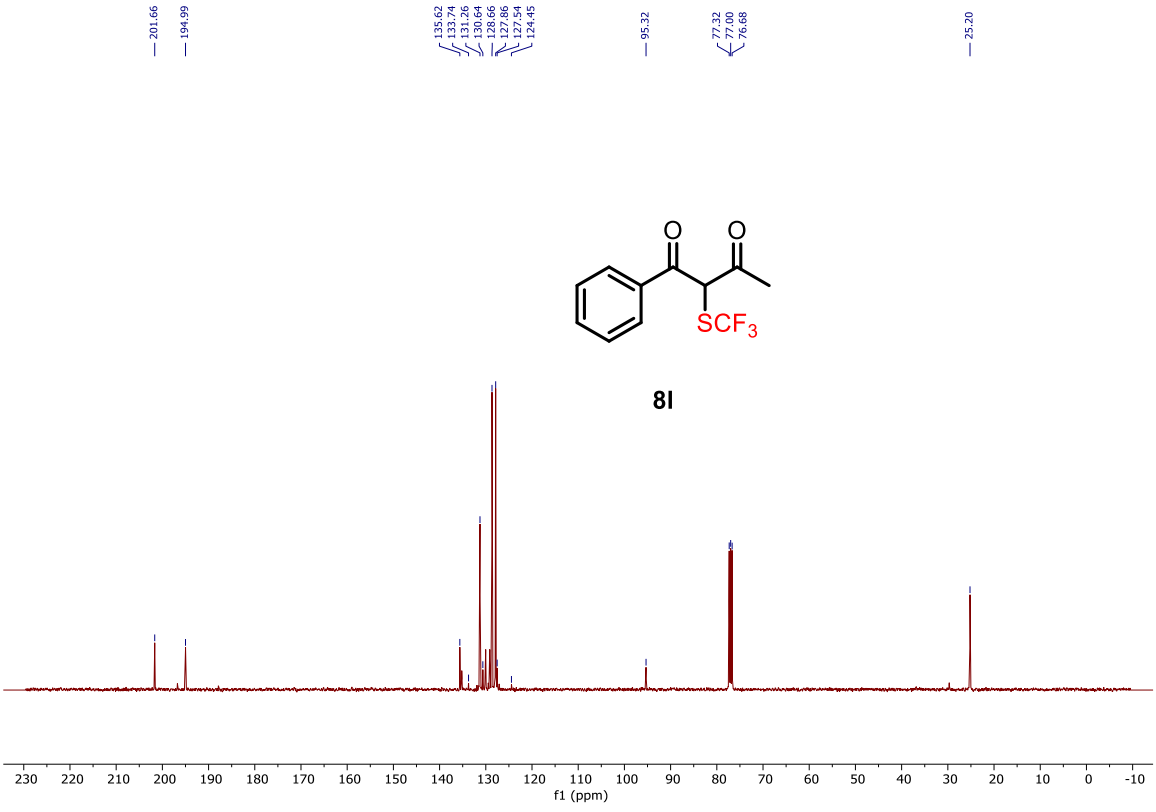
8l

^{1}H NMR (400 MHz, $CDCl_3$) 8l



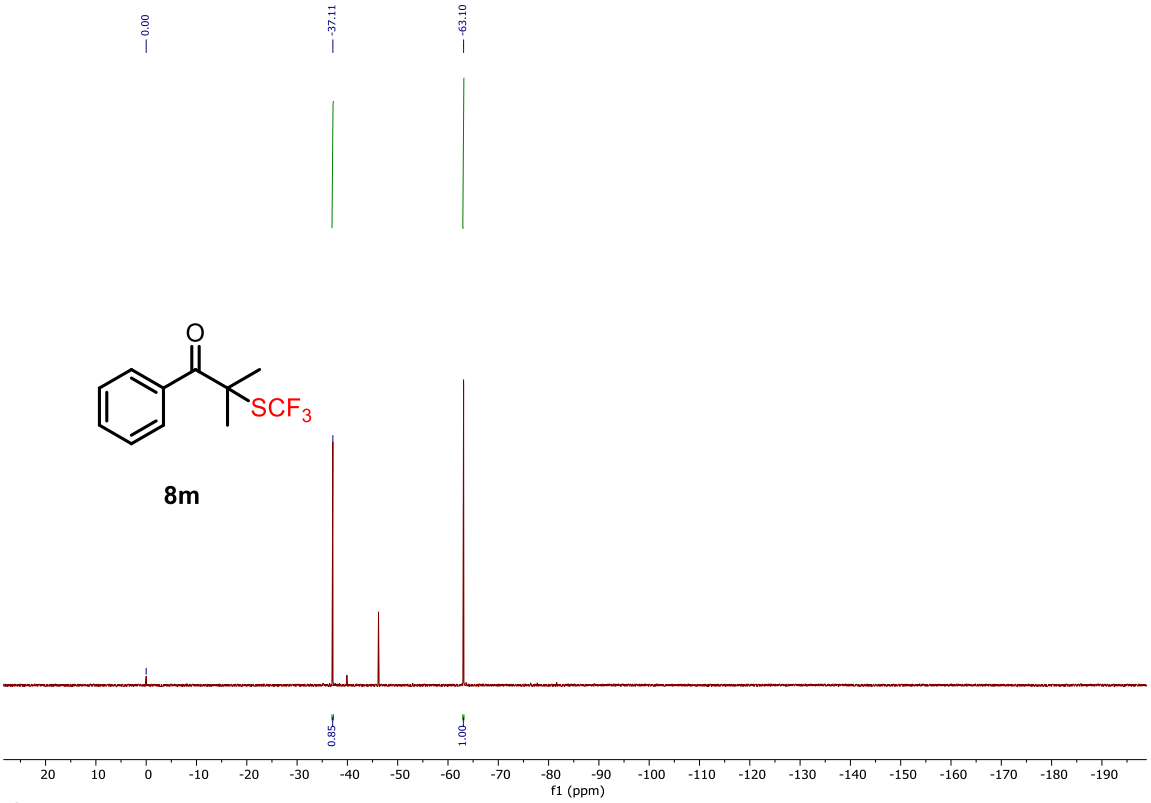
8l

^{13}C NMR (100 MHz, $CDCl_3$) 8l



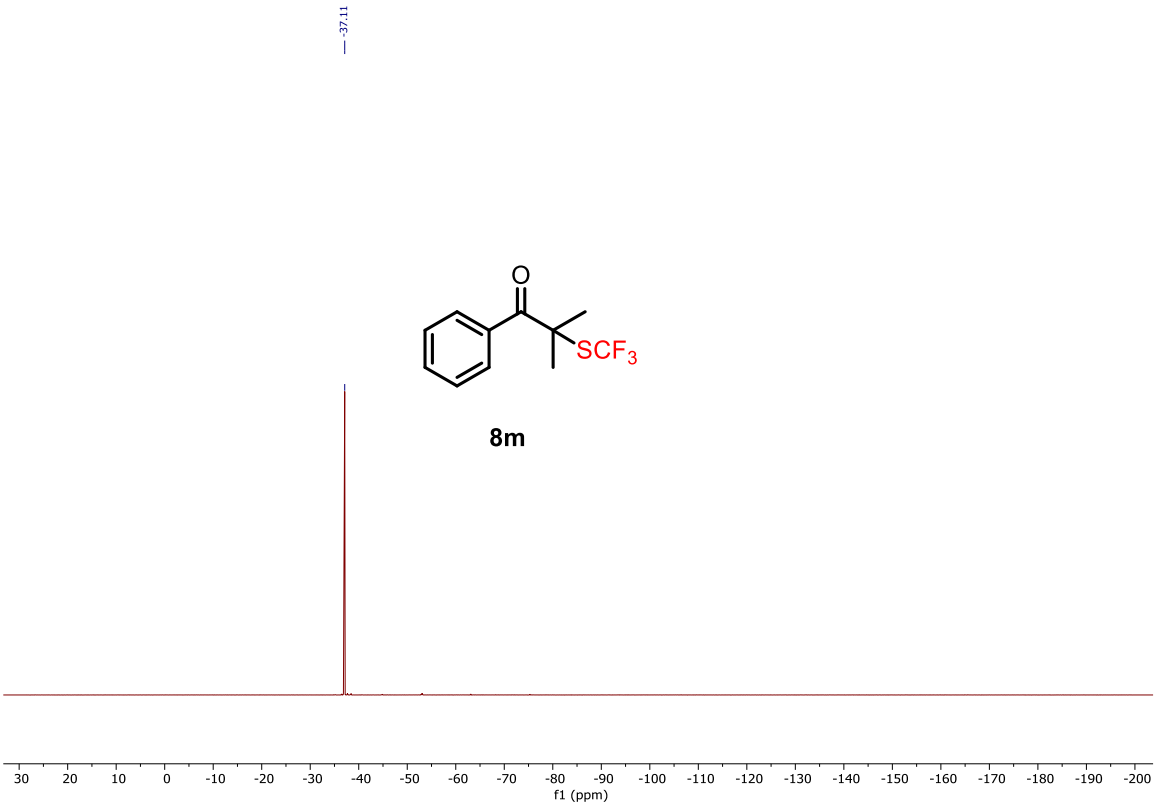
8l

^{19}F NMR (376 MHz, $CDCl_3$) yield of 8m



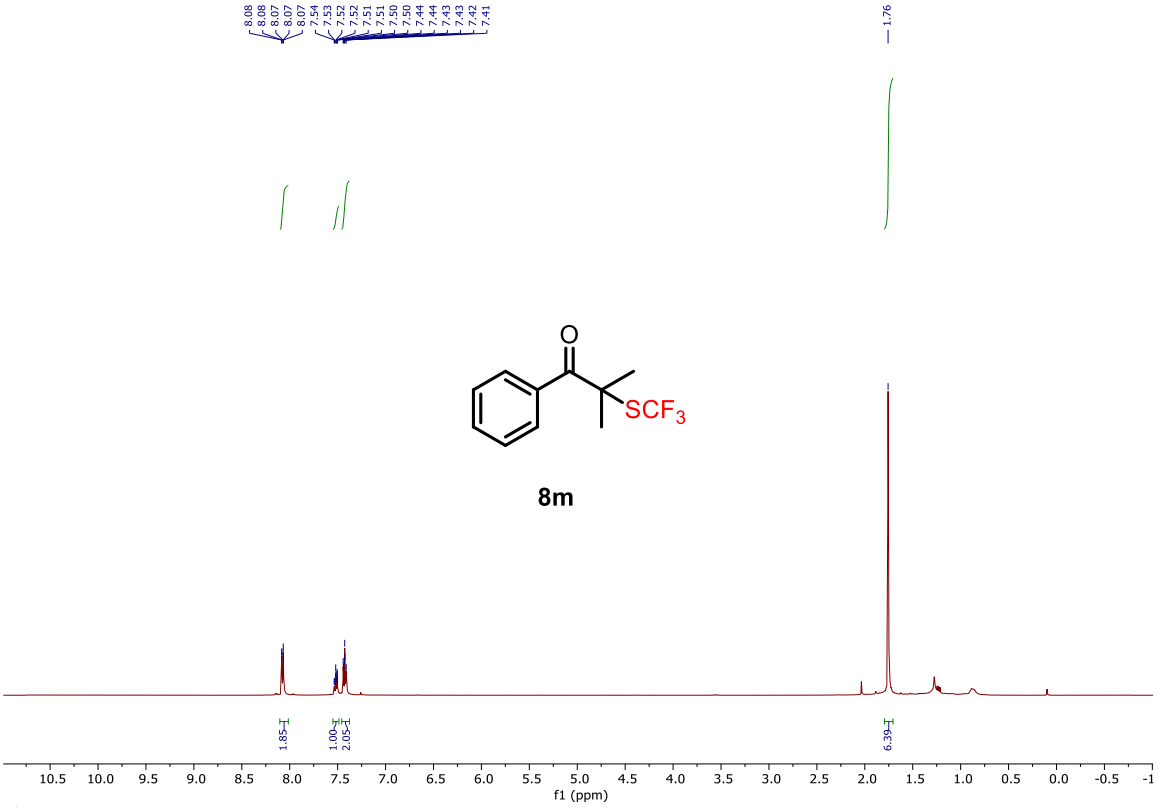
8m

^{19}F NMR (376 MHz, $CDCl_3$) 8m



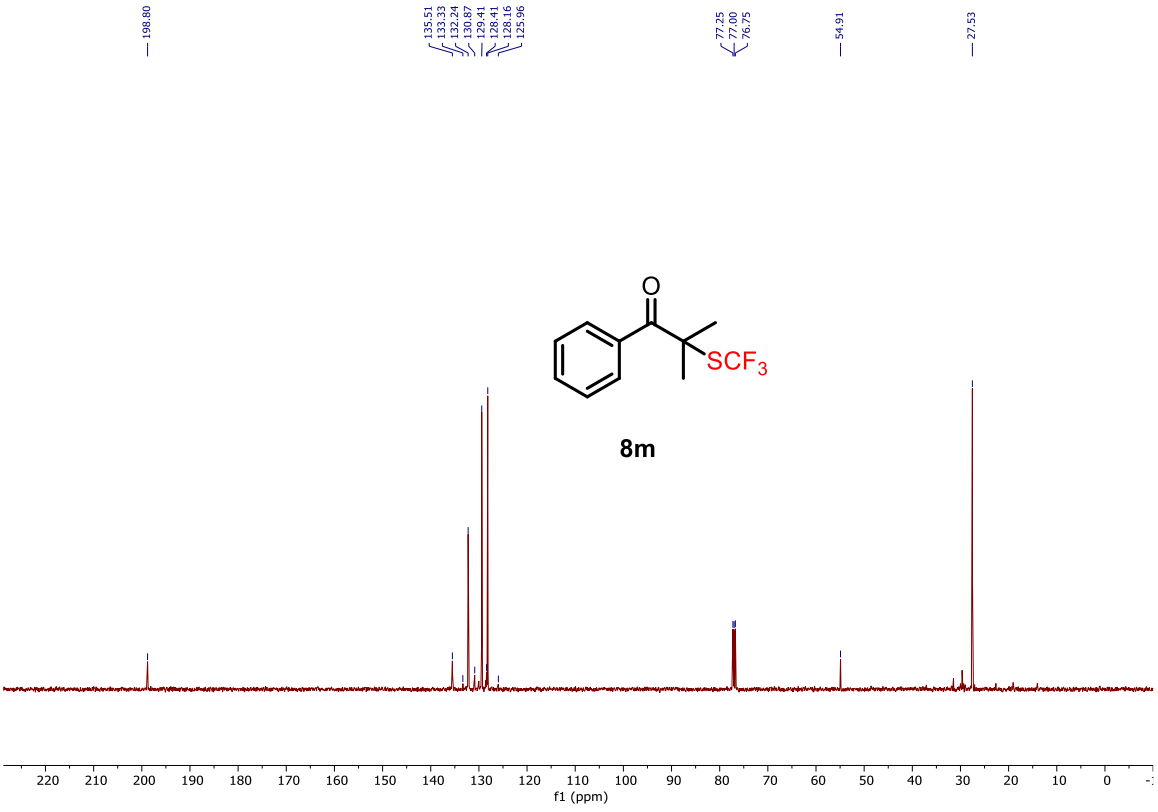
8m

^{1}H NMR (500 MHz, $CDCl_3$) 8m



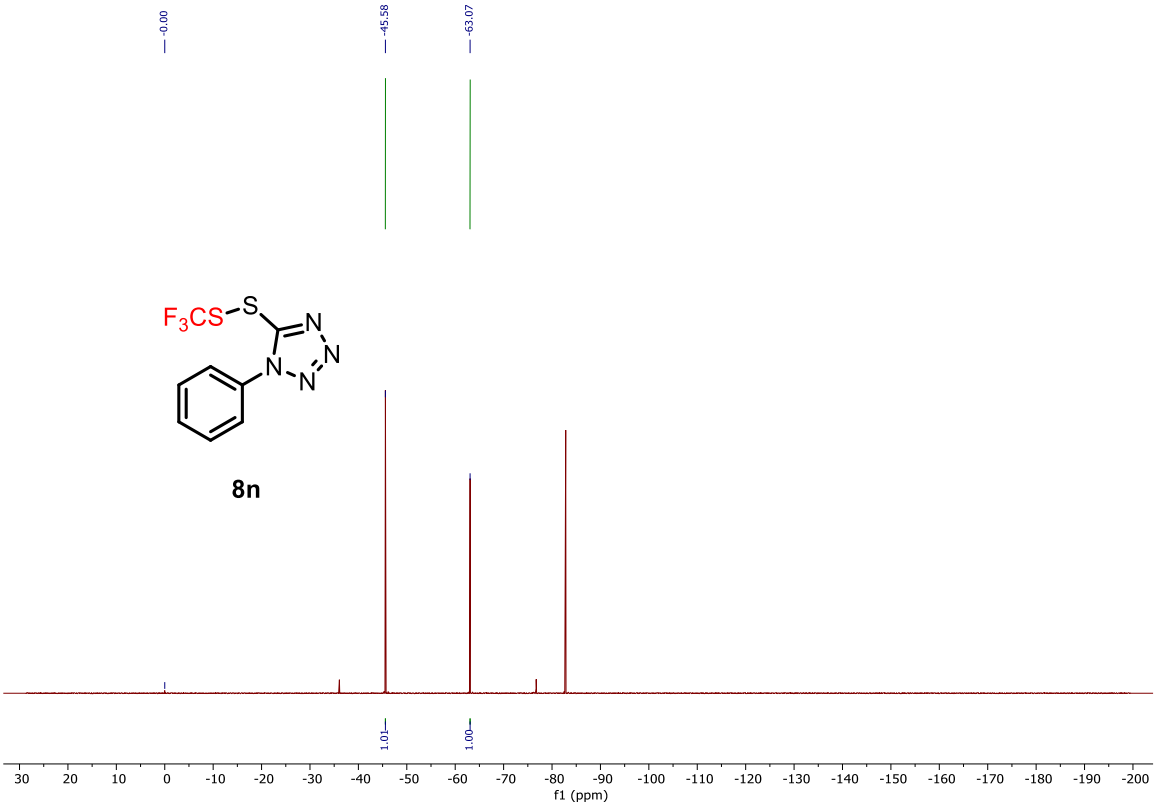
8m

^{13}C NMR (126 MHz, $CDCl_3$) 8m

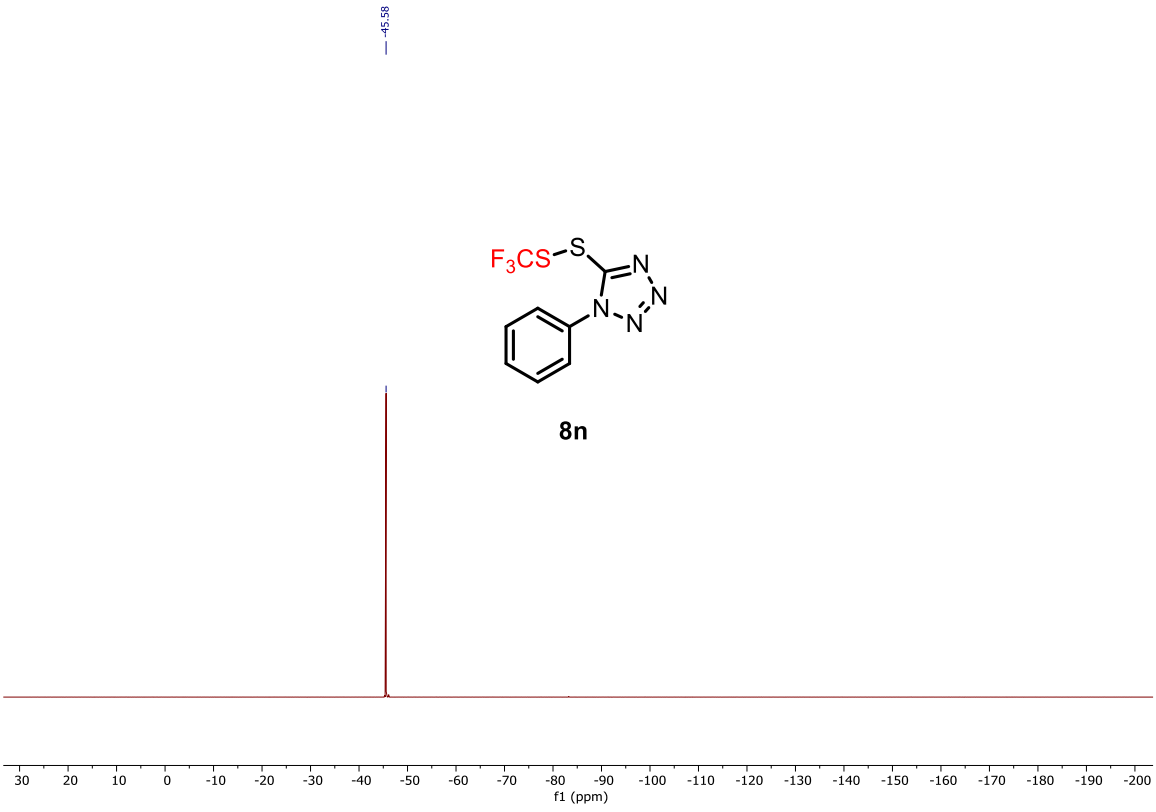


8m

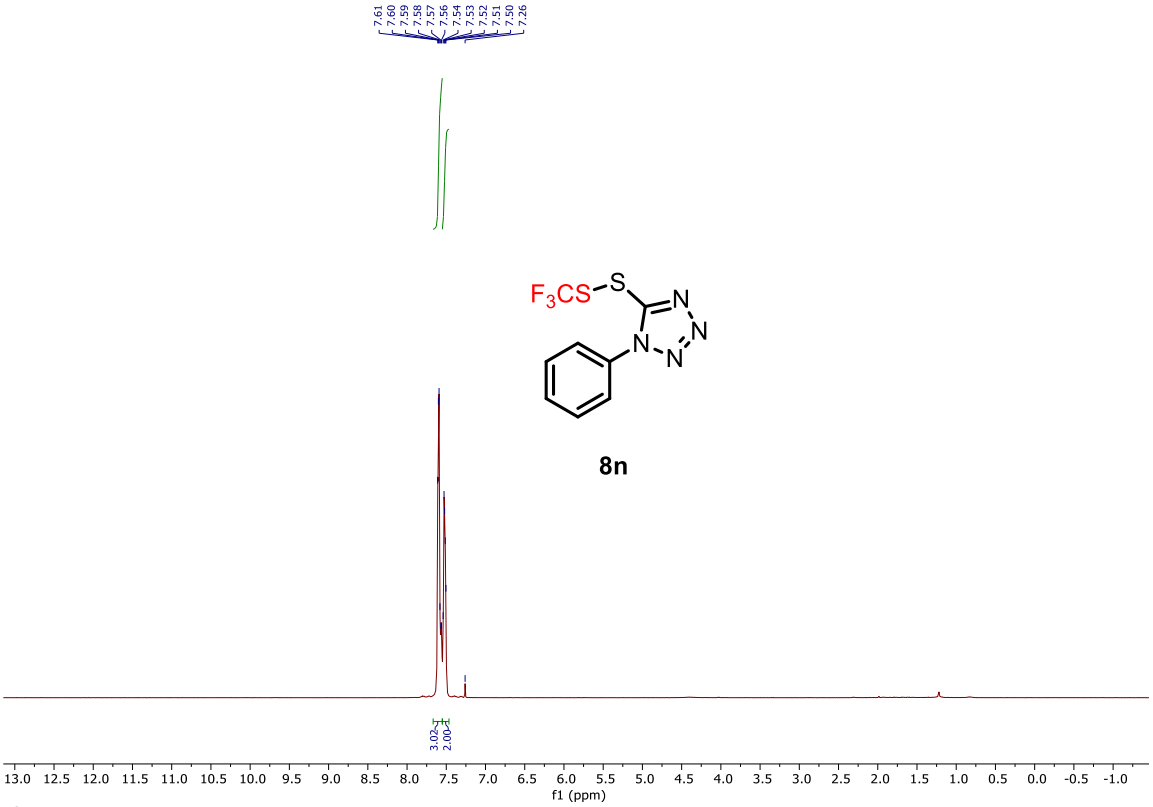
^{19}F NMR (376 MHz, $CDCl_3$) yield of 8n



^{19}F NMR (376 MHz, $CDCl_3$) 8n

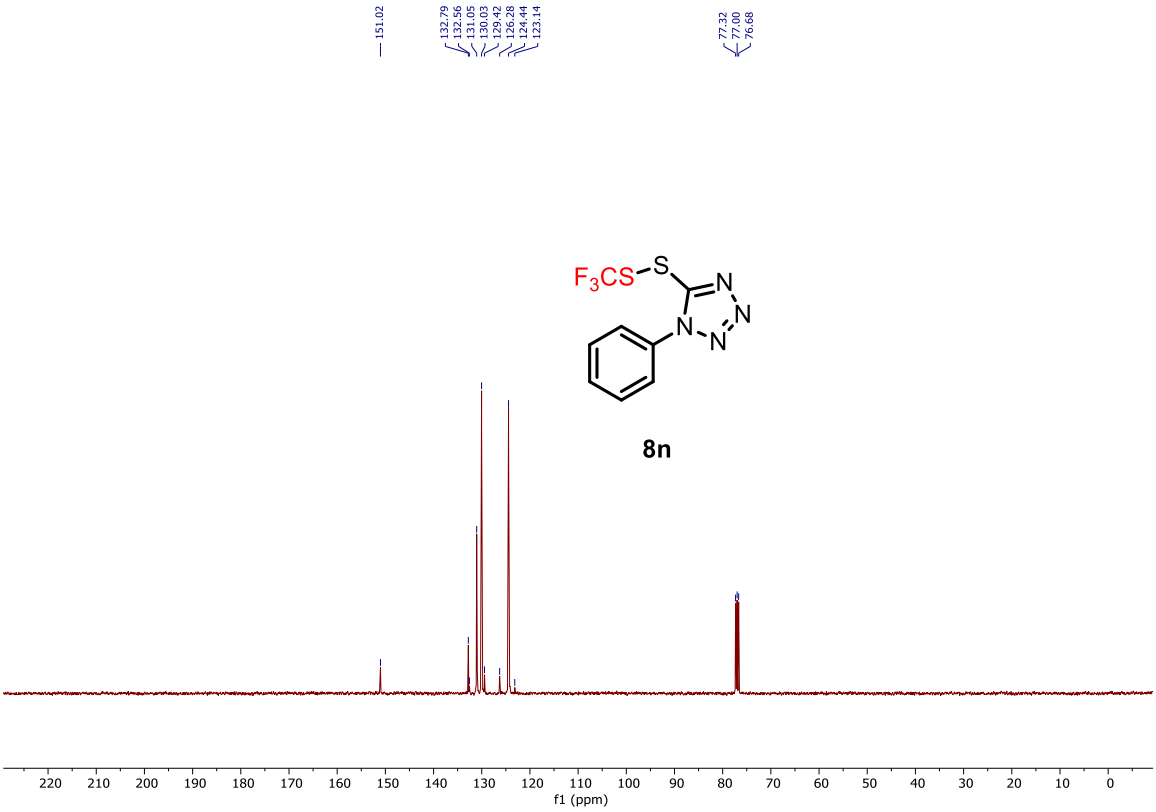


^{1}H NMR (400 MHz, $CDCl_3$) 8n



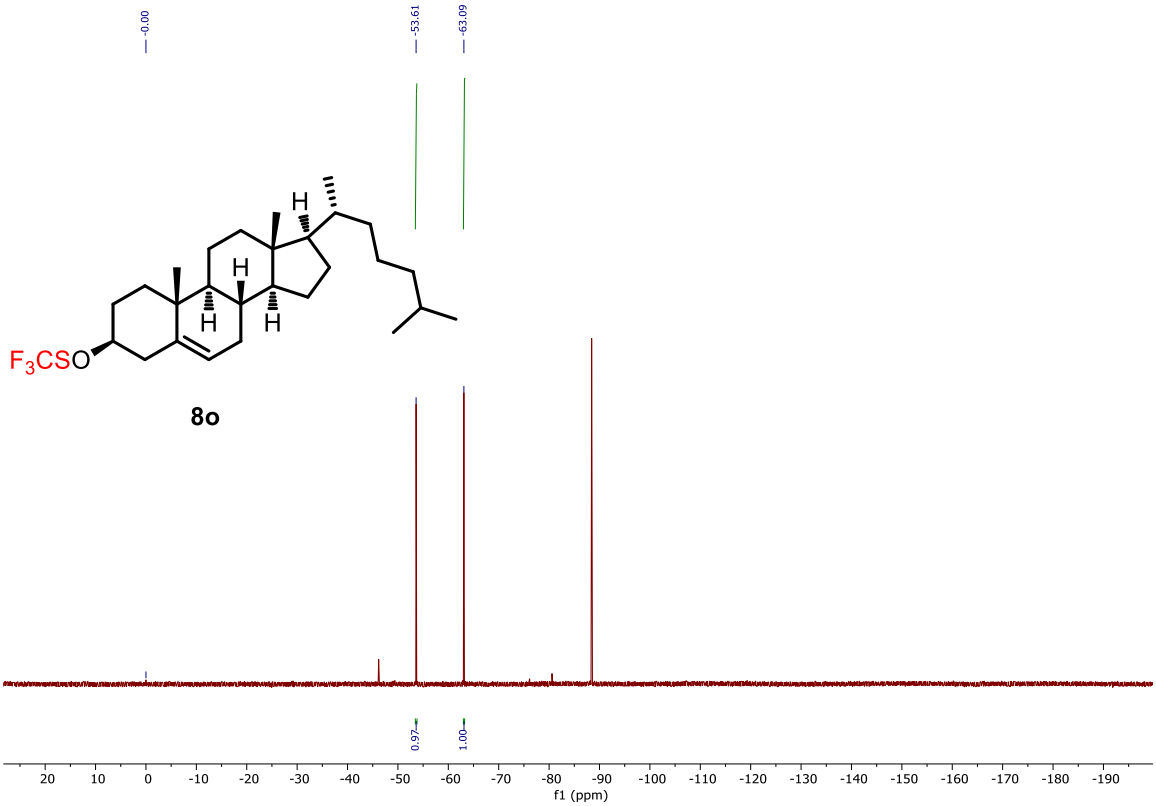
8n

^{13}C NMR (100 MHz, $CDCl_3$) 8n



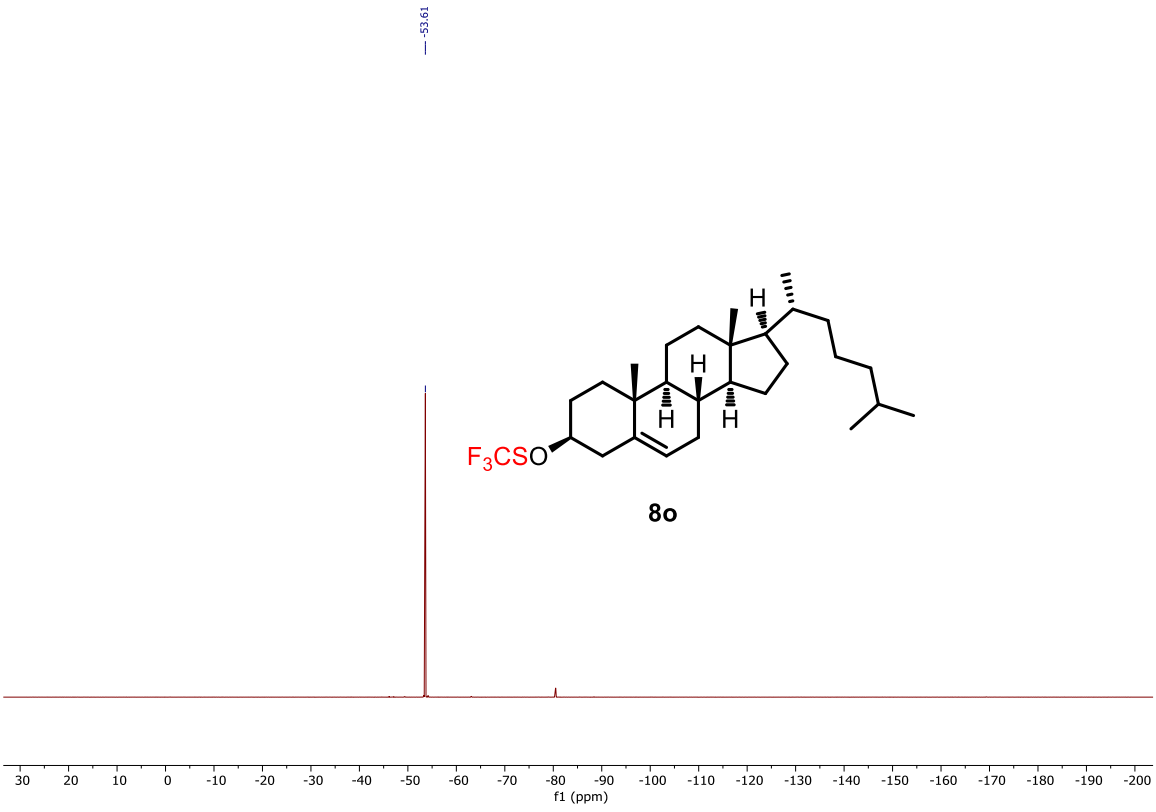
8n

^{19}F NMR (376 MHz, $CDCl_3$) yield of 8o



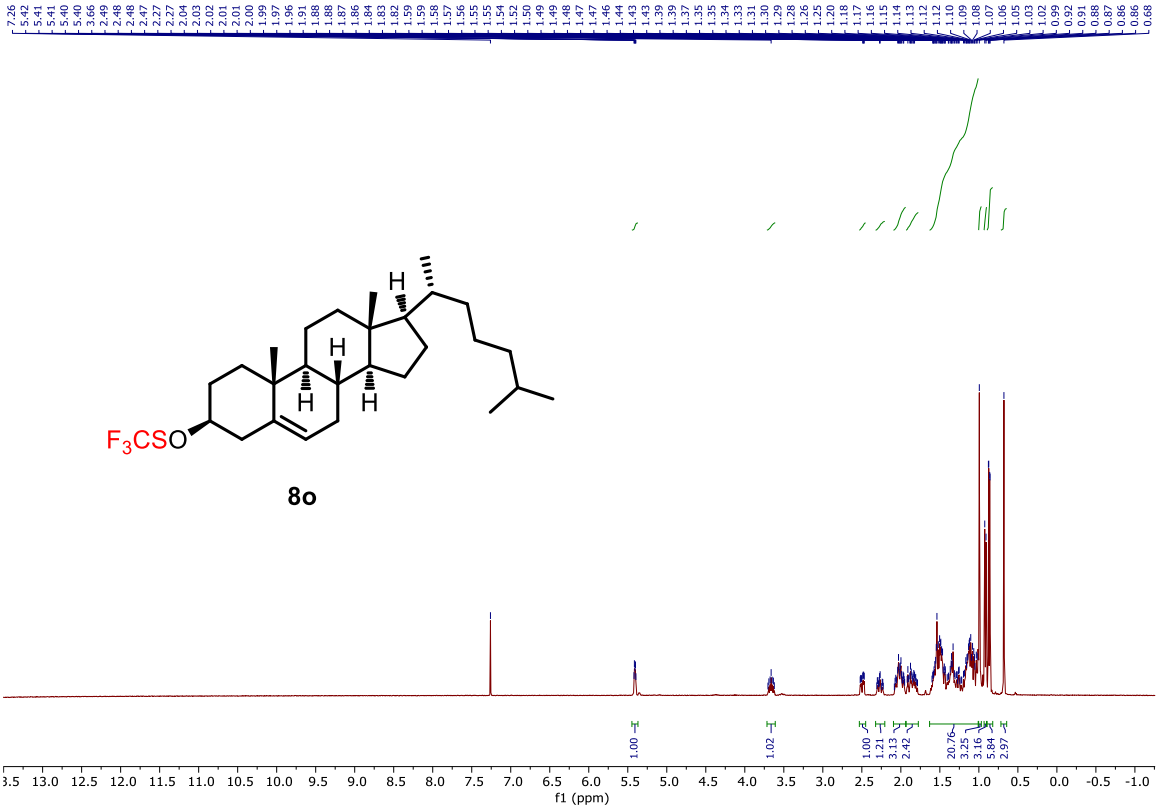
8o

^{19}F NMR (376 MHz, $CDCl_3$) 8o



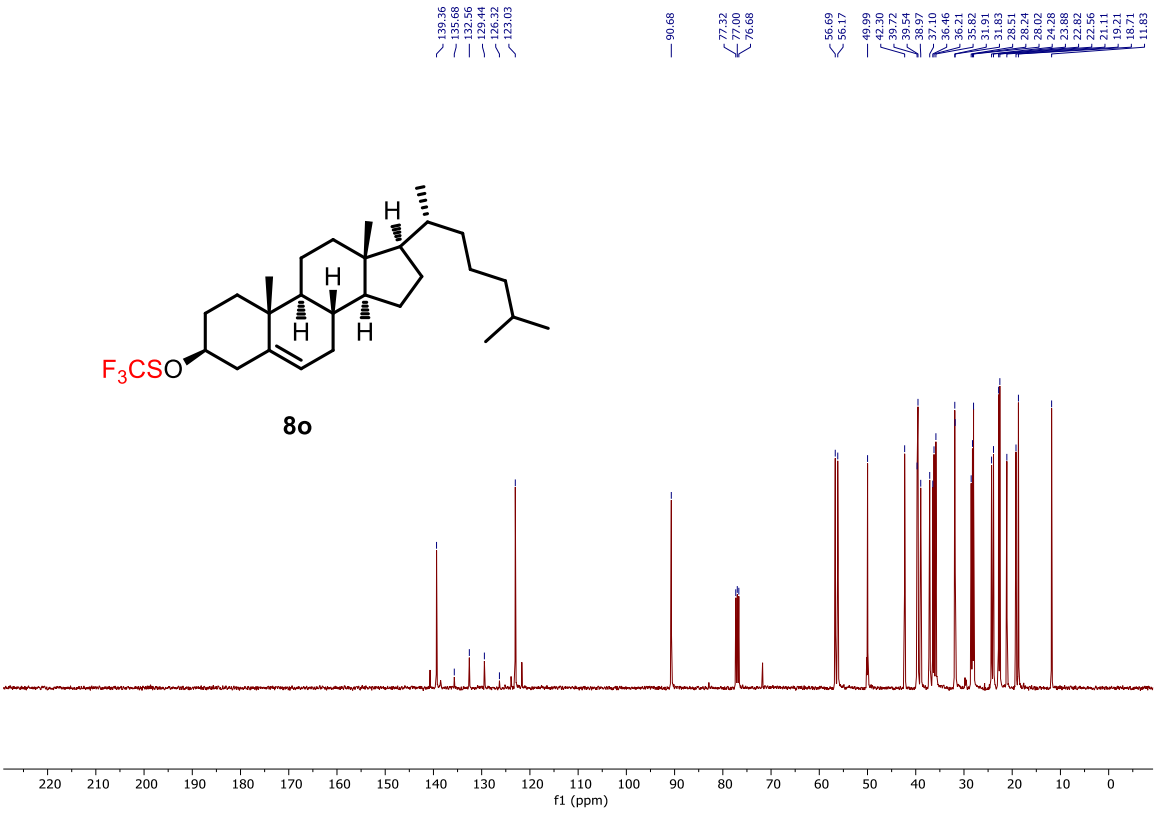
8o

^{1}H NMR (400 MHz, $CDCl_3$) 8o



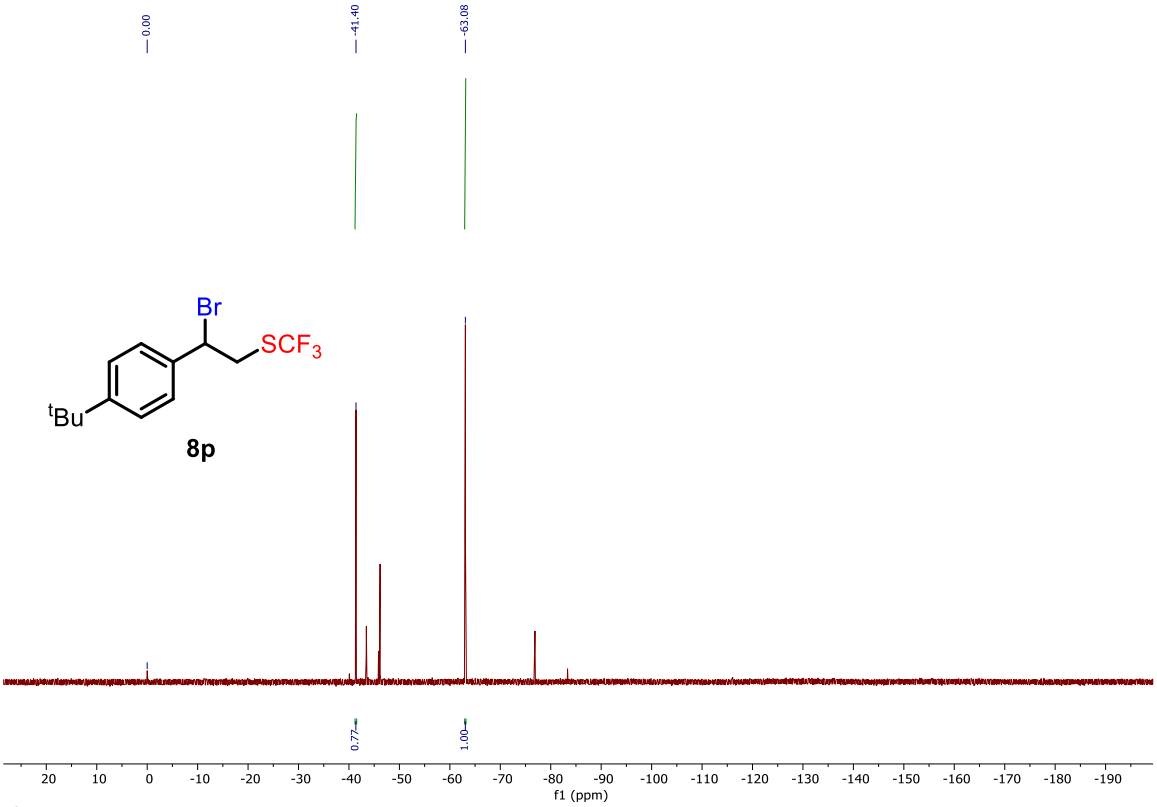
8o

^{13}C NMR (100 MHz, $CDCl_3$) 8o

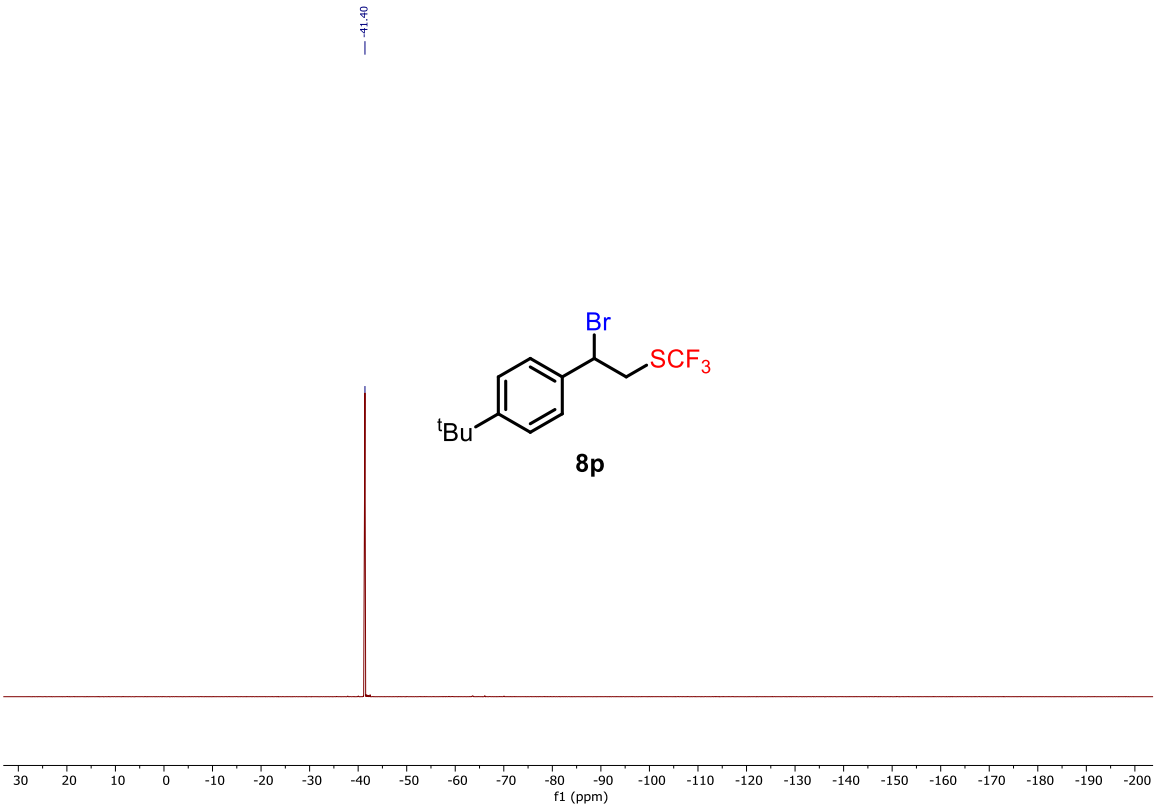


8o

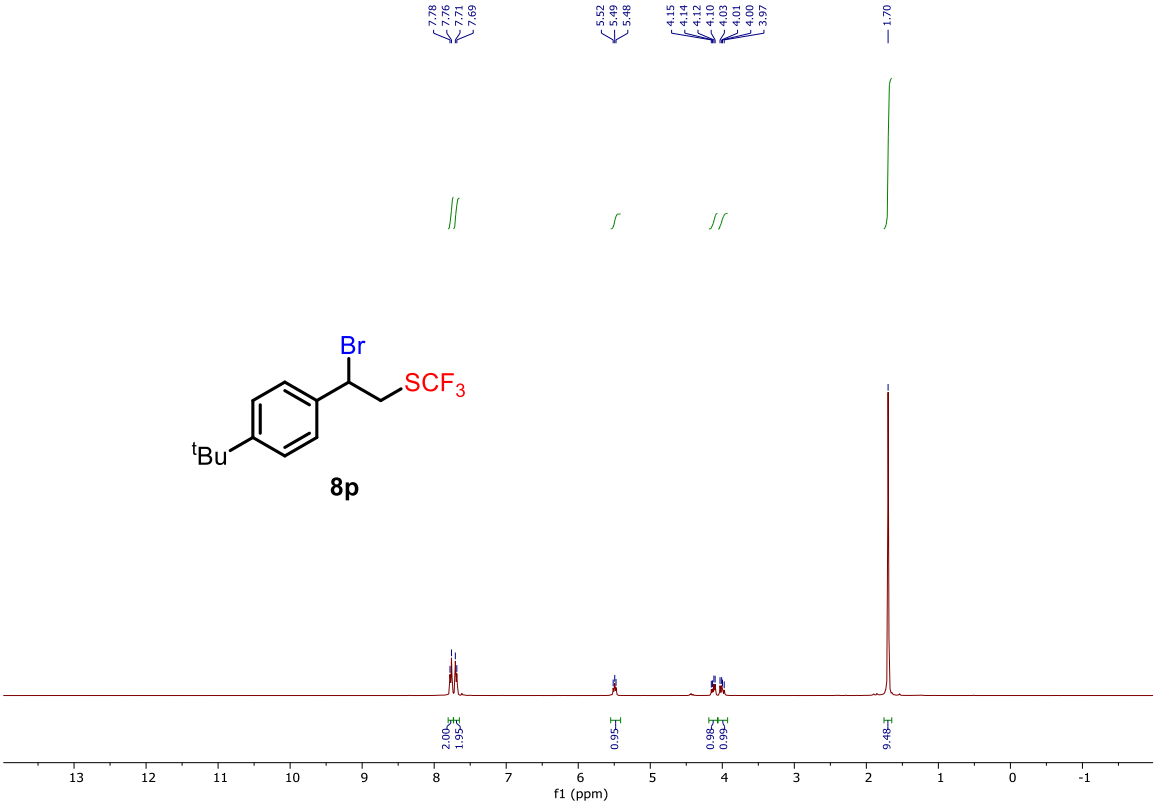
^{19}F NMR (376 MHz, $CDCl_3$) yield of 8p



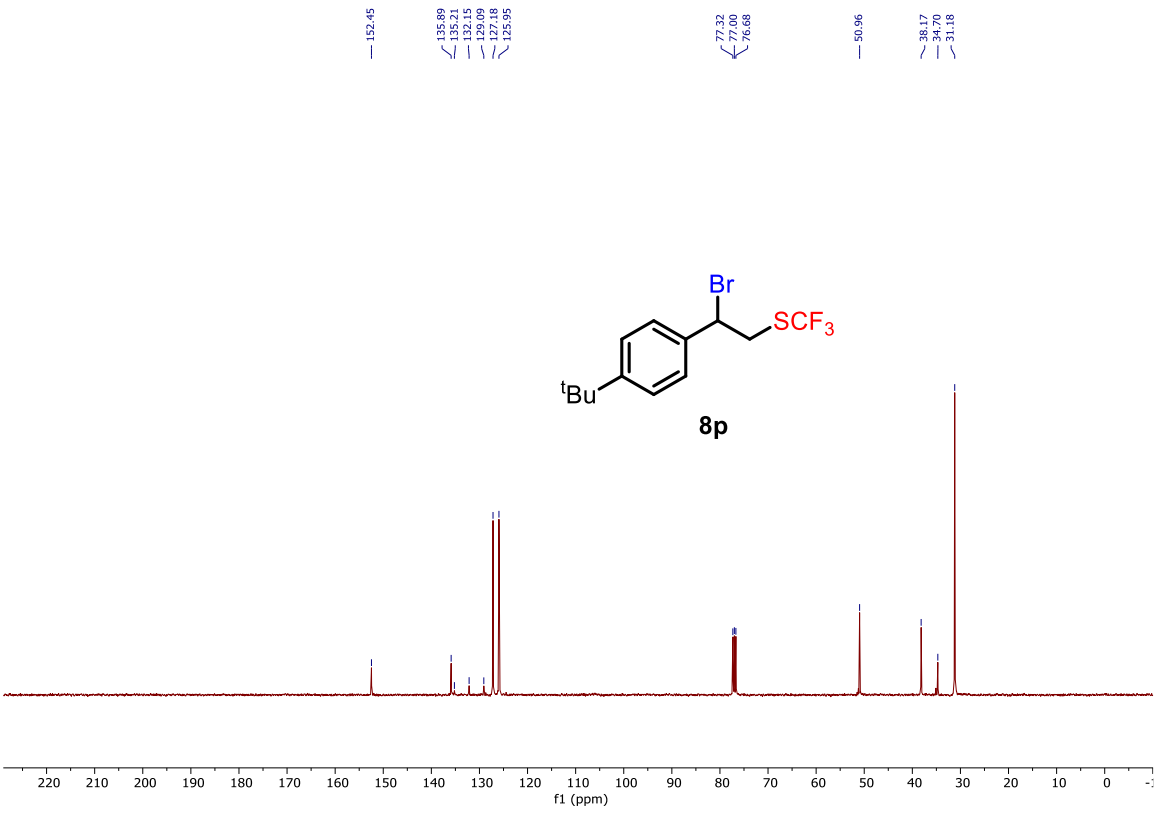
^{19}F NMR (376 MHz, $CDCl_3$) 8p



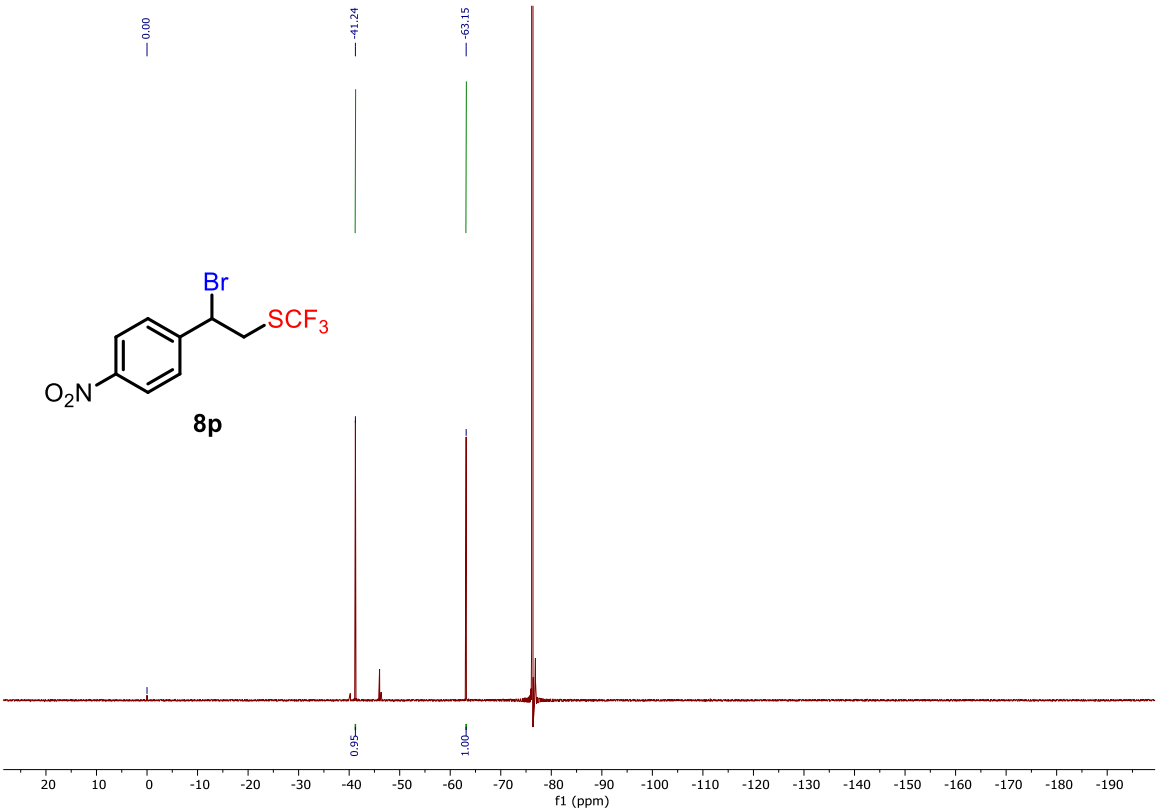
^{1}H NMR (400 MHz, $CDCl_3$) 8p



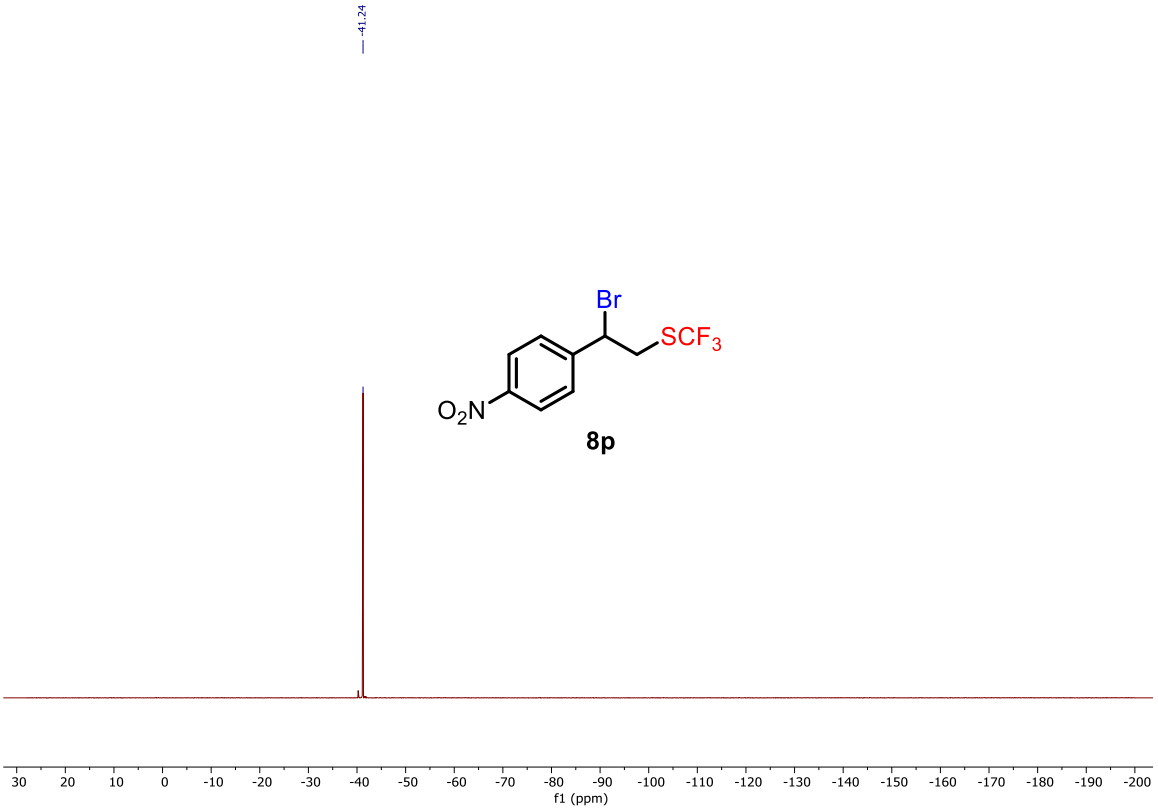
^{13}C NMR (100 MHz, $CDCl_3$) 8p



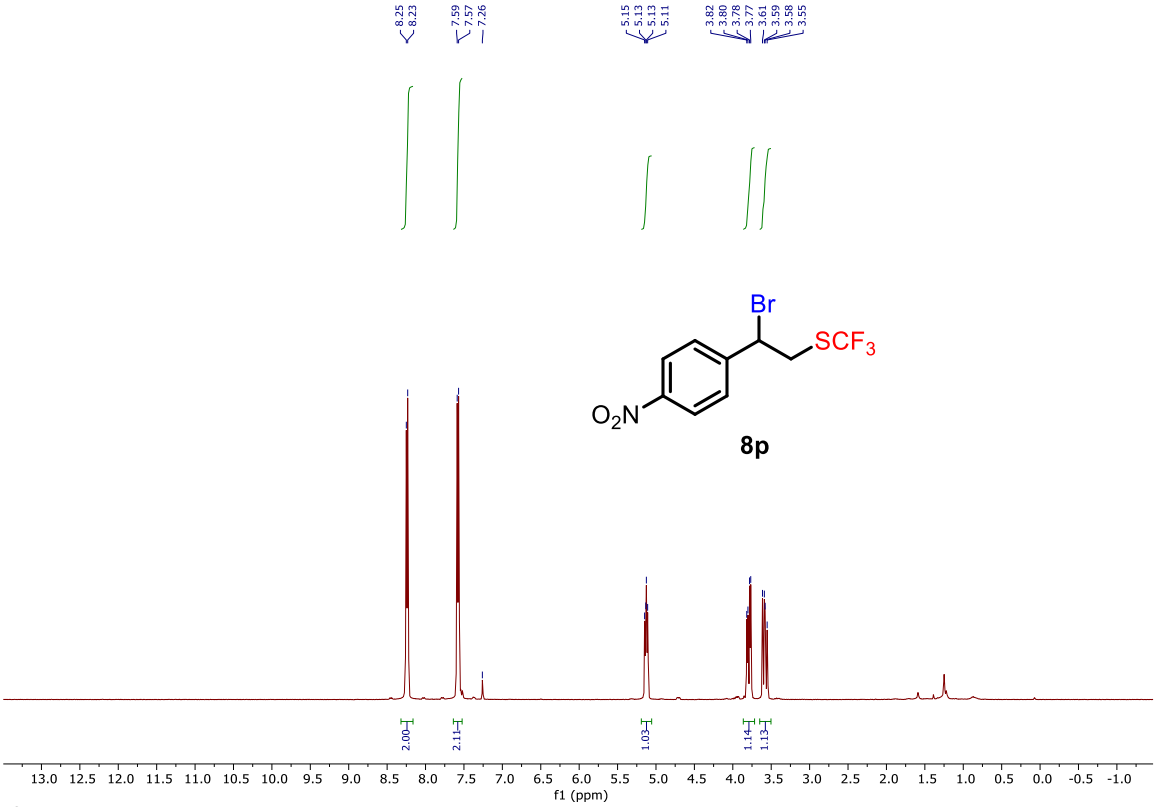
^{19}F NMR (376 MHz, $CDCl_3$) yield of 8q



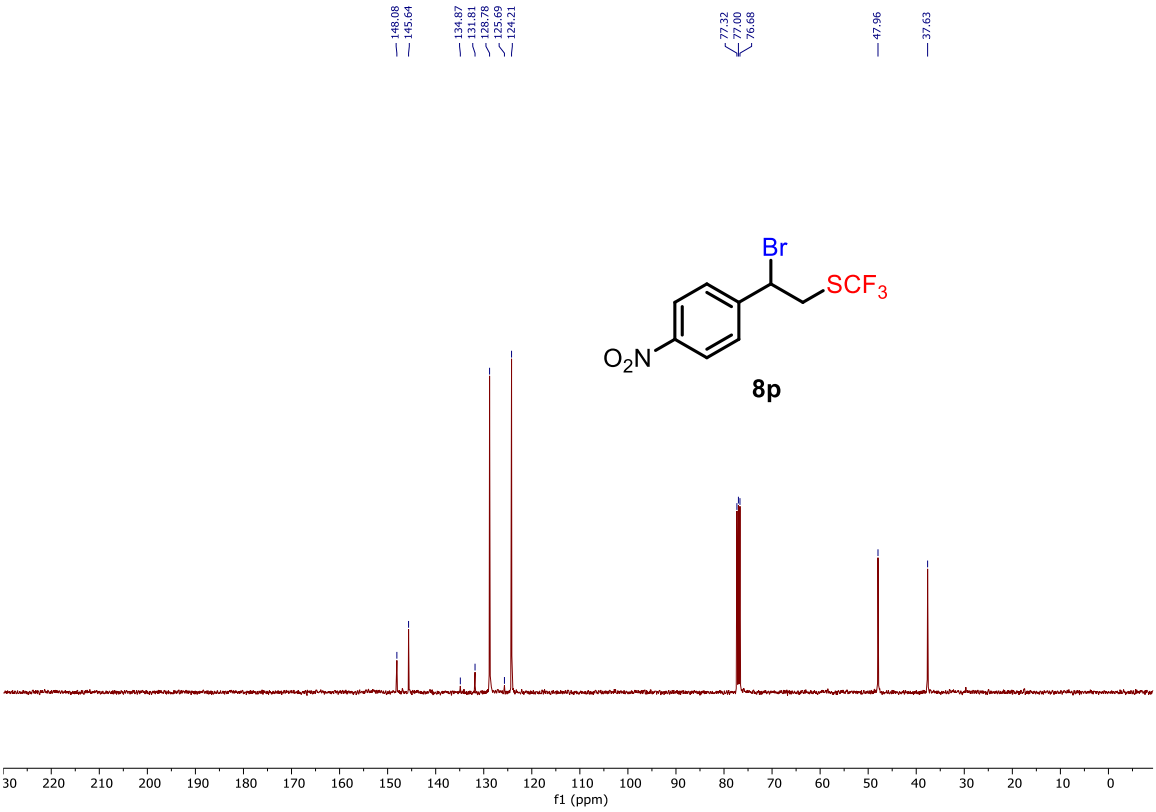
^{19}F NMR (376 MHz, $CDCl_3$) 8q



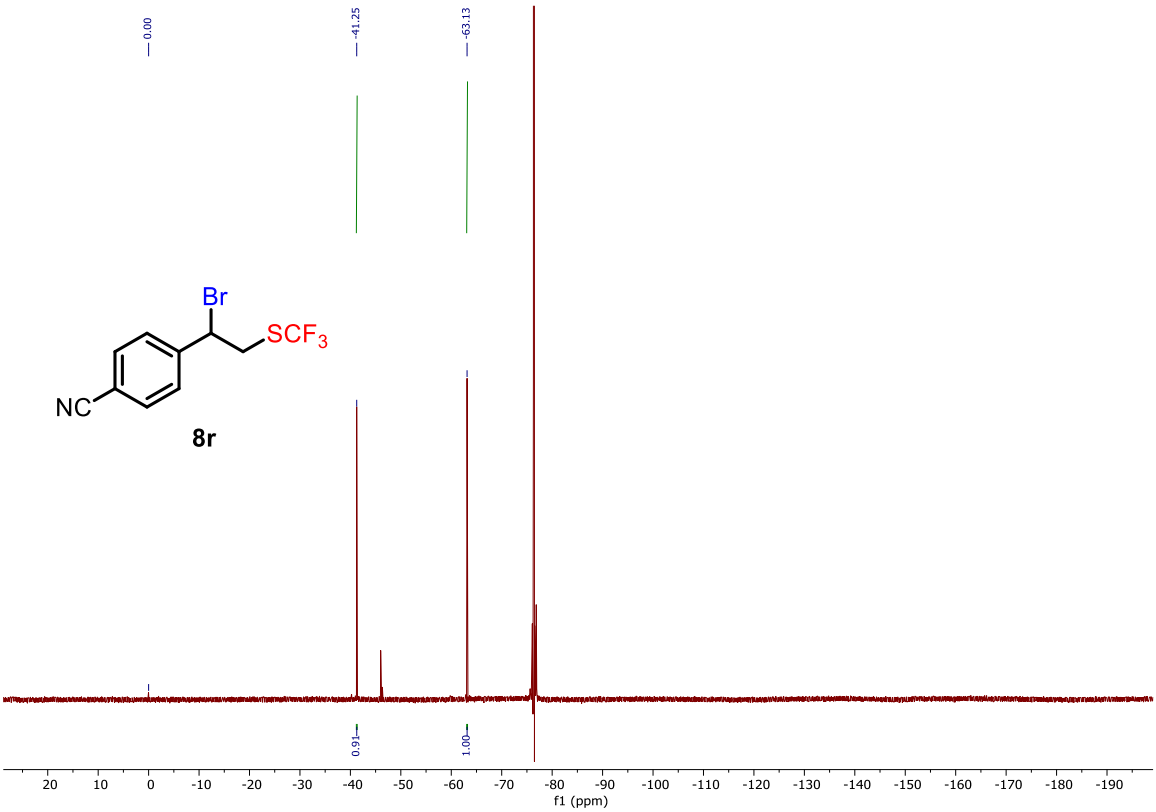
^{1}H NMR (400 MHz, $CDCl_3$) 8q



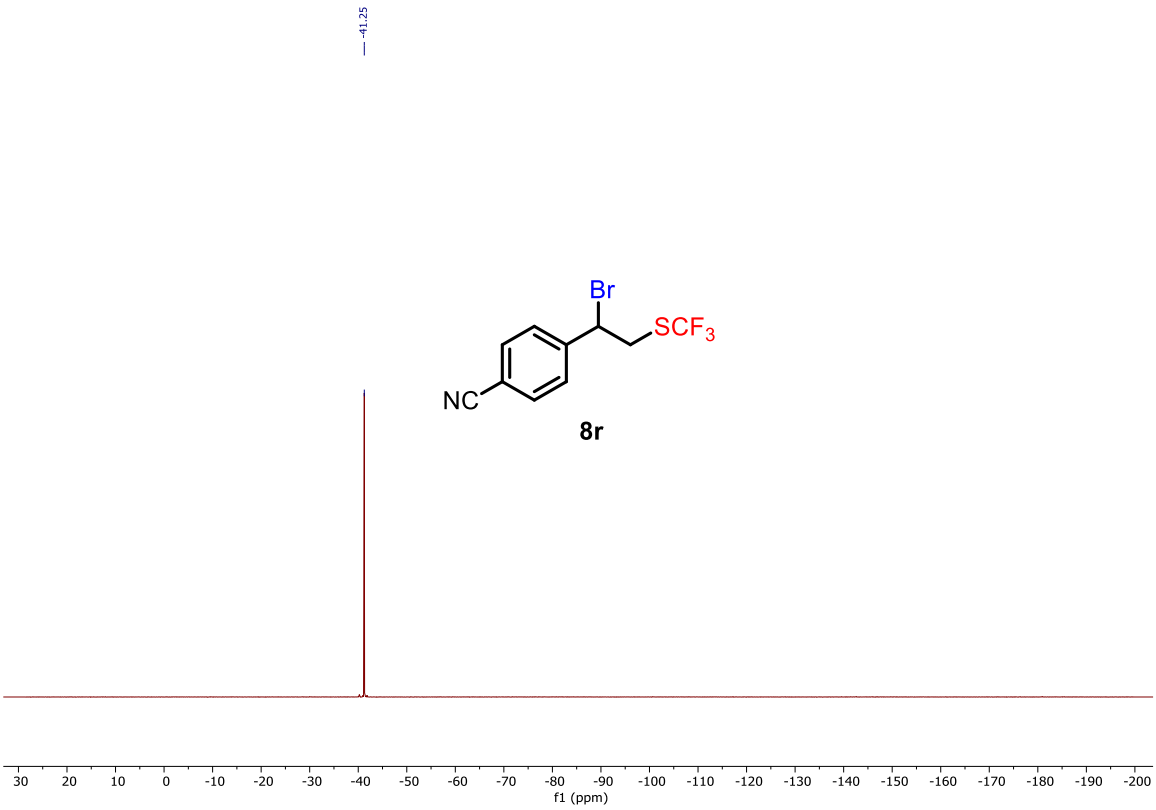
^{13}C NMR (100 MHz, $CDCl_3$) 8q



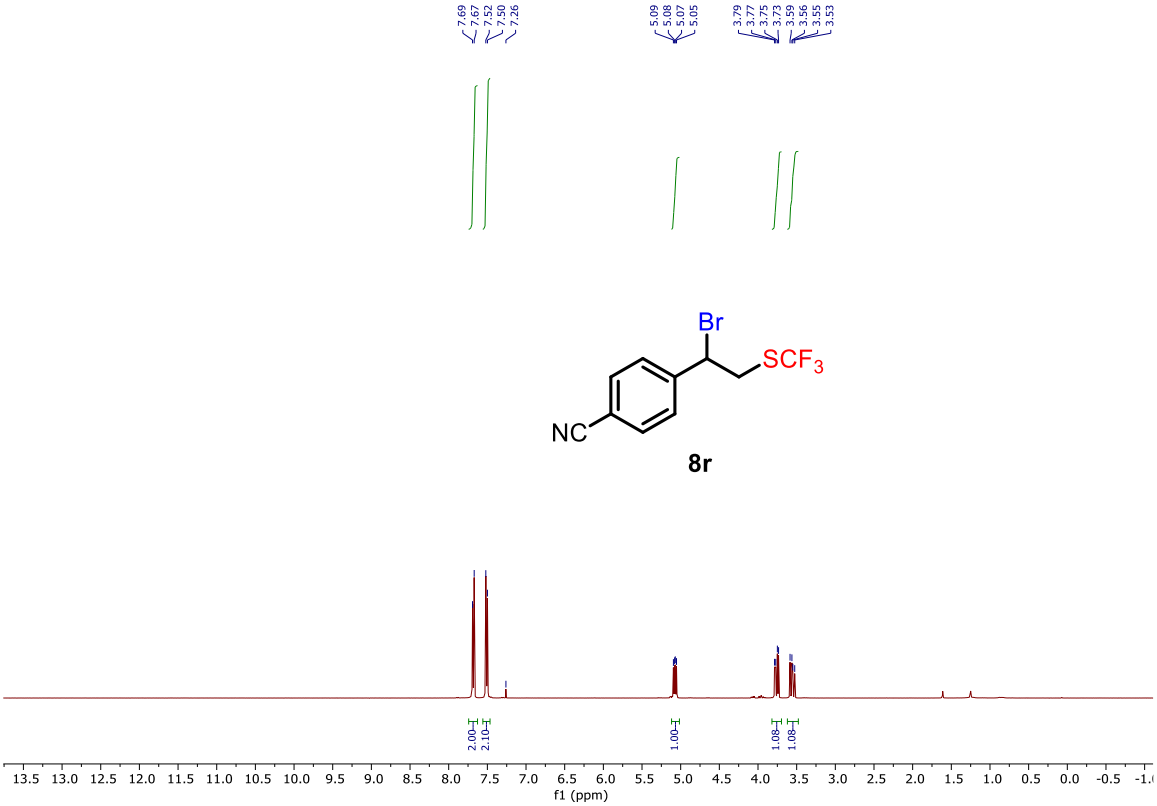
^{19}F NMR (376 MHz, $CDCl_3$) yield of 8r



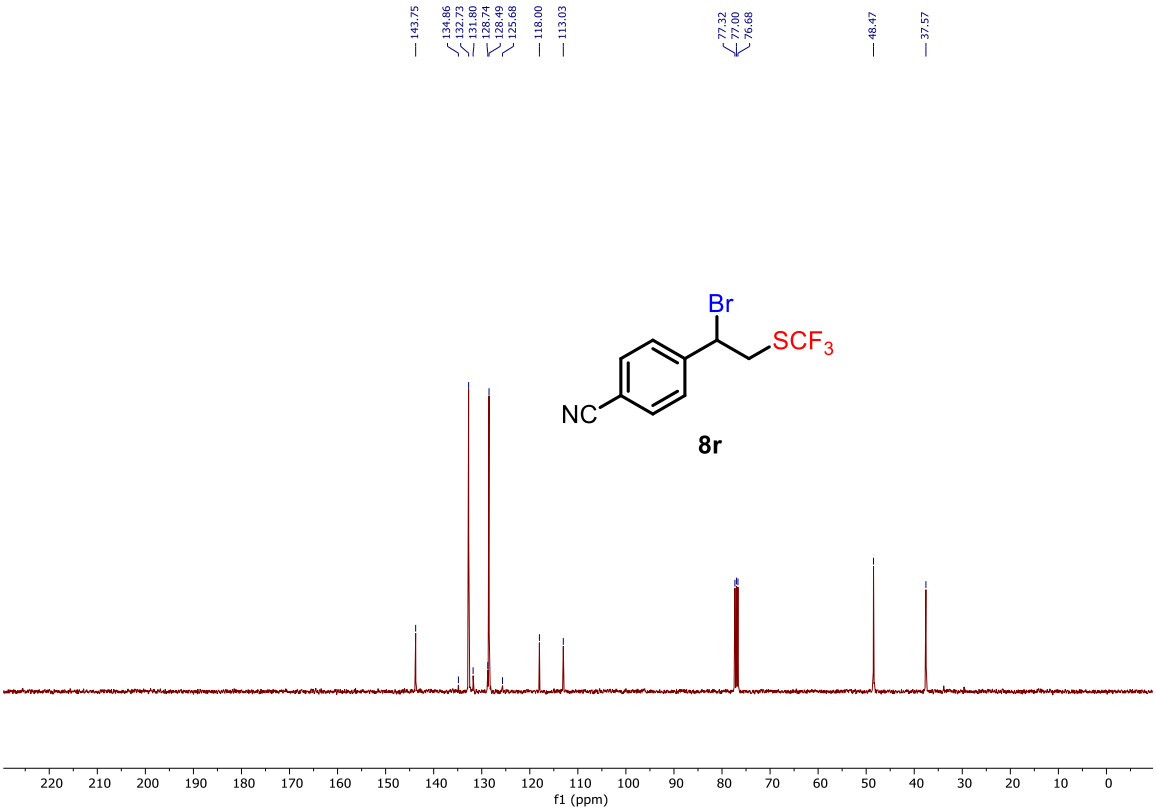
^{19}F NMR (376 MHz, $CDCl_3$) 8r



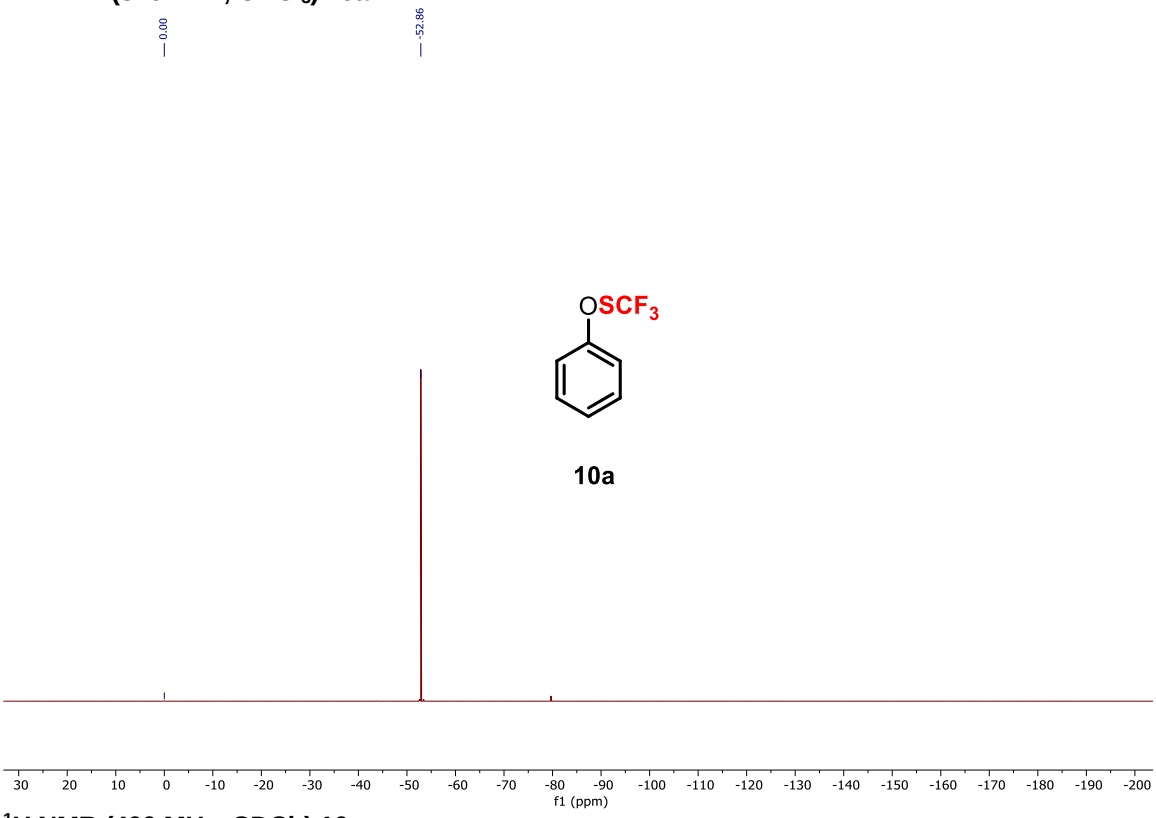
^{1}H NMR (400 MHz, $CDCl_3$) 8r



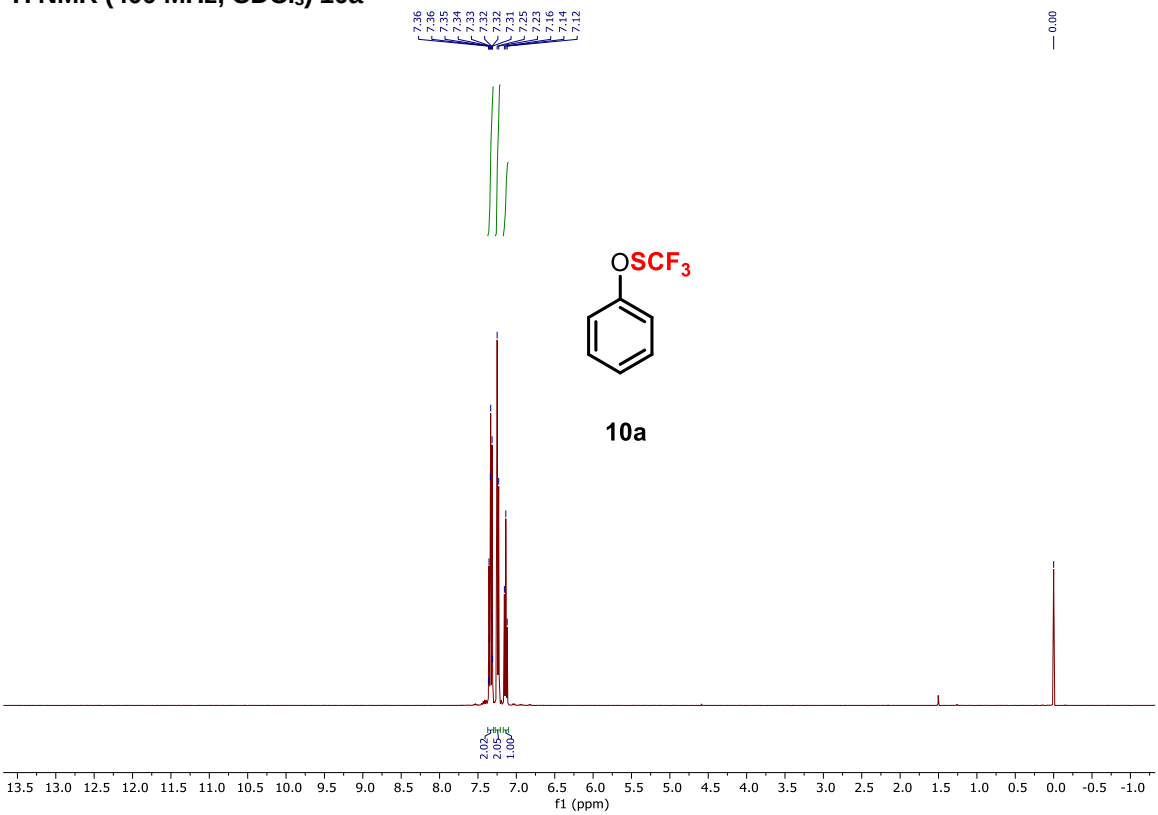
^{13}C NMR (100 MHz, $CDCl_3$) 8r



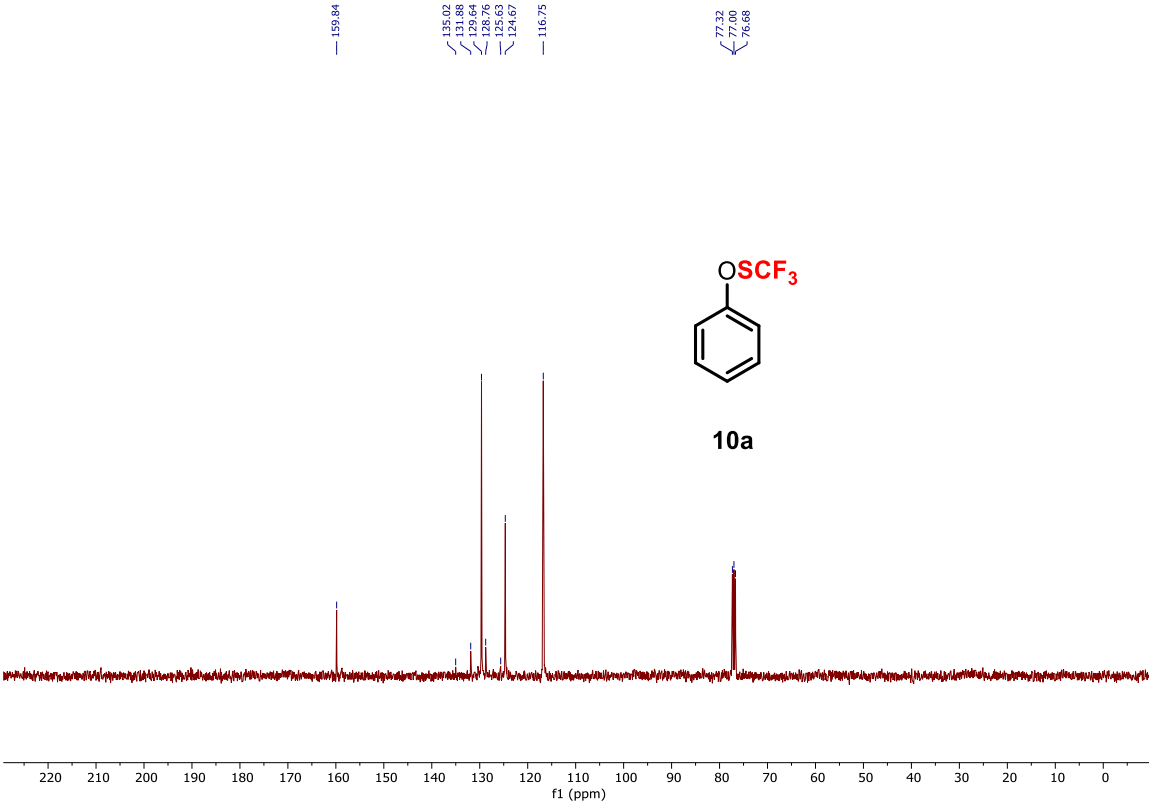
^{19}F NMR (376 MHz, $CDCl_3$) 10a



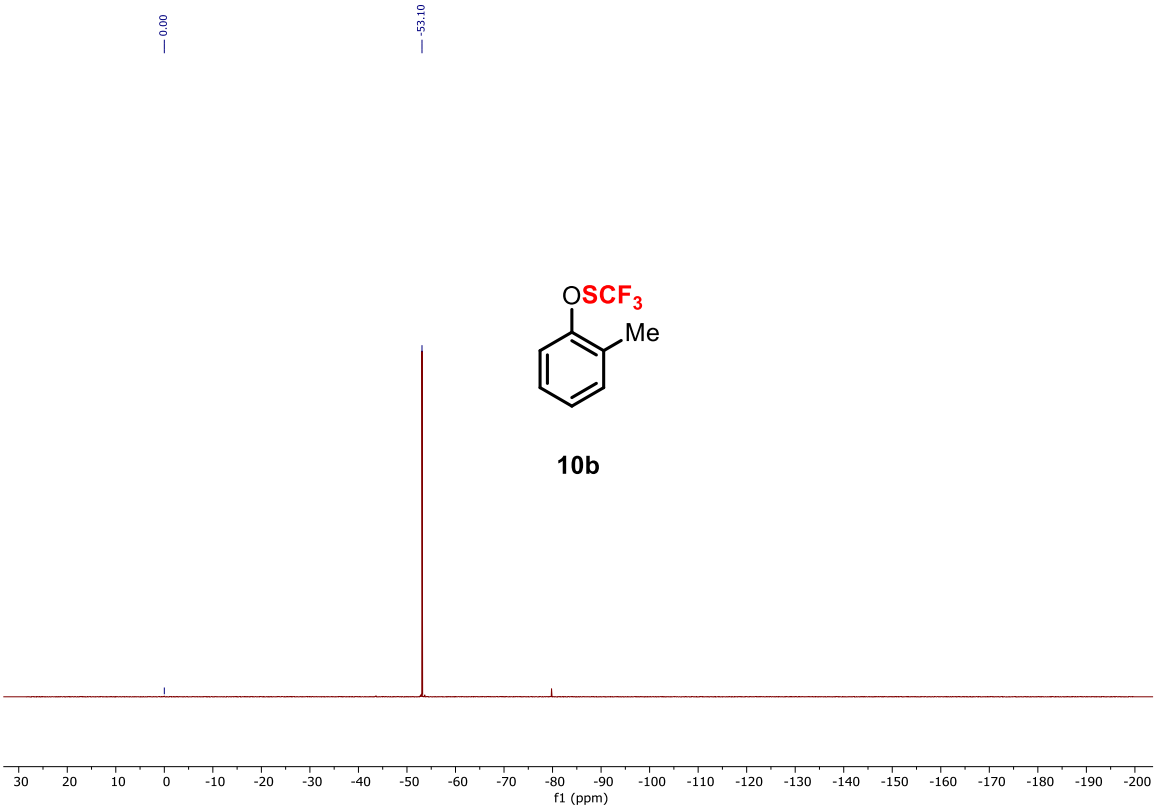
^{1}H NMR (400 MHz, $CDCl_3$) 10a



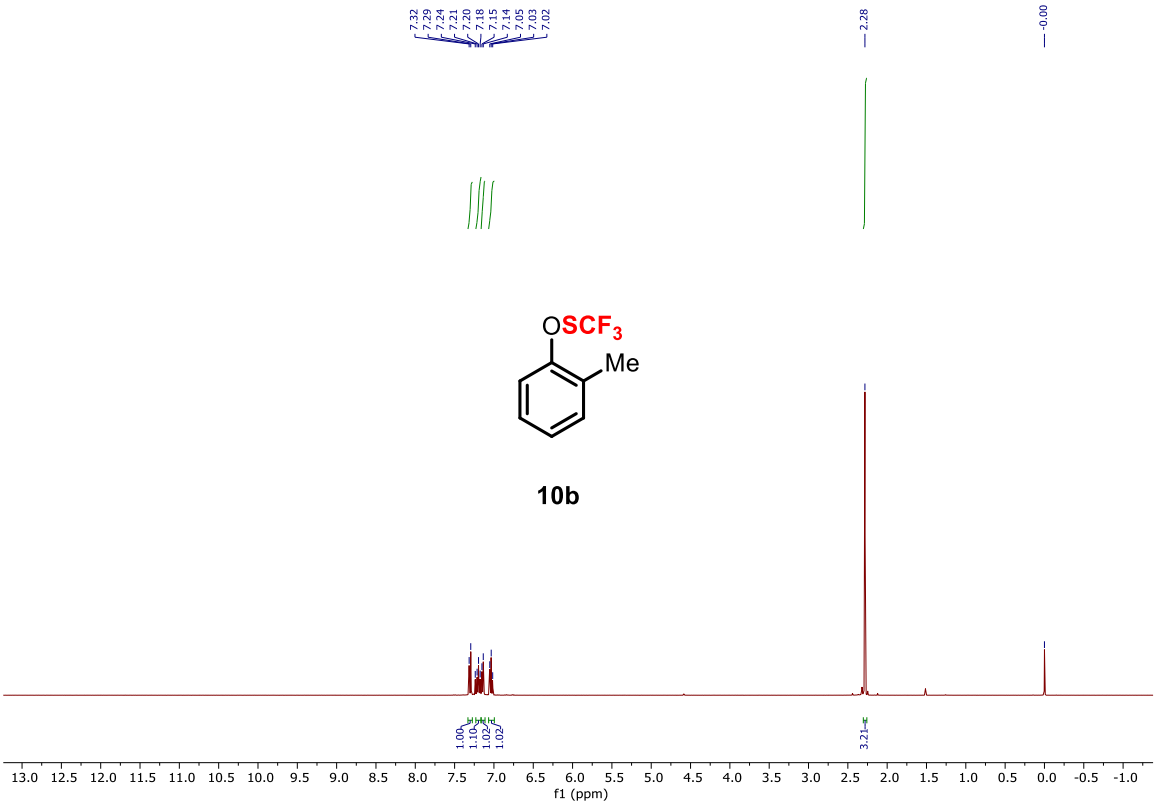
^{13}C NMR (100 MHz, $CDCl_3$) 10a



^{19}F NMR (376 MHz, $CDCl_3$) 10b

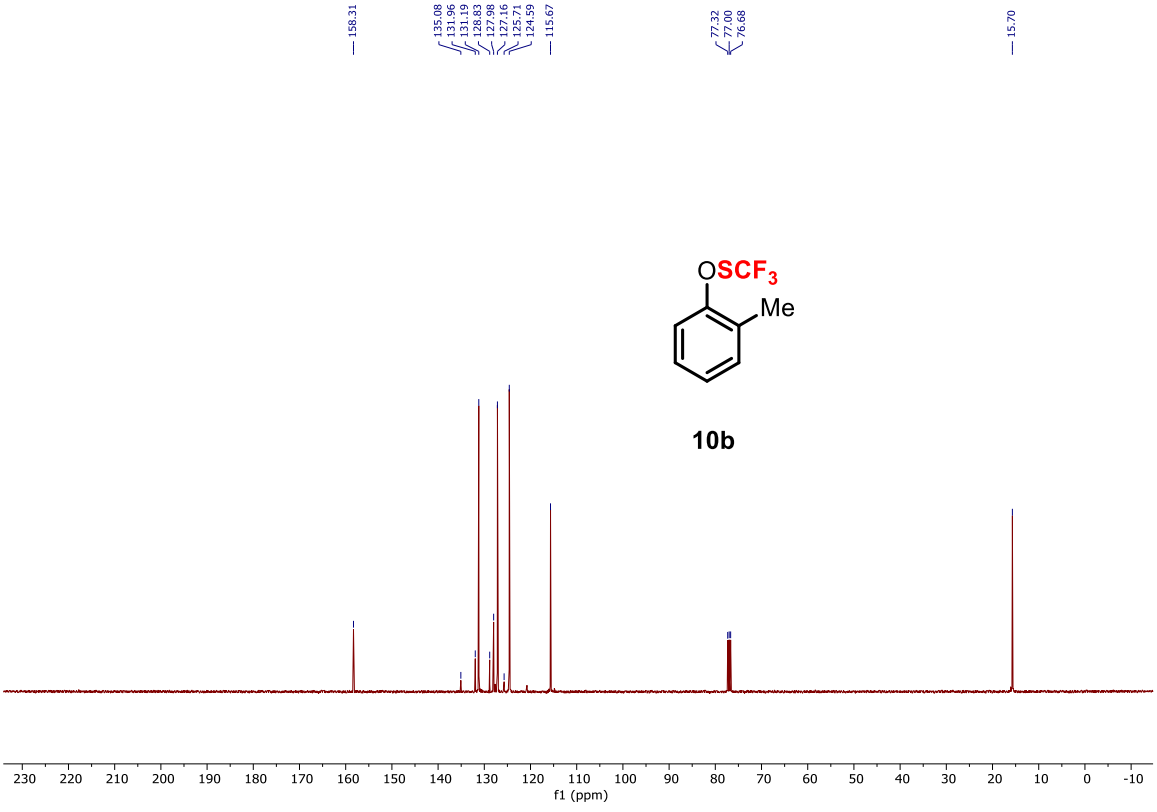


^{1}H NMR (400 MHz, $CDCl_3$) 10b



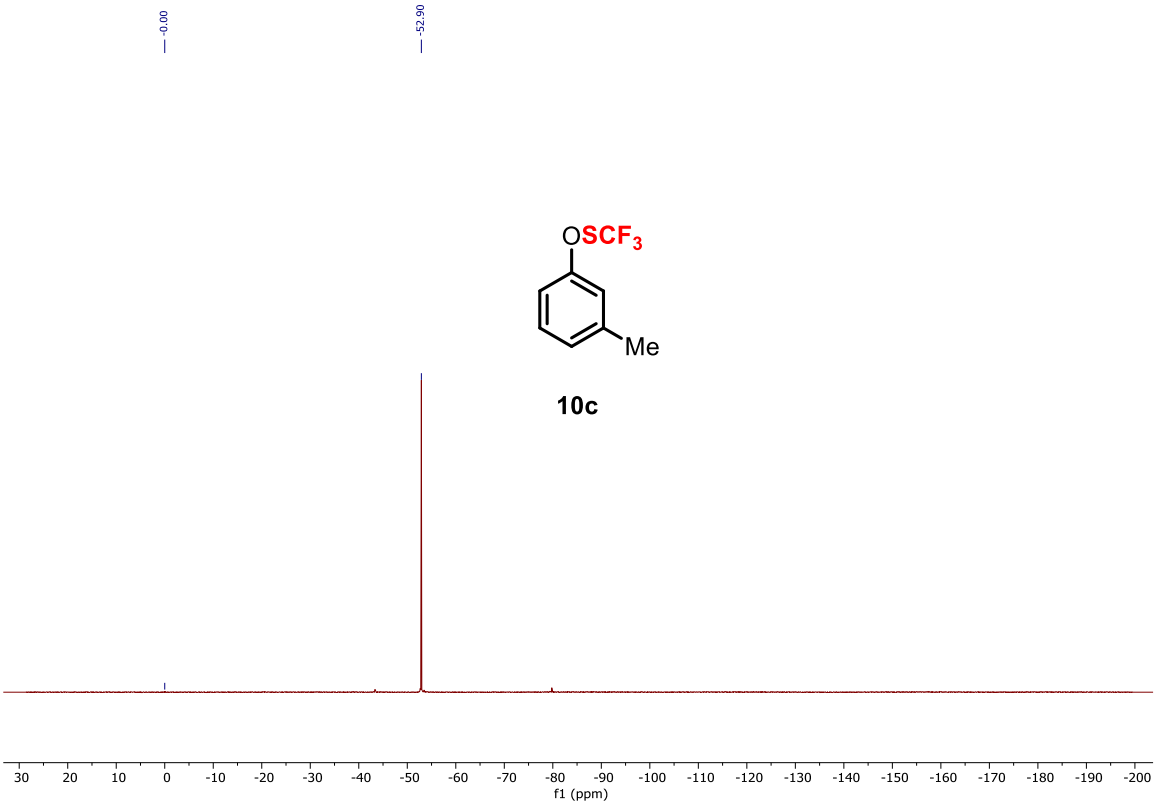
10b

^{13}C NMR (100 MHz, $CDCl_3$) 10b

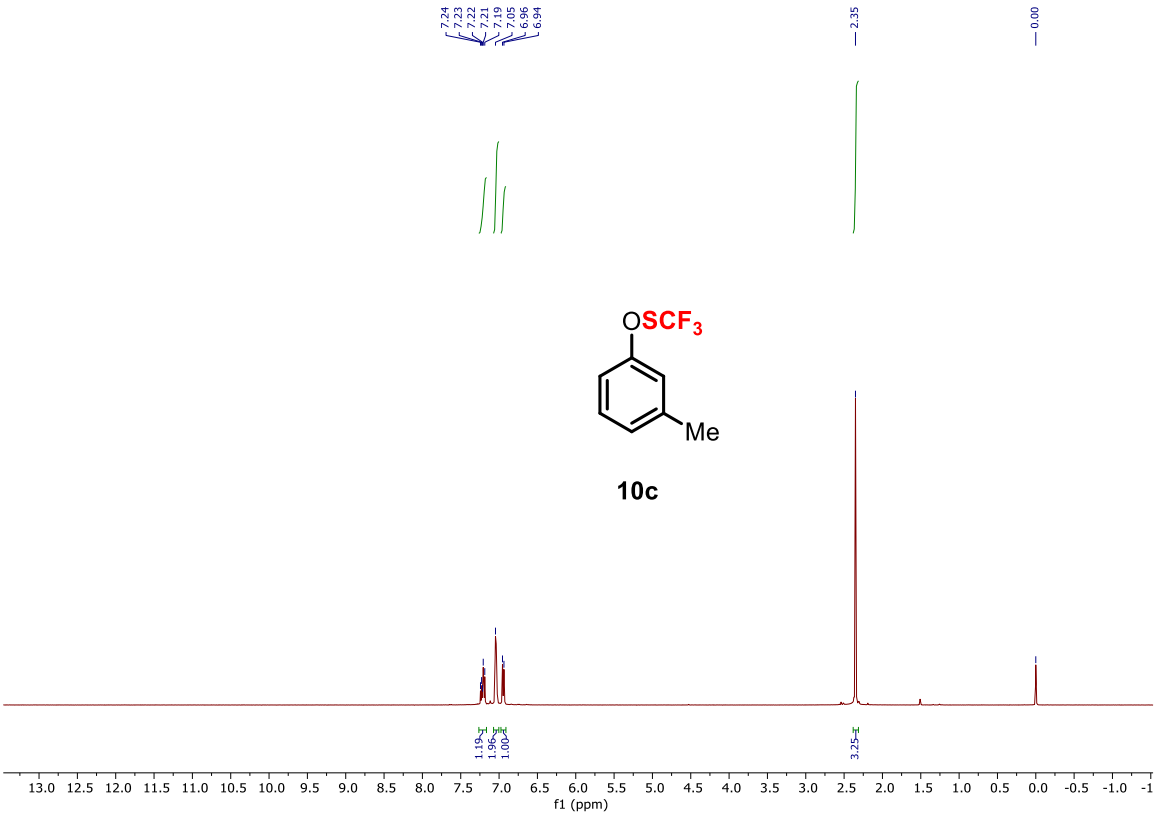


10b

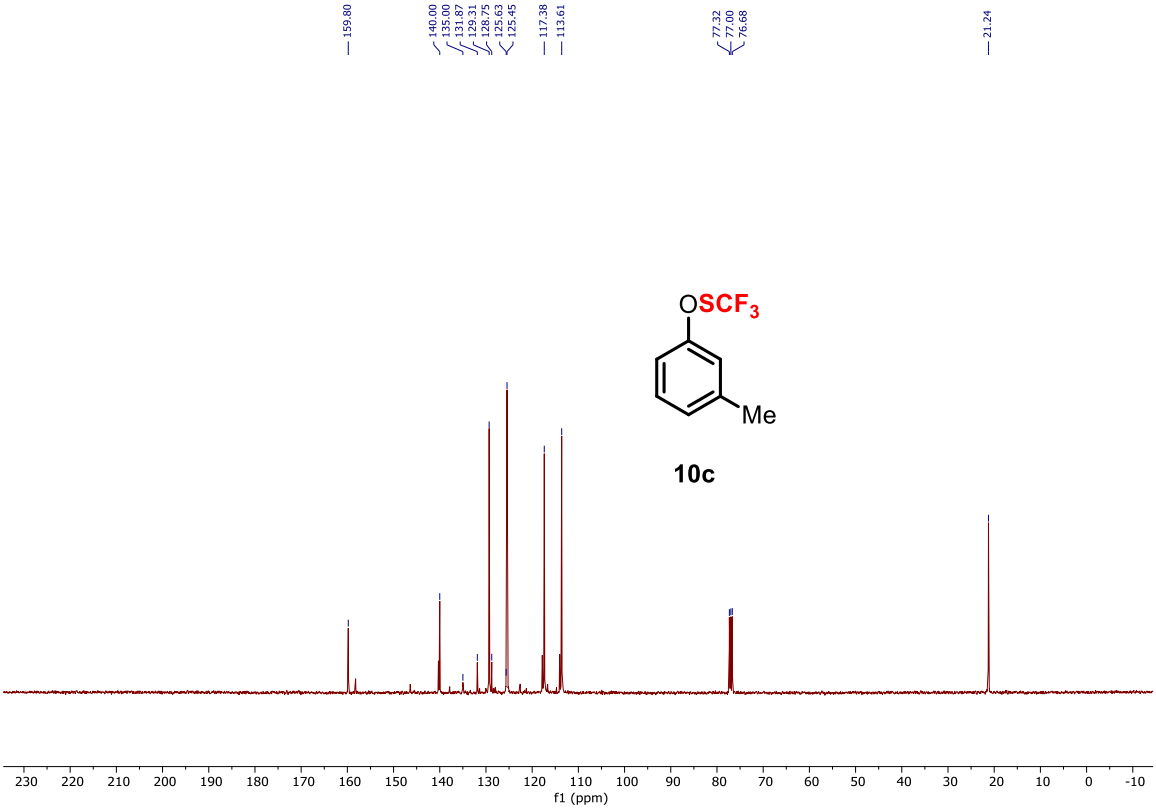
^{19}F NMR (376 MHz, $CDCl_3$) 10c



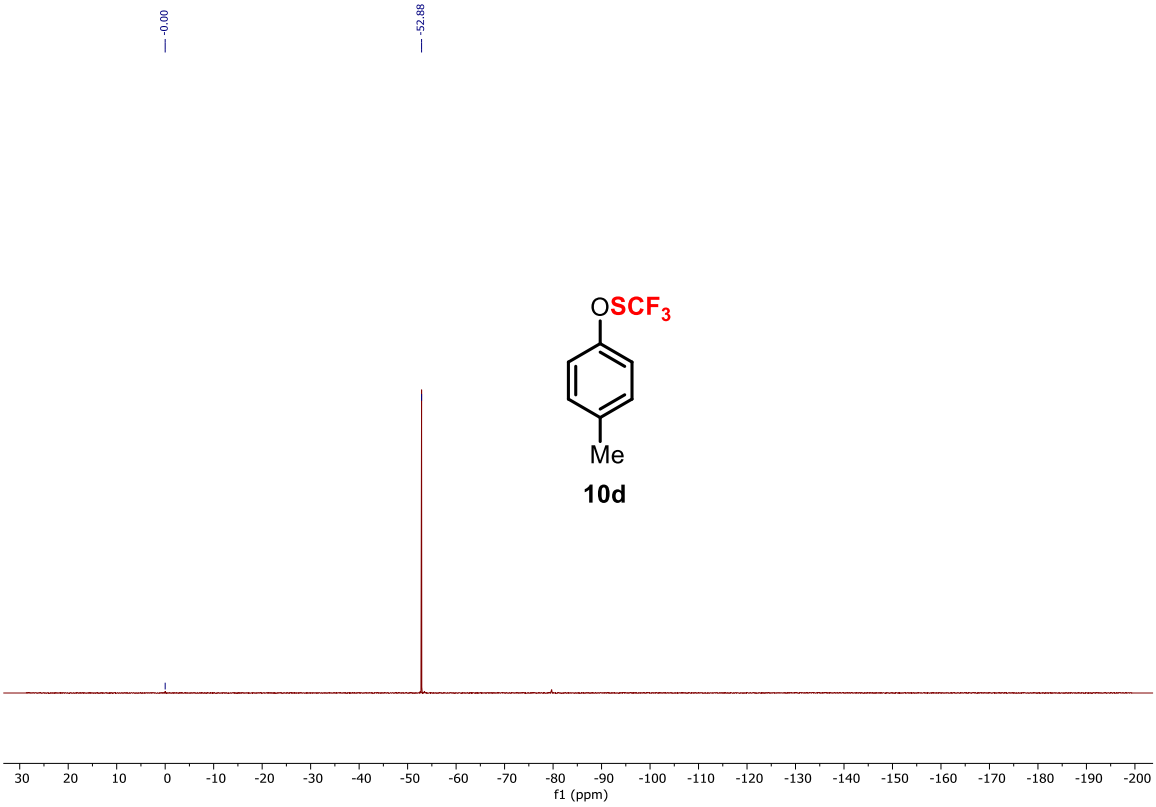
^{1}H NMR (400 MHz, $CDCl_3$) 10c



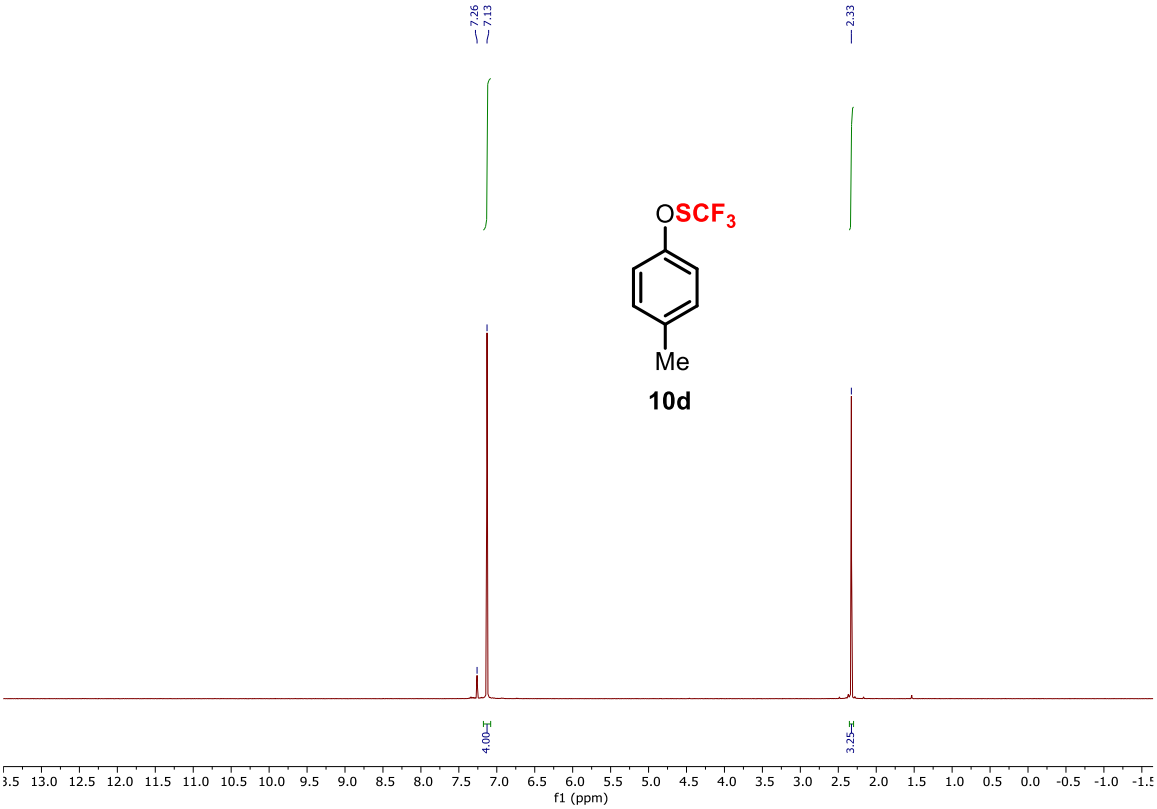
^{13}C NMR (100 MHz, $CDCl_3$) 10c



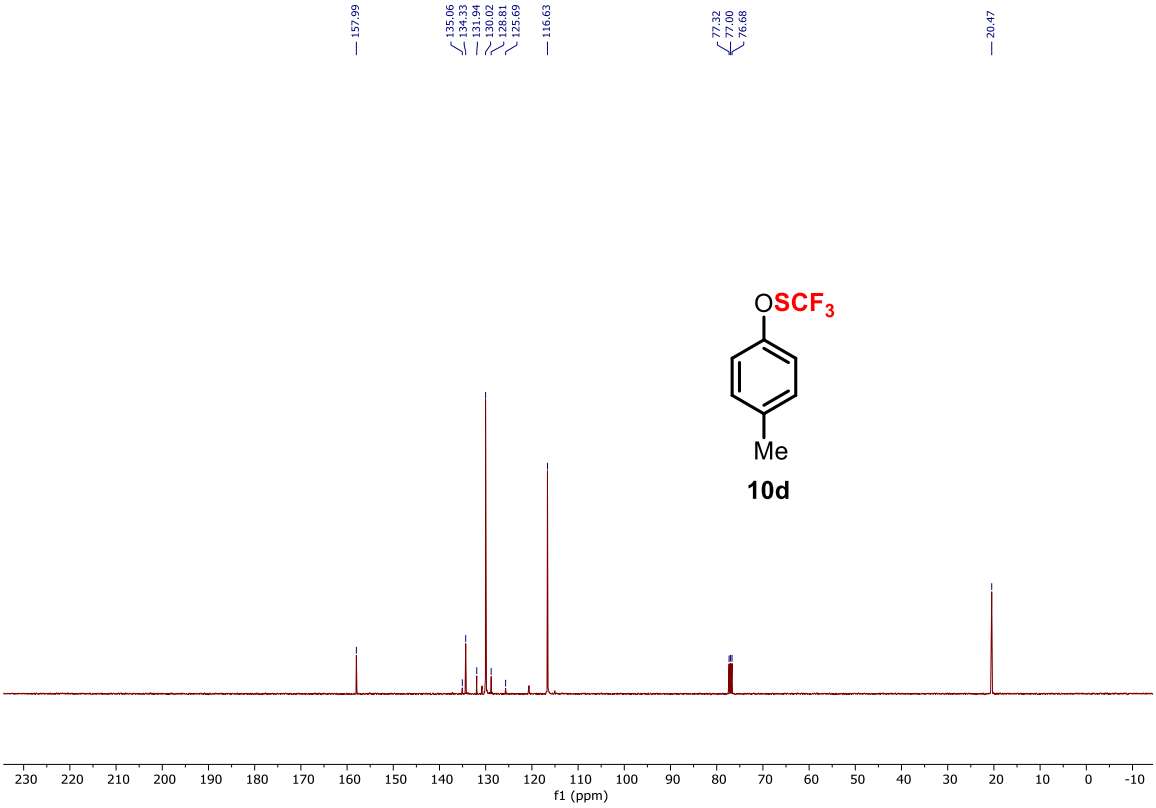
^{19}F NMR (376 MHz, $CDCl_3$) of 10d



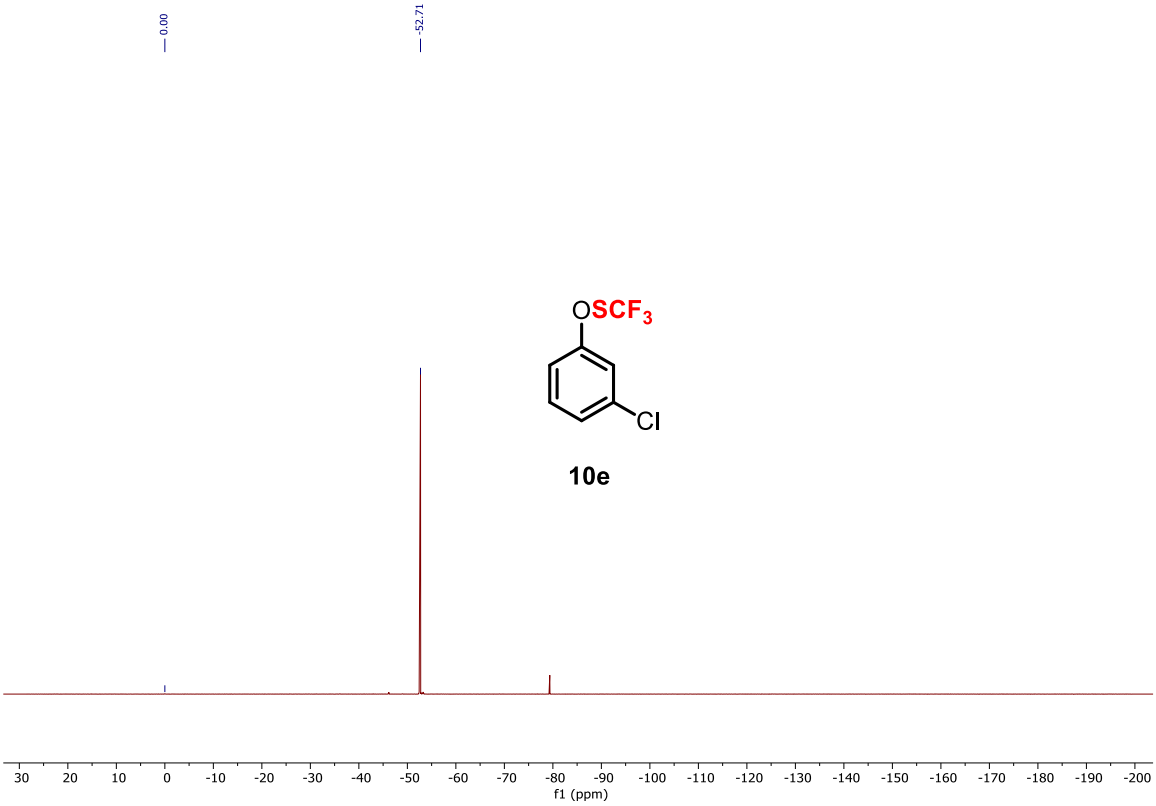
^{1}H NMR (400 MHz, $CDCl_3$) of 10d



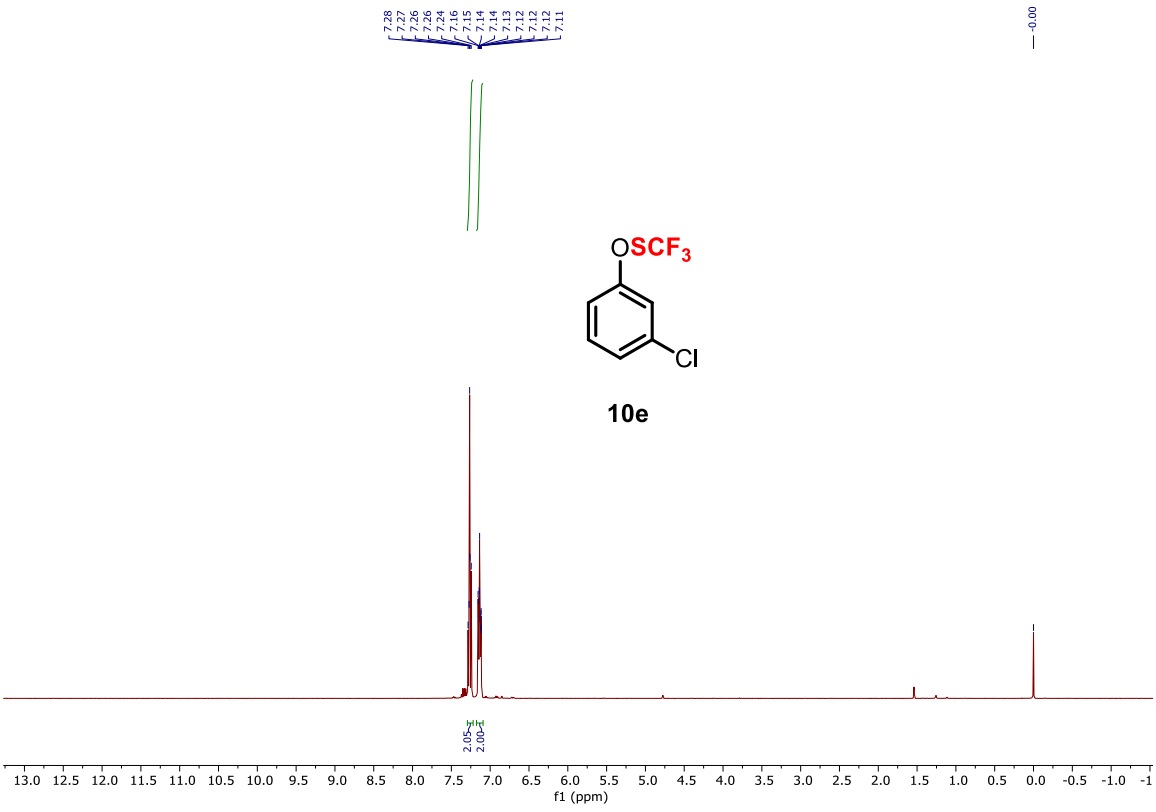
^{13}C NMR (100 MHz, $CDCl_3$) of 10d



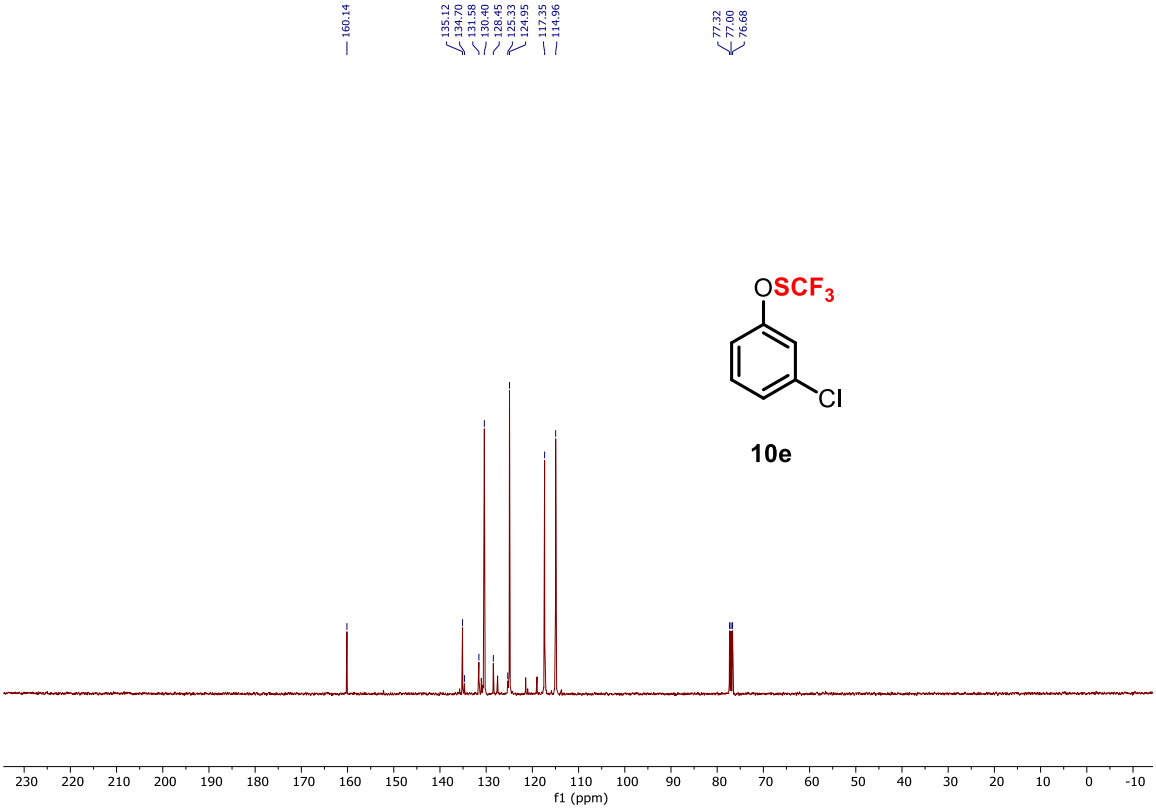
^{19}F NMR (376 MHz, $CDCl_3$) of 10e



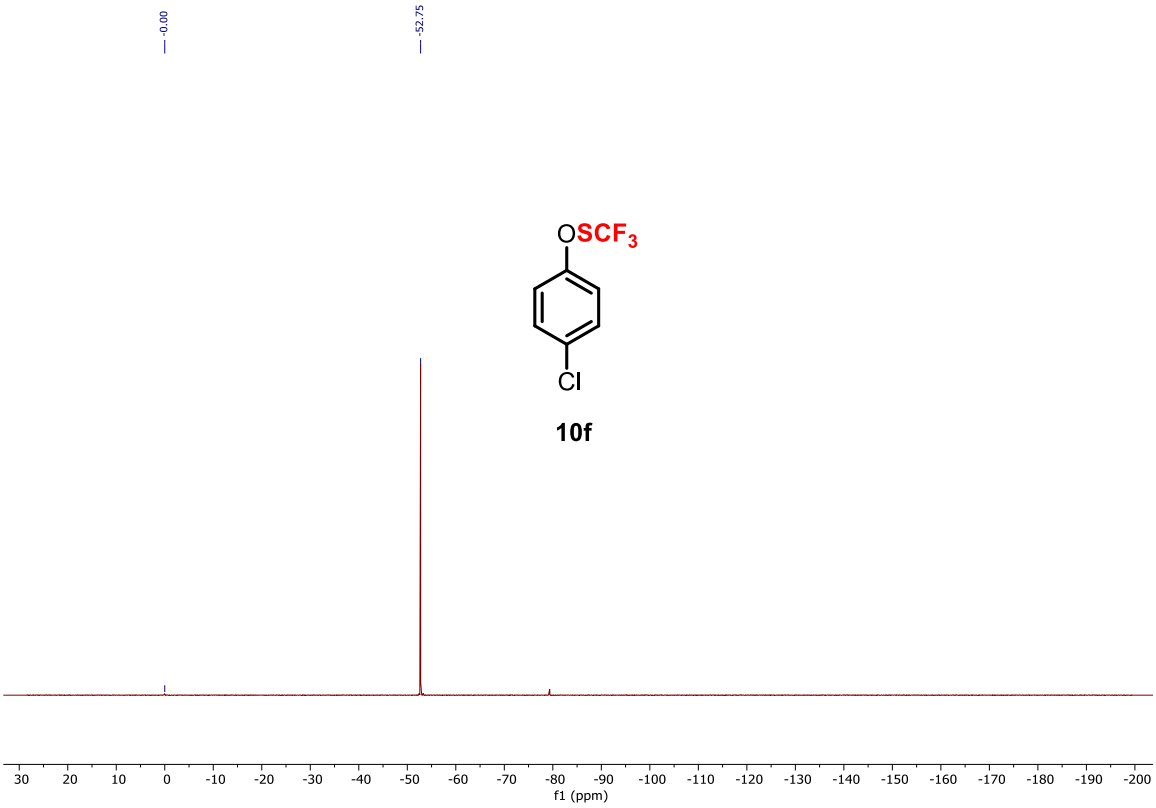
^{1}H NMR (400 MHz, $CDCl_3$) of 10e



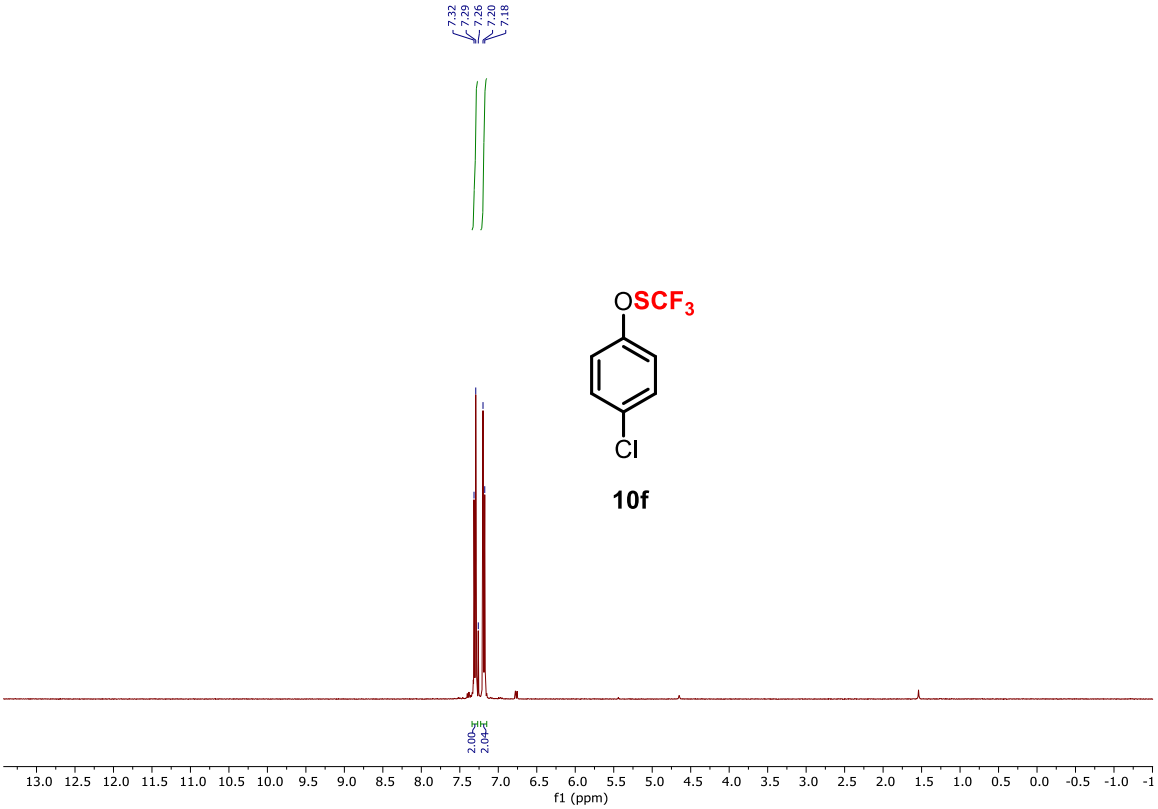
^{13}C NMR (100 MHz, $CDCl_3$) of 10e



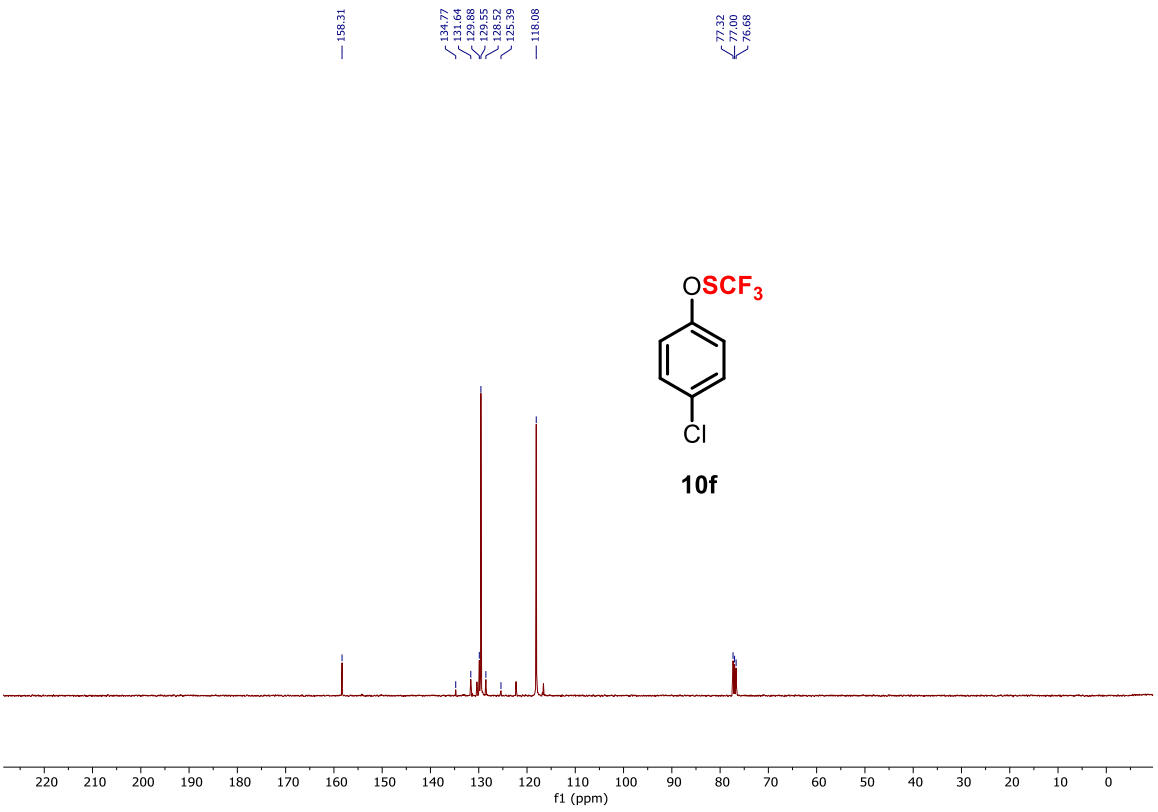
^{19}F NMR (376 MHz, $CDCl_3$) of 10f



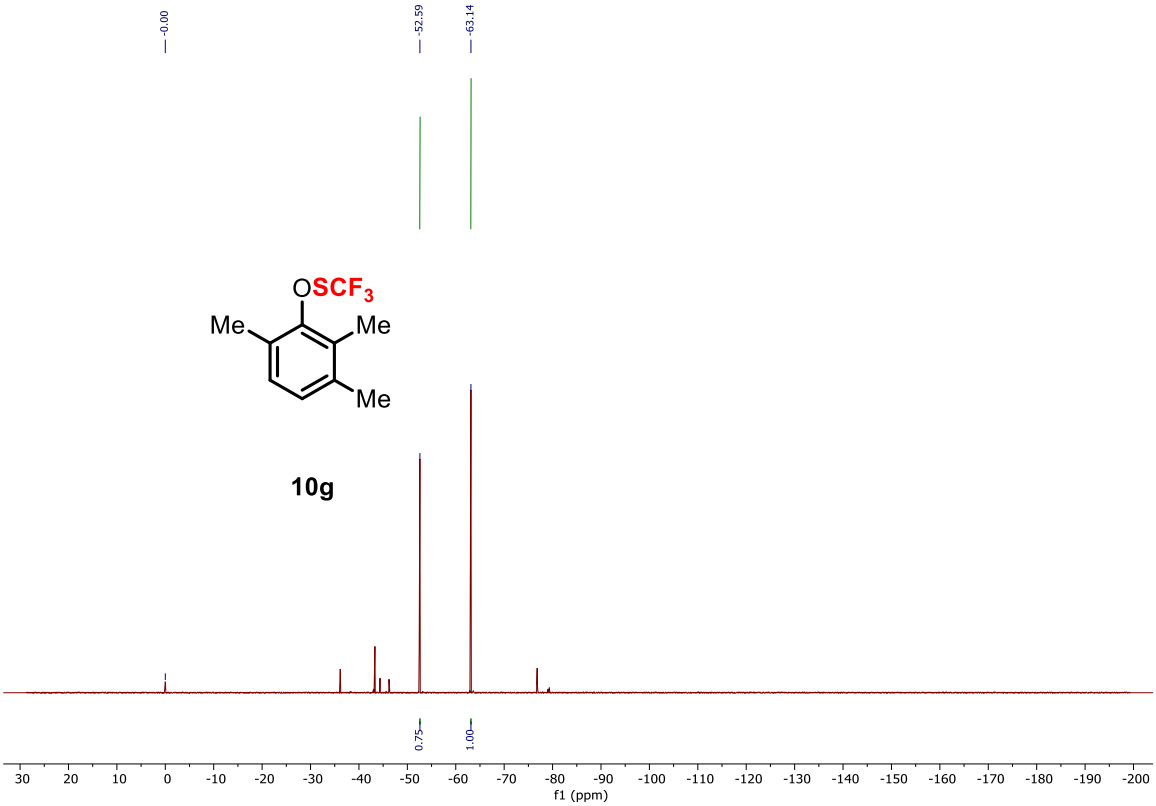
^{1}H NMR (400 MHz, $CDCl_3$) of 10f



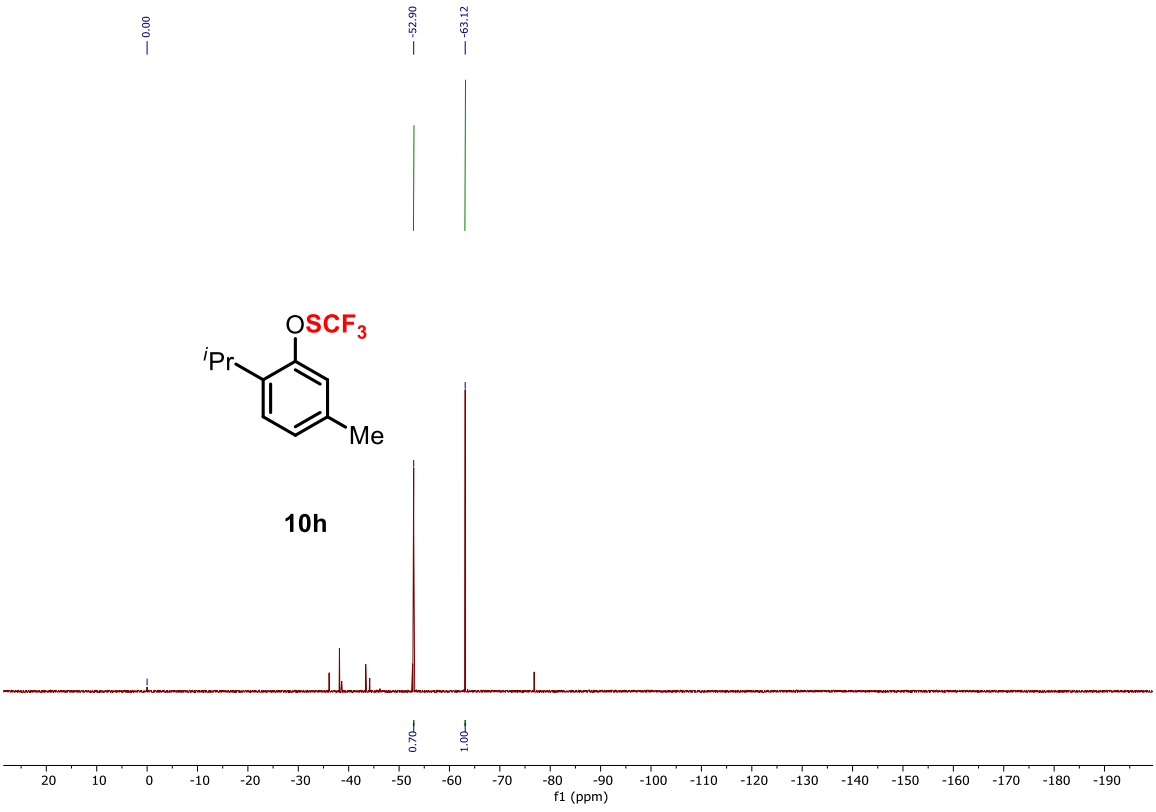
^{13}C NMR (100 MHz, $CDCl_3$) of 10f



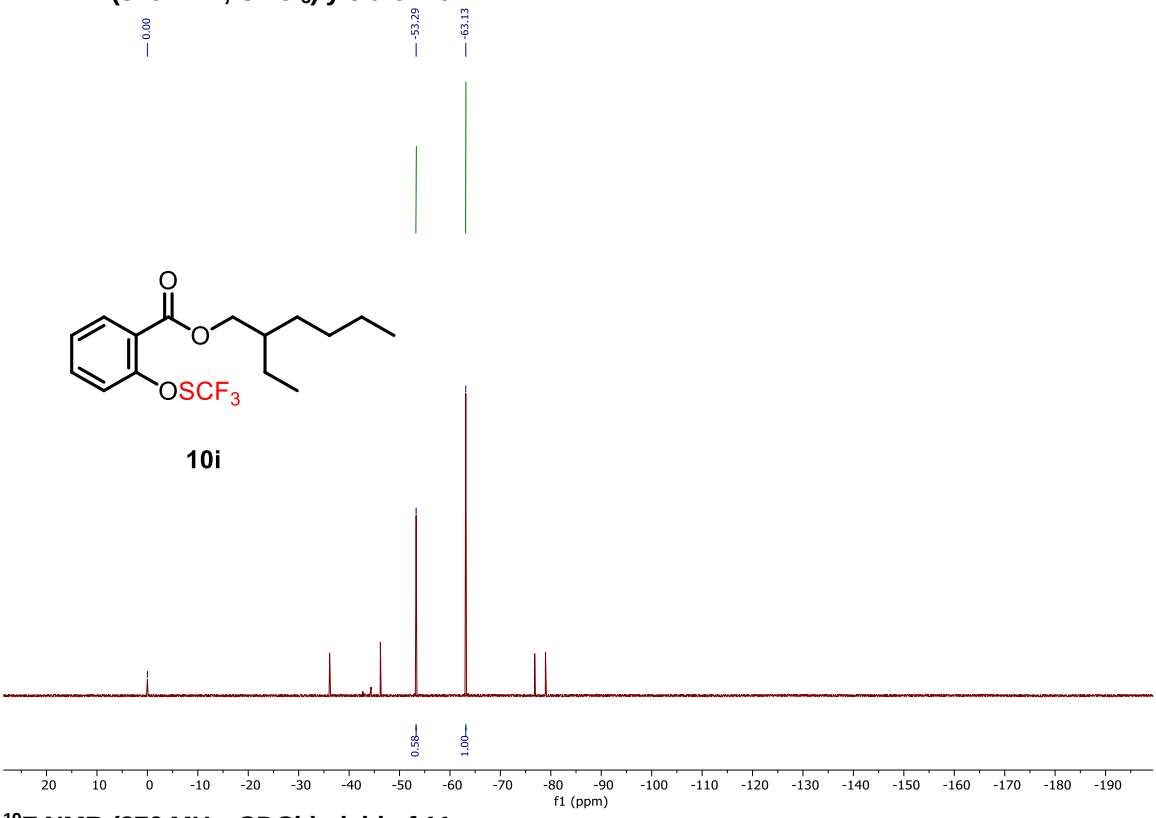
^{19}F NMR (376 MHz, $CDCl_3$) yield of 10g



^{19}F NMR (376 MHz, $CDCl_3$) yield of 10h

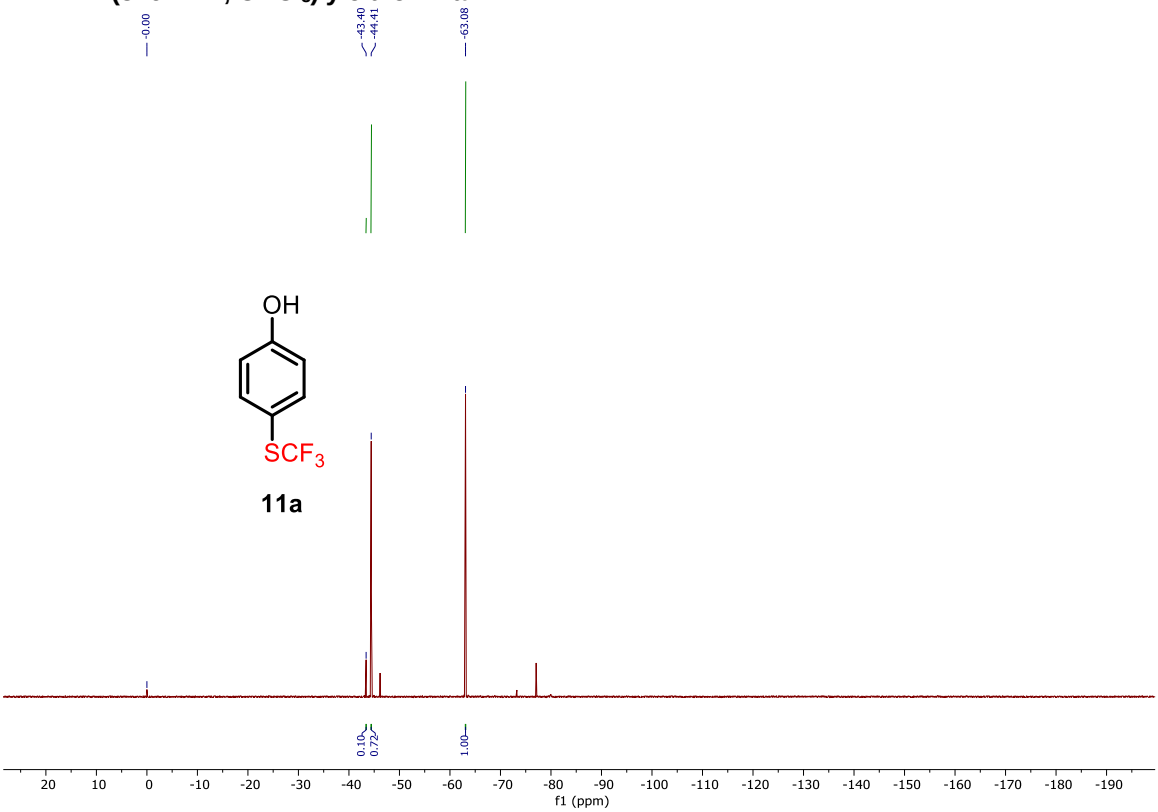


^{19}F NMR (376 MHz, $CDCl_3$) yield of 10i



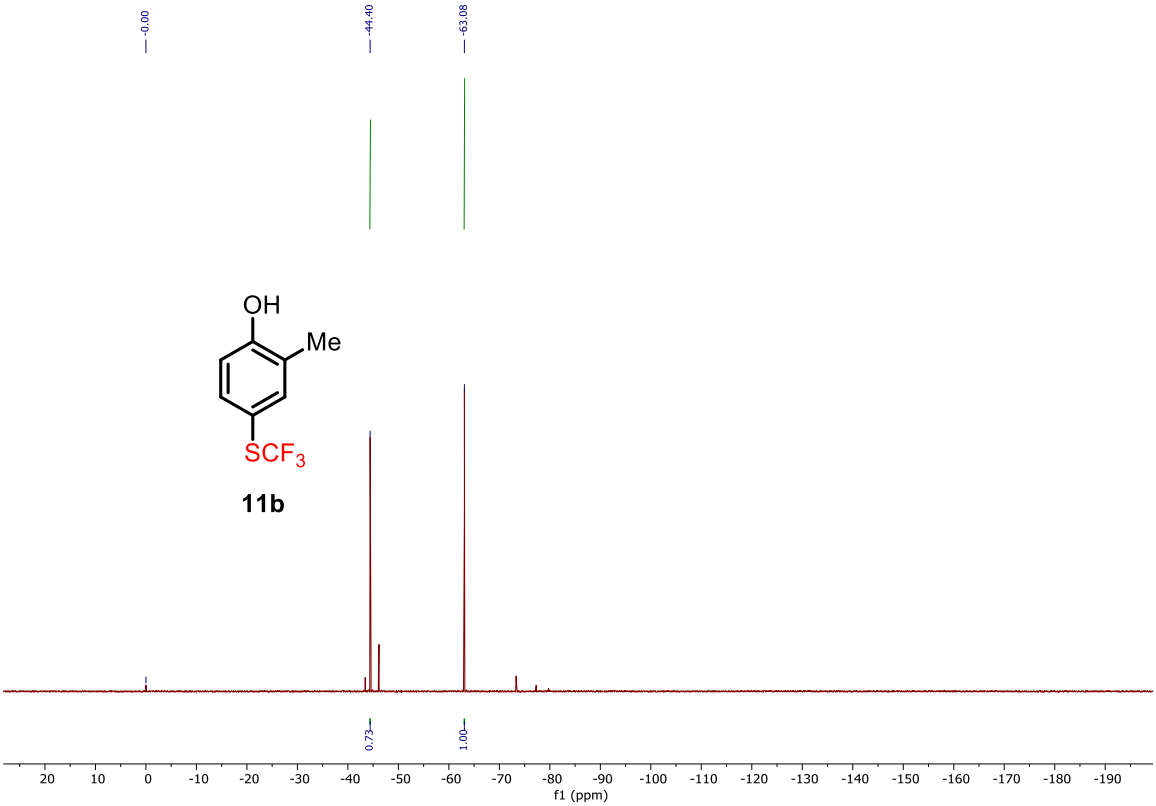
10i

^{19}F NMR (376 MHz, $CDCl_3$) yield of 11a

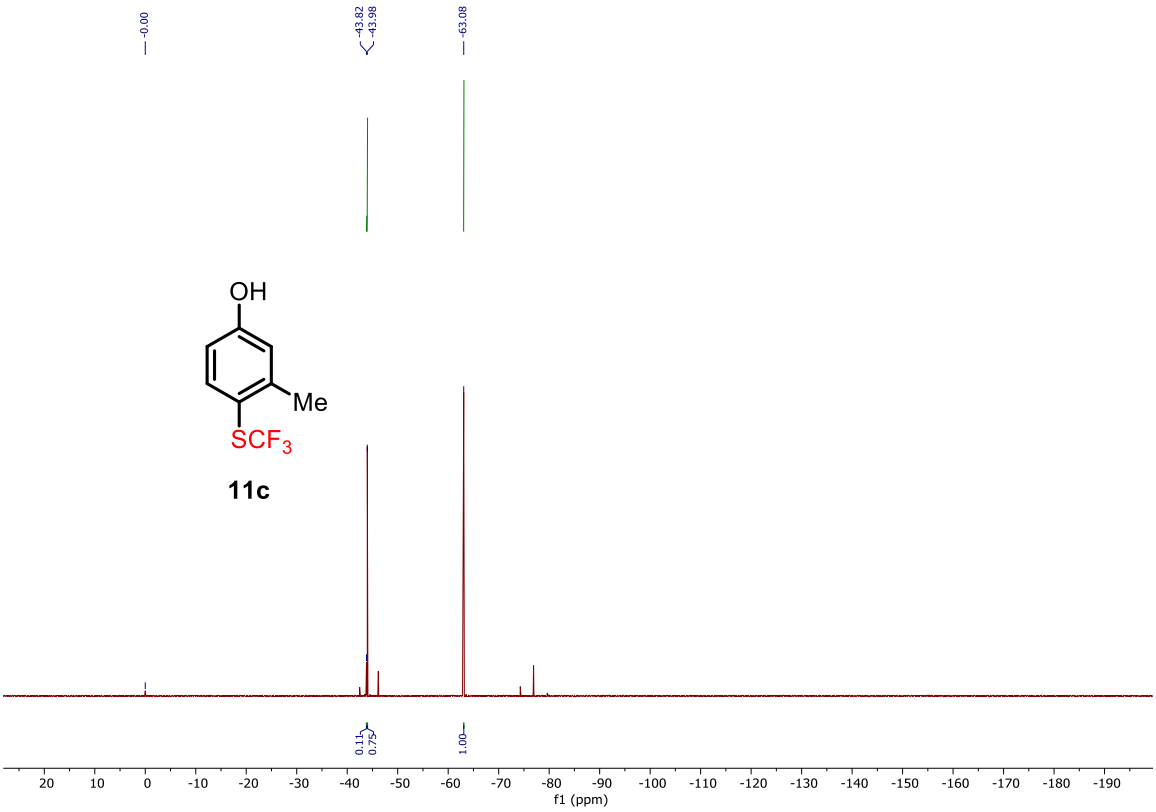


11a

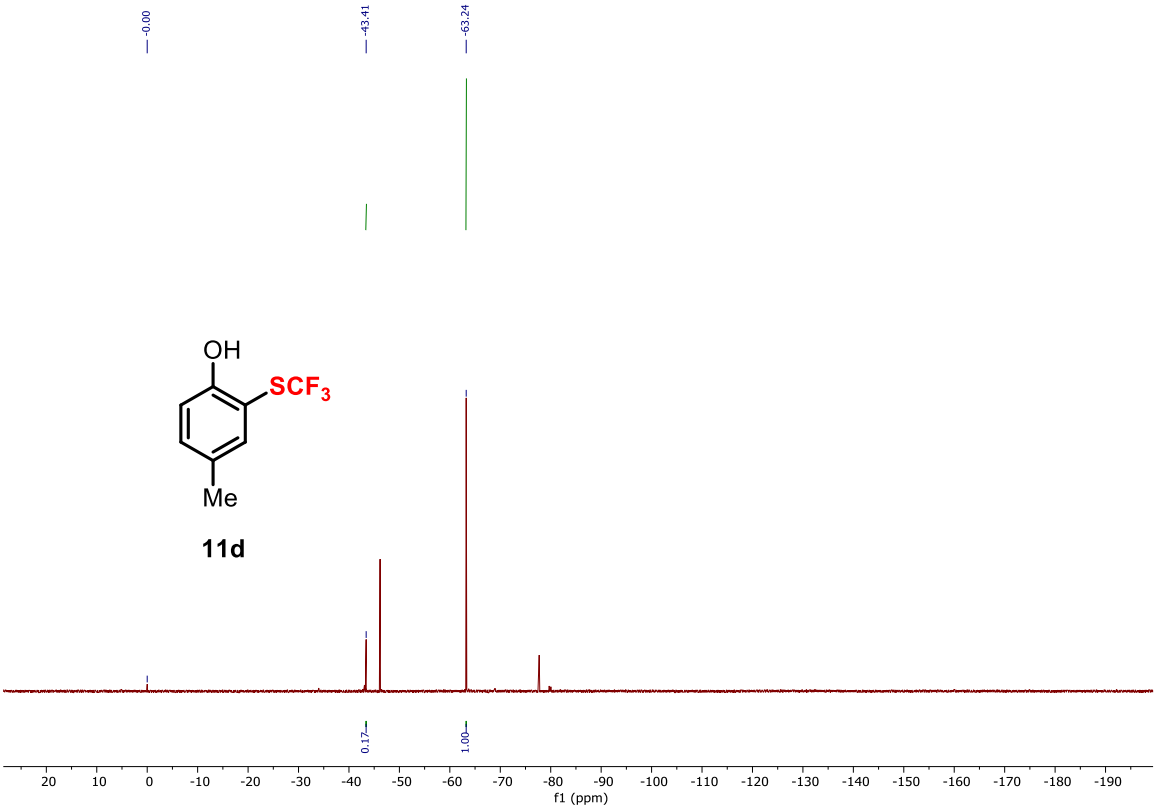
^{19}F NMR (376 MHz, $CDCl_3$) yield of 11b



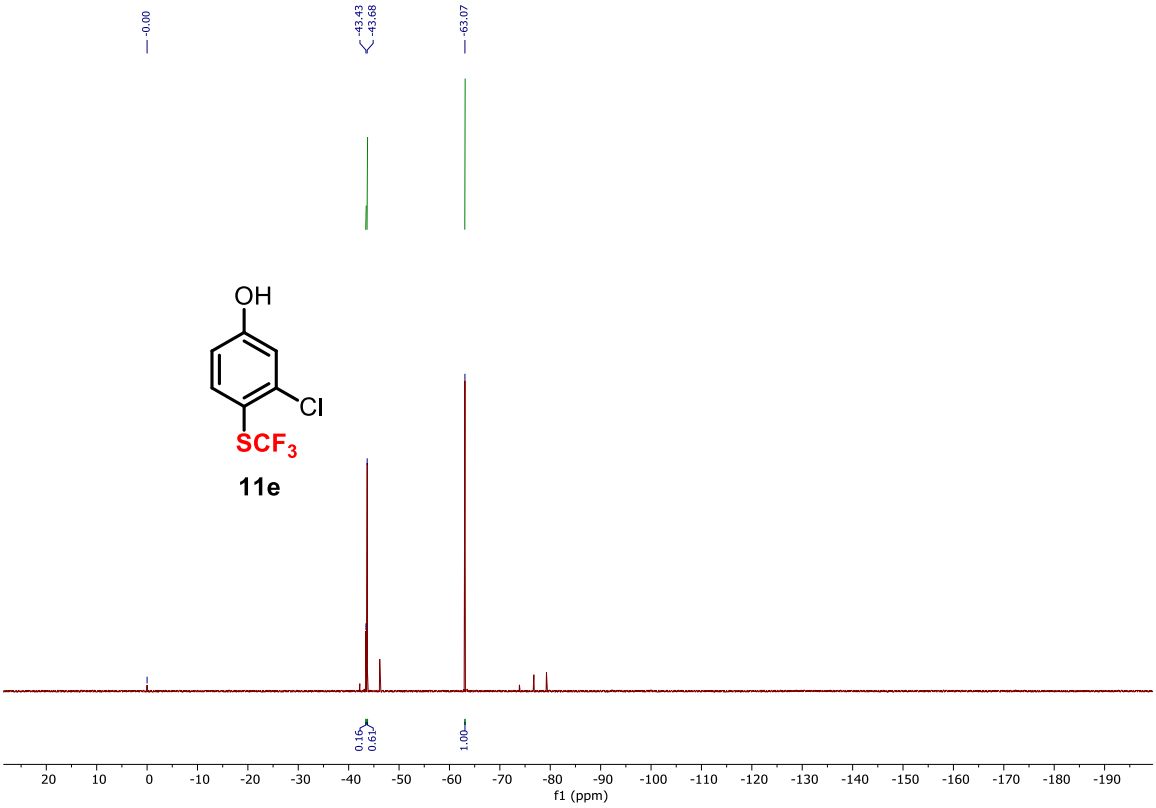
^{19}F NMR (376 MHz, $CDCl_3$) yield of 11c



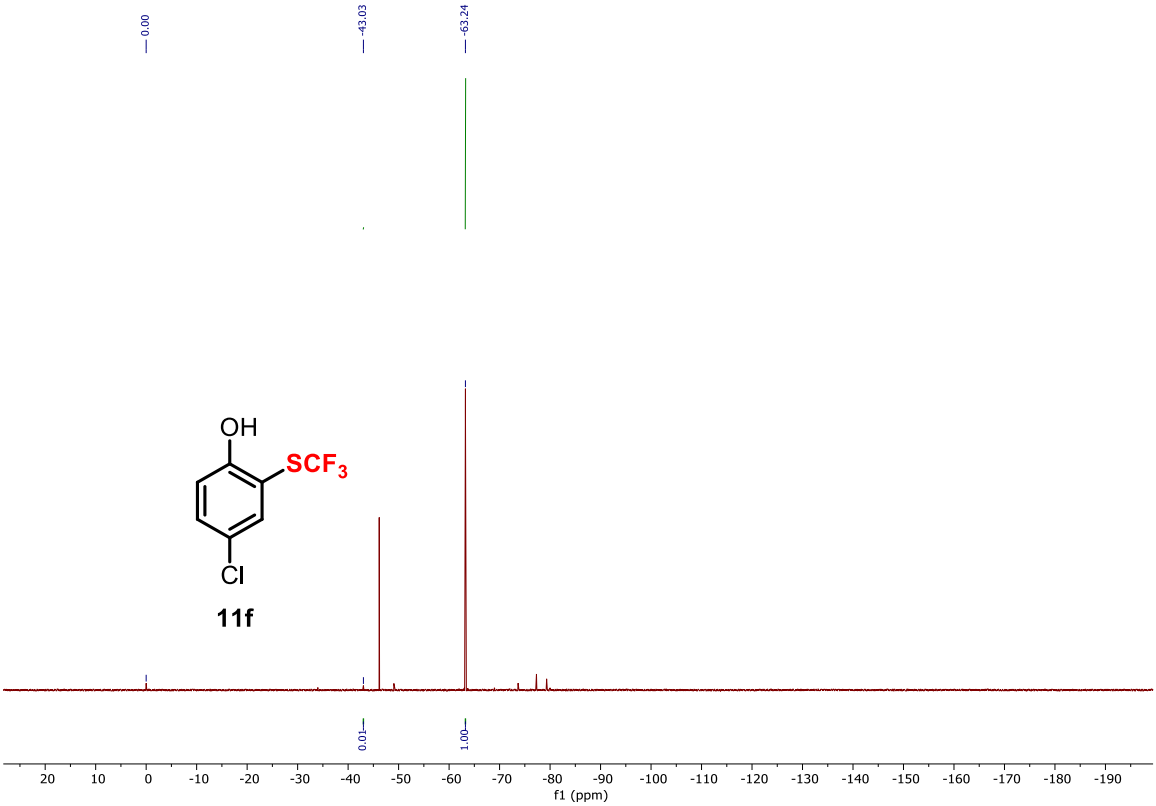
^{19}F NMR (376 MHz, $CDCl_3$) yield of 11d



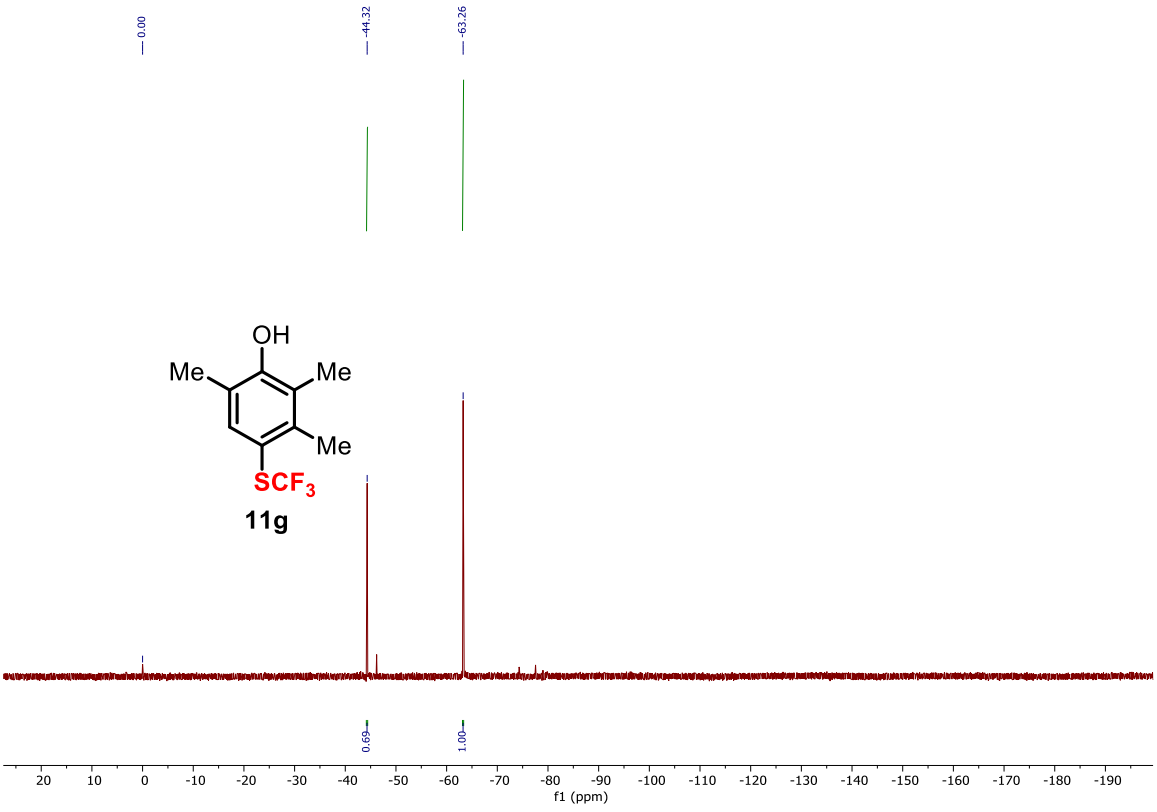
^{19}F NMR (376 MHz, $CDCl_3$) yield of 11e



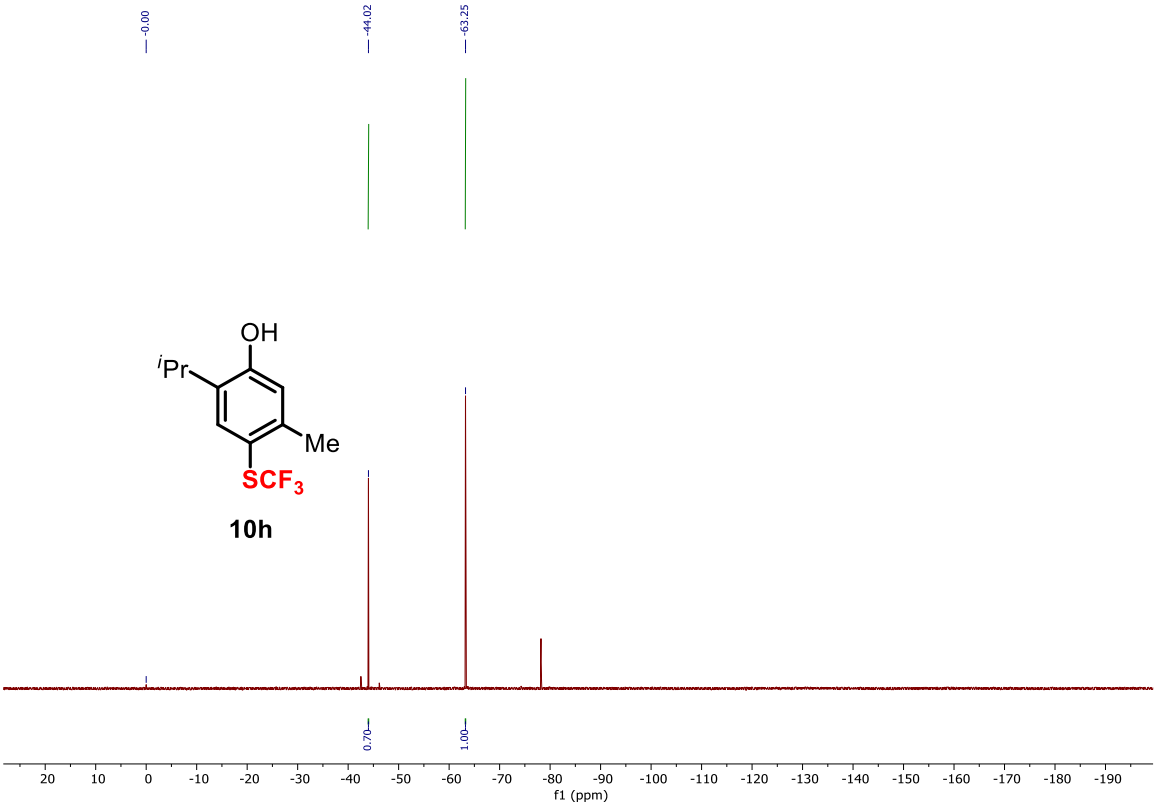
^{19}F NMR (376 MHz, $CDCl_3$) yield of 11f



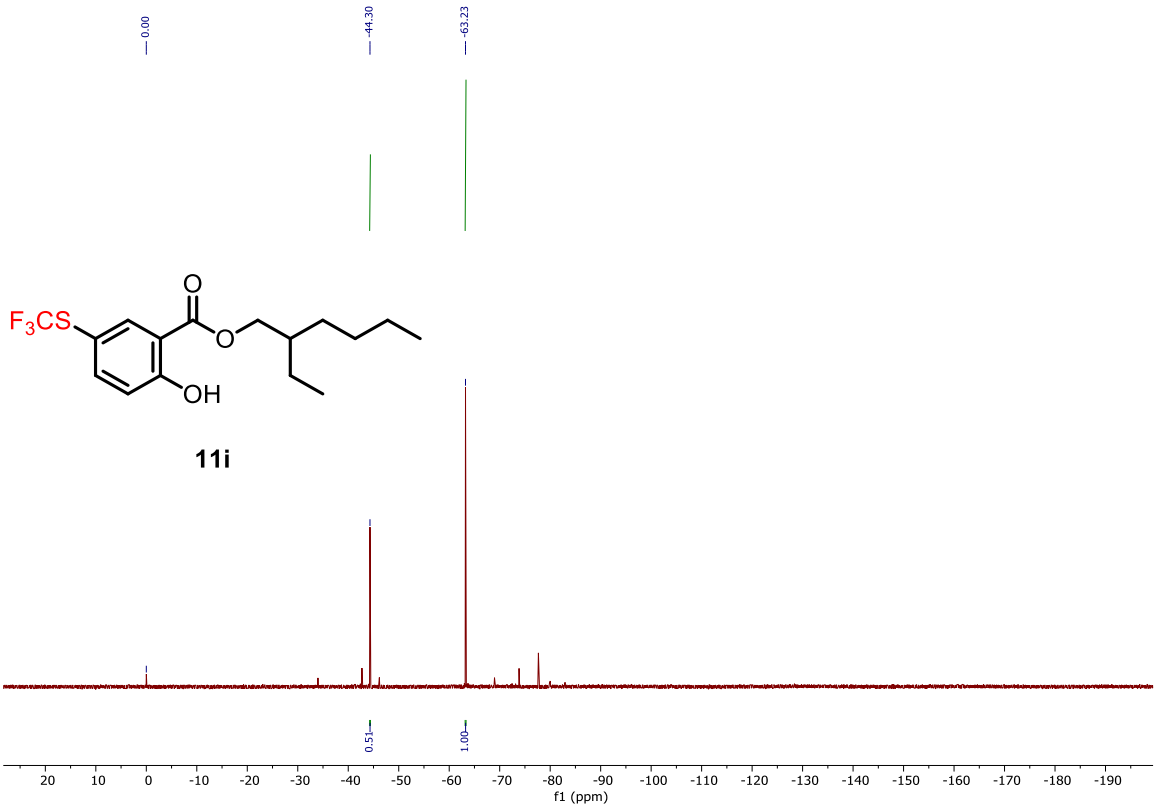
^{19}F NMR (376 MHz, $CDCl_3$) yield of 11g



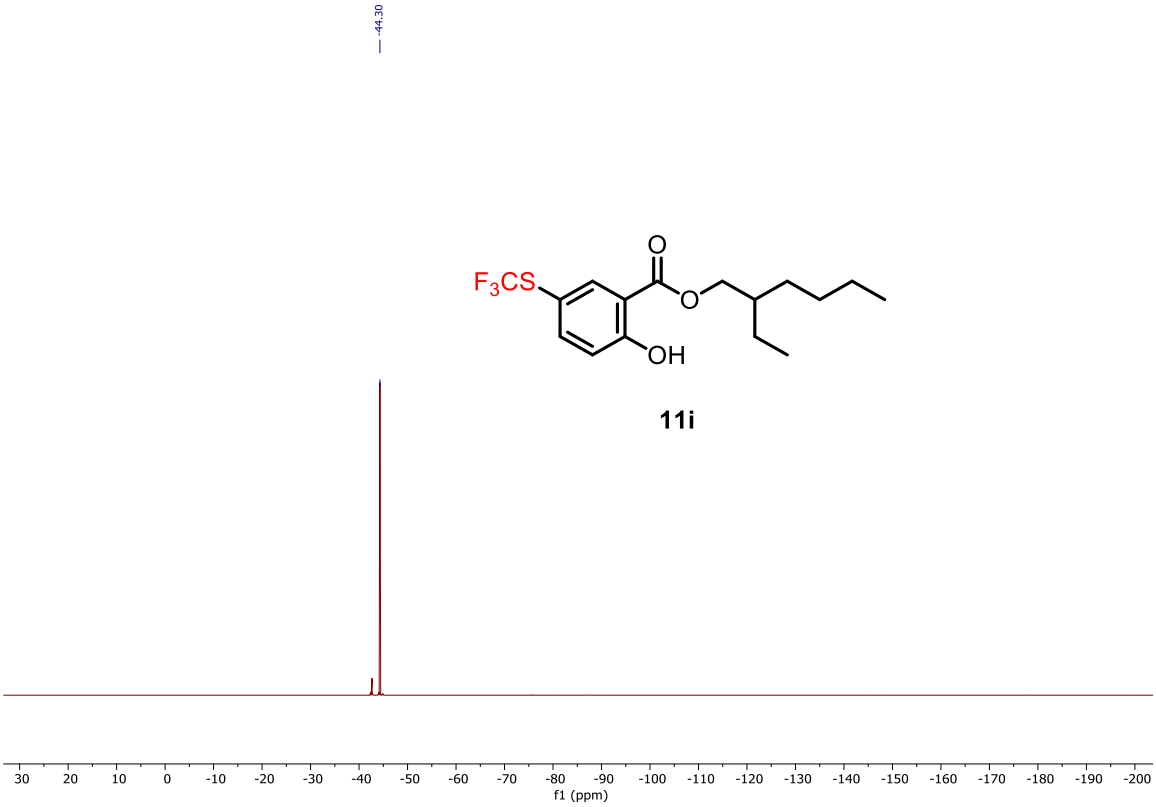
^{19}F NMR (376 MHz, $CDCl_3$) yield of 11h



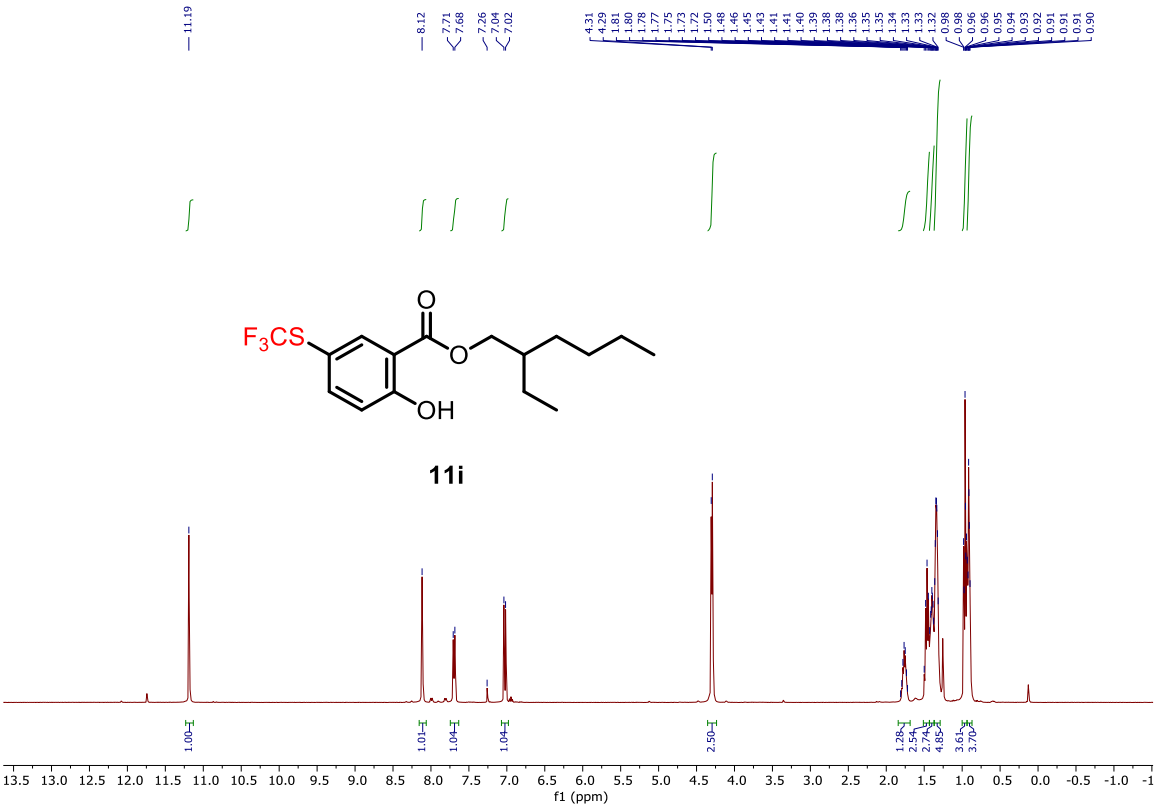
^{19}F NMR (376 MHz, $CDCl_3$) yield of 11i



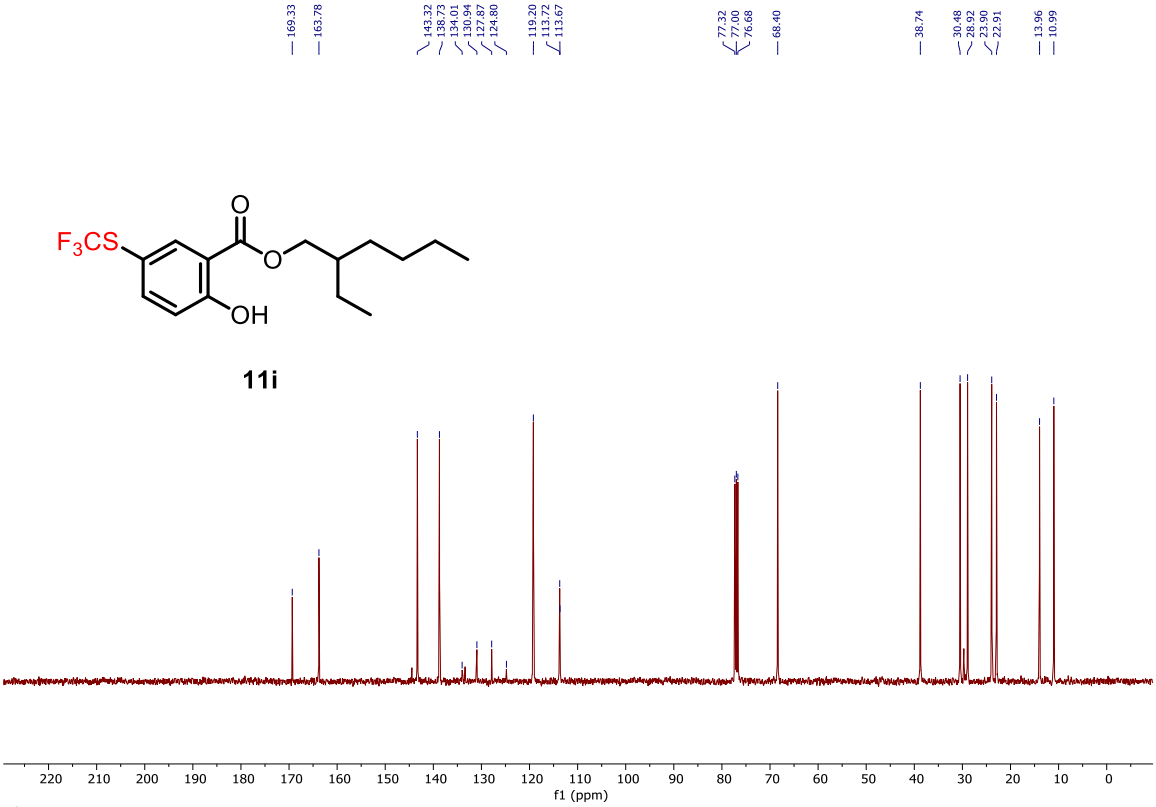
^{19}F NMR (376 MHz, $CDCl_3$) 11i



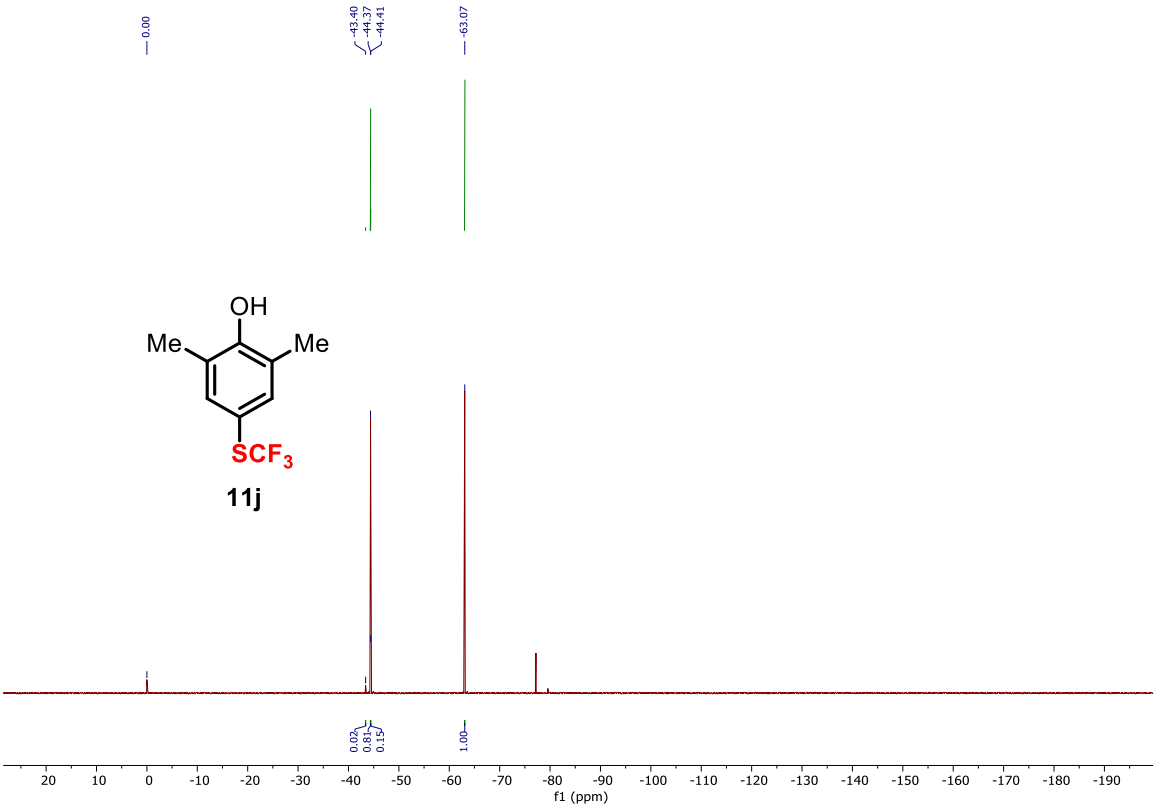
^{1}H NMR (400 MHz, $CDCl_3$) 11i



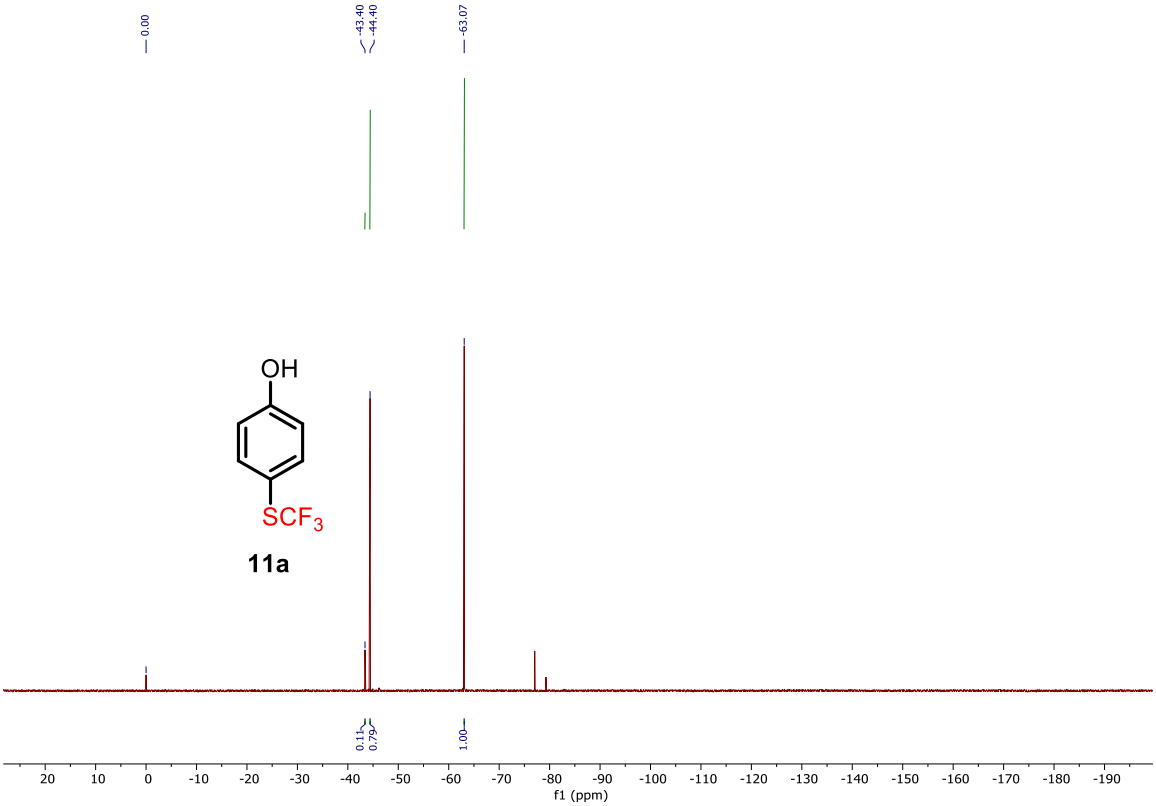
^{13}C NMR (100 MHz, $CDCl_3$) 11i



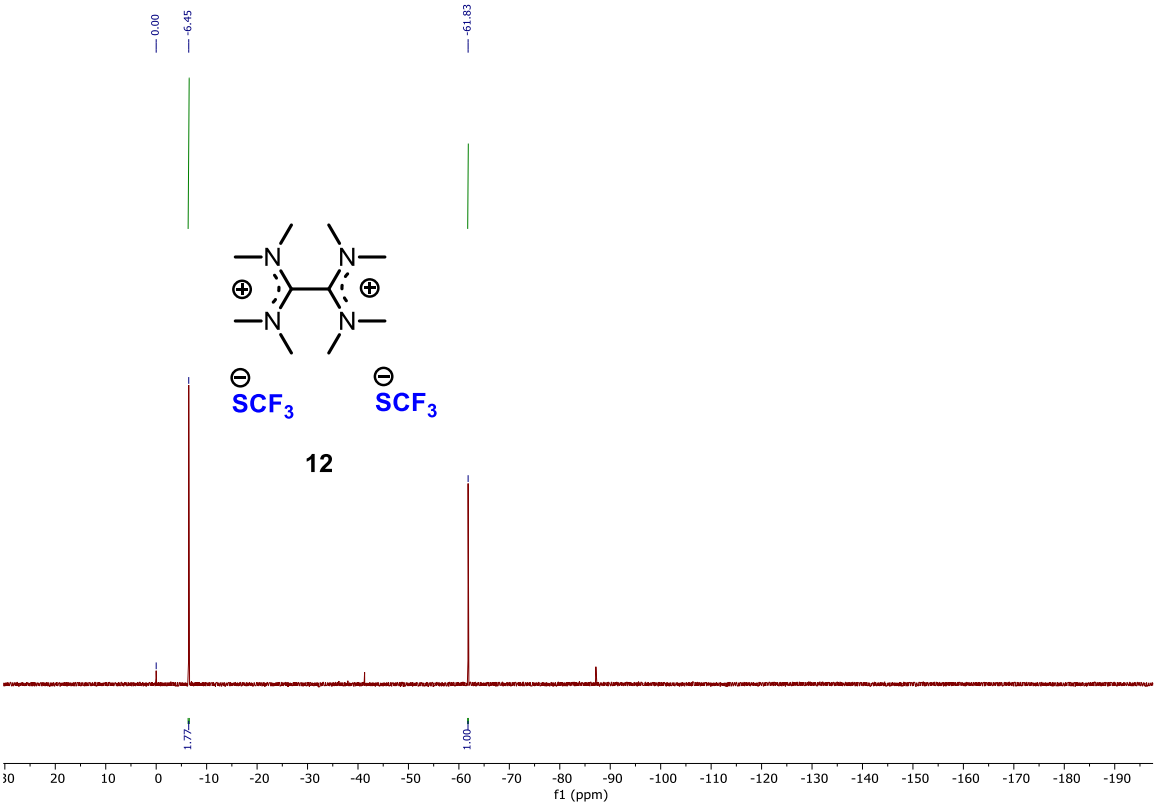
^{19}F NMR (376 MHz, $CDCl_3$) yield of 11j (mechanistic studies)



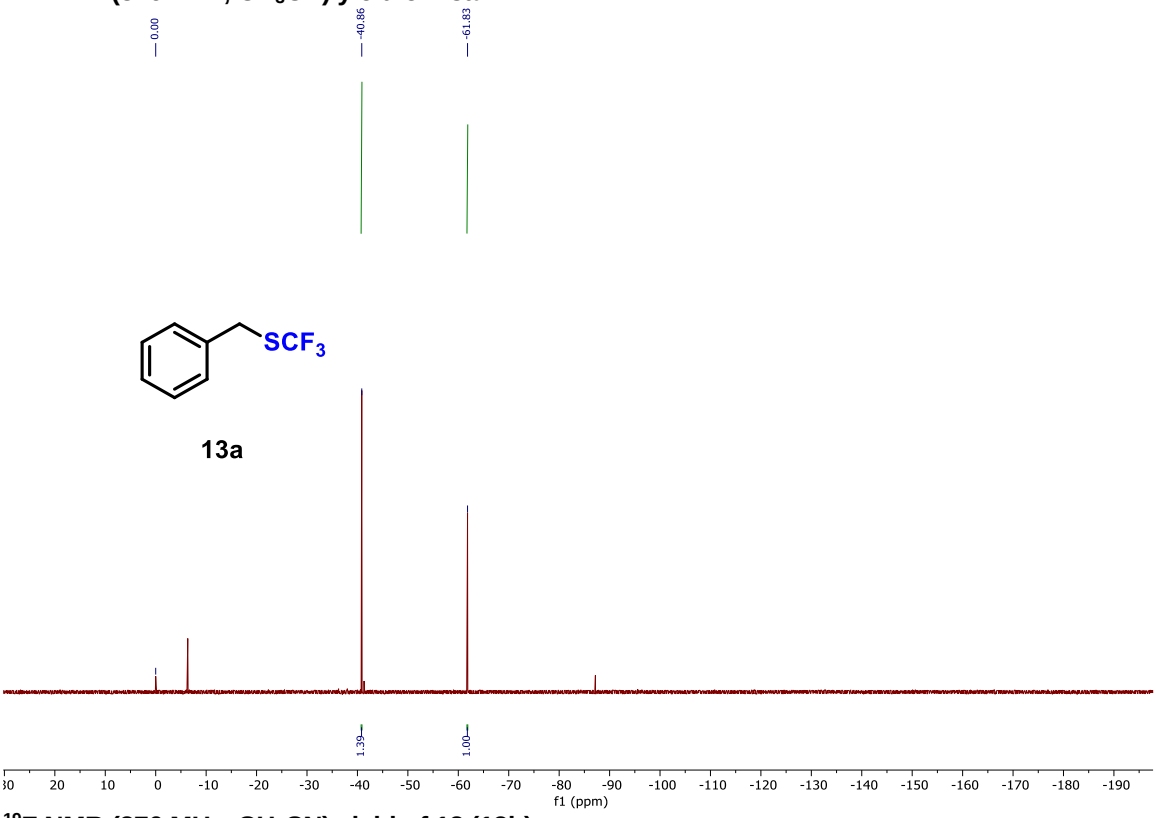
^{19}F NMR (376 MHz, $CDCl_3$) yield of 11a (mechanistic studies)



^{19}F NMR (376 MHz, CH_3CN) yield of 12 (13a)

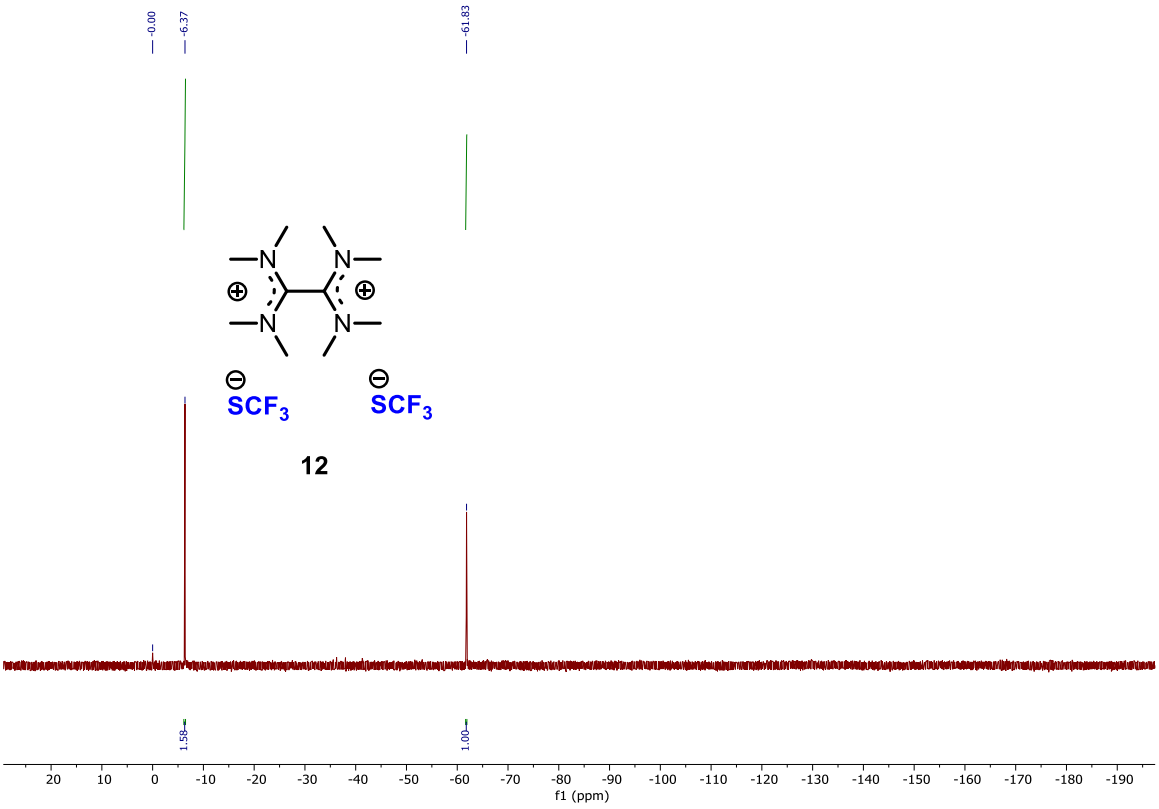


^{19}F NMR (376 MHz, CH_3CN) yield of 13a



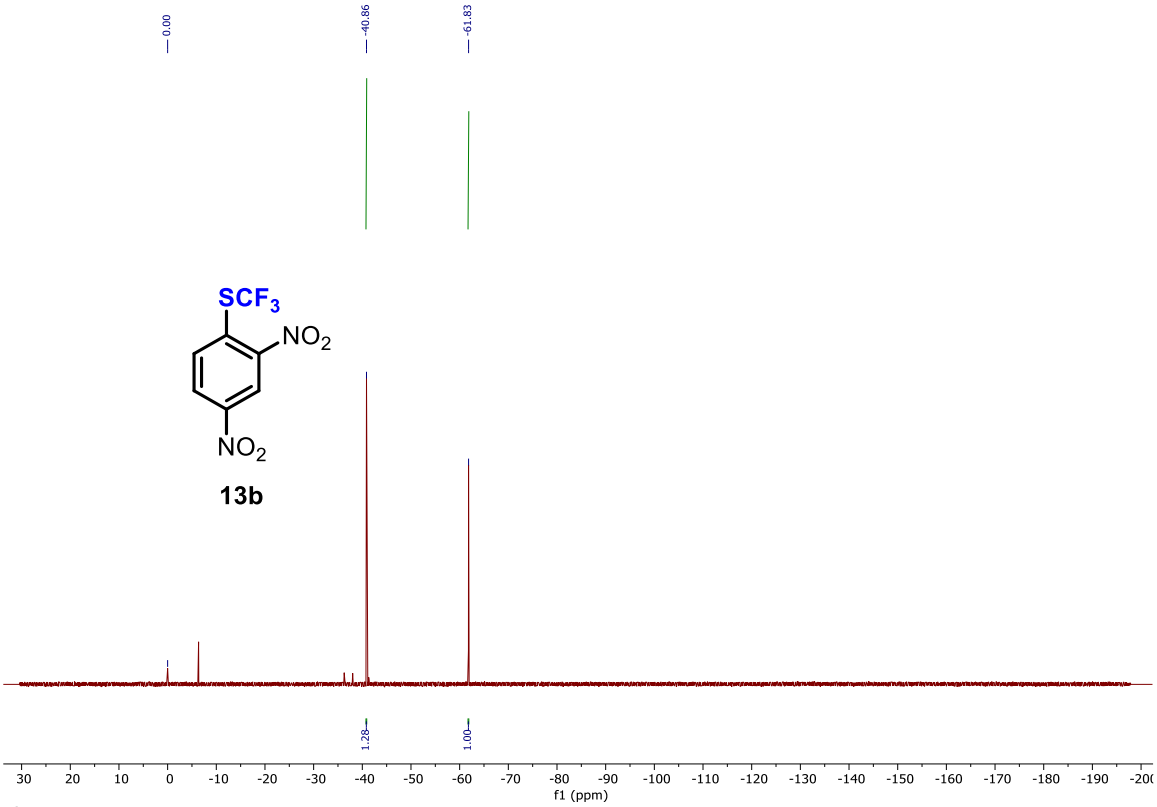
13a

^{19}F NMR (376 MHz, CH_3CN) yield of 12 (13b)

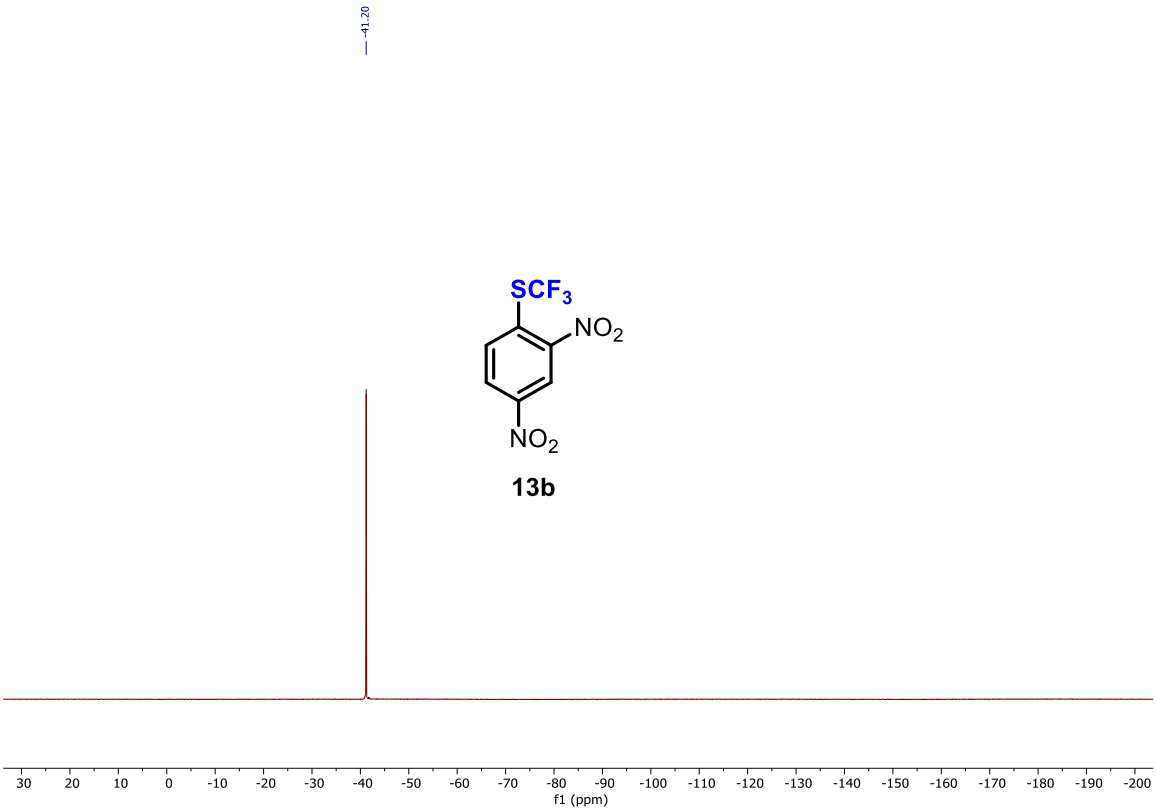


12

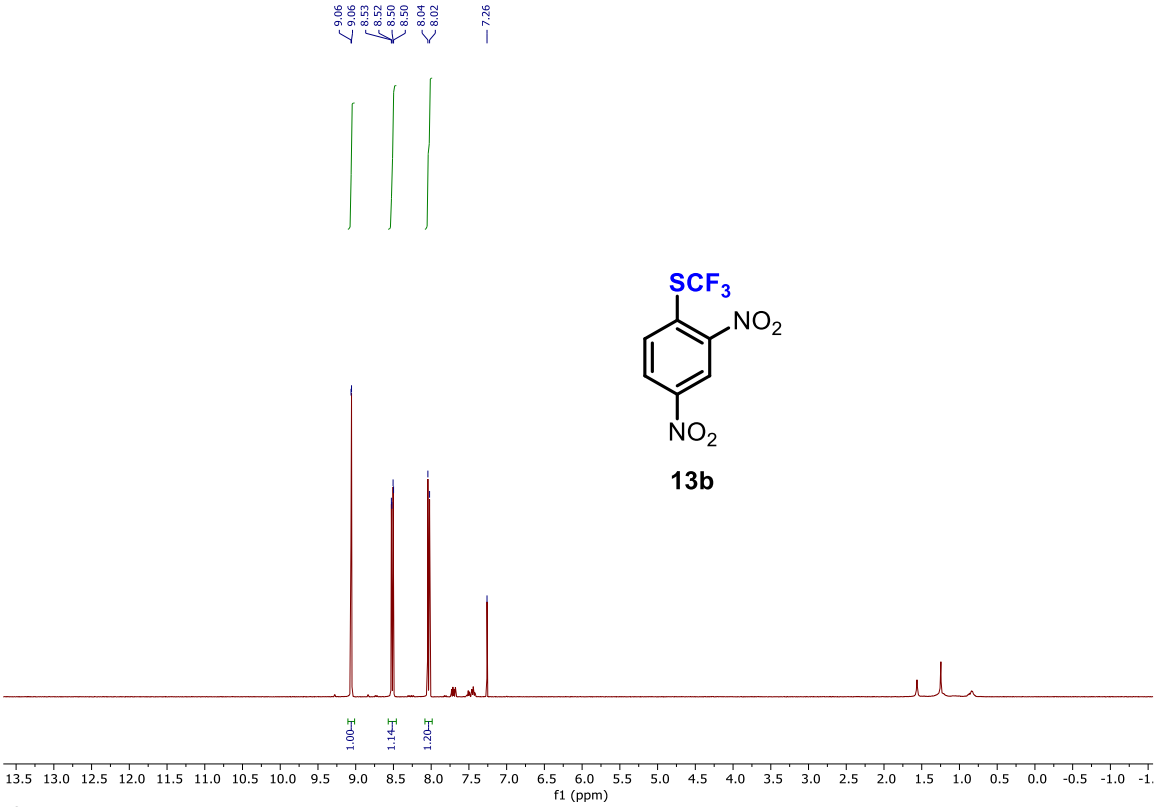
^{19}F NMR (376 MHz, CH_3CN) yield of 13b



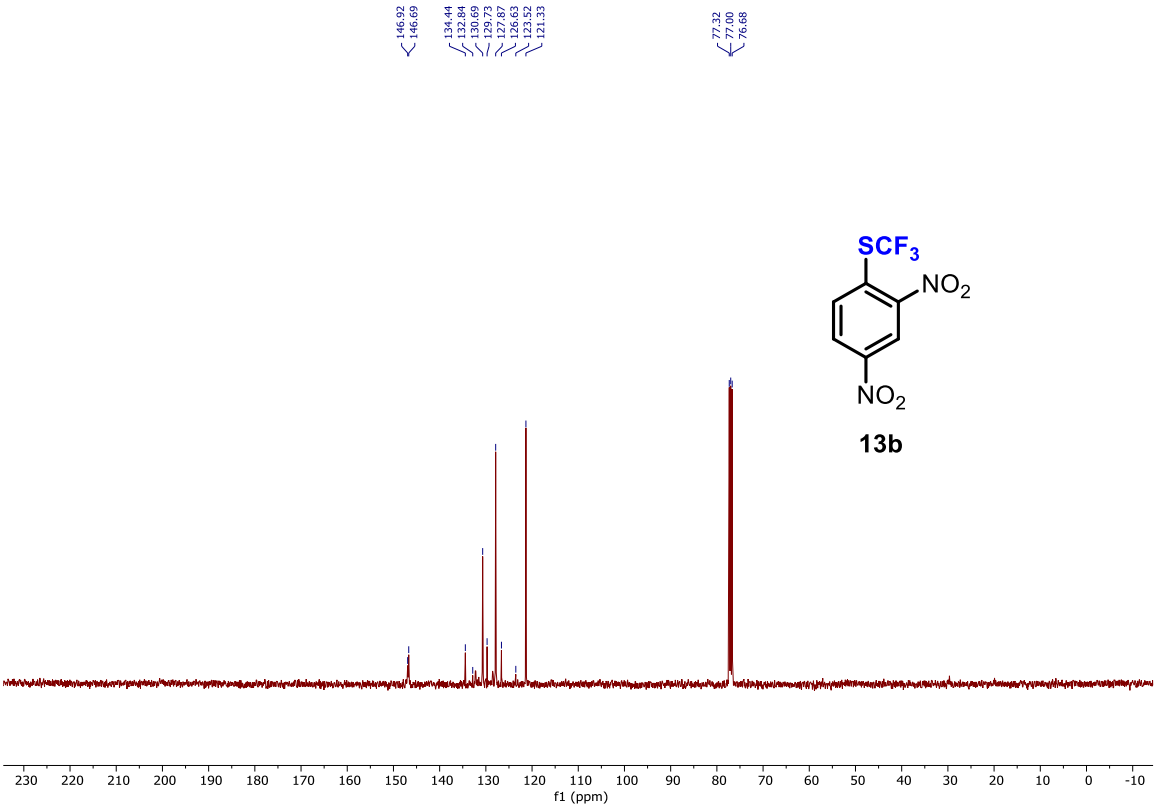
^{19}F NMR (376 MHz, $CDCl_3$) 13b



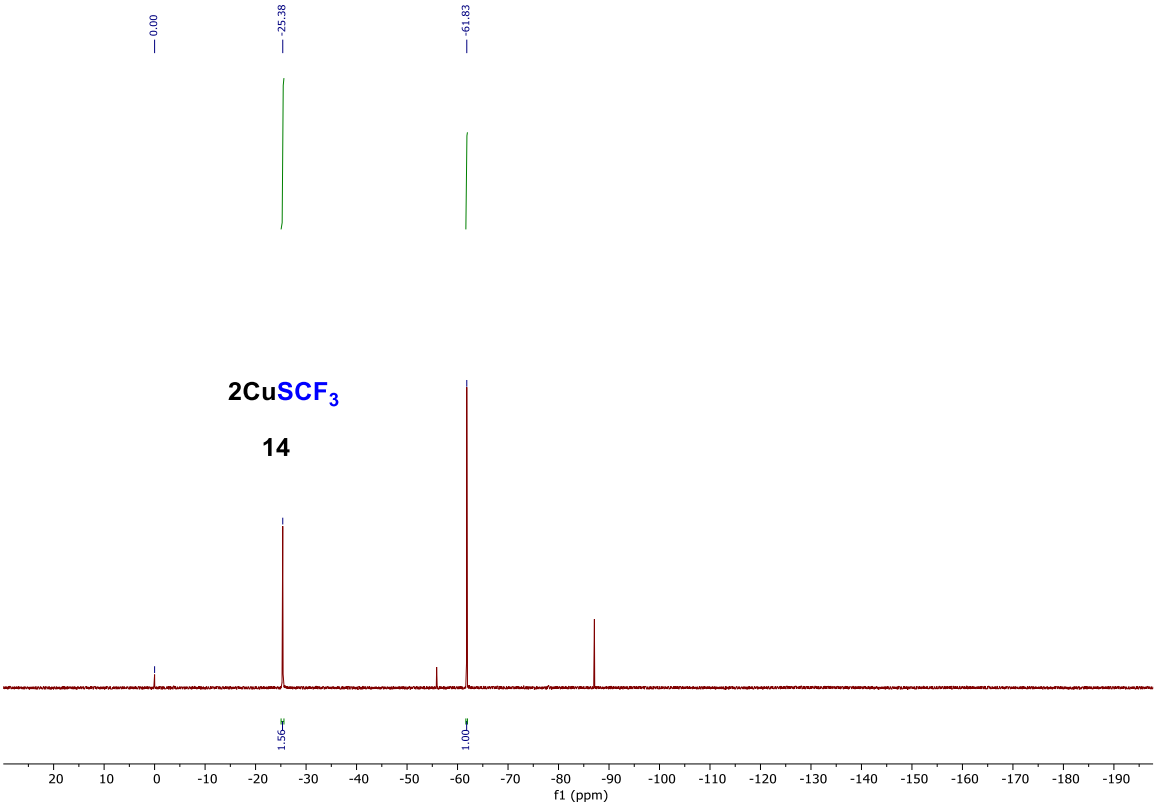
^{1}H NMR (400 MHz, $CDCl_3$) 13b



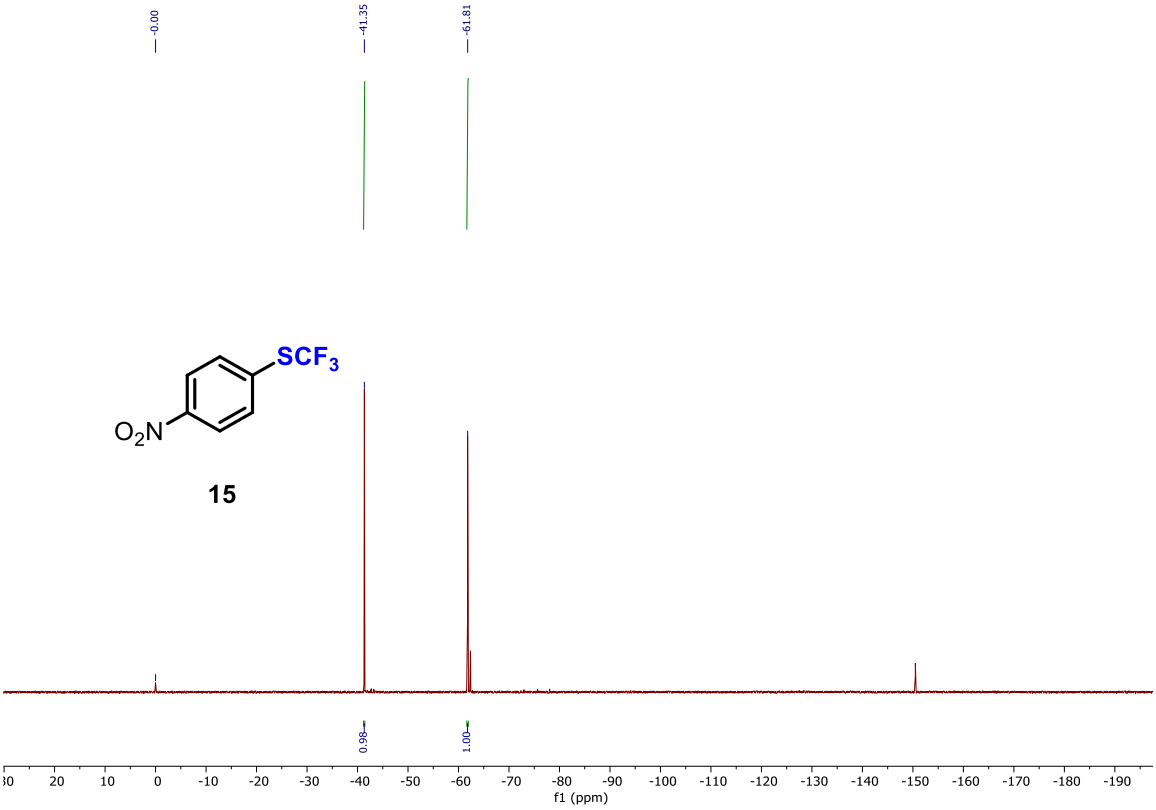
^{13}C NMR (100 MHz, $CDCl_3$) 13b



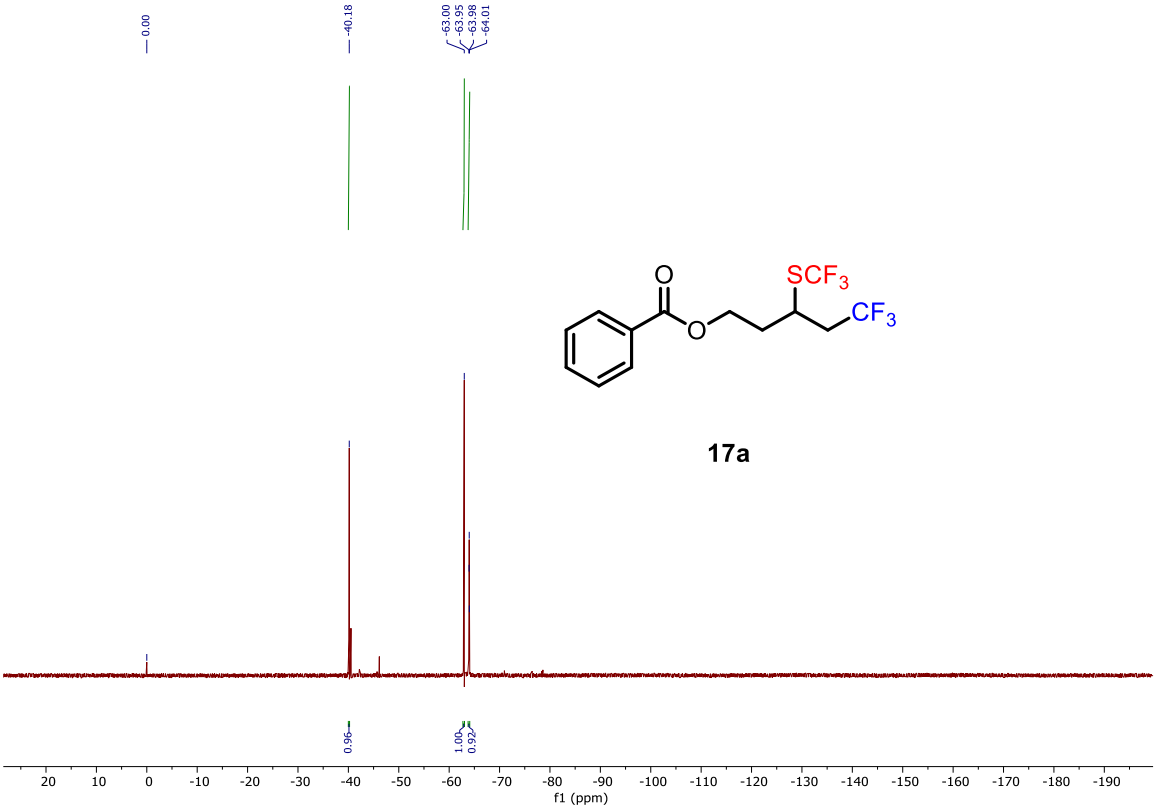
^{19}F NMR (376 MHz, $CDCl_3$) yield of 14



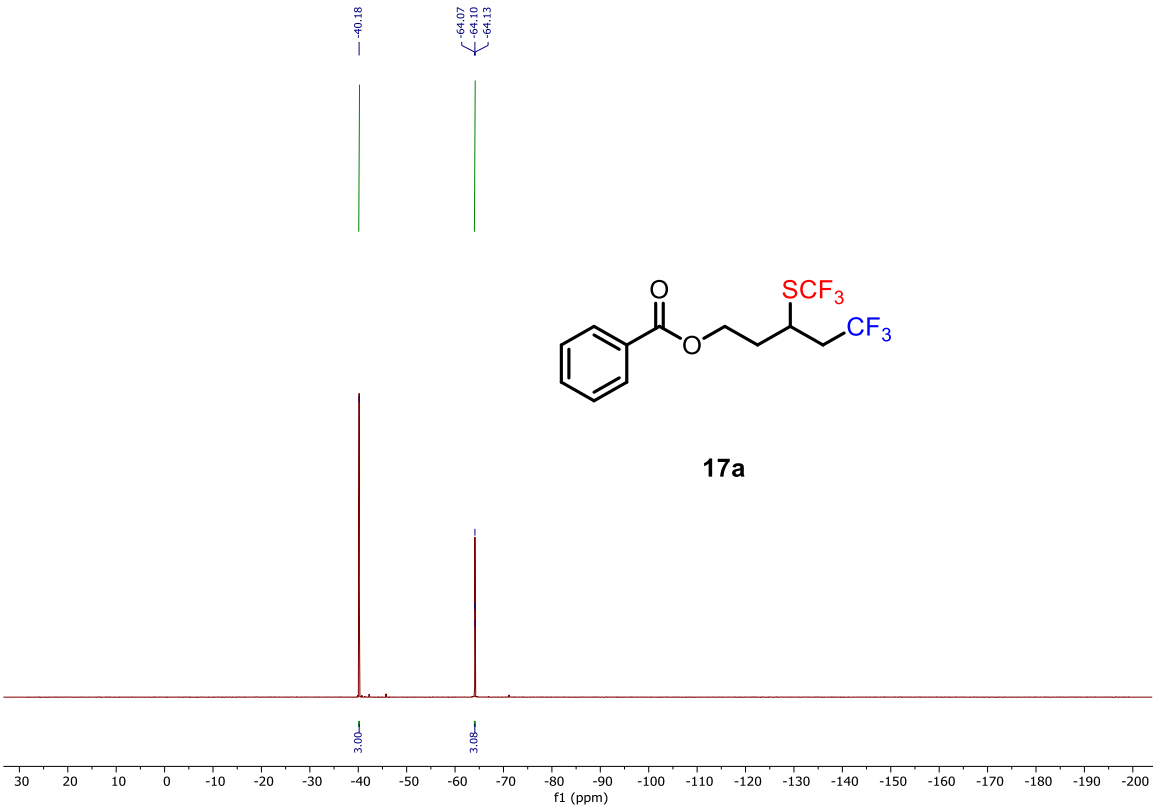
^{19}F NMR (376 MHz, $CDCl_3$) yield of 15



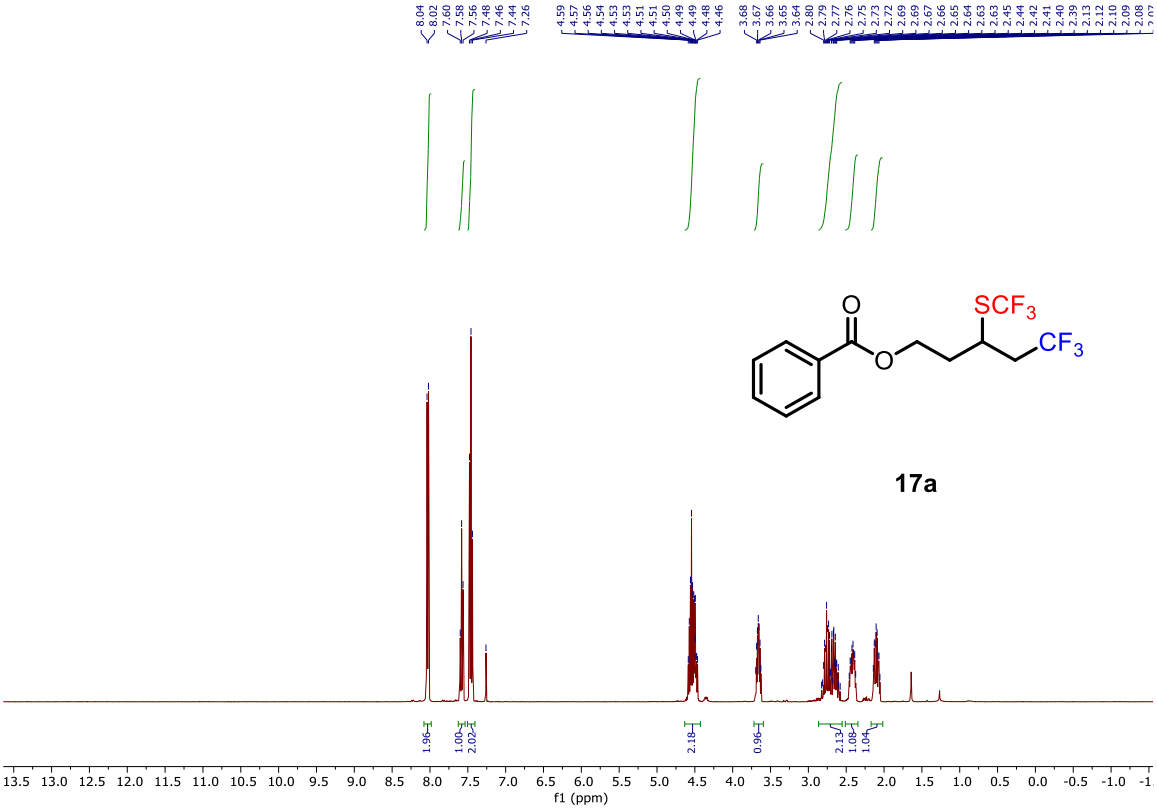
^{19}F NMR (376 MHz, $CDCl_3$) yield of 17a



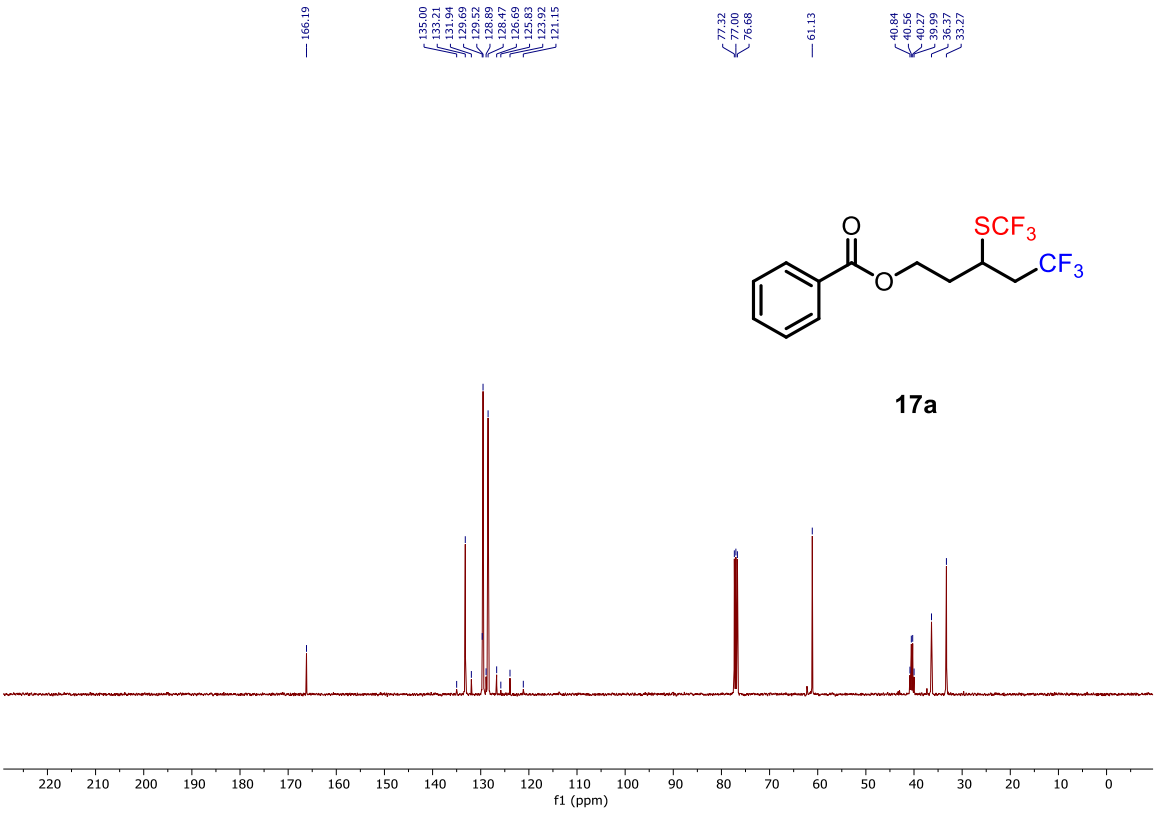
^{19}F NMR (376 MHz, $CDCl_3$) 17a



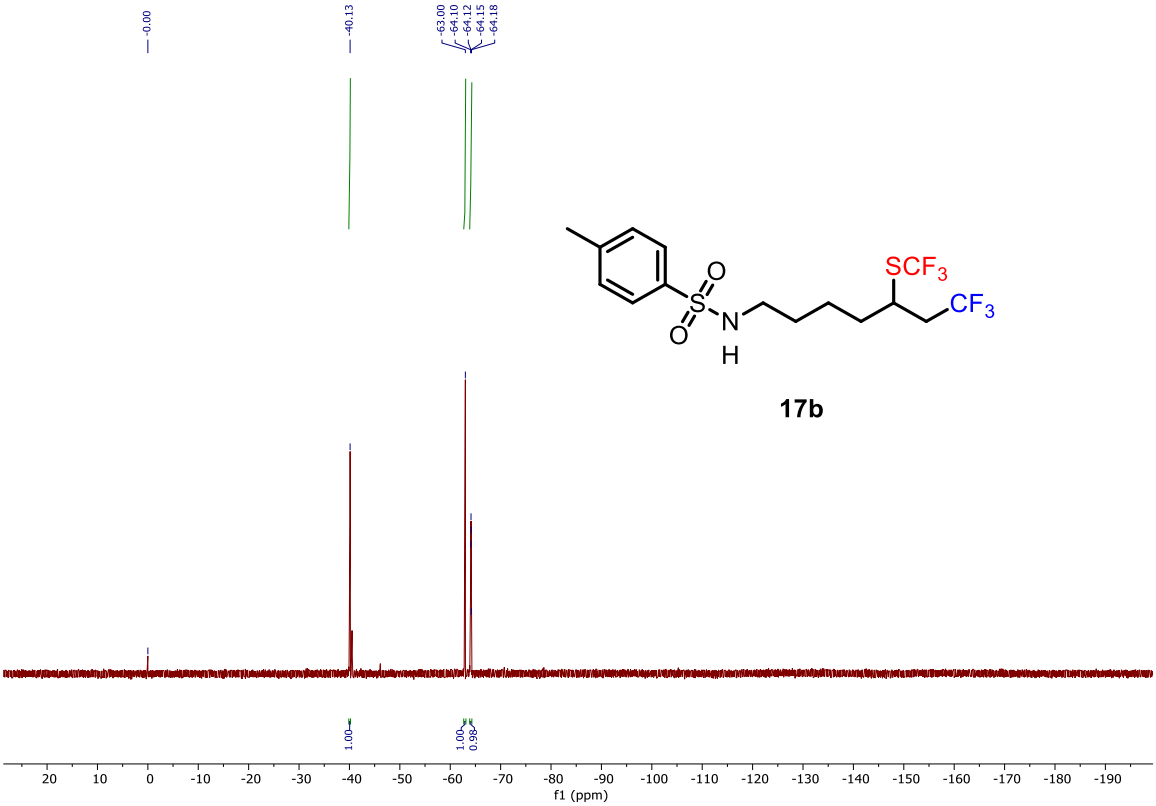
^{1}H NMR (400 MHz, $CDCl_3$) 17a



^{13}C NMR (100 MHz, $CDCl_3$) 17a

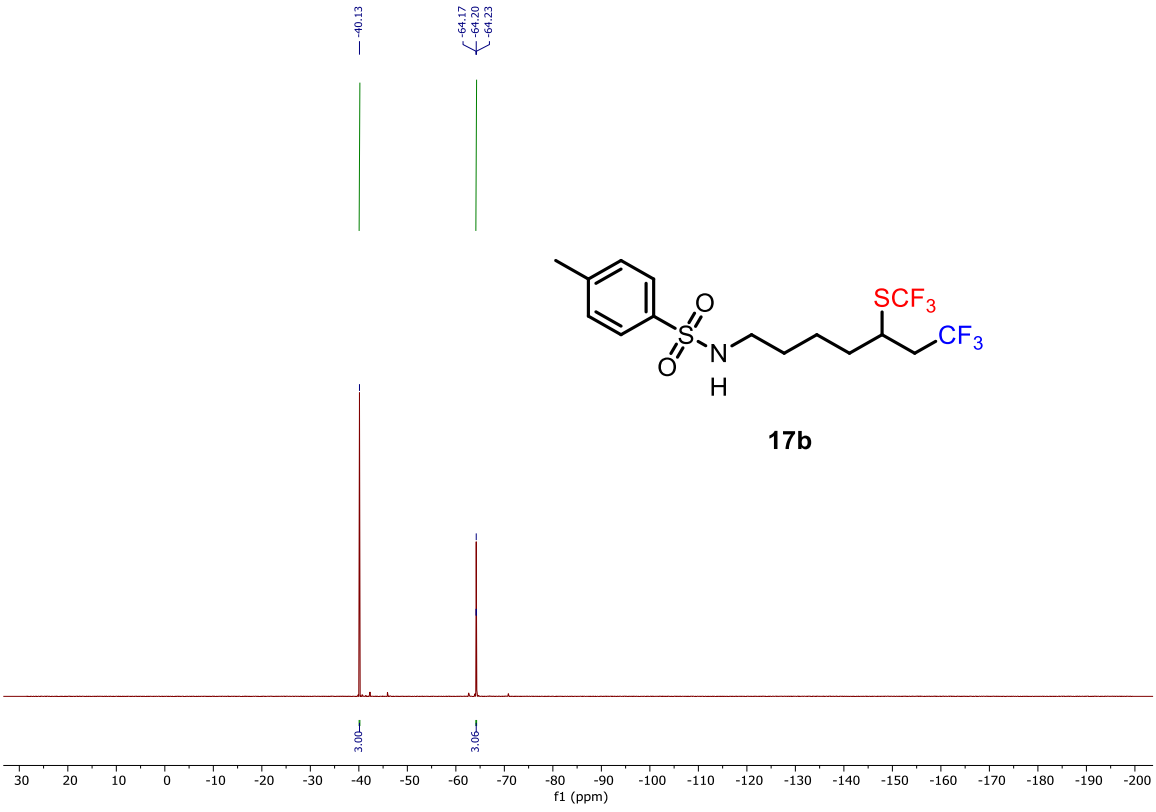


^{19}F NMR (376 MHz, $CDCl_3$) yield of 17b



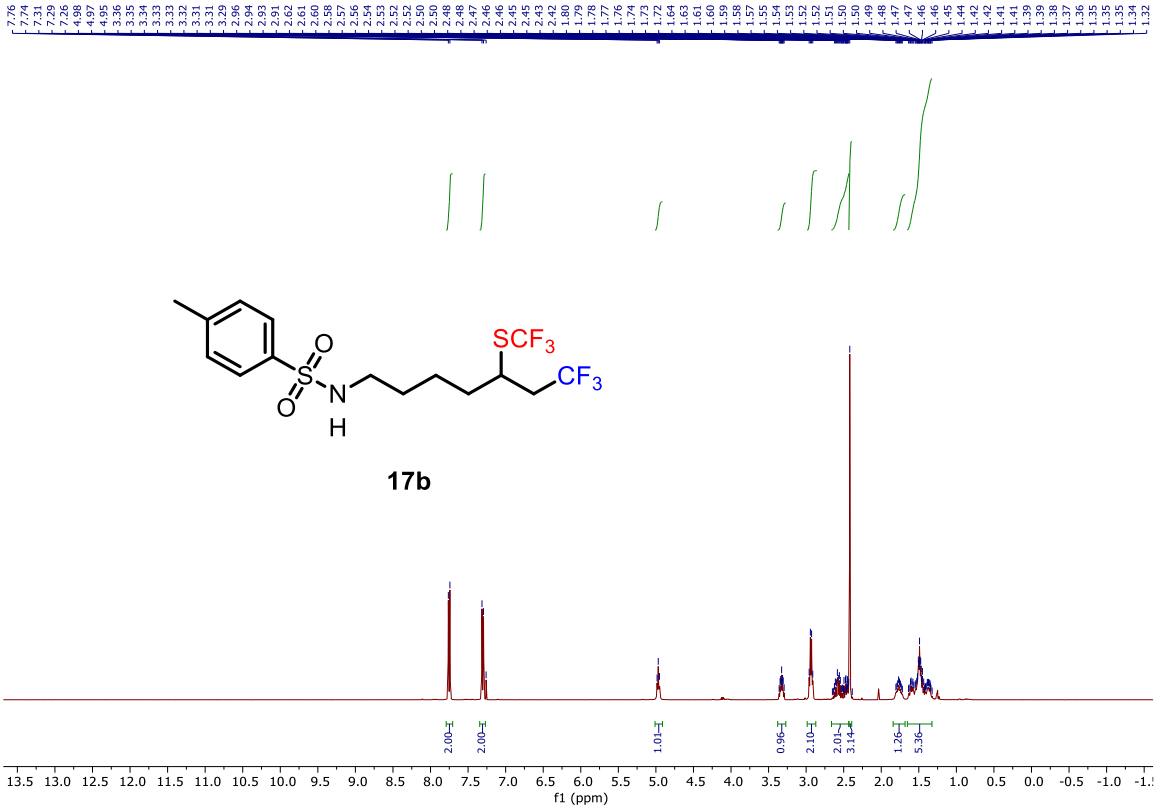
17b

^{19}F NMR (376 MHz, $CDCl_3$) 17b

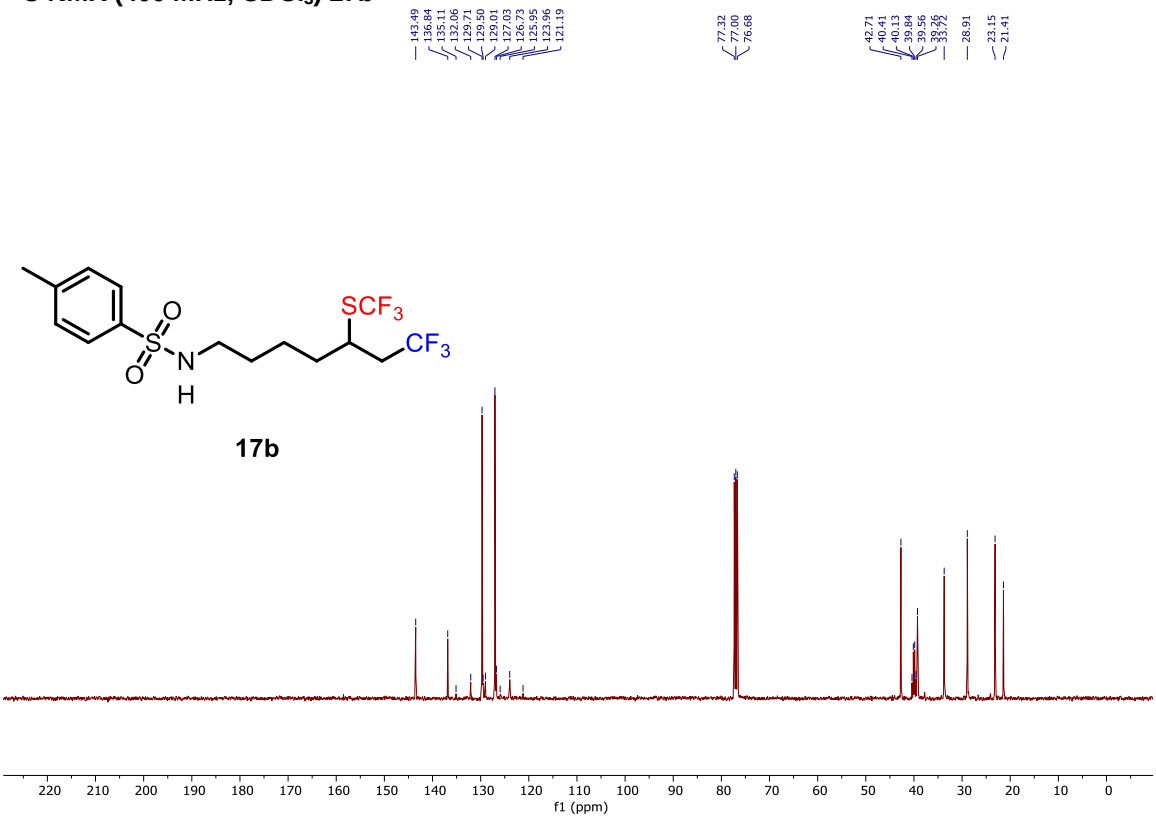


17b

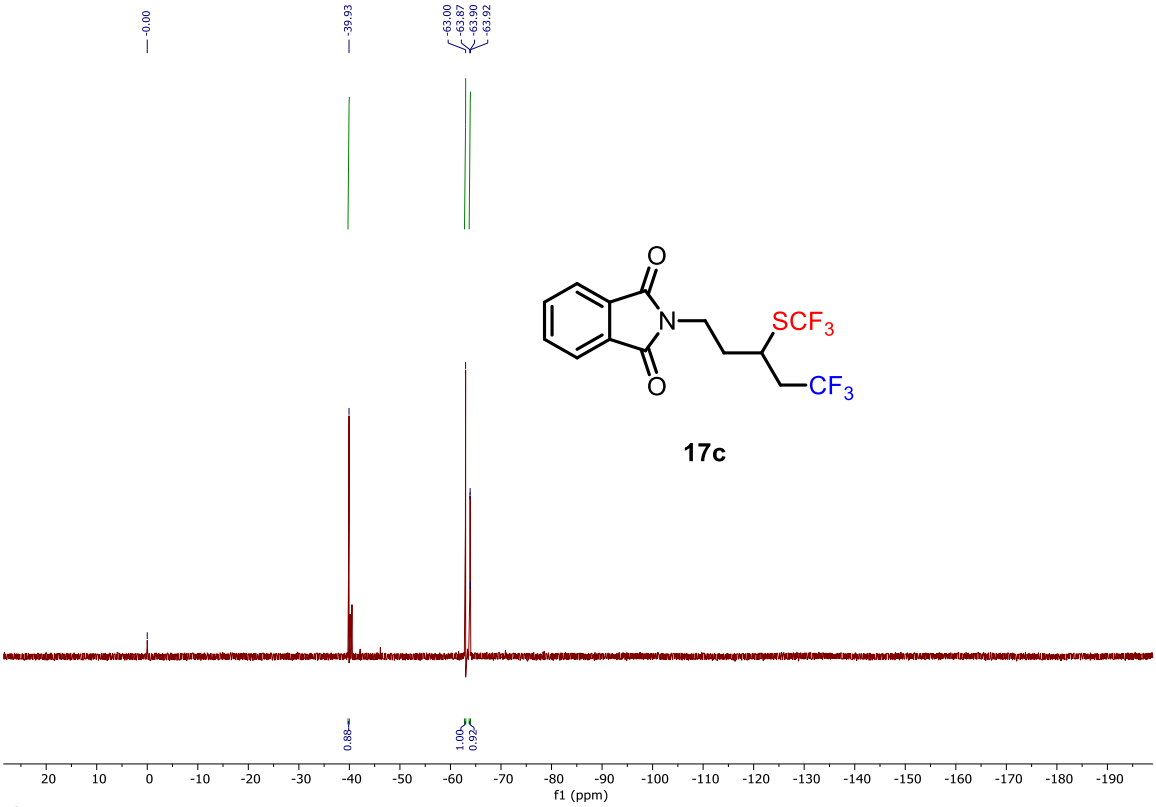
^{1}H NMR (400 MHz, $CDCl_3$) 17b



^{13}C NMR (400 MHz, $CDCl_3$) 17b

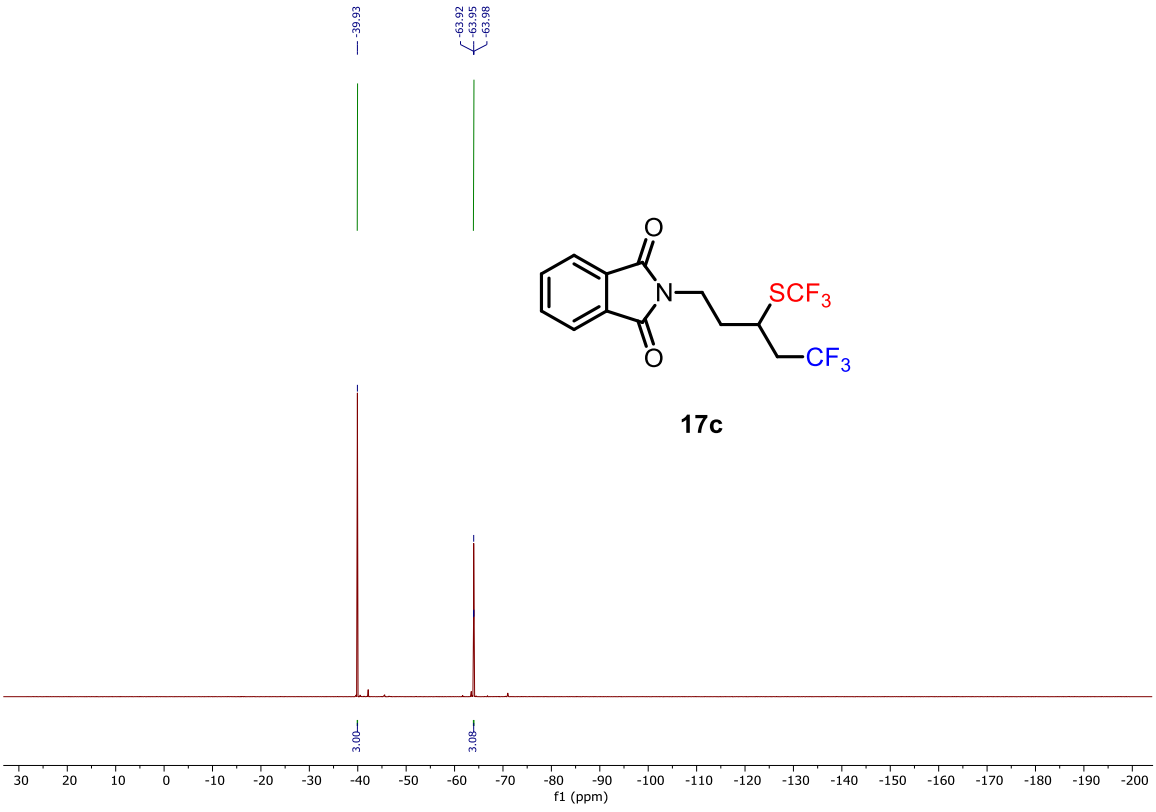


^{19}F NMR (376 MHz, $CDCl_3$) yield of 17c



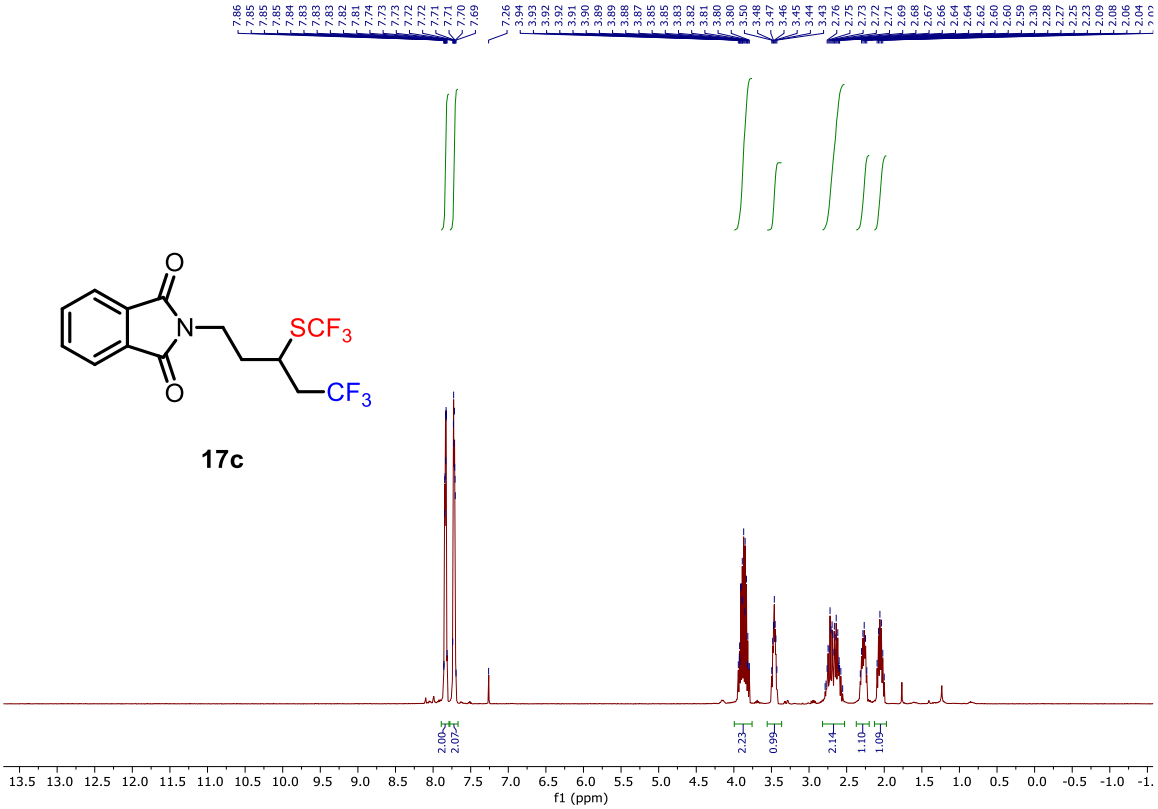
17c

^{19}F NMR (376 MHz, $CDCl_3$) 17c

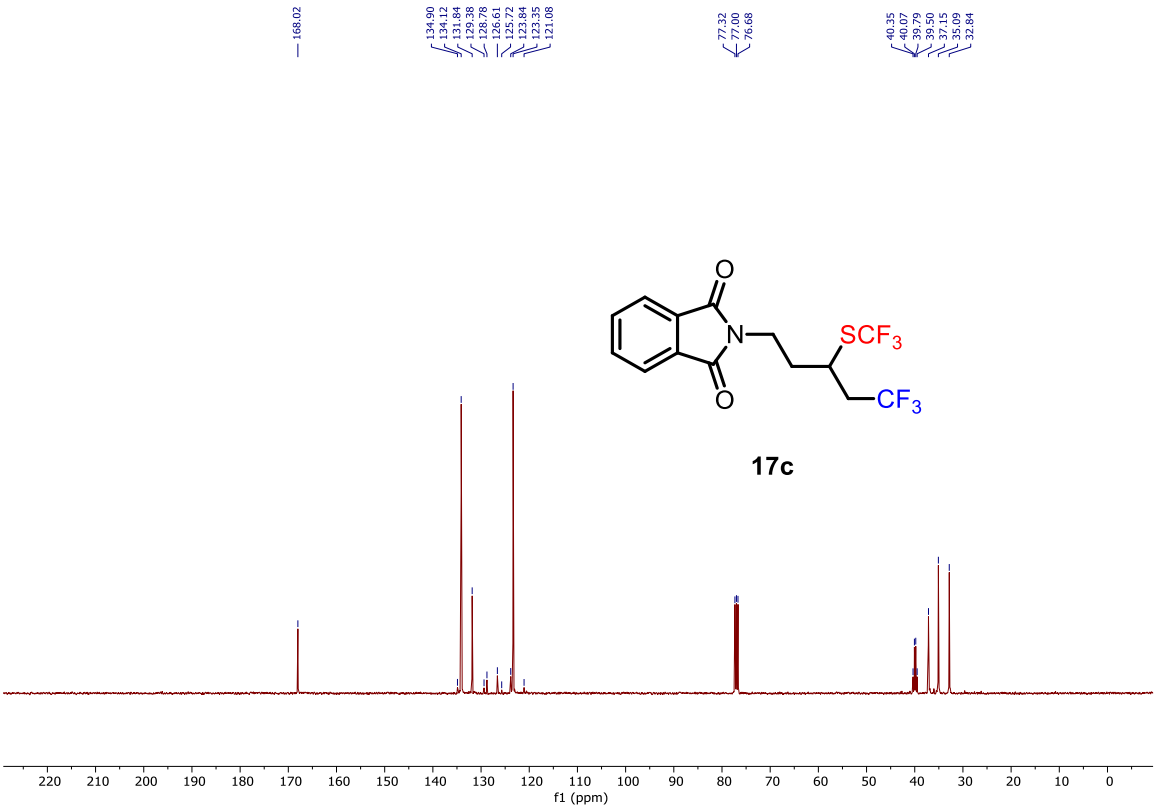


17c

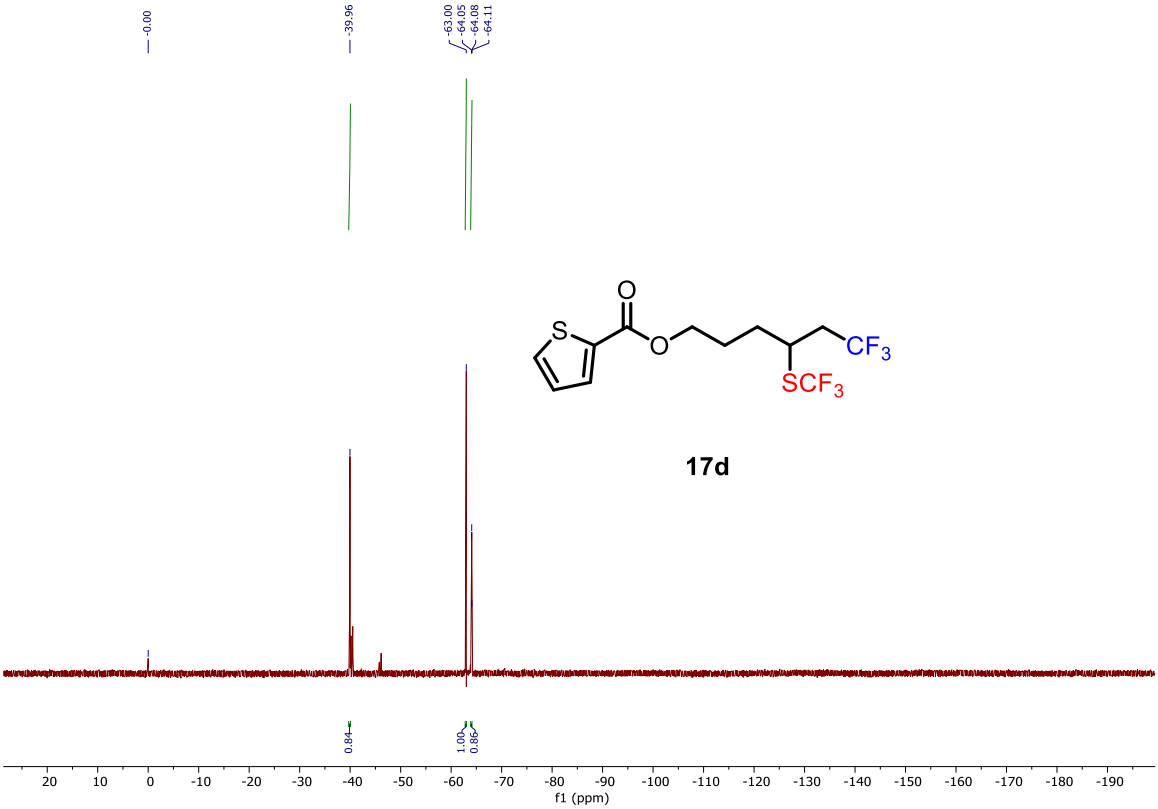
^{1}H NMR (400 MHz, $CDCl_3$) 17c



^{13}C NMR (100 MHz, $CDCl_3$) 17c

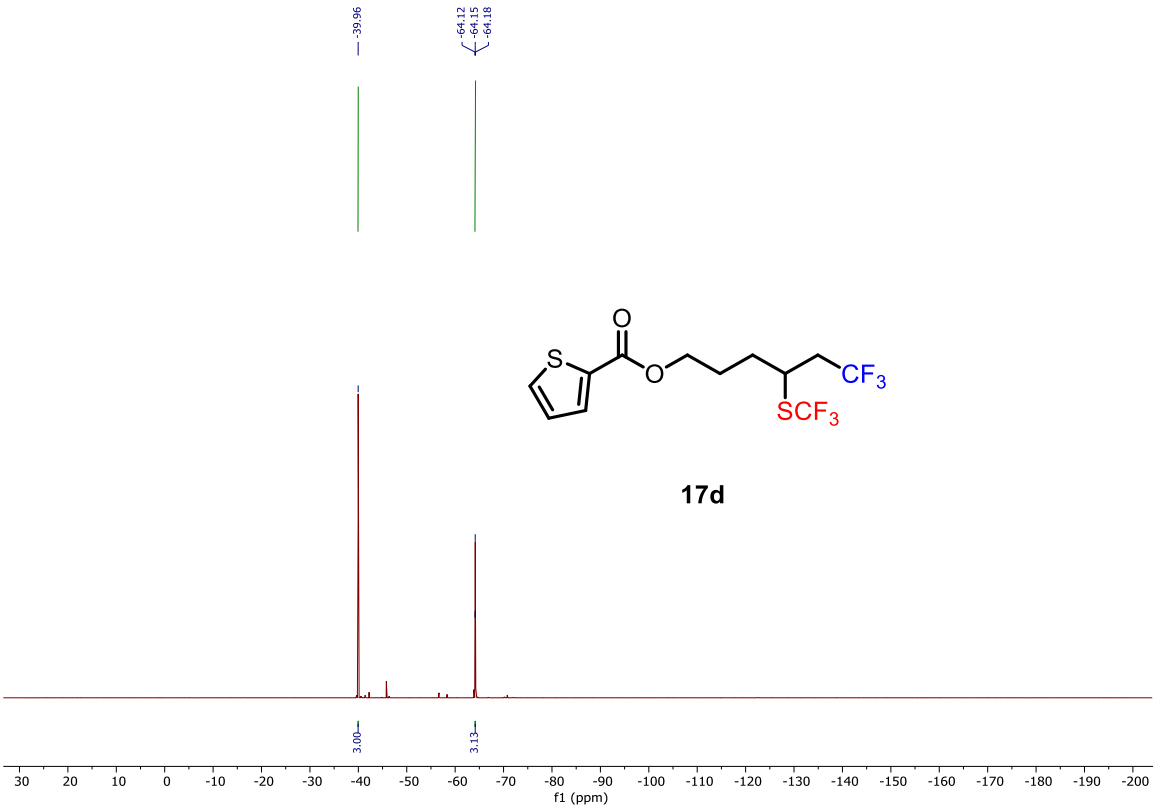


^{19}F NMR (376 MHz, $CDCl_3$) yield of 17d



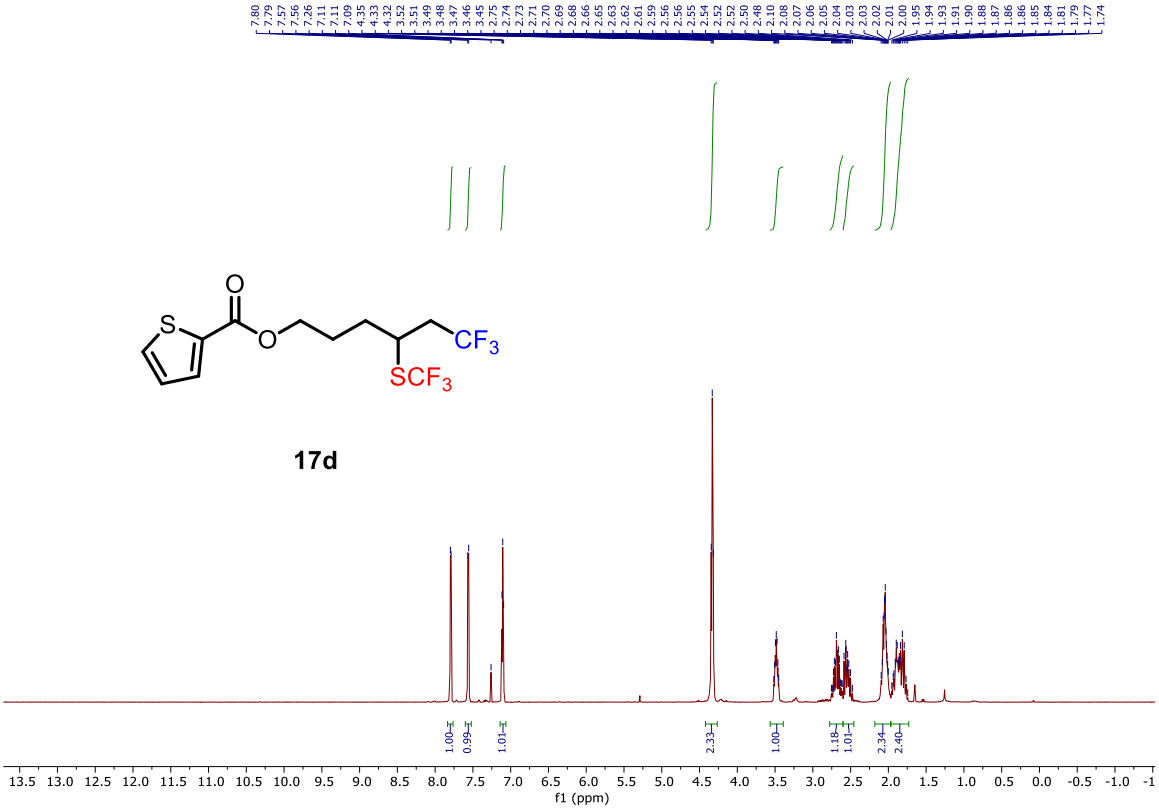
17d

^{19}F NMR (376 MHz, $CDCl_3$) 17d

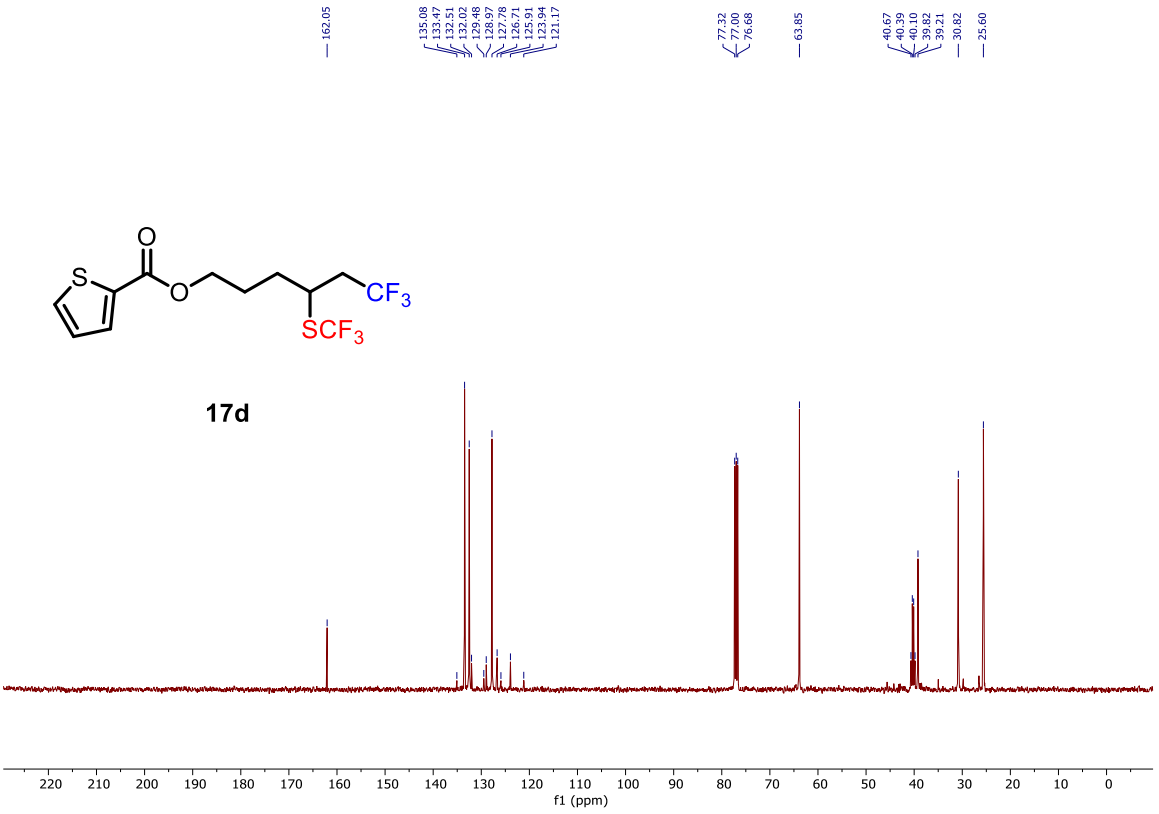


17d

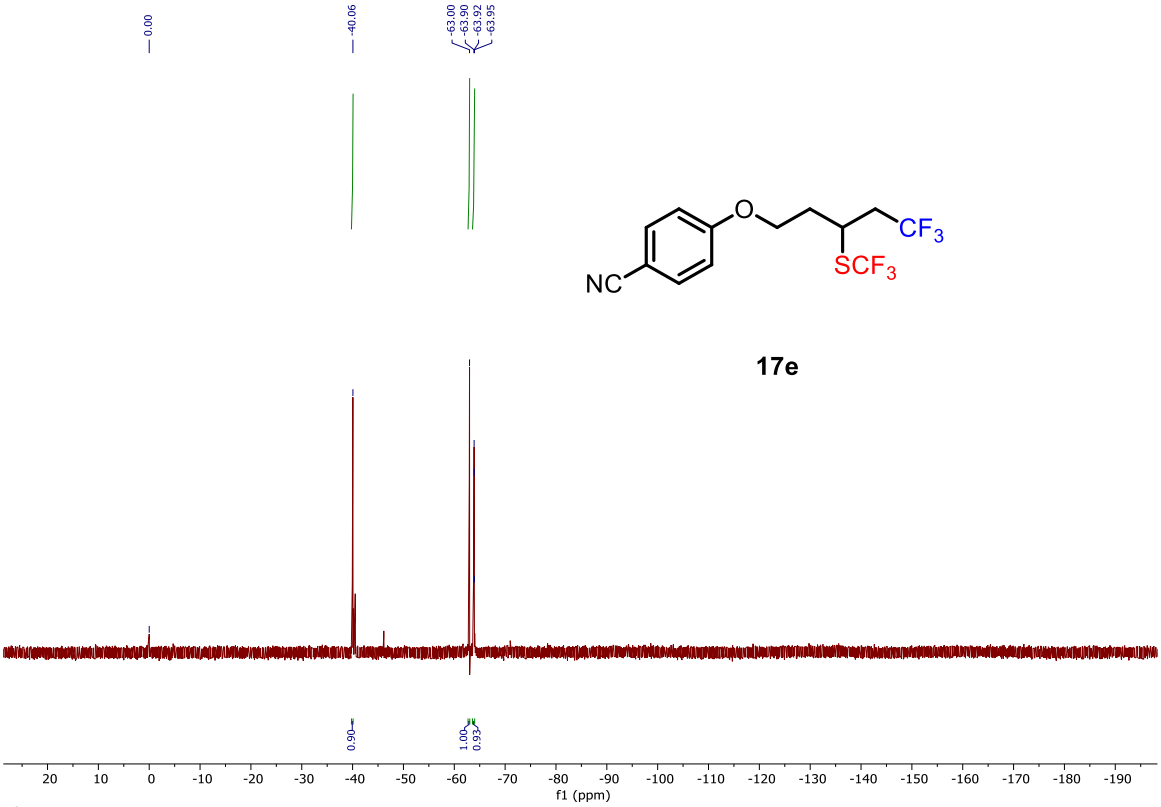
^{1}H NMR (400 MHz, $CDCl_3$) 17d



^{13}C NMR (100 MHz, $CDCl_3$) 17d

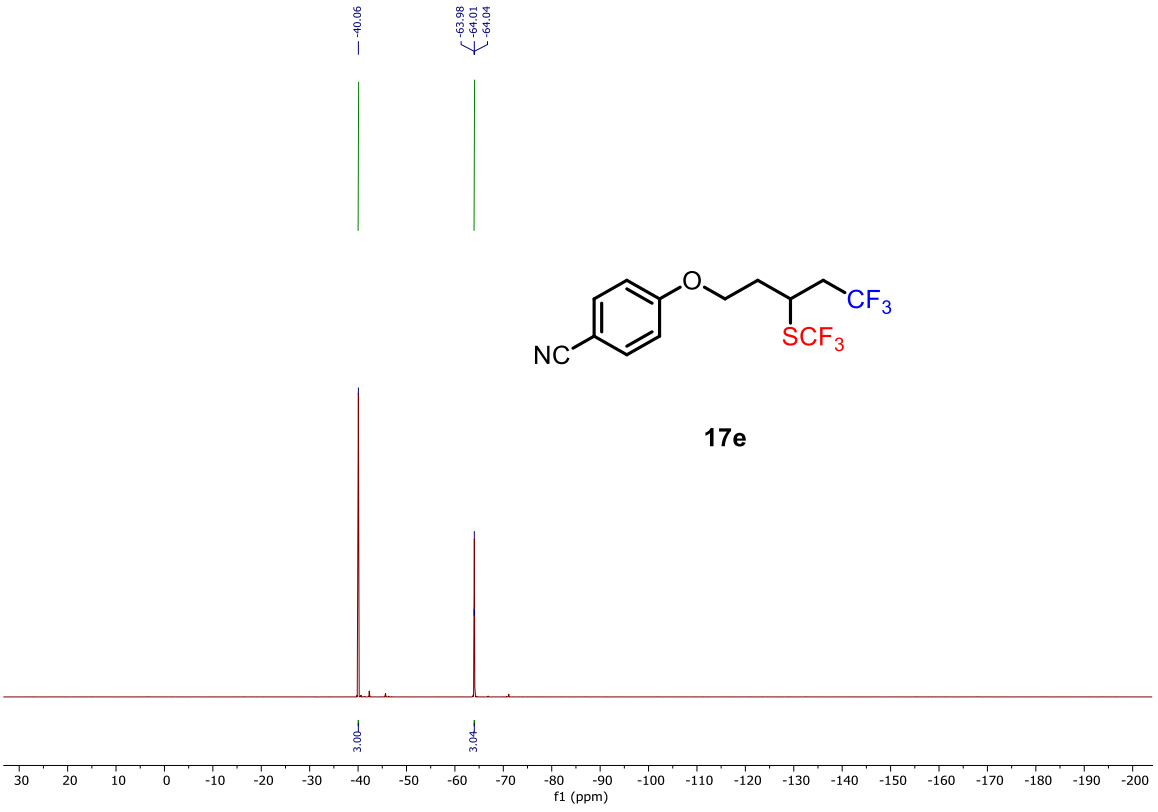


^{19}F NMR (376 MHz, $CDCl_3$) yield of 17e



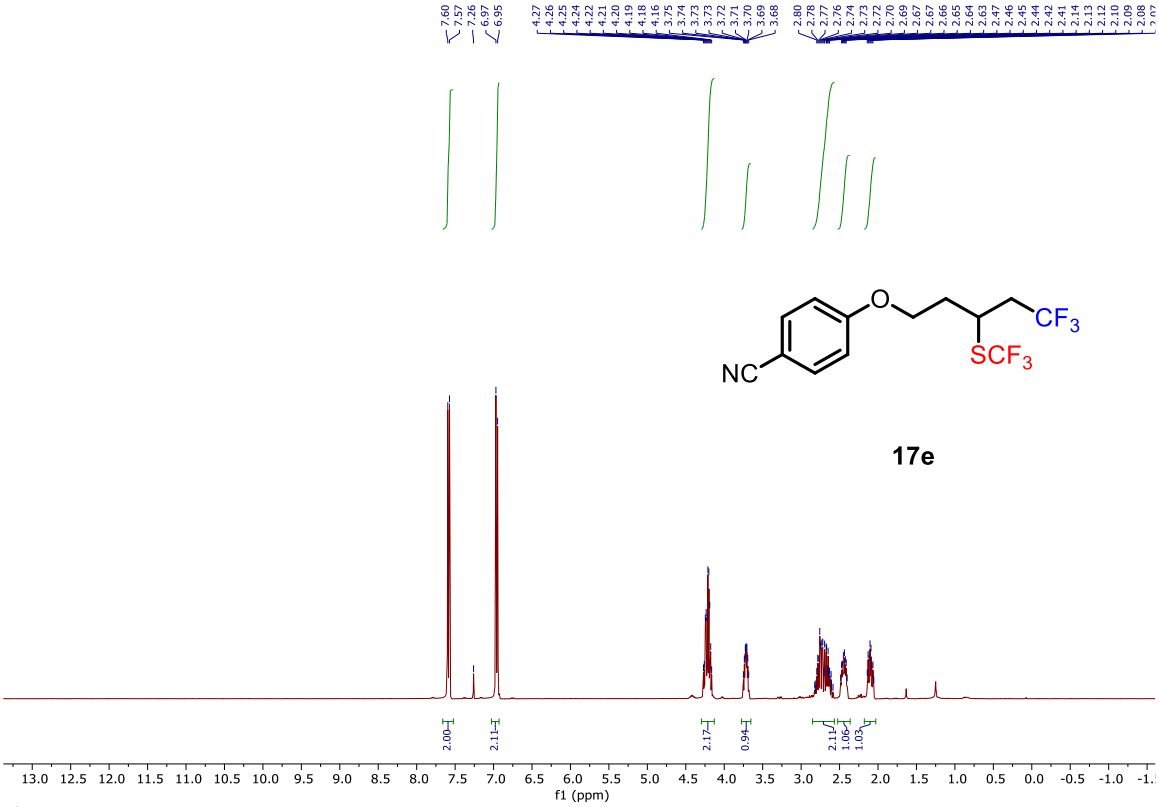
17e

^{19}F NMR (376 MHz, $CDCl_3$) 17e

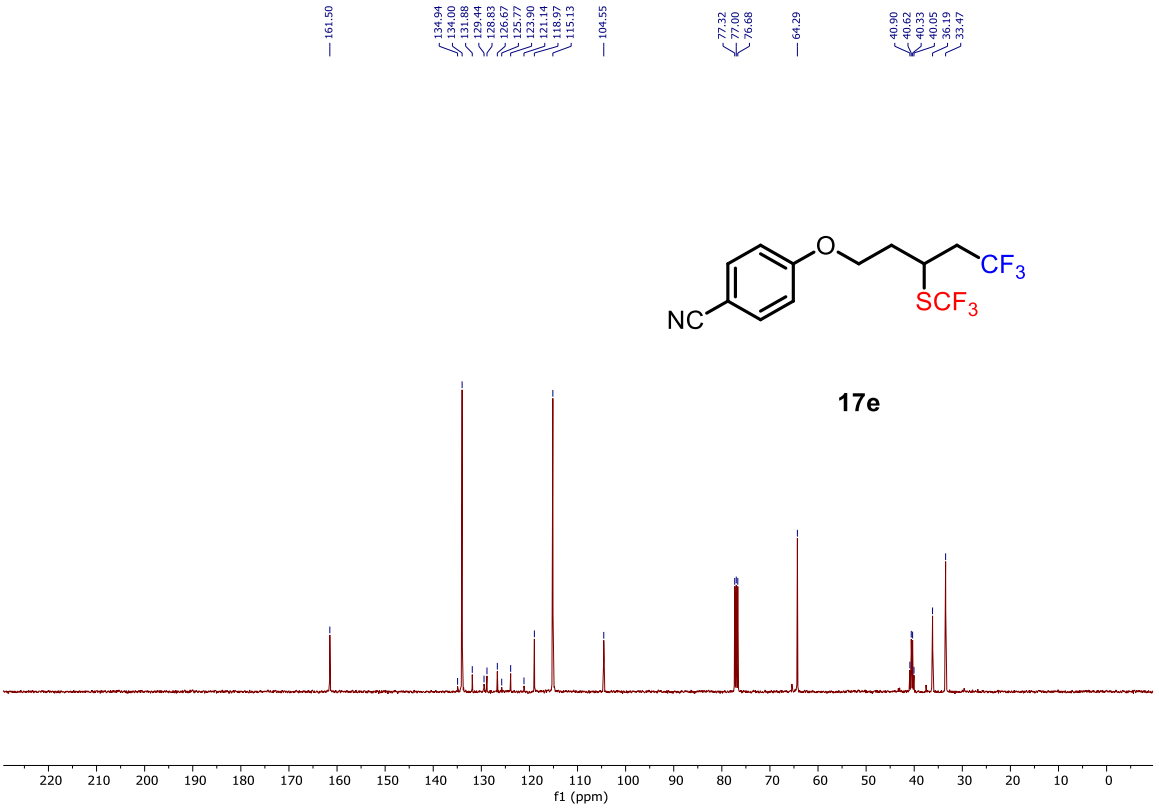


17e

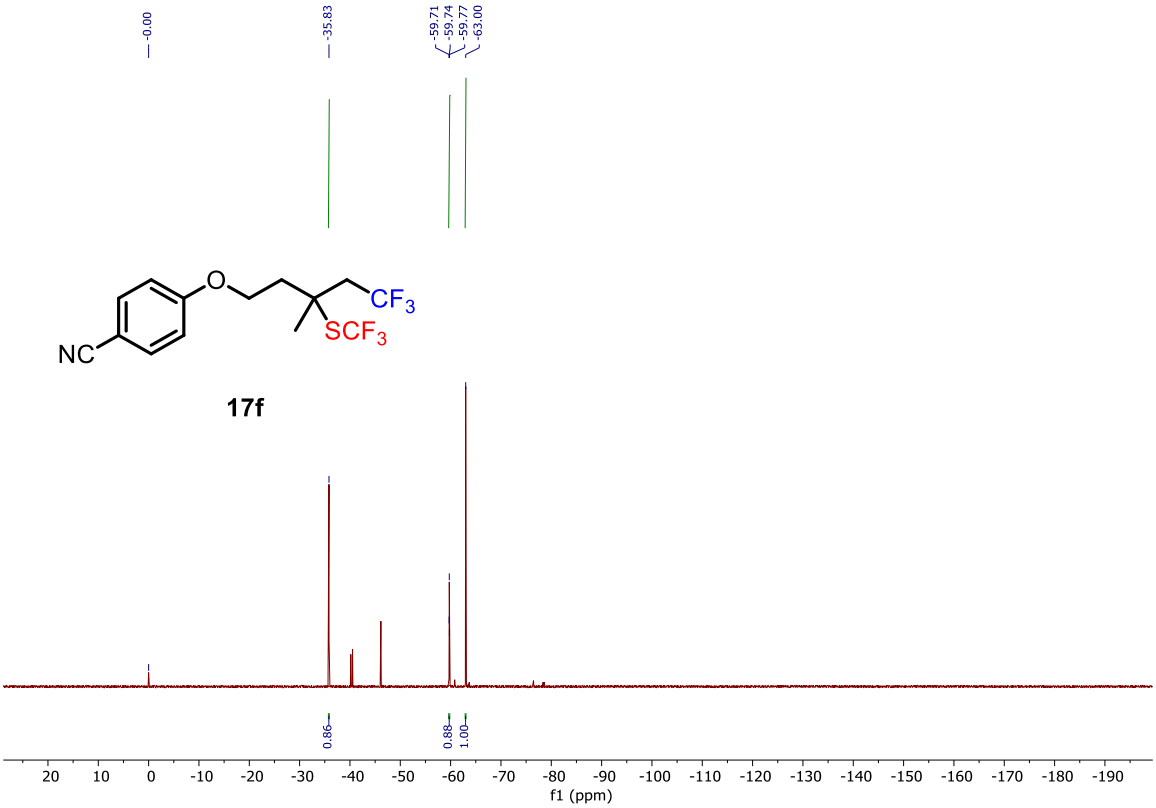
^{1}H NMR (400 MHz, $CDCl_3$) 17e



^{13}C NMR (100 MHz, $CDCl_3$) 17e

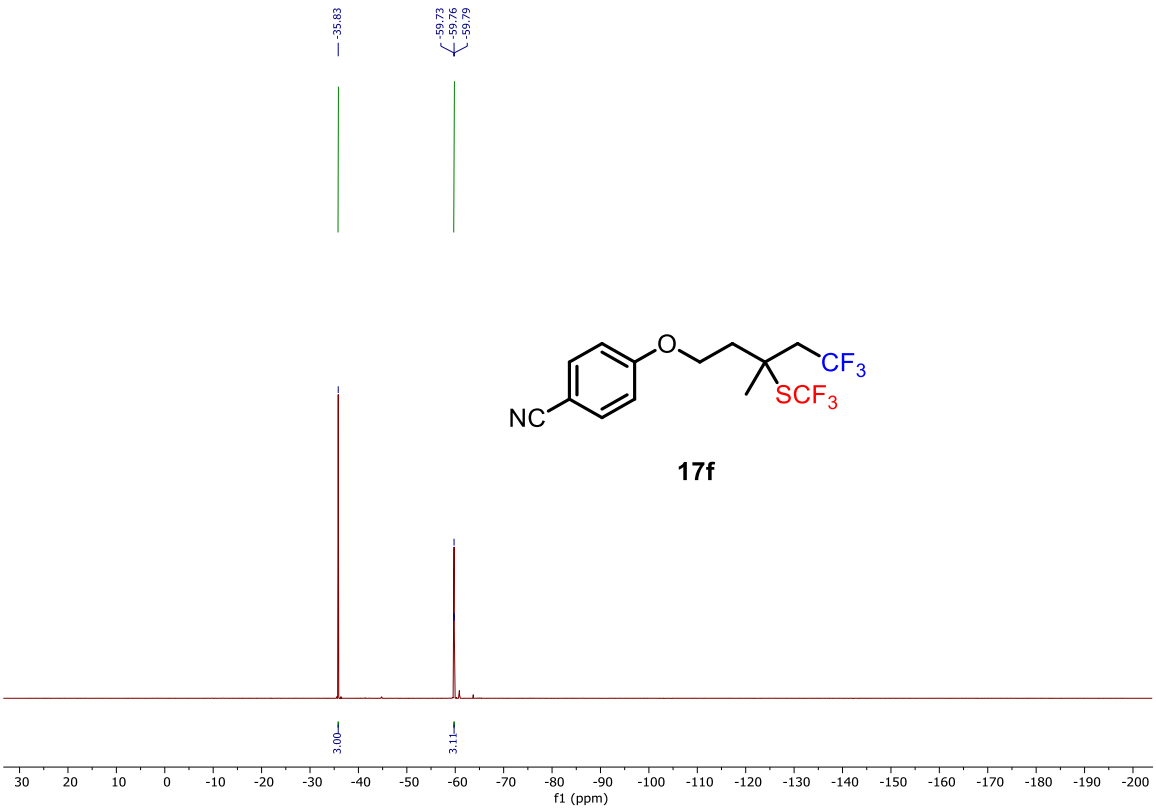


^{19}F NMR (376 MHz, $CDCl_3$) yield of 17f



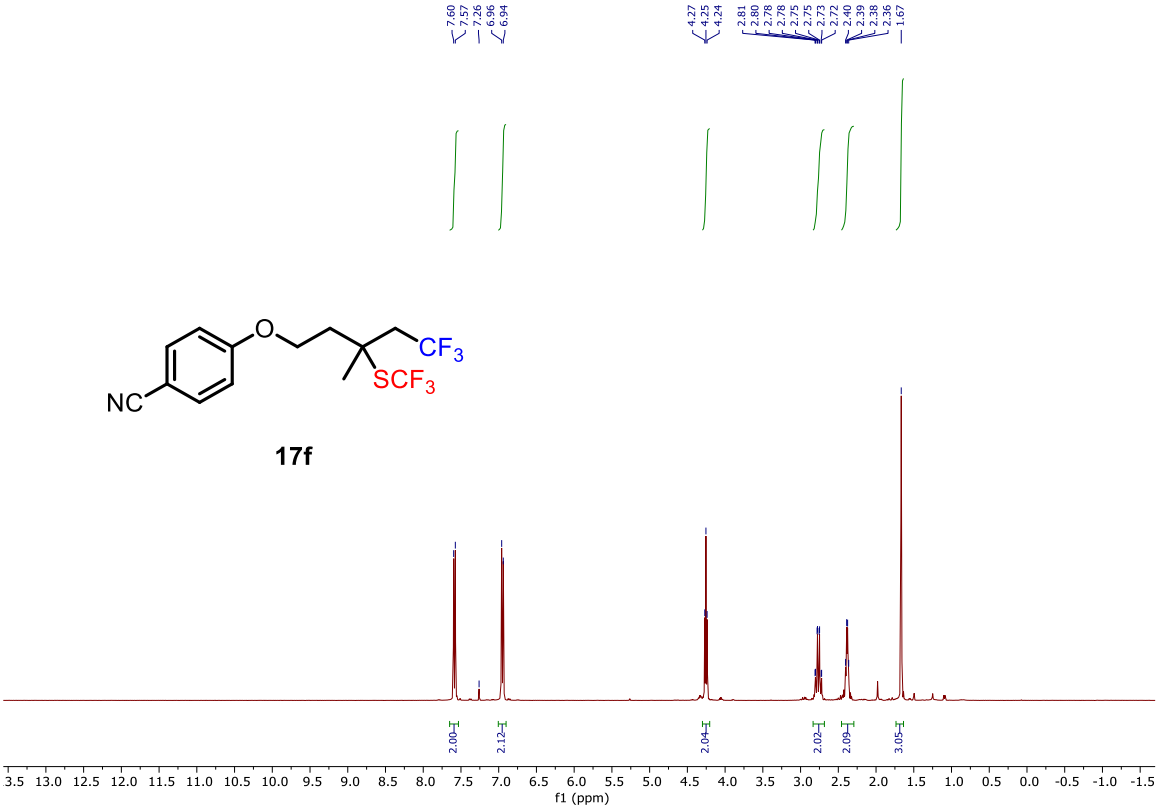
17f

^{19}F NMR (376 MHz, $CDCl_3$) 17f



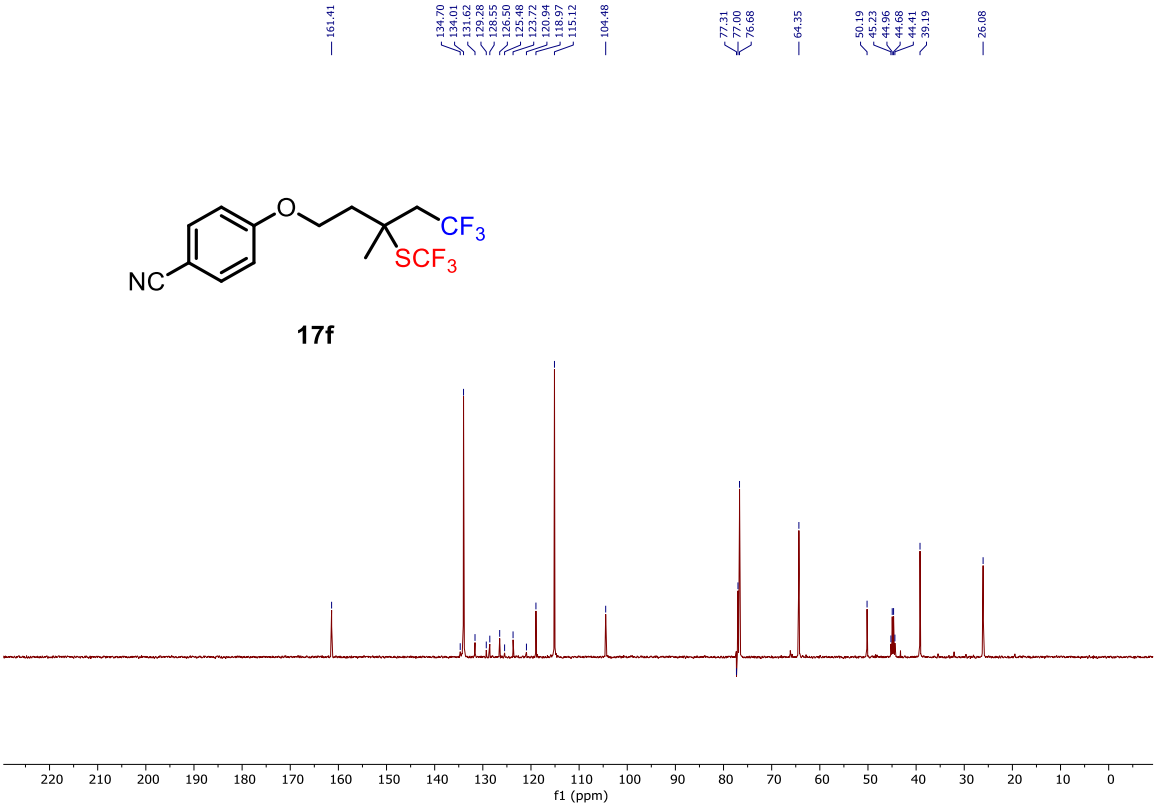
17f

^{1}H NMR (400 MHz, $CDCl_3$) 17f



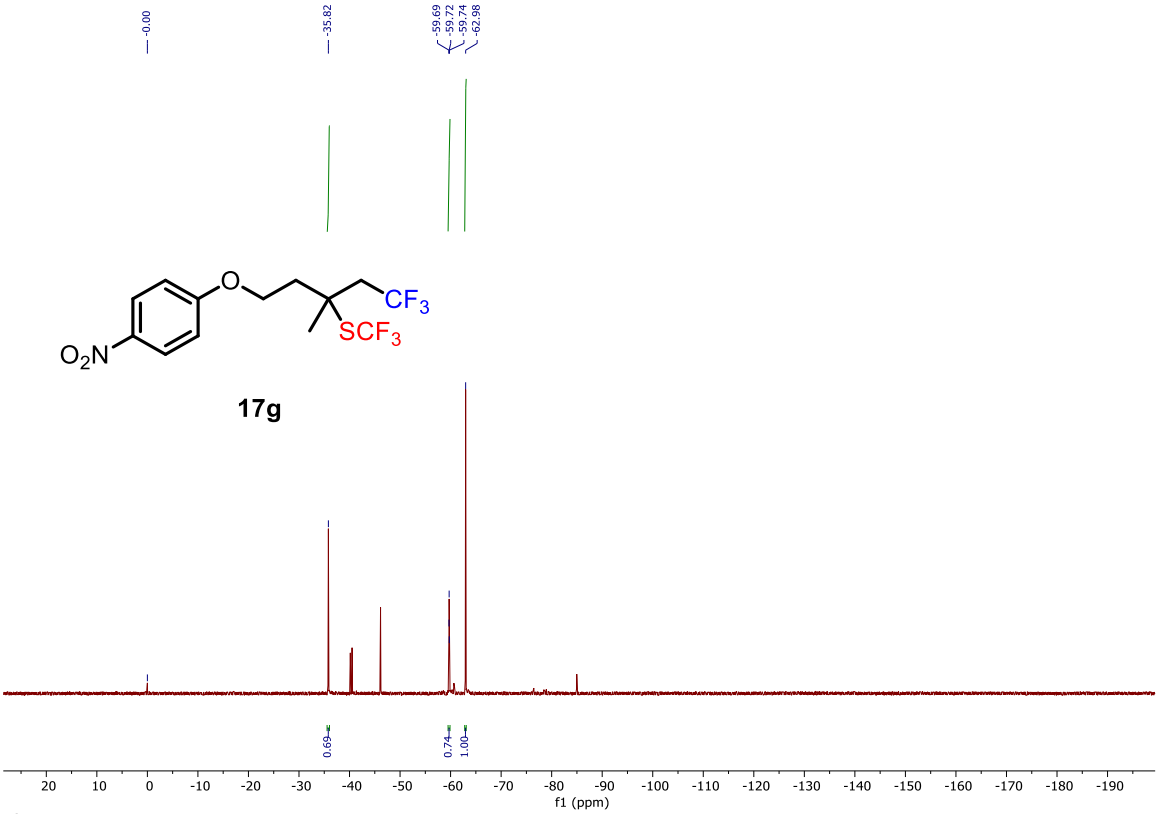
17f

^{13}C NMR (100 MHz, $CDCl_3$) 17f



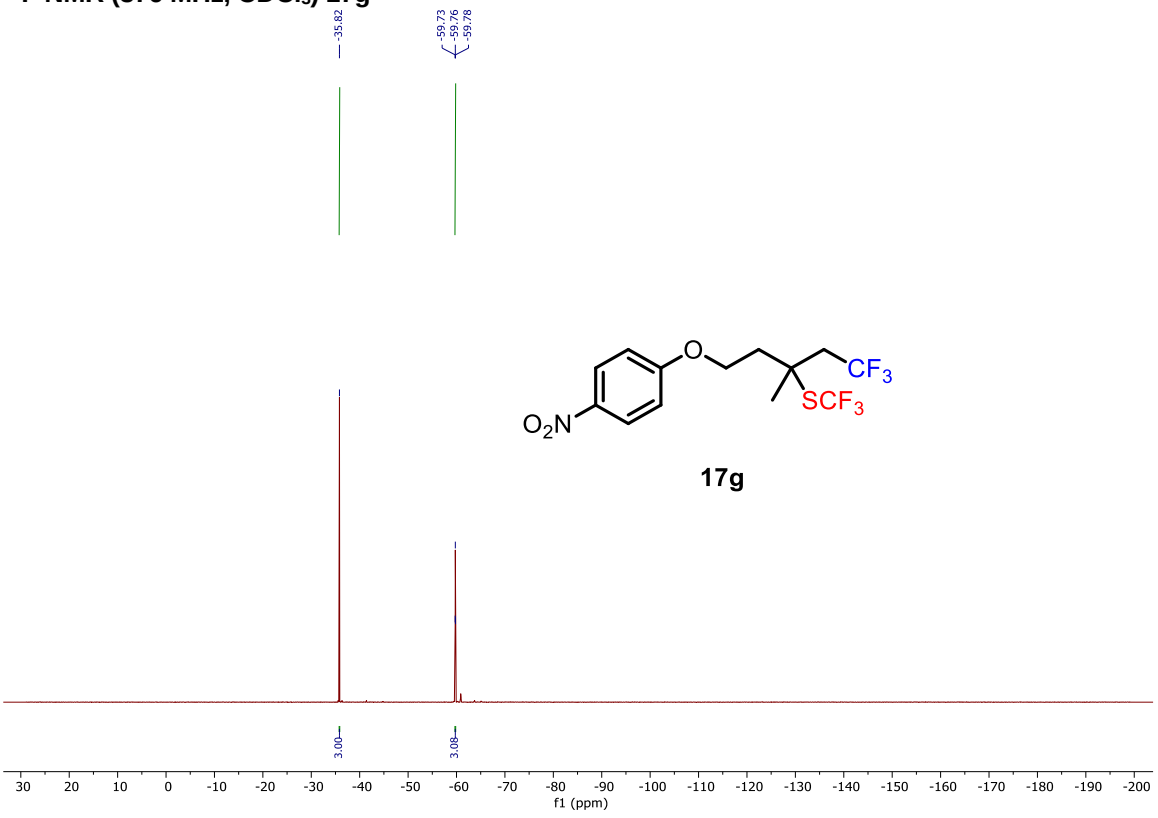
17f

^{19}F NMR (376 MHz, $CDCl_3$) yield of 17g



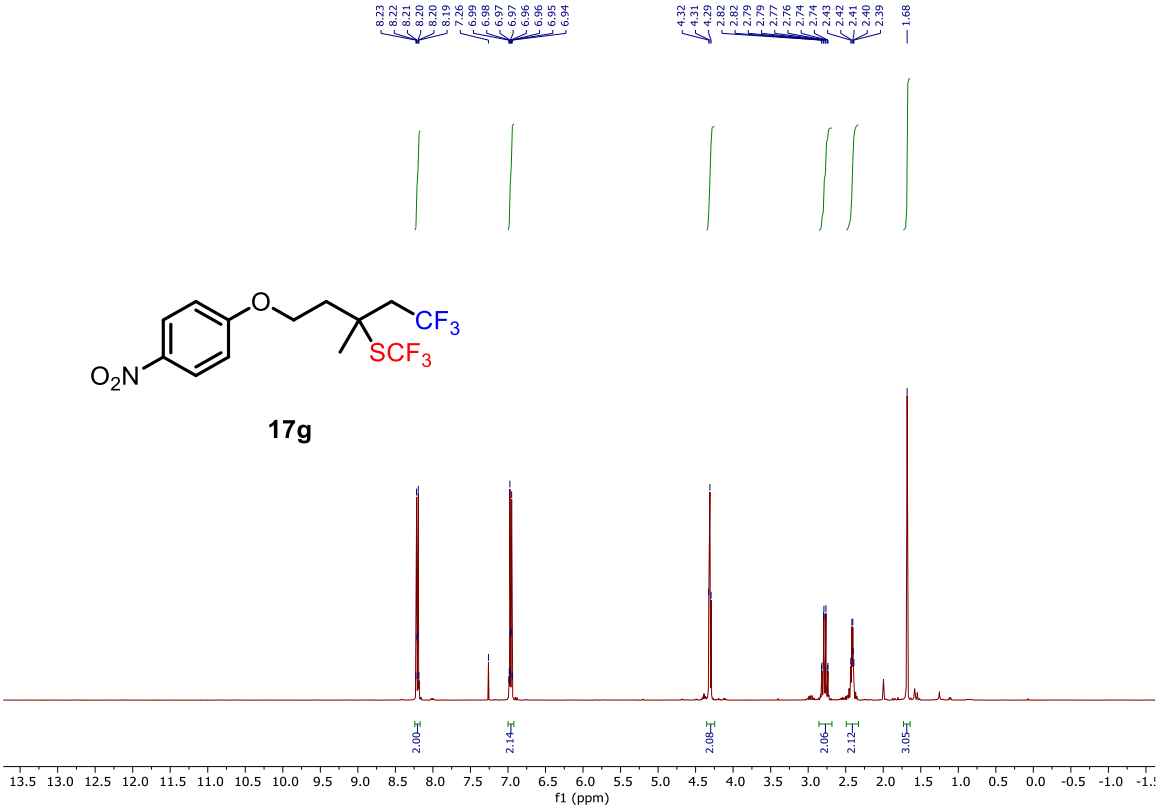
17g

^{19}F NMR (376 MHz, $CDCl_3$) 17g



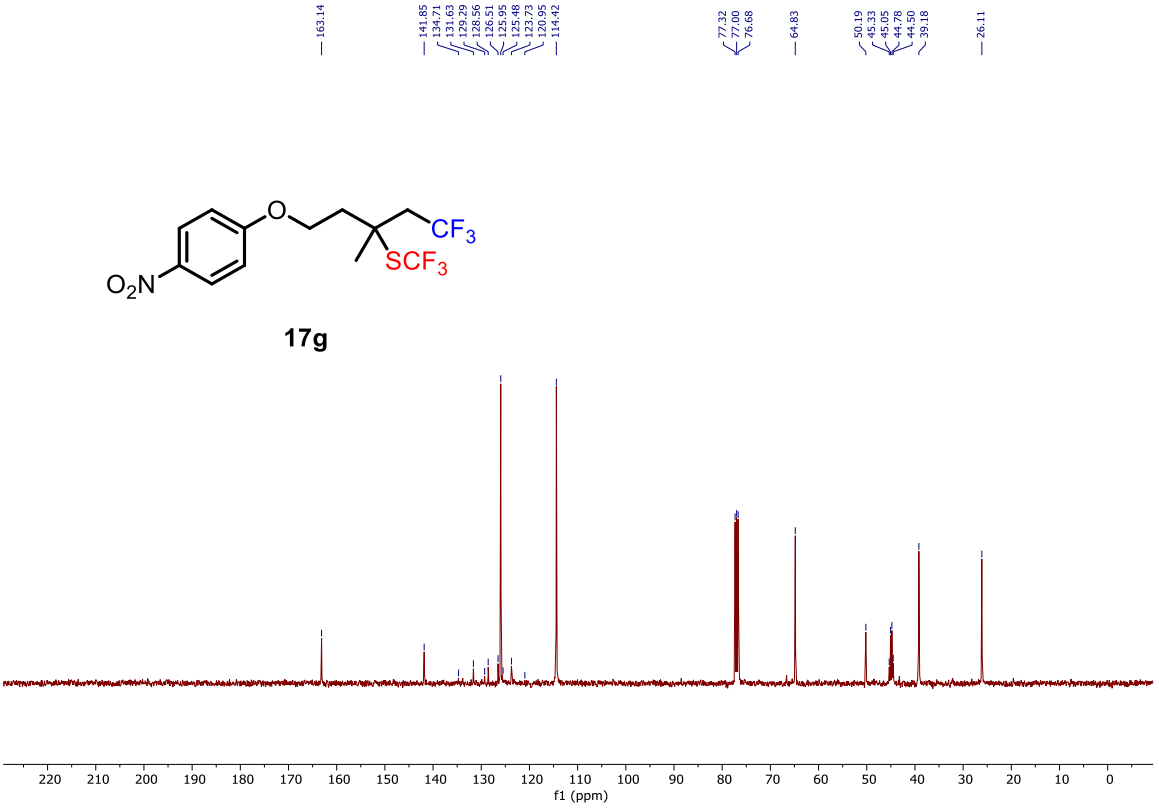
17g

^{1}H NMR (400 MHz, $CDCl_3$) 17g



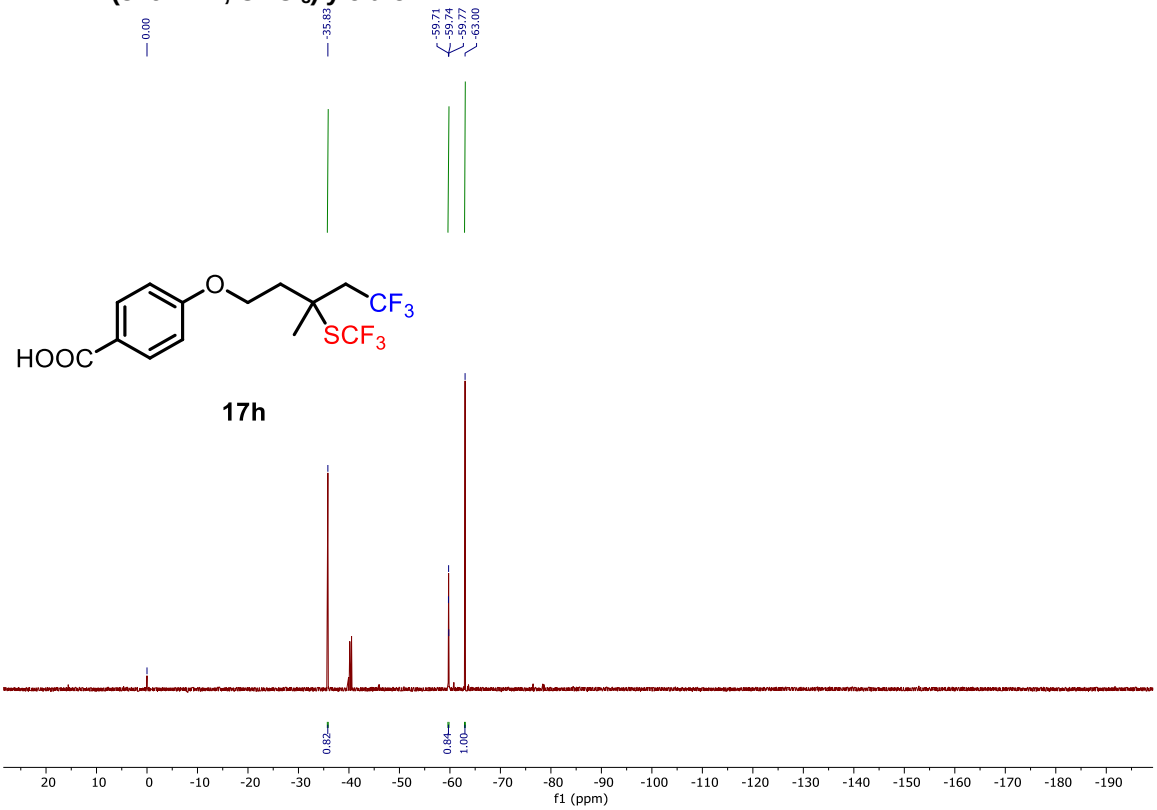
17g

^{13}C NMR (100 MHz, $CDCl_3$) 17g

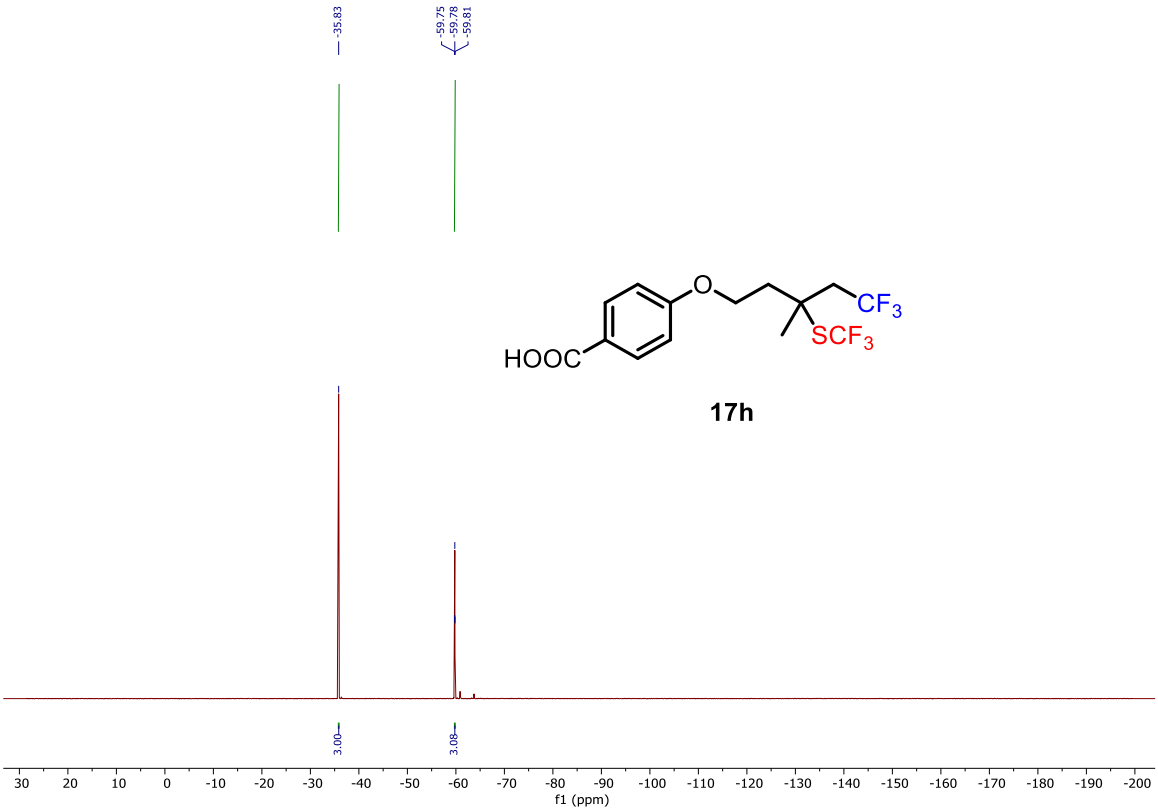


17g

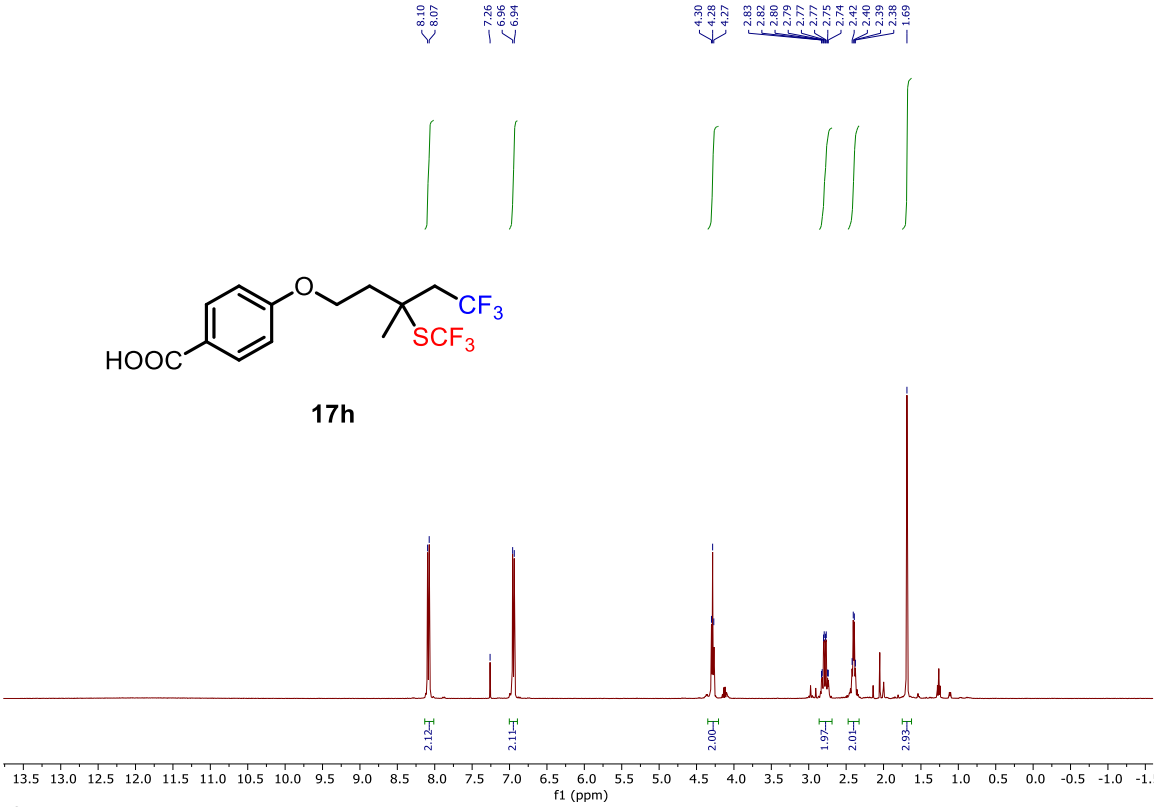
^{19}F NMR (376 MHz, $CDCl_3$) yield of 17h



^{19}F NMR (376 MHz, $CDCl_3$) 17h

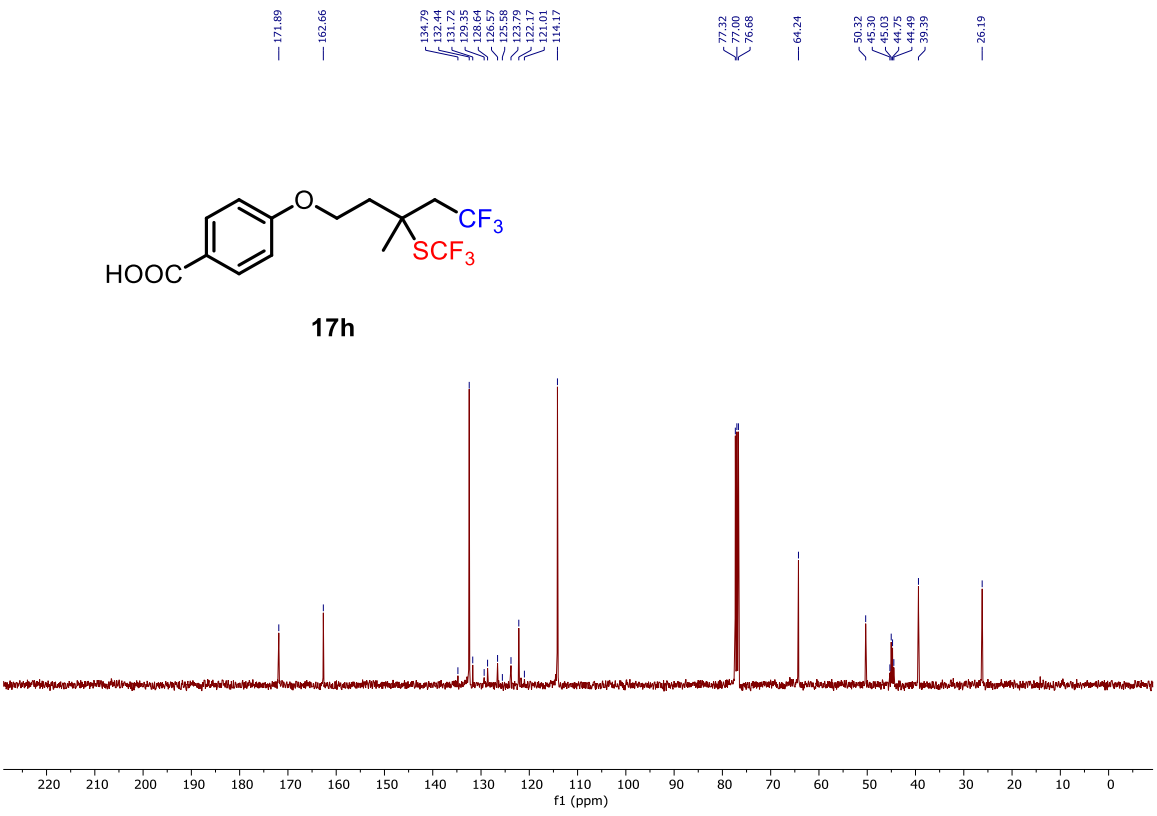


^{1}H NMR (400 MHz, $CDCl_3$) 17h



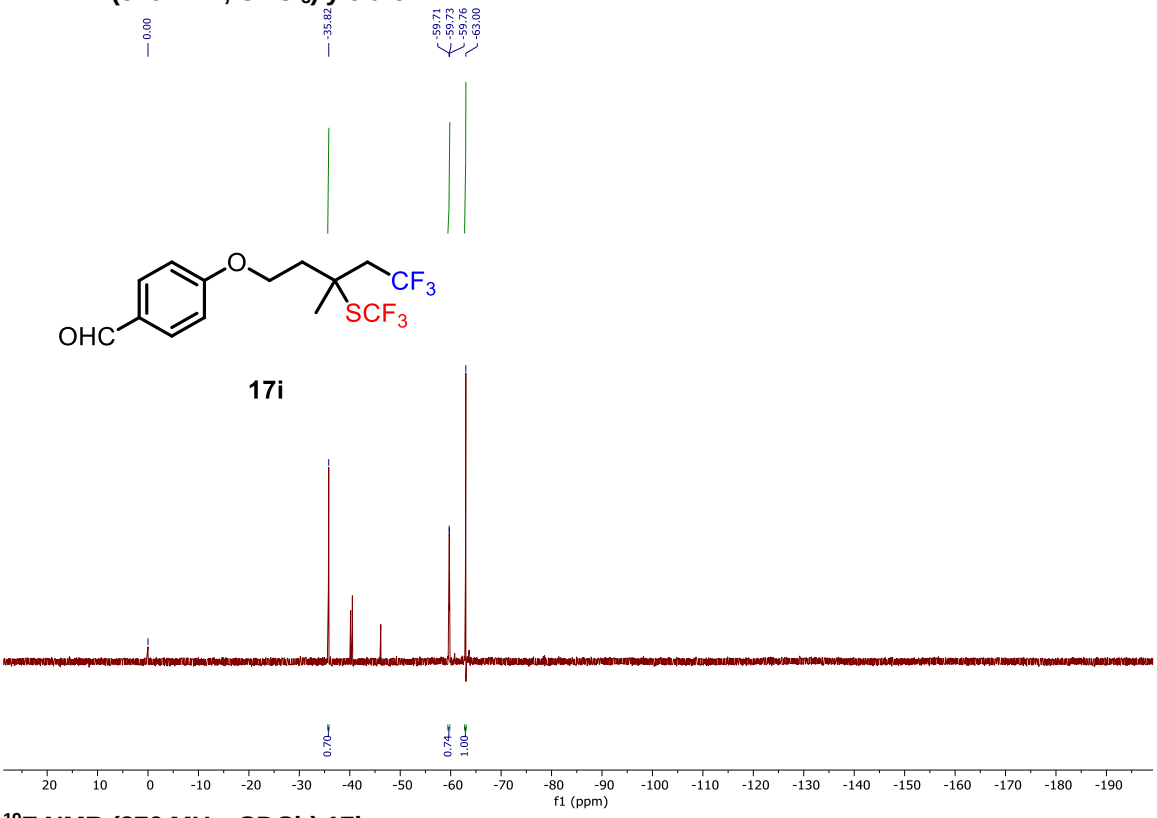
17h

^{13}C NMR (100 MHz, $CDCl_3$) 17h



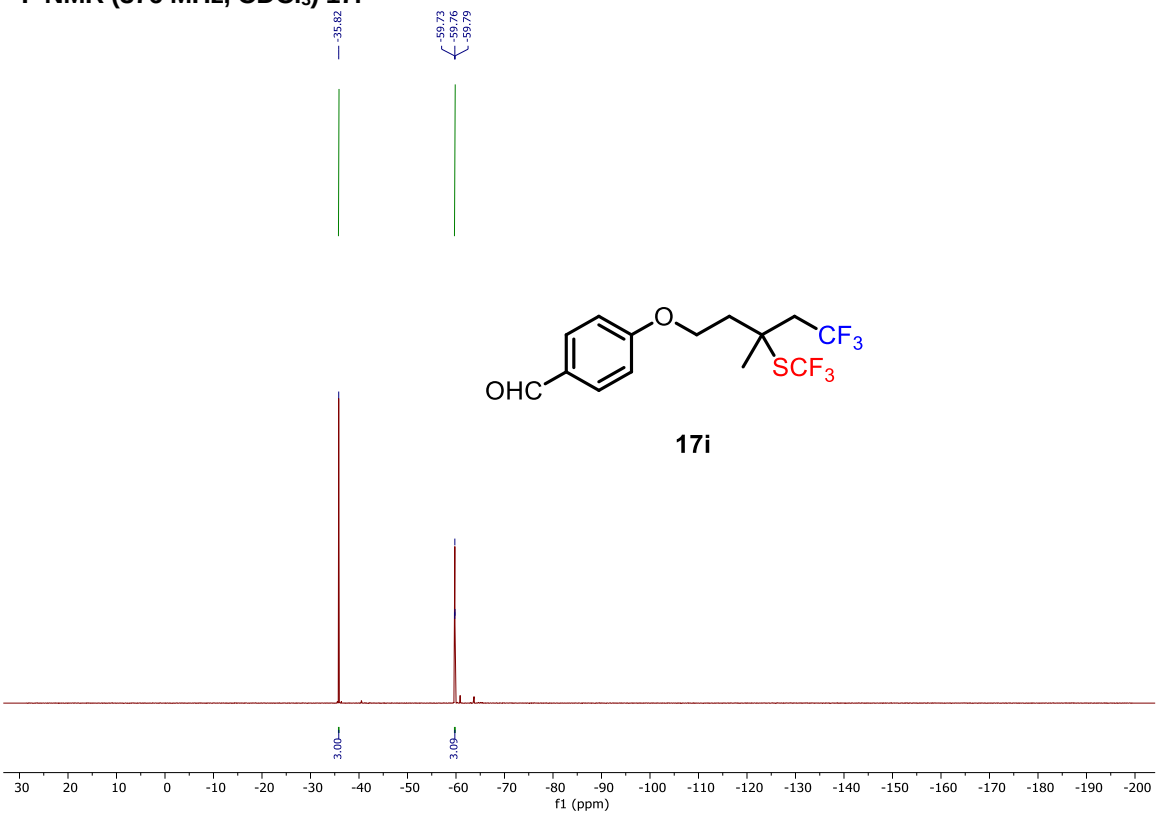
17h

^{19}F NMR (376 MHz, $CDCl_3$) yield of 17i



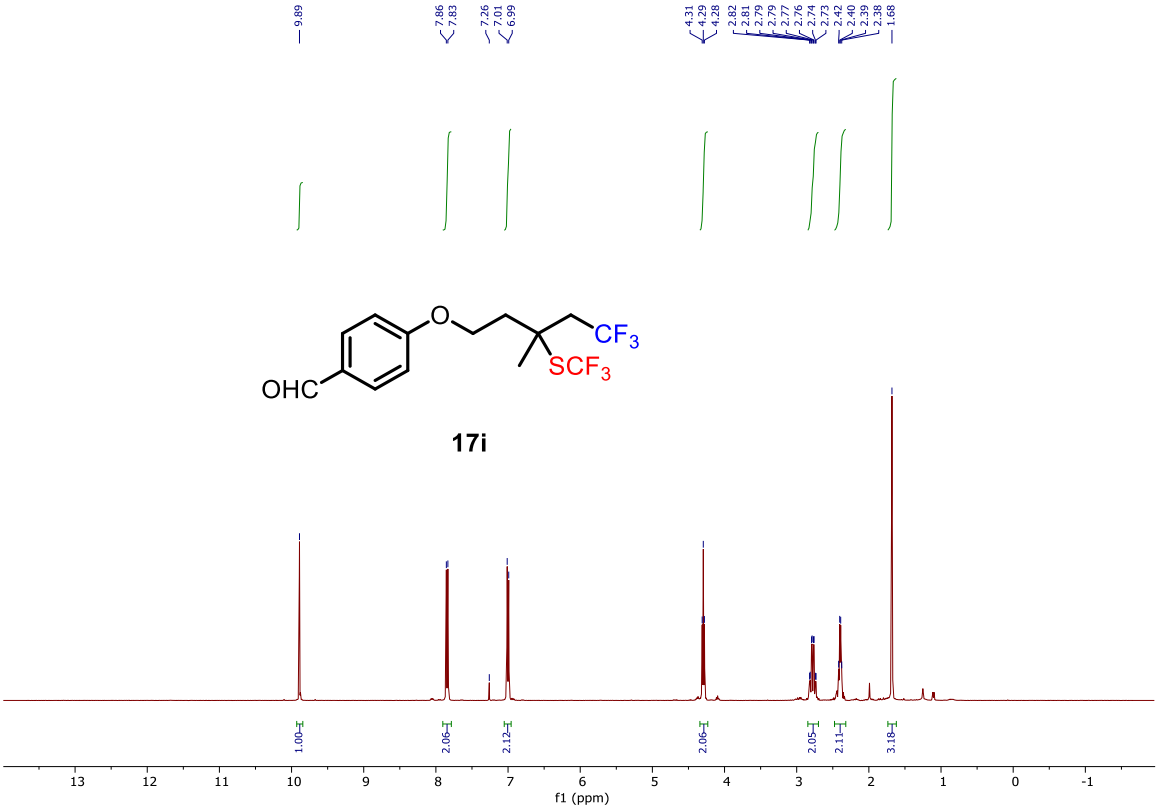
17i

^{19}F NMR (376 MHz, $CDCl_3$) 17i



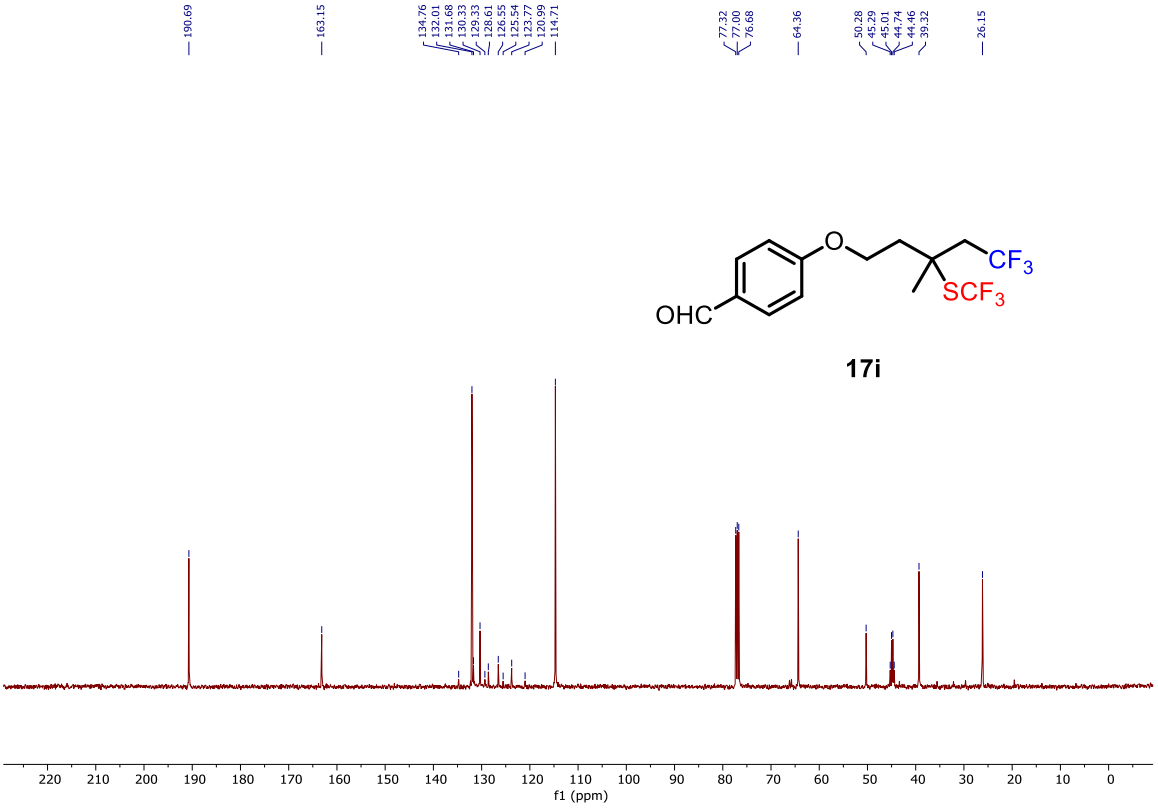
17i

^{1}H NMR (400 MHz, $CDCl_3$) 17i



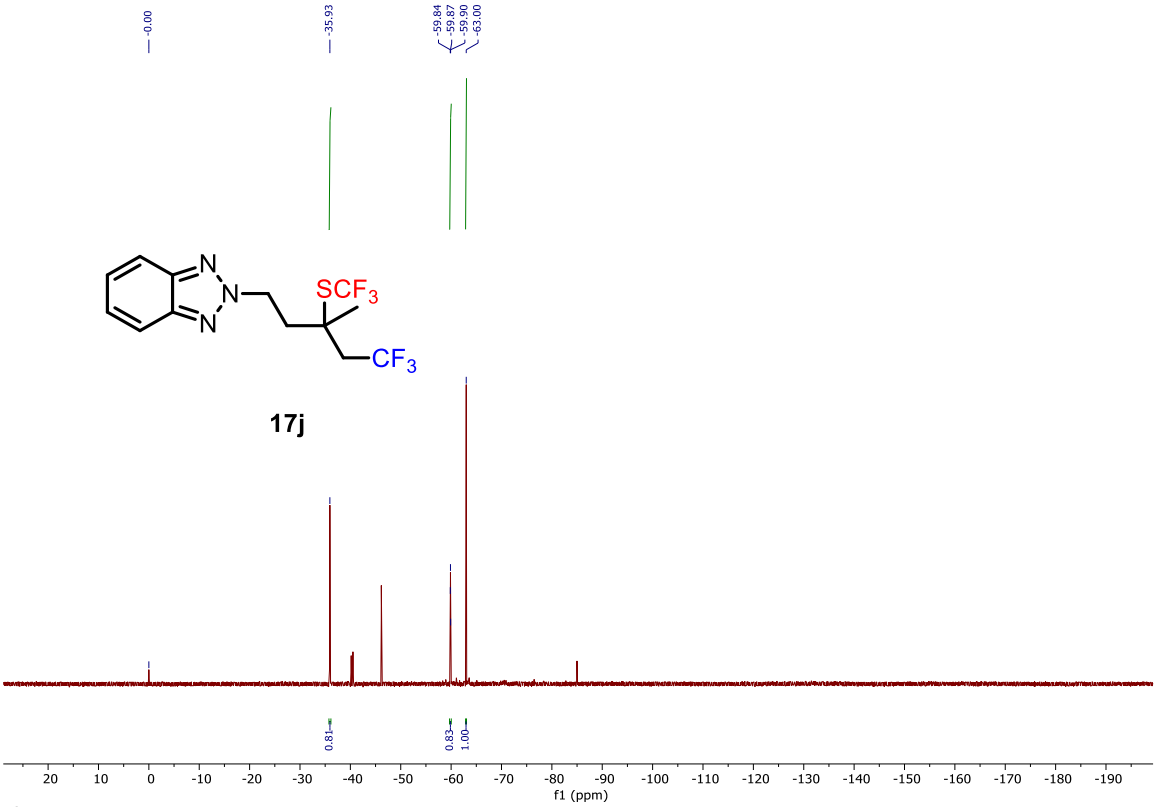
17i

^{13}C NMR (100 MHz, $CDCl_3$) 17i



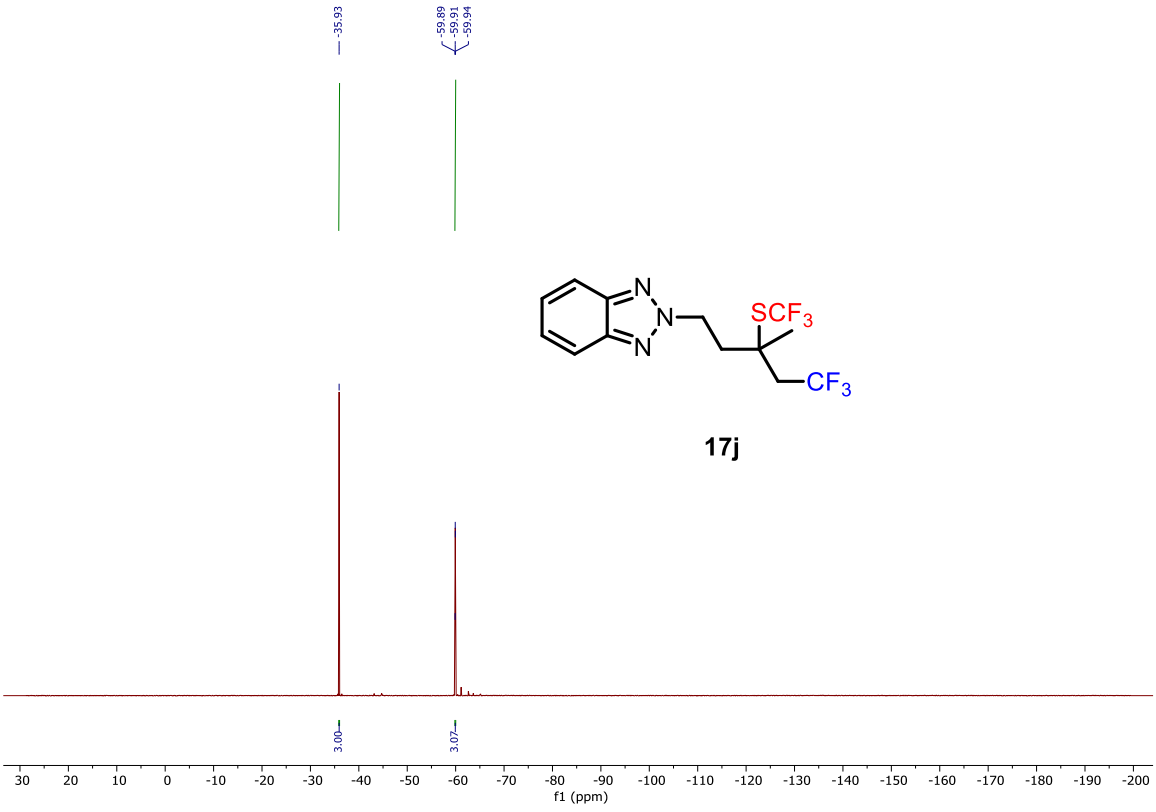
17i

^{19}F NMR (376 MHz, $CDCl_3$) yield of 17j



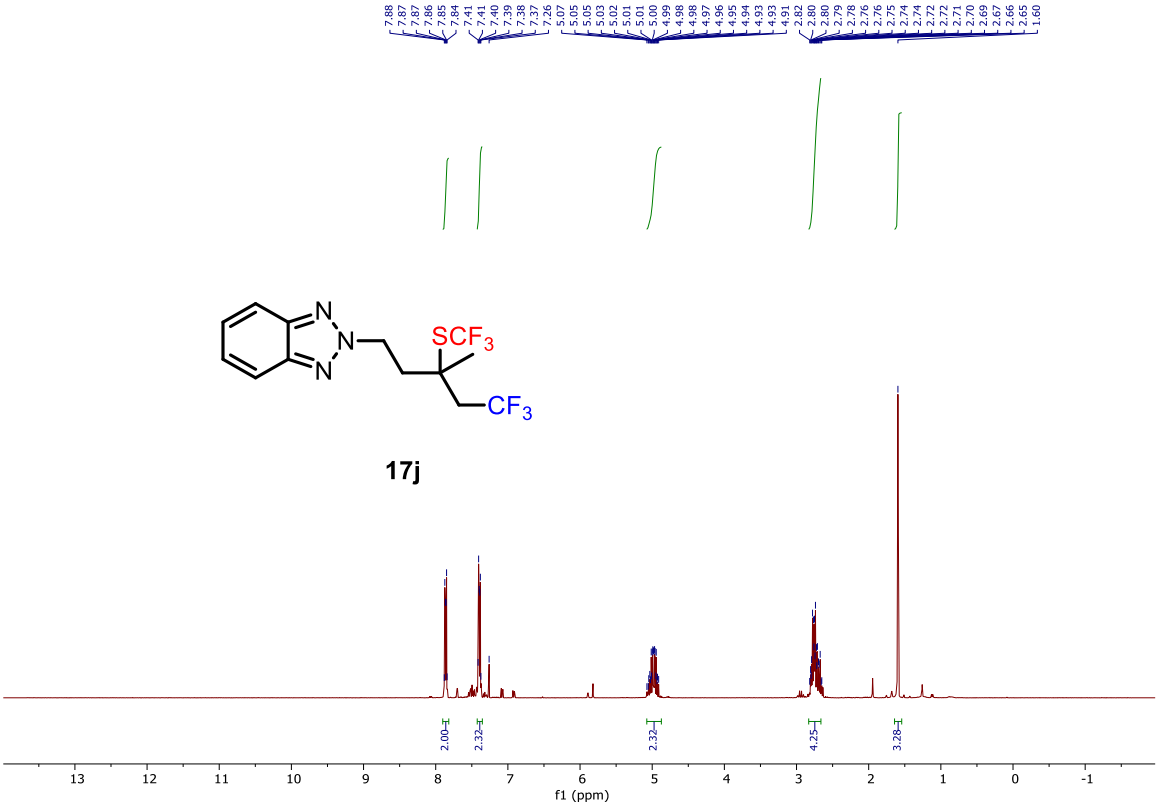
17j

^{19}F NMR (376 MHz, $CDCl_3$) 17j



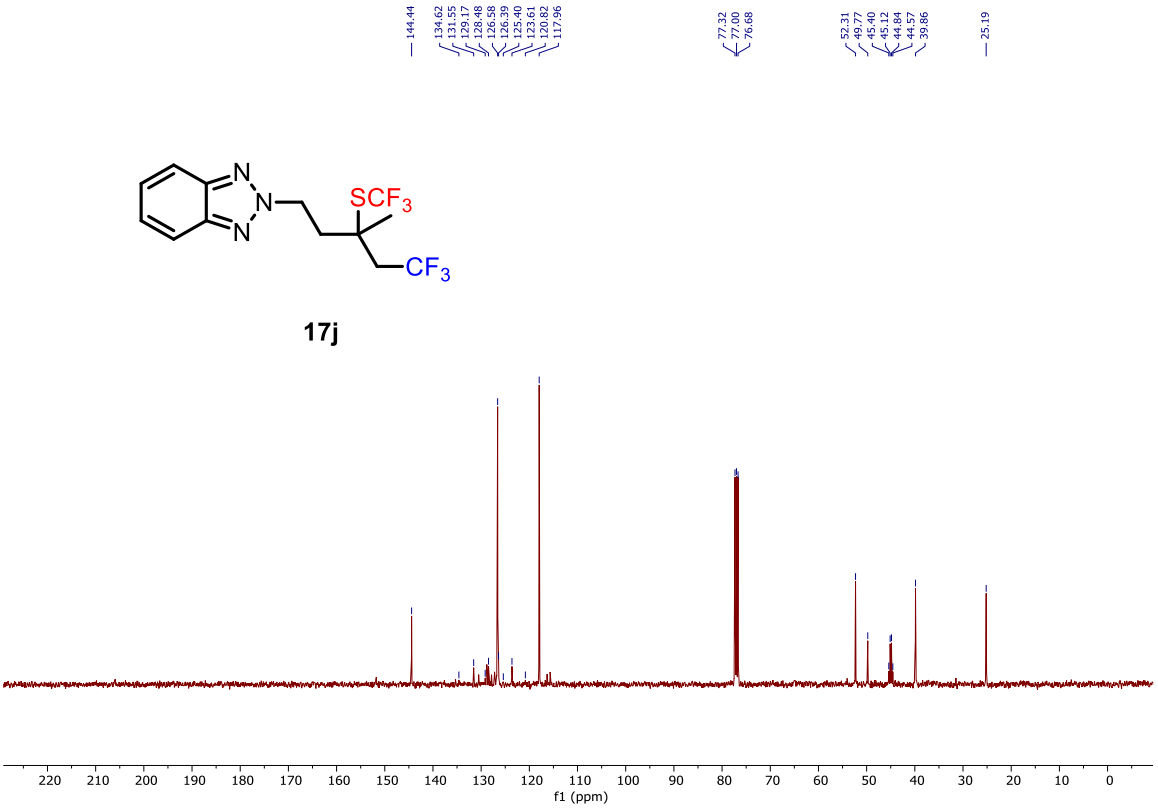
17j

^{1}H NMR (400 MHz, $CDCl_3$) 17j



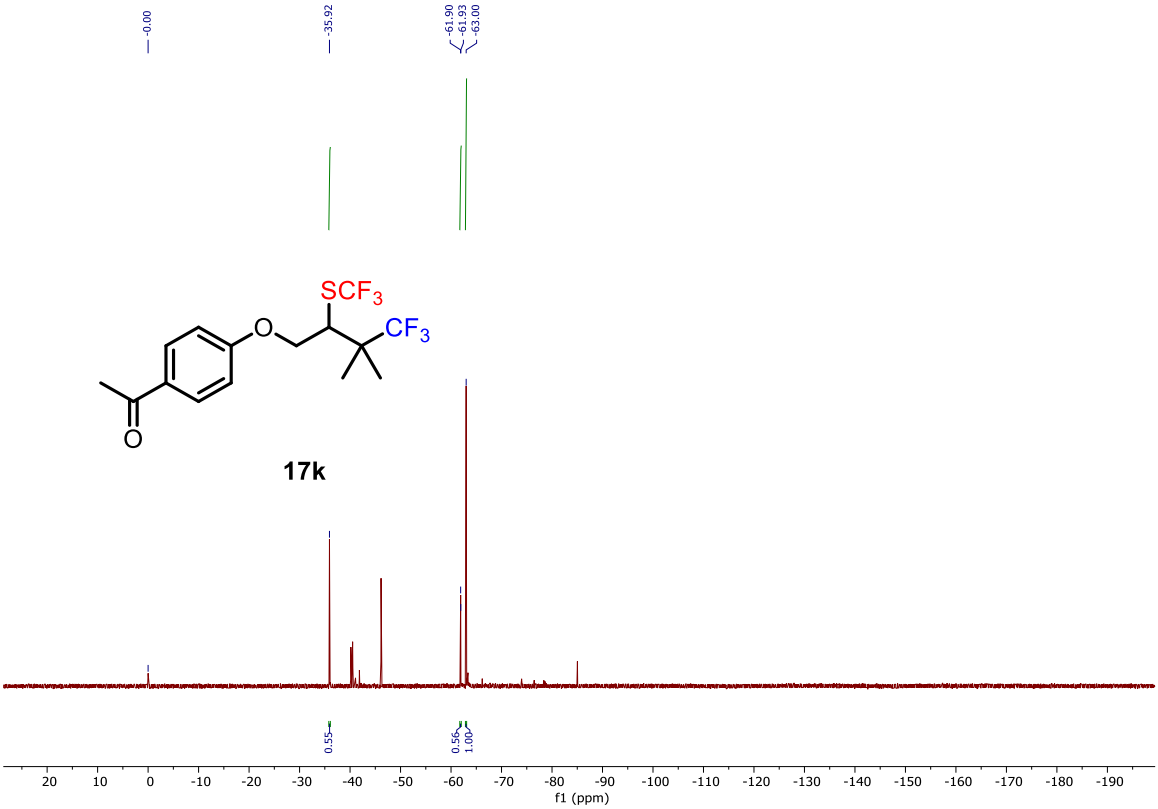
17j

^{13}C NMR (100 MHz, $CDCl_3$) 17j

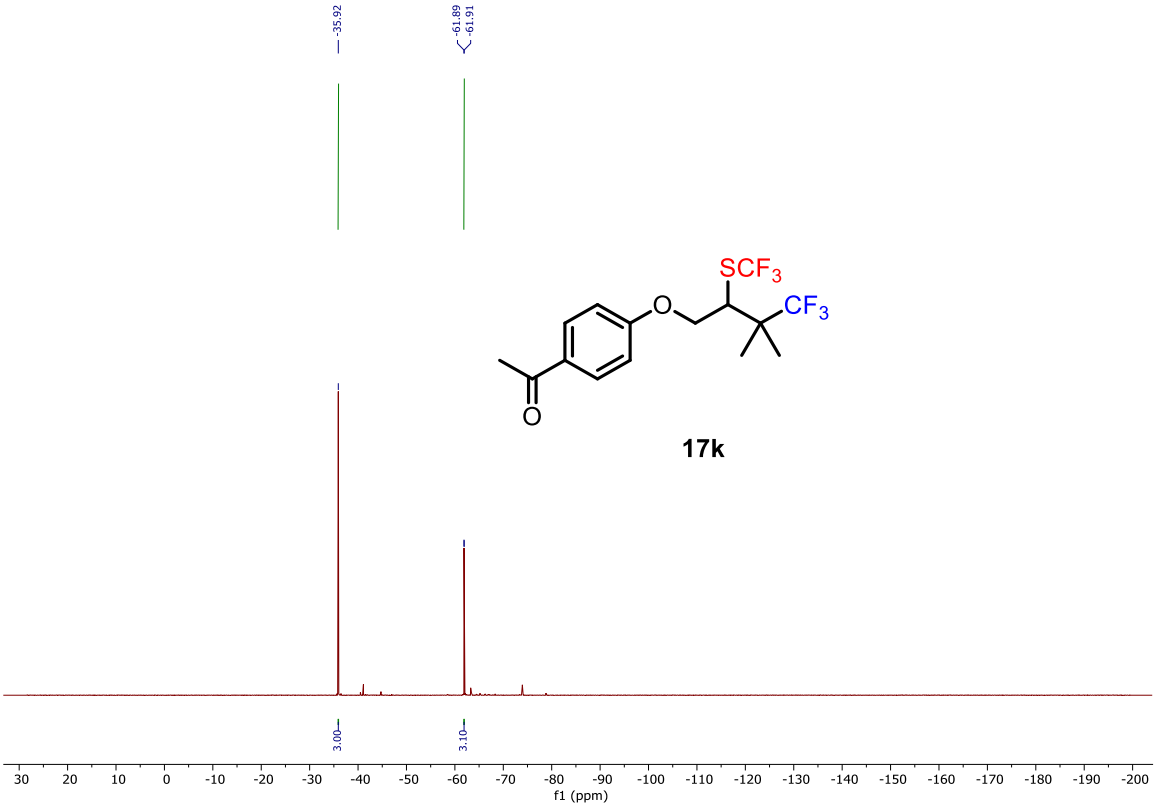


17j

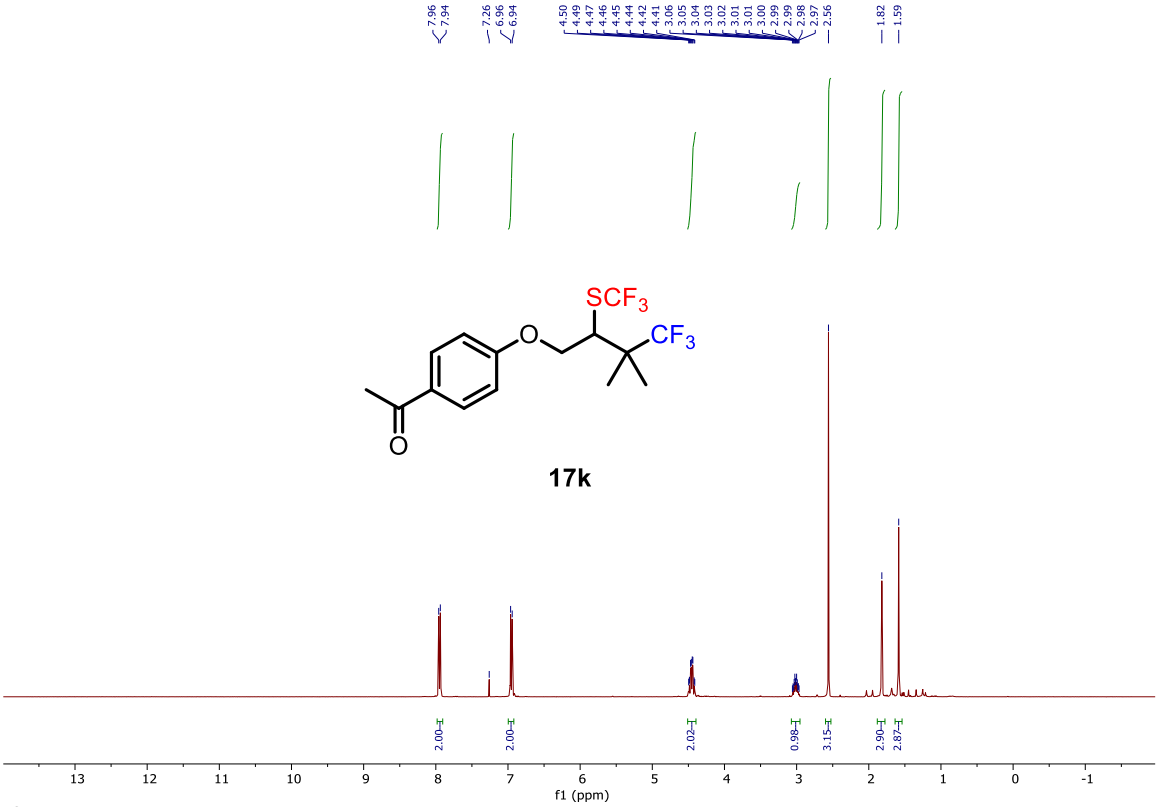
^{19}F NMR (376 MHz, $CDCl_3$) yield of 17k



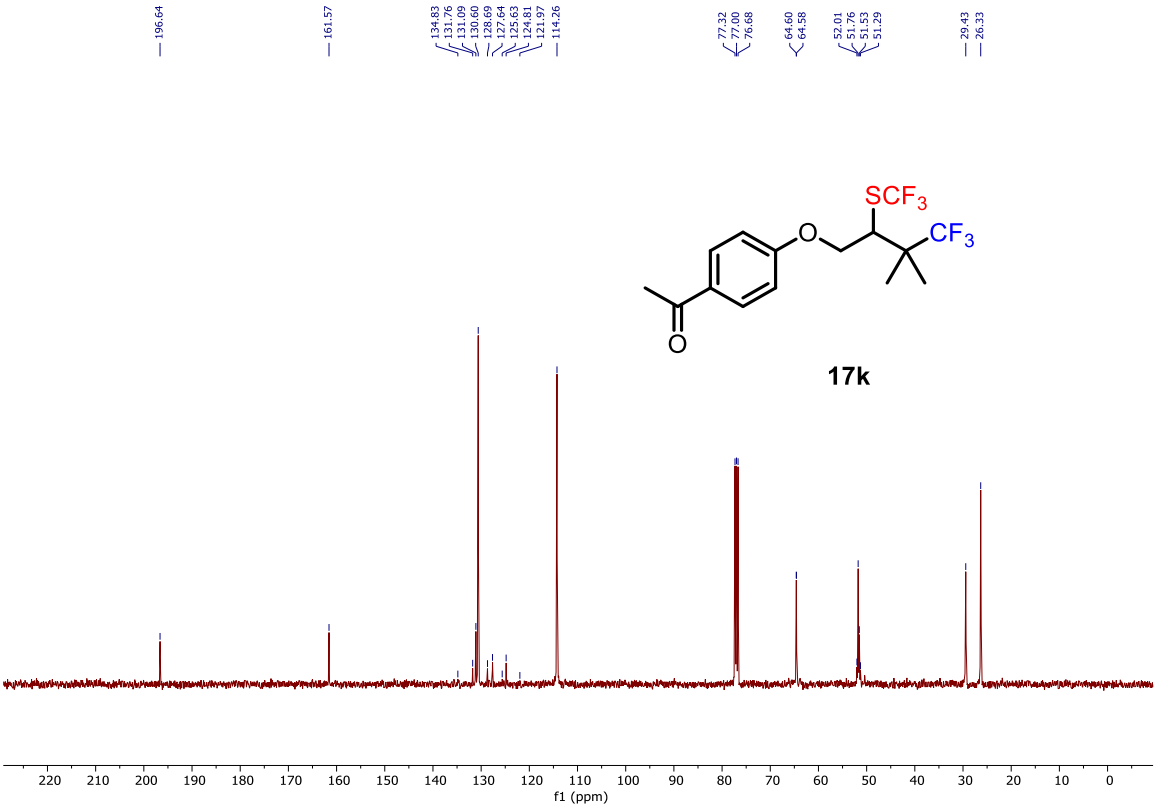
^{19}F NMR (376 MHz, $CDCl_3$) 17k



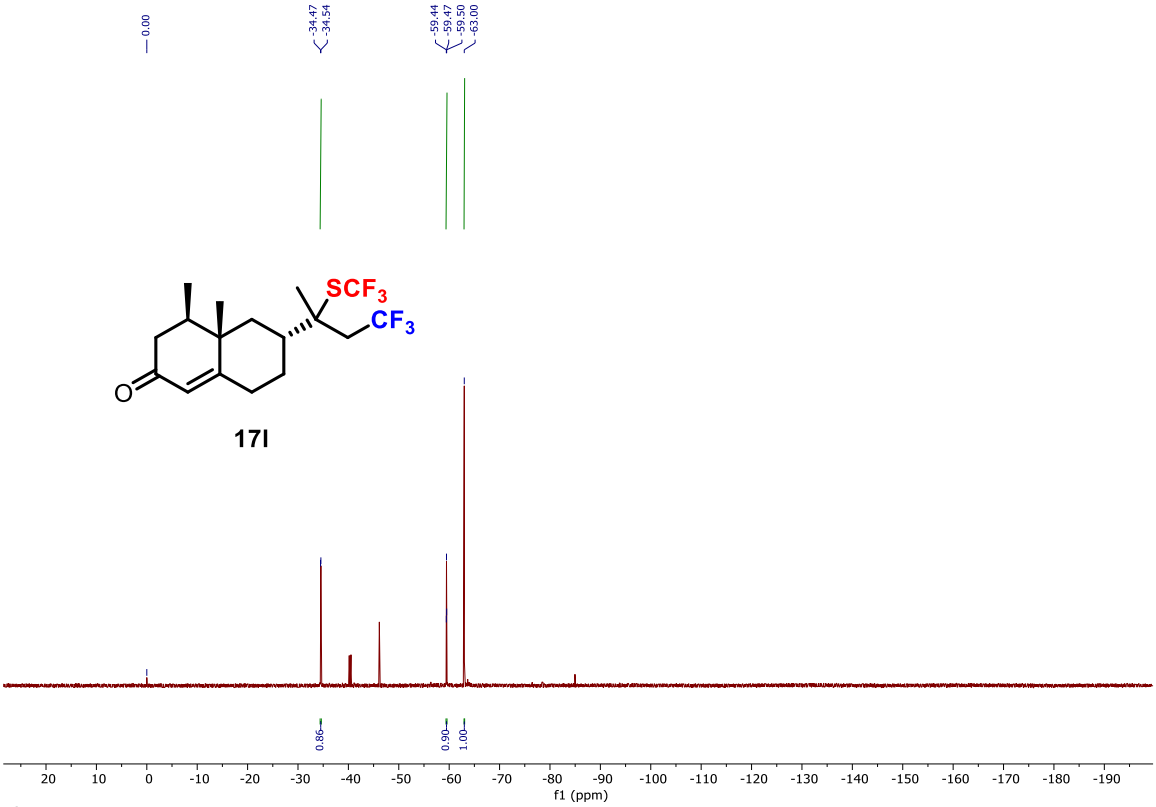
^{1}H NMR (400 MHz, $CDCl_3$) 17k



^{13}C NMR (100 MHz, $CDCl_3$) 17k

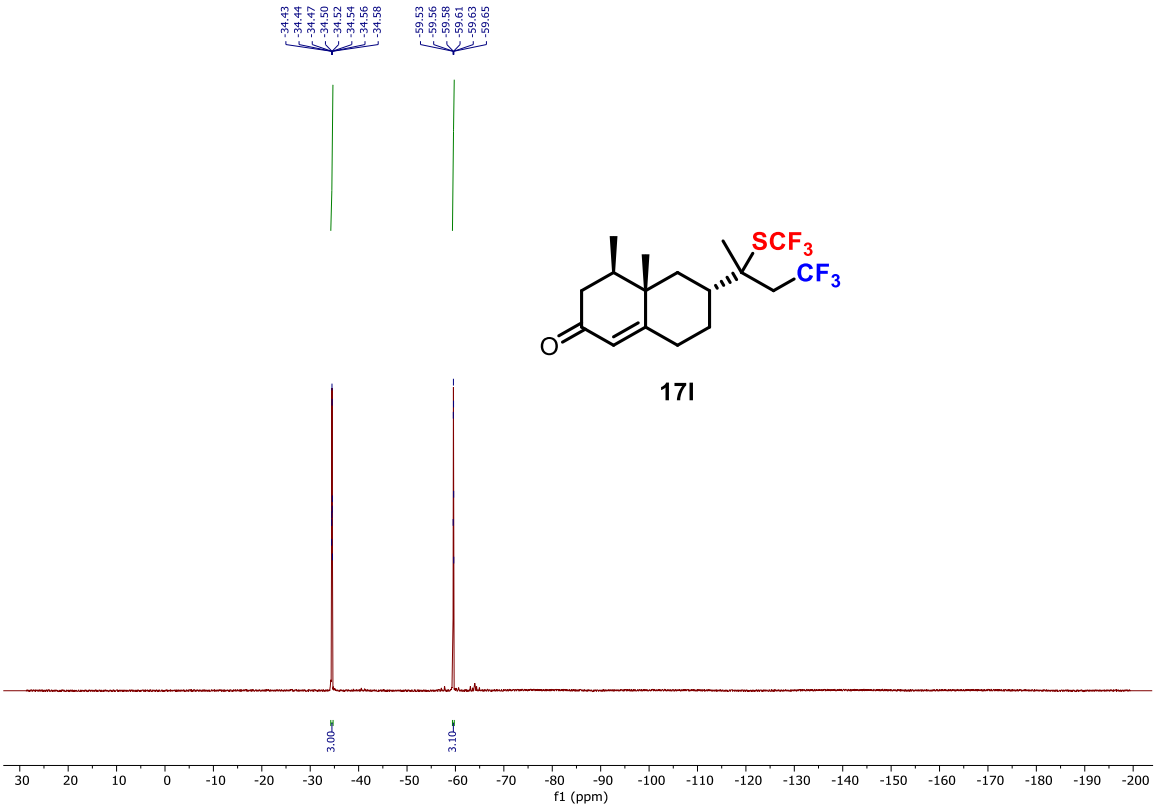


^{19}F NMR (376 MHz, $CDCl_3$) yield of 17l



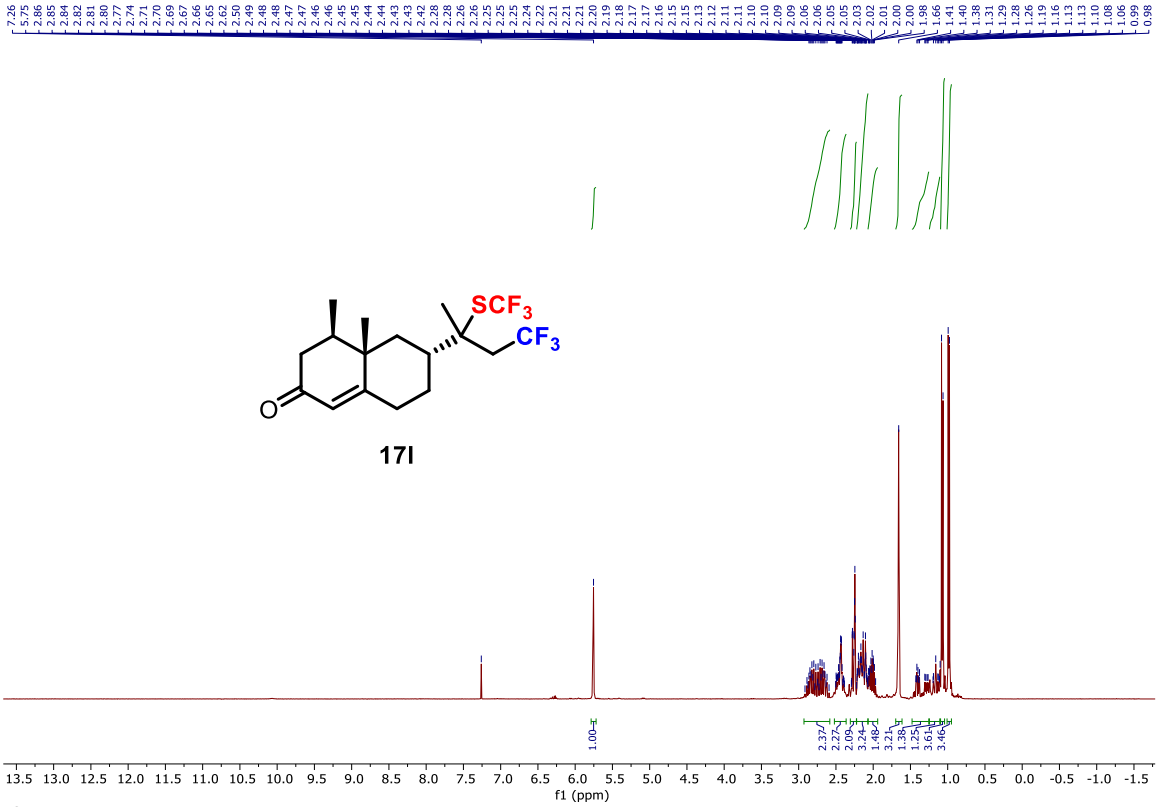
17l

^{19}F NMR (376 MHz, $CDCl_3$) 17l

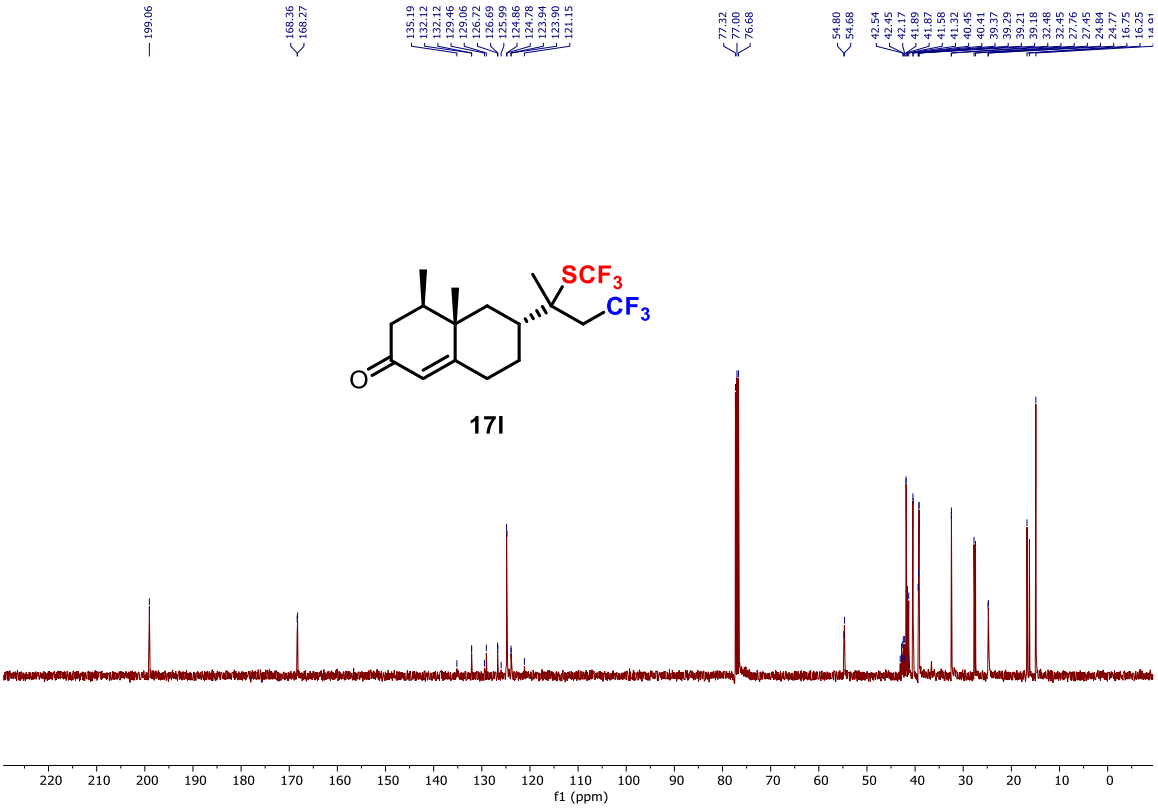


17l

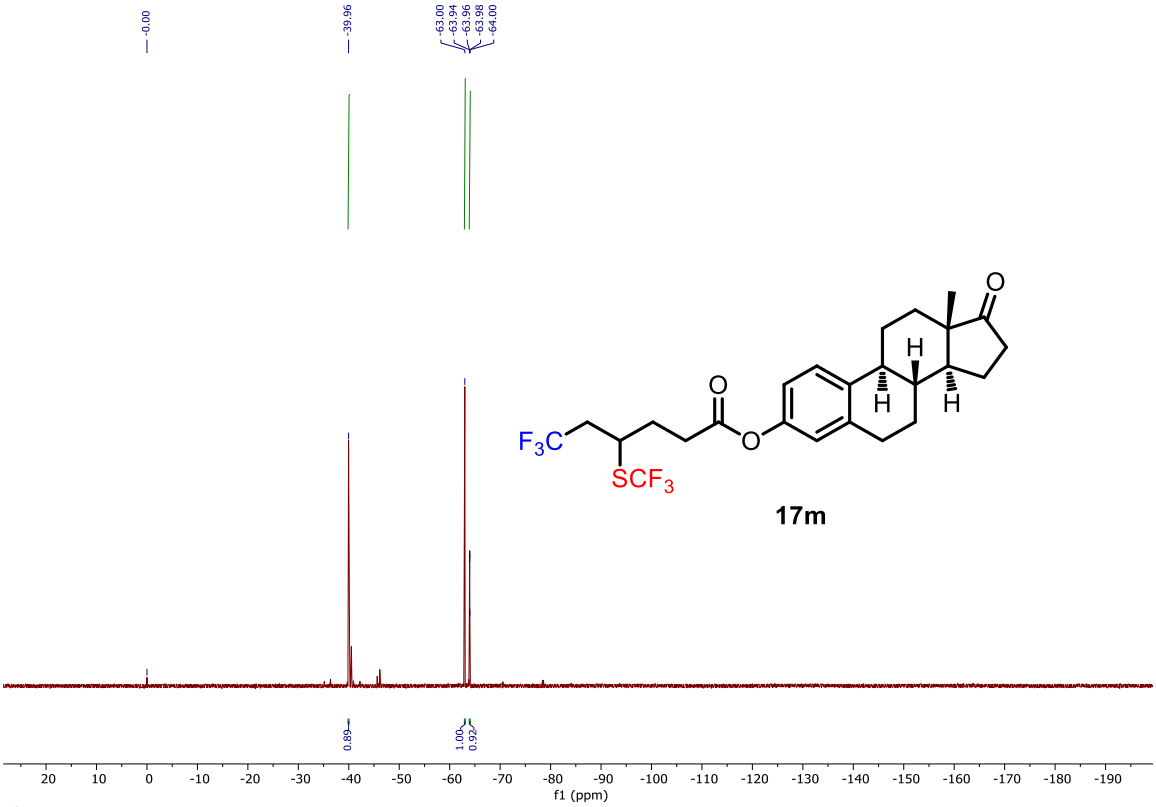
^{1}H NMR (400 MHz, $CDCl_3$) 17l



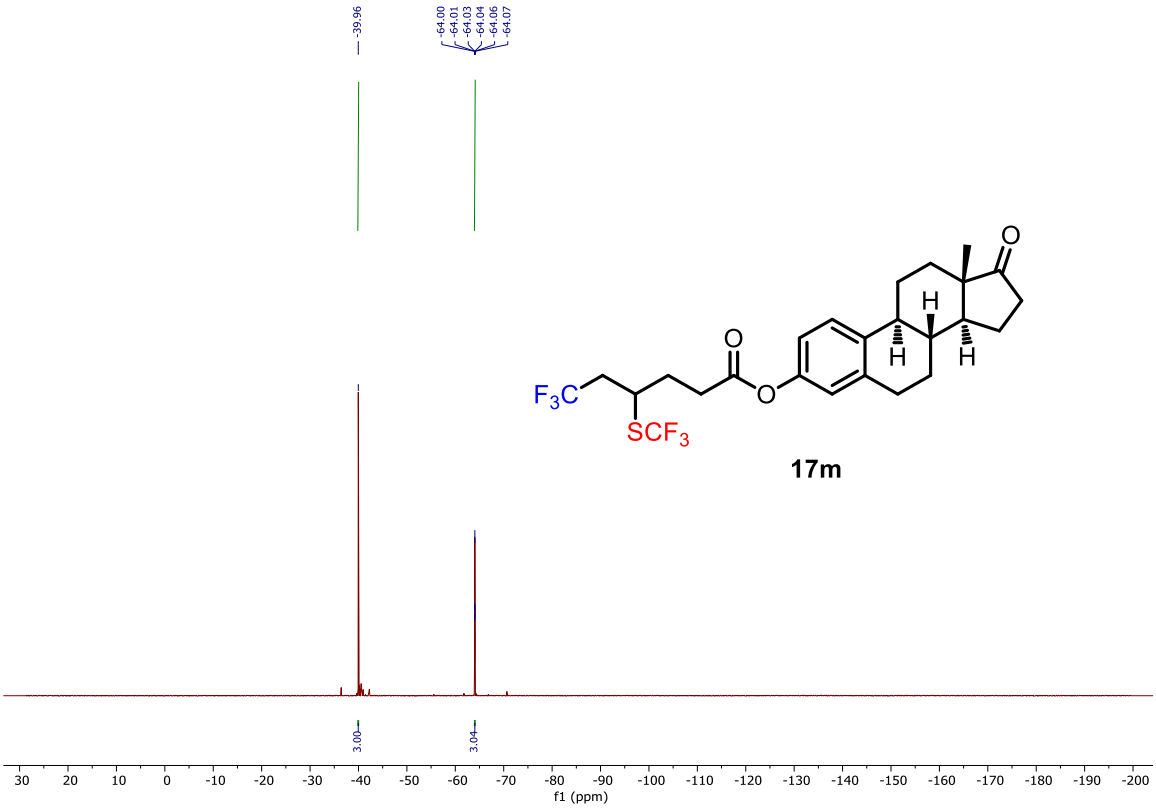
^{13}C NMR (100 MHz, $CDCl_3$) 17l



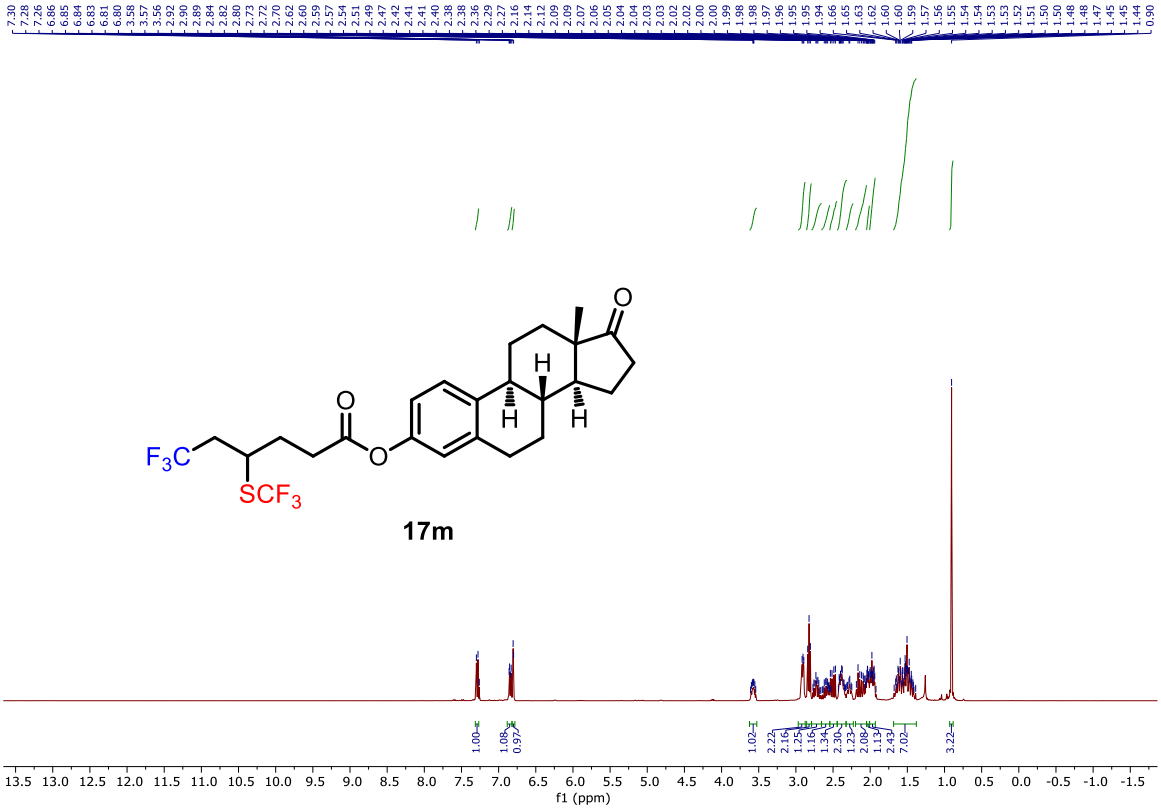
^{19}F NMR (376 MHz, $CDCl_3$) yield of 17m



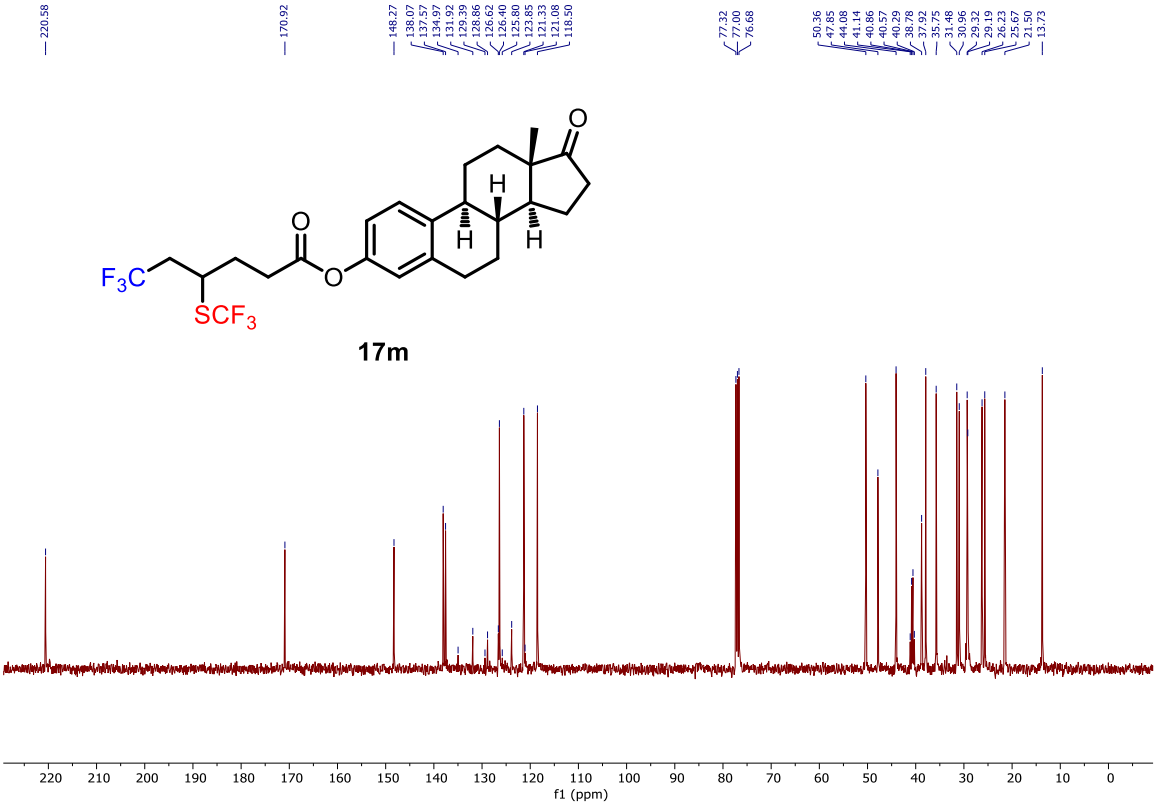
^{19}F NMR (376 MHz, $CDCl_3$) 17m



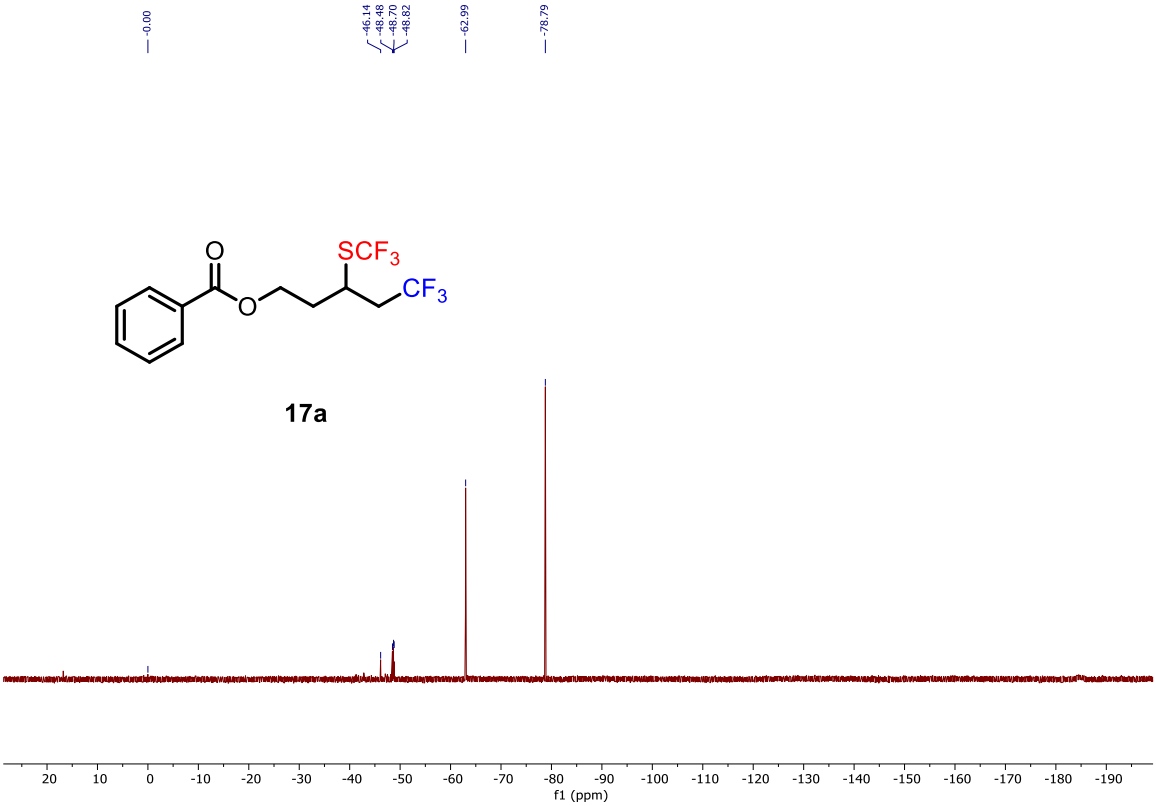
^{1}H NMR (400 MHz, $CDCl_3$) 17m



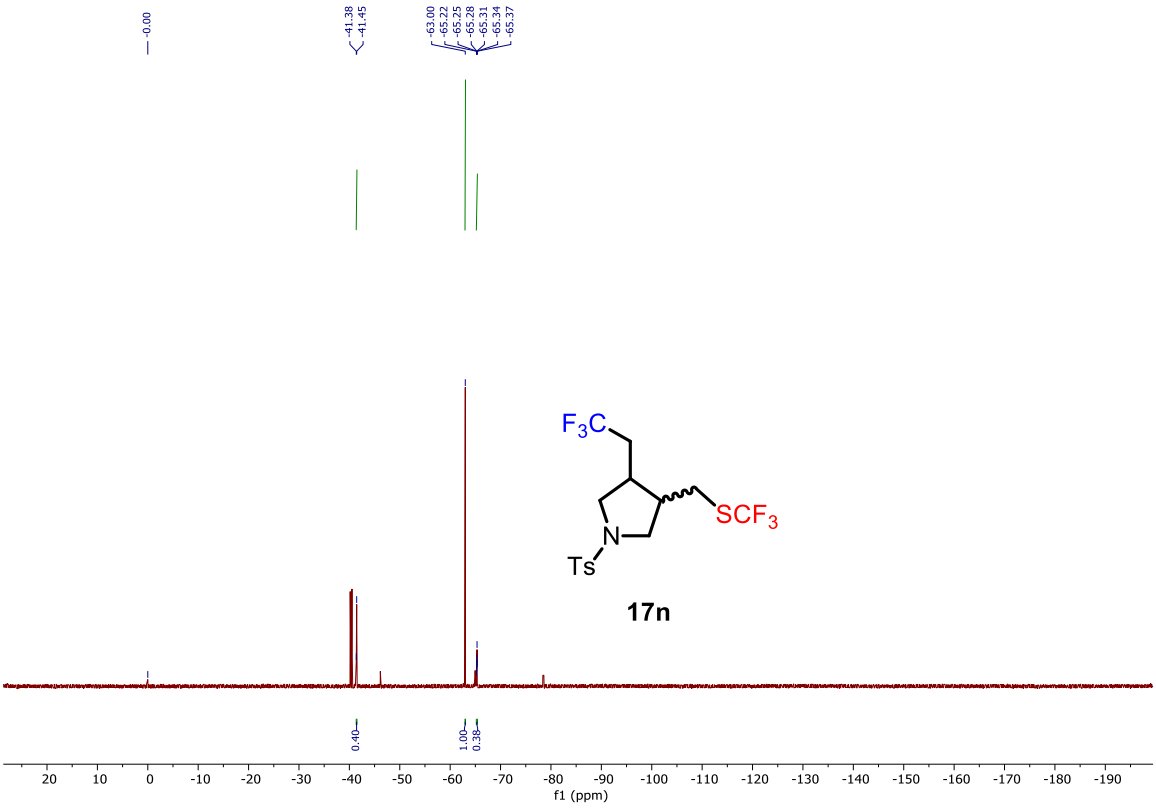
^{13}C NMR (100 MHz, $CDCl_3$) 17m



^{19}F NMR (376 MHz, $CDCl_3$) yield of 17a-TEMPO



^{19}F NMR (376 MHz, $CDCl_3$) yield of 17n

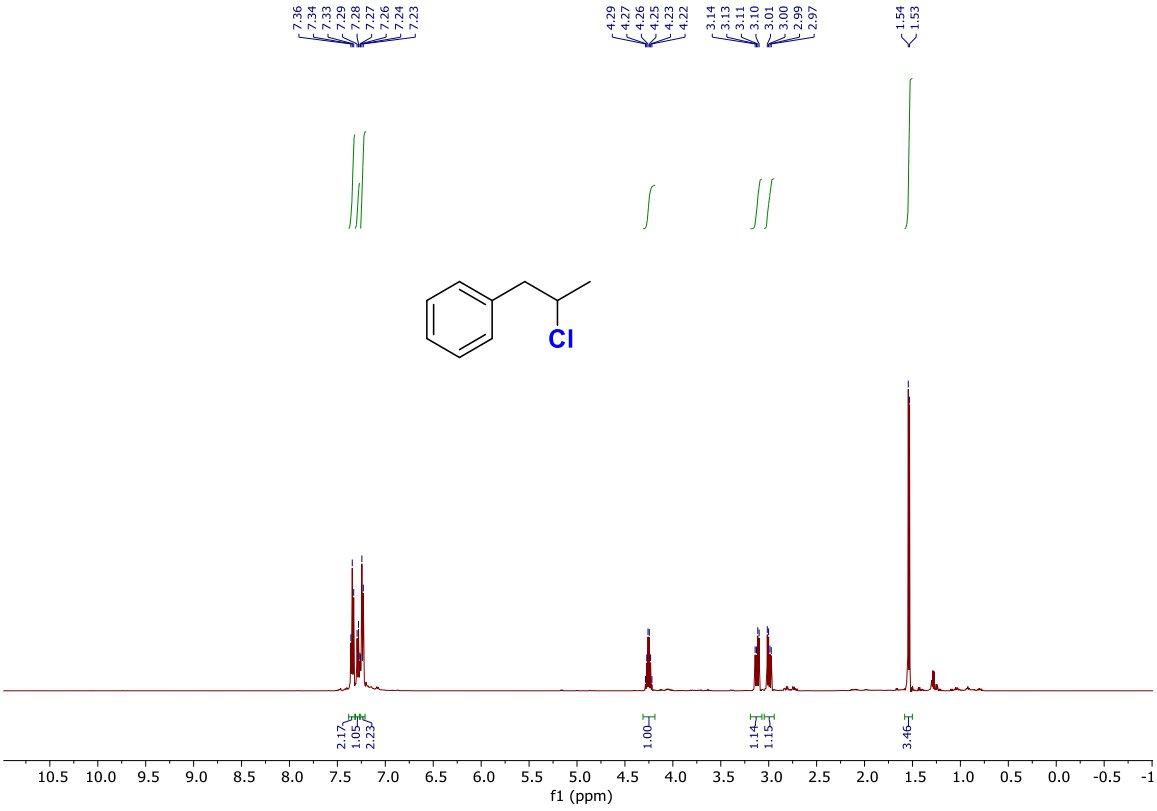


APPENDIX C

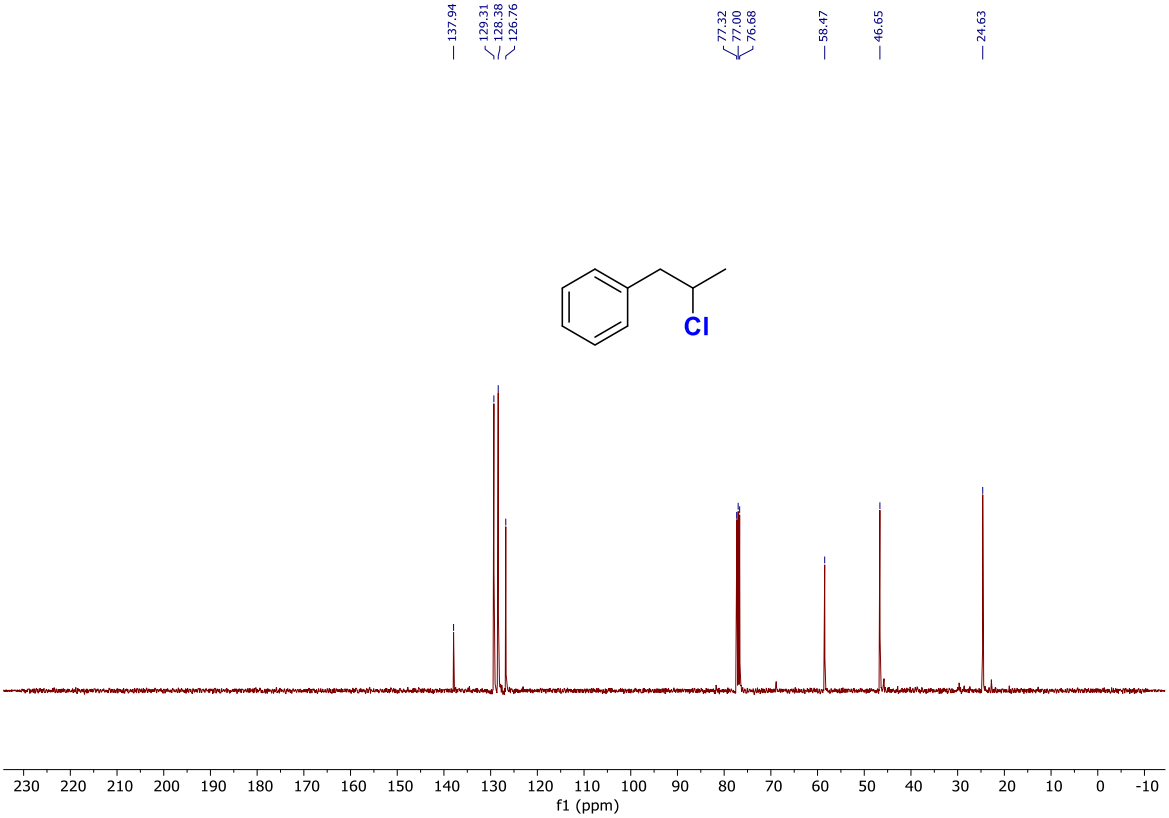
NMR SPECTRA OF COMPOUNDS PREPARED IN CHAPTER 4

C.1 ^{1}H, and ^{13}C NMR spectral data

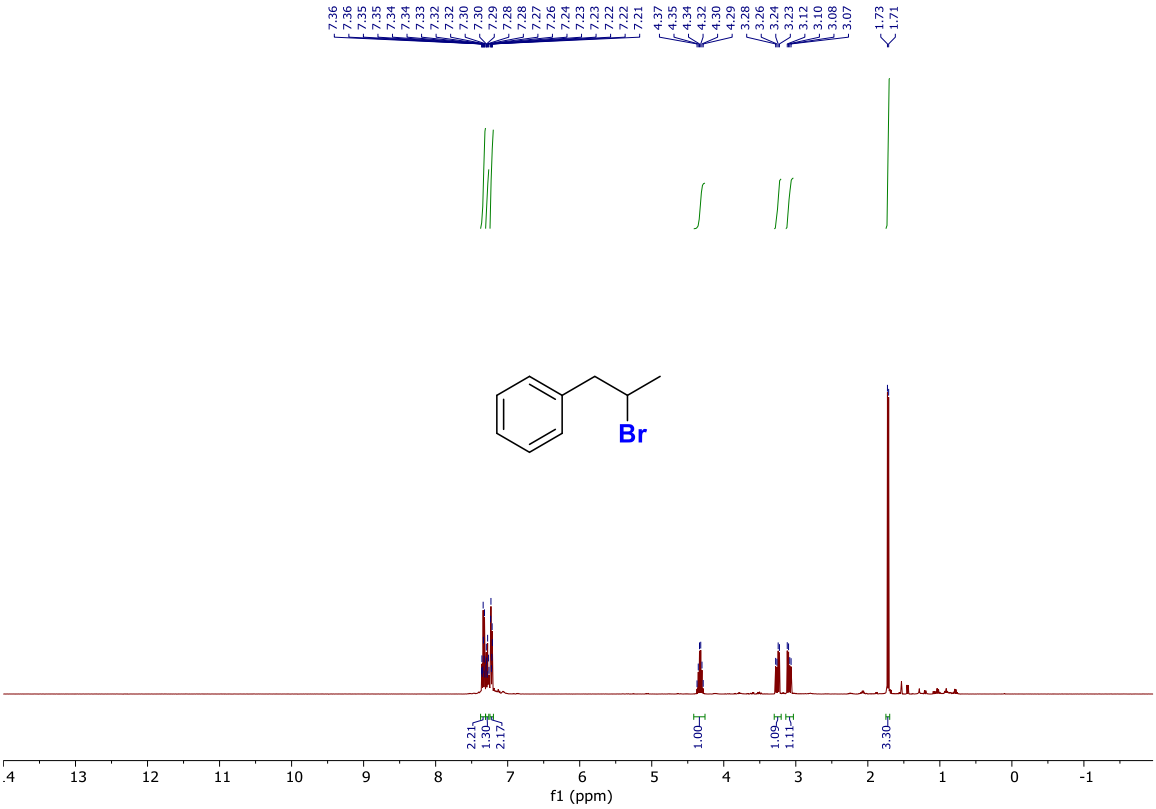
^{1}H NMR (500 MHz, $CDCl_3$) 2a-Cl



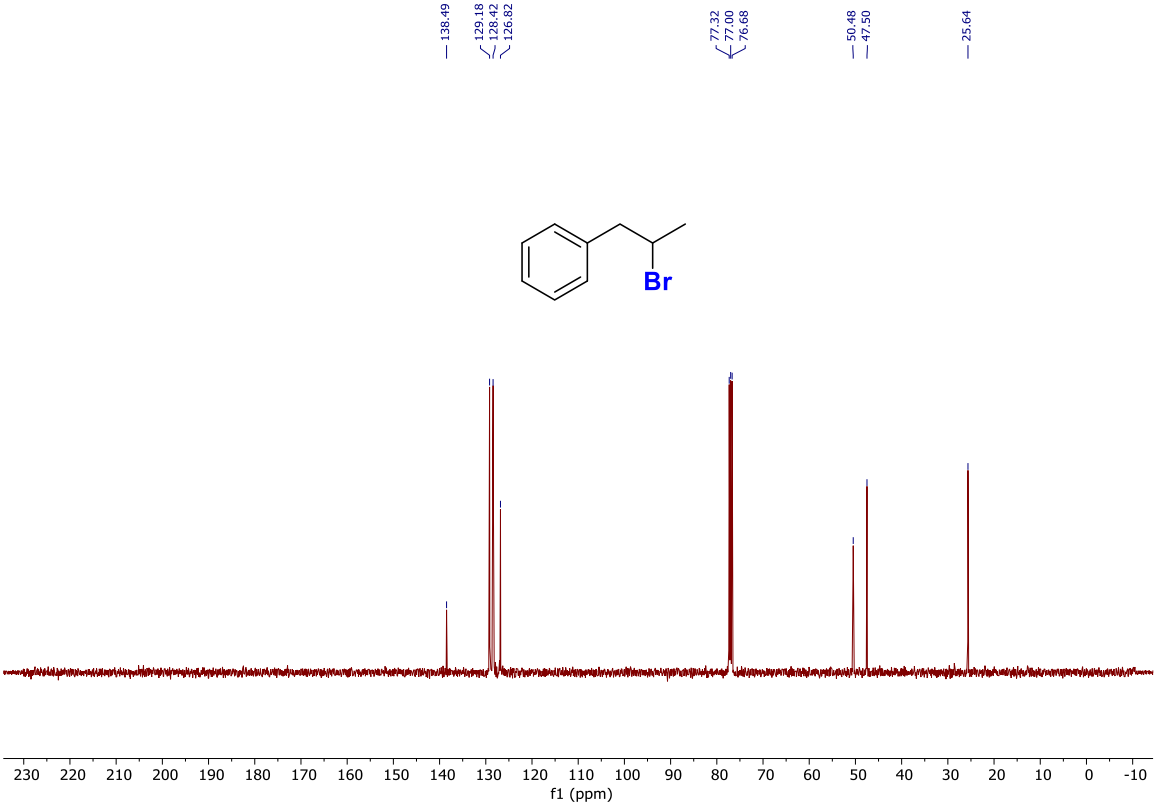
^{13}C NMR (100 MHz, $CDCl_3$) 2a-Cl



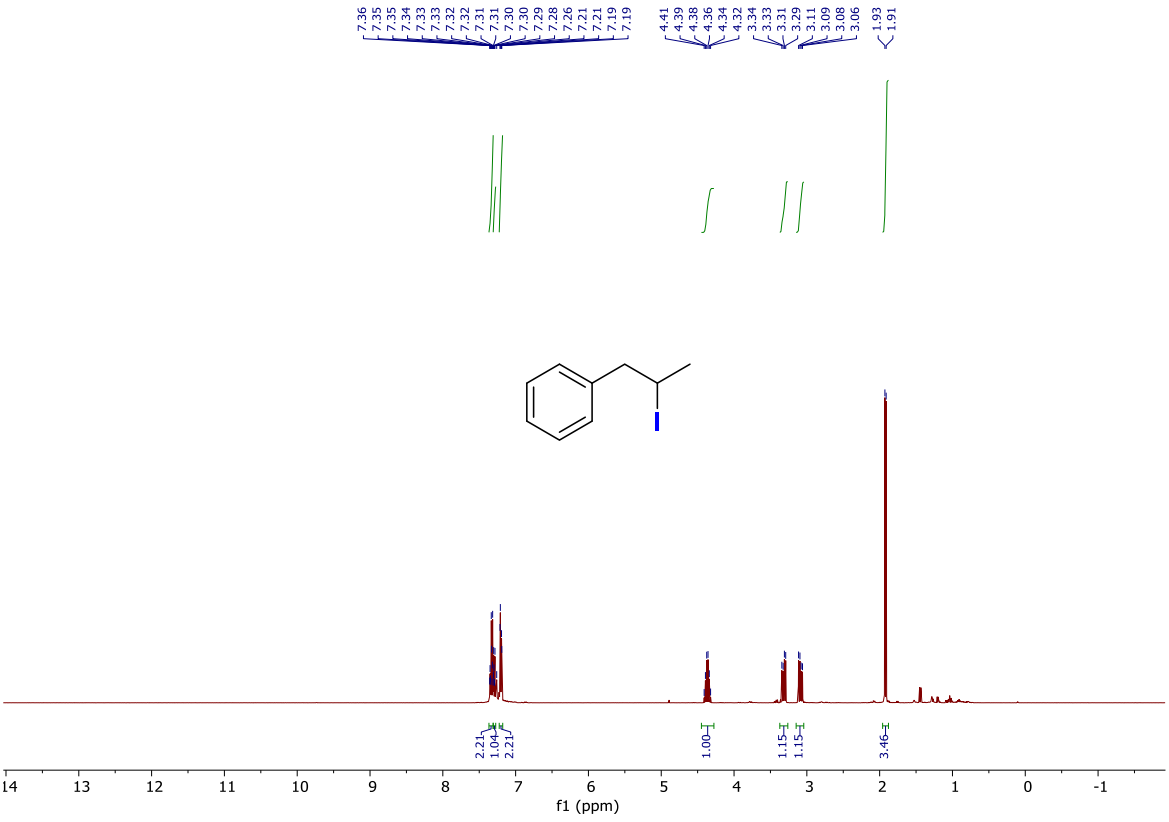
^{1}H NMR (400 MHz, $CDCl_3$) 2a-Br



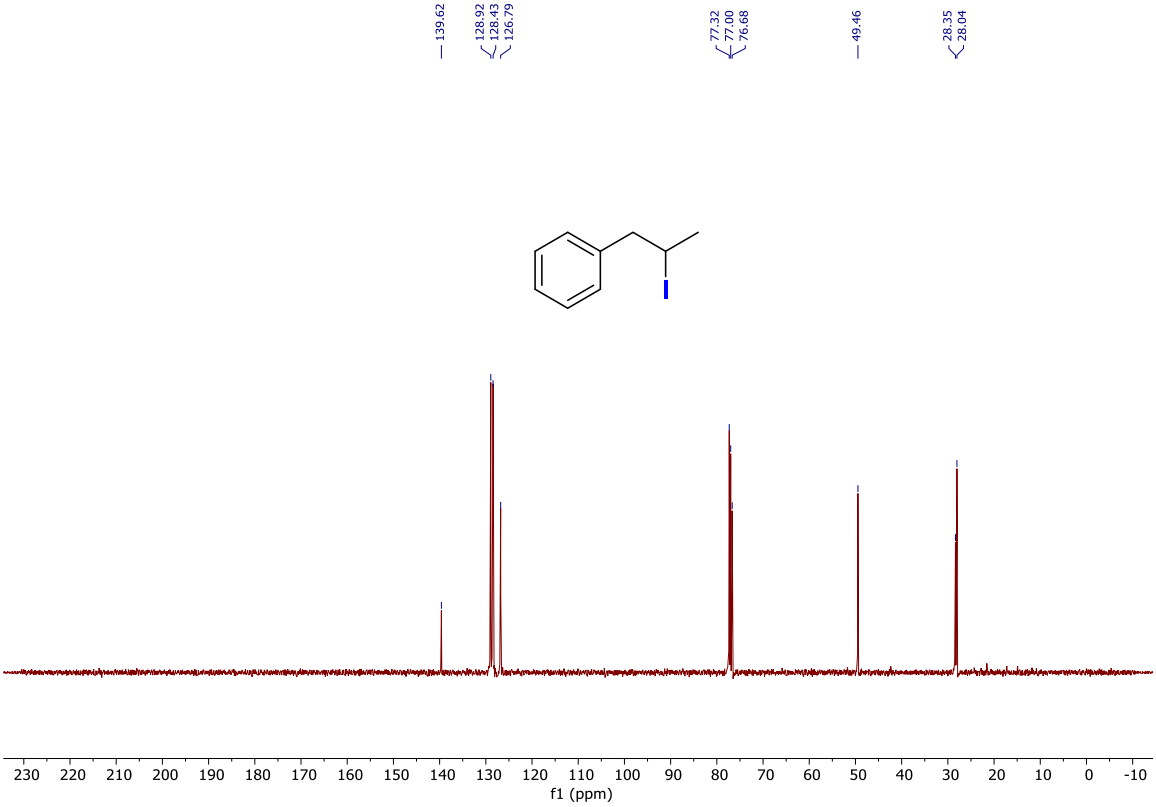
^{13}C NMR (100 MHz, $CDCl_3$) 2a-Br



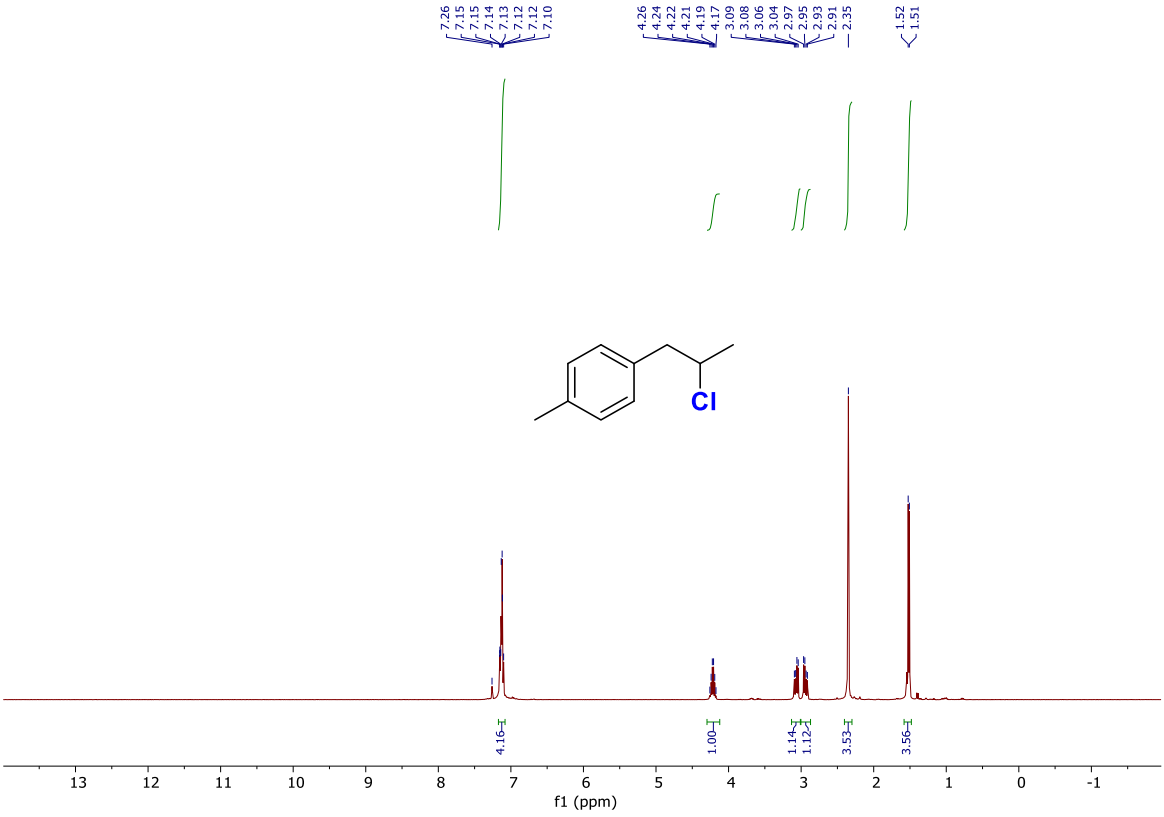
^{1}H NMR (400 MHz, $CDCl_3$) 2a-I



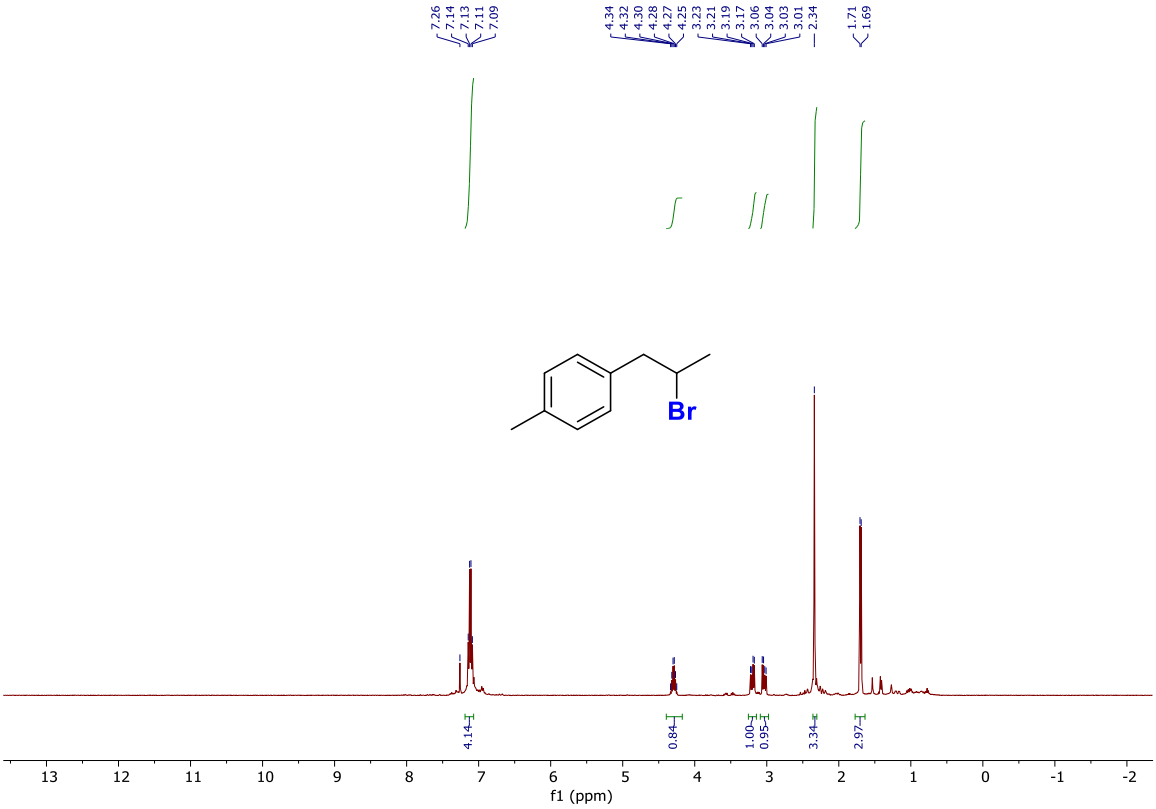
^{13}C NMR (100 MHz, $CDCl_3$) 2a-I



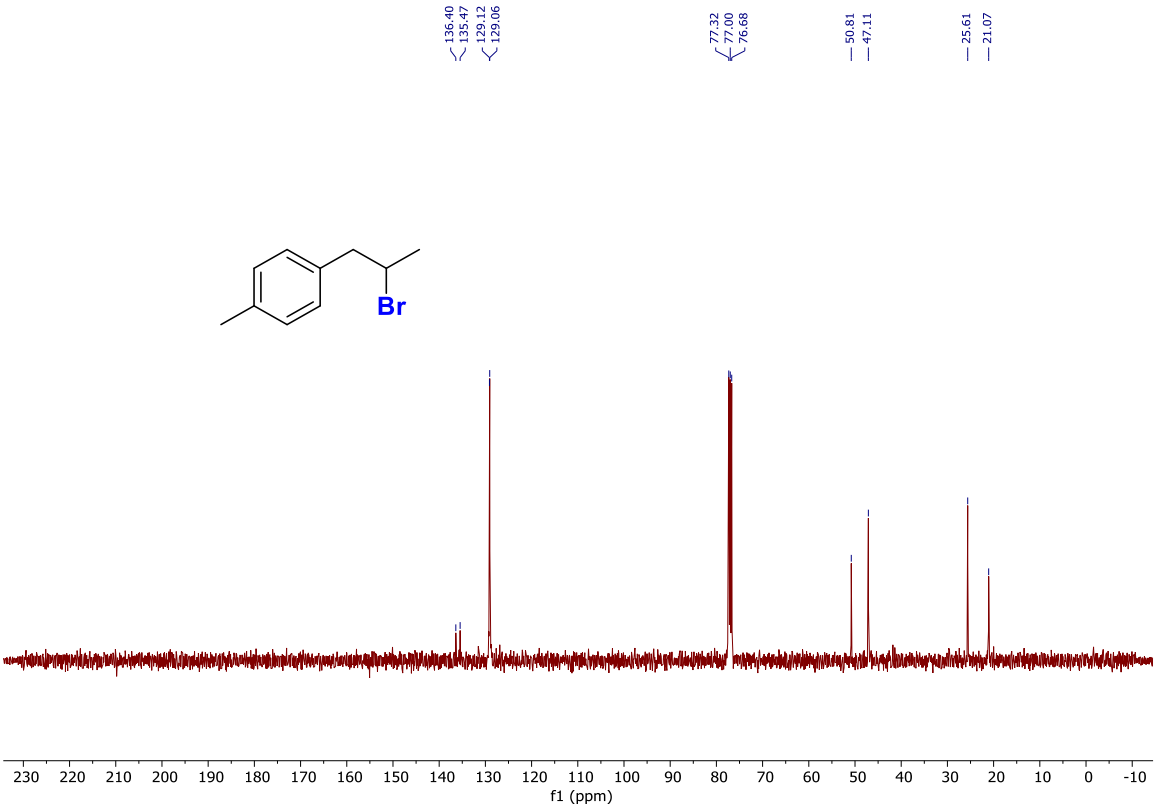
^{1}H NMR (400 MHz, $CDCl_3$) 2b-Cl



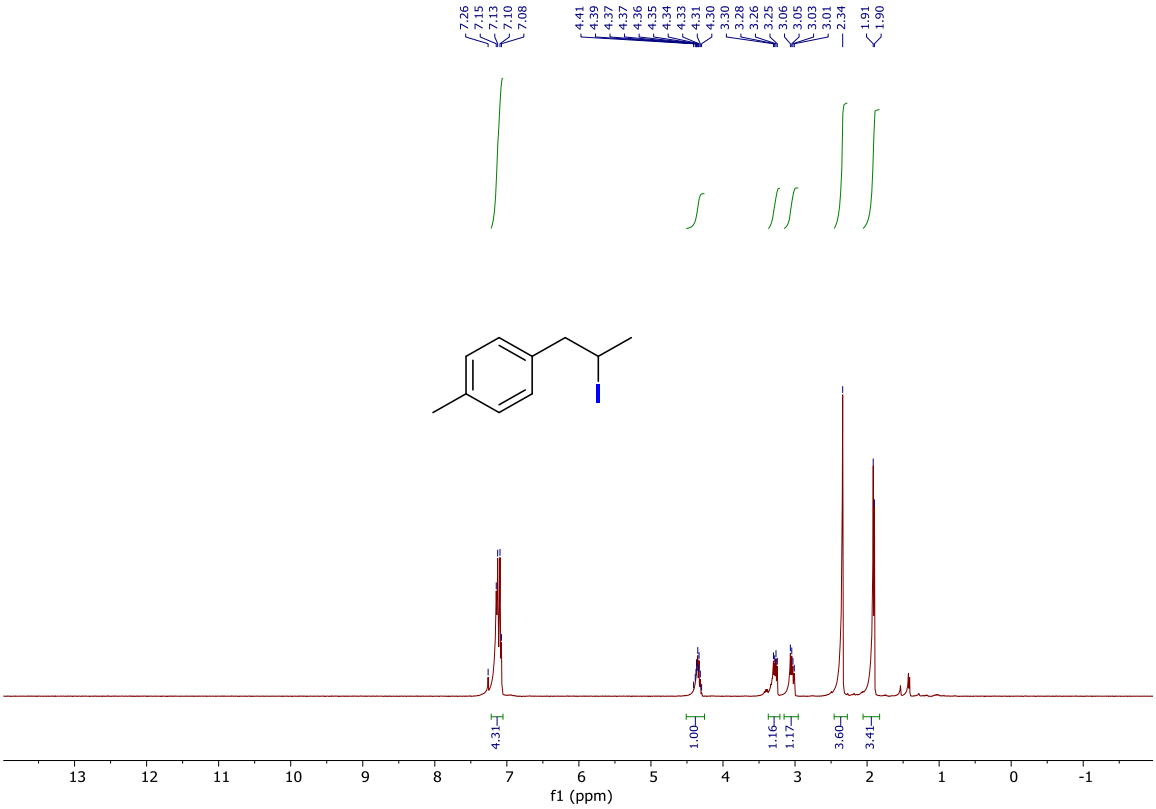
^{1}H NMR (400 MHz, $CDCl_3$) 2b-Br



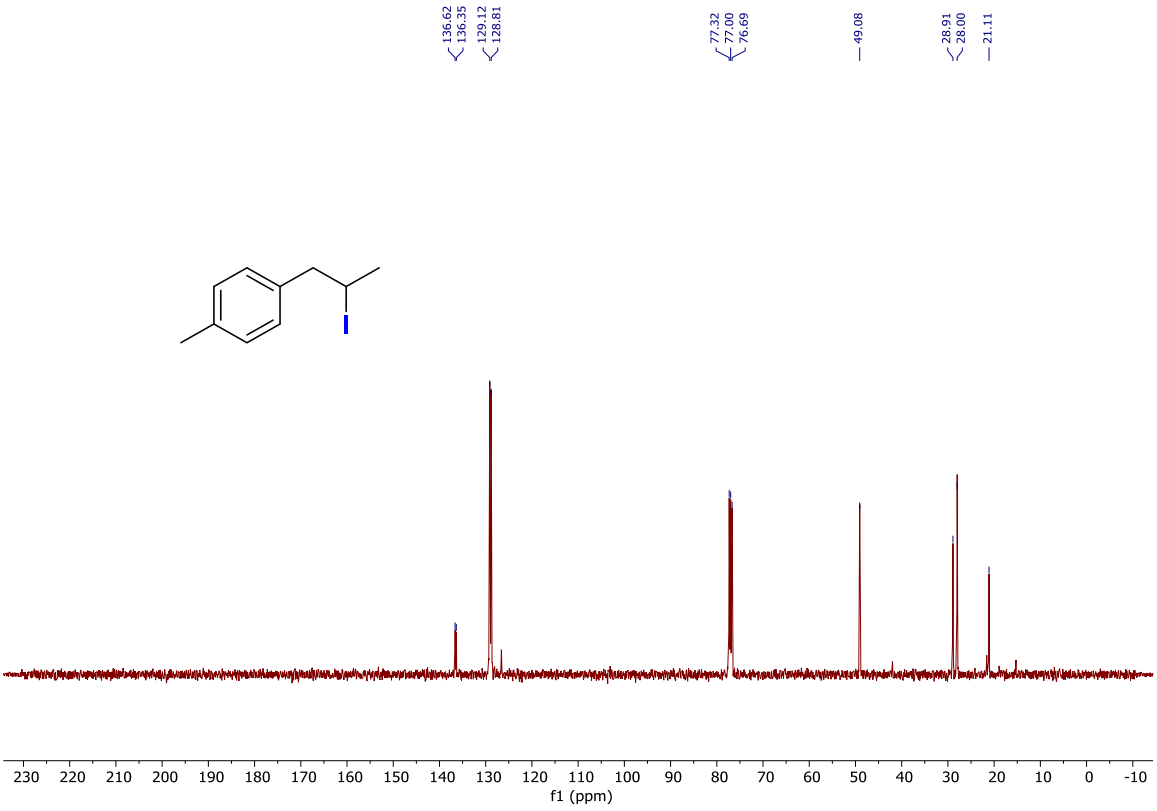
^{13}C NMR (100 MHz, $CDCl_3$) 2b-Br



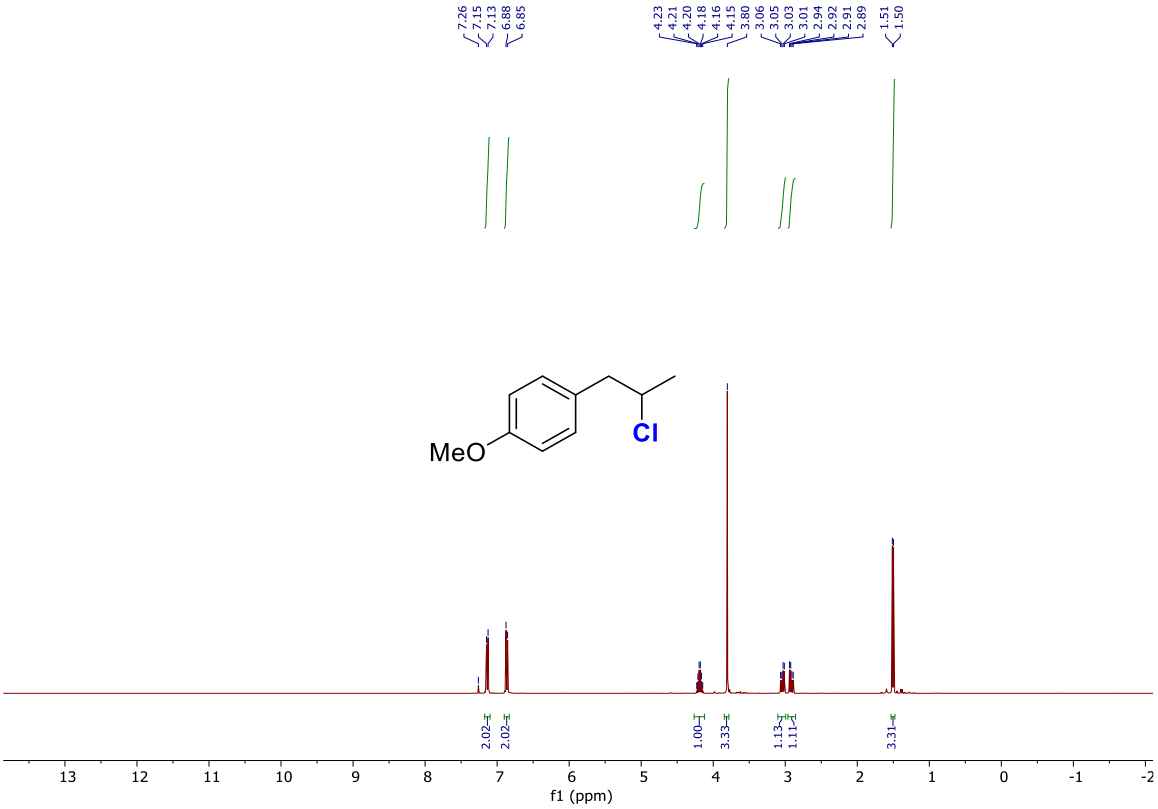
^{1}H NMR (400 MHz, $CDCl_3$) 2b-I



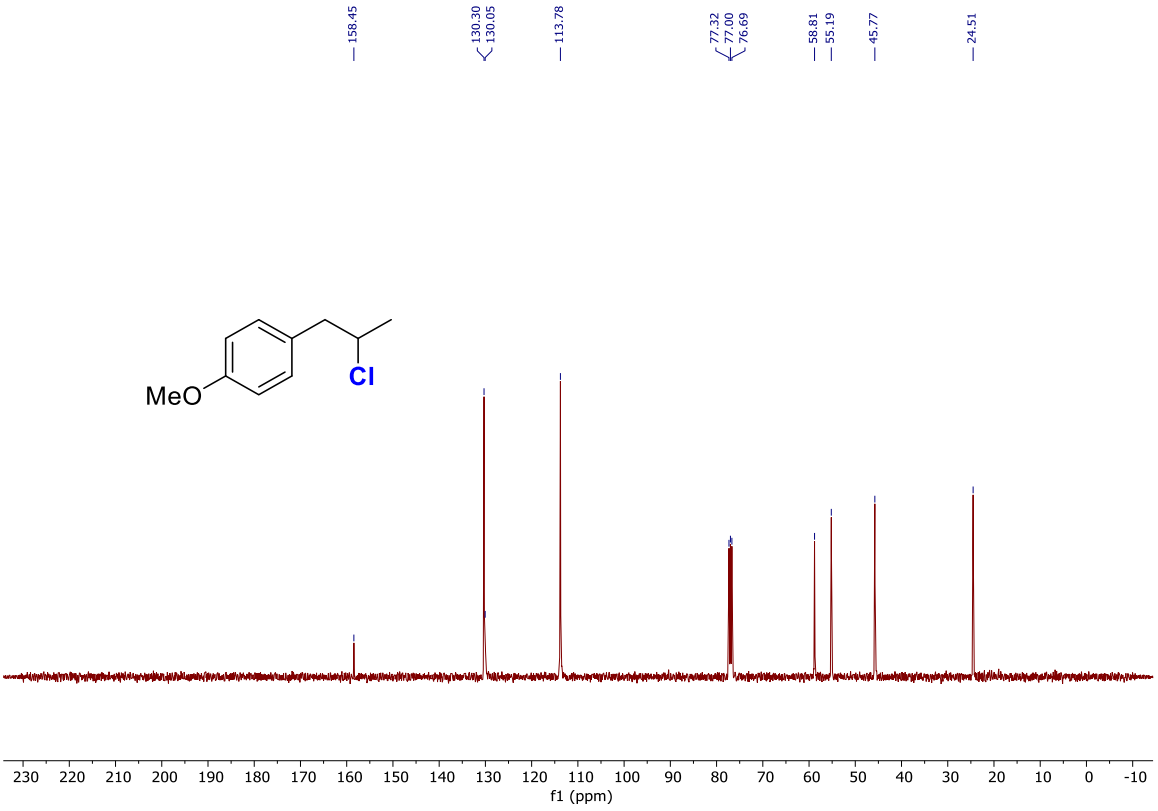
^{13}C NMR (100 MHz, $CDCl_3$) 2b-I



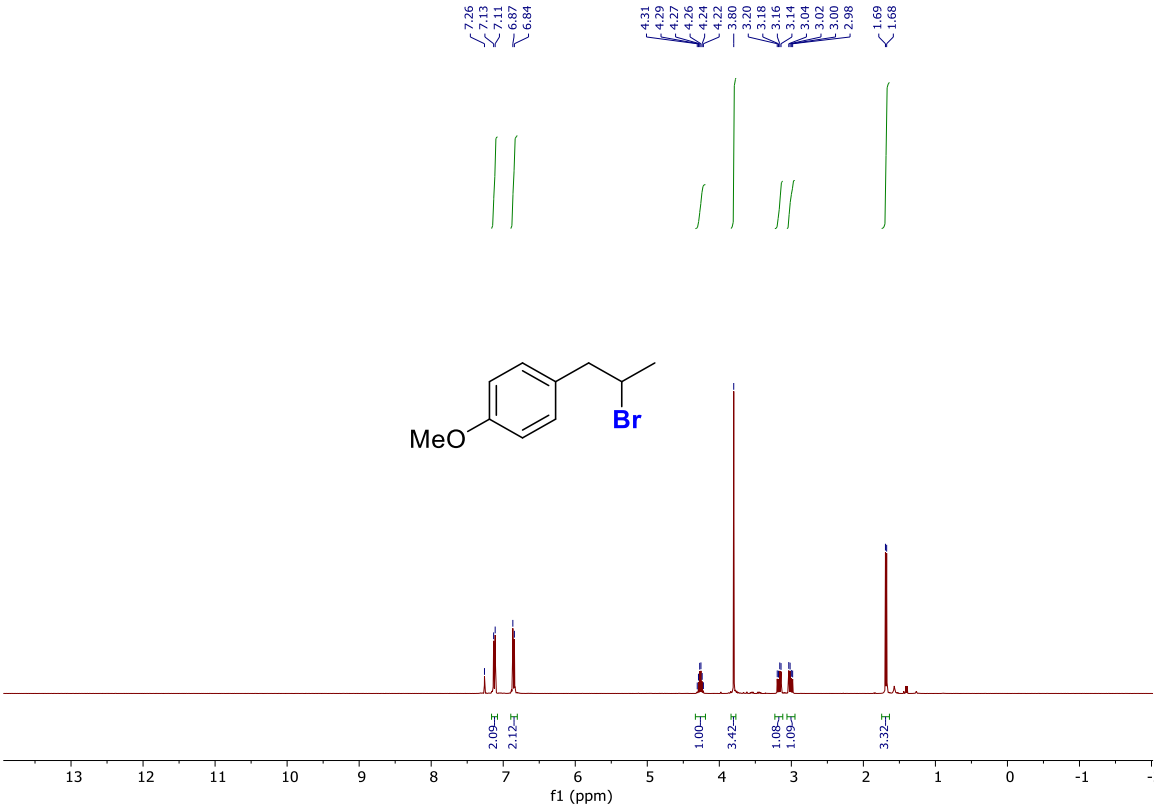
^{1}H NMR (400 MHz, $CDCl_3$) 2c-Cl



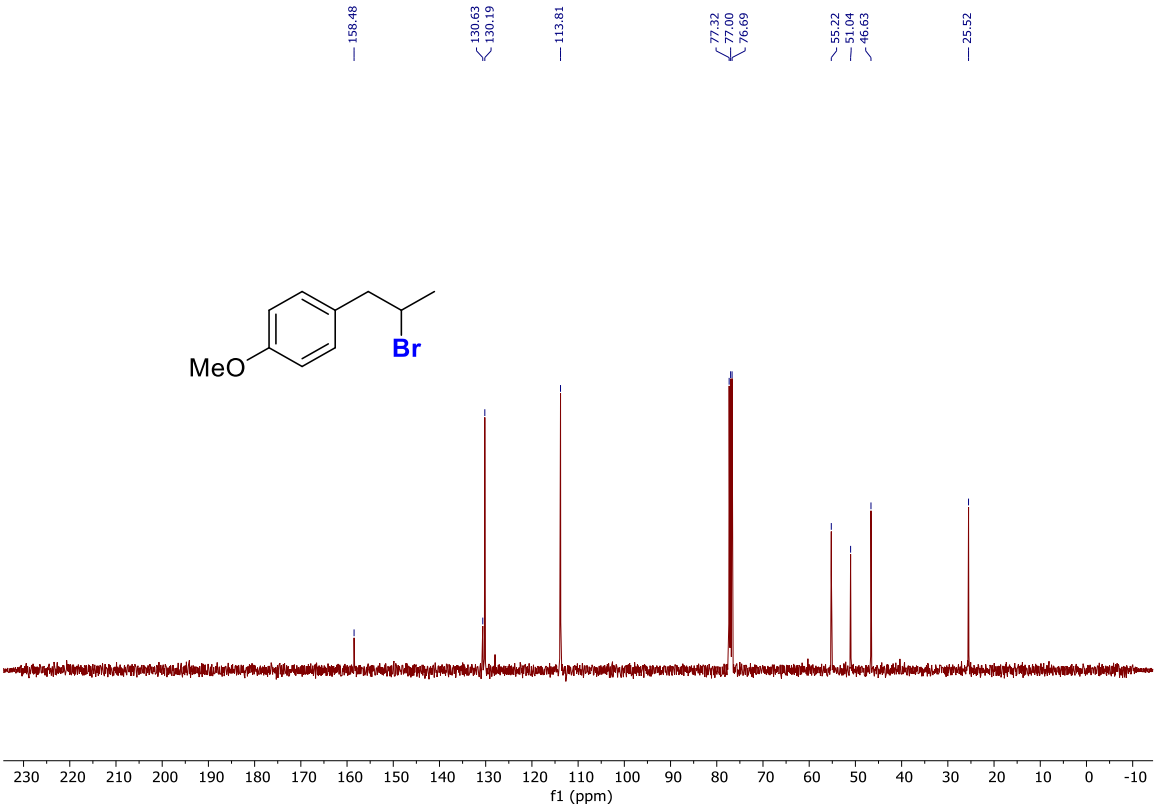
^{13}C NMR (100 MHz, $CDCl_3$) 2c-Cl



^{1}H NMR (400 MHz, $CDCl_3$) 2c-Br



^{13}C NMR (100 MHz, $CDCl_3$) 2c-Br



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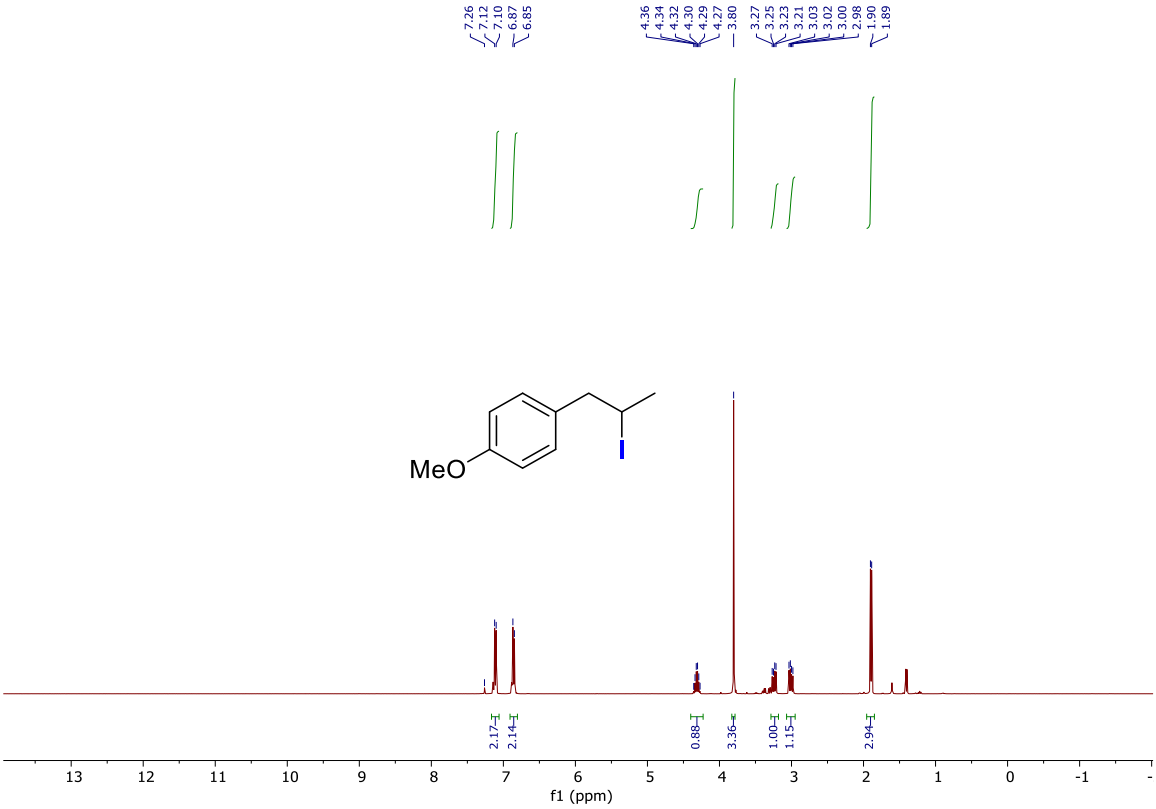

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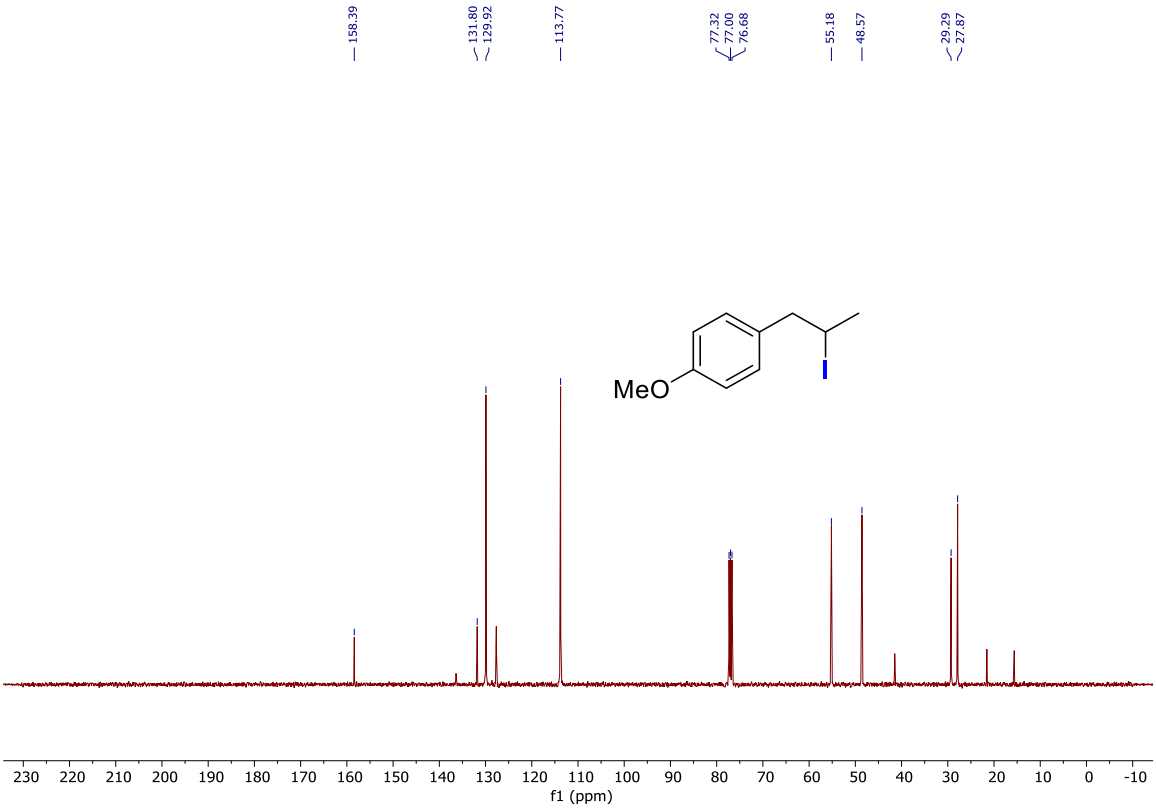

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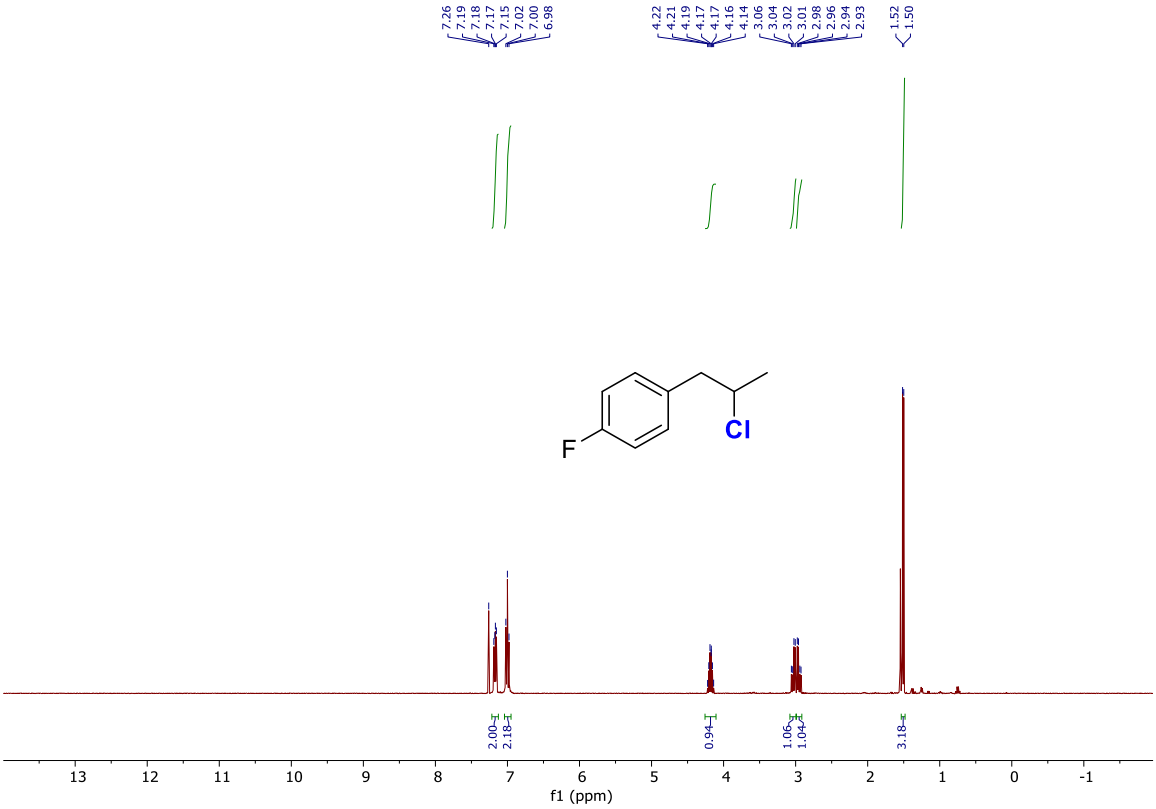

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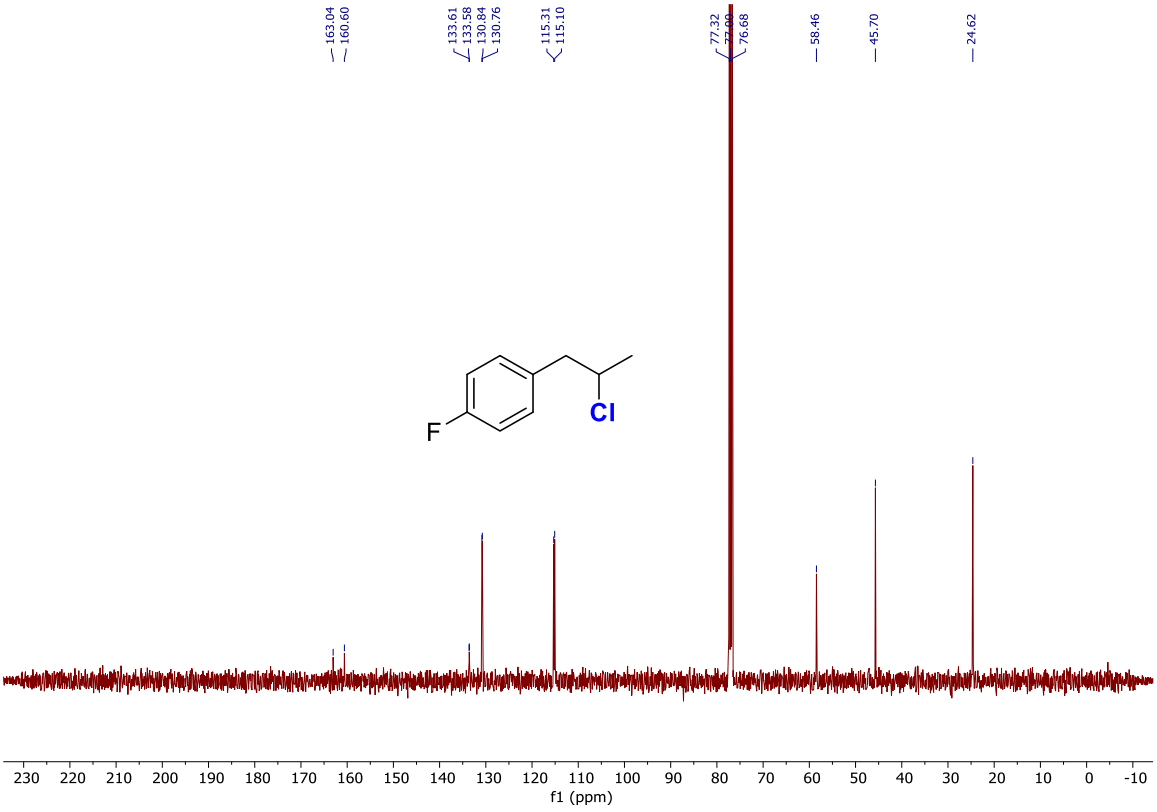

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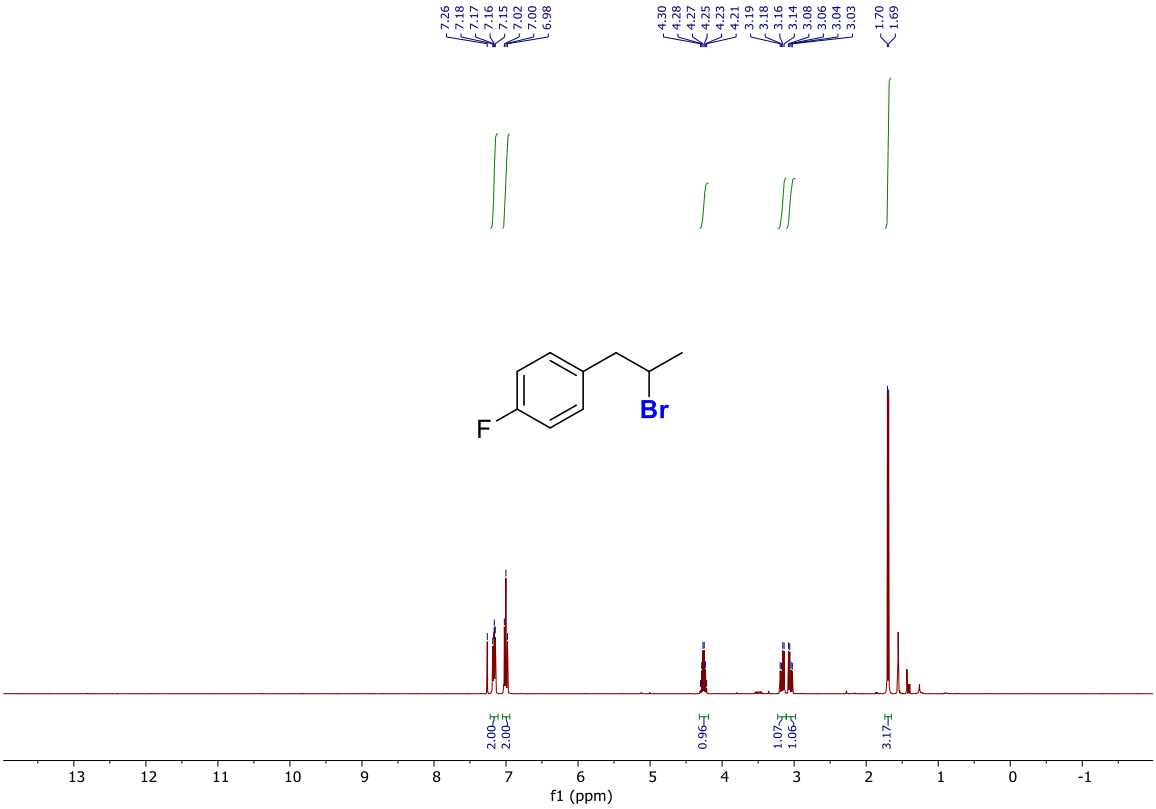

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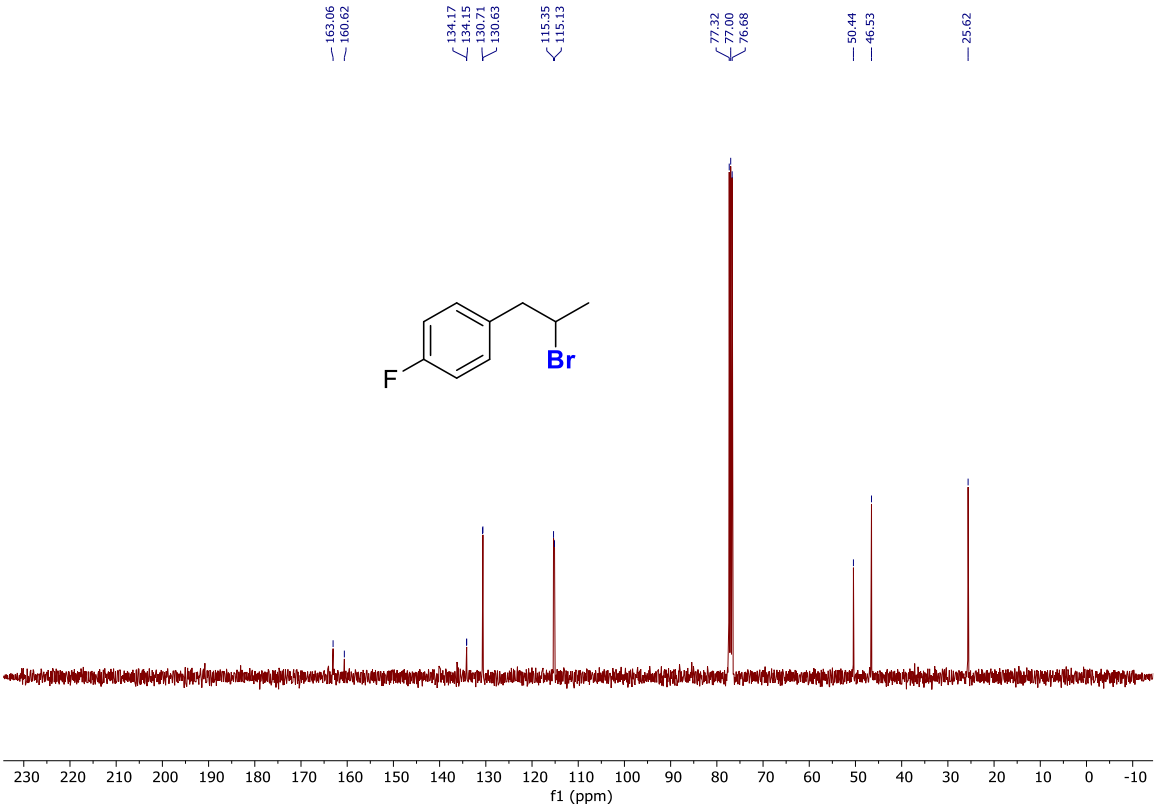

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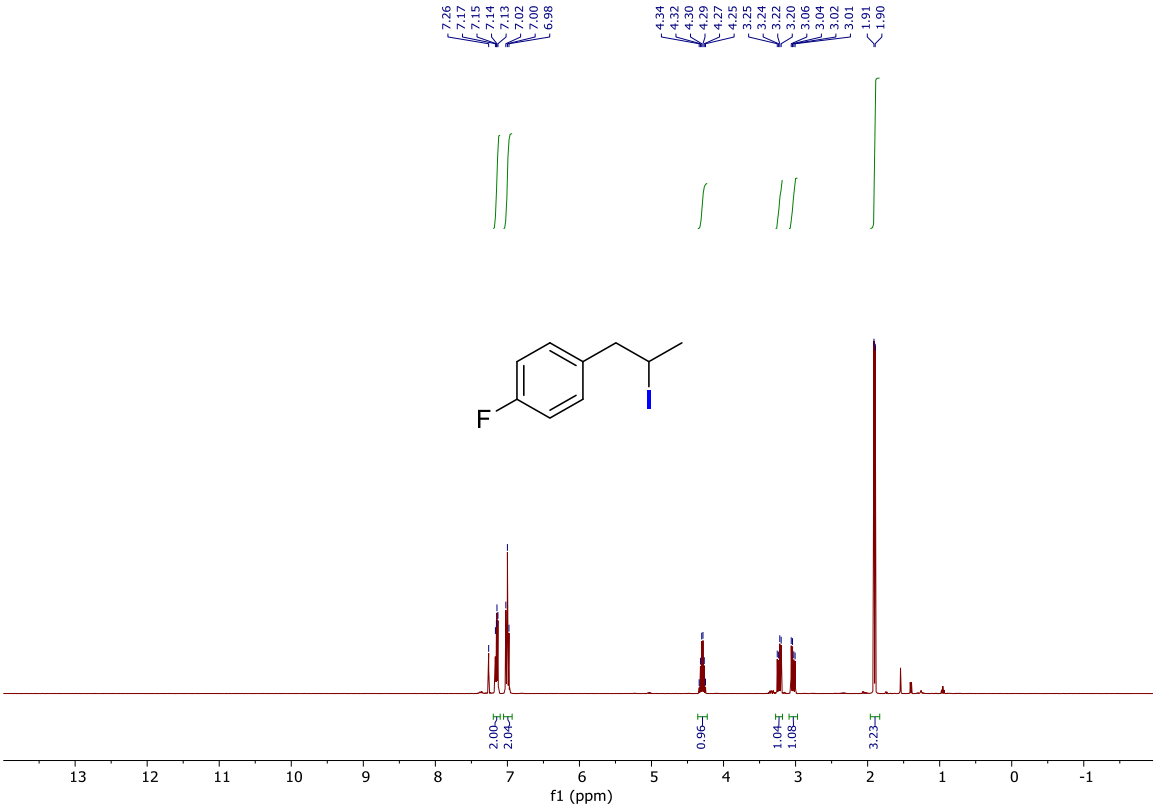

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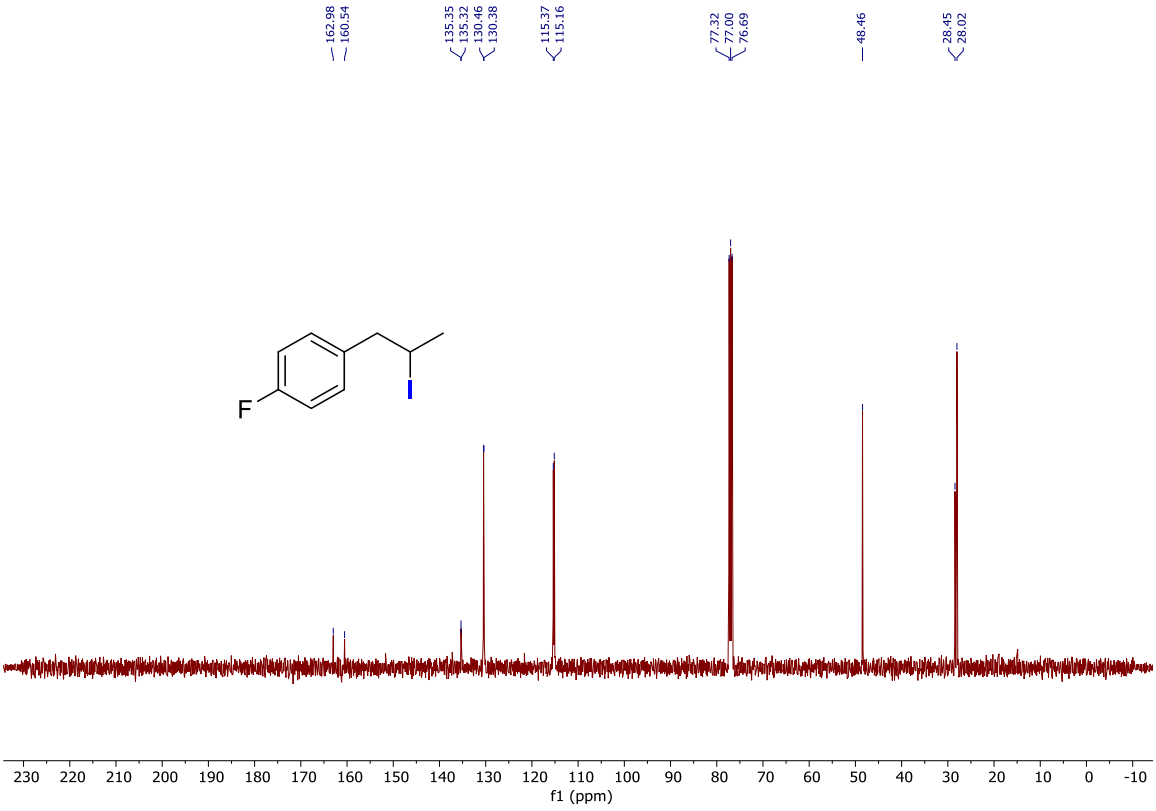

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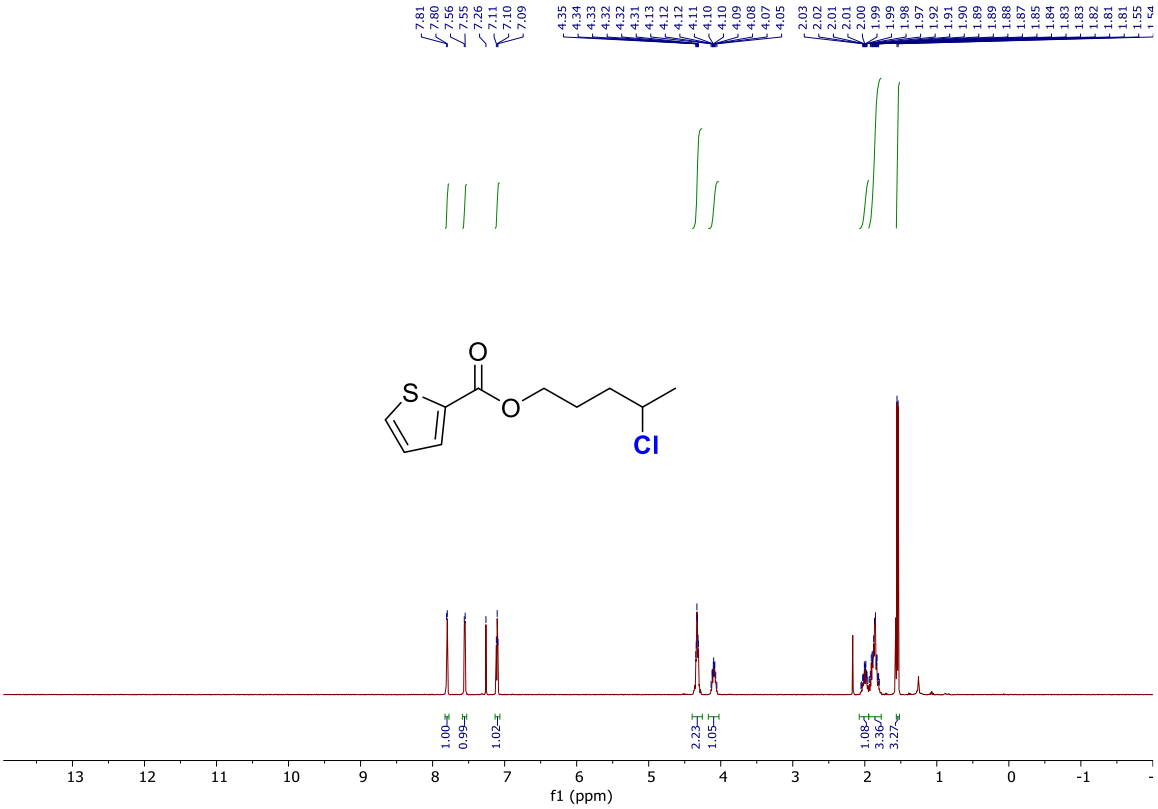

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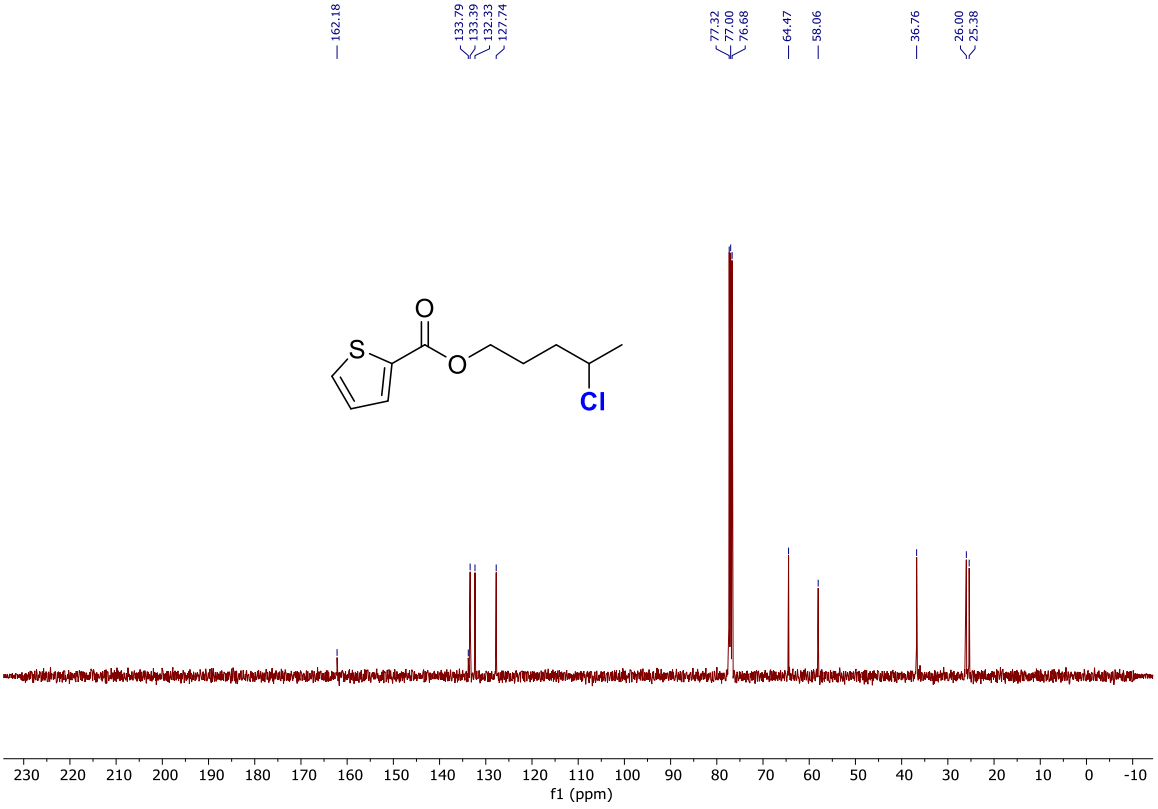

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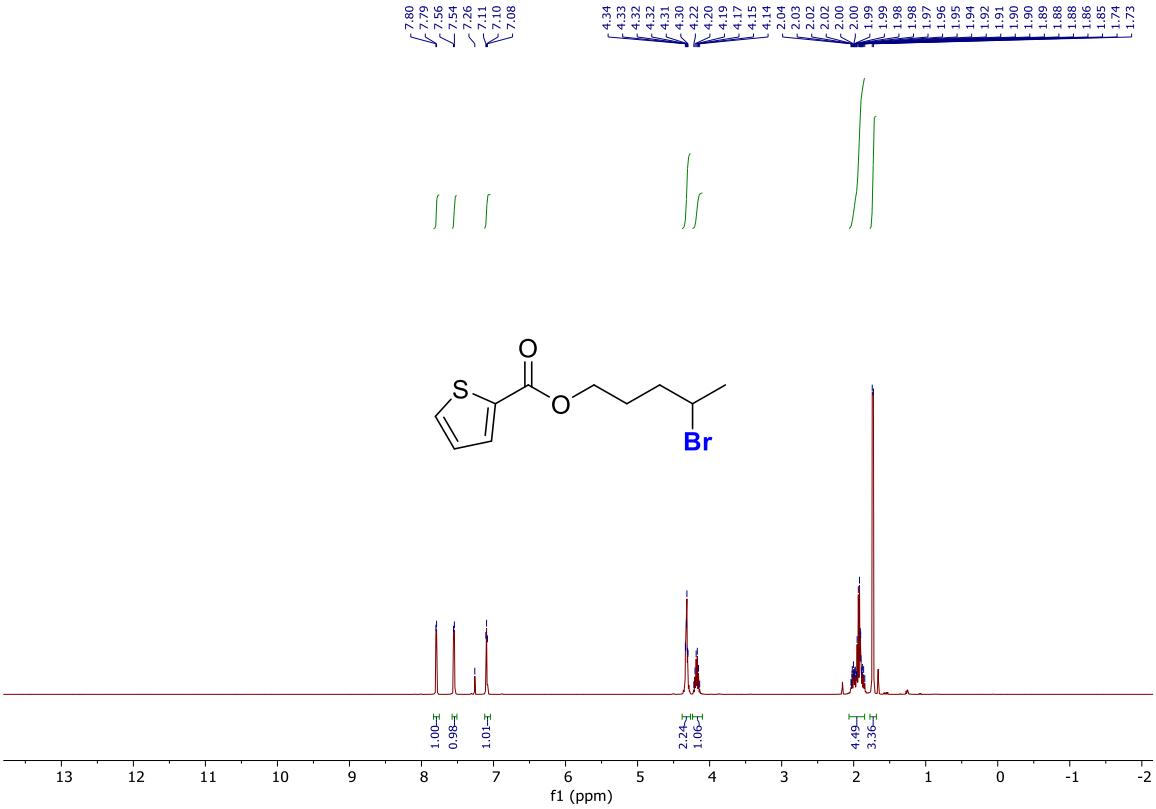

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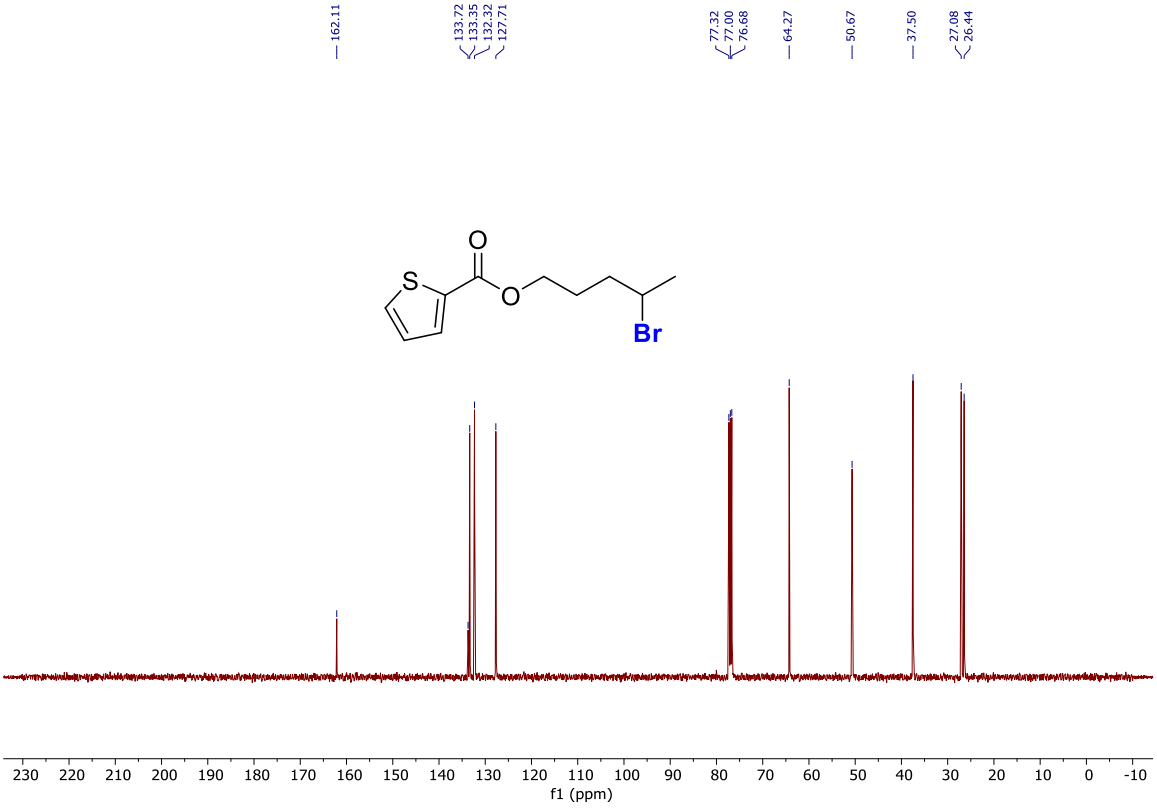

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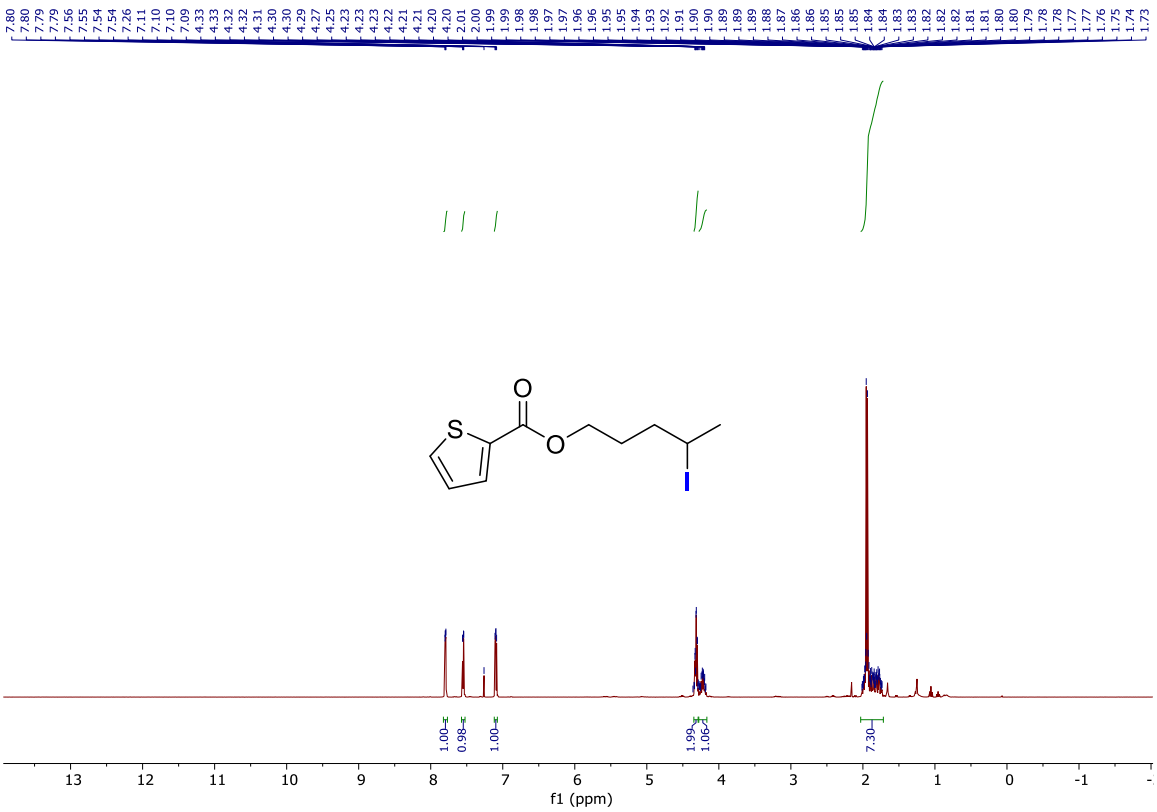

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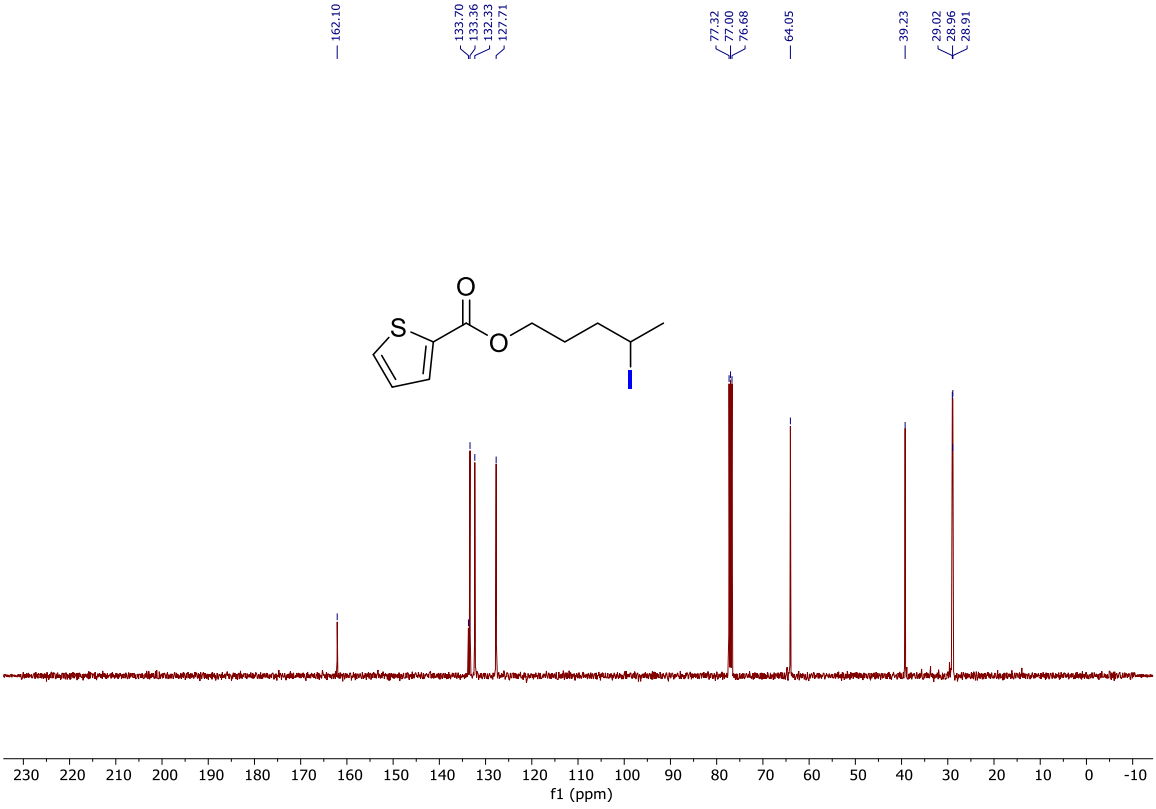

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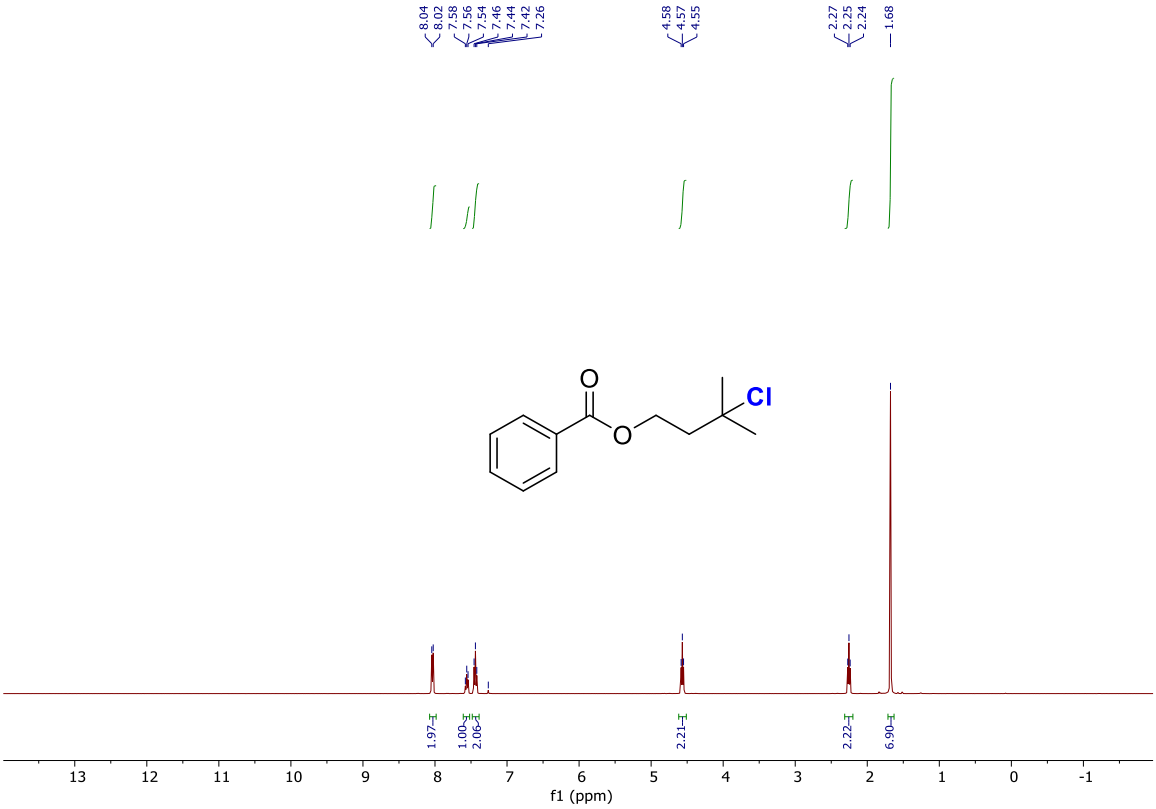

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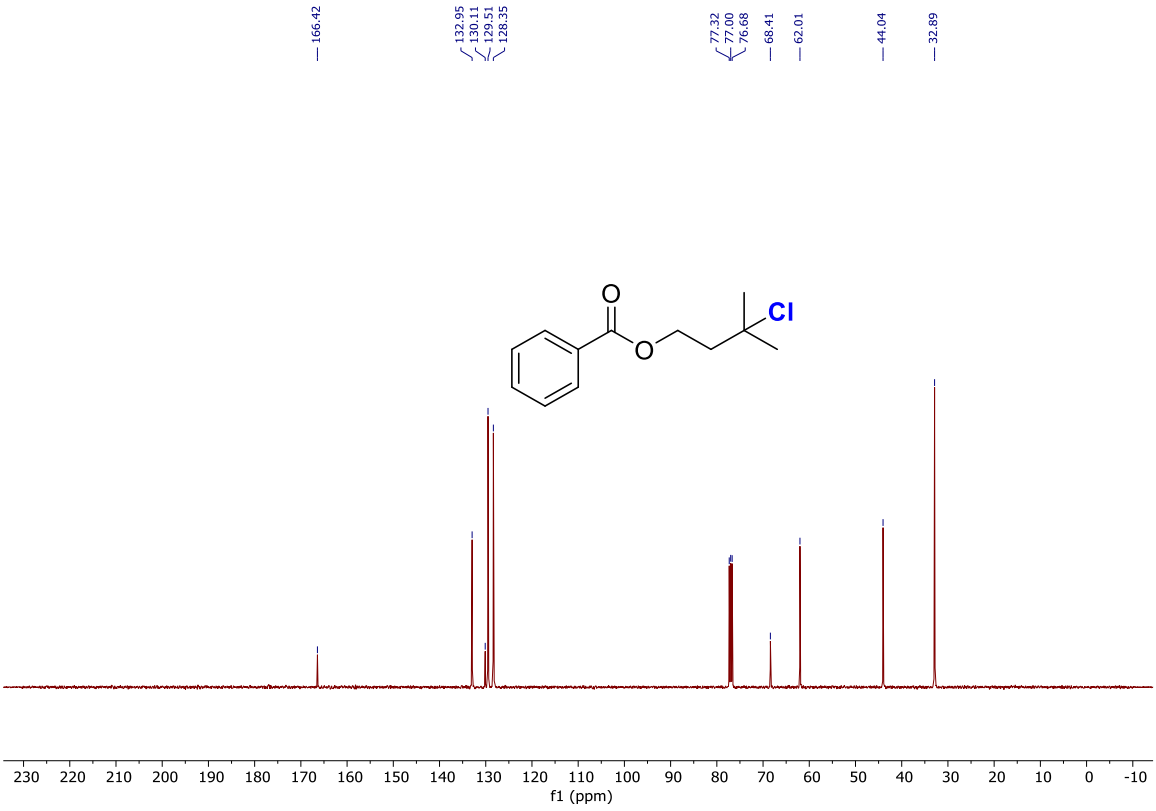

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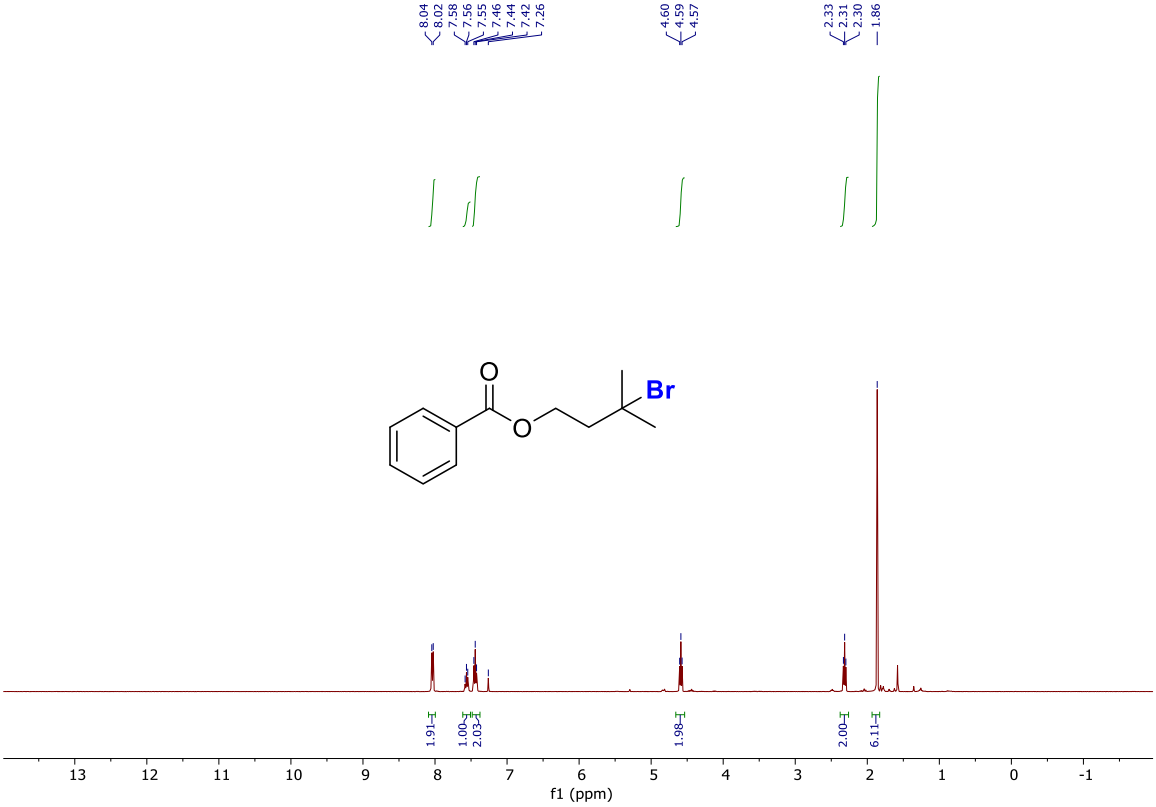

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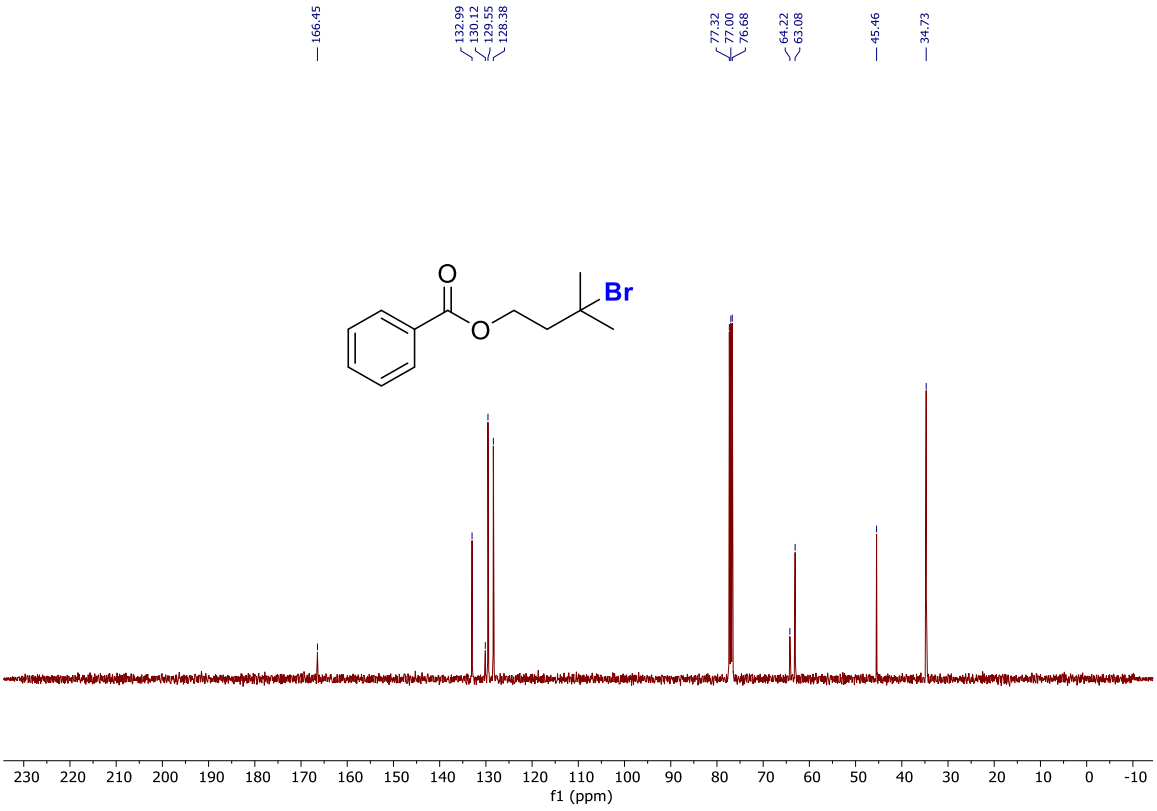

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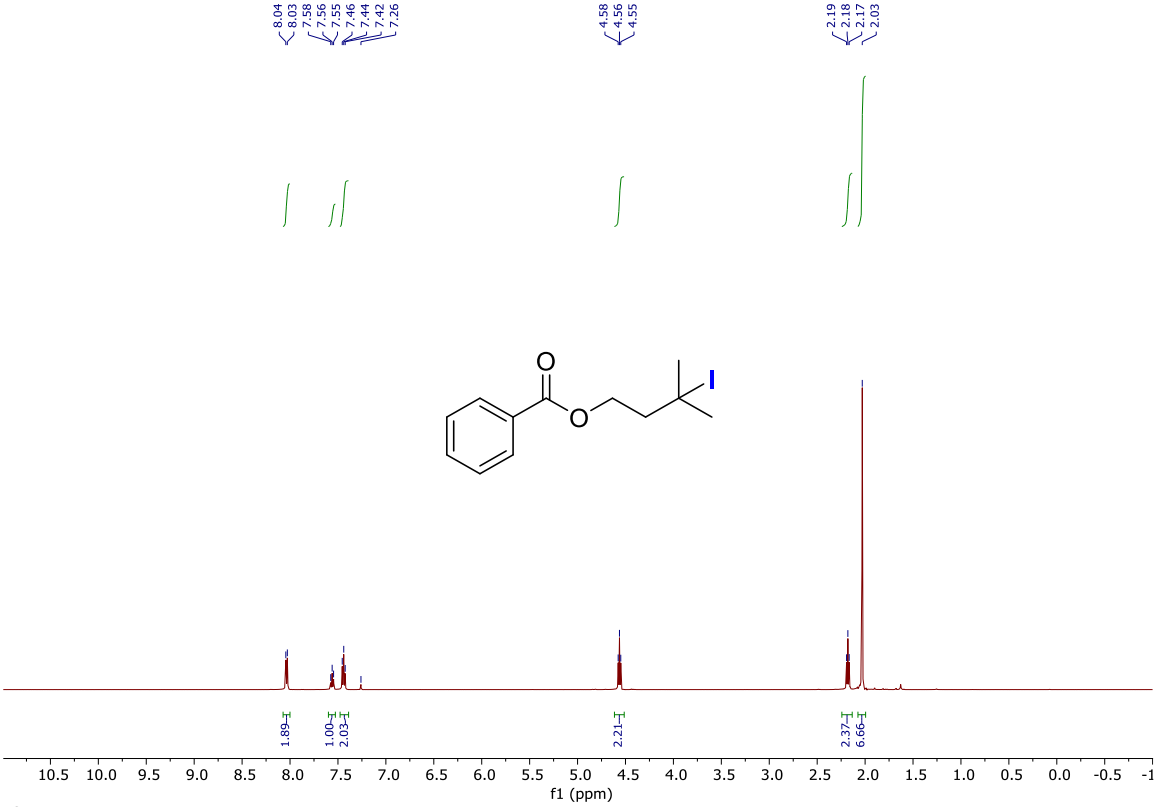

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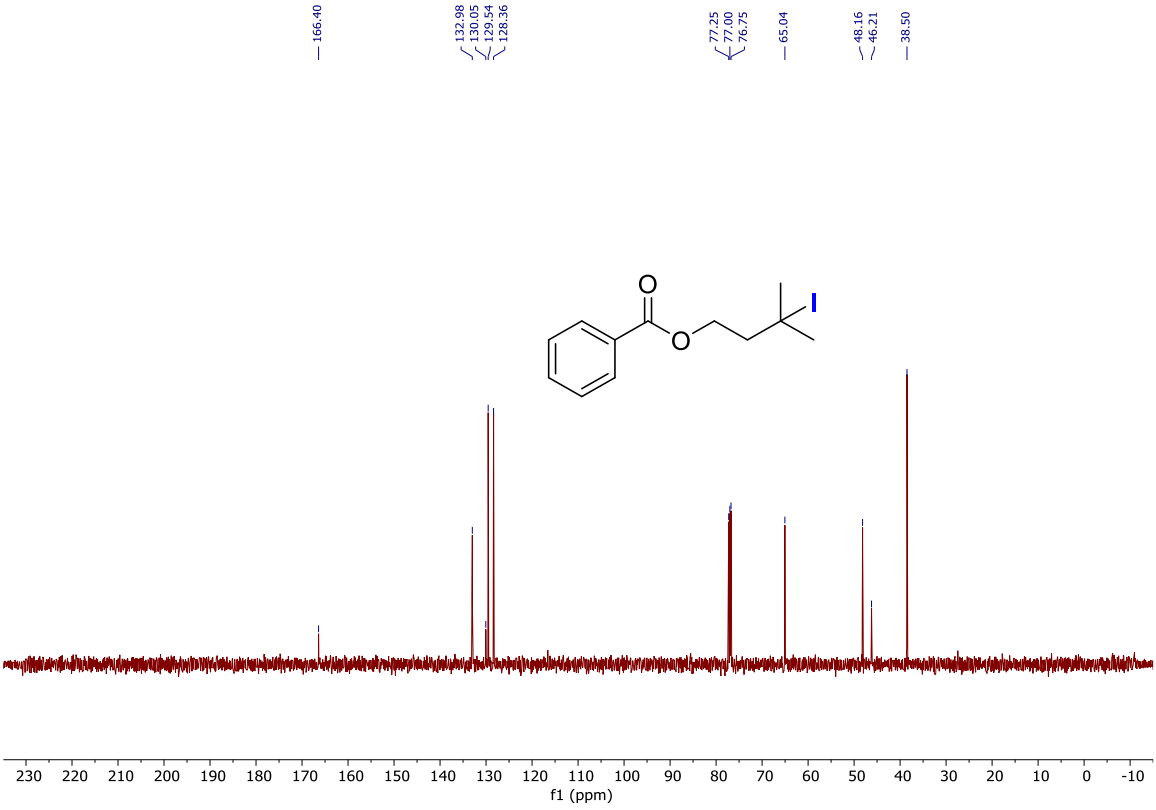

APPENDIX D

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Y. Yang, G. B. Hammond, T. Umemoto, *Angew. Chem. Int. Ed.* **2022**, *61*, e202211688.

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CURRICULUM VITA

Yuhao Yang

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Address: 783 Frederick Stamm Ct, Apt 3, Louisville, Kentucky 40217

EDUCATION

University of Louisville — Louisville, KY, USA
Organic Chemistry — August 2018– Present
Ph.D. — (Expected graduation in April 2023)

Donghua University — Shanghai, China
Applied Chemistry — September 2014– May 2018
BS

PROFESSIONAL EXPERIENCE

University of Louisville, Louisville, KY, USA — August 2018– Present

Graduate Teaching/Research Assistant

- Developed a novel trifluoromethylthiolating (SCF_3) reagent. This reagent, unlike other expensive SCF_3 reagents, was easily prepared from commercially cheap starting materials in one step. It can serve as both electrophilic, nucleophilic, and radical SCF_3 source. It can also be used to prepare many other SCF_3 reagents by virtue of its high reactivity (Ongoing...).

- Designed and synthesized a novel fluorinating agent, *N*-fluoro-*N*-(*tert*-butyl)-*tert*-butanesulfonamide (NFBB), which can fluorinate varieties of organolithium species in unprecedented high yields. NFBB was prepared in excellent yield using NFSI or diluted F_2/N_2 and was easily purified by simple distillation. With NFBB, a conceptually new "self-sustaining" fluorination methodology of active methylene compounds was also developed. The selectively obtained fluorinated compounds have wide applications in the pharmaceutical and agrochemical fields. **NFBB will be commercialized by Tokyo Chemical Industry Co., Ltd. (TCI)**.

- Compiled and published a comprehensive review for the development of *N*-F electrophilic fluorinating agents from a historical perspective.

- Involved in the development of gold catalyzed C-SCF_3/$SeCF_3$ cross-coupling reactions with organohalides.

- Involved in the development of a catalyst-free dihalogenation methodology which is widely applicable with exclusive regio- and stereoselectivity.

- Managed the work of two undergraduate students on a project involving hydrogen bonding assisted hydrohalogenation of alkene using aqueous HX solutions. Lead one master's student on the novel SCF_3 reagent project.

- Three years GTA experience, included CHEM 207/208 (analytical chemistry lab), CHEM 344 (organic chemistry lab), and CHEM 341 (organic chemistry recitation).

Donghua University, Shanghai, China March 2016– March 2018

Undergraduate Research Assistant

- Involved in the development of a robot arm for automated organic synthesis. The robot arm was controlled by the Python code for the automated pickup and dropping of a PTFE pill containing a reactant or catalyst of the organic reaction.

- Involved in the development of a highly efficient chemo-selective electrochemical oxidation of thioethers to sulfoxides and sulfones.

- Involved in the development of an environmentally friendly electrocatalytic protocol for the chlorination and bromination of electron-rich arenes and aromatic boronic acids.

RESEARCH COMMUNICATIONS

Publications

1. **Yang, Y**.; Miraghaee, S.; Pace, R.; Hammond, G. B.; Umemoto, T. One-Step Preparable and Easy-to-handle *S*-Trifluoromethyl Trifluoromethanesulfonothioate: A Highly Reactive, Versatile and Atom-Efficient Trifluoromethylthiolating Reagent Generating CF_3S^+, double CF_3S^-, and $CF_3S^{\bullet}/CF_3^{\bullet}$ Sources. **2023**. (Manuscript in preparation)

2. **Yang, Y.**; Hammond, G. B.; Umemoto, T. Self-Sustaining Fluorination of Active Methylene Compounds and High-Yielding Fluorination of Highly Basic Aryl and Alkenyl Lithium Species with a Sterically Hindered *N*-Fluorosulfonamide Reagent. *Angew. Chem. Int. Ed.* **2022**, *61*, e202211688. **(IF: 16.82)**

3. Mudshinge, S.; **Yang, Y.**; Xu, B.; Hammond, G. B.; Lu, Z. Gold(I/III)-Catalyzed Trifluoromethylthiolation and Trifluoromethylselenolation of Organohalides. *Angew. Chem. Int. Ed*. **2022**, *61*, e202115687. **(IF: 16.82)**

4. Umemoto, T.; **Yang, Y.**; Hammond, G. B. Development of N-F fluorinating agents and their fluorinations: Historical perspective. *Beilstein J. Org. Chem.* **2021**, *17,* 1752–1813. **(IF: 2.88)**

5. Zeng, X.; Liu, S.; **Yang, Y.**; Yang, Y.; Hammond, G. B.; Xu, B. Regio- and Stereoselective Synthesis of 1,2-Dihaloalkenes Using In-Situ-Generated ICl, IBr, BrCl, I_2, and Br_2. *Chem* **2020**, *6*, 1018-1031. **(IF: 25.83)**

6. Liu, S.; Chen, B.; Yang, Y.; **Yang, Y.**; Chen, Q.; Zeng, X.; Xu, B., Electrochemical Oxidations of Thioethers: Modulation of Oxidation Potential Using a Hydrogen Bonding Network. *Electrochem. Commun.* **2019**, *109*, 106583. **(IF: 4.72)**

7. Chen, B.; Yang, Y.; **Yang, Y.**; Liu, S.; Chen, Q.; Zeng, X.; Xu, B., Effects of the Hydrogen Bonding Network on Electrophilic Activation and Electrode Passivation: Electrochemical Chlorination and Bromination of Aromatics. *ChemElectroChem* **2019**, *6*, 3726-3730. **(IF: 4.78)**

Conferences

1. **ACS Meeting (Spring 2023)**
   Indianapolis, IN
   Oral talk: Self-sustaining and highly selective fluorination of carbanions with *N*-fluoro-*N*-(tert-butyl)-tert-butanesulfonamide: new solutions to old problems. Yuhao Yang, Gerald B. Hammond, Teruo Umemoto

2. **National Organic Chemistry Symposium (2022)**
   San Diego, CA
   Poster: Selective Fluorination of Highly Basic Anionic Species: A New Solution to An Old Problem. Yuhao Yang, Gerald B. Hammond, Teruo Umemoto

3. **25th Winter Fluorine Conference (2022)**
   Clearwater Beach, FL
   Poster: Highly Effective Fluorination of (hetero)Aryl and Alkenyl Lithiums with *N*-fluoro-*N*-(*tert*-butyl)-*tert*-butanesulfonamide. Yuhao Yang, Gerald B. Hammond, Teruo Umemoto

4. **36th Herbert C. Brown Symposium (2019)**
   West Lafayette, IN

FELLOWSHIPS AND AWARDS

- Arno Spatola Fellowship, University of Louisville, 2022
- National Organic Symposium Travel Award, American Chemical Society, 2022