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Development and novel applications of halogenating agents.

Sagar Ravso Mudshinge
University of Louisville

DEVELOPMENT AND NOVEL APPLICATIONS OF HALOGENATING AGENTS

By

Sagar Ravso Mudshinge

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by the following Dissertation Committee:

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Dr. Gerald B. Hammond
Dissertation Director

_____

Dr. Michael H. Nantz

_____

Dr. Craig Grapperhaus

_____

Dr. Roland Valdes Jr.

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ABSTRACT

DEVELOPMENT AND NOVEL APPLICATIONS OF HALOGENATING AGENTS

Sagar Mudshinge

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Organic halides are extensively utilized as synthetic intermediates in areas such as pharmaceuticals, agrochemicals, and material polymers. While many halogenating agents have been developed, they continue to have low efficiency or selectivity, are difficult to handle, and often have limited substrate scope. To address this issue, our laboratory has developed novel halogenating agents with improved stability and efficiency. In these studies, we demonstrated a novel application of halogenating reagent, HCl·DMPU, in the nitrile synthesis. We developed a novel method for C−SCF_3/$SeCF_3$ cross-coupling reactions using gold redox catalysis. We developed a novel trifluoromethylating agent in a cost-effective and highly efficient manner. We also attempted the development of dithiadication based electrophilic trifluoromethylating agents.

With the objective of exploring other applications of HCl·DMPU beyond chlorination, we found a novel application of HCl·DMPU in one-pot conversion of aldehydes to nitriles. This method exhibited broad substrate scope with high yields for the aromatic, aliphatic, and α,β-unsaturated aldehydes incorporating various functional groups. We developed a novel application of halogenating agents like $AgSCF_3$ and [(NMe_4)($SeCF_3$)] in combination with commercially available gold catalyst [(MeDalphos)AuCl] for trifluoromethylthiolation (-SCF_3) and trifluoromethylselenolation (-$SeCF_3$) of the diverse array of aromatic, alkenyl and alkynyl halides and obtained the corresponding trifluoromethylthio and trifluoromethylseleno derivatives in good

to excellent yields under mild reaction conditions . This protocol was successfully utilized in late-stage modification of various drug derivatives.

In our quest of developing novel halogenating agents, we invented a newer version of Umemoto reagent II in one-pot synthesis from inexpensive starting material. This reagent is more powerful than Umemoto reagent II. and its applicability in the trifluoromethylation of various nucleophiles was demonstrated. In an attempt to explore the uncharted territory of trifluoromethylation, we designed and attempted to synthesize dithiadication electrophilic trifluoromethylating agents endowed with two transferable trifluoromethyl groups. However, our efforts to date have not produced satisfactory results.

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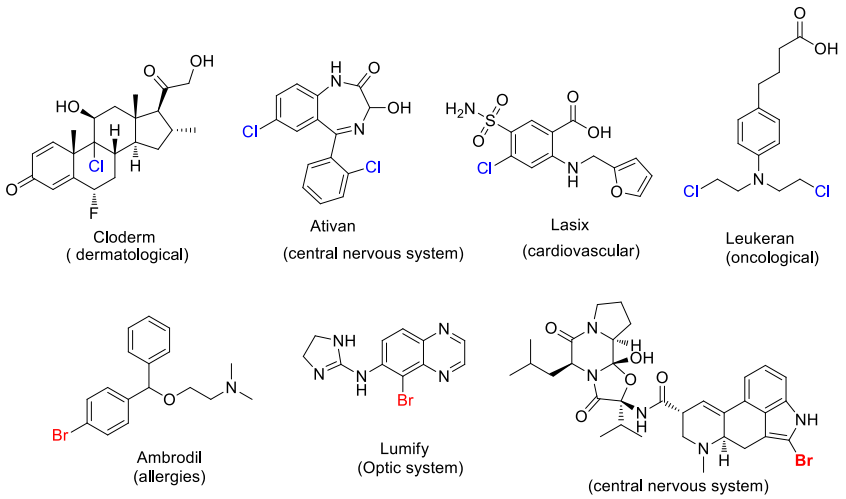
1.0.INTRODUCTION

1.1. Background of halogenation

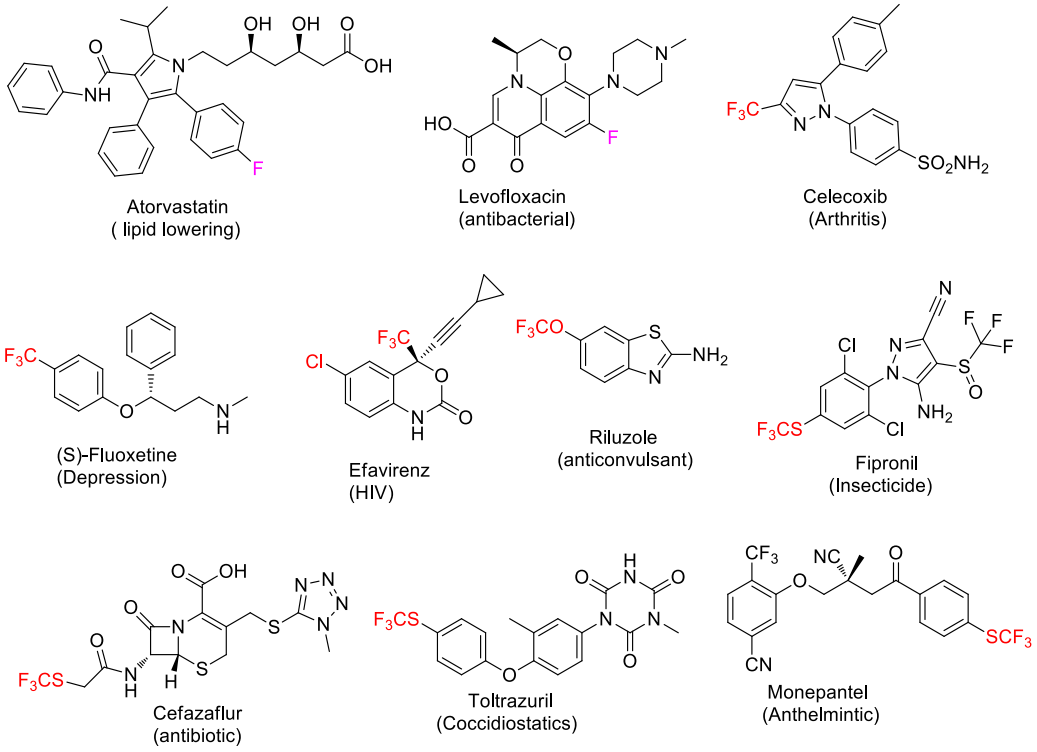
The halogens are elements located at group 17 of the modern periodic table which include non-metals viz. fluorine (F), chlorine (Cl), bromine (Br), and iodine (I). The trifluoromethyl (CF_3) group and some of the chalcogens (Oxygen, Sulfur and Selenium) comprised of CF_3 viz. trifluoromethoxy ($-OCF_3$), trifluoromethylsulfenyl ($-SCF_3$), and trifluoromethylselenoyl ($-SeCF_3$) etc. could be regarded as extended members of the halogen family.[1] Halogens have found enormous applications in all areas of life. For example, chlorinated and brominated compounds play crucial roles in synthetic transformations as these are very good handles to build molecular complexity by means of coupling, radical, and nucleophilic reactions. Moreover, chlorine is widely used in water treatment, synthetic polymers, agrochemicals, and pharmaceuticals,[2] whereas bromine is an essential component of fire-retardants, biocides, drilling fluids and pharmaceuticals.[2]

Figure 1. Examples of chlorine and bromine-containing pharmaceuticals



Fluorine needs special attention because this smallest halogen stands tall among halogens in terms of reactivity. Its highest electronegativity (4.0 in Pauling scale), extremely low polarizability, and strong C–F bond forming ability (averages about 116 kcal/mol),[1] provide fluoro-organic compounds with astounding electronic, physical, and biological properties as compared with its non-fluorinated counterparts. Hence, fluorinated organic compounds have been widely employed in numerous research fields, ranging from polymers, liquid crystals, photovoltaic solar cells,[3-4] diagnostic tools like positron emission tomography (PET),[5-6] magnetic resonance imaging (MRI),[7] and the fluorous reagents used in synthetic processes.[8-9] Since fluorine atom (F) is sterically close but electronically opposite to a hydrogen atom (H), fluorine has emerged as a "magic element" in agro,[10-11] and medicinal chemistry.[12-13] Approximately 30% of all agrochemicals and 20% of all pharmaceuticals on the market contain fluorine. Among the fluorinated compounds, much attention has recently been paid to trifluoromethylated compounds, including trifluoromethyl group containing other chalcogens, as it alters the physicochemical and biological properties of a given drug; for instance, stability, lipophilicity, and membrane permeability of drug candidates can be improved when fluorine is incorporated. In the same context, CF_3S and CF_3Se are of significant interest,[14-16] due to their inherently high Hansch lipophilicity parameters (CF_3S: π_R = 1.44, CF_3Se: π_R = 1.29) vs. (CF_3O: π_R = 1.04, CF_3: π_R = 0.88, F: π_R = 0.14)[17] and strong electron-withdrawing effects (Hammett constants CF_3S: σ_p = 0.50, CF_3Se: σ_p = 0.45) vs. (CF_3O: σ_p = 0.35, CF_3: σ_p = 0.54, F: σ_p = 0.06)[18]. The unique Hansch parameters of CF_3S and CF_3Se provide the medicinal chemist with a convenient tool for adjusting the lipophilicity of bioactive molecules, whereas their electron-withdrawing properties and considerable steric hindrance enhance the metabolic stability of the molecules containing these fluorinated groups.

Figure 2. Examples of fluorine containing pharmaceuticals



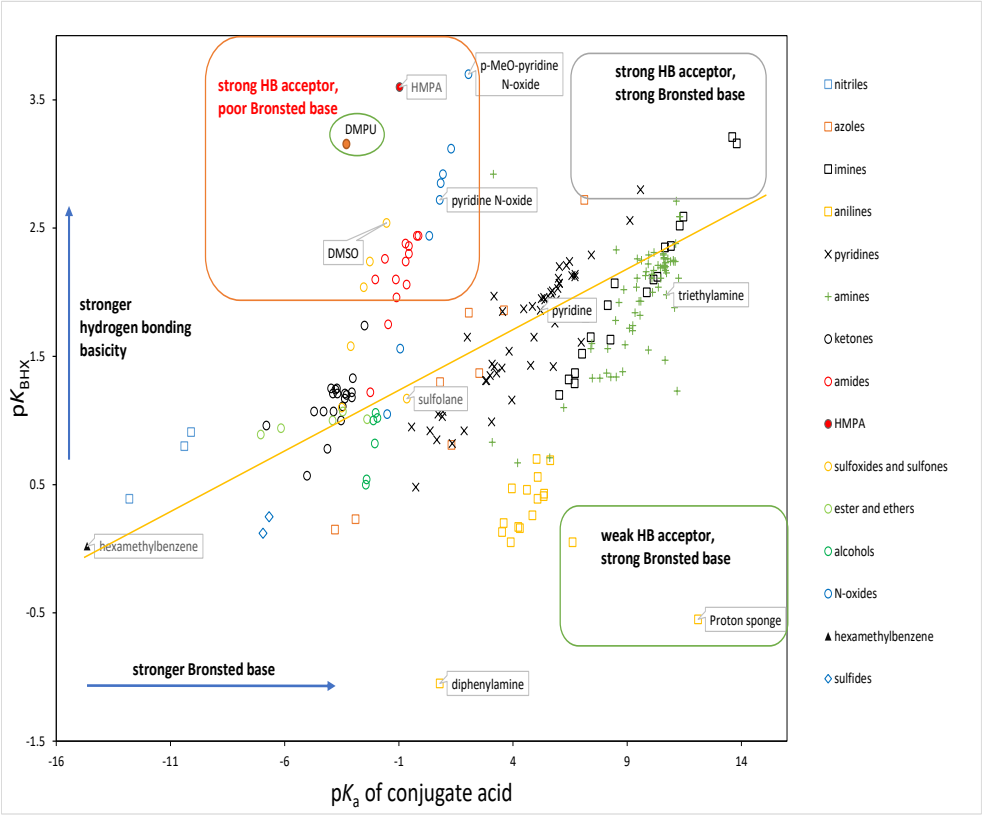
The process of introducing halogens on organic compounds is called halogenation, and considering broad scope of the halogens, the halogenation of organic compounds has become an active research area. Although there are various halogenating agents that have been developed to transfer the halogens by nucleophilic, radical or and electrophilic,[19-20] pathways, poor atom economy and production of stoichiometric amounts of by-products makes them unfitting for large-scale transformations. On the other hand, the use of conventional aqueous acid sources such as HCl, HBr, and HF are still in use due to their easy availabilty and low cost of production. However, hydrogen halides are gases at ambient temperature causing difficulties in their handling. Indeed, aqueous solutions of halide are being used to serve the purpose of hydrohalogenation but this approach is not pragmatic for moisture sensitive reactions.

1.2. DMPU based halogenating agents

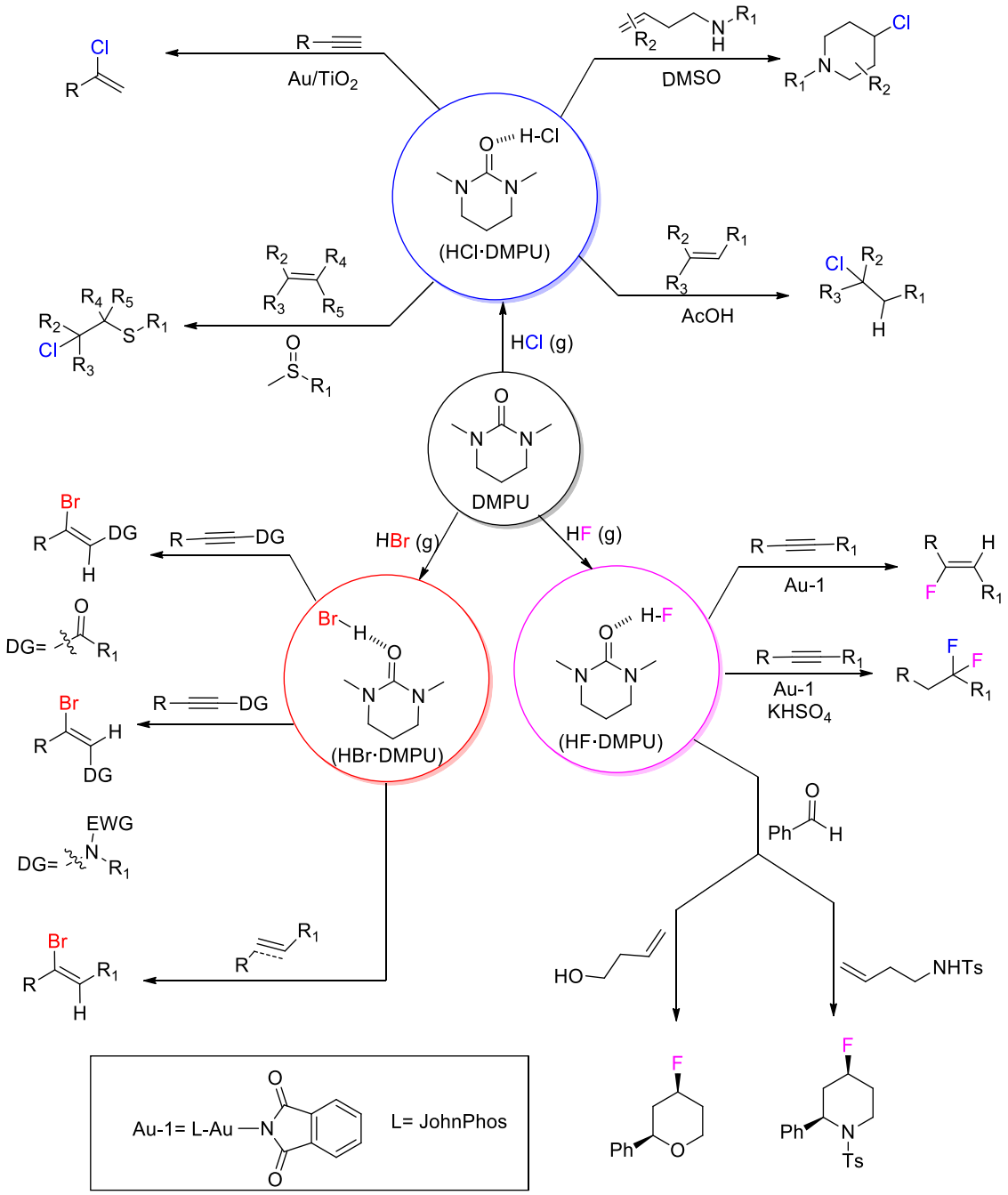
To address the aforementioned issues, various concentrations of organic solutions of HX have been prepared and made commercially available due to their solubilities in organic solvents.[21]

Despite these efforts, the stability and strength (concentration) of such hydrogen halide solutions are still major concerns. Inspired by the Abraham[22-27] and Laurence[28] databases we envisioned utilizing hydrogen bonding between a hydrogen bond acceptor and an HX molecule to obtain more concentrated and bench-stable hydrogen halides. Using their databases, we plotted a trend where a larger pK_{BHX} value indicates higher hydrogen-bond basicity or a better hydrogen bond acceptor characteristic (Figure). Based on this plot, we found that 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) formed a stable complex with HF, HCl and HBr molecules. In addition, DMPU is non-nucleophilic, so it won't compete with halides in nucleophilic reactions. Our newly formulated solutions of HF·DMPU, HCl·DMPU and HBr·DMPU exhibited higher reactivity than its predecessors in a wide scope of transformations ranging from halogenations of alkyne and alkenes to the formation of functionalized pyran and piperidine moieties.[29-34] Considering this wide scope of synthetic utility of HCl·DMPU, we envisioned to exploit it for synthetic transformations other than halogenation and hydrohalogentaion (Scheme 1).

Figure 3. pK_{BHX} and pKa scale



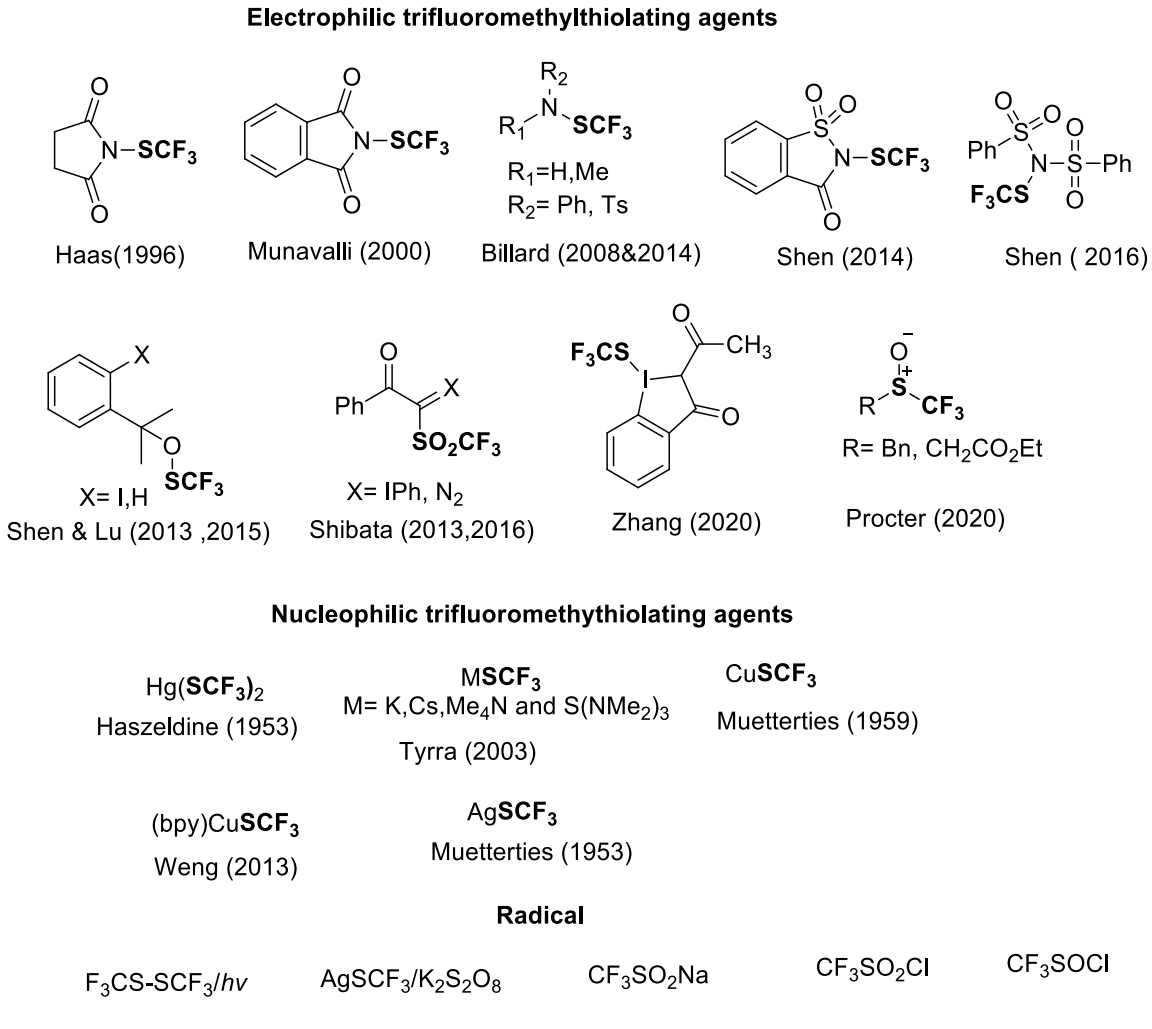
Scheme 1. Applications of DMPU based halogenating agents in halogenation of organic compounds.



1.3. Trifluoromethylthiolation(-SCF_3) of organic compounds

Recent reported efforts have pursued strategies for the synthesis of trifluoromethylthiol-containing compounds. These strategies mainly include electrophilic,[35-36] nucleophilic,[15, 37-39] and radical trifluoromethylthiolation (Figure 4).[40]

Figure 4. Examples of trifluoromethylthiolating agents



1.3.1. Electrophilic trifluoromethylthiolating agents

The development of electrophilic trifluoromethylthiolating reagents having various organic compounds as SCF_3 carrier began with the seminal work of Haas who developed a succinimide skeleton containing SCF_3 reagent.[41] The progress of N-SCF_3 based reagents was continued further with different amide skeletons viz., phthalimide, saccharin and aryl sulfonamide.[42-43] At the same time, O-SCF_3 based reagents were developed Very recently the first hypervalent trifluoromethylthio-iodine(III) reagent was developed by the Zhang group.[36] Another breakthrough in this area was achieved very recently by the Procter group where an interrupted Pummerer reaction was employed to establish trifluoromethyl sulfoxides as novel trifluoromethylthiolating agents.[35] These reagents have been used to achieve trifluoromethylthiolations by electrophilic

Csp^2–H bond functionalization of carbon, nitrogen, oxygen and sulfur nucleophiles.[39] Most of these reagents have some common issues that limit their broad scale applicability. First of all, most of these reagents are synthesized through multiple steps, making them relatively expensive. Additionally, in many of these reagents, the SCF_3 group is carried by large organic compounds that are abandoned during trifluoromethylthiolation, causing significant amounts of waste and poor atom economy. Another serious issue is the requirement of a nucleophilic SCF_3 reagent in a key step of synthesis, making them even more expensive.

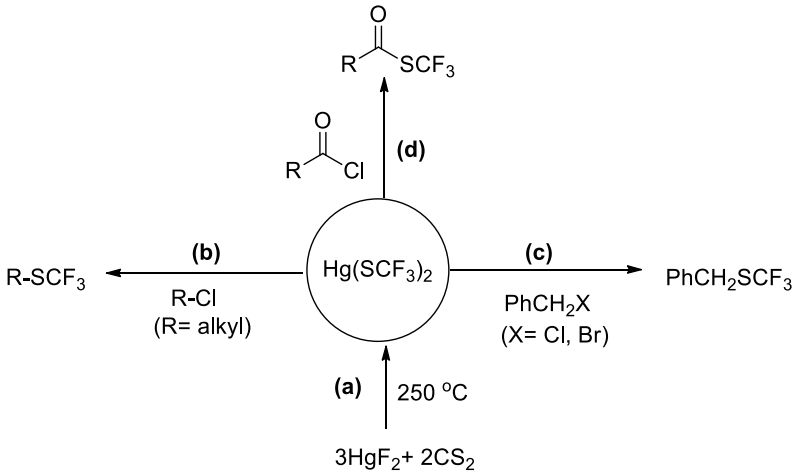
1.3.2. Nucleophilic trifluoromethylthiolating agents

Just like electrophilic SCF_3 reagents, nucleophilic SCF_3 agents have experienced significant improvements in their methods of preparation and their applicability. The following section covers some of the noteworthy examples from this category.

1.3.2.1. Bis(trifluoromethylthio) Mercury $Hg(SCF_3)_2$

$Hg(SCF_3)_2$ was the first nucleophilic trifluoromethylthiolation reagent,[39] prepared by heating carbon disulfide with mercury fluoride at 250°C (Scheme 2a). $Hg(SCF_3)_2$ exhibited good reactivity towards alkyl, benzylic and acyl halides, producing the corresponding trifluoromethyl alkyl sulfides, trifluoromethyl benzyl sulfide, and trifluoromethyl thiol acylate (Scheme 2b-2d). But, due to its corrosive and highly toxic nature, its practical application was discontinued.[37]

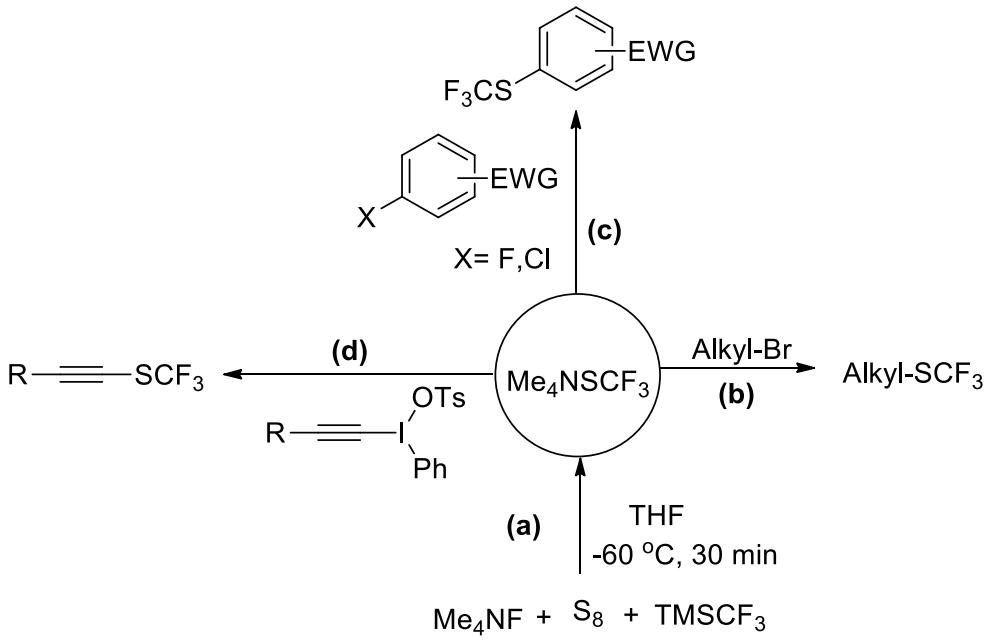
Scheme 2. Synthesis and representative examples of applications of $Hg(SCF_3)_2$



1.3.2.2 $MSCF_3$ (M = K, Cs, Me_4N, and $S(NMe_2)_3$)

These are examples of ionic nucleophilic trifluoromethylthiolating reagents. Several reagents from this class have found limited applications, as they are synthesized from highly toxic starting materials such as $C(S)F_2$ or CF_3SSCF_3 via multistep procedures, [44-48] but, Me_4NSCF_3 is a most sought after reagent from this class due to its convenient one-pot method of the preparation and good nucleophilicity. Yagupolskii et al. devised a one-pot preparation of Me_4NSCF_3 from $TMSCF_3$ (Ruppert-Prakash reagent), elemental sulfur in diglyme or tetrahydrofuran (THF) in the presence of anhydrous Me_4NF (Scheme 3a).[49] Me_4NSCF_3 shows good reactivity towards alkyl bromides (Scheme 3b), electron deficient arenes (Scheme 3c)[49] and alkynyl(phenyl) iodoniums (Scheme 3d)[50]. Despite its good nucleophilicity, the moisture sensitivity of this reagent impedes its application on large scale.

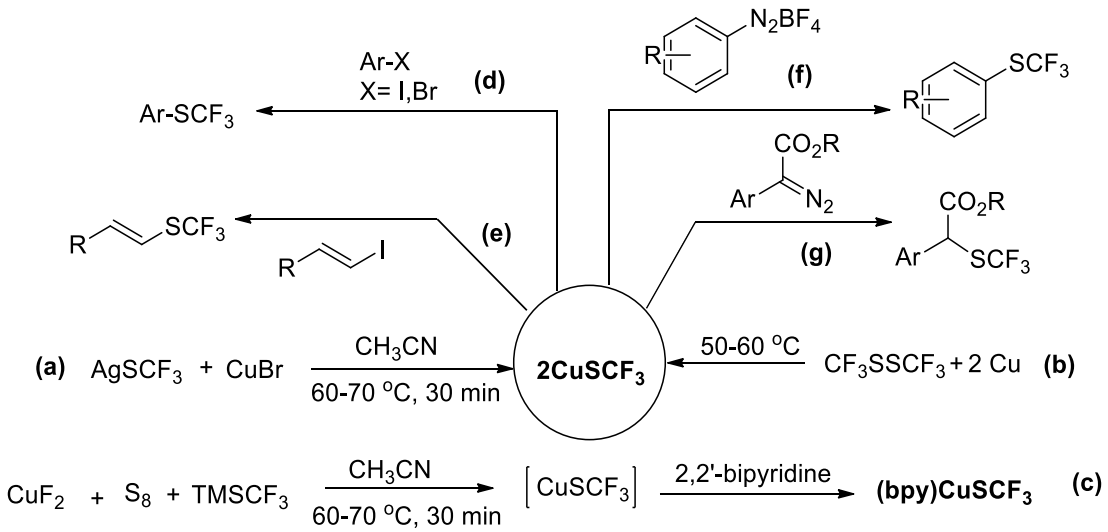
Scheme 3. Representative examples of synthesis and applications of Me_4NSCF_3



1.3.2.3. Copper Trifluoromethylthiolate ($CuSCF_3$) & Trifluoromethylthiolated Copper(I) Complexes

While $HgSCF_3$ and $MSCF_3$ have found limited applications in trifluoromethylthiolations of organic compounds, organometallic reagents like $CuSCF_3$ and trifluoromethylthiolated copper(I) complexes are among the most widely used nucleophilic trifluoromethylating agents. Yagupolskii et al. reported two different methods for the preparation of $CuSCF_3$. The first method utilizes CuBr with $AgSCF_3$ in acetonitrile at 60–70 °C to deliver $CuSCF_3$ quantitatively (Scheme-4a). But the prerequisite synthesis of a trifluoromethylthio derivative of silver is one of the limitations of this method. Other methods involve use of activated copper powder with bis(trifluoromethyl) disulfide in DMF, N-methyl pyrrolidone (NMP), or hexamethylphosphoric triamide (HMPA) (Scheme-4b). However, the use of highly toxic bis(trifluoromethyl) disulfide is a major concern of this synthetic route. The applications of $CuSCF_3$ are depicted below, where it was treated with diverse coupling partners such as heteroaryl halides (Scheme-4d).[51], alkenyl iodides (Scheme-4e),[52] diazonium salts (Scheme-4f),[53] and α-diazo esters (Scheme-4g)[54] to deliver the corresponding trifluoromethylthiolated products. Despite its wider use, $CuSCF_3$ suffers from stability and solubility issues. These issues were addressed recently by Weng et al. by installing a bidentate nitrogen ligand such as 2,2′ -bipyridine (bpy) on a copper metal center of $CuSCF_3$ generating (bpy)$CuSCF_3$ (Scheme-4c).[55] Subsequently other ligands such as bis(diphenylphosphino)ferrocene and triphenyl phosphine were employed by the Vicic group to make ligated $CuSCF_3$ reagents.[56] These stable complexes have excellent reactivity towards various electrophilic partners, such as aryl, alkyl, vinyl, and acyl halides.[55-62]

Scheme 4. Representative examples of synthesis and applications of $CuSCF_3$



1.3.2.4. Silver Trifluoromethylthiolate ($AgSCF_3$):The reagent of choice for transition metal catalyzed trifluoromethylthiolation

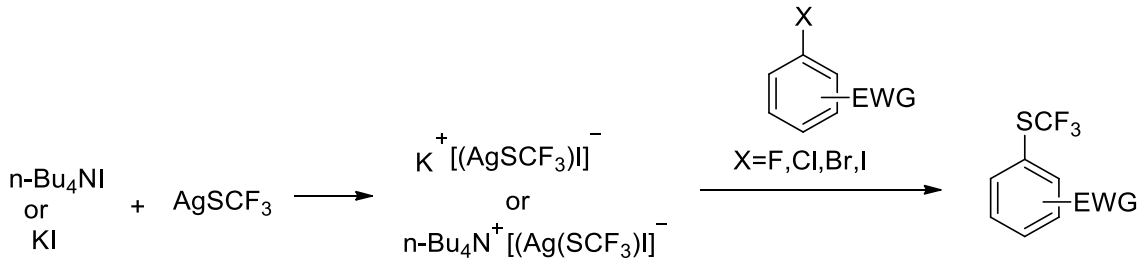
As depicted above, starting from $Hg(SCF_3)_2$, or $MSCF_3$ to ligated $CuSCF_3$ complexes have shortcomings, among them toxicity, longer steps of preparation and poor stability. In this context silver trifluoromethylthiolate ($AgSCF_3$) outperforms other nucleophilic regents. First of all, it involves a very high yielding one-step method of preparation**.** No special purification techniques are required. It has relatively better stability over other reagents, and it is easy to handle. All of these qualities make $AgSCF_3$ an important tool in the chemist's toolbox.

1.3.2.4.1. Activation of $AgSCF_3$

Unlike other SCF_3 reagents, the reaction of $AgSCF_3$ with aryl halides was not reported until 2000. This low reactivity of $AgSCF_3$ is due to the covalent bond nature of the Ag–S bond in $AgSCF_3$. This issue was circumvented by the pioneering work of the Clark group.[63] During their study they found that the addition of KI or n-Bu_4NI to the mixture of $AgSCF_3$ could generate ate-type silver trifluoromethylthiolate species $[Ag(SCF_3)I]^-$, significantly enhancing the reactivity of $AgSCF_3$ toward aryl halides (Scheme 5). Beside the trifluoromethylthiolation of aromatic compounds, this

strategy was successfully utilized in the trifluoromethylation of aliphatic compounds such as alkyl halides [64] (Scheme 6h) and alcohols [65] (Scheme 6g).

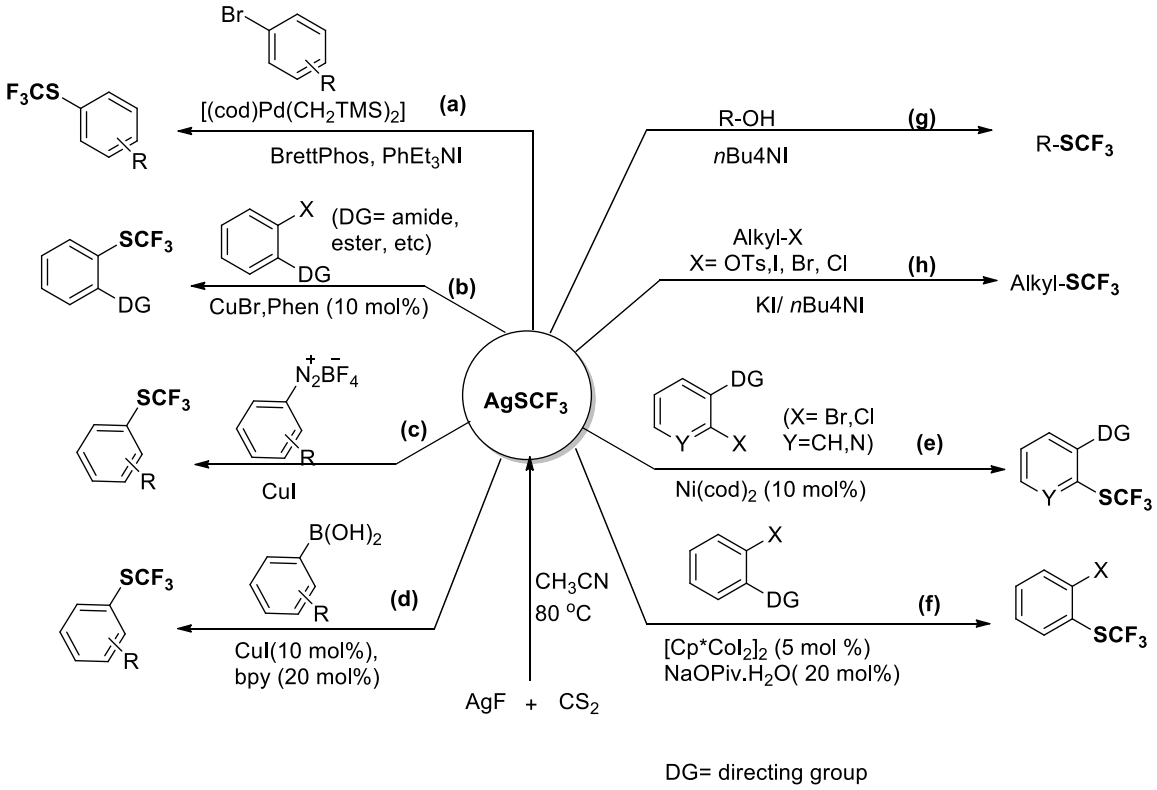
Scheme 5. Representative pathway for the activation of $AgSCF_3$ for aromatic trifluoromethylthiolation



1.3.2.4.2. Emergence of transition metal catalyzed trifluoromethylthiolation using $AgSCF_3$

The report by Clark paved the way for $AgSCF_3$ mediated transition metal catalyzed trifluoromethylthiolation of aromatic halides. A general method of Pd-catalyzed trifluoromethylthiolation of various aryl bromides in the presence of $AgSCF_3$ and $PhEt_3NI$ was reported by Buchwald et al. (scheme 6a).[66] The first Cu-catalyzed trifluoromethylthiolation of aryl bromides and iodides was achieved by the Liu group where various coordinating groups were pre-installed on the aryl halides to achieve this transformation (Scheme 6b).[67] Another finding on copper (I) promoted trifluoromethylthiolation or arenediazonium salts was reported by the Feng group where a stable $AgSCF_3$ was used for the first time (Scheme 6c).[68] A copper-catalyzed direct oxidative trifluoromethylthiolation of aryl boronic acids with $AgSCF_3$ was achieved by the Cao group where $AgSCF_3$ served as both, a source of SCF_3 and an oxidant (Scheme 6d).[69] A mild protocol of ligand or additive-free *ortho*-selective trifluoromethylthiolation of aryl chlorides and bromides was achieved by Love et al. using $Ni(cod)_2$ and $AgSCF_3$ (Scheme 6e).[70] The redox neutral and directing group-assisted trifluoromethylthiolation of arenes was reported recently via cobalt(III)-catalyzed C(sp^2)-H activation and coupling with $AgSCF_3$ (Scheme 6f).[71]

Scheme 6. Representative examples of synthesis and applications of $AgSCF_3$

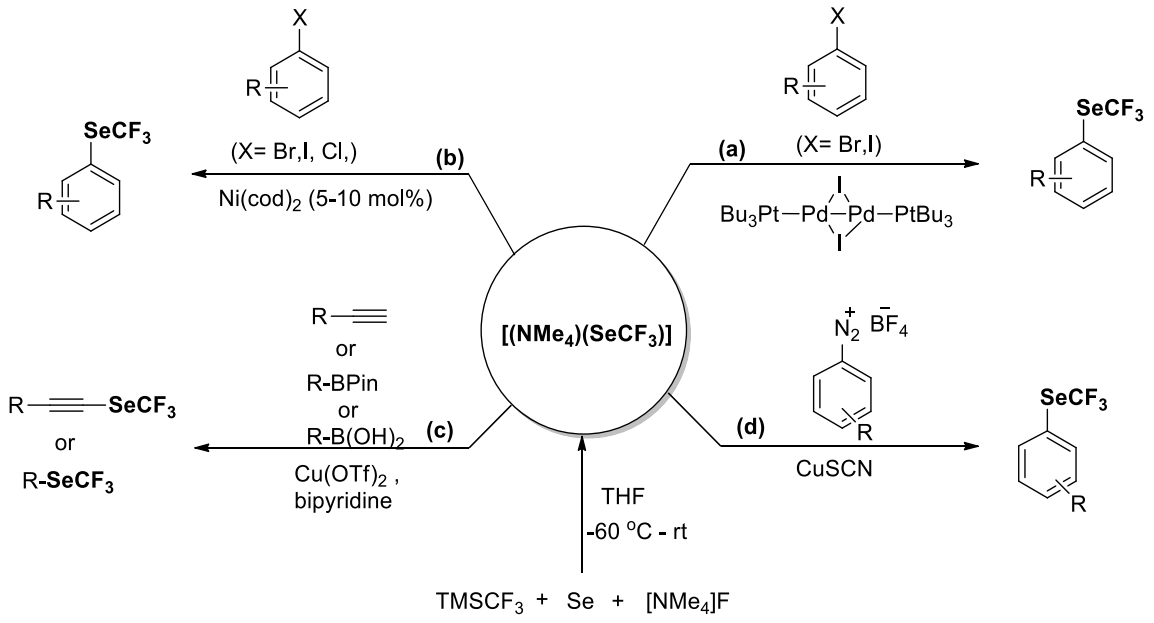


1.4. Trifluoromethylselenolation of organic compounds

As described in an earlier section, the $SeCF_3$ group offers a promising potential in the development of pharmaceuticals due to its high lipophilicity. The $SeCF_3$ moiety could be installed on organic molecules by nucleophilic, electrophilic, or by radical pathways using different reagents but this area is underdeveloped compared to other chalcogens. Nucleophilic reagents have shown promising results in this regard but very few reagents are available, among them $CuSeCF_3$;DMF,[72] $[bpyCuSeCF_3]_2$[73] and tetramethylammonium trifluoromethylselenolate $[(NMe_4)(SeCF_3)]$[49]. Because of its high nucleophilicity and thermal stability $[(NMe_4)(SeCF_3)]$ has found very good applications in transition metal catalyzed trifluoromethylselenolation. The seminal work on catalytic trifluoromethylselenolation of aryl iodides using the bench-stable dinuclear Pd^I complex $[\{(PtBu_3)PdI_2\}]$ and $[(NMe_4)(SeCF_3)]$ was reported by Schoenebeck et al. in 2015 (Scheme 7a).[74] The same group also reported chemoselective nickel-catalyzed trifluoromethylselenolation of aryl iodides for the first time in 2017.[75] An interested finding on Ni

based trifluoromethylselenolation was reported by Zhang et al. using [(NMe_4)($SeCF_3$)] on aryl halides (Scheme 7b).[76] Recently, a useful strategy for the Cu catalyzed trifluoromethylselenolation was achieved by Rueping et al. on alkynes and alkyl boron derivatives where $Cu(OTf)_2$ reagent played the dual role of transition-metal catalyst and an oxidant (scheme 7c).[77] Another application of Cu catalyzed Sandmeyer-type trifluoromethylselenolation of diazonium salts with $(Me_4N)SeCF_3$ was reported by Sandmeyer et al. (Scheme 7d).[78]

Scheme 7. Representative examples of synthesis and applications of [(NMe_4)($SeCF_3$)]

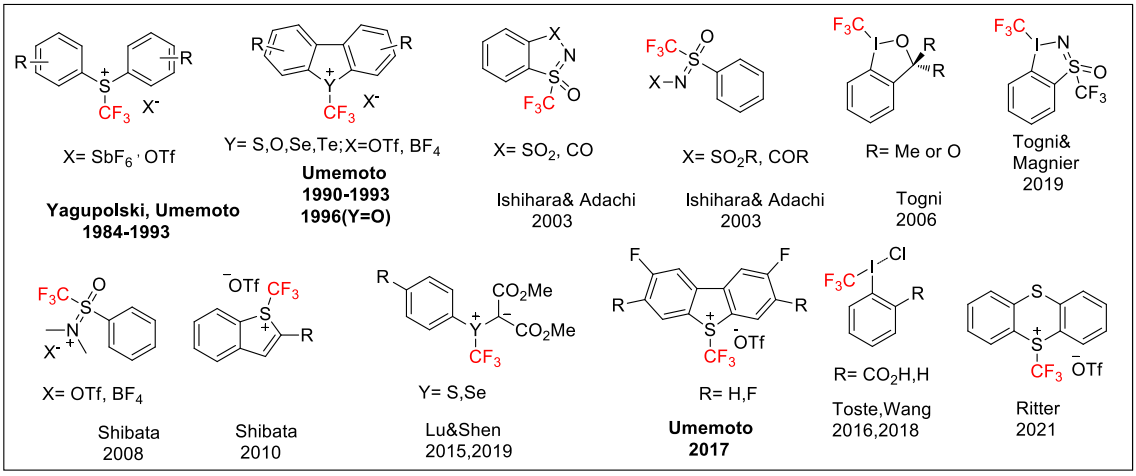


An overlook of trifluoromethylthiolation(-SCF_3) and trifluoromethylselenolation (-$SeCF_3$) of organic compounds by nucleophilic reagents shows the need for developing more effective and widely applicable pathways for these transformations. Considering the effectiveness of $AgSCF_3$ and [(NMe_4)($SeCF_3$)] over the other reagents, combining these reagents with appropriate transition metals can open new avenues in installing SCF_3 and $SeCF_3$ on organic compounds.

1.5. Trifluoromethylation(-CF_3) of organic compounds

Trifluoromethylating reagents are classified as radical, nucleophilic, or electrophilic, based on the character of CF_3 group While nucleophilic CF_3 reagents have seen enormous progress over time, the development of electrophilic CF_3 reagents has lingered behind because the generation of the trifluoromethyl cation (CF_3^+) is difficult due to the very electronegative fluorine atoms. In the quest for taming the trifluoromethyl cation (CF_3^+), many electrophilic trifluoromethylating agents have been reported to date. (Figure 5).

Figure 5. Electrophilic trifluoromethylating agents

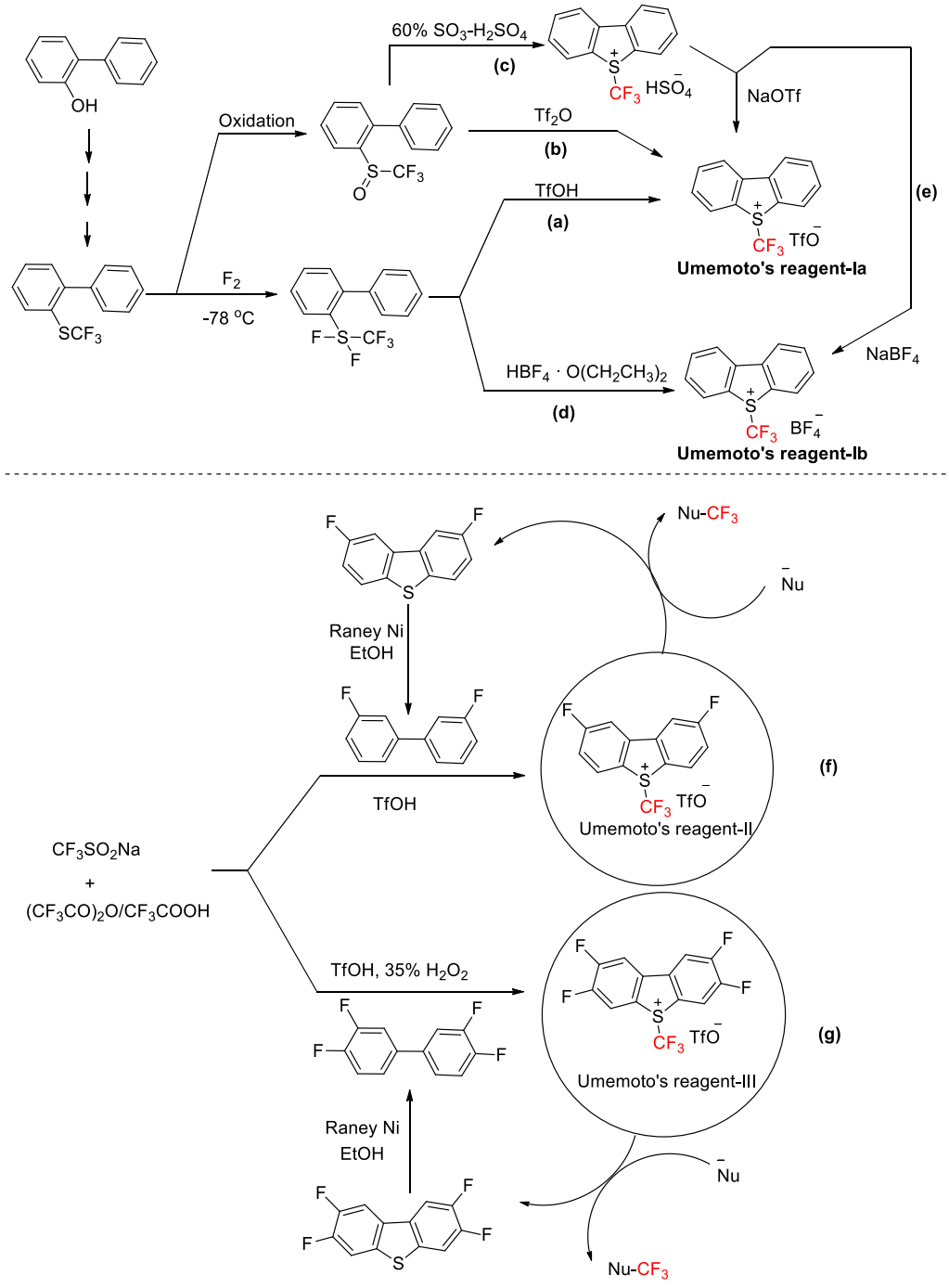


The development of these reagents started with reports of novel reagents by Yagupolski and Umemoto from 1984-1993[72, 79] and in 1996[80-81]. In the following years, the design, and synthesis of electrophilic trifluoromethylation reagents have been extensively developed. Shibata developed *S*-(trifluoromethyl)sulfoximinium and *S*-(trifluoromethyl)benzothiophenium salts.[82-83] However these reagents suffer from low reactivity. Reagents based on hypervalent iodine were developed by Togni,[84] Magnier,[85] and Toste[85-86] but instability associated with them makes them unsuitable for industrial applications.[19] Excluding oxygen, all other chalcogen-containing CF_3 reagents developed by Umemoto show exceptional thermal stability and high oxidation potential, making them an ideal reagent in trifluoromethylation reactions. [85, 87-89]

1.5.1. Synthesis of Umemoto reagents

The synthesis of these reagents is described below (scheme 8). The synthetic pathways clearly show the evolution in the synthetic strategy of these reagents. The synthesis of Umemoto reagents Ia[79] and Ib[79] involve multiple steps of preparation or harsh reaction conditions, reaction with fluorine gas (Scheme 8a-8e).[79, 90] Newer reagents like Umemoto reagents **II** and **III** have addressed most of the issues associated with Umemoto reagents **Ia** and **Ib** and offer several advantages. The first advantage is that it involves a one-pot method of preparation. The second advantage is the recyclability of byproducts from these reagents; for example, difluorinated or tetra fluorinated dibenzothiophene, after reacting with nucleophiles, regenerate 2,8-difluoro and 2,3,7,8-tetrafluoro biphenyls by a simple process of desulfurization in the presence of Raney Nickel. Lastly, the most important advantage of these reagents over Umemoto reagents **Ia** and **Ib** is their higher trifluoromethylation power. The reduction in synthetic steps and higher yield have given these reagents (II and III) an edge over its predecessors in terms of cost and industrial scale production .[79, 91-92]

Scheme 8. Synthesis of Umemoto reagents



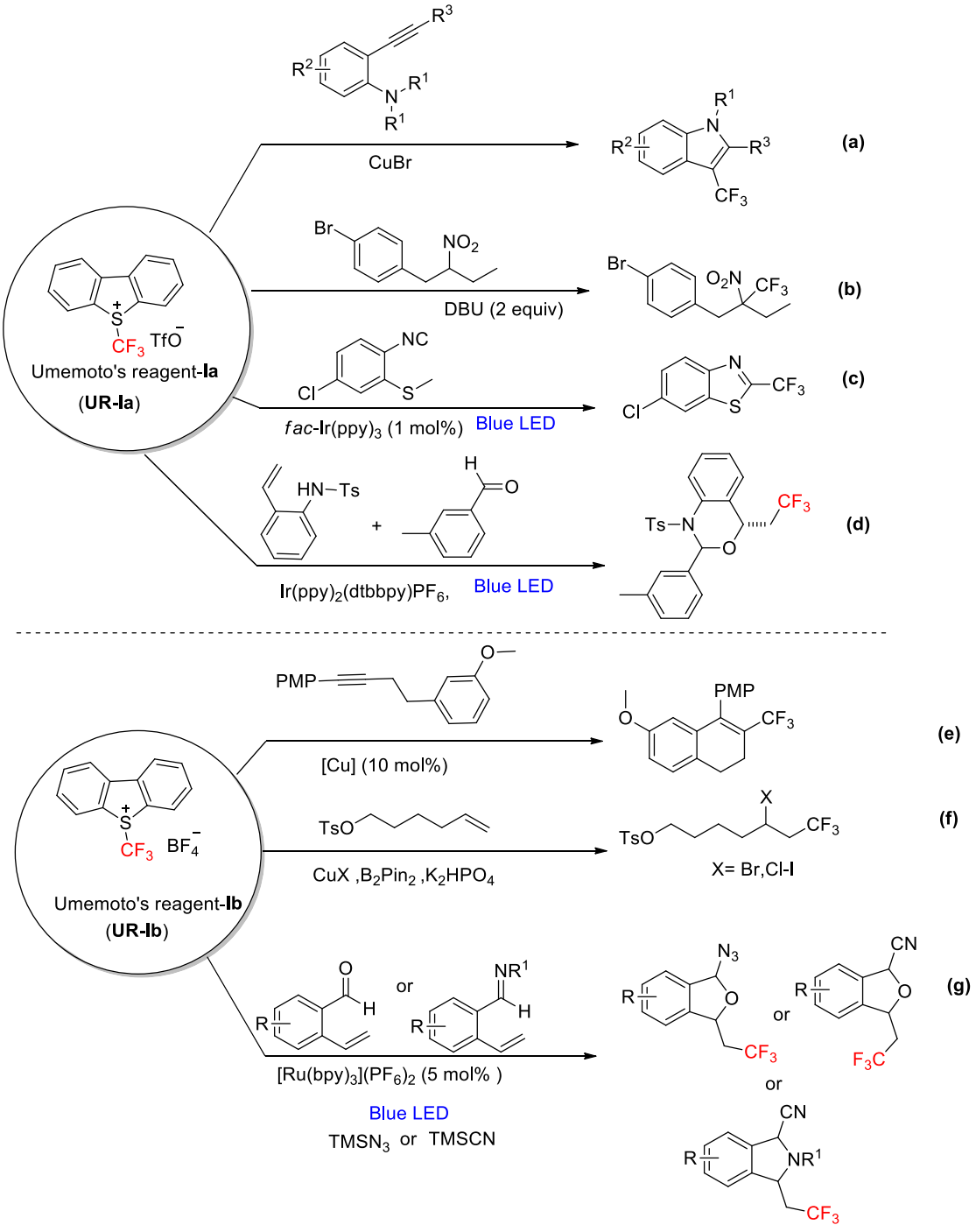
1.5.2. Applications of Umemoto reagents:

Umemoto reagents have been featured prominently in numerous reports. Recent selected applications are depicted below. A wide range of copper assisted trifluoromethylation using

Umemoto reagents **Ia** and **Ib** have been reported. Various 3-trifluoromethyl-indoles were obtained in excellent yield by treating 2-alkynylanilines with Umemoto reagent **Ia** in the presence of stoichiometric amount of CuBr (Scheme 9a).[93] Another excellent application of copper catalyzed trifluoromethylation using Umemoto reagent **Ib** was reported by Fu et al.; this involves the difunctionalization based endo-type trifluoromethylarylation of alkynes producing CF_3-containing cyclic tetra-substituted alkenes (Scheme 9e).[94] The copper catalyzed strategy was also applied to alkene substrates .Synthesis of a wide range of β-halotrifluoromethylated alkanes by copper(I) halide (CuX, X = Cl, Br, and I) mediated halotrifluoromethylation of unactivated alkenes in the presence of Umemoto reagent **Ib** was achieved by Jung and Han et al. (Scheme 9f).[95] Interestingly, due to their high electrophilicity, Umemoto reagents can form EDA (electron donor-acceptor) complex with electron donor species. This approach was executed by the Watson group for synthesizing complex quaternary α-(trifluoromethyl)nitroalkanes in a highly diastereoselective manner utilizing Umemoto reagent **Ia** and DBU (Scheme 9b).[96]

Umemoto reagents are among the most preferred reagents when it comes to the photoredox catalyzed trifluoromethylation strategy. Representative recent applications are depicted below. Umemoto reagent **Ia** was also used very effectively in the synthesis of trifluoromethylated benzothiazoles by subjecting 2-isocyanoaryl thioethers to visible-light-induced radical cascade cyclization (Scheme 9c).[97] In 2019, the Rao and Chen group developed a photo-assisted generation of trifluoromethylated aza-ortho-quinone methides, which after reacting with aldehydes via a hetero-Diels−Alder reaction delivered trifluoromethylated dihydrobenzoxazines under mild conditions in excellent diastereoselective manner (Scheme 9g).[98] The visible-light photoredox promoted trifluoromethylation in multi-component reactions, applied by Masson and coworkers, involved an Umemoto reagent **Ib** assisted three-component tandem process for the synthesis of CF_3-containing phthalans and isoindolines from readily accessible starting materials aldehydes and imines, including chiral ones (Scheme 9g).[99]

Scheme 9- Representative applications of Umemoto reagents Ia and Ib

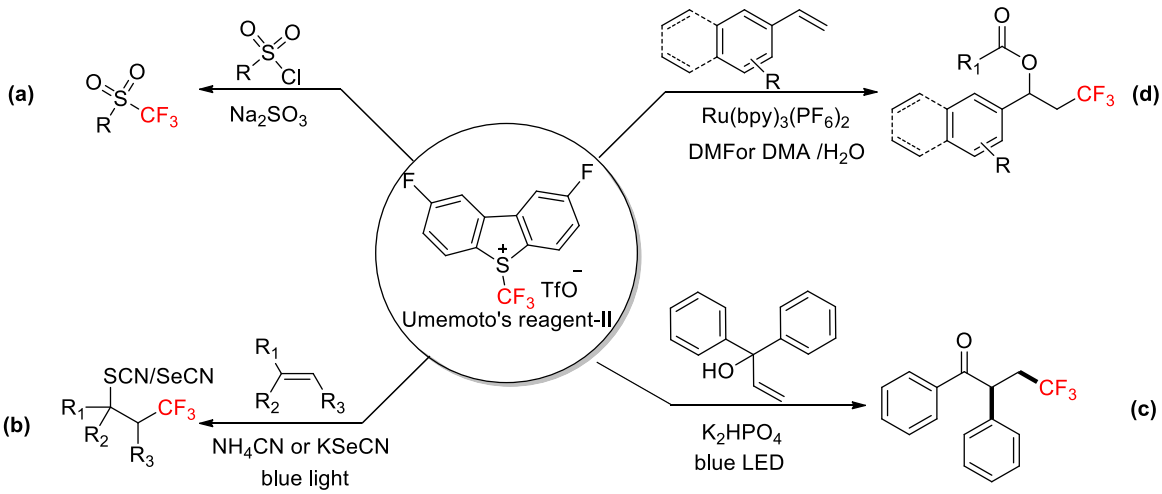


The Umemoto reagent II has also found applications in some important transformations. Recently, this reagent was used in the preparation of trifluoromethyl sulfones from commercially available arylsulfonyl chlorides (Scheme 10a).[100] Umemoto reagent II was recently used in a

photocatalyst and additive-free green protocol for the intermolecular trifluoromethyl-thio(seleno)cyanation of alkenes promoted by visible light (Scheme 10b).[101] Yu et al. demonstrated recently the effectiveness and utility of Umemoto reagent II over its predecessors in the chemoselective synthesis of trifluoromethylated ketones by radical trifluoromethylation-triggered aryl migration of hydroxy alkenes (Scheme 10c).[102] Just like its predecessors, Umemoto reagent II was used in photo-redox catalysis due to its high electrophilicity and oxidation potential. She et al. utilized this reagent in visible-light-induced multi-component acyloxy-trifluoromethylation of arylalkenes using $Ru(bpy)_3(PF_6)_2$ as the photoredox catalyst (Scheme 10d).[103]

Regardless of the superiority of Umemoto reagents over other electrophilic reagents, the limited commercial availability and high purchasing cost is impeding the wider use of these reagents. In this regard, the development of inexpensive and powerful CF_3 reagent can boost the progress of electrophilic trifluoromethylation transformations.

Scheme 10. Representative applications of Umemoto reagent II



1.6. Research aims

1.6.1. Aim 1 HCl·DMPU-assisted one-pot and metal-free conversion of aldehydes to nitriles

We considered expanding the utility of HCl•DMPU beyond halogenation and hydrohalogenation reactions.[29, 31-34] Considering the importance of nitriles in pharmaceuticals and agrochemicals, we aimed to develop a novel, one pot approach of the nitrile synthesis using commercially available aldehydes. HCl•DMPU played a dual role of an oxime activator, protonating the oxime intermediate and also as a non-nucleophilic base to abstract the proton from the protonated oxime intermediate, eventually leading to nitrile formation. Milder reaction conditions make this protocol an environmentally benign alternative for nitrile synthesis. The reaction scope, functional group tolerance and scalability was also investigated.

1.6.2. Aim 2: $AgSCF_3$ and $[(NMe_4)(SeCF_3)]$ mediated trifluoromethylthiolation ($-SCF_3$) and trifluoromethylselenolation ($-SeCF_3$) of organohalides using gold(I/III) catalysis

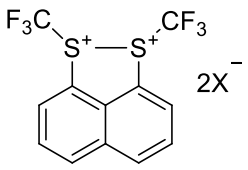
We sought to exploit the stability and reactivity of $AgSCF_3$ and $[(NMe_4)(SeCF_3)]$ respectively in trifluoromethylthiolation and trifluoromethylselenolation of organic halides using bench stable gold catalyst [(MeDalphos)AuCl]. All previous reports on transition metal catalyzed trifluromethylthiolation and trifluoromethylselenolation suffered from harsh reaction conditions (high temperature, air- or moisture- sensitivity), limited substrate scope, or high catalyst loading. We solved these issues by developing a 'one-stop shop' synthesis of a diverse array of $C-SCF_3/SeCF_3$ cross-coupled products. This approach was evaluated for mechanistic details, scalability, functional group tolerance and late-stage modifications on pharmaceutically valuable intermediates.

1.6.3. Aim 3: Development and applications of the novel trifluoromethylating (-CF_3)reagent:S-(trifluoromethyl)-2,8bis(trifluoromethoxy) dibenzothiophenium triflate

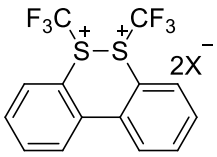
We aimed to develop a bench-stable and more powerful trifluoromethylating agent and achieved it by developing a dibenzothiophene-based novel trifluoromethylating reagent. It is structurally similar to Umemoto reagent II but exhibits higher reactivity. The broad reactivity of this reagent was tested towards various nucleophiles. The use of inexpensive starting materials and a one-pot operation make this reagent a suitable candidate for practical trifluoromethylation reactions.

1.6.4. Aim 4: Attempt to develop a new type of dithiadications-type trifluoromethylating agents

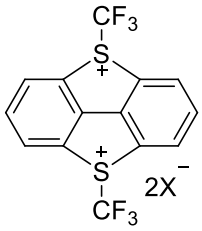
We designed dithiadication-type electrophilic trifluoromethylating agents aiming more powerful and high CF_3-content reagents as shown below. However, our efforts to date have not produced satisfactory results.



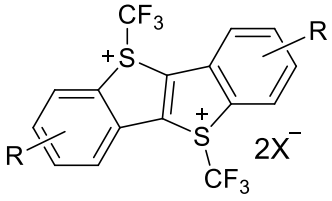
I



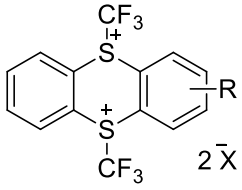
II-A



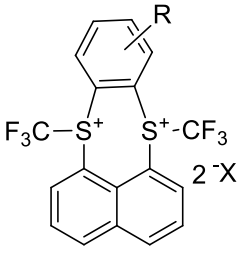
II-B



III



IV



V

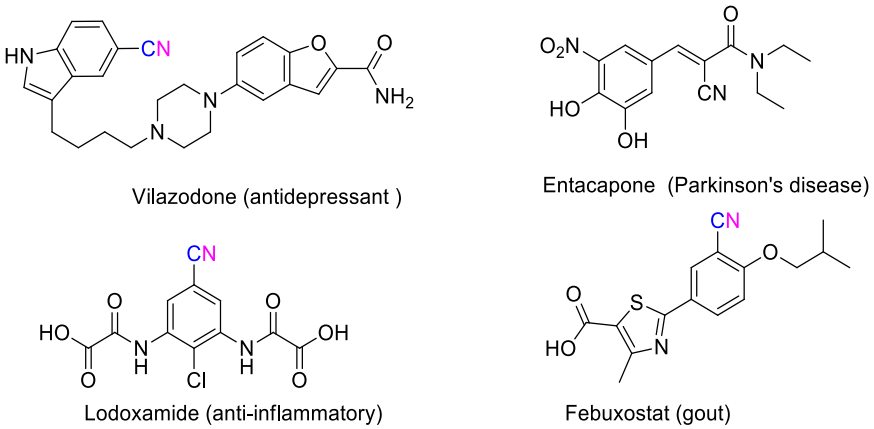
2.0. HCl•DMPU ASSISTED ONE-POT AND METAL-FREE CONVERSION OF ALDEHYDES TO NITRILES[1]

2.1. Background

As mentioned in chapter 1, we followed our objective of finding novel applications of HCl•DMPU, beyond halogenation and successfully developed HCl•DMPU assisted one-pot conversion of aldehydes to nitriles using sustainable chemistry methods. Sustainable chemistry methods involving efforts to reduce the toxicity and harsh reaction conditions of chemical reactions are becoming increasingly more popular. In this context, the ideal strategy for sustainable chemistry would be an oxidant and metal-free synthesis. For the synthetic chemist, nitriles are valuable synthetic lynchpins from which a variety of functional groups like amides, carboxylic acids, ketones, amines, and esters can derived[104]. Moreover, the nitrile group is one of the most significant functionalities found in natural products, biologically relevant compounds, agrochemicals, dyes, and material science.[105-108] Many nitrile-containing pharmacophores are present in numerous pharmaceutically active drug molecules such as vilazodone,[106, 109] entacapone,[110] lodoxamide[111] and febuxostat[112] (Figure.6)

[1] This work was published prior to dissertation. Mudshinge, S. R.; Potnis, C. S.; Xu, B.; Hammond, G. B., *Green Chem* **2020,** *22* (13), 4161-4164.

Figure 6. Nitrile containing pharmaceutical drugs

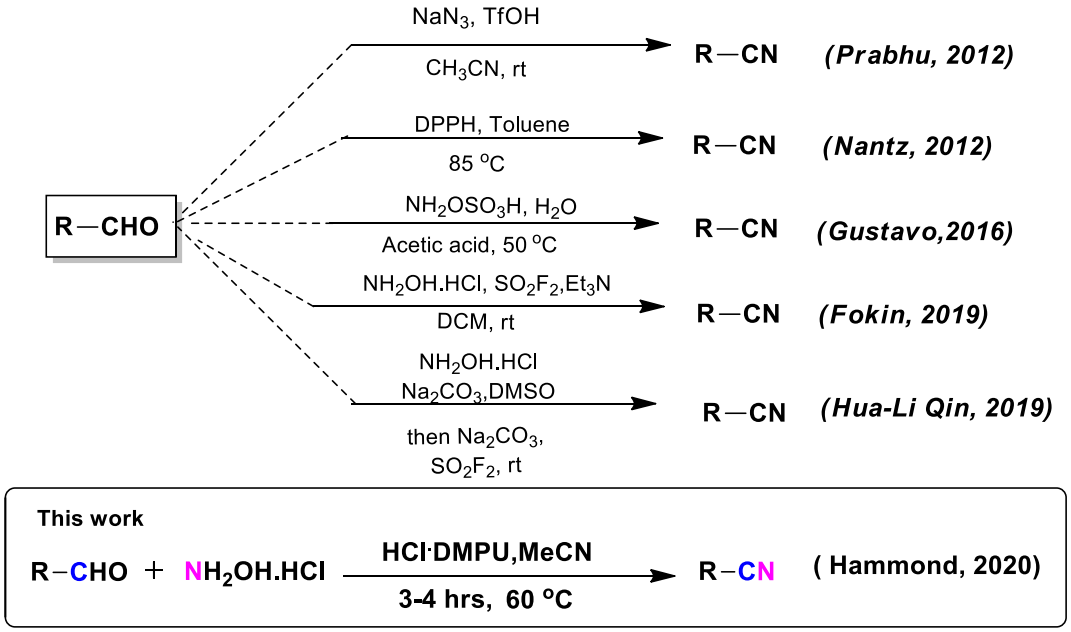


Frequently used traditional methods for the construction of the nitrile moiety include the Sandmeyer reaction[113], Rosenmund-von Braun reaction[114-115], transoximation of aldehydes[116], Kolbe's nitrile synthesis[117] and cyanide-halide exchange reactions.[118-120] But most of these methodologies suffer from the use of heavy metal and highly toxic reagents, complicated operations, and harsh reaction conditions. These shortcomings have been addressed by the development of more efficient and sustainable methodologies for nitrile synthesis in the last few decades.

Of the several starting materials used for nitrile synthesis, some of the most common are aldehydes,[116, 121-134] alcohols,[135] and amines[136]. As aldehydes are easily available, inexpensive, and environmentally benign, they are preferred over other starting materials (Figure 7). Different nitrogen[116, 121, 123, 127-128, 130, 133] sources have been developed as well. Despite the tremendous progress made in the synthesis of nitriles from aldehydes, there are still drawbacks in terms of toxicity of reagents,[123-125] harsh reaction conditions,[126] or substrate scope. To address these issues in the current methods, we designed an environmentally benign alternative using HCl•DMPU.[32, 137-139] This reagent is highly concentrated, easily prepared and bench stable. We found that HCl•DMPU complex plays a dual role of proton donor as well as a non-nucleophilic base, obviating the need for any external base or metal

catalyst. We are pleased to report a HCl•DMPU mediated one-pot synthesis of nitriles from aldehydes. Our protocol eliminates the use of metal catalysts and external oxidants.

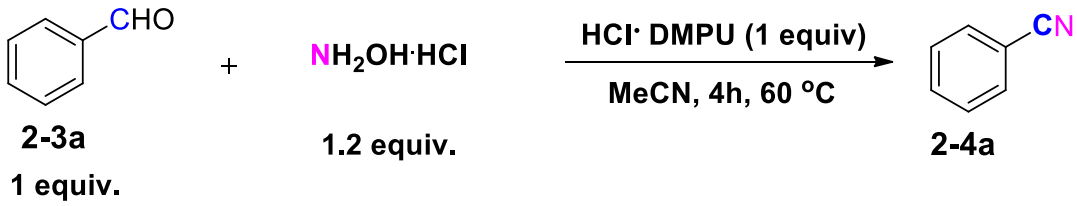
Figure 7. Selected examples of nitrile synthesis from aldehydes



2.2. Results and discussion

We initiated our investigation by reacting benzaldehyde, **2-3a** (1 equiv) with HCl•DMPU (1 equiv) and hydroxylamine hydrochloride (1.2 equiv) at 60 ° C with acetonitrile as the solvent. To our delight, the desired product, **2-4a** was formed in 98% yield. None of the other solvents screened (**Table 1**) were superior to acetonitrile. In the absence of HCl•DMPU, the reaction did not proceed further after yielding the oxime. The reactivity of the oxime with our standard conditions was checked by treating synthesized oxime (**2-19**)[140] under our standard conditions, and we were pleased to observe the desired nitrile product (**2-4f**) in 95%. (Refer to the experimental section for more details).

Table 1. Reaction condition optimization



2-3a
1 equiv.

1.2 equiv.

2-4a

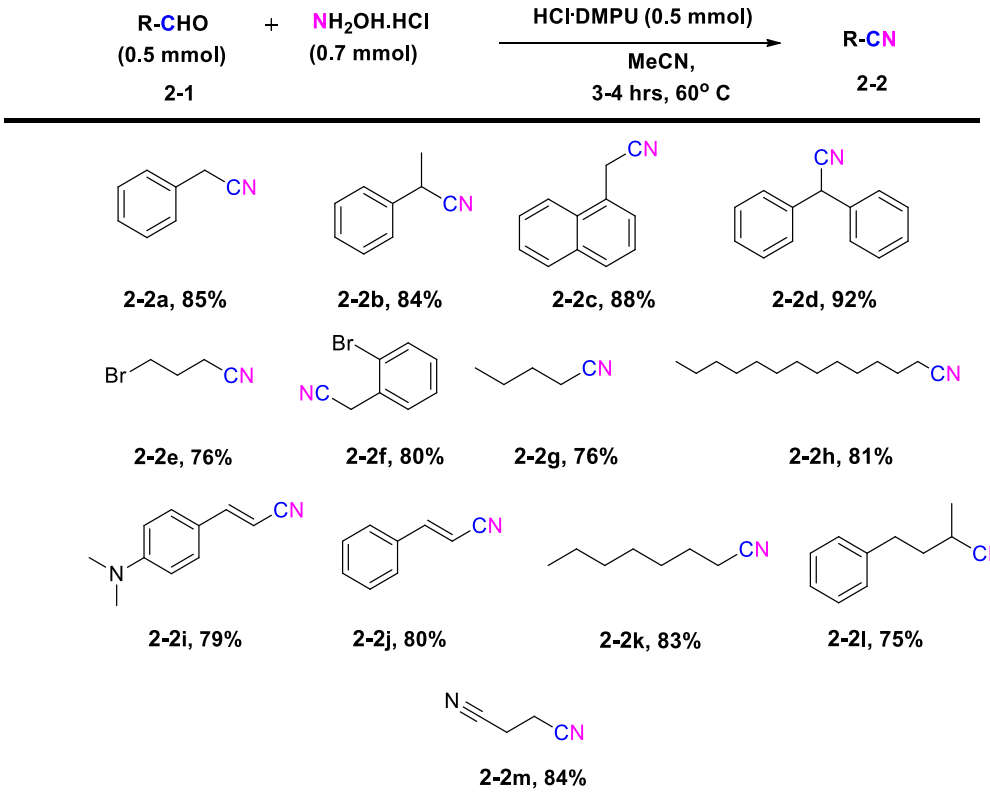
Entry	Deviation from standard condition	% Conversion[a]
1	none	98
2	without HCl·DMPU	0[b]
3	DMPU instead of HCl·DMPU	0[b]
4	MeOH instead of MeCN	10
5	EtOH instead of MeCN	12
6	DCM instead of MeCN	20
7	EtOAc instead of MeCN	18
8	DCE instead of MeCN	23
9	Toluene instead of MeCN	21
10	rt instead of 60 °C	29

*All reactions were performed on 0.5 mmol scale at 60 °C for 4 h.[a] Determined by GC–MS with dodecane as the internal standard.
[b]Formation of oxime.

After standardizing this protocol, the substrate scope was assessed using several aliphatic and α,β-unsaturated aldehydes (Table 2). We were gratified to observe broad functional group tolerance. Notably, an array of aliphatic aldehydes such as (**2**-**1a**) to (**2**-**1h**), (**2**-**1k**) and (**2**-**1m**) underwent this protocol smoothly giving the corresponding nitrile products in 76-92% yields. Branched aliphatic aldehydes, (**2**-**1b**) and (**2**-**1l**) also worked very well. Substrates bearing naphthalene (**2**-**1c**) and diarylmethane (**2**-**1d**) moieties delivered nitrile derivatives in excellent yields. Interestingly, α,β-unsaturated aldehydes such as (**2**-**1i**) and

(**2-1j**) were successfully converted to nitrile derivatives in 79% and 80% yields respectively with complete retention of the double bond geometry.

Table 2 Scope of aliphatic aldehydes[a]



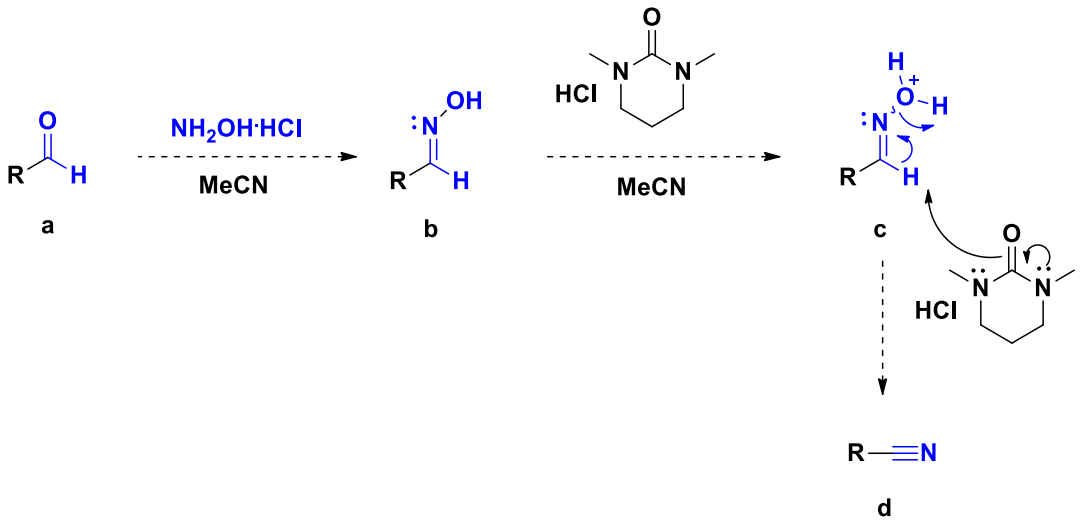
[a] All yields are isolated yields.

We further assessed this protocol on aromatic aldehydes utilizing various electron-donating and electron-withdrawing groups. The corresponding nitriles were obtained in excellent yields (**2-3a to 2-3x**, Table 3). Several para-substituted aldehydes incorporating methoxy (**2-3d**), nitro (**2-3f**), thio (**2-3g**), iodo (**2-3h**), chloro (**2-3i**) and cyano (**2-3j**) substituents were tolerated, delivering the nitrile products in excellent yields of 92-96%. At the same time, we evaluated ortho-substituted aldehydes such as (**2-3l**) and (**2-3m**), which gave the corresponding 2-(trifluoromethyl) benzonitrile (**2-3l**) and 2-fluorobenzonitrile (**2-3m**) in 92% and 94% yield, respectively. These results indicated that the steric hindrance of the ortho position did not influence the reactivity of these aldehyde

substrates. Polyaromatic substrates such as naphthalene (**2-3k**) and anthracene (**2-3n**) derivatives were successfully transformed, giving 97% and 95% yields, respectively. Given the importance and broad applications of heterocyclic molecules in the pharmaceutical sector and medicinal chemistry, we examined various heterocyclic aldehydes (Table 3). A wide range of aldehydes incorporating sulfur (**2-3s**) oxygen (**2-3p, 2-3t, 2-3u**) and nitrogen atoms (**2-3q** and **2-3v**) in aromatic rings were efficiently converted to their nitrile derivatives in excellent yields. Various other functionalities such as amide (**2-3w**) and ester (**2-3x**) also delivered the corresponding nitriles in excellent yields.

A plausible mechanism for this nitrile synthesis is depicted below (Scheme 11). Initially, the nucleophilic attack of hydroxylamine hydrochloride to aldehyde **a** gives intermediate oxime **b**, which then undergoes an HCl•DMPU assisted dehydration to give the desired nitrile product **d**. In this process there is no need for an exogenous base because DMPU itself acts as a non-nucleophilic base assisting the proton abstraction from oxime derivatives. The ability of DMPU in the proton abstraction step was demonstrated in our previous report.[31]

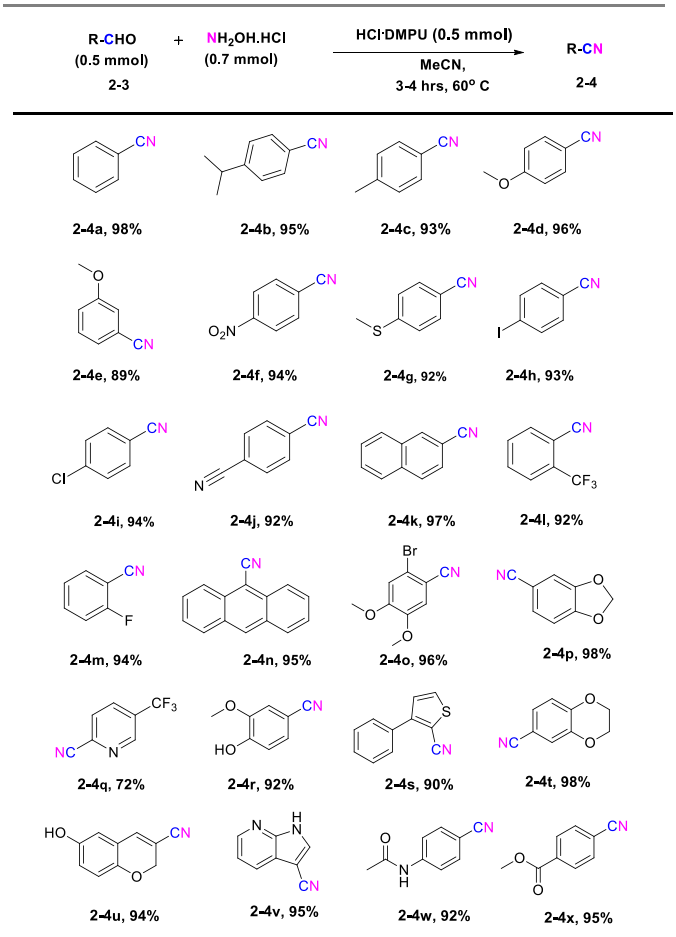
Scheme 11. Proposed reaction mechanism.



The utility of this protocol was demonstrated further by performing several gram-scale synthesis of various precursors of drug molecules (Scheme 12). For example, when 3,4-bis(2-methoxyethoxy)benzaldehyde (**2-7**), derived from aldehyde (**2-5**), was subjected to

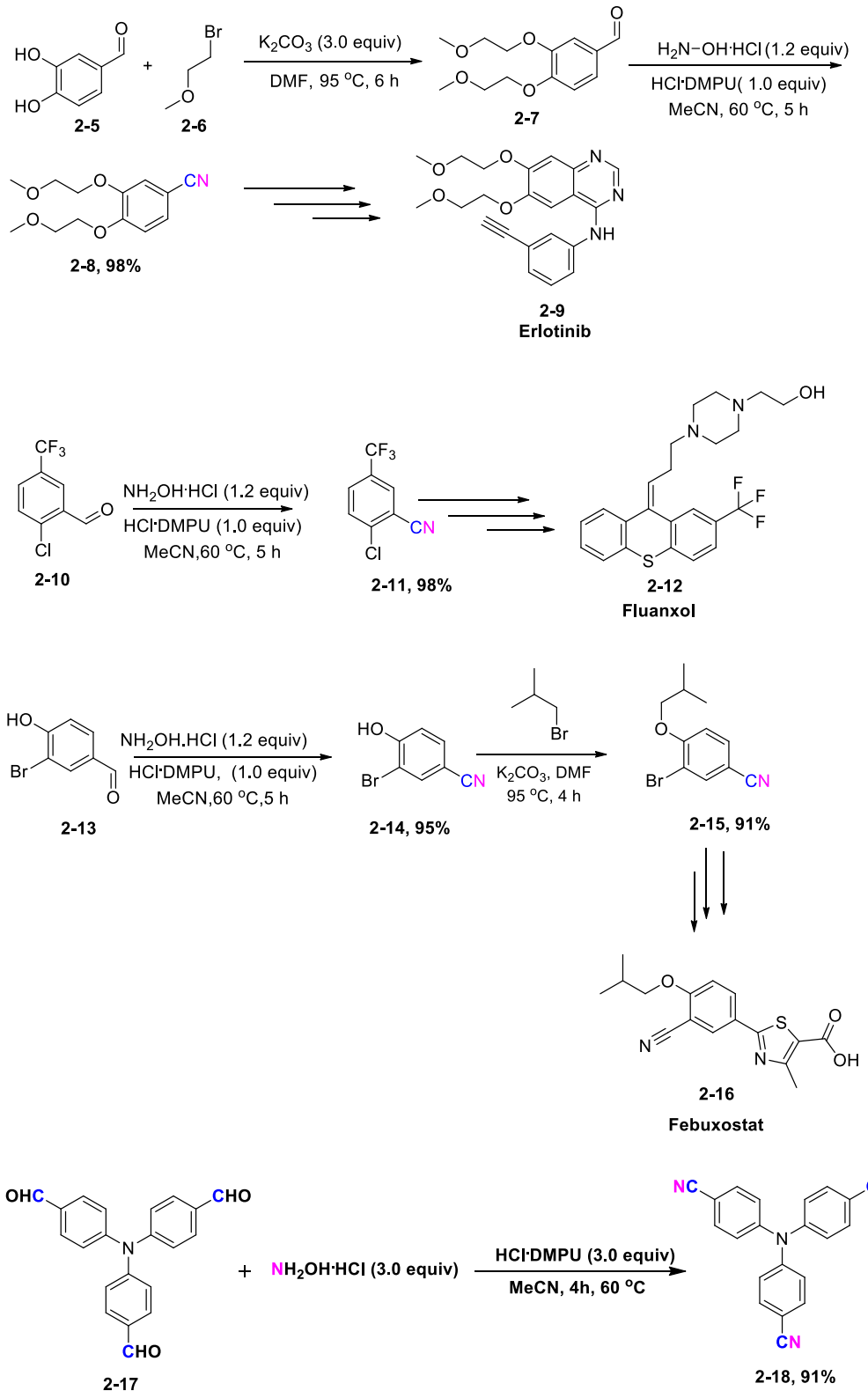
our standard protocol, the corresponding nitrile product (**2-8**) was produced in 98% yield; this product is a key precursor in the synthesis of an anti-cancer drug, Erlotinib (**2-9**).[141] We also examined the synthesis of Fluanxol (**2-12**), an antipsychotic drug, by subjecting 2-chloro-5-(trifluoromethyl)benzaldehyde (**2-10**) to our standard protocol and obtained the nitrile precursor (**2-11**) in 98% yield. Additionally, starting from 3-bromo-4-hydroxybenzaldehyde (**2-13**), we obtained the nitrile precursor (**2-14**) in 95% yield in the formal synthesis of Febuxostat (**2-16**); this drug is indicated in the treatment of gout. Beside the synthesis of drug intermediates, we also performed a gram-scale synthesis of tris-(4-cyanophenyl)amine (**2-18**) from 4,4',4''-triformyltriphenylamine (**2-17**) in 91% yield (Scheme 12). 4-Cyanophenyl)amine (**2-18**) is utilized in the preparation of metal-organic frameworks for high-intensity light emission and other applications.[142]

Table:3 Scope of aromatic and heteroaromatic aldehydes[a]



[a] All yields are isolated yields

Scheme 12. Synthetic applications



2.3. Conclusions

We have successfully developed an efficient and environmentally benign, one-pot HCl•DMPU mediated synthesis of nitriles using inexpensive and readily available starting materials. This approach is compatible with diverse functional groups, providing rapid access to diverse nitriles in good to excellent yields. Additionally, this one-pot process was found to be applicable to the synthesis of key precursors of various drug molecules in the excellent yields.

2.4 Experimental

2.4.1. General Methods

^{1}H and ^{13}C decoupled NMR spectra were recorded either at 400 or 500 MHz and 101 MHz using $CDCl_3$, CD_2Cl_2 or DMSO as a solvent. The chemical shifts are reported in δ (ppm) values (^{1}H and ^{13}C NMR relative to $CHCl_3$, δ 7.26 ppm for ^{1}H NMR and δ 77.16 ppm for ^{13}C NMR and for DMSO δ 2.50 ppm for ^{1}H NMR and δ 39.52 ppm for ^{13}C NMR, multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), m (multiplet), and br (broad). Coupling constants (J) are reported in hertz (Hz). Data for ^{1}H, ^{13}C and ^{19}F NMR were recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (Hz), and integration. All reagents and solvents were employed without further purification. The products were purified using a commercial flash chromatography system. TLC was developed on silica gel 60 F254 aluminum sheets.

2.4.2. General Procedures.

Procedure for Generation of HCl/ DMPU: The reagent HCl·DMPU was prepared as reported in the literature.[32, 137]

2.4.3. General procedure for the synthesis of nitriles (**2-2**) and (**2-4**).

General procedure A: To a stirred solution of aldehyde (0.5 mmol) and hydroxylamine hydrochloride (0.7 mmol) in acetonitrile (1 ml) was added HCl·DMPU (0.5 mmol). The reaction

mixture was vigorously stirred for 3-4 hours at 60 ^{o}C. The progress of the reaction was monitored by TLC. After heating, the reaction mixture was cooled to rt and then diluted with EtOAc (10 ml) and water (10 ml). The layers were then separated, and the organic layer was washed successively with brine (2 x 8 ml). The aqueous layer was extracted with EtOAc (3 x 10 ml). The combined organic layers were dried over anhydrous Na_2SO_4. The filtrate was concentrated under reduced pressure and the crude product was purified by flash column chromatography on silica gel or preparative TLC to give the corresponding nitrile analog using a mixture of ethyl acetate and hexane as an eluent (v/v = 1:9 to 4:6) ratio.

2.4.4. Synthesis of 3,4-bis(2-methoxyethoxy)benzaldehyde (**2-7**).[116]

General procedure B : 3,4-Bis(2-methoxyethoxy)benzaldehyde (**2-7**) was synthesized according to a modified procedure. Under a N_2 atmosphere, 3,4-dihydroxybenzaldehyde 6 (2.0 g, 14.5 mmol), K_2CO_3 (8.0 g, 58 mmol), and DMF (13.2 mL, 1.1 M) were added to a 100 mL round-bottomed flask equipped with a stir bar, and then the reaction mixture was stirred at room temperature for 1 h before 1-bromo-2-methoxyethane 7 (4.84 g, 34.8 mmol) was introduced via syringe. Then, the reaction was allowed to react at 100 °C for an additional 5 h. After completion, the reaction was diluted with water and extracted with dichloromethane (3 × 30 ml). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to dryness. The residue was purified through silica gel chromatography using a mixture of ethyl acetate and hexane (v/v = 2:8) as the gradient eluent to afford the desired product as a yellow oil (2.6 g, 71% yield).

2.4.5. Synthesis of 3-bromo-4-isobutoxybenzonitrile (**2-15**)[143]

General procedure C: 3-bromo-4-isobutoxybenzonitrile (**2-15**) was synthesized according to a modified procedure. Under a N_2 atmosphere, 3-bromo-4-hydroxybenzonitrile (**2-14**) (2.0 g, 10.0 mmol), K_2CO_3 (3.0 g, 22 mmol), and DMF (4 mL) were added to a 50-mL round-bottomed flask equipped with a stirring bar, and then the mixture was stirred at room temperature for 1 h before 1-bromo-2-methylpropane (1.64 g, 12 mmol) was introduced through the syringe. Then, the

reaction was allowed to react at 95 °C for an additional 3 h. After completion, the reaction was diluted with water and extracted with dichloromethane (3 × 30 mL). Then, the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to dryness. The residue was purified through silica gel chromatography using a mixture of ethyl acetate and hexane (v/v = 1:9) as the gradient eluent to afford the desired product as a yellow oil (2.9 g, 91% yield).

2.4.6. General procedure for the synthesis of nitriles (**2-8**), (**2-11**) and (**2-14**).

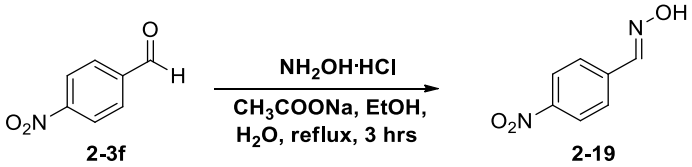
General procedure D: To a stirred solution of aldehyde (10 mmol) and hydroxylamine hydrochloride (12 mmol) in acetonitrile (5 ml) was added HCl·DMPU (10 mmol). The reaction mixture was vigorously stirred for 3-4 hours at 60 ^{O}C. The progress of the reaction was monitored by TLC. After heating, the reaction mixture was cooled at rt and then diluted by EtOAc (2 x 10ml) and water (2 x 10 ml). The layers were then separated, and the organic layer was washed successively with brine (2 x 10ml). The aqueous layer was extracted with EtOAc (3 x 10 ml). The combined extract was dried over anhydrous Na_2SO_4. The filtrate was concentrated under reduced pressure and the crude product was purified by flash column chromatography on silica gel or preparative TLC to give the corresponding nitrile analog both with a mixture of ethyl acetate and hexane as an eluent (v/v = 1:9 to 2:8)

2.4.7. General procedure for the synthesis of nitrile (**2-18**).

General procedure E: To a stirred solution of aldehyde (3.29 g, 10 mmol) and hydroxylamine hydrochloride (2.07g, 30 mmol) in acetonitrile (5 ml) was added HCl·DMPU (3.6g, 30 mmol). The reaction mixture was vigorously stirred for 3-4 hours at 60 ^{O}C. The progress of the reaction was monitored by TLC. After heating, the reaction mixture was cooled to room temperature and then diluted by EtOAc (2 x 10ml) and water (2 x 10 ml). The layers were then separated, and the organic layer was washed successively with brine (2 x 10ml). The aqueous layer was extracted with EtOAc (3 x 10 ml). The combined organic extract was dried over anhydrous Na_2SO_4. The filtrate was concentrated under reduced pressure and the crude product was purified by flash

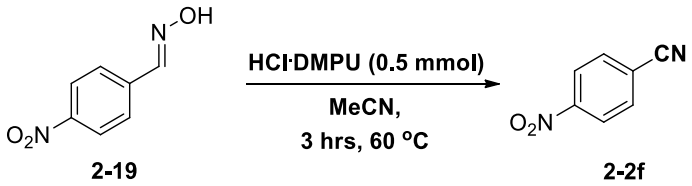
column chromatography on silica gel or preparative TLC to give the corresponding nitrile analog both with a mixture of ethyl acetate and hexane as eluent (v/v = 2:8).

2.4.8. General procedure for the synthesis of oxime (**2-19**).[140]



General procedure F: A mixture of aldehyde, **2-3f** (2 mmol), $NH_2OH{\cdot}HCl$ (4.5 mmol), CH_3COONa (7.5 mmol), ethyl alcohol (0.5 mL) and water (2 mL) were placed in a 50 mL round-bottomed flask with a reflux condenser. Then the mixture was stirred under reflux, the progress was monitored by TLC. After the reaction was complete, the contents were poured into a 100 mL beaker. After cooling, the precipitate was filtered with suction, thoroughly washed with water, and dried under vacuum, then recrystallization with ethyl alcohol to obtain a pure solid, **2-19.**

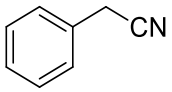
2.4.9. General procedure for the synthesis of nitrile (**2-4f**) from oxime (**2-19**).



General procedure G: To a stirred solution of oxime, **2-19** (0.5 mmol) in acetonitrile (1 ml) was added HCl·DMPU (0.5 mmol). The reaction mixture was vigorously stirred for 3 hours at 60 ^{o} C. The progress of the reaction was monitored by TLC. After heating, the reaction mixture was cooled at rt and then diluted with EtOAc (10 ml) and water (10 ml). The layers were then separated, and the organic layer was washed successively with brine (2 x 8 ml). The aqueous layer was extracted with EtOAc (3 x 10 ml). The combined organic extract was dried over anhydrous Na_2SO_4. The filtrate was concentrated under reduced pressure and the crude product was purified by flash column chromatography on silica gel or preparative TLC to give the corresponding nitrile analog with a mixture of ethyl acetate and hexane as an eluent.

2.4.10.Physical and spectroscopic data of compounds

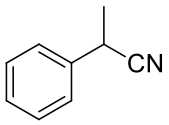
2-phenylacetonitrile (2-2a)[144]



(**2-2a**)

Colorless oil (72.4 mg, 85 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 2H), 7.32 – 7.26 (m, 3H), 3.72 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.8, 129.0, 127.9, 117.7, 30.8, 23.5.

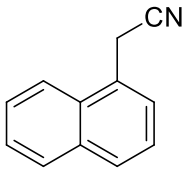
2-phenylpropanenitrile (2-2b)[145]



(2-2b)

Colorless oil (51.2 mg, 84 % yield).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.32 (m, 5H), 3.92 (q, *J* = 7.3 Hz, 1H), 1.66 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0, 129.1, 128.0, 126.7, 121.6, 31.2, 21.4.

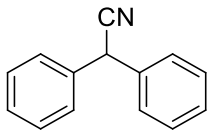
2-(napthalen-1-yl)acetonitrile (2-2c)[146]



(2-2c)

Yellow oil (75.6 mg, 88 % yield).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.82 (m, 3H), 7.64 – 7.53 (m, 3H), 7.47 (t, *J* = 7.7 Hz, 1H), 4.11 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.4, 130.5, 128.9, 128.8, 126.8, 126.2, 126.1, 125.5, 125.2, 122.1, 117.4, 21.4.

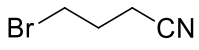
2,2-diphenylacetonitrile (2-2d)[147]



(2-2d)

Pale-yellow solid (90.1 mg, 92 % yield).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.31 (m, 10H), 5.15 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$)) δ 136.0, 129.3, 128.3, 127.8, 119.7, 42.7.

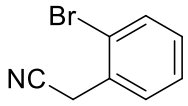
4-bromobutanenitrile (2-2e)[148]



2-2e

Colorless oil (56.2 mg, 76 % yield).^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 – 3.39 (m, 2H), 2.67 – 2.42 (m, 2H), 2.32 – 2.10 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 118.3, 30.6, 28.1, 15.9.

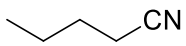
2-(2-bromophenyl)acetonitrile (2-2f)[149]



2-2f

Colorless oil (79.2 mg, 80 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.55 (m, 1H), 7.51 (d, *J* = 7.4 Hz, 1H), 7.35 (dd, *J* = 10.8, 4.2 Hz, 1H), 7.21 (dd, *J* = 14.7, 7.2 Hz, 1H), 3.82 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.0, 129.8, 129.6, 128.1, 123.6, 116.8, 109.9, 24.8.

Pentanenitrile (2-2g)[150]



2-2g

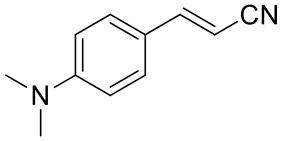
Colorless oil (32.7 mg, 76 % yield).^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (t, *J* = 7.1 Hz, 2H), 1.79 – 1.66 (m, 2H), 1.57 (dq, *J* = 14.6, 7.3 Hz, 2H), 1.04 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 119.8, 27.3, 21.8, 16.8, 13.2.

Tetradecanenitrile (2-2h)[122]

2-2h

Colorless oil (86.0 mg, 81 % yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.34 (t, *J* = 7.2 Hz, 2H), 1.72 – 1.62 (m, 2H), 1.45 (dd, *J* = 14.8, 7.1 Hz, 2H), 1.29 (d, *J* = 15.1 Hz, 18H), 0.89 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 119.8, 31.8, 29.6, 29.4, 29.3, 29.2, 28.7, 28.6, 25.3, 22.6, 17.1, 14.0.

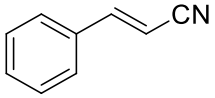
E-3-(4-(dimethylamino)phenyl)acrylonitrile (2-2i)[151]



2-2i

Colorless oil (67.9 mg, 79 % yield).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.36 (m, 2H), 7.32 (d, *J* = 1.1 Hz, 1H), 6.72 (d, *J* = 8.8 Hz, 2H), 5.63 (d, *J*= 16.4 Hz, 1H), 3.09 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 150.5, 130.9, 129.0, 121.5, 119.7, 111.7, 89.5, 40.1.

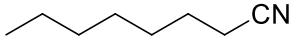
3-Phenylacrylonitrile (2-2j)[122]



2-2j

Colorless oil (51.6 mg, 80 % yield).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.59 (m, 5H), 7.58-7.46 (s, 1H), 6.08 (d, *J* = 16.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 133.7, 131.4, 129.3, 127.5, 118.3, 96.5.

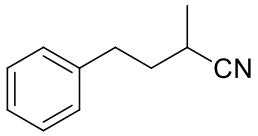
Octanenitrile (2-2k) [152]



2-2k

Colorless oil (45.6 mg, 83 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (t, *J* = 7.1 Hz, 2H), 1.70 – 1.59 (m, 2H), 1.43 (dd, *J* = 14.4, 6.6 Hz, 2H), 1.30 (d, *J* = 8.5 Hz, 6H), 0.88 (t, *J* = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 119., 31.3, 28.4, 28.2, 25.2, 22.3, 16.9, 13.8.

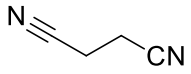
2-methyl-4-phenylbutanenitrile (2-2l)[153]



2-2l

Colorless oil (60.0 mg, 75 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (t, *J* = 7.3 Hz, 2H), 7.33 (dd, *J* = 19.1, 7.4 Hz, 3H), 3.05 – 2.93 (m, 1H), 2.87 (dd, *J* = 14.9, 7.1 Hz, 1H), 2.69 (dd, *J* = 15.0, 7.0 Hz, 1H), 2.06 (dt, *J* = 17.8, 6.8 Hz, 1H), 1.96 (dt, *J* = 13.6, 6.9 Hz, 1H), 1.44 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 128.3, 128.1, 126.1, 122.5, 35.4, 32.9, 24.6, 17.7.

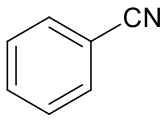
Butanedinitrile(2-2m)[154]



2-2m

Colorless oil (32.7 mg, 84 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.78 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.1, 14.6.

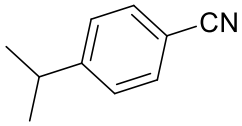
Benzonitrile (2-4a)[155]



2-4a

Colorless oil (50.4 mg, 98 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.53 (m, 3H), 7.43 (t, *J* = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.7, 132.0, 129.0, 118.8, 112.3.

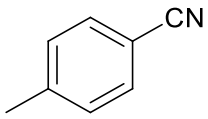
4-isopropylbenzonitrile (2-4b)[156]



2-4b

Colorless oil (69.0 mg, 95 % yield).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.52 (d, 2H), 7.34 – 7.29 (d, 2H), 2.95 (dt, *J* = 13.8, 6.9 Hz, 1H), 1.25 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 132.3, 127.4, 119.2, 109.7, 34.5, 23.6.

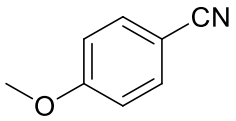
4-methylbenzonitrile (2-4c)[157]



2-4c

Pale-yellow solid (54.4 mg, 93 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 131.9, 129.7, 119.0, 109.2, 21.7.

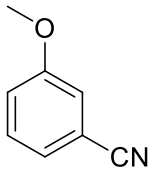
4-methoxybenzonitrile (2-4d)[157]



2-4d

White solid (63.3 mg, 96 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 133.9, 119.1, 114.7, 103.9, 55.5.

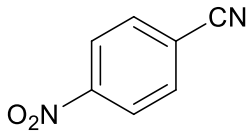
3-methoxybenzonitrile (2-4e) [145]



2-4e

Clear yellow oil (59.6 mg, 89 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 1H), 7.20 – 7.15 (m, 1H), 7.08 – 7.03 (m, 2H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 130.2, 124.3, 119.2, 118.6, 116.7, 113.1, 55.4.

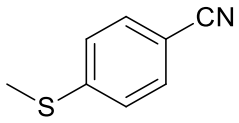
4-nitrobenzonitrile (2-4f)[157]



2-4f

Yellow solid (70.0 mg, 94 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 7.6 Hz, 2H), 7.89 (d, *J* = 7.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 133.6, 124.4, 118.4, 116.9.

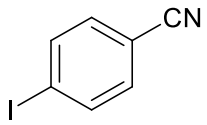
4-(methylthio)benzonitrile (2-4g)[157]



2-4g

Colorless oil (69.0 mg, 92 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.5 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0, 132.0, 125.3, 118.8, 107.5, 14.5.

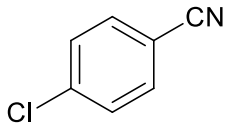
4-iodobenzonitrile (2-4h) [158]



2-4h

Colorless oil (106.4 mg, 93 % yield).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.3 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 132.7, 117.7, 111.2, 99.8.

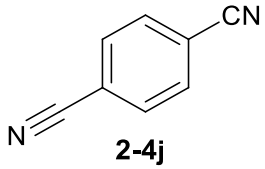
4-chlorobenzonitrile (2-4i)[159]



2-4i

White solid (64.5 mg, 94 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.6 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 133.3, 129.6, 117.9, 110.7.

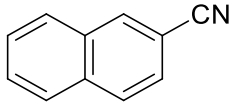
1,4-benzenedicarbonitrile (2-4j)[160]



2-4j

Colorless oil (58.8 mg, 92 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.85 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.7, 116.9, 116.7.

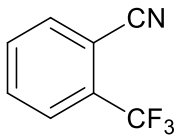
2-naphthonitrile (2-4k)[161]



2-4k

White solid (74.2 mg, 97 % yield).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.86 (t, *J* = 8.5 Hz, 3H), 7.63 – 7.54 (m, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 134.5, 134.0, 132.1, 129.1, 128.9, 128.3, 128.0, 127.6, 126.2, 119.2, 109.3.

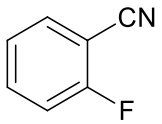
2-(trifluoromethyl)benzonitrile (2-4l)[162]



2-4l

Colorless oil (78.6 mg, 92 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 18.1, 7.6 Hz,2H), 7.73 (dt, *J* = 21.0, 7.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.6, 132.7, 132.6 (q, *J*= 3.2 Hz), 126.6 (q, *J* = 4.6 Hz) , 122.2 (q, *J*= 273.2 Hz) 115.3, 110.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.02.

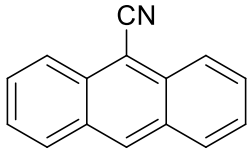
2-fluorobenzonitrile (2-4m)[163]



2-4m

Colorless oil (56.8 mg, 94 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.70 (m, 2H), 7.58 – 7.14 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2 (d, *J*=259 Hz), 135.2, 135.1, 133.6, 124.9, 116.7, 116.5, 114.0, 101.7, 101.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ -106.1 (m, 1F)

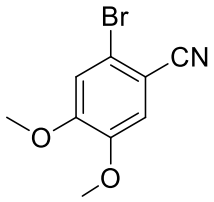
Anthracene-9-carbonitrile (2-4n)[164]



2-4n

White solid (96.4 mg,95 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.37 (d, *J* = 8.7 Hz, 2H), 8.03 (d, *J* = 8.5 Hz, 2H), 7.68 (dd, *J* = 8.2, 7.1 Hz, 2H), 7.59 – 7.52 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.1, 132.6, 130.4, 128.8, 126.2, 125.1, 117.1, 105.2.

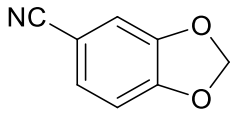
2-bromo-4,5-dimethoxybenzonitrile (2-4o)[165]



2-4o

White solid (115.6 mg,96 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (s, 1H), 7.00 (s, 1H), 3.89 (s, 3H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 148.4, 117.5, 117.5, 115.4, 115.1, 106.8, 56.4, 56.3.

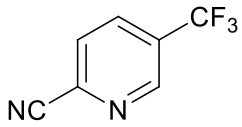
Benzo[d][1,3]dioxole-5-carbonitrile (2-4p)[166]



2-4p

White solid (71.5 mg, 98 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.04 (d, *J* = 1.5 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 6.07 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 147.9, 128.1, 118.8, 111.3, 109.0, 104.9, 102.1.

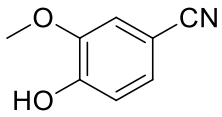
5-(trifluoromethyl)picolinonitrile (2-4q)[167]



2-4q

Colorless oil (61.5 mg, 72 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.12 (d, *J* = 10.2 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 137.2, 134.7, 128.4 (q J= 118 Hz), 123.4, 121.2, 116.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.17.

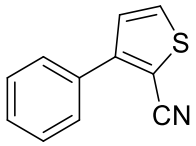
4-hydroxy-3-methoxybenzonitrile (2-4r)[168]



2-4r

White solid (68.5 mg, 92 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.06 (d, *J* = 1.5 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 6.00 (s, 1H), 3.91 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 146.5, 126.9, 119.2, 115.1, 113.6, 103.2, 56.1.

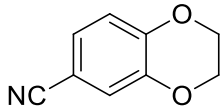
3-phenylthiophene-2-carbonitrile (2-4s)[169]



2-4s

White solid (82.8 mg, 90 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.66 (s, 1H), 7.54 (d, *J* = 7.3 Hz, 2H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.98, 136.09, 133.5, 129.0, 128.2, 126.6, 126.3, 114.0, 110.5.

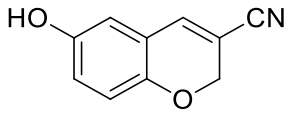
2,3-dihydrobenzo[b][1,4]dioxine-6-carbonitrile (2-4t)[156]



2-4t

White solid (78.4 mg, 98 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.17 (m, 2H), 6.97 (d, *J* = 8.5 Hz, 1H), 4.37 (dd, *J* = 3.5, 1.5 Hz, 2H), 4.35 – 4.33 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 143.8, 125.9, 121.2, 118.9, 118.2, 104.5, 64.6, 64.14.

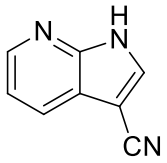
6-hydroxy-2H-chromene-3-carbonitrile (2-4u)



2-4u

Colorless oil (81.3 mg, 94 % yield). ^{1}H NMR (400 MHz, DMSO) δ 9.40 (s, 1H), 7.58 (s, 1H), 6.78 (d, *J* = 21.1 Hz, 3H), 4.82 (s, 2H). ^{13}C NMR (100 MHz, DMSO) δ 152.6, 147.0, 139.8, 121.2, 119.7, 117.3, 114.6, 104.0, 64.0

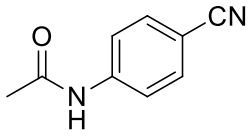
1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (2-4v)[170]



2-4v

Colorless oil (67.6 mg, 95 % yield). ^{1}H NMR (500 MHz, DMSO) δ 8.30 (d, *J* = 1.6 Hz, 1H), 8.29 (d, *J* = 1.6 Hz, 1H), 8.26 (dd, *J* = 4.7, 1.6 Hz, 1H), 8.24 (s,1H), 7.75 (s, 1H), 7.14 (dd, *J* = 7.9, 4.7 Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ 148.0, 143.8, 138.3, 131.1, 127.7, 118.6, 116.7, 105.9.

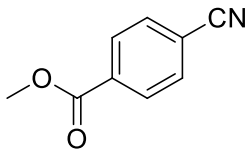
N-(4-cyanophenyl)acetamide (2-4w)[124]



2-4w

Colorless oil (64.3mg, 92 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (q, *J* = 8.8 Hz, 4H), 7.08 (s, 1H), 2.04 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 168.13, 141.51, 132.92, 119.05, 118.42, 106.80, 24.43.

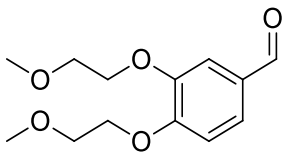
Methyl 4-cyanobenzoate (2-4x)[124]



2-4x

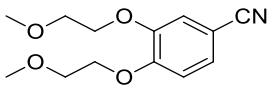
Colorless oil (76.3 mg, 95 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.2 Hz, 2H), 7.55 (d, *J* = 8.2 Hz, 2H), 3.77 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 165.08, 133.59, 131.88, 129.75, 117.62, 116.07, 77.10, 77.02, 76.71, 76.43, 52.39.

3,4bis(2-methoxyethoxy)benzaldehyde (2-7)[171]



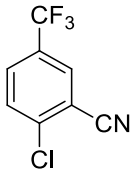
Yellow oil (2.30g, 96 % yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.84 (s, 1H), 7.52 – 7.39 (m, 2H), 7.01 (d, *J* = 8.1 Hz, 1H), 4.27 – 4.17 (m, 5H), 3.85 – 3.78 (m, 5H), 3.47 (d, *J* = 0.9 Hz, 7H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.85, 154.36, 149.22, 130.29, 126.73, 112.50, 111.80, 59.32, 59.24.

3,4-bis(4-methoxybutoxy)benzonitrile (2-8)[171]



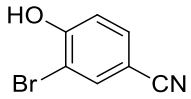
White solid (2.48 g, 98 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, *J* = 5.7, 1.9 Hz, 1H), 7.14 – 7.08 (m, 1H), 6.93 – 6.85 (m, 1H), 4.24 – 4.05 (m, 4H), 3.81 – 3.68 (m, 4H), 3.46 – 3.27 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$)δ 152.88, 148.87, 126.77, 119.09, 117.05, 113.49, 104.16, 70.76, 70.65, 69.02, 68.59, 59.22.

2-chloro-5-(trifluoromethyl)benzonitrile (2-11)[172]



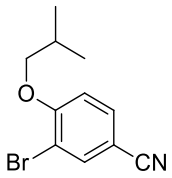
White solid (2.08 g, 98 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.84 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.90, 131.11 (q, *J*= 3.1 Hz), 131.01, 130.67 (q, *J*=3.6 Hz), 129.96(q, *J*=34.3), 122.70 (q, *J*= 272.7 Hz), 114.77, 114.53. ^{19}F NMR (376 MHz, $CDCl_3$) δ 63.7.

3-bromo-4-hydroxybenzonitrile (2-14)[173]



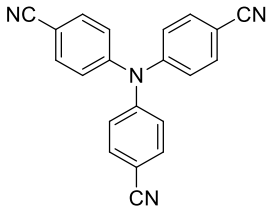
Brown solid (1.86 g, 95 % yield).^{1}H NMR (400 MHz, DMSO) δ 11.35 (s, 1H), 7.86 (d, *J* = 2.0 Hz, 1H), 7.48 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ 158.84, 137.07, 133.64, 118.38, 117.06, 110.11, 102.80.

3-bromo-4-isobutoxybenzonitrile (2-15) [171]



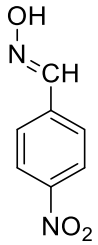
White solid (2.98 g, 91 % yield).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 2.0 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 1H), 3.80 – 3.78 (m, 2H), 2.13 (dt, *J* = 13.2, 6.6 Hz, 1H), 1.03 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.03, 136.55, 132.92, 117.78, 112.59, 104.79, 75.61, 28.14, 18.99.

4,4',4''-nitrilotribenzonitrile (2-18)[142]



White solid (2.85 g, 91 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.1 Hz, 6H), 7.17 (d, *J* = 8.2 Hz,6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.19, 133.95, 124.59, 118.26, 108.01.

(E)-4-nitrobenzaldehyde oxime (2-19)[140]



Yellow solid (302 mg, 91 % yield).^{1}H NMR (400 MHz, CDCl3)δ 8.26 (d, *J* = 7.1 Hz,2H), 8.21 (s, 1H), 7.86 (s, 1H), 7.76 (d, *J* = 7.1 Hz, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ 148.51, 138.24, 127.79, 124.18.

3.0. SYNTHESIS AND APPLICATIONS OF S(TRIFLUOROMETHYL)-2,8 BIS(TRIFLUOROMETHOXY)DIBENZOTHIOPHENIUM TRIFLATE

3.1. Background

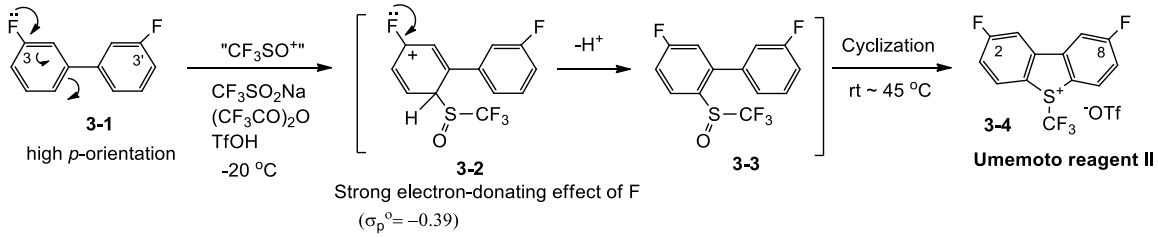
After exploring the novel applications of halogenating agents, we developed a novel trifluoromethylating agent which can efficiently install the trifluoromethyl group on the organic compounds. In recent years, a trifluoromethyl group (CF_3) has found enormous applications in agrochemicals and pharmaceuticals because strong electron withdrawing nature and suitable steric factor of CF_3 group offer improved pharmacokinetics to the agrochemicals and drug molecules such as better metabolic stability, membrane permeability and bioavailability.[174-175] This led to the development of many trifluoromethylating agents which are categorized as radical, nucleophilic, or electrophilic, based on the nature of CF_3 group.[176-177] The electrophilic CF_3 reagents have witnessed much slower growth compared to other classes due to inherent difficulty in generating trifluoromethyl cation (CF_3^+). A significant contribution in this field was given by Umemoto, Togni, Shibata, Shen etc. (Figure 5). In this context, Umemoto[79, 90-92, 178] and Togni's reagents[84, 179-180] are among the most widely used trifluoromethylating agents. However, Togni's reagent is unsuitable for scale-up applications due to its instability arising from hypervalent iodine skeleton which could lead to potential explosion.[181] On the other hand, the synthesis of the first generation Umemoto reagent require multiple steps of synthesis leading to the higher cost of the preparation.[79] Recently, this problem was circumvented by Umemoto et al. by developing high yielding one-pot preparation of second-generation Umemoto reagent **3-4** (Scheme 15).[91] However, availability of the **3-4** is limited because of the patent issue, hampering the wider use of this reagent.

To address these issues associated with contemporary Umemoto reagent II (**3-4**), we attempted a newer version of the Umemoto reagent that is cost-effective and more powerful than Umemoto reagent II. Herein, we report the synthesis and application of 2,8-bis(trifluoromethoxy)-S-(trifluoromethyl)dibenzothiophenium triflate (**3-7**).

3.2. Results and discussion

The astonishingly strong *p*-activation effect by the fluorine atom was demonstrated by Umemoto et al. in their previous report on one-pot synthesis of 2,8-difluoro-*S*-(trifluoromethyl)dibenzothiophenium triflate (Umemoto reagent II) from 3,3'-difluorobiphenyl (**3-1**).[91] In their studies it was observed that, despite the electron-withdrawing effect (Hammett constant s_p = +0.06) of fluorine atom located at the 3 or 3'-position, it activates the *para*-position (Hammett constant s_R = -0.39) even at lower temperatures like -20 °C producing the reaction intermediate species stabilized by the fluorine atom such as **3-2** that was then converted to **3-4** under the reaction conditions.

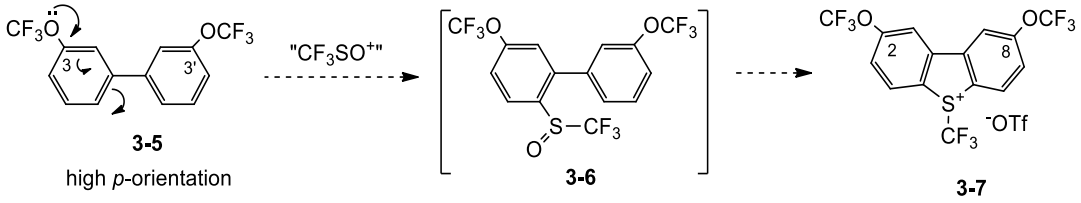
Scheme 15. A successful one-pot reaction of 3,3'-difluorobiphenyl (3-1) giving Umemoto reagent II



In the same context, we designed and developed a one-pot synthesis of 2,8-bis(trifluoromethoxy)-*S*-(trifluoromethyl)dibenzothiophenium triflate (**3-7**) from 3,3'-bis(trifluoromethoxy)biphenyl (**3-5**). As shown in Scheme 16, a CF_3O group has a larger Hammett constant s_p (0.35)[18] than that of F (+0.06), but still negative s_R value (-0.04),[18] though the absolute value is smaller than that of F (s_R = -0.39). The s_p value indicates that CF_3O has a stronger electron-withdrawing effect than F, while the s_R value indicates that CF_3O has still electron-donating effect in the substitution reaction in the

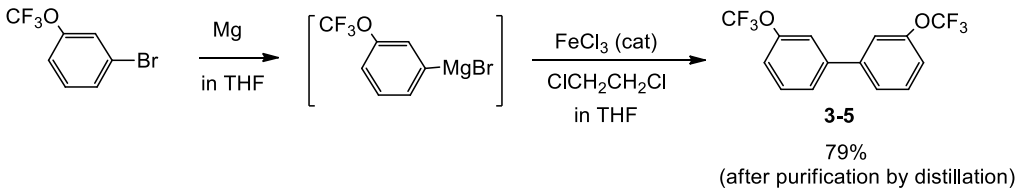
same way as F though its effect is smaller than F. Actually, a high *p*-orientation (*p*/*o*=9/1) of nitration of CF_3O-C_6H_5 was reported,[182] which is close to the case of F-C_6H_5 in nitration (*p*/*o* = 14.5/1).[183]

Scheme 16. Design of one-pot synthesis of 2,8-bis(CF_3O)-*S*-CF_3-dibenzothiophenium triflate 3-7 from 3-5



3-5 was synthesized by the $FeCl_3$-catalyzed homo coupling reaction[184] of 3-(trifluoromethoxy)phenylmagnesium bromide derived from commercially available and inexpensive 3-(trifluoromethoxy)bromobenzene (Scheme 17), which provided **3-5** in high yield.

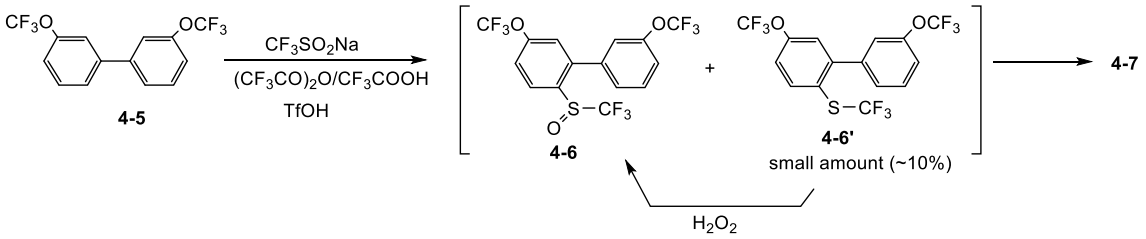
Scheme 17. Preparation of 3,3'-bis(trifluoromethoxy)biphenyl, 3-5



3.2.1.One-pot synthesis of (**3-7**) from 3-5)

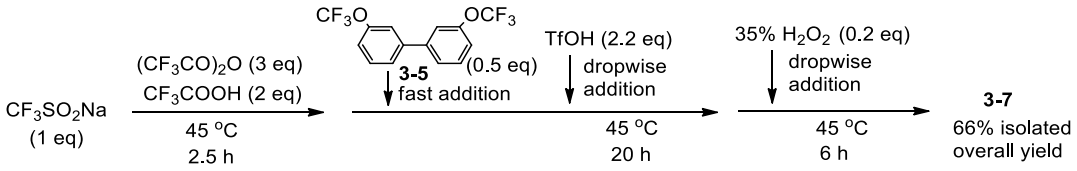
We adopted the same approach for the synthesis of **3-7** which was used previously by Umemoto et al. for synthesizing Umemoto reagent II, using CF_3SO_2Na/$(CF_3CO)_2O$/CF_3COOH/TfOH (Scheme 18). During this reaction we observed a small amount of sulfide **3-6'**(~10%) in addition to product **3-7** and intermediate sulfoxide **3-6** by F-NMR analysis of the reaction mixture. The complete conversion of **3-6'** to **3-6** was achieved with the addition of a small amount of 35% H_2O_2, which eventually led to the cyclized final product **3-7** (Scheme 19).

Scheme 18. A one-pot reaction of biphenyl 3-5 for synthesis of 3-7



Scheme 19 depicts the experimental operation performed to get **3-7**. CF_3SO_2Na (1 eq) was stirred in a mixture of $(CF_3CO)_2O$ (3 eq)/CF_3COOH (2 eq) at 45 °C (oil bath temperature) for 2.5 h and, to the resulting mixture, biphenyl **3-5** (0.5 eq) was added and then triflic acid (2.2 eq) was slowly added over a period of 1.25 h at 45 °C. The resulting mixture was stirred for 20 h and a small amount of 35% H_2O_2 (0.2 eq) in CF_3COOH was slowly added for 2.2 h and the resulting mixture was stirred for 6 h at 45 °C. The reaction mixture was evaporated, and the resulting residue was washed with a 1:1 mixture of water and toluene. The resulting precipitates were collected by filtration to give final product **3-7** in 66% isolated yield (based on **3-5**). **3-7** is non-hygroscopic and stable salt. The isolation method was very simple and easy. In this way, **3-7** was successfully synthesized in a satisfactory yield by the one-pot method. We chose the amount of CF_3SO_2Na necessary to consume biphenyl **3-5**. Therefore, the actual amount may depend on its purity.

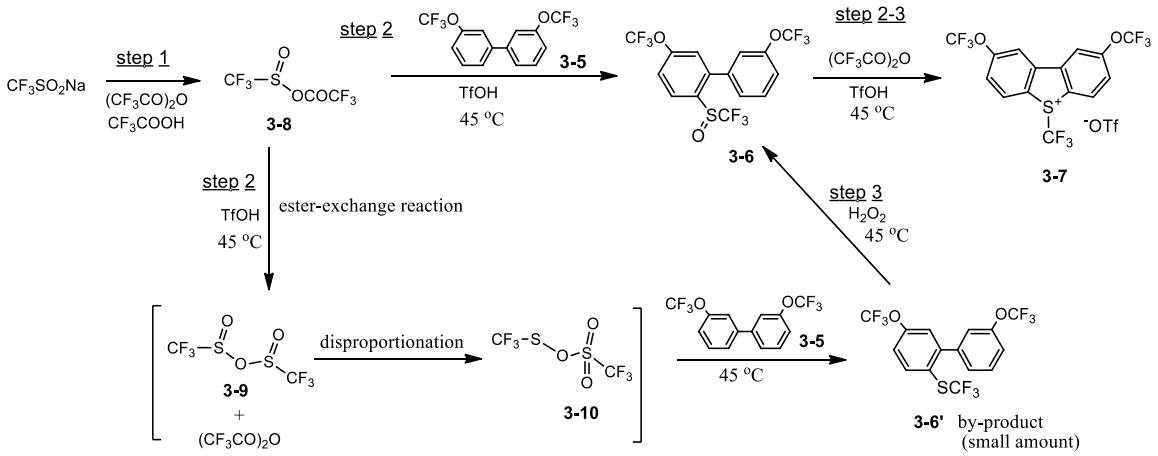
Scheme 19. One-pot procedure for synthesis of *S*-CF_3-2,8-bis(CF_3O)dibenzothiophenium triflate 3-7



We postulated that the reaction mechanism of the one-pot reactions would be the same as the reported in the synthesis of *S*-(trifluoromethyl)-2,3,7,8-tetrafluorodibenzotiophenium triflate.[92] As shown in Scheme 20, in step 1, CF_3SO_2Na would react with $(CF_3CO)_2O$ in the presence of

CF_3COOH to form **3-8**, which reacts with biphenyl **3-5** in the presence of strong acid,TfOH to give intermediate sulfoxide **3-6** in step 2. Sulfoxide **3-6** then would undergoe cyclization by reacting with $(CF_3CO)_2O$ and TfOH to give final product **3-7**. A small amount of sulfide **3-6'** could be formed by the reaction of biphenyl **3-5** with a strong CF_3S^+ reagent **3-10** which might be generated by ester-exchange reaction of **3-8** followed by disproportionation of **3-9**.

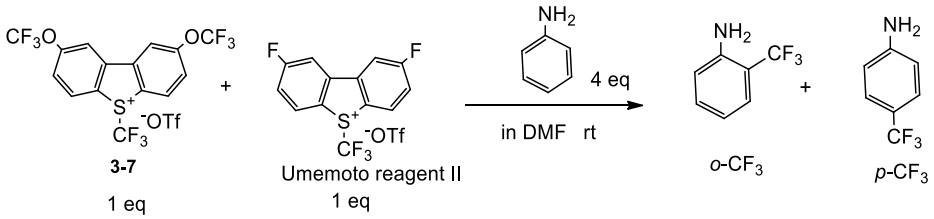
Scheme 20. Proposed reaction mechanism for the one-pot synthesis of 3-7



3.2.2. Reactivity of S-(trifluoromethyl)-2,8-bis(trifluoromethoxy)dibenzothiophenium triflate (**3-7**)

It was expected that **3-7** would be more reactive than Umemoto reagent II (**3-4**) because of the higher electron-withdrawing effect of the CF_3O group than that of F atom. Their relative reactivity was examined by the reaction with aniline, which can form *o*-CF_3- and *p*-CF_3-anilines in good yields (Scheme 21). The mixture of **3-7** (1 eq), Umemoto reagent II (1 eq), and aniline (4 eq) in DMF was stirred at room temperature for 3 h and analyzed by ^{19}F NMR, showing the 50% conversion of **3-7** and 31% conversion of **3-4**. After 26 h, **3-7** was consumed in 90%, while the consumption of **3-4** was only 53%. The yields of *o*-CF_3 and *p*-CF_3-aniline were 45% and 21%, respectively, after 26 h. As **3-7** was consumed in much higher amount than Umemoto reagent II, the newer reagent **3-7** clearly has an edge over **3-4** in terms of reactivity.

Scheme 21. Controlled reaction of bis(CF_3O) salt 3-7 and Umemoto reagent II with aniline



reaction time	CF_3 reagent	conversion of reagent [a]	Yields of CF_3-aniines[b]	
			o-CF_3	*p*-CF_3
3 h	**3-7**	50%	37%	18%
	Umemoto reagent II	31%		
26 h	**3-7**	90%	45%	21%
	Umemoto reagent II	53%		

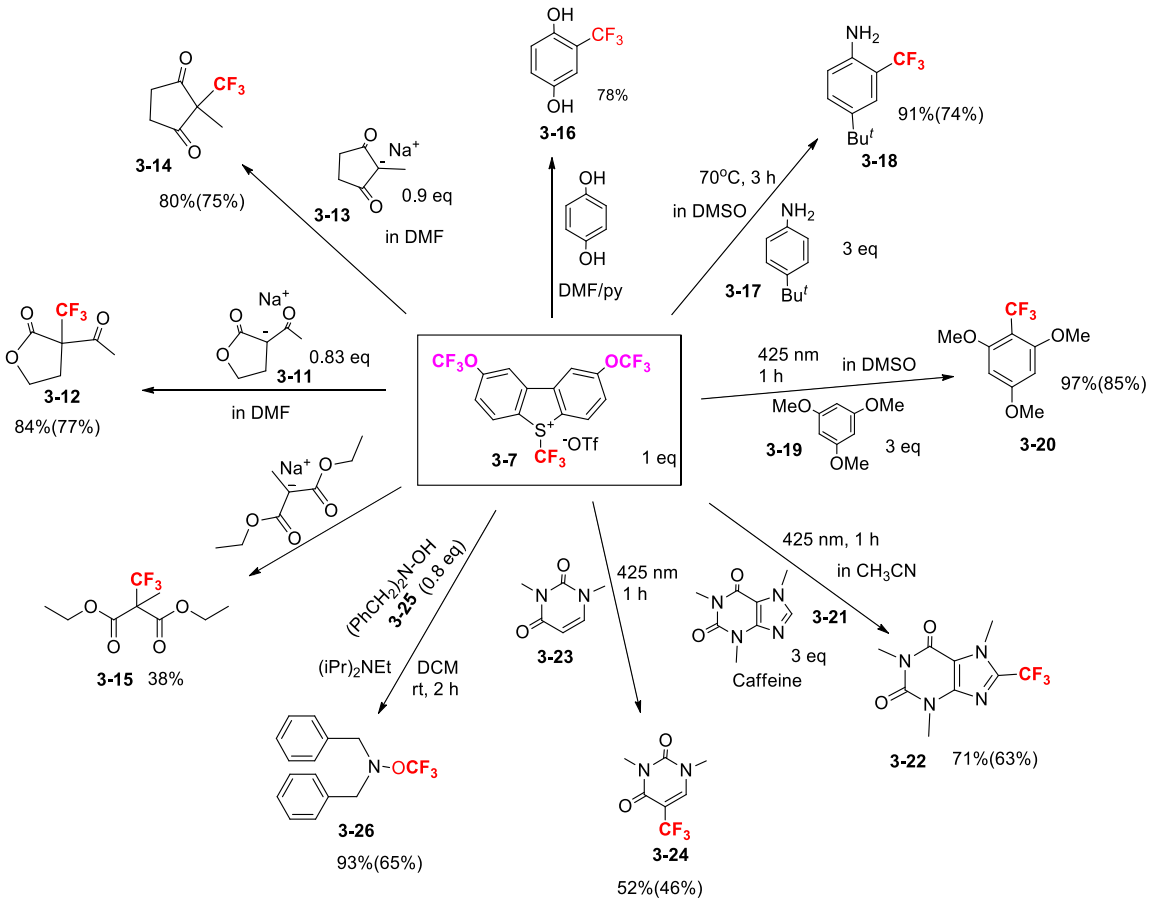
a. The conversion was detemined by ^{19}F NMR analysis of the reaction mixture.
b. ^{19}F NMR yields were calculated based on aniline (4 mmol, 2 equiv) in 3 h and 26 h. *Note*: another 2 eq of aniline acted as a base for this reaction.

We tested the reactivity of our reagent **3-7** with a variety of carbon and oxygen nucleophiles, as showcased in Scheme 22. Keto ester and diketone substrates were trifluoromethylated effectively to deliver **3-12** and **3-14** in high yields**.** It should be noted that **3-12** is an important intermediate for the preparation of useful 1-(trifluoromethyl)cyclopropane-1-carboxylic acid.[9-1] When we extended this scope to other carbonyl compound such as dimethyl 2-methylmalonate, it gave dimethyl 2-methyl-2-(trifluoromethyl)malonate **3-15** in low yield (38%). Then we switched our attention to trifluoromethylation of activated aromatic compounds such as *p*-hydroquinone and 4-*tert*-butylaniline and derived the corresponding trifluoromethylated derivatives **3-16** and **3-18** in good to excellent yields. Although thermal trifluoromethylation of 1,3,5-trimethoxybenzene **3-19** with **3-7** was difficult, photo-assisted trifluoromethylation of **4-19** was achieved smoothly with **3-7** at 425 nm irradiation without using any photo-redox catalyst to give CF_3 product **3-20** in high yield. During this reaction, we found that the irradiation at visible light 425 nm gave a higher yield compared to the reported method which utilized less visible light 375 nm in combination with Umemoto reagent II.[185] This suggests that the CT complex intermediate of **3-19** and **3-7** is excited by lower energy than that of **3-19** and Umemoto reagent II because of higher electron-deficiency

of powerful **3-7**. We further extended this mild photo-assisted trifluoromethylation approach on interesting heterocyclic compounds such as caffeine **3-21** and *N,N'*-dimethyluracil **3-23** producing corresponding trifluoromethylated derivatives in 71 and 52% yields, respectively.[186-187]

To determine the efficiency of **3-7** towards the oxygen nucleophiles, we chose secondary hydroxylamines because this area is much underdeveloped.[179] When we treated *N*-hydroxy-*N,N*-dibenzylamine **3-25** with **3-7,** the corresponding trifluoromethylated derivative **3-26** was obtained in excellent yield (93%). When the same reaction was performed using Umemoto reagent II, it provided **3-26** in only 39% yield. This shows a remarkable difference in reactivity between **3-7** and Umemoto reagent II towards secondary hydroxylamines. We subjected two additional secondary hydroxylamines, **3-45** and **3-46**, equipped with cyano and ester functionalities respectively for *O*-trifluoromethylation and obtained **3-47** and **3-48** in good yields (please refer experimental section, 4.4.8).

Scheme 22. Typical trifluoromethylation examples with 3-7.



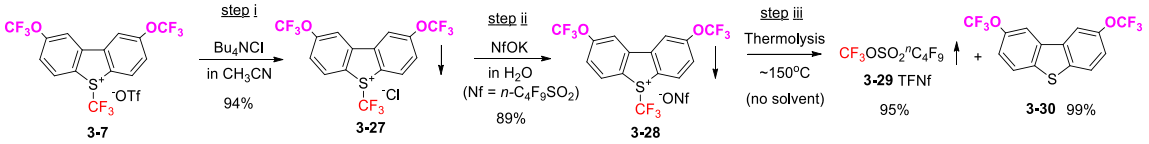
Note: Yields were determined by ^{19}F NMR of the reaction mixtures and those in parentheses were isolated yields.

3.2.3. Preparation of trifluoromethyl nonaflate (TFNf, **3-29**) using **3-7**

Trifluoromethyl nonaflate (TFNf) was developed recently by our research group as an easy-to-handle, stable, and reactive trifluoromethoxylating agent using Umemoto reagent II.[178] In the same context, we developed an efficient and high yielding method of preparation of TFNf using **3-7**. As depicted in the Scheme 23, the treatment of **3-7** with tetrabutylammonium chloride produced **3-27** in excellent yield (step i), which was further treated with potassium nonaflate to give nonaflate **3-28** in 89% yield (step ii). The thermolysis of neat nonaflate **3-28** around 150 °C provided TFNf **3-29** in 95% yield and another byproduct dibenzothiophene **3-30** in 99% yield (step iii). The steps i and ii were fast counter-anion replacement reactions affording **3-27** and **3-28**

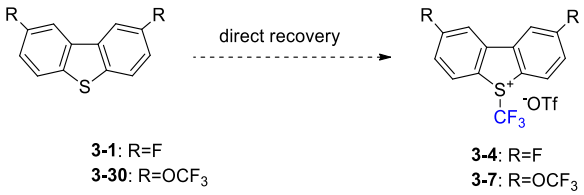
which were obtained by simple filtration. At step iii, the product TFNf was isolated very smoothly during the thermolysis without any contamination from the side product 2,8-bis(CF_3O)dibenzothiophene **3-30**, making this method better than the previous approach where Umemoto reagent II was employed to get **3-29,** generating side product 2,8-difluorodibenzothiophene, which tends to get easily sublimated, contaminating the product TFNf. The merit of our current approach could be attributed to the strong lipophilic nature of CF_3O groups of **3-7**, compared to the F atoms in Umemoto reagent II.

Scheme 23. Preparation of TFNf 3-29 using 3-7



3.2.4. Attempt to directly recover **3-4** and **3-7** from their dibenzothiophenes **3-1** and **3-30**

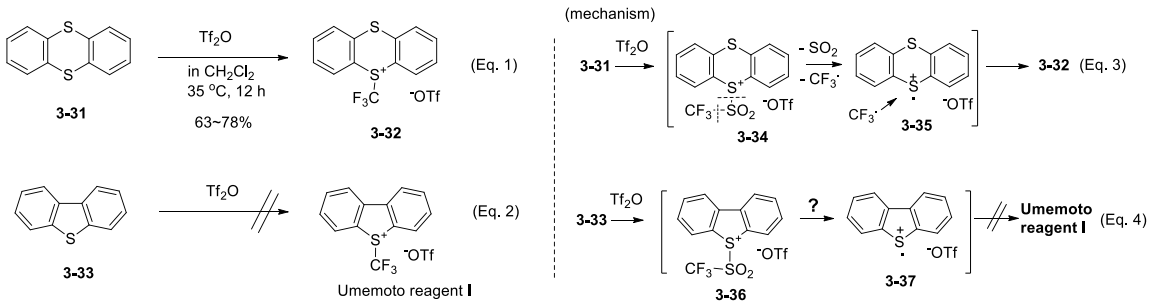
Scheme 24. Direct conversion of dibenzothiophene derivatives to the CF_3 reagents



3-30 and **3-1** were produced quantitatively after the thermolysis or by trifluoromethylation reactions of substrates with **3-7** or Umemoto reagent II. Therefore, if the side product **3-30** or **3-1** could be directly recovered to the CF_3 reagent **3-7** or Umemoto reagent II, the practicability of these CF_3 reagents would become very high (Scheme 24). Recently, Ritter and coworkers reported a single step synthesis of novel trifluoromethylating agent, trifluoromethyl thianthrenium triflate **3-32**, from thianthrene **3-31** (Scheme 25, Eq. 1).[186] They suggested reactive S radical cation species **3-35** as a key intermediate for the formation of the product **3-32** (Eq. 3). However, when Ritter[186] and us subjected dibenzothiophene **3-33,** Umemoto reagent I was not formed (Eq.

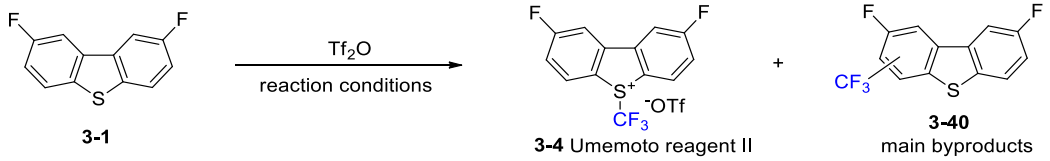
2). We thought that the expected key species **3-37** could not be formed or an extremely short-lived species might form, which decomposed before the combination with the CF_3 radical.

Scheme 25. Reaction of thianthrene 3-31 and dibenzothiophene 3-33 with Tf_2O



We speculated that **3-1** and **3-30** might undergo the desired reaction to give Umemoto reagent II and **3-7**, because the 2,8-diF or bis(CF_3O) substituents in **3-1** or **3-30** could stabilize the corresponding key radical cation species enough to combine with the CF_3 radical. Therefore, we first examined the possibility using 2,8-diF **3-1** as shown in Table 9. We observed the desired product Umemoto reagent II, **3-4,** but in low yield (run 1), while lots of isomeric trifluoromethylated dibenzothiophenes **3-40** were formed.

Table 9. Reaction of 3-1 with Tf_2O



Run	1	Tf_2O	solvent	additive	conditions	Isolated Product[a] **3-4** (crude)	**3-1** (unreacted)	byproducts
1	1.1g (5 mmol)	2 eq	DCE 2 mL	non	50°C, 24 h	35%	3%	**3-40**
2	1.1g (5 mmol)	2 eq	DCE 1 mL	PhH 1 eq	50°C, 24 h	48%	6%	**3-40** + $PhCF_3$
3	1.1g (5 mmol)	2 eq	DCE 1 mL	PhH 2 eq	50°C, 24 h	52% (40%[c])	7%	**3-40** + $PhCF_3$
4[b]	1.1 g (5 mmol)	2 eq	DCE 1 mL	PhH 2 eq	50°C, 26 h	53% (42%[c])	1%	**3-40** + $PhCF_3$

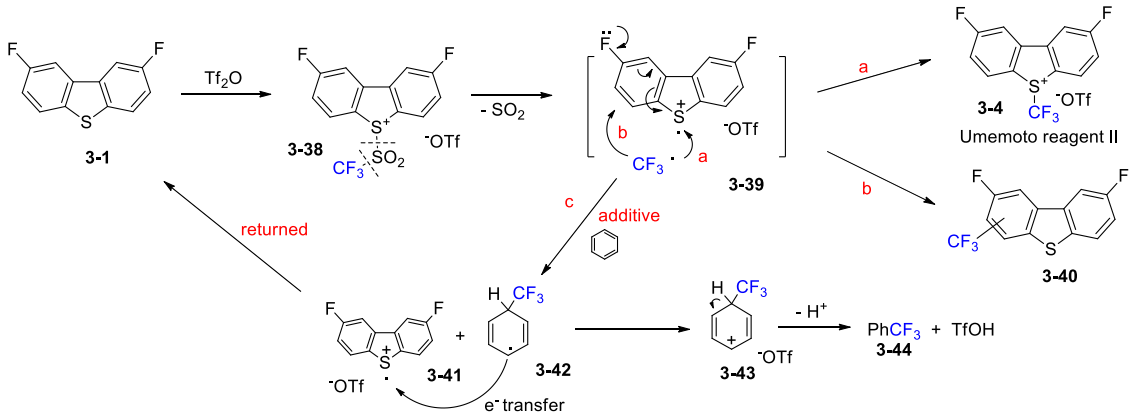
DCM=CH_2Cl_2, DCE=1,2-dichloroethane. PhH=benzene. $PhCF_3$=benzotrifluoride

a. Isolated products were contminated by small amounts of unidentifid impurities. b. The reaction was carried out in a sealed glass reactor.

c. The yield in the parentheses was that of purified product.

As shown in Scheme 26, the formation of byproducts **3-40** can be explained by route *b* in which the CF_3 radical attacked carbon sites on the rings, while route *a* in which the CF_3 radical attacked the sulfur site can give the desired product Umemoto reagent II.

Scheme 26. Proposed reaction processes of 3-1 with Tf_2O

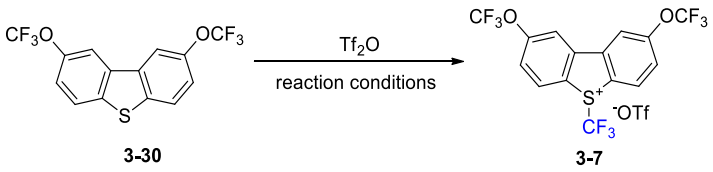


We thought that the addition of some amount of a CF_3 radical trap such as benzene could increase the yield of the desired product, because benzene could react with the CF_3 radical to form radical species **3-41** and **3-42**; **3-41** could accept an electron from **3-42** to give back **3-1**, while **3-42** could be transformed to benzotrifluoride **3-44** through **3-43**. The addition of benzene increased the yield of Umemoto reagent II **3-4**. Actually, **3-4** was obtained in moderate yields as shown in runs 3 and 4 in Table 9.

Based on the results on 2,8-difluoro derivative **3-1**, we tried the conversion of 2,8-bis(CF_3O)dibenzothiophene **3-30** to the *S*-CF_3 triflate **3-7** as shownn in Table 10. It needed

elevated reaction temperature and excess of Tf_2O (3 eq) because of the lesser reactivity of **3-30** compared to **3-1**.

Table 10. Reaction of 3-30 with Tf_2O



3-30 **3-7**

Run	**3-30**	Tf_2O	solvent	additive	conditions	Isolated Product **3-7** (crude)	**3-30** (unreacted)
1	0.880 g (2.5 mmol)	2.5 eq	DCE 0.5 mL	PhH 4.5 eq	65° C, 44 h	very low yield[a]	a lot
2	0.704 g (2 mmol)	3 eq	non	PhCl 4 eq	70° C, 48 h	34%[c]	9%
3[b]	0.704 g (2 mmol)	3 eq	non	PhCl 4 eq	70° C, 48 h	38%[d]	4%

DCE=1,2-dichloroethane. PhH=benzene. PhCl=Chlorobenzene.
a.The prodcut could not be isolated because the yield was very low and a lot of benzotrifluoride was formed in this reaction. b. The reaction was carried out in a sealed glass reactor. c. The purity of this crude product was estimated to be around 90% in mol ratio. d) The purity of this crude product was estimated to be around 87% in mol ratio.

For this case, the addition of benzene as an additive resulted in the very low yield of **3-7** while it formed large amounts of $PhCF_3$ (Run 1). Therefore, we used less reactive chlorobenzene without solvent (Runs 2,3). A sealed reactor was better than an open reactor (run 3). The product was precipitated by adding toluene and water to the reaction mixture and then isolating the product by filtration. The obtained product was contaminated with unidentified impurities. Therefore, it had to be purified by recrystallization or others. Unfortunately, the yield of **3-7** was unsatisfactory because the effect of the CF_3O substituents to facilitate route a (Scheme 26) was less than the F substituents.

3.3. Conclusion

We have successfully developed an affordable, easy-to-handle and bench-stable novel trifluoromethylating agent which is more powerful than Umemoto reagent II. The broad synthetic applicability of this reagent was demonstrated towards various nucleophiles.

3.4. Experimental

3.4.1. General experimental details

^{1}H, ^{19}F, and ^{13}C NMR spectra were measured on 400, 376, and 100 MHz spectrometers, respectively. 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). CF_3SO_2Na was purchased and dried at 80 ^{o}C for 1 hour by a vacuum pump before use. 3-(Trifluoromethoxy)bromobenzene, CF_3COOH, $(CF_3CO)_2O$, CF_3SO_3H (TfOH), $(CF_3SO_2)_2O$ (Tf_2O), potassium nonafluorobutanesulfonate (nonflate), and other commercial reagents were used without further purification. Solvents like tetrahydrofuran (THF), dimethylformamide (DMF), dimethylsulfoxide (DMSO), acetonitrile (ACN), and dichloromethane (DCM) were dried by the standard methods. 2,8-Difluorodibenzothiophene was prepared by the reported thermolysis of S-(trifluoromethyl)-2,8-dibenzothiophenium nonaflate.[178]

3.4.2. Preparation of 3,3'-bis(trifluoromethoxy)biphenyl (**3-5**)

In a 250 mL-three necked flask equipped with a dropping funnel, a thermometer, a condenser, a magnetic stirrer, and an argon inlet and outlet cock, were added 5.55 g (228 mmol, 1.1 eq) of Mg, dry THF 167 mL (commercially bought), and a trace amount of I_2. Into the dropping funnel, 50.0 g (207 mmol) of 3-(CF_3O)-bromobenzene was added, and then some amount of 3-(CF_3O)-bromobenzene (about 1/8 parts) was dropped to the 250 mL-flask. The reaction mixture was stirred, and the Grignard reaction started soon. After that, the remaining 3-(CF_3O)-bromobenzene in the dropping funnel was added dropwise for 50 min (maximum temp was 42 ^{o}C during

addition). After the addition, the reaction mixture was stirred for 45 min at rt and then for 2 h on 45 ^{o}C oil bath. On the other hand, in a 500 mL-three necked flask equipped with a dropping funnel, a thermometer, a magnetic stirrer, and an argon inlet and outlet cock, were added 1.0 g (6.21 mmol) of anhydrous $FeCl_3$, 63 mL of dry THF, and 9.8 mL (12.3 g, 124 mmol, 0.6 eq) of $ClCH_2CH_2Cl$. The resulting Grignard reagent solution was transferred to the dropping funnel through a fluoropolymer tube by argon pressure and added dropwise to the 500 mL-flask for 50 min (under water bath cooling; sometimes a small amount of ice was added; the temp was in a range of 36 ~ 15 ^{o}C). After the addition, the reaction mixture was stirred at rt overnight (13 h). The liquid layer was transferred to a flask and the solvent was evaporated using a rotary evaporator. The residue and the precipitated layer of the reaction mixture were combined and then the mixture was mixed with water (400 mL) and extracted with diethyl ether (200 mL). The aqueous layer was extracted with diethyl ether (50 mL x 2). The combined ether layer was washed with brine (50 mL x 2) and dried with $MgSO_4$ and filtered. The solvent was evaporated using a rotary evaporator and the reside was distilled under reduced pressure, giving **5** 26.0 g (78%) as pure product **3-5**: B.p. 102-103 ^{o}C/9 mmHg. Another reaction using 150 g of the starting material, 3-(CF_3O)-bromobenzene gave 78.9 g (79%) of pure **3-5** after the distillation. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.51 (m, 4H), 7.43 (d, *J* = 2.4 Hz, 2H), 7.27 (m, 2H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 149.80, 141.76, 130.32, 125.50, 120.53 (q, *J* = 257.4 Hz) 120.27, 119.79. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -57.70. HRMS (EI method): Chemical Formula $C_{14}H_8F_6O_2$ (M); theoretical mass for M: 322.0428. Found: (M)+ = 322.0427.

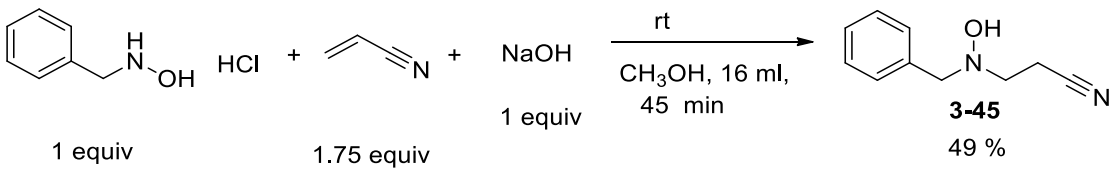
3.4.3. Synthesis of *S*-(trifluoromethyl)-2,8-bis(trifluoromethoxy)dibenzothiophenium triflate (**3-7**)

CF_3SO_2Na (7.56 g, 48.5 mmol mmol) was put in a flask (reactor) and dried in vacuum at 80 ^{o}C (oil bath temp) for 1 h. After that, the reactor was cooled to rt, and a mixture of $(CF_3CO)_2O$ (20.2 ml, 146 mmol) and CF_3COOH (7.4 mL, 97 mmol) was added to the reactor for 18 min on a water bath cooling. The reaction mixture was stirred on an oil bath at 45 ^{o}C for 2.5 h and **3-5** (7.80 g, 24.2 mmol) was added through a dropping funnel (Note: after the dropping, 2 mL of $(CF_3CO)_2O$

was used for washing the dropping funnel and dropped to the reaction mixture). Triflic acid (TfOH, 9.0 mL, 30.1 mmol) was dropwise added through the dropping funnel to the reaction mixture on the oil bath (45 ^{o}C) for 1.25 h (Note: after the dropping, 2 mL of $(CF_3CO)_2O$ was used for washing the dropping funnel and dropped to the reaction mixture). The reaction mixture was stirred at 45 ^{o}C for 20.3 h. After that, a mixture of 35% H_2O_2 (470 mg) and CF_3COOH (4 mL) was added dropwise to the reaction mixture on the oil bath (45 ^{o}C) for 2.2 h and then the reaction mixture was stirred for 6 h at 45 ^{o}C. The reaction mixture was evaporated using a rotary evaporator. Toluene (30 mL) was added to the residue and toluene was evaporated. This process (the addition and evaporation of toluene) was repeated three times. To the resulting residue, water (100 mL) and toluene (100 mL) were added, and the mixture was stirred vigorously at rt for 4 h. The resulting precipitates were filtered and washed with water (10 mL x 2) and then with toluene (25 mL x 3) to give white solid of the product **3-7** (9.07 g after dried, 66% yield). M.p. 157-158 ^{o}C (with decomposition) (recrystallized from CH_3CN/Et_2O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (d, J = 8.9 Hz, 2H), 8.68 (d, J = 2.6 Hz, 2H), 7.85 (ddd, J = 8.9, 2.5, 1.2 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.40, 142.64, 132.14, 125.63, 124.17, 122.82 (q, J = 332 Hz),120.64 (q, J = 321 Hz) 119.75 (q, J = 259.8 Hz), 118.09. ^{19}F NMR (376 MHz, DMSO-d_6) δ -51.61 (3F, s, SCF_3), -56.34 (6F, s, 2xOCF_3), -77.35 (3F, s, SCF_3). HRMS (ESI method): Chemical Formula $C_{16}H_6F_{12}O_5S_2$ (M); theoretical mass for $(M\text{-}CF_3SO_3)^+$: 420.9939. Found: 420.9941.

3.4.4. Preparation of the secondary hydroxylamine substrates

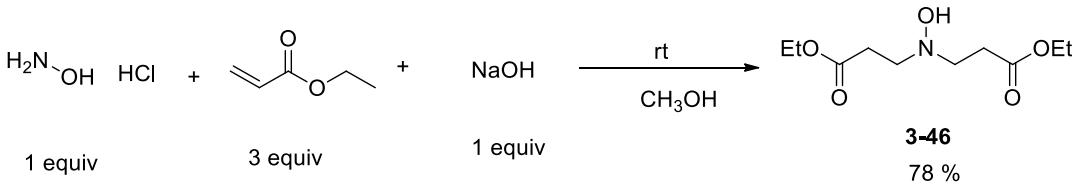
Synthesis of 3-[benzyl(hydroxy)amino]propanenitrile (**3-45**)



This compound was synthesized according to modified procedure reported in literature.[179]

N-benzylhydroxylamine hydrochloride (0.65 g, 4 mmol, 1 eq) was dissolved in methanol (16 mL). Sodium hydroxide (0.16 g, 4 mmol, 1 eq) was added at once as solid and the resulting mixture was stirred for 10 min. Then ethyl acrylate (0.37 g, 7 mmol, 1.75 eq) was added. After stirring for 15 min at rt, TLC analysis (mobile phase: 1/1 hexane/ethyl acetate) indicated complete consumption of starting material. The reaction mixture was vacuum filtered and then evaporated on a rotary evaporator to get the crude product, which was then purified using flash chromatography to get light yellow solid (0.35 g, 49%) (Eluent, EtOAc:hexane 1:5 v/v). Rf (EtOAc:hexane 1:5 v/v) = 0.4 (UV). The NMR data of the title compound was in agreement with the literature reference.[179]

Synthesis of diethyl 3,3'-(hydroxyimino)dipropanoate (**3-46**)[179]



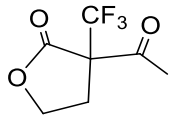
Hydroxylamine hydrochloride (2.5 g, 36 mmol, 1 eq) was dissolved in methanol (150 mL). Sodium hydroxide (1.47 g, 35 mmol, 1 eq) was added at once as solid and the resulting mixture was stirred for 15 min. Then ethyl acrylate (10.8 g, 108 mmol, 3 eq) was added. After stirring for 10 min at rt, TLC analysis (mobile phase: 1/1 hexane/ethyl acetate) indicated complete conversion. The reaction mixture was vacuum filtered and then evaporated to dryness using a rotary evaporator and dried further at high vacuum overnight producing viscous light-yellow oil (6.5 g, 78%). Rf (EtOAc:hexane, 1:1 v/v) = 0.5 (UV). The NMR data of the title compound was in agreement with the literature reference.[179]

3.4.5. Trifluoromethylation of nucleophilies **3-12**, **3-14**, and **3-15** with **3-7**

General procedure: Under an argon atmosphere, (1 mmol) of NaH (60% in oil) was added to a stirred solution of the nucleophile (1 mmol) in 3 mL of dry DMF cooled in an ice bath. Then the mixture was stirred at room temperature for 20 min. After the mixture was cooled to -45^{0}C, **3-**

7 (1.2 mmol) was added and the reaction mixture was stirred for 20 min and then warmed to room temperature over a period of ca. 1 h. The reaction mixture was then quenched with water and extracted with ethyl acetate (3 x 10 ml), washed with brine, and dried over sodium sulfate and filtered. It was then evaporated in a rotary rotavapor under reduced pressure to get the crude product, which was then purified by flash chromatography.

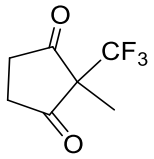
3-Acetyl-3-(trifluoromethyl)dihydrofuran-2(3H)-one (**3-12**)



3-12

Colorless oil (150 mg, 77%) (Eluent, EtOAc:hexane 1:5 v/v). Rf (EtOAc:hexane 1:5 v/v) = 0.55 (UV). The NMR data of the title compound accorded with the reference.[79]

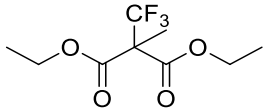
2-Methyl-2-(trifluoromethyl)cyclopentan-1,3-dione (**3-14**)



3-14

Colorless oil (135 mg, 75%) (Eluent, EtOAc:hexane 1:5 v/v). Rf (EtOAc:hexane 1:5 v/v) = 0.4 (UV). The NMR data of the title compound accorded with the reference.[79]

Diethyl 2-methyl-2-(trifluoromethyl)malonate (**3-15**)



3-15

Colorless oil (75 mg, 31%) (Eluent, EtOAc:hexane 1:10 v/v). Rf (EtOAc:hexane 1:10 v/v) = 0.48 (UV). The NMR data of the title compound was in accordance with the literature reference.[79]

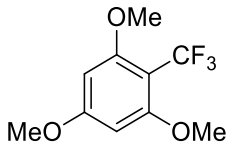
3.4.6. Trifluoromethylation of 4-*tert*-butylaniline (**3-17**) with **3-7**

An 8 mL-glass vial was charged with 4-*tert*-butylaniline (**3-17**) (1.5 mmol, 3.0 equiv) and **3-7** (0.5 mmol, 1 equiv) under argon atmosphere followed by addition of 0.5 ml of dry DMSO. The resulting solution was heated at 70^0 C for 3 h. Then it was quenched with water. The resulting mixture was then extracted with ethyl acetate (3 x 10 mL) and dried over sodium sulfate and evaporated under reduced pressure to get the crude product, which was then purified by flash chromatography to get **3-18** as colorless oil in (80 mg, 74%) (Eluent, EtOAc:hexane 3:7 v/v). Rf (EtOAc:hexane 3:7 v/v) = 0.39 (UV). The NMR data of the title compound was in agreement with the literature reference.[180]

3.4.7. Photo-trifluoromethylation of **3-19**, **3-21**, and **3-23** with **3-7**

General procedure: An 8 mL-glass vial was charged with the substrate (0.6 mmol, 3.0 equiv), **3-7** (0.2 mmol, 1 equiv) and sodium bicarbonate (1.2 equiv) under argon atmosphere followed by addition of 2 ml of dry DMSO or acetonitrile. The solution was sparged with argon via submerged needle for 5 min. Then the reaction mixture was subjected to photo-irradiation (425 nm) at room temperature until the CF_3 reagent was consumed completely (1-3 h). After completion of the reaction, it was quenched with water. The resulting mixture was then extracted with ethyl acetate (3 x 10 mL) and dried over sodium sulfate and evaporated under reduced pressure to get crude mass which was then purified by flash chromatography to get the product **3-20**, **3-22**, or **3-24**.

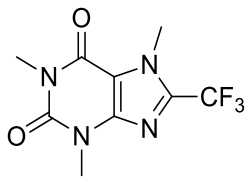
1,3,5-Trimethoxy-2-(trifluoromethyl)benzene (**3-20**)



3-20

White solid(40 mg, 85%) (Eluent, EtOAc:hexane 1:9 v/v). Rf (EtOAc:hexane 1:9 v/v) = 0.45 (UV). The NMR data of the title compound was in agreement with the literature reference.[185]

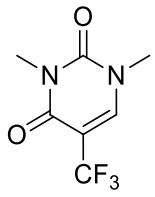
1,3,7-Trimethyl-8-(trifluoromethyl)-1H-purine-2,6(3H,7H)-dione (**3-22**)



3-22

White solid (33 mg, 63%) (Eluent, EtOAc:hexane 1:3 v/v). Rf (EtOAc:hexane 1:3 v/v) = 0.34 (UV). The NMR data of the title compound was in agreement with the literature reference.[186]

1,3-Dimethyl-5-(trifluoromethyl)pyrimidine-2,4(1H,3H)-dione (**3-24**)[188]



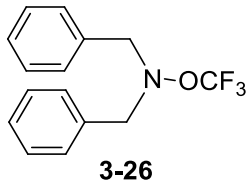
3-24

Colorless liquid (19 mg, 46 %) (Eluent, EtOAc:hexane, 1:3 v/v). Rf (EtOAc:hexane, 1:3 v/v) = 0.3 (UV). The NMR data of the title compound was in agreement with the literature reference.[188]

3.4.8. *O*-Trifluoromethylation of secondary hydroxylamines with **3-7**

General procedure: An 8 mL-glass vial was charged with a secondary hydroxylamine (0.4 mmol, 1.0 equiv) and **3-7** (1.25 equiv) under argon atmosphere and 1 ml of dry dichloromethane (DCM) was added. After five minutes of stirring, a solution of diisopropylethylamine (DIPEA) in 1 ml of dry DCM was added to the above reaction mixture over 1 minute and stirred further at room temp for 2 h. After that, 0.5 ml of sat. aq. $NaHCO_3$ was added into the reaction mixture and stirred for 10 minutes. The organic layer was separated, and the aqueous layer was extracted twice with DCM. The combined organic layer was dried over sodium sulfate, filtered, and evaporated under reduced pressure to get crude mass which was then purified by HPLC or flash chromatography to get the desired product.

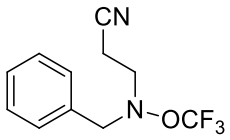
N,N-Dibenzyl-*N*-(trifluoromethoxy)amine (**3-26**)



3-26

Colorless oil (73 mg, 65%) (Eluent, 100 % acetonitrile, purified by Eazy-Prep HPLC). Rf (EtOAc:hexane, 0.5:10 v/v) = 0.41 (UV). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 (m, 10H), 4.07 (s, 4H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 135.14, 129.82, 128.36, 127.95, 62.40. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -63.30. The NMR data of the title compound was in agreement with the literature reference.[179]

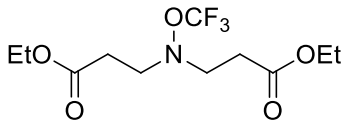
3-[*N*-Benzyl-*N*-(trifluoromethoxy)amino]propanenitrile (**3-47**)



3-47

Colorless oil (67 mg, 69 %) (Eluent, EtOAc:hexane 1:10 v/v). Rf (EtOAc:hexane 2:10 v/v) = 0.38 (UV). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 (tdd, *J* = 8.4, 5.4, 2.4 Hz, 5H), 4.22 (s, 2H), 3.06 (t, *J* = 7.0 Hz, 2H), 2.59 (t, *J* = 7.0 Hz, 2H).^{13}C NMR (100 MHz, Chloroform-*d*) δ 133.6, 129.6, 128.9, 128.6, 123.0 (q, *J* =257.9), 117.5, 64.47, 52.43, 15.98. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -63.35. The NMR data of the title compound was in accordance with the reference.[179]

Diethyl 3,3'-[(trifluoromethoxy)azanediyl]dipropanoate (**3-48**)



3-48

Colorless oil (90 mg, 75 %) (Eluent, EtOAc:hexane 2:10 v/v). Rf (EtOAc:hexane 3:10 v/v) = 0.5 (UV). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.15 (q, *J* = 7.1 Hz, 4H), 3.27 (t, *J* = 7.2 Hz, 4H), 2.61 (t, *J* = 7.2 Hz, 4H), 1.26 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.25, 122.78 (q, *J* = 256.8 Hz), 60.65, 54.47, 31.34, 14.04. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -62.82. The NMR data of the title compound was in accordance with the reference. [179]

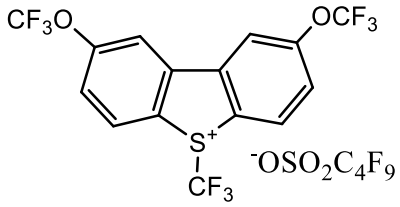
3.4.9. Preparation of trifluoromethyl nonaflate (NFTf, **3-27**) using **3-7**

Step 1: Preparation of S-(trifluoromethyl)-2,8-bis(trifluoromethoxy)dibenzothiophenium chloride **3-27**.

Into a solution of Bu_4NCl 13.35 g (43.9 mmol) in 40 mL of CH_3CN, was added a solution of triflate, **3-7** (25.0 g, 43.9 mmol) in 70 mL of CH_3CN portionwise (with a pipet) for 5 min under vigorous

stirring. After the reaction mixture was stirred for 3 h, the resulting precipitates were collected by filtration and washed with cold CH_3CN (10 mL x 2), giving 18.79 g (94%) of the product **3-27**. M.p. 189-190 ^oC (with decomposition) (recrystallized from CH_3CN). ^1H NMR (400 MHz, DMSO-d_6) δ 8.90 (d, J = 8.8 Hz, 2H), 8.75 (d, J = 2.5 Hz, 2H), 7.90 (d, J = 8.9 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.98, 142.64, 131.49, 128.93, 124.64, 124.11, 119.99 (q, J = 257 Hz), 119.60 (CF_3, q, J = 336 Hz)118.13. ^{19}F NMR (376 MHz, DMSO-d_6) δ -52.08 (s, CF_3), -56.26 (s, 2xOCF_3). HRMS (ESI method): Chemical Formula $C_{15}H_6ClF_9O_2S$ (M); theoretical mass for $(M\text{-}Cl)^+$: 420.9939. Found: 420.9940.

Step 2: Preparation of S-(trifluoromethyl)-2,8-bis(trifluoromethoxy)dibenzothiophenium nonaflate **3-28**.



3-28

A solution of 1.00 g (2.19 mmol) of chloride **3-27** in 6 mL of MeOH was added by one-portion into a stirred solution of $C_4F_9SO_3K$ (0.741 g, 2.19 mmol) in 4 mL of MeOH heated on an oil bath (60 ^oC) (Note: 1 mL of MeOH was used by washing the vessel and added to the reaction mixture). After the addition, the reaction mixture was continued to be stirred in the oil bath (60 ^oC) for 5 min and the reaction mixture was cooled to rt. The reaction mixture was evaporated using a rotary evaporator and 16 mL of water was added to the residue. Much solid formed. After the reaction mixture was stirred for 1 h, the solids were collected by filtration and washed with water (3 mL x 3) and then toluene (3 mL x 3) and dried, giving 1.41 g (89%) of the product, nonaflate **3-28**. M.p. 127-128 ^oC (recrystallized from CH_3CN/Et_2O). ^1H NMR (400 MHz, DMSO-d_6) δ 8.85 (d, J = 8.9 Hz, 2H), 8.79 (d, J = 2.5 Hz, 2H), 7.97 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.94, 143.15, 132.63, 126.07, 124.58, 123.32 (q, J = 330.2 Hz), 120.25 (q, J = 259.6 Hz), 118.56, 116.67 (d, J = 33.8 Hz), 116.27 (d, J = 21.5 Hz), 113.78 (q, J = 33.7, 33.1 Hz), 111.1-110.6 (m), 108.98 (d, J =

37.7 Hz). ^{19}F NMR ($CFCl_3$ in DMSO-d_6) -51.59 (3F, s, SCF_3), -56.34 (6F, s, 2xCF_3O), -80.03 (3F, t, J=10 Hz, CF_3), -114,37 (2F, br, CF_2), -120.93 (2F, br, CF_2), -125.23 (2F, t, J=13 Hz, CF_2). HRMS (ESI method): Chemical Formula $C_{19}H_6F_{18}O_5S_2$ (M); theoretical mass for $(M\text{-}C_4F_9SO_3)^+$: 420.9939. Found: 420.9940.

Step 3: Preparation of trifluoromethyl nonaflate (TFNf, **3-27**).

In a 20 mL-glass reactor connecting to a distillation apparatus, we placed 7.20 g (10 mmol) of nonaflate **3-28**. The reactor was heated up in an oil bath. The solid of **3-28** melted at 140 ^{o}C (oil bath temperature) and the thermolysis of **3-28** happened at 149 ^{o}C (oil bath). Most of the thermolysis of **3-28** completed soon. The oil bath was heated to 160 ^{o}C and then argon gas was flowed through the reactor slowly to effectively remove the product **3-27** into the collector (cooled on an ice bath). The weight of the obtained **3-27** was 3.48 g (95%). The NMR data of **3-27** was in accordance with those of the authentic sample.

Another product, 2,8-bis(trifluoromethoxy)dibenzothiophene **3-30** was left in the reactor. The yield of **3-30** was 3.47 g (99%). **3-30**: M.p. 93-95 ^{o}C (recrystallized from methanol). ^{1}H NMR (in $CDCl_3$) δ 7.95 (s, 2H), 7.85 (d, J=8.8 Hz), 7.38 (d, J=8.8 Hz). ^{19}F NMR (in $CDCl_3$, standard $CFCl_3$) δ -58.47 (s, CF_3O). ^{13}C NMR (100 MHz, Chloroform-*d*)) δ 146.88, 138.68, 135.86, 123.93, 120.88, 120.66 (q, *J* = 257.4 Hz),114.38. HRMS (EI method): Chemical Formula $C_{14}H_6F_6O_2S$ (M); Theoretical mass for M^+: 351.9993. Found: M^+ = 351.9989.

3.4.10. Reaction of 2,8-difluoro and -bis(trifluoromethoxy)dibenzothiophene **3-1** and **3-30** with triflic anhydride (Tf_2O)

Reaction of **3-1** with Tf_2O:

A typical procedure (run 4 in Table 1): Under an argon atmosphere, 1.10 g (5 mmol) of **3-1** was put in a pressure reactor (glassware) and then 1 mL of dry 1,2-dichloroethane, 0.89 mL (10 mmol) of dry benzene, and 1.7 mL (10 mmol) of Tf_2O were added. The reactor was sealed and stirred in an oil bath (50 ^{o}C) for 26 h. After the reaction mixture was stirred at room temperature

(rt) overnight (18 h), the reactor was opened. Toluene (12 mL) and then water (10 mL) were added to the reaction mixture cooled in an ice bath and then the mixture was stirred vigorously at ~~(~~rt~~)~~ overnight. The resulting precipitate was filtered and washed with toluene (5 mL x 3) to give 1.17 g (53%, crude) of crude **3-4**. The crude product was stirred in 5 mL of THF for 3 h, followed by filtration, giving 0.92 g (42%) of pure **3-4** (Umemoto reagent II).

Reaction of **3-30** with Tf_2O:

A typical procedure (run 3 in Table 2): Under an argon atmosphere, 0.704 g (2 mmol) of **3-30** was placed in a pressure reactor (glassware), and then 0.81 mL of dry chlorobenzene and1.0 mL (6 mml) of Tf_2O were added. The reactor was sealed and stirred in an oil bath (70 ^oC) for 48 h. After the reaction mixture was stirred at rt overnight (17 h), the reactor was opened. Toluene (8 mL) and then water (8 mL) were added to the reaction mixture cooled on an ice bath and then the mixture was stirred vigorously at rt for 5 h. The resulting precipitate was filtered and washed with water (3 mL) and then toluene (5 mL x 3) to give 0.433 g (38%, crude) of crude **3-30**. The purity was estimated to be around 87% in mol ratio. To get the pure product, the crude product needed to be purified by recrystallization or other methods.

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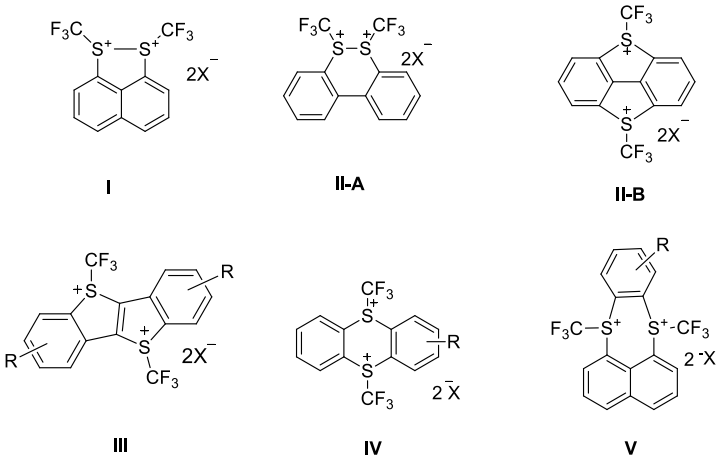
4.0. DESIGN AND ATTEMPTS TO SYNTHESIZE NEW DITHIADICATION-TYPE TRIFLUOROMETHYLATING AGENTS

4.1. Background

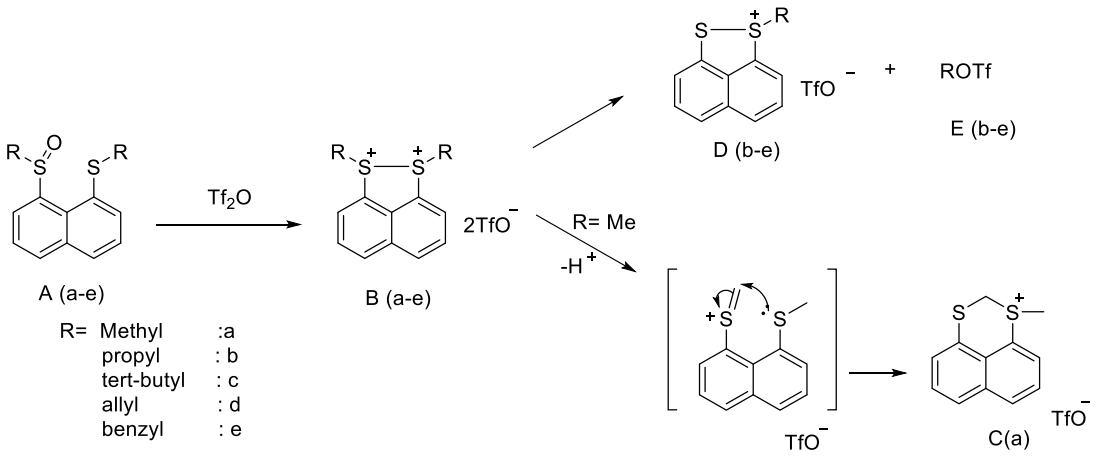
As described in the previous section, many kinds of electrophilic trifluoromethylating agents have been developed. However, these electrophilic trifluoromethylating agents still possess significant drawbacks such as low-atom economy and insufficient reactivity. To address this long-standing challenge associated with the electrophilic trifluoromethylating agents, we designed novel diCF_3 dithiadication-containing electrophilic trifluoromethylating agents **I–V** (Figure 8). We expected that these designed novel reagents could be powerful and could endow two transferable trifluoromethyl groups, in contrast to the existing trifluoromethylating agents, which transfer only a single trifluoromethyl group in a molecule, making the process of trifluoromethylation much more efficient than existing methods.

Figure 8. Novel diCF_3 dithiadication-containing electrophilic trifluoromethylating agents



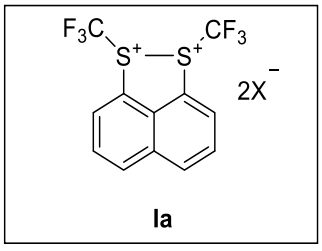
In hydrocarbon chemistry, there are some impressive reports of dialkyl dithiadication generation by Furukawa et al (Scheme 27).[189-192] These studies indicated that alkyl (R) cation species (except R=Me) were generated from the dithiadication (B) and combined with the counteranion TfO^- to form ROTf (E).

Scheme 27. Alkyl dithiadication (B) generation reported by Furukawa et al.



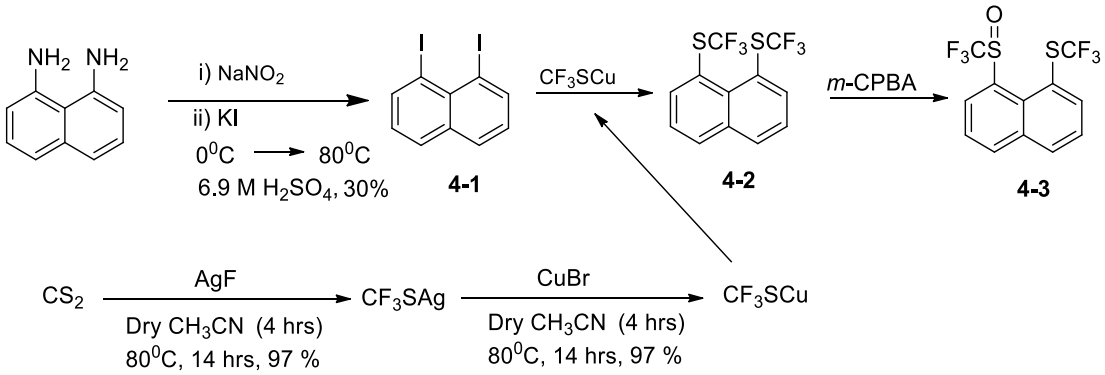
We adopted a similar approach for the synthesis of diCF_3 dithiadication-trifluoromethylating agents **I**. The lack of hydrogen on CF_3 group could lead to a highly reactive dithiadication equipped with two transferable trifluoromethyl groups, contrary to the existing trifluoromethylating agents with a single trifluoromethyl group. We expected dication **I** to be a unique CF_3 reagent of very high electrophilic reactivity and with high CF_3 content.

4.2. Attempt to synthesize 1,8-di(CF_3S)naphthalene dication **Ia**



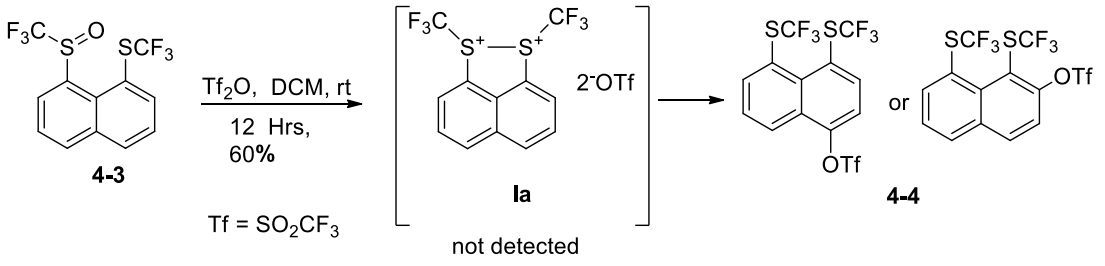
1,8-Diiodonaphthalene **4-1** was synthesized under the Sandmeyer reaction conditions (Scheme 28).[193] This compound was then reacted with CF_3SCu to deliver di(CF_3S)-substituted naphthalene **4-2**.[194] CF_3SCu was prepared in high yield by the reaction of CS_2 with AgF, followed by treatment with CuBr.[194] Disulfide **4-2** was subjected to oxidation to obtain mono-sulfoxide **4-3**, which is a precursor for aim-**Ia**.[195]

Scheme 28. Synthesis of precursor 4-3



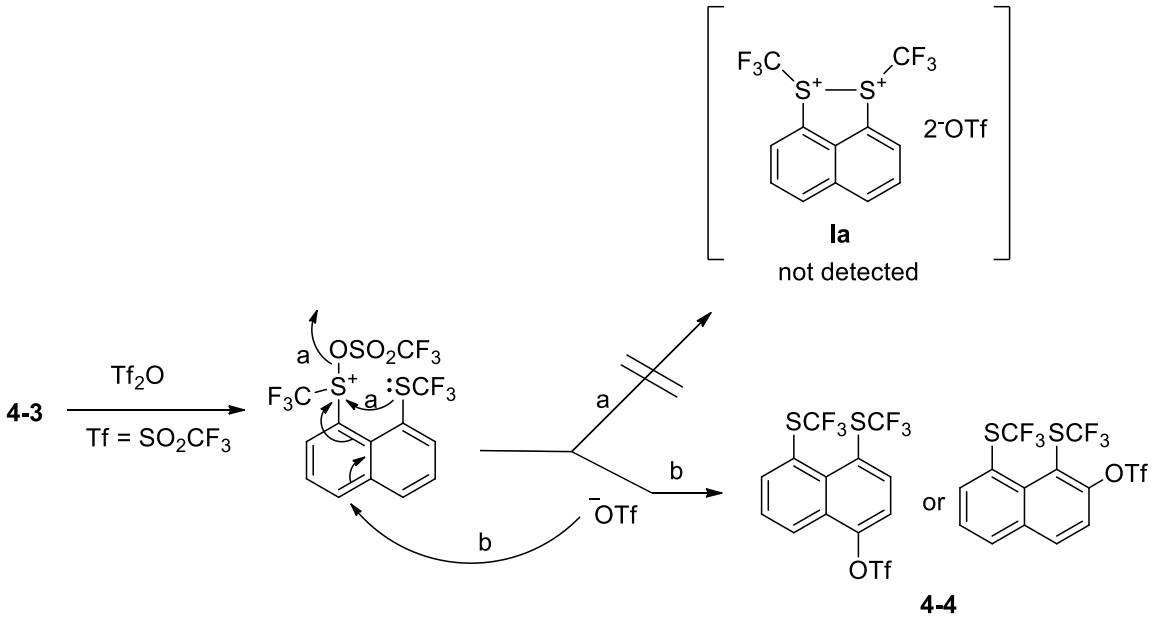
Mono-sulfoxide **4-3** was treated with triflic anhydride (Tf_2O) to obtain the desired **Ia**. Unfortunately, **Ia** was not detected during this experiment (Scheme 29). Instead, **4-4** was formed as a major product, which was isolated by column chromatography with up to 60% yield. We conducted ^{19}F NMR tracing experiment of the reaction of **4-4** with Tf_2O at -65 ^oC to room temperature. There were no peaks observed for **Ia**. The signals of **4-4** started to appear rapidly with a rise in temperature, leading eventually to the complete consumption of **4-3** (Refer experimental section, 5.9.13.).

Scheme 29. Attempt to synthesize 1,8-di(CF_3S)naphthalene dication Ia



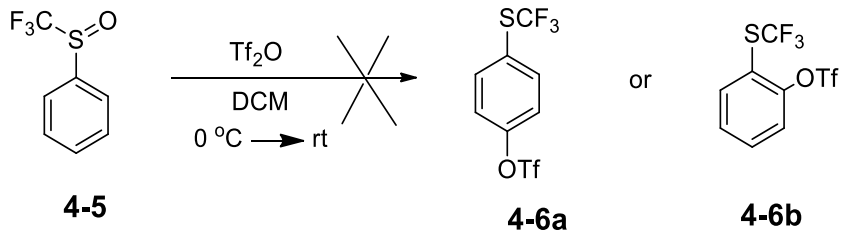
The structure of **4-4** was strongly suggested by NMR, GC-Mass analysis, and quantum calculations, although the final identification of the substitution position of OTf could not be made. Scheme 30 depicts our proposed mechanism for the formation of **4-4**.

Scheme 30. Proposed mechanism for the formation of 4-4



As shown in Scheme 31, we carried out the reaction of trifluoromethyl phenyl sulfoxide **4-5** with Tf_2O under the same conditions, but a reaction did not happen, and large amount of starting material remains unreacted. triflate **4-6a** or **4-6b** was not observed in this reaction.

Scheme 31. Control experiment to check the reactivity of the case of CF_3S-benzene ring

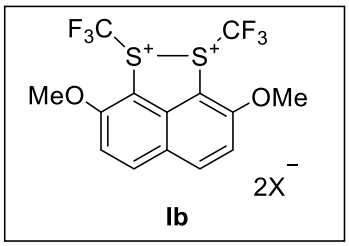


These results suggested that our proposed dication **Ia** was a highly unstable, reactive species, and that it was immediately transformed to **4-4**, probably, by attack of a triflate anion to the

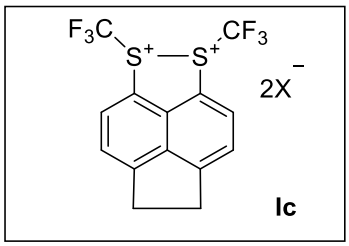
activated naphthalene ring (Scheme 30). Since the nucleophilicity of triflate anion is extremely low, this event implied an extraordinarily high reactivity of the dication **Ia**.

As Umemoto et al. have shown that the reactivity and stability of the CF_3S-cation-trifluoromethylating agents are greatly affected by the electronic nature of the aromatic ring substituents,[8,9] electron-donating substituents might increase the stability of the dication **Ia**. Therefore, we tried to synthesize the dithiadications **Ib** and **Ic** in which the 2- or 4-positions of the naphthalene ring are blocked with electron-donating substituents; this could reduce the reactivity of the naphthalene ring and prevent the triflate attack, eventually leading to the stabilization of the dithiadications.

4.3. Attempt to synthesize 2,7- and 4,5-disubstituted 1,8-di(CF_3S)-naphthalene dications **Ib** and **Ic**



Ib

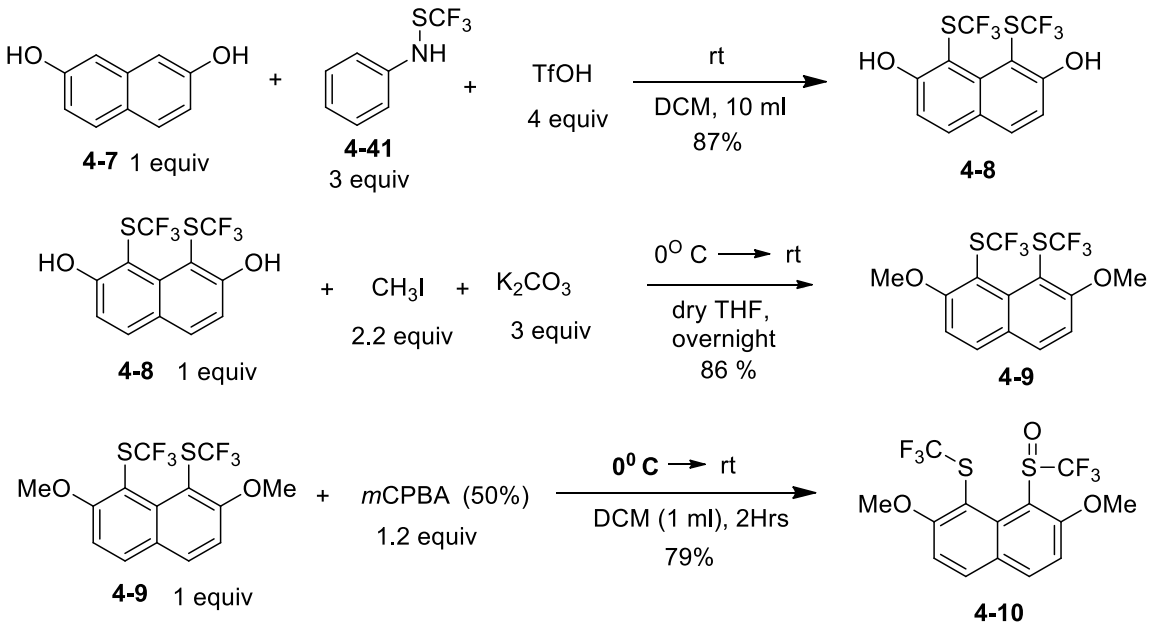


Ic

4.3.1. Preparation of precursor **4-10** and attempts to synthesize **Ib**

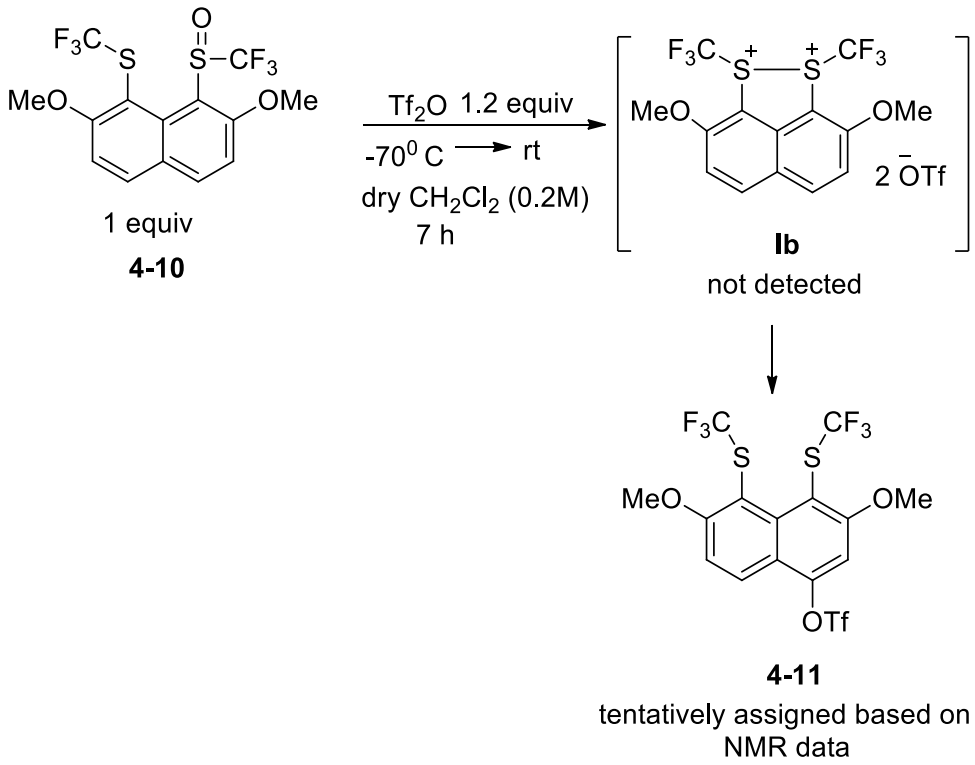
Precursor **4-10** for **Ib** was prepared from **4-7** (Scheme 32). According to the reported method,[10] 2,7-dihydroxynaphthalene **4-7** was bistrifluoromethylsulfenylated to give **4-8** in good yield, which was then dimethylated and oxidized to give precursor **4-10** in good yield.

Scheme 32. Preparation of precursor 4-10



Precursor **4-10** was treated with Tf_2O, similarly to **4-3** (Scheme 33). But, the expected **Ib** was not detected, instead compound **4-11** was obtained and its structural identification was made tentatively based on ^{1}H and ^{19}F NMR analysis. The fact that the expected 2,7-dimethoxy-dithiadication **Ib** was not detected and instead **4-11** was formed suggested the extreme instability and high reactivity of **Ib**. This result also confirmed that the electron-donating effect of 2,7-bis(methoxy) substituents was not sufficient to stabilize **Ib**.

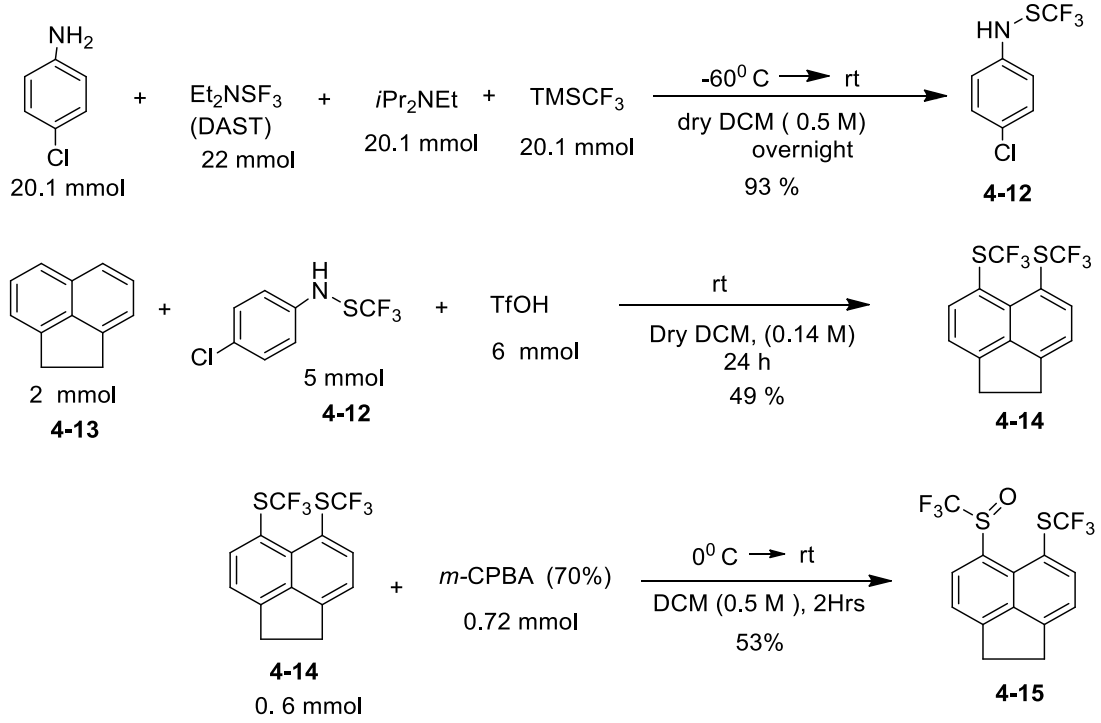
Scheme 33. Attempt to synthesize Ib



4.3.2. Preparation of precursor **4-15** and attempts to synthesize **Ic**

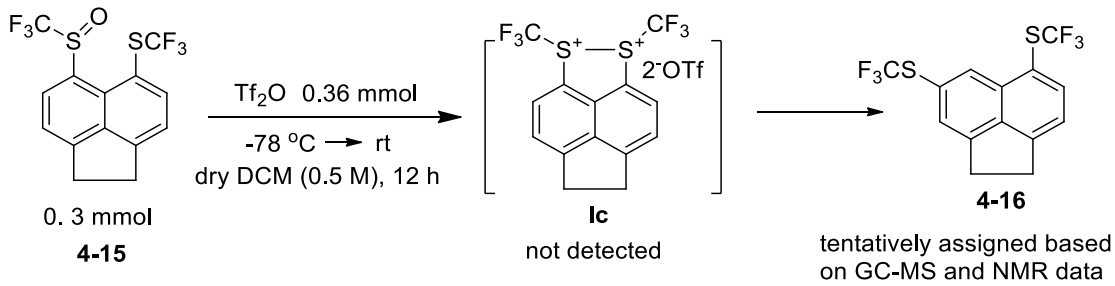
A synthetic route for precursor **4-15** is shown in Scheme 34. According to the reported method,[11] trifluoromethylsulfenylating reagent **4-12** was prepared in 93% yield. Acenaphthene **4-13** was treated with **4-12** to get bistrifluoromethylsulfenylated product **4-14** in 49% yield. **4-14** was then subjected to oxidation by *m*-CPBA to get precursor **4-15** in 53% yield.

Scheme 34. Preparation of precursor 4-15



As shown in Scheme 35, precursor **4-15** was treated with Tf_2O, similarly to **4-3** or **4-10**. The expected **Ic** was not detected, instead a new compound **4-16** was obtained. The structure of **4-16** was tentatively assigned by the analysis of GC-Mass and NMR data. We could not explain the mechanism for the formation of **4-16**. The fact that the acenaphthene dithiadication **Ic** was not detected suggested the extreme instability and high reactivity of **Ic**. This reaction validated that the electron-donating effect of the 4,5-ethylene substituent was not enough to stabilize **Ic**.

Scheme 35. Attempt of synthesis of Ic

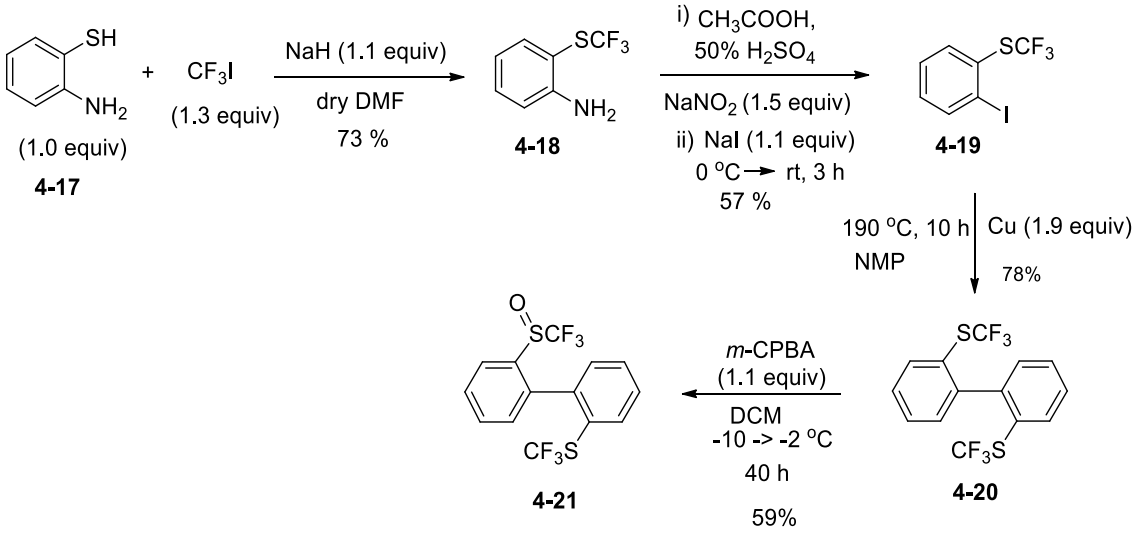


From the above results, we thought that the main reason of the instability of the dithadications **Ia-c** might be due to the high reactivity of the naphthalene nucleus. Therefore, next we tried to synthesize the dithiadications which do not have the naphthalene nucleus, as discussed below.

4.4. Attempt to synthesize 2,2'-di(CF_3S)biphenyl dication **II-A** and 5,5'-di(CF_3)-dibenzo[bc,fg][1,4]dithiapentalene dication **II-B**

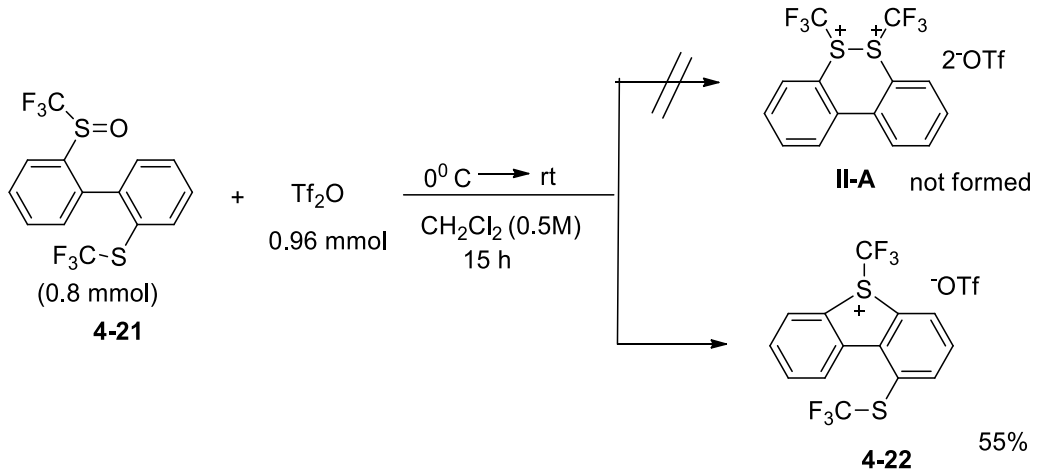
After several attempts, we figured out a successful synthetic route of precursor **4-21** needed to synthesize **II-A** (Scheme 36). 2-Mercaptoaniline **4-17** was treated with CF_3I to obtain trifluoromethylthio derivative **4-18** in 73% yield, which was then transformed to 2-(CF_3S)iodobenzene **4-19** in 57% yield by diazotizaton followed by treatment with NaI. **4-19** was dimerized by Cu to give the bis(CF_3S)biphenyl **4-20** in 78% yield, which was further oxidized with *m*-CPBA to produce the precursor **4-21** in 59% yield.

Scheme 36. Synthesis of precursor 4-21



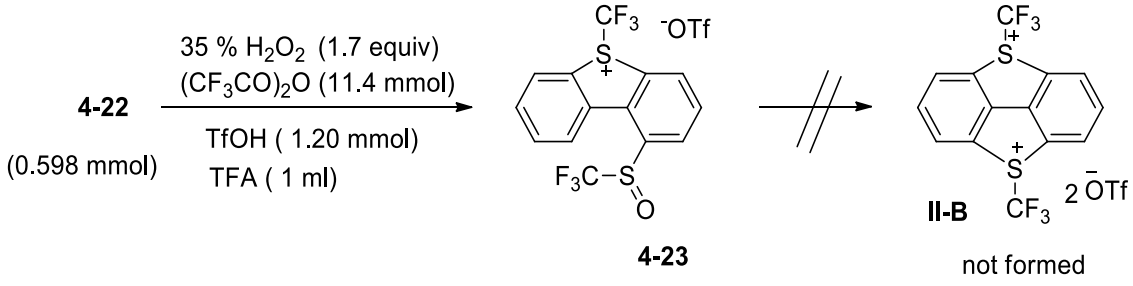
We tried to synthesize **II-A** as shown in Scheme 37. The treatment of 4-21 with Tf_2O provided salt **4-22**, but not II-A. The sulfonium intermediate reacted with the benzene ring, not with another S-CF_3, giving **4-22** as a stable salt in 55% yield.

Scheme 37. Attempt of synthesis of II-A

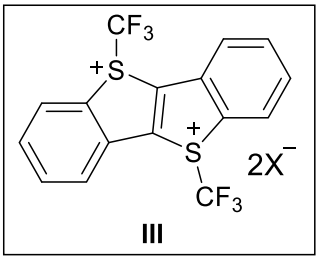


Then, we tried the synthesis of II-B as shown in Scheme 38. Salt **4-22** was oxidized with $H_2O_2/(CF_3CO)_2O$ to give sulfoxide **4-23**, which was then treated with Tf_2O. However, the last reaction did not happen. **II-B** was not formed. We thought that the main reason of the failure was the deactivation of the benzene ring by the strongly electron-withdrawing sulfonium moiety and the high strain of the expected product.

Scheme 38. Attempt of synthesis of II-B



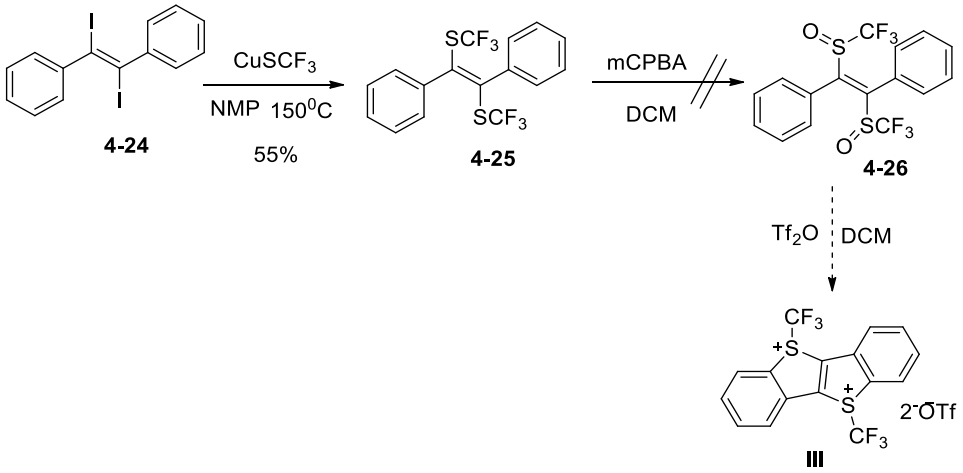
4.5. Attempt to synthesize 5,5'-di(CF_3)-dibenzothieno[3,2-b]thiophene dication **III**



III

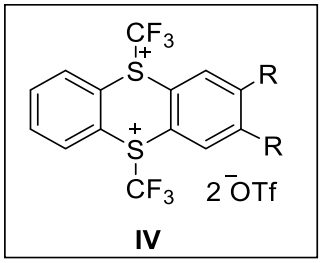
Next, we sought to synthesize another new system **III** in which dithiadication moieties are separated by a π-bond spacer (a vinylene unit). As shown in Scheme 39, we planned the synthesis of dication **III** from diiodide **4-24**.

Scheme39. Proposed plan for synthesis of dication III



We prepared **4-25** in 55% yield by the reaction of **4-24** with $CuSCF_3$. We then tried the oxidation of **4-25** with *m*-CPBA**.** However, the expected precursor **4-26** was not produced, probably, due to unexpected reactions of the vinylene unit. Therefore, we failed to synthesize **III**.

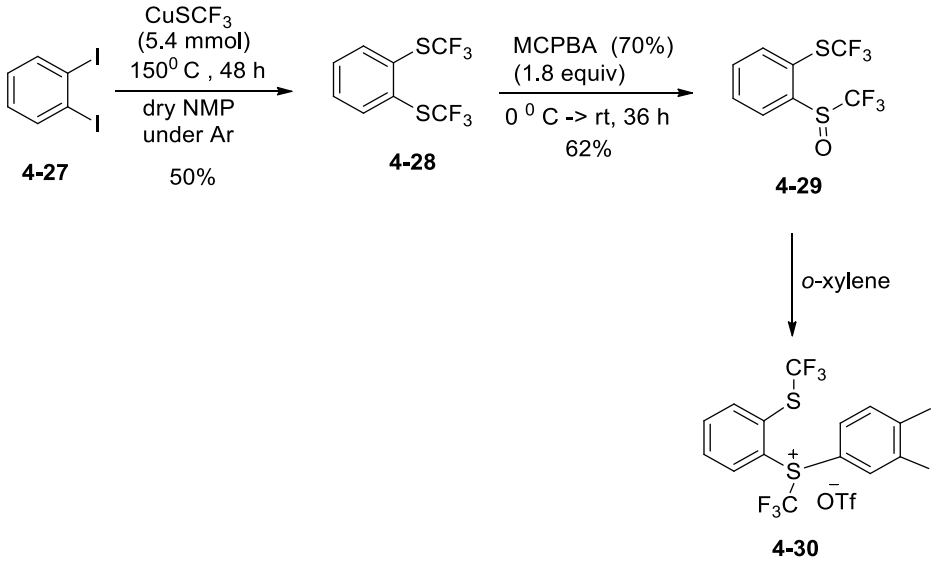
4.6. Attempt to synthesize di(CF_3S)dithianthrene dication **IV**



IV

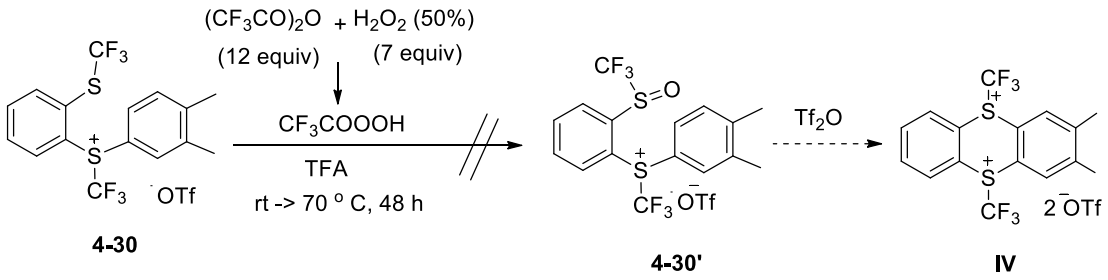
Next, we designed the di(CF_3)dithianthrene dication **IV** in which R=Me. We planned the synthesis of precursor **4-30** according to the reported procedure (Scheme 40).[12] 1,2-diiodobenzene **4-27** was reacted with $CuSCF_3$ to give 1,2-bis(CF_3S)benzene **4-28** in 50% isolated yield. Then, **4-28** was oxidized with *m*-CPBA to give sulfoxide **4-29** in 62% yield. We chose *o*-xylene rather than benzene or toluene for the condensation reaction with **4-29**, because *o*-xylene is more reactive than benzene or toluene. Sulfoxide **4-29** was reacted with *o*-xylene in the presence of triflic anhydride (Tf_2O) to produce **4-30** in 40% yield. We also tried the reaction of **4-29** with 1,3,5-trimethoxybenzene instead of *o*-xylene. However, the corresponding product was obtained in very low yield (10% by F-NMR). Therefore, it was not pursued further.

Scheme 40. Synthesis of precursor 4-30

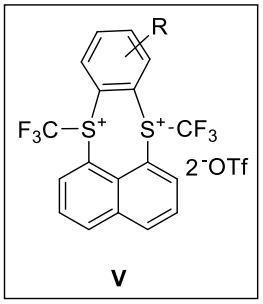


As shown in Scheme 41, the isolated **4-30** was treated with CF_3COOOH, derived from $(CF_3CO)_2O$ and 50% aq H_2O_2, in trifluoroacetic acid (TFA) at rt to 70 ^oC for a long time (48 h). However, the expected oxidation did not happen. Therefore, we abandoned the synthesis of **IV**.

Scheme 41. Attempt to synthesize **IV**

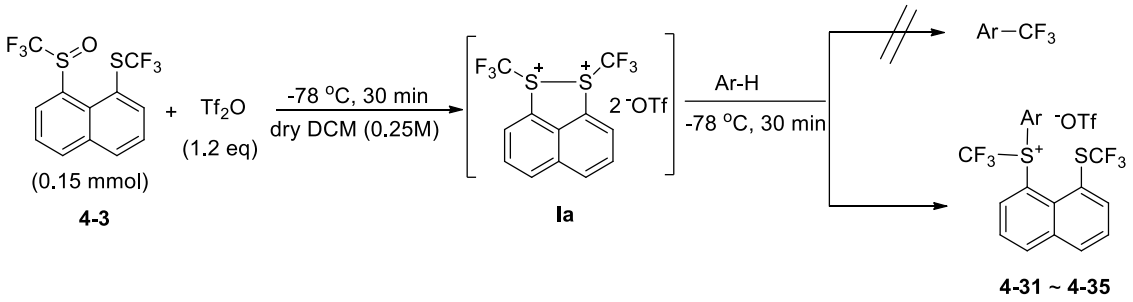


4.7. Attempt to synthesize di(CF_3S) dithiadication **V**



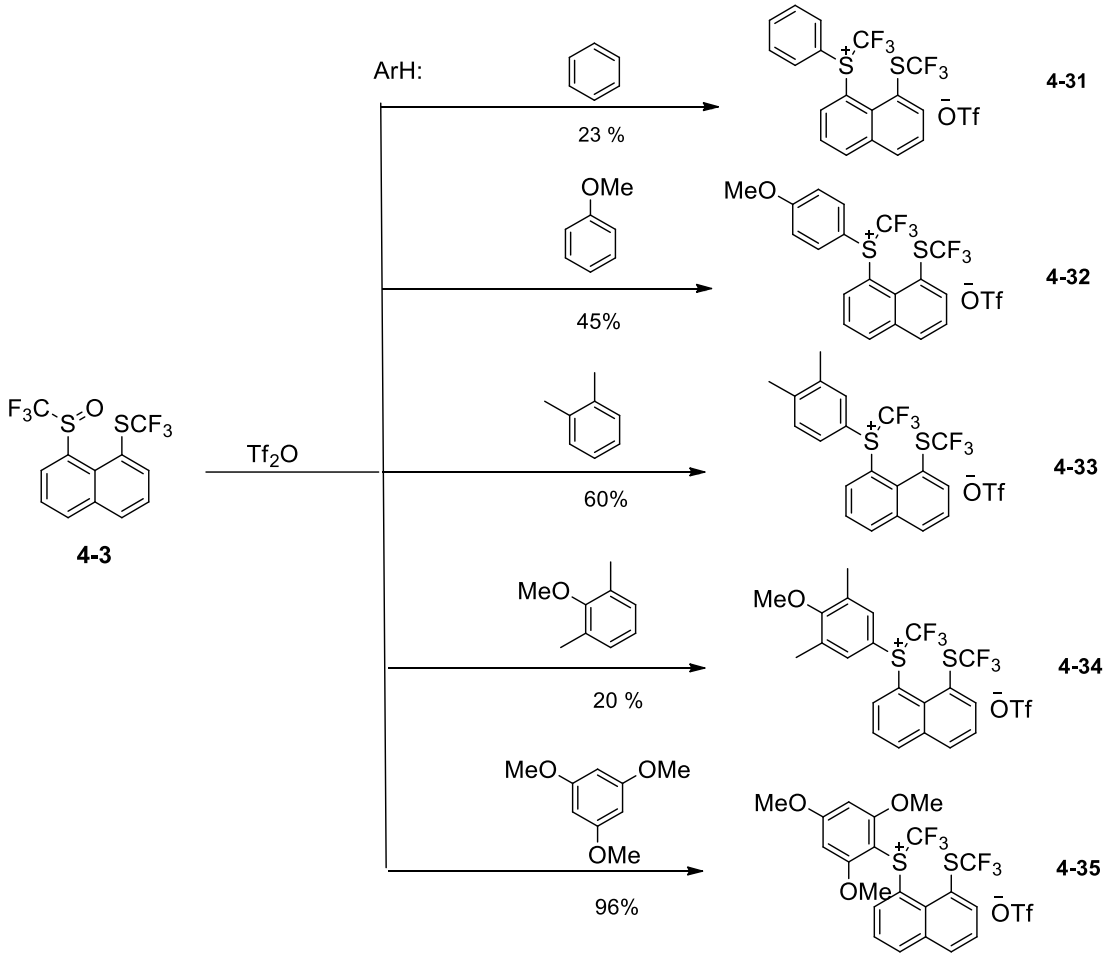
As described above, we failed to detect the 1,8-di(CF_3S)naphthalene dications **Ia-c**. As shown in Scheme 42, we treated **4-3** with Tf_2O in the presence of an aromatic compound to determine if trifluoromethylation of the aromatic compound may happen. But we found that, instead of the trifluoromethylation, the condensation with the aromatic compounds occurred to give sulfonium compounds **4-31** ~ **4-35**.

Scheme 42. Reactions of 4-3 with aromatics and Tf_2O



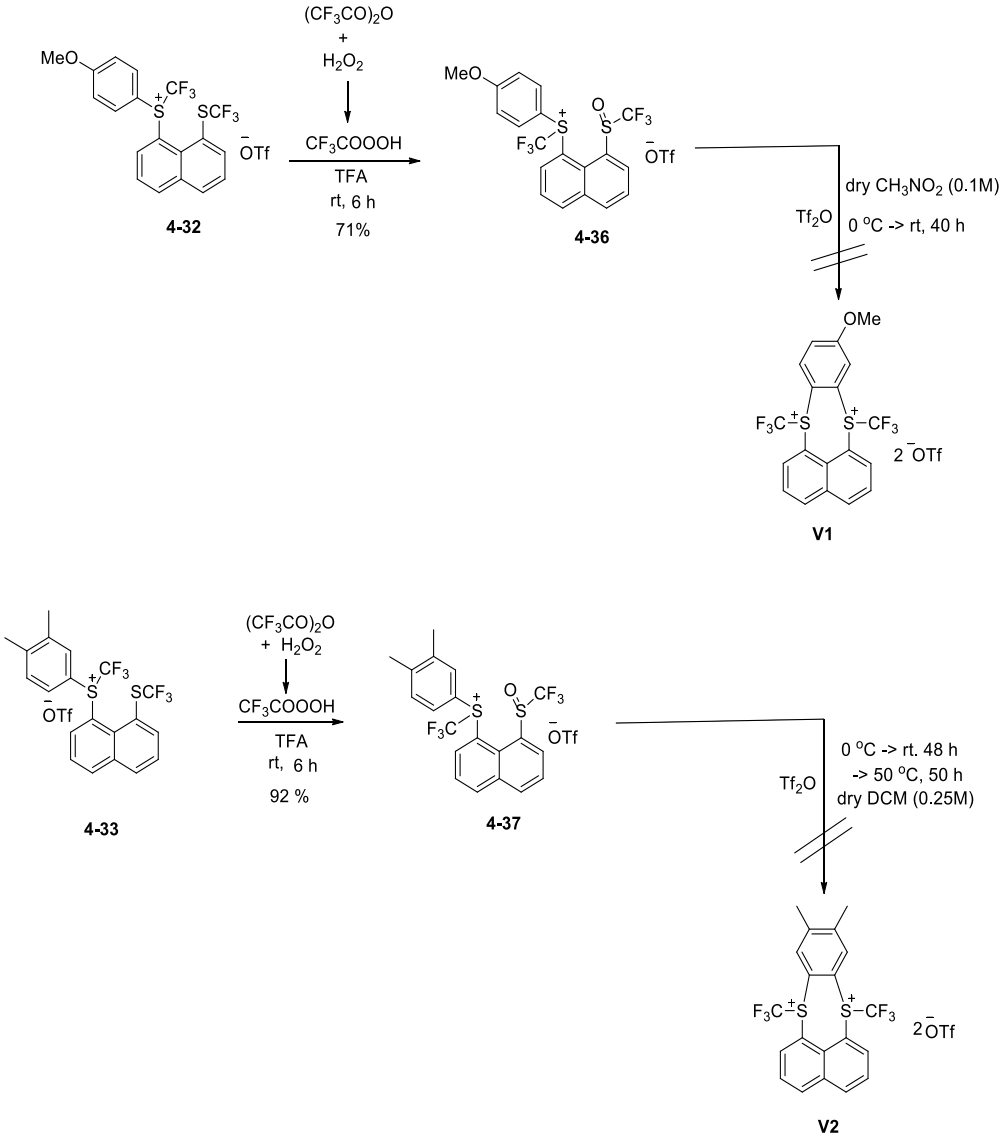
As shown in Scheme 43, we conducted the reactions using benzene, anisole, *o*-xylene, 2,6-dimethylanisole, and 1,3,5-trimethoxybenzene and obtained **4-31**, **4-32**, **4-33**, **4-34**, and **4-35** in 23, 45, 60, 20, and 96% yields, respectively. It is worth noting that the reaction with 1,3,5-trimethoxybenzene proceeded very smoothly, giving an excellent yield (96%) of **4-35.**

Scheme 43. Synthesis of sulfonium salts 4-31 to 4-35



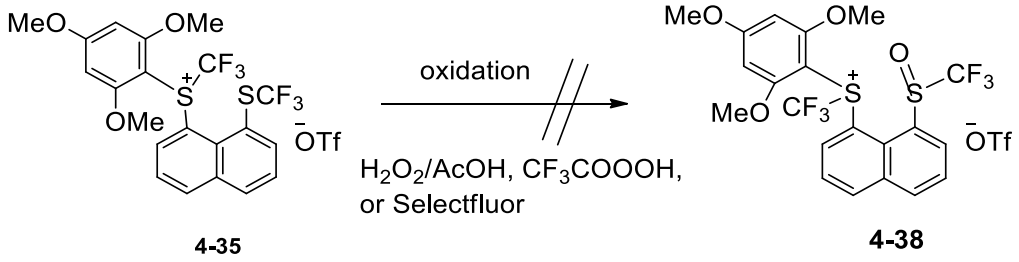
From these results, we designed dithiadications **V** and tried to synthesize them according to Scheme 44. Thus, **4-32** was oxidized with CF_3COOOH to give precursor **4-36** in 71% yield, which was then treated with Tf_2O. However, the expected **V1** was not obtained. Similarly, precursor **4-37** was synthesized in 92% yield and then treated with Tf_2O, but the expected **V2** was not obtained.

Scheme 44. Attempt of synthesis of V1 and V2



We tried to oxidize **4-35** with a different oxidizing agents such as H_2O_2/AcOH, CF_3COOOH, or Selectfluor, but expected outcome was not obtained (Scheme 45).

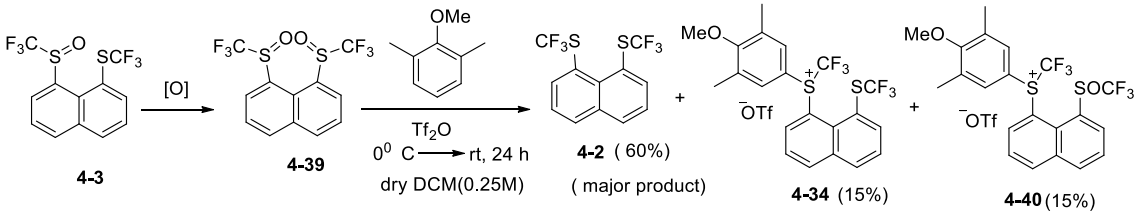
Scheme 45. Attempt to oxidize 4-35 with different oxidants



4-35 **4-38**

We then tried a different approach, the reaction of disulfoxide **4-39**, which was prepared from monosulfoxide **4-3**, with 2,6-dimethylanisole in the presence of Tf_2O as shown in Scheme 46. We did not detect the expected dithiadication product like **V**, but three products **4-2**, **4-34**, and **4-40**, formed in 60, 15, and 15% yields, respectively. It is worth noting that the major product was disulfide **4-2**, which was apparently the product resulting from the reduction of **4-39**. The mechanism for the formation of **4-2** is unclear. A unpredictable occurrence might have taken place in this reaction.

Scheme 46. Reaction of 4-39 with 2,6-dimethylanisole and Tf_2O



4-3 **4-39**

4.8. Conclusion

By developing CF_3S-based dithiadication trifluoromethylating agents, we wanted to address the pending issues associated with electrophilic trifluoromethylation of organic compounds. However, all attempts to synthesize them failed. However, our approaches and works could reveal many interesting reactions of bis(CF_3S) compounds and, thus, provide leads for new interesting and unpredictable chemistry of di(CF_3S) and their dication compounds.

Acknowledgement:

I greatly appreciate the efforts of Mr. Ryoya Takahashi (exchange student from the group of Professor Takahiko Akiyama, Gakushuin University) for performing the experiments to synthesize precursors **4-9** and **4-20**.

4.9. Experimental

4.9.1. General

^{1}H, ^{19}F, and ^{13}C NMR spectra were measured on 400, 376, and 100 MHz spectrometers, respectively. 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). CF_3COOH, $(CF_3CO)_2O$, CF_3SO_3H (TfOH), $(CF_3SO_2)_2O$ (Tf_2O) and other commercial reagents were used without further purification. Solvents like tetrahydrofuran (THF), dimethylformamide (DMF) acetonitrile (I), and dichloromethane (DCM) were dried by the standard methods.

4.9.2. Preparation of disulfides **4-2**, **4-25** and **4-28.**

Disulfides were prepared according to the reported literature procedures.[194,260-1]

4.9.3. Preparation of disulfides **4-20.**

A dry 2-necked flask with a magnetic stirrer was charged with iodide **4-19** (5.47 g, 18 mmol), Cu powder (2.17 g, 34.2 mmol) and *N*-methylpyrrolidinone (NMP) (4.17 Ml, 43.2 mmol), and the mixture was stirred under Ar gas in a 190℃ oil bath for 10 hrs. Then the reaction mixture was cooled to room temperature and diluted with ether and filtered through Celite. The filtrate was washed with brine, dried using Na_2SO_4, and filtered. The filtrate was evaporated, and the resulting residue was purified by column chromatography (only hexane) to get **4-20** (2.48 g) in 78% yield.

4.9.4. Preparation of mono-sulfoxides **4-3**, **4-10**, **4-15, 4-21**, and **4-29**.

Mono-sulfoxdes were prepared according to the reported literature procedures.[195]

4.9.5. Synthesis of **4-4**, **4-11**, or **4-16**

To an 8 ml dry reaction glass vial, sulfoxide **4-3**, **4-10** or **4-15** (0.3 to 0.5 mmol, 1 equiv) was added under argon. Dry dichloromethane (DCM) was added and stirred to get the clear solution (0.2 ~ 0.5 M). It was then cooled to -78 ^{o}C and triflic anhydride (Tf_2O) (1.2 equiv) was added in dropwise fashion to the above solution and stirred at same temperature for 30 minures. It was then allowed to warm to -40 ^{o}C, -30 ^{o}C and 0 ^{o}C succesively and the progress of reaction was monitored by ^{19}F NMR. Since the conversion of the starting sulfoxide was very slow, it was then allowed to stir at room temperature for 7 h to overninght. After the consumption of the sulfoxide, the reaction mixture was evaPOrated. the resuLTant residue was loaded over silica and purified over column chromatography to get **4-4**, **4-11**, or **4-16** in 60%, 44%, or 53% yield, respectively.

4.9.6. Experimental procedure in the attempt of synthesizing **II II A**

To an 8 ml dry reaction glass vial, sulfoxide **4-21** (0.8 mmol, 1 equiv) was added under argon, to which dry DCM was added and stirred to get the clear solution (0.5 M). It was then cooled to 0 ^{o}C and triflic anhydride (1.2 equiv) was added in dropwise fashion to the above solution and allowed to warm to room temperature and kept at room temperature for 15 h. After the consumption of the sulfoxide, the reaction mixture was evaporated. The resultant residue was washed with diethyl ether to get **4-22** in 55% yield.

4.9.7. Synthesis of the sulfonium precursors **4-31** to **4-35**

To an 8 ml dry reaction glass vial sulfoxide **4-3** (0.1 to 0.6 mmol, 1 equiv) was added under argon, to which dry DCM was added and stirred to get the clear solution (0.25 M). It was then cooled to -70 ^{o}C and Tf_2O (1.2 equiv) was added in dropwise fashion to the above solution and stirred at the same temperature for 30 min and then benzene, anisole, *o*-xylene, 2,6-

dimethylanisole or 1,3,5-trimethoxybenzene was added. It was then allowed to warm to room temperature and kept stirring overninght. After the consumption of the sulfoxide, the reaction mixture was evaporated. The resultant residue was washed with diethyl ether to get sulfonium compound **4-31**, **4-32**, **4-33**, **4-34**, or **4-35** in 23, 45, 60, 20, or 96% yield, respectively.

4.9.8. Preparation of *N*-(trifluoromethylthio)aniline **4-41**

A dried 2-necked vessel was successively charged under argon with diisopropylethylamine (DIPEA) (3.8 Ml, 21.8 mmol) and anhydrous DCM (44 Ml). The resulting mixture was cooled to -60 ºC before the addition of DAST (3.3 Ml, 24.2 mmol), followed by the addition of $TMSCF_3$ (3.8 Ml, 23.4 mmol) for 20 min. After being stirred for 1 h at -60 ºC, aniline (2 Ml, 22 mmol) was added at -60 ºC. The reaction mixture was then warmed up to room temperature and stirred for 40 h. After this period, the reaction mixture was quenched with 1M $NaHCO_3$ and three subsequent extractions were performed using DCM followed by a wash with brine. The organic phase was then dried with Na_2SO_4 followed by filtration. After evaporation of the solvent, the crude was purified by chromatography (Hex/DCM) to afford the desired product **4-41** in 96% yield. NMR data is in accordance with the literature.[196]

4.9.9. Preparation of 1,8-bis(trifluoromethylthio)-2,7-dimethoxynaphthalene **4-9**

1,8-Bis(trifluoromethylthio)-2,7-dihydroxynaphthalene **4-8** was prepared according to the literature.[197]

A solution of **4-8** (2.18 g, 6.05 mmol), CH_3I (1 Ml, 15.9 mmol), and K_2CO_3 (2.09 g, 15.1 mmol) in THF (20 Ml) was stirred for 16 h at room temperature. After this period, the mixture was quenched with aq NH_4Cl, followed by three subsequent extractions with ether, washing with brine, and drying with Na_2SO_4. The resulting product was purified by column chromatography (Hex/EtOAc). However, the product was not pure because some reaction intermediates were present. Therefore, the product was treated again with the same amounts of CH_3I and K_2CO_3 in THF and the mixture was stirred for 3 days. The reaction mixture was quenched with aq NH_4Cl,

followed by three subsequent extractions with ether, washing with brine, and drying with Na_2SO_4. The resulting product was purified by column chromatography (Hex/EtOAc) to give **4-9** in 86% yield. Recrystallization from hexane/EtOAc resulted in 1.554 g (4 mmol) (66%) of pure **4-9**.

4.9.10. Preparation of 2-(trifluoromethylthio)aniline **4-18**

Under argon atmosphere, NaH (60% in oil, 7.22 g, 24 mmol) was added portionwise to a solution of thiophenol **4-17** (16.7 Ml, 151 mmol) in 65 Ml of DMF on an ice bath, and the reaction mixture was stirred for 30 min. Next, CF_3I (42 g, 214 mmol) was dissolved in 100 Ml of DMF and the resulting CF_3I/DMF solution was added to the thiophenol solution. The mixture was then stirred for an additional 18 h at room temperature. The reaction mixture was diluted with water and three extractions with ether were performed. The combined organic layer was washed with brine and dried with Na_2SO_4. Upon filtration and evaporation of ether under reduced pressure, the crude product remained. The pure product **4-18** (8.21 g) was obtained in 73% yield by distillation of the crude product under reduced pressure: bp 110 ^oC/89 mmHg. *Note*: the condenser of the distillation apparatus was flowed by a little warm water, because the melting point of **4-18** was 31 ^oC.

4.9.11. Preparation of 2-(trifluoromethylthio)iodobenzene **4-19**

To a stirred mixture of AcOH (80 Ml) and 50% H_2SO_4 (60 Ml) cooled at 0 ^oC, was added **4-18** (21.8 g, 113 mmol). The reaction mixture was stirred for 15 min at 0 ^oC and then a solution of $NaNO_2$ (9.36 g, 136 mmol) in a minimal volume of water was added dropwise. The reaction mixture was stirred for 1 h at 0 ^oC and then allowed to warm to room temperature, where it was stirred for an additional 15 min, and then again cooled to 0 ℃. Then, a solution of NaI (18.7 g, 125 mmol) in water (17 Ml) was added. The reaction mixture was stirred for 30 min at 0 ^oC and then allowed to warm to room temperature. After 30 min, water was added. Three extractions with Et_2O were performed, and the combined organic layer was washed with water and then brine, and dried with Na_2SO_4. The reaction mixture was evaporated and the remaining residue was

purified by column chromatography (hexane) and then distilled under reduced pressure, giving the product **4-19** (19.5 g) in 57% yield: bp 120 ^{o}C/90 mmHg.

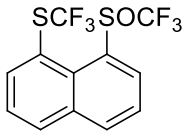
4.9.12. Physical and spectroscopic data of compounds

1,8-Bis[(trifluoromethyl)thio]naphthalene (**4-2**)

4-2

White solid (6.83 g, 83%). NMR data is in accordance with the literature.[198,]

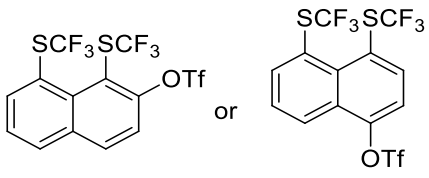
1-(Trifluoromethyl)-8-[(trifluoromethyl)sulfinyl]naphthalene (**4-3**)



4-3

White solid (5.53 g, 83%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.77 (d, *J* = 7.5 Hz, 1H), 8.19 (d, *J* = 8.2 Hz, 2H), 8.12 (d, *J* = 7.2 Hz, 1H), 7.84 (t, *J* = 7.8 Hz, 1H), 7.66 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 142.28, 135.95, 134.65, 134.02, 133.90, 133.36, 128.69 (q, *J* = 309 Hz)128.44, 126.58, 126.18, 125.88 (q, *J* = 337 Hz), 118.79. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -43.99 (s, SCF_3, 3F), -69.75 (s, $SOCF_3$, 3F),

1,8-Bis(thrifluoromethylthio)-2-(triflyloxy)naphthalene or 1,8-bis(trifluoromethylthio)-4-(triflyloxy)naphthalene (**4-4**)

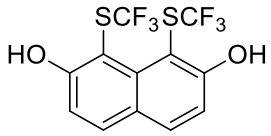


4-4

(Viscous solid, 125 mg, 53%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.33 (d, *J* = 8.5 Hz, 1H), 8.21 (d, *J* = 7.3 Hz, 1H), 8.12 (d, *J* = 8.3 Hz, 1H), 7.74 (m, 1H), 7.60 (d, *J* = 8.3 Hz, 1H).^{13}C NMR (100 MHz, Chloroform-*d*) δ 147.56, 140.93, 138.21, 137.28, 128.98 (q, *J* = 310.2 Hz), 127.92, 125.15,

123.24, 118.65 (q, *J* = 318.2 Hz). 117.98. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -42.69 (s, SCF_3,3F), -42.79 (s, SCF_3, 3F), -73.23 (s, SO_2CF_3, 3F) .

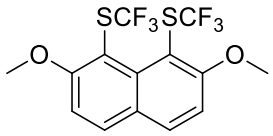
1,8-Bis[(trifluoromethyl)thio]-2,7-dihydroxynaphthalene (**4-8**)[197]



4-8

Colorless oil (2.18 g , 86%).^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 (m, 2H), 6.66 (m, 2H), 3.94 (s, 2H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -44.50 (s, SCF_3, 6F),

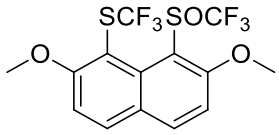
2,7-Dimethoxy-1,8-bis(trifluoromethylthio)naphthalene (**4-9**)



4-9

Colorless oil (1.554 g, 86%).^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.90 (d, *J* = 9.0 Hz, 1H), 7.23 (d, *J* = 9.0 Hz, 1H), 4.04 (s, 3H).

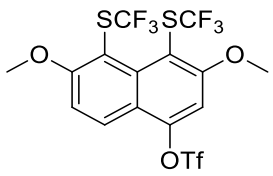
2,7-Dimethoxy-1-(trifluoromethylthio)-8-[(trifluoromethyl)sulfinyl]naphthalene (**4-10**)



4-10

Colorless oil (110 mg , 44%).Colorless oil (342 mg , 79%).^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.97 (dd, *J* = 9.0, 6.2 Hz, 2H), 7.26 (d, *J* = 1.4 Hz, 1H), 7.24 (d, *J* = 2.4 Hz, 1H), 4.13 (s, 3H), 4.06 (s, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -44.44 (s, SCF_3, 3F), -60.86(s, $SOCF_3$, 3F).

2,7-Dimethoxy-1,8-bis[(trifluoromethyl)thio]-4-(triflyloxy)naphthalene (**4-11**)



4-11

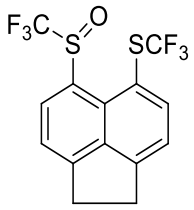
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.16 (d, *J* = 9.4 Hz, 1H), 7.36 (d, *J* = 9.3 Hz, 1H), 7.23 (s, 1H), 4.08 (s, 3H), 4.05 (s, 3H).^{19}F NMR (376 MHz, Chloroform-*d*) δ -42.81 (s, SCF_3), -42.83 (s, SCF_3, 3F), -72.99(s, Otf, 3F).

5,6-Bis[(trifluoromethyl)thio]acenaphthene (**4-14**)

4-14

White solid (347 mg , 49%).^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.01 (d, *J* = 7.3 Hz, 2H), 7.40 (d, *J* = 7.3 Hz, 2H), 3.46 (s, 4H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -43.34 (s, SCF_3, 3F).

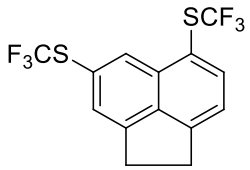
5-[(Trifluoromethyl)thio]-6-[(trifluoromethyl)sulfinyl]acenaphthene (**4-15**)



4-15

White solid (112 mg , 53%).^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.63 (d, *J* = 7.6 Hz, 1H), 8.02 (d, *J* = 7.2 Hz, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 7.2 Hz, 1H), 3.54 (s, 4H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -44.11 (s, SCF_3, 3F), -71.25 (s, $SOCF_3$, 3F).

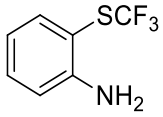
5,7-Bis[(trifluoromethyl)thio]acenaphthene (**4-16**)



4-16

(Eluent, 100% Hexane; Rf (EtOAc:hexane 1:10 v/v) = 0.61 (UV).^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.41 (s, 1H), 7.93 (d, *J* = 7.3 Hz, 1H), 7.57 (s, 1H), 7.41 (d, *J* = 7.2 Hz, 1H), 3.47 (s, 4H), 2.16 (d, *J* = 1.3 Hz, 16H), 2.00 (d, *J* = 1.4 Hz, 12H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -42.37 (s, SCF_3, 3F), 42.59 (s, SCF_3, 3F). GC-MS (ESI) *m*/*z* calcd for $C_{14}H_{18}F_6S_2$, 353.9972; found ,354.1

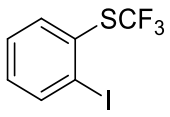
2-[(Trifluoromethyl)thio]aniline (**4-18**)



4-18

Colorless oil (8.21 g , 73%).^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.47 (ddd, *J* = 7.8, 1.1, 0.6 Hz, 1H), 7.27 (m, 1H), 6.75 (m, 2H), 4.47 (s, 2H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -42.84 (s, SCF_3, 3F).

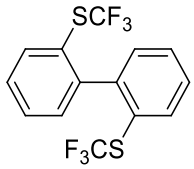
2-[(Trifluoromethyl)thio]iodobenzene (**4-19**)



4-19

Colorless oil (19.5 g , 57%).^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.80 (m, 1H), 7.41 (td, *J* = 7.6, 1.4 Hz, 1H), 7.14 (ddd, *J* = 8.0, 7.4, 1.6 Hz, 1H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -42.17(s, SCF_3, 3F).

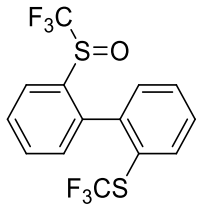
2,2'-Bis[(trifluoromethyl)thio]-1,1'-biphenyl (**4-20**)



4-20

Colorless oil (2.48 g, 78%).^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.81 (d, *J* = 7.8 Hz, 2H), 7.55 (m, 2H), 7.48 (m, 2H), 7.34 (d, *J* = 7.5 Hz, 2H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -42.22 (s, SCF_3, 3F).

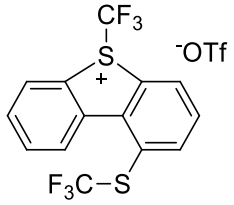
2-[(Trifluoromethyl)thio]-2'-(trifluoromethylsulfinyl)-1,1'-biphenyl (**4-21**)



4-21

White solid (333 mg , 53%).^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.21 (dd, *J* = 6.6, 3.0 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.72 (m, 2H), 7.57 (m, 2H), 7.33 (m, 2H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -41.17 (s, SCF_3, 0.6 F), -41.68 (s, SCF_3, 2.4F), -72.45 (s, $SOCF_3$, 0.6 F), 72.52 (s, $SOCF_3$, 2.4F).

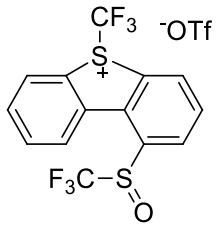
5-(Trifluoromethyl)-1-[(trifluoromethyl)thio]-5H-dibenzo[b,d]thiophen-5-ium triflate (**4-22**)



4-22

White solid (363 mg , 90%).^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 9.33 (m, 1H), 8.63 (d, *J* = 8.1 Hz, 1H), 8.48 (d, *J* = 8.1 Hz, 1H), 8.38 (d, *J* = 7.9 Hz, 1H), 8.16 (td, *J* = 7.9, 1.2 Hz, 1H), 7.98 (m, 2H). ^{19}F NMR (376 MHz, Acetonitrile-d_3) δ -43.09 (s, SCF_3, 3F), -53.41 (s, SCF_3, 3F), -79.38 (s, Otf, 3F).

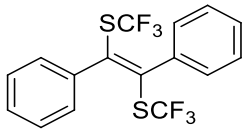
5-(Trifluoromethyl)-1-[(trifluoromethyl)sulfinyl]-5H-dibenzo[b,d]thiophen-5-ium triflate (**4-23**)



4-23

White solid (180 mg , 59%).^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.71 (q, J = 8.0, 7.4 Hz, 2H), 8.46 (m, 2H), 8.14 (dt, J = 17.7, 7.9 Hz, 2H), 7.97 (t, J = 7.9 Hz, 1H). ^{19}F NMR (376 MHz, Acetonitrile-d_3) δ -52.59 (s, SCF_3, 1.3 F), -53.02 (s, SCF_3, 1.7 F), -73.37 (s, $SOCF_3$, 1.3 F), -73.61 (s, $SOCF_3$, 1.7 F), -79.37 (s, Otf, 3F).

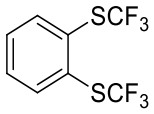
I-1,2-Diphenyl-1,2-bis[(trifluoromethyl)thio]ethene (**4-24**)



4-24

White solid (500 mg , 55 %).^{1}H NMR (400 MHz, Chloroform-d) δ 7.55 (m, 4H), 7.36 (dd, J = 5.3, 2.1 Hz, 6H). ^{19}F NMR (376 MHz, Chloroform-d) δ -39.09 (s, SCF_3, 3F).

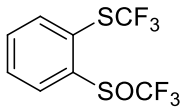
1,2-Bis[(trifluoromethyl)thio]benzene (**4-28**)



4-28

Colorless oil (124 mg , 50%).^{1}H NMR (400 MHz, Chloroform-d) δ 7.87 (dd, J = 5.8, 3.5 Hz, 2H), 7.54 (dd, J = 5.9, 3.5 Hz, 2H). ^{19}F NMR (376 MHz, Chloroform-d) δ -41.87 (s, SCF_3, 6F).

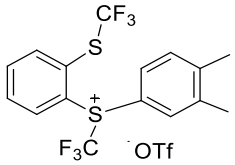
1-(Trifluoromethyl)-2-[(trifluoromethyl)sulfinyl]benzene (**4-29**)



4-29

Viscous oil (80 mg , 62%).^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.20 (d, *J* = 9.0 Hz, 1H), 7.85 (dt, *J* = 7.3, 3.6 Hz, 2H), 7.74 (m, 1H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -42.07 (s, SCF_3, 3F), -72.12 (s, $SOCF_3$, 3F).

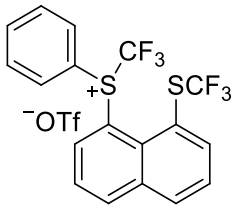
(3,4-Dimethylphenyl)(trifluoromethyl)[2-(trifluoromethylthio)phenyl]sulfonium triflate (**4-30**)



4-30

White solid (53 mg , 40 %).^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.33 (m, 1H), 8.24 (m, 1H), 8.12 (m, 2H), 7.80 (d, *J* = 8.2 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 1H), 2.42 (s, 3H), 2.38 (s, 3H). ^{19}F NMR (376 MHz, Acetonitrile-d_3) δ -42.86 (s, SCF_3, 3F), -48.66(s, SCF_3, 3F), -79.53 (s, Otf, 3F).

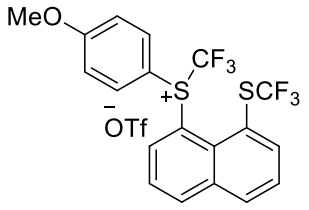
Phenyl(trifluoromethyl)[8-(trifluoromethylthio)-1-naphthyl]sulfonium triflate (**4-31**)



4-31

White solid (80 mg , 23 %).^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.60 (d, *J* = 8.2 Hz, 1H), 8.49 (d, *J* = 7.8 Hz, 1H), 8.39 (d, *J* = 7.0 Hz, 1H), 8.23 (d, *J* = 7.3 Hz, 1H), 8.05 (d, *J* = 8.1 Hz, 2H), 7.98 (t, *J* = 8.0 Hz, 1H), 7.89 (m, 1H), 7.79 (m, 3H). ^{19}F NMR (376 MHz, Acetonitrile-d_3) δ -45.97 (s, SCF_3, 3F), -48.47 (s, SCF_3, 3F), -79.35 (s, Otf, 3F).

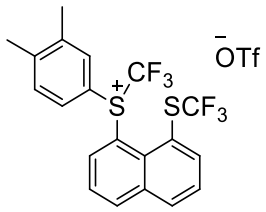
(4-Methoxyphenyl)(trifluoromethyl)[8-(trifluoromethylthio)-1-naphthyl)sulfonium triflate (**4-32**)



4-32

White solid (40 mg, 45%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.78 (s, 1H), 8.51 (s, 1H), 8.32 (d, *J* = 8.1 Hz, 1H), 8.25 (d, *J* = 7.1 Hz, 1H), 8.16 (s, 3H), 7.82 (t, *J* = 7.5 Hz, 1H), 7.35 (s, 2H), 3.96 (s, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -44.34 (s, SCF_3, 3F), -48.39 (s, SCF_3, 3F), -78.25 (s, Otf, 3F).

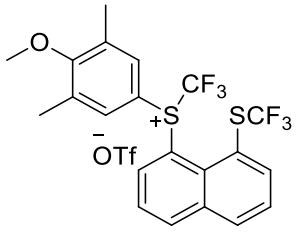
(3,4-Dimethylphenyl)(trifluoromethyl)[8-(trifluoromethylthio)-1-naphthyl]sulfonium triflate (**4-33**)



4-33

White solid (52 mg, 60%).^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.74 (d, *J* = 7.7 Hz, 1H), 8.52 (d, *J* = 8.1 Hz, 1H), 8.31 (d, *J* = 8.1 Hz, 1H), 8.25 (d, *J* = 7.2 Hz, 1H), 8.19 (t, *J* = 8.0 Hz, 1H), 7.88 (m, 2H), 7.81 (m, 1H), 7.59 (d, *J* = 8.1 Hz, 1H), 2.44 (m, 6H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -44.77 (s, SCF_3, 3F), -47.75 (s, SCF_3, 3F), -78.40 (s, Otf, 3F).

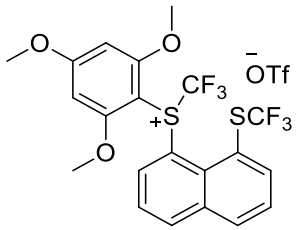
(4-Methoxy-3,5-dimethylphenyl)(trifluoromethyl)[8-(trifluoromethylthio)-1-naphthyl]sulfonium triflate (**4-34**)



4-34

White solid (12 mg, 20%).^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.74 (d, *J* = 7.8 Hz, 1H), 8.52 (d, *J* = 8.2 Hz, 1H), 8.32 (d, *J* = 8.2 Hz, 1H), 8.22 (q, *J* = 7.8 Hz, 2H), 7.80 (d, *J* = 5.5 Hz, 3H), 3.83 (s, 3H), 2.42 (s, 6H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -44.84 (s, SCF_3, 3F), -47.73 (s, SCF_3, 3F), -78.36 (s, Otf, 3F).

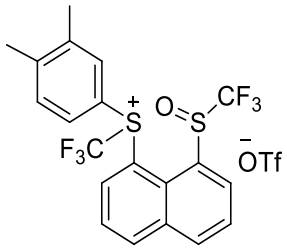
(Trifluoromethyl)[8-(trifluoromethylthio)-1-naphthyl](2,4,6-trimethoxyphenyl)sulfonium triflate(**5-35**)



4-35

Light pink solid (286 mg, 45%).^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.60 (d, *J* = 7.9 Hz, 1H), 8.49 (dd, *J* = 8.2, 1.1 Hz, 1H), 8.35 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.21 (d, *J* = 7.3 Hz, 1H), 8.04 (t, *J* = 8.0 Hz, 1H), 7.79 (m, 1H), 6.38 (s, 2H), 3.99 (s, 3H), 3.93 (s, 6H).^{19}F NMR (376 MHz, Chloroform-*d*) δ -44.73 (s, SCF_3, 3F), -47.64 (s, SCF_3, 3F), -78.36 (s, Otf, 3F).

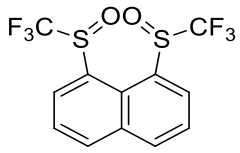
(3,4-Dimethylphenyl)(trifluoromethyl)[8-(trifluoromethylsulfinyl)-1-naphthyl]sulfonium triflate (**4-37**)



4-37

White solid (50 mg, 92%).^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.28 (d, *J* = 7.7 Hz, 1H), 9.02 (d, *J* = 7.7 Hz, 1H), 8.81 (d, *J* = 7.5 Hz, 1H), 8.74 (t, *J* = 8.1 Hz, 2H), 8.68 (d, *J* = 8.1 Hz, 1H), 8.51 (t, *J* = 7.6 Hz, 3H), 8.41 (t, *J* = 7.9 Hz, 1H), 8.06 (t, *J* = 7.8 Hz, 2H), 7.99 (m, 3H), 7.71 (dd, *J* = 11.5, 8.2 Hz, 2H), 2.51 (s, 3H), 2.49 (s, 3H), 2.47 (s, 3H), 2.44 (s, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -48.39 (s, SCF_3, 1.46F) , -48.63 (d, *J* = 2.6 Hz, s, SCF_3, 1.54F), -67.67 (s, $SOCF_3$, 1.46F), -68.29 (d, *J* = 2.8 Hz (s, $SOCF_3$, 1.54F), -78.30 (s, Otf, 3F).

1,8-Bis[(trifluoromethyl)sulfinyl]naphthalene (**4-39**)

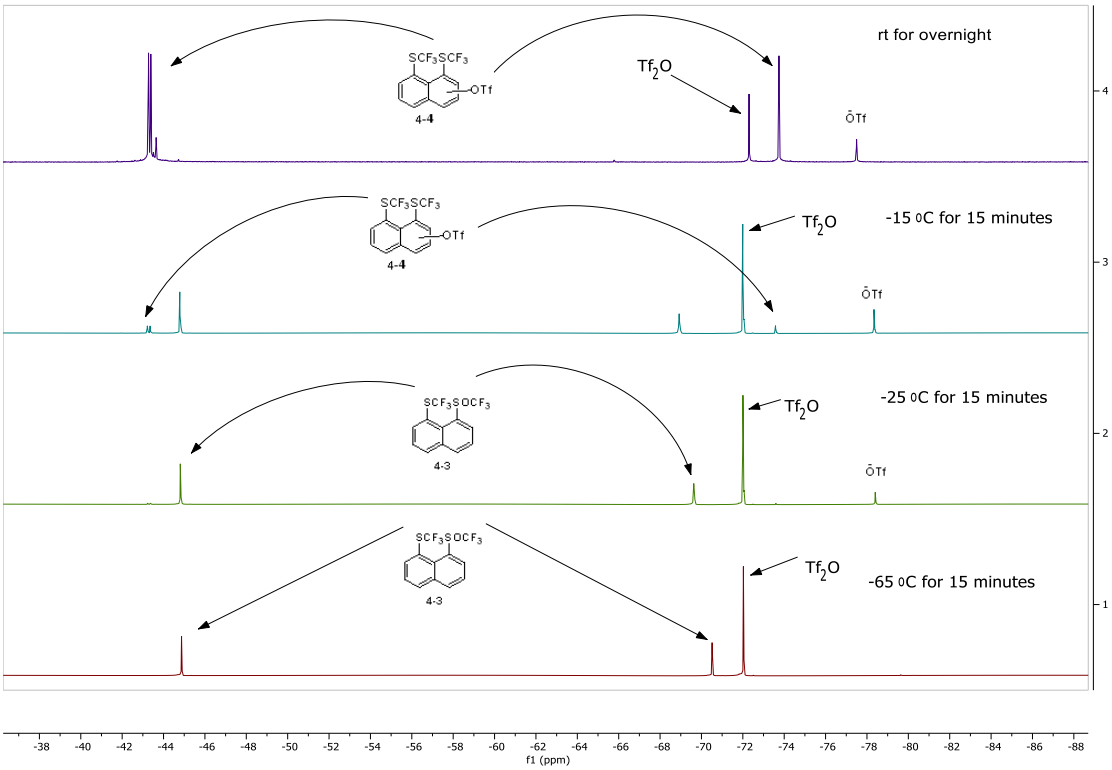


4-39

White solid (336 mg, 62%).^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.74 (d, *J* = 7.5 Hz, 2H), 8.35 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.94 (m, 2H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -70.54 (s, $SOCF_3$, 6F).

4.9.13. ^{19}F NMR tracing experiment of the reaction of **4-3** with Tf_2O

A dry NMR tube was charged with **4-3** (0.06 mmol, 1 equiv), and 0.5 ml of dry CD_2Cl_2 was added to it. The NMR tube was shaken well to completely dissolve **4-3** and then it was placed in an NMR spectrometer at -65 ^{0}C for 10 minutes. This was followed by slow addition of Tf_2O (0.072 mmol, 1.2 equiv) to the NMR tube and ^{19}F NMR spectrum was recorded after 15 minutes. The temperature was raised by 5 ^{0}C after every 15 minutes followed by NMR measurements. NMR spectra was recorded until the temperature reached to 25 ^{o}C. The conversion of the starting material **4-3** was initiated around -25 ^{0}C, producing **4-4** in trace amount. The amount of **4-4** increased with an increase in temperature. Eventually **4-3** was consumed completely producing **4-4** as the major product. No signs of **Ia** was observed during this study. The NMR analysis of this study at selected temperatures is shown below.



5.0. GOLD(I/III)-CATALYZED TRIFLUOROMETHYLTHIOLATION AND TRIFLUOROMETHYLSELENOLATION OF ORGANOHALIDES

5.1. Background

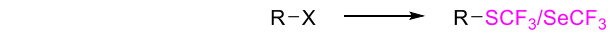
After exploring the novel applications of HCl•DMPU in the nitrile synthesis as described in chapter 2, we continued our efforts in finding novel applications of the other halogenating agents, such as $AgSCF_3$ and Me_4NseCF_3 in the trifluoromethylthiolation (-CF_3S) and trifluoromethylselenolation (-CF_3Se) of organic halides using Au pre-catalyst (MeDalphos)AuCl. CF_3S and CF_3Se are of significant interest[14-16] because of their inherently high Hansch lipophilicity parameters (CF_3S: π_R = 1.44, CF_3Se: π_R = 1.29) vs. (CF_3O: π_R = 1.04, CF_3: π_R = 0.88, F: π_R = 0.14)[17] and strong electron-withdrawing effects (Hammett constants CF_3S: σ_p = 0.50, CF_3Se: σ_p = 0.45) vs. (CF_3O: σ_p = 0.35, CF_3: σ_p = 0.54, F: σ_p = 0.06)[18]. The unique Hansch parameters of CF_3S and CF_3Se offer enhanced lipophilicity to the bioactive molecules, whereas their electron-withdrawing properties and considerable steric hindrance provide additional metabolic stability to the molecules containing these fluorinated groups. No wonder, synthetic methodologies that introduce SCF_3 and $SeCF_3$ are being actively chased.[15-16, 37, 199-202]. In this context, the direct trifluoromethylthiolation and trifluoromethylselenolation of organohalides with palladium,[66, 203-204] nickel,[75-76, 205-206] and copper[55, 207-208] have been most successful (Scheme 13 A)

[2]

[2] This work was published prior to the dissertation. Mudshinge, S. R.; Yang, Y.; Xu, B.; Hammond, G. B.; Lu, Z., *Angew. Chem.Int. Ed.* **2022,** *61* (12), e202115687

Scheme 47. Au(I)/Au(III)-catalyzed C-SCF_3/$SeCF_3$ coupling reactions.

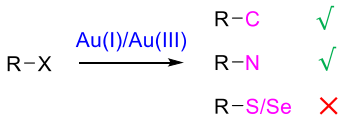
A. Transition metal-catalyzed direct trifluoromethyl- thiolation/selenolation:



	previous work			this work	
R−X	Pd	Co	Cu*	Au	• *Wide substrates scope*
Aryl halide	√	√	√	√	• *Mild reaction condition*
Alkenyl halide	×	×	√	√	• *Good to excellent yield*
Alkynyl halide	×	×	√	√	• *Scalable* • *> 60 examples*
					• *High functional group compability*

*stoichiometric catalyst, high temperature

B. Au(I)/Au(III)-catalyzed C-X coupling triggered by MeDalPhos ligand:



Despite their gains, palladium, nickel, and copper-based methods suffer from harsh reaction conditions (high temperature, air, or moisture-sensitivity), high catalyst loading and limited substrate scope. An even more debilitating drawback is that none of these metals can single-handedly catalyze the synthesis of aryl, alkenyl, and alkynyl trifluoromethylthio- and selenoethers. Palladium and nickel have been reported only for the synthesis of aryl trifluoromethylthio- and selenoethers. Although copper catalyzed protocols are used beyond the synthesis of aryl trifluoromethylthio- and selenoethers, it suffers from use of stoichiometric amount of copper with a ligand at very high temperatures.[14-16]

Our goal is to develop a 'one-stop shop' synthesis of aryl/alkenyl/alkynyl trifluoromethylthio-and selenoethers using gold catalysis. Even though gold-catalysis have made significant advances in the construction of C-C and C-X bonds, progress in gold-catalyzed cross-coupling reactions has been hampered by the difficulty in promoting oxidative addition to organohalides.[209] To overcome this hurdle, strong external oxidants or an aryl diazonium salt as an electrophile to form the active Au(III)-Ar intermediates have been reported, but these strategies have resulted in the restricted

number of compatible coupling partners and reduced functional group tolerance.[210-213] Recently, Bourissou and co-workers reported that a hemilabile (P,N) ligand (MeDalPhos) triggered the key oxidative addition of aryl/alkynyl/alkenyl halides to gold(I) under ambient conditions.[214-218] The resulting active gold (III) complex enabled C-C,[214-215] and C-N,[217, 219] cross-coupling reactions under mild conditions. However, the Au-catalyzed reactions of organosulfur compounds is a tough task as they are known for their catalyst poisoning and highly aurophilic properties. Although there are reports of the stoichiometric gold-mediated cysteine bioconjugation[220] and hybrid nanocluster construction[221], gold-catalyzed C-S/Se cross-couplings are still elusive (Scheme 13 B)

5.2. Results and discussion

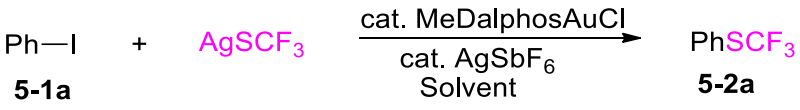
Our initial emphasis was the conversion of aryl halides to the corresponding $ArSCF_3$. We chose phenyl iodide **5-1a** as the model substrate in conjunction with the Au pre-catalyst (MeDalphos)AuCl (Table 4). We selected $AgSCF_3$ as the nucleophilic SCF_3 source due to its stability and easy availability. Furthermore, as a silver salt, it can also serve as a gold pre-catalyst activator, eliminating the need for additional silver activators.

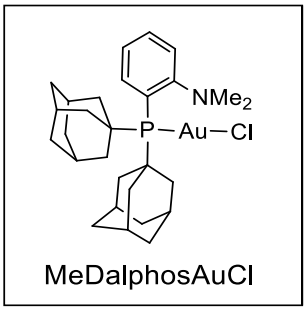
The reaction was conducted in dichloroethane at rt for 24 hours and delivered the trifluoromethylthiolated **5-2a** in 80% yield with 20% starting material remaining (entry 2). Pronounced effects of polarity of solvents were observed as the reaction did not proceed when a polar solvent like acetonitrile or dimethylformamide were utilized (see experimental section, 3.4.2.1. for more details). A significant counterion effect was observed during the silver activator screening because the silver activator with lower gold affinity[222-224] counterion exhibited faster kinetics[217, 225] (see entries 5, 6, and 7, SbF_6^- >BF_4^- >NTf_2^-). The screening of silver activators revealed that 0.2 equivalent of $AgSbF_6$ gave the highest conversion (entry 5 *vs.* entry 8). A 5 mol% of gold pre-catalyst was optimal as the reaction yield decreased dramatically with lesser amounts (entry 5 vs. entry 9). Concentration (0.2 M) was also crucial (compare entry 1 vs. entries 10, 11). Control experiments revealed that both the gold catalyst and the silver activator were crucial (entries 12, 13, 14). The reaction without silver activator was sluggish (entry 13), and only

gave a 23% yield of product after 24 hours. This result indicated that $AgSCF_3$ could activate the gold pre-catalyst, albeit at a much slower rate than $AgSbF_6$ (entry 13). The reaction with exclusion of gold catalyst did not proceed at all, even after 30 hours (entry 14). However, when the gold pre-catalyst was introduced to the reaction mixture, the reaction resumed and was completed in 2 hours with full conversion. After extensive reaction condition screenings, we found that reacting 0.2 mmol of phenyl iodide **5-1a** with 5 mol% of (MeDalphos)AuCl pre-catalyst, 1.05 equiv of $AgSCF_3$, and 0.2 equiv of $AgSbF_6$ in 1 Ml dichloroethane (DCE) gave the best yield of the desired product **5-2a** (entry 15). It should be noted that when another nucleophilic SCF_3 reagent like Me_4NSCF_3 was utilized, the reaction gave a lower yield (entry 16, see the experimental section, 3.4.2.1.for more details)).

With the optimized reaction conditions in hand, we explored the reaction scope for the trifluoromethylthiolation of aryl halides. The reaction furnished trifluoromethylthiolated products in good to excellent yields (Table 4). Aryl iodides with diverse functionalities such as ethers (**5-2b** to **5-2d**, **5-2n, 5-2bb to 5-2dd**), halides (**5-2e** to **5-2g** and **5-2cc**), ketones (**5-2j**, **5-2x**, **5-2cc**), aldehyde (**5-2k**), nitro (**5-2l**, **5-2dd**), nitrile (**5-2m**), esters (**5-2p**), amine (**5-2q**), phenol (**5-2r**), carboxylic acids (**5-2s**, **5-2cc**), triflate (**5-2t**), amide (**5-2dd**), and medicinally important fluorine functionalities (**5-2n**,**5-2o**) were well-tolerated. An important feature of our protocol is that it tolerated both acidic (**5-2s**,**5-2cc**) and basic (**5-2q**) functional groups, which is unprecedented with other transition metal catalysts. Both electron-rich and electron-deficient aromatic iodides, as well as a polyaromatic (**5-2 v**), were efficiently converted in good yields. The reactions with electron-rich aryl iodides were faster than with their electron-withdrawing counterparts (**5-2b** vs. **5-2e**, **5-2j**, and **5-2m**,). *Ortho*-substituted aryl iodides gave a decreased yield vis-à-vis *para-/meta*-substituted derivatives (**5-2d** vs. **5-2b**, **5-2c**). The potential of this strategy in multiple trifluoromethylthiolation was highlighted with polyiodoarenes when two CF_3S groups were installed in high yield in just one step when 1,8-diiodonaphthalene was employed (**5-2v**).

Table 4. Reaction condition optimization for Au(I)/Au(III)-catalyzed trifluoromethylation of phenyl iodide[a]





Entry	Deviation	Yield (**5-2a**, %)[b]
1	no	95
2	rt, 24 h	80
3	0.5 Ml THF as solvent, rt, 24 h	2
4	0.5 Ml CH_3CN as solvent, rt, 24 h	0
5	0.2 equiv $AgSbF_6$, 60 °C, 1h	80
6	0.2 equiv $AgBF_4$, 60 °C, 1h	57
7	0.2 equiv $AgNTf_2$, 60 °C, 1h	42
8	0.1 equiv $AgSbF_6$, 60 °C, 1h	31
9	2 mol% MeDalPhosAuCl, 60 °C, 1h	32
10	0.25 Ml DCE, 70 °C	88
11	1 Ml DCE, 70 °C	90
12[c]	No MeDalPhosAuCl, No $AgSbF_6$, 70 °C, 1 h	0
13[d]	No $AgSbF_6$, 70 °C, 1 h	1
14[e]	No MeDalPhosAuCl, 70 °C, 30 h	0
15	Scaled up with 0.2 mmol **5-1a**, 1h	100
16[f]	Me_4NSCF_3 was used instead of $AgSCF_3$	81

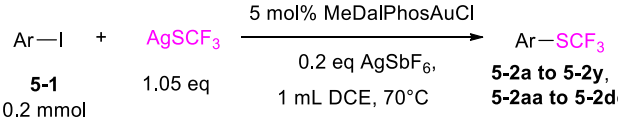
[a]Conditions: Unless otherwise noted, reactions were conducted as follows: An 8-Ml reaction vial was loaded with MeDalPhosAuCl (5 mol%), $AgSCF_3$ (1.05 equiv) and 0.5 Ml DCE. PhI (0.1 mmol) was added, and the resulting mixture was stirred at rt for 1 min. $AgSbF_6$ (0.2 equiv) was then added, and the reaction was stirred at rt for 1 min before stirring at 70 °C for 1 h. [b]Yields were determined by GC. [c]24 h, 0% yield; [d]24 h, 23% yield; [e]when 5 mol% Au was re-introduced, the reaction gave 100% yield in 2 h. [f] Me_4NSCF_3 (0.2 equiv) and $AgSbF_6$ (1.2 equiv) were applied.

Moreover, this strategy worked excellently with heteroaryl iodides substrates, including thiophene (**5-2w**), furan (**5-2x**), and pyridine (**5-2y**), producing the corresponding trifluoromethylthiolates in

very good yields. These results highlighted the mild conditions and excellent functional group tolerance of our methodology. Additionally, our protocol also showed high chemo selectivity as the trifluoromethylthiolation only occurred at the C(sp^2)-I site, leaving other common coupling sites, such as bromide (**5-2g**), chloride (**5-2f**), triflate (**5-2t**), boronic ester (**5-2u**) intact. Particularly, the selective trifluoromethylthiolation of C(sp^2)–I over C(sp^2)–Br is noteworthy because differentiation of C–I versus C–Br is a significant challenge that has eluded other transition metal-catalysis (for any type of bond formation). These intact coupling sites provide useful handles for orthogonal functionalization.

Our protocol provides a reliable synthetic tool for the late-stage modification of drug molecules, as evidenced by the smooth conversion of **5-2cc** and **5-2dd** in the high yields. For example, the trifluoromethylthiolated fenofibric acid (**5-2cc**) was obtained in a 95% isolated yield. Fenofibric acid is used to reduce cholesterol and fatty substance levels in the blood. Although various functionalities were tethered to the fenofibric acid (e.g., chloride, ketone, ether, and carboxylic acid) these remained intact using our mild protocol. Recently, it was found that fenofibric acid could reduce Covid-19 infections by up to 70%. Considering its extensive history of clinical use and relatively good safety profile, fenofibric acid derivatives might become potential therapeutic agents to treat SARS-CoV-2 infections.[226] A similar outcome was observed in the reaction with nimesulide (**5-2dd**), a nonsteroidal anti-inflammatory drug repurposed for Covid-19 infection treatment,[227] which was converted to the corresponding product in 92% isolated yield These examples further authenticate that our trifluoromethylthiolation protocol is suitable for the late-stage, protecting-group-free modification of bioactive molecules. The scalability and robustness of this protocol was further evaluated using 1 mmol of aryl iodide **5-1aa** (430 mg) and a lesser amount of gold pre-catalyst (2.5 mol%). The corresponding product **5-2aa** was obtained in excellent yield (92%) without requiring precautions, albeit a longer reaction time of 6 h was necessary.

Table 5. Substrate scope of trifluoromethylthiolation of aryl Halides[a,b]

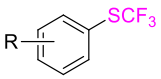


5-1
0.2 mmol

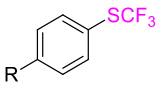
1.05 eq

5-2a to 5-2y,
5-2aa to 5-2dd

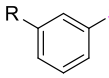
Aryl idodides with various functionalities:



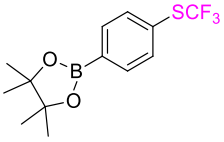
5-2a, R = H, 1 h, 61% (95%)[c]
5-2b, R = 4-MeO, 1.5 h, 92% (96%)[c]
5-2c, R = 3-MeO, 1.5 h, 90% (95%)[c]
5-2d, R = 2-MeO, 1.5 h, 79% (82%)[c]
5-2e, R = 4-F, 7 h, (91%)[c]
5-2f, R = 4-Cl, 4 h, 87% (91%)[c]
5-2g, R = 4-Br, 4 h, 91% (97%)[c]



5-2h, R = t-Bu, 0.75 h, 92% (96%)[c]
5-2i, R = Ph, 2 h, 93%
5-2j, R = Acetyl, 3 h, 91% (97%)[c]
5-2k, R = CHO, 1.5 h, 90% (100%)[c]
5-2l, R = NO_2, 24 h, 67%
5-2m, R = CN, 24 h, 85% (100%)[c]
5-2n, R = OCF_3, 8 h, 62% (93%)[c]
5-2o, R = CF_3, 2 h, (100%)[c]



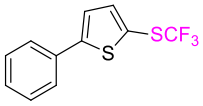
5-2p, R = COOMe, 4 h, 87% (93%)[c]
5-2q, R = NH_2, 19 h, 80% (86%)[c]
5-2r, R = OH, 1 h, 92% (98%)[c]
5-2s, R = COOH, 10 h, 93% (100%)[c]
5-2t, R = OTf, 19 h, 87% (99%)[c]



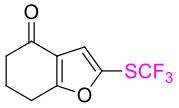
5-2u, 6 h,90% (100%)[c]

5-2v, 1 h, 92%[d]

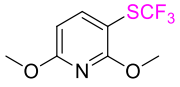
Heteroaryl iodides :



5-2w, 2 h, 96%

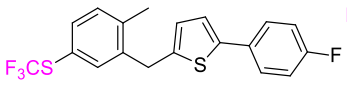


5-2x, 3 h, 95%

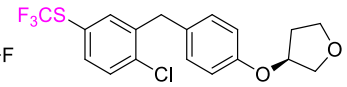


5-2y, 1.5 h, 86%

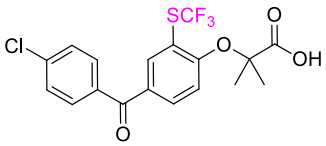
late-stage modification of bioactive molecules:



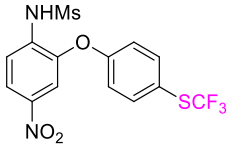
Canagliflozin intermediate
5-2aa, 1 h, 93%[e]



Empagliflozin intermediate
5-2bb, 6 h,92%



From Fenofibric acid
5-2cc, 2 h, 95%

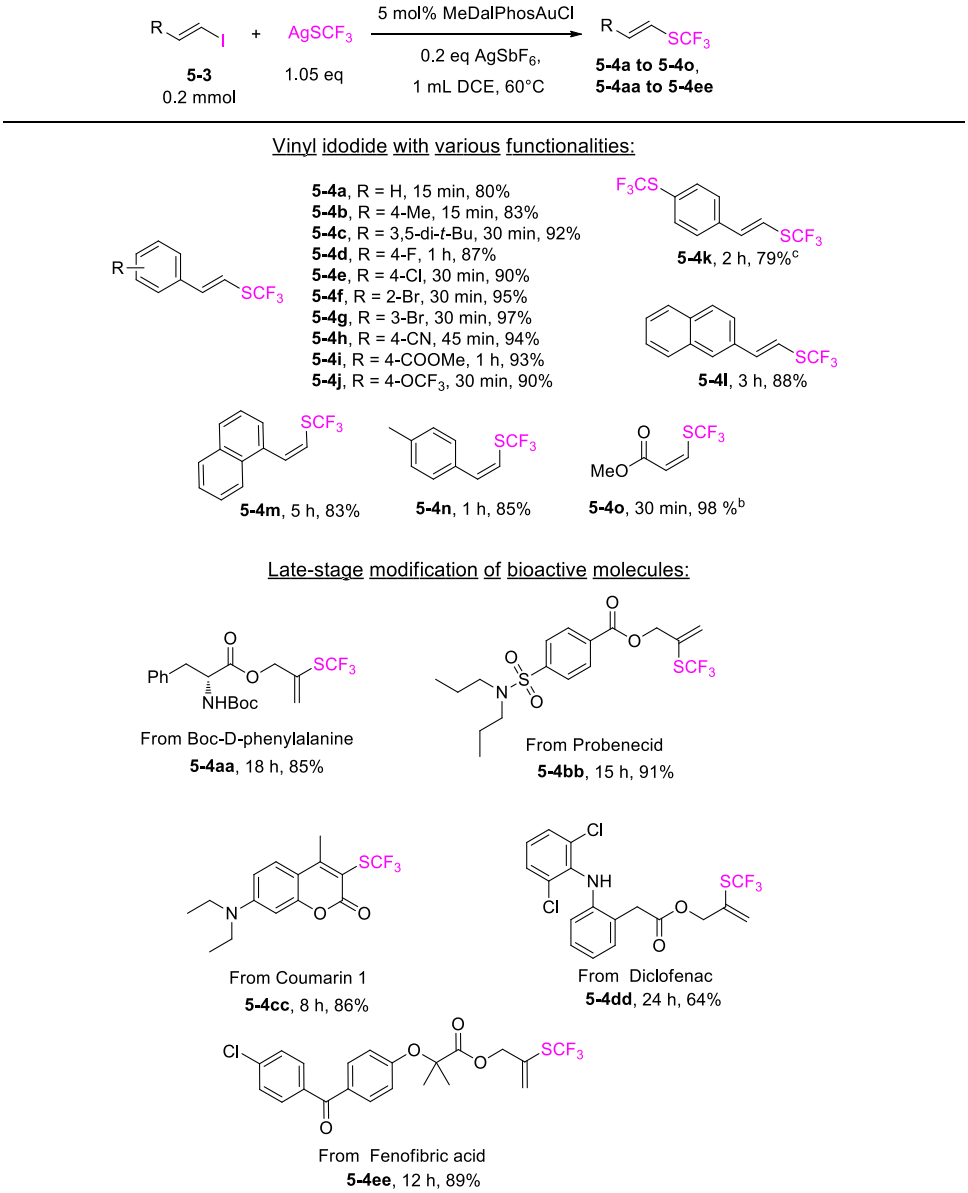


From nimesulide
5-2dd, 1 h, 92%

[a]Reaction conditions: Unless otherwise noted, reactions were conducted as follows: An 8-Ml reaction vial was loaded with MeDalPhosAuCl (5 mol%), $AgSCF_3$ (1.05 equiv) and 1 Ml DCE. Aryl iodide **1** (0.2 mmol) was added and the resulting mixture was stirred at rt for 1 min. $AgSbF_6$ (0.2 equiv) was then added and the reaction was stirred at rt for 1 min before stirring at 70 °C; [b]Isolated yields; [c]NMR yields in parenthesis with benzotrifluoride as an internal standard; [d]10 mol% MeDalPhosAuCl, 0.4 equiv of $AgSbF_6$, and 2.1 equiv of $AgSCF_3$ was applied; [e] 92% isolated yield was obtained when 1 mmol **5-1aa**, 2.5 mol% MeDalPhosAuCl, 0.2 equiv of $AgSbF_6$, 1.05 equiv of $AgSCF_3$ and 5 Ml DCE was applied.

We then switched our focus on vinyl iodides. Few methods have been reported for the reaction with vinyl halides.[228] Our protocol was able to convert a variety of vinyl iodides into vinyl trifluoromethyl thioethers at low reaction temperature (Table 6).

Table 6. Substrate scope of trifluoromethylthiolation of vinyl halides[a,b]



[a]Reaction conditions: Unless otherwise noted, reactions were conducted as follows: An 8-Ml reaction vial was loaded with MeDalPhosAuCl (5 mol%), $AgSCF_3$ (1.05 equiv) and 1 Ml DCE. Vinyl iodide **3** (0.2 mmol) was added, and the resulting mixture was stirred at rt for 1 min. $AgSbF_6$ (0.2 equiv) was then added and the reaction was stirred at rt for 1 min before stirring at 60 °C; [b]Isolated yields; [c]NMR yields in parenthesis with benzotrifluoride as an internal standard; [d]10 mol% MeDalPhosAuCl, 0.4 equiv of $AgSbF_6$, and 2.1 equiv of $AgSCF_3$ was applied.

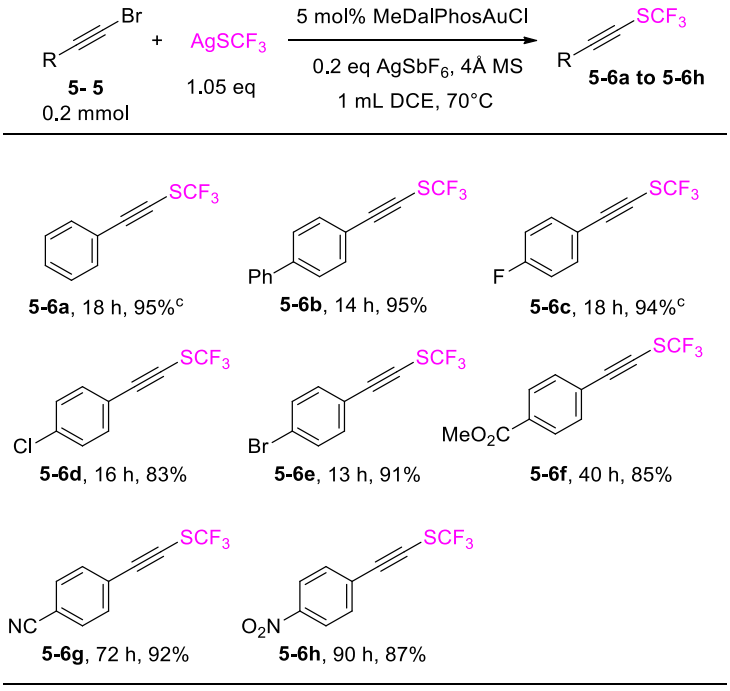
Just like in the trifluoromethylthiolation of aryl iodides, our reaction conditions tolerated different functional groups, such as halides (**5-4d** to **5-4g, 4ee**), nitrile (**5-4h**), esters (**5-4i, 5-4o**, **5-4aa to 5-4ee**), amides (**5-4aa**, **5-4bb**), amines (**5-4cc**, **5-4dd**) ether (**5-4ee**) and trifluoromethoxyl ether (**5-4j**). The reaction outcome was not influenced by both electron-withdrawing/-donating substituents and their position on the aromatic ring of styrenyl iodides. Various alkyl (**5-4o**, **5-4aa** to **5-4ee**), and aryl (**5-4a** to **5-4n**), di- (**5-4a** to **5-4n**, **5-4aa**, **5-4bb**, **5-4dd**, **5-4ee**), and tetrasubstituted (**5-4cc**) vinyl iodides all gave the corresponding products in excellent yields, without affecting the initial Z/E isomer ratio. The complete retention of the olefin geometry suggested that the reaction proceeded via an oxidative addition–reductive elimination pathway. Both internal (**5-4aa** to **5-4ee**) and terminal (**5-4a** to **5-4o**) vinyl iodides, either in *cis*- or *trans*-configuration (**5-4m** vs. **5-4l**), worked very well. An extended reaction time was necessary when working with internal vinyl iodides, probably because of the steric effect in the oxidative addition step (**5-4aa** to **5-4ee**) (see Scheme 14). It was noteworthy that the double trifluoromethylthiolation took place in high yield when aryl and vinyl iodides appeared in the same molecule (**5-4k**).

We next assessed our protocol with a vinyl iodide-containing bioactive molecule. These reactions gave the corresponding vinyl trifluoromethylthioethers in good to excellent isolated yields (**5-4aa** to **5-4ee**). For instance, we obtained the trifluoromethylthiolated probenecid (**5-4bb**) in a 91% isolated yield. Probenecid is a classic uricosuric agent used in patients with renal impairment. In another example, Diclofenac-tethered vinyl iodide was converted to the corresponding product in 64% yield. Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) primarily used to treat mild-to-moderate pain associated with arthritis. Additionally, fenofibric acid-tethered vinyl iodide was smoothly converted to the trifluoromethylthiolated fenofibrate derivative in 89% isolated yield. All along, these examples demonstrated the robustness and efficiency of our protocol.

Our protocol also worked with alkynyl halides. We first attempted it on alkynyl iodide but found a low yield of the trifluoromethylthiolation product. Rather, homocoupling was the main reaction. However, alkynyl bromides gave satisfactory results with our modified protocol after we added molecular sieves to the reaction to prevent a hydration side reaction. Various substituted phenyl acetylene iodides were examined, and all of them gave good yields. Different functional groups

like halides (**5-6c to 5-6e**), ester (**5-6f**), nitrile (**5-6g**), and nitro (**5-6h**) were well-tolerated (Table 7). A pronounced effect of substituent electronics of the phenyl ring on the rate of reaction was observed. Substrates with electron-withdrawing functionalities needed significantly extended reaction times (**5-6f**, **5-6g**, **5-6h**).

Table 7. Substrate scope of trifluoromethylthiolation of alkynyl halides[a,b]

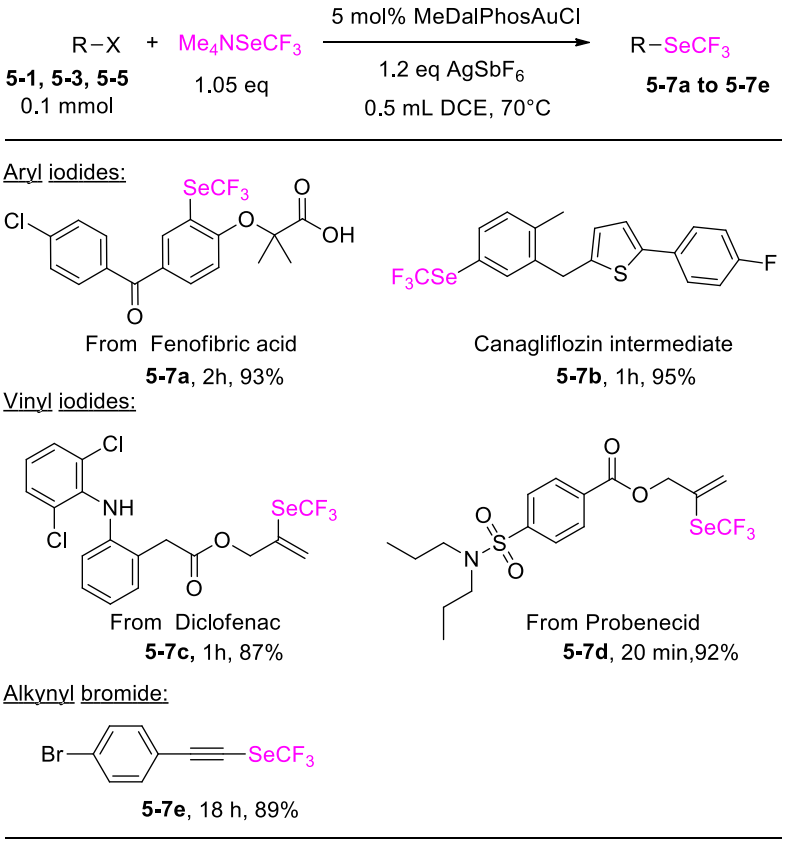


[a]Reaction conditions: Unless otherwise noted, reactions were conducted as follows: An 8-Ml reaction vial was loaded with MeDalPhosAuCl (5 mol%), $AgSCF_3$ (1.05 equiv), 4 Å molecular sieves (20 mg), and 1 Ml DCE. Alkynyl bromide **5** (0.2 mmol) was added, and the resulting mixture was stirred at rt for 1 min. $AgSbF_6$ (0.2 equiv) was then added and the reaction was stirred at rt for 1 min before stirring at 60 °C; [b]Isolated yields; [c]NMR yields in parenthesis with benzotrifluoride as an internal standard.

Trifluoromethylselenide (−$SeCF_3$) is an another important trifluoromethylated chalcogen that has been actively studied due to its similar properties with the trifluoromethylthioether group (-SCF_3).[75, 204] However, trifluoromethylselenides are relatively scarce, probably due to the limited synthetic options available. In this context, we were pleased to observe an efficient trifluoromethylselenolation with the above three categories of halides (aryl, alkenyl and alkynyl). We first evaluated our protocol using $AgSeCF_3$ as the trifluoromethylselenating reagent, but the trifluoromethylselenolation reaction with 4-*tert*-butylphenyl iodide gave poor conversion. However,

the same reaction showed complete conversion when 1.05 equivalent of Me_4NSeCF_3 was employed instead of $AgSeCF_3$ and 1.2 equivalent of $AgSbF_6$ was utilized as the silver activator. To demonstrate the practicality of this method, we used this protocol on several drug molecule substrates equipped with an aryl iodide moiety (**5-7a**, **5-7b**) or tethered to a vinyl iodide (**5-7c**, **5-7d**) and obtained excellent isolated yields of trifluoromethylselenolated products (Table 8). Our protocol also worked well with alkynyl bromide, delivering the corresponding trifluoromethylselenide in an excellent yield (**5-7e**). This wide range of applications by just one catalyst has never been reported with other transition-metal catalysts.

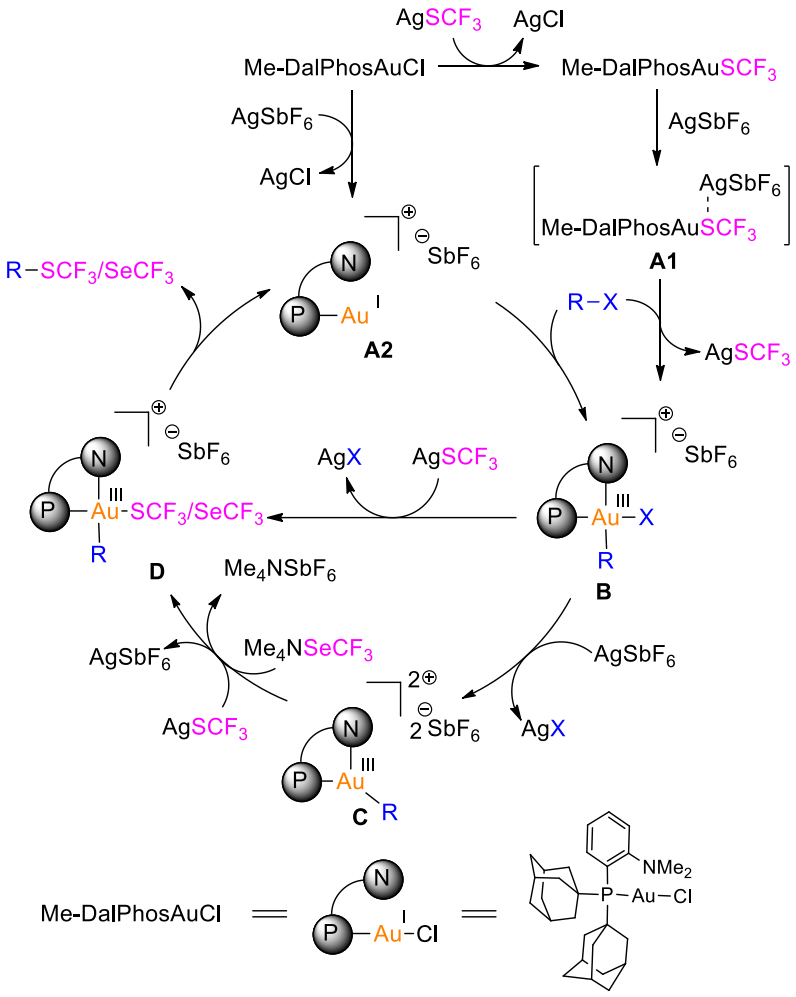
Table 8. Substrate scope of trifluoromethylselenolation of aryl/alkenyl/alkynyl halides[a,b]



[a]Reaction conditions: Unless otherwise noted, reactions were conducted as follows: A 8-Ml reaction vial was loaded with MeDalPhosAuCl (5 mol%), Me_4NSCF_3 (1.05 equiv), and 0.5 Ml DCE. Organohalide (0.2 mmol) was added, and the resulting mixture was stirred at rt for 1 min. $AgSbF_6$ (1.2 equiv) was then added, and the reaction was stirred at rt for 1 min before stirring at 70 °C; [b]Isolated yields.

Based on previous reports on MeDalPhos-enabled gold-catalyzed C−X cross-coupling[214-219, 229-232] and other transition metal-catalyzed trifluoromethylthiolation mechanisms [52, 55, 66], we proposed the following reaction mechanism (Scheme 14). First of all, MeDalPhosAuSCF$_3$ could be generated by the activation of MeDalPhosAuCl with AgSCF$_3$ as verified by ^{31}P and ^{19}F NMR (see experimental section for more details). This intermediate is too inert and has to be activated by AgSbF$_6$ (see experimental section for more details) to form the active intermediate **A1** for the oxidative addition with organohalides, which then forms the Au(III) intermediate **B** with the aryl/vinyl/alkynyl group *trans* to the nitrogen.[214-218] Intermediate **B** undergoes transmetalation with AgSCF$_3$ to deliver the intermediate **D**, which then undergoes reductive elimination to furnish the C−SCF$_3$ bond formation, regenerating the Au(I) intermediate **A2** for the next catalytic cycle. Alternatively, intermediate **B** could also undergo another halide abstraction with AgSbF$_6$ and deliver a more electrophilic Au(III) species **C**, which then reacts with AgSCF$_3$ or Me$_4$NseCF$_3$ to form the intermediate **D**. This scenario is especially true for the trifluoromethylselenolation reaction in which the cationic Au(I) intermediate **A2**, instead of **A1**, is generated from the halide abstraction of MeDalPhosAuCl by AgSbF$_6$.

Scheme 48. Plausible mechanism for the Au(I)/Au(III)-catalyzed C-SCF_3 /$SeCF_3$ cross-coupling reactions.



The following NMR studies were performed to validate the purported catalytic cycle. First,1-iodo-4-trifluoromethoxybenzene was added to the preformed MeDalPhosAuSCF_3 solution in CD_2Cl_2 at room temperature. We found that no reaction happened even when the reaction temperature was raised to 70 °C with reaction time of 17 hours. But the subsequent addition of the $AgSbF_6$ to the reaction mixture at room temperature gave a 3% yield of product and 6% of intermediate **B**, but 76% of the iodide starting material remained. Meanwhile, the MeDalPhosAuSCF_3 signal in F-NMR disappeared, and two new peaks appeared. Merely heating the reaction to 70 °C converted intermediate **B** and all the remaining starting material to the product in 70% NMR yield after 1 hour (see experimental section, 3.4.6.2 and 3.4.6.3 for more details).

3.3. Conclusion

We have developed the first gold-catalyzed C−SCF_3/$SeCF_3$ cross-coupling reaction. The generality of this protocol facilitates an efficient 'one-stop shop' synthesis of a diverse array of C−SCF_3/$SeCF_3$ cross-coupled products. This synthetic protocol features broad functional group compatibility, simple operation, mild reaction conditions, and overall excellent yields. The robustness and scalability of this reaction, in the late-stage functionalization of bioactive molecules, proves that our method is a competitive alternative to the synthesis of trifluoromethylthio- and selenoethers, which may stimulate further applications in pharmaceutical and agrochemical research and development.

Work contribution:

I highly acknowledge Dr. Zhichao Lu and Mr. Yuhao Yang for their contributions in the successful completion of this project. Dr.Lu performed preliminary experiments for mechanistic details, optimization of the reaction conditions and substrate scope for the aryl iodides. Yuhao Yang performed few experiments to investigate the mechanism of the reaction.

5.4. Experimental:

5.4.1. General experimental details

^{1}H NMR spectra were recorded at 400 MHz or 500 MHz, ^{13}C NMR spectra were recorded in 100 MHz, and ^{19}F NMR were recorded at 376 MHz using $CDCl_3$ as the solvent, unless otherwise noted. The chemical shifts are reported in (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), p (pentet), h (hextet), m (multiplet) and br (broad). Coupling constants, *J*, are reported in Hertz.

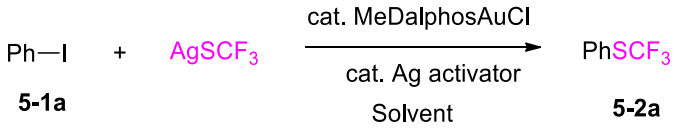
$AgSCF_3$,[233] $AgSeCF_3$,[234] and Me_4NseCF_3[204] were prepared according to the literatures. MeDalPhosAuCl was prepared according to the literature method but without glovebox.[231] Solvents like dichloromethane (DCM), diethyl ether (Et_2O), dimethylformamide (DMF),

dichloroethane (DCE), dimethoxyethane (DME), acetonitrile (I), and tetrahydrofuran (THF) were chemically dried using a commercial solvent purification system. All other reagents and solvents were employed without further purification. The products were purified using a 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–MeCN gradient (100:0 to 0:100) for 40 min at a flow rate of 19 Ml/min. TLC was developed on Merck silica gel 60 F254 aluminum sheets and $KmnO_4$ stain was used for TLC developing. $KmnO_4$ stain was prepared by dissolving $KmnO_4$ (1.5 g), K_2CO_3 (10 g), and NaOH (10 wt%, 1.25 Ml) in 200 Ml water. All NMR solvents were purchased from Cambridge Isotope Laboratories, Inc. HRMS data was obtained from Indiana University Bloomington Mass Spectral Facility using Thermo LTQ-Orbitrap XL mass spectrometer with ESI or EI ionization sources.

For all the substrates, we provided references, detailed synthetic procedures, and NMR spectra (^{1}H NMR spectra) to characterize it.

5.4.2. Trifluoromethylthiolation of (hetero)aryl iodides

5.4.2.1. Reaction condition optimization



6. Effect of solvents on the reaction[a]

Entry	Reaction condition	GC Yield (5-1a/5-2a)
1	**5-1a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, rt, 24h	20% / **80%**[b]
2	**5-1a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCM, 0.2 eq $AgSbF_6$ was added, rt, 24h	12% / **88%**[c]
3	**5-1a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml THF, 0.2 eq $AgSbF_6$ was added, rt, 24h	98% / **2%**
4	**5-1a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml Et_2O, 0.2 eq $AgSbF_6$ was added, rt, 24h	99% / **1%**
5	**5-1a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml Toluene, 0.2 eq $AgSbF_6$ was added, rt, 24h	94% / **6%**
6	**5-1a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DMF, 0.2 eq $AgSbF_6$ was added, rt, 24h	100% / **0%**
7	**5-1a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DMA, 0.2 eq $AgSbF_6$ was added, rt, 24h	100% / **0%**
8	**5-1a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml I, 0.2 eq $AgSbF_6$ was added, rt, 24h	100% / **0%**
9	**5-1a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml EtOAc, 0.2 eq $AgSbF_6$ was added, rt, 24h	95% / **5%**

[a] Experimental procedure: An 8-Ml glass vial was loaded with 5 mol% Au catalyst, 1.05 eq $AgSCF_3$, and 0.5 Ml DCE sequentially. 0.1 mmol **5-1a** was then added, and the mixture was stirred for 1 min before 0.2 eq $AgSbF_6$ was added. The resulting mixture was stirred at rt for 24 h. The reaction was then monitored with GC/MS, [b] 60 °C, 1h, 80% yield; 2h, 100% yield; [c] 60 °C, 1h, 72% yield.

b. Effect of silver activator on the reaction[a]

Entry	Reaction condition	GC Yield (5-1a/5-2a)
1	**5-1a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 60 °C, 1h	20% / **80%**
2	**5-1a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgNTf_2$ was added, 60 °C, 1h	58% / **42%**
3	**5-1a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgPF_6$ was added, 60 °C, 1h	29% / **71%**
4	**5-1a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgBF_4$ was added, 60 °C, 1h	43% / **57%**

[a] Experimental procedure: An 8-Ml glass vial was loaded with 5 mol% Au catalyst, 1.05 eq $AgSCF_3$, and 0.5 Ml DCE sequentially. 0.1 mmol **5-1a** was then added, and the mixture was stirred for 1 min before 0.2 eq silver activator was added. The resulting mixture was stirred at 60 °C for 1h. The reaction was then monitored with GC/MS.

c. Effect of gold pre-catalyst on the reaction[a]

Entry	Reaction condition	GC Yield (5-1a/5-2a)
1	**5-1a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 60 °C, 1h	20% / **80%**
2	**5-1a** + $AgSCF_3$ + 3 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 60 °C, 1h	39% / **61%**
3	**5-1a** + $AgSCF_3$ + 2 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 60 °C, 1h	68% / **32%**

[a] Experimental procedure: An 8-Ml glass vial was loaded with x mol% Au catalyst, 1.05 eq $AgSCF_3$, and 0.5 Ml DCE sequentially. 0.1 mmol **5-1a** was then added, and the mixture was stirred for 1 min before 0.2 eq AgSbF6 was added. The resulting mixture was stirred at 60 °C for 1h. The reaction was then monitored with GC/MS.

d. Effect of silver activator amount on the reaction[a]

Entry	Reaction condition	GC Yield (5-1a/5-2a)
1	**5-1a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.1 eq $AgSbF_6$ was added, 60 °C, 1h	69% / **31%**
2	**5-1a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 60 °C, 1h	20% / **80%**
3	**5-1a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.3 eq $AgSbF_6$ was added, 60 °C, 1h	6% / **94%**

[a] Experimental procedure: An 8-Ml glass vial was loaded with 5 mol% Au catalyst, 1.05 eq $AgSCF_3$, and 0.5 Ml DCE sequentially. 0.1 mmol **5-1a** was then added, and the mixture was stirred for 1 min before x eq $AgSbF_6$ was added. The resulting mixture was stirred at 60 °C for 1h. The reaction was then monitored with GC/MS.

e. Effect of temperature on the reaction[a]

Entry	Reaction condition	GC Yield (5-1a/5-2a)
1	**5-1a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 50 ^{o}C, 1h	49% / **51%**
2	**5-1a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCM, 0.2 eq $AgSbF_6$ was added, 50 ^{o}C, 1h	44% / **56%**
3	**5-1a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 60 ^{o}C, 1h	20% / **80%**
4	**5-1a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCM, 0.2 eq $AgSbF_6$ was added, 50 ^{o}C, 1h	28% / **72%**
5	**5-1a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 70 ^{o}C, 1h	5% / **95%**
6	**5-1a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 80 ^{o}C, 1h	5% / **95%**

[a] Experimental procedure: An 8-Ml glass vial was loaded with 5 mol% Au catalyst, 1.05 eq $AgSCF_3$, and 0.5 Ml DCE/DCM sequentially. 0.1 mmol **5-1a** was then added, and the mixture was stirred for 1 min before 0.2 eq $AgSbF_6$ was added. The resulting mixture was stirred at X ^{o}C for 1h. The reaction was then monitored with GC/MS.

f. Effect of concentration on the reaction[a]

Entry	Reaction condition	GC Yield (5-1a/5-2a)
1	**5-1a** + $AgSCF_3$ + 5 mol% **Au** in 0.25 Ml DCE, 0.3 eq $AgSbF_6$ was added, 70 °C, 0.5 h	12% / **88%**
2	**5-1a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.3 eq $AgSbF_6$ was added, 70 °C, 0.5 h	7% / **93%**[b]
3	**5-1a** + $AgSCF_3$ + 5 mol% **Au** in 1 Ml DCE, 0.3 eq $AgSbF_6$ was added, 70 °C, 0.5 h	10% / **90%**

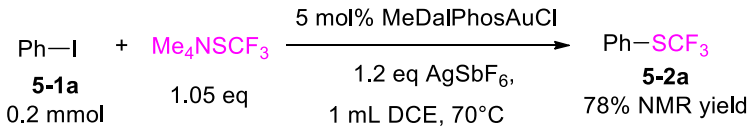
[a] Experimental procedure: An 8-Ml glass vial was loaded with 5 mol% Au catalyst, 1.05 eq $AgSCF_3$, and x Ml DCE sequentially. 0.1 mmol **5-1a** was then added, and the mixture was stirred for 1 min before 0.3 eq $AgSbF_6$ was added. The resulting mixture was stirred at 70 °C for 0.5 h. The reaction was then monitored with GC/MS. [b] 1 h, 94% yield.

g. Control experiment[a]

Entry	Reaction condition	GC Yield (5-1a/5-2a)
1	**5-1a** + $AgSCF_3$ + 0 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 70 °C, 30h	100% / **0%**[b]
2	**5-1a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0 eq $AgSbF_6$ was added, 70 °C, 1h	100% / **1%**[c]
3	**5-1a** + $AgSCF_3$ + 0 mol% **Au** in 0.5 Ml DCE, 0 eq $AgSbF_6$ was added, 70 °C, 1h	100% / **0%**[d]
4	**5-1a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 70 °C, 1h	5% / **95%**[e]

[a] Experimental procedure: An 8-Ml glass vial was loaded with x mol% Au catalyst, 1.05 eq $AgSCF_3$, and 0.5 Ml solvent sequentially. 0.1 mmol **5-1a** was then added, and the mixture was stirred for 1 min before x eq $AgSbF_6$ was added. The resulting mixture was stirred at 70 °C for 1 h. The reaction was then monitored with GC/MS. [b] when 5 mol% Au was added and the reaction was stirred at 70 °C for 2 h, 100% yield; [c] 24 h, 23% yield. [d] 24 h, 0% yield. [e] 1.5 h, 100% yield.

h. Me_4NSCF_3 as the SCF_3 reagent

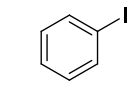


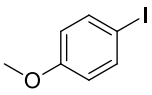
Procedure: under nitrogen atmosphere, an 8-Ml reaction vial fitted with a stirring bar was loaded with MeDalPhosAuCl (5 mol%), Me4$NSCF_3$ (1.05 equiv) [235] and 1 Ml dry DCE. Phenyl iodide (0.2 mmol) was added, and the resulting mixture was stirred at room temperature for 1 min. $AgSbF_6$ (1.2 equiv) was then added and the reaction was stirred at room temperature for 1 min before

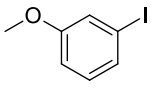
being heated to 70 °C on a block heater. After heating at 70 °C for 1 h and cooling down to room temperature, 26.8 mg of $PhCF_3$ (0.1836 mmol) was added to the reaction mixture as the internal standard and 80 µL of the upper clear layer was taken out for F-NMR analysis (78% NMR yield). 20 µL of the upper clear layer was taken out for GC-MS analysis (81% GC yield with 19% starting material remained).

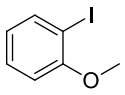
5.4.2.2. Preparation of (hetero)aryl iodides

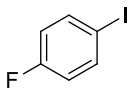
The following aryl iodide substrates are commercially available and were used directly without further purification:

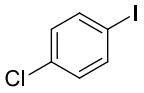

5-1a

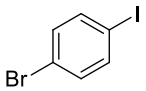

5-1b

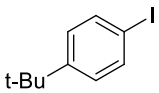

5-1c

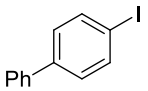

5-1d


5-1e


5-1f


5-1g


5-1h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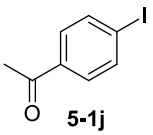
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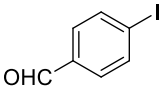
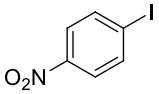
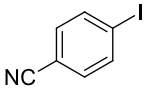

5-1k


5-1l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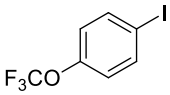
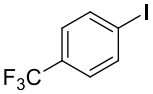
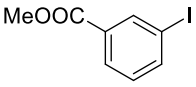
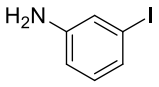
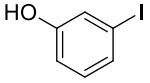
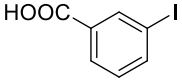

5-1n

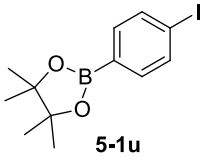

5-1o

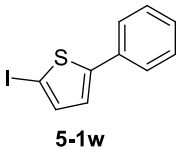

5-1p

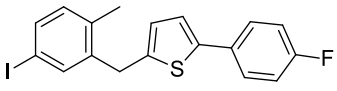

5-1q

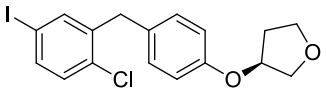

5-1r


5-1s

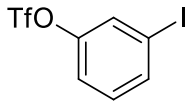

5-1u


5-1w


5-1aa

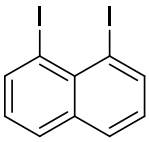

5-1bb

The compound **5-1t** was prepared according to the reported method.[236] Clear yellow oil, 330 mg, 94 % yield. R_f = 0.64 (hexane/ethyl acetate = 10/1). The NMR data accords with the reference.[236]



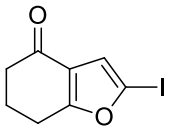
5-1t

The compound **5-1v** was prepared according to the reported method.[237] Light yellow solid, 250 mg, 66% yield. R_f = 0.45 (hexane). The NMR data accords with the reference.[237]

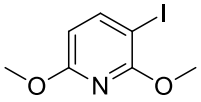


5-1v

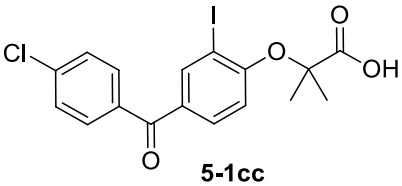
The compound 5-1x, 5-1y, 5-1cc, 5-1dd were prepared according to the reference[238]



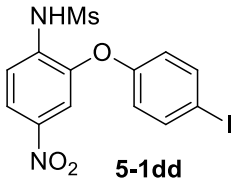
5-1x



5-1y

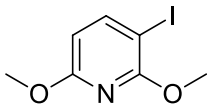


5-1cc



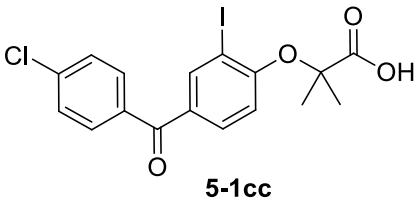
5-1dd

5-1x: Colorless solid, 215 mg, 82 % yield based on 1 mmol tetrahydrobenzofuranone starting material. R_f = 0.5 (Hexane). The NMR data accords with the reference.[238]



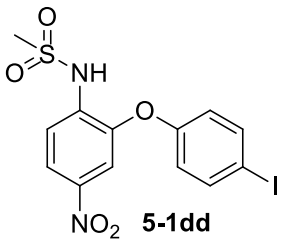
5-1y

5-1y: Colorless solid, 236 mg, 89 % yield based on 1 mmol of 2,6-dimethoxypyridine. R_f = 0.52 (hexane/ethyl acetate = 10/1). The NMR data accords with the reference.[238]



5-1cc

5-1cc: Colorless solid, 211 mg, 95 % yield based on 0.5 mmol Fenofibric acid. R_f = 0.06 (ethyl acetate).The NMR data accords with the reference.[238]

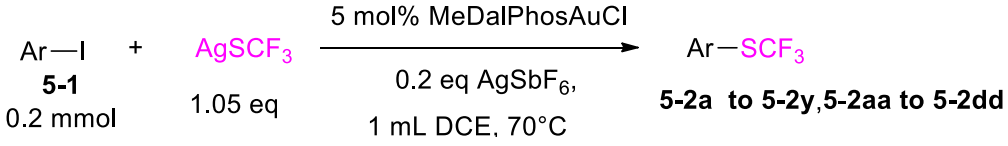


5-1dd

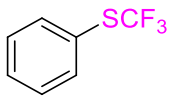
5-1dd: Pale yellow solid, 180 mg, 83 % yield based on 0.5 mmol Nimesulide starting material. R_f = 0.34 (hexane/ ethyl acetate = 10/3).The NMR data accords with the reference.[238]

5.4.2.3 Trifluoromethylthiolation of (hetero)aryl iodides

General procedure:

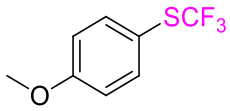


An 8-Ml reaction vial fitted with a stirring bar was loaded with MeDalPhosAuCl (5 mol%), $AgSCF_3$ (1.05 equiv) and 1 Ml DCE. Aryl iodide **5-1** (0.2 mmol) was added and the resulting mixture was stirred at room temperature for 1 min. $AgSbF_6$ (0.2 equiv) was then added and the reaction was stirred at room temperature for 1 min before being heated to 70 °C on a block heater. The reaction was monitored with GC/MS. Upon completion, the reaction mixture was diluted with 2 Ml DCM and then filtered through a short silica pad (Length: 15 mm, I.D.: 15 mm), eluted with mixed solvent (hexane/EtOAc) until no product 2 was remained on the column. The filtrate was concentrated and purified with flash chromatography using hexane/ethyl acetate to give the desired product **5-2**.



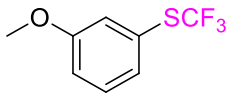
5-2a

5-2a: colorless oil, 22 mg, 61% yield. R_f = 0.66 (hexane). The NMR data accords with the reference.[239]



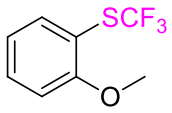
5-2b

5-2b: colorless oil, 38 mg, 92% yield. R_f = 0.21 (hexane). The NMR data accords with the reference.[55]



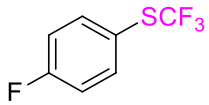
5-2c

5-2c: colorless oil, 37 mg, 90% yield. R_f = 0.21 (hexane). The NMR data accords with the reference.[240]



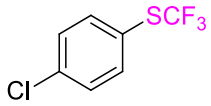
5-2d

5-2d: colorless oil, 33 mg, 79% yield. R_f = 0.15 (hexane). The NMR data accords with the reference.[241]



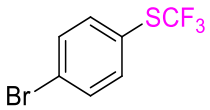
5-2e

5-2e: 91% F-NMR yield. The NMR data accords with the reference.[240]



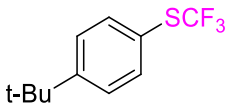
5-2f

5-2f: colorless oil, 37 mg, 87% yield. R_f = 0.67 (hexane). The NMR data accords with the reference.[242]



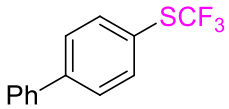
5-2g

5-2g: colorless oil, 47 mg, 91% yield. R_f = 0.67 (hexane). The NMR data accords with the reference.[242]



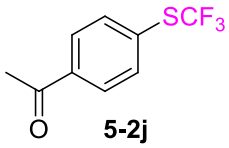
5-2h

5-2h: colorless oil, 43 mg, 92% yield. R_f = 0.63 (hexane). The NMR data accords with the reference.[55]



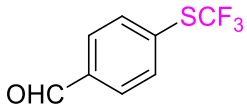
5-2i

5-2i: colorless oil, 47 mg, 93% yield. R_f = 0.37 (hexane). The NMR data accords with the reference.[55]



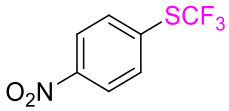
5-2j

5-2j: yellow oil, 32 mg, 91% yield. R_f = 0.44 (hexane/ethyl acetate = 4/1). The NMR data accords with the reference.[55]



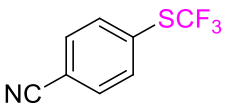
5-2k

5-2k: white solid, 37 mg, 90% yield. R_f = 0.48 (hexane/ethyl acetate = 4/1). The NMR data accords with the reference.[56]



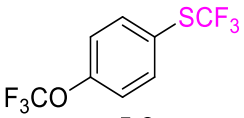
5-2l

5-2l: colorless oil, 30 mg, 67% yield. R_f = 0.66 (hexane/ethyl acetate = 4/1). The NMR data accords with the reference.[55]



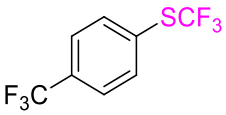
5-2m

5-2m: light violet solid, 35 mg, 85% yield. R_f = 0.58 (hexane/ethyl acetate = 4/1). The NMR data accords with the reference.[55]



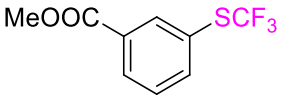
5-2n

5-2n: colorless oil, 33 mg, 62% yield. R_f = (hexane/ethyl acetate = 4/1). The NMR data accords with the reference.[243]



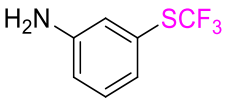
5-2o

5-2o: 100% F-NMR yield. The NMR data accords with the reference.[242]



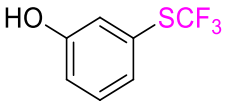
5-2p

5-2p: colorless oil, 41 mg, 87% yield. R_f = 0.56 (hexane/ethyl acetate = 4/1). The NMR data accords with the reference.[244]



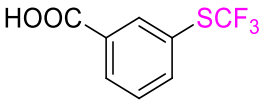
5-2q

5-2q: light brown oil, 31 mg, 80% yield. R_f = 0.24 (hexane/ethyl acetate = 4/1). The NMR data accords with the reference.[241]



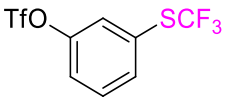
5-2r

5-2r: white solid, 36 mg, 92% yield. R_f = 0.36 (hexane/ethyl acetate = 4/1). The NMR data accords with the reference.[245]



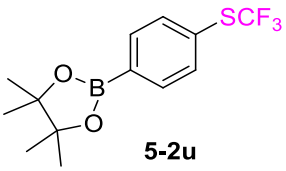
5-2s

5-2s: white solid, 42 mg, 93% yield. R_f = 0.44 (ethyl acetate). The NMR data accords with the reference.[244]



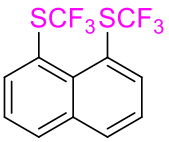
5-2t

5-2t: colorless oil, 57 mg, 87% yield. R_f = 0.68 (hexane/ethyl acetate = 4/1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.8 Hz, 1H), 7.60 (s, 1H), 7.55 (t, *J* = 8.1 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.4, 136.0, 131.1, 129.1 (q, *J* = 307.1 Hz), 128.8, 127.0, 124.0, 118.7 (q, *J* = 319.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -42.28 (s, 3F), -72.65 (s, 3F). HRMS: (EI) m/z: $[M]^+$ Calcd for $C_8H_4F_6O_3S_2$ 325.9506, Found: 325.9501.



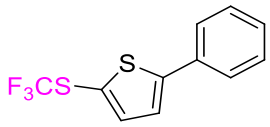
5-2u

5-2u: white solid, 55 mg, 90% yield. R_f = 0.68 (hexane/ethyl acetate 4/1). The NMR data accords with the reference.[246]



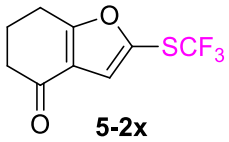
5-2v

5-2v: light yellow solid, 60 mg, 92% yield. R_f = 0.47 (hexane). The NMR data accords with the reference.[56]



5-2w

5-2w: light yellow solid, 48 mg, 92% yield. R_f = 0.41 (hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.4 Hz, 2H), 7.43 (m, 4H), 7.32 (d, *J* = 3.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 140.5, 133.3, 129.1, 128.4 (q, *J* = 307 Hz), 128.7, 126.1, 123.9, 119.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -43.74 (s, 3F). HRMS: (EI) m/z: $[M]^+$ Calcd for $C_{11}H_7F_3S_2$ 259.9941, Found: 259.9937.

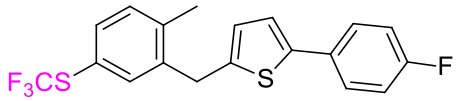


5-2x

5-2x: colorless solid, 45 mg, 95 % yield. R_f = 0.21 (hexane/ethyl acetate = 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (s, 1H), 2.93 (t, *J* = 6.3 Hz, 2H), 2.52 (dd, *J* = 7.3, 5.7 Hz, 2H), 2.21 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.0, 171.5, 136.2, 127.7 (q, *J* = 307 Hz) 123.2, 120.5, 37.46, 23.59, 22.10. ^{19}F NMR (376 MHz, $CDCl_3$) δ -43.74 (s, 3F). HRMS: (ESI) m/z: $[M + H]^+$ Calcd for $C_9H_8F_3O_2S$ 237.0192, Found: 237.0191.

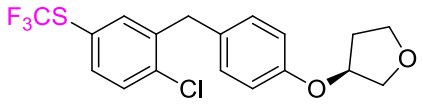
5-2y

5-2y: colorless oil, 41 mg, 86% yield. R_f = 0.52 (hexane/ethyl acetate = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 1H), 6.36 (d, *J* = 8.2 Hz, 1H), 4.01 (s, 3H), 3.96 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 164.1, 150.0, 129.3 (q, *J* = 310 Hz), 102.9, 96.0, 54.2, 53.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -43.77 (s, 3F). HRMS: (ESI) m/z: $[M + H]^+$ Calcd for $C_8H_9F_3NO_2S$ 240.0301, Found: 240.0301.



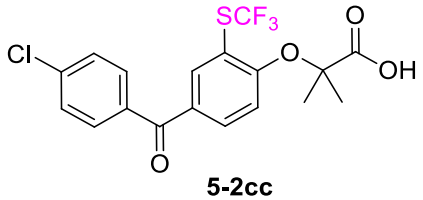
5-2aa

5-2aa: white solid, 71 mg, 93% yield. R_f = 0.12 (hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.43 (m, 4H), 7.24 (d, *J* = 8.1 Hz, 1H), 7.04 (m, 3H), 6.67 (s, 1H), 4.14 (s, 2H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2 (d, *J* = 245.8 Hz), 142.0, 141.9, 139.9, 139.7, 137.2, 134.9, 131.6, 130.7 (d, *J* = 2.7 Hz), 129.7 (q, *J* = 306.5 Hz), 128.1, 127.1 (d, *J* = 7.9 Hz), 126.2, 122.7, 121.6, 115.7 (d, *J* = 21.7 Hz), 33.8, 19.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ -43.18 (s, 3F), -115.12 (m, 1F). HRMS: (EI) m/z: $[M]^+$ Calcd for $C_{19}H_{14}F_4S_2$ 382.0473, Found: 382.0469.



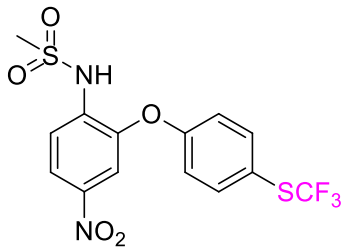
5-2bb

5-2bb: light yellow oil, 72 mg, 92% yield. R_f = 0.36 (hexane/ethyl acetate = 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.29 (m, 3H), 7.09 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 4.97 – 4.80 (m, 1H), 4.05 (s, 2H), 4.02 – 3.94 (m, 3H), 3.90 (m, 1H), 2.25 – 2.10 (m, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 140.7, 138.4, 137.5, 135.1, 130.7, 130.6, 130.0, 129.3 (q, *J* = 307.0 Hz), 122.9, 115.5, 77.3, 73.1, 67.1, 38.2, 33.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -42.67 (s, 3F). HRMS: (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{16}ClF_3O_2S$ 388.0512, Found: 388.0508.



5-2cc

5-2cc: white solid, 80 mg, 95% yield. R_f = 0.06 (ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (br, 1H), 8.08 (s, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.1 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 1H), 1.77 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 177.6, 160.0, 140.6, 139.2, 135.4, 134.2, 131.2, 131.0, 129.4 (q, *J* = 309.0 Hz), 128.8, 116.2, 115.7, 80.6, 25.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ -41.95 (s, 3F). HRMS: (ESI) m/z: $[M – H]^-$ Calcd for $C_{18}H_{13}O_4ClF_3S$ 417.0181, Found: 417.0173.

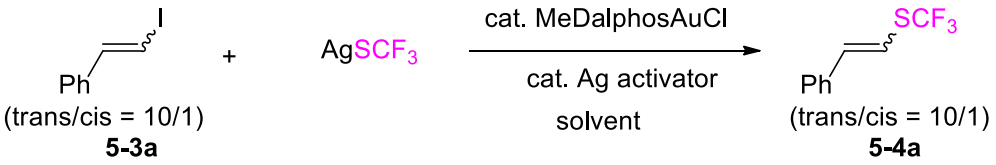


5-2dd

5-2dd: light yellow solid, 75 mg, 92% yield. R_f = 0.35 (hexane/ethyl acetate = 7/3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.81 (d, *J* = 9.0 Hz, 1H), 7.77 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.35 (s, 1H), 7.11 (d, *J* = 8.7 Hz, 2H), 3.16 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 144.6, 143.6, 138.9, 134.7, 129.4 (q, *J* = 307 Hz), 121.1, 120.6, 119.7, 117.6, 113.5, 40.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ -42.31 (s, 3F). HRMS: (ESI) m/z: $[M - H]^-$ Calcd for $C_{14}H_{10}O_5N_2F_3S_2$ 406.9989, Found: 406.9983.

5.4.3. Trifluoromethylthiolation of alkenyl iodides

5.4.3.1 Reaction condition optimization



6. Effect of solvents on the reaction[a]

Entry	Reaction condition	GC Yield (5-3a/5-4a)
1	**5-3a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, rt, 1h	63% / **37%**[b]
2	**5-3a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCM, 0.2 eq $AgSbF_6$ was added, rt, 1h	75% / **25%**
3	**5-3a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml THF, 0.2 eq $AgSbF_6$ was added, rt, 1h	93% / **7%**
4	**5-3a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml Et_2O, 0.2 eq $AgSbF_6$ was added, rt, 1h	88% / **12%**
5	**5-3a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml Toluene, 0.2 eq $AgSbF_6$ was added, rt, 1h	87% / **13%**
6	**5-3a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DMF, 0.2 eq $AgSbF_6$ was added, rt, 1h	100% / **0%**
7	**5-3a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DMA, 0.2 eq $AgSbF_6$ was added, rt, 1h	100% / **0%**
8	**5-3a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml I, 0.2 eq $AgSbF_6$ was added, rt, 1h	100% / **0%**
9	**5-3a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml EtOAc, 0.2 eq $AgSbF_6$ was added, rt, 1h	80% / **20%**

[a] Experimental procedure: An 8-Ml glass vial was loaded with 5 mol% Au catalyst, 1.05 eq $AgSCF_3$, and 0.5 Ml DCE sequentially. 0.1 mmol **5-3a** was then added, and the mixture was stirred for 1 min before 0.2 eq $AgSbF_6$ was added. The resulting mixture was stirred at rt for 1h. The reaction was then monitored with GC/MS. [b] rt, 18 h, 100% yield.

b. Effect of silver activator on the reaction[a]

Entry	Reaction condition	GC Yield (5-3a/5-4a)
1	**5-3a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, rt, 1h	63% / **37%**
2	**5-3a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq AgOTf was added, rt, 1h	94% / **6%**
3	**5-3a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgNTf_2$ was added, rt, 1h	88% / **26%**
4	**5-3a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgPF_6$ was added, rt, 1h	94% / **6%**
5	**5-3a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgBF_4$ was added, rt, 1h	87% / **13%**
6	**5-3a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgNO_3$ was added, rt, 1h	99% / **1%**
7	**5-3a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq AgOAc was added, rt, 1h	100% / **0%**

[a] Experimental procedure: An 8-Ml glass vial was loaded with 5 mol% Au catalyst, 1.05 eq $AgSCF_3$, and 0.5 Ml DCE sequentially. 0.1 mmol **5-3a** was then added, and the mixture was stirred for 1 min before 0.2 eq silver activator was added. The resulting mixture was stirred at rt for 1h. The reaction was then monitored with GC/MS.

c. Effect of gold pre-catalyst on the reaction[a]

Entry	Reaction condition	GC Yield (5-3a/5-5-4a)
1	**5-3a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, rt, 1h	63% / **37%**
2	**5-3a** + $AgSCF_3$ + 3 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, rt, 1h	88% / **12%**
3	**5-3a** + $AgSCF_3$ + 2 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, rt, 1h	96% / **4%**

[a] Experimental procedure: An 8-Ml glass vial was loaded with x mol% Au catalyst, 1.05 eq $AgSCF_3$, and 0.5 Ml DCE sequentially. 0.1 mmol **5-3a** was then added, and the mixture was stirred for 1 min before 0.2 eq AgSbF6 was added. The resulting mixture was stirred at rt for 1h. The reaction was then monitored with GC/MS.

d. Effect of silver activator amount on the reaction[a]

Entry	Reaction condition	GC Yield (5-3a/5-4a)
1	**5-3a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.1 eq $AgSbF_6$ was added, rt, 1h	83% / **17%**
2	**5-3a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, rt, 1h	63% / **37%**
3	**5-3a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.3 eq $AgSbF_6$ was added, rt, 1h	83% / **17%**

[a] Experimental procedure: An 8-Ml glass vial was loaded with 5 mol% Au catalyst, 1.05 eq $AgSCF_3$, and 0.5 Ml DCE sequentially. 0.1 mmol **5-3a** was then added, and the mixture was stirred for 1 min before x eq $AgSbF_6$ was added. The resulting mixture was stirred at rt for 1h. The reaction was then monitored with GC/MS.

e. Effect of concentration on the reaction[a]

Entry	Reaction condition	GC Yield (5-3a/5-4a)
1	**3-3a** + $AgSCF_3$ + 5 mol% **Au** in 0.25 Ml DCE, 0.2 eq $AgSbF_6$ was added, rt, 1h	71% / **29%**
2	**3-3a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, rt, 1h	63% / **37%**
3	**3-3a** + $AgSCF_3$ + 5 mol% **Au** in 1 Ml DCE, 0.2 eq $AgSbF_6$ was added, rt, 1h	80% / **20%**

[a] Experimental procedure: An 8-Ml glass vial was loaded with 5 mol% Au catalyst, 1.05 eq $AgSCF_3$, and x Ml DCE sequentially. 0.1 mmol **3-3a** was then added, and the mixture was stirred for 1 min before 0.2 eq $AgSbF_6$ was added. The resulting mixture was stirred at rt for 1h. The reaction was then monitored with GC/MS.

f. Effect of temperature on the reaction[a]

Entry	Reaction condition	GC Yield (3-3a/3-3-4a)
1	**5-3a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 40 °C, 1 h	8% / **92%**
2	**5-3a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 50 °C, 1 h	3% / **97%**
3	**5-3a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 60 °C, 1 h	0% / **100%**
4	**5-3a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 70 °C, 1 h	8% / **92%**

[a] Experimental procedure: An 8-Ml glass vial was loaded with 5 mol% Au catalyst, 1.05 eq $AgSCF_3$, and 0.5 Ml DCE sequentially. 0.1 mmol **5-3a** was then added, and the mixture was stirred for 1 min before 0.3 eq $AgSbF_6$ was added. The resulting mixture was stirred at X °C for 1 h. The reaction was then monitored with GC/MS. [b] the reaction completed in 0.5 h when 0.2 mmol scale reaction was conducted.

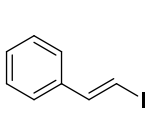
g. Control experiment[a]

Entry	Reaction condition	GC Yield (5-3a/5-4a)
1	**5-3a** + $AgSCF_3$ + 0 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, rt, 1h	100% / **0%**[b]
2	**5-3a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0 eq $AgSbF_6$ was added, rt, 1h	100% / **0%**[c]
3	**5-3a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, rt, 1h	63% / **37%**

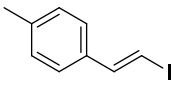
[a] Experimental procedure: An 8-Ml glass vial was loaded with x mol% Au catalyst, 1.05 eq $AgSCF_3$, and 0.5 Ml solvent sequentially. 0.1 mmol **5-3a** was then added, and the mixture was stirred for 1 min before x eq $AgSbF_6$ was added. The resulting mixture was stirred at room temperature for 1h. The reaction was then monitored with GC/MS. [b] rt, 5h, 0% yield, then stirred at 60 °C for 16 h, still no reaction; [c] rt, 5h, 2% yield, then stirred at 60 °C for 16 h, 36% yield.

5.4.3.2. Preparation of alkenyl iodides

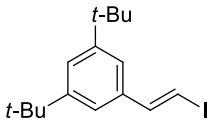
a. General synthetic procedure for I-β-Aryl Vinyl Iodides 5-3a to 5-3l[247]



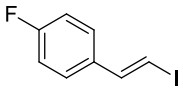
5-3a



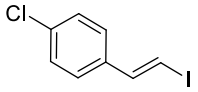
5-3b



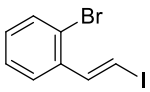
5-3c



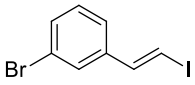
5-3d



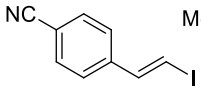
5-3e



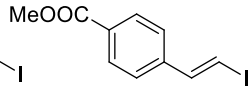
5-3f



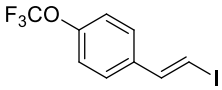
5-3g



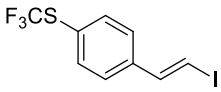
5-3h



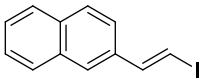
5-3i



5-3j

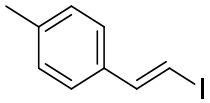


5-3k



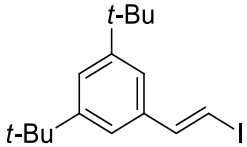
5-3l

Method I: A solution of CH_2I_2 (121 Ml, 1.5 mmol) in THF (0.5 Ml) was added dropwise to a solution of NaHMDS (0.55 g, 3.0 mmol) in THF (2 Ml) and ether (2 Ml) at –78 °C (dry ice/acetone bath) in the dark. After 20 min, a solution of the benzyl bromide substrate (1.0 mmol) in THF (1 Ml) was added dropwise manner. The reaction mixture was stirred further for 90 min and then removed from the cold bath to warm to rt. After 30 min, the solution of DBU (149 Ml, 1.0 mmol) was added dropwise and stirred for 1 h before ether (15 Ml) was added. The mixture was filtered through a plug of celite/silica and the solvent removed under reduced pressure. The residue was purified by chromatography to provide the pure vinyl iodides **5-3b**, **5-3c**, **5-3d**, **5-3f**, **5-3g**, **5-3l**.



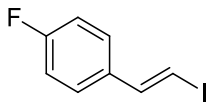
5-3b

5-3b: white solid, 210 mg, 86% yield based on 1 mmol benzyl bromide starting material. R_f = 0.55 (hexane). The NMR data accords with the reference.[247]



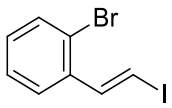
5-3c

5-3c: (E/Z = 99/1), pale yellow solid, 904 mg, 66% yield based on 4 mmol benzyl bromide starting material. R_f = 0.55 (hexane). The NMR data accords with the reference.[248]



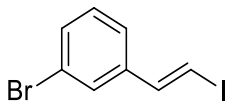
5-3d

5-3d: (E/Z = 97/3), light yellow liquid, 207 mg, 84% yield based on 1 mmol benzyl bromide starting material. R_f = 0.58 (hexane). The NMR data accords with the reference.[249]



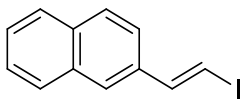
5-3f

5-3f: (E/Z > 99/1), Pale yellow oil, 260 mg, 84% yield based on 1 mmol benzyl bromide starting material. R_f = 0.5 (hexane). The NMR data accords with the reference.[247]



5-3g

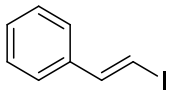
5-3g: (E/Z > 99/1), pale yellow oil, 250 mg, 81% yield based on 1 mmol benzyl bromide starting material. R_f = 0.58 (hexane). The NMR data accords with the reference.[247]



5-3l

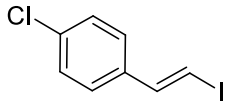
5-3l: (E/Z = 98/2), yellow solid, 184 mg, 66% yield based on 1 mmol benzyl bromide starting material. R_f = 0.54 (hexane). The NMR data accords with the reference.[247]

Method II: A solution of CH_2I_2 (161 Ml, 2.0 mmol) in THF (0.5 Ml) was added dropwise to a solution of LiHMDS (0.36 g, 1.0 mmol) in THF (2 Ml) and ether (2Ml) at –78 °C (dry ice/acetone bath) in the dark. After 20 min, a solution of the benzyl bromide substrate (1.0 mmol) in THF (1 Ml) was added in dropwise fashion. The reaction mixture was stirred at –78 ºC and allowed to warm to rt slowly over 16 h. Then solution of DBU (298 Ml, 2.0 mmol) was added dropwise and the stirred further for 1 h before ether (15 mL) was adDEd. The mixture was filtered through a plug of celite/silica and the solvent removed under reduced pressure. The residue was purified by flash chromatography to provide the vinyl iodides **5-3a**, **5-3e**, **5-3h**, **5-3i**, **5-3j** and **5-3k**.



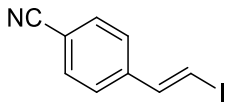
5-3a

5-3a: (E/Z = 90/10), orange oil, 598 mg, 65% yield based on 4 mmol alkyne starting material. R_f = 0.6 (hexane). The NMR data accords with the reference.[247]



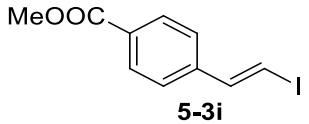
5-3e

5-3e: (E/Z = 98/2), yellow solid, 198 mg, 75% yield based on 1 mmol benzyl bromide starting material. R_f = 0.6 (hexane). The NMR data accords with the reference.[249]



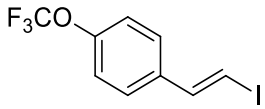
5-3h

5-3h: (E/Z > 99/1), pale yellow solid, 153 mg, 60% yield based on 1 mmol benzyl bromide starting material. R_f = 0.4 (hexane/ethyl acetate 10/1). The NMR data accords with the reference.[247]



5-3i

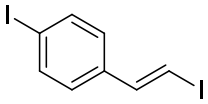
5-3i: (E/Z > 99/1), pale white solid, 500 mg, 87% yield based on 2 mmol benzyl bromide starting material. R_f = 0.6 (hexane/ethyl acetate = 5/1). The NMR data accords with the reference.[250]



5-3j

5-3j: (E/Z = 97/3), clear oil, 534 mg, 85% yield based on 2 mmol benzyl bromide starting material. R_f = 0.61 (hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 15.0 Hz, 1H), 7.32 (d, *J* = 8.7 Hz, 2H), 7.17 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 14.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0,

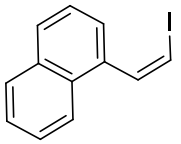
143.5, 136.4, 127.3, 121.1, 120.4 (q, *J* = 256 Hz), 77.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.97 (s, 3F). GCMS: (EI) m/z: $[M]^+$ Calcd for $C_9H_6F_3IO$ 313.9415, found 314.0.



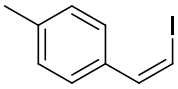
5-3k

5-3k: (E/Z = 91/9), light yellow solid, 254 mg, 71% yield based on 1 mmol benzyl bromide starting material. R_f = 0.61 (hexane). The NMR data accords with the reference.[251]

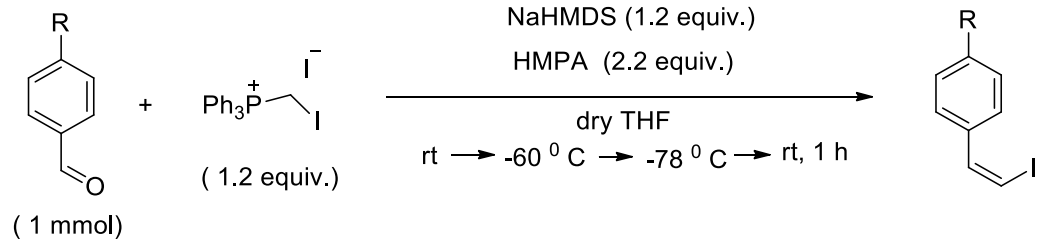
b. Synthesis of (Z)-β-Aryl Vinyl Iodides 5-3m, 5-3n:[252]



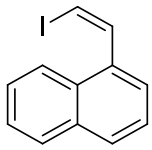
5-3m



5-3n

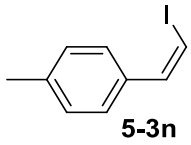


(iodomethyl)triphenylphosphonium iodide (1.2 equiv.), synthesized according to the reference[253], was added in dry THF (giving a 2.3 M solution) followed by dropwise addition of 0.5 M solution of NaHMDS in tetrahydrofuran (1.2 eq). After addition was complete, the reaction mixture was cooled to -60 °C and HMPA (2.2 eq.) was added, and the solution was further cooled to -78 °C. The aromatic aldehyde (1 mmol) was then added, the reaction mixture stirred for five minutes and warmed to room temperature. After 60 minutes, diethyl ether was added, and the reaction mixture was filtered through a pad of Celite. The resultant crude material was purified by normal phase flash chromatography (hexane) to give the desired (Z)-vinyl iodides **5-3m**, **5-3n**.



5-3m

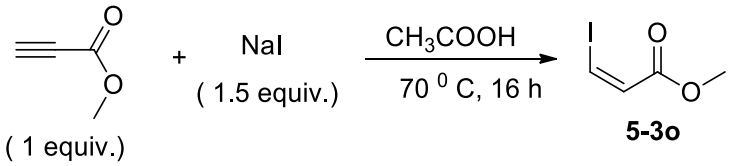
5-3m: (Z/E = 94/6) yellow solid, 140 mg, 50% yield. R_f = 0.63 (hexane). The NMR data accords with the reference.[254]



5-3n

5-3n: (Z/E = 78/22), light yellow liquid, 121 mg, 50% yield. R_f = 0.59 (hexane). The NMR data accords with the reference.[252]

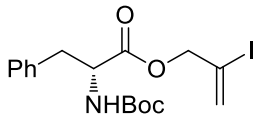
c. Synthetic procedure for 5-3o.[255]



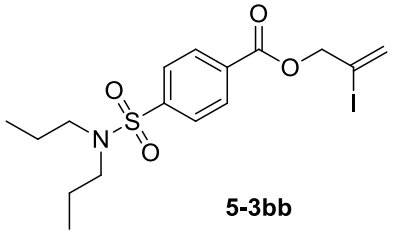
To the solution of sodium iodide (13.27 g, 88.5 mmol, 1.5 equiv) in acetic acid (7 Ml, 1.7 M), methyl propiolate (4.9 Ml, 59.0 mmol, 1 equiv) was added at room temperature and then stirred at 70 °C for 16 h. The mixture was cooled to room temperature, diluted with water (12 Ml) and diethyl ether (12 Ml), and then the separated aqueous phase was extracted with diethyl ether (2×15 Ml). The combined organic extracts were neutralized with a 3 M aqueous solution of potassium hydroxide, washed with brine (20 Ml), and then dried over $MgSO_4$, filtered, and concentrated in vacuo to obtain the vinyl iodide **5-3o** (2.2 g, 88 %) as a yellow oil.

5-3o: yellow oil, 2.2 g, 88 % yield. R_f = 0.59 (hexane/ethyl acetate 5/1). The NMR data accords with the reference.[255]

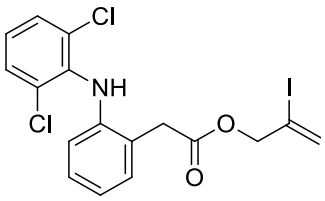
d. General synthetic procedure for 5-3aa, 5-3bb, 5-3dd, and 5-3ee[178]



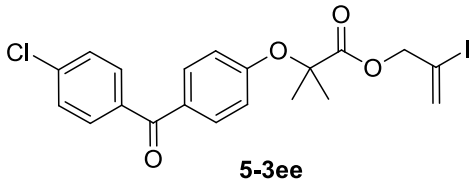
5-3aa



5-3bb

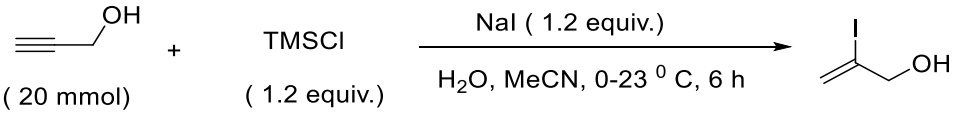


5-3dd

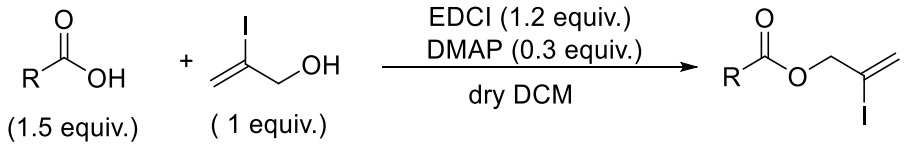


5-3ee

Procedure for synthesis of 2-iodoprop-2-en-1-ol.[256]

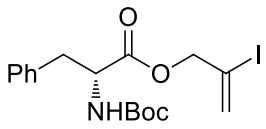


A solution of NaI (3.60 g, 24.0 mmol) in MeCN (40 Ml) was allowed to cool to 0 °C and then charged with TMSCl (3.05 Ml, 24.0 mmol). The mixture was allowed to stir for 30 min at 0 °C, after which H_2O (216 Ml, 12.0 mmol) was added, immediately followed by propargyl alcohol (1.16 Ml, 20.0 mmol). The solution was allowed to stir at 23 °C for 6 h, and then quenched by the addition of a saturated solution of aqueous $NaHCO_3$ (110 Ml). The mixture was washed with Et_2O (3 × 70 Ml). The combined organic layers were washed with a saturated solution of aqueous $Na_2S_2O_3$ (3 × 90 Ml) and dried over $MgSO_4$ and then filtered. The resultant organic layer was evaporated in vacuo to afford dark oil, which was purified by silica gel chromatography (Hexane/EtOAc = 8/2) to furnish 2-iodoprop-2-en-1-ol as colorless oil (2.4 g, 65% yield). The NMR data accords with the reference.[256]



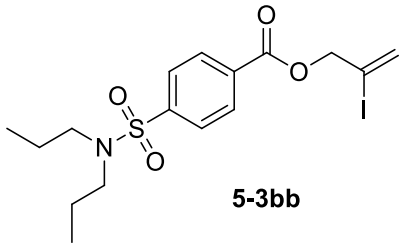
A 50-Ml flask fitted with a stirring bar was charged with a solution of the carboxylic acid (1.5 equiv.), the alcohol (1 equiv.), and 4-dimethylaminopyridine (DMAP) (0.3 equiv) in dichloromethane (8 Ml or 12 Ml). 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide Hydrochloride

(EDCI) (1.2 equiv) was then added, and the reaction mixture was stirred overnight at room temperature. After the reaction was completed, the resulting mixture was evaporated in vacuo. The resulting residue was purified by column chromatography using hexane/ethyl acetate to afford the desired ester **5-3aa**, **5-3bb**, **5-3dd**, **5-3ee**.



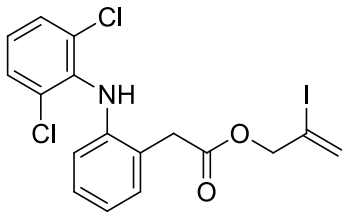
5-3aa

5-3aa: colorless solid, 600 mg, 70% yield based on 2 mmol 2-iodoprop-2-en-1-ol starting material. R_f = 0.43 (hexane/ethyl acetate = 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 3H), 7.16 (m, 2H), 6.29 (s, 1H), 5.91 (s, 1H), 4.92 (d, *J* = 8.3 Hz, 1H), 4.68 (m, 3H), 3.13 (m, 2H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 155.1, 135.8, 129.3, 128.6, 127.9, 127.1, 100.9, 80.1, 71.5, 54.4, 38.2, 28.3. GCMS: (EI) m/z: $[M]^+$ Calcd for $C_{17}H_{22}INO_4$ 431.0594, found 431.0.



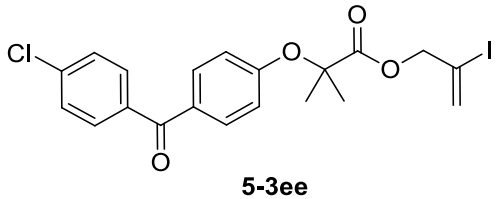
5-3bb

5-3bb: white solid, 363 mg, 80% yield based on 1 mmol 2-iodoprop-2-en-1-ol starting material. R_f = 0.22 (hexane/ethyl acetate = 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.5 Hz, 2H), 7.89 (d, *J* = 8.4 Hz, 2H), 6.45 (d, *J* = 1.7 Hz, 1H), 6.00 (m, 1H), 4.94 (s, 2H), 3.10 (m, 4H), 1.54 (p, *J* = 7.5 Hz, 4H), 0.87 (t, *J* = 7.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 144.7, 132.8, 130.4, 128.1, 127.1, 101.5, 71.7, 49.9, 21.9, 11.1. GCMS: (EI) m/z: $[M]^+$ Calcd for $C_{16}H_{22}INO_4S$ 451.0314, found 451.0.



5-3dd

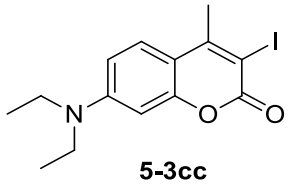
5-3dd: white solid, 420 mg, 61% yield based on 1.5 mmol 2-iodoprop-2-en-1-ol starting material. R_f = 0.60 (hexane/ethyl acetate = 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.1 Hz, 2H), 7.28 (s, 1H), 7.13 (s, 1H), 7.00 (m, 2H), 6.78 (s, 1H), 6.58 (d, *J* = 8.1 Hz, 1H), 6.30 (s, 1H), 5.92 (s, 1H), 4.76 (s, 2H), 3.91 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 142.7, 137.8, 130.9, 129.5, 128.9, 128.2, 127.4, 124.1, 124.0, 122.2, 118.5, 101.6, 71.2, 38.3. GCMS: (EI) m/z: $[M]^+$ Calcd for $C_{17}H_{14}Cl_2INO_2$ 460.9446, found 460.9.



5-3ee

5-3ee: white solid, 485 mg, 67% yield based on 1.5 mmol 2-iodoprop-2-en-1-ol starting material. R_f = 0.48 (hexane/ethyl acetate = 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (m, 4H), 7.45 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.9 Hz, 2H), 6.32 (s, 1H), 5.93 (s, 1H), 4.77 (s, 2H), 1.72 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 172.6, 159.4, 138.4, 136.3, 132.0, 131.2, 130.6, 128.5, 117.6, 100.9, 79.4, 71.8, 25.5. GCMS: (EI) m/z: $[M]^+$ Calcd for $C_{20}H_{18}ClIO_4$ 483.9938, found 484.0.

The compound 5-3cc was synthesized according to the reference [238]

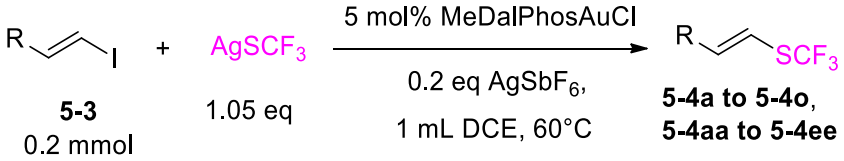


5-3cc

5-3cc: light yellow solid, 165 mg, 92% yield based on 0.5 mmol of Coumarin. R_f = 0.32 (hexane/ethyl acetate = 4/1).The NMR data accords with the reference.[238]

5.4.3.3. Trifluoromethylthiolation of alkenyl iodides

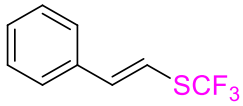
General procedure:



5-3
0.2 mmol

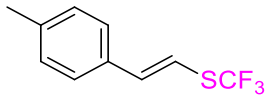
5-4a to 5-4o,
5-4aa to 5-4ee

An 8-Ml reaction vial fitted with a stirring bar was loaded with MeDalPhosAuCl (5 mol%), $AgSCF_3$ (1.05 equiv) and 1 Ml DCE. Alkenyl iodide **5-3** (0.2 mmol) was added and the resulting mixture was stirred at room temperature for 1 min. $AgSbF_6$ (0.2 equiv) was then added and the reaction was stirred at room temperature for 1 min before being heated to 60 °C on a block heater. The reaction was monitored with GC/MS. Upon completion, the reaction mixture was diluted with 2 Ml DCM and then filtered through a short silica pad (Length: 15 mm, I.D.: 15 mm), eluted with mixed solvent (Hexane/EtOAc) until no product **5-4** was remained on the column. The filtrate was concentrated and purified with Teledyne ISCO flash chromatography EZ Prep using a 150 mm × 20 mm column (packing material: RediSep Prep C18, 100 Å, 5 μm) with a H_2O–MeCN gradient (100:0 to 0:100) for 40 min at a flow rate of 19 Ml/min.



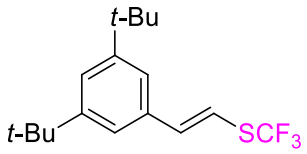
5-4a

5-4a: (E/Z = 96/4) Colorless oil, 33 mg, 81 % yield. R_f = 0.76 (hexane). The NMR data accords with the reference.[257]



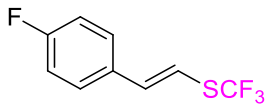
5-4b

5-4b: (E/Z > 99/1) Colorless oil, 36 mg, 83 % yield. R_f = 0.77 (hexane). The NMR data accords with the reference.[52]



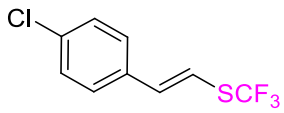
5-4c

5-4c: (E/Z = 99/1) white solid, 58 mg, 92 % yield. R_f = 0.78 (hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 1.8 Hz, 1H), 7.24 (d, *J* = 1.8 Hz, 2H), 7.07 (d, *J* = 15.2 Hz, 1H), 6.70 (d, *J* = 15.2 Hz, 1H), 1.35 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 143.2, 134.4, 129.6 (q, *J* = 307 Hz) 121.2, 110.4, 34.9, 31.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -42.87 (s, 3F). HRMS: (EI) m/z: $[M]^+$ Calcd for $C_{17}H_{23}F_3S$ 316.1473, found 316.1469.



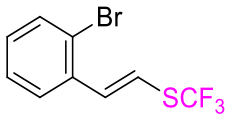
5-4d

5-4d: (E/Z = 97/3) Colorless oil, 39 mg, 88 % yield. R_f = 0.57 (hexane). The NMR data accords with the reference.[258]



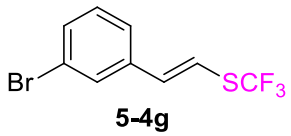
5-4e

5-4e: (E/Z = 98/2) Colorless oil, 43 mg, 90 % yield. R_f = 0.58 (hexane). The NMR data accords with the reference.[257]



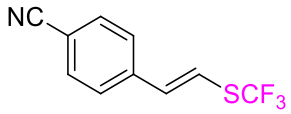
5-4f

5-4f: (E/Z > 99/1) Colorless oil, 54 mg, 95 % yield. R_f = 0.57 (hexane). The NMR data accords with the reference.[257]



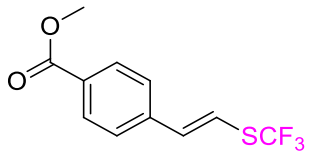
5-4g

5-4g: (E/Z = 98/2) Colorless oil, 55 mg, 97 % yield. R_f = 0.57 (hexane). The NMR data accords with the reference.[258]



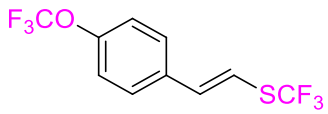
5-4h

5-4h: (E/Z > 99/1) white solid, 43 mg, 94 % yield. R_f = 0.66 (hexane/ethyl acetate = 5/1). The NMR data accords with the reference.[257]



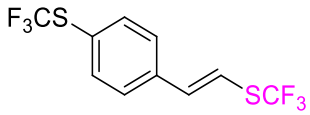
5-4i

5-4i: (E/Z > 99/1) white solid, 49 mg, 93 % yield. R_f = 0.72 (hexane/ethyl acetate = 5/1). The NMR data accords with the reference.[257]



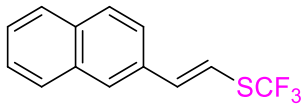
5-4j

5-4j: (E/Z = 97/3) Colorless oil, 52 mg, 90 % yield. R_f = 0.5 (hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.7 Hz, 2H), 7.21 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 15.3 Hz, 1H), 6.74 (d, *J* = 15.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 138.9, 133.7, 129.5 (q, *J* = 307 Hz) 128.2, 121.3, 120.4 (q, *J* = 257 Hz), 113.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -42.73 (s, 3F), -57.96 (s, 3F). HRMS: (EI) m/z: $[M]^+$ Calcd for $C_{10}H_6F_6OS$ 288.0044, found 288.0039.



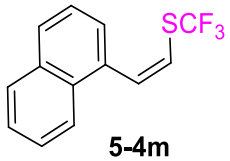
5-4k

5-4k: (E/Z = 93/7) colorless oil, 48 mg, 79 % yield. R_f = 0.78 (hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 8.3 Hz, 2H), 6.96 (d, *J* = 15.5 Hz, 1H), 6.85 (d, *J* = 15.4 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -42.45 (s, 3F), -42.59 (s, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 137.5, 136.6, 136.3, 129.4 (q, *J* = 307 Hz), 129.0 (q, *J* = 307 Hz), 127.5, 115.1. HRMS: (EI) m/z: $[M]^+$ Calcd for $C_{10}H_6F_6S_2$ 303.9815, found 303.9811.



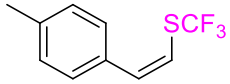
5-4l

5-4l: (E/Z = 98/2) white solid, 45 mg, 88 % yield. R_f = 0.75 (hexane). The NMR data accords with the reference.[257]



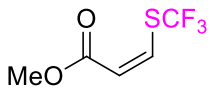
5-4m

5-4m: (Z/E = 98/2) light yellow solid, 42 mg, 83 % yield. R_f = 0.75 (hexane). The NMR data accords with the reference.[259]



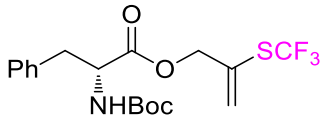
5-4n

5-4n: (Z/E = 78/22) light yellow oil, 37 mg, 85% yield. R_f = 0.77 (hexane). The NMR data accords with the reference.[259]



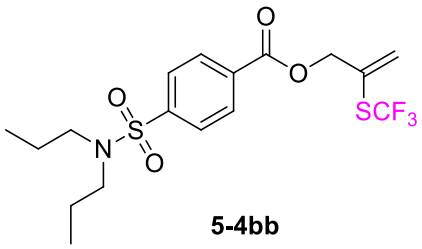
5-4o

5-4o: 99 % NMR yield. The NMR data accords with the reference.[52]



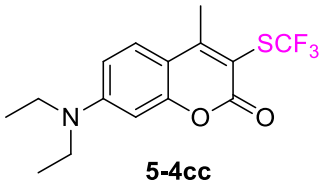
5-4aa

5-4aa: white solid, 69 mg, 85% yield. R_f = 0.44 (hexane/ethyl acetate = 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.21 (m, 3H), 7.15 (d, *J* = 6.6 Hz, 2H), 5.88 (s, 2H), 4.95 (s, 1H), 4.73 (s, 2H), 4.64 (s, 1H), 3.10 (s, 2H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 155.1, 135.7, 130.9, 129.3 (q, *J* = 307.0 Hz), 129.2, 128.6, 127.1, 80.1, 66.6, 54.5, 38.3, 28.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -40.92 (s, 3F). HRMS: (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{22}O_4NF_3NaS$ 428.1114, Found: 428.1116.



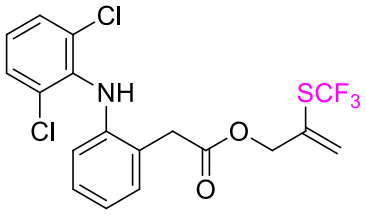
5-4bb

5-4bb: colorless oil, 78 mg, 91% yield. R_f = 0.44 (hexane/ethyl acetate = 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.1 Hz, 2H), 7.89 (d, *J* = 8.1 Hz, 2H), 6.09 (s, 1H), 6.01 (s, 1H), 5.00 (s, 2H), 3.10 (t, *J* = 7.5 Hz, 4H), 1.55 (h, *J* = 7.5 Hz, 4H), 0.87 (t, *J* = 7.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 144.7, 132.6, 131.0, 130.3, 129.8, 129.3 (q, *J* = 307.4 Hz), 127.1, 67.0, 49.9, 21.9, 11.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ -40.83 (s, 3F). HRMS: (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{22}O_4NF_3NaS_2$ 448.0835, Found: 448.0835.



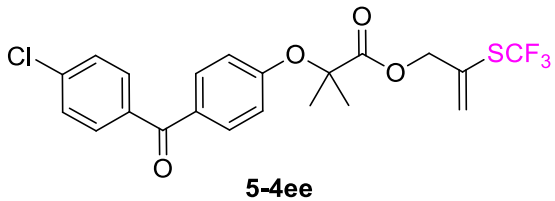
5-4cc

5-4cc: yellow solid, 57 mg, 86% yield. R_f = 0.24 (hexane/ethyl acetate = 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 9.3 Hz, 1H), 6.61 (d, *J* = 8.9 Hz, 1H), 6.46 (s, 1H), 3.43 (m, 4H), 2.70 (s, 3H), 1.12 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 160.7, 156.2, 152.1, 129.6 (q, *J* = 309.7 Hz), 127.7, 109.1, 109.0, 103.1, 97.0, 44.9, 18.0, 12.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -42.76 (s, 3F). HRMS: (ESI) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{16}O_2NF_3NaS$ 354.0746, Found: 354.0747.



5-4dd

5-4dd: light yellow oil, 56 mg, 64% yield. R_f = 0.62 (hexane/ethyl acetate = 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.0 Hz, 2H), 7.24 (s, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 6.98 (q, *J* = 7.4, 6.8 Hz, 2H), 6.74 (s, 1H), 6.56 (d, *J* = 8.1 Hz, 1H), 5.89 (s, 2H), 4.80 (s, 2H), 3.89 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 142.7, 137.7, 130.9, 130.5, 129.6, 129.5, 129.3 (q, *J* = 307.6 Hz), 128.9, 128.2, 124.1, 123.9, 122.2, 118.4, 66.5, 38.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ -40.86 (s, 3F). HRMS: (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{14}O_2NCl_2F_3NaS$ 457.9967, Found: 457.9966.

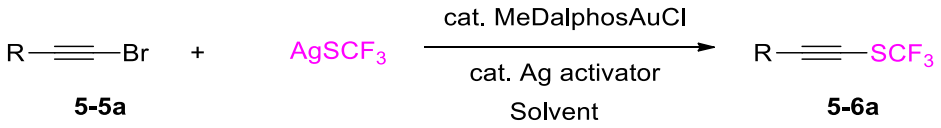


5-4ee

5-4ee: colorless oil, 82 mg, 89% yield. R_f = 0.48 (hexane/ethyl acetate = 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.60 (m, 4H), 7.44 (d, *J* = 7.7 Hz, 2H), 6.87 (d, *J* = 7.9 Hz, 2H), 5.89 (s, 2H), 4.81 (s, 2H), 1.71 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 172.8, 159.4, 138.4, 136.3, 132.0, 131.1, 131.0, 130.7, 129.5, 129.2 (q, *J* = 307.7 Hz), 128.5, 117.4, 79.4, 66.9, 25.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -41.14 (s, 3F). HRMS: (ESI) m/z: $[M + H]^+$ Calcd for $C_{21}H_{19}O_4ClF_3S$ 459.0639, Found: 459.0640.

5.4.4. Trifluoromethylthiolation of alkynyl halides

5.4.4.1. Reaction condition optimization



6. Effect of solvents on the reaction[a]

Entry	Reaction condition	GC Yield (5-5a/5-6a)
1	**5-5a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCM, 0.2 eq $AgSbF_6$ was added, 70 °C, 2 h	31% / **35%**
2	**5-5a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 70 °C, 2 h	47% / **47%**
3	**5-5a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml THF, 0.2 eq $AgSbF_6$ was added, 70 °C, 2 h	56% / **7%**
4	**5-5a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml EtOAc, 0.2 eq $AgSbF_6$ was added, 70 °C, 2 h	54% / **25%**
5	**5-5a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml Toluene, 0.2 eq $AgSbF_6$ was added, 70 °C, 2 h	21% / **38%**
6	**5-5a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml I, 0.2 eq $AgSbF_6$ was added, 70 °C, 2 h	58% / **5%**
7	**5-5a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DMF, 0.2 eq $AgSbF_6$ was added, 70 °C, 2 h	74% / **3%**

[a] Experimental procedure: An 8-Ml glass vial was loaded with 5 mol% Au catalyst, 1.05 eq $AgSCF_3$, and 0.5 Ml DCE sequentially. 0.1 mmol **5-5a** was then added, and the mixture was stirred for 1 min before 0.2 eq $AgSbF_6$ was added. The resulting mixture was stirred at 70 ^oC for 2 h. The reaction was then monitored with GC/MS.

b. Effect of silver activator on the reaction[a]

Entry	Reaction condition	GC Yield (5-5a/5-6a)
1	**5-5a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 70 °C, 2 h	47% / **47%**
2	**5-5a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq AgOTf was added, 70 °C, 2 h	77% /**23%**
3	**5-5a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgNTf_2$ was added, 70 °C, 2 h	64% / **20%**
4	**5-5a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgPF_6$ was added, 70 °C, 2 h	42% / **27%**
5	**5-5a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgBF_4$ was added, 70 °C, 2 h	59% / **22%**

[a] Experimental procedure: An 8-Ml glass vial was loaded with 5 mol% Au catalyst, 1.05 eq $AgSCF_3$, and 0.5 Ml DCE sequentially. 0.1 mmol **5-5a** was then added, and the mixture was stirred for 1 min before 0.2 eq silver activator was added. The resulting mixture was stirred at 70 °C for 2 h. The reaction was then monitored with GC/MS.

c. Effect of gold pre-catalyst on the reaction[a]

Entry	Reaction condition	GC Yield (5-5a/5-6a)
1	**5-5a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 70 °C, 2h	47% / **47%**
2	**5-5a** + $AgSCF_3$ + 3 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 70 °C, 2h	56% / **40%**
3	**5-5a** + $AgSCF_3$ + 1 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 70 °C, 2h	77% / **18%**

[a] Experimental procedure: An 8-Ml glass vial was loaded with x mol% Au catalyst, 1.05 eq $AgSCF_3$, and 0.5 Ml DCE sequentially. 0.1 mmol **5-5a** was then added, and the mixture was stirred for 1 min before 0.2 eq $AgSbF_6$ was added. The resulting mixture was stirred at 70 °C for 2 h. The reaction was then monitored with GC/MS.

d. Effect of silver activator amount on the reaction[a]

Entry	Reaction condition	GC Yield (5-5a/5-6a)
1	**5-5a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.1 eq $AgSbF_6$ was added, 70 °C, 2 h	67% / **33%**
2	**5-5a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 70 °C, 2 h	47% / **47%**
3	**5-5a** + $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.3 eq $AgSbF_6$ was added, 70 °C, 2 h	13% / **33%**

[a] Experimental procedure: An 8-Ml glass vial was loaded with 5 mol% Au catalyst, 1.05 eq $AgSCF_3$, and 0.5 Ml DCE sequentially. 0.1 mmol **5-5a** was then added, and the mixture was stirred for 1 min before x eq $AgSbF_6$ was added. The resulting mixture was stirred at 70 °C for 2 h. The reaction was then monitored with GC/MS.

e. Effect of $AgSCF_3$ amount on the reaction[a]

Entry	Reaction condition	GC Yield (5-5a/5-6a)
1	**5-5a** + 1.05 eq $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 70 °C, 2 h	47% / **47%**
2	**5-5a** + 1.3 eq $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 70 °C, 2 h	55% /**43%**
3	**5-5a** + 1.5 eq $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 70 °C, 2 h	41% / **30%**
4	**5-5a** + 1.8 eq $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 70 °C, 2 h	48% / **28%**
5	**5-5a** + 2.0 eq $AgSCF_3$ + 5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 70 °C, 2 h	50% / **27%**

[a] Experimental procedure: An 8-Ml glass vial was loaded with 5 mol% Au catalyst, x eq $AgSCF_3$, and 0.5 Ml DCE sequentially. 0.1 mmol **5-5a** was then added, and the mixture was stirred for 1 min before 0.2 eq $AgSbF_6$ was added. The resulting mixture was stirred at 70 °C for 2 h. The reaction was then monitored with GC/MS.

f. Effect of concentration on the reaction[a]

Entry	Reaction condition	GC Yield (5-5a/5-6a)
1	**5-5a** + $AgSCF_3$ + 5 mol% Au in 0.25 Ml DCE, 0.2 eq $AgSbF_6$ was added, 70 °C, 2 h	27% / **47%**
2	**5-5a** + $AgSCF_3$ + 5 mol% Au in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 70 °C, 2 h	47% / **47%**
3	**5-5a** + $AgSCF_3$ + 5 mol% Au in 1 Ml DCE, 0.2 eq $AgSbF_6$ was added, 70 °C, 2 h	38% / **16%**

[a] Experimental procedure: An 8-Ml glass vial was loaded with 5 mol% Au catalyst, 1.05 eq $AgSCF_3$, and x Ml DCE sequentially. 0.1 mmol **5-5a** was then added, and the mixture was stirred for 1 min before 0.2 eq $AgSbF_6$ was added. The resulting mixture was stirred 70 ^oC for 2 h. The reaction was then monitored with GC/MS.

g. Effect of temperature on the reaction[a]

Entry	Reaction condition	GC Yield (5-5a/5-6a)
1	**5-5a** + $AgSCF_3$ + 5 mol% Au in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 50 ^oC, 2 h	62% **/ 13%**
2	**5-5a** + $AgSCF_3$ +5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 60 ^oC, 2 h	45% / **20%**
3	**5-5a** + $AgSCF_3$ +5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 70 ^oC, 2 h	47% / **47%**
4	**5-5a** + $AgSCF_3$ +5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 80 ^oC, 2 h	35% / **59%**
5	**5-5a** + $AgSCF_3$ +5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 70 ^oC, 12 h	13% / **82%**
6	**5-5a** + $AgSCF_3$ +5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 80 ^oC, 12 h	0% / **80%**
7	**5-5a** + $AgSCF_3$ +5 mol% **Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 70 ^oC, 24 h	0% / **92%**[b]

[a] Experimental procedure: An 8-Ml glass vial was loaded with 5 mol% Au catalyst, 1.05 eq $AgSCF_3$, and 0.5 Ml DCE/DCM sequentially. 0.1 mmol **5-5a** was then added, and the mixture was stirred for 1 min before 0.2

eq $AgSbF_6$ was added. The resulting mixture was stirred at X °C for designated time. The reaction was then monitored with GC/MS. [b] 10 mg activated molecular sieves was added, 18 h, 96% product.

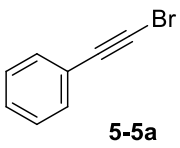
h. Control experiment[a]

Entry	Reaction condition	GC Yield (5-5a/5-6a)
1	**5-5a** + $AgSCF_3$ + **0 mol% Au** in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 70 °C, 2 h	**75% / 0%**
2	**5-5a** + $AgSCF_3$ + 5 mol% Au in 0.5 Ml DCE, 0 eq $AgSbF_6$ was added, 70 °C, 2 h	55% / **11%**
3	**5-5a** + $AgSCF_3$ + 5 mol% Au in 0.5 Ml DCE, 0.2 eq $AgSbF_6$ was added, 70 °C, 2 h	47% / **47%**

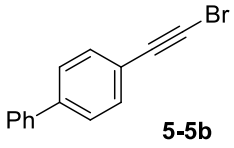
[a] Experimental procedure: An 8-Ml glass vial was loaded with x mol% Au catalyst, 1.05 eq $AgSCF_3$, and 0.5 Ml solvent sequentially. 0.1 mmol **5-5a** was then added, and the mixture was stirred for 1 min before x eq $AgSbF_6$ was added. The resulting mixture was stirred at 70 °C for 2 h. The reaction was then monitored with GC/MS.

5.4.4.2. Preparation of alkynyl bromides

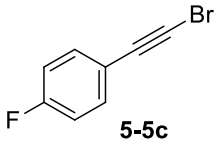
General procedure for the Synthesis of bromoalkynes.[260]



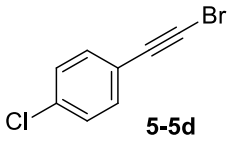
5-5a



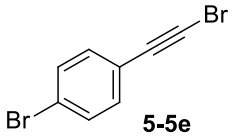
5-5b



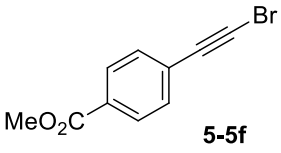
5-5c



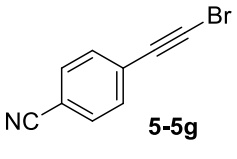
5-5d



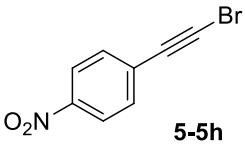
5-5e



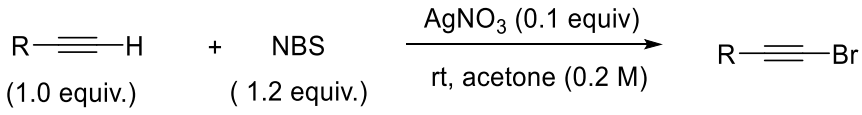
5-5f



5-5g

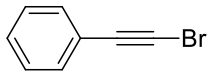


5-5h



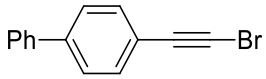
To a solution of alkyne (1.0 equiv.) was added *N*-bromosuccinimide (1.2 equiv) and silver nitrate (0.1 equiv). The mixture was allowed to stir at room temperature under protection from light until completion of the reaction. The mixture was then passed through short plug of silica and eluted with additional 20 ml of acetone and concentrated

under reduced pressure to get crude product. The crude product was purified by column chromatography to give the desired bromoalkynes **5-5a** to **5-5h**.



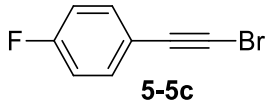
5-5a

5-5a: orange oil, 1.47 g, 81% yield based on 10 mmol alkyne starting material. R_f = 0.82 (hexane). The NMR data accords with the reference.[260]



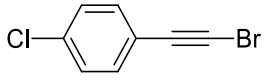
5-5b

5-5b: white solid, 225 mg, 88 % yield based on 1 mmol alkyne starting material. R_f = 0.7 (hexane). The NMR data accords with the reference.[261]



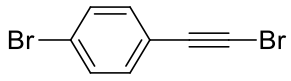
5-5c

5-5c: colorless oil, 1.2 g, 74 % yield based on 8.2 mmol alkyne starting material. R_f = 0.56 (hexane). The NMR data accords with the reference.[261]



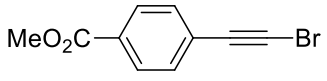
5-5d

5-5d: Light yellow solid, 352 mg, 82 % yield. R_f = 0.59 (hexane). The NMR data accords with the reference.[260]



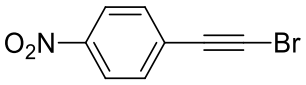
5-5e

5-5e: light brown solid, 478 mg, 92% yield based on 2 mmol alkyne starting material. R_f = 0.6 (hexane). The NMR data accords with the reference.[260]



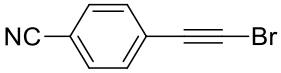
5-5f

5-5f: white solid, 190 mg, 80% yield based on 1 mmol alkyne starting material. R_f = 0.71 (hexane/ethyl acetate = 5/1). The NMR data accords with the reference.[260]



5-5g

5-5g: yellow solid, 367 mg, 81% yield based on 2 mmol alkyne starting material. R_f = 0.66 (hexane/ethyl acetate = 10/1). The NMR data accords with the reference.[260]

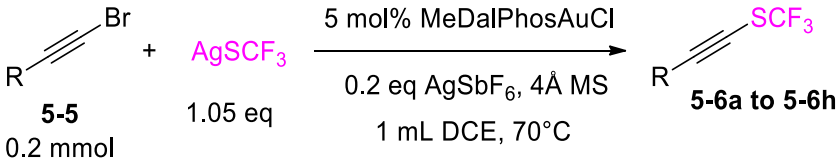


5-5h

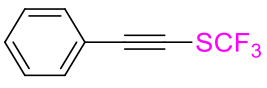
5-5h: white solid, 333 mg, 81% yield based on 2 mmol alkyne starting material. R_f = 0.75 (hexane/ethyl acetate = 10/1). The NMR data accords with the reference.[261]

5.4.4.3 Trifluoromethylthiolation of alkynyl bromides

General procedure:

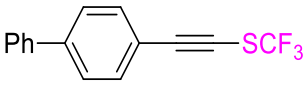


An 8-Ml reaction vial fitted with a stirring bar was loaded with MeDalPhosAuCl (5 mol%), $AgSCF_3$ (1.05 equiv) and 1 Ml DCE. Alkynyl bromide **5-5** (0.2 mmol) was added, and the resulting mixture was stirred at room temperature for 1 min. $AgSbF_6$ (0.2 equiv) was then added and the reaction was stirred at room temperature for 1 min before being heated to 70 °C on a block heater. The reaction was monitored with GC/MS. Upon completion, the reaction mixture was diluted with 2 Ml DCM and then filtered through a short silica pad (Length: 15 mm, I.D.: 15 mm), eluted with mixed solvent (Hexane/EtOAc) until no product 5-6 was remained on the column. The filtrate was concentrated and purified with Teledyne ISCO flash chromatography EZ Prep using a 150 mm × 20 mm column (packing material: RediSep Prep C18, 100 Å, 5 μm) with a H_2O–MeCN gradient (100:0 to 0:100) for 40 min at a flow rate of 19 Ml/min.



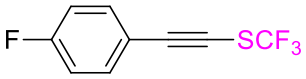
5-6a

5-6a: 95% NMR yield. The NMR data accords with the reference.[262]



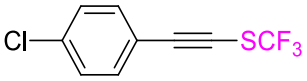
5-6b

5-6b: white solid, 53 mg, 95% yield. R_f = 0.68 (hexane). The NMR data accords with the reference.[262]



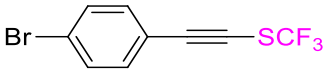
5-6c

6c: 94% NMR yield. The NMR data accords with the reference.[262]



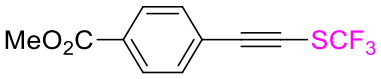
5-6d

5-6d: yellow oil, 39 mg, 82% yield. R_f = 0.6 (hexane). The NMR data accords with the reference.[263]



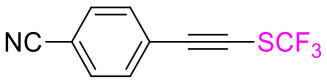
5-6e

5-6e: light brown solid, 49 mg, 87% yield. R_f = 0.6 (hexane). The NMR data accords with the reference.[263]



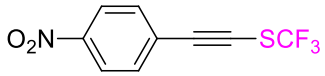
5-6f

5-6f: white solid 44 mg, 85% yield. R_f = 0.69 (hexane/ethyl acetate = 5/1). The NMR data accords with the reference.[264]



5-6g

5-6g: white solid 42 mg, 92% yield. R_f = 0.75 (hexane/ethyl acetate = 10/1). The NMR data accords with the reference.[233]

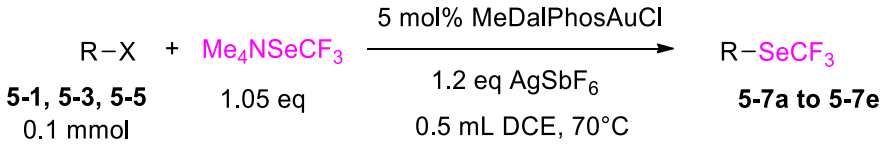


5-6h

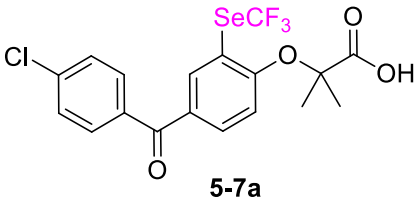
5-6h: yellow solid 43 mg, 87% yield. R_f = 0.65 (hexane/ethyl acetate = 10/1). The NMR data accords with the reference.[233]

5.4.5. Trifluoromethylselenolation of organohalides

General procedure:

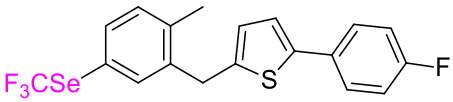


An 8-Ml reaction vial fitted with a stirring bar was loaded with MeDalPhosAuCl (5 mol%), Me_4NSCF_3 (1.05 equiv) and 0.5 Ml DCE. Organohalide **5-1/5-3/5-5** (0.1 mmol) was added and the resulting mixture was stirred at room temperature for 1 min. $AgSbF_6$ (1.2 equiv) was then added and the reaction was stirred at room temperature for 1 min before being heated to 70 °C on a block heater. The reaction was monitored with GC/MS. Upon completion, the reaction mixture was diluted with 2 Ml DCM and then filtered through a short silica pad (Length: 15 mm, I.D.: 15 mm), eluted with mixed solvent (hexane/EtOAc) until no product, **5-7** was remained on the column. The filtrate was concentrated and purified with flash chromatography using hexane/ethyl acetate to give the desired product **5-7**.



5-7a

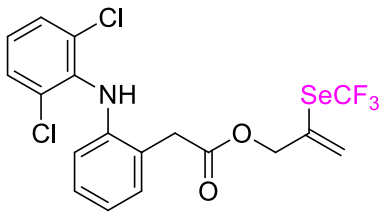
5-7a: colorless oil, 43 mg, 93% yield. R_f = 0.05 (ethyl acetate). ^{1}H NMR (400 MHz, *d*-DMSO) δ 7.87 (s, 1H), 7.75 – 7.65 (m, 1H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 1H), 1.46 (s, 6H). ^{13}C NMR (100 MHz, *d*-DMSO) δ 192.3, 173.8, 158.6, 138.2, 137.4, 135.6, 133.8, 131.2, 130.1, 128.7, 122.6 (q, *J* = 332.7 Hz), 115.4, 114.7, 80.5, 24.9. ^{19}F NMR (376 MHz, *d*-DMSO) δ -34.50 (s, 3F). HRMS: (ESI) m/z: $[M - H]^-$ Calcd for $C_{18}H_{13}O_4ClF_3Se$ 464.9624, Found: 464.9612.



5-7b

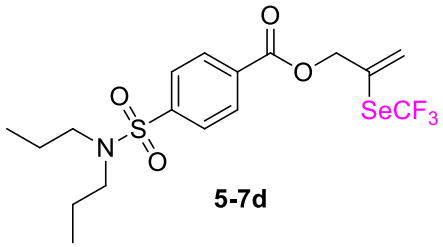
5-7b: light yellow solid, 41 mg, 95% yield. R_f = 0.12 (hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.54 – 7.42 (m, 2H), 7.21 (d, *J* = 7.8 Hz, 1H), 7.04 (m, 3H), 6.67 (s, 1H), 4.14 (s, 2H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2 (d, *J* = 246.9 Hz), 142.2, 141.9, 139.8, 139.3, 138.0, 135.6, 131.7, 130.7, 127.2 (d, *J* = 8.0 Hz), 126.2, 122.7, 122.5 (q, *J* = 331.6 Hz),

119.8, 115.7 (d, J = 21.8 Hz), 33.9, 19.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.03 (m, 1F), -36.39 (s, 3F). HRMS: (EI) m/z: $[M]^+$ Calcd for $C_{19}H_{14}F_4Sse$ 429.9918, Found: 429.9916.



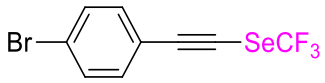
5-7c

5-7c: light yellow oil, 42 mg, 87% yield. R_f = 0.56 (hexane/ethyl acetate = 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 5.4 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 6.99 (m, 2H), 6.77 (s, 1H), 6.57 (d, J = 7.3 Hz, 1H), 6.07 (s, 1H), 5.94 (s, 1H), 4.87 (s, 2H), 3.89 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 142.7, 137.7, 130.9, 130.5, 129.5, 128.9, 128.4, 128.2, 124.1, 123.9, 122.3 (q, J = 332.9 Hz), 122.2, 118.4, 68.0, 38.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ -34.37 (s, 3F). HRMS: (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{14}O_2NCl_2F_3NaSe$ 505.9407, Found: 505.9403.



5-7d

5-7d: colorless oil, 43 mg, 92% yield. R_f = 0.37 (hexane/ethyl acetate = 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.2 Hz, 2H), 7.89 (d, J = 8.3 Hz, 2H), 6.26 (s, 1H), 6.05 (s, 1H), 5.06 (s, 2H), 3.10 (t, J = 7.6 Hz, 4H), 1.55 (h, J = 7.6 Hz, 4H), 0.87 (t, J = 7.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 144.7, 132.7, 131.1, 130.4, 128.5, 127.1, 125.6 (q, J = 331.2 Hz), 68.4, 49.9, 21.9, 11.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ -34.52 (s, 3F). HRMS: (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{22}O_4NF_3NaSSe$ 496.0279, Found: 496.0277.

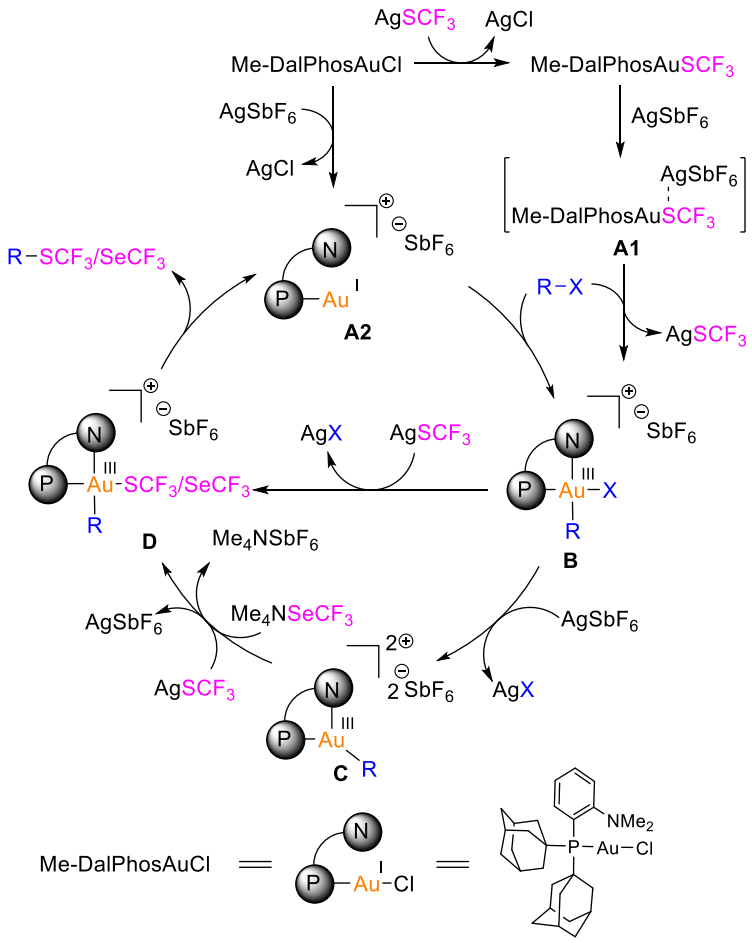


5-7e

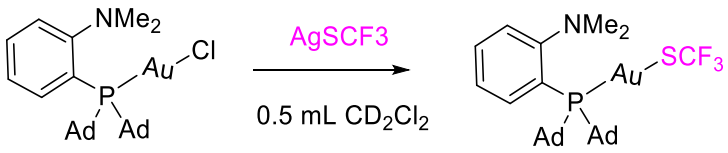
5-7e: light yellow solid, 29 mg, 89% yield. R_f = 0.51 (hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.3, 131.8, 124.0, 120.9, 120.6 (q, J = 335.3 Hz), 106.0, 63.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ -35.96 (s, 3F). HRMS: (EI) m/z: $[M]^+$ Calcd for $C_9H_{3\text{-}4b}Rf_3Se$ 327.8614, Found: 327.8604.

5.4.6. Proposed mechanistic rationale and control experiments:

5.4.6.1 Plausible mechanism

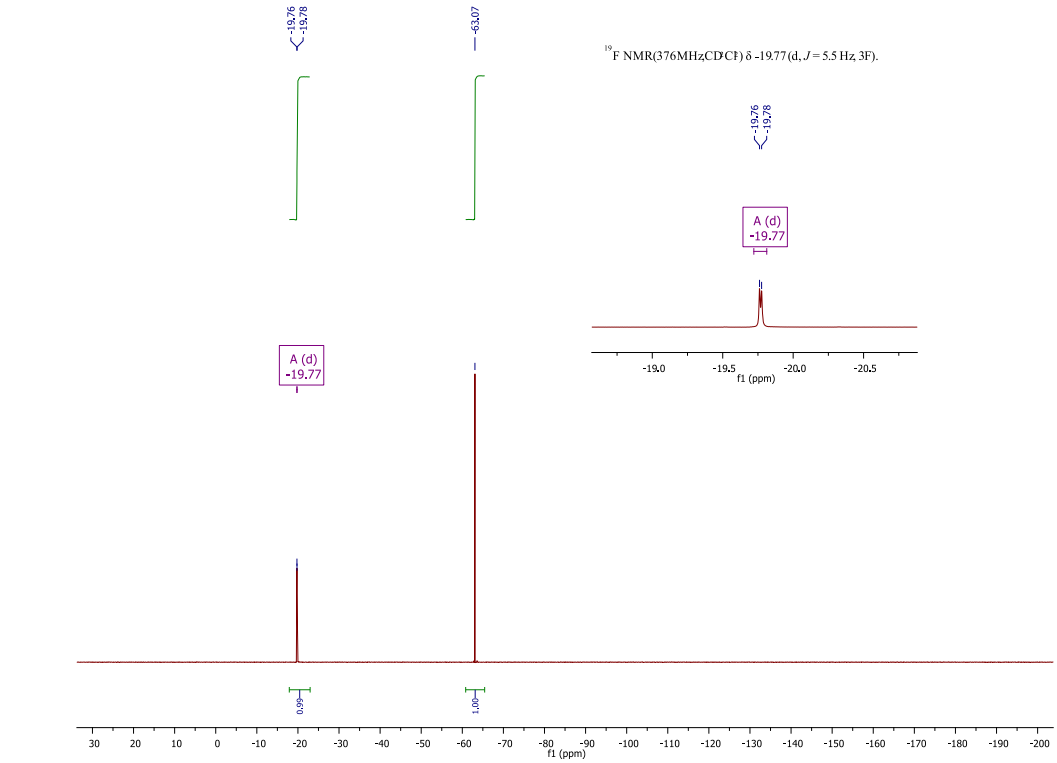


5.4.6.2 NMR study for the MeDalphosAuCl activation with $AgSCF_3$



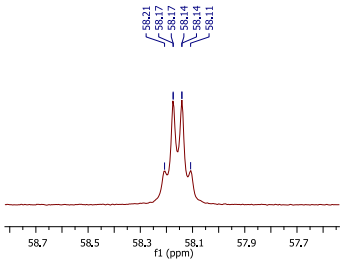
An NMR tube charged with MeDalphosAuCl (9.8 mg, 0.015 mmol) in CD_2Cl_2 (0.5 Ml) was added with $AgSCF_3$ (3.1 mg, 0.015 mmol). The tube was gently shaken, and the mixture stayed at room temperature for 15 min. 1 equivalent of benzotrifluoride was then added as an internal standard for ^{31}P NMR and ^{19}F NMR analysis. The reaction gave MeDalphosAuSCF$_3$ in 99% NMR yield and the NMRs clearly showed a F-P coupling ($J_{P\text{-}F}$ = 5.5 Hz) as a doublet in ^{19}F NMR and a quartet in ^{31}P NMR, which proved the addition of SCF_3 to the gold center.

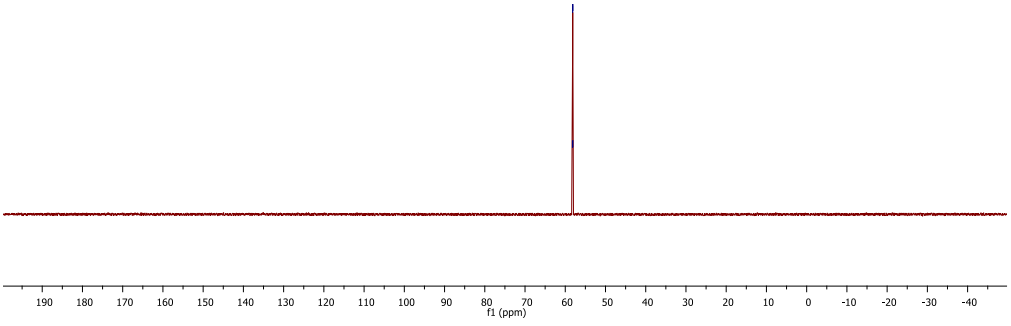
^{19}F NMR and ^{31}P NMR for the reaction:



^{19}F NMR(376MHz,CDCl$_3$) δ -19.77 (d, J = 5.5 Hz, 3F).

^{31}P NMR(162MHz, cdcl$_3$) δ 58.16 (q, J = 5 Hz, 1P).

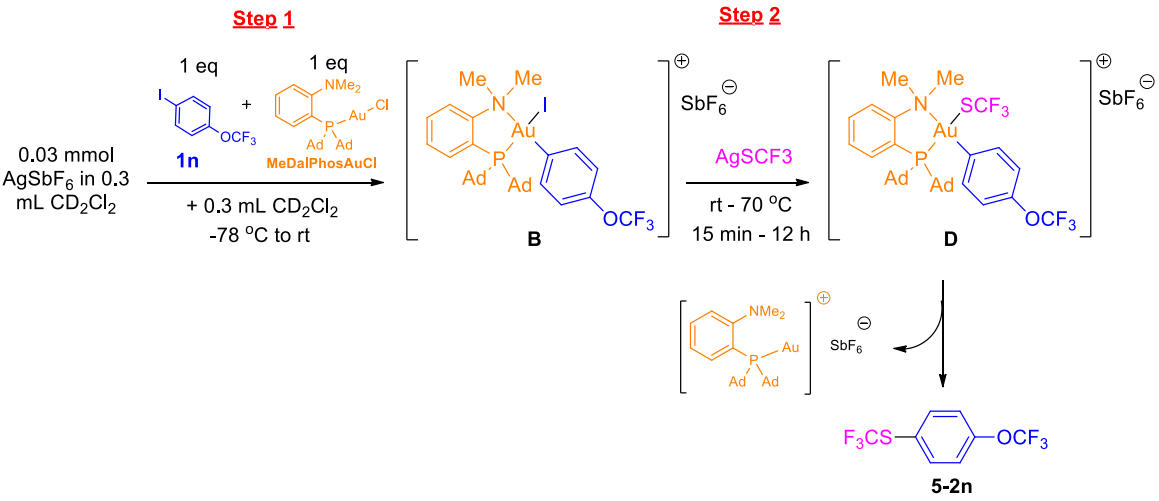




5.4.6.3 Monitoring the Au-catalyzed trifluoromethylthiolation reaction with ^{31}P and ^{19}F NMR

a. Monitoring intermediate B and D

We firstly prepared the Au(III)-aryl intermediate B with 1n, $AgSbF_6$, and MeIDalPhosAuCl following the procedure described by Bourissou and co-workers (Step 1),[214] which was characterized by ^{31}P and ^{19}F NMR. The resulting solution was then subjected with 1 equiv of $AgSCF_3$ and heated at 70 °C for 15 min. The intermediate B was consumed (confirmed by ^{31}P and ^{19}F NMR) to form 2n in 72% NMR yield. We also carried out the HRMS analysis of the reaction solution to find the intermediate D but failed.



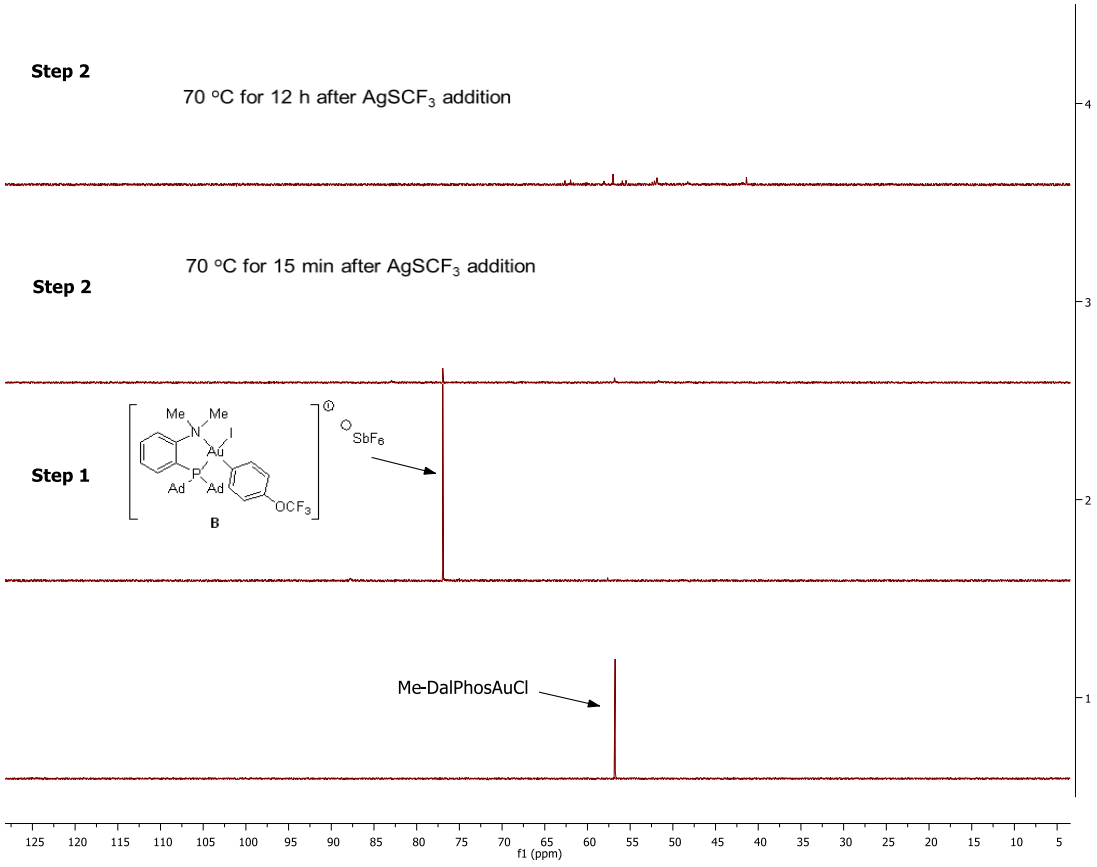
Procedure:

Step 1: An NMR tube charged with $AgSbF_6$ (10.3 mg, 0.03 mmol) in CD_2Cl_2 (0.3 Ml) was cooled to −78 °C. Next, a solution of MeDalphosAuCl (19.6 mg, 0.03 mmol) and 4-trifluoromethoxyiodobenzene 1n (8.91 mg, 0.03 mmol) in CD_2Cl_2 (0.3 Ml) was added to the NMR tube slowly. The tube was gently shaken and allowed to warm to room temperature for 15 min. The formation of the Au(III) complex B was monitored and confirmed by ^{31}P and ^{19}F NMR.

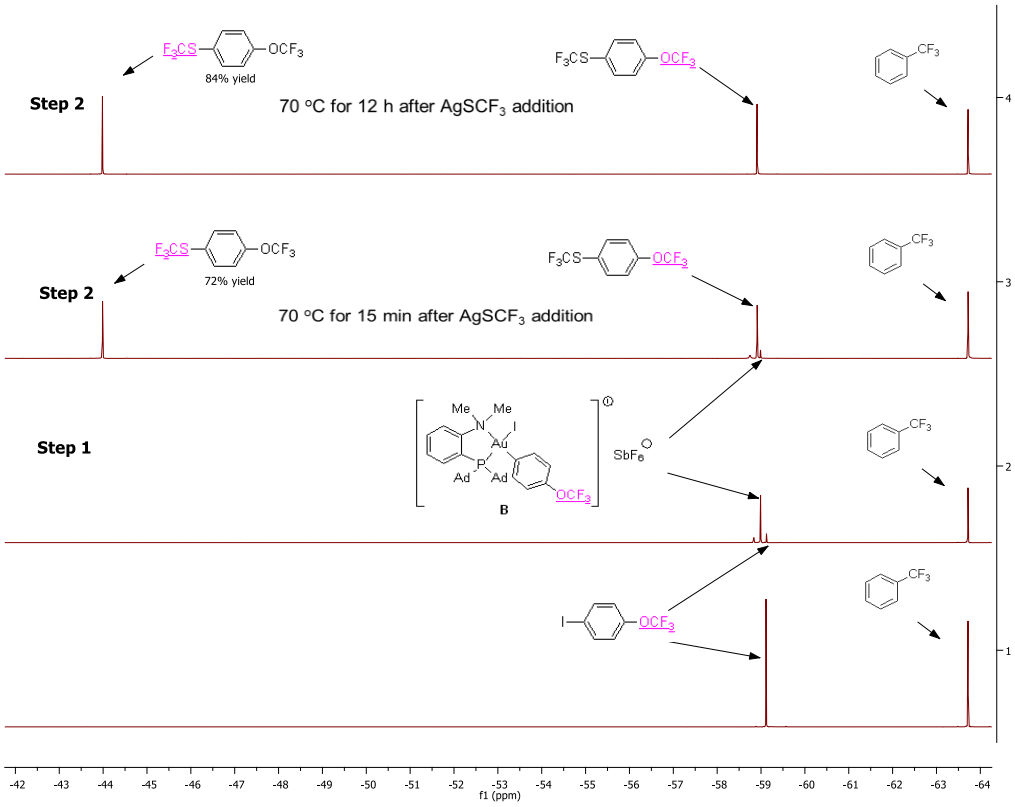
Step 2: Another NMR tube charged with $AgSCF_3$ (6.3 mg, 0.03 mmol) in CD_2Cl_2 (0.3 Ml) was then cooled to −78 °C and the step 1 reaction mixture of Au(III) complex B was slowly added via syringe. The tube was then gently shaken and allowed to warm to 70 °C for 15 min. It was then

cooled to room temperature and ^{31}P NMR and ^{19}F NMR was recorded, which showed Au(III) complex B was consumed and product 2n was formed in 72% yield (determined by ^{19}F-NMR using benzotrifluoride as an internal standard).

^{31}P-NMR for the NMR experiment:

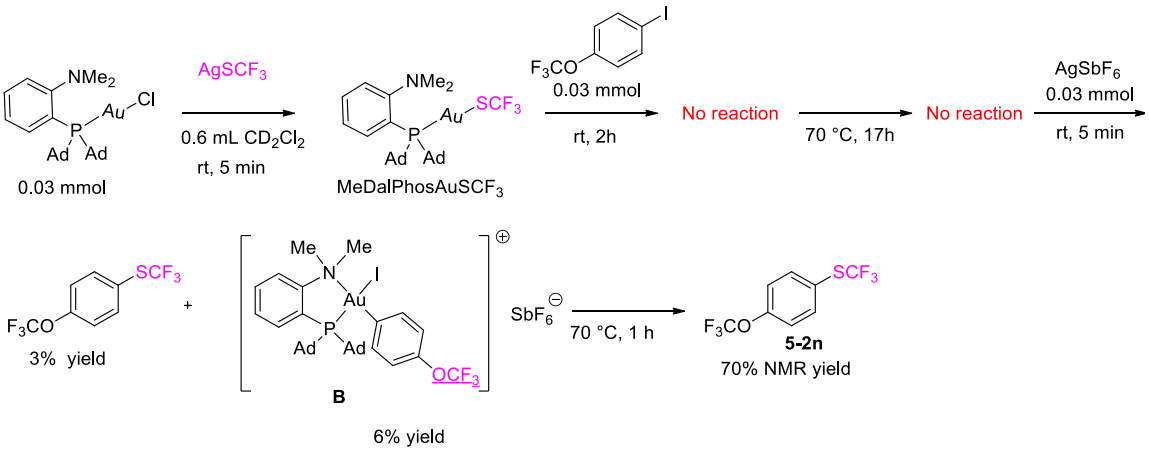


^{19}F-NMR for the NMR experiment:

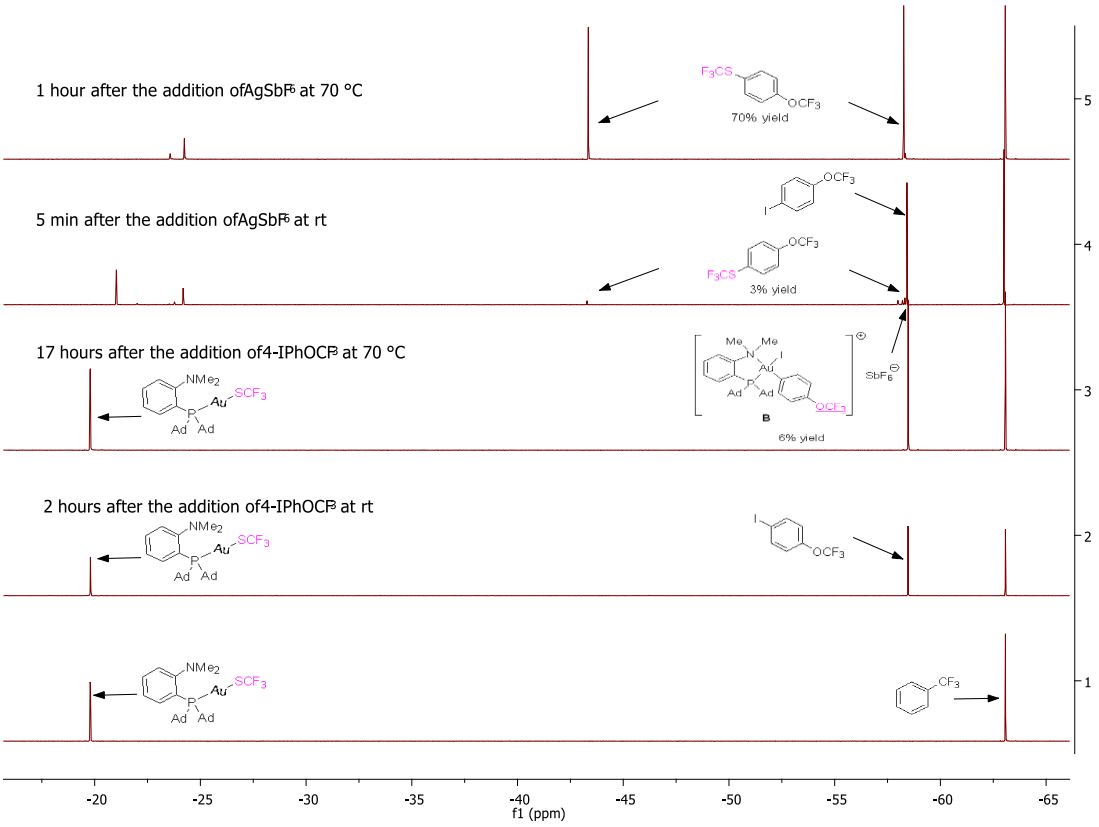


b. Monitoring reaction with preformed MeDalPhosAuSCF$_3$

We then conducted the following reactions with the preformed MeDalPhosAuSCF$_3$: We added the 4-trifluoromethoxylphenyl iodide **1n** to the preformed MeDalPhosAuSCF$_3$ solution in CD_2Cl_2 at room temperature. We found that no reaction happened even the reaction temperature was raised to 70 °C and reaction time was extended to 17 hours. However, the subsequential addition of the $AgSbF_6$ to the reaction mixture at room temperature gave 3% yield of product and 6% of the oxidative addition intermediate **B**, with 76% of the iodide starting material remained. The MeDalPhosAuSCF$_3$ peak in F-NMR (-19.78 ppm) disappeared, and two new peaks formed (-21.03 ppm and -24.19 ppm). Heating the reaction to 70 °C converted **B** and all remained starting material in 1 hour, which afforded the product **5-2n** in 70% NMR yield.

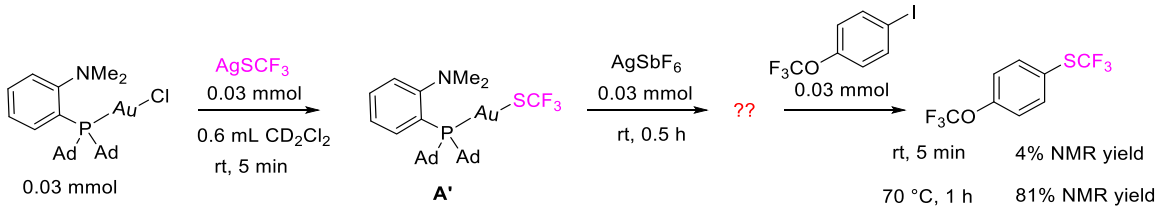


Procedure: NMR tube charged with $PhCF_3$(0.03 mmol), $AgSCF_3$ (6.3 mg, 0.03 mmol) and MeDalphosAuCl (19.6 mg, 0.03 mmol) was added CD_2Cl_2 (0.6 Ml) at room temperature. The tube was gently shaken for 5 min and the reaction was then monitored with ^{31}P and ^{19}F NMR, which showed the formation of the $MeDalphosAuSCF_3$. 4-trifluoromethoxylphenyl iodide (0.03 mmol) was then added to the reaction and the reaction was monitored after 2 hours. The reaction temperature was raised to 70 °C and reaction time was extended to 17 hours. The reaction was monitored again. Then, $AgSbF_6$ was introduced to the reaction mixture at room temperature and the reaction was monitored after 5 min. The reaction was heated to 70 °C and then was monitored after 1hour, which showed all the starting material and Au(III) complex B were consumed and product 2n was formed in 70% yield (determined by ^{19}F-NMR using benzotrifluoride as an internal standard).

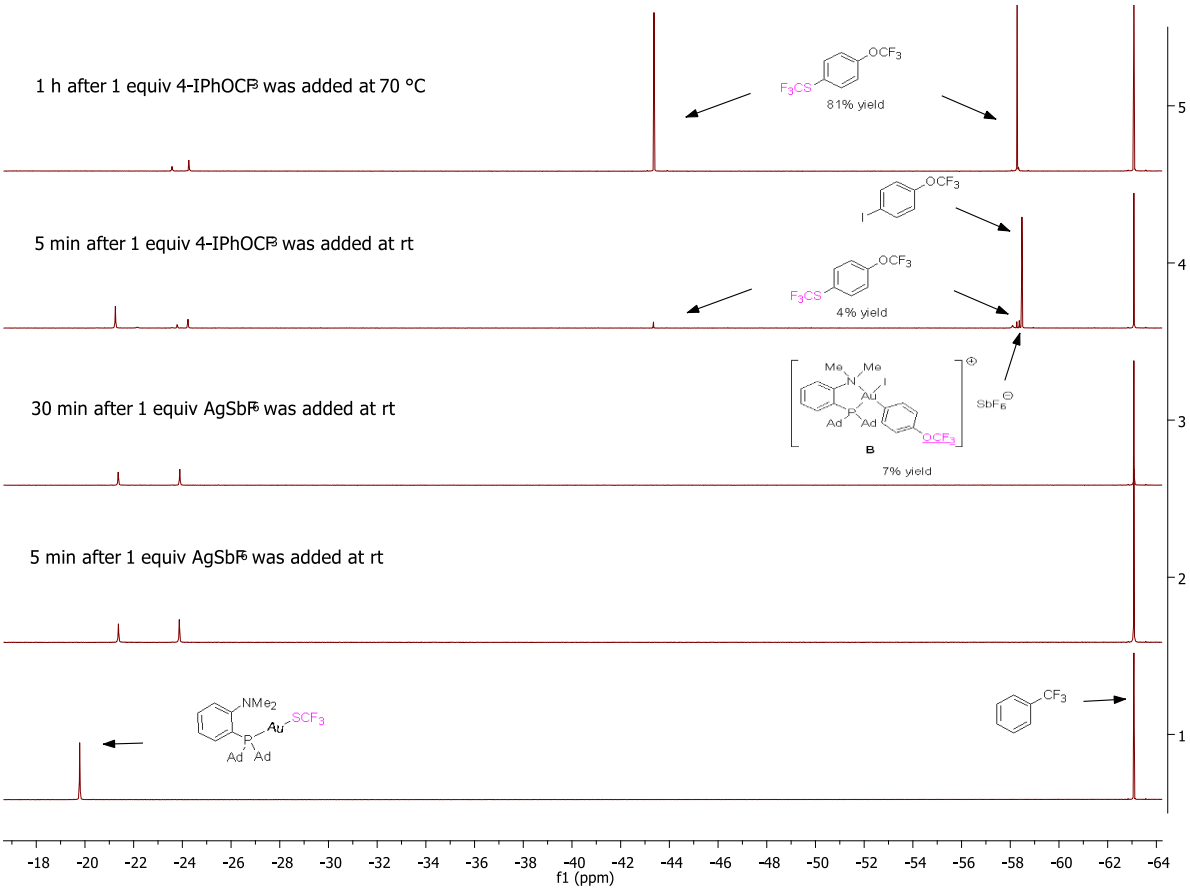


c. Monitoring activation of MeDalPhosAuSCF$_3$ by AgSbF$_6$

To further prove the interaction between $AgSbF_6$ and MeDalPhosAuCl, we also conducted the following reaction: Adding $AgSbF_6$ to the preformed MeDalPhosAuSCF$_3$ solution in CD_2Cl_2, we found the MeDalPhosAuSCF$_3$ peak (-19.78 ppm) in F-NMR disappeared, and two new peaks formed (-21.37 ppm and -23.87 ppm). Although it is hard to determine the new formed intermediate structures, it should be in kinds of activated forms of MeDalPhosAuSCF$_3$-$AgSbF_6$ (**A1**), and this intermediate can go through oxidative addition with the organohalide substrates and then deliver the product in 81% yield.

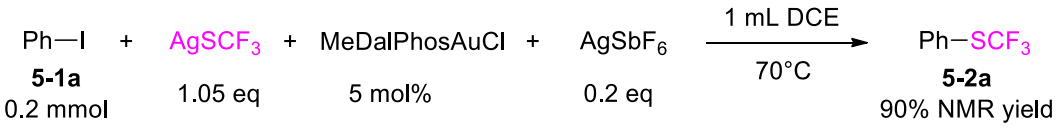


Procedure: An NMR tube charged with $PhCF_3$(0.03 mmol), $AgSCF_3$ (6.3 mg, 0.03 mmol) and MeDalphosAuCl (19.6 mg, 0.03 mmol) was added CD_2Cl_2 (0.6 Ml) at room temperature. The tube was gently shaken for 5 min and the reaction was then monitored with ^{31}P and ^{19}F NMR, which showed the formation of the MeDalphosAuSCF$_3$. $AgSbF_6$ was introduced to the reaction mixture at room temperature and the reaction was monitored after 30 min. 4-trifluoromethoxylphenyl iodide (0.03 mmol) was then added to the reaction and the reaction was monitored after 5 min. The reaction was heated to 70 °C and then was monitored after 1 hour, which showed all the starting material and Au(III) complex B were consumed and product **2n** was formed in 81% yield (determined by ^{19}F-NMR using benzotrifluoride as an internal standard).



d. Reaction regardless of $AgSbF_6$ and $AgSCF_3$ addition order to MeDalPhosAuCl

We then conducted the following reaction by mixing all the reagents and starting material like $AgSbF_6$, MeDalPhosAuCl, $AgSCF_3$, aryl iodide together first and then added DCE. Regardless the addition order of the $AgSbF_6$ and $AgSCF_3$ to MeDalPhosAuCl, the reaction still gave good yield (vs 95% yield in the case of $MeDalPhosAuSCF_3$ formation).



Procedure: An 8-Ml reaction vial fitted with a stirring bar was loaded with MeDalPhosAuCl (5 mol%), $AgSCF_3$ (1.05 equiv), phenyl iodide **5-1a** (0.2 mmol), and $AgSbF_6$ (0.2 equiv). 1 Ml DCE was then added, and the resulting mixture was stirred at 70 °C for 1 hour. The reaction was monitored with NMR which showed product **5-2a** was formed in 90% yield (determined by ^{19}F-NMR using benzotrifluoride as an internal standard).

6.0. SUMMARY AND OUTLOOK

We have successfully demonstrated a novel application of HCl·DMPU by developing a practical and green protocol of one-pot conversion of aldehydes to nitriles. We found that HCl·DMPU complex acts as dual source of acid as well as a non-nucleophilic base. Additionally, this protocol requires inexpensive and readily available reagents and is compatible with diverse functional groups, providing rapid access to diverse nitriles in good to excellent yields. This one-pot process was also successfully utilized in the synthesis of key intermediates for various drug molecules in excellent yields.

We continued our efforts of finding novel applications of halogenating agents and successfully developed the first C−SCF_3/$SeCF_3$ cross-coupling reactions using gold redox catalysis by employing $AgSCF_3$ or Me_4NSeCF_3. This unprecedented finding works well with aryl, alkenyl and alkynyl halides. A simple procedure, mild reaction conditions, excellent yields and broad functional group tolerance are some of the features of this method. The scalability and robustness of this reaction was further demonstrated by the late-stage functionalization of bioactive molecules. This proves that our method is a great alternative to the synthesis of trifluoromethylthio- and selenoethers, which may stimulate further applications in pharmaceutical and agrochemical research and development.

In our quest for developing novel halogenating agents, we invented a novel, easy-to-handle, and bench-stable electrophilic trifluoromethylating agent, *S*-(trifluoromethyl)-2,8-bis(trifluoromethoxy)dibenzothiophenium triflate that is more powerful than Umemoto reagent II. This reagent was synthesized from inexpensive starting materials in a one-pot operation, making this reagent highly affordable. The reactivity of this reagent was demonstrated successfully on various kinds of nucleophiles. Finally, we designed and attempted to synthesize novel

dithiadication electrophilic trifluoromethylating agents endowed with two transferable trifluoromethyl groups. However, we could not get the expected outcome.

The future direction of our research is to explore new applications of our reagent, powerful *S*-(trifluoromethyl)-2,8-bis(trifluoromethoxy)dibenzothiophenium triflate, in trifluoromethylation of organic compounds which may have significant medicinal value.

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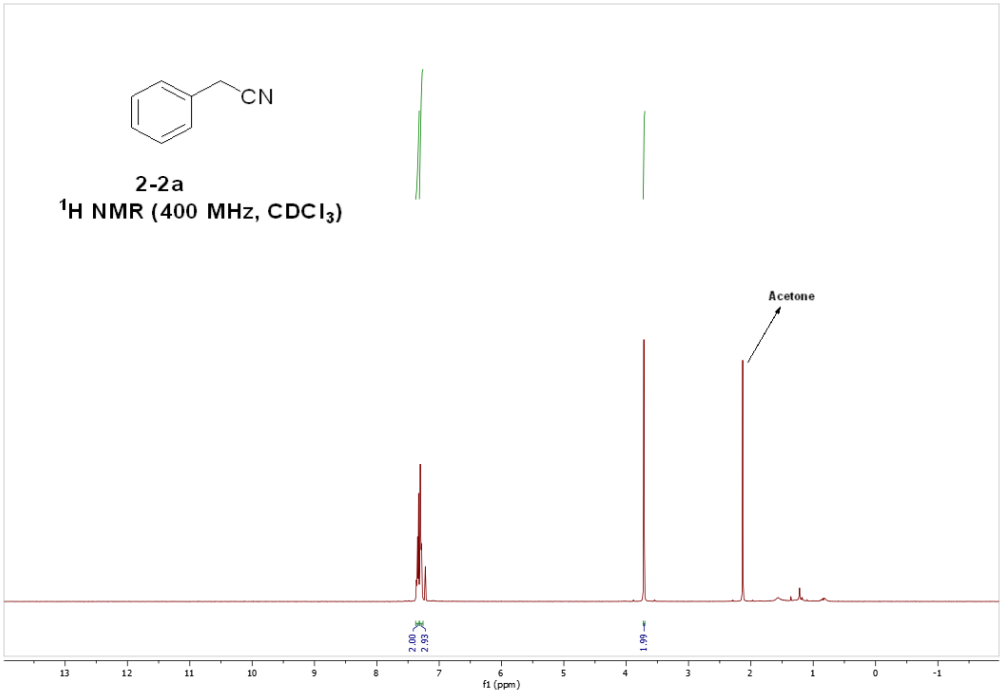
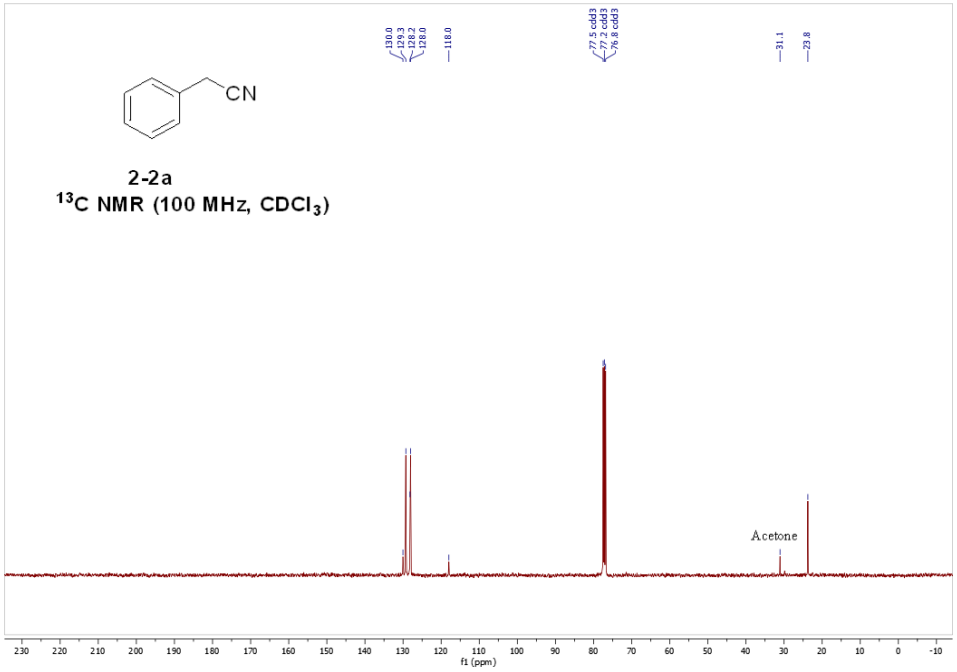
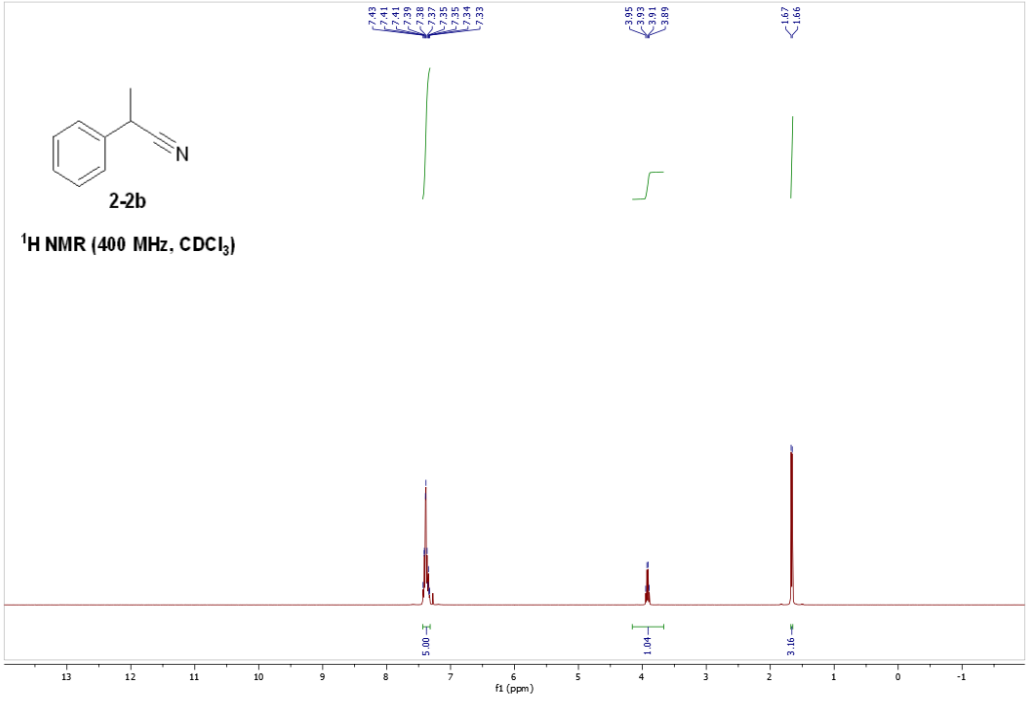
APPENDIX A: HCl•DMPU ASSISTED ONE-POT AND METAL-FREE CONVERSION OF ALDEHYDES TO NITRILES

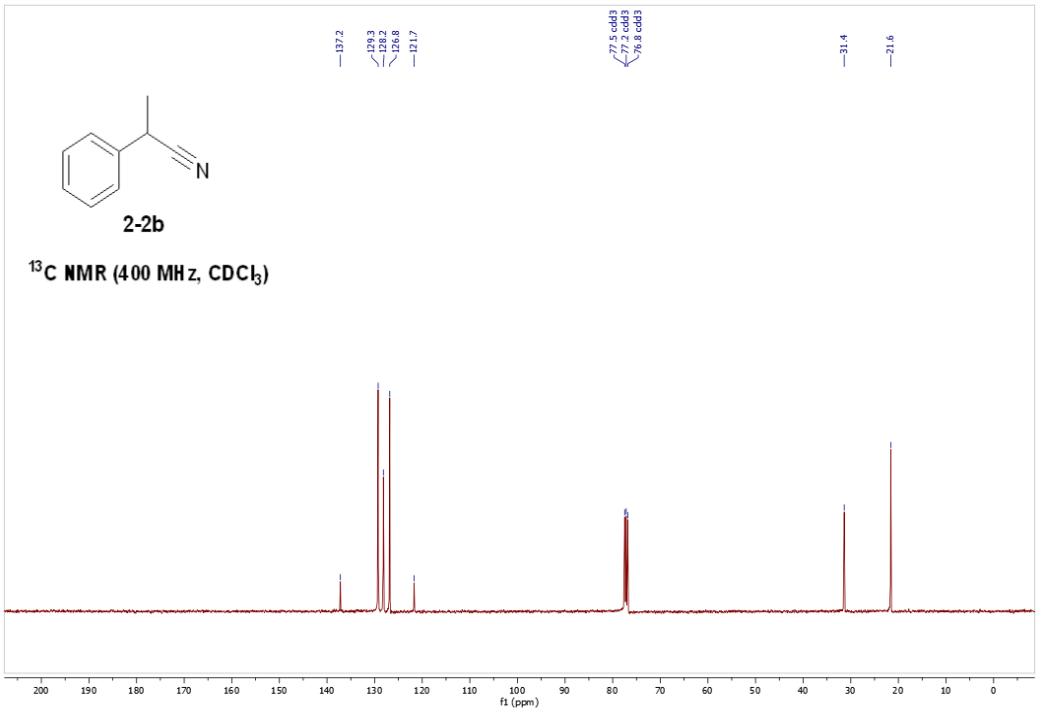
2.4.11. ^{1}H NMR and ^{13}C NMR spectra of compounds

2.4.11.1. NMR spectral data for **2-2a** to **2-2m**.



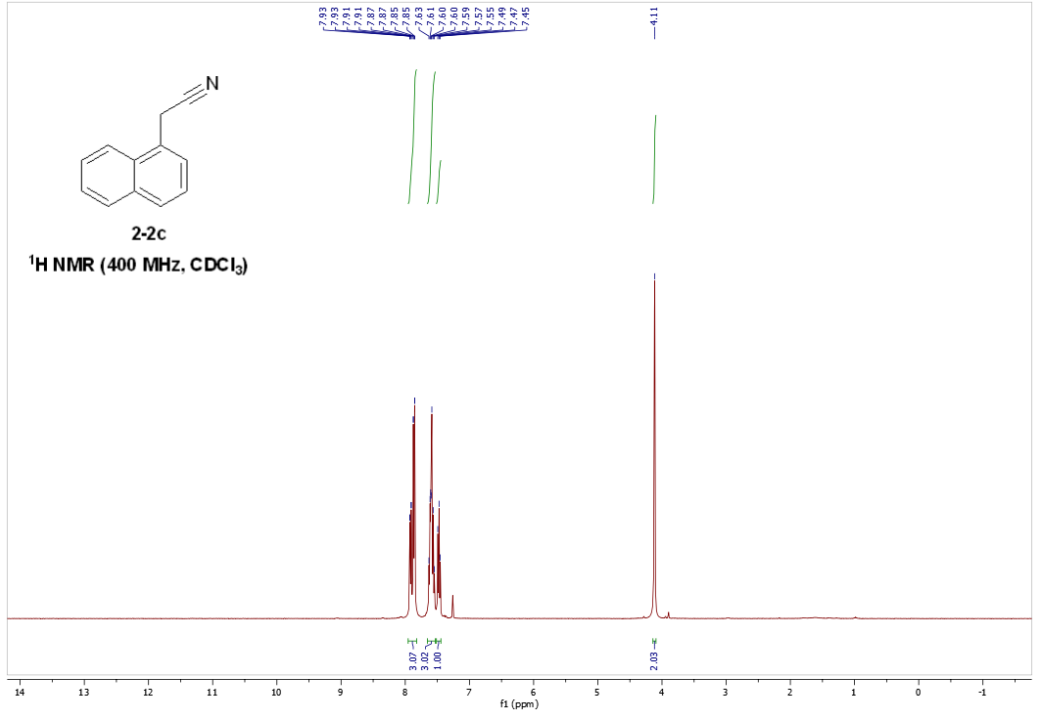

CN
2-2a
13C NMR (100 MHz, CDCl3)
130.0
129.3
128.2
128.0
118.0
77.5 cdd3
77.2 cdd3
76.8 cdd3
31.1
23.8
Acetone
f1 (ppm)


N
2-2b
1H NMR (400 MHz, CDCl3)
7.43
7.41
7.41
7.39
7.38
7.37
7.35
7.35
7.34
7.33
3.95
3.93
3.91
3.89
1.67
1.66
5.00
1.04
3.16
f1 (ppm)



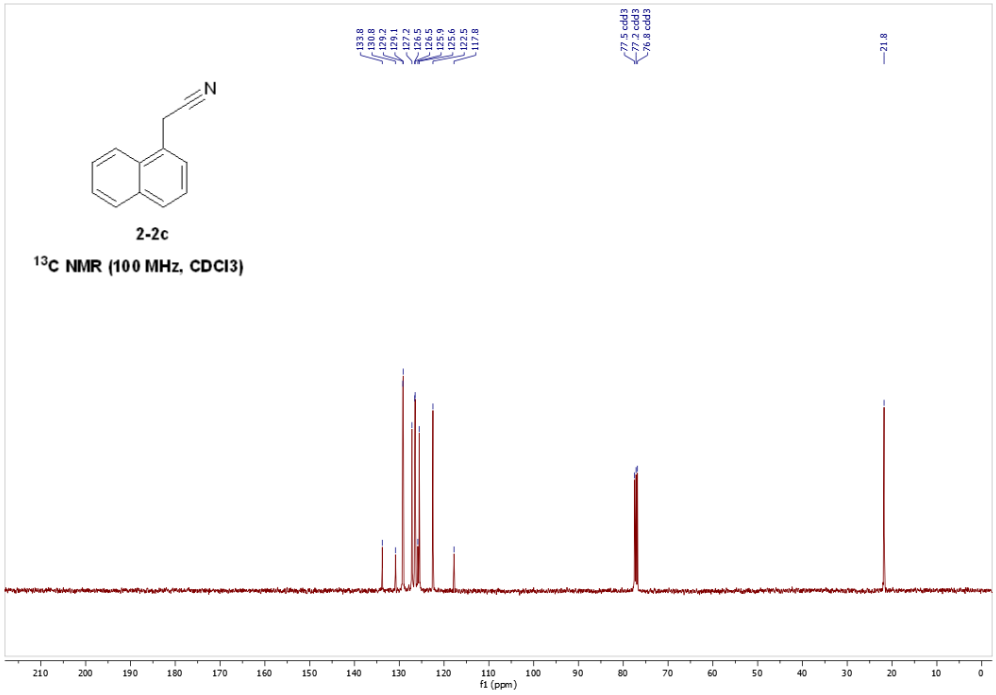
2-2b

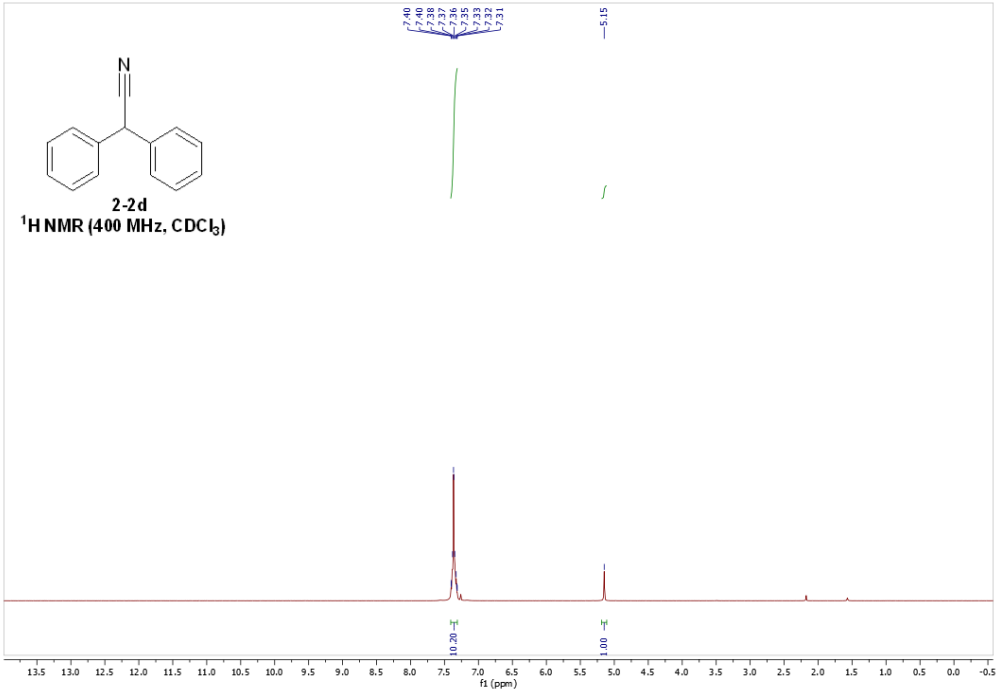
^{13}C NMR (400 MHz, $CDCl_3$)

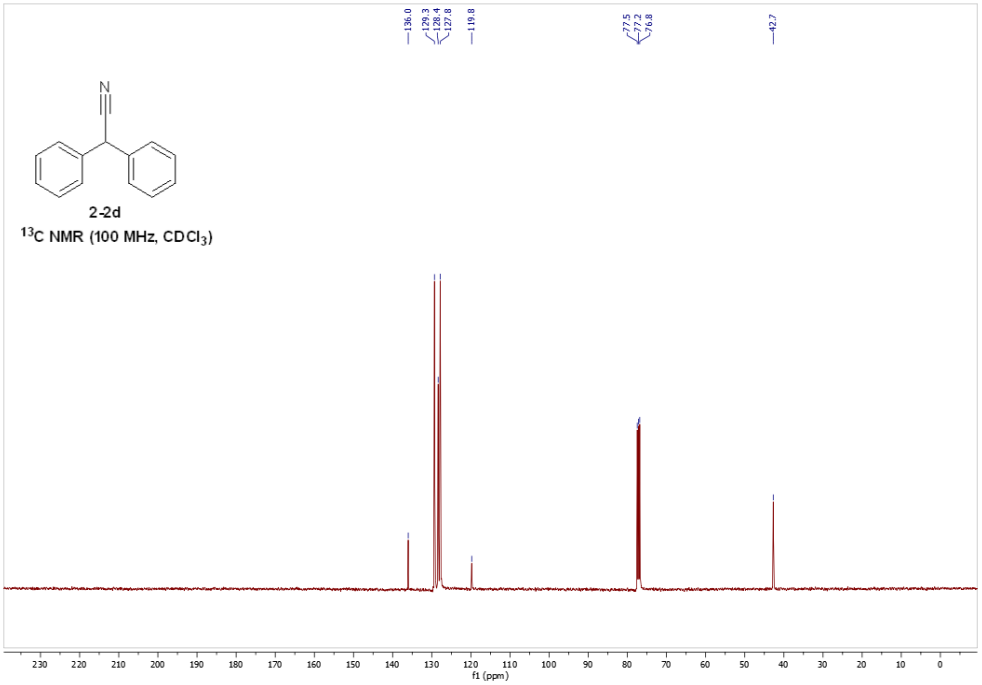


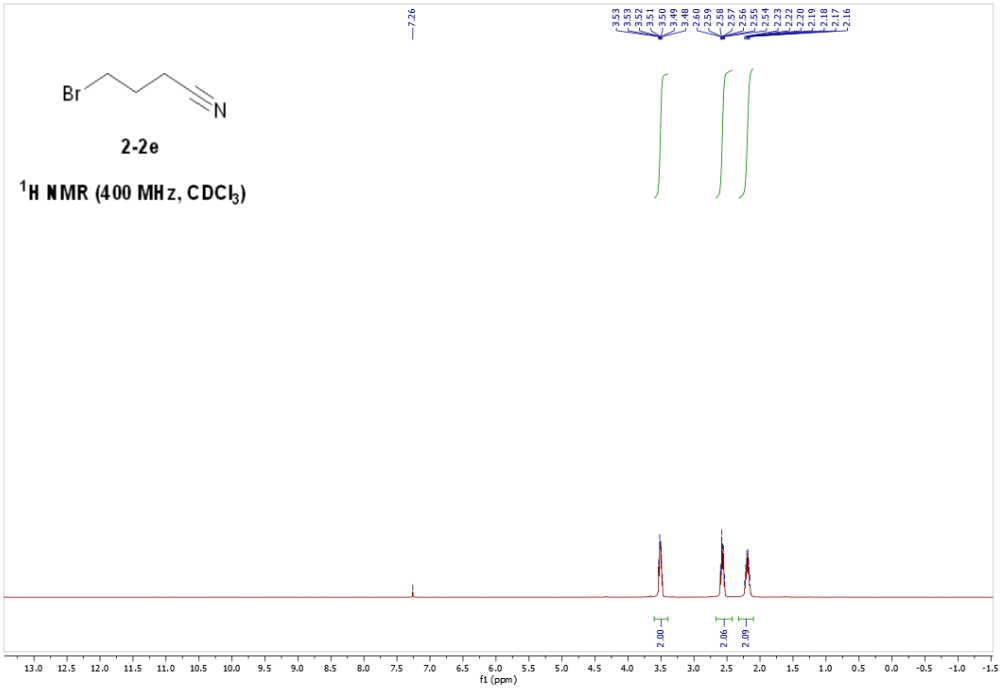
2-2c

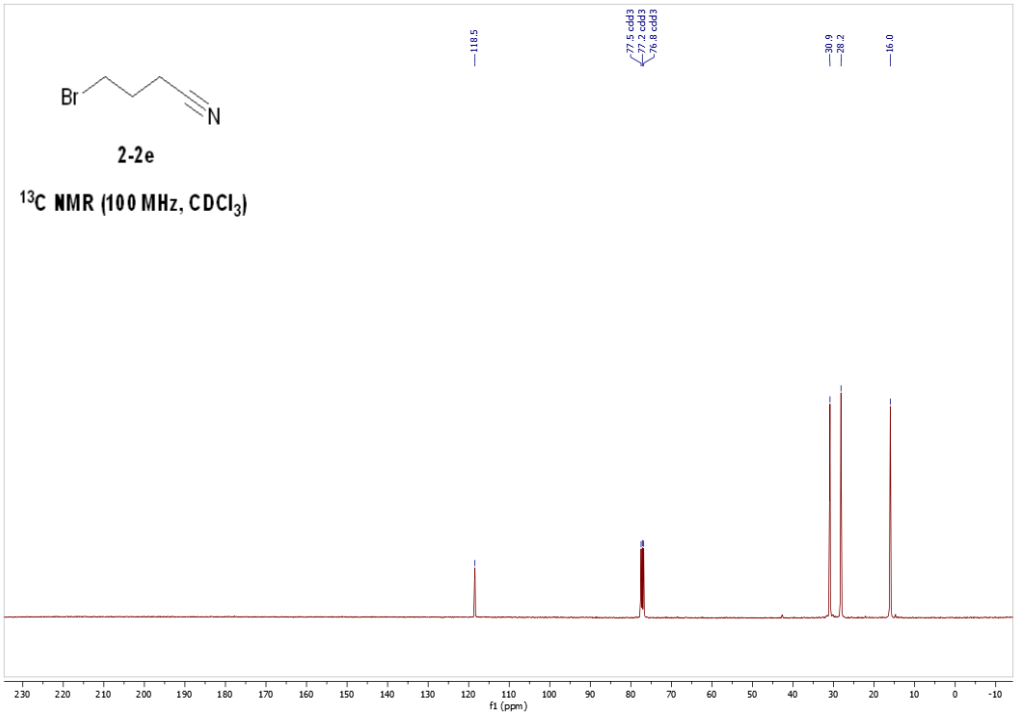
^{1}H NMR (400 MHz, $CDCl_3$)

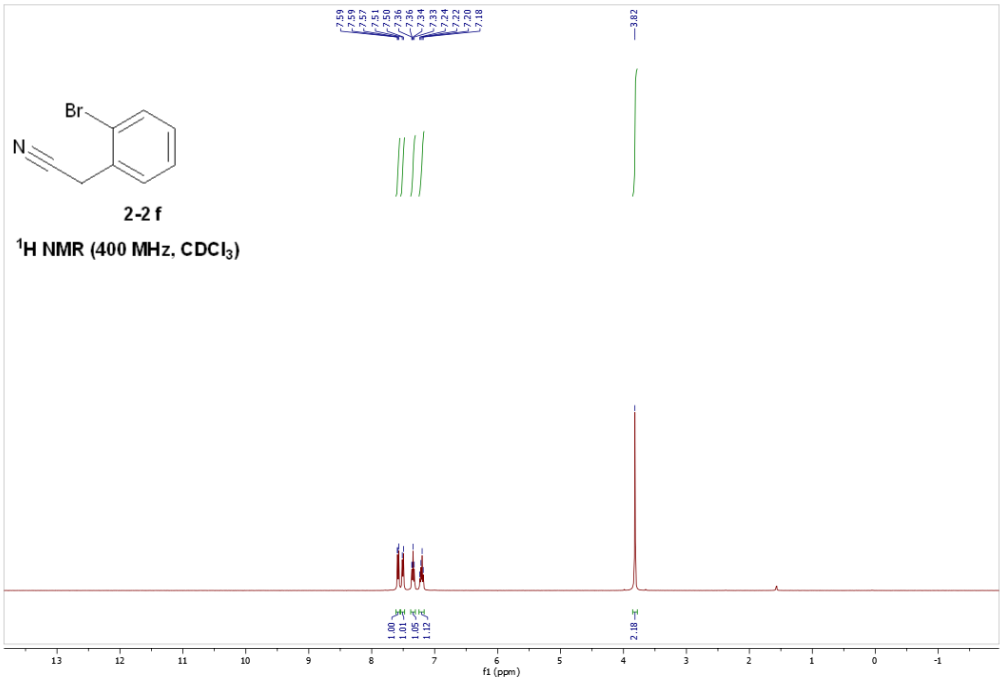

N
2-2c
13C NMR (100 MHz, CDCl3)
133.8
130.8
129.2
129.1
127.2
126.5
126.5
125.9
125.6
122.5
117.8
77.5 cdd3
77.2 cdd3
76.8 cdd3
21.8
f1 (ppm)

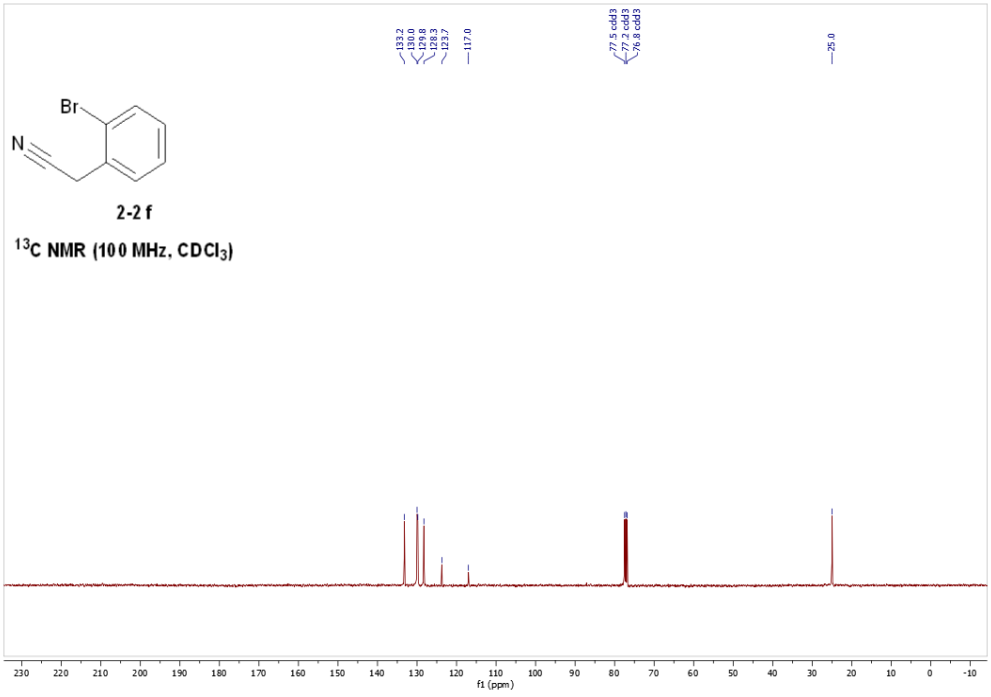

N
2-2d
1H NMR (400 MHz, CDCl3)
7.40
7.40
7.38
7.37
7.36
7.35
7.33
7.32
7.31
5.15
10.20
1.00
f1 (ppm)


N
2-2d
^{13}C NMR (100 MHz, $CDCl_3$)
136.0
129.3
128.4
127.8
119.8
77.5
77.2
76.8
42.7
f1 (ppm)


Br
N
2-2e
^{1}H NMR (400 MHz, $CDCl_3$)
7.26
3.53
3.52
3.51
3.50
3.49
3.48
3.47
3.46
2.60
2.59
2.58
2.57
2.56
2.55
2.54
2.23
2.22
2.20
2.19
2.18
2.17
2.16
2.00
2.06
2.09
f1 (ppm)

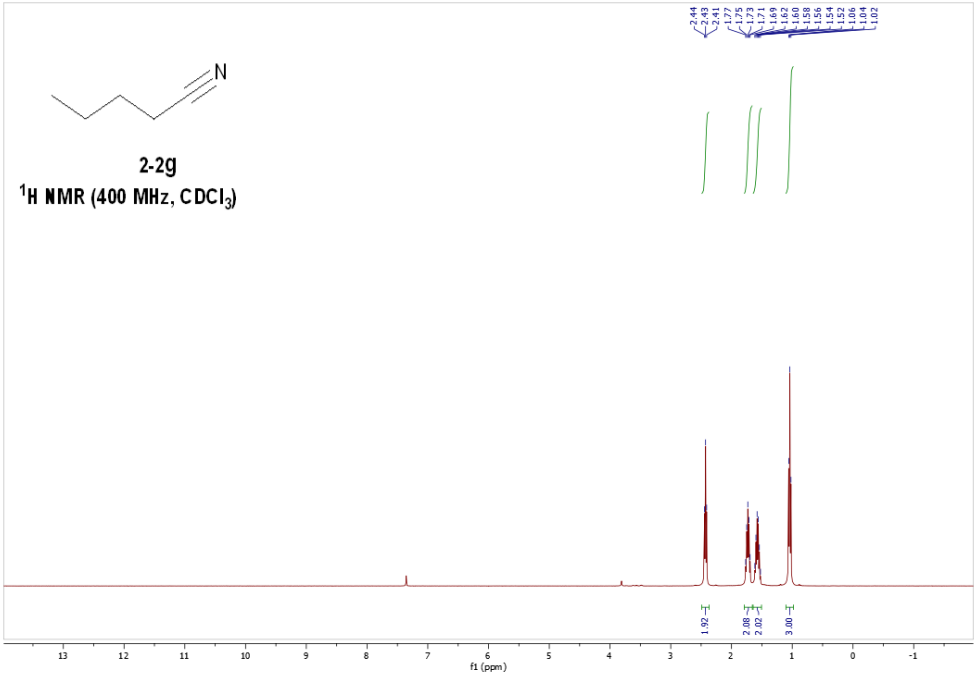

Br
N
2-2e
^{13}C NMR (100 MHz, CDCl$_3$)
118.5
77.5 cdd3
77.2 cdd3
76.8 cdd3
30.9
28.2
16.0
f1 (ppm)


Br
N
2-2 f
^{1}H NMR (400 MHz, CDCl$_3$)
7.59
7.59
7.57
7.51
7.50
7.36
7.34
7.33
7.24
7.22
7.20
7.18
3.82
1.00
1.01
1.05
1.12
2.18
f1 (ppm)



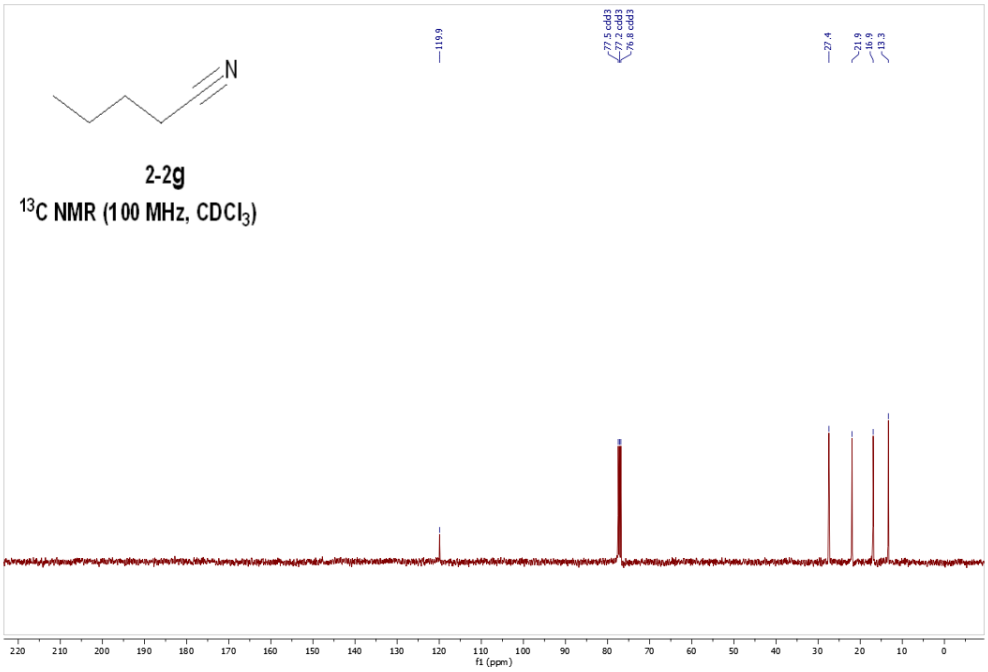
2-2 f

^{13}C NMR (100 MHz, $CDCl_3$)



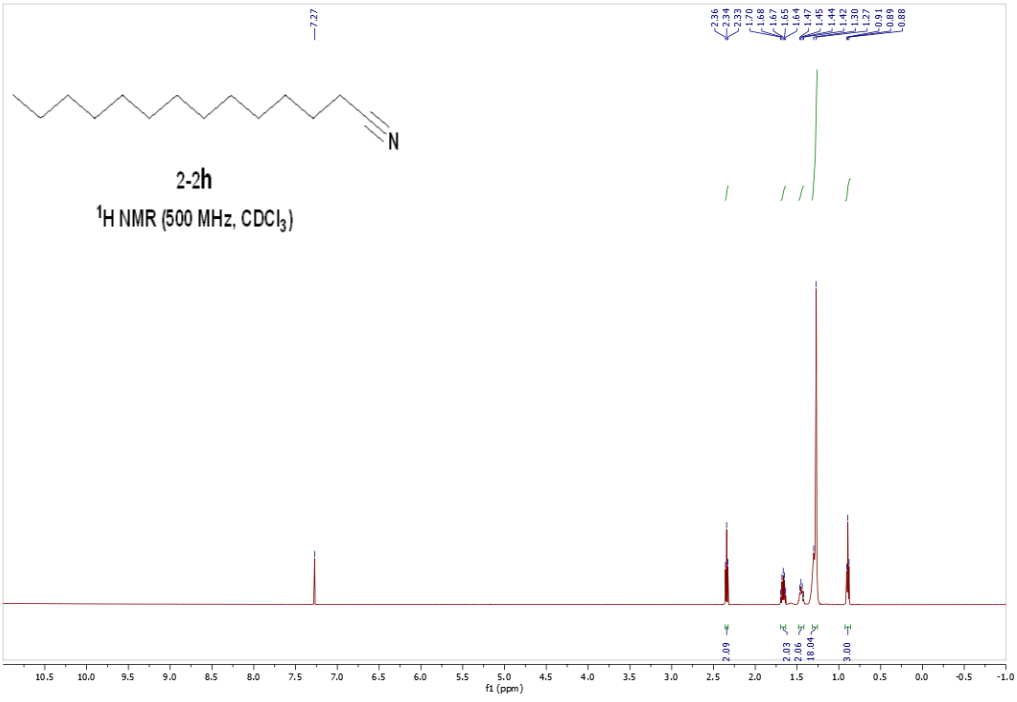
2-2g

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



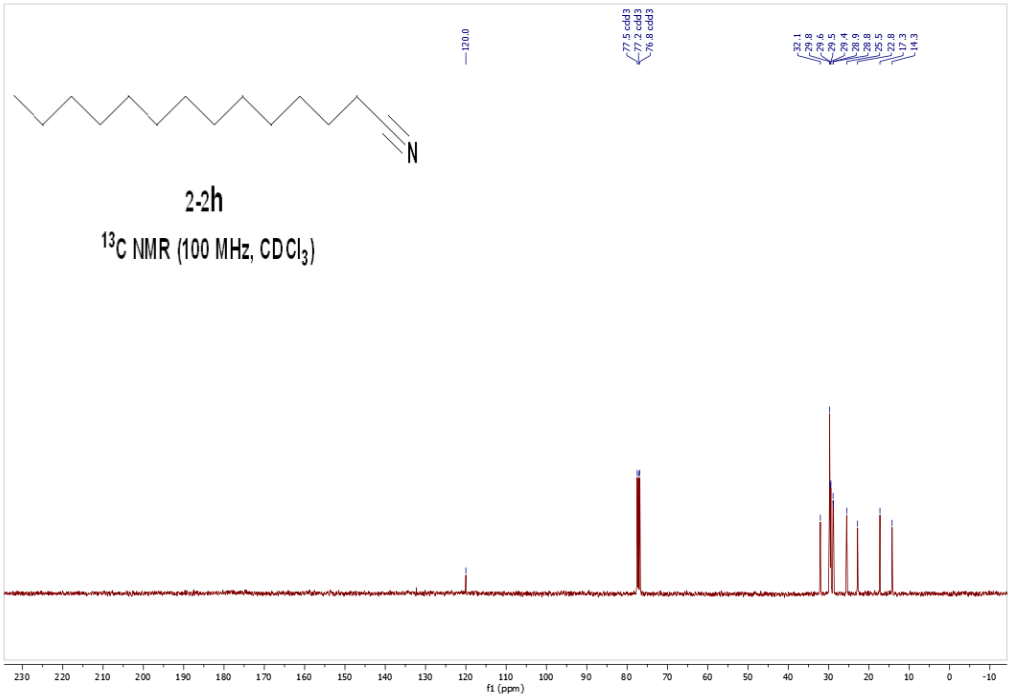
2-2g

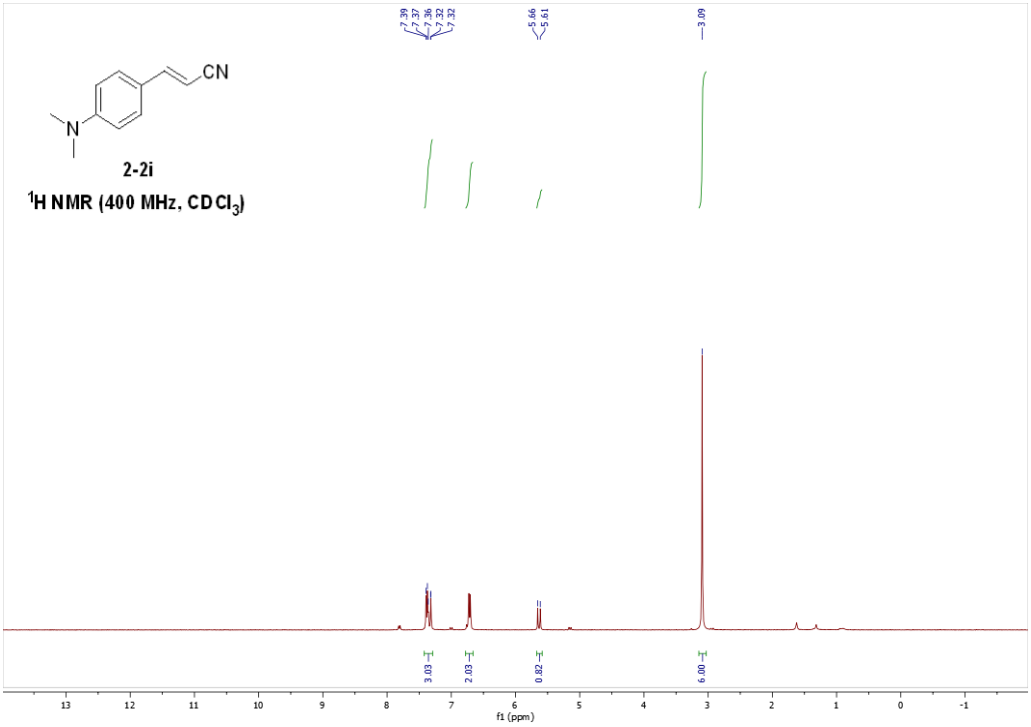
^{13}C NMR (100 MHz, $CDCl_3$)

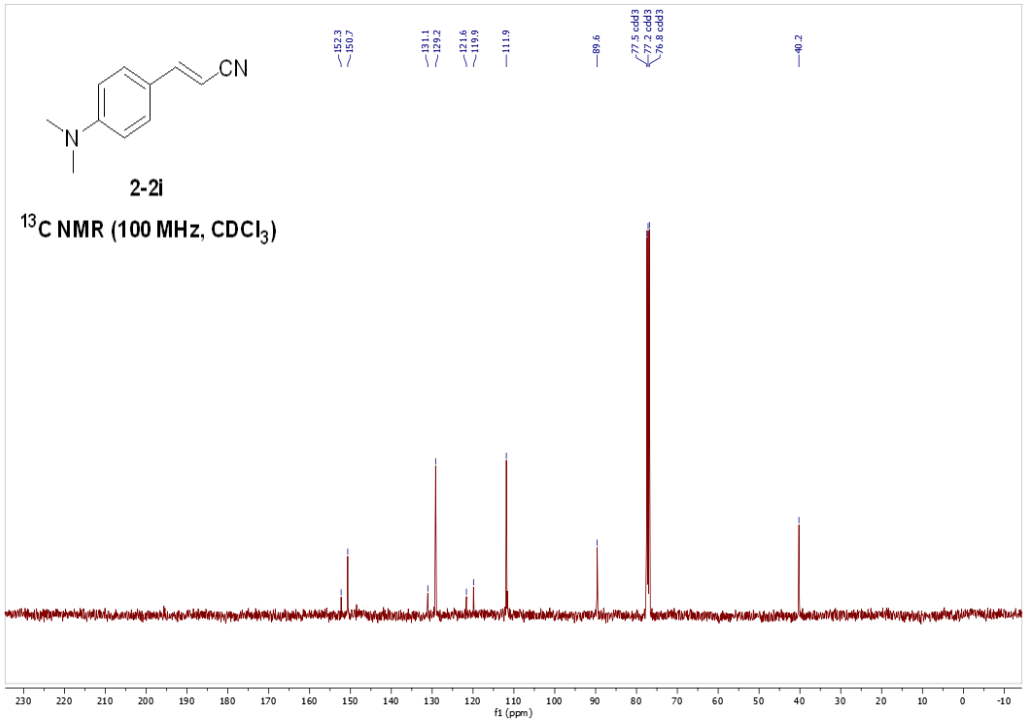


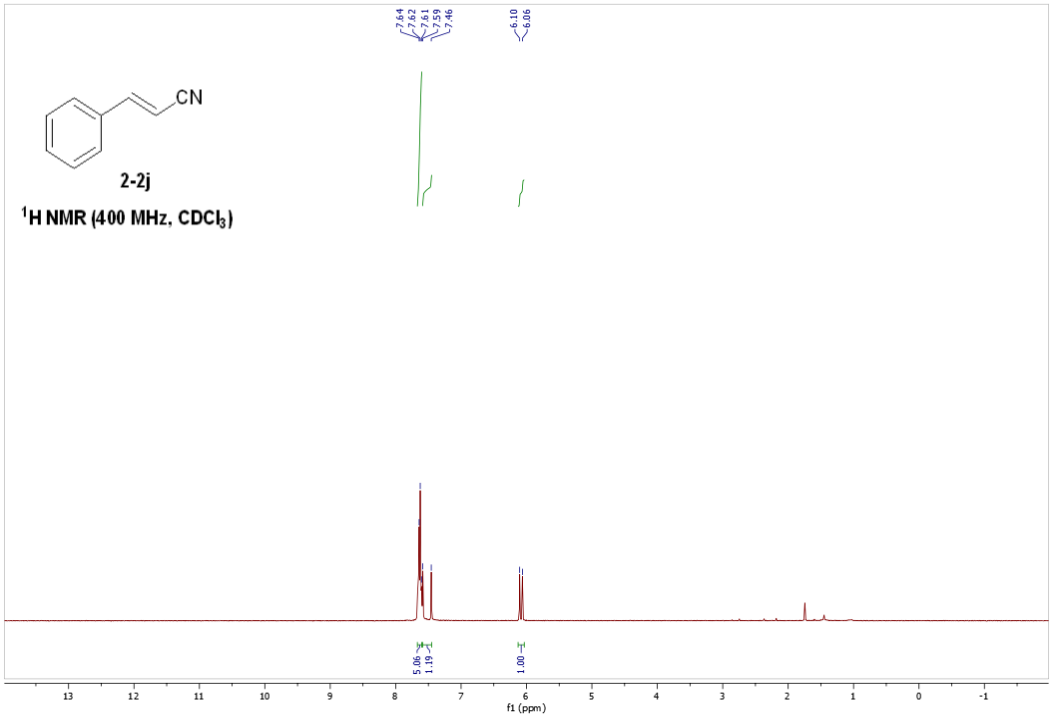
2-2h

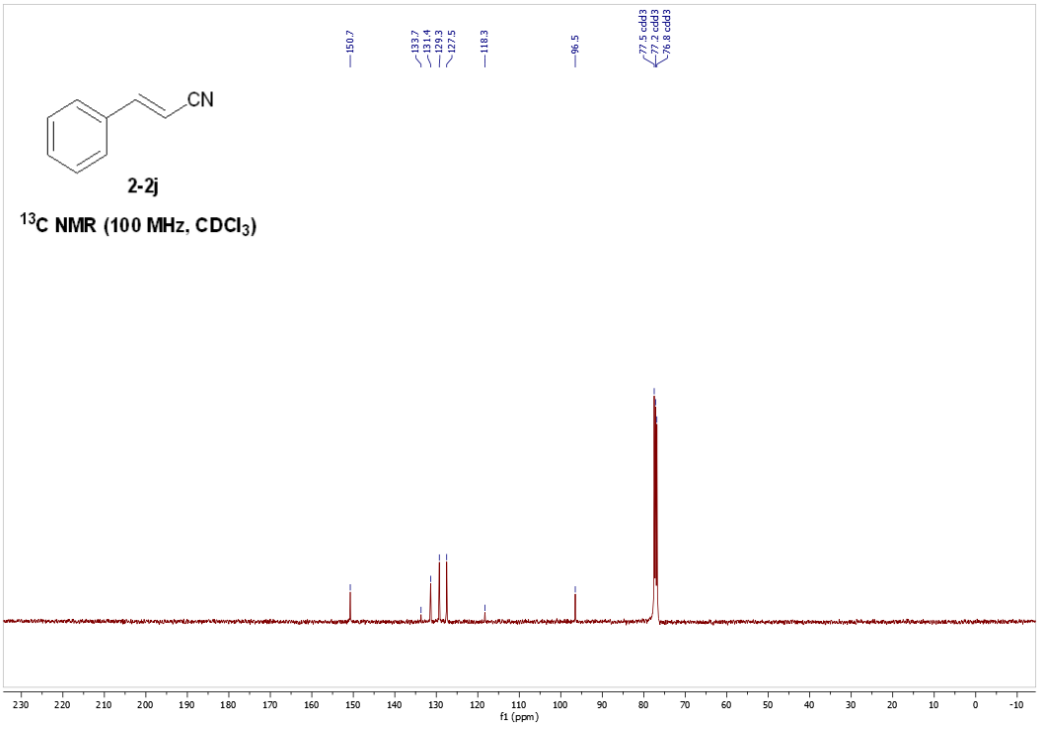
^{1}H NMR (500 MHz, $CDCl_3$)

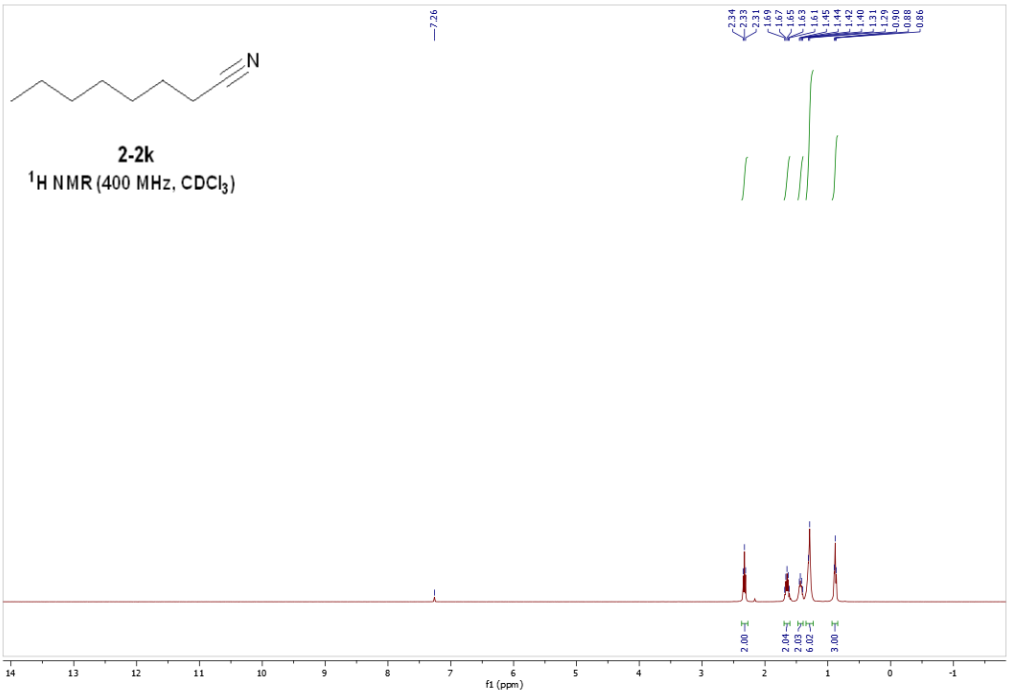

N
2-2h
^{13}C NMR (100 MHz, $CDCl_3$)
f1 (ppm)

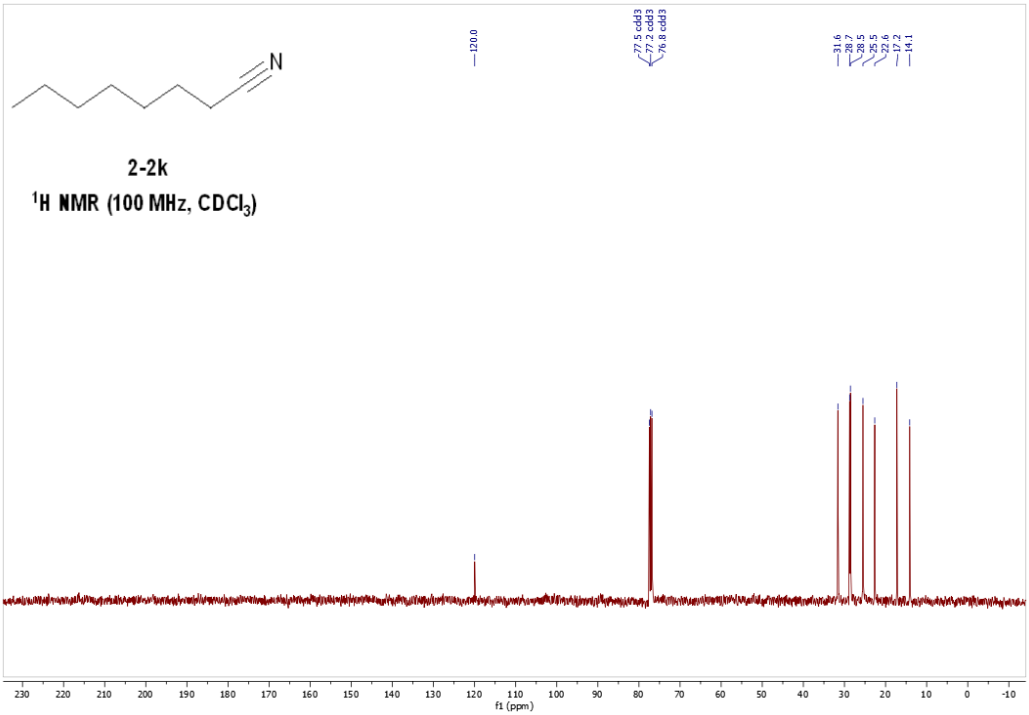

CN
N
2-2i
^{1}H NMR (400 MHz, $CDCl_3$)
f1 (ppm)

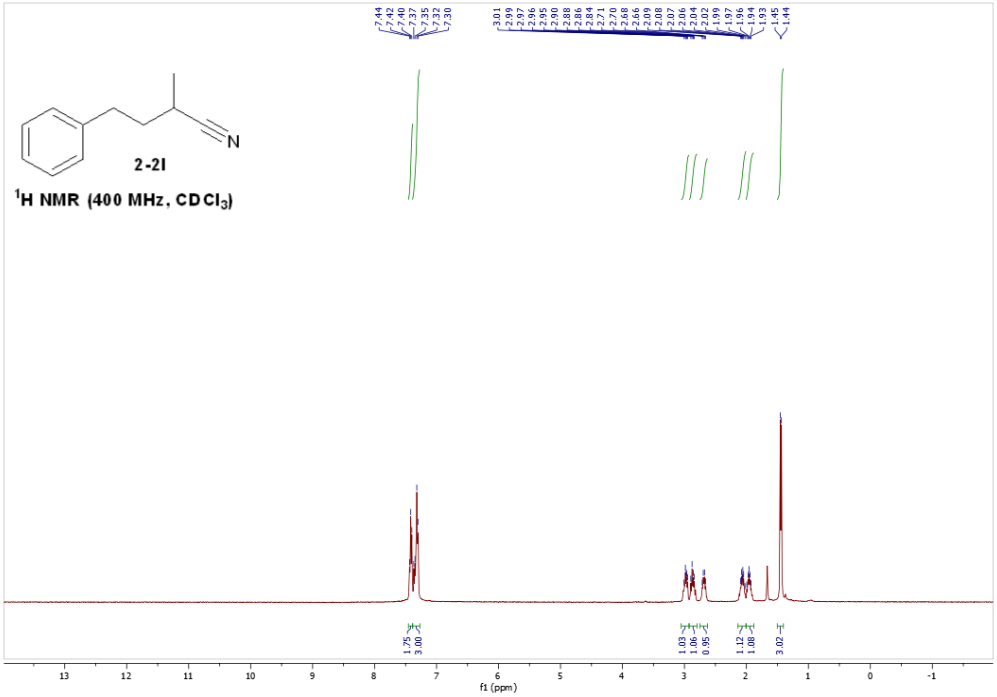

CN
N
2-2i
^{13}C NMR (100 MHz, $CDCl_3$)
152.3
150.7
131.1
129.2
121.6
119.9
111.9
89.6
77.5 cdd3
77.2 cdd3
76.8 cdd3
40.2
f1 (ppm)

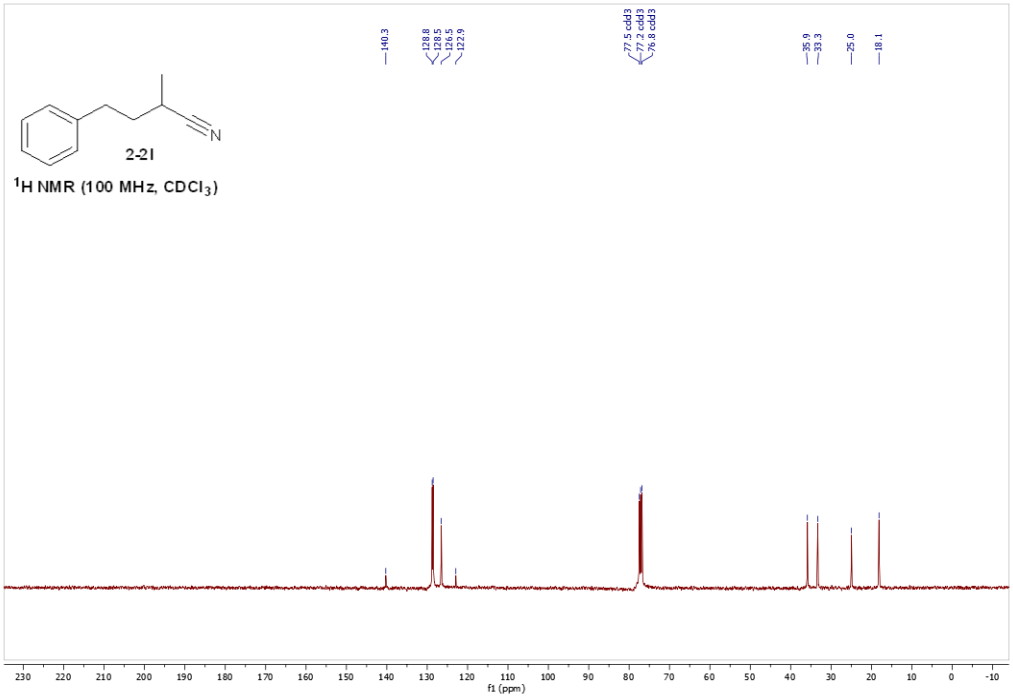

CN
2-2j
^{1}H NMR (400 MHz, $CDCl_3$)
7.64
7.62
7.61
7.59
7.46
6.10
6.06
5.06
1.19
1.00
f1 (ppm)

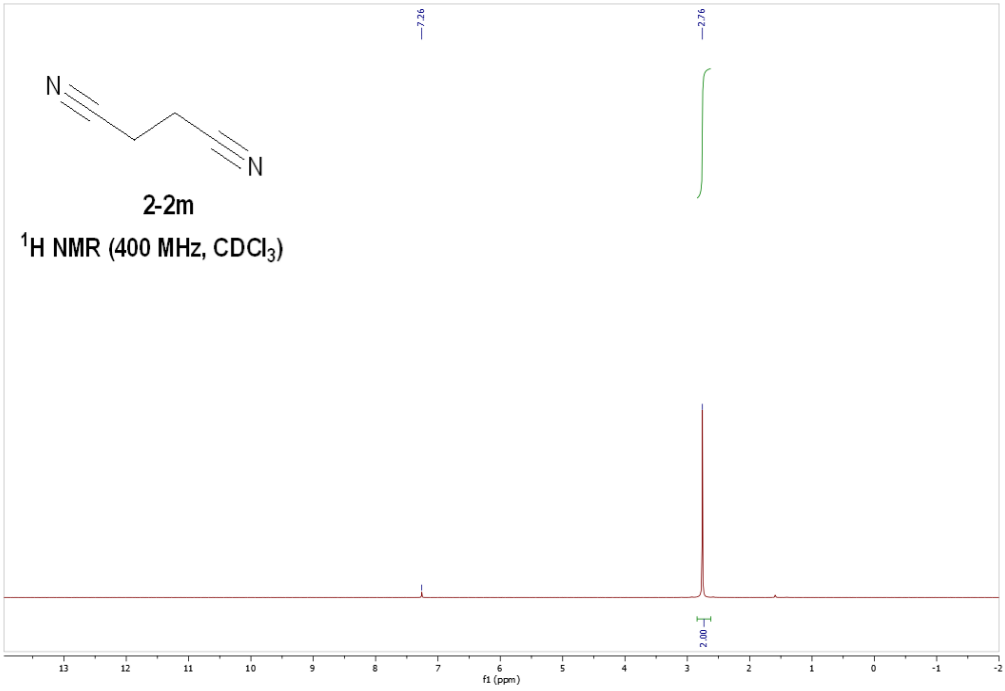

150.7
133.7
131.4
129.3
127.5
118.3
96.5
77.5 cdd3
77.2 cdd3
76.8 cdd3
CN
2-2j
13C NMR (100 MHz, CDCl3)
f1 (ppm)

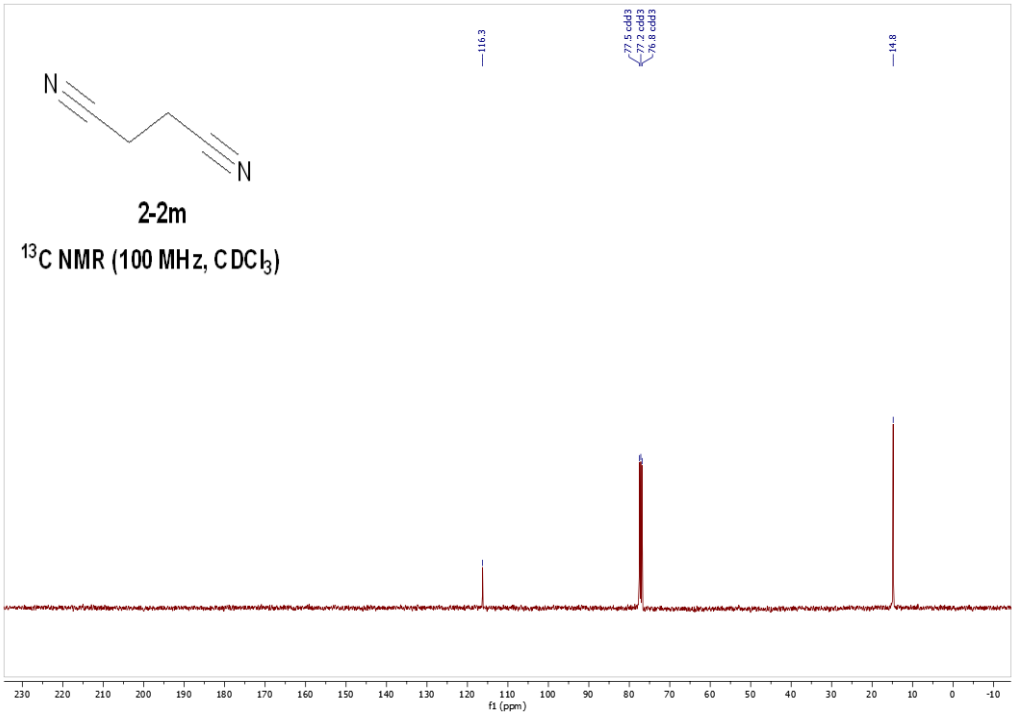

7.26
2.34
2.33
2.31
1.69
1.67
1.65
1.63
1.61
1.45
1.44
1.42
1.40
1.31
1.29
0.90
0.88
0.86
N
2-2k
1H NMR (400 MHz, CDCl3)
2.00
2.04
2.03
6.02
3.00
f1 (ppm)


N
2-2k
^{1}H NMR (100 MHz, $CDCl_3$)
120.0
77.5 cdd3
77.2 cdd3
76.8 cdd3
31.6
28.7
28.5
25.5
22.6
17.2
14.1
f1 (ppm)

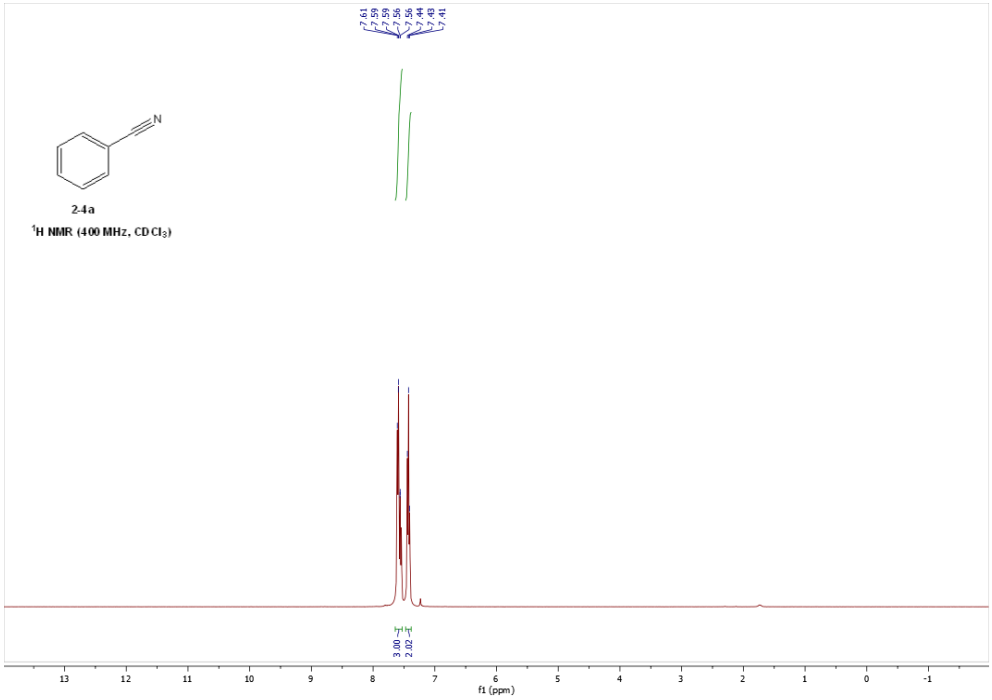

N
2-2l
^{1}H NMR (400 MHz, $CDCl_3$)
7.44
7.42
7.40
7.37
7.35
7.32
7.30
3.01
2.99
2.97
2.96
2.95
2.90
2.88
2.86
2.84
2.71
2.70
2.68
2.66
2.09
2.08
2.07
2.06
2.04
2.02
1.99
1.97
1.96
1.94
1.93
1.45
1.44
1.75
3.00
1.03
1.06
0.95
1.12
1.08
3.02
f1 (ppm)

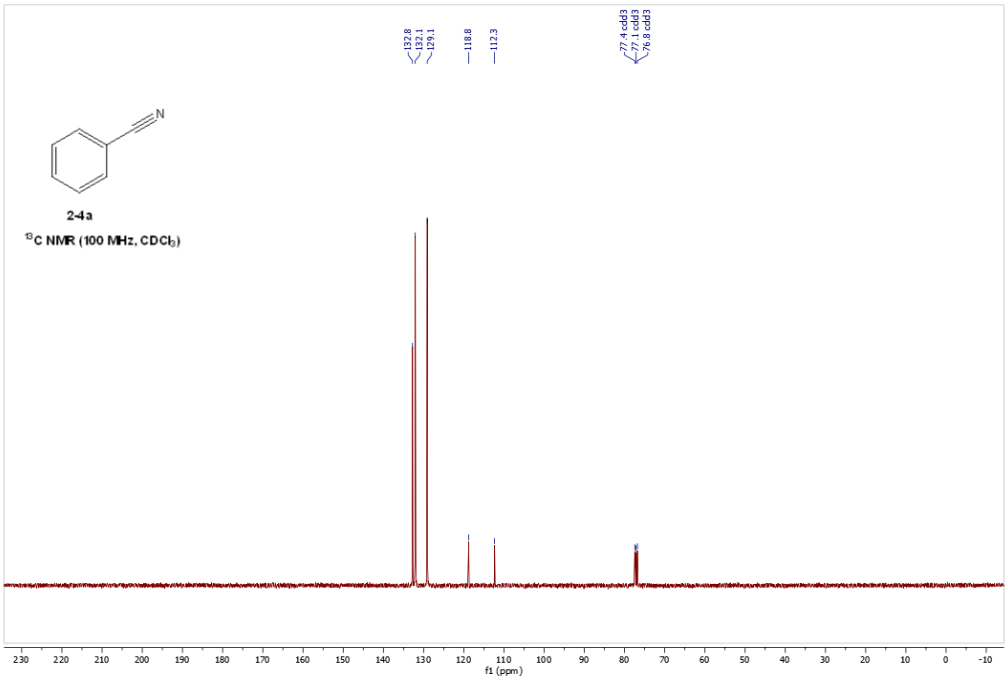

140.3
128.8
128.5
126.5
122.9
77.5 cdd3
77.2 cdd3
76.8 cdd3
35.9
33.3
25.0
18.1
N
2-2l
^{1}H NMR (100 MHz, CDCl$_3$)
f1 (ppm)

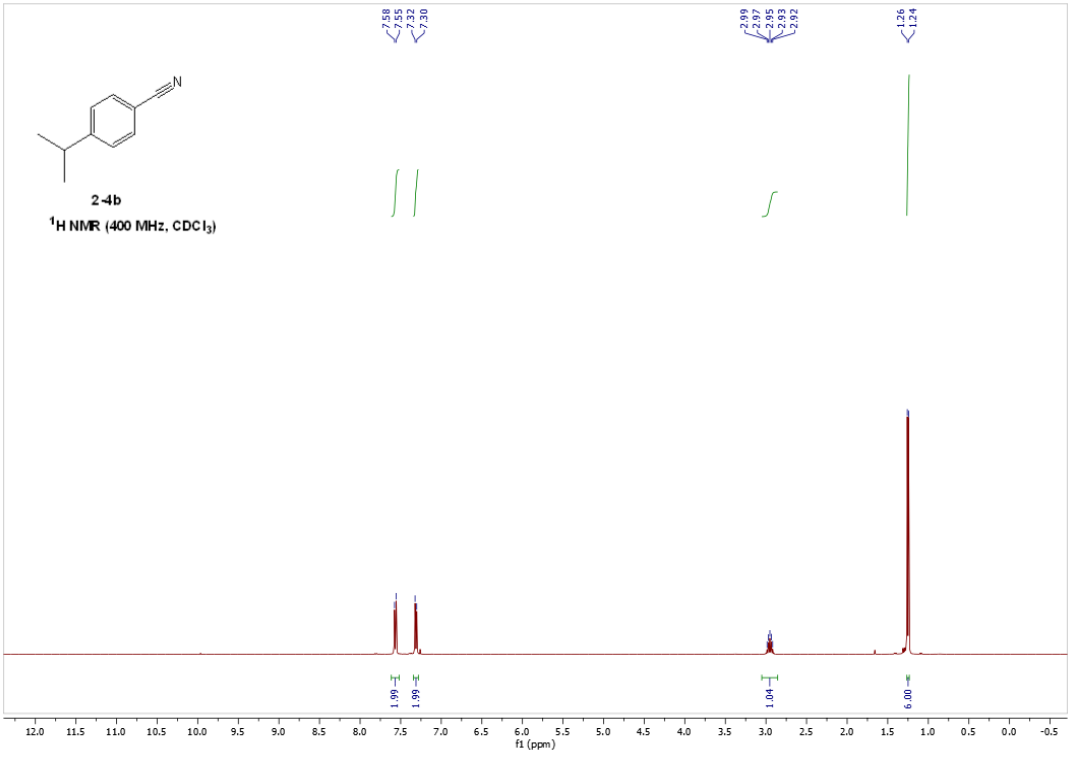

7.26
2.76
N
N
2-2m
^{1}H NMR (400 MHz, CDCl$_3$)
2.00
f1 (ppm)

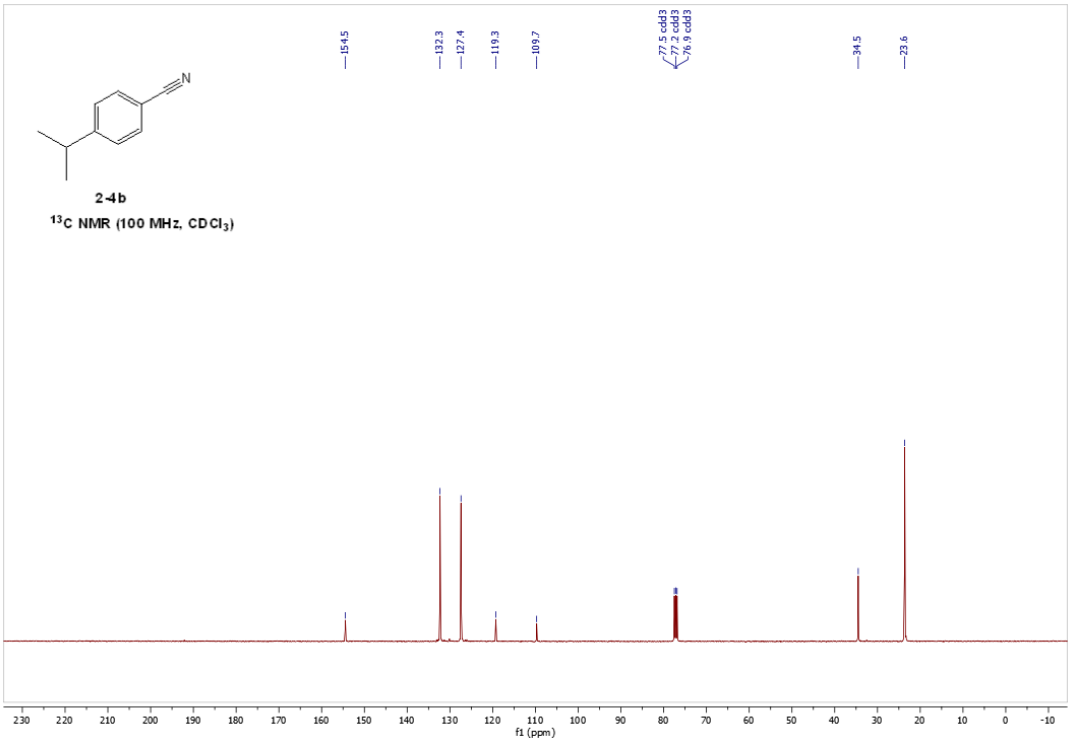


2.4.11.2. NMR spectral data for **2-4a** to **2-4x**.



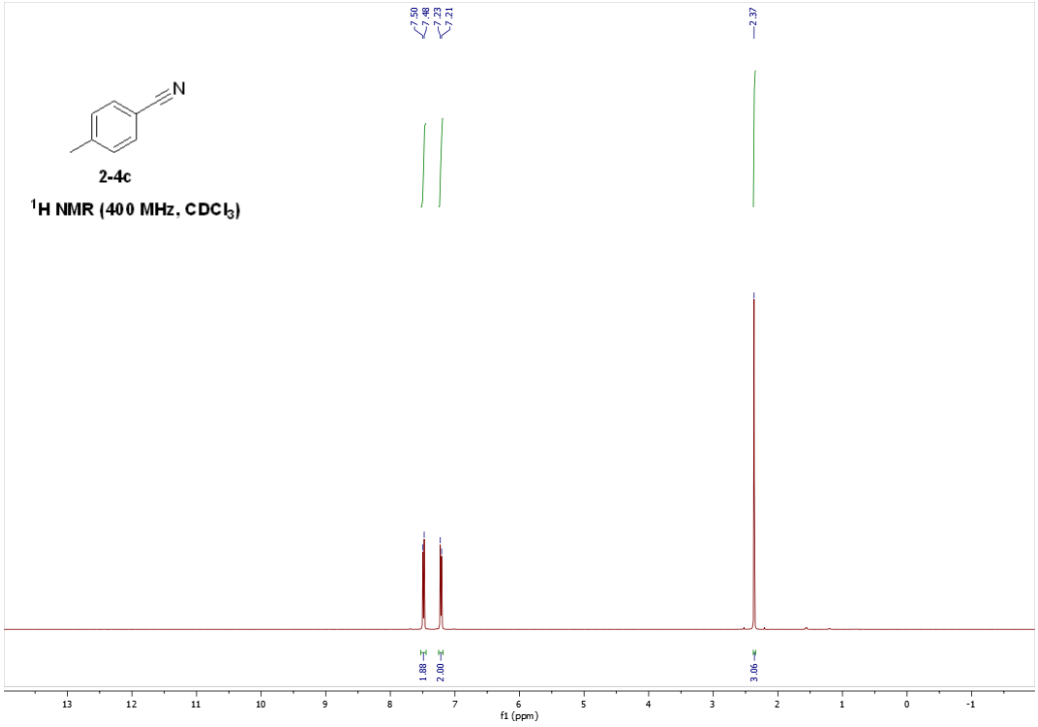

132.8
132.1
129.1
118.8
112.3
77.4 cdd3
77.1 cdd3
76.8 cdd3
N
2-4a
13C NMR (100 MHz, CDCl3)
f1 (ppm)


7.58
7.55
7.32
7.30
2.99
2.97
2.95
2.93
2.92
1.26
1.24
N
2-4b
1H NMR (400 MHz, CDCl3)
1.99
1.99
1.04
6.00
f1 (ppm)



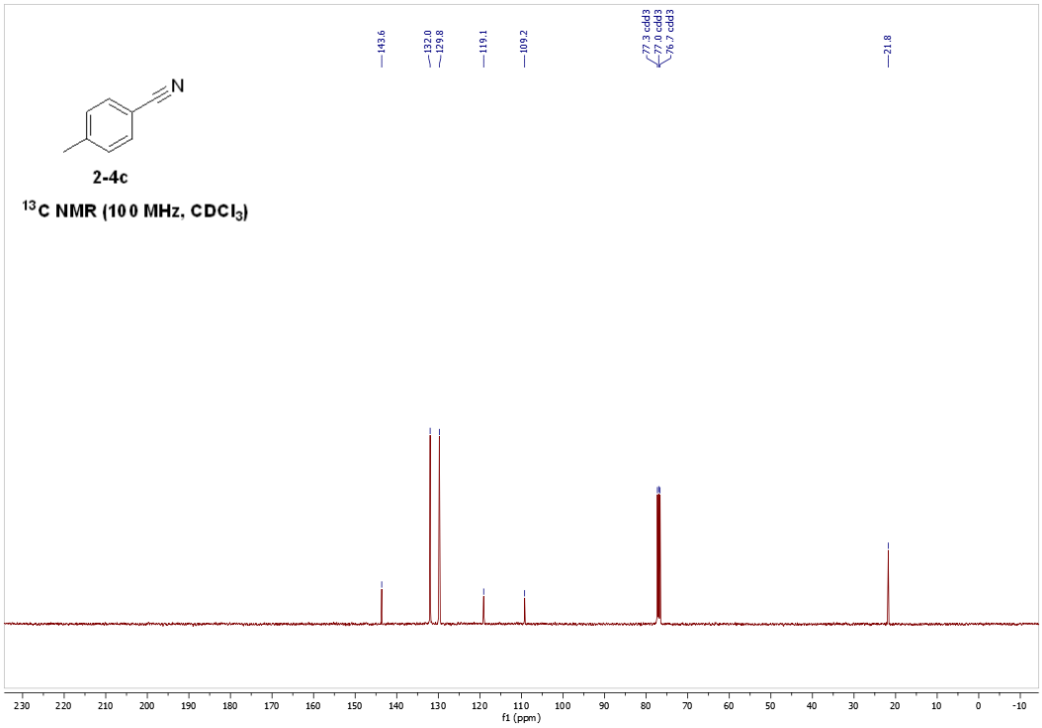
2-4b

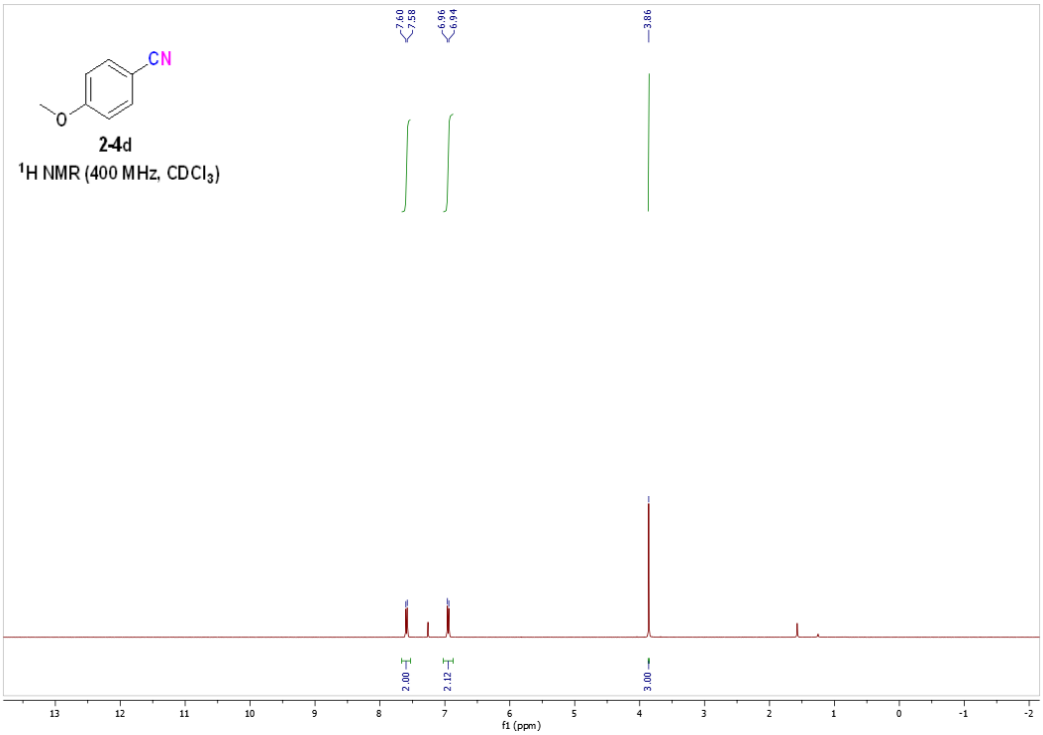
^{13}C NMR (100 MHz, $CDCl_3$)

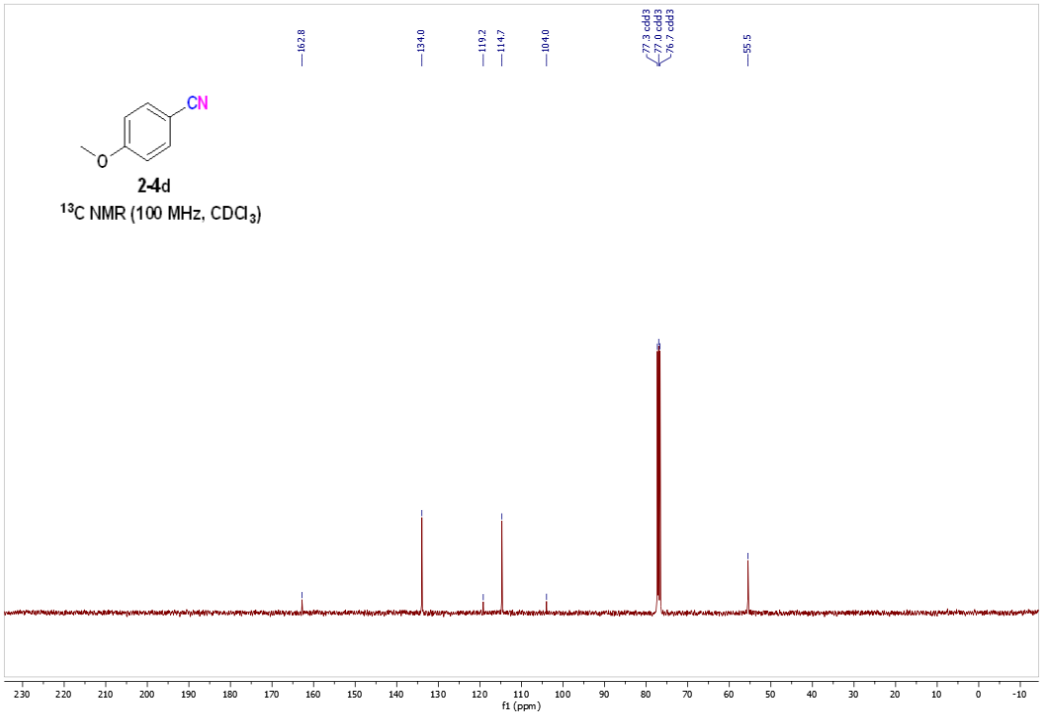


2-4c

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

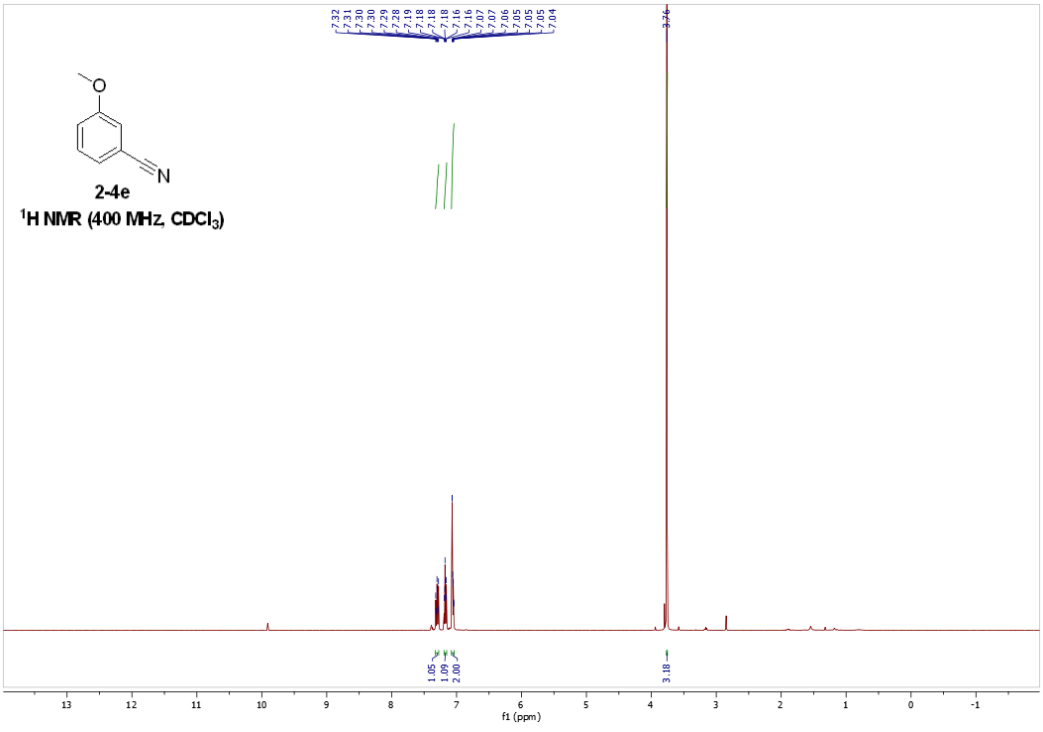

N
2-4c
13C NMR (100 MHz, CDCl3)
143.6
132.0
129.8
119.1
109.2
77.3 cdd3
77.0 cdd3
76.7 cdd3
21.8
f1 (ppm)


CN
O
2-4d
1H NMR (400 MHz, CDCl3)
7.60
7.58
6.96
6.94
3.86
2.00
2.12
3.00
f1 (ppm)



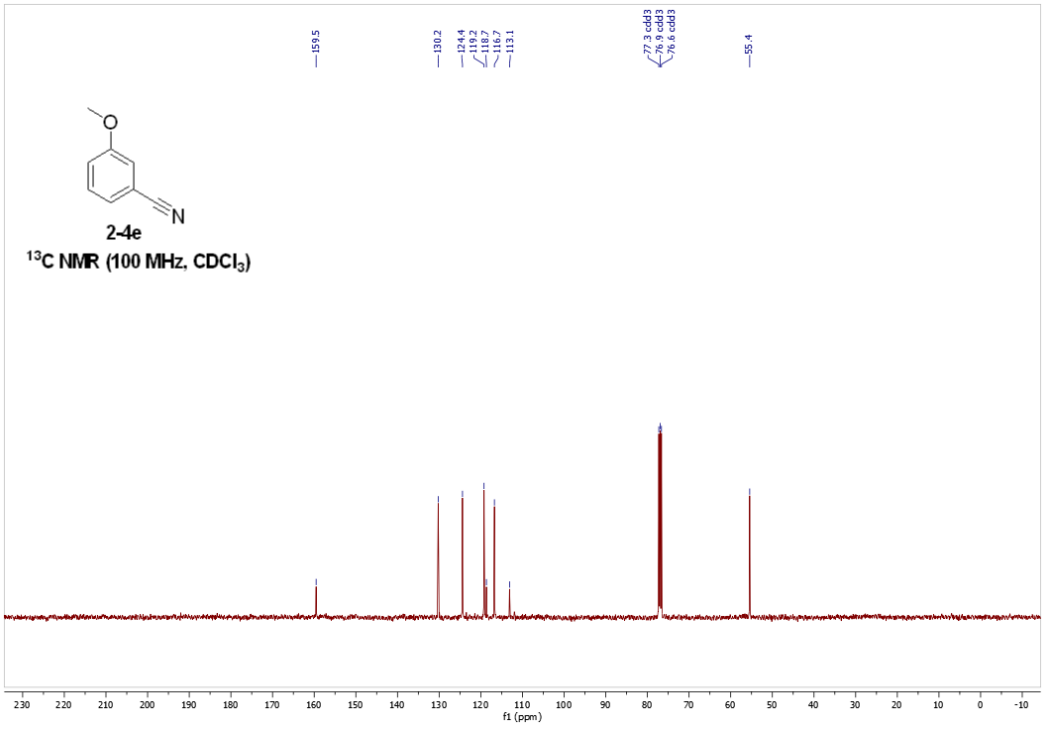
2-4d

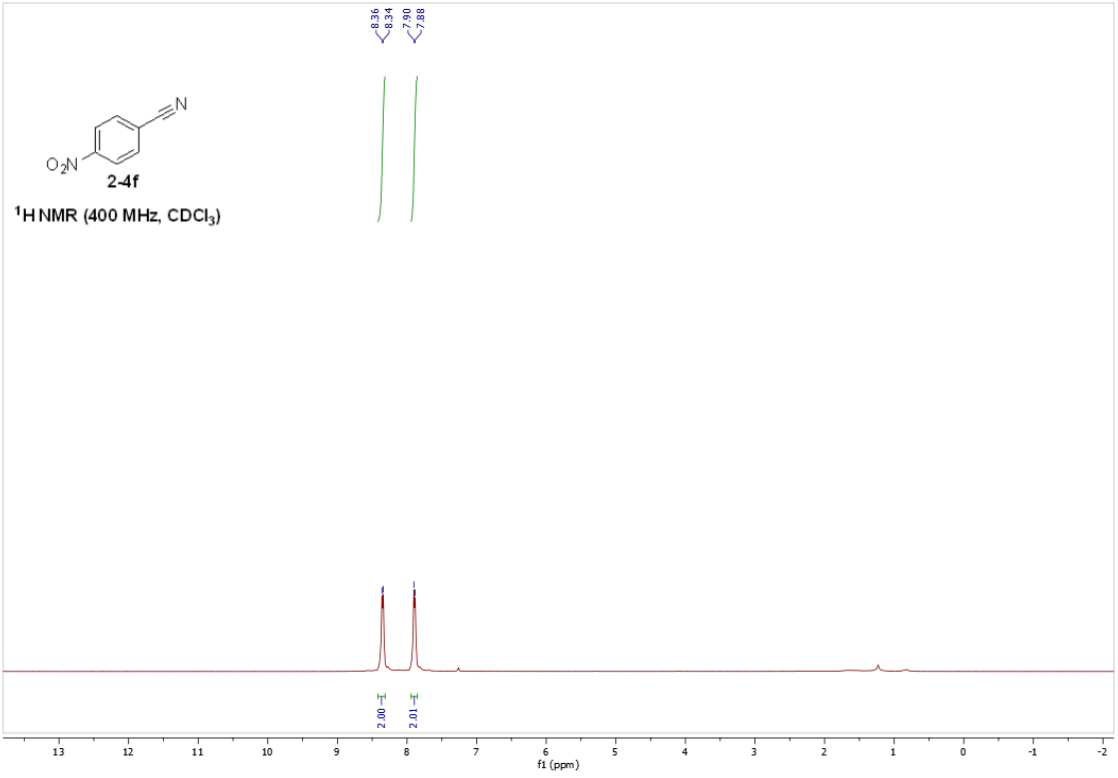
^{13}C NMR (100 MHz, $CDCl_3$)

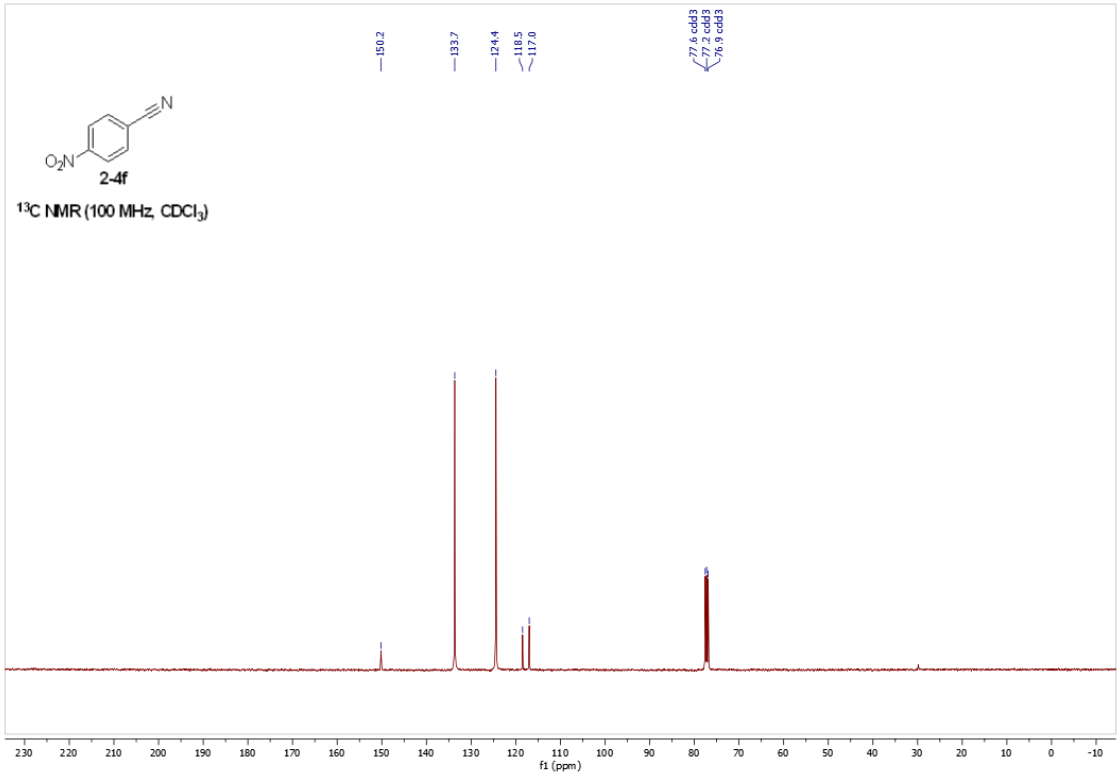


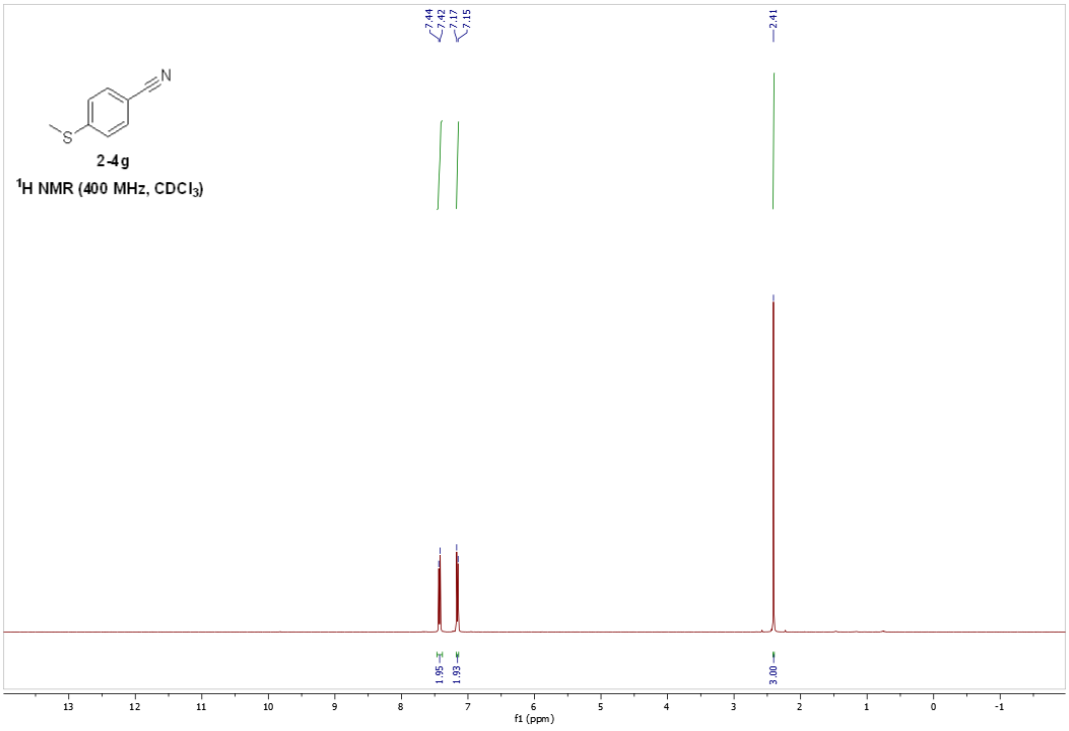
2-4e

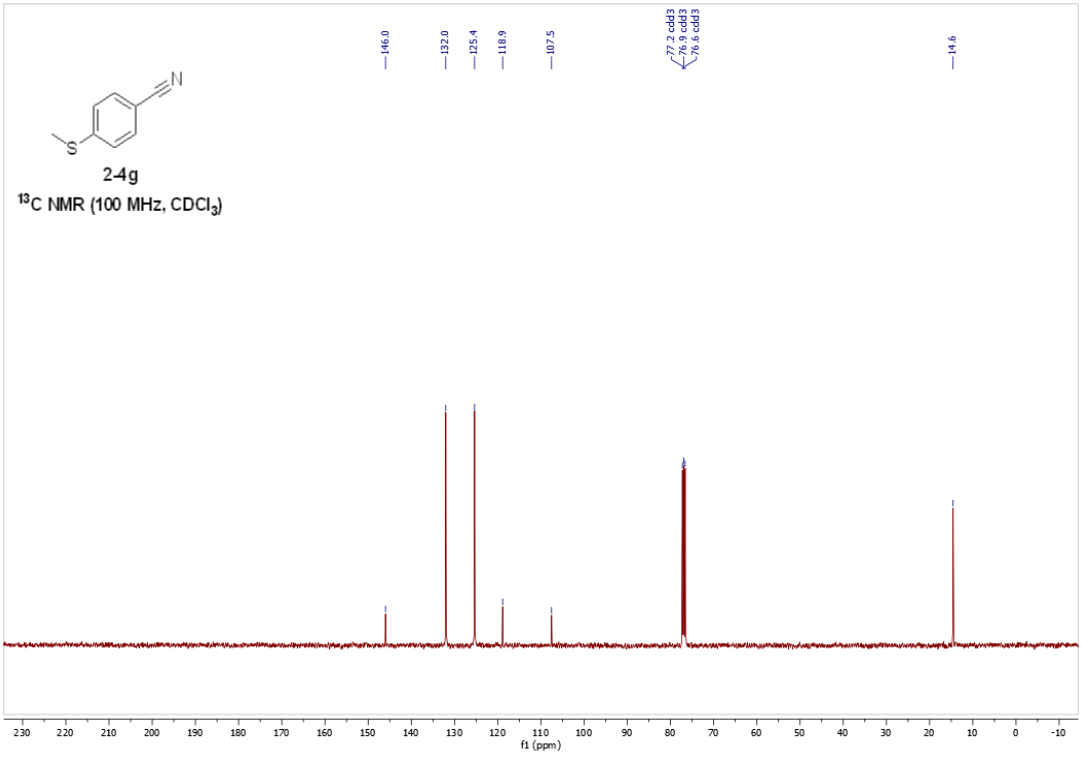
^{1}H NMR (400 MHz, $CDCl_3$)

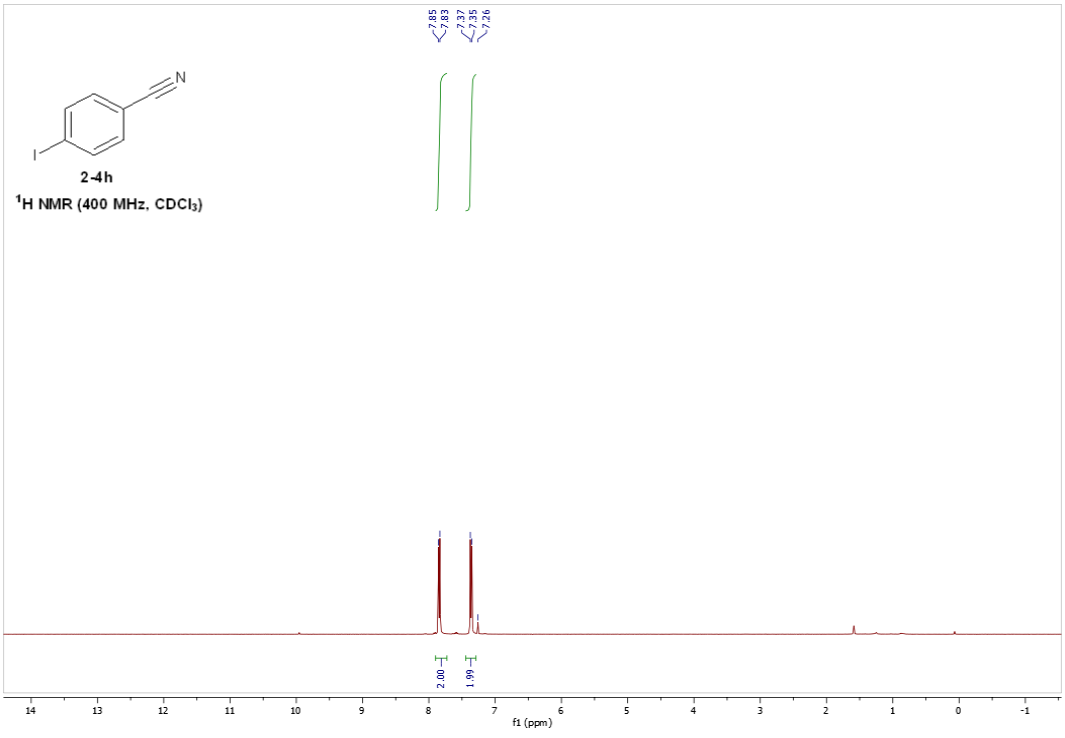

159.5
130.2
124.4
119.2
117.7
116.7
113.1
77.3 cdd3
76.9 cdd3
76.6 cdd3
55.4
O
N
2-4e
13C NMR (100 MHz, CDCl3)
f1 (ppm)

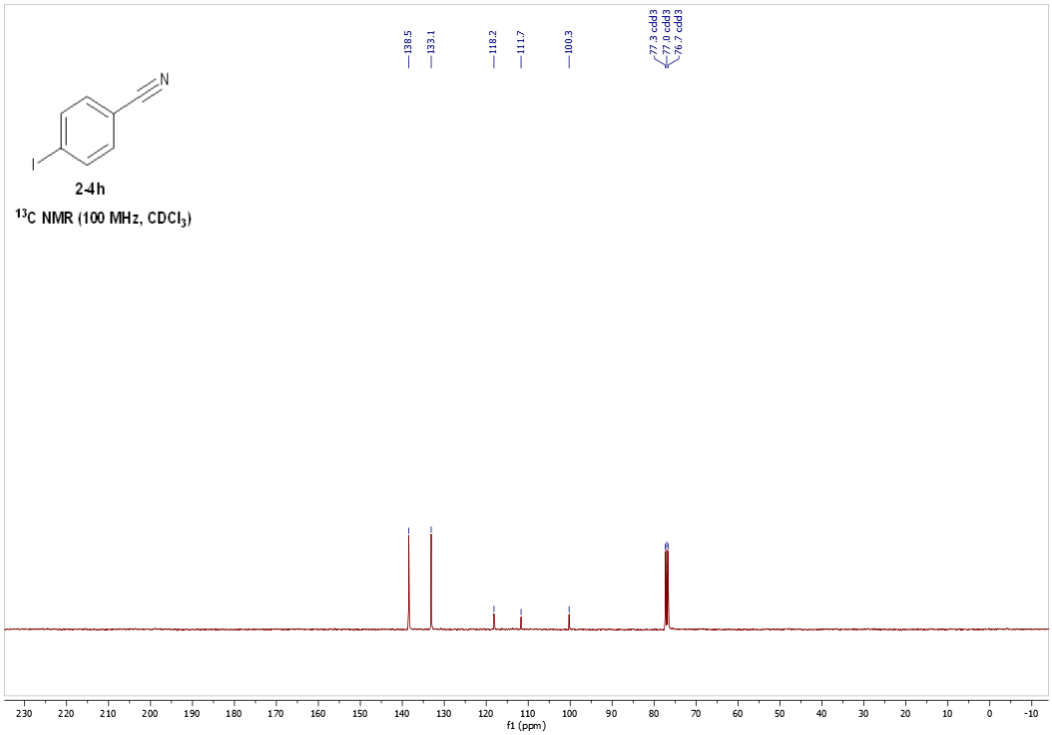

8.36
8.34
7.90
7.88
N
O2N
2-4f
1H NMR (400 MHz, CDCl3)
2.00
2.01
f1 (ppm)

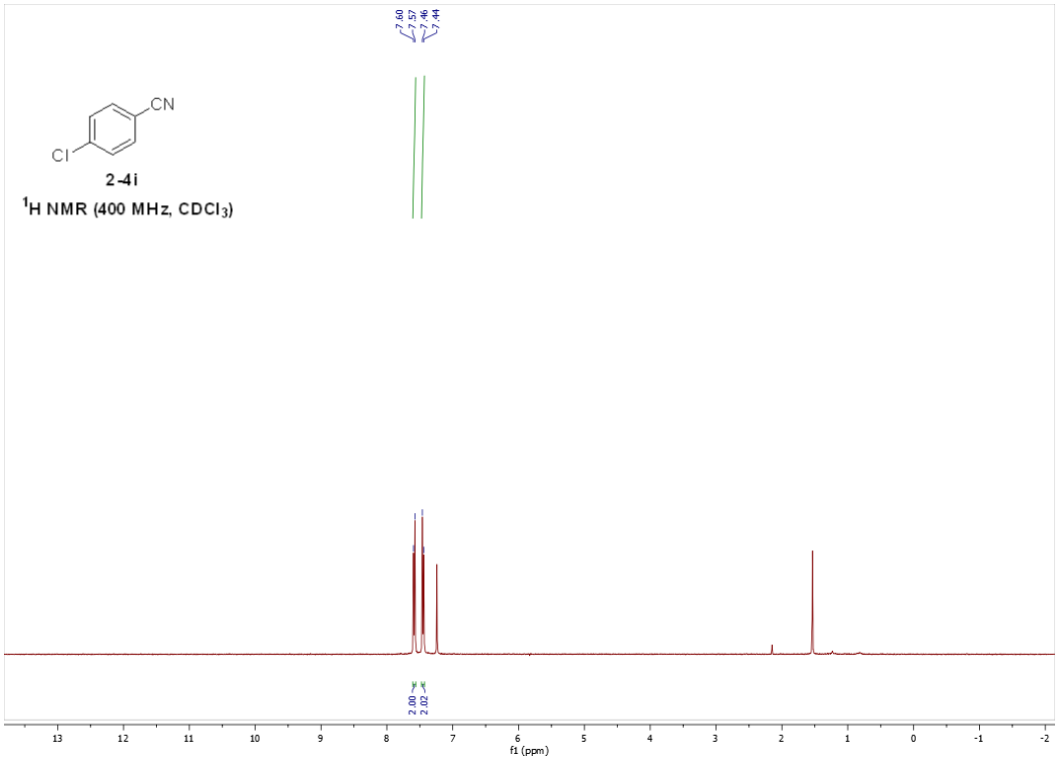

150.2
133.7
124.4
118.5
117.0
77.6 cdd3
77.2 cdd3
76.9 cdd3
2-4f
13C NMR (100 MHz, CDCl3)
f1 (ppm)

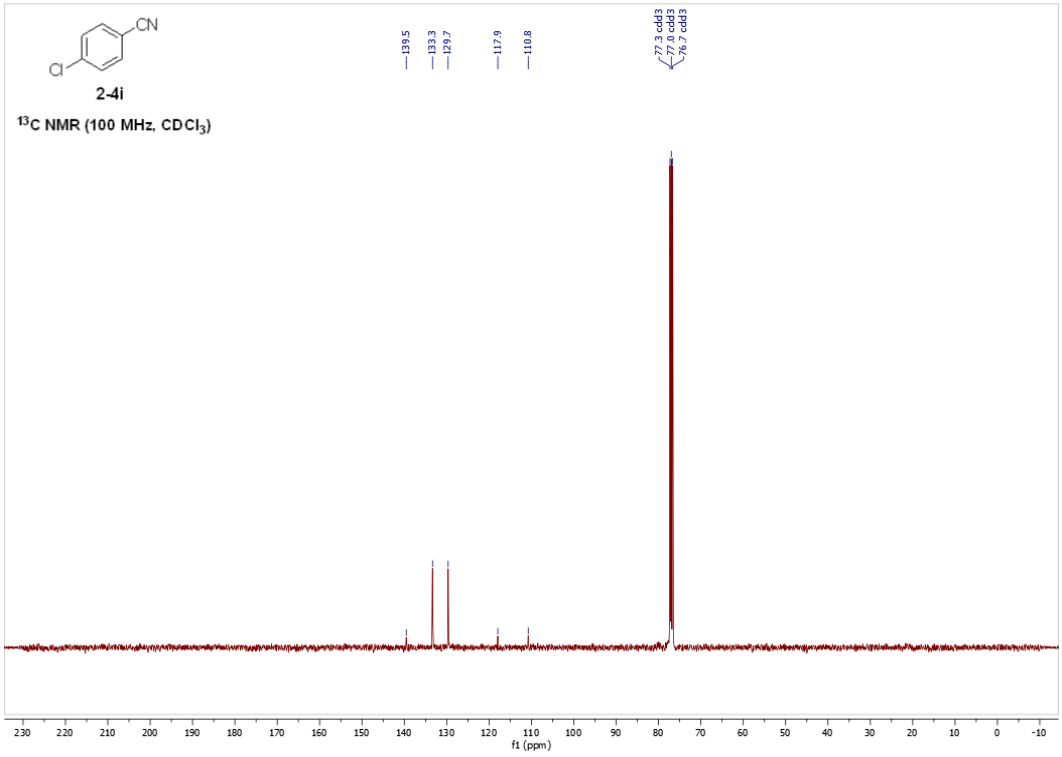

7.44
7.43
7.12
7.15
2.41
2-4g
1H NMR (400 MHz, CDCl3)
1.95
1.93
3.00
f1 (ppm)

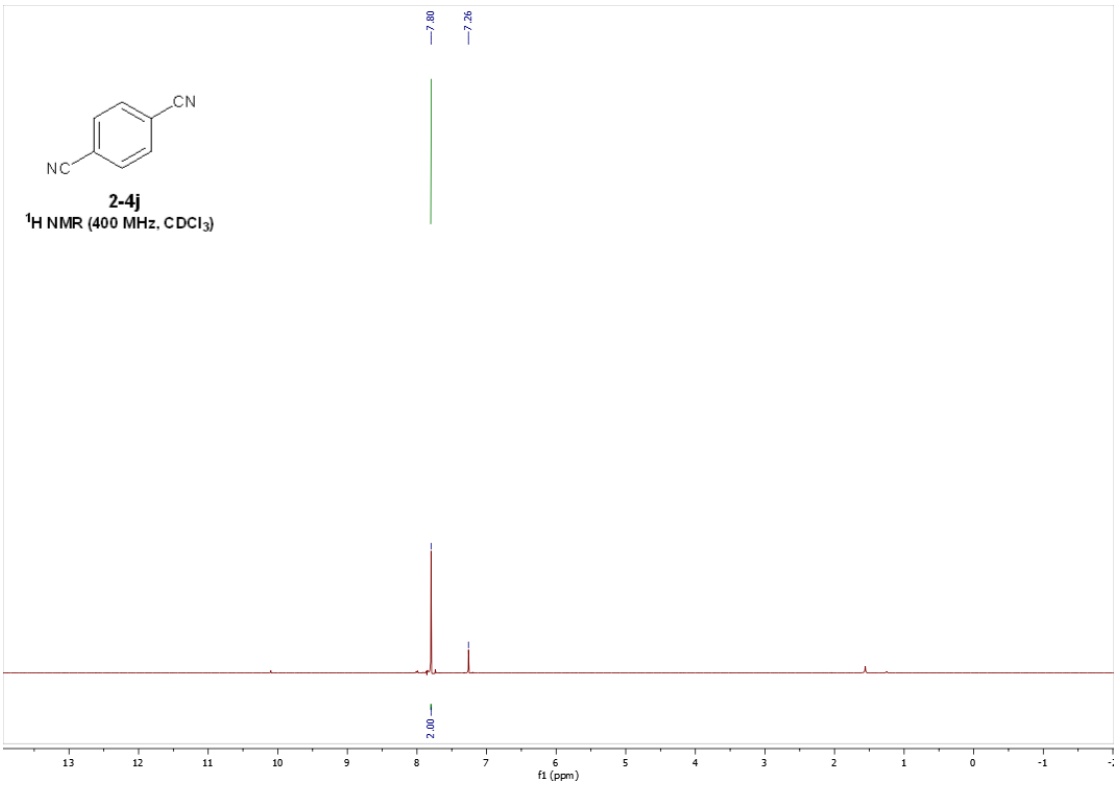

146.0
132.0
125.4
118.9
107.5
77.2 cdd3
76.9 cdd3
76.6 cdd3
14.6
N
S
2-4g
13C NMR (100 MHz, CDCl3)
f1 (ppm)

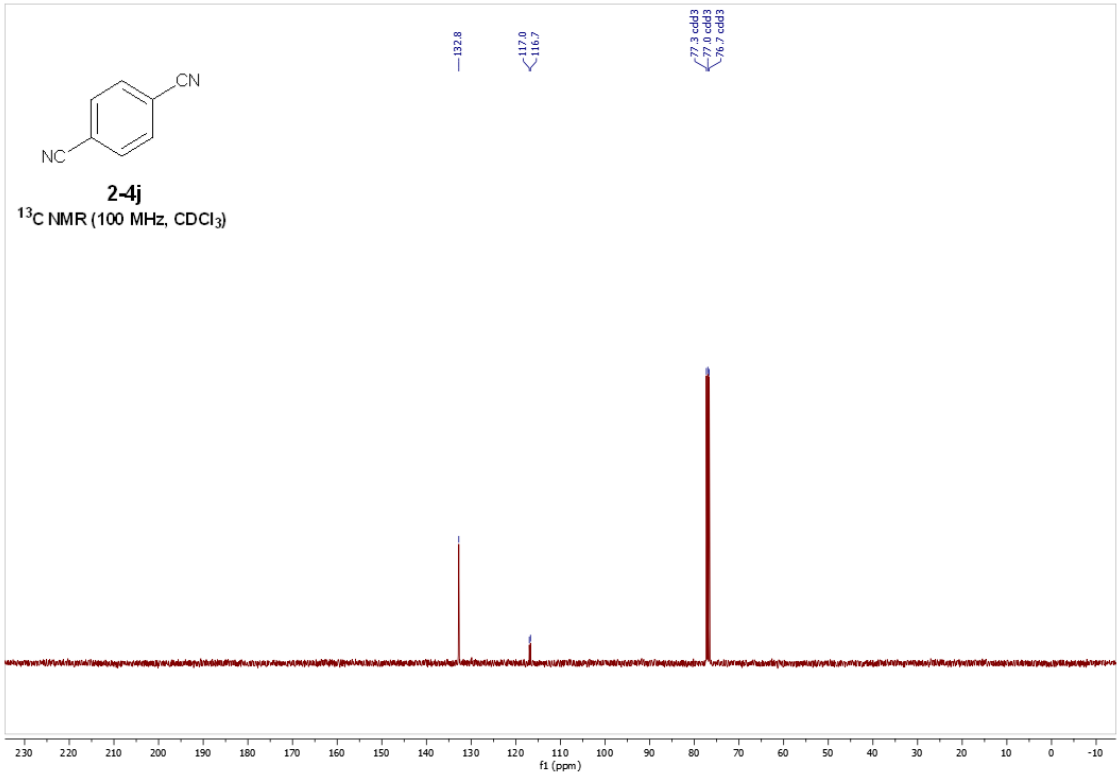

7.85
7.83
7.37
7.35
7.26
N
I
2-4h
1H NMR (400 MHz, CDCl3)
2.00
1.99
f1 (ppm)

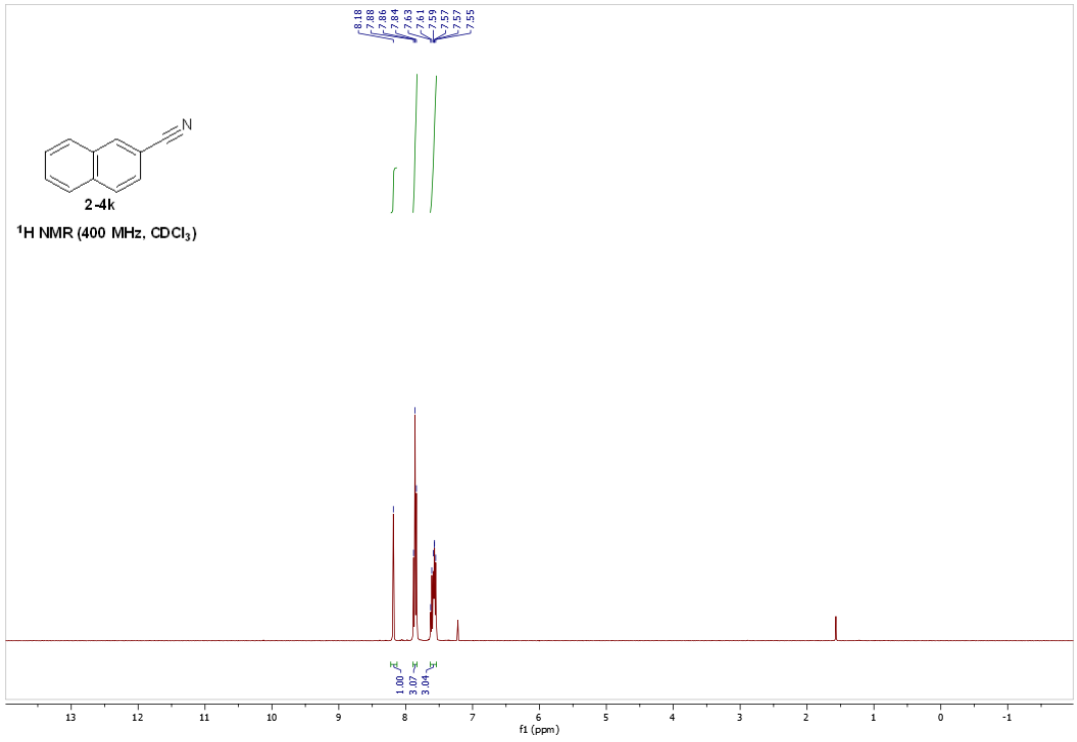

138.5
133.1
118.2
111.7
100.3
77.3 cdd3
77.0 cdd3
76.7 cdd3
N
I
2-4h
^{13}C NMR (100 MHz, $CDCl_3$)
f1 (ppm)

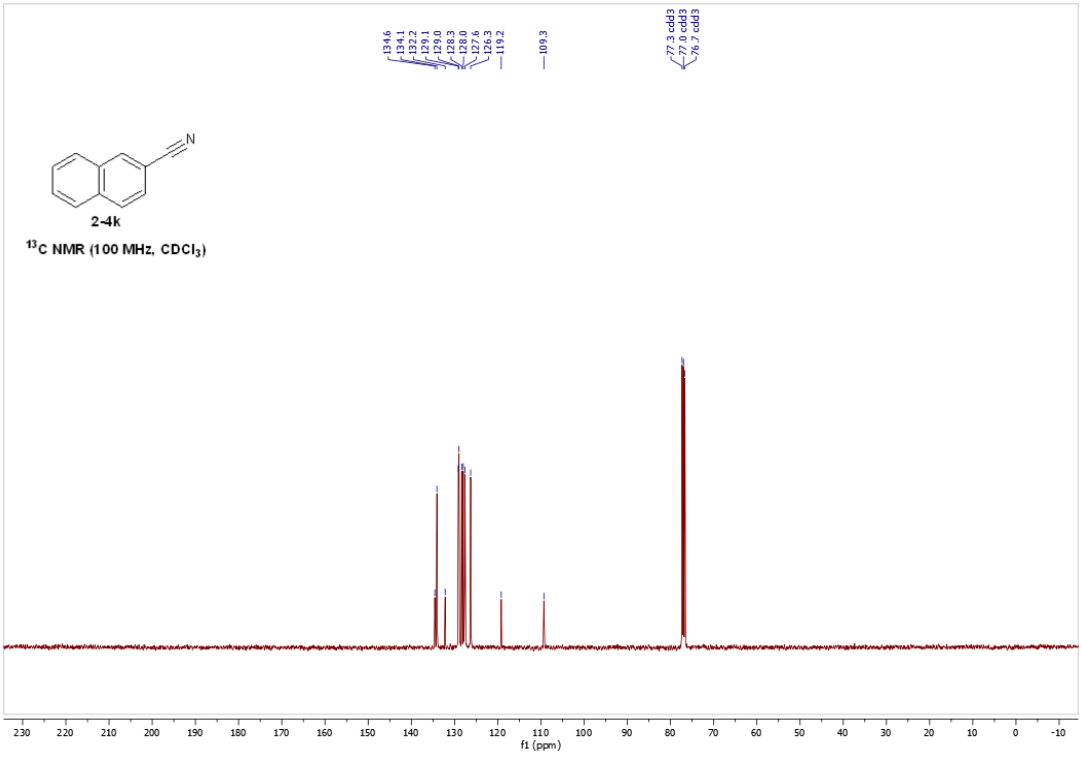

7.60
7.57
7.46
7.44
CN
Cl
2-4i
^{1}H NMR (400 MHz, $CDCl_3$)
2.00
2.02
f1 (ppm)

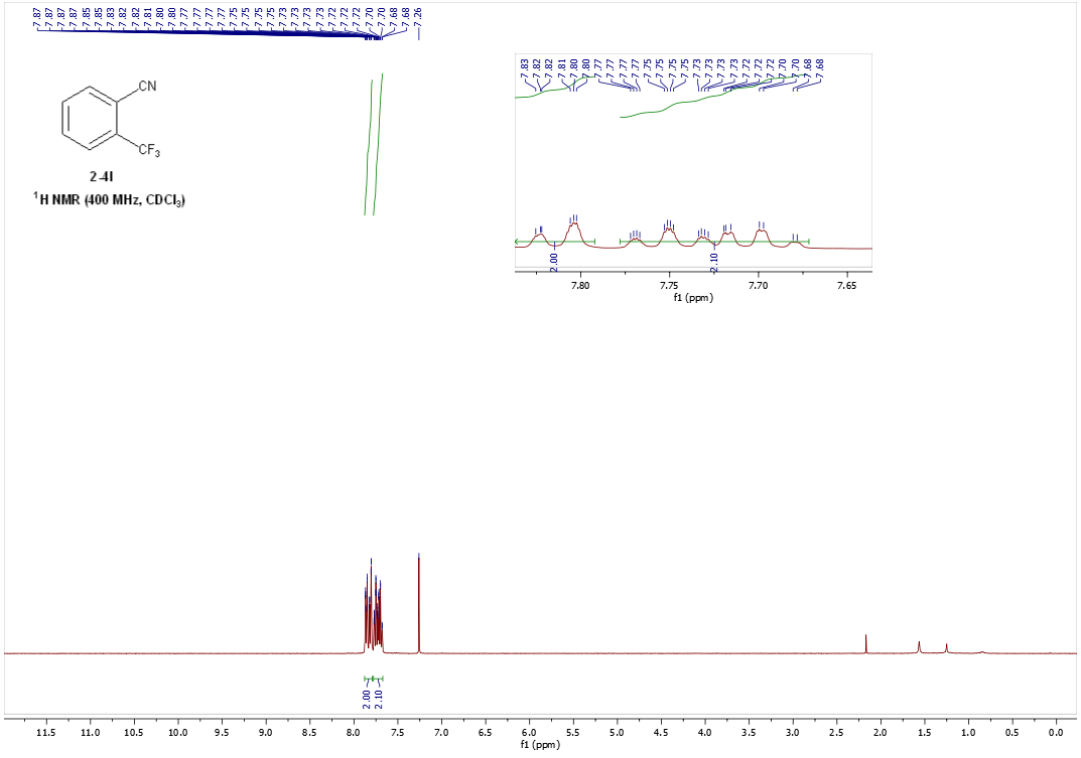

CN
Cl
2-4i
^{13}C NMR (100 MHz, CDCl$_3$)
139.5
133.3
129.7
117.9
110.8
77.3 cdd3
77.0 cdd3
76.7 cdd3
f1 (ppm)

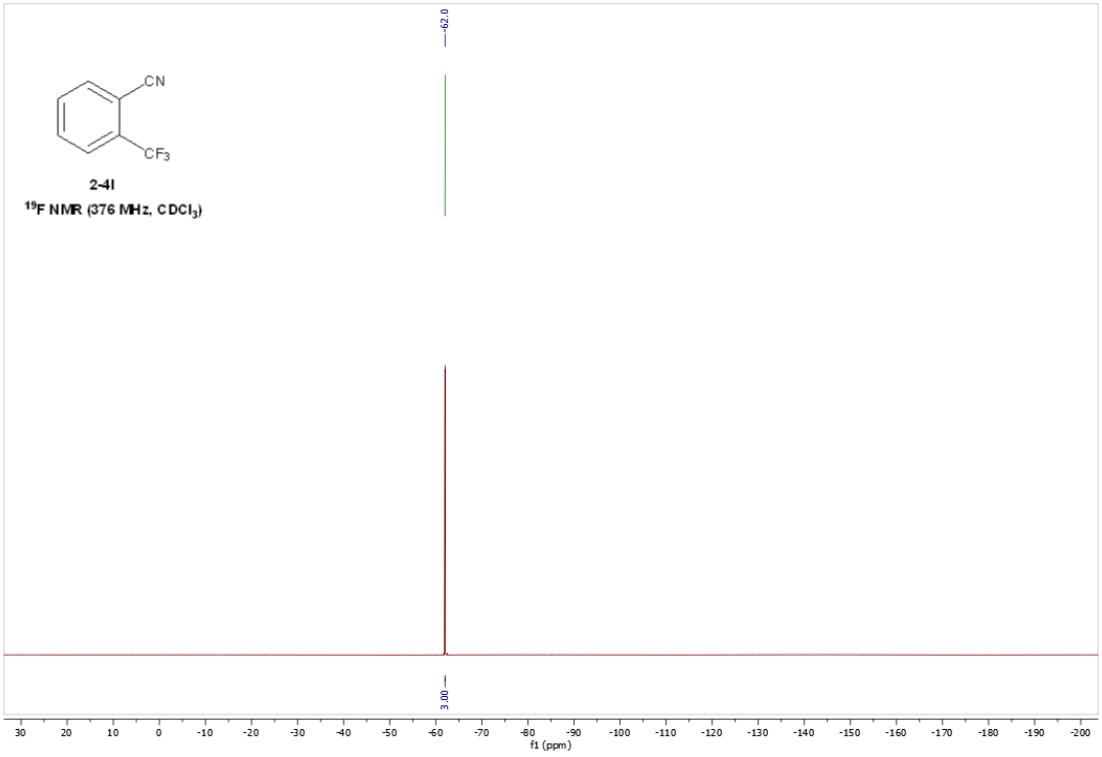

CN
NC
2-4j
^{1}H NMR (400 MHz, CDCl$_3$)
7.80
7.26
2.00
f1 (ppm)

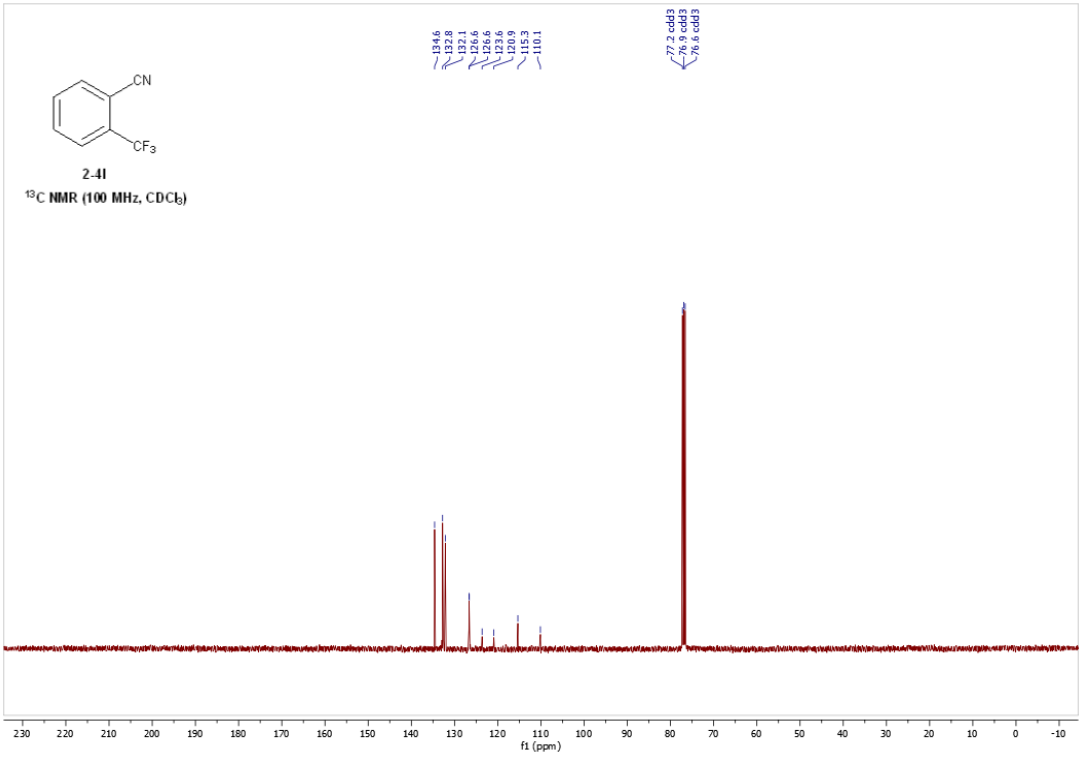

CN
NC
2-4j
^{13}C NMR (100 MHz, $CDCl_3$)
132.8
117.0
116.7
77.3 cdd3
77.0 cdd3
76.7 cdd3
f1 (ppm)

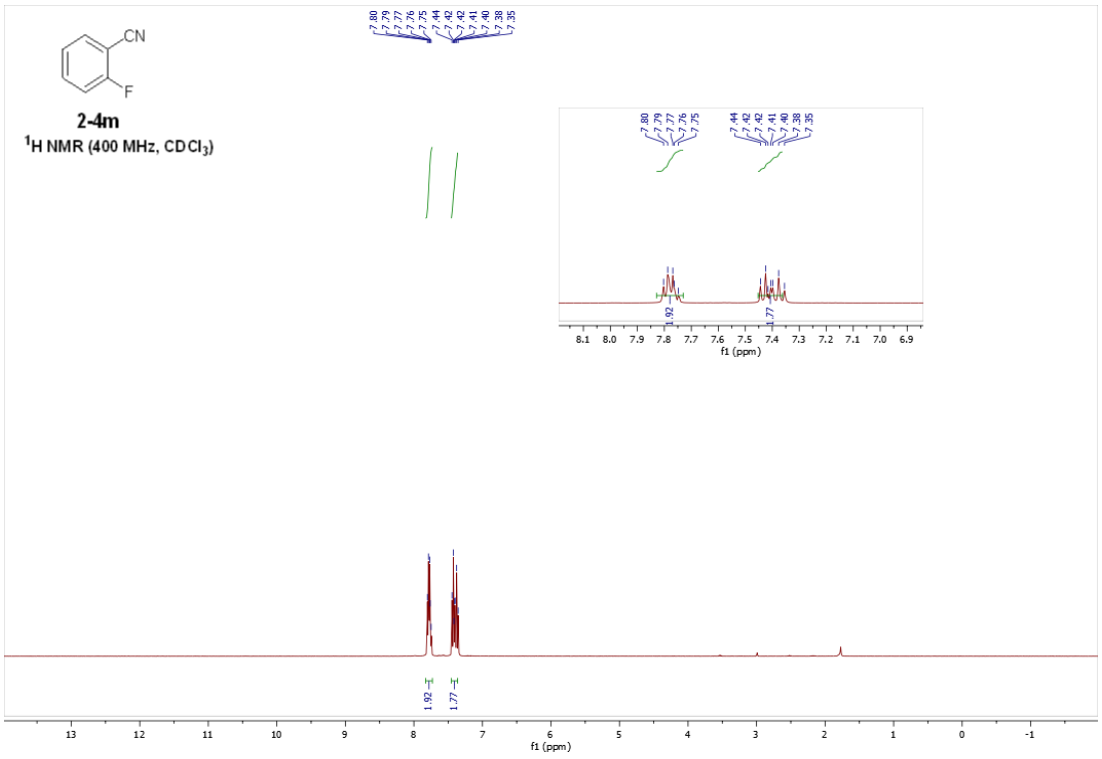

N
2-4k
^{1}H NMR (400 MHz, $CDCl_3$)
8.18
7.88
7.86
7.84
7.63
7.61
7.59
7.57
7.57
7.55
1.00
3.07
3.04
f1 (ppm)

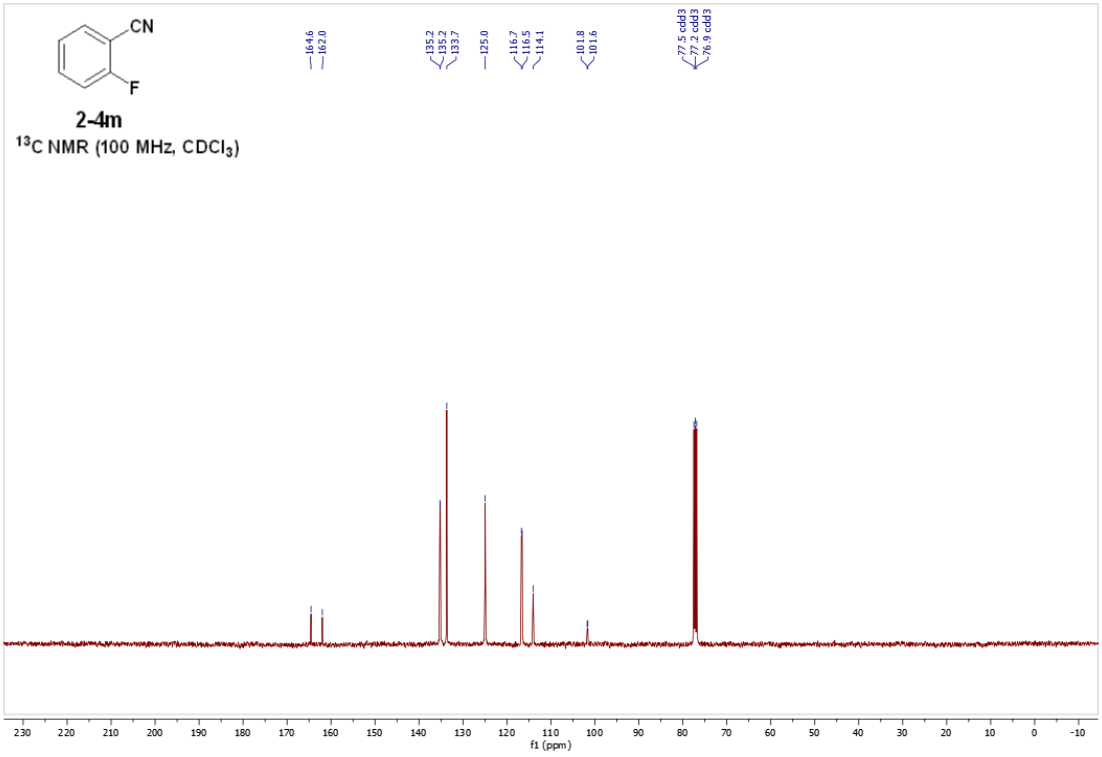

134.6
134.1
132.2
129.1
129.0
128.3
128.0
127.6
126.3
119.2
109.3
77.3 cdd3
77.0 cdd3
76.7 cdd3
N
2-4k
13C NMR (100 MHz, CDCl3)
f1 (ppm)

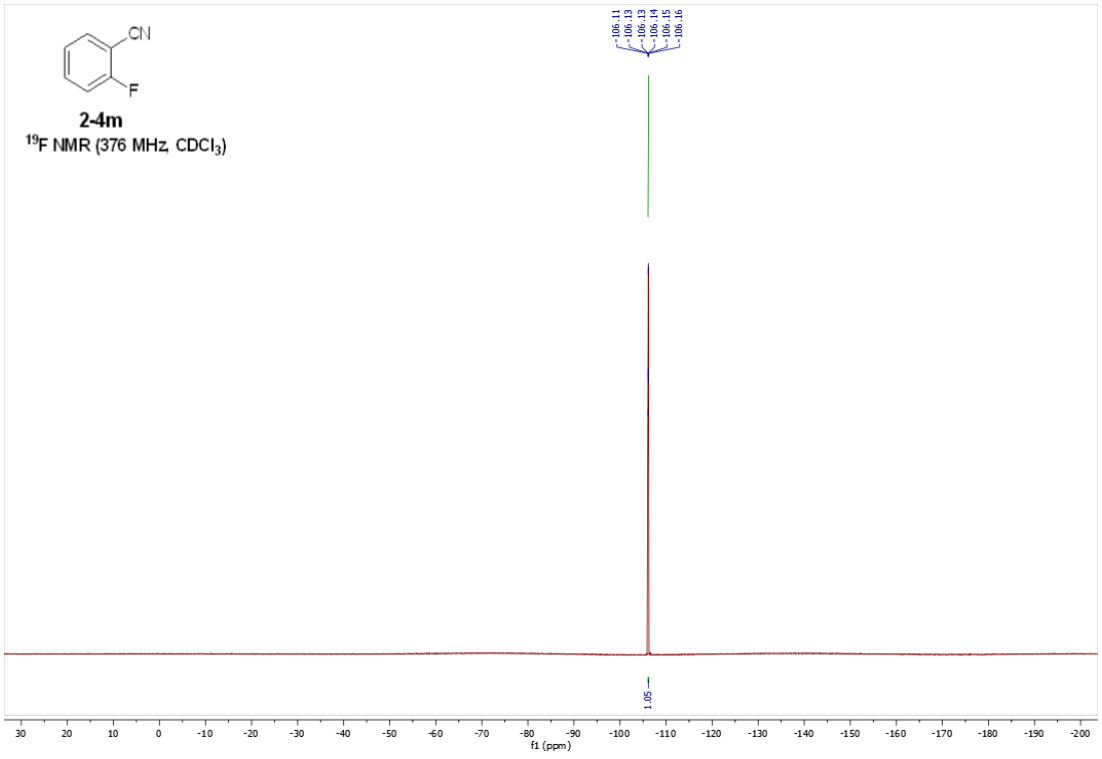

CN
CF3
2-4l
1H NMR (400 MHz, CDCl3)
2.00
2.10
f1 (ppm)

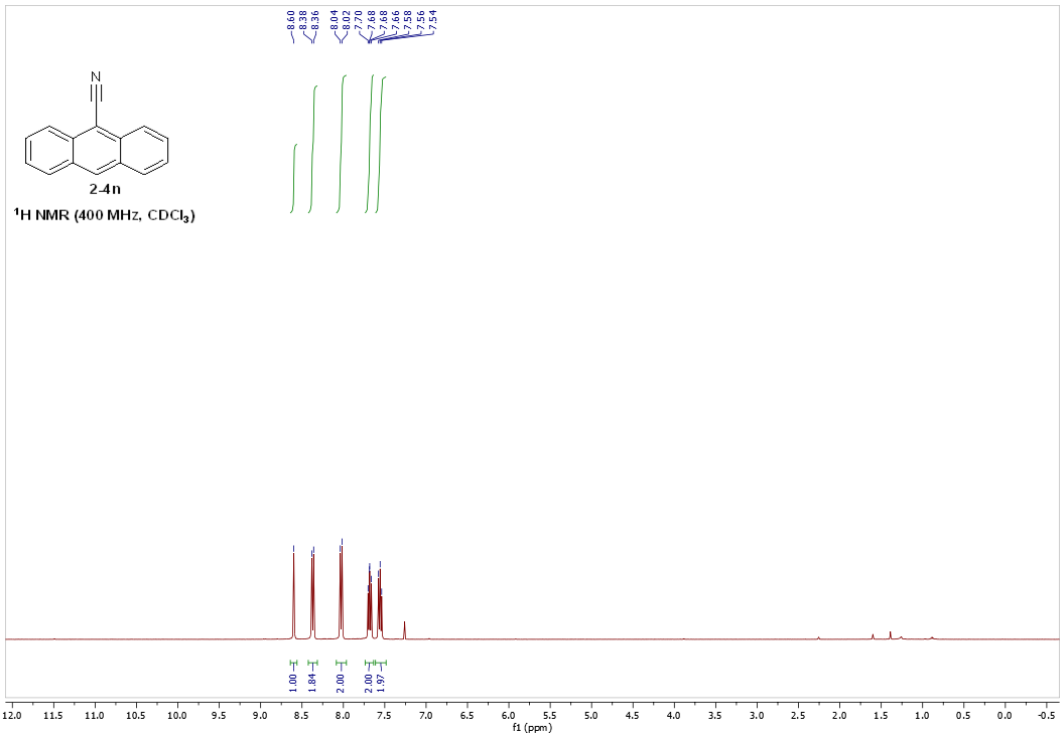

CN
CF3
2-4l
19F NMR (376 MHz, CDCl3)
-62.0
3.00
f1 (ppm)

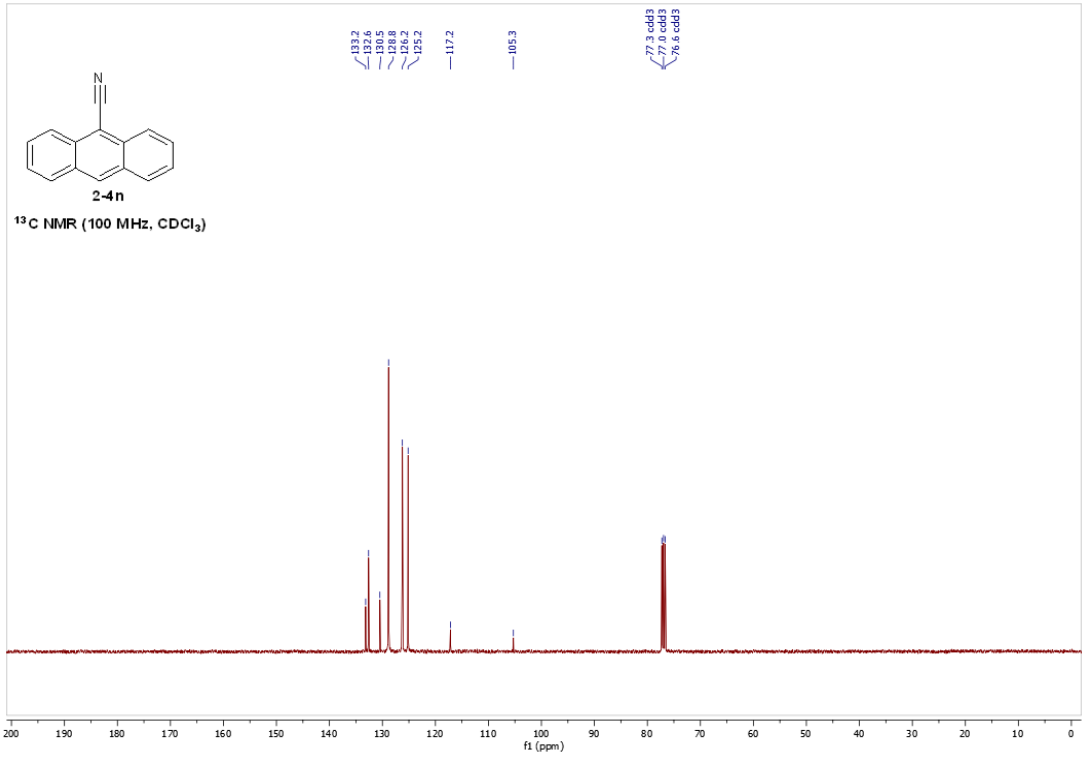

CN
CF3
2-4l
13C NMR (100 MHz, CDCl3)
134.6
132.8
132.1
131.6
126.6
123.6
120.9
115.3
110.1
77.2 cdd3
76.9 cdd3
76.6 cdd3
f1 (ppm)

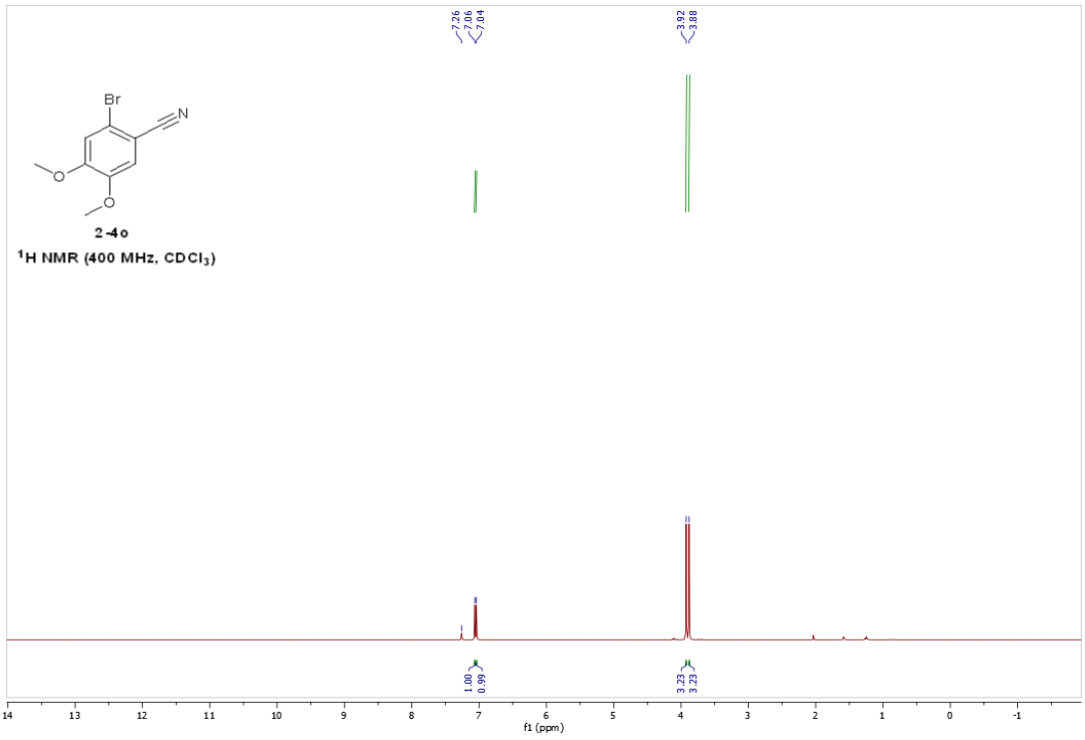

CN
F
2-4m
^{1}H NMR (400 MHz, $CDCl_3$)
7.80
7.79
7.77
7.76
7.75
7.44
7.42
7.42
7.41
7.40
7.38
7.35
1.92
1.77
f1 (ppm)

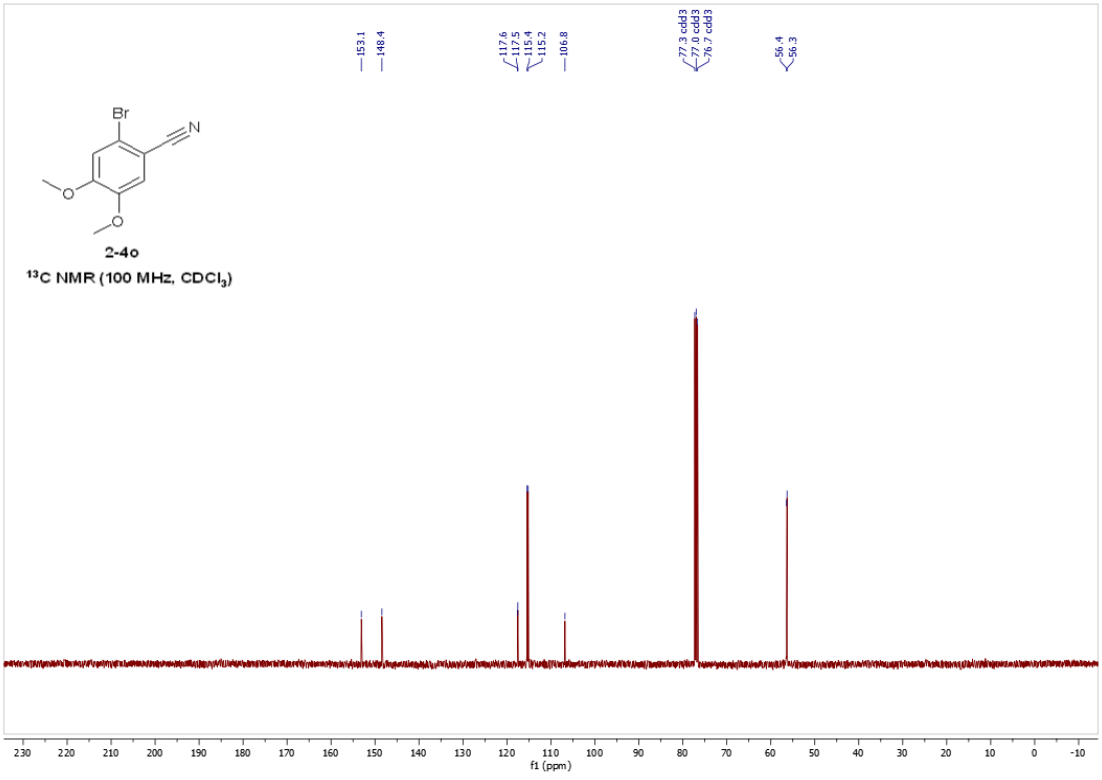

CN
F
2-4m
^{13}C NMR (100 MHz, CDCl$_3$)
164.6
162.0
135.2
135.2
133.7
125.0
116.7
116.5
114.1
101.8
101.6
77.5 cdd3
77.2 cdd3
76.9 cdd3
f1 (ppm)

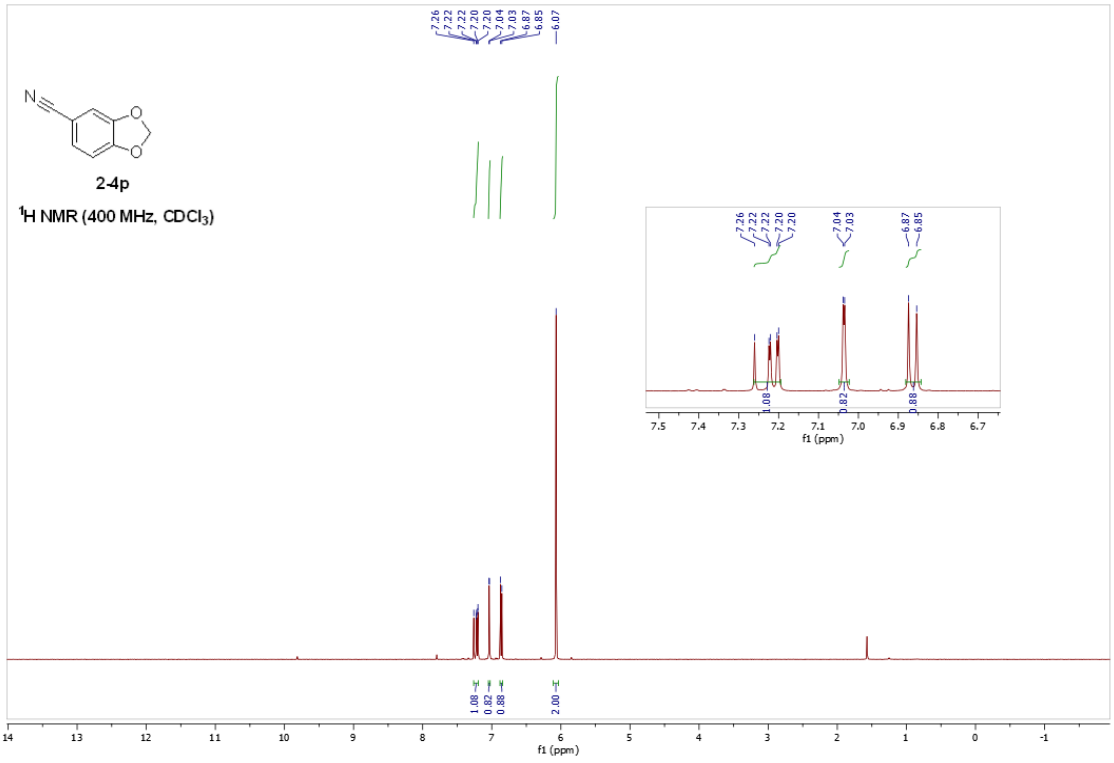

CN
F
2-4m
^{19}F NMR (376 MHz, CDCl$_3$)
-106.11
-106.13
-106.13
-106.14
-106.15
-106.16
1.05
f1 (ppm)

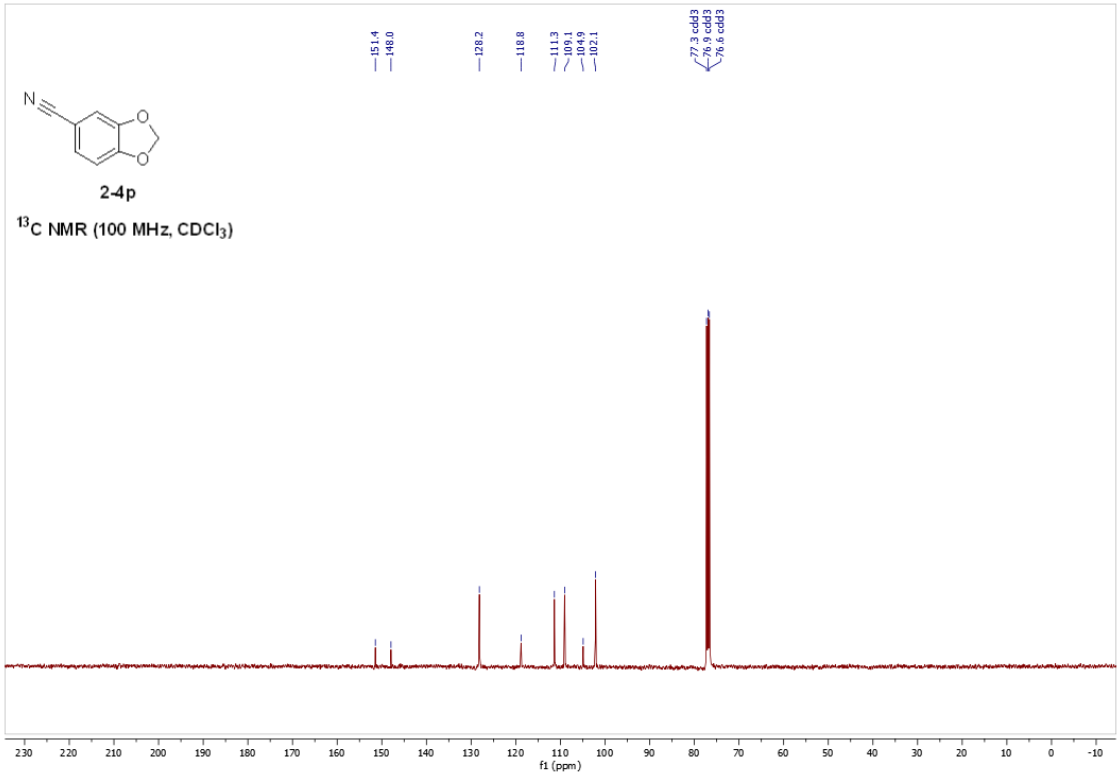

8.60
8.38
8.36
8.04
8.02
7.70
7.68
7.66
7.58
7.56
7.54
N
2-4n
^{1}H NMR (400 MHz, $CDCl_3$)
1.00
1.84
2.00
2.00
1.97
f1 (ppm)

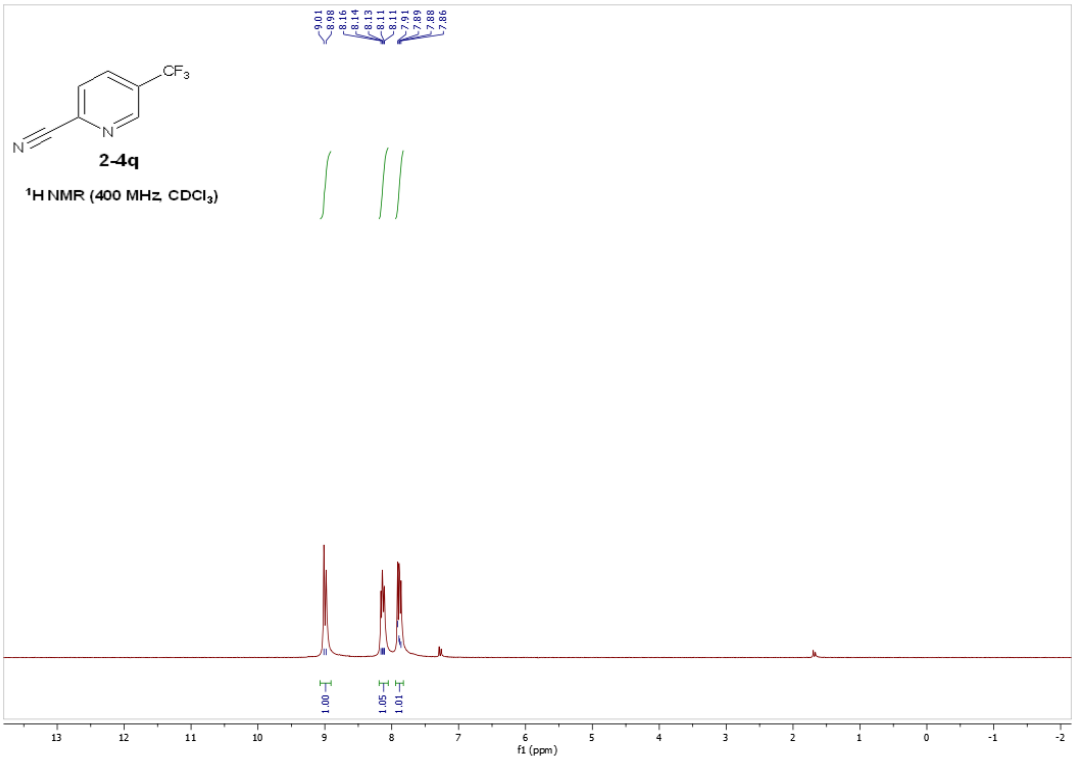

133.2
132.6
130.5
128.8
126.2
125.2
117.2
105.3
77.3 cdd3
77.0 cdd3
76.6 cdd3
N
2-4n
^{13}C NMR (100 MHz, $CDCl_3$)
f1 (ppm)

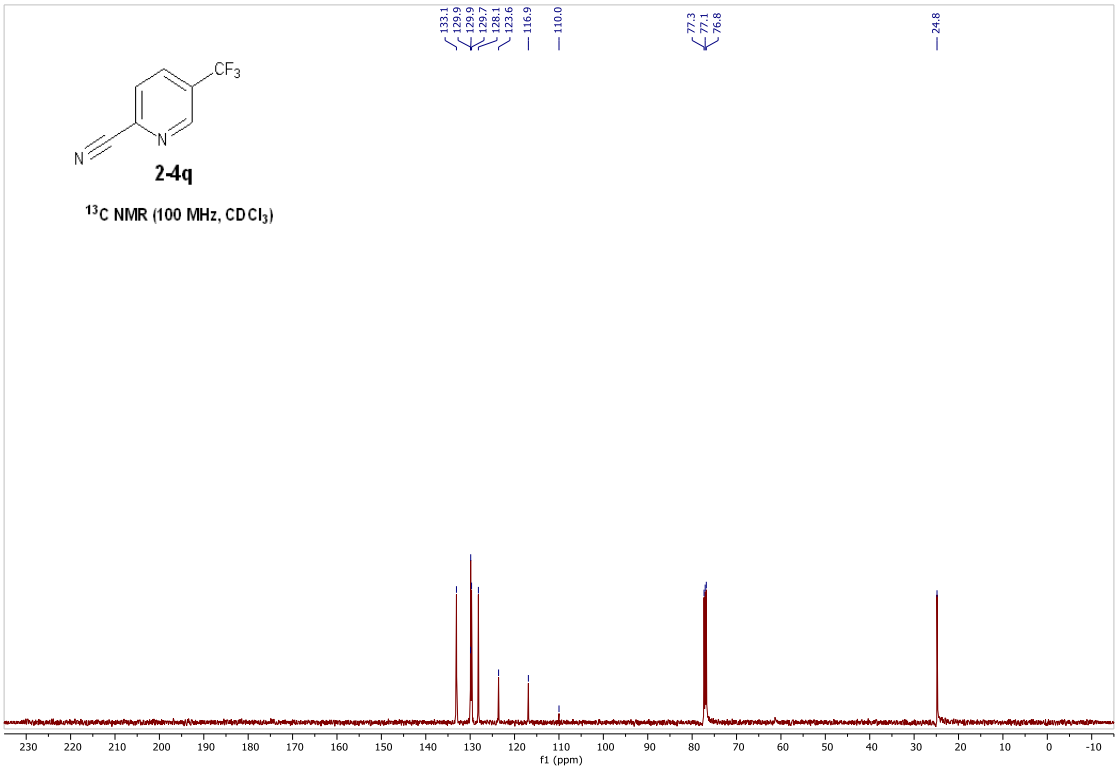

7.26
7.06
7.04
3.92
3.88
Br
N
O
O
2-4o
^{1}H NMR (400 MHz, $CDCl_3$)
1.00
0.99
3.23
3.23
f1 (ppm)

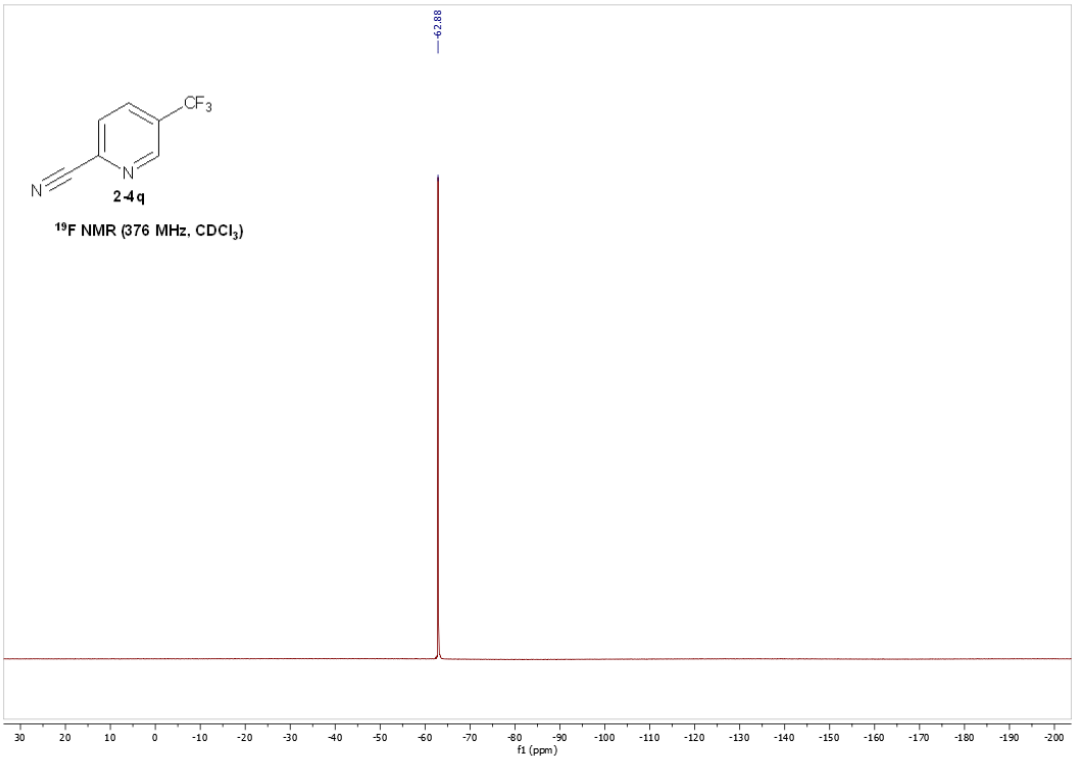

153.1
148.4
117.6
117.5
115.4
115.2
106.8
77.3 cdd3
77.0 cdd3
76.7 cdd3
56.4
56.3
Br
N
O
O
2-4o
^{13}C NMR (100 MHz, $CDCl_3$)
f1 (ppm)


2-4p
^{1}H NMR (400 MHz, $CDCl_3$)
f1 (ppm)


2-4p
^{13}C NMR (100 MHz, $CDCl_3$)
f1 (ppm)

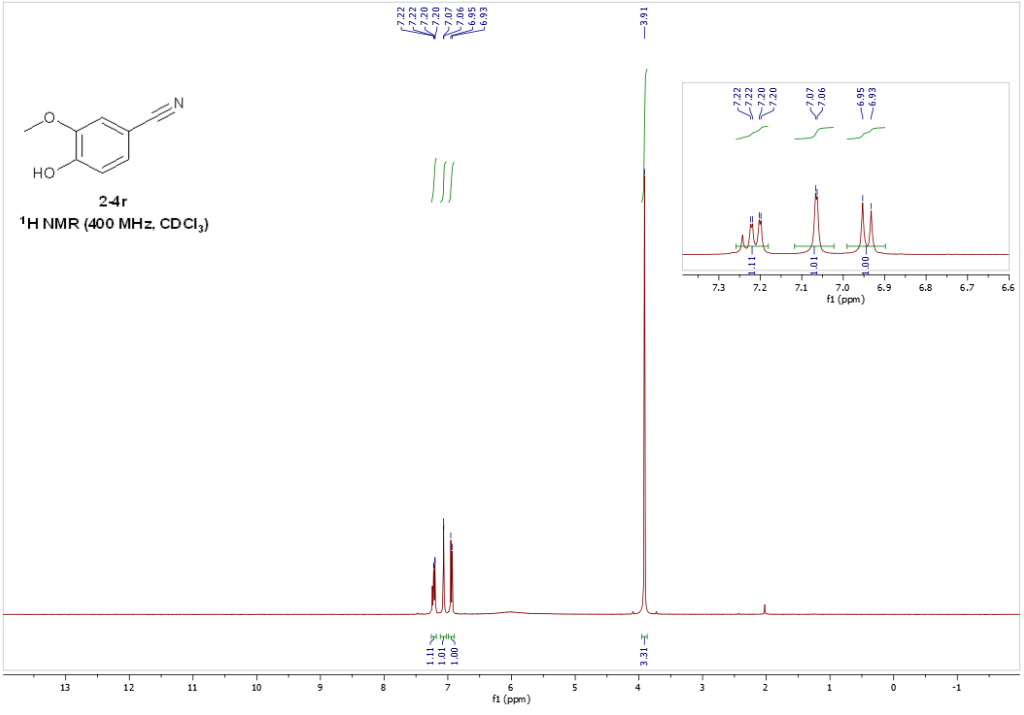

2-4q
^{1}H NMR (400 MHz, CDCl$_3$)
f1 (ppm)


2-4q
^{13}C NMR (100 MHz, CDCl$_3$)
f1 (ppm)



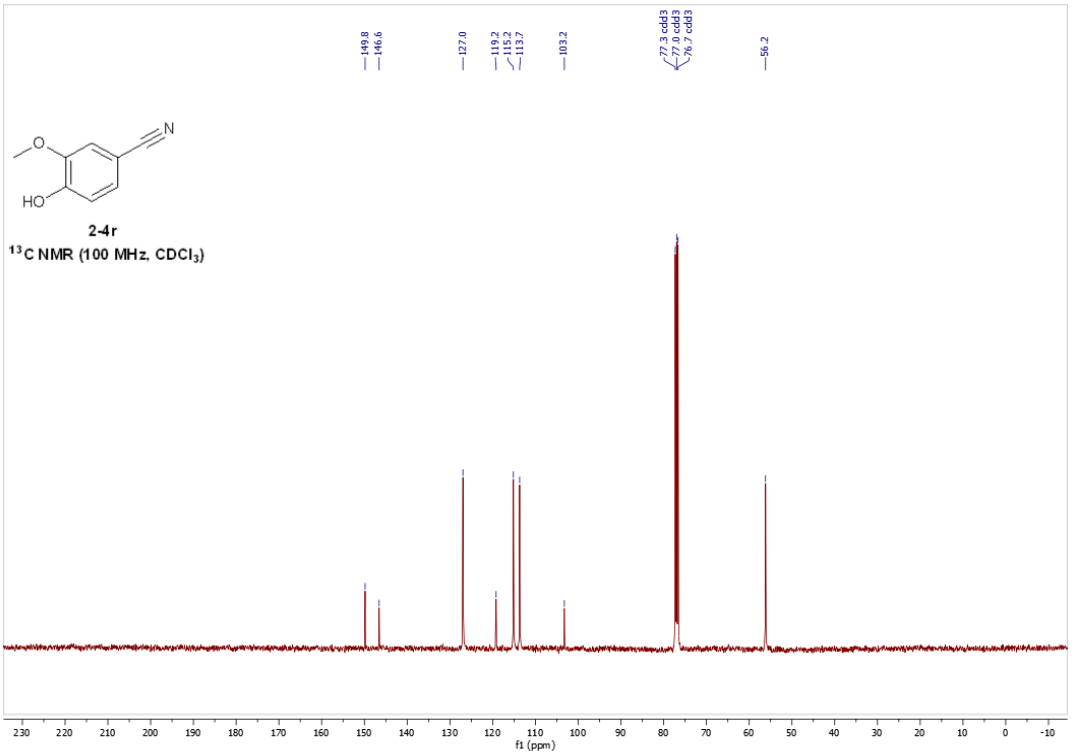
2-4q

^{19}F NMR (376 MHz, $CDCl_3$)



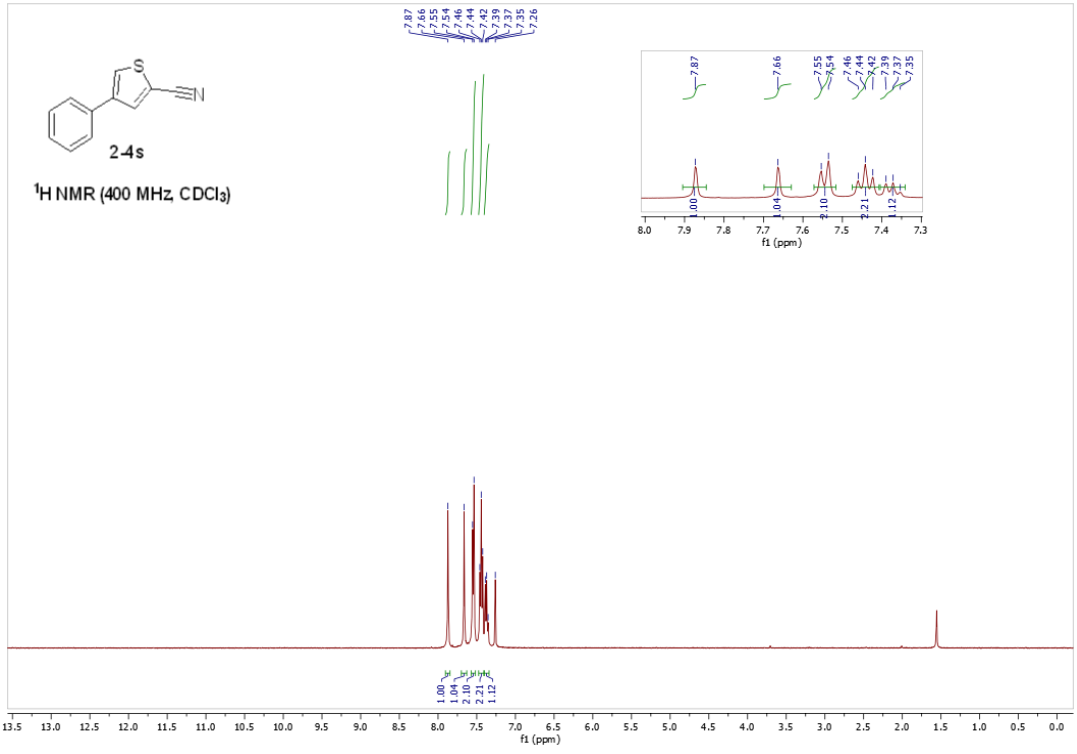
2-4r

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



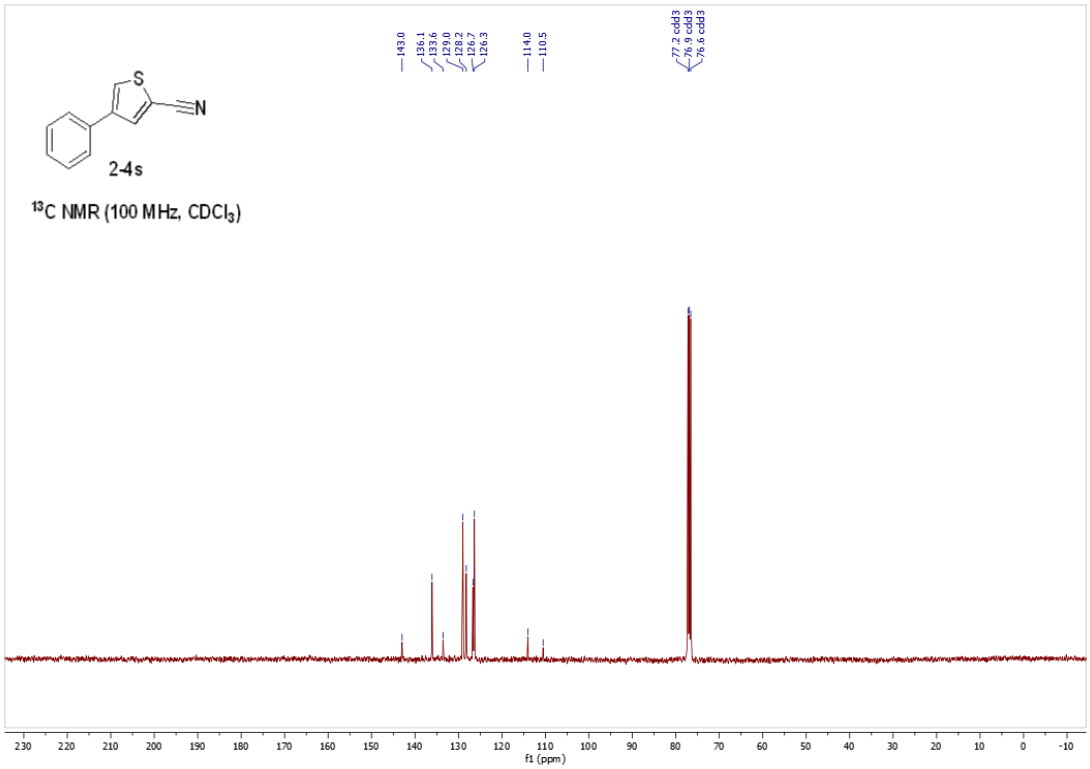
2-4r

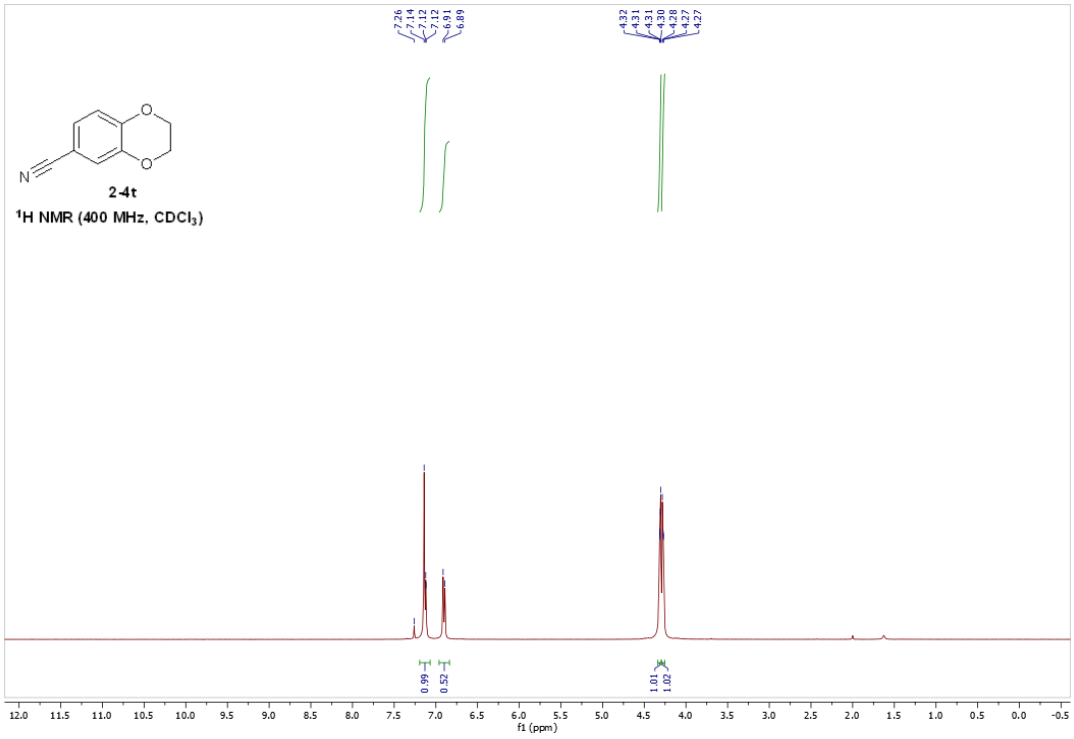
^{13}C NMR (100 MHz, $CDCl_3$)

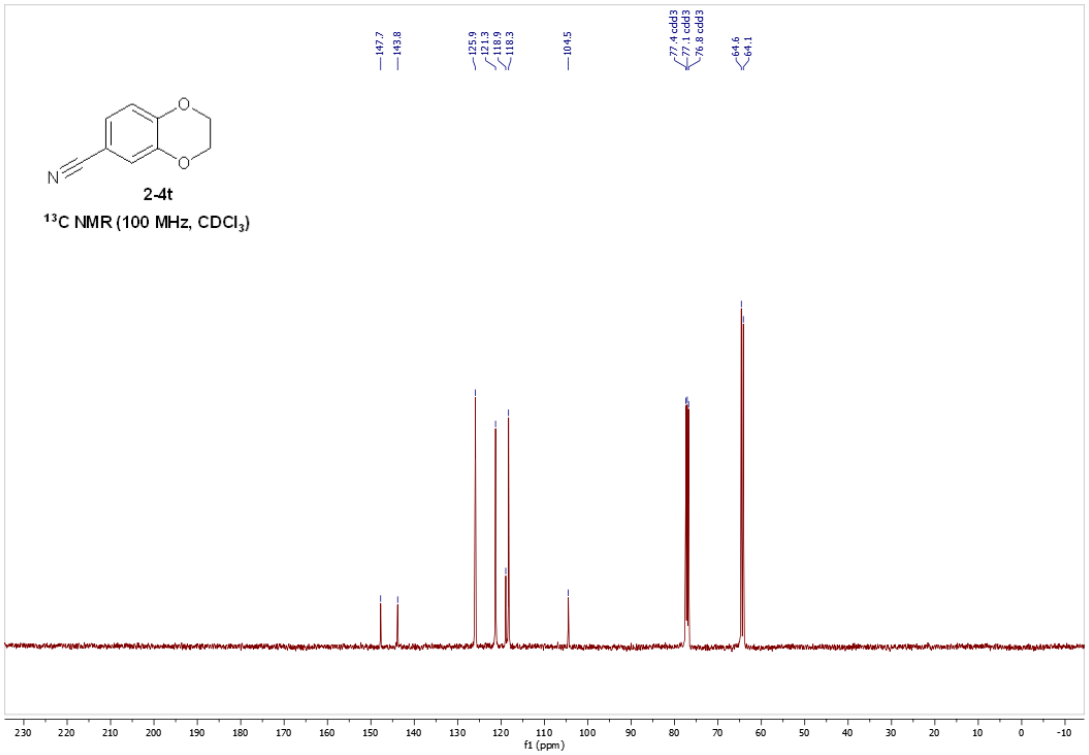


2-4s

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

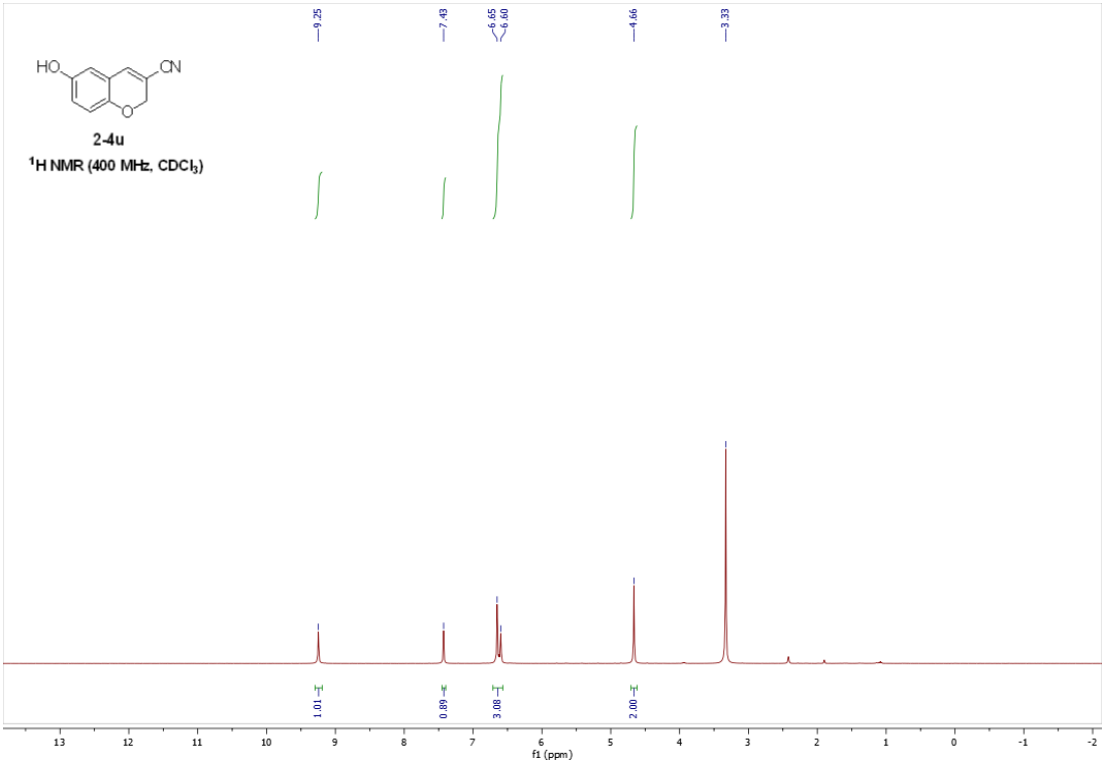

S
N
2-4s
^{13}C NMR (100 MHz, $CDCl_3$)
143.0
136.1
133.6
129.0
128.2
126.7
126.3
114.0
110.5
77.2 cdd3
76.9 cdd3
76.6 cdd3
f1 (ppm)


O
O
N
2-4t
^{1}H NMR (400 MHz, $CDCl_3$)
7.26
7.14
7.12
7.12
6.91
6.89
4.32
4.31
4.31
4.30
4.28
4.27
4.27
0.99
0.52
1.01
1.02
f1 (ppm)



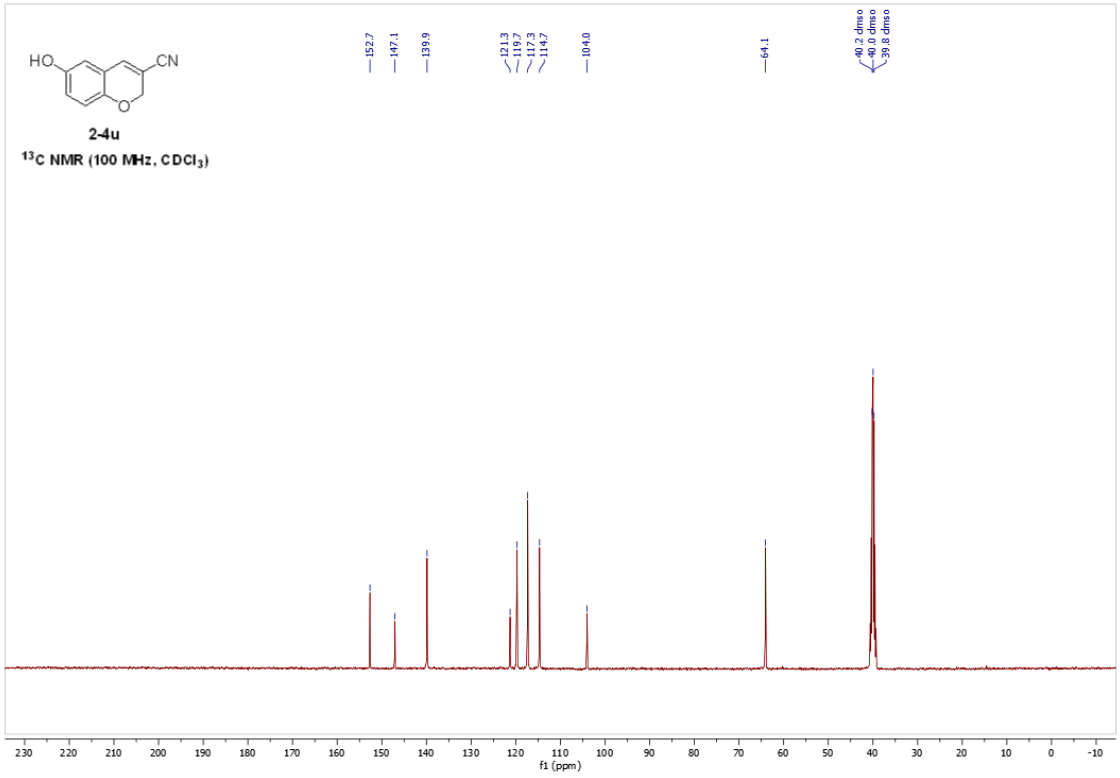
2-4t

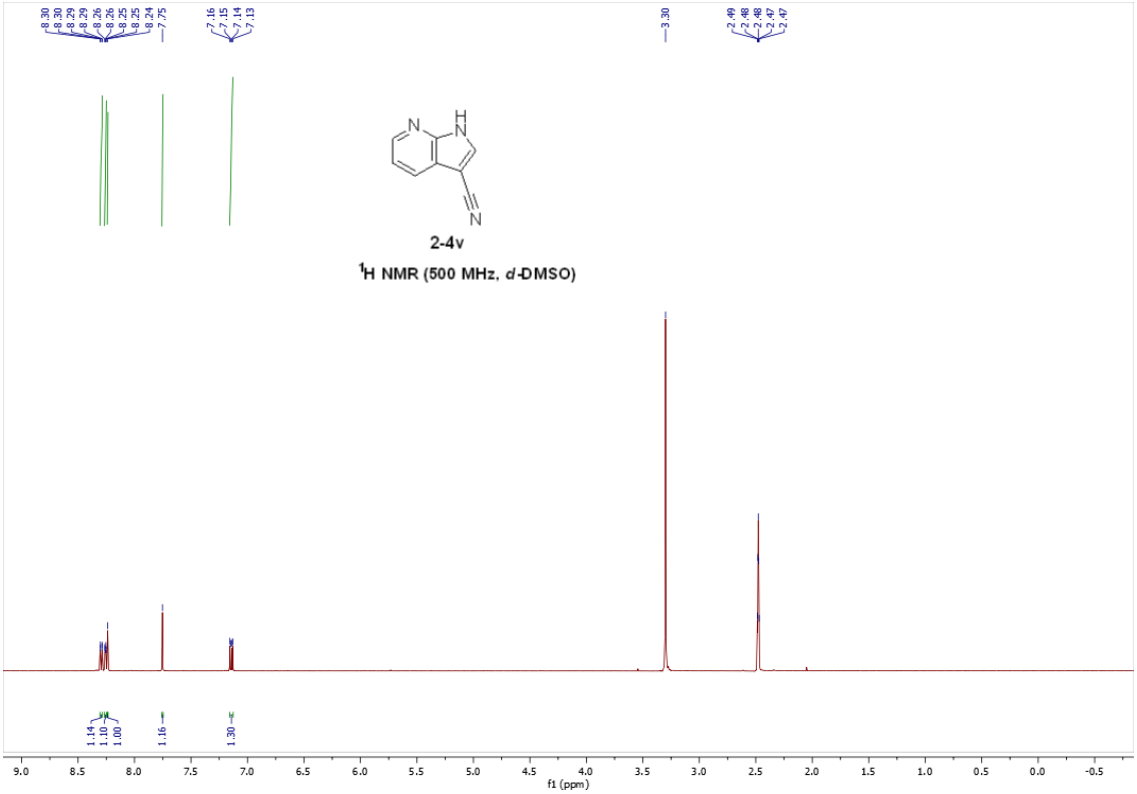
^{13}C NMR (100 MHz, $CDCl_3$)

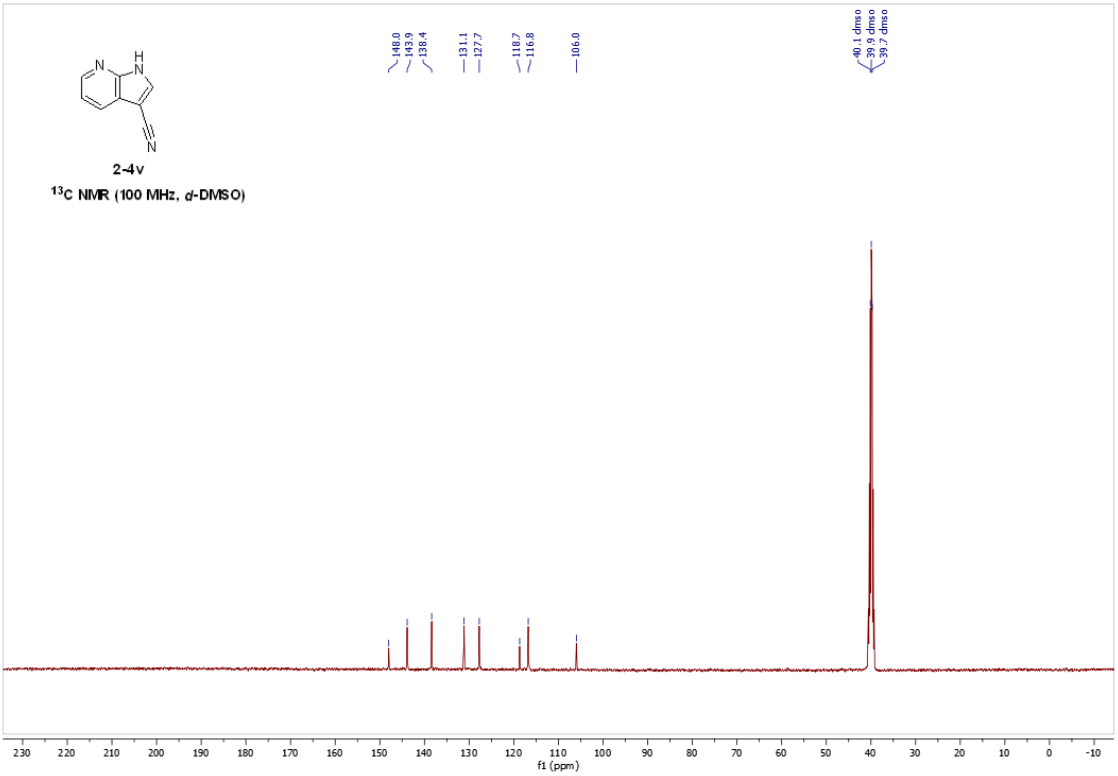


2-4u

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

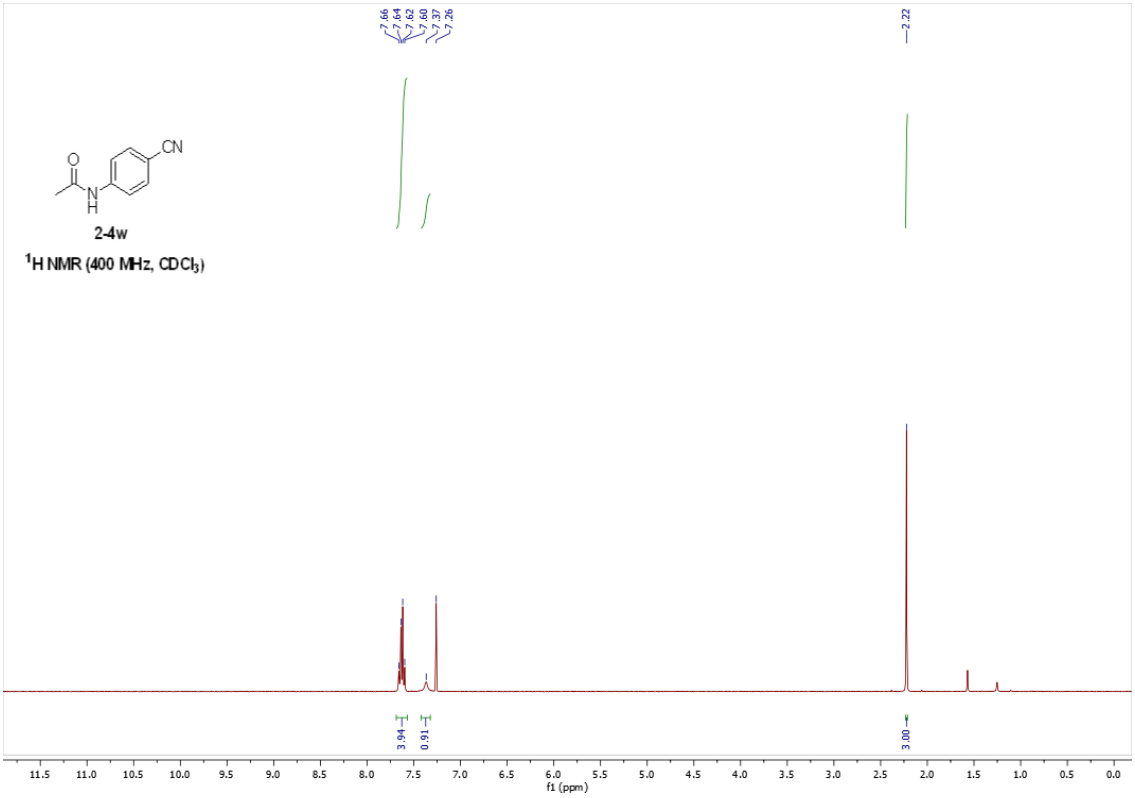

HO
CN
O
2-4u
^{13}C NMR (100 MHz, $CDCl_3$)
152.7
147.1
139.9
121.3
119.7
117.3
114.7
104.0
64.1
40.2 dmso
40.0 dmso
39.8 dmso
f1 (ppm)


8.30
8.30
8.29
8.29
8.26
8.26
8.25
8.25
8.24
7.75
7.16
7.15
7.14
7.13
3.30
2.49
2.48
2.48
2.47
2.47
N
H
N
N
2-4v
^{1}H NMR (500 MHz, *d*-DMSO)
1.14
1.10
1.00
1.16
1.30
f1 (ppm)



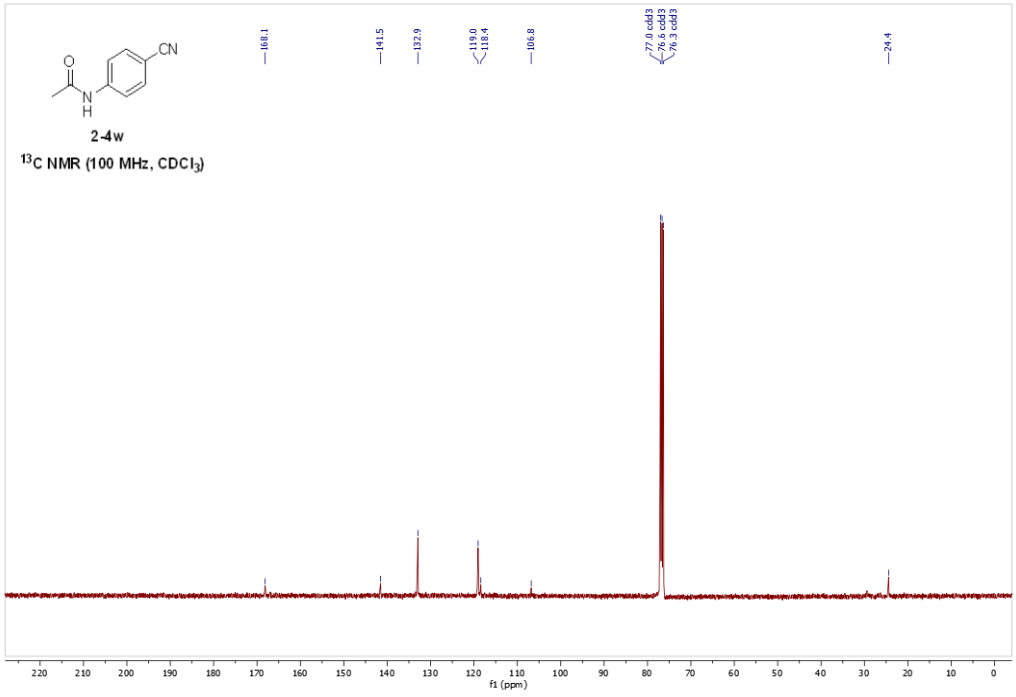
2-4v

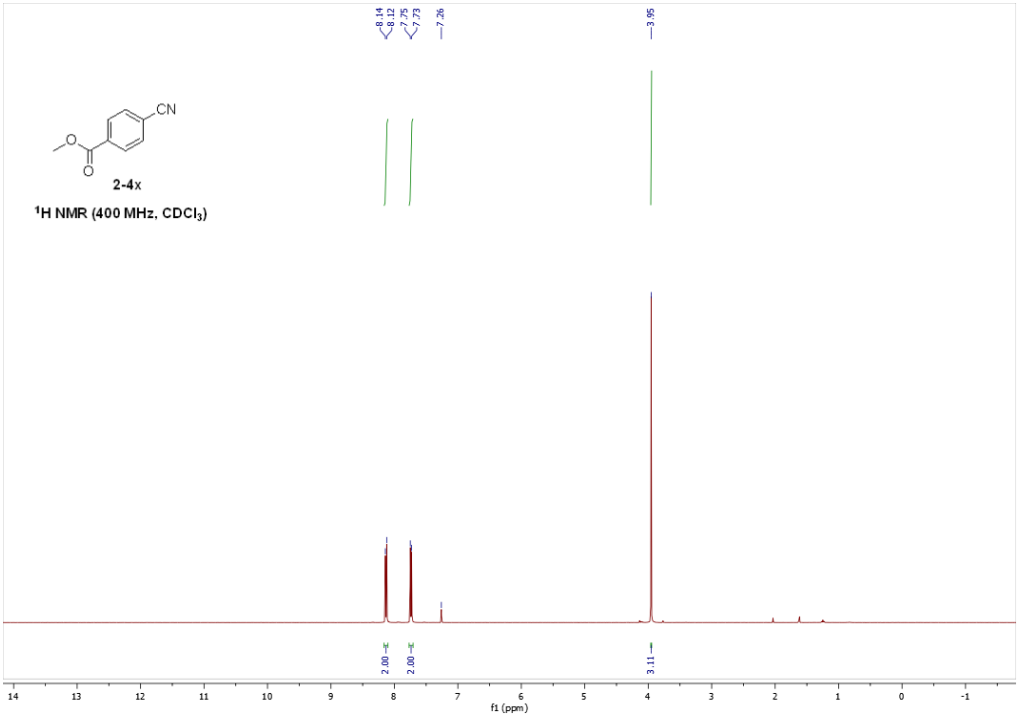
^{13}C NMR (100 MHz, *d*-DMSO)

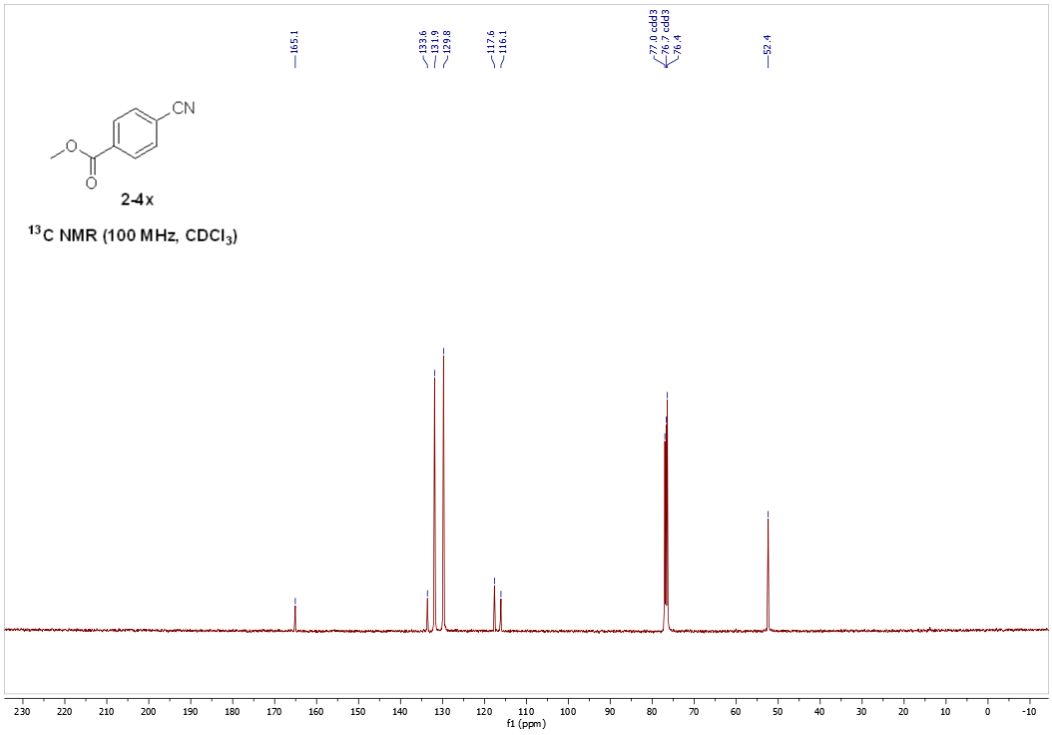


2-4w

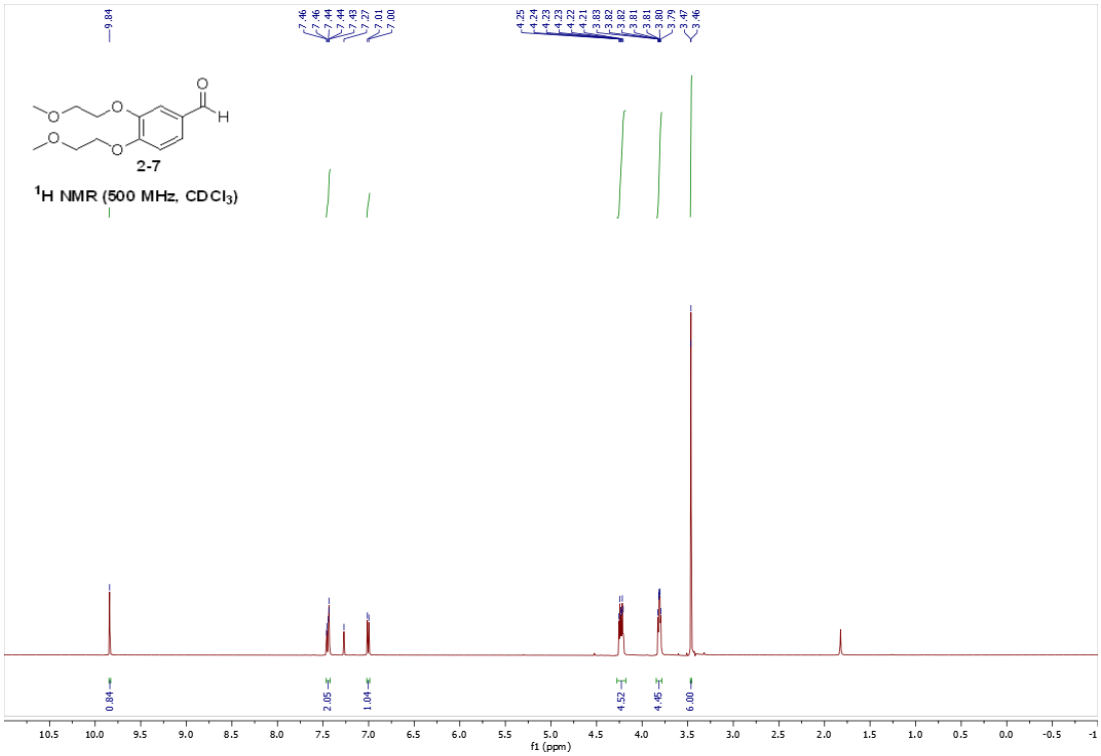
^{1}H NMR (400 MHz, $CDCl_3$)

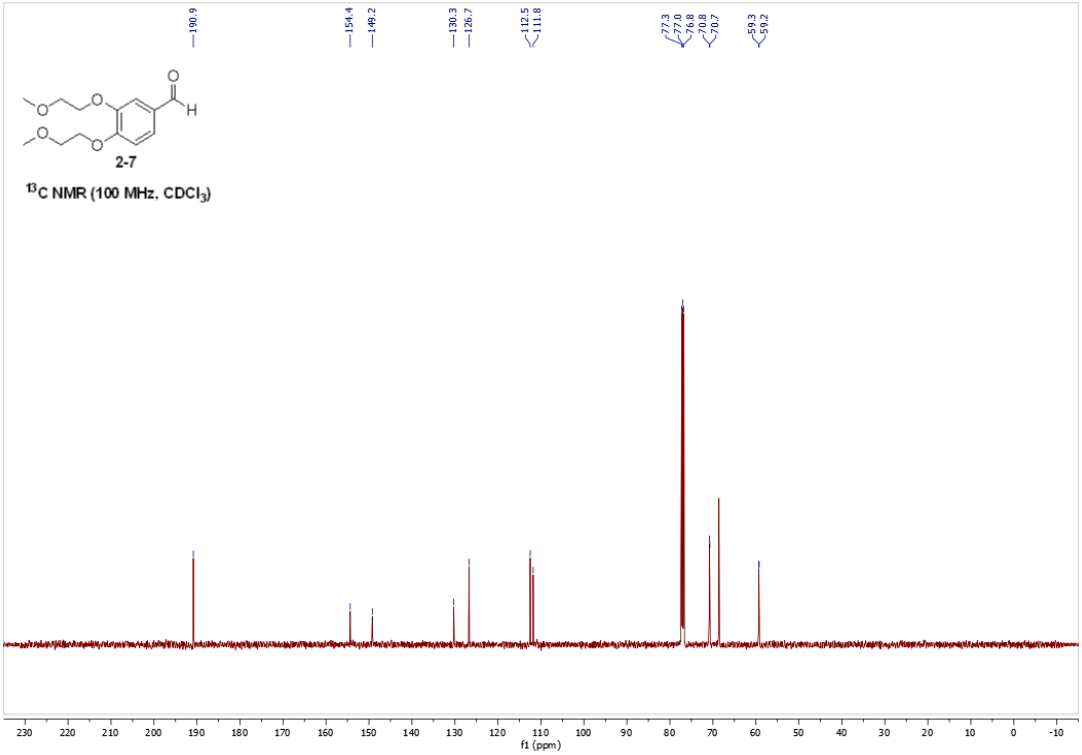

2-4w
^{13}C NMR (100 MHz, CDCl$_3$)
168.1
141.5
132.9
119.0
118.4
106.8
77.0 cdd3
76.6 cdd3
76.3 cdd3
24.4
f1 (ppm)

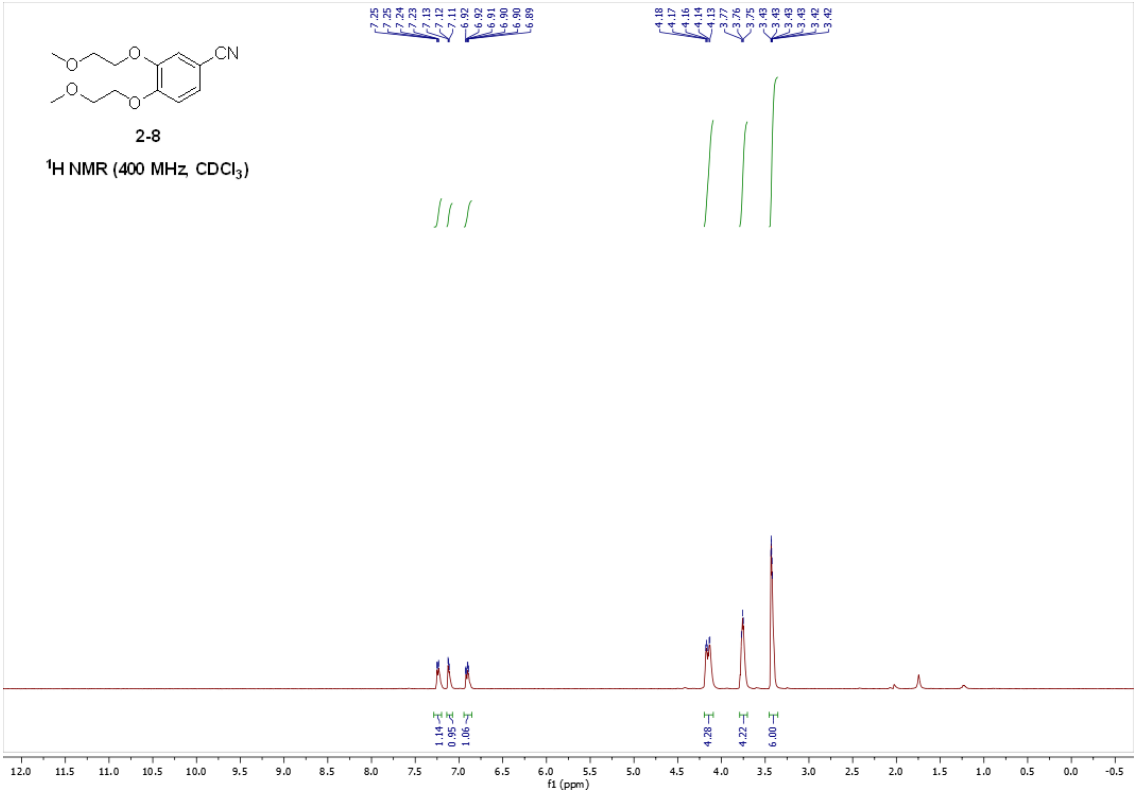

2-4x
^{1}H NMR (400 MHz, CDCl$_3$)
8.14
8.12
7.75
7.73
7.26
3.95
2.00
2.00
3.11
f1 (ppm)

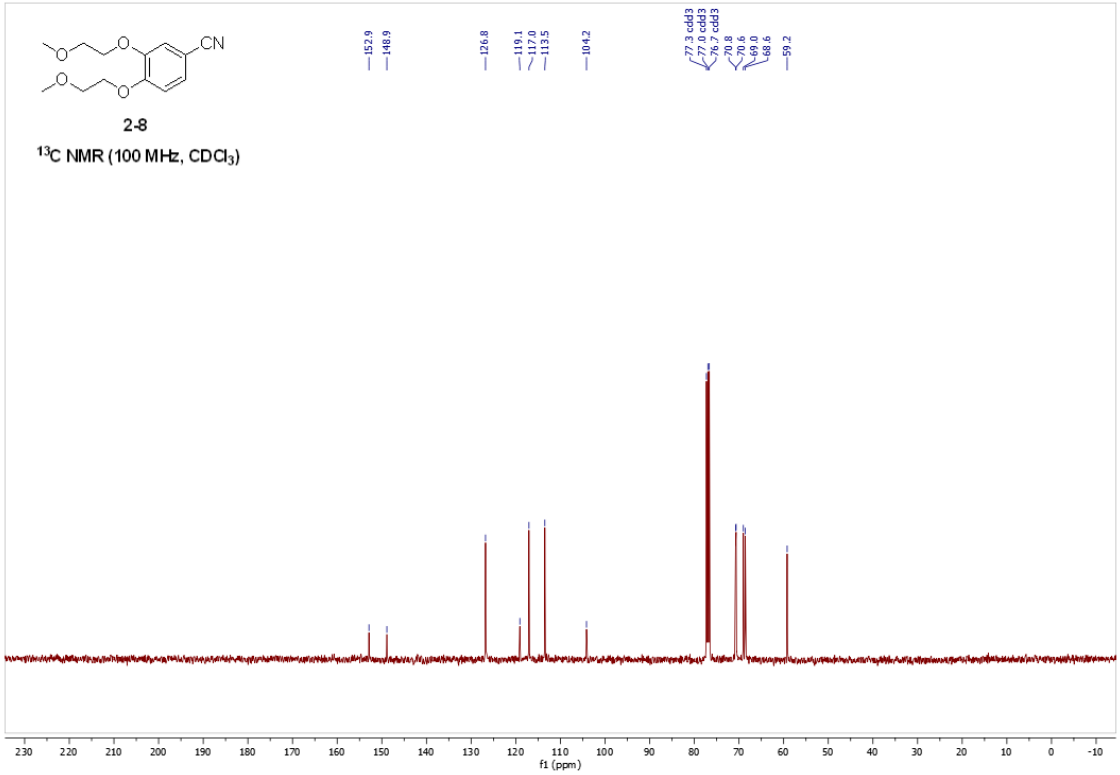

165.1
133.6
131.9
129.8
117.6
116.1
77.0 cdd3
76.7 cdd3
76.4
52.4
CN
O
O
2-4x
^{13}C NMR (100 MHz, CDCl$_3$)
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

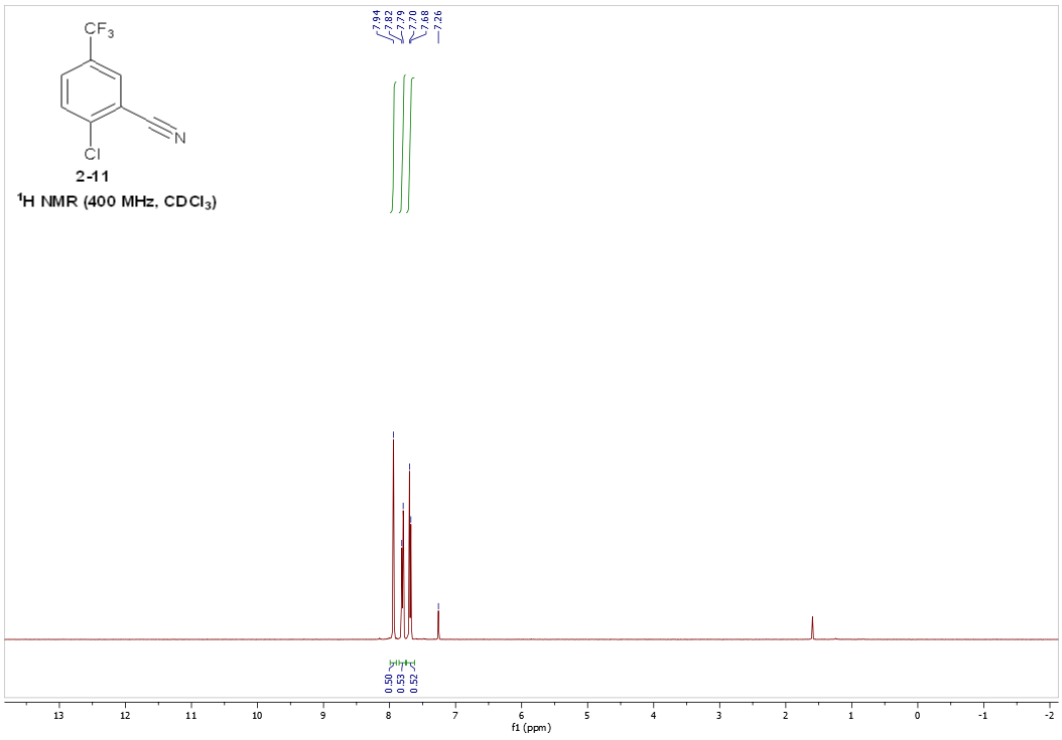
2.4.11.3. NMR spectral data for **2-7**, **2-8**, **2-11**, **2-14**, **2-15**, **2-18**, and **2-19**

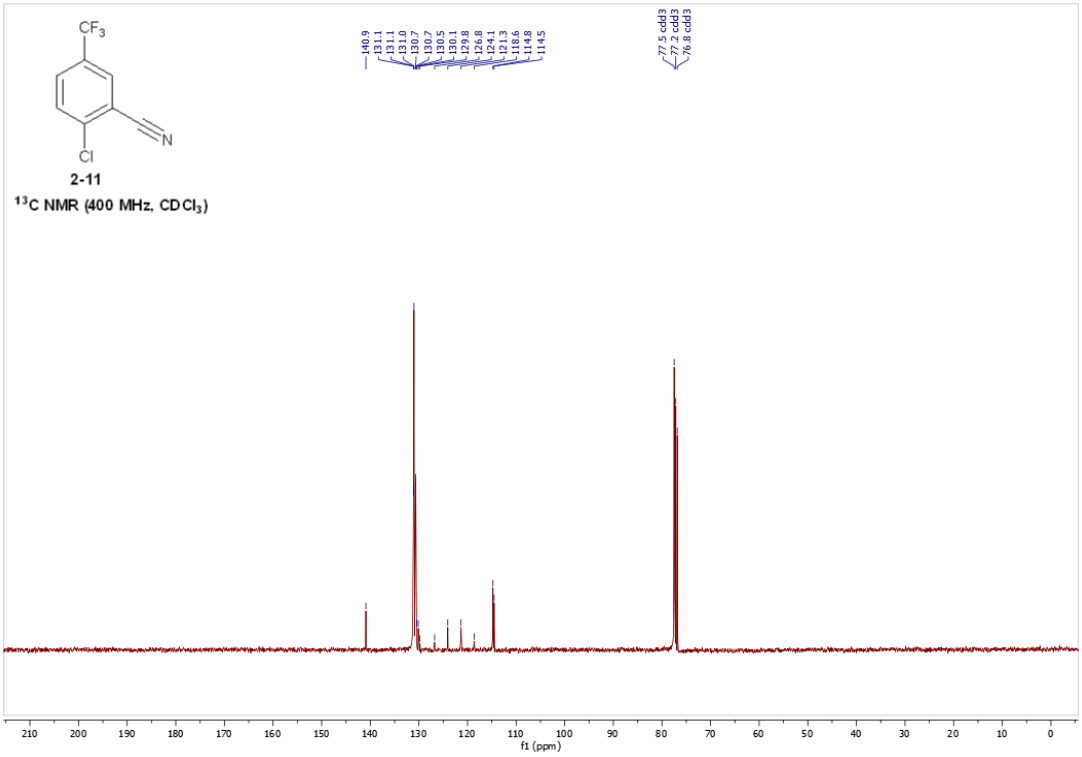


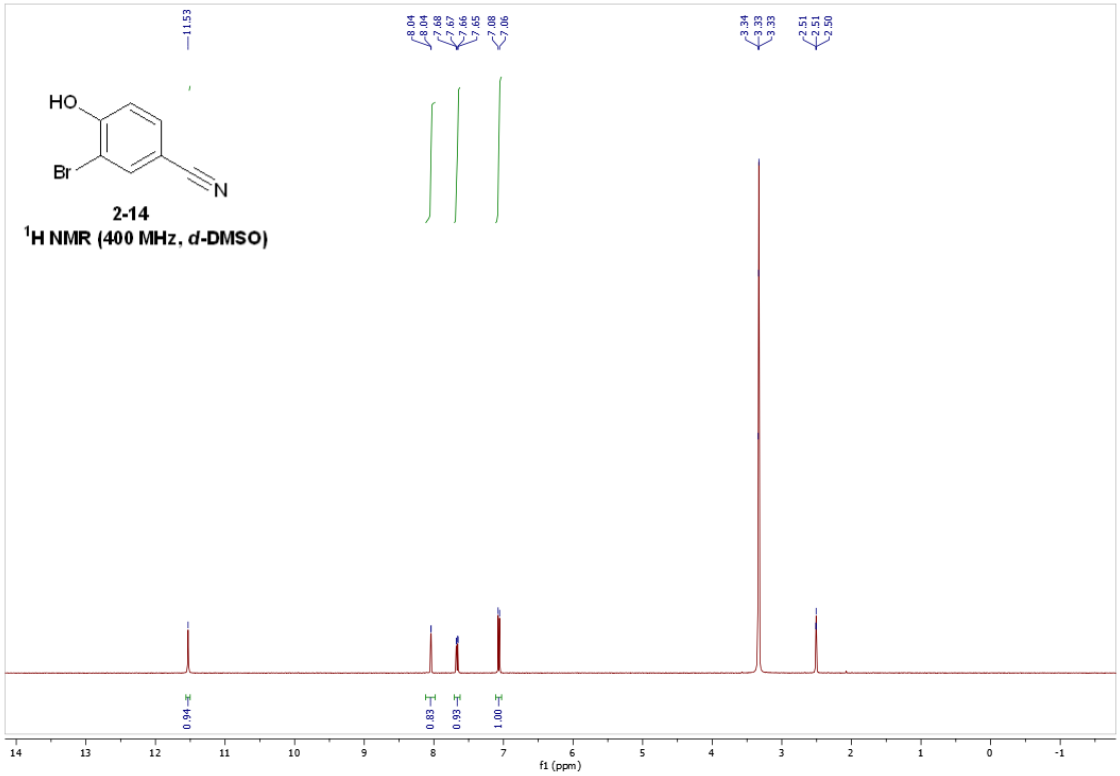


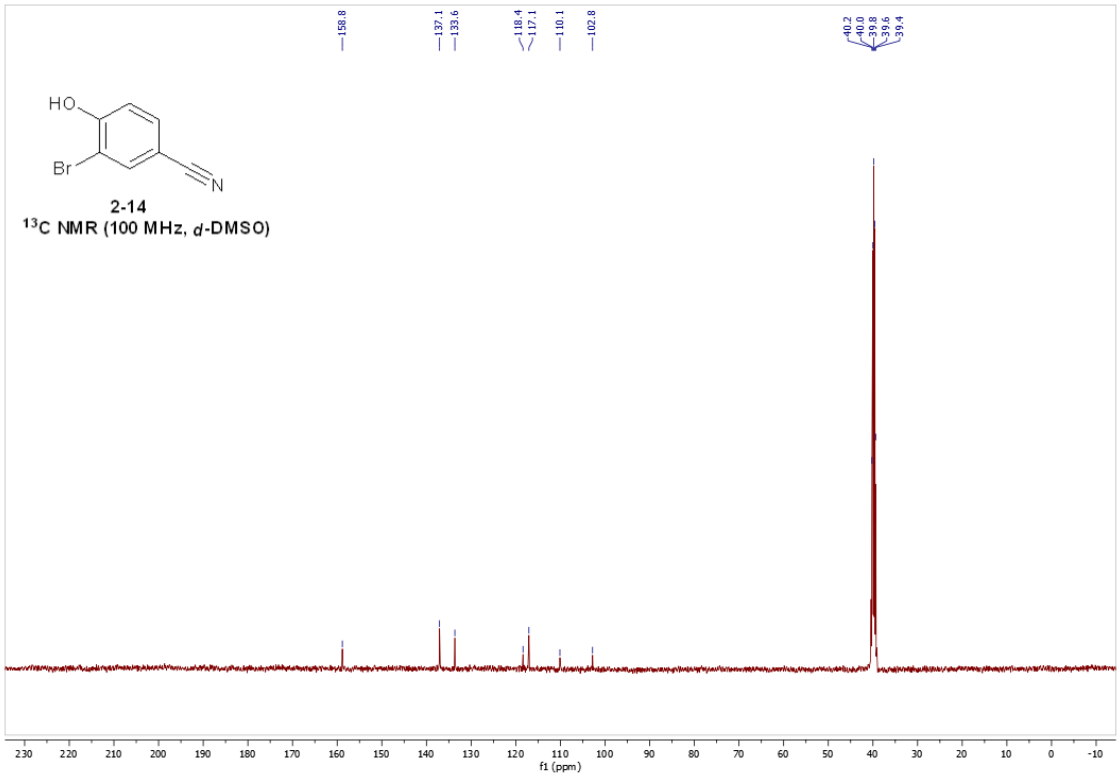

2-8
^{1}H NMR (400 MHz, $CDCl_3$)
f1 (ppm)


2-8
^{13}C NMR (100 MHz, $CDCl_3$)
f1 (ppm)

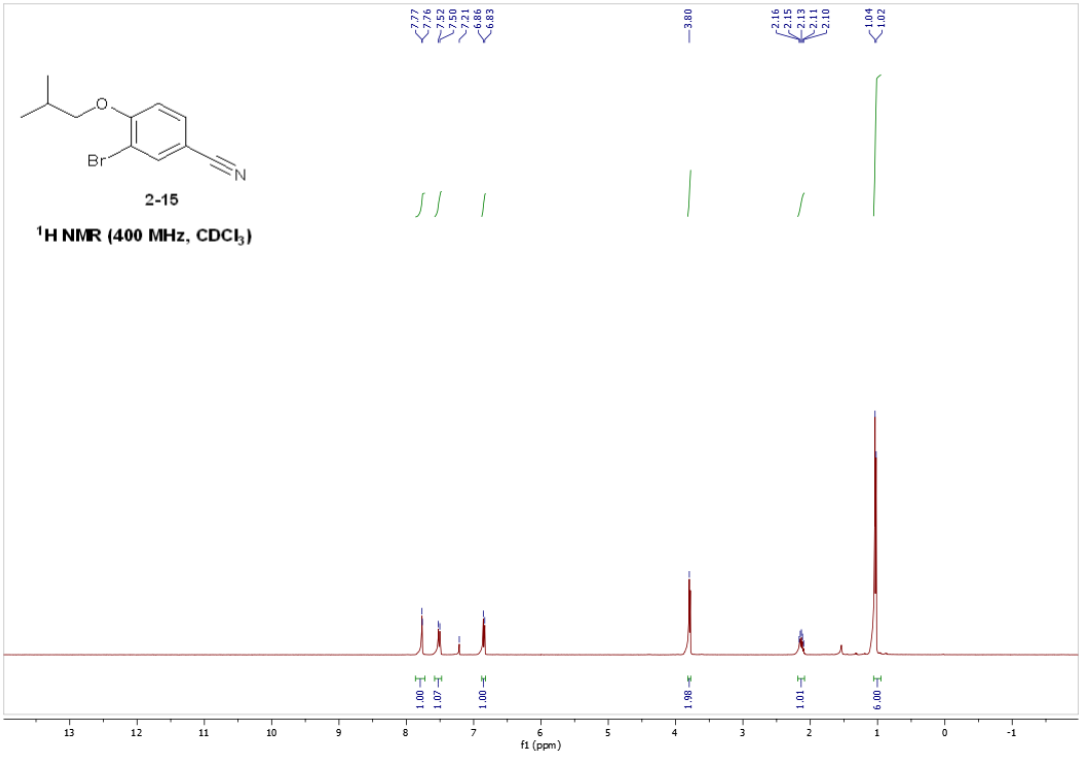

CF3
N
Cl
2-11
1H NMR (400 MHz, CDCl3)
7.94
7.82
7.79
7.70
7.68
7.26
0.50
0.53
0.52
f1 (ppm)


CF3
N
Cl
2-11
13C NMR (400 MHz, CDCl3)
140.9
131.1
131.1
131.0
130.7
130.7
130.5
130.1
129.8
126.8
124.1
117.3
116.6
114.8
114.5
77.5 cdd3
77.2 cdd3
76.8 cdd3
f1 (ppm)


11.53
8.04
8.04
7.68
7.67
7.66
7.65
7.08
7.06
3.34
3.33
3.33
2.51
2.51
2.50
HO
Br
N
2-14
1H NMR (400 MHz, d-DMSO)
0.94
0.83
0.93
1.00
f1 (ppm)

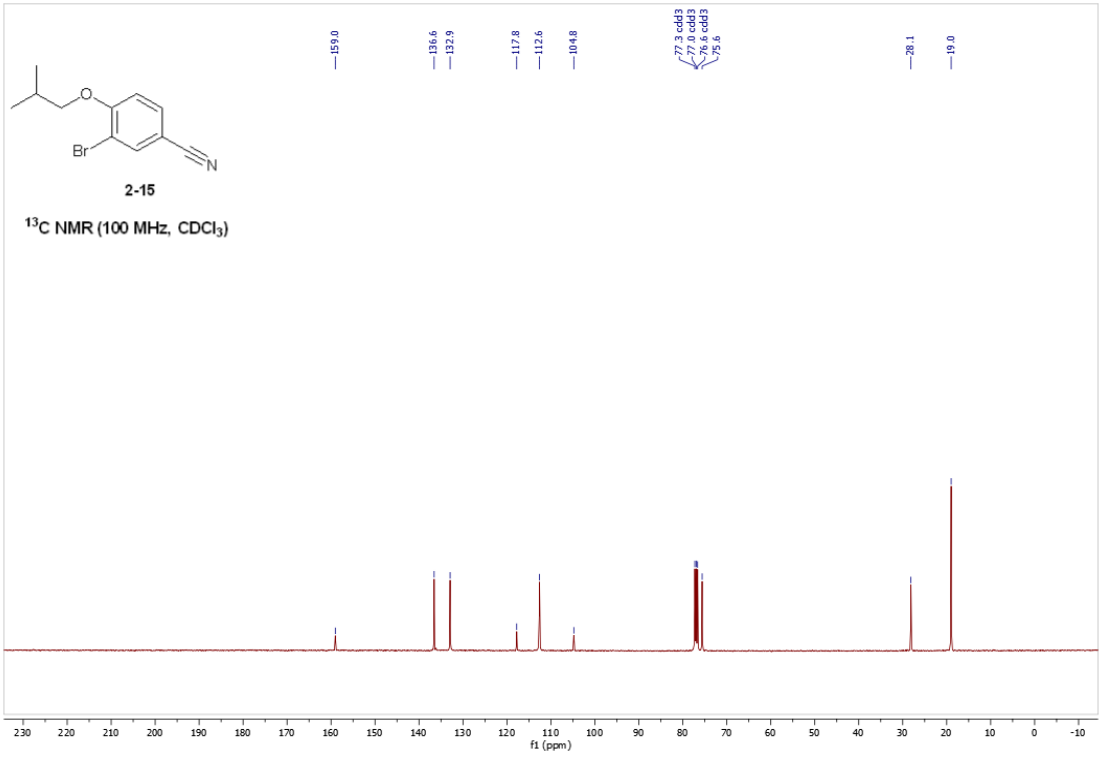

158.8
137.1
133.6
118.4
117.1
110.1
102.8
40.2
40.0
39.8
39.6
39.4
HO
Br
N
2-14
13C NMR (100 MHz, d-DMSO)
f1 (ppm)

16



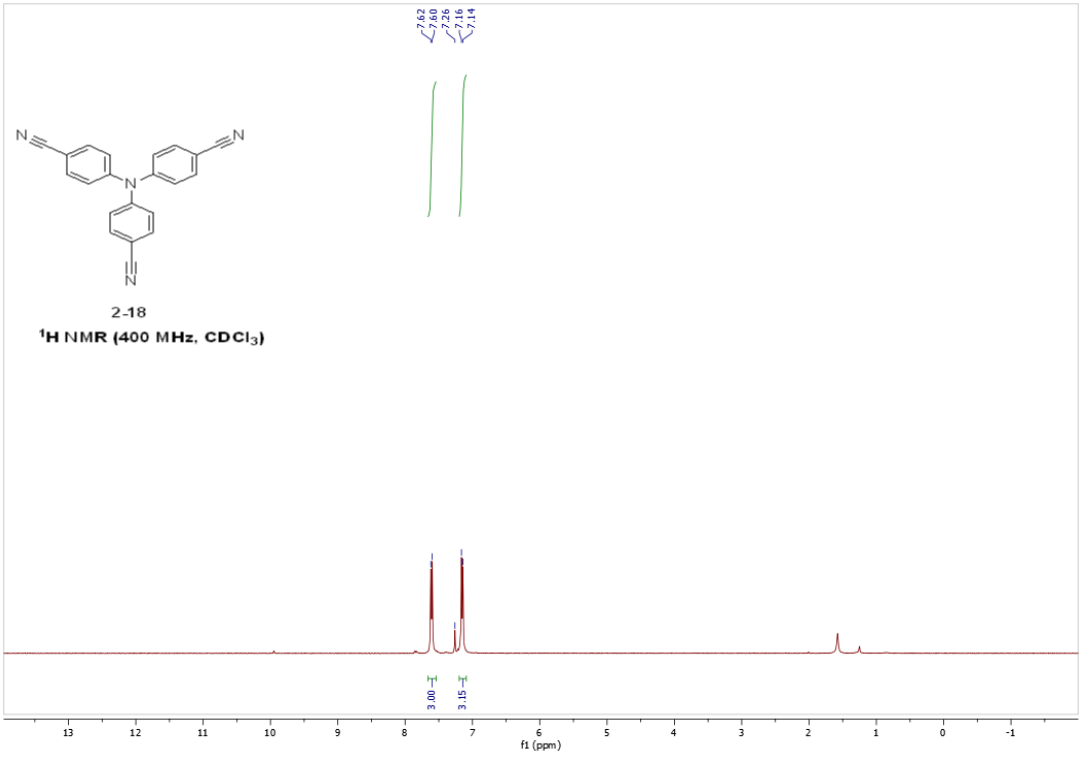
2-15

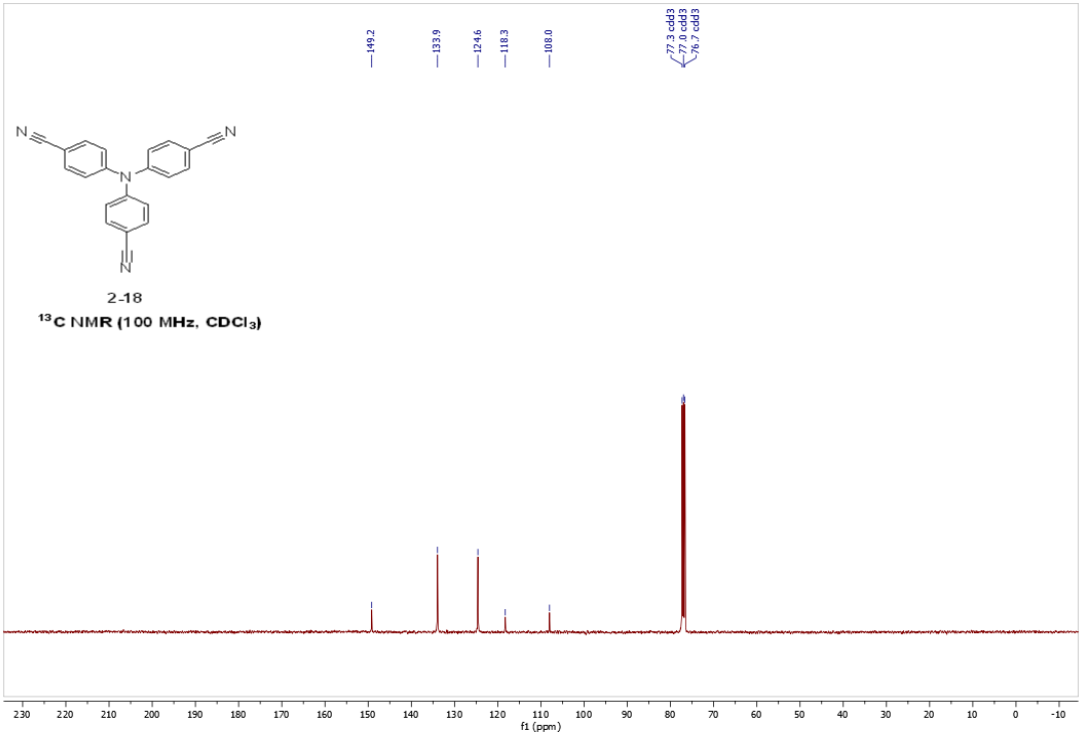
^{1}H NMR (400 MHz, $CDCl_3$)

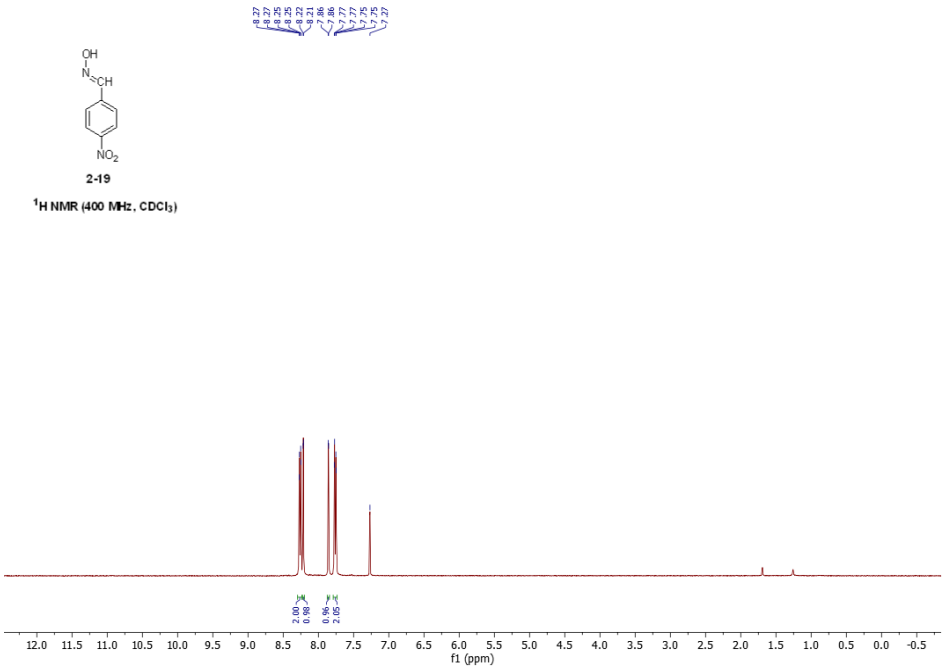


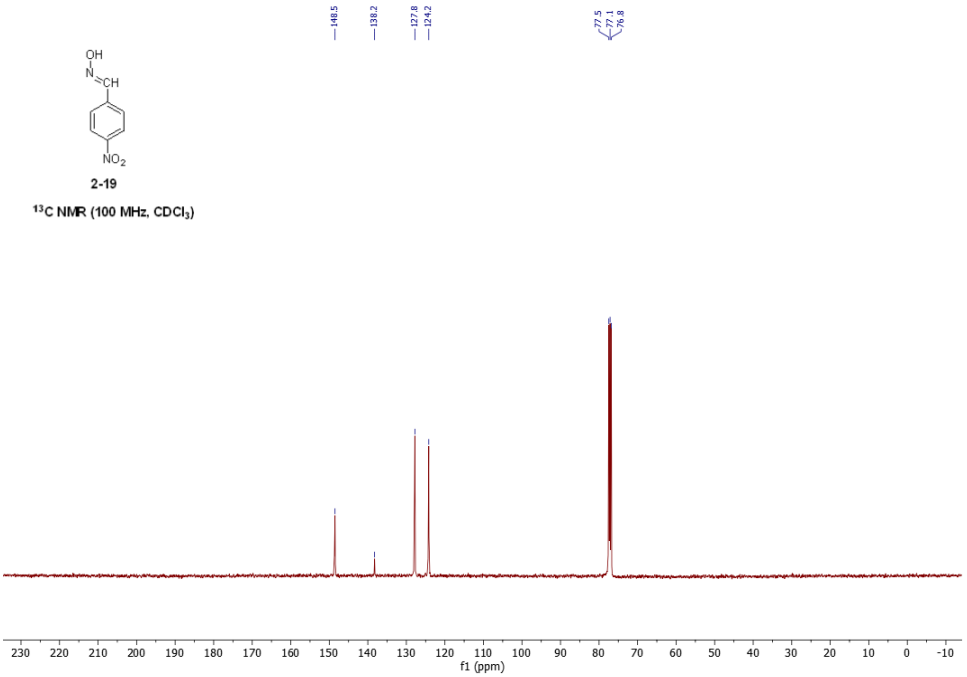
2-15

^{13}C NMR (100 MHz, $CDCl_3$)


7.62
7.60
7.26
7.16
7.14
2-18
^{1}H NMR (400 MHz, CDCl$_3$)
3.00
3.15
f1 (ppm)

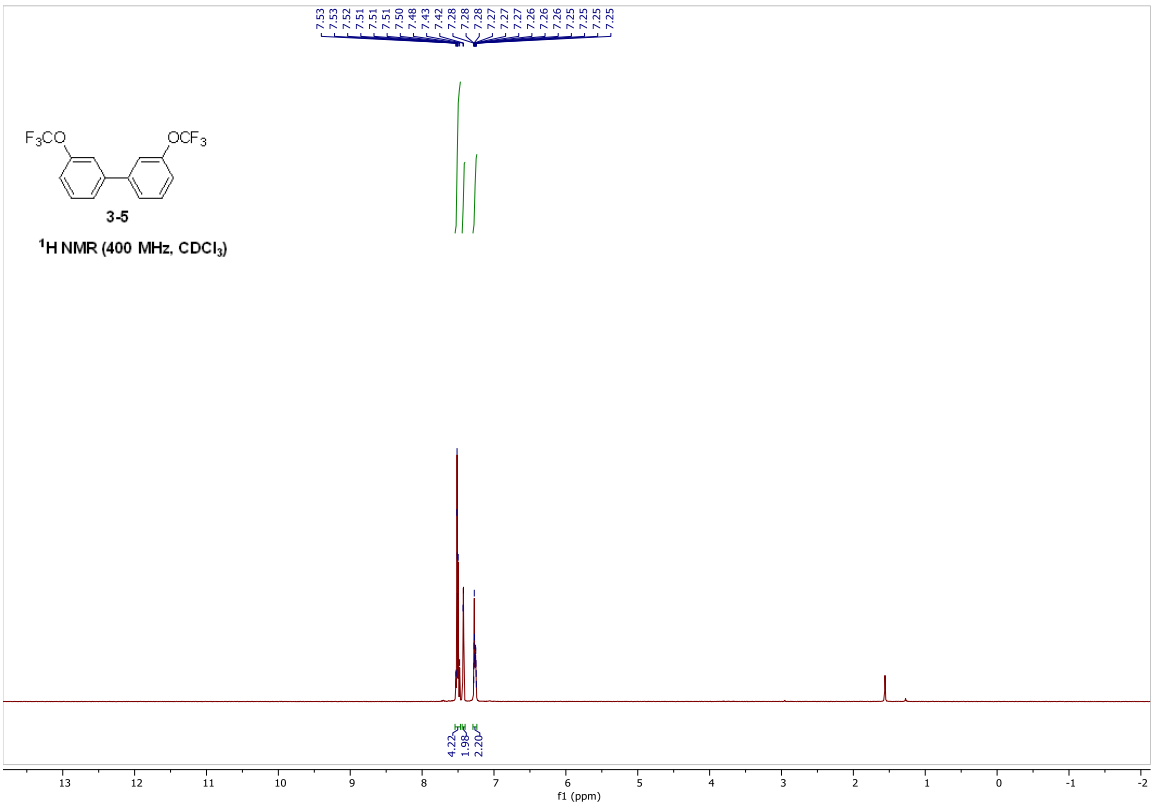

149.2
133.9
124.6
118.3
108.0
77.3 cdd3
77.0 cdd3
76.7 cdd3
2-18
^{13}C NMR (100 MHz, CDCl$_3$)
f1 (ppm)

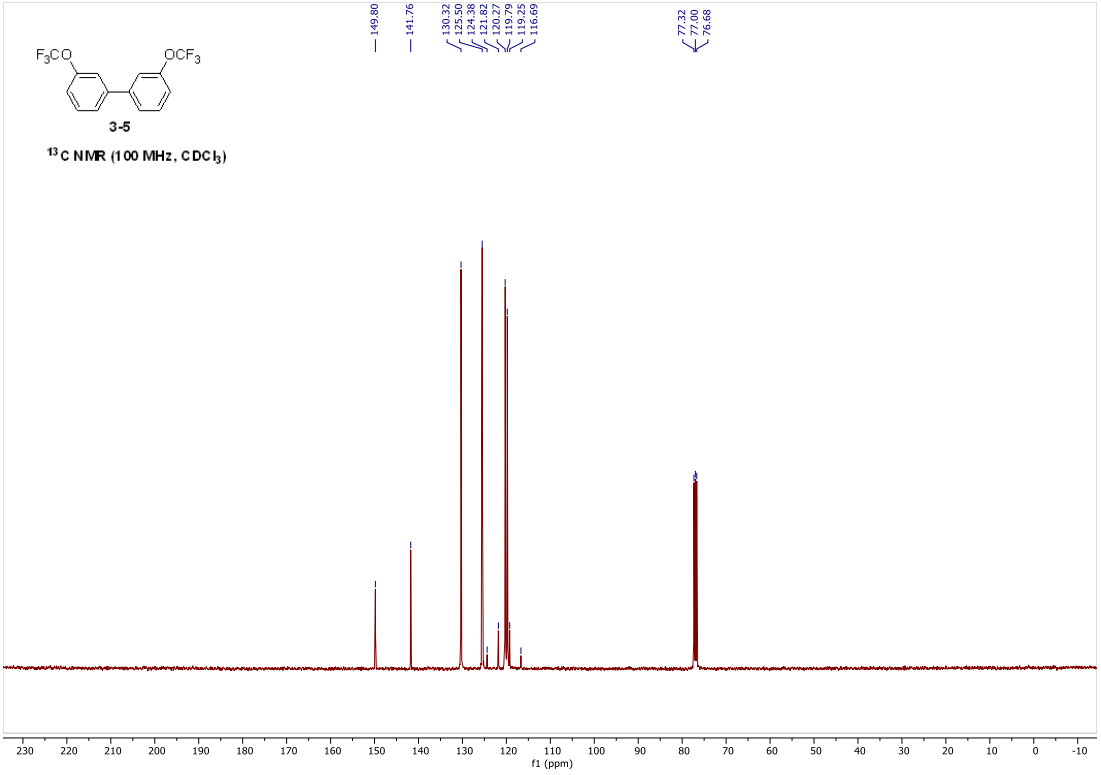

8.27
8.27
8.25
8.25
8.22
7.91
7.86
7.77
7.77
7.75
7.75
7.27
OH
N
CH
NO2
2-19
1H NMR (400 MHz, CDCl3)
3.00
0.98
0.96
2.05
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

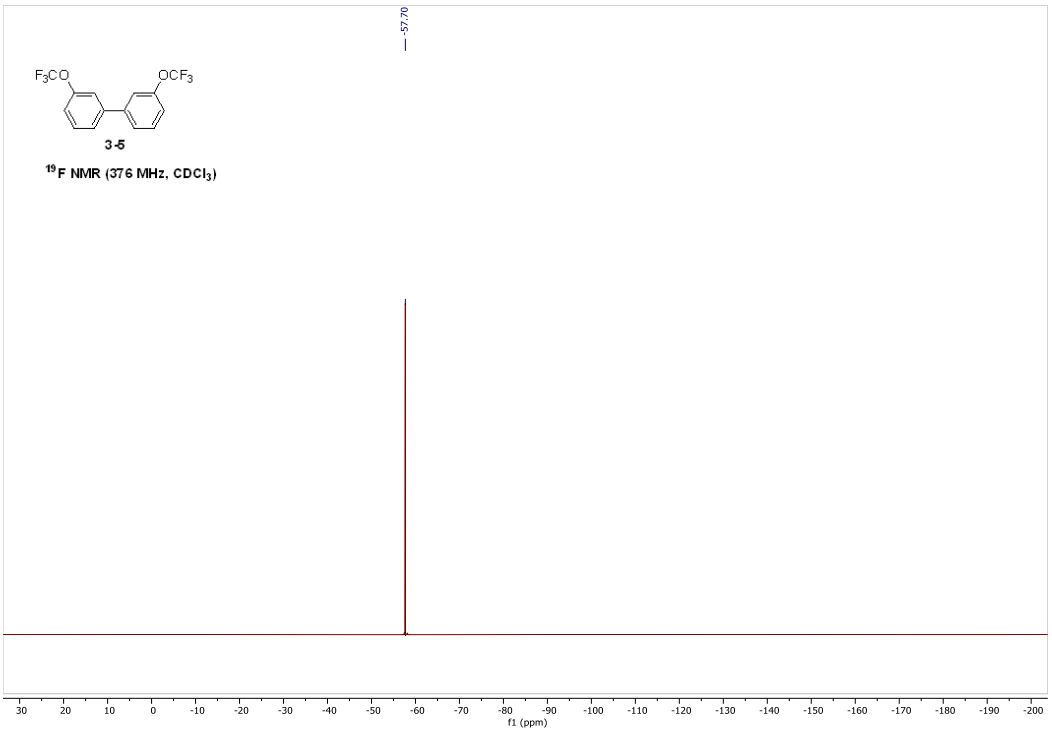

148.5
138.2
127.8
124.2
77.5
77.1
76.8
OH
N
CH
NO2
2-19
13C NMR (100 MHz, CDCl3)
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

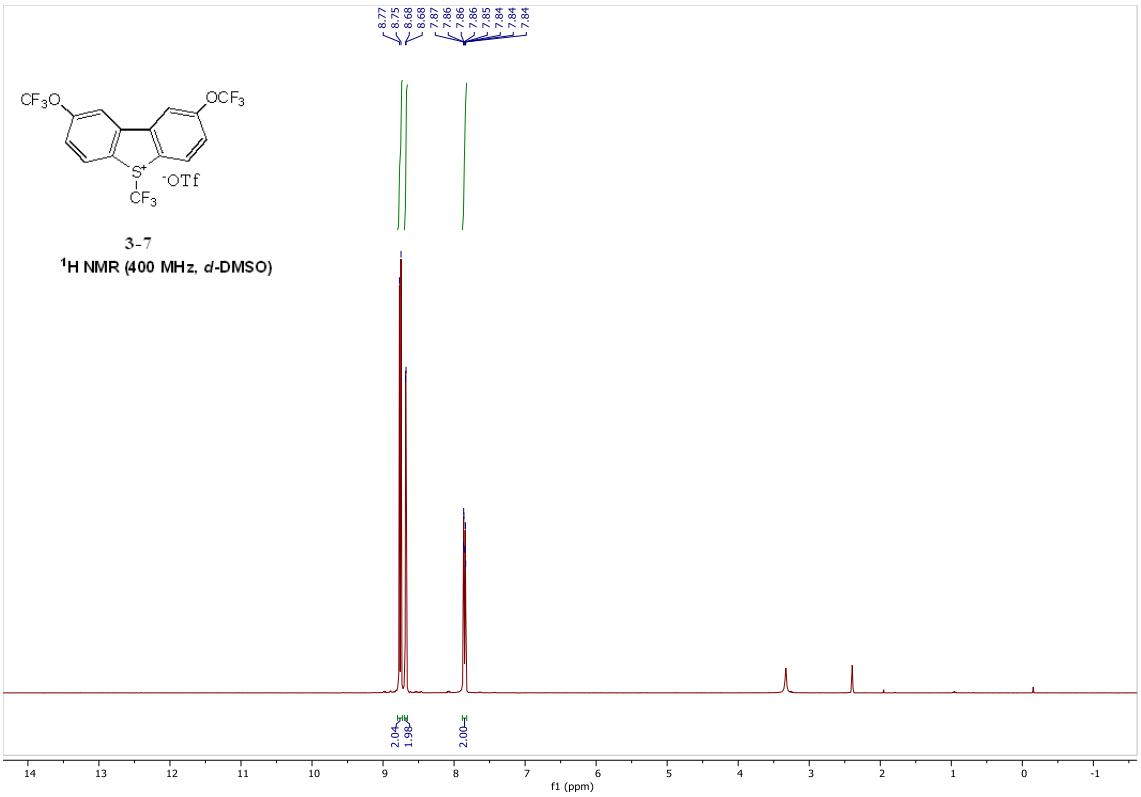
APPENDIX B: SYNTHESIS AND APPLICATIONS OF S(TRIFLUOROMETHYL)-2,8 BIS(TRIFLUOROMETHOXY)DIBENZOTHIOPHENIUM TRIFLATE

3.4.11. NMR spectra of compounds **3-5** to **3-48**



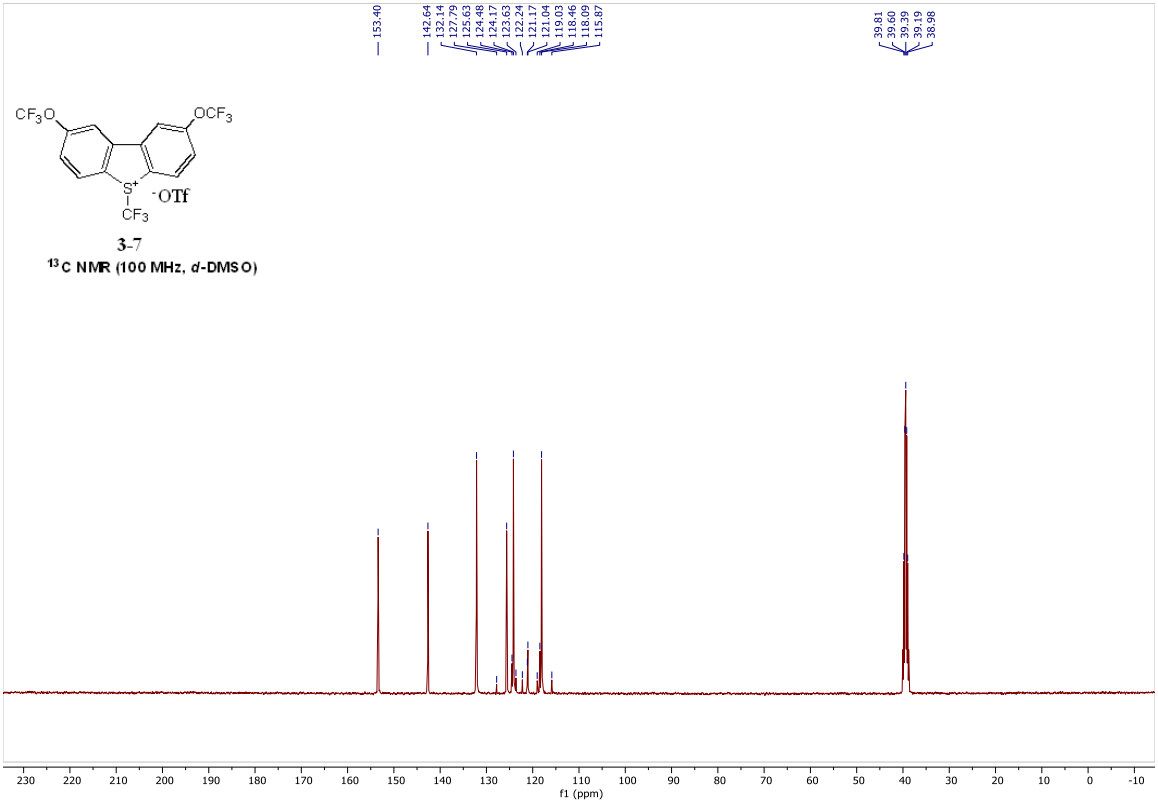

149.80
141.76
130.32
125.50
124.38
121.82
120.27
119.79
119.25
116.69
77.32
77.00
76.68
F3CO
OCF3
3-5
13C NMR (100 MHz, CDCl3)
f1 (ppm)


-57.70
F3CO
OCF3
3-5
19F NMR (376 MHz, CDCl3)
f1 (ppm)



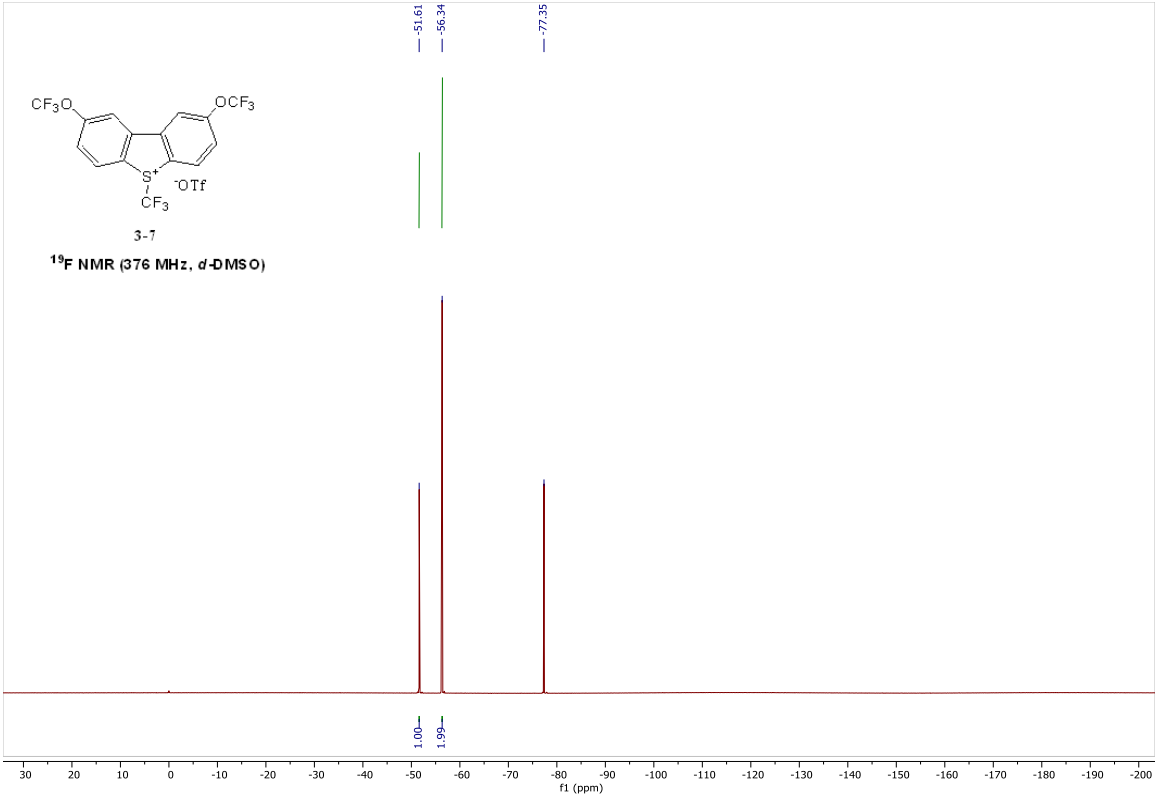
3-7

^{1}H NMR (400 MHz, *d*-DMSO)



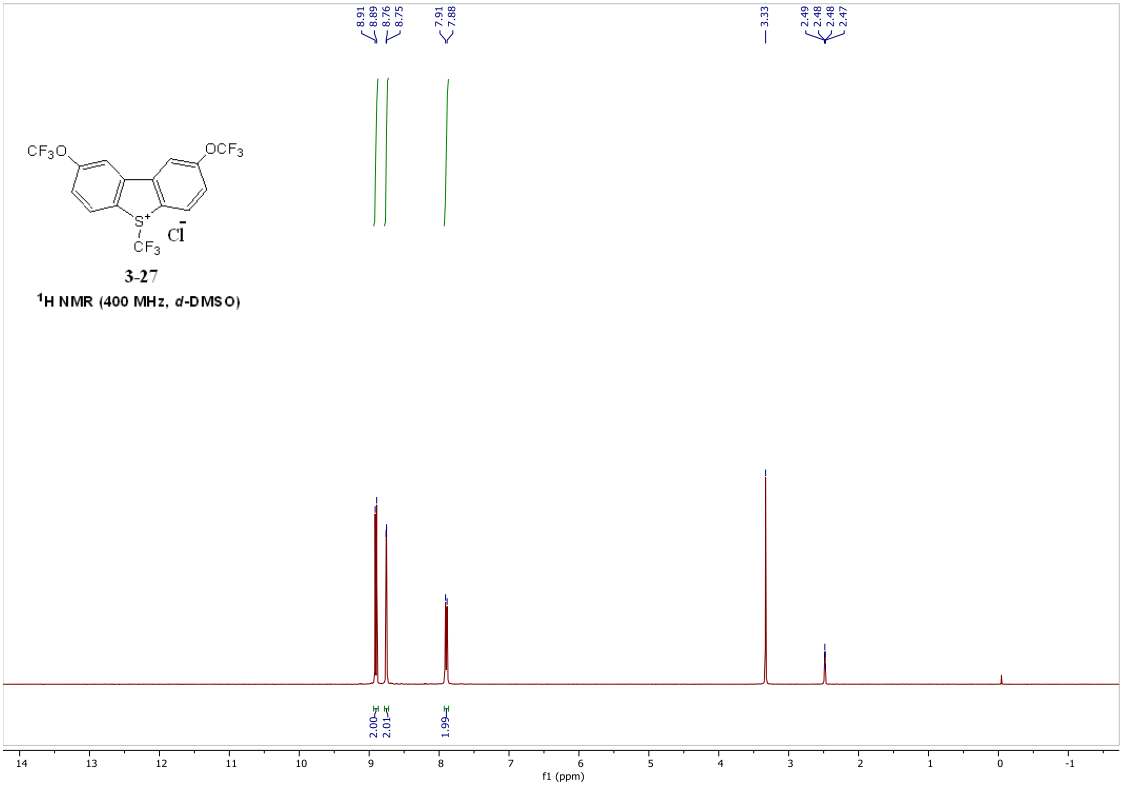
3-7

^{13}C NMR (100 MHz, *d*-DMSO)



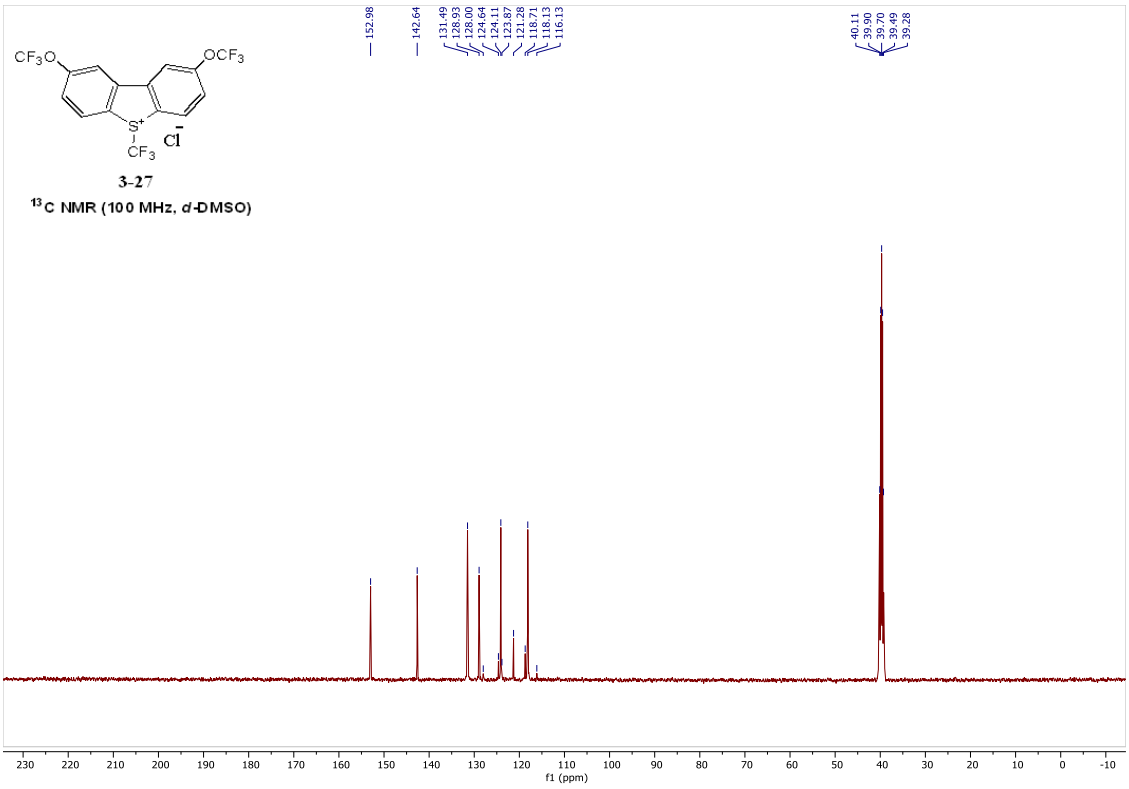
3-7

^{19}F NMR (376 MHz, *d*-DMSO)



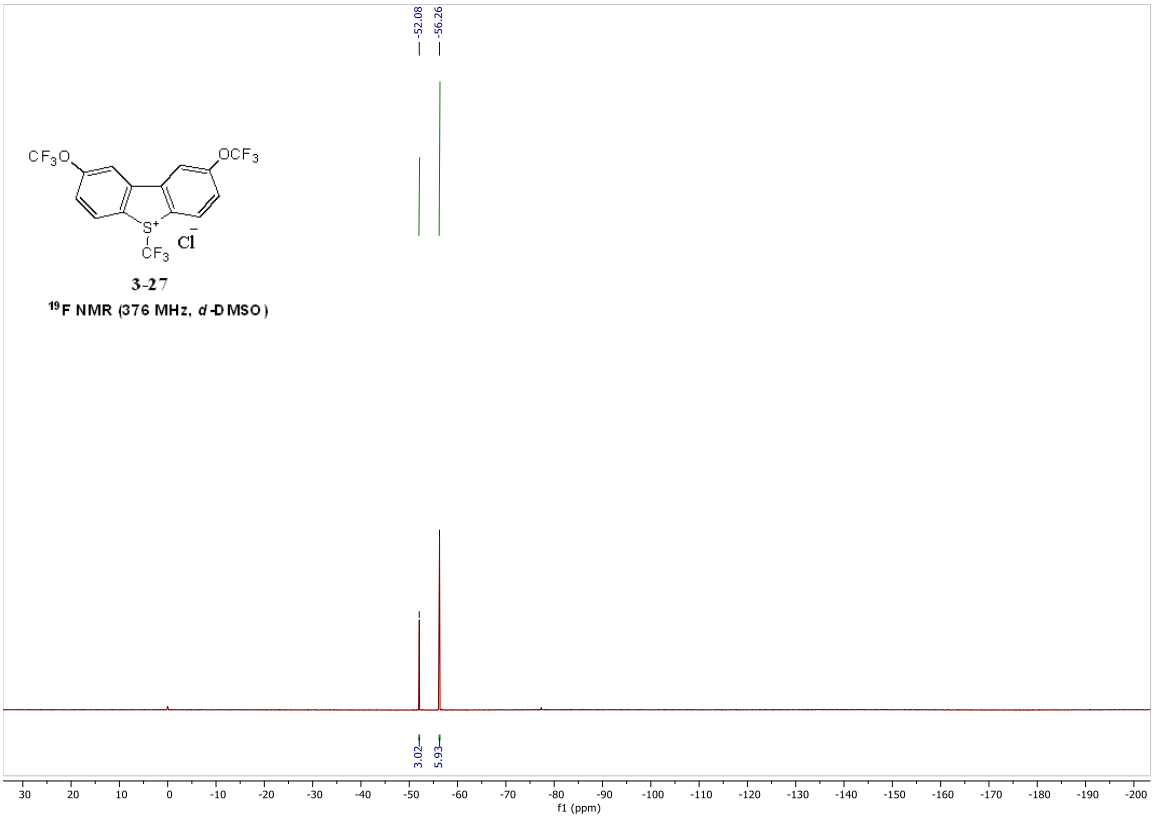
3-27

^{1}H NMR (400 MHz, *d*-DMSO)



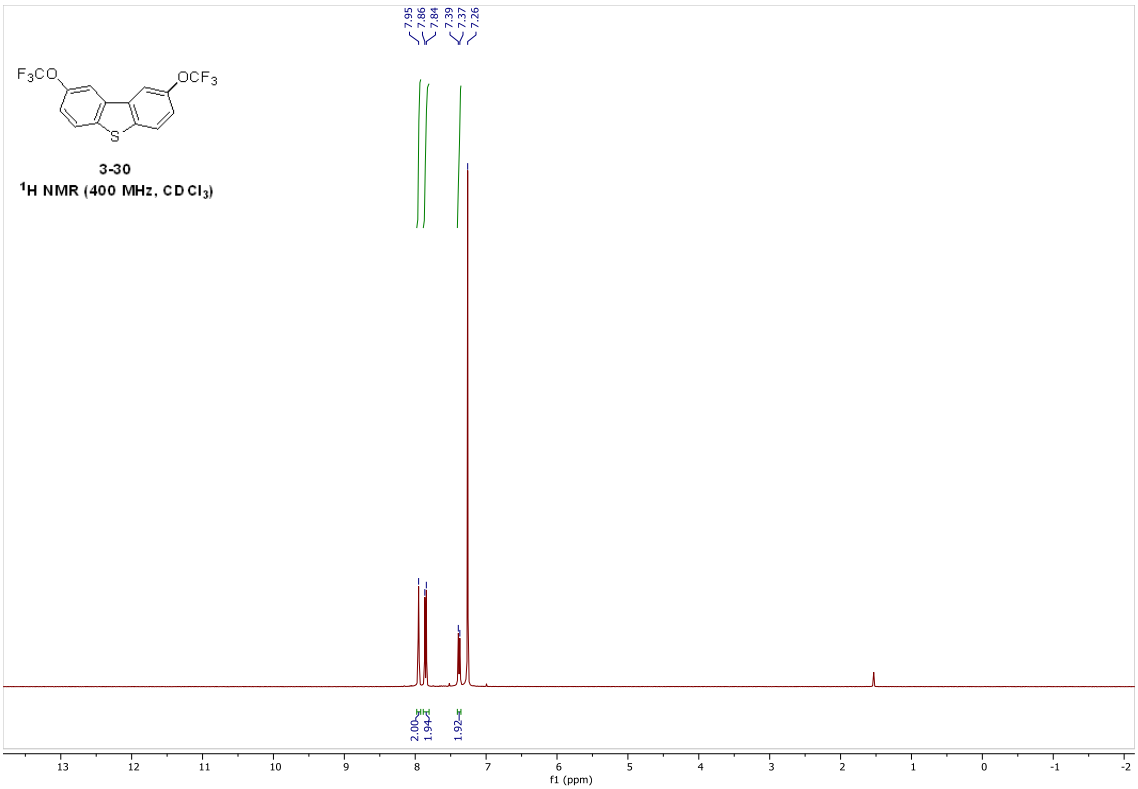
3-27

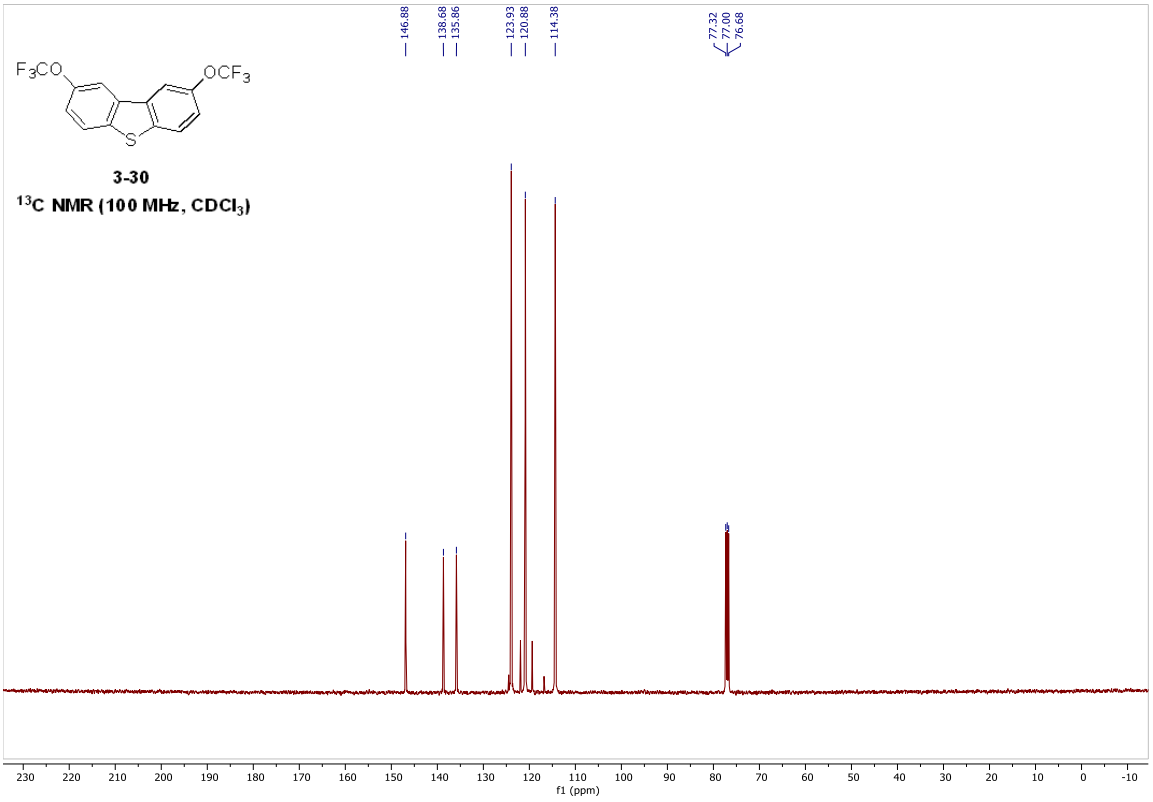
^{13}C NMR (100 MHz, *d*-DMSO)

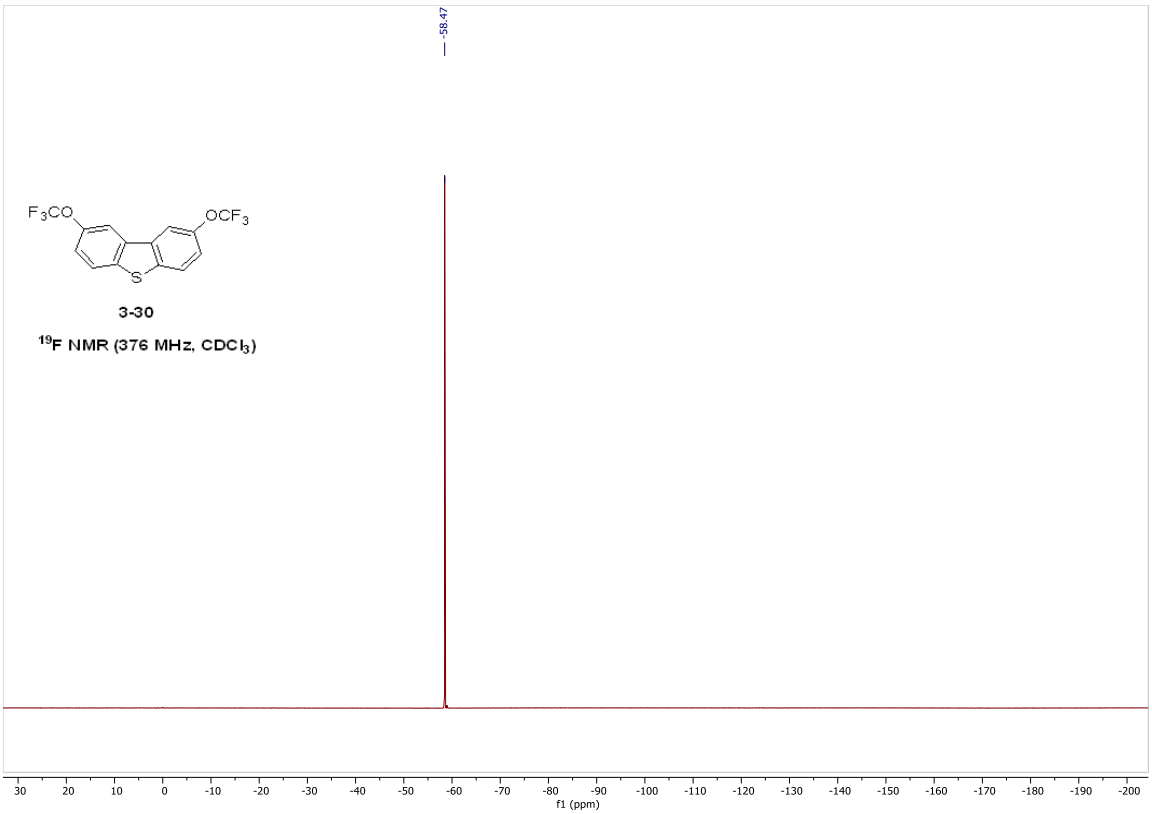


3-27

^{19}F NMR (376 MHz, *d*-DMSO)

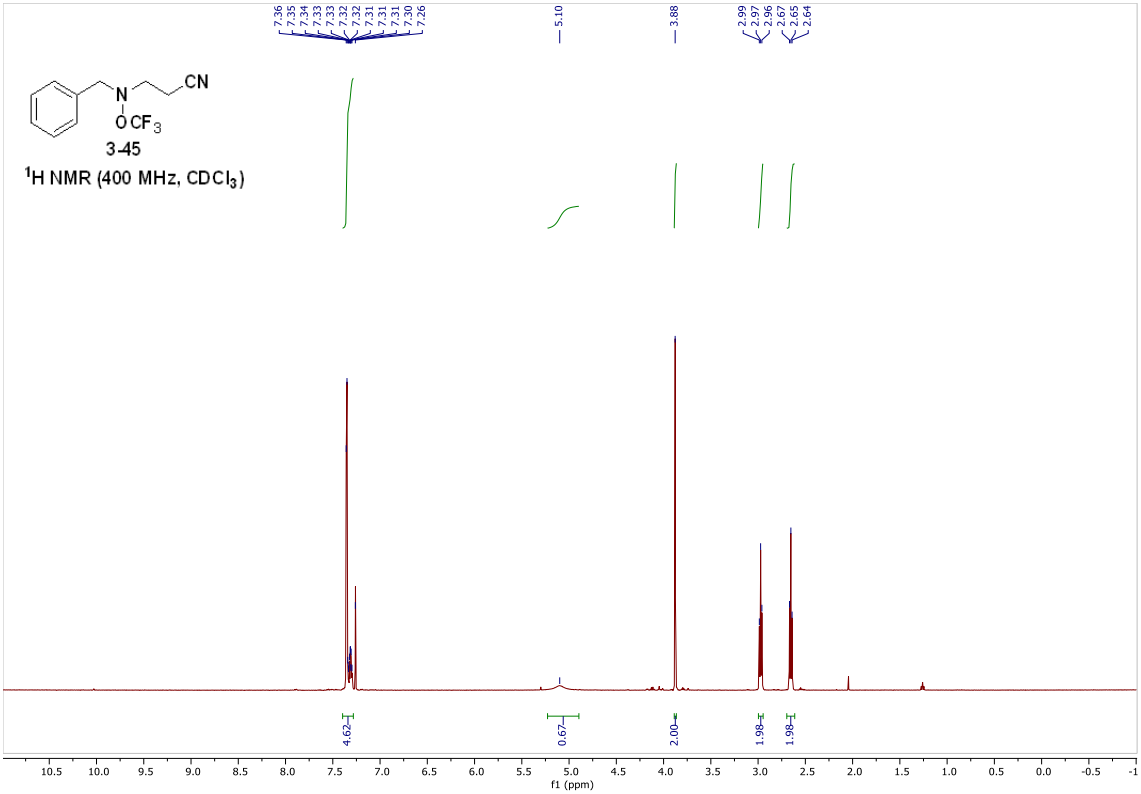

7.95
7.86
7.84
7.39
7.37
7.26
F3CO
OCF3
S
3-30
1H NMR (400 MHz, CDCl3)
2.00
1.94
1.92
f1 (ppm)


146.88
138.68
135.86
123.93
120.88
114.38
77.32
77.00
76.68
F3CO
OCF3
S
3-30
13C NMR (100 MHz, CDCl3)
f1 (ppm)



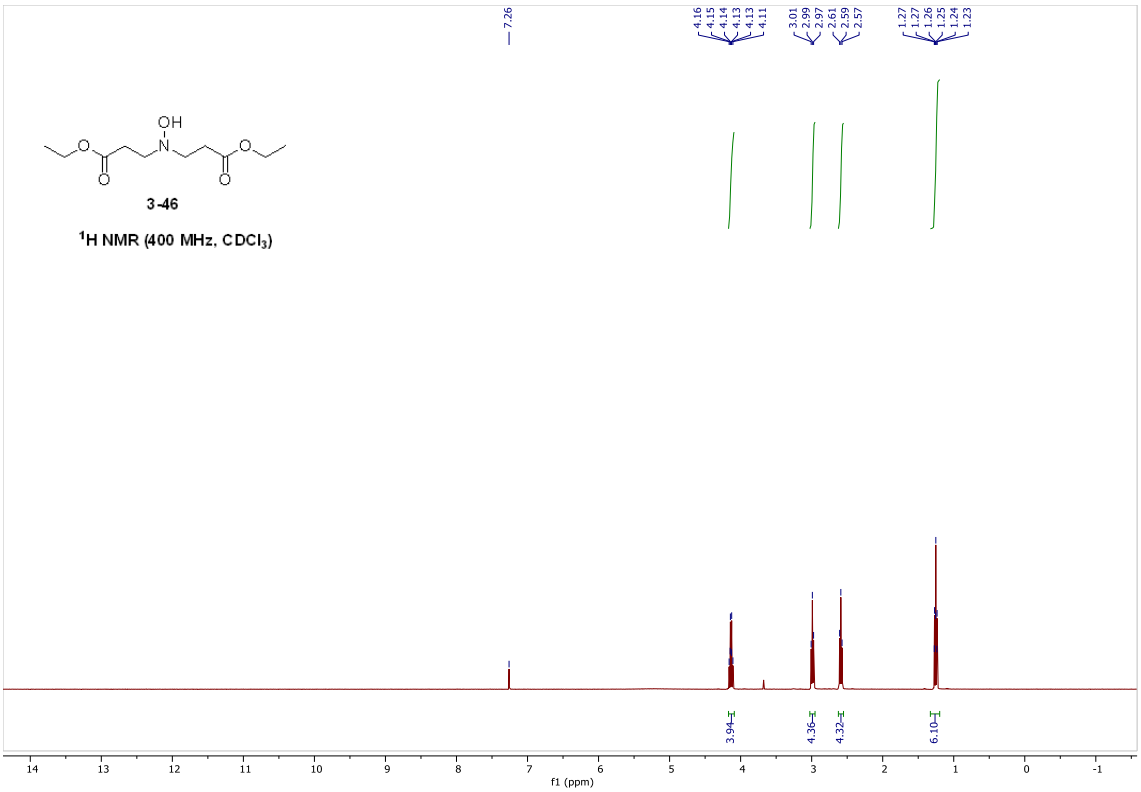
3-30

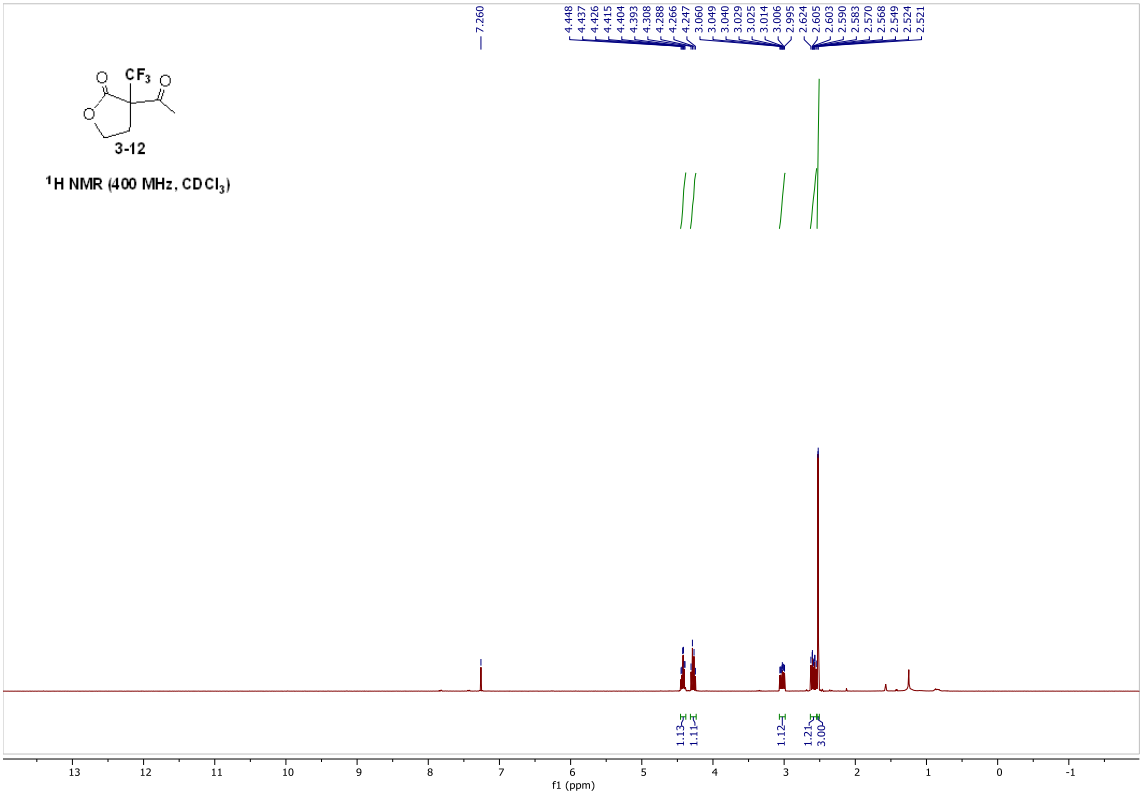
^{19}F NMR (376 MHz, $CDCl_3$)

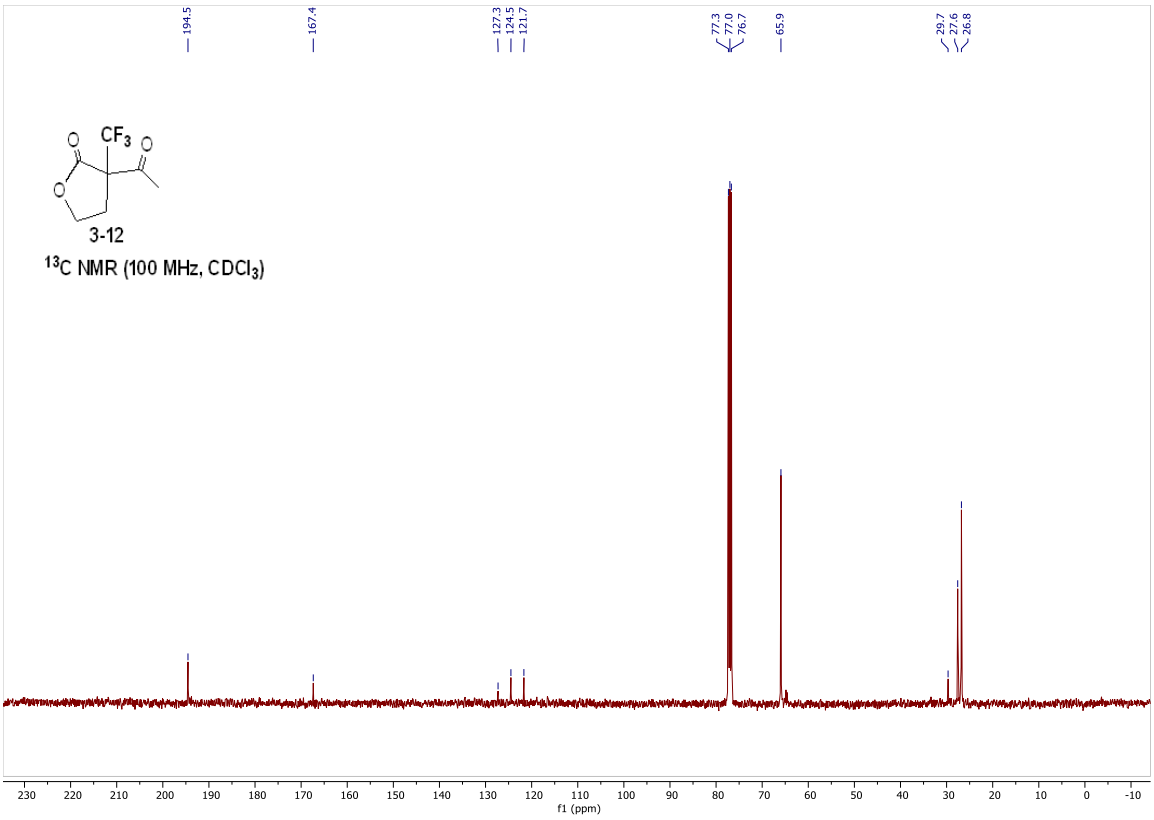


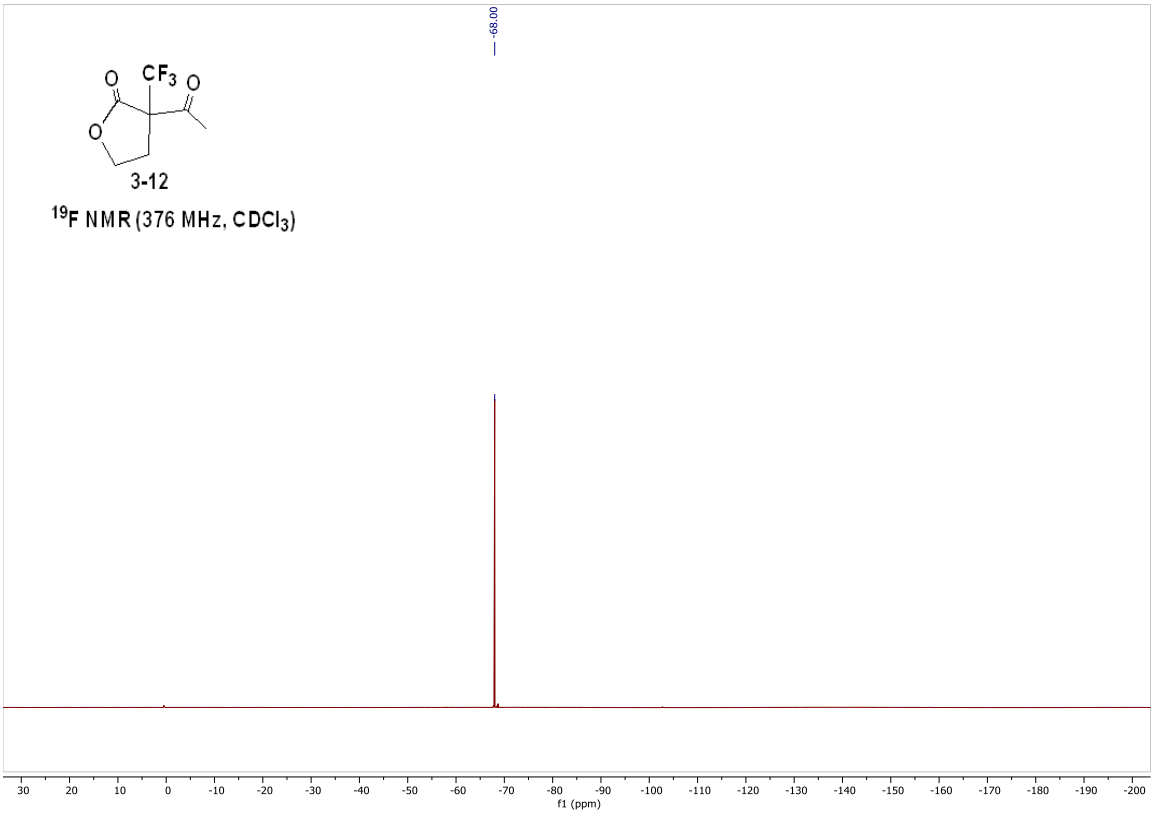
3-45

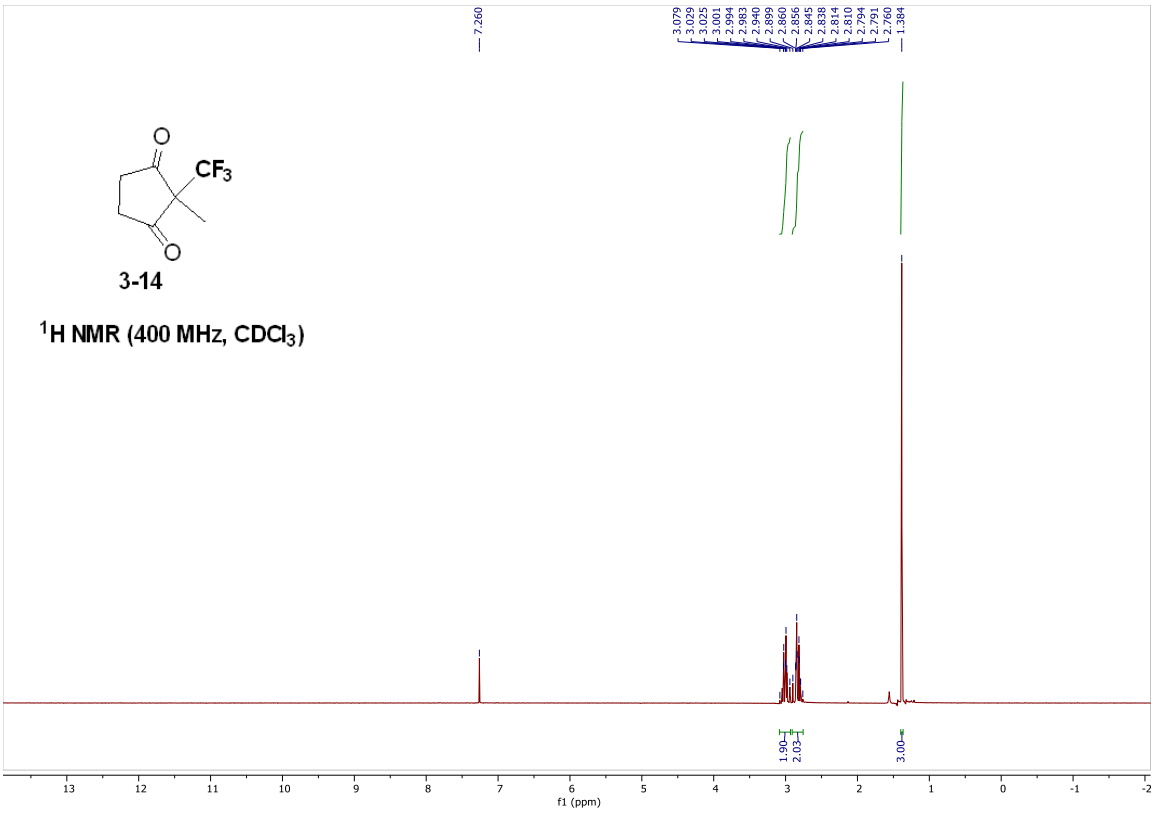
^{1}H NMR (400 MHz, $CDCl_3$)


OH
N
O
O
O
O
3-46
^{1}H NMR (400 MHz, $CDCl_3$)
7.26
4.16
4.15
4.14
4.13
4.11
3.01
2.99
2.97
2.61
2.59
2.57
1.27
1.27
1.26
1.25
1.24
1.23
3.94
4.36
4.32
6.10
f1 (ppm)


CF_3
O
O
O
O
3-12
^{1}H NMR (400 MHz, $CDCl_3$)
7.260
4.448
4.437
4.426
4.415
4.404
4.393
4.308
4.288
4.266
4.247
3.060
3.049
3.040
3.029
3.015
3.014
3.006
2.995
2.624
2.605
2.603
2.590
2.583
2.570
2.568
2.549
2.524
2.521
1.13
1.11
1.12
1.21
3.00
f1 (ppm)

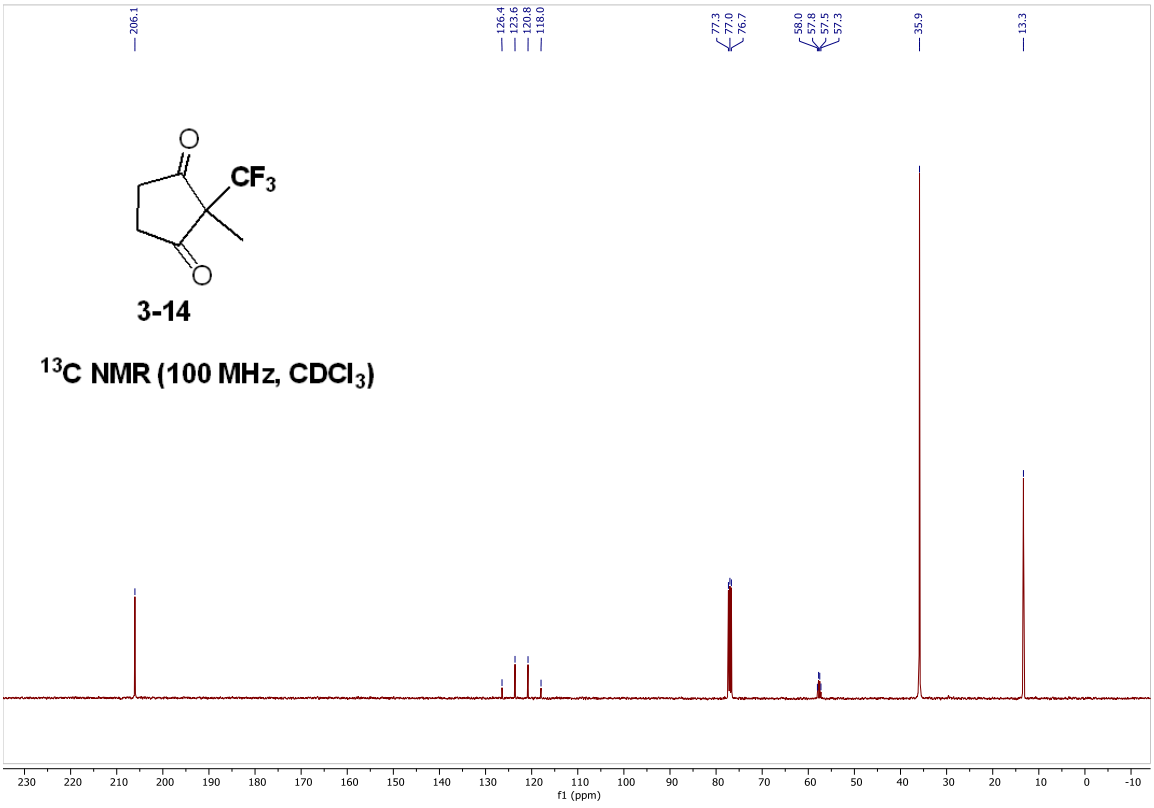

194.5
167.4
127.3
124.5
121.7
77.3
77.0
76.7
65.9
29.7
27.6
26.8
CF3
O
O
O
3-12
13C NMR (100 MHz, CDCl3)
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


-68.00
CF3
O
O
O
3-12
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)



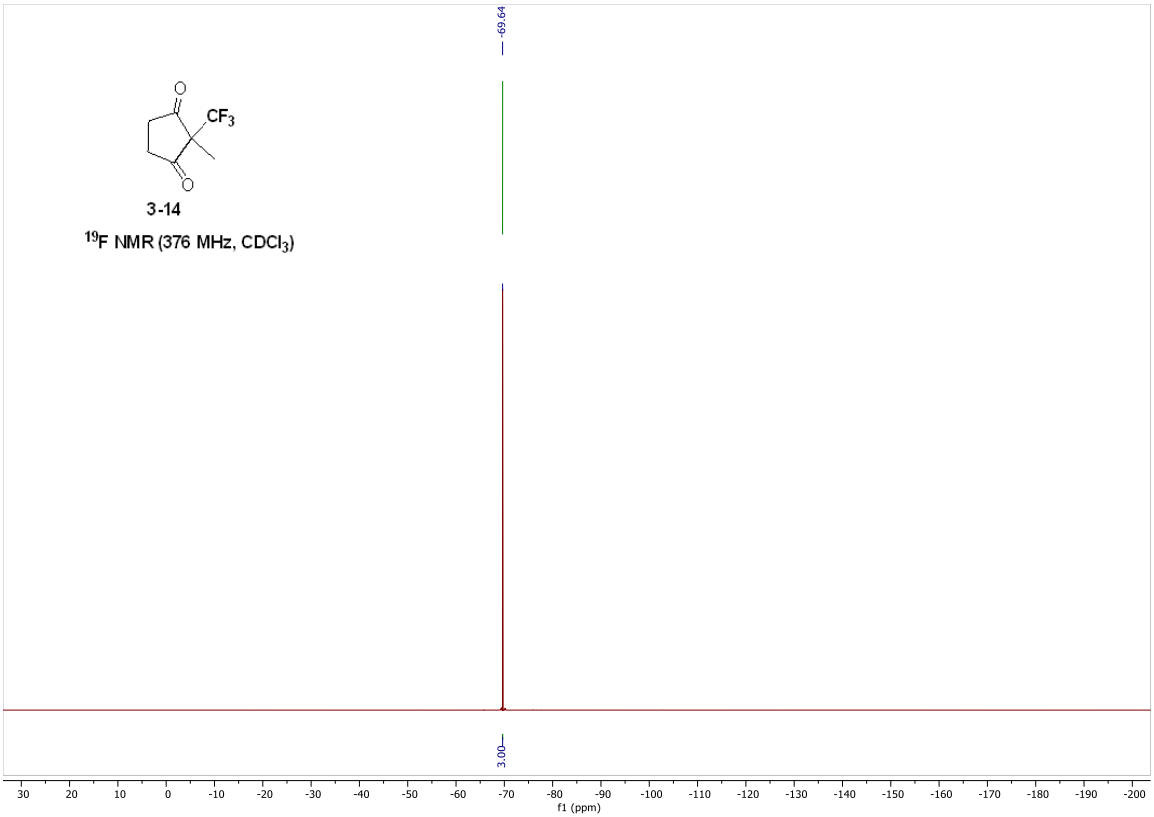
3-14

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



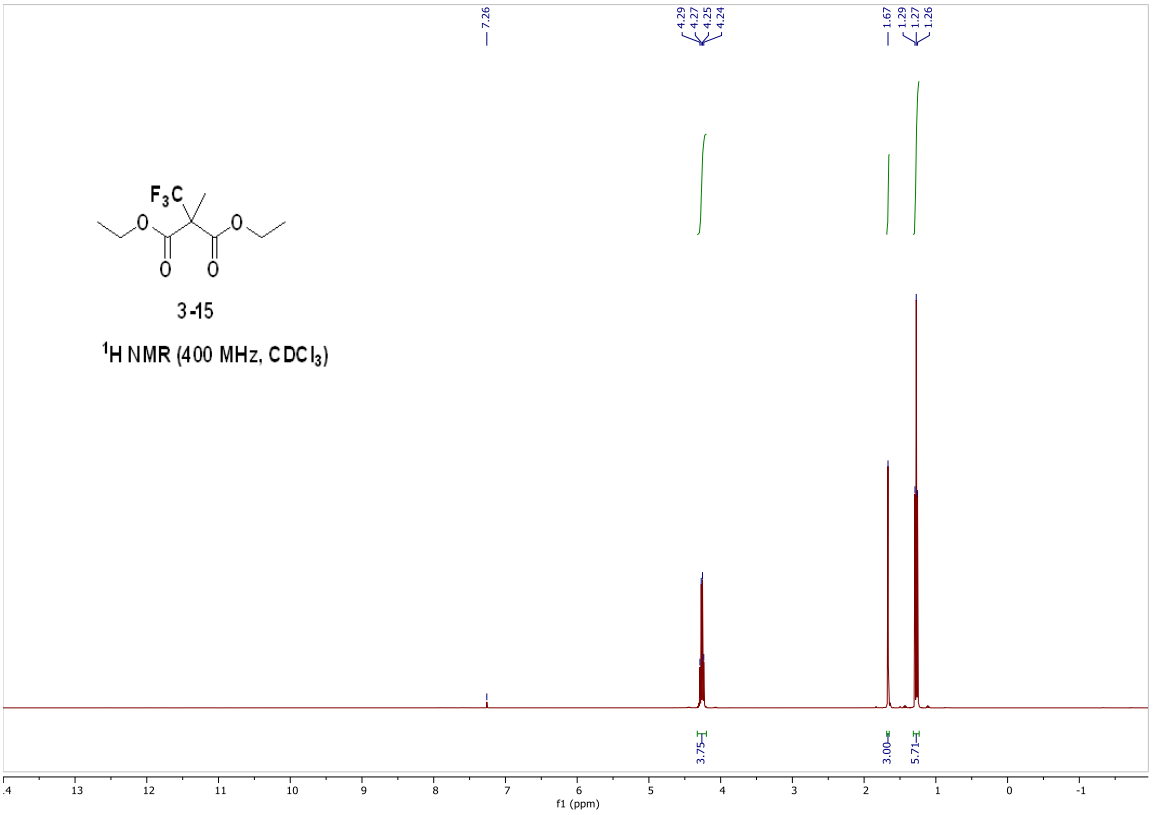
3-14

^{13}C NMR (100 MHz, $CDCl_3$)



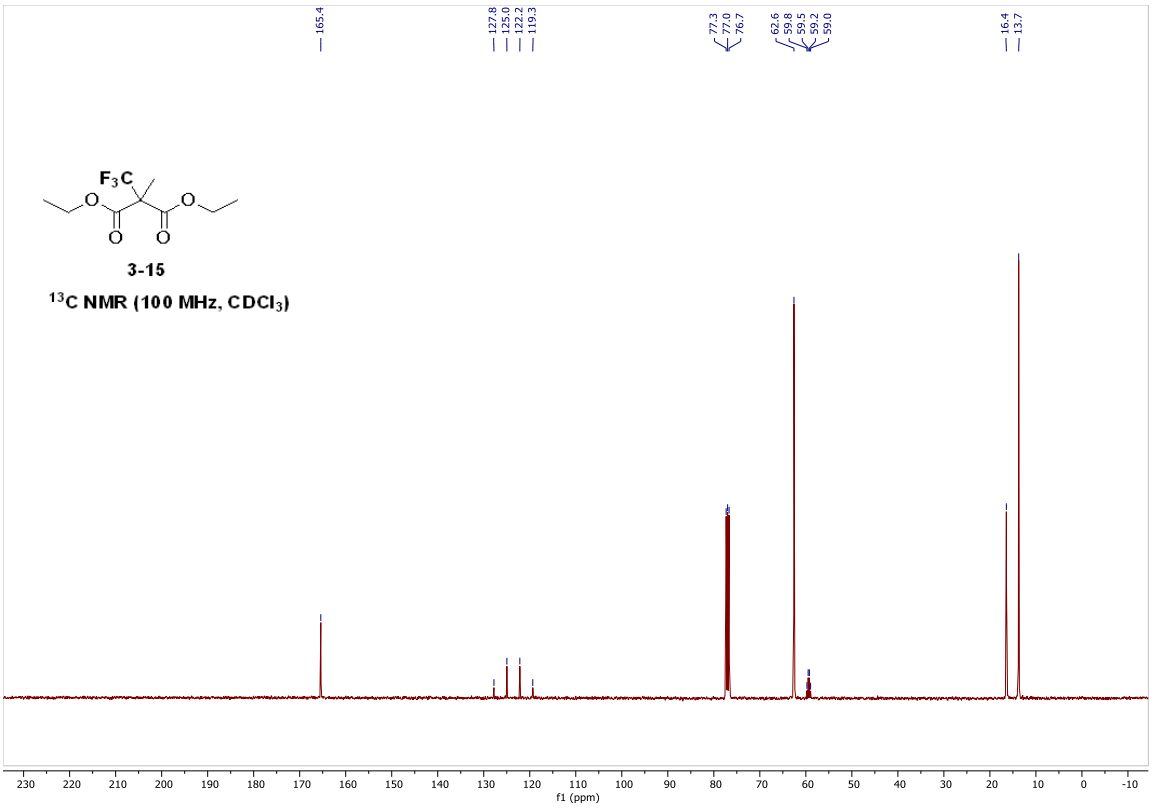
3-14

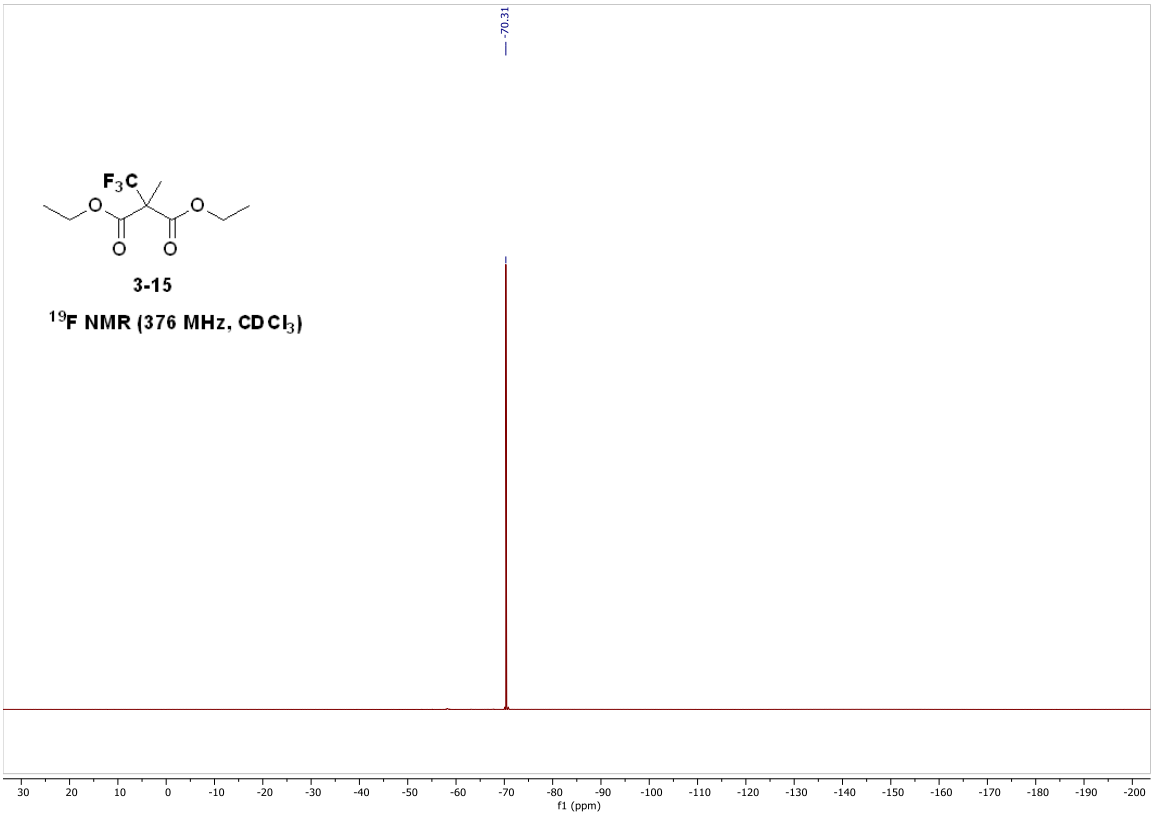
^{19}F NMR (376 MHz, $CDCl_3$)

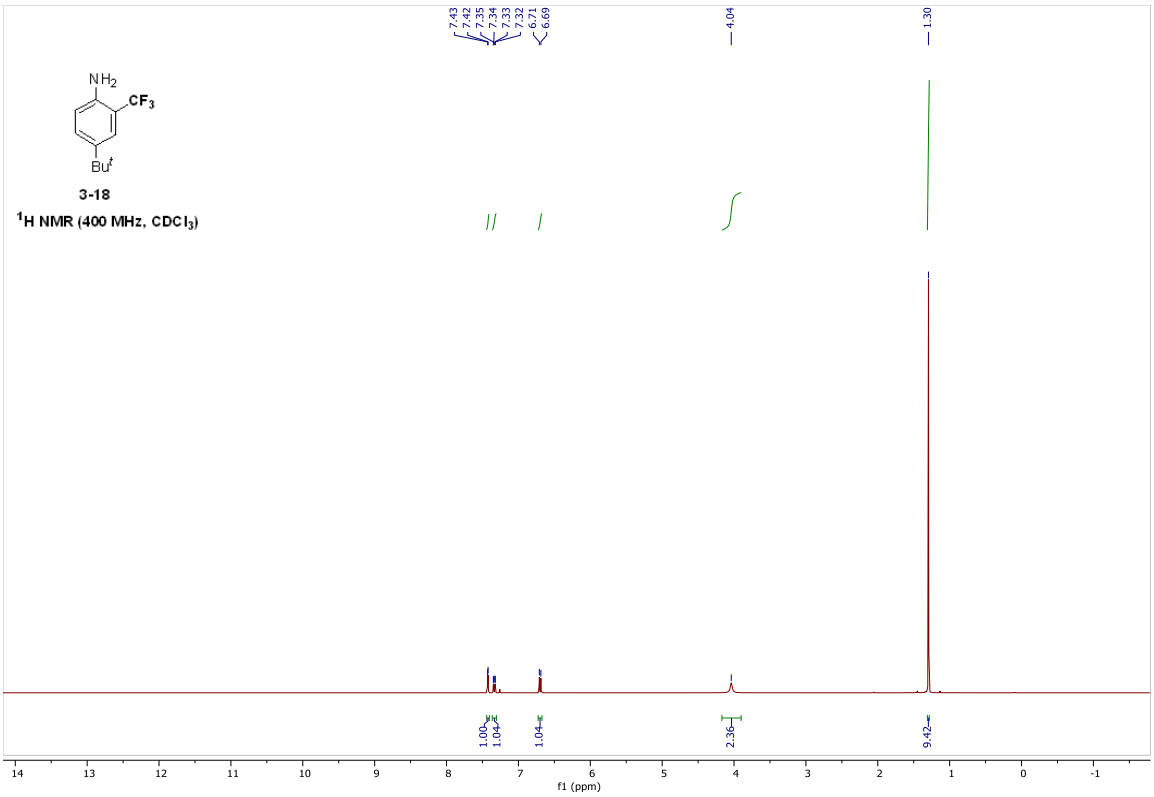


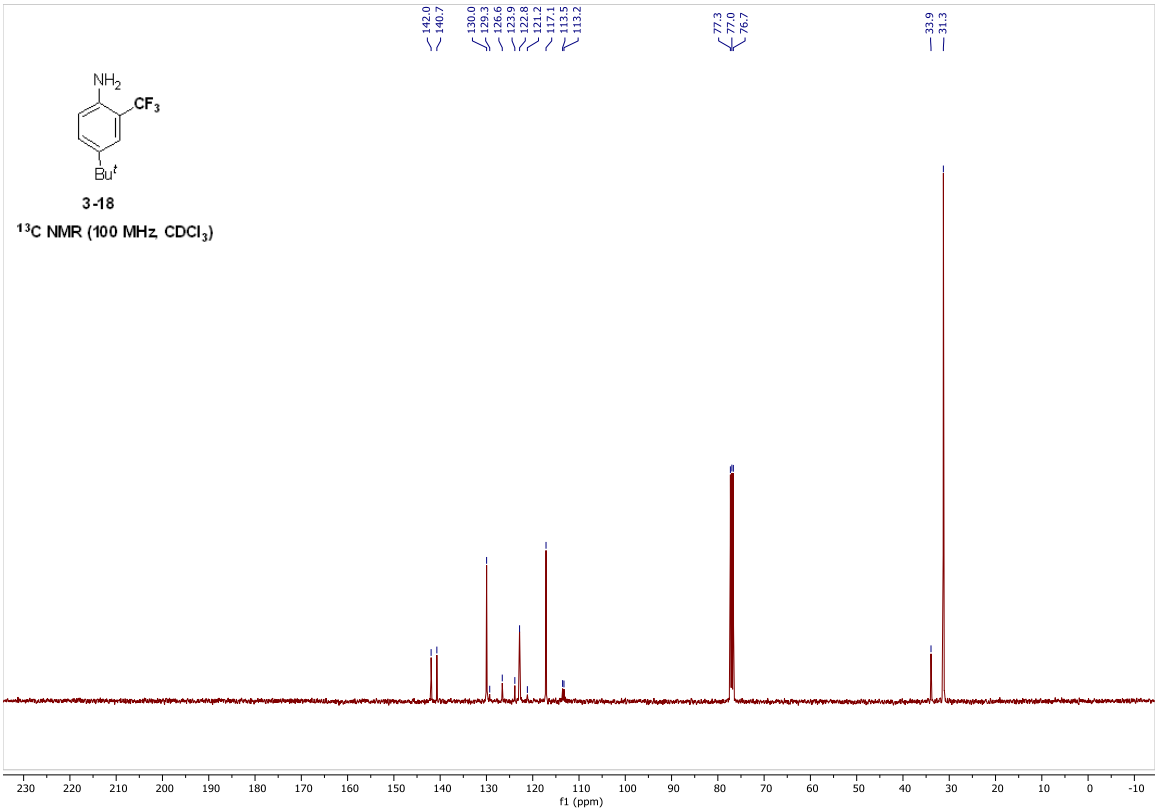
3-15

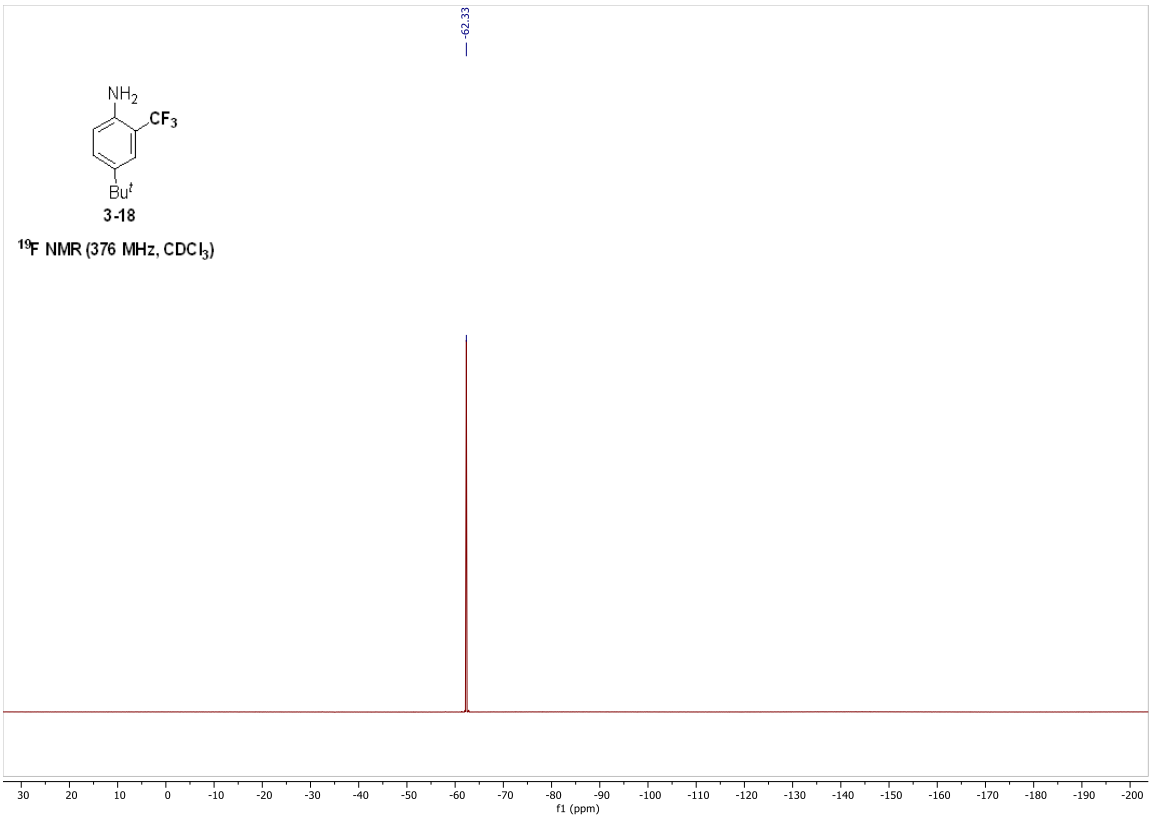
^{1}H NMR (400 MHz, $CDCl_3$)

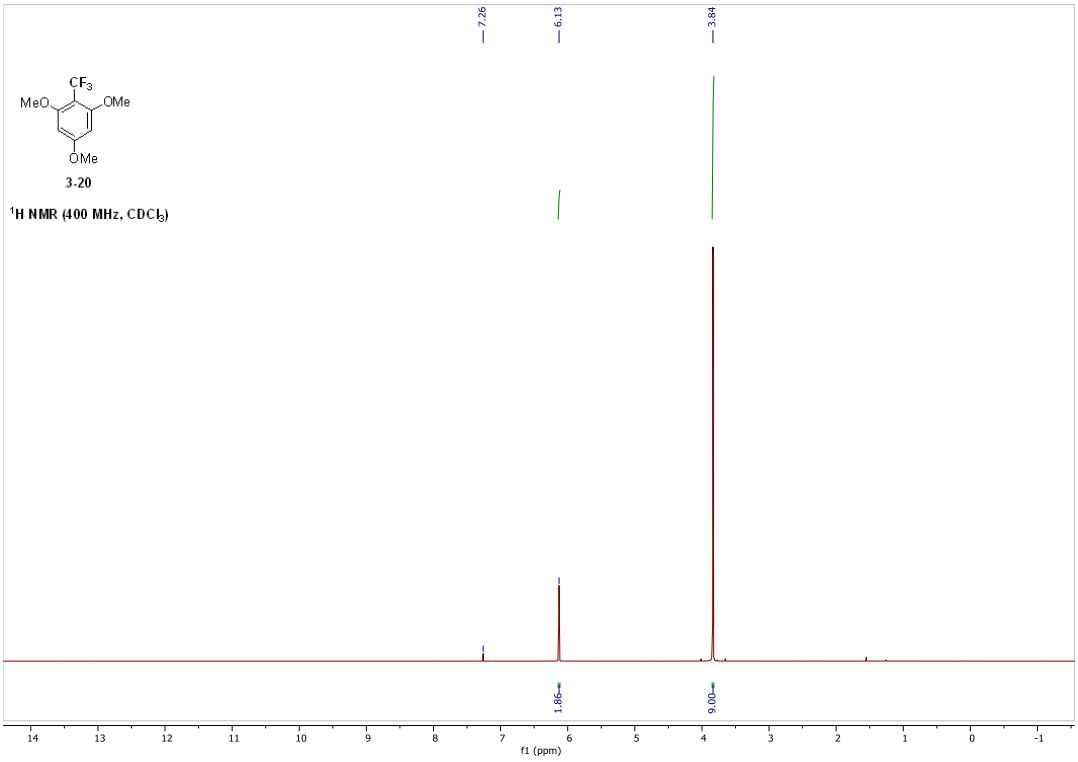

165.4
127.8
125.0
122.2
119.3
77.3
77.0
76.7
62.6
59.8
59.5
59.2
59.0
16.4
13.7
F3C
O
O
O
O
3-15
13C NMR (100 MHz, CDCl3)
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

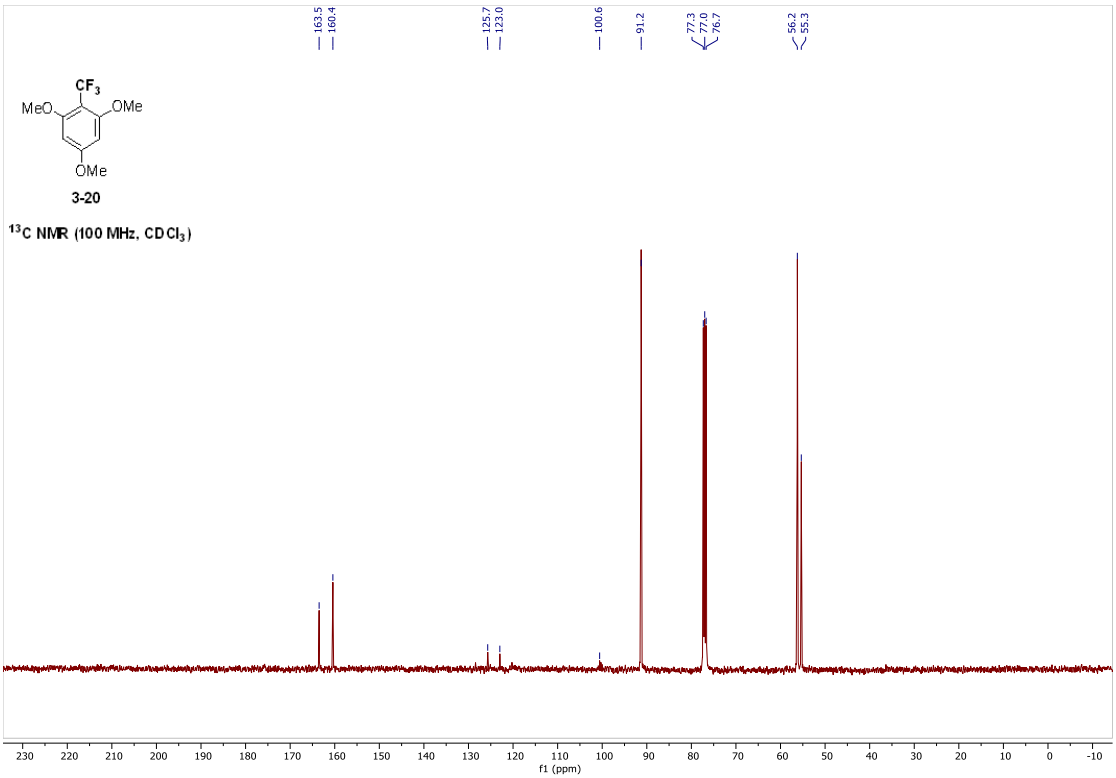

-70.31
F3C
O
O
O
O
3-15
19F NMR (376 MHz, CDCl3)
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

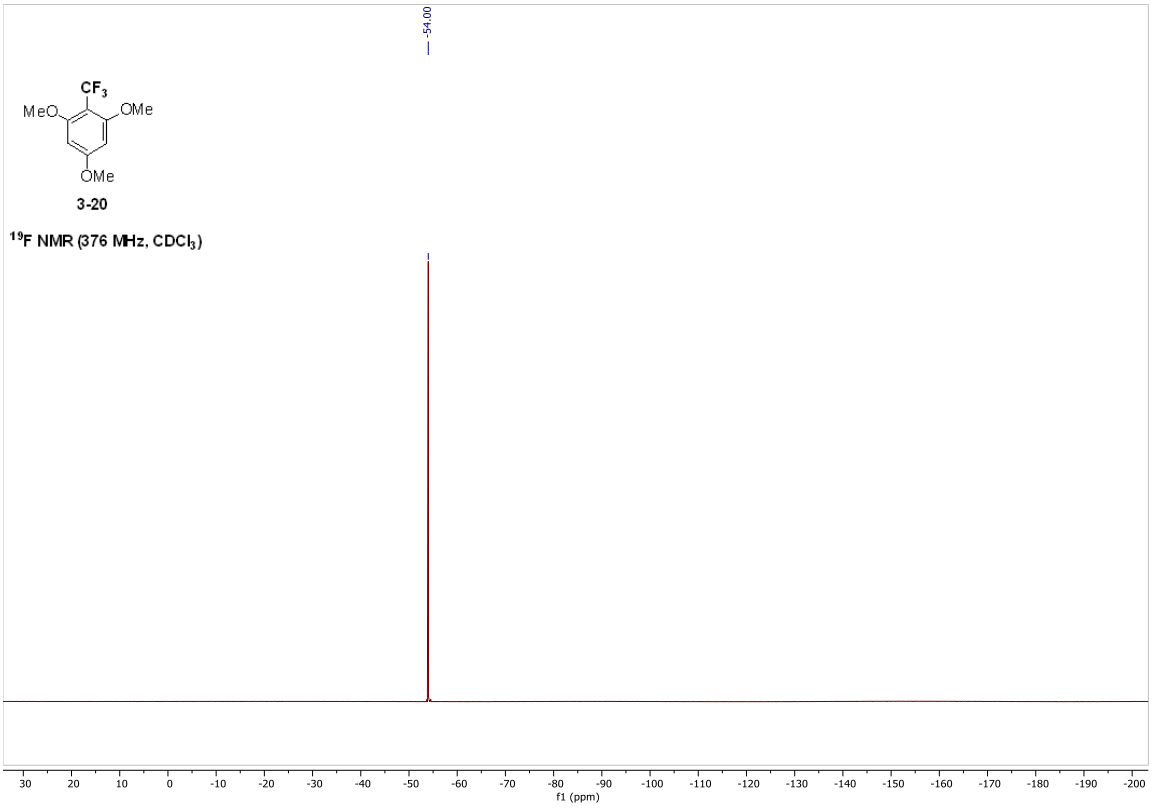

7.43
7.42
7.35
7.34
7.33
7.32
6.71
6.69
4.04
1.30
NH2
CF3
But
3-18
1H NMR (400 MHz, CDCl3)
1.00
1.04
1.04
2.36
9.42
f1 (ppm)

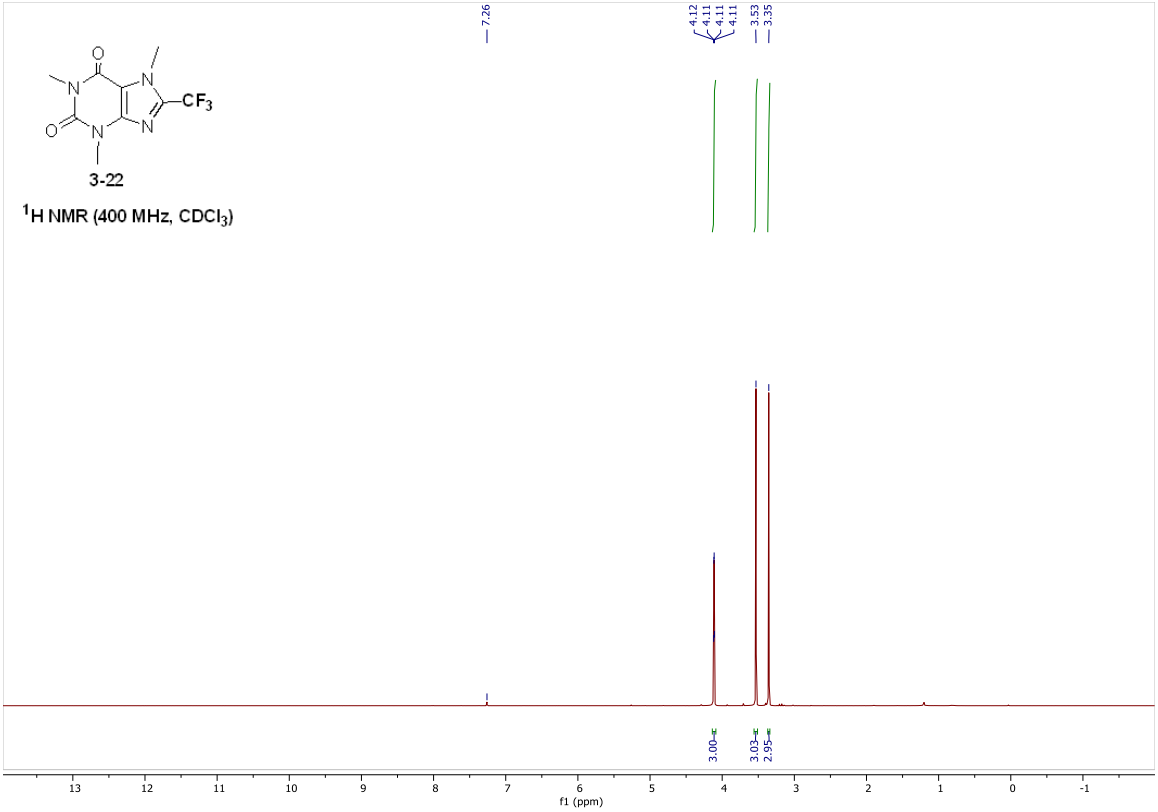

142.0
140.7
130.0
129.3
126.6
123.9
122.8
121.2
117.1
113.5
113.2
77.3
77.0
76.7
33.9
31.3
NH2
CF3
But
3-18
13C NMR (100 MHz, CDCl3)
f1 (ppm)


-62.33
NH2
CF3
But
3-18
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
6.13
3.84
CF3
MeO
OMe
OMe
3-20
1H NMR (400 MHz, CDCl3)
1.86
9.00
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)

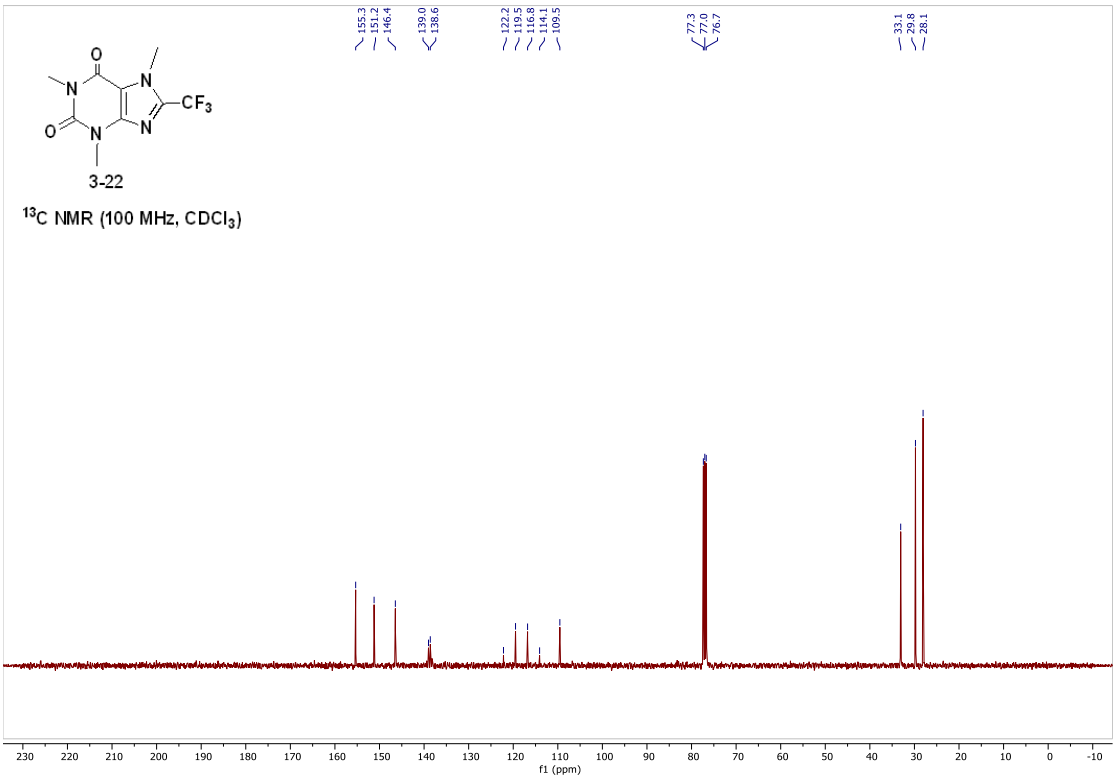

163.5
160.4
125.7
123.0
100.6
91.2
77.3
77.0
76.7
56.2
55.3
CF3
MeO
OMe
OMe
3-20
13C NMR (100 MHz, CDCl3)
f1 (ppm)


-54.00
CF3
MeO
OMe
OMe
3-20
19F NMR (376 MHz, CDCl3)
f1 (ppm)



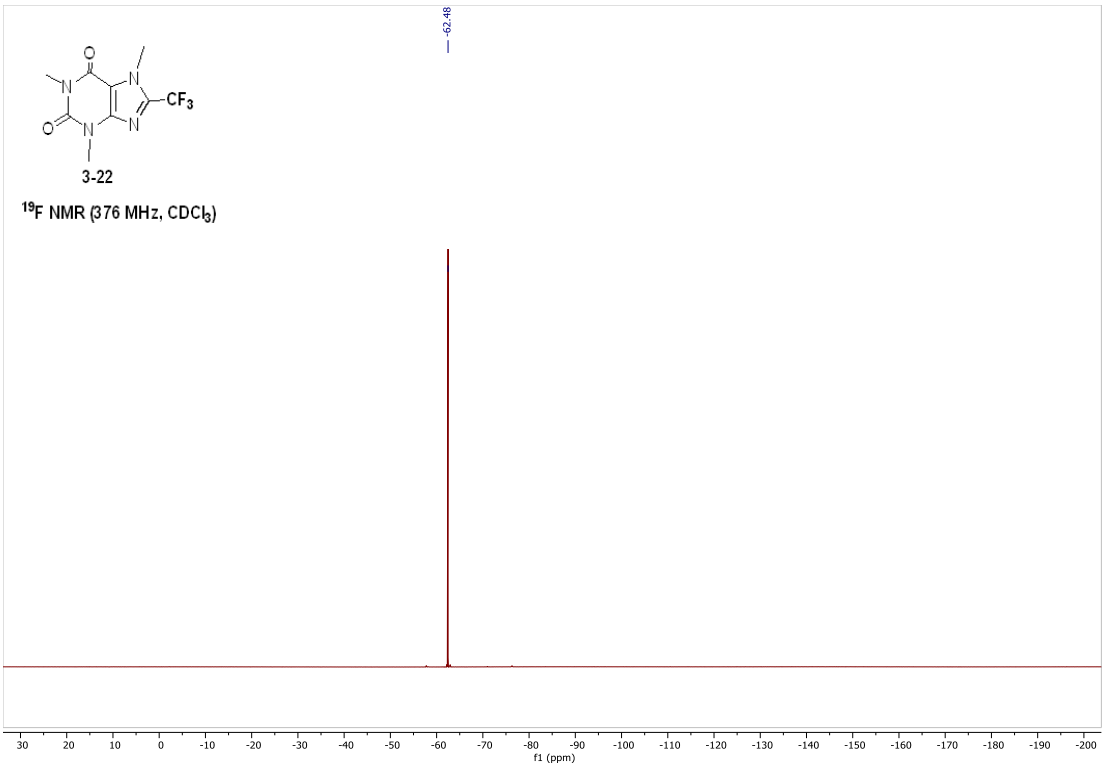
3-22

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



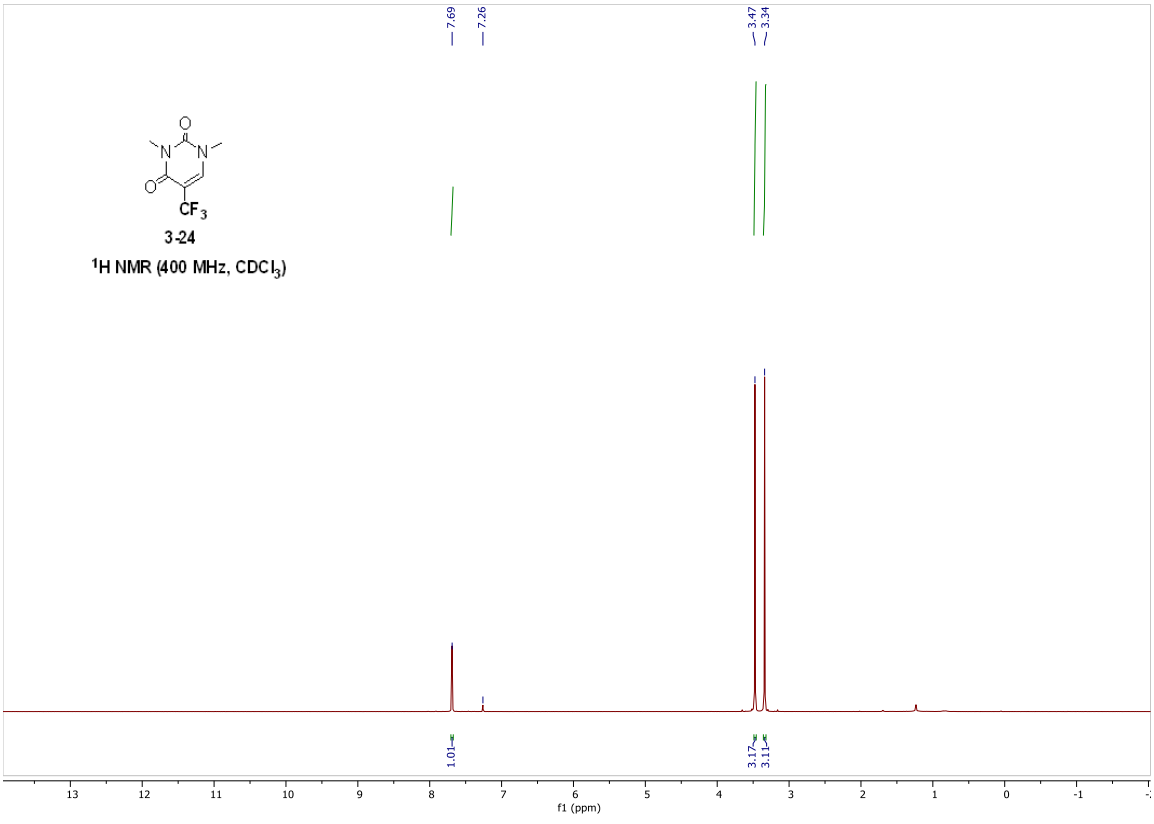
3-22

^{13}C NMR (100 MHz, $CDCl_3$)



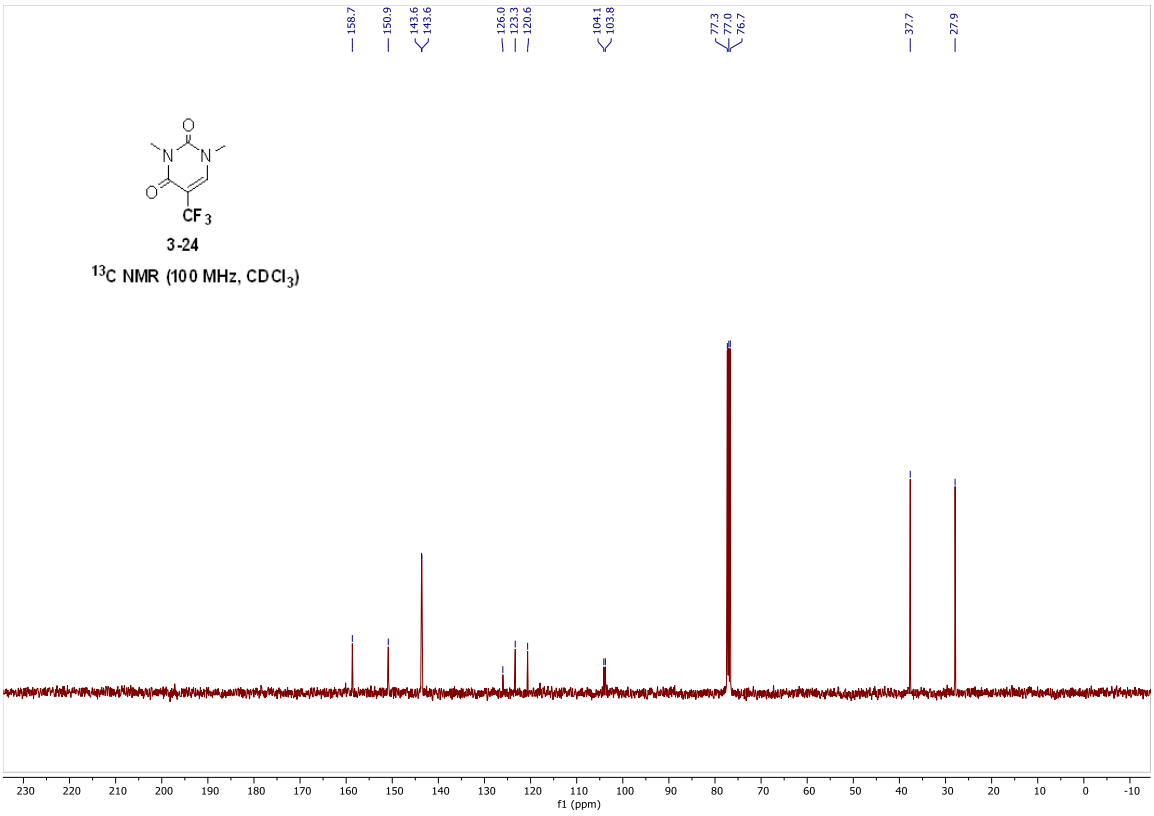
3-22

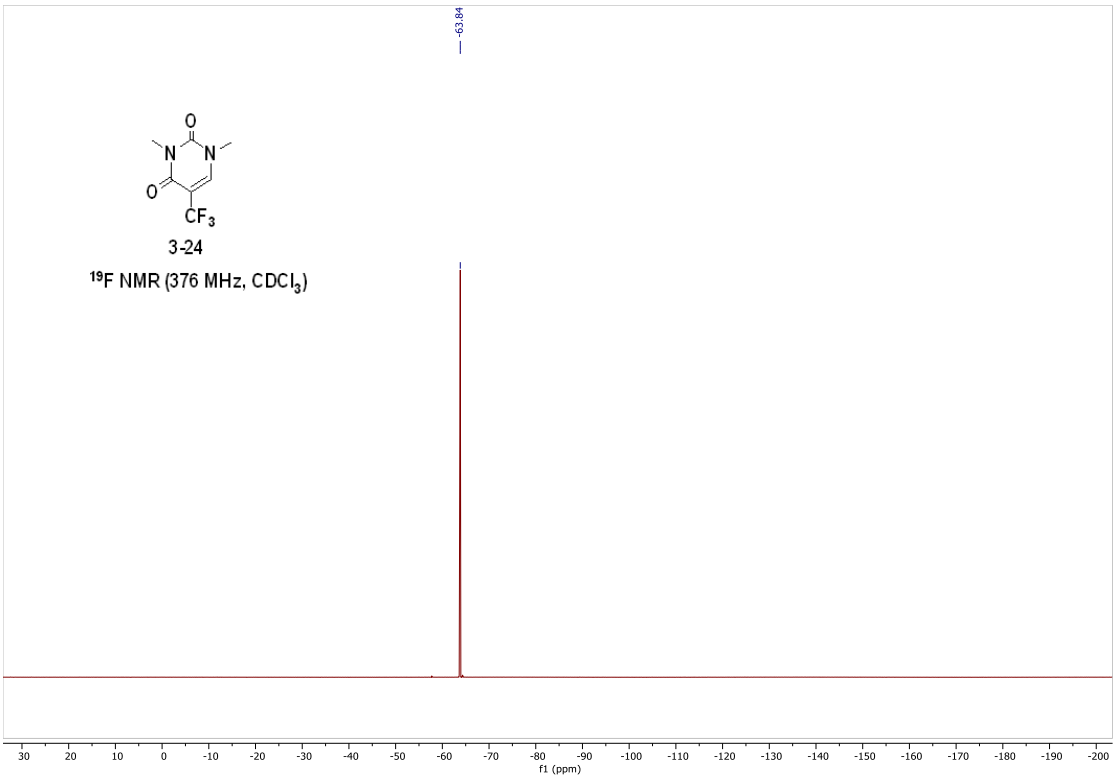
^{19}F NMR (376 MHz, $CDCl_3$)

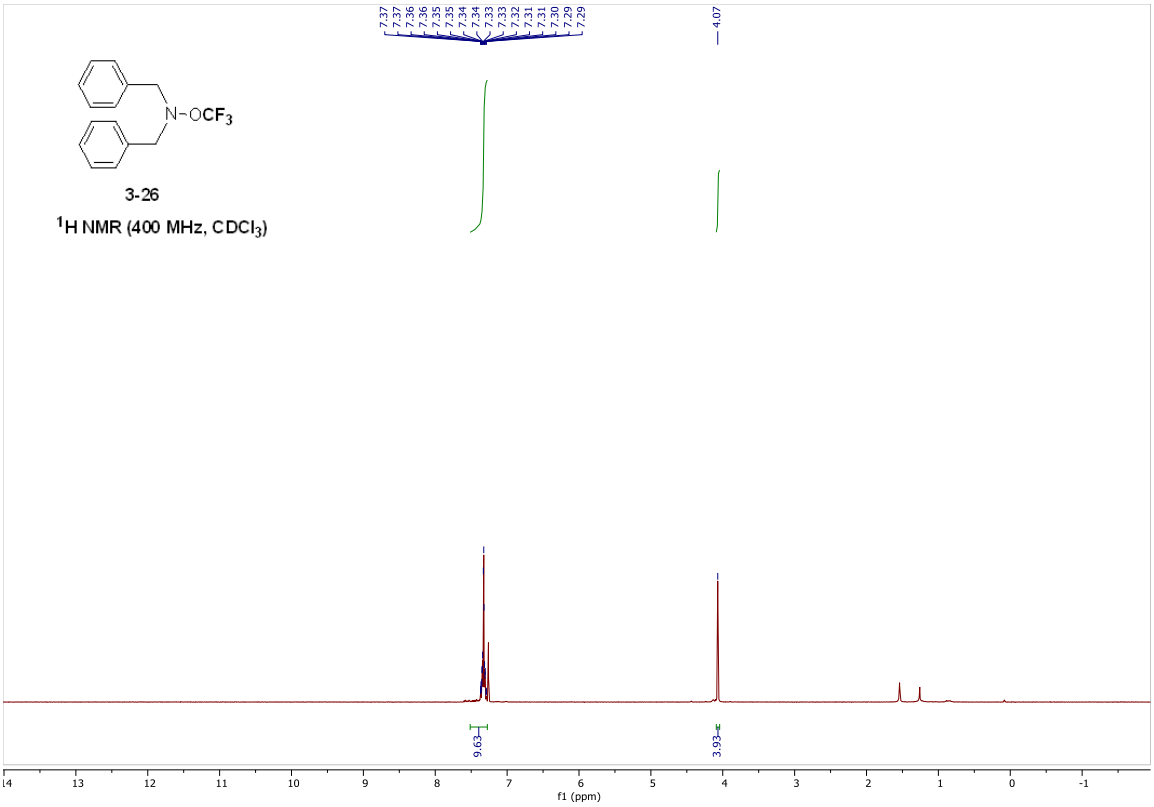


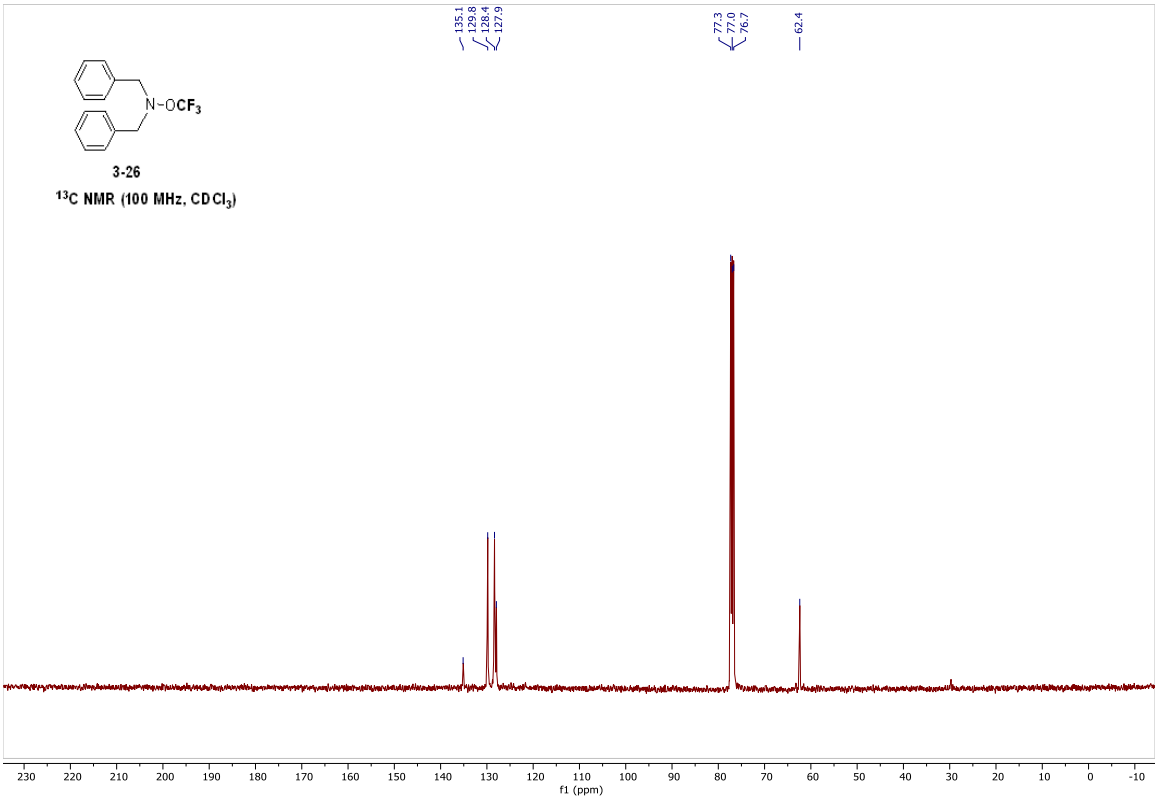
3-24

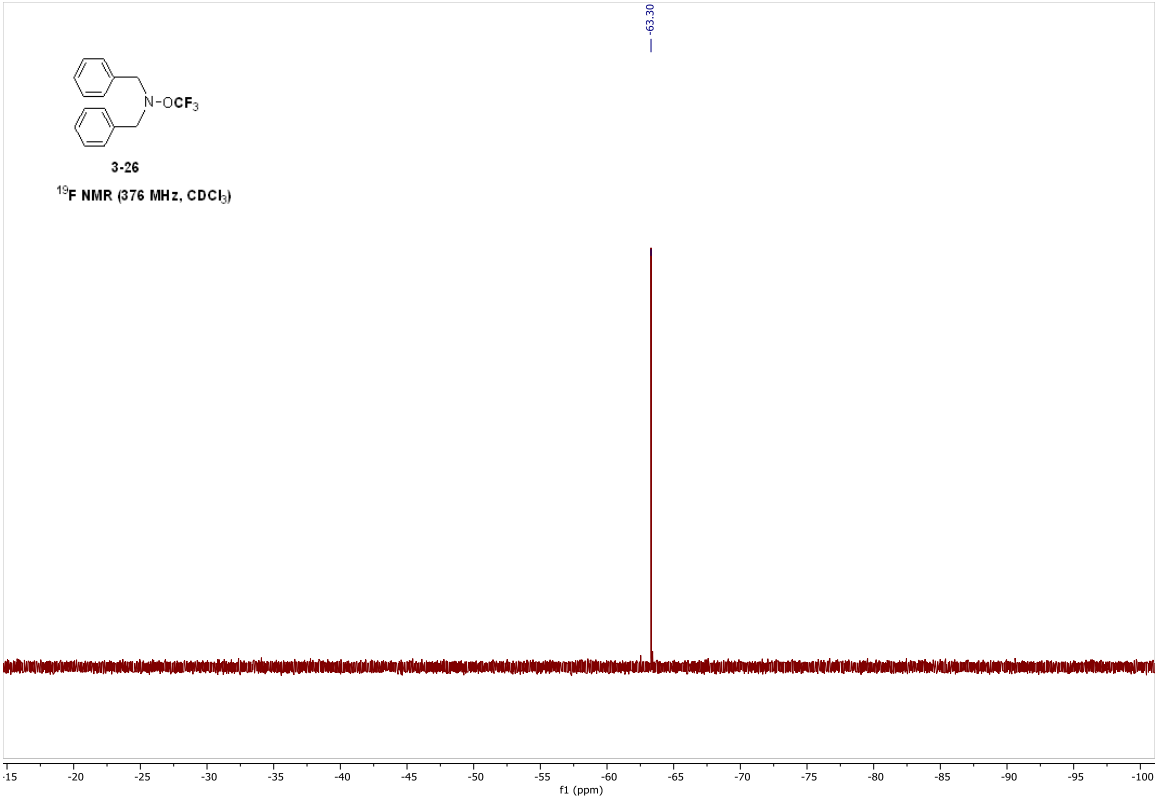
^{1}H NMR (400 MHz, $CDCl_3$)

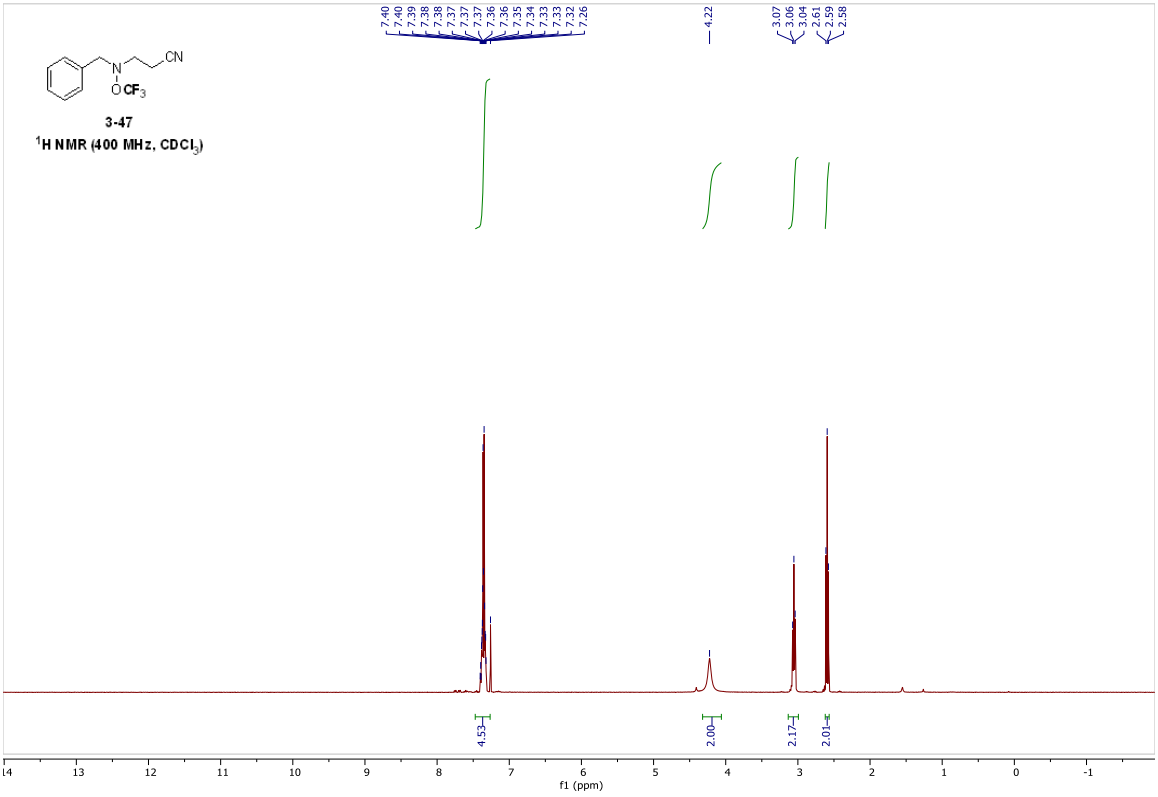

158.7
150.9
143.6
143.6
126.0
123.3
120.6
104.1
103.8
77.3
77.0
76.7
37.7
27.9
3-24
^{13}C NMR (100 MHz, CDCl$_3$)
f1 (ppm)

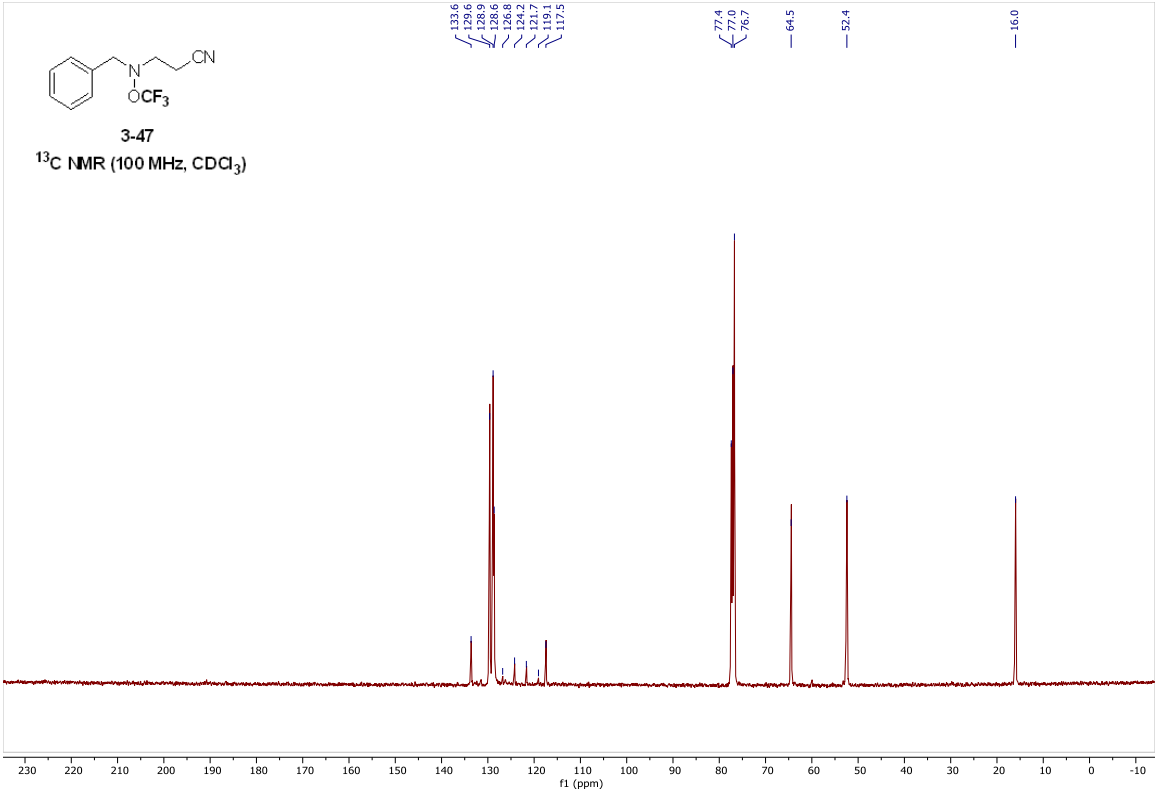

-63.84
3-24
^{19}F NMR (376 MHz, CDCl$_3$)
f1 (ppm)


7.37
7.37
7.36
7.36
7.35
7.35
7.34
7.34
7.33
7.32
7.31
7.31
7.30
7.29
7.29
4.07
N-OCF3
3-26
1H NMR (400 MHz, CDCl3)
9.63
3.93
f1 (ppm)


135.1
129.8
128.4
127.9
77.3
77.0
76.7
62.4
N-OCF3
3-26
13C NMR (100 MHz, CDCl3)
f1 (ppm)

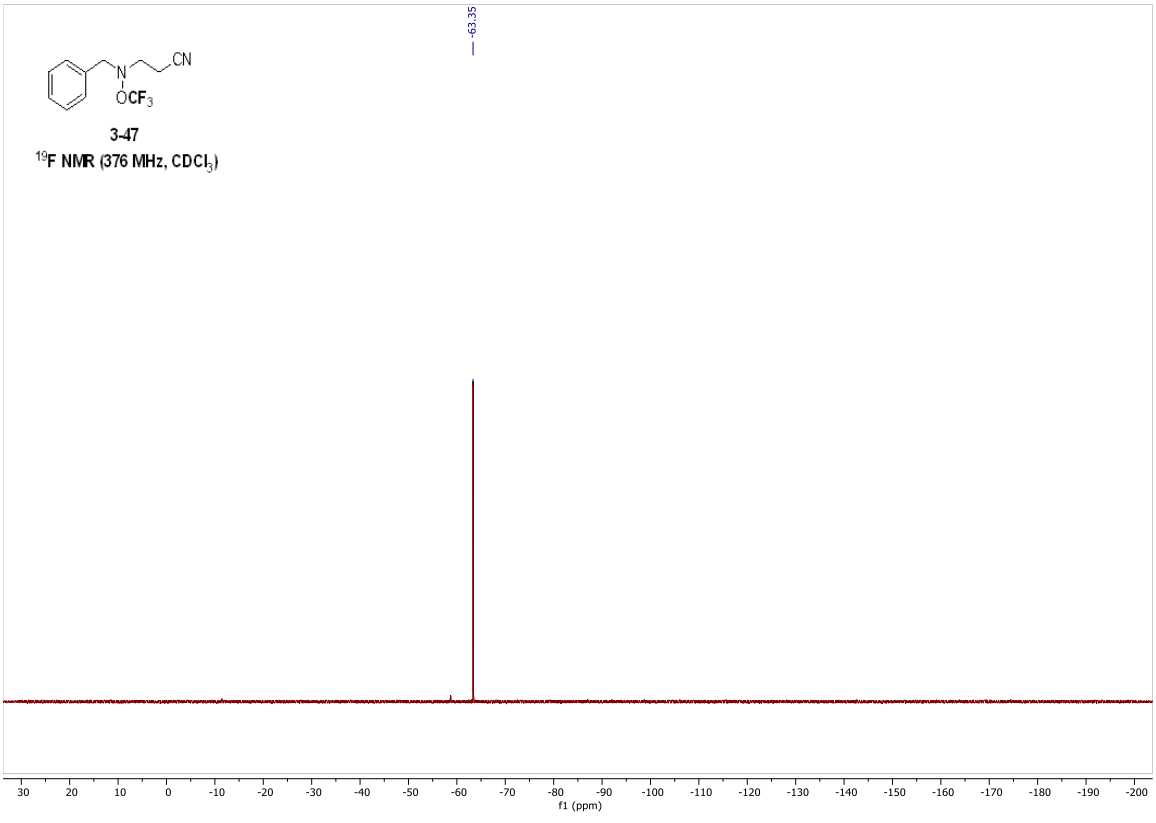

N-OCF3
3-26
19F NMR (376 MHz, CDCl3)
-63.30
f1 (ppm)


CN
N
OCF3
3-47
1H NMR (400 MHz, CDCl3)
7.40
7.40
7.39
7.38
7.38
7.37
7.37
7.37
7.36
7.36
7.35
7.34
7.33
7.33
7.32
7.26
4.22
3.07
3.06
3.04
2.61
2.59
2.58
4.53
2.00
2.17
2.01
f1 (ppm)



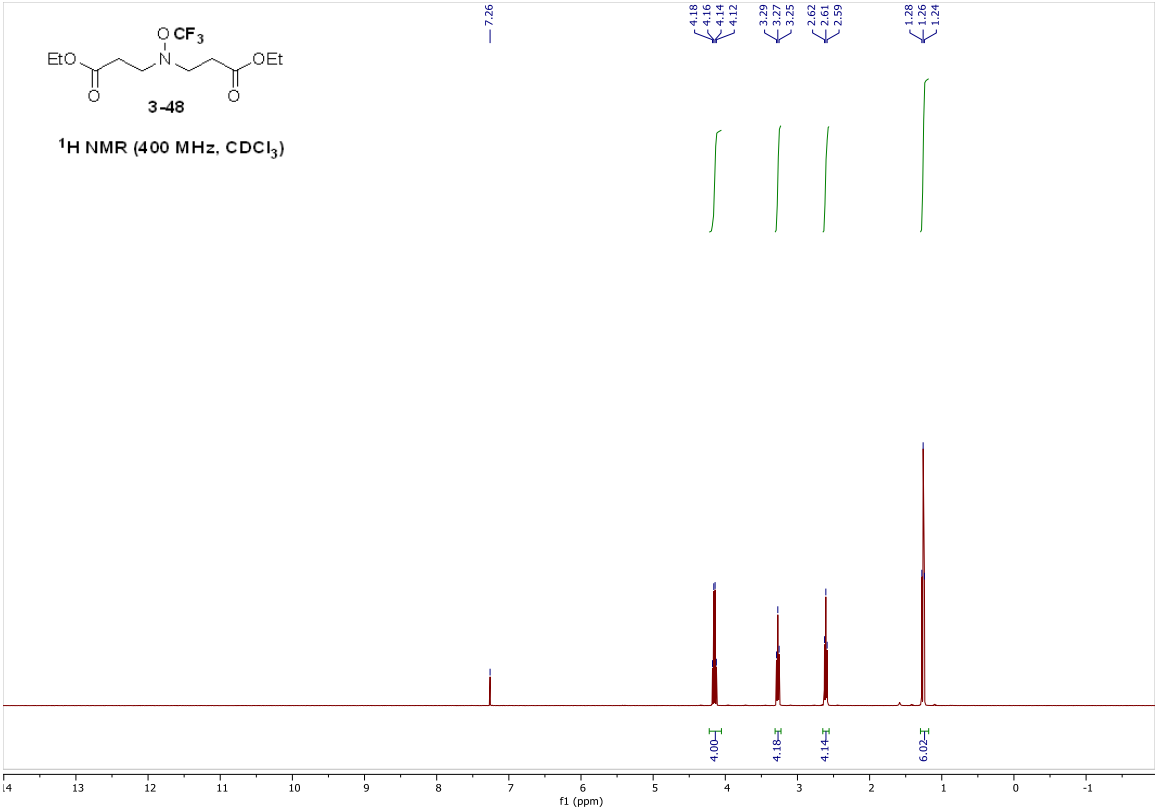
3-47

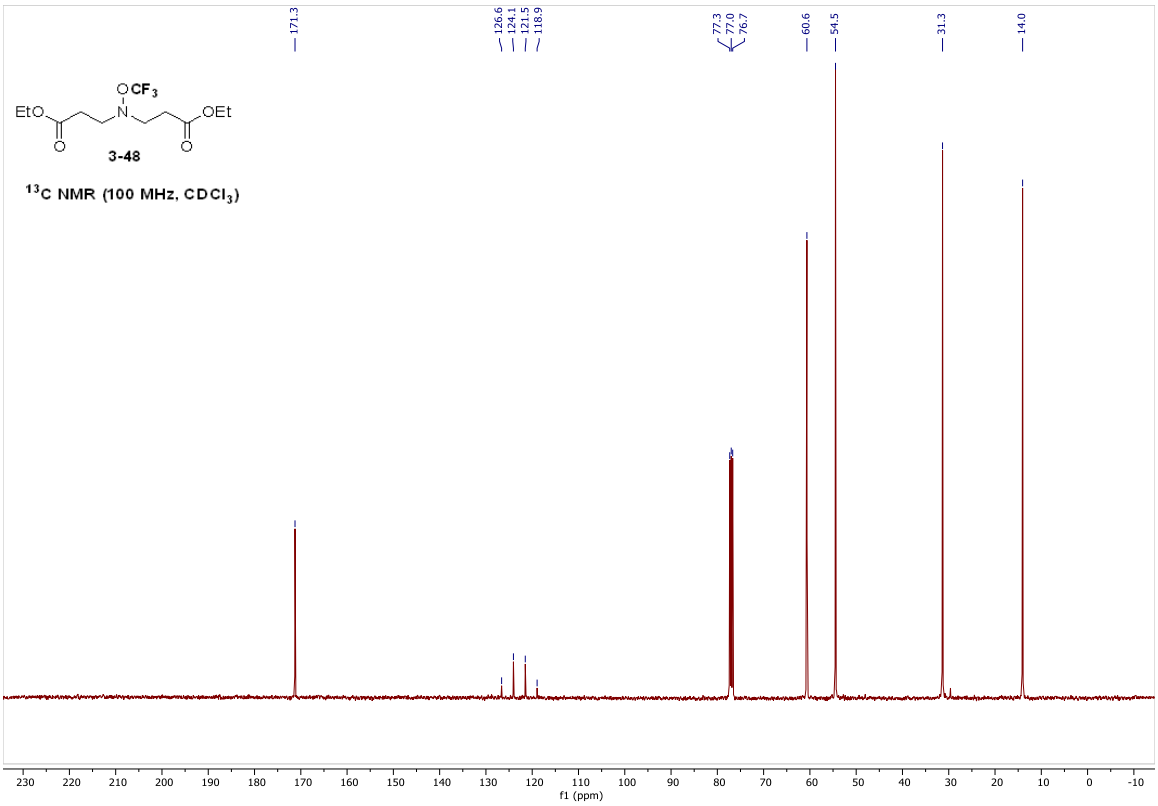
^{13}C NMR (100 MHz, $CDCl_3$)

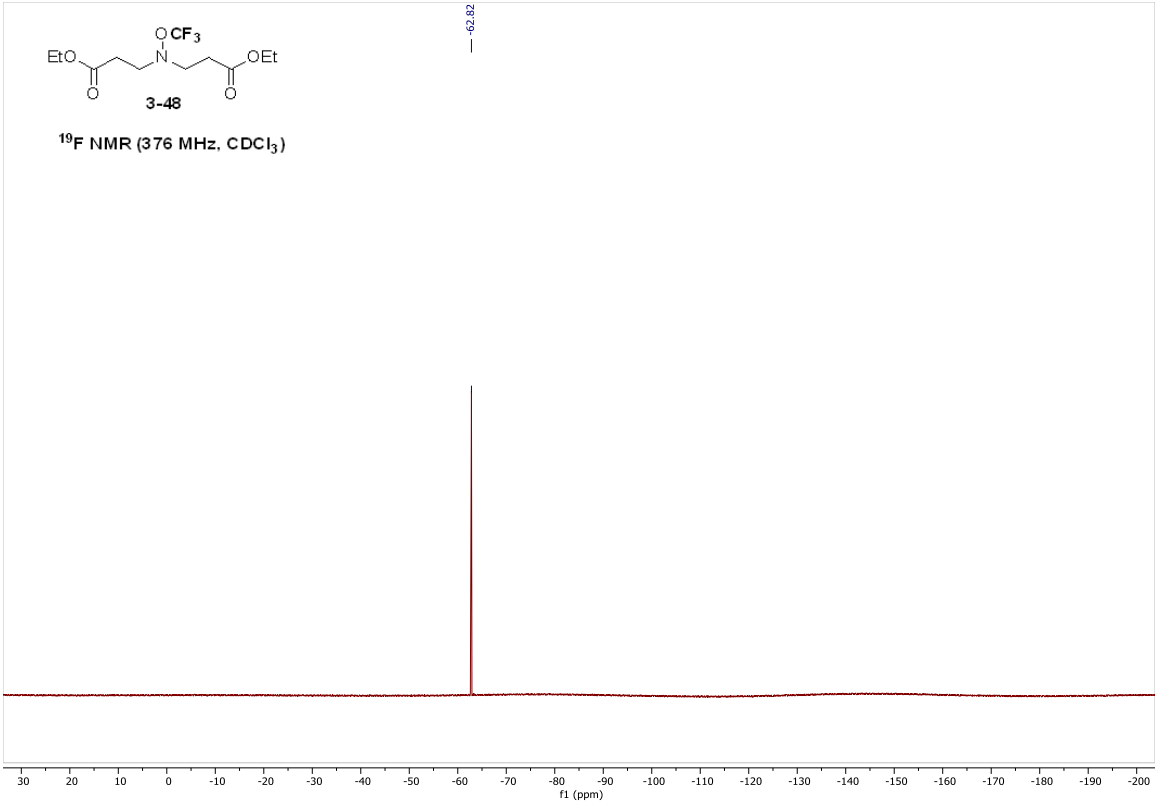


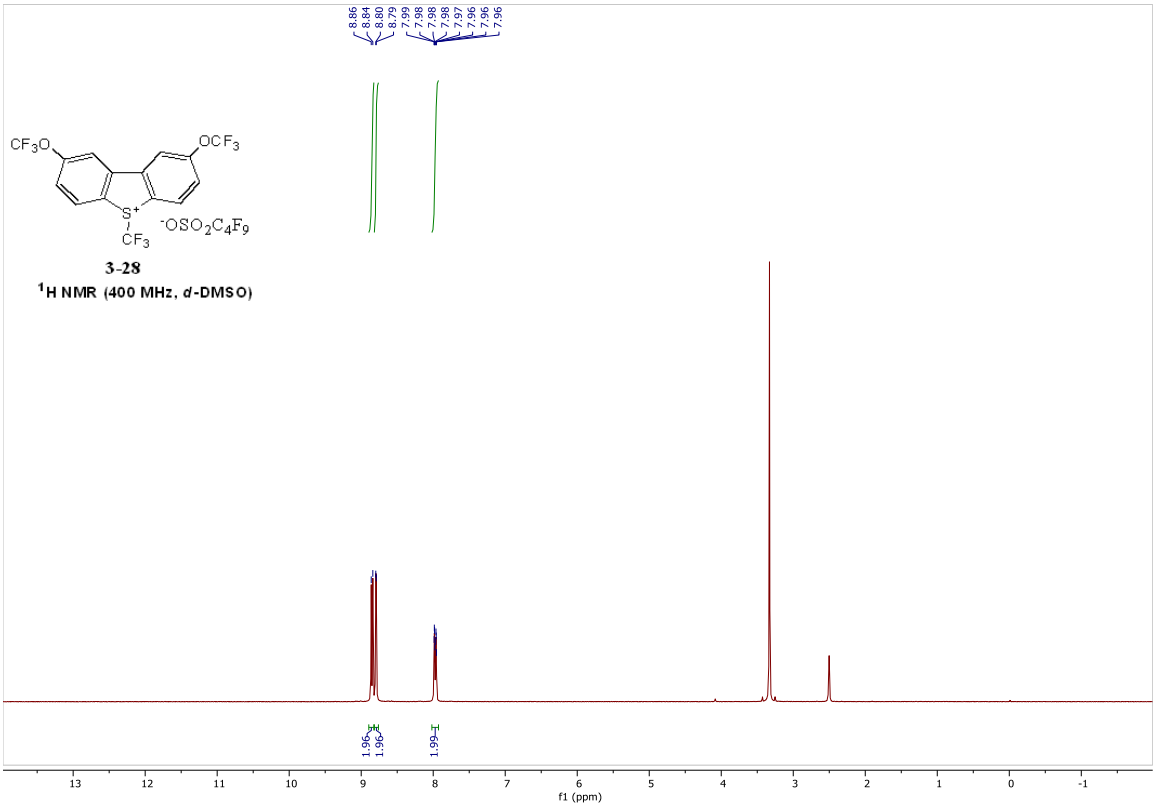
3-47

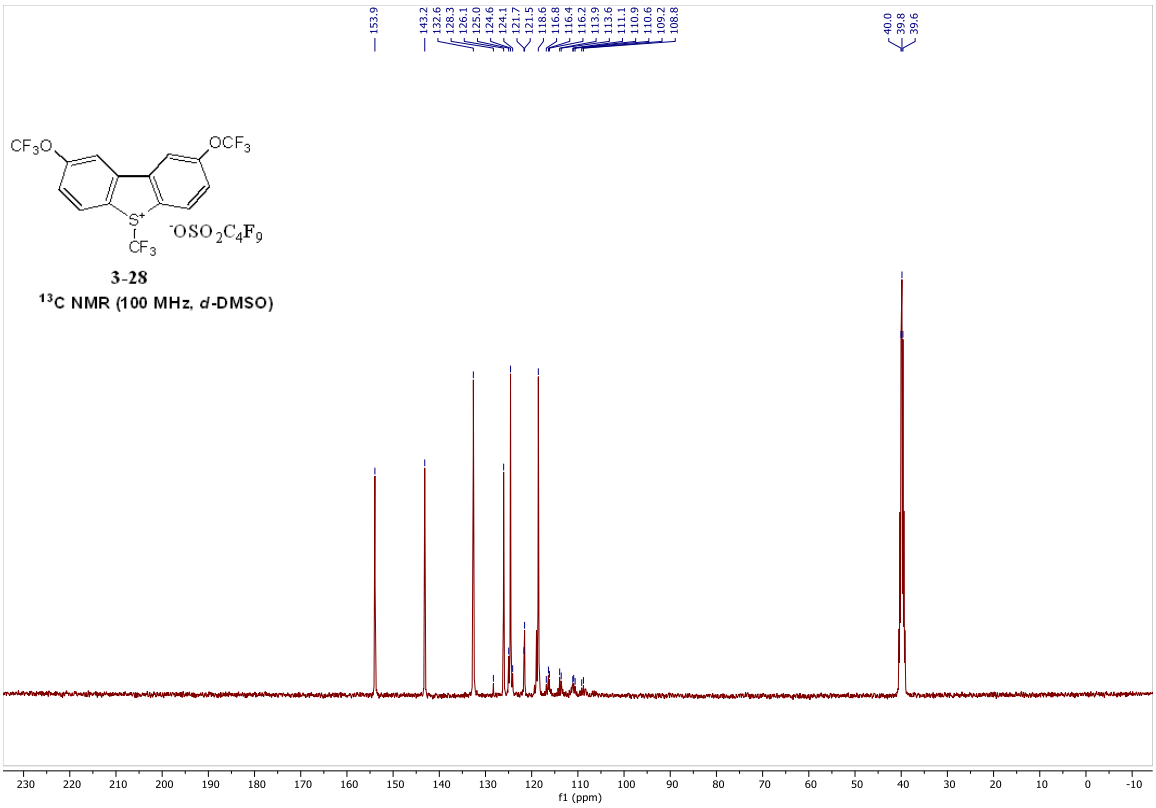
^{19}F NMR (376 MHz, $CDCl_3$)


OCF3
EtO
N
OEt
O
O
O
3-48
1H NMR (400 MHz, CDCl3)
7.26
4.18
4.16
4.14
4.12
3.29
3.27
3.25
2.62
2.61
2.59
1.28
1.26
1.24
4.00
4.18
4.14
6.02
f1 (ppm)


OCF3
EtO
N
OEt
O
O
O
3-48
13C NMR (100 MHz, CDCl3)
171.3
126.6
124.1
121.5
118.9
77.3
77.0
76.7
60.6
54.5
31.3
14.0
f1 (ppm)

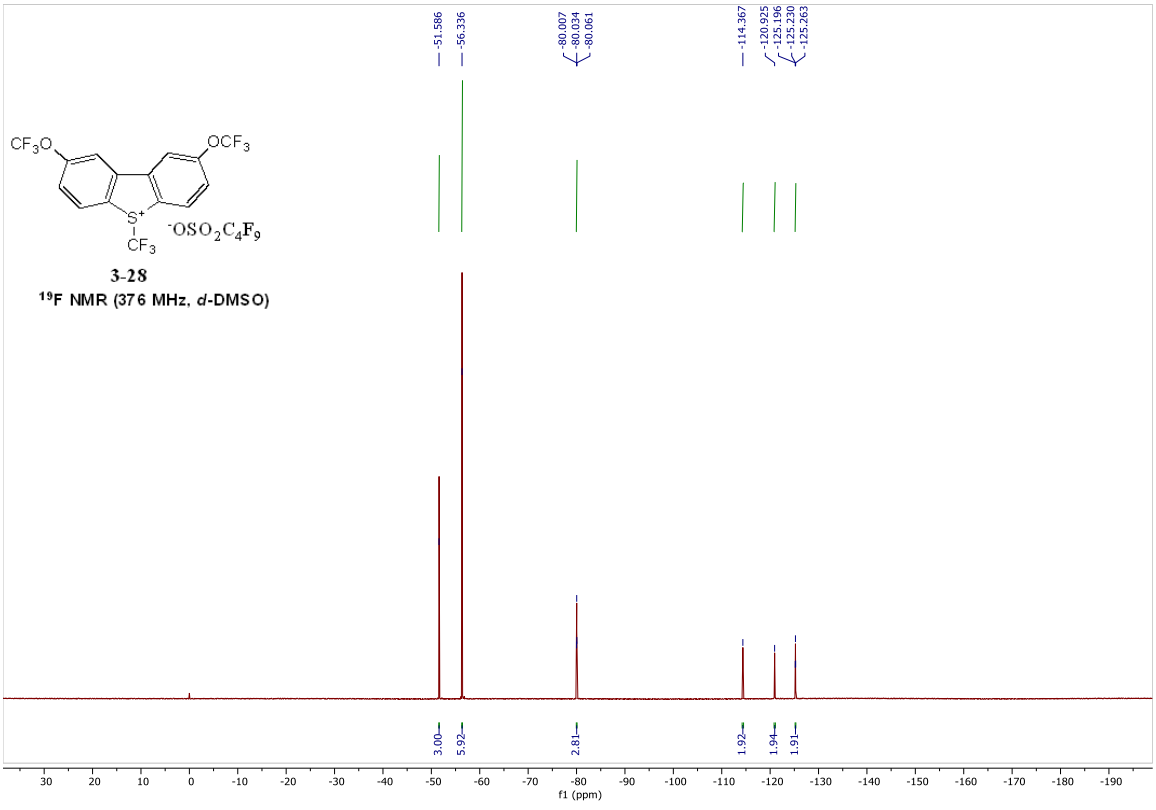

EtO
OCF3
N
OEt
O
O
O
3-48
19F NMR (376 MHz, CDCl3)
-62.82
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)


8.86
8.84
8.80
8.79
7.99
7.98
7.98
7.98
7.97
7.96
7.96
7.96
CF3O
OCF3
S+
CF3
-OSO2C4F9
3-28
1H NMR (400 MHz, d-DMSO)
1.96
1.96
1.99
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)



3-28

^{13}C NMR (100 MHz, *d*-DMSO)

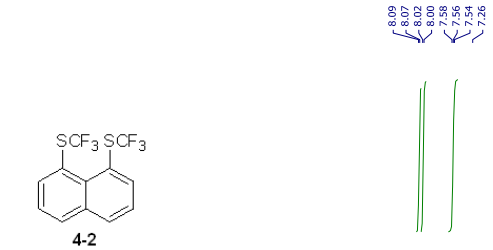


3-28

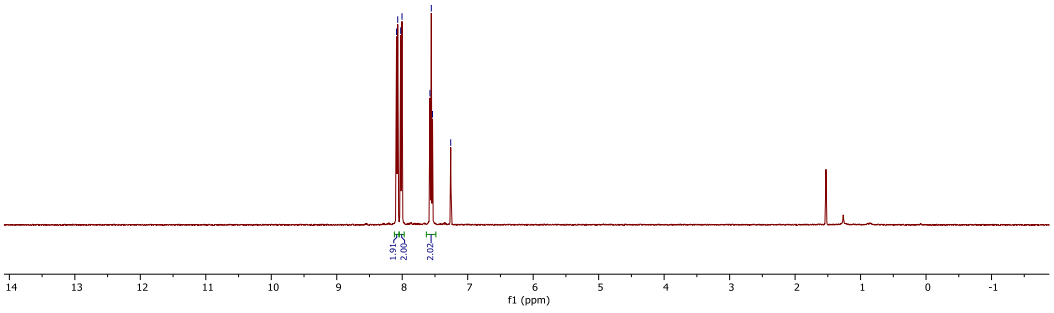
^{19}F NMR (376 MHz, *d*-DMSO)

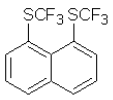
APPENDIX C: NMR DATA OF DESIGN AND ATTEMPTS TO SYNTHESIZE NEW DITHIADICATION-TYPE TRIFLUOROMETHYLATING AGENTS

4.9.14. NMR Spectral data of compounds **4-2** to **4-39**



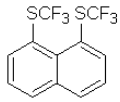
4-2
^{1}H NMR (400 MHz, $CDCl_3$)





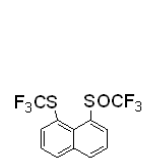
4-2

^{13}C NMR (100 MHz, $CDCl_3$)



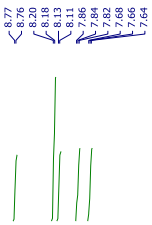
4-2

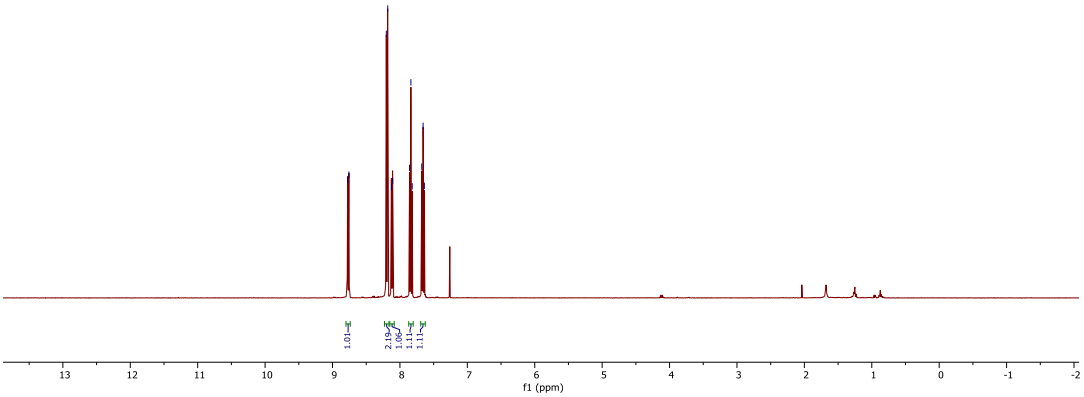
^{19}F NMR (376 MHz, $CDCl_3$)

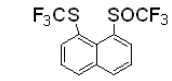


4-3

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

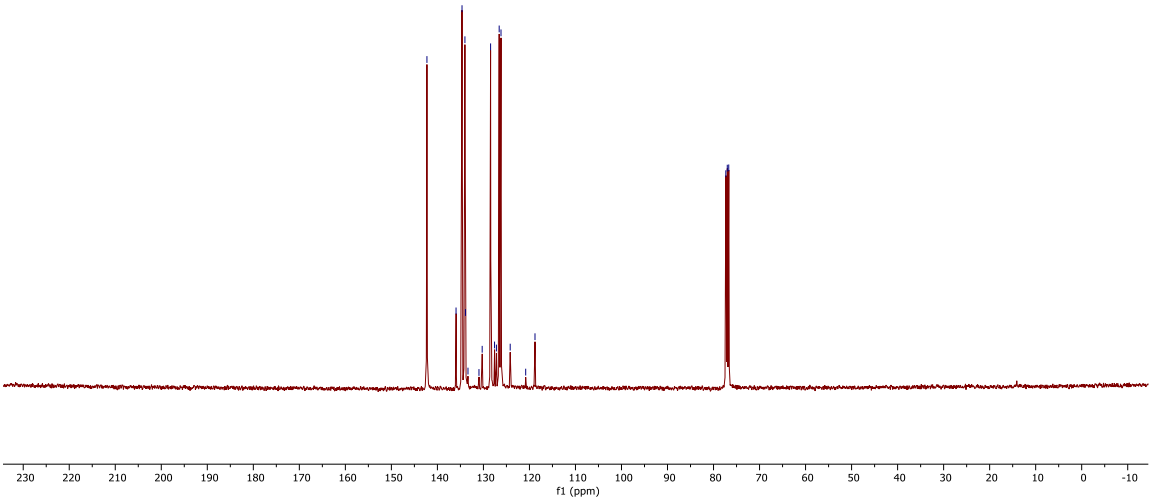


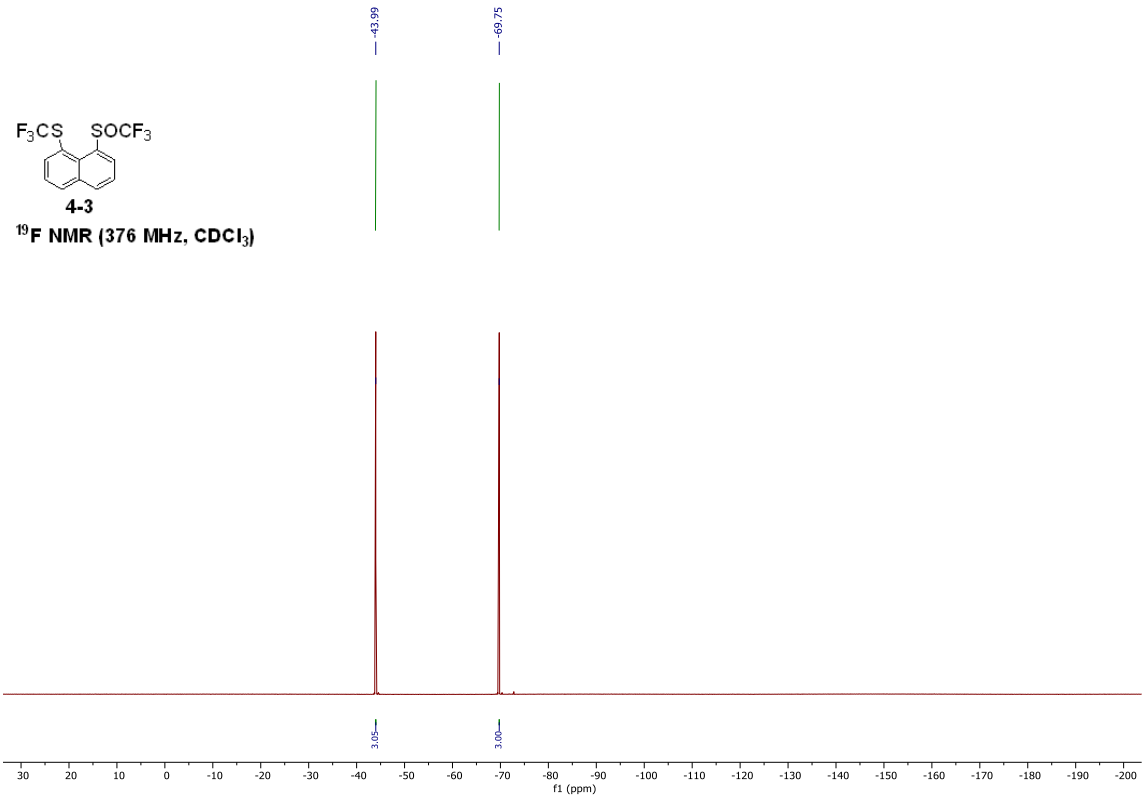


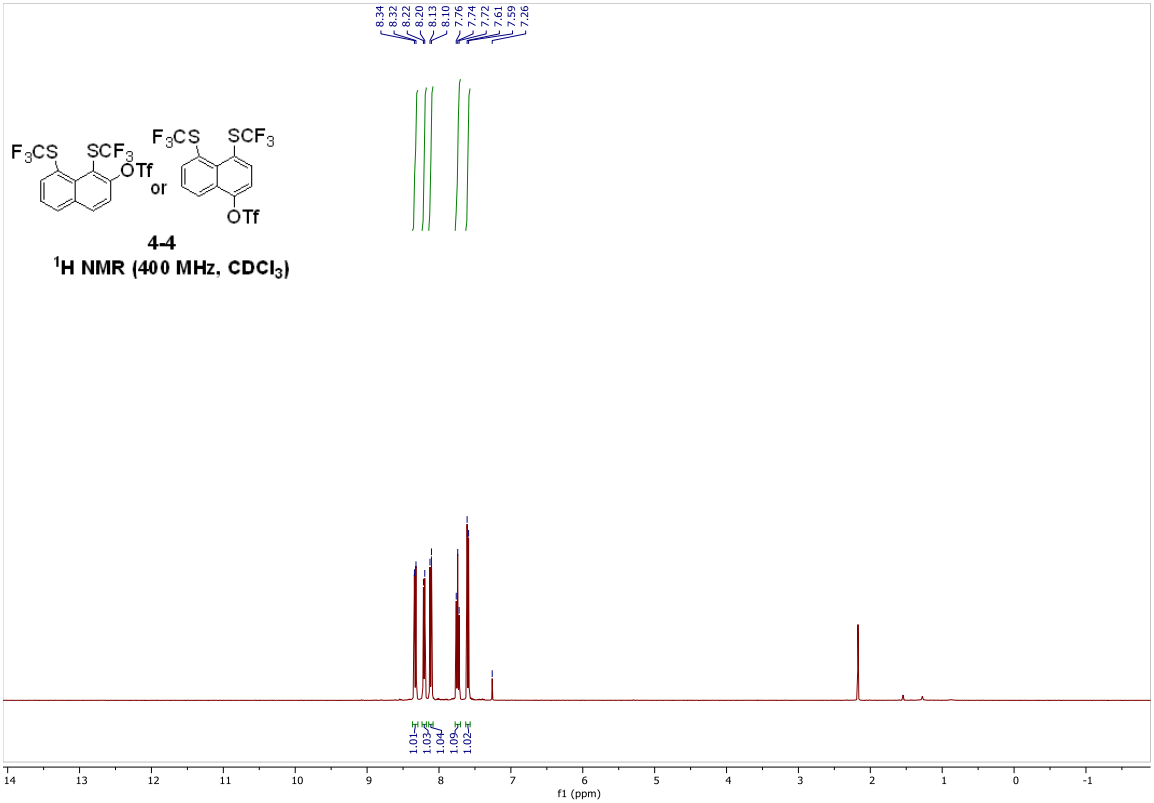


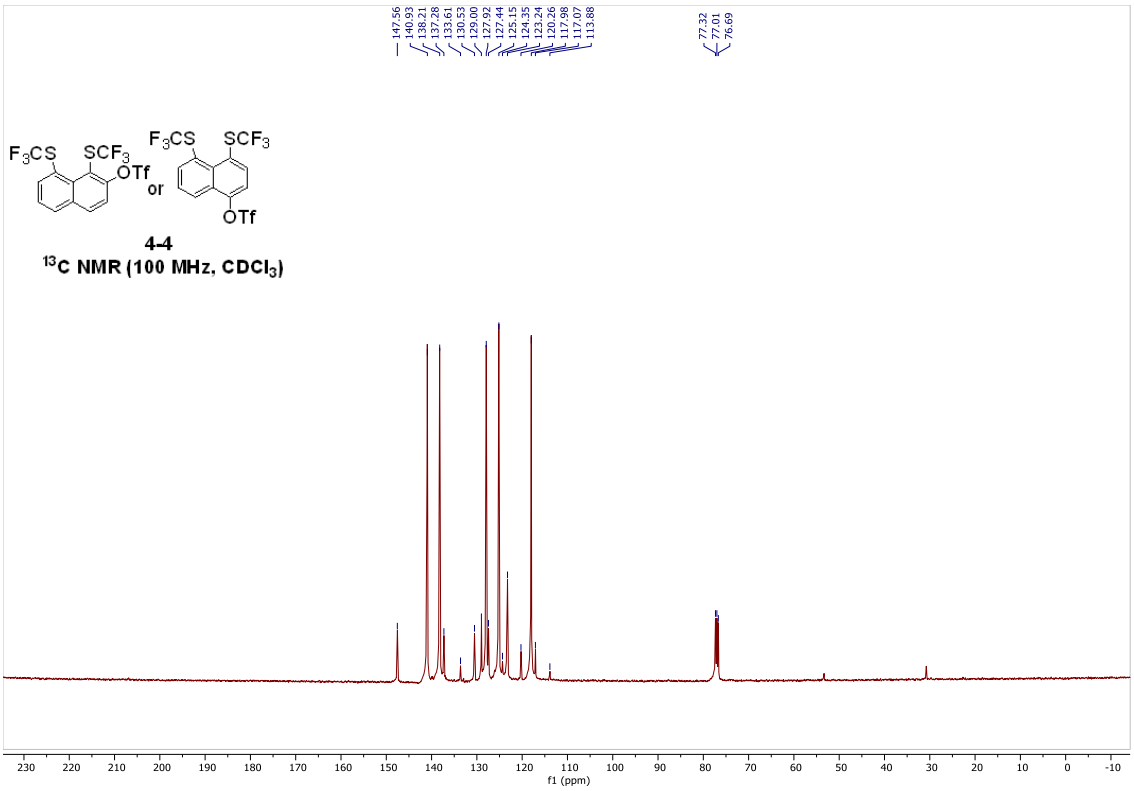
4-3

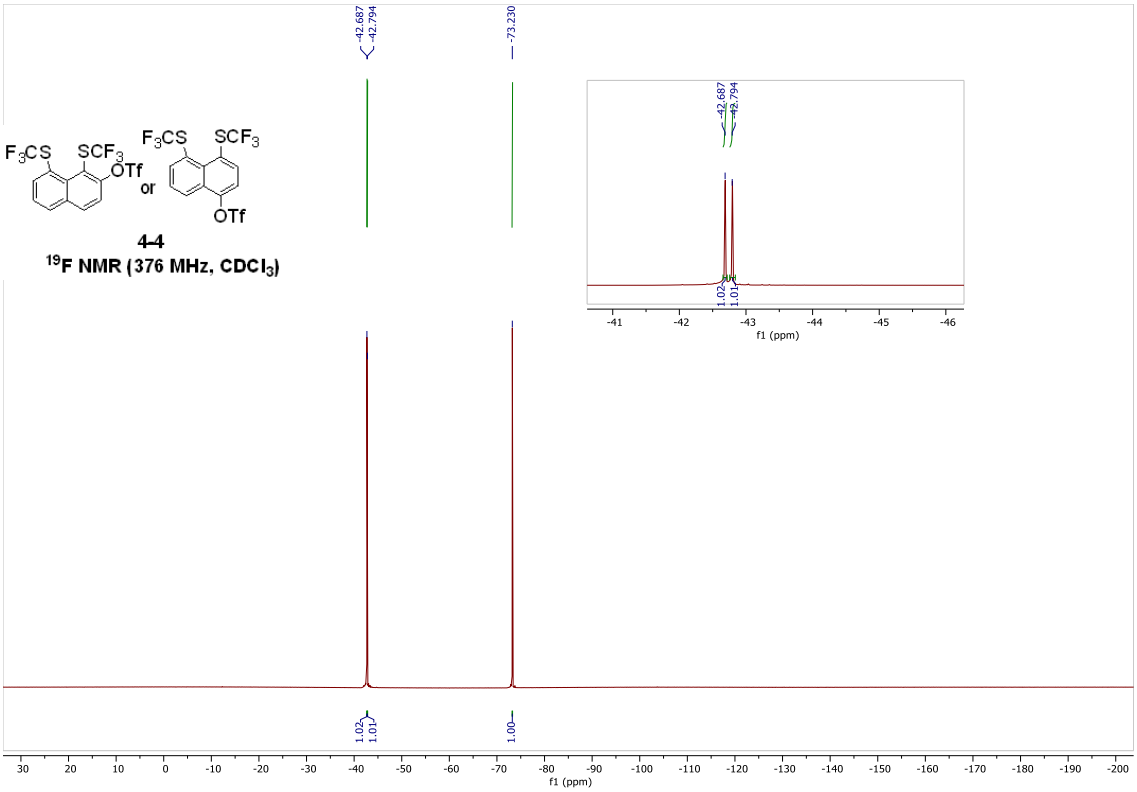
^{13}C NMR (100 MHz, $CDCl_3$)

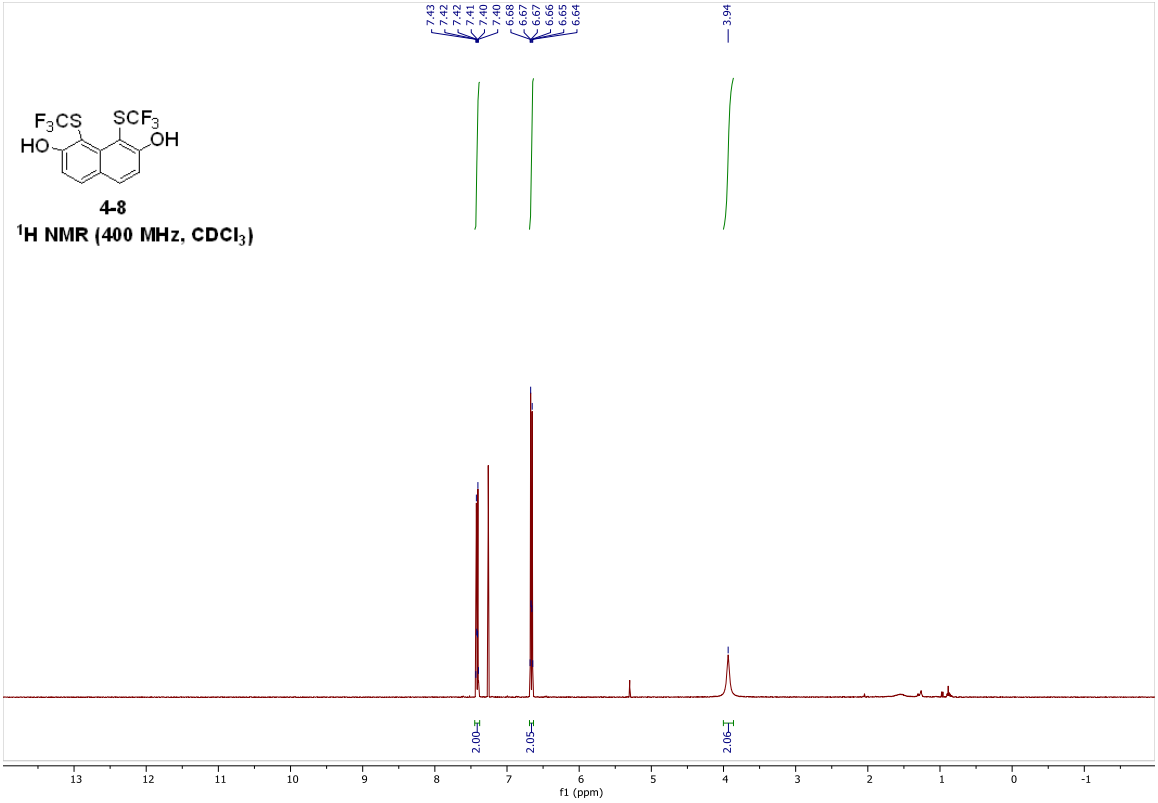



F3CS
SOCF3
4-3
19F NMR (376 MHz, CDCl3)
-43.99
-69.75
3.05
3.00
f1 (ppm)


F3CS
SCF3
OTf
or
F3CS
SCF3
OTf
4-4
1H NMR (400 MHz, CDCl3)
8.34
8.32
8.22
8.20
8.13
8.10
7.76
7.74
7.72
7.61
7.59
7.26
1.01
1.03
1.04
1.09
1.02
f1 (ppm)

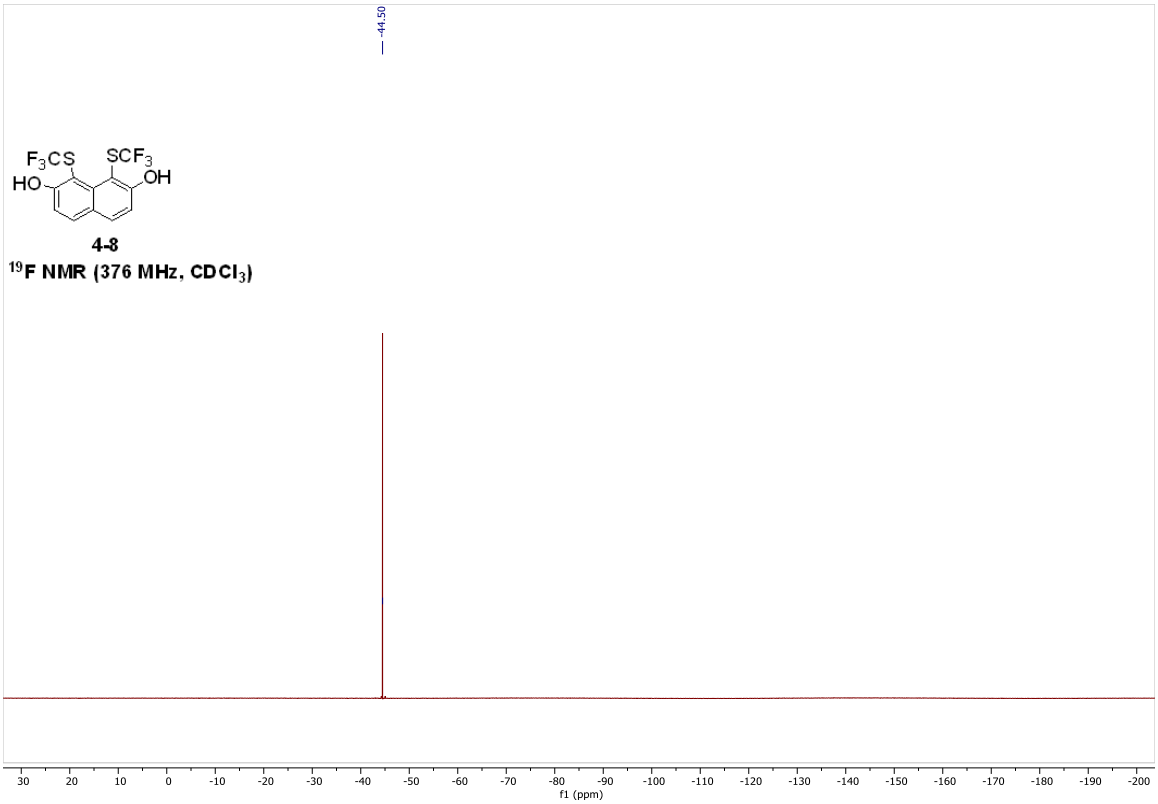

147.56
140.93
138.21
137.28
133.61
130.53
129.00
127.92
127.44
125.15
124.35
123.24
120.26
117.98
117.07
113.88
77.32
77.01
76.69
F3CS
SCF3
OTf
or
F3CS
SCF3
OTf
4-4
13C NMR (100 MHz, CDCl3)
f1 (ppm)


-42.687
-42.794
-73.230
F3CS
SCF3
OTf
or
F3CS
SCF3
OTf
4-4
19F NMR (376 MHz, CDCl3)
1.02
1.01
1.00
f1 (ppm)



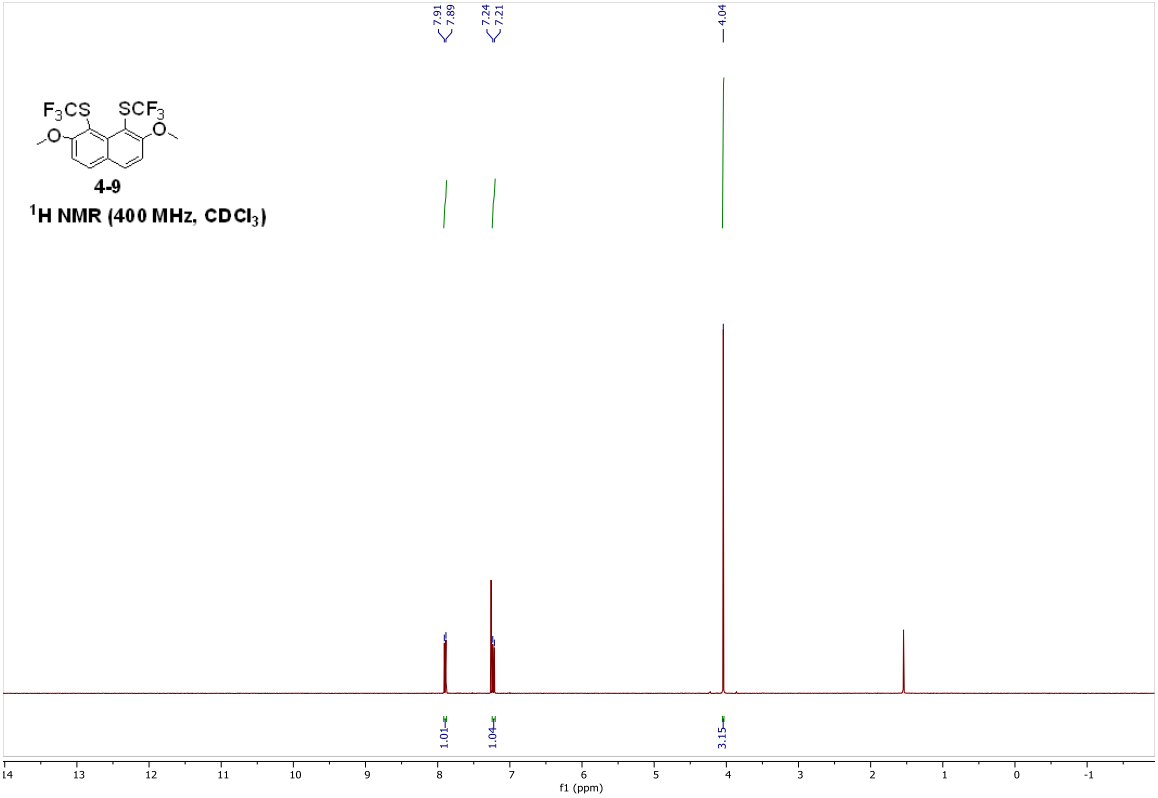
4-8

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



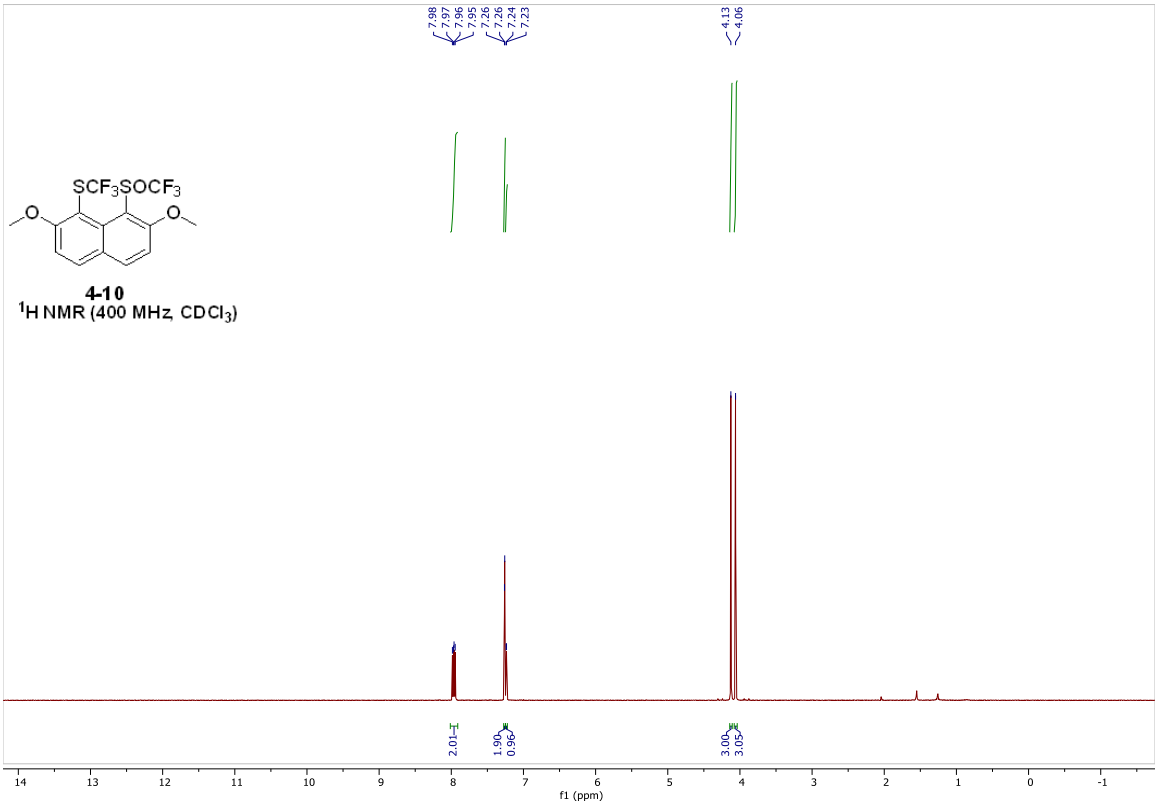
4-8

^{19}F NMR (376 MHz, $CDCl_3$)



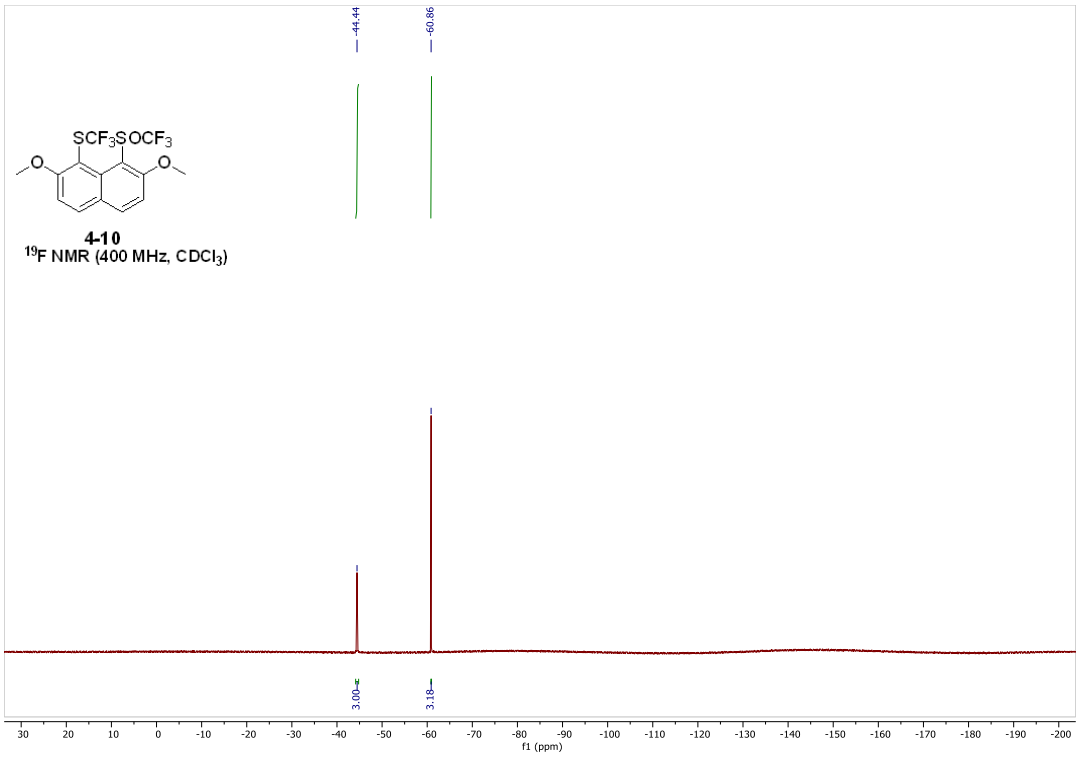
4-9

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



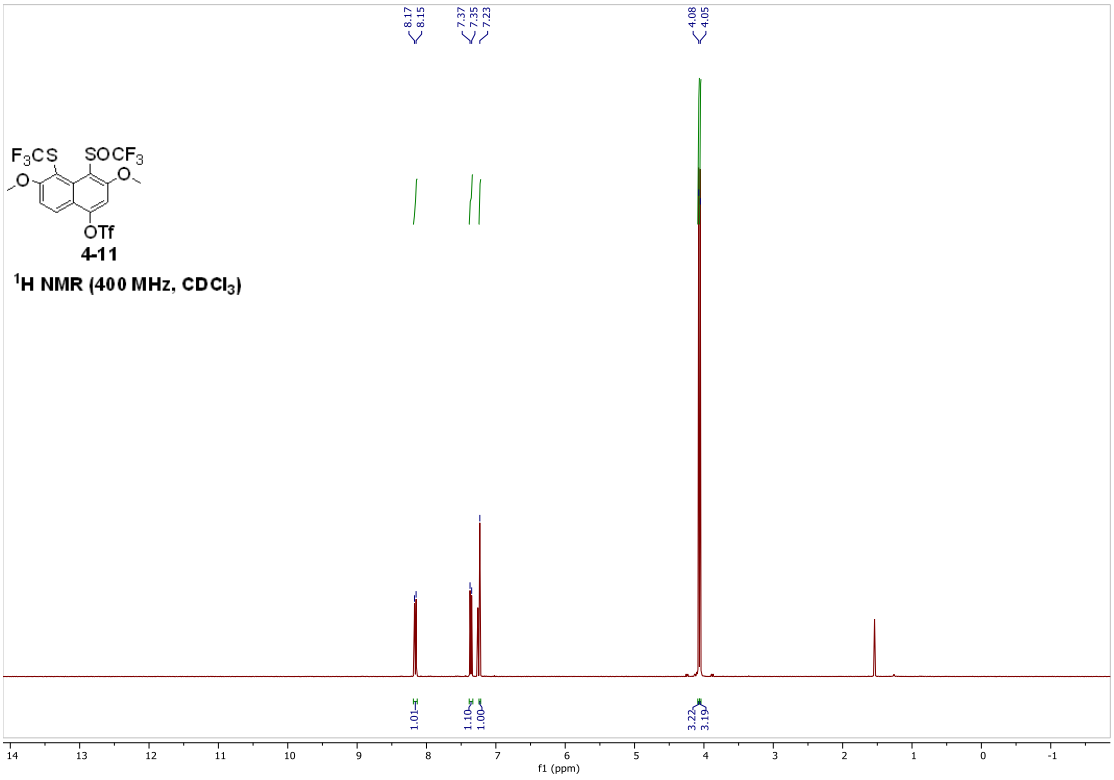
4-10

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



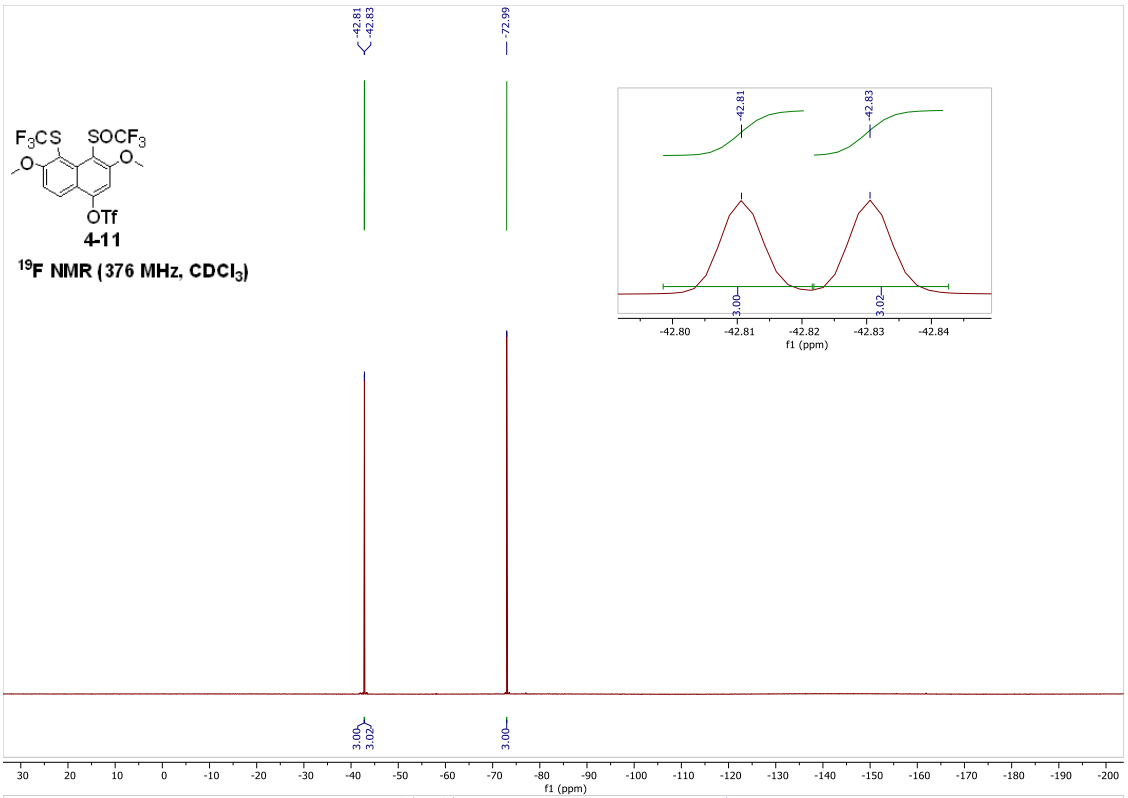
4-10

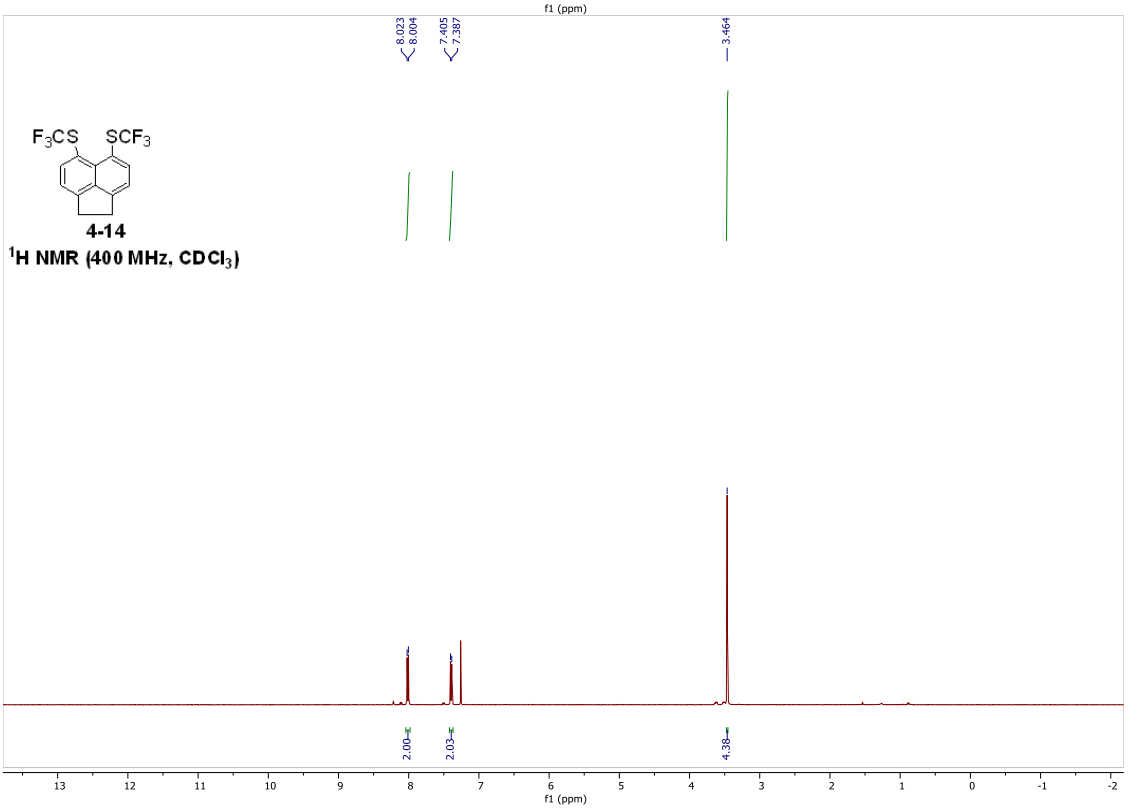
^{19}F NMR (400 MHz, $CDCl_3$)

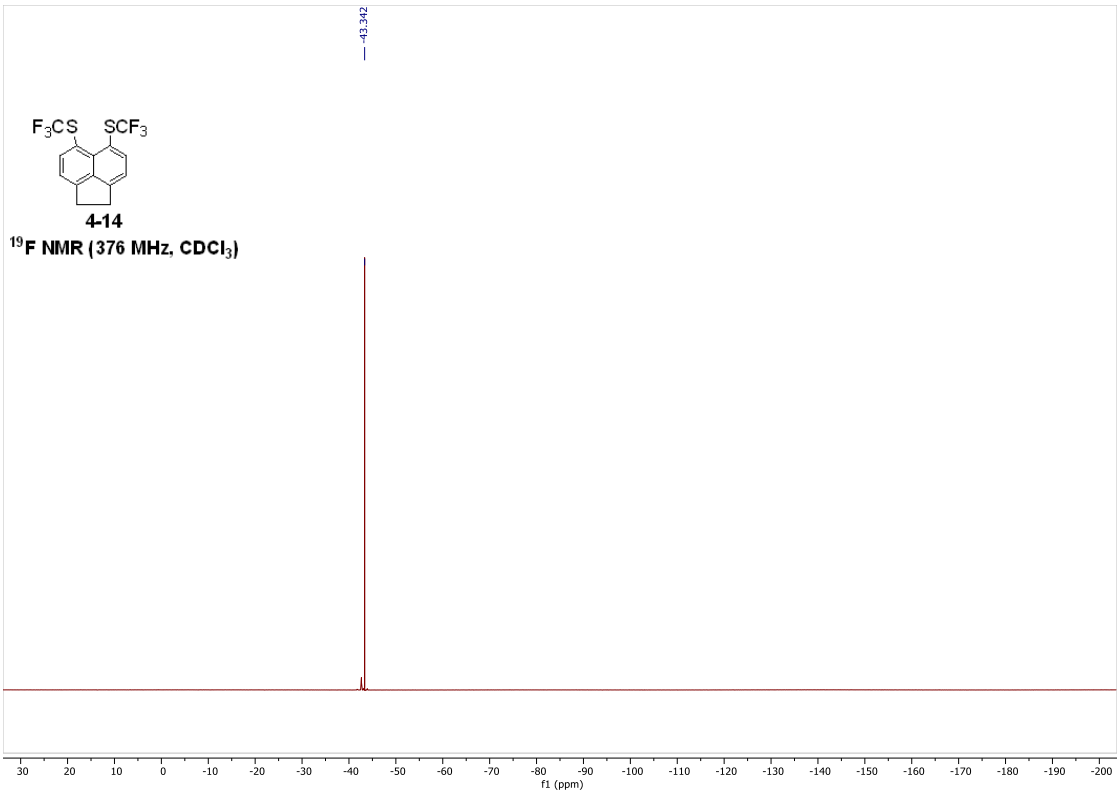


4-11

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

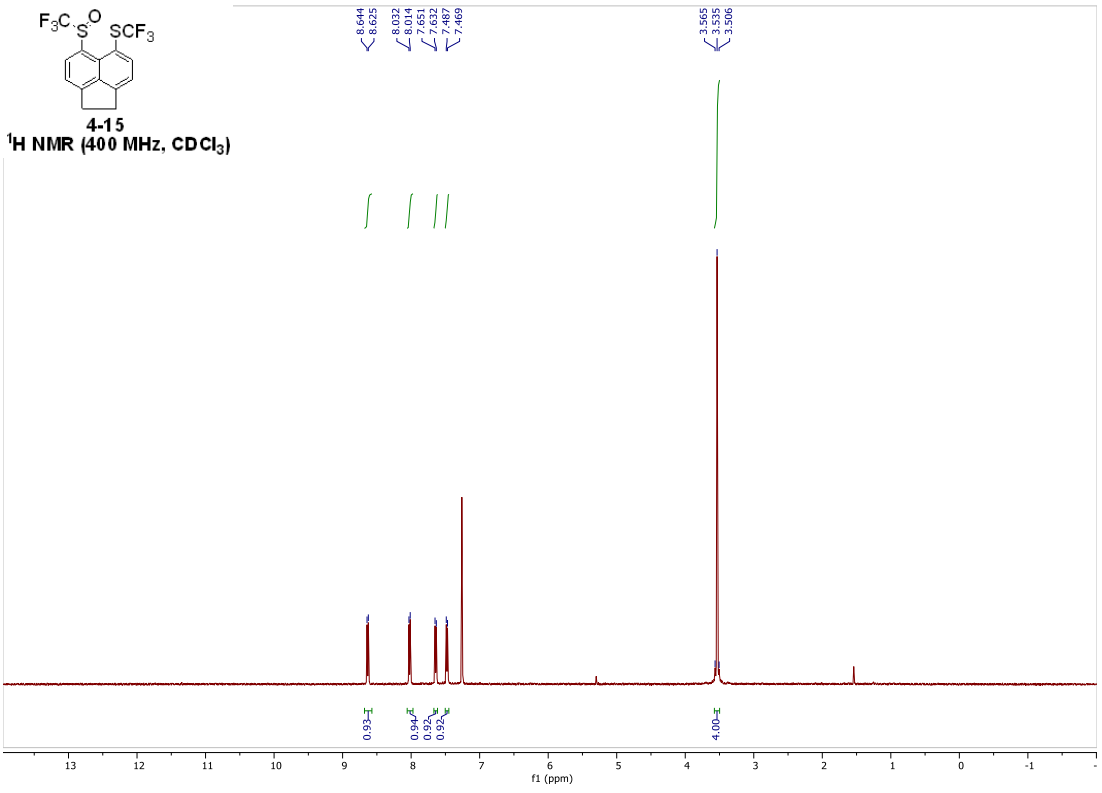

-42.81
-42.83
-72.99
F3CS
SOCF3
O
O
OTf
4-11
19F NMR (376 MHz, CDCl3)
3.00
3.02
3.00
f1 (ppm)


8.023
8.004
7.405
7.387
3.464
F3CS
SCF3
4-14
1H NMR (400 MHz, CDCl3)
2.00
2.03
4.38
f1 (ppm)



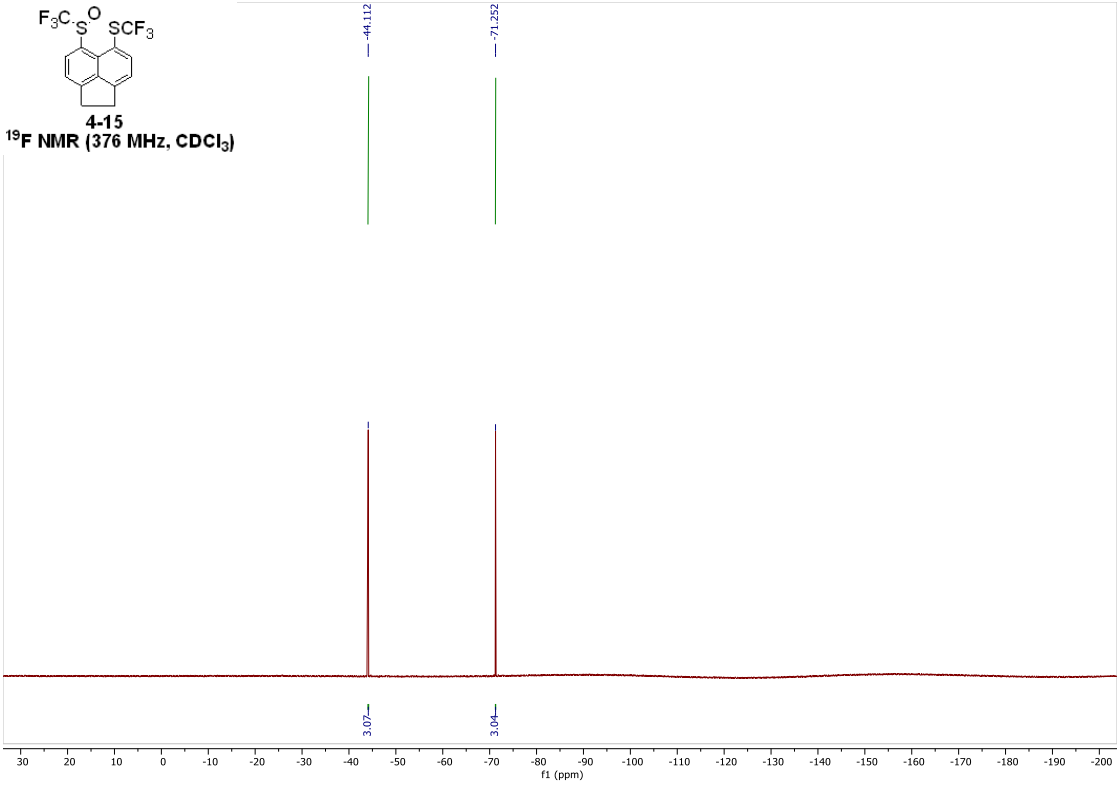
4-14

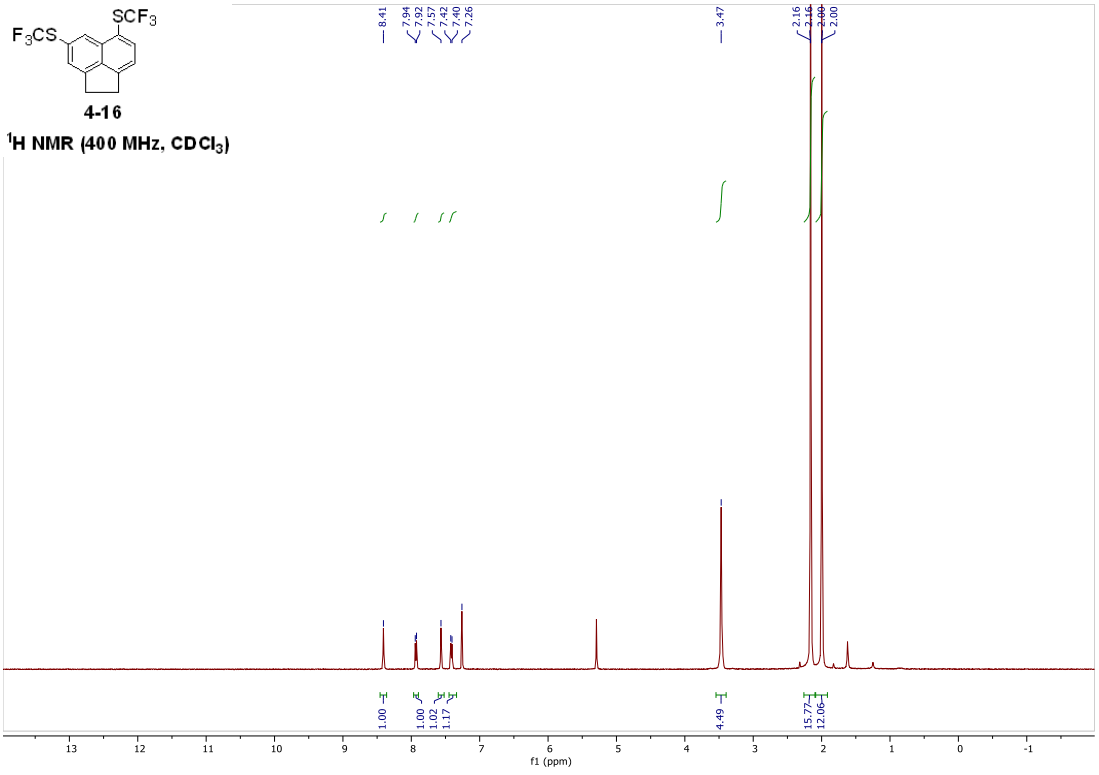
^{19}F NMR (376 MHz, $CDCl_3$)

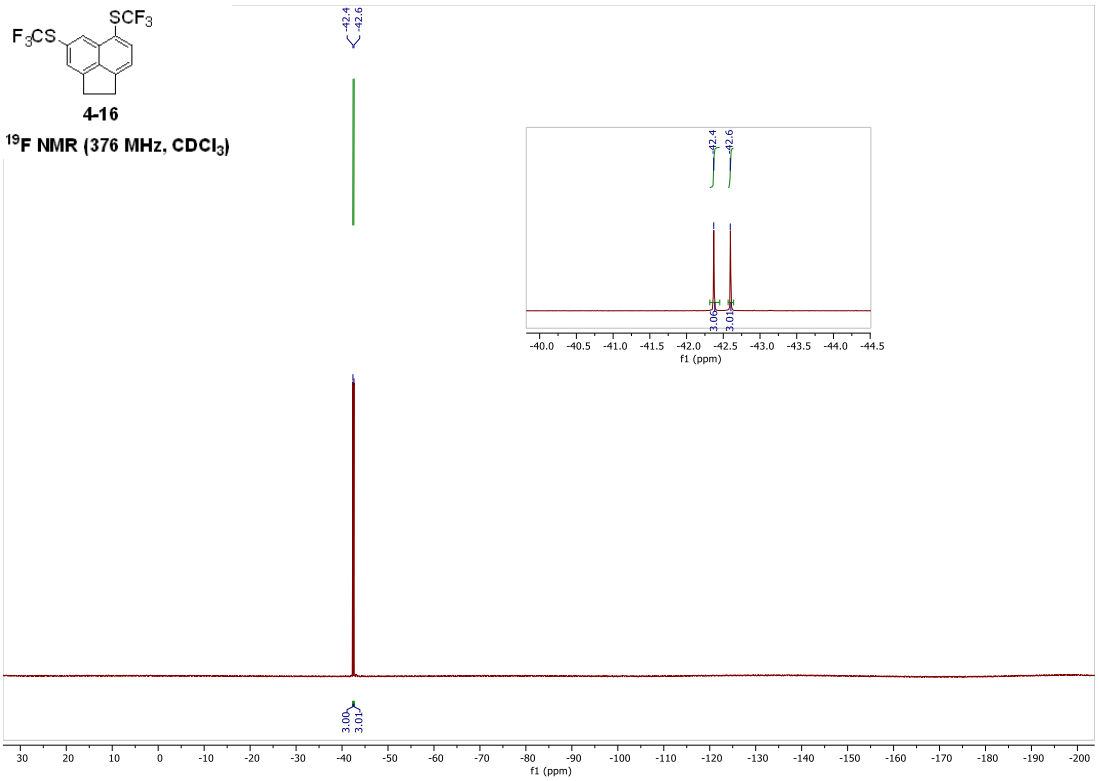


4-15

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

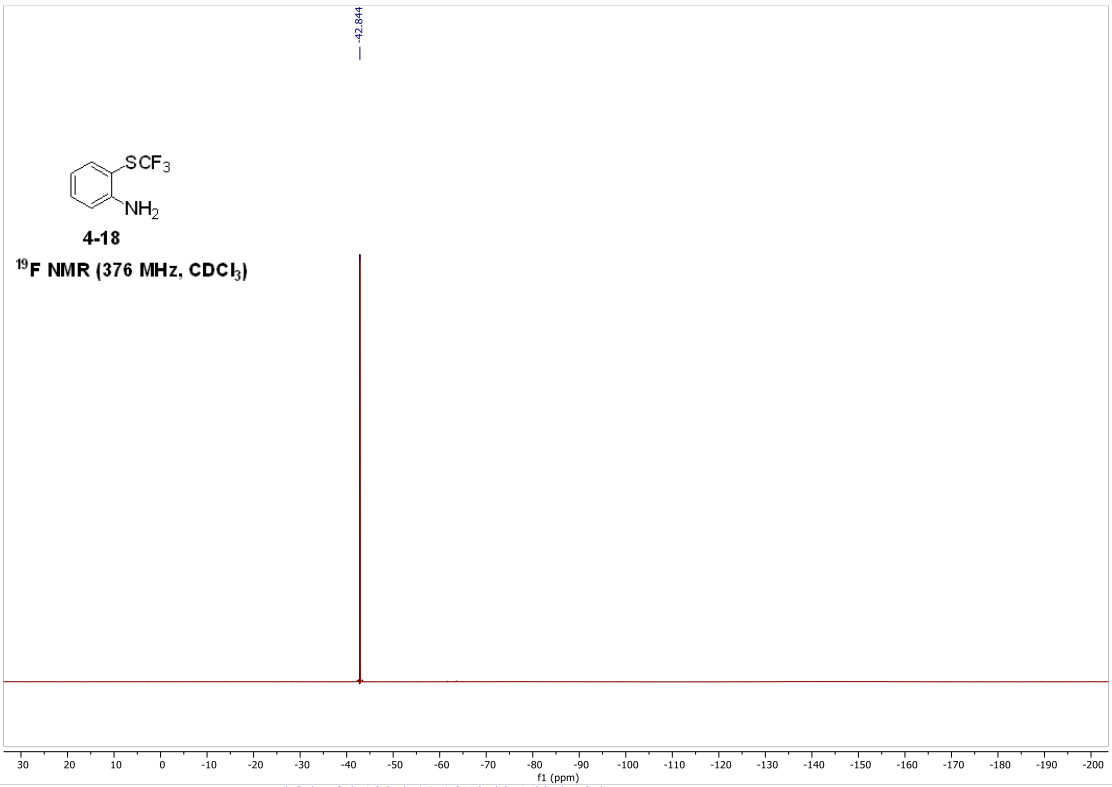

F3C
S
O
SCF3
4-15
19F NMR (376 MHz, CDCl3)
-44.112
-71.252
3.07
3.04
f1 (ppm)

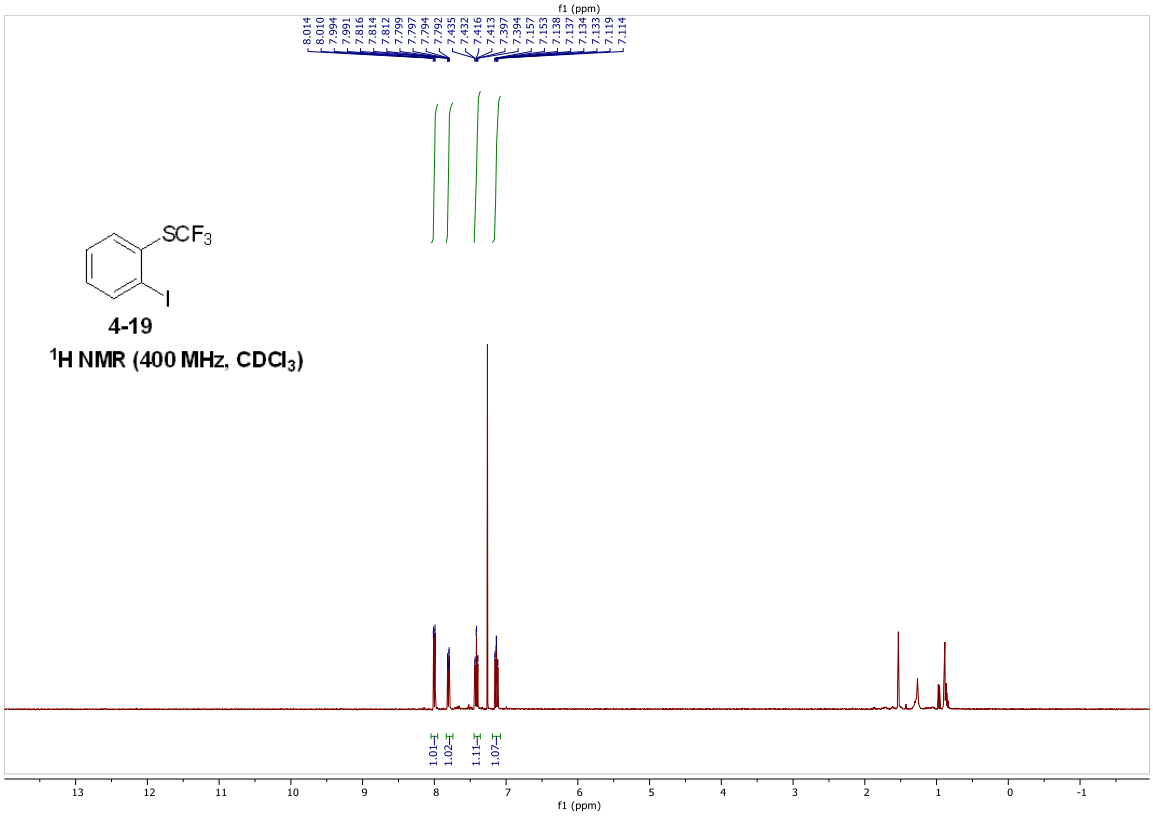

F3CS
SCF3
4-16
1H NMR (400 MHz, CDCl3)
8.41
7.94
7.92
7.57
7.42
7.40
7.26
3.47
2.16
2.00
1.00
1.00
1.02
1.17
4.49
15.77
12.06
f1 (ppm)

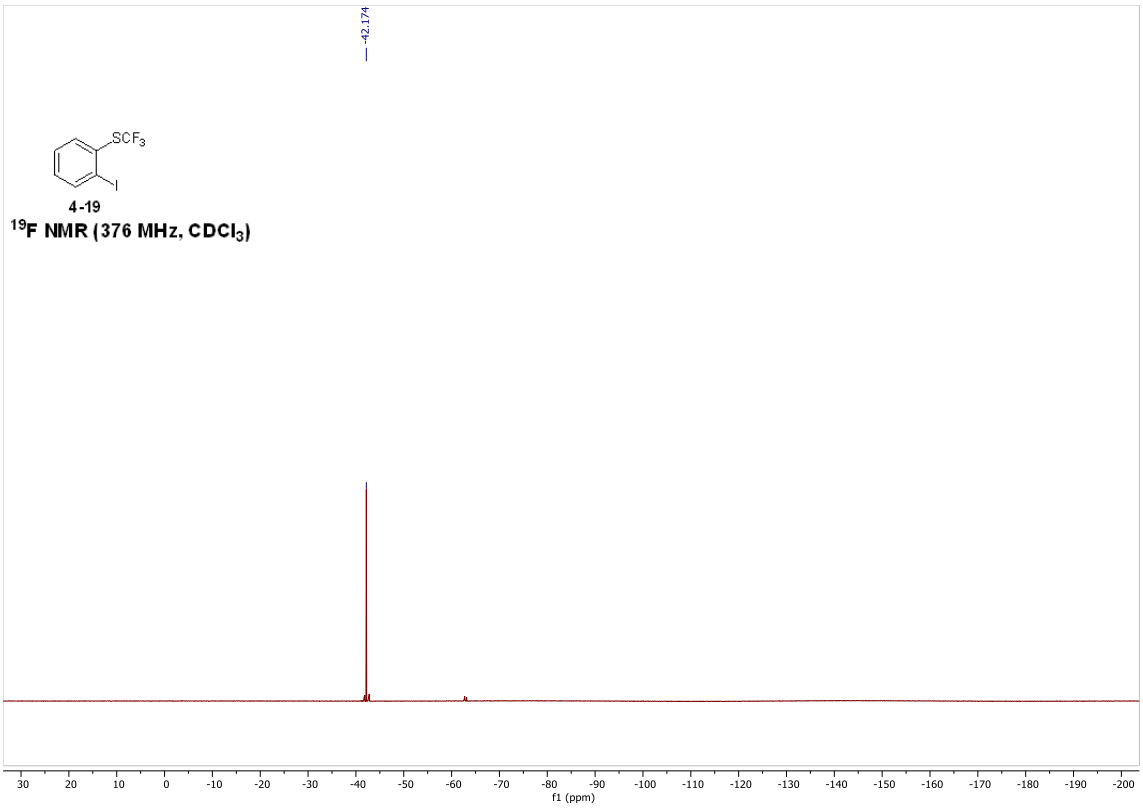


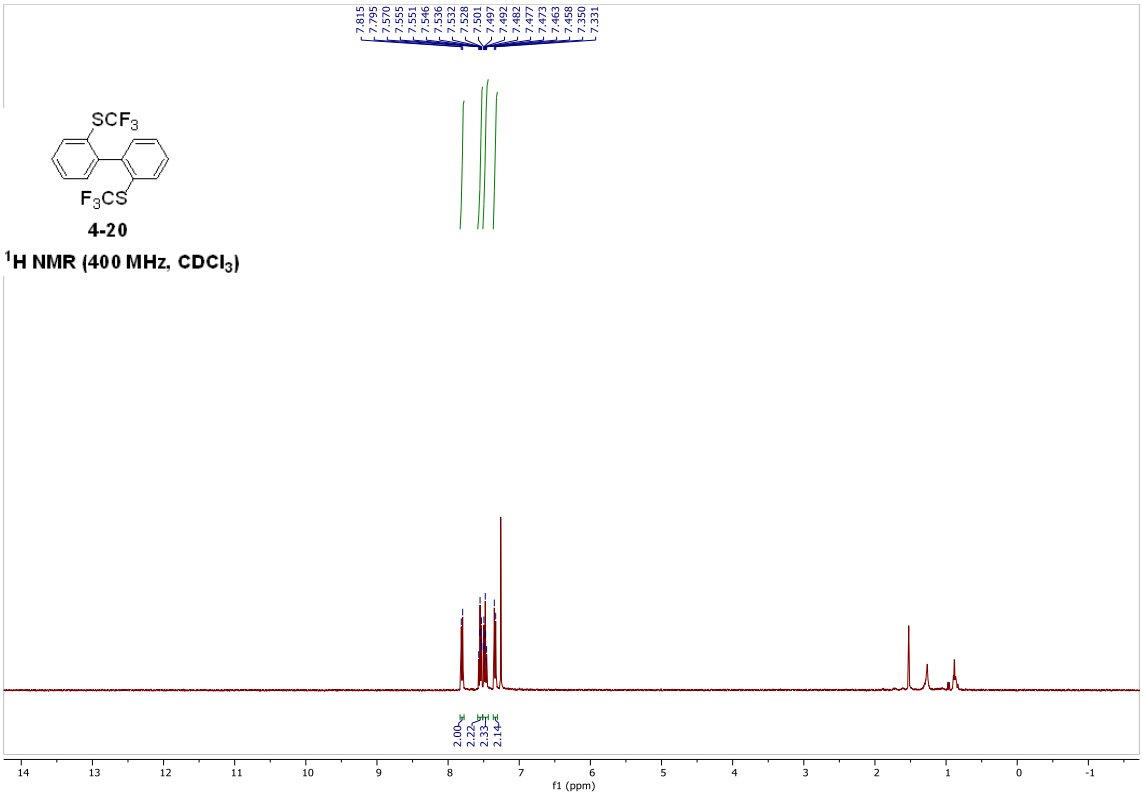
4-16

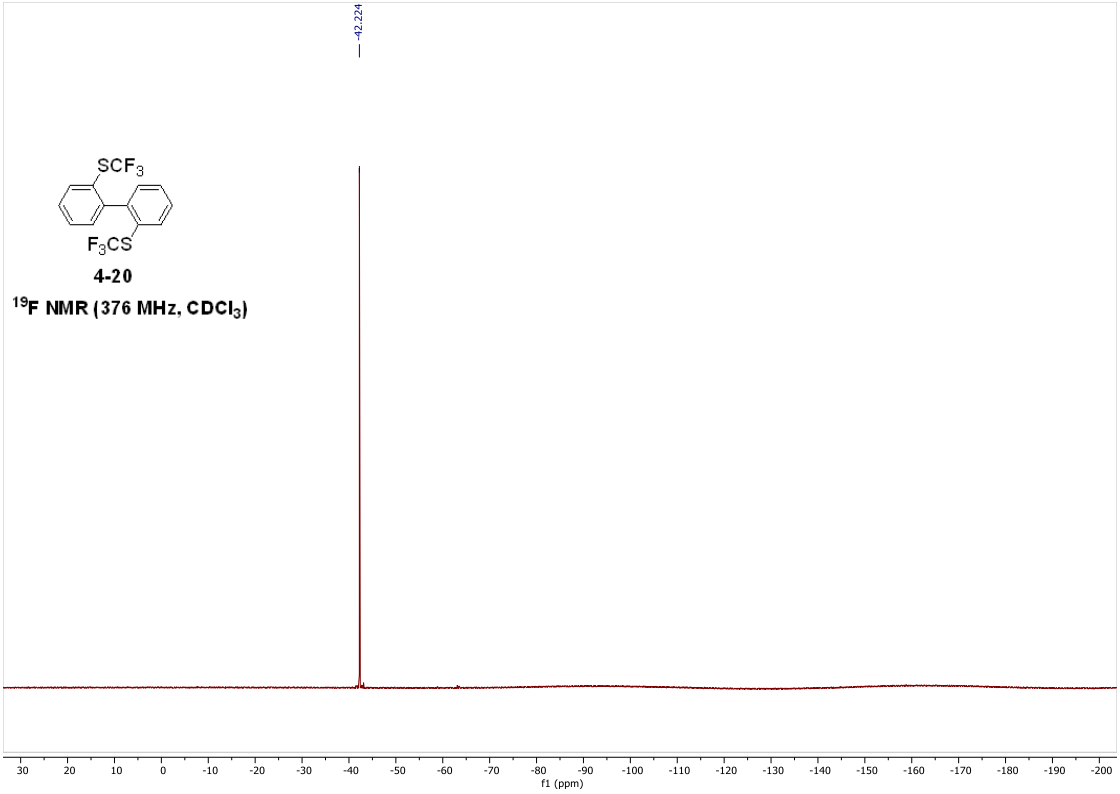
^{19}F NMR (376 MHz, $CDCl_3$)

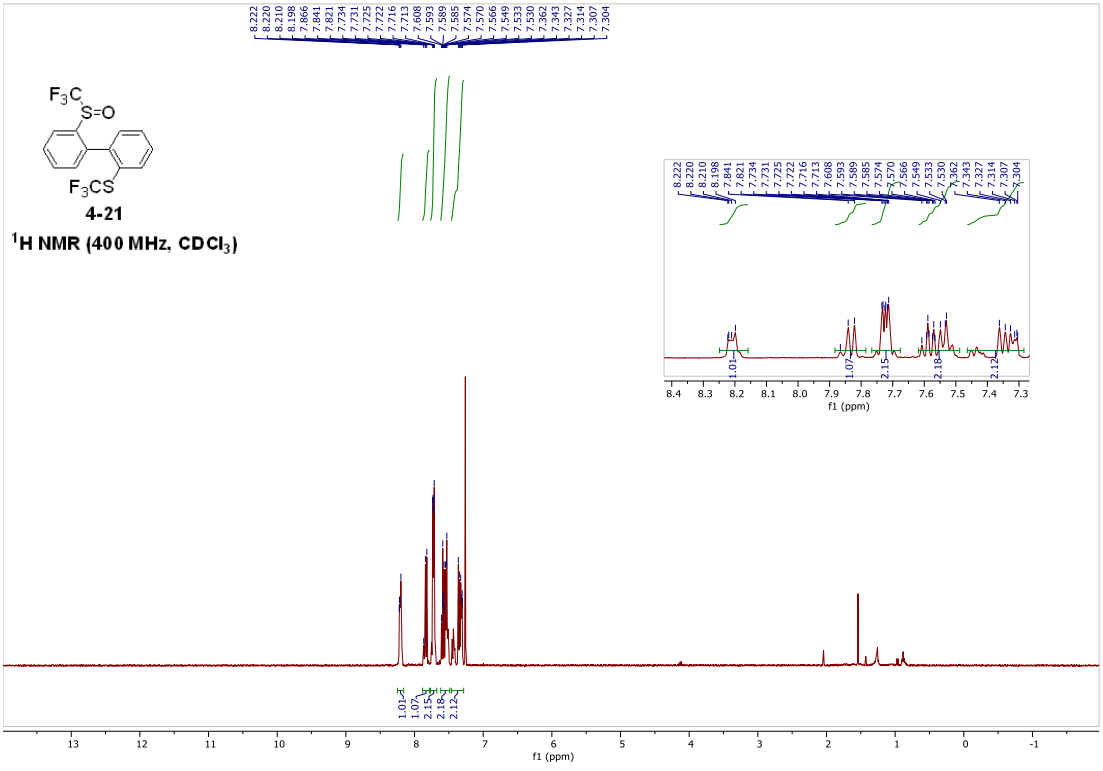

-42.844
SCF3
NH2
4-18
19F NMR (376 MHz, CDCl3)
f1 (ppm)

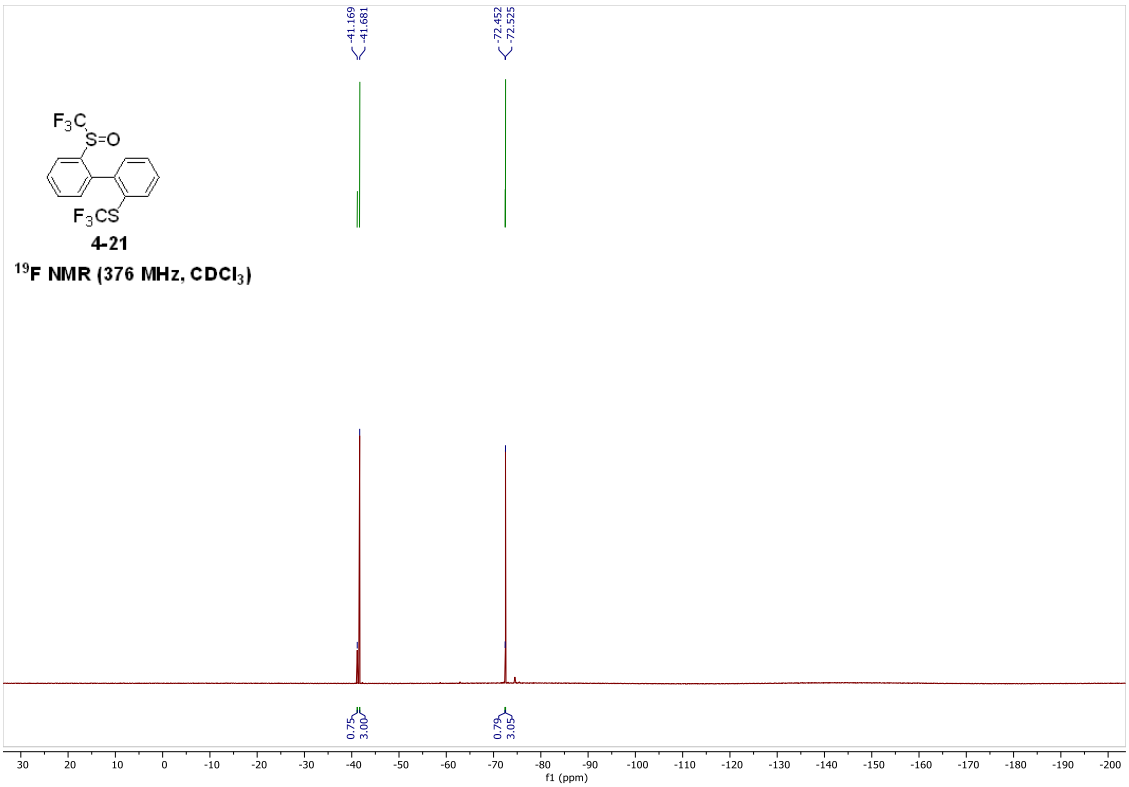

8.014
8.010
7.994
7.991
7.816
7.814
7.812
7.799
7.797
7.794
7.792
7.435
7.432
7.416
7.413
7.397
7.394
7.157
7.153
7.138
7.137
7.134
7.133
7.119
7.114
SCF3
I
4-19
1H NMR (400 MHz, CDCl3)
1.01
1.02
1.11
1.07
f1 (ppm)


-42.174
SCF3
I
4-19
19F NMR (376 MHz, CDCl3)
f1 (ppm)


7.815
7.795
7.750
7.555
7.551
7.546
7.536
7.532
7.528
7.501
7.497
7.492
7.482
7.477
7.473
7.463
7.458
7.350
7.331
SCF3
F3CS
4-20
1H NMR (400 MHz, CDCl3)
2.00
2.22
2.33
2.14
f1 (ppm)

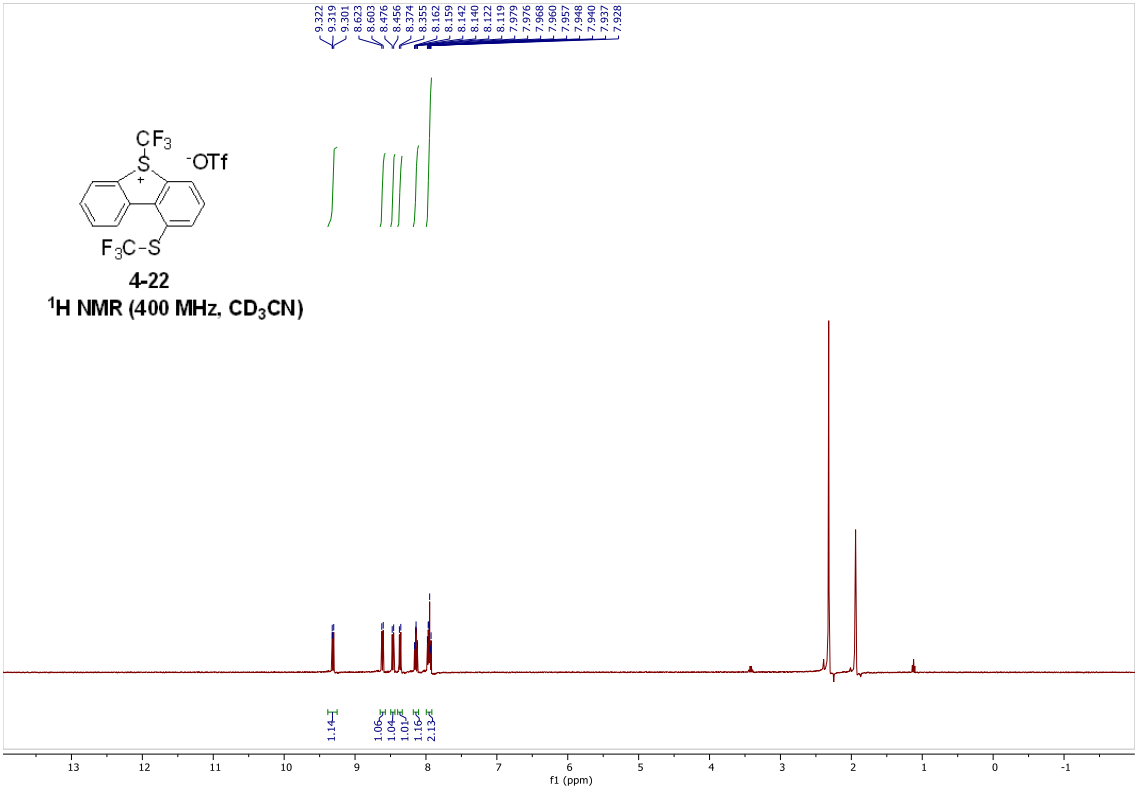

42.224
SCF3
F3CS
4-20
19F NMR (376 MHz, CDCl3)
f1 (ppm)


F3C
S=O
F3CS
4-21
1H NMR (400 MHz, CDCl3)
f1 (ppm)



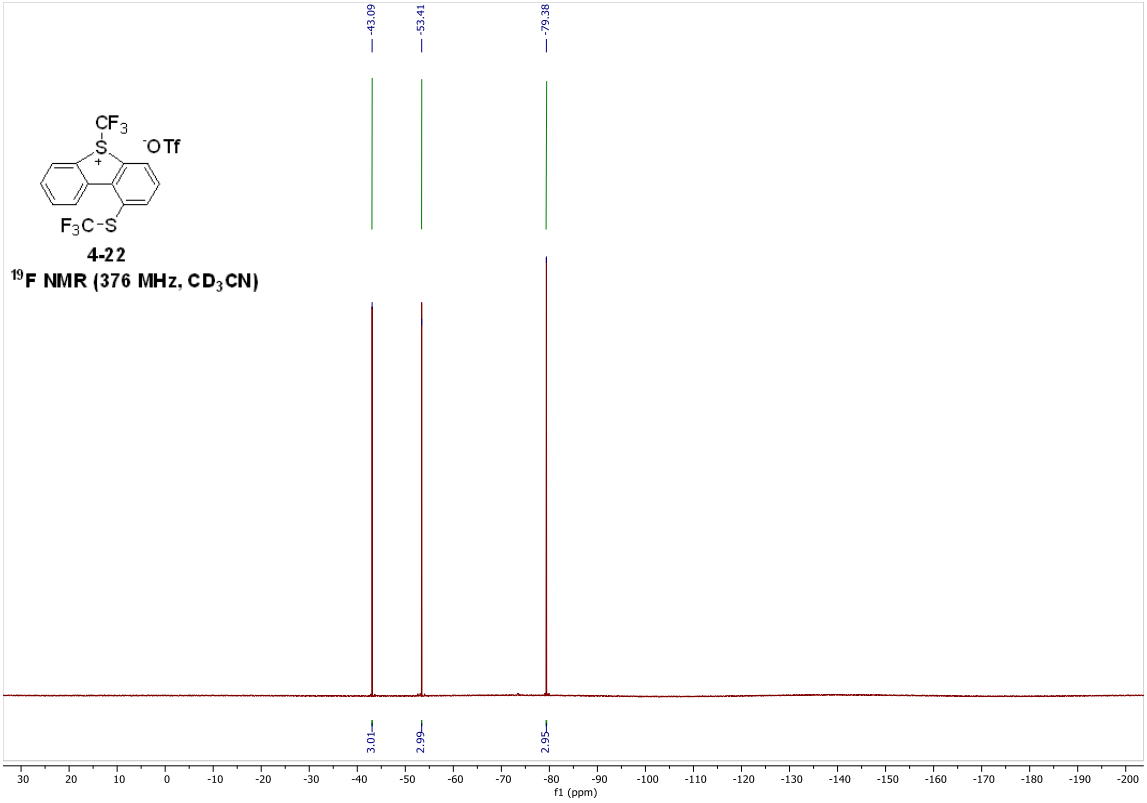
4-21

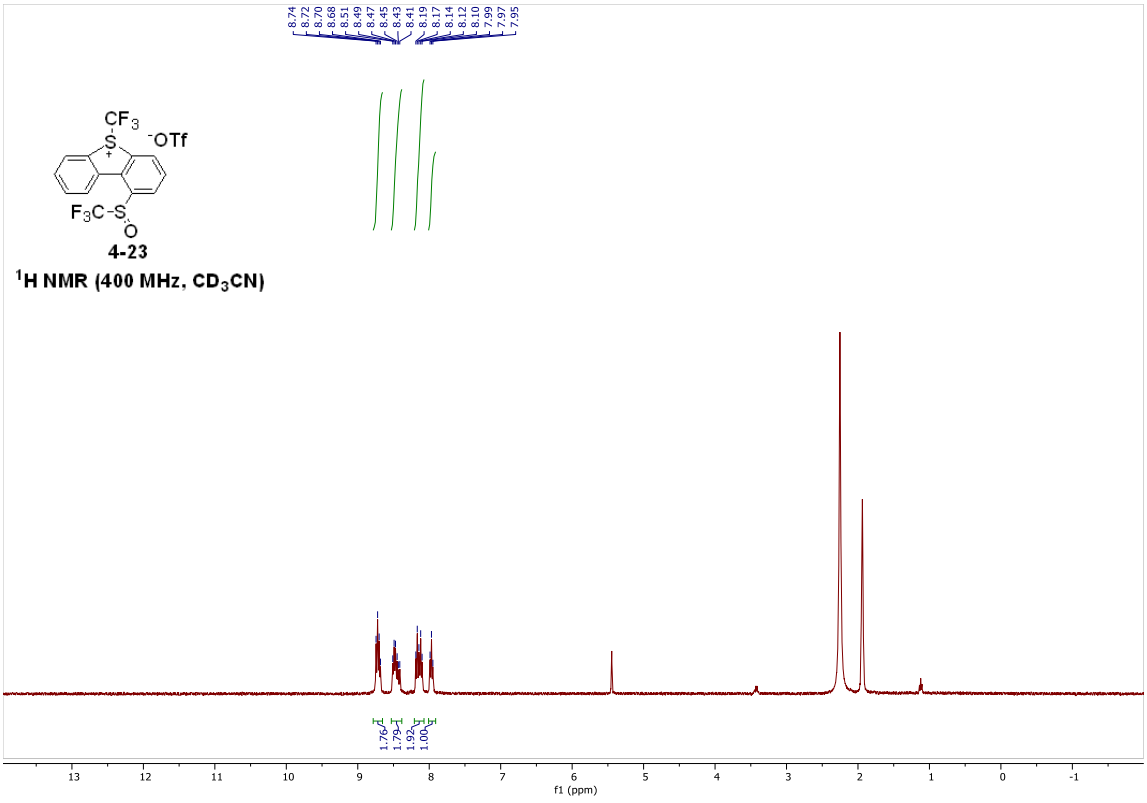
^{19}F NMR (376 MHz, $CDCl_3$)

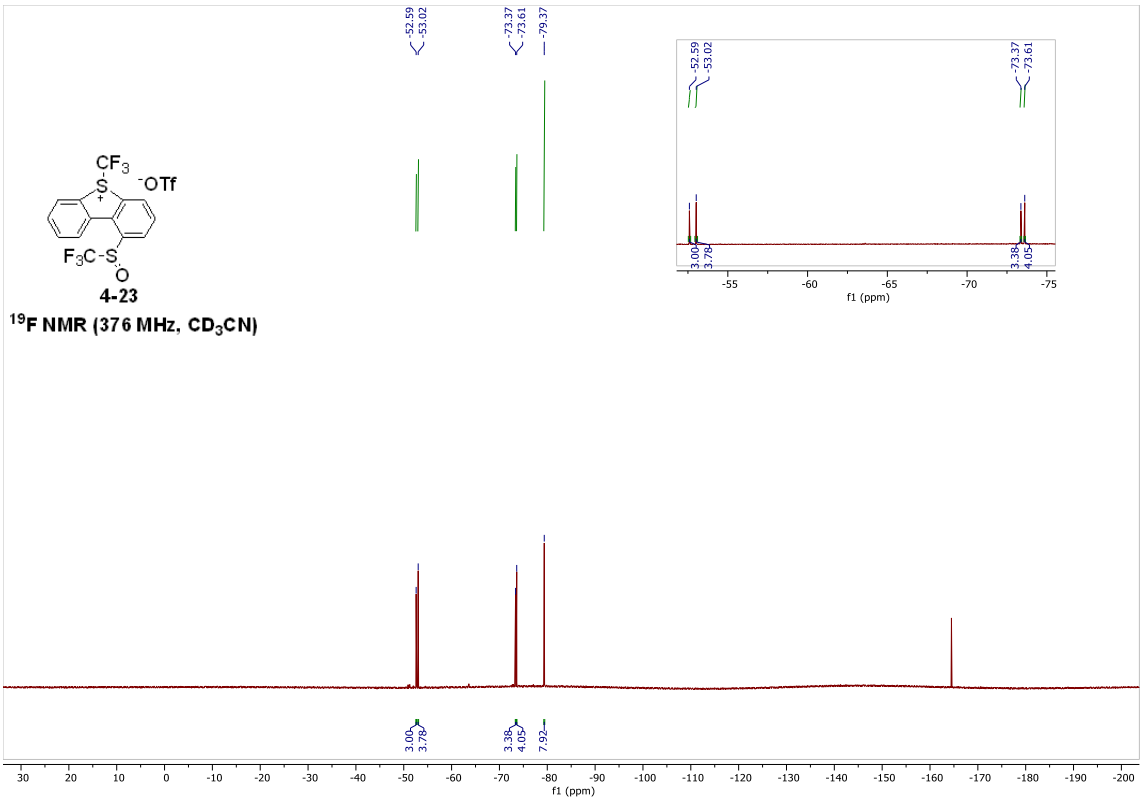


4-22

^{1}H NMR (400 MHz, CD_3CN)

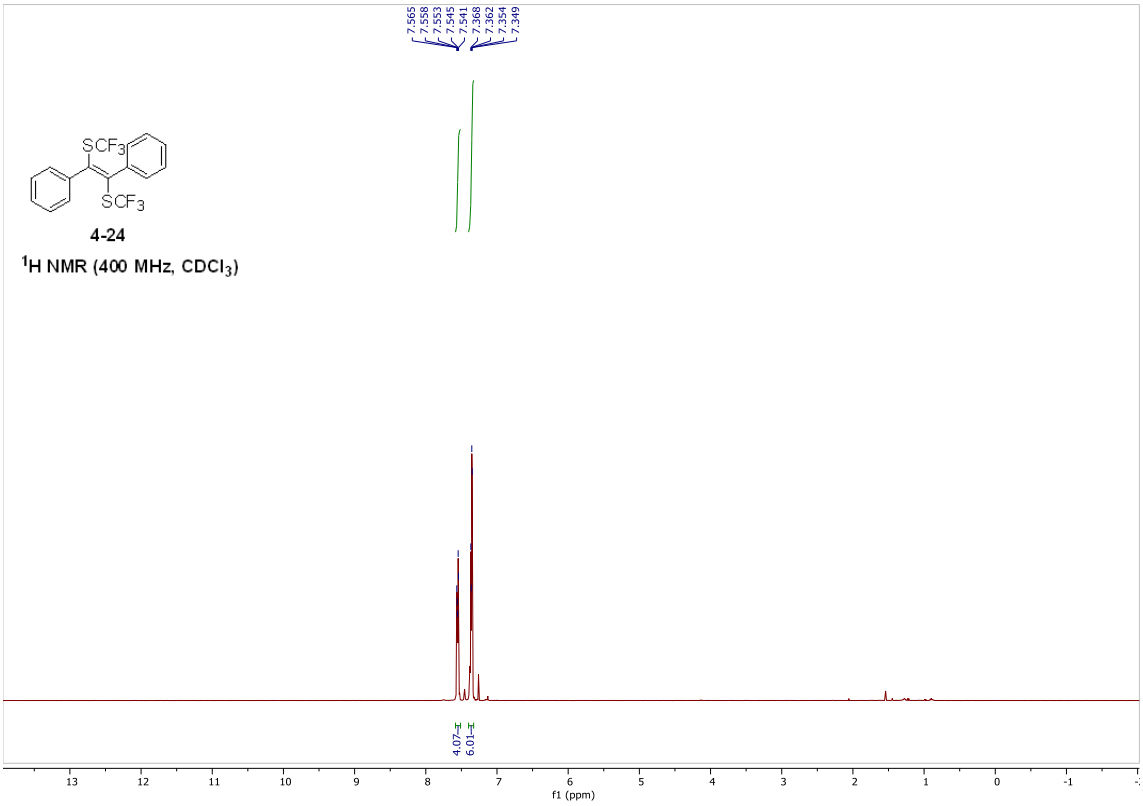

-43.09
-53.41
-79.38
CF3
OTf
F3C-S
4-22
19F NMR (376 MHz, CD3CN)
3.01
2.99
2.95
f1 (ppm)


8.74
8.72
8.70
8.68
8.51
8.49
8.47
8.45
8.43
8.41
8.19
8.17
8.14
8.12
8.10
7.99
7.97
7.95
CF3
OTf
F3C-S
O
4-23
1H NMR (400 MHz, CD3CN)
1.76
1.79
1.92
1.00
f1 (ppm)



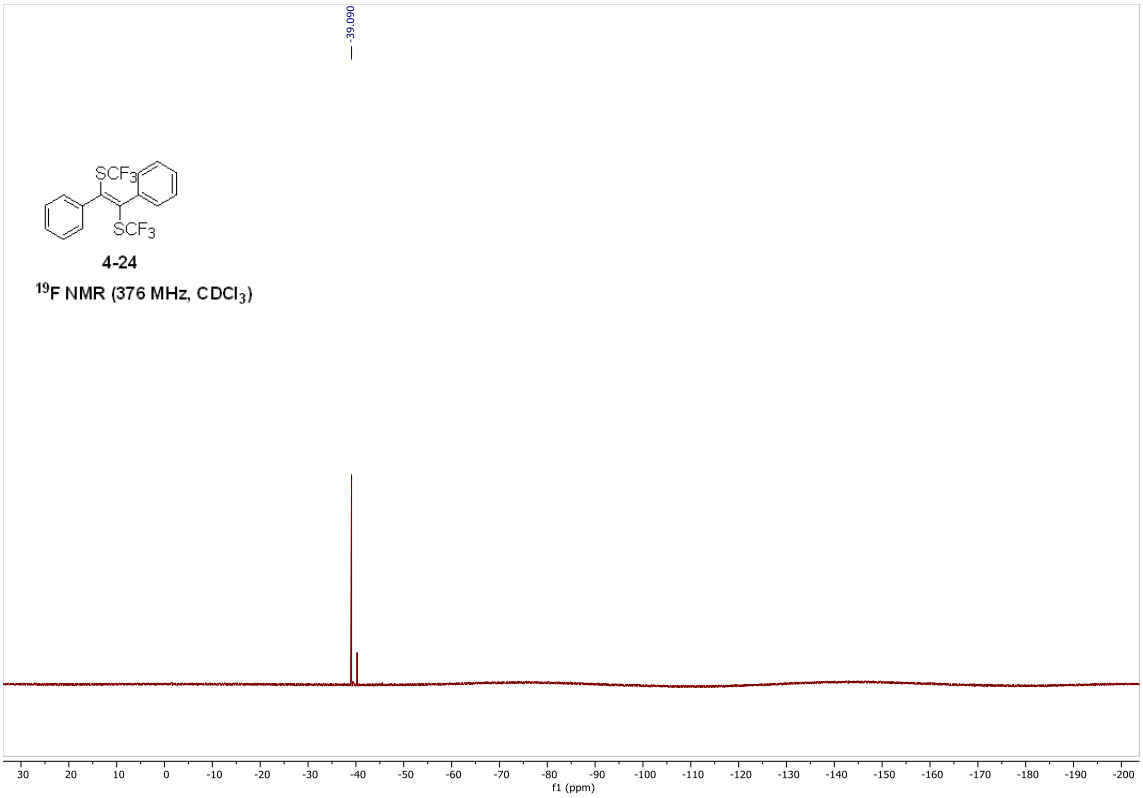
4-23

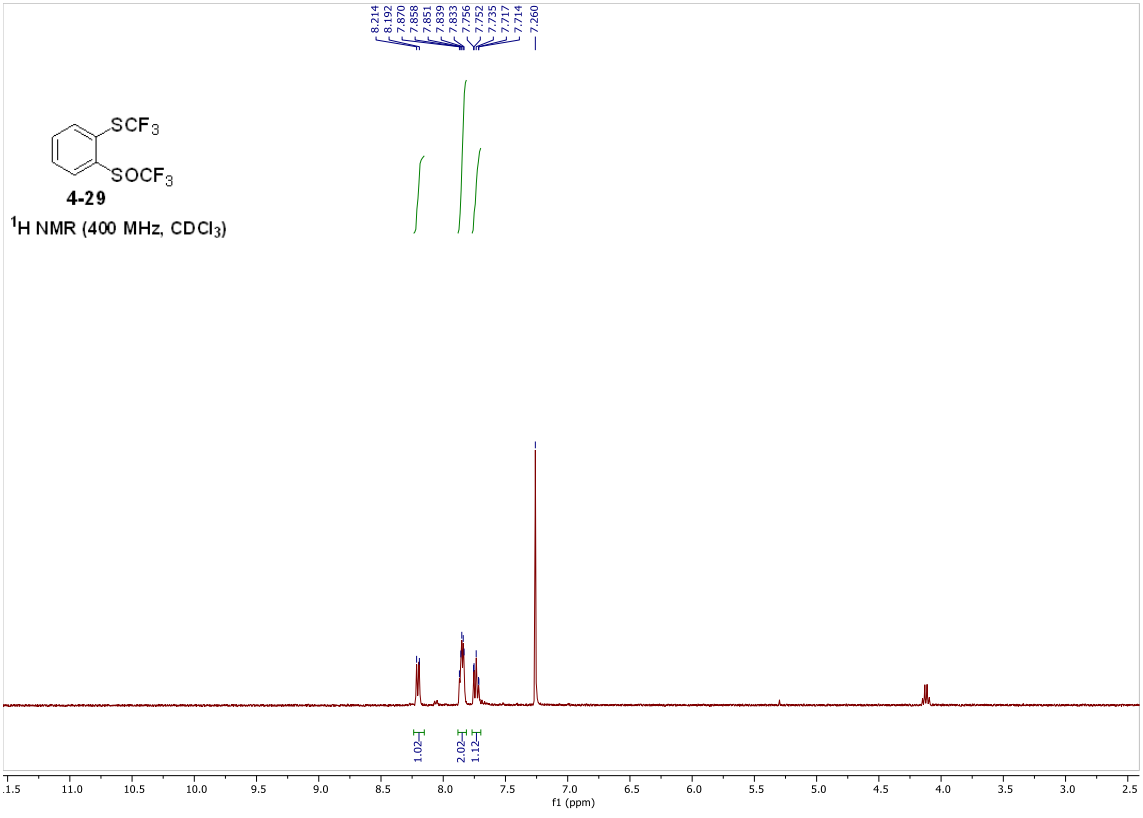
^{19}F NMR (376 MHz, CD_3CN)

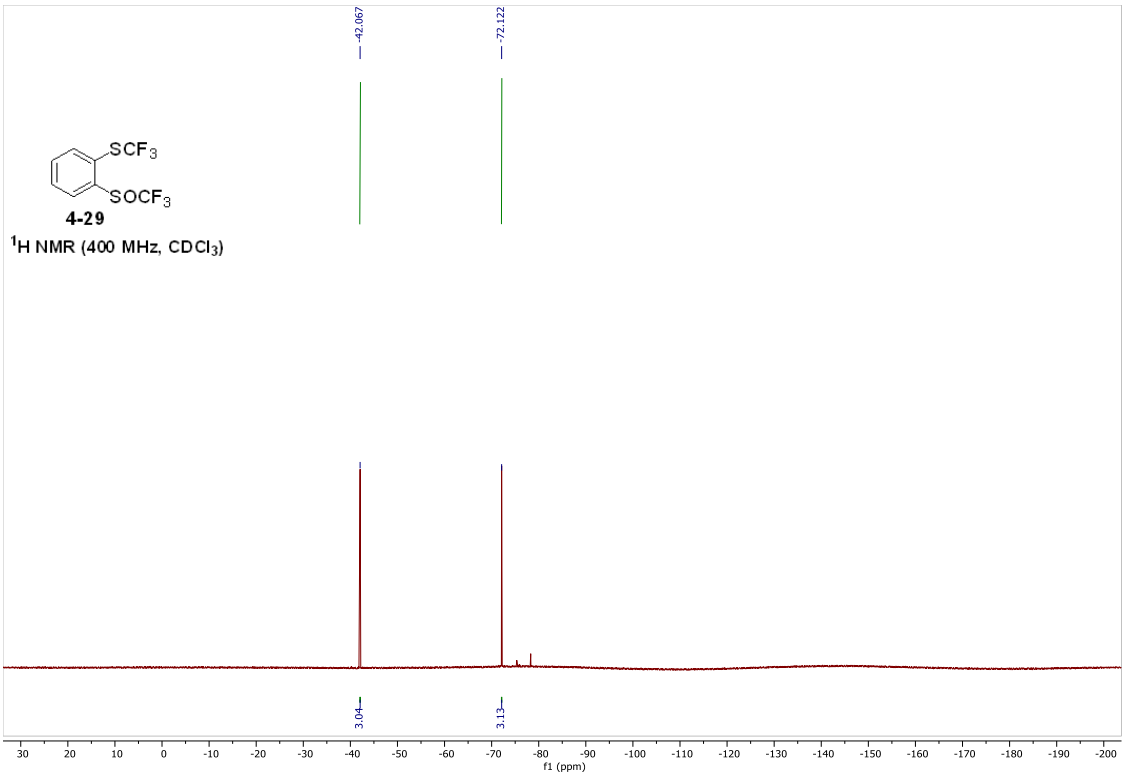


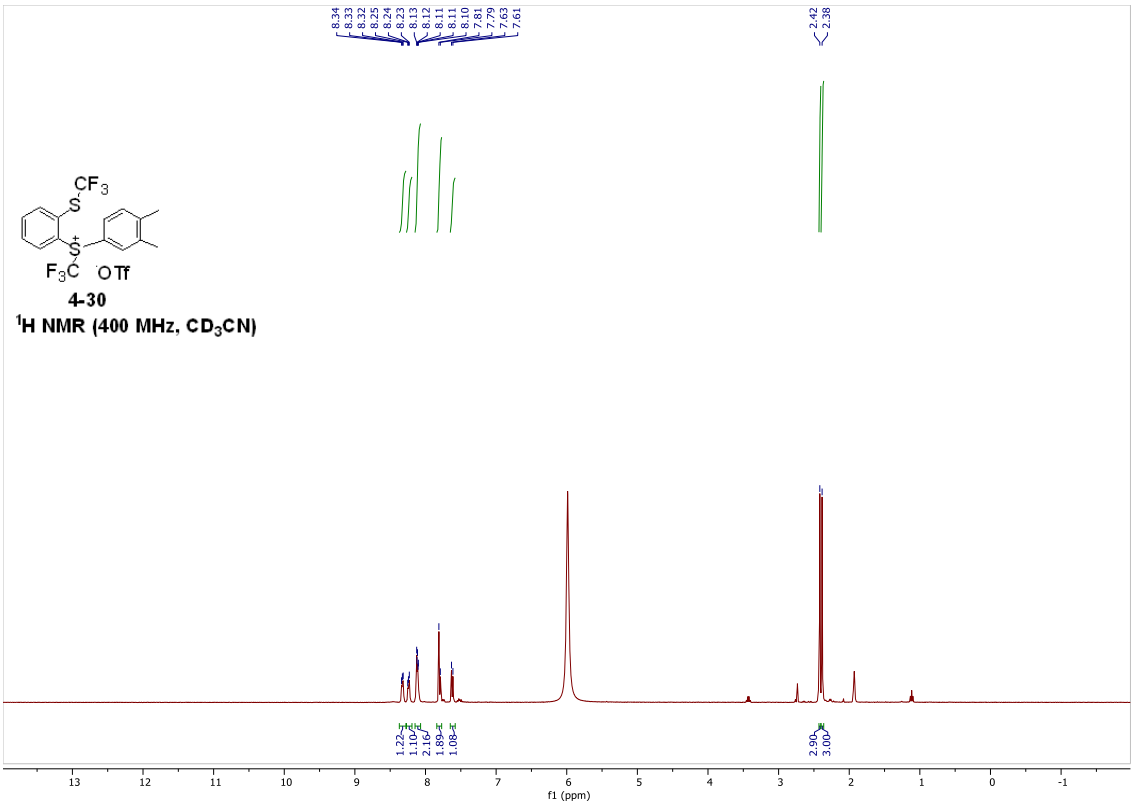
4-24

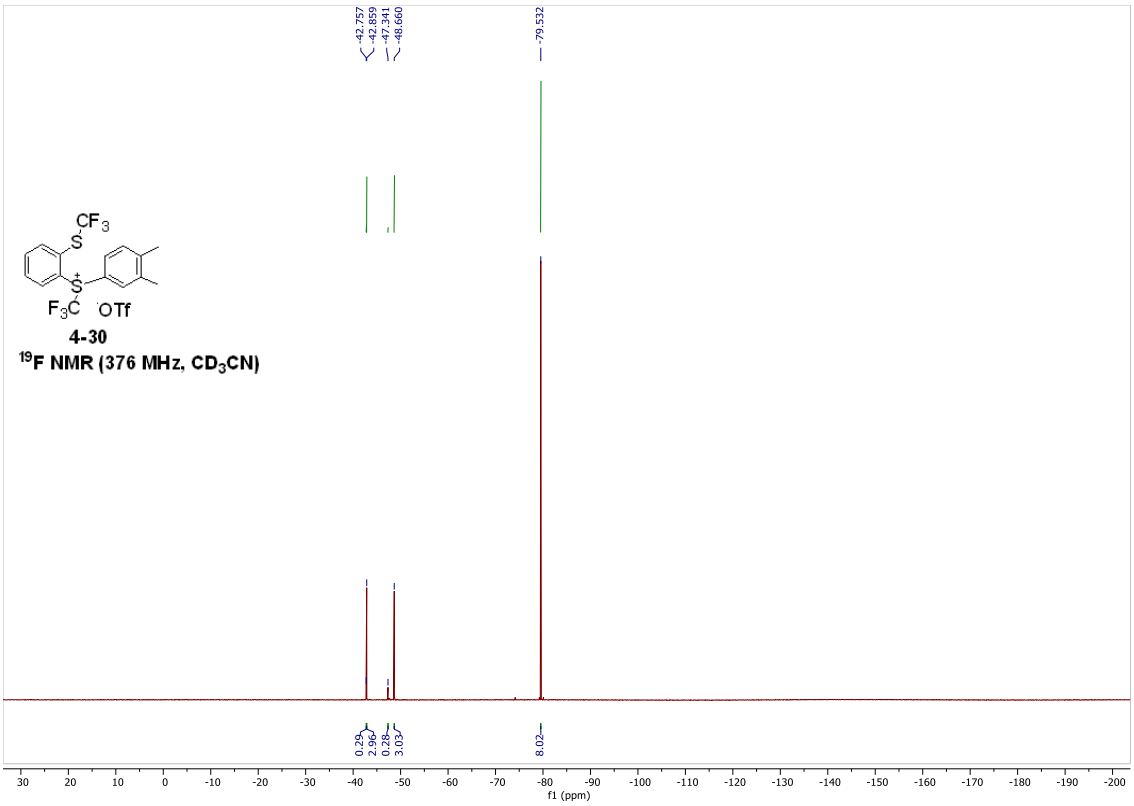
^{1}H NMR (400 MHz, $CDCl_3$)


-39.090
SCF3
SCF3
4-24
19F NMR (376 MHz, CDCl3)
f1 (ppm)


8.214
8.192
8.070
7.858
7.851
7.839
7.833
7.756
7.752
7.735
7.717
7.714
7.260
SCF3
SOCF3
4-29
1H NMR (400 MHz, CDCl3)
1.02
2.02
1.12
f1 (ppm)

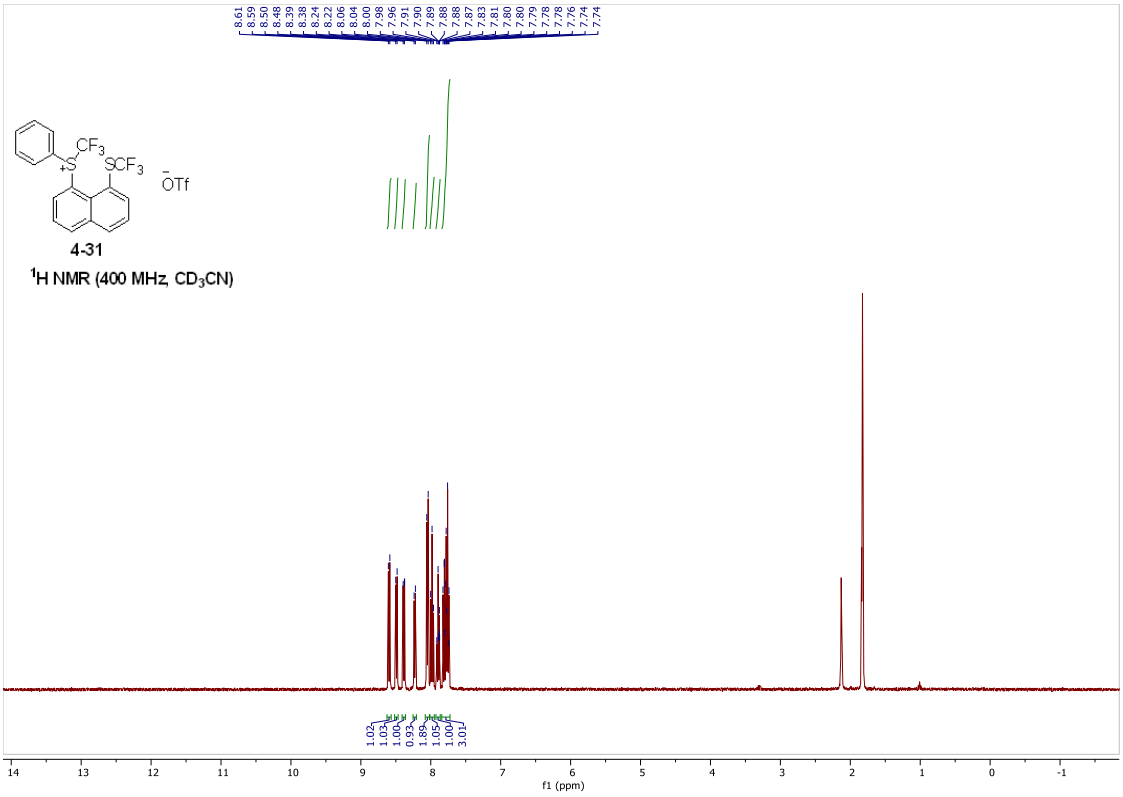

-42.067
-72.122
SCF3
SOCF3
4-29
1H NMR (400 MHz, CDCl3)
3.04
3.13
f1 (ppm)


8.34
8.33
8.32
8.25
8.24
8.23
8.13
8.12
8.11
8.11
8.10
7.81
7.79
7.63
7.61
2.42
2.38
CF3
S
S+
F3C
OTf
4-30
1H NMR (400 MHz, CD3CN)
1.22
1.10
2.16
1.89
1.08
2.90
3.00
f1 (ppm)



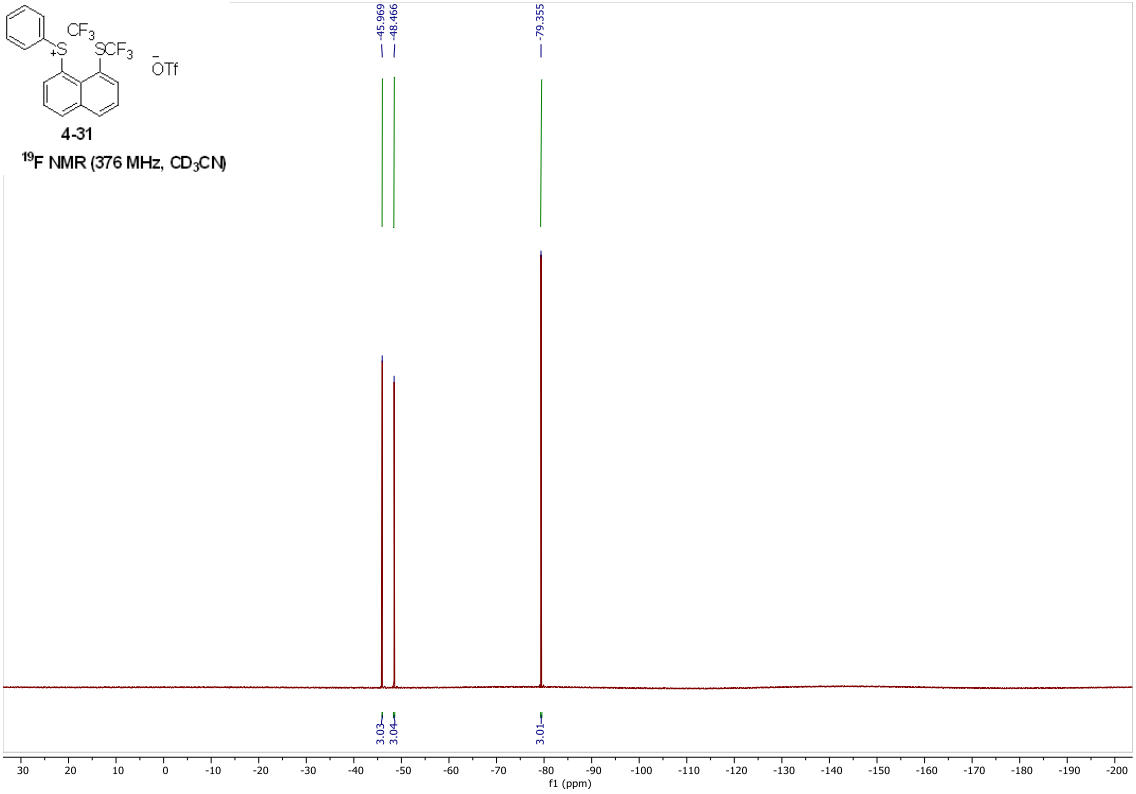
4-30

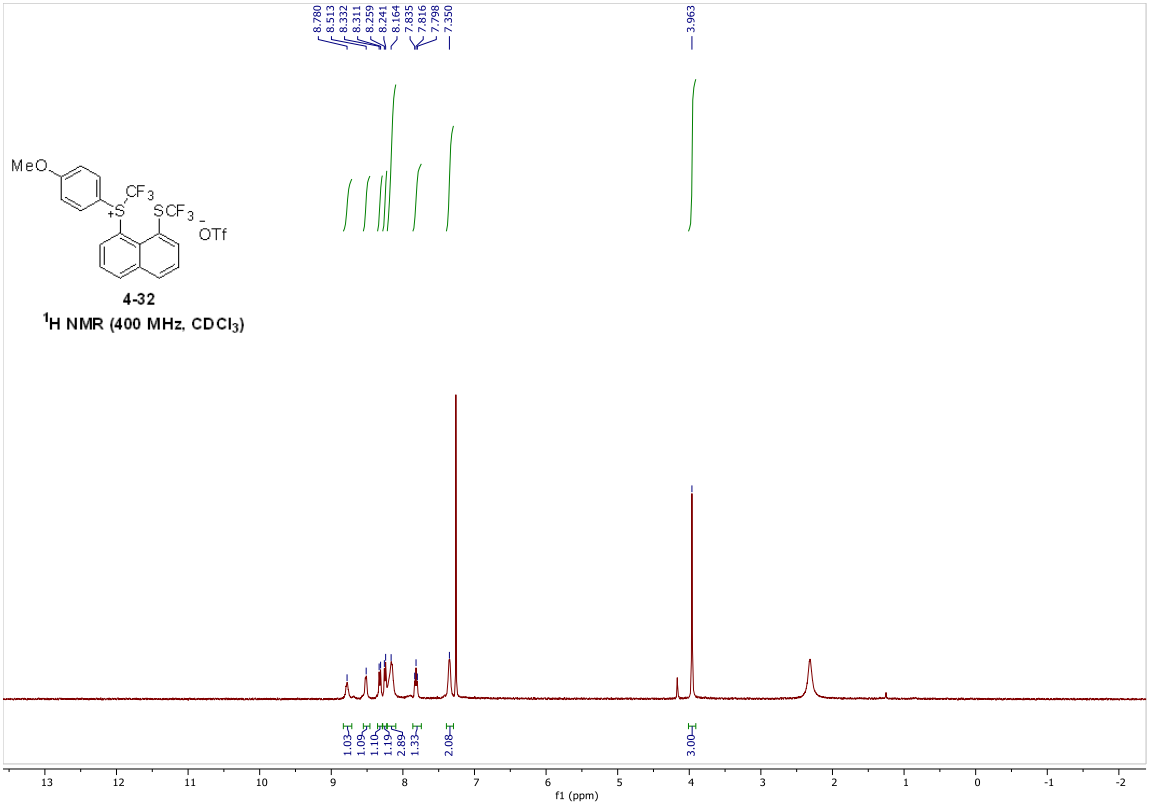
^{19}F NMR (376 MHz, CD_3CN)

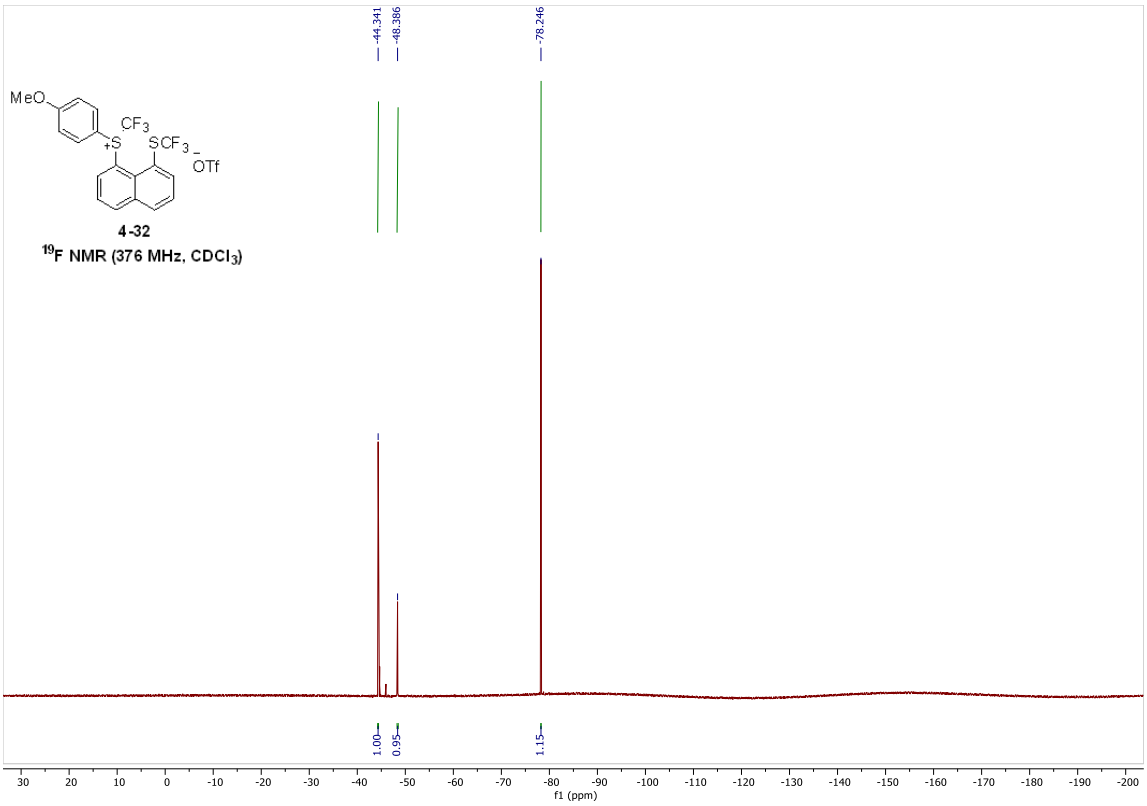


4-31

^{1}H NMR (400 MHz, CD_3CN)

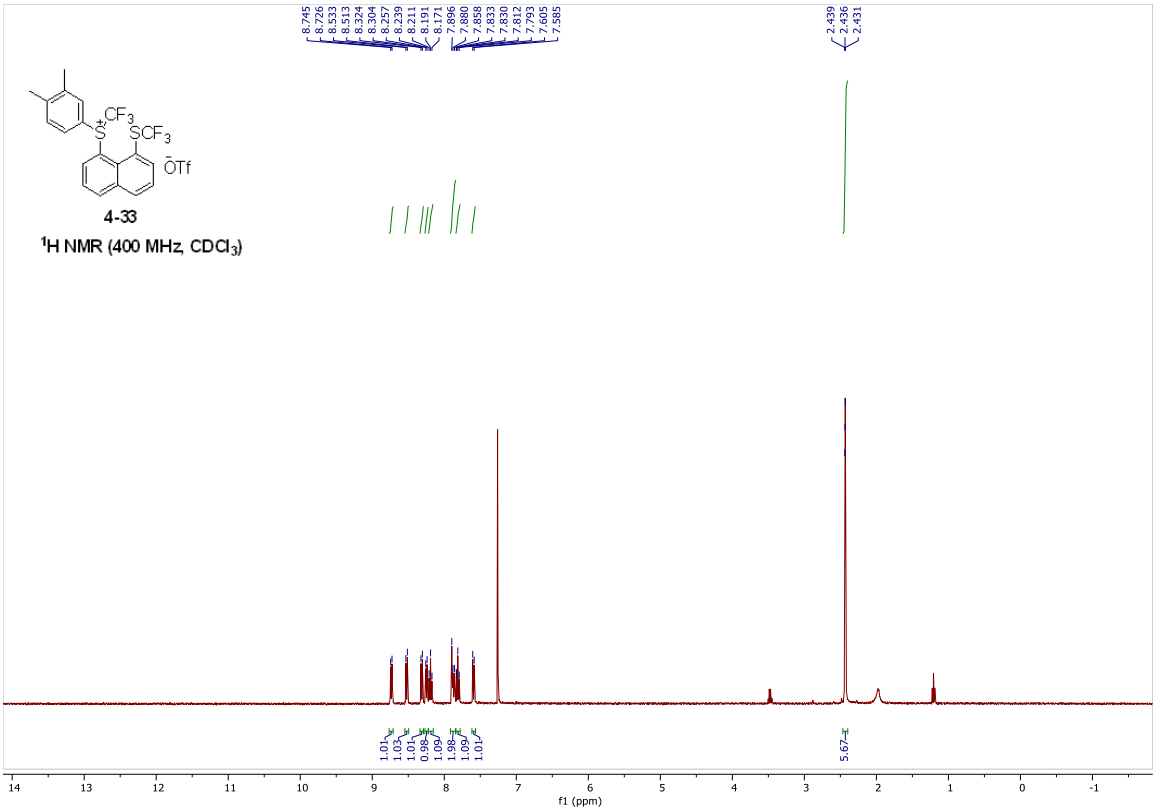

CF3
S
SCF3
OTf
4-31
19F NMR (376 MHz, CD3CN)
-45.969
-48.466
-79.355
3.03
3.04
3.01
f1 (ppm)


MeO
CF3
S
SCF3
OTf
4-32
1H NMR (400 MHz, CDCl3)
8.780
8.513
8.332
8.311
8.259
8.241
8.164
7.835
7.816
7.798
7.350
3.963
1.03
1.09
1.10
1.19
2.89
1.33
2.08
3.00
f1 (ppm)



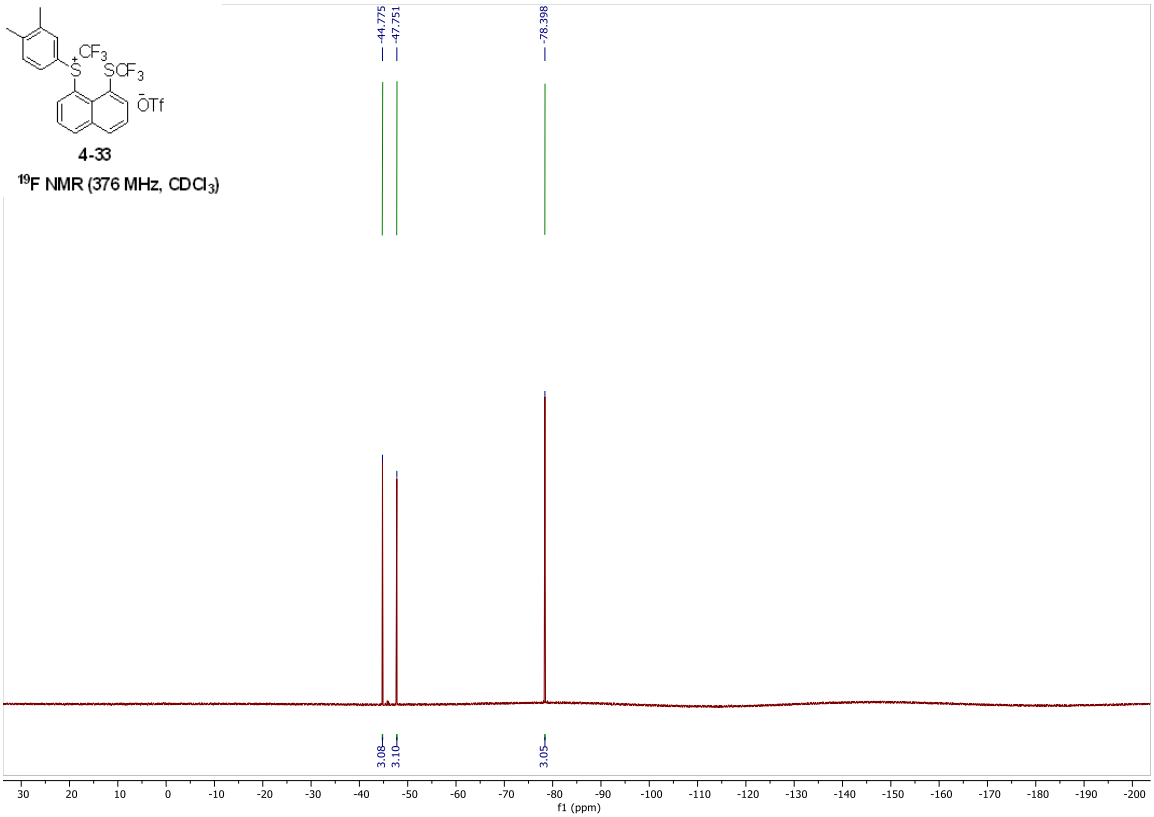
4-32

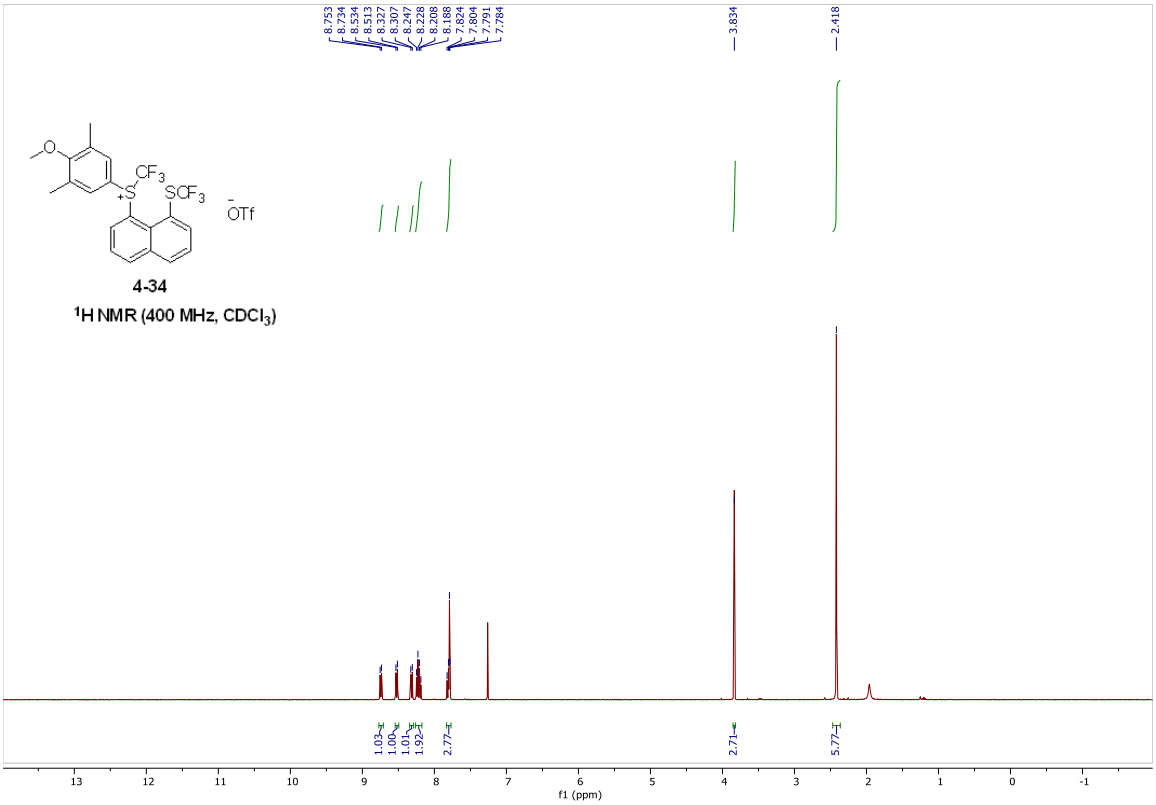
^{19}F NMR (376 MHz, $CDCl_3$)

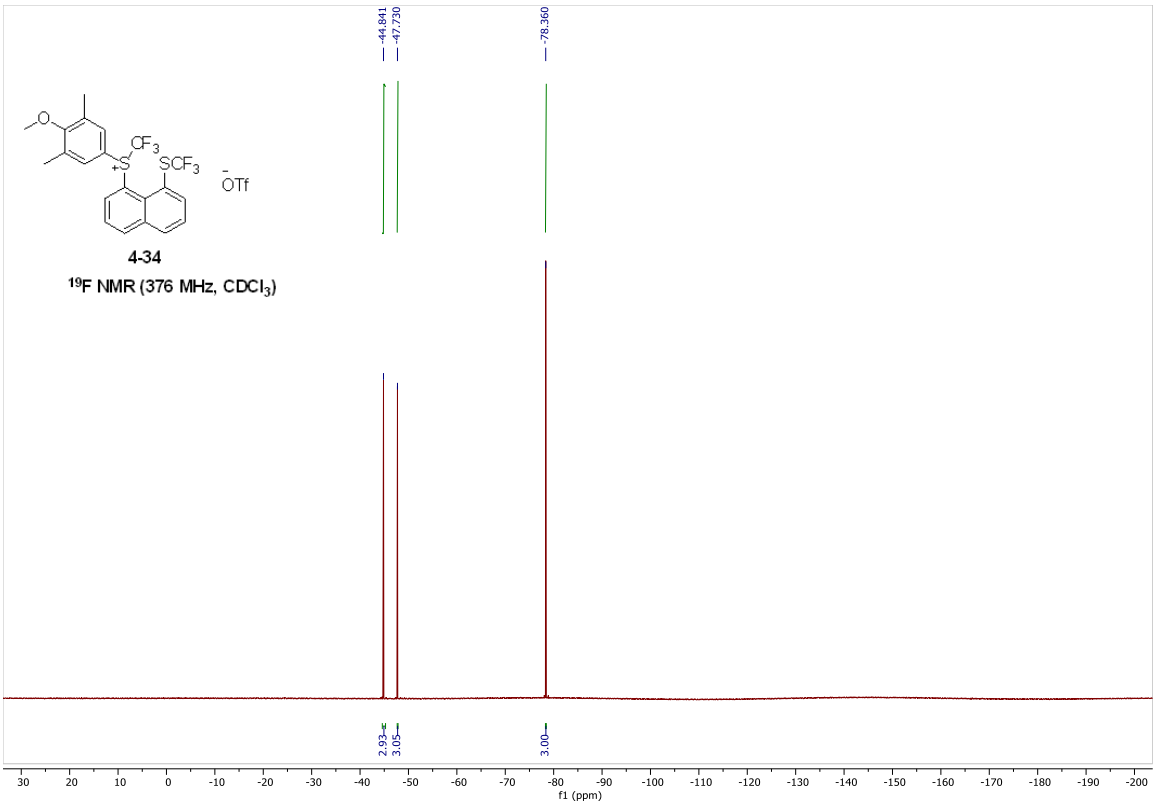


4-33

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

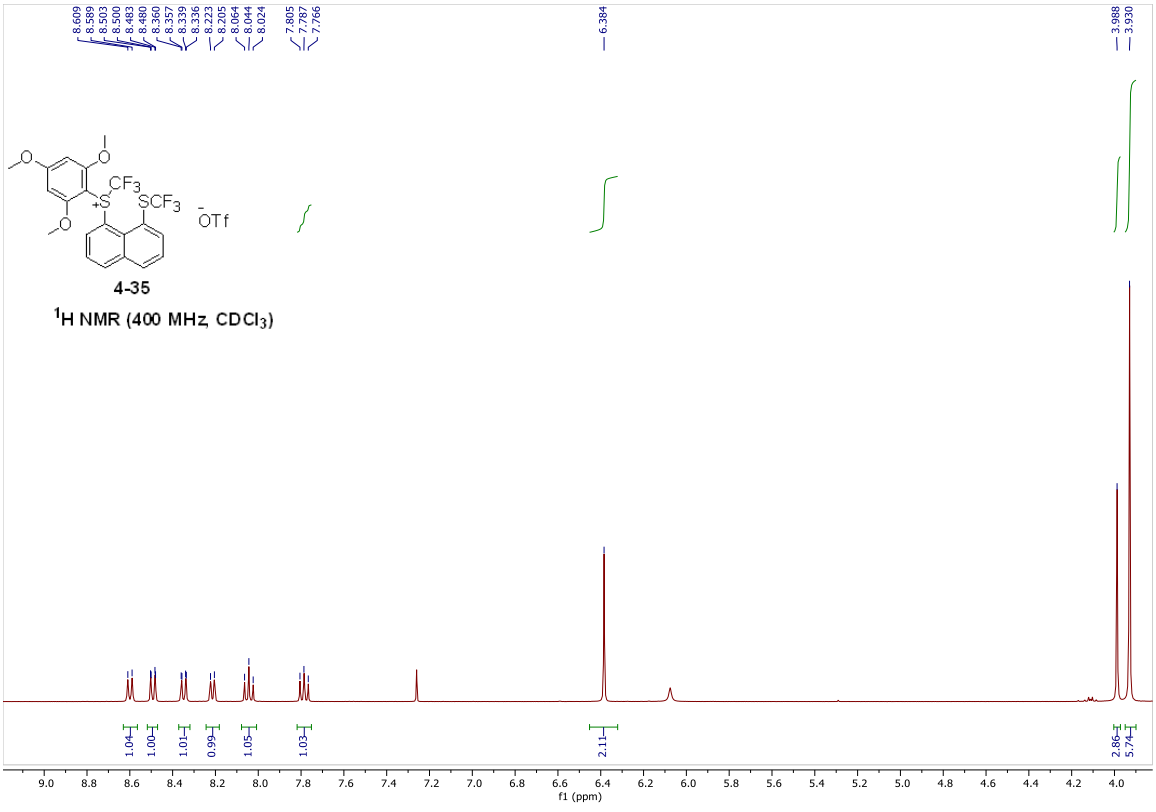

CF3
SCF3
OTf
4-33
19F NMR (376 MHz, CDCl3)
-44.775
-47.751
-78.398
3.08
3.10
3.05
f1 (ppm)


8.753
8.734
8.534
8.513
8.327
8.307
8.247
8.228
8.208
8.188
7.824
7.804
7.791
7.784
3.834
2.418
CF3
SCF3
OTf
4-34
1H NMR (400 MHz, CDCl3)
1.03
1.00
1.01
1.92
2.77
2.71
5.77
f1 (ppm)



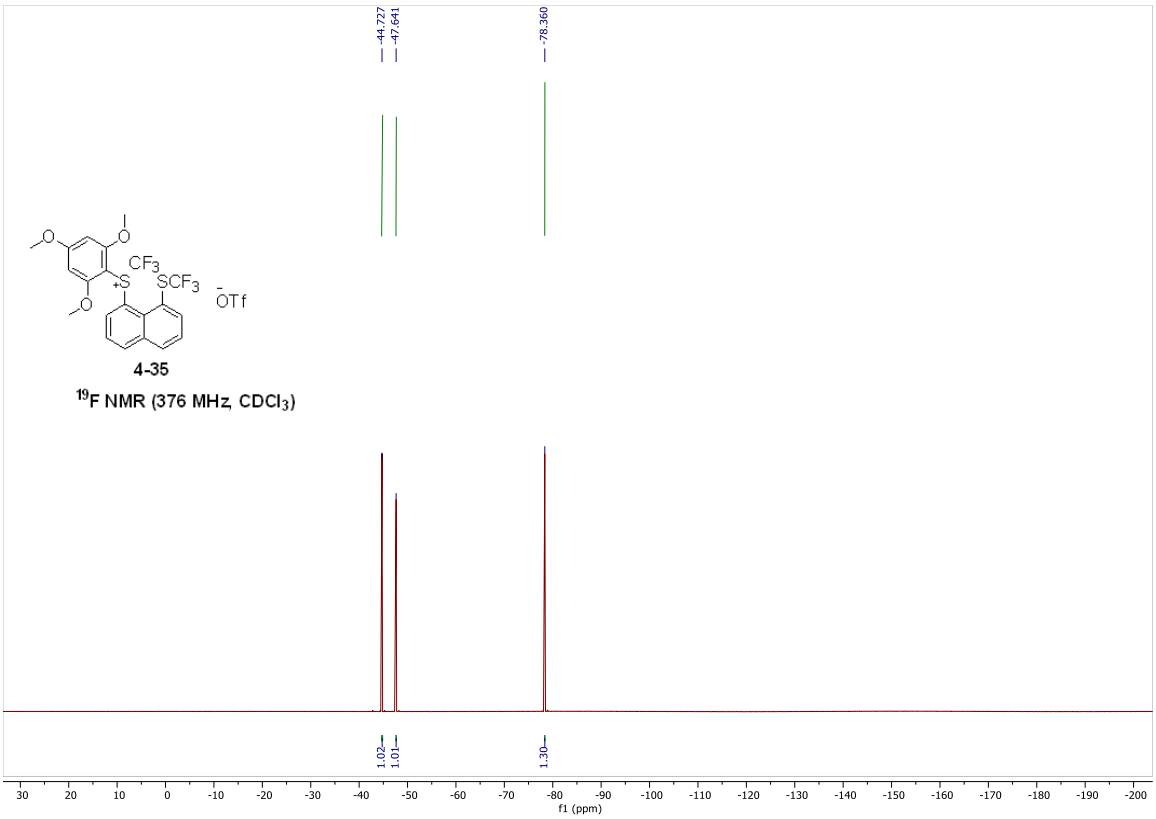
4-34

^{19}F NMR (376 MHz, $CDCl_3$)



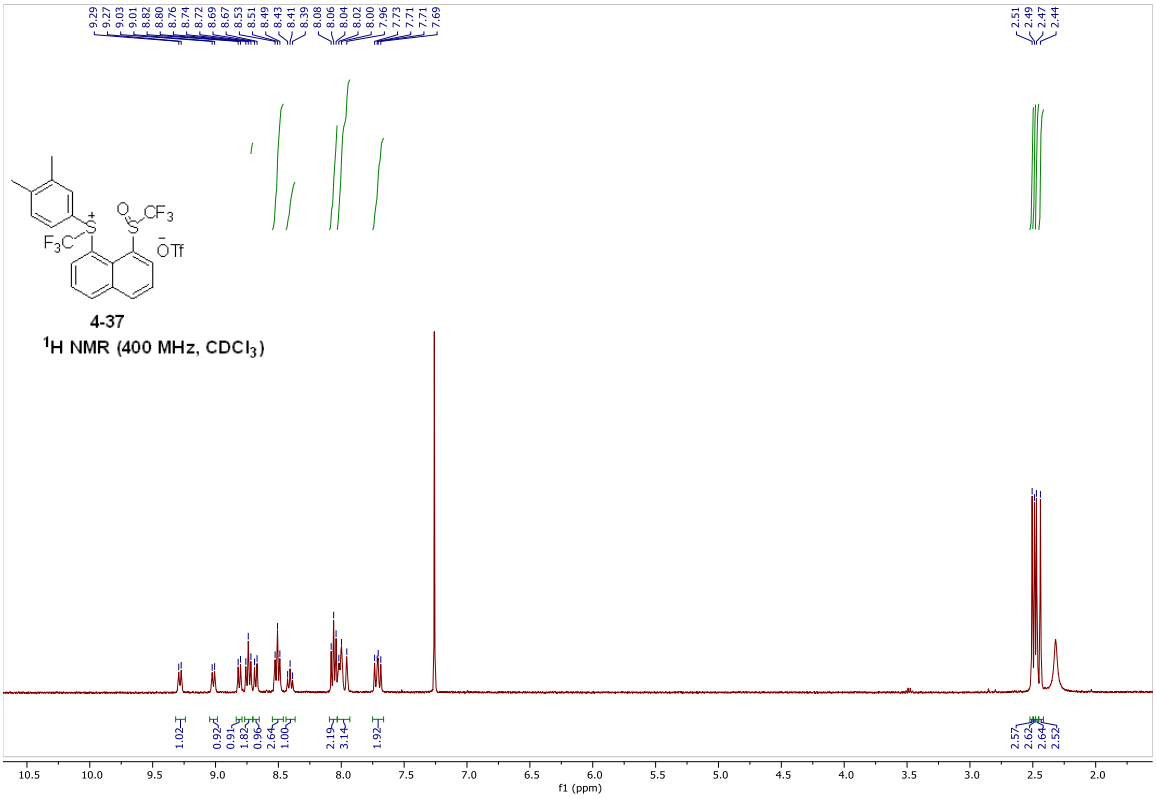
4-35

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



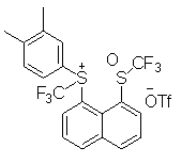
4-35

^{19}F NMR (376 MHz, $CDCl_3$)



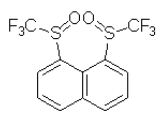
4-37

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



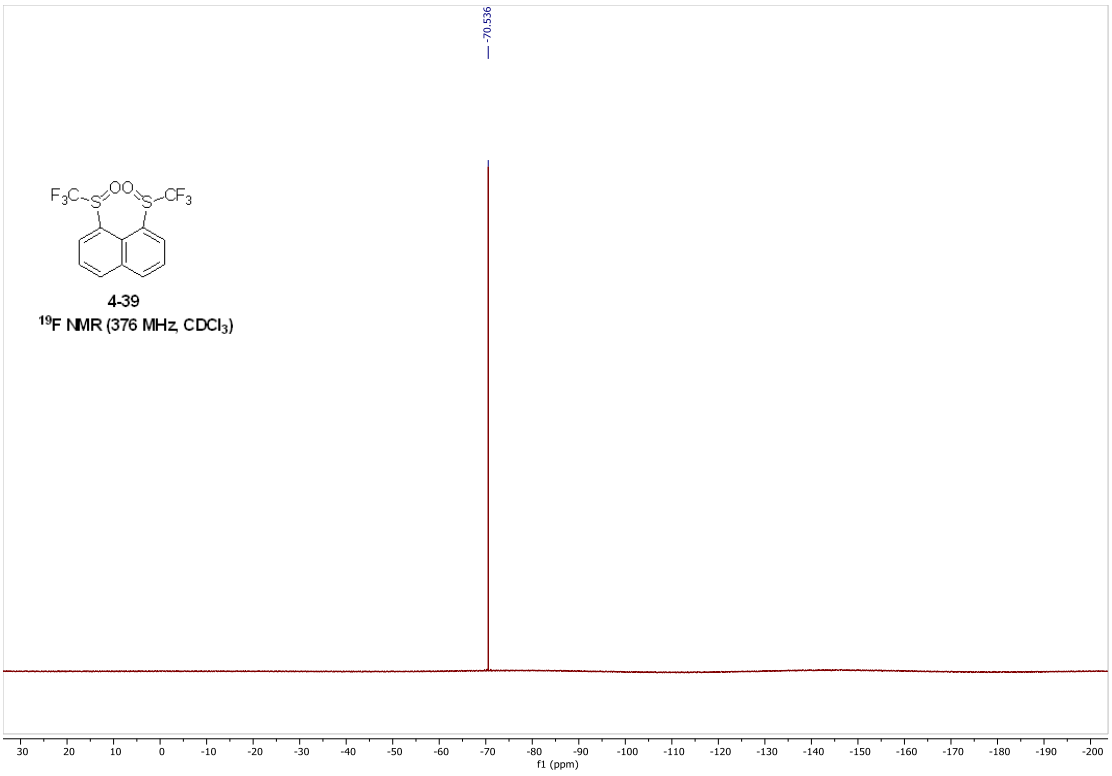
4-37

^{19}F NMR (376 MHz, $CDCl_3$)



4-39

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



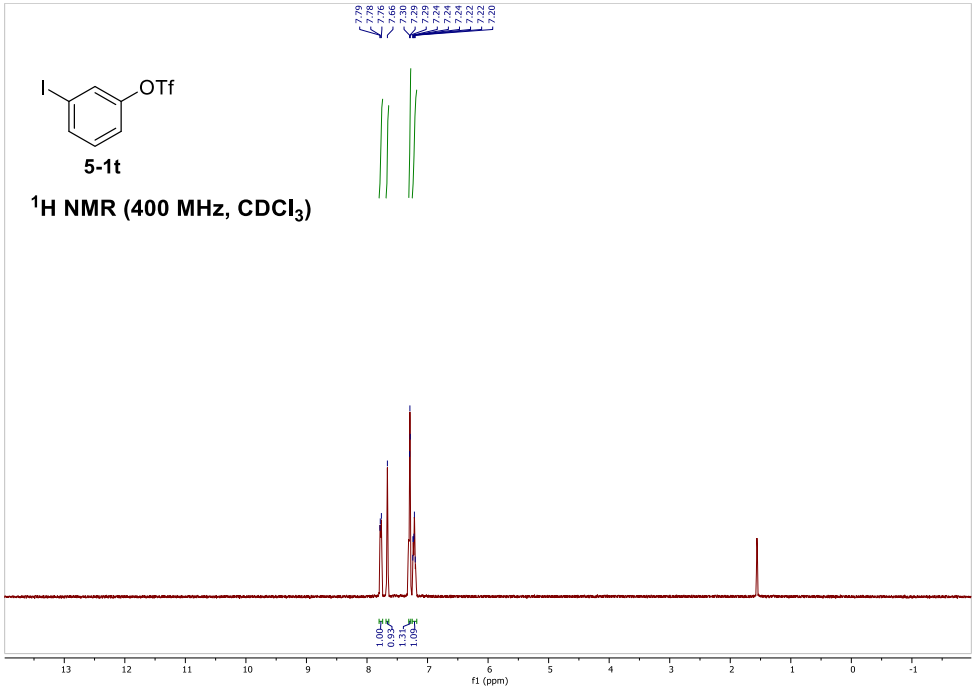
4-39

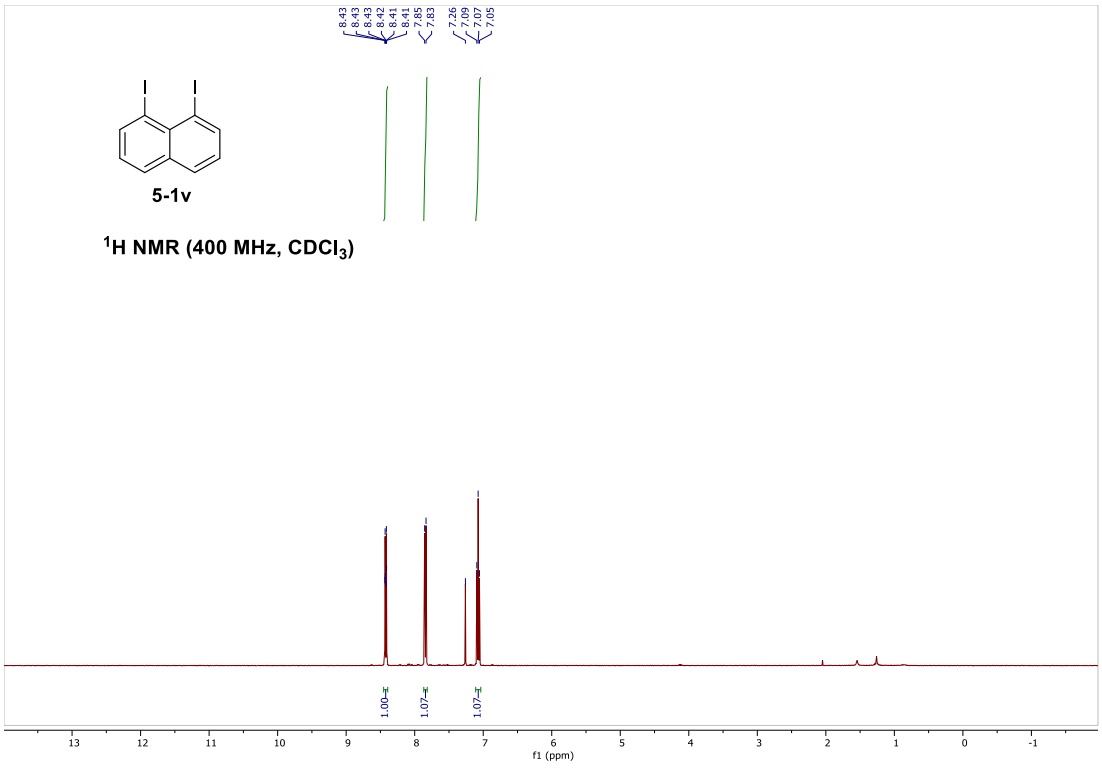
^{19}F NMR (376 MHz, $CDCl_3$)

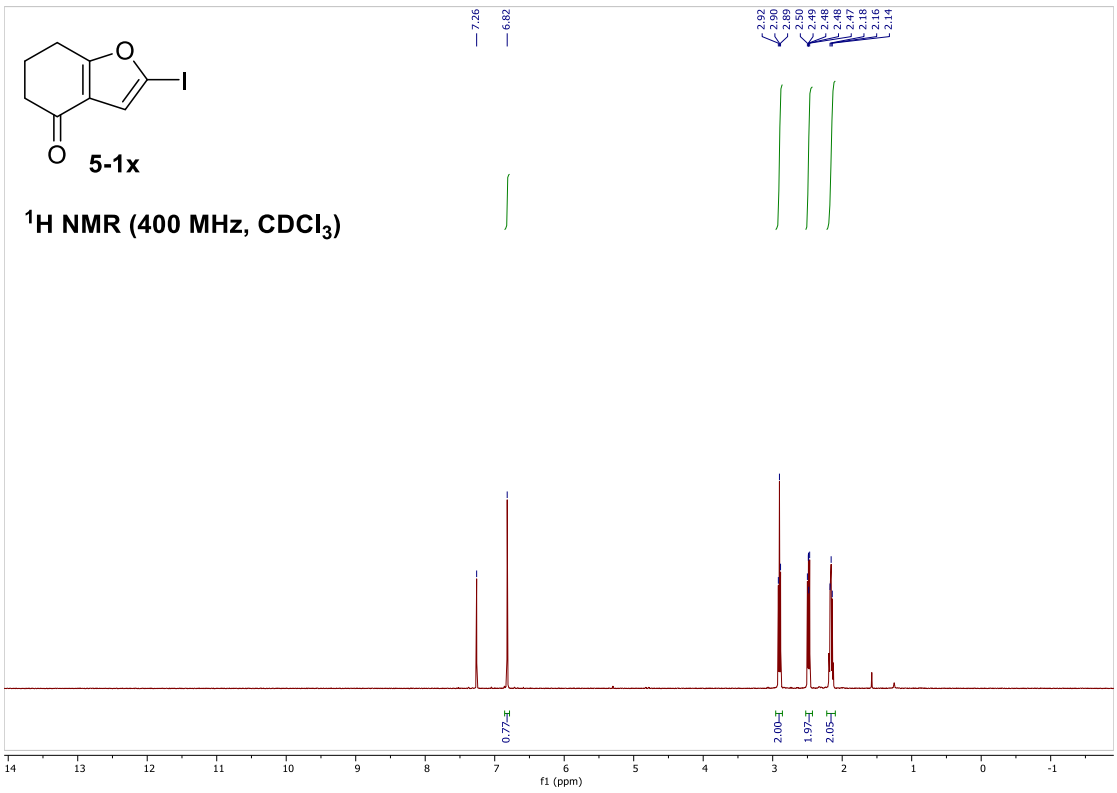
APPENDIX D: NMR DATA FOR GOLD(I/III)-CATALYZED TRIFLUOROMETHYLTHIOLATION AND TRIFLUOROMETHYLSELENOLATION OF ORGANOHALIDES

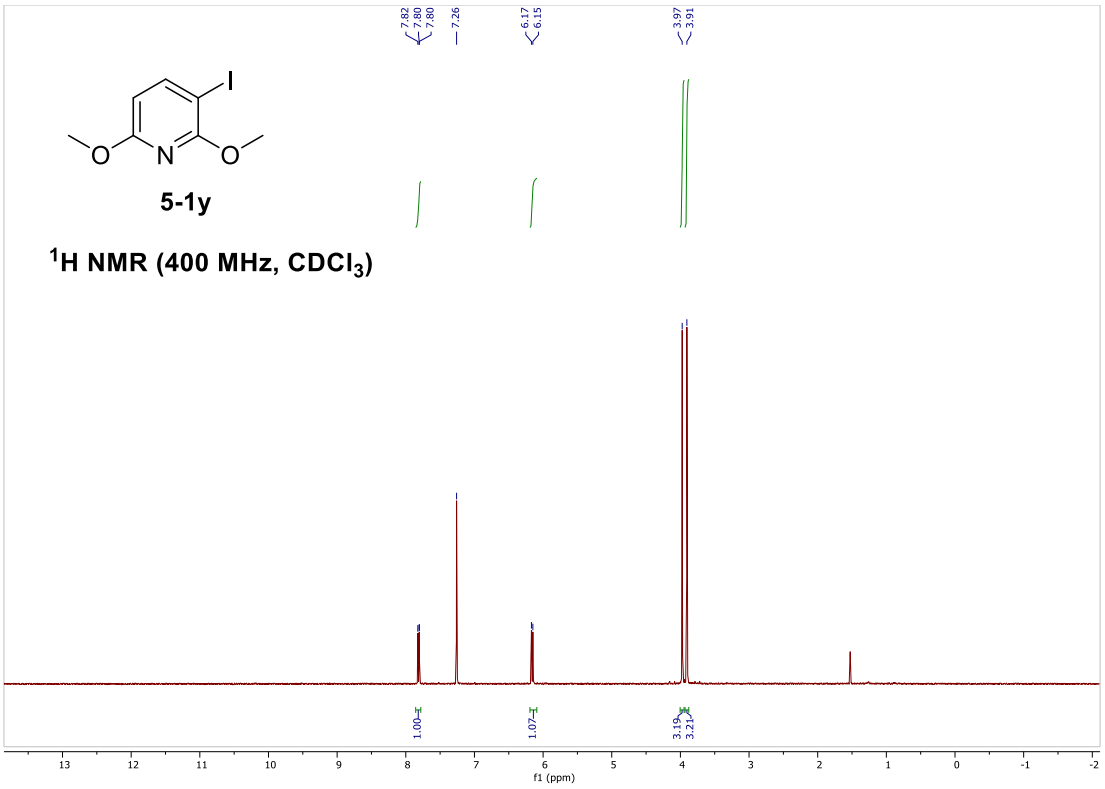
5.4.7. ^{1}H, ^{13}C, and ^{19}F NMR spectra

5.4.7.1. Synthesized aryl iodide substrates (**5-1t, 5-1v, 5-1x,5-1y, 5-1cc and 5-1dd**)



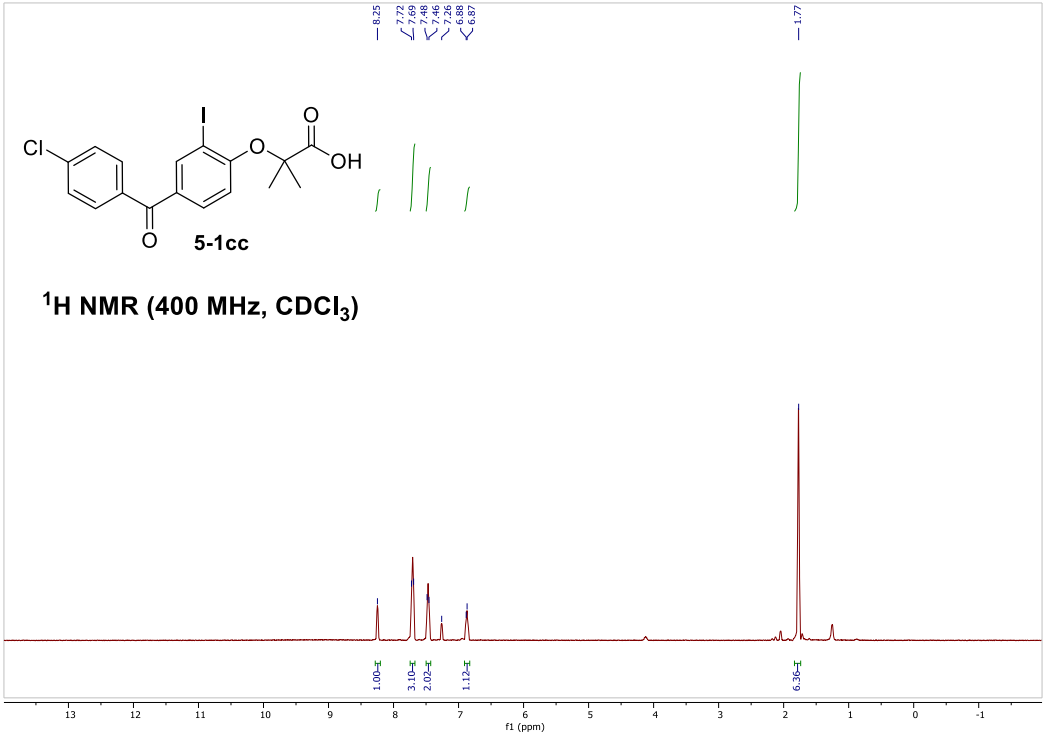

8.43
8.43
8.43
8.42
8.41
8.41
7.85
7.83
7.26
7.09
7.07
7.05
5-1v
1H NMR (400 MHz, CDCl3)
1.00
1.07
1.07
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


7.26
6.82
2.92
2.90
2.89
2.50
2.49
2.48
2.48
2.47
2.18
2.16
2.14
O
I
O
5-1x
1H NMR (400 MHz, CDCl3)
0.77
2.00
1.97
2.05
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)



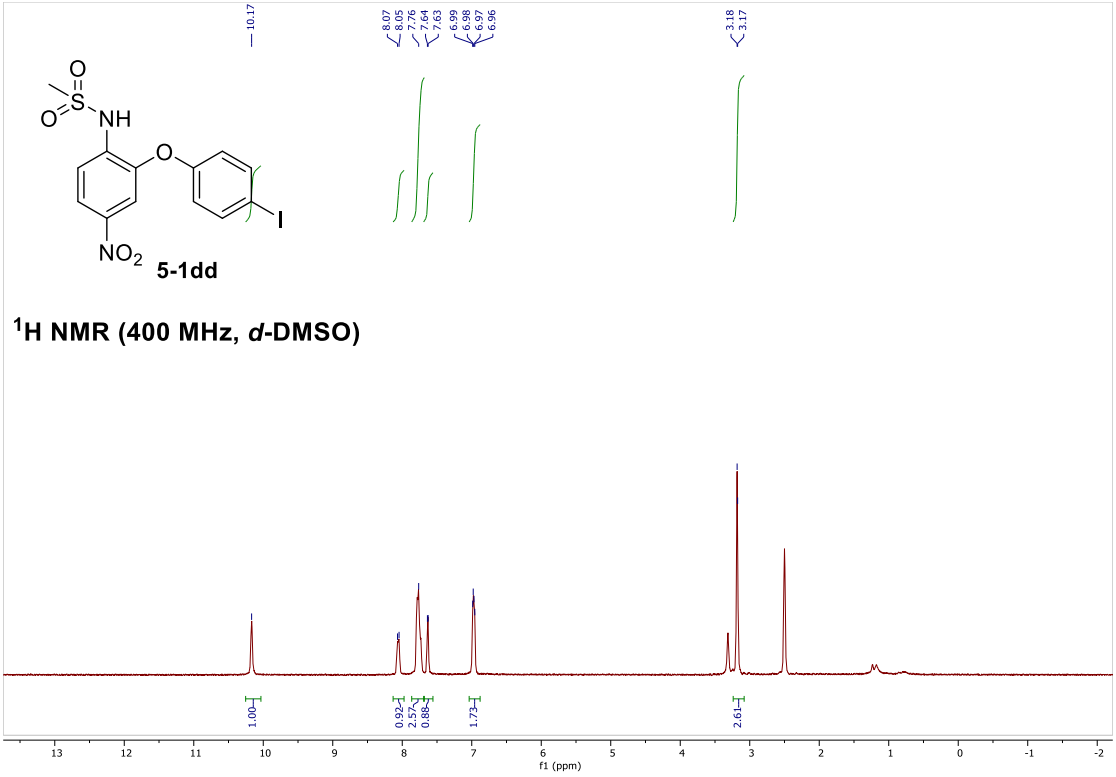
5-1y

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



5-1cc

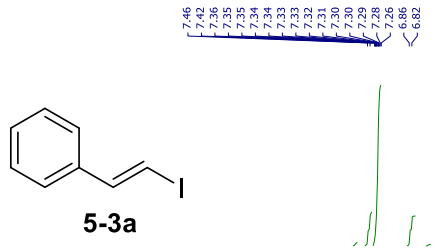
^{1}H NMR (400 MHz, $CDCl_3$)



5-1dd

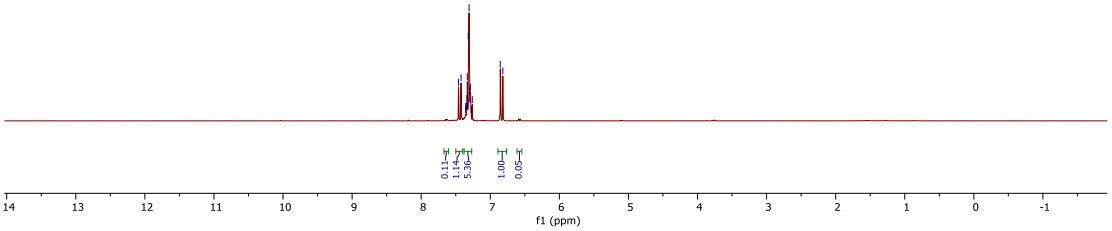
^{1}H NMR (400 MHz, *d*-DMSO)

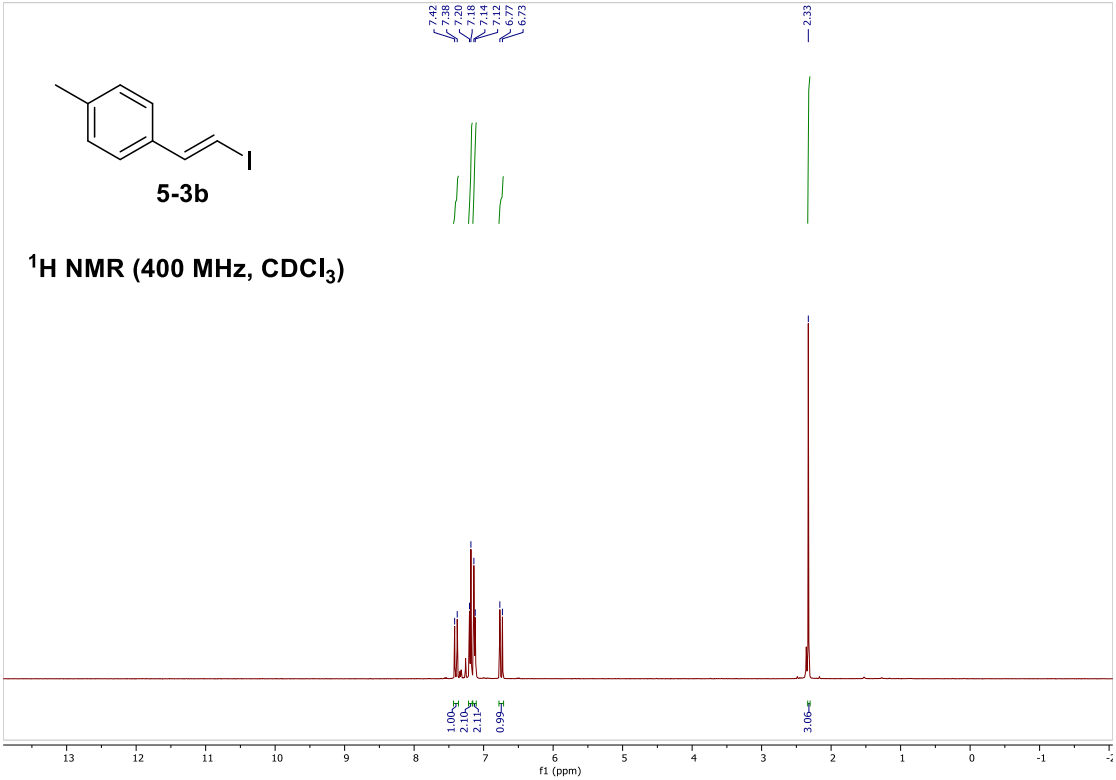
5.4.7.2. Synthesized alkenyl iodide substrates



5-3a

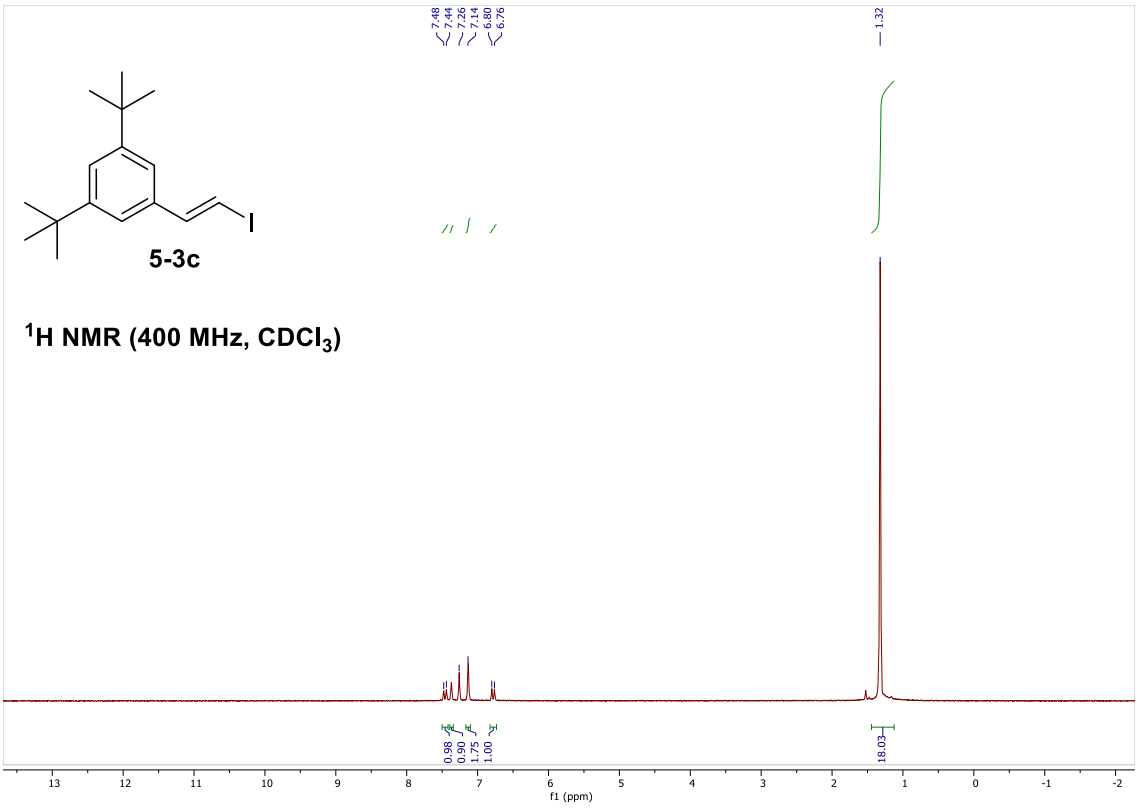
^{1}H NMR (400 MHz, $CDCl_3$)





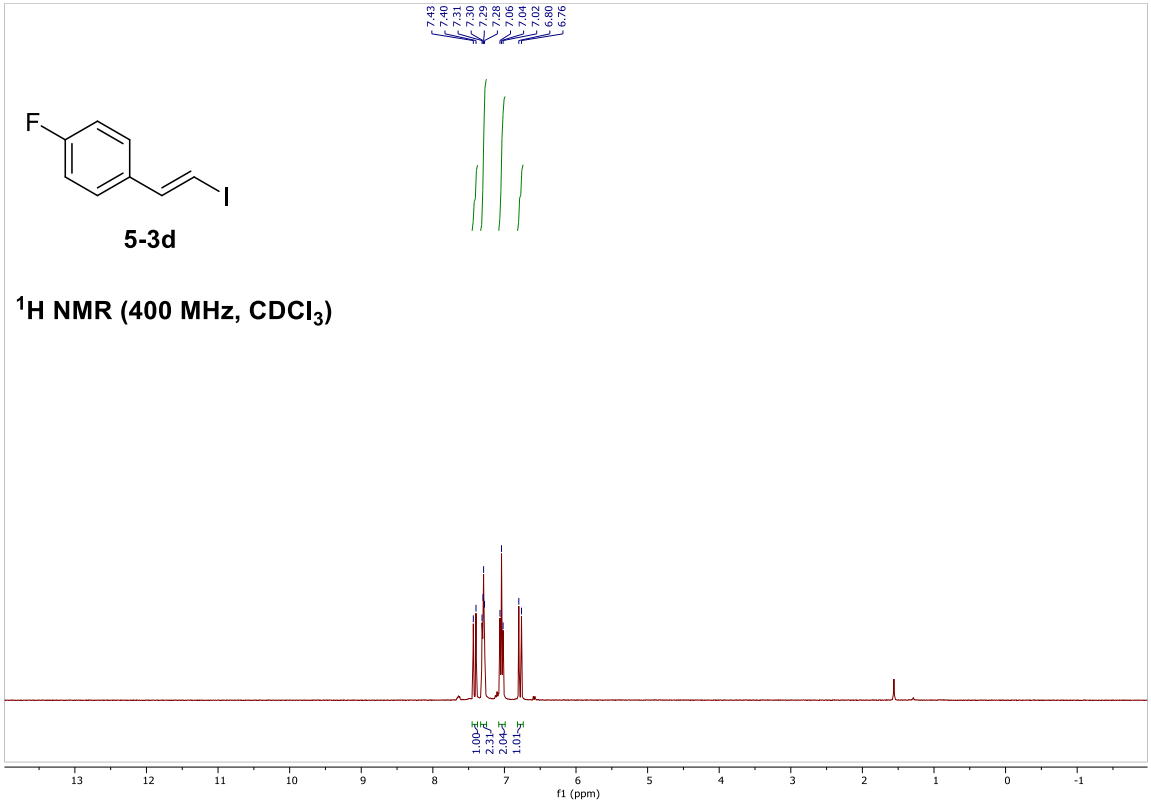
5-3b

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



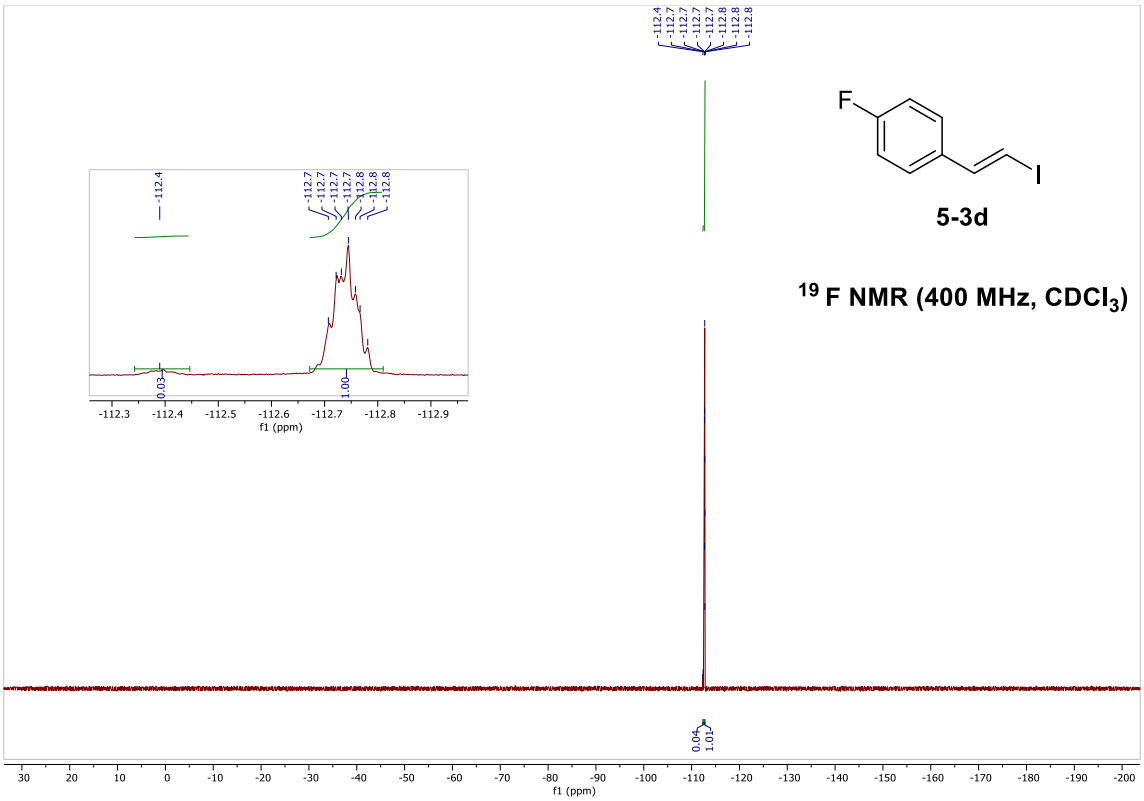
5-3c

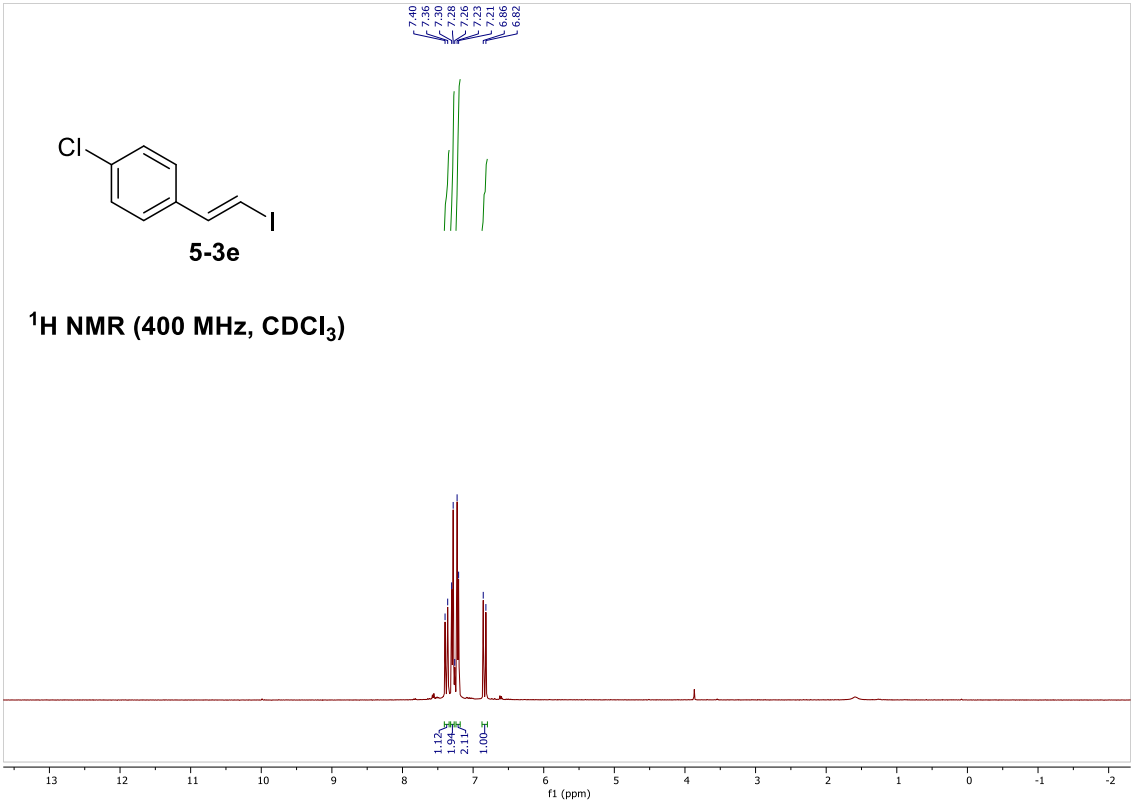
^{1}H NMR (400 MHz, $CDCl_3$)

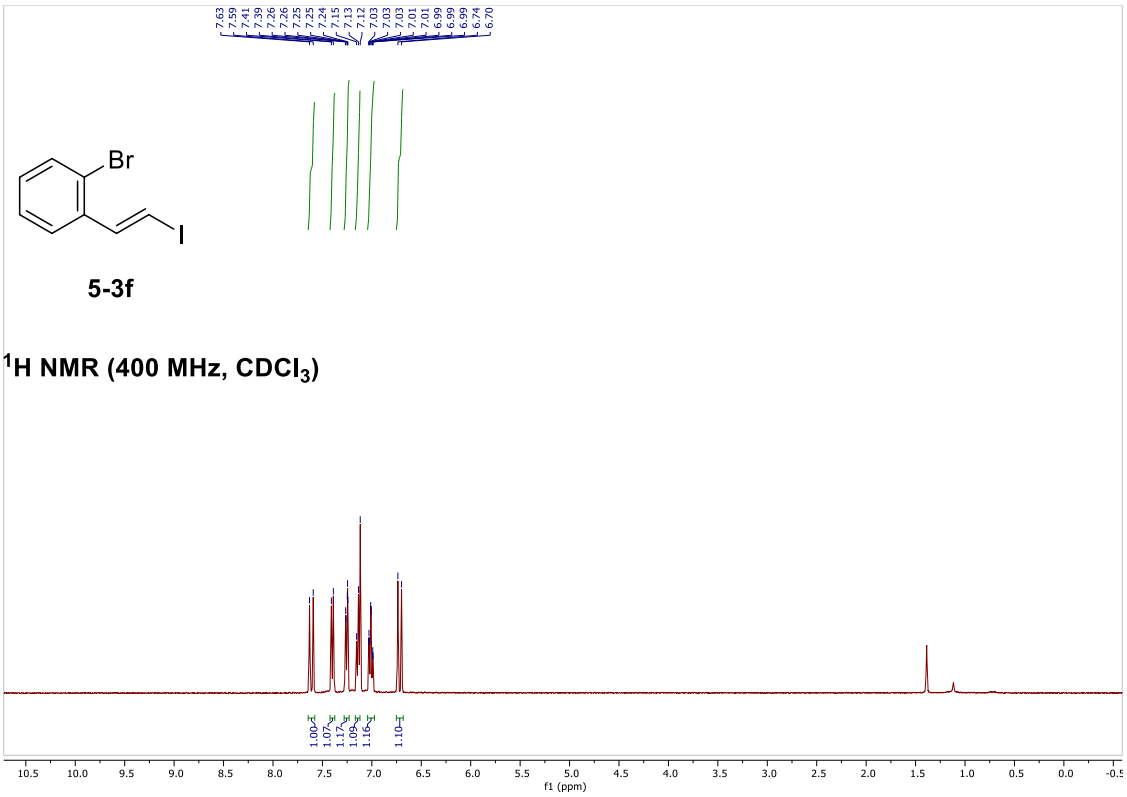


5-3d

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

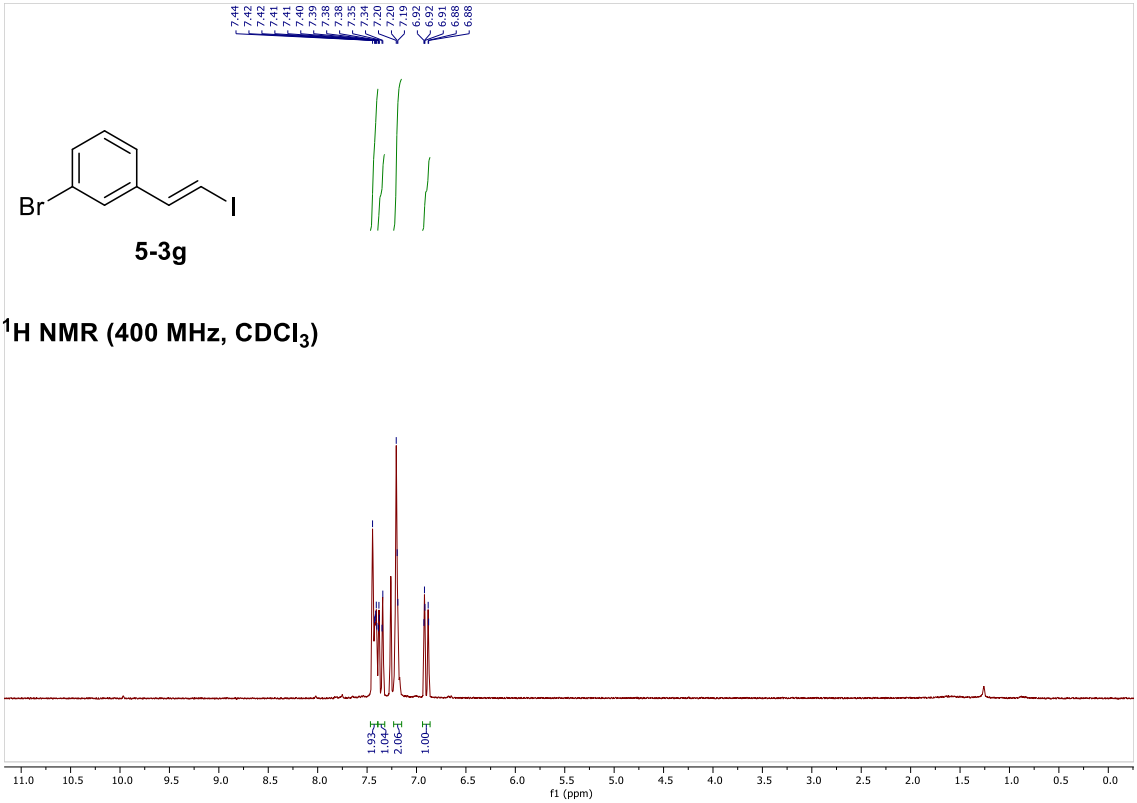

F
I
5-3d
19 F NMR (400 MHz, CDCl3)
f1 (ppm)


Cl
I
5-3e
1H NMR (400 MHz, CDCl3)
f1 (ppm)



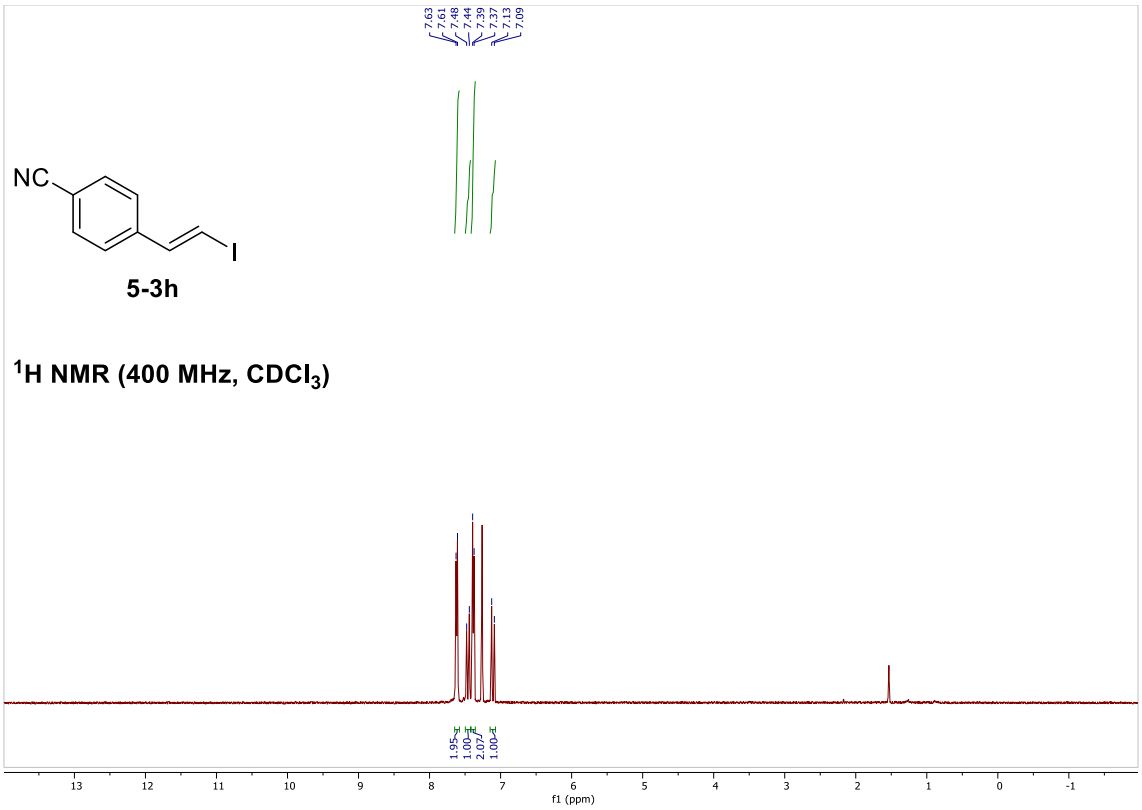
5-3f

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



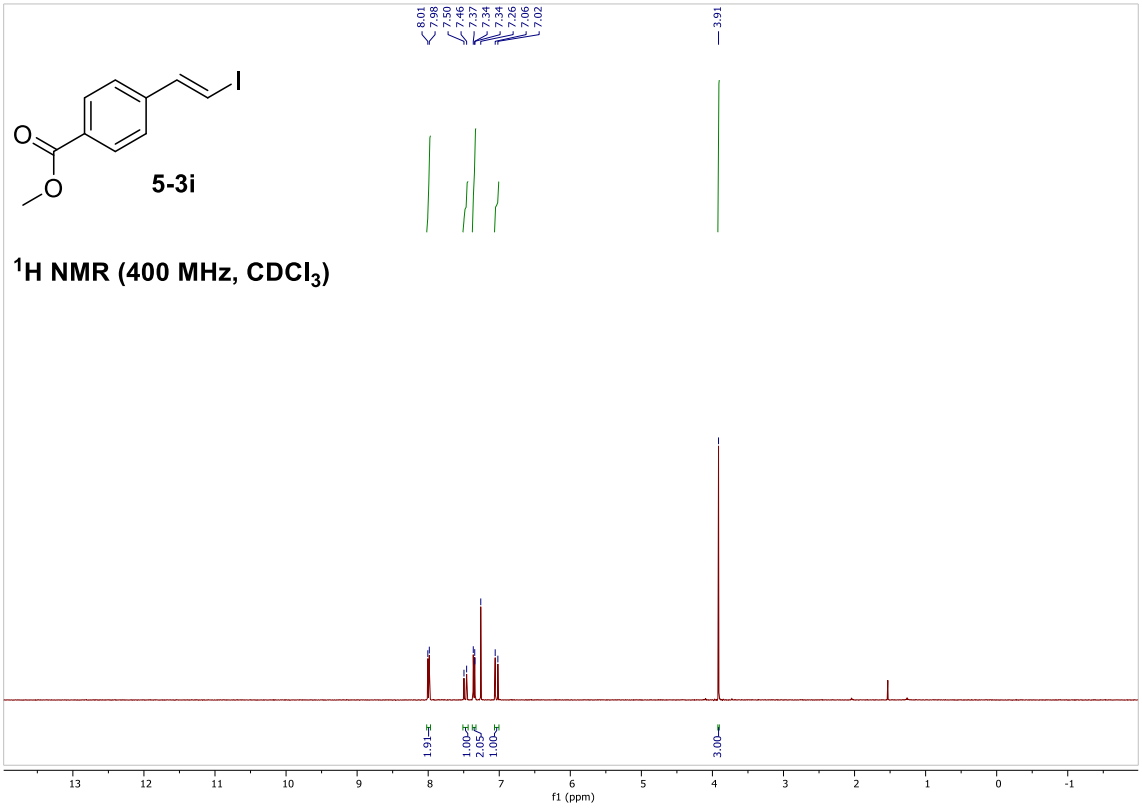
5-3g

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



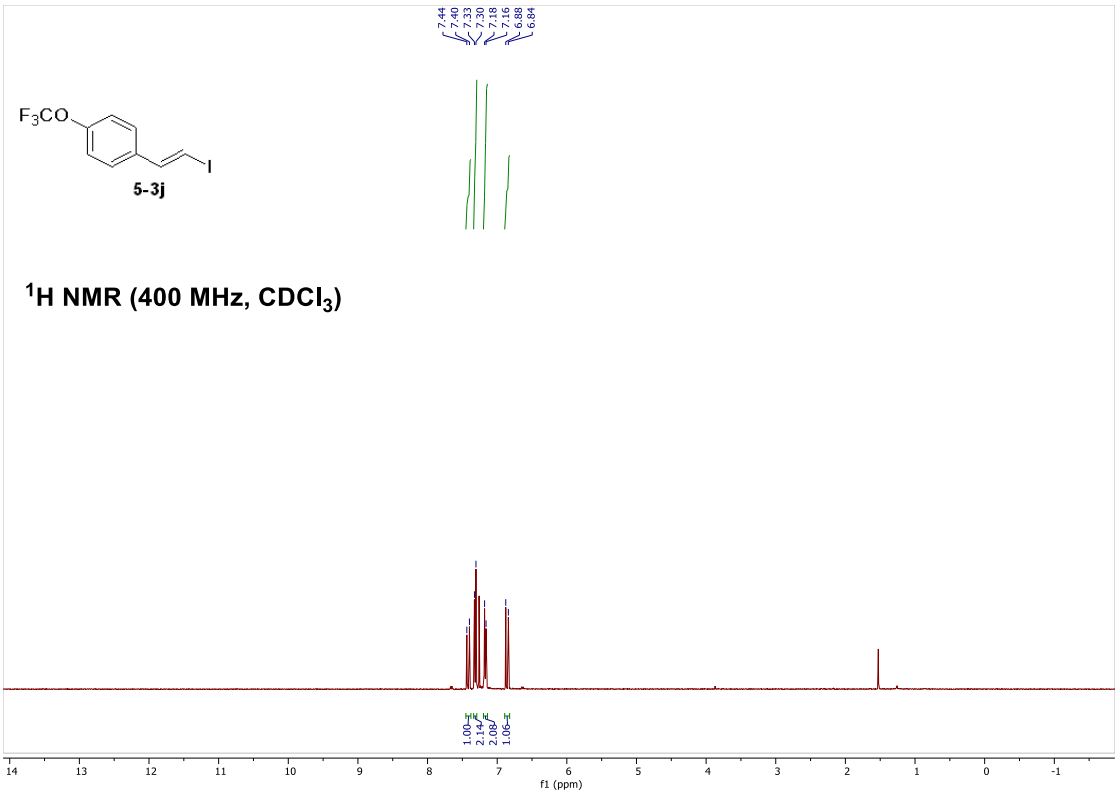
5-3h

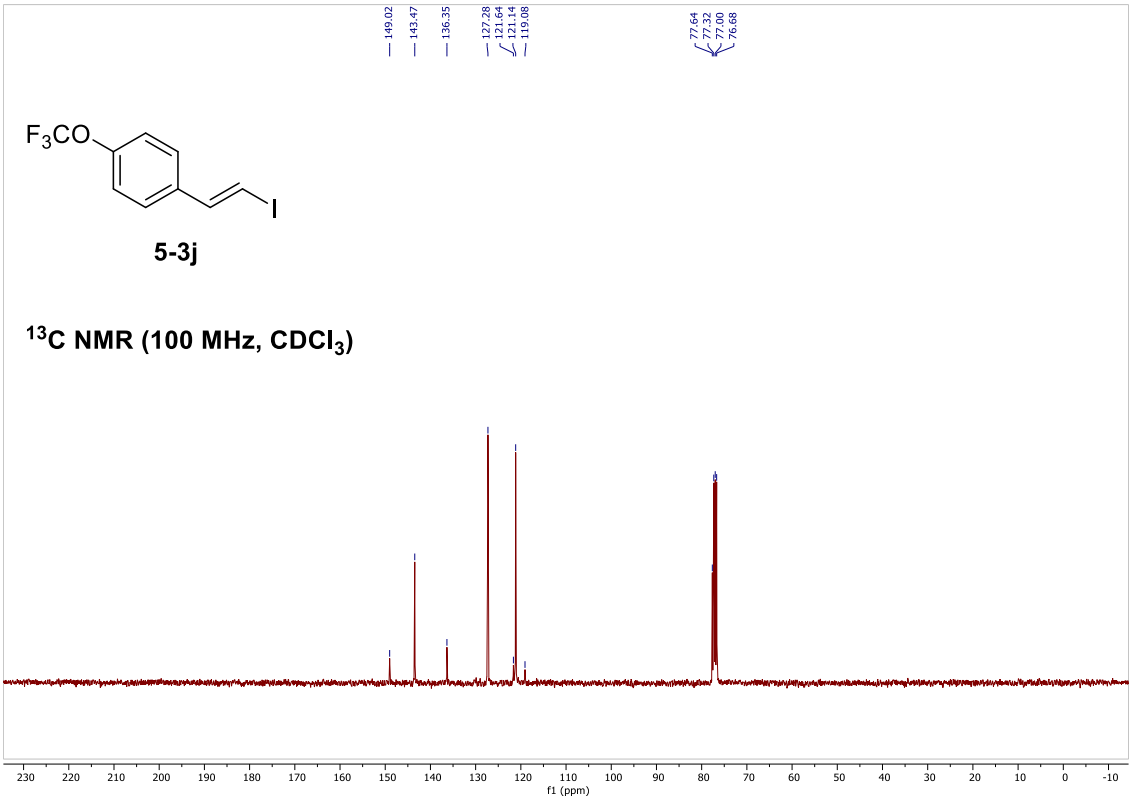
^{1}H NMR (400 MHz, $CDCl_3$)

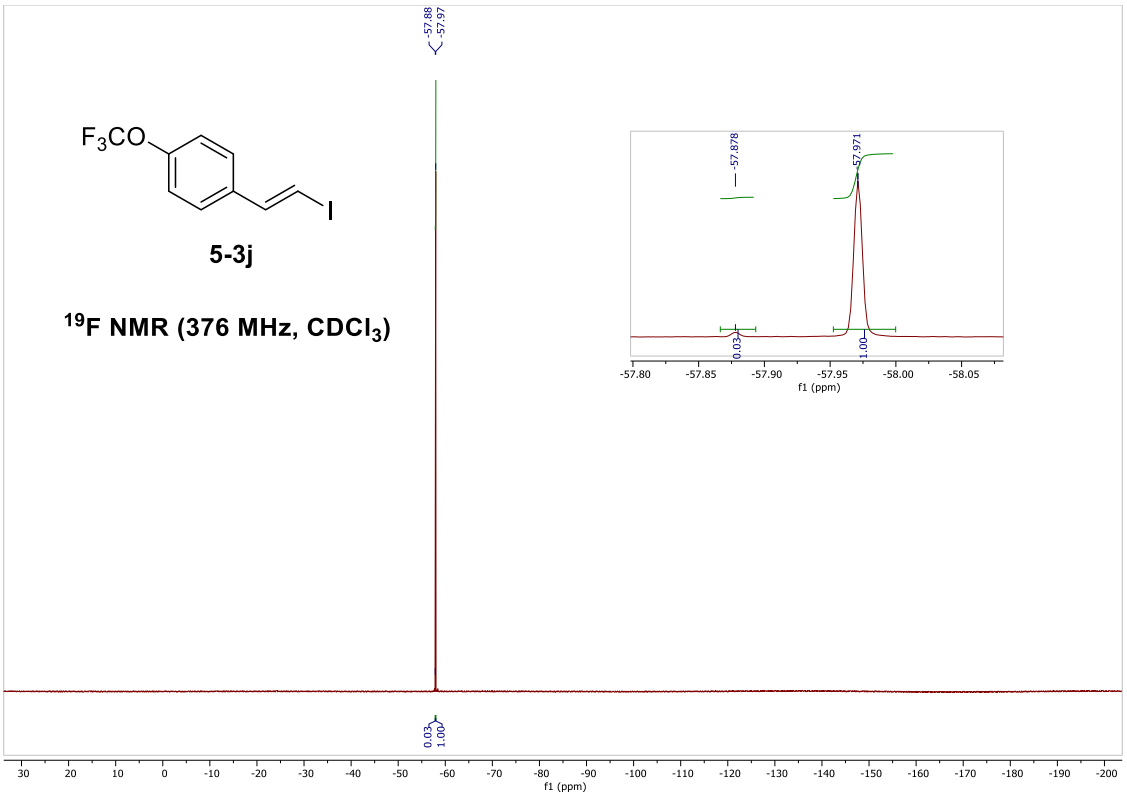


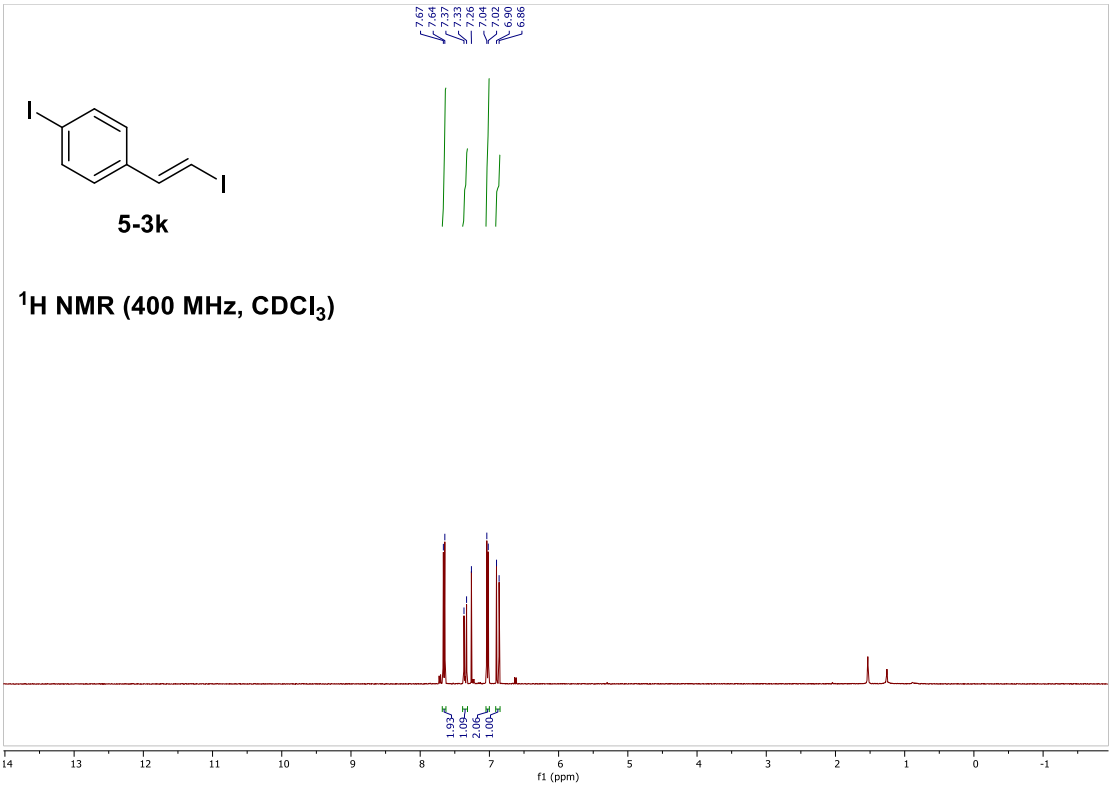
5-3i

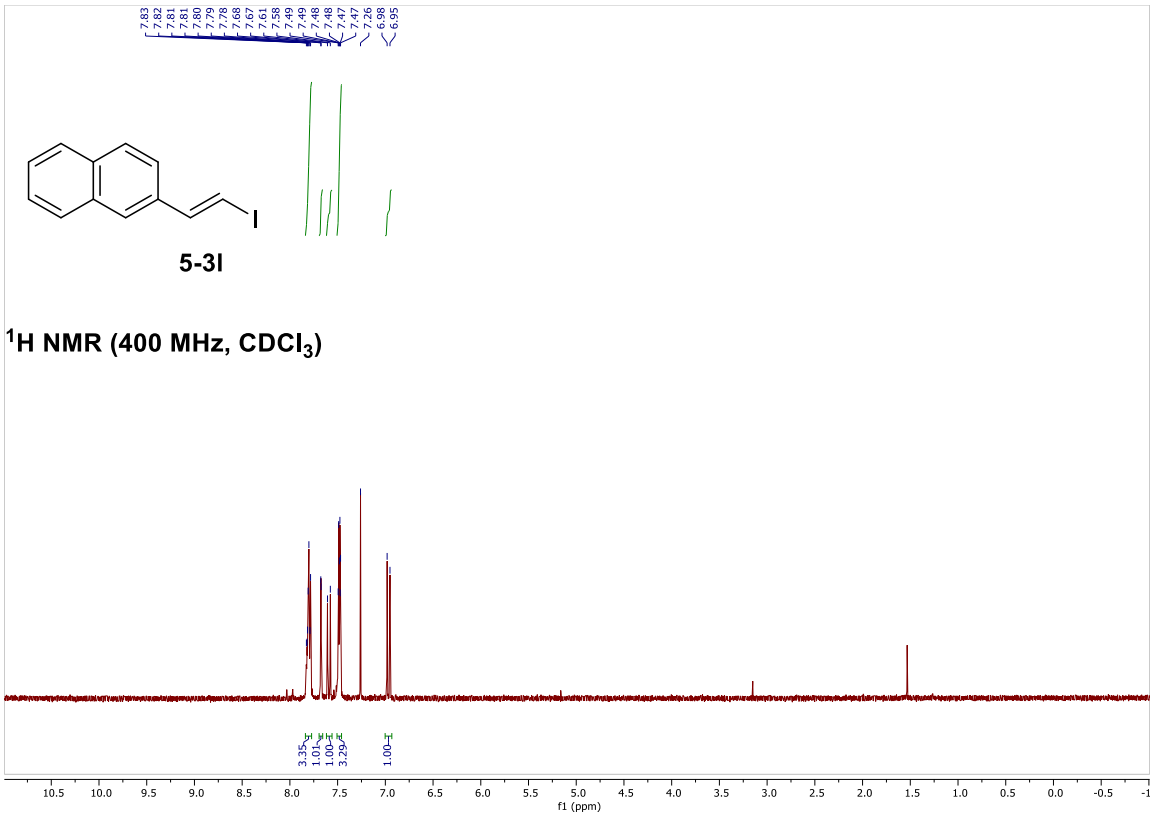
^{1}H NMR (400 MHz, $CDCl_3$)


7.44
7.40
7.33
7.30
7.18
7.16
6.88
6.84
F3CO
I
5-3j
1H NMR (400 MHz, CDCl3)
1.00
2.14
2.08
1.06
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)


149.02
143.47
136.35
127.28
121.64
121.14
119.08
77.64
77.32
77.00
76.68
F3CO
I
5-3j
13C NMR (100 MHz, CDCl3)
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

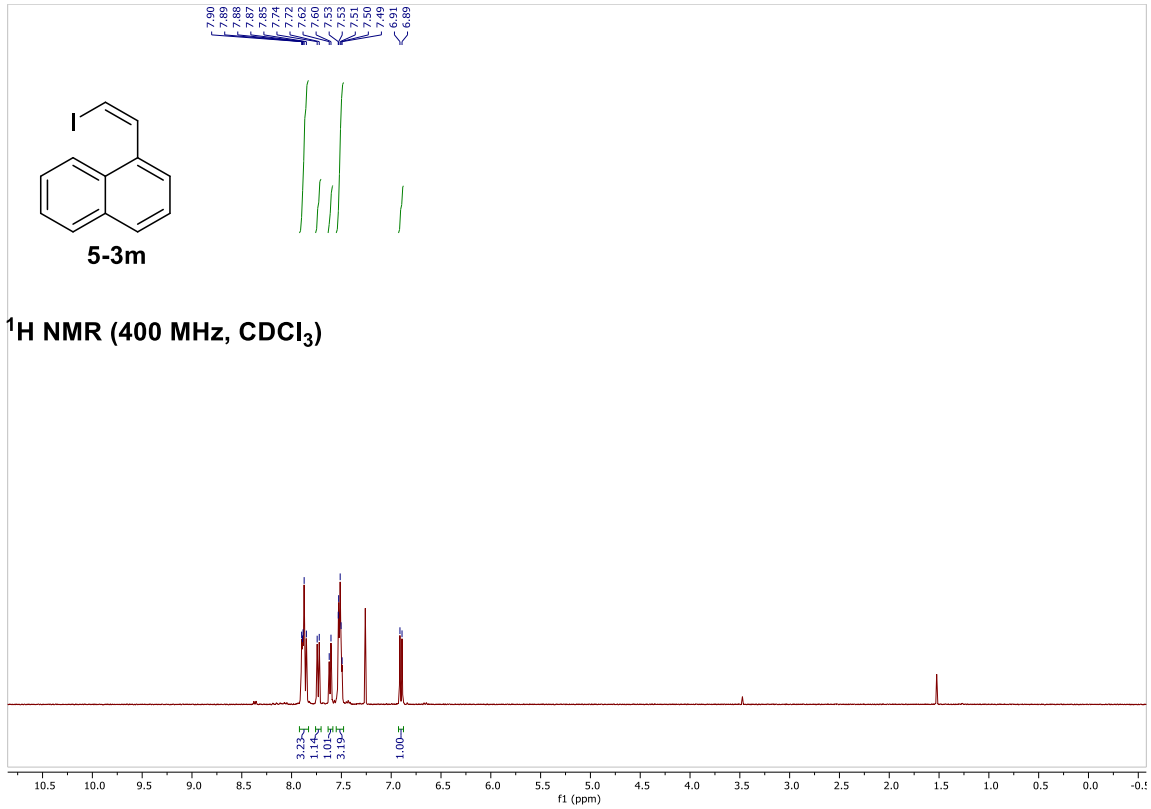

F3CO
I
5-3j
19F NMR (376 MHz, CDCl3)
-57.88
-57.97
-57.878
-57.971
0.03
1.00
f1 (ppm)


I
I
5-3k
1H NMR (400 MHz, CDCl3)
7.67
7.64
7.37
7.33
7.26
7.04
7.02
6.90
6.86
1.93
1.09
2.06
1.00
f1 (ppm)



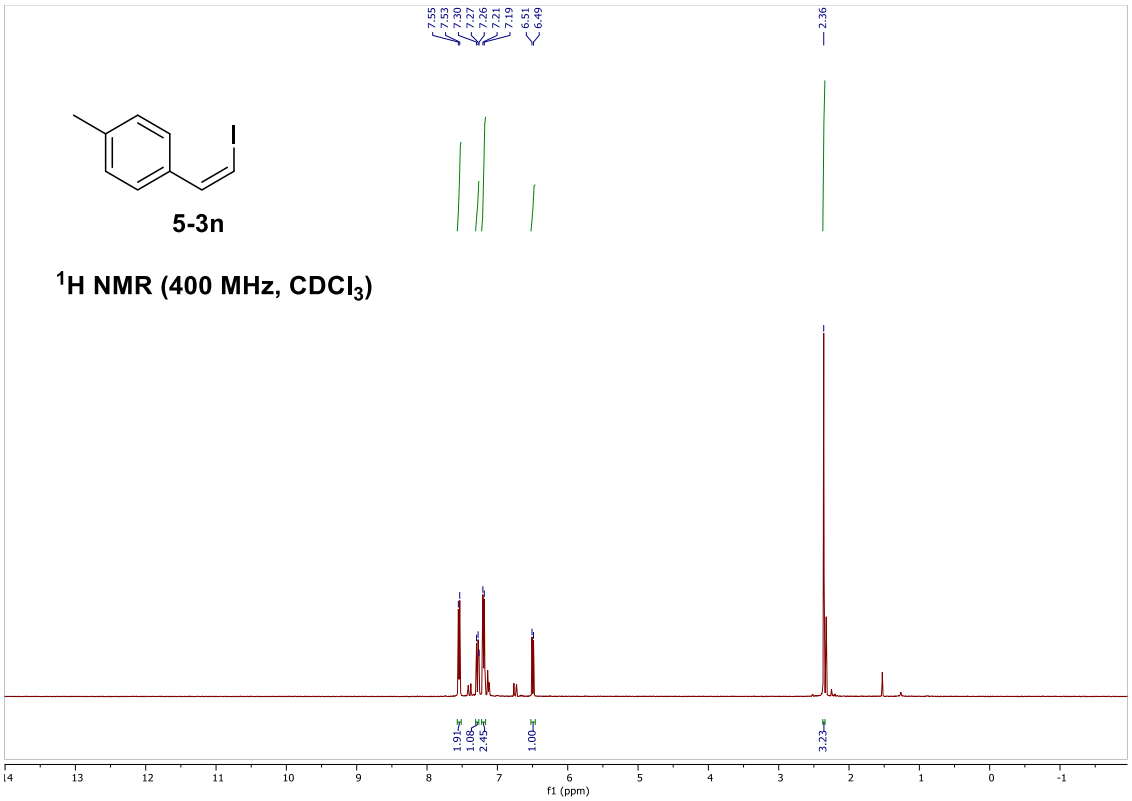
5-3l

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



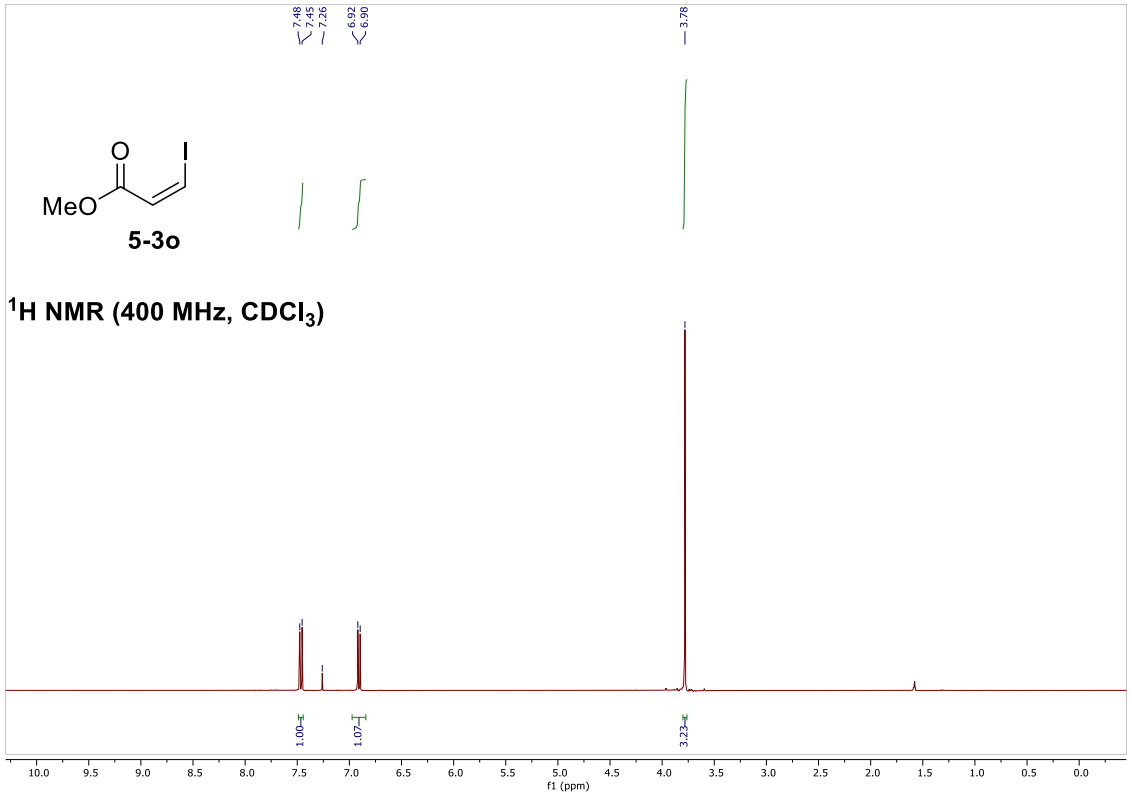
5-3m

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



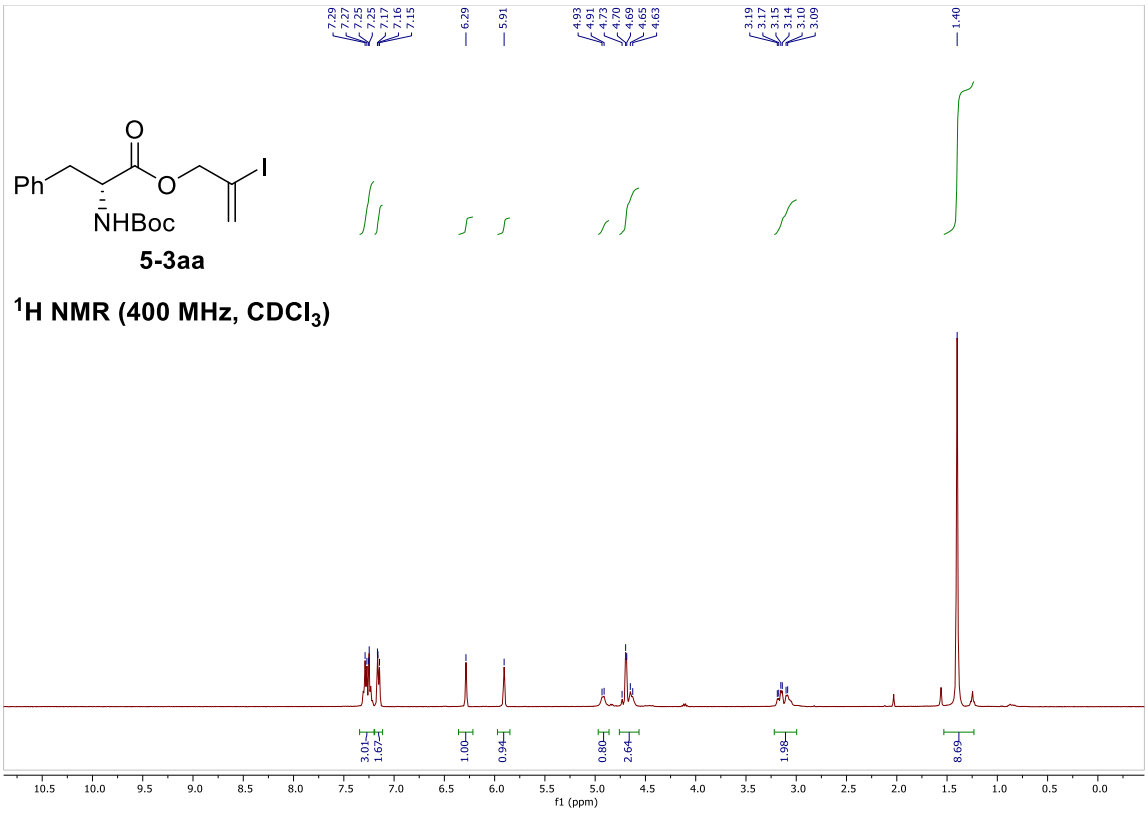
5-3n

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



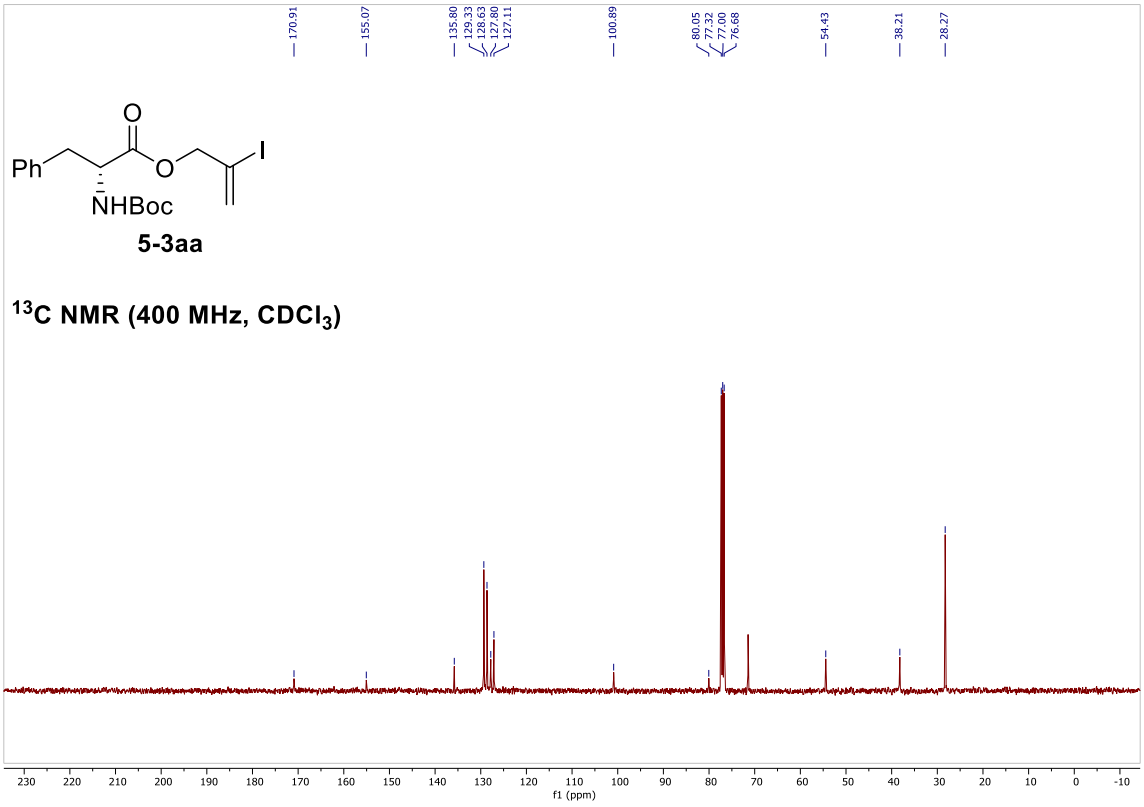
5-3o

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



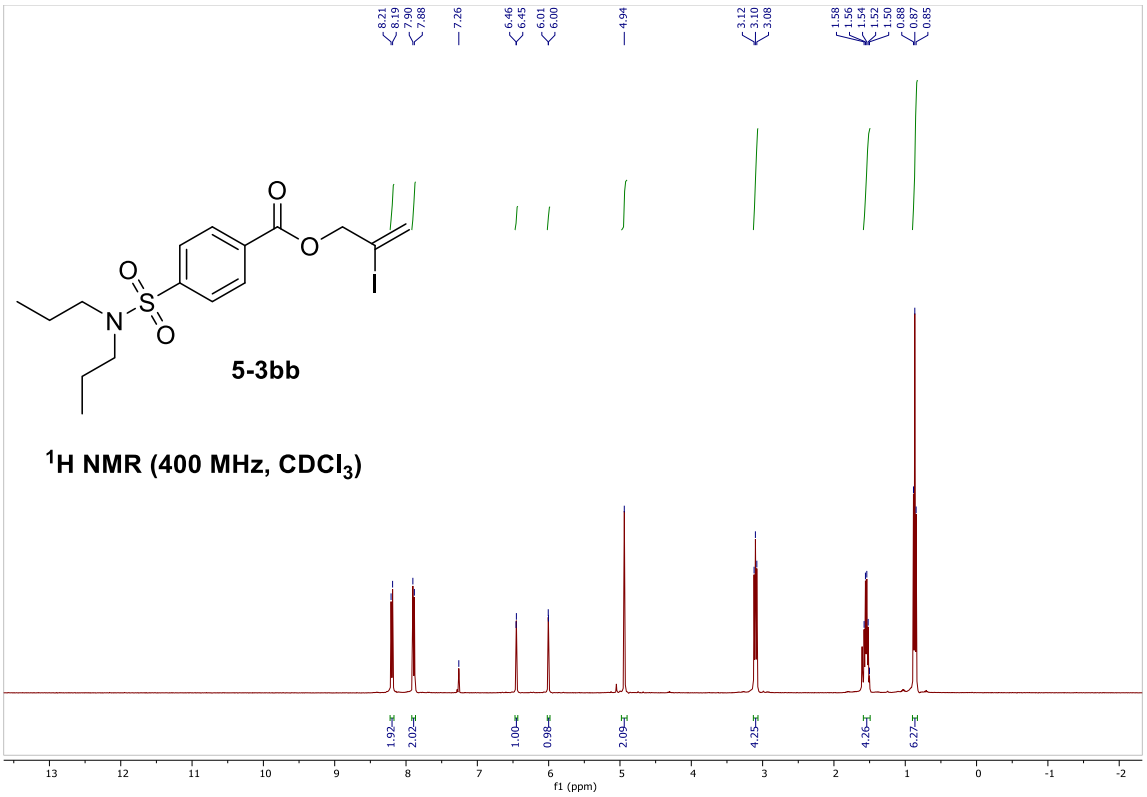
5-3aa

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



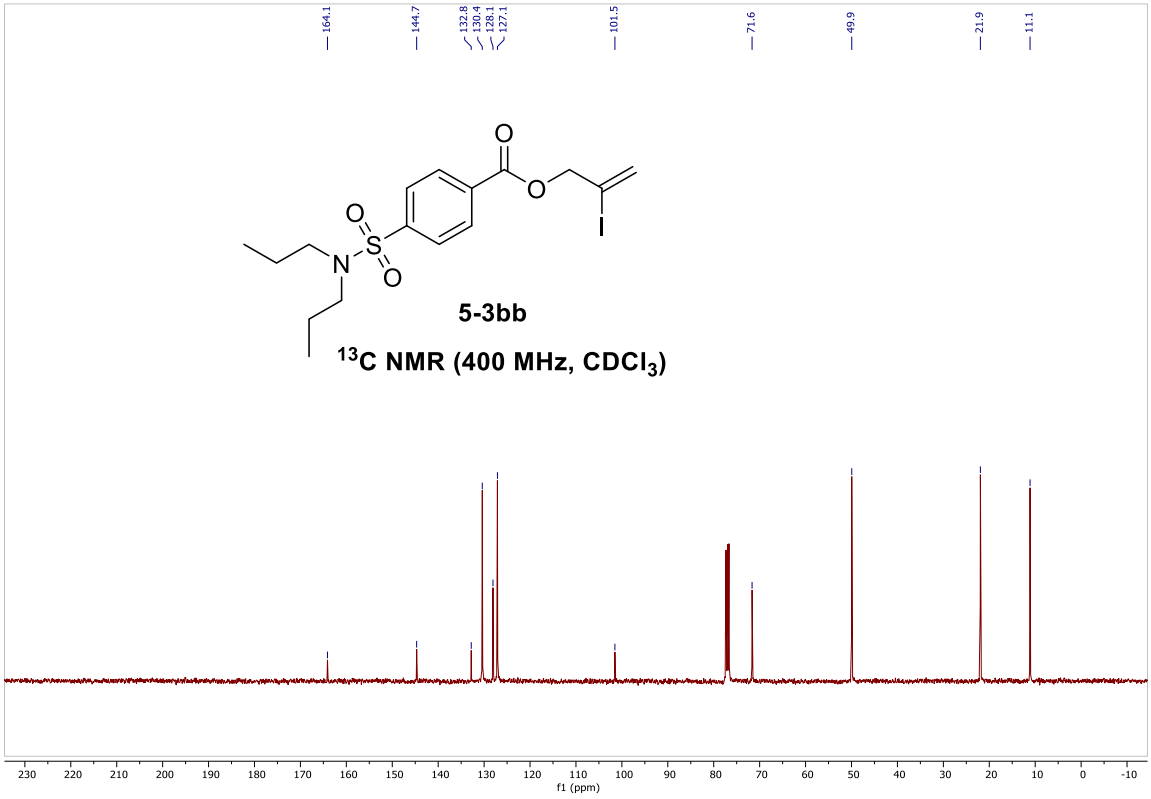
5-3aa

^{13}C NMR (400 MHz, $CDCl_3$)



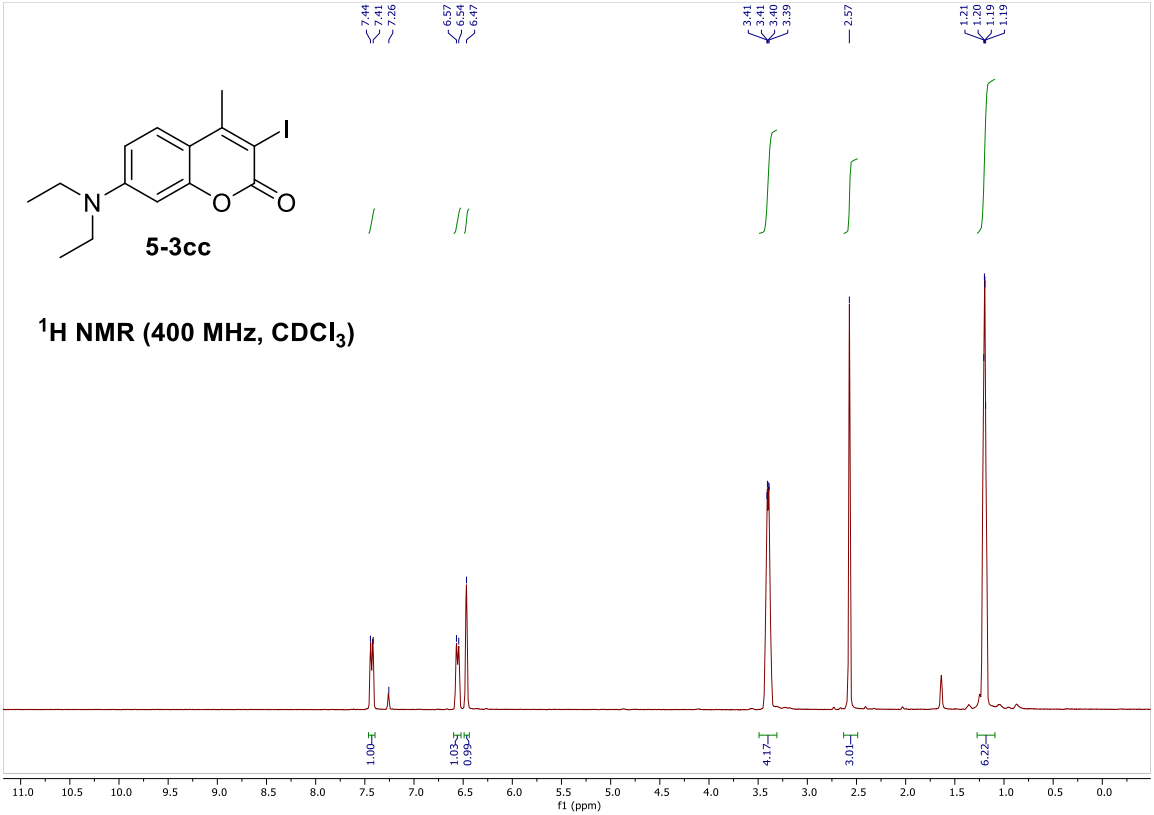
5-3bb

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



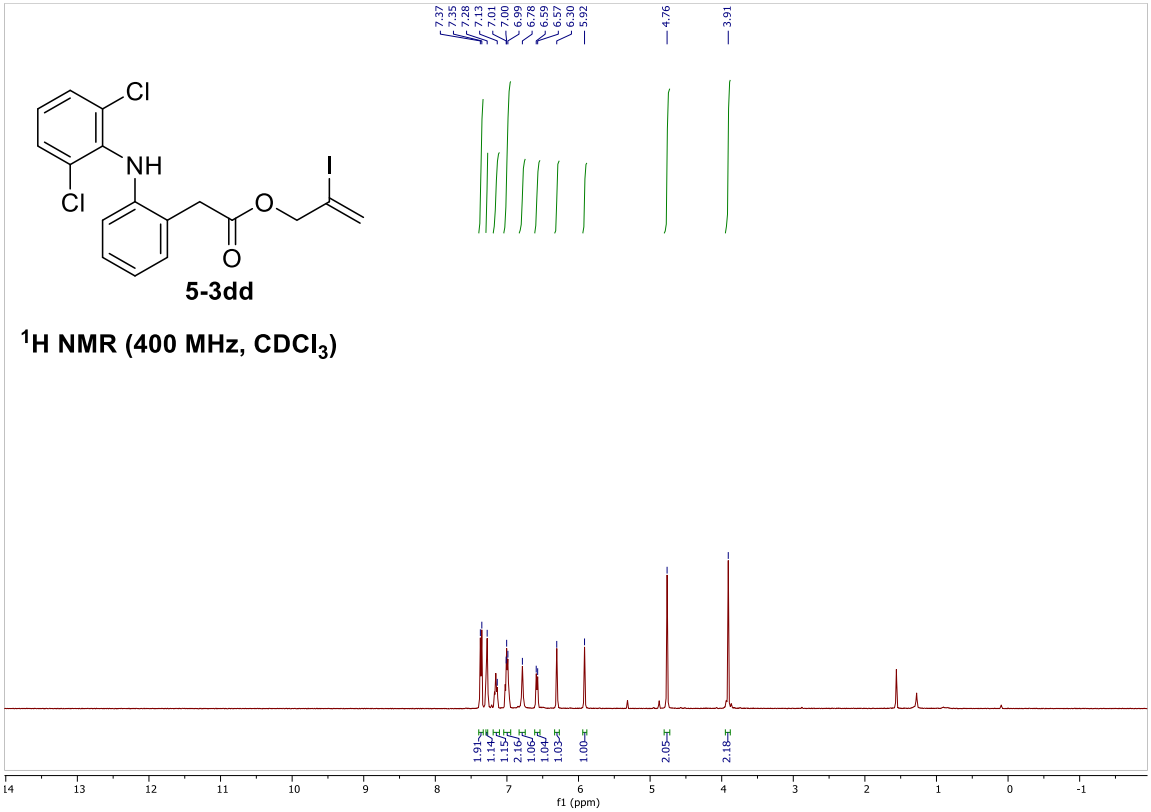
5-3bb

^{13}C NMR (400 MHz, $CDCl_3$)



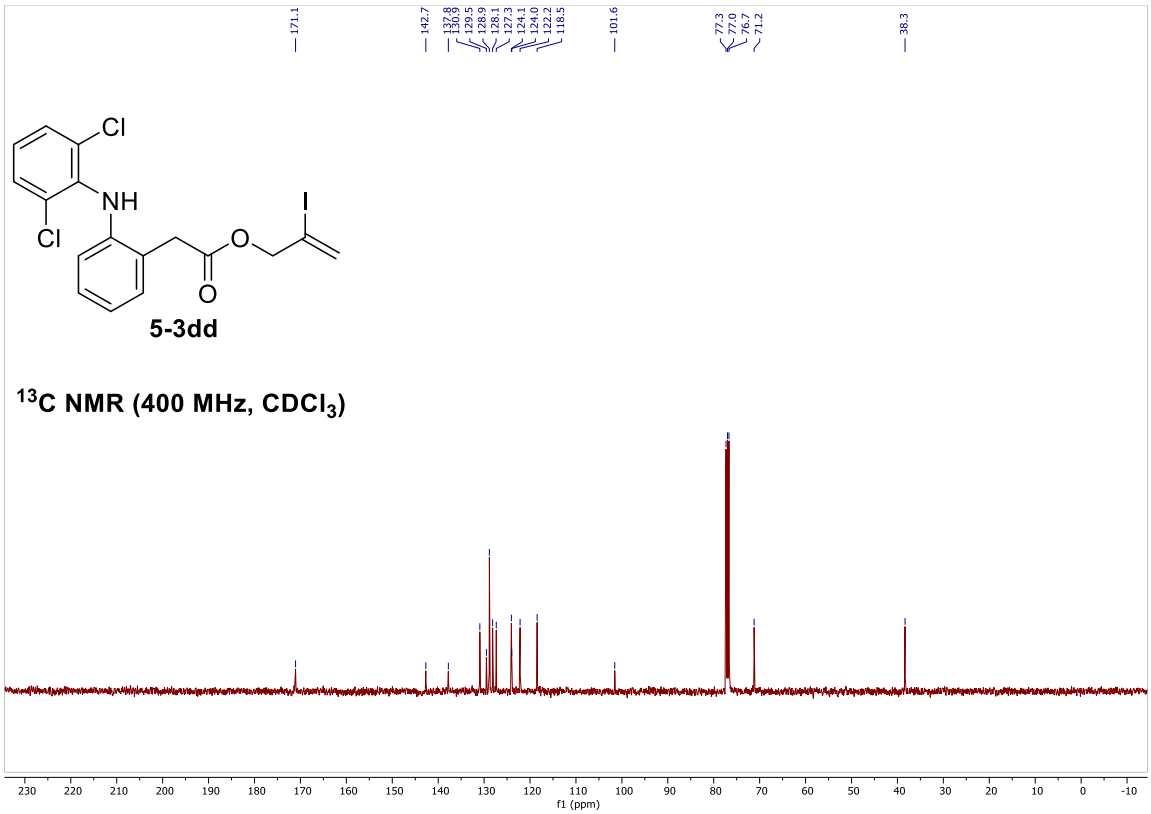
5-3cc

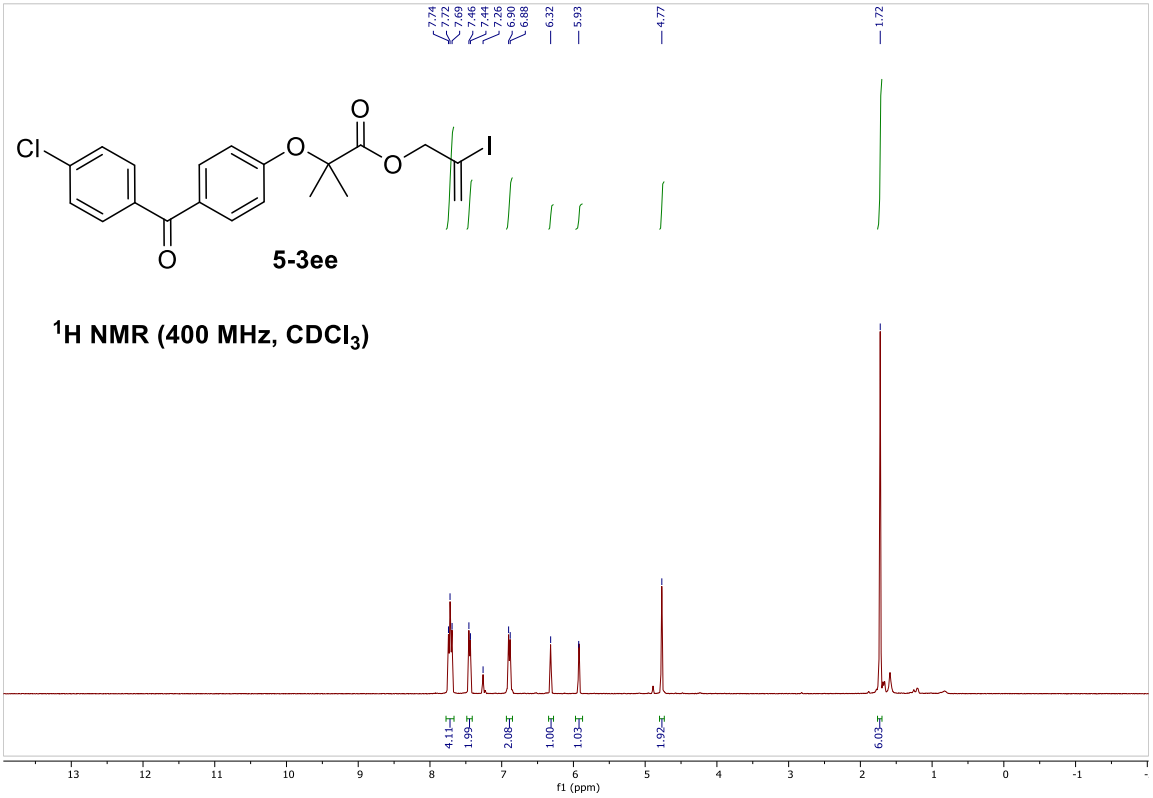
^{1}H NMR (400 MHz, $CDCl_3$)

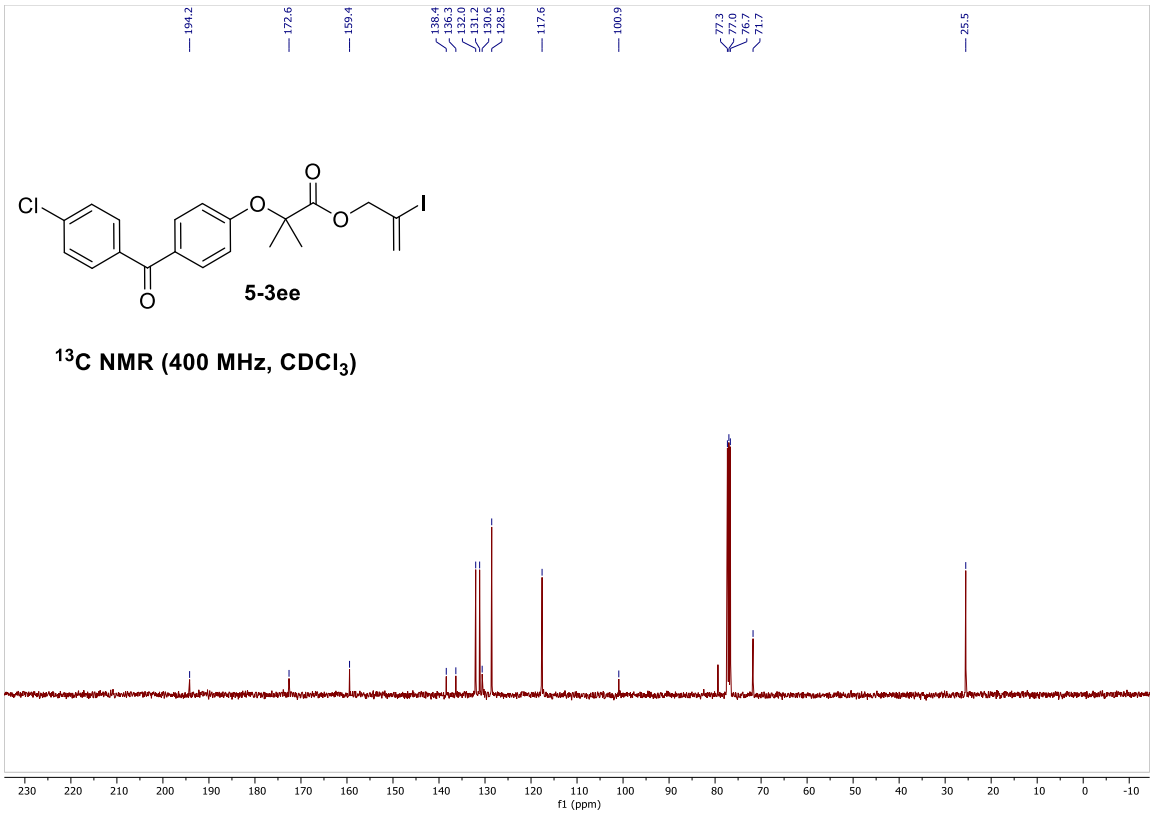


5-3dd

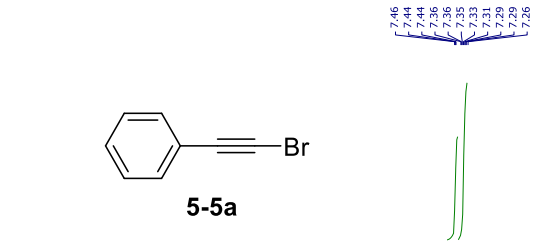
^{1}H NMR (400 MHz, $CDCl_3$)


171.1
142.7
137.8
130.9
129.5
129.0
128.1
127.3
124.1
124.0
122.2
118.5
101.6
77.3
77.0
76.7
71.2
38.3
Cl
NH
Cl
I
O
O
5-3dd
13C NMR (400 MHz, CDCl3)
f1 (ppm)


7.74
7.72
7.69
7.46
7.44
7.26
6.90
6.88
6.32
5.93
4.77
1.72
Cl
O
O
O
I
O
5-3ee
1H NMR (400 MHz, CDCl3)
4.11
1.99
2.08
1.00
1.03
1.92
6.03
f1 (ppm)

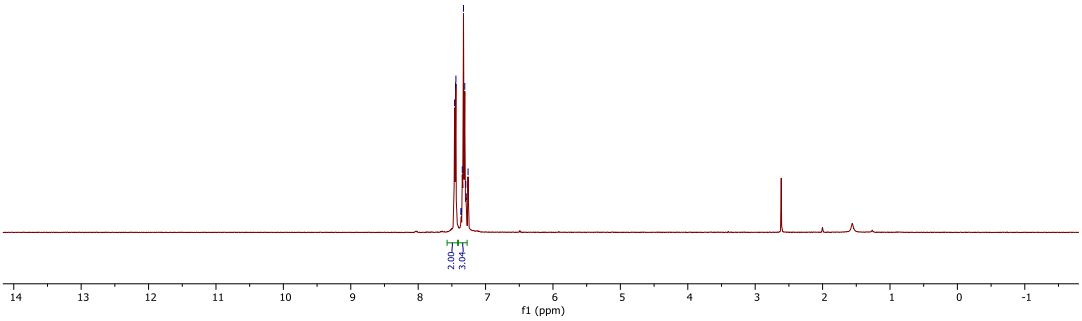

194.2
172.6
159.4
138.4
136.3
132.0
131.2
130.6
128.5
117.6
100.9
77.3
77.0
76.7
71.7
25.5
Cl
O
O
O
O
I
5-3ee
13C NMR (400 MHz, CDCl3)
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

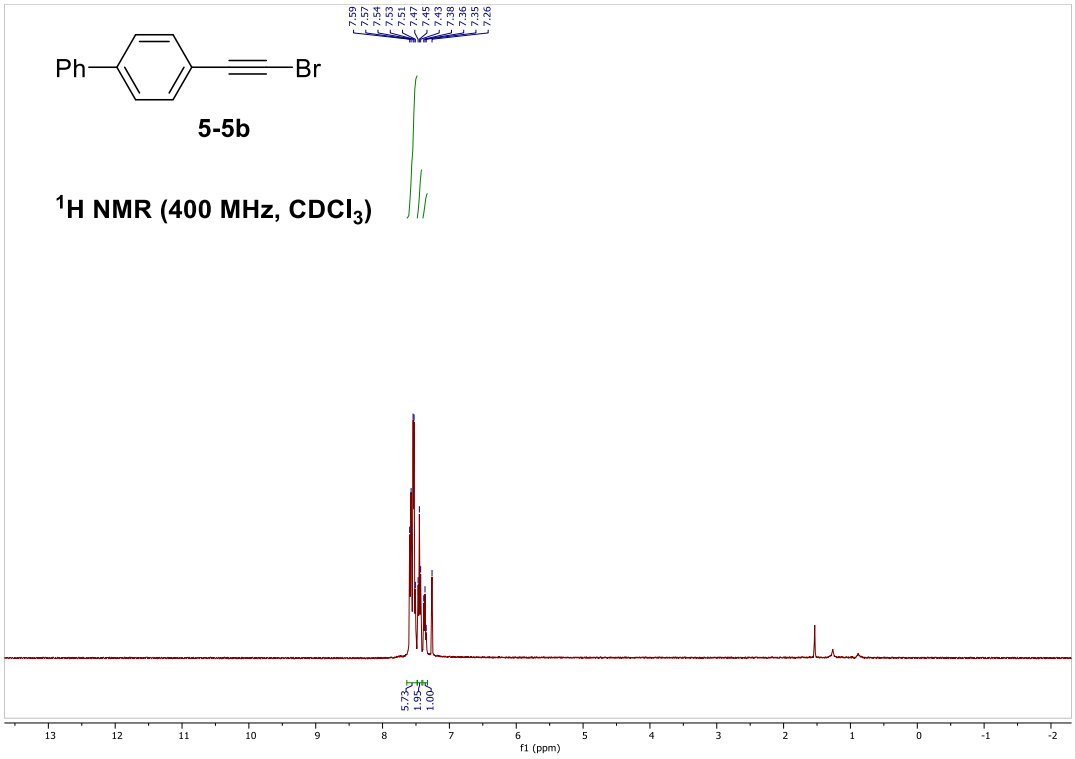
5.4.7.3 Synthesized alkynyl bromide substrates



5-5a

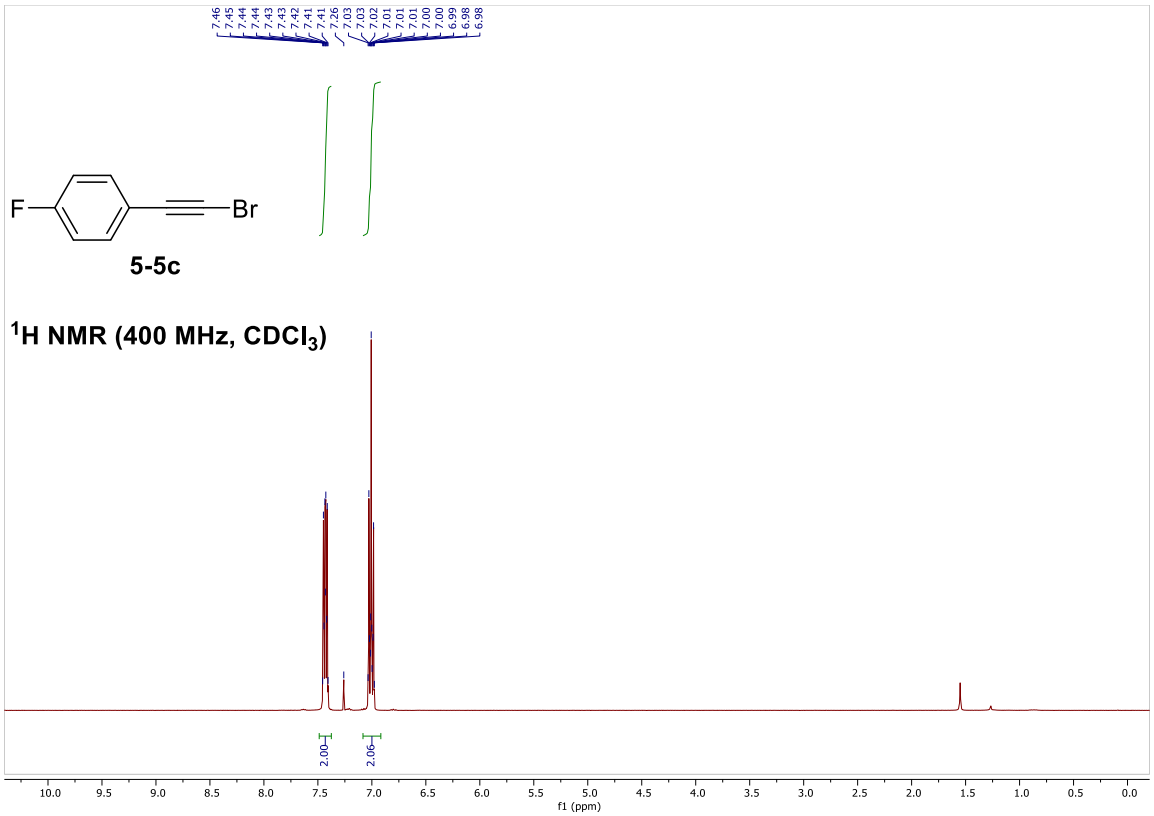
^{1}H NMR (400 MHz, $CDCl_3$)





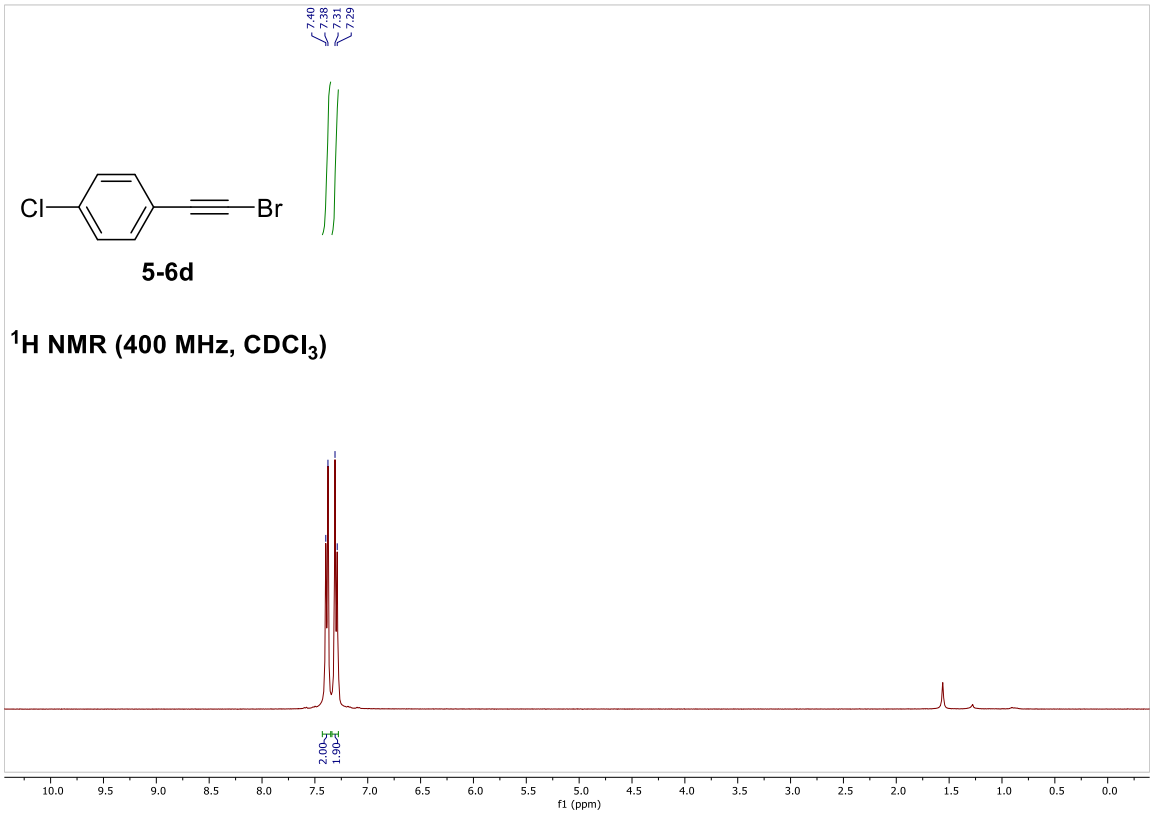
5-5b

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



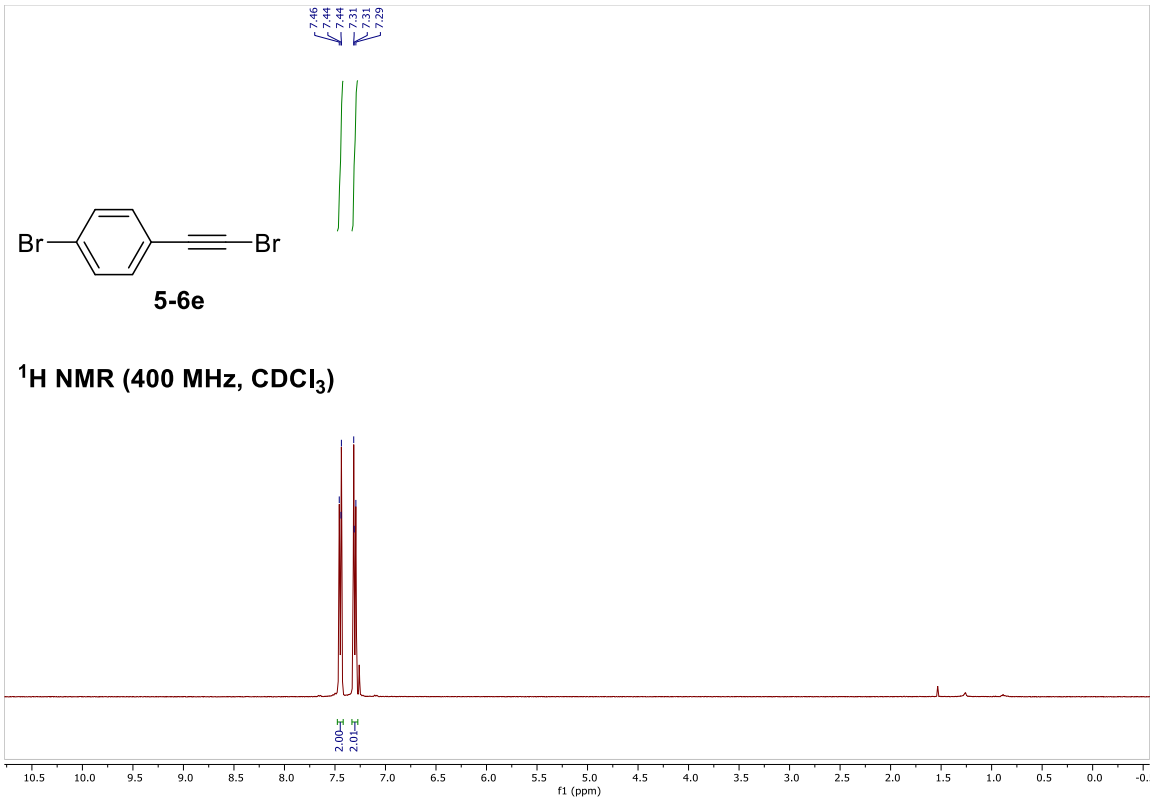
5-5c

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



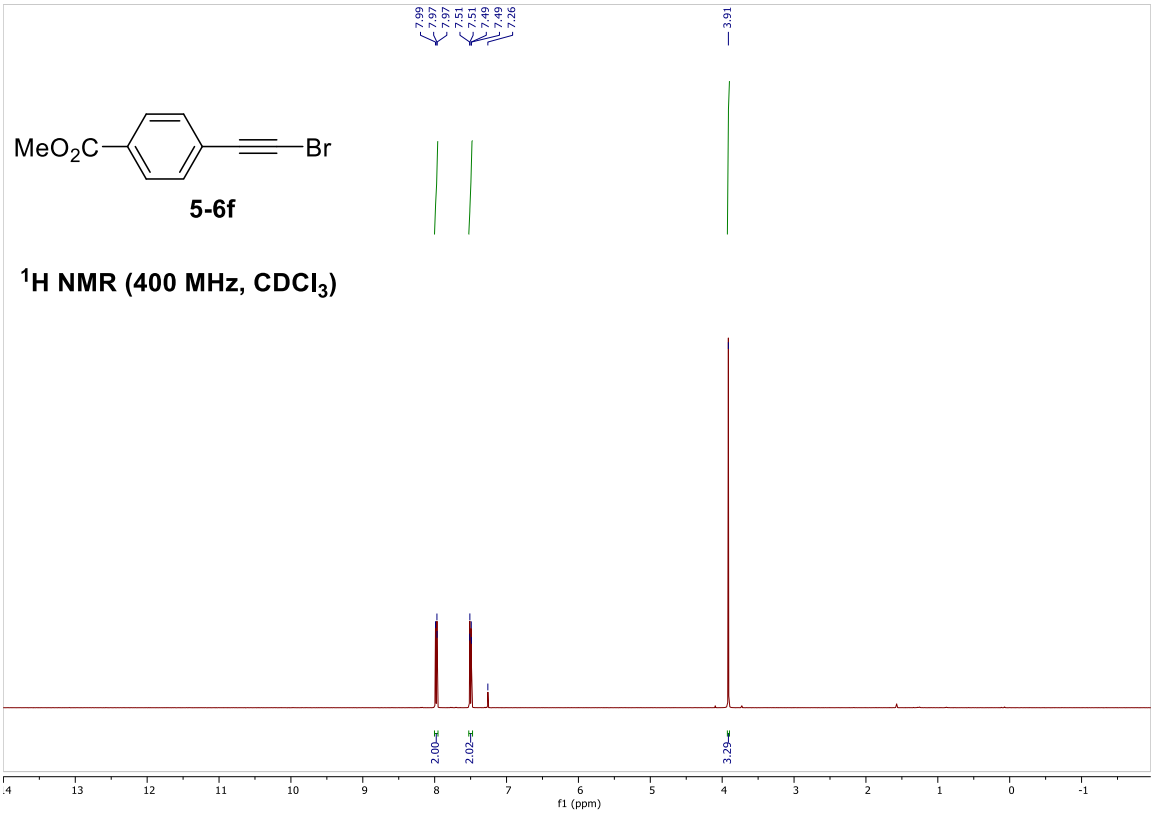
5-6d

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



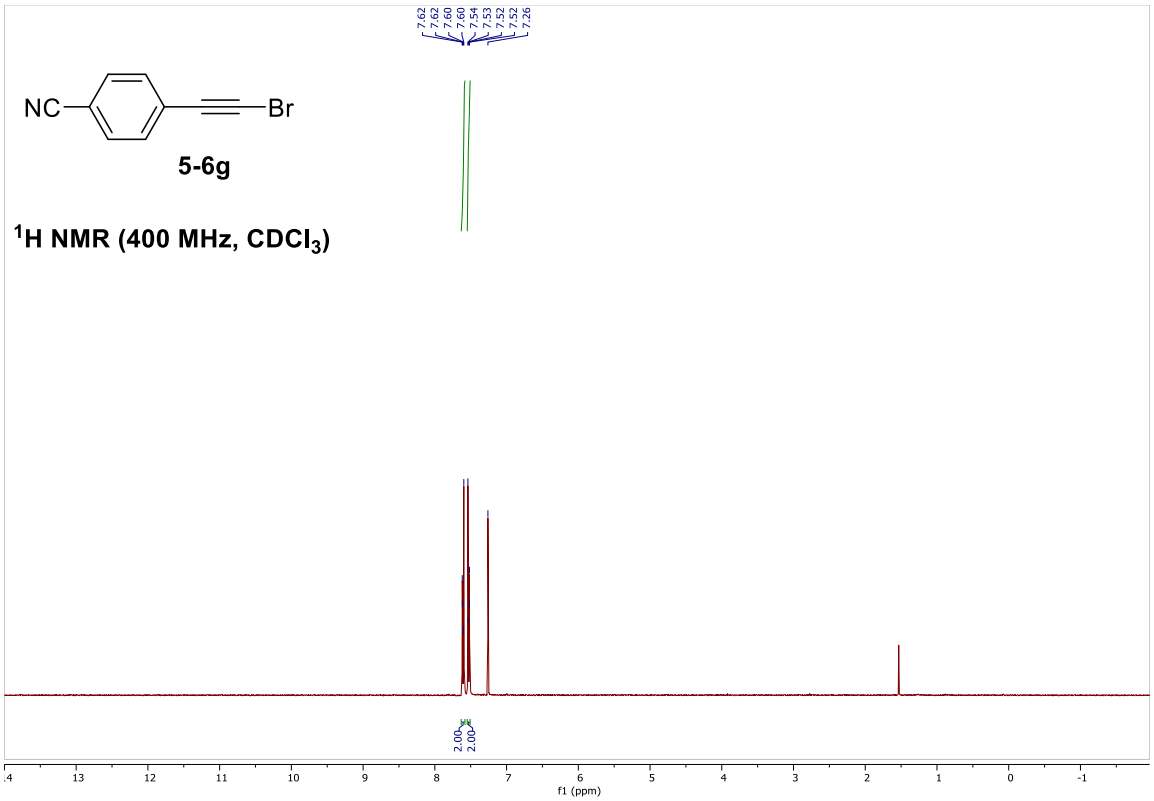
5-6e

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



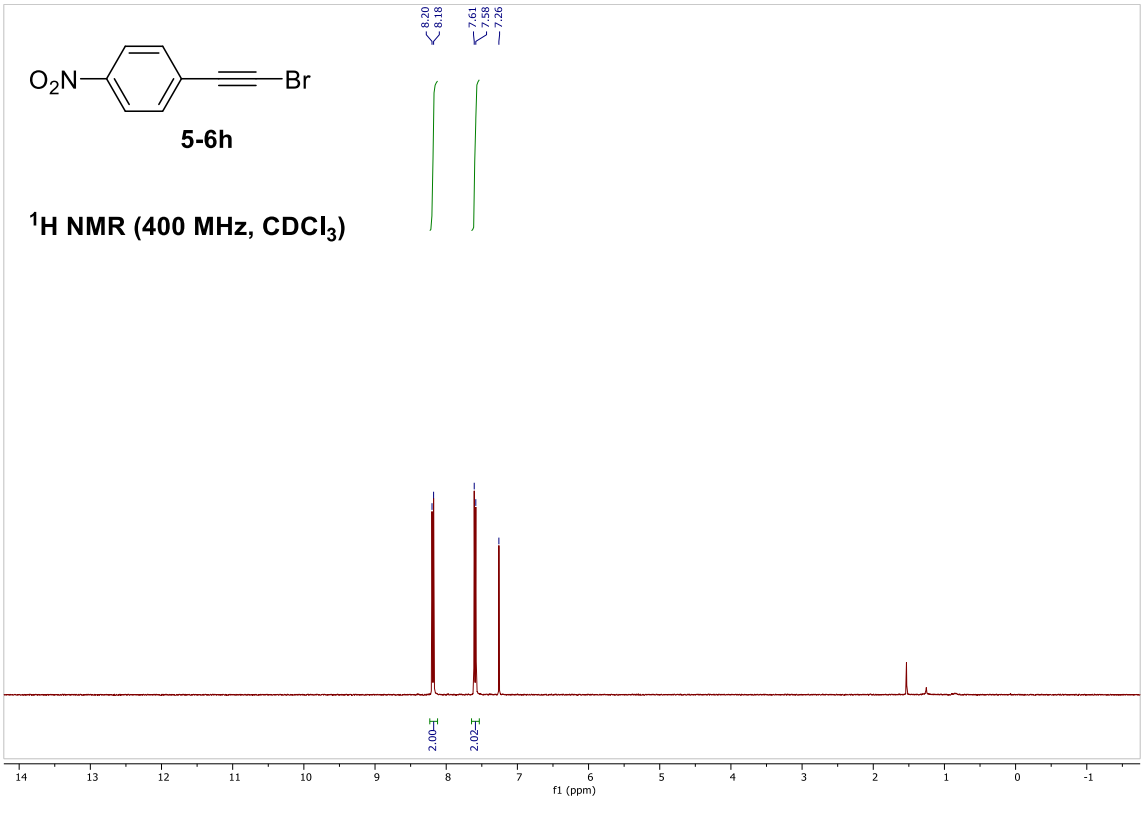
5-6f

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



5-6g

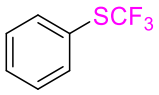
^{1}H NMR (400 MHz, $CDCl_3$)



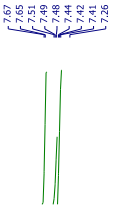
5-6h

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

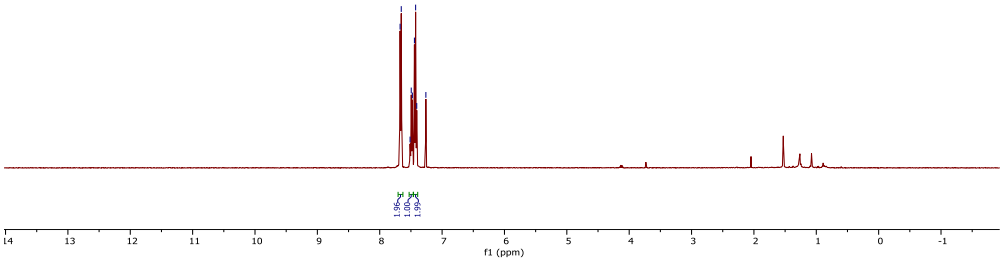
5.4.7.4. Trifluoromethylthiolation products from aryl iodide substrates

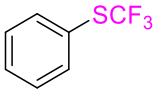


5-2a



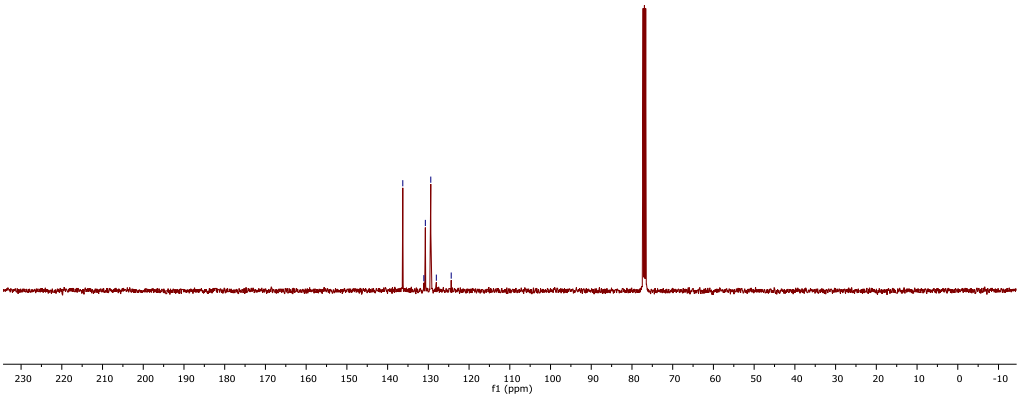
^{1}H NMR (400 MHz, $CDCl_3$)

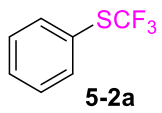




5-2a

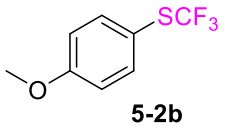
^{13}C NMR (100 MHz, $CDCl_3$)





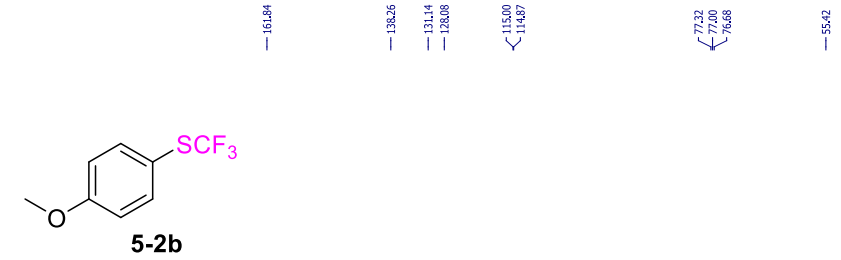
5-2a

^{19}F NMR (376 MHz, $CDCl_3$)



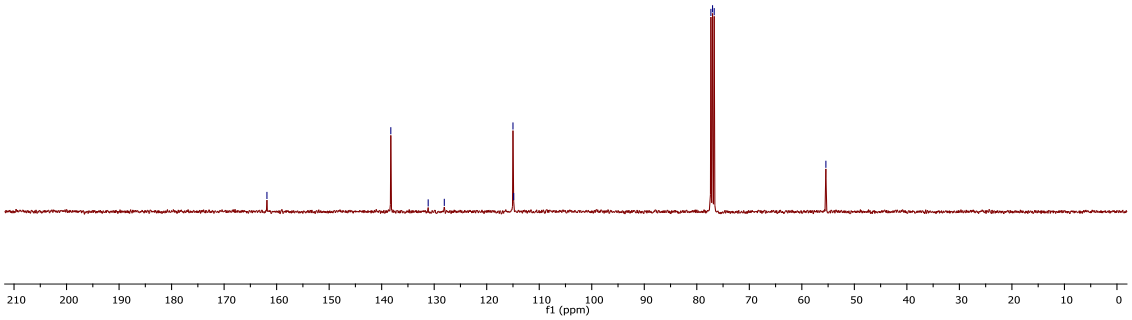
5-2b

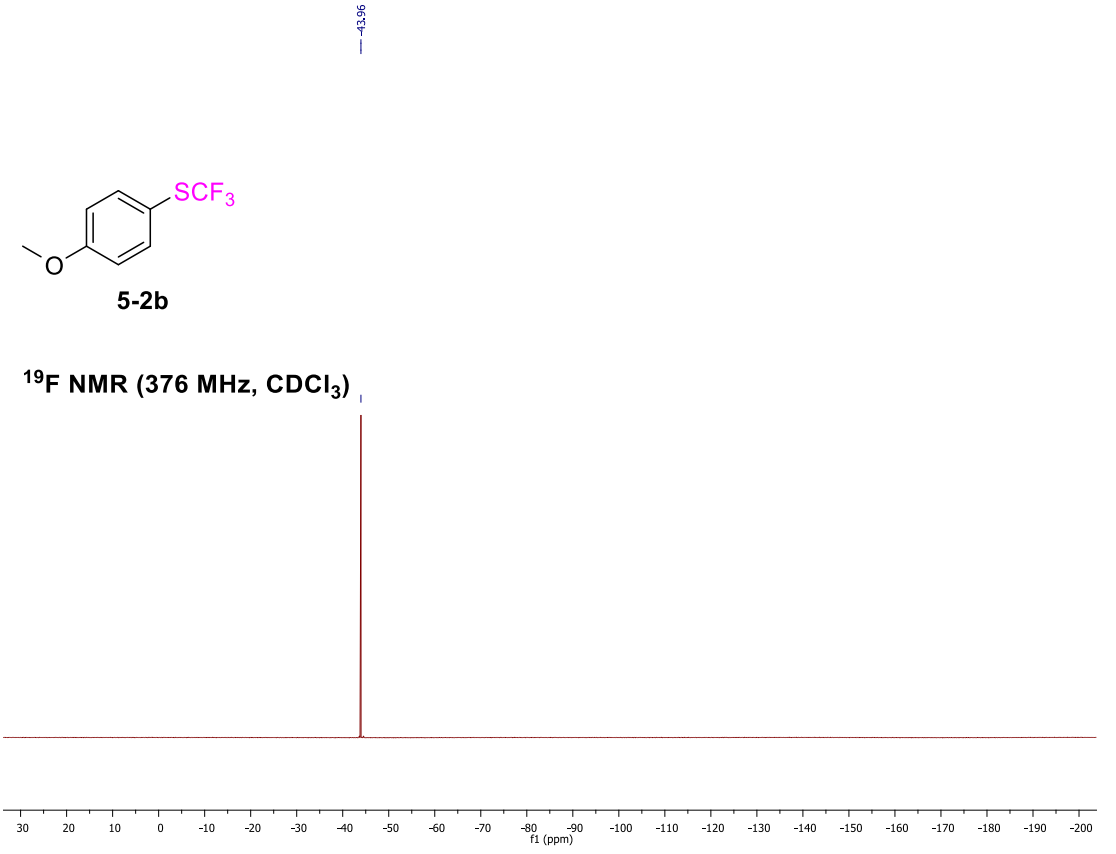
^{1}H NMR (400 MHz, $CDCl_3$)



5-2b

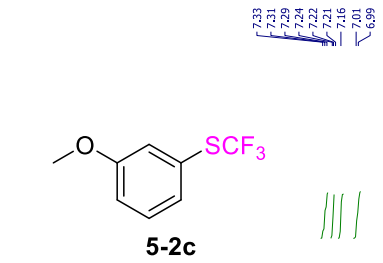
^{13}C NMR (100 MHz, $CDCl_3$)





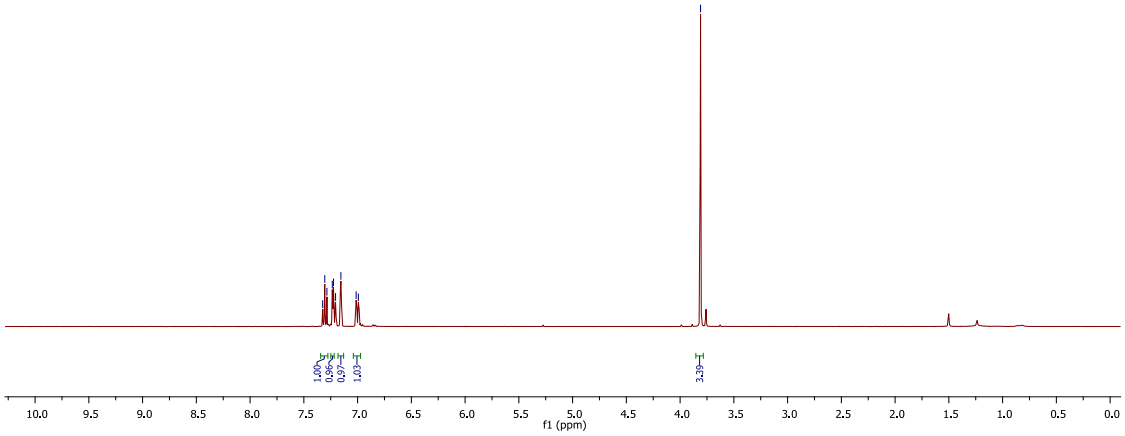
5-2b

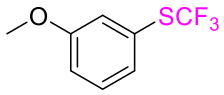
^{19}F NMR (376 MHz, $CDCl_3$)



5-2c

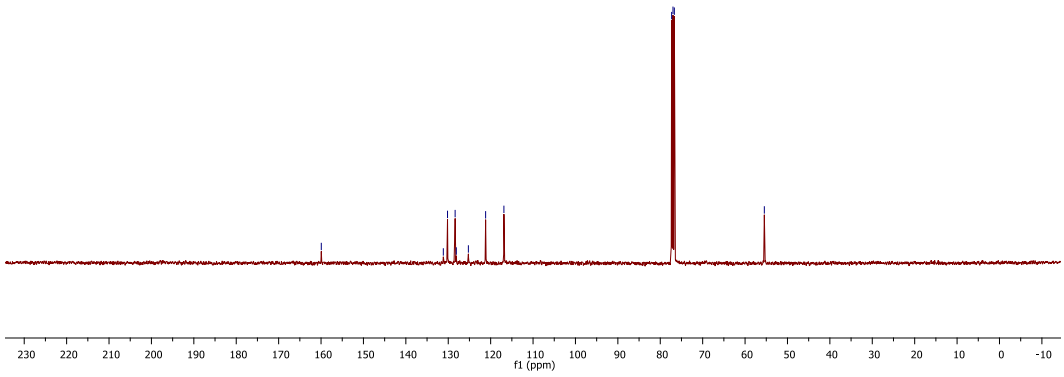
^{1}H NMR (400 MHz, $CDCl_3$)





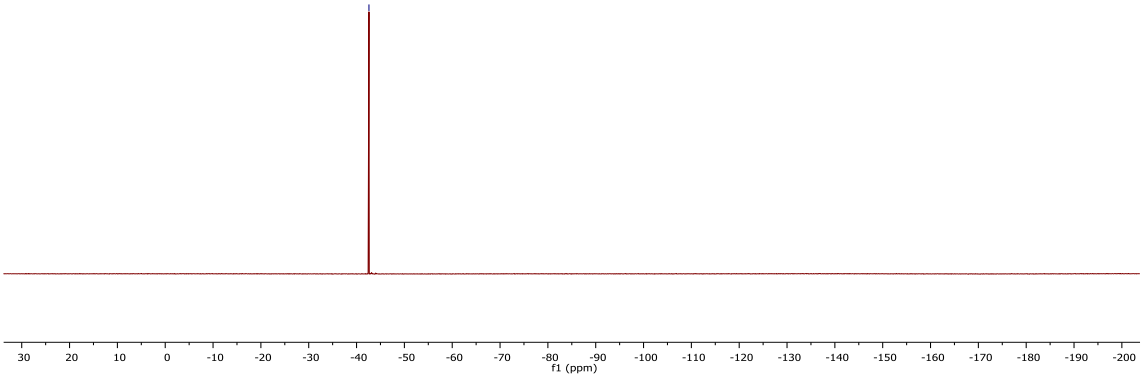
5-2c

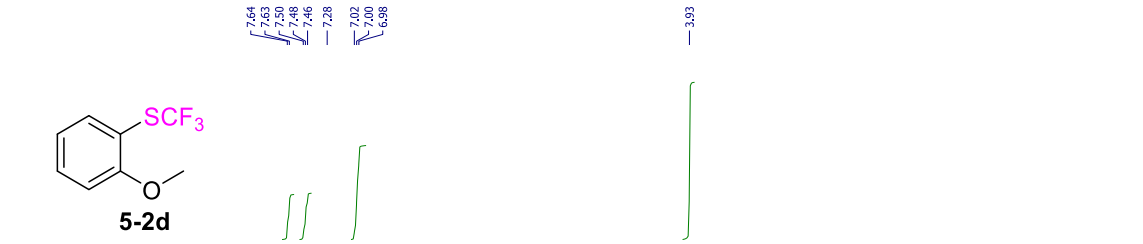
^{13}C NMR (100 MHz, $CDCl_3$)



5-2c

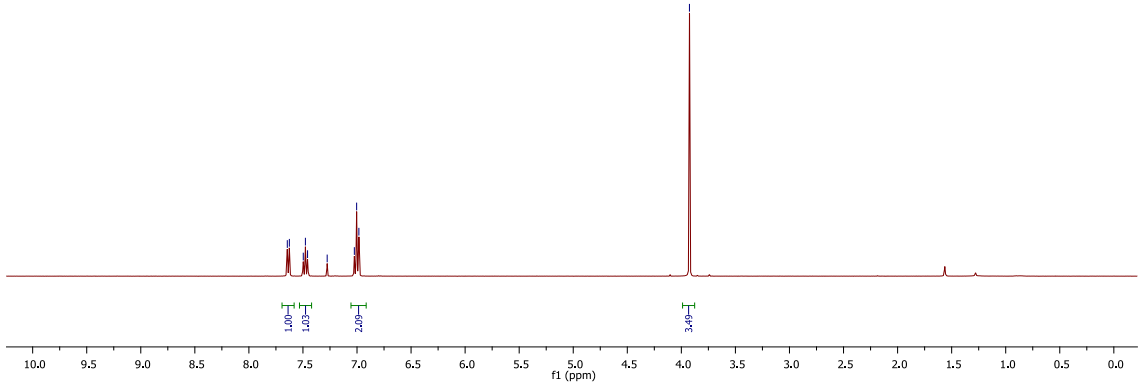
^{19}F NMR (376 MHz, $CDCl_3$)

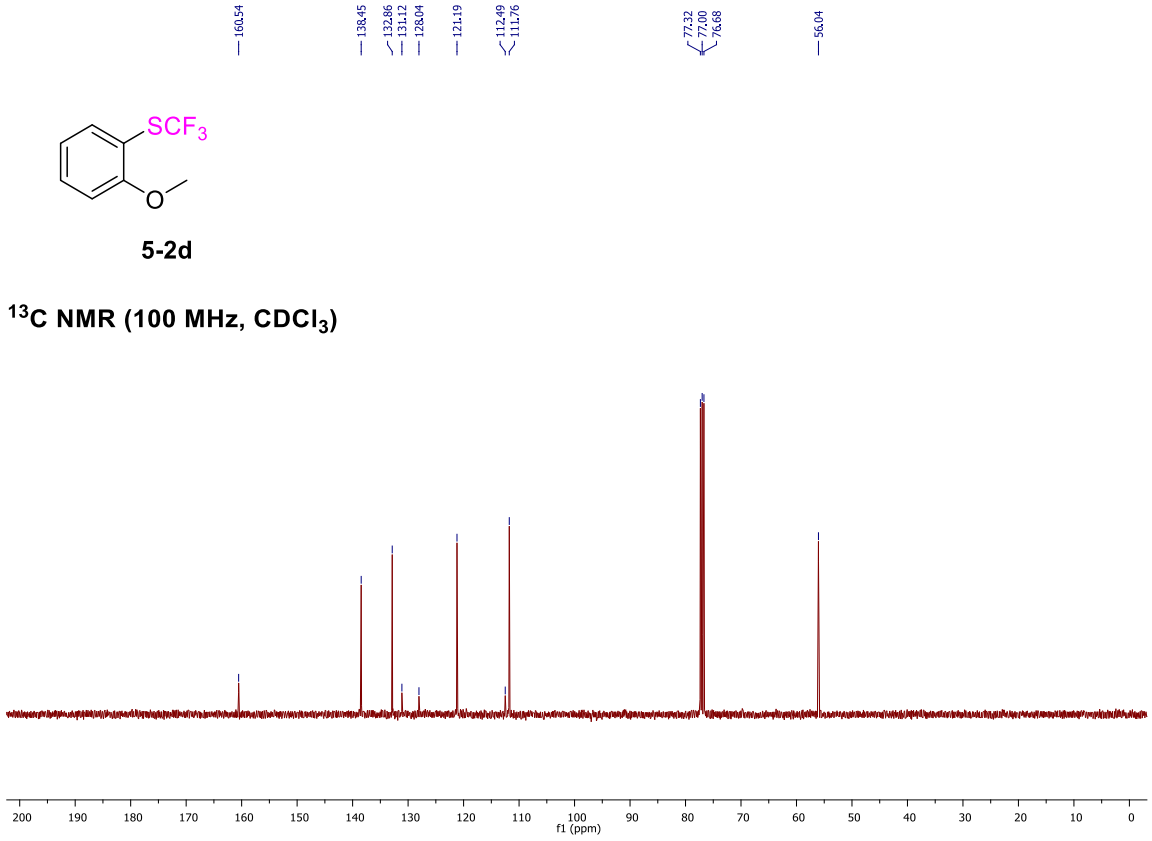




5-2d

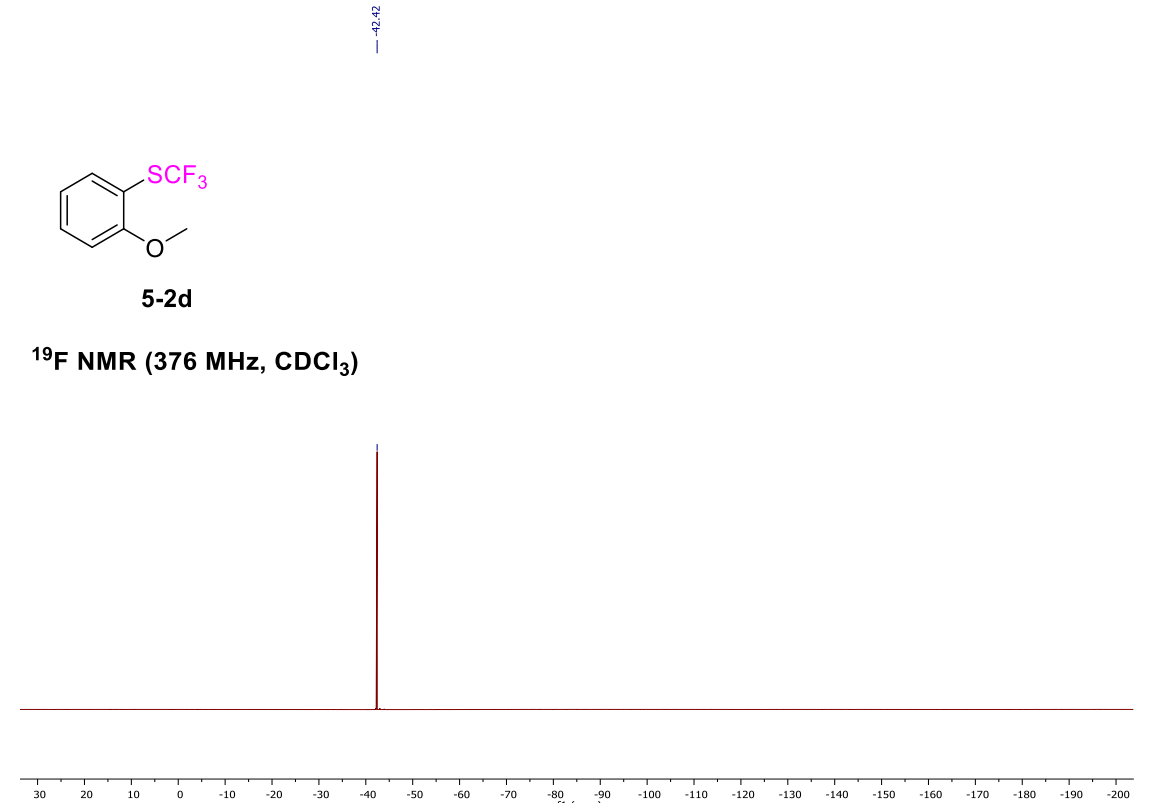
^{1}H NMR (400 MHz, $CDCl_3$)





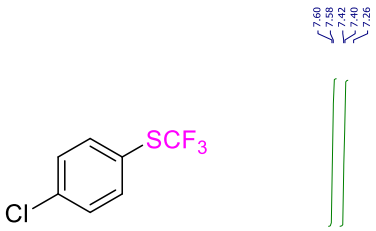
5-2d

^{13}C NMR (100 MHz, $CDCl_3$)



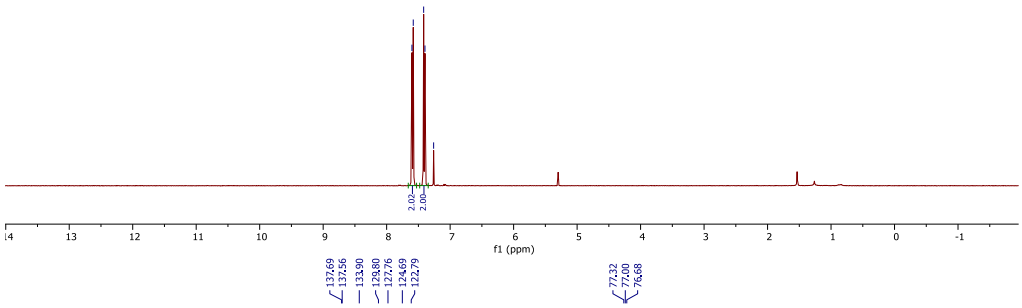
5-2d

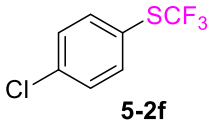
^{19}F NMR (376 MHz, $CDCl_3$)



5-2f

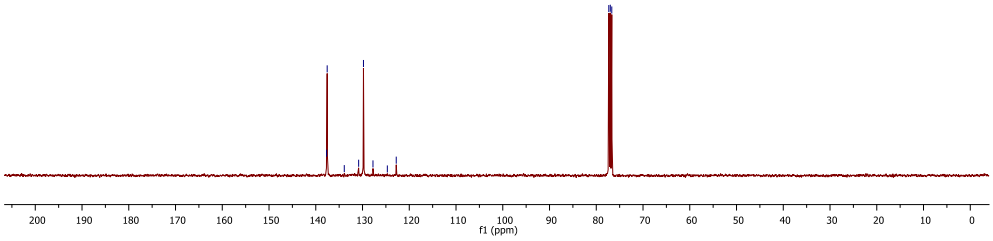
^{1}H NMR (400 MHz, $CDCl_3$)

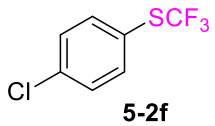




5-2f

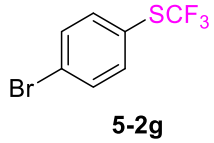
^{13}C NMR (100 MHz, $CDCl_3$)





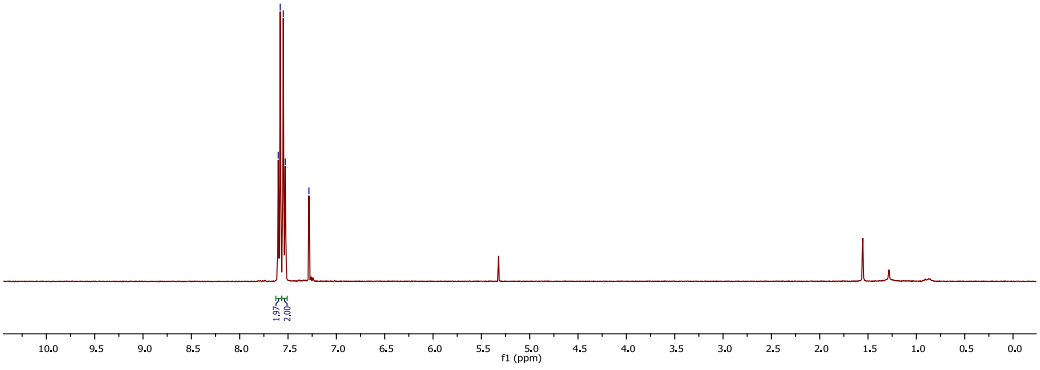
5-2f

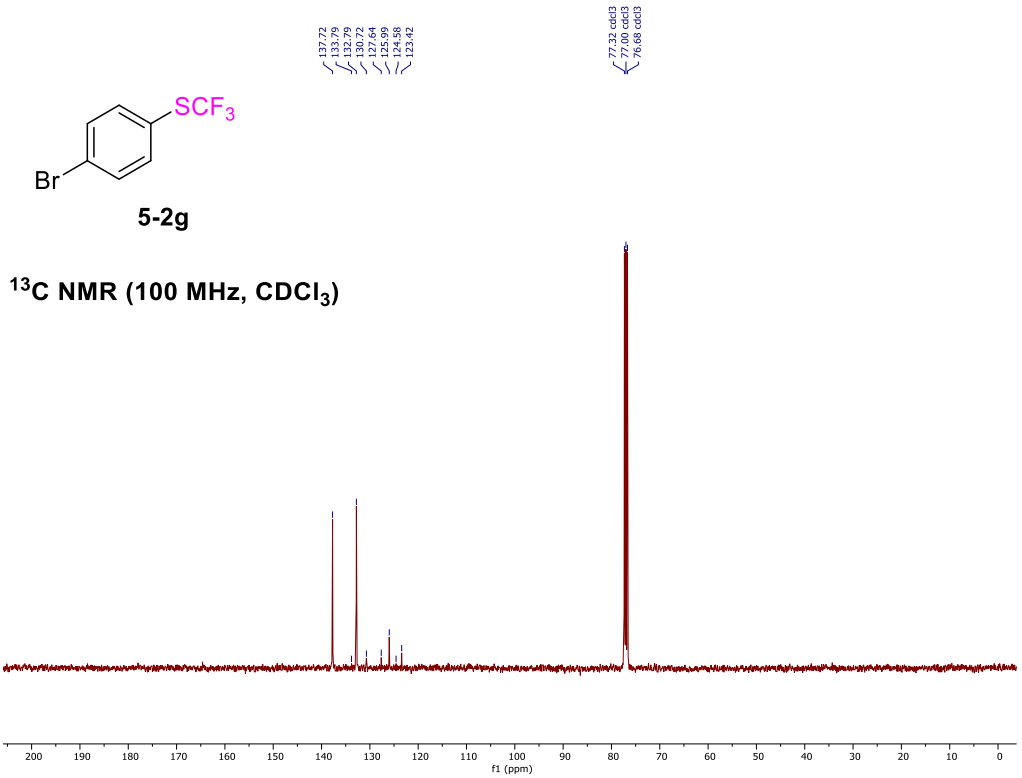
^{19}F NMR (376 MHz, $CDCl_3$)



5-2g

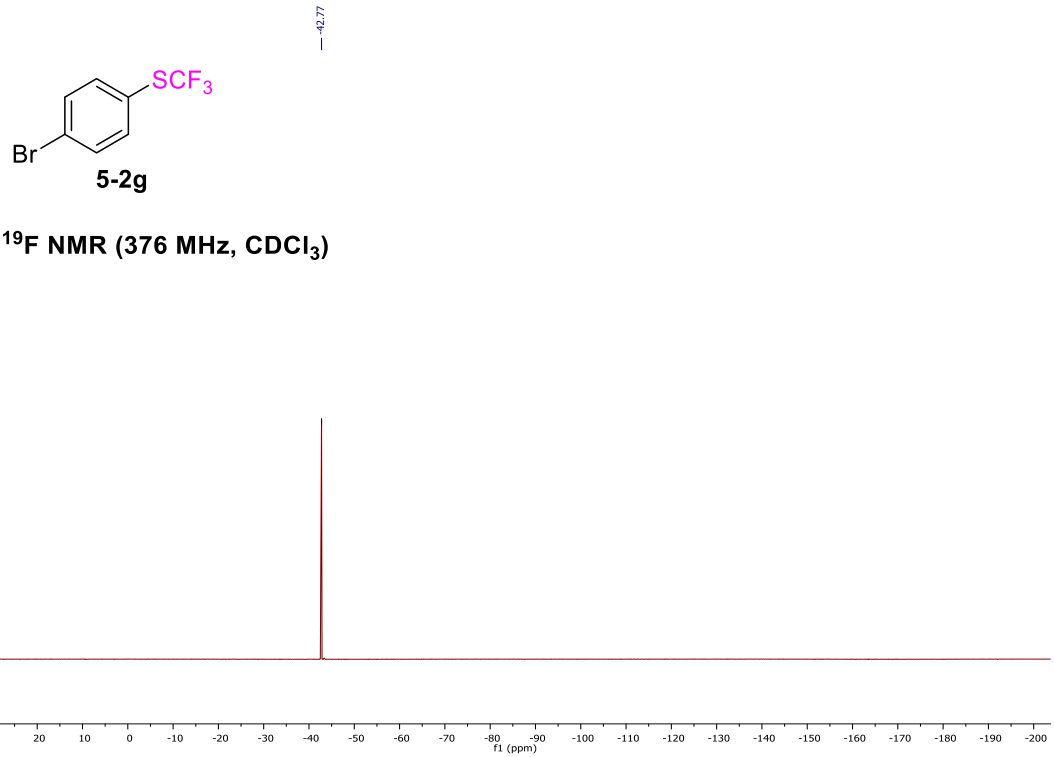
^{1}H NMR (400 MHz, $CDCl_3$)





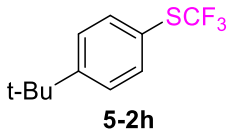
5-2g

^{13}C NMR (100 MHz, $CDCl_3$)



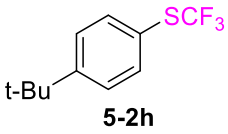
5-2g

^{19}F NMR (376 MHz, $CDCl_3$)



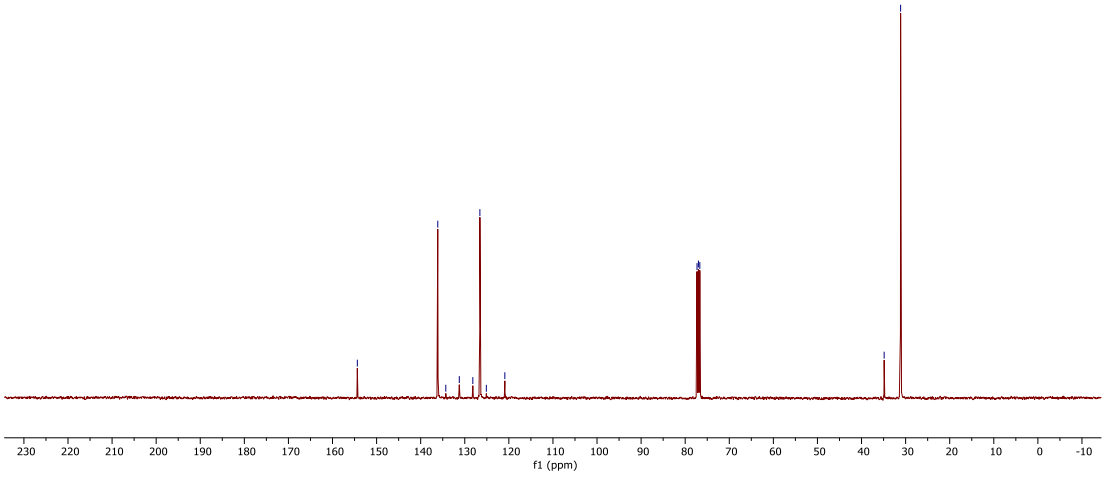
5-2h

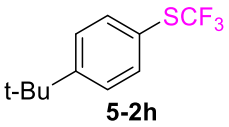
^{1}H NMR (400 MHz, $CDCl_3$)



5-2h

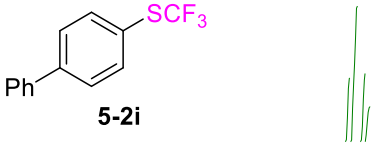
^{13}C NMR (100 MHz, $CDCl_3$)





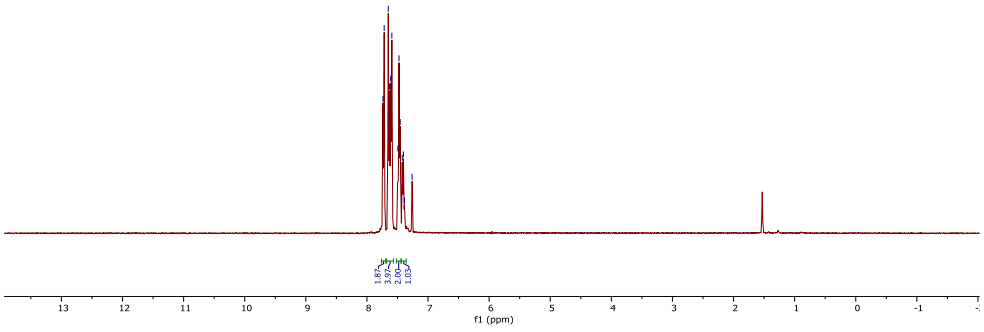
5-2h

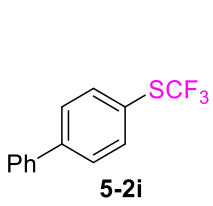
^{19}F NMR (376 MHz, $CDCl_3$)



5-2i

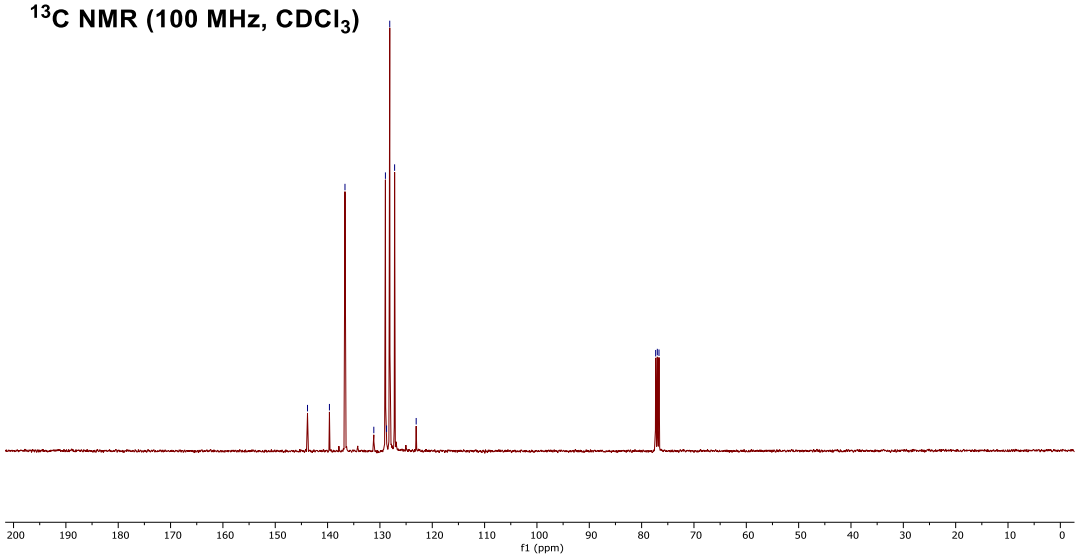
^{1}H NMR (400 MHz, $CDCl_3$)

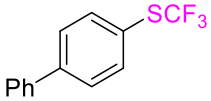




5-2i

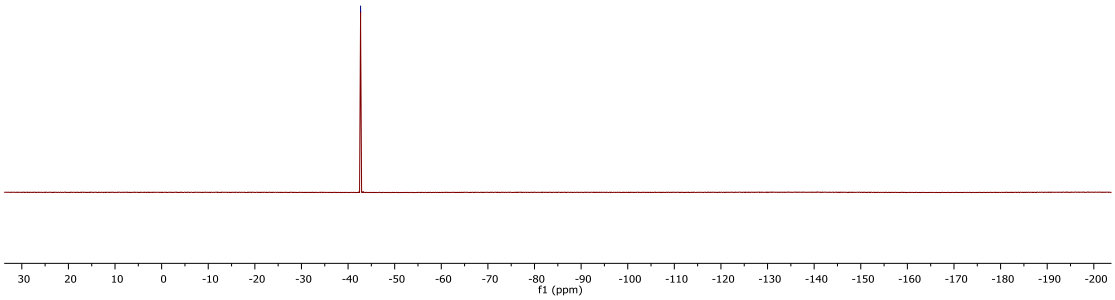
^{13}C NMR (100 MHz, $CDCl_3$)

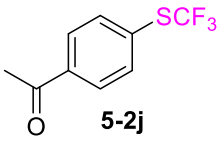




5-2i

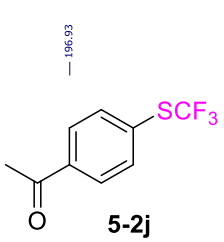
^{19}F NMR (376 MHz, $CDCl_3$)





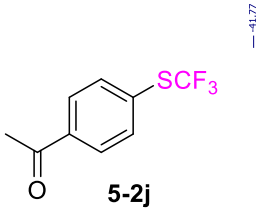
5-2j

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



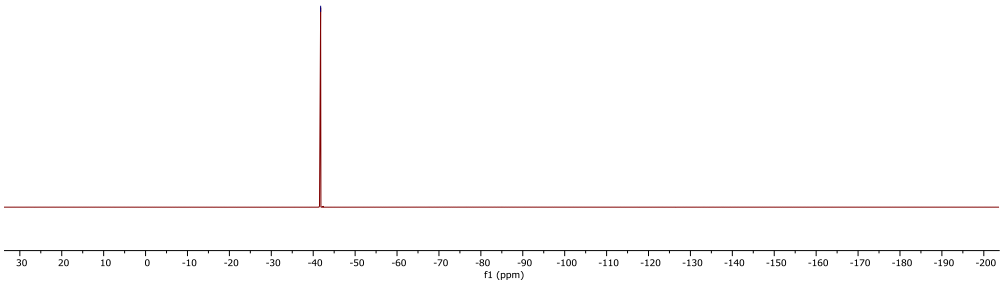
5-2j

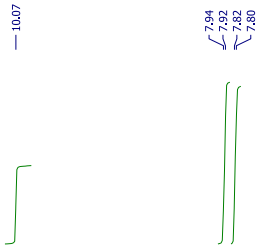
^{13}C NMR (100 MHz, $CDCl_3$)

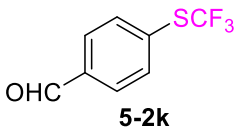


5-2j

^{19}F NMR (376 MHz, $CDCl_3$)

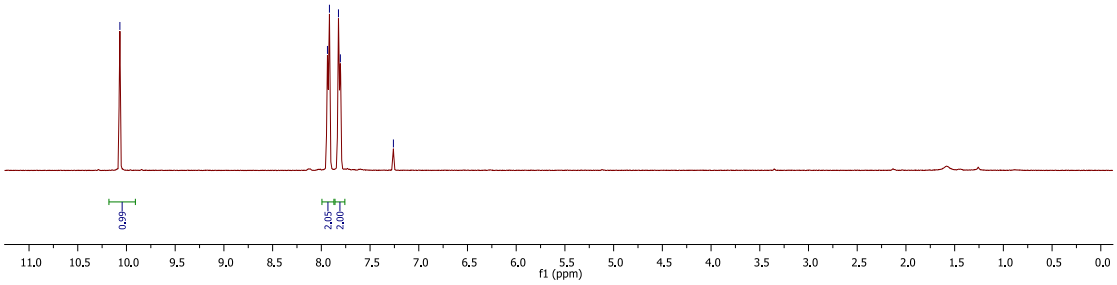


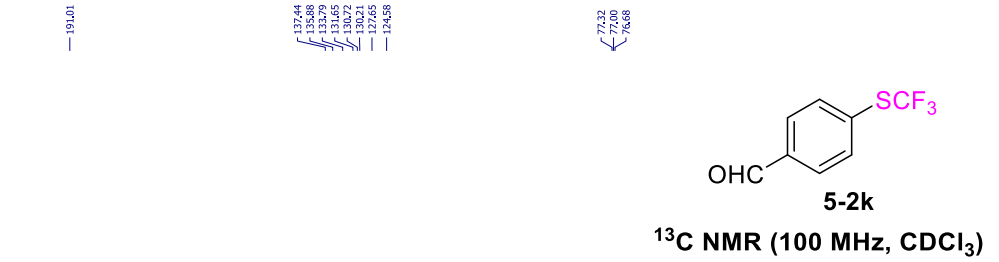




5-2k

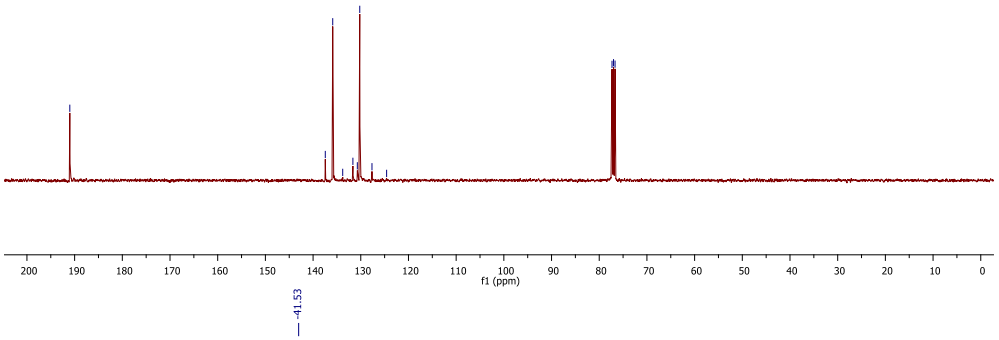
^{1}H NMR (400 MHz, $CDCl_3$)

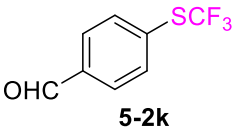




5-2k

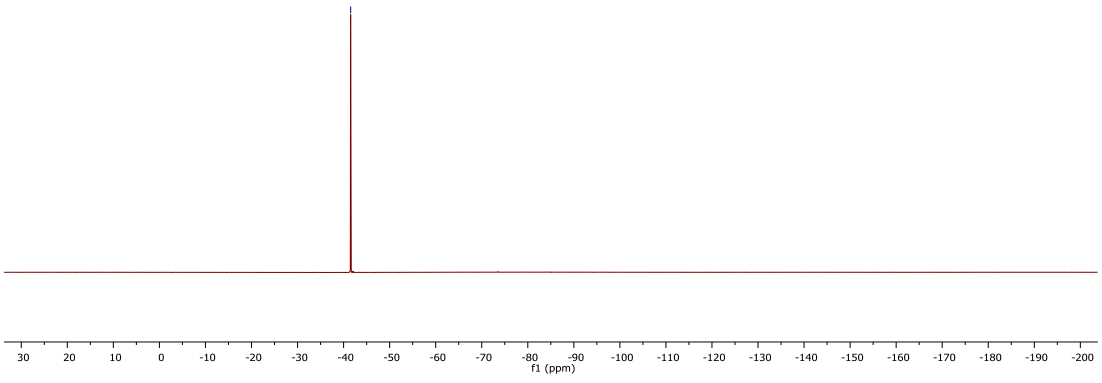
^{13}C NMR (100 MHz, $CDCl_3$)

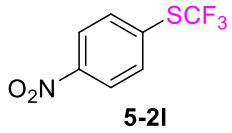




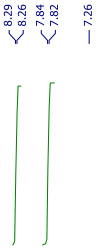
5-2k

^{19}F NMR (376 MHz, $CDCl_3$)

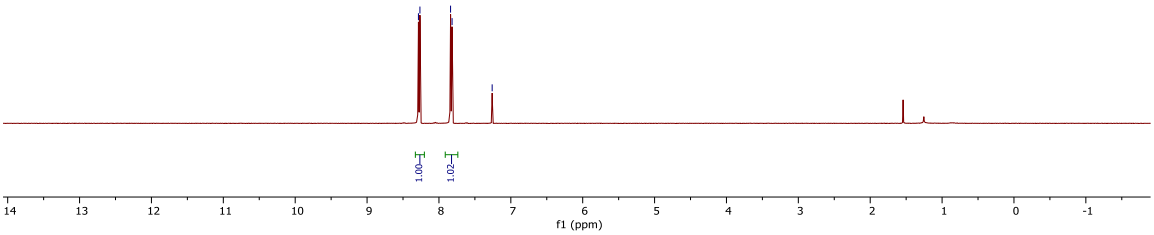


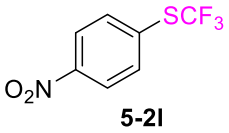


5-2l



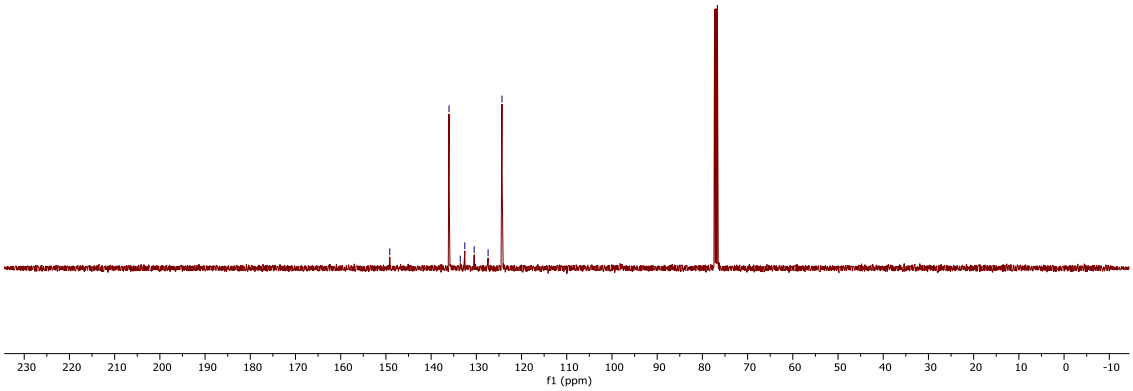
^{1}H NMR (400 MHz, $CDCl_3$)

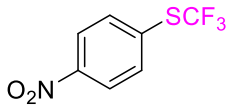




5-2l

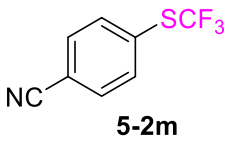
^{13}C NMR (100 MHz, $CDCl_3$)





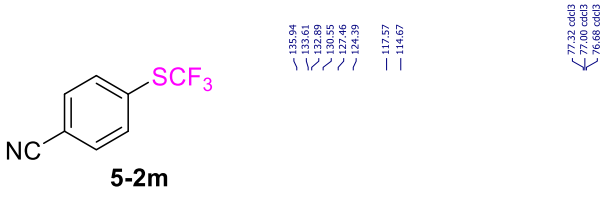
5-2l

^{19}F NMR (376 MHz, $CDCl_3$)



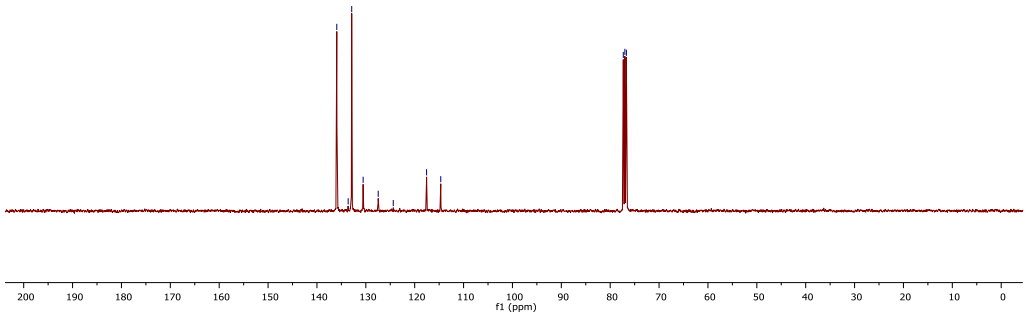
5-2m

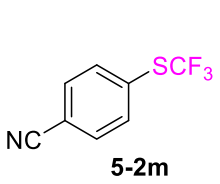
^{1}H NMR (400 MHz, $CDCl_3$)



5-2m

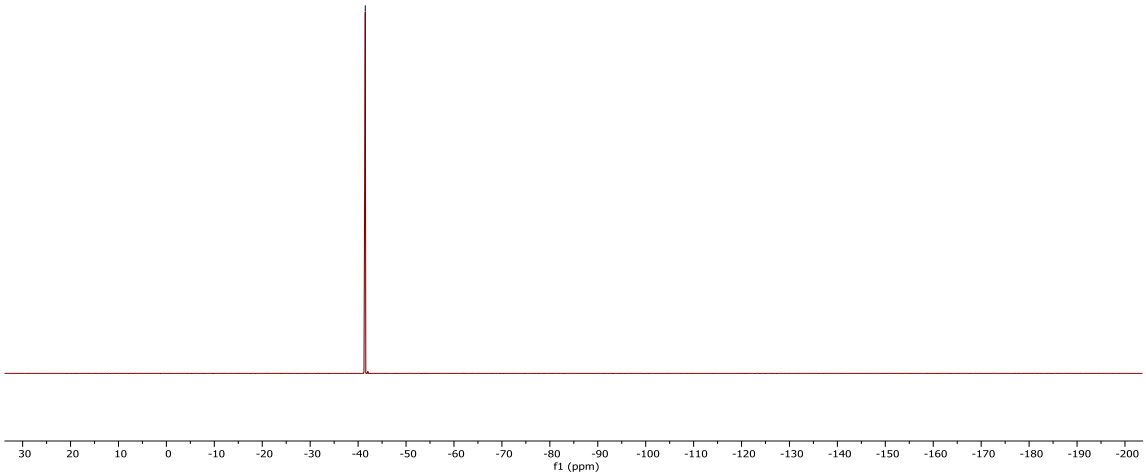
^{13}C NMR (100 MHz, $CDCl_3$)

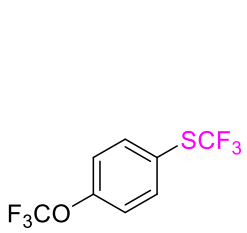




5-2m

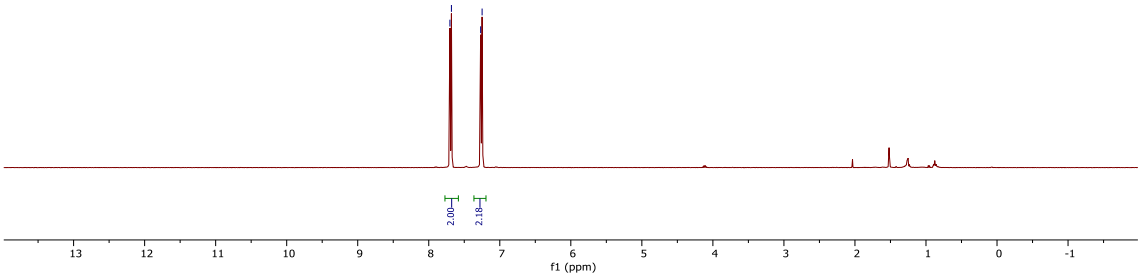
^{19}F NMR (376 MHz, $CDCl_3$)

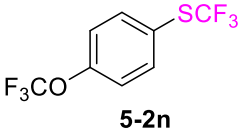




5-2n

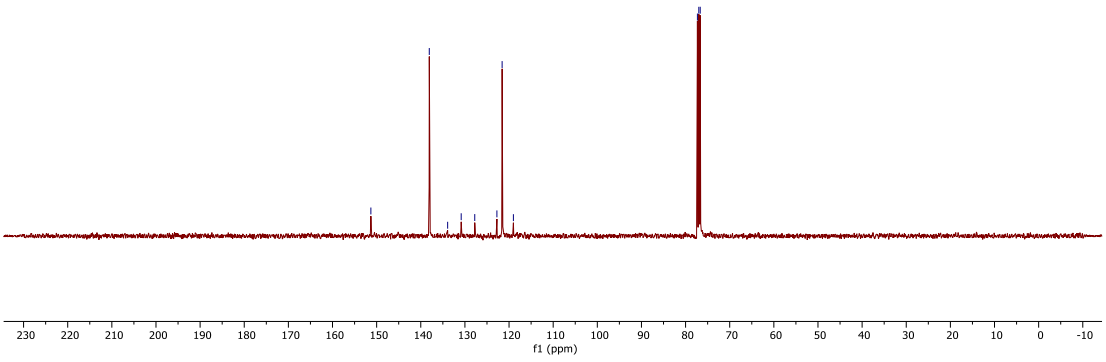
^{1}H NMR (400 MHz, $CDCl_3$)

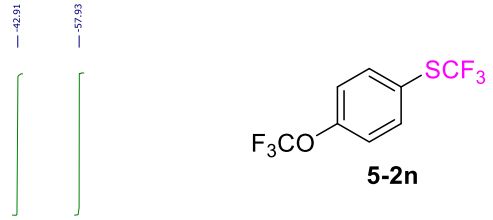




5-2n

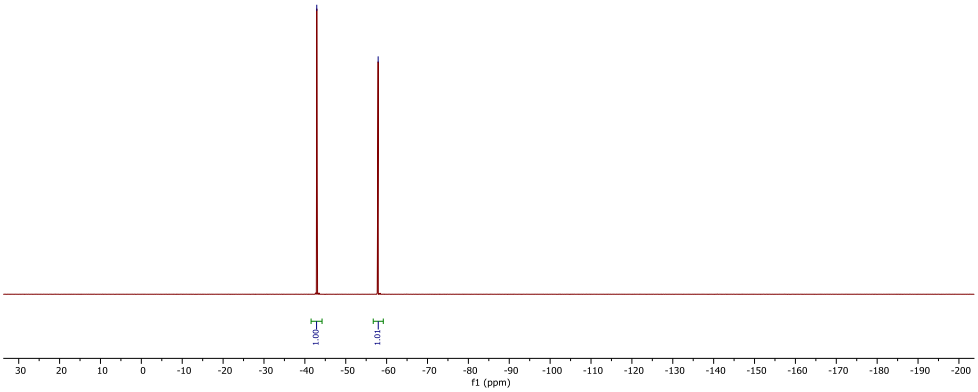
^{13}C NMR (100 MHz, $CDCl_3$)





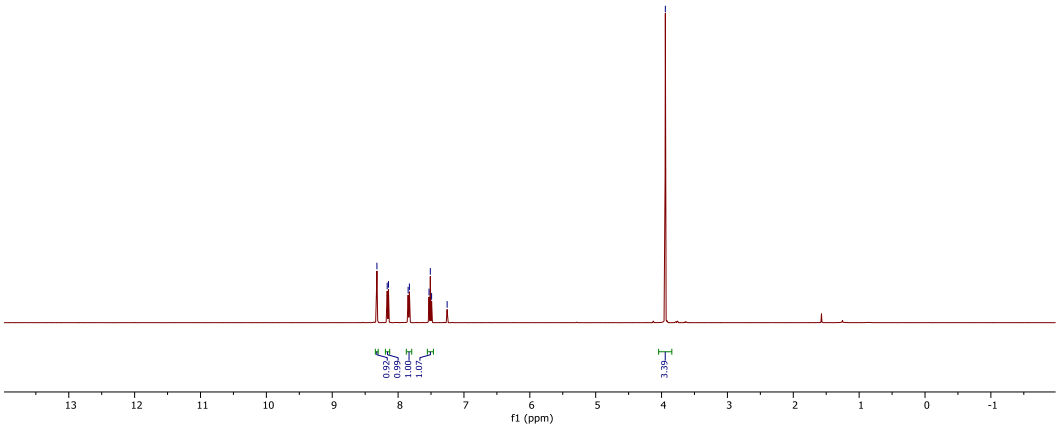
5-2n

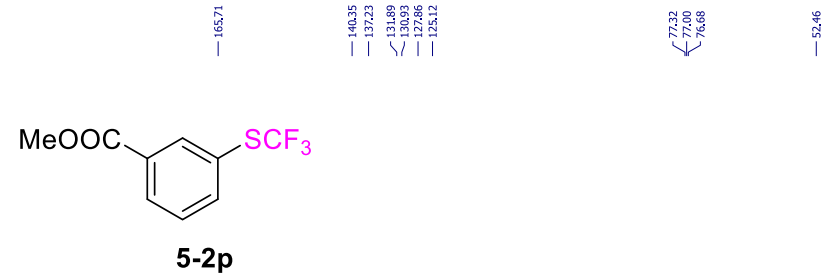
^{19}F NMR (376 MHz, $CDCl_3$)



5-2p

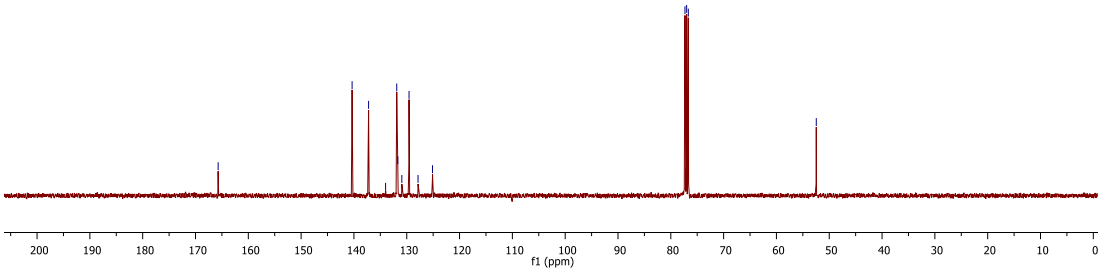
^{1}H NMR (400 MHz, $CDCl_3$)

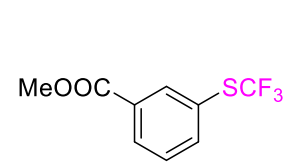




5-2p

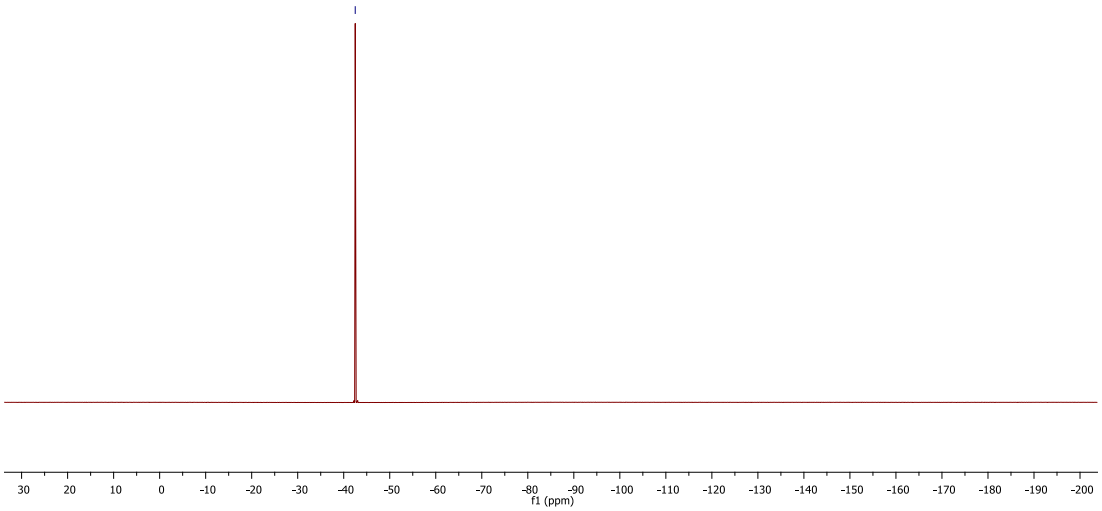
^{13}C NMR (100 MHz, $CDCl_3$)

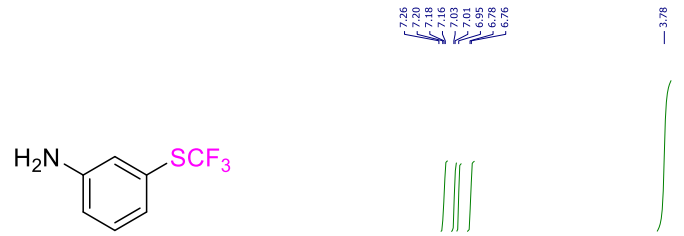




5-2p

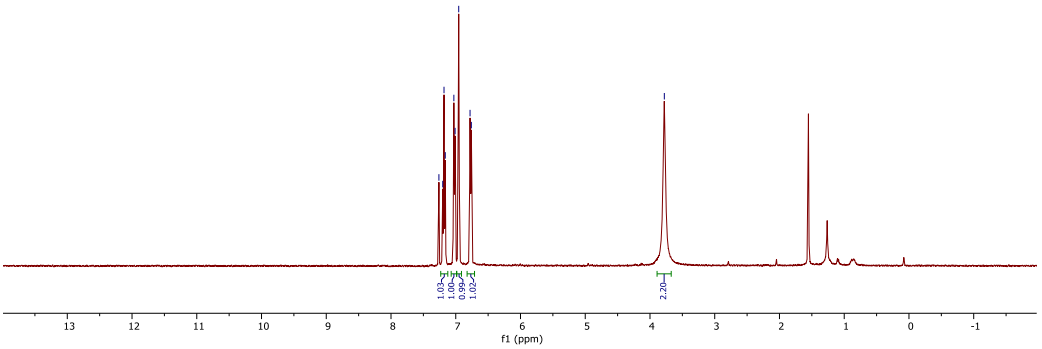
^{19}F NMR (376 MHz, $CDCl_3$)

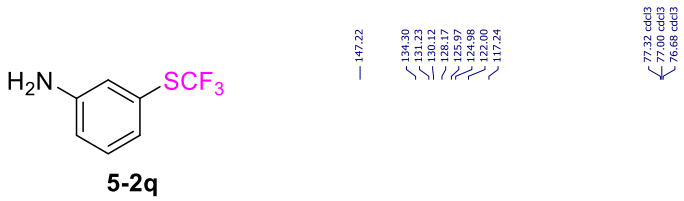




5-2q

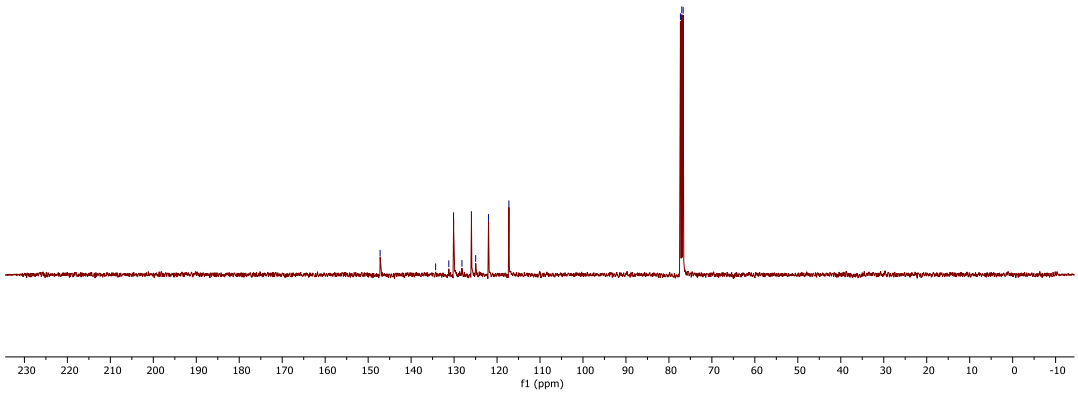
^{1}H NMR (400 MHz, $CDCl_3$)

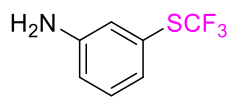




5-2q

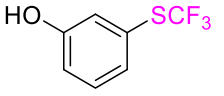
^{13}C NMR (100 MHz, $CDCl_3$)





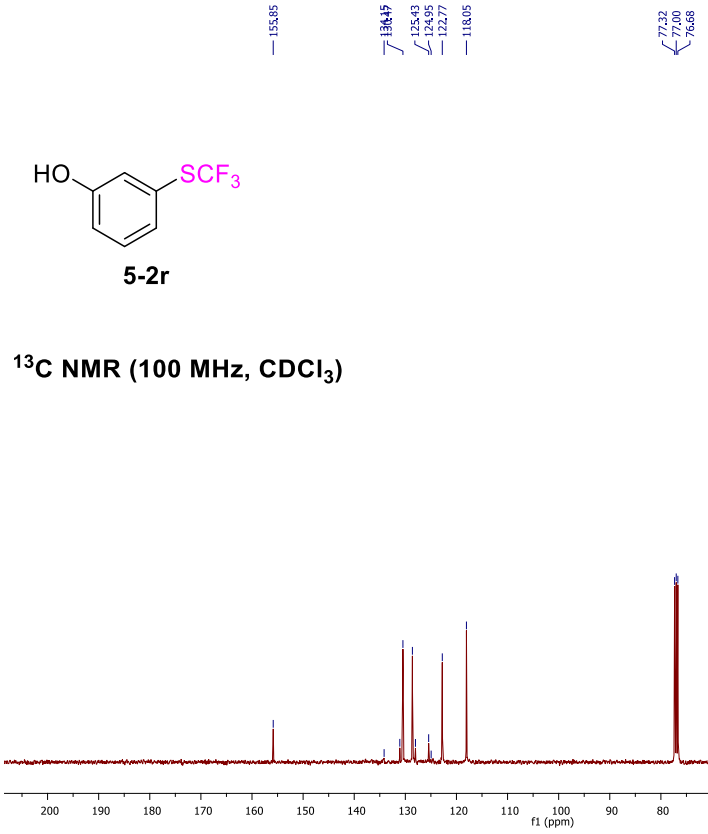
5-2q

^{19}F NMR (376 MHz, $CDCl_3$)



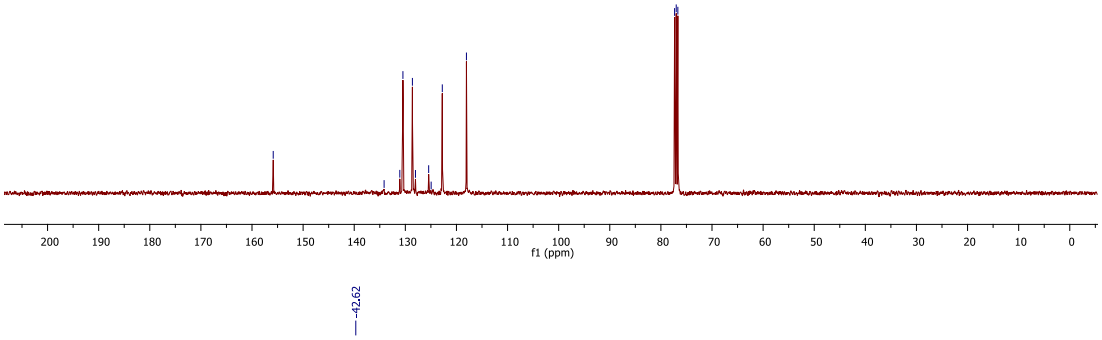
5-2r

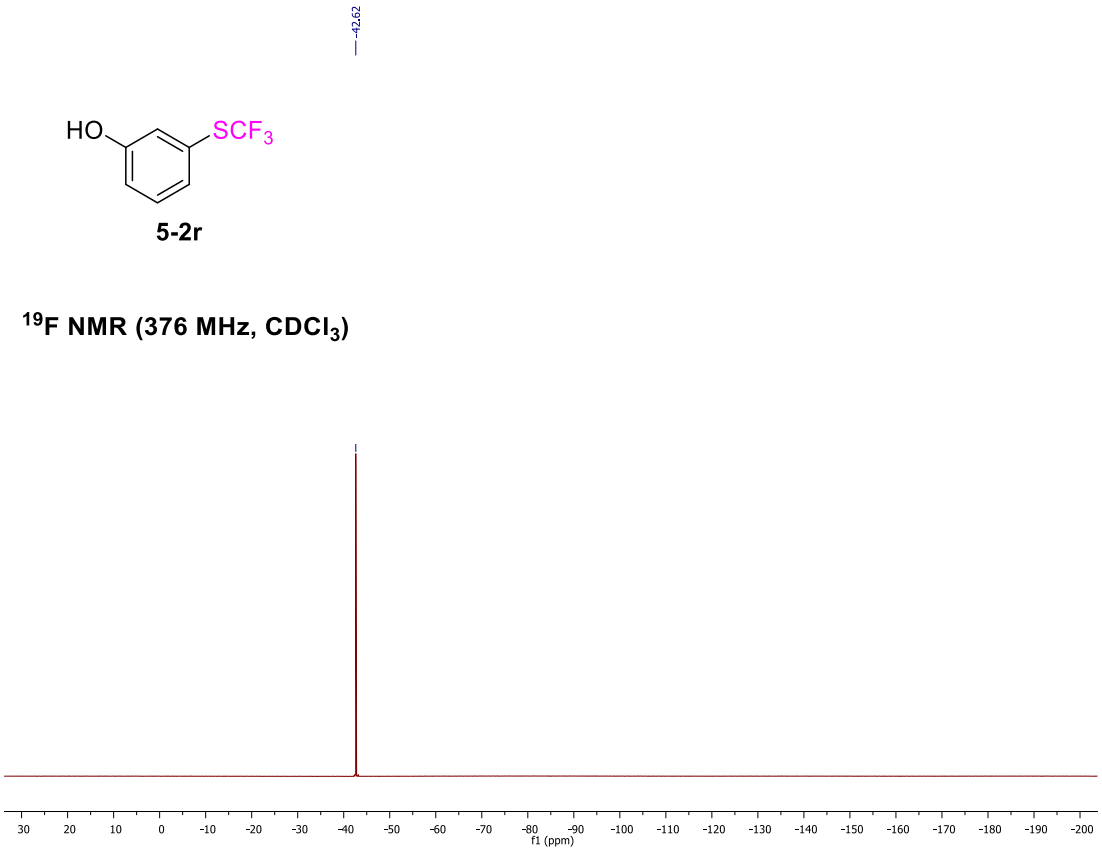
^{1}H NMR (400 MHz, $CDCl_3$)



5-2r

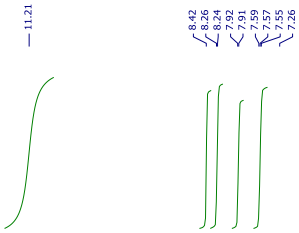
^{13}C NMR (100 MHz, $CDCl_3$)

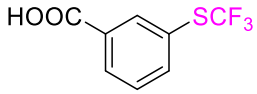




5-2r

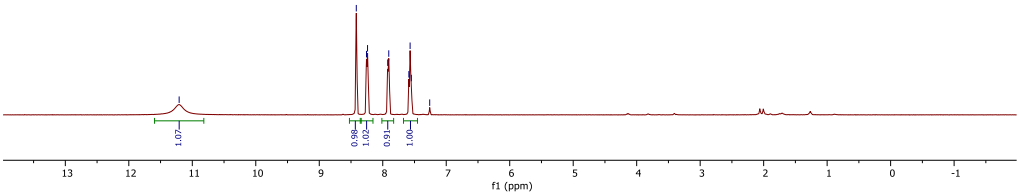
^{19}F NMR (376 MHz, $CDCl_3$)

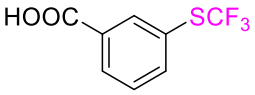




5-2s

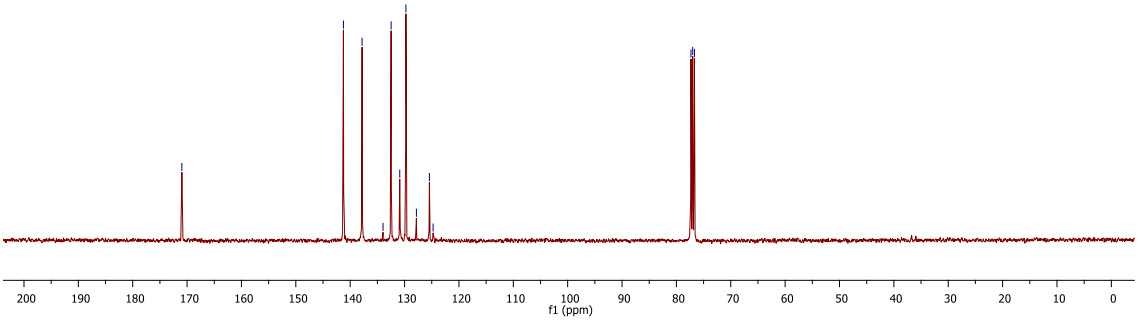
^{1}H NMR (400 MHz, $CDCl_3$)

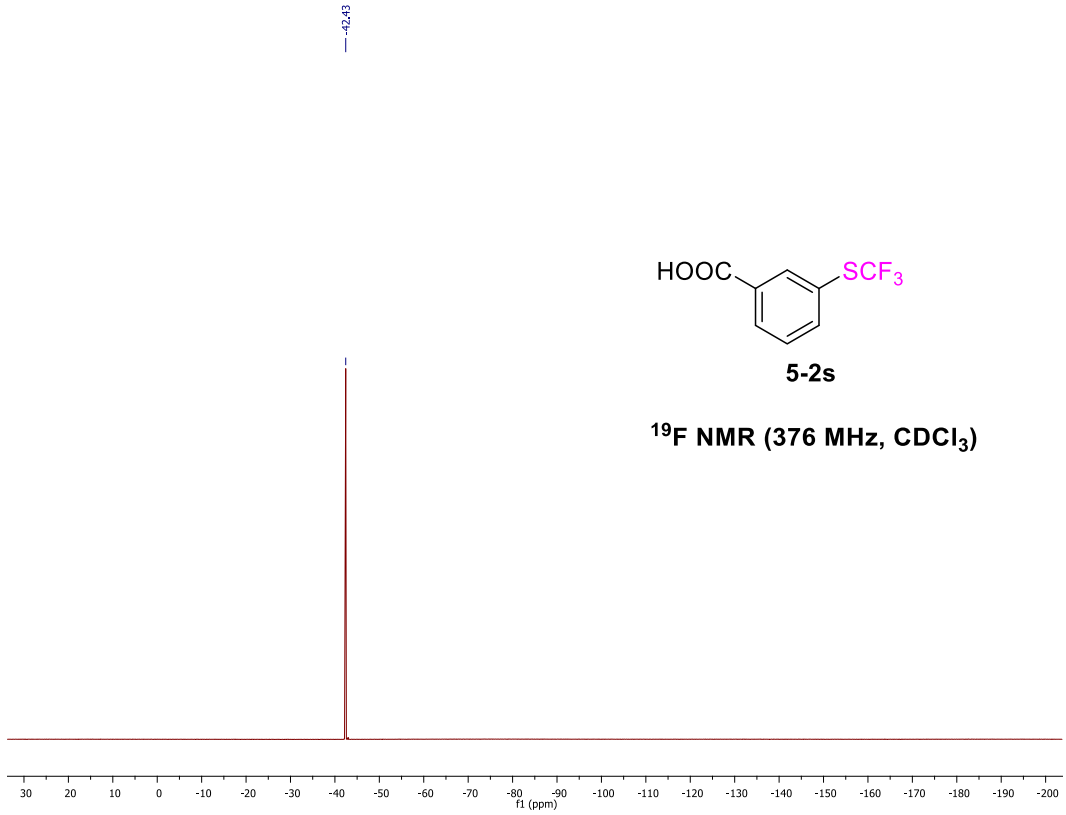




5-2s

^{13}C NMR (100 MHz, $CDCl_3$)

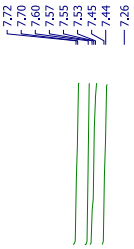




HOOC, SCF_3

5-2s

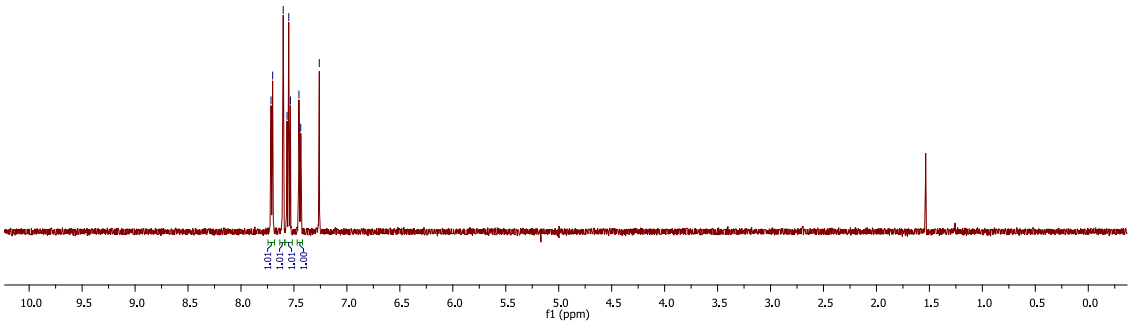
^{19}F NMR (376 MHz, $CDCl_3$)

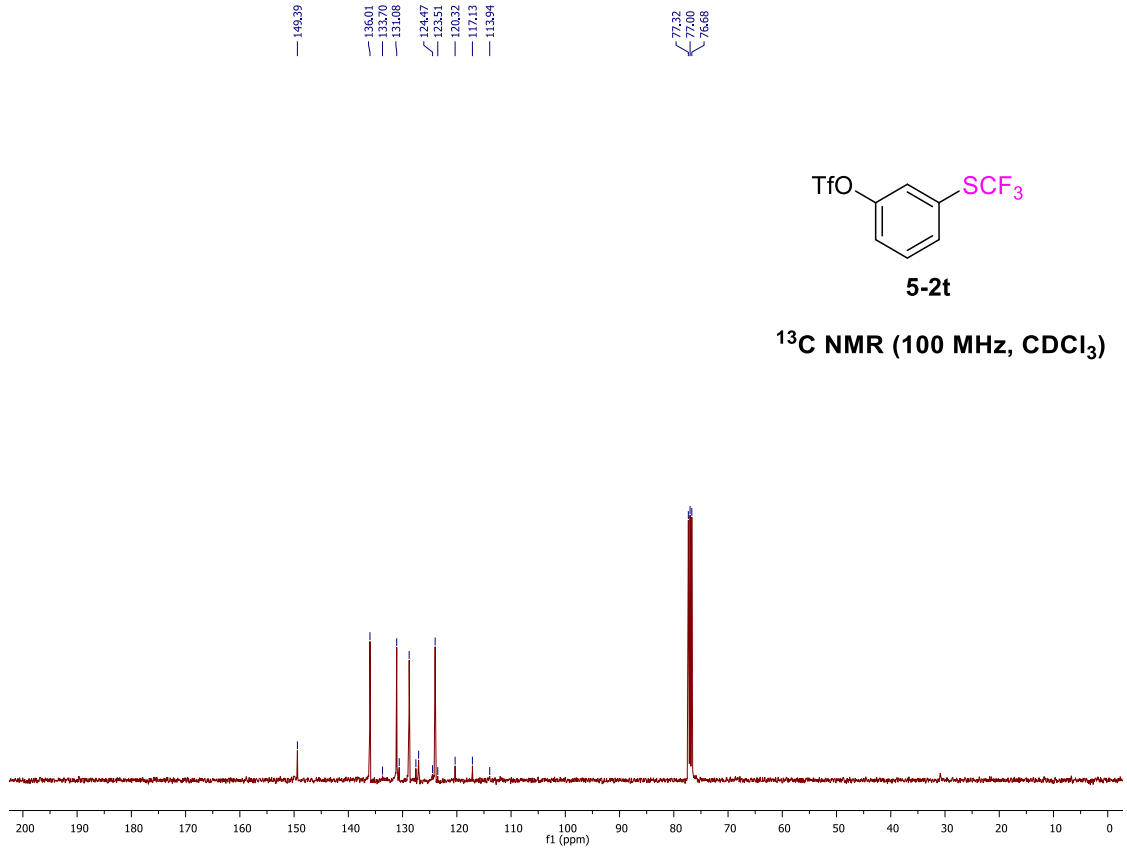


TfO, SCF_3

5-2t

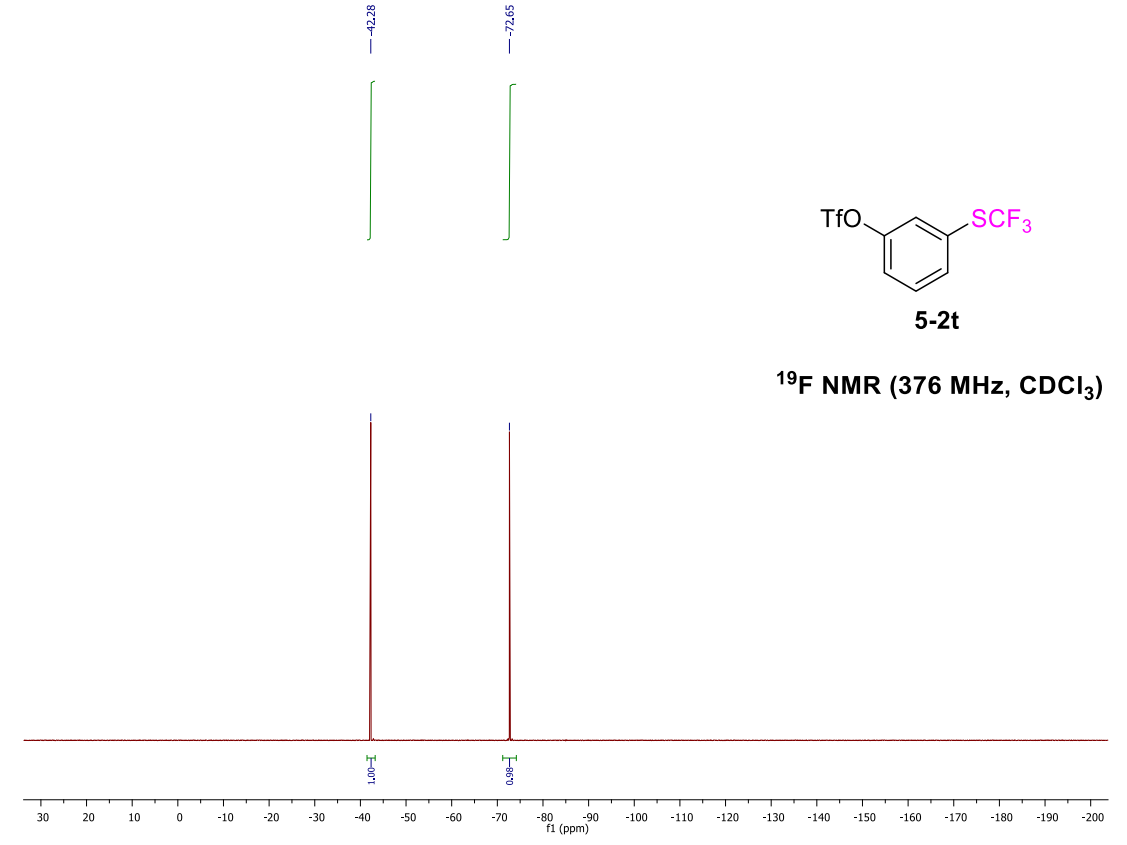
^{1}H NMR (500 MHz, $CDCl_3$)





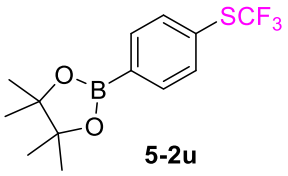
5-2t

^{13}C NMR (100 MHz, $CDCl_3$)



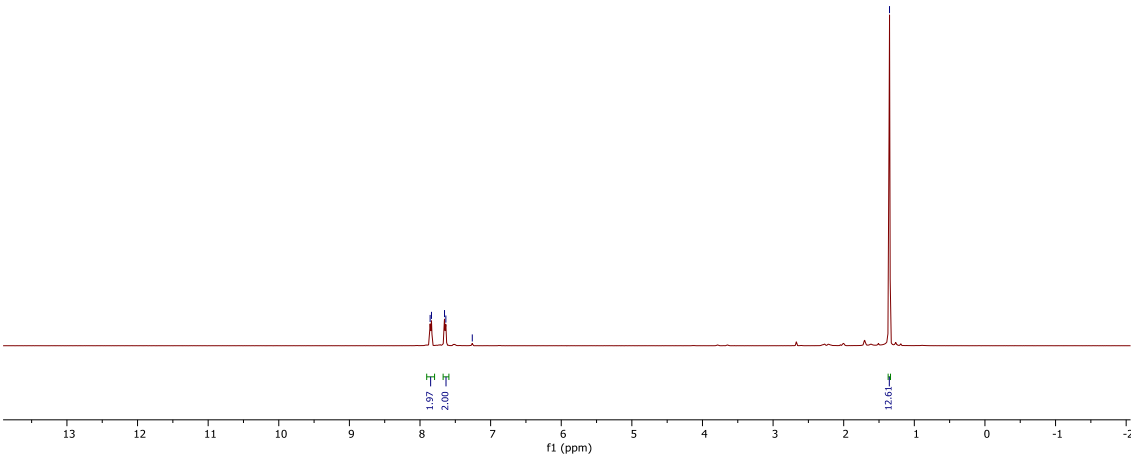
5-2t

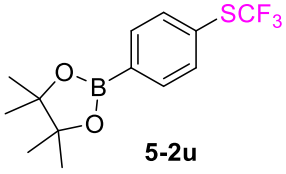
^{19}F NMR (376 MHz, $CDCl_3$)



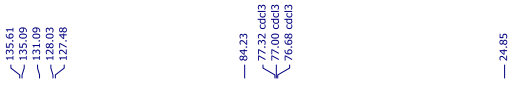
5-2u

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

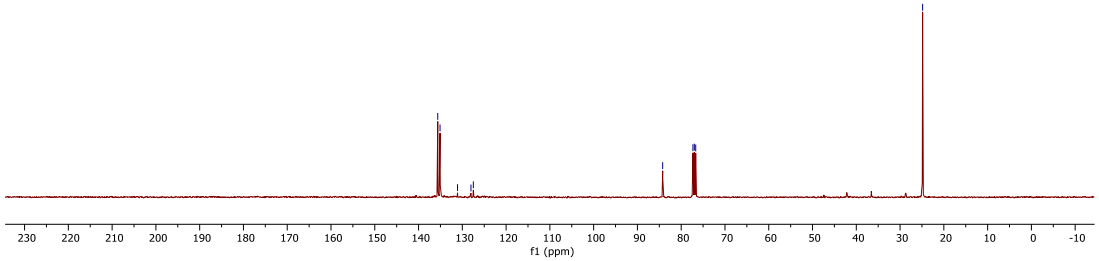


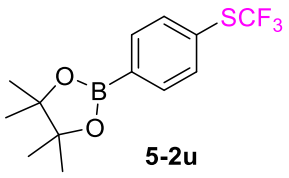


5-2u



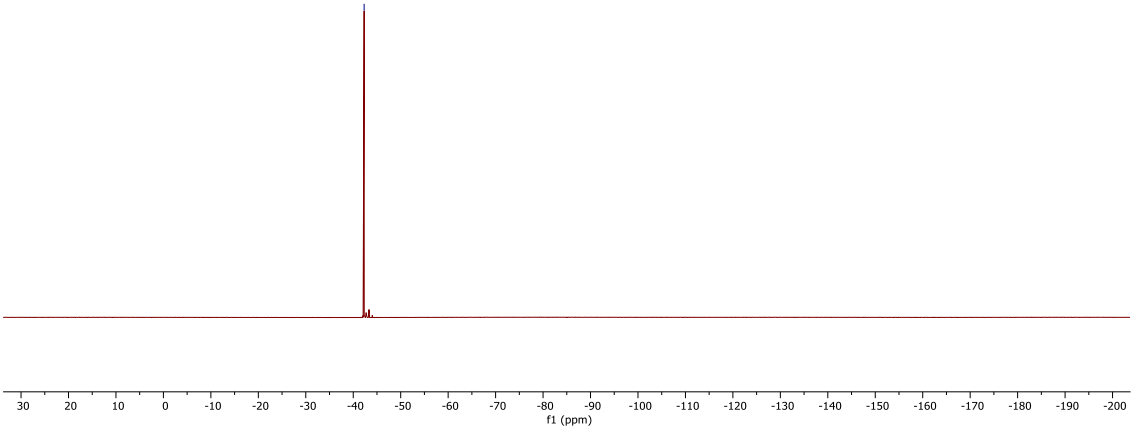
^{13}C NMR (100 MHz, $CDCl_3$)





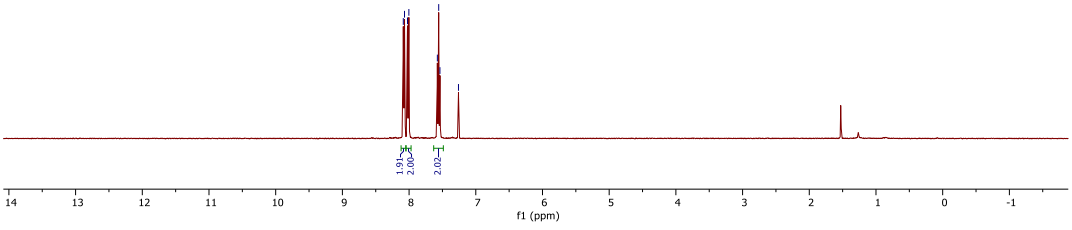
5-2u

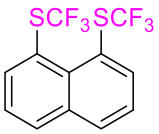
^{19}F NMR (376 MHz, $CDCl_3$)



5-2v

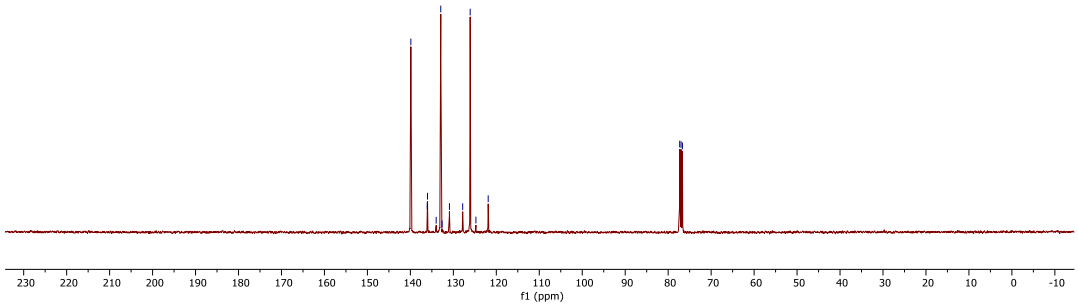
^{1}H NMR (400 MHz, $CDCl_3$)





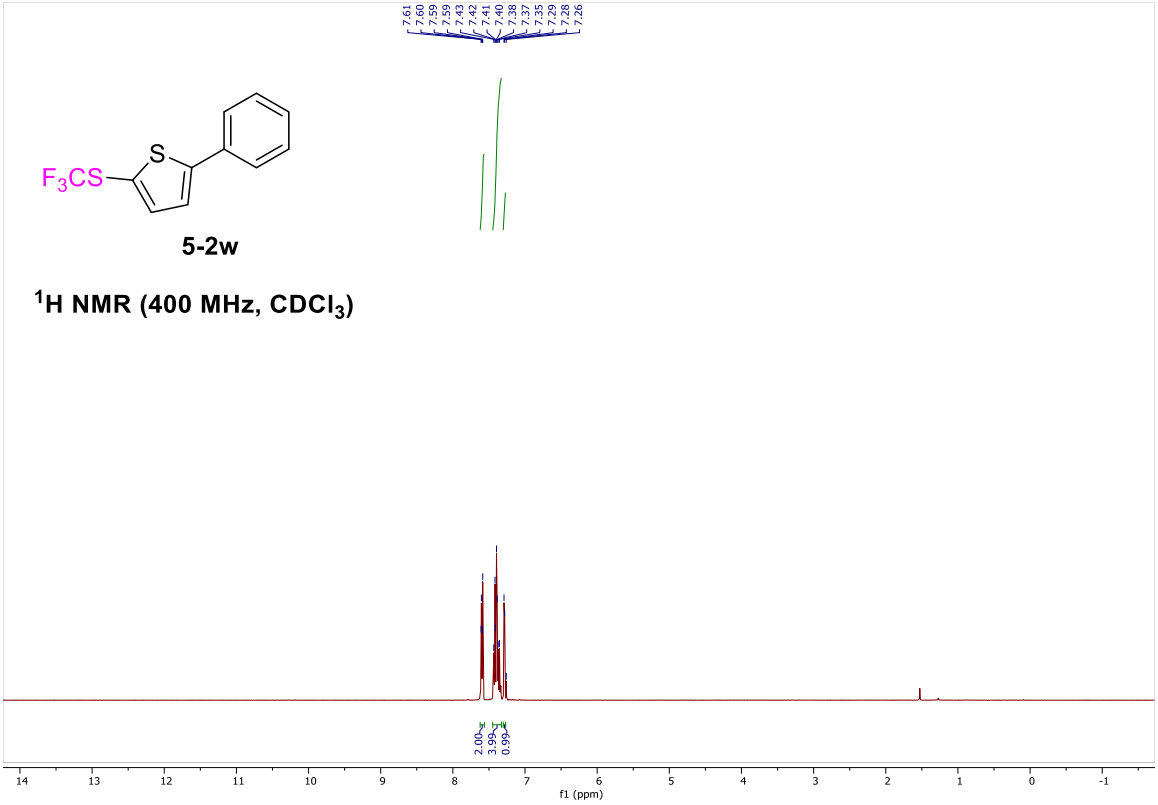
5-2v

^{13}C NMR (100 MHz, $CDCl_3$)



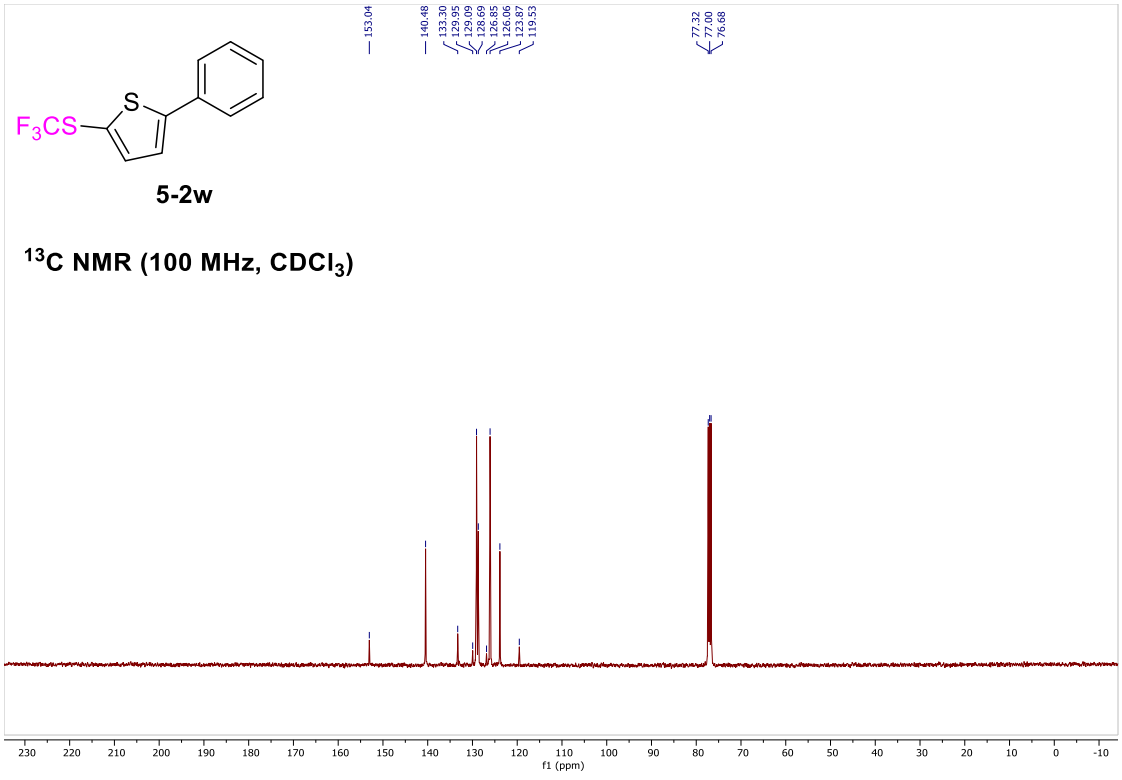
5-2v

^{19}F NMR (376 MHz, $CDCl_3$)



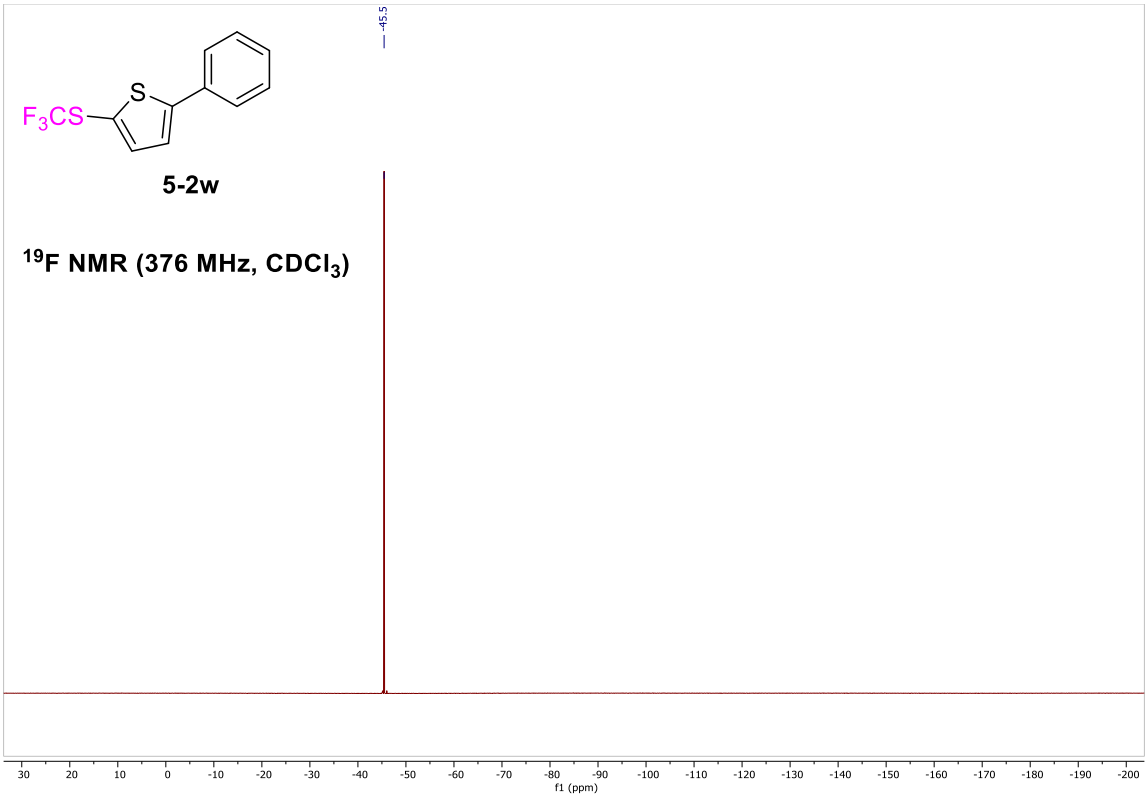
5-2w

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



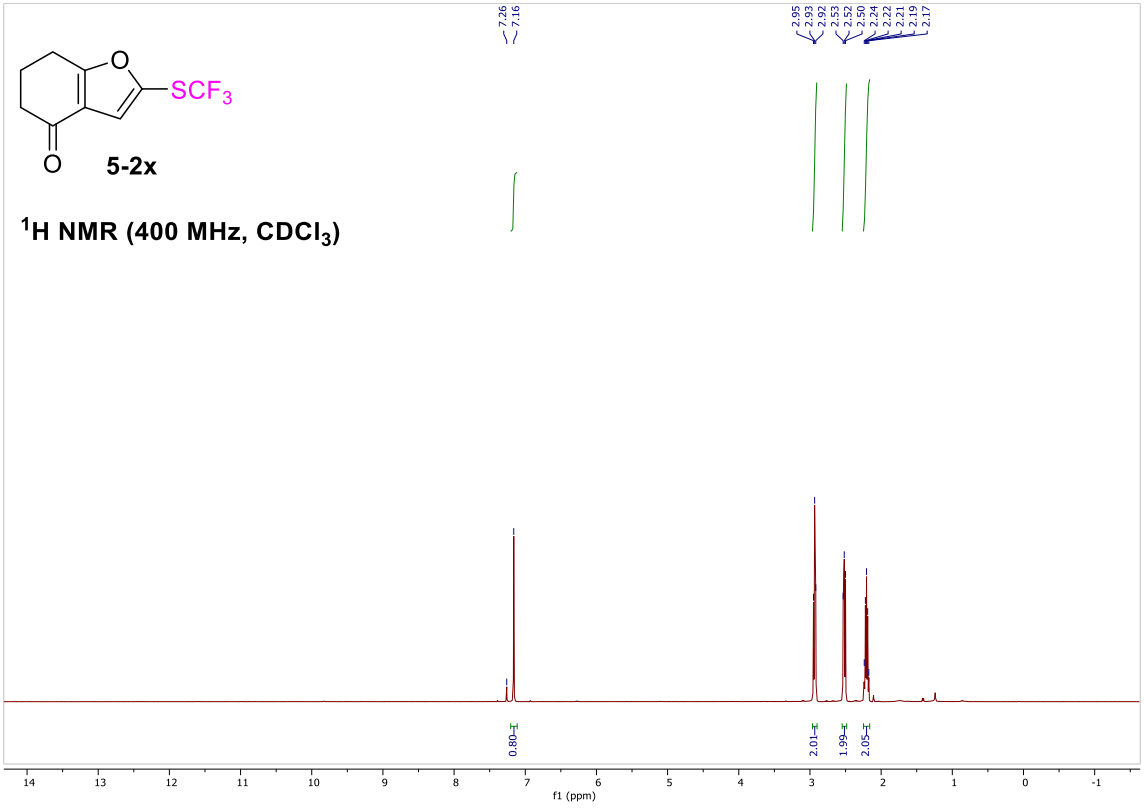
5-2w

^{13}C NMR (100 MHz, $CDCl_3$)



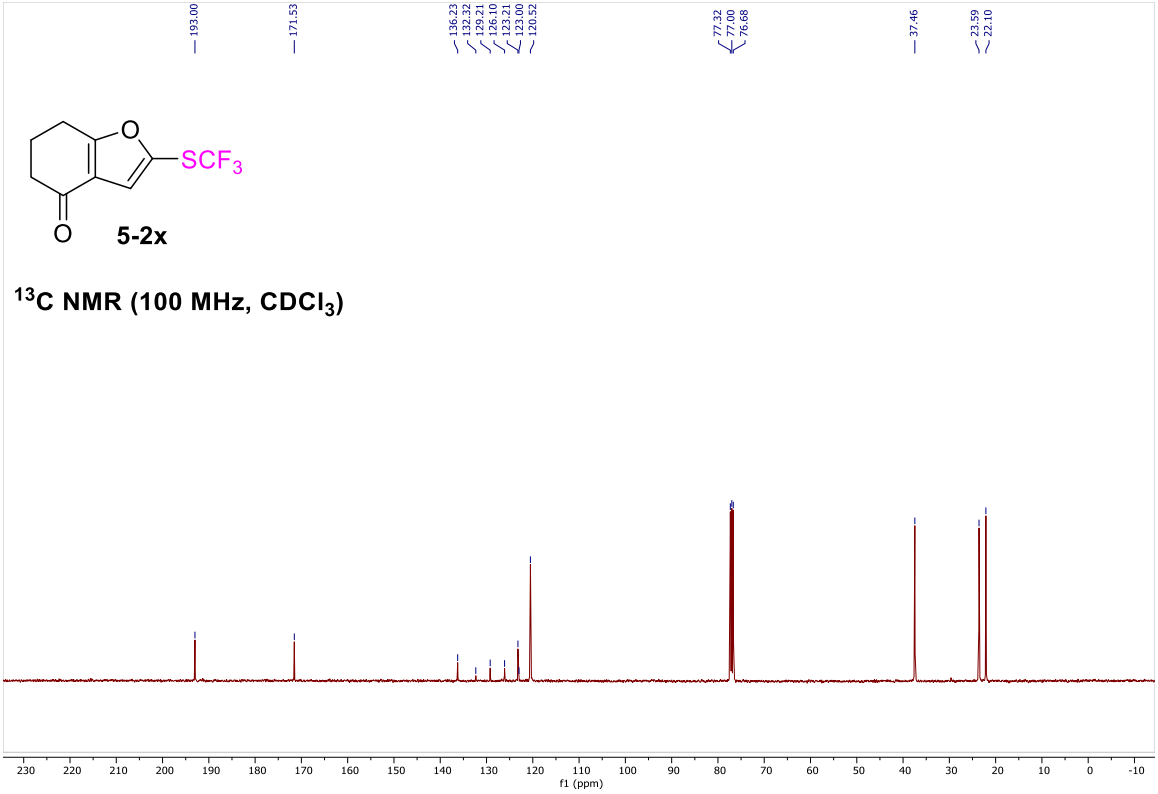
5-2w

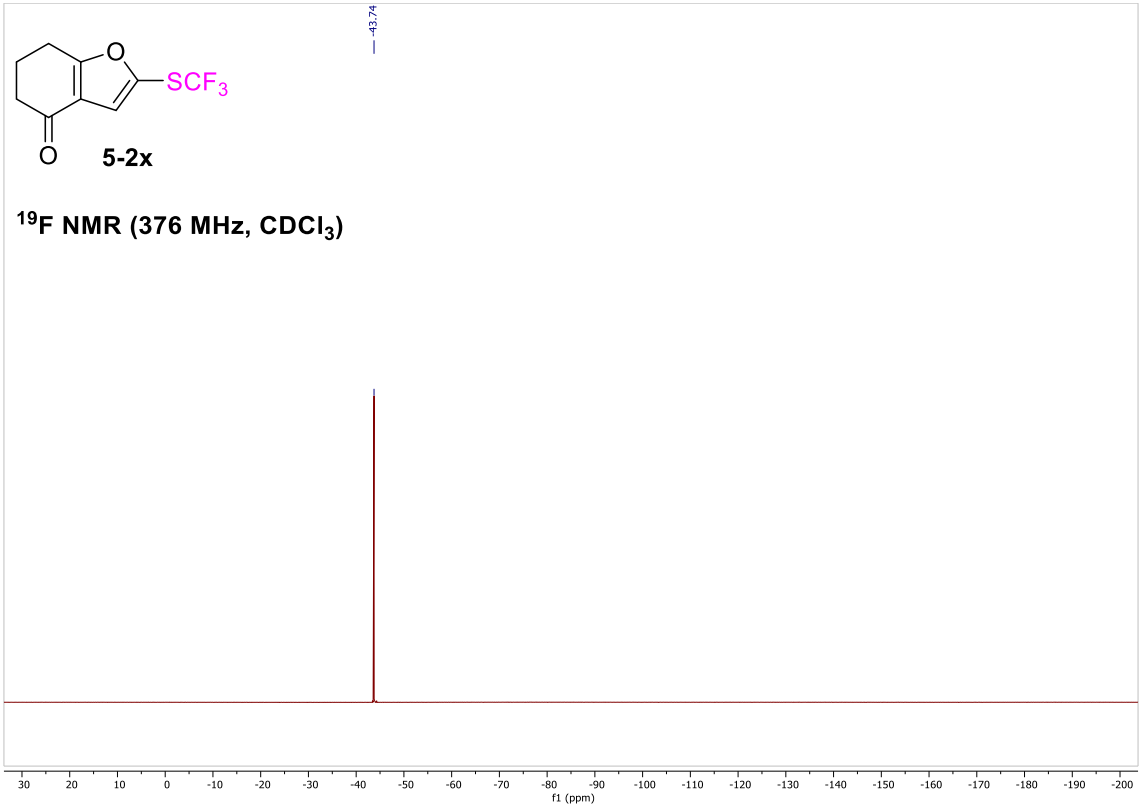
^{19}F NMR (376 MHz, $CDCl_3$)

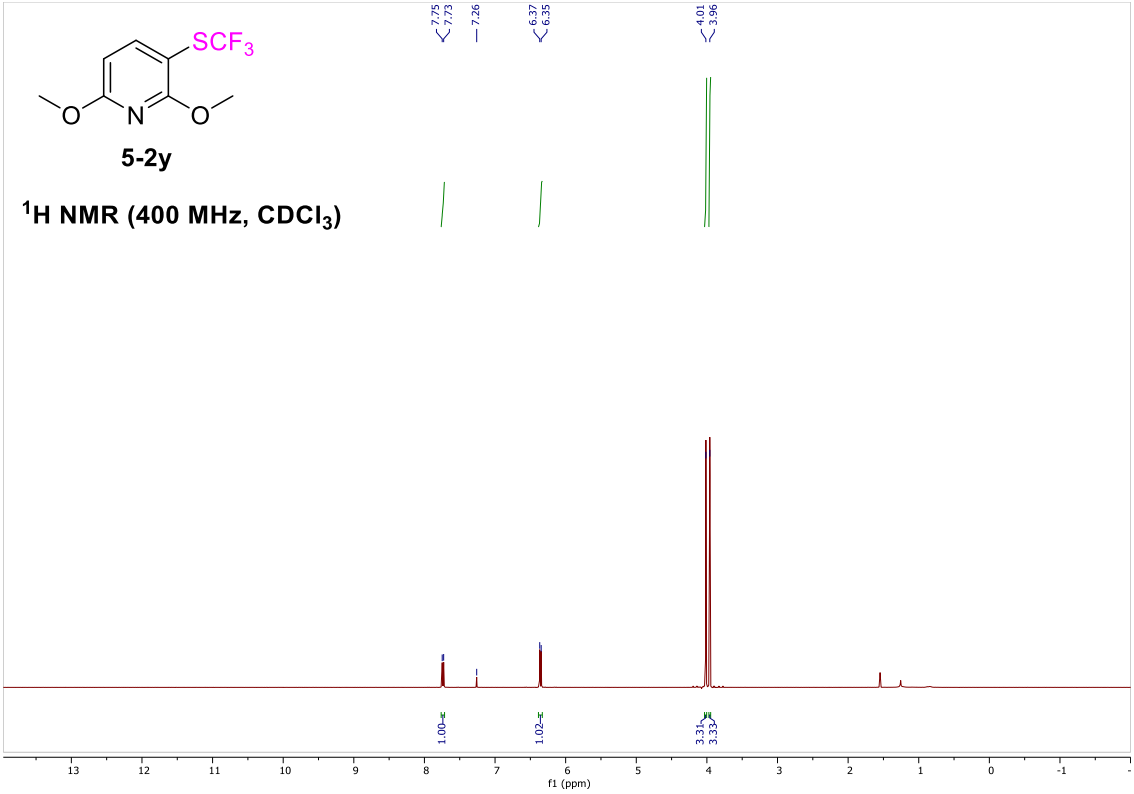


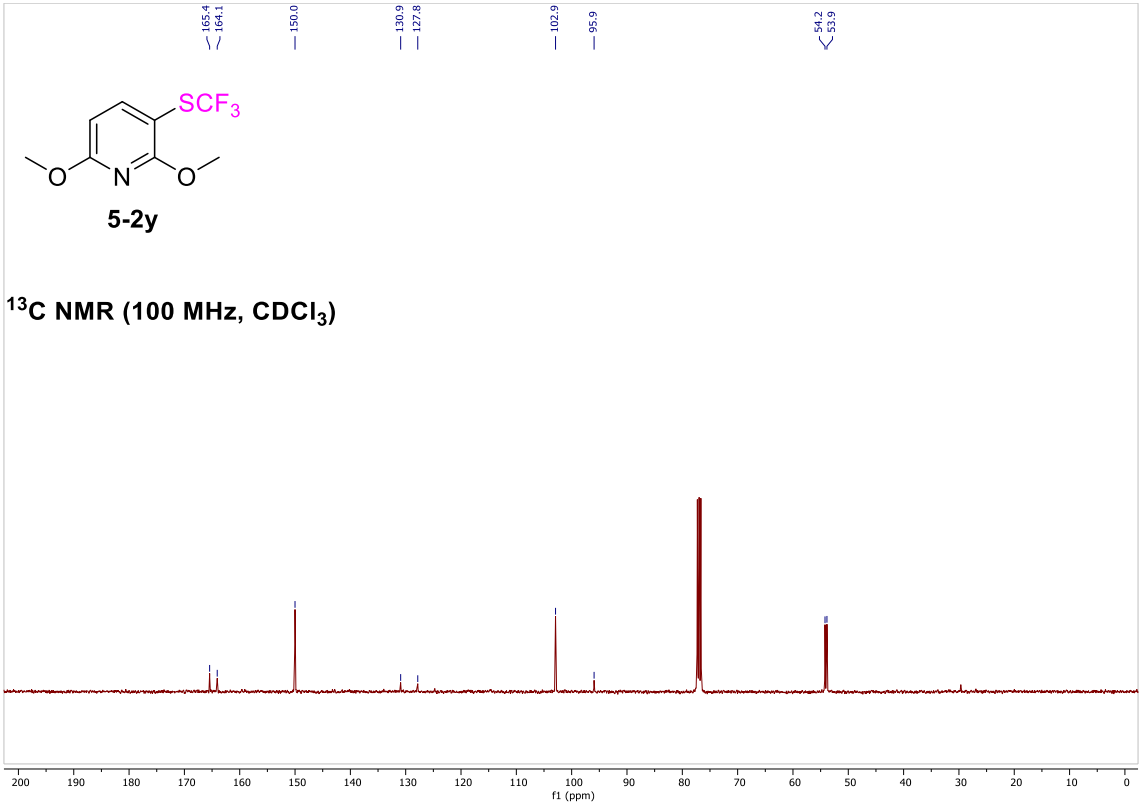
5-2x

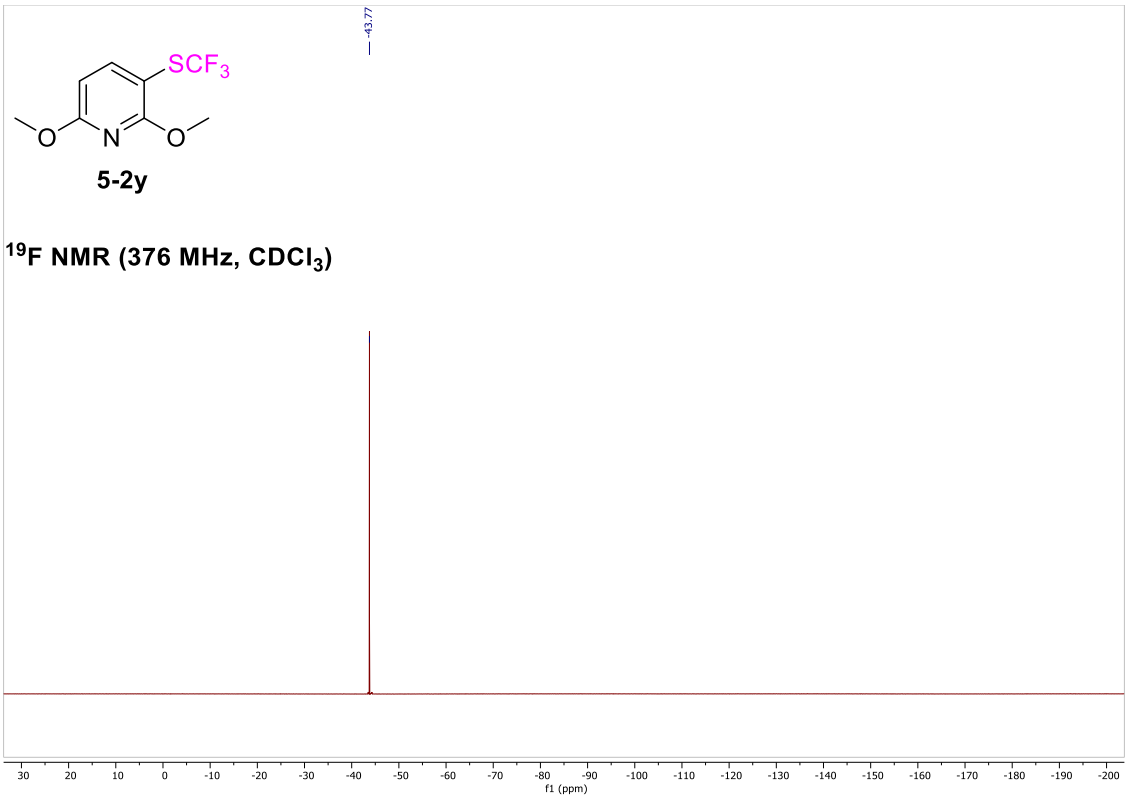
^{1}H NMR (400 MHz, $CDCl_3$)


193.00
171.53
136.23
132.32
129.21
126.10
123.21
123.00
120.52
77.32
77.00
76.68
37.46
23.59
22.10
O
SCF3
O
5-2x
13C NMR (100 MHz, CDCl3)
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


-43.74
O
SCF3
O
5-2x
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)

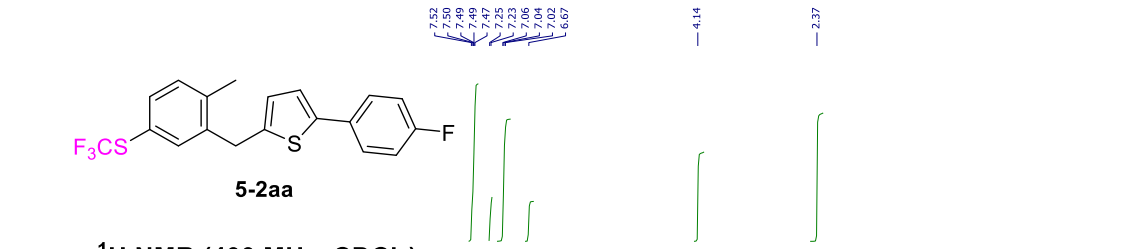

SCF3
O
N
O
5-2y
1H NMR (400 MHz, CDCl3)
7.75
7.73
7.26
6.37
6.35
4.01
3.96
1.00
1.02
3.31
3.33
f1 (ppm)


SCF3
O
N
O
5-2y
13C NMR (100 MHz, CDCl3)
165.4
164.1
150.0
130.9
127.8
102.9
95.9
54.2
53.9
f1 (ppm)



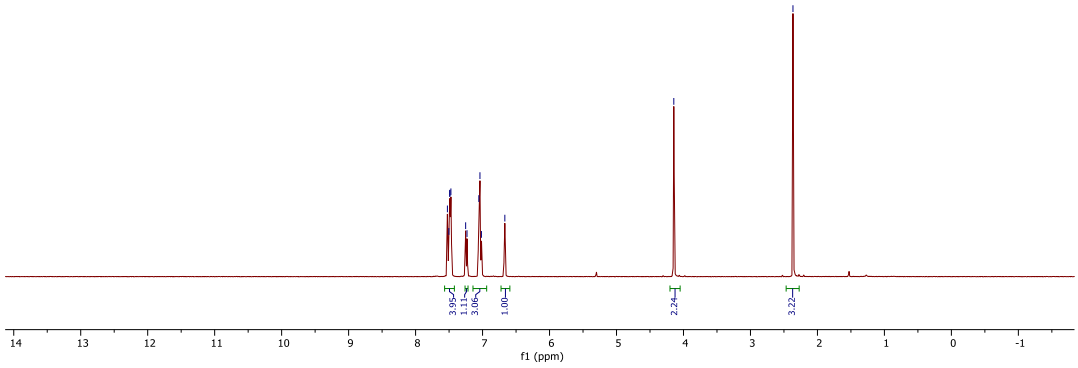
5-2y

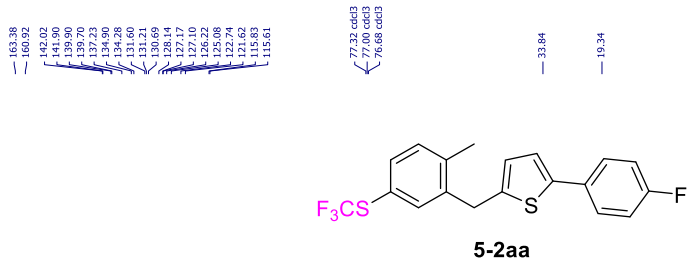
^{19}F NMR (376 MHz, $CDCl_3$)



5-2aa

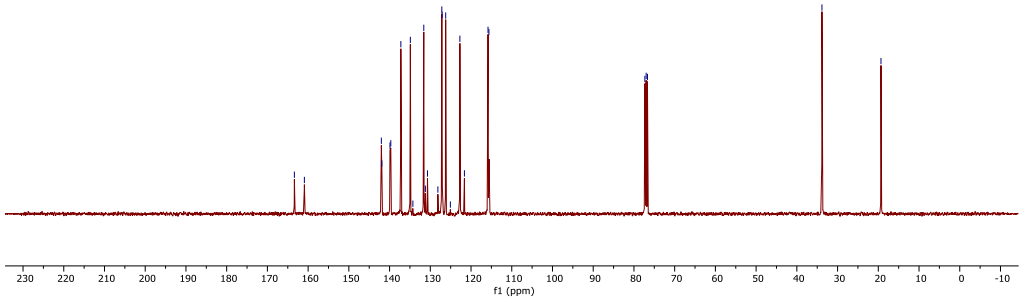
^{1}H NMR (400 MHz, $CDCl_3$)

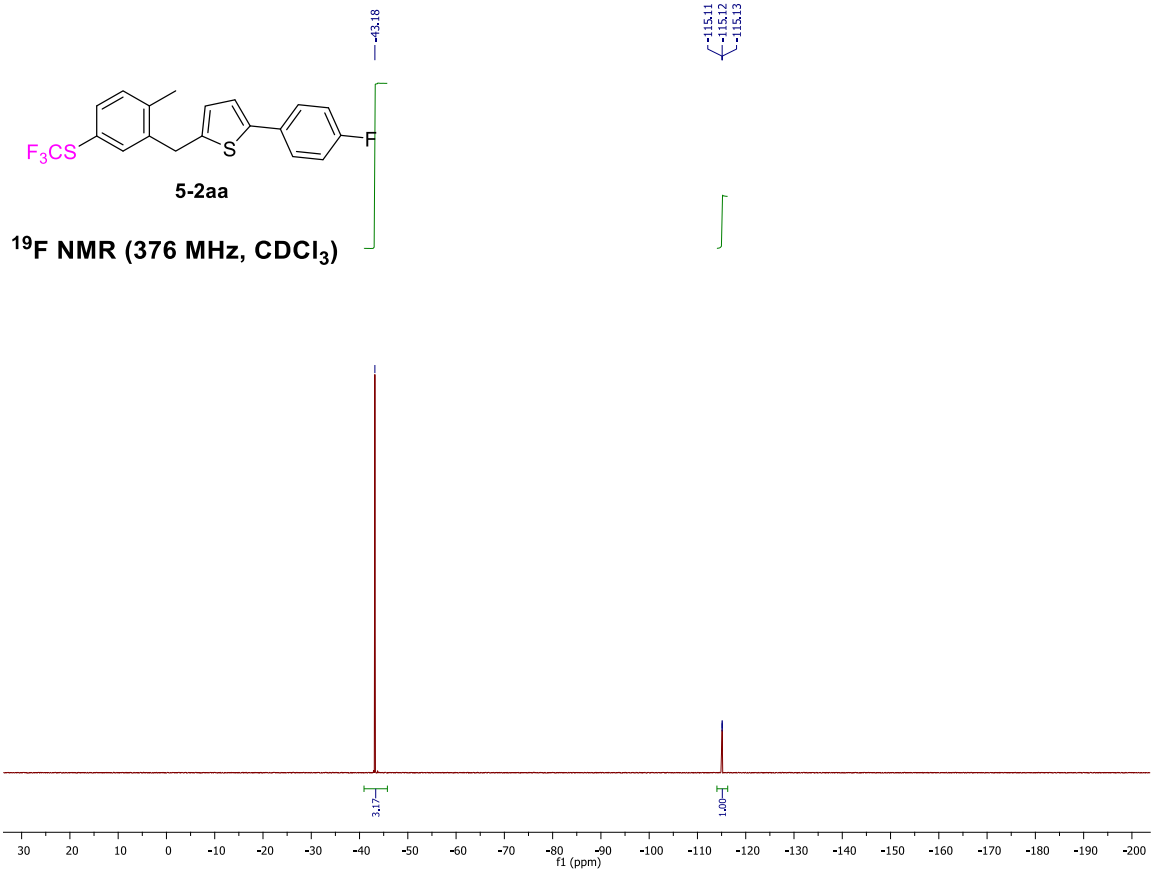




5-2aa

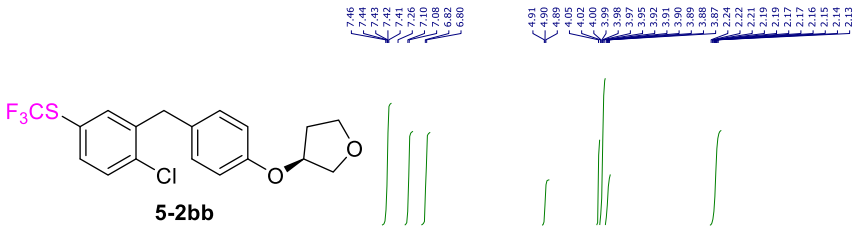
^{13}C NMR (100 MHz, $CDCl_3$)





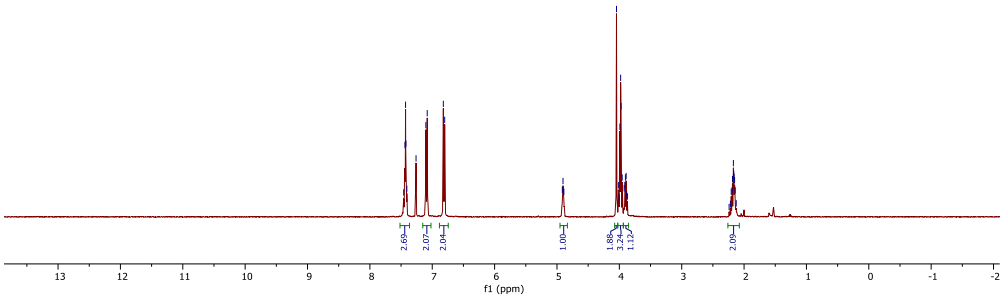
5-2aa

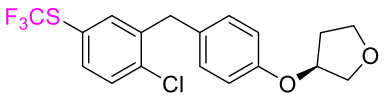
^{19}F NMR (376 MHz, $CDCl_3$)



5-2bb

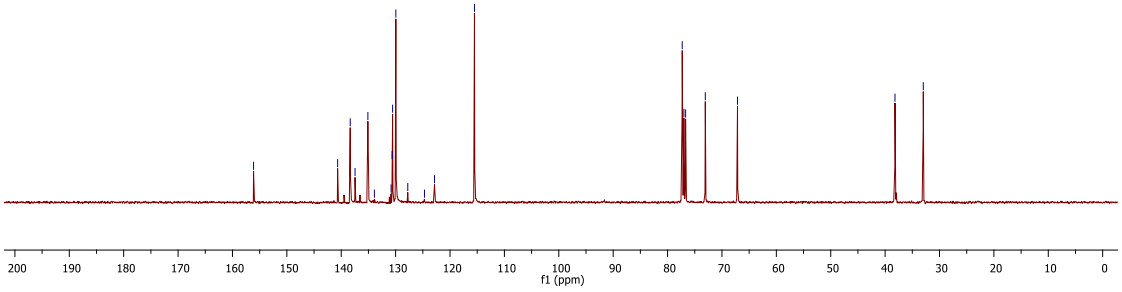
^{1}H NMR (400 MHz, $CDCl_3$)

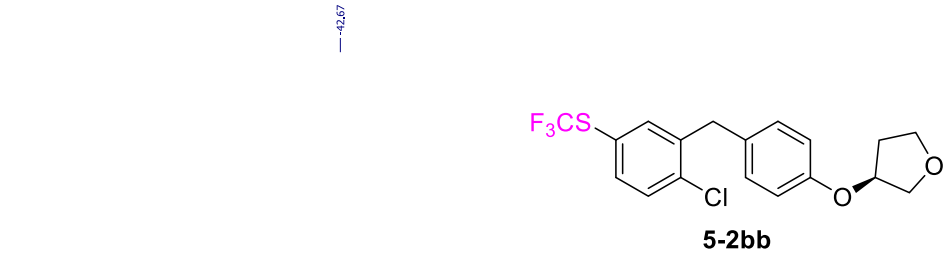




5-2bb

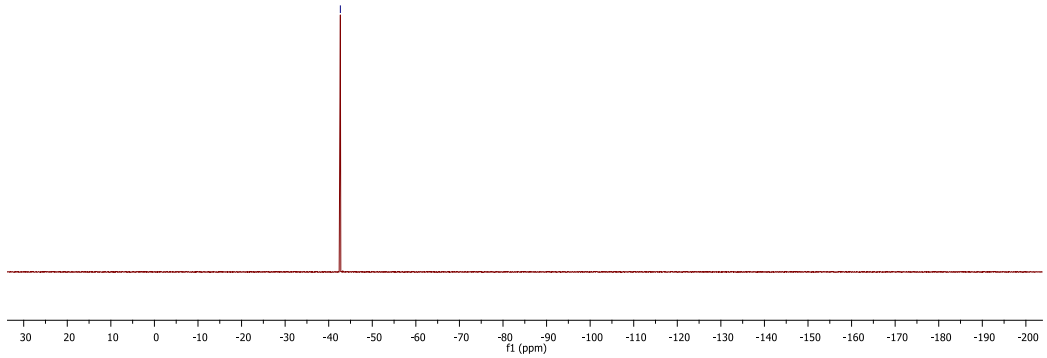
^{13}C NMR (100 MHz, $CDCl_3$)

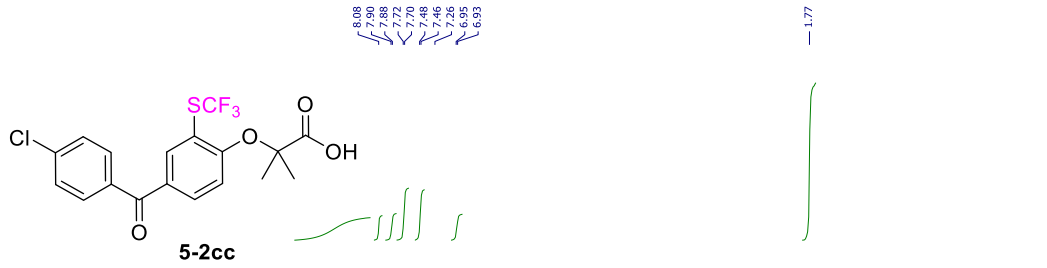




5-2bb

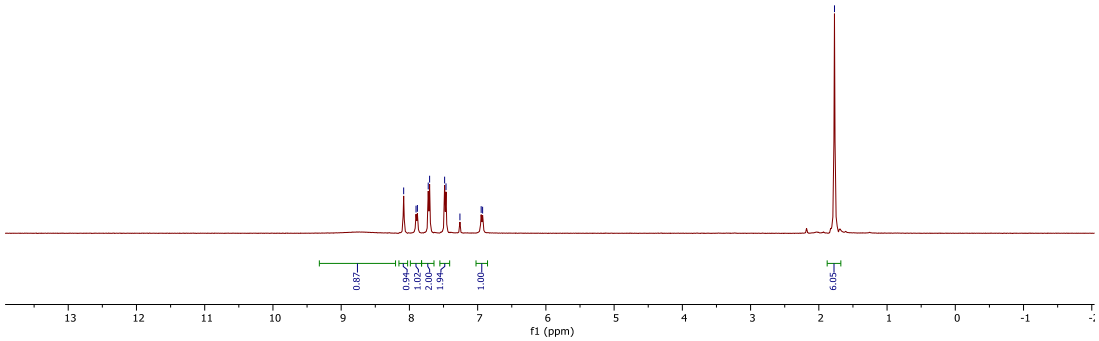
^{19}F NMR (376 MHz, $CDCl_3$)

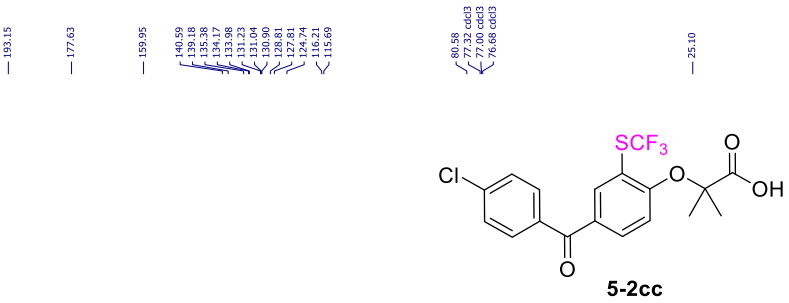




5-2cc

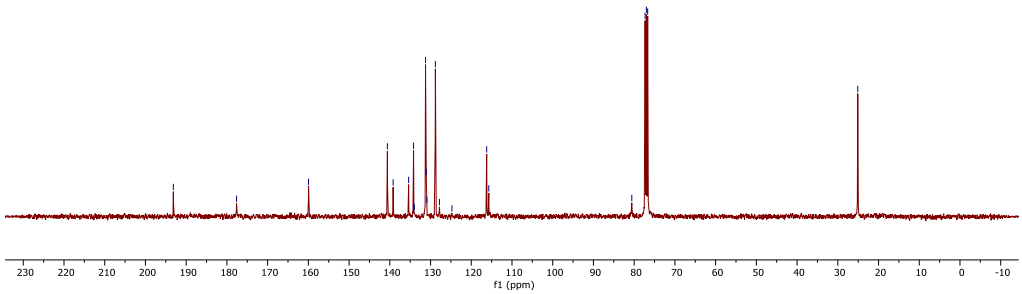
^{1}H NMR (400 MHz, $CDCl_3$)

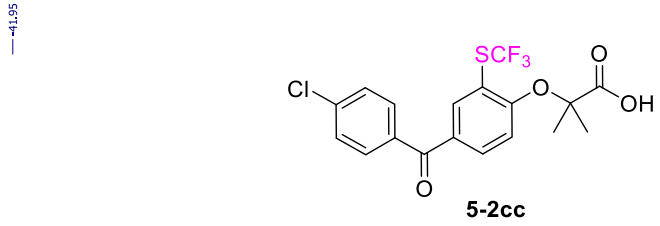




5-2cc

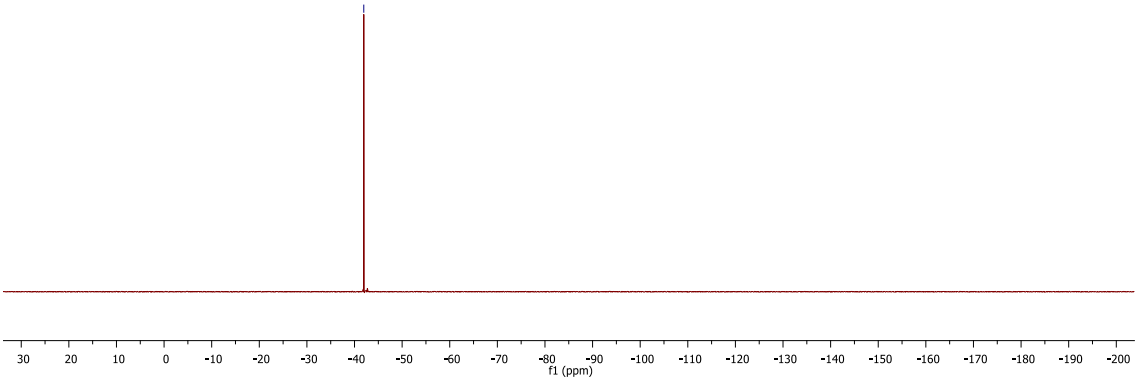
^{13}C NMR (100 MHz, $CDCl_3$)

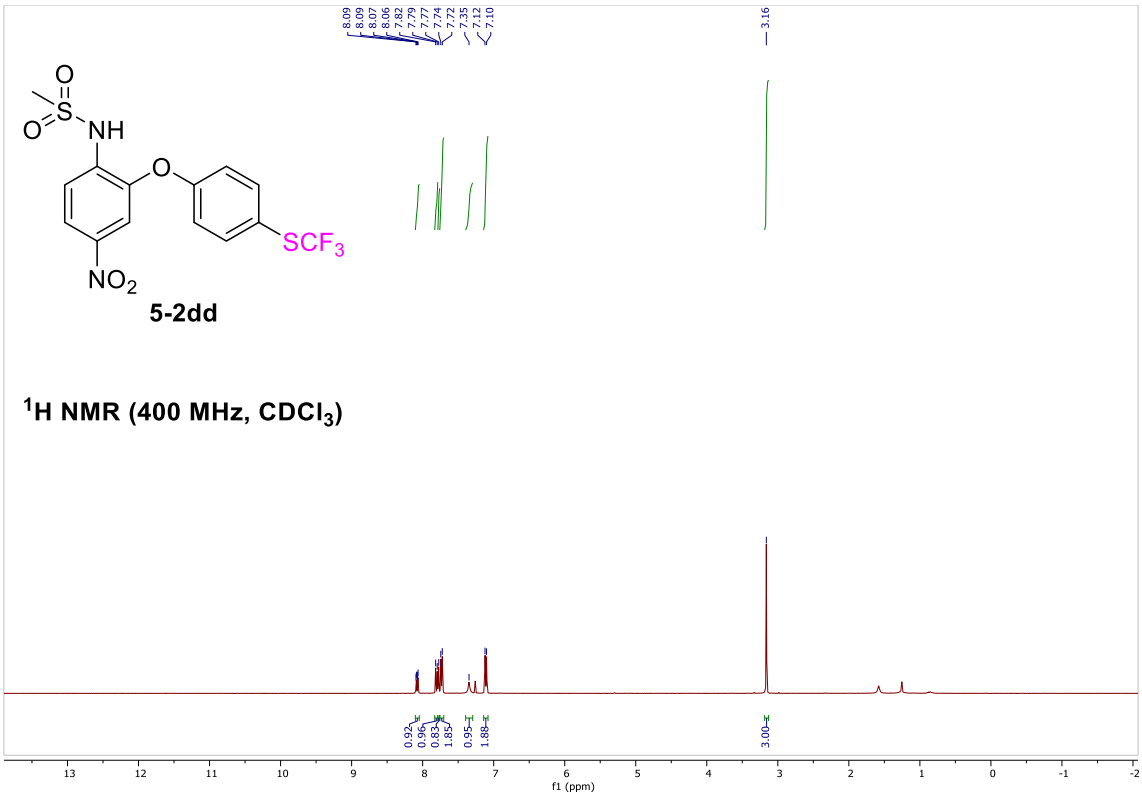




5-2cc

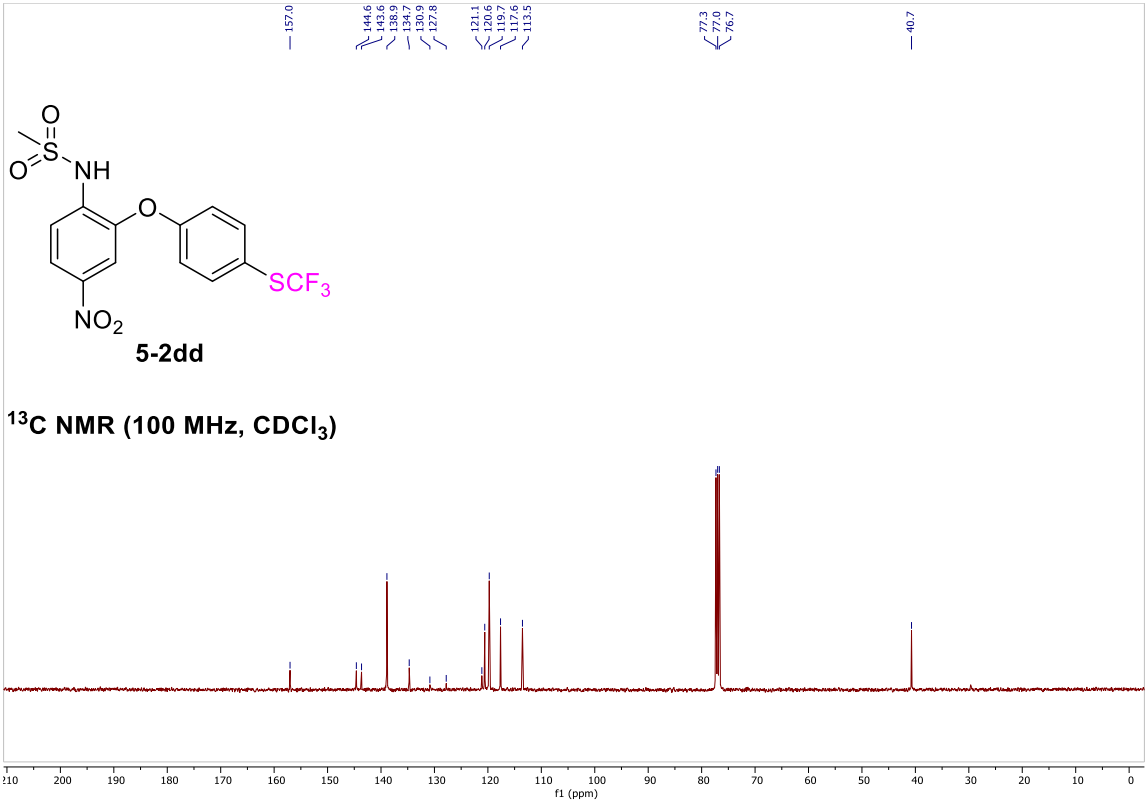
^{19}F NMR (376 MHz, $CDCl_3$)





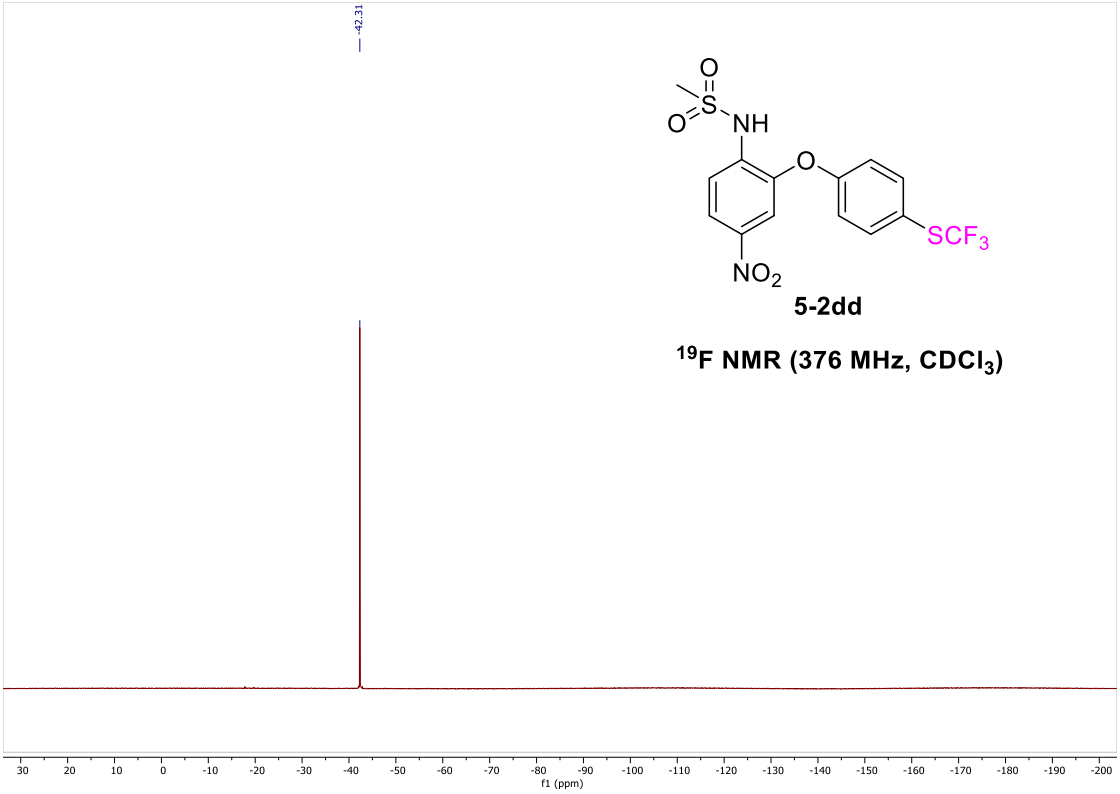
5-2dd

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

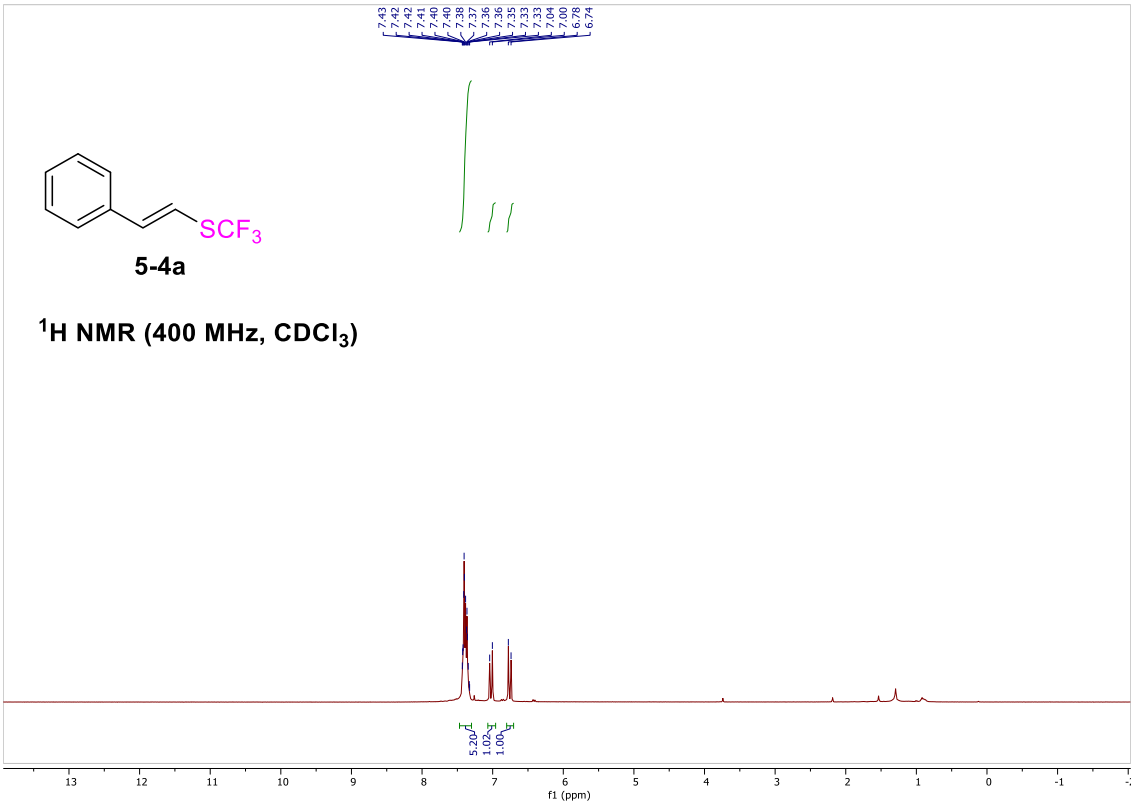


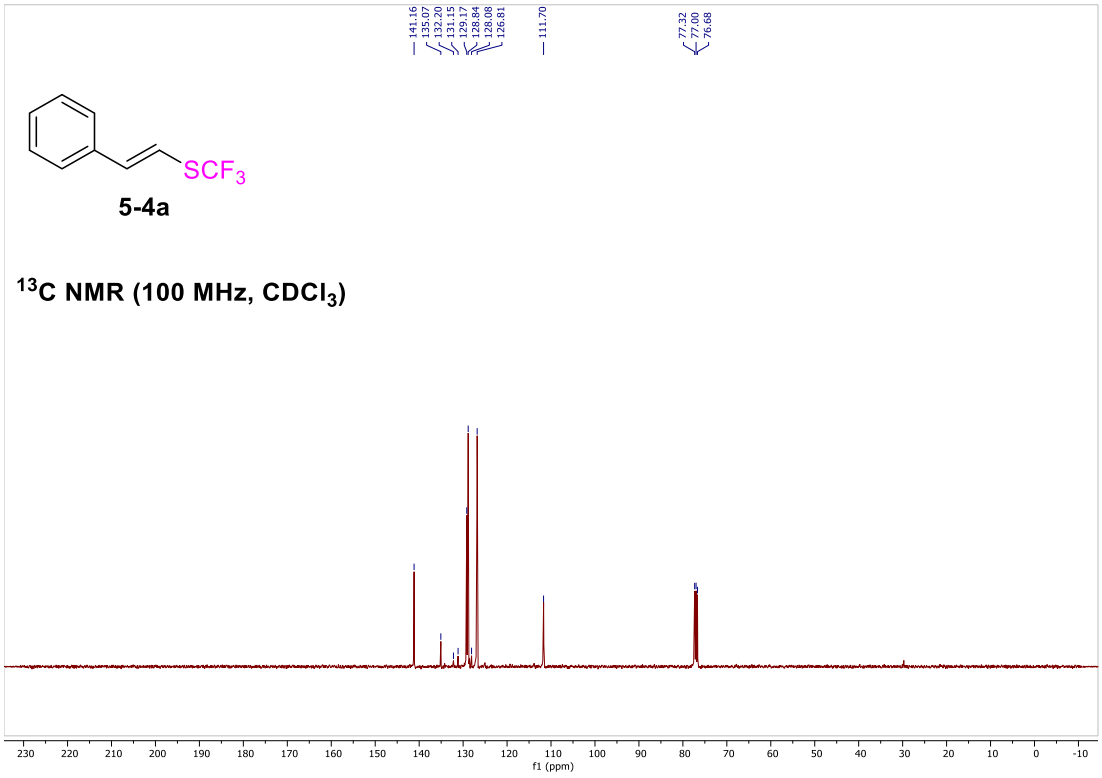
5-2dd

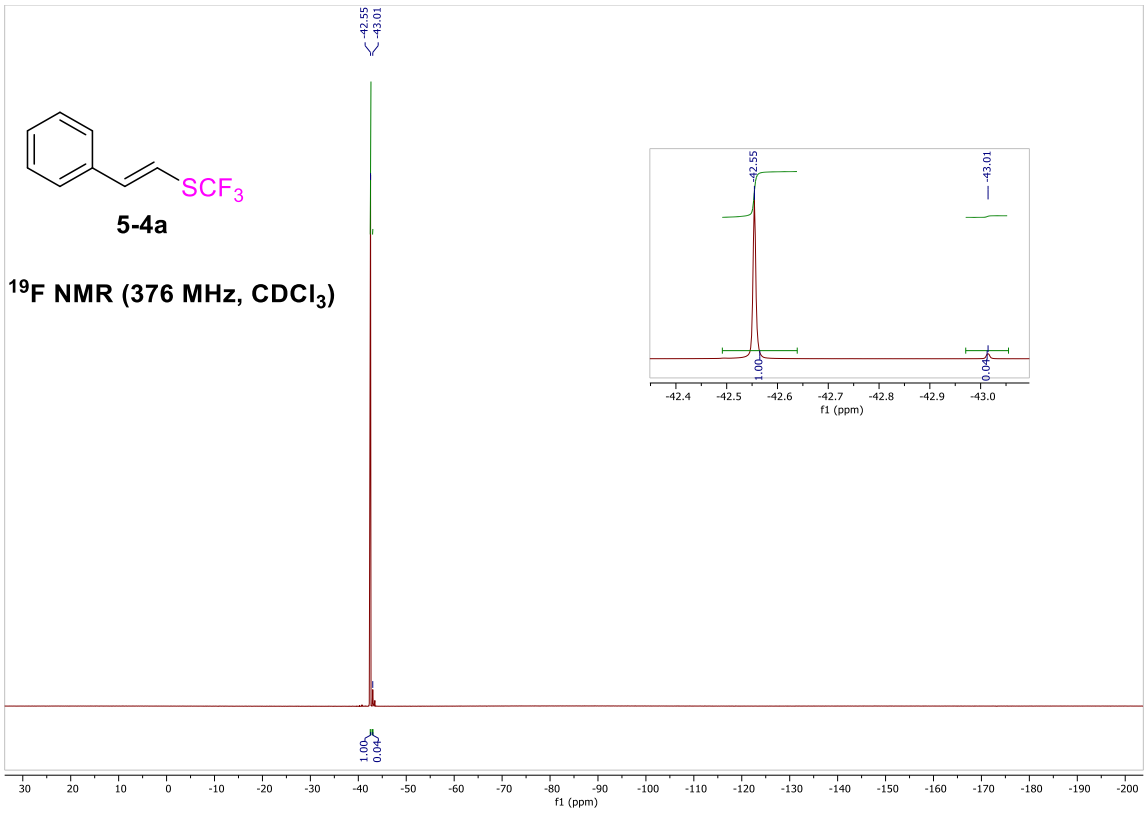
^{13}C NMR (100 MHz, $CDCl_3$)

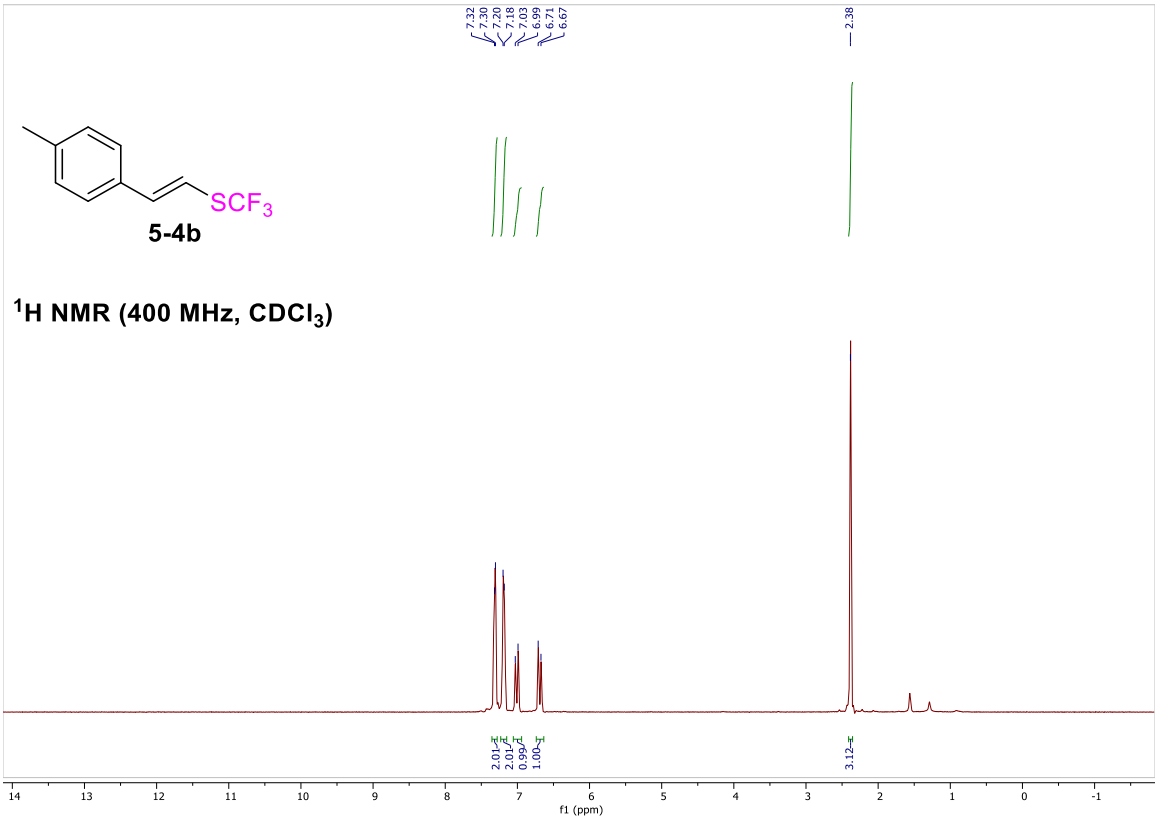

-42.31
O
S
O
NH
O
SCF3
NO2
5-2dd
19F NMR (376 MHz, CDCl3)
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

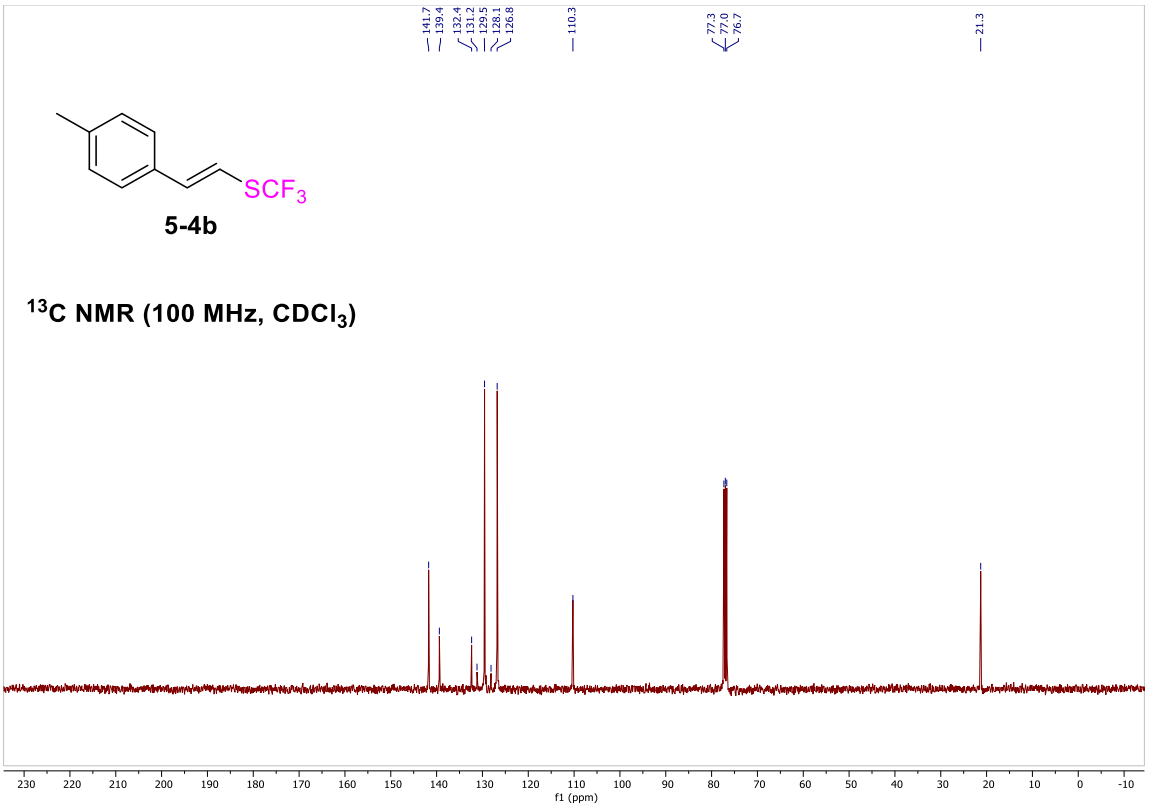
5.4.7.5. Trifluoromethylthiolation products from alkenyl iodide substrates

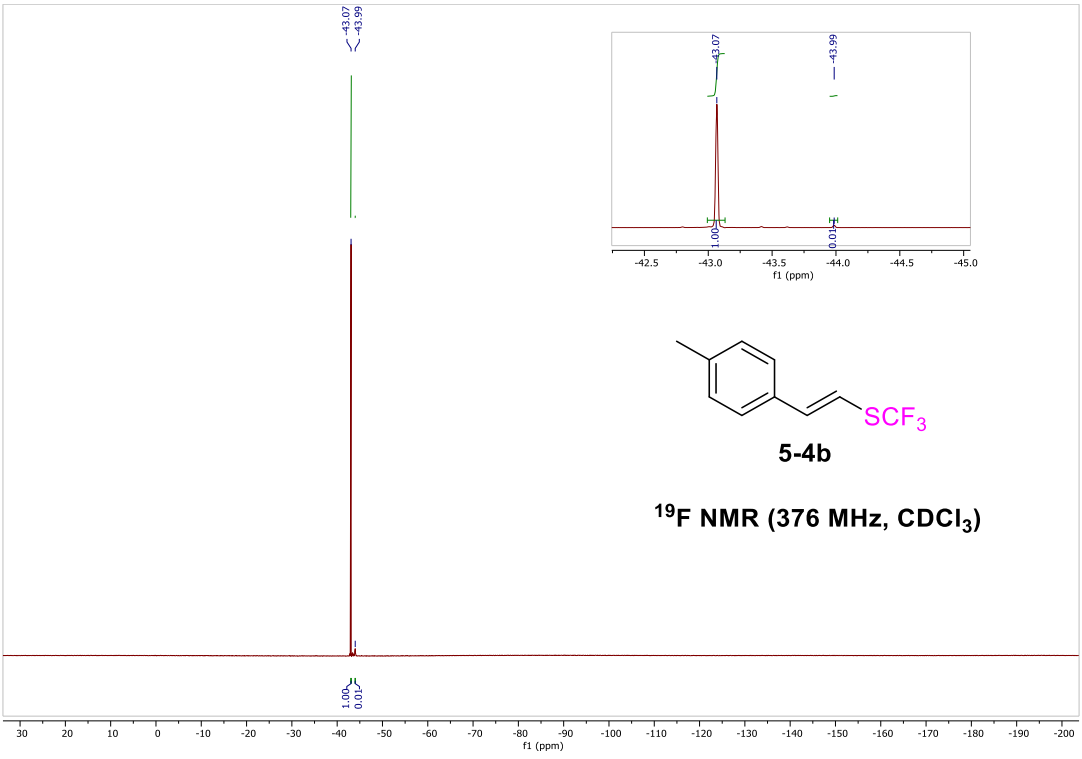


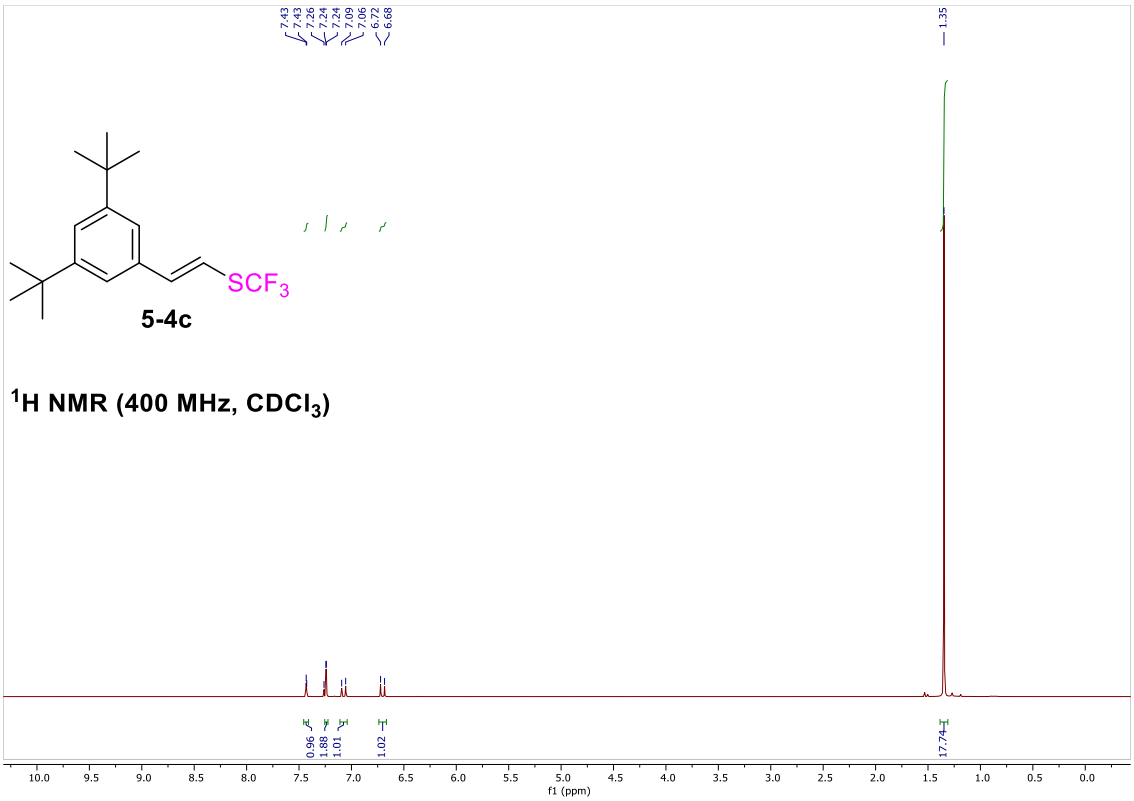



SCF3
5-4a
19F NMR (376 MHz, CDCl3)
-42.55
-43.01
1.00
0.04
f1 (ppm)


SCF3
5-4b
1H NMR (400 MHz, CDCl3)
7.32
7.30
7.20
7.18
7.03
6.99
6.71
6.67
2.38
2.01
2.01
0.99
1.00
3.12
f1 (ppm)

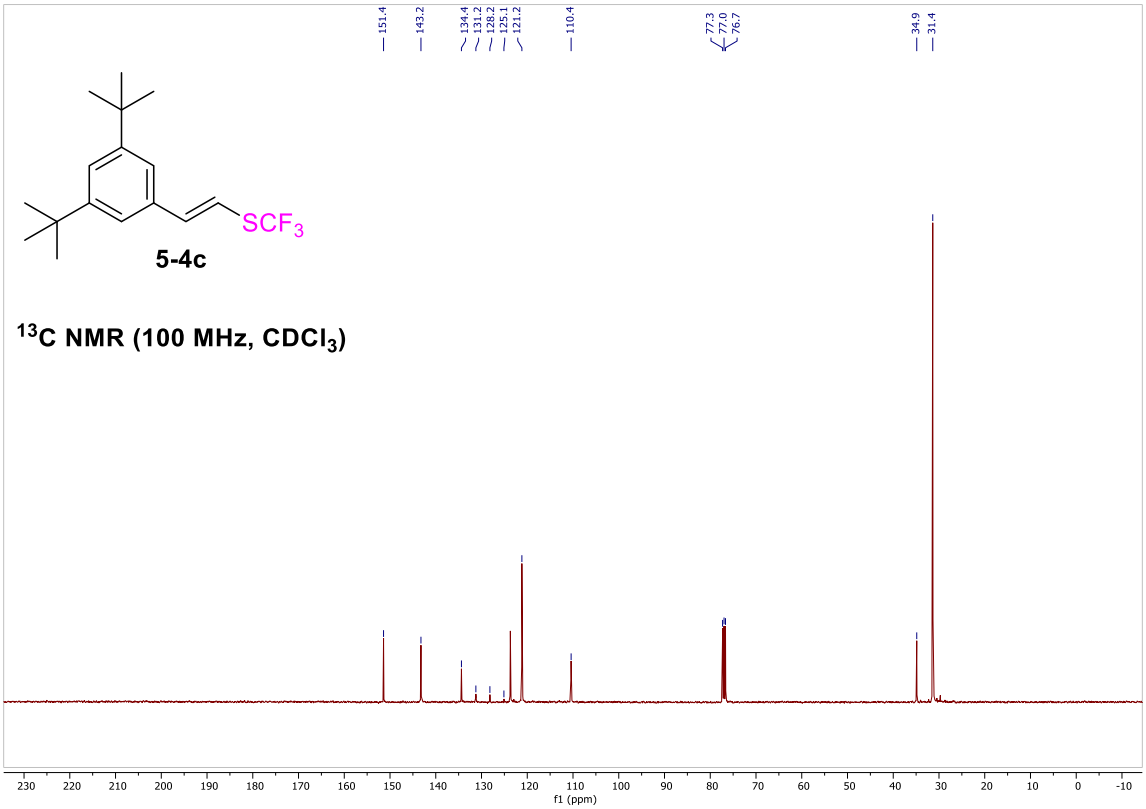

141.7
139.4
132.4
131.2
129.5
128.1
126.8
110.3
77.3
77.0
76.7
21.3
SCF3
5-4b
13C NMR (100 MHz, CDCl3)
f1 (ppm)


-43.07
-43.99
1.00
0.01
f1 (ppm)
SCF3
5-4b
19F NMR (376 MHz, CDCl3)



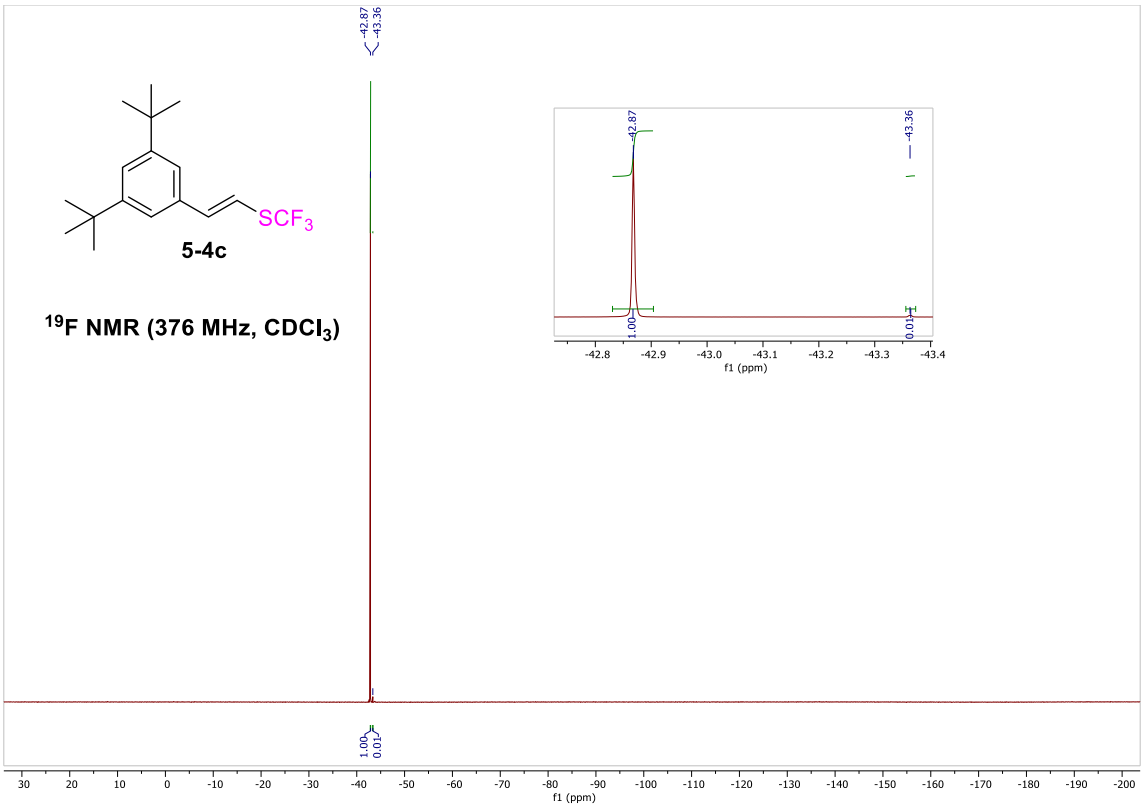
5-4c

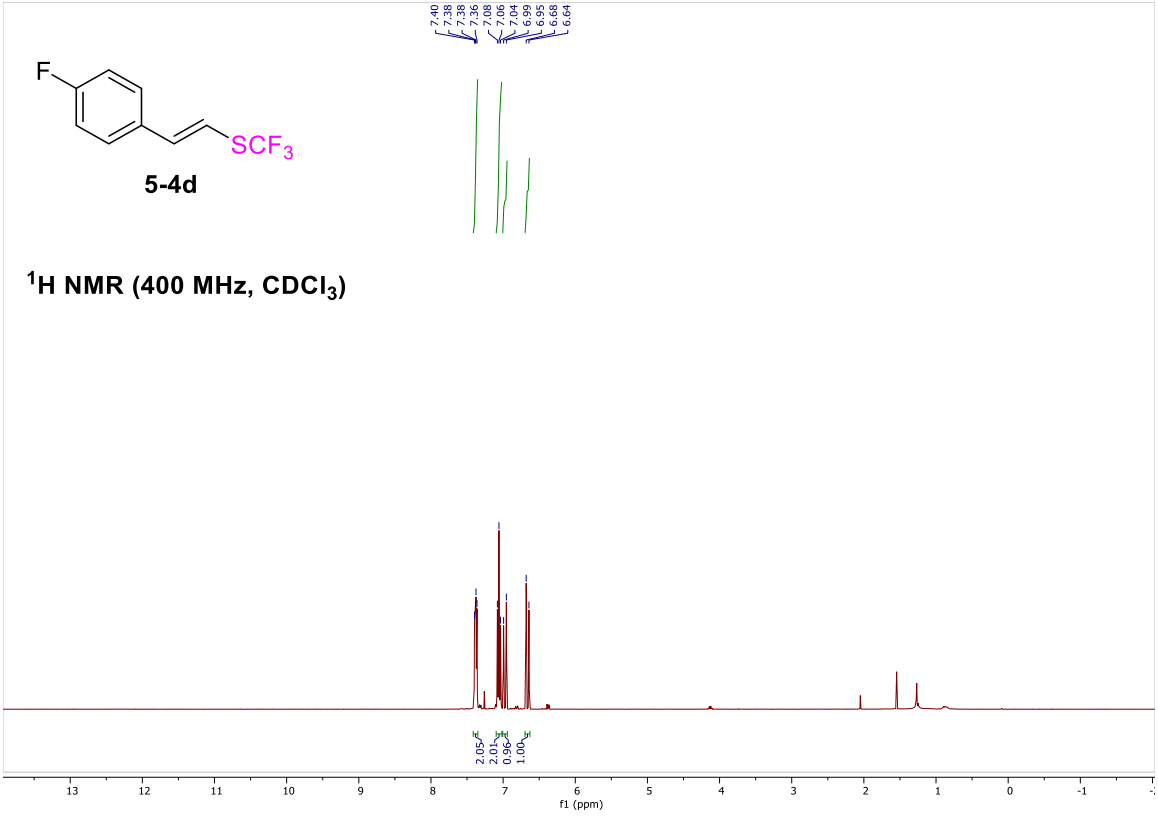
^{1}H NMR (400 MHz, $CDCl_3$)

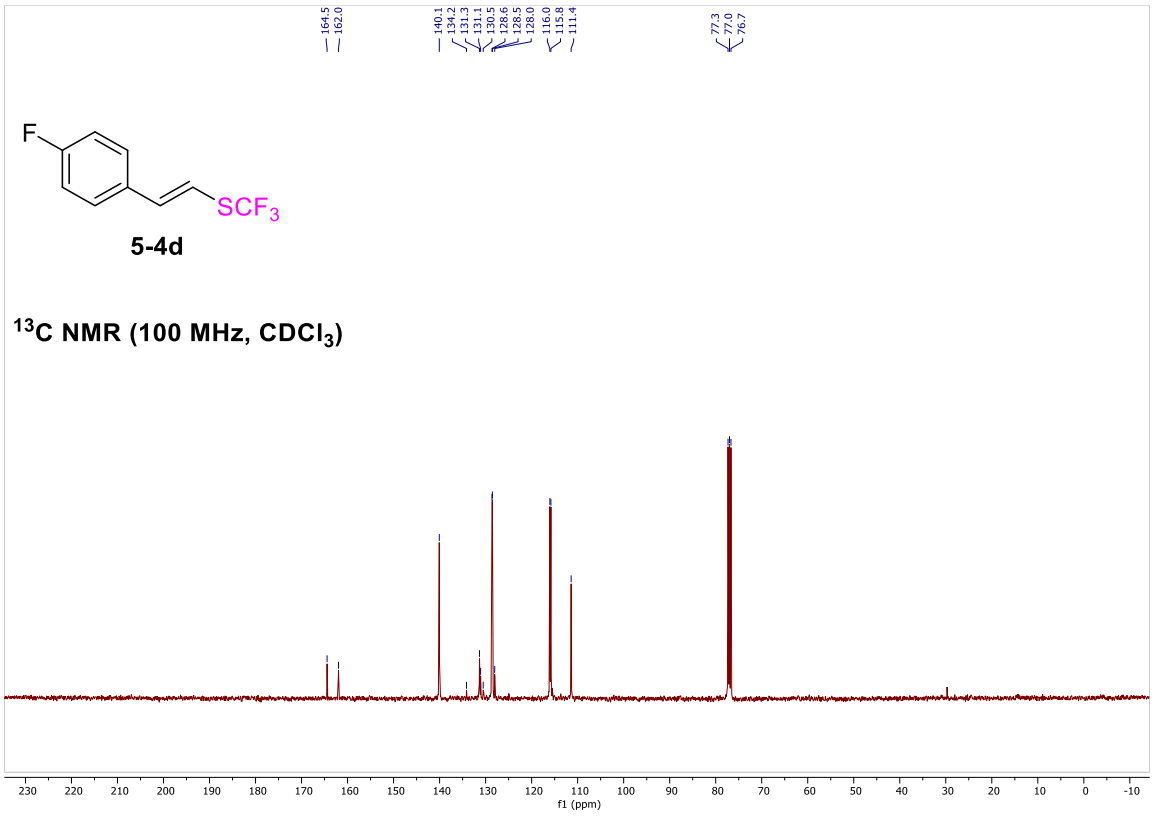


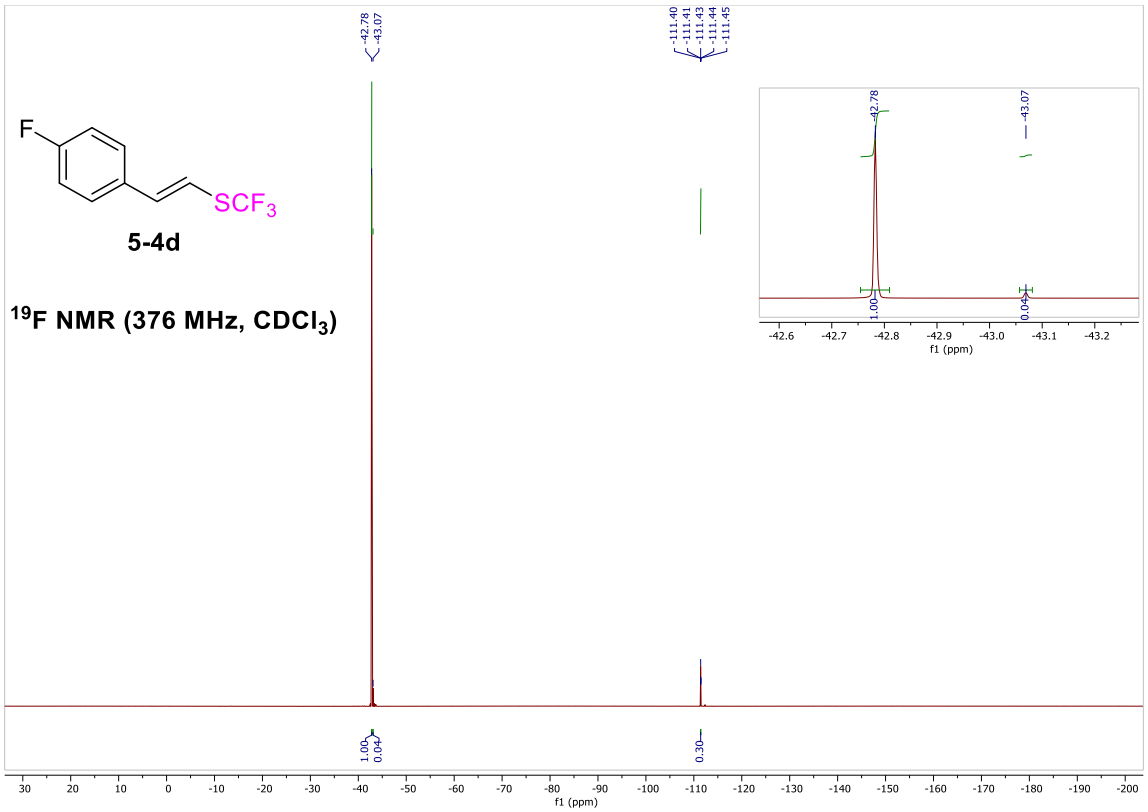
5-4c

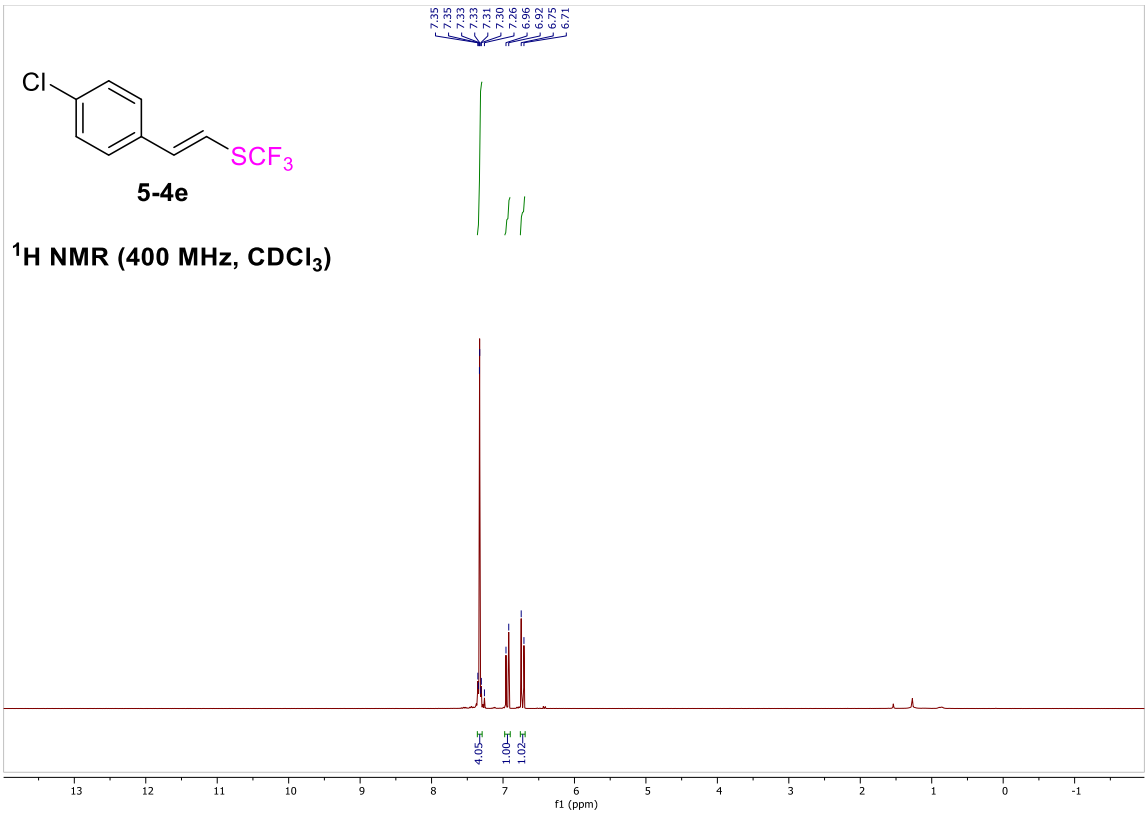
^{13}C NMR (100 MHz, $CDCl_3$)

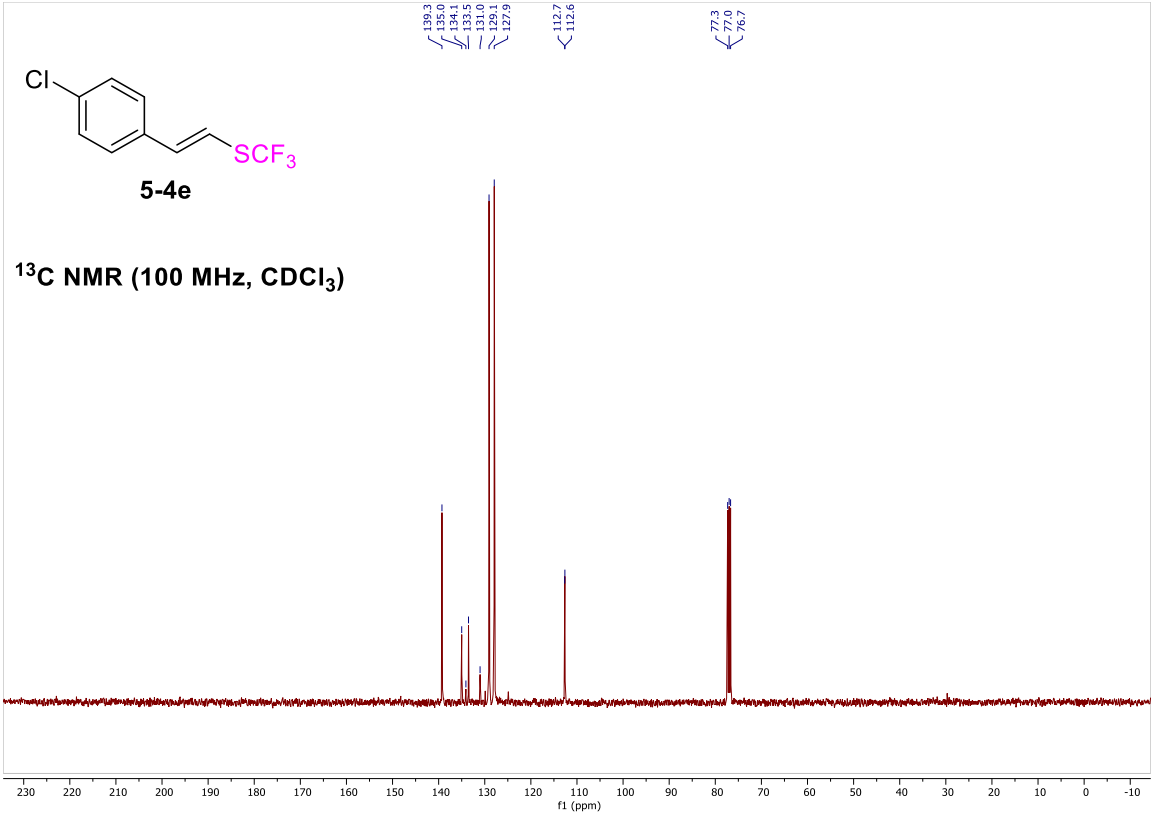

-42.87
-43.36
SCF3
5-4c
19F NMR (376 MHz, CDCl3)
1.00
0.01
f1 (ppm)

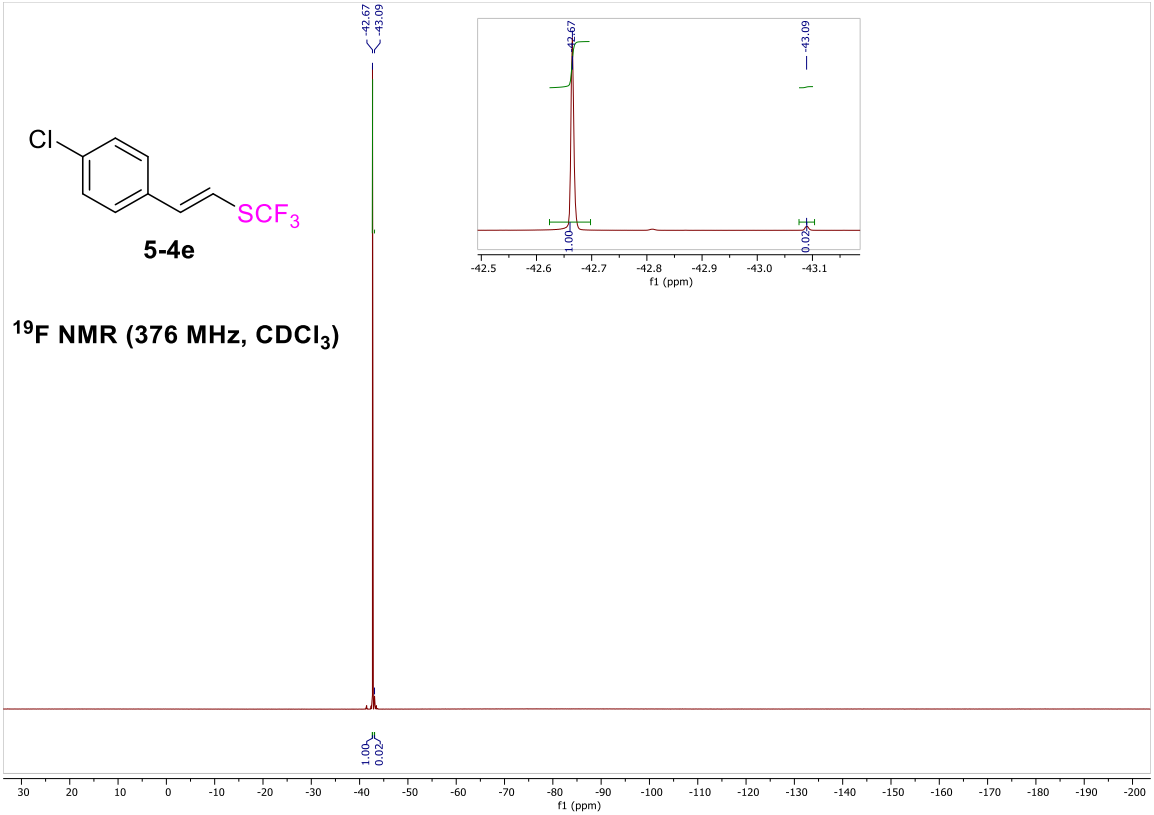

7.40
7.38
7.38
7.36
7.08
7.06
7.04
6.99
6.95
6.68
6.64
F
SCF3
5-4d
1H NMR (400 MHz, CDCl3)
2.05
2.01
0.96
1.00
f1 (ppm)

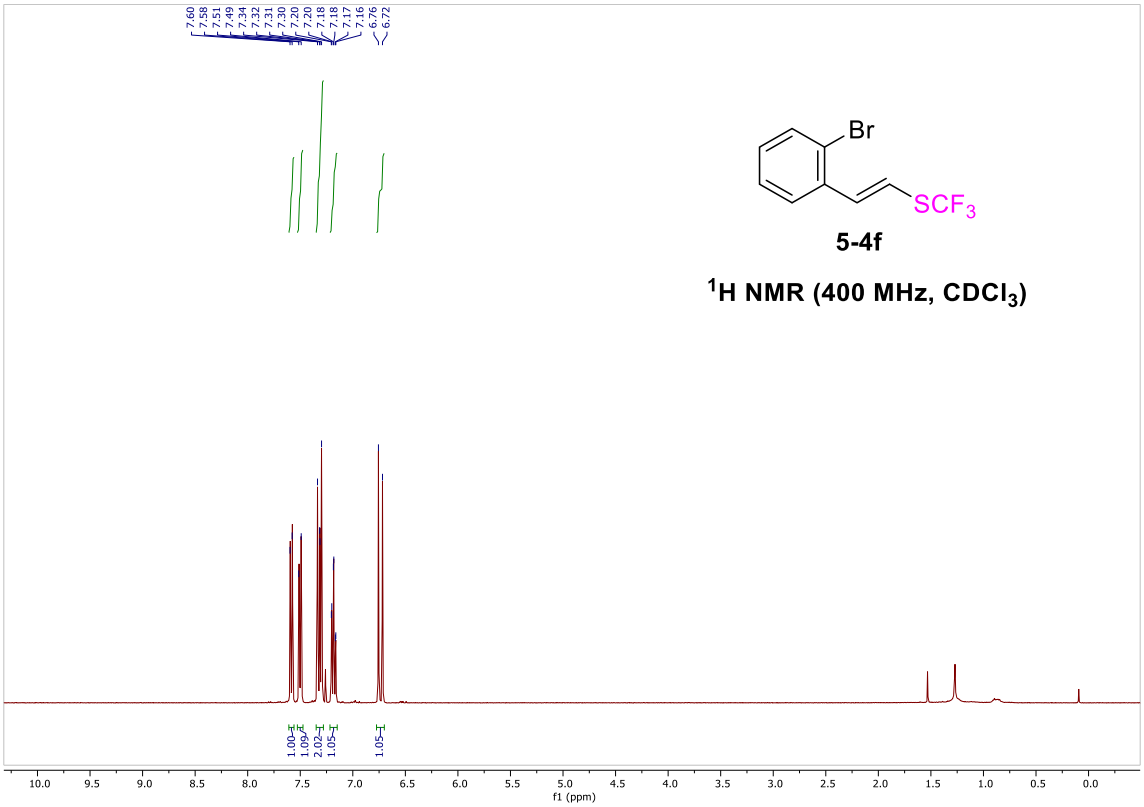

164.5
162.0
140.1
134.2
131.3
131.1
130.5
128.6
128.5
128.0
116.0
115.8
111.4
77.3
77.0
76.7
F
SCF3
5-4d
13C NMR (100 MHz, CDCl3)
f1 (ppm)

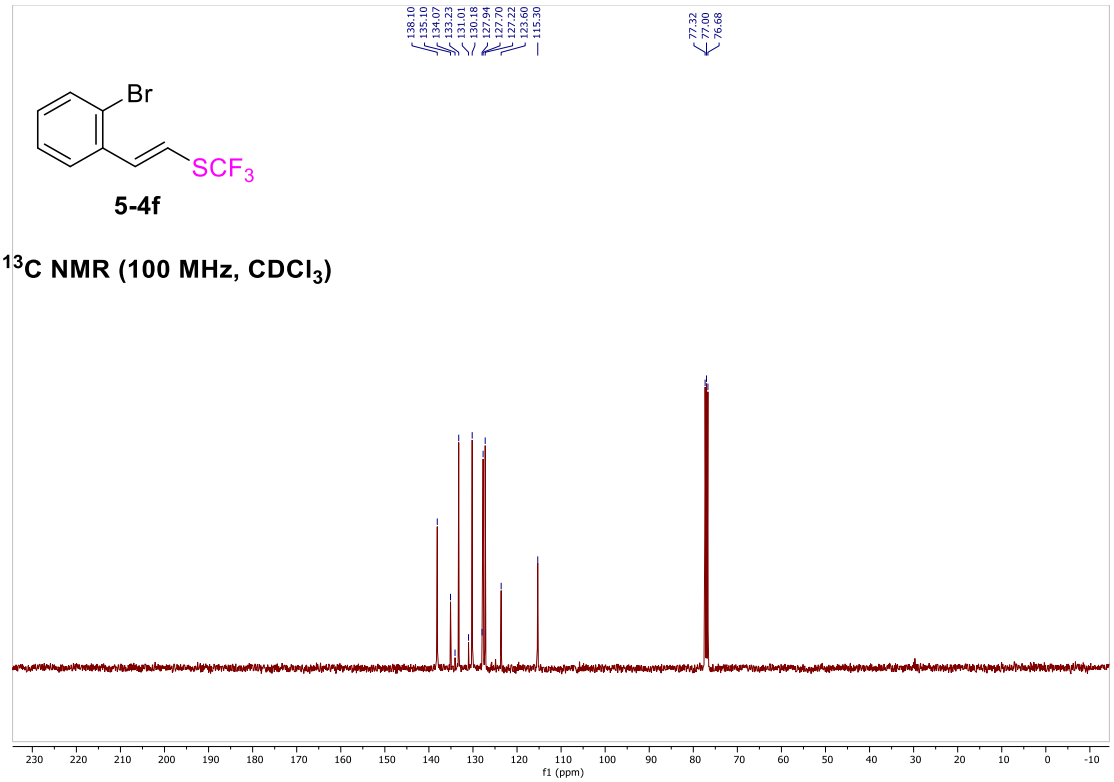

-42.78
-43.07
-111.40
-111.41
-111.43
-111.44
-111.45
F
SCF3
5-4d
19F NMR (376 MHz, CDCl3)
1.00
0.04
0.30
f1 (ppm)


Cl
SCF3
5-4e
1H NMR (400 MHz, CDCl3)
7.35
7.35
7.33
7.33
7.31
7.30
7.26
6.96
6.92
6.75
6.71
4.05
1.00
1.02
f1 (ppm)


Cl
SCF3
5-4e
13C NMR (100 MHz, CDCl3)
139.3
135.0
134.1
133.5
131.0
129.1
127.9
112.7
112.6
77.3
77.0
76.7
f1 (ppm)

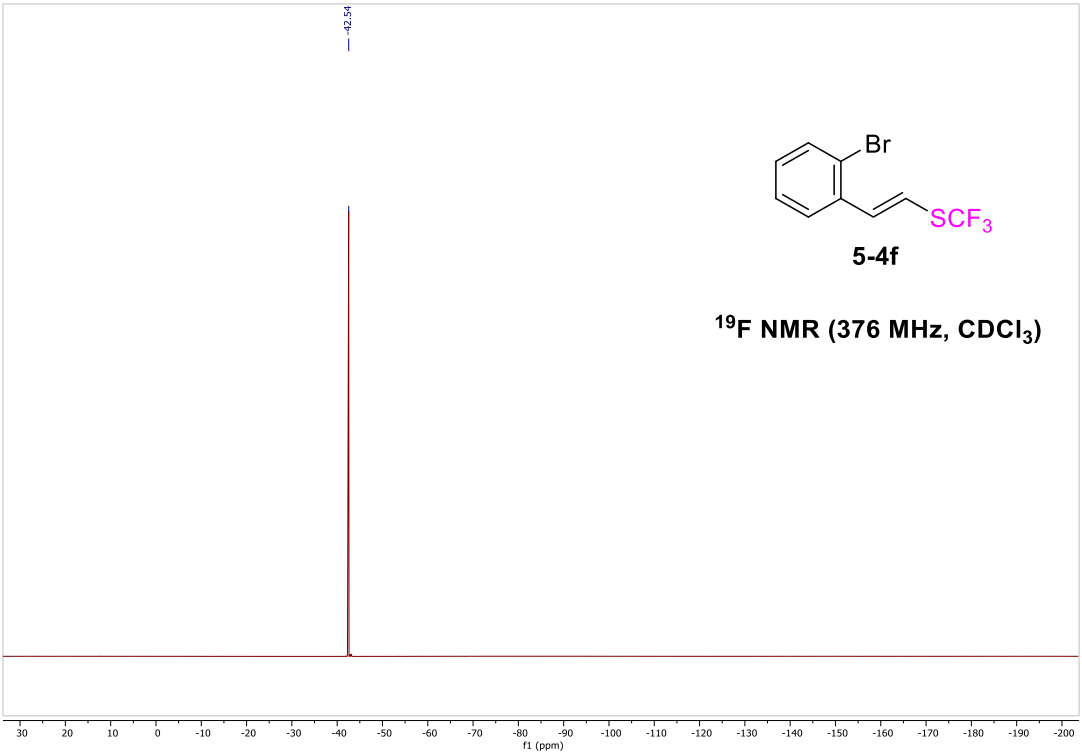

Cl
SCF3
5-4e
19F NMR (376 MHz, CDCl3)
-42.67
-43.09
1.00
0.02
f1 (ppm)


Br
SCF3
5-4f
1H NMR (400 MHz, CDCl3)
7.60
7.58
7.51
7.49
7.34
7.32
7.31
7.30
7.20
7.20
7.18
7.18
7.17
7.16
6.76
6.72
1.00
1.09
2.02
1.05
1.05
f1 (ppm)



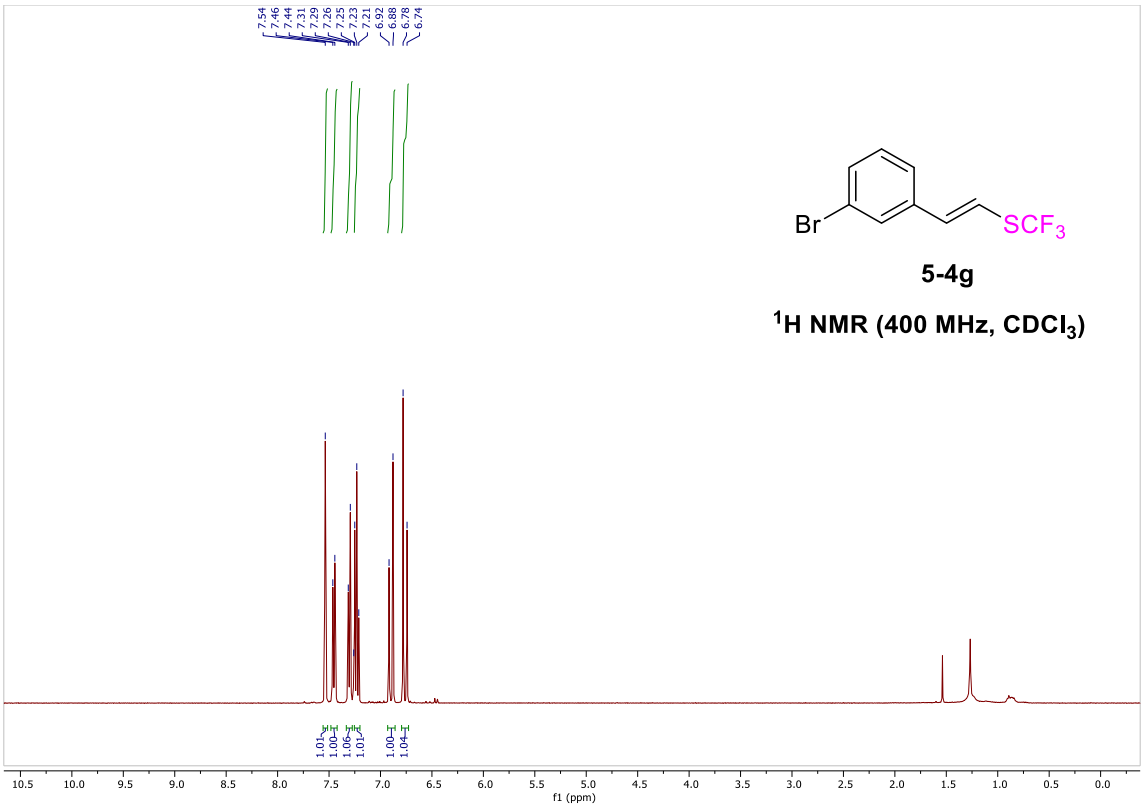
5-4f

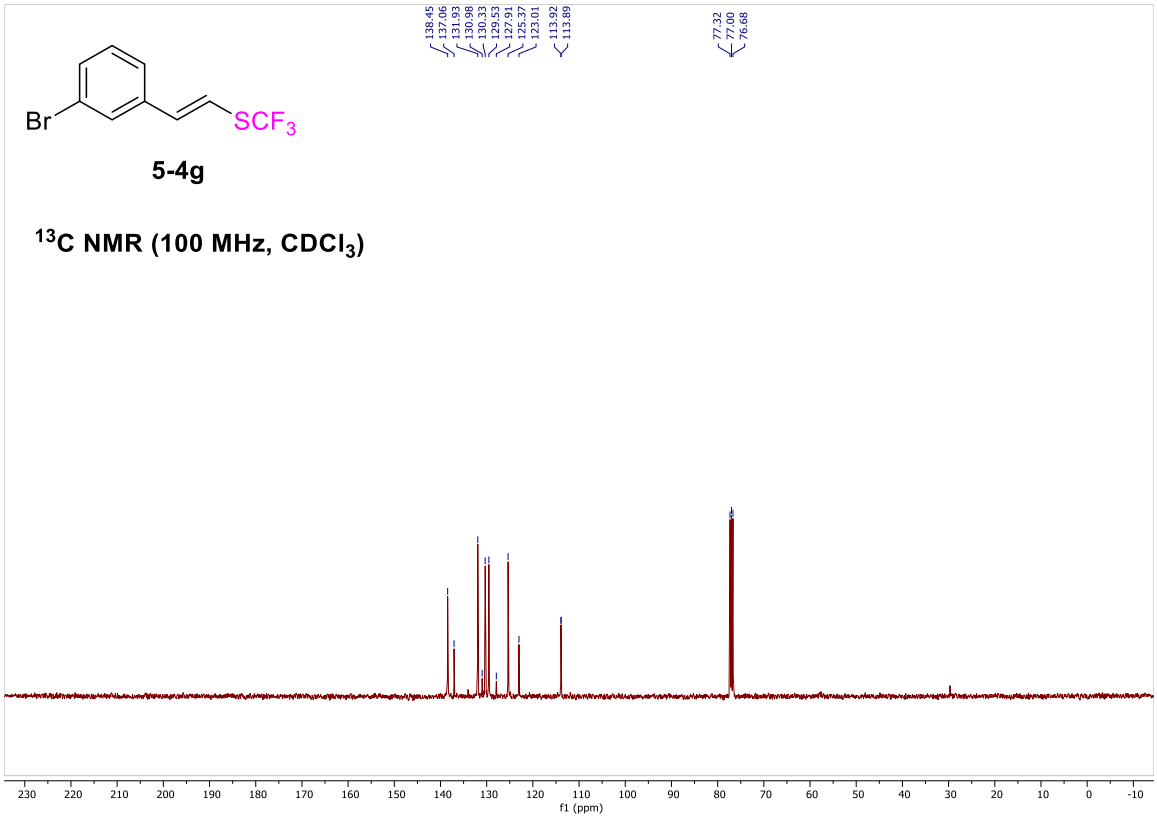
^{13}C NMR (100 MHz, $CDCl_3$)

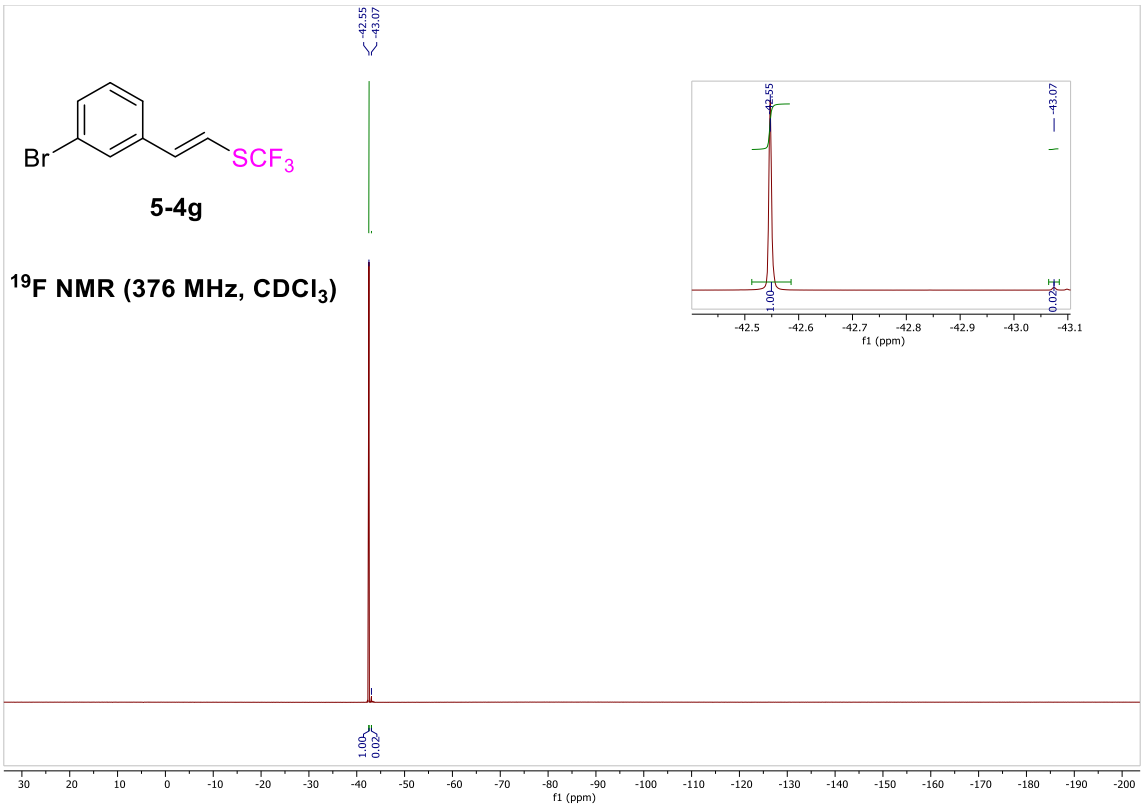


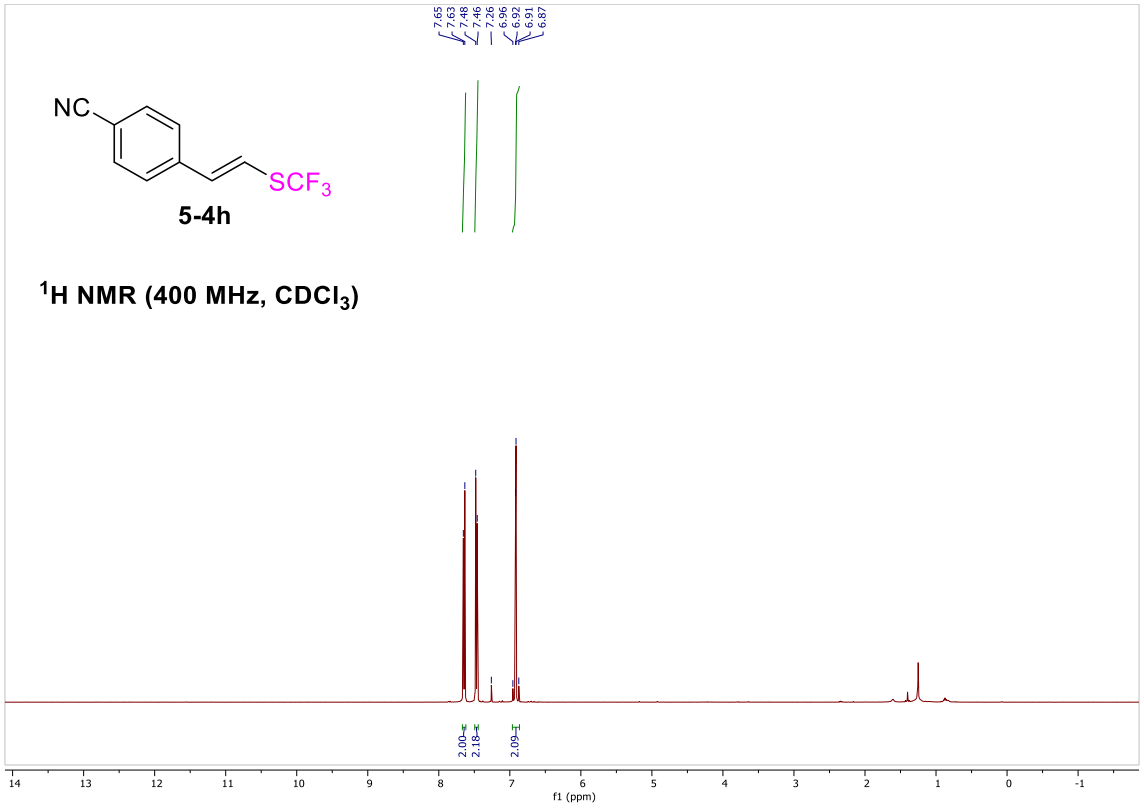
5-4f

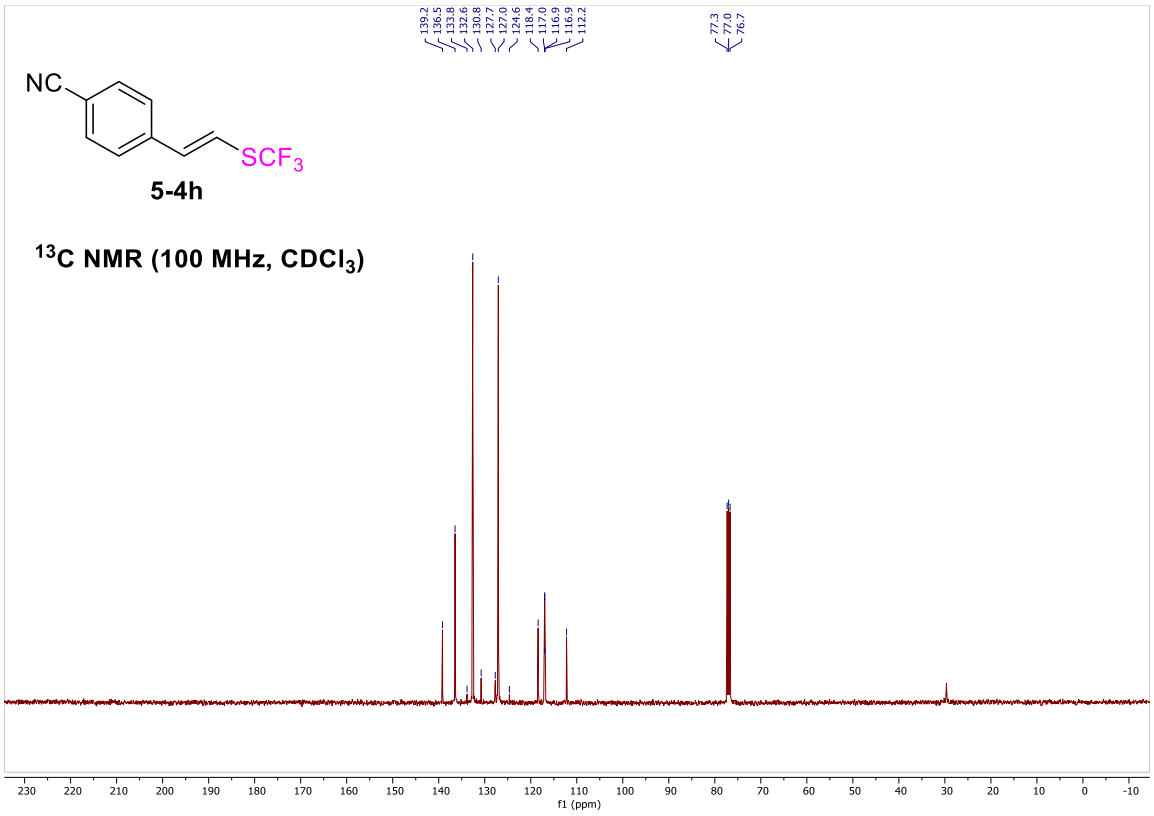
^{19}F NMR (376 MHz, $CDCl_3$)

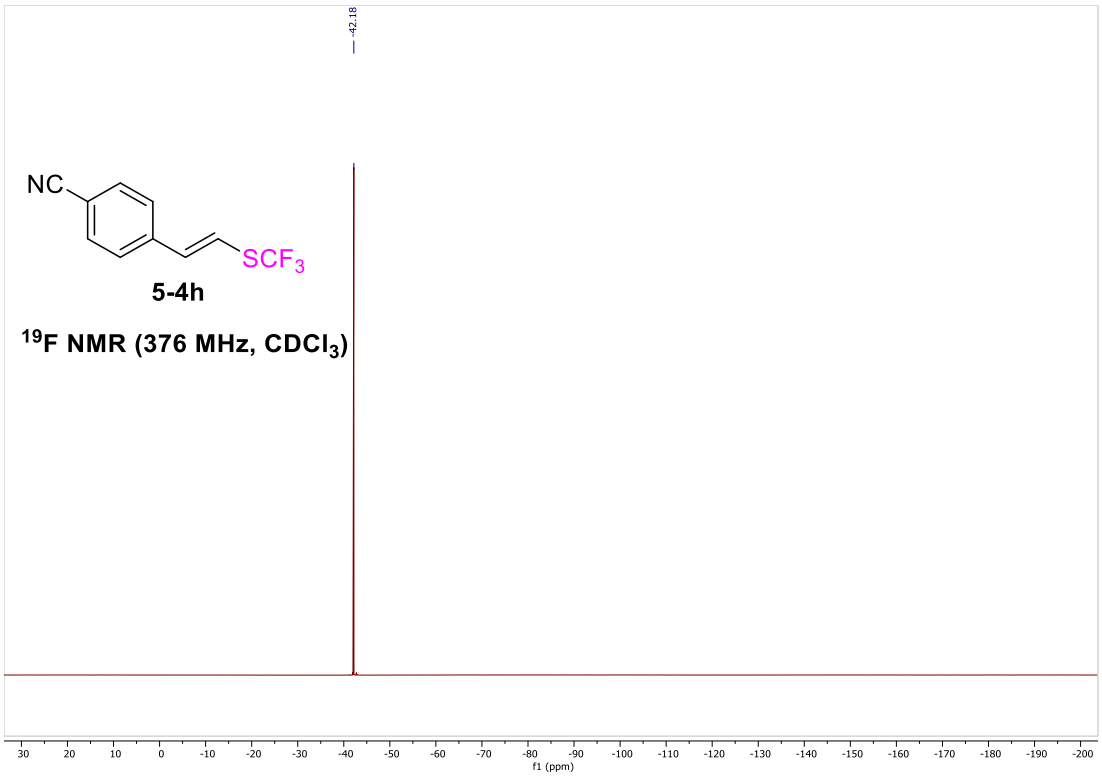

7.54
7.46
7.44
7.31
7.29
7.26
7.25
7.23
7.21
6.92
6.88
6.78
6.74
Br
SCF3
5-4g
1H NMR (400 MHz, CDCl3)
1.01
1.00
1.06
1.01
1.00
1.04
f1 (ppm)

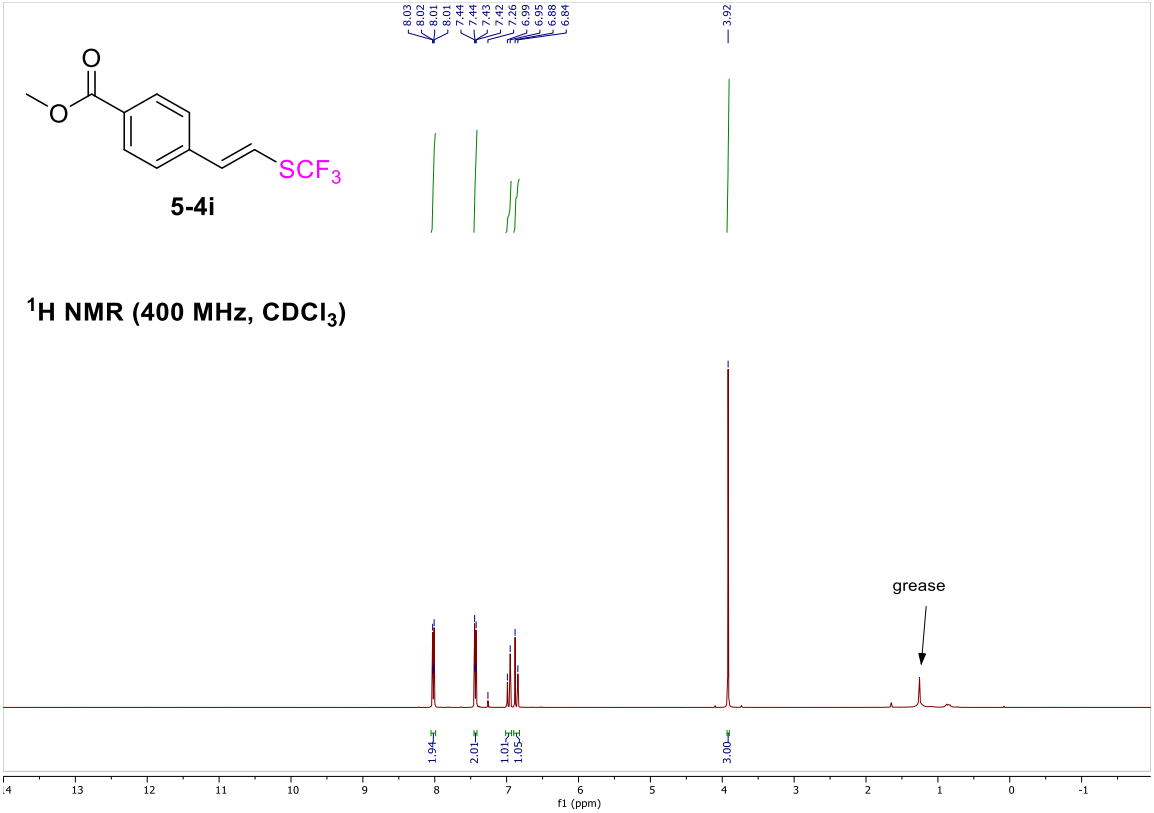

138.45
137.06
131.93
130.98
130.33
129.53
127.91
125.37
123.01
113.92
113.89
77.32
77.00
76.68
Br
SCF3
5-4g
13C NMR (100 MHz, CDCl3)
f1 (ppm)

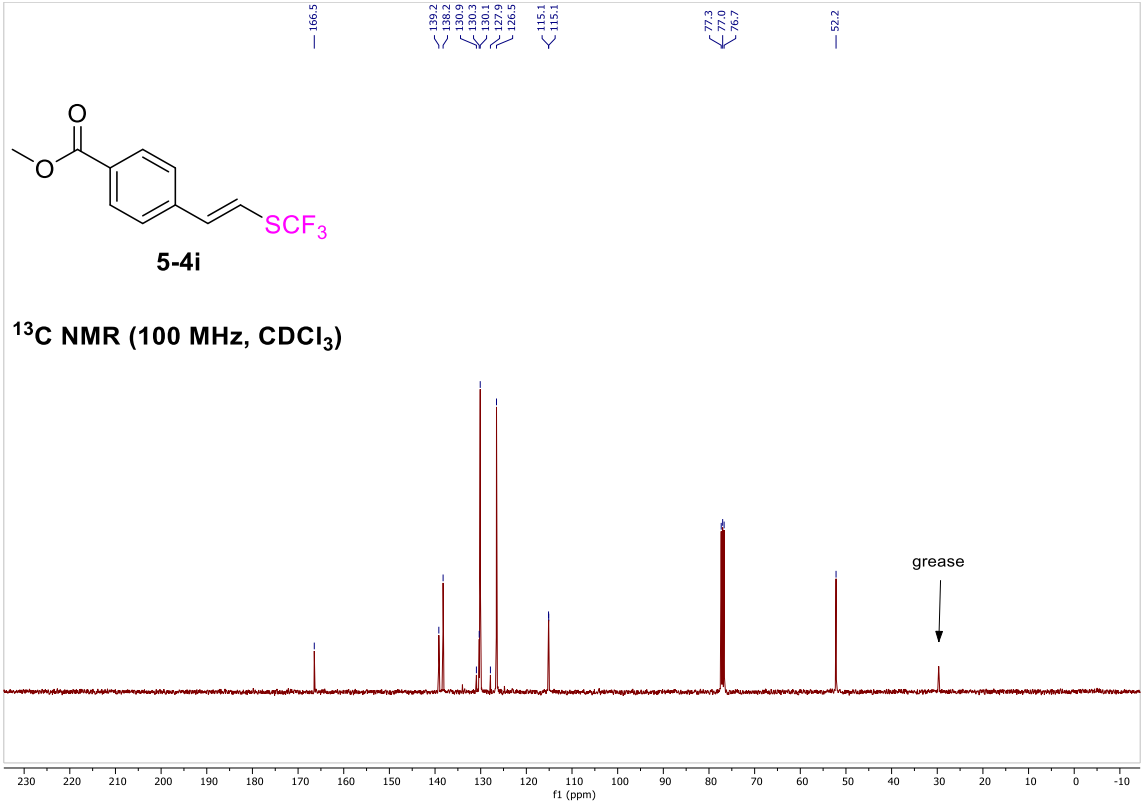

Br
SCF3
5-4g
19F NMR (376 MHz, CDCl3)
f1 (ppm)

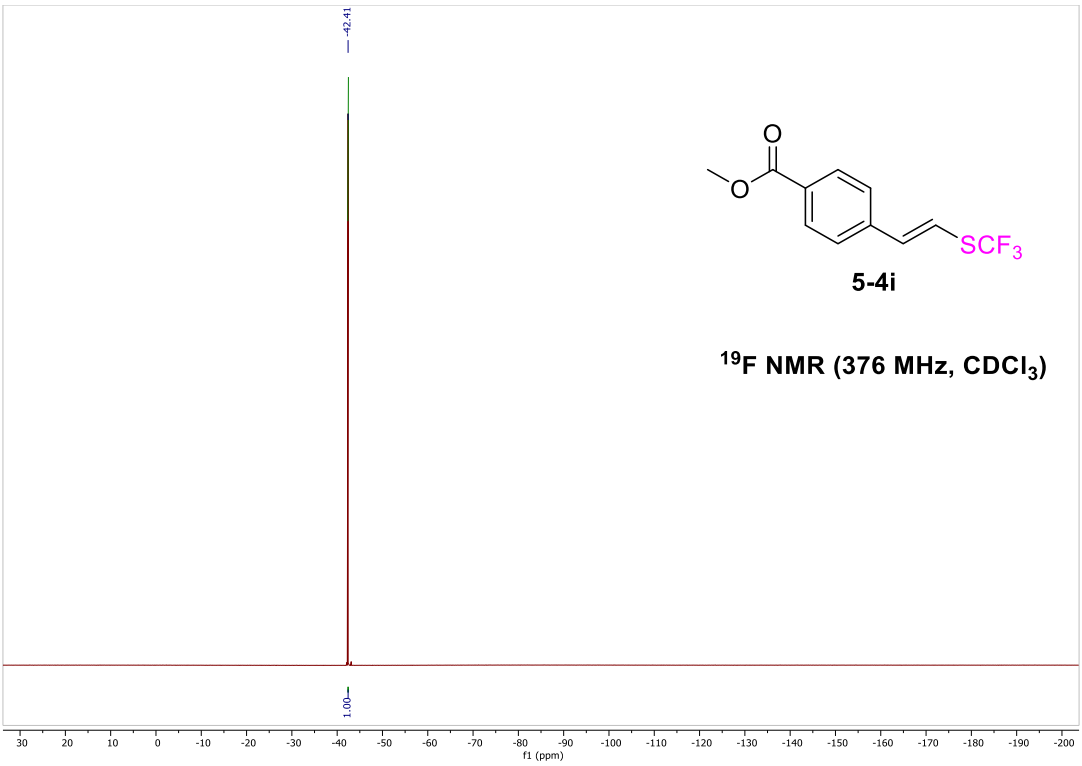

NC
SCF3
5-4h
1H NMR (400 MHz, CDCl3)
f1 (ppm)


NC
SCF3
5-4h
13C NMR (100 MHz, CDCl3)
139.2
136.5
133.8
132.6
130.8
127.7
127.0
124.6
118.4
117.0
116.9
116.9
112.2
77.3
77.0
76.7
f1 (ppm)


-42.18
NC
SCF3
5-4h
19F NMR (376 MHz, CDCl3)
f1 (ppm)

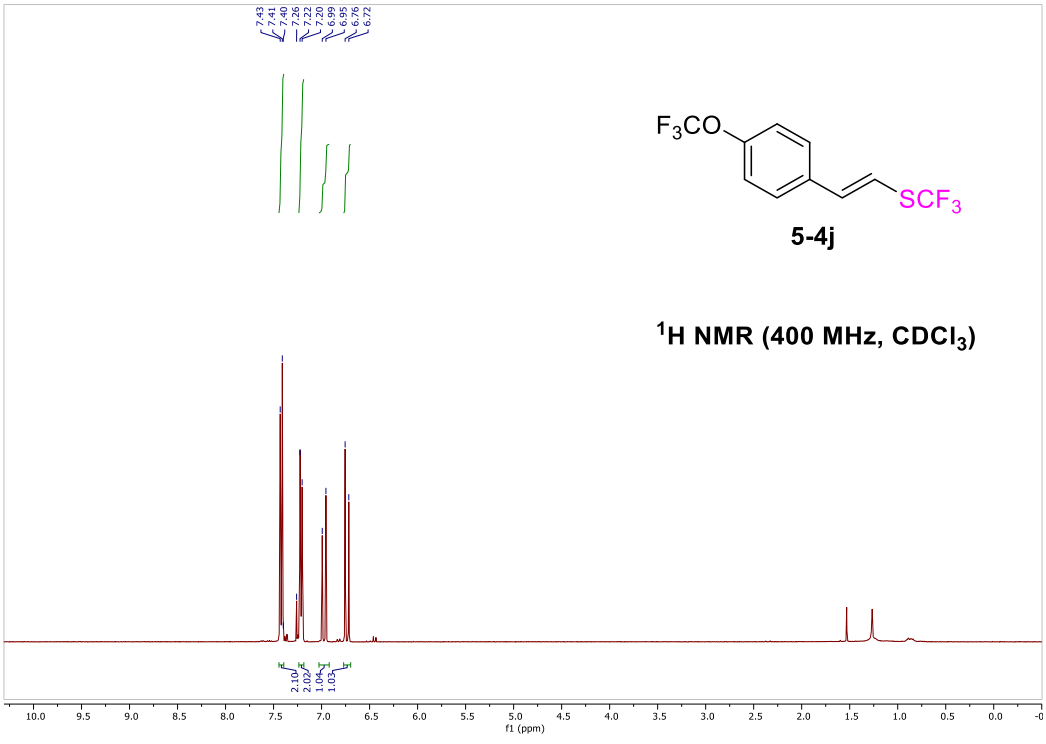

8.03
8.02
8.01
8.01
7.44
7.44
7.43
7.42
7.26
6.99
6.95
6.88
6.84
3.92
SCF3
5-4i
1H NMR (400 MHz, CDCl3)
grease
1.94
2.01
1.01
1.05
3.00
f1 (ppm)


166.5
139.2
138.2
130.9
130.3
130.1
127.9
126.5
115.1
115.1
77.3
77.0
76.7
52.2
SCF3
5-4i
13C NMR (100 MHz, CDCl3)
grease
f1 (ppm)



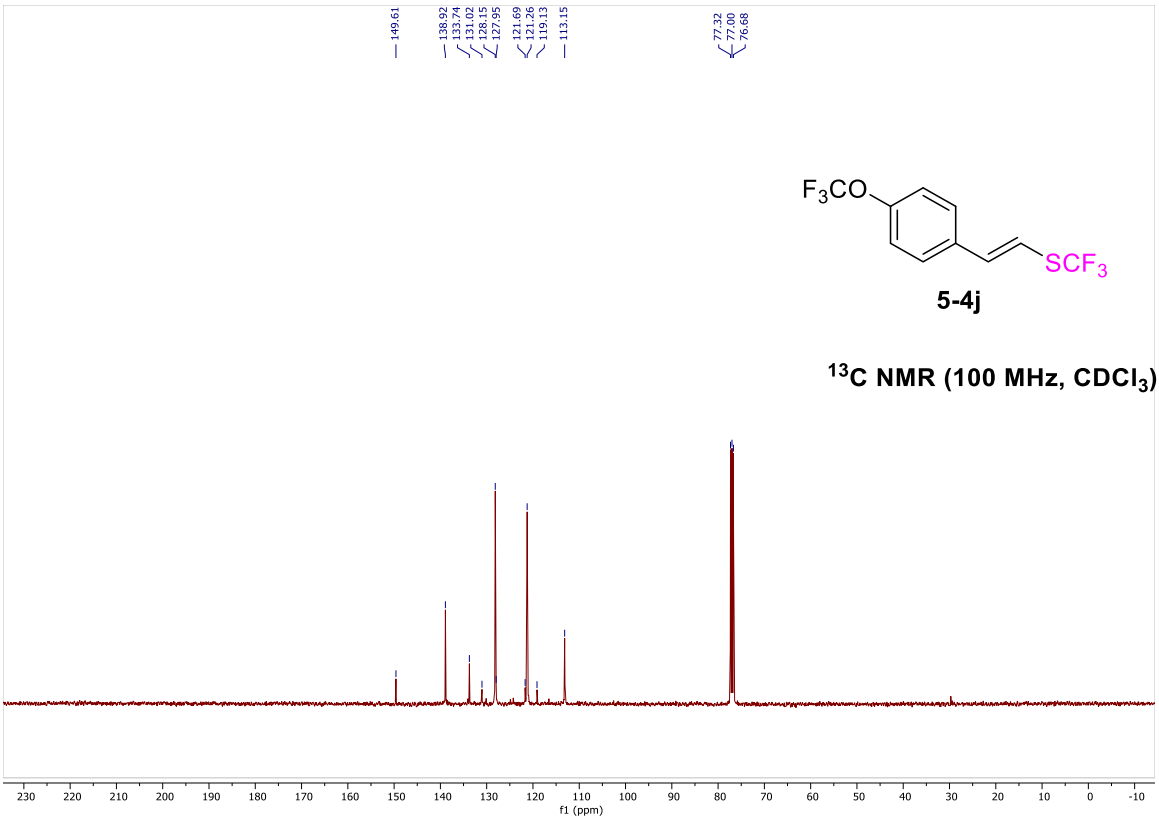
5-4i

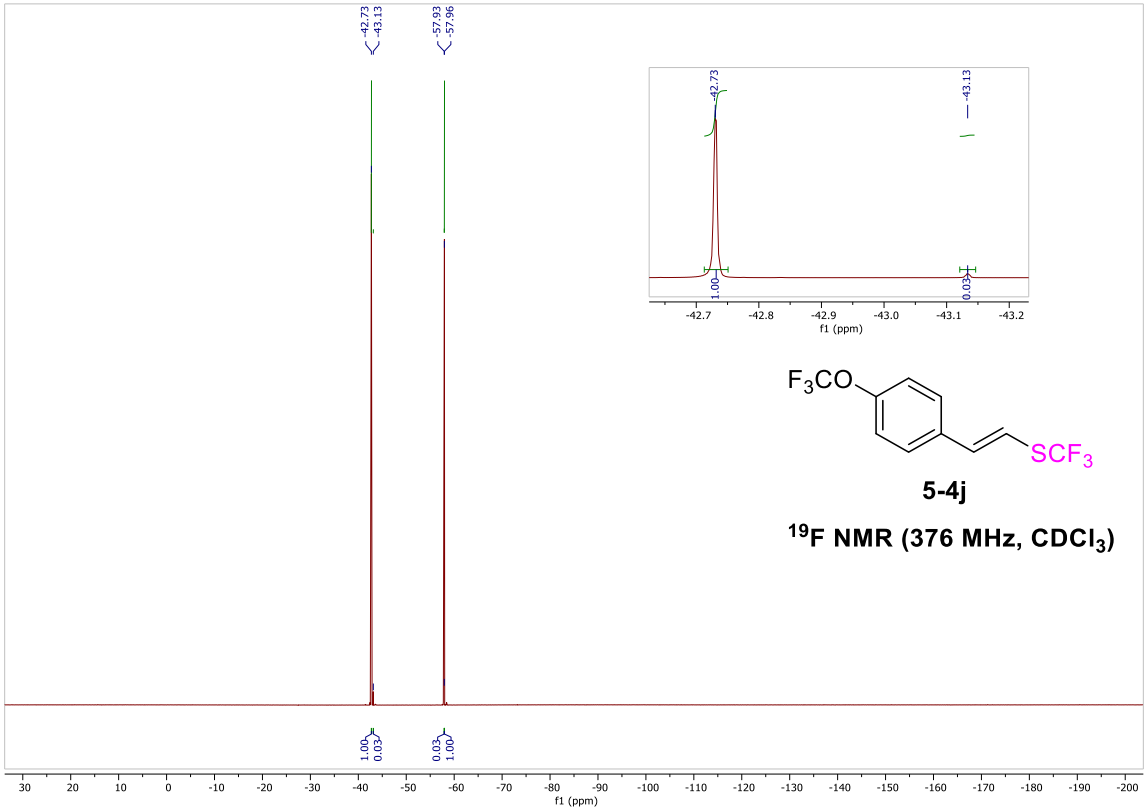
^{19}F NMR (376 MHz, $CDCl_3$)

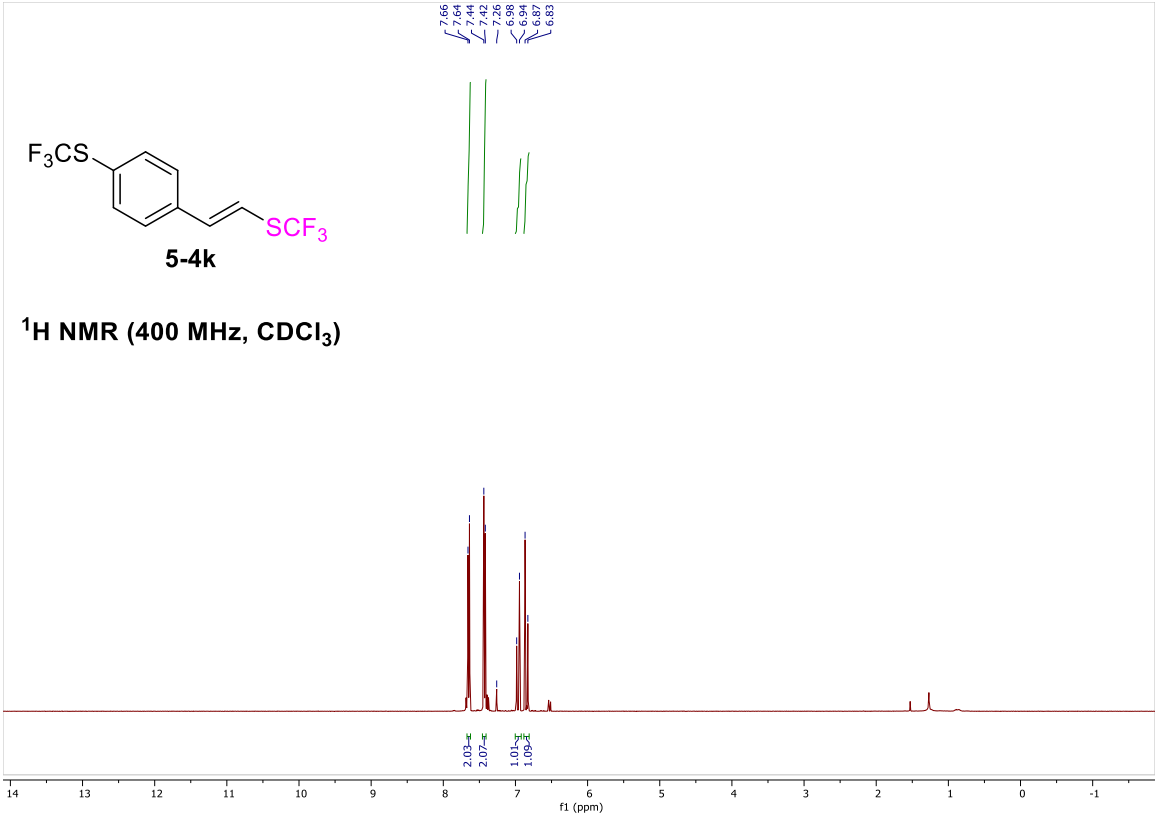


5-4j

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

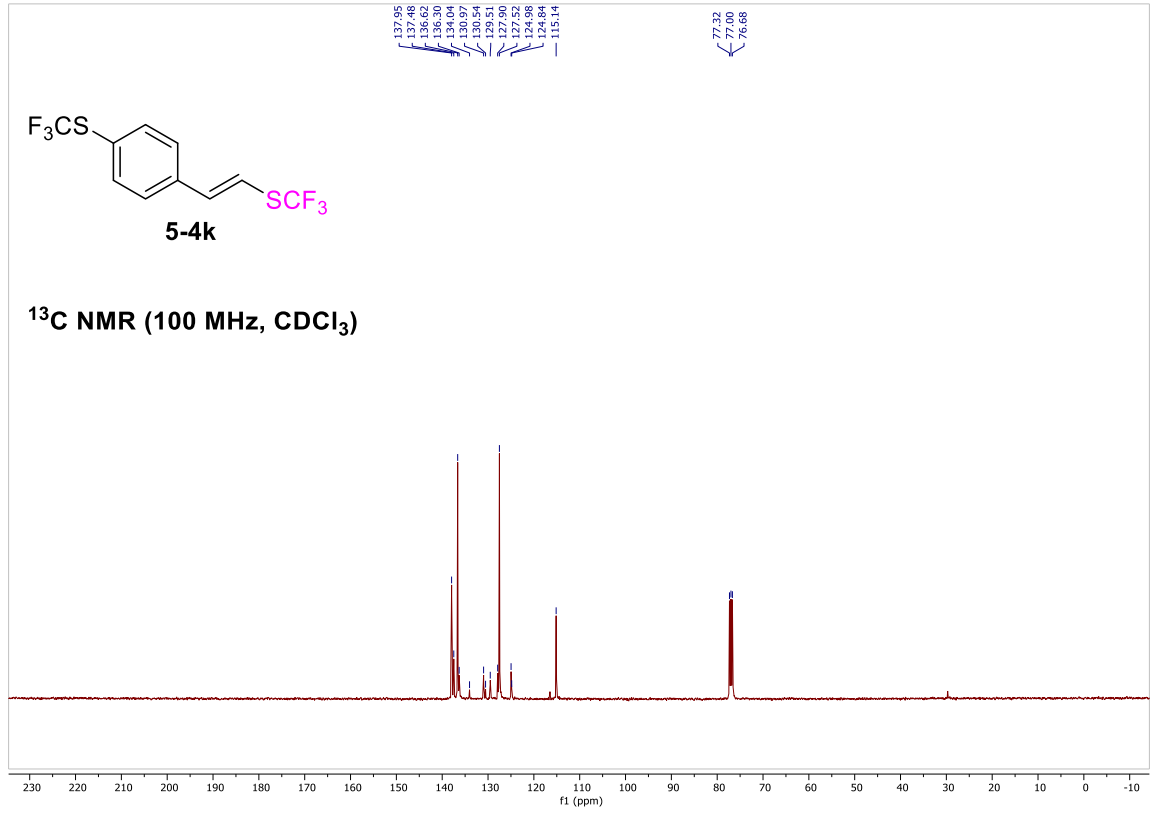

149.61
138.92
133.74
131.02
128.15
127.95
121.69
121.26
119.13
113.15
77.32
77.00
76.68
F3CO
SCF3
5-4j
13C NMR (100 MHz, CDCl3)
f1 (ppm)


-42.73
-43.13
-57.93
-57.96
1.00
0.03
0.03
1.00
f1 (ppm)
F3CO
SCF3
5-4j
19F NMR (376 MHz, CDCl3)



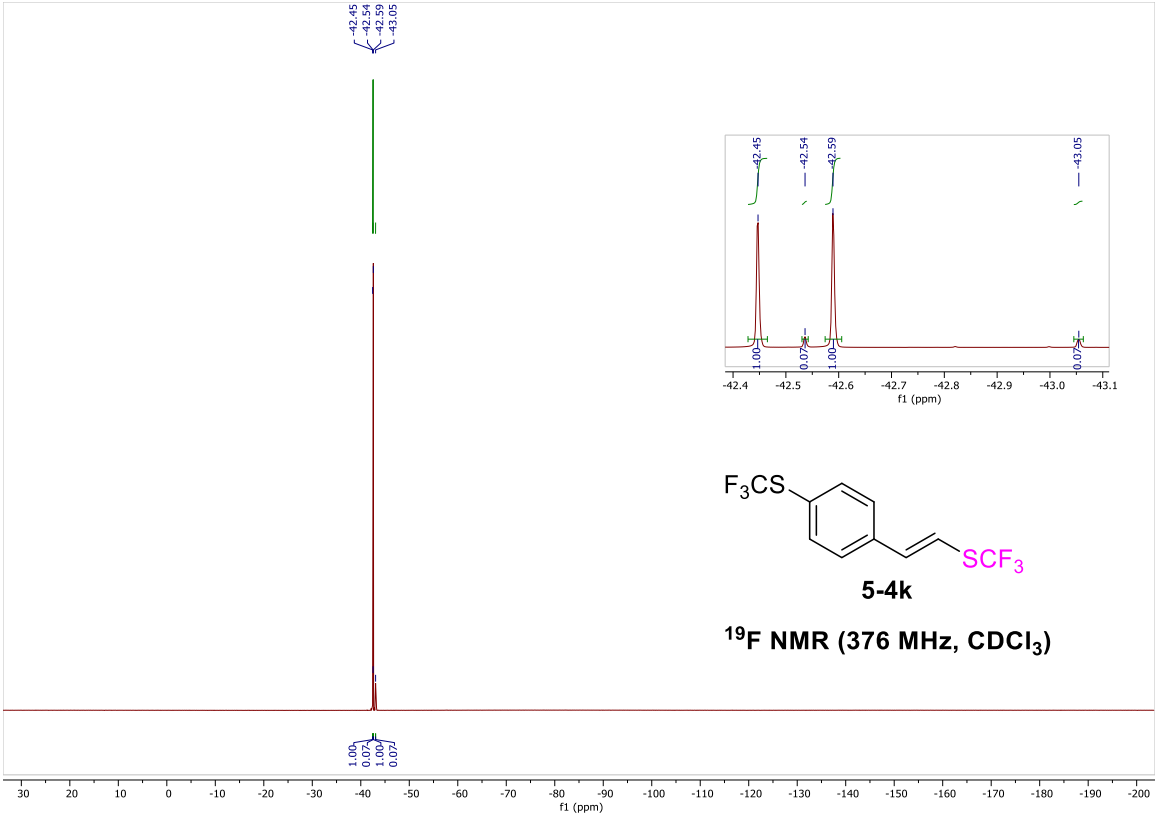
5-4k

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



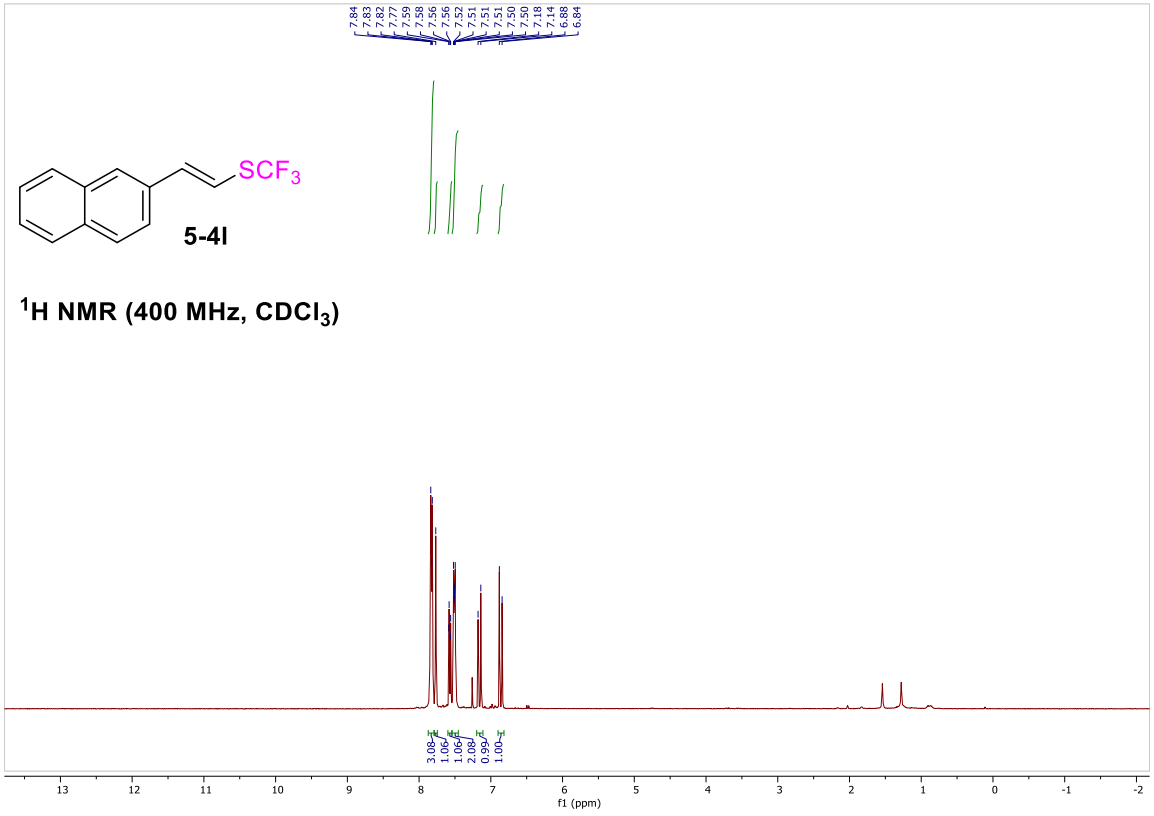
5-4k

^{13}C NMR (100 MHz, $CDCl_3$)



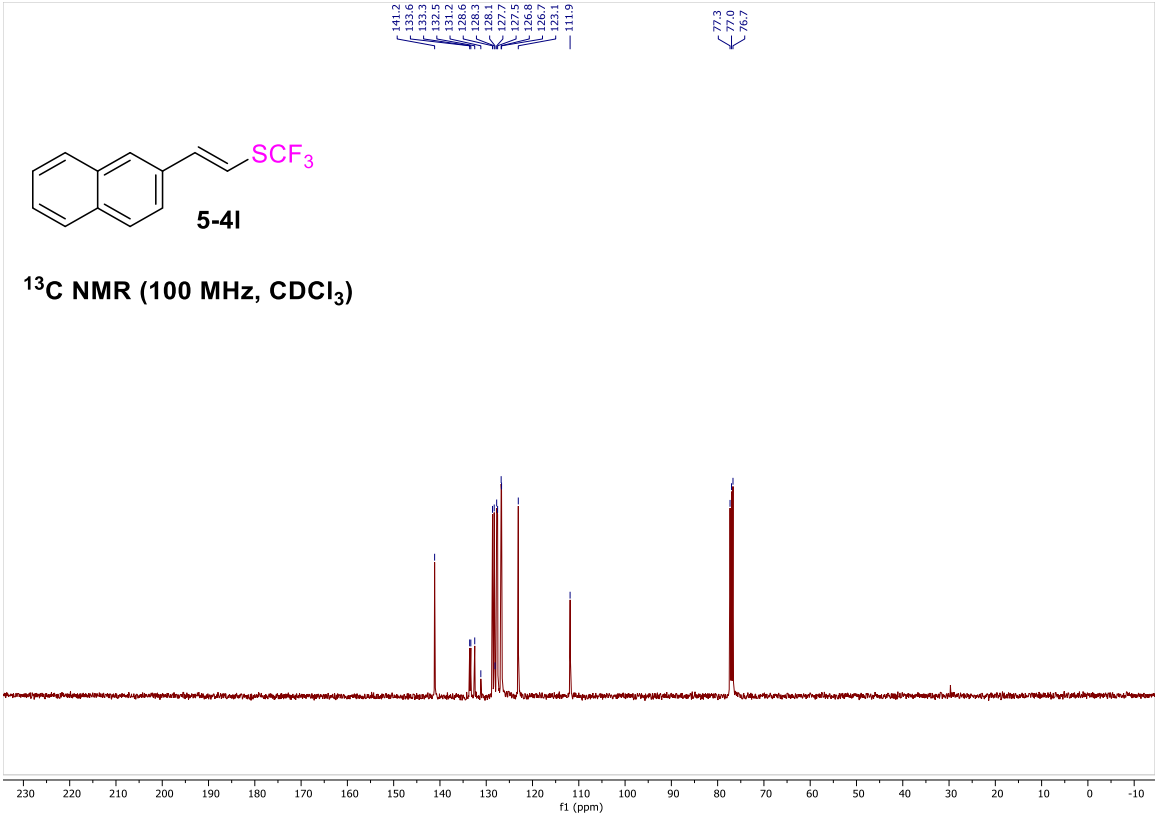
5-4k

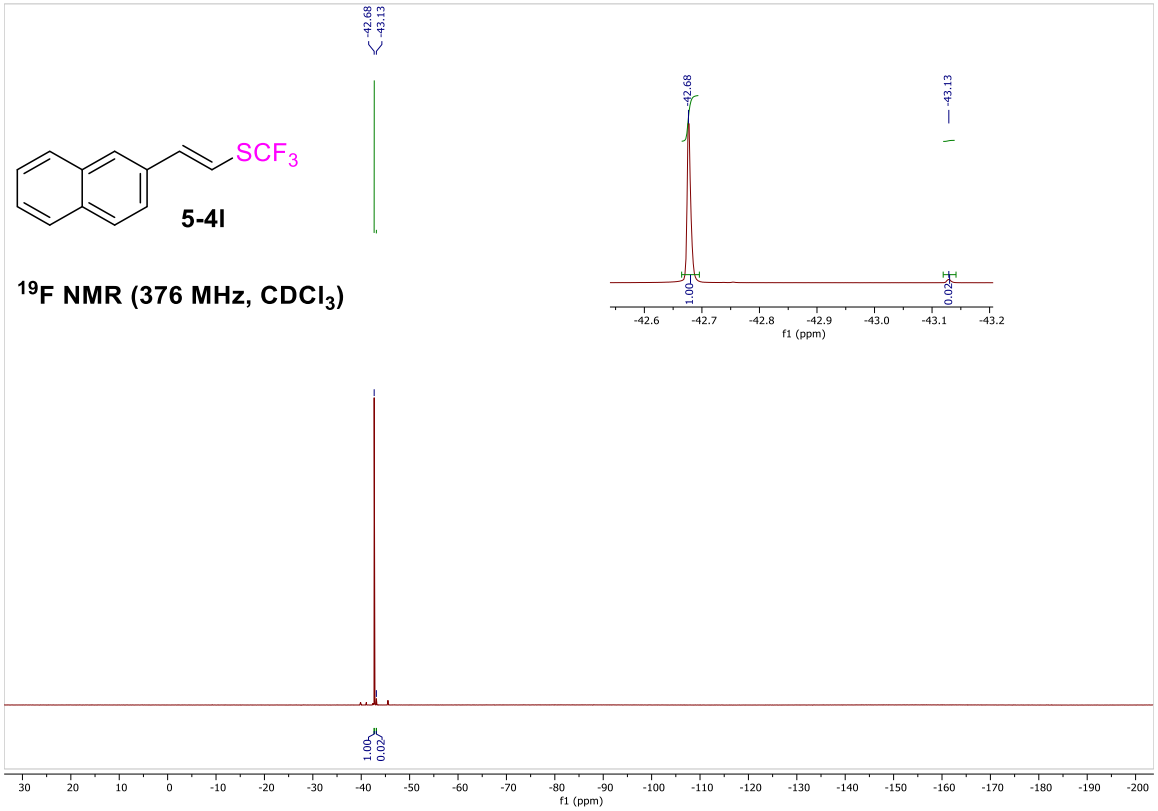
^{19}F NMR (376 MHz, $CDCl_3$)

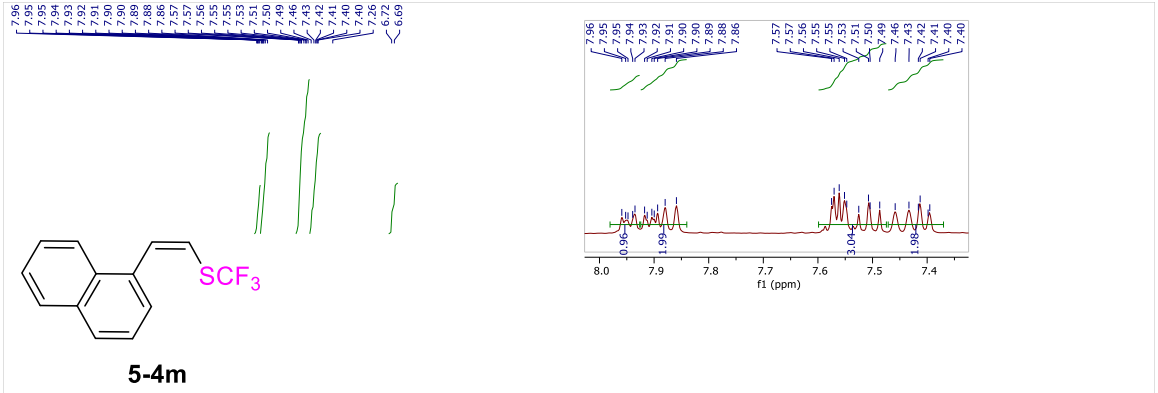


5-4l

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

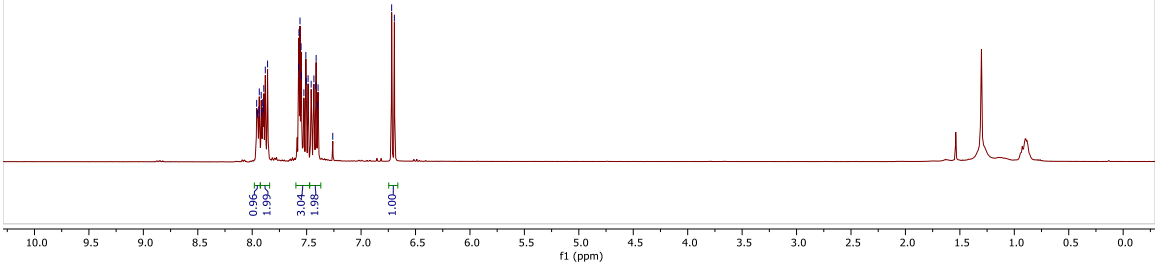

141.2
133.6
133.3
132.5
131.2
128.6
128.3
128.1
127.7
127.5
126.8
126.7
123.1
111.9
77.3
77.0
76.7
SCF3
5-4l
13C NMR (100 MHz, CDCl3)
f1 (ppm)

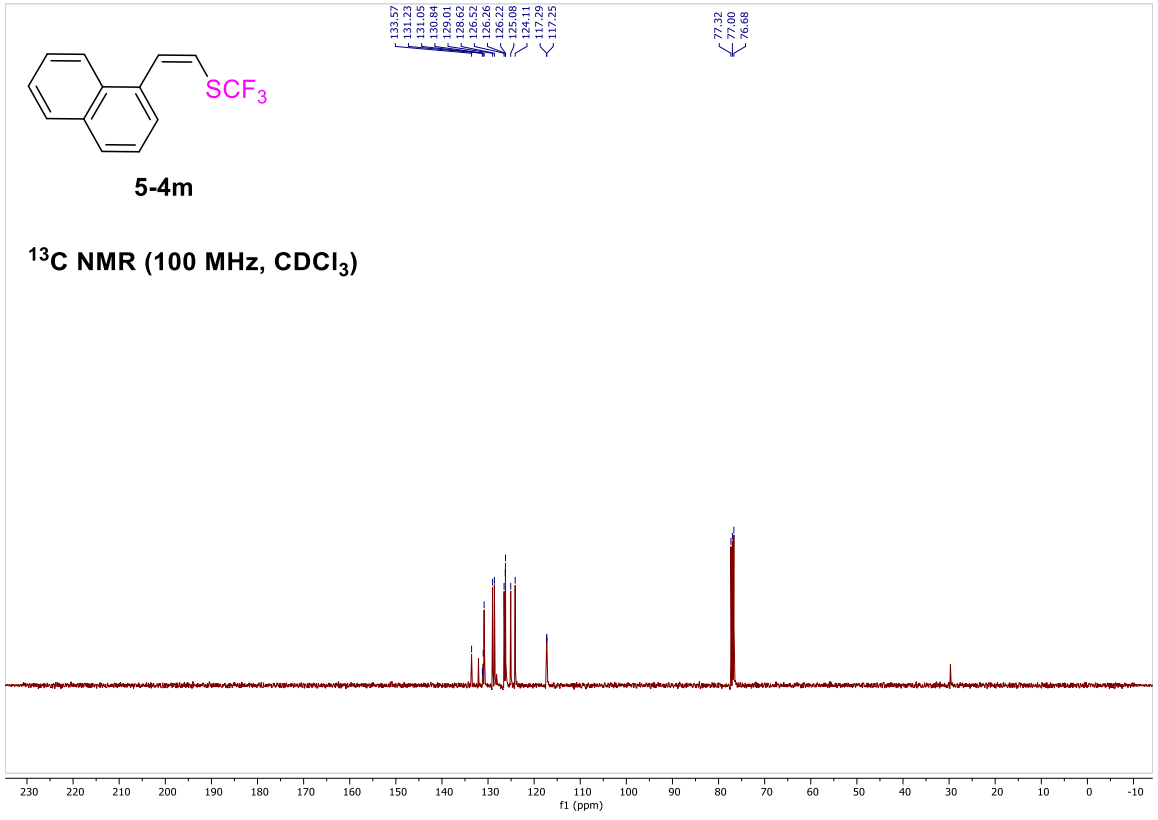

-42.68
-43.13
SCF3
5-4l
19F NMR (376 MHz, CDCl3)
1.00
0.02
f1 (ppm)



5-4m

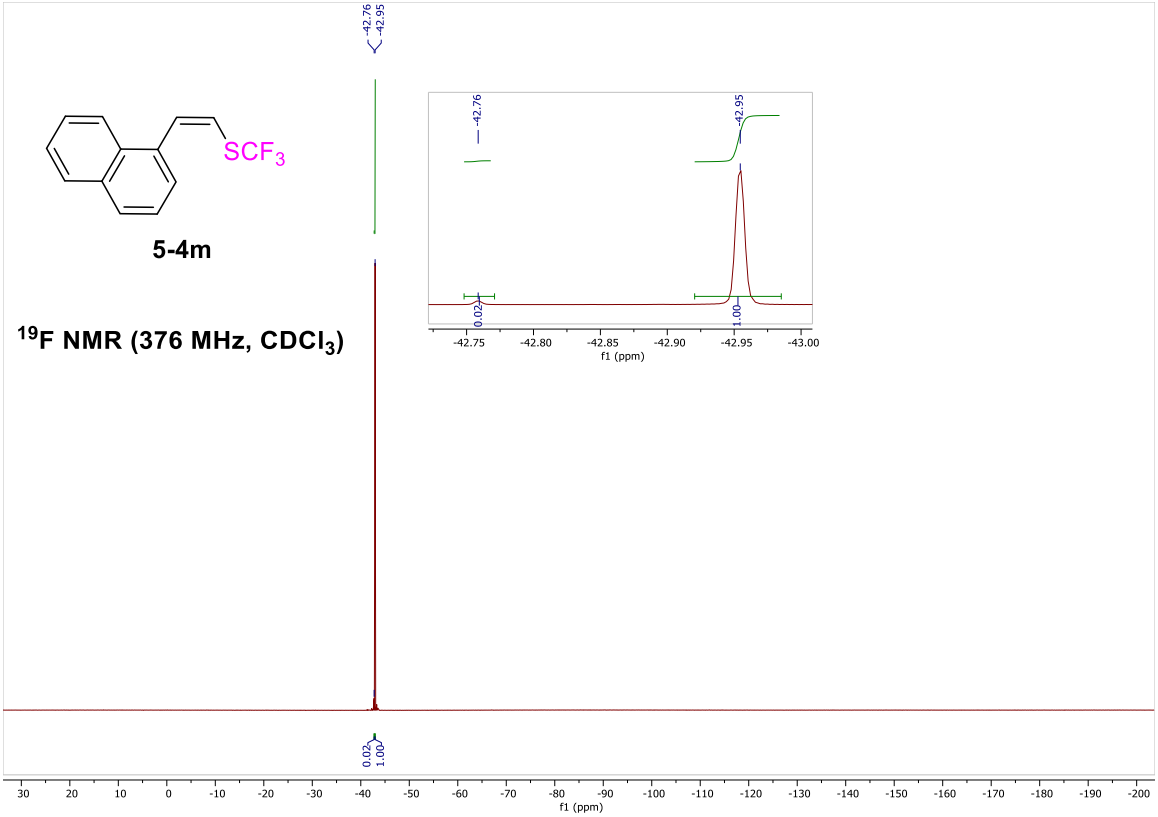
^{1}H NMR (400 MHz, $CDCl_3$)

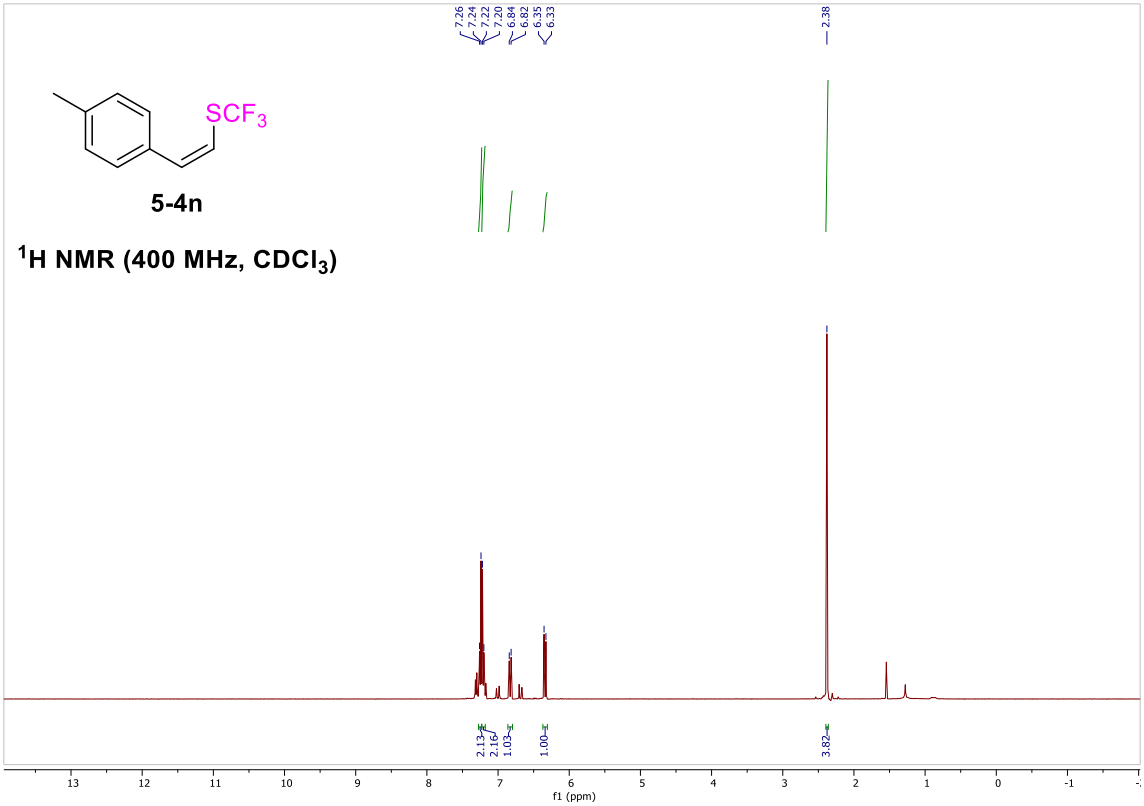


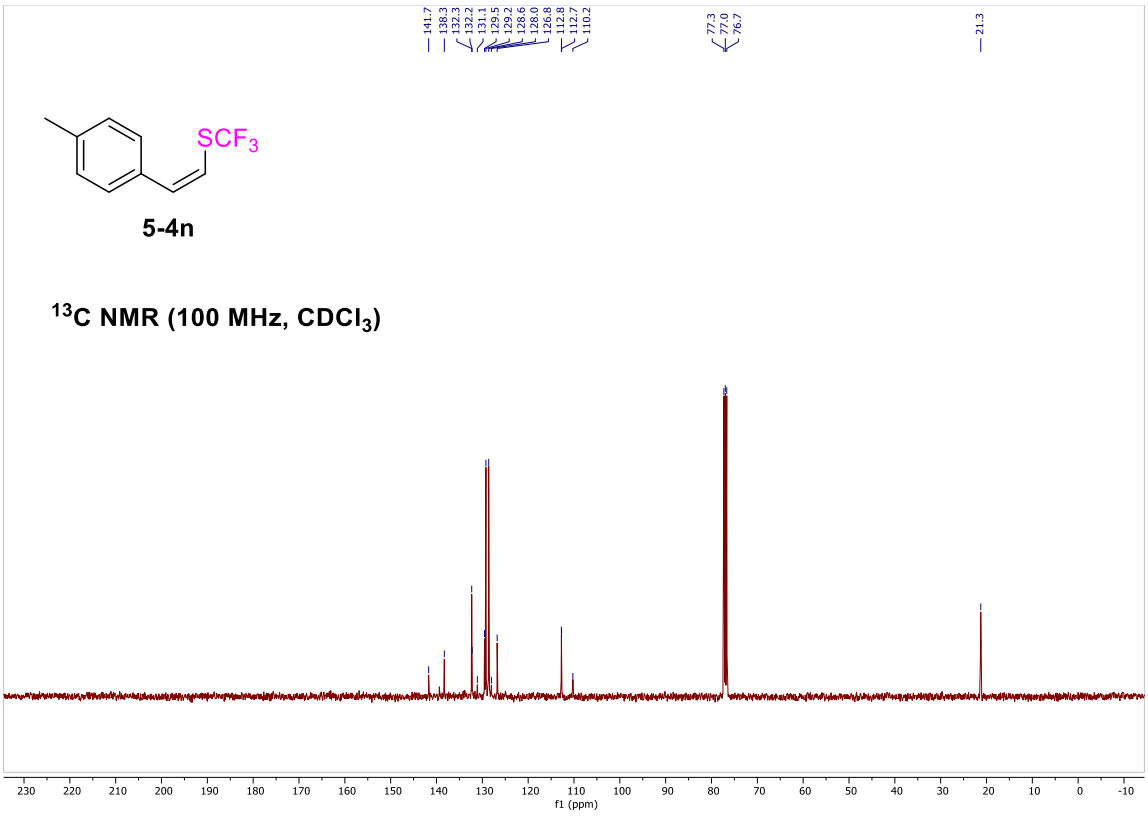


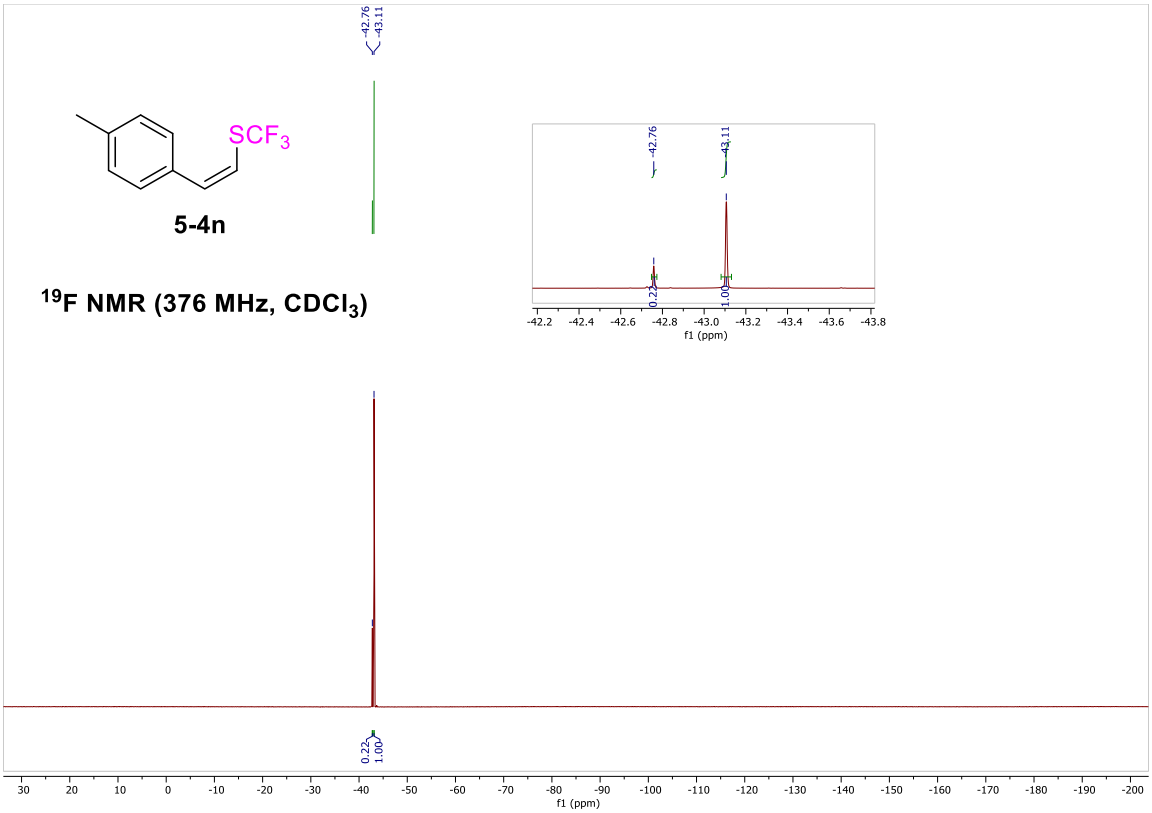
5-4m

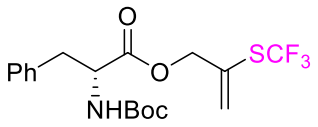
^{13}C NMR (100 MHz, $CDCl_3$)


SCF3
5-4m
19F NMR (376 MHz, CDCl3)
-42.76
-42.95
f1 (ppm)


SCF3
5-4n
1H NMR (400 MHz, CDCl3)
7.26
7.24
7.22
7.20
6.84
6.82
6.35
6.33
2.38
f1 (ppm)

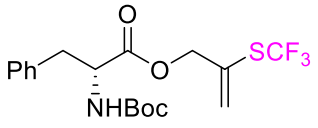

141.7
138.3
132.3
132.2
131.1
129.5
128.2
128.0
126.8
112.8
112.7
110.2
77.3
77.0
76.7
21.3
SCF3
5-4n
13C NMR (100 MHz, CDCl3)
f1 (ppm)


-42.76
-43.11
SCF3
5-4n
19F NMR (376 MHz, CDCl3)
0.22
1.00
f1 (ppm)



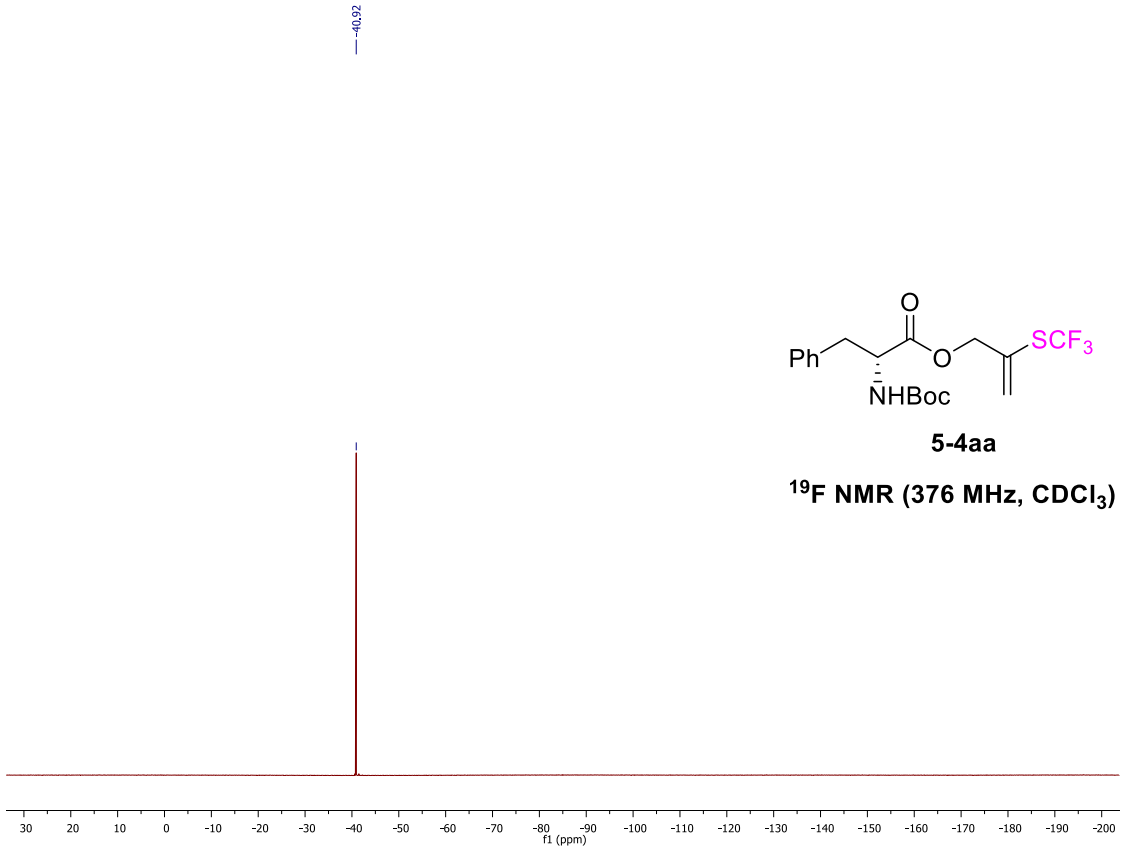
5-4aa

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



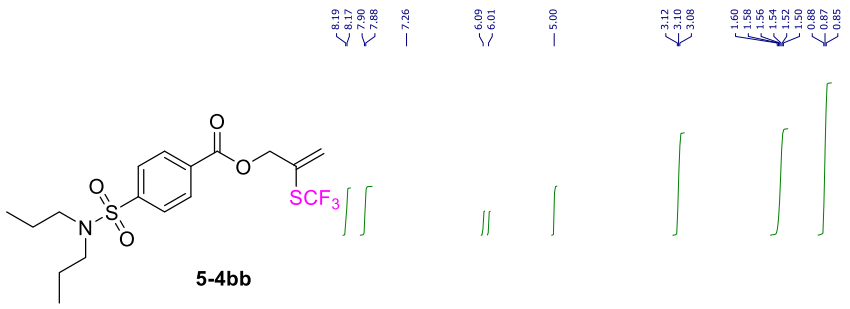
5-4aa

^{13}C NMR (100 MHz, $CDCl_3$)



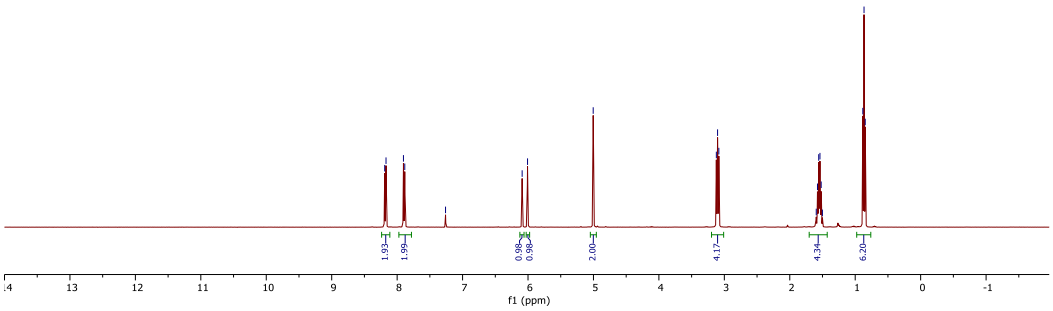
5-4aa

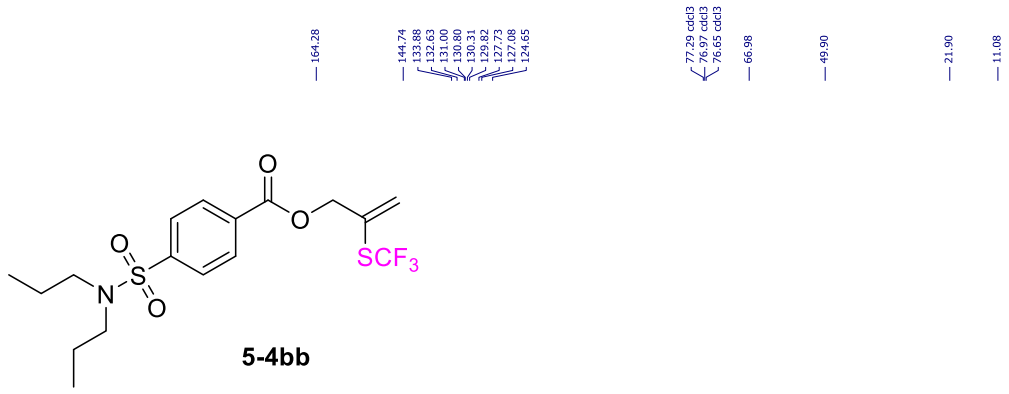
^{19}F NMR (376 MHz, $CDCl_3$)



5-4bb

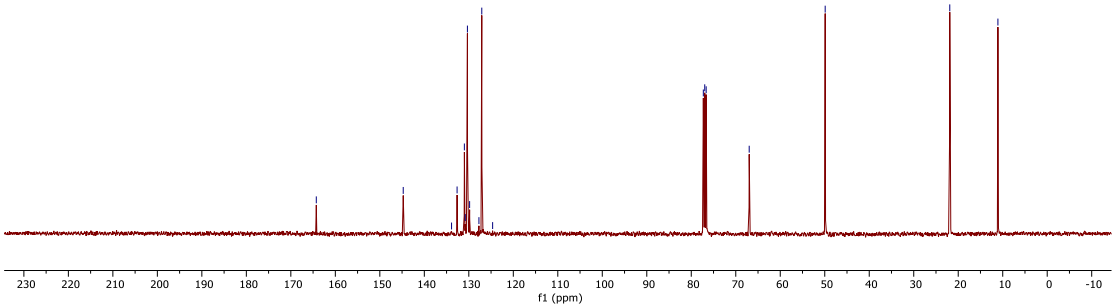
^{1}H NMR (400 MHz, $CDCl_3$)

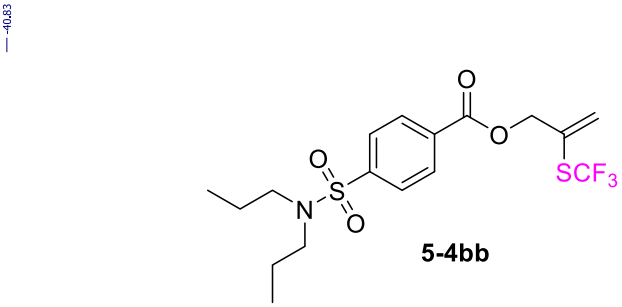




5-4bb

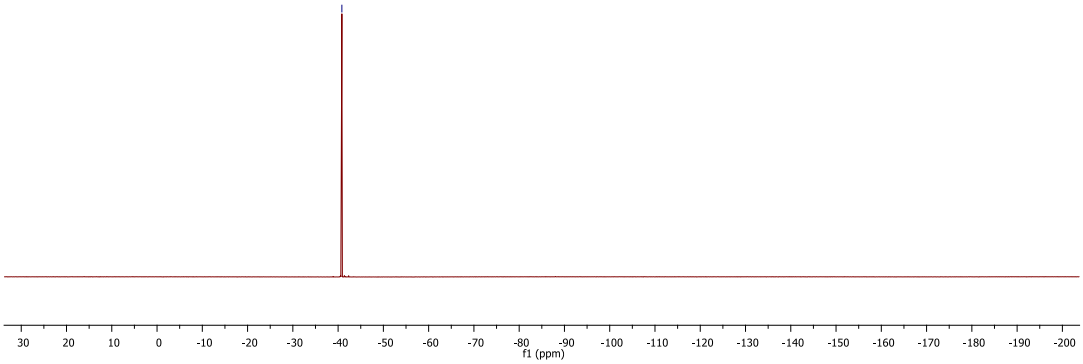
^{13}C NMR (100 MHz, $CDCl_3$)

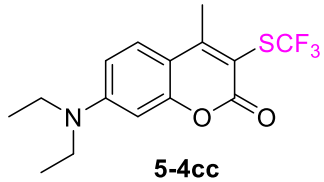




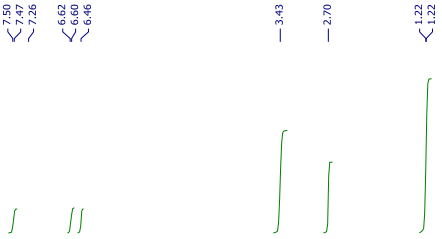
5-4bb

^{19}F NMR (376 MHz, $CDCl_3$)

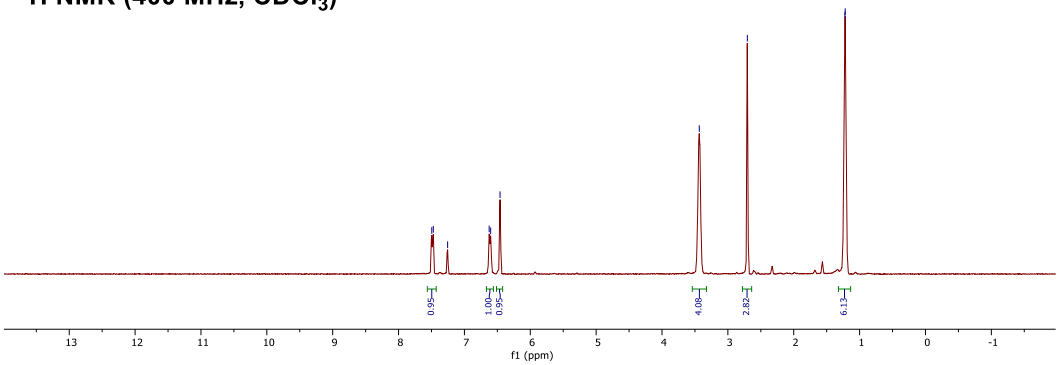


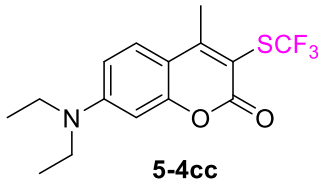


5-4cc



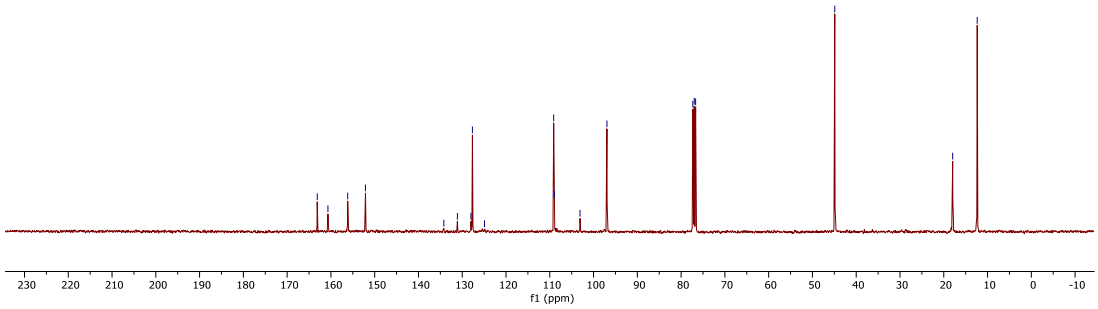
^{1}H NMR (400 MHz, $CDCl_3$)

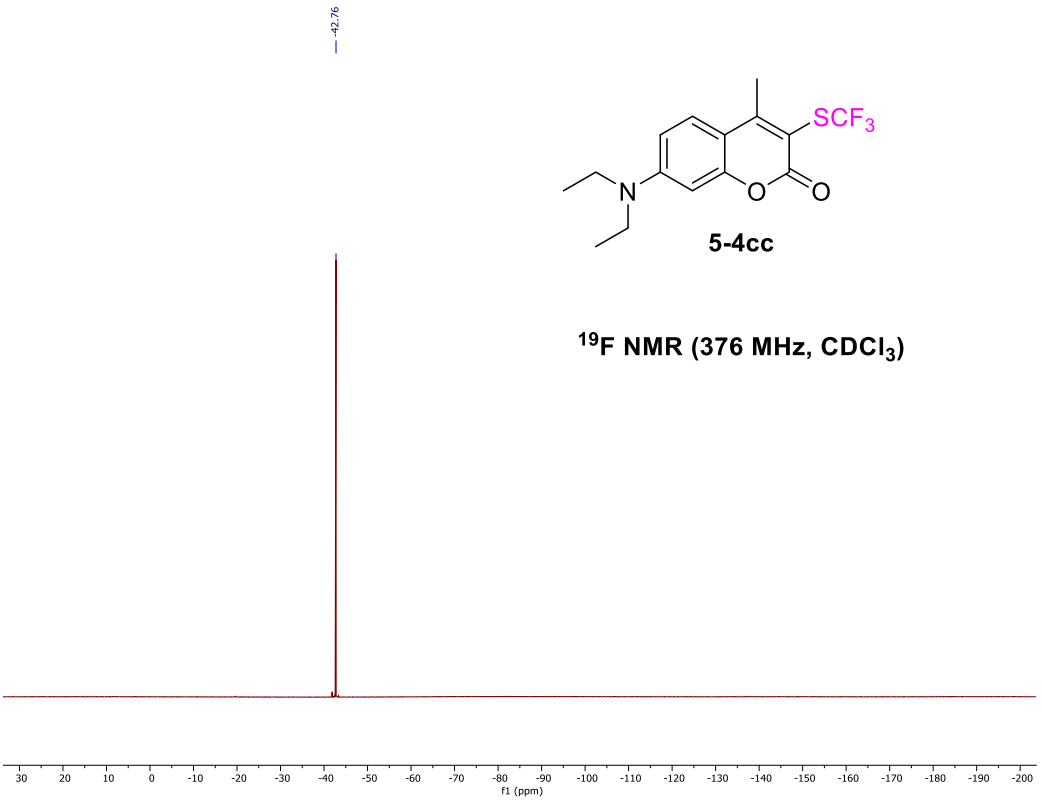




5-4cc

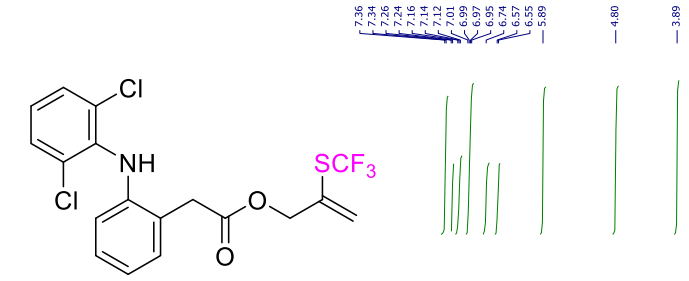
^{13}C NMR (100 MHz, $CDCl_3$)





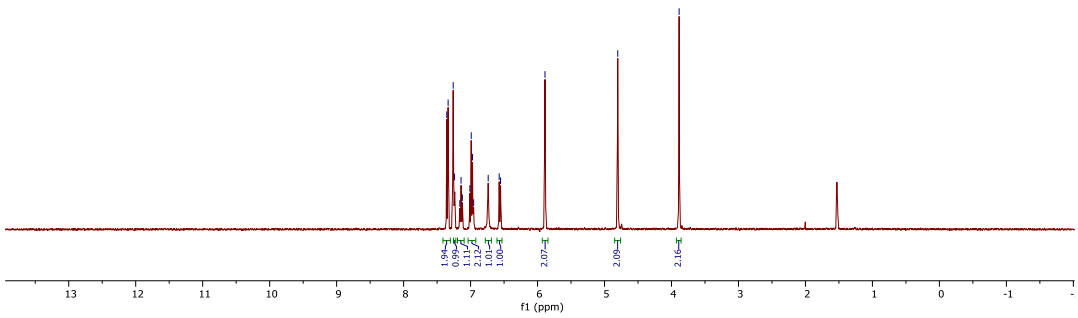
5-4cc

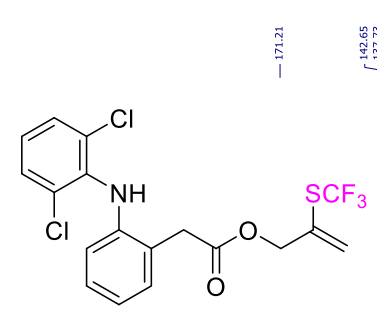
^{19}F NMR (376 MHz, $CDCl_3$)



5-4dd

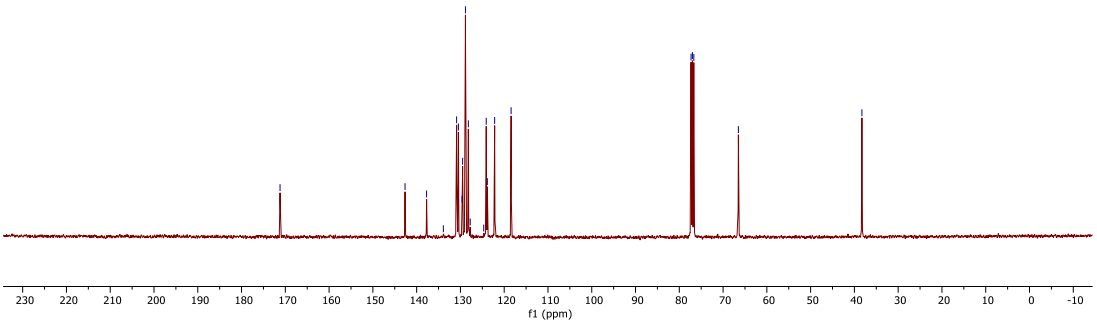
^{1}H NMR (400 MHz, $CDCl_3$)

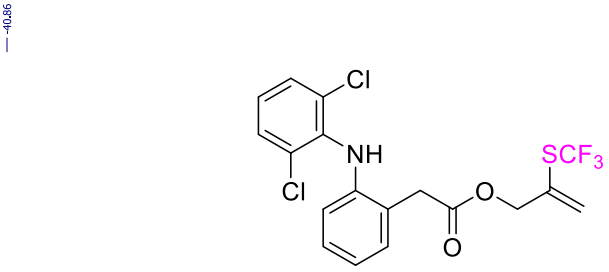




5-4dd

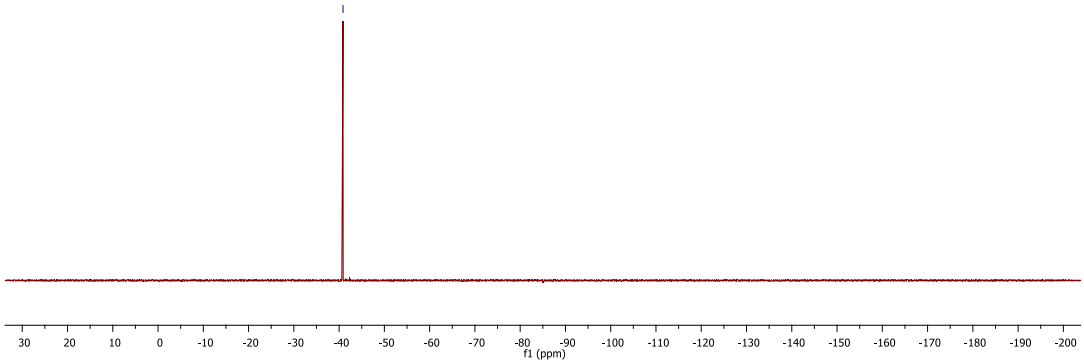
^{13}C NMR (100 MHz, $CDCl_3$)

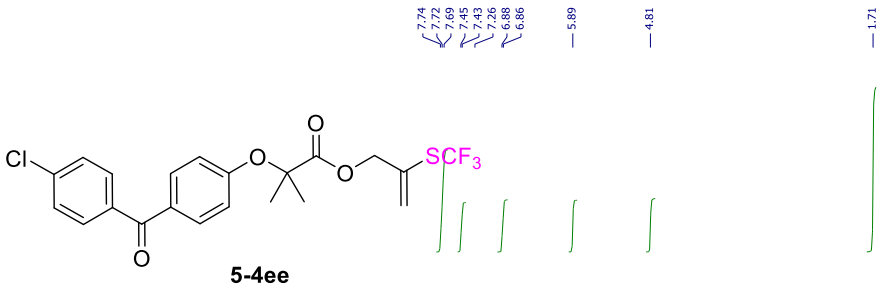




5-4dd

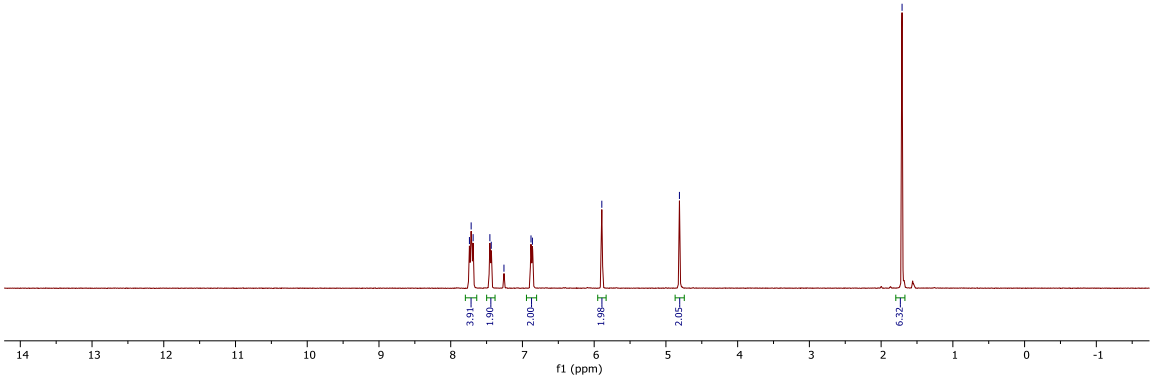
^{19}F NMR (376 MHz, $CDCl_3$)

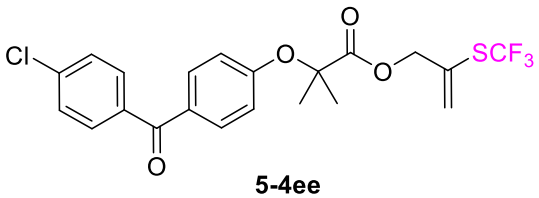




5-4ee

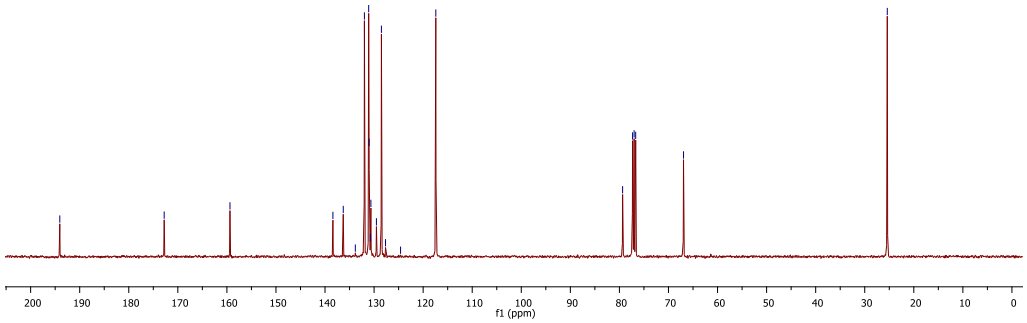
^{1}H NMR (400 MHz, $CDCl_3$)

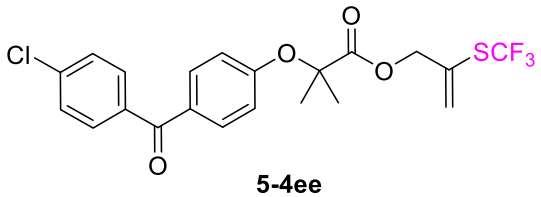




5-4ee

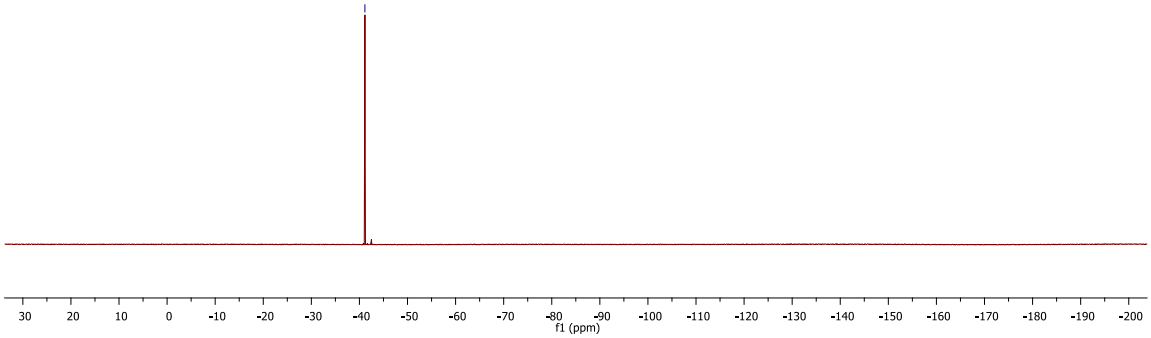
^{13}C NMR (100 MHz, $CDCl_3$)



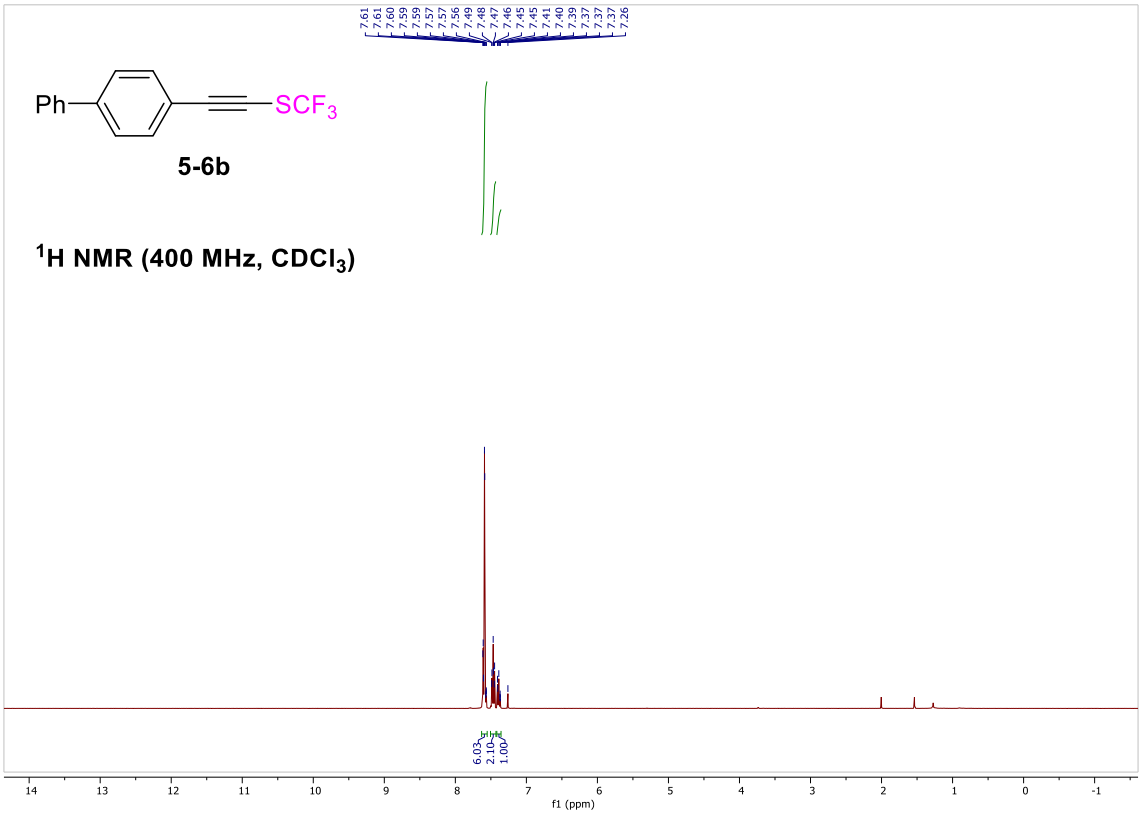


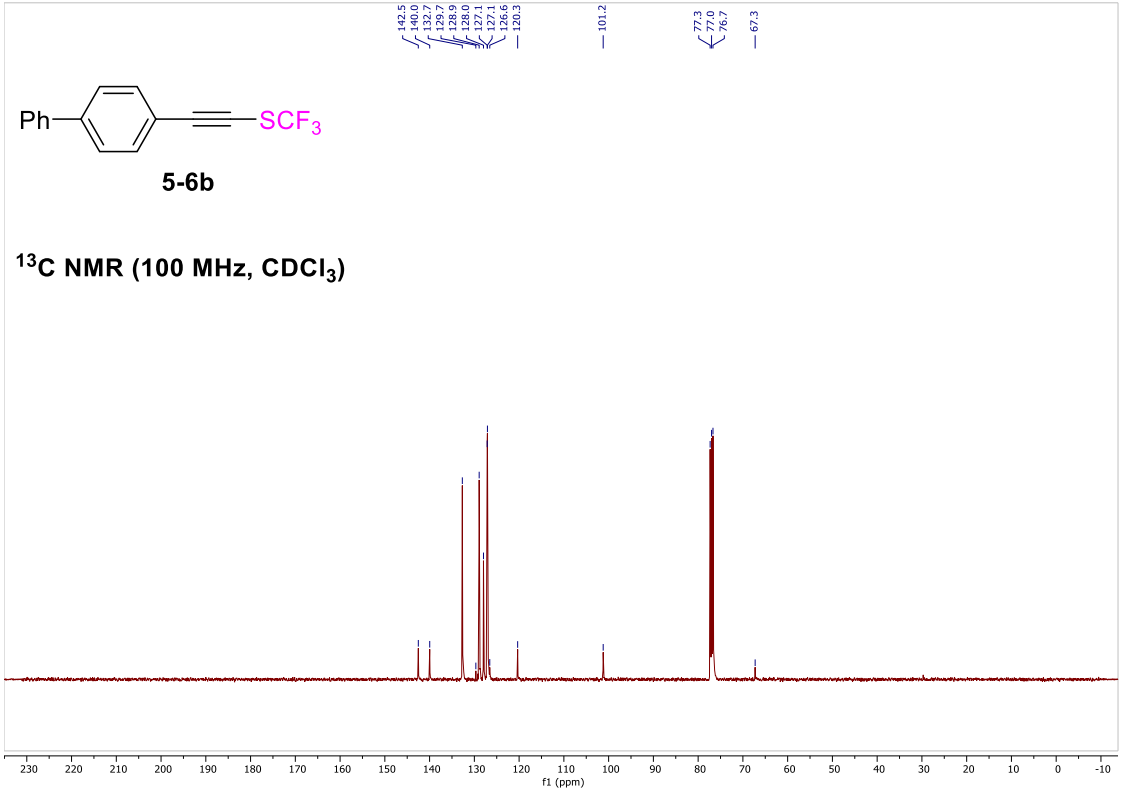
5-4ee

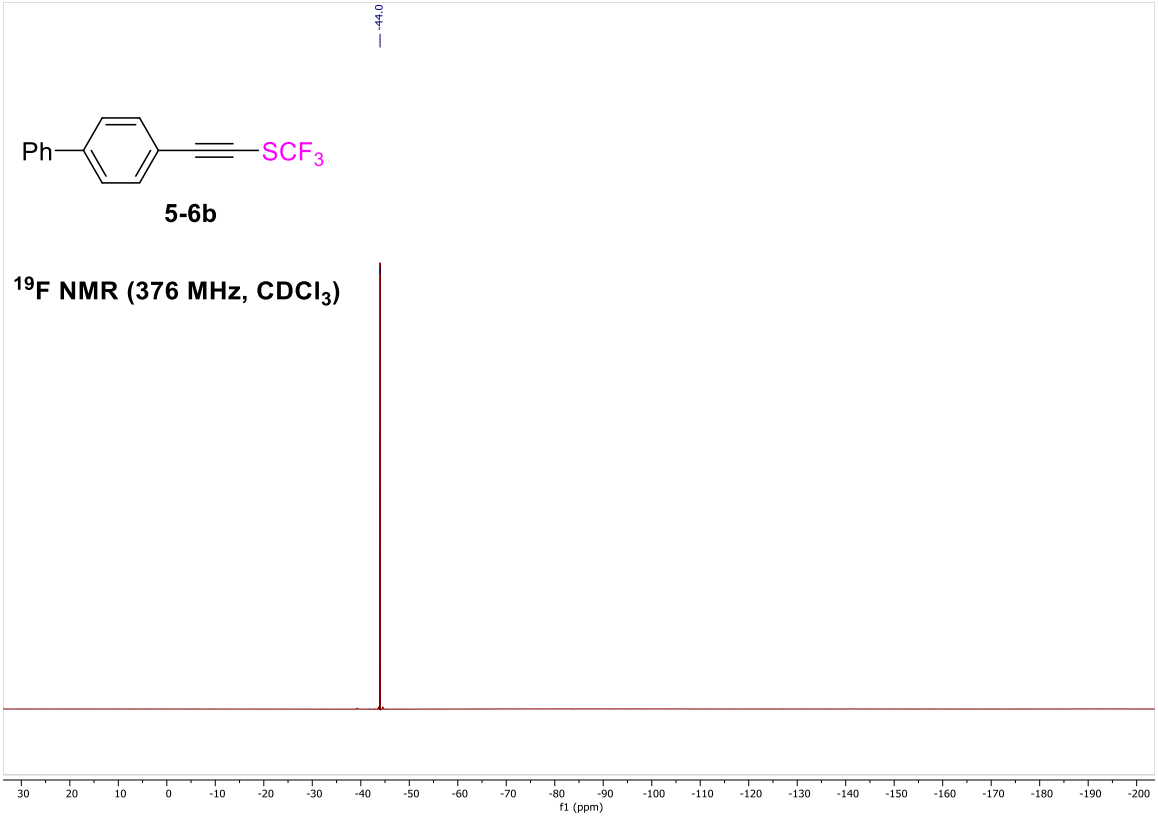
^{19}F NMR (376 MHz, $CDCl_3$)

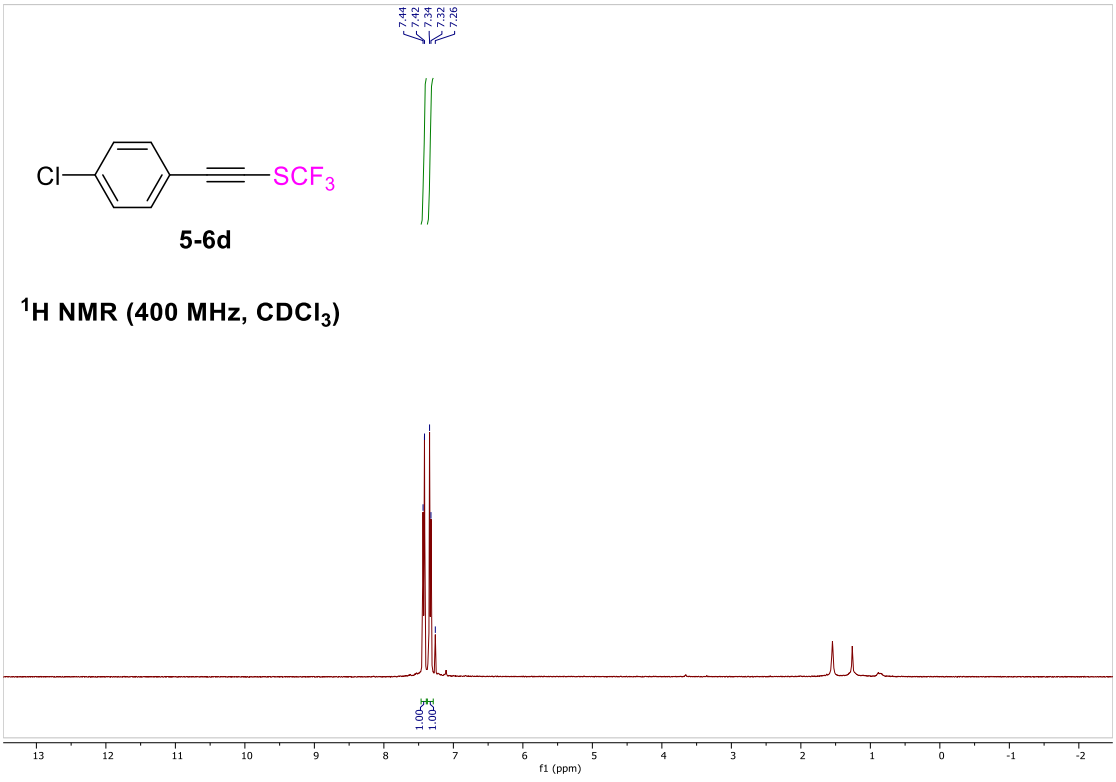


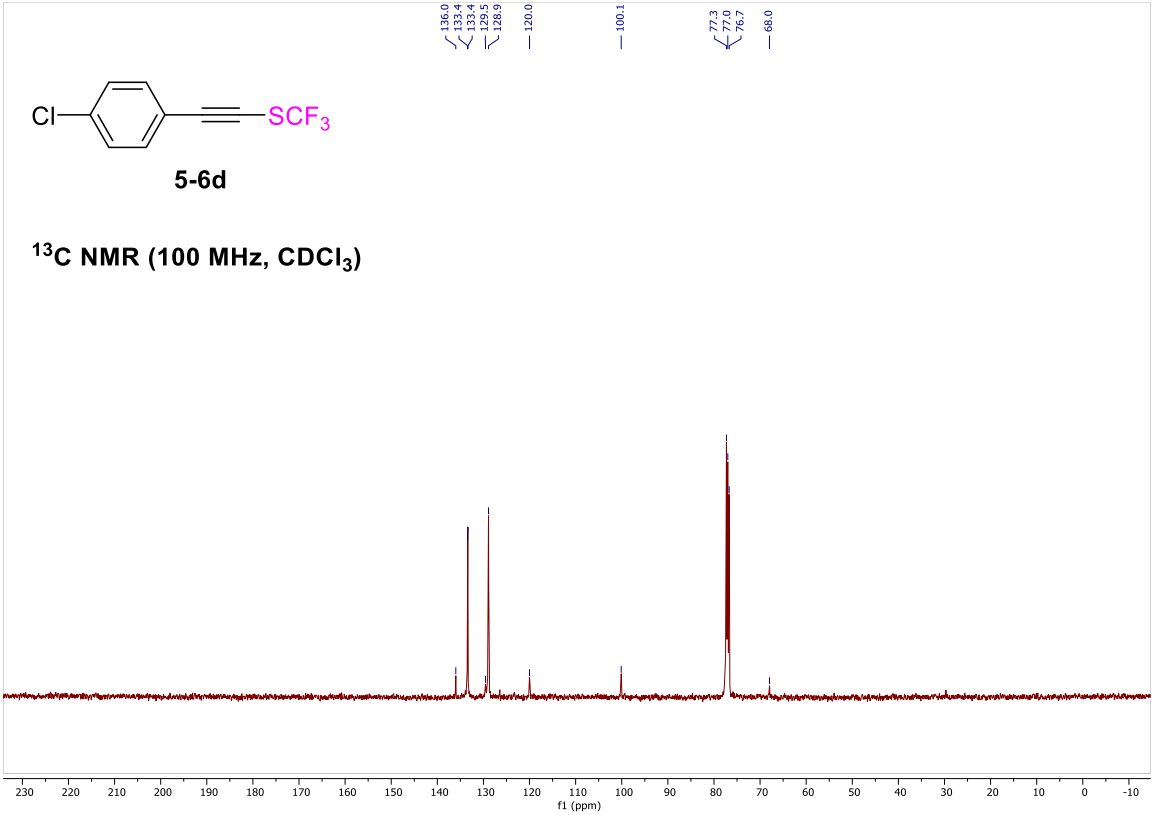
5.4.7.6. Trifluoromethylthiolation products from alkynyl bromide substrates





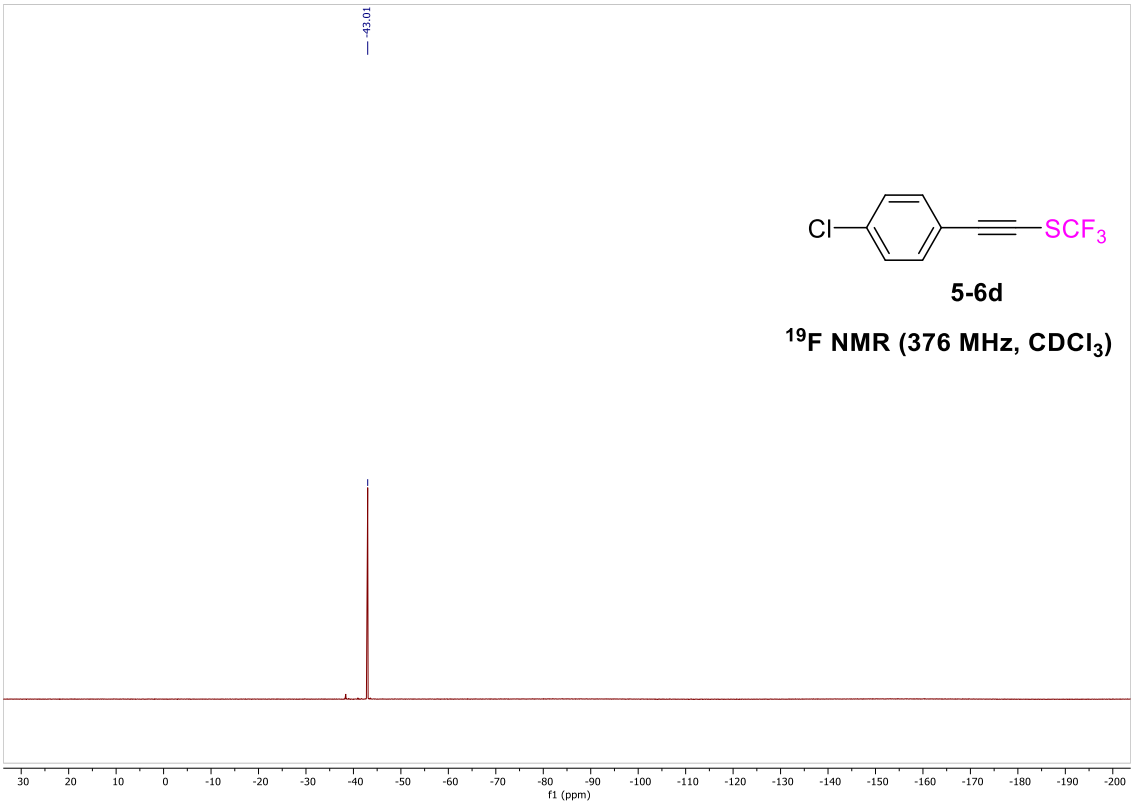

-44.0
Ph
SCF3
5-6b
19F NMR (376 MHz, CDCl3)
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)


7.44
7.42
7.34
7.32
7.26
Cl
SCF3
5-6d
1H NMR (400 MHz, CDCl3)
1.00
1.00
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
f1 (ppm)



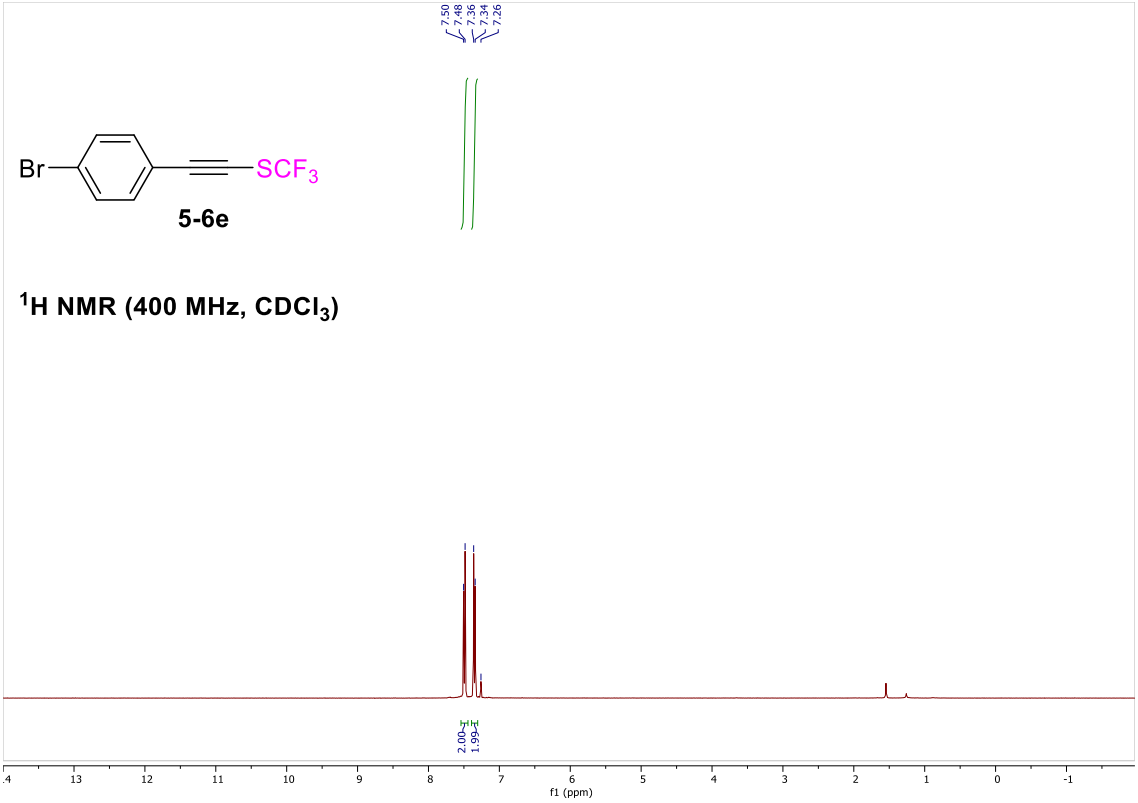
5-6d

^{13}C NMR (100 MHz, $CDCl_3$)

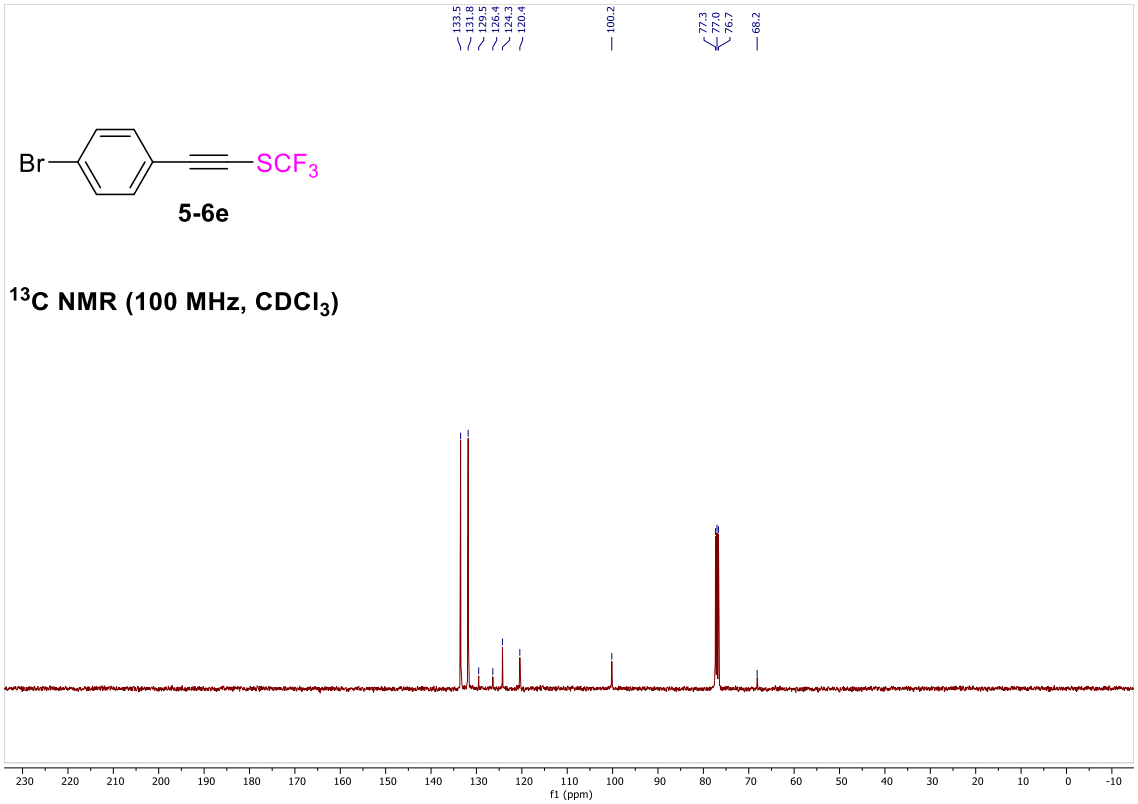


5-6d

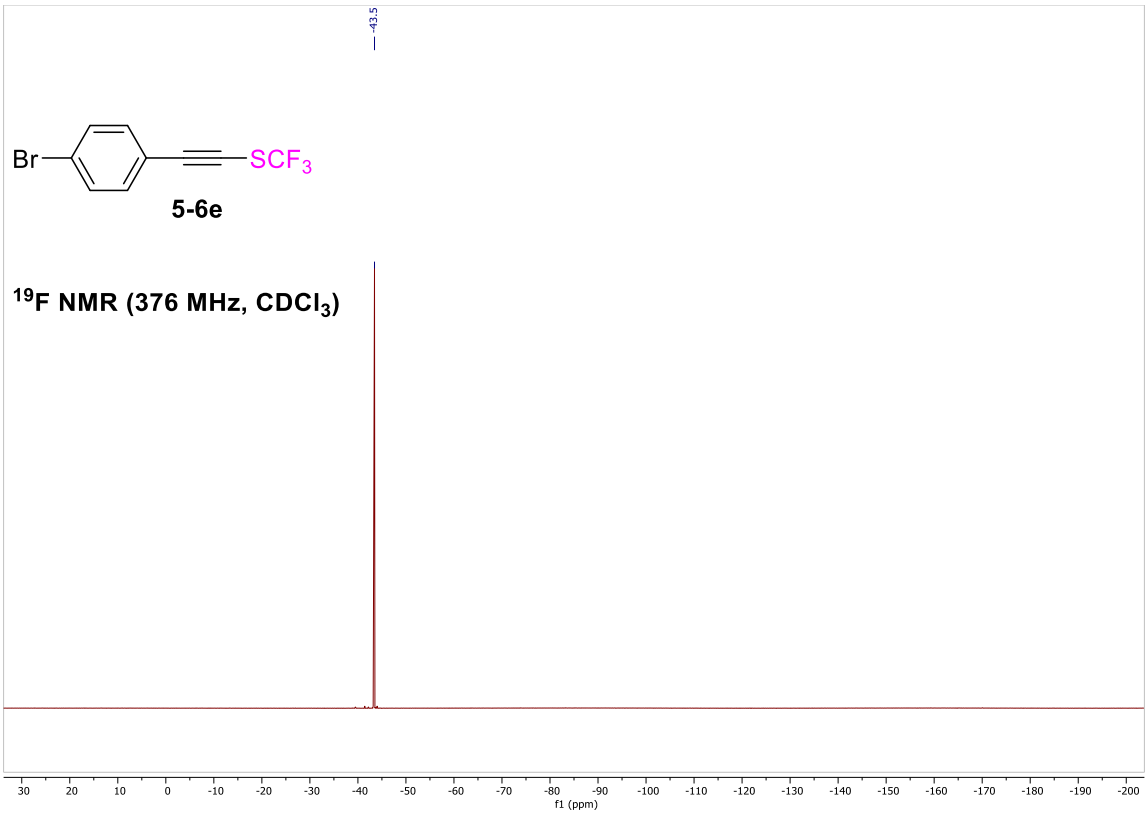
^{19}F NMR (376 MHz, $CDCl_3$)

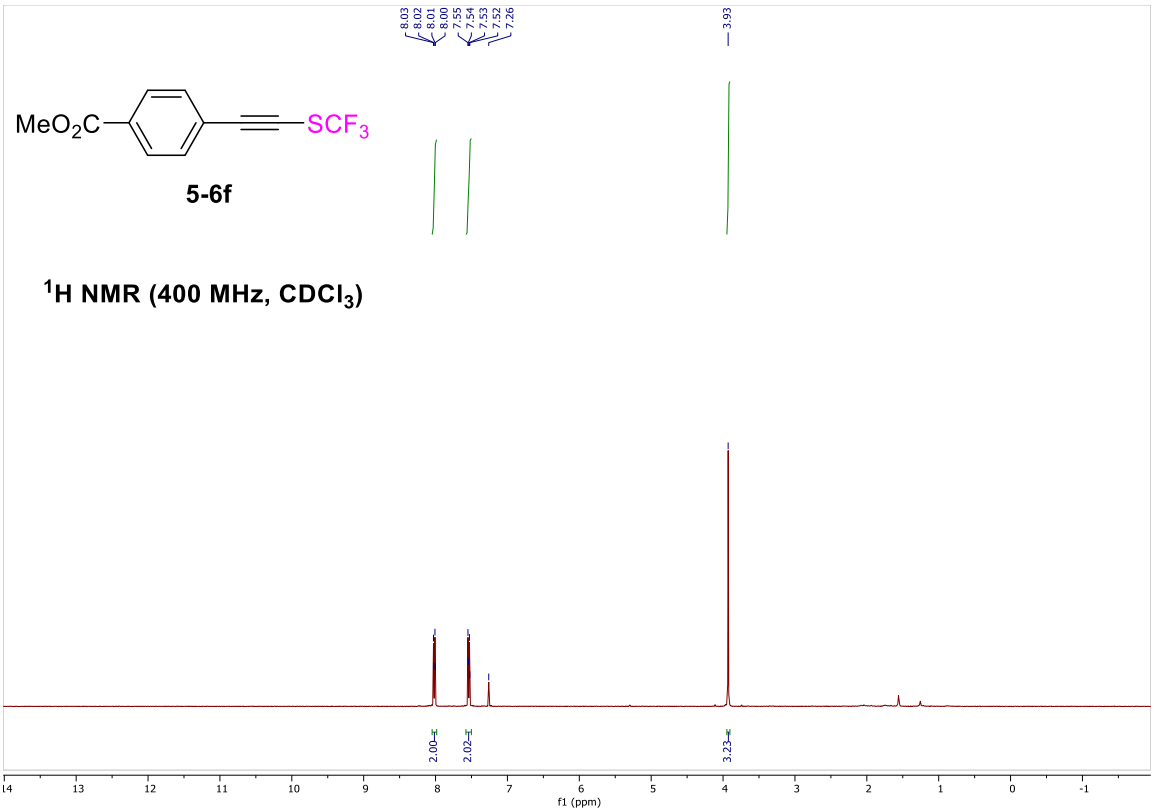


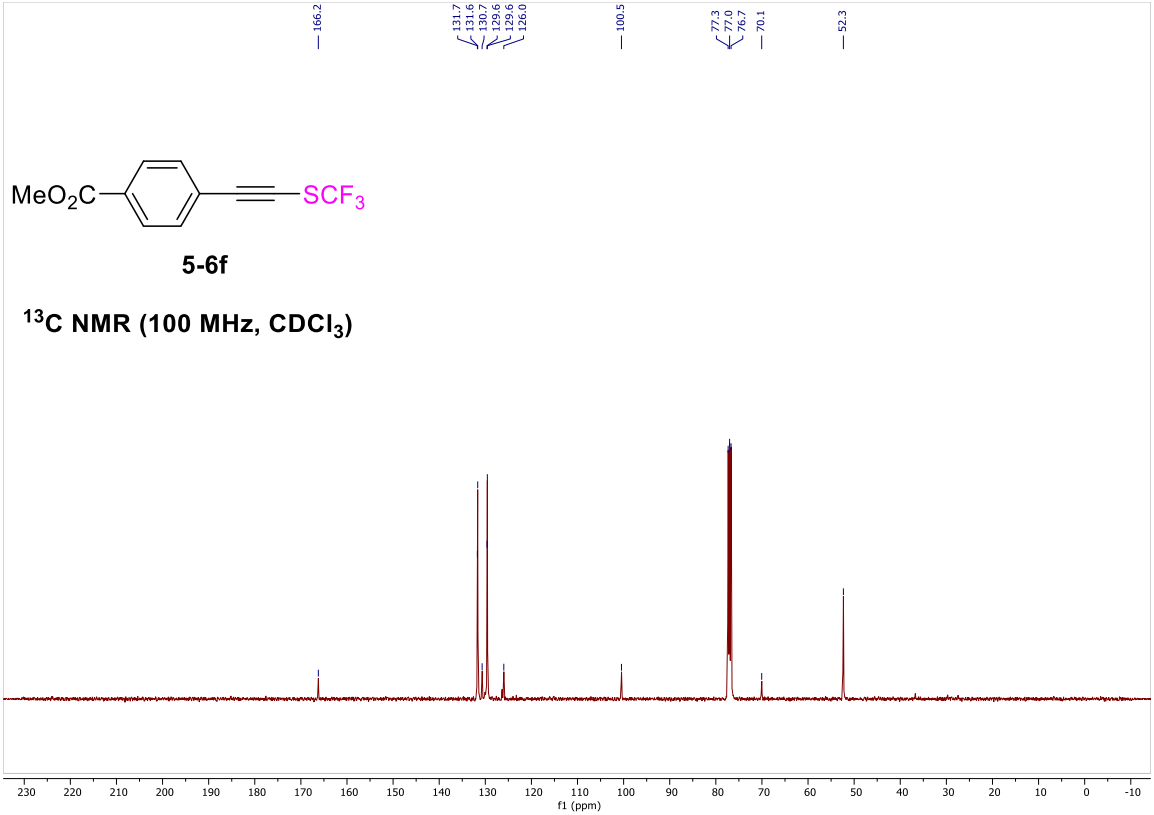
^{1}H NMR (400 MHz, $CDCl_3$)

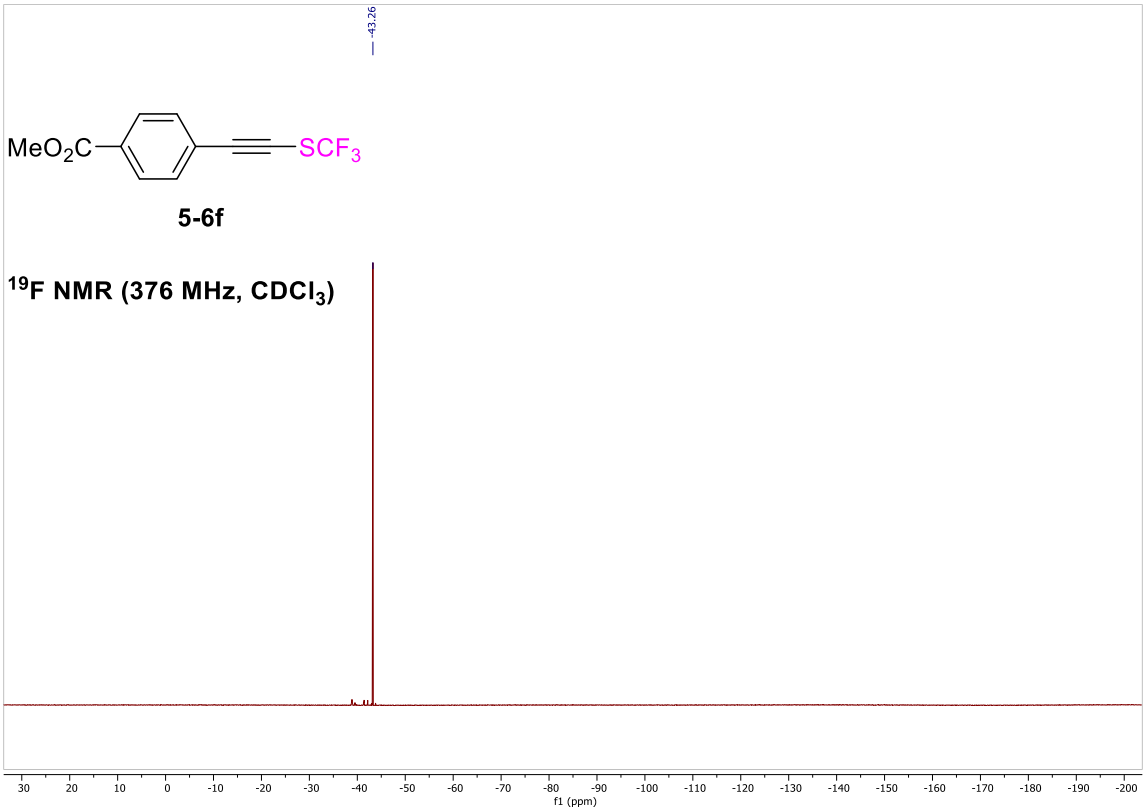


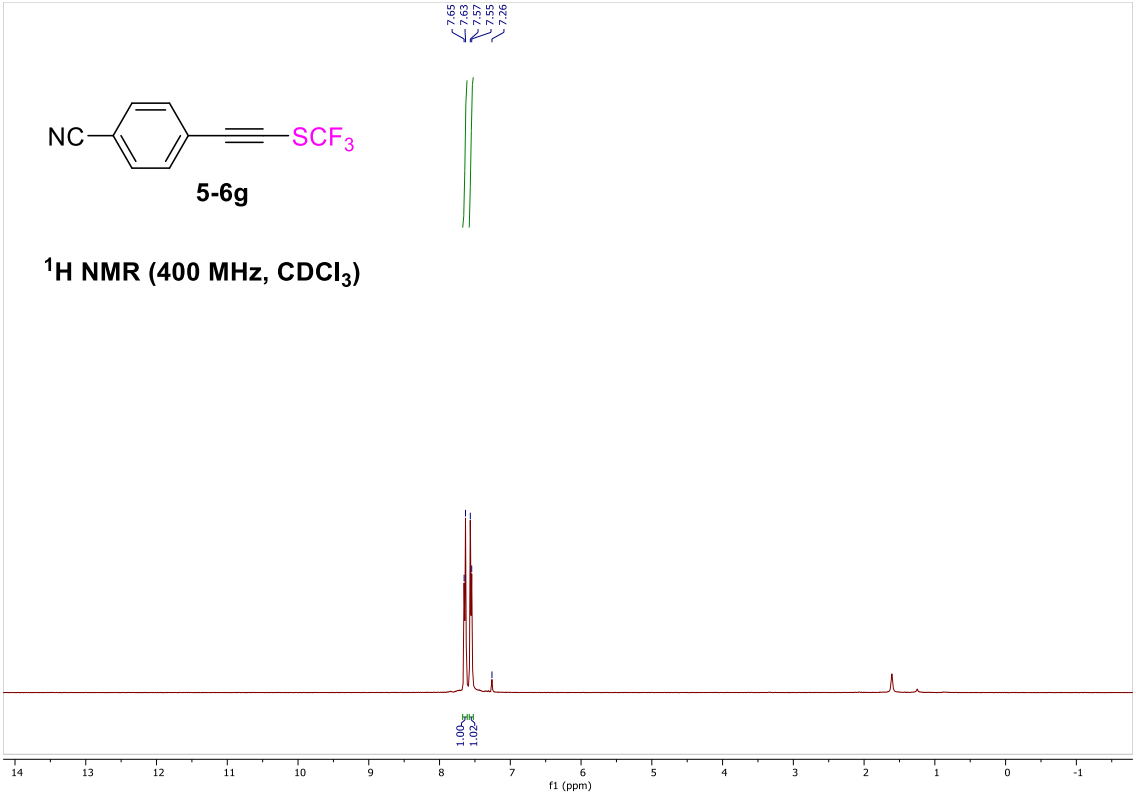
^{13}C NMR (100 MHz, $CDCl_3$)

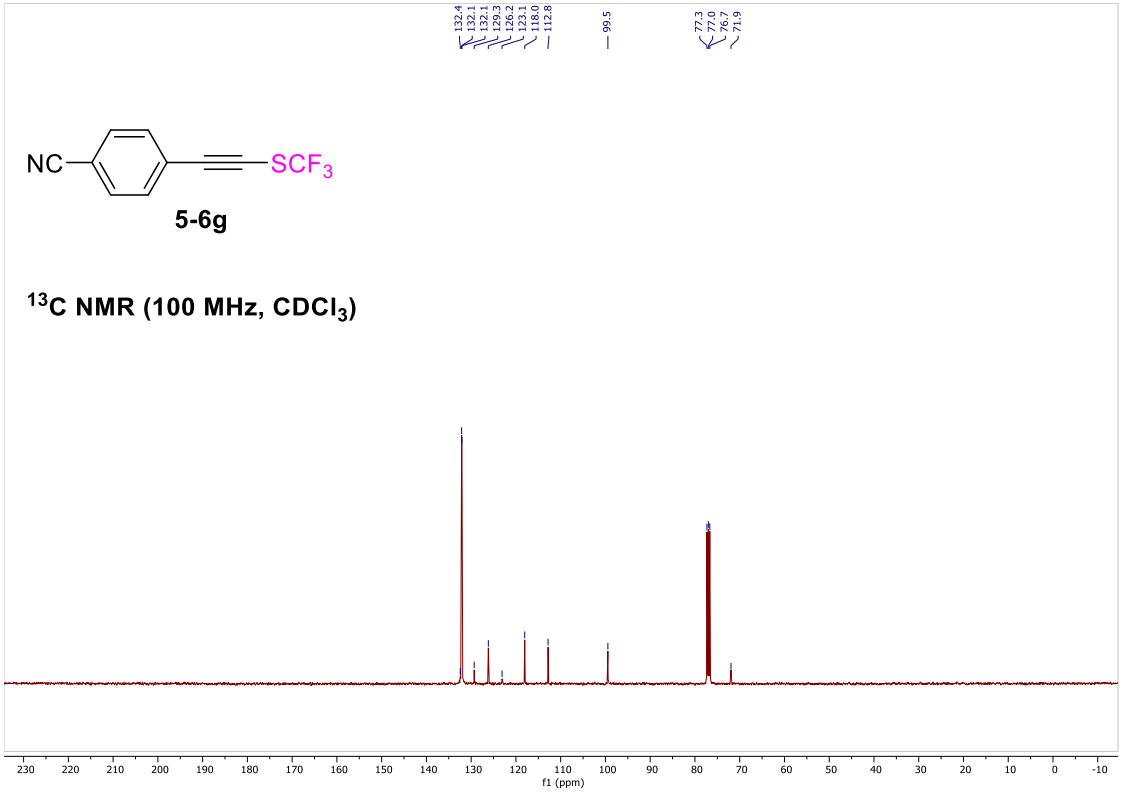

-43.5
Br
SCF3
5-6e
19F NMR (376 MHz, CDCl3)
f1 (ppm)

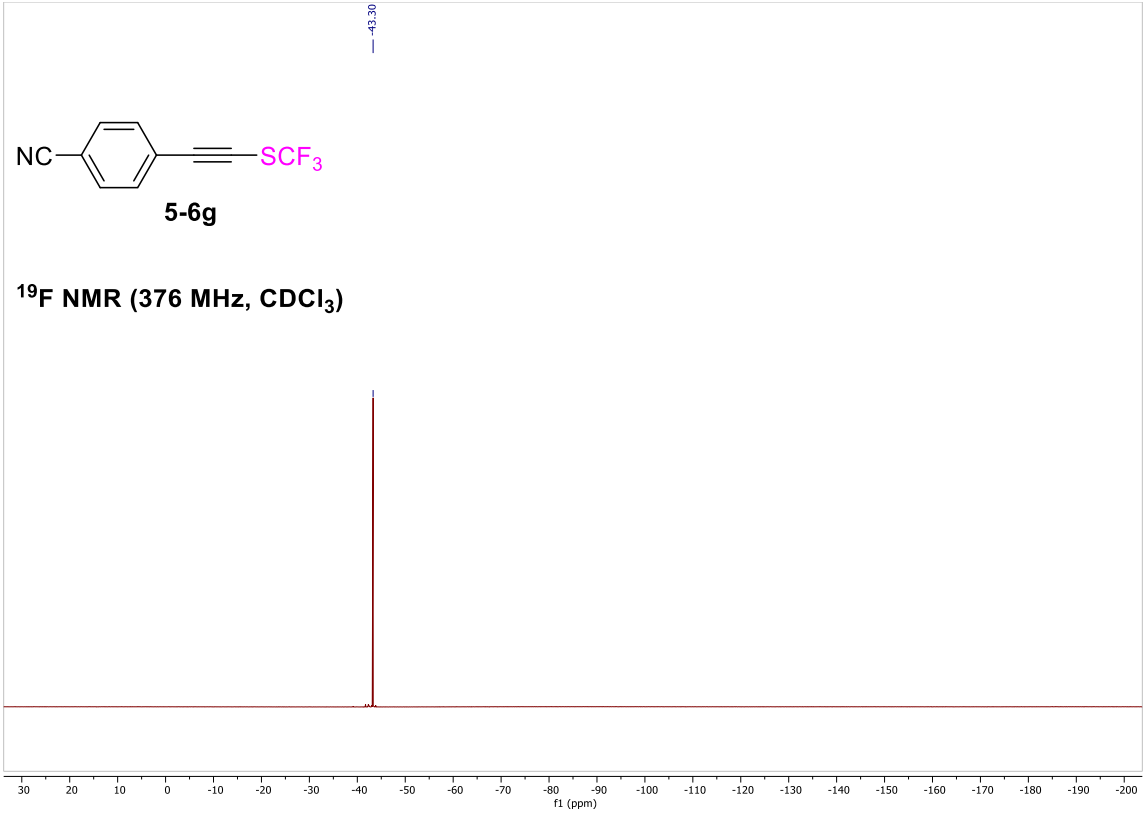

8.03
8.02
8.01
8.00
7.55
7.54
7.53
7.52
7.26
3.93
MeO2C
SCF3
5-6f
1H NMR (400 MHz, CDCl3)
2.00
2.02
3.23
f1 (ppm)

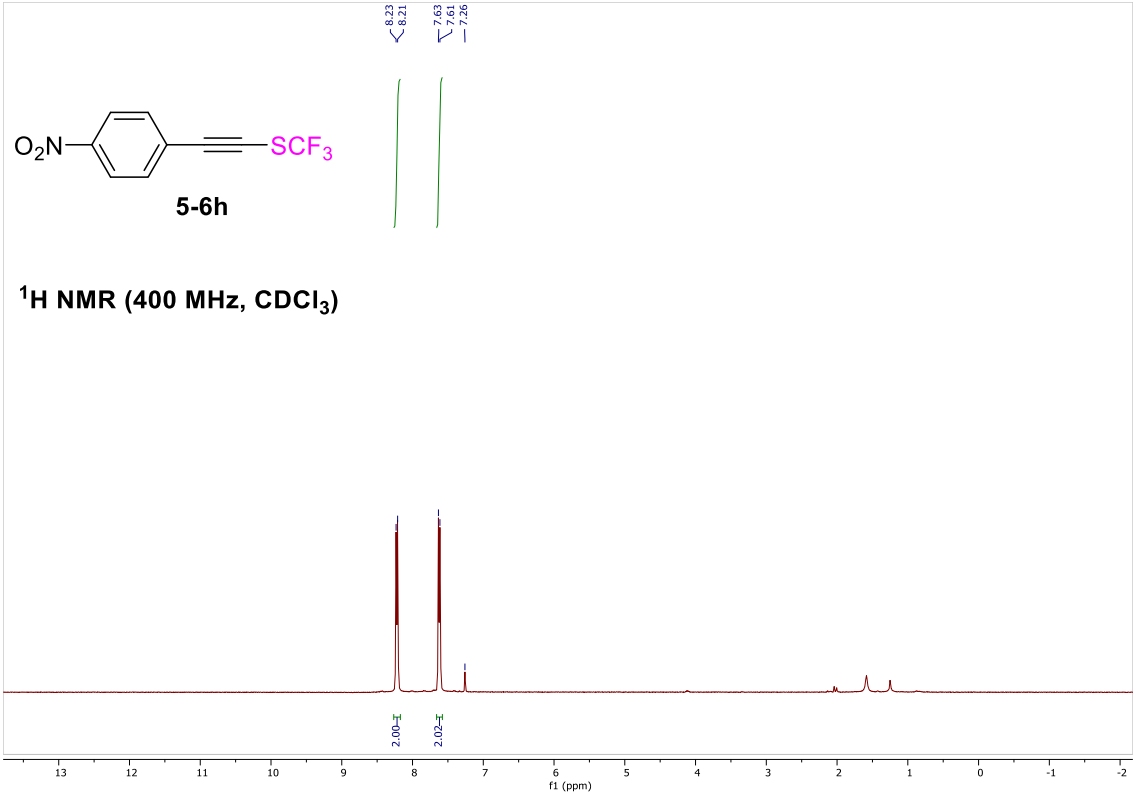

166.2
131.7
131.6
130.7
129.6
129.6
126.0
100.5
77.3
77.0
76.7
70.1
52.3
MeO2C
SCF3
5-6f
13C NMR (100 MHz, CDCl3)
f1 (ppm)

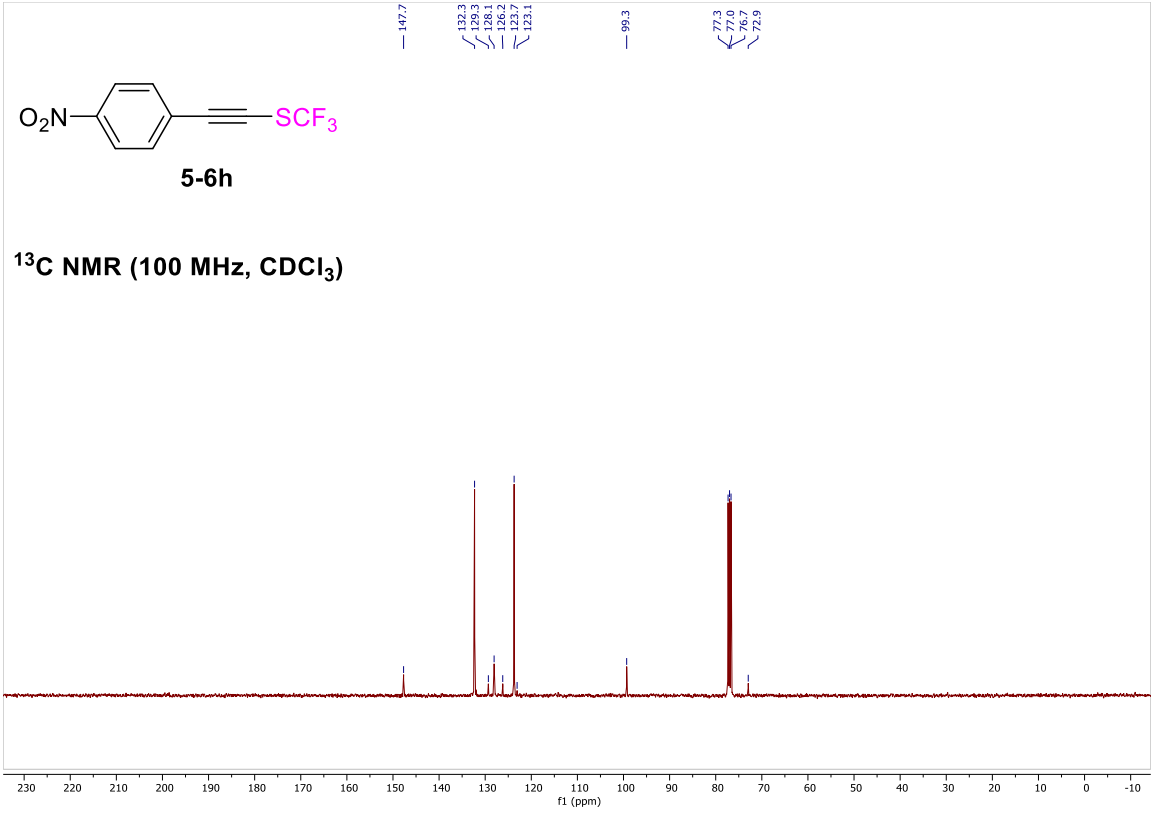

-43.26
MeO2C
SCF3
5-6f
19F NMR (376 MHz, CDCl3)
f1 (ppm)

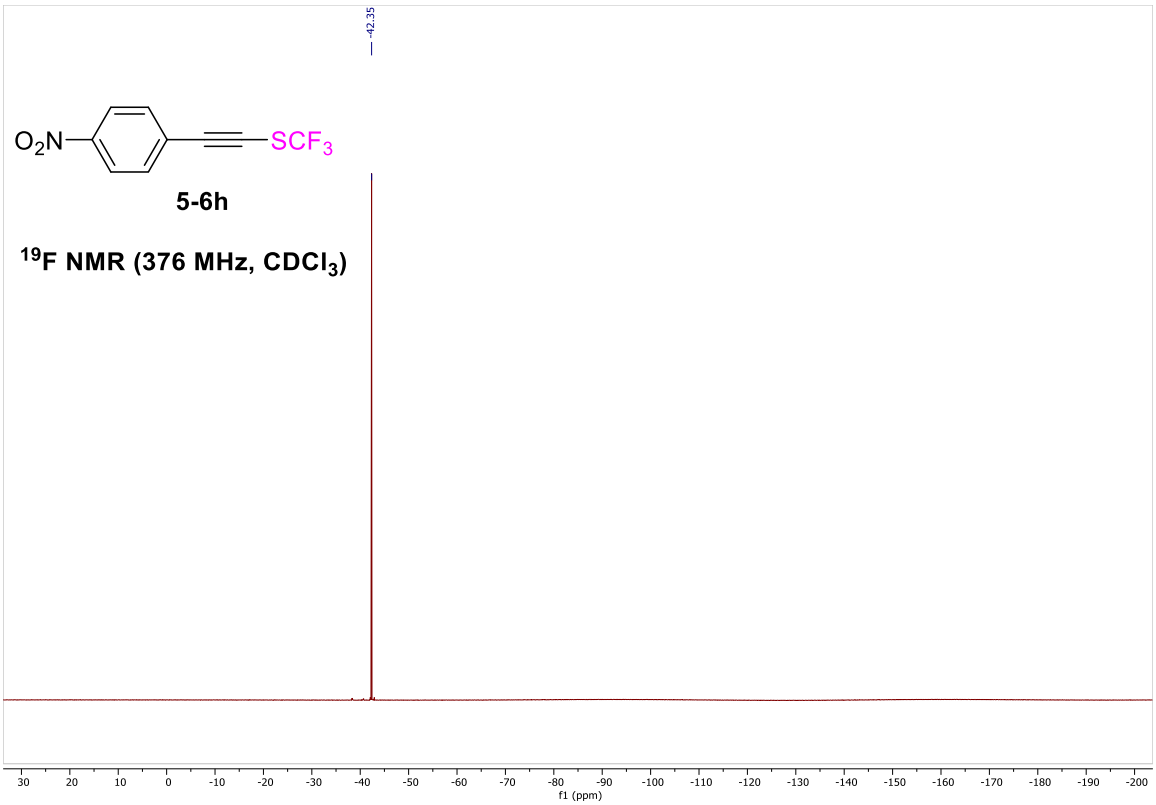

7.65
7.63
7.57
7.55
7.26
NC
SCF3
5-6g
1H NMR (400 MHz, CDCl3)
1.00
1.02
f1 (ppm)


132.4
132.1
132.1
129.3
125.2
123.1
118.0
112.8
99.5
77.3
77.0
76.7
71.9
NC
SCF3
5-6g
13C NMR (100 MHz, CDCl3)
f1 (ppm)

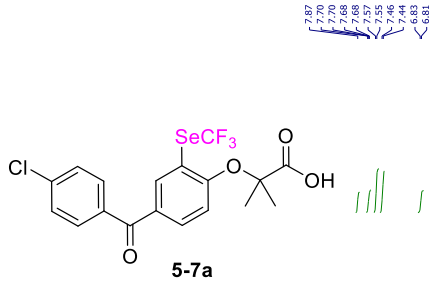

-43.30
NC
SCF3
5-6g
19F NMR (376 MHz, CDCl3)
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)


8.23
8.21
7.63
7.61
7.26
O2N
SCF3
5-6h
1H NMR (400 MHz, CDCl3)
2.00
2.02
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
f1 (ppm)


147.7
132.3
129.3
128.1
126.2
123.7
123.1
99.3
77.3
77.0
76.7
72.9
O2N
SCF3
5-6h
13C NMR (100 MHz, CDCl3)
f1 (ppm)

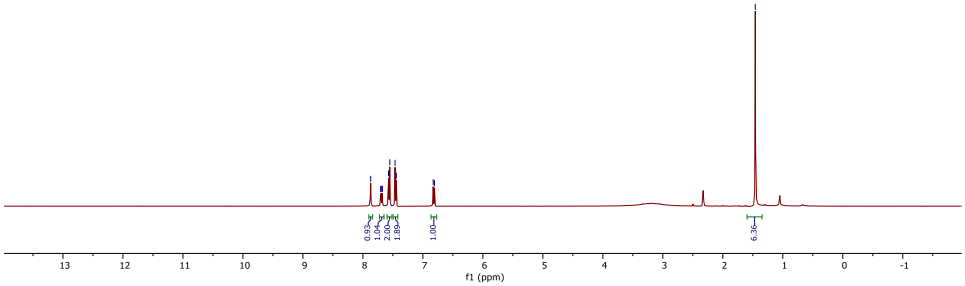

-42.35
O2N
SCF3
5-6h
19F NMR (376 MHz, CDCl3)
f1 (ppm)

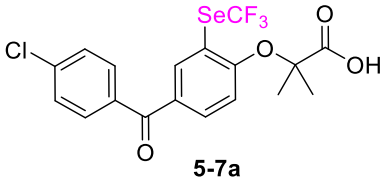
5.4.7.7. Trifluoromethylselenolation products



5-7a

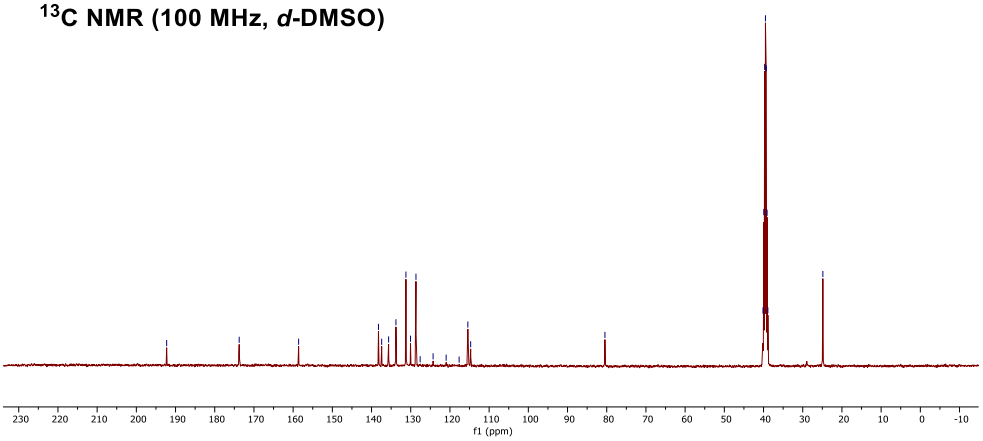
^{1}H NMR (400 MHz, *d*-DMSO)

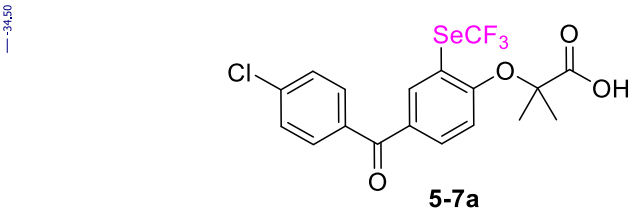




5-7a

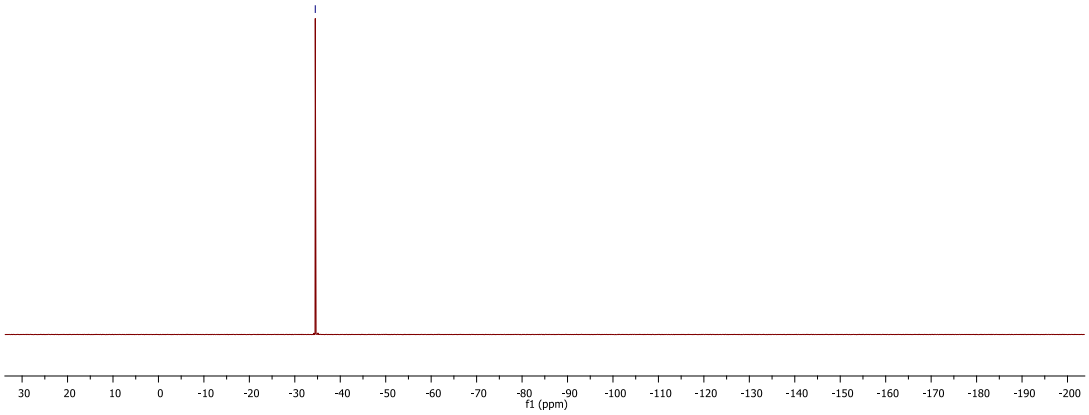
^{13}C NMR (100 MHz, *d*-DMSO)

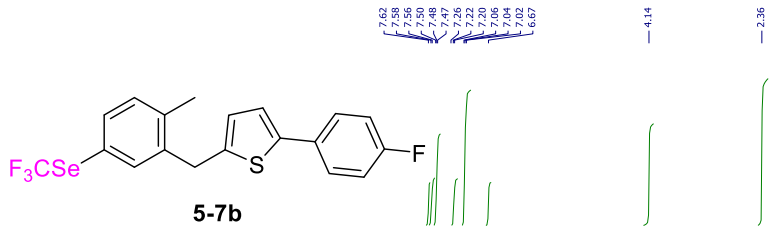




5-7a

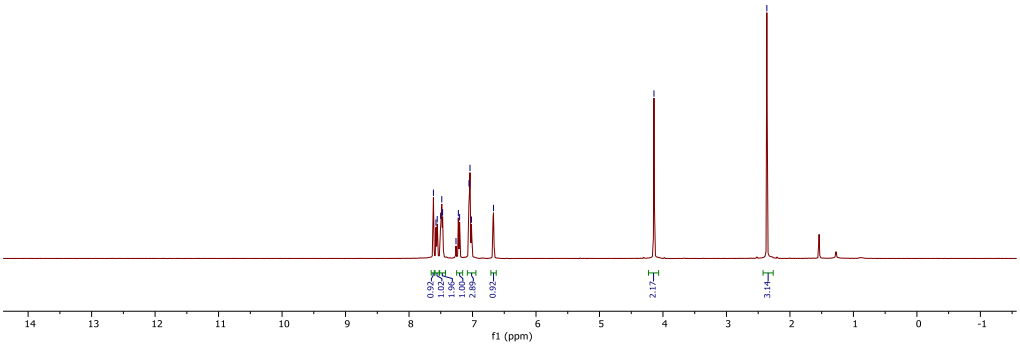
^{19}F NMR (376 MHz, *d*-DMSO)

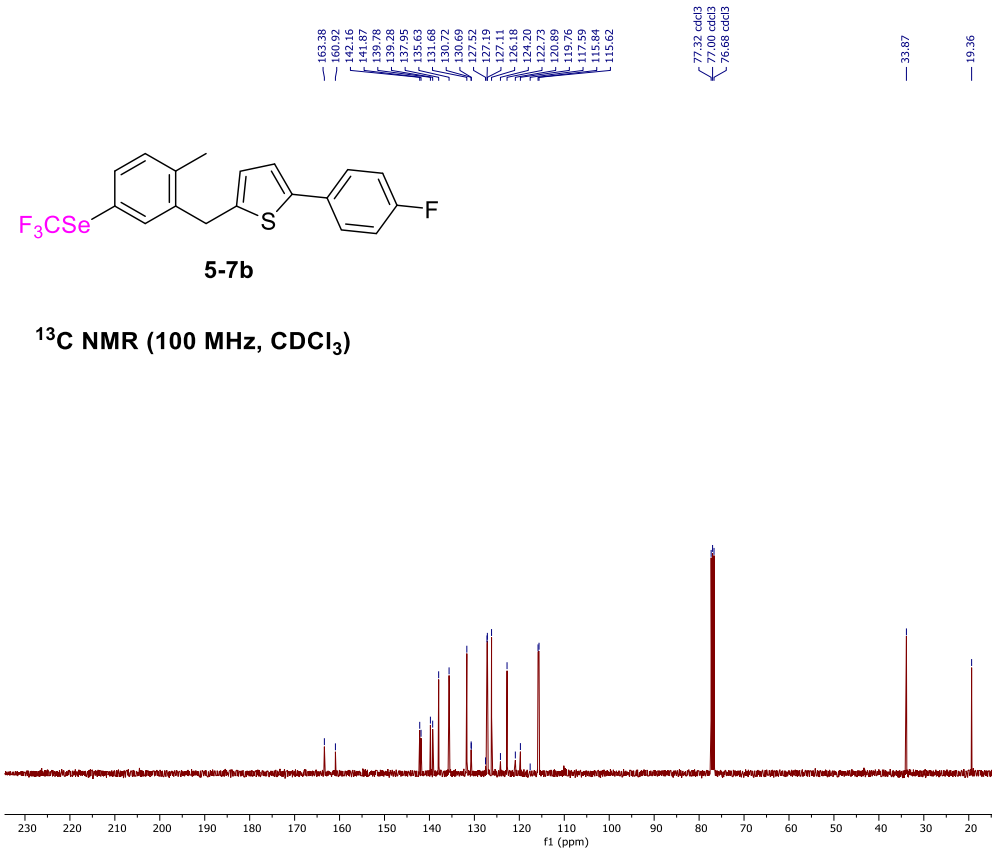


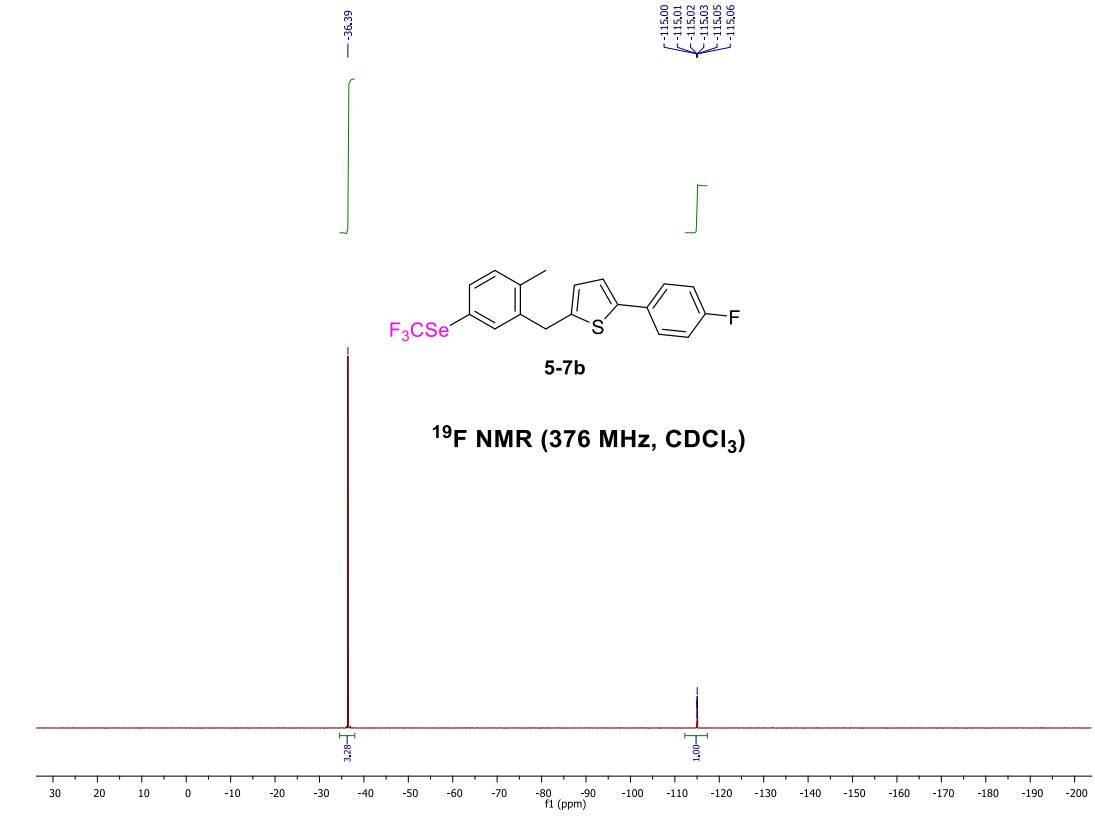


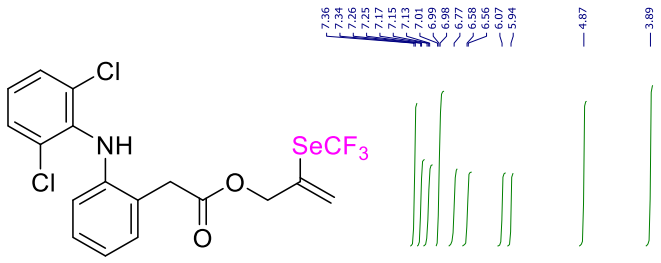
5-7b

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



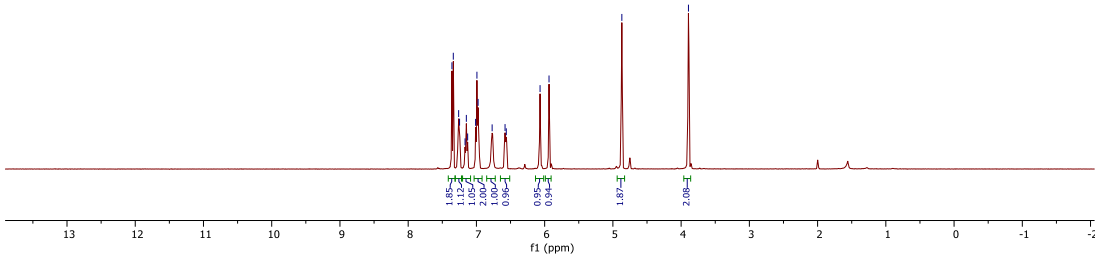

163.38
160.92
142.16
141.87
139.78
139.28
137.95
135.63
131.68
130.72
130.69
127.52
127.19
127.11
126.18
124.20
122.73
120.89
119.76
117.99
115.84
115.62
77.32 cdcl3
77.00 cdcl3
76.68 cdcl3
33.87
19.36
F3CSe
S
F
5-7b
13C NMR (100 MHz, CDCl3)
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

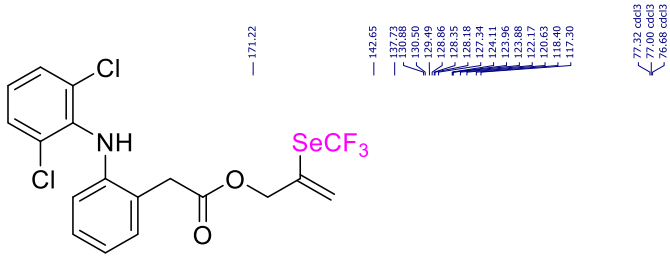

-36.39
-115.00
-115.01
-115.02
-115.03
-115.05
-115.06
F3CSe
S
F
5-7b
19F NMR (376 MHz, CDCl3)
3.28
1.00
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)



5-7c

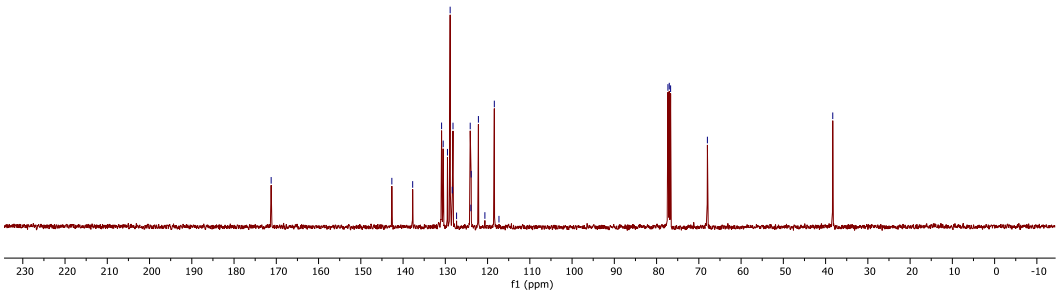
^{1}H NMR (400 MHz, $CDCl_3$)

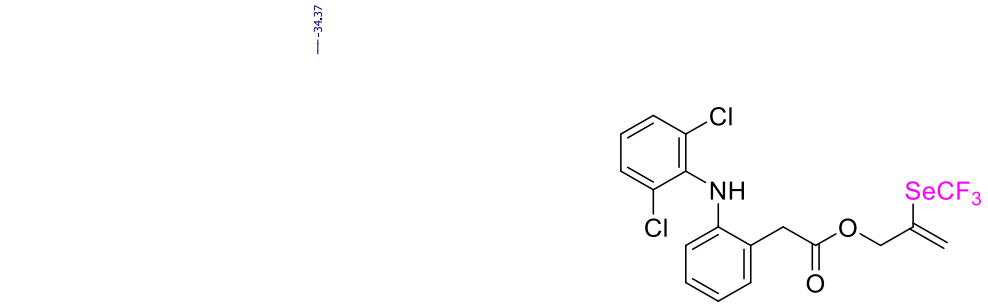




5-7c

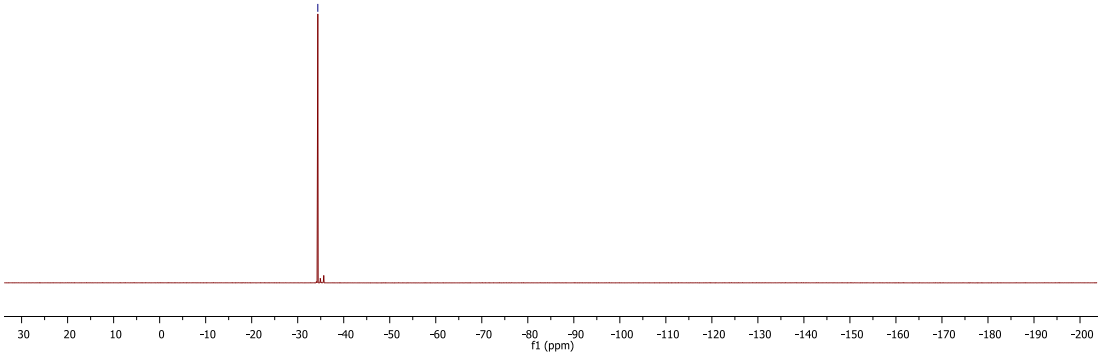
^{13}C NMR (100 MHz, $CDCl_3$)

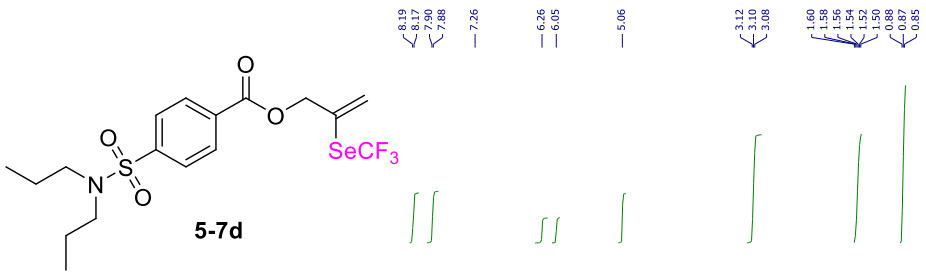




5-7c

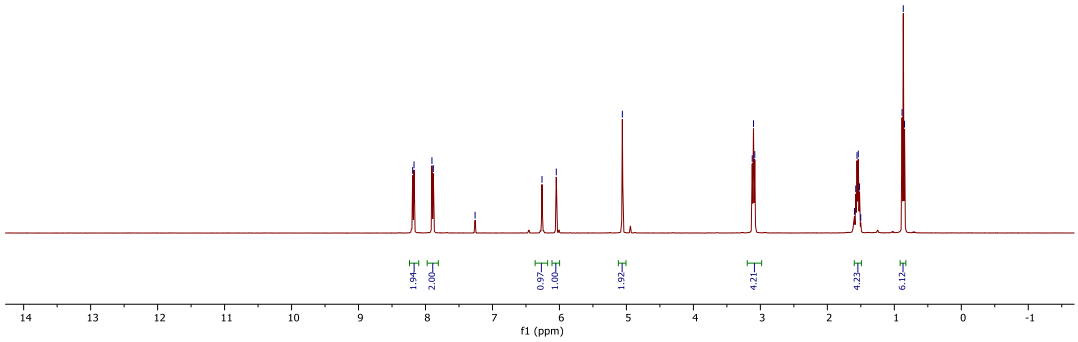
^{19}F NMR (376 MHz, $CDCl_3$)

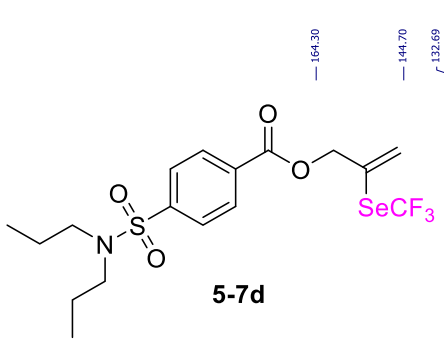




5-7d

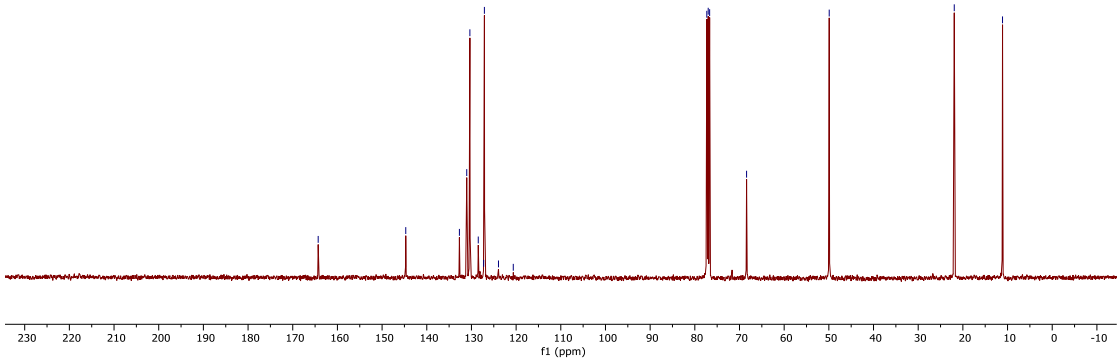
^{1}H NMR (400 MHz, $CDCl_3$)

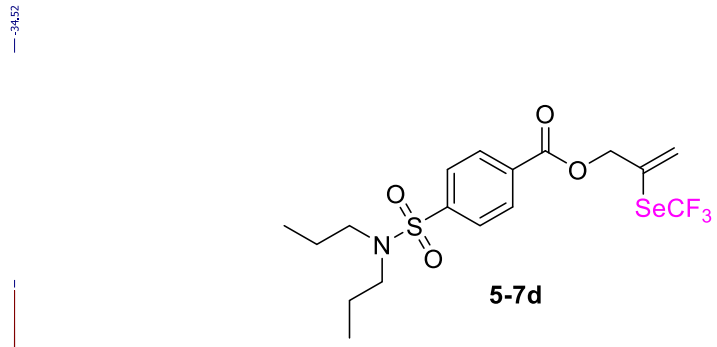




5-7d

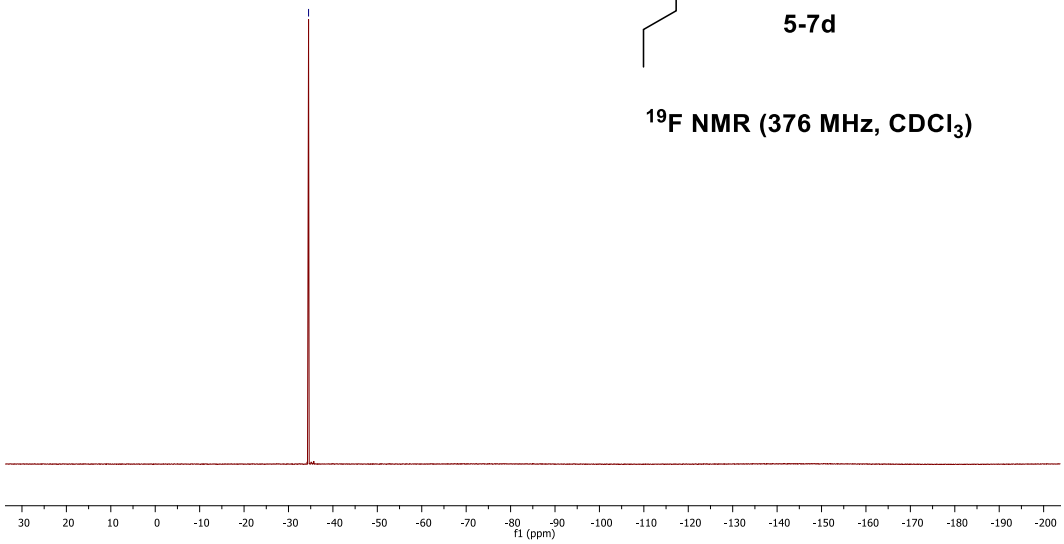
^{13}C NMR (100 MHz, $CDCl_3$)

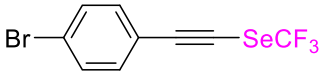




5-7d

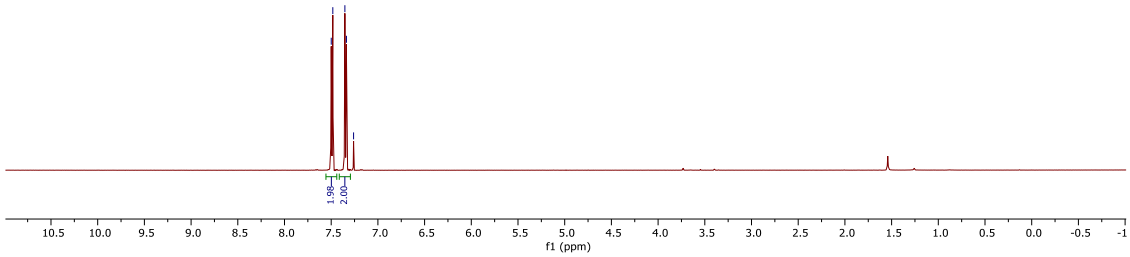
^{19}F NMR (376 MHz, $CDCl_3$)

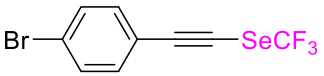




5-7e

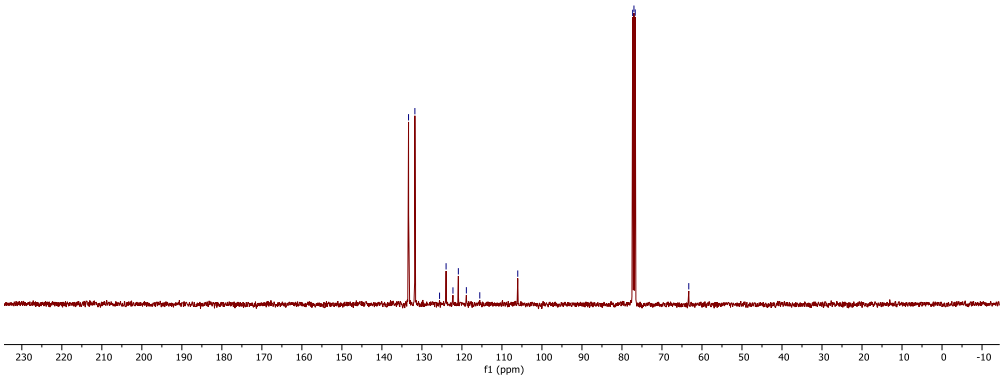
^{1}H NMR (500 MHz, $CDCl_3$)

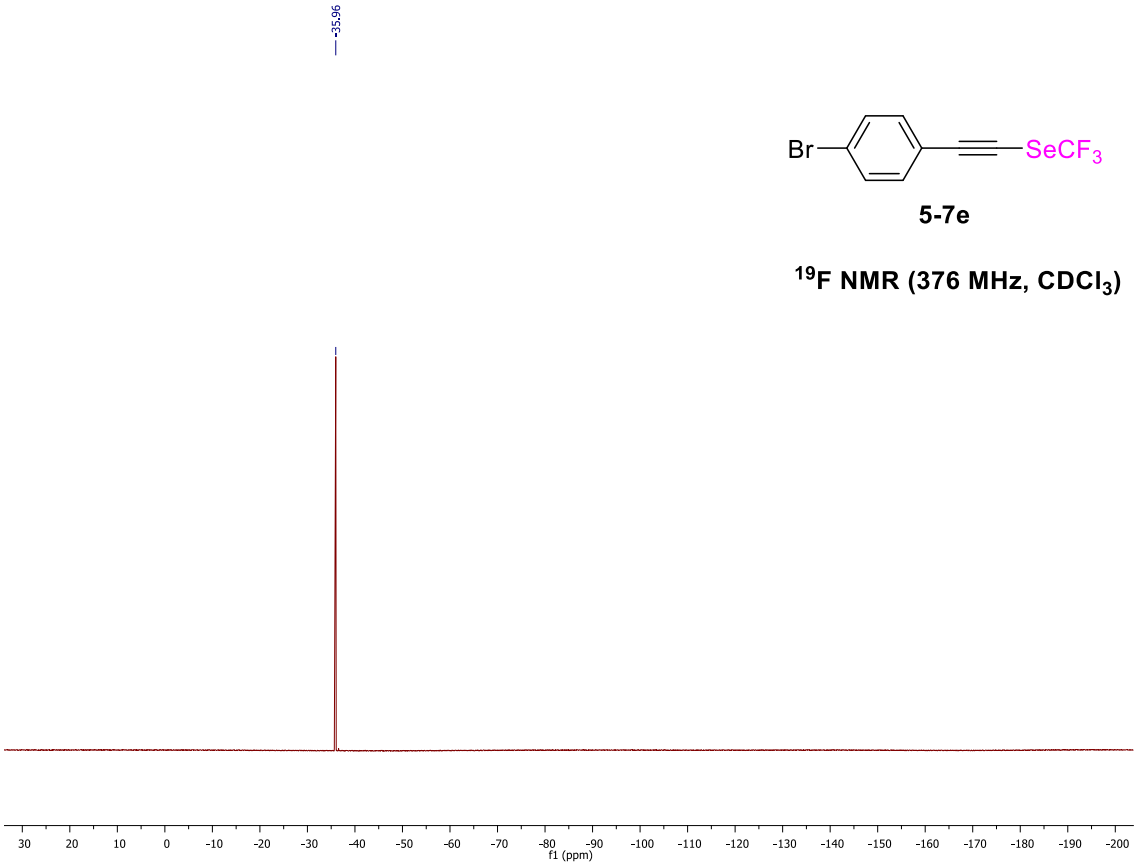




5-7e

^{13}C NMR (100 MHz, $CDCl_3$)





5-7e

^{19}F NMR (376 MHz, $CDCl_3$)

APPENDIX E: LIST OF ABBREVIATIONS

CT complex: Charge-transfer complex

DCE: 1,2-Dichloroethane

DCM: Dichloromethane

DMA: Dimethyl acetamide

DMPU: N, N'-Dimethylpropyleneurea

DMSO: Dimethylsulfoxide

dr: Diastereomeric ratio

EI: Electrospray Ionization

EtOAc: Ethyl acetate

GC: Gas liquid chromatography

h: Hour

HBD: Hydrogen bond donor

HBA: Hydrogen bond acceptor

HCl: Hydrogen chloride

HBr: Hydrogen bromide

HF: Hydrogen fluoride

HFIP: 1,1,1,3,3,3-Hexafluoro-2-propanol

HOAc: Acetic acid

HRMS: High resolution mass spectroscopy

Hz: Hertz

IR: Infrared

M: Molar

m: meta

mg: milligram

min: minute**mL**: milliliter

mmol: millimole

NBS: N-Bromosuccinimide

NCS: N-Chlorosuccinimide

NMR: Nuclear magnetic resonance spectroscopy

o: Ortho

p: Para

ppm: Parts per million

tert: Tertiary

TMS: Trimethylsilyl

TFA: Trifluoroacetic acid

TfOH: Trifluoromethanesulfonic acid

THF: Tetrahydrofuran

TLC: Thin layer chromatography

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S. R. Mudshinge, C. S. Potnis, B. Xu and G. B. Hammond, *Green Chem.*, 2020,**22**, 4161-4164.

CURRICULUM VITAE

Name: Mudshinge Sagar R.

Home Address: 779 Theodore Burnett Ct. Apt# 3, Louisville, KY 40218

E-mail: mudshinge23@gmail.com

Phone: (502)-819-7645

SUMMARY:

- Published 7 peer-reviewed scientific papers
- Over 10-year professional background on organic chemistry covering the field of organometallic chemistry, fluorine Chemistry, and medicinal chemistry.
- 4 years of teaching experience.
- Awarded Doctoral Dissertation Completion Award at University of Louisville

EDUCATION:

- PhD in Chemistry — Aug 2017– present
  University of Louisville, Louisville, KY, USA — GPA: 3.67/4.0
- NIPER, Mohali, Punjab, India
  Medicinal Chemistry — June 2012 – May 2014
- Bachelor in pharmacy — June 2009 – Jun 2012
  Pune University, Maharashtra, India.

INDUSTRIAL EXPERIENCE:

Glenmark Pharmaceuticals Ltd. Mumbai, India. — Jan 2015 – Jun 2017

As a Research Associate, performed synthesis of small molecule inhibitors for potency and permeability determinations and subsequent scale up for *in vitro* / *in vivo* pharmacokinetic and toxicological analyses.

HONORS and AWARDS:

- DAAD RISE award 2019
- Doctoral Dissertation Completion Award, UofL 2021

PUBLICATIONS:

(1) **Mudshinge, S. R.**; Lu, Zhicahao; Hammond, G.B. Gold(I/III)-Catalyzed Trifluoromethylthiolation and Trifluoromethylselenolation of Organohalides. *Angew. Chem*. *Int. Ed* (tentatively accepted, confirmation number- 202115687R1.) **(IF- 15.34)**

(2) Lu, Z.; Li, T.; **Mudshinge, S. R**.; Xu, B.; Hammond, G. B. Optimization of Catalysts and Conditions in Gold(I) Catalysis—Counterion and Additive Effects. *Chem. Rev.* **2021,** 121 (14), 8452. **(IF- 60.62)**

(3) **Mudshinge, S. R.**; Umemoto, T; Hammond, G.B. Synthesis and Application of *S*-(trifluoromethyl)-2,8-bis(trifluoromethoxy)dibenzothiophenium triflate (Manuscript under preparation).

(4) **Mudshinge, S. R**.; Potnis, C. S.; Xu, B.; Hammond, G. B. HCl·DMPU-assisted one-pot and metal-free conversion of aldehydes to nitriles. *Green Chem.* **2020,** 22 (13), 4161-4164. (**IF- 9.480**) (Featured on cover page)

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(6) Kumar, K.; **Mudshinge, S. R.**; Goyal, S.; Gangar, M.; Nair, V. A. A catalyst free, one pot approach for the synthesis of quinoxaline derivatives via oxidative cyclisation of 1,2-diamines and phenacyl bromides *Tetrahedron Lett.* **2015,** 56 (10), 1266. (**IF-2.275**)

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PRESENTATIONS:

1. **Mudshinge, Sagar**; Potnis**,** Chinmay; Xu, Bo; Hammond, Gerald. Greener Approach for the One Pot Synthesis of Nitriles **Oral**, University of Louisville, Belknap Campus, Louisville, Kentucky, USA12 March 2021.
2. **Mudshinge, Sagar**; Ebule, Rene; Nantz, Michael; Mashuta, Mark; Hammond, Gerald; Xu, Bo**.** 5+1 Protic Acid-Assisted aza-Pummerer Approach for the Synthesis of 4-

Chloropiperidines from Homoallylic Amines. **Poster**, 36th H.C. Brown Symposium, Purdue University, West Lafayette, Indiana, USA 18 April 2019.

3. **Mudshinge, Sagar**; Ebule, Rene; Nantz, Michael; Mashuta, Mark; Hammond, Gerald; Xu, Bo**.**Metal Free Halogenation of Organic Compounds **Poster**, 24th Winter Fluorine Conference, Clearwater, Florida, USA.13 Jan 2019.