Synthesis and Evaluation of New Reagents for Organofluorine Chemistry

Inaugural-Dissertation
to obtain the academic degree
Doctor rerum naturalium (Dr. rer. nat.)

submitted to the Department of Biology, Chemistry, Pharmacy
of Freie Universität Berlin

by

Matteo Tironi, M. Sc.

from Berlin, Germany

2022

Authors Declaration

Hereby, I declare that the submitted thesis is my own work and was prepared autonomously without the help of other sources than the ones cited and acknowledged. The work was not submitted to any prior doctoral procedure.

Matteo Tironi, October 2022

The presented research was carried out under the supervision of Prof. Dr. Matthew N. Hopkinson from October 2019 until December 2021 at the Department of Biology, Chemistry, and Pharmacy of the Freie Universität Berlin. From January 2022 until August 2022, I was a visiting student under the supervision of Prof. Dr. Matthew N. Hopkinson at the School of Natural and Environmental Sciences of the Newcastle University, Newcastle upon Tyne, United Kingdom.

1. Reviewer:	Prof. Dr. Matthew Hopkinson School of Natural and Environmental Sciences, Newcastle University, United Kingdom.
2. Reviewer:	Prof. Dr. Beate Koksch Institute of Chemistry and Biochemistry, Freie Universität Berlin.
Date of Defense:	20.01.2023

Table of contents

Thanks

I would like to start by thanking Prof. Dr. Matthew N. Hopkinson for his invaluable supervision throughout my doctoral work. He always took time to discuss the research projects, the research results, and ways to improve my experience as a whole, despite all the hardships we had to face in these three years due to the pandemic situation. He is a very knowledgeable, patient, and friendly person and helped incredibly in creating a productive and friendly work environment.

I would also like to thank Prof. Dr. Beate Koksch for being my second supervisor., as well as all Prof. Paulus and Prof. Müller for agreeing to be part of my doctoral commission.

Over time the research group grew considerably, and I would like to thank all the group members (Stefan Dix, Andreas Mavroskoufis, Arushi Garg, Lilian Maas, Michael Jakob and all the students that worked with us throughout these years) for the time spent together.

Very heartfelt thanks also go to the Studienstiftung der Deutschen Volkes for the financial support they have given me during my work, as well as the networking opportunities they have offered me. In particular I would like to thank Prof. Dr. Peter Antes and Prof. Dr. Thomas Ertl for the excellent support they have given me in dealing with matters related to my scholarship.

I also want to thank the friends I've made during these years, both in Germany and England, for their kind words and for the lasting bonds we've formed that helped me coping with the hardest moments I've faced, making me feel at home.

Dulcis in fundo, a very special thank for my family, my mom and my two sisters Mara and Sabrina, for the incredible support they have given me despite being very far away, without which I wouldn't be where I am today.

Abstract

In this thesis, novel synthetic approaches to introduce fluorinated functional groups were investigated. Expanding upon the work previously carried out by our group, the reagents BT-SCF_2H and BT-$SeCF_2H$ were introduced, and their reactivity toward alcohols and acids was investigated.

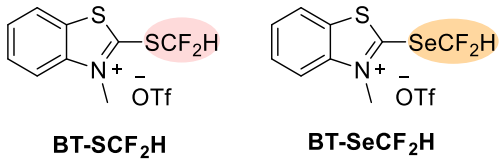
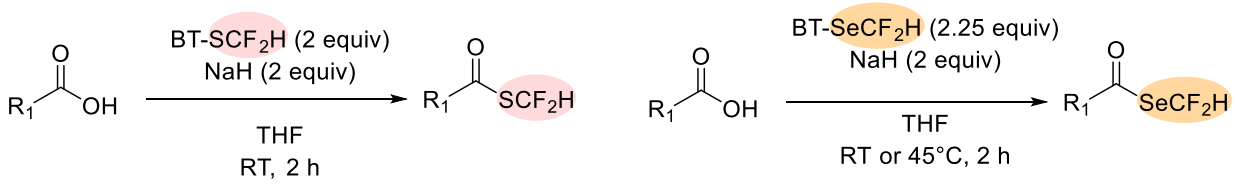


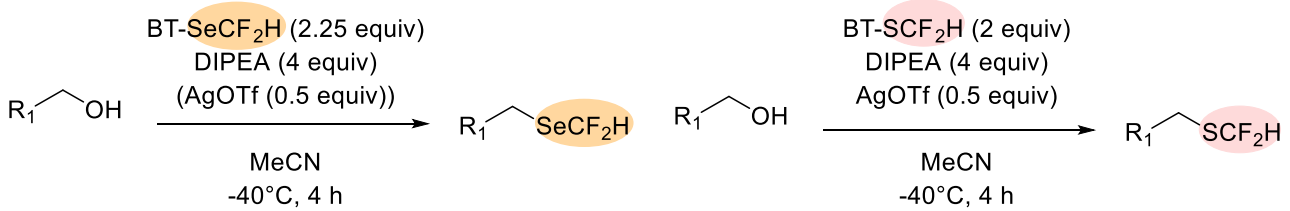
Fig.1: The newly developed BT-SCF_2H and BT-$SeCF_2H$ reagents.

A wide scope of carboxylic acids, both aliphatic and aromatic, were successfully converted into the corresponding difluoromethylthio- and -seleno esters under mild conditions in good to excellent yields, representing the first method to access these valuable compounds directly from carboxylic acids through a nucleophilic reaction. As suggested by computational calculations, the mechanism likely proceeds through an unusual 4-membered transition state, with no release of the free unstable anion.



Scheme 1: Deoxydifluoromethylthiolation and -selenylation of carboxylic acids.

The difluoromethylchalcogenation of alcohols proved to be more challenging that the corresponding trifluoromethylchalcogenation previously published by our group, owing to the lower stability of partially fluorinated anions. Whilst the reaction proceeds without any additive with BT-$SeCF_2H$, the yields are low with all but the most activated substrates. The addition of silver triflate proved to be the key to enabling this valuable transformation, increasing the yield, and expanding the alcohol scope with BT-$SeCF_2H$, and enabling the difluoromethylthiolation of benzylic alcohols altogether.



Scheme 2: Deoxydifluoromethylthiolation and -selenylation of alcohols.

Zusammenfassung

In dieser Arbeit wurden neue synthetische Ansätze zur Einführung fluorierter funktioneller Gruppen untersucht. In Erweiterung der zuvor von unserer Arbeitsgruppe durchgeführten Arbeiten wurden die Reagenzien BT-SCF_2H und BT-$SeCF_2H$ eingeführt und ihre Reaktivität gegenüber Alkoholen und Carbonsäuren untersucht.

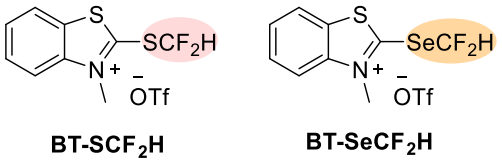
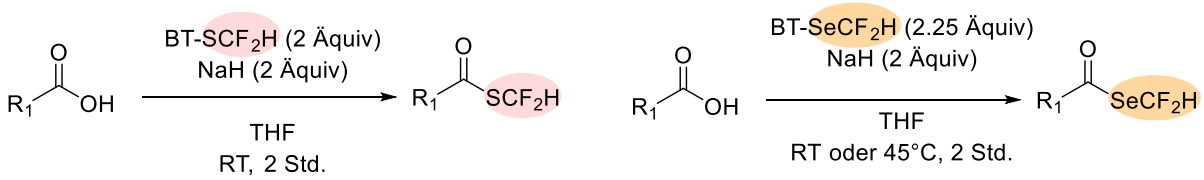


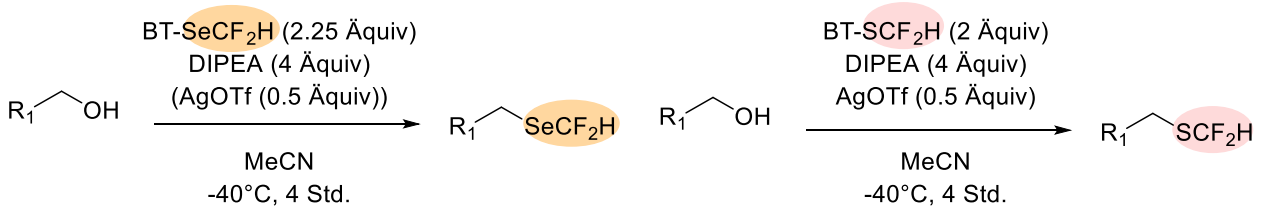
Abb.1: Die neu entwickelten Reagenzien BT-SCF_2H und BT-$SeCF_2H$.

Eine Vielzahl von Carbonsäuren wurden unter milden Bedingungen erfolgreich in die entsprechenden Difluormethylthio- und -selenoester in guter bis ausgezeichneter Ausbeute umgewandelt, was die erste Methode darstellt, diese wertvollen Verbindungen direkt aus Carbonsäuren durch eine nukleophile Reaktion zu gewinnen. Wie aus Berechnungen hervorgeht, läuft der Mechanismus wahrscheinlich über einen ungewöhnlichen 4-gliedrigen Übergangszustand ab, ohne dass das freie instabile Anion freigesetzt wird.



Schema 1: Deoxydifluormethylthiolierung und -selenylierung von Carbonsäuren.

Die Difluormethylchalkogenierung von Alkoholen erwies sich aufgrund schwieriger als die entsprechende Trifluormethylchalkogenierung, die unsere Arbeitsgruppe zuvor veröffentlicht hatte. Während die Reaktion mit BT-$SeCF_2H$ ohne jeglichen Zusatz abläuft, sind die Ausbeuten bei allen außer den am stärksten aktivierten Substraten gering. Die Zugabe von Silbertriflat war entscheidend für diese wertvolle Umwandlung. Damit wurden höhere Ausbeuten erzielt, der Umfang der Alkoholsubstrate mit BT-$SeCF_2H$ erweitert und die Difluormethylthiolierung von Benzylalkoholen mit BT-SCF_2H überhaupt ermöglicht.



Schema 2: Deoxydifluormethylthiolierung und -selenylierung von Alkoholen.

Abbreviations

18-crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane
2-MBT	2-Mercaptobenzothiazole
4-FAc	4-fluoroacetate
4-FT	4-fluorothreonine
5'-FDA	5'-fluoro-5'-deoxyadenosine
5'-FDAS	5'-fluoro-5'-deoxyadenosine synthase
acac	acetylacetonate
AIBN	Azobisisobutyronitrile
Ar	aryl
ATRA	Atom transfer radical addition
B3LYP	Becke, 3-parameter, Lee–Yang–Parr
bmim	1-butyl-3-methylimidazolium
Bn	benzyl
bpy	2,2'-bipyridine
BrettPhos	2-(Dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl
BT-SCF_2H	2-((difluoromethyl)thio)-3-methylbenzo[*d*]thiazol-3-ium trifluoromethanesulfonate
BT-SCF_3	3-Methyl-2-((trifluoromethyl)thio)benzo[*d*]thiazol-3-ium trifluoromethanesulfonate
BT-$SCFH_2$	2-((fluoromethyl)thio)-3-methylbenzo[*d*]thiazol-3-ium trifluoromethanesulfonate
BT-$SeCF_2H$	2-((difluoromethyl)selanyl)-3-methylbenzo[*d*]thiazol-3-ium trifluoromethanesulfonate
BT-$SeCF_3$	3-Methyl-2-((trifluoromethyl)selanyl)benzo[*d*]thiazol-3-ium trifluoromethanesulfonate
BT-SR_f	2-((perfluoroalkyl)thio)-3-methylbenzo[*d*]thiazol-3-ium trifluoromethanesulfonate
CFCs	Chlorofluorocarbons
CFL	Compact fluorescent lamp
CoA	Coenzyme A
COD	1,5-Cyclooctadiene
Cy	cyclohexyl
DAST	diethylaminosulfur trifluoride
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
dF(CF_3)ppy	3,5-difluoro-2-(5-trifluoromethyl)-2-pyridine

DFT	density-functional theory
DIPEA	Diisopropylethylamine
DIPEA	*N,N*-Diisopropylethylamine
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMF	dimethylformamide
DMPU	N,N'-Dimethylpropyleneurea
DMSO	dimethyl sulfoxide
DPPF	1,1'-Bis(diphenylphosphino)ferrocene
dppf	1,1'-Bis(diphenylphosphino)ferrocene
DT	Decatungstate
dtbbpy	4,4'-Di-*tert*-butyl-2,2'-dipyridyl
dtbpy	4,4'-di-tert-butyl-2,2'-bipyridine
EDG	Electron donating group
equiv	equivalents
Et	ethyl
EtOAc	Ethyl acetate
EWG	Electron withdrawing group
Glu	Glutamate
GWP	Global warming power
HAD	Hydrogen atom donor
HAT	hydrogen atom transfer
HFCs	Hydrofluorocarbons
HFIP	hexafluoro-2-propanol
*i*Pr	*Iso*-propyl
IPr	(1,3-bis(2,6-bis(diphenylmethyl)-4-methylphenyl)imidazo-2-ylidene)
LDA	Lithium diisopropylamide
LED	light-emitting diode
LUMO	Lowest unoccupied molecular orbital
M	molarity
Me	methyl
MeCN	acetonitrile

Mes	Mesitylene
MRSA	Methicillin-Resistant *Staphylococcus Aureus*
Ms	mesyl
MS	Molecular sieves
mTOR	mechanistic target of rapamycin
MW	microwave
NBS	N-bromosuccinimide
n-Bu	normal butyl
NFSI	*N*-fluorobenzenesulfonimide
NHC	N-Heterocyclic carbene
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
NSAID	Non-steroidal anti-inflammatory drug
OAc	acetoxy
ODS	Ozone depleting substance
OTf	triflate
PET	Positron emission tomography
PFAS	Persistent fluorinated substance
PFK-1	Phosphofructokinase 1
PFOA	Perfluorooctanoic acid
PFOS	Perfluorosulfonic acid
Ph	phenyl
PhMe	toluene
Phth	Phthalimide
PI3Kα	phosphoinositide 3-kinases alpha
PIDA	phenyliodine(III) diacetate
PIFA	[Bis(trifluoroacetoxy)iodo]benzene
$PivO^-$	Pivalate (2,2-Dimethylpropanoate)
pK_a	negative base-10 logarithm of the acid dissociation constant
ppm	parts per million
ppy	2-phenylpyridine
PTFE	Polytetrafluoroethylene

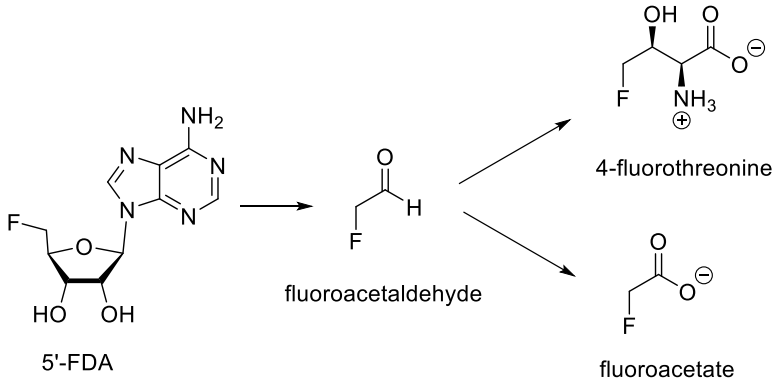
PTH	10-phenylphenothiazine
RT	room temperature
R_f	perfluorinated alkyl chain
RuPhos	2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
SAM	*S*-adenosyl-L-methionine
SCE	saturated calomel electrode
SDS	Sodium dodecyl sulfate
SET	single electron transfer
SIPr	1,3-Bis(2,6-diisopropylphenyl)imidazolidine
S_N2	bimolecular nucleophilic substitution
S_NAr	nucleophilic aromatic substitution
SOMO	Singly occupied
$S_{RN}1$	unimolecular radical nucleophilic substitution
$t_{1/2}$	half-life of a medicinal compound in blood plasma
TBA	tetra-*n*-butylammonium
TBHP	*tert*-Butyl hydroperoxide
t-Bu	*tert*-butyl
TDAE	tetrakis(dimethylamino)ethylene
TDS	(2,3-dimethylbutan-2-yl)dimethylsilyl
TEA	Triethylamine
terpy	Terpyridine
TFA	Trifluoracetic acid
THF	tetrahydrofuran
TMEDA	*N*,*N*,*N*′,*N*′-Tetramethylethane-1,2-diamine
TMS	Tetramethylsilyl
t-Pent	*tert*-pentyl
t_R	Time of retention
Ts	Tosyl (p-toluenesulfonyl)
UV	ultraviolet
XantPhos	(9,9-Dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphane)
XPhos	Dicyclohexyl[2′,4′,6′-tris(propan-2-yl)[1,1′-biphenyl]-2-yl]phosphane

1. Background: history of fluorine chemistry and its applications

1.1 Natural occurrence of fluorinated compounds

Just like the other elements, fluorine atoms are formed in the nuclear fusion process known as stellar nucleosynthesis[1], in which lighter elements are fused to form heavier atoms whilst releasing energy. However, fluorine is a fairly rare element in the universe, because it is not a major product of stellar nucleosynthesis and it can easily react further to form other elements, so it can only be released under special circumstances[2]. One such example are asymptotic giant branch stars, in which the fusion reaction is intermittent, where convection currents allow fluorine atoms formed in the inner part of the star to escape before being consumed. These atoms could be detected and identified due to the observation of the rotation-vibration lines of the HF molecule near such stars[3]. Another process that allows the formation of fluorine atoms is the bombardment of neon atoms in type II supernovae by neutrinos[4].

Fluorine is however quite abundant in the Earth's crust, being the 13th most common element at 600-700 ppm by mass. Because of its high reactivity, fluorine does not occur in its elemental form, except in inclusions in uranium-containing fluoride-rich minerals such as Antozonite[5] since fluorine gas is produced by radiolysis due to beta radiation inside these minerals. Usually, fluorine occurs as fluoride salts in the crust or in the oceans. Fluoride concentration in the sea is relatively low, owing to the low solubility of fluoride salts. On land, however, fluoride salts are common. Large amounts of fluoride salts can be found in minerals such as Na_3AlF_6 (cryolite), CaF_2 (fluorite), and $Ca_5(PO_4)_3F$ (fluorapatite), which represent the major commercial sources of fluorine.



Scheme 3: Some key naturally occurring fluorinated organic compounds.

Despite its relative abundance, fluorine is seldom incorporated into biosynthesis pathways, with only a few naturally occurring fluorinated organic compounds being known (Scheme 3)[6].

The first one to be discovered and the most widely studied is the exceptionally toxic sodium fluoroacetate, which can be found in over 40 plant species of Australian, Brazilian and African shrubs, that use it as a way to defend themselves from herbivores[7]. It is widely used as a pesticide against mammalians, especially rats.

Sodium fluoroacetate's high toxicity comes from its ability to interfere with metabolism. In particular, it gets converted *in vivo* into fluoroacetyl-CoA, which reacts with oxaloacetate and leads to the formation of 2-fluorocitrate, which is a powerful inhibitor of aconitase, thus blocking the Krebs cycle and leading to a citrate build up[8]. Citrate is an inhibitor of phosphofructokinase-1 (PFK-1), an enzyme that catalyzes a key step of the glycolytic pathway. Fluorocitrate is also able to inhibit citrate transport within the cell[9]. A key intermediate in the biosynthesis of fluoroorganic compounds is the metabolite 5'-fluoro-5'-deoxyadenosine (5'-FDA), synthesized by the enzyme 5'-fluoro-5'-deoxyadenosine synthase (5'-FDAS) from *S*-adenosyl-L-methionine (SAM) and fluoride. This leads to the formation of fluoroacetaldehyde, a precursor of both 4-fluorothreonine (4-FT) and fluoroacetate (FAc) (Scheme 3)[10].

1.2 Early history of fluorine chemistry

Fluorine is a relative newcomer in terms of human applications. In antiquity, fluorite was reportedly used by Persians to carve cups and other utensils, however such artifacts are hard to find because of the mineral's softness[11]. The discovery of fluorine and its first metallurgical applications were developed by the Saxon scholar Georgius Agricola[12]. He observed that adding fluorite (also called fluorspar) to molten metal ores reduces their viscosity and lowers the melting temperature, thus making their smelting easier. Because of this property, he called the mineral fluores (latin for fluxes).

Andres Sigismund Marggraf discovered in 1764 that treating fluorite with sulfuric acid at high temperature produces an acid capable of corroding glass[13]. This compound was later dubbed "fluorspar acid" or, in English, fluoric acid. André-Marie Ampère demonstrated that this acid was made of hydrogen and an unknown element analogous to chlorine[14]. Because of that, the British chemist Sir Humphry Davy suggested the name fluorine for the element, formed by the fluor- prefix from fluoric acid and the -ine suffix in analogy to chlorine. The name was adopted into various European languages (German, English, Italian, Latin etc.), but some (such as Greek and Russian) use a name derived from the Greek word "phthorios" (meaning destructive), suggested by Ampère himself.

Several chemists in the 19th century tried to isolate elemental fluorine, often resulting in serious injuries and even death, because of the highly toxic and corrosive nature of HF and F_2, which are capable of attacking glass and metal, as well as the explosive nature of the recombination reaction of H_2 and F_2[15].

It was only in 1886 that the French chemist Henri Moissan finally succeeded in synthesizing and characterizing elemental fluorine by electrolysing a mixture of potassium fluoride and hydrogen fluoride[16]. For this achievement, Moissan won the Nobel prize in Chemistry in 1906.

During World War 2, fluorine chemistry grew in importance as fluorine (as UF_6) was crucial in the uranium enrichment process for the Manhattan project, which led to the development of the first nuclear bomb[17].

The first applications of artificial organofluorine compounds were developed in the 1930s and 40s by DuPont, with the development of ChloroFluoroCarbons (CFCs) such as Freon-12 (dichlorodifluoromethane), used as refrigerants, and Teflon™ (polytetrafluoroethylene), used for coatings[18].

CFCs came under great scrutiny in the 70s and 80s because of their role in the ozone layer depletion, eventually being phased out with the Montreal convention[19] and replaced by hydrofluorocarbons (HFC). HFCs themselves, however, pose serious problems as they are potent greenhouse gasses, with trifluoromethane (CF_3H) for instance having a global warming potential (GWP) 11700 stronger than CO_2[20]. This has led to the ratification of the Kigali amendment of the Montreal convention to reduce their use significantly in the next few decades.

1.3 Modern day applications

The primary use of fluorine-containing minerals in the 21st century is still in the area of metallurgy: fluorine-containing species help to lower the melting point of alloys, reduce the viscosity of the resulting slag, and aid purification from unwanted contaminants.

The scope of applications of fluorinated molecules has however expanded significantly in the last decades: owing to its high electronegativity and low polarizability, fluorine substitution can dramatically influence the physical, chemical, and biological properties of organic compounds. These properties have led to fluorinated molecules being employed in the fields of materials, agrochemicals, and pharmaceuticals (Fig. 2)[21]. In the field of material sciences, fluorinated materials such as Teflon™ or Goretex™, both based on the PTFE polymer, have found numerous domestic and industrial applications because of their stability and repellent properties[22]. PFOA (perfluorooctanoic acid) and PFOS (perfluorooctanesulfonic acid) are two of the most widespread surfactants and emulsifiers industrially, albeit they are being phased out due to concerns about their effects on human health[23].

As previously mentioned, most high-performance refrigerant gasses, such as CFCs (e.g. Freon 22) and HFCs (e.g. R-134a), contain fluorine. Sulfur hexafluoride (SF_6), another important fluorinated gas, is widely employed in electronics, with 80% of the global production being used as a gaseous dielectric medium in high voltage applications[24].

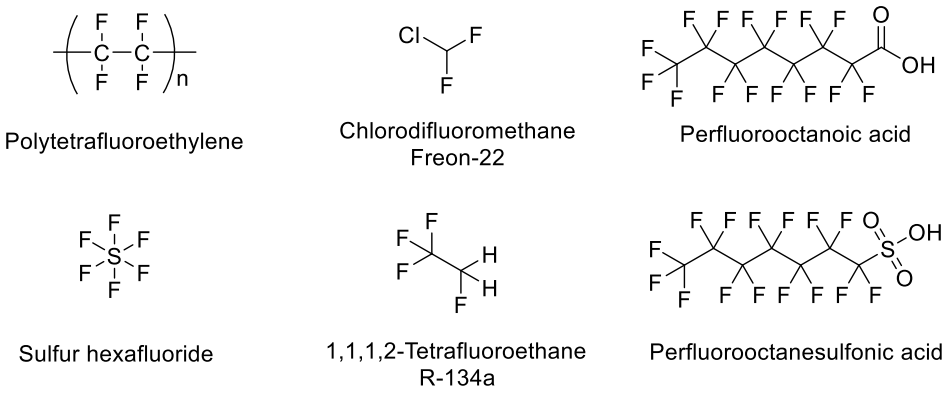


Fig. 2: Some of the most widely used fluorinated materials industrially

Even more interestingly for the purposes of this work, in the fields of agrochemistry and pharmaceutics, there has been a huge increase in the number of fluorinated bioactive compounds being developed and marketed, with the share of fluorinated drugs being on the rise. Despite fluorinated chemicals representing roughly 20% of pharmaceuticals on the market, 37% of small molecule drugs approved between 2015 and 2019 contain at least one fluorine atom, showing a promising future for fluoropharmaceuticals[25]. Similar numbers can be observed for agrochemicals, with a significant jump in the share of fluorinated chemicals in recent years[26].

The first major step in the incorporation of fluorine in bioactive molecules was achieved in 1954, when Field proved that replacing the 9α hydrogen of cortisol with fluorine improved its anti-inflammatory capabilities manyfold [27] Since then, the various effects of the substitution with fluorine or fluorinated functional groups on the properties of drug compounds have been extensively studied, and the number of fluorinated drugs has increased hand in hand with the increased availability of synthetic methods to access these valuable compounds[28]. Fluorine or fluorinated groups can affect a number of parameters (Fig. 3), such as the preferred conformation of the molecule, its pK_a, membrane permeability, binding affinity for enzymatic active sites, metabolic stability and pharmacokinetic properties. These particular properties allow fluorine and fluorinated moieties to act as bioisosteres for a number of pharmaceutically relevant functional groups, with fluorine itself being an isostere of hydrogen[29]. Another key aspect of fluorine substitution is the possibility for radiolabelling, with ^{18}F being one of the most common nuclides used for the synthesis of PET tracers[30]. (Fig. 3).

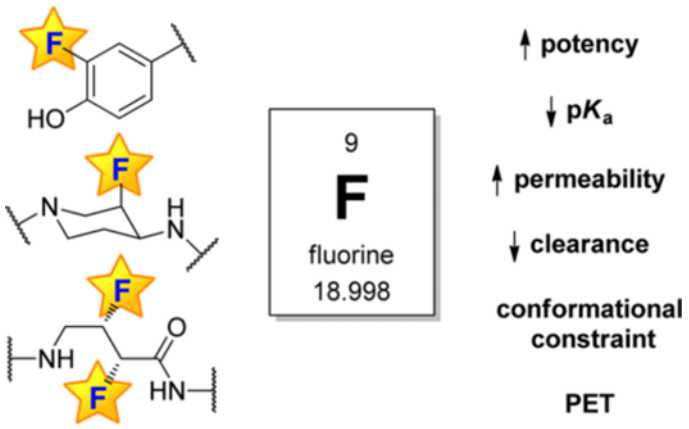
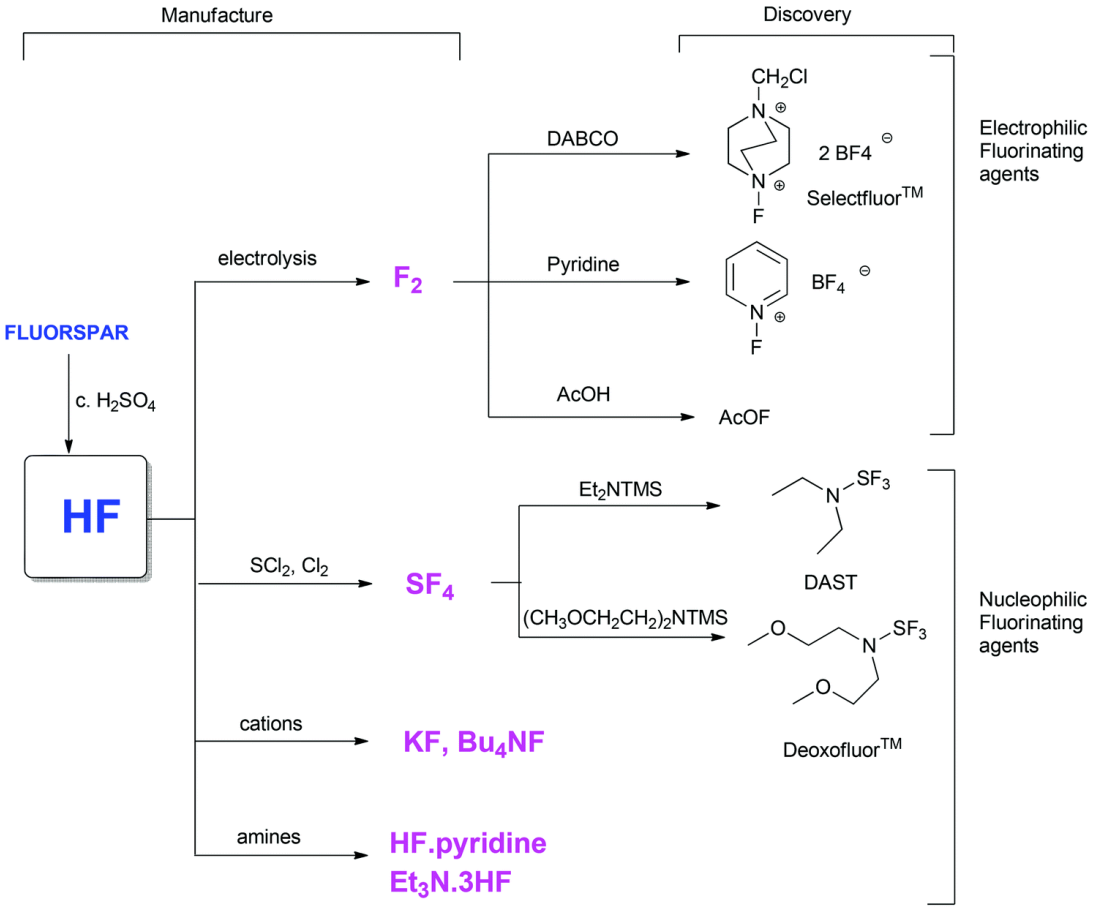


Fig. 3: Impacts of fluorine substitution on the properties of drug compounds. Reprinted with permission from[28] Copyright © 2015 American Chemical Society.

2 C-F bond formation

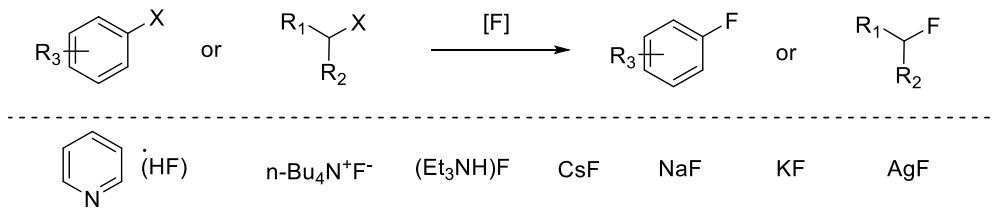
As previously mentioned, a key limiting factor to the development of new fluorinated commercial compounds is the lack, especially in the previous decades, of a reliable, selective and practical way to introduce fluorine and fluorinated functional groups. That's why large efforts were devoted to the development of such methodologies. The two simplest sources of fluorine are HF, derived directly from fluoride-containing minerals extracted in nature via acid treatment, and F_2, obtained via electrolysis of HF. Whilst these chemicals are cheap and widely available, and thus commonly used at an industrial level, they pose several problems in terms of safety and selectivity when employed in a standard research lab. As a result, several new fluorinating reagents have developed in the last decades, that offer improved selectivity and are easier to handle (Scheme 4).



Scheme 4: Bulk chemicals such as HF, F_2, or KF are often employed in the industrial production of fluorinating building blocks, but they don't meet the safety and selectivity requirements to be used in late-stage functionalization reactions, which reagents such as Selectfluor™ or diethylaminosulfur trifluoride (DAST) can offer.[21e] Reproduced from Ref. 21e with permission from the Royal Society of Chemistry.

These fluorinating reagents can broadly be classified as nucleophilic, electrophilic and radical depending on the fashion in which fluorine is introduced.

Nucleophilic reagents, chiefly HF and its salts such as KF, Bu_4NF, HF-Pyridine, or Et_3N-$(HF)_3$, substitute leaving groups, such as (pseudo)halogens on alkyl- or aryl residues (Scheme 5).



Scheme 5: General nucleophilic fluorination reaction with a selection of commonly used fluoride sources.

Another major nucleophilic fluorination reaction is deoxyfluorination, which can be performed by various reagents (Figure 4).

The first reagent to be employed in this reaction was SF_4[31] which, despite displaying an excellent reactivity and being able to deoxyfluorinate alcohols, ketones, aldehydes and carboxylic acids, is however a toxic corrosive gas which cannot be handled on a lab scale without proper equipment. Moreover, SF_4 presents selectivity issues with carbonyl-containing compounds, leading to the formation of fluorinated ether side products[32]. All of these factors led to the development of several related reagents by substitution of one or more fluorine atoms in SF_4, including aminosulfuranes such as DAST, Deoxofluor™ and Xtal-Fluor™, and aryl sulfur trifluorides such as FLUOLEAD™. These reagents are safer and easier to handle than SF_4 and have thus largely superseded it in laboratory procedures. With all of these reagents, the driving force of the reaction is the formation of stable S-O bonds, thus forming a leaving group *in situ* which is then displaced by fluoride, either added from an exogenous source or formed by the reagent itself (Scheme 6)[33]. An important limitation of these reagent is that phenols are not suitable substrates for deoxyfluorination.

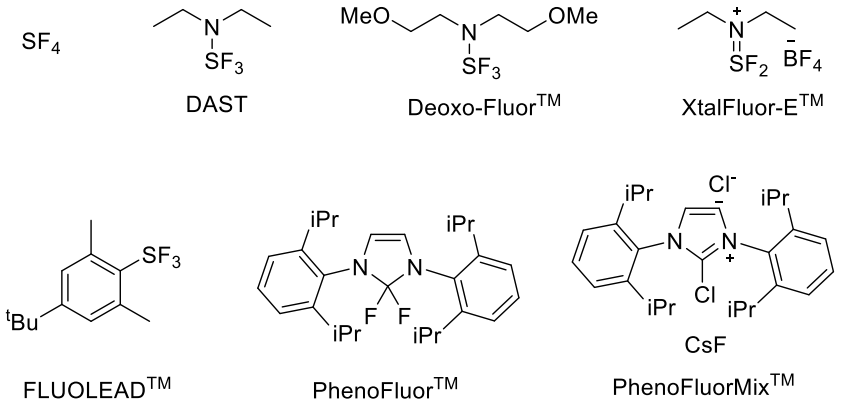
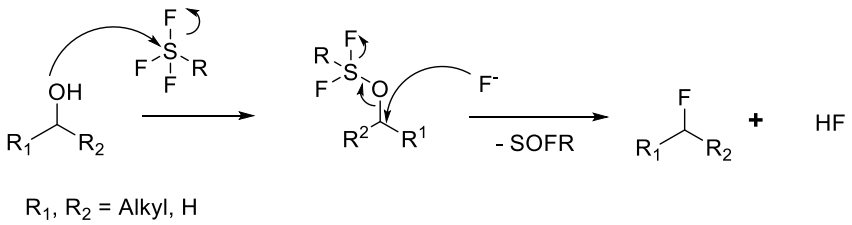
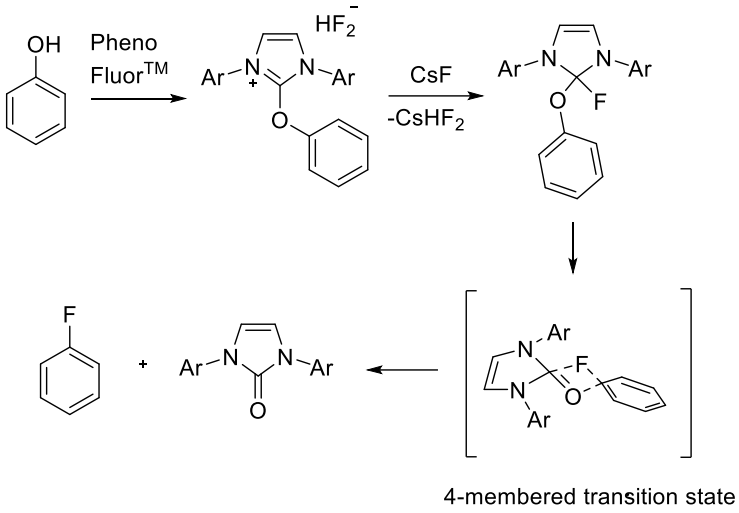


Fig. 4: A selection of commonly used deoxyfluorination reagents.



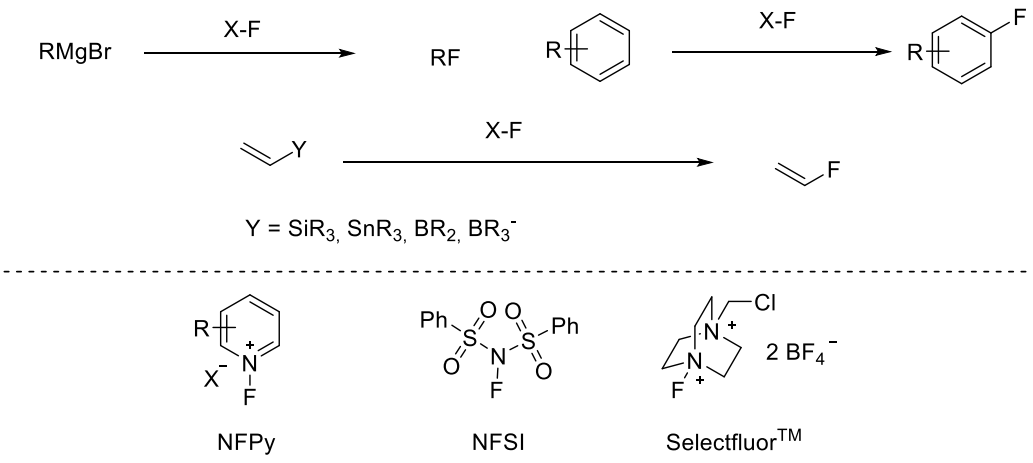
Scheme 6: Mechanism of deoxyfluorination with S-F reagents

This issue was solved with the development of the imidazole-derivatives Phenofluor™ and PhenoFluorMix™, which are capable of performing the deoxyfluorination of phenols via a concerted nucleophilic aromatic substitution. This reaction proceeds via a single four-membered transition state, which avoids the problems associated with conventional S_NAr chemistry (Scheme 7)[34].



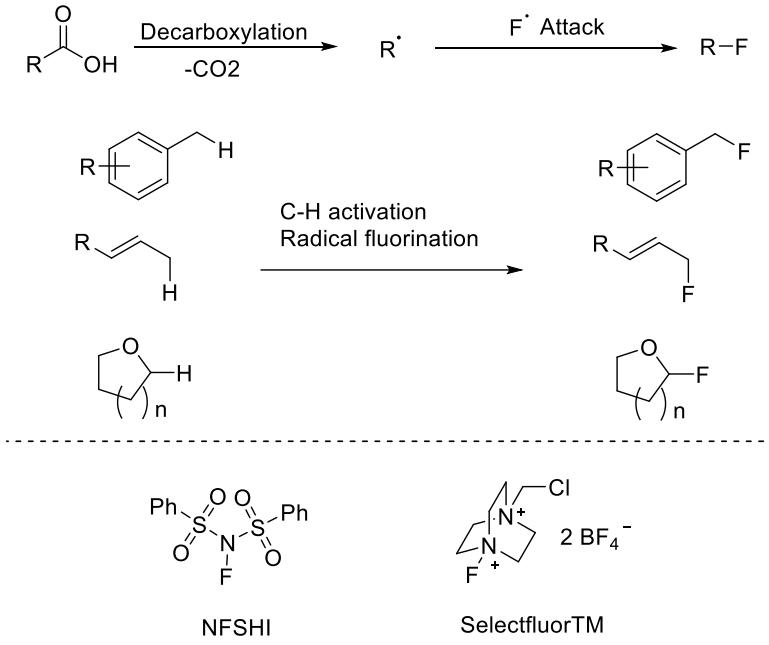
Scheme 7: Proposed mechanism for the deoxyfluorination of phenols with PhenoFluor™.[34a]

Electrophilic fluorination is the other major pathway to access fluorinated derivatives. The archetypal reagent for this reaction class is F_2, which however can only be handled with special equipment and suffers from low selectivity. Older reagents such as O-F reagents (e.g. CF_3OF) suffer from similar limitations, being very reactive and not very stable[35]. A significant breakthrough was represented by the introduction of N-F reagents, which represent a more practical and useful alternative. N-F reagents can be broadly divided into three classes on the basis of their structure: N-Fluoropyridinium derivatives (e.g. NFPy), sulfonyl derivatives (e.g. NFSI) and quaternary ammonium ($R_3NF^+ A^-$) salts (e.g. Selectfluor™). They can be used for the fluorination of a diverse array of nucleophilic substrates such as Grignard reagents, electron-rich arenes, alkenes, and alkynes, or substrates that bear labile and nucleophilic bonds such as silanes, organic stannanes, and boranes[36] (Scheme 8).



Scheme 8: Electrophilic fluorination of carbanions, electron-rich arenes, alkenes, alkynes, silanes, organic stannanes, and boranes together with a selection of suitable reagents.

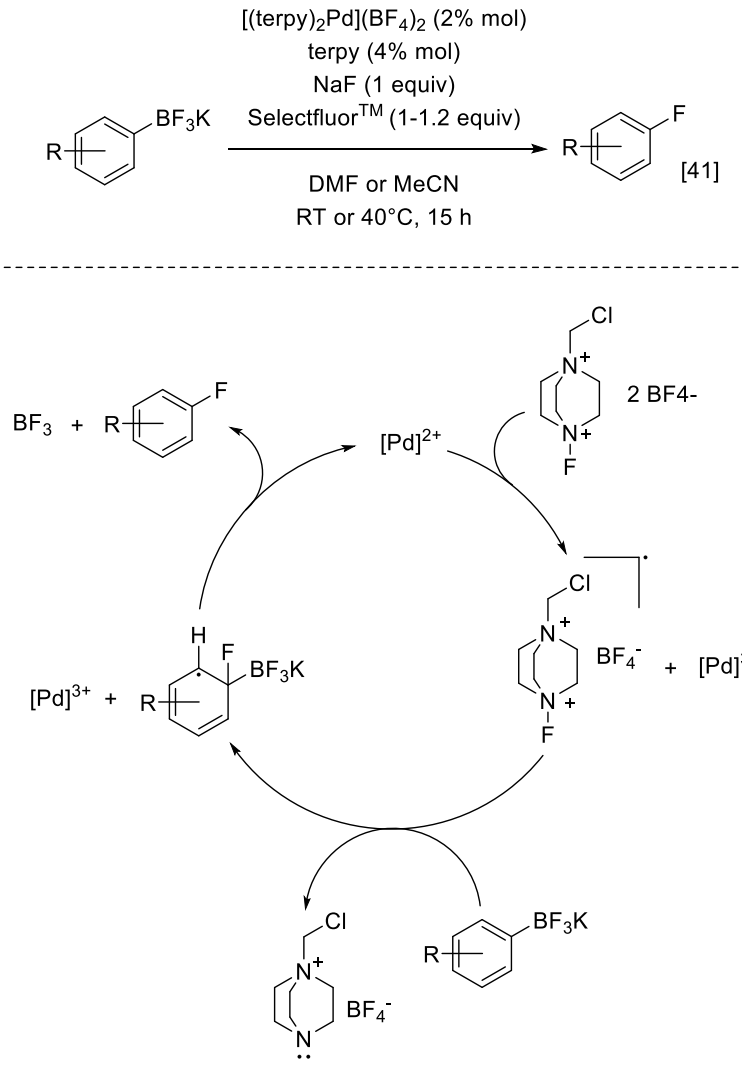
Radical fluorination mostly makes use of reagents developed for electrophilic fluorination[36], such as Selectfluor™ or *N*-fluorobenzenesulfonimide (NFSI). Common methods to generate carbon-centred radicals to couple with radical fluorine include decarboxylation (which can happen either thermally[37] or photocatalytically[38]) and C-H activation of susceptible bonds[39] (such as benzylic, allylic and α to a heteroatom, Scheme 9).



Scheme 9: General radical fluorination via decarboxylation or C-H activation with a selection of radical fluorine sources.

These methodologies are however usually applied to alkyl radicals; aryl radicals being harder to access. For instance, Liu[40] achieved the decarboxylative formation of aryl radicals, which were trapped with Selectfluor™. This methodology is however limited to benzoic acid derivatives bearing a directing group (e.g. -OH, -NH_2) in the *ortho* position.

A different approach was proposed by Ritter[41] with the Pd-catalyzed fluorination of aryl trifluoroborates with Selectfluor™, which according to the authors proceeds through a Pd(II)/Pd(III) catalytic cycle (Scheme 10).



Scheme 10: Palladium-catalyzed radical fluorination of aryl trifluoroborates.

3 The SCF_3 and $SeCF_3$ Groups

3.1 Applications of the SCF_3 group

Aside from fluorine and trifluoromethyl (CF_3), which have been investigated the most and are present in over 80% of fluorine-containing pharmaceuticals[25], other underexplored fluorinated functional groups have recently seen an upsurge in interest. The similar trifluoromethylthio (-SCF_3) and trifluoromethylselenyl ($SeCF_3$) groups are two of them.

Compared to CF_3, XCF_3 groups (X = S, Se) are much more hydrophobic, with a higher lipophilicity but a comparable electron-withdrawing power (Table 1)[42]. The increased lipophilicity can be valuable for the regulation of the kinetic properties of drugs, as well as their increased ability to permeate through membranes[43].

The introduction of these functional group therefore enables the fine-tuning of the properties of pharmaceutical- and agrochemical compounds.

parameter	CF_3	SCF_3	$SeCF_3$
Π	0.88	1.44	1.29
σ_p	0.54	0.50	0.45

Table 1: Hydrophobicity (expressed as the Hansch parameter Π) and electron-withdrawing power (expressed as the Hammett parameter) of CF_3, SCF_3 and $SeCF_3$[42d].

Another relevant property of X-CF_3 groups is their ability to assume unusual conformations: for instance, in Ar-X-CF_3, the X-CF_3 is orthogonal to the aromatic plane, owing to the reduced electronic overlap between the chalcogen and the ring, as well as hyperconjugative interactions between the σ^* orbitals of the C-F bonds and the lone pairs on the chalcogen[21b].

Several -SCF_3 containing molecules are already available on the market, such as Toltrazuril, Tiflorex and Cefazaflur (Fig. 5a). Toltrazuril is a coccidiostatic drug used in animal farming to fight protozoan infections in mammalians and birds[44]. Tiflorex is an anorectic drug, used as an appetite suppressant for obese patients[45]. Cefazaflur is a drug belonging to the cephalosporin family that has bacteriostatic properties[46].

In contrast, the development of -$SeCF_3$ containing bioactive molecules is still in its infancy, with no such molecules being already on the market as of 2022. Despite that, selenium containing bioactive molecules in general are drawing increasing attention on an academic level and trifluoromethylselenylated derivatives are no exception.

In 2019, Tlili and Gampe[47] synthesized the -SCF_3 and -$SeCF_3$ analogs of two -OCF_3-containing drugs: Riluzole, used for the Amyotrophic Lateral Sclerosis (ALS) treatment, and Pretomanid, an antibiotic used in the treatment of tuberculosis. They found that, excluding a significantly higher lipophilicity, the higher chalcogen containing analogs do not differ significantly from the parent molecule in a number of pharmacologically relevant parameters, suggesting that they might act as suitable analogs. Crucially, the selenium-containing molecules did not seem to be less stable or more toxic than the other analogs.

Building on this trend of increased interest in selenium-containing drugs, in two reports in 2020 and 2021, Zhang[48] introduced several $SeCF_3$-containing NSAID derivatives which show promising antitumoral abilities (Fig. 5b).

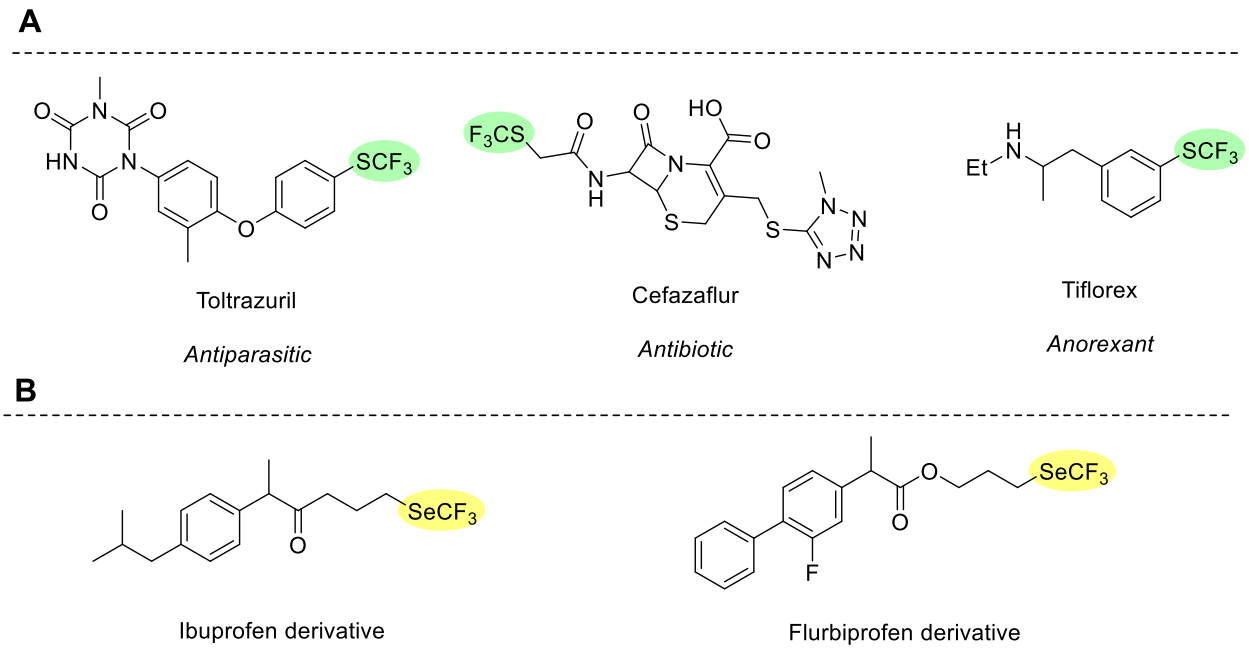


Fig. 5a: Pharmaceuticals that contain the SCF_3^- group: Toltrazuril, Tiflorex, and Cefazaflur. **Fig. 5b:** NSAID derivatives reported by Zhang with antitumoral activity

3.2 Synthesis of Trifluoromethylthiolated Compounds

Because of their similar properties and reactivity, the methods used to obtain -SCF_3 and -$SeCF_3$ are often very similar and will be discussed together. A wide range of direct or indirect methods are known for the introduction of the XCF_3-group into a compound. Indirect methods mostly revolve around the trifluoromethylation of sulfur containing precursors (such as thiols, disulfides or thiocyanates, or the corresponding Se-containing species).

Halogen exchange methodologies from -$SCCl_3$ are also known, however their applicability is limited by the harsh conditions required, low yields and the difficulty of attaining complete halogen exchange[49].

For direct methods, a wide range of nucleophilic, electrophilic and radical trifluoromethylthiolation and -selenylation reagents are available.

3.2.1 Trifluoromethylation of thiols, disulfides and thiocyanates. (And the Se equivalents)

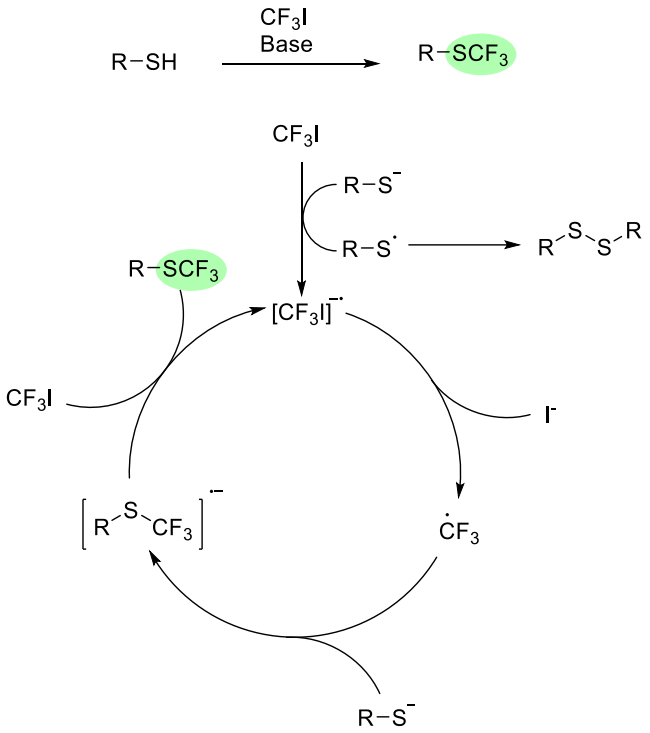
Strategies for the formation of the X-CF_3 bond can be classified as radical and nucleophilic.

Electrophilic *S*- and *Se*-trifluoromethylations seem to be elusive. Despite reports stating that classic electrophilic trifluoromethylating reagents, such as the Togni reagents[50] or the Umemoto reagent[51], are capable of reacting with thiols, the formation of disulfides as side products in these reactions suggest a radical mechanism, which was confirmed by EPR studies in the case of trifluoromethylation with Togni reagents[52]. Considering that Umemoto also reports the formation of disulfides and his reagent is also known to be able to generate CF_3 radicals[53], reactions with this reagent also likely proceeds via a radical mechanism.

The most commonly employed sources of CF_3 radicals are CF_3I and CF_3SO_2Na.

Radical trifluoromethylation with CF_3I under basic conditions has long been established; the first report dating back to the pioneering work of Haszeldine[54] in 1972. The reaction proceeds, in contrast to non-perfluorinated alkyl iodides, via an $S_{RN}1$ mechanism, in which CF_3I is first reduced to its radical anion (usually initiated by SET from the substrate itself), then undergoes mesolysis to release the CF_3 radical, which then attacks the thiolate anion and transfers an electron to another molecule of CF_3I as a part of a radical chain reaction (Scheme 11). An issue with this reaction is the formation of disulfides[55], which leads to lower yields and smaller possible reaction scopes. This issue can be resolved by introducing stoichiometric amounts of reductants, such as tetrakis(dimethylamino)ethylene (TDAE)[56], HCOONa[57] or $Na_2S_2O_4$[58], or using photoredox conditions, such as the $Ru(bpy)_2Cl_2$/TEA system proposed for in flow trifluoromethylation by Noël[59]. The use of a reductant also allows for the direct use of disulfides as starting materials. A noteworthy aspect of radical trifluoromethylation is that it is chemoselective for *S*-trifluoromethylation, being able to tolerate free -OH and -NH_2 groups[55, 57-59].

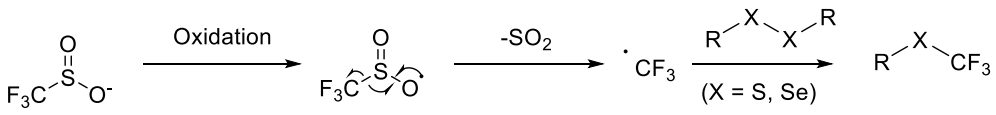
Because of the instability of selenols toward oxidation, diselenides must be reduced *in situ* in order to be trifluoromethylated. Reported examples of amenable reductants include Rongalite[60], TDAE[56] and $NaBH_4$[61].



Scheme. 11: Mechanism of the trifluoromethylation of thiols with CF_3I.

CF_3SO_2Na, also known as the Langlois reagent, is a popular CF_3 radical source under oxidative conditions. The reaction proceeds via oxidation to the CF_3SO_2 radical, which then extrudes SO_2 to generate the CF_3 radical (Scheme 12).

The oxidation can be achieved with stoichiometric oxidants such as I_2O_5[62] or $K_2S_2O_8$[63] at high temperature, as reported by Ma for the addition to disulfides and diselenides, or tBuOOH in the presence of a Cu catalyst[64]. Both thiols and disulfides are suitable substrates for these procedures, as thiols get oxidized *in situ* to disulfides regardless. Diselenides are preferred for Se because of their higher stability. Photocatalytic methods starting from disulfides were reported by Hopkinson[61] using an Ir catalyst, and Singh[65] using eosin Y, both under blue light irradiation. An interesting photocatalyst-free UV-mediated approach was proposed by Wang[66] in which acetone, the solvent, absorbs light and acts as a photooxidant.

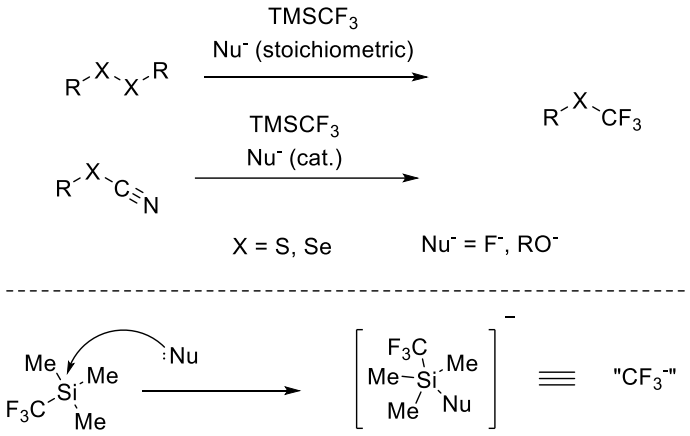


Scheme. 12: Trifluoromethylation of disulfides/diselenides with CF_3SO_2Na

In the field of nucleophilic trifluoromethylation, by far the most widespread reagent is $TMSCF_3$, also known as the Ruppert-Prakash reagent, which is capable of acting as a source of CF_3^- via nucleophilic activation (typically with fluorides or alkoxides).

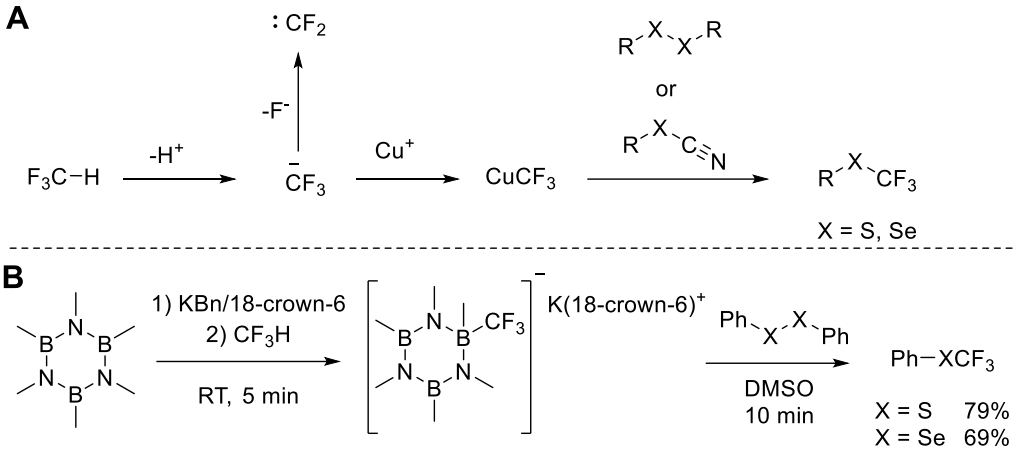
Activators such as TBAF[67], CsF[68] and tBuOLi[69] have all been successfully applied to the nucleophilic trifluormethylation of disulfides and diselenides with $TMSCF_3$ (Scheme 13).

Possible alternative substrates for nucleophilic trifluoromethylation are thio- and selenocyanates. These reagents allow for a broader scope and have the added benefit of requiring catalytic amounts of activator, because the CN^- anion released *in situ* can act as an activator itself. This has led them to be the substrate of choice for nucleophilic trifluoromethylation leading to both $-SCF_3$[70] and $-SeCF_3$[70a, 71] containing compounds. Since KSCN and KSeCN are both cheap, albeit toxic, commercially available salts, they are suitable reagents for one-pot procedures, such as Rueping's[72] method to access aryl trifluoromethylselenides starting from anilines.



Scheme. 13: Trifluoromethylation of disulfides/diselenides and thio- and selenocyanates with $TMSCF_3$, and nucleophilic activation of $TMSCF_3$ via formation of an "-ate" complex.

The desire to develop more atom economical approaches to trifluoromethylation led to the exploration of the reactivity of fluoroform (CF_3H). Fluoroform can be easily deprotonated under basic conditions, but the tendency to eliminate a fluoride to generate difluorocarbene means that the CF_3^- requires stabilization. The most widespread approach is to use a Cu salt with a strong base, which generates $CuCF_3$ *in situ*, which then reacts with the *S*- or *Se*-containing precursor (Scheme 14a). This approach has been successfully employed with disulfides/diselenides[73], thiocyanates[74] and selenocyanates[75]. Alternative approaches to the stabilization of CF_3^- include the use of a borazine reported by Szymczak[76], which is capable of generating a stable CF_3-containing adduct directly from fluoroform, which is suitable for nucleophilic reactions, e.g. with disulfides and diselenides (Scheme 14b).



Scheme. 14a: Copper-catalyzed trifluoromethylation of $(RX)_2$ and RXCN with CF_3H. **Scheme. 14b:** Hexamethylborazine-mediated trifluoromethylation of phenyl disulfide and phenyl diselenide reported by Szymczak.

3.2.2 Direct Trifluoromethylthiolation and trifluoromethylselenylation

Direct methods to introduce $-XCF_3$ onto a diverse range of molecules are of particular interest and have garnered increasing attention in recent years. This has led to the development of novel trifluoromethylthiolating (Fig. 6a) and -selenylating (Fig. 6b) reagents that are more stable and can be employed under milder conditions in comparison to older reagents such as trifluoromethylsulfenyl chloride ($Cl\text{-}SCF_3$) and bis(trifluoromethyl)disulfide ($CF_3S\text{-}SCF_3$), which are highly toxic and volatile gasses.

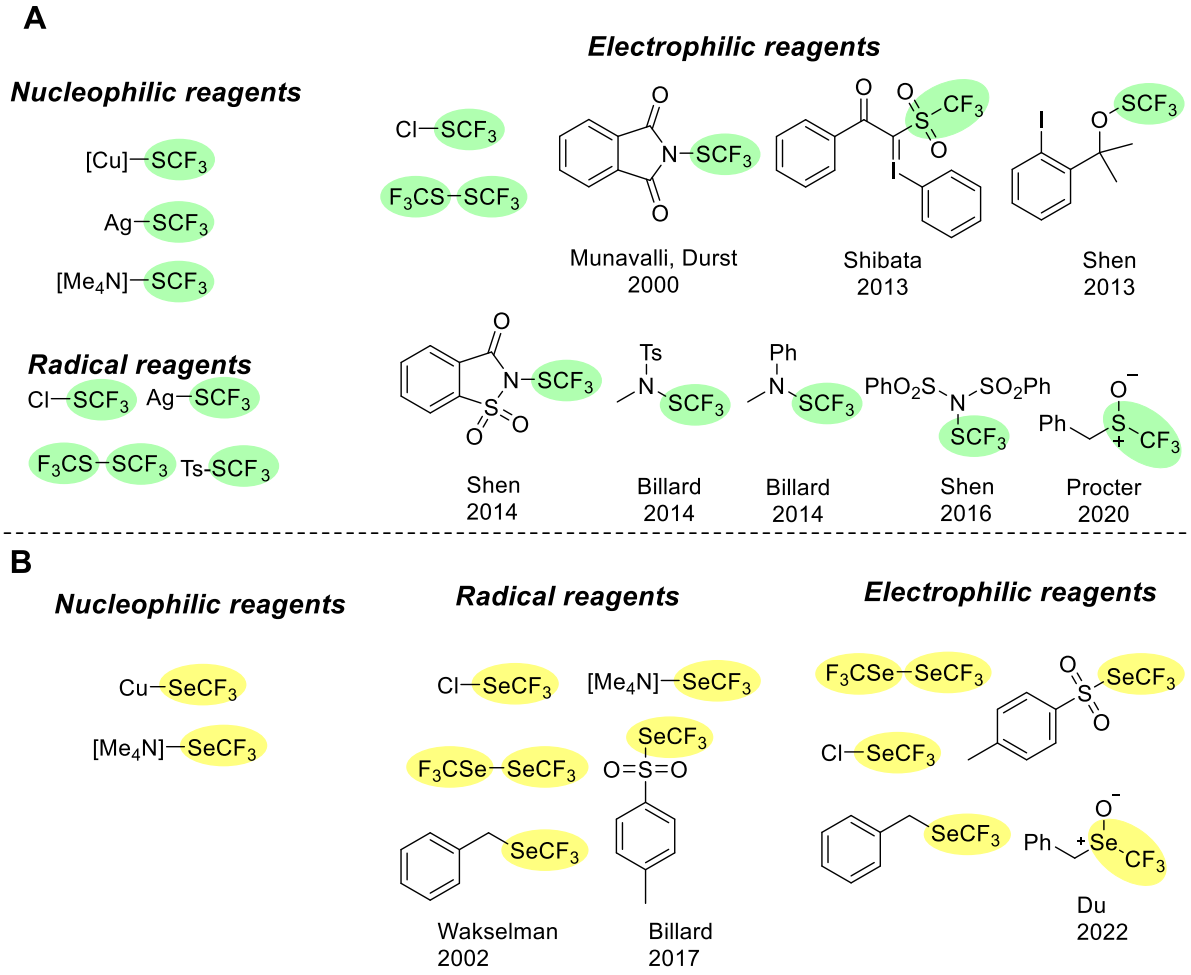
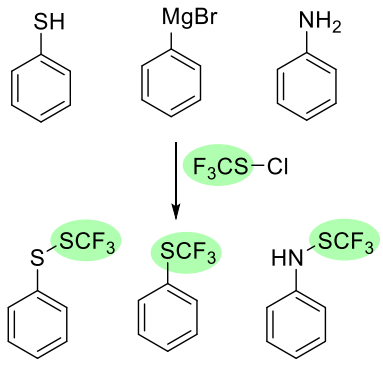


Figure 6a: An overview of electrophilic, nucleophilic and radical trifluoromethylthiolating reagents. **Figure 6b:** An overview over electrophilic, nucleophilic and radical trifluoromethylselenylating reagents.

3.2.3 Electrophilic Trifluoromethylthiolation

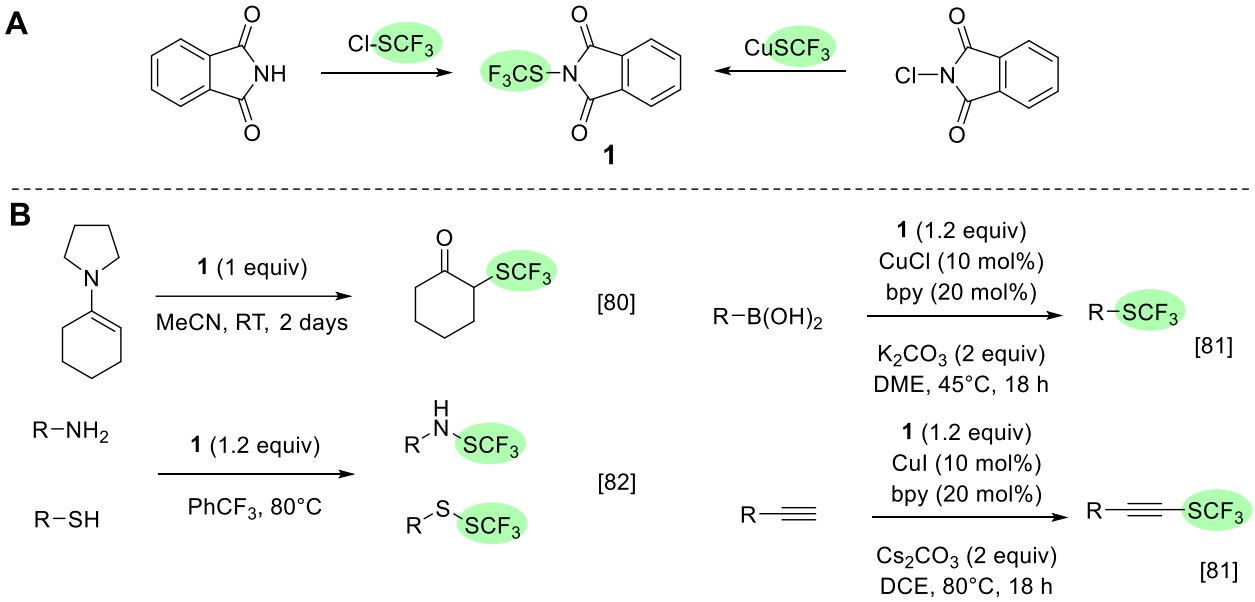
Electrophilic trifluoromethylthiolating and selenylating reagents are largely derived from $ClXCF_3$, the first reagent to be developed in the 1960s. Early reports include the trifluoromethylthiolation of amines and phosphines[77], of Grignard reagents[78] and of thiols[79] (Scheme 15). These reactions are however limited by the difficulty of handling the gaseous $ClXCF_3$ reagent, as well as its low chemoselectivity.



Scheme 15: Trifluoromethylthiolation of selected nucleophiles with $ClSCF_3$

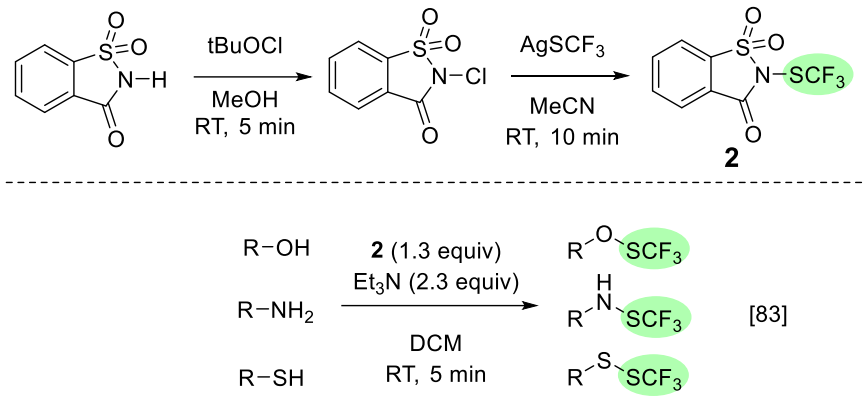
In 2000, Munavalli[80] introduced *N*-trifluoromethylthio phthalimide (**1**) as the first of a new generation of electrophilic trifluoromethylthiolating reagents, obtained by electrophilic trifluoromethylthiolation of potassium phthalimide with $ClSCF_3$. Another synthetic approach, proposed by Rueping[81], involves the nucleophilic trifluoromethythiolation of *N*-chlorophthalimide (Scheme 16a).

Reagent **1** was first employed by Munavalli for the α-trifluoromethylthiolation of enamines[80], and then was later extended to other reactions, such as the copper-catalyzed trifluoromethylthiolation of terminal alkynes and boronic acids[81], as well as the trifluoromethylthiolation[82] of amines and thiols, in which a good chemoselectivity is displayed, for instance selectively trifluoromethylating -NH_2 over -OH groups, and aliphatic amines over anilines. This reagent, however, often requires high temperature or the use of an activator to work effectively (Scheme 16b).



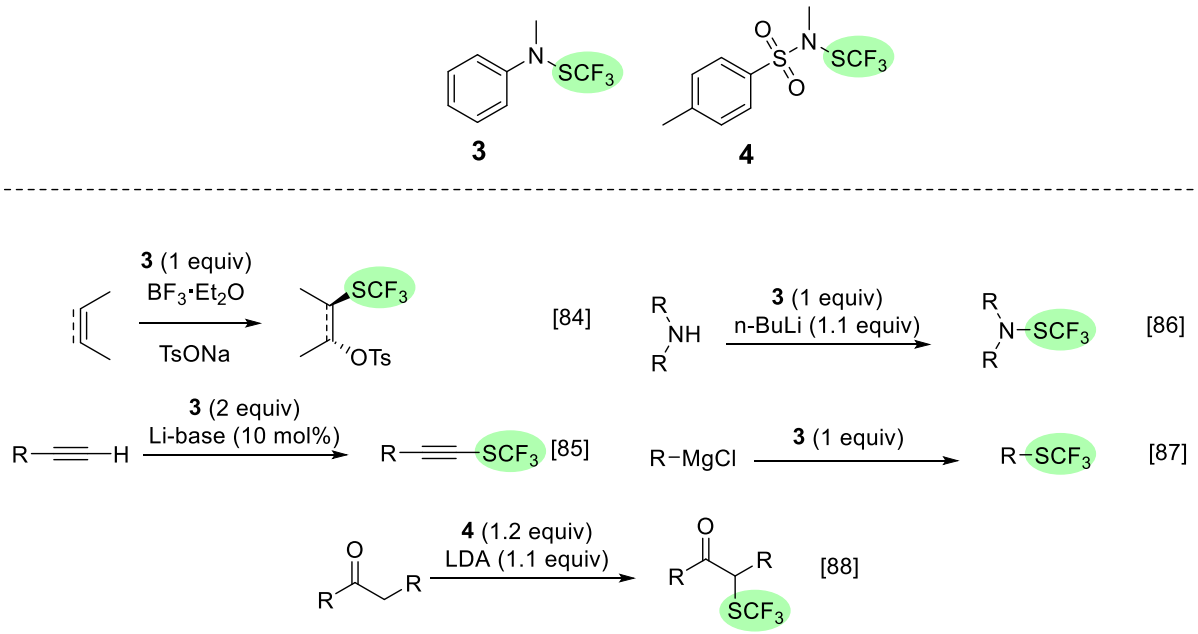
Scheme 16a: Synthesis of reagent **1. Scheme 16b:** Selected trifluoromethylthiolation reactions of nucleophiles with reagent **1**.

In 2014, Shen[83] introduced a related reagent, *N*-(trifluoromethylthio)saccharin (**2**), obtained via nucleophilic trifluoromethylthiolation with $AgSCF_3$ of *N*-chloro-saccharin. In comparison to the phthalimide derivative, reagent **2** is more reactive, albeit less stable. It was applied to the trifluoromethylthiolation of a number of C, N, O and S based nucleophiles (Scheme 17).



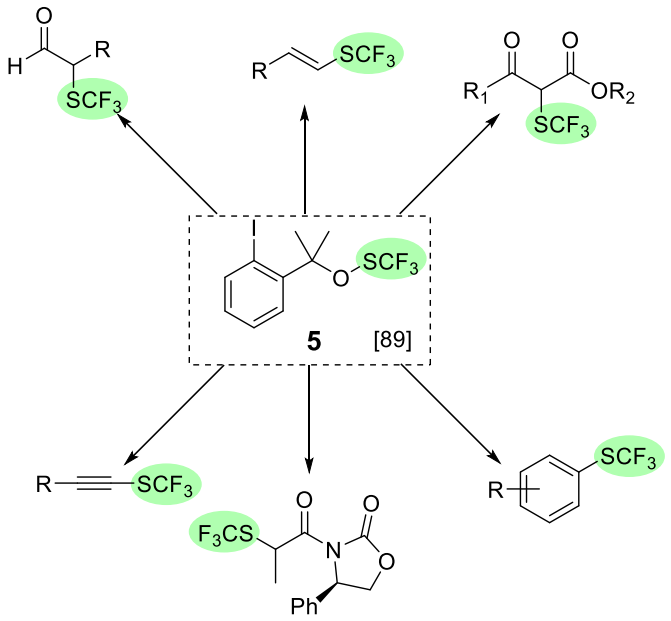
Scheme 17: Synthesis of reagent **2** and its use in selected **t**rifluoromethylthiolation reactions with nucleophiles.

Another pioneer in the field was Billard, who introduced the $PhNMeSCF_3$ (**3**) reagent in 2008. This useful electrophilic trifluoromethylthiolating reagent is capable of functionalizing alkenes[84], terminal alkynes[85], amines[86] and Grignard reagents[87]. This reagent, however, requires activation from either Brønsted or Lewis acids, and exhibited scope limitations, such as the inability to α-trifluoromethylthiolate carbonyl compounds. This issue was resolved with the development of the next generation reagent $TsNMeSCF_3$[88] (**4**) (Scheme 18).



Scheme 18: Electrophilic trifluoromethylthiolating reagents **3** and **4** introduced by Billard, and some selected applications.

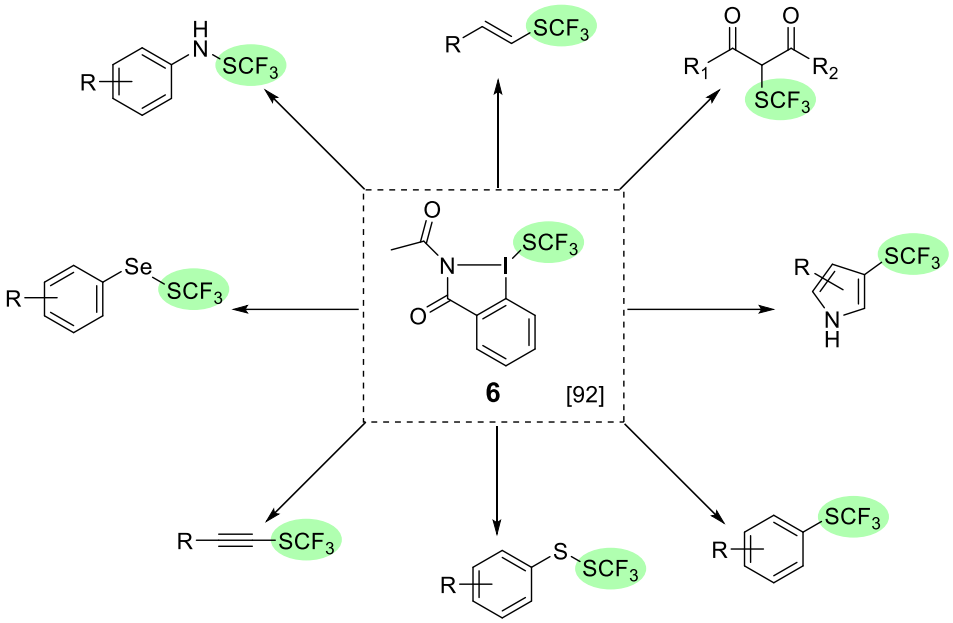
A different class of electrophilic trifluoromethylthiolating reagents is represented by *O*-SCF_3 thioperoxides, such as reagent **5**, introduced by Shen[89], that is capable of efficiently trifluoromethylthiolating a variety of substrates, such as terminal alkynes, aryl and vinyl boronic acids, β-ketoesters, aldehydes and amides (Scheme 19).



Scheme 19: Electrophilic trifluoromethylthiolating reagent **5** and some selected applications.

Initially postulated to be a hypervalent iodine species, analogous to the trifluoromethylating Togni reagent I[50], it was later revealed by Buchwald[90] via crystallographic data that the -SCF_3 is actually bonded to the oxygen atom. Shen later synthesised a large number of structurally diverse thioperoxide-based reagents[91], whose reactivity is largely analogous to the one of reagent **5**, proving that iodine plays no role in its reactivity.

A true hypervalent iodine trifluoromethylthiolating reagent remained elusive until 2020, when Zhang[92] introduced reagent **6**, in which the distal acetyl group on the benziodazole backbone provides the stabilization required via a secondary bonding interaction between an iodine center and the carbonyl oxygen of the acetyl group, as demonstrated via crystallographic analysis. This reagent is capable of acting as an electrophilic source of -SCF_3 for a large number of substrates, including β-dicarbonyl compounds, electron rich (hetero)arenes, boronic acids, sulfinates, amines, selenols and thiols (Scheme 20).

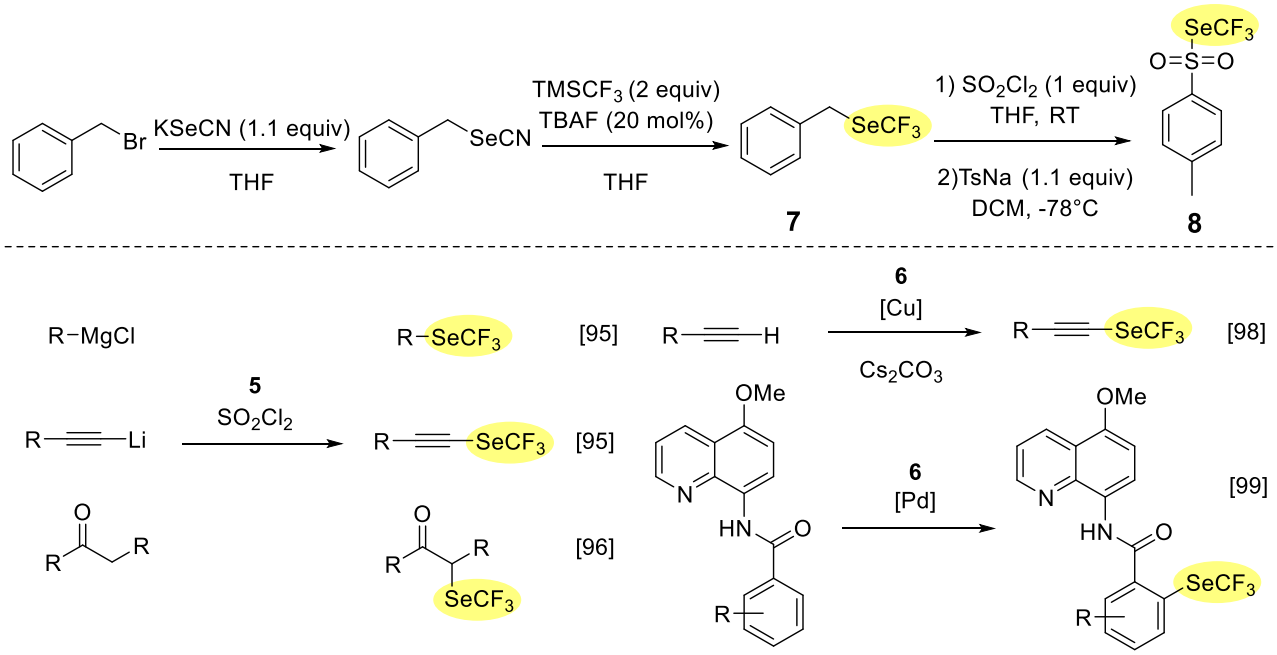


Scheme 20: Electrophilic trifluoromethylthiolating reagent **6** and some selected applications.

Unfortunately, the field of electrophilic trifluoromethylselenylation is much less developed (Scheme 21). Until recently the only reagent available was $ClSeCF_3$, which suffers from much of the same limitations as $ClSCF_3$, being a toxic gas. Despite its limitations, early reports describe its usefulness for reactions such as the trifluoromethylselenylation of amines[93].

The impracticality of these gaseous reagents led to the development of molecules capable of releasing them *in situ*. Wakselman[94] reported the first practical *in situ* synthesis of Cl-$SeCF_3$ via oxidation of $BnSeCF_3$ (**7**) with SO_2Cl_2. This strategy was later greatly built upon by the Billard group, which exploited $BnSeCF_3$ as a practical source of $ClSeCF_3$ *in situ* for a number of important electrophilic trifluoromethylselenylation reactions. Procedures have now been developed for the trifluoromethylselenylation of Grignard reagents[95], terminal alkynes[95] and carbonyl compounds[96].

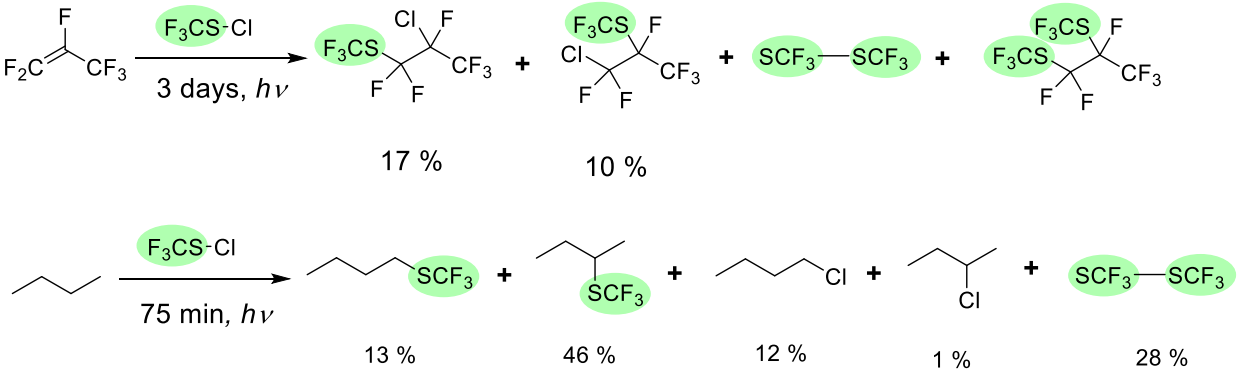
Another electrophilic reagent introduced by the Billard group, derived from $BnSeCF_3$, is $TsSeCF_3$(**8**)[97], obtained via addition of *in situ* generated $ClSeCF_3$ to sodium *p*-tolyl sulfinate. Among its uses as an electrophilic trifluoromethylselenylating reagent are the Cu-catalyzed trifluoromethylselenylation of terminal alkynes[98] and the Pd-catalyzed *ortho*-directed C-H functionalization of 8-aminoquinoline derivatives[99].



Scheme 21: Synthesis and selected applications of electrophilic trifluoromethylselenylating reagents **7** and **8**.

3.2.4 Radical Trifluoromethylthiolation and -selenylation

The first direct radical trifluoromethylthiolation was reported by Harris[100] in 1962 with the trifluoromethylthiolation of alkenes using Cl-SCF_3, followed in 1966 by the trifluoromethylthiolation of alkanes[101]. Aside from the safety concerns, these early UV-mediated radical reactions suffered from low regioselectivity, with dichlorinated, di(trifluoromethylthio)lated and ATRA products being formed as a mixture (Scheme 22). A major side-product of these reactions is the $(CF_3S)_2$ dimer, which likewise can itself act as a trifluoromethylthiolating reagent with alkenes under UV irradiation, as reported by Haran[102].

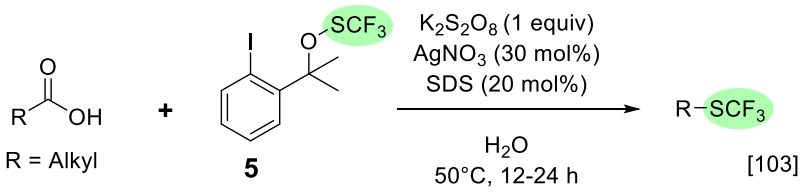


Scheme 22: Radical trifluoromethylthiolation of alkenes and alkanes with $ClSCF_3$ reported by Harris.

More recently, the electrophilic trifluoromethylthiolating reagents discussed in the previous section have found application as sources of SCF_3radicals as well.

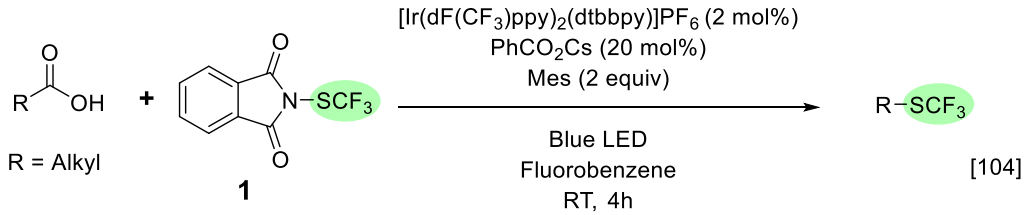
The reaction can proceed through the generation of an alkyl/aryl radical followed by an atom transfer step, or involve the addition of the SCF_3 radical to a suitable substrate.

The first radical trifluoromethylthiolation reaction using electrophilic reagents was reported by Shen[103], using the thioperoxide reagent **5**, developed by his group, as the SCF_3 source and carboxylic acids as the radical source. The reaction proceeds through a silver-catalyzed decarboxylation in the presence of $K_2S_2O_8$ as the oxidant to generate the alkyl radical, followed by the transfer of the SCF_3 group.



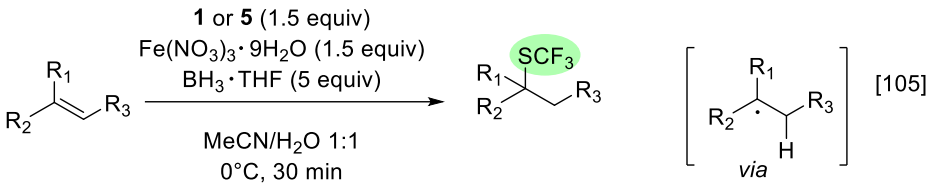
Scheme 23: Decarboxylative trifluoromethylthiolation of alkyl carboxylic acids with reagent **5**.

This procedure led to low yields with alkyl primary carboxylic acids (20-30%). This limitation was overcome by Glorius[104], who disclosed a Ir-catalyzed photoredox decarboxylative trifluoromethylthiolation protocol, using the phthalimide-derived reagent **1**. The strongly oxidating excited state of the photocatalyst $[Ir^{III}(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ is capable of oxidizing the carboxylate, which upon decarboxylation furnished the alkyl radical, which reacts with **1**.



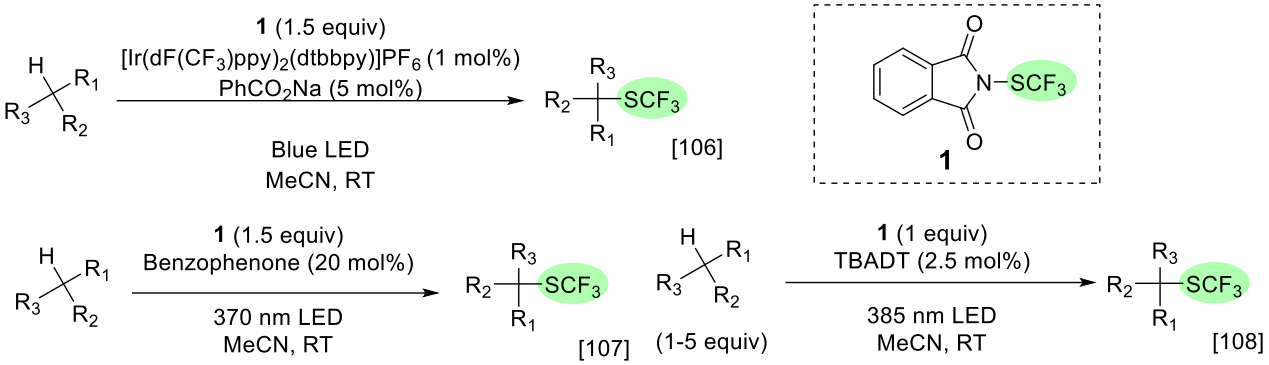
Scheme 24: Decarboxylative trifluoromethylthiolation of alkyl carboxylic acids with reagent **1**.

Another important transformation achievable through an atom transfer mechanism is the hydrotrifluoromethylthiolation of alkenes. Shen[105] developed a Fe-catalyzed protocol capable of functionalizing unactivated alkenes using either phthalimide **1** or thioperoxide **5** as the SCF3 transfer reagent, and BH_3·THF as the hydrogen source. The reaction presents Markovnikov selectivity and proceeds via an alkyl radical intermediate.



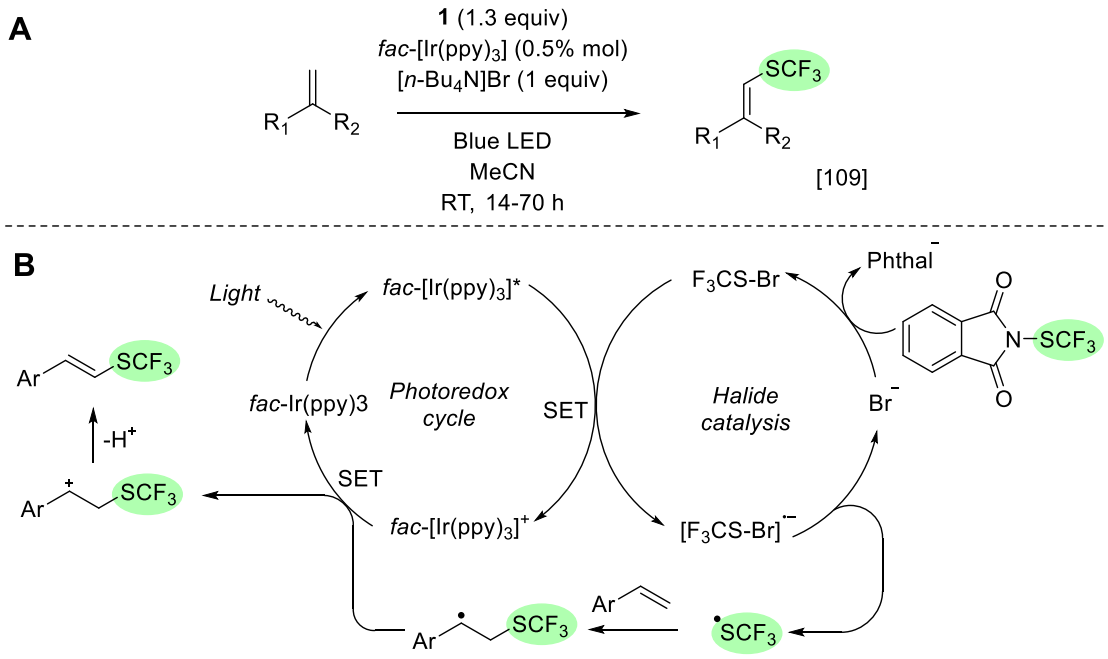
Scheme 25: Radical hydrotrifluoromethylthiolation of alkenes.

A very desirable yet elusive transformation is the direct trifluoromethylthiolation of C(sp^2)-H bonds, which was achieved by Glorius[106] using Phth-SCF_3 (**1**) as the radical trifluoromethylthiolating reagent, and benzoate as HAT catalyst. In this highly selective transformation, methine C-H are directly trifluoromethylthiolated under mild photoredox conditions. Other similar photoredox direct C-H trifluoromethylthiolation reactions were subsequently reported by Britton[107] and König[108].



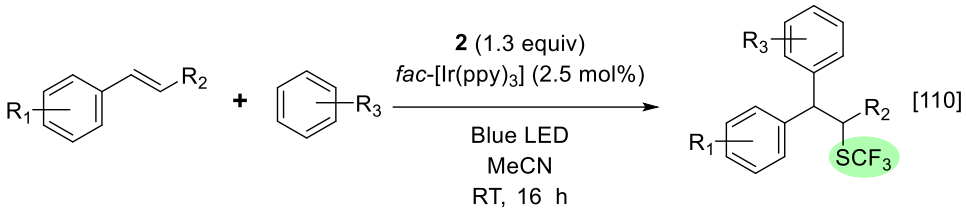
Scheme 26: Radical trifluoromethylthiolation of C(sp^3)-H with reagent **1**.

A different approach is represented by radical addition reactions, in which the SCF_3 adds onto double bonds. In 2016 Glorius and Hopkinson[109] developed a photocatalytic trifluoromethylthiolation protocol for styrenes using phthalimide **1**. [*n*-Bu_4N]Br plays a key role in this reaction, catalytically forming $BrSCF_3$ *in situ*, which acts as the actual SCF_3 radical source. SCF_3 then attacks the alkene, forming a carbon-centered radical, that is then oxidized by the photocatalyst to reform the double bond. Similar conditions could be extended to the cyclization of acrylamides.



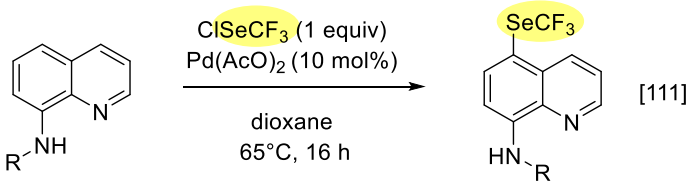
Scheme 27: Radical trifluoromethylthiolation of alkenes.

A similar acrylamide cyclization was achieved by Magnier[110] using an Ir based photocatalyst and saccharine derivative **2** as the trifluoromethylthiolating reagent. In the same work, the addition of electron-rich (hetero)arenes was also reported, allowing for efficient bifunctionalization of alkenes.



Scheme 28: Radical aryltrifluoromethylthiolation of styrenes with reagent **2**.

In a similar fashion to electrophilic trifluoromethylthiolating reagents, electrophilic trifluoromethylselenylating reagents have also found applications as sources of $SeCF_3$ radicals. For instance, the Billard group exploited $BnSeCF_3$ and related $BnSeR_f$ compounds as radical sources in the C-H functionalization of 8-aminoquinolines (Scheme 29)[111].

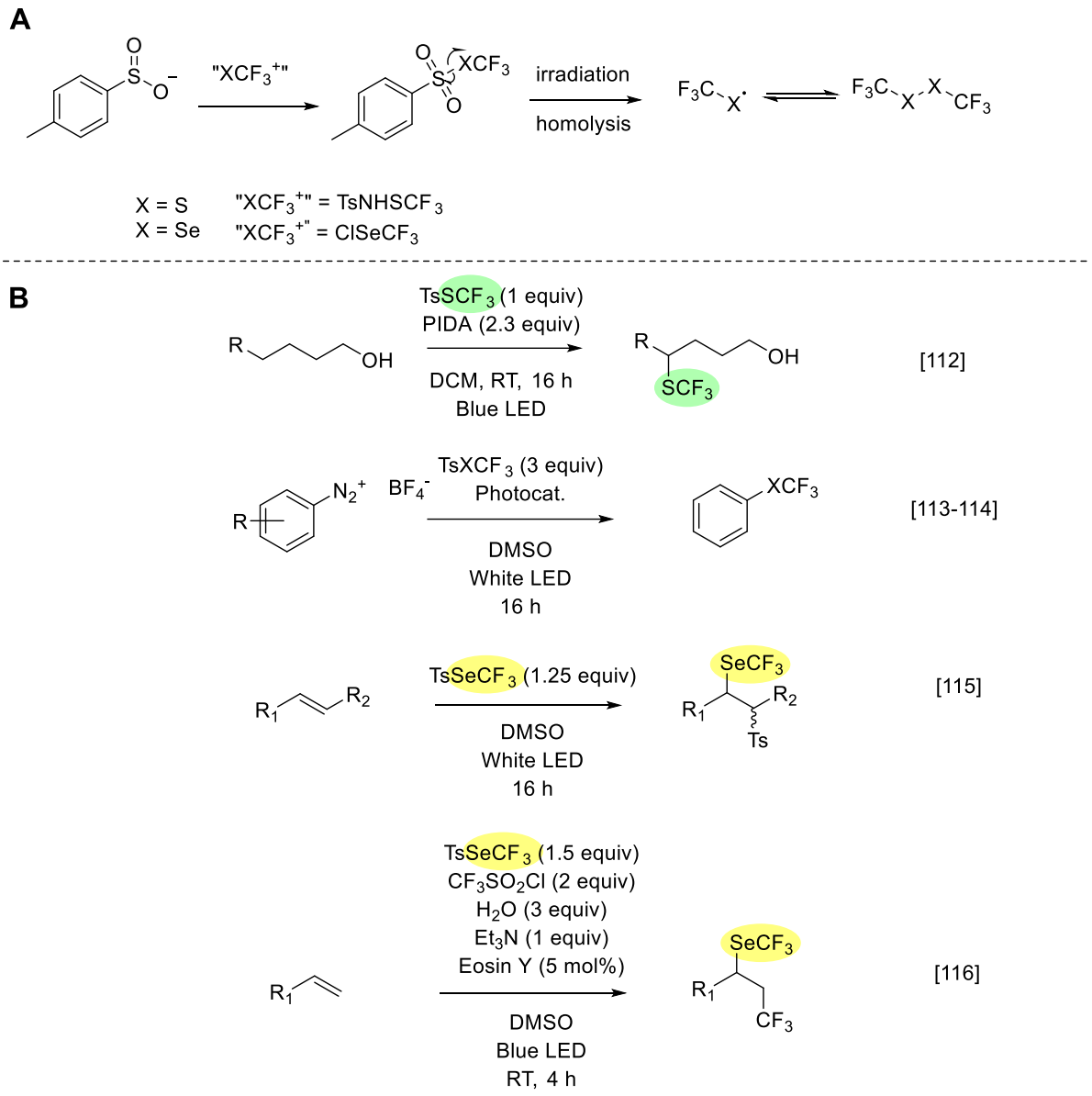


Scheme 29: Regioselective Pd-catalyzed radical trifluoromethylselenylation of 8-aminoquinolines.

A derived reagent, which is also capable of generating XCF_3 radicals is $TsXCF_3$ (X = S, Se), which can act as a XCF_3 radical source under irradiation. This then forms the corresponding $(CF_3X)_2$ dimer *in situ*, which is postulated to be the actual reagent (Scheme 30a).

This versatile reagent has found several applications (Scheme 30b). For instance, $TsSCF_3$ was used by Besset[112] as an SCF_3 radical source in the trifluoromethylthiolation of aliphatic alcohols via 1,5-HAT. The reaction starts with the formation of a dialkoxyiodobenzene intermediate, which undergoes homolytic photolysis to generate the alkoxy radical *in situ*, which then abstracts the 4-hydrogen atom generating a *C*-centered radical, that couples with the SCF_3 radical.

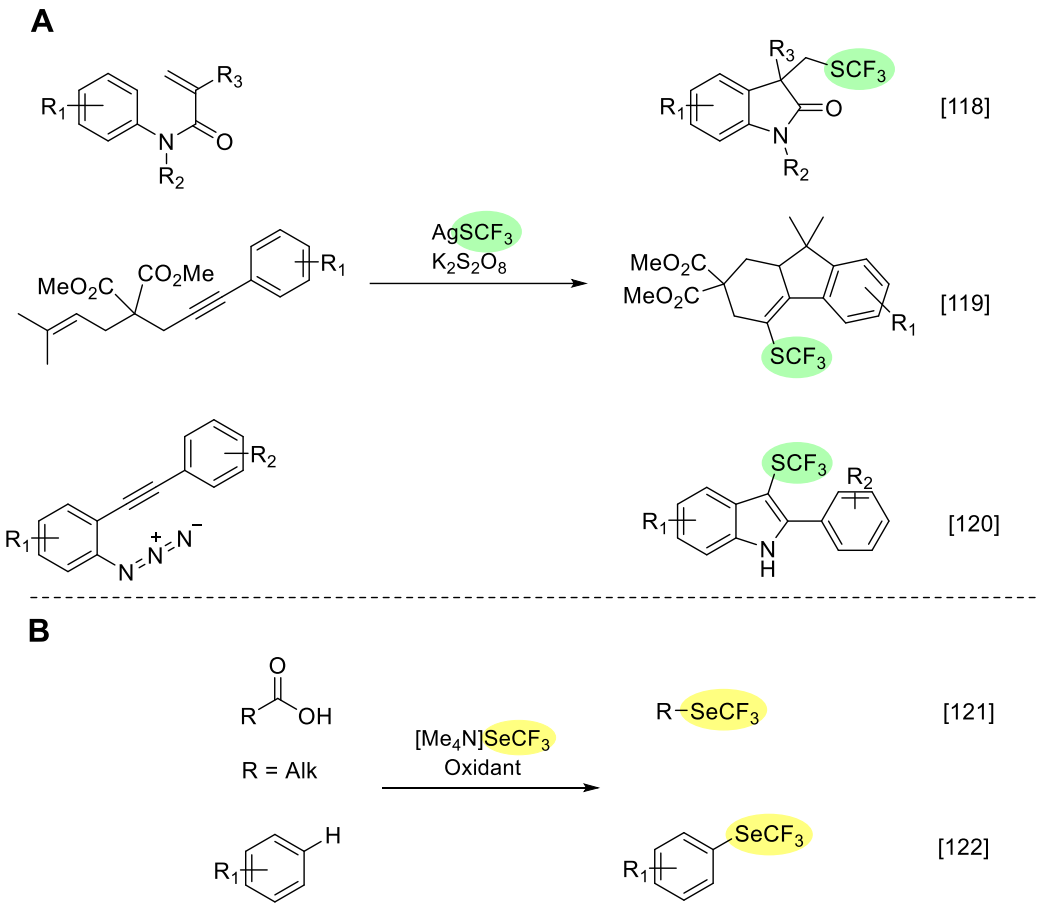
Another example is the photocatalytic trifluoromethylthiolation of aryl diazonium salts reported by Tlili[113], in which the diazonium salt is reduced by the photocatalyst, releases N_2 to generate an aryl radical and then reacts with the *in situ*-generated $(CF_3S)_2$ dimer to form the product. An analogous reaction could be performed with the *Se*-containing $TsSeCF_3$ reagent[114]. The same reagent could be used in the trifluoromethylselenylation of alkenes and alkynes[115], in which the reagent adds across the multiple bond in an ATRA fashion. A similar addition to alkenes was reported by Xu[116], in which the trifluoromethylselenylation is combined with the addition of various radicals (such as CF_3 generated from CF_3SO_2Cl) across the double bond.



Scheme 30a: Synthesis and activation of the $TsSeCF_3$ reagent. **Scheme 30b:** Selected radical reactions with $TsXCF_3$.

In an interesting work from Lu[117], $TsSCF_3$ is activated by AgF, forming $AgSCF_3$ *in situ,* which then gets oxidized by persulfate to generate the SCF_3 radical, that is finally trapped by an acrylamide. Oxidation with stoichiometric oxidants of SCF_3^-/$SeCF_3^-$ anions is in fact quite a common strategy to access the corresponding radicals (Scheme 31a), for instance this strategy has been applied to $AgSCF_3$ to obtain SCF_3 radicals for several reactions, such as addition to acrylamides[118], 1,6-enyne cyclization[119] and the synthesis of indoles[120].

With $[Me_4N]SeCF_3$, the most commonly employed $SeCF_3^-$ source, other examples were reported (Scheme 31b), such as the decarboxylative trifluoromethylselenylation of aliphatic acids[121] and C-H functionalization of electron-rich (hetero)arenes[122].

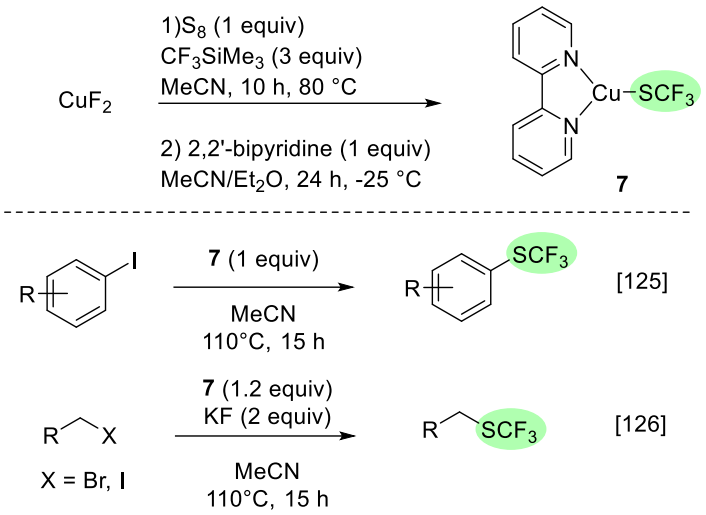


Scheme 31a: Selected radical reactions with $AgSCF_3$ **Scheme 31b:** Selected reported radical reactions with $[Me_4N]SeCF_3$

3.2.5 Nucleophilic Trifluoromethylthiolation

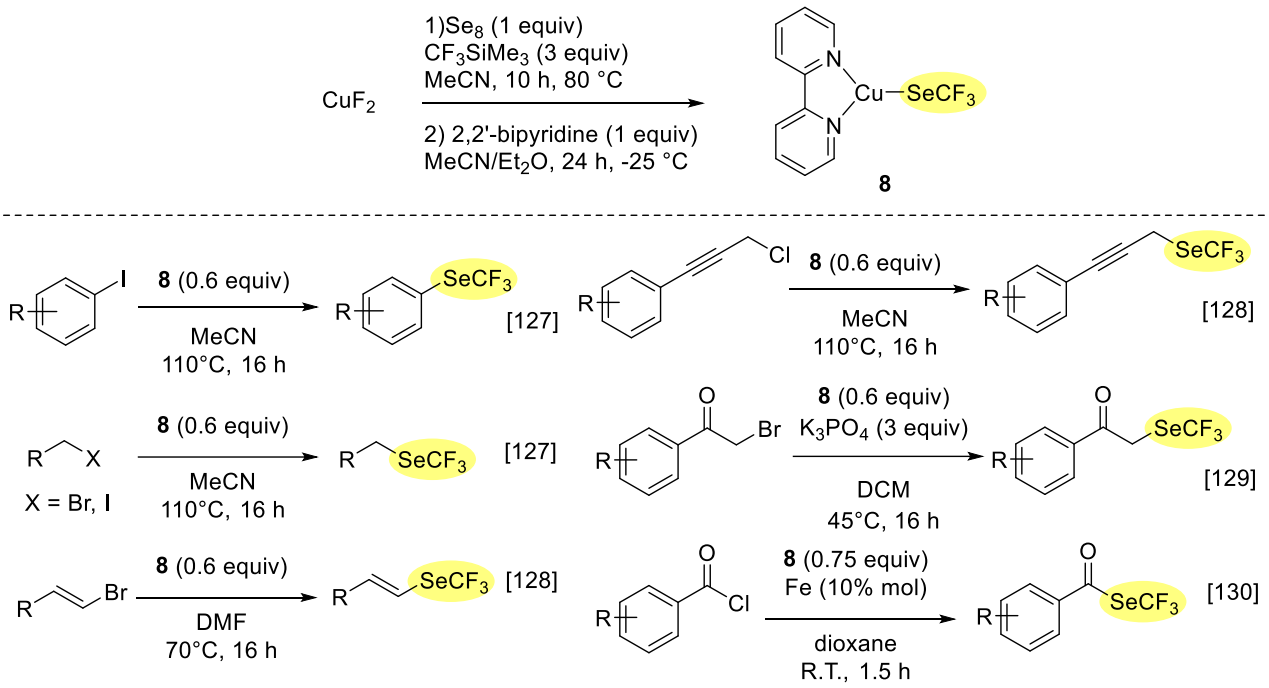
In spite of the availability of a variety of $MXCF_3$ salts capable of acting as sources of $^-XCF_3$ anions (such as $Hg(XCF_3)_2$[93, 123], $CsXCF_3$[124]), the cations of choice used by most works in the literature are Cu, Ag and $[NMe_4]$, because of their ability to efficiently stabilize the ions, which are otherwise prone to β-fluoride elimination.

Cu-XCF_3 has long remained underexplored in comparison to their TMA and Ag counterparts, because of their ill-defined structure. For instance, Weng[125] reported the formation of $[Cu]SCF_3$ complexes *in situ* from $TMSCF_3$, S_8, CuI and either 2,2'-bipyridine (bpy) or 1,10-phenanthroline (phen). It was observed that, whilst in the presence of bpy, a monomeric complex (**7**) was obtained, with phen, a less reactive dimer was obtained. Both complexes were capable of installing the -SCF_3 group onto aryl iodides and bromides. The authors propose a Cu(I)/Cu(III) oxidative addition/reductive elimination cross coupling pathway. The same group later used reagent **7** for the trifluoromethylthiolation of alkyl halides[126]. In this case, the reaction is postulated to proceed via an S_N2 mechanism (Scheme 32).



Scheme 32: Synthesis of copper complex **7** introduced by Weng and some selected applications.

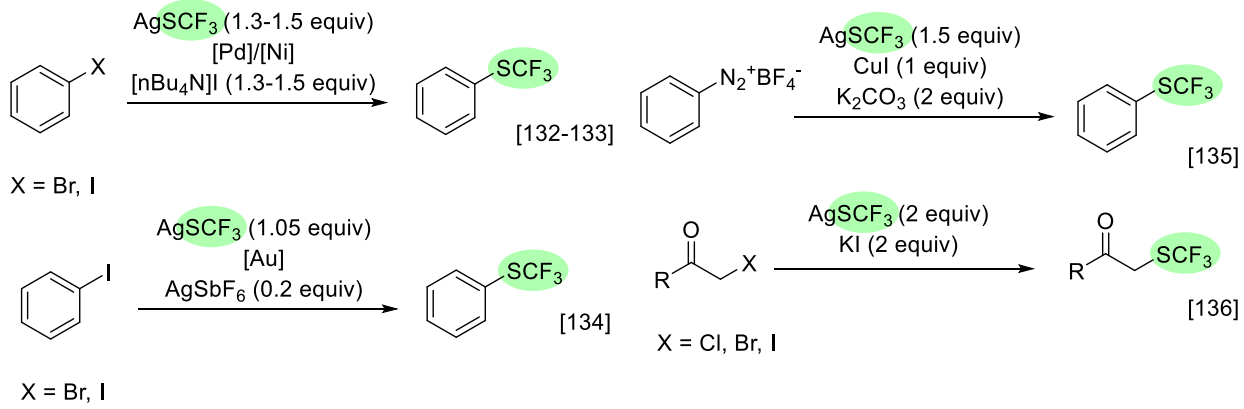
Weng later extended this methodology to the corresponding *Se*-containing complex, obtaining the analogous $[bpyCuSeCF_3]_2$ species (**8**); although with selenium, the monomeric and dimeric forms were formed in an equilibrium in an almost equal amount. Complex **8** was used for the trifluoromethylselenylation of aryl and alkyl halides[127], propargyl and vinyl halides[128] and α-haloketones[129] (Scheme 33). The mechanism is not radical in nature, and is postulated to involve Cu(I)/Cu(III) cross coupling. Another interesting application of complex **8** is the Fe-catalyzed trifluoromethylselenylation of acid chlorides to obtain trifluoromethylselenoesters.[130]



Scheme 33: Synthesis of copper complex **8** introduced by Weng and some selected applications.

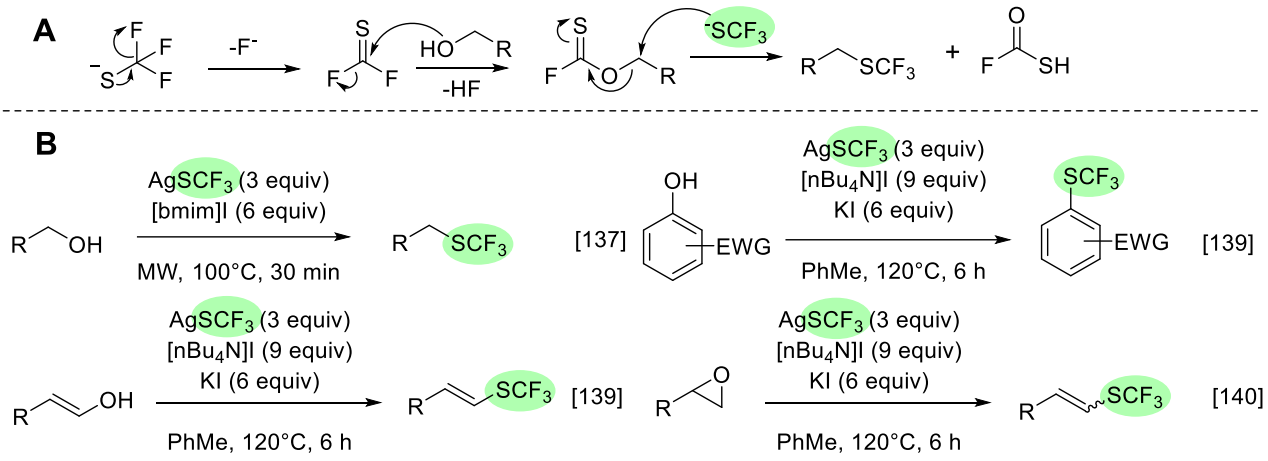
$AgSCF_3$ is by far the most used nucleophilic trifluoromethylthiolating reagent (Scheme 34). First prepared by Man[131] in 1959 via metathesis from $Hg(SCF_3)_2$ and $AgNO_3$, it has been used in many nucleophilic trifluoromethylthiolation reactions.

For instance, $AgSCF_3$ was used in trifluoromethylthiolative cross coupling reactions, such as Buchwald's[132] Pd-catalyzed cross coupling or Ghosh's[133] Ni-catalyzed trifluoromethylthiolation of aryl iodides. In both cases, the addition of stoichiometric NBu_4I was needed to facilitate the transmetalation step by generating a silver "-ate" complex, thus increasing its nucleophilicity. In contrast, the Au-catalyzed cross coupling proposed by Lu[134] only requires catalytic $AgSbF_6$ as an activator and has a broader scope, being also able to functionalize alkenyl and alkynyl halides. $AgSCF_3$ can also be a source of $^-SCF_3$ in Sandmeyer reactions[135] and the trifluoromethylthiolation of α-haloketones[136].



Scheme 34: Selected applications of $AgSCF_3$ as a nucleophilic reagent.

A deoxytrifluoromethylthiolation of alcohols was introduced by Magnier[137] using excess $AgSCF_3$. An equivalent of SCF_3^- undergoes β-fluoride elimination to generate difluorothiophosgene, that gets attacked by the alcohol, forming a carbonofluorothioate, which acts as a leaving group in a nucleophilic substitution with another equivalent of $AgSCF_3$ to yield the $RSCF_3$ product (Scheme 35a). This mechanism was originally proposed by Billard[138]. In his work, the SCF_3^- anion was generated from the electrophilic reagent $TsN(Me)SCF_3$ via nucleophilic activation with $[NBu_4]I$. Similar deoxytrifluoromethylthiolation reactions have been reported with vinyl alcohols and electron deficient arenes[139], and epoxides[140](Scheme 35b).



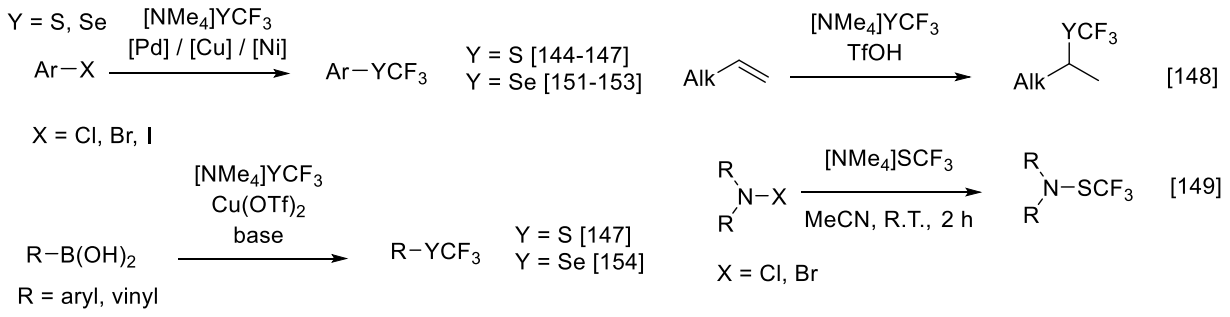
Scheme 35a: Deoxytrifluoromethylthiolation mechanism with $AgSCF_3$ **Scheme 35b:** Selected examples of deoxytrifluoromethylthiolation reactions with $AgSCF_3$.

$AgSeCF_3$, despite being known since the 1980s[141], has seen very limited usage, mostly because of its lower nucleophilicity; for instance it is unable to react with aryl iodides under the conditions used for $AgSCF_3$[142].

$[NMe_4]SCF_3$ can be easily obtained from $[NMe_4]F$, S_8 and $TMSCF_3$ under anhydrous conditions. It is generally less stable than the more popular $AgSCF_3$[143], but it is cheaper and is metal-free. It has recently been exploited as a source of SCF_3^- in numerous transformations, such as in Pd-[144], Cu-[145] and Ni-catalyzed[146] cross couplings with aryl halides, S_N2 reactions with alkyl halides[124a], a Cu-catalyzed cross coupling with aryl boronic acids[147] and hydrotrifluoromethylthiolation of alkenes[148]. It could also be employed as an SCF_3-source in the synthesis of electrophilic N-SCF_3 reagents[149] described in the previous section.

Its higher instability toward β-fluoride elimination in the presence of a base such as Et_3N was exploited by the Schoenebeck[150] group to access the "C=S" synthon, thus synthesizing isothiocyanates and thioureas under mild conditions from anilines. Under the same conditions, $AgSCF_3$ is completely unreactive.

Likewise, $[NMe_4]SeCF_3$ can be obtained from $[NMe_4]F$, Se_8 and $TMSCF_3$[151], and can perform analogous reactions (e.g. Pd[152]/Ni[153]/Cu[151] -catalyzed cross coupling with aryl halides, S_N2 reactions with alkyl halides and cross coupling with boronic acids[154]).



Scheme 36: Selected applications of $[Me_4N]SCF_3$ and $[Me_4N]SeCF_3$ as a nucleophilic reagent.

4. The CF_2H group

4.1 Properties

Unlike the more widely employed trifluoromethyl moiety and its derived XCF_3 functional groups (X = S, Se, O), the difluoromethyl group ($-CF_2H$) remains relatively underexplored in terms of representation in newly marketed bioactive molecules.

This emerging fluorinated functional group has recently drawn a great amount of interest[155] because of its ability to fine-tune the physico-chemical properties of the molecules in which it is introduced.

Despite what is commonly assumed of fluorinated functional groups, the introduction of a difluoromethyl group does not always result in an increased lipophilicity. For instance, for $R-CF_2H$ compounds in which R is an alkyl or aryl group, the lipophilicity is lower than the corresponding non-fluorinated derivatives, whilst the replacement of the methyl group with a difluoromethyl group leads to an increased lipophilicity in sulfones, sulfoxides and α-methyl ethers[156].

Another interesting aspect of the $-CF_2H$ group is its tendency to adopt peculiar spatial conformations. Unlike the $-CF_3$ group, which is isotropic along the bonding axis, the $-CF_2H$ is anisotropic, and can thus adopt different orientations. An interesting example of this phenomenon is anisole and its fluorinated derivatives. Whilst in anisole, the $-CH_3$ group is coplanar with the aromatic ring, and in trifluoromethoxy benzene the $C-O-CF_3$ is orthogonal to the aromatic ring, the situation in difluoromethoxy benzene is more complex, with two possible conformations (*endo-endo* and *endo-exo*; *endo* being *gauche* to the C-O-C backbone and thus *antiperiplanar* to the two oxygen sp^3-type lone pair orbitals) that have a different lipophilicity and can easily interconvert depending on the surrounding environment[157] (Fig. 7).

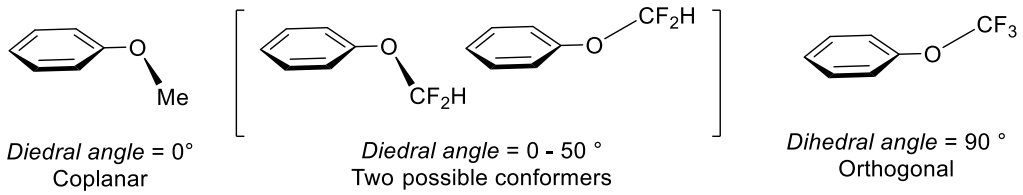


Fig. 7: Conformation of fluorinated anisoles.

The most interesting aspect of the difluoromethyl group however is its ability to engage in hydrogen bonding, acting as a bioisostere of alcohols or thiols in a lipophilic environment.

Multiple studies suggest that the hydrogen bond donor strength is highly dependent on the nature of the atom to which the $-CF_2H$ group is bonded. For instance, Saphier measured the A acidity parameter (HB acidity, the ability of a molecule to act as a hydrogen-bond donor) of a series of $Ar-XCF_2H$ compounds.

Whilst Ar-CF_2H possesses a very weak hydrogen bonding donor strength (A = 0.057), Ar-OCF_2H and Ar-SCF_2H are moderate hydrogen bond donors (A = 0.104 and 0.094 respectively), with a strength comparable to thiophenol (A = 0.12), but far smaller than phenol (A = 0.62)[158].

Despite that, Lippard[159] could obtain and characterize a dimeric crystal structure of *o*-nitro-α,α-difluorotoluene, analogous to the one formed by *o*-nitrophenol (Fig. 8), showing that -CF_2H is nonetheless a viable bioisostere of the -OH group, and could in principle be exploited to design molecules that can disrupt other hydrogen bonding interactions.

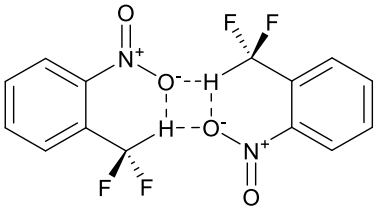
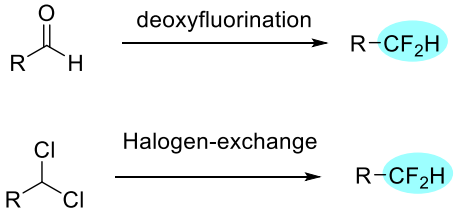


Fig 8: *o*-nitro-α,α-difluorotoluene dimer.

Because of its relevance, several synthetic methods to introduce -CF_2H into a variety of structurally diverse molecules have been developed.

Aside from traditional fluorination approaches (Scheme 37, for further details see chapter 2) such as the deoxyfluorination of aldehydes with deoxyfluorinating reagents, both sulfur-based[160] and others[161], and halogen exchange[49b, 162], a number of direct difluoromethylation approaches have been developed in the last decades. Direct methods are particularly attractive because of their amenability toward late-stage functionalization.



Scheme 37: Traditional indirect strategies for the formation of the -CF_2H group.

These can be broadly divided into three groups depending on which atom is attached to the difluoromethyl moiety: an sp^2-hybridized carbon, an sp^3-hybridized carbon or a heteroatom.

4.2 Synthetic approaches: C(sp^2)-CF_2H

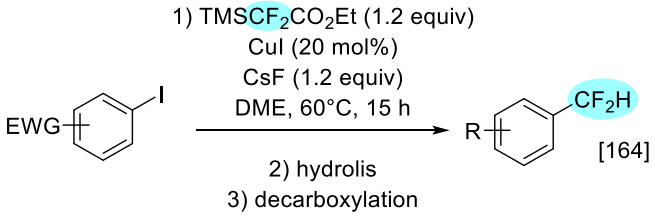
The incorporation of a -CF_2H group into (hetero)arenes is one of the most explored difluoromethylation transformations because several molecules in the drug development pipeline contain this structural motif, owing to its ability to enhance the drug's potency.

One example was offered by Wymann, who demonstrated that the CF_2H group in the mTORC1/2-selective inhibitor PQR620 is capable of engaging in bonding with a Glu residue in mTOR, thus playing a crucial role in achieving a >1000-fold mTOR selectivity over PI3Kα[163].

The -CF_2H moiety can be introduced directly or in a stepwise fashion, starting with the introduction of a -CF_2Y motif followed by a deprotection step.

Copper-based systems are attractive for -CF_2H cross-coupling reactions although these processes are more challenging than the corresponding -CF_3 cross coupling because of the more difficult transmetallation and oxidative addition steps. The reductive elimination step, on the other hand, is easier with -CF_2H than with -CF_3.

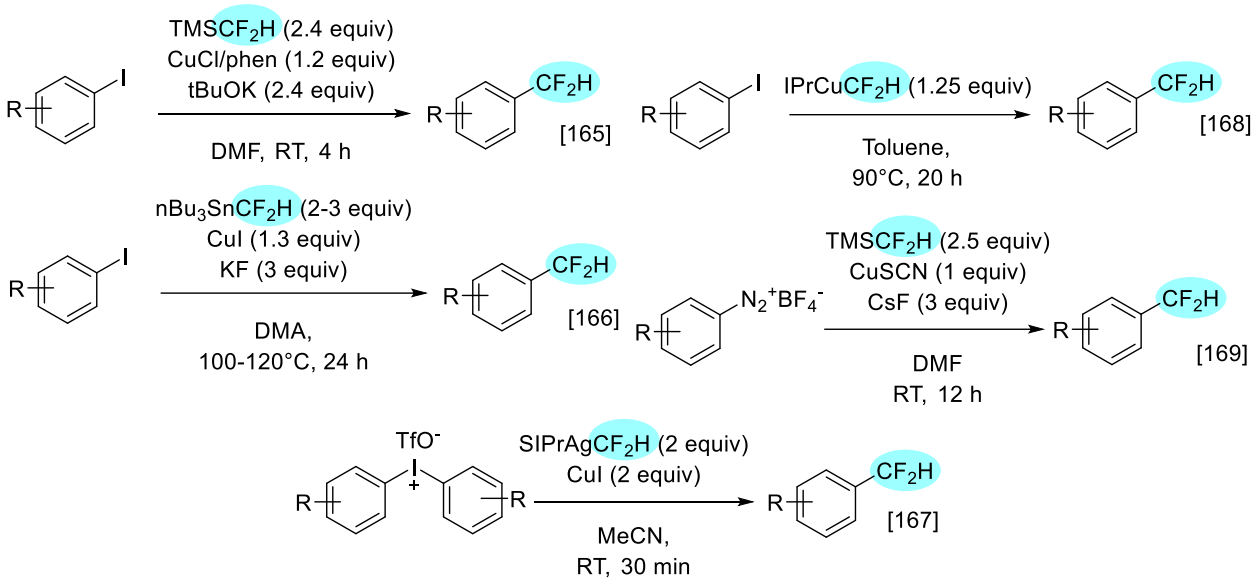
The first copper-mediated difluoromethylation of iodoarenes was reported by Amii[164] in 2011, in which he used an indirect method using $TMSCF_2CO_2Et$ as a source of the -CF_2H moiety. The -CF_2CO_2Et is first installed via cross-coupling, followed by a hydrolysis and a decarboxylation step (Scheme 38).



Scheme 38: Copper-mediated difluoromethylation reported by Amii.

Thereafter, copper-mediated cross coupling protocols to directly install -CF_2H onto iodoarenes (or diaryl iodonium salts) have been developed, using $TMSCF_2H$[165], nBu_3SnCF_2H[166] or silver[167]- and copper[168]-based NHC complexes as difluoromethyl sources.

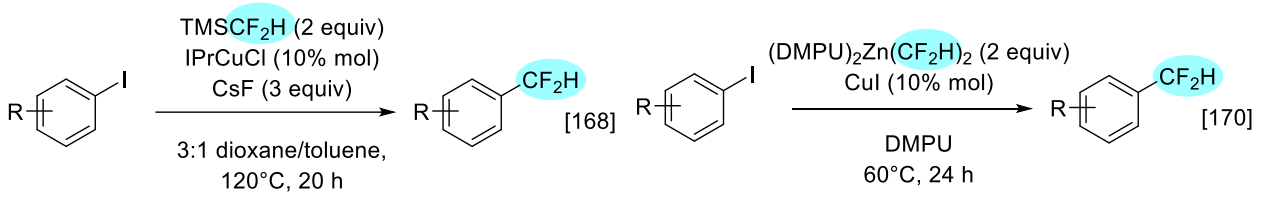
An alternative approach illustrated by Goossen[169] involves Sandmeyer reactions using *in situ*-prepared diazonium salts from anilines as cross coupling partners with $TMSCF_2H$ as the difluoromethyl source.



Scheme 39: Selected copper-mediated difluoromethylation reactions of aryl iodides and diaryl iodonium salts.

All these methodologies however require stoichiometric amounts of copper. One of the hurdles toward the development of catalytic approaches is the instability of the intermediate cuprate species. This problem was first overcome by Mikami[170], who used $(DMPU)_2Zn(CF_2H)_2$ (the Vicic reagent) as a difluoromethyl source in a copper-catalyzed cross coupling with aryl iodides.

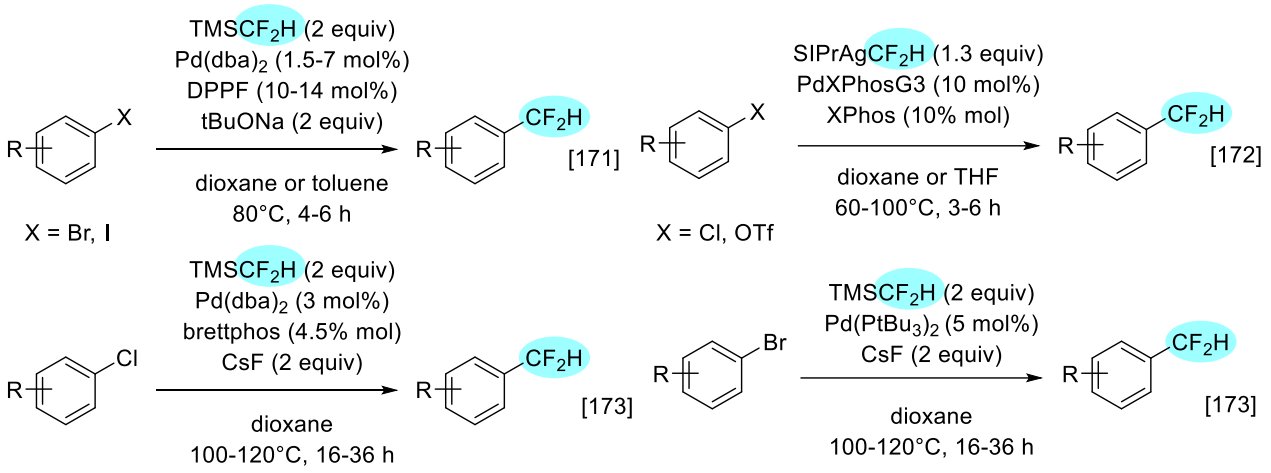
A catalytic procedure using the aforementioned copper-NHC complex generated from a precursor *in situ* was also developed by Sanford.[168].



Scheme 40: Selected copper-catalyzed difluoromethylation reactions of aryl iodides.

Palladium is by far the preferred metal used in difluoromethyl cross couplings (Scheme 41). In comparison to Cu, oxidative addition occurs more readily at Pd^0, but the transmetallation step is slower.

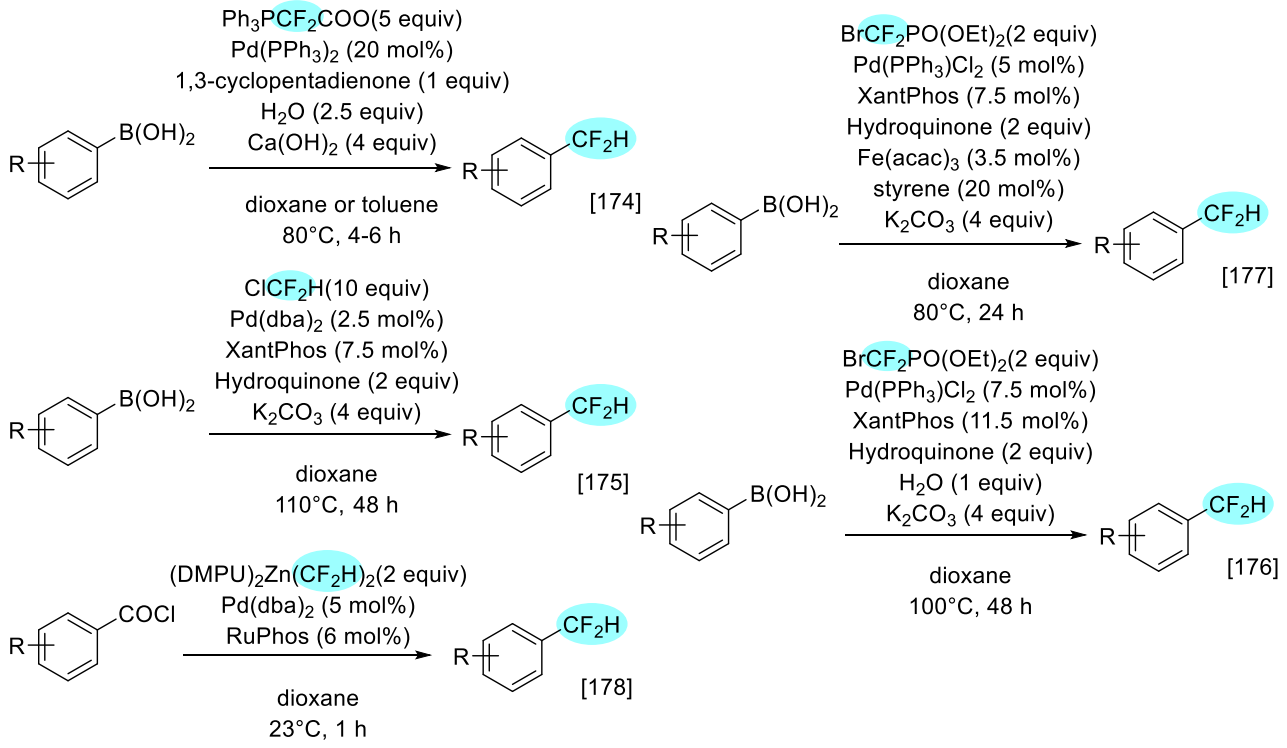
This latter issue was first overcome by Shen[171], who envisioned a cooperative Pd/Ag catalytic system to install -CF_2H onto aryl iodides and bromides. The key [(SIPr)Ag(CF_2H)] reagent is formed *in situ* from $TMSCF_2H$ and [(SIPr)AgCl]. The use of stoichiometric amounts of the NHC-Ag complex allows for a broader scope of coupling partners, such as (hetero)aryl chlorides and triflates[172]. Recently, Sanford developed a similar methodology that does not require any other metal, to directly install -CF_2H onto aryl chlorides and bromides using $TMSCF_2H$[173].



Scheme 41: Selected Pd-catalyzed difluoromethylation of aryl (pseudo)halides

Another potential approach involves the use of difluorocarbene precursors as difluoromethyl sources in the presence of a HAT reagent (such as hydroquinone), to generate a difluorocarbene-metal complex *in situ* ($M{=}CF_2$) (Scheme 42). This strategy is particularly useful with aryl boronic acids, which are desirable substrates because of their commercial availability and synthetic accessibility. Several difluorocarbene sources have been reported, such as PDFA[174], CHF_2Cl[175], $BrCF_2PO(OEt)_2$[176] and $BrCF_2CO_2Et$[177].

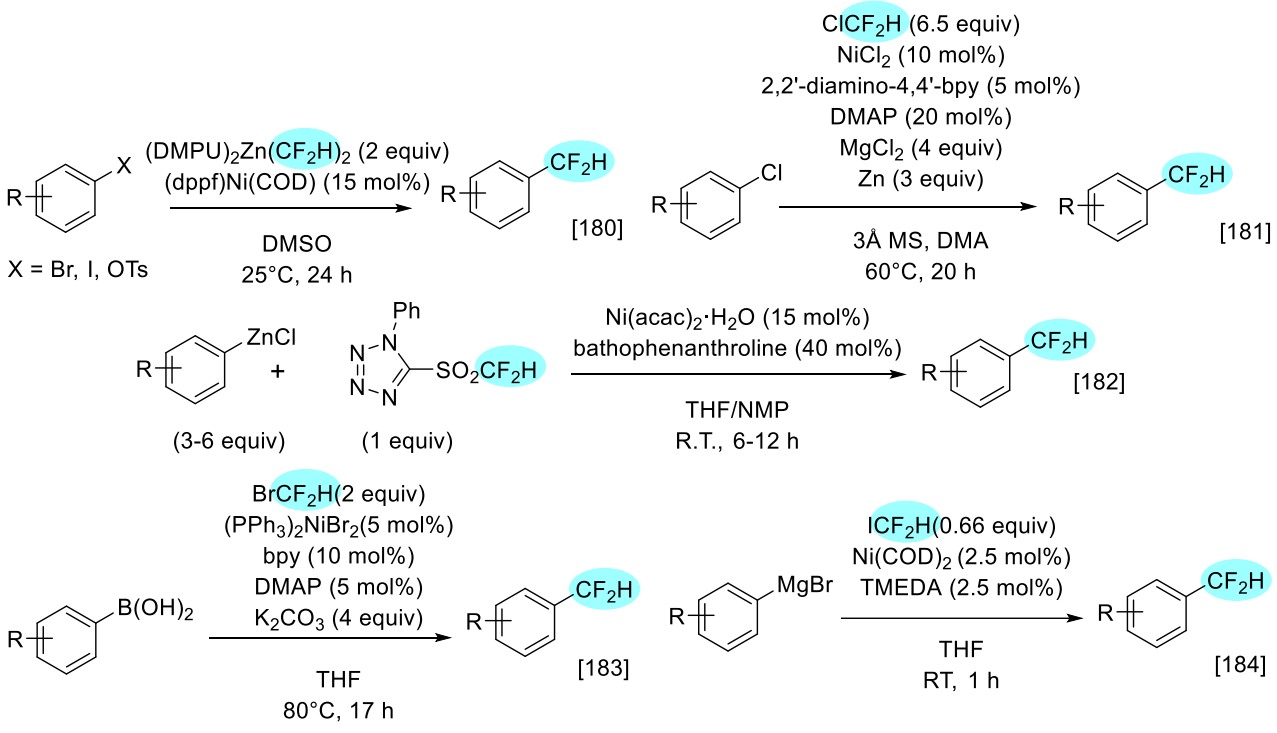
An interesting decarbonylative procedure was proposed by Ritter[178], in which aroyl chlorides act as sources of the aryl moiety with the Vicic reagent being the nucleophilic -CF_2H source.



Scheme 42: Selected Pd-catalyzed difluoromethylation of aryl boronic acids and aroyl chlorides.

A third commonly used metal used in Ar-CF_2H cross coupling reactions is Nickel (Scheme 43). Nickel has a wider range of accessible oxidation states than palladium, enabling both two electron oxidative additions and single electron processes. This results in an easier overall oxidative addition to the metal and an easier transmetallation[179].

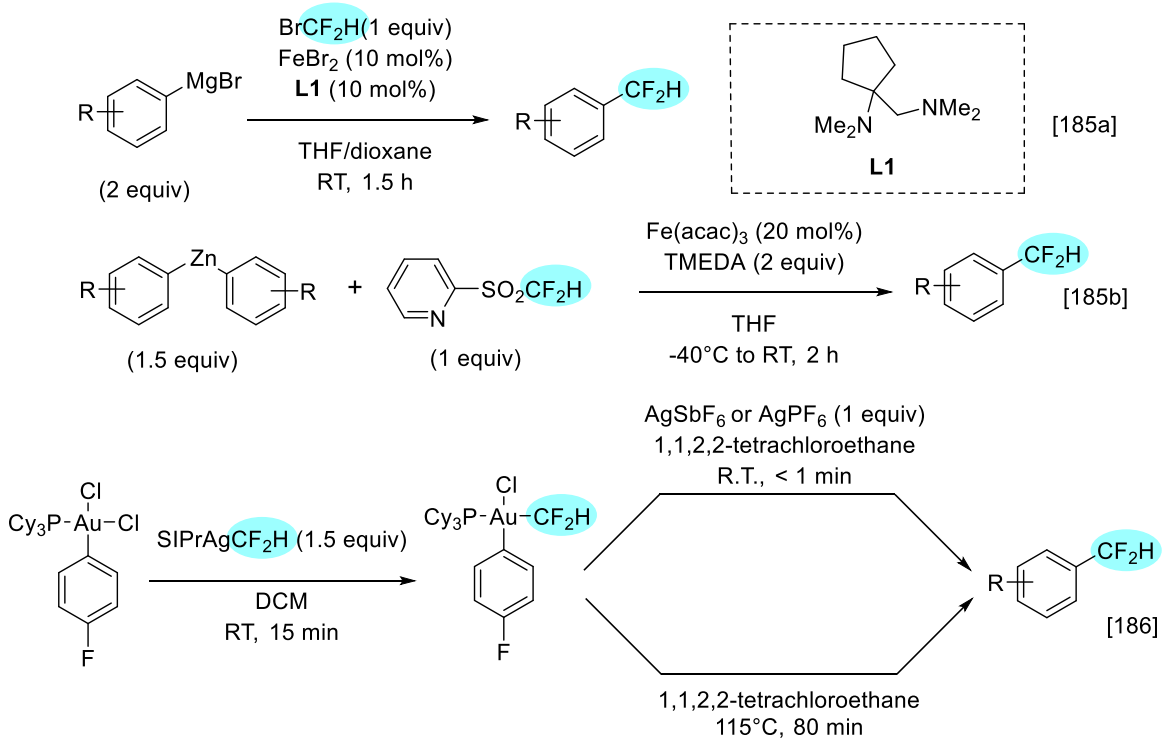
These beneficial properties were exploited by Vicic[180] to develop a Ni-catalyzed cross coupling reaction between $(DMPU)_2Zn(CF_2H)_2$ and aryl halides, which is postulated to involve a Negishi Ni^0/Ni^{II} redox shuttle. Baran[181] developed an elegant protocol using a redox active difluoromethyl sulfone reagent as a -CF_2H source and arylzinc reagents as cross coupling partners. In this case, the mechanism is postulated to be more complex; first a reduction of the nickel(II) species by the aryl zinc reagent itself (which is used in large excess) occurs followed by transmetallation to nickel and a subsequent oxidation of the nickel aryl complex by the sulfone reagent. This then fragments to yield the CF_2H radical, which itself then adds to the nickel complex species with final reductive elimination furnishing the product. A similar mechanism was proposed by Zhang[182], who used $CHClF_2$, aryl chlorides and excess zinc as a reductant. Other reported Ni-catalyzed cross coupling reactions involving $CHXF_2$ as a difluoromethyl source use aryl boronic acids[183] and Grignard reagents[184] as coupling partners.



Scheme 43: Selected Ni-catalyzed difluoromethylations.

Lastly, the other two metals used as catalysts in difluoromethylation cross coupling reactions in the literature are Fe[185], which has the benefit of being abundant and cheap, and Au[186], which like Ag forms stable complexes with -CF_2H (Scheme 44).

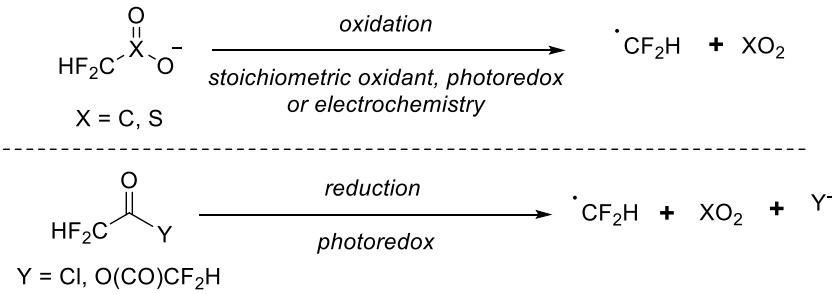
Crucially, these complexes have proved able to reductively eliminate Ar-CF_2H species. The reaction can occur at room temperature in less than a minute in the presence of stoichiometric $AgSbF_6$ or $AgPF_6$, whereas the reaction requires higher temperatures and longer reaction times in the absence of a silver source. The authors suggest that Ag might be abstracting the chloride from the Au complex, thus forming a more reactive cationic $[Au(PCy)_3(CF_2H)]^+$ intermediate.



Scheme 44: Selected Fe and Au-catalyzed difluoromethylations.

A completely different approach toward the formation of C(sp^2)-CF_2H bonds is represented by C-H activation via addition of the CF_2H radical to (hetero)arenes. Compared to CF_3, CF_2H has a higher SOMO energy and is more nucleophilic[187], leading to different reactivity and selectivity.

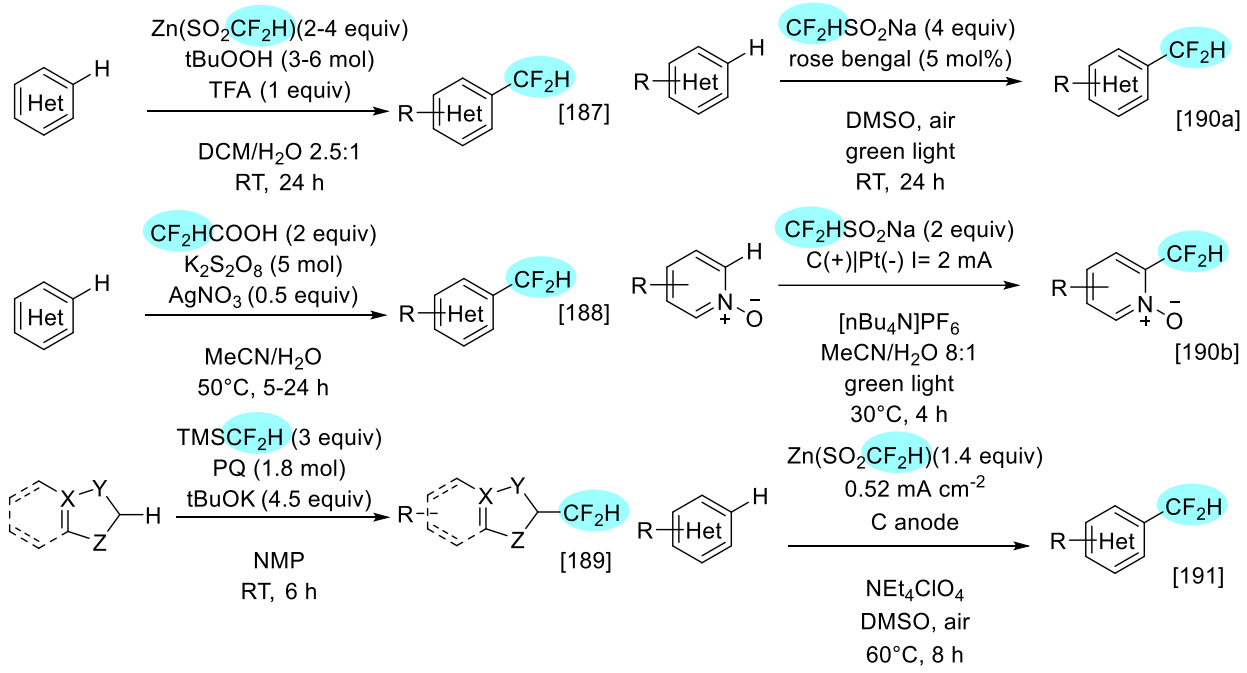
There are two main strategies to generate CF_2H radicals: oxidative activation and reductive activation (Scheme 45).



Scheme 45: CF_2H radical formation.

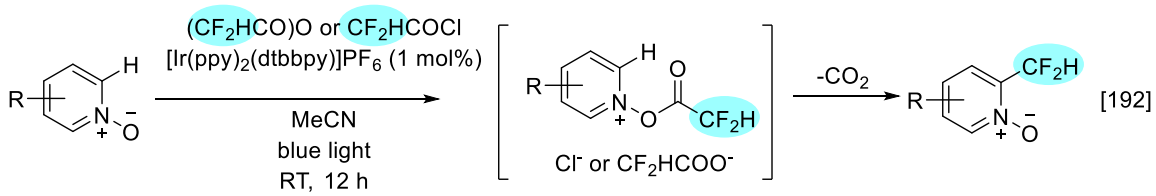
Oxidative activation was the first strategy to be developed with the pioneering work from Baran[187], who used $Zn(SO_2CF_2H)_2$ in the presence of excess tBuOOH as oxidant to yield the CF_2H radical for the C-H activation of heteroarenes. The predicted higher nucleophilicity of the CF_2H radical in comparison to the CF_3 radical was exemplified by the difluoromethylation of dihydroquinine, which was selective for C2 rather than C7; the latter being the preferred site for CF_3 radical addition.

Other examples of reagents capable of furnishing the difluoromethyl radical in the presence of stoichiometric oxidant are CF_2HCOOH[188] and $TMSCF_2H/CuCN$[189](involving the formation of the transient species $CuCF_2H$). Photochemical and electrochemical activation modes were reported with sulfinate salts such as CF_2HSO_2Na[190] and $Zn(SO_2CF_2H)_2$ [191].



Scheme 46: Selected C-H activation reactions of heteroarenes with CF_2H radicals obtained via oxidation.

An alternative way to obtain the CF_2H radical is via photocatalytic reduction, as shown in the work of Stephenson[192], in which CF_2HCOCl and $(CF_2HCO)_2O$ could be used to difluoromethylate pyridine *N*-oxides via the formation of a transient photoactive *N*-acyloxy species (Scheme 47).



Scheme 47: Difluoromethylation of pyridine *N*-oxides via *N*-acyoxy intermediates reported by Stephenson.

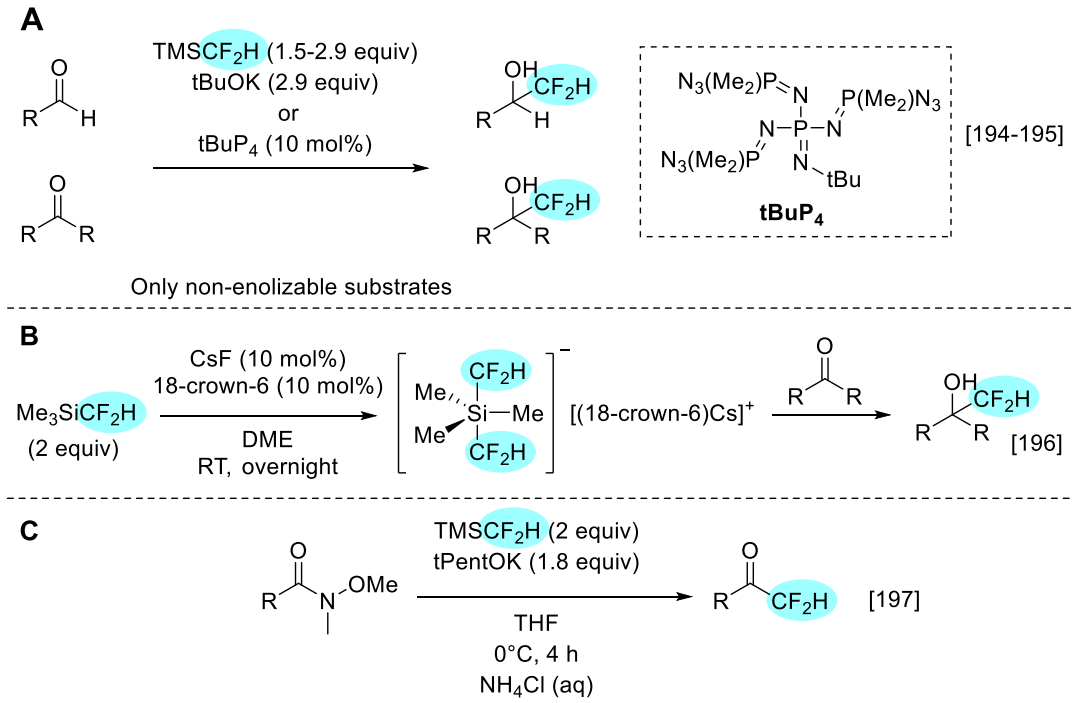
4.3 Synthetic approaches: C(sp^3)-CF_2H

The C(sp^3)-CF_2H motif has attracted significant interest as a bioisostere of aliphatic alcohols and thiols, and has already found application in several drugs[193].

Like for C(sp^2)-CF_2H, traditional deoxyfluorination routes remain the preferred synthetic method industrially to construct the -CF_2H moiety, however their lack of selectivity and low functional group tolerance has driven increasing interest in the development of direct difluoromethylation procedures.

By far the most prevalent nucleophilic difluoromethylating reagent is $TMSCF_2H$, which however requires activation via addition of a nucleophile to furnish the reactive -ate complex under harsher conditions than $TMSCF_3$, thus limiting the substrate scope.

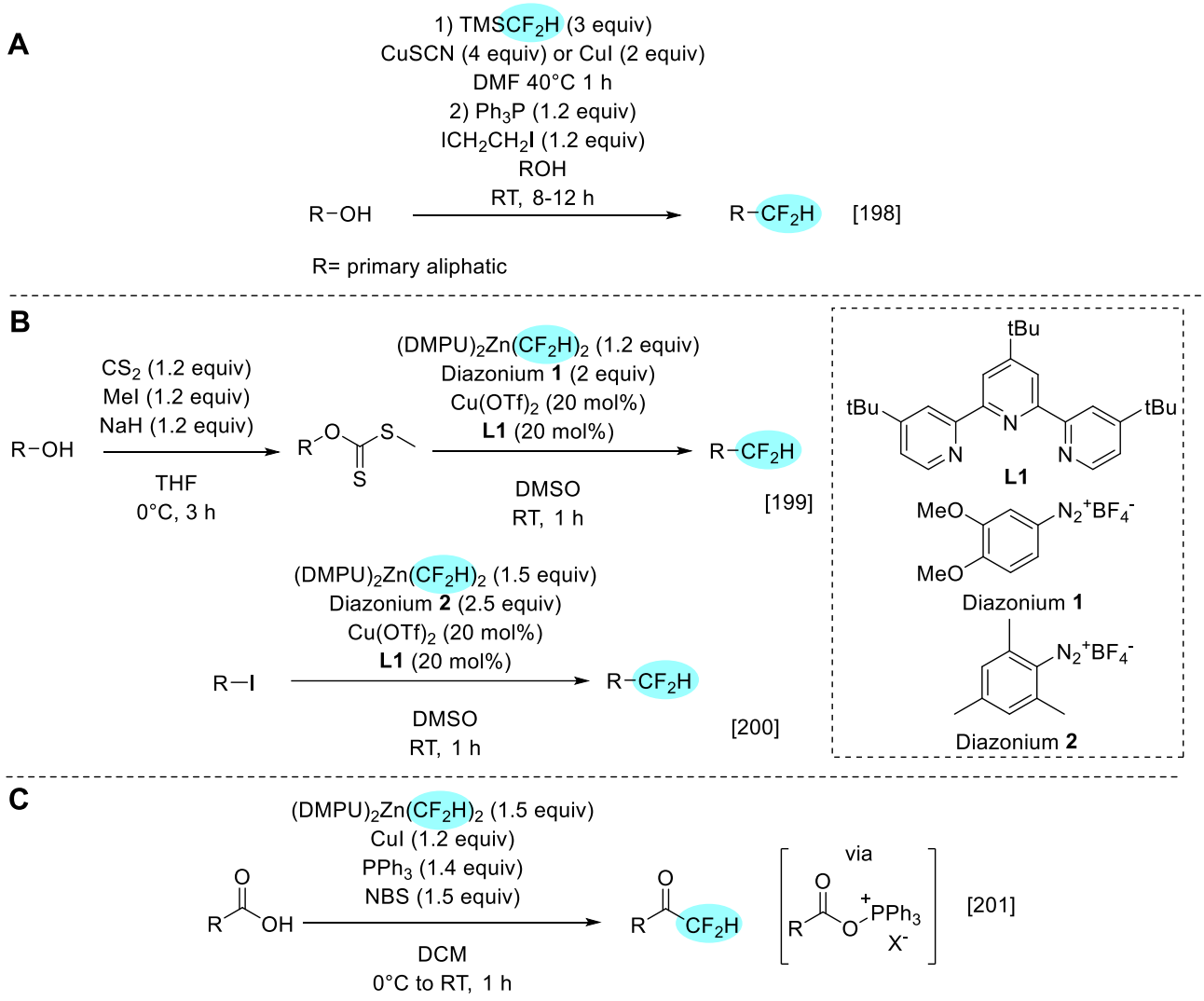
The use of the bulky bases tBuOK[194] and phosphazenes[195] allows the activation to occur under mild conditions in the nucleophilic addition to carbonyls, but the high basicity of these species makes enolisable aldehydes and ketones unsuitable substrates (Scheme 48a). This issue was resolved by Hu[196] by using excess $TMSCF_2H$ and a crown ether. Under these conditions, the pentacoordinate complex $[(CH_3)_3SiCF_2HNu]^-$, instead of directly adding to the carbonyl, is attacked by another equivalent of $TMSCF_2H$ to form $[(CH_3)_3Si(CF_2H)_2]^-$, which is stabilized by the cesium-crown ether complex counterion (Scheme 48b). A different way to avoid enolization was proposed by Pace[197], who used Weinreb amides as carbonyl compounds, obtaining difluoromethylketones as products (Scheme 48c).



Scheme 48a: Nucleophilic difluoromethylation of non-enolizable carbonyl compounds **Scheme 48b:** Nucleophilic difluoromethylation of enolizable carbonyl compounds **Scheme 48c:** Nucleophilic difluoromethylation of Weinreb amides.

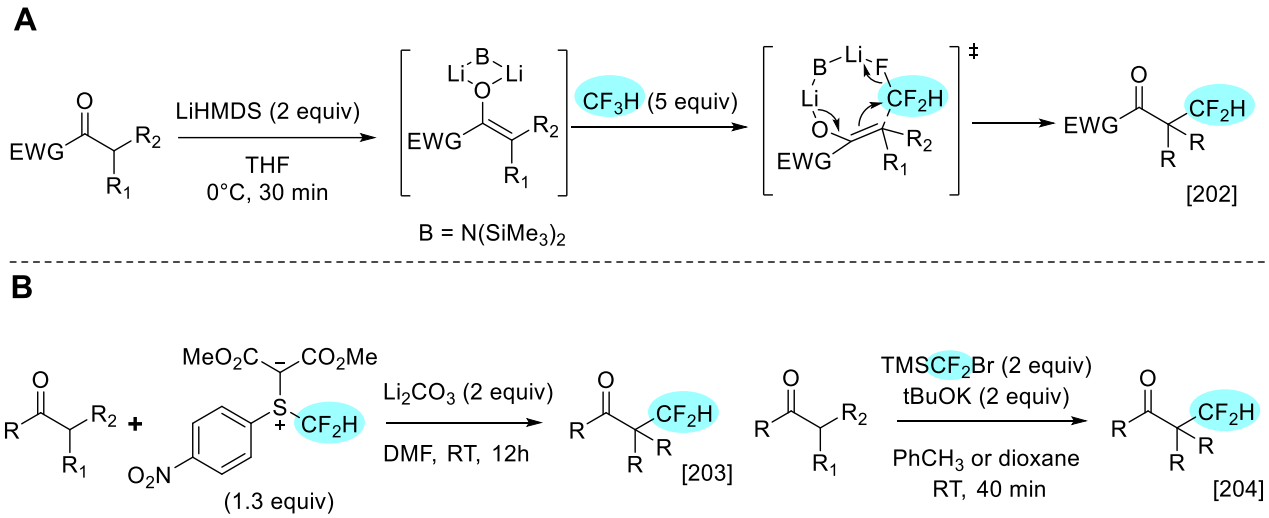
An alternative approach is represented by the deoxydifluoromethylation of primary alcohols, reported by Xiao[198]. Their system involves activation of alcohols with Ph_3P and ICH_2CH_2I reacting with stoichiometric preformed [$CuCF_2H$] (Scheme 49a). The scope of the reaction was expanded to secondary alcohols by Liu[199], who devised a two-step reaction, in which alcohols are first trapped with CS_2 and MeI to yield the corresponding xanthate ester, which then undergoes an aryl radical initiated copper-catalysed Barton-McCombie type reaction with DMSF as the CF_2H radical source and a diazonium salt as the radical initiator. A very similar Negishi cross coupling was developed by the same group[200] using alkyl iodides as substrates (Scheme 49b).

Recently, Prakash[201] reported the deoxydifluoromethylation of acids under similar conditions, with [$CuCF_2H$] derived from $(DMPU)_2Zn(CF_2H)_2$ and CuI, and Ph_3P and NBS activating the carboxylic acid functional group toward deoxygenation (Scheme 49c).



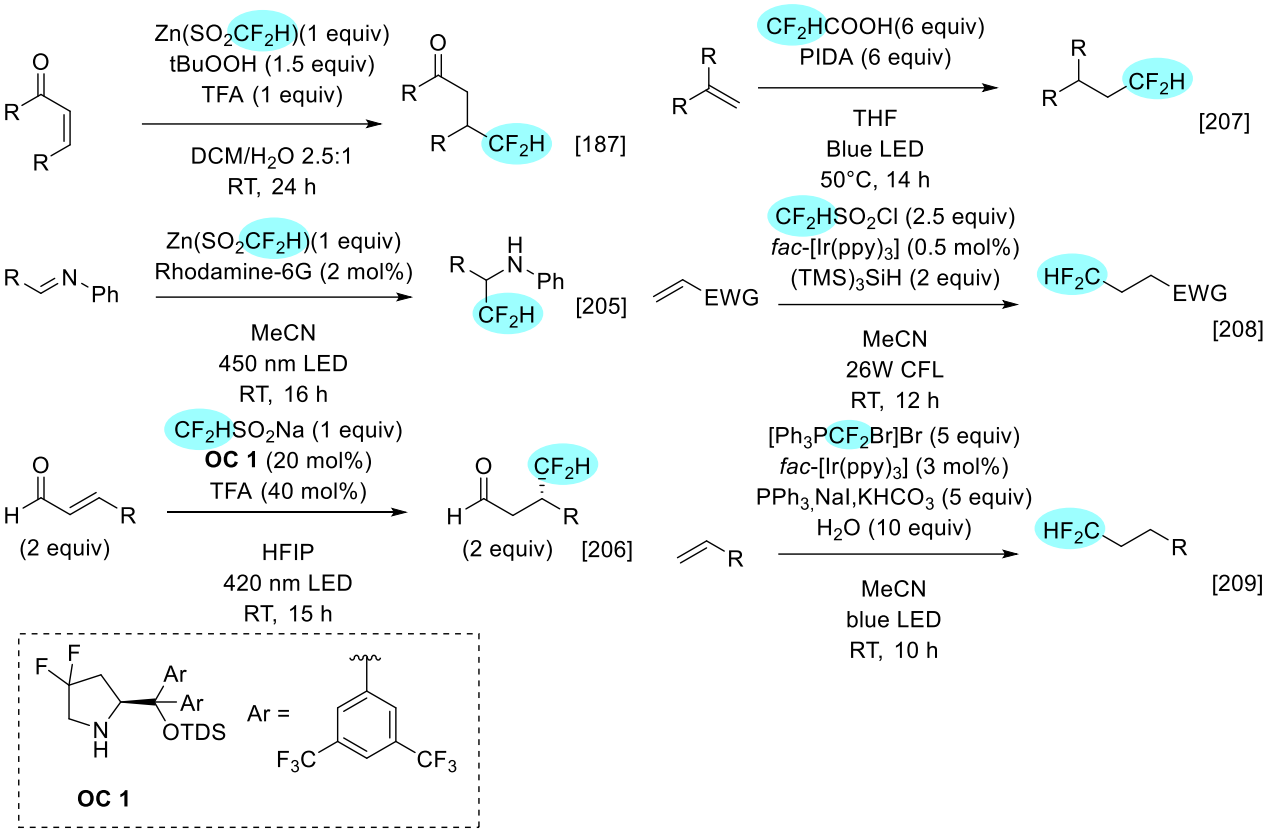
Scheme 49a: Copper-mediated deoxydifluoromethylation with $TMSCF_2H$. **Scheme 49b:** Diazonium-initiated radical difluoromethylation reactions. **Scheme 49c:** Copper-mediated deoxydifluoromethylation with the Vicic reagent.

In terms of electrophilic difluoromethylation, the most widely used reagent is $ClCF_2H$, which is an ozone depleting gas, so there is a push to employ alternative sources. One promising alternative, because of its low cost, is CF_3H (fluoroform). The strength of the C-F bond (117 kcal/mol) however represents a challenge to its activation. This issue was overcome by Mikami[202] in his protocol for the addition of CF_3H to lithium enolates (Scheme 50a). The authors propose that the high formation enthalpy of LiF constitutes the driving force of this reaction, enabling the use of the normally nucleophilic CF_3H (which can be easily deprotonated to CF_3^-) as a source of the "CF_2H^+" synthon. Interestingly, the authors postulate that the mechanism does not involve a difluorocarbene intermediate, unlike other procedures for the electrophilic addition to enolates, which employ difluorocarbene sources such as Shen's difluoromethyl sulfonium ylide[203] and Hu's $TMSCF_2Br$[204] (Scheme 50b). All of these methodologies are however limited to α-substituted carbonyl compounds



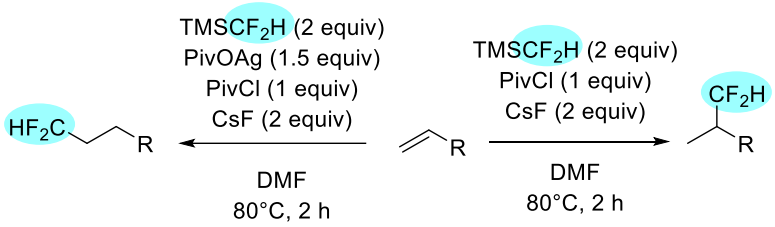
Scheme 50a: Electrophilic difluoromethylation of lithium enolates with CF_3H **Scheme 50b:** Electrophilic difluoromethylation with difluorocarbene precursors.

Radical difluoromethylation methodologies for forming C(sp^3)-CF_2H bonds largely use the same radical sources as for C(sp^2)-CF_2H species. For instance, in the radical hydrodifluoromethylation of double bonds, $Zn(SO_2CF_2H)_2$[187, 205], CF_2HSO_2Na[206] and CF_2HCOOH[207] could be used as CF_2H radical sources under oxidative conditions, and $ClSO_2CF_2H$[208] and $[Ph_3PCF_2Br]Br$[209] under reductive photoredox conditions (Scheme 51). The hydrogen atom added across the double bond can be provided by an exogenous hydrogen atom donor (HAD) or by the reaction solvent.



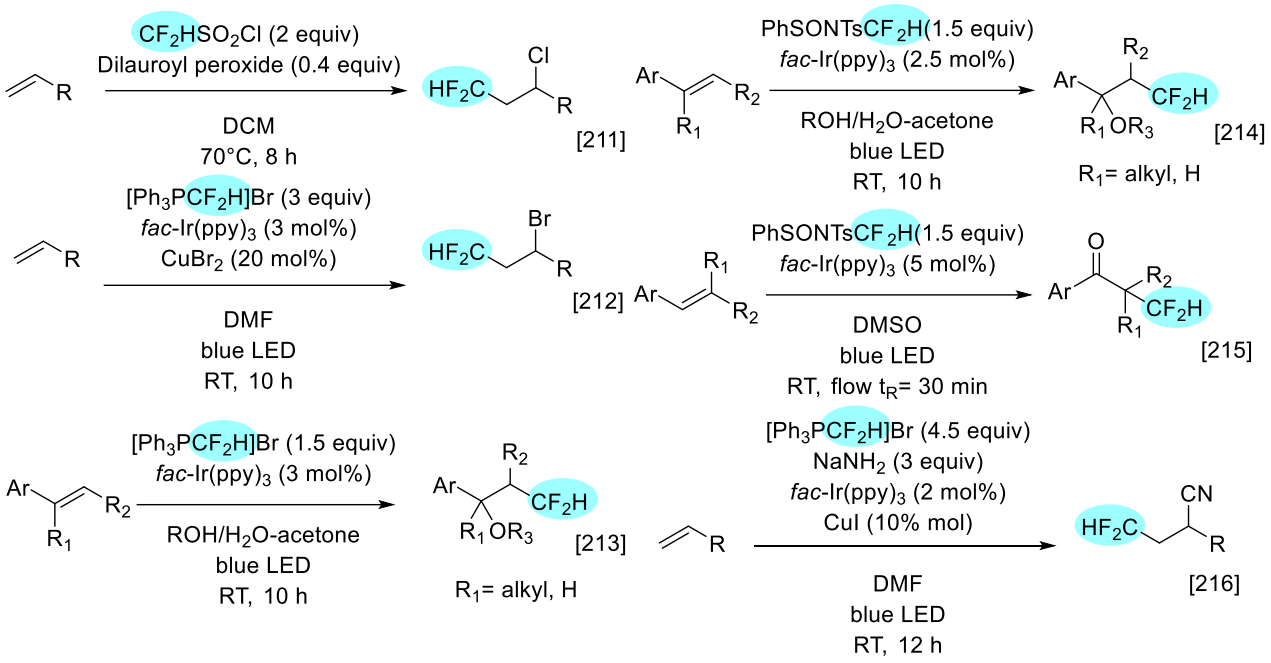
Scheme 51: Selected radical hydrodifluoromethylation of double bonds with various CF_2H radical sources.

In a recent interesting report, Qing[210] provided a way to control the regioselectivity of the difluoromethylation of alkenes with $TMSCF_2H$. The addition follows a Markovnikov or anti-Markovnikov selectivity depending on the presence of absence of Ag (Scheme 52).



Scheme 52: Regioselective silver catalyzed hydrodifluoromethylation introduced by Qing.

The possibility of adding two different functional groups across double bonds enables interesting difunctionalization reactions (Scheme 53). The second group adding could be part of the difluoromethylating reagent (such as in the difluoromethylchlorination and -bromination reported by Dolbier[211] and Qing[212] respectively), come from the solvent (such as in the alkoxydifluoromethylation and oxydifluoromethylation reported by Qing[213] and Akita[214], or the ketodifluoromethylation reported Akita[215], in which DMSO donates its oxygen atom getting reduced to SMe_2), or be formed *in situ* (such as in the cyanodifluoromethylation reported by Xiao[216], in which CN^- is produced by the reaction of difluorocarbene with added $NaNH_2$).



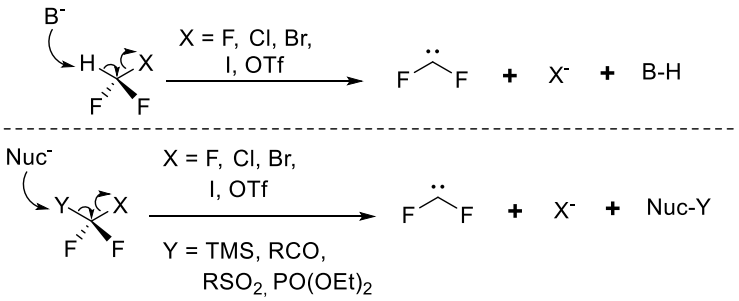
Scheme 53: Selected bifunctionalization reactions via radical difluoromethylation of alkenes.

4.4 Synthetic approaches: X-CF_2H (X = O, S, Se)

Note: In this section the formation of X-CF_2H (X = O, S, Se) bonds will be discussed. Direct difluoromethylthiolation and -selenylation reactions, in which the whole SCF_2H or $SeCF_2H$ moiety is installed onto substrates as an entire group, will be discussed in Chapter 6.

By far, the most common way to install a -CF_2H group onto a heteroatom is via difluorocarbene insertion. It is therefore a major goal to develop a broad range of difluorocarbene sources which can be activated under different conditions, to improve chemoselectivity and functional group tolerance.

Difluorocarbene sources can be divided in two groups according to their activation mode: basic and nucleophilic (Scheme 54).



Scheme 54: Difluorocarbene formation.

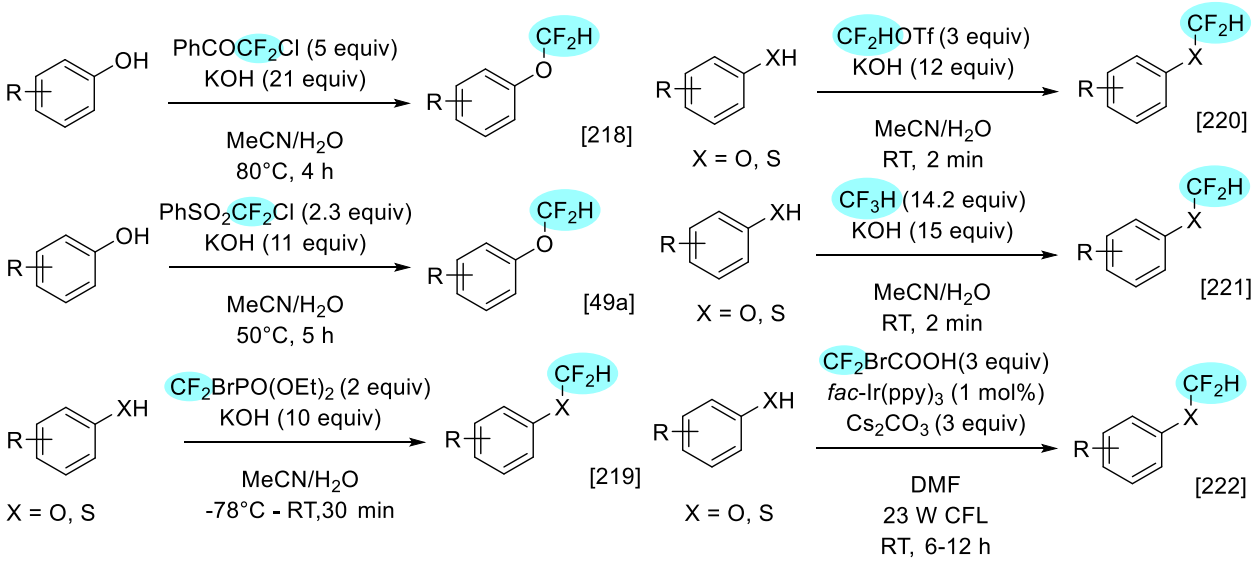
The first sources of difluorocarbene were identified as far back as the 1960s[217]. However, the need to have harsh activation conditions and high toxicity severely limited the scope of applications of these early examples. Another issue is posed by the widespread use of $ClCH_2F$, a notorious ozone-depleting substance (ODS).

The Hu group led much of the early efforts in the 2000s to develop new non-CFC derived difluorocarbene sources, introducing reagents such as $PhCOCF_2Cl$[218] and $PhSO_2CF_2Cl$[49a] for the difluoromethylation of phenols, which however still require high temperatures and long reaction times to be effective.

In 2009, Zafran[219] introduced $BrCF_2P(O)(OEt)_2$, a non-ODS difluorocarbene source capable of efficiently functionalizing (thio)phenols at RT. In 2013, Hartwig[220] developed $TfOCF_2H$, a liquid non-ODS difluorocarbene source that reacts quickly under relatively mild conditions; however with phenols bearing electron donating groups (EDGs), the formation of aryl triflates via attack on sulfur was a major side product. The issue was solved replacing the $-CF_3$ side chain with the bulkier $-(CF_2)_3CF_3$ chain.

Dolbier[221] first reported the use of CF_3H as a cheap, non-ODS difluorocarbene source for the difluoromethylation of (thio)phenols, but a large excess is needed to overcome the low solubility of CF_3H in acetonitrile.

In 2017, Fu[222] reported the first difluorocarbene generation under photoredox catalysis with $BrCF_2HCOOH$ and an Ir-based photocatalyst for the difluoromethylation of (thio)phenols.



Scheme 55: Selected examples of difluoromethylations of (thio)phenols with difluorocarbene precursors.

Unlike phenols, aliphatic alcohols do not require deprotonation to be employed in these reactions, however the basic conditions required to activate many difluorocarbene sources lead to low yields and to undesired side-reactions, such as S_N2 reactions on the C-F bonds of the difluoromethyl group with alkoxides[223].

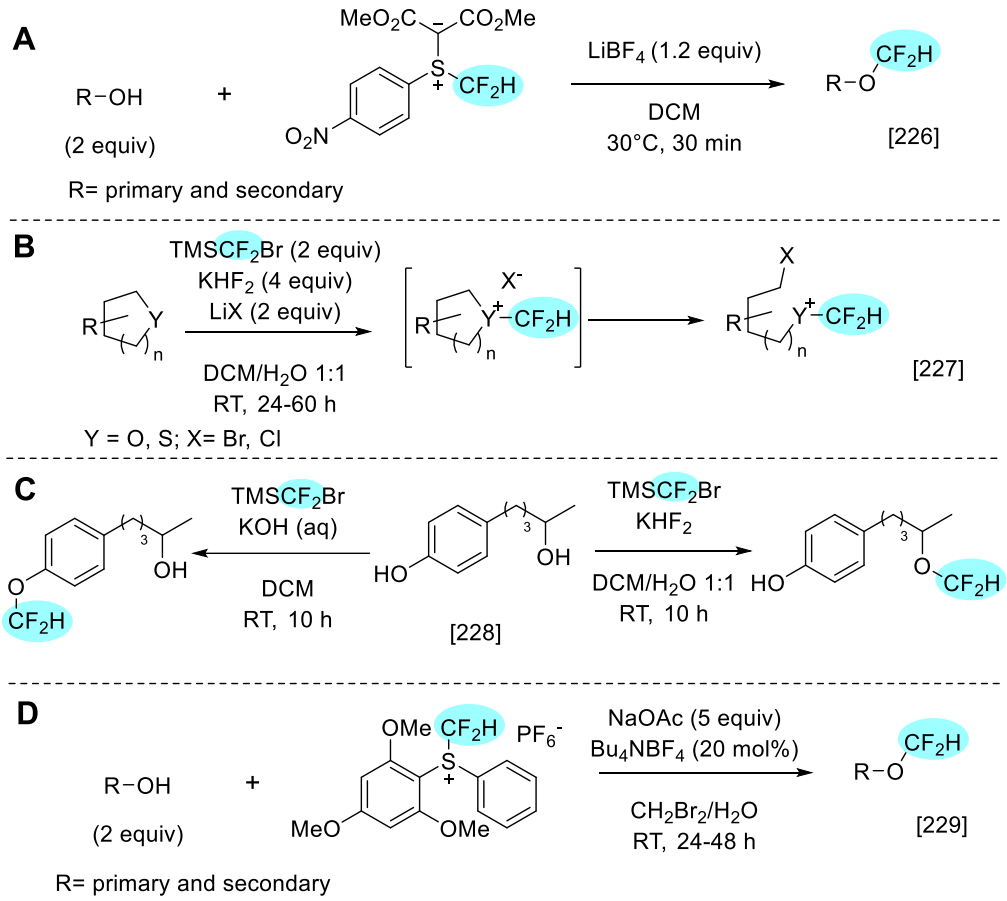
Early attempts to develop reagents that can be activated under neutral conditions, such as the photochemical formation of difluorocarbene from difluorodiaziridine reported by Robertson[224] or the pyrolytic activation of hexafluoropropene reported by Mizukado[225] suffer from extremely limited reaction scopes and are not generally applicable.

In 2016, Shen[226] introduced a sulfonium ylide reagent capable of performing the difluoromethylation of alcohols under neutral conditions (Scheme 56a), with $LiBF_4$ used as the additive. This method is capable of efficiently functionalizing a broad scope of aliphatic alcohols.

Lithium also plays a key role in a recently reported ring-opening difluoromethylation from Hu[227](Scheme 56b), in which difluorocarbene generated with KH_2F as an additive attacks cyclic (thio)ethers, leading to ring-opening reactions with concomitant addition of a halide ion derived from LiX (X = Cl, Br).

The desire to develop chemoselective synthetic protocols that allow for the functionalization of aliphatic alcohols in the presence of phenolic -OH groups has driven recent research from the Hu group. Exploiting the ability of alcohols to react under neutral or even slightly acidic conditions, Hu[228] developed a procedure in which difluorocarbene generated from $TMSCF_2Br$ selectively attacks alcohols or phenols depending on the additive (KH_2F and KOAc respectively, Scheme 56c).

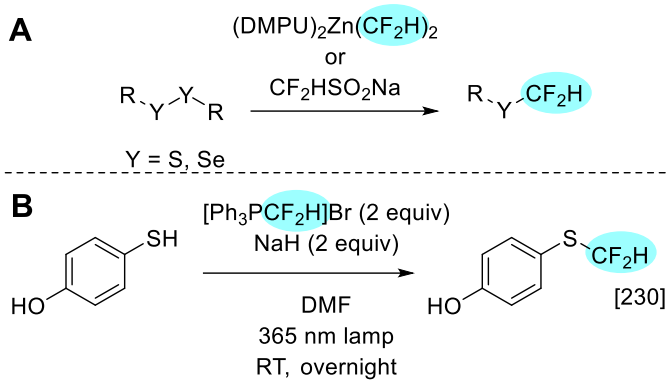
Similarly, Zhang[229] reported a *S*-(difluoromethyl)sulfonium salt capable of selectively reacting with aliphatic alcohols and thiols in the presence of functional groups such as phenols, alkenes and *N*-heterocycles, not usually tolerated by traditional difluorocarbene approaches (Scheme 56d).



Scheme 56a: Difluoromethylation of aliphatic alcohols sulfonium ylide. **Scheme 56b:** Ring-opening difluoromethylation-halogenation of cyclic (thio)ethers. **Scheme 56c:** Chemoselective difluoromethylation of alcohols under neutral or basic conditions. **Scheme 56d:** Difluoromethylation of alcohols with diaryl sulfonium salts.

Unlike oxygen, sulfur and selenium can be difluoromethylated in a single electron radical process, using previously mentioned CF_2H radical sources such as $(DMPU)_2Zn(CF_2H)_2$[187] and CF_2HSO_2Na[63] (Scheme 57a). Despite the presence of stoichiometric oxidants, this did not hinder the reaction as disulfides/diselenides are reactive toward CF_2H radicals themselves.

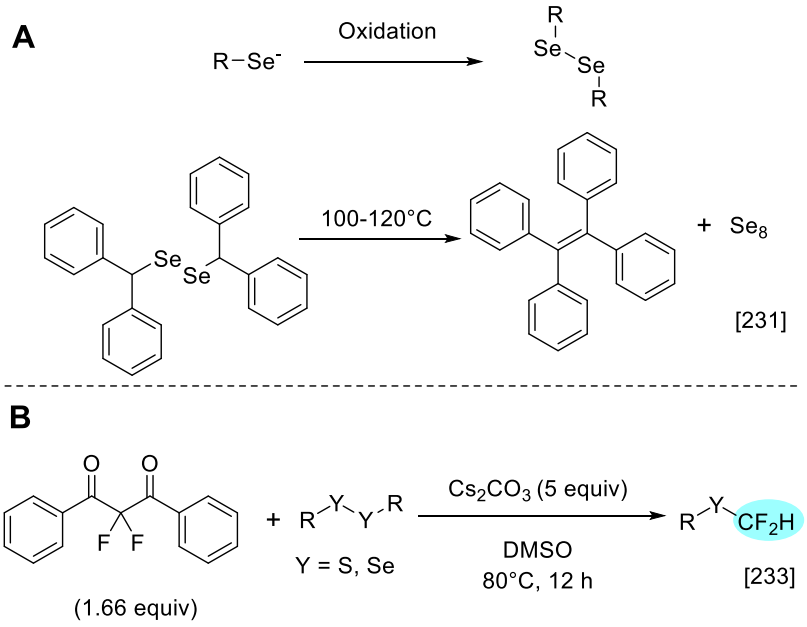
In 2017, Studer[230] introduced $[Ph_3P(CF_2H)]Br$ as a CF_2H radical source under photocatalytic conditions for the chemoselective addition to Ar-SH, even in the presence of oxygen and nitrogen based nucleophilic groups (Scheme 57b). One example with Se is reported, albeit with lower yields.



Scheme 57a: Radical difluoromethylation of disulfides and diselenides. **Scheme 57b:** Chemoselective difluoromethylation of thiols introduced by Studer.

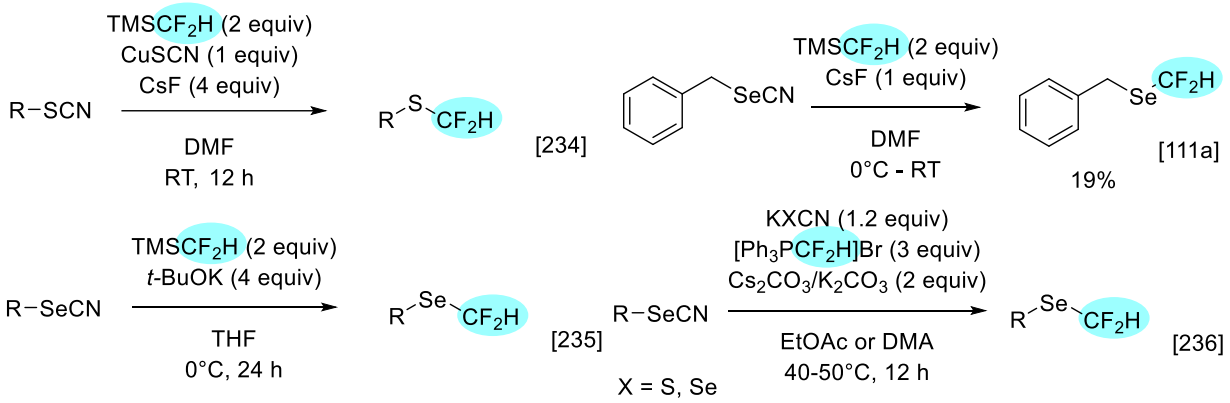
The difluoromethylation of selenols suffers from an additional difficulty in comparison to the difluoromethylation of alcohols and thiols: their instability toward oxidation as well as their lower thermal stability[231] (Scheme 58a). Because of the harsh conditions needed to activate difluorocarbene precursors, the scope of difluoromethylated selenols remains small, and is mostly limited to $ArSeCF_2H$[232], owing to the higher stability toward oxidation of the $ArSe^-$ selenol.

In 2016, Lu[233] disclosed a difluoromethylthiolation reaction of disulfides (one example with phenyl diselenide is also reported) using difluoroacetophenones as the source of the -CF_2H moiety under thermal activation (Scheme 58b).



Scheme 58a: Instability toward oxidation of selenolates and thermal instability of diselenides. **Scheme 58b:** Difluoromethylation of disulfides and diselenides with α-Fluorodiaroylmethanes.

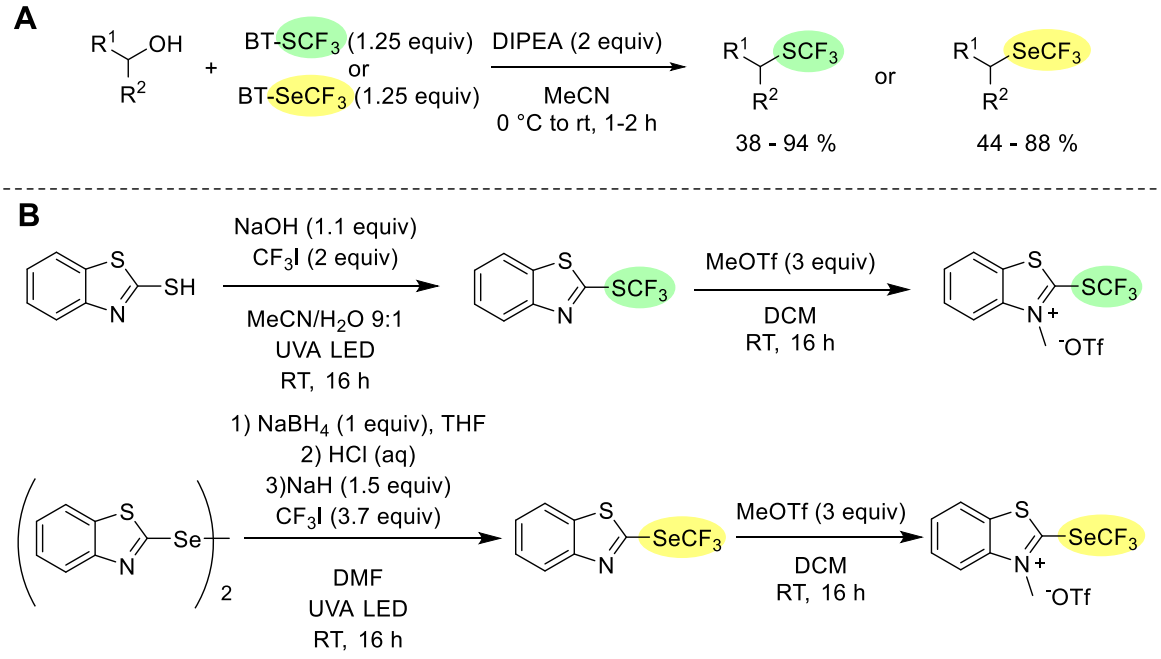
These synthetic difficulties were brilliantly overcome by Billiard[111a] in 2016. Inspired by Goossen's[234] copper-catalyzed difluoromethylation of thiocyanates with $TMSCF_2H$, he introduced the nucleophilic difluoromethylation of benzyl selenocyanate (which can be accessed via nucleophilic substitution of BnBr with $SeCN^-$) with $TMSCF_2H$, which was applied to a broad scope of aliphatic and aromatic selenocyanates by Zhang[235] in 2018. This reaction allows access to a variety of $RSeCF_2H$ compounds, both aromatic and aliphatic. Crucially, however, this methodology is not very effective for the preparation of $BnSeCF_2H$, a key reagent in direct difluoromethylselenylation (see section 6.2). Recently, Xiao[236] reported $[Ph_3P(CF_2H)]Br$ as an alternative nucleophilic difluoromethyl source for the addition to selenocyanates and thiocyanates in a one-pot protocol directly from alkyl halides.



Scheme 59: Nucleophilic difluoromethylation of thio- and selenocyanates.

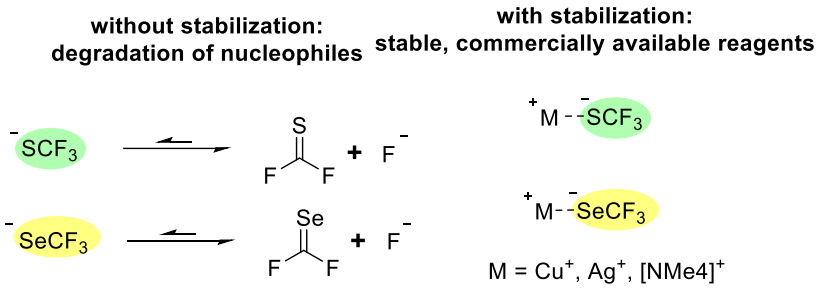
5. Scientific goal

The overall goal of this project is to develop new synthetic methods to access valuable organofluorine compounds. This work is based on the previous work carried out by our group[61], in which we introduced the benzothiazolium reagent as a practical way to install valuable -SCF_3 and -$SeCF_3$ moieties onto alcohols in a nucleophilic deoxytrifluoromethylthiolation and -selenylation of alcohols (Scheme 60a). These reagents are air- and moisture-stable crystalline solids and can be easily synthesized from cheap precursors (Scheme 60b), such as 2-mercaptobenzothiazole (2-MBT), a bulk chemical used for rubber vulcanization, and CF_3I, a comparatively inexpensive trifluoromethylating reagent.



Scheme 60a: Trifluoromethylthiolation and -selenylation of alcohols. **Scheme 60b:** Synthesis of the BT-SCF_3 and BT-$SeCF_3$ reagents.

Nucleophilic approaches to these functional groups are limited by the tendency of the corresponding anions to undergo β-fluoride elimination, forming the fluoro thio- or selenophosgenes[237] (Scheme 61).

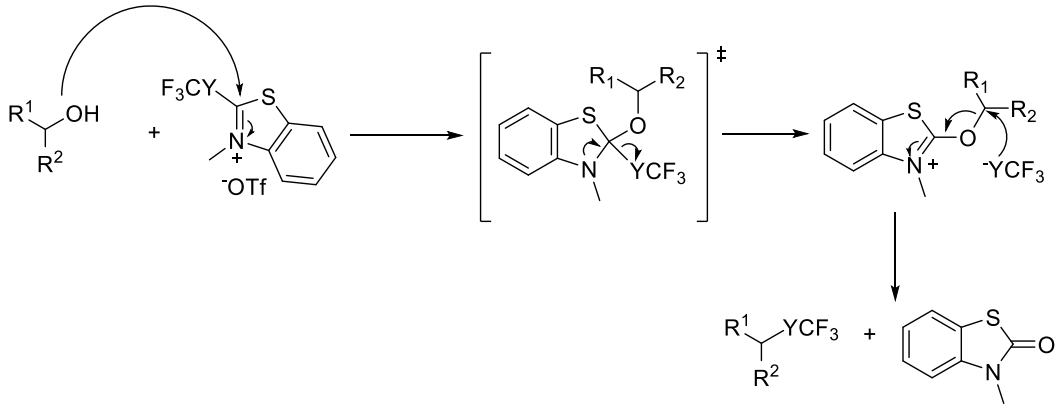


Scheme 61: Stabilization of trifluoromethylchalcogenate nucleophiles is key to preventing their degradation.

Although there are relatively stable, commercially available sources of these anions, their use is limited by their high cost and limited stability under many reaction conditions withlarge excesses being often required to be effective.

It would therefore be beneficial to generate these anions in a controlled manner *in situ*, so as to improve the reactivity of the anion with the substrate. Benzothiazolium (BT) reagents developed in our research group are particularly suitable for this purpose because not only do they release the anion gradually *in situ* via the nucleophilic attack by alcohols, but they also concomitantly form an activated alkoxy benzothiazolium electrophile, thus facilitating the subsequent attack by the $^{-}YCF_3$ anion, the formation of a stable benzothiazolone side product being a major driving force (Scheme 62).

The reagents BT-SCF_3 and BT-$SeCF_3$ could be employed for the trifluoromethylthiolation and -selenylation of a wide scope of primary and secondary alcohols under mild conditions, without using any metal-containing additive.



Scheme 62: Reaction mechanism of deoxygenative functionalization of aliphatic alcohols with BT-YCF_3 (Y = S, Se) involving the formation *in situ* of the unstable anion.

Encouraged by these results, we started exploring other BT reagents and other oxygen-containing substrates to expand the range of applications of these reagents.

In particular, we were very interested in extending this concept to the difluoromethylated derivatives of these reagents, BT-SCF_2H and BT-$SeCF_2H$. in comparison to the -SCF_3 and -$SeCF_3$ groups, the nucleophilic difluoromethylthiolation and -selenylation is even more challenging, because the corresponding anions are less stable, owing to their increased propensity toward β-fluoride elimination, due to the cooperative nature of C-F bonds, which makes the carbon-fluorine bonds weaker in the -CF_2H group in comparison to -CF_3.

As a result, to date there currently exists only one other known nucleophilic -SCF_2H source[238], and no nucleophilic sources at all are known for -$SeCF_2H$.

The synthesis of these reagents, optimization of the reaction conditions, the scope and limitations of deoxygentive functionalization reactions using them, as well as the plausible mechanisms will thus be discussed, as well as other applications of the BT reagents that have been developed in our group and the future outlook.

6. Publications

OL | Organic Letters

pubs.acs.org/OrgLett Letter

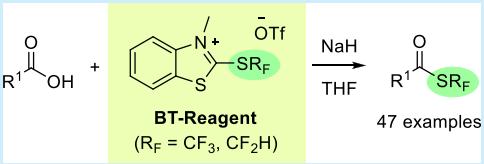
Deoxygenative Tri- and Difluoromethylthiolation of Carboxylic Acids with Benzothiazolium Reagents

Matteo Tironi,[†] Lilian M. Maas,[†] Arushi Garg, Stefan Dix, Jan P. Götze, and Matthew N. Hopkinson*

Cite This: *Org. Lett.* 2020, 22, 8925–8930 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Deoxygenative syntheses of fluorinated thioesters directly from carboxylic acids have been developed employing benzothiazolium reagents. The process using BT-SCF_3 represents an attractive approach toward these SCF_3-containing compounds that avoids the use of metal $^-SCF_3$ salts or preactivated acyl electrophiles. Moreover, the *in situ* activation of BT-SCF_2H allows for an unprecedented nucleophilic difluoromethylthiolation reaction. DFT calculations support a mechanistic scenario involving a four-membered transition state where acyl substitution occurs without the formation of an unstable free $^-SCF_2H$ anion.

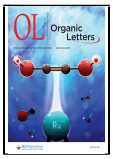


Fluorinated compounds play an important role in the agrochemical and pharmaceutical industry.[1] However, due to a scarcity of naturally occurring fluorinated molecules, the production of fluorinated targets relies heavily on synthetic organic chemistry. Among the various fluorine-containing functional groups, fluoroalkylthio groups such as the SCF_3 moiety have attracted considerable attention recently due to their lipophilic yet polar nature and several fluoroalkylthiolated pharmaceuticals and agrochemicals have been developed.[2]

The renewed interest in the SCF_3 group in particular has been spurred to a large extent by the development of new electrophilic trifluoromethylthiolating reagents capable of operating under mild conditions, which have supplanted the previously available toxic gases F_3CS-Cl and F_3CS-SCF_3.[2b,d,3] In contrast, nucleophilic trifluoromethylthiolation relies on a few comparatively expensive salts such as $AgSCF_3$, $CuSCF_3$, and $[Me_4N]SCF_3$. In 2019, we reported a new purely organic reagent for nucleophilic trifluoromethylthiolation suitable for the deoxygenative functionalization of aliphatic alcohols: the benzothiazolium salt BT-SCF_3.[4] This solid reagent can be easily prepared on a multigram scale in two steps from the inexpensive starting material 2-mercaptobenzothiazole (MBT) and is bench stable at least over several months. In the presence of an alcohol and the amine base $NEt(iPr)_2$, however, addition/elimination at the C2 carbon releases $^-SCF_3$, which then reacts with the intermediate 2-alkoxybenzothiazolium salt to afford a wide range of trifluoromethylthioethers under mild conditions.[5] This "*in situ* activation" approach is particularly attractive for nucleophilic trifluoromethylthiolation as the free $^-SCF_3$ anion is unstable toward β-fluoride elimination.[6] Using BT-SCF_3, this anion is generated in a controlled fashion together with a highly reactive electrophile. As such, nucleophilic trifluoromethylthiolation is expected to proceed rapidly while the concentration of $^-SCF_3$ in the reaction mixture remains low (Scheme 1a).

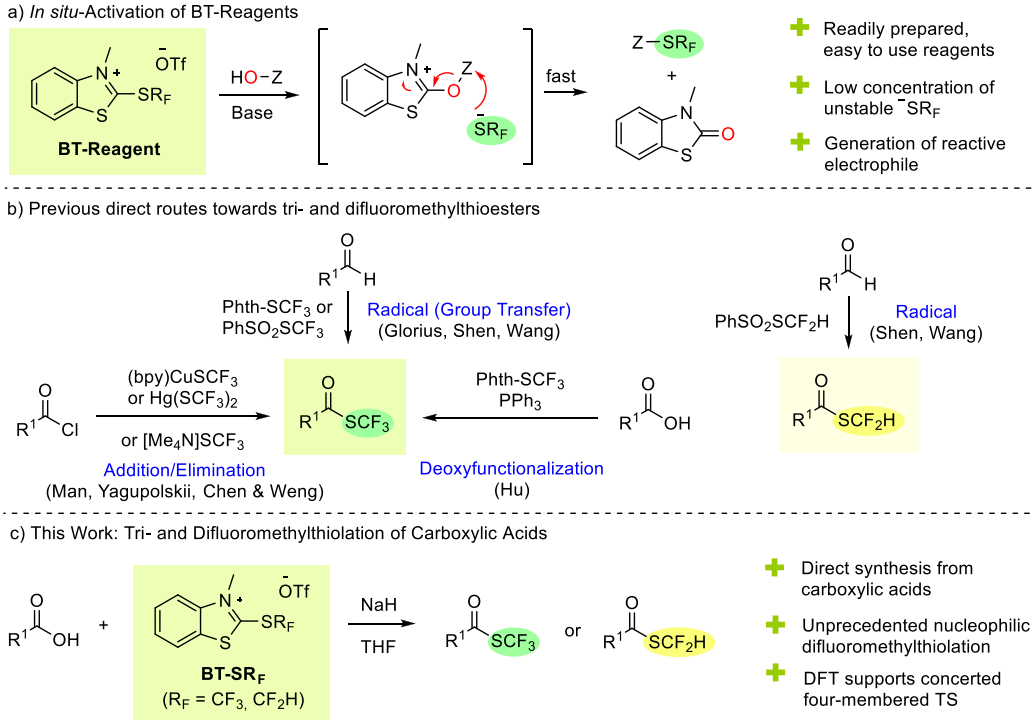
Having identified BT-SCF_3 as a convenient reagent for the trifluoromethylthiolation of alcohols, we considered whether other important classes of fluoroalkylthiolated compounds could be similarly prepared in a deoxygenative fashion from readily available substrates. For example, deoxytrifluoromethylthiolation of carboxylic acids with BT-SCF_3 would provide facile access to trifluoromethylthioesters. Whereas trifluoromethylthioethers have been widely studied, the corresponding esters remain relatively underexplored despite the potential for applications in pharmaceuticals and agrochemicals.[2] Most reported synthetic routes toward trifluoromethylthioesters involve addition/elimination of $^-SCF_3$ salts to acid chlorides, which in addition to employing expensive, relatively unstable, or even toxic $^-SCF_3$ sources, require preformation of the acyl electrophile and generate stoichiometric amounts of metal chloride waste.[7] A selection of recent reports have instead employed electrophilic trifluoromethylthiolating reagents such as Phth-SCF_3 (Phth = phthalimide) or $PhSO_2SCF_3$, which while still expensive, are bench stable and easily handled. The groups of Glorius,[8] Shen,[9] and Wang[10] have developed radical methodologies involving SCF_3 group transfer onto acyl radicals generated via hydrogen atom transfer (HAT) from aldehydes.[11] The only synthesis of trifluoromethylthioesters directly from carboxylic acids was reported recently by Hu and co-workers.[12] This method uses an umpolung approach that employs Phth-SCF_3 as an electrophilic trifluoromethylthiolating reagent together with triphenylphosphine as a stoichiometric reductant and an iron(III) catalyst.

Received: October 6, 2020
Published: November 4, 2020



https://dx.doi.org/10.1021/acs.orglett.0c03328
Org. Lett. 2020, 22, 8925–8930

Scheme 1. Previous Direct Syntheses of Tri- and Difluoromethylthioesters and In Situ Activation of BT Reagents



Partially fluorinated difluoromethylthioesters have been even less studied. In addition to the lipophilic and electron-withdrawing characteristics typical for fluoroalkylthio groups, the SCF_2H moiety can engage in hydrogen bonding interactions in biological systems.[13] These beneficial properties have duly led to the development of SCF_2H containing pharmaceuticals and agrochemicals such as flomoxef sodium and pyriprole. While there are currently no difluoromethylthioester-containing pharmaceuticals, a structurally similar monofluoromethylthioester motif is found in the corticosteroid medication fluticasone. Synthetic routes toward SCF_2H-substituted compounds are comparatively limited with most approaches involving difluoromethylation of a sulfur-containing substrate. In recent years, a few direct methods for installing the entire SCF_2H group onto organic molecules have been introduced, employing a selection of mostly electrophilic or radical difluoromethylthiolating reagents.[14] To date, however, only two methods both involving group transfer from $PhSO_2SCF_2H$ onto aldehyde-derived acyl radicals have been reported for the synthesis of difluoromethylthioesters (Scheme 1b).[9,14]

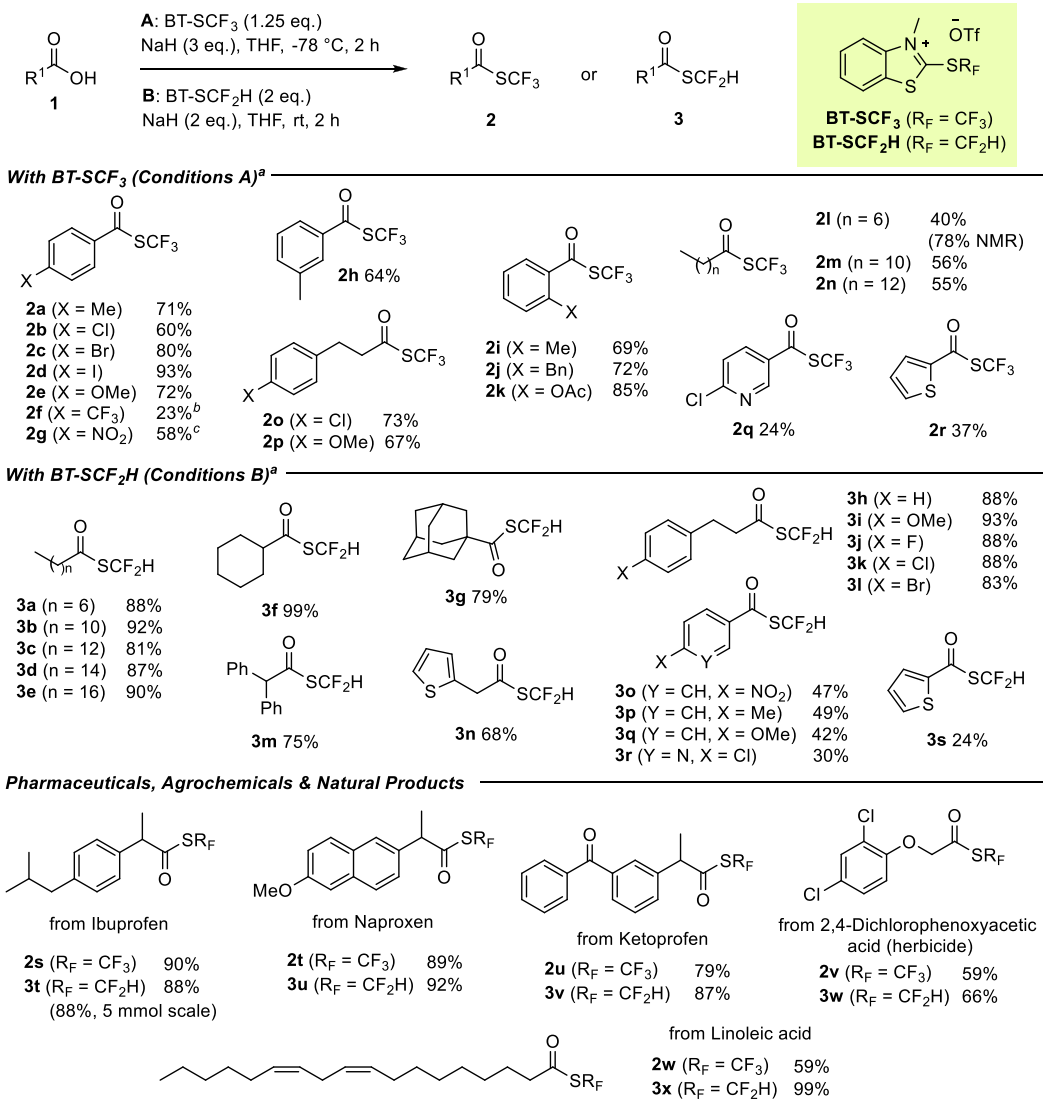
Herein, we report a transition metal free methodology for the direct deoxygenative fluoroalkylthiolation of readily available carboxylic acids via *in situ* activation of BT-SR_F reagents. The method using BT-SCF_3 provides aryl and alkyl trifluoromethylthioesters without any additives other than an inorganic base. The similarly efficient synthesis of difluoromethylthioesters using the novel reagent BT-SCF_2H is especially noteworthy. Not only is this method the only reported approach toward these partially fluorinated compounds from simple carboxylic acids, it also constitutes a rare example of a formally nucleophilic difluoromethylthiolation reaction. The success of this method despite the well-known instability of the $^-SCF_2H$ anion suggests that *in situ* activation of BT reagents could provide a strategy for conducting nucleophilic reactions of otherwise unstable fluorinated or nonfluorinated anions (Scheme 1c).

We began our study by reacting preformed cesium 4-methylbenzoate with BT-SCF_3 (1.25 equiv)[4,15] in MeCN. After 2 h at rt, we were pleased to observe the formation of the desired trifluoromethylthioester **2a** in 39% NMR yield. With the aim of developing an efficient set of conditions for the direct deoxyfunctionalization of the free carboxylic acid **1a**, a survey of different bases and solvents was conducted. The combination of NaH (3 equiv) and THF proved to be optimum, while dilution to 0.033 M, dropwise addition of the acid, and a lower reaction temperature of −78 °C suppressed the formation of side products resulting from nucleophilic attack of a second carboxylate anion or ring-opening of THF.[16]

With a set of optimized conditions established, an investigation into the reaction scope with variously substituted carboxylic acids **1** was conducted (Scheme 2). A wide range of aryl derivatives could be successfully converted into the corresponding thioesters in generally moderate to good yields. Electronically diverse functional groups such as −OMe and $-NO_2$ were well tolerated, while halogen-substituted products that are potentially amenable to further functionalization through cross-coupling methodologies were efficiently provided. As demonstrated by Hu and co-workers, aromatic trifluoromethylthioesters can be converted into the corresponding aryl thioethers via palladium-catalyzed decarbonylation.[12,17] As such, the deoxygenative trifluoromethylthiolation could serve as the first part of a facile two-step synthesis of valuable trifluoromethylthioethers from readily available carboxylic acids. The standard reaction conditions with BT-SCF_3 could also be applied to a series of alkyl carboxylic acids with the corresponding thioesters being formed in isolated yields up to 73%.

https://dx.doi.org/10.1021/acs.orglett.0c03328
Org. Lett. 2020, 22, 8925−8930

Scheme 2. Scope of Deoxygenative Tri- and Difluoromethylthiolation of Acids Using BT-SCF_3 and BT-SCF_2H



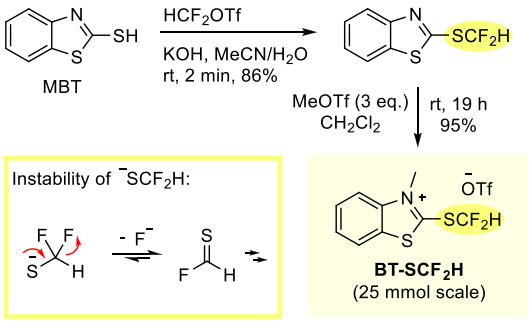
[a]Isolated yields, 0.5 mmol scale. For full conditions, see the SI. [b]No dropwise addition of acid, 0.1 M concentration, stirred for 2 h at rt. [c]No dropwise addition of acid, 0.033 M concentration, stirred for 2 h at rt.

Having developed a practical protocol for the deoxytrifluoromethylthiolation of carboxylic acids, we next turned our attention to the deoxygenative synthesis of difluoromethylthioesters. According to the general mechanism outlined in Scheme 1a, addition of a carboxylate to the C2 carbon of the 2-difluoromethylthio-substituted benzothiazolium salt BT-SCF_2H would result in the generation of the $^-SCF_2H$ anion. Whereas nucleophilic pathways are often employed to install the SCF_3 group, direct difluoromethylthiolation reactions are almost exclusively electrophilic or radical in character. The scarcity of nucleophilic methods can be explained by the very low stability of $^-SCF_2H$ toward β-fluoride elimination. Despite many attempts over the years, only one stable $^-SCF_2H$ salt has been successfully isolated to date: the N-heterocyclic carbene (NHC)-stabilized silver complex [SIPrAg(SCF_2H)] (SIPr = 1,3-(2,6-diisopropylphenyl)imidazolinylidene). This compound, which was introduced in 2015 by Shen and coworkers,[18] has been employed as a stoichiometric source of SCF_2H groups in transition-metal-mediated cross-coupling reactions but, to the best of our knowledge, no applications in direct nucleophilic substitution reactions, including for the synthesis of difluoromethylthioesters, have been reported.[18,19]

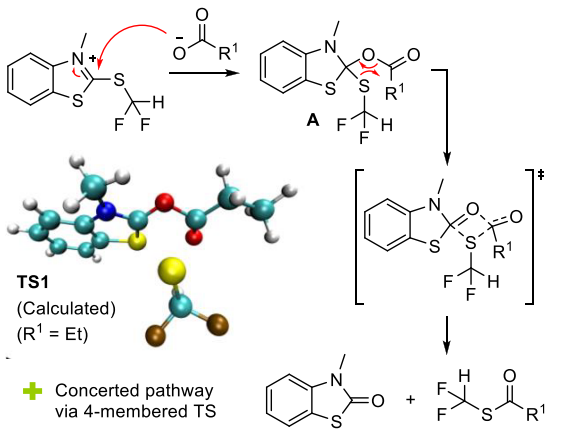
In order to investigate the feasibility of nucleophilic difluoromethylthiolation using BT reagents, we first synthesized the new compound BT-SCF_2H. As for BT-SCF_3, BT-SCF_2H was efficiently prepared in a two-step protocol starting from MBT. Formal insertion of difluorocarbene obtained from HCF_2OTf into the S−H bond of MBT[20] followed by *N*-methylation with methyl triflate afforded the desired salt in high yields on scales up to at least 25 mmol. BT-SCF_2H was obtained as a pale yellow solid and, like BT-SCF_3, is bench stable over at least several months under ambient conditions (Scheme 3). In a test experiment, 1.25 equiv of BT-SCF_2H was then reacted with octanoic acid and NaH (3 equiv) in THF. After 2 h at rt, we were delighted to observe clean formation of the desired difluoromethylthioester **3a** in 72% NMR yield. The

https://dx.doi.org/10.1021/acs.orglett.0c03328
Org. Lett. 2020, 22, 8925−8930

Scheme 3. Synthesis of BT-SCF_2H



Scheme 4. Proposed Mechanism via Four-Membered TS



success of this transformation suggests that *in situ* activation of BT reagents can enable unprecedented nucleophilic difluoromethylthiolation reactions and that BT-SCF_2H itself could serve as a practical formal "$^{-}SCF_2H$" source.

A short optimization study led to the set of conditions shown in Scheme 2 (conditions B). Preforming the carboxylate with NaH for 30 min before addition of BT-SCF_2H led to the highest yields of thioesters **3** while, in contrast to the deoxytrifluoromethylthiolation reaction, cooling of the reaction mixture to −78 °C was not required. A survey of carboxylic acid substrates allowed for the facile synthesis of a range of diverse difluoromethylthioesters in generally good to excellent yields up to 99%. The method proved to be tolerant of several commonly encountered functional groups, such as nitro groups, halogens, heterocycles, and alkoxy groups. The reagent also proved capable of efficiently converting sterically encumbered substrates with the thioester of adamantane carboxylic acid (**3g**) being afforded in 79% yield. In general, aliphatic carboxylic acids reacted most smoothly although aromatic and heteroaromatic substrates could also be successfully converted in moderate yields.

The scope of both the deoxytrifluoromethylthiolation and difluoromethylthiolation reactions was then tested further with a selection of pharmaceuticals, agrochemicals, and natural products (Scheme 2). CF_3- or CF_2H-thioesters of several blockbuster drugs such as ibuprofen or naproxen as well as naturally occurring species such as linoleic acid could be obtained directly from the parent compounds in excellent yields using BT-SCF_3 or BT-SCF_2H. Moreover, the practical utility of the deoxyfunctionalization process was demonstrated by the gram-scale synthesis of ibuprofen derivative **3t** in 88% isolated yield (5 mmol scale).

The remarkable success of the deoxydifluoromethylthiolation reaction led us to consider the reaction mechanism more closely. Given the well-documented instability of $^{-}SCF_2H$, we considered whether an alternative mechanistic scenario to that outlined in Scheme 1a that avoids the intermediate formation of a free anion could be operating. In particular, a concerted process involving a four-membered transition state from intermediate **A** (Scheme 4) could provide the thioester product and thiocarbamate byproduct directly. Similar concerted mechanisms have been previously proposed in deoxygenative fluorination reactions of phenols using the imidazolium-based reagent Phenofluor.[21] In order to test this hypothesis, DFT calculations (B3LYP/def2-SVP)[22] were carried out on model intermediate **A** (R^1 = Et). As predicted, a concerted mechanism proceeding through the four-membered transition state **TS1** (Scheme 4) was found to be the most favored pathway for the deoxydifluoromethylthiolation reaction (energy barrier = 12.3 kcalmol^{-1} cf. 34.1 kcalmol^{-1} for release of $^{-}SCF_2H$). Moreover, an albeit more asynchronous concerted pathway was also predicted for the analogous trifluoromethylthiolation (see the SI). These results suggest BT reagents could open up hitherto unfeasible nucleophilic reaction pathways by circumventing the generation of an unstable free anion nucleophile.

In conclusion, fluorine-containing benzothiazolium salts have been employed as efficient reagents for deoxygenative substitution reactions of unactivated carboxylic acids. A wide range of trifluoromethylthioesters could be conveniently prepared using BT-SCF_3, while the novel reagent BT-SCF_2H allowed for an unprecedented nucleophilic difluoromethylthiolation reaction. The success of this latter transformation can be explained by the involvement of a four-membered concerted transition state that avoids the formation of the unstable $^{-}SCF_2H$ anion. As such, BT reagents could facilitate otherwise unachievable nucleophilic reaction pathways and further investigations of this concept for the formal installation of $^{-}SCF_2H$ or other unstable anions are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03328.

Experimental procedures, characterization data, and computational details (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Matthew N. Hopkinson − *Institut für Chemie und Biochemie, Freie Universität Berlin, 14195 Berlin, Germany;* orcid.org/0000-0002-0183-0466; Email: matthew.hopkinson@fu-berlin.de

Authors

Matteo Tironi − *Institut für Chemie und Biochemie, Freie Universität Berlin, 14195 Berlin, Germany*

Lilian M. Maas − *Institut für Chemie und Biochemie, Freie Universität Berlin, 14195 Berlin, Germany*

Arushi Garg − *Institut für Chemie und Biochemie, Freie Universität Berlin, 14195 Berlin, Germany*

https://dx.doi.org/10.1021/acs.orglett.0c03328
Org. Lett. 2020, 22, 8925−8930

Stefan Dix − *Institut für Chemie und Biochemie, Freie Universität Berlin, 14195 Berlin, Germany*
Jan P. Götze − *Institut für Chemie und Biochemie, Freie Universität Berlin, 14195 Berlin, Germany*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c03328

Author Contributions

†M.T. and L.M.M. contributed equally to this work.

Notes

The authors declare the following competing financial interest(s): M.N.H. and S.D. are coinventors on a European and International Patent Application concerning the synthesis and use of benzothiazolium reagents for installing fluorine-containing functional groups (EP 3 677 576 A1; WO 2020141195 A1).

■ ACKNOWLEDGMENTS

This work is funded by the Dahlem Research School and the Studienstiftung des deutschen Volkes (scholarship to M.T.). Financial support from the Daimler und Benz Stiftung (Project Nr. 32-04/18), the State of Berlin (Elsa Neumann scholarship to A.G.), the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation), Project-IDs 387284271-SFB 1349 and 393271229 (gefördert durch die Deutsche Forschungsgemeinschaft (DFG) - Projektnummer 387284271 - SFB 1349 and 393271229), and the Fonds der Chemischen Industrie (Sachkostenzuschuss) is also gratefully acknowledged. The theoretical calculations were prepared, executed, and evaluated by QoD Technologies GmbH. We acknowledge the assistance of the Core Facility BioSupraMol supported by the DFG.

■ REFERENCES

(1) Selected reviews: (a) Müller, K.; Faeh, C.; Diederich, F. Fluorine in Pharmaceuticals: Looking Beyond Intuition. *Science* **2007**, *317*, 1881−1886. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Fluorine in medicinal chemistry. *Chem. Soc. Rev.* **2008**, *37*, 320−330. (c) Berger, R.; Resnati, G.; Metrangolo, P.; Weber, E.; Hulliger, J. Organic fluorine compounds: a great opportunity for enhanced materials properties. *Chem. Soc. Rev.* **2011**, *40*, 3496−3508. (d) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001−2011). *Chem. Rev.* **2014**, *114*, 2432−2506. (e) Fujiwara, T.; O'Hagan, D. Successful fluorine-containing herbicide agrochemicals. *J. Fluorine Chem.* **2014**, *167*, 16−29. (f) Harsanyi, A.; Sandford, G. Organofluorine chemistry: applications, sources and sustainability. *Green Chem.* **2015**, *17*, 2081−2086. (g) Campbell, M. G.; Ritter, T. Modern Carbon−Fluorine Bond Forming Reactions for Aryl Fluoride Synthesis. *Chem. Rev.* **2015**, *115*, 612−633. (h) Ni, C.; Hu, J. The unique fluorine effects in organic reactions: recent facts and insights into fluoroalkylations. *Chem. Soc. Rev.* **2016**, *45*, 5441−5454. (i) Szpera, R.; Moseley, D. F. J.; Smith, L. B.; Sterling, A. J.; Gouverneur, V. The Fluorination of C−H Bonds: Developments and Perspectives. *Angew. Chem., Int. Ed.* **2019**, *58*, 14824−14848. (j) Koike, T.; Akita, M. Recent progress in photochemical radical di- and mono-fluoromethylation. *Org. Biomol. Chem.* **2019**, *17*, 5413−5419.

(2) Reviews: (a) Xu, X.-H.; Matsuzaki, K.; Shibata, N. Synthetic Methods for Compounds Having CF_3−S Units on Carbon by Trifluoromethylation, Trifluoromethylthiolation, Triflylation, and Related Reactions. *Chem. Rev.* **2015**, *115*, 731−764. (b) Shao, X.; Xu, C.; Lu, L.; Shen, Q. Shelf-Stable Electrophilic Reagents for Trifluoromethylthiolation. *Acc. Chem. Res.* **2015**, *48*, 1227−1236. (c) Barata-Vallejo, S.; Bonesi, S.; Postigo, A. Late stage trifluoromethylthiolation strategies for organic compounds. *Org. Biomol. Chem.* **2016**, *14*, 7150−7182. (d) Chachignon, H.; Cahard, D. State-of-the-Art in Electrophilic Trifluoromethylthiolation Reagents. *Chin. J. Chem.* **2016**, *34*, 445−454. (e) Barthelemy, A.-L.; Magnier, E.; Dagousset, G. Direct Trifluoromethylthiolation Reactions Involving Radical Processes. *Synthesis* **2018**, *50*, 4765−4776.

(3) Selected examples: (a) Munavalli, S.; Rohrbaugh, D. K.; Rossman, D. I.; Berg, F. J.; Wagner, G. W.; Durst, H. D. Trifluoromethylsulfenylation of Masked Carbonyl Compounds. *Synth. Commun.* **2000**, *30*, 2847−2854. (b) Ferry, A.; Billard, T.; Langlois, B. R.; Bacqué, E. Trifluoromethanesulfanylamides as Easy-to-Handle Equivalents of the Trifluoromethanesulfanyl Cation (CF_3S^+): Reaction with Alkenes and Alkynes. *Angew. Chem., Int. Ed.* **2009**, *48*, 8551−8555. (c) Shao, X.; Wang, X.; Yang, T.; Lu, L.; Shen, Q. An Electrophilic Hypervalent Iodine Reagent for Trifluoromethylthiolation. *Angew. Chem., Int. Ed.* **2013**, *52*, 3457−3460. (d) Yang, Y.-D.; Azuma, A.; Tokunaga, E.; Yamasaki, M.; Shiro, M.; Shibata, N. Trifluoromethanesulfonyl Hypervalent Iodonium Ylide for Copper-Catalyzed Trifluoromethylthiolation of Enamines, Indoles, and β-Keto Esters. *J. Am. Chem. Soc.* **2013**, *135*, 8782−8785. (e) Alazet, S.; Zimmer, L.; Billard, T. Electrophilic Trifluoromethylthiolation of Carbonyl Compounds. *Chem. - Eur. J.* **2014**, *20*, 8589−8593. (f) Xu, C.; Ma, B.; Shen, Q. *N*-Trifluoromethylthiosaccharin: An Easily Accessible, Shelf-Stable, Broadly Applicable Trifluoromethylthiolating Reagent. *Angew. Chem., Int. Ed.* **2014**, *53*, 9316−9320. (g) Zhang, P.; Li, M.; Xue, X.-S.; Xu, C.; Zhao, Q.; Liu, Y.; Wang, H.; Guo, Y.; Lu, L.; Shen, Q. *N*-Trifluoromethylthio-dibenzenesulfonimide: A Shelf-Stable, Broadly Applicable Electrophilic Trifluoromethylthiolating Reagent. *J. Org. Chem.* **2016**, *81*, 7486−7509. (h) Bonazaba Milandou, L. J. C.; Carreyre, H.; Alazet, S.; Greco, G.; Martin-Mingot, A.; Nkounkou Loumpangou, C.; Ouamba, J.-M.; Bouazza, F.; Billard, T.; Thibaudeau, S. Superacid-Catalyzed Trifluoromethylthiolation of Aromatic Amines. *Angew. Chem., Int. Ed.* **2017**, *56*, 169−172. (i) Yang, X.-G.; Zheng, K.; Zhang, C. Electrophilic Hypervalent Trifluoromethylthio-Iodine(III) Reagent. *Org. Lett.* **2020**, *22*, 2026−2031. (j) Wang, D.; Carlton, C. G.; Tayu, M.; McDouall, J. J. W.; Perry, G. J. P.; Procter, D. J. Trifluoromethyl Sulfoxides: Reagents for Metal-Free C−H Trifluoromethylthiolation. *Angew. Chem., Int. Ed.* **2020**, *59*, 15918−15922.

(4) Dix, S.; Jakob, M.; Hopkinson, M. N. Deoxytrifluoromethylthiolation and Selenylation of Alcohols by Using Benzothiazolium Reagents. *Chem. - Eur. J.* **2019**, *25*, 7635−7639.

(5) Review on substitution reactions of benzothiazolium salts: (a) Mukaiyama, T. New Synthetic Reactions Based on the Onium Salts of Aza-Arenes. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 707−721. Selected examples: (b) Mukaiyama, T.; Hojo, K. 2-Halo-3-ethylbenzothiazolium Salts as Reactive Coupling Reagents. *Chem. Lett.* **1976**, *5*, 267−270. (c) Hojo, K.; Mukaiyama, T. Synthesis of Alkyl Halides from Alcohols by the Reaction with 2-Alkoxy-3-ethylbenzothiazolium Salts. *Chem. Lett.* **1976**, *5*, 619−622. (d) Souto-Bachiller, F.; Bates, G. S.; Masamune, S. 2-Chloro-*N*-methylbenzothiazolium trifluoromethanesulphonate: an efficient condensing agent for the preparation of thiol esters and amides. *J. Chem. Soc., Chem. Commun.* **1976**, 719−720. (e) Mukaiyama, T.; Hojo, K. Optical Interconversion of Enantiomeric Secondary Alcohols using 2-Fluorobenzothiazolium Salt. *Chem. Lett.* **1976**, *5*, 893−896. (f) Kobayashi, S.; Tsutsui, M.; Mukaiyama, T. Biogenetic-like Cyclization of Farnesol and Neolidol to Bisabolene by the use of 2-Fluorobenzothiazolium Salt. *Chem. Lett.* **1977**, *6*, 1169−1172. (g) Souto-Bachiller, F. A.; Masamune, S. Reactions of the 2-alkoxy-*N*-methylbenzothiazolium ion and its synthetic utility. *Tetrahedron Lett.* **1977**, *18*, 1881−1884. (h) Mitsunobu, O.; Takemasa, A.; Endo, R. Intermolecular Dehydration between Carboxylic Acids and Alcohols by the use of Diethyl Azodicarboxylate and 3-Methylbenzothiazole-2-selone. *Chem. Lett.* **1984**, *13*, 855−858. (i) Ravi, D.; Babu Mereyala, H. A new mild method for the synthesis of esters and

benzenethiol esters by activation of pyridine-2-thiol or benzothiazol-2-thiol esters by methyl iodide. *Tetrahedron Lett.* **1989**, *30*, 6089−6090.
(6) Selected reports: (a) Haszeldine, R. N.; Kidd, J. M. Perfluoroalkyl derivatives of sulphur. Part III. Some reactions of trifluoromethanethiol, and spectroscopic properties of the > C:S group. *J. Chem. Soc.* **1955**, *0*, 3871−3880. (b) Tavener, S. J.; Adams, D. J.; Clark, J. H. Trifluoromethylthiolation of aromatic substrates using thiophosgene-fluoride salt reagents, and formation of by-products with multi-carbon chains. *J. Fluorine Chem.* **1999**, *95*, 171−176. (c) Liu, J.-B.; Xu, X.-H.; Chen, Z.-H.; Qing, F.-L. Direct Dehydroxytrifluoromethylthiolation of Alcohols Using Silver(I) Trifluoromethanethiolate and Tetra-*n*-butylammonium Iodide. *Angew. Chem., Int. Ed.* **2015**, *54*, 897−900. (d) Glenadel, Q.; Tlili, A.; Billard, T. Metal-Free Direct Dehydroxytri-fluoromethylthiolation of Alcohols via the Umpolung Reactivity of Trifluoromethanesulfenamides. *Eur. J. Org. Chem.* **2016**, *2016*, 1955−1957. (e) Scattolin, T.; Deckers, K.; Schoenebeck, F. Efficient Synthesis of Trifluoromethyl Amines through a Formal Umpolung Strategy from the Bench-Stable Precursor $(Me_4N)SCF_3$. *Angew. Chem., Int. Ed.* **2017**, *56*, 221−224. (f) Scattolin, T.; Pu, M.; Schoenebeck, F. Investigation of (Me_4N)-SCF_3 as a Stable, Solid and Safe Reservoir for $S = CF_2$ as a Surrogate for Thiophosgene. *Chem. - Eur. J.* **2018**, *24*, 567−571.
(7) (a) Man, E. H.; Coffman, D. D.; Muetterties, E. L. Synthesis and Properties of Bis-(trifluoromethylthio)-mercury. *J. Am. Chem. Soc.* **1959**, *81*, 3575−3577. (b) Kremlev, M. M.; Tyrra, W.; Naumann, D.; Yagupolskii, Y. L. S-Trifluoromethyl esters of thiocarboxylic acids, $RC(O)SCF_3$. *Tetrahedron Lett.* **2004**, *45*, 6101−6104. (c) Zhang, M.; Chen, J.; Chen, Z.; Weng, Z. Copper-mediated effective synthesis of *S*-trifluoromethyl esters by trifluoromethylthiolation of acid chlorides. *Tetrahedron* **2016**, *72*, 3525−3530.
(8) Mukherjee, S.; Patra, T.; Glorius, F. Cooperative Catalysis: A Strategy To Synthesize Trifluoromethyl-thioesters from Aldehydes. *ACS Catal.* **2018**, *8*, 5842−5846.
(9) Xu, B.; Li, D.; Lu, L.; Wang, D.; Hu, Y.; Shen, Q. Radical fluoroalkylthiolation of aldehydes with $PhSO_2SR_f$ (R_f = CF_3, C_2F_5, CF_2H or CH_2F): a general protocol for the preparation of fluoroalkylthioesters. *Org. Chem. Front.* **2018**, *5*, 2163−2166.
(10) Wang, M.-Y.; Zhu, X.-Q.; Zhang, X.-L.; Guo, R.-L.; Jia, Q.; Wang, Y.-Q. Synthesis of trifluoromethylthioesters from aldehydes via a visible light-promoted radical process. *Org. Biomol. Chem.* **2020**, *18*, 5918−5926.
(11) Reviews on fluoroalkyl thiosulfonate reagents: (a) Pannecoucke, X.; Besset, T. Use of $ArSO_2SR_f$ reagents: an efficient tool for the introduction of SR_f moieties. *Org. Biomol. Chem.* **2019**, *17*, 1683−1693. (b) Mampuys, P.; McElroy, C. R.; Clark, J. H.; Orru, R. V. A.; Maes, B. U. W. Thiosulfonates as Emerging Reactants: Synthesis and Applications. *Adv. Synth. Catal.* **2020**, *362*, 3−64.
(12) Mao, R.; Bera, S.; Cheseaux, A.; Hu, X. Deoxygenative trifluoromethylthiolation of carboxylic acids. *Chem. Sci.* **2019**, *10*, 9555−9559.
(13) Reviews: (a) Xiong, H.-Y.; Pannecoucke, X.; Besset, T. Recent Advances in the Synthesis of SCF_2H- and SCF_2FG-Containing Molecules. *Chem. - Eur. J.* **2016**, *22*, 16734−16749. (b) Xiao, X.; Zheng, Z.-T.; Li, T.; Zheng, J.-L.; Tao, T.; Chen, L.-M.; Gu, J.-Y.; Yao, X.; Lin, J.-H.; Xiao, J.-C. Recent Advances in Difluoromethylthiolation. *Synthesis* **2020**, *52*, 197−207.
(14) (a) Guo, S.-H.; Zhang, X.-L.; Pan, G.-F.; Zhu, X.-Q.; Gao, Y.-R.; Wang, Y.-Q. Synthesis of Difluoromethylthioesters from Aldehydes. *Angew. Chem., Int. Ed.* **2018**, *57*, 1663−1667. For an indirect approach via difluorocarbene insertion, see: (b) Krishnamurti, V.; Barrett, C.; Ispizua-Rodriguez, X.; Coe, M.; Prakash, G. K. S. Aqueous Base Promoted *O*-Difluoromethylation of Carboxylic Acids with $TMSCF_2Br$: Bench-Top Access to Difluoromethyl Esters. *Org. Lett.* **2019**, *21*, 9377−9380.
(15) An improved large-scale synthesis of BT-SCF_3 was developed starting from MBT and CF_3I (see the SI).
(16) Trifluoromethylthioethers resulting from ring opening of THF were observed as minor side products during the optimization study. For a similar ring-opening process affording trifluoromethylethers, see: Fantasia, S.; Welch, J. M.; Togni, A. Reactivity of a Hypervalent Iodine Trifluoromethylating Reagent toward THF: Ring Opening and Formation of Trifluoromethyl Ethers. *J. Org. Chem.* **2010**, *75*, 1779−1782.
(17) For a related decarbonylation of acid chlorides under the same conditions, see: Malapit, C. A.; Ichiishi, N.; Sanford, M. S. Pd-Catalyzed Decarbonylative Cross-Couplings of Aroyl Chlorides. *Org. Lett.* **2017**, *19*, 4142−4145.
(18) Wu, J.; Gu, Y.; Leng, X.; Shen, Q. Copper-Promoted Sandmeyer Difluoromethylthiolation of Aryl and Heteroaryl Diazonium Salts. *Angew. Chem., Int. Ed.* **2015**, *54*, 7648−7652.
(19) Applications in palladium-catalyzed cross-coupling: (a) Wu, J.; Liu, Y.; Lu, C.; Shen, Q. Palladium-catalyzed difluoromethylthiolation of heteroaryl bromides, iodides, triflates and aryl iodides. *Chem. Sci.* **2016**, *7*, 3757−3762. (b) Wu, J.; Lu, C.; Lu, L.; Shen, Q. Pd-Catalyzed Difluoromethylthiolation of Aryl Chlorides, Bromides and Triflates. *Chin. J. Chem.* **2018**, *36*, 1031−1034.
(20) For a related process with aromatic thiols, see Fier, P. S.; Hartwig, J. F. Synthesis of Difluoromethyl Ethers with Difluoromethyltriflate. *Angew. Chem., Int. Ed.* **2013**, *52*, 2092−2095.
(21) Review: (a) Neumann, C. N.; Ritter, T. Facile C−F Bond Formation through a Concerted Nucleophilic Aromatic Substitution Mediated by the PhenoFluor Reagent. *Acc. Chem. Res.* **2017**, *50*, 2822−2833. For a related mechanism with aryl fluorosulfonates, see: (b) Schimler, S. D.; Cismesia, M. A.; Hanley, P. S.; Froese, R. D. J.; Jansma, M. J.; Bland, D. C.; Sanford, M. S. Nucleophilic Deoxyfluorination of Phenols via Aryl Fluorosulfonate Intermediates. *J. Am. Chem. Soc.* **2017**, *139*, 1452−1455.
(22) (a) *Gaussian 16*, Revision C.01; Frisch, M. J. et al. Gaussian, Inc., Wallingford, CT, 2016. (b) Becke, A. D. Density-functional exchange-energy approximation with correct asymptotic behavior. *Phys. Rev. A: At., Mol., Opt. Phys.* **1988**, *38*, 3098−3100. (c) Lee, C.; Yang, W.; Parr, R. G. Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1988**, *37*, 785−789. (d) Weigend, F.; Ahlrichs, R. Balanced basis sets of split valence, triple zeta valence and quadruple zeta valence quality for H to Rn: Design and assessment of accuracy. *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297−3305. (e) Barone, V.; Cossi, M.; Tomasi, J. Geometry optimization of molecular structures in solution by the polarizable continuum model. *J. Comput. Chem.* **1998**, *19*, 404−417. (f) Ayala, P. Y.; Schlegel, H. B. A combined method for determining reaction paths, minima, and transition state geometries. *J. Chem. Phys.* **1997**, *107*, 375−384.

https://dx.doi.org/10.1021/acs.orglett.0c03328
Org. Lett. 2020, 22, 8925−8930

ORGANIC CHEMISTRY FRONTIERS

CCS 中国化学会 CHINESE CHEMICAL SOCIETY

SIOC 1950

ROYAL SOCIETY OF CHEMISTRY

RESEARCH ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Org. Chem. Front.*, 2021, **8**, 6026

Deoxygenative nucleophilic difluoromethylselenylation of carboxylic acids and alcohols with BT-$SeCF_2H$†

Matteo Tironi, Stefan Dix and Matthew N. Hopkinson *

Received 29th July 2021,
Accepted 22nd August 2021

DOI: 10.1039/d1qo01104a

rsc.li/frontiers-organic

The benzothiazolium salt BT-$SeCF_2H$ is introduced as an efficient nucleophilic reagent for transferring difluoromethylselenyl groups onto organic molecules. $SeCF_2H$-Containing selenoesters could be prepared upon deoxygenative substitution of readily available carboxylic acids, while silver catalysis allowed for efficient formation of (difluoromethyl)selenoethers, including the established electrophilic reagent $BnSeCF_2H$, directly from simple alcohols. To the best of our knowledge, these deoxygenative reactions represent the first reported nucleophilic difluoromethylselenylation processes and thus open up new approaches to prepare valuable fluorinated compounds.

Introduction

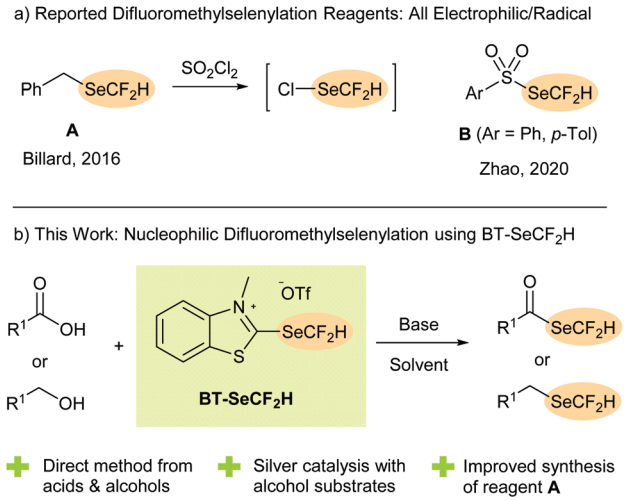
Incorporating fluorine atoms and larger fluorine-containing functional groups is a tried and tested method for modulating the physical characteristics, biological activity and bioavailability of organic compounds.[1] While well-established moieties such as the CF_3 group remain the most widely studied, the investigation of alternative fluorinated motifs that offer new possibilities for fine-tuning a molecule's properties has become a major area of research.[2] Organoselenium derivatives are fundamental for many biological functions, with selenium itself being an essential human micronutrient. Multiple selenoethers and selenoesters have accordingly attracted attention as potential therapeutics including as anticancer, anti-microbial and anti-viral agents.[3] Selenium derivatives have also found applications in materials science[4] and as versatile synthetic intermediates and catalysts, especially in oxidation and radical chemistry.[5]

Combining the beneficial effects of fluorine substitution with organoselenium chemistry is an attractive approach for developing new functional (bio)molecules and materials. In recent years, significant research interest has focused on fluoroalkylselenyl groups with the $SeCF_3$ moiety in particular being the subject of several studies.[6] The difluoromethylselenyl group ($SeCF_2H$), on the other hand, has been less extensively investigated despite the well-known advantages partially fluorinated groups can offer over the corresponding perfluoro analogues (*e.g.* lipophilicity modulation, conformational effects, potential for hydrogen bonding).[1,7] One reason for the lack of studies on the $SeCF_2H$ group is the scarcity of synthetic routes to access it. Traditionally, indirect methods involving either insertion of difluorocarbene into a selenol[8] or formal nucleophilic difluoromethylation of a diselenide or cyanoselenide were employed.[9] Direct difluoromethylselenylation methods, in which $SeCF_2H$ is installed as a whole group, do not require access to a selenium-containing precursor and allow $SeCF_2H$ to be more readily studied alongside other fluorinated or non-fluorinated groups in structure–activity relationship (SAR) investigations. To date, however, only two reagent classes have been developed for direct difluoromethylselenylation, with both serving as electrophilic or radical sources of the $SeCF_2H$ group. The selenoether $BnSeCF_2H$ (**A**, Scheme 1a), which is itself produced only in low yield (13–36%) from BnSeCN, typically requires *in situ* activation with SO_2Cl_2, with $ClSeCF_2H$ serving as the actual difluoromethylselenylation reagent.[10] Sulfonyl derivatives **B** (Ar = Ph, *p*-Tol, Scheme 1a) react under milder conditions but are themselves synthesised from **A**.[11] While nucleophilic approaches are commonly employed to install the $SeCF_3$ group, to the best of our knowledge, no direct nucleophilic difluoromethylselenylation method has been reported and there are currently no sources of the $^-SeCF_2H$ anion available.

In 2019, we introduced 2-fluoroalkylchalcogenyl-substituted benzothiazolium salts as new reagents for installing fluorine-containing groups onto organic molecules. These BT-reagents can be prepared from relatively inexpensive starting materials and serve as practical sources of fluoroalkylchalcogenyl anions in synthetically appealing deoxygenative functionalisation reac-

Institut für Chemie und Biochemie, Freie Universität Berlin, Fabeckstrasse 34-36, 14195 Berlin, Germany. E-mail: matthew.hopkinson@fu-berlin.de

†Electronic supplementary information (ESI) available: Experimental procedures, reaction optimisation, and characterisation data. See DOI: 10.1039/d1qo01104a



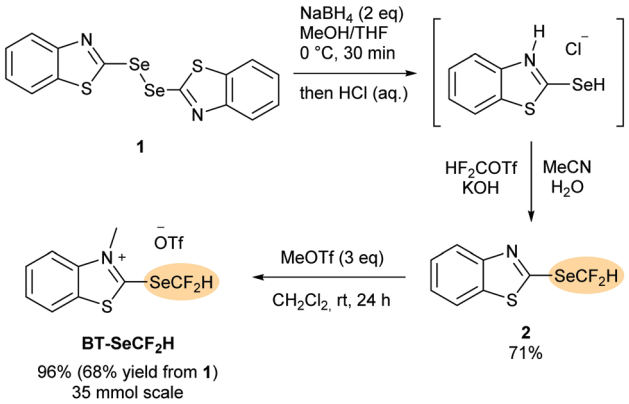
Scheme 1 (a) Established electrophilic and radical difluoromethylselenylation reagents. (b) This work: BT-$SeCF_2H$ as a nucleophilic reagent in deoxygenative substitution reactions of carboxylic acids and aliphatic alcohols.

tions of readily available aliphatic alcohols[12] and carboxylic acids.[13,14] In addition to perfluoroalkyl derivatives such as BT-SR_F ($R_F = C_nF_{2n-1}$) and BT-$SeCF_3$, recent work showed that the partially fluorinated analogue BT-SCF_2H could be successfully engaged in efficient deoxygenative difluoromethylthiolation reactions, providing (difluoromethyl)thioesters directly from carboxylic acids under mild conditions.[13] Inspired by these results, we considered whether a (difluoromethyl)selenium analogue could be accessed and, if so, whether it would act as a source of hitherto unexplored $^-SeCF_2H$ anions for nucleophilic transformations. Herein, we report the successful synthesis of BT-$SeCF_2H$ and its application as a reagent in unprecedented deoxygenative difluoromethylselenylation reactions (Scheme 1b). In addition to providing $SeCF_2H$-containing selenoesters from diverse carboxylic acids, silver catalysis allowed for the efficient synthesis of (difluoromethyl)selenoethers, including the established electrophilic reagent Bn$SeCF_2H$ (**A**), directly from unactivated alcohols.

Results and discussion

Synthesis of BT-$SeCF_2H$

The synthesis of the new benzothiazolium salt BT-$SeCF_2H$ is shown in Scheme 2. As for the other BT-reagents,[12–14] a two-stage approach was envisaged proceeding through a neutral non-methylated benzothiazole intermediate. In the first step, bis(benzothiazole)diselenide **1**[15] was reduced to the corresponding selenol using $NaBH_4$. Following precipitation as the benzothiazolium chloride adduct, subsequent treatment with difluorocarbene generated under basic conditions from HCF_2OTf afforded the stable heteroarene **2**, which could be isolated in 71% yield upon column chromatography.



Scheme 2 Synthesis of BT-$SeCF_2H$.

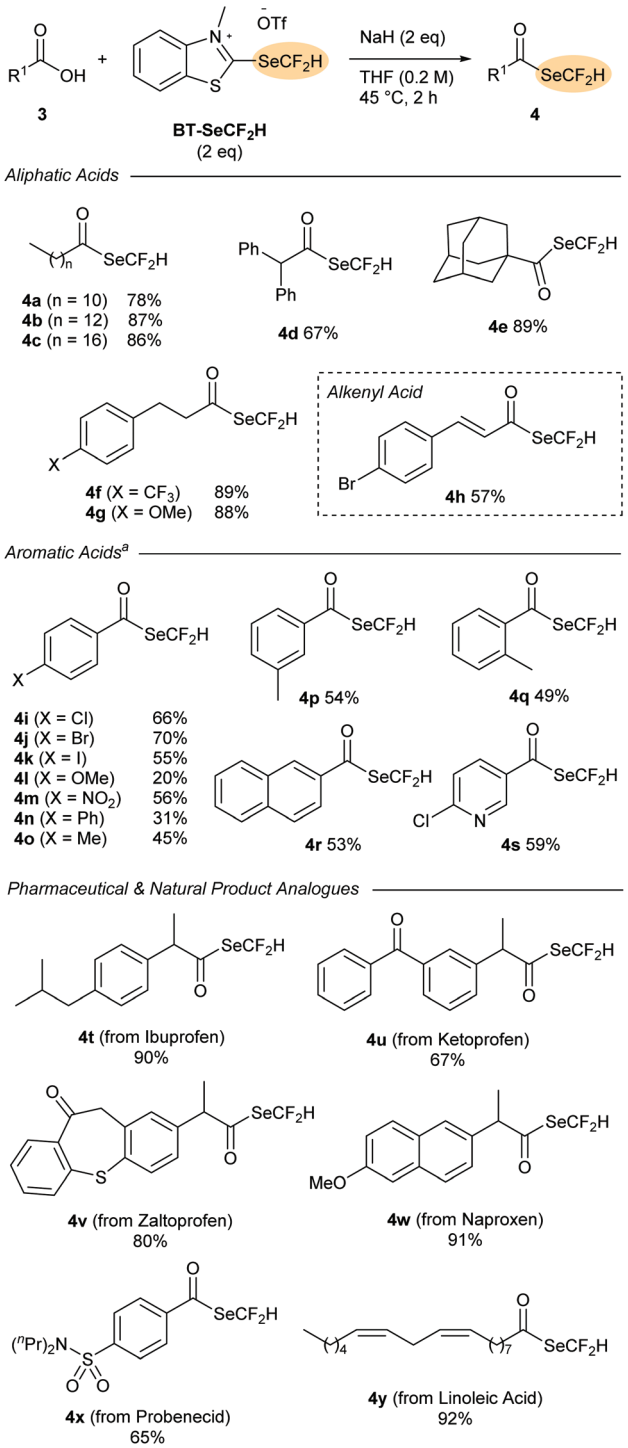
N-Methylation using methyl trifluoromethanesulfonate in CH_2Cl_2 at rt followed by precipitation with diethyl ether afforded BT-$SeCF_2H$ in 96% yield (overall yield of 68% from **1**, 35 mmol scale). BT-$SeCF_2H$ was obtained as an off-white solid that required no further purification and is stable at least over several months when stored under air at room temperature.

Deoxydifluoromethylselenylation of carboxylic acids

With BT-$SeCF_2H$ in hand, we sought to investigate its reactivity as a nucleophilic difluoromethylselenylating reagent. Inspired by the successful application of BT-SCF_2H in deoxygenative substitution reactions of carboxylic acids,[13] BT-$SeCF_2H$ (1.25 eq.) was first reacted with *n*-dodecanoic acid **3a** and NaH (2 eq.) in THF. After 2 h at rt, we were delighted to observe clean formation of the (difluoromethyl)selenoester **4a** in 45% NMR yield. Selenoesters have found multiple applications as pharmaceutical candidates and synthetic reagents, but studies on difluoromethyl derivatives are lacking.[16] In 2020, Wang and co-workers reported the only methodology for preparing (difluoromethyl)selenoesters; a radical process from aldehydes employing Bn$SeCF_2H$ (**A**) together with AIBN.[10f] The successful synthesis of (difluoromethyl)selenoesters using BT-$SeCF_2H$ not only offers a complementary route starting from readily available carboxylic acids, it also represents the first reported nucleophilic difluoromethylselenylation process. Mechanistically, **4a** likely results from an initial attack of the carboxylate to the 2-position of BT-$SeCF_2H$ followed either by elimination of $^-SeCF_2H$ and subsequent addition/elimination to a 2-carboxybenzothiazolium intermediate, or alternatively through a concerted rearrangement process.‡ Increasing the amount of BT-$SeCF_2H$ to 2 eq. and raising the reaction temperature to 45 °C improved the NMR yield to 81%, with **4a** being isolated in 78% yield after column chromatography.

The scope of the deoxygenative difluoromethylselenylation reaction was then tested with a range of carboxylic acid derivatives **3** (Scheme 3). A wide selection of aliphatic substrates

‡A concerted mechanism proceeding through a 4-membered transition state was suggested by DFT studies on the related deoxydifluoromethylthiolation of carboxylic acids with BT-SCF_2H (see ref. 13).



Scheme 3 Scope of the deoxydifluoromethylselenylation of carboxylic acids. Conditions: **3** (0.3 mmol), BT-$SeCF_2H$ (2 eq.), NaH (2 eq.) in THF (0.2 M), 45 °C, 2 h. Isolated yields. [a]Reactions conducted at rt.

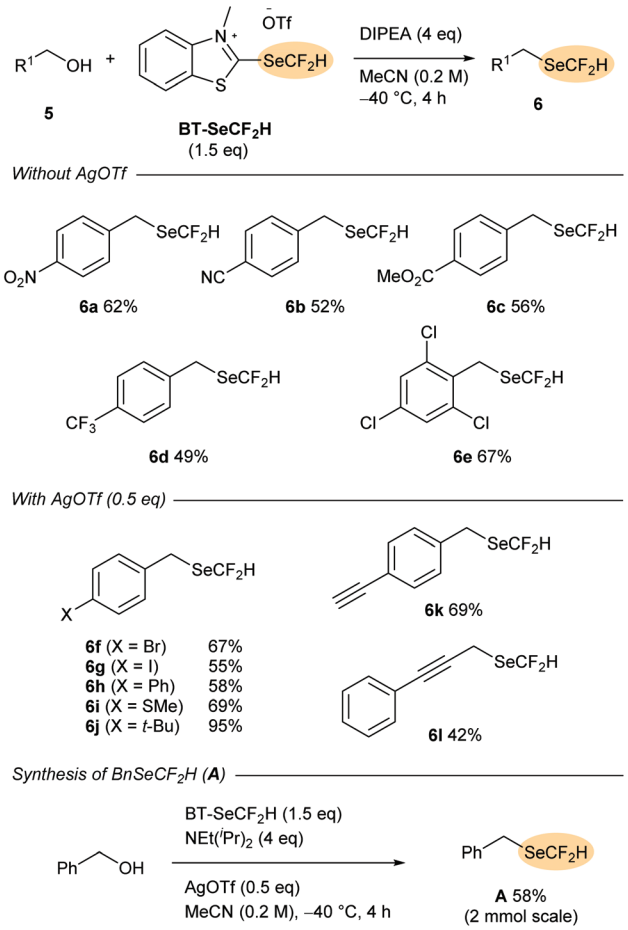
could be successfully converted into the corresponding (difluoromethyl)selenoesters **4a–g** in excellent yields (67–89%). Primary, secondary and even tertiary derivatives were all tolerated with 1-adamantanecarboxylic acid **3e** providing selenoester **4e** in 89% yield after column chromatography. Aromatic acids could also be successfully employed with these reactions being conducted at room temperature. A wide range of functional groups were tolerated with electron-neutral and comparatively electron-deficient moieties leading to the highest yields. The successful formation of the halogen-substituted products **4i–k** is particularly noteworthy as these compounds could serve as $SeCF_2H$-containing building blocks amenable to subsequent functionalisation through cross-coupling. As demonstrated by the series **4o–q**, substituents at the *ortho*-, *meta*- and *para*-positions were tolerated with little difference in the product yields observed.

Finally, the applicability of the deoxydifluoromethylselenylation method to the synthesis of $SeCF_2H$-containing pharmaceutical analogues was evaluated. A range of (difluoromethyl)selenoesters of common non-steroidal anti-inflammatory drugs (NSAIDs) could be prepared in excellent yields directly from the pharmaceutical compound (**4t–w**, 67–91%). The sulphonamide probenecid (**3x**), which is used to treat gout, could also be converted in 65% yield, while the naturally occurring fatty acid linoleic acid (**3y**) provided selenoester **4y** in 92% yield.

Deoxydifluoromethylselenylation of alcohols

Having established the reactivity of BT-$SeCF_2H$ as a nucleophilic reagent for the difluoromethylselenylation of carboxylic acids, we next turned our attention to the synthesis of selenoethers directly from aliphatic alcohols. Although more widely studied than (difluoromethyl)selenoesters, synthetic routes to alkyl-$SeCF_2H$ compounds are largely limited to indirect methods that require pre-installation of a diselenide or cyanoselenide motif onto the substrate.[9] To date, only a handful of direct difluoromethylselenylation reactions affording aliphatic products have been disclosed involving either nucleophilic attack onto *in situ*-activated $BnSeCF_2H$ (**A**)[10c,e] or, in a very recent report from Zhang and co-workers, radical group transfer from $PhSO_2SeCF_2H$ (**B**).[11c]

In an initial test reaction, 4-nitrobenzyl alcohol **5a** was reacted with BT-$SeCF_2H$ (1.25 eq.) and $NEt(^iPr)_2$ (2 eq.) in MeCN at rt. After 2 h, ^1H and ^{19}F NMR indicated the formation of the desired selenoether **6a** in 42% yield. Increasing the amount of reagent and base and adding them in portions, as well as the optimisation of the temperature (−40 °C) and reaction time (4 h) allowed for an increase in the NMR yield of **6a** to 65% with the pure product being isolated in 62% yield after column chromatography. At this stage, the generality of the method was tested with a selection of benzylic alcohols (Scheme 4). While a series of substrates bearing electron-withdrawing substituents such as –CN, $–CF_3$ and $–CO_2Me$ provided the corresponding (difluoromethyl)selenoethers **6a–e** in good yields, more electron-rich derivatives reacted only with low efficiency. Addition of these alcohols to the BT-reagent followed by elimination of $^-SeCF_2H$ would lead to a comparatively less electrophilic 2-alkoxybenzothiazolium intermediate. Nucleophilic substitution at this species is likely less favoured, and decomposition of the $^-SeCF_2H$ anion may outcompete product formation. With the aim of providing a stabilising



Scheme 4 Scope of the deoxydifluoromethylselenylation of aliphatic alcohols. Conditions: **5** (0.3 mmol), BT-$SeCF_2H$ (2 eq.), $NEt(^iPr)_2$ (2 eq.) and, where indicated AgOTf (0.5 eq.), in MeCN (0.2 M), –40 °C, 2 h then additional BT-$SeCF_2H$ (0.25 eq.), $NEt(^iPr)_2$ (2 eq.) added, stirred for another 2 h at –40 °C. Isolated yields.

counter-cation, which could increase the lifetime of $^-SeCF_2H$ in the reaction medium, silver(I) salts were tested as catalytic additives. While 4-bromobenzyl-containing selenoether **6f** was provided in only 31% yield under the standard conditions described above, addition of Ag_2O (0.25 eq., 0.5 eq. of Ag^+) led to an increase in NMR yield to 63%. Moreover, selenoether **6f** was obtained in 81% NMR yield (67% isolated) when the reaction was conducted in the presence of AgOTf (0.5 eq.).

Under these silver catalysis conditions, good yields were obtained with a selection of electron-neutral and electron-rich benzyl alcohols (**5g–k**, up to 95% with 4-(*tert*-butyl)benzyl alcohol **5h**), while the propargylic substrate **5l** also reacted with moderate efficiency (42% yield of **6l**). Notably, the method is also tolerant of terminal alkynes (**6k**), which are known to be activated by silver(I). Finally, direct deoxytrifluoromethylselenylation of benzyl alcohol was tested as a method for preparing BnSeCF_2H (**A**). This electrophilic and radical difluoromethylselenylation reagent was introduced by Billard and co-workers in 2016[10a] and has been previously synthesised from benzyl bromide in a two-step sequence involving nucleophilic difluoromethylation of BnSeCN.[10a,e,11c] Subjecting BnOH to the optimised conditions with BT-$SeCF_2H$ (1.5 eq.), AgOTf (0.5 eq.) and $NEt(^iPr)_2$ (4 eq.) resulted in smooth formation of the established reagent **A**, which could be isolated in 58% yield after column chromatography on a 2 mmol scale. This yield is notably higher than that obtained in the previously-reported difluoromethylation of BnSeCN (13–36%)[10a,e,11c] and suggests that direct deoxygenative difluoromethylselenylation could serve as a useful complementary approach to prepare reagent **A** and, by extension, its derivatives **B**.

Conclusions

In conclusion, BT-$SeCF_2H$ has been introduced as a practical reagent for hitherto unexplored nucleophilic difluoromethylselenylation reactions. Deoxygenative substitution of carboxylic acids provides (difluoromethyl)selenoesters, while silver catalysis allows for the efficient synthesis of benzylic and propargylic CF_2H-substituted selenoethers, including the established electrophilic reagent Bn$SeCF_2H$ (**A**), directly from unactivated alcohols. In opening up nucleophilic approaches, we believe this work will inspire new routes towards difluoromethylselenylated compounds and accelerate the study of the $SeCF_2H$ group in medicinal and materials chemistry.

Conflicts of interest

M.N.H. and S.D. are co-inventors on a European and International Patent Application concerning the synthesis and use of benzothiazolium reagents for installing fluorine-containing functional groups (EP 3 677 576 A1; WO 2020141195 A1).

Acknowledgements

This work is funded by the Dahlem Research School, the Studienstiftung des deutschen Volkes (scholarship to M.T.) and the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – Project-ID 387284271 – SFB 1349 (gefördert durch die Deutsche Forschungsgemeinschaft (DFG) – Projektnummer 387284271 – SFB 1349). Financial support from the Fonds der Chemischen Industrie (FCI, Sachkostenzuschuss) is also gratefully acknowledged. We would like to acknowledge the assistance of the Core Facility BioSupraMol supported by the DFG.

Notes and references

1 Selected reviews: (*a*) K. Müller, C. Faeh and F. Diederich, Fluorine in Pharmaceuticals: Looking Beyond Intuition, *Science*, 2007, **317**, 1881; (*b*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, Fluorine in medicinal chemistry, *Chem. Soc. Rev.*, 2008, **37**, 320; (*c*) R. Berger,

G. Resnati, P. Metrangolo, E. Weber and J. Hulliger, Organic fluorine compounds: a great opportunity for enhanced materials properties, *Chem. Soc. Rev.*, 2011, **40**, 3496; (*d*) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001–2011), *Chem. Rev.*, 2014, **114**, 2432; (*e*) T. Fujiwara and D. O'Hagan, Successful fluorine-containing herbicide agrochemicals, *J. Fluorine Chem.*, 2014, **167**, 16; (*f*) A. Harsanyi and G. Sandford, Organofluorine chemistry: applications, sources and sustainability, *Green Chem.*, 2015, **17**, 2081; (*g*) M. G. Campbell and T. Ritter, Modern Carbon–Fluorine Bond Forming Reactions for Aryl Fluoride Synthesis, *Chem. Rev.*, 2015, **115**, 612; (*h*) C. Ni and J. Hu, The unique fluorine effects in organic reactions: recent facts and insights into fluoroalkylations, *Chem. Soc. Rev.*, 2016, **45**, 5441; (*i*) R. Szpera, D. F. J. Moseley, L. B. Smith, A. J. Sterling and V. Gouverneur, The Fluorination of C–H Bonds: Developments and Perspectives, *Angew. Chem., Int. Ed.*, 2019, **58**, 14824; (*j*) T. Koike and M. Akita, Recent progress in photochemical radical di- and mono-fluoromethylation, *Org. Biomol. Chem.*, 2019, **17**, 5413; (*k*) M. Inoue, Y. Sumii and N. Shibata, Contribution of Organofluorine Compounds to Pharmaceuticals, *ACS Omega*, 2020, **5**, 10633.

2 D. Cahard and J.-A. Ma, *Emerging Fluorinated Motifs: Synthesis, Properties and Applications*, Wiley-VCH, Weinheim, 2020.

3 Selected reviews: (*a*) C. W. Nogueira, G. Zeni and J. B. T. Rocha, Organoselenium and Organotellurium Compounds: Toxicology and Pharmacology, *Chem. Rev.*, 2004, **104**, 6255; (*b*) M. P. Rayman, Selenium and human health, *Lancet*, 2012, **379**, 1256; (*c*) V. K. Jain and K. I. Priyadarsini, *Organoselenium Compounds in Biology and Medicine: Synthesis, Biological and Therapeutic Treatments*, Royal Society of Chemistry, Cambridge (UK), 2018.

4 Selected reviews: (*a*) M. A. Malik, M. Afzaal and P. O'Brien, Precursor Chemistry for Main Group Elements in Semiconducting Materials, *Chem. Rev.*, 2010, **110**, 4417; (*b*) Q. Li, Y. Zhang, Z. Chen, X. Pan, Z. Zhang, J. Zhu and X. Zhu, Organoselenium chemistry-based polymer synthesis, *Org. Chem. Front.*, 2020, **7**, 2815.

5 Selected reviews: (*a*) A. T. Diplock and F. D. Kurzer, Organic Selenium Compounds: Their Chemistry and Biology, *Biochem. Soc. Trans.*, 1974, **2**, 571; (*b*) T. Wirth, Organoselenium Chemistry in Stereoselective Reactions, *Angew. Chem., Int. Ed.*, 2000, **39**, 3740; (*c*) D. M. Freudendahl, S. A. Shahzad and T. Wirth, Recent Advances in Organoselenium Chemistry, *Eur. J. Org. Chem.*, 2009, 1649; (*d*) D. Freudendahl, S. Santoro, S. Shahzad, C. Santi and T. Wirth, Green Chemistry with Selenium Reagents: Development of Efficient Catalytic Reactions, *Angew. Chem., Int. Ed.*, 2009, **48**, 8409.

6 Reviews: (*a*) A. Tlili, E. Ismalaj, Q. Glenadel, C. Ghiazza and T. Billard, Synthetic Approaches to Trifluoromethylselenolated Compounds, *Chem. – Eur. J.*, 2018, **24**, 3659; (*b*) C. Ghiazza and A. Tlili, Copper-promoted/copper-catalyzed trifluoromethylselenolation reactions, *Beilstein J. Org. Chem.*, 2020, **16**, 305.

7 (*a*) J. A. Erickson and J. I. McLoughlin, Hydrogen Bond Donor Properties of the Difluoromethyl Group, *J. Org. Chem.*, 1995, **60**, 1626; (*b*) Q. A. Huchet, B. Kuhn, B. Wagner, H. Fischer, M. Kansy, D. Zimmerli, E. M. Carreira and K. Müller, On the polarity of partially fluorinated methyl groups, *J. Fluorine Chem.*, 2013, **152**, 119; (*c*) Y. Zafrani, D. Yeffet, G. Sod-Moriah, A. Berliner, D. Amir, D. Marciano, E. Gershonov and S. Saphier, Difluoromethyl Bioisostere: Examining the "Lipophilic Hydrogen Bond Donor" Concept, *J. Med. Chem.*, 2017, **60**, 797.

8 (*a*) H. Suzuki, M. Yoshinaga, K. Takaoka and Y. Hiroi, Simple Synthesis of Aryl Difluoromethyl Selenides and Tellurides, *Synthesis*, 1985, 497; (*b*) V. P. Mehta and M. F. Greaney, S-, N-, and, Se-Difluoromethylation Using Sodium Chlorodifluoroacetate, *Org. Lett.*, 2013, **15**, 5036; (*c*) N. B. Heine and A. Studer, Radical Difluoromethylation of Thiols with (Difluoromethyl)triphenylphosphonium Bromide, *Org. Lett.*, 2017, **19**, 4150.

9 (*a*) Y.-m. Lin, W.-b. Yi, W.-z. Shen and G.-p. Lu, A Route to α-Fluoroalkyl Sulfides from α-Fluorodiaroylmethanes, *Org. Lett.*, 2016, **18**, 592; (*b*) T. Dong, J. Nie and C.-P. Zhang, A convenient, transition metal-free synthesis of difluoromethyl selenoethers from organic selenocyanates and $TMSCF_2H$, *Tetrahedron*, 2018, **74**, 5642; (*c*) S. Jin, Z. Kuang and Q. Song, Precise Construction of SCF_2H or $SeCF_2H$ Groups on Heteroarenes Generated in Situ from CF_3-Containing 1,3-Enynes, *Org. Lett.*, 2020, **22**, 615.

10 (*a*) Q. Glenadel, E. Ismalaj and T. Billard, Benzyltrifluoromethyl (or Fluoroalkyl) Selenide: Reagent for Electrophilic Trifluoromethyl (or Fluoroalkyl) Selenolation, *J. Org. Chem.*, 2016, **81**, 8268; (*b*) C. Ghiazza, T. Billard and A. Tlili, Trifluoromethyl- and Fluoroalkylselenolations of Alkynyl Copper(I) Compounds, *Chem. – Eur. J.*, 2017, **23**, 10013; (*c*) C. Ghiazza, Q. Glenadel, A. Tlili and T. Billard, Trifluoromethylselenolation and Fluoroalkylselenolation of Alkenes by Electrophilic Addition, *Eur. J. Org. Chem.*, 2017, 3812; (*d*) Q. Glenadel, E. Ismalaj and T. Billard, A Metal-Free Route to Heterocyclic Trifluoromethyl- and Fluoroalkylselenolated Molecules, *Org. Lett.*, 2018, **20**, 56; (*e*) C. Ghiazza, A. Tlili and T. Billard, Direct α-C–H Trifluoromethylselenolation of Carbonyl Compounds, *Eur. J. Org. Chem.*, 2018, 3680; (*f*) R.-L. Guo, X.-Q. Zhu, X.-L. Zhang and Y.-Q. Wang, Synthesis of difluoromethylselenoesters from aldehydes via a radical process, *Chem. Commun.*, 2020, **56**, 8976.

11 (*a*) K. Lu, Q. Li, X. Xi, T. Zhou and X. Zhao, Metal-Free Difluoromethylselenolation of Arylamines Under Visible-Light Photocatalysis, *J. Org. Chem.*, 2020, **85**, 1224; (*b*) K. Lu, X. Xi, T. Zhou, L. Lei, Q. Li and X. Zhao, Copper-catalysed direct difluoromethylselenolation of aryl boronic acids with Se-(difluoromethyl) 4-methylbenzenesulfonoselenoate,

Tetrahedron Lett., 2021, **68**, 152897; (*c*) H. Zhang, F. Yu, C. Li, P. Tian, Y. Zhou and Z.-Y. Cao, Iron-Catalyzed, Site-Selective Difluoromethylthiolation ($-SCF_2H$) and Difluoromethylselenation ($-SeCF_2H$) of Unactivated C(sp^3)–H Bonds in *N*-Fluoroamides, *Org. Lett.*, 2021, **23**, 4721.

12 (*a*) S. Dix, M. Jakob and M. N. Hopkinson, Deoxytrifluoromethylthiolation and Selenylation of Alcohols by Using Benzothiazolium Reagents, *Chem. – Eur. J.*, 2019, **25**, 7635–7639; (*b*) A. Ariamajd, N. J. Gerwien, B. Schwabe, S. Dix and M. N. Hopkinson, Benzothiazolium salts as reagents for the deoxygenative perfluoroalkylthiolation of alcohols, *Beilstein J. Org. Chem.*, 2021, **17**, 83.

13 M. Tironi, L. M. Maas, A. Garg, S. Dix, J. P. Götze and M. N. Hopkinson, Deoxygenative Tri- and Difluoromethylthiolation of Carboxylic Acids with Benzothiazolium Reagents, *Org. Lett.*, 2020, **22**, 8925.

14 M. N. Hopkinson and S. Dix, Fluorine-containing compounds for use as nucleophilic reagents for transferring functional groups onto high value organic compounds, *Eur. Pat. Appl* EP19150201, 2019; M. N. Hopkinson and S. Dix, Fluorine-containing compounds for use as nucleophilic reagents for transferring functional groups onto high value organic compounds, *International Pat. Appl*. PCT/EP2020/050031, 2020.

15 K. Shibata and O. Mitsunobu, Preparation of 1,4-Dienes from 2-(2-Hydroxyalkylseleno)benzothiazoles by the Reaction Involving Se→O Azaaromatic Ring Rearrangement, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 3163.

16 Selected examples of selenoesters in medicine: (*a*) N. Díaz-Argelich, I. Encío, D. Plano, A. P. Fernandes, J. A. Palop and C. Sanmartín, Novel Methylselenoesters as Antiproliferative Agents, *Molecules*, 2017, **22**, 1288; (*b*) A. Csonka, A. Kincses, M. Nové, Z. Vadas, C. Sanmartín, E. Dominguez-Álvarez and G. Spengler, Selenoesters and Selenoanhydrides as Novel Agents Against Resistant Breast Cancer, *Anticancer Res.*, 2019, **39**, 3777; (*c*) M. L. De la Cruz-Claure, A. A. Cèspedes-Llave, M. T. Ulloa, M. Benito-Lama, E. Domínguez-Álvarez and A. Bastida, Inhibition–Disruption of Candida glabrata Biofilms: Symmetrical Selenoesters as Potential Anti-Biofilm Agents, *Microorganisms*, 2019, **7**, 664; (*d*) T. Mosolygó, A. Kincses, A. Csonka, Á. S. Tönki, K. Witek, C. Sanmartín, M. A. Marć, J. Handzlik, K. Kieć-Kononowicz, E. Domínguez-Álvarez and G. Spengler, Selenocompounds as Novel Antibacterial Agents and Bacterial Efflux Pump Inhibitors, *Molecules*, 2019, **24**, 1487; (*e*) G. Spengler, A. Kincses, T. Mosolygó, M. A. Marć, M. Nové, M. Gajdács, C. Sanmartín, H. E. McNeil, J. M. A. Blair and E. Domínguez-Álvarez, Antiviral, Antimicrobial and Antibiofilm Activity of Selenoesters and Selenoanhydrides, *Molecules*, 2019, **24**, 4264. Selected examples of selenoesters as synthetic intermediates: (*f*) A. P. Kozikowski and A. Ames, Copper(I) promoted acylation reactions. A transition metal mediated version of the Friedel-Crafts reaction, *J. Am. Chem. Soc.*, 1980, **102**, 860; (*g*) D. L. Boger and R. J. Mathvink, Tandem free-radical alkene addition reactions of acyl radicals, *J. Am. Chem. Soc.*, 1990, **112**, 4003; (*h*) E. Wenkert and D. Chianelli, Nickel-catalysed decarbonylation of thioesters, *J. Chem. Soc., Chem. Commun.*, 1991, 627; (*i*) S. Grélaud, V. Desvergnes and Y. Landais, Stereocontrolled $(Me_3Si)_3Si$ H-Mediated Radical and Ionic Hydride Transfer in Synthesis of 2,3,5-Trisubstituted THF, *Org. Lett.*, 2016, **18**, 1542; (*j*) G. Pandey, S. K. Tiwari, B. Singh, K. Vanka and S. Jain, *p*-Selective (sp^2)-C–H functionalization for an acylation/alkylation reaction using organic photoredox catalysis, *Chem. Commun.*, 2017, **53**, 12337; (*k*) X. Fan and Z. Gu, Palladium/Norbornene-Catalyzed *Ortho*-Acylation and *Ipso*-Selenation via C(O)–Se Bond Cleavage: Synthesis of α-Carbonyl Selane, *Org. Lett.*, 2018, **20**, 1187.

EurJOC
European Journal of Organic Chemistry

Research Article
doi.org/10.1002/ejoc.202101557

Chemistry Europe
European Chemical Societies Publishing

www.eurjoc.org

Silver-Catalyzed Nucleophilic Deoxydifluoromethylthiolation of Activated Aliphatic Alcohols with BT–SCF_2H

Matteo Tironi[a, b] and Matthew N. Hopkinson*[a, b]

Deoxygenative conversion of alcohols into difluoromethylthioethers is reported using 2-((difluoromethyl)thio)-3-methylbenzo[*d*]thiazol-3-ium triflate (BT–SCF_2H) as a source of $^{-}SCF_2H$ anions. The presence of silver(I) triflate as a catalyst was found to be crucial for stabilizing the *in situ*-generated anion, while the concomitant formation of a reactive 2-(alkoxy)benzothiazolium electrophile likely ensures a fast onward substitution reaction, avoiding the build-up of $^{-}SCF_2H$. To the best of our knowledge, this process represents the first report of a direct nucleophilic substitution reaction with $^{-}SCF_2H$ and delivers products containing the medicinally relevant difluoromethylthio motif in a single step from widely available alcohols.

Introduction

Substitution of drug or agrochemical candidates with fluorine has become a widespread strategy for improving their bioavailability and *in vivo* activity.[1] While single fluorine atoms and the trifluoromethyl (CF_3) group remain the most widely incorporated fluorine-containing motifs, recent efforts have increasingly focused on so-called emerging fluorinated groups such as OCF_3, SCF_3 or SF_5.[2] These moieties impart differing influences on the parent molecule and their incorporation in place of F atoms or CF_3 groups can result in an improvement or fine-tuning of the compound's lipophilicity and other steric and electronic properties. Partially fluorinated motifs such the difluoromethylthio (SCF_2H) group have been the subject of considerable recent interest.[3] In addition to this group's high hydrophobicity and strong electron-withdrawing properties, the relatively acidic hydrogen atom in SCF_2H is potentially available for hydrogen bonding, opening up new possibilities for beneficial intermolecular interactions *in vivo*.[4] As a result of these attractive features, several pharmaceutical and agrochemical candidates featuring the SCF_2H motif have been developed, including the insecticide Pyriprole and the antibiotic Flomoxef sodium (Scheme 1a).

Difluoromethylthio-substituted molecules are most commonly synthesized via difluoromethylation of the corresponding thiol, disulfide or thiocyanate.[3] Considering the limited availability of such moieties in many organic substrates, one-pot procedures have been developed that involve the *in-situ* synthesis of sulfur-containing intermediate species.[5] Recently, however, a selection of direct difluoromethylthiolation methodologies have been developed, in which the entire SCF_2H group is attached in one step.[3] These approaches do not require the pre-installation of a sulfur-containing moiety onto the substrate and thus extend the scope of compounds amenable for substitution with SCF_2H. The development of difluoromethylthiolation reactions relies on the availability of suitable reagents. Significant progress in this respect has been made for electrophilic and radical difluoromethylthiolation with Shen and co-workers developing several synthetically useful reagents such as *N*-(difluoromethyl)phthalimide (**A**, Scheme 1b) and $PhSO_2SCF_2H$ (**B**).[6–9] Nucleophilic difluoromethylthiolation, on the other hand, has been much less widely applied, largely due to the apparent instability of the $^{-}SCF_2H$ anion.[10] To date, only one metal-SCF_2H complex has been successfully prepared and employed as a source of $^{-}SCF_2H$: the *N*-heterocyclic carbene containing silver(I) species (SIPr)$AgSCF_2H$ (**C**, Scheme 1b, SIPr = 1,3-bis-(2,6-diisopropylphenyl)imidazolinylidene). This compound was introduced by Shen and co-workers in 2015 and has been applied in copper and palladium-catalyzed reactions affording aromatic (difluoromethyl)thioethers from aryl diazonium salts, halides and triflates.[11]

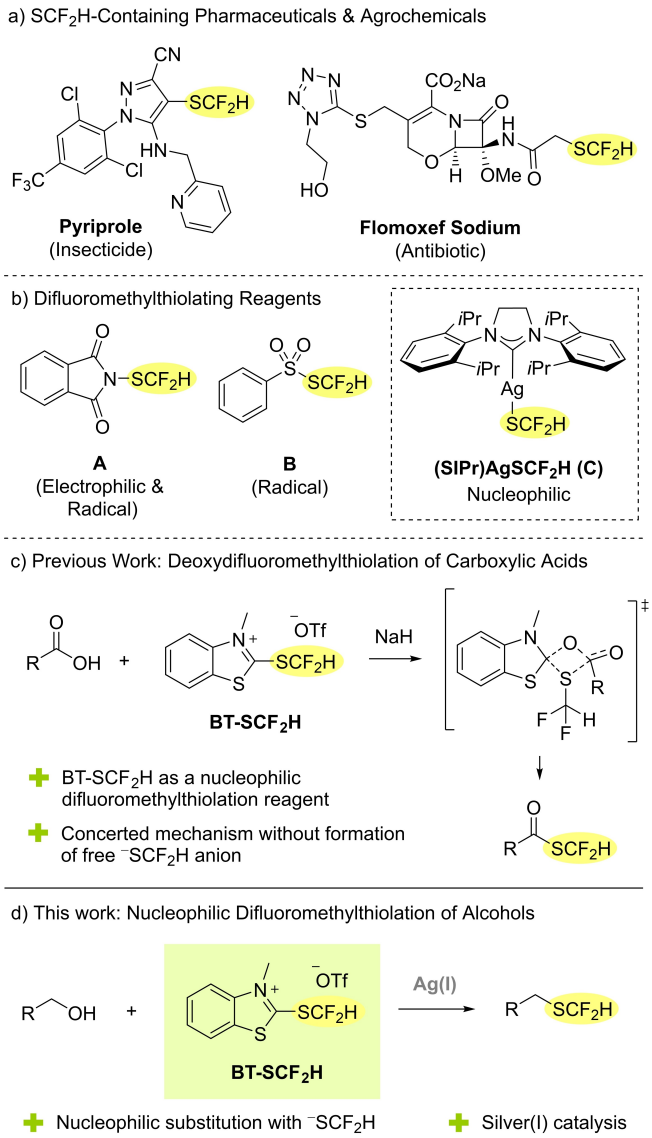
In 2019, we introduced benzothiazolium salts as new nucleophilic reagents for installing valuable fluorine-containing groups into organic molecules.[12,13] Initially, these reagents were employed in deoxygenative trifluoromethylthiolation and selenylation reactions of aliphatic alcohols[12,14] while subsequent work focused on the synthesis of (fluoroalkyl)thio- and selenoesters directly from widely available carboxylic acids.[14b,15,16] In addition to (trifluoromethyl)thiolation using BT–SCF_3, in the latter project, (difluoromethyl)thioesters could

[a] *M. Tironi, Dr. M. N. Hopkinson*
Institute of Chemistry and Biochemistry
Freie Universität Berlin
Fabeckstrasse 34–36, 14195 Berlin, Germany
[b] *M. Tironi, Dr. M. N. Hopkinson*
School of Natural and Environmental Sciences
Newcastle University
Bedson Building, Newcastle upon Tyne, NE1 7RU, UK
E-mail: matthew.hopkinson@newcastle.ac.uk
https://blogs.ncl.ac.uk/matthewhopkinson/

Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202101557

Research Article
doi.org/10.1002/ejoc.202101557

Chemistry Europe
European Chemical Societies Publishing

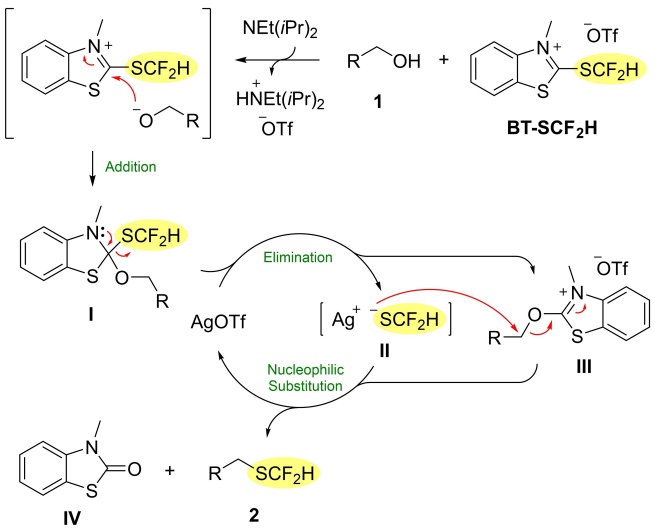


Scheme 1. a) Examples of SCF_2H-containing agrochemicals and pharmaceuticals. b) Difluoromethylthiolation reagents. c) Previous work: Deoxydifluoromethylthiolation of carboxylic acids with BT–SCF_2H. d) This work: Silver-catalyzed deoxygenative nucleophilic difluoromethylthiolation of alcohols with BT–SCF_2H.

be prepared employing 2-((difluoromethyl)thio)-3-methylbenzo[*d*]thiazol-3-ium triflate (BT–SCF_2H, Scheme 1c). This compound, which can be synthesized in two steps from inexpensive 2-(mercapto)benzothiazole (MBT), serves as a nucleophilic source of the SCF_2H group and thus represents only the second such reagent alongside (SIPr)AgSCF_2H (**C**). DFT calculations on the deoxydifluoromethylthiolation reaction, however, suggested that a concerted mechanism involving a four-membered ring transition state was likely operating and that free $^-SCF_2H$ anions were not formed during the process.[12] We therefore became interested in investigating the scope of BT–SCF_2H as a general nucleophilic difluoromethylthiolation reagent and, more specifically, in determining whether BT–SCF_2H could serve as a practical source of $^-SCF_2H$ anions for nucleophilic substitution reactions. Here we report the successful application of BT–SCF_2H in a silver-catalyzed deoxygenative difluoromethylthiolation of alcohols. To the best of our knowledge, this reaction represents the first report of a nucleophilic substitution involving $^-SCF_2H$ and provides (difluoromethyl)thioethers in a single step from simple alcohols (Scheme 1d).

Results and Discussion

The development of a successful nucleophilic deoxydifluoromethylthiolation of alcohols requires that substitution with $^-SCF_2H$ outcompetes any decomposition of the anion. Several features of reactions involving benzothiazolium reagents are well suited to this requirement. Firstly, rather than being present throughout the reaction, $^-SCF_2H$ is instead released in a controlled manner upon addition/elimination of the alcohol to BT–SCF_2H. Furthermore, this step results in the simultaneous generation of a highly reactive 2-(alkoxy)benzothiazolium electrophile, which can then react directly with $^-SCF_2H$, ensuring the concentration of the unstable anion in the reaction mixture remains low (Scheme 2). Initial experiments reacting 4-bromobenzyl alcohol (**1a**) with BT–SCF_2H (1.2 & 0.3 equiv., two additions) and NEt(*i*Pr)$_2$ (2.0 & 2.0 equiv.), however, were not encouraging. After 4 h at −40 °C in MeCN, the desired product **2a** was not observed by ^1H and ^{19}F NMR (Table 1, entry 1). Hypothesizing that the provision of alternative, more covalently binding cations may help to stabilize the *in situ*-generated $^-SCF_2H$ anion, we next tested sources of silver(I). Alcohol **1a** was thus reacted under the same conditions in the presence of 0.1 equiv. of AgOTf. To our delight, difluoromethylthioether **2a** was formed in 30% ^1H NMR yield, while increasing the loading up to 0.5 equiv. provided **2a** in 61% ^1H NMR yield (Table 1, entries 2,3). To the best of our knowledge, this reaction represents the first known example of

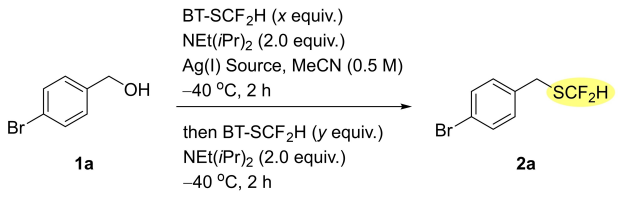


Scheme 2. Proposed mechanism for the deoxygenative nucleophilic difluoromethylthiolation of alcohols with BT–SCF_2H.

Research Article
doi.org/10.1002/ejoc.202101557

Chemistry Europe
European Chemical Societies Publishing

Table 1. Optimization table using **1a** as model substrate.



1a **2a**

Entry[a]	Equiv. BT–SCF_2H (*x* & *y*)	Ag(I) Source	NMR Yield of **2a**[b]
1	1.2 & 0.3	–	–
2	1.2 & 0.3	AgOTf (0.1 equiv.)	30%
3	1.2 & 0.3	AgOTf (0.5 equiv.)	61%
4	1.2 & 0.3	AgOTf (0.7 equiv.)	58%
5	1.2 & 0.3	AgOTf (1.0 equiv.)	37%
6	1.5 (one addition)	AgOTf (0.5 equiv.)	55%
7	1.5 & 0.5	AgOTf (0.5 equiv.)	70%
8	2.0 & 0.5	AgOTf (0.5 equiv.)	69%
9	2.0 & 1.0	AgOTf (0.5 equiv.)	57%
10	1.5 & 0.5	AgOTf (0.2 equiv.)	40%
11	1.5 & 0.5	(SIPr)AgOTf (0.2 equiv.)	55%
12	1.5 & 0.5	(SIPr)AgOTf (0.1 equiv.)	37%

[a] Conditions, **1a** (0.15 mmol), BT–SCF_2H (*x* equiv.), $NEt(iPr)_2$ (2.0 equiv.) in MeCN (0.5 M), −40 °C, 2 h then additional BT–SCF_2H (*y* equiv.), $NEt(iPr)_2$ (2.0 equiv.) added, −40 °C, 2 h. [b] ^1H NMR with CH_2Br_2 as internal reference.

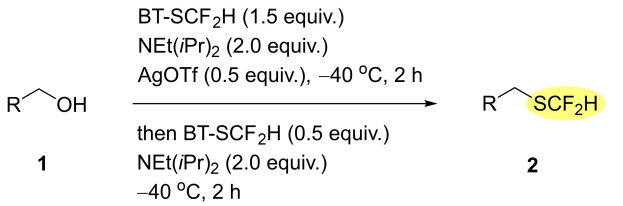
a direct nucleophilic substitution reaction with $^-SCF_2H$ and suggests that even simple silver(I) salts can help to stabilize the anion sufficiently to allow for downstream reactions.

The proposed role of the catalyst is shown in Scheme 2. Addition of the alkoxide to the C2-position of BT–SCF_2H first results in the tetrahedral intermediate **I**. At this stage, an interaction between the sulfur atom and Ag(I) may aid elimination of the difluoromethylthiolate anion, generating an $AgSCF_2H$ species **II**. This salt is expected to be comparatively stable by virtue of the soft, more covalent bonding situation present in silver(I) thiolate complexes. Nucleophilic substitution at the reactive 2-(alkoxy)benzothiazolium species **III** by $AgSCF_2H$ (**II**) would then deliver the product **2**, the thiocarbamate by-product **IV** and regenerate the silver(I) catalyst.

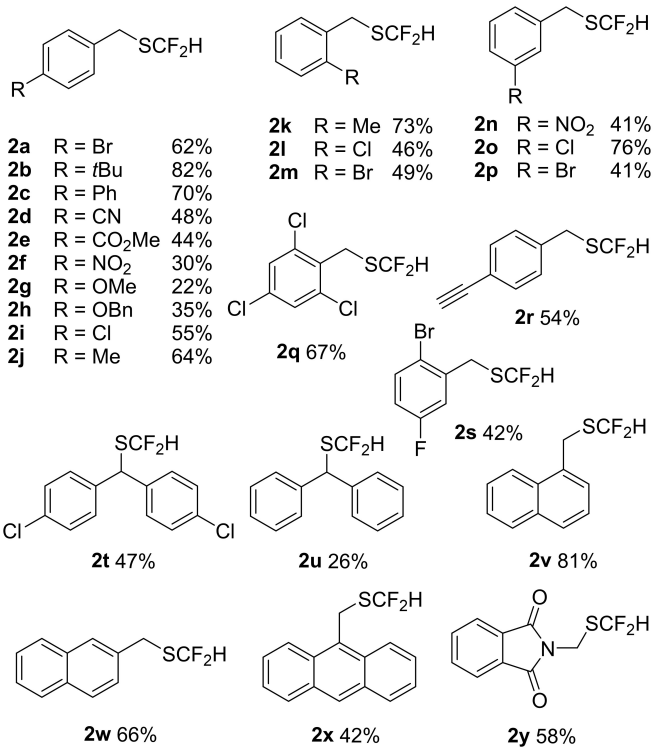
Raising the loading of AgOTf further did not result in an increase in reaction efficiency with 0.7 or 1.0 equiv. delivering **2a** in lower yields (58% and 37%, respectively, Table 1, entries 4,5). Addition of BT–SCF_2H (1.5 equiv) all together at the beginning of the reaction rather than in two separate portions led to a decrease in ^1H NMR yield to 55%, however increasing the overall amount to 2.0 equiv. (1.5 & 0.5 equiv.) delivered **2a** in an improved yield of 70% (Table 1, entries 6,7). Further increasing the equivalents of BT–SCF_2H did not lead to a higher yield of **2a** (Table 1, entries 8,9).

At this point in the study, NHC-coordinated silver(I) complexes were tested as additives in place of AgOTf. While **2a** was provided in only 40% ^1H NMR yield using 0.2 equiv. of AgOTf, this could be improved to 55% when the reaction was conducted using 0.2 equiv. of (SIPr)AgOTf (Table 1, entries 10,11). In this case, the previously reported stable (SIPr)$AgSCF_2H$ (**C**) species would be formed during the reaction. Decreasing the loading of (SIPr)AgOTf further to 0.1 equiv., however, led to a drop in yield to 37% (Table 1, entry 12). Due to its commercial availability and much lower overall cost compared to (SIPr)AgOTf, further studies were conducted AgOTf, despite the requirement for a higher loading of 0.5 equiv.

With optimized conditions in hand, the scope and limitations of the deoxydifluoromethylthiolation reaction with a selection of aliphatic alcohols were investigated (Scheme 3). Using the conditions from Table 1, entry 7, a wide range of primary benzylic alcohols **1a–o** could be successfully converted into the corresponding thioethers **2a–o** in generally good yields. While substrates bearing relatively electron-neutral groups such a 4-*tert*-butyl and 4-phenyl provided the highest yields (**2b** = 82%, **2c** = 70%), strongly electron-withdrawing and electron-donating groups such a 4-nitro and 4-benzyloxy were also tolerated (**2f** = 30%, **2h** = 35%). Halogen substituents amenable to subsequent cross-coupling reactions could be



1 **2**



Scheme 3. Scope and limitations. Conditions: **1** (0.4 mmol), BT–SCF_2H (1.5 equiv.), $NEt(iPr)_2$ (2.0 equiv.), AgOTf (0.5 equiv.) in MeCN (0.5 M), −40 °C, 2 h then additional BT–SCF_2H (0.5 equiv.), $NEt(iPr)_2$ (2.0 equiv.) added, −40 °C, 2 h. Isolated yields.

incorporated successfully with the previously discussed 4-Br as well as the 4-Cl-containing difluoromethylthioethers **2a** and **2i** being delivered in 62% and 55% isolated yield, respectively. Remarkably, despite the well-known susceptibility of terminal alkynes towards activation by silver(I), 4-(ethynyl)benzyl alcohol **1r** reacted smoothly, providing product **2r** in 54% yield. Substitution at the *ortho*- and *meta*-positions was also tolerated, as exemplified for product **2s** (42%). The secondary (diarylmethyl)alcohols **1t** and **1u** could be successfully converted in moderate yields while extended aromatic systems such as naphthyl or anthracyl could be successfully incorporated in place the phenyl group (**2v**=81%, **2w**=66%, **2x**=42%). Unfortunately, however, secondary alcohols featuring one aryl and one alkyl substituent were not suitable substrates. The method was also not limited to alcohols featuring neighboring aromatic groups with the phthalimide-containing product **2y** being delivered in 58% isolated yield. Unfortunately, however, primary or secondary aliphatic alcohols without activating heteroatoms were not suitable substrates.

Conclusion

In conclusion, BT–SCF_2H has been employed as a nucleophilic difluoromethylthiolating reagent in a deoxygenative substitution of activated aliphatic alcohols. The combination of the benzothiazolium reagent and the silver(I) catalyst AgOTf was crucial for overcoming the inherent instability of the $^-SCF_2H$ anion. The method is operationally simple and delivers aliphatic difluoromethylthioethers from readily available alcohols without requiring pre-activation of the electrophile. To the best of our knowledge, this process represents the first reported example of a direct nucleophilic substitution reaction involving $^-SCF_2H$ and further studies exploring BT-reagents as convenient sources of otherwise inaccessible fluorine-containing anions are ongoing in our laboratory.

Experimental Section

General procedure: BT–SCF_2H (1.5 equiv.), silver triflate (0.5 equiv.) and the alcohol (**1**, 1.0 equiv., 0.4 mmol) were added to dry MeCN (0.5 M) under argon. $NEt(iPr)_2$ (2.0 equiv.) was then added, and the reaction mixture was stirred for 2 h at −40 °C. Additional BT–SCF_2H (0.5 equiv.) and $NEt(iPr)_2$ (2.0 equiv.) were then added, and the reaction mixture was stirred for a further 2 h. The solids were subsequently filtered off, the solvent was removed under reduced pressure and the difluoromethylthioethers **2** were finally isolated using flash column chromatography over silica gel.

Acknowledgements

Financial support from the Studienstiftung des deutschen Volkes (scholarship to M.T.) and the Fonds der Chemischen Industrie (FCI, Sachkostenzuschuss) is gratefully acknowledged. We thank Dr. Stefan Dix and Arushi Garg (both FU Berlin) for initial experiments and helpful discussions. We would like to acknowledge the assistance of the Core Facility BioSupraMol supported by the DFG.

Data Availability Statement

Research data are not shared.

Keywords: Alcohols · Benzothiazolium salts · Deoxygenative reactions · Difluoromethylthio · Fluorine

[1] Selected Reviews: a) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881; b) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320; c) R. Berger, G. Resnati, P. Metrangolo, E. Weber, J. Hulliger, *Chem. Soc. Rev.* **2011**, *40*, 3496; d) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432; e) T. Fujiwara, D. O'Hagan, *J. Fluorine Chem.* **2014**, *167*, 16; f) A. Harsanyi, G. Sandford, *Green Chem.* **2015**, *17*, 2081; g) M. G. Campbell, T. Ritter, *Chem. Rev.* **2015**, *115*, 612; h) C. Ni, J. Hu, *Chem. Soc. Rev.* **2016**, *45*, 5441; i) R. Szpera, D. F. J. Moseley, L. B. Smith, A. J. Sterling, V. Gouverneur, *Angew. Chem. Int. Ed.* **2019**, *58*, 14824; j) T. Koike, M. Akita, *Org. Biomol. Chem.* **2019**, *17*, 5413; k) M. Inoue, Y. Sumii, N. Shibata, *ACS Omega* **2020**, *5*, 10633; l) Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai, N. Shibata, *iScience* **2020**, *23*, 101467.

[2] a) D. Cahard, J.-A. Ma, *Emerging Fluorinated Motifs: Synthesis, Properties and Applications*, Wiley-VCH, Weinheim, **2020**; selected reviews on the SCF_3 group:; b) X.-H. Xu, K. Matsuzaki, N. Shibata, *Chem. Rev.* **2015**, *115*, 731; c) S. Barata-Vallejo, S. Bonesi, A. Postigo, *Org. Biomol. Chem.* **2016**, *14*, 7150; d) H. Chachignon, D. Cahard, *Chin. J. Chem.* **2016**, *34*, 445; e) A.-L. Barthelemy, E. Magnier, G. Dagousset, *Synthesis* **2018**, *50*, 4765; selected reviews on the OCF_3 group: f) A. Tlili, F. Toulgoat, T. Billard, *Angew. Chem. Int. Ed.* **2016**, *55*, 11726; g) T. Besset, P. Jubault, X. Pannecoucke, T. Poisson, *Org. Chem. Front.* **2016**, *3*, 1004; selected reviews on the SF_5 group: h) S. Altomonte, M. Zanda, *J. Fluorine Chem.* **2012**, *143*, 57; i) P. R. Savoie, J. T. Welch, *Chem. Rev.* **2015**, *115*, 1130; j) P. Das, E. Tokunaga, N. Shibata, *Tetrahedron Lett.* **2017**, *58*, 4803.

[3] Reviews: a) H.-Y. Xiong, X. Pannecoucke, T. Besset, *Chem. Eur. J.* **2016**, *22*, 16734; b) X. Xiao, Z.-T. Zheng, T. Li, J.-L. Zheng, T. Tao, L.-M. Chen, J.-Y. Gu, X. Yao, J.-H. Lin, J.-C. Xiao, *Synthesis* **2020**, *52*, 197.

[4] a) J. A. Erickson, J. I. McLoughlin, *J. Org. Chem.* **1995**, *60*, 1626; b) Q. A. Huchet, B. Kuhn, B. Wagner, H. Fischer, M. Kansy, D. Zimmerli, E. M. Carreira, K. Müller, *J. Fluorine Chem.* **2013**, *152*, 119; c) Y. Zafrani, D. Yeffet, G. Sod-Moriah, A. Berliner, D. Amir, D. Marciano, E. Gershonov, S. Saphier, *J. Med. Chem.* **2017**, *60*, 797.

[5] Selected examples: a) B. Bayarmagnai, C. Matheis, K. Jouvin, L. J. Goossen, *Angew. Chem. Int. Ed.* **2015**, *54*, 5753; b) K. Jouvin, C. Matheis, L. J. Goossen, *Chem. Eur. J.* **2015**, *21*, 14324; c) J. Yu, J.-H. Lin, J.-C. Xiao, *Angew. Chem. Int. Ed.* **2017**, *56*, 16669; d) T. Ding, L. Jiang, W. Yi, *Org. Lett.* **2018**, *20*, 170; e) P. Zhang, W. Chen, M. Liu, H. Wu, *Org. Lett.* **2019**, *21*, 9326; f) T. Ding, L. Jiang, W. Yi, *Chem. Commun.* **2020**, *56*, 3995; g) M. Zhang, J.-H. Lin, J.-C. Xiao, *J. Org. Chem.* **2021**, *86*, 13153.

[6] Review: J. Wu, Q. Shen, *Acc. Chem. Res.* **2021**, *54*, 2946.

[7] Selected reactions involving Phthalimide-SCF_2H (**A**): a) D.-H. Zhu, Y. Gu, L. Lu, Q. Shen, *J. Am. Chem. Soc.* **2015**, *137*, 10547; b) L. Candish, L. Pitzer, A. Gómez-Suárez, F. Glorius, *Chem. Eur. J.* **2016**, *22*, 4753; c) W. Xu, J. Ma, X.-A. Yuan, J. Dai, J. Xie, C. Zhu, *Angew. Chem. Int. Ed.* **2018**, *57*, 10357; d) H. Kondo, M. Maeno, K. Sasaki, M. Guo, M. Hashimoto, M. Shiro, N. Shibata, *Org. Lett.* **2018**, *20*, 7044; related chiral reagent: e) H. Zhang, X. Wan, Q. Shen, *Chin. J. Chem.* **2019**, *37*, 1041.

[8] Selected reactions involving $PhSO_2SCF_2H$ (**B**): a) D.-H. Zhu, X.-X. Shao, X. Hong, L. Lu, Q. Shen, *Angew. Chem. Int. Ed.* **2016**, *55*, 15807; b) J. Li, D. Zhu, L. Lv, C.-J. Li, *Chem. Sci.* **2018**, *9*, 5781; c) S.-H. Guo, X.-L. Zhang, G.-F. Pan, X.-Q. Zhu, Y.-R. Gao, Y.-Q. Wang, *Angew. Chem. Int. Ed.* **2018**, *57*, 1663; d) B. Xu, D. Wang, Y. Hu, Q. Shen, *Org. Chem. Front.* **2018**, *5*, 1462; e) B. Xu, D. Li, L. Lu, D. Wang, Y. Hu, Q. Shen, *Org. Chem. Front.* **2018**, *5*, 2163; f) W. Wang, S. Zhang, H. Zhao, S. Wang, *Org. Biomol. Chem.* **2018**, *16*, 8565; g) H. Li, Z. Cheng, C.-H. Tung, Z. Xu, *ACS Catal.* **2018**, *8*, 8237; h) W. Liu, P. Liu, L. Lv, C.-J. Li, *Angew. Chem. Int. Ed.* **2018**, *57*, 13499; i) X. Shao, X. Hong, L. Lu, Q. Shen, *Tetrahedron* **2019**, *75*, 4156; j) J. Dong, F.

Yue, X. Wang, H. Song, Y. Liu, Q. Wang, *Org. Lett.* **2020**, *22*, 8272; k) H. Zhang, F. Yu, C. Li, P. Tian, Y. Zhou, Z.-Y. Cao, *Org. Lett.* **2021**, *23*, 4721.

[9] Examples of direct difluoromethylthiolation involving *in situ*-generated electrophilic and radical reagents: a) S. Arimori, O. Matsubara, M. Takada, M. Shiro, N. Shibata, *R. Soc. Open Sci.* **2016**, *3*, 160102; b) Z. Huang, O. Matsubara, S. Jia, E. Tokunaga, N. Shibata, *Org. Lett.* **2017**, *19*, 934; c) Q. Yan, L. Jiang, W. Yi, Q. Liu, W. Zhang, *Adv. Synth. Catal.* **2017**, *359*, 2471; d) L. Jiang, W. Yi, Q. Liu, *Adv. Synth. Catal.* **2016**, *358*, 3700; e) X. Zhao, T. Li, B. Yang, D. Qiu, K. Lu, *Tetrahedron* **2017**, *73*, 3112; f) L. Jiang, Q. Yan, R. Wang, T. Ding, W. Yi, W. Zhang, *Chem. Eur. J.* **2018**, *24*, 18749; g) L. Jiang, T. Ding, W.-B. Yi, X. Zeng, W. Zhang, *Org. Lett.* **2018**, *20*, 2236; h) J. Wei, K. Bao, Y. Wang, R. Sheng, J. Hu, *Org. Biomol. Chem.* **2020**, *18*, 4556.

[10] Free (fluoroalkyl)thiolate anions are known to be unstable towards β-fluoride elimination. See for example: a) R. N. Haszeldine, J. M. Kidd, *J. Chem. Soc.* **1955**, 3871; b) T. Scattolin, K. Deckers, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2017**, *56*, 221; c) T. Scattolin, M. Pu, F. Schoenebeck, *Chem. Eur. J.* **2018**, *24*, 567.

[11] a) J. Wu, Y. Gu, X. Leng, Q. Shen, *Angew. Chem. Int. Ed.* **2015**, *54*, 7648; b) J. Wu, Y. Liu, C. Lu, Q. Shen, *Chem. Sci.* **2016**, *7*, 3757; c) J. Wu, C. Lu, L. Lu, Q. Shen, *Chin. J. Chem.* **2018**, *36*, 1031.

[12] S. Dix, M. Jakob, M. N. Hopkinson, *Chem. Eur. J.* **2019**, *25*, 7635.

[13] M. N. Hopkinson, S. Dix, Fluorine-containing compounds for use as nucleophilic reagents for transferring functional groups onto high value organic compounds, *Eur. Pat. Appl.* EP19150201, Jan 3, 2019, International Pat. Appl. PCT/EP2020/050031, Jan 2, 2020.

[14] a) A. Ariamajd, N. J. Gerwien, B. Schwabe, S. Dix, M. N. Hopkinson, *Beilstein J. Org. Chem.* **2021**, *17*, 83; b) M. Tironi, S. Dix, M. N. Hopkinson, *Org. Chem. Front.* **2021**, *8*, 6026.

[15] M. Tironi, L. M. Maas, A. Garg, S. Dix, J. P. Götze, M. N. Hopkinson, *Org. Lett.* **2020**, *22*, 8925.

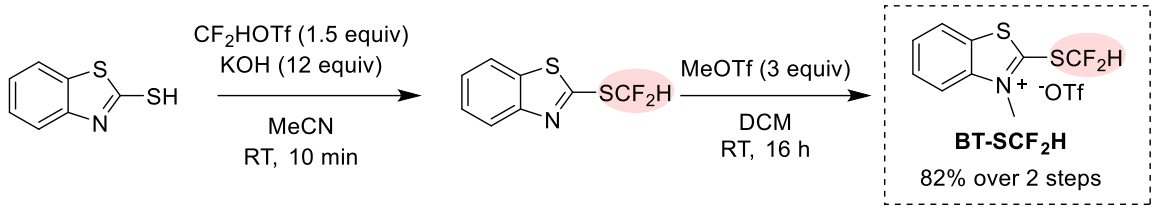
[16] Report on the activation of THF by BT–SCF_2H and related reagents: L. M. Maas, J. R. Schmid, C. Fasting, P. Voßnacker, A. Mavroskoufis, M. N. Hopkinson, *Tetrahedron* **2021**, *101*, 132512.

Manuscript received: December 23, 2021
Revised manuscript received: April 4, 2022
Accepted manuscript online: April 8, 2022

7. Discussion of published results

7.1 Deoxygenative Tri- and Difluoromethylthiolation of Carboxylic Acids with Benzothiazolium Reagents[239]

After attempting different difuorocarbene sources, the BT-SCF_2H reagent could be prepared in two steps from 2-MBT using the CF_2HOTf reagent[240] with a procedure adapted from Hartwig's pioneering work [220] (Scheme 63). In comparison to his work, we found that, with 2-MBT, it was possible to reduce the amount of difluoromethylating reagent from 3 equiv to 1.5 equiv whilst retaining the same yield, thus making the synthesis of the reagent more efficient.



Scheme 63: synthesis of the BT-SCF_2H reagent.

Initial attempts to employ the BT-SCF_2H reagent under the same conditions as the BT-SCF_3 to perform the deoxydifluoromethylthiolation of alcohols were however not successful, with no product detected.

Gratifyingly, however, we found that both BT-SCF_2H and BT-SCF_3 are capable of reacting with carboxylic acids to furnish the corresponding difluoro- and trifluorothioesters.

Thioesters are important molecules, playing key roles in the metabolism. Since they have a higher bond energy in comparison to esters, their formation is often a strategy employed in metabolic pathways to make activated acyl groups[241], such as in the formation of the derivatives of CoA, e.g. acetyl-CoA in the Krebs cycle or fatty acid-CoA in the β-oxidation of fatty acids.

The use of thioesters in nature is so ubiquitous that several xenobiotics, including some drugs, form a thioester derivative *in vivo.* Whilst the increased reactivity due to the formation of a thioester derivative capable of transferring acyl groups could contribute to the side effects of some drugs containing the carboxylic acid motif[242], this tendency to acts as acyl transfer agents can also be exploited in designing novel drugs, such as for antitumoral[243] or antiviral agents[244]. Another potential application of thioesters in drug design is to act as masked thiols[245].

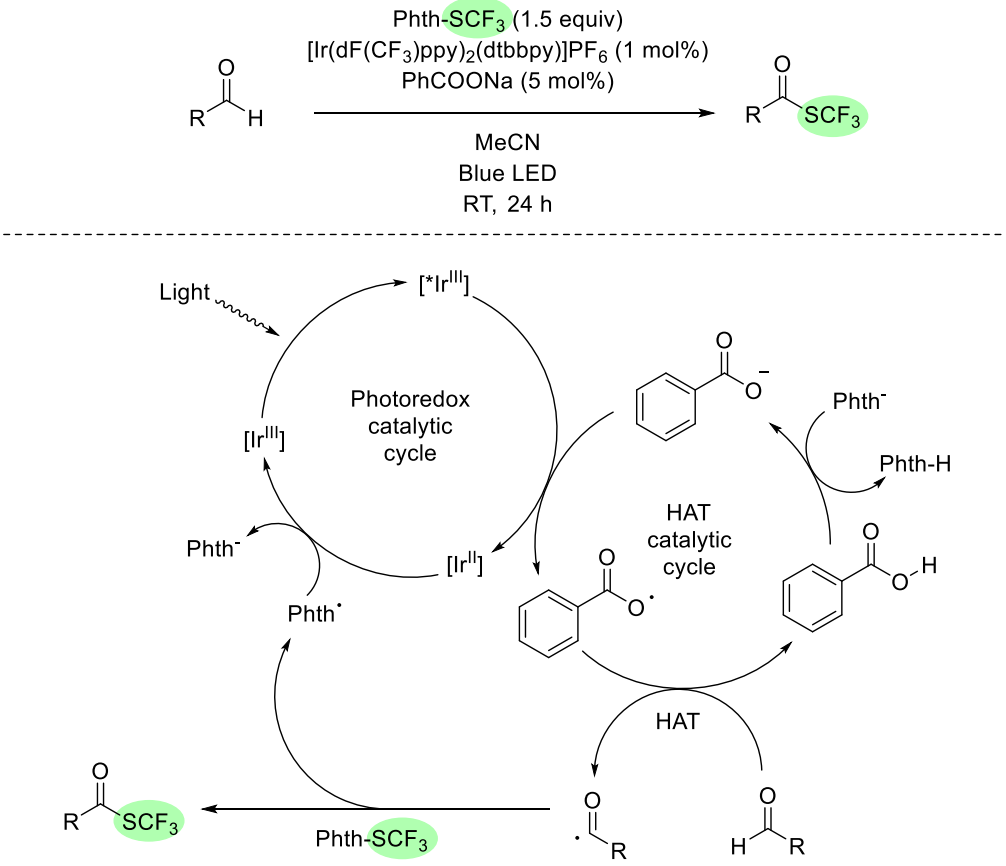
The conceptually simplest way to access thioesters, via reaction of a carbonyl electrophile (e.g. acid chloride) and a thiol nucleophile, remains the most widespread way to synthesize these compounds.

In contrast, synthetic approaches toward difluoro- and trifluoromethylthioesters are somewhat limited. Strategies to access trifluoromethylthioesters reacting various SCF_3 anion sources with acid chlorides have been reported, such as with $Hg(SCF_3)_2$[131], $[NMe]_4SCF_3$[246] and $(bpy)CuSCF_3$[247], but these methods, in addition to using expensive, relatively unstable, or even toxic $-SCF_3$ sources, require preactivation of the acyl electrophile and produce stoichiometric amounts of metal chloride waste. This approach isn't viable at all for difluoromethylthioesters because of the instability of the corresponding anion.

Another possible way would be the difluoro- and trifluoromethylation of thioacids, but the inaccessibility of these species, as well as *O*- vs *S*-alkylation selectivity issues severely restrict the viability of this approach, with only one example of difluoromethylation of thiobenzoic acid reported in the literature[248].

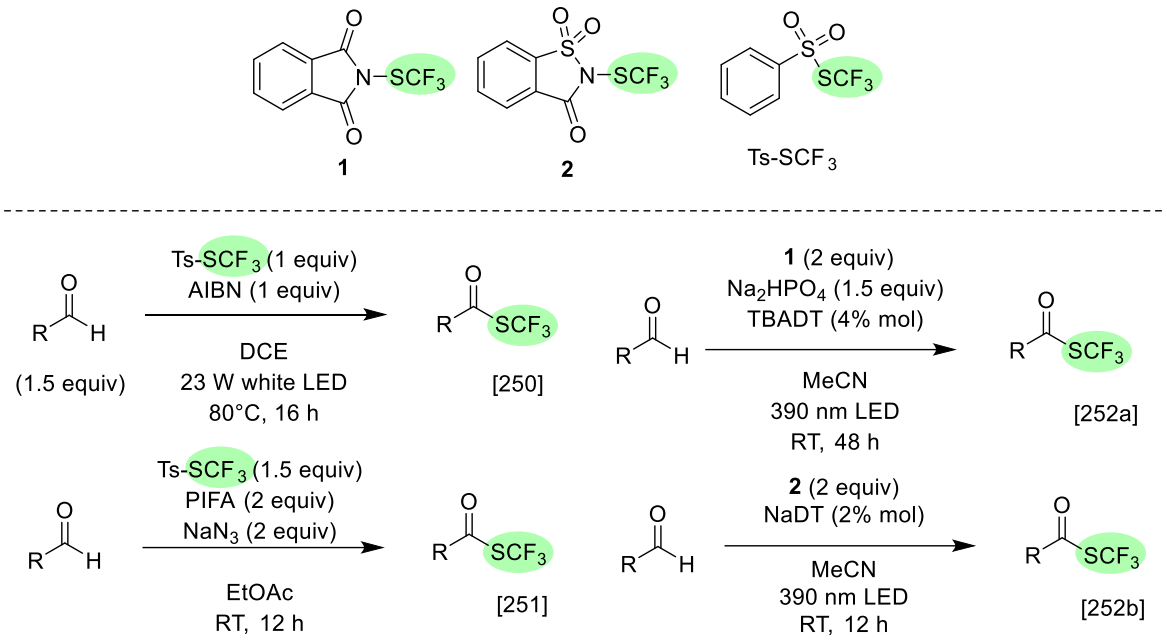
A more general approach to access trifluoro- and difluoromethylthioesters is represented by the radical trifluoro- and difluoromethylthiolation of aldehydes via hydrogen atom transfer (HAT).

The radical trifluoromethylthiolation of aldehydes was first reported by Glorius[249] in 2018, developing an ingenious cooperative photoredox/HAT system, in which catalytic benzoate acts as both a hydrogen atom and electron shuttle., and Phth-SCF_3 as the SCF_3 radical source (Scheme 64). The reaction has good chemoselectivity for C(O)-H bonds over other sensitive C-H bonds.



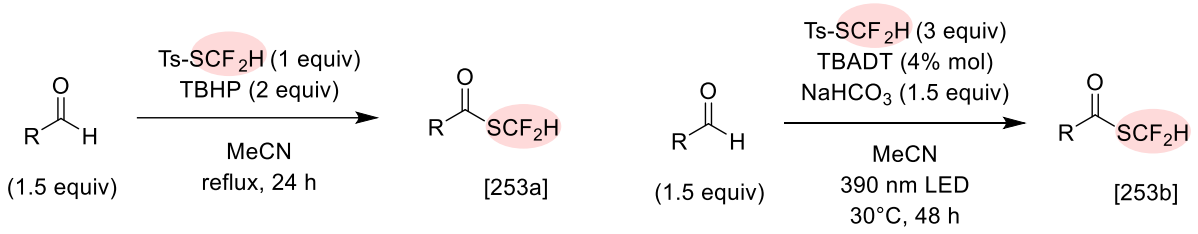
Scheme 64: Radical trifluoromethylthiolation of aldehydes as reported by Glorius.

Other similar methods involve the generation of the acyl radical either with a radical initiator such as AIBN[250] or PIFA/NaN_3[251], or a suitable photocatalyst, such as TBADT or NaDT (DT = decatungstate, Scheme 65)[252].



Scheme 65: Radical trifluoromethylthiolation reactions of aldehydes.

Similar methodologies were developed for the difluoromethylation[253] of aldehydes using Ts-SCF_2H as the difluoromethylthio transfer reagent (Scheme 66).

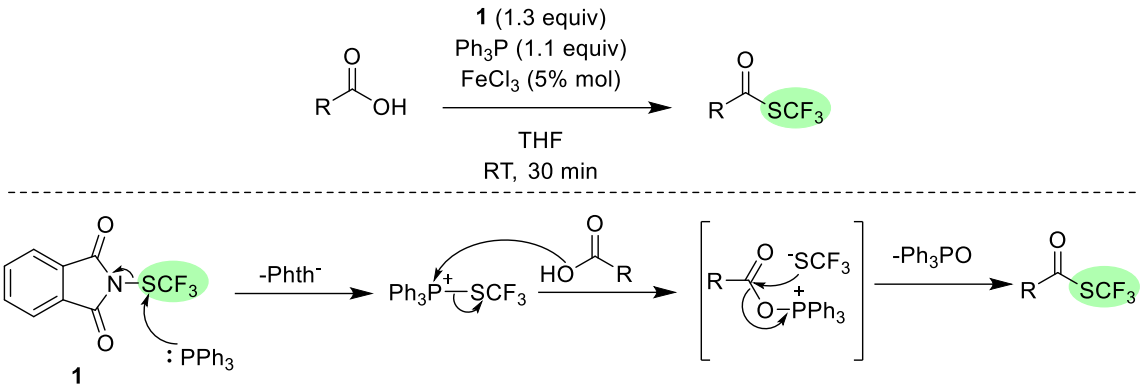


Scheme 66: Radical difluoromethylthiolation reactions of aldehydes.

Whilst these methods represent an improvement in comparison to previous methodologies, they have limitations, such as the use of aldehydes, which are less stable than other carbonyl-containing compounds, or the competition with C-H activation of other bonds, especially in aliphatic substrates. Another issue is the need for long reaction times and/or high temperatures.

A more desirable carbonyl precursor would be carboxylic acids, which are generally more stable and easily accessible than aldehydes.

Except the one herein discussed, only one other deoxytrifluoromethylthiolation of carboxylic acids has been reported to date. In Hu's work, an umpolung strategy is adopted, in which triphenylphosphine acts as a stoichiometric reductant, and the electrophilic Phth-SCF_3 (**1**) reagent acts as the SCF_3 source (Scheme 67).



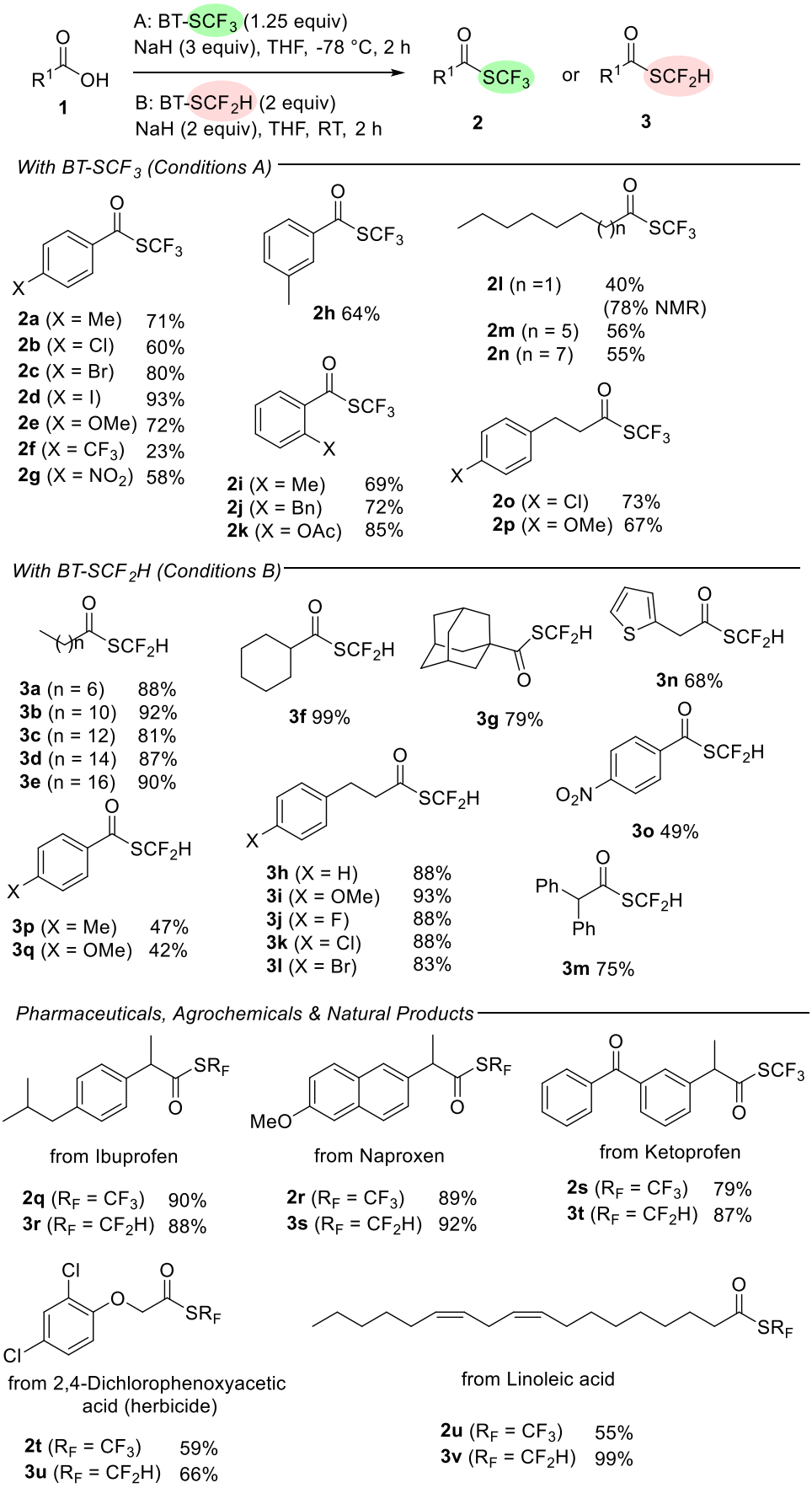
Scheme 67: Deoxytrifluoromethylthiolation of acids according to Hu and the proposed mechanism.

In our work, we report a transition metal free methodology for the direct deoxygenative tri- and difluoromethlthiolation of readily available carboxylic acids.

In comparison to Hu's methodology, which makes use of both a stoichiometric source of the SCF_3 anion and a stoichiometric oxyphilic reagent to activate acids, BT-reagents are capable of playing both roles at once, since the *in situ* release of the ^-SR_f is concomitant with the formation of an activated acyloxybenzothiazolium electrophile. This method does not require any additive except a cheap organic base. The deoxydifluoromethylthiolation reaction is particularly noteworthy because it represents a nucleophilic reaction with the elusive $^-SCF_2H$ anion.

The experimental part of this work concerning the trifluoromethylthiolation reaction was carried out by Lilian M. Maas. In the initial hit, preformed cesium 4-methylbenzoate was reacted with BT-SCF_3 (1.25 equiv) in MeCN. After 2 h at rt, we were pleased to observe the formation of the corresponding trifluoromethylthioester in 39% NMR yield. Increasing the dilution, adding the acid dropwise and lowering the temperature to -78°C helped in improving the efficiency of the reaction, as well as allowing us to directly use the carboxylic acid with a base instead of a preformed carboxylate. Reducing the concentration of the acid by adding it dropwise and increasing the dilution overall helped in reducing the formation of carboxylic anhydrides (formed by attack of a second carboxylate molecule onto the acyloxybenzothiazolium intermediate. Reducing the temperature, on the other hand, helped in stabilizing the $^-SCF_3$ formed *in situ*, thus avoiding the formation of fluoride (that can attack the acyloxybenzothiazolium intermediate forming acid fluorides) and minimizing the THF ring-opening side reaction[254].

The experimental work on the deoxygenative difluoromethylthiolation of carboxylic acids using BT-SCF_2H were carried out by myself. The optimized conditions involve the preformation of the carboxylate for 30 minutes, and notably the reaction proceeds at room temperature, with no reaction detected at all at -78°C.



Scheme 68: Scope of Deoxygenative Tri- and Difluoromethylthiolation of Acids Using BT-SCF_3 and BT-SCF_2H. Adapted from[239]

Both reagents present an excellent reaction scope with yields from moderate to excellent, albeit BT-SCF_3 proved to be more effective with aromatic carboxylic acids, whilst BT-SCF_2H yields better results with aliphatic acids.

A broad range of electronically diverse functional groups such as −OMe and $-NO_2$ were well tolerated, while halogen-substituted products that could be further functionalized through cross-coupling methodologies were efficiently obtained. Sterically encumbered substrates such as adamantane carboxylic acid also proved suitable.

Encouraged by these promising results, the scope of these reactions was broadened to blockbuster drugs (such as NSAIDs like Naproxen and Ibuprofen, whose difuoromethylated derivative could be prepared on a gram scale with a yield of 88%), a natural product (linoleic acid) and an herbicide 2,4-Dichlorophenoxyacetic acid.

Intrigued by the unprecedented nucleophilic difluoromethylation of carboxylic acids, as well as by the different optimal reaction conditions, we wondered whether the mechanism did indeed involve the formation of the free anion, as postulated in our previous work with alcohols, or if a concerted mechanism was at play, similar to the one reported by Ritter[34b] (See scheme 7 Chapter 2) in the deoxyfluorination of phenols with the imidazolium-based Phenofluor™ reagent.

As expected, according to the DFT (B3LYP/def2-SVP) calculations (conducted by QoD Technologies GmbH in collaboration with Dr. J. P. Götze, FU Berlin), the difluoromethylthiolation reaction proceeds through a 4-membered transition state, which has an energy significantly lower than the pathway involving the formation of the free $^{-}SCF_2H$ anion (energy barrier = 12.3 $kcalmol^{-1}$ cf. 34.1 $kcalmol^{-1}$), whereas the trifluoromethylthiolation proceeds through an asynchronous non-cyclic transition state, and the energy barrier (5.2 $kcalmol^{-1}$) is considerably lower than for the difluoromethylthiolation reaction. This might explain why the difluoromethylthiolation reaction does not occur at low temperature and why side products such as anhydrides were not an issue with BT-SCF_2H.

In conclusion, in this work we developed an efficient way to synthesize tri- and difluromethylthioesters directly from carboxylic acids under mild conditions using the BT reagents developed by our group. Notably, their employment allows for the nucleophilic installation of unstable anions via a concerted mechanism.

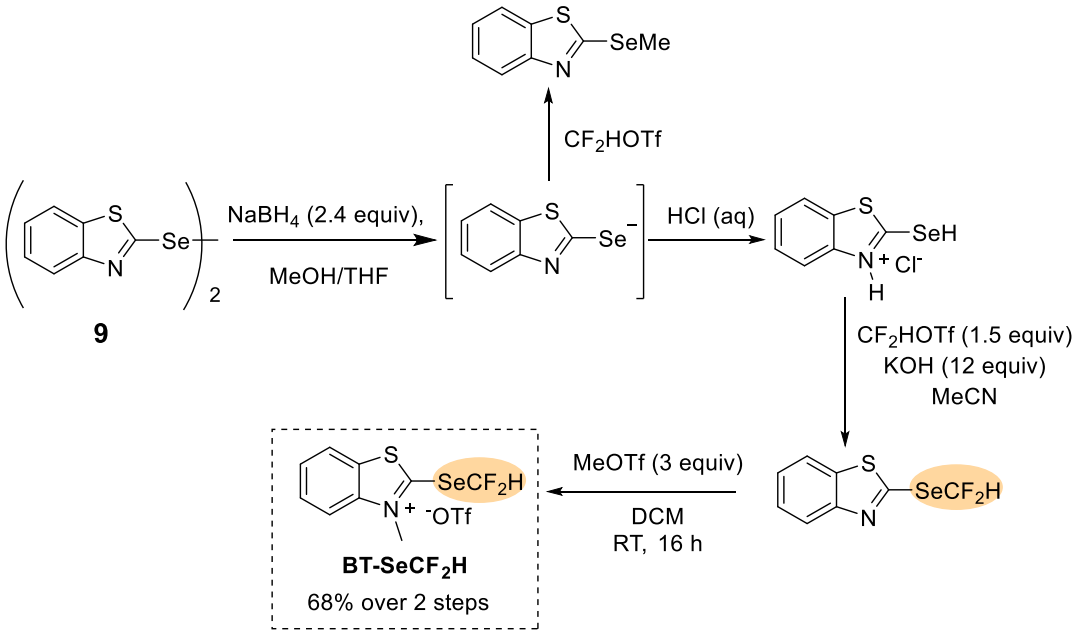
7.2 Deoxygenative nucleophilic difluoromethylselenylation of carboxylic acids and alcohols with BT-SeCF$_2$H[255]

The successful difluoromethylthiolation of acids inspired us to explore the corresponding reaction with the selenium-containing analog of the BT-SCF$_2$H reagent, BT-SeCF$_2$H.

The synthesis of the reagent is similar to the one employed to prepare the trifluoromethylated BT-SeCF$_3$ reagent. The diselenide (**9**) (which itself can be obtained from 2-chlorobenzothiazole, Se$_8$ and NaBH$_4$), is reduced with NaBH$_4$ and then precipitated via addition of HCl to form the benzothiazolium chloride salt, followed by the difluoromethylation with the same difluorocarbene used for BT-SCF$_2$H, CF$_2$HOTf, under basic conditions (Scheme 69).

The reason for the precipitation step before the addition of the difluorocarbene source is twofold: on the one hand all the traces of sodium borohydride are removed, thus preventing it from interfering with the following step; on the other hand, the benzothiazolium chloride precipitate was found to be stable enough to be handled under air, thus facilitating the synthetic procedure. Attempts to skip the precipitation with HCl and perform the difluoromethylation reaction in a one-pot fashion directly after the reduction step were unsuccessful, with only the *Se*-methylated derivative being obtained, presumably because of a reductive defluorination reaction between the -SeCF$_2$H and leftover NaBH$_4$.

The difluoromethylated intermediate was then *N*-methylated with MeOTf to obtain the BT-SeCF$_2$H reagent as a white crystalline solid which is bench stable over several months.



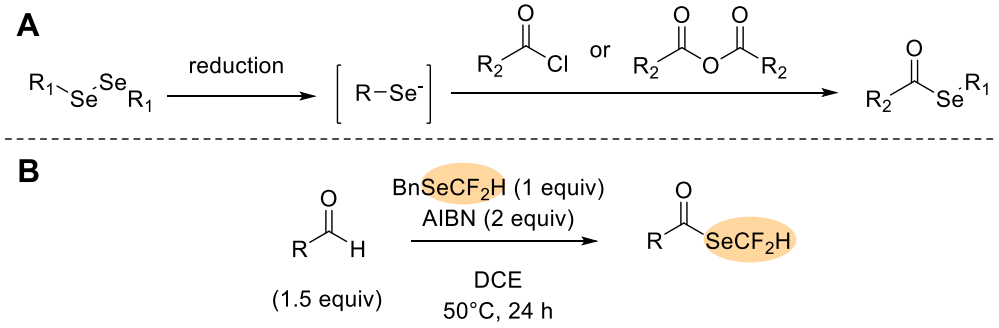
Scheme 69: Synthesis of BT-SeCF$_2$H reagent. Precipitation of benzothiazolium chloride is key for avoiding deleterious defluorination.

To our delight, initial results showed that BT-$SeCF_2H$ could perform the difluoromethylselenylation of acids under similar conditions to the difluoromethylthiolation explored in our previous work, representing the first deoxydifluoromethylselenylation and the first nucleophilic difluoromethylselenylation reaction to be reported.

Selenoesters are an underexplored class of molecules, which have recently drawn increased interest as a valuable motif in drug design. Despite the known toxicity of selenium compounds[256], which can increase oxidative stress and cause damage to the DNA, these properties can be modulated and exploited to design novel molecules containing the selenoester motif. For instance, selenoesters have been examined as drug candidates for the treatment of breast cancer[257], colon cancer[258], prostate cancer[259] and as anti-MRSA antibiotics[260].

Selenoesters can be accessed via reduction *in situ* (with several reductants such as In[261], Mg[262], Zn[263] and $NaBH_4$[264]) of the diselenide precursor to the unstable selenolate followed by the reaction with an acid chloride/anhydride (Scheme 70a). This procedure however is not suitable for the synthesis of difluoromethylselenoesters, because of the lack of sources of $^-SeCF_2H$.

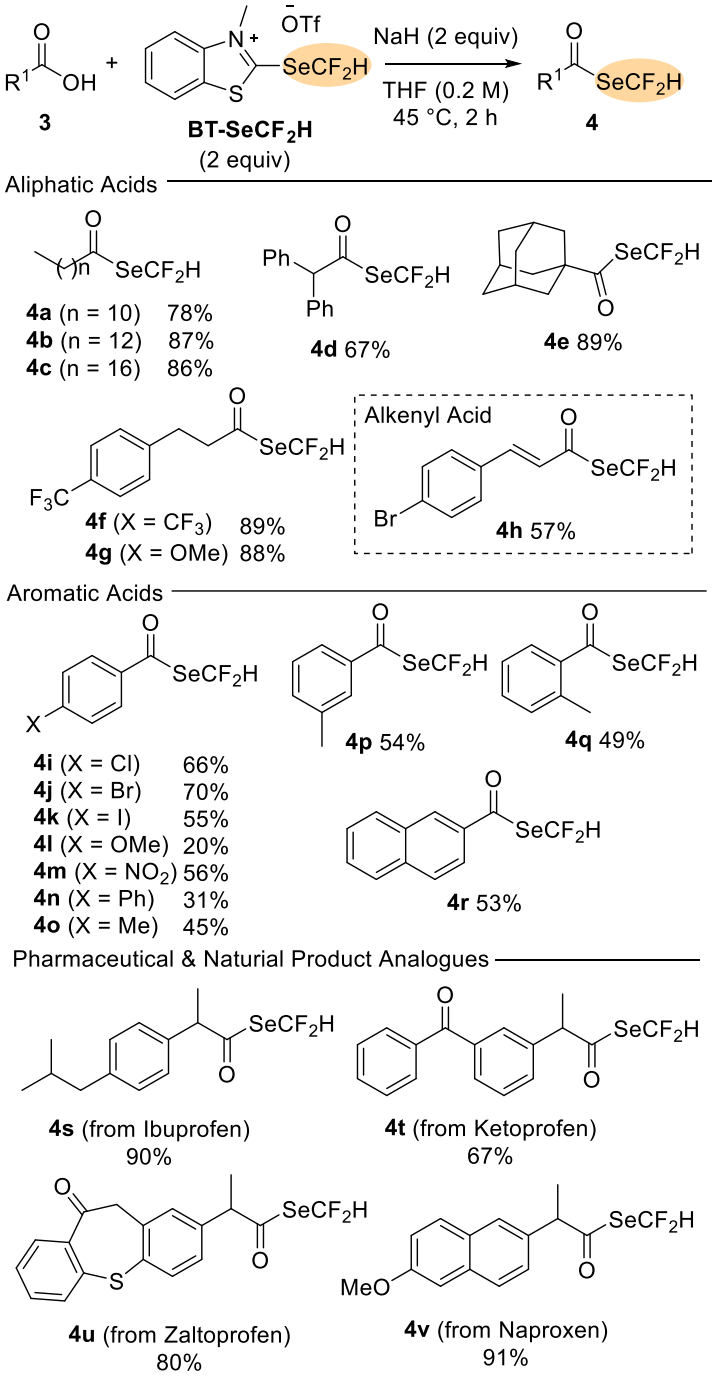
The first successful synthesis of difluoromethylselenoesters was reported by Wang[265], using a HAT strategy with aldehydes and $BnSeCF_2H$ as the radical $SeCF_2H$ source (Scheme 70b). This reaction suffers from similar limitations as the previously discussed radical tri- and difluoromethylthiolation reactions, suffering from competing C-H activation, long reaction times at high temperature and using less-desirable aldehyde feedstock. Moreover, in this work, a 1.5 equiv excess of the starting aldehyde had to be used, making it poorly suitable for late-stage functionalization of valuable molecules.



Scheme 70a: Synthesis of selenoesters via reduction of diselenides followed by reaction with acid chlorides or anhydrides. **Scheme 70b:** Radical difluoromethylselenylation of aldehydes.

After optimization of the reaction conditions using *p*-nitro benzoic acid as a model substrate, we explored the scope of the difluoromethylselenylation of carboxylic acids with BT-$SeCF_2H$, finding that a wide range of primary, secondary and tertiary acids aliphatic acids could react at 45°C, whereas room temperature proved to be optimal for aromatic acids.

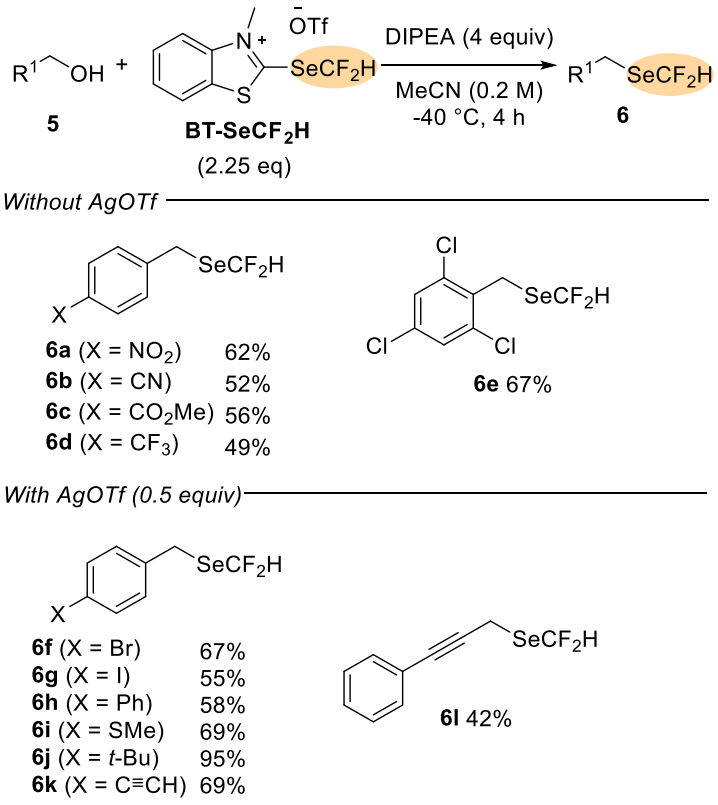
As in the difluoromethylthiolation reaction, we obtained higher yields on average with aliphatic acids (67-89%) than with aromatic acids (31-70%). Several key functional groups were well tolerated, such as halogens, that could be exploited for cross-coupling reactions, or the nitro group, that is known to be potentially troublesome under radical conditions. Finally, the deoxydifluoromethylselenylation reaction was employed to obtain several derivatives of drugs containing the carboxylic acid moiety, in good to excellent yield (65-92%).



Scheme 71: Scope of deoxydifluoromethylselenylation of carboxylic acids. Adapted from[255].

Having established its reactivity with carboxylic acids, we wondered whether BT-$SeCF_2H$ could act as a nucleophilic source of the $SeCF_2H$ group in the deoxydifluoromethylselenylation of alcohols. Despite having previously had little success with BT-SCF_2H, we reasoned that the $^-SeCF_2H$ anion should be more stable than $^-SCF_2H$, owing to the larger size of selenium and the resultant worse overlap between its orbitals with p orbitals at the adjacent carbon that would be involved in the formation of a C=Se double bond, thus reducing the driving force for the β-fluoride elimination side reaction.

We were pleased to observe that BT-$SeCF_2H$ (1.25 equiv) is indeed capable of reacting with 4-nitrobenzyl alcohol in the presence of DIPEA (1.5 equiv) at room temperature to yield the corresponding difluoromethylselane in 45% yield. Reducing the temperature to -40°C and increasing the amount of DIPEA to 4 equiv increased the yield to 65%. Unfortunately, only EWG-bearing benzylic alcohols proved suitable substrates under these conditions, with substrates such as 4-bromobenzyl alcohol yielding only 31%. We wondered whether introducing a counterion capable of stabilizing the *in situ*-formed unstable $^-SeCF_2H$ anion would lead to an improvement in the reaction yield. We turned our attention to silver, that, as previously discussed is capable of stabilizing unstable chalogen anions owing to its soft, more covalent bonding. Indeed, we found that introducing a source of Ag^+ (the most effective one proved to be AgOTf) in the mixture greatly improves the reaction yield and its scope by stabilizing the anion formed *in situ*, thus enabling the transformation of unactivated benzylic alcohols.



Scheme 72: Scope of deoxydifluoromethylselenylation of alcohols. Adapted from [255]

Despite the limited scope of this transformation, it goes to fill a crucial niche in the chemistry of difluoromethylselenylated compounds, because as seen with Wang's[265] work, $BnSeCF_2H$, as well as the derived $TsSeCF_2H$ introduced by Zhang[266], are, to the best of our knowledge, the only two known reagents for the direct installation of the $-SeCF_2H$ moiety.

The prior state-of-the-art procedure to access $BnSeCF_2H$ revolves around the nucleophilic difluoromethylation of selenocyanates with $TMSCF_2H$, introduced by Billard[111a]. Despite the wide scope of this methodology, benzylic substrates are unfortunately not particularly effective, with very low yields reported (19-36%).

In contrast, we could prepare $BnSeCF_2H$ on a 2 mmol scale in one step starting from cheap benzylic alcohol in 58% isolated yield.

This work thus not only reports the first nucleophilic $-SeCF_2H$ source and the first direct synthesis of difluoromethylselenoesters and -ethers from commonly available carboxylic acids and alcohols but could also further boost the development of new difluoromethylselenylating procedures as a whole by enabling a more efficient route to access a key electrophilic reagent in the field: $BnSeCF_2H$.

7.3 Silver-Catalyzed Nucleophilic Deoxydifluoromethylthiolation of Activated Aliphatic Alcohols with BT–SCF_2H[267]

Encouraged by the key role played by silver catalysis in the difluoromethylselenylation of alcohols made us wonder whether silver would be similarly able to stabilize the $^-SCF_2H$ anion, thus enabling the deoxydifluoromethylthiolation of alcohols we were previously unable to achieve.

Indeed, reacting 4-bromobenzyl alcohol with BT-SCF_2H (1.2 & 0.3 equiv., two additions) and $NEt(iPr)_2$ (2.0 & 2.0 equiv) and AgOTf (0.5 equiv) furnished the corresponding difluoromethylthiolated product in 61 % ^1H NMR yield. In contrast, under the same conditions but without silver, no product formation at all was observed, proving how crucial silver is for the stabilization of $^-SCF_2H$.

The only other known nucleophilic source of SCF_2H is the NHC-silver complex $SIPrAgSCF_2H$ introduced by Shen[238] (Fig. 9). In his work, Shen synthesized this complex via reaction of $SIPrAgCF_2H$ with elemental sulfur, but we reasoned that it would be possible to access the same complex *in situ* by introducing in the reaction mixture SIPrAg complexes with labile ligands, which would then be displaced by $^-SCF_2H$.

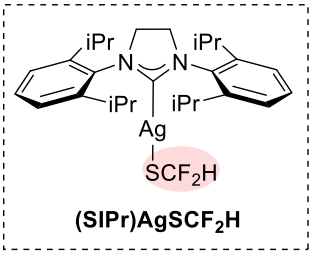
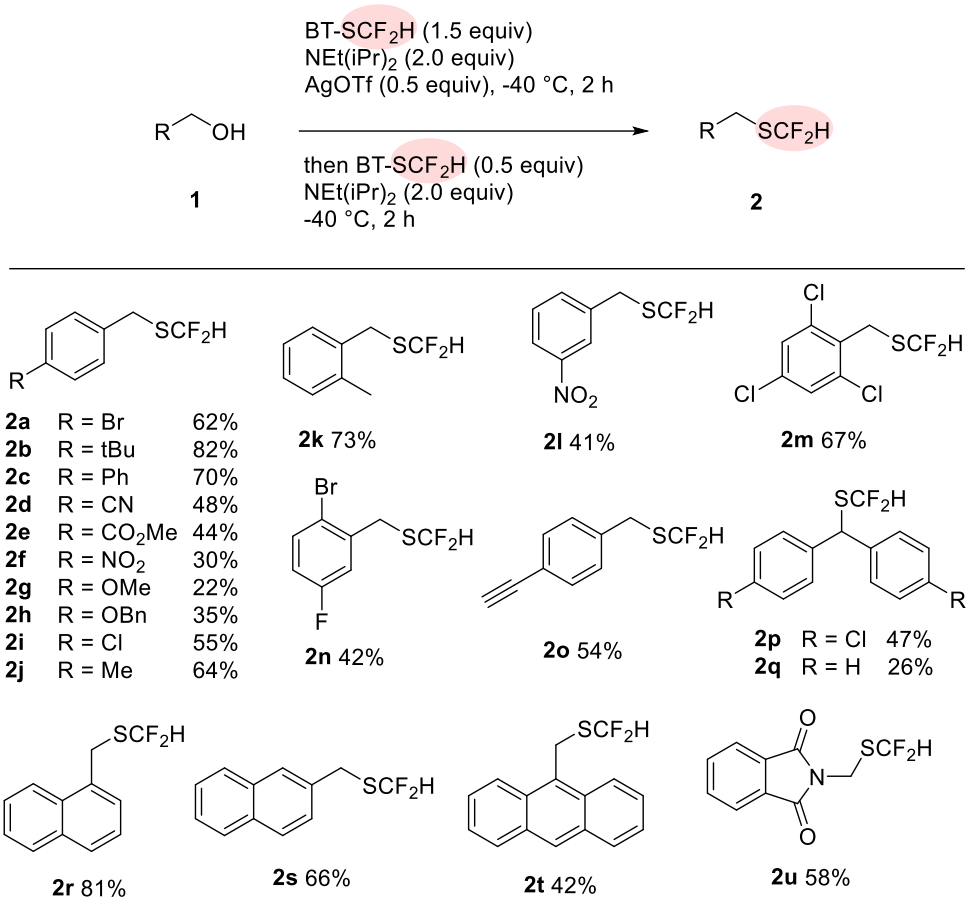


Fig. 9: SIPrAgSCF_2H, the only other known nucleophilic source of SCF_2H.

The best SIPr-Ag complex proved to be SIPrAgOTf, and it was found that with it, a catalyst loading of 20 mol% led to a ^1H NMR yield of 55% in the reaction with 4-bromobenzylic alcohol, whereas with AgOTf and the same catalyst loading, a lower yield of 40% was obtained.

Considering the considerably higher cost of SIPrAgOTf (which is not commercially available and must be prepared over 3 steps) and the small difference in the catalytic efficiency, we reasoned that it would be better to conduct further studies with AgOTf, despite the higher catalyst loading required.

With optimized conditions in hand, we investigated the deoxydifluoromethylthiolation reaction scope with several primary and secondary benzylic alcohols, bearing diverse substituents and with different substitution patterns. Key functional groups amenable for cross coupling, such as halogens and terminal alkynes, were tolerated. Terminal alkynes are particularly noteworthy because they are known for being activated by silver[268]. Another interesting observation was that secondary alcohols featuring two neighboring aromatic groups were suitable substrates. Unfortunately, unactivated primary and secondary alcohols were not amenable for this reaction.

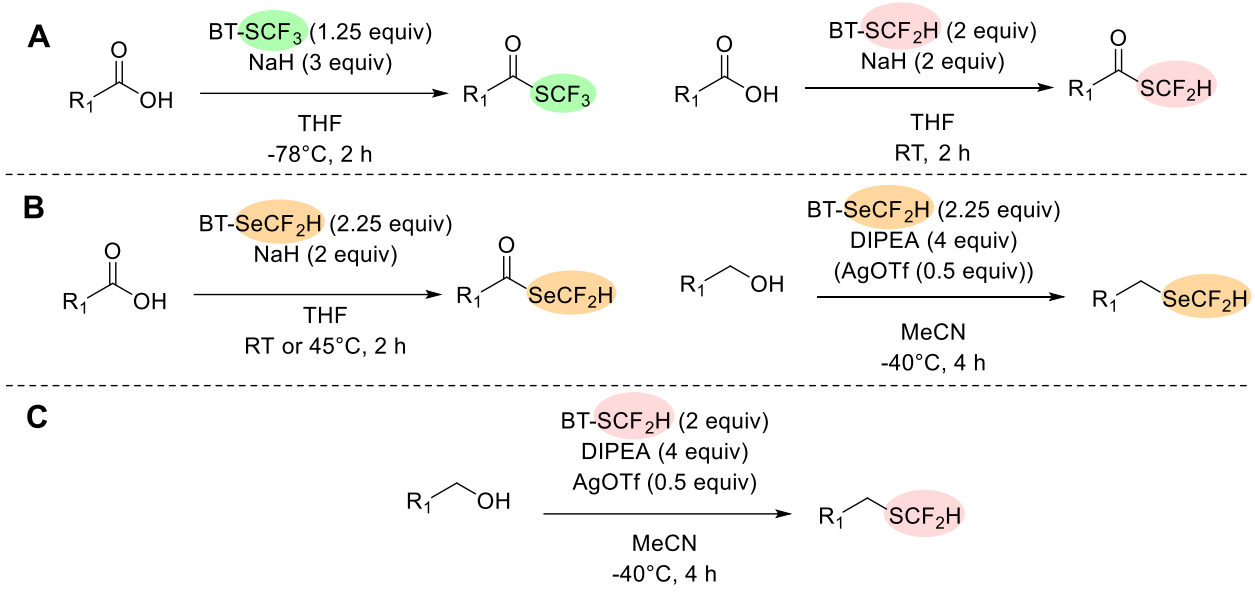


Scheme 73: Scope of the silver-catalyzed deoxydifluoromethylthiolation of alcohols. Adapted from[267]

Despite the scope limitation of our methodology, this work further proves that BT reagents are a valuable source of unstable anions for nucleophilic deoxygenative reactions, especially with the aid of silver catalysis. To the best of our knowledge, this process also represents the first reported example of a direct nucleophilic substitution reaction involving $^{-}SCF_2H$.

8. Outlook

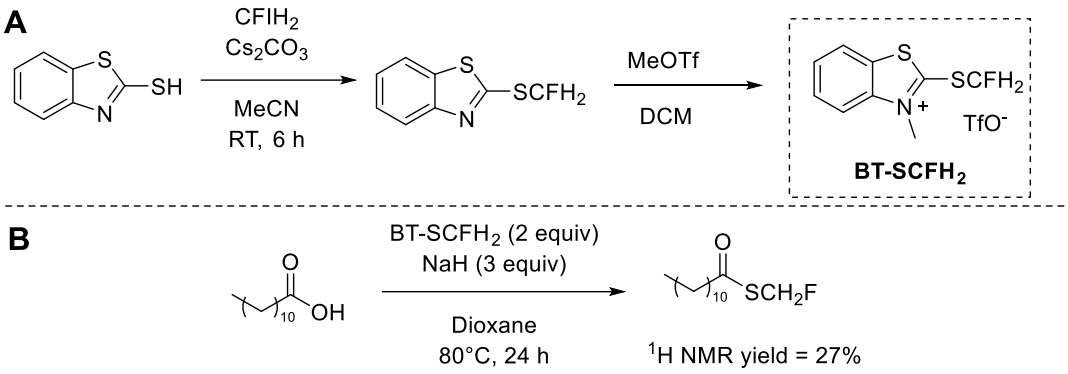
The occurrence of a concerted transition state in the reactions with acids enables the direct installation of unstable anions onto non-activated carboxylic acids without the release of the free nucleophile. This strategy, here exploited to install the -SCF_2H and -$SeCF_2H$ could be expanded to other fluorinated or non-fluorinated functional groups.



Scheme 74a: Deoxytri- and difluoromethylthiolation of carboxylic acids. **Scheme 74b:** Deoxydifluoromethylselenylation of carboxylic acids and alcohols. **Scheme 74c:** Silver catalyzed deoxydifluoromethylthiolation of alcohols.

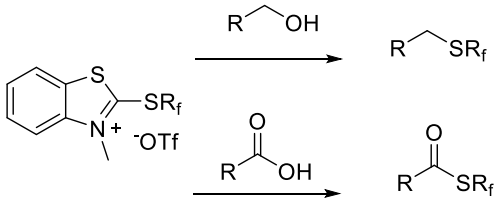
Following our successful development of the difluoromethylthiolation reaction with carboxylic acids, we wondered whether this concept could be expanded to the corresponding monofluoromethylated reagent, BT-$SCFH_2$. Whilst we were able to efficiently prepare this reagent (84% over two steps, Scheme 75a)[254], it proved unable to efficiently react with carboxylic acids. In particular, it was found that the reaction requires higher temperatures and a longer reaction time than the difluoromethylthiolation reaction, and despite the complete consumption of BT-$SCFH_2$ (2 equiv), in the crude mixture of the reaction with dodecanoic acid, ^{1}H NMR peaks compatible with the literature reference for S-(fluoromethyl)-dodecanethioate[269] were detected, however only ^{1}H NMR yields up to 27% could be obtained (Scheme 75b). Considering that, according to the DFT calculations performed with the tri- and difluoromethylthiolation reaction, there was an increased energy barrier going from -SCF_3 to -SCF_2H, we concluded that the energy barrier with -$SCFH_2$ was likely even higher, explaining why the reaction requires a higher temperature and a longer reaction time.

At the same time, however, given the cooperative nature of C-F bonds, the C-F bond in CFH_2 is weaker than in -CF_2H, thus making it more susceptible to unwanted side reactions (eg. β-fluoride elimination), especially considering the higher temperatures required. Not being able to make the transformation more efficient, we decided not to pursue this project further.



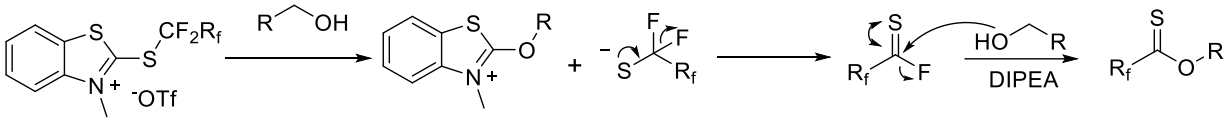
Scheme 75a: Synthesis of BT-$SCFH_2$ **Scheme 75b:** Deoxyfluoromethythiolation of dodecanoic acid with BT-$SCFH_2$.

Another possible variation of the BT concept is represented by BT-SR_f perfluoroalkyl reagents (Scheme 76). In these reagents, the strongly electron-withdrawing perfluorinated side chain further reduces the stability of the thiolate ^-SR_f anion. Despite these challenges, our group was able to develop a deoxyperfluoroalkylthiolation of alcohols procedure[270], capable of efficiently installing the $-SC_2F_5$ and $-SC_3F_7$ groups onto benzylic and propargylic alcohols. Considering the similarity between BT-SCF_3 and BT-SR_f in terms of reactivity with alcohols, we wondered whether these reagents were capable of furnishing the corresponding perfluoroalkylthioesters by reacting with carboxylic acids. Preliminary results from our group confirm that indeed such reactivity is possible, and further studies will be carried out to optimize the reaction conditions and explore a scope of suitable substrates.



Scheme 76: Deoxyperfluoroalkylthiolation of alcohols and acids with BT-$SC_nF_{(2n+1)}$

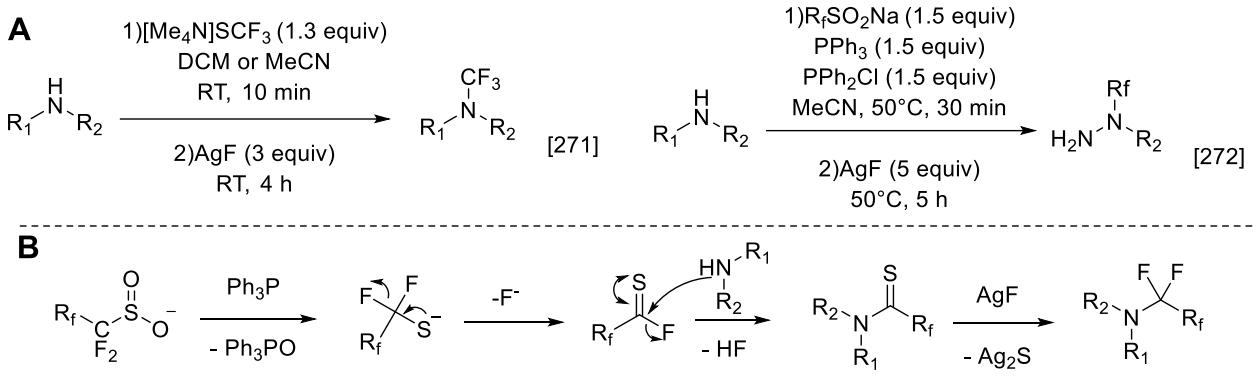
One of the issues with the deoxyperfluoroalkylthiolation of alcohols is however the tendency of longer perfluorinated chains to destabilize the ^-SR_f anion, leading to the formation of significant amounts thiocarbonyl fluoride species, which can react further to form other side products (Scheme 77).



Scheme 77: Formation of thionoesters from BT-SR_f reagents and alcohols.

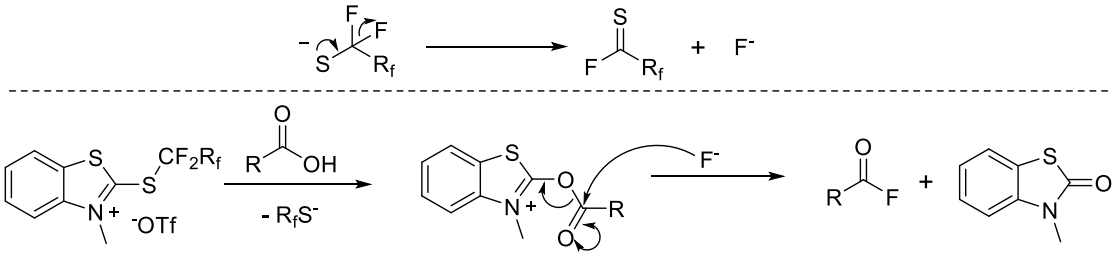
Whilst these side products were undesired for that procedure, the BT reagents could be exploited as convenient sources of the thiocarbonyl fluoride intermediate, which could represent an interesting gateway toward other valuable compounds.

For instance, the thiocarbonyl fluoride was a key intermediate in Schönebeck's synthesis of trifluoromethyl amines with $[Me_4N]SCF_3$[271] (Scheme 78a), and in Yi's related perfluoroalkylation of amines with R_fSO_2Na/PPh_3[272] (Scheme 78b). In these reactions, the carbon-sulfur double bond is replaced by a $-CF_2-$ moiety via desulfurative fluorination with AgF.



Scheme 78a: Trifluoromethylation of secondary amines as reported by Schönebeck. **Scheme 78b:** Perfluoroalkylation of secondary amines reported by Yi.

Another relevant side product of the β-fluoride elimination side reaction is fluoride itself (Scheme 79a) which, as discussed in section 6.1, is capable of reacting with the acyloxy benzothiazolium intermediate to form acid fluorides, a compound first identified as a side product of the deoxytrifluoromethylthiolation reaction with BT-SCF_3 (Scheme 79b). These useful compounds could potentially be trapped with various nucleophiles to furnish several important carbonyl derivatives.



Scheme 79a: β-fluoride elimination from $^{-}SR_f$ anions. **Scheme 79b:** Deoxyfluorination of carboxylic acids using BT reagents.

In conclusion, the work presented in this thesis has greatly expanded the applicability of the benzothiazolium reagent strategy, proving its validity and versatility as a nucleophilic source of valuable fluorinated moieties. The many avenues in which this versatile reagent class can be employed will certainly lead to future developments in the field of fluoro-organic chemistry.

9. Publications and author contributions

Deoxygenative Tri- and Difluoromethylthiolation of Carboxylic Acids with Benzothiazolium Reagents

Matteo Tironi, Lilian M. Maas, Arushi Garg, Stefan Dix, Jan P. Götze, and Matthew N. Hopkinson

Org. Lett. **2020**, 22, 8925-8930.

https://doi.org/10.1021/acs.orglett.0c03328

Abstract

Deoxygenative syntheses of fluorinated thioesters directly from carboxylic acids have been developed employing benzothiazolium reagents. The process using BT-SCF_3 represents an attractive approach toward these SCF_3-containing compounds that avoids the use of metal–SCF_3 salts or preactivated acyl electrophiles. Moreover, the *in situ* activation of BT-SCF_2H allows for an unprecedented nucleophilic difluoromethylthiolation reaction. DFT calculations support a mechanistic scenario involving a four-membered transition state where acyl substitution occurs without the formation of an unstable free $^{-}SCF_2H$ anion.

Contribution of Authors

Jun.-Prof. Dr. Matthew Hopkinson developed the concept for the BT-Reagents. Stefan Dix developed the synthesis of the BT-SCF_3 reagent and oversaw initial experiments on the deoxygenative reactions. Arushi Garg developed the synthesis of the BT-SCF_2H reagent and obtained the first hit in the deoxytri- and difluoromethylation of carboxylic acids. Lilian M. Maas synthesized the BT-SCF_3 reagent needed for the project, optimized the deoxytrifluoromethylthiolation reaction, and isolated and characterized the trifluoromethylthioester products. I optimized the synthesis of the BT-SCF_2H reagent, synthesized the reagent needed for the project, optimized the deoxydifluoromethylthiolation reaction, and isolated and characterized the difluoromethylthioester products. Dr. Jan P. Götze handled the computational calculations. Jun.-Prof. Dr. Matthew Hopkinson supervised the project and wrote the publication with contributions from all authors. Lilian M. Maas and I wrote the supporting information.

Deoxygenative nucleophilic difluoromethylselenylation of carboxylic acids and alcohols with BT-$SeCF_2H$

Matteo Tironi, Stefan Dix and Matthew N. Hopkinson

Org. Chem. Front., **2021**,*8,* 6026-6031.

https://doi.org/10.1039/D1QO01104A

Abstract

The benzothiazolium salt BT-$SeCF_2H$ is introduced as an efficient nucleophilic reagent for transferring difluoromethylselenyl groups onto organic molecules. $SeCF_2H$-Containing selenoesters could be prepared upon deoxygenative substitution of readily available carboxylic acids, while silver catalysis allowed for efficient formation of (difluoromethyl)selenoethers, including the established electrophilic reagent $BnSeCF_2H$, directly from simple alcohols. To the best of our knowledge, these deoxygenative reactions represent the first reported nucleophilic difluoromethylselenylation processes and thus open up new approaches to prepare valuable fluorinated compounds.

Contribution of Authors

Prof. Dr. Matthew Hopkinson developed the concept for the BT-Reagents. Stefan Dix first synthesized the BT-$SeCF_2H$ reagent and performed the first deoxydifluoromethylselenylation reaction of carboxylic acids. I optimized the synthesis of the BT-$SeCF_2H$ reagent, optimized the deoxydifluoromethylselenylation of carboxylic acid and synthesized, isolated and characterized the difluoromethylselenoesters. I also developed the deoxydifluoromethylselenylation of alcohols, optimized it, and isolated and characterized the difluoromethylselane compounds. Prof. Dr. Matthew Hopkinson supervised the project and wrote the publication, with the contribution of the other authors. I wrote the supporting information.

Silver-Catalyzed Nucleophilic Deoxydifluoromethylthiolation of Activated Aliphatic Alcohols with BT–SCF_2H

Matteo Tironi and Matthew N. Hopkinson
Eur. J. Org. Chem. **2022**,2022, 18, e202101557.

https://doi.org/10.1002/ejoc.202101557

Abstract

Deoxygenative conversion of alcohols into difluoromethylthioethers is reported using 2-((difluoromethyl)thio)-3-methylbenzo[*d*]thiazol-3-ium triflate (BT–SCF_2H) as a source of $^-SCF_2H$ anions. The presence of silver(I) triflate as a catalyst was found to be crucial for stabilizing the *in situ*-generated anion, while the concomitant formation of a reactive 2-(alkoxy)benzothiazolium electrophile likely ensures a fast onward substitution reaction, avoiding the build-up of $^-SCF_2H$. To the best of our knowledge, this process represents the first report of a direct nucleophilic substitution reaction with $^-SCF_2H$ and delivers products containing the medicinally relevant difluoromethylthio motif in a single step from widely available alcohols.

Contribution of Authors

Prof. Dr. Matthew Hopkinson developed the concept for the BT-Reagents. I optimized the deoxydifluoromethylthiolation of alcohols and synthesized, isolated and characterized the difluoromethylthioether compounds. Prof. Dr. Matthew Hopkinson supervised the project and wrote the publication, with my contribution. I wrote the supporting information.

10. References

[1] A. Coc, *J. Phys. Conf. Ser.* **2016**, *665*, 012001.

[2] A. Renda, Y. Fenner, B. K. Gibson, A. I. Karakas, J. C. Lattanzio, S. Campbell, A. Chieffi, K. Cunha, V. V. Smith, *Mon. Notices Royal Astron. Soc.* **2004**, *354*, 575-580.

[3] A. Jorissen, V. V. Smith, D. L. Lambert, *Astron. Astrophys.* **1992**, *261*, 164.

[4] S. E. Woosley, W. C. Haxton, *Nature* **1988**, *334*, 45-47.

[5] J. Schmedt auf der Günne, M. Mangstl, F. Kraus, *Angew. Chem. Int. Ed.* **2012**, *51*, 7847-7849.

[6] J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432-2506.

[7] J. S. C. Marais, *Onderstepoort Jour. Vet. Sci. Animal Ind.* **1944**, *20*.

[8] A. T. Proudfoot, S. M. Bradberry, J. A. Vale, *Toxicol. Rev.* **2006**, *25*, 213-219.

[9] C. M. Timperley, in *Fluorine Chemistry at the Millennium* (Ed.: R. E. Banks), Elsevier Science Ltd, Oxford, **2000**, pp. 499-538.

[10] C. Dong, F. Huang, H. Deng, C. Schaffrath, J. B. Spencer, D. O'Hagan, J. H. Naismith, *Nature* **2004**, *427*, 561-565.

[11] A. Tressaud, M. Vickers, *J. Glass Stud.* **2007**, *49*, 143-152.

[12] G. Agricola, *De Re Metallica Libri XII, Vol. 4*, marix Verlag, Wiesbaden, **2015**.

[13] A. Marggraf, *Mémoires de l'Académie royale des sciences et belles-lettres* **1770**, *24*, 3-11.

[14] A.-M. Ampère, *Essai d'une classification naturelle pour les corps simples*, De l'Imprimerie de Feugueray, **1816**.

[15] M. E. Weeks, *J. Chem. Educ.* **1932**, *9*, 1915.

[16] A. Tressaud, *Angew. Chem. Int. Ed.* **2006**, *45*, 6792-6796.

[17] H. Goldwhite, *J. Fluor. Chem.* **1986**, *33*, 109-132.

[18] T. Okazoe, *Proc. Jpn. Acad. B: Phys. Biol. Sci.* **2009**, *85*, 276-289.

[19] M. J. Molina, F. S. Rowland, *Nature* **1974**, *249*, 810-812.

[20] W. Han, Y. Li, H. Tang, H. Liu, *J. Fluor. Chem.* **2012**, *140*, 7-16.

[21] aS. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320-330; bK. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881-1886; cR. Berger, G. Resnati, P. Metrangolo, E. Weber, J. Hulliger, *Chem. Soc. Rev.* **2011**, *40*, 3496-3508; dT. Fujiwara, D. O'Hagan, *J. Fluor. Chem.* **2014**, *167*, 16-29; eA. Harsanyi, G. Sandford, *Green Chem.* **2015**, *17*, 2081-2086.

[22] aM. Calafat Antonia, L.-Y. Wong, Z. Kuklenyik, A. Reidy John, L. Needham Larry, *Environ. Health Perspect.* **2007**, *115*, 1596-1602; bT. Stahl, D. Mattern, H. Brunn, *Environ. Sci. Eur.* **2011**, *23*, 38.

[23] J. L. Domingo, M. Nadal, *Environ. Res.* **2019**, *177*, 108648.

[24] C. T. Dervos, P. Vassiliou, *J. Air Waste Manag. Assoc.* **2000**, *50*, 137-141.

[25] M. Inoue, Y. Sumii, N. Shibata, *ACS Omega* **2020**, *5*, 10633-10640.

[26] Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai, N. Shibata, *iScience* **2020**, *23*, 101467.

[27] J. Fried, E. F. Sabo, *J. Am. Chem. Soc.* **1954**, *76*, 1455-1456.

[28] E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315-8359.

[29] N. A. Meanwell, *J. Med. Chem.* **2018**, *61*, 5822-5880.

[30] R. Bar-Shalom, A. Y. Valdivia, M. D. Blaufox, *Semin. Nucl. Med.* **2000**, *30*, 150-185.

[31] W. C. Smith, C. W. Tullock, E. L. Muetterties, W. R. Hasek, F. S. Fawcett, V. A. Engelhardt, D. D. Coffman, *J. Am. Chem. Soc.* **1959**, *81*, 3165-3166.

[32] J. A. Wilkinson, *Chem. Rev.* **1992**, *92*, 505-519.

[33] C. Ni, M. Hu, J. Hu, *Chem Rev* **2015**, *115*, 765-825.

[34] aP. Tang, W. Wang, T. Ritter, *J. Am. Chem. Soc.* **2011**, *133*, 11482-11484; bC. N. Neumann, T. Ritter, *Acc. Chem. Res.* **2017**, *50*, 2822-2833.

[35] S. Rozen, *Chem. Rev.* **1996**, *96*, 1717-1736.

[36] P. A. Champagne, J. Desroches, J.-D. Hamel, M. Vandamme, J.-F. Paquin, *Chem. Rev.* **2015**, *115*, 9073-9174.

[37] C.-T. Li, X. Yuan, Z.-Y. Tang, *Tetrahedron Lett.* **2016**, *57*, 5624-5627.

[38] aM. Rueda-Becerril, O. Mahé, M. Drouin, M. B. Majewski, J. G. West, M. O. Wolf, G. M. Sammis, J.-F. Paquin, *J. Am. Chem. Soc.* **2014**, *136*, 2637-2641; bS. Ventre, F. R. Petronijevic, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2015**, *137*, 5654-5657.
[39] aJ. K. Bower, A. D. Cypcar, B. Henriquez, S. C. E. Stieber, S. Zhang, *J. Am. Chem. Soc.* **2020**, *142*, 8514-8521; bA. Vasilopoulos, D. L. Golden, J. A. Buss, S. S. Stahl, *Org. Lett.* **2020**, *22*, 5753-5757; cS. Bloom, C. R. Pitts, D. C. Miller, N. Haselton, M. G. Holl, E. Urheim, T. Lectka, *Angew. Chem. Int. Ed.* **2012**, *51*, 10580-10583; dJ.-B. Xia, C. Zhu, C. Chen, *J. Am. Chem. Soc.* **2013**, *135*, 17494-17500.
[40] D. Wang, Z. Yuan, Q. Liu, P. Chen, G. Liu, *Chin. J. Chem* . **2018**, *36*, 507-514.
[41] A. R. Mazzotti, M. G. Campbell, P. Tang, J. M. Murphy, T. Ritter, *J. Am. Chem. Soc.* **2013**, *135*, 14012-14015.
[42] aC. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165-195; bA. Tlili, F. Toulgoat, T. Billard, *Angew. Chem. Int. Ed.* **2016**, *55*, 11726-11735; cA. Leo, C. Hansch, D. Elkins, *Chem. Rev.* **1971**, *71*, 525-616; dX.-H. Xu, K. Matsuzaki, N. Shibata, *Chem. Rev.* **2015**, *115*, 731-764.
[43] M. Bassetto, S. Ferla, F. Pertusati, *Future Med. Chem.* **2015**, *7*, 527-546.
[44] S. Noack, H. D. Chapman, P. M. Selzer, *Parasitol. Res.* **2019**, *118*, 2009-2026.
[45] aT. Silverstone, J. Fincham, J. Plumley, *Br. J. Clin. Pharmacol.* **1979**, *7*, 353-356; bJ. N. André, L. G. Dring, G. Gillet, C. Mas-Chamberlin, *Br. J. Pharmacol* **1979**, *66*, 506P-506P.
[46] G. W. Counts, D. Gregory, D. Zeleznik, M. Turck, *Antimicrob. Agents Chemother.* **1977**, *11*, 708-711.
[47] C. Ghiazza, T. Billard, C. Dickson, A. Tlili, C. M. Gampe, *ChemMedChem* **2019**, *14*, 1586-1589.
[48] aX. He, M. Zhong, S. Li, X. Li, Y. Li, Z. Li, Y. Gao, F. Ding, D. Wen, Y. Lei, Y. Zhang, *Eur. J. Med. Chem.* **2020**, *208*, 112864; bX. He, Y. Nie, M. Zhong, S. Li, X. Li, Y. Guo, Z. Liu, Y. Gao, F. Ding, D. Wen, Y. Zhang, *Eur. J. Med. Chem.* **2021**, *218*, 113384.
[49] aJ. Zheng, Y. Li, L. Zhang, J. Hu, G. J. Meuzelaar, H.-J. Federsel, *Chem. Commun.* **2007**, 5149-5151; bJ. M. Kremsner, M. Rack, C. Pilger, C. Oliver Kappe, *Tetrahedron Lett.* **2009**, *50*, 3665-3668.
[50] I. Kieltsch, P. Eisenberger, A. Togni, *Angew. Chem. Int. Ed.* **2007**, *46*, 754-757.
[51] S. Verhoog, C. W. Kee, Y. Wang, T. Khotavivattana, T. C. Wilson, V. Kersemans, S. Smart, M. Tredwell, B. G. Davis, V. Gouverneur, *J. Am. Chem. Soc.* **2018**, *140*, 1572-1575.
[52] J. Charpentier, N. Früh, A. Togni, *Chem. Rev.* **2015**, *115*, 650-682.
[53] C.-P. Zhang, Z.-L. Wang, Q.-Y. Chen, C.-T. Zhang, Y.-C. Gu, J.-C. Xiao, *Chem. Commun.* **2011**, *47*, 6632-6634.
[54] R. N. Haszeldine, B. Hewitson, B. Higginbottom, R. B. Rigby, A. E. Tipping, *J. Chem. Soc., Chem. Commun.* **1972**, 249-250.
[55] A. Harsányi, É. Dorkó, Á. Csapó, T. Bakó, C. Peltz, J. Rábai, *J. Fluor. Chem.* **2011**, *132*, 1241-1246.
[56] C. Pooput, M. Medebielle, W. R. Dolbier, *Org. Lett.* **2004**, *6*, 301-303.
[57] L. V. Sokolenko, I. I. Maletina, L. M. Yagupolskii, Y. L. Yagupolskii, *Synlett* **2010**, *2010*, 2075-2078.
[58] R. K. Orlova, L. V. Sokolenko, L. A. Babadzhanova, A. A. Filatov, Y. L. Yagupolskii, *J. Fluor. Chem.* **2022**, *261-262*, 110004.
[59] N. J. W. Straathof, B. J. P. Tegelbeckers, V. Hessel, X. Wang, T. Noël, *Chem. Sci.* **2014**, *5*, 4768-4773.
[60] E. Magnier, E. Vit, C. Wakselman, *Synlett* **2001**, *2001*, 1260-1262.
[61] S. Dix, M. Jakob, M. N. Hopkinson, *Chem. Eur. J.* **2019**, *25*, 7635-7639.
[62] J.-J. Ma, W.-B. Yi, G.-P. Lu, C. Cai, *Catal. Sci. Technol.* **2016**, *6*, 417-421.
[63] J.-j. Ma, Q.-r. Liu, G.-p. Lu, W.-b. Yi, *J. Fluor. Chem.* **2017**, *193*, 113-117.
[64] B. R. Langlois, E. Laurent, N. Roidot, *Tetrahedron Lett.* **1991**, *32*, 7525-7528.
[65] S. Soni, P. Pali, M. A. Ansari, M. S. Singh, *J. Org. Chem.* **2020**, *85*, 10098-10109.
[66] B.-Q. Cao, Y.-F. Qiu, X. Zhang, Z.-H. Zhu, Z.-J. Quan, X.-C. Wang, *Eur. J. Org. Chem.* **2019**, *2019*, 1208-1214.
[67] T. Billard, B. R. Langlois, *Tetrahedron Lett.* **1996**, *37*, 6865-6868.
[68] C. Zheng, C. Jiang, S. Huang, K. Zhao, Y. Fu, M. Ma, J. Hong, *Org. Lett.* **2021**, *23*, 6982-6986.
[69] aR. Yao, Y. Ling, W. Chen, L. Lu, Q. Shen, *Org. Process Res. Dev.* **2022**, *26*, 299-306; bY. Liu, Y. Ling, H. Ge, L. Lu, Q. Shen, *Chin. J. Chem* . **2021**, *39*, 1667-1682.
[70] aT. Billard, S. Large, B. R. Langlois, *Tetrahedron Lett.* **1997**, *38*, 65-68; bY. Lv, W. Pu, H. Cui, J. He, Q. Zhang, *Synth. Commun.* **2016**, *46*, 1223-1229.

[71] A. De-Zordo Banliat, K. Grollier, A. Damond, T. Billard, G. Dagousset, E. Magnier, B. Pégot, *Tetrahedron* **2021**, *101*, 132507.
[72] P. Nikolaienko, M. Rueping, *Chem. Eur. J.* **2016**, *22*, 2620-2623.
[73] S. Large, N. Roques, B. R. Langlois, *J. Org. Chem.* **2000**, *65*, 8848-8856.
[74] S. Potash, S. Rozen, *J. Fluor. Chem.* **2014**, *168*, 173-176.
[75] aC. Aharon, S. Rozen, *J. Fluor. Chem.* **2021**, *250*, 109866; bS. Potash, S. Rozen, *J. Org. Chem.* **2014**, *79*, 11205-11208.
[76] J. B. Geri, M. M. Wade Wolfe, N. K. Szymczak, **2018**, *57*, 1381-1385.
[77] H. Emeléus, S. Nabi, *J. Chem. Soc.* **1960**, 1103-1108.
[78] W. A. Sheppard, *J. Org. Chem.* **1964**, *29*, 895-898.
[79] S. Andreades, J. Harris Jr, W. A. Sheppard, *J. Org. Chem.* **1964**, *29*, 898-900.
[80] S. Munavalli, D. K. Rohrbaugh, D. I. Rossman, F. J. Berg, G. W. Wagner, H. D. Durst, *Synth. Commun.* **2000**, *30*, 2847-2854.
[81] R. Pluta, P. Nikolaienko, M. Rueping, *Angew. Chem. Int. Ed.* **2014**, *53*, 1650-1653.
[82] R. Pluta, M. Rueping, *Chem. Eur. J.* **2014**, *20*, 17315-17318.
[83] C. Xu, B. Ma, Q. Shen, *Angew. Chem. Int. Ed.* **2014**, *53*, 9316-9320.
[84] A. Ferry, T. Billard, B. R. Langlois, E. Bacqué, *Angew. Chem. Int. Ed.* **2009**, *48*, 8551-8555.
[85] S. Alazet, L. Zimmer, T. Billard, *Angew. Chem. Int. Ed.* **2013**, *52*, 10814-10817.
[86] S. Alazet, K. Ollivier, T. Billard, *Beilstein J. Org. Chem.* **2013**, *9*, 2354-2357.
[87] F. Baert, J. Colomb, T. Billard, *Angew. Chem. Int. Ed.* **2012**, *51*, 10382-10385.
[88] S. Alazet, L. Zimmer, T. Billard, *Chem. Eur. J.* **2014**, *20*, 8589-8593.
[89] X. Shao, X. Wang, T. Yang, L. Lu, Q. Shen, *Angew. Chem. Int. Ed.* **2013**, *52*, 3457-3460.
[90] E. V. Vinogradova, P. Müller, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2014**, *53*, 3125-3128.
[91] X. Shao, C. Xu, L. Lu, Q. Shen, *J. Org. Chem.* **2015**, *80*, 3012-3021.
[92] X.-G. Yang, K. Zheng, C. Zhang, *Org. Lett.* **2020**, *22*, 2026-2031.
[93] H. Emeléus, N. Welcman, *J. Chem. Soc.* **1963**, 1268-1271.
[94] E. Magnier, C. Wakselman, *Collect. Czech. Chem. Commun.* **2002**, *67*, 1262-1266.
[95] Q. Glenadel, E. Ismalaj, T. Billard, *Eur. J. Org. Chem.* **2017**, *2017*, 530-533.
[96] C. Ghiazza, A. Tlili, T. Billard, *Eur. J. Org. Chem.* **2018**, *2018*, 3680-3683.
[97] Q. Glenadel, C. Ghiazza, A. Tlili, T. Billard, *Adv. Synth. Catal.* **2017**, *359*, 3414-3420.
[98] C. Ghiazza, V. Debrauwer, T. Billard, A. Tlili, *Chem. Eur. J.* **2018**, *24*, 97-100.
[99] K. Grollier, E. Chefdeville, E. Jeanneau, T. Billard, *Chem. Eur. J.* **2021**, *27*, 12910-12916.
[100] J. F. Harris, *J. Am. Chem. Soc.* **1962**, *84*, 3148-3153.
[101] J. F. Harris, *J. Org. Chem.* **1966**, *31*, 931-935.
[102] G. Haran, D. W. A. Sharp, *J. Chem. Soc., Perkin Trans. 1* **1972**, 34-38.
[103] F. Hu, X. Shao, D. Zhu, L. Lu, Q. Shen, *Angew. Chem. Int. Ed.* **2014**, *53*, 6105-6109.
[104] L. Candish, L. Pitzer, A. Gómez-Suárez, F. Glorius, *Chem. Eur. J.* **2016**, *22*, 4753-4756.
[105] T. Yang, L. Lu, Q. Shen, *Chem. Commun.* **2015**, *51*, 5479-5481.
[106] S. Mukherjee, B. Maji, A. Tlahuext-Aca, F. Glorius, *J. Am. Chem. Soc.* **2016**, *138*, 16200-16203.
[107] H. Zhang, Q. Wang, Y. Wang, Z. Yuan, F. Gao, R. Britton, *Asian J. Org. Chem.* **2021**, *10*, 2566-2570.
[108] T. E. Schirmer, A. B. Rolka, T. A. Karl, F. Holzhausen, B. König, *Org. Lett.* **2021**, *23*, 5729-5733.
[109] R. Honeker, R. A. Garza-Sanchez, M. N. Hopkinson, F. Glorius, *Chem. Eur. J.* **2016**, *22*, 4395-4399.
[110] G. Dagousset, C. Simon, E. Anselmi, B. Tuccio, T. Billard, E. Magnier, *Chem. Eur. J.* **2017**, *23*, 4282-4286.
[111] aQ. Glenadel, E. Ismalaj, T. Billard, *J. Org. Chem.* **2016**, *81*, 8268-8275; bC. Ghiazza, M. Ndiaye, A. Hamdi, A. Tlili, T. Billard, *Tetrahedron* **2018**, *74*, 6521-6526.
[112] M. Barday, R. Blieck, L. Ruyet, T. Besset, *Tetrahedron* **2020**, *76*, 131153.
[113] C. Ghiazza, C. Monnereau, L. Khrouz, T. Billard, A. Tlili, *Synthesis* **2019**, *51*, 2865-2870.
[114] C. Ghiazza, V. Debrauwer, C. Monnereau, L. Khrouz, M. Médebielle, T. Billard, A. Tlili, *Angew. Chem. Int. Ed.* **2018**, *57*, 11781-11785.
[115] C. Ghiazza, L. Khrouz, C. Monnereau, T. Billard, A. Tlili, *Chem. Commun.* **2018**, *54*, 9909-9912.
[116] Y. Lei, J. Yang, Y. Wang, H. Wang, Y. Zhan, X. Jiang, Z. Xu, *Green Chem.* **2020**, *22*, 4878-4883.

[117] X. Zhao, B. Yang, A. Wei, J. Sheng, M. Tian, Q. Li, K. Lu, *Tetrahedron Lett.* **2018**, *59*, 1719-1722.
[118] F. Yin, X.-S. Wang, *Org. Lett.* **2014**, *16*, 1128-1131.
[119] Y.-F. Qiu, X.-Y. Zhu, Y.-X. Li, Y.-T. He, F. Yang, J. Wang, H.-L. Hua, L. Zheng, L.-C. Wang, X.-Y. Liu, Y.-M. Liang, *Org. Lett.* **2015**, *17*, 3694-3697.
[120] J. Phetcharawetch, N. M. Betterley, V. Reutrakul, D. Soorukram, P. Leowanawat, C. Kuhakarn, *J. Fluor. Chem.* **2021**, *250*, 109878.
[121] Q.-Y. Han, K.-L. Tan, H.-N. Wang, C.-P. Zhang, *Org. Lett.* **2019**, *21*, 10013-10017.
[122] aQ.-Y. Han, C.-L. Zhao, T. Dong, J. Shi, K.-L. Tan, C.-P. Zhang, *Org. Chem. Front.* **2019**, *6*, 2732-2737; bA. De Zordo-Banliat, L. Barthélémy, F. Bourdreux, B. Tuccio, G. Dagousset, B. Pégot, E. Magnier, *Eur. J. Org. Chem.* **2020**, *2020*, 506-509.
[123] R. Haszeldine, J. Kidu, *J. Chem. Soc.* **1953**, 3219-3225.
[124] aW. Tyrra, D. Naumann, B. Hoge, Y. L. Yagupolskii, *J. Fluor. Chem.* **2003**, *119*, 101-107; bA. Darmadi, A. Haas, B. Koch, *Zeitschrift für Naturforschung B* **1980**, *35*, 526-529.
[125] Z. Weng, W. He, C. Chen, R. Lee, D. Tan, Z. Lai, D. Kong, Y. Yuan, K.-W. Huang, *Angew. Chem. Int. Ed.* **2013**, *52*, 1548-1552.
[126] Q. Lin, L. Chen, Y. Huang, M. Rong, Y. Yuan, Z. Weng, *Org. Biomol. Chem.* **2014**, *12*, 5500-5508.
[127] C. Chen, L. Ouyang, Q. Lin, Y. Liu, C. Hou, Y. Yuan, Z. Weng, *Chem. Eur. J.* **2014**, *20*, 657-661.
[128] M. Rong, R. Huang, Y. You, Z. Weng, *Tetrahedron* **2014**, *70*, 8872-8878.
[129] Y. Yang, X. Lin, Z. Zheng, G. Lin, Y. Zhang, Y. You, Z. Weng, *J. Fluor. Chem.* **2017**, *204*, 1-5.
[130] J. Wang, M. Zhang, Z. Weng, *J. Fluor. Chem.* **2017**, *193*, 24-32.
[131] E. H. Man, D. D. Coffman, E. L. Muetterties, *J. Am. Chem. Soc.* **1959**, *81*, 3575-3577.
[132] G. Teverovskiy, D. S. Surry, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2011**, *50*, 7312-7314.
[133] C. S. Gravatt, J. W. Johannes, E. R. King, A. Ghosh, *J. Org. Chem.* **2022**, *87*, 8921-8927.
[134] S. R. Mudshinge, Y. Yang, B. Xu, G. B. Hammond, Z. Lu, *Angew. Chem. Int. Ed.* **2022**, *61*, e202115687.
[135] C. Zheng, Y. Liu, J. Hong, S. Huang, W. Zhang, Y. Yang, G. Fang, *Tetrahedron Lett.* **2019**, *60*, 1404-1407.
[136] M. Jiang, F. Zhu, H. Xiang, X. Xu, L. Deng, C. Yang, *Org. Biomol. Chem.* **2015**, *13*, 6935-6939.
[137] E. Anselmi, C. Simon, J. Marrot, P. Bernardelli, L. Schio, B. Pégot, E. Magnier, *Eur. J. Org. Chem.* **2017**, *2017*, 6319-6326.
[138] Q. Glenadel, A. Tlili, T. Billard, *Eur. J. Org. Chem.* **2016**, *2016*, 1955-1957.
[139] Y.-L. Liu, X.-H. Xu, F.-L. Qing, *Tetrahedron* **2018**, *74*, 5827-5832.
[140] H.-T. Chen, Y. Huang, F.-L. Qing, X.-H. Xu, *Tetrahedron Lett.* **2020**, *61*, 151628.
[141] A. Haas, *J. Fluor. Chem.* **1986**, *32*, 415-439.
[142] T. Billard, F. Toulgoat, in *Emerging Fluorinated Motifs*, **2020**, pp. 691-721.
[143] S. J. Tavener, D. J. Adams, J. H. Clark, *J. Fluor. Chem.* **1999**, *95*, 171-176.
[144] G. Yin, I. Kalvet, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2015**, *54*, 6809-6813.
[145] J. Xu, X. Mu, P. Chen, J. Ye, G. Liu, *Org. Lett.* **2014**, *16*, 3942-3945.
[146] aG. Yin, I. Kalvet, U. Englert, F. Schoenebeck, *J. Am. Chem. Soc.* **2015**, *137*, 4164-4172; bI. Kalvet, Q. Guo, G. J. Tizzard, F. Schoenebeck, *ACS Catalysis* **2017**, *7*, 2126-2132; cC.-P. Zhang, D. A. Vicic, *J. Am. Chem. Soc.* **2012**, *134*, 183-185.
[147] C.-P. Zhang, D. A. Vicic, *Chem. Asian J.* **2012**, *7*, 1756-1758.
[148] J. Shi, C.-P. Zhang, *Molecules* **2020**, *25*, 4535.
[149] S. Kovács, B. Bayarmagnai, L. J. Goossen, *Adv. Synth. Catal.* **2017**, *359*, 250-254.
[150] T. Scattolin, A. Klein, F. Schoenebeck, *Org. Lett.* **2017**, *19*, 1831-1833.
[151] W. Tyrra, D. Naumann, Y. L. Yagupolskii, *J. Fluor. Chem.* **2003**, *123*, 183-187.
[152] M. Aufiero, T. Sperger, A. S.-K. Tsang, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2015**, *54*, 10322-10326.
[153] aJ.-B. Han, T. Dong, D. A. Vicic, C.-P. Zhang, *Org. Lett.* **2017**, *19*, 3919-3922; bA. B. Dürr, H. C. Fisher, I. Kalvet, K.-N. Truong, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2017**, *56*, 13431-13435.
[154] Q. Lefebvre, R. Pluta, M. Rueping, *Chem. Commun.* **2015**, *51*, 4394-4397.
[155] J. B. I. Sap, C. F. Meyer, N. J. W. Straathof, N. Iwumene, C. W. am Ende, A. A. Trabanco, V. Gouverneur, *Chem. Soc. Rev.* **2021**, *50*, 8214-8247.
[156] aY. Zafrani, G. Sod-Moriah, D. Yeffet, A. Berliner, D. Amir, D. Marciano, S. Elias, S. Katalan, N. Ashkenazi, M. Madmon, E. Gershonov, S. Saphier, *J. Med. Chem.* **2019**, *62*, 5628-5637; bQ. A. Huchet,

N. Trapp, B. Kuhn, B. Wagner, H. Fischer, N. A. Kratochwil, E. M. Carreira, K. Müller, *J. Fluor. Chem.* **2017**, *198*, 34-46.
[157] L. Xing, D. C. Blakemore, A. Narayanan, R. Unwalla, F. Lovering, R. A. Denny, H. Zhou, M. E. Bunnage, *ChemMedChem* **2015**, *10*, 715-726.
[158] Y. Zafrani, D. Yeffet, G. Sod-Moriah, A. Berliner, D. Amir, D. Marciano, E. Gershonov, S. Saphier, *J. Med. Chem.* **2017**, *60*, 797-804.
[159] C. D. Sessler, M. Rahm, S. Becker, J. M. Goldberg, F. Wang, S. J. Lippard, *J. Am. Chem. Soc.* **2017**, *139*, 9325-9332.
[160] aP. R. Melvin, D. M. Ferguson, S. D. Schimler, D. C. Bland, M. S. Sanford, *Org. Lett.* **2019**, *21*, 1350-1353; bG. S. Lal, G. P. Pez, R. J. Pesaresi, F. M. Prozonic, H. Cheng, *J. Org. Chem.* **1999**, *64*, 7048-7054; cF. Beaulieu, L.-P. Beauregard, G. Courchesne, M. Couturier, F. LaFlamme, A. L'Heureux, *Org. Lett.* **2009**, *11*, 5050-5053; dR. P. Singh, J. n. M. Shreeve, *Synthesis* **2002**, *2002*, 2561-2578; eT. Umemoto, R. P. Singh, Y. Xu, N. Saito, *J. Am. Chem. Soc.* **2010**, *132*, 18199-18205.
[161] aT. Furuya, T. Fukuhara, S. Hara, *J. Fluor. Chem.* **2005**, *126*, 721-725; bO. Cohen, Y. Hagooly, S. Rozen, *Tetrahedron* **2009**, *65*, 1361-1365; cO. Roy, B. Marquet, J.-P. Alric, A. Jourdan, B. Morel, B. R. Langlois, T. Billard, *J. Fluor. Chem.* **2014**, *167*, 74-78.
[162] A. J. Bloodworth, K. J. Bowyer, J. C. Mitchell, *Tetrahedron Lett.* **1987**, *28*, 5347-5350.
[163] D. Rageot, T. Bohnacker, A. Melone, J.-B. Langlois, C. Borsari, P. Hillmann, A. M. Sele, F. Beaufils, M. Zvelebil, P. Hebeisen, W. Löscher, J. Burke, D. Fabbro, M. P. Wymann, *J. Med. Chem.* **2018**, *61*, 10084-10105.
[164] K. Fujikawa, Y. Fujioka, A. Kobayashi, H. Amii, *Org. Lett.* **2011**, *13*, 5560-5563.
[165] X.-L. Jiang, Z.-H. Chen, X.-H. Xu, F.-L. Qing, *Org. Chem. Front.* **2014**, *1*, 774-776.
[166] G. K. S. Prakash, S. K. Ganesh, J.-P. Jones, A. Kulkarni, K. Masood, J. K. Swabeck, G. A. Olah, *Angew. Chem. Int. Ed.* **2012**, *51*, 12090-12094.
[167] Y. Gu, D. Chang, X. Leng, Y. Gu, Q. Shen, *Organometallics* **2015**, *34*, 3065-3071.
[168] J. R. Bour, S. K. Kariofillis, M. S. Sanford, *Organometallics* **2017**, *36*, 1220-1223.
[169] C. Matheis, K. Jouvin, L. J. Goossen, *Org. Lett.* **2014**, *16*, 5984-5987.
[170] H. Serizawa, K. Ishii, K. Aikawa, K. Mikami, *Org. Lett.* **2016**, *18*, 3686-3689.
[171] Y. Gu, X. Leng, Q. Shen, *Nat. Commun.* **2014**, *5*, 5405.
[172] aJ. Wu, Y. Liu, C. Lu, Q. Shen, *Chem. Sci.* **2016**, *7*, 3757-3762; bC. Lu, Y. Gu, J. Wu, Y. Gu, Q. Shen, *Chem. Sci.* **2017**, *8*, 4848-4852.
[173] D. M. Ferguson, C. A. Malapit, J. R. Bour, M. S. Sanford, *J. Org. Chem.* **2019**, *84*, 3735-3740.
[174] X.-Y. Deng, J.-H. Lin, J.-C. Xiao, *Org. Lett.* **2016**, *18*, 4384-4387.
[175] Z. Feng, Q.-Q. Min, X.-P. Fu, L. An, X. Zhang, *Nat. Chem.* **2017**, *9*, 918-923.
[176] X.-P. Fu, X.-S. Xue, X.-Y. Zhang, Y.-L. Xiao, S. Zhang, Y.-L. Guo, X. Leng, K. N. Houk, X. Zhang, *Nat. Chem.* **2019**, *11*, 948-956.
[177] Z. Feng, Q.-Q. Min, X. Zhang, *Org. Lett.* **2016**, *18*, 44-47.
[178] F. Pan, G. B. Boursalian, T. Ritter, *Angew. Chem. Int. Ed.* **2018**, *57*, 16871-16876.
[179] J. B. Diccianni, T. Diao, *Trends Chem.* **2019**, *1*, 830-844.
[180] L. Xu, D. A. Vicic, *J. Am. Chem. Soc.* **2016**, *138*, 2536-2539.
[181] R. R. Merchant, J. T. Edwards, T. Qin, M. M. Kruszyk, C. Bi, G. Che, D.-H. Bao, W. Qiao, L. Sun, M. R. Collins, O. O. Fadeyi, G. M. Gallego, J. J. Mousseau, P. Nuhant, P. S. Baran, *Science* **2018**, *360*, 75-80.
[182] C. Xu, W.-H. Guo, X. He, Y.-L. Guo, X.-Y. Zhang, X. Zhang, *Nat. Commun.* **2018**, *9*, 1170.
[183] X.-P. Fu, Y.-L. Xiao, X. Zhang, *Chin. J. Chem* . **2018**, *36*, 143-146.
[184] H. Motohashi, K. Mikami, *Org. Lett.* **2018**, *20*, 5340-5343.
[185] aL. An, Y.-L. Xiao, S. Zhang, X. Zhang, *Angew. Chem. Int. Ed.* **2018**, *57*, 6921-6925; bW. Miao, Y. Zhao, C. Ni, B. Gao, W. Zhang, J. Hu, *J. Am. Chem. Soc.* **2018**, *140*, 880-883.
[186] S. Liu, K. Kang, S. Liu, D. Wang, P. Wei, Y. Lan, Q. Shen, *Organometallics* **2018**, *37*, 3901-3908.
[187] Y. Fujiwara, J. A. Dixon, R. A. Rodriguez, R. D. Baxter, D. D. Dixon, M. R. Collins, D. G. Blackmond, P. S. Baran, *J. Am. Chem. Soc.* **2012**, *134*, 1494-1497.
[188] T. T. Tung, S. B. Christensen, J. Nielsen, *Chem. Eur. J.* **2017**, *23*, 18125-18128.
[189] S.-Q. Zhu, Y.-L. Liu, H. Li, X.-H. Xu, F.-L. Qing, *J. Am. Chem. Soc.* **2018**, *140*, 11613-11617.

[190] aW. Zhang, X.-X. Xiang, J. Chen, C. Yang, Y.-L. Pan, J.-P. Cheng, Q. Meng, X. Li, *Nat. Commun.* **2020**, *11*, 638; bD. Zhang, J. Cai, J. Du, Q. Wang, J. Yang, R. Geng, Z. Fang, K. Guo, *Org. Lett.* **2022**, *24*, 1434-1438.
[191] A. G. O'Brien, A. Maruyama, Y. Inokuma, M. Fujita, P. S. Baran, D. G. Blackmond, *Angew. Chem. Int. Ed.* **2014**, *53*, 11868-11871.
[192] A. C. Sun, E. J. McClain, J. W. Beatty, C. R. J. Stephenson, *Org. Lett.* **2018**, *20*, 3487-3490.
[193] aC. Han, S. M. Kelly, T. Cravillion, S. J. Savage, T. Nguyen, F. Gosselin, *Tetrahedron* **2019**, *75*, 4351-4357; bR. D. Cink, K. A. Lukin, R. D. Bishop, G. Zhao, M. J. Pelc, T. B. Towne, B. D. Gates, M. M. Ravn, D. R. Hill, C. Ding, S. C. Cullen, J. Mei, M. R. Leanna, J. Henle, J. G. Napolitano, N. K. Nere, S. Chen, A. Sheikh, J. M. Kallemeyn, *Org. Process Res. Dev.* **2020**, *24*, 183-200.
[194] Y. Zhao, W. Huang, J. Zheng, J. Hu, *Org. Lett.* **2011**, *13*, 5342-5345.
[195] G.-F. Du, Y. Wang, C.-Z. Gu, B. Dai, L. He, *RSC Advances* **2015**, *5*, 35421-35424.
[196] D. Chen, C. Ni, Y. Zhao, X. Cai, X. Li, P. Xiao, J. Hu, *Angew. Chem. Int. Ed.* **2016**, *55*, 12632-12636.
[197] M. Miele, A. Citarella, N. Micale, W. Holzer, V. Pace, *Org. Lett.* **2019**, *21*, 8261-8265.
[198] W. Zhang, J.-H. Lin, W. Wu, Y.-C. Cao, J.-C. Xiao, *Chin. J. Chem .* **2020**, *38*, 169-172.
[199] A. Cai, W. Yan, W. Liu, *J. Am. Chem. Soc.* **2021**, *143*, 9952-9960.
[200] A. Cai, W. Yan, C. Wang, W. Liu, *Angew. Chem. Int. Ed.* **2021**, *60*, 27070-27077.
[201] X. Ispizua-Rodriguez, S. B. Munoz, V. Krishnamurti, T. Mathew, G. K. S. Prakash, *Chem. Eur. J.* **2021**, *27*, 15908-15913.
[202] T. Iida, R. Hashimoto, K. Aikawa, S. Ito, K. Mikami, *Angew. Chem. Int. Ed.* **2012**, *51*, 9535-9538.
[203] J. Zhu, H. Zheng, X.-S. Xue, Y. Xiao, Y. Liu, Q. Shen, *Chin. J. Chem .* **2018**, *36*, 1069-1074.
[204] Q. Xie, Z. Zhu, L. Li, C. Ni, J. Hu, *Angew. Chem. Int. Ed.* **2019**, *58*, 6405-6410.
[205] A. F. Garrido-Castro, A. Gini, M. C. Maestro, J. Alemán, *Chem. Commun.* **2020**, *56*, 3769-3772.
[206] R. I. Rodríguez, M. Sicignano, J. Alemán, *Angew. Chem. Int. Ed.* **2022**, *61*, e202112632.
[207] C. F. Meyer, S. M. Hell, A. Misale, A. A. Trabanco, V. Gouverneur, *Angew. Chem. Int. Ed.* **2019**, *58*, 8829-8833.
[208] X.-J. Tang, Z. Zhang, W. R. Dolbier Jr., *Chem. Eur. J.* **2015**, *21*, 18961-18965.
[209] Q.-Y. Lin, X.-H. Xu, K. Zhang, F.-L. Qing, *Angew. Chem. Int. Ed.* **2016**, *55*, 1479-1483.
[210] J. Yang, S. Zhu, F. Wang, F.-L. Qing, L. Chu, *Angew. Chem. Int. Ed.* **2021**, *60*, 4300-4306.
[211] C. S. Thomoson, X.-J. Tang, W. R. Dolbier, *J. Org. Chem.* **2015**, *80*, 1264-1268.
[212] Q.-Y. Lin, Y. Ran, X.-H. Xu, F.-L. Qing, *Org. Lett.* **2016**, *18*, 2419-2422.
[213] Y. Ran, Q.-Y. Lin, X.-H. Xu, F.-L. Qing, *J. Org. Chem.* **2016**, *81*, 7001-7007.
[214] Y. Arai, R. Tomita, G. Ando, T. Koike, M. Akita, *Chem. Eur. J.* **2016**, *22*, 1262-1265.
[215] Y. Nakayama, G. Ando, M. Abe, T. Koike, M. Akita, *ACS Catalysis* **2019**, *9*, 6555-6563.
[216] M. Zhang, J.-H. Lin, J.-C. Xiao, *Angew. Chem. Int. Ed.* **2019**, *58*, 6079-6083.
[217] aS. A. Faqua, W. G. Duncan, R. M. Silverstein, *Tetrahedron Lett.* **1964**, *5*, 1461-1463; bA. De Cat, R. van Poucke, R. Pollet, P. Schots, *Bull. Soc. Chim. Belg.* **1965**, *74*, 270-280.
[218] L. Zhang, J. Zheng, J. Hu, *J. Org. Chem.* **2006**, *71*, 9845-9848.
[219] Y. Zafrani, G. Sod-Moriah, Y. Segall, *Tetrahedron* **2009**, *65*, 5278-5283.
[220] P. S. Fier, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2013**, *52*, 2092-2095.
[221] C. S. Thomoson, W. R. Dolbier, *J. Org. Chem.* **2013**, *78*, 8904-8908.
[222] J. Yang, M. Jiang, Y. Jin, H. Yang, H. Fu, *Org. Lett.* **2017**, *19*, 2758-2761.
[223] J. Mizukado, Y. Matsukawa, H.-d. Quan, M. Tamura, A. Sekiya, *J. Fluor. Chem.* **2006**, *127*, 400-404.
[224] R. A. Mitsch, J. E. Robertson, *J. Heterocycl. Chem.* **1965**, *2*, 152-156.
[225] J. Mizukado, Y. Matsukawa, H.-d. Quan, M. Tamura, A. Sekiya, *J. Fluor. Chem.* **2005**, *126*, 365-369.
[226] J. Zhu, Y. Liu, Q. Shen, *Angew. Chem. Int. Ed.* **2016**, *55*, 9050-9054.
[227] R. Zhang, Q. Li, Q. Xie, C. Ni, J. Hu, *Chem. Eur. J.* **2021**, *27*, 17773-17779.
[228] Q. Q. Xie, C. F. Ni, R. Y. Zhang, L. C. Li, J. Rong, J. B. Hu, *Angew. Chem. Int. Ed.* **2017**, *56*, 3206-3210.
[229] G.-K. Liu, X. Li, W.-B. Qin, X.-S. Peng, H. N. C. Wong, L. Zhang, X. Zhang, *Chem. Commun.* **2019**, *55*, 7446-7449.
[230] N. B. Heine, A. Studer, *Org. Lett.* **2017**, *19*, 4150-4153.
[231] J. Y. C. Chu, J. W. Lewicki, *J. Org. Chem.* **1977**, *42*, 2491-2493.

[232] aH. Suzuki, M. Yoshinaga, K. Takaoka, Y. Hiroi, *Synthesis* **1985**, *1985*, 497-499; bK. Uneyama, K. Maeda, Y. Tokunaga, N. Itano, *J. Org. Chem.* **1995**, *60*, 370-375.
[233] Y.-m. Lin, W.-b. Yi, W.-z. Shen, G.-p. Lu, *Org. Lett.* **2016**, *18*, 592-595.
[234] B. Bayarmagnai, C. Matheis, K. Jouvin, L. J. Goossen, *Angew. Chem. Int. Ed.* **2015**, *54*, 5753-5756.
[235] T. Dong, J. Nie, C.-P. Zhang, *Tetrahedron* **2018**, *74*, 5642-5649.
[236] M. Zhang, J.-H. Lin, J.-C. Xiao, *J. Org. Chem.* **2021**, *86*, 13153-13159.
[237] J. G. Knight, in *Science of Synthesis: Category 3, Compounds with Four and Three Carbon Heteroatom Bonds, Vol. 18*, Georg Thieme Verlag KG, Stuttgart, **2005**.
[238] J. Wu, Y. Gu, X. Leng, Q. Shen, *Angew. Chem. Int. Ed.* **2015**, *54*, 7648-7652.
[239] M. Tironi, L. M. Maas, A. Garg, S. Dix, J. P. Götze, M. N. Hopkinson, *Org. Lett.* **2020**, *22*, 8925-8930.
[240] V. V. Levin, A. D. Dilman, P. A. Belyakov, M. I. Struchkova, V. A. Tartakovsky, *J. Fluor. Chem.* **2009**, *130*, 667-670.
[241] C. Skonberg, J. Olsen, K. G. Madsen, S. H. Hansen, M. P. Grillo, *Expert Opin. Drug Metab. Toxicol.* **2008**, *4*, 425-438.
[242] aJ. Olsen, I. Bjørnsdottir, J. Tjørnelund, S. Honoré Hansen, *J. Pharm. Biomed. Anal.* **2002**, *29*, 7-15; bM. P. Grillo, L. Z. Benet, *Drug Metab. Dispos.* **2002**, *30*, 55-62; cT. Lassila, J. Hokkanen, S.-M. Aatsinki, S. Mattila, M. Turpeinen, A. Tolonen, *Chem. Res. Toxicol.* **2015**, *28*, 2292-2303.
[243] Y. Kanda, T. Ashizawa, S. Kakita, Y. Takahashi, M. Kono, M. Yoshida, Y. Saitoh, M. Okabe, *J. Med. Chem.* **1999**, *42*, 1330-1332.
[244] L. Deshmukh, V. Tugarinov, D. H. Appella, G. M. Clore, *Angew. Chem. Int. Ed.* **2018**, *57*, 2687-2691.
[245] N. V. Bhilare, S. Dhaneshwar, A. Sinha, A. D. Kandhare, S. L. Bodhankar, *Curr. Drug Deliv.* **2016**, *13 4*, 611-620.
[246] M. M. Kremlev, W. Tyrra, D. Naumann, Y. L. Yagupolskii, *Tetrahedron Lett.* **2004**, *45*, 6101-6104.
[247] M. Zhang, J. Chen, Z. Chen, Z. Weng, *Tetrahedron* **2016**, *72*, 3525-3530.
[248] V. Krishnamurti, C. Barrett, X. Ispizua-Rodriguez, M. Coe, G. K. S. Prakash, *Org. Lett.* **2019**, *21*, 9377-9380.
[249] S. Mukherjee, T. Patra, F. Glorius, *ACS Catalysis* **2018**, *8*, 5842-5846.
[250] M.-Y. Wang, X.-Q. Zhu, X.-L. Zhang, R.-L. Guo, Q. Jia, Y.-Q. Wang, *Org. Biomol. Chem.* **2020**, *18*, 5918-5926.
[251] B. Xu, D. Li, L. Lu, D. Wang, Y. Hu, Q. Shen, *Org. Chem. Front.* **2018**, *5*, 2163-2166.
[252] aX. Wang, J. Dong, Y. Liu, H. Song, Q. Wang, *Chin. Chem. Lett.* **2021**, *32*, 3027-3030; bZ. Ye, Z. Lei, X. Ye, L. Zhou, Y. Wang, Z. Yuan, F. Gao, R. Britton, *J. Org. Chem.* **2022**, *87*, 765-775.
[253] aX. L. Z. Shi-Huan Guo, Gao-Fei Pan, Xue-Qing Zhu, Ya-Ru Gao, Yong-Qiang Wang, *Angew. Chem. Int. Ed. Engl.* **2017**, *57*, 1663-1667; bJ. Dong, F. Yue, X. Wang, H. Song, Y. Liu, Q. Wang, *Org. Lett.* **2020**, *22*, 8272-8277.
[254] L. M. Maas, J. R. Schmid, C. Fasting, P. Voßnacker, A. Mavroskoufis, M. N. Hopkinson, *Tetrahedron* **2021**, *101*, 132512.
[255] M. Tironi, S. Dix, M. N. Hopkinson, *Org. Chem. Front.* **2021**.
[256] J. Brozmanová, D. Mániková, V. Vlčková, M. Chovanec, *Arch. Toxicol.* **2010**, *84*, 919-938.
[257] aS. Dobiasová, N. Szemerédi, D. Kučerová, K. Koucká, R. Václavíková, H. Gbelcová, T. Ruml, E. Domínguez-Álvarez, G. Spengler, J. Viktorová, *Scientific Reports* **2022**, *12*, 6548; bA. Csonka, A. Kincses, M. NovÉ, Z. Vadas, C. SanmartÍN, E. DomÍNguez-ÁLvarez, G. Spengler, *Anticancer Res.* **2019**, *39*, 3777.
[258] M. Gajdács, G. Spengler, C. Sanmartín, M. A. Marć, J. Handzlik, E. Domínguez-Álvarez, *Bioorganic & Medicinal Chemistry Letters* **2017**, *27*, 797-802.
[259] E. Domínguez-Álvarez, D. Plano, M. Font, A. Calvo, C. Prior, C. Jacob, J. A. Palop, C. Sanmartín, *Eur. J. Med. Chem.* **2014**, *73*, 153-166.
[260] T. Mosolygó, A. Kincses, A. Csonka, S. Tönki Á, K. Witek, C. Sanmartín, M. A. Marć, J. Handzlik, K. Kieć-Kononowicz, E. Domínguez-Álvarez, G. Spengler, *Molecules* **2019**, *24*.
[261] G. Marin, A. L. Braga, A. S. Rosa, F. Z. Galetto, R. A. Burrow, H. Gallardo, M. W. Paixão, *Tetrahedron* **2009**, *65*, 4614-4618.
[262] K. Ren, M. Wang, P. Liu, L. Wang, *Synthesis* **2010**, *2010*, 1078-1082.

[263] A. J. de Oliveira, S. A. de Oliveira, L. G. Vasconcelos, E. L. Dall'Oglio, L. C. C. Vieira, A. L. Stein, *Tetrahedron Lett.* **2021**, *80*, 153317.
[264] A. Temperini, F. Piazzolla, L. Minuti, M. Curini, C. Siciliano, *J. Org. Chem.* **2017**, *82*, 4588-4603.
[265] R.-L. Guo, X.-Q. Zhu, X.-L. Zhang, Y.-Q. Wang, *Chem. Commun.* **2020**, *56*, 8976-8979.
[266] H. Zhang, F. Yu, C. Li, P. Tian, Y. Zhou, Z.-Y. Cao, *Org. Lett.* **2021**, *23*, 4721-4725.
[267] M. Tironi, M. N. Hopkinson, *Eur. J. Org. Chem.* **2022**, *2022*, e202101557.
[268] G. Fang, X. Bi, *Chem. Soc. Rev.* **2015**, *44*, 8124-8173.
[269] S.-H. Guo, M.-Y. Wang, G.-F. Pan, X.-Q. Zhu, Y.-R. Gao, Y.-Q. Wang, *Adv. Synth. Catal.* **2018**, *360*, 1861-1869.
[270] A. Ariamajd, N. J. Gerwien, B. Schwabe, S. Dix, M. N. Hopkinson, *Beilstein J. Org. Chem.* **2021**, *17*, 83-88.
[271] T. Scattolin, K. Deckers, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2017**, *56*, 221-224.
[272] S. Liang, J. Wei, L. Jiang, J. Liu, Y. Mumtaz, W. Yi, *Chem. Commun.* **2019**, *55*, 8536-8539.

11. Appendix: Supporting information

Supporting Information

Deoxygenative Tri- and Difluoromethylthiolation of Carboxylic Acids with Benzothiazolium Reagents

Matteo Tironi,‡ Lilian M. Maas,‡ Arushi Garg, Stefan Dix, Jan P. Götze and Matthew N. Hopkinson*

Institut für Chemie und Biochemie, Freie Universität Berlin

Fabeckstrasse 34–36

14195 Berlin, Germany

Contents

1 General Information

Unless otherwise stated, all reactions were performed under argon as inert gas. The glass apparatus used was heated in an oil pump vacuum and purged with argon. Screw-cap reaction vessels were flushed with argon. All purchased chemicals were used without further treatment. THF was dried and distilled over sodium in the presence of benzophenone and CH_2Cl_2 was obtained from a MB-SPS-800 (Braun) solvent purification system. All dry solvents were stored over molecular sieves (3 or 4 Å). Pentane, CH_2Cl_2 and EtOAc used for column chromatography were distilled prior to use. For UVA reactions, UVA light was provided by a UV-LED chip by MERUEM TOPSION (365–370 nm, 20 W).

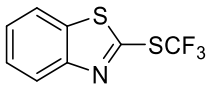
Thin-layer chromatography was performed on silica gel coated aluminium plates ALUGRAM® Xtra SIL G/UV254 (Macherey-Nagel). The product spots were detected by UV light (254 nm) or as permanganate stains. Flash column chromatography was performed with silica gel 60 M (0.040–0.063 mm, 230–400 mesh, Macherey-Nagel).

^1H, ^{19}F and ^{13}C NMR spectra were acquired on a JEOL ECS 400 (400 MHz), JEOL ECZ 400 (400 MHz), JEOL ECX 400 (400 MHz), JEOL ECP 500/ Bruker Avance 500 (500 MHz), Varian INOVA 600 (600 MHz) or a Bruker Avance 700 (700 MHz) and analysed on MestReNova. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethyl silane (TMS) and coupling constants (J) are presented in hertz (Hz). CD_3CN or $CDCl_3$ were used as deuterated solvent and the residual solvent signals are used as the reference in the ^1H and ^{13}C NMR spectra. ^{19}F NMR spectra are reported relative to $CFCl_3$ and are not calibrated by an internal reference. ^1H NMR yields were measured using CH_2Br_2 as an internal standard. The multiplicities are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet.

C-H-N-S Analysis was obtained on ELEMENTAR Vario El elemental analyzer and High-resolution mass spectra were measured with an Agilent (6210 ESI-TOF; 4 µL/min, 1.0 bar, 4 kV) instrument. Infrared spectra were measured with a NICOLET spectrometer (iS10) equipped with an ATR unit (NICOLET SMART DuraSampl*IR*). Only diagnostic absorption bands are reported.

2 Synthesis of BT-SCF_3 and BT-SCF_2H

2.1 Synthesis of 2-((trifluoromethyl)thio)benzo[d]thiazole

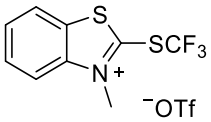


Sodium hydroxide (1.1 equiv., 55 mmol, 2.20 g) was added to 2-mercaptobenzothiazole (1.0 equiv., 50 mmol, 8.36 g) in MeCN/H_2O (9:1, 100 mL) in a Schlenk flask and the suspension was stirred until the solids were dissolved. The solution was frozen using liquid nitrogen and ICF_3 (2.0 equiv., 100 mmol, 19.6 g) was condensed in. The flask was very shortly ventilated with air and a balloon was attached to the Schlenk flask. The mixture was allowed to warm to rt and was stirred vigorously for 16 h under irradiation of UVA LEDs (λ_{max} = 360 nm) at rt. Afterwards the crude mixture was filtered through Celite® using CH_2Cl_2 (5 x 60 mL). The mixture was concentrated, redissolved with pentane, and filtered through anhydrous Na_2SO_4 using pentane (4 x 40 mL). Again, the mixture was concentrated and filtered through SiO_2 (10 g) using pentane (1000 mL) as eluent. After the mixture was concentrated, the crude product (9.84 g) was afforded as a yellow oil and was used without further purification.

^{1}H NMR (400 MHz, Chloroform-d) δ = 8.14 (d, *J* = 8.2 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.56 (dd, *J* = 8.2, 7.2 Hz, 1H), 7.49 (dd, *J* = 8.0, 7.2 Hz, 1H). **^{19}F NMR (376 MHz, Chloroform-d) δ** = -40.1.

The characterization data agree with literature values.[1]

2.2 Synthesis of BT-SCF_3



Crude 2-((trifluoromethyl)thio)benzo[d]thiazole (1.0 equiv., assumed 29.8 mmol, 7.0 g) was dissolved in dry CH_2Cl_2 (1.0 M) and methyl trifluoromethanesulfonate (1.5 equiv., 44.7 mmol, 4.9 mL) was added dropwise. The reaction mixture was stirred for 50 h at rt and the product was then precipitated with diethyl ether. The crude product was re-dissolved in CH_2Cl_2, precipitated with diethyl ether a second time, and dried *in vacuo*. BT-SCF_3 was acquired as an off-white solid (10.6 g, 26.5 mmol, 75% over two steps), m.p. = 100–103 °C.

^{1}H NMR (400 MHz, Acetonitrile-d_3) δ = 8.39 (d, *J* = 7.1 Hz, 1H), 8.27 (d, *J* = 8.6 Hz, 1H), 8.08 – 8.03 (m, 1H), 8.00 – 7.94 (m, 1H), 4.44 (s, 3H). **^{19}F NMR (565 MHz, Acetonitrile-d_3) δ** = -39.1, -79.3. **^{13}C NMR (151 MHz, Acetonitrile-d_3) δ** = 160.5, 143.7, 134.0, 132.3, 131.5, 127.5 (q, *J* = 314 Hz, SCF_3), 125.2, 121.7 (q, *J* = 321 Hz), 119.3, 39.9.

The characterization data agree with literature values.[1]

2.3 Synthesis of Difluoromethyl trifluoromethanesulfonate

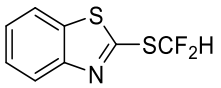
$TiCl_4$ (1 mol% , 1.38 mmol, 152 µL) was added dropwise to TfOH (1.2 equiv., 165.6 mmol, 15 mL) under vigorous stirring at rt for 5 mins. The homogeneous yellow solution was evacuated at 13–20 mbar until gas evolution ceased. The mixture was cooled to -20 ºC, $TMSCF_3$ (1.0 equiv., 138 mmol, 20.5 mL) was added, and the mixture was kept for 2 min. The cooling bath was replaced by an ice bath, which was kept for another 2 mins, and the mixture was stirred at rt for 1 h. Volatile materials were distilled off under vacuum (133 mbar) and the crude product was collected

in a cold trap. The collected liquid was purified via vacuum distillation to obtain difluoromethyl trifluoromethanesulfonate (21.6 g, 108 mmol, 78 %).

^{1}H NMR (400 MHz, Chloroform-d) δ = 6.85 (t, *J* = 68.0 Hz, 1H). **^{19}F NMR (376 MHz, Chloroform-d) δ** = -74.6, -82.2 (d, *J* = 68 Hz).

The characterization data agrees with literature values.[2]

2.4 Synthesis of 2-((difluoromethyl)thio)benzo[d]thiazole

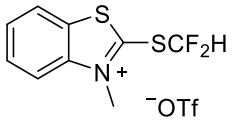


2-Mercaptobenzothiazole (1.0 equiv., 29 mmol, 4.9 g) was dissolved in MeCN (58 mL) in a 100 mL vial equipped with magnetic stirring bar. Aqueous KOH (6 M, 58 mL) was added and the mixture was stirred rapidly at rt. Difluoromethyl trifluoromethanesulfonate (1.5 equiv., 43.5 mmol, 5.1 mL) was added in one portion and the reaction mixture was stirred vigorously at rt for 2 mins. The reaction mixture was then diluted with water (100 mL) and extracted with diethyl ether (3 x 50 mL). The combined organic layers were concentrated *in vacuo* to afford 2-((difluoromethyl)thio)benzo[d]thiazole (25 mmol, 5.43 g, 86 %).

^{1}H NMR (400 MHz, Chloroform-d) δ = 8.01 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.72 (t, *J* = 56.3 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H). **^{19}F NMR (376 MHz, Chloroform-d) δ** = -93.1 (d, *J* = 56 Hz). **^{13}C NMR (151 MHz, Chloroform-d) δ** = 157.2 (t, *J* = 4 Hz), 153.0, 136.1, 126.8, 125.8, 123.0, 121.3, 120.4 (t, *J* = 277 Hz).

The characterization data agrees with literature values.[3]

2.5 Synthesis of BT-SCF$_2$H

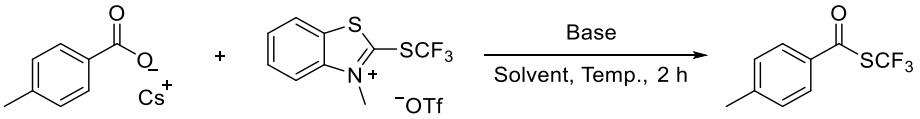


Methyl trifluoromethanesulfonate (3.0 equiv., 75 mmol, 8.2 mL) was added dropwise to a flame dried Schlenk flask with dry CH_2Cl_2 (0.1 M) and 2-((difluoromethyl)thio)benzo[d]thiazole (1.0 equiv., 25 mmol, 5.42 g). The reaction mixture was stirred at rt for 19 h and was then precipitated with diethyl ether. The solid was filtered off and washed with diethyl ether (3 x 20 mL). After drying *in vacuo*, BT-SCF$_2$H (9.60 g, 24.0 mmol, 95 %) was obtained as a pale yellow solid, m.p. = 100–102 °C.

^{1}H NMR (600 MHz, Acetonitrile-d$_3$): δ = 8.32 (d, *J* = 8.3 Hz, 1H), 8.18 (d, *J* = 8.6 Hz, 1H), 7.97 (t, *J* = 7.9 Hz, 1H), 7.88 (t, *J* = 7.8 Hz, 1H), 7.58 (t, *J* = 53.6 Hz, 1H), 4.30 (s, 3H). **^{19}F NMR (565 MHz, Acetonitrile-d$_3$) δ** = -79.2, -91.5 (d, *J* = 54 Hz). **^{13}C NMR (151 MHz, Acetonitrile-d$_3$) δ** = 165.5, 142.3, 131.5, 130.7, 129.6, 124.0, 122.2 (q, *J* = 321 Hz), 118.5 (t, *J* = 284 Hz), 117.4, 38.5. **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3025, 1582, 1469, 1448, 1393, 1314, 1249, 1142, 1066, 1029, 757, 733, 638, 571. **C-H-N-S Analysis**: Anal. Calcd for $C_{10}H_8F_5NO_3S_3$: C, 31.50; H, 2.11; N, 3.67; S, 25.22. Found: C, 31.53; H, 2.12; N, 3.72; S, 25.12.

3 Optimization of the Deoxytrifluoromethylthiolation and -difluoromethylthiolation of Carboxylic acids with BT-SCF_3 and BT-SCF_2H

3.1 Optimization Tables for BT-SCF_3

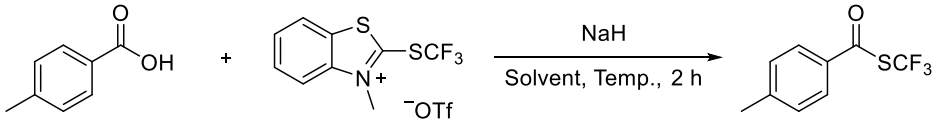


2a

Entry[a]	Equiv. of BT-SCF_3	Solvent	Base	Temperature	Yield of 2a[b]
1	1.25	MeCN (0.1 M)	-	rt	37 %
2	1.25	CH_2Cl_2 (0.1 M)	-	rt	56 %
3	1.25	EtOAc (0.1 M)	-	rt	61 %
4	1.25	Dioxane (0.1 M)	-	rt	61 %
5	1.25	DMF (0.1 M)	-	rt	62 %
6	1.25	THF (0.1 M)	-	rt	69 %
7	1.25	THF (0.1 M)	LiBr (2.0 equiv.)	rt	19 %
8	1.25	THF (0.1 M)	NaBr (2.0 equiv.)	rt	56 %
9	1.25	THF (0.1 M)	Li_2CO_3 (2.0 equiv.)	rt	39 %
10	1.25	THF (0.1 M)	NaH (2.0 equiv.)	rt	66 %

[a] Reaction procedure: BT-SCF_3, 4-methylbenzoate and base dissolved in solvent and stirred at rt for 2 h. [b] Yields calculated by ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard.

Table S1. Optimization of the Deoxytrifluoromethylthiolation of cesium 4-methylbenzoate with BT-SCF_3.



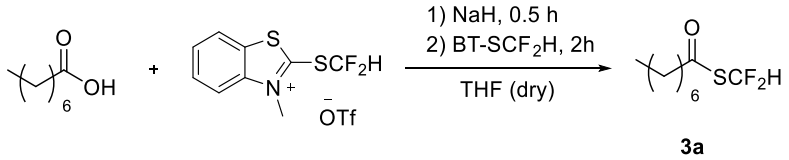
2a

Entry	Equiv. of BT-SCF_3	Solvent	Equiv. of Base	Temperature	Yield of 2a[c]
1[a]	1.25	THF (0.1 M)	4.0	rt	39 %
2[a]	1.25	THF (0.1 M)	3.0	rt	42 %
3[a]	1.25	CH_2Cl_2 (0.1 M)	3.0	rt	35 %
4[a]	1.25	EtOAc (0.1 M)	3.0	rt	28 %
5[a]	1.25	Dioxane (0.1 M)	3.0	rt	42 %
6[a]	1.25	DMF (0.1 M)	3.0	rt	42 %
7[a]	1.25	THF (0.1 M)	3.0	50 °C	16 %
8[a]	1.25	THF (0.1 M)	3.0	0 °C	69 %
9[a]	1.25	THF (0.1 M)	3.0	-10 °C	70 %
10[a]	1.25	THF (0.1 M)	3.0	-78 °C	72 %
11[a]	2.0	THF (0.1 M)	3.0	0 °C	49 %
12[a]	1.1	THF (0.1 M)	3.0	0 °C	30 %
13[a]	1.25	THF (0.033 M)	3.0	0 °C	73 %
14[a]	1.25	THF (0.025 M)	3.0	0 °C	68 %
15[b]	1.25	THF (0.033 M)	3.0	-78 °C	82 %

[a] Reaction procedure: BT-SCF_3, 4-methylbenzoic acid and base were dissolved in the solvent and the reaction mixture was stirred at rt for 2 h before being concentrated *in vacuo*. [b] Reaction procedure: 4-Methylbenzoic acid in THF was added dropwise over 20 min to BT-SCF_3 and NaH in dry THF at -78 °C. The mixture was stirred at -78 °C for 2 h and then concentrated *in vacuo*. [c] Yields calculated by ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard.

Table S2. Optimization of the Deoxytrifluoromethylthiolation of 4-Methylbenzoic acid with BT-SCF_3.

3.2 Optimization Tables for BT-SCF$_2$H

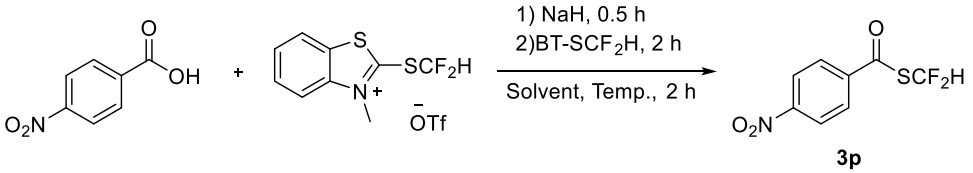


3a

Entry[a]	Equiv. of BT-SCF$_2$H	Solvent	Base	Yield of 3a[b]
1	1.25	THF	3	72%
2	2	THF	3	95%
3	3	THF	3	96%
4	2	THF	1.25	60%
5	2	THF	2	Quant.

[a] Reaction procedure: Octanoic acid and NaH were dissolved in THF and stirred at rt for 30 mins. BT-SCF$_2$H was then added and the reaction mixture was stirred at rt for 2 h before being concentrated *in vacuo*. [b] Yields calculated by ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard.

Table S3. Optimization of the Deoxydifluoromethylthiolation of octanoic acid **1l** with BT-SCF$_2$H.



3p

Entry[a]	Equiv. of BT-SCF$_2$H	Solvent	Equiv. of Base	Temperature	Yield of 3p[b]
1	2	DCM (0.1 M)	2	rt	42%
2	2	Et_2O (0.1 M)	2	rt	45%
3	2	THF (0.1 M)	2	rt	59%
4	2	Toluene (0.1 M)	2	rt	19%
5	2	MeCN (0.1 M)	2	rt	31%
6	2	THF (0.1 M)	2	0°C	49%
7	2	THF (0.1 M)	2	-78°C	45%
8	2	THF (0.05 M)	2	rt	61%
9	2	THF (0.025 M)	2	rt	66%

[a] Reaction procedure: 4-Nitrobenzoic acid and NaH were dissolved in the solvent and stirred for 30 mins at rt. BT-SCF$_2$H was then added and the reaction mixture was stirred at rt for 2 h before being concentrated *in vacuo*. [b] Yields calculated by ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard.

Table S3. Optimization of the Deoxydifluoromethylthiolation of 4-nitrobenzoic acid with BT-SCF$_2$H.

4 Scope and Limitations of the Deoxytrifluoromethylthiolation and -difluoromethylthiolation of Carboxylic Acids

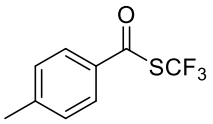
4.1 General Procedures for the Deoxytrifluoromethylthioesterification of Carboxylic acids

Method A: Sodium hydride (3.0 equiv.) and BT-SCF_3 (1.25 equiv.) was added to dry THF at -78 °C. A solution of the carboxylic acid (1.0 equiv., 0.5 mmol) in dry THF was added dropwise over 20 mins and the reaction mixture (0.033 M) was stirred for 2 h at -78 °C. The reaction mixture was allowed to warm to rt and was quenched with ammonium chloride (sat. in water) until a pH value of 6 was reached. The crude mixture was dissolved in CH_2Cl_2 and washed with water (2 x). The aqueous phases were extracted with CH_2Cl_2 (3 x) and the combined organic phases were dried over magnesium sulphate. The drying agent was filtered off and washed with CH_2Cl_2. The solvent was removed under reduced pressure and the trifluoromethylthioesters were isolated using column chromatography (SiO_2).

Method B: Sodium hydride (3.0 equiv.), BT-SCF_3 (1.25 equiv.) and the carboxylic acid (1.0 equiv., 0.5 mmol) was added to dry THF (0.033 M for **2g** and 0.1 M for **2f**) and the reaction mixture was stirred for 2 h at rt. The solids were filtered off, the solvent removed under reduced pressure and the trifluoromethylthioesters were isolated using flash column chromatography (SiO_2).

4.2 Characterization Data for Deoxytrifluoromethylthiolation Products 2

***S*-(trifluoromethyl) 4-methylbenzothioate (2a)**



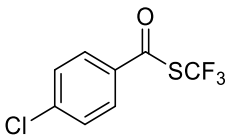
2a

According to Method A, thioester **2a** (78 mg, 71%) was obtained from 4-methylbenzoic acid **1a** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2, 40:1) as a white solid.

^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.74 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 2.43 (s, 3H). **^{19}F NMR (377 MHz, $CDCl_3$) δ** = -39.4. **^{13}C NMR (101 MHz, $CDCl_3$) δ** = 182.9, 146.6, 132.7 (q, *J* = 3 Hz), 130.0, 128.3 (q, *J* = 309 Hz), 127.9, 21.9.

The characterization data agree with the literature values.[4]

***S*-(trifluoromethyl) 4-chlorobenzothioate (2b)**



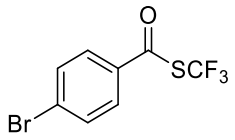
2b

According to Method A, thioester **2b** (72 mg, 60 %) was obtained from 4-chlorobenzoic acid **1b** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2, 10:1) as a light-yellow oil.

^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.80 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 8.8 Hz, 2H). **^{19}F NMR (377 MHz, $CDCl_3$) δ** = -39.6. **^{13}C NMR (101 MHz, $CDCl_3$) δ** = 182.3, 141.9, 133.6 (q, *J* = 3 Hz), 129.7, 129.1, 128.0 (q, *J* = 310 Hz).

The characterization data agree with the literature values.[5]

***S*-(trifluoromethyl) 4-bromobenzothioate (2c)**



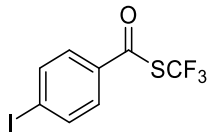
2c

According to Method A, thioester **2c** (114 mg, 80 %) was obtained from 4-bromobenzoic acid **1c** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2, 10:1) as colourless crystals.

^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.93 – 7.56 (m, 4H). **^{19}F NMR (377 MHz, $CDCl_3$) δ** = -39.6. **^{13}C NMR (101 MHz, $CDCl_3$) δ** = 182.5, 134.0 (q, *J* = 3 Hz), 132.7, 130.6, 129.1, 127.9 (q, *J* = 310 Hz).

The characterization data agree with the literature values.[5]

***S*-(trifluoromethyl) 4-iodobenzothioate (2d)**



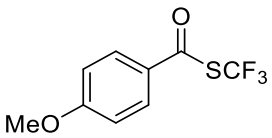
2d

According to Method A, thioester **2d** (132 mg, 93 %) was obtained from 4-iodobenzoic acid **1d** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2, 10:1) as light-yellow crystals.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.87 (d, *J* = 8.0 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 2H). **^{19}F NMR (471 MHz, $CDCl_3$) δ** = -39.4. **^{13}C NMR (126 MHz, $CDCl_3$) δ** = 182.9, 138.7, 134.5, 128.8, 127.9 (q, *J* = 310 Hz), 103.5.

The characterization data agree with the literature values.[5]

***S*-(trifluoromethyl) 4-methoxybenzothioate (2e)**



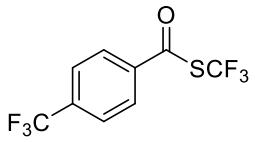
2e

According to Method A, thioester **2e** (85 mg, 72 %) was obtained from 4-methoxybenzoic acid **1e** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2, 10:1) as light-orange crystals.

^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.80 (d, *J* = 9.1 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 3.87 (s, 3H). **^{19}F NMR (377 MHz, $CDCl_3$) δ** = -39.5. **^{13}C NMR (101 MHz, $CDCl_3$) δ** = 181.6 (q, *J* = 1 Hz), 165.2, 130.2, 129.9 (q, *J* = 309 Hz), 127.9 (q, *J* = 3 Hz), 114.5, 55.8.

The characterization data agree with the literature values.[5]

***S*-(trifluoromethyl) 4-(trifluoromethyl)benzothioate (2f)**



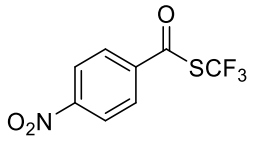
2f

According to Method B, thioester **2f** (31 mg, 23 %) was obtained from 4-(trifluoromethyl)benzoic acid **1f** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2 15:1) as a light-yellow liquid.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.98 (d, *J* = 12.0 Hz, 2H), 7.79 (d, *J* = 12.1 Hz, 2H).**^{19}F NMR (565 MHz, $CDCl_3$) δ** = -39.5, -63.3. **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 182.8, 137.9, 136.4 (q, *J* = 33 Hz), 128.2, 127.8 (q, *J* = 310 Hz), 127.8 (q, *J* = 310 Hz), 123.3 (q, *J* = 273 Hz).

The characterization data agree with the literature values.[5]

***S*-(trifluoromethyl) 4-nitrobenzothioate (2g)**



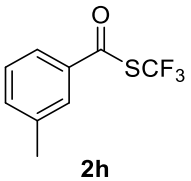
2g

According to Method B, thioester **2g** (72 mg, 58 %) was obtained from 4-nitrobenzoic acid **1g** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2 20:1) as a light-orange solid.

^{1}H NMR (401 MHz, $CDCl_3$) δ = 8.37 (d, *J* = 8.7 Hz, 2H), 8.04 (d, *J* = 8.7 Hz, 2H). **^{19}F NMR (377 MHz, $CDCl_3$) δ** = -39.6. **^{13}C NMR (101 MHz, $CDCl_3$) δ** = 182.3, 151.5, 139.5 (q, *J* = 3 Hz), 128.9, 127.6 (q, *J* = 311 Hz), 124.6.

The characterization data agree with the literature values.[6, 7]

***S*-(trifluoromethyl) 3-methylbenzothioate (2h)**

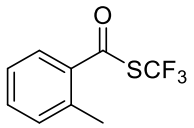


2h

According to Method A, thioester **2h** (71 mg, 64%) was obtained from 3-methylbenzoic acid **1h** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2, 40:1) as a colourless oil.

^{1}H NMR (401 MHz, $CDCl_3$): δ = 7.70 – 7.60 (m, 2H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.45 – 7.33 (m, 1H), 2.43 (s, 3H). **^{19}F NMR (377 MHz, $CDCl_3$): δ** = -39.8. **^{13}C NMR (101 MHz, $CDCl_3$) δ** = 183.5 (q, *J* = 1 Hz), 139.5, 136.0, 135.3 (q, *J* = 3 Hz), 129.2, 128.2 (q, *J* = 309 Hz), 128.2, 125.0, 21.4. **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3046, 2927, 2863, 1704, 1603, 1586, 1248, 1147, 1009, 999, 951, 934, 816, 777, 761, 690, 677, 586. **HRMS (ESI) m/z:** $[M+Na]^+$ calcd for $C_9H_7OSF_3Na$ 243.0067; Found 243.0068.

***S*-(trifluoromethyl) 2-methylbenzothioate (2i)**



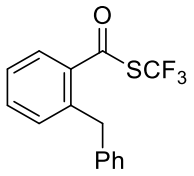
2i

According to Method A, thioester **2i** (77 mg, 69%) was obtained from 2-methylbenzoic acid **1i** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2, 40:1) as a colourless oil.

^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.69 (d, *J* = 8.1 Hz, 1H), 7.53 – 7.44 (m, 1H), 7.31 (d, *J* = 8.3 Hz, 2H), 2.53 (s, 3H). **^{19}F NMR (377 MHz, $CDCl_3$) δ** = -40.5. **^{13}C NMR (101 MHz, $CDCl_3$) δ** = 184.5 (q, *J* = 1 Hz), 138.9, 134.6 (q, *J* = 3 Hz), 133.7, 132.5, 128.1 (q, *J* = 309 Hz), 129.0, 126.4, 21.1.

The characterization data agree with the literature values.[4]

***S*-(trifluoromethyl) 2-(phenylmethyl) benzothioate (2j)**

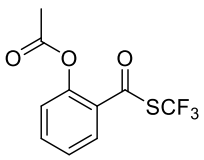


2j

According to Method A, thioester **2j** (107 mg, 72 %) was obtained from 2-(phenylmethyl) benzoic acid **1j** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2, 10:1) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 8.3 Hz, 3H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 2H), 4.28 (s, 2H). **^{19}F NMR (565 MHz, $CDCl_3$): δ** = -40.5. **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 185.2, 141.1, 139.7, 135.1 (q, *J* = 3 Hz), 133.6, 132.1, 127.9 (q, *J* = 310 Hz), 129.3, 128.8, 128.6, 126.9, 126.5, 38.9. **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3068, 3029, 2924, 2854, 1719, 1597, 1571, 1495, 1483, 1453, 1147, 1094, 1030, 878, 809, 759, 735, 696, 675, 647, 609, 590, 563. **HRMS (ESI) m/z:** $[M+Na]^+$ calcd for $C_{15}H_{11}OSF_3Na$ 319.0375; Found 319.0365.

2-(((trifluoromethyl)thio)carbonyl)phenyl acetate (2k)



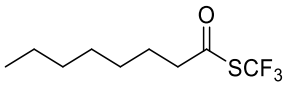
2k

According to Method A, thioester **2k** (112 mg, 85 %) was obtained from acetylsalicylic acid **1k** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2, 2:1) as a colourless oil.

^{1}H NMR (401 MHz, $CDCl_3$) *δ* = 7.82 (d, *J* = 7.8 Hz, 1H), 7.64 (t, *J* = 7.7 Hz, 1H), 7.37 (t, *J* = 7.7 Hz, 1H), 7.20 (d, *J* = 8.2 Hz, 1H), 2.37 (s, 3H). **^{19}F NMR (377 MHz, $CDCl_3$) *δ*** = -40.5. **^{13}C NMR (101 MHz, $CDCl_3$) *δ*** = 181.1 (q, *J* = 1 Hz), 169.0, 148.8, 135.5, 129.7, 127.8 (q, *J* = 311 Hz), 128.1 (q, *J* = 3 Hz), 126.6, 124.6, 21.2.

The characterization data agree with the literature values.[6]

***S*-(trifluoromethyl) octanethioate (2l)**



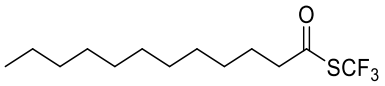
2l

According to Method A, thioester **2l** (46 mg, 40 %) was obtained from octanoic acid **1l** on a 0.5 mmol scale after flash column chromatography (pentane) as a colourless oil.

^{1}H NMR (401 MHz, $CDCl_3$) δ = 2.60 (t, *J* = 7.4 Hz, 2H), 1.67 (dt, *J* = 7.5, 7.4 Hz, 2H), 1.40 – 1.16 (m, 8H), 0.95 – 0.79 (m, 3H). **^{19}F NMR (377 MHz, $CDCl_3$) δ** = -40.3. **^{13}C NMR (101 MHz, $CDCl_3$) δ** = 190.5 (q, *J* = 1 Hz), 127.9 (q, *J* = 310 Hz), 44.8 (q, *J* = 3 Hz), 31.6, 28.9, 28.8, 24.9, 22.7, 14.1.

The characterization data agree with the literature values.[4]

***S*-(trifluoromethyl) dodecanethioate (2m)**

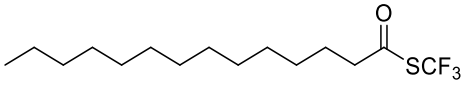


2m

According to Method A, thioester **2m** (78 mg, 56 %) was obtained from dodecanoic acid **1m** on a 0.5 mmol scale after flash column chromatography (pentane) as a colourless oil.

^{1}H NMR (401 MHz, $CDCl_3$): δ = 2.61 (t, *J* = 7.5 Hz, 2H), 1.69 (p, *J* = 7.4 Hz, 2H), 1.39 – 1.19 (m, 16H), 0.92 – 0.82 (m, 3H). **^{19}F NMR (377 MHz, $CDCl_3$): δ** = -40.1. **^{13}C NMR (176 MHz, $CDCl_3$) δ** = 190.5, 127.9 (q, *J* = 310 Hz), 44.8 (q, *J* = 3 Hz), 32.1, 29.7, 29.6, 29.5, 29.3, 28.8, 24.9, 22.8, 14.3. One alkyl ^{13}C peak could not be distinguished due to overlapping signals. **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2961, 2924, 2855, 1746, 1467, 1405, 1372, 1304, 1153, 1106, 950, 761, 722, 688, 573. **HRMS**: It was not possible to find a molecular ion for this compound via ESI or EI. Diagnostic fragments consistent with the reported structure were observed, however. **(EI) m/z:** $[M]^+$ Calcd for $C_{12}H_{23}OS$ 215.1464; Found 215.1479; Calcd for $C_{12}H_{23}O$ 183.1743; Found 183.1764; Calcd for SCF_3 100.9667; Found 100.9656; Calcd for CF_3 68.9947; Found 68.9941.

***S*-(trifluoromethyl) tetradecanethioate (2n)**

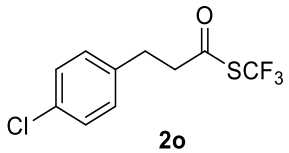


2n

According to Method A, thioester **2n** (86 mg, 55 %) was obtained from tetradecanoic acid **1n** on a 0.5 mmol scale after flash column chromatography (pentane) as a colourless oil.

^{1}H NMR (401 MHz, $CDCl_3$): δ = 2.61 (t, *J* = 7.5 Hz, 2H), 1.69 (p, *J* = 7.2 Hz, 2H), 1.39 – 1.21 (m, 20H), 0.93 – 0.83 (m, 3H). **^{19}F NMR (377 MHz, $CDCl_3$): δ** = -40.1. **^{13}C NMR (176 MHz, $CDCl_3$) δ** = 190.4, 127.9 (q, *J* = 310 Hz), 44.8 (q, *J* = 3 Hz), 32.1, 29.8, 29.8, 29.8, 29.7, 29.5, 29.4, 29.3, 28.8, 24.9, 22.9, 14.3. **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2958, 2924, 2854, 1747, 1464, 1402, 1375, 1307, 1153, 1107, 989, 950, 761, 722, 688, 574. **HRMS**: It was not possible to find a molecular ion for this compound via ESI or EI. Diagnostic fragments consistent with the reported structure were observed, however. **(EI) m/z:** $[M]^+$ Calcd for $C_{14}H_{27}OS$ 243.1777; Found 243.1764; Calcd for $C_{14}H_{27}O$ 211.2056; Found 211.2057; Calcd for SCF_3 100.9667; Found 100.9661; Calcd for CF_3 68.9947; Found 68.9941.

***S*-(trifluoromethyl) 3-(4-chloro)propanethioate (2o)**

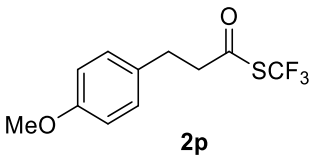


2o

According to Method A, thioester **2o** (98 mg, 73 %) was obtained from 3-(4-chlorophenyl)propanoic acid **1o** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2, 10:1) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 8.3 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 3.08 – 2.77 (m, 4H). **^{19}F NMR (565 MHz, $CDCl_3$): δ** = -40.0. **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 189.5, 137.4, 132.8, 129.8, 129.0, 127.6 (q, *J* = 310 Hz), 45.9 (q, *J* = 3 Hz), 29.9. **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3034, 2929, 2860, 1740, 1493, 1450, 1409, 1149, 1110, 1092, 1033, 1015, 957, 904, 812, 760, 743, 695, 629, 574. **HRMS (ESI) m/z:** $[M+Na]^+$ Calcd for $C_{10}H_8ClOSF_3Na$ 290.9829; Found 290.9833.

***S*-(trifluoromethyl) 3-(4-methoxyphenyl)propanethioate (2p)**

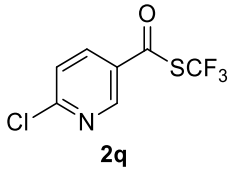


2p

According to Method A, thioester **2p** (88 mg, 67 %) was obtained from 3-(4-methoxyphenyl)propanoic acid **1p** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2, 5:1) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.15 – 7.06 (m, 2H), 6.90 – 6.81 (m, 2H), 3.80 (s, 3H), 2.98 – 2.87 (m, 4H). **^{19}F NMR (565 MHz, $CDCl_3$): δ** = -40.1. **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 189.7, 158.6, 130.9, 127.8 (q, *J* = 310 Hz), 129.4, 114.3, 55.4, 46.5 (q, *J* = 3 Hz), 29.8. **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3004, 2936, 2838, 1740, 1612, 1585, 1513, 1466, 1442, 1406, 1301, 1247, 1147, 1105, 1031, 955, 900, 823, 783, 760, 694, 572. **HRMS (ESI) m/z:** $[M+Na]^+$ Calcd for $C_{11}H_{11}O_2SF_3Na$ 287.0324; Found 287.0331.

***S*-(trifluoromethyl) 6-chloropyridine-3-carbothioate (2q)**



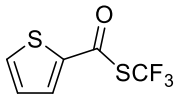
2q

According to Method A, thioester **2q** (29 mg, 24 %) was obtained from 6-chloronicotinic acid **1q** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2, 2:1) as a white solid.

^{1}H NMR (600 MHz, $CDCl_3$) *δ* = 8.86 (d, *J* = 2.5 Hz), 8.08 (dd, *J* = 8.4, 2.6 Hz), 7.51 (d, *J* = 8.4 Hz). **^{19}F NMR (565 MHz, $CDCl_3$) *δ*** = -39.0. **^{13}C NMR (151 MHz, $CDCl_3$) *δ*** = 181.2 (q, *J* = 1 Hz), 157.8, 149.1, 137.4, 130.0 (q, *J* = 3 Hz), 127.5 (q, *J* = 311 Hz), 125.2.

The characterization data agree with the literature values.[6]

***S*-(trifluoromethyl) thiophene-2-carbothioate (2r)**



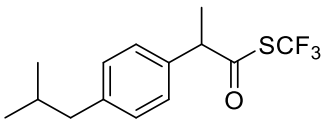
2r

According to Method A, thioester **2r** (39 mg, 37 %) was obtained from 2-thiophenecarboxylic acid **1r** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2, 10:1) as a light-yellow solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.79 (d, *J* = 4.9 Hz), 7.76 (d, *J* = 3.9 Hz), 7.18 (dd, *J* = 4.8, 3.9 Hz). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -38.8. **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 174.8 (q, *J* = 1 Hz), 139.7 (q, *J* = 3 Hz), 135.9, 133.4, 128.7, 127.9 (q, *J* = 310 Hz).

The characterization data agree with the literature values.[7]

***S*-(trifluoromethyl) 2-(4-isobutylphenyl)propanethioate (2s)**



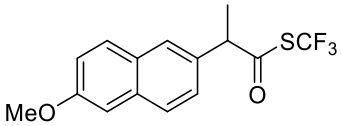
2s

According to Method A, thioester **2s** (131 mg, 90 %) was obtained from ibuprofen **1s** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2, 15:1) as a colourless oil.

^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.24 – 7.13 (m, 4H), 3.85 (q, *J* = 7.1 Hz, 1H), 2.50 (d, *J* = 7.2 Hz, 2H), 1.88 (d(hept), *J* = 13.4, 6.7 Hz, 1H), 1.58 (d, *J* = 7.1 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 6H). **^{19}F NMR (377 MHz, $CDCl_3$) δ** = -40.6. **^{13}C NMR (101 MHz, $CDCl_3$) δ** = 193.0, 142.5, 134.4, 130.0, 128.4, 128.1 (q, *J* = 310 Hz), 55.0 (q, *J* = 3 Hz), 45.2, 30.3, 22.5, 17.7.

The characterization data agree with the literature values.[5]

***S*-(trifluoromethyl) 2-(6-methoxynaphthalen-2-yl)propanethioate (2t)**



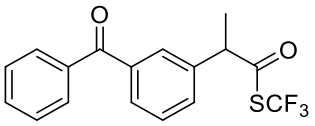
2t

According to Method A, thioester **2t** (140 mg, 89 %) was obtained from naproxen **1t** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2, 10:1) as a light-yellow oil.

^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.80 – 7.73 (m, 2H), 7.71 – 7.67 (m, 1H), 7.34 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.21 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.16 (d, *J* = 2.5 Hz, 1H), 4.00 (q, *J* = 7.0 Hz, 1H), 3.94 (s, 3H), 1.66 (d, *J* = 7.0 Hz, 3H). **^{19}F NMR (377 MHz, $CDCl_3$) δ** = -40.4. **^{13}C NMR (101 MHz, $CDCl_3$) δ** = 193.0, 158.4, 134.6, 132.1, 129.5, 129.0 128.1, 128.0 (q, *J* = 310 Hz), 127.9, 126.3, 119.7, 105.8, 55.5, 55.3 (q, *J* = 3 Hz), 17.7.

The characterization data agree with the literature values.[5]

***S*-(trifluoromethyl) 2-(3-benzoylphenyl)propanethioate (2u)**



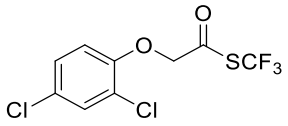
2u

According to Method A, thioester **2u** (133 mg, 79 %) was obtained from ketoprofen **1u** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2, 4:1 → 2:1) as a light-yellow oil.

^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.84 – 7.72 (m, 4H), 7.61 (tt, *J* = 6.8, 1.3 Hz, 1H), 7.57 – 7.44 (m, 4H), 3.95 (q, *J* = 7.1 Hz, 1H), 1.61 (d, *J* = 7.1 Hz, 3H). **^{19}F NMR (377 MHz, $CDCl_3$) δ** = -40.2. **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 196.1, 192.1, 138.6, 137.7, 137.3, 132.9, 132.2, 130.3, 130.2, 130.0, 129.3, 128.5, 127.8 (q, *J* = 310 Hz), 55.0, 17.8.

The characterization data agree with the literature values.[5]

***S*-(trifluoromethyl) 2-(2,4-dichlorophenoxy)ethanethioate (2v)**

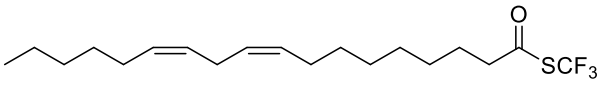


2v

According to Method A, thioester **2v** (90 mg, 59 %) was obtained from 2-(2,4-dichlorophenoxy)acetic acid **1v** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2, 10:1) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 2.5 Hz, 1H), 7.23 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 1H), 4.72 (s, 2H). **^{19}F NMR (565 MHz, $CDCl_3$): δ** = -40.4. **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 190.3 (d, *J* = 1 Hz), 151.4, 130.9, 128.7, 128.0, 127.9 (q, *J* = 311 Hz), 124.6, 115.1, 73.2 (q, *J* = 2 Hz). **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3101, 2955, 2921, 2851, 1729, 1586, 1573, 1477, 1427, 1387, 1359, 1289, 1262, 1155, 1127, 1060, 867, 805, 761, 751, 631. **HRMS (EI) m/z:** $[M]^+$ Calcd for $C_9H_5Cl_2O_2SF_3$ 303.9339; Found 303.9335.

***S*-(trifluoromethyl) (9*Z*,12*Z*)-octadeca-9,12-dienethioate (2w)**



2w

According to Method A, thioester **2w** (107 mg, 59 %) was obtained from linoleic acid **1w** on a 0.5 mmol scale after flash column chromatography (pentane) as a colourless oil.

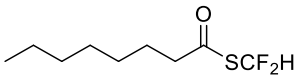
^{1}H NMR (401 MHz, $CDCl_3$): δ = 5.47 – 5.25 (m, 4H), 2.81 – 2.73 (m, 2H), 2.61 (t, *J* = 7.4 Hz, 2H), 2.05 (q, *J* = 6.8 Hz, 4H), 1.69 (p, *J* = 7.4 Hz, 2H), 1.41 – 1.17 (m, 14H), 0.94 – 0.84 (m, 3H). **^{19}F NMR (377 MHz, $CDCl_3$): δ** = -40.1. **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 190.4, 130.4, 130.0, 128.3, 128.0, 127.9 (q, *J* = 310 Hz), 44.8, 31.7, 29.6, 29.5, 29.2, 29.1, 28.8, 27.3, 27.3, 25.8, 24.8, 22.7, 14.2. **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3009, 2925, 2855, 1747, 1465, 1405, 1310, 1155, 1113, 953, 761, 723, 688, 572. **HRMS (EI) m/z:** $[M]^+$ Calcd for $C_{19}H_{31}OSF_3$ 364.2048; Found 364.2041.

4.3 General Procedure for the Deoxydifluoromethylthioesterification of Carboxylic acids

Sodium hydride (2.0 equiv.) and the acid (1.0 equiv., 0.5 mmol) were dissolved in dry THF (0.05 M for aliphatic and 0.0125 M for aromatic substrates) and were allowed to react for 0.5 h before BT-SCF_2H (2.0 equiv,) was added and the mixture was stirred for 2 h at rt. The reaction was quenched with ammonium chloride (sat. in water) until a pH value of 6 was reached. The crude mixture was dissolved in CH_2Cl_2 and washed with water (2 x). The aqueous phases were extracted with CH_2Cl_2 (3 x) and the combined organic phases were dried over magnesium sulphate. The drying agent was filtered off and washed with CH_2Cl_2. The solvent was removed under reduced pressure and the difluoromethylthioesters were isolated using column chromatography (SiO_2).

4.4 Characterization Data for Deoxydifluoromethylthiolation Products 3

***S*-(difluoromethyl) octanethioate (3a)**



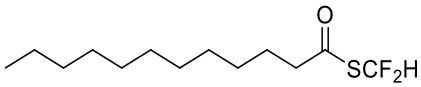
3a

According to the general procedure, thioester **3a** (92 mg, 88%) was obtained from octanoic acid **1l** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2 20:1) as a colourless oil.

^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.30 (t, *J* = 55.1 Hz, 1H), 2.61 (t, *J* = 7.6 Hz, 2H), 1.68 (p, *J* = 7.3 Hz, 2H), 1.40 – 1.17 (m, 8H), 0.88 (t, *J* = 7.0 Hz, 3H).**^{19}F NMR (377 MHz, $CDCl_3$) δ** = -100.1 (d, *J* = 55 Hz). **^{13}C NMR (101 MHz, $CDCl_3$) δ** = 195.0, 120.3 (t, *J* = 270 Hz), 45.1 (t, *J* = 2 Hz), 31.6, 28.9, 28.8, 24.9, 22.6, 14.1.

The characterization data agree with the literature values.[8]

***S*-(difluoromethyl) dodecanethioate (3b)**



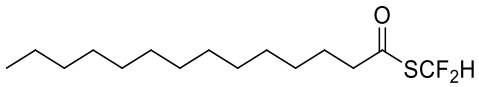
3b

According to the general procedure, thioester **3b** (123 mg, 92%) was obtained from dodecanoic acid **1m** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2 40:1) as a colourless oil.

^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.30 (t, *J* = 55.1 Hz, 1H), 2.61 (t, *J* = 7.5, 2H), 1.68 (p, *J* = 7.5 Hz, 2H), 1.37-1.19 (m, 16H), 0.88 (t, *J* = 7 Hz, 3H). **^{19}F NMR (377 MHz, $CDCl_3$) δ** = -100.3 (d, *J* = 55 Hz, 2F). **^{13}C NMR (101 MHz, $CDCl_3$) δ** = 194.8, 120.2 (t, *J* = 270 Hz), 45.0 (t, *J* = 3 Hz), 31.9, 29.6, 29.5, 29.3, 29.3, 29.1, 28.7, 24.8, 22.7, 14.1.

The characterization data agree with the literature values.[8]

***S*-(difluoromethyl) tetradecanethioate (3c)**

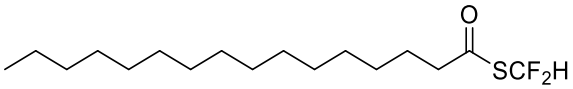


3c

According to the general procedure, thioester **3c** (119 mg, 81%) was obtained from tetradecanoic acid **1n** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2 40:1) as a colourless oil.

^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.30 (t, *J*= 55.2 Hz, 1H), 2.61 (t, *J* = 7.5 Hz, 2H), 1.68 (p, *J* = 7.4 Hz, 2H), 1.40 – 1.23 (m, 20H), 0.87 (t, *J* = 7 Hz, 3H). **^{19}F NMR (377 MHz, $CDCl_3$) δ** = -100.3 (d, *J* = 55 Hz, 2F). **^{13}C NMR (101 MHz, $CDCl_3$) δ** = 194.8, 120.2 (t, *J* = 270 Hz), 45.0 (t, *J* = 2 Hz), 31.9, 29.7, 29.6, 29.6, 29.5, 29.3, 29.3, 29.1, 28.7, 24.8, 22.7, 14.1. **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2924, 2851, 1720, 1469, 1292, 1060, 785, 739, 592. **HRMS (EI) m/z:** $[M]^+$ Calcd for $C_{15}H_{28}OSF_2$ 294.1829; Found 294.1833.

***S*-(difluoromethyl) hexadecanethioate (3d)**

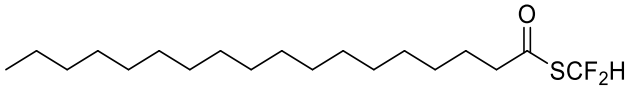


3d

According to the general procedure, thioester **3d** (141 mg, 87%) was obtained from hexadecenoic acid **1x** on a 0.5 mmol scale after flash column chromatography (pentane) as a colourless oil.

^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.30 (t, *J* = 55.1 Hz, 1H), 2.61 (t, *J* = 7.5 Hz, 2H), 1.68 (p, *J* = 7.4 Hz, 2H), 1.36-1.21 (m, 24H), 0.88 (t, *J* = 6.7 Hz, 3H). **^{19}F NMR (377 MHz, $CDCl_3$) δ** = -100.2 (d, *J* = 55 Hz). **^{13}C NMR (101 MHz, $CDCl_3$) δ** = 194.8, 120.2 (t, *J* = 270 Hz), 45.0 (t, *J* = 2 Hz), 31.9, 29.7, 29.7, 29.6, 29.6, 29.6, 29.5, 29.3, 29.3, 29.1, 28.7, 24.8, 22.7, 14.1. **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2933, 2836, 1714, 1512, 1246, 1182, 1035, 962, 825, 782, 702, 546. **HRMS (ESI) m/z:** $[M+Na]^+$ Calcd for $C_{17}H_{32}OSF_2Na$ 345.2040; Found 345.2041.

***S*-(difluoromethyl) octadecanethioate (3e)**

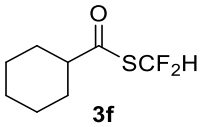


3e

According to the general procedure, thioester **3e** (157 mg, 90%) was obtained from octadecanoic acid **1y** on a 0.5 mmol scale after flash column chromatography (pentane) as a white solid, m.p. = 34–35 °C.

^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.30 (t, *J* = 55.1 Hz, 1H), 2.61 (t, *J* = 7.5 Hz, 2H), 1.68 (p, *J* = 7.4 Hz, 2H), 1.38 – 1.17 (m, 28H), 0.88 (t, *J* = 6.8 Hz, 3H). **^{19}F NMR (377 MHz, $CDCl_3$) δ** = -100.2 (d, *J* = 55 Hz). **^{13}C NMR (101 MHz, $CDCl_3$) δ** = 194.9, 120.2 (t, *J* = 270 Hz), 45.0 (t, *J* = 2 Hz), 31.9, 29.7, 29.7, 29,7, 29.7, 29.6, 29.6, 29.6, 29.5, 29.4, 29.3, 29.1, 28.7, 24.8, 22.7, 14.1. **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2964, 2915, 2848, 1702, 1472, 1405, 1298, 1115, 1038, 959, 773, 718, 580. **HRMS (ESI) m/z:** $[M+Na]^+$ Calcd for $C_{19}H_{36}OSF_2Na$ 373.2353; Found 373.2350.

***S*-(difluoromethyl) cyclohexanecarbothioate (3f)**



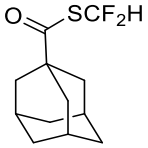
3f

According to the general procedure, thioester **3f** (96 mg, 99%) was obtained from cyclohexanecarboxylic acid **1z** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2 20:1) as a colourless oil.

^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.27 (t, *J* = 55.3 Hz, 1H), 2.49 (tt, *J* = 11.3, 3.6 Hz, 1H), 2.01 – 1.90 (m, 2H), 1.87 – 1.74 (m, 2H), 1.70 – 1.61 (m, 1H), 1.54 – 1.40 (m, 2H), 1.38 – 1.14 (m, 3H). **^{19}F NMR (377 MHz, $CDCl_3$) δ** = -100.1 (d, *J* = 55 Hz, 2F). **^{13}C NMR (101 MHz, $CDCl_3$) δ** = 198.3, 120.3 (t, *J* = 270 Hz), 53.4, 28.9, 25.4, 25.2.

The characterization data agree with the literature values.[8]

***S*-(difluoromethyl) (3r,5r,7r)-adamantane-1-carbothioate (3g)**



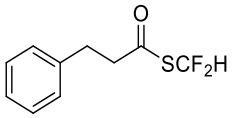
3g

According to the general procedure, thioester **3g** (97 mg, 79%) was obtained from 1-adamantanecarboxylic acid **1aa** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2 30:1) as a white solid.

^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.23 (t, *J* = 55.4 Hz, 1H), 2.08 (s, 3H), 1.89 (d, *J* = 3.3 Hz, 6H), 1.80 – 1.65 (m, 6H). **^{19}F NMR (377 MHz, $CDCl_3$) δ** = -100.0 (d, *J* = 56 Hz, 2F). **^{13}C NMR (101 MHz, $CDCl_3$) δ** = 201.8, 120.6 (t, *J* = 269 Hz), 49.6, 38.7, 36.2, 27.9.

The characterization data agree with the literature values.[8]

***S*-(difluoromethyl) 3-phenylpropanethioate (3h)**



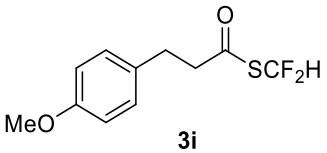
3h

According to the general procedure, thioester **3h** (95 mg, 88%) was obtained from 3-phenylpropanoic acid **1bb** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2 20:1) as a colourless oil.

^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.32 (t, *J* = 55.2 Hz, 1H), 7.32 (t, *J* = 7.7 Hz, 2H), 7.25 (t, *J* = 7.3 Hz, 1H), 7.19 (d, *J* = 6.9 Hz, 2H), 3.06 – 2.90 (m, 1H). **^{19}F NMR (377 MHz, $CDCl_3$) δ** = -100.1 (d, *J* = 56 Hz, 2F). **^{13}C NMR (101 MHz, $CDCl_3$) δ** = 194.0, 139.1, 128.7, 128.3, 126.7, 120.0 (t, *J* = 270 Hz), 46.4 (t, *J* = 3 Hz), 30.6.

The characterization data agree with the literature values.[8]

***S*-(difluoromethyl) 3-(4-methoxyphenyl)propanethioate (3i)**

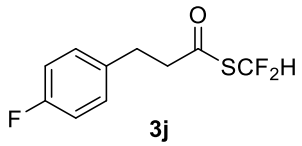


3i

According to the general procedure, thioester **3i** (115 mg, 93%) was obtained from 3-(4-methoxyphenyl)propanoic acid **1p** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2 9:1) as a yellow oil.

^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.31 (t, *J* = 55.1 Hz, 1H), 7.10 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 3.79 (s, 3H), 2.99 – 2.86 (m, *J* = 4.2 Hz, 4H). **^{19}F NMR (377 MHz, $CDCl_3$) δ** = -100.3 (d, *J* = 55 Hz). **^{13}C NMR (101 MHz, $CDCl_3$) δ** = 194.1, 158.4, 131.0, 129.3, 120.0 (t, *J* = 270 Hz), 114.1, 55.2, 46.7 (t, *J* = 2 Hz), 29.8. **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2943, 2839, 1714, 1512, 1246, 1179, 1032, 965, 825, 782, 699, 546. **HRMS (EI) m/z:** $[M]^+$ Calcd for $C_{11}H_{12}O_2SF_2$ 246.0526; Found 246.0523.

***S*-(difluoromethyl) 3-(4-fluoro)propanethioate (3j)**

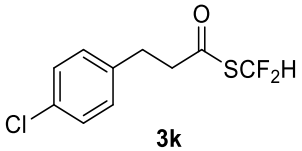


3j

According to the general procedure, thioester **3j** (103 mg, 88%) was obtained from 3-(4-fluoro)propanoic acid **1cc** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2 20:1) as a colourless oil.

^{1}H NMR (401 MHz, $CDCl_3$) δ = δ 7.30 (t, *J* = 55.3 Hz, 1H), 7.16 – 7.09 (m, 2H), 7.02 – 6.93 (m, 2H), 3.01 – 2.87 (m, 4H). **^{19}F NMR (377 MHz, $CDCl_3$) δ** = -100.0 (d, *J* = 55 Hz), -116.0 – -116.2 (m). **^{13}C NMR (101 MHz, $CDCl_3$) δ** = 193.9 (d, *J* = 2 Hz), 161.8 (d, *J* = 245 Hz), 134.8, 129.9 (d, *J* = 8 Hz), 120.0 (t, *J* = 271 Hz), 115.6 (d, *J* = 21 Hz), 46.6 – 46.4 (m), 29.9. **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2933, 1717, 1509, 1295, 1222, 1158, 1038, 962, 821, 782, 705, 534. **HRMS (EI) m/z:** $[M]^+$ Calcd for $C_{10}H_9OSF_3$ 234.0326; Found 234.0320.

***S*-(difluoromethyl) 3-(4-chloro)propanethioate (3k)**

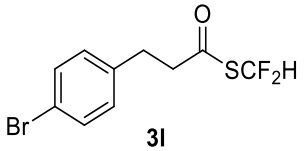


3k

According to the general procedure, thioester **3k** (110 mg, 88%) was obtained from 3-(4-chloro)propanoic acid **1o** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2 20:1) as a colourless oil.

^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.29 (t, *J* = 55.0 Hz, 1H), 7.28 – 7.24 (m, 2H), 7.13 – 7.07 (m, 2H), 3.02 – 2.87 (m, 4H). **^{19}F NMR (377 MHz, $CDCl_3$) δ** = -99.9 (d, *J* = 56 Hz). **^{13}C NMR (101 MHz, $CDCl_3$) δ** = 193.8 (t, *J* = 3 Hz), 137.6, 132.7, 129.7, 128.9, 120.0 (t, *J* = 271 Hz), 46.2 (t, *J* = 3 Hz), 30.0. **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2933, 1711, 1491, 1408, 1292, 1087, 1038, 962, 812, 785, 748, 696, 628, 531. **HRMS (EI) m/z:** $[M]^+$ Calcd for $C_{10}H_9OSClF_2$ 250.0031; Found 250.0022.

***S*-(difluoromethyl) 3-(4-bromo)propanethioate (3l)**

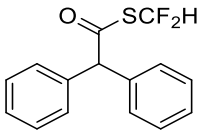


3l

According to the general procedure, thioester **3l** (123 mg, 83%) was obtained from 3-(4-bromo)propanoic acid **1dd** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2 20:1) as a colourless oil.

^{1}H NMR (401 MHz, $CDCl_3$) δ = δ 7.42 (d, *J* = 8.2 Hz, 2H), 7.30 (t, *J* = 54.9 Hz, 1H), 7.06 (d, *J* = 7.0 Hz, 2H), 3.00 – 2.86 (m, 4H). **^{19}F NMR (377 MHz, $CDCl_3$) δ** = -99.9 (d, *J* = 55 Hz). **^{13}C NMR (101 MHz, $CDCl_3$) δ** = 193.8 (d, *J* = 3 Hz), 138.1, 131.9, 130.2, 120.7, 120.0 (t, *J* = 271 Hz), 46.1 (t, *J* = 2 Hz), 30.0. **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2927, 1714, 1488, 1295, 1038, 1008, 965, 812, 785, 742, 598. **HRMS (EI) m/z:** $[M]^+$ Calcd for $C_{10}H_9OSBrF_2$ 293.9526; Found 293.9513.

***S*-(difluoromethyl) 2,2-diphenylethanethioate (3m)**

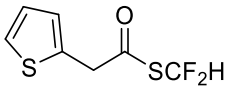


3m

According to the general procedure, thioester **3m** (105 mg, 75%) was obtained from 2,2-diphenylacetic acid **1ee** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2 20:1) as a colourless oil.

^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.34 (t, *J* = 55.4 Hz, 1H), 7.43 – 7.30 (m, 10H), 5.20 (s, 1H). **^{19}F NMR (377 MHz, $CDCl_3$) δ** = -100.0 (d, *J* = 55 Hz, 2F). **^{13}C NMR (101 MHz, $CDCl_3$) δ** = 195.2, 136.6, 129.1, 129.0, 128.2, 120.2 (t, *J* = 271 Hz), 66.1 (t, *J* = 3 Hz). **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3031, 1711, 1494, 1451, 1292, 1060, 987, 779, 733, 693, 604, 537. **HRMS (ESI) m/z:** $[M+Na]^+$ Calcd for $C_{15}H_{12}OSF_2Na$ 301.0475; Found 301.0464.

***S*-(difluoromethyl) 2-(thiophen-2-yl)ethanethioate (3n)**

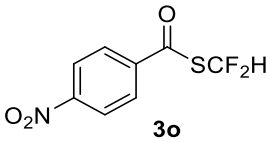


3n

According to the general procedure, thioester **3n** (71 mg, 68%) was obtained from 2-(thiophen-2-yl)acetic acid **1ff** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2 20:1) as an orange oil.

^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.32 (dd, *J* = 4.9, 1.5 Hz, 1H), 7.25 (t, *J* = 54.9 Hz, 1H), 7.06 – 6.96 (m, 2H), 4.07 (s, 2H). **^{19}F NMR (377 MHz, $CDCl_3$) δ** = -100.0 (d, *J* = 55 Hz). **^{13}C NMR (101 MHz, $CDCl_3$) δ** = 193.0, 132.0, 129.1, 127.6, 126.9, 120.2 (t, *J* = 271 Hz), 44.8 (t, *J* = 3 Hz). **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3114, 2918, 1711, 1295, 1038, 855, 788, 705, 598. **HRMS (EI) m/z:** $[M]^+$ Calcd for $C_7H_6OS_2F_2$ 207.9828; Found 207.9823.

***S*-(difluoromethyl) 4-nitrobenzothioate (3o)**



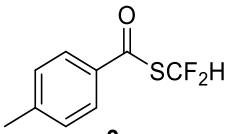
3o

According to the general procedure, thioester **3o** (55 mg, 47%) was obtained from 4-nitrobenzoic acid **1g** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2 8:1) as a yellow solid.

^{1}H NMR (401 MHz, $CDCl_3$) δ = 8.38 – 8.32 (m, 2H), 8.10 – 8.02 (m, 2H), 7.50 (t, *J* = 54.9, 1H). **^{19}F NMR (377 MHz, $CDCl_3$) δ** = -99.0 (d, *J* = 55 Hz). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 186.3 (t, *J* = 4 Hz), 151.3, 139.9 (d, *J* = 3 Hz), 128.7, 124.4, 120.0 (t, *J* = 273 Hz).

The characterization data agree with the literature values.[8]

***S*-(difluoromethyl) 4-methylbenzothioate (3p)**



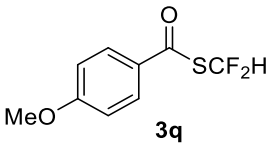
3p

According to the general procedure, thioester **3p** (50 mg, 49%) was obtained from 4-methylbenzoic acid **1a** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2 40:1) as a yellow solid.

^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.79 (d, *J* = 8.3 Hz, 2H), 7.49 (t, *J* = 55.3 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 2.44 (s, 3H). **^{19}F NMR (377 MHz, $CDCl_3$) δ** = -99.3 (d, *J* = 56 Hz). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 186.9 (t, *J* = 3 Hz), 146.2, 133.2 (t, *J* = 3 Hz), 129.8, 127.8, 120.8 (t, *J* = 270 Hz), 21.9.

The characterization data agree with the literature values.[8]

***S*-(difluoromethyl) 4-methoxybenzothioate (3q)**



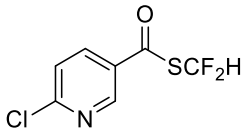
3q

According to the general procedure, thioester **3q** (46 mg, 42%) was obtained from 4-methoxybenzoic acid **1e** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2 8:1) as a red solid.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 7.86 (d, *J* = 9.1 Hz, 2H), 7.48 (t, *J* = 55.4 Hz, 1H), 6.96 (d, *J* = 9.1 Hz, 2H), 3.89 (s, 3H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -99.2 (d, *J* = 55 Hz). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 185.6 (d, *J* = 3 Hz), 165.0, 130.1, 128.4 (t, *J* = 3 Hz), 120.9 (t, *J* = 270 Hz), 114.3, 55.8.

The characterization data agree with the literature values.[8]

***S*-(difluoromethyl) 6-chloropyridine-3-carbothioate (3r)**

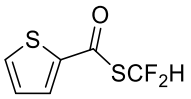


3r

According to the general procedure, thioester **3r** (34 mg, 30%) was obtained from 2-(2,4-dichlorophenoxy)acetic acid **1q** on a 0.5 mmol scale after flash column chromatography (pentane / ethyl acetate 60:1) as a white solid, m.p. = 58–59 °C.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 8.89 (s, 1H), 8.10 (dd, *J* = 8.4, 2.5 Hz, 1H), 7.50 (t, *J* = 55.0 Hz, 1H), 7.49 (d, *J* = 8.2 Hz, 1H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -98.9 (d, *J* = 54 Hz). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 185.2 (d, *J* = 4 Hz), 157.5, 149.1, 137.3, 130.3, 125.0, 119.8 (t, *J* = 273 Hz). **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3056, 2927, 1674, 1573, 1460, 1360, 1295, 1216, 1066, 1020, 898, 849, 782, 736, 656, 598. **HRMS (ESI) m/z:** $[M+H]^+$ Calcd for $C_7H_5ClF_2NOS$ 223.9748; Found 223.9741.

***S*-(difluoromethyl) thiophene-2-carbothioate (3s)**



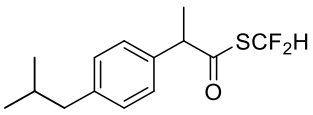
3s

According to the general procedure, thioester **3s** (23 mg, 24%) was obtained from thiophene-2-carboxylic acid **1r** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2 15:1) as a colourless oil.

^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.79 (d, *J* = 3.9 Hz, 1H), 7.76 (d, *J* = 3.7 Hz, 1H), 7.50 (t, *J* = 55.1 Hz, 1H), 7.20 – 7.15 (m, 1H). **^{19}F NMR (377 MHz, $CDCl_3$) δ** = -98.6 (d, *J* = 54 Hz). **^{13}C NMR (101 MHz, $CDCl_3$) δ** = 178.8 (d, *J* = 4 Hz), 140.3 (d, *J* = 4 Hz), 135.2, 133.0, 128.5, 120.4 (t, *J* = 271 Hz).

The characterization data agree with the literature values.[14]

***S*-(difluoromethyl) 2-(4-isobutylphenyl)propanethioate (3t)**



3t

According to the general procedure, thioester **3t** (123 mg, 88%) was obtained from 2-(4-isopropylphenyl)propanoic acid **1s** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2 40:1) as a colourless oil.

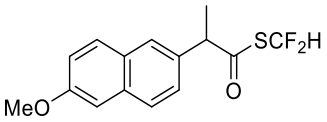
Following the same procedure, the thioester **3t** was obtained on a larger scale:

Sodium hydride (240 mg, 2.0 equiv., 10 mmol) and 2-(4-isopropylphenyl)propanoic acid **1s** (1.03 g, 1.0 equiv., 5.0 mmol) were dissolved in dry THF (0.05 M, 100 mL) and were allowed to react for 0.5 h before BT-SCF_2H (3.81 g, 2.0 equiv., 10.0 mmol) was added and the mixture was stirred for 2 h at rt. The reaction was quenched with ammonium chloride (sat. in water) until a pH value of 6 was reached. The crude mixture was dissolved in CH_2Cl_2 and washed with water (2 x). The aqueous phases were extracted with CH_2Cl_2 (3 x) and the combined organic phases were dried over magnesium sulphate. The drying agent was filtered off and washed with CH_2Cl_2. The

solvent was removed under reduced pressure and the difluoromethylthioester **3r** (1.22 g, mmol, 88 %) was obtained after column chromatography (pentane / CH_2Cl_2, 40:1).

^{1}H NMR (401 MHz, $CDCl_3$) δ = δ 7.24 (t, *J* = 55.4 Hz, 1H), 7.21 – 7.12 (m, 4H), 3.8 (6q, *J* = 7.1 Hz, 1H), 2.50 (d, *J* = 7.2 Hz, 2H), 1.89 (hept, *J* = 6.6 Hz, 1H), 1.58 (d, *J* = 7.1 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 6H). **^{19}F NMR (377 MHz, $CDCl_3$) δ** = -99.1 (dd, *J* = 257, 55 Hz), -100.7(dd, *J* = 259, 55 Hz). **^{13}C NMR (101 MHz, $CDCl_3$) δ** = 197.4 (t, *J* = 2 Hz), 142.1, 135.0, 129.9, 128.2, 120.4 (t, *J* = 270 Hz), 55.0 (t, *J* = 2 Hz), 45.2, 30.3, 22.5, 17.7. **IR (ATR)**: ṽ [cm^{-1}] = 2958, 1711, 1292, 1057, 999, 931, 791, 736, 546. **C-H-N-S Analysis:** Anal. Calcd for $C_{15}H_{12}F_2OS$: C, 61.74; H, 6.66; S, 11.77. Found: C, 61.77; H, 6.67; S, 11.92.

S-(difluoromethyl) 2-(6-methoxynaphthalen-2-yl)propanethioate (3u)

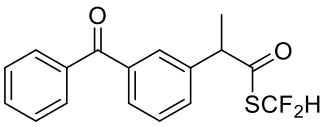


3u

According to the general procedure, thioester **3u** (136 mg, 92%) was obtained from 2-(6-methoxynaphthalen-2-yl)propanoic acid **1t** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2 12:1) as a colourless oil.

^{1}H NMR (401 MHz, $CDCl_3$) δ = δ 7.75 (dd, *J* = 8.7, 6.6 Hz, 2H), 7.68 (s, 1H), 7.34 (d, *J* = 8.5 Hz, 1H), 7.24 (t, *J* = 55.4 Hz, 1H), 7.19 (d, *J* = 8.9 Hz, 1H), 7.15 (s, 1H), 4.00 (q, *J* = 7.2 Hz, 1H), 3.93 (s, 3H), 1.65 (d, *J* = 7.3 Hz, 3H).**^{19}F NMR (377 MHz, $CDCl_3$) δ** = -99.1 (dd, *J* = 259, 55 Hz), -100.7 (dd, *J* = 259, 55 Hz). **^{13}C NMR (101 MHz, $CDCl_3$) δ** = 197.3, 158.3, 134.4, 132.8, 129.5, 129.0, 127.8, 127.6, 126.3 (d, *J* = 2 Hz), 120.4 (t, *J* = 270 Hz), 119.6, 105.8, 55.5, 55.3 (t, *J* = 2 Hz), 17.7. **IR (ATR)**: ṽ [cm^{-1}] = 2924, 1711, 1604, 1454, 1271, 1228, 1176, 1069, 1038, 996, 941, 910, 855, 821, 785, 699, 577, 540. **HRMS (EI) m/z:** $[M]^+$ Calcd for $C_{15}H_{14}O_2SF_2$ 296.0683; Found 296.0674.

S-(difluoromethyl) 2-(3-benzoylphenyl)propanethioate (3v)

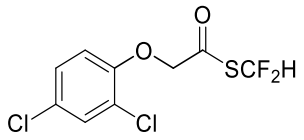


3v

According to the general procedure, thioester **3v** (140 mg, 87%) was obtained from 2-(3-benzoylphenyl) propanoic acid **1u** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2 12:1) as a white solid, m.p. = 88–89 °C.

^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.79 (d, *J* = 6.9 Hz, 2H), 7.77 – 7.70 (m, 2H), 7.65 – 7.55 (m, 1H), 7.55 – 7.44 (m, 4H), 7.23 (t, *J* = 55.2 Hz, 1H), 3.95 (q, *J* = 7.1 Hz, 1H), 1.59 (d, *J* = 7.1 Hz, 3H).**^{19}F NMR (377 MHz, $CDCl_3$) δ** = -99.2 (dd, *J* = 255, 55 Hz), -100.3 (dd, *J* = 259, 55 Hz). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 196.5, 196.2, 138.4, 138.3, 137.3, 132.8, 132.1, 130.2, 130.1, 129.9, 129.2, 128.5, 120.1 (t, *J* = 271 Hz), 55.1 (d, *J* = 3 Hz), 17.9. **IR (ATR)**: ṽ [cm^{-1}] = 3068, 2982, 2936, 1711, 1659, 1595, 1448, 1280, 1057, 922, 785, 745, 708, 638, 580. **HRMS (ESI) m/z:** $[M+Na]^+$ Calcd for $C_{17}H_{14}O_2SF_2Na$ 343.0581; Found 343.0593.

***S*-(difluoromethyl) 2-(2,4-dichlorophenyl)ethanethioate (3w)**

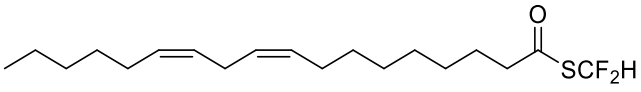


3w

According to the general procedure, thioester **3w** (96 mg, 66%) was obtained from 2-(2,4-dichlorophenoxy)acetic acid **1v** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2 7:1) as a white solid, m.p. = 76–78 °C.

^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.43 (d, *J* = 2.5 Hz, 1H), 7.35 (t, *J* = 55.0 Hz, 1H), 7.20 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 1H), 4.72 (s, 2H).**^{19}F NMR (377 MHz, $CDCl_3$) δ** = -100.4 (d, *J* = 55 Hz). **^{13}C NMR (101 MHz, $CDCl_3$) δ** = 194.3 (d, *J* = 3 Hz), 151.6, 130.8, 128.4 (d, *J* = 2 Hz), 127.9 (d, *J* = 2 Hz), 124.6, 119.6 (t, *J* = 271 Hz), 115.0 (d, *J* = 3 Hz), 73.3 (t, *J* = 2 Hz). **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2905, 1702, 1479, 1433, 1292, 1252, 1048, 870, 806, 788, 751, 644, 534. **HRMS (EI) m/z:** $[M]^+$ Calcd for $C_9H_6O_2SCl_2F_2$ 285.9434; Found 285.9442.

***S*-(difluoromethyl) (9Z,12Z)-octadeca-9,12-dienethioate (3x)**



3x

According to the general procedure, thioester **3x** (171 mg, 99%) was obtained from linoleic acid **1w** on a 0.5 mmol scale after flash column chromatography (pentane / CH_2Cl_2 20:1) as a colourless oil.

^{1}H NMR (401 MHz, $CDCl_3$) δ = 7.30 (t, *J* = 55.2 Hz, 1H), 5.45 – 5.27 (m, 4H), 2.77 (t, *J* = 6.2 Hz, 2H), 2.61 (t, *J* = 7.5 Hz, 2H), 2.05 (q, *J* = 6.8 Hz, 4H), 1.68 (p, *J* = 7.3 Hz, 2H), 1.43 – 1.20 (m, 14H), 0.89 (t, *J* = 6.9 Hz, 3H). **^{19}F NMR (377 MHz, $CDCl_3$) δ** = -100.2 (d, *J* = 55 Hz, 2F).**^{13}C NMR (101 MHz, $CDCl_3$) δ** = 194.8, 130.2, 128.9, 128.1, 127.9, 120.2 (t, *J* = 270 Hz), 45.0, 31.5, 29.5, 29.3, 29.0, 28.9, 28.7, 27.2, 27.1, 25.6, 24.8, 22.6, 14.0. **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2924, 1711, 1424, 1356, 1222, 1090, 904, 537. **HRMS (ESI) m/z:** $[M+Na]^+$ Calcd for $C_{19}H_{32}OSF_2Na$ 369.2040; Found 369.2044.

5 Computational Studies

Computational results were prepared, executed, and evaluated by QoD Technologies GmbH using the Gaussian16 package,[9] the B3LYP functional and a def2-SVP basis set[10-12] with the THF solvent in the framework of a polarizable continuum model (PCM).[13] Pathways/transition states were obtained via QST3.[14]

Two potential mechanistic pathways from tetrahedral intermediate **A** (R = Et) were investigated for both the difluoromethylthiolation (X = H) and trifluoromethylthiolation (X = F) reactions: **Path I** involving a stepwise elimination of the ^-SR_F anion followed by reaction with the resulting active ester and the concerted **Path II** involving a four-membered transition state (Figure S1).

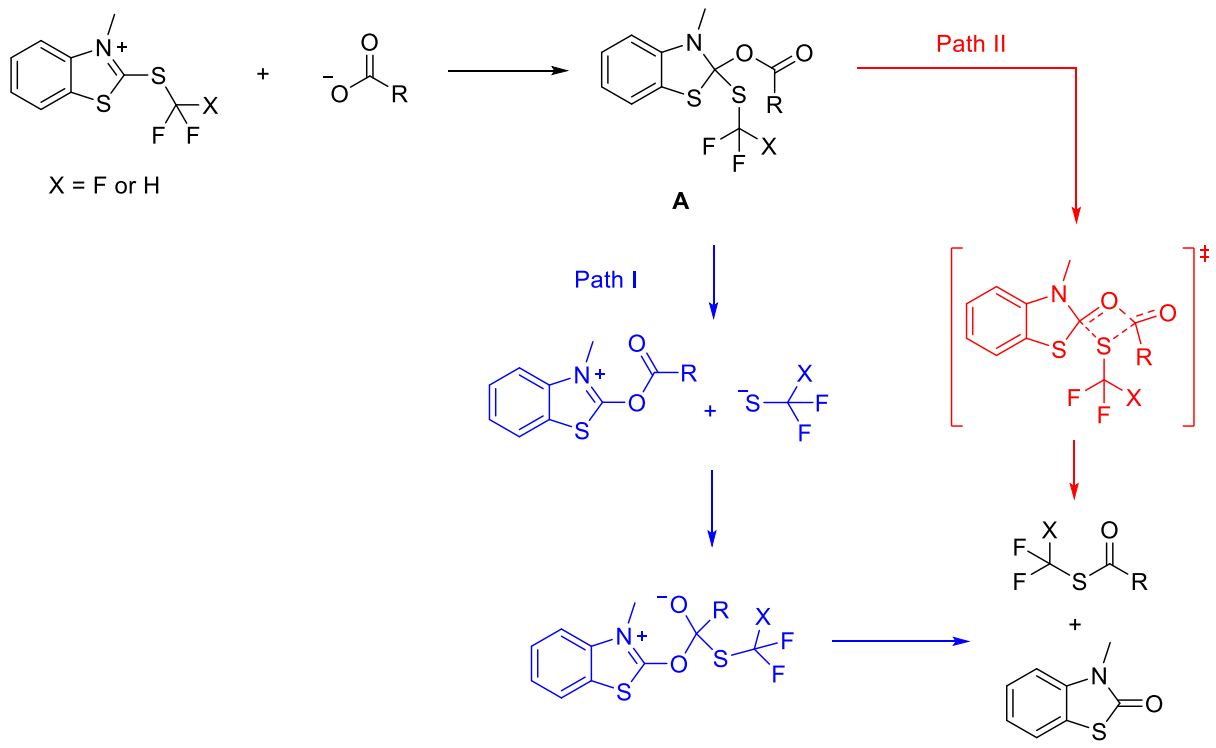


Figure S1. Calculated mechanisms from intermediate **A** (R = Et, X = H or F).

As shown in Figures S2 and S3, **Path II** was found to be considerably more energetically favoured than **Path I** for the difluoromethylthiolation reaction (energy barrier E_f = 0.533 eV for **Path II** vs. E_f = 1.477 eV for **Path I**). A four-membered cyclic transition state was identified.

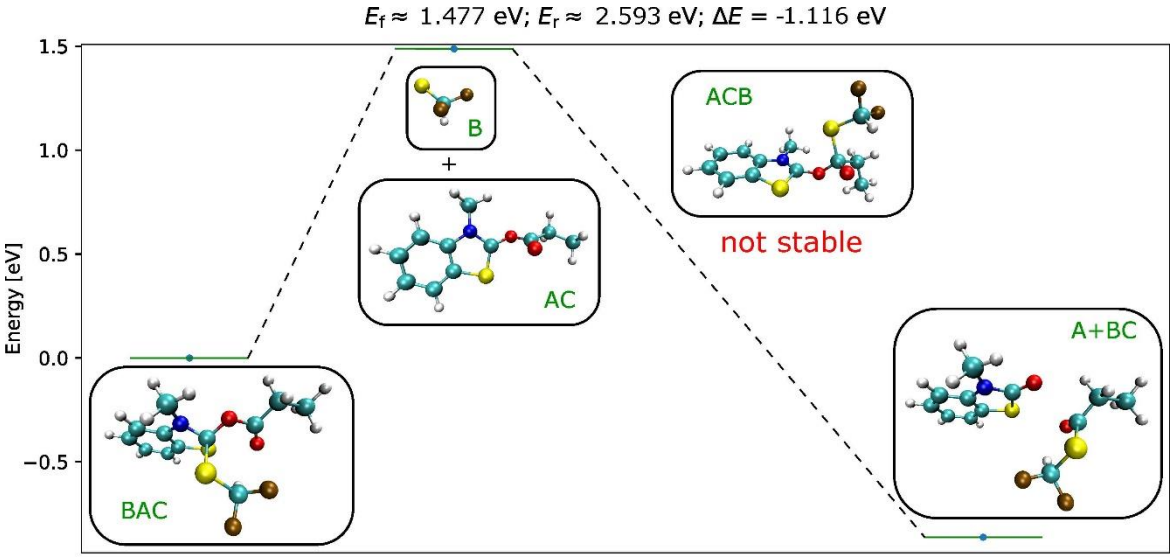


Figure S2. Calculated energy profile for stepwise **Path I** (X = H).

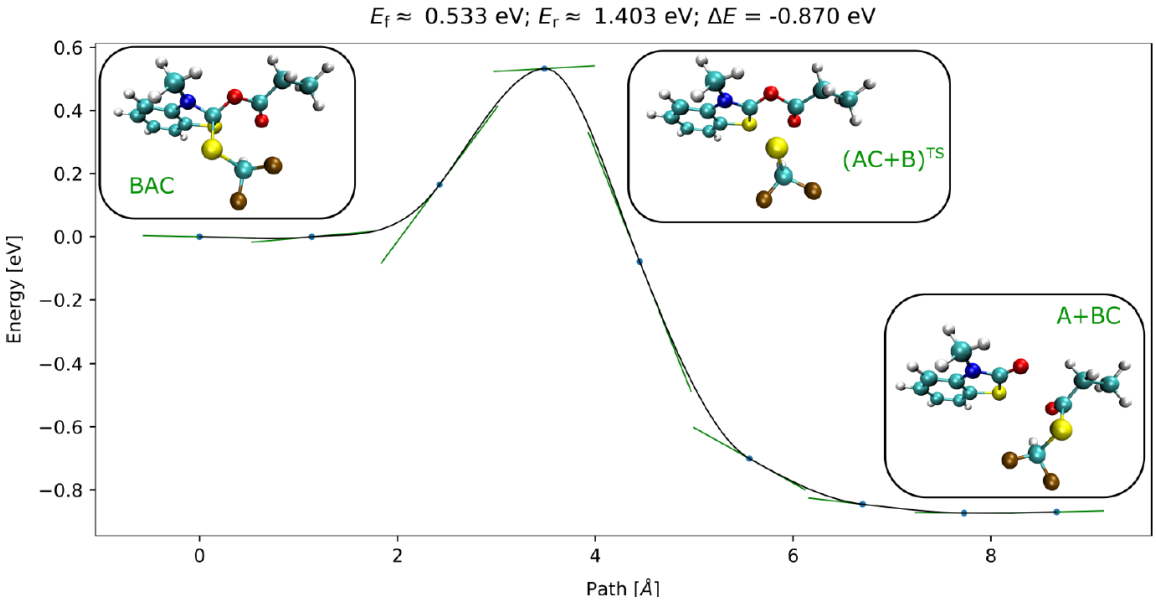


Figure S3. Calculated energy profile for concerted **Path II** (X = H).

The energy barriers for both pathways were considerably lower for the trifluoromethylthiolation reaction compared to the difluoromethylthiolation (E_f = 1.176 eV for **Path I**, E_f = 0.225 eV for **Path II**, Figures S4 and S5). A concerted mechanism was again found to be more energetically favoured than a true stepwise pathway although a more asynchronous, non-cyclic transition state was identified for this process.

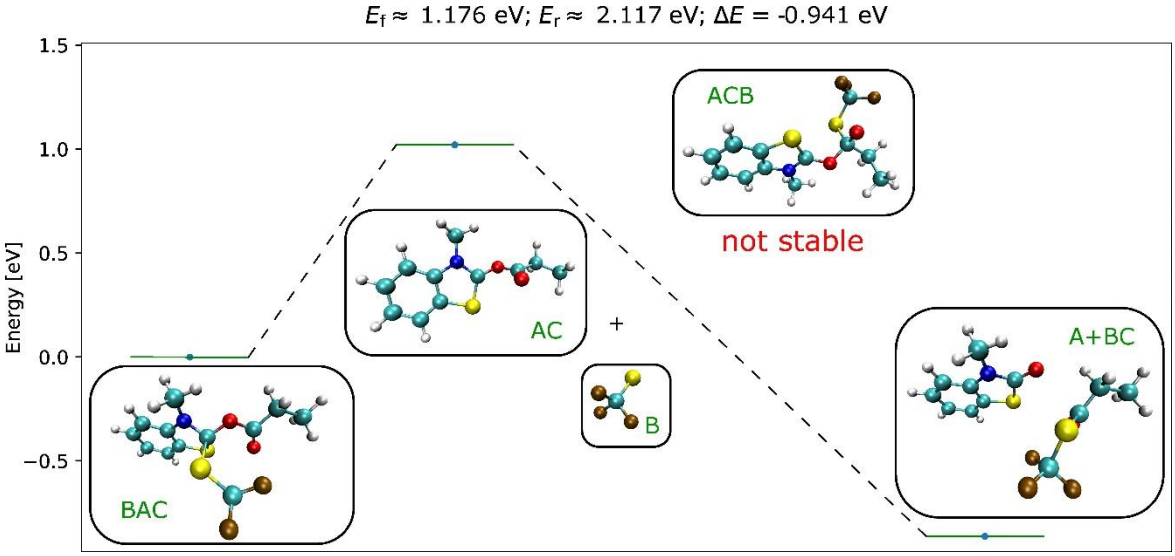


Figure S4. Calculated energy profile for stepwise **Path I** (X = F).

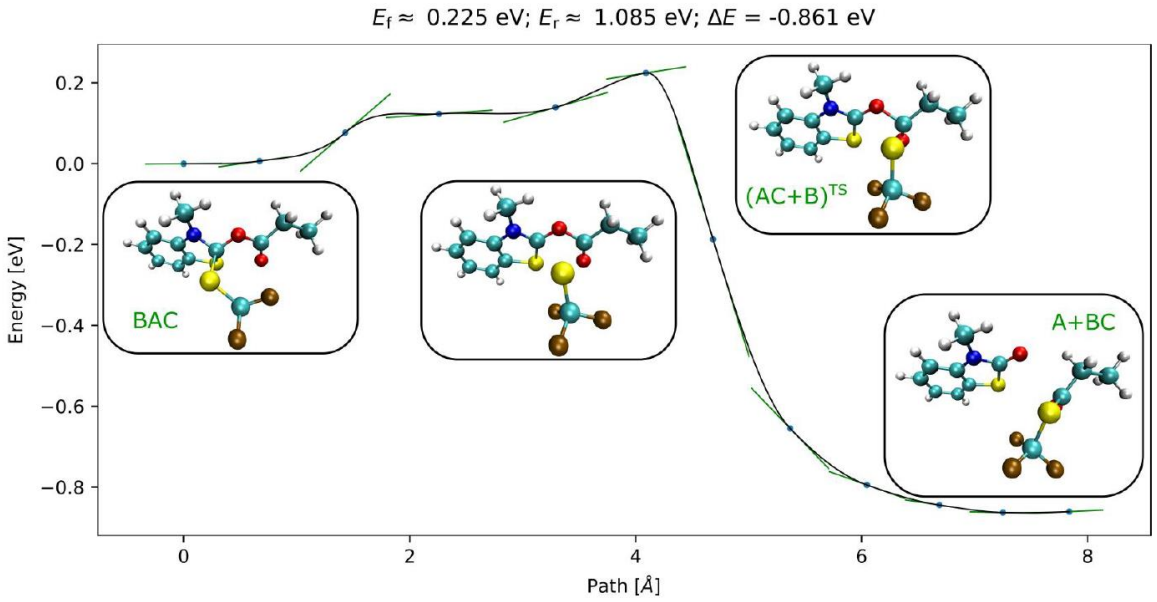


Figure S5. Calculated energy profile for concerted **Path II** (X = F).

Comparison of SCF energies and stationary point characters (in atomic units):
(Note: NEB reoptimizes geometries at start, thus slight differences occur between methods)

PATH I, X=H

Molecule	Energy/E_h	# of img. Freq.
BAC	-1665.58786736	0
B	-636.403816190	0
AC	-1029.12977234	0
A+BC	-1665.62889589	0

PATH I, X=F

Molecule	Energy	
BAC	-1764.76296551	0
B	-735.589966118	0
AC	-1029.12977234	0
A+BC	-1764.79755022	0

PATH II, X=H

Molecule	Energy	
BAC	-1665.5878208	
(AC+B)^TS/NEB	-1665.5684059	
A+BC	-1665.619422	
(AC+B)^TS/QST3	-1665.57491093	1

PATH II, X=F

Molecule	Energy	
BAC	-1764.7568848	
(AC+B)^TS/NEB	-1764.748627	
A+BC	-1764.7885121	
(AC+B)^TS/QST3	-1764.75454173	1

Geometries of minima, pre-NEB optimization:

X=H

Compound BAC

C	-3.290590	0.291474	1.756902
C	-2.170035	-0.051441	1.009563
C	-2.294152	-0.601145	-0.281344
C	-3.559775	-0.792687	-0.840172
C	-4.689939	-0.447434	-0.084363
C	-4.562813	0.087190	1.199972
H	-5.452195	0.356328	1.773271
H	-5.682329	-0.594096	-0.516443
H	-3.671329	-1.201384	-1.844780
N	-1.070532	-0.918902	-0.865310
C	-0.980176	-1.390393	-2.236882
H	-1.331115	-0.633125	-2.960017
H	0.060629	-1.648465	-2.460252
H	-1.592567	-2.296521	-2.352547
C	0.042321	-0.291652	-0.244891
S	0.392015	1.306727	-1.246501
C	1.560549	2.220750	-0.191683
F	2.850558	1.927150	-0.501685
F	1.387794	3.542483	-0.432969
H	1.386760	2.002245	0.871452
S	-0.470536	0.063901	1.501648
O	1.146397	-1.160929	-0.358906
C	2.245100	-1.007437	0.425996
O	2.289625	-0.208642	1.328068
C	3.341566	-1.946427	0.007710
C	4.565992	-1.873380	0.909597
H	5.343888	-2.564327	0.554274
H	4.984701	-0.856268	0.920955
H	4.312161	-2.142574	1.945743
H	3.588198	-1.691026	-1.037559
H	2.912041	-2.961298	-0.032636
H	-3.181807	0.715317	2.757304

Compound B

S	0.395972	1.277296	-1.236932
C	1.506594	2.187780	-0.232646
F	2.862468	1.931876	-0.494603
F	1.418716	3.579965	-0.394063
H	1.393930	2.022433	0.856853

Compound AC

C	-3.341657	0.356729	1.722932
C	-2.231813	-0.150036	1.042593
C	-2.351434	-0.660709	-0.260221
C	-3.582774	-0.680992	-0.921701
C	-4.687864	-0.175863	-0.239913
C	-4.570197	0.336424	1.064587
H	-5.454601	0.725748	1.571931
H	-5.662536	-0.178522	-0.730749

H	-3.677563	-1.075718	-1.933083
N	-1.120365	-1.112926	-0.757681
C	-0.977550	-1.694325	-2.095768
H	-1.292841	-0.953661	-2.842311
H	0.068541	-1.966238	-2.259166
H	-1.611510	-2.588132	-2.165308
C	-0.116460	-0.961356	0.102080
S	-0.570165	-0.253167	1.616038
O	1.088607	-1.348751	-0.261159
C	2.213955	-1.217674	0.600969
O	2.077003	-0.755683	1.690229
C	3.437378	-1.721859	-0.086963
C	4.680841	-1.652713	0.790066
H	5.550168	-2.028899	0.233564
H	4.890185	-0.618810	1.100549
H	4.560336	-2.263272	1.696838
H	3.545971	-1.131211	-1.013581
H	3.217794	-2.749561	-0.423704
H	-3.248720	0.755808	2.733821

Compound A+BC

C	-3.077040	0.562930	1.725452
C	-1.984494	-0.079182	1.143070
C	-2.041837	-0.557956	-0.177431
C	-3.197085	-0.396632	-0.947024
C	-4.291416	0.238752	-0.359495
C	-4.235722	0.710854	0.961672
H	-5.105344	1.207506	1.396085
H	-5.203103	0.376388	-0.943868
H	-3.243066	-0.745311	-1.978417
N	-0.840583	-1.157481	-0.572072
C	-0.582067	-1.608668	-1.934527
H	-0.312118	-0.731459	-2.542816
H	0.252319	-2.316437	-1.925618
H	-1.476935	-2.103748	-2.327372
C	0.144199	-1.016940	0.324636
S	-0.400892	-0.366869	1.854812
O	1.257320	-1.719028	0.159659
H	-3.024266	0.941281	2.747555
S	1.498372	1.098749	-0.950824
C	0.692821	2.321946	0.049087
F	1.108809	3.605509	-0.232900
F	-0.682970	2.345336	-0.149506
H	0.839784	2.170181	1.132772
C	2.414352	-1.310444	0.860567
O	2.318394	-0.779364	1.926140
C	3.645155	-1.716090	0.116772
C	4.901291	-1.056517	0.670337
H	5.786454	-1.398040	0.115543
H	4.827799	0.036829	0.571508
H	5.042452	-1.296129	1.734282
H	3.480577	-1.470743	-0.943149
H	3.697854	-2.819166	0.169778

X=F

Compound BAC

C	-2.862794	0.195536	2.032945
C	-1.768583	-0.029716	1.204708
C	-1.939576	-0.361778	-0.152110
C	-3.223255	-0.461405	-0.693762
C	-4.325388	-0.238352	0.143400
C	-4.152629	0.085677	1.492049
H	-5.021304	0.260302	2.130038
H	-5.332374	-0.315375	-0.272528
H	-3.367717	-0.705527	-1.746503
N	-0.740944	-0.559563	-0.827437
C	-0.693710	-0.880137	-2.242724
H	-1.112772	-0.062019	-2.849704
H	0.346966	-1.046390	-2.539478
H	-1.262928	-1.801827	-2.436122
C	0.426667	-0.216943	-0.121725
S	1.360039	1.307425	-0.881024
C	0.022858	2.536312	-0.923222
F	-0.487638	2.823631	0.279220
F	0.536661	3.662445	-1.433210
F	-1.011879	2.174060	-1.702447
S	-0.055855	0.042753	1.638378
O	1.386093	-1.245597	-0.302874
C	2.503679	-1.294418	0.481913
O	2.714517	-0.493248	1.355039
C	3.371812	-2.461428	0.097077
C	4.624267	-2.582610	0.954540
H	5.223533	-3.447145	0.634627
H	5.248478	-1.680394	0.872928
H	4.365812	-2.715167	2.015618
H	3.614803	-2.344560	-0.972821
H	2.742536	-3.365651	0.155040
H	-2.718974	0.455149	3.083700

Compound B

S	0.401904	1.287154	-1.285839
C	1.512040	2.196399	-0.303747
F	2.849321	1.944034	-0.535409
F	1.426088	3.568297	-0.433774
F	1.388327	2.003466	1.057380

Compound AC

(See X=H)

Compound A+BC

C	-3.442020	0.444459	1.575093
C	-2.329969	-0.128161	0.954505
C	-2.448248	-0.761370	-0.293135
C	-3.678450	-0.841833	-0.950723
C	-4.787487	-0.270292	-0.326258
C	-4.672241	0.365437	0.921010
H	-5.556112	0.804926	1.387077
H	-5.760069	-0.318526	-0.819498

```
H      -3.771127   -1.331852   -1.919919
N      -1.218054   -1.255851   -0.744950
C      -1.060463   -1.924373   -2.034800
H      -1.399240   -1.251711   -2.834277
H      -0.003910   -2.166505   -2.179853
H      -1.659024   -2.845566   -2.047742
C      -0.199954   -1.030774    0.096079
S      -0.670340   -0.180163    1.544778
O       0.981321   -1.442852   -0.199701
H      -3.349407    0.939254    2.543233
S       2.047674    1.223009   -0.835811
C       2.356278    2.380369    0.468934
F       3.569590    2.228118    1.073891
F       2.334977    3.670010    0.036601
H       1.455480    2.328788    1.485815
C       2.182560   -0.887735    0.576058
O       1.987243   -0.595738    1.721787
C       3.406203   -1.493834   -0.049398
C       4.691712   -0.849569    0.453305
H       5.565428   -1.361817    0.024803
H       4.719572    0.210353    0.167223
H       4.756609   -0.908855    1.549989
H       3.316613   -1.438618   -1.141395
H       3.369898   -2.564439    0.229821
```

Geometries of minima, after NEB optimization:

```
X=H

NEB educt (BAC)

C       -3.29213805       0.29249518       1.75949084
C       -2.17115409      -0.05080312       1.01048027
C       -2.29566847      -0.60144197      -0.28097238
C       -3.56211636      -0.79291408      -0.84039539
C       -4.69253454      -0.44743166      -0.08387825
C       -4.56455947       0.08755116       1.20127827
H       -5.45362147       0.35699452       1.77476561
H       -5.68505118      -0.59405937      -0.51668086
H       -3.67155103      -1.20167922      -1.84602685
N       -1.07129892      -0.92061768      -0.86608697
C       -0.98026884      -1.39139134      -2.23786108
H       -1.33045855      -0.63377823      -2.96092640
H        0.06082296      -1.64944296      -2.46161181
H       -1.59235866      -2.29756145      -2.35475371
C        0.04253440      -0.29267889      -0.24662676
S       -0.46961172       0.06396535       1.49923143
O        1.14823954      -1.16004516      -0.36039866
H       -3.18221533       0.71670619       2.76076539
S        0.39338155       1.30897757      -1.24818930
C        1.56056798       2.22197414      -0.19287376
F        2.85093383       1.92955642      -0.50098847
F        1.39015544       3.54440382      -0.43148738
H        1.38569853       2.00148828       0.86916863
C        2.24656876      -1.00832790       0.42685441
O        2.28718319      -0.21103276       1.33032638
C        3.34376567      -1.94648336       0.00866236
```

C	4.56761945	-1.87395941	0.90979957
H	5.34663329	-2.56454500	0.55559091
H	4.98597484	-0.85672450	0.92190202
H	4.31395736	-2.14268491	1.94610570
H	3.58820941	-1.69187173	-1.03745895
H	2.91277048	-2.96064791	-0.03370480

NEB product (A+BC)

C	-3.31822555	0.21702705	1.70575736
C	-2.18686578	-0.18231399	0.99848488
C	-2.29106667	-0.65080873	-0.32812318
C	-3.53768310	-0.72475861	-0.95513762
C	-4.67152595	-0.33167517	-0.23657395
C	-4.56598500	0.13542067	1.07931567
H	-5.46229063	0.43440487	1.62516263
H	-5.65234755	-0.39672304	-0.71171072
H	-3.62783970	-1.08940685	-1.97920145
N	-1.06354529	-1.02123445	-0.87032277
C	-0.90294964	-1.49615672	-2.23500325
H	-1.27003926	-0.73930375	-2.94525551
H	0.16633182	-1.66692707	-2.40285259
H	-1.45370897	-2.43702355	-2.38959709
C	0.02102633	-0.91659535	-0.02535673
S	-0.51584760	-0.21562032	1.55271573
O	1.16162548	-1.23731122	-0.28478491
H	-3.23132646	0.58009711	2.73112348
S	2.97922122	1.62778868	-0.47821748
C	1.87822757	2.87219193	0.27541528
F	2.51178357	4.06362682	0.38275521
F	0.79265439	3.06195288	-0.50999734
H	1.57070283	2.51717951	1.27106581
C	3.11716613	0.48725418	0.93400050
O	2.56565030	0.67255244	1.98916088
C	4.04869540	-0.66467153	0.64323352
C	5.33311460	-0.56938483	1.47593039
H	5.97752697	-1.43597134	1.26518928
H	5.89755584	0.34489017	1.23329166
H	5.10218892	-0.56035089	2.55223554
H	4.27640071	-0.69718943	-0.43326279
H	3.48444820	-1.57534452	0.89493079

X=F

NEB educt (BAC)

C	-3.30570738	0.21869825	1.77974960
C	-2.18119143	-0.12345295	1.03788648
C	-2.29957709	-0.62181942	-0.27383210
C	-3.56123483	-0.77959274	-0.85253753
C	-4.69419974	-0.43412001	-0.10014503
C	-4.57354308	0.06202445	1.19987856
H	-5.46456804	0.33878358	1.76778993
H	-5.68442460	-0.54626747	-0.54713666
H	-3.67195252	-1.15754192	-1.86945506
N	-1.06715096	-0.91857113	-0.85568181
C	-0.96112833	-1.38635476	-2.22827523
H	-1.30793881	-0.62768815	-2.95155431

```
H        0.08282595      -1.64046665      -2.44011357
H       -1.57120715      -2.29396874      -2.34891001
C        0.02899574      -0.30979535      -0.19768952
S       -0.48937395      -0.04405764       1.55500207
O        1.16405840      -1.10259750      -0.38077273
H       -3.20094746       0.60949576       2.79306817
S        0.28003294       1.38437056      -1.15613892
C        1.57313536       2.31029947      -0.27793035
F        2.79396206       1.75885844      -0.39308412
F        1.63320750       3.52703844      -0.84287709
F        1.33408768       2.47842417       1.02418810
C        2.23240122      -1.04297682       0.46897355
O        2.23359897      -0.35391589       1.45429948
C        3.33960898      -1.94413952      -0.00420613
C        4.57533533      -1.88644270       0.88555293
H        5.34776382      -2.57007808       0.50425215
H        4.99599850      -0.86969870       0.91265872
H        4.33556510      -2.17866587       1.91913544
H        3.56905169      -1.65600598      -1.04459785
H        2.92492632      -2.96578514      -0.06399725

NEB product (A+BC)

C       -3.39982787       0.13181237       1.75582482
C       -2.29791028      -0.35856224       1.05633336
C       -2.41766228      -0.74484775      -0.29507281
C       -3.64436303      -0.65036882      -0.95681363
C       -4.74633825      -0.15968191      -0.25039540
C       -4.62736442       0.22885863       1.08992468
H       -5.49850895       0.61095898       1.62525161
H       -5.71143431      -0.08058022      -0.75494566
H       -3.74449993      -0.95552659      -1.99882310
N       -1.22424432      -1.20942769      -0.83983784
C       -1.10450848      -1.63821712      -2.22320559
H       -1.40713996      -0.82470015      -2.90025606
H       -0.05658973      -1.89335698      -2.41226815
H       -1.73286842      -2.52253056      -2.41311449
C       -0.14669102      -1.24549126       0.01763524
S       -0.65029733      -0.60437244       1.62908902
O        0.96889866      -1.64115657      -0.24840565
H       -3.30679513       0.43300977       2.80131270
S        2.55774529       1.22756121      -0.75498064
C        1.82202678       2.67512868       0.08994105
F        2.70529663       3.31519448       0.85792065
F        1.40277312       3.52481033      -0.85678922
F        0.77503139       2.35619305       0.84908958
C        3.10456098       0.27267391       0.70846267
O        2.87030492       0.62297385       1.83128995
C        3.89614376      -0.95473278       0.32546876
C        5.18369680      -1.06709418       1.14324094
H        5.72947142      -1.98298934       0.87557013
H        5.84760567      -0.20830967       0.96210534
H        4.95745103      -1.10241001       2.21835266
H        4.09469935      -0.94993077      -0.75641619
H        3.22315901      -1.80343600       0.52128992
```

Geometries of transition states (NEB and QST3):

X=H

NEB TS

C	-3.34417413	0.32844652	1.73490334
C	-2.19252890	-0.08859276	1.06476152
C	-2.26134169	-0.61563158	-0.23544187
C	-3.48423907	-0.73828542	-0.90107634
C	-4.63442367	-0.33728450	-0.22201390
C	-4.56727968	0.18798080	1.07989365
H	-5.48512918	0.48361141	1.59138129
H	-5.60490795	-0.44168949	-0.71038217
H	-3.54154029	-1.14828112	-1.90922602
N	-1.00172961	-1.01174953	-0.70519236
C	-0.77962380	-1.48855777	-2.06940665
H	-1.09573824	-0.70141114	-2.76773058
H	0.28657651	-1.68724405	-2.20518426
H	-1.36126779	-2.40366554	-2.24232294
C	-0.02074360	-0.82260908	0.17565149
S	-0.53789530	-0.08732713	1.66441169
O	1.15564304	-1.35246207	-0.04686392
H	-3.28794071	0.73320311	2.74649938
S	1.77546854	1.33703635	-1.32899738
C	1.80008373	2.56765985	-0.05946101
F	3.03181519	3.19553089	0.07414198
F	0.91247193	3.61001093	-0.29308742
H	1.55213046	2.17095726	0.94118440
C	2.28975770	-0.85813913	0.66820743
O	2.13044674	-0.22679427	1.67193708
C	3.53803851	-1.47841727	0.13130637
C	4.75280852	-1.17383148	0.99856537
H	5.61755322	-1.76244605	0.66117152
H	5.01394574	-0.10678272	0.94717536
H	4.55560244	-1.42399360	2.05183733
H	3.66010578	-1.12633480	-0.90369298
H	3.33706996	-2.56284819	0.07175767

QST3 TS

C	-3.077040	0.562930	1.725452
C	-1.984494	-0.079182	1.143070
C	-2.041837	-0.557956	-0.177431
C	-3.197085	-0.396632	-0.947024
C	-4.291416	0.238752	-0.359495
C	-4.235722	0.710854	0.961672
H	-5.105344	1.207506	1.396085
H	-5.203103	0.376388	-0.943868
H	-3.243066	-0.745311	-1.978417
N	-0.840583	-1.157481	-0.572072
C	-0.582067	-1.608668	-1.934527
H	-0.312118	-0.731459	-2.542816
H	0.252319	-2.316437	-1.925618
H	-1.476935	-2.103748	-2.327372
C	0.144199	-1.016940	0.324636
S	-0.400892	-0.366869	1.854812

O	1.257320	-1.719028	0.159659
H	-3.024266	0.941281	2.747555
S	1.498372	1.098749	-0.950824
C	0.692821	2.321946	0.049087
F	1.108809	3.605509	-0.232900
F	-0.682970	2.345336	-0.149506
H	0.839784	2.170181	1.132772
C	2.414352	-1.310444	0.860567
O	2.318394	-0.779364	1.926140
C	3.645155	-1.716090	0.116772
C	4.901291	-1.056517	0.670337
H	5.786454	-1.398040	0.115543
H	4.827799	0.036829	0.571508
H	5.042452	-1.296129	1.734282
H	3.480577	-1.470743	-0.943149
H	3.697854	-2.819166	0.169778

X=F

NEB TS

C	-3.34325916	0.27962382	1.76500626
C	-2.20645800	-0.17049116	1.09022947
C	-2.29206073	-0.66353258	-0.22268947
C	-3.51530026	-0.71126101	-0.89802704
C	-4.64970260	-0.27183126	-0.21671929
C	-4.56695743	0.21472777	1.09936247
H	-5.47286578	0.54484523	1.61110413
H	-5.61945771	-0.31036556	-0.71625299
H	-3.58481217	-1.08699490	-1.91867527
N	-1.04843033	-1.09157573	-0.70070179
C	-0.84720071	-1.54597419	-2.07467536
H	-1.12190736	-0.72815081	-2.75540632
H	0.20698767	-1.79769658	-2.21581409
H	-1.47404106	-2.42655174	-2.26769961
C	-0.05445560	-0.91143261	0.16937382
S	-0.55212327	-0.22948137	1.68466590
O	1.11919483	-1.45377271	-0.08408571
H	-3.27504262	0.66000384	2.78525748
S	1.23692579	1.36333979	-1.41002673
C	1.67912529	2.56006063	-0.20354700
F	2.93906252	2.40446878	0.31652184
F	1.66717695	3.85040706	-0.66409082
F	0.86487325	2.59174776	0.89766093
C	2.25779971	-1.06130584	0.65385739
O	2.13908855	-0.42042932	1.65302803
C	3.48911297	-1.63010828	0.03316161
C	4.73644000	-1.37835062	0.87013003
H	5.59645079	-1.90942233	0.43869687
H	4.97037728	-0.30460853	0.90802396
H	4.59613161	-1.73109197	1.90288351
H	3.56273699	-1.18519928	-0.97366660
H	3.29763037	-2.70530825	-0.12434493

QST3 TS

C	-3.442020	0.444459	1.575093
C	-2.329969	-0.128161	0.954505

C	-2.448248	-0.761370	-0.293135
C	-3.678450	-0.841833	-0.950723
C	-4.787487	-0.270292	-0.326258
C	-4.672241	0.365437	0.921010
H	-5.556112	0.804926	1.387077
H	-5.760069	-0.318526	-0.819498
H	-3.771127	-1.331852	-1.919919
N	-1.218054	-1.255851	-0.744950
C	-1.060463	-1.924373	-2.034800
H	-1.399240	-1.251711	-2.834277
H	-0.003910	-2.166505	-2.179853
H	-1.659024	-2.845566	-2.047742
C	-0.199954	-1.030774	0.096079
S	-0.670340	-0.180163	1.544778
O	0.981321	-1.442852	-0.199701
H	-3.349407	0.939254	2.543233
S	2.047674	1.223009	-0.835811
C	2.356278	2.380369	0.468934
F	3.569590	2.228118	1.073891
F	2.334977	3.670010	0.036601
F	1.455480	2.328788	1.485815
C	2.182560	-0.887735	0.576058
O	1.987243	-0.595738	1.721787
C	3.406203	-1.493834	-0.049398
C	4.691712	-0.849569	0.453305
H	5.565428	-1.361817	0.024803
H	4.719572	0.210353	0.167223
H	4.756609	-0.908855	1.549989
H	3.316613	-1.438618	-1.141395
H	3.369898	-2.564439	0.229821

6 Literature

[1] S. Dix, M. Jakob, M. N. Hopkinson, *Chem. Eur. J.* **2019**, *25*, 7635-7639.

[2] V. V. Levin, A. D. Dilman, P. A. Belyakov, M. I. Struchkova, V. A. Tartakovsky, *J. Fluorine Chem.* **2009**, *130*, 667-670.

[3] V. P. Mehta, M. F. Greaney, *Org. Lett.* **2013**, *15*, 5036-5039.

[4] S. Mukherjee, T. Patra, F. Glorius, *ACS Catal.* **2018**, *8*, 5842-5846.

[5] R. Mao, S. Bera, A. Cheseaux, X. Hu, *Chem. Sci.* **2019**, *10*, 9555-9559.

[6] M. Zhang, J. Chen, Z. Chen, Z. Weng, *Tetrahedron* **2016**, *72*, 3525-3530.

[7] M. M. Kremlev, W. Tyrra, D. Naumann, Y. L. Yagupolskii, *Tetrahedron Lett.* **2004**, *45*, 6101-6104.

[8] S.-H. Guo, X.-L. Zhang, G.-F. Pan, X.-Q. Zhu, Y.-R. Gao, Y.-Q. Wang, *Angew. Chem. Int. Ed.* **2018**, *57*, 1663-1667.

[9] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, Williams, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, D. J. Fox, Wallingford, CT, **2016**.

[10] A. D. Becke, *Phys. Rev. A* **1988**, *38*, 3098-3100.

[11] C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785-789.

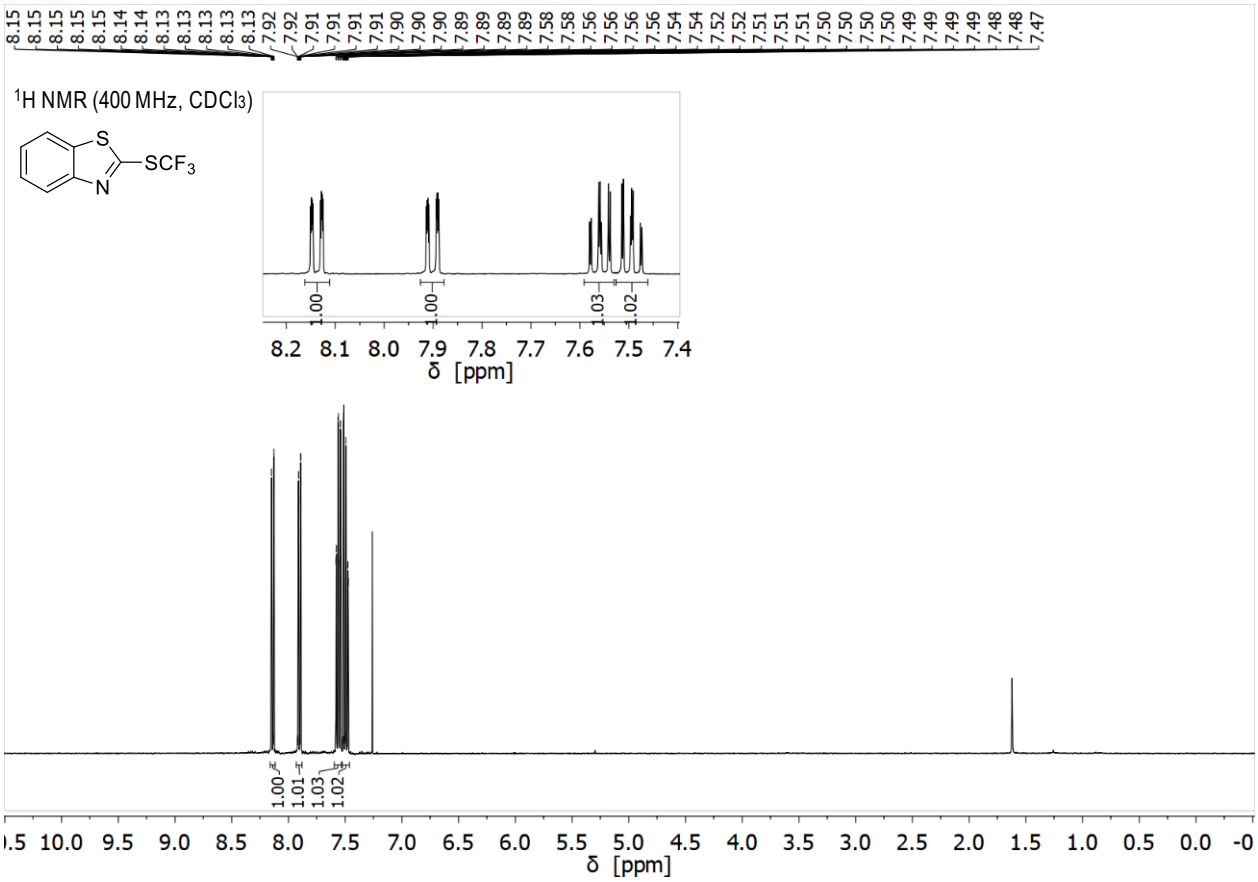
[12] F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297-3305.

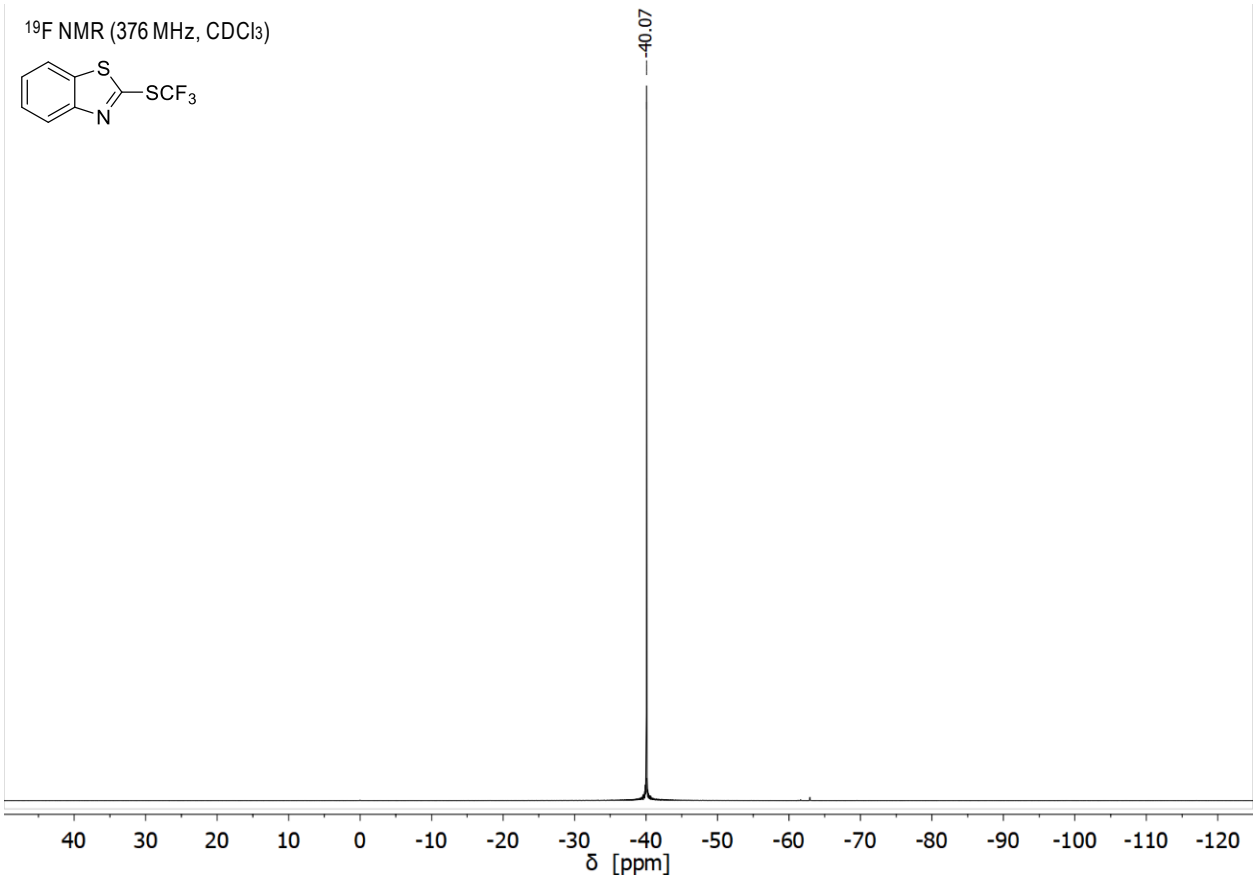
[13] V. Barone, M. Cossi, J. Tomasi, *J. Comput. Chem.* **1998**, *19*, 404-417.

[14] P. Y. Ayala, H. B. Schlegel, *J. Chem. Phys.* **1997**, *107*, 375-384.

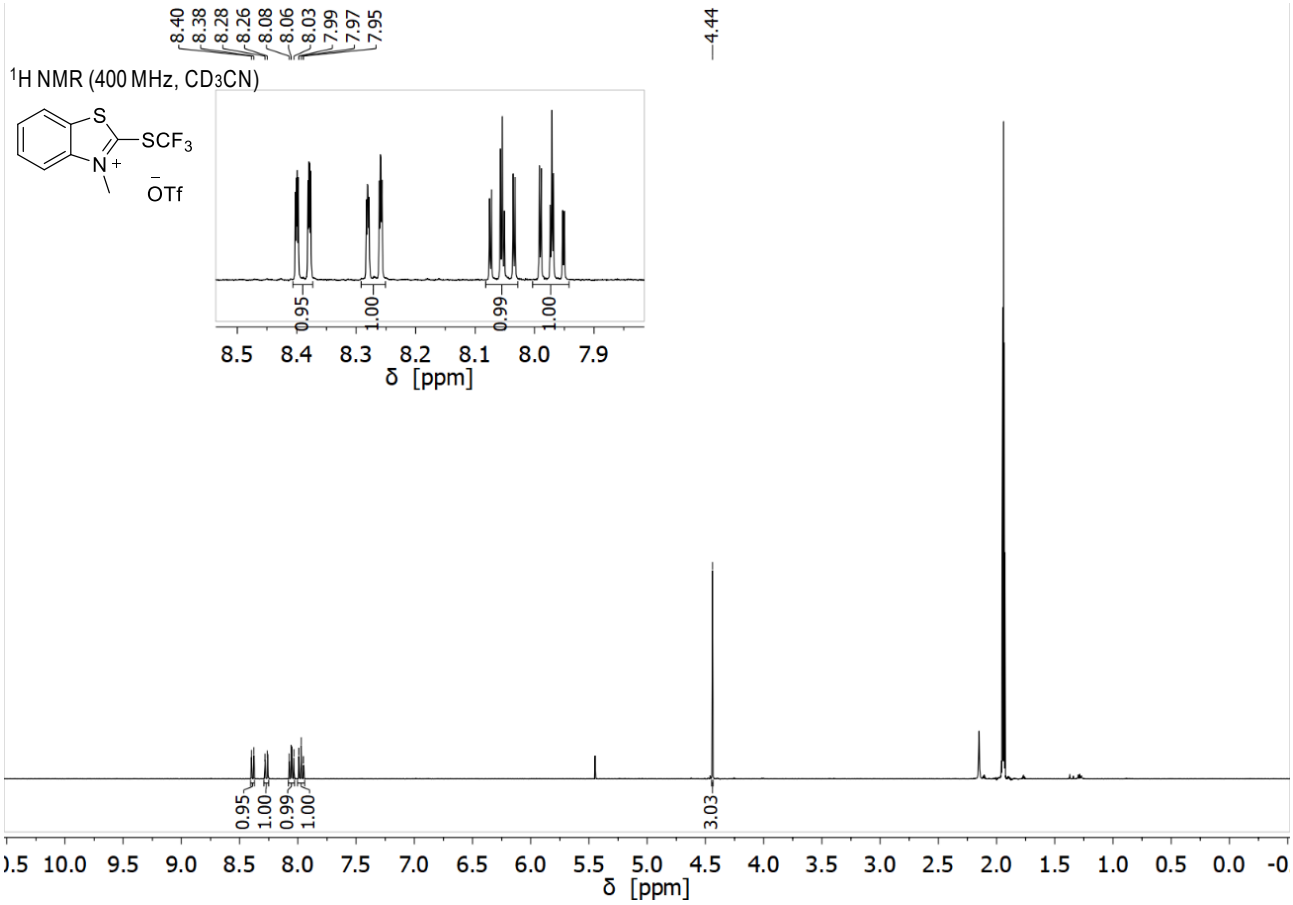
7 NMR Spectra

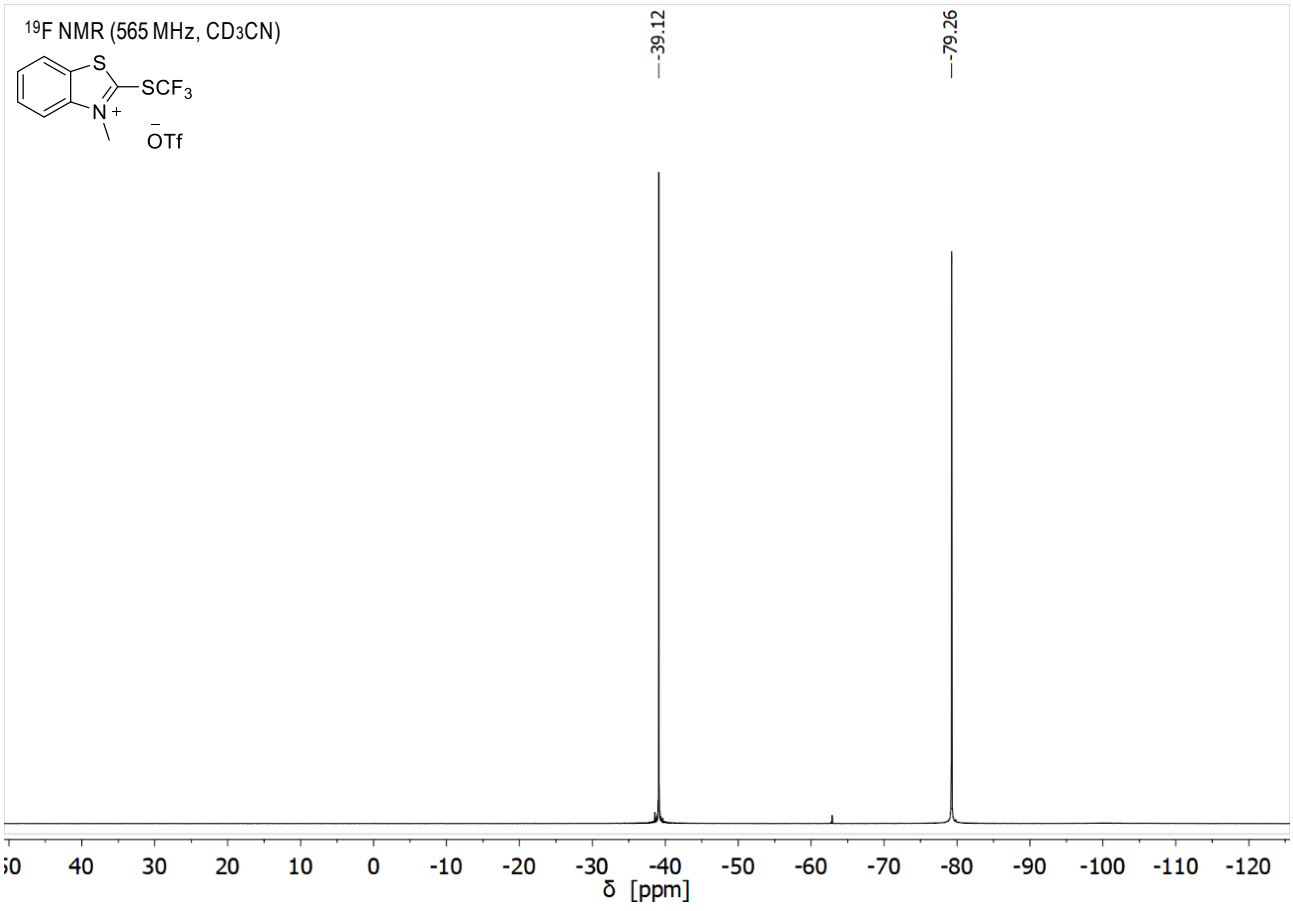
2-((Trifluoromethyl)thio)benzo[d]-thiazole



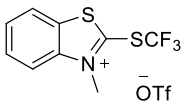


3-methyl-2-((trifluoromethyl)thio)benzo[d]thiazol-3-ium trifluoromethanesulfonate (BT-SCF_3)

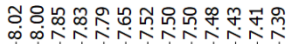


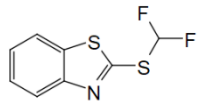


^{13}C NMR (151 MHz, CD_3CN)

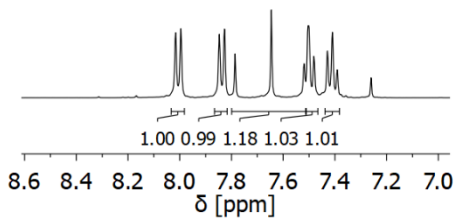


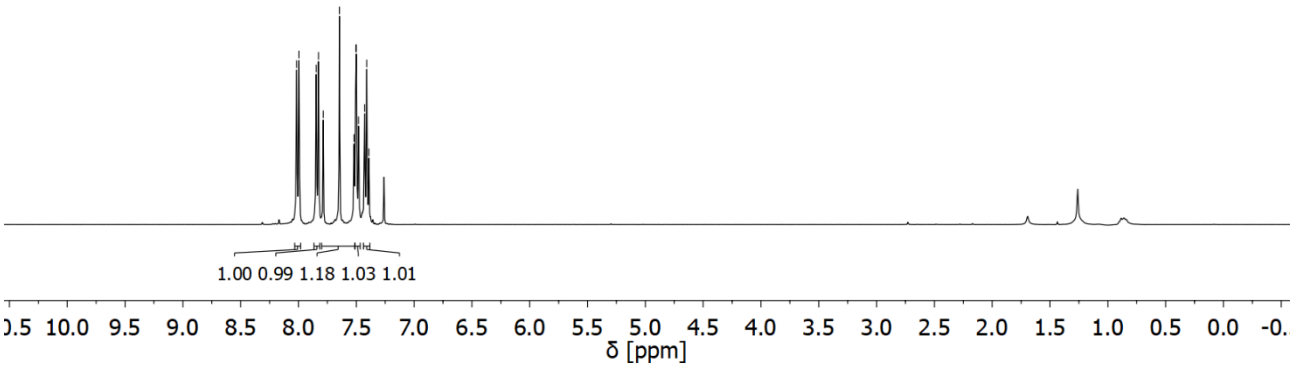
2-((difluoromethyl)thio)benzo[d]thiazole



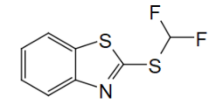


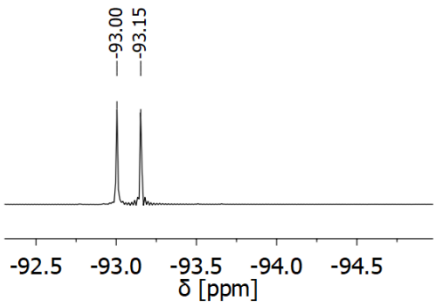
^{1}H NMR (400 MHz, $CDCl_3$)



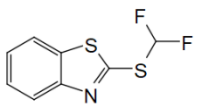


^{19}F NMR (376 MHz, $CDCl_3$)



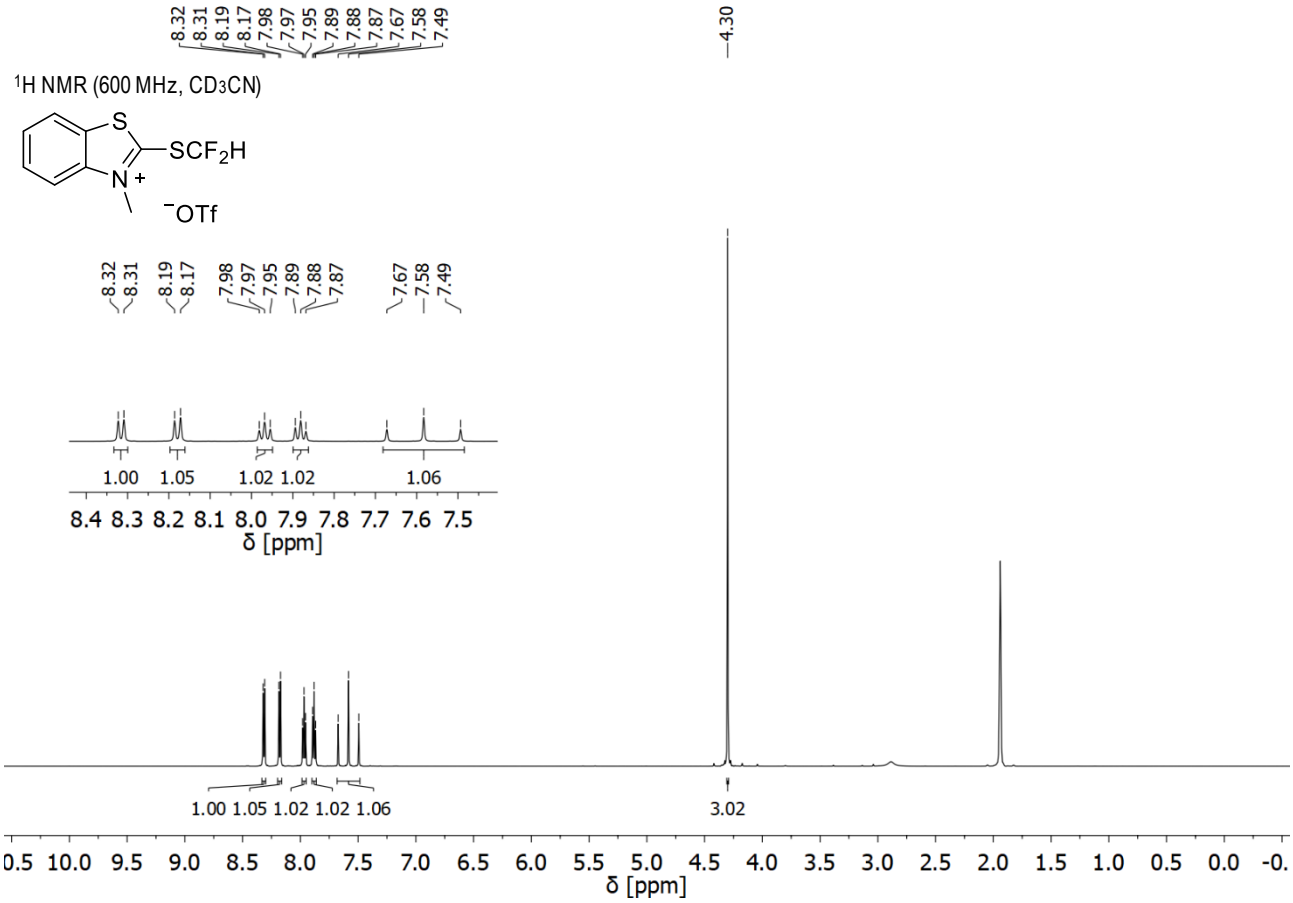


^{13}C NMR (151 MHz, $CDCl_3$)

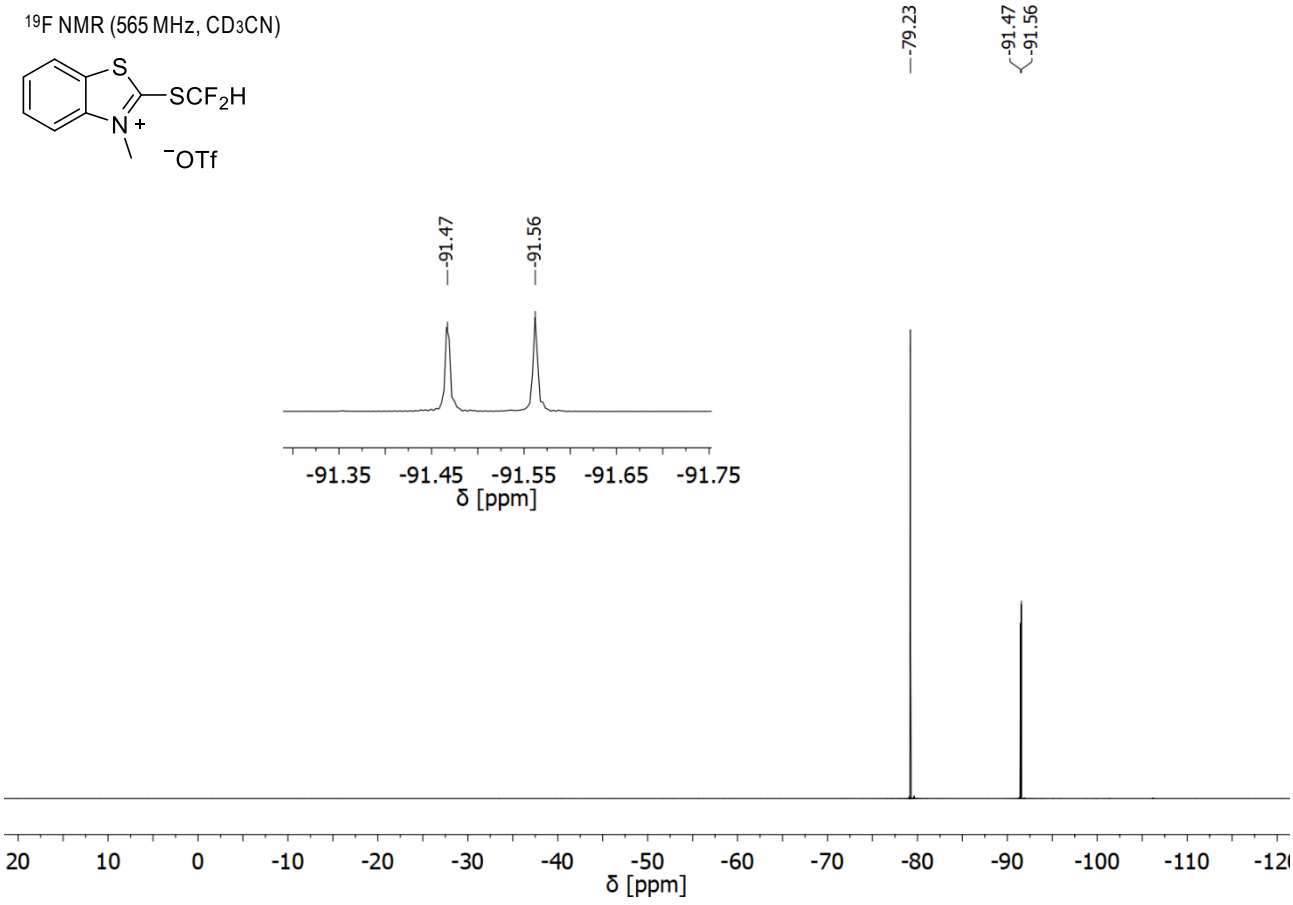


3-methyl-2-((difluoromethyl)thio)benzo[d]thiazol-3-ium trifluoromethanesulfonate (BT-SCF_2H)

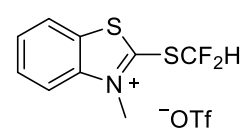
^1H NMR (600 MHz, CD_3CN)



^{19}F NMR (565 MHz, CD_3CN)

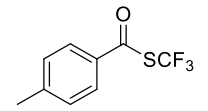


^{13}C NMR (151 MHz, CD_3CN)

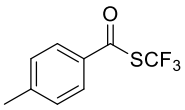


S-(trifluoromethyl) 4-methylbenzothioate **2a**

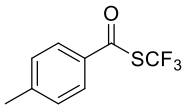
^{1}H NMR (401 MHz, $CDCl_3$)



^{19}F NMR (377 MHz, $CDCl_3$)

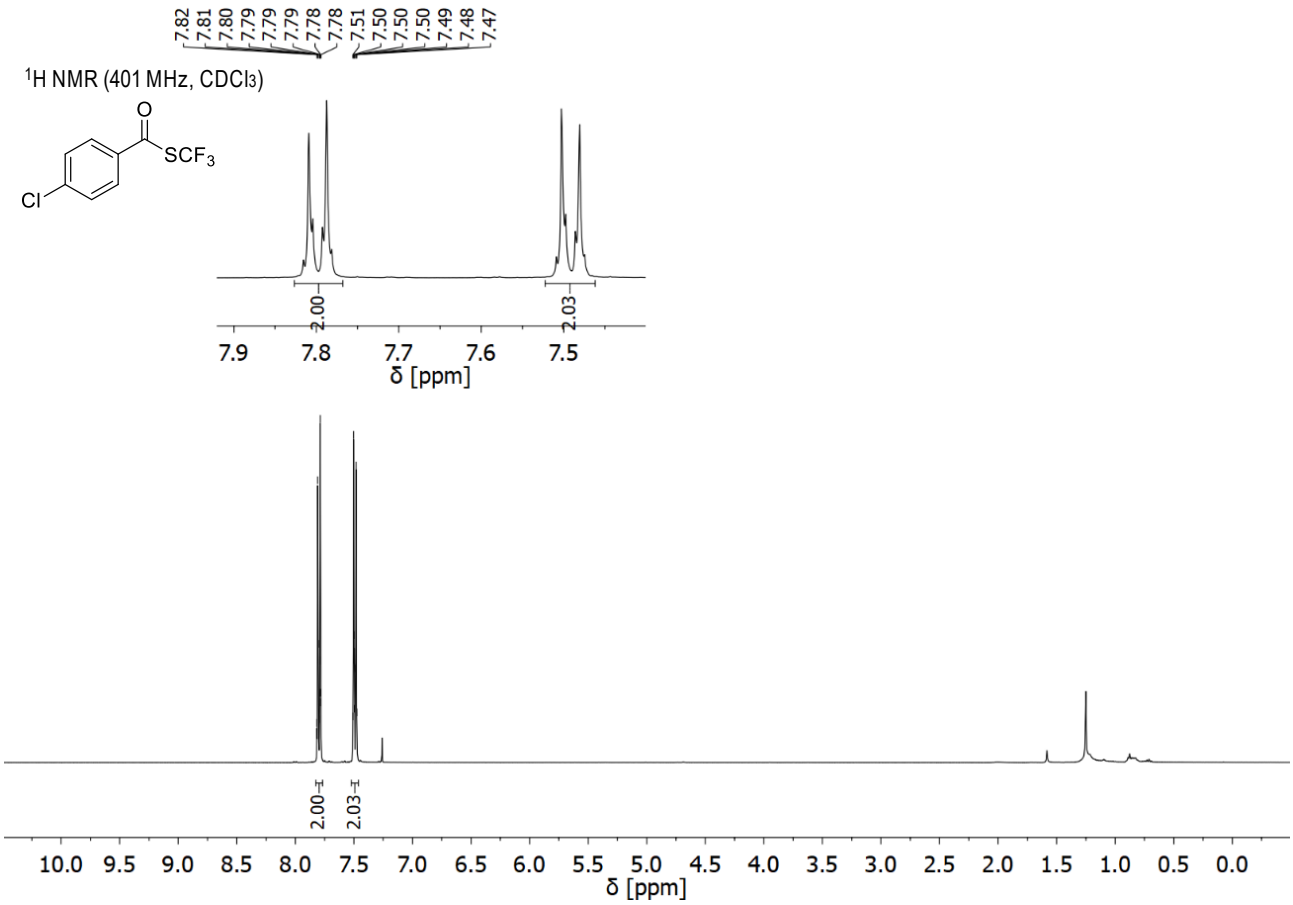


^{13}C NMR (101 MHz, $CDCl_3$)

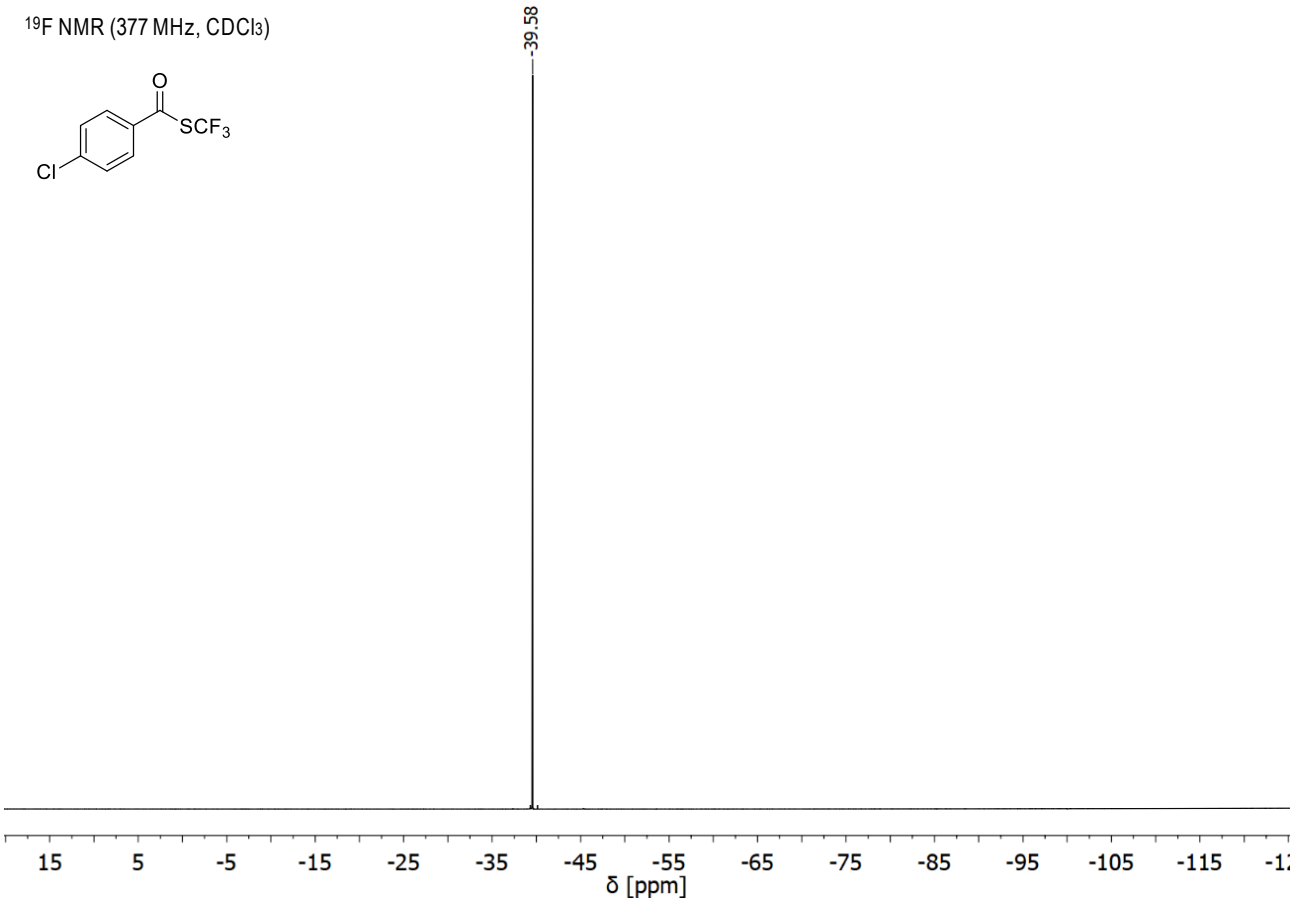


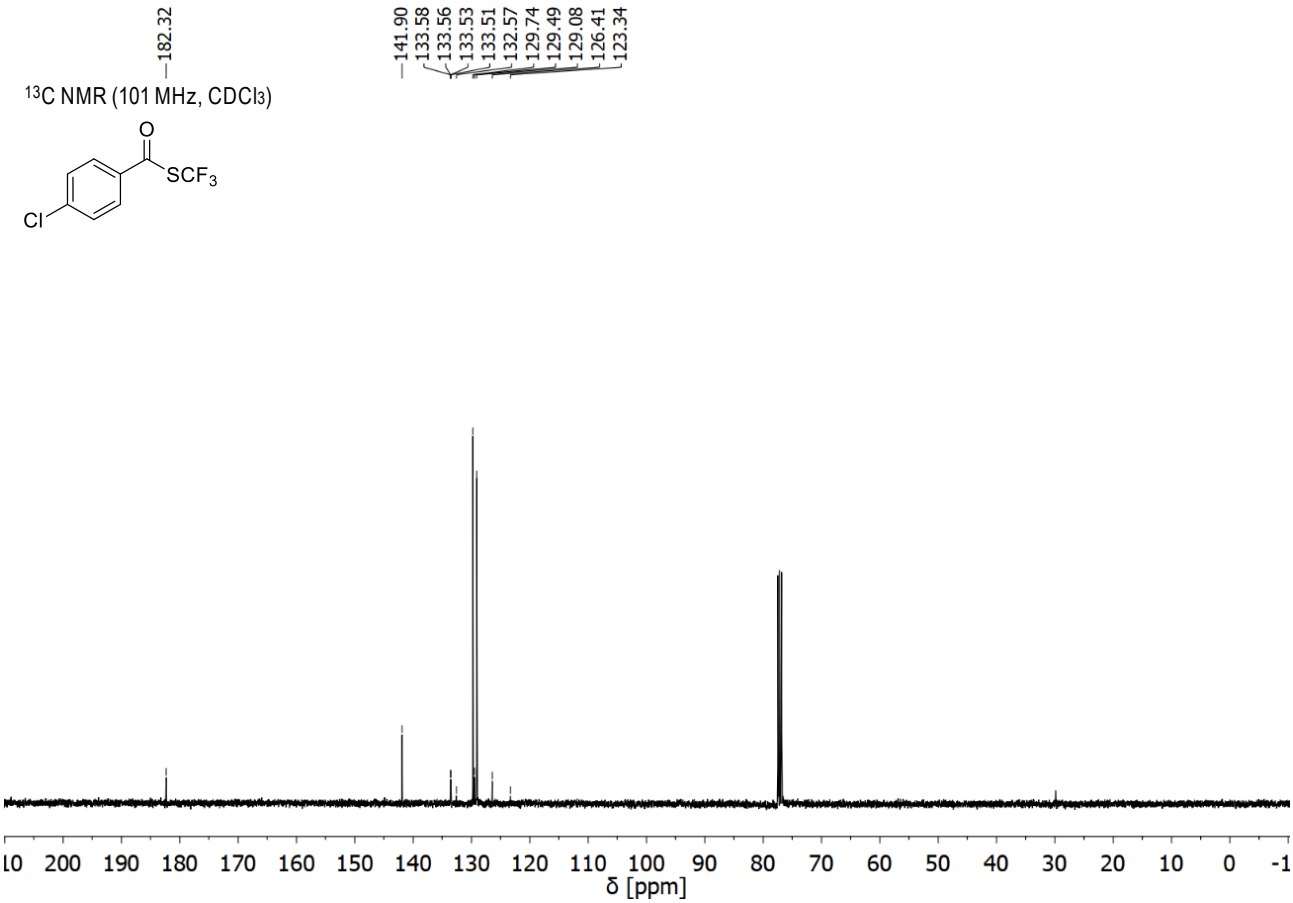
S-(trifluoromethyl) 4-chlorobenzothioate **2b**

^{1}H NMR (401 MHz, $CDCl_3$)

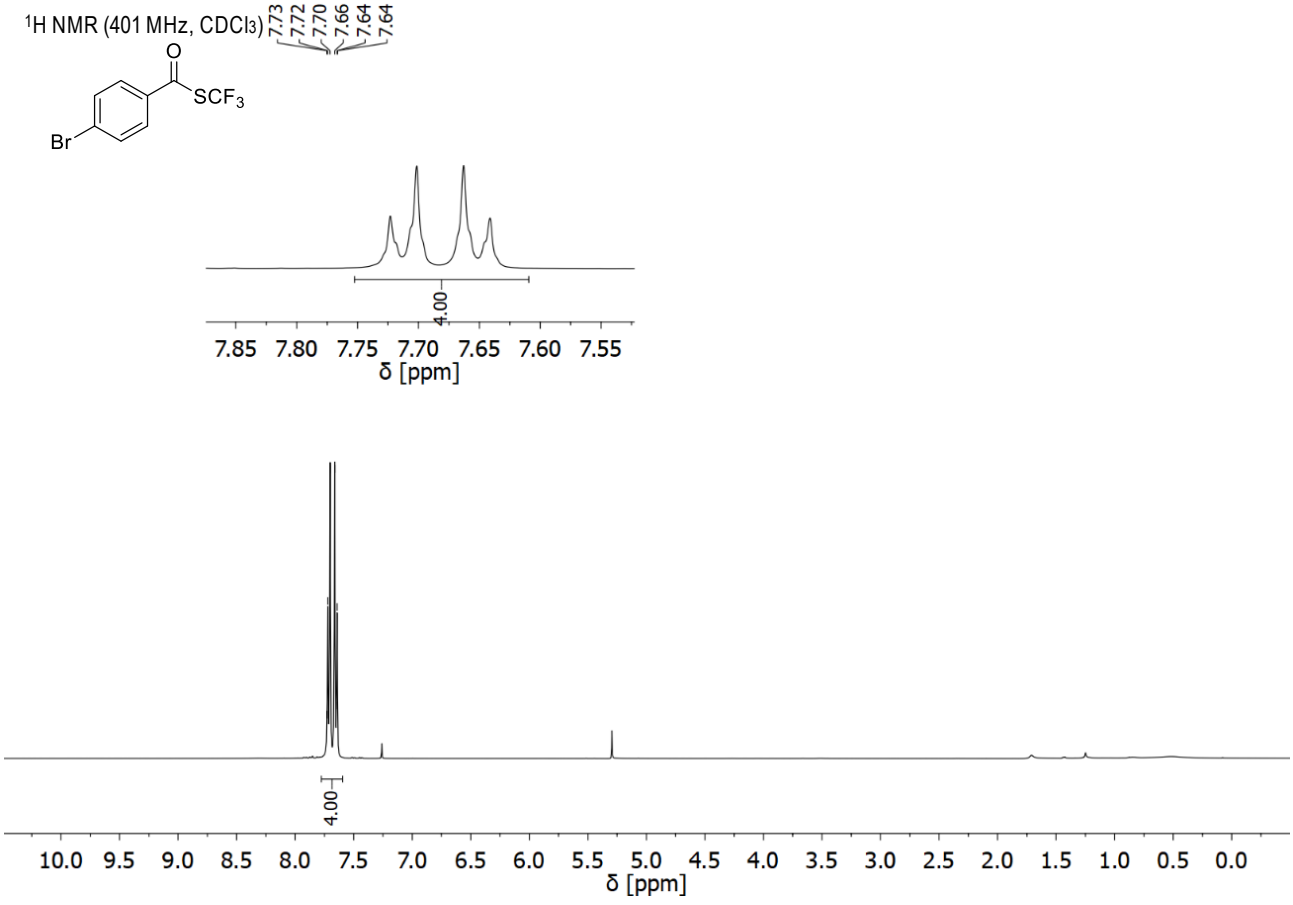


^{19}F NMR (377 MHz, $CDCl_3$)

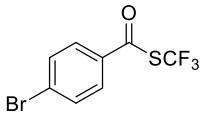


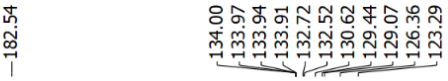


S-(trifluoromethyl) 4-bromobenzothioate **2c**

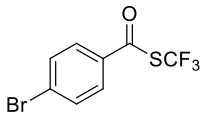


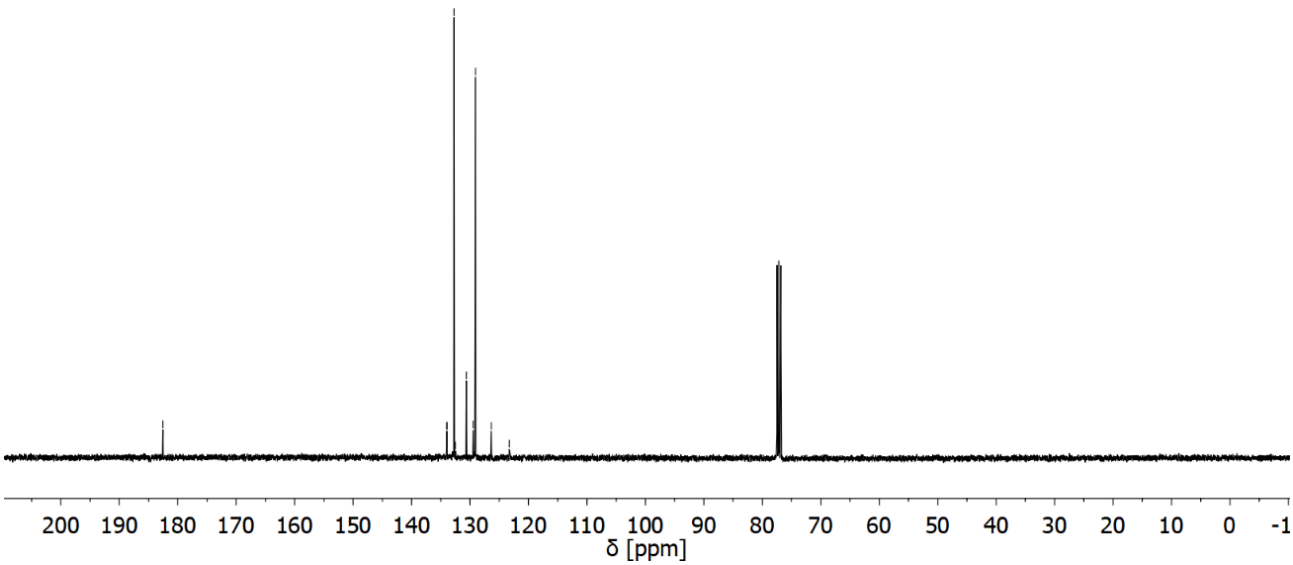
^{19}F NMR (377 MHz, $CDCl_3$)





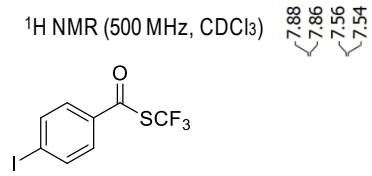
^{13}C NMR (101 MHz, $CDCl_3$)

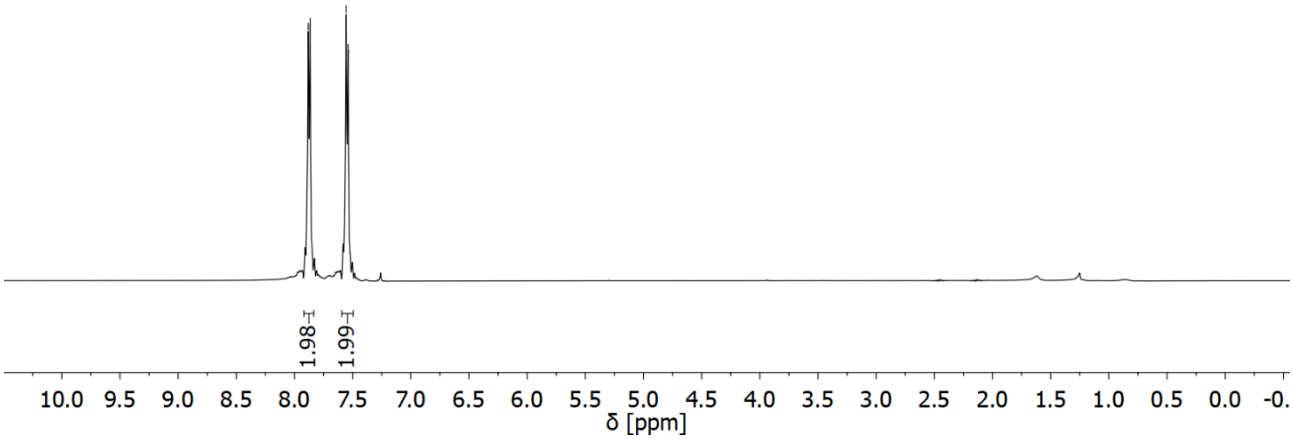




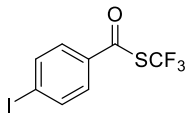
S-(trifluoromethyl) 4-iodobenzothioate **2d**

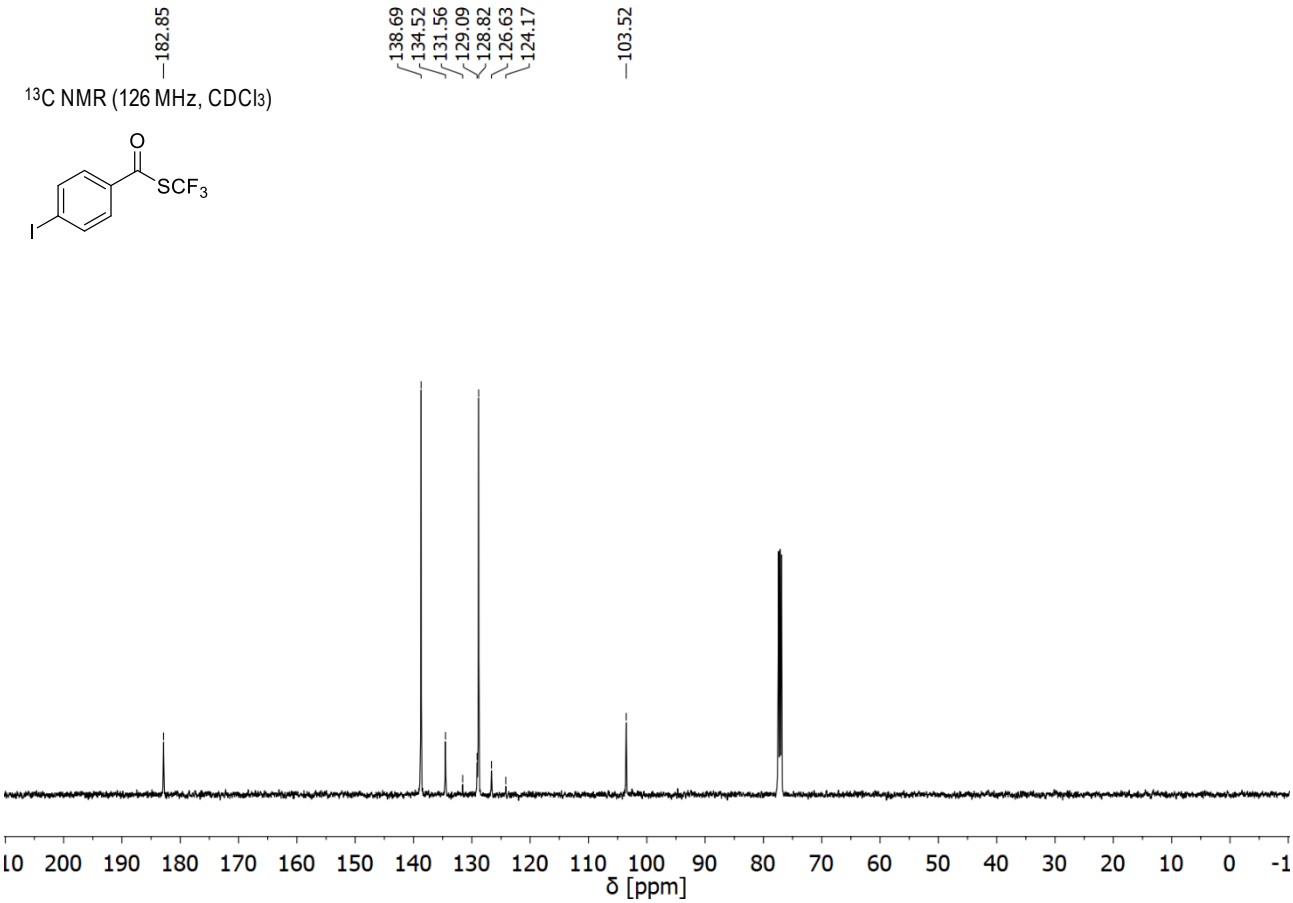
^{1}H NMR (500 MHz, $CDCl_3$)



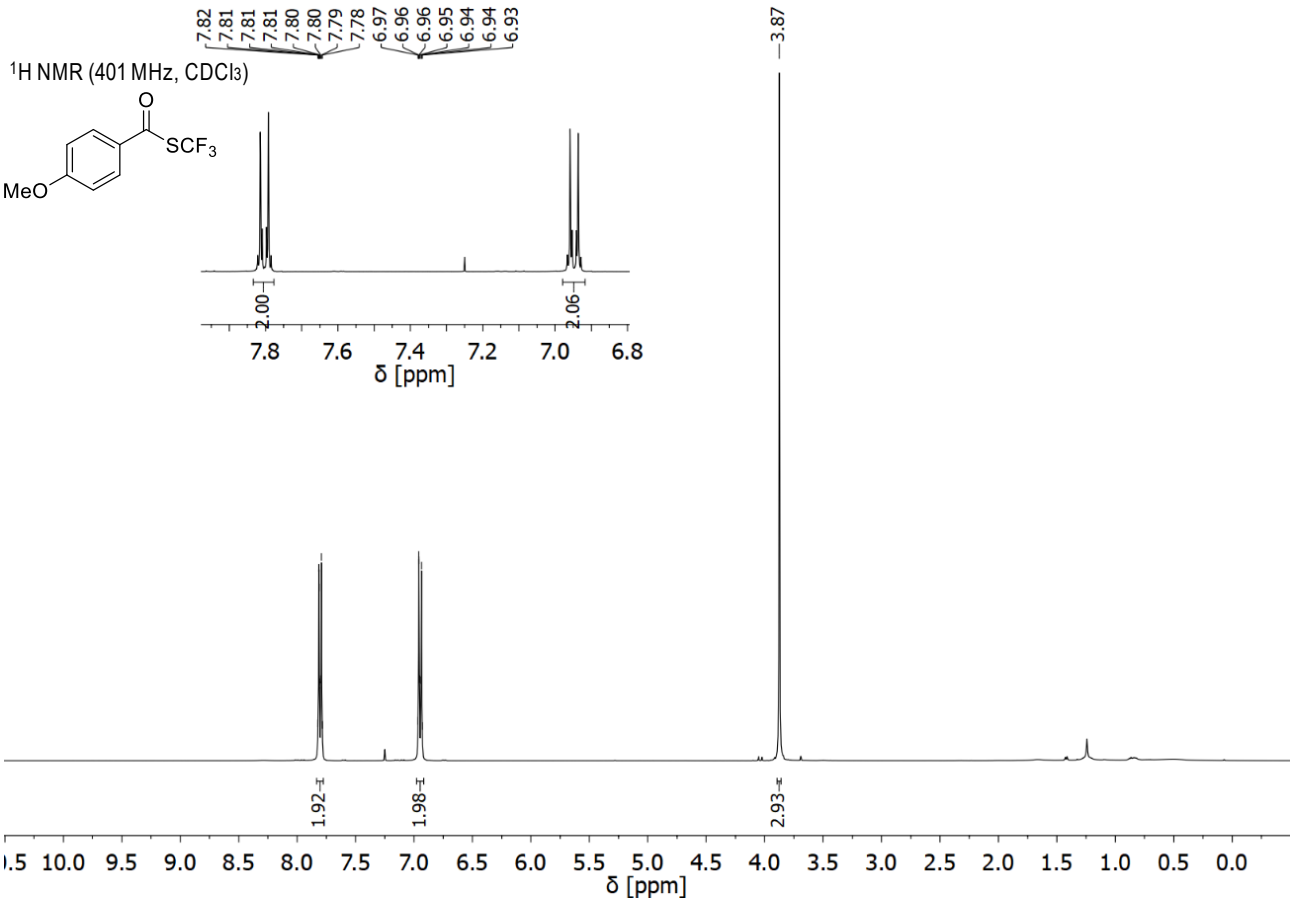


^{19}F NMR (471 MHz, $CDCl_3$)

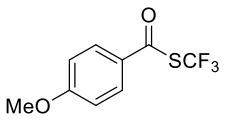




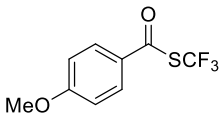
S-(trifluoromethyl) 4-methoxybenzothioate **2e**



^{19}F NMR (377 MHz, CDCl$_3$)

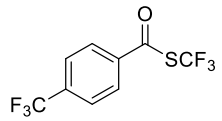


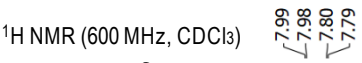
^{13}C NMR (101 MHz, CDCl$_3$)

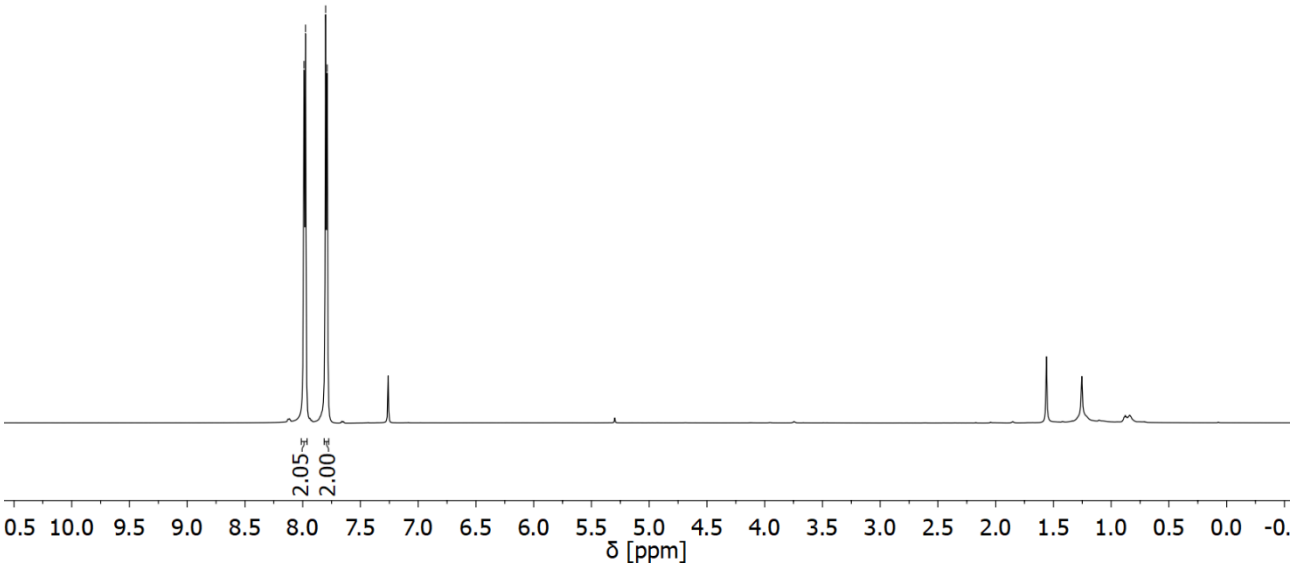


S-(trifluoromethyl) 4-(trifluoromethyl)benzothioate **2f**

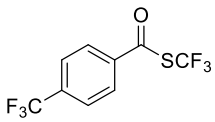
^{1}H NMR (600 MHz, $CDCl_3$)

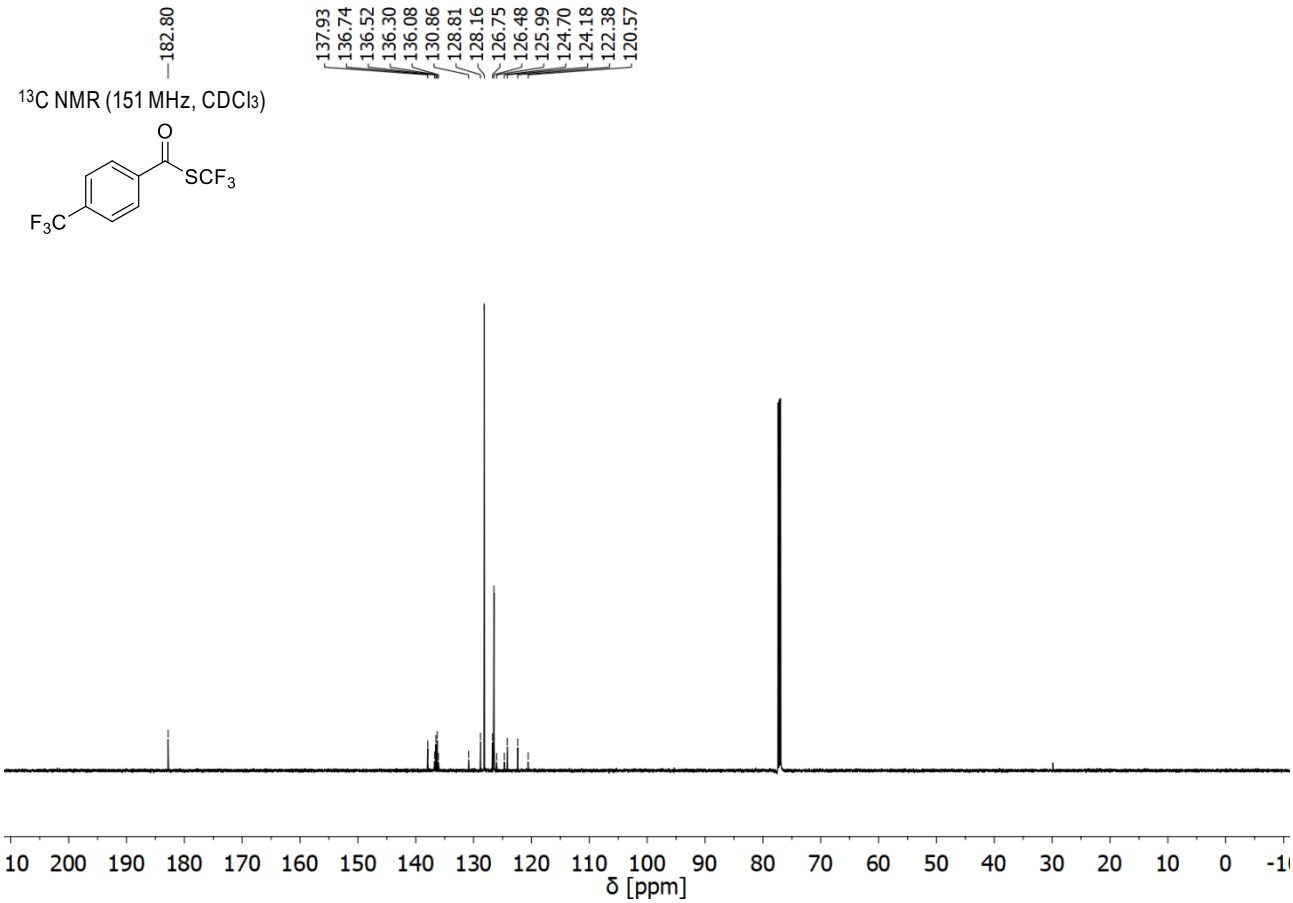




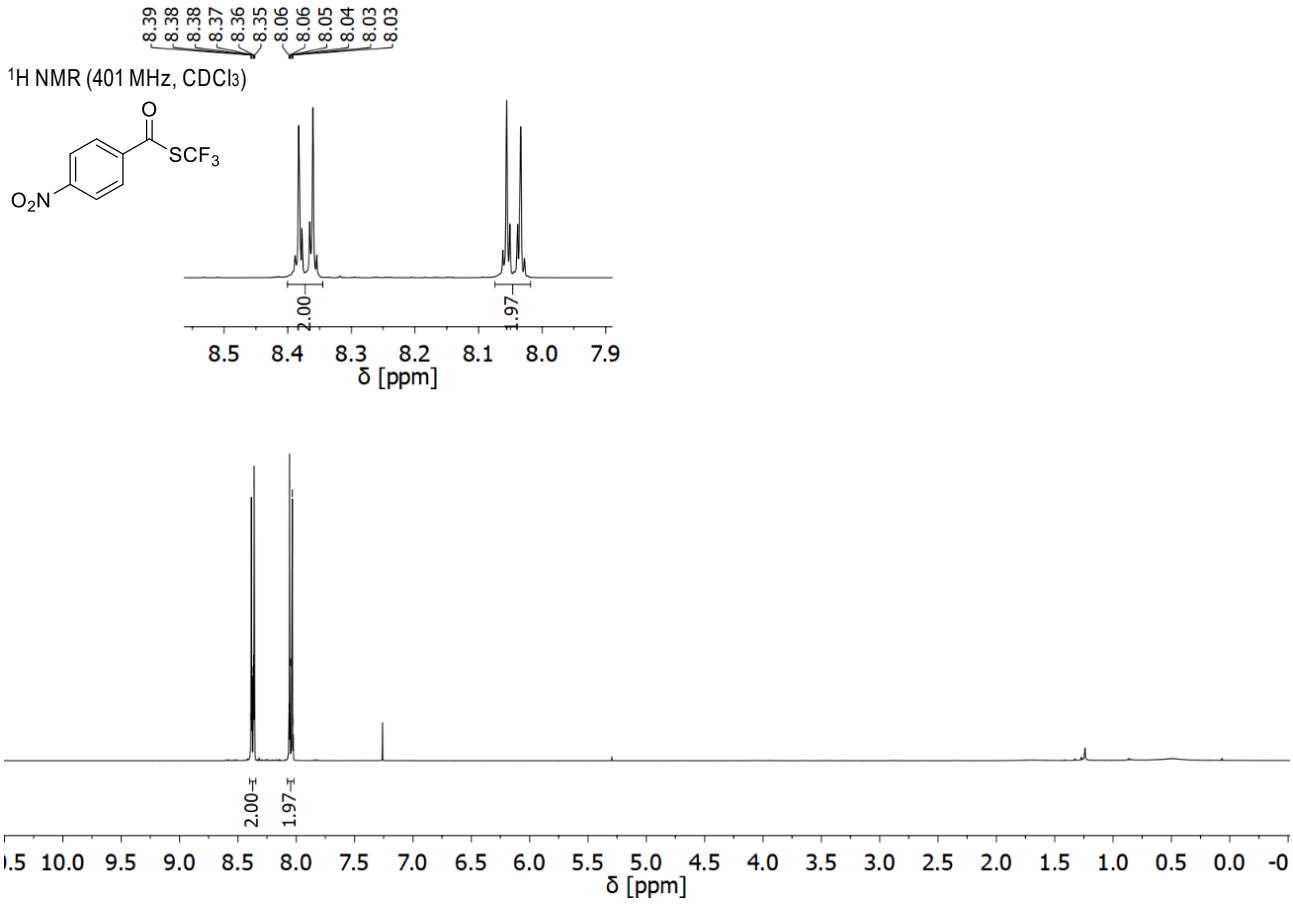


^{19}F NMR (565 MHz, $CDCl_3$)

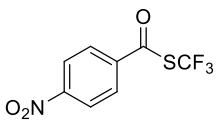




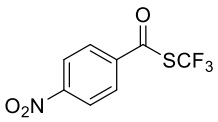
S-(trifluoromethyl) 4-nitrobenzothioate **2g**



^{19}F NMR (377 MHz, CDCl$_3$)

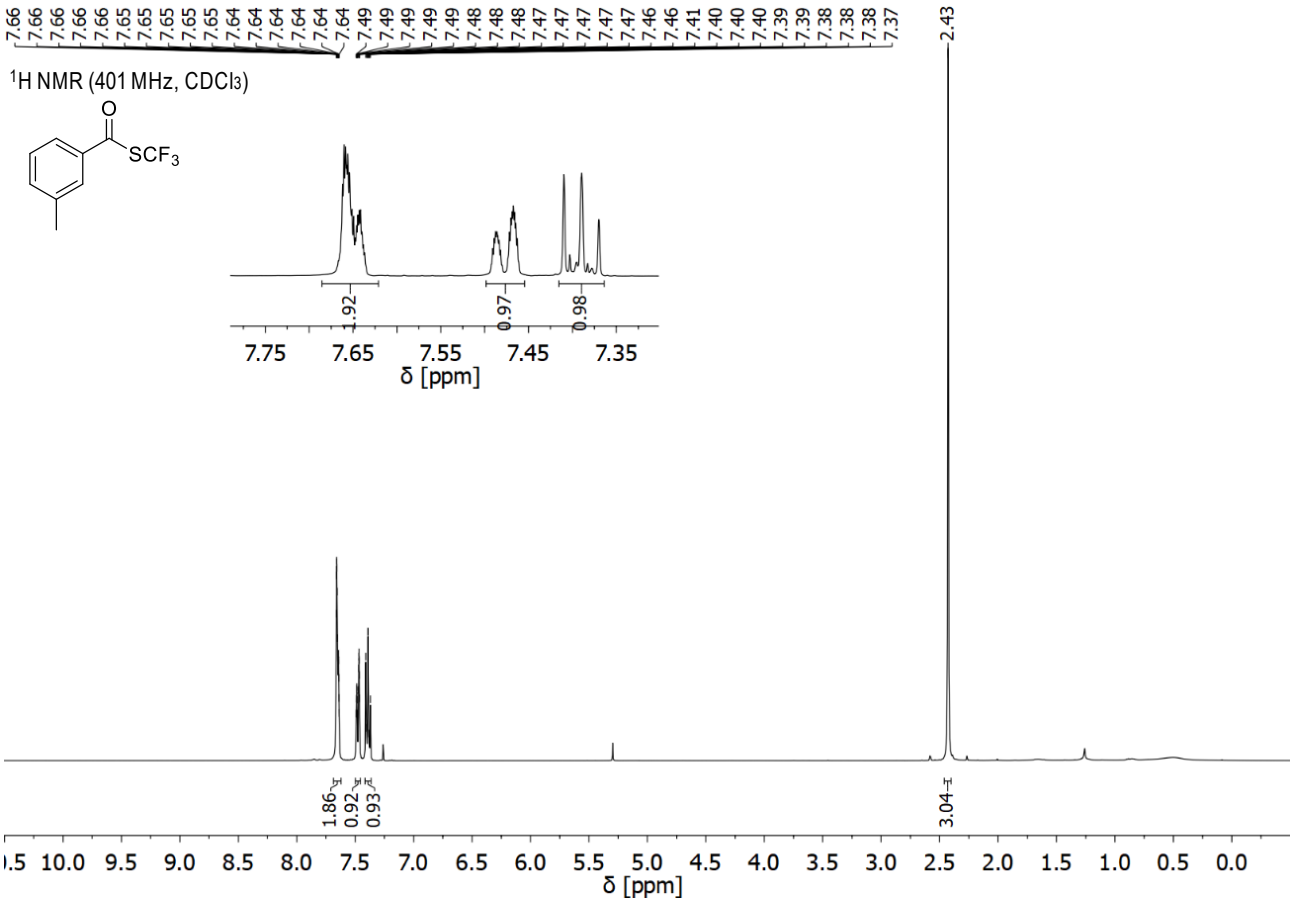


^{13}C NMR (101 MHz, CDCl$_3$)

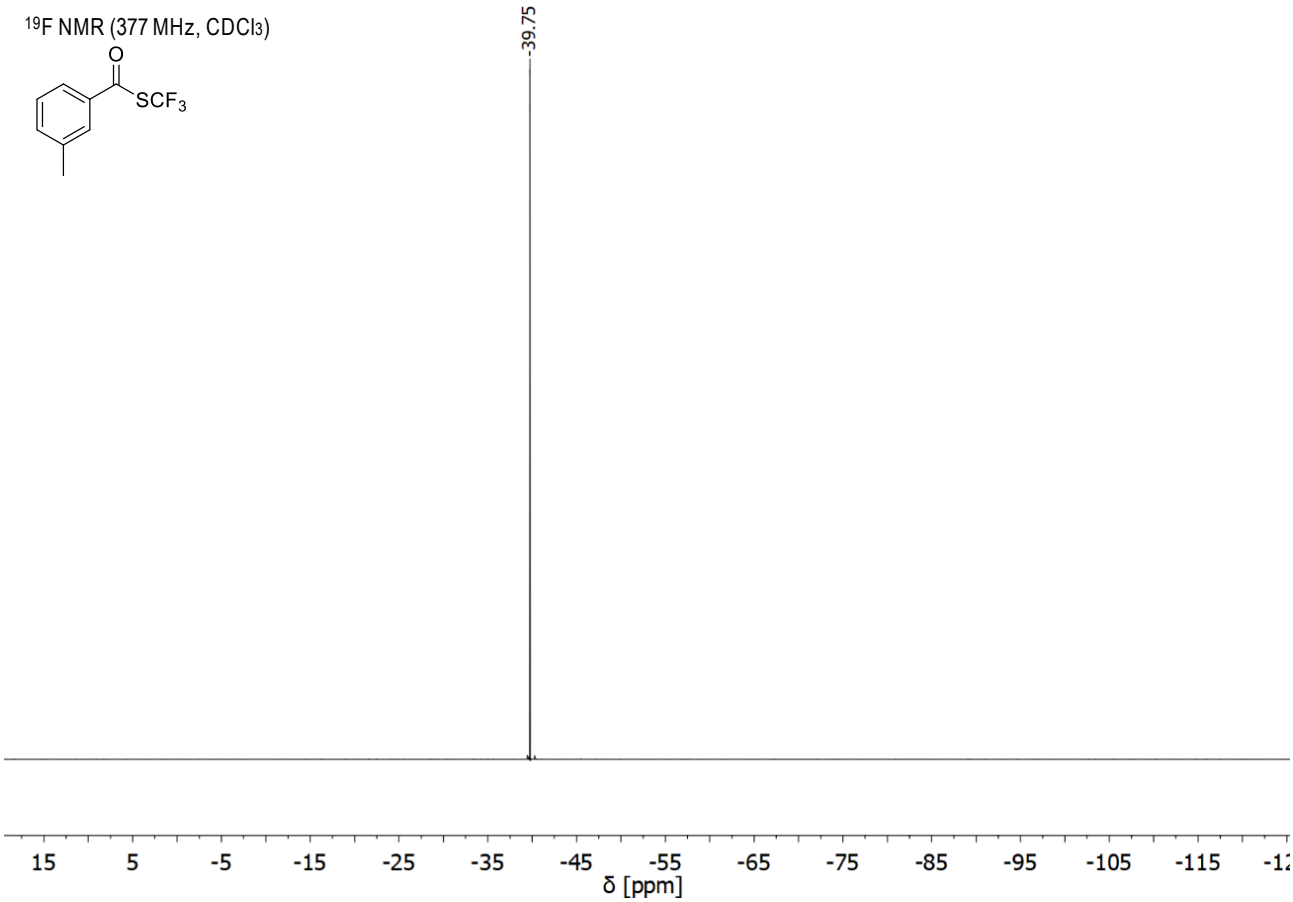


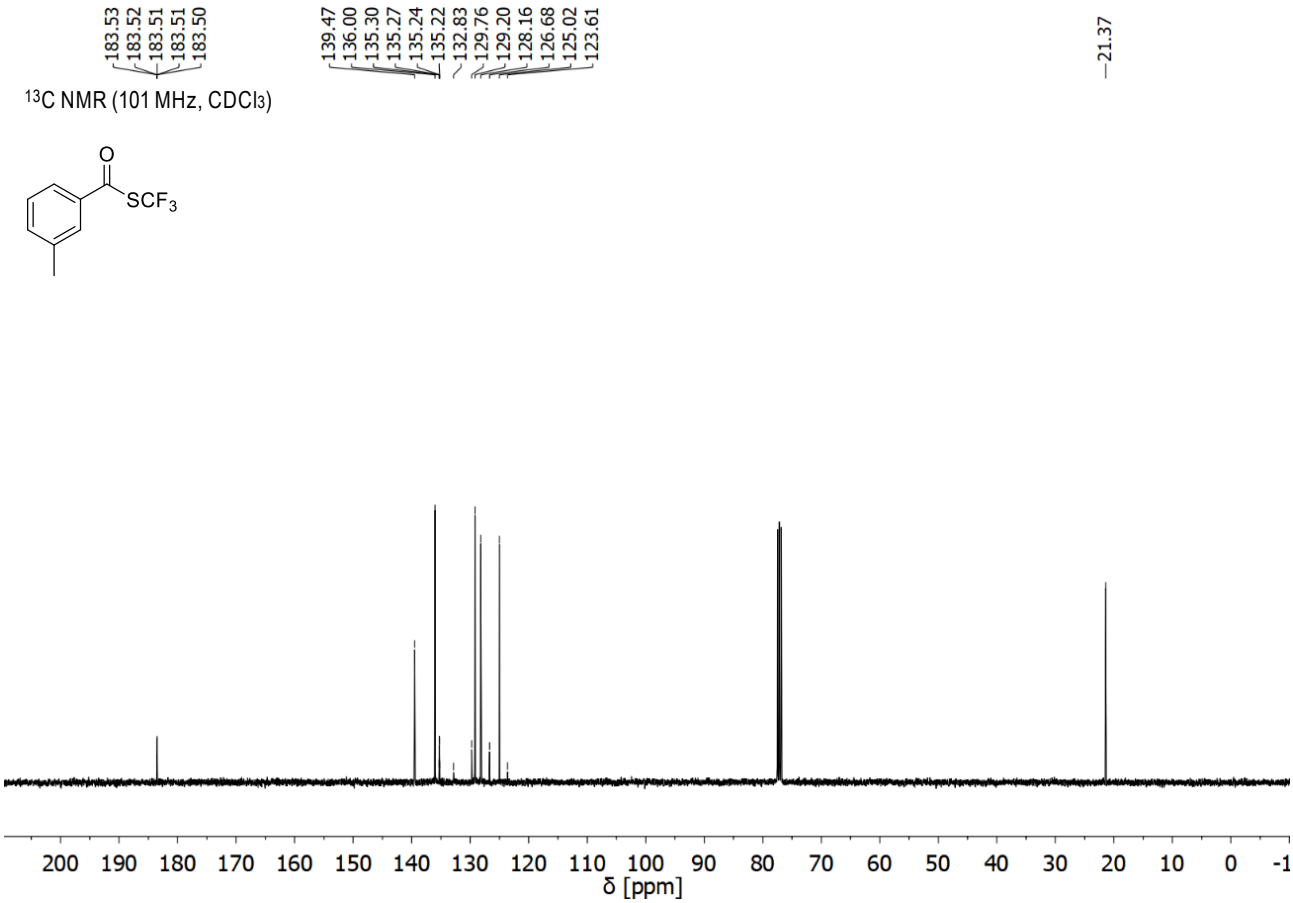
S-(trifluoromethyl) 3-methylbenzothioate **2h**

^{1}H NMR (401 MHz, $CDCl_3$)



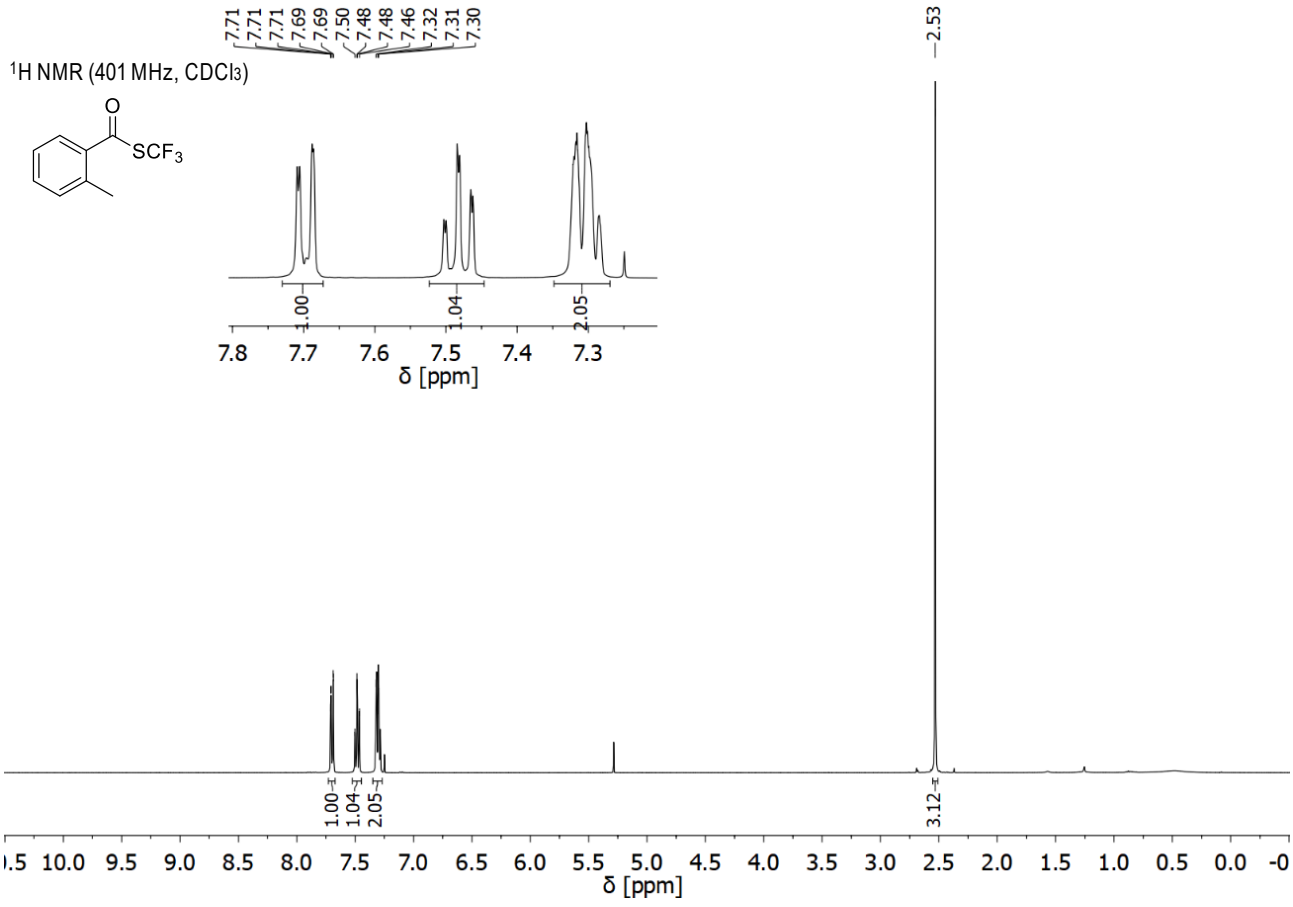
^{19}F NMR (377 MHz, $CDCl_3$)





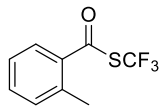
^{13}C NMR (101 MHz, $CDCl_3$)

S-(trifluoromethyl) 2-methylbenzothioate **2i**

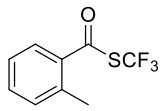


^{1}H NMR (401 MHz, $CDCl_3$)

^{19}F NMR (377 MHz, CDCl$_3$)

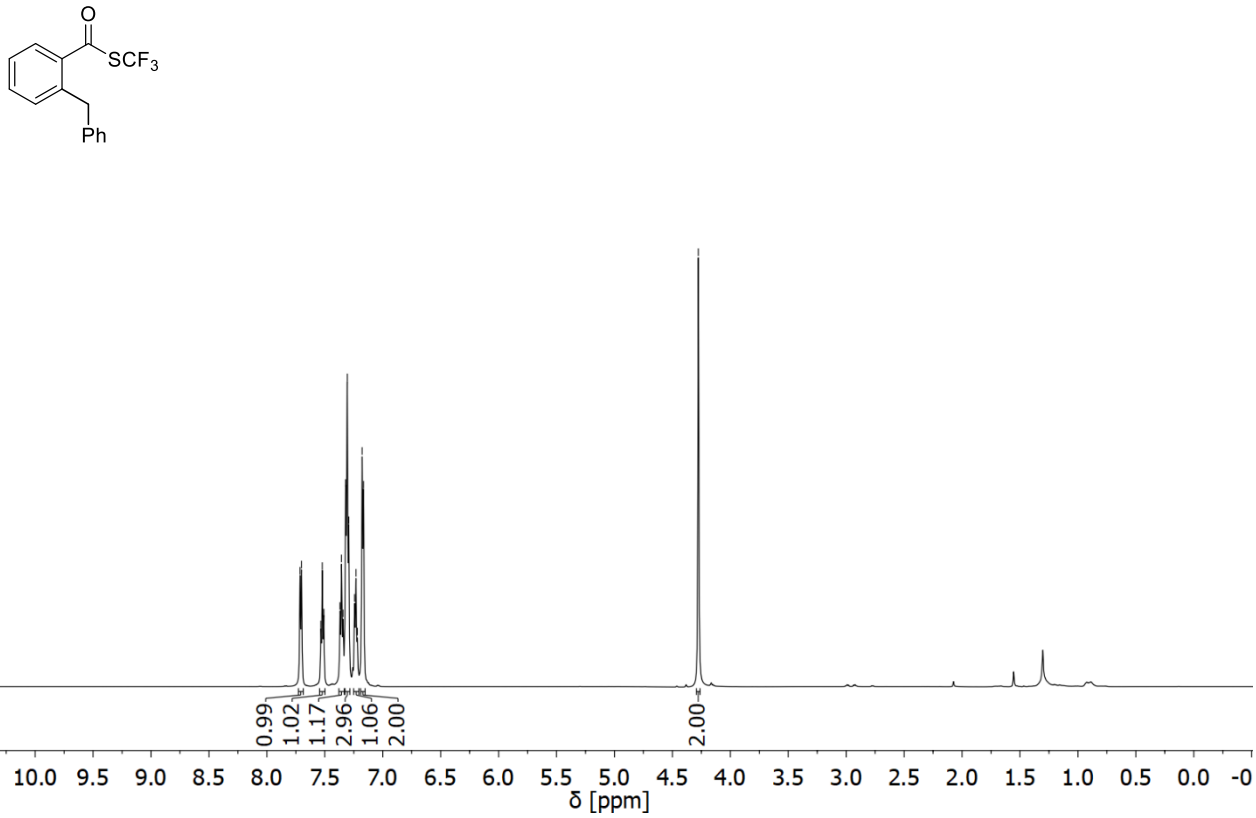


^{13}C NMR (101 MHz, CDCl$_3$)

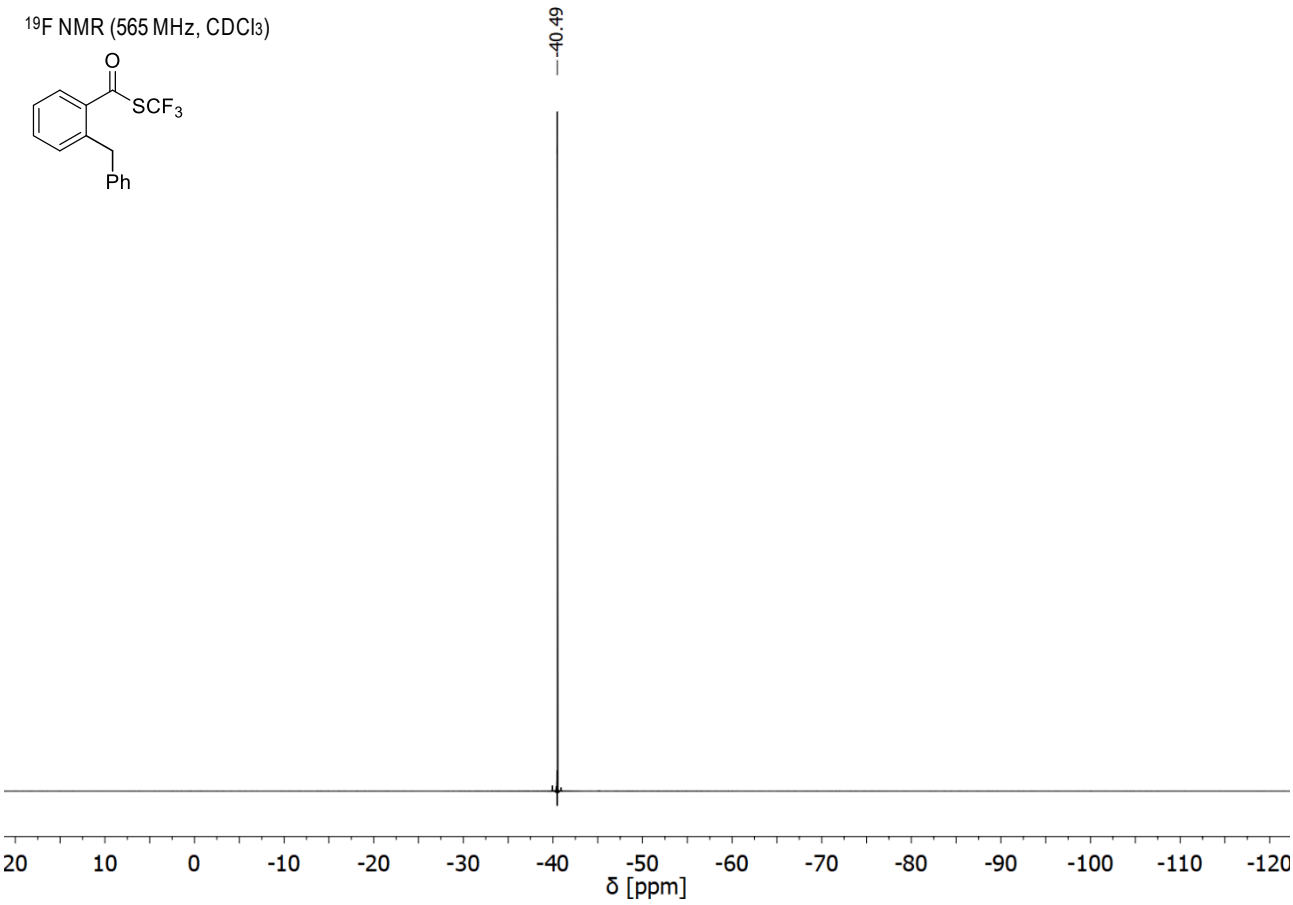


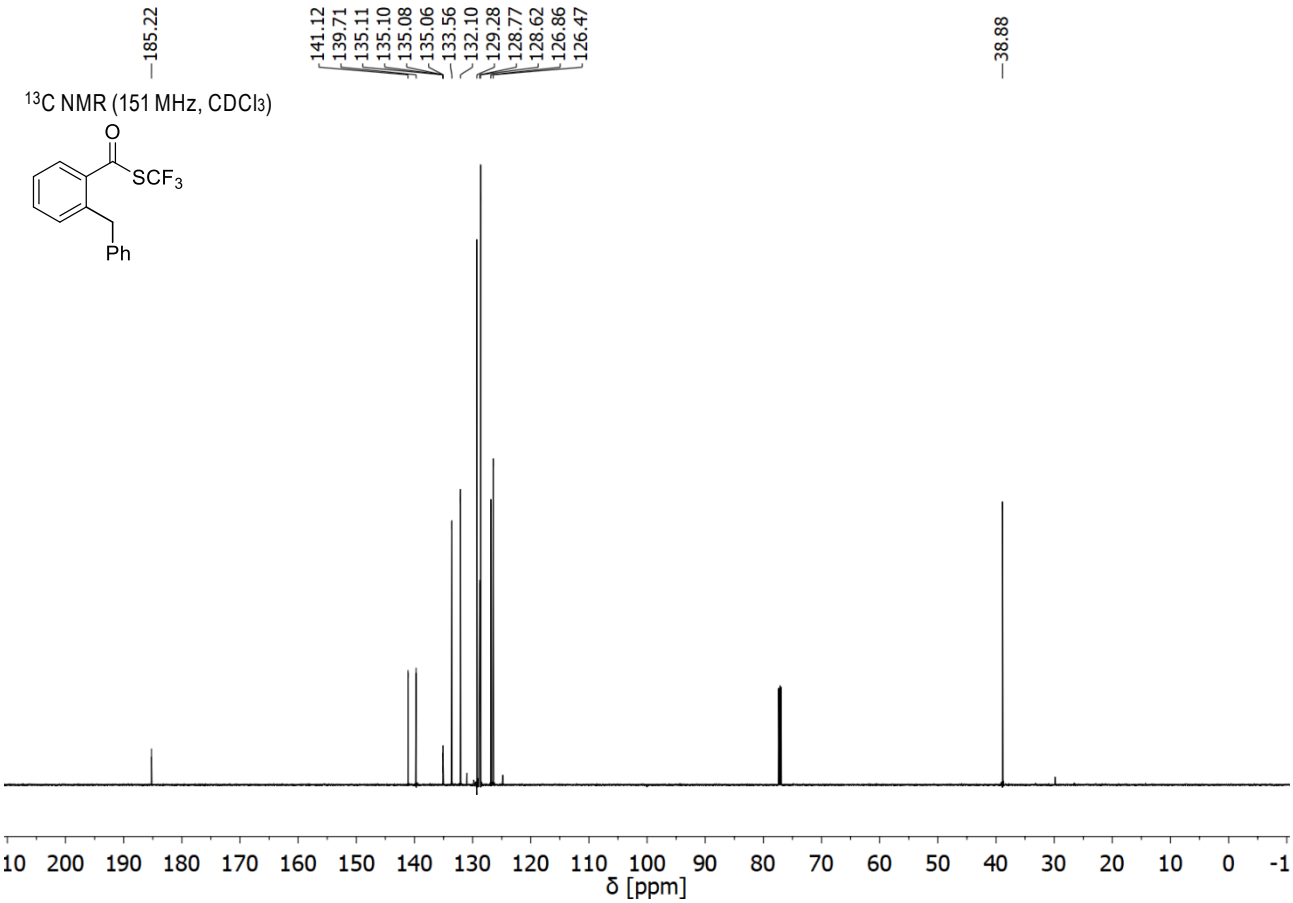
S-(trifluoromethyl) 2-(phenylmethyl) benzothioate **2j**

^{1}H NMR (600 MHz, $CDCl_3$)

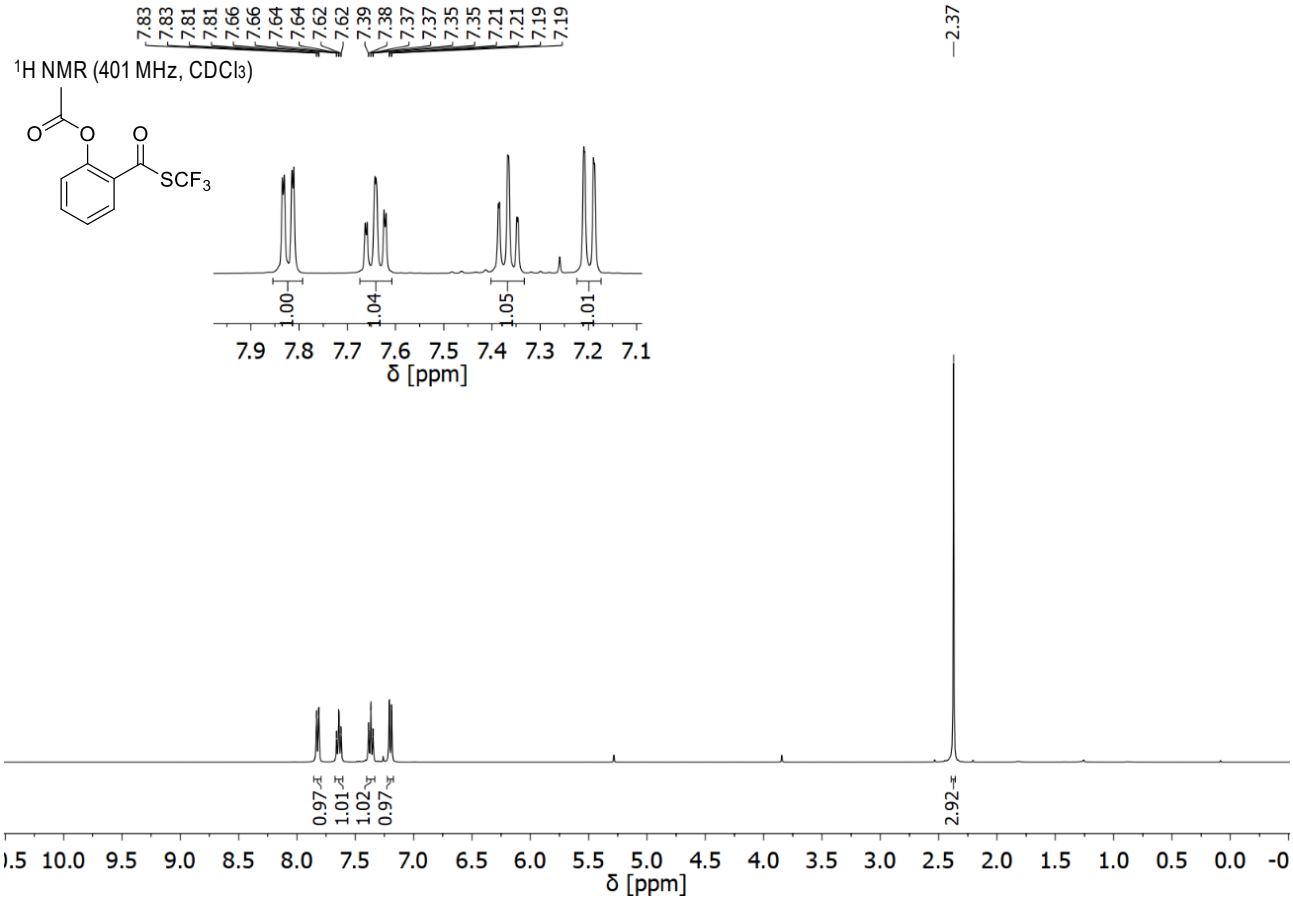


^{19}F NMR (565 MHz, $CDCl_3$)

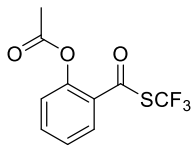




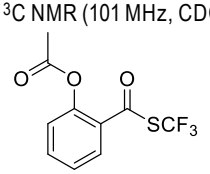
2-(((trifluoromethyl)thio)carbonyl)phenyl acetate **2k**



^{19}F NMR (377 MHz, CDCl$_3$)

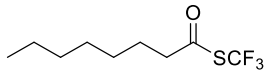


^{13}C NMR (101 MHz, CDCl$_3$)

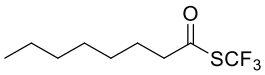


S-(trifluoromethyl) octanethioate **2l**

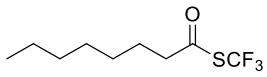
^{1}H NMR (401 MHz, $CDCl_3$)



^{19}F NMR (377 MHz, $CDCl_3$)

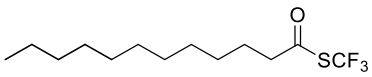


^{13}C NMR (101 MHz, $CDCl_3$)

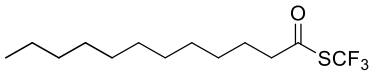


S-(trifluoromethyl) dodecanethioate **2m**

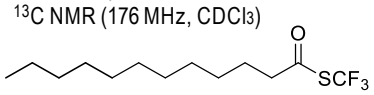
^{1}H NMR (401 MHz, $CDCl_3$)



^{19}F NMR (377 MHz, CDCl$_3$)

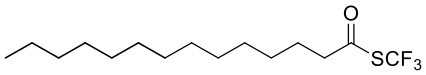


^{13}C NMR (176 MHz, CDCl$_3$)

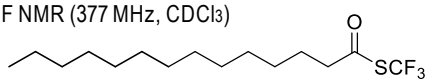


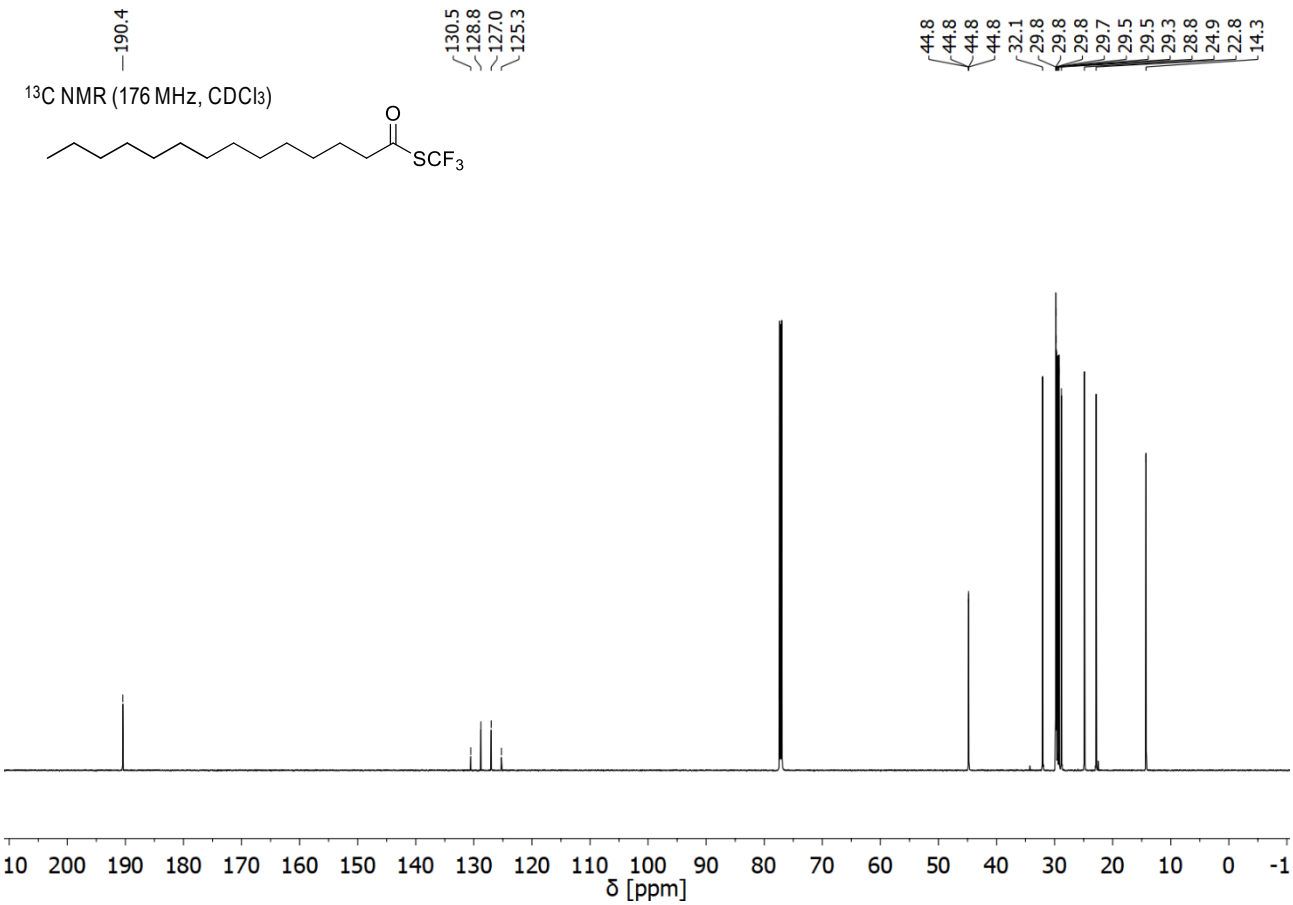
S-(trifluoromethyl) tetradecanethioate **2n**

^{1}H NMR (401 MHz, $CDCl_3$)

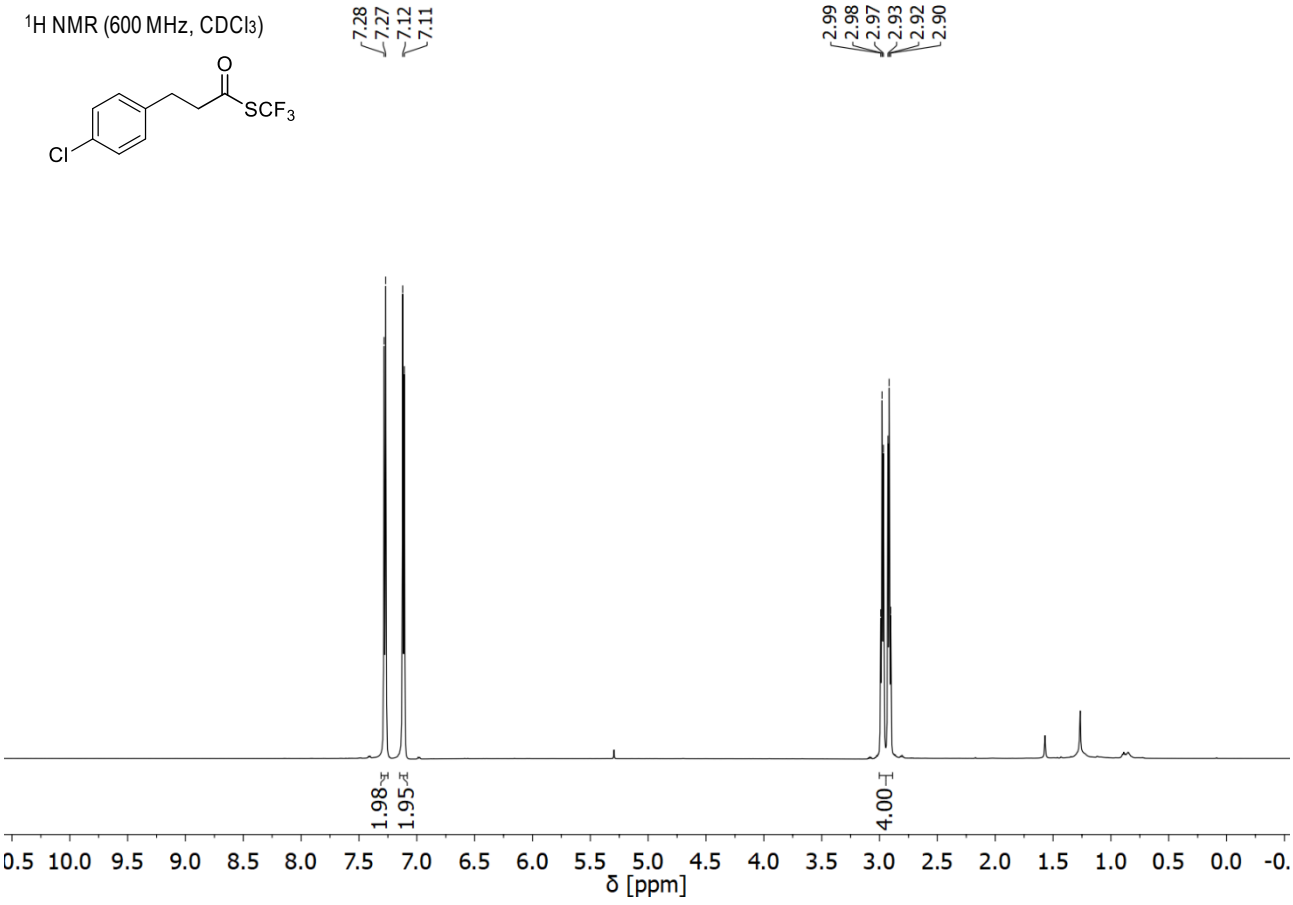


^{19}F NMR (377 MHz, $CDCl_3$)

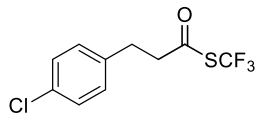




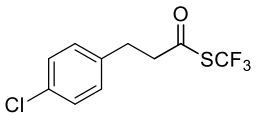
S-(trifluoromethyl) 3-(4-chloro)propanethioate **2o**



^{19}F NMR (565 MHz, $CDCl_3$)

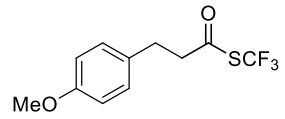


^{13}C NMR (151 MHz, $CDCl_3$)

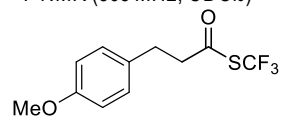


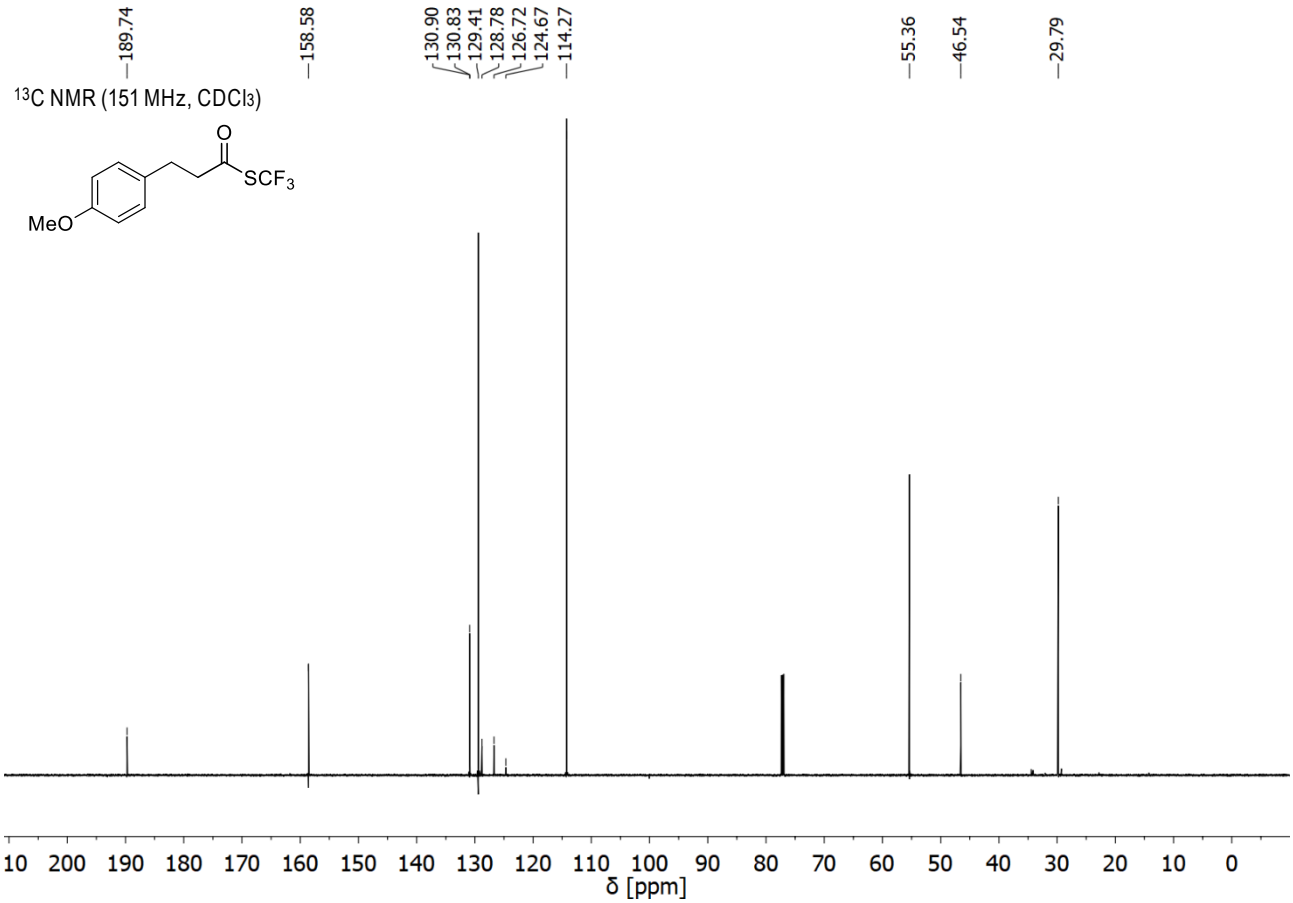
S-(trifluoromethyl) 3-(4-methoxy)propanethioate **2p**

^{1}H NMR (600 MHz, $CDCl_3$)

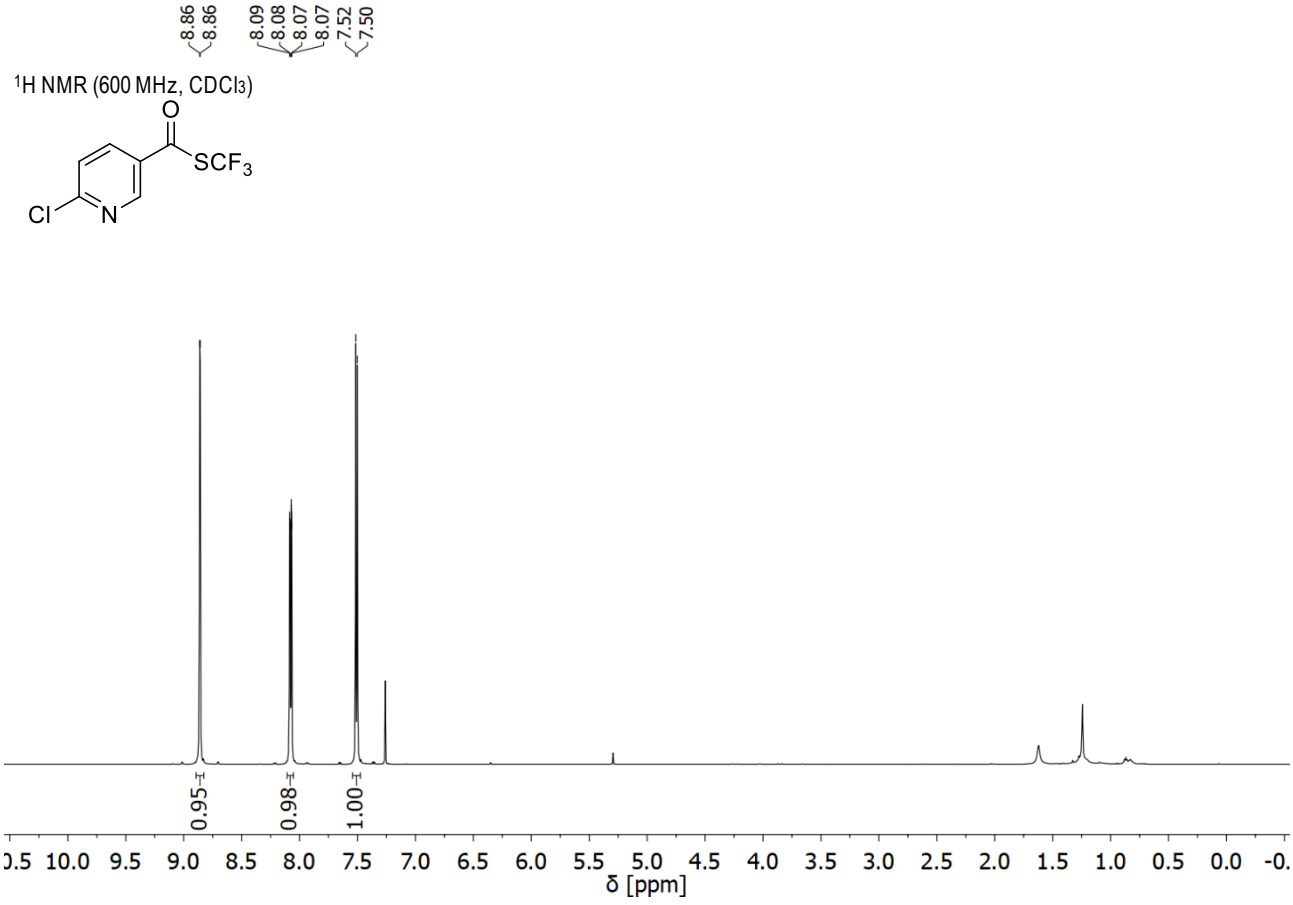


^{19}F NMR (565 MHz, $CDCl_3$)

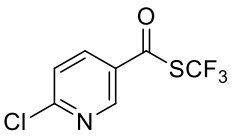




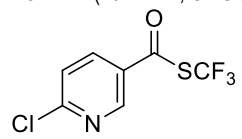
S-(trifluoromethyl) 6-chloropyridine-3-carbothioate **2q**



^{19}F NMR (565 MHz, $CDCl_3$)

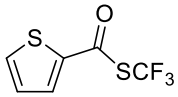


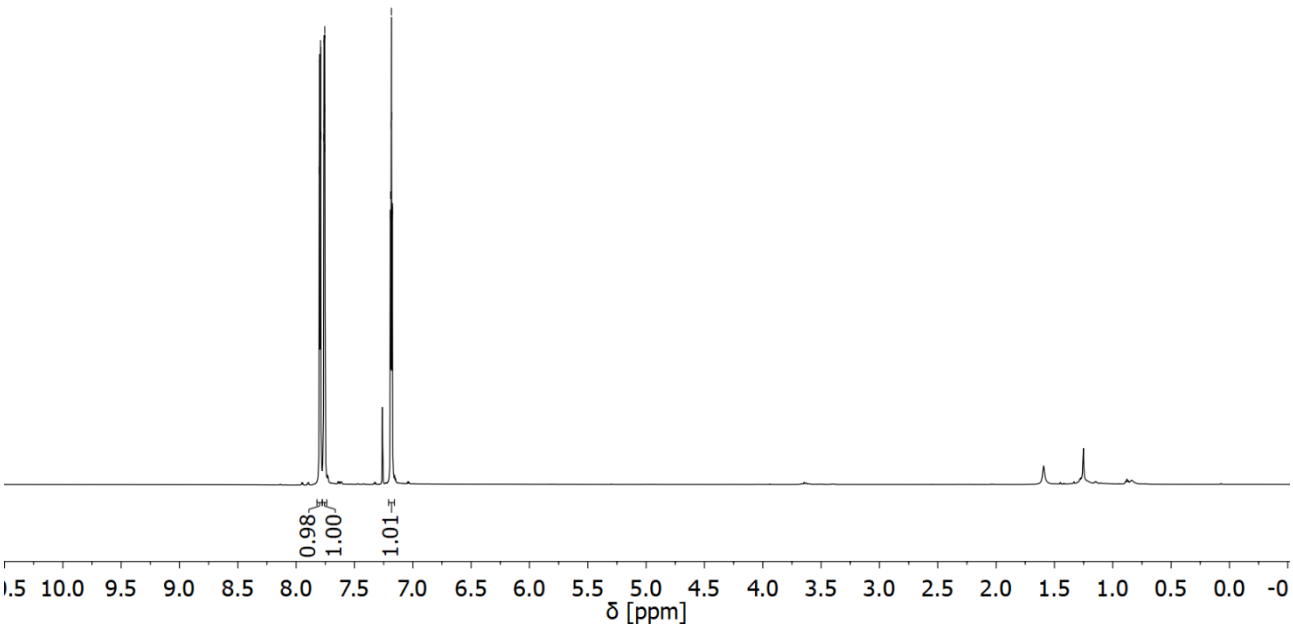
^{13}C NMR (151 MHz, $CDCl_3$)



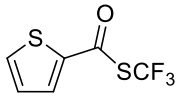
S-(trifluoromethyl) thiophene-2-carbothioate **2r**

^{1}H NMR (600 MHz, $CDCl_3$)

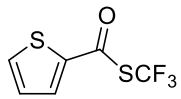




^{19}F NMR (565 MHz, $CDCl_3$)

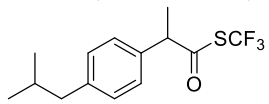


^{13}C NMR (151 MHz, $CDCl_3$)

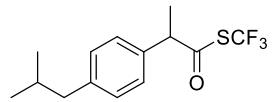


S-(trifluoromethyl) 2-(4-isobutylphenyl)propanethioate **2s**

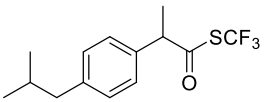
^{1}H NMR (401 MHz, $CDCl_3$)



^{19}F NMR (377 MHz, $CDCl_3$)

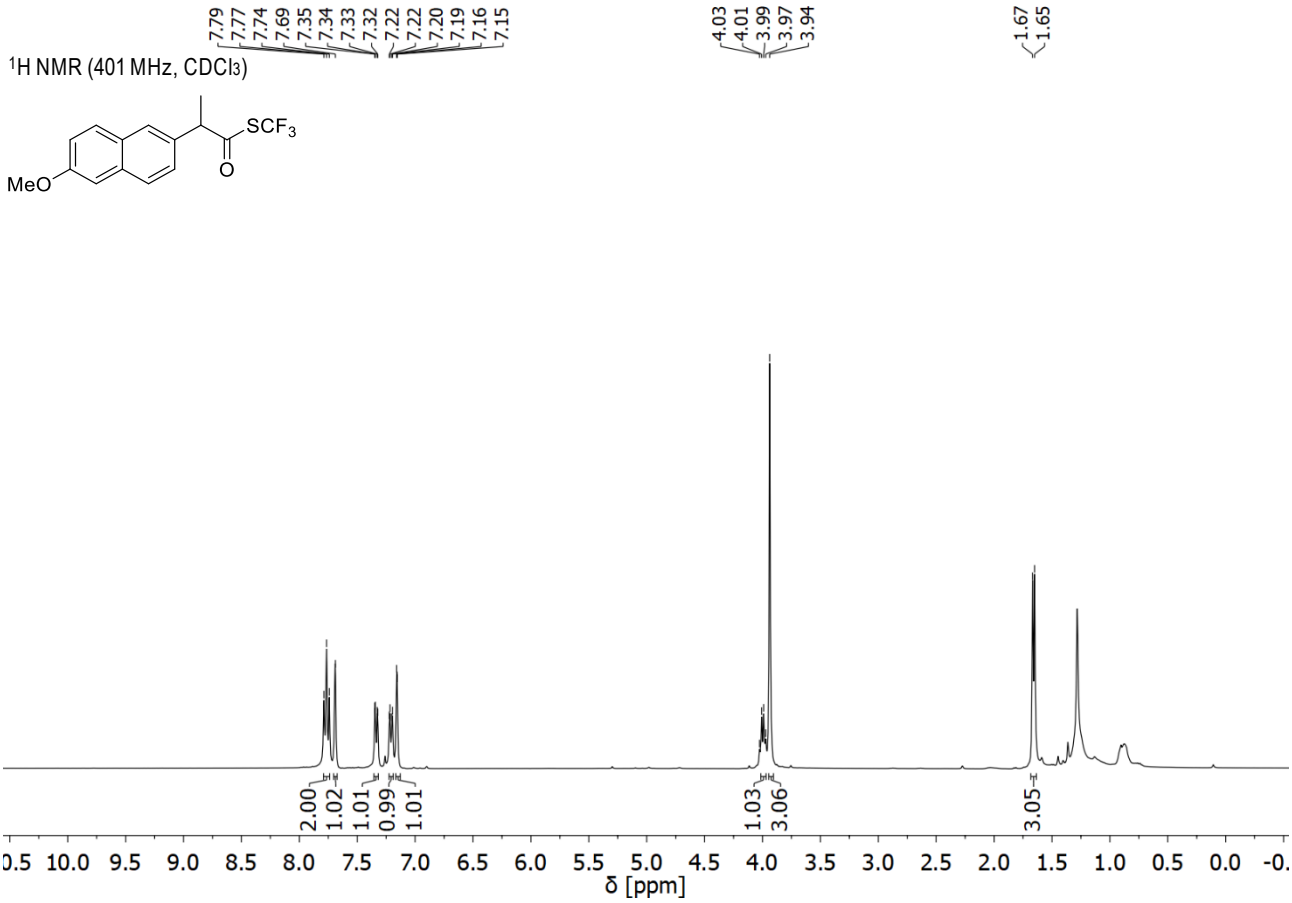


^{13}C NMR (101 MHz, $CDCl_3$)

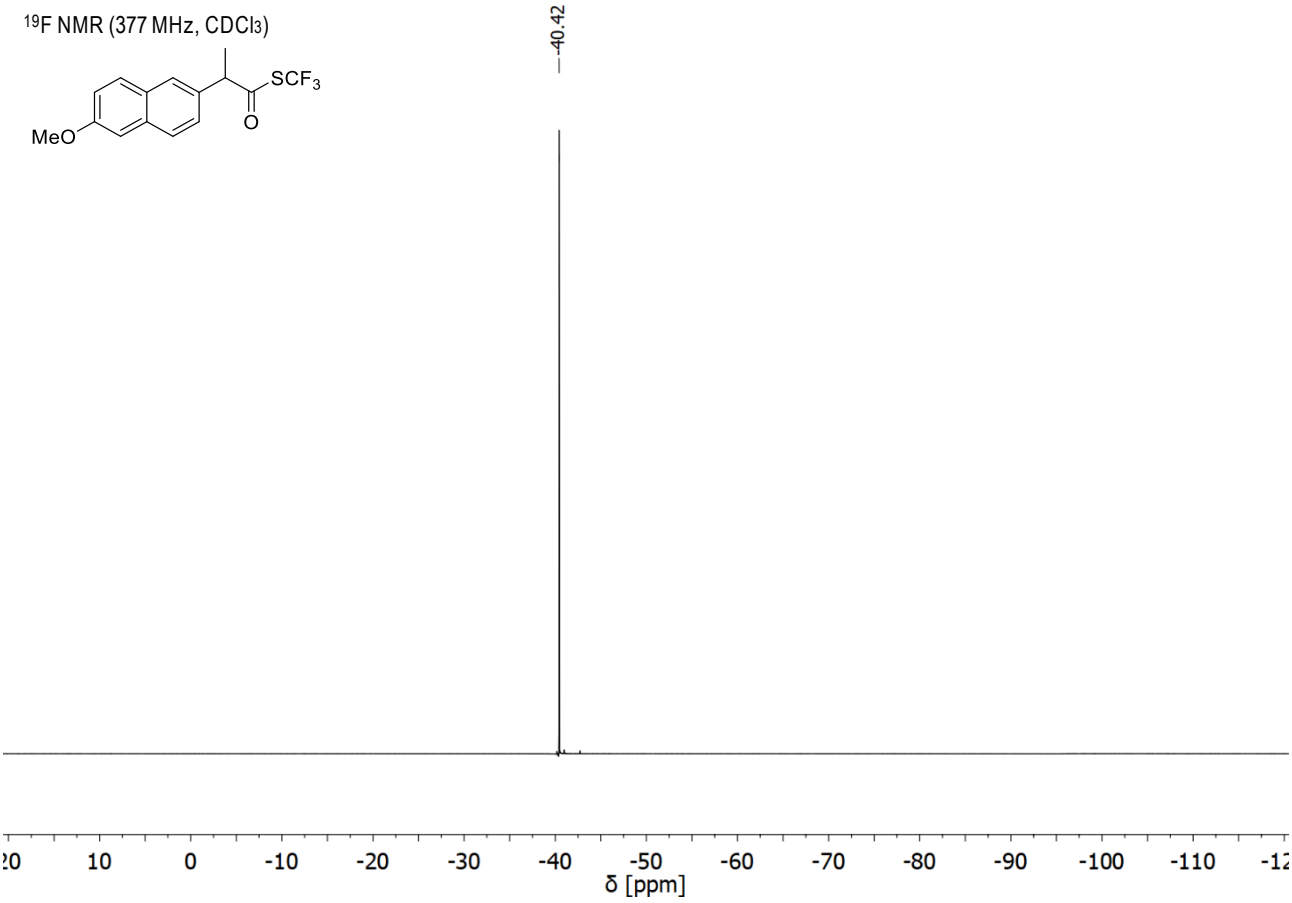


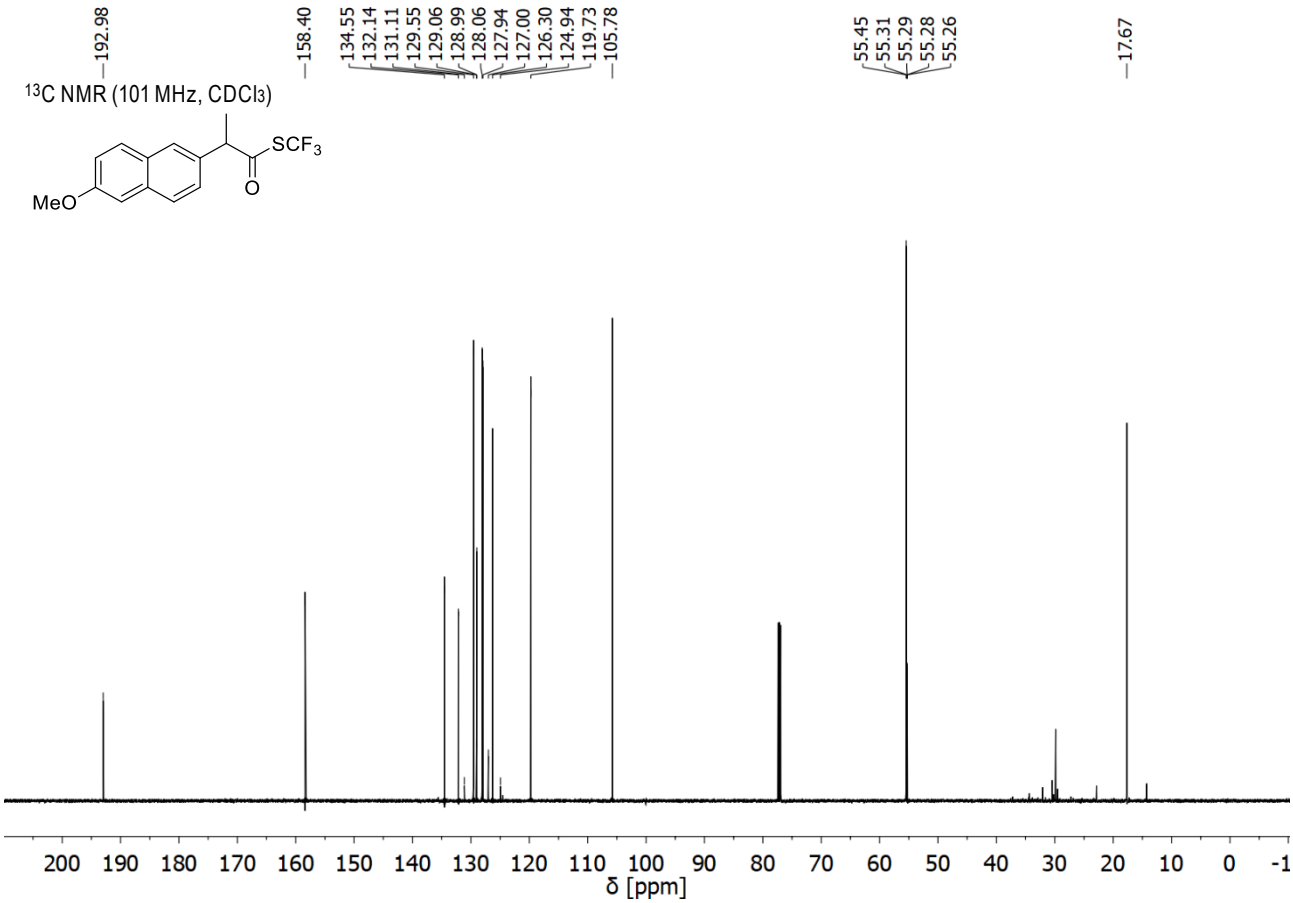
S-(trifluoromethyl) 2-(6-methoxynaphthalen-2-yl)propanethioate **2t**

^{1}H NMR (401 MHz, $CDCl_3$)

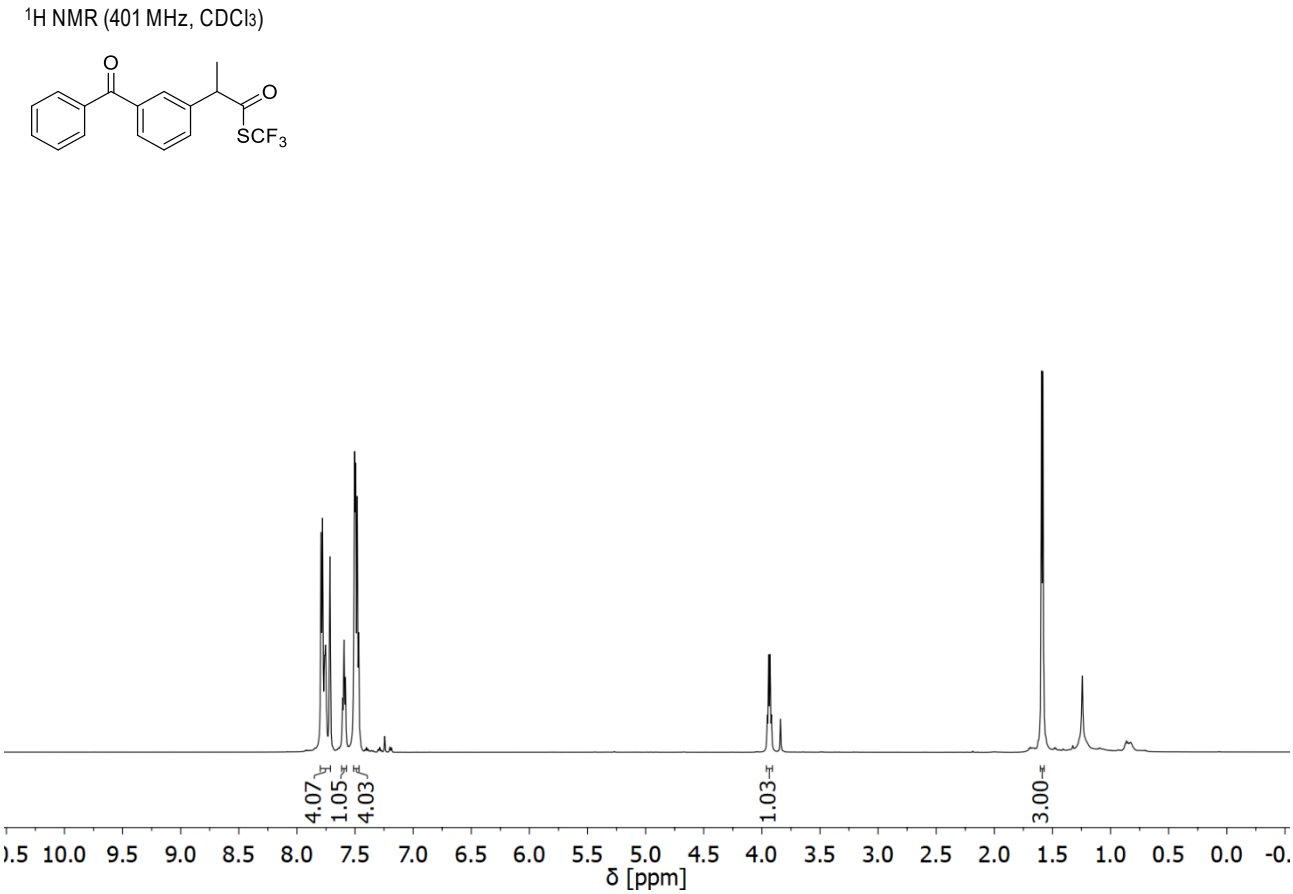


^{19}F NMR (377 MHz, $CDCl_3$)

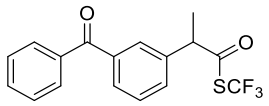


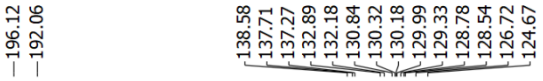


S-(trifluoromethyl) 2-(3-benzoylphenyl)propanethioate **2u**

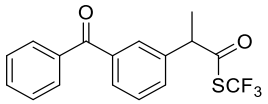


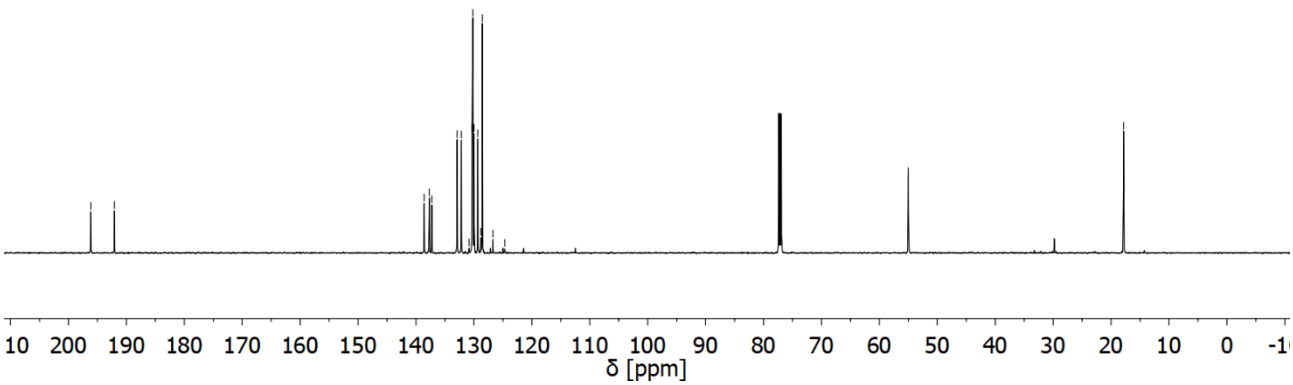
^{19}F NMR (377 MHz, CDCl$_3$)





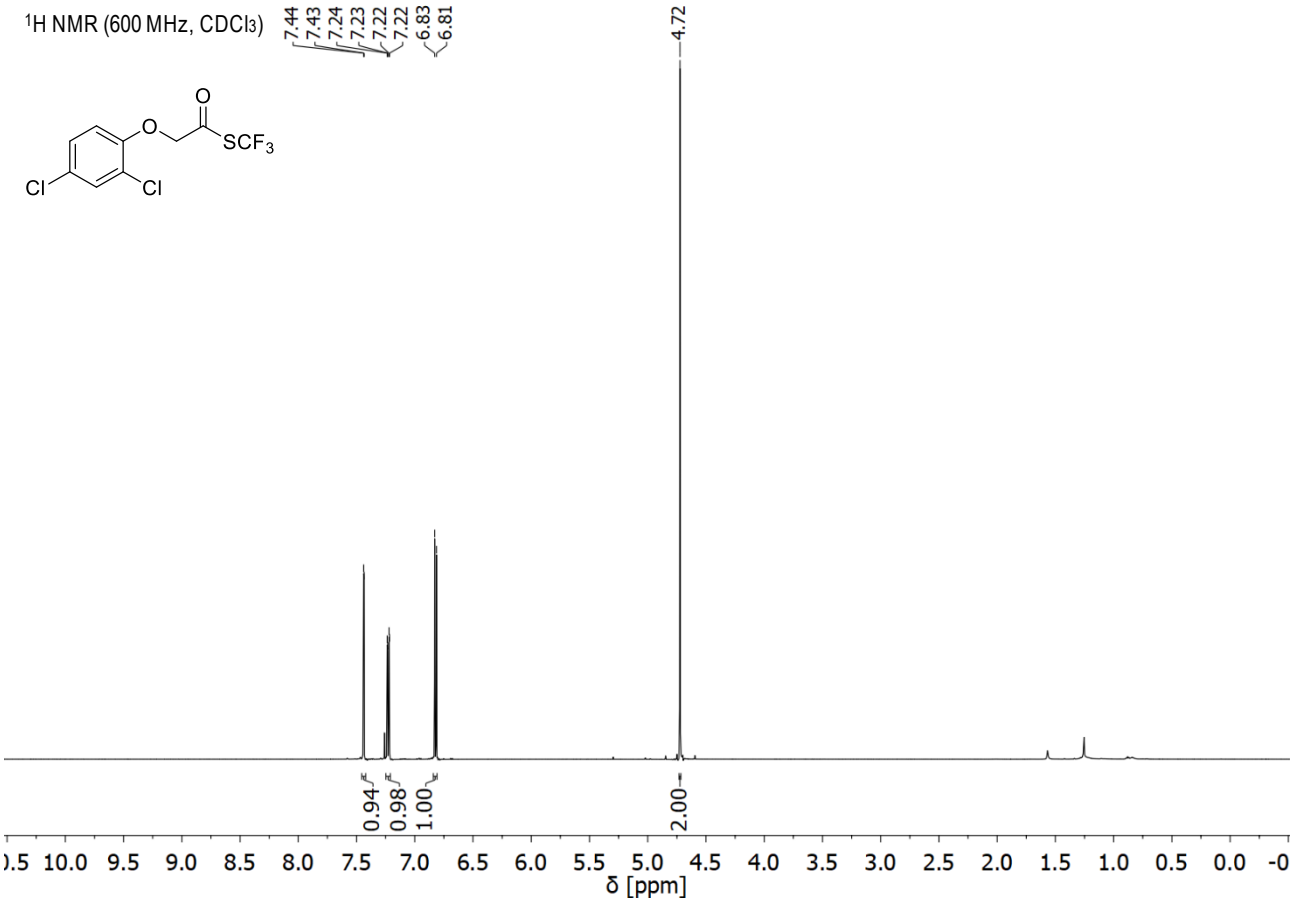
^{13}C NMR (151 MHz, CDCl$_3$)



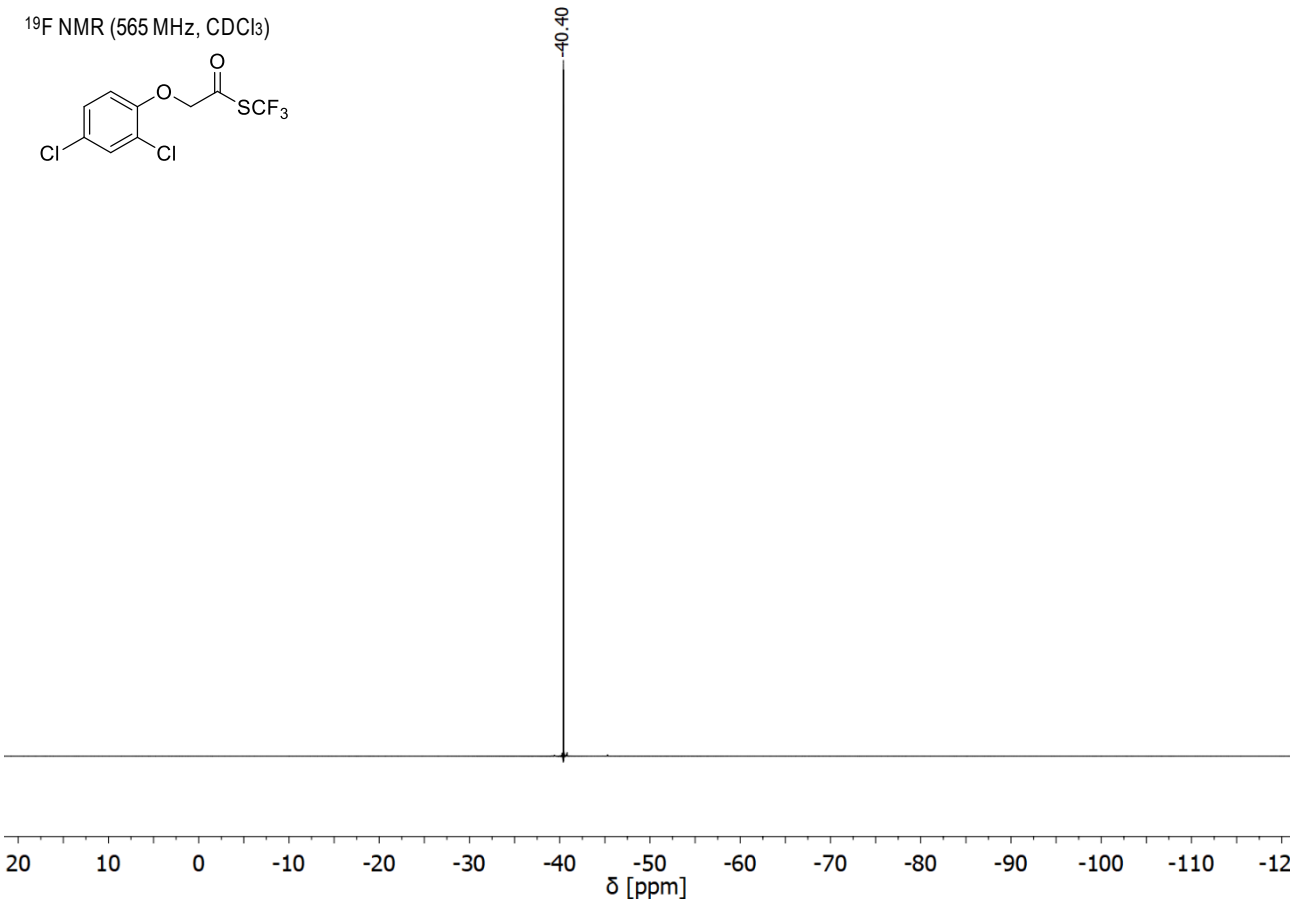


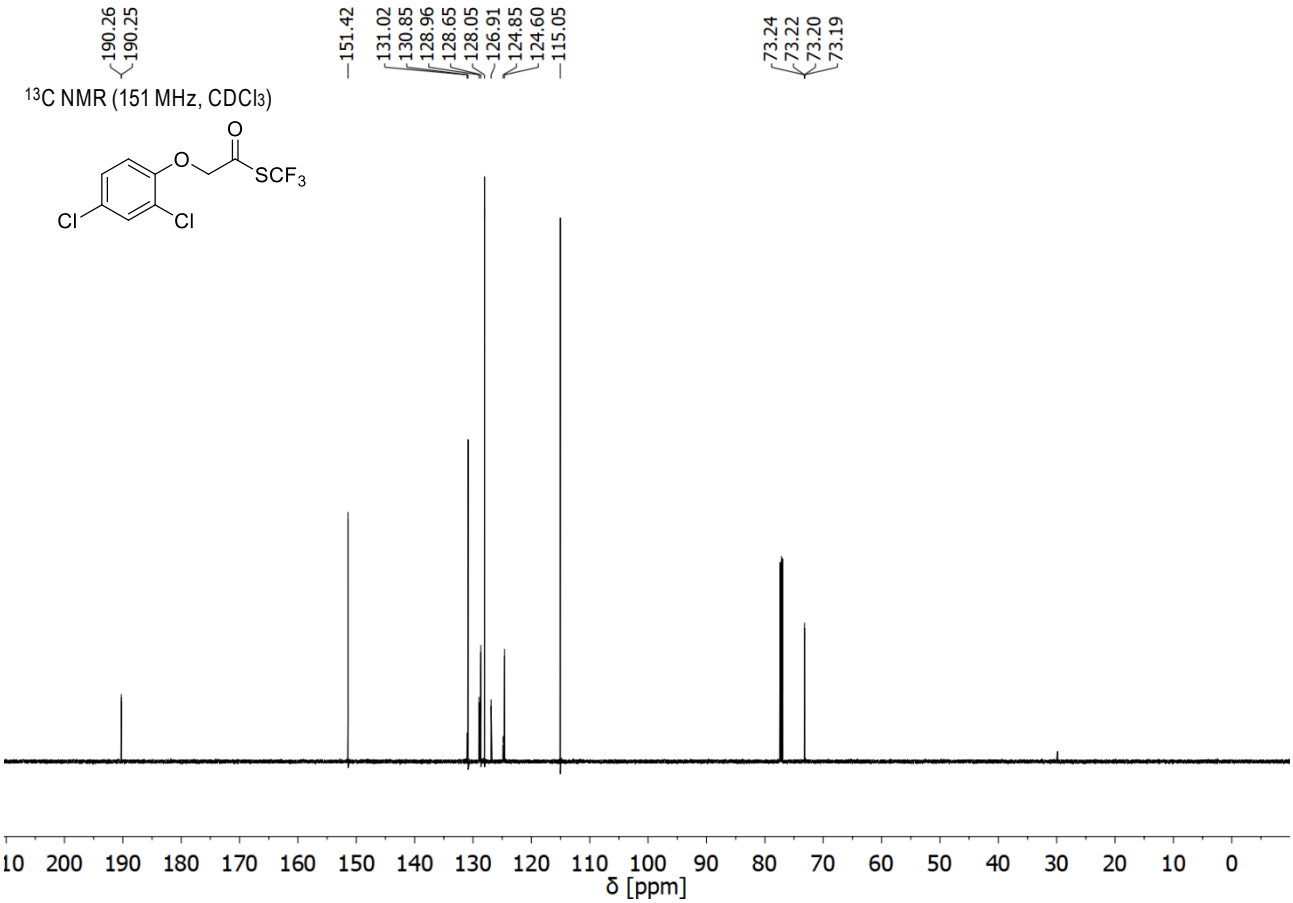
S-(trifluoromethyl) 2-(2,4-dichlorophenoxy)ethanethioate **2v**

^{1}H NMR (600 MHz, $CDCl_3$)

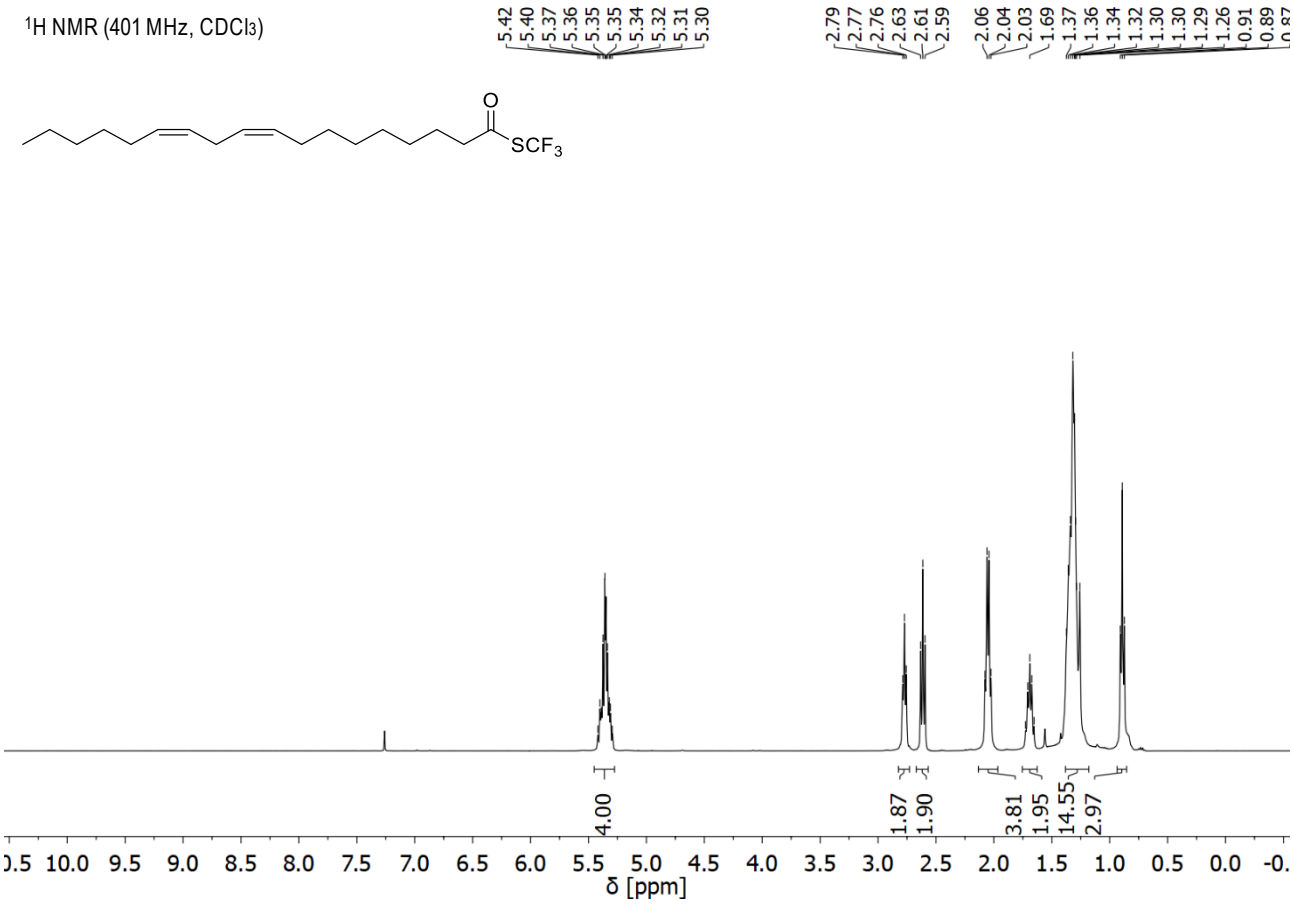


^{19}F NMR (565 MHz, $CDCl_3$)

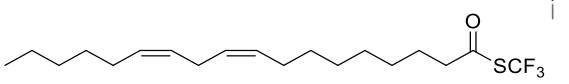




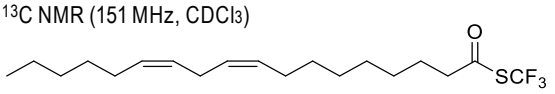
S-(trifluoromethyl) (9Z,12Z)-octadeca-9,12-dienethioate **2w**



^{19}F NMR (377 MHz, CDCl$_3$)

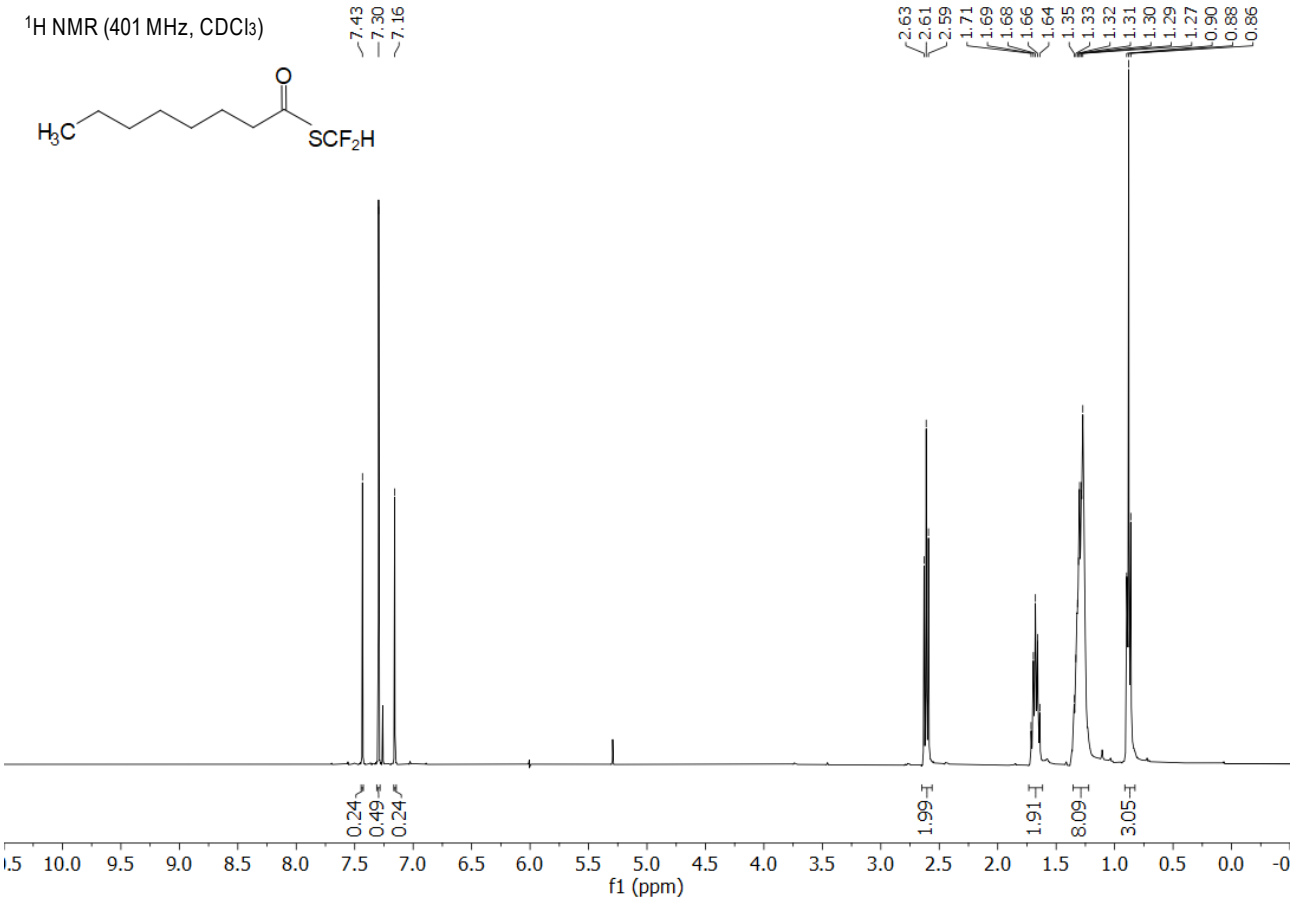


^{13}C NMR (151 MHz, CDCl$_3$)

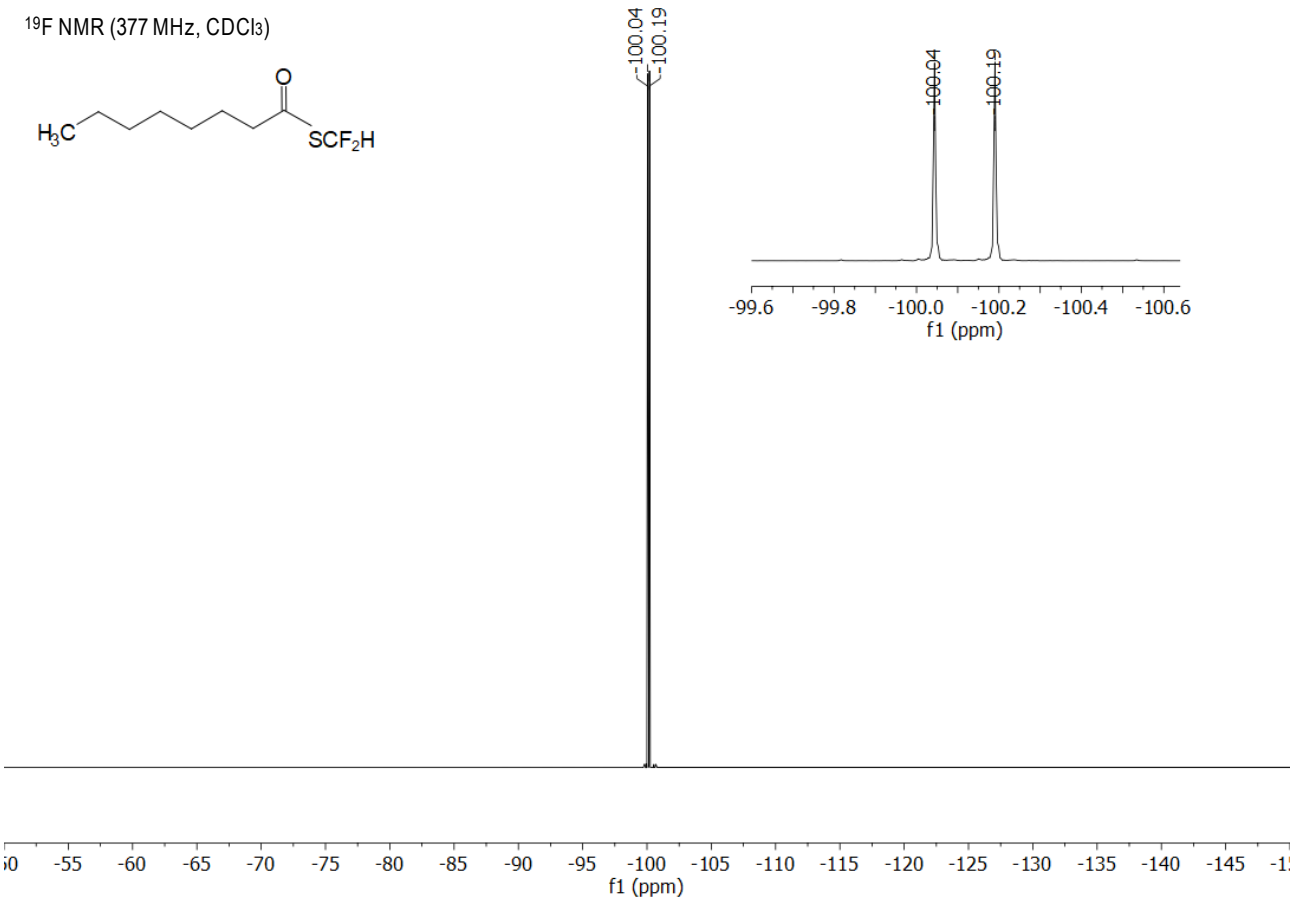


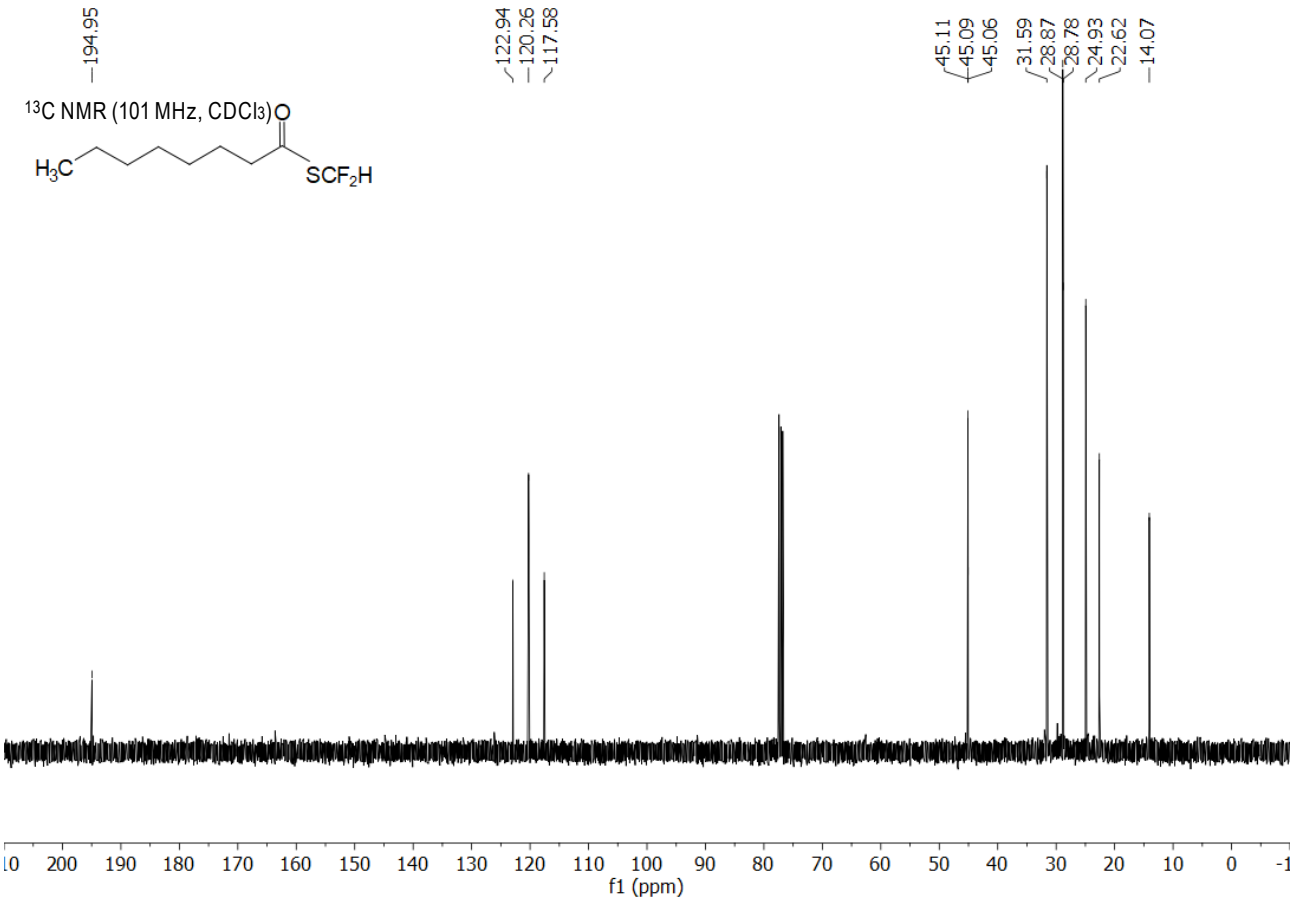
S-(difluoromethyl) octanethioate **3a**

^{1}H NMR (401 MHz, $CDCl_3$)

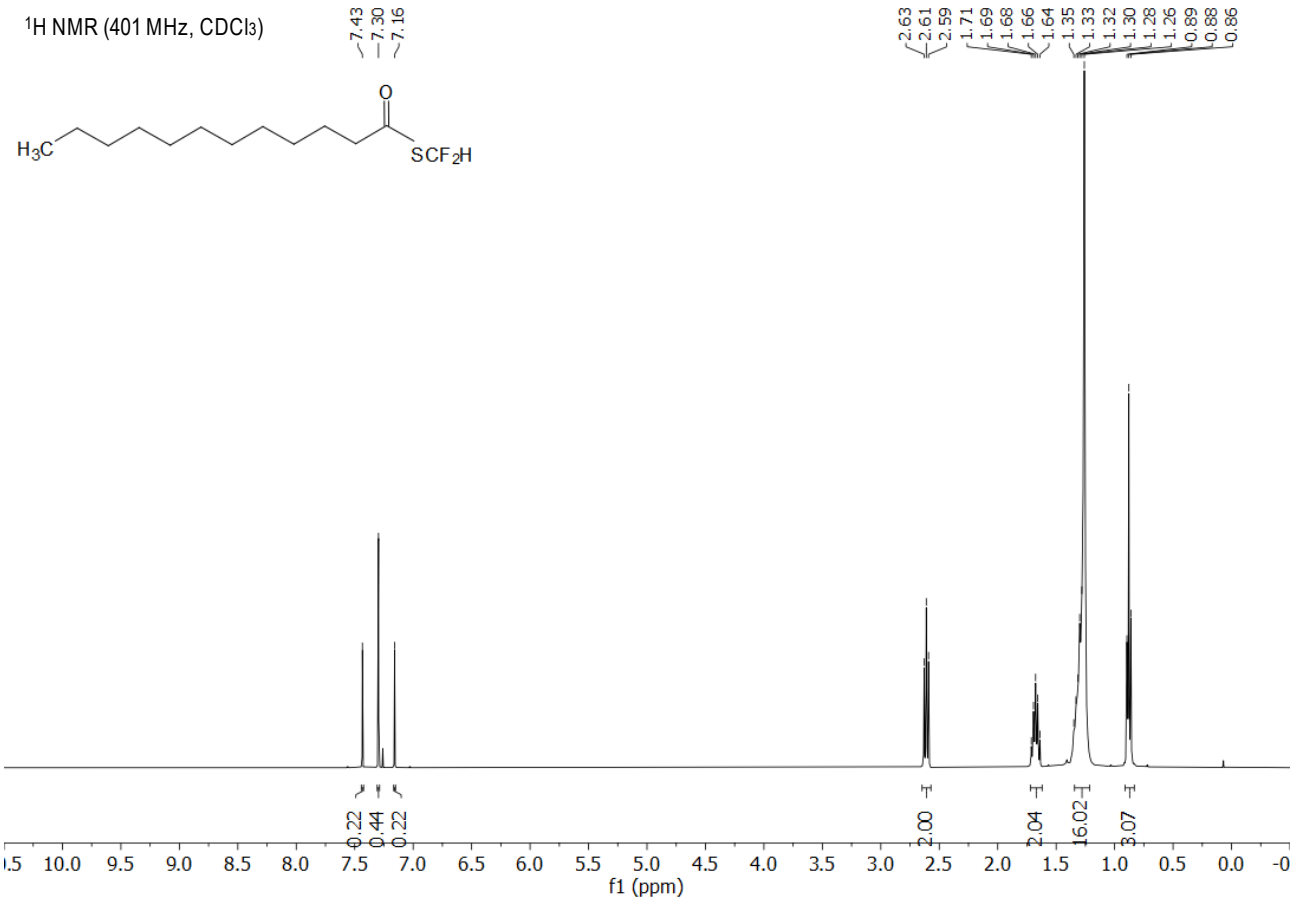


^{19}F NMR (377 MHz, $CDCl_3$)

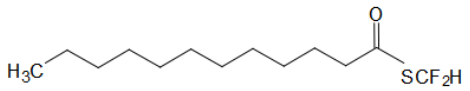




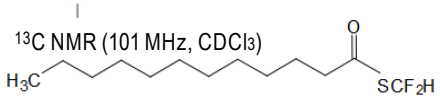
S-(difluoromethyl) dodecanethioate **3b**



^{19}F NMR (377 MHz, CDCl$_3$)

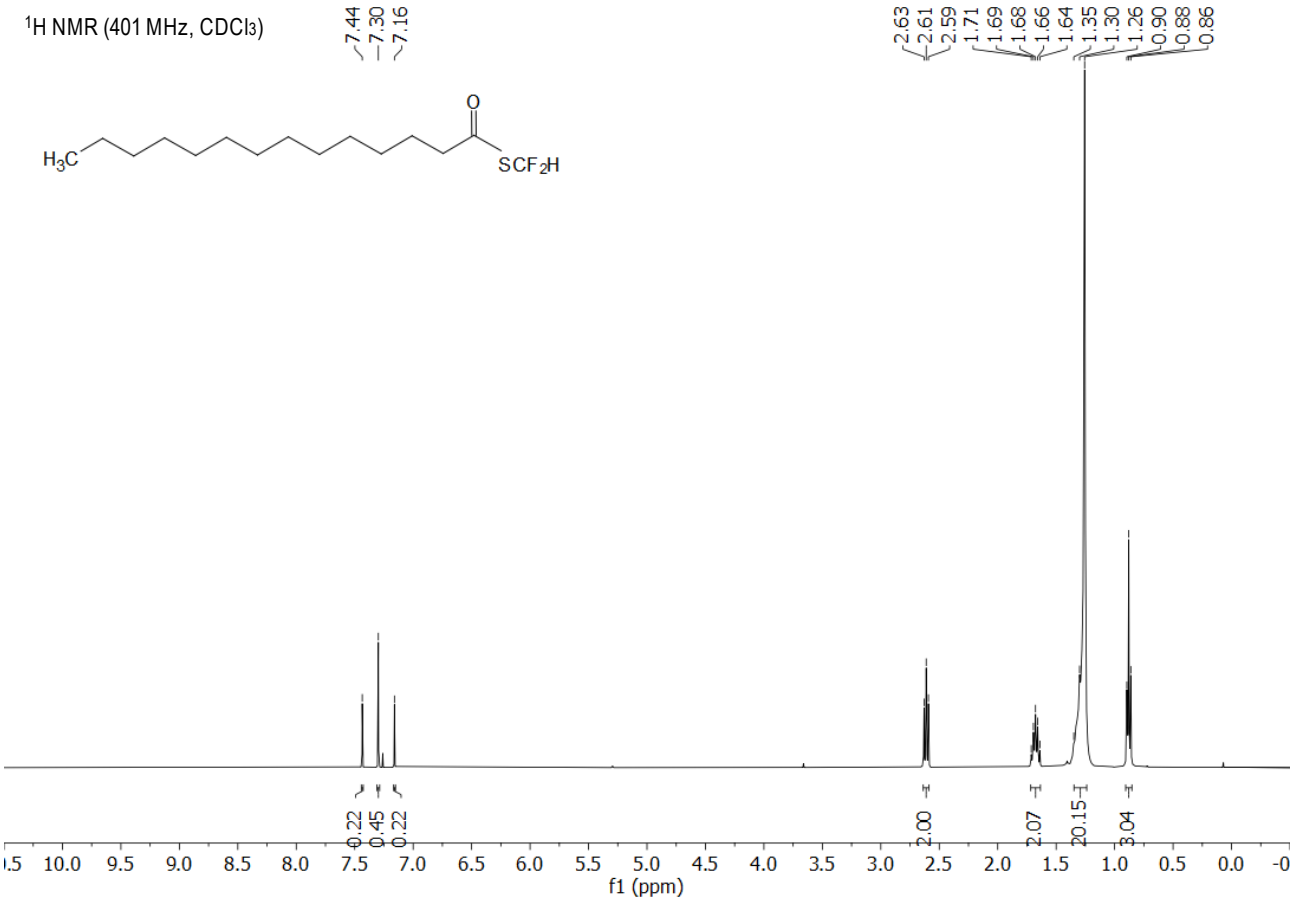


^{13}C NMR (101 MHz, CDCl$_3$)

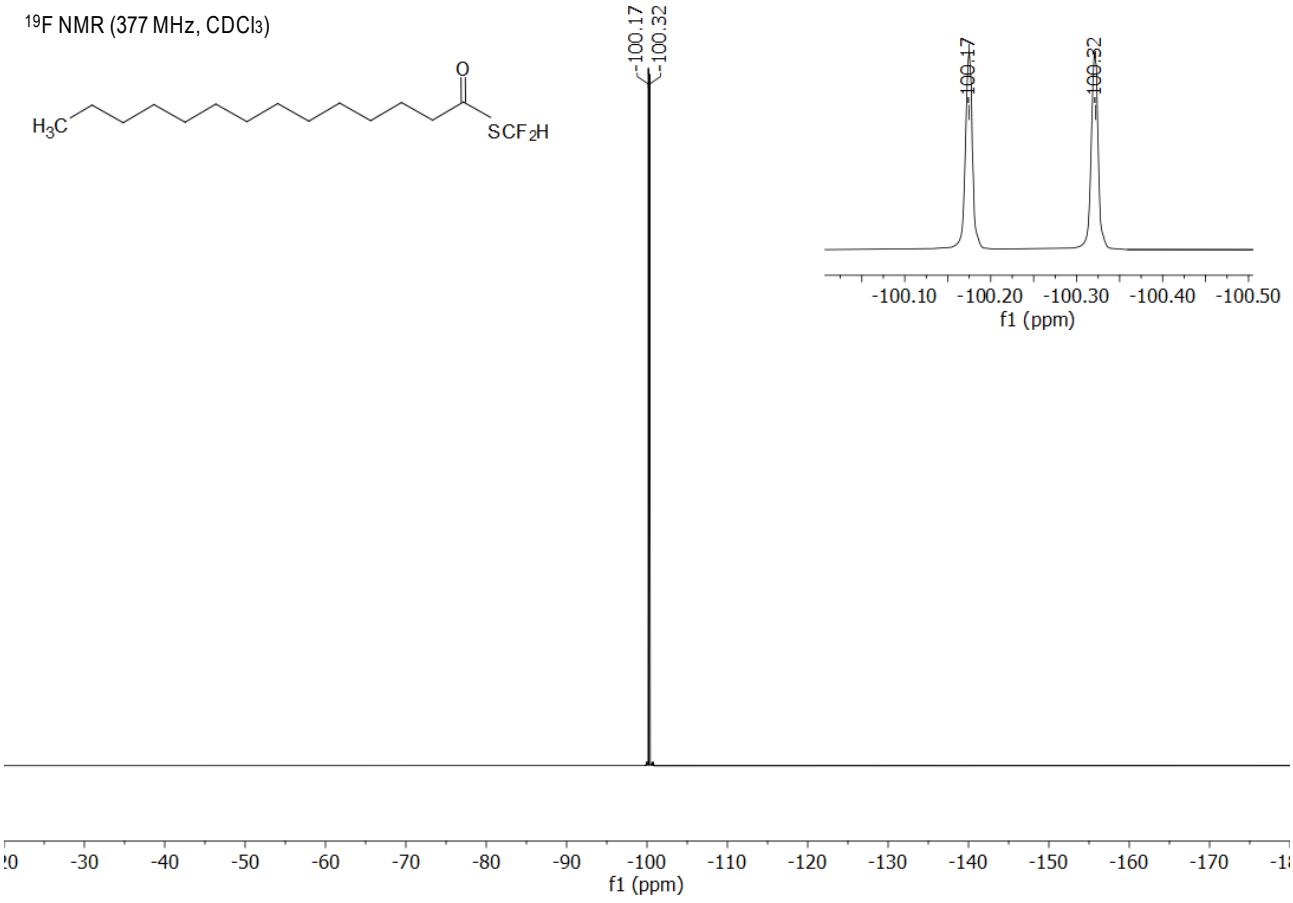


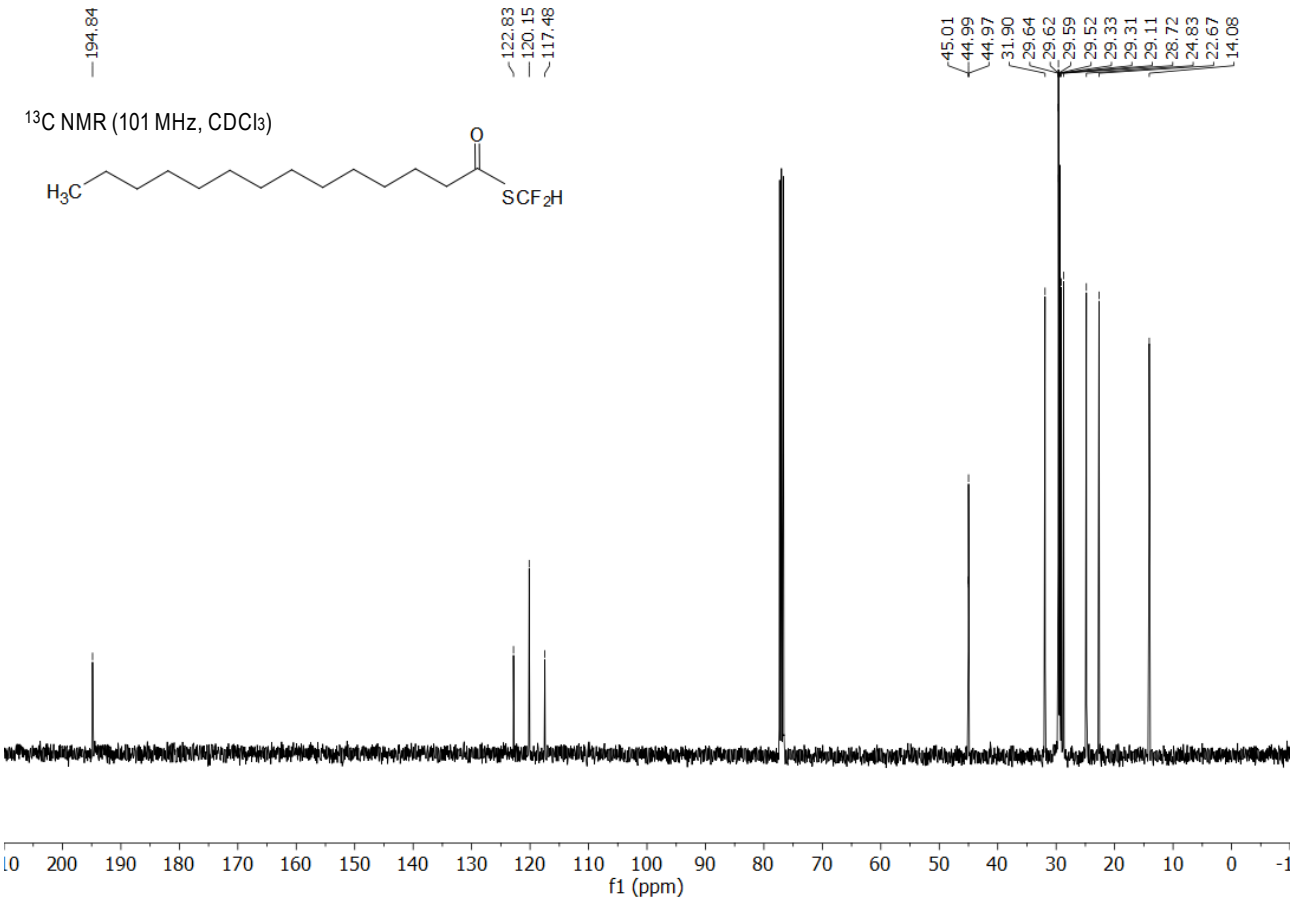
S-(difluoromethyl) tetradecanethioate **3c**

^{1}H NMR (401 MHz, $CDCl_3$)

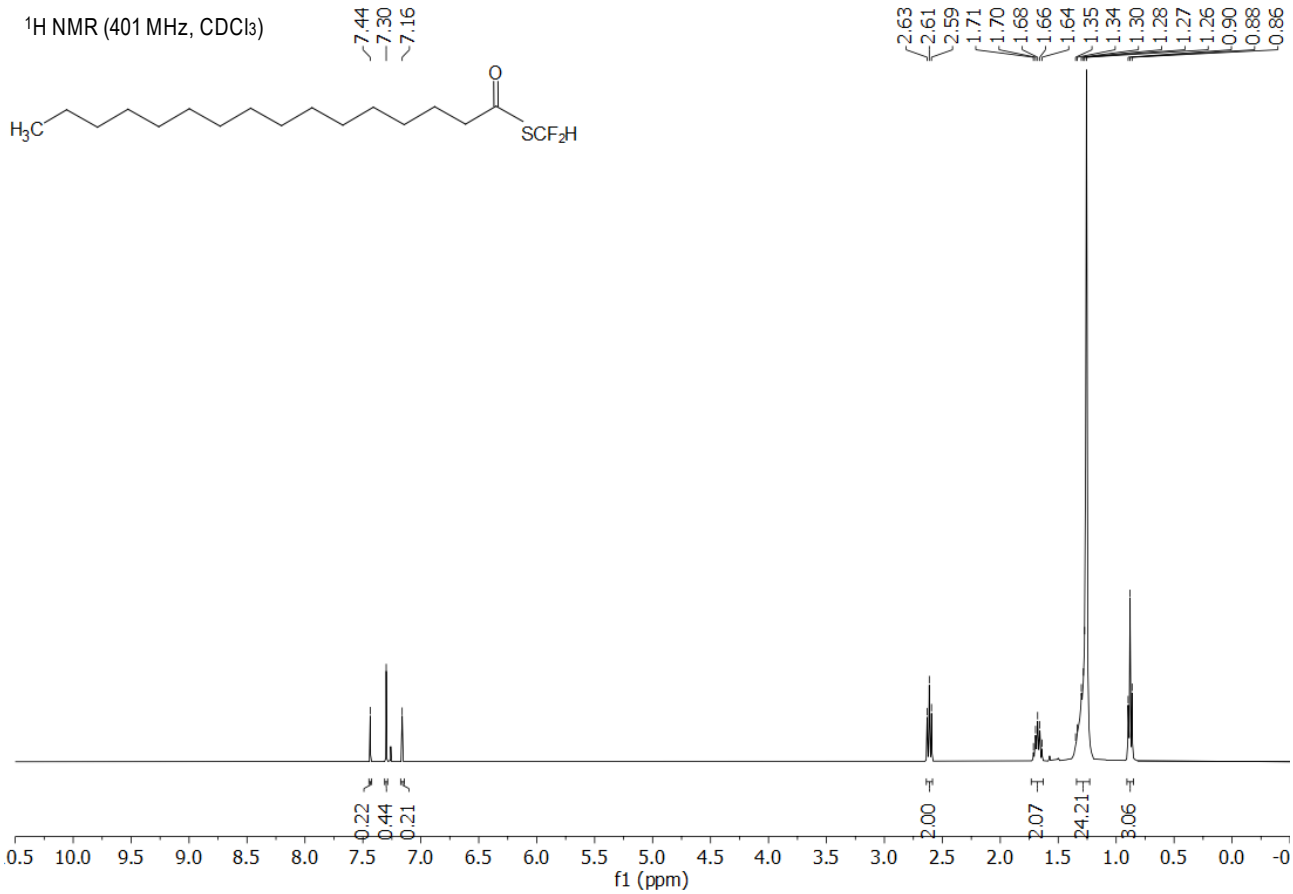


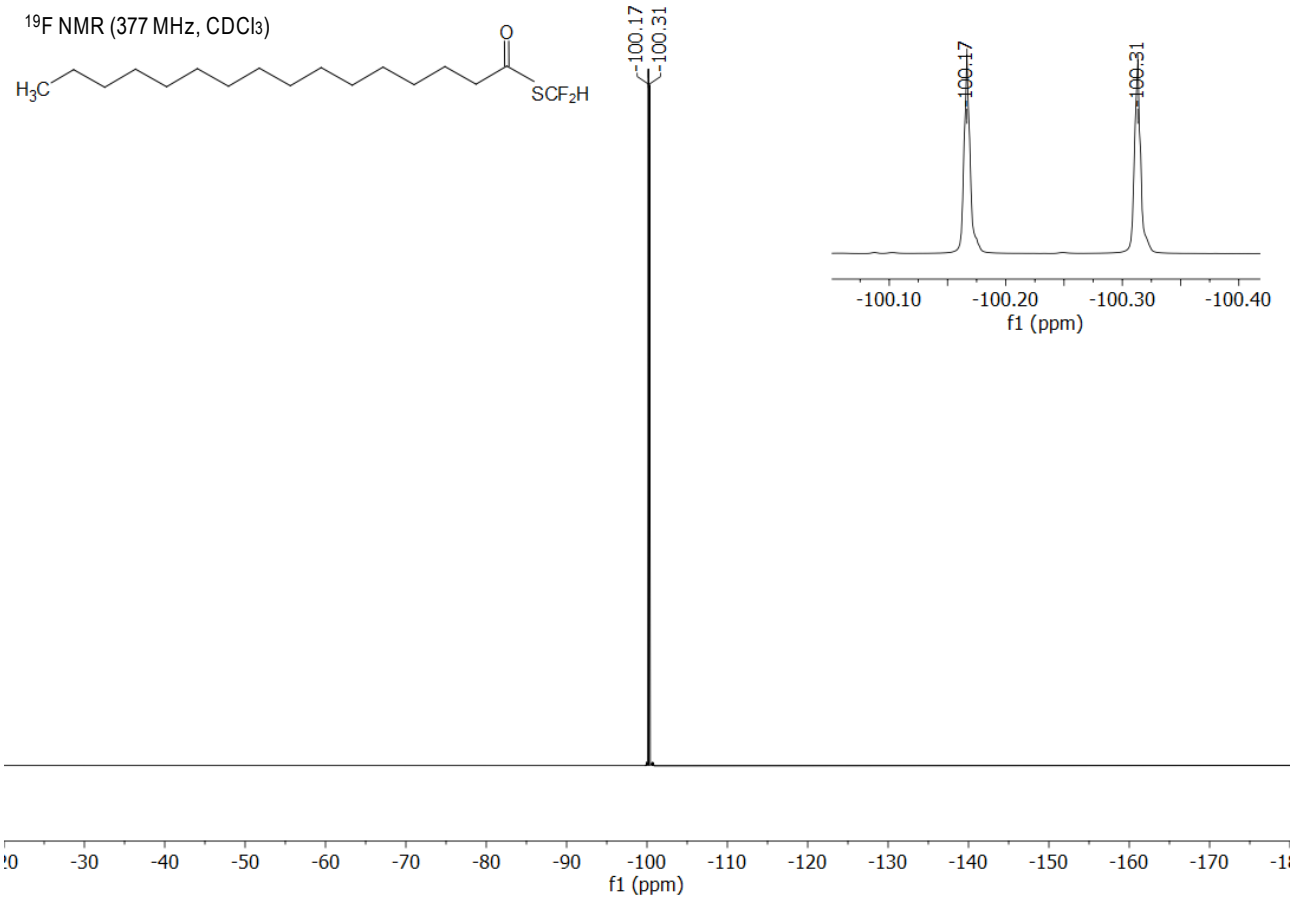
^{19}F NMR (377 MHz, $CDCl_3$)

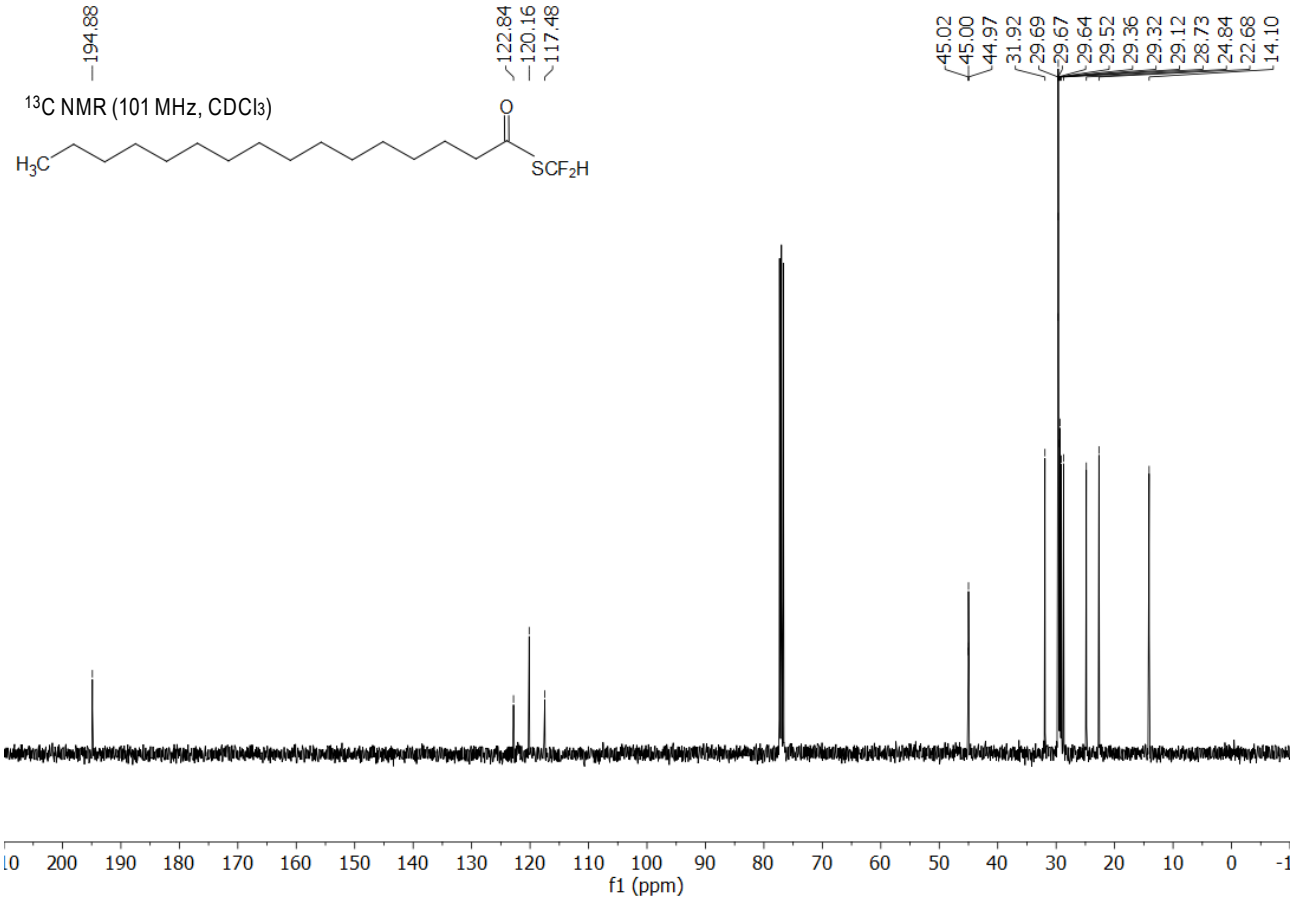




S-(difluoromethyl) hexadecanethioate **3d**

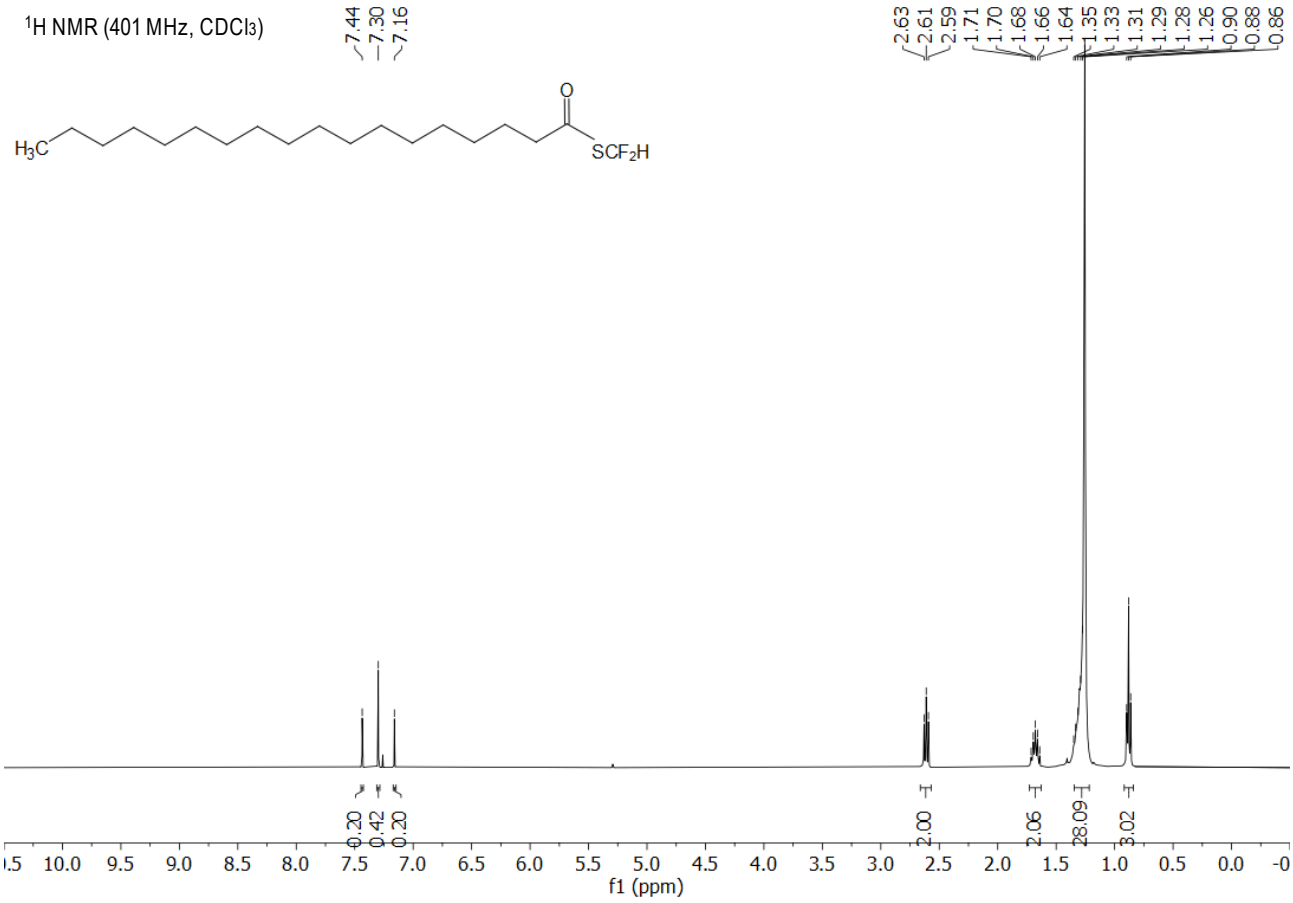



19F NMR (377 MHz, CDCl3)
H3C
O
SCF2H
-100.17
-100.31
-100.10
-100.20
-100.30
-100.40
f1 (ppm)
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
f1 (ppm)

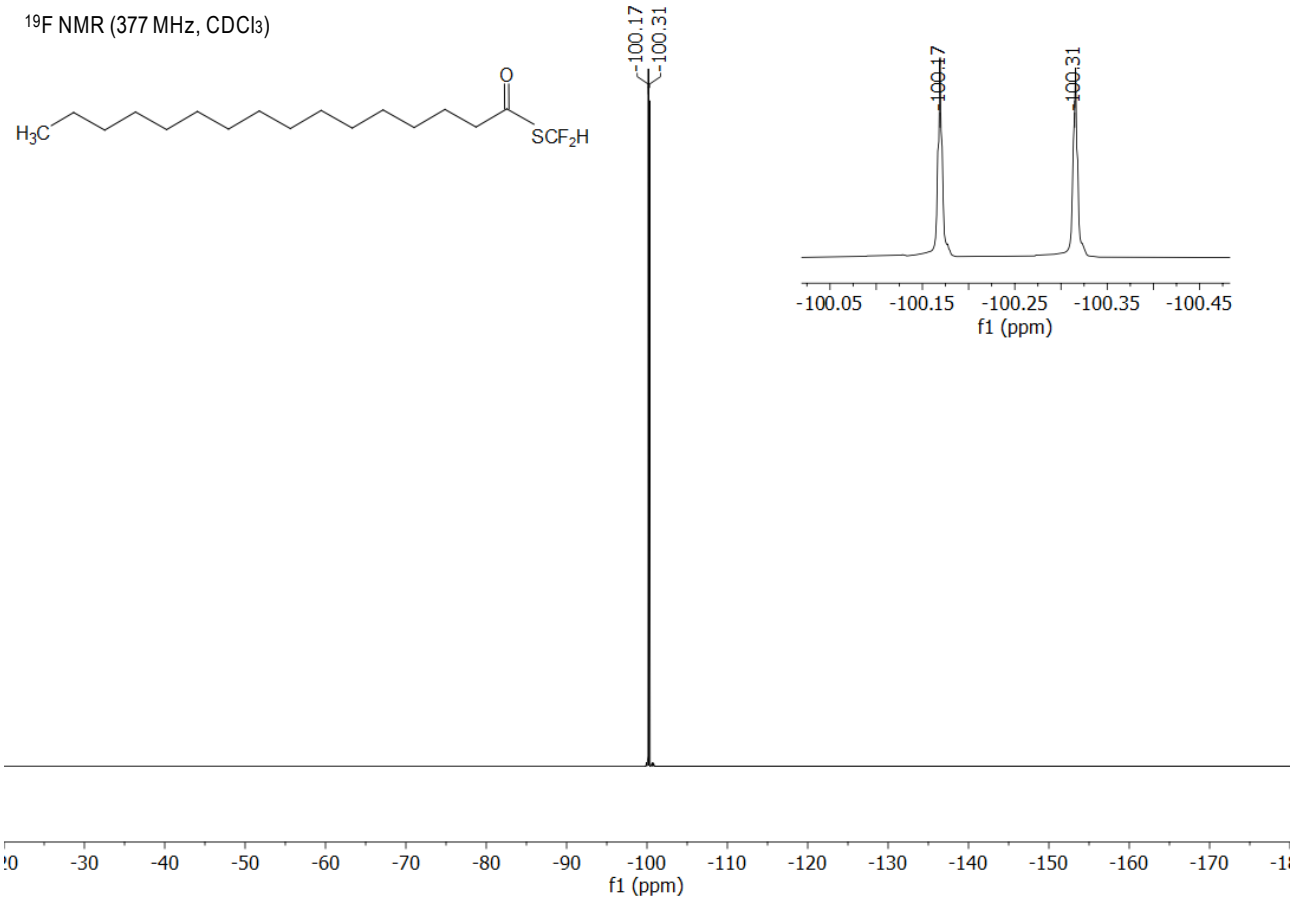

194.88
122.84
120.16
117.48
45.02
45.00
44.97
31.92
29.69
29.67
29.64
29.52
29.36
29.32
29.12
28.73
24.84
22.68
14.10
13C NMR (101 MHz, CDCl3)
H3C
O
SCF2H
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

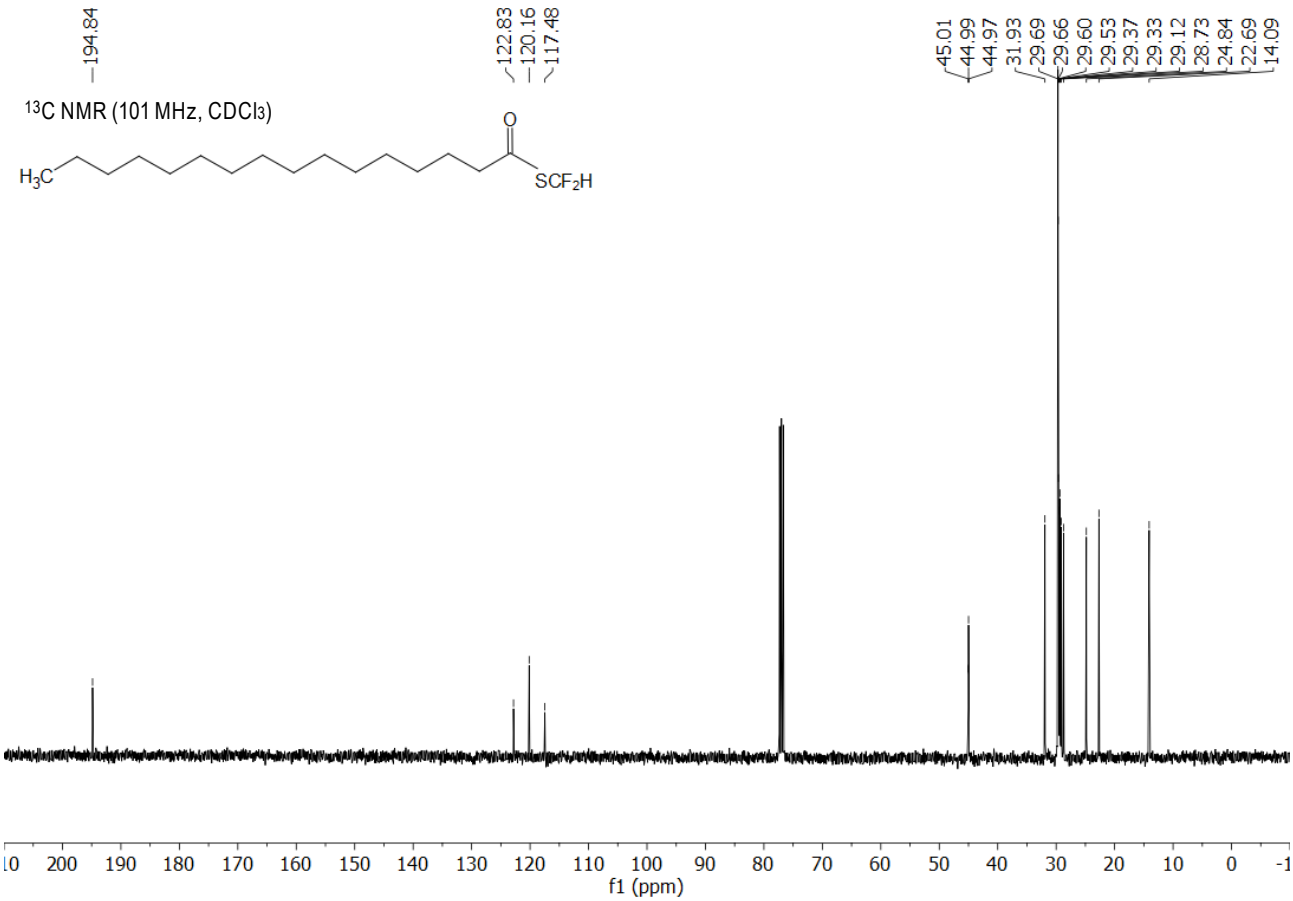
S-(difluoromethyl) octadecanethioate **3e**

^{1}H NMR (401 MHz, $CDCl_3$)

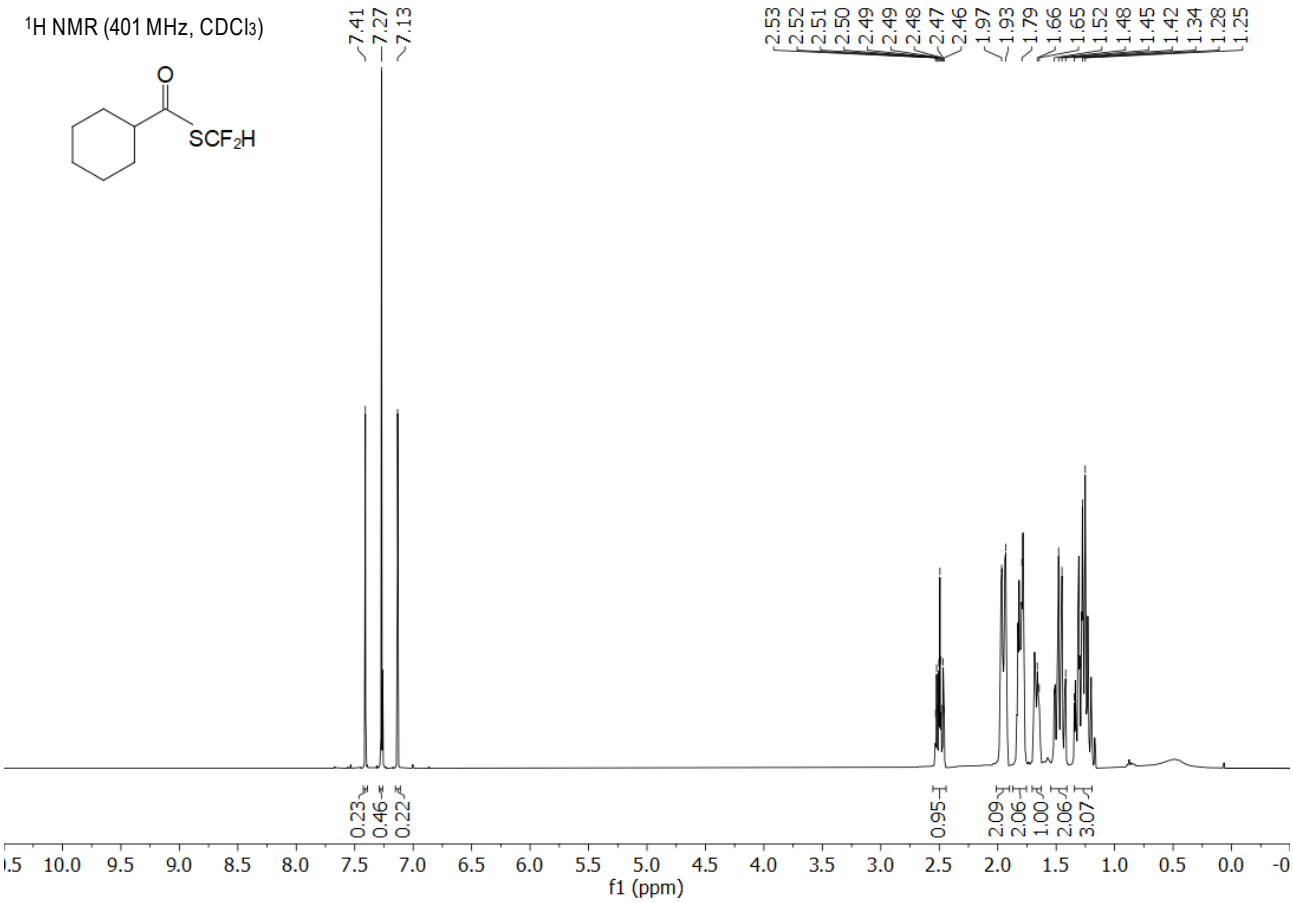


^{19}F NMR (377 MHz, $CDCl_3$)

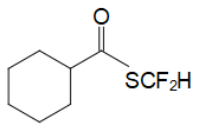


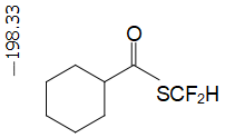


S-(difluoromethyl) cyclohexanecarbothioate **3f**



^{19}F NMR (377 MHz, $CDCl_3$)

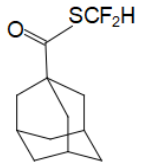




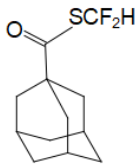
^{13}C NMR (101 MHz, $CDCl_3$)

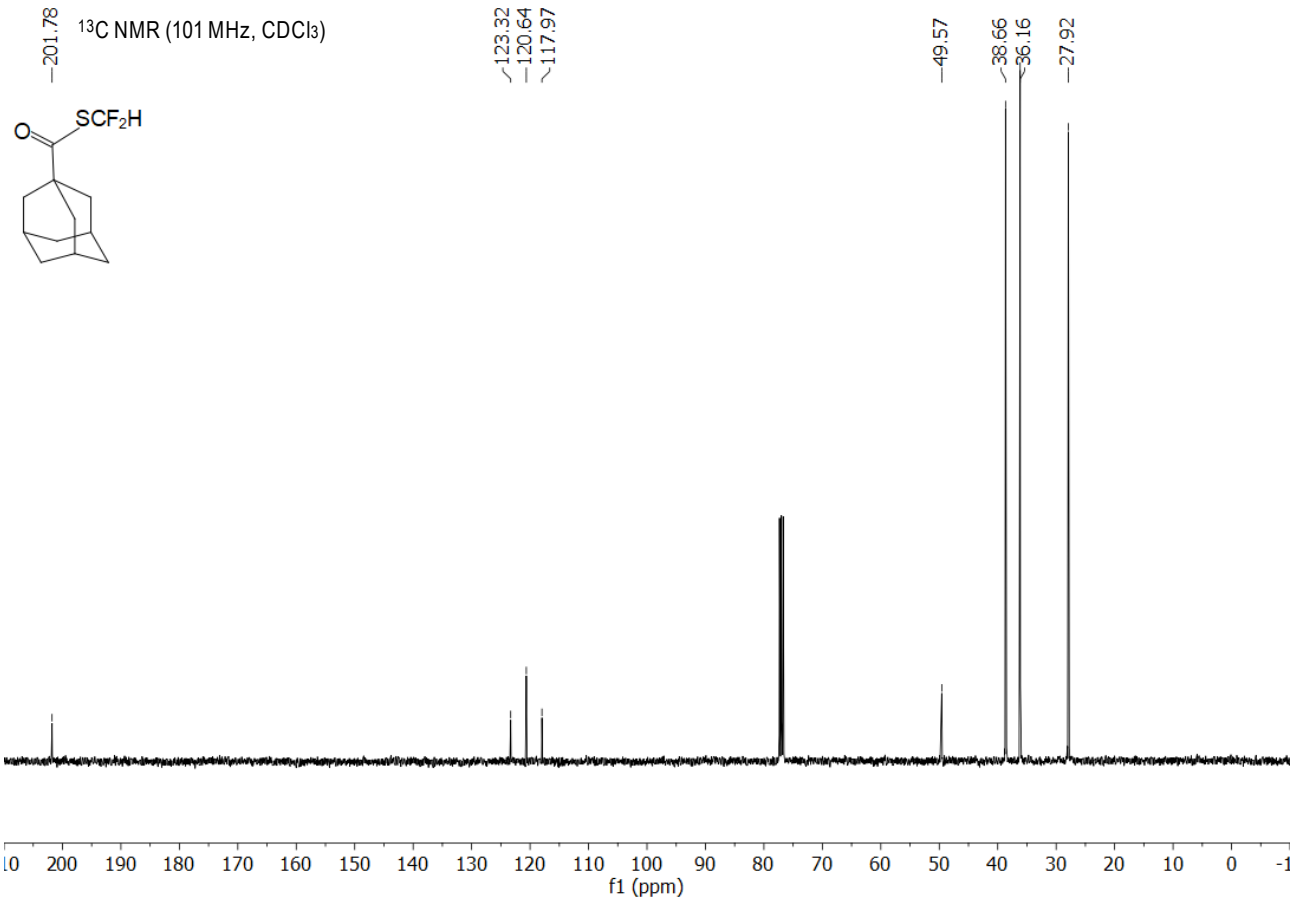
S-(difluoromethyl) (3r,5r,7r)-adamantane-1-carbothioate **3g**

^{1}H NMR (401 MHz, $CDCl_3$)

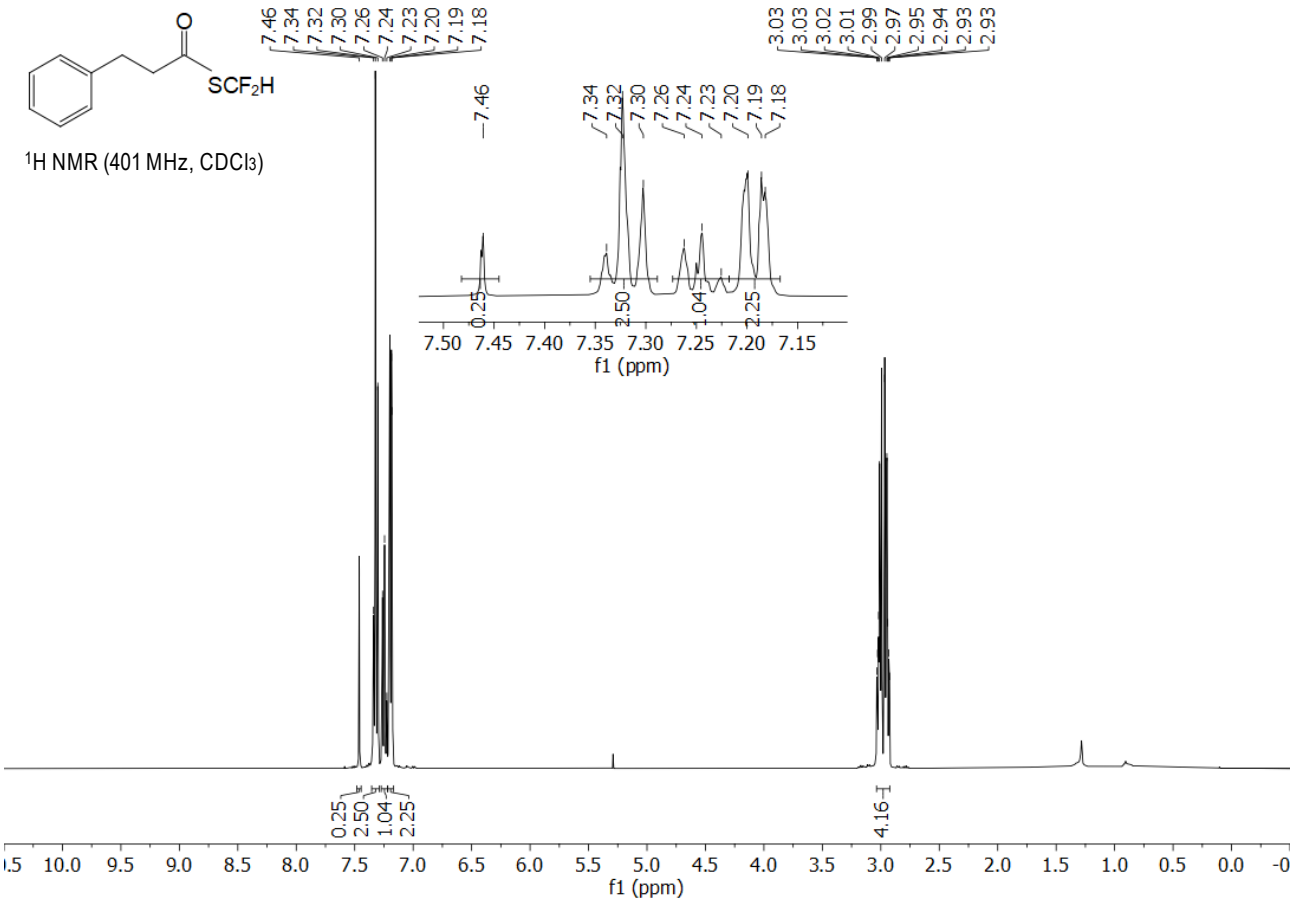


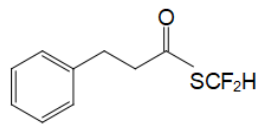
^{19}F NMR (377 MHz, $CDCl_3$)



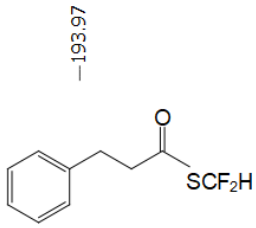


S-(difluoromethyl) 3-phenylpropanethioate **3h**





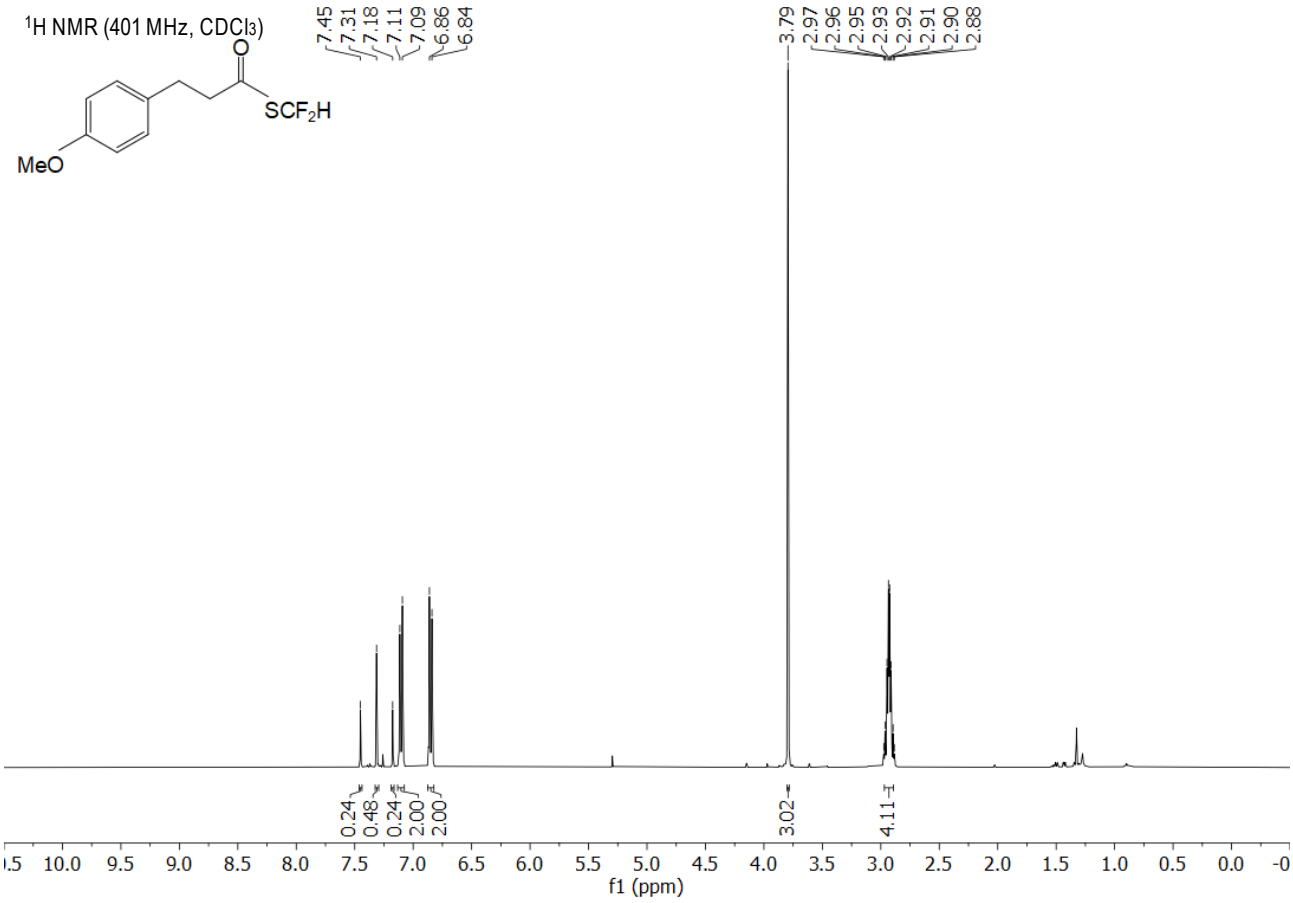
^{19}F NMR (377 MHz, $CDCl_3$)



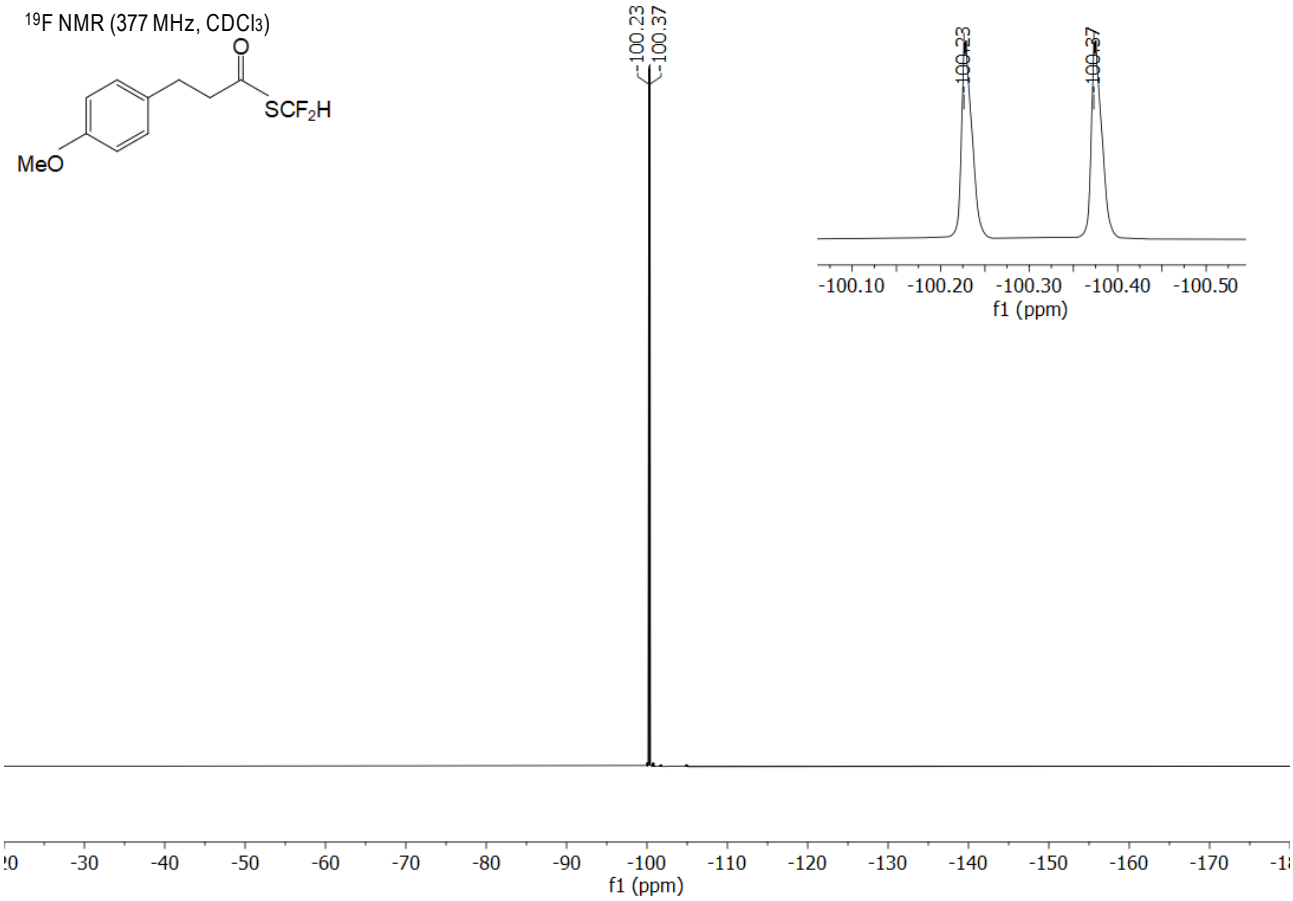
^{13}C NMR (101 MHz, $CDCl_3$)

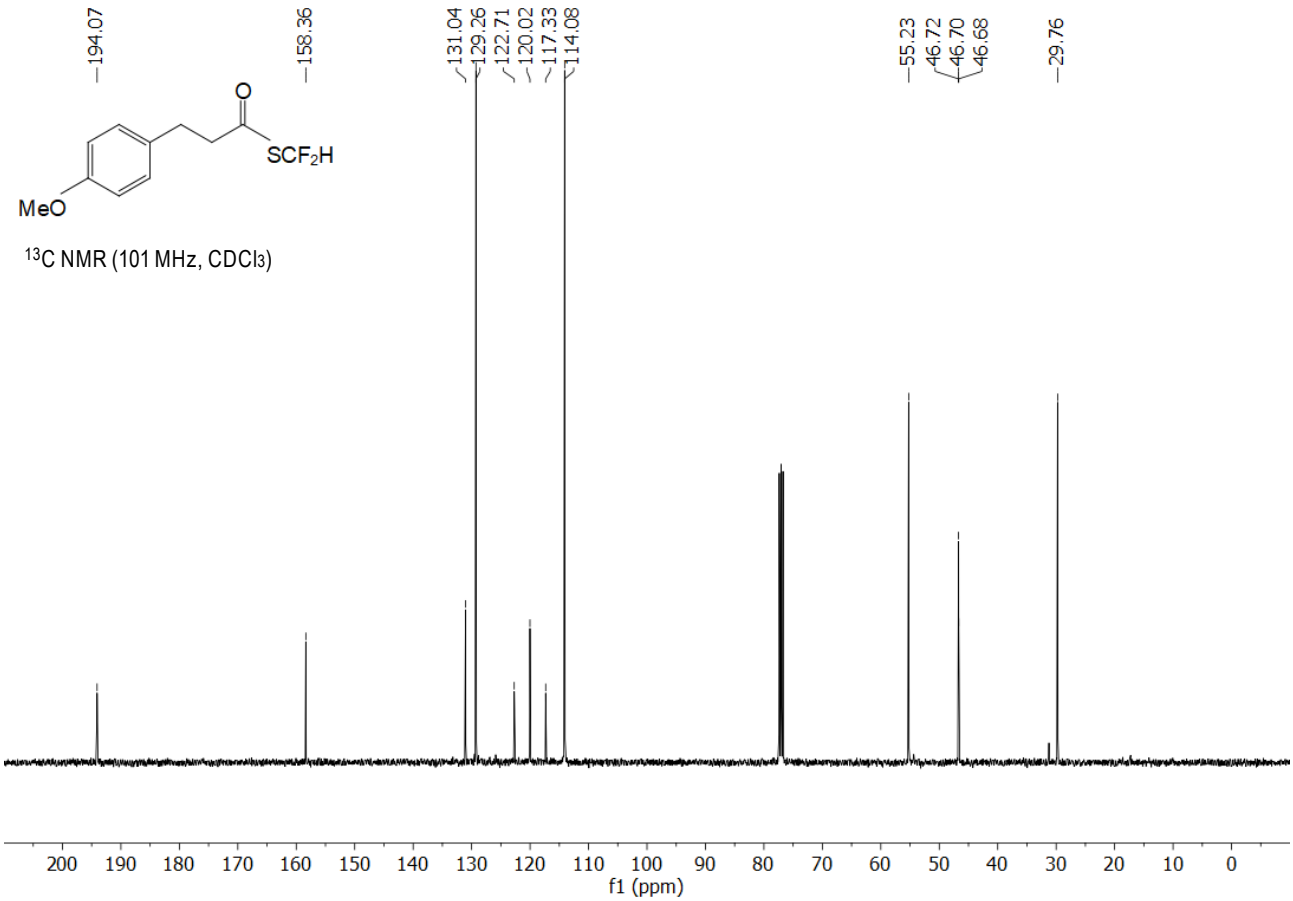
S-(difluoromethyl) 3-(4-methoxyphenyl)propanethioate **3i**

^{1}H NMR (401 MHz, $CDCl_3$)

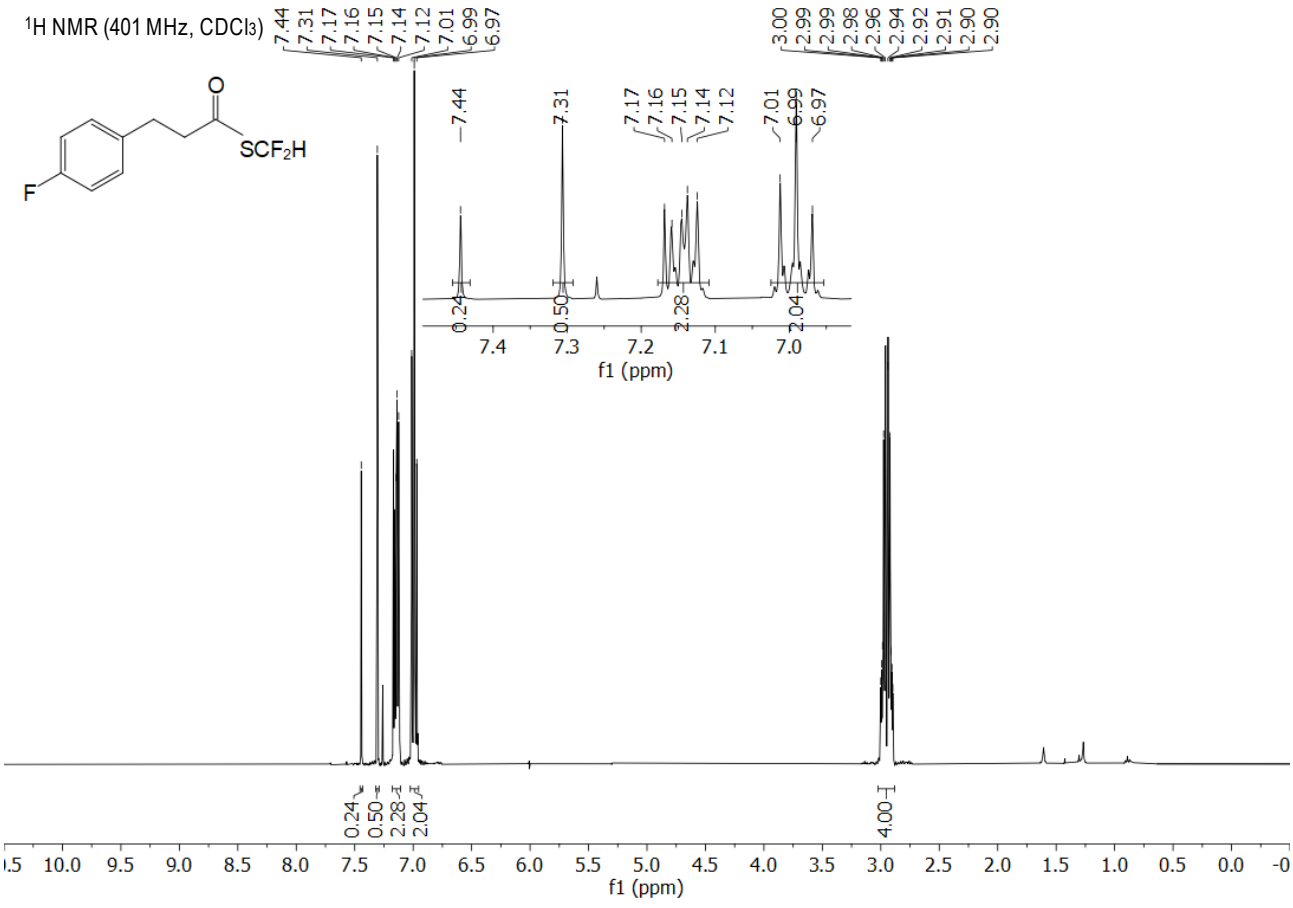


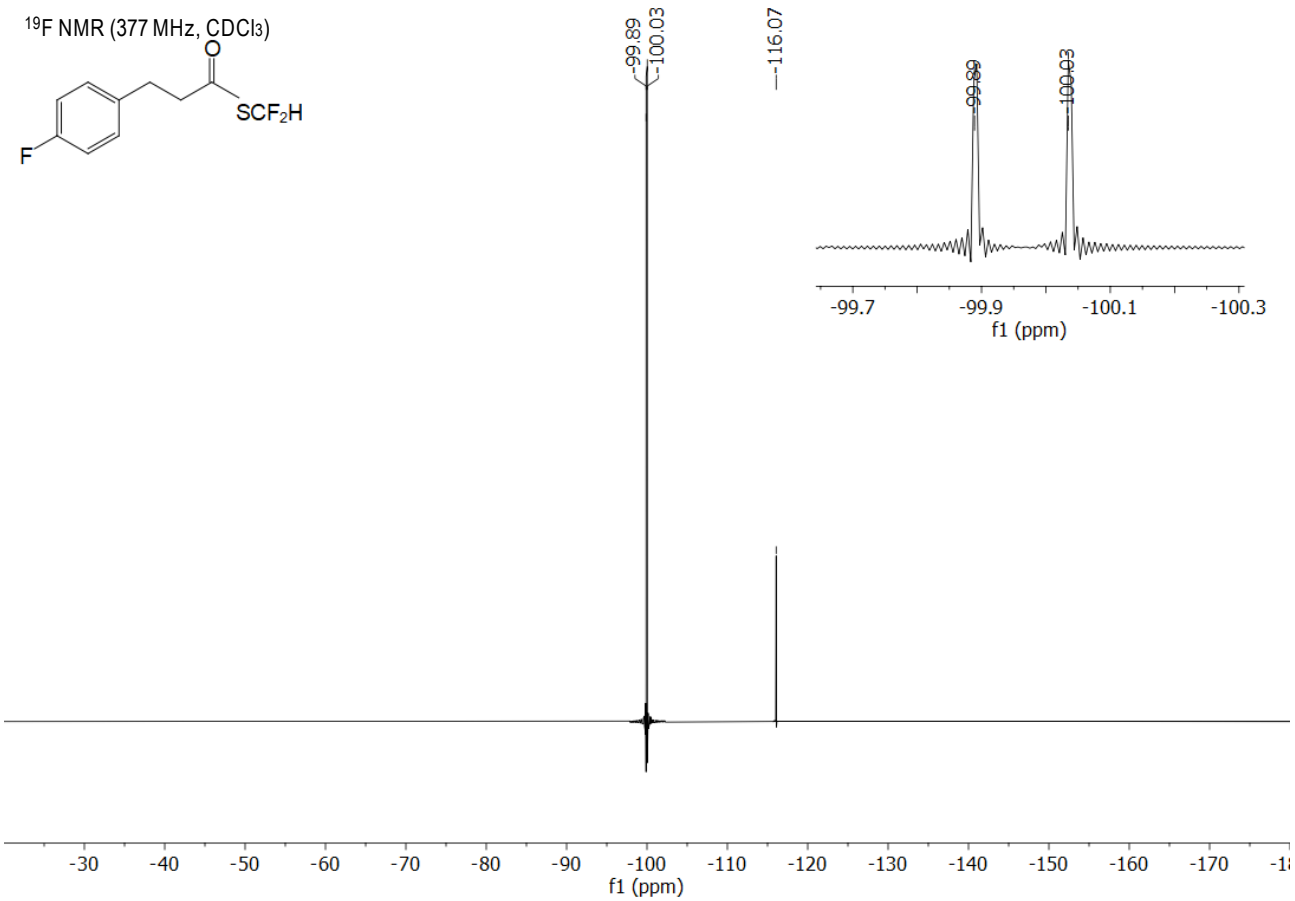
^{19}F NMR (377 MHz, $CDCl_3$)

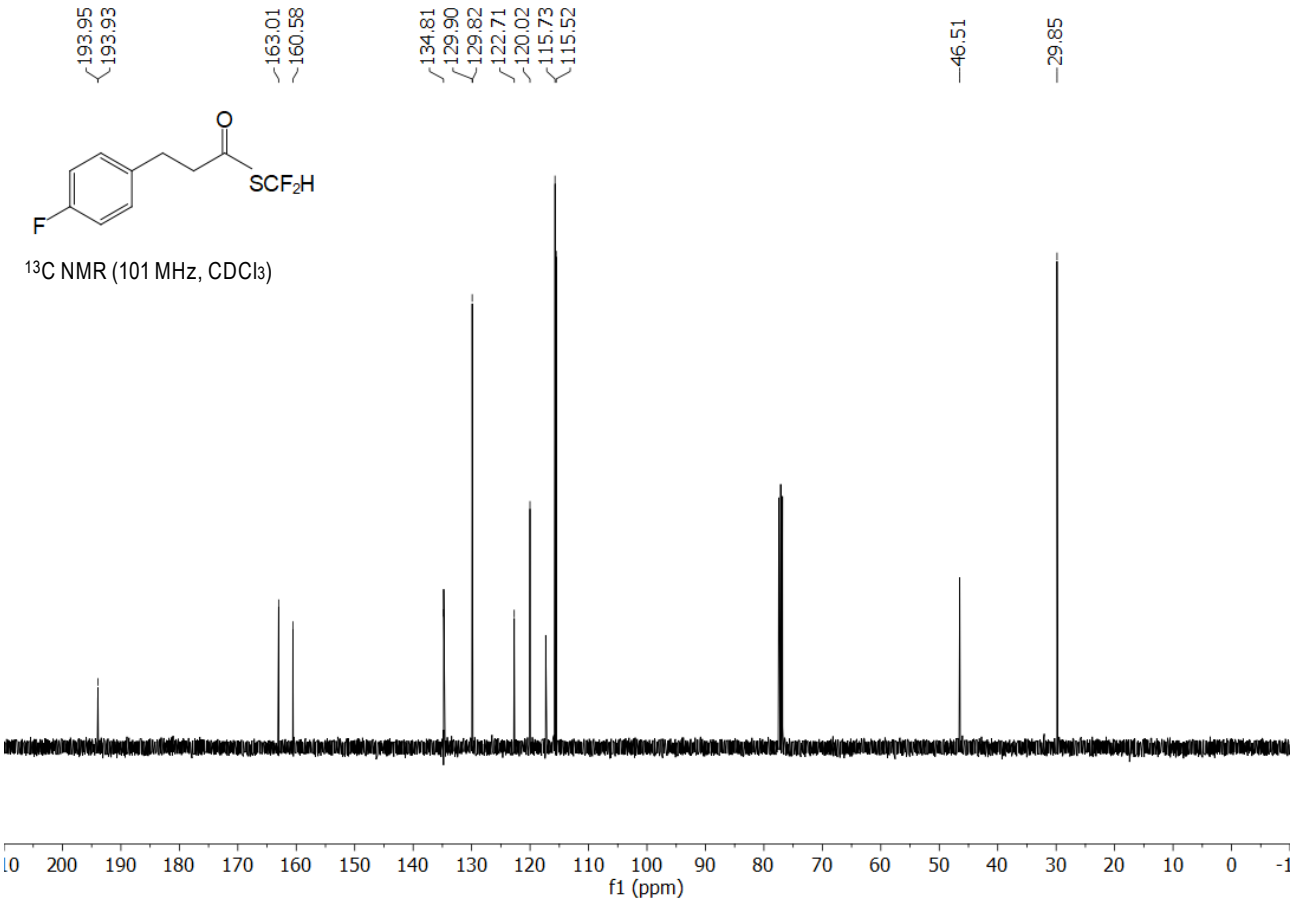




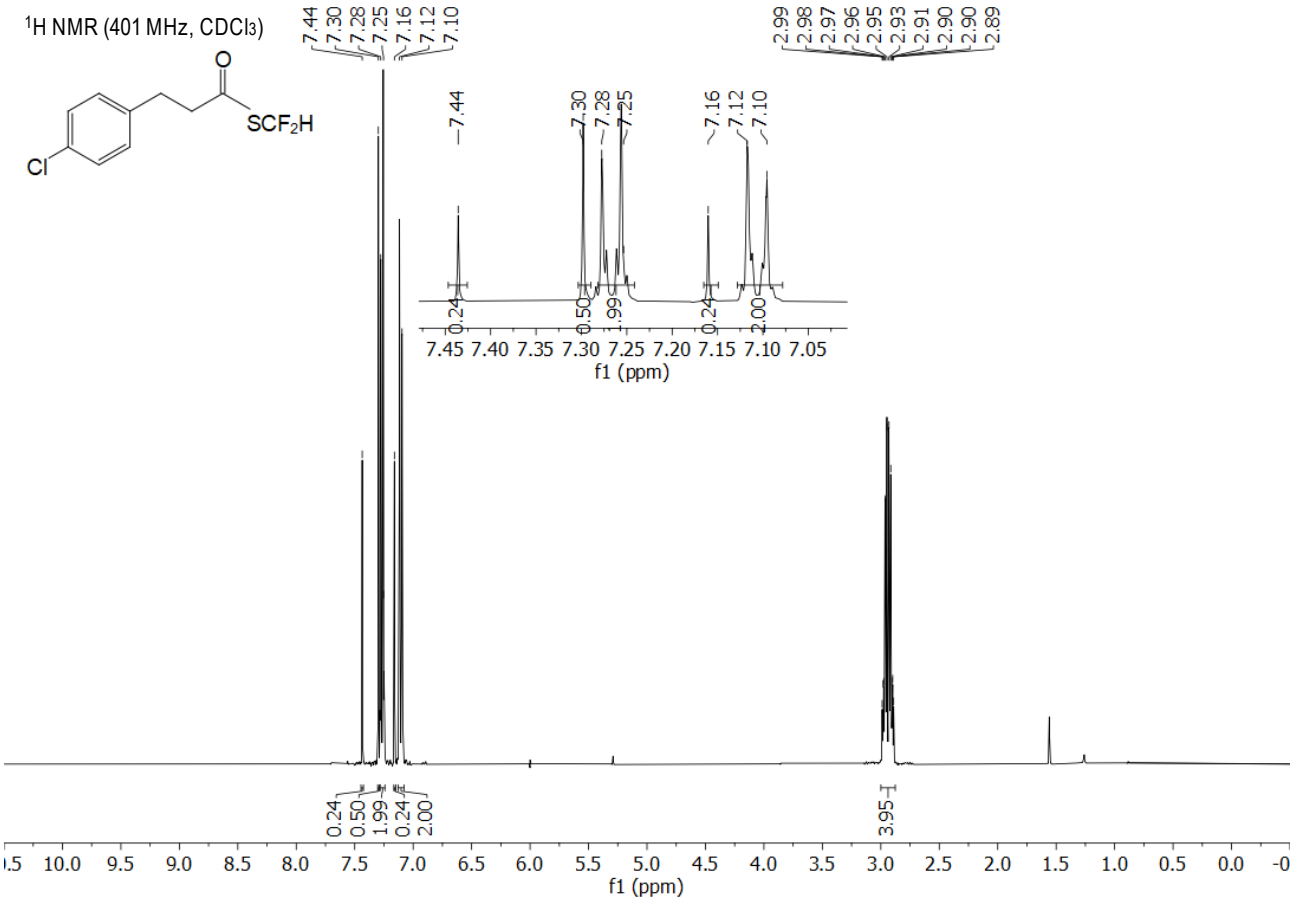
S-(difluoromethyl) 3-(4-fluoro)propanethioate **3j**

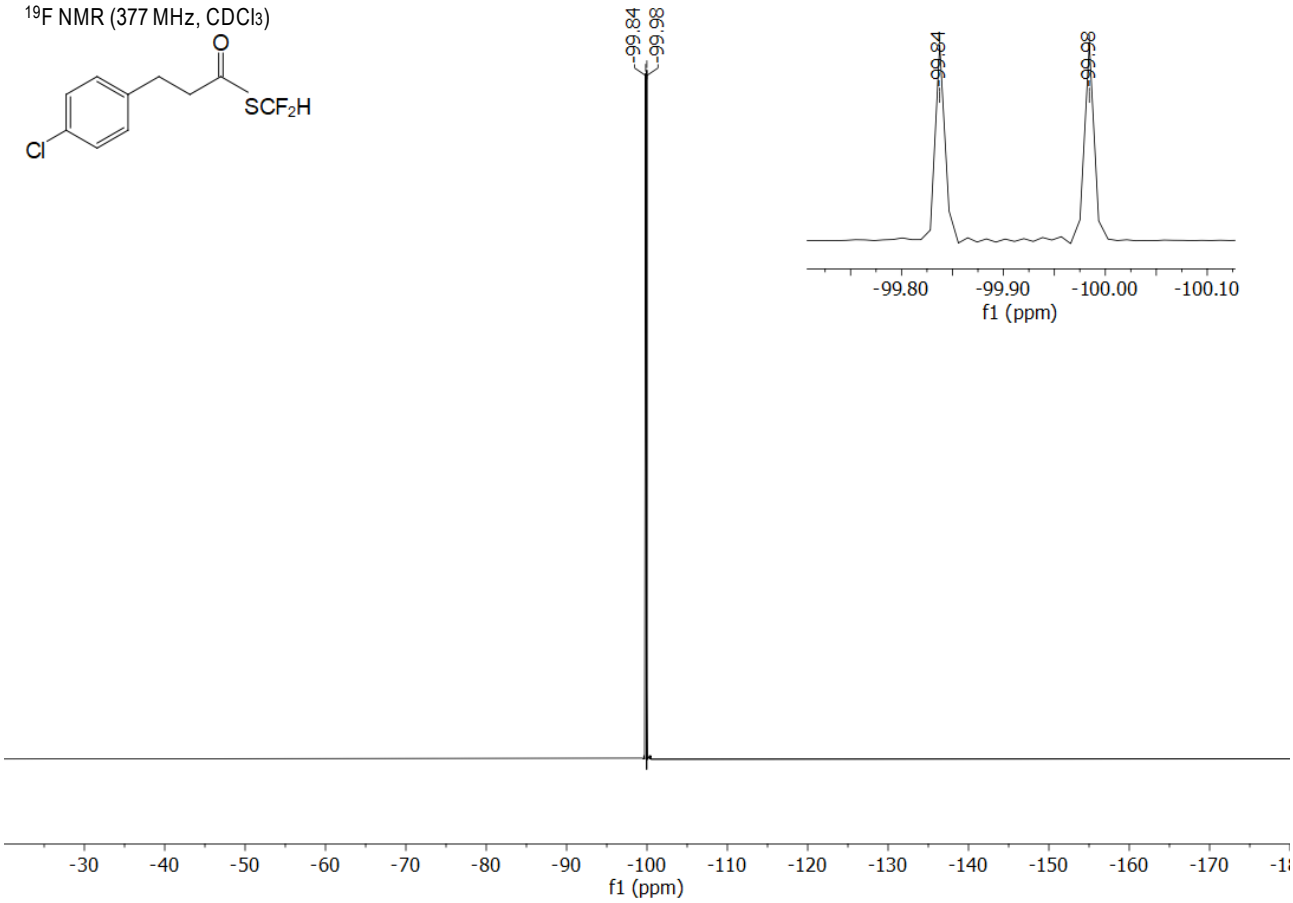


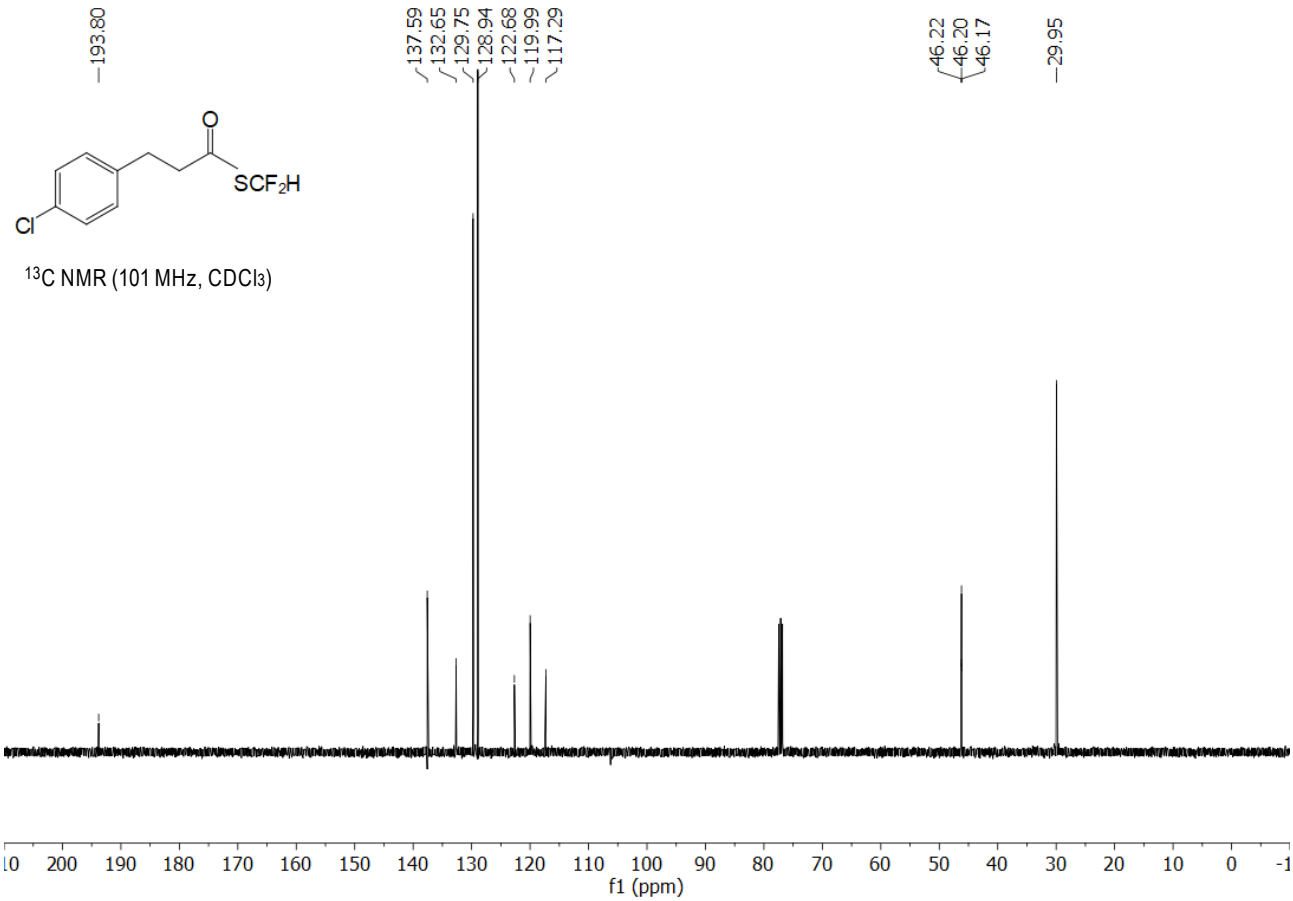

19F NMR (377 MHz, CDCl3)
O
SCF2H
F
-99.89
-100.03
-116.07
-99.89
-100.03
-99.7
-99.9
-100.1
-100.3
f1 (ppm)
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
f1 (ppm)


193.95
193.93
163.01
160.58
134.81
129.90
129.82
122.71
120.02
115.73
115.52
46.51
29.85
O
SCF2H
F
13C NMR (101 MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

S-(difluoromethyl) 3-(4-chloro)propanethioate **3k**

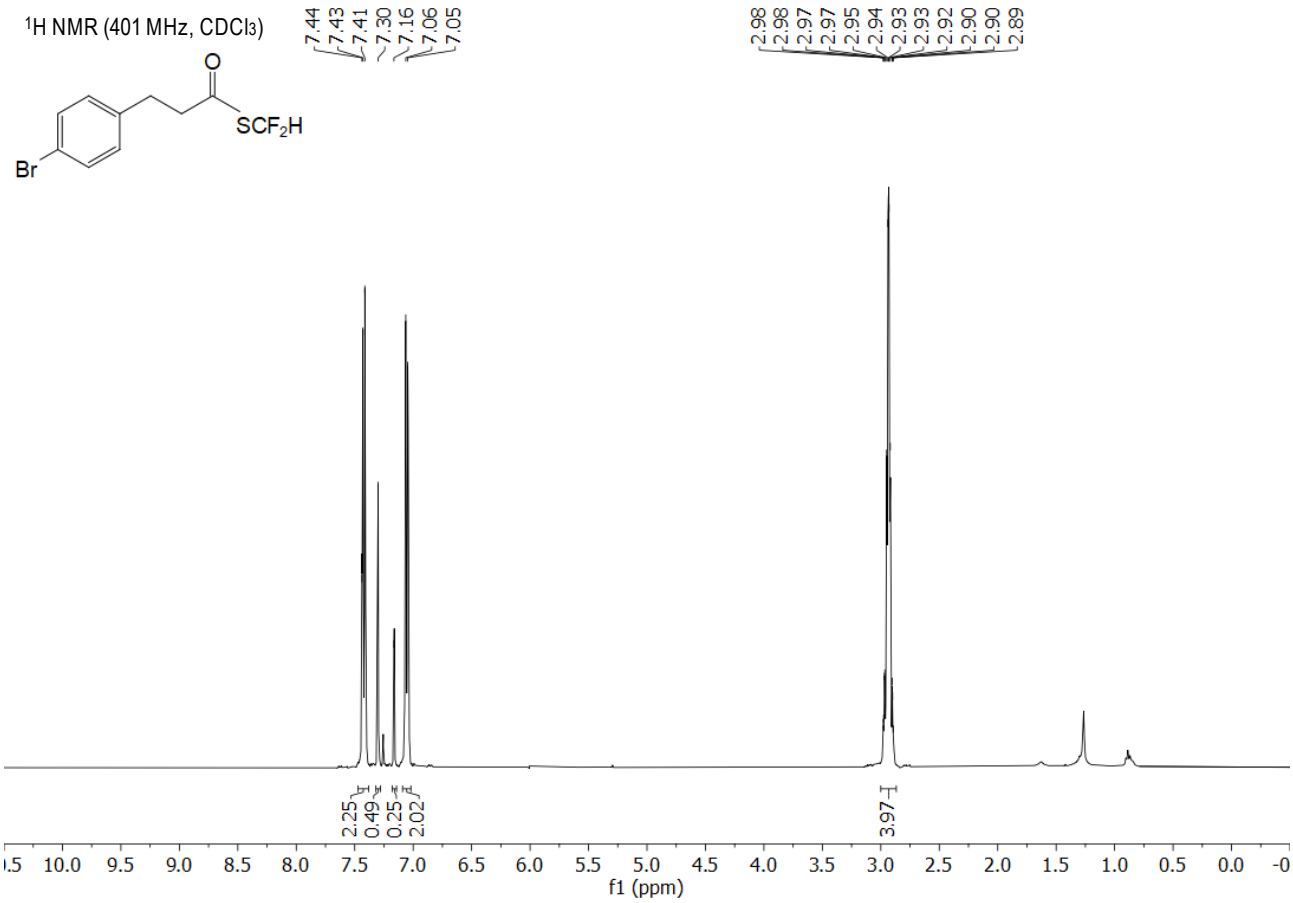






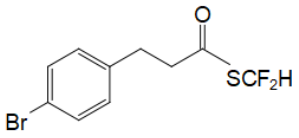
^{13}C NMR (101 MHz, $CDCl_3$)

S-(difluoromethyl) 3-(4-bromo)propanethioate **3l**

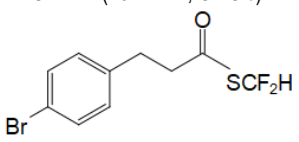


^{1}H NMR (401 MHz, $CDCl_3$)

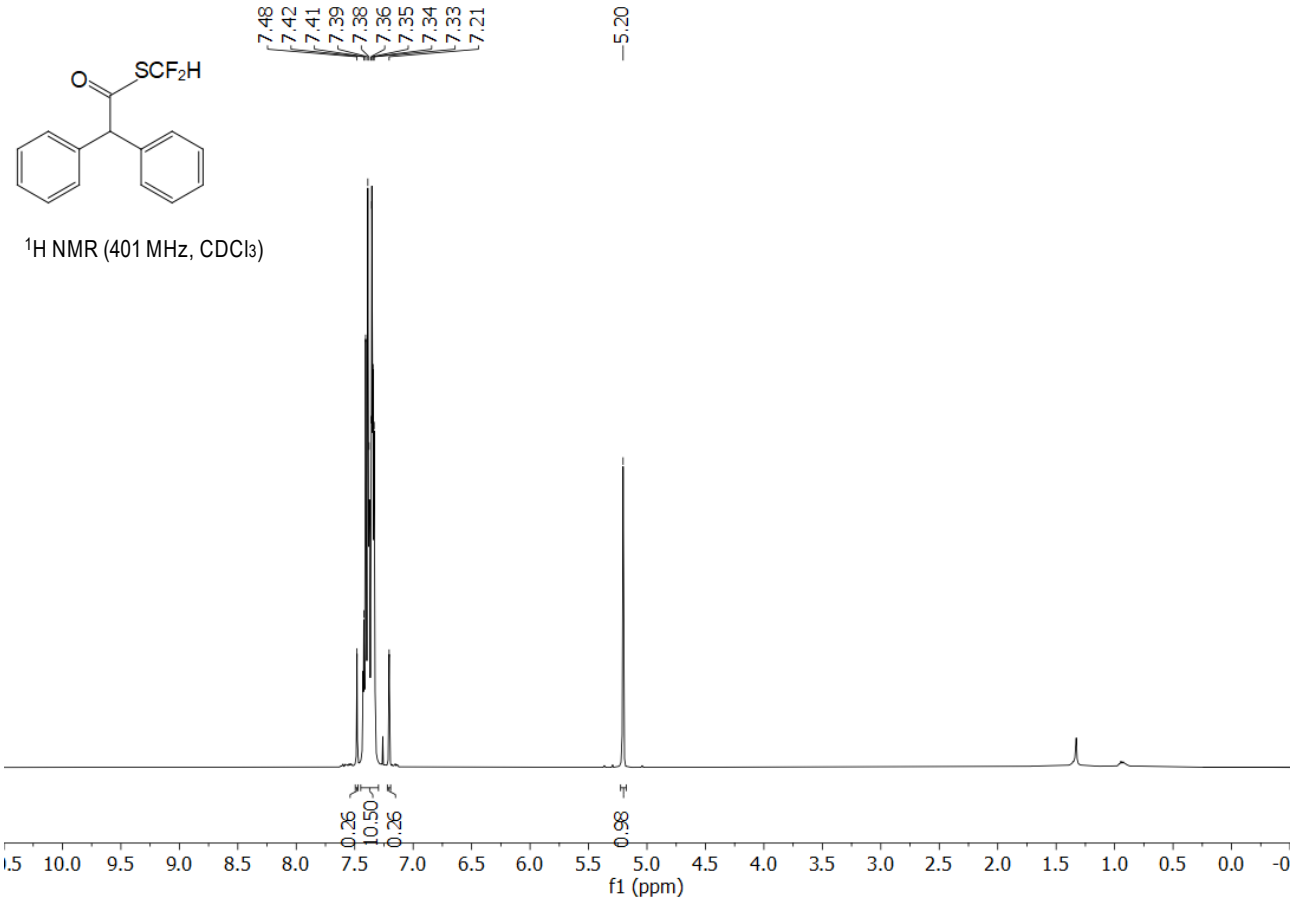
^{19}F NMR (377 MHz, CDCl$_3$)



^{13}C NMR (101 MHz, CDCl$_3$)

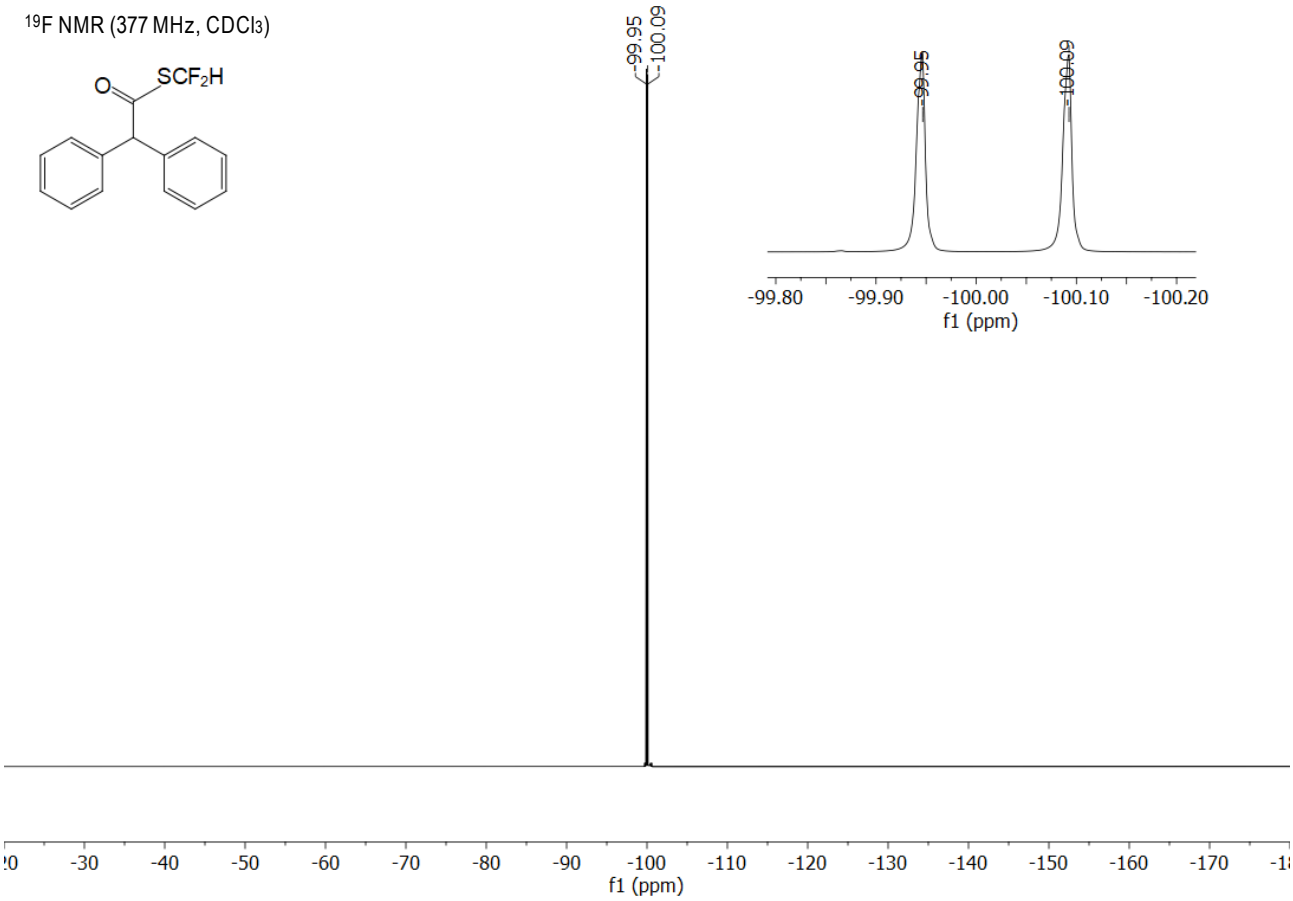


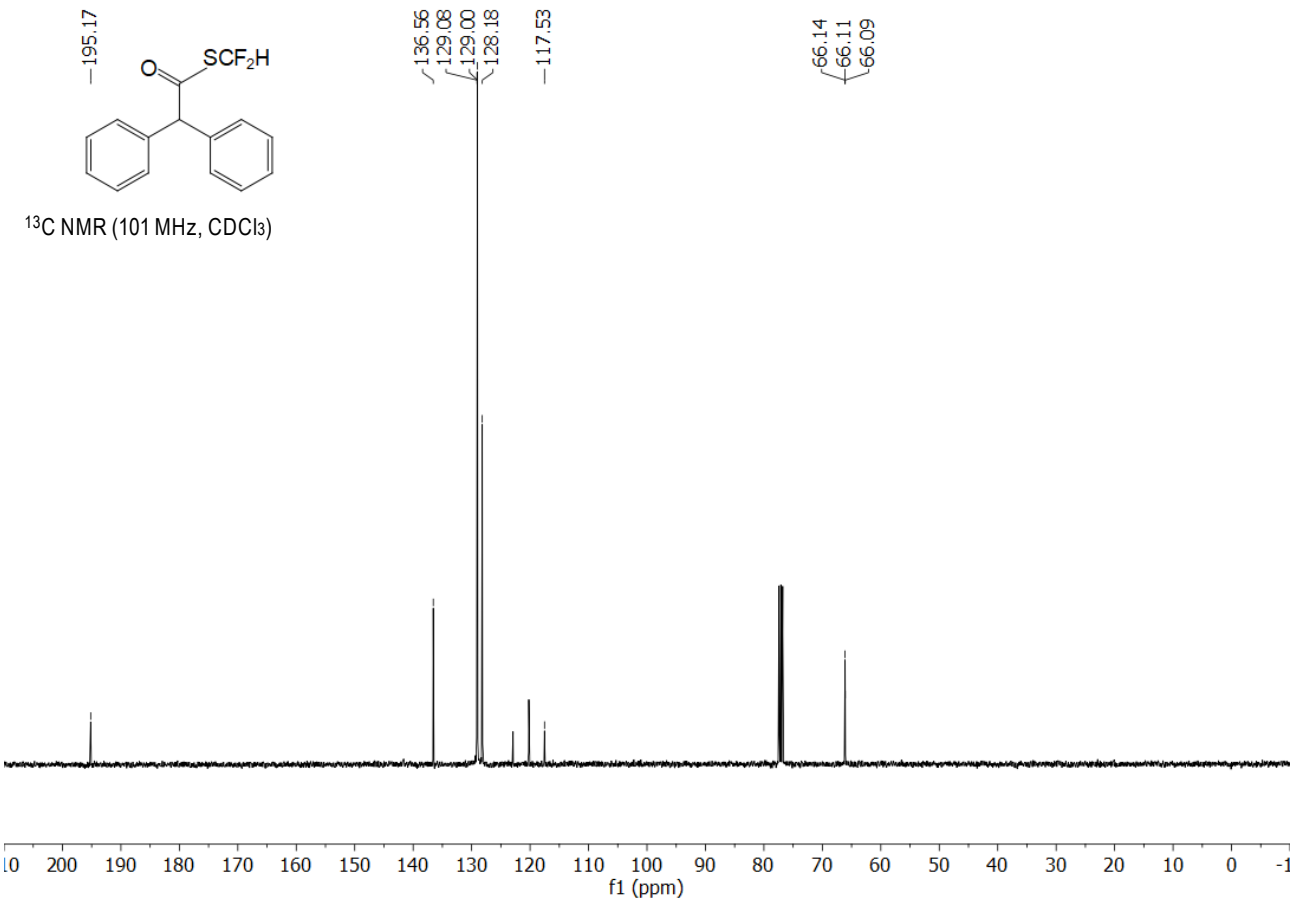
S-(difluoromethyl) 2,2-diphenylethanethioate **3m**



^{1}H NMR (401 MHz, $CDCl_3$)

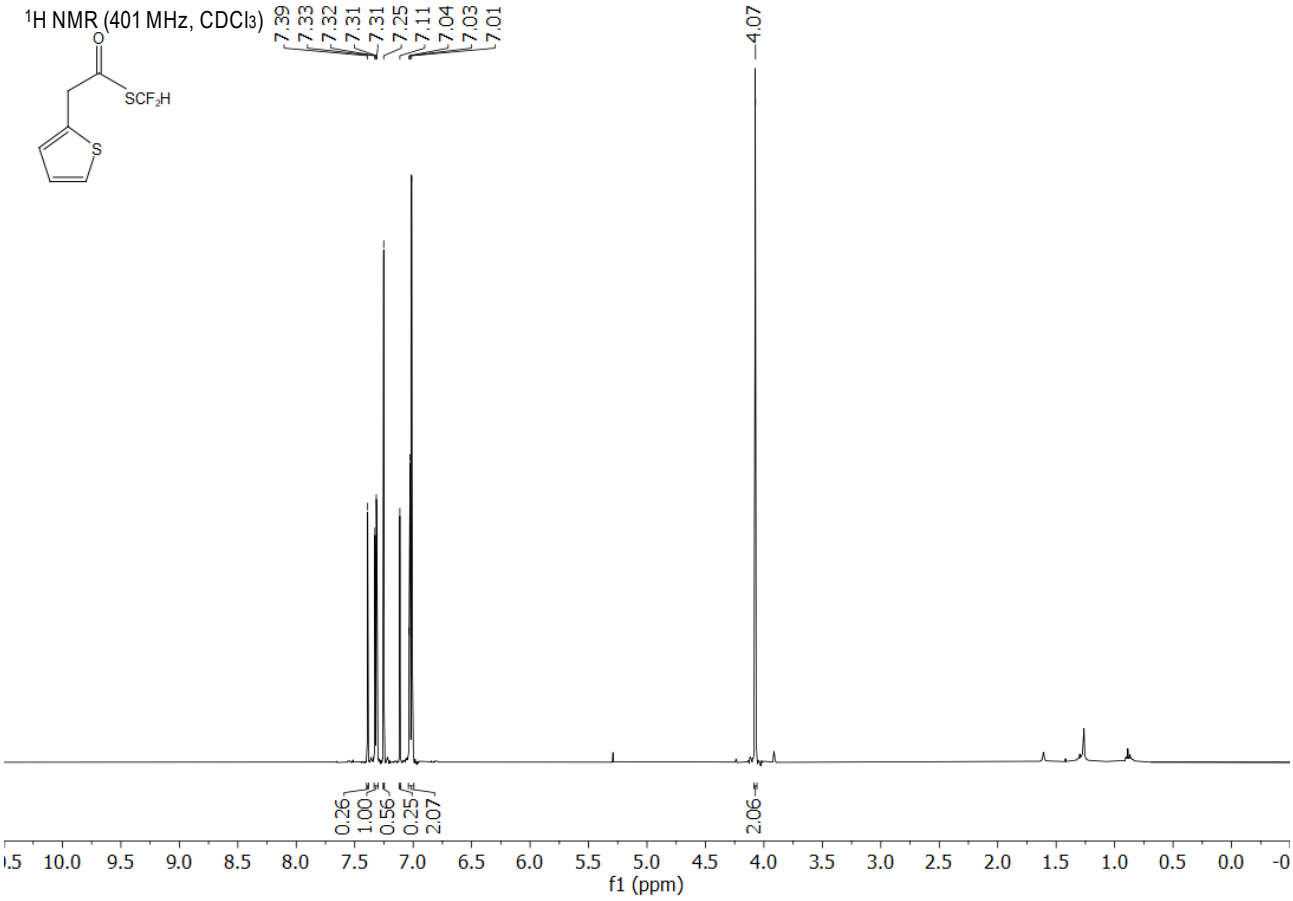
^{19}F NMR (377 MHz, $CDCl_3$)





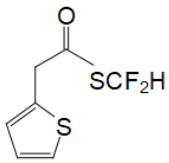
^{13}C NMR (101 MHz, $CDCl_3$)

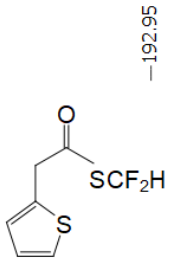
S-(difluoromethyl) 2-(thiophen-2-yl)ethanethioate **3n**



^{1}H NMR (401 MHz, $CDCl_3$)

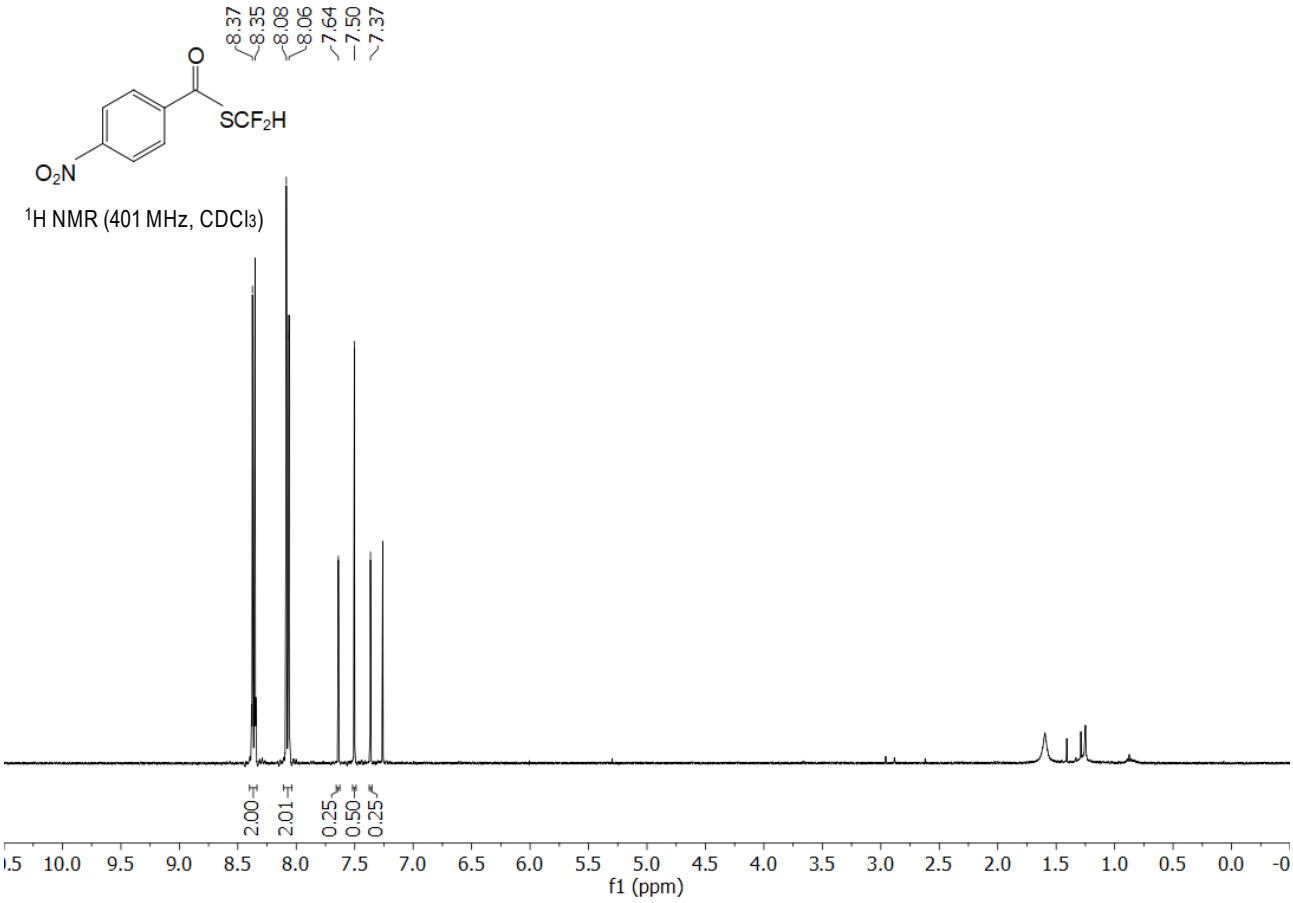
^{19}F NMR (377 MHz, CDCl$_3$)

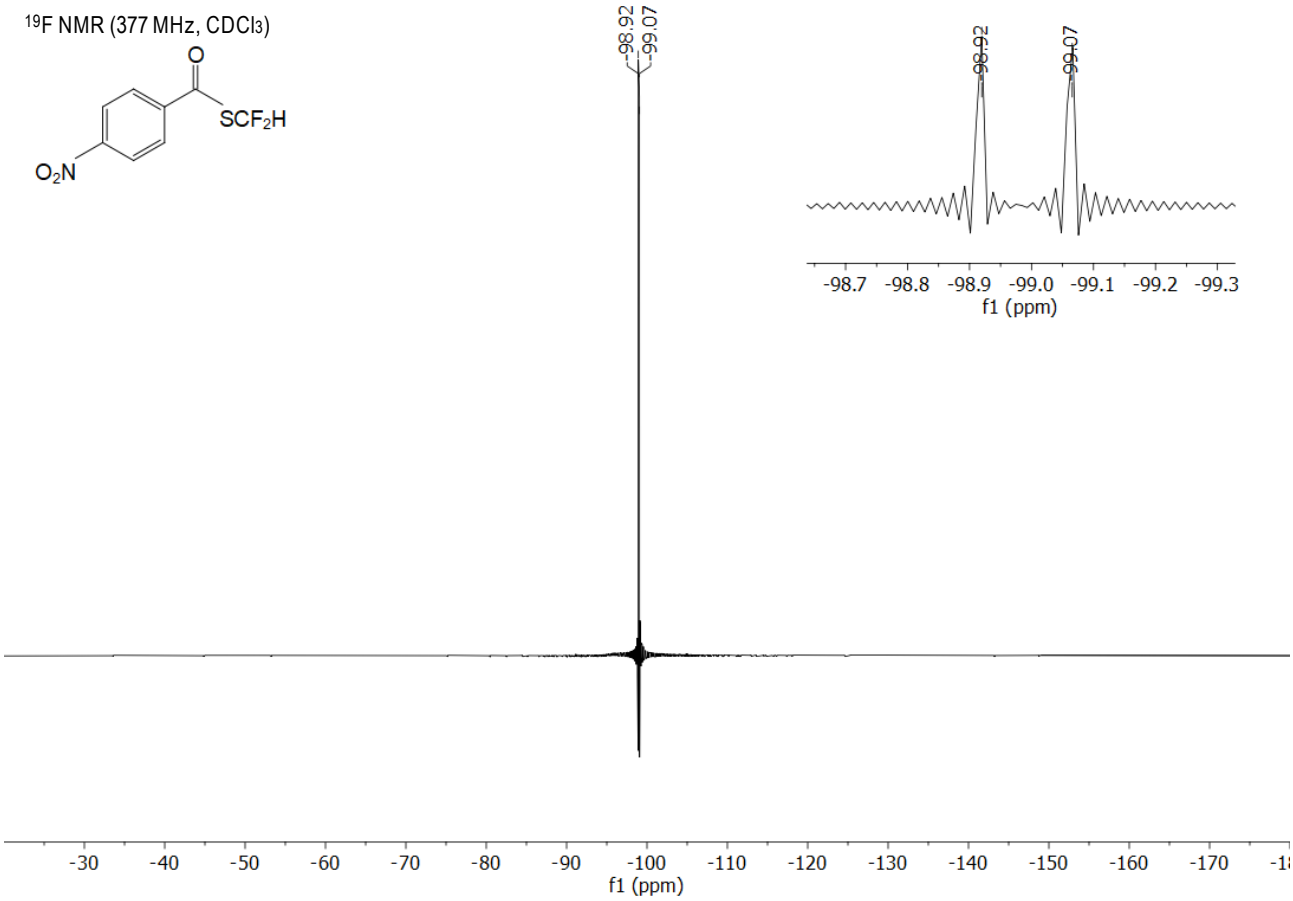


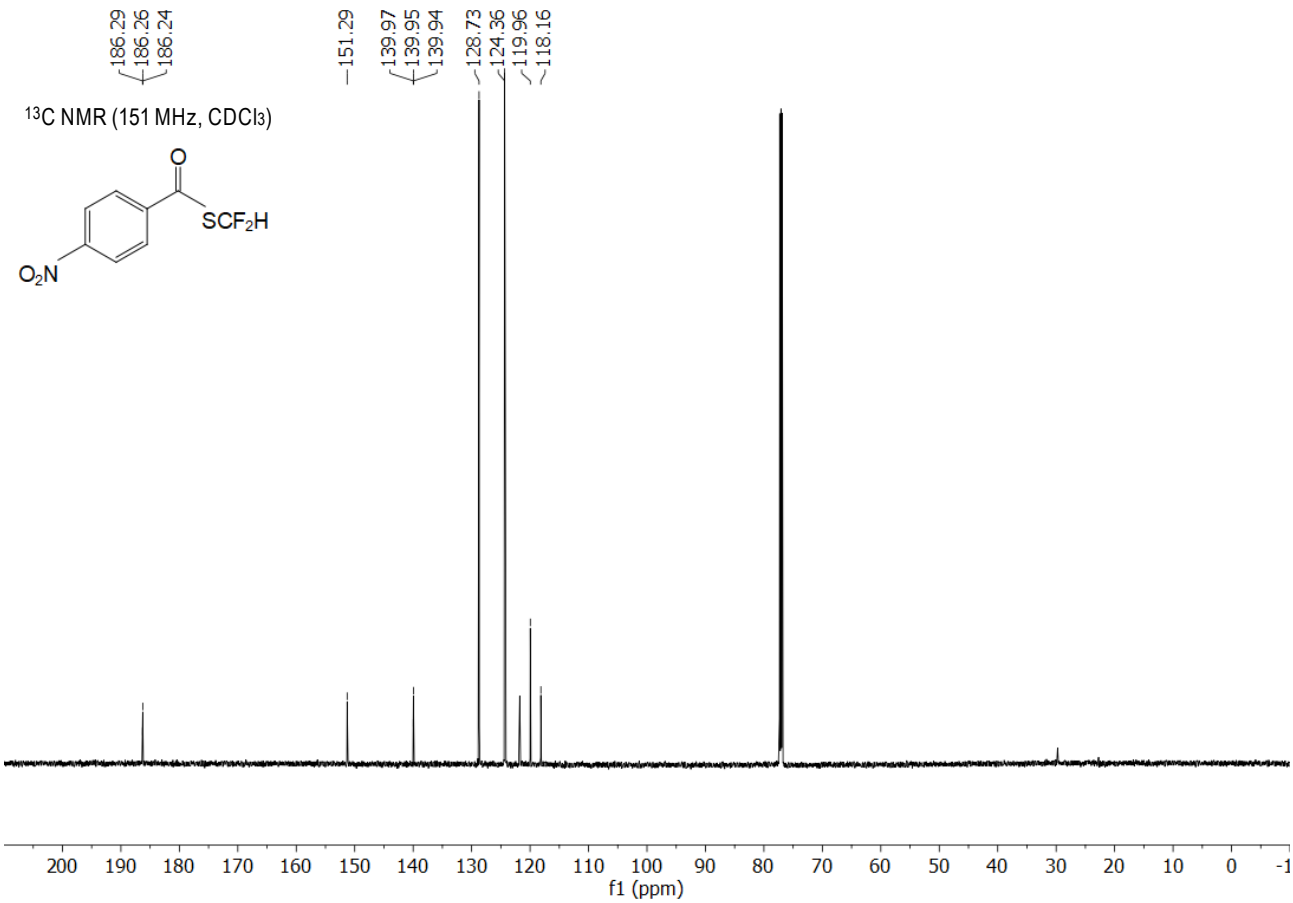


^{13}C NMR (101 MHz, CDCl$_3$)

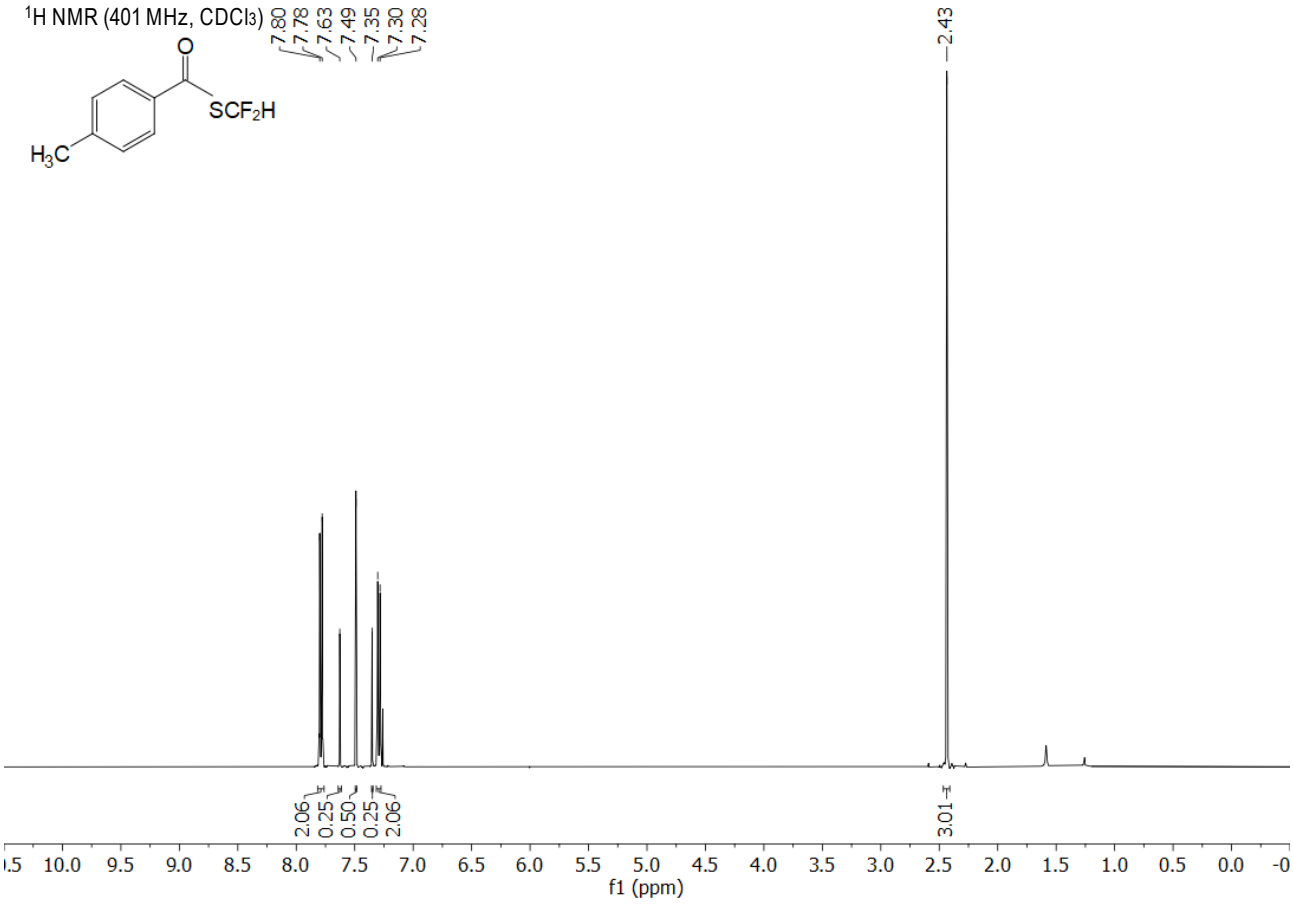
S-(difluoromethyl) 4-nitrobenzothioate **3o**



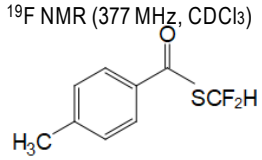


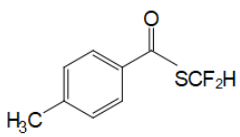


S-(difluoromethyl) 4-methylbenzothioate **3p**



^{19}F NMR (377 MHz, CDCl$_3$)

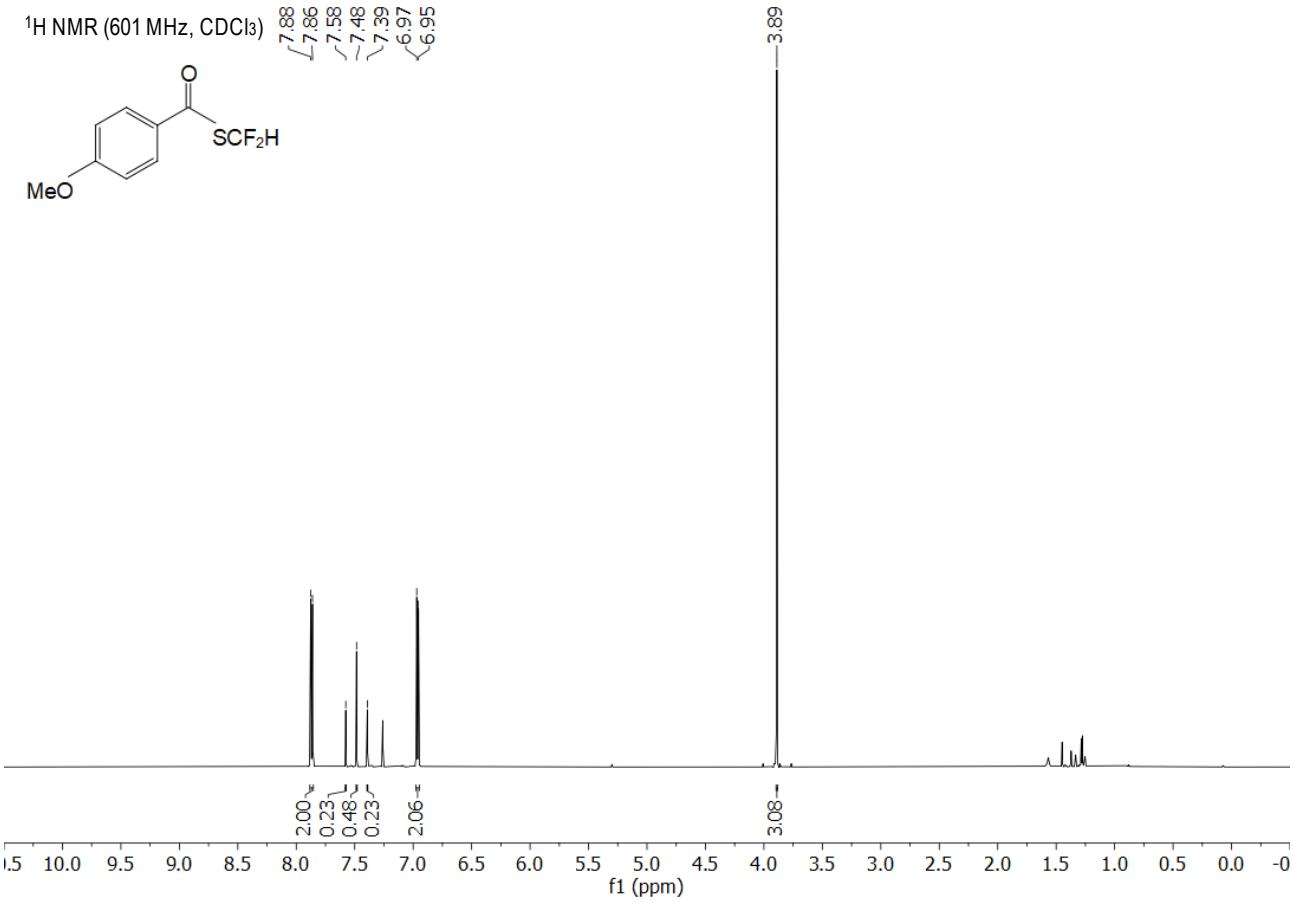




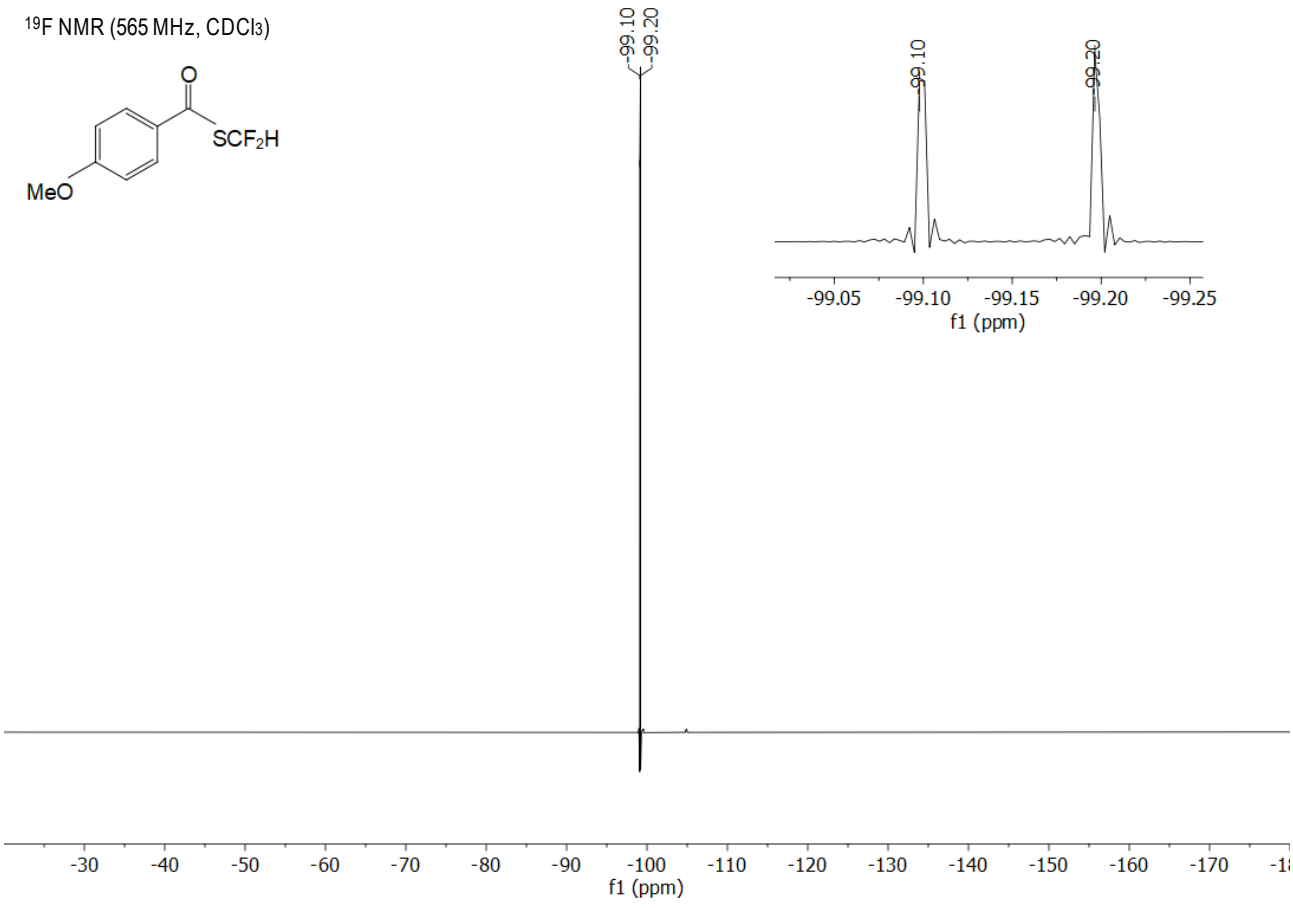
^{13}C NMR (151 MHz, CDCl$_3$)

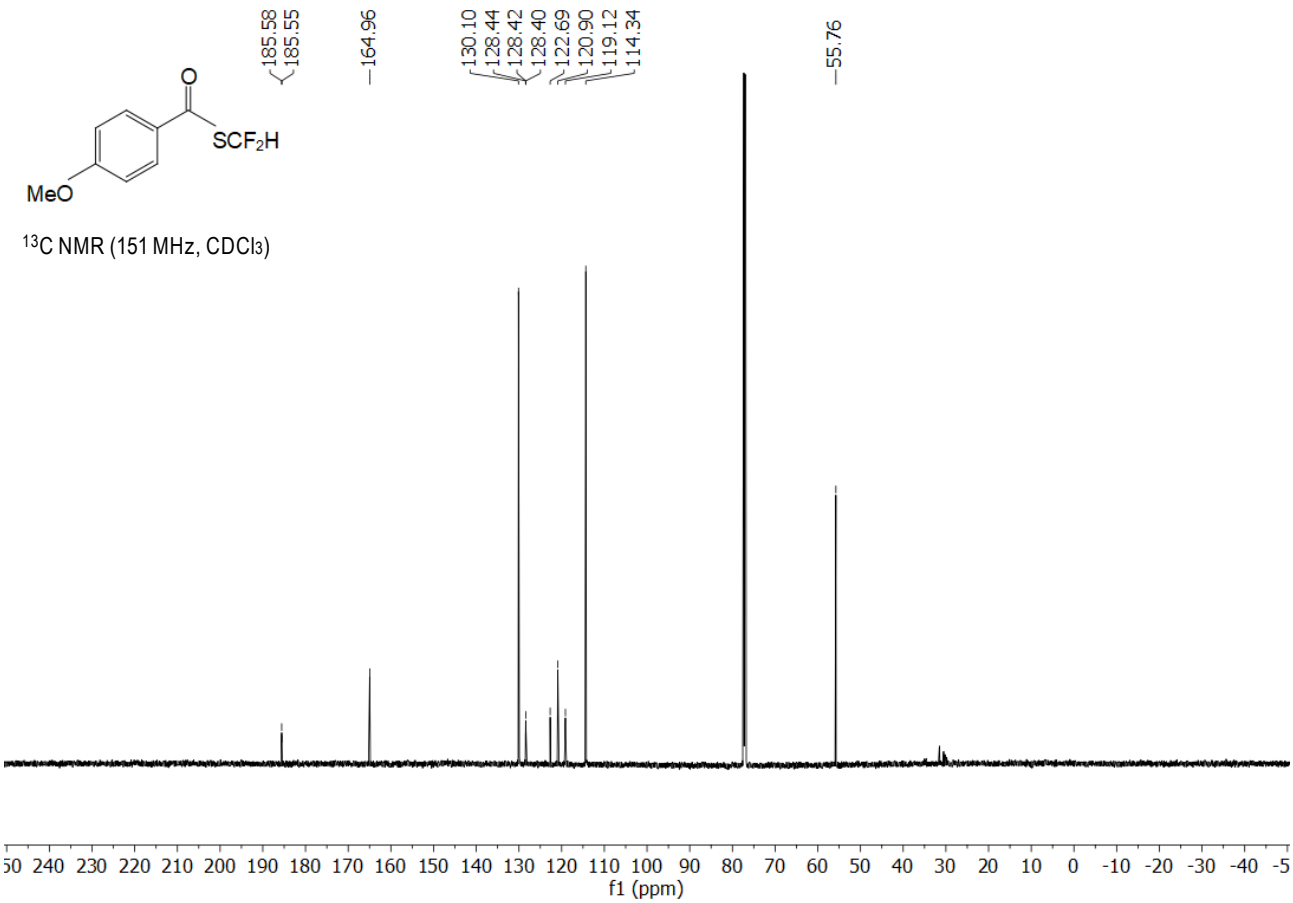
S-(difluoromethyl) 4-methoxybenzothioate **3q**

^{1}H NMR (601 MHz, $CDCl_3$)

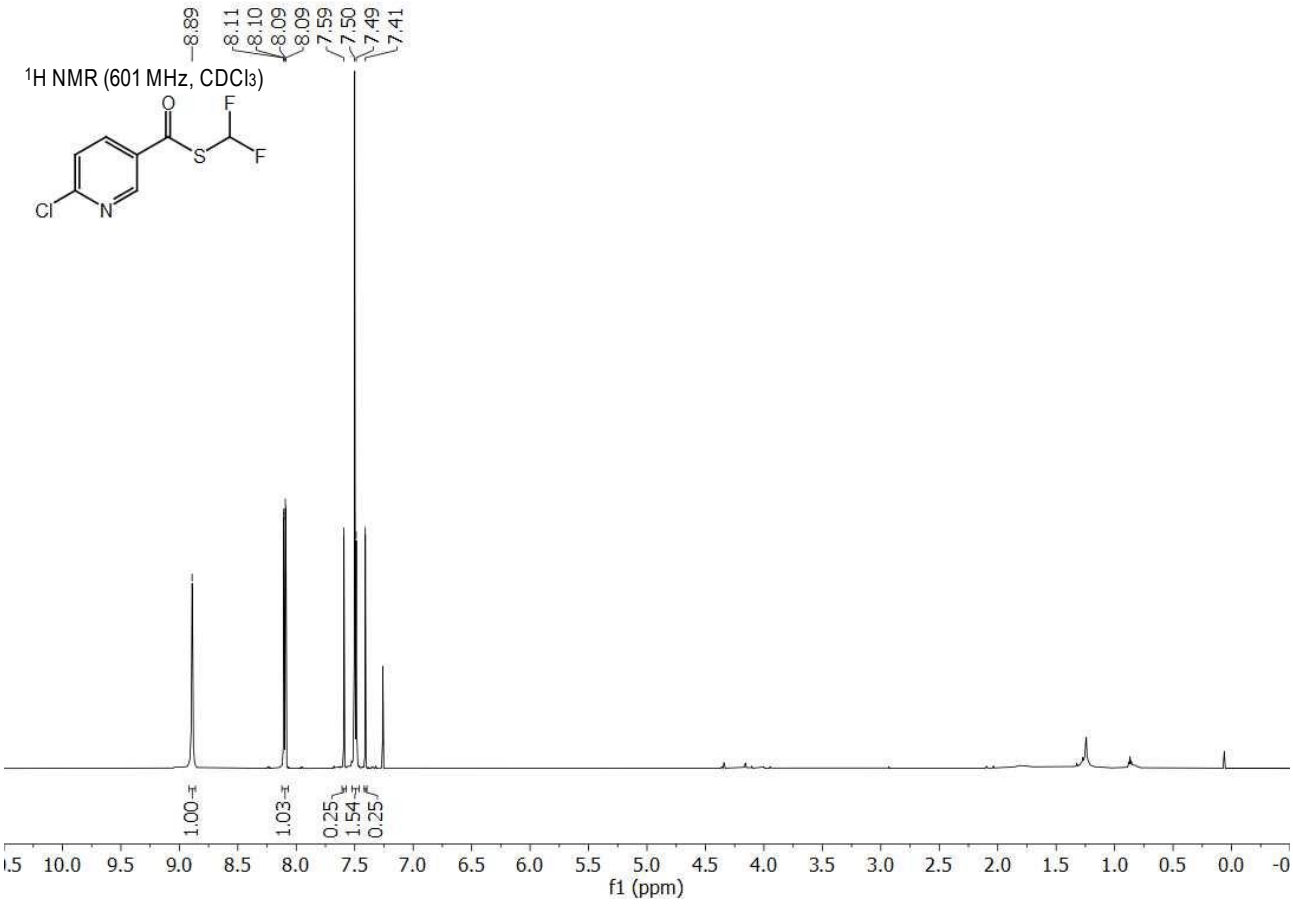


^{19}F NMR (565 MHz, $CDCl_3$)

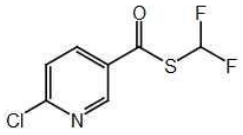




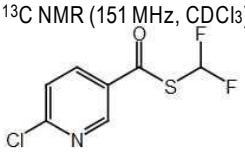
S-(difluoromethyl) 6-chloropyridine-3-carbothioate **3r**



^{19}F NMR (565 MHz, $CDCl_3$)

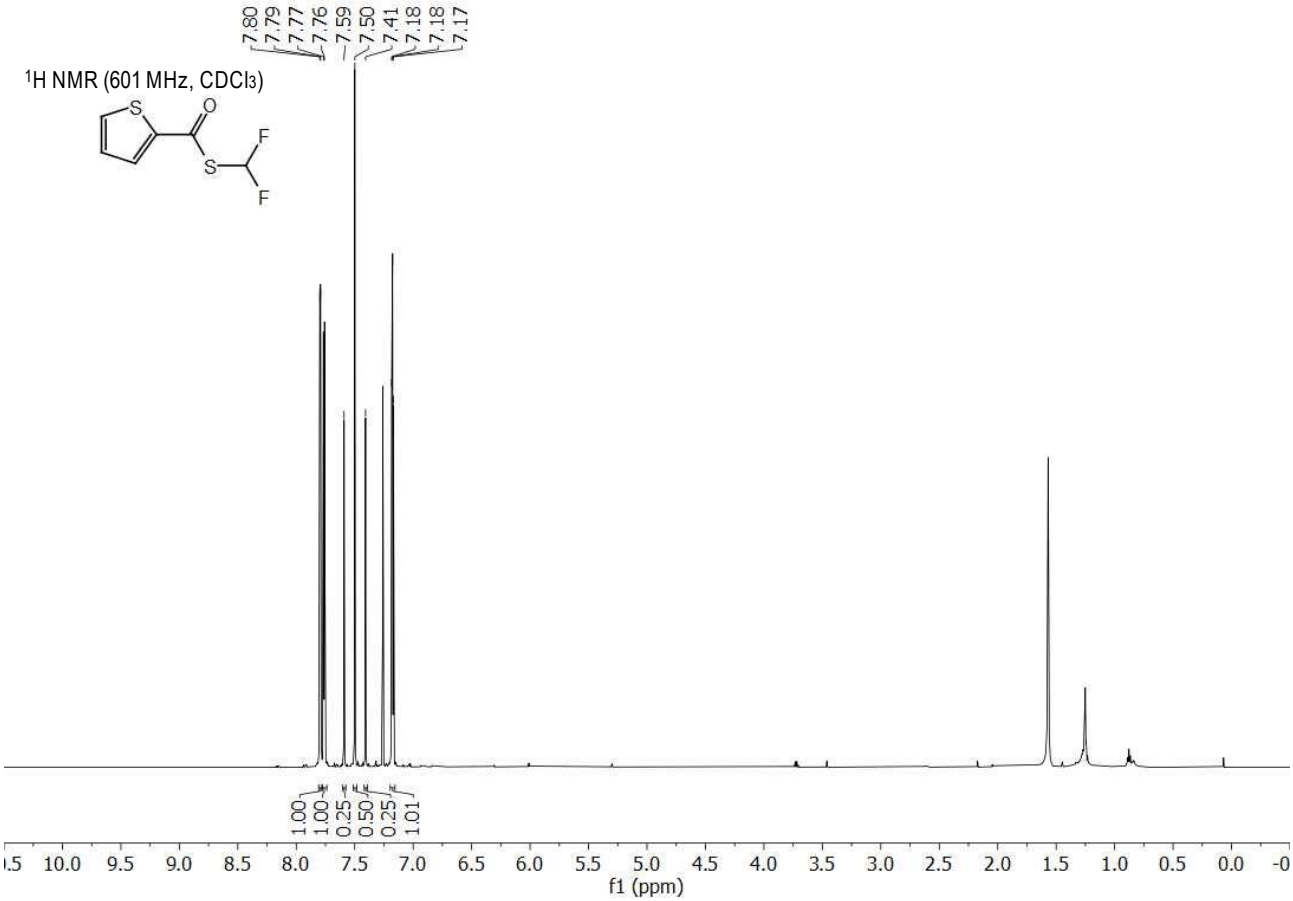


^{13}C NMR (151 MHz, $CDCl_3$)

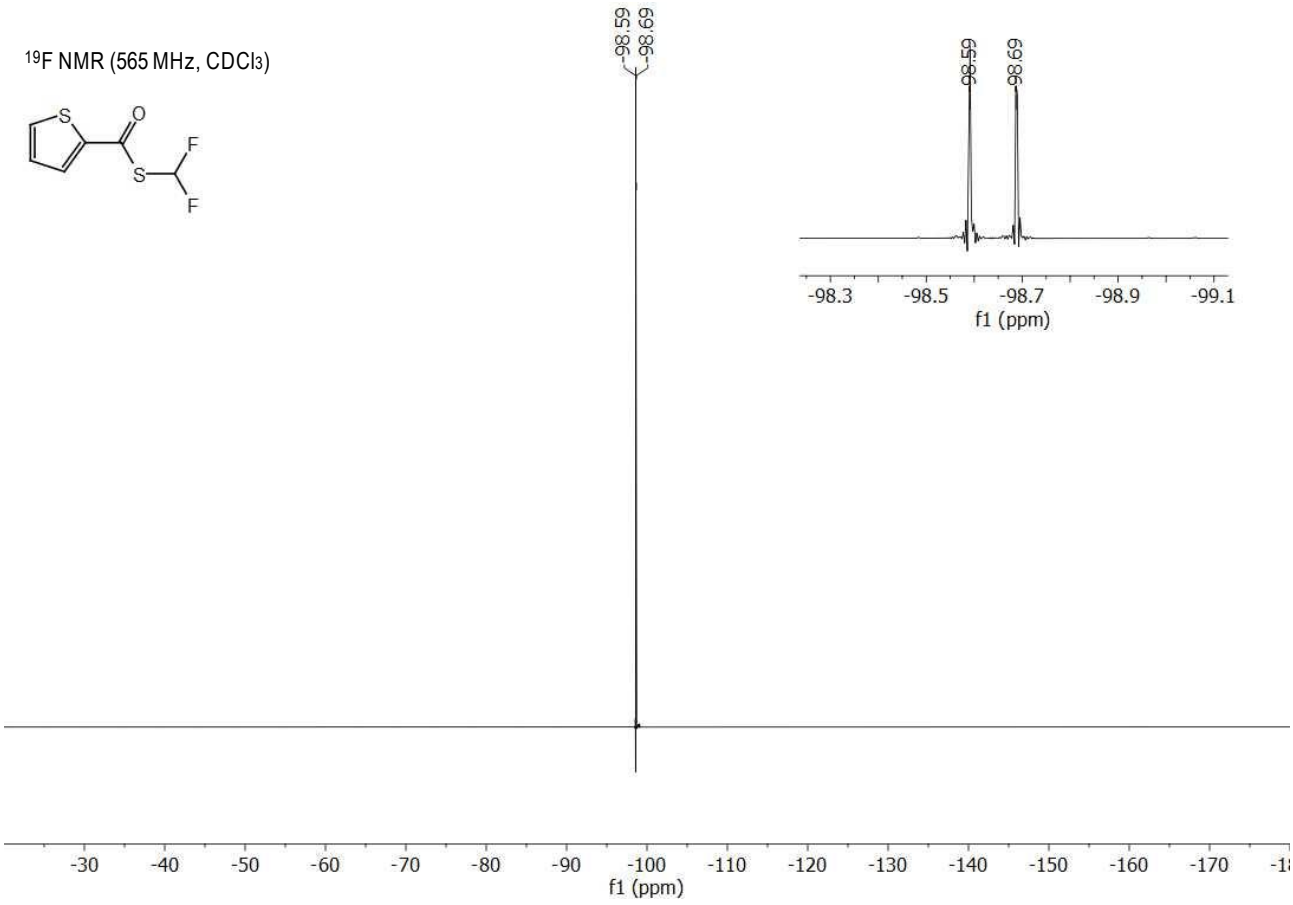


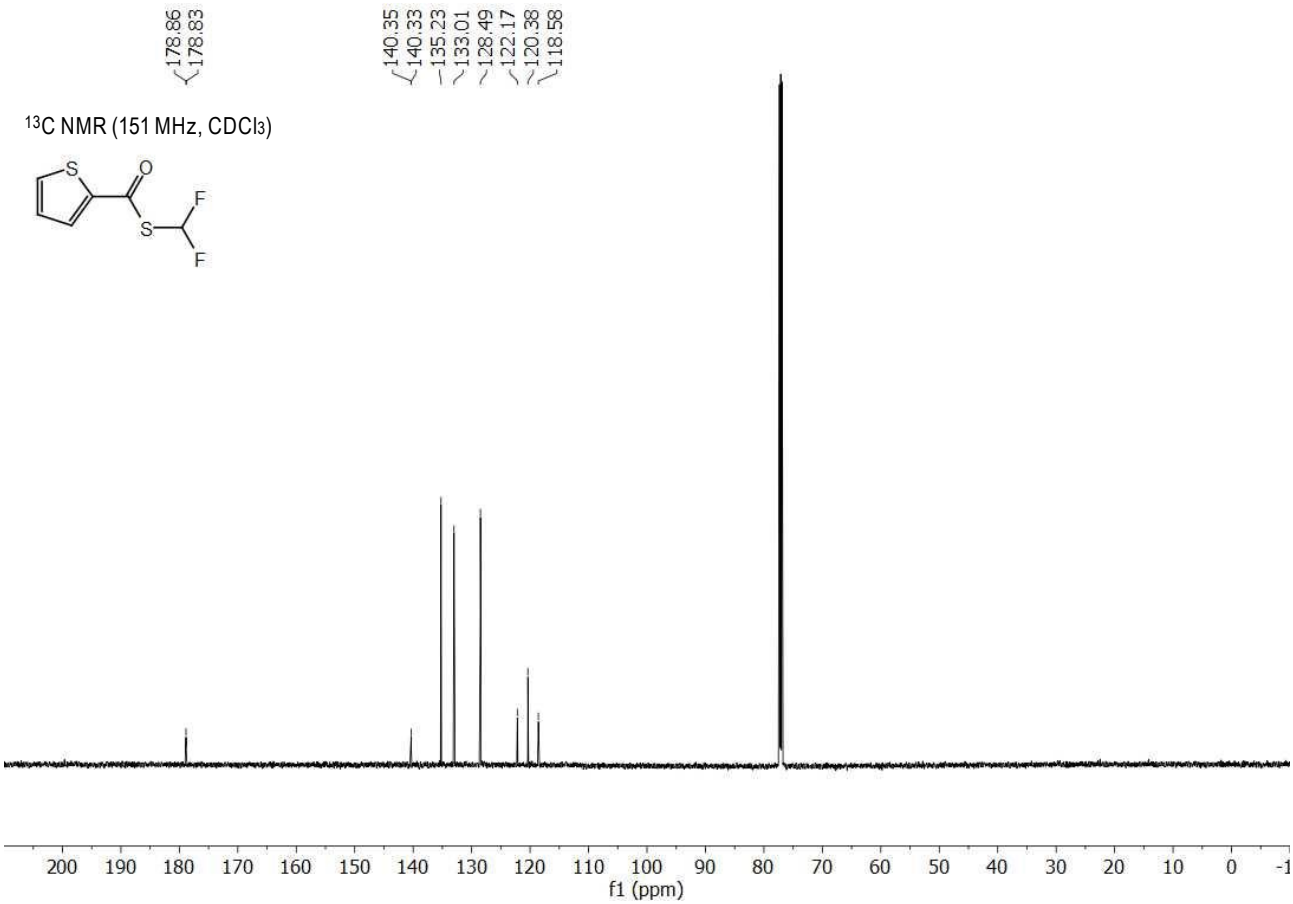
S-(difluoromethyl) thiophene-2-carbothioate **3s**

^{1}H NMR (601 MHz, $CDCl_3$)

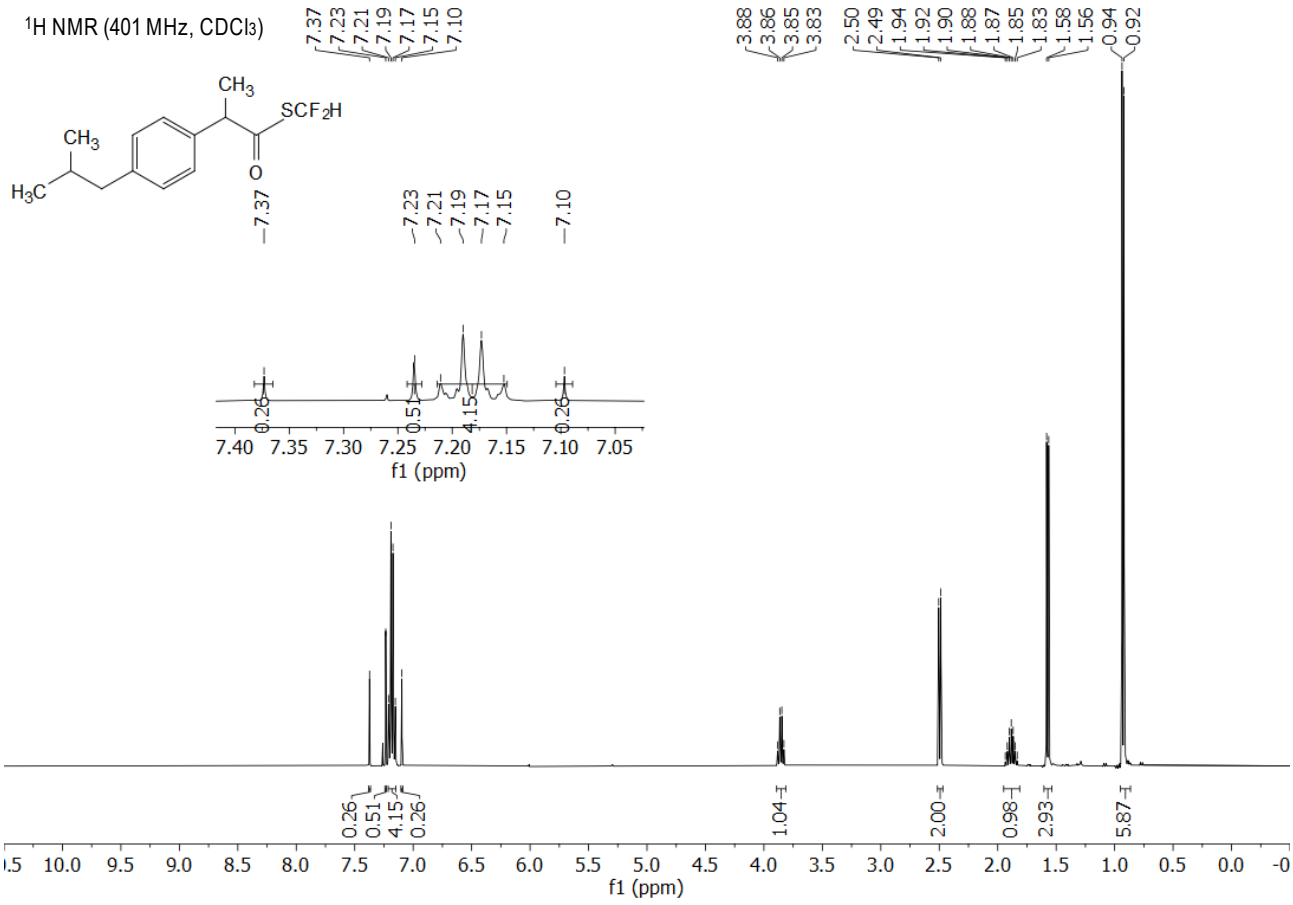


^{19}F NMR (565 MHz, $CDCl_3$)

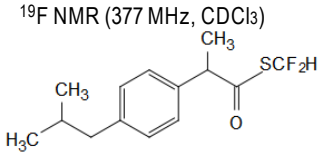




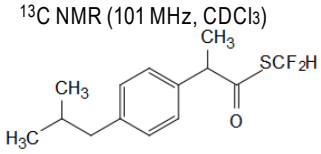
S-(difluoromethyl) 2-(4-isobutylphenyl)propanethioate **3t**



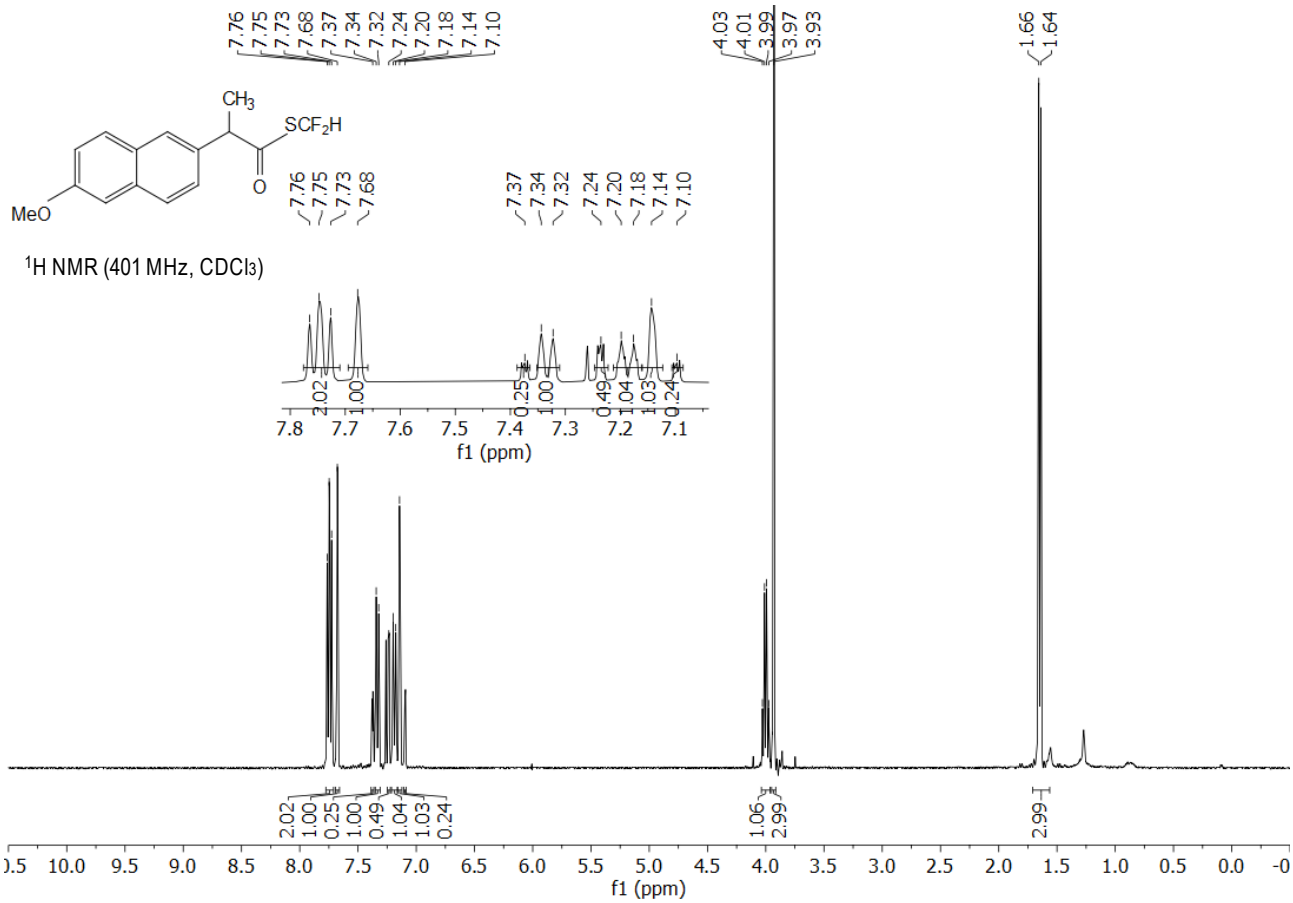
^{19}F NMR (377 MHz, CDCl$_3$)

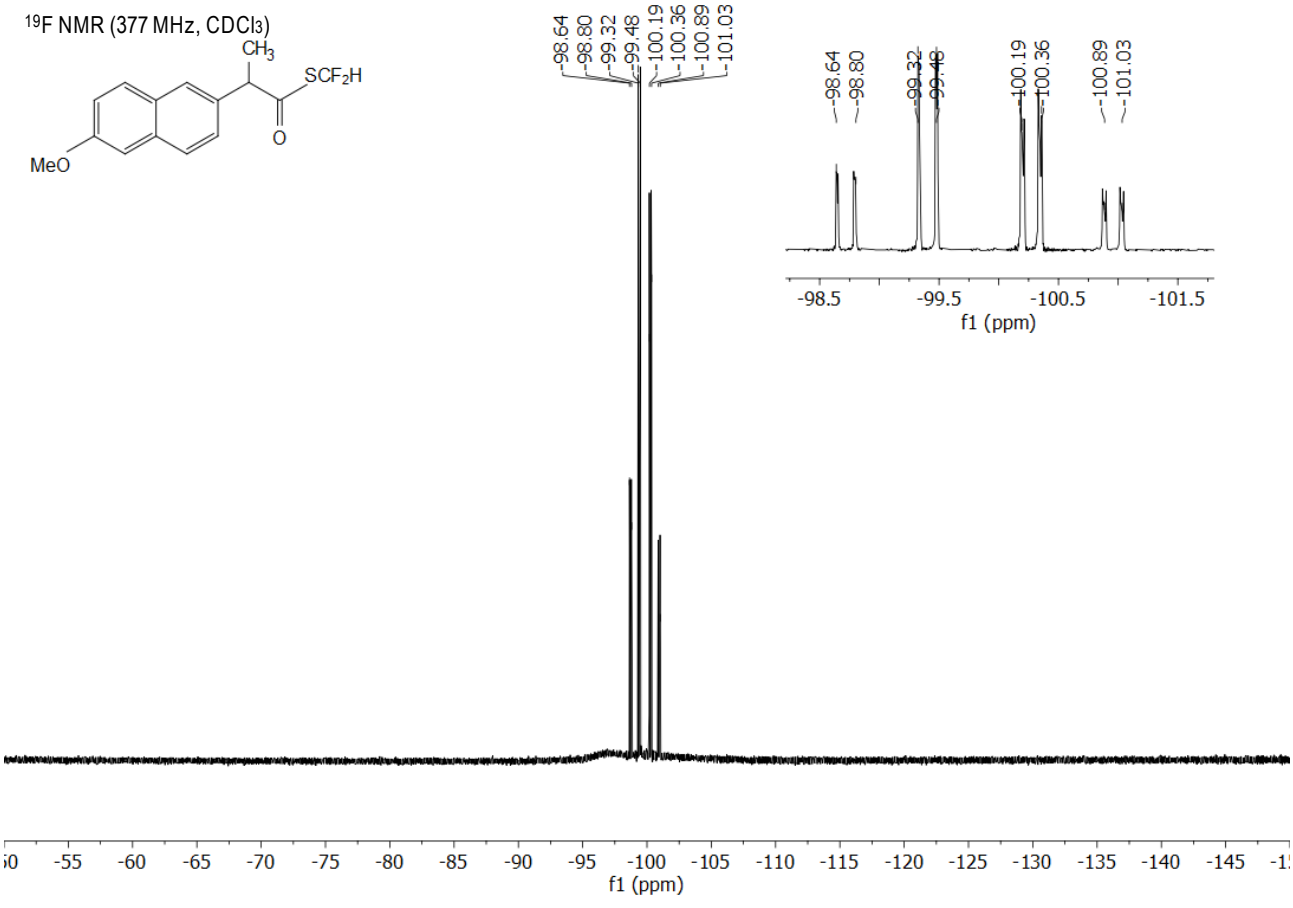


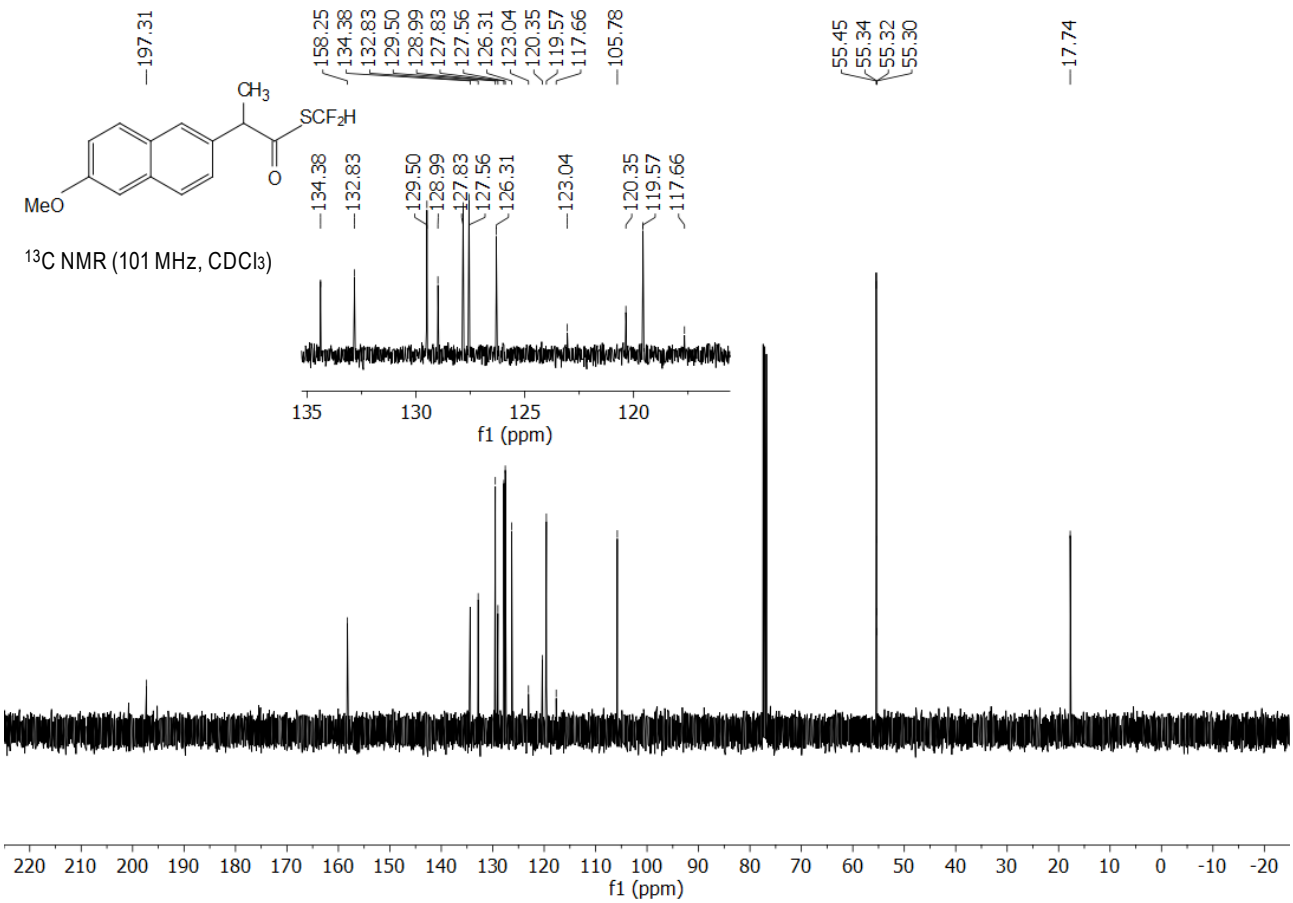
^{13}C NMR (101 MHz, CDCl$_3$)



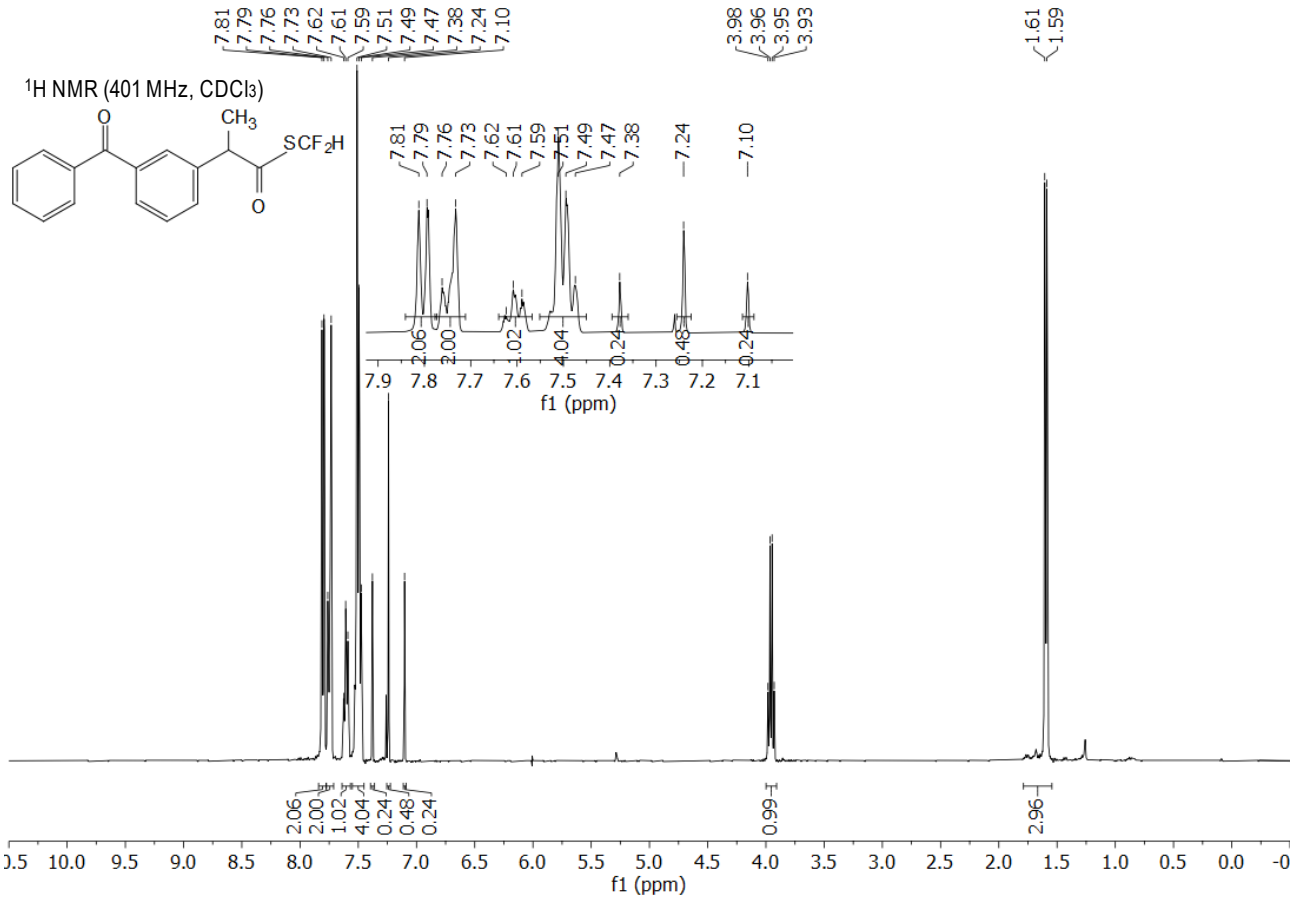
S-(difluoromethyl) 2-(6-methoxynaphthalen-2-yl)propanethioate **3u**



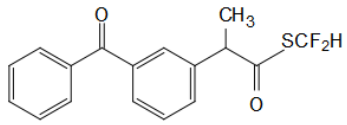




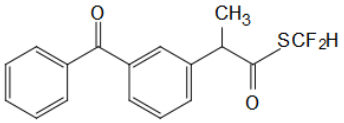
S-(difluoromethyl) 2-(3-benzoylphenyl)propanethioate **3v**



^{19}F NMR (377 MHz, CDCl$_3$)

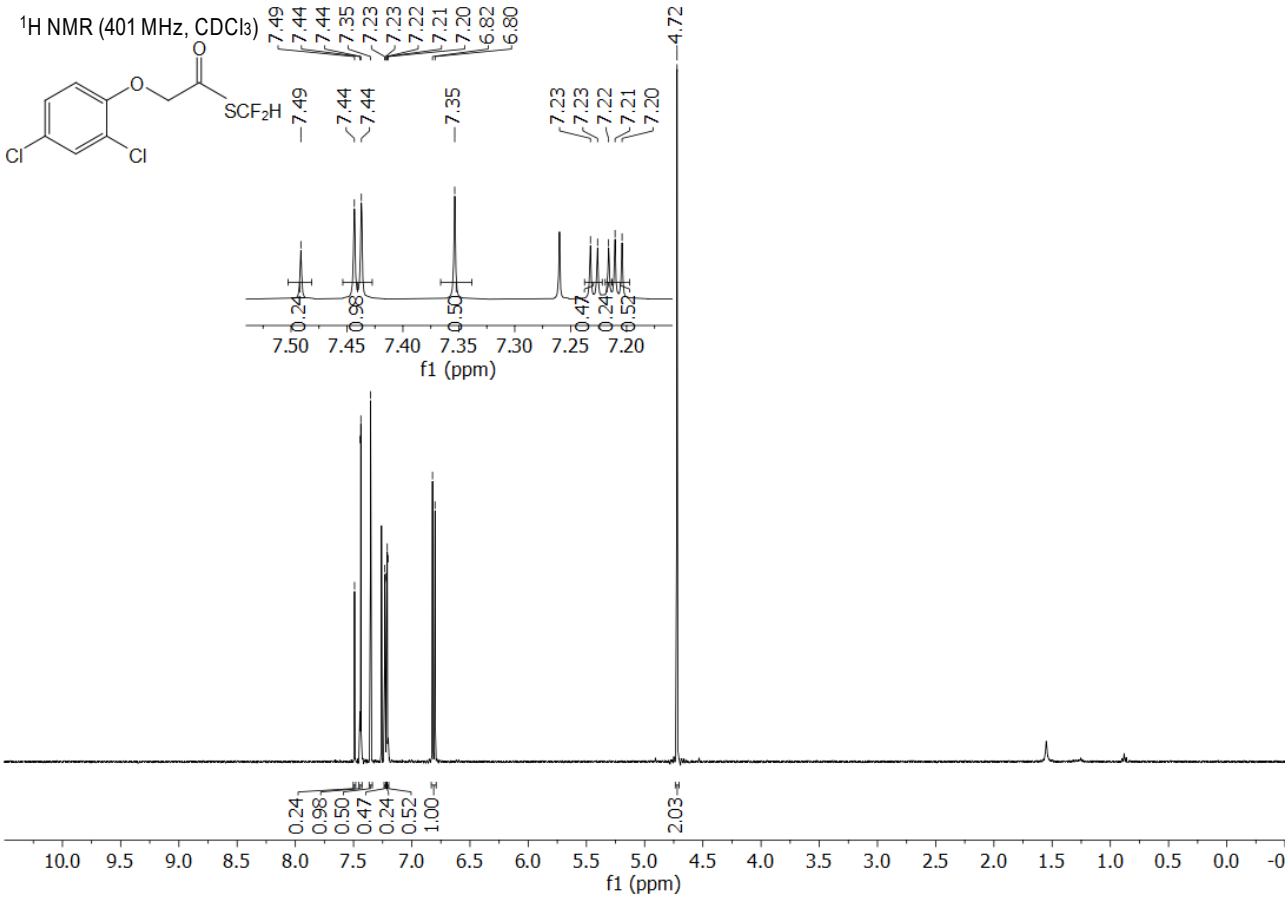


^{13}C NMR (151 MHz, CDCl$_3$)

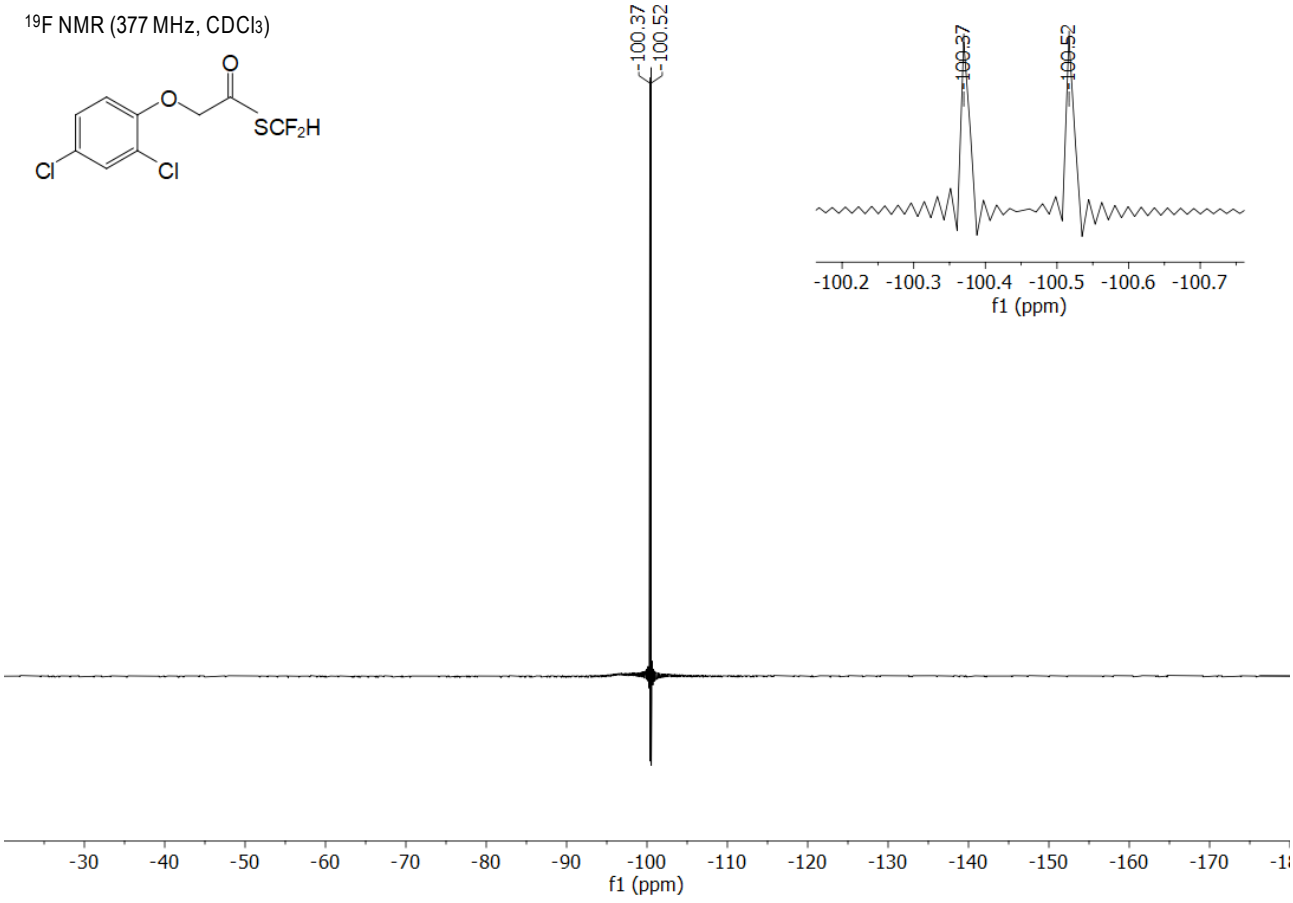


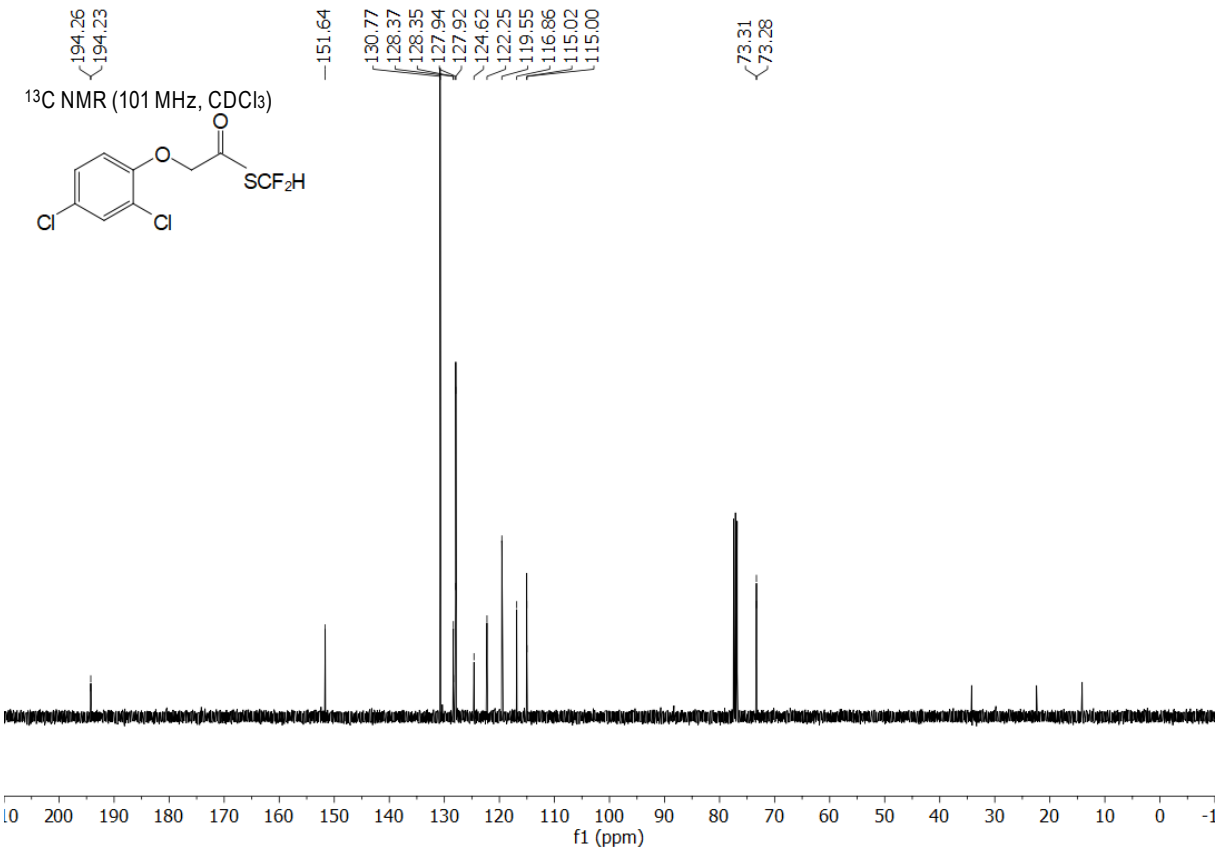
S-(difluoromethyl) 2-(2,4-dichlorophenyl)ethanethioate **3w**

^{1}H NMR (401 MHz, $CDCl_3$)

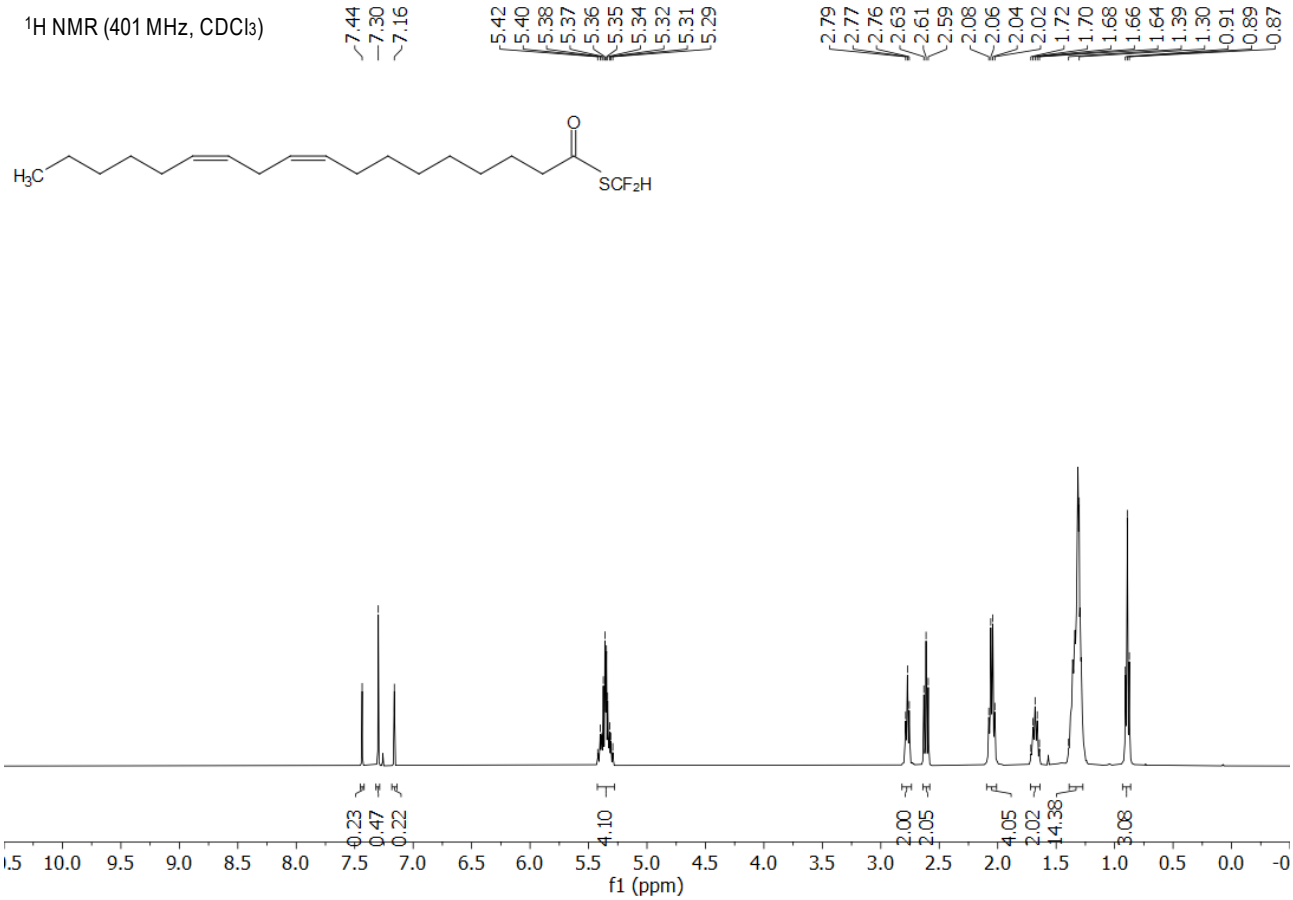


^{19}F NMR (377 MHz, $CDCl_3$)

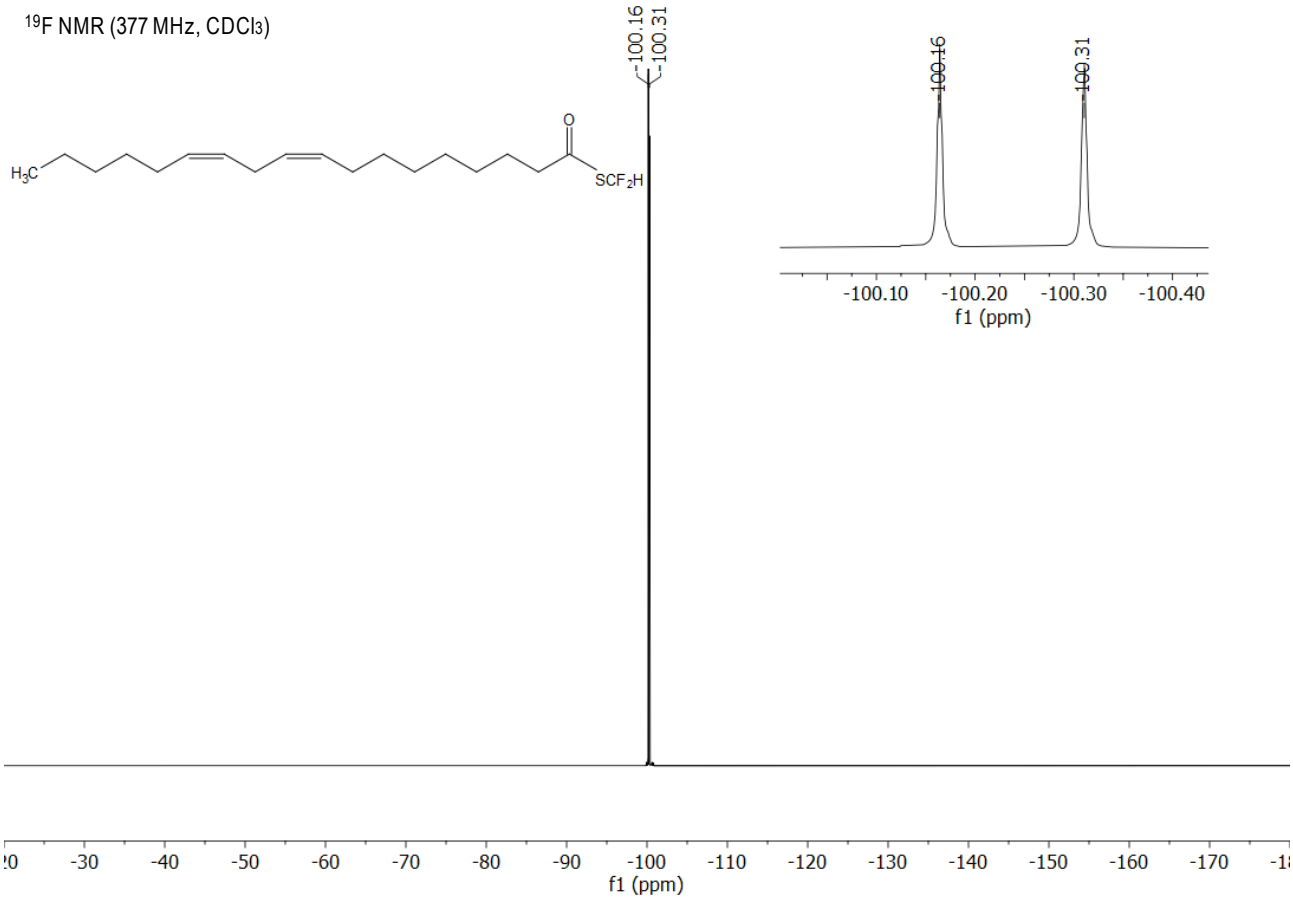




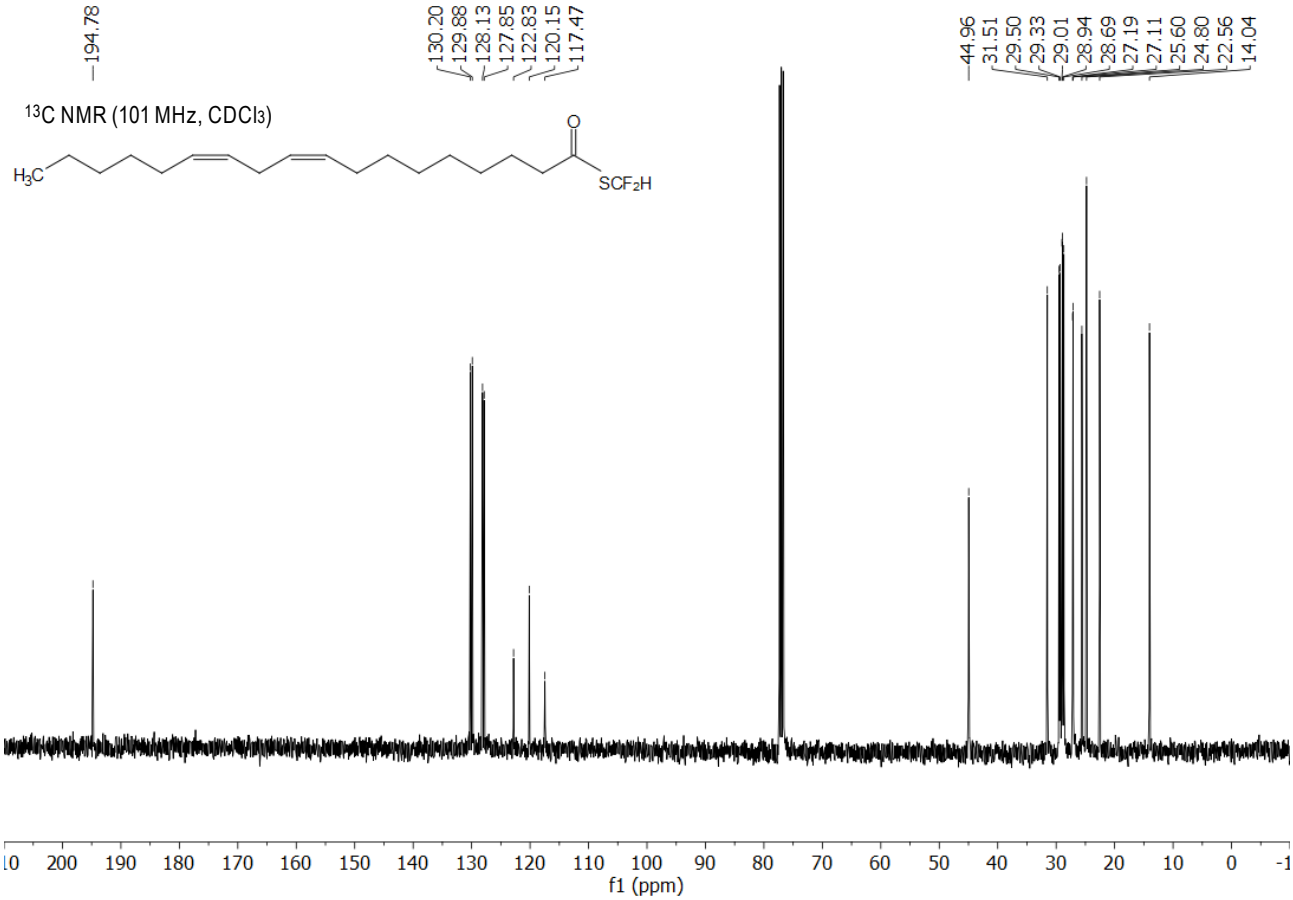
S-(difluoromethyl) (9Z,12Z)-octadeca-9,12-dienethioate **3x**



^{19}F NMR (377 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)



Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

Deoxygenative Nucleophilic Difluoromethylselenylation of Carboxylic Acids and Alcohols with BT-SeCF_2H

Matteo Tironi,[a] Stefan Dix,[a] and Matthew N. Hopkinson*[a]

Contents

1 General Information

Unless otherwise stated, all reactions were performed under argon as inert gas. The glass apparatus used was heated in an oil pump vacuum and purged with argon. Screw-cap reaction vessels were rinsed with argon. All purchased chemicals were used without further treatment. Used THF was dried and distilled over sodium in the presence of benzophenone and DCM was taken from the solvent purification system MB-SPS-800 (Braun). All dry solvents were stored over molecular sieves (3 or 4 Å). The solvents pentane, DCM and EtOAc used for column chromatography were distilled prior to use. 2-Bis(benzo[*d*]thiazol-2-yl)diselane was prepared according to the procedure of Mitsunobu.[1] All other starting materials were purchased from commercial suppliers and used as received.

Thin-layer chromatography was performed on silica gel coated aluminium plates ALUGRAM® Xtra SIL G/UV254 (Macherey-Nagel). The product spots were detected by UV light (254 nm) or as permanganate stains. Flash column chromatography was performed with silica gel 60 M (0.040–0.063 mm, 230–400 mesh, Macherey-Nagel).

^{1}H, ^{19}F and ^{13}C NMR spectra were acquired on a JEOL ECS 400 (400 MHz), JEOL ECZ 400 (400 MHz), JEOL ECX 400 (400 MHz), JEOL ECP 500/ Bruker Avance 500 (500 MHz), Varian INOVA 600 (600 MHz) or a Bruker Avance 700 (700 MHz) and analysed on MestReNova. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethyl silane (TMS) and coupling constants (J) are presented in hertz (Hz). CD_3CN or $CDCl_3$ are used as deuterated solvent and the residual solvent signals are used as reference in the ^{1}H and ^{13}C NMR spectra. ^{19}F NMR spectra are not calibrated by an internal reference, but with $CFCl_3$ as reference. ^{1}H NMR yields were measured using CH_2Br_2 as an internal standard. The multiplicities have been explained using the following abbreviations : s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet.

CHN Analysis was obtained on an ELEMENTAR Vario El elemental analyzer and High-resolution mass spectra were measured with an Agilent (6210 ESI-TOF; 4 µL/min, 1.0 bar, 4 kV) instrument. Infrared spectra were measured with a NICOLET spectrometer (iS10) equipped with an ATR unit (NICOLET SMART DuraSampl*IR*) and only diagnostic absorption bands are reported.

Safety Notice: As recommended for all organoselenium compounds, the synthesis of BT-$SeCF_2H$ and all deoxygenative difluoromethylselenylation reactions (including work-up, purification) should be conducted in well-ventilated fumehoods using appropriate personal protective equipment.

2 Synthesis of BT-SeCF$_2$H

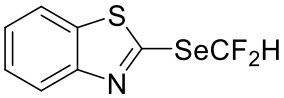
2.1 Synthesis of difluoromethyl trifluoromethanesulfonate

Difluoromethyl trifluoromethanesulfonate was prepared according to a literature procedure:[2] $TiCl_4$ (1 mol%, 2.21 mmol, 243 µL) was added dropwise to TfOH (1.2 equiv., 288 mmol, 25.5 mL) under vigorous stirring at room temperature for 5 mins. The homogeneous yellow solution was evacuated at 13–20 mbar until gas evolution ceased. The mixture was cooled to -20 ºC, $TMSCF_3$ (1.0 equiv., 221.5 mmol, 32.8 mL) was added, and the mixture was kept for 2 min. The cooling bath was replaced by an ice bath, which was kept for 2 min, and the mixture was stirred at room temperature for 1 hour. Volatile materials were distilled off under a vacuum of 133 mbar in a cold trap. The collected liquid was purified via vacuum distillation to provide HCF_2OTf as a colorless liquid (34.6 g, 172.8 mmol, 78 %).

^{1}H NMR (400 MHz, Chloroform-d) δ = 6.85 (t, *J* = 68.0 Hz, 1H). **^{19}F NMR (376 MHz, Chloroform-d) δ** = -74.60 (s), -82.17 (d, *J* = 68.2 Hz).

The characterization data agrees with literature values.[2]

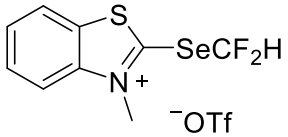
2.2 Synthesis of 2-((trifluoromethyl)thio)benzo[*d*]thiazole



2-Bis(benzo[d]thiazol-2-yl)diselane[1] (**1**, 1.1 eq, 26.5 mmol, 11.3 g) was suspended in degassed MeOH/THF (4:1, 350 mL) and $NaBH_4$ (2.4 eq, 57.8 mmol, 2.2 g) was added portionwise under vigorous stirring at 0 °C. After 10 min, degassed 1M HCl (80 mL) was added, and the precipitate was washed with degassed H_2O (3 x 50 mL). The solid was added to a degassed solution of 6M KOH (55 mL) and MeCN (55 mL) before difluoromethyl trifluoromethanesulfonate (2 eq, 48.2 mmol, 9.64 g) was added to the mixture at 0 °C. The mixture was stirred for 15 min at 0 °C and was diluted with H_2O (100 mL) and extracted with diethyl ether (200 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, Pentane/DCM 10:1). Yellow solid (**2**, 9.1 g, 34.45 mmol, 71 %).

^{1}H NMR (400 MHz, Chloroform-d) δ = 8.03 (d, *J* = 8.2 Hz, 1H), 7.84 (t, *J* = 54.3 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H). **^{19}F NMR (376 MHz, Chloroform-d) δ** = -89.93 (d, *J* = 54.3 Hz). **^{13}C NMR (101 MHz, Chloroform-d$_3$) δ** = 153.18, 151.24, 136.56, 126.14, 125.13, 122.40, 120.75, 117.65 (t, *J* = 290.6 Hz). **IR (ATR)**: ṽ [cm^{-1}] =1460, 1392, 1296, 1252, 1105, 1050, 952, 749, 565. **HRMS (ESI) m/z:** $[M+Na]^+$Calcd for $C_8H_5F_2NSSe$ 264.9276; Found 264.9296. Melting point = 77-79 °C

2.3 Synthesis of 2-((difluoromethyl)selanyl)-3-methylbenzo[*d*]thiazol-3-ium trifluoromethanesulfonate (BT-$SeCF_2H$)

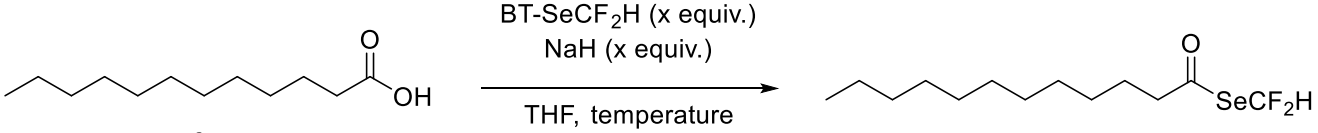


2-((Trifluoromethyl)thio)benzo[d]thiazole (1.0 equiv., 34.45 mmol, 9.1 g) was dissolved in dry CH_2Cl_2 (1.0 M) and methyl trifluoromethanesulfonate (3 equiv., 103.4 mmol, 11.4 mL) was added dropwise. The reaction mixture was stirred overnight at rt and the product was precipitated with diethyl ether. The crude product was redissolved with CH_2Cl_2, precipitated with diethyl ether a second time, and dried *in vacuo*. BT-$SeCF_2H$ was obtained as an off-white solid (14.2 g, 33.2 mmol, 96 %, 68 % over two steps from **1**).

^{1}H NMR (600 MHz, Acetonitrile-d_3) δ = 8.31 (d, *J* = 8.3 Hz, 1H), 8.18 (d, *J* = 8.6 Hz, 1H), 7.95 (t, *J* = 7.7 Hz, 1H), 7.86 (t, *J* = 7.7 Hz, 1H), 7.77 (d, *J* = 52.4 Hz, 1H), 4.33 (s, 3H).**^{19}F NMR (565 MHz, Acetonitrile-d_3) δ** = -79.23, -87.86 (d, *J* = 52.5 Hz). **^{13}C NMR (151 MHz, Acetonitrile-d_3) δ** = 163.91, 143.60, 133.74, 131.22, 130.03, 124.61, 121.80 (q, *J* = 320.8 Hz), 118.45 (t, *J* = 295.4 Hz), 40.71. **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 1581, 1440, 1390, 1265, 1245, 1223, 1144, 1067, 1028, 756, 674, 637, 572. **HRMS (ESI) m/z:** $[M]^+$Calcd for $C_9H_8F_2NSSe$ 279,9505; Found 279,9497. Melting point = 110-112°C

3 Optimization of the Deoxydifluoromethyselenylation of carboxylic acids and alcohols with BT-$SeCF_2H$

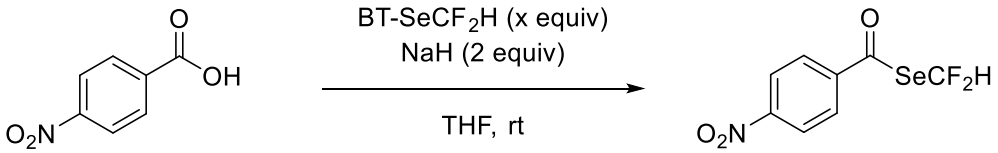
3.1 Optimization table with aliphatic acid 3a



3a **4a**

Equiv. of BT-$SeCF_2H$	Equiv. of NaH	Temperature	NMR Yield of 4a
2	2	-78°C	traces
2	2	-40°C	traces
1.25	2	rt	45%
2	2	rt	60 %
2	2	45°C	81%

3.2 Optimization table with aromatic acid 3m

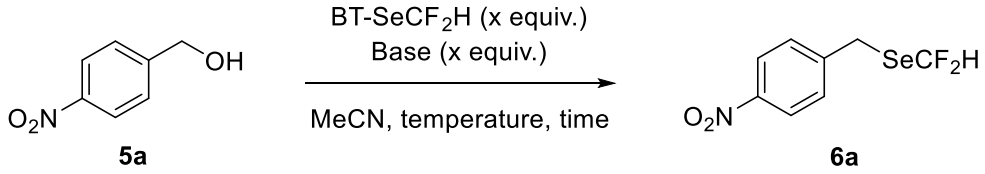


3m **4m**

Equiv. of BT-$SeCF_2H$	NMR Yield of 4m
1.3	23%
1.6	59%
2	91%

3.3 Optimization tables with alcohols

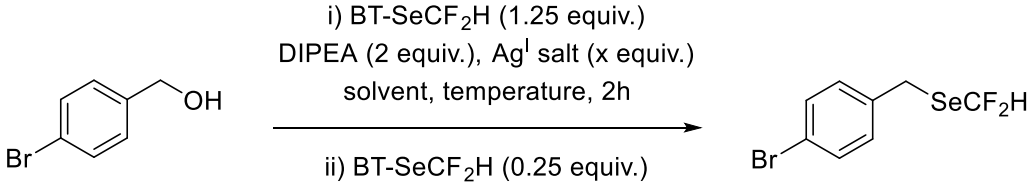
3.3.1 Optimization table with electron deficient substrate 5a



5a **6a**

Equiv. of BT-$SeCF_2H$	Base	Equiv. of Base	Temp.	Time	Notes	NMR Yield of 6a
1.25	DIPEA	2	r.t.	2 h		42%
1.25	DIPEA	2	r.t.	4 h		35%
1.5	DIPEA	2	r.t.	2 h		40%
2	DIPEA	2	r.t.	2 h		33%
2	DIPEA	2	r.t	4 h	Portion-wise addition of BTSeCF_2H (0.75 after 2 h)	39%
1.25	DIPEA	2	-40°C	2 h		45%
1.25	DIPEA	2	-40°C	4 h		46%
1.25	NaH	2	-40°C	2 h		29%
1.25	Proton sponge	2	-40°C	2 h		33%
1.25	DIPEA	2	-40°C	2 h	degassed	42%
1.5	DIPEA	4	-40°C	4 h	0.25 equiv. of BTSeCF_2H and 2 equiv. of DIPEA were added after 2 h	65%

3.3.2 Optimization table with electron rich substrate 5f



5f **6f**

Silver(I) salt	Equiv. of Silver(I) salt	Solvent	Temperature	NMR Yield of 6f
-----	-----	MeCN	-40°C	31%
-----	-----	DCM	-78°C	12%
Ag_2O	0.5 (1 equiv. of Ag^+)	DCM	-78°C	41%
-----	-----	THF	-78°C	traces
Ag_2O	0.5 (1 equiv. of Ag^+)	THF	-78°C	29%
Ag_2O	0.15 (0.3 equiv. of Ag^+)	MeCN	-40°C	51%
Ag_2O	0.2 (0.4 equiv. of Ag^+)	MeCN	-40°C	58%
Ag_2O	0.25 (0.5 equiv. of Ag^+)	MeCN	-40°C	63%
Ag_2O	0.5 (1 equiv. of Ag^+)	MeCN	-40°C	50%
Ag_2O	1 (2 equiv. of Ag^+)	MeCN	-40°C	50%
Ag_2O	1.5 (3 equiv. of Ag^+)	MeCN	-40°C	48%
Ag_2O	2 (4 equiv. of Ag^+)	MeCN	-40°C	44%
$AgNO_3$	0.5	MeCN	-40°C	70%
AgOTf	0.5	MeCN	-40°C	81%

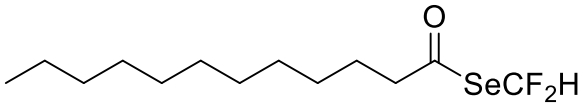
4 Scope and Limitations of the Deoxydifluoromethylselenylation of carboxylic acids and alcohols

4.1 General Procedures for the Deoxydifluoromethylselenylesterification of Carboxylic acids

Sodium hydride (2.0 equiv.) and the acid (1.0 equiv., 0.3 mmol) were dissolved in dry THF (at 45°C for aliphatic acids, at rt for aromatic acids) and were allowed to react for 0.5 h. BT-$SeCF_2H$ (2.0 equiv,) was added and the mixture was stirred for 2 h at rt. The reaction mixture was filtered through a silica pad to remove solids and the crude difluororomethylselenoesters were isolated using column chromatography (SiO_2).

4.2 Characterization Data for Deoxydifluoromethylselenylester Products 4

***Se*-(difluoromethyl) dodecaneselenoate (4a)**

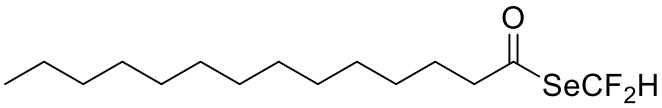


According to the general procedure, selenoester **4a** (73 mg, 78%) was obtained from dodecanoic acid **3a** on a 0.3 mmol scale after flash column chromatography (pentane) as a colorless oil.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 7.44 (t, *J* = 53.5 Hz, 1H), 2.68 (t, *J* = 7.5 Hz, 2H), 1.68 (p, *J* = 7.5 Hz, 2H), 1.37 – 1.22 (m, 16H), 0.88 (t, *J* = 7.0 Hz, 3H).**^{19}F NMR (565 MHz, $CDCl_3$) δ** = -96.16 (d, *J* = 53.4 Hz).**^{13}C NMR (151 MHz, $CDCl_3$) δ** = 198.20, 120.15 (t, *J* = 283.4 Hz), 49.19, 32.04, 29.70, 29.67, 29.46, 29,46, 29.28, 28.82, 24.96, 22.82, 14.25.

The characterization data agree with the literature values.[3]

***Se*-(difluoromethyl) tetradecaneselenoate (4b)**

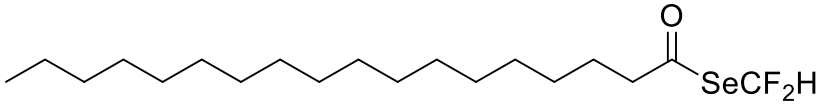


According to the general procedure, selenoester **4b** (89 mg, 87%) was obtained from tetradecanoic acid **4b** on a 0.3 mmol scale after flash column chromatography (pentane) as a colorless oil.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 7.44 (t, *J* = 53.5 Hz, 1H), 2.68 (t, *J* = 7.5 Hz, 2H), 1.68 (p, *J* = 7.5 Hz, 2H), 1.38 – 1.19 (m, 20H), 0.88 (t, *J* = 7.0 Hz, 3H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -96.15 (d, *J* = 53.6 Hz). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 198.18, 120.15 (t, *J* = 283.3 Hz), 49.19, 32.07, 29.80, 29.78, 29.75, 29.68, 29.50, 29.47, 29.29, 28.83, 24.96, 22.84, 14.25.

The characterization data agree with the literature values.[3]

***Se*-(difluoromethyl) octadecaneselenoate (4c)**

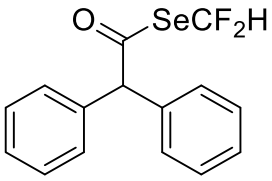


According to the general procedure, selenoester **4c** (103 mg, 86%) was obtained from octadecanoic acid **3c** on a 0.3 mmol scale after flash column chromatography (pentane) as a colorless oil.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 7.44 (t, *J* = 53.5 Hz, 1H), 2.68 (t, *J* = 7.5 Hz, 2H), 1.68 (p, *J* = 7.5 Hz, 2H), 1.42 – 1.16 (m, 28H), 0.88 (t, *J* = 6.9 Hz, 3H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -96.15 (d, *J* = 53.0 Hz). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 198.15, 120.15 (t, *J* = 283.3 Hz), 49.18, 32.09, 29.85, 29.83, 29.83, 29.82, 29.80, 29.79, 29.76, 29.68, 29.52, 29.47, 29.29, 28.83, 24.96, 22.85, 14.25.

The characterization data agree with the literature values.[3]

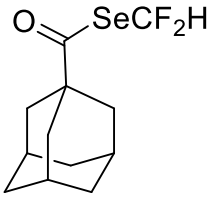
***Se*-(difluoromethyl) 2,2-diphenylethaneselenoate (4d)**



According to the general procedure, selenoester **4d** (66 mg, 67%) was obtained from 2,2-diphenylacetic acid **3d** on a 0.3 mmol scale after flash column chromatography (pentane/DCM 20:1) as a yellow oil.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 7.43 (t, *J* = 53.3 Hz, 1H), 7.41 – 7.30 (m, 10H), 5.17 (s, 1H).**^{19}F NMR (565 MHz, $CDCl_3$) δ** = -96.59 (d, *J* = 53.3 Hz).**^{13}C NMR (151 MHz, $CDCl_3$) δ** = 199.37, 136.39, 129.49, 129.10, 128.44, 120.30 (t, *J* = 283.9 Hz), 69.44. **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3029, 1715, 1494, 1452, 1269, 1056, 977, 728, 686, 643, 589. **HRMS (ESI) m/z:** $[M+Na]^+$ Calcd for $C_{15}H_{12}F_2NaOSe$ 348.9919; Found 348.9913.

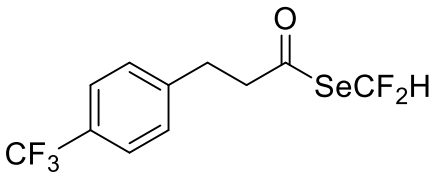
***Se*-(difluoromethyl)-adamantane-1-carboselenoate (4e)**



According to the general procedure, selenoester **4e** (78 mg, 89%) was obtained from adamantane 1-carboxylic acid **3e** on a 0.3 mmol scale after flash column chromatography (pentane) as a white solid.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 7.37 (t, *J* = 53.8 Hz, 1H), 2.09 (s, 3H), 1.88 (d, *J* = 3.0 Hz, 6H), 1.80 – 1.66 (m, 6H).**^{19}F NMR (565 MHz, $CDCl_3$) δ** = -96.57 (d, *J* = 53.5 Hz).**^{13}C NMR (151 MHz, $CDCl_3$) δ** = 206.04, 120.17 (t, *J* = 282.4 Hz), 52.55, 38.83, 36.35, 28.12. **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2928, 2850, 1708, 1452, 1273, 1059, 983, 910, 784, 755, 664. **HRMS (ESI) m/z:** $[M+Na]^+$Calcd for $C_{12}H_{16}F_2NaOSe$ 317.0232; Found 317.0240. Melting Point = 35-36°C.

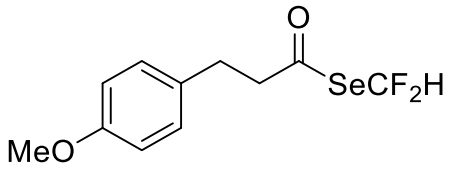
***Se*-(difluoromethyl) 3-(4-trifluoromethylphenyl)propaneselenoate (4f)**



According to the general procedure, selenoester **4f** (68 mg, 68%) was obtained from 3-(4-trifluoromethylphenyl)propanoic acid **3f** on a 0.3 mmol scale after flash column chromatography (pentane/DCM 40:1) as a yellow oil.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 7.57 (d, *J* = 8.1 Hz, 2H), 7.45 (t, *J* = 53.4 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 3.09 – 3.02 (m, 4H).**^{19}F NMR (565 MHz, $CDCl_3$) δ** = -62.39(s, 3F), -95.88 (d, *J* = 53.0 Hz, 2F).**^{13}C NMR (151 MHz, $CDCl_3$) δ** = 196.77, 143.16, 129.29 (q, *J* = 32.6 Hz), 128.83, 125.81 (q, *J* = 3.8 Hz), 124.26 (q, *J* = 271.9 Hz), 119.82 (t, *J* = 284.3 Hz), 49.98, 30.33. **IR (ATR)**: ṽ [cm^{-1}] = 2932, 1724, 1619, 1332, 1271, 1163, 1121, 1065, 944, 826, 687. **HRMS (EI) m/z:** [M]$^+$ Calcd for $C_{11}H_9F_5OSe$ 331.9739; Found 331.9740.

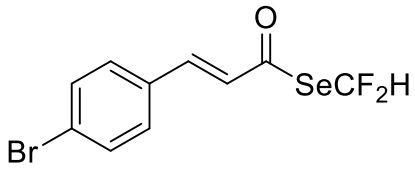
***Se*-(difluoromethyl) 3-(4-methoxyphenyl)propaneselenoate (4g)**



According to the general procedure, selenoester **4g** (77 mg, 88%) was obtained from 3-(4-methoxyphenyl)propanoic acid **3g** on a 0.3 mmol scale after flash column chromatography (pentane/DCM 20:1) as a yellow oil.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 7.45 (t, *J* = 53.5 Hz, 1H), 7.10 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 3.79 (s, 3H), 3.01 – 2.92 (m, 4H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -96.00 (d, *J* = 53.0 Hz).**^{13}C NMR (151 MHz, $CDCl_3$) δ** = 197.28, 158.53, 131.02, 129.40, 119.99 (t, *J* = 283.7 Hz), 114.24, 55.38, 50.88, 29.87. **IR (ATR)**: ṽ [cm^{-1}] = 2936, 2837, 1721, 1612, 1245, 1178, 1029, 822, 780, 685. **HRMS (ESI) m/z:** [M+H]$^+$ Calcd for $C_{11}H_{13}F_2O_2Se$ 295.0049; Found 295.0052.

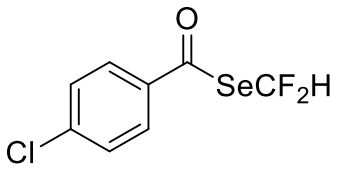
***Se*-(difluoromethyl) (*E*)-3-(4-bromophenyl)prop-2-eneselenoate (4h)**



According to the general procedure, selenoester **4h** (67 mg, 57%) was obtained from (*E*)-3-(4-bromophenyl)acrylic acid **3h** on a 0.3 mmol scale after flash column chromatography (pentane/DCM,50:1) as a yellow solid.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 7.56 (t, *J* = 53.5 Hz, 1H), 7.55 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 15.6 Hz, 1H), 7.41 (d, *J* = 8.6 Hz, 2H), 6.63 (d, *J* = 15.8 Hz, 1H).**^{19}F NMR (565 MHz, $CDCl_3$) δ** = -95.63 (d, *J* = 53.8 Hz). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 188.06, 142.44, 132.61, 132.18, 130.20, 126.89 – 126.65 (m), 126.24, 120.08 (t, *J* = 283.9 Hz). **IR (ATR)**: ṽ [cm^{-1}] = 2923, 1688, 1605, 1583, 1487, 1400, 1266, 1076, 1007, 974, 881, 806, 757, 685. **HRMS (EI) m/z:** [M]$^+$Calcd for $C_{10}H_7BrF_2OSe$ 339.8814; Found 339.8825. Melting Point = 103-105°C.

***Se*-(difluoromethyl) 4-chlorobenzoselenoate (4i)**

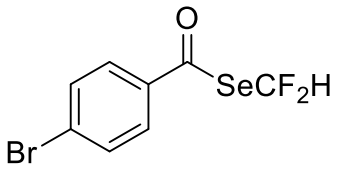


According to the general procedure, selenoester **4i** (53 mg, 66%) was obtained from 4-chlorobenzoic acid **3i** on a 0.3 mmol scale after flash column chromatography (pentane) as a yellow solid.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 7.75 (d, *J* = 8.6 Hz, 2H), 7.61 (t, *J* = 53.5 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 2H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -95.66 (d, *J* = 54.0 Hz).**^{13}C NMR (151 MHz, $CDCl_3$) δ** = 190.00, 141.61, 136.18, 129.72, 128.97, 120.12 (t, *J* = 284.3 Hz).

The characterization data agree with the literature values.[3]

***Se*-(difluoromethyl) 4-bromobenzoselenoate (4j)**

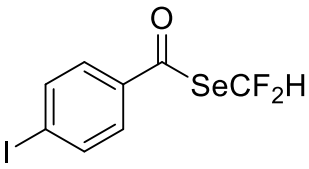


According to the general procedure, selenoester **4j** (66 mg, 70%) was obtained from 4-bromobenzoic acid **3j** on a 0.3 mmol scale after flash column chromatography (pentane) as a yellow solid.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 7.68 – 7.63 (m, 4H), 7.60 (d, *J* = 53.5 Hz, 1H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -95.68 (d, *J* = 53.7 Hz). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 190.27, 136.60, 132.71, 130.34, 128.98, 120.07 (t, *J* = 284.4 Hz).

The characterization data agree with the literature values.[3]

***Se*-(difluoromethyl) 4-iodobenzoselenoate (4k)**

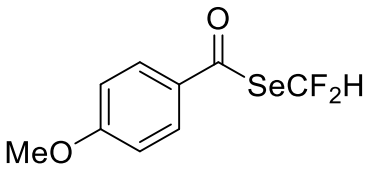


According to the general procedure, selenoester **4k** (60 mg, 55%) was obtained from 4-iodobenzoic acid **3k** on a 0.3 mmol scale after flash column chromatography (pentane) as a yellow solid.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 7.88 (d, *J* = 8.5 Hz, 2H), 7.60 (t, *J* = 53.5 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 2H).**^{19}F NMR (565 MHz, $CDCl_3$) δ** = -95.67 (d, *J* = 53.9 Hz).**^{13}C NMR (151 MHz, $CDCl_3$) δ** = 190.65, 138.70, 137.18, 128.77, 120.03 (t, *J* = 284.4 Hz), 103.24.

The characterization data agree with the literature values.[3]

***Se*-(difluoromethyl) 4-methoxybenzoselenoate (4l)**

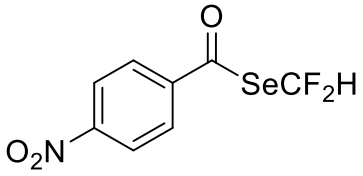


According to the general procedure, selenoester **4l** (16 mg, 20%) was obtained from 4-methoxybenzoic acid **3l** on a 0.3 mmol scale after flash column chromatography (pentane/AcOEt 30:1) as a yellow solid.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 7.78 (d, *J* = 8.9 Hz, 1H), 7.61 (t, *J* = 53.6 Hz, 0H), 6.96 (d, *J* = 9.1 Hz, 1H), 3.89 (s, 2H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -95.84 (d, *J* = 54.0 Hz). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 188.91, 165.08, 130.61, 130.21, 120.55 (t, *J* = 283.1 Hz), 114.54, 55.85.

The characterization data agree with the literature values.[3]

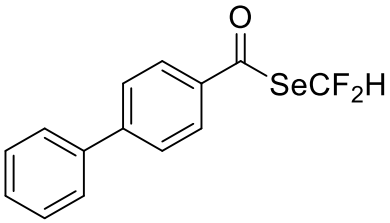
***Se*-(difluoromethyl) 4-nitrobenzoselenoate (4m)**



According to the general procedure, selenoester **4m** (47 mg, 56%) was obtained from 4-nitrobenzoic acid **3m** on a 0.3 mmol scale after flash column chromatography (pentane/AcOEt,30:1) as a yellow solid.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 8.35 (d, *J* = 8.9 Hz, 2H), 8.00 (d, *J* = 8.6 Hz, 2H), 7.63 (t, *J* = 53.3 Hz, 1H).**^{19}F NMR (565 MHz, $CDCl_3$) δ** = -95.37 (d, *J* = 52.9 Hz). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 190.38, 151.33, 142.13, 128.61, 124.60, 119.74 (t, *J* = 285.8 Hz). **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2926, 2855, 1693, 1606, 1529, 1347, 1266, 1195, 1068, 891, 840, 733, 686. **HRMS (ESI) m/z:** $[M]^+$ Calcd for $C_8H_5F_2NNaO_3Se$ 303.9300; Found 303.9311.

***Se*-(difluoromethyl) [1,1'-biphenyl]-4-carboselenoate (4n)**

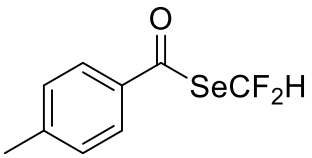


According to the general procedure, selenoester **4n** (34 mg, 45%) was obtained from [1,1'-biphenyl]-4-carboxylic acid **3n** on a 0.3 mmol scale after flash column chromatography (pentane/DCM 30:1) as a white solid.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 7.89 (d, *J* = 8.6 Hz, 2H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.65 (t, *J* = 53.7 Hz, 1H), 7.63 (d, *J* = 8.6 Hz, 2H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.44 (t, *J* = 7.3 Hz, 1H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -95.83 (d, *J* = 52.7 Hz).**^{13}C NMR (151 MHz, $CDCl_3$) δ** = 190.55, 147.84, 139.40, 136.46, 129.25, 128.87, 128.33, 127.92, 127.45, 120.34 (t, *J* = 283.6 Hz).

The characterization data agree with the literature values.[3]

***Se*-(difluoromethyl) 4-methylbenzoselenoate (4o)**

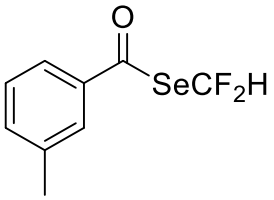


According to the general procedure, selenoester **4o** (34 mg, 45%) was obtained from 4-methyl benzoic acid **3o** on a 0.3 mmol scale after flash column chromatography (pentane) as a yellow solid.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 7.71 (d, *J* = 8.4 Hz, 2H), 7.61 (t, *J* = 53.4 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 2.43 (s, 3H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -95.97 (d, *J* = 53.9 Hz).**^{13}C NMR (151 MHz, $CDCl_3$) δ** = 190.48, 146.34, 135.38, 130.01, 127.87, 120.41 (t, *J* = 283.3 Hz), 21.97.

The characterization data agree with the literature values.[3]

***Se*-(difluoromethyl) 3-methylbenzoselenoate (4p)**

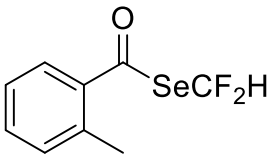


According to the general procedure, selenoester **4p** (40 mg, 54%) was obtained from 3-methylbenzoic acid **3p** on a 0.3 mmol scale after flash column chromatography (pentane) as a yellow solid.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 7.61 (t, *J* = 53.5 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 2H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 2.43 (s, 3H).**^{19}F NMR (565 MHz, $CDCl_3$) δ** = -96.03 (d, *J* = 52.7 Hz).**^{13}C NMR (151 MHz, $CDCl_3$) δ** = 191.25, 139.45, 137.90, 135.81, 129.21, 128.07, 125.04, 120.35 (t, *J* = 283.4 Hz), 21.38.

The characterization data agree with the literature values.[3]

***Se*-(difluoromethyl) 2-methylbenzoselenoate (4q)**

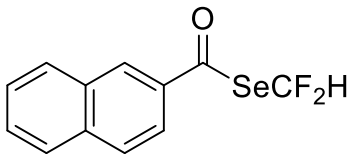


According to the general procedure, selenoester **4q** (37 mg, 49%) was obtained from 2-methyl benzoic acid **3q** on a 0.3 mmol scale after flash column chromatography (pentane) as a yellow oil.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 7.70 (d, *J* = 7.9 Hz, 1H), 7.55 (t, *J* = 53.6 Hz, 1H), 7.48 (t, *J* = 7.6, 7.1 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 7.7 Hz, 1H), 2.52 (s, 3H).**^{19}F NMR (565 MHz, $CDCl_3$) δ** = -96.59 (d, *J* = 53.5 Hz). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 192.32, 137.64, 137.39, 133.39, 132.34, 129.49, 126.58, 120.82 (t, *J* = 283.2 Hz), 21.10.

The characterization data agree with the literature values.[3]

***Se*-(difluoromethyl) naphthalene-2-carboselenoate (4r)**

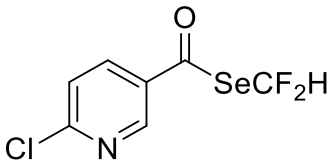


According to the general procedure, selenoester **4r** (45 mg, 53%) was obtained from 2-naphthoic acid **3r** on a 0.3 mmol scale after flash column chromatography (pentane) as a colourless oil.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 8.34 (s, 1H), 7.98 (d, *J* = 8.1 Hz, 1H), 7.94 – 7.87 (m, 2H), 7.82 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.69 (t, *J* = 53.5 Hz, 1H), 7.68-7.65 (m, 1H), 7.63 – 7.57 (m, 1H).**^{19}F NMR (565 MHz, $CDCl_3$) δ** = -95.78 (d, *J* = 54.0 Hz).**^{13}C NMR (151 MHz, $CDCl_3$) δ** = 190.91, 136.47, 135.07, 132.49, 130.02, 129.86, 129.54, 129.32, 128.07, 127.60, 122.64, 120.38 (t, *J* = 283.7 Hz).

The characterization data agree with the literature values.[3]

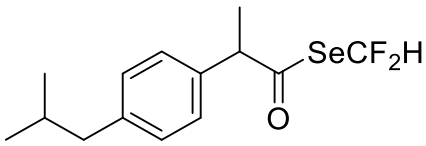
Se-(difluoromethyl) 6-chloropyridine-3-carboselenoate (4s)



According to the general procedure, selenoester **4s** (48 mg, 59%) was obtained from 6-chloronicotinic acid **3s** on a 0.3 mmol scale after flash column chromatography (pentane:ethyl acetate, 70:1) as a yellow solid.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 8.80 (d, *J* = 2.6 Hz, 1H), 8.01 (dd, *J* = 8.4, 2.6 Hz, 1H), 7.62 (t, *J* = 53.3 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 1H).**^{19}F NMR (565 MHz, $CDCl_3$) δ** = -95.23 (d, *J* = 53.7 Hz).**^{13}C NMR (151 MHz, $CDCl_3$) δ** = δ 188.92, 157.47, 148.94, 137.15, 132.48, 125.16, 119.56 (t, *J* = 285.9 Hz). **IR (ATR)**: ṽ [cm^{-1}] = 2923, 1675, 1572, 1462, 1365, 1206, 1064, 1018, 880, 842, 735, 683, 633. **HRMS (ESI) m/z:** $[M+Na]^+$Calcd for $C_7H_4ClF_2NNaOSe$ 293.9013; Found 293.9024. Melting Point = 87-88°C.

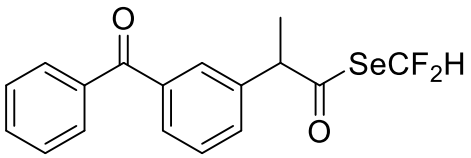
***Se*-(difluoromethyl) 2-(6-methoxynaphthalen-2-yl)propaneselenoate (4t)**



According to the general procedure, selenoester **4t** (86 mg, 90%) was obtained from Ibuprofen **3t** on a 0.3 mmol scale after flash column chromatography (pentane) as a colourless oil.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 7.32 (t, *J* = 53.7 Hz, 1H), 7.21 – 7.15 (m, 4H), 3.84 (q, *J* = 7.1 Hz, 1H), 2.50 (d, *J* = 7.2 Hz, 2H), 1.88 (hept, *J* = 6.7 Hz, 1H), 1.56 (d, *J* = 7.2 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 6H).**^{19}F NMR (565 MHz, $CDCl_3$) δ** = -96.68 (dd, *J* = 252.3, 53.2 Hz).**^{13}C NMR (151 MHz, $CDCl_3$) δ** = 201.39, 142.53, 134.37, 129.91, 128.76, 120.29 (t, *J* = 282.9 Hz), 58.31, 45.21, 30.29, 22.48, 17.30. **IR (ATR)**: ṽ [cm^{-1}] = 2956, 2869, 1716, 1465, 1367, 1272, 1060, 915, 846, 686, 548. **HRMS (EI) m/z:** $[M]^+$Calcd for $C_{14}H_{18}F_2OSe$ 320.0491; Found 320.0483.

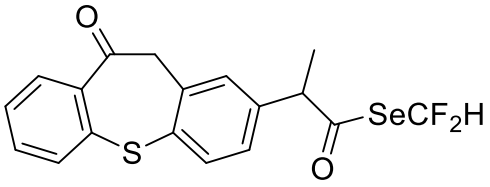
***Se*-(difluoromethyl) 2-(3-benzoylphenyl)propaneselenoate (4u)**



According to the general procedure, selenoester **4u** (74 mg, 67%) was obtained from Ketoprofen **3u** on a 0.3 mmol scale after flash column chromatography (pentane/AcOEt 35:1) as a colourless oil.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 7.81 (d, *J* = 8.0 Hz, 2H), 7.78 (d, *J* = 6.7 Hz, 1H), 7.73 (s, 1H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.54 – 7.48 (m, 4H), 7.36 (t, *J* = 53.5 Hz, 1H), 3.96 (q, *J* = 7.1 Hz, 1H), 1.60 (d, *J* = 7.1 Hz, 3H).**^{19}F NMR (565 MHz, $CDCl_3$) δ** = -96.20 (dd, *J* = 266.4, 55.2 Hz).**^{13}C NMR (151 MHz, $CDCl_3$) δ** = 200.27, 196.18, 138.50, 137.74, 137.33, 132.88, 132.57, 130.35, 130.34, 130.22, 129.21, 128.55, 120.01 (t, *J* = 284.0 Hz), 58.53, 17.51. **IR (ATR)**: ṽ [cm^{-1}] = 2982, 1715, 1657, 1597, 1448, 1271, 1055, 910, 820, 786, 687. **HRMS (ESI) m/z:** $[M+Na]^+$Calcd for $C_{17}H_{14}F_2NaO_2Se$ 391.0025; Found 391.0025.

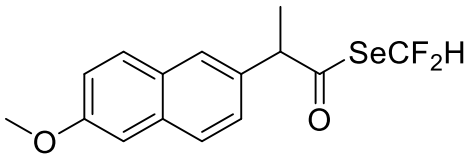
***Se*-(difluoromethyl) 2-(10-oxo-10,11-dihydrodibenzo[*b*,*f*]thiepin-2-yl)propaneselenoate (4v)**



According to the general procedure, selenoester **4v** (99 mg, 80%) was obtained from Zaltoprofen **3v** on a 0.3 mmol scale after flash column chromatography (pentane/ethyl acetate, 60:1) as a yellow oil.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 8.20 (d, *J* = 7.9 Hz, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.37 (s, 1H), 7.34 (t, *J* = 53.5 Hz, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.13 (d, *J* = 7.9, 1H), 4.38 (s, 2H), 3.88 (q, *J* = 7.1 Hz, 1H), 1.54 (d, *J* = 7.1 Hz, 3H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -95.57 (dd, *J* = 251.5, 53.1 Hz), -96.78 (dd, *J* = 251.2, 52.5 Hz).**^{13}C NMR (151 MHz, $CDCl_3$) δ** = 199.96, 191.05, 139.88, 139.42, 138.59, 136.16, 135.05, 132.77, 131.98, 131.68, 130.98, 129.60, 127.44, 127.10, 119.93 (t, *J* = 284.0 Hz), 58.29, 51.12, 17.52. **IR (ATR)**: ṽ [cm^{-1}] =2982, 1715, 1670, 1587, 1429, 1283, 1056, 930, 897, 729, 681. **HRMS (ESI) m/z:** $[M+Na]^+$ Calcd for $C_{18}H_{14}F_2NaO_2SSe$ 434.9745; Found 434.9761.

***Se*-(difluoromethyl) 2-(6-methoxynaphthalen-2-yl)propaneselenoate (4w)**

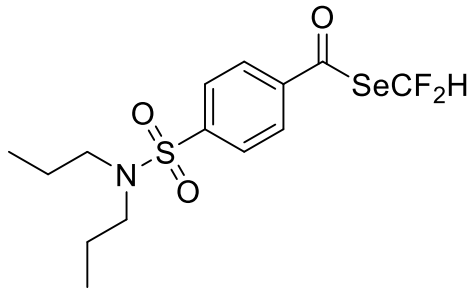


According to the general procedure, selenoester **4w** (94 mg, 91%) was obtained from Naproxen **3w** on a 0.3 mmol scale after flash column chromatography (pentane/DCM 15:1) as an off-white solid.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 7.76 (t, *J* = 9.1 Hz, 2H), 7.70 (d, *J* = 1.9 Hz, 1H), 7.36 (t, *J* = 53.5 Hz, 1H), 7.33 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.21 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.16 (d, *J* = 2.7 Hz, 1H), 4.00 (q, *J* = 7.1 Hz, 1H), 3.94 (s, 3H), 1.65 (d, *J* = 7.1 Hz, 3H).**^{19}F NMR (565 MHz, $CDCl_3$) δ** = -96.29 (dd, *J* = 252.8, 53.2 Hz).**^{13}C NMR (151 MHz, $CDCl_3$) δ** = 201.25, 158.39, 134.61, 132.19, 129.58, 128.93, 128.26, 127.90, 126.69, 120.25 (t, *J* = 283.2, 282.1 Hz), 119.67, 105.82, 58.63,

55.47, 17.36. **IR (ATR)**: ṽ [cm^{-1}] =2984, 2938, 1714, 1601, 1454, 1270, 1231, 1176, 1161, 1062, 1037, 933, 907, 855, 819, 683. **HRMS (ESI) m/z:** [M+Na]$^{+}$Calcd for $C_{15}H_{14}F_2NaO_2Se$ 367.0025; Found 367.0020. Melting Point = 96-98°C.

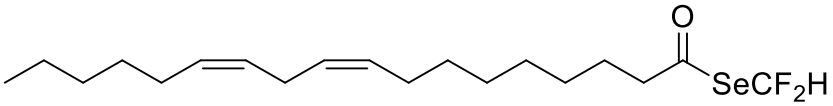
***Se*-(difluoromethyl) 4-(*N*,*N*-dipropylsulfamoyl)benzoselenoate (4x)**



According to the general procedure, selenoester **4x** (78 mg, 65%) was obtained from Probenecid **3x** on a 0.3 mmol scale after flash column chromatography (pentane/AcOEt 30:1) as a yellow solid.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 7.95 – 7.89 (m, 4H), 7.61 (t, *J* = 53.4 Hz, 1H), 3.11 (t, *J* = 7.7 Hz, 4H), 1.55 (h, *J* = 7.7 Hz, 4H), 0.86 (t, *J* = 7.4 Hz, 6H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -95.59 (d, *J* = 53.6 Hz). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 190.57, 146.10, 140.31, 128.18, 127.90, 119.87 (t, *J* = 285.0 Hz), 50.07, 22.06, 11.24. **IR (ATR)**: ṽ [cm^{-1}] =2970, 2937, 2877, 1693, 1461, 1397, 1338, 1266, 1181, 1061, 977, 880, 799, 730, 684, 564. **HRMS (ESI) m/z:** [M+H]$^{+}$ Calcd for $C_{14}H_{20}F_2NO_3SSe$ 400.0297; Found 400.0301. Melting Point = 54-56°C

***Se*-(difluoromethyl) (9*Z*,12*Z*)-octadeca-9,12-dieneselenoate (4y)**



According to the general procedure, selenoester **4y** (109 mg, 92%) was obtained from linoleic acid on a 0.3 mmol scale after flash column chromatography (pentane) as a yellow oil.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 7.44 (t, *J* = 53.5 Hz, 1H), 5.42 – 5.30 (m, 4H), 2.77 (t, *J* = 6.9 Hz, 2H), 2.68 (t, *J* = 7.5 Hz, 2H), 2.05 (q, *J* = 7.0 Hz, 4H), 1.68 (p, *J* = 7.4 Hz, 2H), 1.40 – 1.25 (m, 14H), 0.89 (t, *J* = 7.0 Hz, 3H).**^{19}F NMR (565 MHz, $CDCl_3$) δ** = -96.13 (d, *J* = 53.5 Hz).**^{13}C NMR (151 MHz, $CDCl_3$) δ** = 198.13, 130.39, 130.05, 128.31, 128.01, 120.13 (t, *J* = 283.4 Hz), 49.16, 31.67, 29.65, 29.49, 29.18, 29.08, 28.78, 27.35, 27.27, 25.77, 24.93, 22.72, 14.21. **IR (ATR)**: ṽ [cm^{-1}] = 2929, 2857, 2288, 2205, 1646, 1516, 1457, 1380, 1284, 1097, 972, 873, 799, 773, 677, 575. **HRMS (ESI) m/z:** [M+Na]$^{+}$Calcd for $C_{19}H_{32}F_2NaOSe$ 417.1484; Found 417.1490.

4.3 General Procedure for the Deoxydifluoromethylselenylation of Alcohols

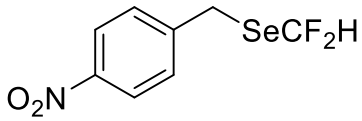
4.3 General Procedure for the Deoxydifluoromethylselenylation of Alcohols

Method A: BT-$SeCF_2H$ (1.25 equiv.) and the alcohol (1.0 equiv., 0.5 mmol) were added to dry MeCN (0.5M) at –40 °C in a Schlenk tube under argon. DIPEA (2 equiv.) was added dropwise and the reaction mixture was stirred for 2 h at –40 °C, after which an additional 2 equiv. of DIPEA and 0.25 equiv. of BT-$SeCF_2H$ were added. The reaction was stirred for a further 2 hours, after which the crude mixture was filtered through a silica pad and the solvent was removed *in vacuo*. The crude difluoromethylselenoethers were isolated using column chromatography (SiO_2).

Method B: BT-$SeCF_2H$ (1.25 equiv.), AgOTf (0.5 equiv) and the alcohol (1.0 equiv., 0.5 mmol) were added to dry MeCN (0.5M) at –40 °C in a Schlenk tube under argon. DIPEA (2 equiv.) was added dropwise and the reaction mixture was stirred for 2 h at –40 °C, after which an additional 2 equiv. of DIPEA and 0.25 equiv. of BT-$SeCF_2H$ were added. The reaction was stirred for a further 2 hours, after which the crude mixture was filtered through a silica pad and the solvent was removed *in vacuo*. The crude difluoromethylselenoethers were isolated using column chromatography (SiO_2).

4.4 Characterization Data for Deoxydifluoromethylselenoether Products 6

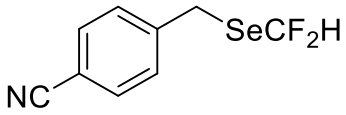
(Difluoromethyl)(4-nitrobenzyl)selane (6a)



According to Method A, selenoether **6a** (82 mg, 62%) was obtained from (4-nitrophenyl)methanol **5a** on a 0.5 mmol scale after flash column chromatography (pentane/ethyl acetate, 50:1) as a yellow oil.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 8.17 (d, *J* = 8.1,2H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.14 (t, *J* = 54.6 Hz, 1H), 4.16 (s, 2H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -92.03 (d, *J* = 54.2 Hz).**^{13}C NMR (151 MHz, $CDCl_3$) δ** = 147.20, 145.73, 129.97, 124.15, 115.18 (t, *J* = 288.4 Hz), 24.99 (t, *J* = 3.3 Hz). **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 1598, 1519, 1192, 1042, 908, 860, 799, 698, 599. **HRMS (EI) m/z:** $[M]^+$ Calcd for $C_8H_7F_2NO_2Se$ 266.9610; Found 266.9618.

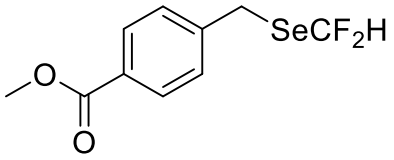
4-(((Difluoromethyl)selanyl)methyl)benzonitrile (6b)



According to Method A, selenoether **6b** (68 mg, 52%) was obtained from 4-(hydroxymethyl)benzonitrile **5b** on a 0.5 mmol scale after flash column chromatography (pentane/ethyl acetate, 30:1) as a yellow oil.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 7.61 (d, *J* = 8.0, 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.12 (t, *J* = 54.7 Hz, 1H), 4.11 (s, 2H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -92.12 (d, *J* = 54.6 Hz).**^{13}C NMR (151 MHz, $CDCl_3$) δ** = 143.55, 132.68, 129.84, 118.68, 115.20 (t, *J* = 288.3 Hz), 111.33, 25.39 (t, *J* = 3.1 Hz). **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2228, 1606, 1508, 1413, 1279, 1029, 847, 689, 605, 544. **HRMS (EI) m/z:** $[M]^+$ Calcd for $C_9H_7F_2NSe$ 246.9712; Found 246.9726.

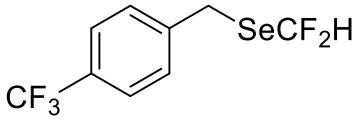
Methyl 4-(((difluoromethyl)selanyl)methyl)benzoate (6c)



According to Method A, selenoether **6c** (78 mg, 56%) was obtained from methyl 4-(hydroxymethyl)benzoate **5c** on a 0.5 mmol scale after flash column chromatography (pentane/ethyl acetate, 30:1) as a yellow oil.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 7.99 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.09 (t, *J* = 55.0 Hz, 1H), 4.12 (s, 2H), 3.91 (s, 3H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -92.52 (d, *J* = 55.5 Hz).**^{13}C NMR (151 MHz, $CDCl_3$) δ** = 166.75, 142.94, 130.19, 129.32, 129.08, 115.39 (t, *J* = 287.8 Hz), 52.24, 25.73 (t, *J* = 2.9 Hz). **IR (ATR)**: ṽ [cm^{-1}] = 2953, 1713, 1610, 1455, 1275, 1179, 1032, 863, 769, 690. **HRMS (EI) m/z:** $[M]^+$ Calcd for $C_{10}H_{10}F_2O_2Se$ 279.9814; Found 279.9827.

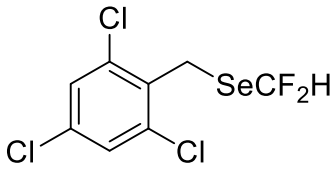
(Difluoromethyl)(4-(trifluoromethyl)benzyl)selane (6d)



According to Method A, selenoether **6d** (71 mg, 49%) was obtained from methyl (4-(trifluoromethyl)phenyl)methanol **5d** on a 0.5 mmol scale after flash column chromatography (pentane/CH_2Cl_2, 30:1) as a yellow oil.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 7.58 (d, *J* = 8.1 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.11 (t, *J* = 54.9 Hz, 1H), 4.13 (s, 2H).**^{19}F NMR (565 MHz, $CDCl_3$) δ** = -62.50 (s, 3F), -92.46 (d, *J* = 55.9 Hz, 2F). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 141.94, 129.78 (q, *J* = 32.3 Hz), 129.45, 125.91 (q, *J* = 3.8 Hz), 124.14 (q, *J* = 271.6 Hz), 115.35 (t, *J* = 287.9 Hz), 25.42(t, *J* = 2.7 Hz). **IR (ATR)**: ṽ [cm^{-1}] = 1617, 1418, 1322, 1165, 1120, 1063, 848, 678, 613. **HRMS (EI) m/z:** $[M]^+$ Calcd for $C_9H_7F_5Se$ 289.9633; Found 289.9648.

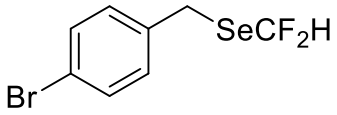
(Difluoromethyl)(2,4,6-trichlorobenzyl)selane (6e)



According to Method A, selenoether **6e** (108 mg, 67%) was obtained from (2,4,6-trichlorophenyl)methanol **5e** on a 0.5 mmol scale after flash column chromatography (pentane) as a yellow oil.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 7.35 (t, *J* = 55.1 Hz, 1H), 7.35 (s, 2H), 4.30 (s, 2H).**^{19}F NMR (565 MHz, $CDCl_3$) δ** = -90.86 (d, *J* = 54.8 Hz).**^{13}C NMR (151 MHz, $CDCl_3$) δ** = 135.67, 134.00, 133.66, 128.61, 115.41 (t, *J* = 287.9 Hz), 20.78 (t, *J* = 2.9 Hz). **IR (ATR)**: ṽ [cm^{-1}] =1579, 1547, 1437, 1374, 1275, 1038, 907, 855, 780, 735, 688, 608. **HRMS (EI) m/z:** $[M]^+$ Calcd for $C_8H_5Cl_3F_2Se$ 323.8590; Found 323.8580.

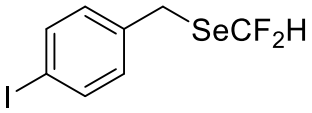
(Difluoromethyl)(4-bromobenzyl)selane (6f)



According to Method B, selenoether **6f** (101 mg, 67%) was obtained from (4-bromophenyl)methanol **5f** on a 0.5 mmol scale after flash column chromatography (pentane) as a yellow oil.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 7.44 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.08 (t, *J* = 55.0 Hz, 1H), 4.05 (s, 2H).**^{19}F NMR (565 MHz, $CDCl_3$) δ** = -92.58 (d, *J* = 55.4 Hz).**^{13}C NMR (151 MHz, $CDCl_3$) δ** = 136.67, 132.06, 130.77, 121.42, 115.51 (t, *J* = 287.5 Hz), 25.52 (t, *J* = 3.0 Hz). **IR (ATR)**: ṽ [cm^{-1}] =1486, 1401, 1275, 1190, 1030, 1005, 825, 676, 596. **HRMS (EI) m/z:** $[M]^+$ Calcd $C_8H_7F_2BrSe$ for 299.8864; Found 299.8857.

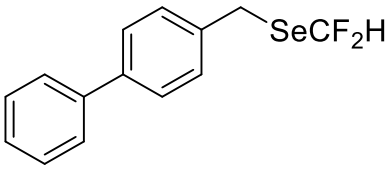
(Difluoromethyl)(4-iodobenzyl)selane (6g)



According to Method B, selenoether **6g** (96 mg, 55%) was obtained from (4-iodophenyl)methanol **5g** on a 0.5 mmol scale after flash column chromatography (pentane) as a yellow oil.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 7.64 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 9.0 Hz, 2H), 7.08 (d, *J* = 55.0 Hz, 1H), 4.03 (s, 2H).**^{19}F NMR (565 MHz, $CDCl_3$) δ** = -92.57 (d, *J* = 55.0 Hz).**^{13}C NMR (151 MHz, $CDCl_3$) δ** = 138.04, 137.34, 131.01, 115.50 (t, *J* = 287.5 Hz), 92.87, 25.63 (t, *J* = 2.8 Hz). **IR (ATR)**: ṽ [cm^{-1}] =1483, 1397, 1276, 1189, 1030, 1005, 796, 689, 590. **HRMS (EI) m/z:** $[M]^+$ Calcd $C_8H_7F_2ISe$ for 347.8726; Found 347.8709.

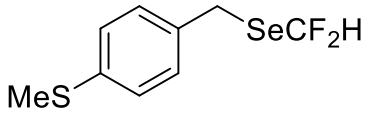
([1,1'-Biphenyl]-4-ylmethyl)(difluoromethyl)selane (6h)



According to the general procedure, selenoether **6h** (86 mg, 58%) was obtained from [1,1'-biphenyl]-4-ylmethanol **5h** on a 0.5 mmol scale after flash column chromatography (pentane/CH2Cl2, 50:1) as a yellow solid.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 7.59 (d, *J* = 7.4 Hz, 2H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.36 (t, *J* = 7.2, 1H), 7.12 (t, *J* = 55.2 Hz, 1H), 4.16 (s, 2H).**^{19}F NMR (565 MHz, $CDCl_3$) δ** = -92.71 (d, *J* = 55.6 Hz). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 140.67, 140.50, 136.49, 129.53, 128.95, 127.67, 127.57, 127.18, 115.77 (t, *J* = 287.1 Hz), 26.10 (t, *J* = 2.8 Hz). **IR (ATR)**: ṽ [cm^{-1}] = 3031, 2970, 1486, 1406, 1274, 1036, 833, 762, 689, 603. **HRMS (EI) m/z:** $[M]^+$ Calcd $C_{14}H_{12}F_2Se$ for 298.0072; Found 298.0072. Melting Point = 40-42 °C.

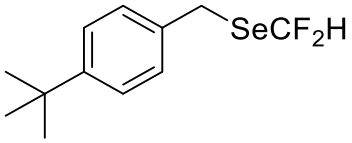
(4-(((Difluoromethyl)selanyl)methyl)phenyl)(methyl)sulfane (6i)



According to Method B, selenoether **6i** (92 mg, 69%) was obtained from (4-(methylthio)phenyl)methanol **5i** on a 0.5 mmol scale after flash column chromatography (pentane/CH_2Cl_2, 50:1) as a yellow oil.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 7.25 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 8.3, 2H), 7.07 (t, *J* = 55.5, 1H), 4.07 (s, 2H), 2.48 (s, 3H).**^{19}F NMR (565 MHz, $CDCl_3$) δ** = -92.74 (d, *J* = 55.7 Hz).**^{13}C NMR (151 MHz, $CDCl_3$) δ** = 137.88, 134.15, 129.55, 126.97, 115.74 (t, *J* = 287.2 Hz), 26.01 (t, *J* = 3.1 Hz), 15.90. **IR (ATR)**: ṽ [cm^{-1}] = 2921, 1558, 1492, 1437, 1271, 1191, 1029, 968, 811, 681, 599. **HRMS (EI) m/z:** $[M]^+$ Calcd for $C_9H_{10}F_2SSe$ 267.9636; Found 267.9623.

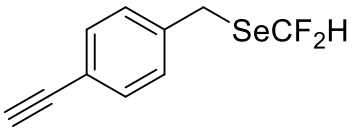
(4-(*tert*-Butyl)benzyl)(difluoromethyl)selane (6j)



According to Method B, selenoether **6j** (132 mg, 95%) was obtained from (4-(tert-butyl)phenyl)methanol **5j** on a 0.5 mmol scale after flash column chromatography (pentane) as a yellow oil.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 7.36 (d, *J* = 8.6 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.09 (t, *J* = 55.2 Hz, 1H), 4.10 (s, 2H), 1.33 (s, 9H).**^{19}F NMR (565 MHz, $CDCl_3$) δ** = -92.90 (d, *J* = 55.8 Hz).**^{13}C NMR (151 MHz, $CDCl_3$) δ** = 150.54, 134.19, 128.75, 125.85, 115.84 (t, *J* = 286.8 Hz), 34.64, 31.39, 26.05 (t, *J* = 2.9 Hz). **IR (ATR)**: ṽ [cm^{-1}] =2963, 1514, 1364, 1294, 1269, 1109, 1035, 909, 833, 734, 691, 609. **HRMS (EI) m/z:** $[M]^+$ Calcd for $C_{12}H_{16}F_2Se$ 278.0385; Found 278.0371.

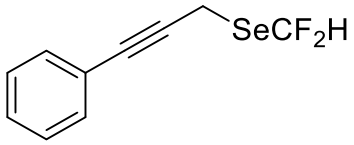
(Difluoromethyl)(4-ethynylbenzyl)selane (6k)



According to Method B, selenoether **6k** (84 mg, 69%) was obtained from (4-ethynylphenyl)methanol **5k** on a 0.5 mmol scale after flash column chromatography (pentane) as a yellow oil.

^{1}H NMR (601 MHz, $CDCl_3$) δ =7.45 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 7.08 (t, *J* = 55.0 Hz, 1H), 4.08 (s, 2H), 3.09 (s, 1H).**^{19}F NMR (565 MHz, $CDCl_3$) δ** = -92.61 (d, *J* = 55.9 Hz).**^{13}C NMR (151 MHz, $CDCl_3$) δ** = 138.44, 132.66, 129.09, 121.32, 115.54 (t, *J* = 287.4 Hz), 83.34, 77.78, 25.98 (t, *J* = 2.4 Hz). **IR (ATR)**: ṽ [cm^{-1}] =3294, 2107, 1506, 1293, 1276, 1191, 1032, 908, 843, 734, 657, 603. **HRMS (EI) m/z:** $[M]^+$ Calcd for $C_{10}H_8F_2Se$ 245.9759 ; Found 245.9748.

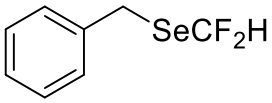
(Difluoromethyl)(3-phenylprop-2-yn-1-yl)selane (6l)



According to Method B, selenoether **6l** (52 mg, 42%) was obtained from 3-phenylprop-2-yn-1-ol **5l** on a 0.5 mmol scale after flash column chromatography (pentane) as a yellow oil.

^{1}H NMR (601 MHz, $CDCl_3$) δ = 7.44 – 7.41 (m, 2H), 7.37 (t, *J* = 55.2 Hz, 1H), 7.33 – 7.30 (m, 3H), 3.76 (s, 2H).**^{19}F NMR (565 MHz, $CDCl_3$) δ** = -93.14 (d, *J* = 55.4 Hz).**^{13}C NMR (151 MHz, $CDCl_3$) δ** = 131.86, 128.64, 128.47, 122.72, 116.04 (t, *J* = 287.5 Hz), 84.48, 84.47, 8.70 (t, *J* = 3.5 Hz). **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 1597, 1490, 1442, 1272, 1190, 1037, 754, 689, 606. **HRMS (EI) m/z:** $[M]^+$ Calcd for $C_{10}H_8F_2Se$ 245.9759; Found 245.9765.

Benzyl(difluoromethyl)selane (A)



According to Method B, selenoether **A** (256 mg, 58%) was obtained from benzylic alcohol on a 2 mmol scale after flash column chromatography (pentane) as a colourless oil.

^{1}H NMR (401 MHz, $CDCl_3$) δ 7.42 – 7.36 (m, 4H), 7.32 (m, 1H), 7.11 (t, *J* = 55.1 Hz, 1H), 4.15 (s, 2H). **^{19}F NMR (377 MHz, $CDCl_3$) δ** = -92.68 (d, *J* = 55.4 Hz).**^{13}C NMR (101 MHz, $CDCl_3$) δ** = 137.42, 129.02, 128.86, 127.45, 115.77 (t, *J* = 286.7 Hz), 26.32 (t, *J* = 2.9 Hz).

The characterization data agree with the literature values.[4]

5 Literature

[1] K. Shibata, O. Mitsunobu, *Bull. Chem. Soc. Jpn.* **1992**, *65*, 3163-3173.

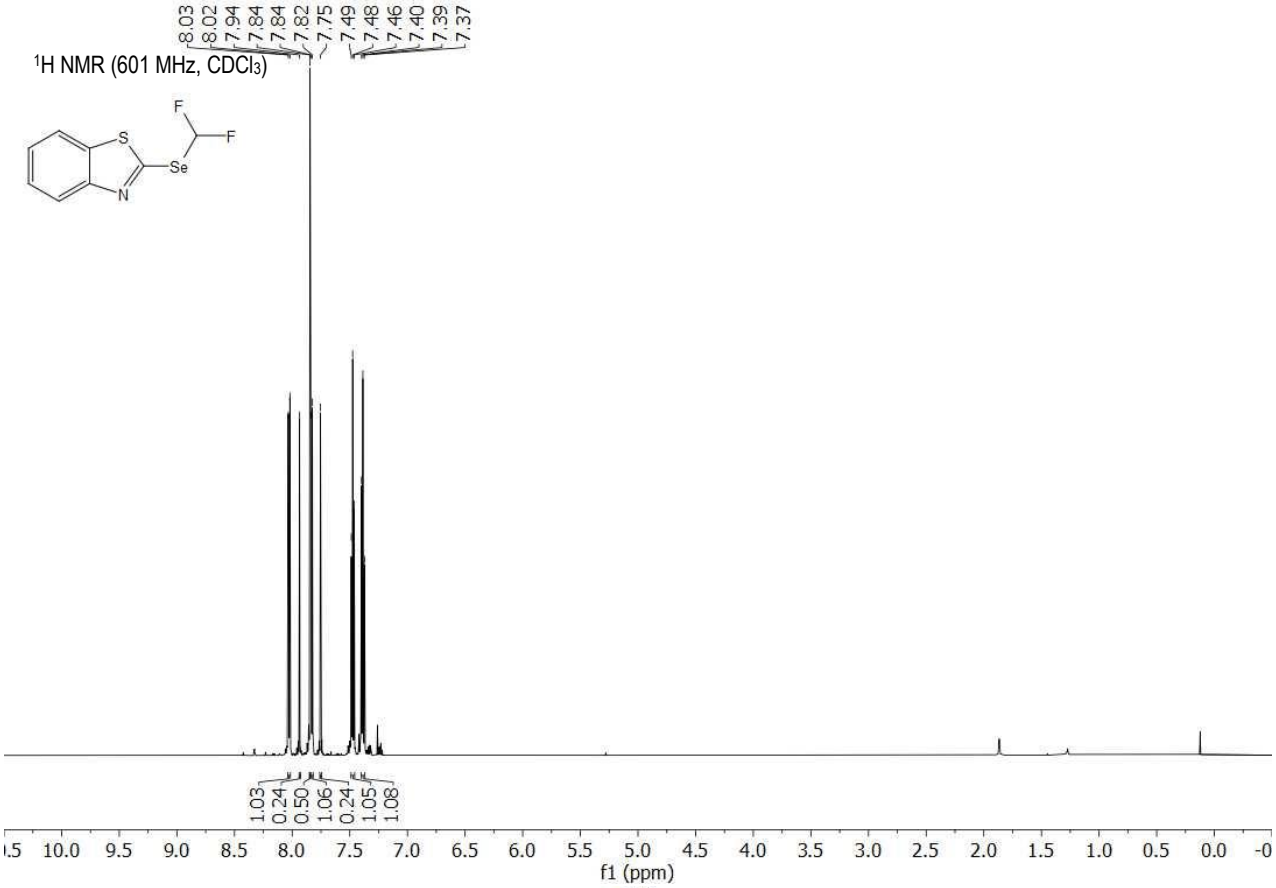
[2] V. V. Levin, A. D. Dilman, P. A. Belyakov, M. I. Struchkova, V. A. Tartakovsky, *J. Fluorine Chem.* **2009**, *130*, 667-670.

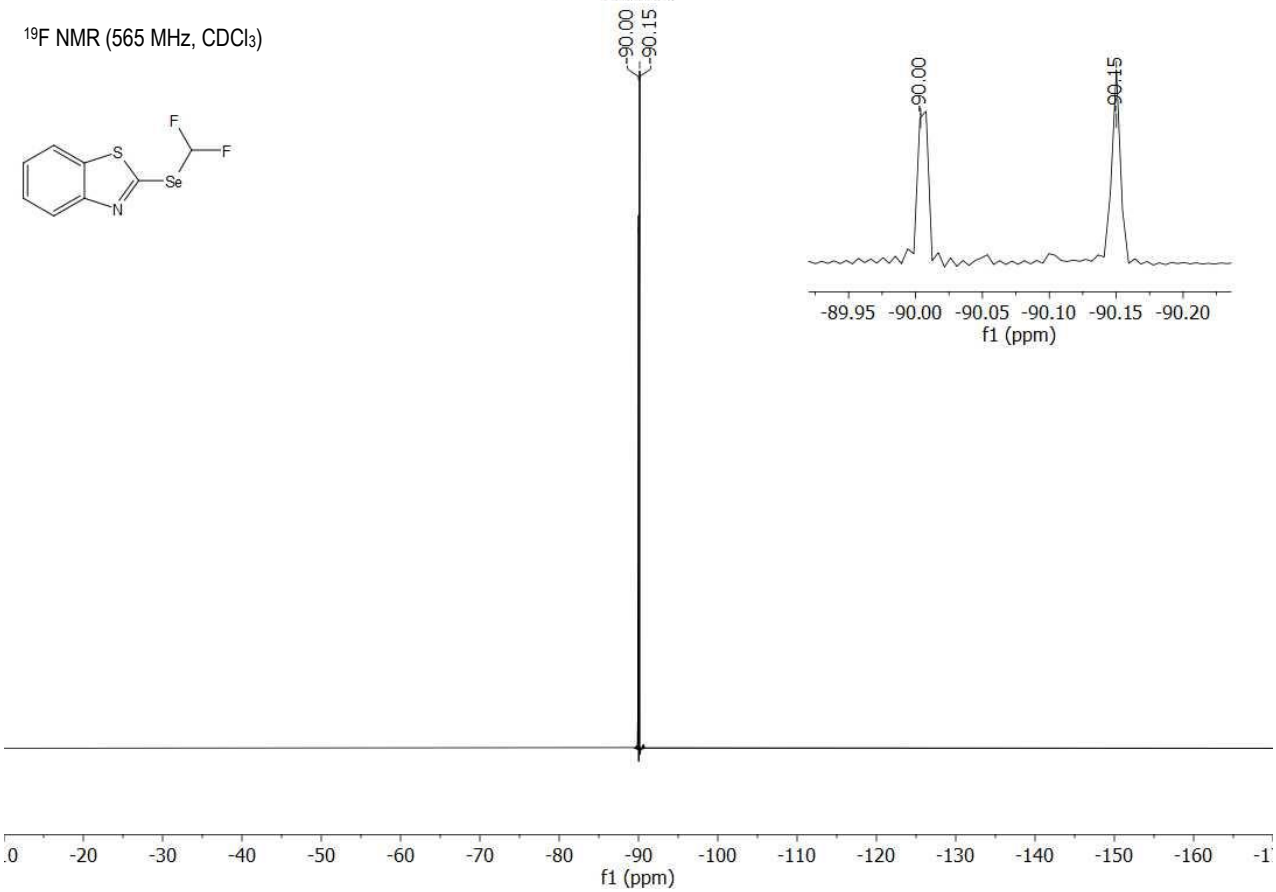
[3] R.-L. Guo, X.-Q. Zhu, X.-L. Zhang, Y.-Q. Wang, *Chem. Commun.* **2020**, *56*, 8976-8979.

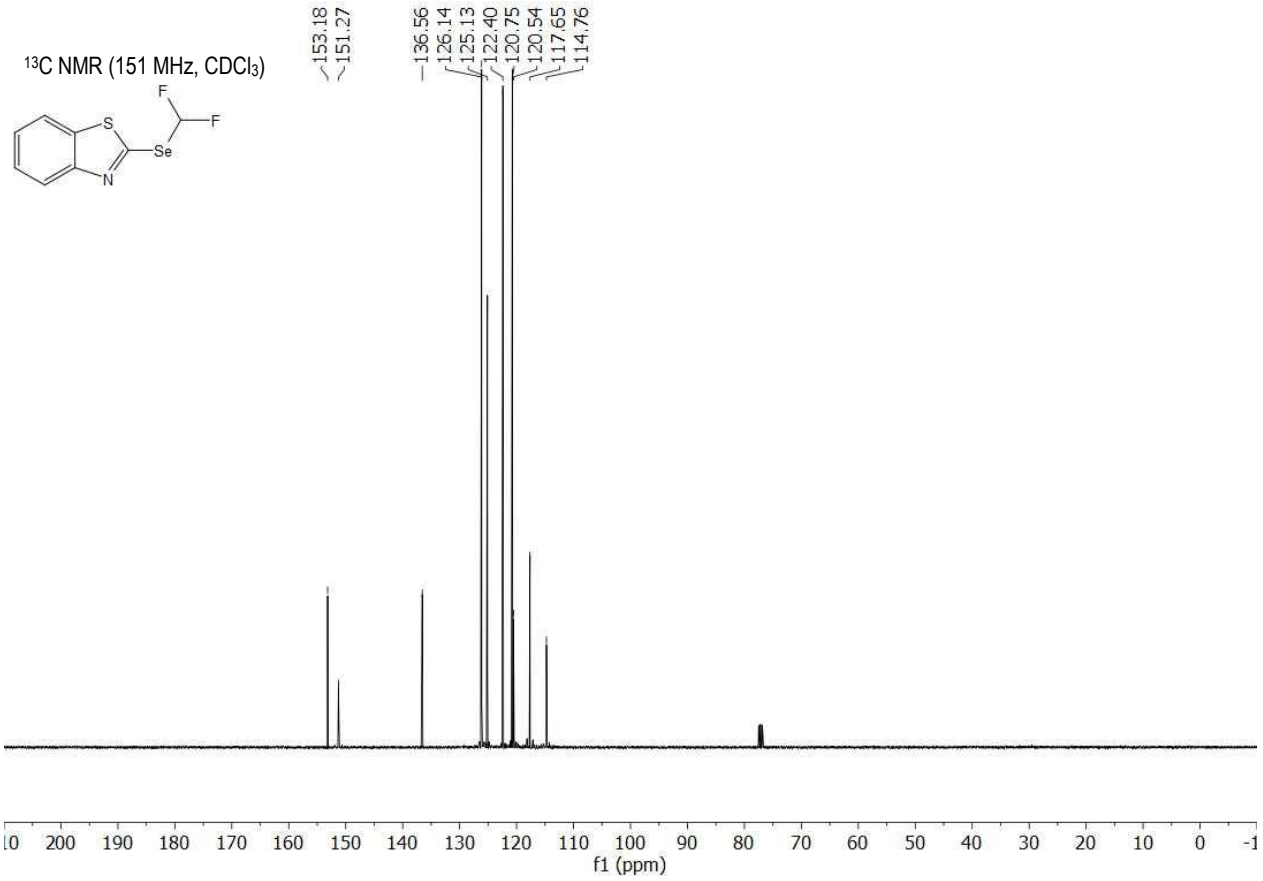
[4] T. Dong, J. Nie, C.-P. Zhang, *Tetrahedron* **2018**, *74*, 5642-5649.

6 NMR Spectra

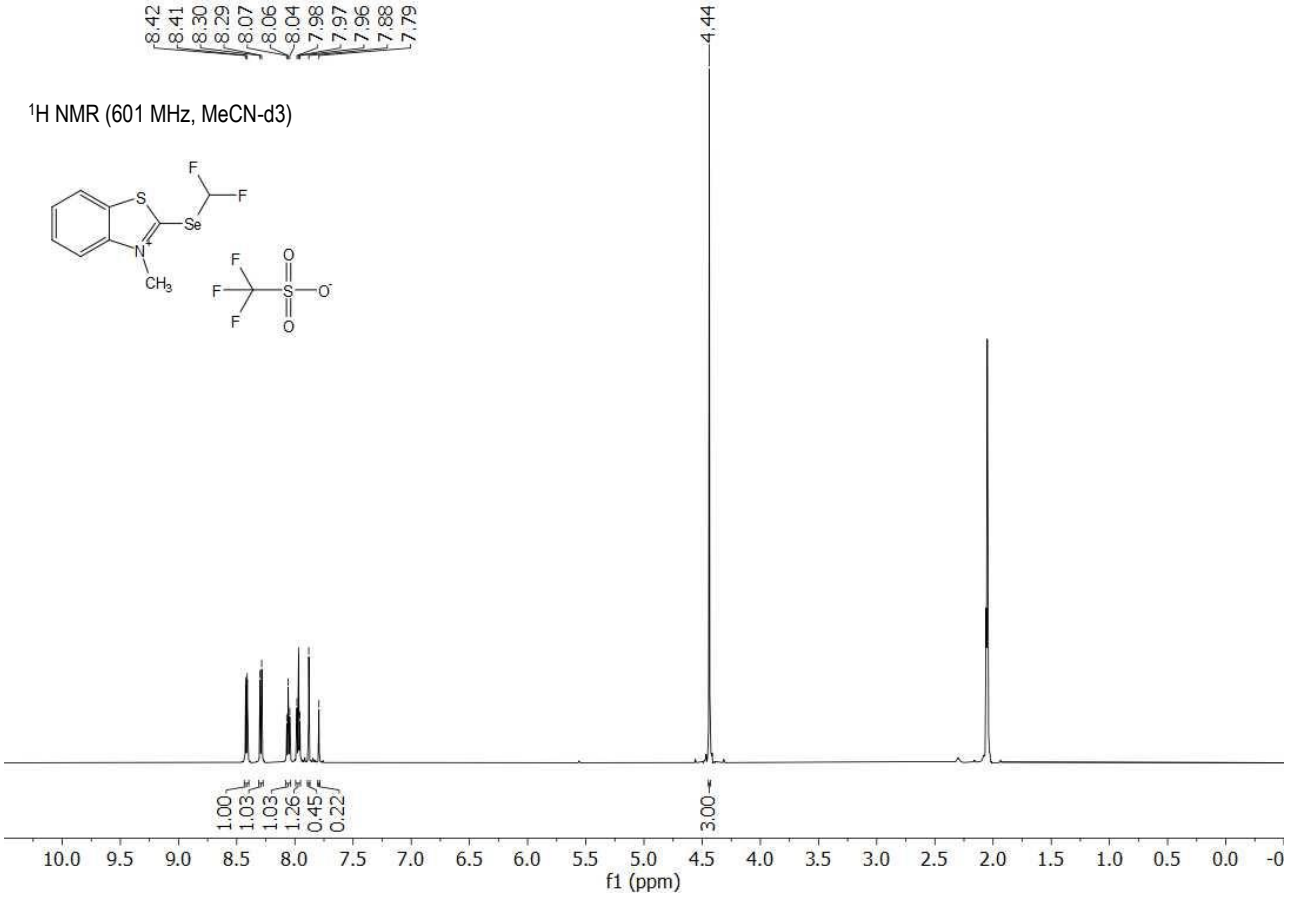
2-((Trifluoromethyl)thio)benzo[*d*]thiazole



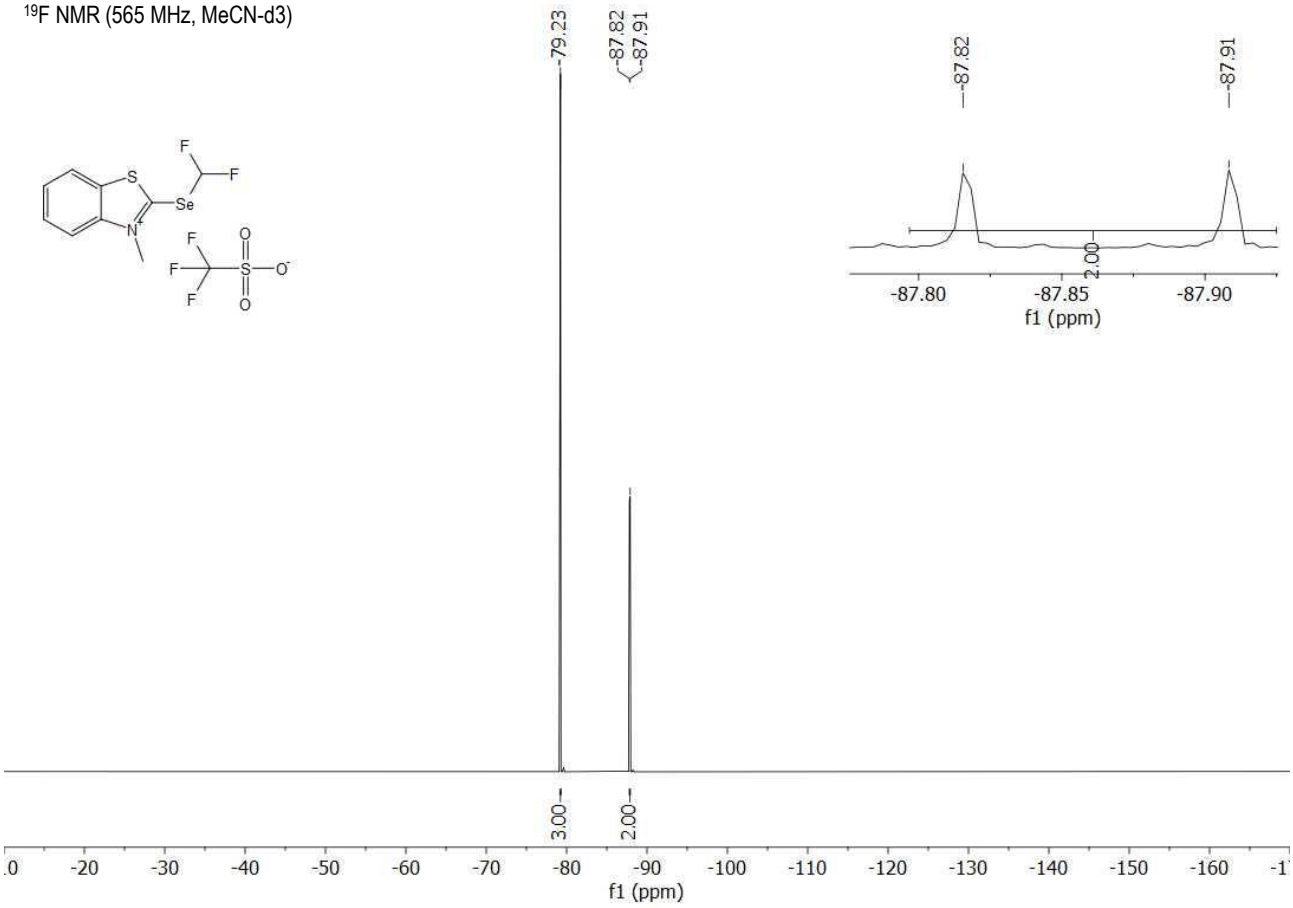




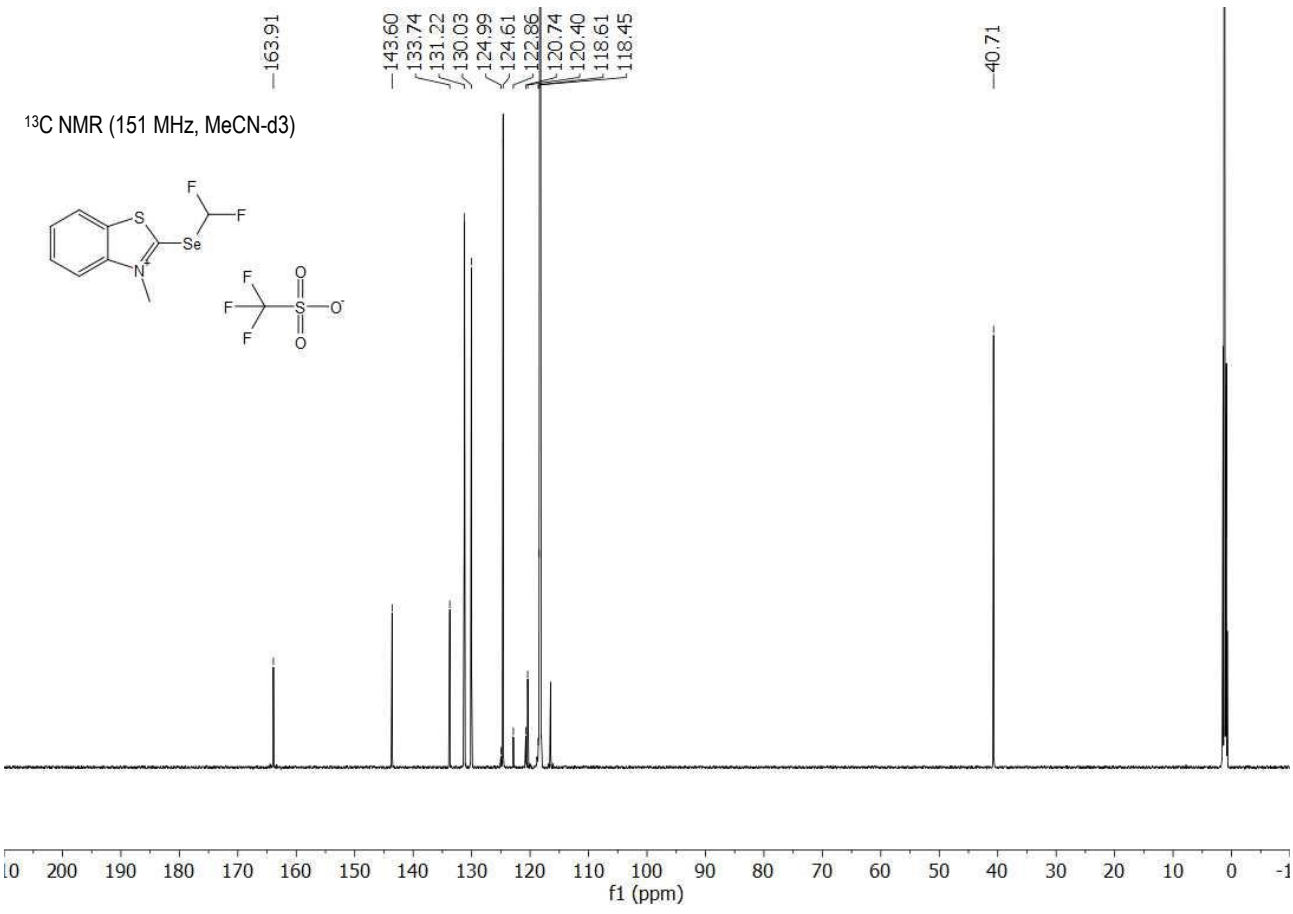
2-((Difluoromethyl)selanyl)-3-methylbenzo[*d*]thiazol-3-ium trifluoromethanesulfonate



^{19}F NMR (565 MHz, MeCN-d3)

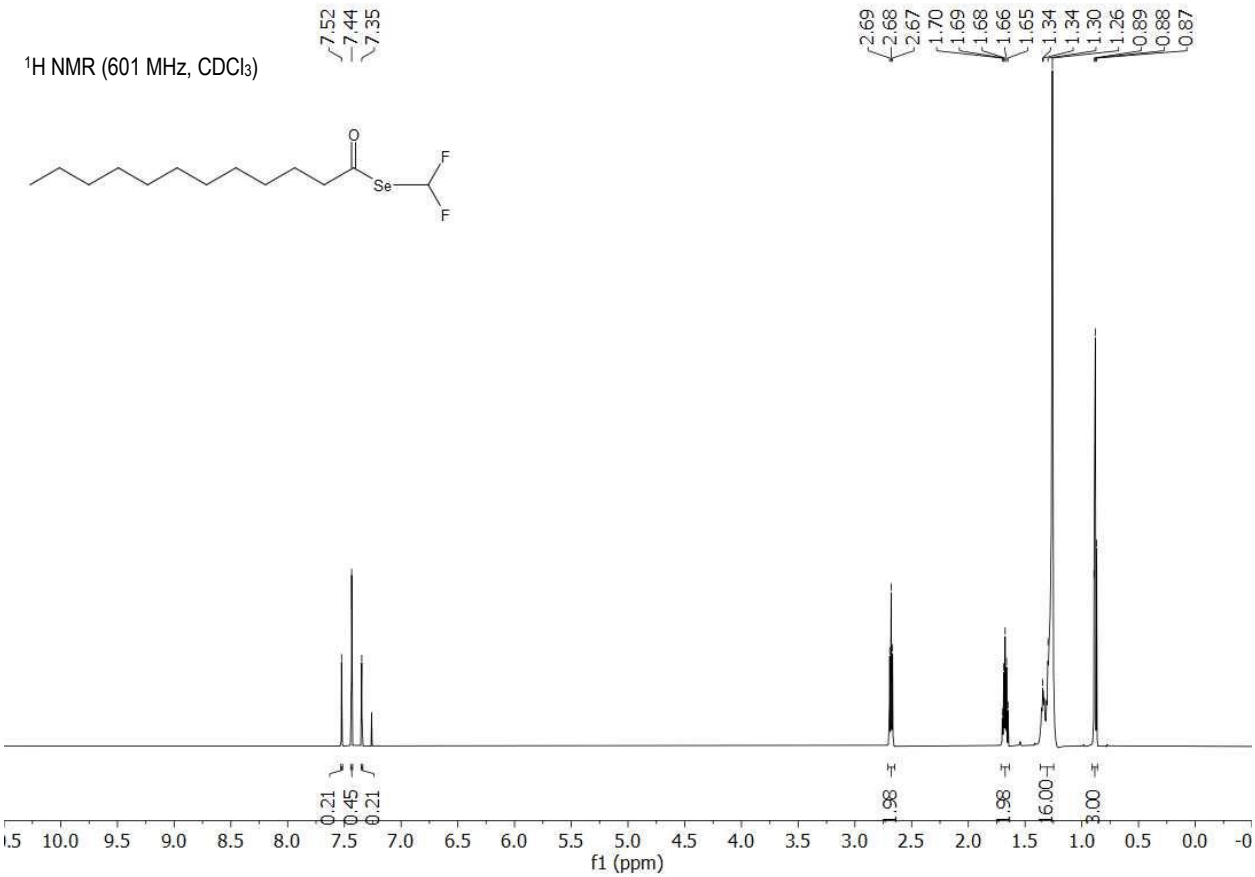


^{13}C NMR (151 MHz, MeCN-d3)

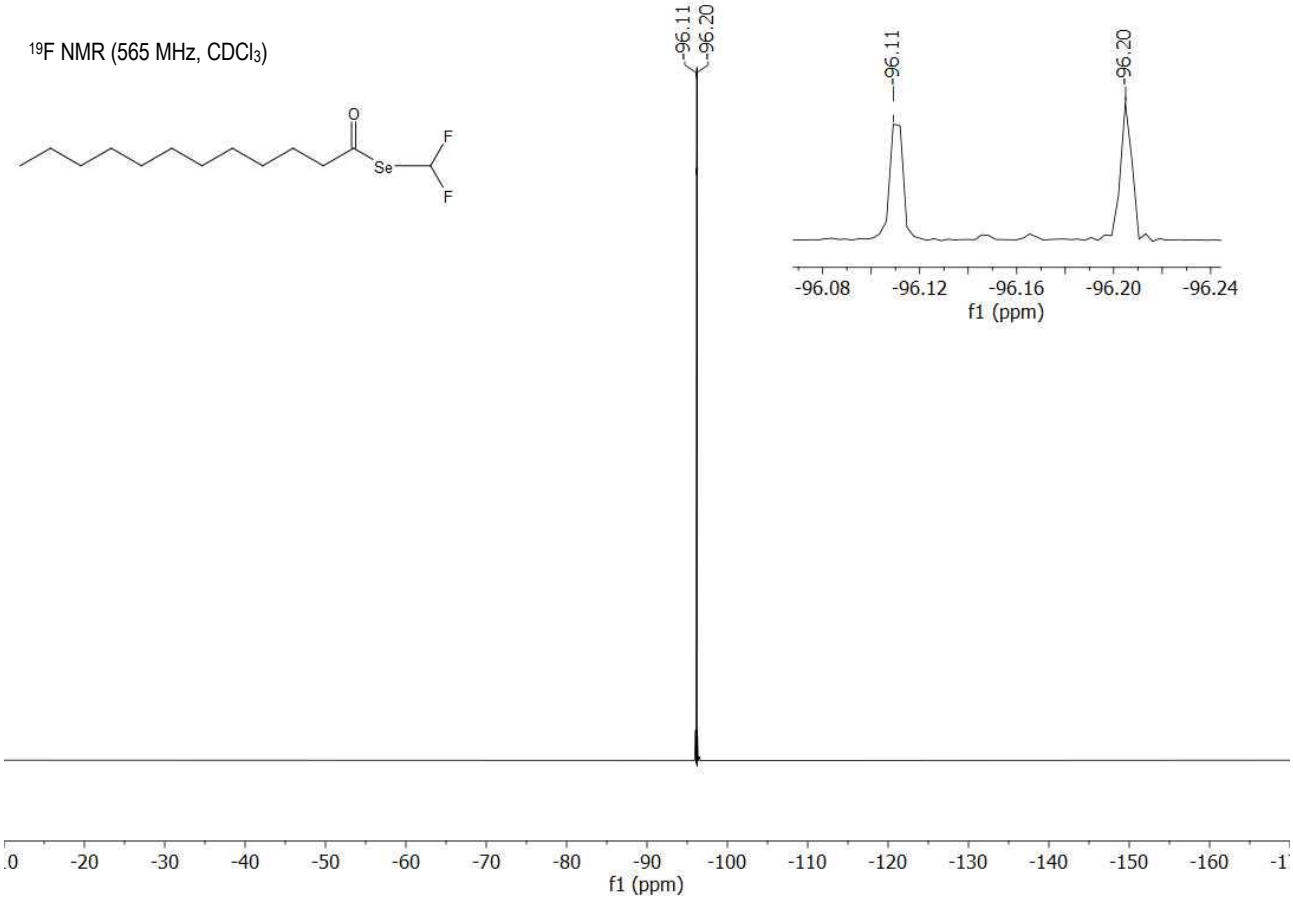


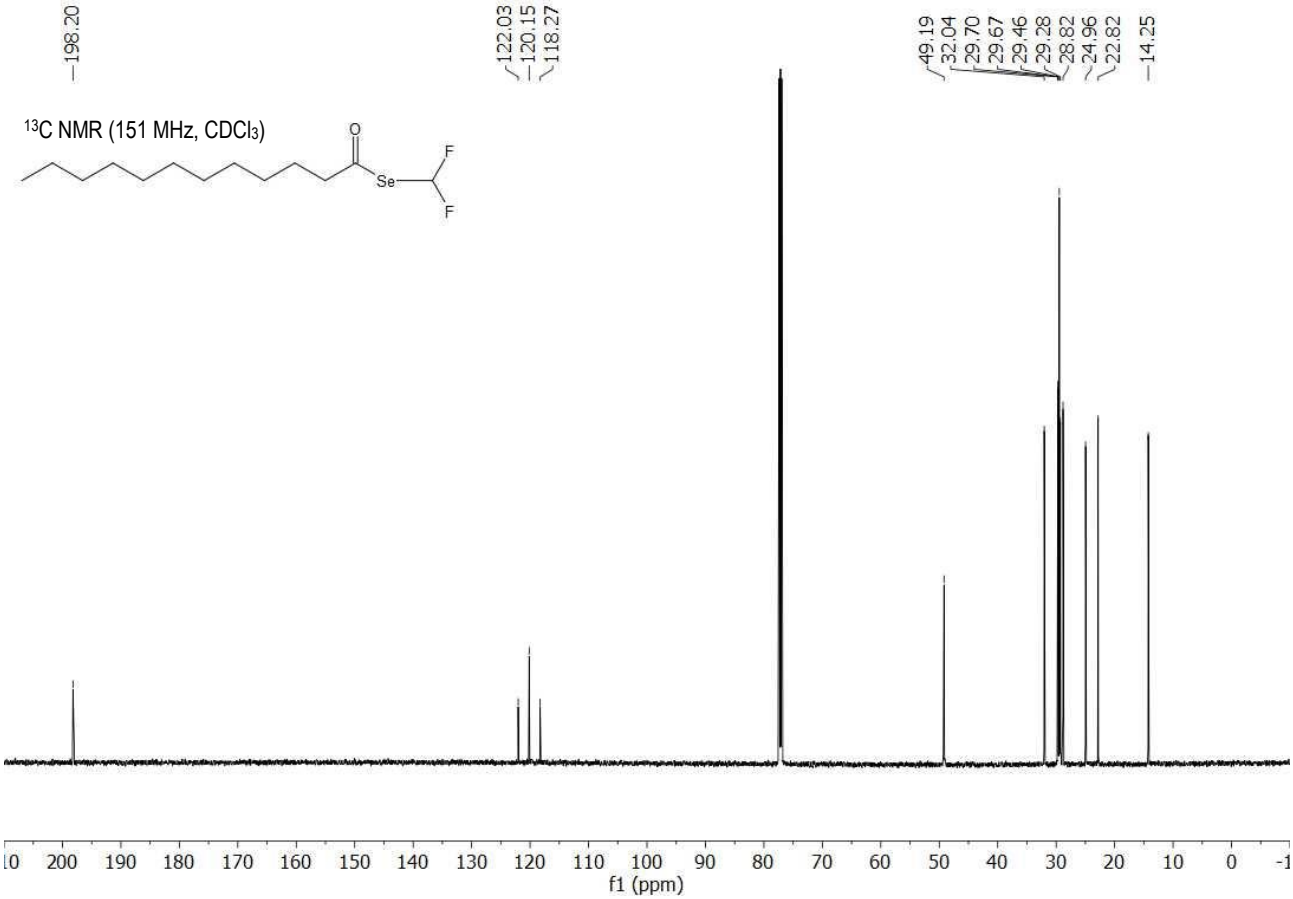
Se-(difluoromethyl) dodecaneselenoate **4a**

^{1}H NMR (601 MHz, $CDCl_3$)

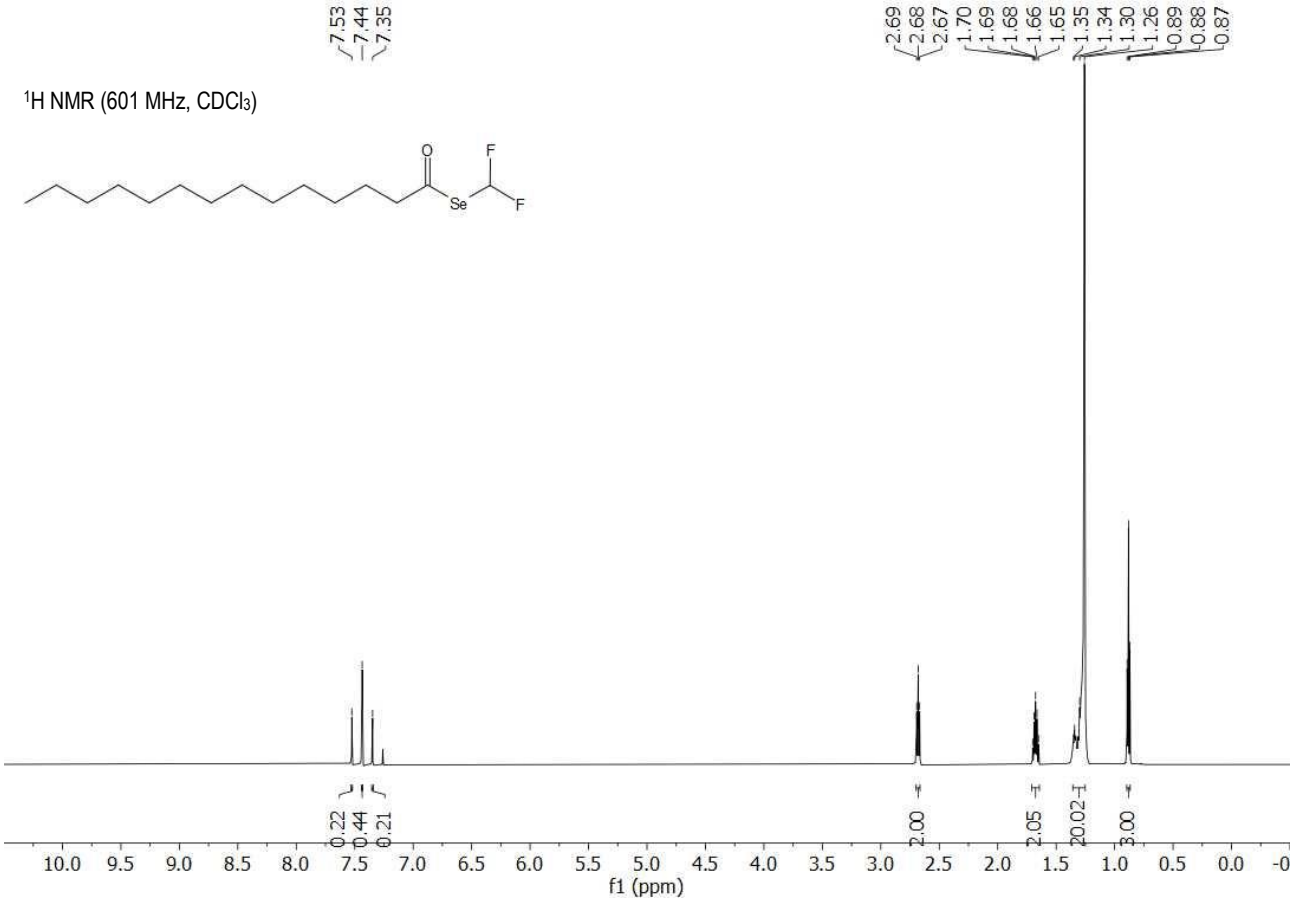


^{19}F NMR (565 MHz, $CDCl_3$)

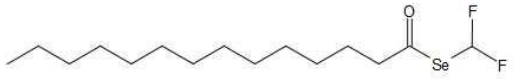




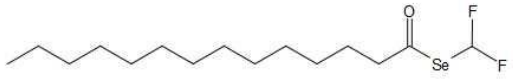
Se-(difluoromethyl) tetradecaneselenoate **4b**



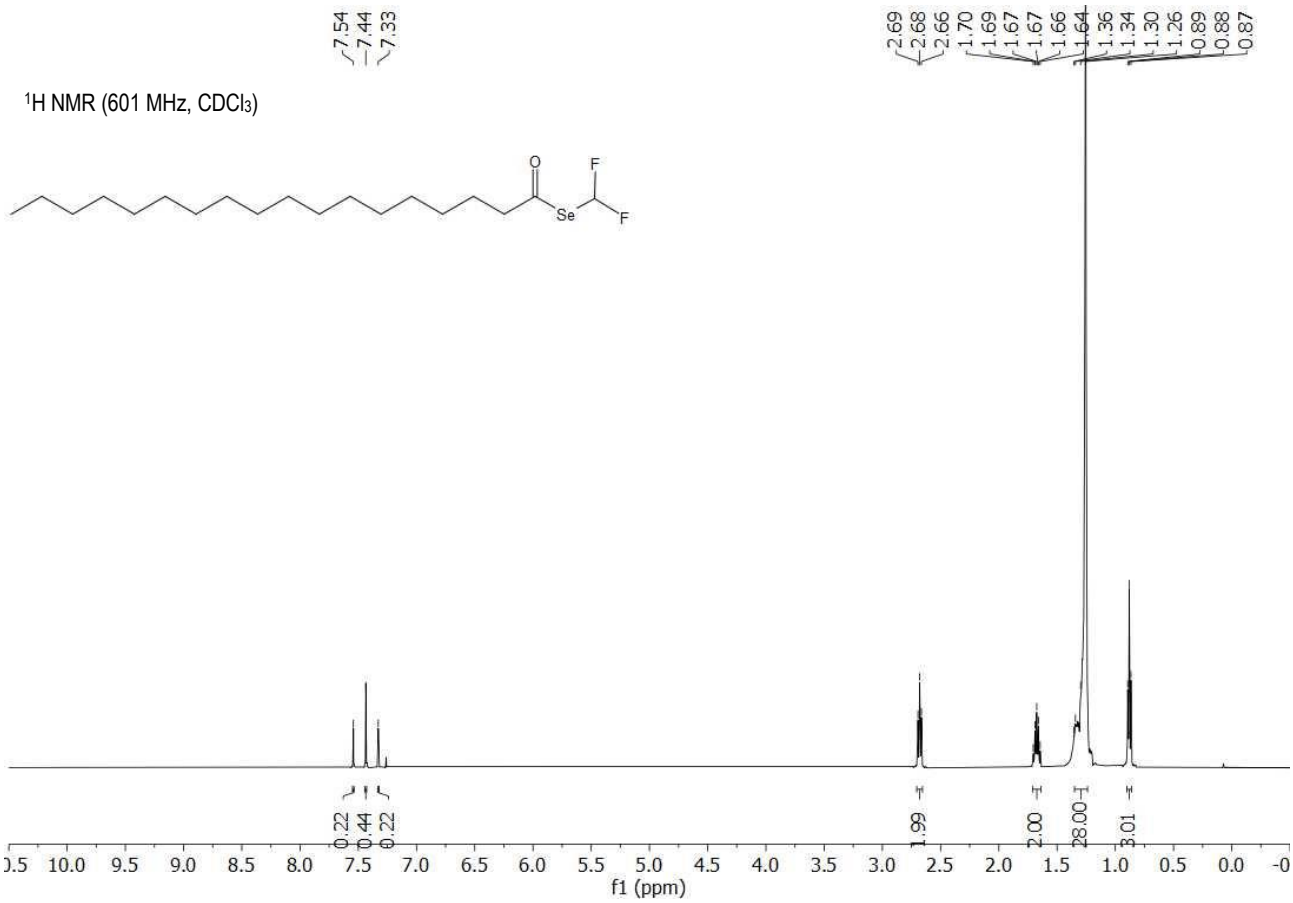
^{19}F NMR (565 MHz, $CDCl_3$)



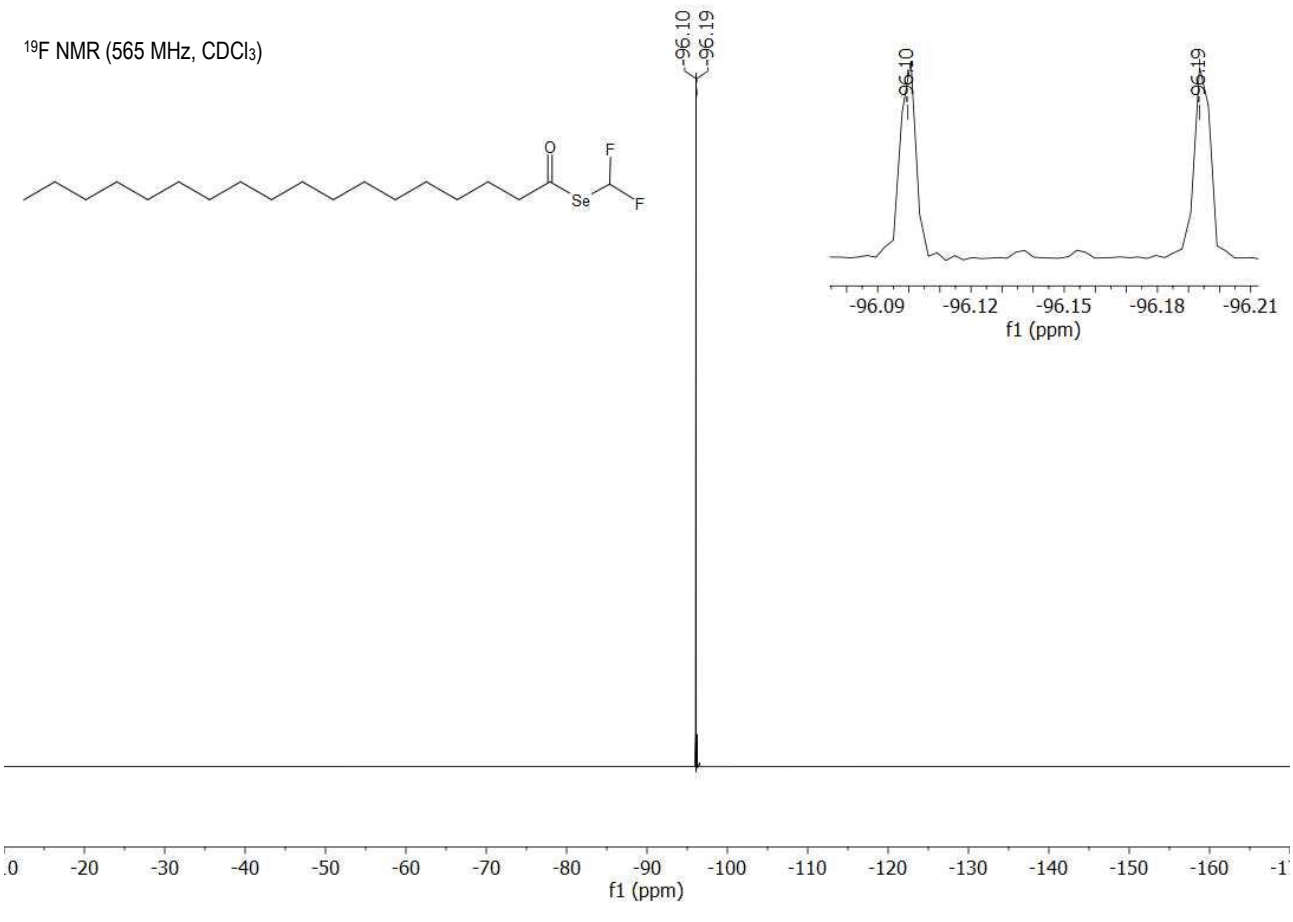
^{13}C NMR (151 MHz, $CDCl_3$)



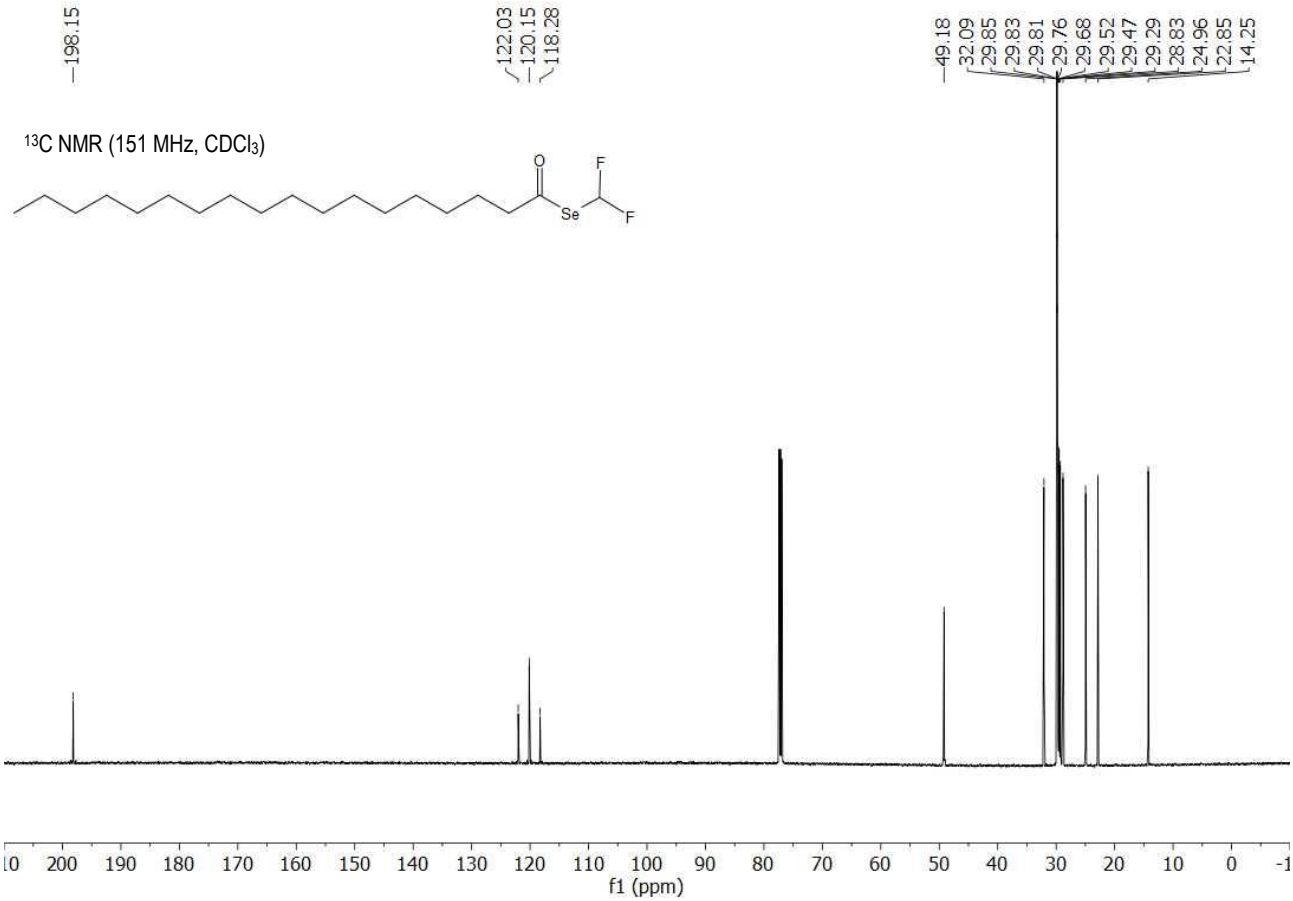
Se-(difluoromethyl) octadecaneselenoate **4c**



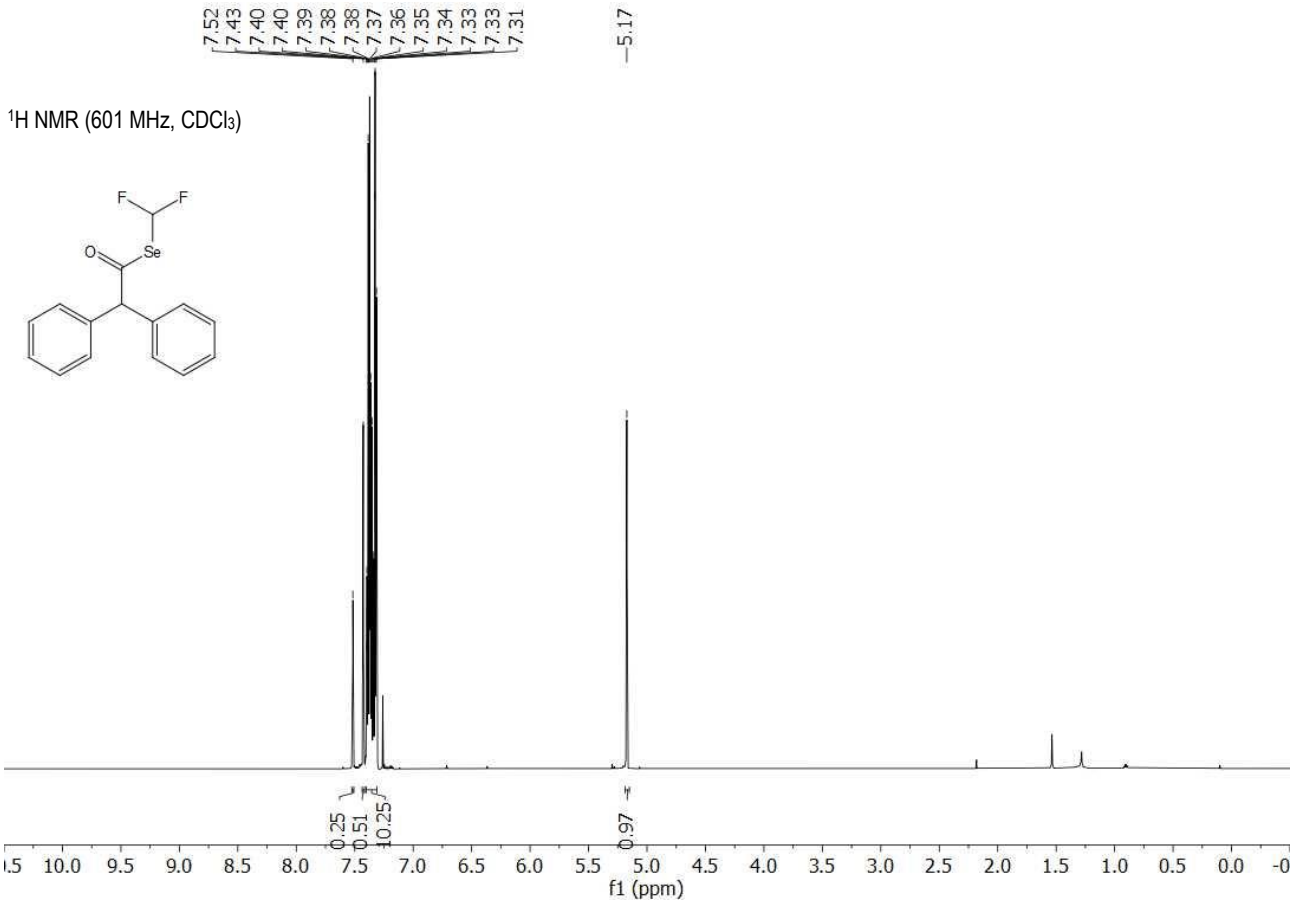
^{1}H NMR (601 MHz, $CDCl_3$)



^{19}F NMR (565 MHz, $CDCl_3$)



Se-(difluoromethyl) 2,2-diphenylethaneselenoate **4d**

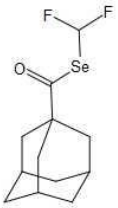


^{19}F NMR (565 MHz, $CDCl_3$)

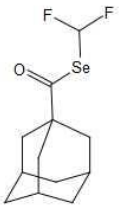
^{13}C NMR (151 MHz, $CDCl_3$)

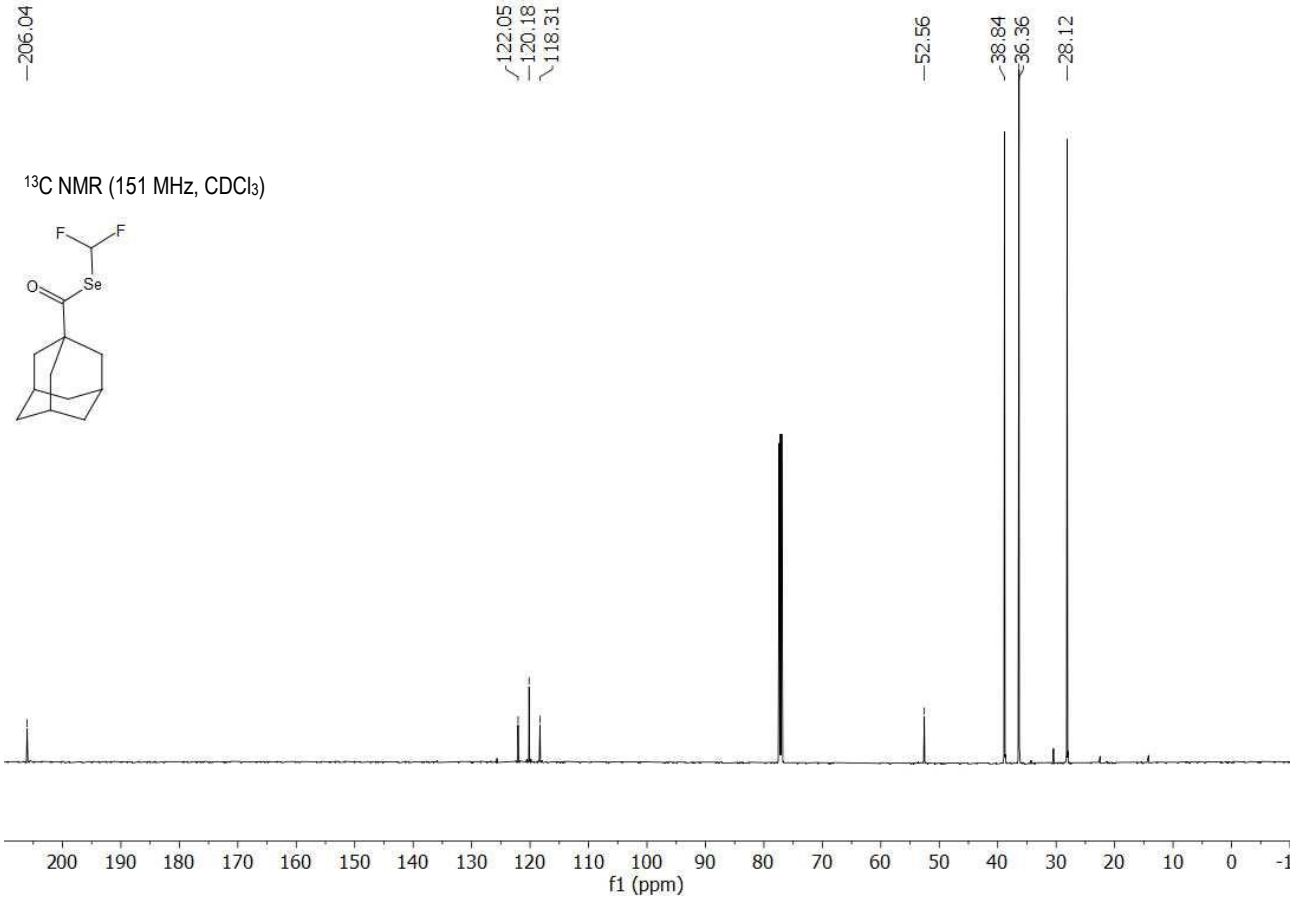
Se-(difluoromethyl)-adamantane-1-carboselenoate **4e**

^{1}H NMR (601 MHz, $CDCl_3$)

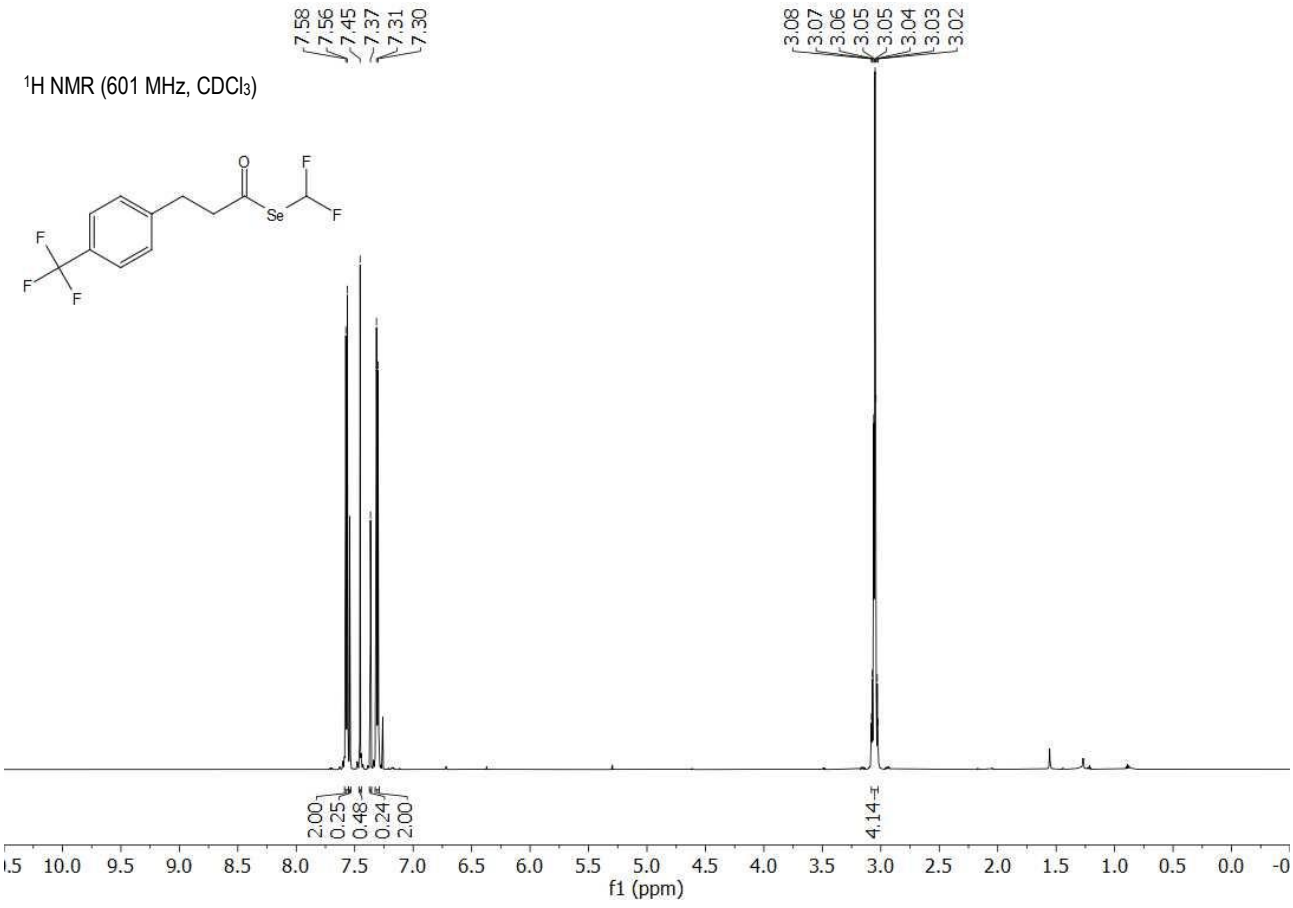


^{19}F NMR (565 MHz, $CDCl_3$)

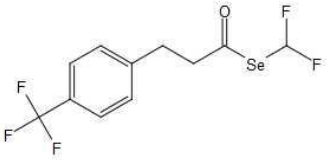




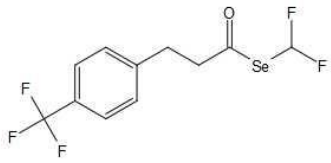
Se-(difluoromethyl) 3-(4-trifluoromethylphenyl)propaneselenoate **4f**



^{19}F NMR (565 MHz, $CDCl_3$)

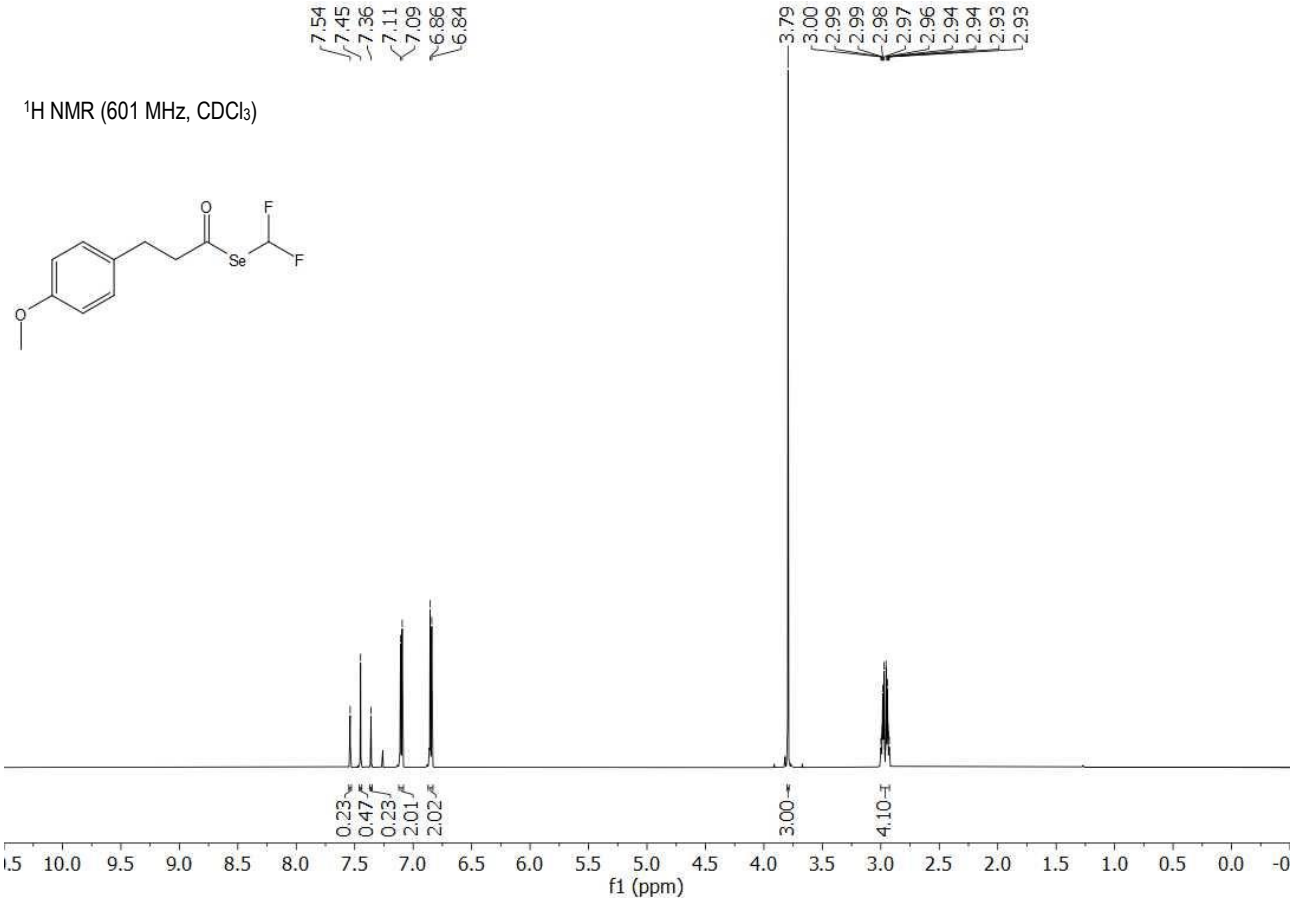


^{13}C NMR (151 MHz, $CDCl_3$)

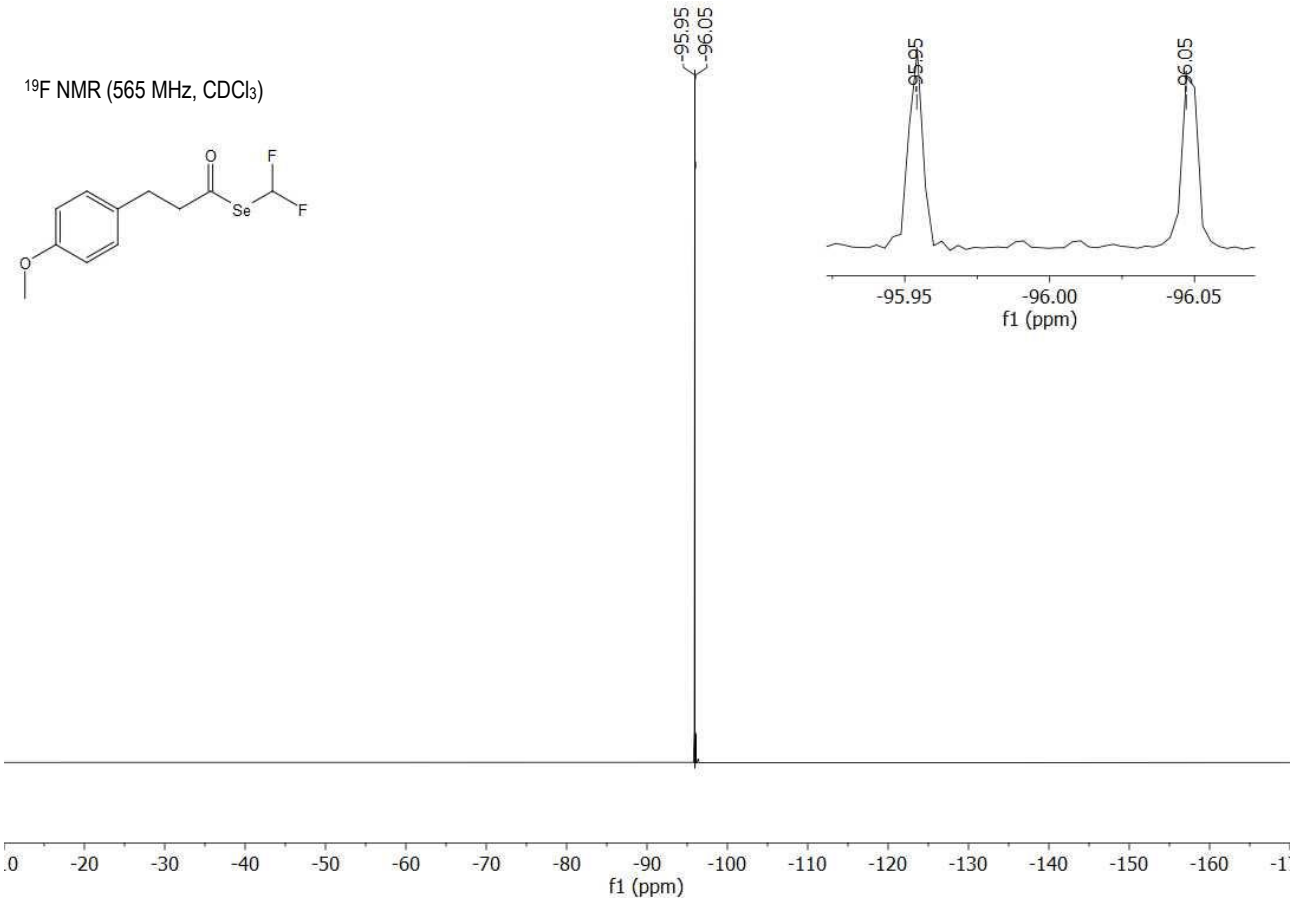


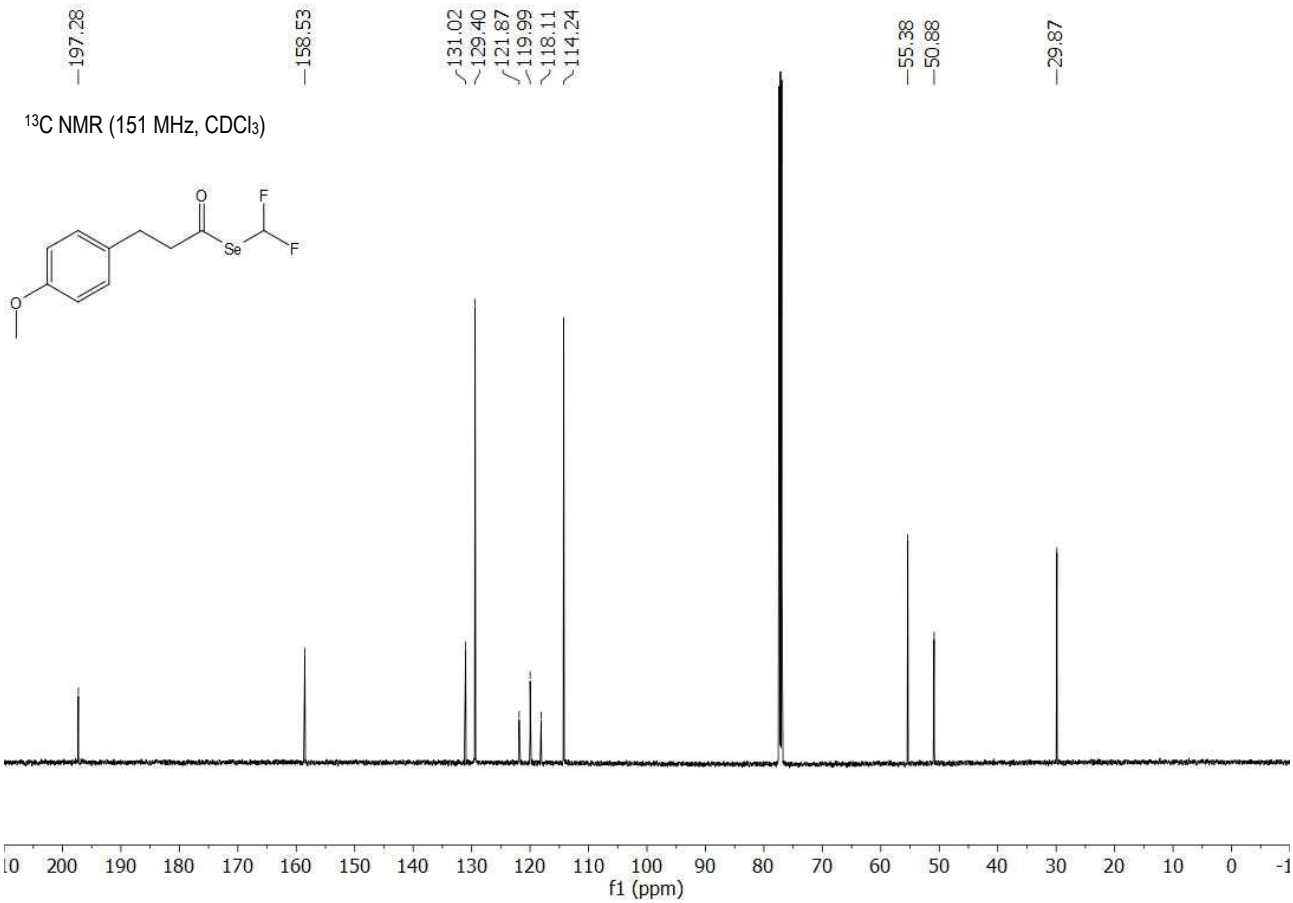
Se-(difluoromethyl) 3-(4-methoxyphenyl)propaneselenoate **4g**

^{1}H NMR (601 MHz, $CDCl_3$)

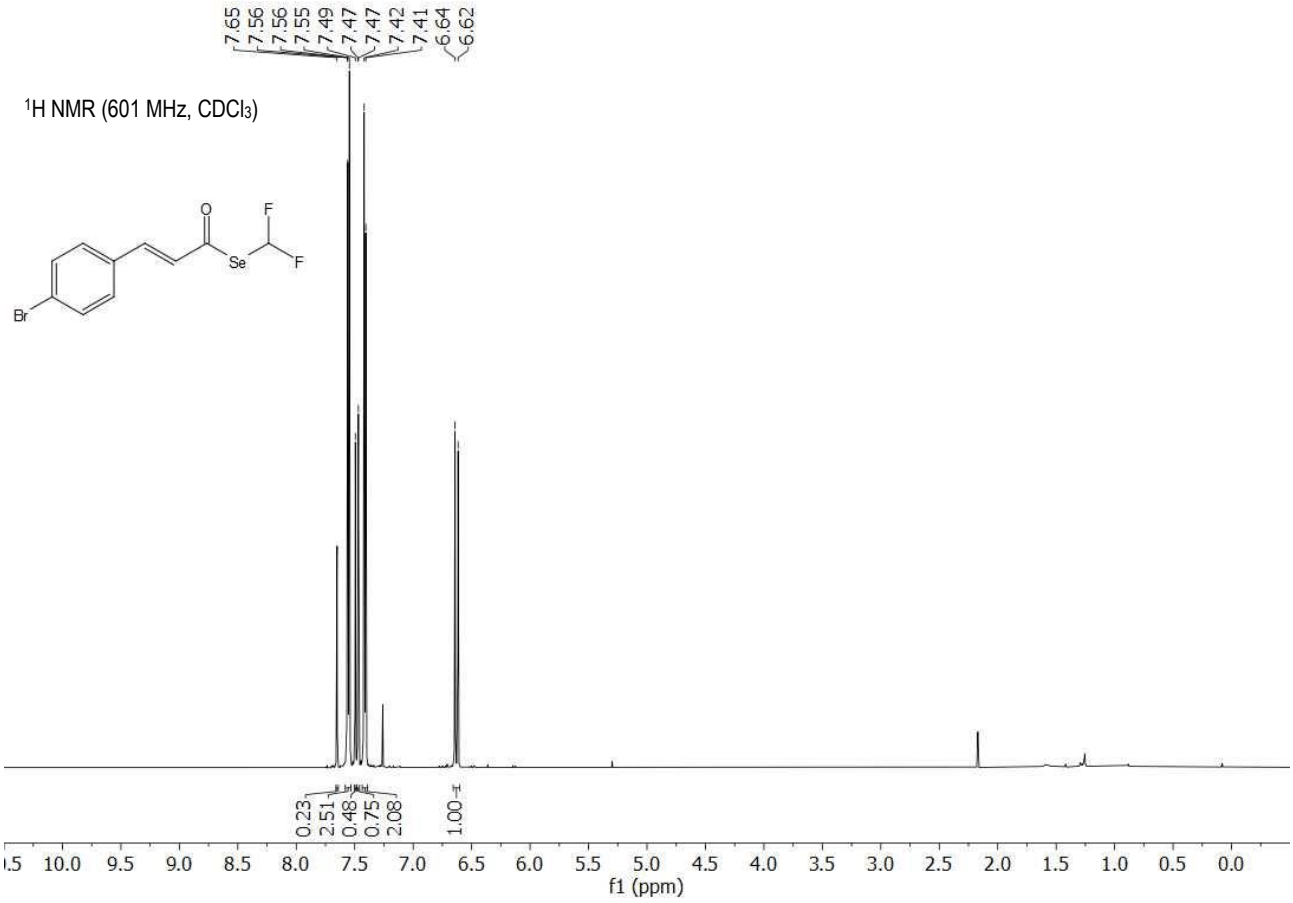


^{19}F NMR (565 MHz, $CDCl_3$)

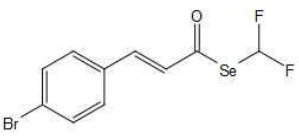




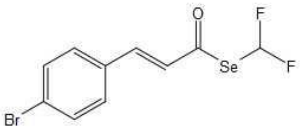
Se-(difluoromethyl) (*E*)-3-(4-bromophenyl)prop-2-eneselenoate **4h**



^{19}F NMR (565 MHz, $CDCl_3$)

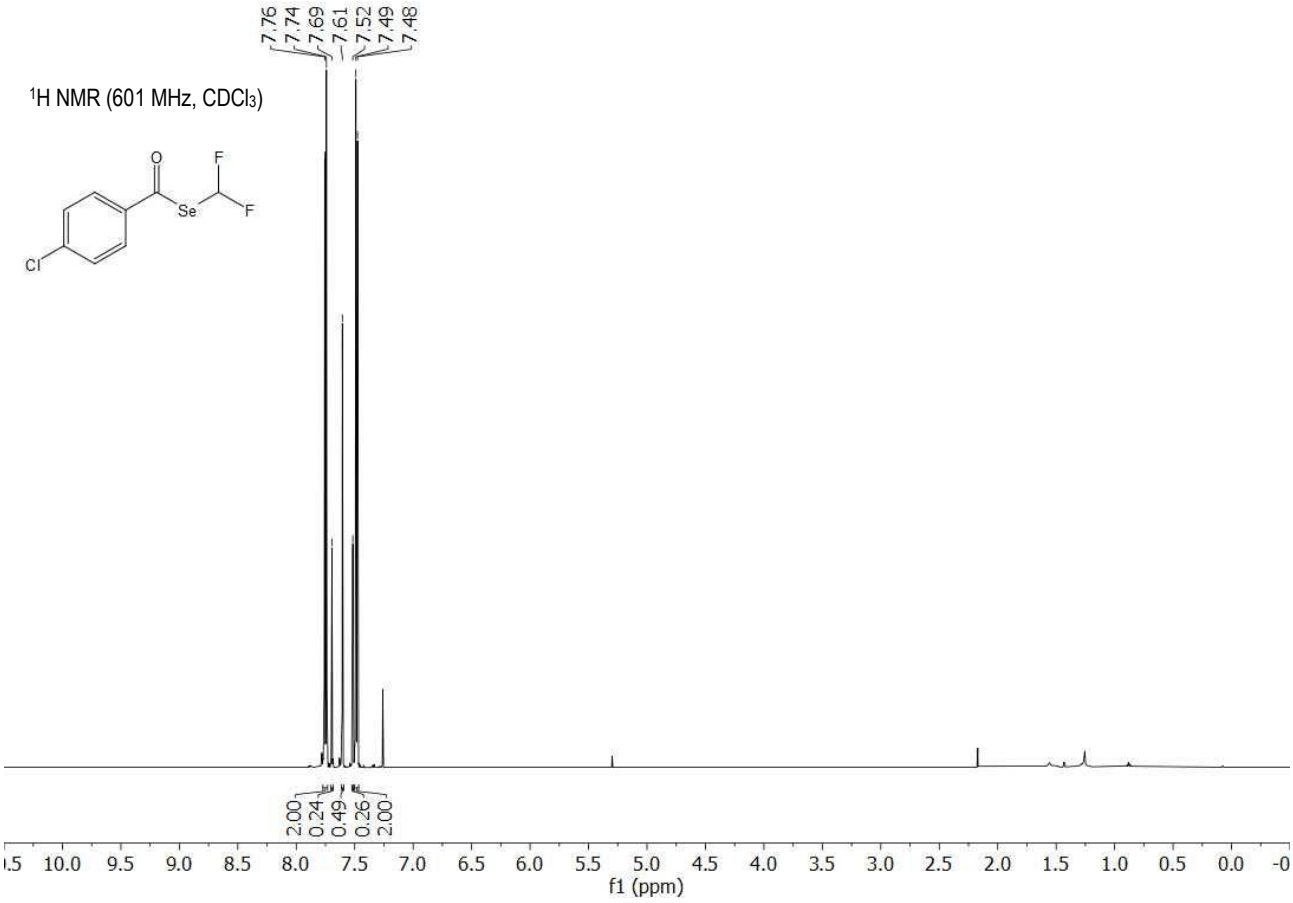


^{13}C NMR (151 MHz, $CDCl_3$)

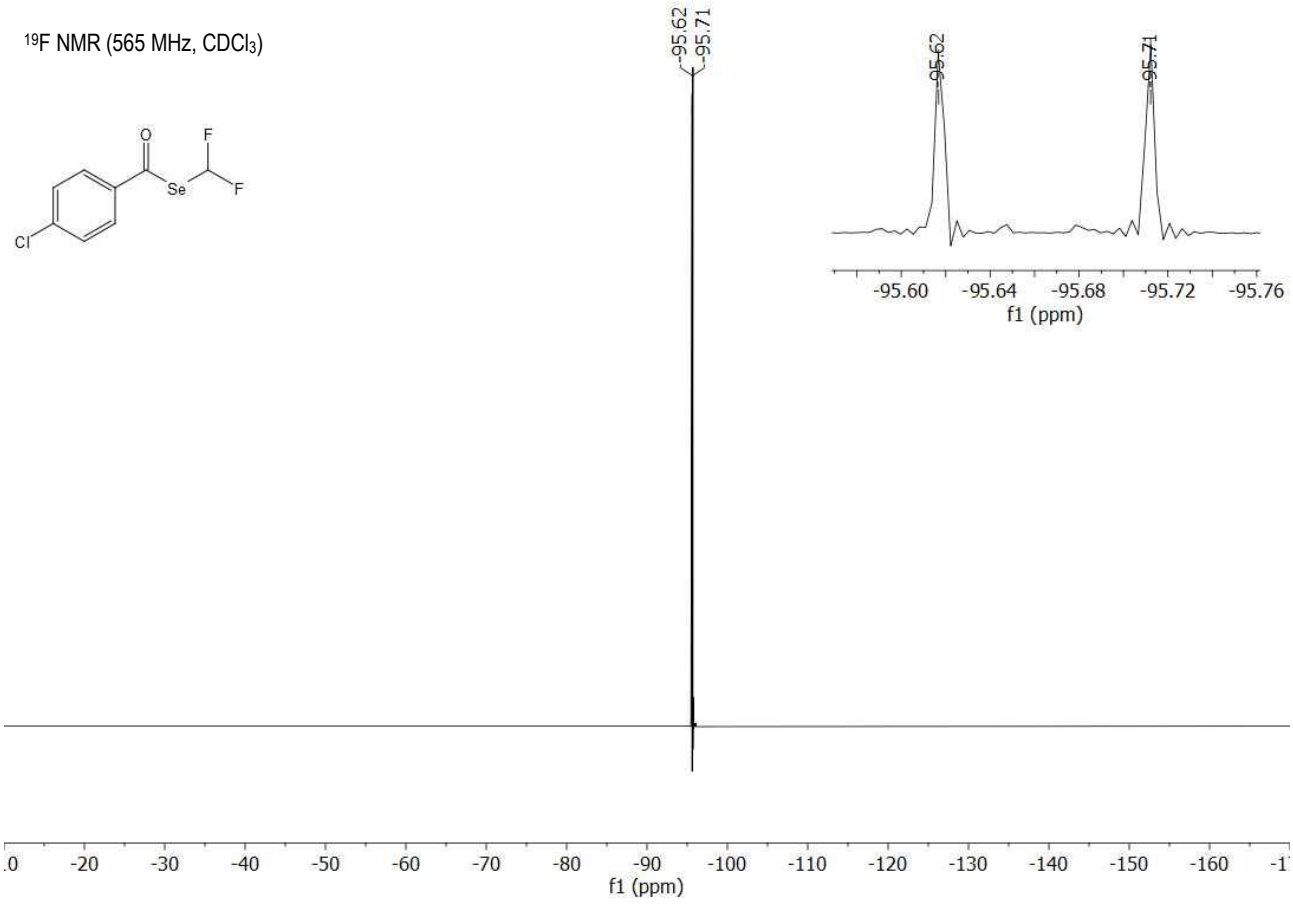


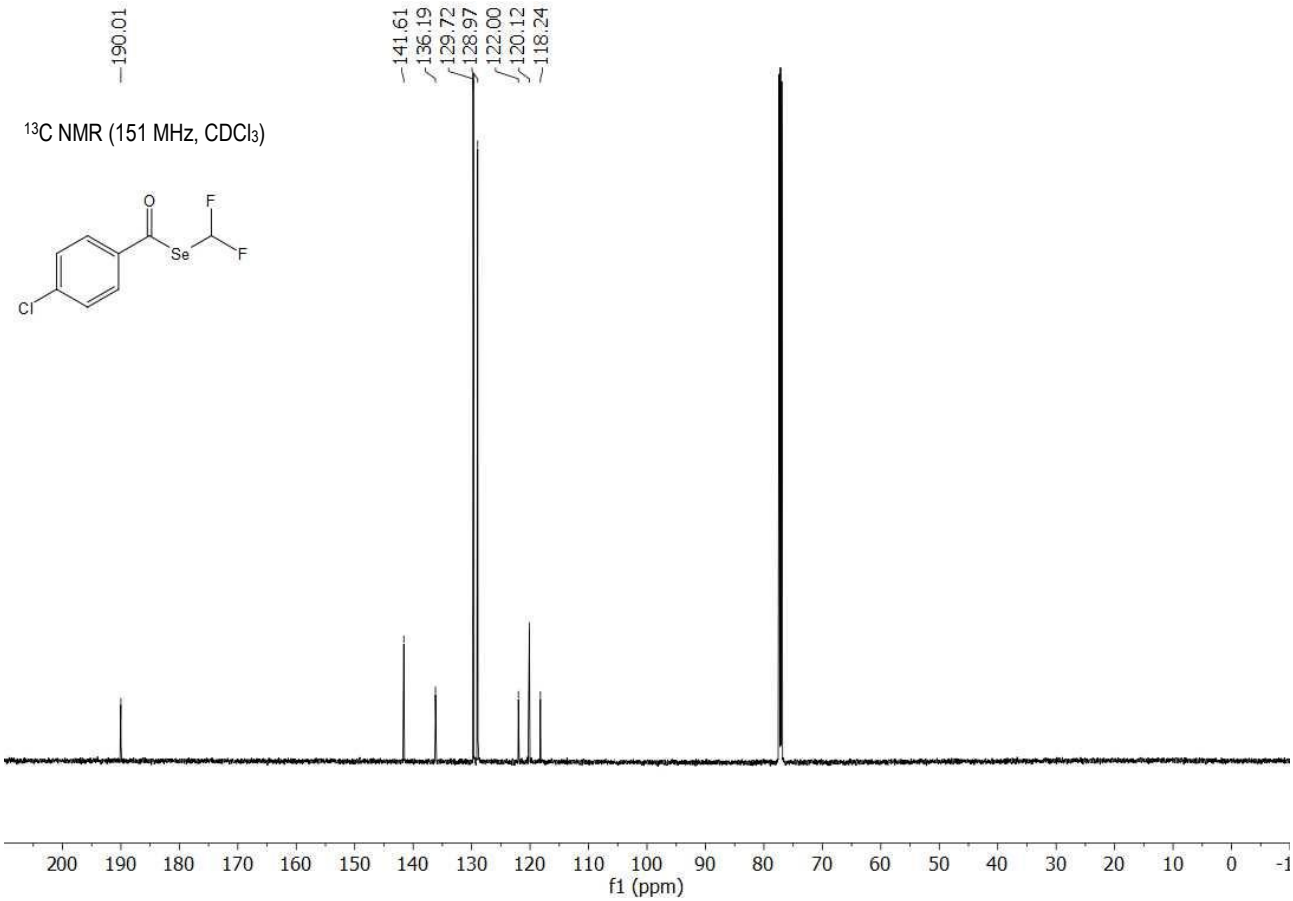
Se-(difluoromethyl) 4-chlorobenzoselenoate **4i**

^{1}H NMR (601 MHz, $CDCl_3$)

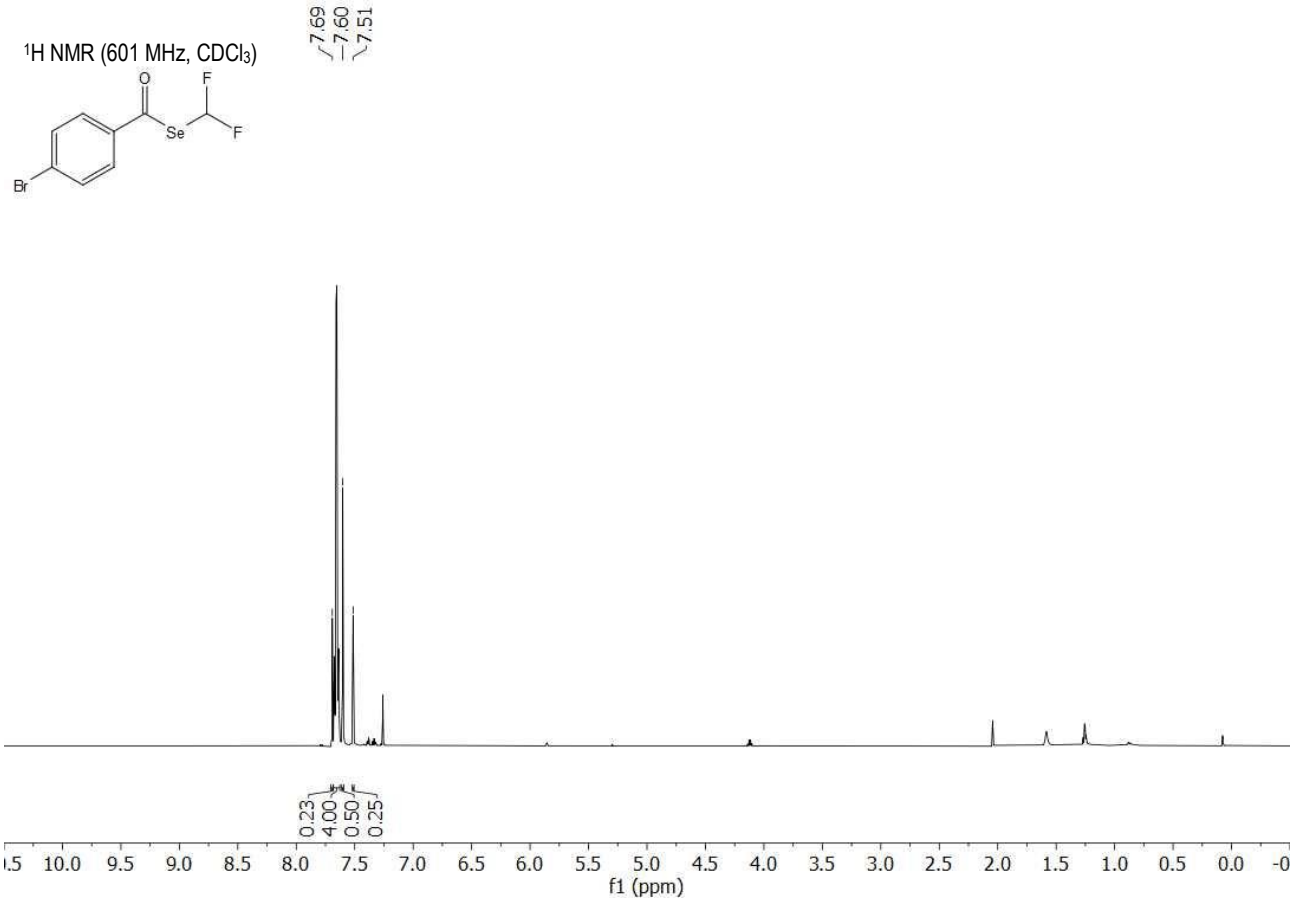


^{19}F NMR (565 MHz, $CDCl_3$)

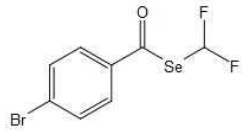




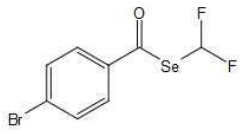
Se-(difluoromethyl) 4-bromobenzoselenoate **4j**



^{19}F NMR (565 MHz, $CDCl_3$)

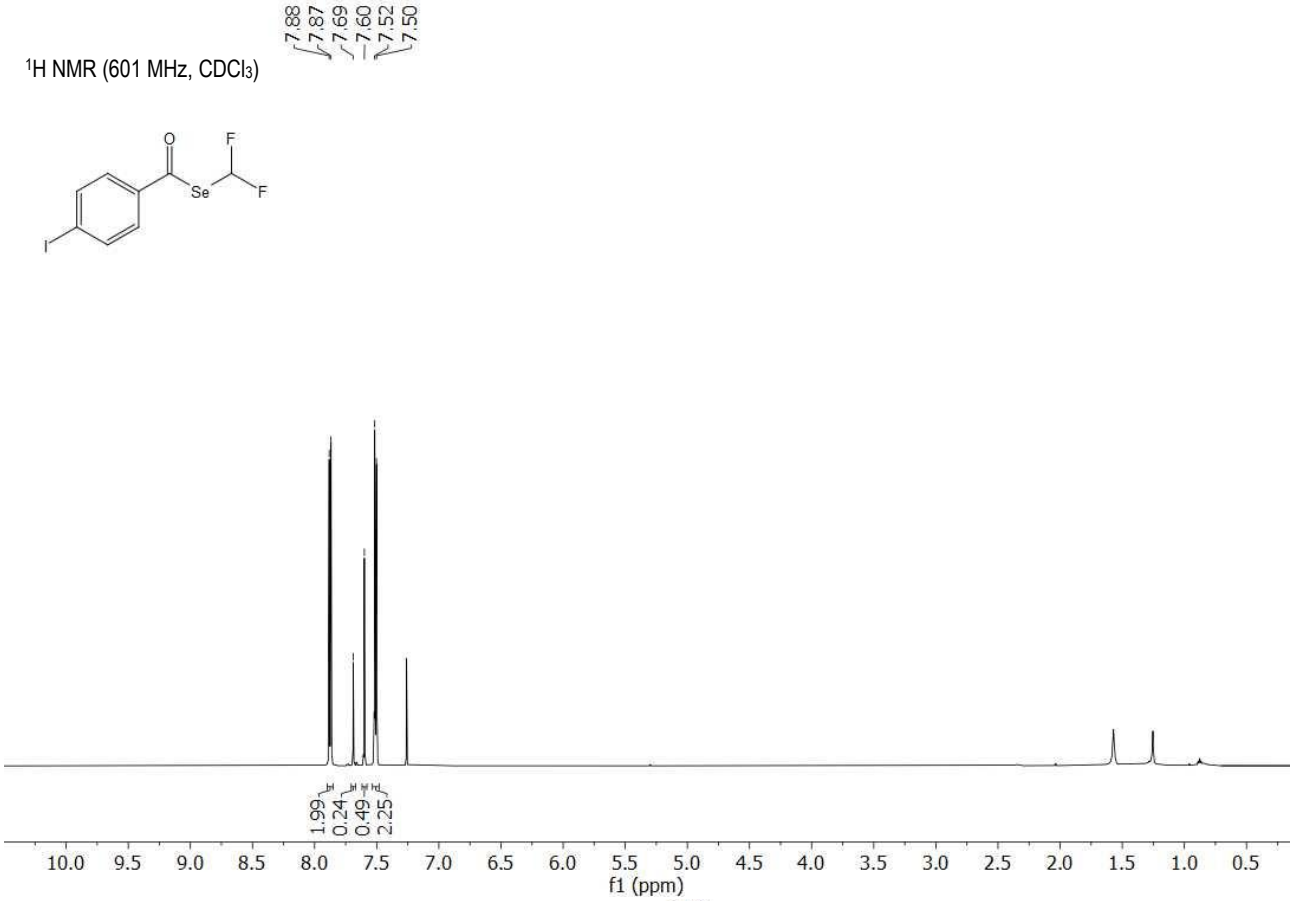


^{13}C NMR (151 MHz, $CDCl_3$)

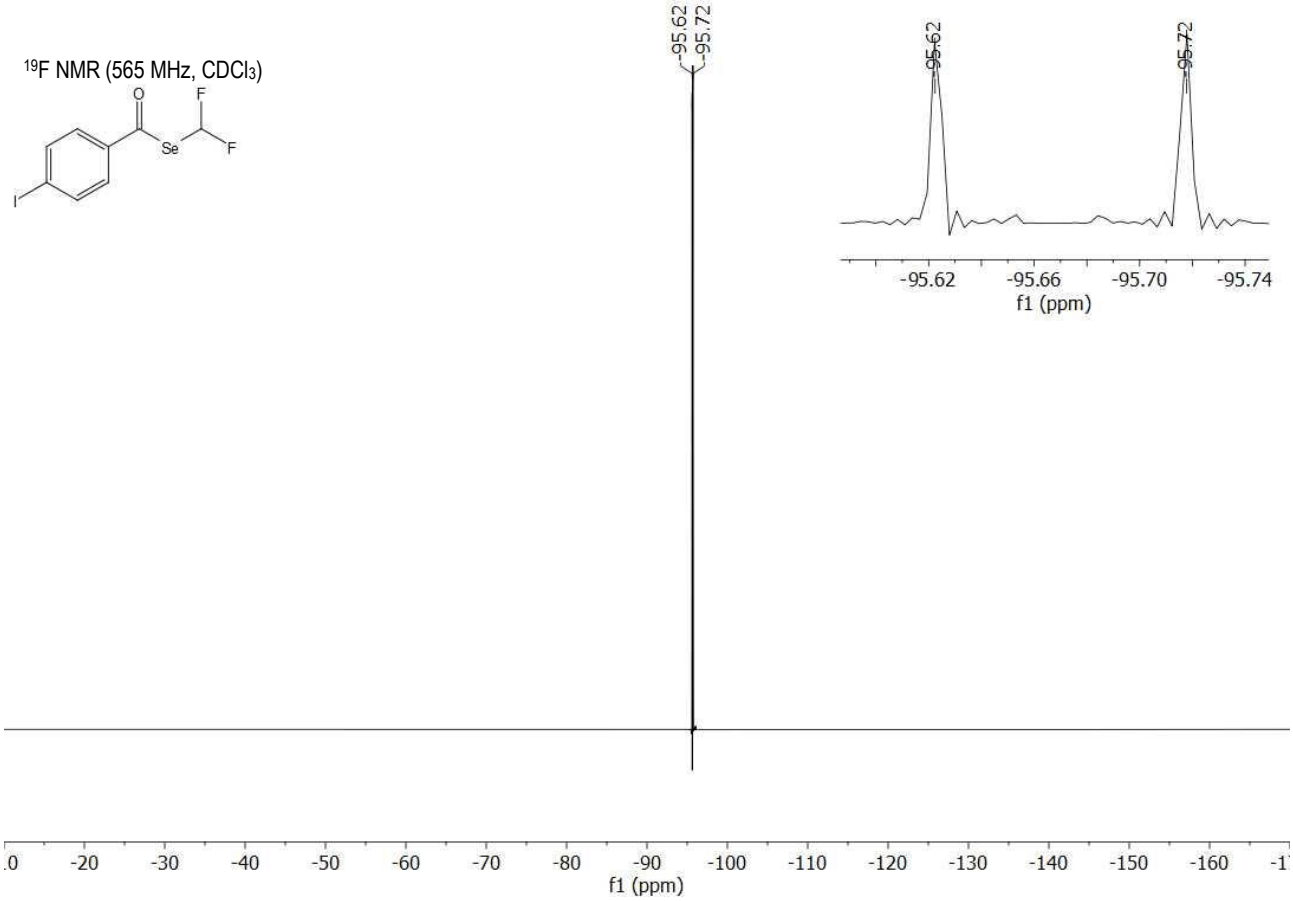


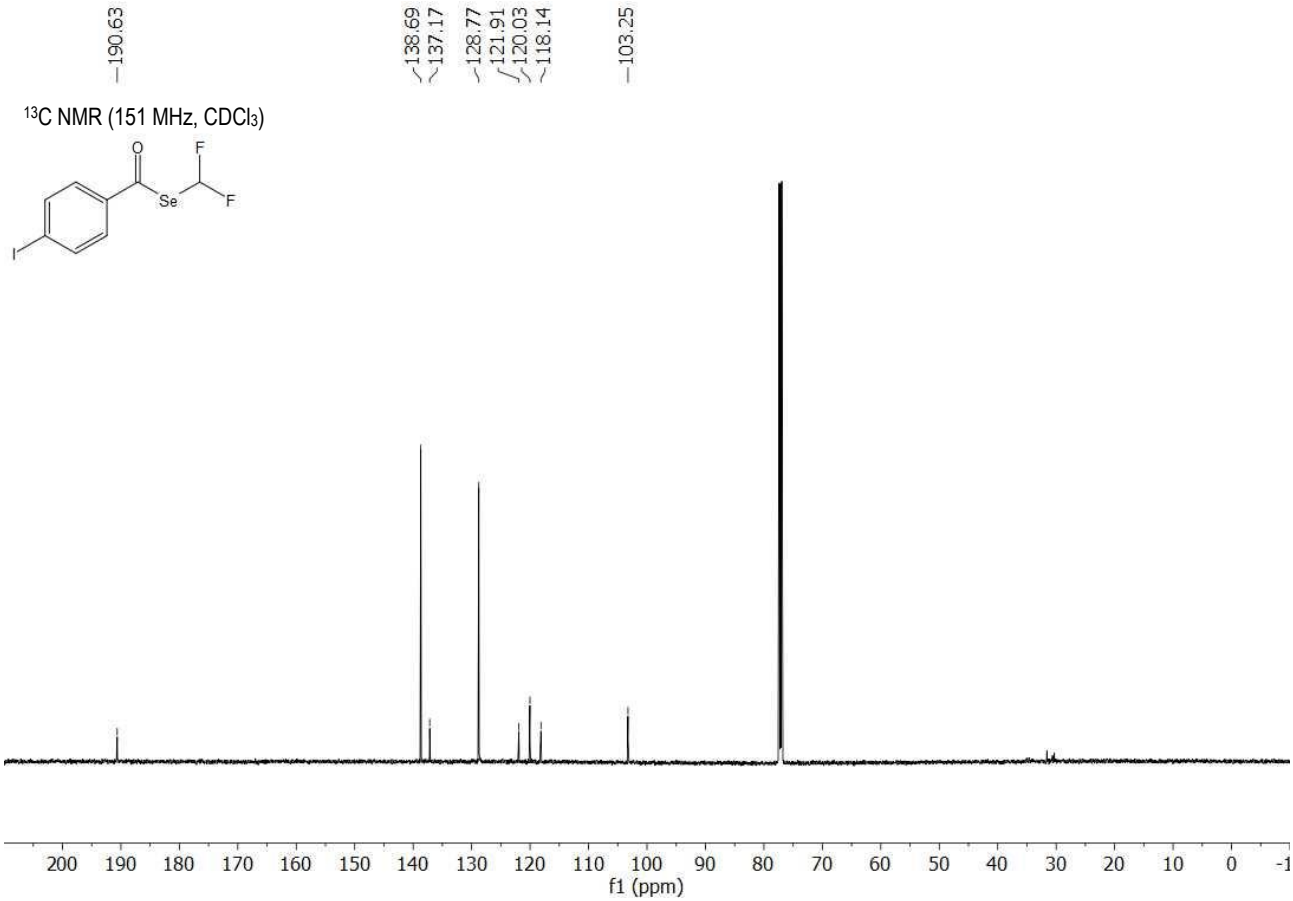
Se-(difluoromethyl) 4-iodobenzoselenoate **4k**

^{1}H NMR (601 MHz, $CDCl_3$)



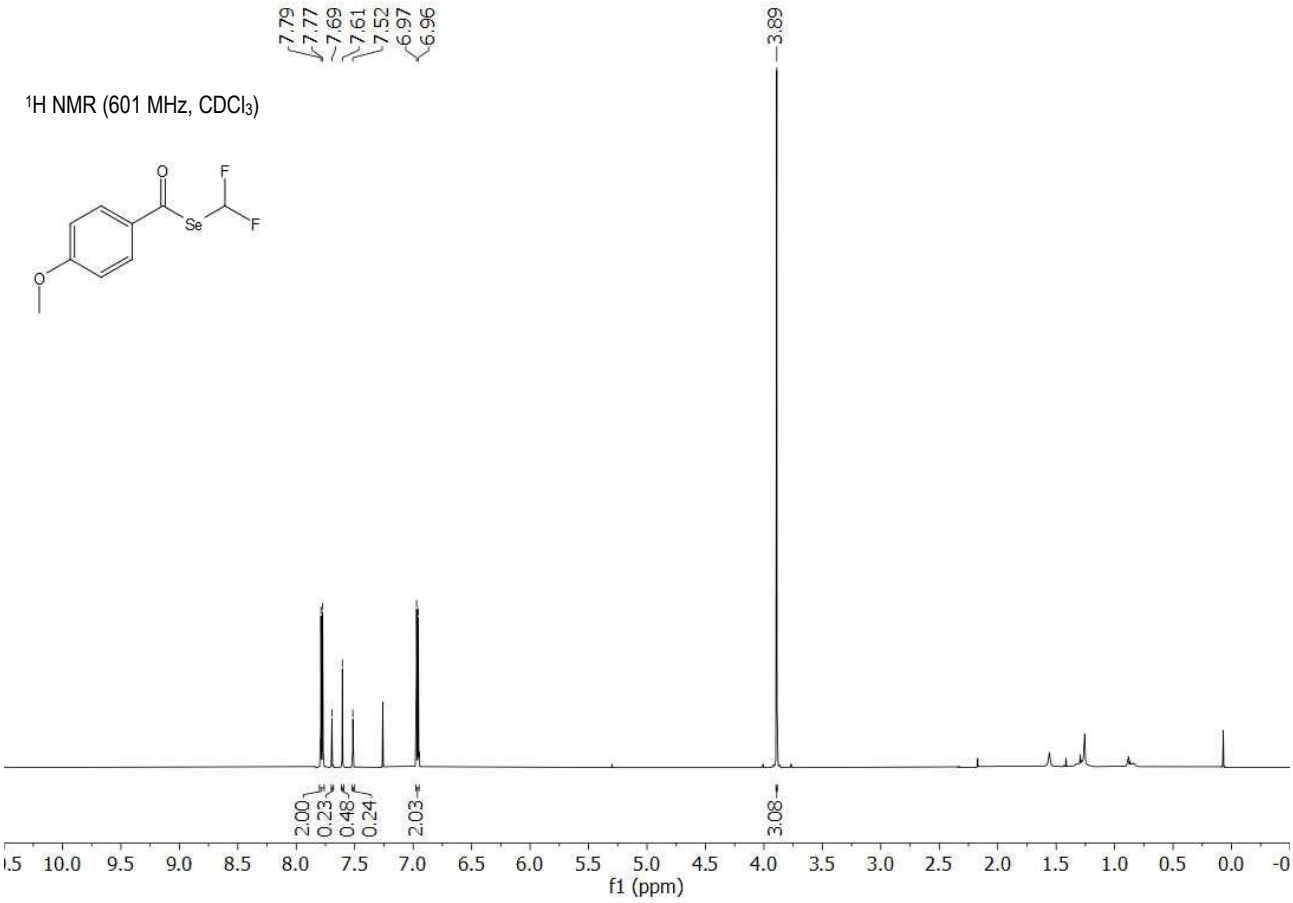
^{19}F NMR (565 MHz, $CDCl_3$)





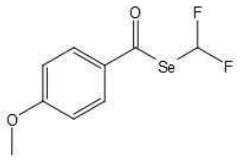
^{13}C NMR (151 MHz, $CDCl_3$)

Se-(difluoromethyl) 4-methoxybenzoselenoate **4l**

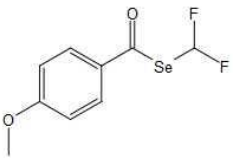


^{1}H NMR (601 MHz, $CDCl_3$)

^{19}F NMR (565 MHz, $CDCl_3$)

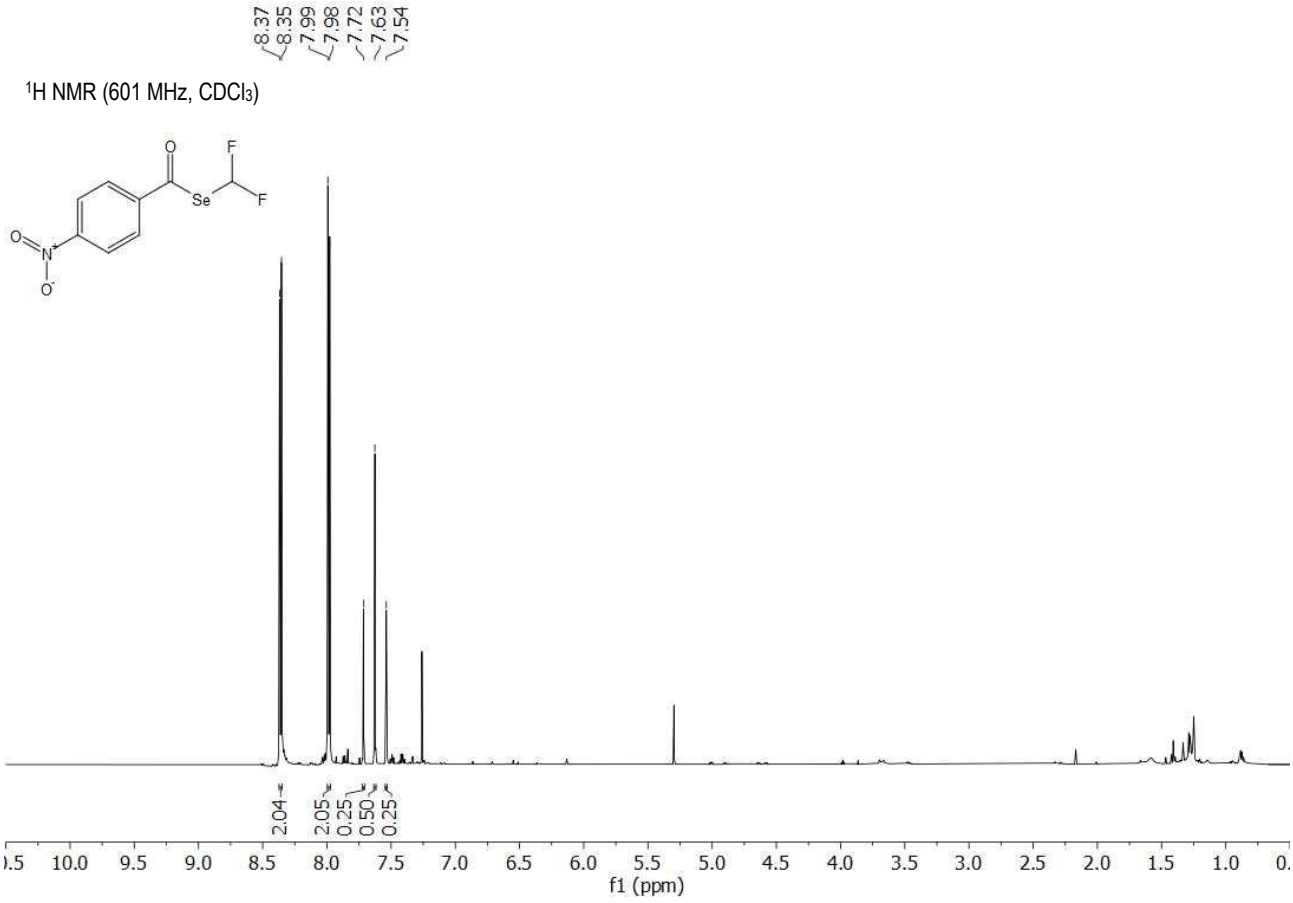


^{13}C NMR (151 MHz, $CDCl_3$)

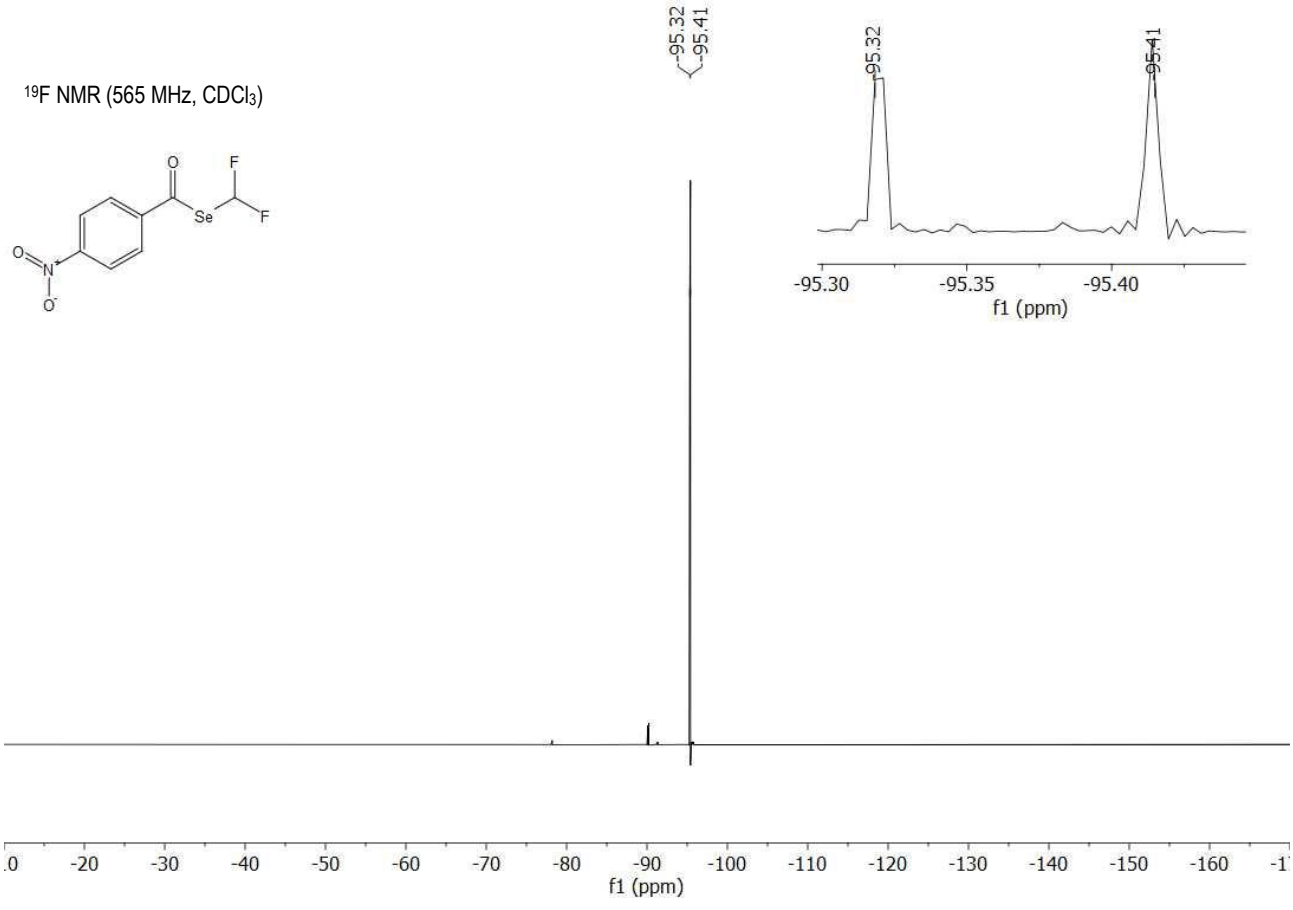


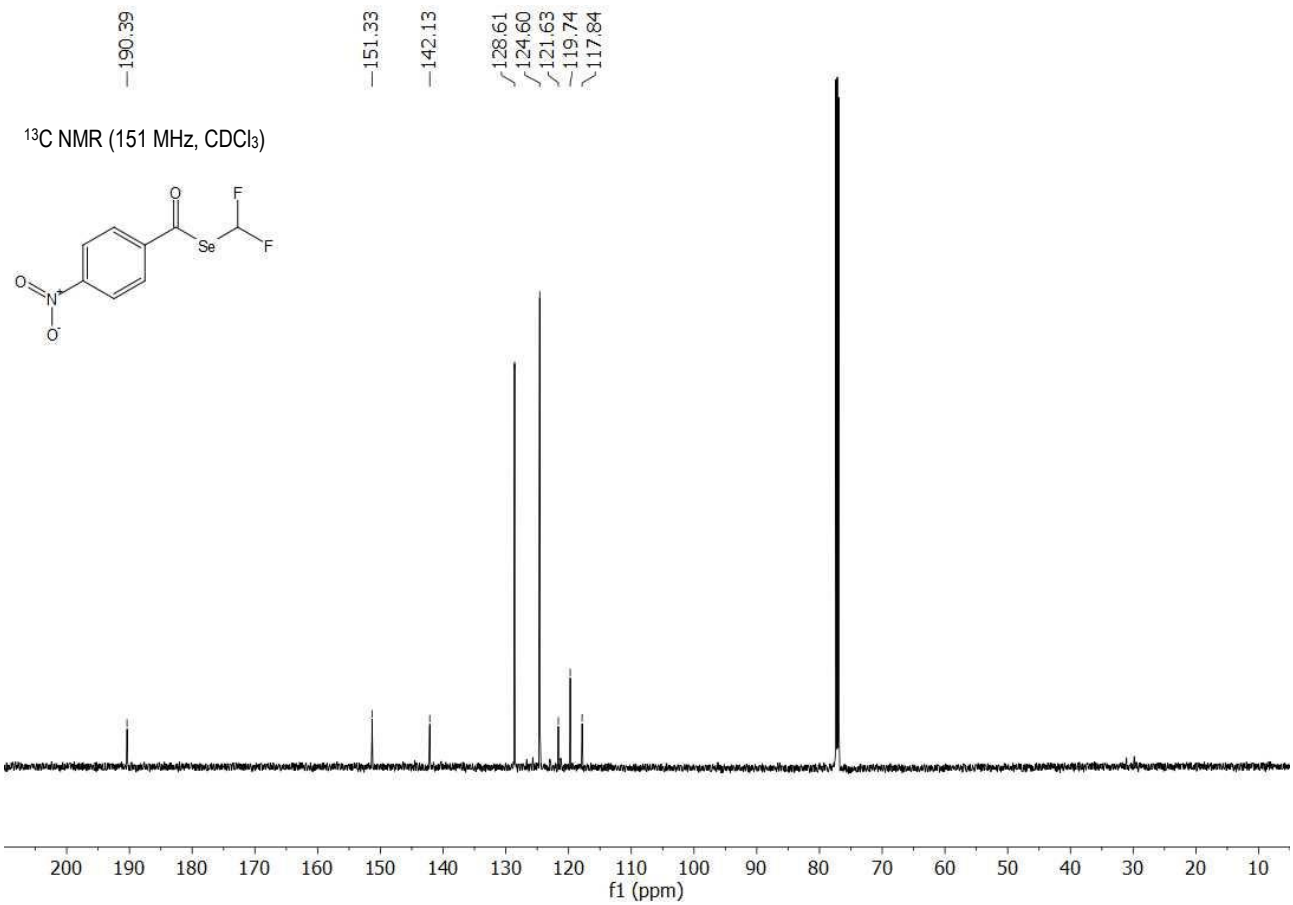
Se-(difluoromethyl) 4-nitrobenzoselenoate **4m**

^{1}H NMR (601 MHz, $CDCl_3$)

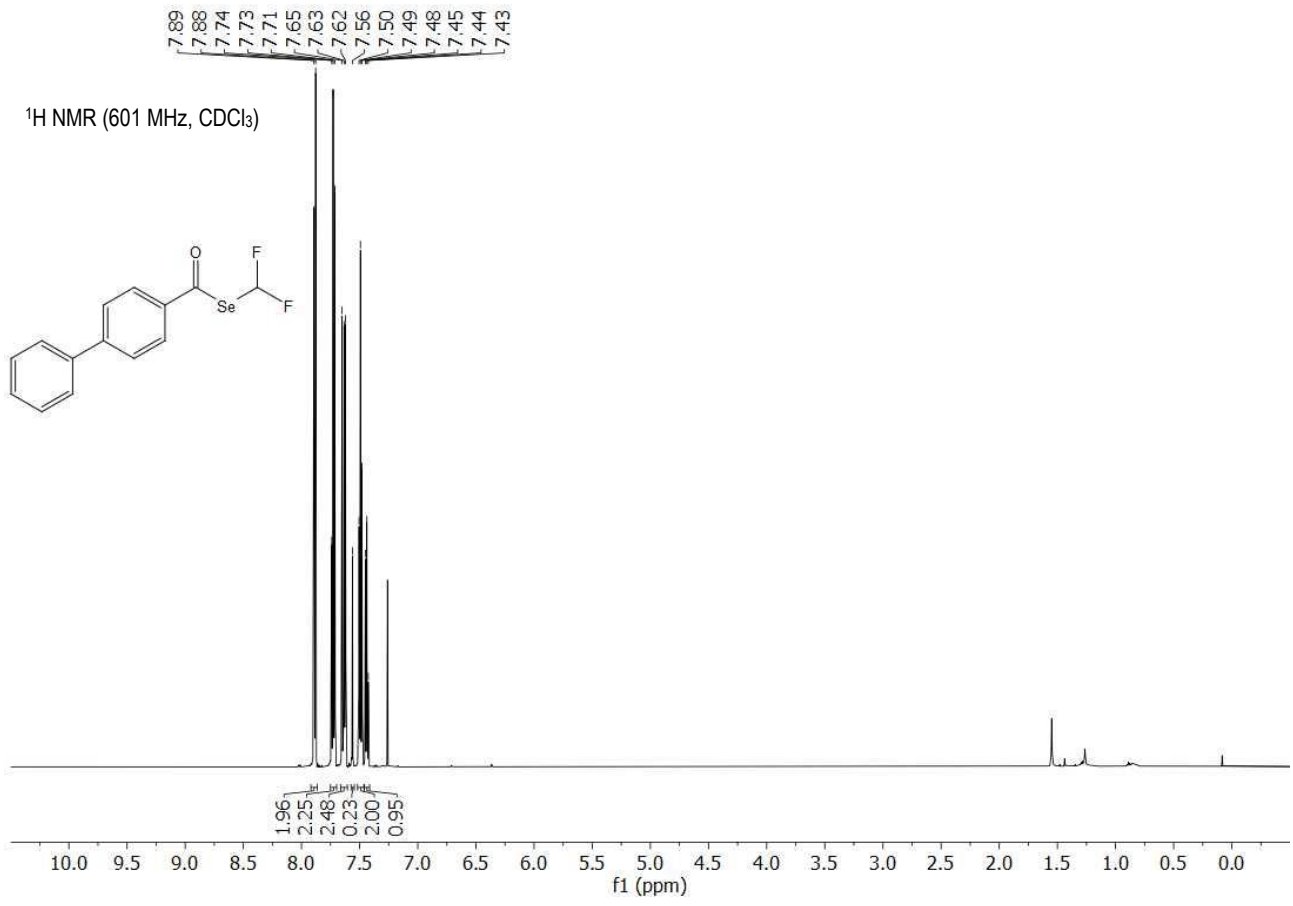


^{19}F NMR (565 MHz, $CDCl_3$)

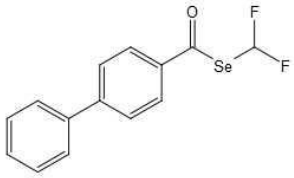




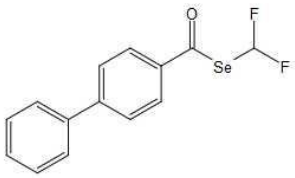
Se-(difluoromethyl) [1,1'-biphenyl]-4-carboselenoate **4n**



^{19}F NMR (565 MHz, $CDCl_3$)

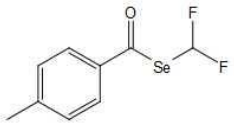


^{13}C NMR (151 MHz, $CDCl_3$)

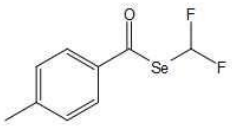


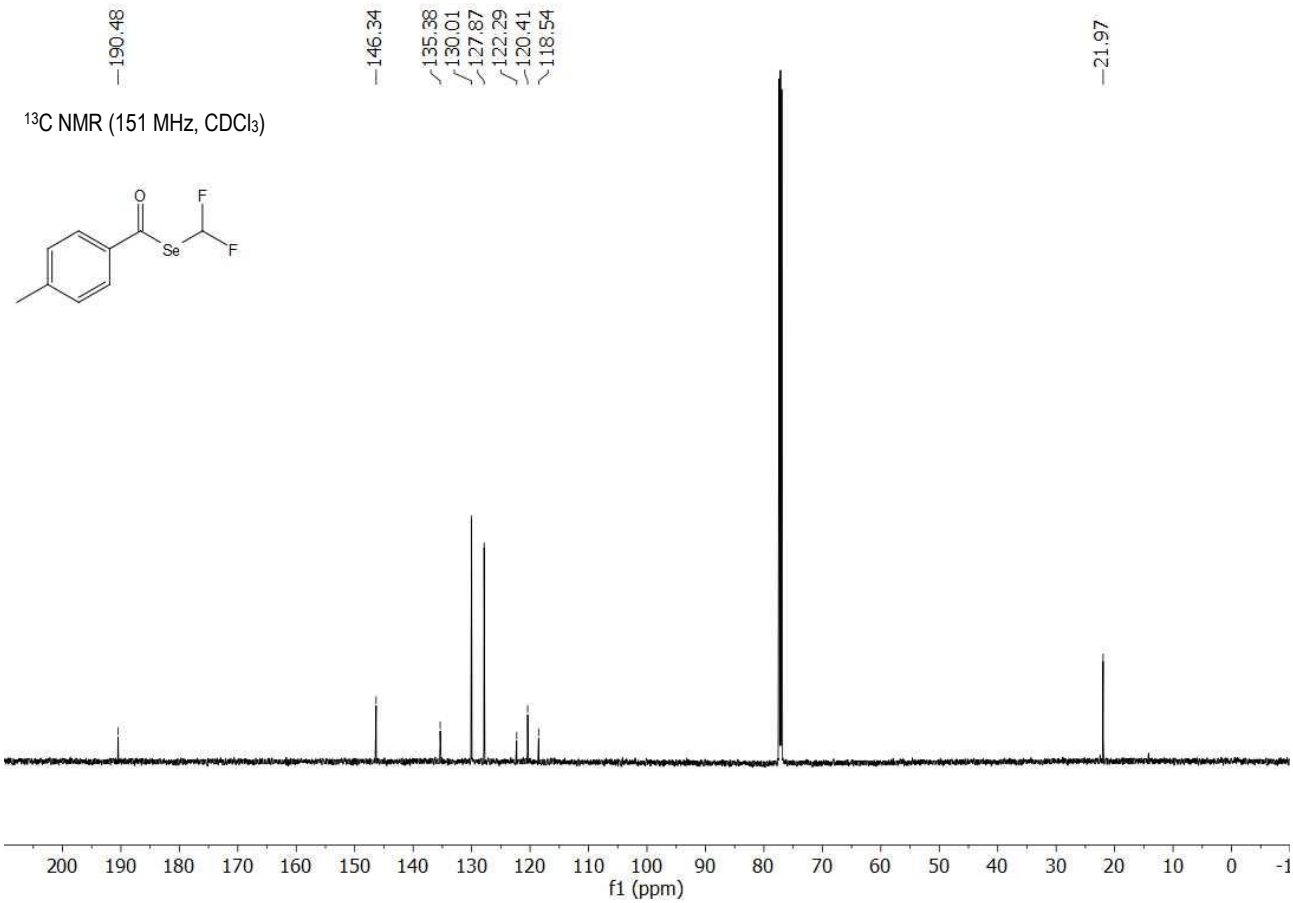
Se-(difluoromethyl) 4-methylbenzoselenoate **4o**

^{1}H NMR (601 MHz, $CDCl_3$)

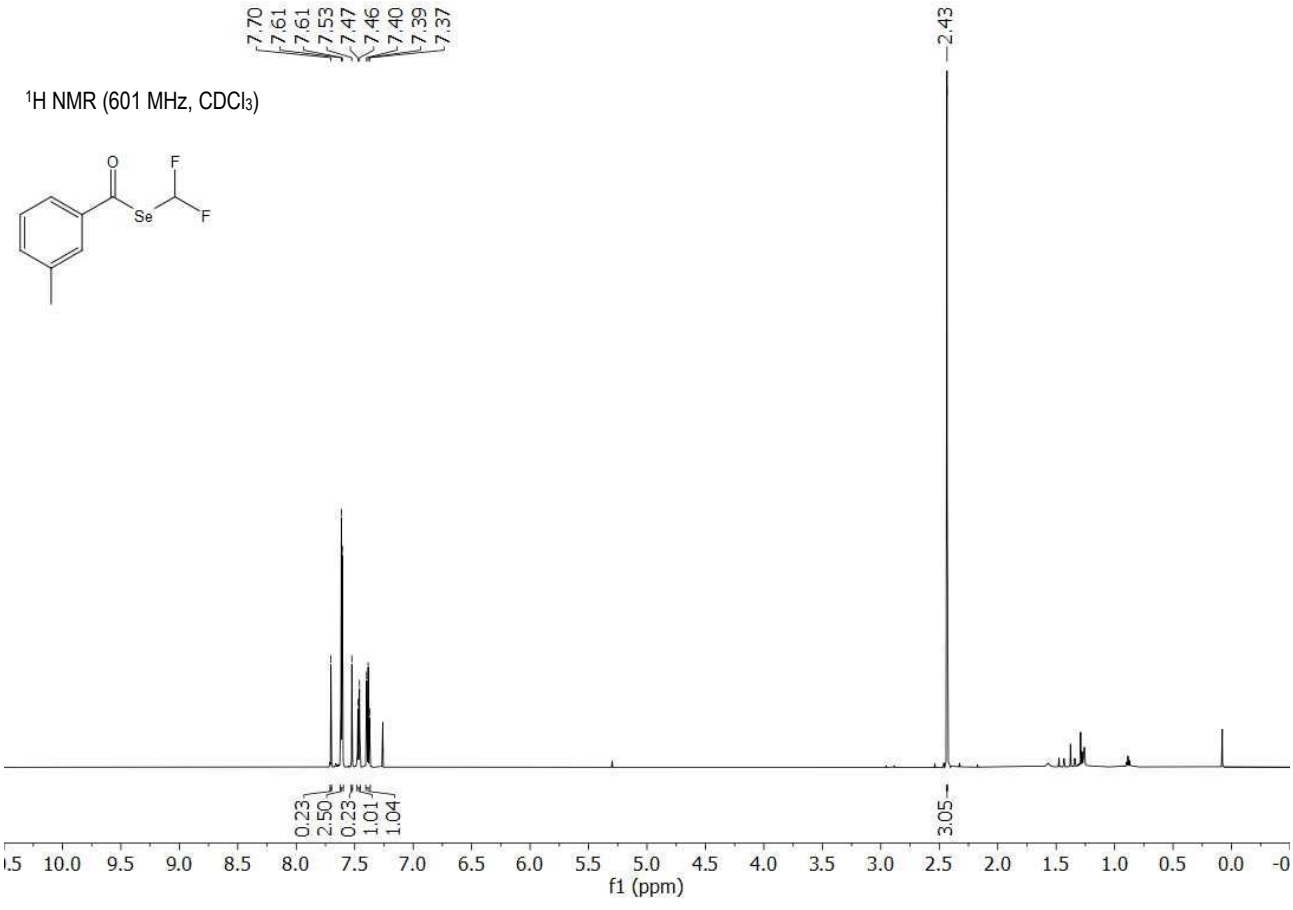


^{19}F NMR (565 MHz, $CDCl_3$)

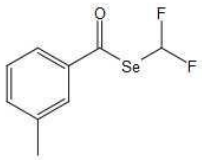




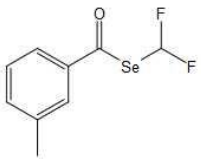
Se-(difluoromethyl) 3-methylbenzoselenoate **4p**



^{19}F NMR (565 MHz, $CDCl_3$)

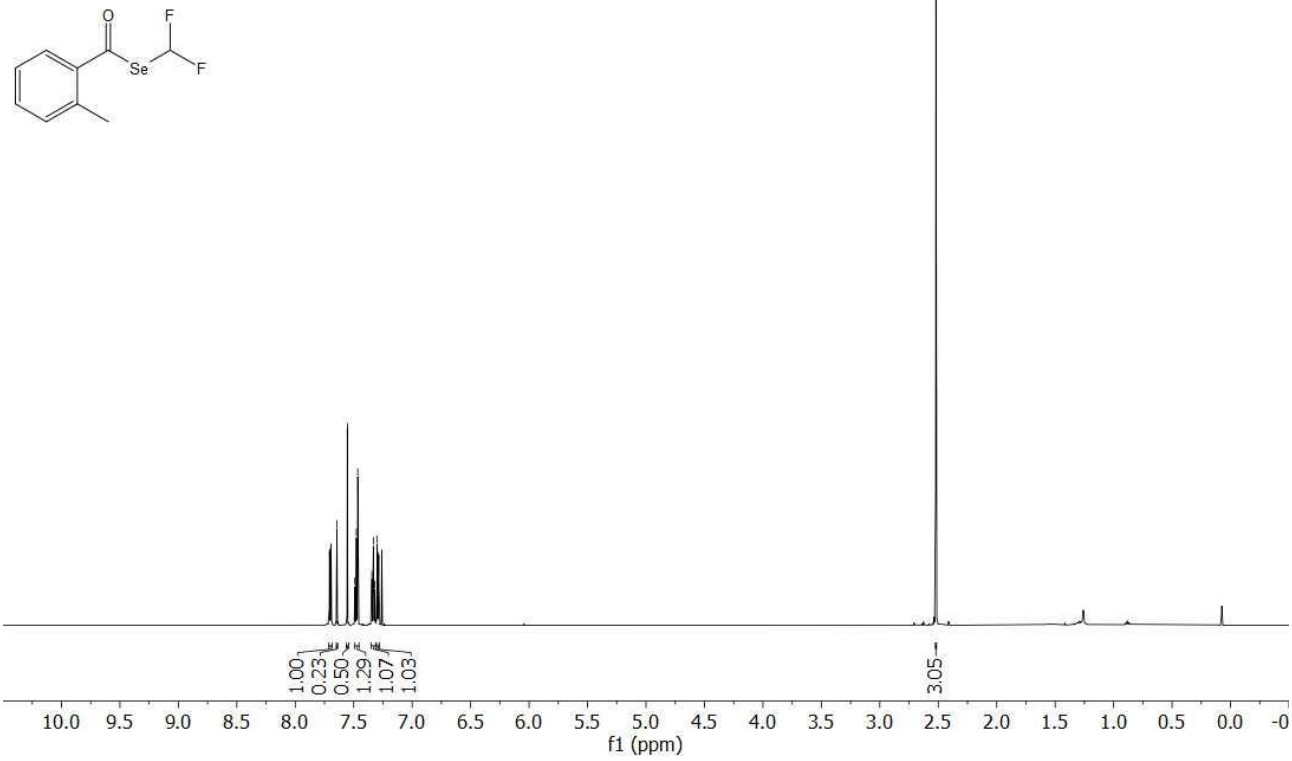


^{13}C NMR (151 MHz, $CDCl_3$)

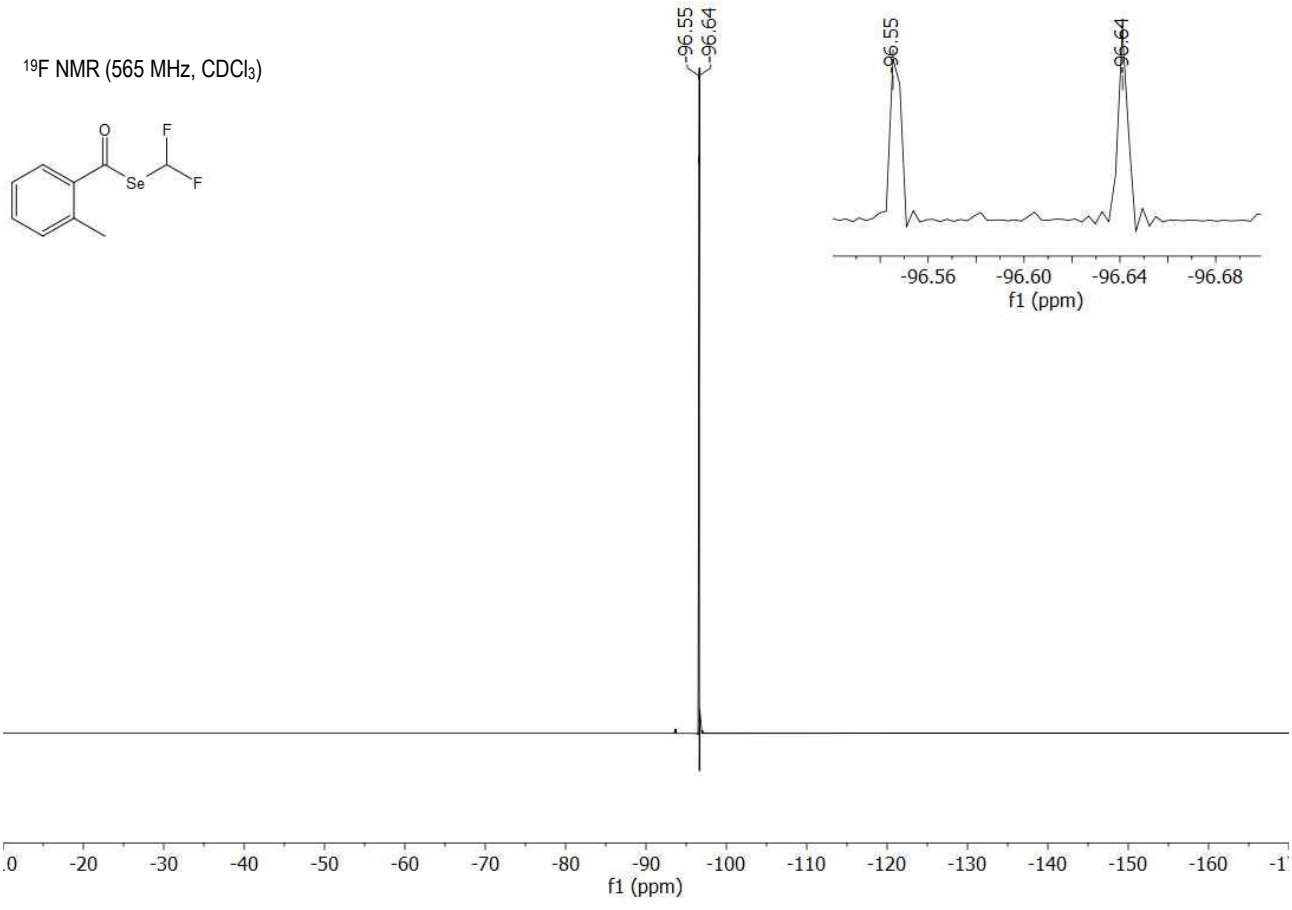


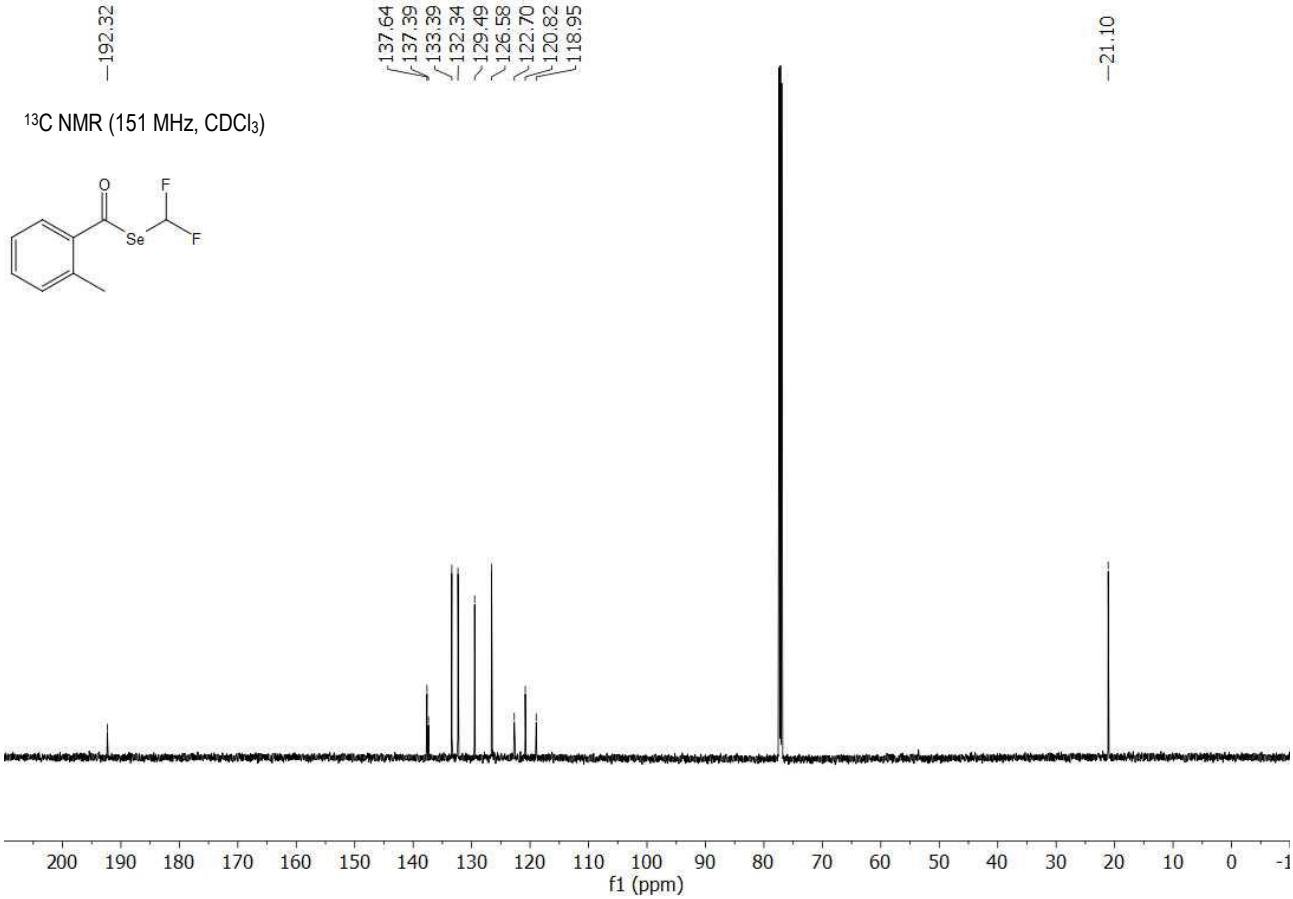
Se-(difluoromethyl) 2-methylbenzoselenoate **4q**

^{1}H NMR (601 MHz, $CDCl_3$)

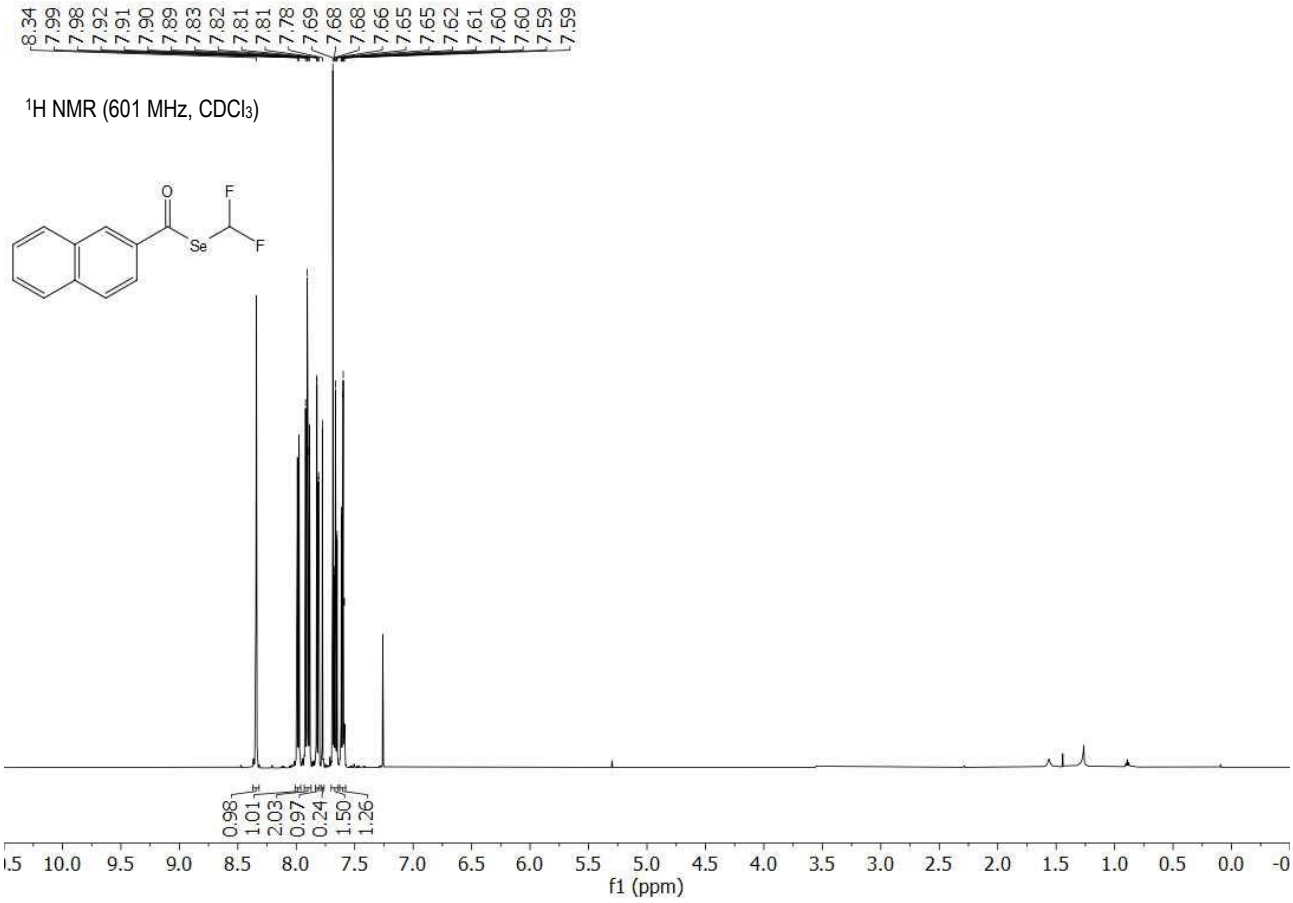


^{19}F NMR (565 MHz, $CDCl_3$)

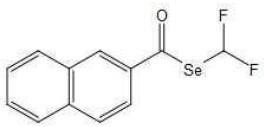




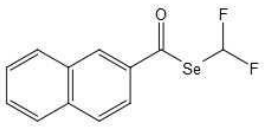
Se-(difluoromethyl) naphthalene-2-carboselenoate **4r**



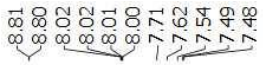
^{19}F NMR (565 MHz, $CDCl_3$)



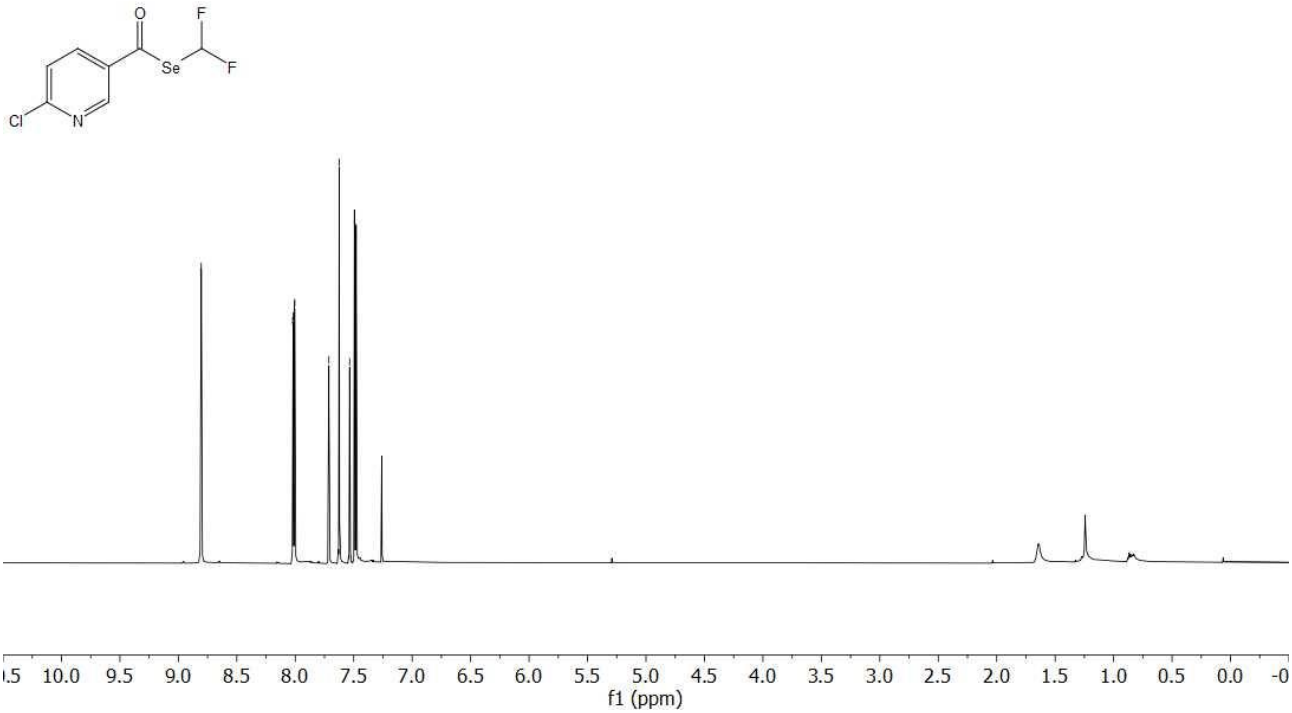
^{13}C NMR (151 MHz, $CDCl_3$)



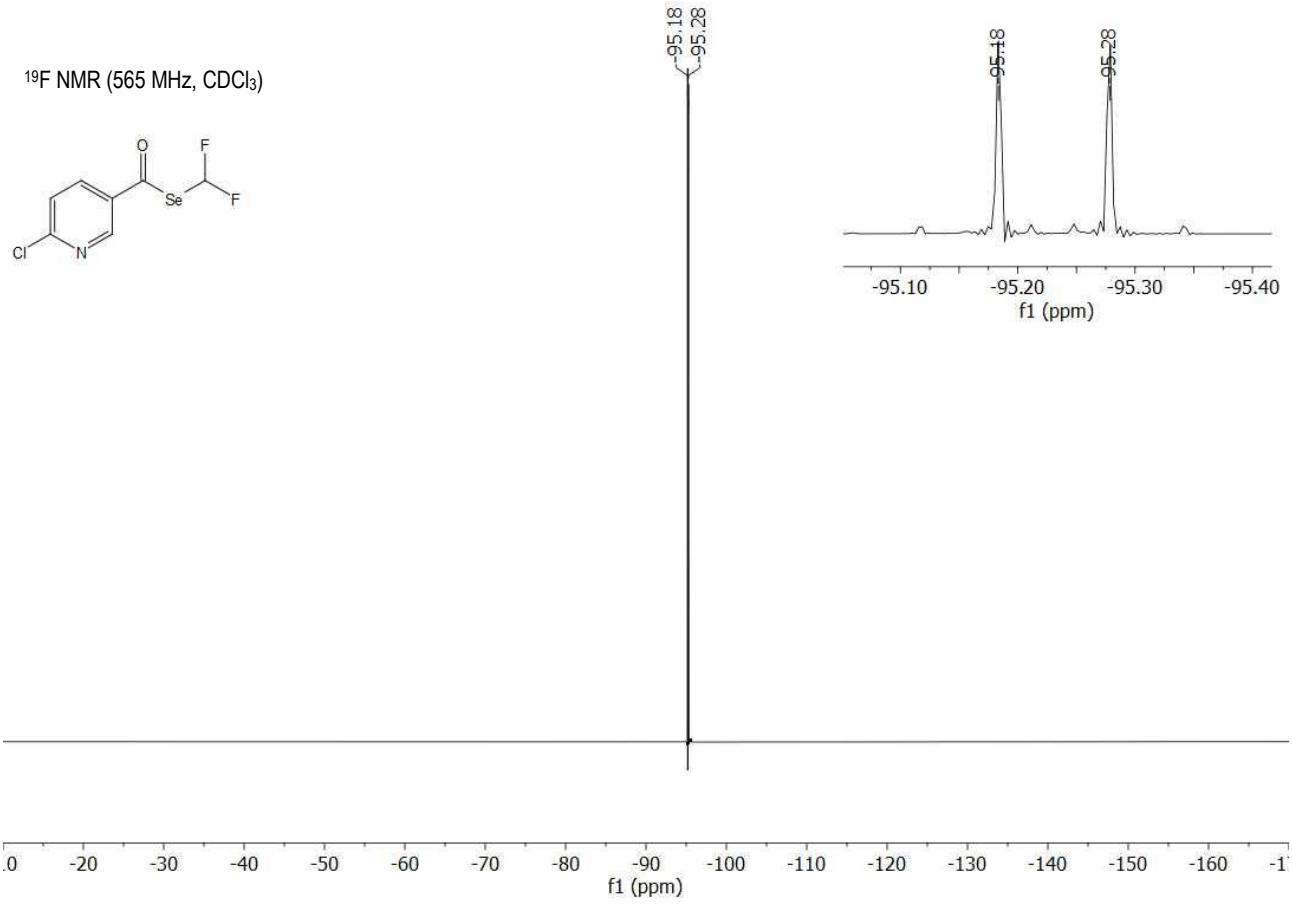
Se-(difluoromethyl) 6-chloropyridine-3-carboselenoate **4s**

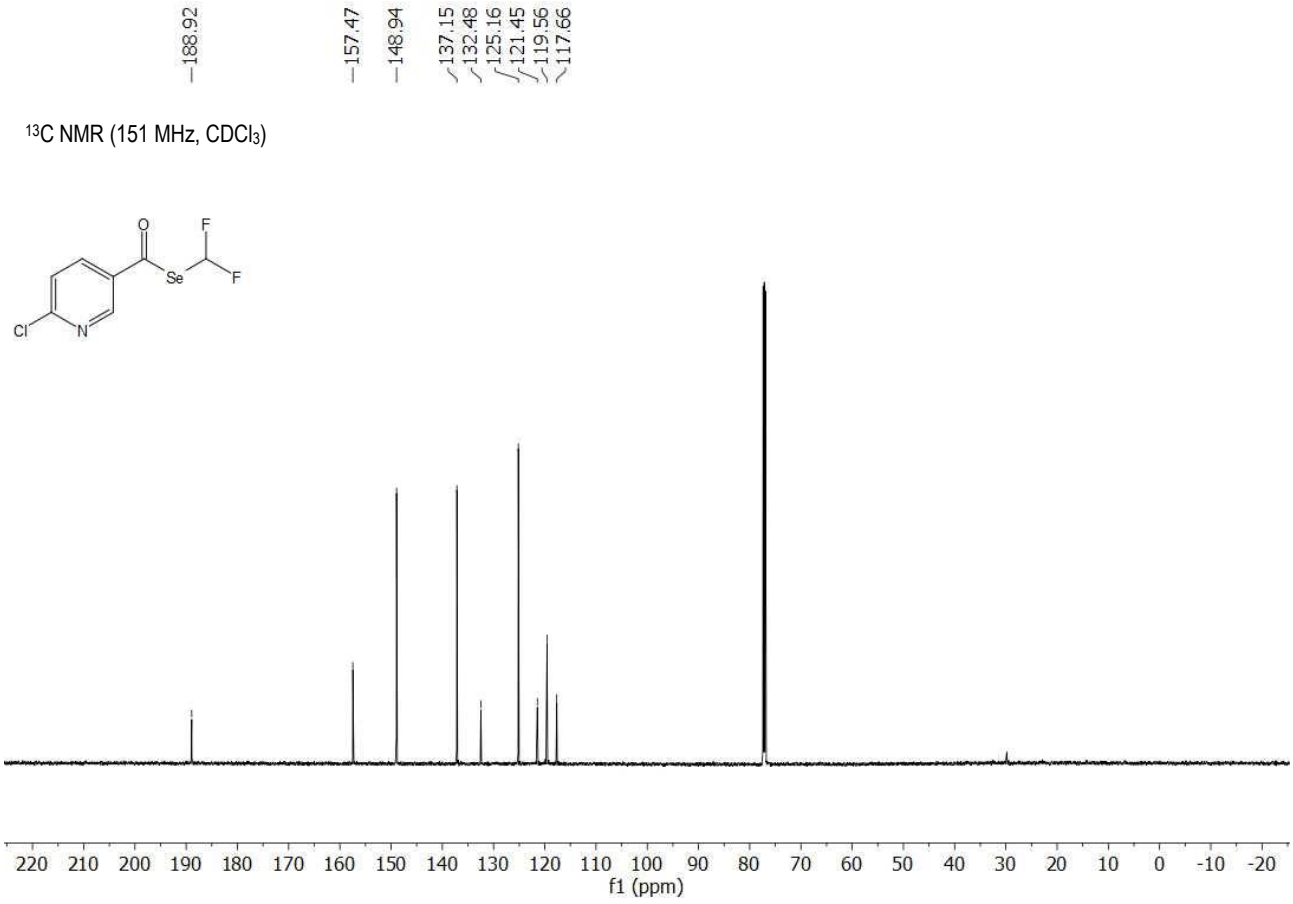


^{1}H NMR (601 MHz, $CDCl_3$)



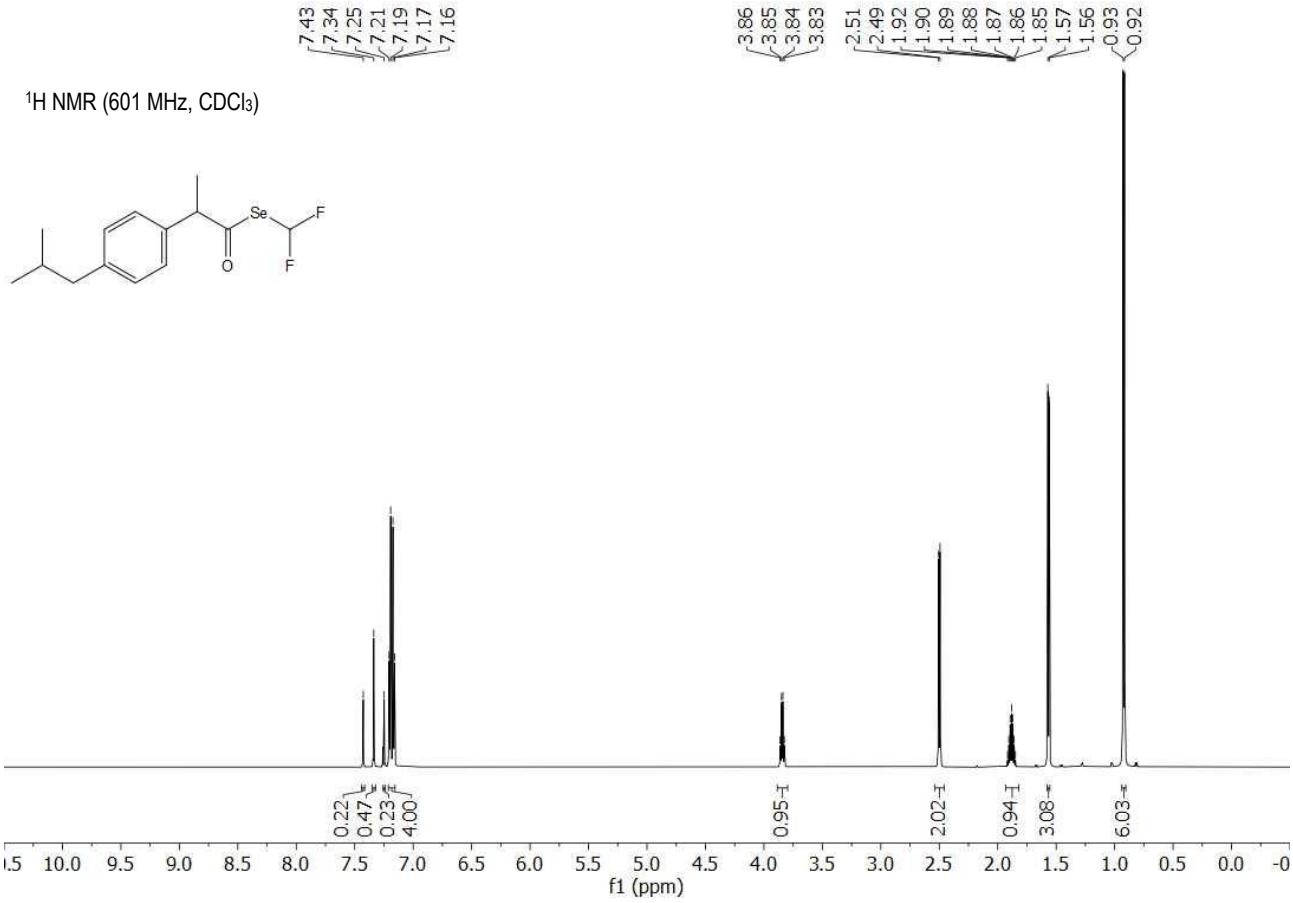
^{19}F NMR (565 MHz, $CDCl_3$)





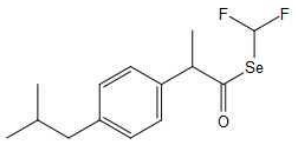
^{13}C NMR (151 MHz, $CDCl_3$)

Se-(difluoromethyl) 2-(6-methoxynaphthalen-2-yl)propaneselenoate **4t**

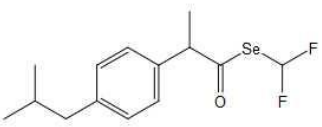


^{1}H NMR (601 MHz, $CDCl_3$)

^{19}F NMR (565 MHz, $CDCl_3$)

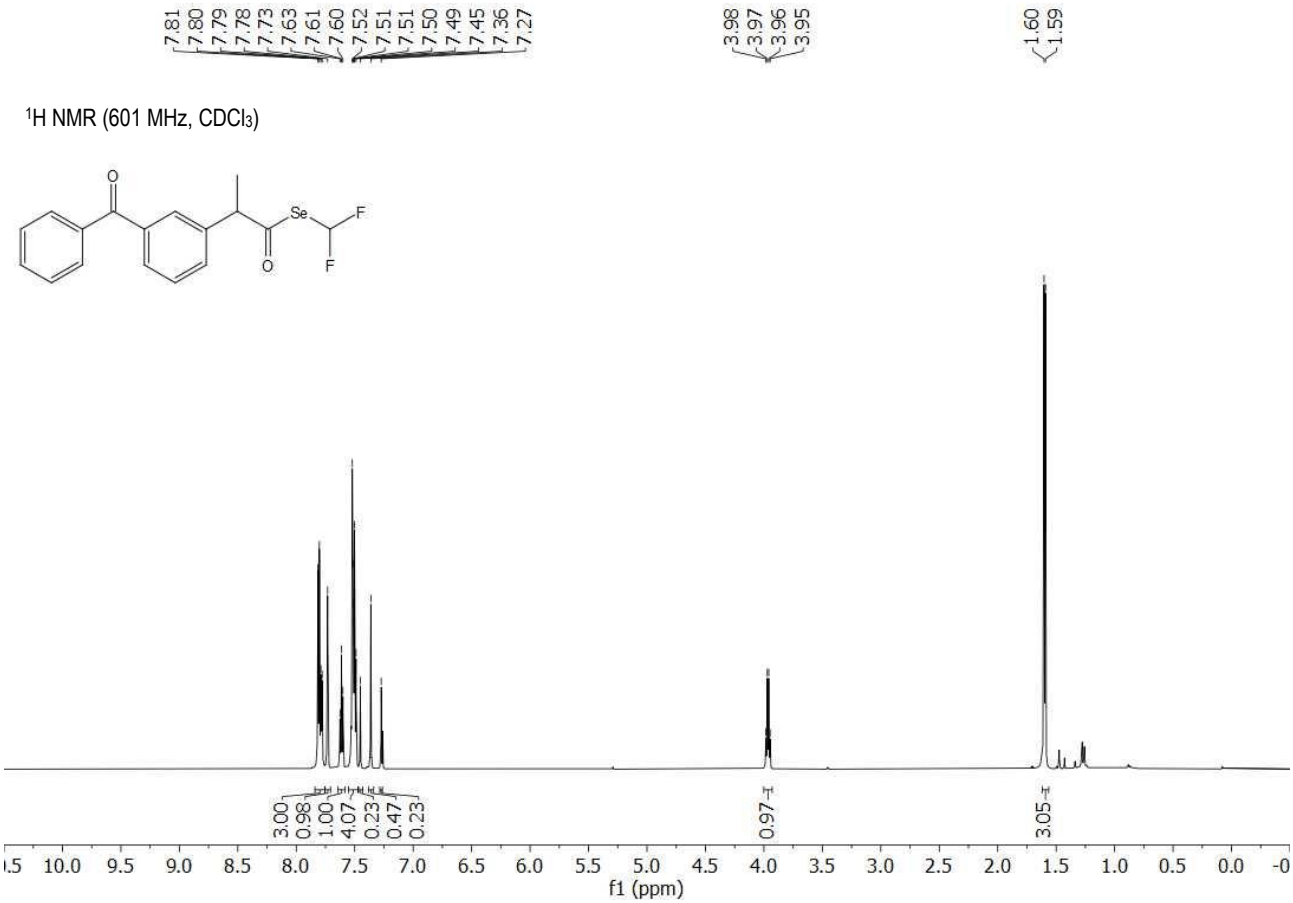


^{13}C NMR (151 MHz, $CDCl_3$)

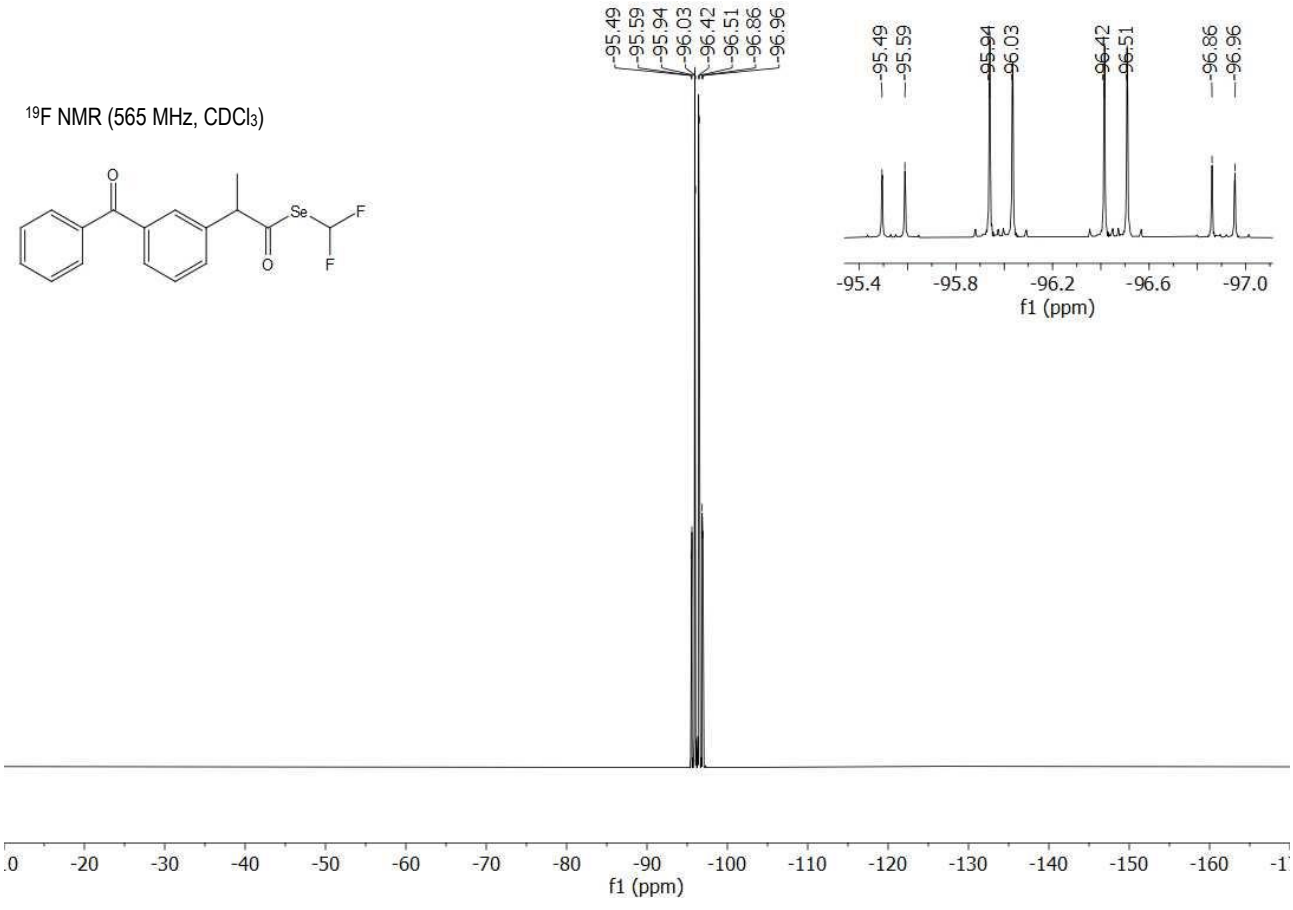


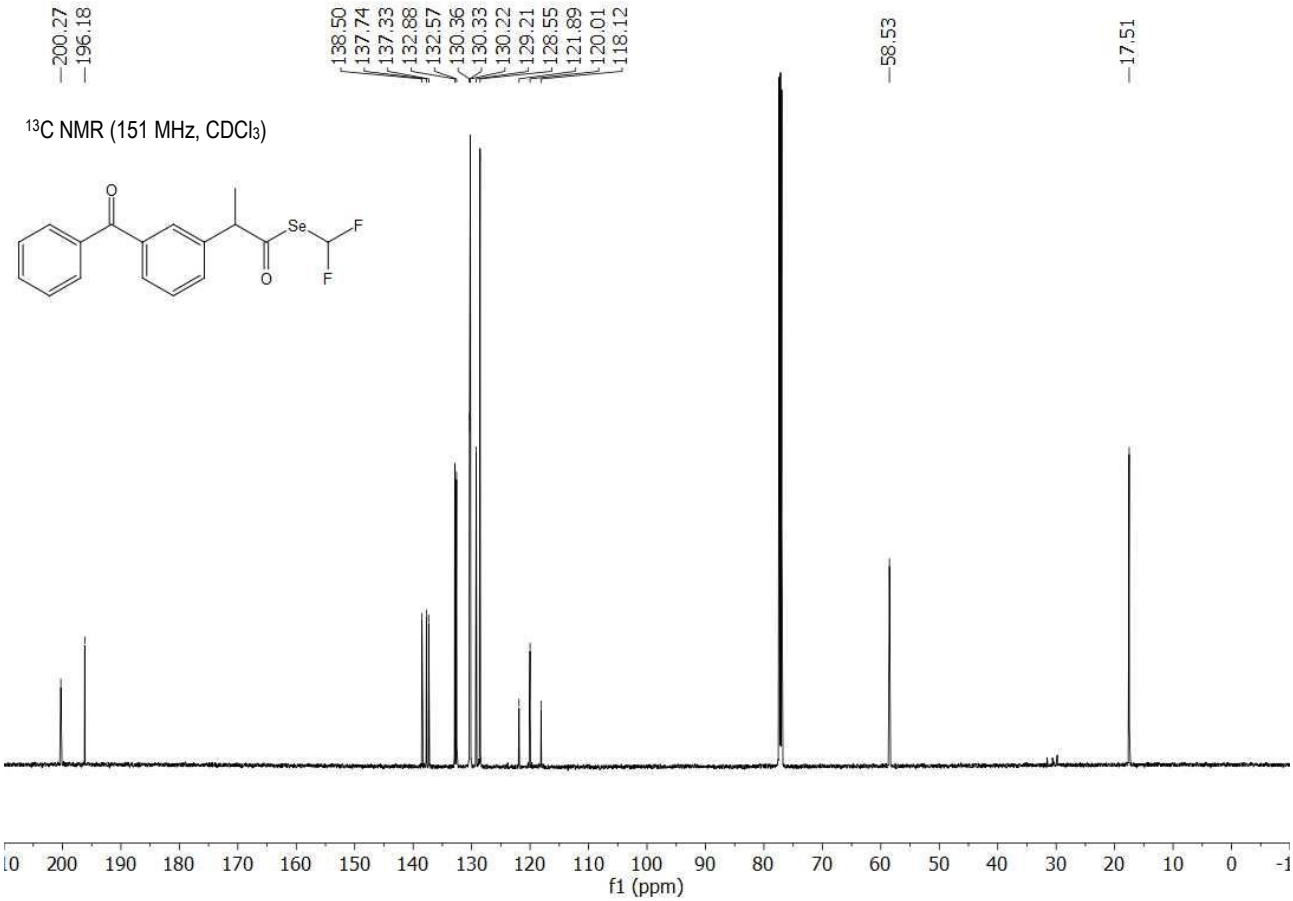
Se-(difluoromethyl) 2-(3-benzoylphenyl)propaneselenoate **4u**

^{1}H NMR (601 MHz, $CDCl_3$)

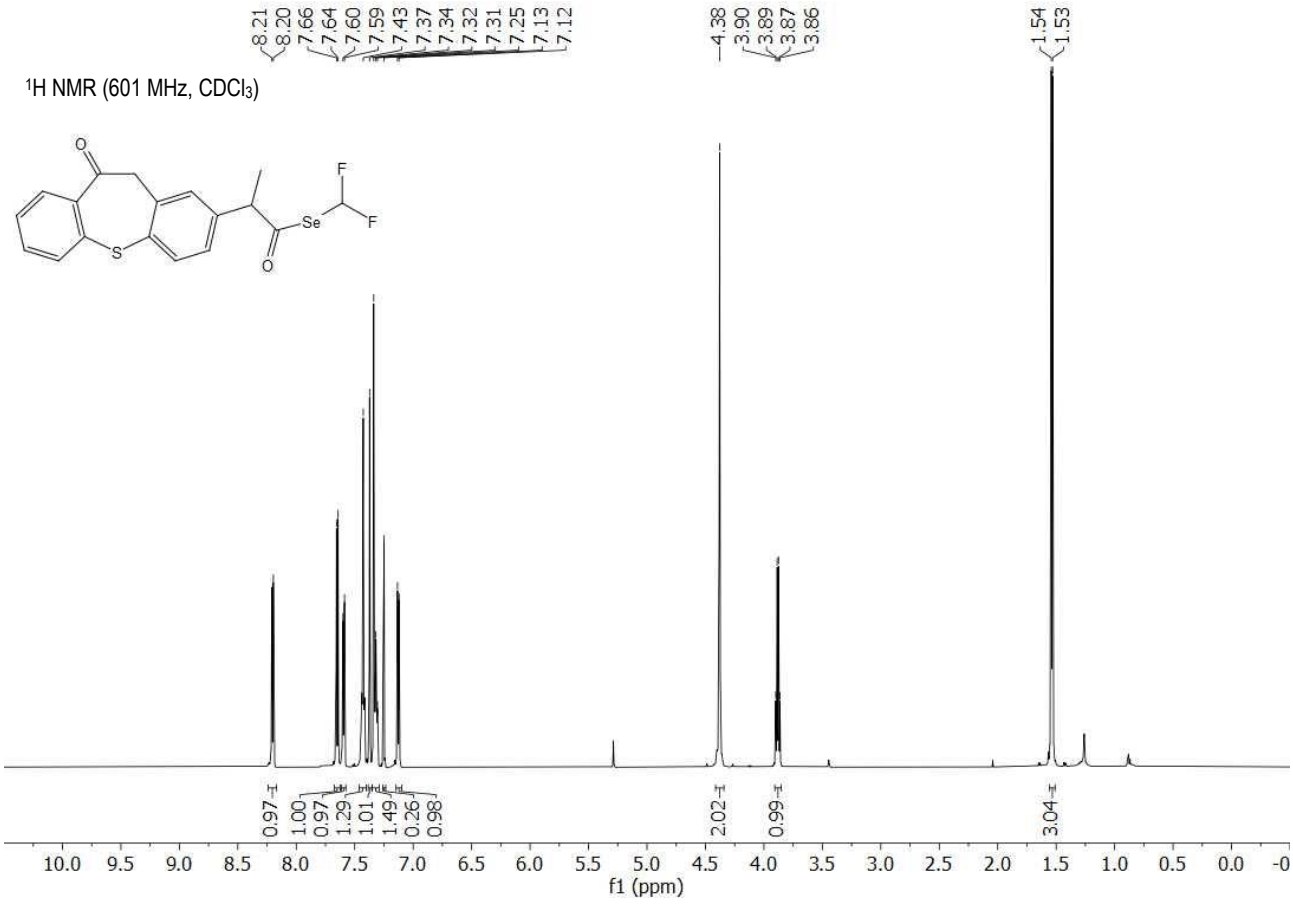


^{19}F NMR (565 MHz, $CDCl_3$)

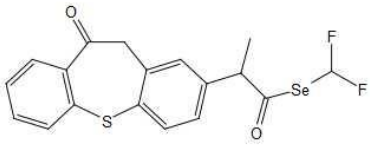




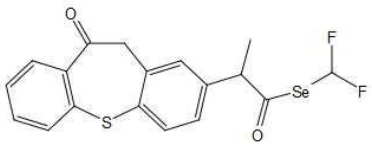
Se-(difluoromethyl) 2-(10-oxo-10,11-dihydrodibenzo[*b*,*f*]thiepin-2-yl)propaneselenoate **4v**



^{19}F NMR (565 MHz, $CDCl_3$)

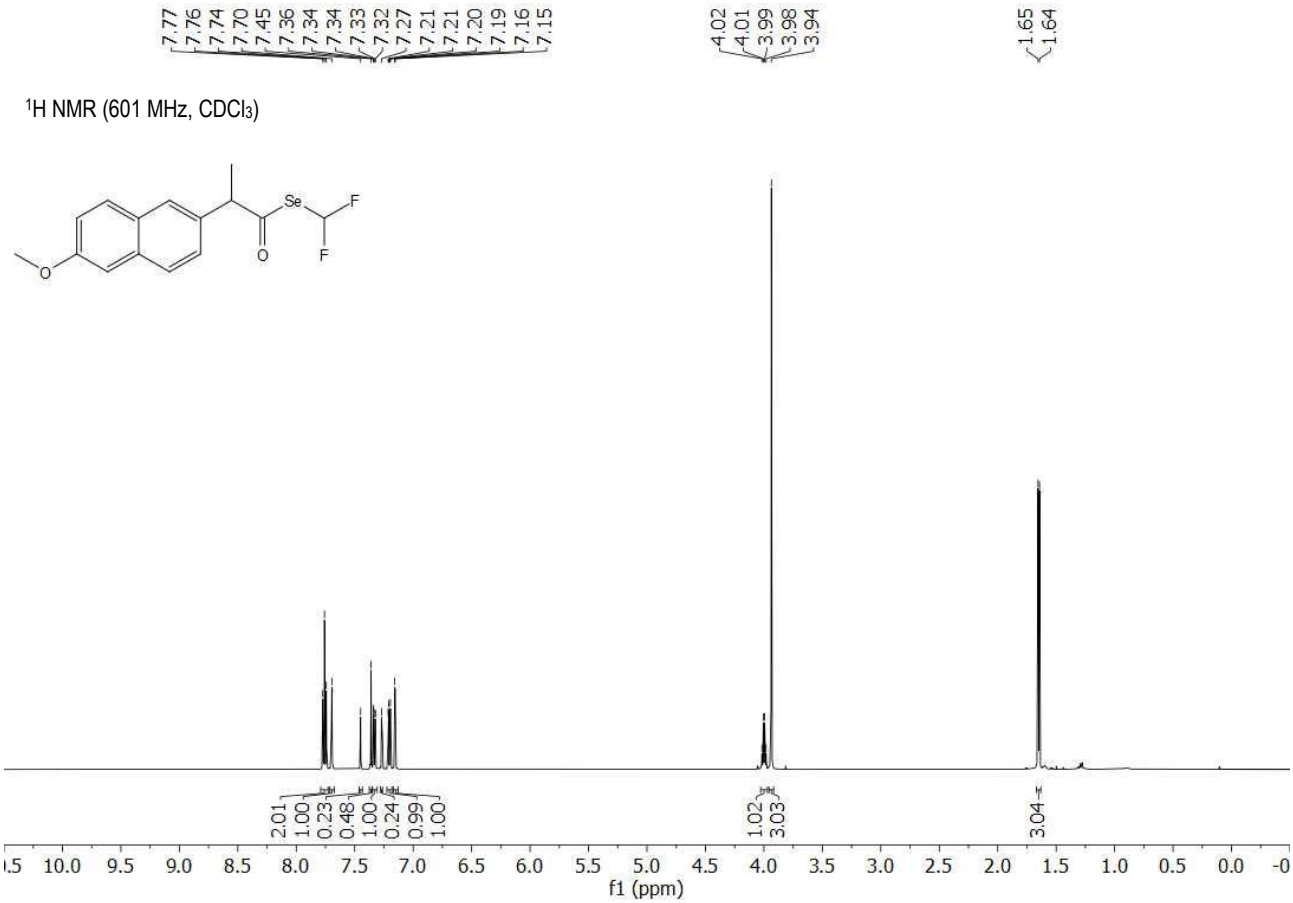


^{13}C NMR (151 MHz, $CDCl_3$)

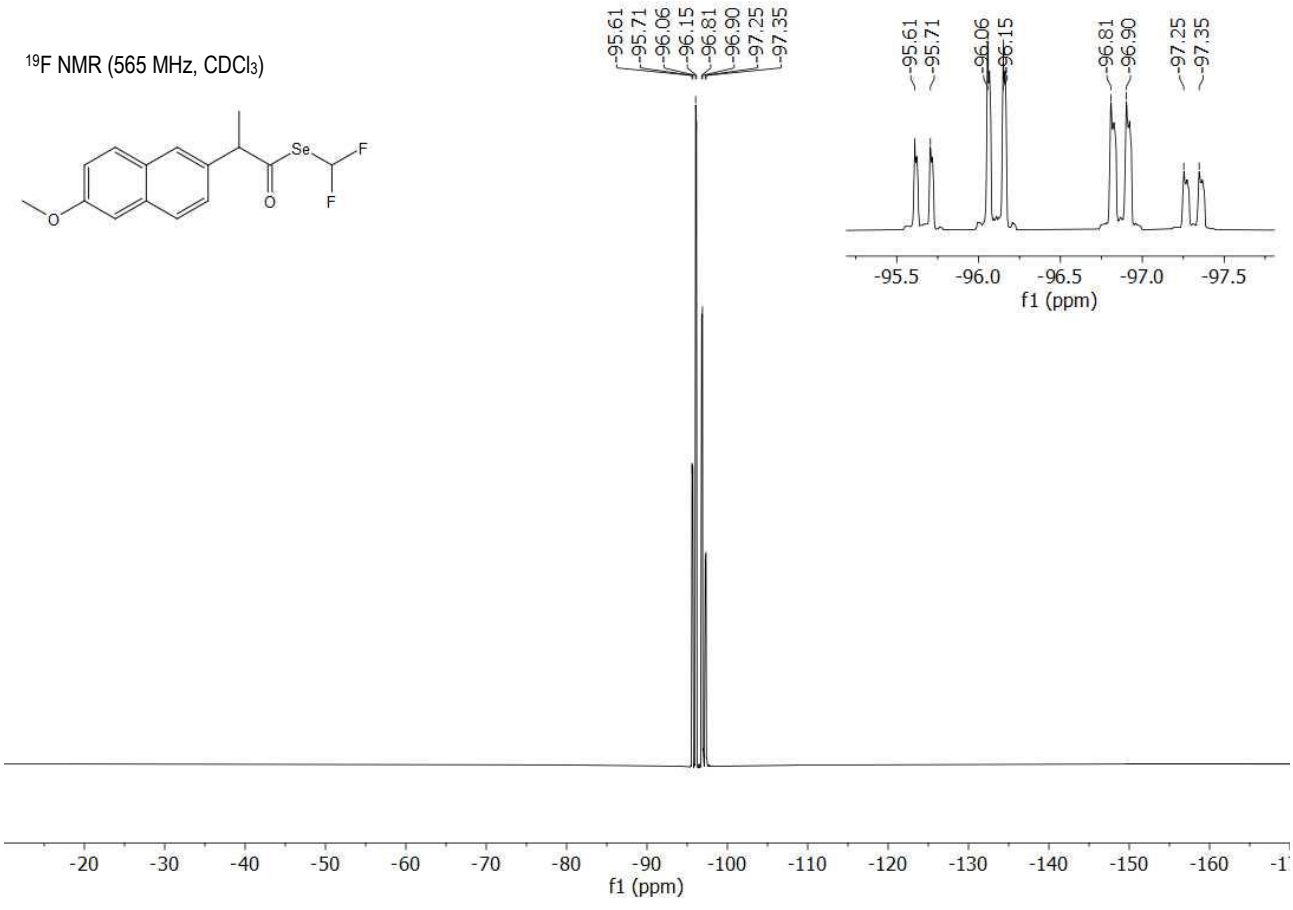


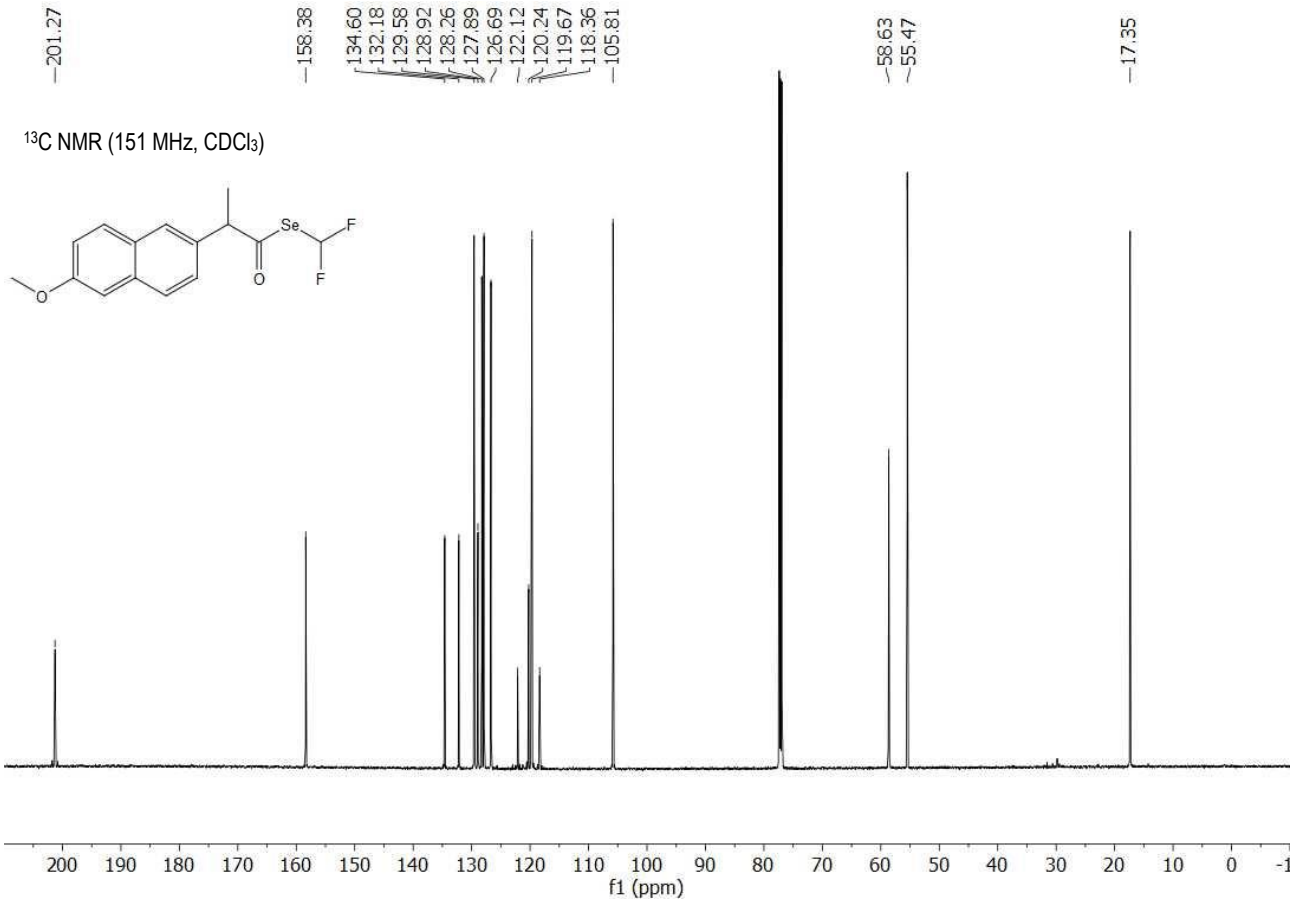
Se-(difluoromethyl) 2-(6-methoxynaphthalen-2-yl)propaneselenoate **4w**

^{1}H NMR (601 MHz, $CDCl_3$)



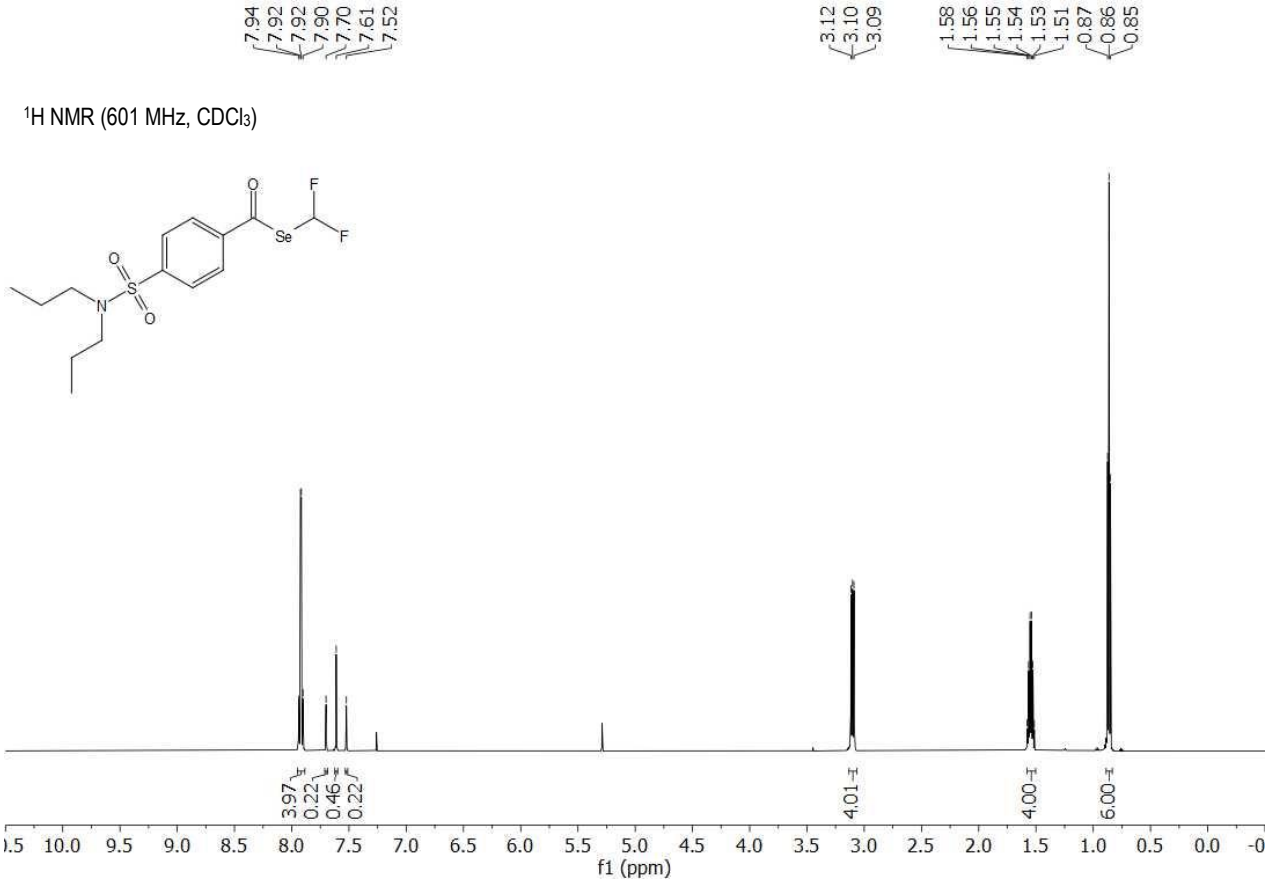
^{19}F NMR (565 MHz, $CDCl_3$)





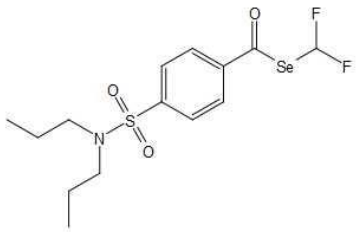
^{13}C NMR (151 MHz, $CDCl_3$)

Se-(difluoromethyl) 4-(*N*,*N*-dipropylsulfamoyl)benzoselenoate **4x**

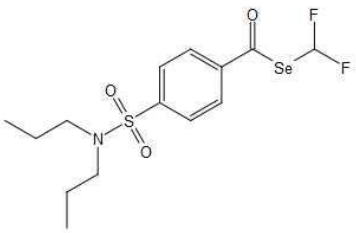


^{1}H NMR (601 MHz, $CDCl_3$)

^{19}F NMR (565 MHz, $CDCl_3$)

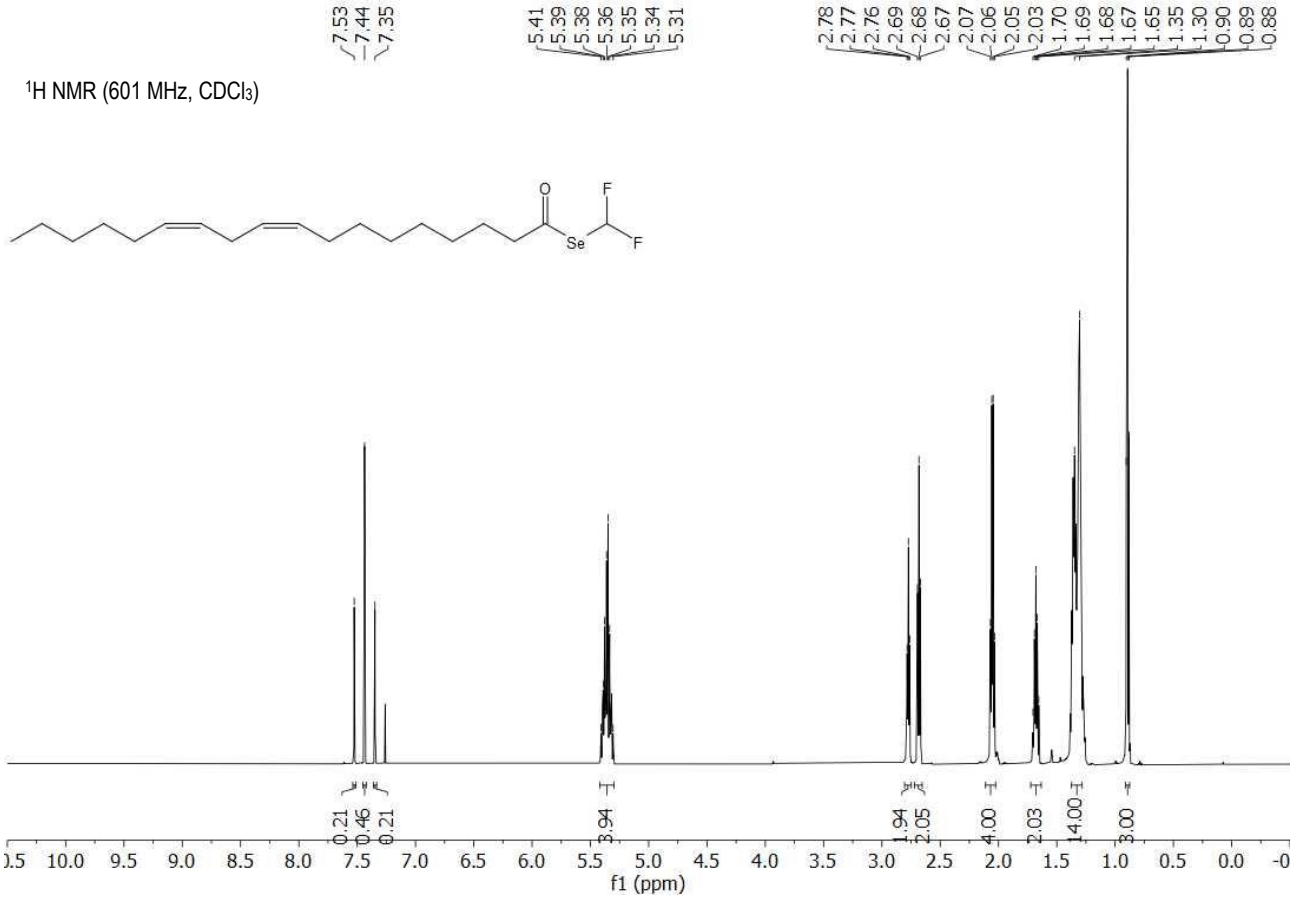


^{13}C NMR (151 MHz, $CDCl_3$)

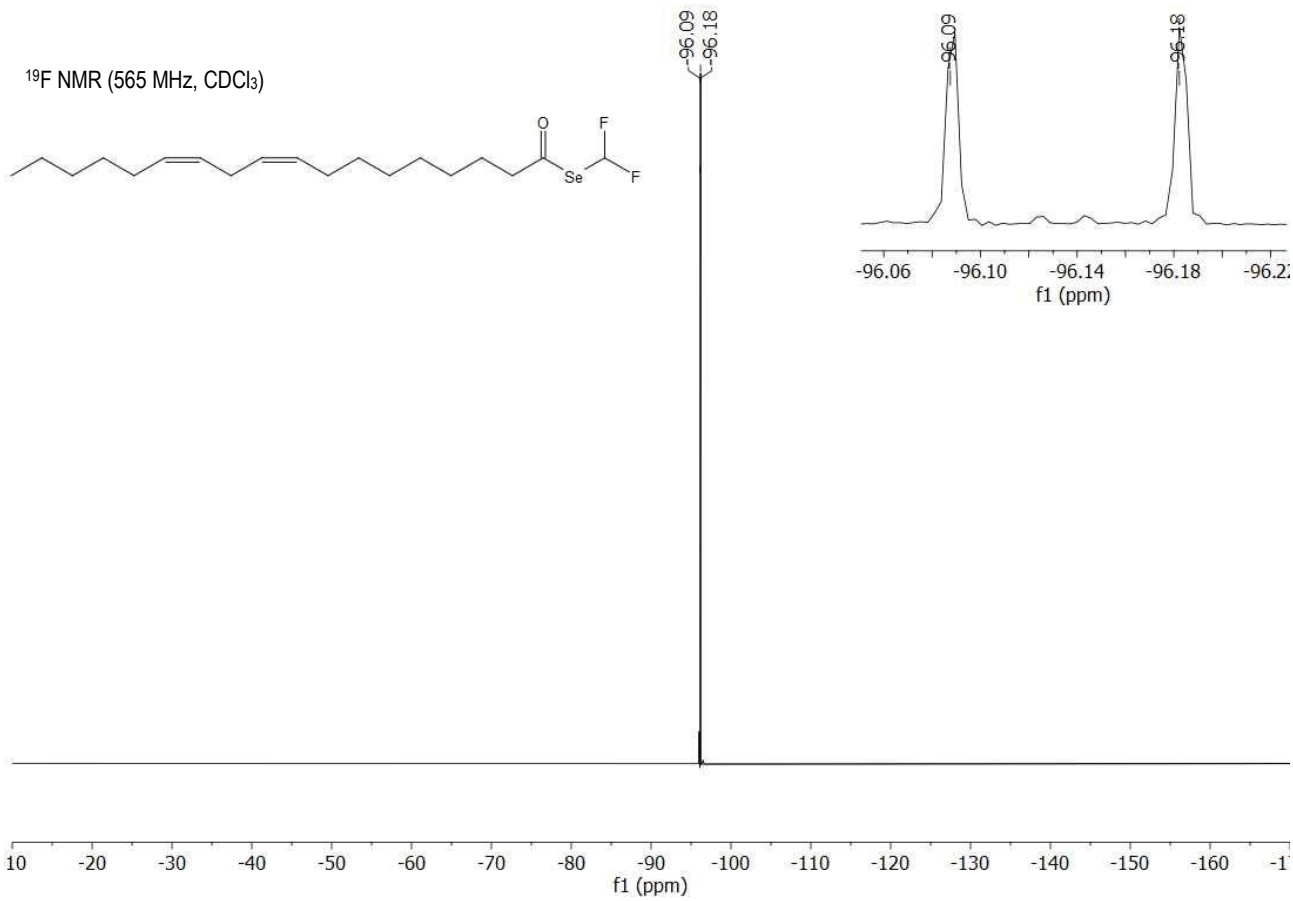


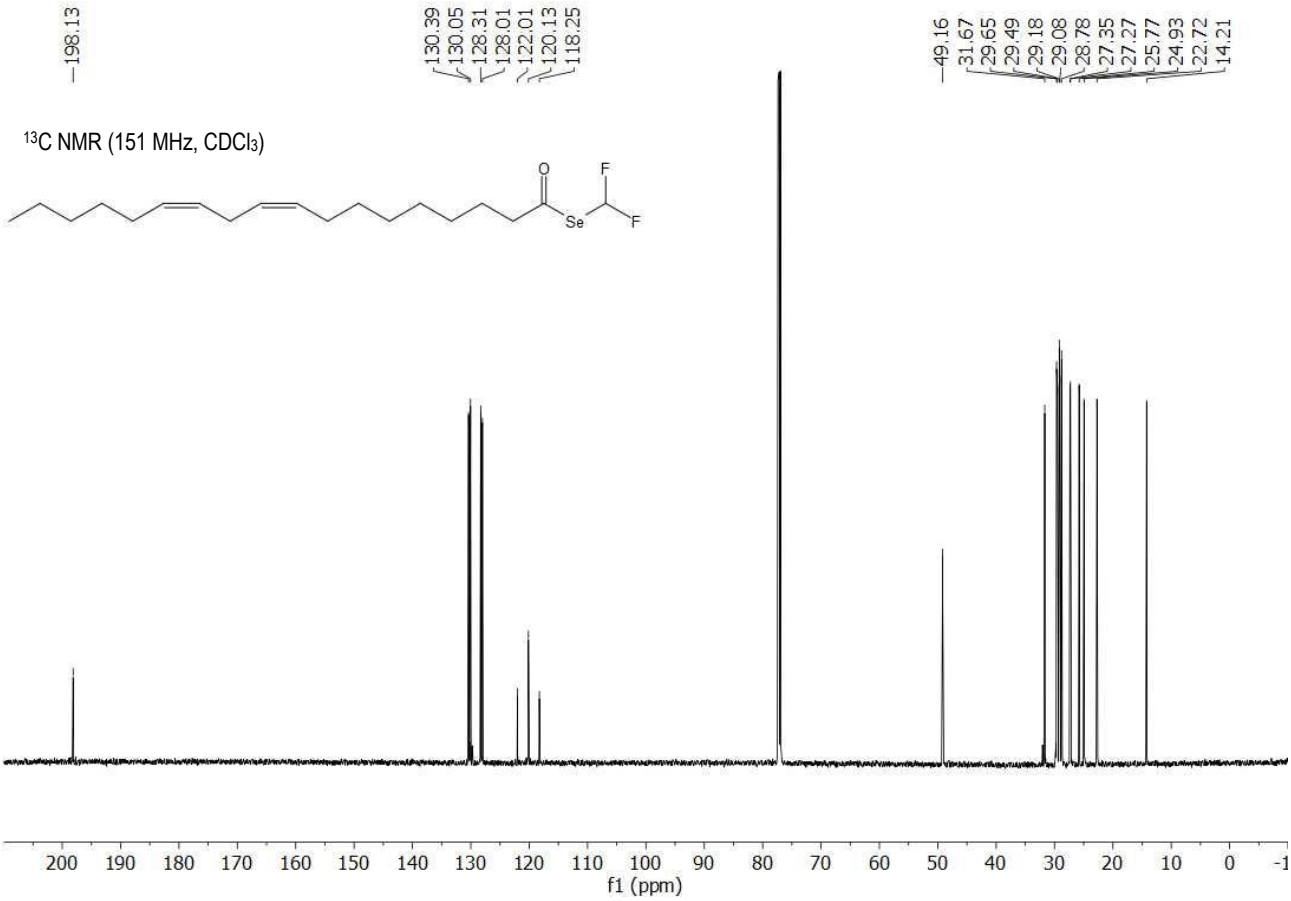
Se-(difluoromethyl) (9*Z*,12*Z*)-octadeca-9,12-dieneselenoate **4v**

^{1}H NMR (601 MHz, $CDCl_3$)

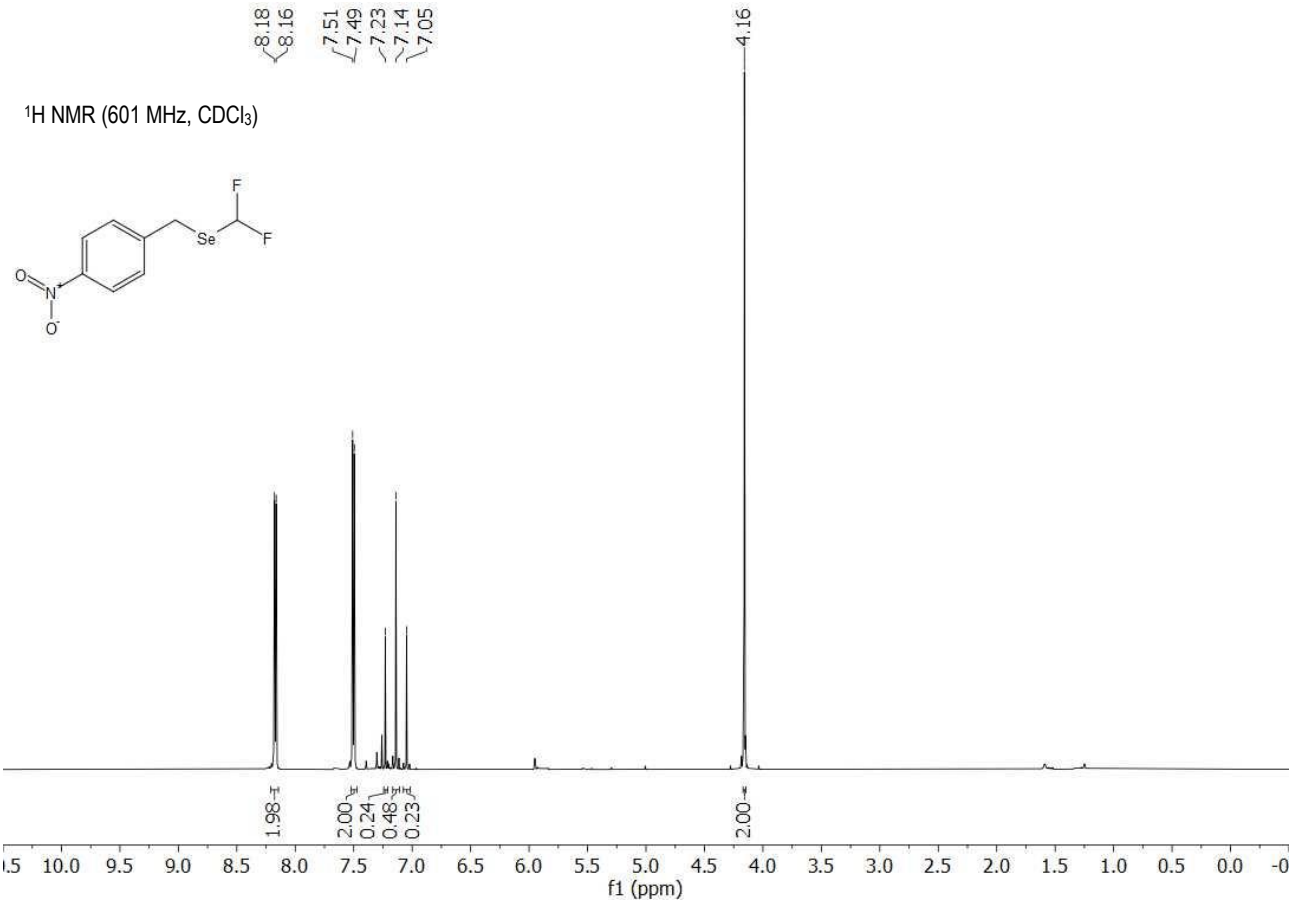


^{19}F NMR (565 MHz, $CDCl_3$)

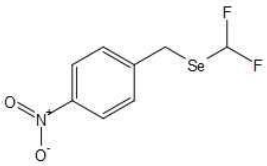




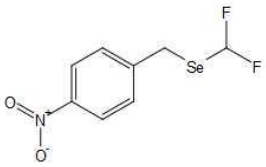
(Difluoromethyl)(4-nitrobenzyl)selane **6a**



^{19}F NMR (565 MHz, $CDCl_3$)

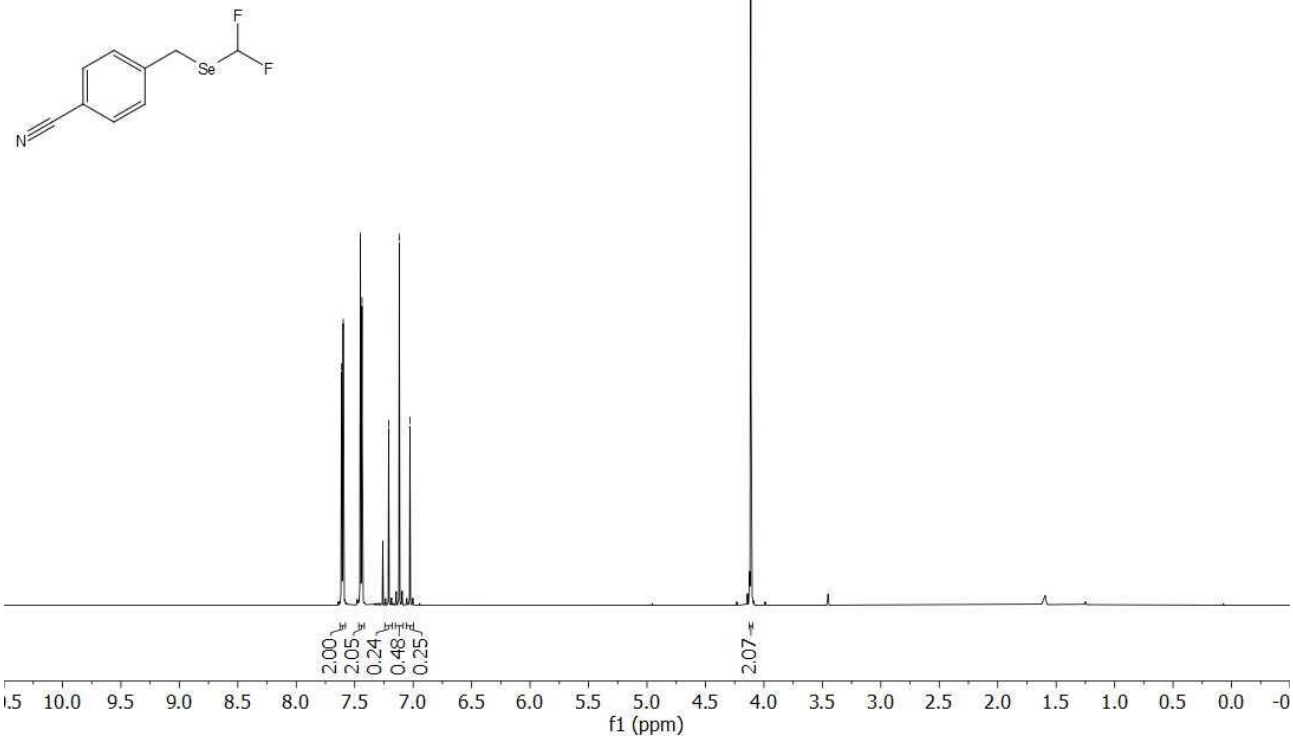


^{13}C NMR (151 MHz, $CDCl_3$)

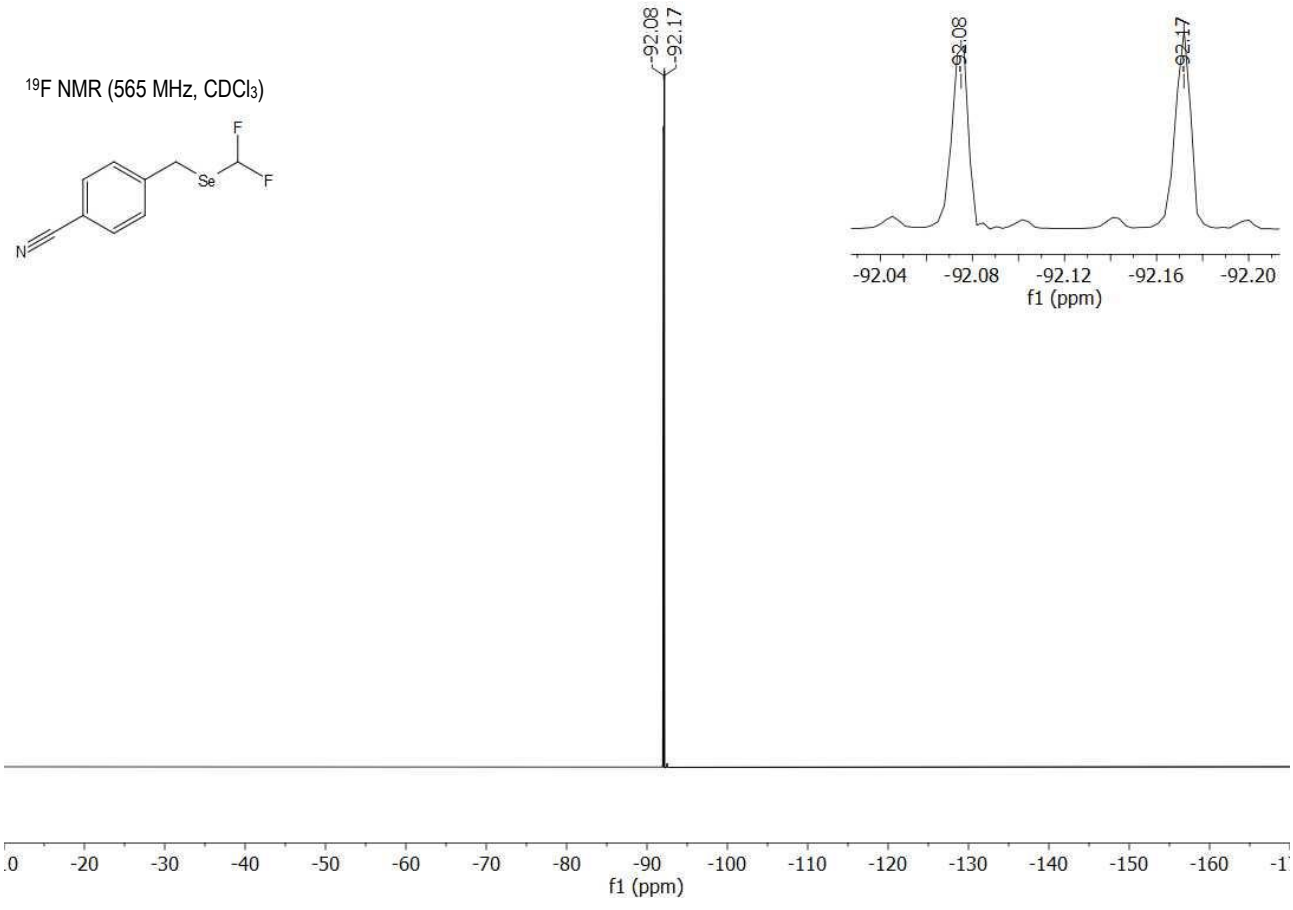


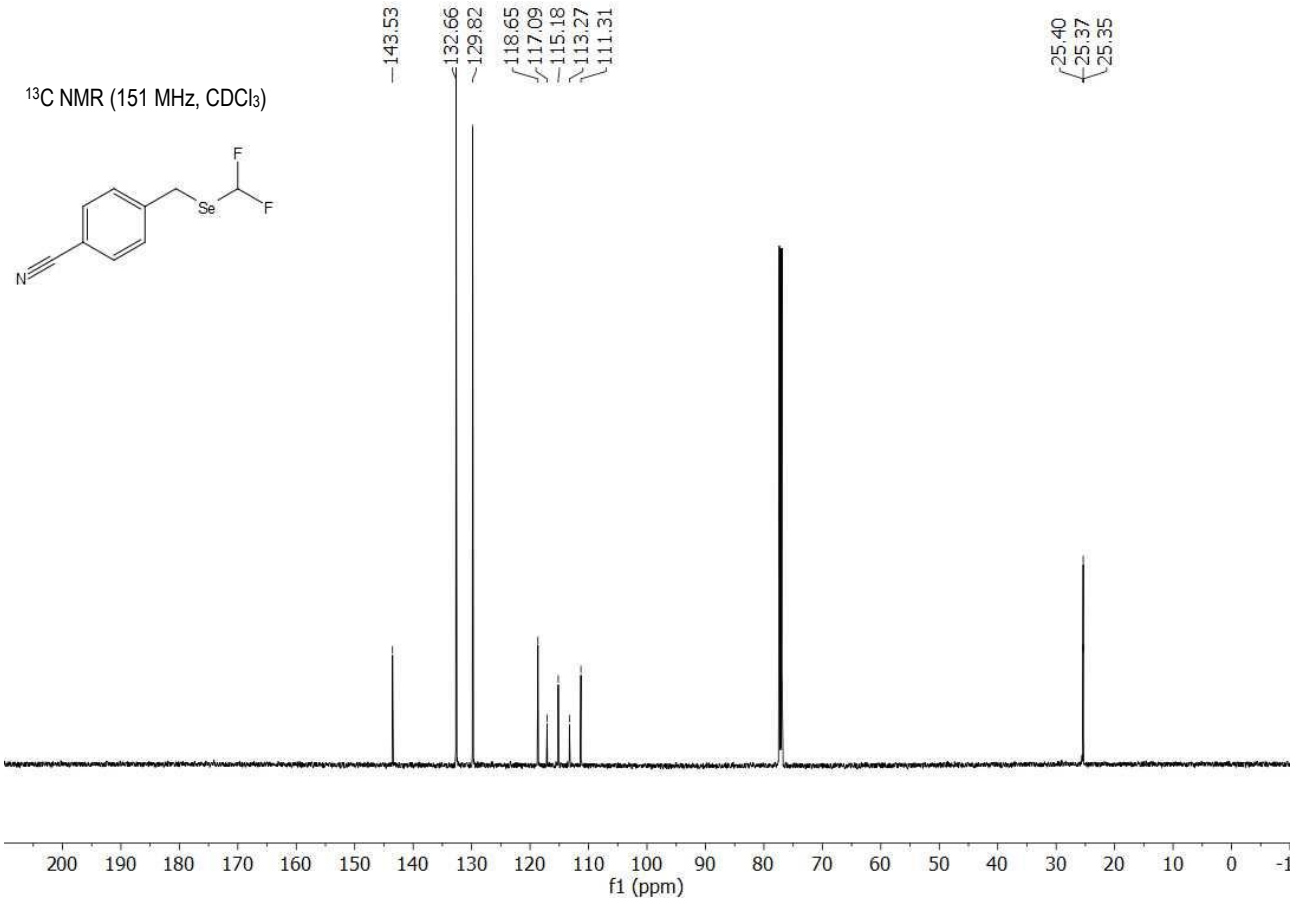
4-(((Difluoromethyl)selanyl)methyl)benzonitrile **6b**

^{1}H NMR (601 MHz, $CDCl_3$)

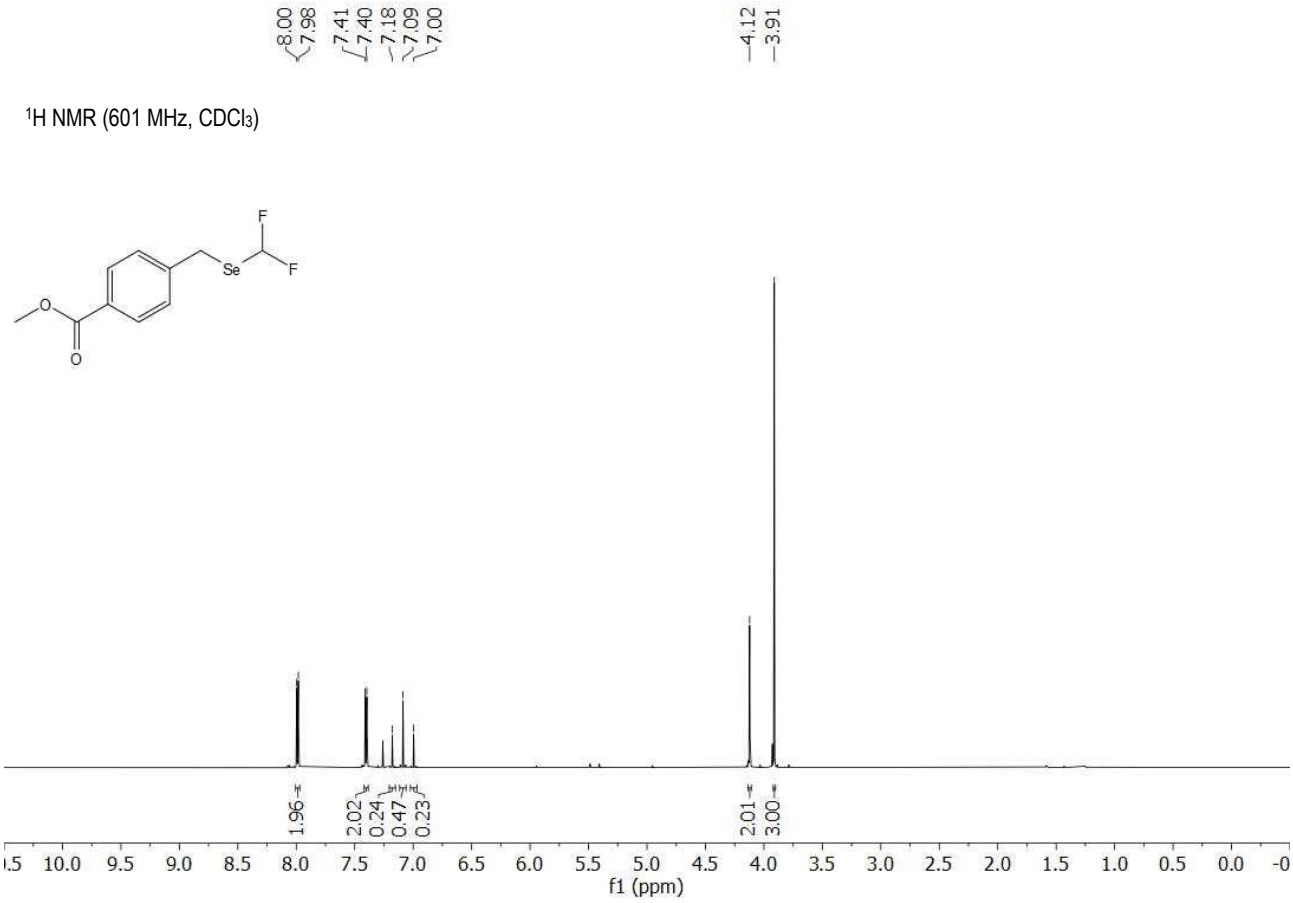


^{19}F NMR (565 MHz, $CDCl_3$)

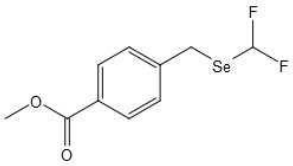




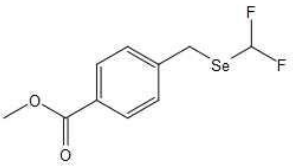
Methyl 4-(((difluoromethyl)selanyl)methyl)benzoate **6c**



^{19}F NMR (565 MHz, $CDCl_3$)

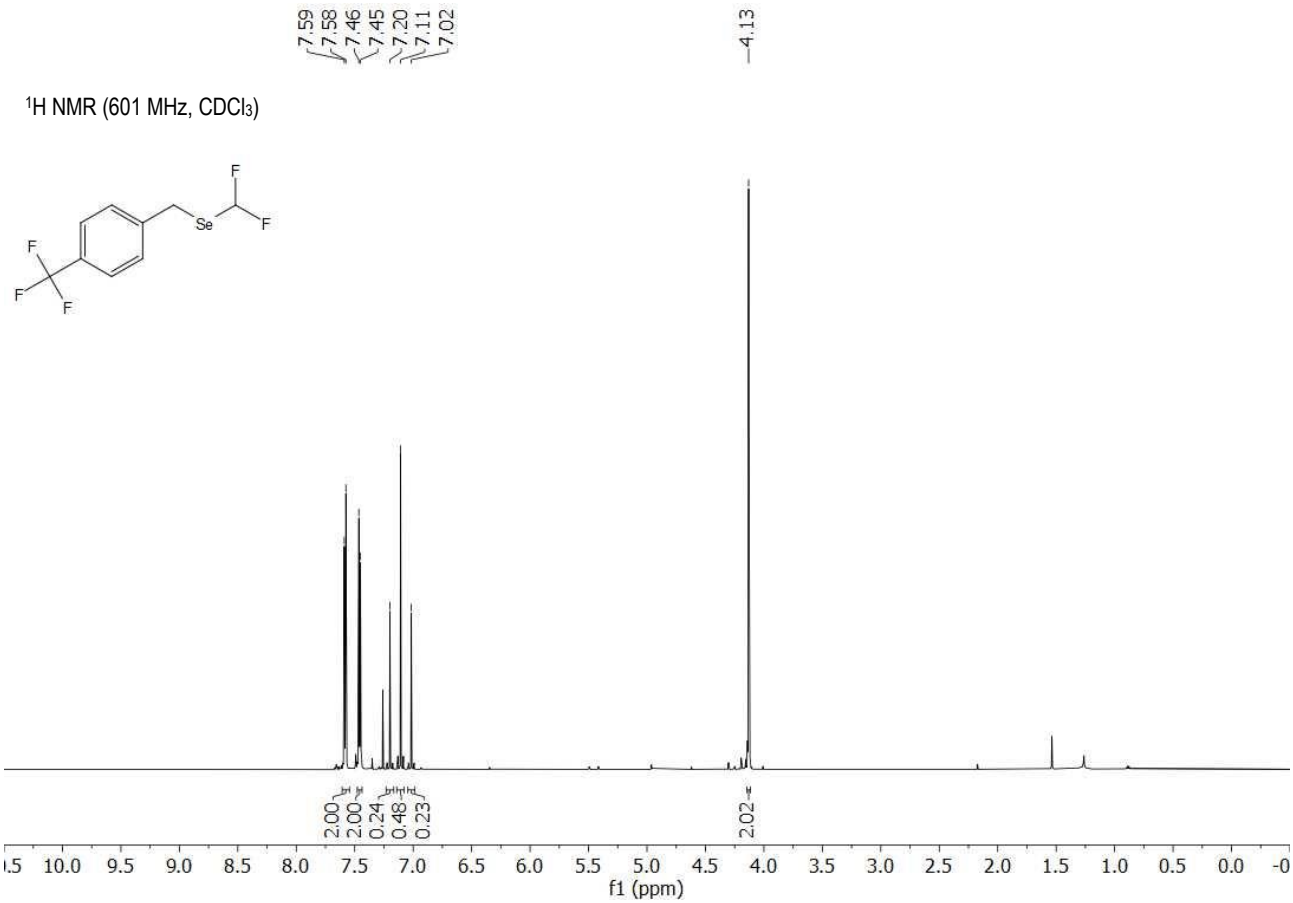


^{13}C NMR (151 MHz, $CDCl_3$)

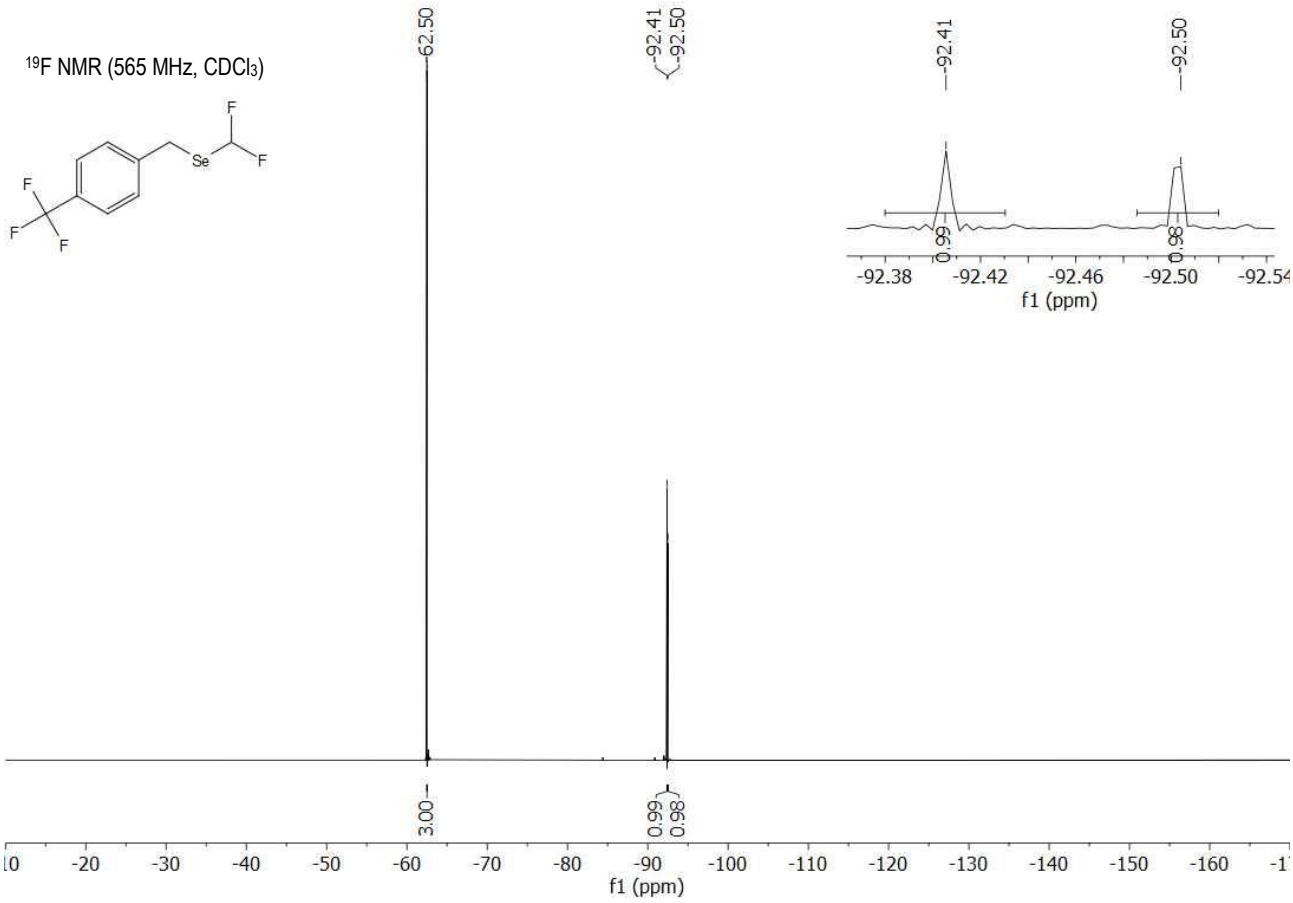


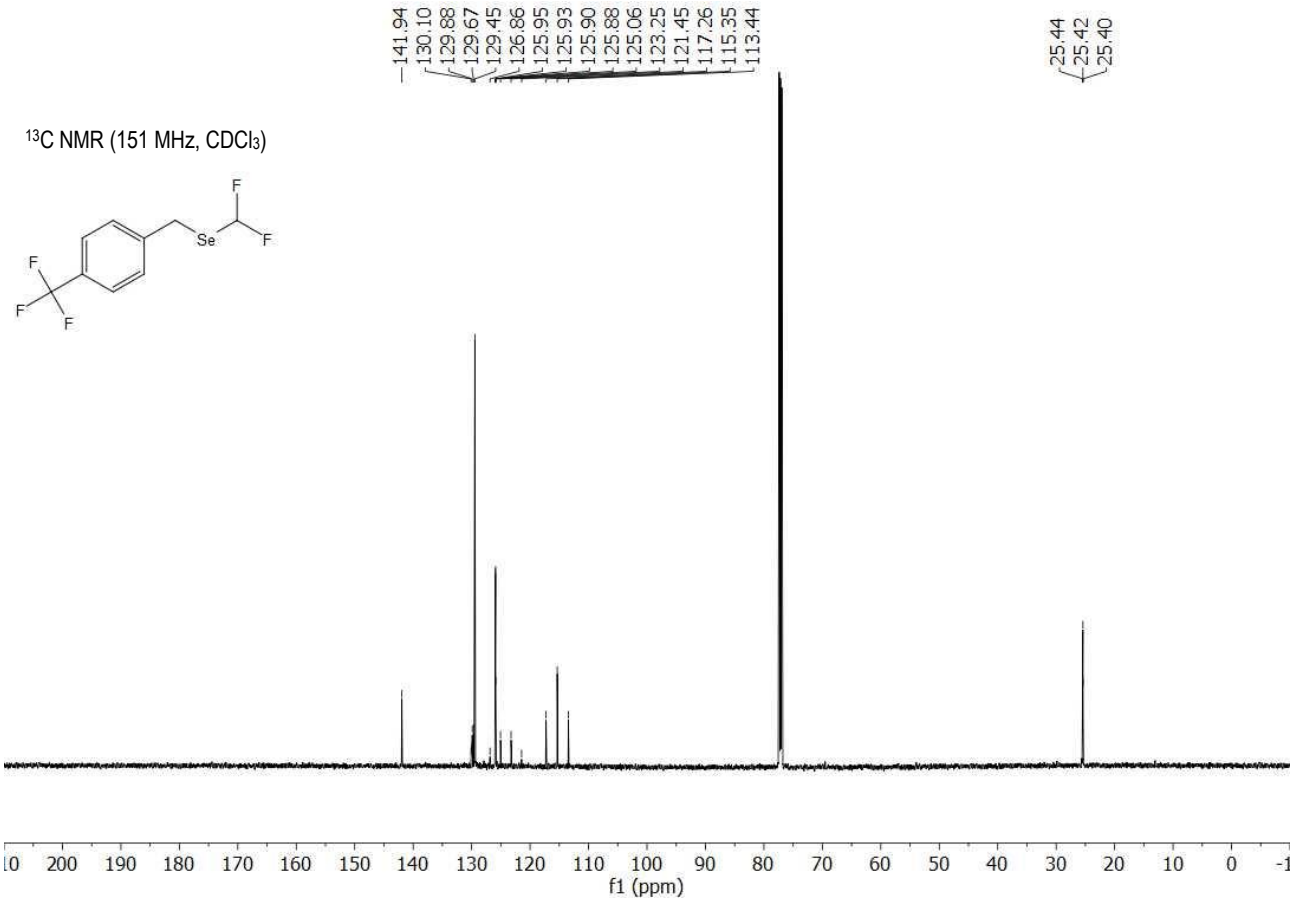
(Difluoromethyl)(4-(trifluoromethyl)benzyl)selane **6d**

^{1}H NMR (601 MHz, $CDCl_3$)



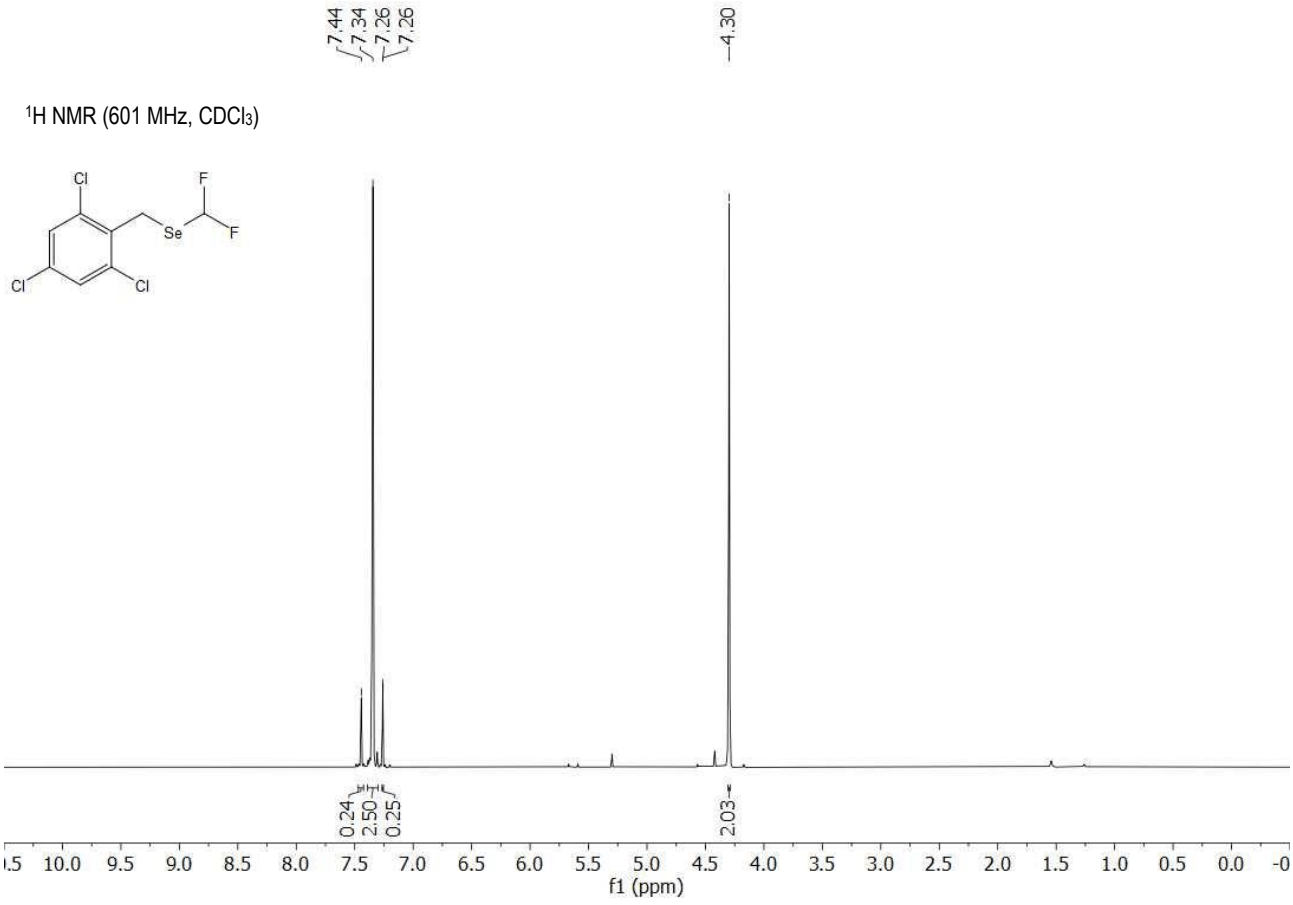
^{19}F NMR (565 MHz, $CDCl_3$)





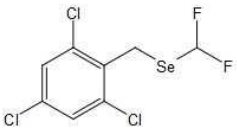
^{13}C NMR (151 MHz, $CDCl_3$)

(Difluoromethyl)(2,4,6-trichlorobenzyl)selane **6e**

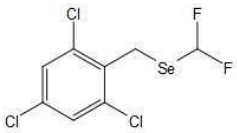


^{1}H NMR (601 MHz, $CDCl_3$)

^{19}F NMR (565 MHz, $CDCl_3$)

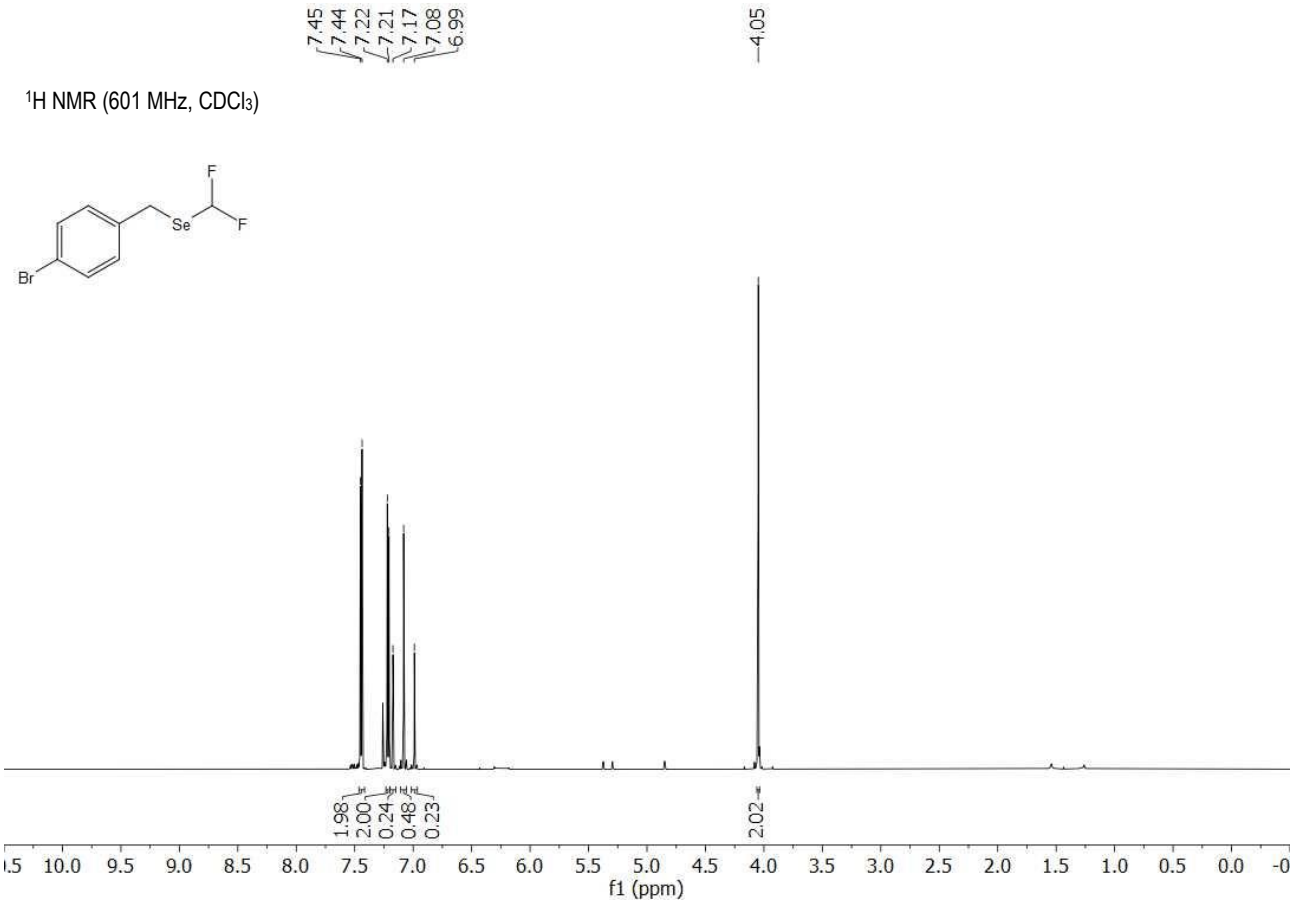


^{13}C NMR (151 MHz, $CDCl_3$)

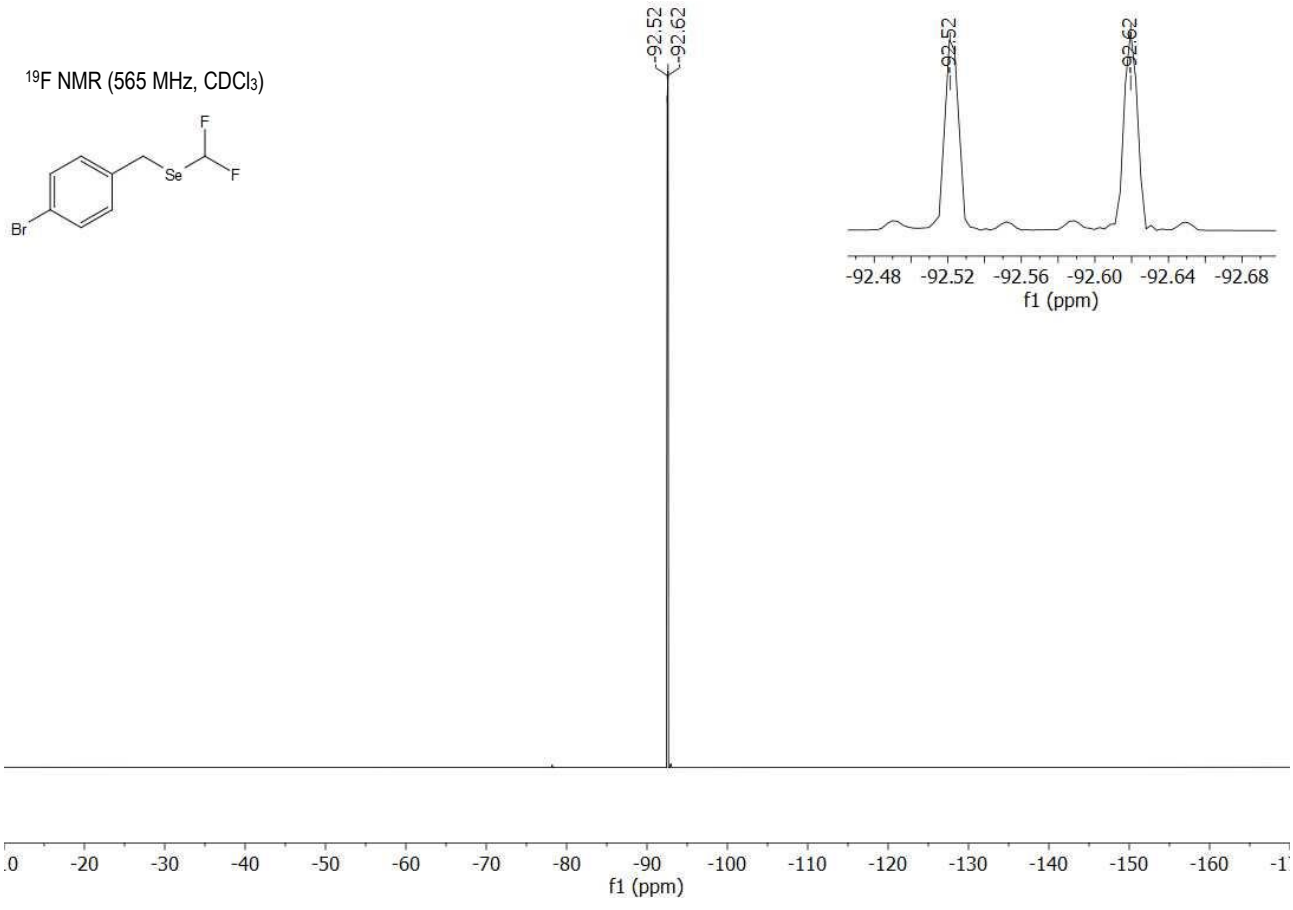


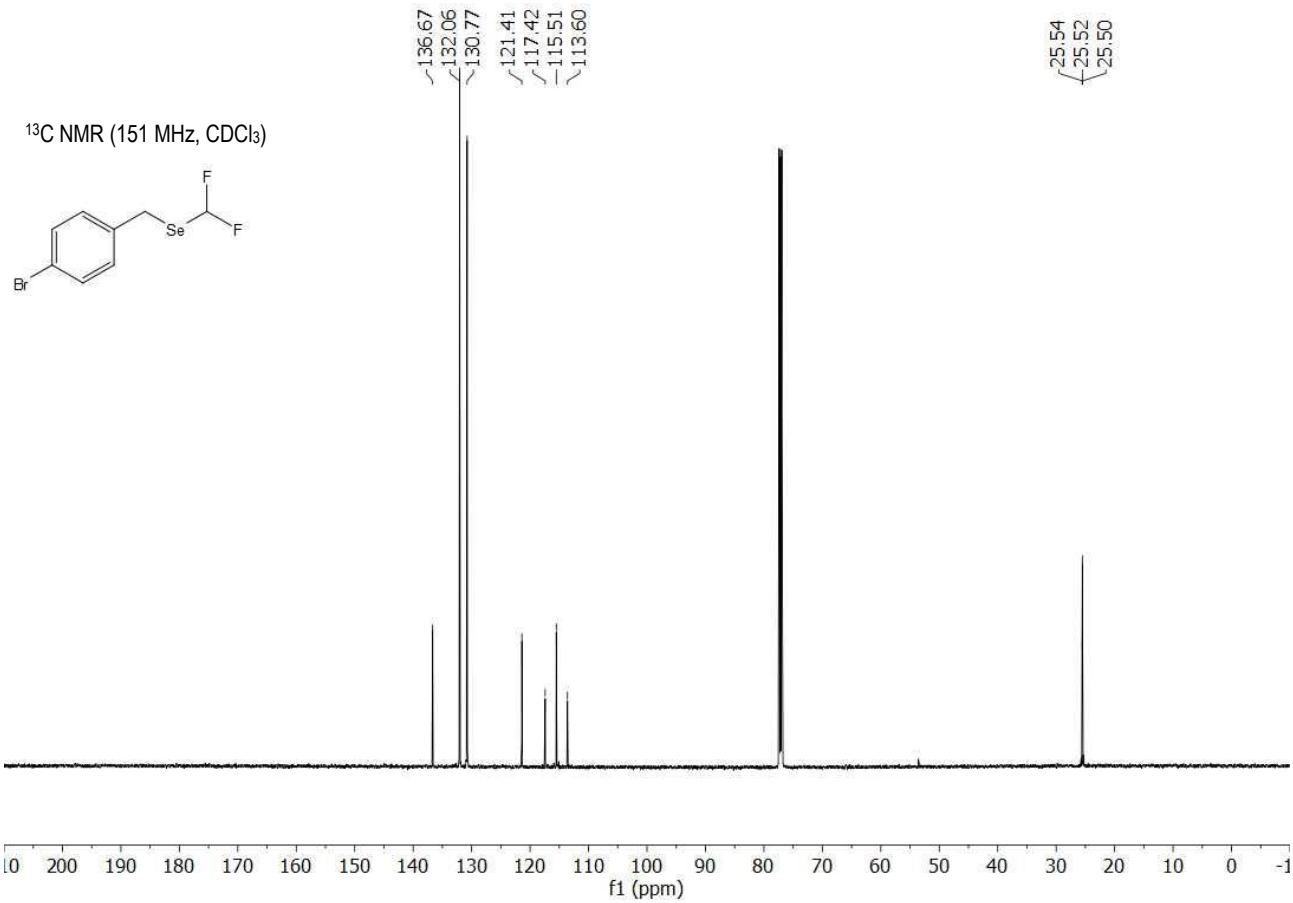
(Difluoromethyl)(4-bromobenzyl)selane **6f**

^{1}H NMR (601 MHz, $CDCl_3$)

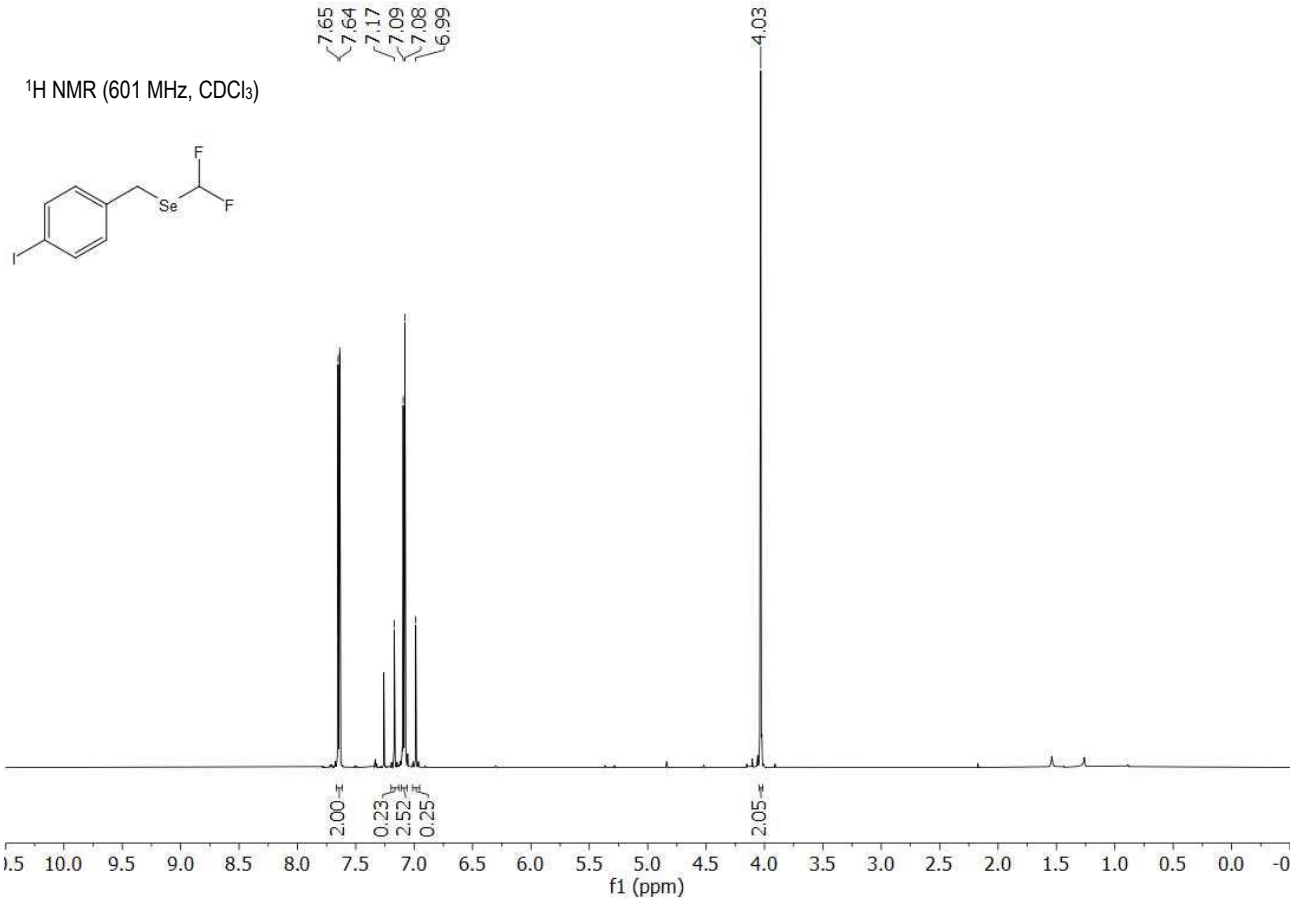


^{19}F NMR (565 MHz, $CDCl_3$)

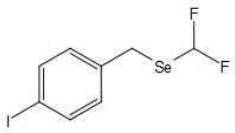




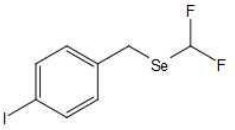
(Difluoromethyl)(4-iodobenzyl)selane **6g**



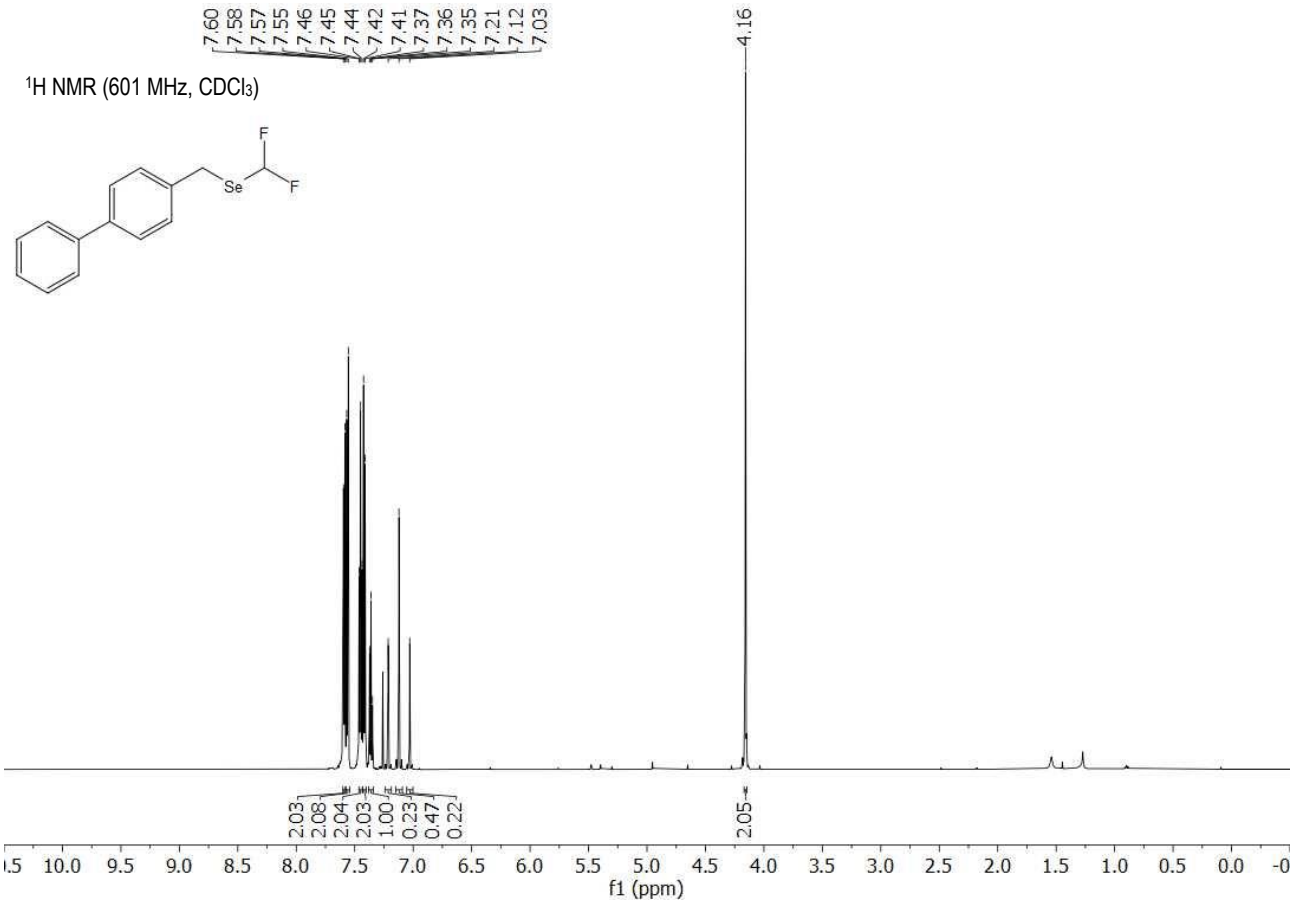
^{19}F NMR (565 MHz, $CDCl_3$)

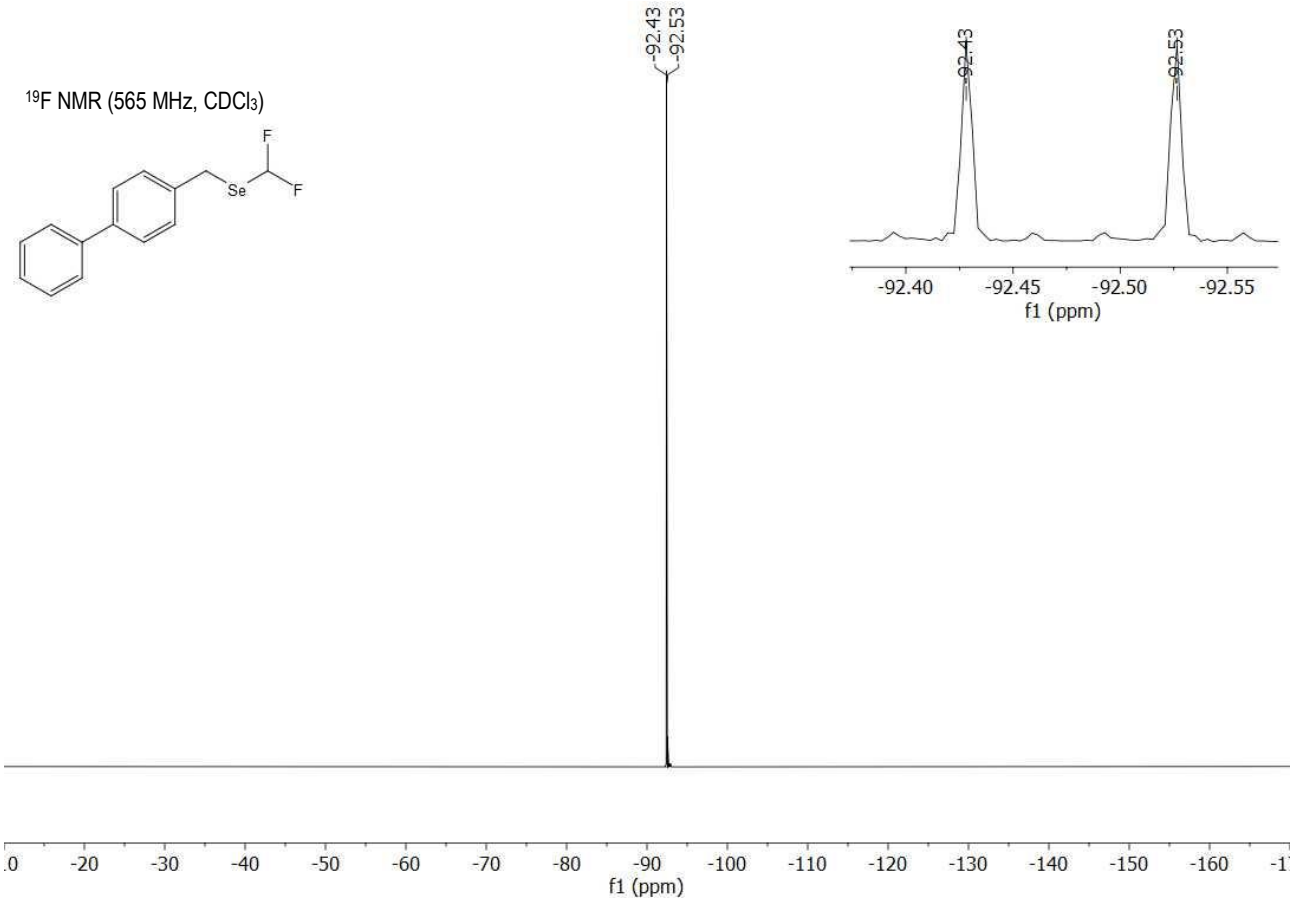


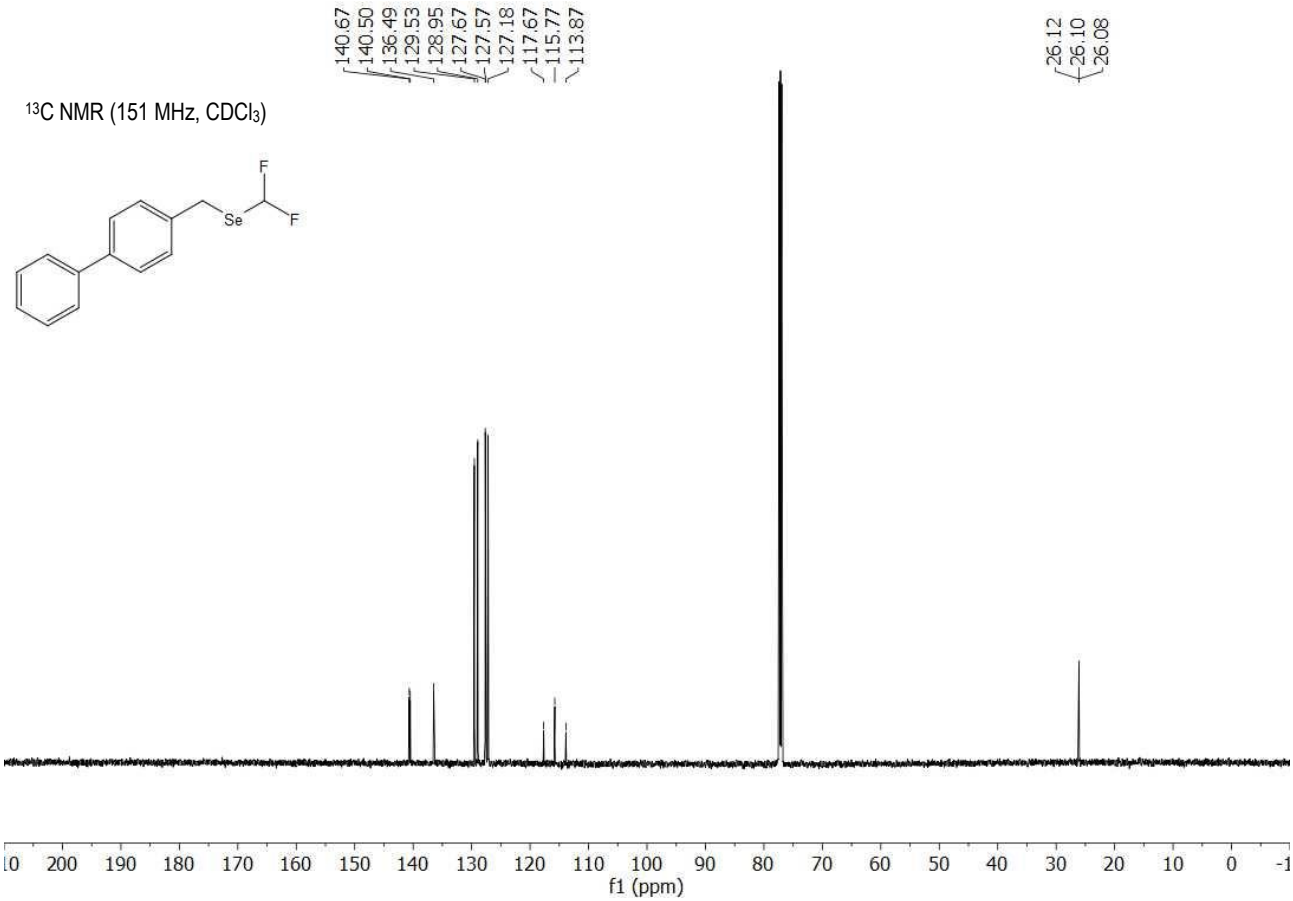
^{13}C NMR (151 MHz, $CDCl_3$)



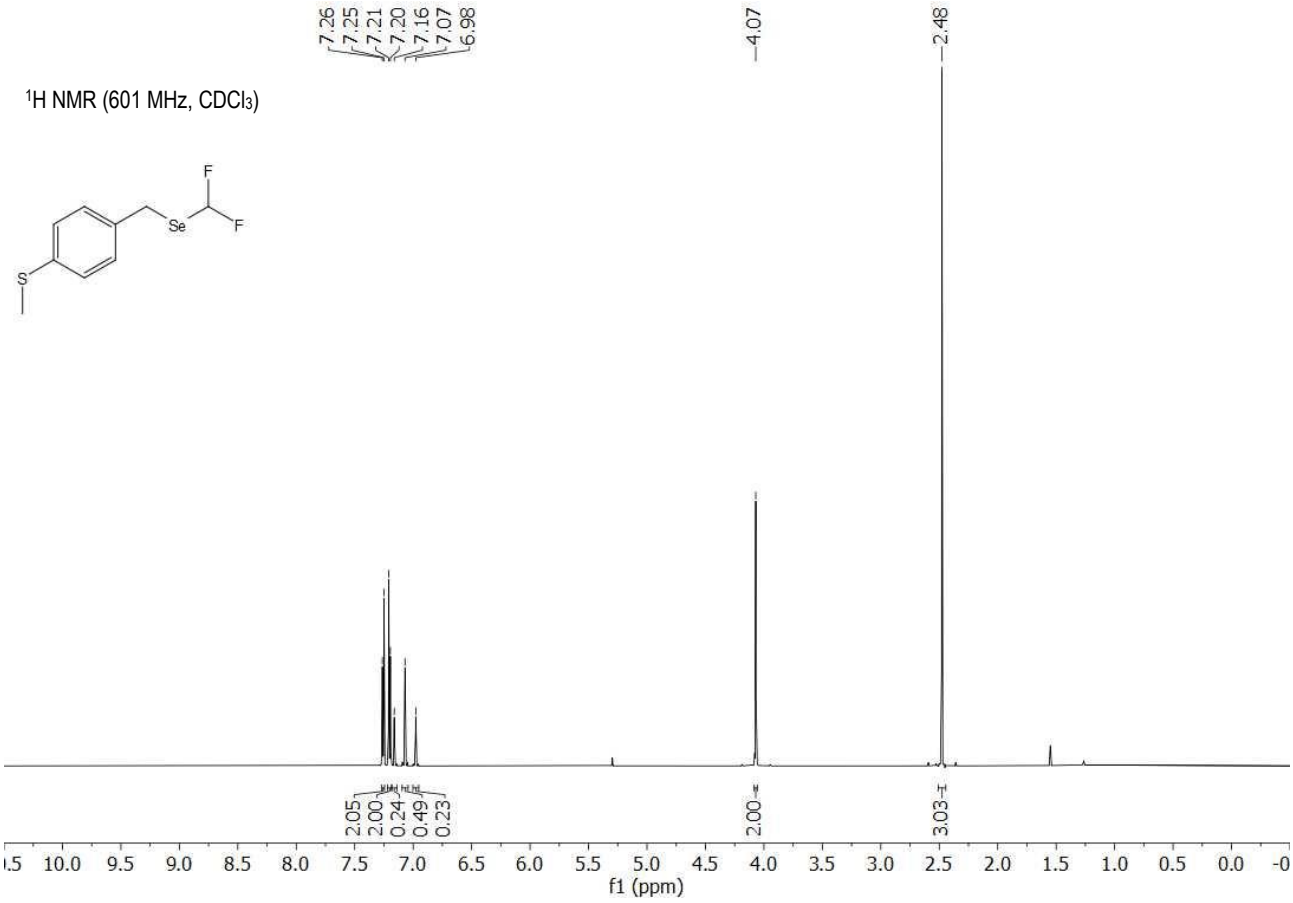
([1,1'-Biphenyl]-4-ylmethyl)(difluoromethyl)selane **6h**



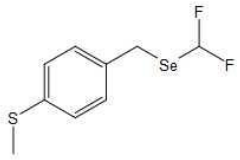




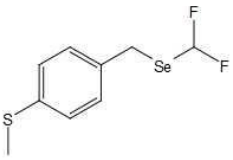
(4-(((Difluoromethyl)selanyl)methyl)phenyl)(methyl)sulfane **6i**



^{19}F NMR (565 MHz, $CDCl_3$)

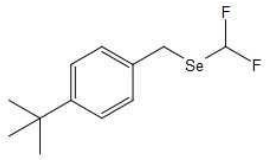


^{13}C NMR (151 MHz, $CDCl_3$)



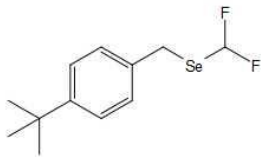
(4-(*tert*-Butyl)benzyl)(difluoromethyl)selane **6j**

^{1}H NMR (601 MHz, $CDCl_3$)



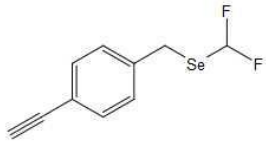
^{19}F NMR (565 MHz, $CDCl_3$)

^{13}C NMR (151 MHz, $CDCl_3$)

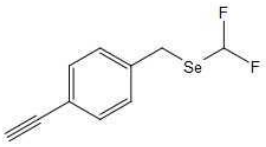


(Difluoromethyl)(4-ethynylbenzyl)selane **6k**

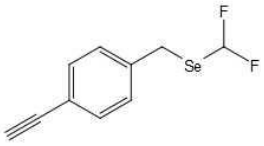
^{1}H NMR (601 MHz, $CDCl_3$)



^{19}F NMR (565 MHz, $CDCl_3$)

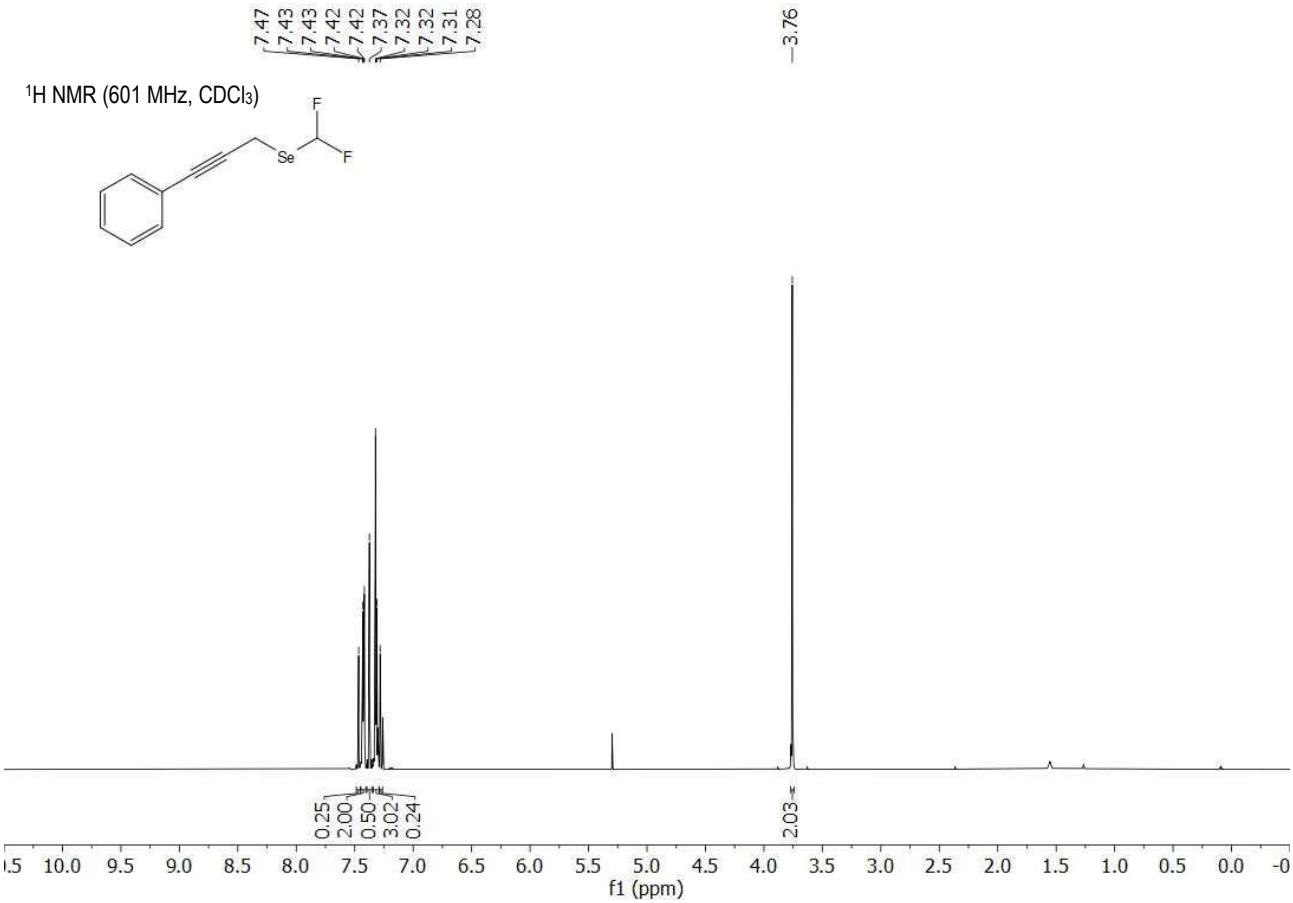


^{13}C NMR (151 MHz, $CDCl_3$)

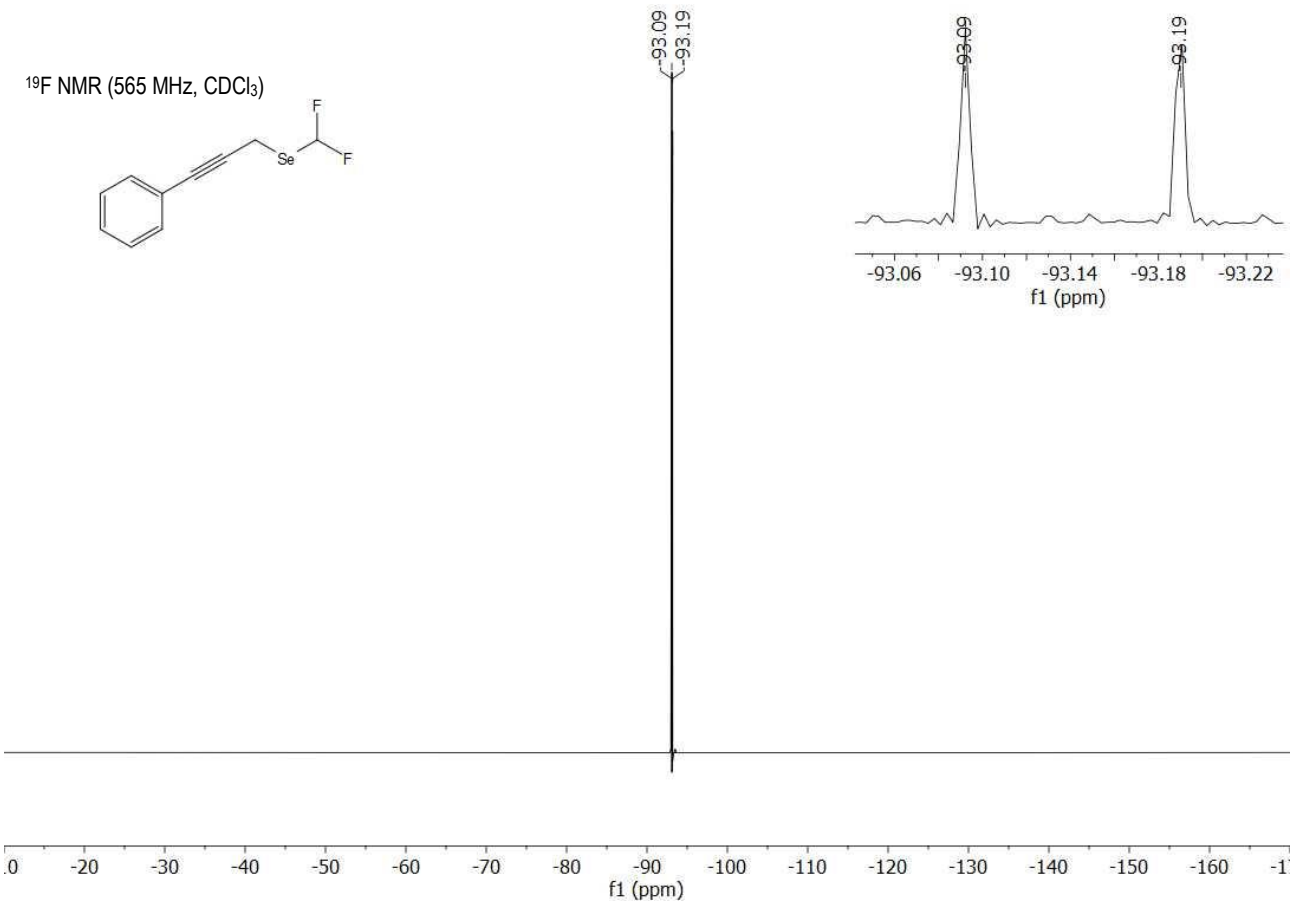


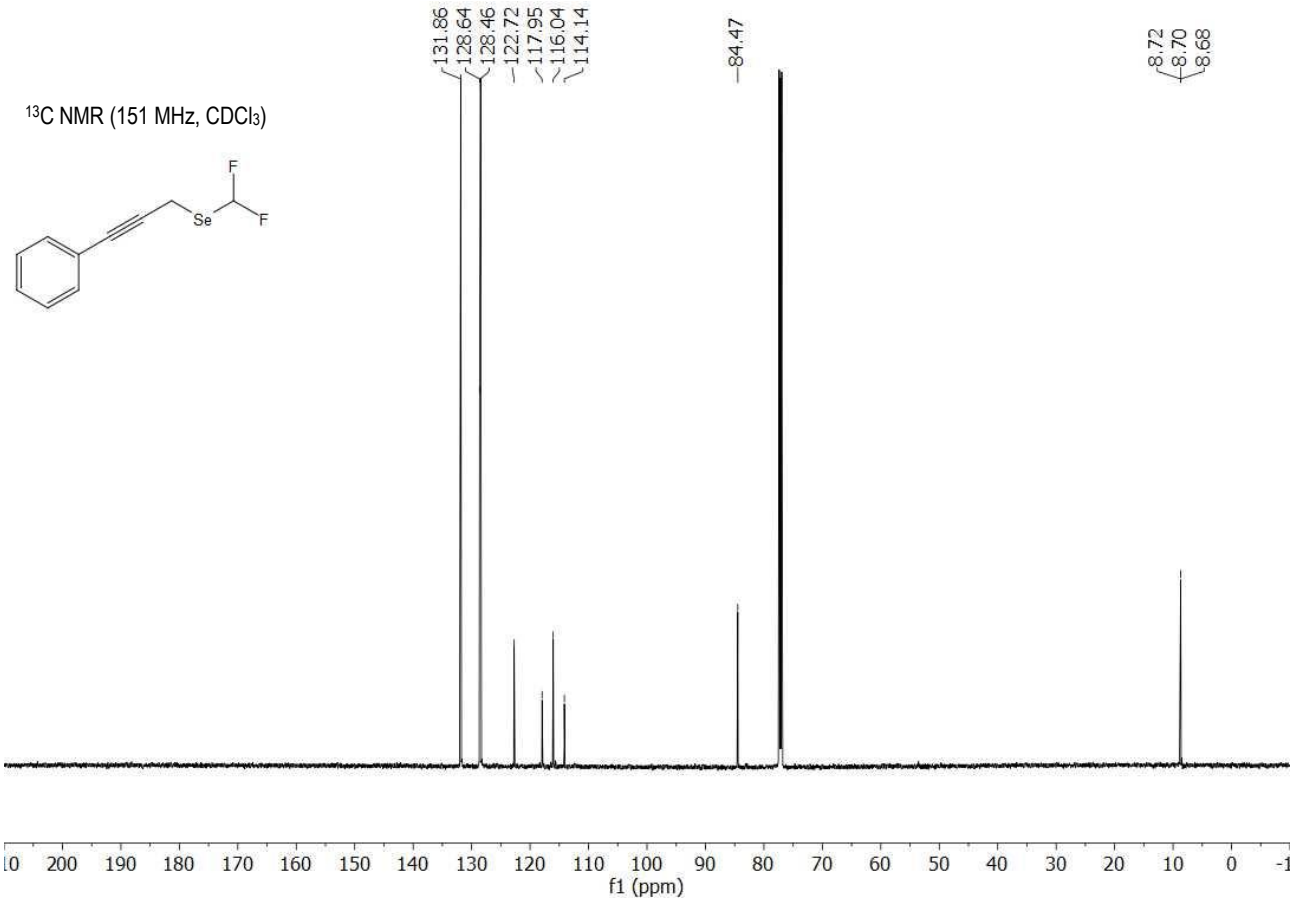
(Difluoromethyl)(3-phenylprop-2-yn-1-yl)selane **6l**

^{1}H NMR (601 MHz, $CDCl_3$)

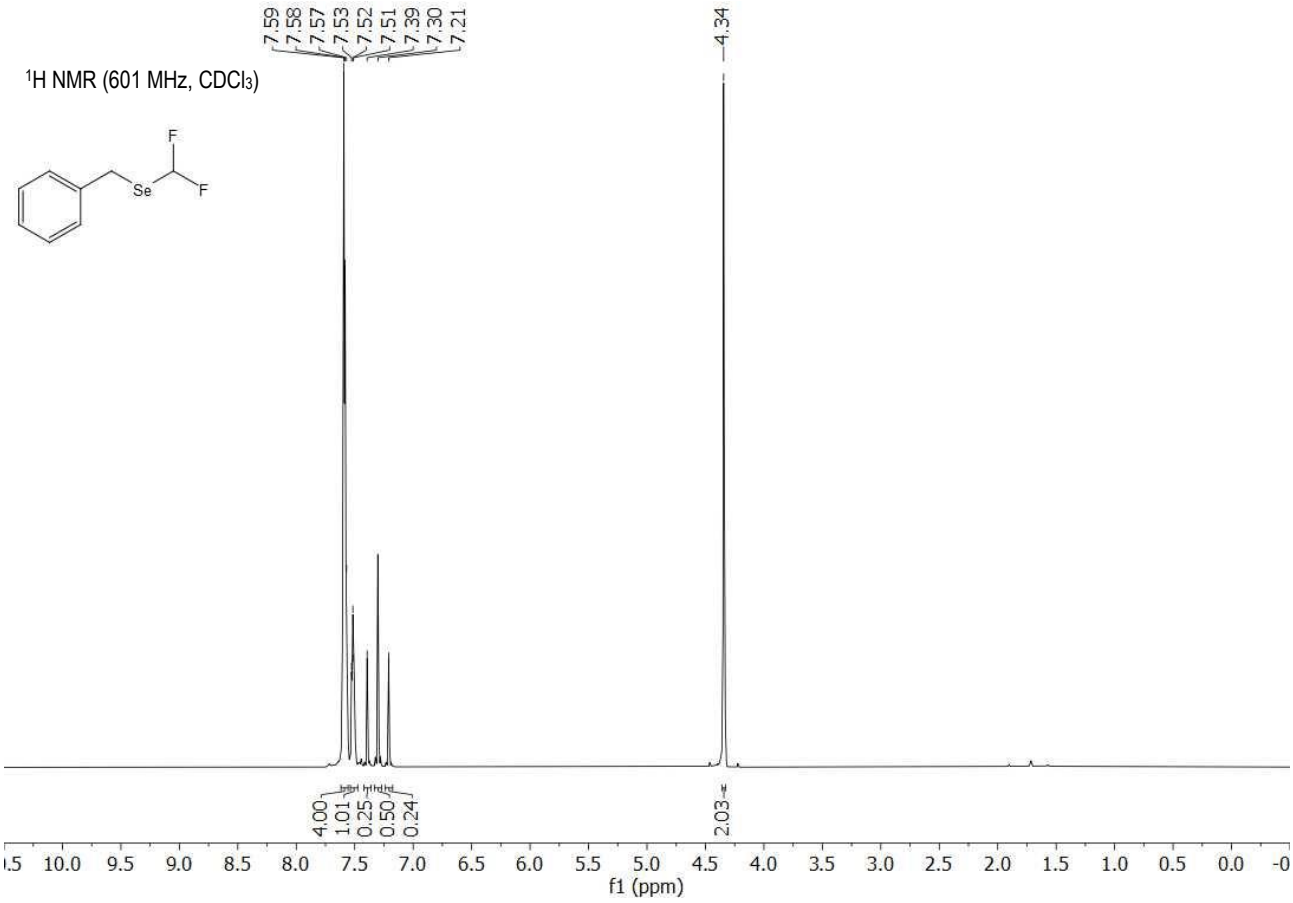


^{19}F NMR (565 MHz, $CDCl_3$)

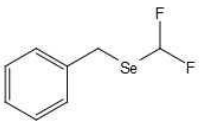




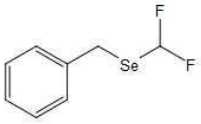
Benzyl(difluoromethyl)selane **A**



^{19}F NMR (565 MHz, $CDCl_3$)



^{13}C NMR (151 MHz, $CDCl_3$)



European Journal of Organic Chemistry

Supporting Information

Silver-Catalyzed Nucleophilic Deoxydifluoromethylthiolation of Activated Aliphatic Alcohols with BT–SCF_2H

Matteo Tironi and Matthew N. Hopkinson*

Contents

1 General Information

Unless otherwise stated, all reactions were performed under argon as inert gas. The glass apparatus used was heated in an oil pump vacuum and purged with argon. Screw-cap reaction vessels were rinsed with argon. All purchased chemicals were used without further treatment. Used DCM was taken from the solvent purification system MB-SPS-800 (Braun). All dry solvents were stored over molecular sieves (3 or 4 Å). The solvents pentane, DCM and EtOAc used for column chromatography were distilled prior to use.

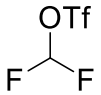
Thin-layer chromatography was performed on silica gel coated aluminium plates ALUGRAM® Xtra SIL G/UV254 (Macherey-Nagel). The product spots were detected by UV light (254 nm) or as permanganate stains. Flash column chromatography was performed with silica gel 60 M (0.040–0.063 mm, 230–400 mesh, Macherey-Nagel).

^{1}H, ^{19}F and ^{13}C NMR spectra were acquired on a JEOL ECS 400 (400 MHz), JEOL ECZ 400 (400 MHz), JEOL ECX 400 (400 MHz), JEOL ECP 500/ Bruker Avance 500 (500 MHz), Varian INOVA 600 (600 MHz) or a Bruker Avance 700 (700 MHz) and analysed on MestReNova. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethyl silane (TMS) and coupling constants (J) are presented in hertz (Hz). CD_3CN or $CDCl_3$ are used as deuterated solvent and the residual solvent signals are used as reference in the ^{1}H and ^{13}C NMR spectra. ^{19}F NMR spectra are not calibrated by an internal reference, but with $CFCl_3$ as reference. ^{1}H NMR yields were measured using CH_2Br_2 as an internal standard. The multiplicities have been explained using the following abbreviations : s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet.

CHN Analysis was obtained on ELEMENTAR Vario El elemental analyzer and High-resolution mass spectra were measured with an Agilent (6210 ESI-TOF; 4 µL/min, 1.0 bar, 4 kV) instrument. Infrared spectra were measured with a NICOLET spectrometer (iS10) equipped with an ATR unit (NICOLET SMART DuraSampl*IR*) and only diagnostic absorption bands are reported.

2 Synthesis of BT-SCF_3 and BT-SCF_2H

2.1 Synthesis of Difluoromethyl trifluoromethanesulfonate (S1)

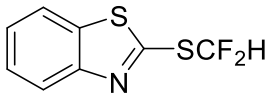


$TiCl_4$ (1 mol% , 1.38 mmol, 152 µL) was added dropwise to TfOH (1.2 equiv., 165.6 mmol, 15 mL) under vigorous stirring at room temperature for 5 mins. The homogeneous yellow solution was evacuated at 13–20 mbar until gas evolution ceased. The mixture was cooled to -20 °C, $TMSCF_3$ (1.0 equiv., 138 mmol, 20.5 mL) was added, and the mixture was left for 2 min. The cooling bath was replaced by an ice bath, which was left for a further 2 min before being left to stir at rt for 1 h. Volatile materials were distilled off under a vacuum of 133 mbar and collected in a cold trap. The collected liquid was purified via vacuum distillation affording product **S1** as a colourless liquid (21.6 g, 108 mmol, 78 %).

^{1}H NMR (400 MHz, Chloroform-d) δ = 6.85 (t, *J* = 68.0 Hz, 1H). **^{19}F NMR (376 MHz, Chloroform-d) δ** = -74.60 (s), -82.17 (d, *J* = 68.2 Hz).

The characterization data agree with literature values.[1]

2.2 Synthesis of 2-((difluoromethyl)thio)benzo[*d*]thiazole (S2)

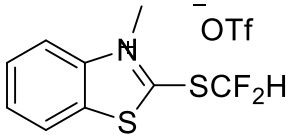


In a 100 mL vial equipped with magnetic stirrer, benzo[*d*]thiazole-2-thiol was placed (1.0 equiv., 29 mmol, 4.9 g) and aqueous KOH (6 M , 58 mL) was added in acetonitrile (58 mL) and stirred rapidly at rt. Difluoromethyl trifluoromethanesulfonate (1.5 equiv., 43.5 mmol, 5.1 mL) was added at once and the reaction mixture was stirred vigorously at rt for 2 mins. The reaction mixture was diluted with water (100 mL) and extracted with ether (3 x 50 mL). The combined organic layers were concentrated *in vacuo* to afford the product **S2**, which required no further purification (25 mmol, 5.43 g, 86 %).

^{1}H NMR (400 MHz, Chloroform-d) δ = 8.01 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.72 (t, *J* = 56.3 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H). **^{19}F NMR (376 MHz, Chloroform-d) δ** = -93.08 (d, *J* = 55.5 Hz).

The characterization data agree with literature values.[2]

2.3 Synthesis of BT-SCF_2H



Methyl triflate (3.0 equiv., 75 mmol, 8.2 mL) was added dropwise to a flame dried Schlenk flask with dry CH_2Cl_2 (0.1 M) and benzothiazole **S2** (1.0 equiv., 25 mmol, 5.42 g). The reaction mixture was stirred at rt for 19 h and was

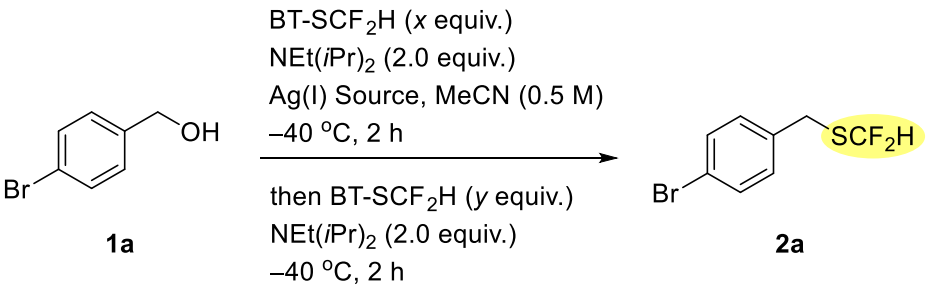
then precipitated with diethyl ether. The solid was filtered off and washed with diethyl ether (3 x 20 mL). After drying *in vacuo*, BT-SCF_2H (9.60 g, 24.0 mmol, 95 %) was obtained as off-yellow solid.

^{1}H NMR (400 MHz, Acetonitrile-d_3): δ = 8.28 (d, *J* = 8.3 Hz, 1H), 8.13 (d, *J* = 8.6 Hz, 1H), 7.95 (t, *J* = 7.9 Hz, 1H), 7.86 (t, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 53.4 Hz, 1H), 4.26 (s, 3H). **^{13}C NMR (126 MHz, Acetonitrile-d_3): δ** = 166.54, 143.28, 132.48, 131.67, 130.59, 124.92, 119.48 (t, *J* = 284.3, 283.5 Hz), 118.40, 39.50. **^{19}F NMR (376 MHz, Acetonitrile-d_3) δ** = -79.28 (s), -91.53 (d, *J* = 53.9 Hz).

The characterization data agree with literature values.[3]

3 Optimization of the Deoxydifluoromethylthiolation of Alcohols with BT-SCF_2H

3.1 Optimization Tables

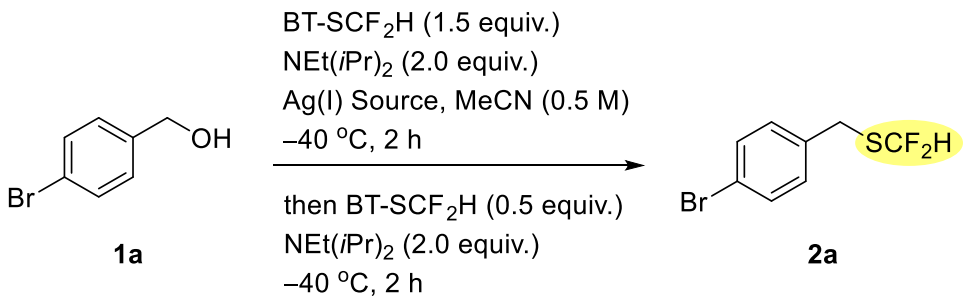


1a **2a**

Entry[a]	Ligand	Equiv. of first portion of BT-SCF_2H (*x*)	Equiv. of second portion of BT-SCF_2H (y)	Equiv. of AgOTf	Other changes from standard conditions	NMR yield of 2a[b]
1	---	1.2	0.3	0	---	---
2	---	1.2	0.3	0.1	---	30%
3	---	---	---	0.1	Slow BT-SCF_2H addition (0.1 equiv. every 15 min total 1.5 equiv.)	35%
4	Phen	1.2	0.3	0.1	---	15%
5	Phen	1.2	0.3	0.1	With precoordination	15%
6	Bpy	1.2	0.3	0.1	---	22%
7	Bpy	1.2	0.3	0.1	With precoordination	27%
8	---	1.2	0.3	0.4	---	43%
9	---	1.2	0.3	0.5	---	61%
10	---	1.5	0	0.5	---	55%
11	---	1.2	0.3	0.5	[M] = 0.25 M	57%
12	---	1.2	0.3	0.7	---	58%
13	---	1.2	0.3	1	---	37%
14	---	1.2	0.3	1	[M] = 0.25 M	45%
15	---	1.2	0.3	1	[M] = 0.125 M	32%
16	---	1.5	0.5	0.5	---	70%
17	---	1.5	0.5	0.5	Slow NEt(*i*Pr)$_2$ addition (0.5 equiv. every 30 min)	65%
18	---	2	0	0.5	slow NEt(*i*Pr)$_2$ addition (0.5 equiv. every 30 min)	59%
19	---	2	0.5	0.5	---	69%
20	---	2.5	0.5	0.5	---	57%

Table S1. Optimization of the Deoxydifluoromethylthiolation of (4-bromophenyl)methanol **1a** with BT-SCF_2H. [a] Conditions, **1a** (0.2 mmol), BT-SCF_2H (*x* equiv.), NEt(*i*Pr)$_2$ (2.0 equiv.) in MeCN (0.5 M), −40 °C, 2 h then additional BT-SCF_2H (*y* equiv.), NEt(*i*Pr)$_2$ (2.0 equiv.) added, −40 °C, 2 h. [b] ^1H NMR with CH_2Br_2 as internal reference. Phen = 1,10-phenanthroline. Bpy = 2,2'-bipyridine.

Silver Salt Optimization



1a **2a**

Entry[a]	Ag(I) Source	Equiv. of Ag(I) Source	Yield of 2a[b]
1	AgOTf	0.2	40%
2	SIPrAgCl	0.2	30%
3	SIPrAgBr	0.2	34%
4	SIPrAgOTf	0.2	55%
5	SIPrAgOTf	0.1	37%
6	SIPrAgOTf	0.05	24%

Table S2. Evaluation of SIPr-coordinated silver(I) complexes. [a] Conditions, **1a** (0.2 mmol), BT-SCF_2H (1.5 equiv.), NEt(*i*Pr)$_2$ (2.0 equiv.) in MeCN (0.5 M), −40 °C, 2 h then additional BT-SCF_2H (0.5 equiv.), NEt(*i*Pr)$_2$ (2.0 equiv.) added, −40 °C, 2 h. [b] ^1H NMR with CH_2Br_2 as internal reference. SIPr = 1,3-Bis-(2,6-diisopropylphenyl)imidazolinylidene.

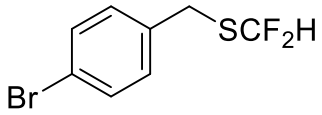
4 Scope and Limitations of the Deoxydifluoromethylthiolation of Alcohols (1)

4.1 General Procedure for the Deoxytrifluoromethylthiolation of Alcohols (1)

General procedure: BT-SCF_2H (1.5 equiv.), silver triflate (0.5 equiv.) and the alcohol (**1**, 1.0 equiv., 0.4 mmol) were added to dry MeCN (0.5 M) under argon. $NEt(iPr)_2$ (2.0 equiv.) was then added, and the reaction mixture was stirred for 2 h at −40 °C. Additional BT-SCF_2H (0.5 equiv.) and $NEt(iPr)_2$ (2.0 equiv.) were then added, and the reaction mixture was stirred for a further 2 h. The solids were subsequently filtered off, the solvent was removed under reduced pressure and the difluoromethylthioethers **2** were finally isolated using flash column chromatography over silica gel.

4.2 Characterization Data for the Deoxydifluoromethylthiolation Products (2)

(4-bromobenzyl)(difluoromethyl)sulfane (2a)

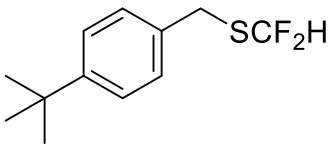


According to the general procedure, thioether **2a** (63 mg, 62%) was obtained from (4-bromophenyl)methanol **1a** on a 0.4 mmol scale after flash column chromatography (pentane) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.47 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 6.74 (t, *J* = 56.3 Hz, 1H), 3.97 (s, 2H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -94.03 (d, *J* = 56.0 Hz). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 135.61, 132.05, 130.70, 121.74, 120.15 (t, *J* = 274.1, 272.9 Hz), 31.11 (t, *J* = 3.6 Hz).

The characterization data agree with the literature values.[4]

(4-(*tert*-butyl)benzyl)(difluoromethyl)sulfane (2b)

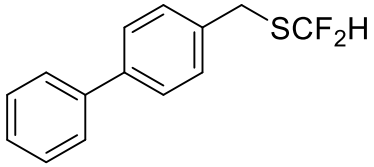


According to the general procedure, thioether **2b** (76 mg, 82%) was obtained from (4-(*tert*-butyl)phenyl)methanol **1b** on a 0.4 mmol scale after flash column chromatography (pentane) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.38 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 6.75 (t, *J* = 56.7 Hz, 1H), 4.02 (s, 2H), 1.34 (s, 9H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -94.37 (d, *J* = 57.1 Hz). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 150.83, 133.18, 128.73, 125.89, 120.48 (t, *J* = 272.5 Hz), 34.68, 31.51 (t, *J* = 3.9 Hz), 31.43.

The characterization data agree with the literature values.[4]

([1,1'-biphenyl]-4-ylmethyl)(difluoromethyl)sulfane (2c)

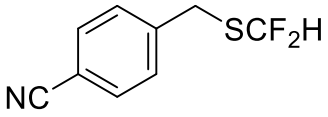


According to the general procedure, thioether **2c** (70 mg, 70%) was obtained from [1,1'-biphenyl]-4-ylmethanol **1c** on a 0.4 mmol scale after flash column chromatography (pentane / EtOAc 100:1) as a yellow solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.59 (t, *J* = 8.4 Hz, 4H), 7.50 – 7.41 (m, 4H), 7.37 (t, *J* = 7.4 Hz, 1H), 6.79 (t, *J* = 56.6 Hz, 1H), 4.08 (s, 2H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -94.13 (d, *J* = 57.0 Hz). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 140.77, 140.66, 135.40, 129.47, 128.96, 127.66, 127.59, 127.20, 120.38 (t, *J* = 273.0 Hz), 31.56 (t, *J* = 3.7 Hz).

The characterization data agree with the literature values.[4]

4-(((difluoromethyl)thio)methyl)benzonitrile (2d)

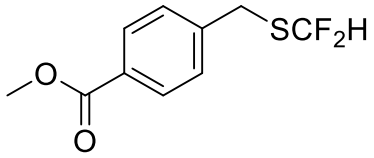


According to the general procedure, thioether **2d** (38 mg, 48%) was obtained from 4-(hydroxymethyl)benzonitrile **1d** on a 0.4 mmol scale after flash column chromatography (pentane/ EtOAc 40:1) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.63 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 8.3 Hz, 2H), 6.77 (t, *J* = 55.9 Hz, 1H), 4.05 (s, 2H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -93.64 (d, *J* = 55.6 Hz). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 142.41, 132.65, 129.74, 119.86 (t, *J* = 274.9, 273.9 Hz), 118.62, 111.65, 31.12 (t, *J* = 3.9 Hz).

The characterization data agree with the literature values.[4]

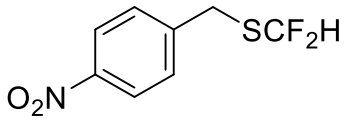
methyl 4-(((difluoromethyl)thio)methyl)benzoate (2e)



According to the general procedure, thioether **2e** (41 mg, 44%) was obtained from methyl 4-(hydroxymethyl)benzoate **1e** on a 0.4 mmol scale after flash column chromatography (pentane / EtOAc 100:1) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.01 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.3 Hz, 2H), 6.75 (t, *J* = 56.2 Hz, 1H), 4.05 (s, 2H), 3.91 (s, 3H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -93.99 (d, *J* = 55.8 Hz). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 166.80, 141.84, 130.20, 129.64, 129.04, 120.09 (t, *J* = 273.6 Hz), 52.30, 31.39 (t, *J* = 3.7 Hz). **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] =2954, 1716, 1611, 1436, 1276, 1179, 1105, 1018, 761, 712. **HRMS (ESI)**: m/z calculated for $[C_{10}H_{11}O_2SF_2]^+$ ($[M+H]^+$): 233.0448, measured: 233.0447.

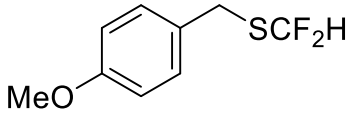
(difluoromethyl)(4-nitrobenzyl)sulfane (2f)



According to the general procedure, thioether **2f** (26 mg, 30%) was obtained from (4-nitrophenyl)methanol **1f** on a 0.4 mmol scale after flash column chromatography (pentane / EtOAc 100:1) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.20 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 8.7 Hz, 2H), 6.79 (t, *J* = 55.8 Hz, 1H), 4.10 (s, 2H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -93.56 (d, *J* = 55.7 Hz). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 147.50, 144.50, 129.91, 124.14, 119.83 (t, *J* = 274.5 Hz), 30.81 (t, *J* = 4.1 Hz). **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 1600, 1517, 1344, 1057, 1015, 858, 750, 706. **HRMS (EI)**: m/z calculated for $[C_8H_7NO_2SF_2]^+$ ($[M]^+$): 219.0166, measured: 219.0163.

(difluoromethyl)(4-methoxybenzyl)sulfane (2g)

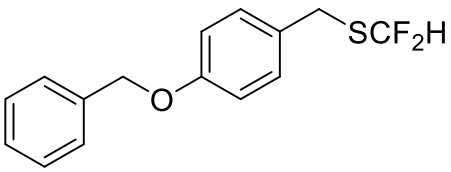


According to the general procedure, thioether **2g** (18 mg, 22%) was obtained from (4-methoxyphenyl)methanol **1g** on a 0.4 mmol scale after flash column chromatography (pentane / EtOAc 100:1) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.27 (d, *J* = 6.9 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.72 (t, *J* = 56.6 Hz, 1H), 3.99 (s, 2H), 3.80 (s, 3H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -94.36 (d, *J* = 55.7 Hz). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 159.24, 130.22, 128.20, 120.50 (t, *J* = 272.7 Hz), 114.34, 55.44, 31.42 (t, *J* = 3.7 Hz).

The characterization data agree with the literature values.[4]

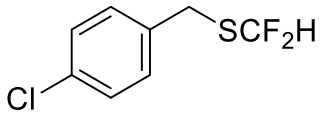
(4-(benzyloxy)benzyl)(difluoromethyl)sulfane (2h)



According to the general procedure, thioether **2h** (55 mg, 73%) was obtained from (4-(benzyloxy)phenyl)methanol **1h** on a 0.4 mmol scale after flash column chromatography (pentane) as a yellow solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.44 (d, *J* = 7.0 Hz, 2H), 7.40 (t, *J* = 7.3 Hz, 2H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.28 (d, *J* = 8.6 Hz, 2H), 6.95 (d, *J* = 8.6 Hz, 2H), 6.73 (t, *J* = 56.6 Hz, 1H), 5.07 (s, 2H), 3.99 (s, 2H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -94.29 (d, *J* = 56.2 Hz). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 158.43, 136.96, 130.23, 128.75, 128.48, 128.17, 127.60, 120.48 (t, *J* = 272.7 Hz), 115.26, 70.18, 31.39 (t, *J* = 3.6 Hz). **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 1606, 1583, 1511, 1454, 1388, 1319, 1299, 1237, 1179, 1055, 1008, 839, 786, 738, 695. **HRMS (EI)**: m/z calculated for $[C_{15}H_{14}OSF_2]^+$ ($[M]^+$):280.0733, measured: 280.0737.

(4-chlorobenzyl)(difluoromethyl)sulfane (2i)

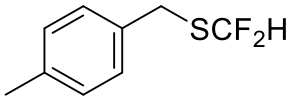


According to the general procedure, thioether **2i** (46 mg, 55%) was obtained from (4-chlorophenyl)methanol **1i** on a 0.4 mmol scale after flash column chromatography (pentane) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.35 – 7.27 (m, 4H), 6.74 (t, *J* = 56.3 Hz, 1H), 3.99 (s, 2H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -94.08 (d, *J* = 55.2 Hz). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 135.08, 133.68, 130.38, 129.10, 120.17 (t, *J* = 273.4 Hz), 31.07 (t, *J* = 4.0 Hz).

The characterization data agree with the literature values.[4]

(difluoromethyl)(4-methylbenzyl)sulfane (2j)

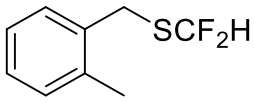


According to the general procedure, thioether **2j** (48 mg, 64%) was obtained from p-tolylmethanol **1j** on a 0.4 mmol scale after flash column chromatography (pentane) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.25 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 7.8 Hz, 2H), 6.73 (t, *J* = 56.7 Hz, 1H), 4.00 (s, 2H), 2.36 (s, 3H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -94.34 (d, *J* = 57.1 Hz). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 137.56, 133.24, 129.62, 128.93, 120.48 (t, *J* = 272.7 Hz), 31.66 (t, *J* = 3.6 Hz), 21.23.

The characterization data agree with the literature values.[4]

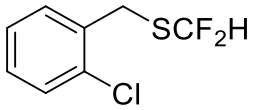
(difluoromethyl)(2-methylbenzyl)sulfane (2k)



According to the general procedure, thioether **2k** (55 mg, 73%) was obtained from *o*-tolylmethanol **1k** on a 0.4 mmol scale after flash column chromatography (pentane) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.28 (d, *J* = 7.3 Hz, 1H), 7.25 – 7.16 (m, 3H), 6.76 (t, *J* = 56.5 Hz, 1H), 4.06 (s, 2H), 2.42 (s, 3H).**^{19}F NMR (565 MHz, $CDCl_3$) δ** = -94.31 (d, *J* = 56.5 Hz).**^{13}C NMR (151 MHz, $CDCl_3$) δ** = 137.00, 133.89, 130.93, 129.99, 128.20, 126.45, 120.49 (t, *J* = 272.7 Hz), 29.77 (t, *J* = 3.6 Hz), 19.18. **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 1494, 1463, 1322, 1246, 1015, 788, 755, 727, 676. **HRMS (EI)**: m/z calculated for $[C_9H_{10}SF_2]^+$ ($[M]^+$): 188.0471, measured: 188.0477.

(difluoromethyl)(2-chlorobenzyl)sulfane (2l)

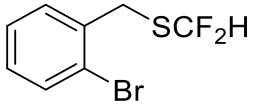


According to the standard methodology thioether **2l** (38 mg, 46%) was obtained from (2-chlorophenyl)methanol **1l** on a 0.4 mmol scale after flash column chromatography (petroleum ether 40-60) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.53 (d, *J* = 7.9, 1H), 7.36 (d, *J* = 7.6, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.10 (t, *J* = 7.6, 1H), 6.77 (t, *J* = 56.3, 1H), 4.09 (s, 2H). **^{19}F NMR (282 MHz, $CDCl_3$) δ** = -93.57 (d, *J* = 56.2 Hz). **^{13}C NMR (75 MHz, $CDCl_3$) δ** = 136.32, 133.24, 130.96, 129.41, 127.84, 124.52, 120.39 (t, *J* = 273.5 Hz), 32.21 (t, *J* = 3.8 Hz).

The characterization data agree with the literature values.[4]

(difluoromethyl)(2-bromobenzyl)sulfane (2m)

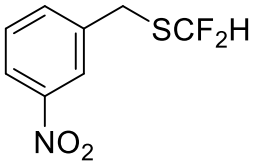


According to the standard methodology thioether **2m** (50 mg, 49%) was obtained from (2-bromophenyl)methanol **1m** on a 0.4 mmol scale after flash column chromatography (petroleum ether 40-60) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.41 – 7.35 (m, 2H), 7.31 – 7.15 (m, 2H), 6.80 (t, *J* = 56.4 Hz, 1H), 4.12 (s, 2H). **^{19}F NMR (282 MHz, $CDCl_3$) δ** = -93.82 (d, *J* = 56.3 Hz). **^{13}C NMR (75 MHz, $CDCl_3$) δ** = 134.70, 134.24, 130.98, 130.00, 129.28, 127.25, 120.44 (t, *J* = 273.4 Hz), 29.57 (t, *J* = 3.9 Hz).

The characterization data agree with the literature values.[5]

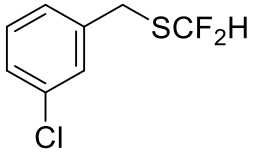
(difluoromethyl)(3-nitrobenzyl)sulfane (2n)



According to the general procedure, thioether **2n** (36 mg, 41%) was obtained from (3-nitrophenyl)methanol **1n** on a 0.4 mmol scale after flash column chromatography (pentane / EtOAc 125:1) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.24 (s, 1H), 8.15 (d, *J* = 8.3 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.9 Hz, 1H), 6.80 (t, *J* = 55.8 Hz, 1H), 4.12 (s, 2H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -93.53 (d, *J* = 55.2 Hz). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 148.59, 139.15, 135.07, 129.91, 123.95, 122.83, 119.86 (t, *J* = 274.3 Hz), 30.75 (t, *J* = 4.0 Hz). **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 1525, 1350, 1317, 1057, 1017, 906, 809, 740, 704. **HRMS (EI)**: m/z calculated for $[C_8H_7NO_2SF_2]^+$ ($[M]^+$): 219.0166, measured: 219.0171.

(difluoromethyl)(3-chlorobenzyl)sulfane (2o)

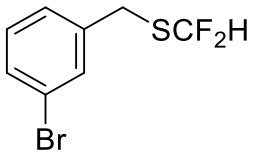


According to the standard methodology thioether **2o** (41 mg, 76%) was obtained from (3-chlorohenyl)methanol **1o** on a 0.4 mmol scale after flash column chromatography (petroleum ether 40-60) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ =7.34 (s, 1H), 7.28 – 7.19 (m, 3H), 6.74 (t, *J* = 56.3 Hz, 1H), 3.97 (s, 1H). **^{19}F NMR (282 MHz, $CDCl_3$) δ** = -94.15 (d, *J* = 56.4 Hz). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 138.61, 134.69, 130.15, 129.12, 128.00, 127.17, 120.10 (t, *J* = 273.5 Hz), 31.14 (t, *J* = 3.8 Hz).

The characterization data agree with the literature values.[6]

(difluoromethyl)(3-bromobenzyl)sulfane (2p)

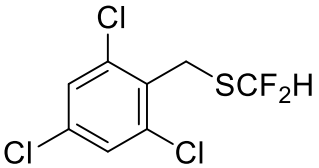


According to the standard methodology thioether **2p** (42 mg, 41%) was obtained from (3-bromophenyl)methanol **1p** on a 0.4 mmol scale after flash column chromatography (petroleum ether 40-60) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.49 (s, 1H), 7.39 (s, 1H), 7.23 (m, 2H), 6.74 (t, *J* = 56.3 Hz, 1H), 3.94 (s, 2H). **^{19}F NMR (282 MHz, $CDCl_3$) δ** = -93.95 (d, *J* = 55.6 Hz). **^{13}C NMR (75 MHz, $CDCl_3$) δ** = 138.94, 131.98, 130.89, 130.43, 127.65, 122.80, 120.21 (t, *J* = 270.4 Hz), 31.10 (t, *J* = 4.2 Hz).

The characterization data agree with the literature values.[7]

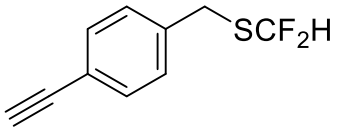
(difluoromethyl)(2,4,6-trichlorobenzyl)sulfane (2q)



According to the general procedure, thioether **2q** (74 mg, 67%) was obtained from (2,4,6-trichlorophenyl)methanol **1q** on a 0.4 mmol scale after flash column chromatography (pentane) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.36 – 7.35 (m, 2H), 6.93 (t, *J* = 56.2 Hz, 1H), 4.27 (s, 2H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -92.75 (d, *J* = 55.7 Hz).**^{13}C NMR (151 MHz, $CDCl_3$) δ** = 136.16, 134.49, 132.18, 128.66, 120.28 (t, *J* = 274.0 Hz), 27.00 (t, *J* = 3.8 Hz). **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 1579, 1549, 1440, 1375, 1320, 1071, 1059, 1027, 855, 786, 741, 657, 561. **HRMS (EI)**: m/z calculated for $[C_8H_5Cl_3SF_2]^+$ ([M]$^+$): 275.9146, measured: 275.9149.

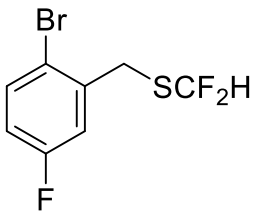
(difluoromethyl)(4-ethynylbenzyl)sulfane (2r)



According to the general procedure, thioether **2r** (43 mg, 54%) was obtained from (4-ethynylphenyl)methanol **1r** on a 0.4 mmol scale after flash column chromatography (pentane / DCM 50:1) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.47 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 6.74 (t, *J* = 56.3 Hz, 1H), 4.01 (s, 2H), 3.09 (s, 1H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -94.08 (d, *J* = 55.6 Hz). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 137.34, 132.65, 129.02, 121.62, 120.18 (t, *J* = 273.5 Hz), 83.29, 77.82, 31.52 (t, *J* = 3.8 Hz). **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3295, 2108, 1508, 1411, 1322, 1247, 1018, 826, 777, 619. **HRMS (EI)**: m/z calculated for $[C_{10}H_8SF_2]^+$ ([M]$^+$): 198.0315, measured: 198.0319.

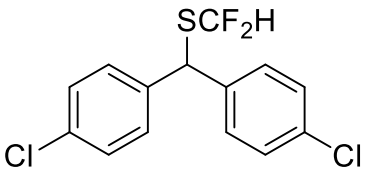
(2-bromo-5-fluorobenzyl)(difluoromethyl)sulfane (2s)



According to the general procedure, thioether **2s** (44 mg, 41%) was obtained from (2-bromo-5-fluorophenyl)methanol **1s** on a 0.4 mmol scale after flash column chromatography (pentane) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.53 (dd, *J* = 8.8, 5.3 Hz, 1H), 7.17 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.95 – 6.85 (m, 1H), 6.83 (t, *J* = 56.3 Hz, 1H), 4.10 (s, 2H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -93.40 (d, *J* = 56.9 Hz, 2F), -113.76 – -113.86 (m, 1F). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 162.01 (d, *J* = 248.0 Hz), 138.61 (d, *J* = 7.4 Hz), 134.45 (d, *J* = 8.2 Hz), 120.14 (t, *J* = 274.5 Hz), 118.62 (d, *J* = 3.5 Hz), 118.02 (d, *J* = 23.4 Hz), 116.68 (d, *J* = 22.4 Hz), 31.93 (t, *J* = 4.0 Hz). **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 1582, 1467, 1409, 1272, 1236, 1059, 1028, 958, 811, 761, 591. **HRMS (EI)**: m/z calculated for $[C_8H_6BrSF_3]^+$ ([M]$^+$): 269.9326, measured: 269.9331.

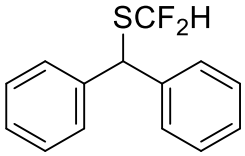
(bis(4-chlorophenyl)methyl)(difluoromethyl)sulfane (2t)



According to the general procedure, thioether **2t** (60 mg, 47%) was obtained from bis(4-chlorophenyl)methanol **1t** on a 0.4 mmol scale after flash column chromatography (pentane / DCM 100:1) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.32 (s, 8H), 6.59 (t, *J* = 56.8 Hz, 1H), 5.54 (s, 1H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -94.75 (d, *J* = 57.8 Hz).**^{13}C NMR (151 MHz, $CDCl_3$) δ** = 138.14, 134.04, 129.63, 129.24, 120.21 (t, *J* = 274.0 Hz), 50.06 (t, *J* = 2.7 Hz). **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 1489, 1404, 1302, 1089, 1065, 1030, 1013, 794, 771, 737, 676. **HRMS (EI)**: m/z calculated for $[C_{14}H_{10}Cl_2SF_2]^+$ ([M]$^+$): 317.9848, measured: 317.9842.

benzhydryl(difluoromethyl)sulfane (2u)

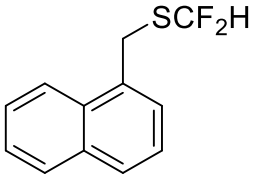


According to the general procedure, thioether **2u** (26 mg, 26%) was obtained from diphenylmethanol **1u** on a 0.4 mmol scale after flash column chromatography (pentane / DCM 100:1) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.43 (d, *J* = 7.5 Hz, 4H), 7.35 (t, *J* = 7.7 Hz, 4H), 7.28 (t, *J* = 7.3 Hz, 2H), 6.56 (t, *J* = 57.4 Hz, 1H), 5.58 (s, 2H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -95.29 (d, *J* = 57.3 Hz). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 139.93, 128.97, 128.33, 127.95, 120.79 (t, *J* = 272.9 Hz), 51.75 (t, *J* = 2.9 Hz).

The characterization data agree with the literature values.[8]

(difluoromethyl)(naphthalen-1-ylmethyl)sulfane (2v)

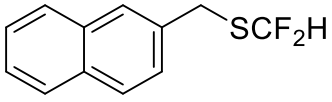


According to the general procedure, thioether **2v** (73 mg, 81%) was obtained from naphthalen-1-ylmethanol **1v** on a 0.4 mmol scale after flash column chromatography (pentane / DCM 50:1) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.09 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.62 – 7.58 (m, 1H), 7.55 – 7.52 (m, 1H), 7.50 (d, *J* = 6.9 Hz, 1H), 7.45 – 7.42 (m, 1H), 6.81 (t, *J* = 56.4 Hz, 1H), 4.51 (s, 2H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -94.47 (d, *J* = 56.8 Hz). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 134.17, 131.58, 131.36, 129.10, 129.02, 127.81, 126.70, 126.22, 125.49, 123.63, 120.54 (t, *J* = 273.0 Hz), 29.45 (t, *J* = 3.8 Hz).

The characterization data agree with the literature values.[4]

(difluoromethyl)(naphthalen-2-ylmethyl)sulfane (2w)

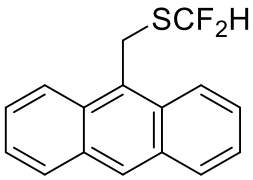


According to the general procedure, thioether **2w** (59 mg, 66%) was obtained from naphthalen-2-ylmethanol **1w** on a 0.4 mmol scale after flash column chromatography (pentane / DCM 50:1) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.91 – 7.80 (m, 3H), 7.79 (s, 1H), 7.54 – 7.47 (m, 3H), 6.77 (t, *J* = 56.6 Hz, 1H), 4.20 (s, 2H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -94.28 (d, *J* = 56.2 Hz). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 133.71, 133.41, 132.85, 128.88, 127.85, 127.77, 126.84, 126.58, 126.34, 120.41 (t, *J* = 273.0 Hz), 32.25 (t, *J* = 3.6 Hz).

The characterization data agree with the literature values.[4]

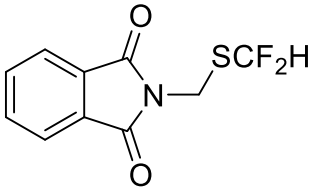
(anthracen-9-ylmethyl)(difluoromethyl)sulfane (2x)



According to the general procedure, thioether **2x** (46 mg, 42%) was obtained from anthracen-9-ylmethanol **1x** on a 0.4 mmol scale after flash column chromatography (pentane / DCM 50:1) as a yellow solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.45 (s, 1H), 8.30 (d, *J* = 8.9 Hz, 2H), 8.03 (d, *J* = 8.9 Hz, 2H), 7.63 – 7.58 (m, 2H), 7.53 – 7.49 (m, 2H), 6.93 (t, *J* = 55.9 Hz, 1H), 5.09 (s, 2H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -93.34 (d, *J* = 55.7 Hz). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 131.60, 130.17, 129.48, 128.48, 126.83, 125.84, 125.33, 123.68, 120.61 (t, *J* = 273.1 Hz), 23.85 (t, *J* = 4.0 Hz). **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3055, 1621, 1446, 1314, 1236, 1032, 997, 895, 770, 732, 704, 558. **HRMS (EI)**: m/z calculated for [C16H12SF2]+ ([M]+): 274.0628, measured: 274.0616.

2-(((difluoromethyl)thio)methyl)isoindoline-1,3-dione (2y)



According to the general procedure, thioether **2y** (60 mg, 47%) was obtained from 2-(hydroxymethyl)isoindoline-1,3-dione **1y** on a 0.4 mmol scale after flash column chromatography (pentane / EtOAc 50:1) as an orange solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.91 – 7.85 (m, 2H), 7.79 – 7.72 (m, 2H), 7.19 (t, *J* = 57.0 Hz, 1H), 4.97 (s, 2H). **^{19}F NMR (565 MHz, $CDCl_3$) δ** = -92.43 (d, *J* = 56.9 Hz). **^{13}C NMR (151 MHz, $CDCl_3$) δ** = 166.96, 134.66, 131.93, 123.91, 120.88 (t, *J* = 273.7 Hz), 35.26 (t, *J* = 4.3 Hz). **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 1778, 1708, 1611, 1465, 1410, 1380, 1275, 1070, 1022, 914, 837, 754, 718, 607. **HRMS (ESI)**: m/z calculated for $[C_{10}H_7NNaO_2SF_2]^+$ ($[M+Na]^+$): 266.0063, measured: 266.0059.

Literature

[1] V. V. Levin, A. D. Dilman, P. A. Belyakov, M. I. Struchkova, V. A. Tartakovsky, *J. Fluor. Chem.*, **2009**, *130*, 667-670.

[2] V. P. Mehta, M. F. Greaney, *Org. Lett.*, **2013**, *15*, 5036-5039.

[3] M. Tironi, L. M. Maas, A. Garg, S. Dix, J. P. Götze, M. N. Hopkinson, *Org. Lett.*, **2020**, *22*, 8925-8930.

[4] T. Ding, L. Jiang, W. Yi, *Chem. Commun.*, **2020**, *56*, 3995-3998.

[5] J. L. Howard, C. Schotten, S. T. Alston, D. L. Browne, *Chem. Commun.*, **2016**, *52*, 8448-8451.

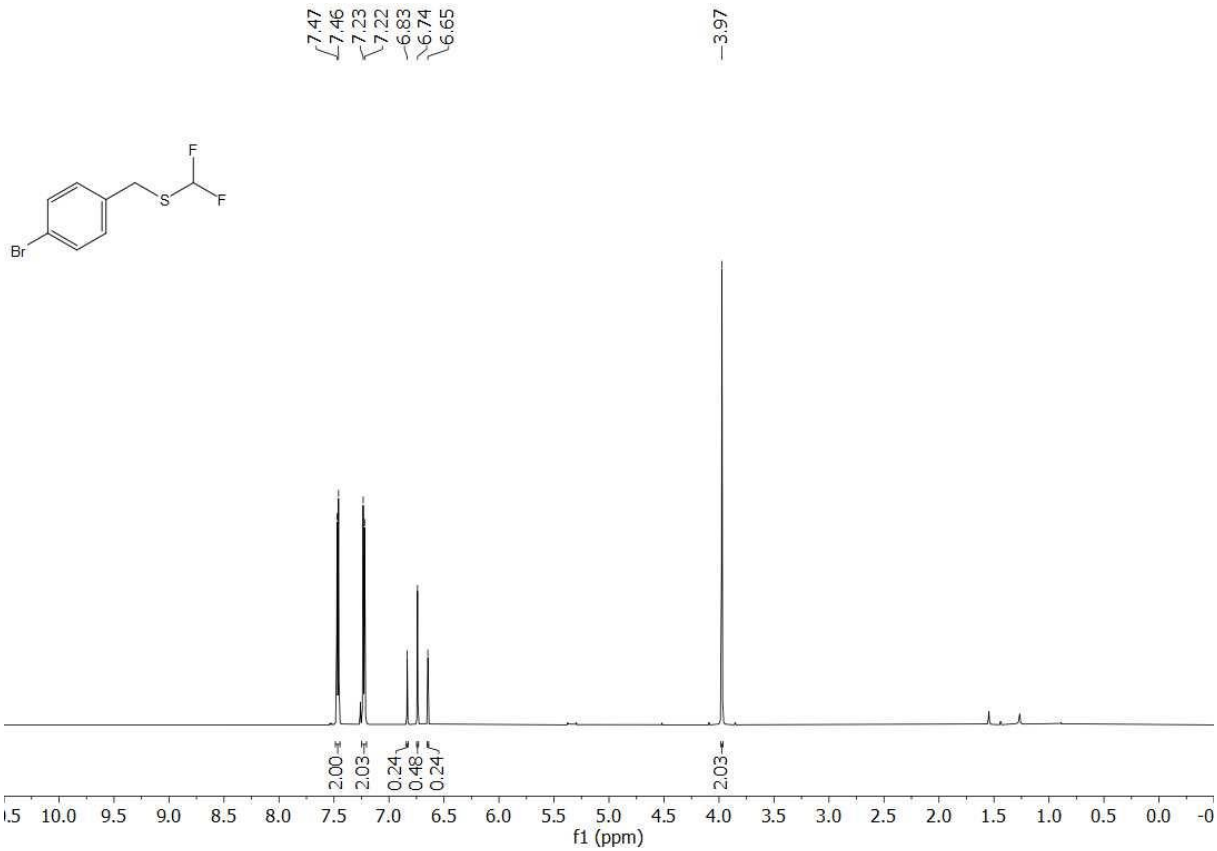
[6] D. Zhu, X. Shao, X. Hong, L. Lu, Q. Shen, *Angew. Chem. Int. Ed.*, **2016**, *55*, 15807-15811.

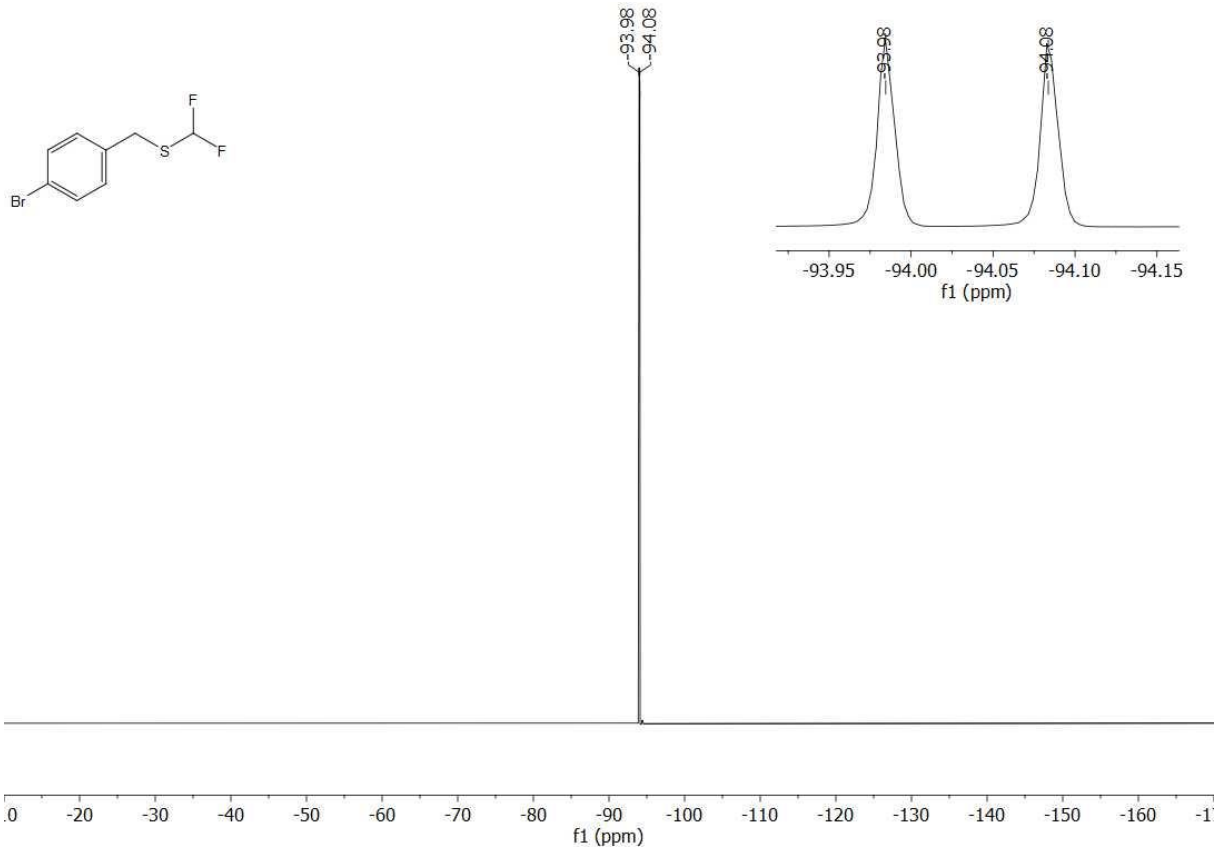
[7] G.-K. Liu, X. Li, W.-B. Qin, X.-S. Peng, H. N. C. Wong, L. Zhang, X. Zhang, *Chem. Commun.*, **2019**, *55*, 7446-7449.

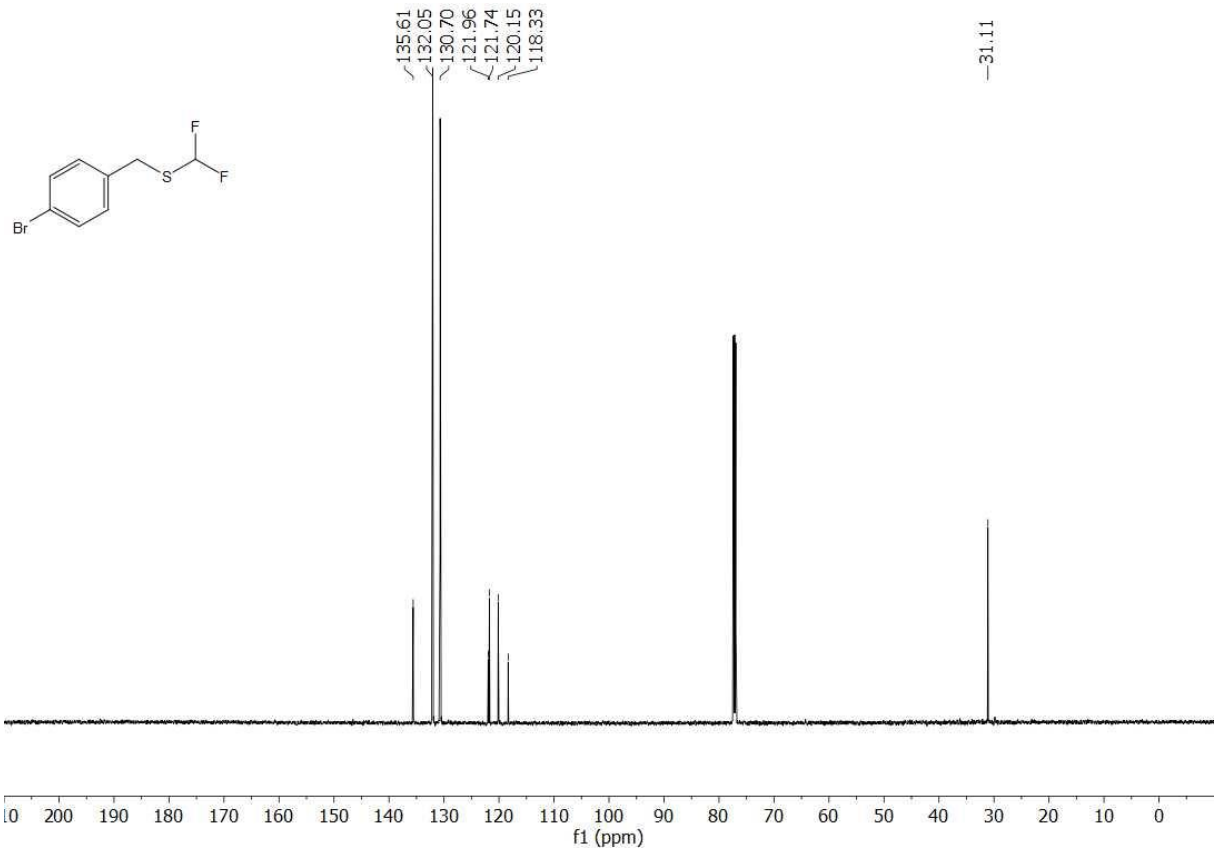
[8] M. Zhang, J.-H. Lin, J.-C. Xiao, *J. Org. Chem.*, **2021**, *86*, 13153-13159.

5 NMR Spectra

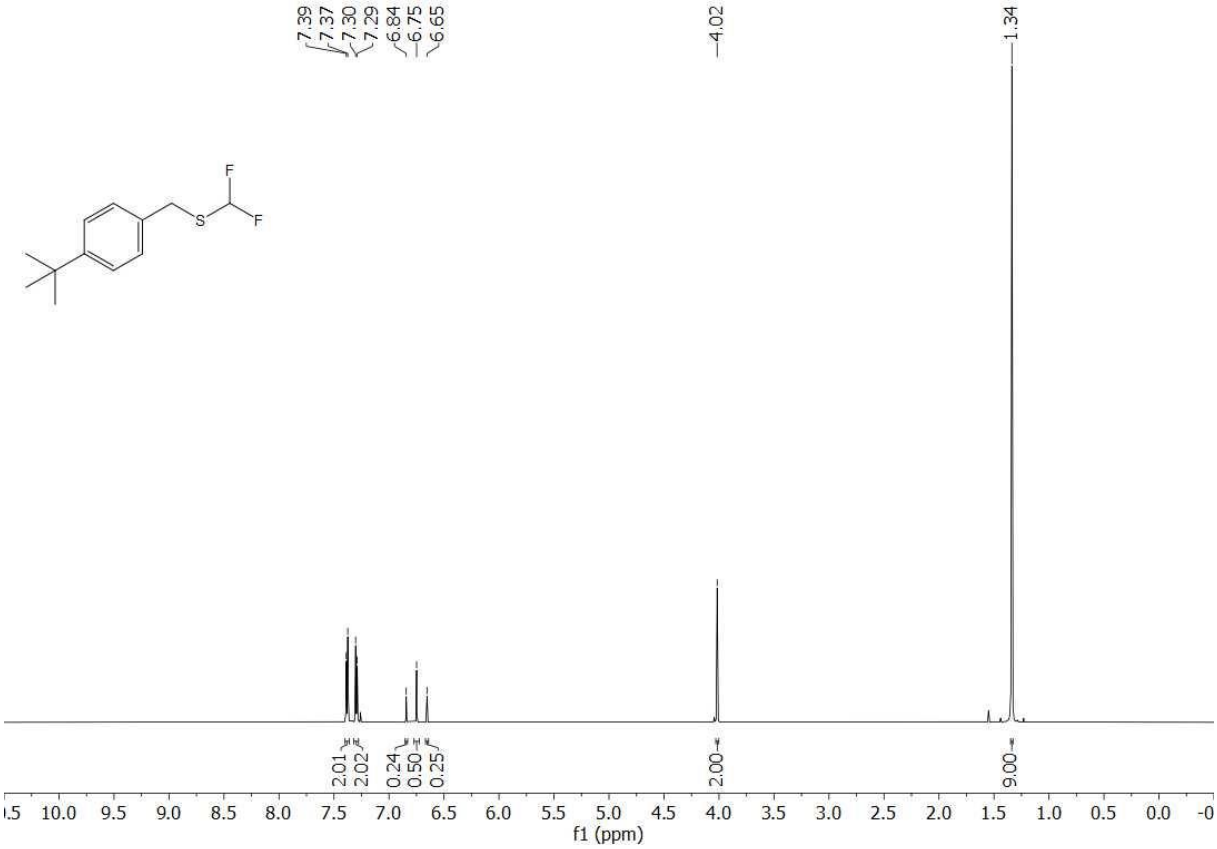
(4-bromobenzyl)(difluoromethyl)sulfane **2a**

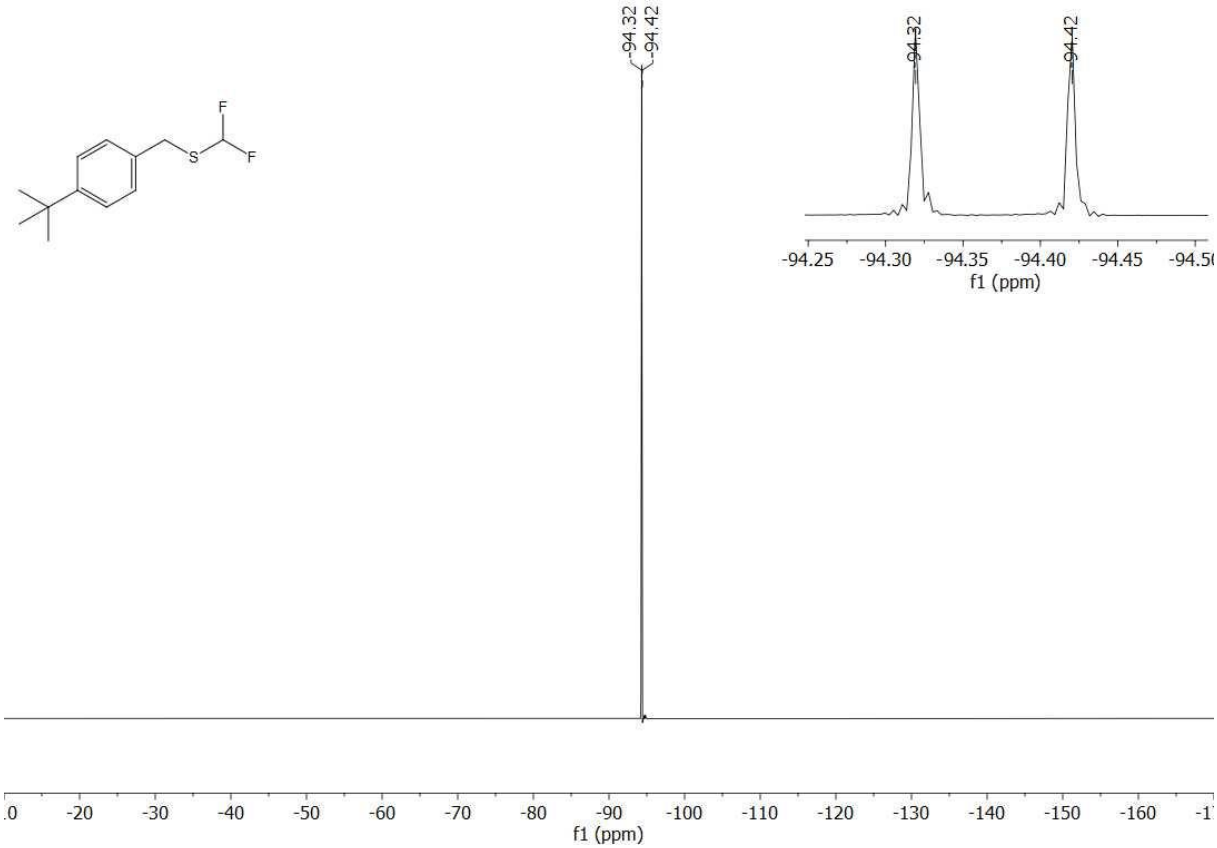


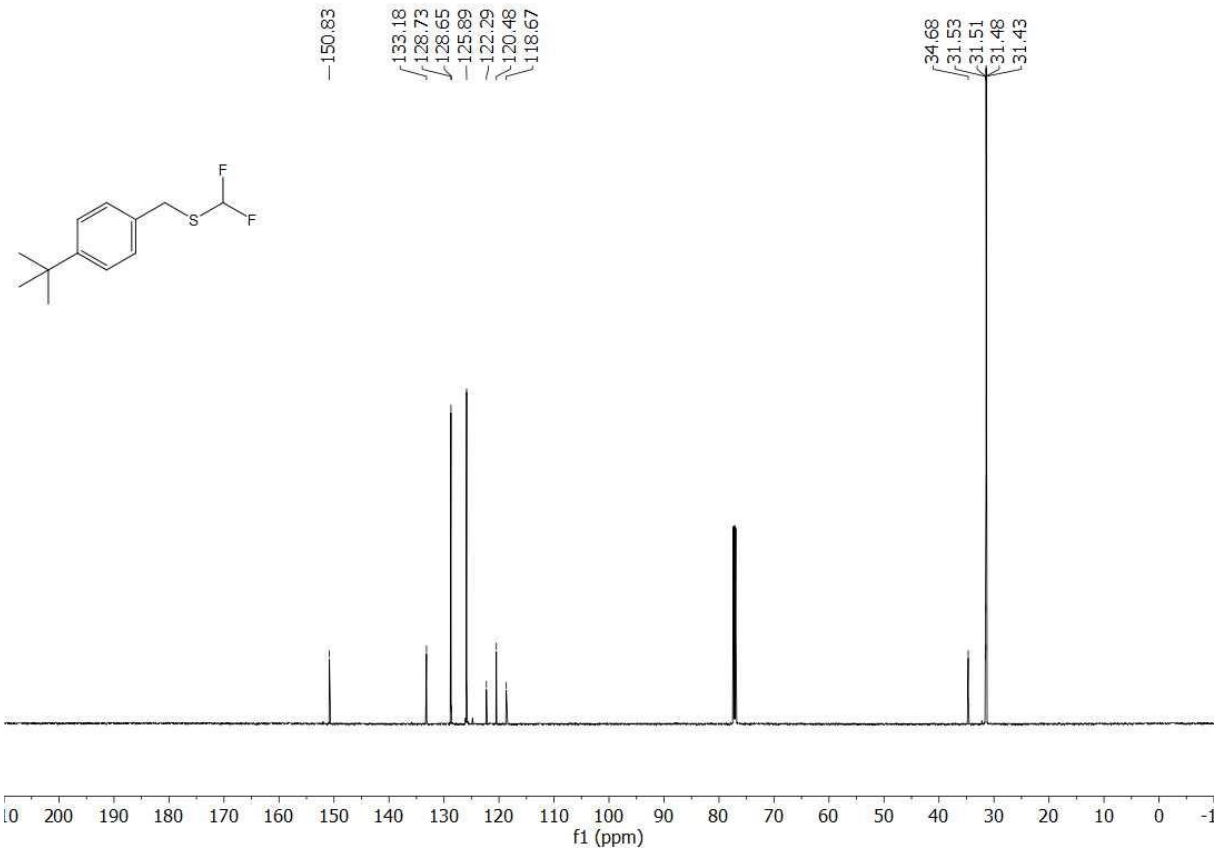



135.61
132.05
130.70
121.96
121.74
120.15
118.33
31.11
F
S
F
Br
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

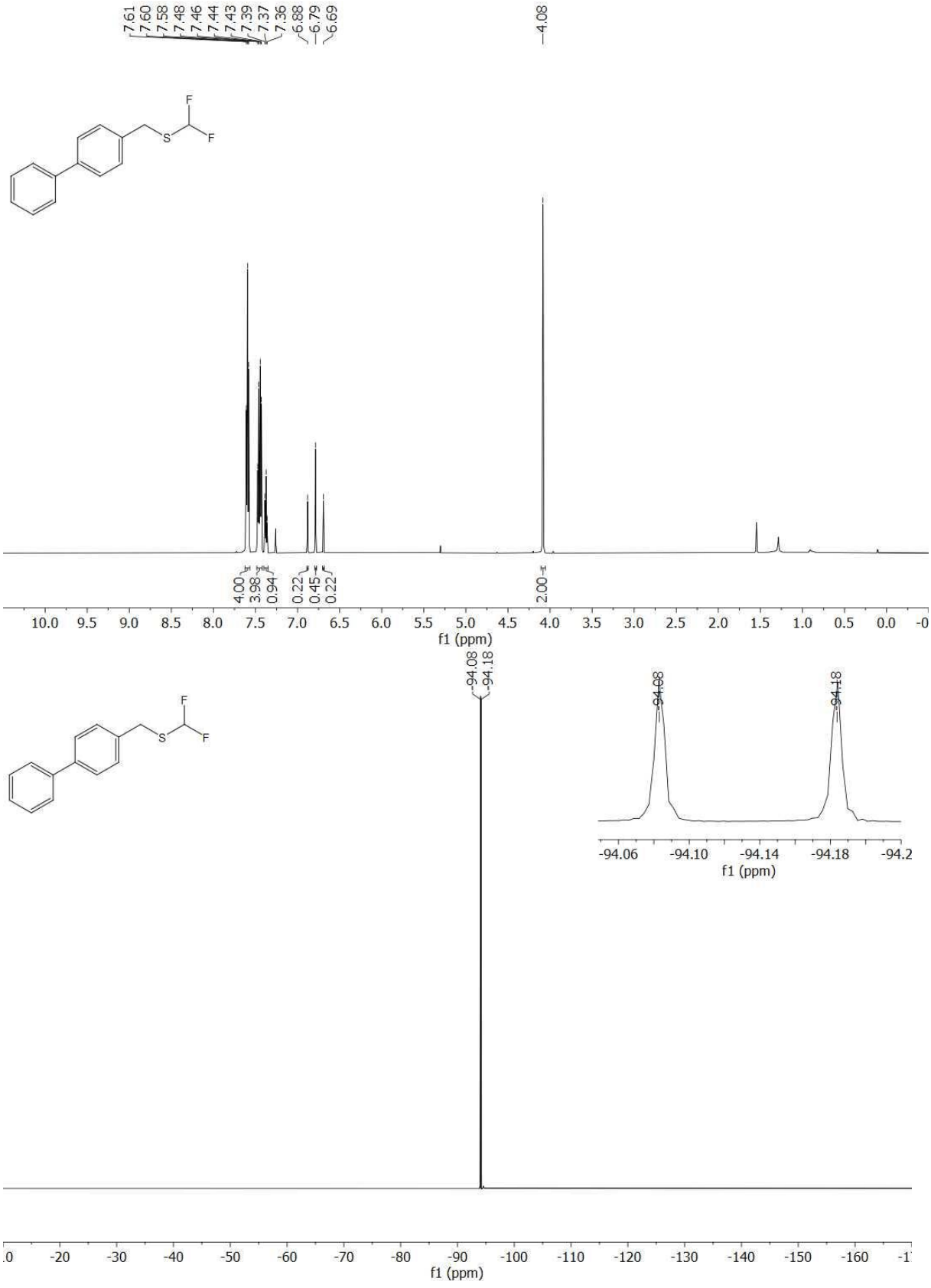
(4-(*tert*-butyl)benzyl)(difluoromethyl)sulfane **2b**

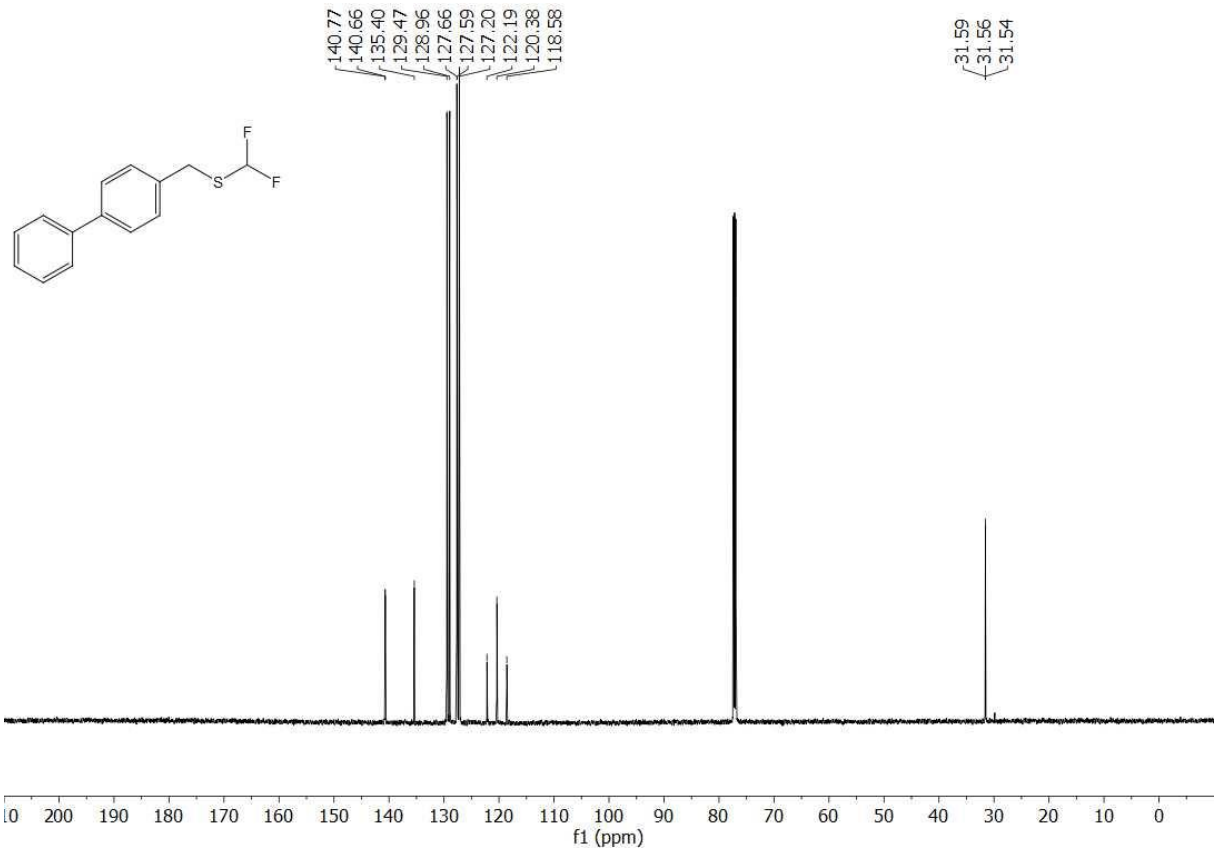




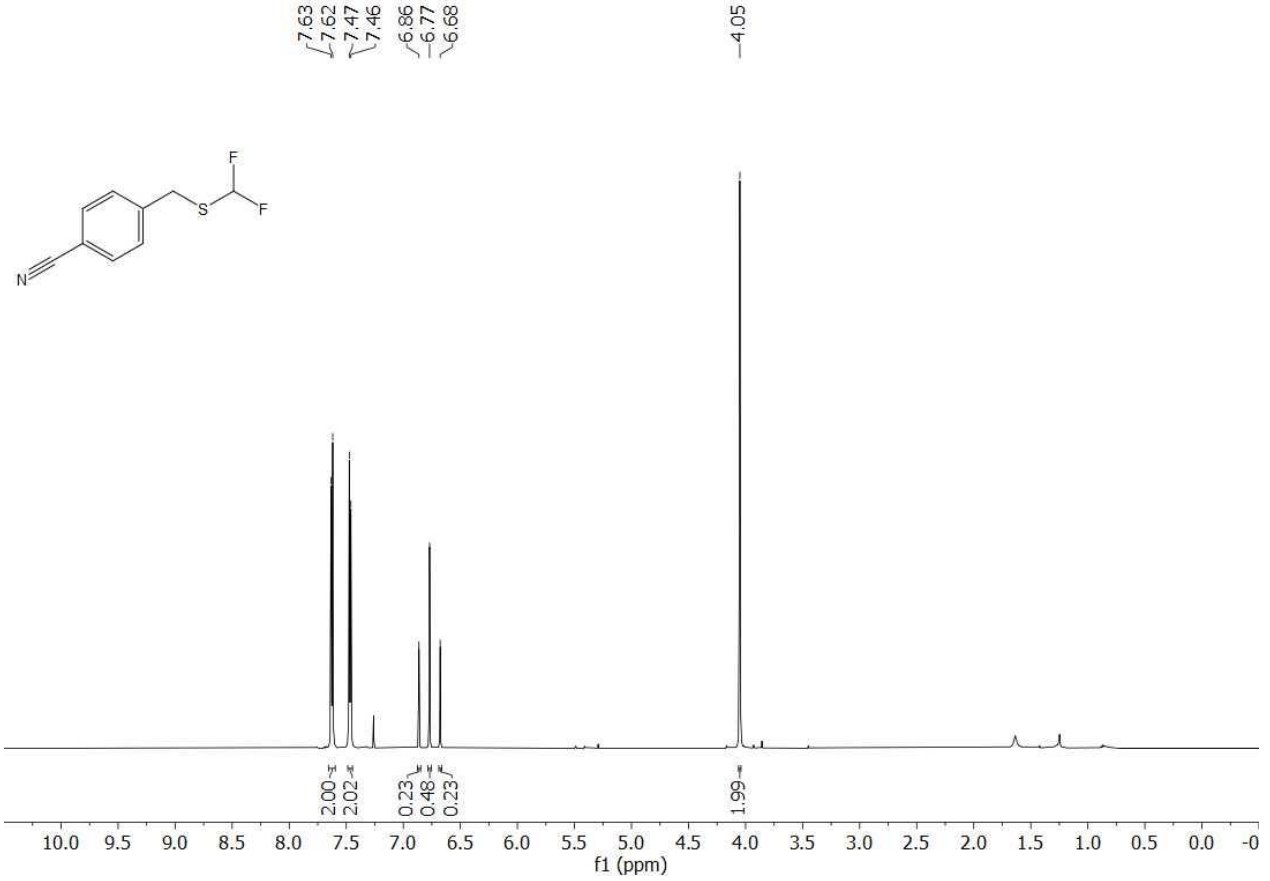

150.83
133.18
128.73
128.65
125.89
122.29
120.48
118.67
34.68
31.53
31.51
31.48
31.43
F
S
F
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

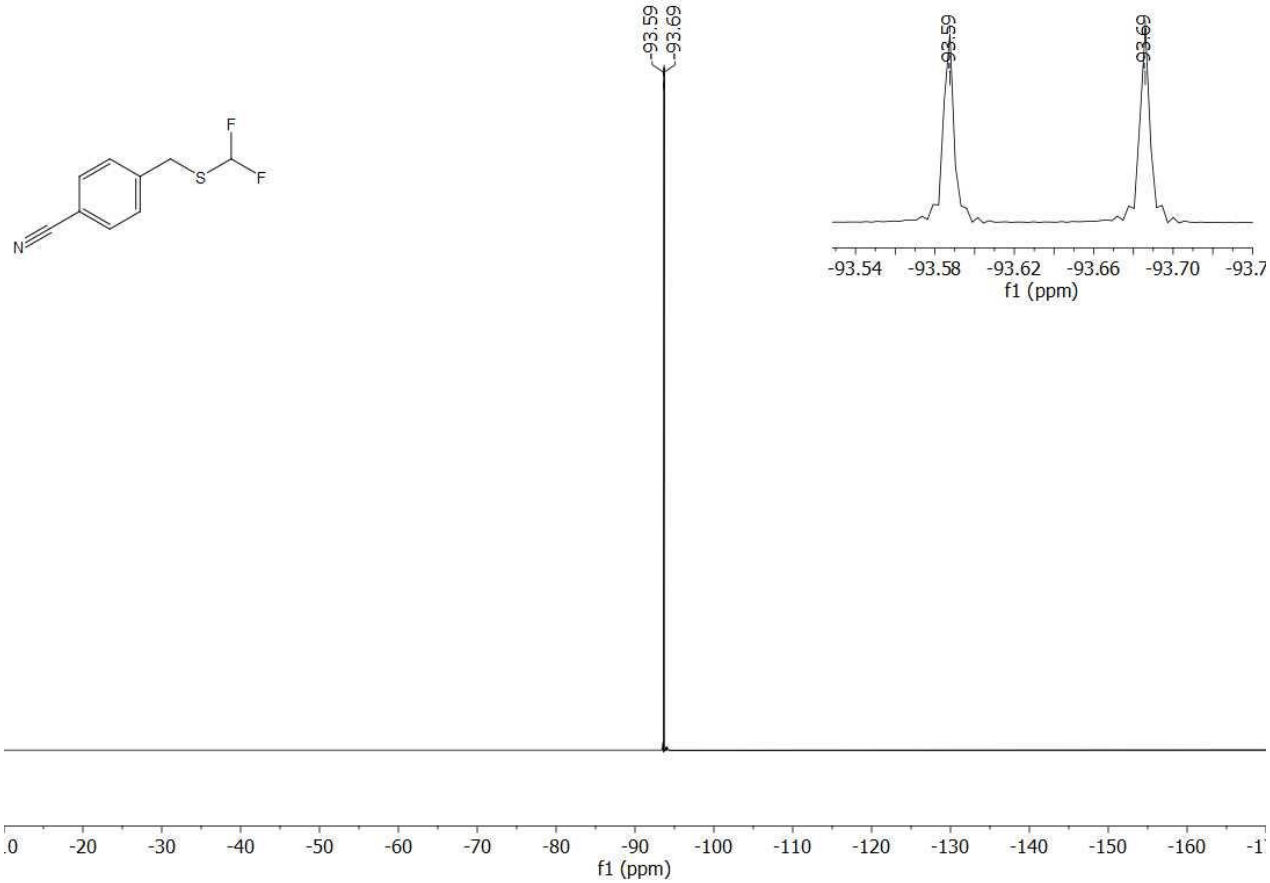
([1,1'-biphenyl]-4-ylmethyl)(difluoromethyl)sulfane **2c**

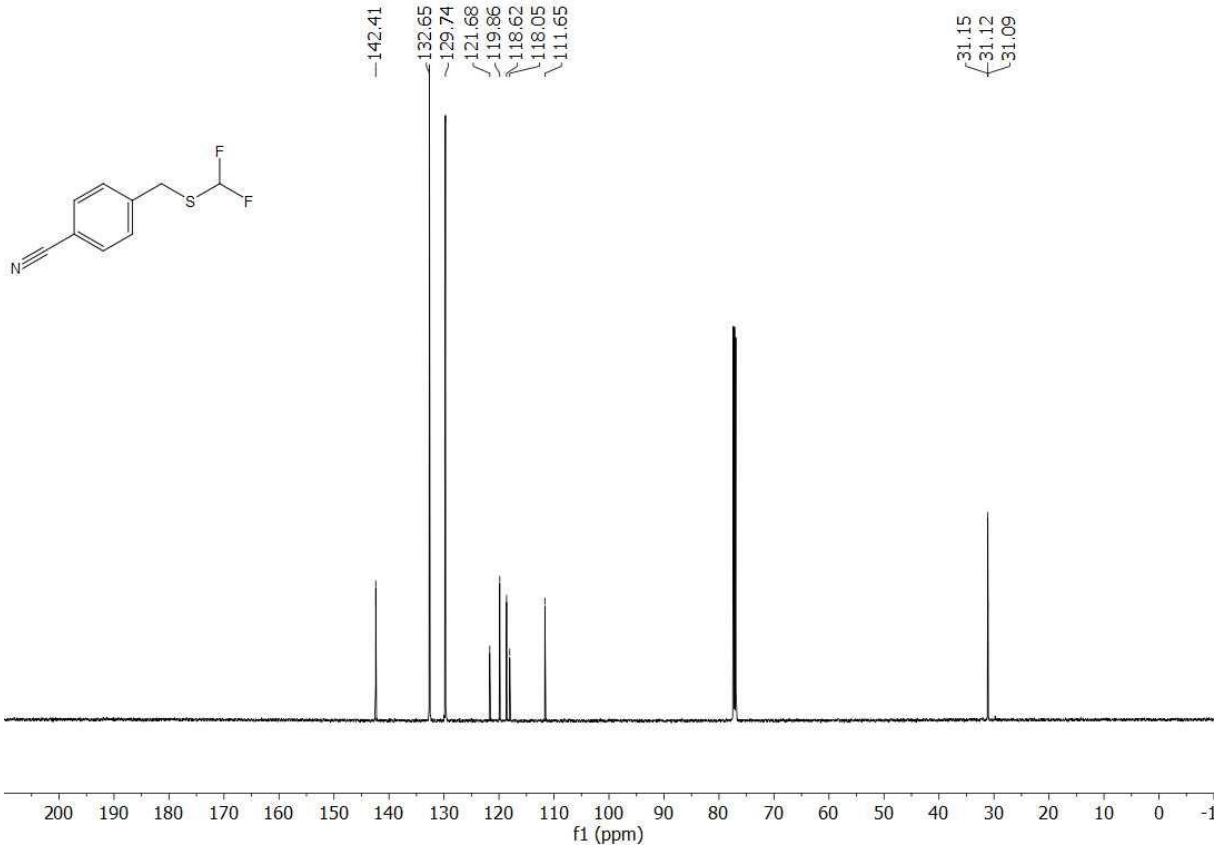



140.77
140.66
135.40
129.47
128.96
127.66
127.59
127.20
122.19
120.38
118.58
31.59
31.56
31.54
F
S
F
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

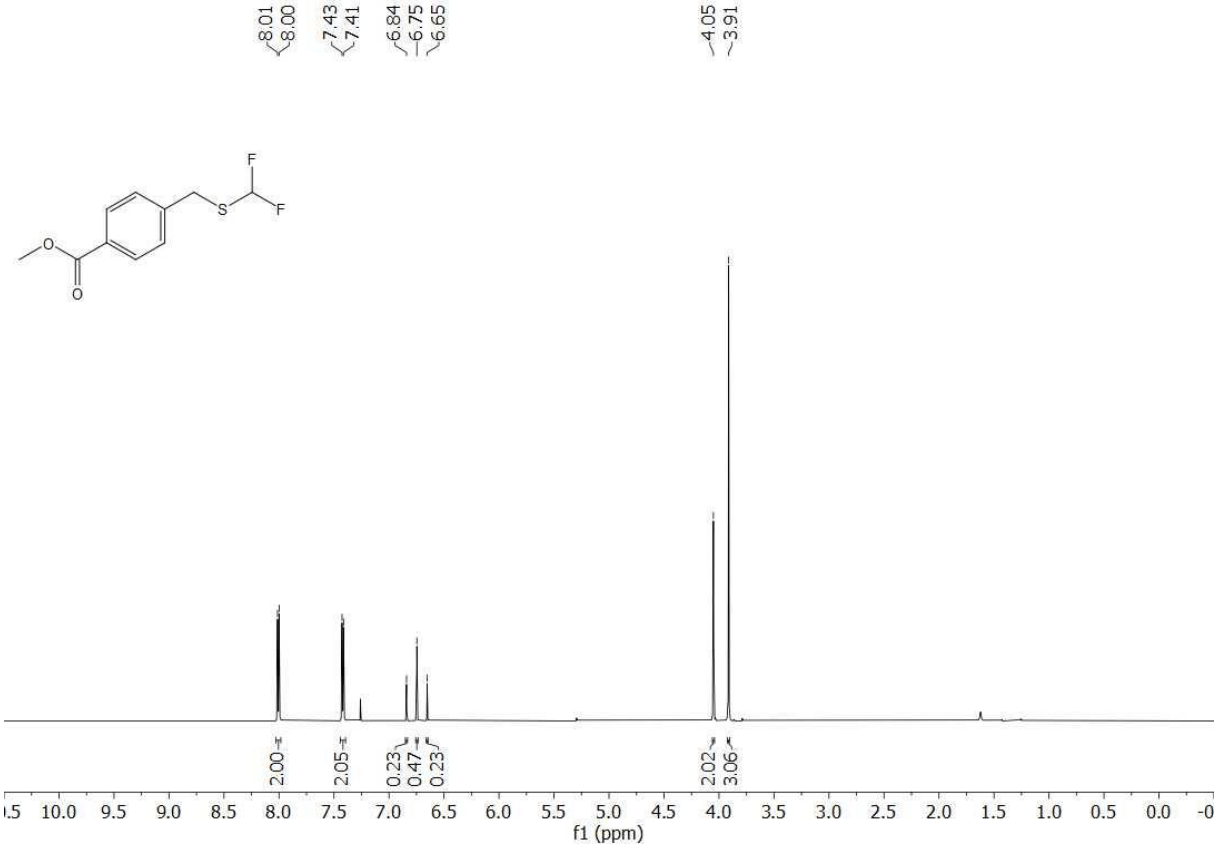
4-(((difluoromethyl)thio)methyl)benzonitrile **2d**

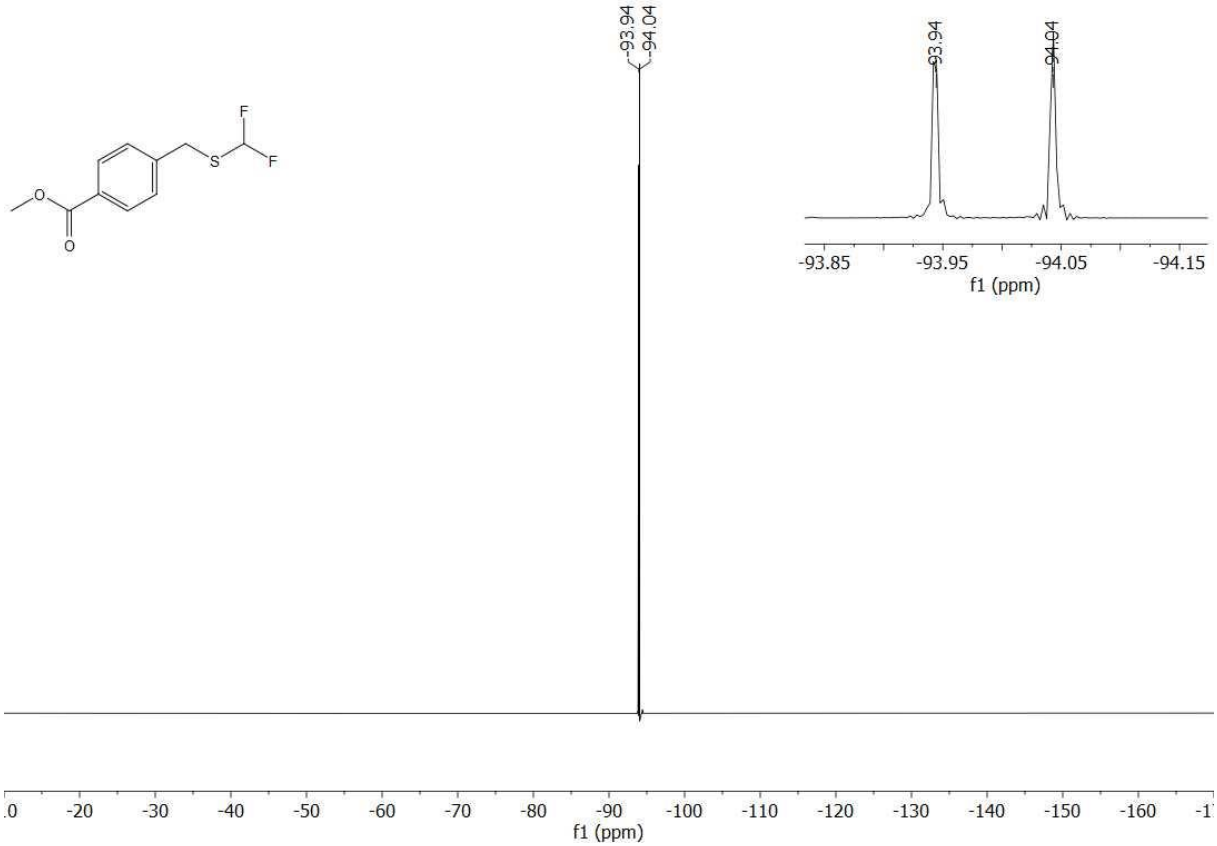


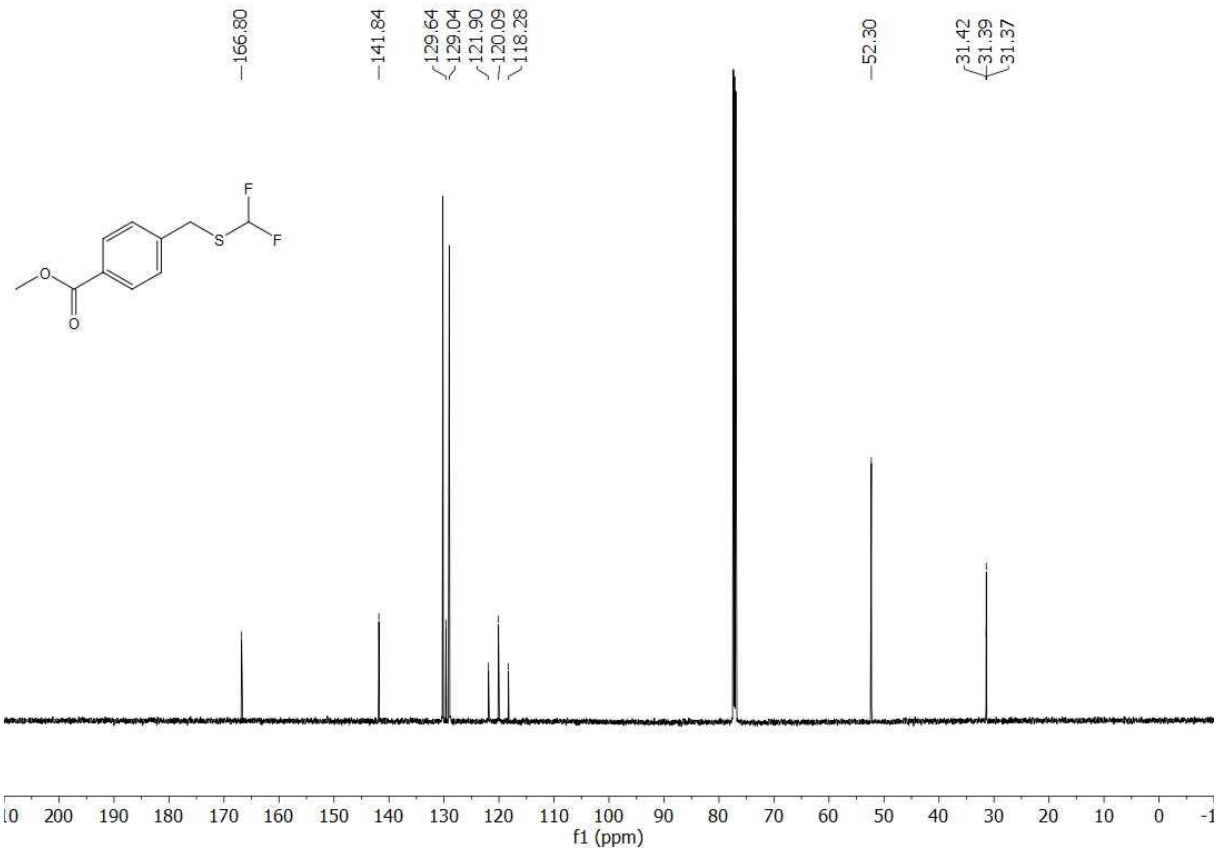



142.41
132.65
129.74
121.68
119.86
118.62
118.05
111.65
31.15
31.12
31.09
F
S
F
N
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

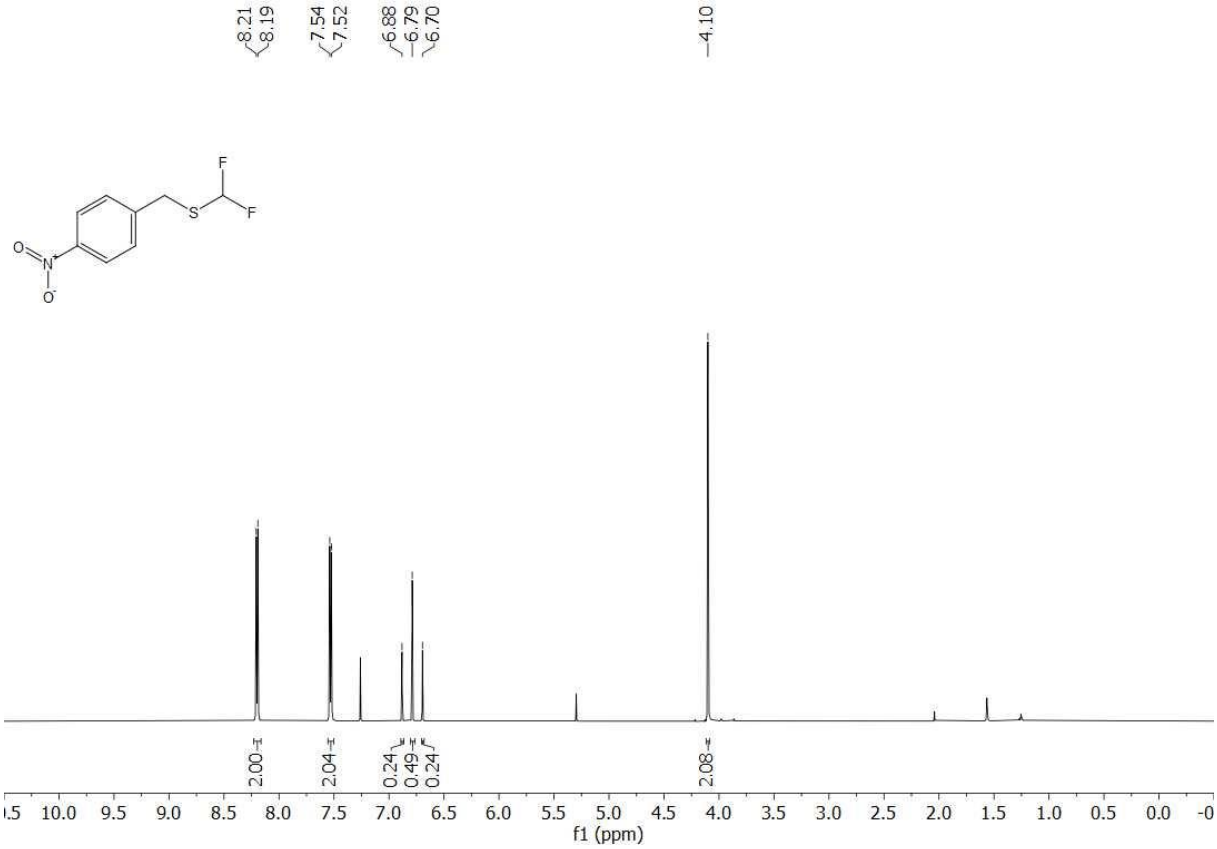
methyl 4-(((difluoromethyl)thio)methyl)benzoate **2e**

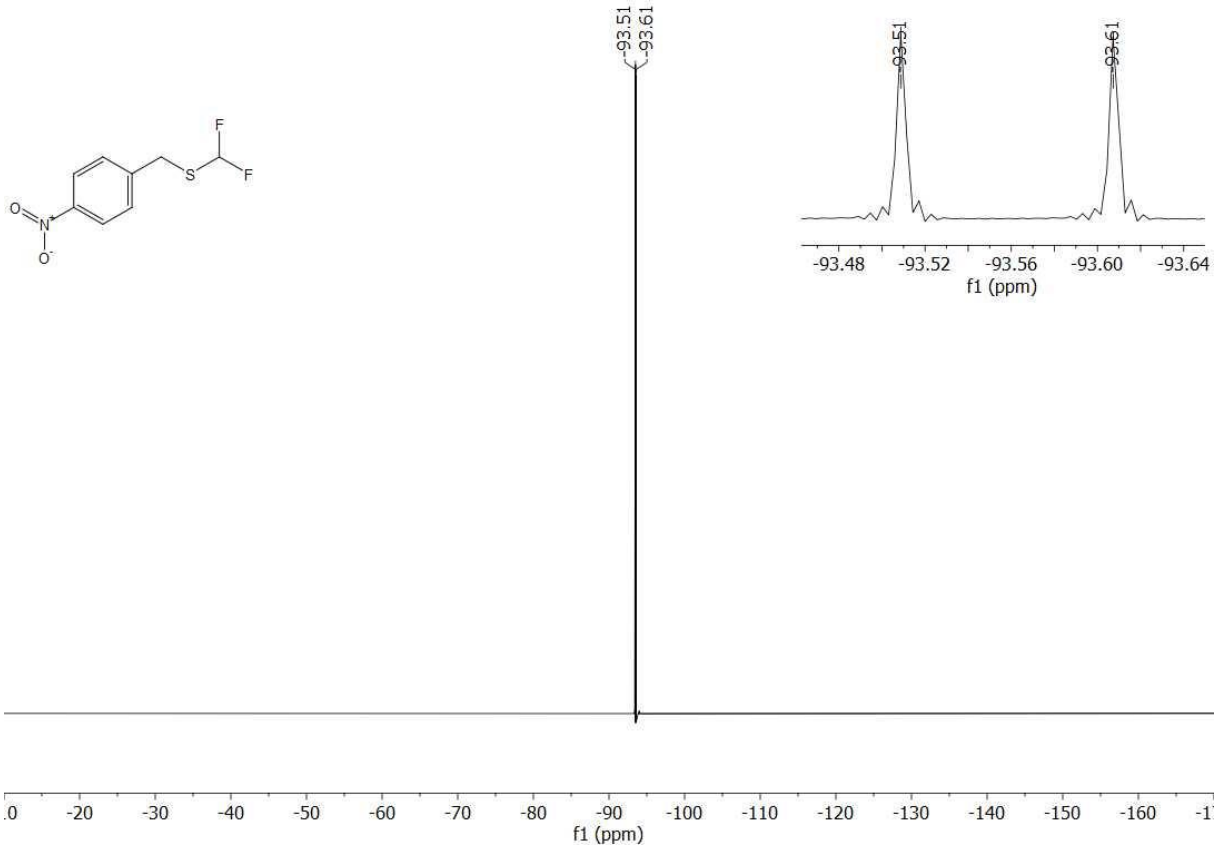


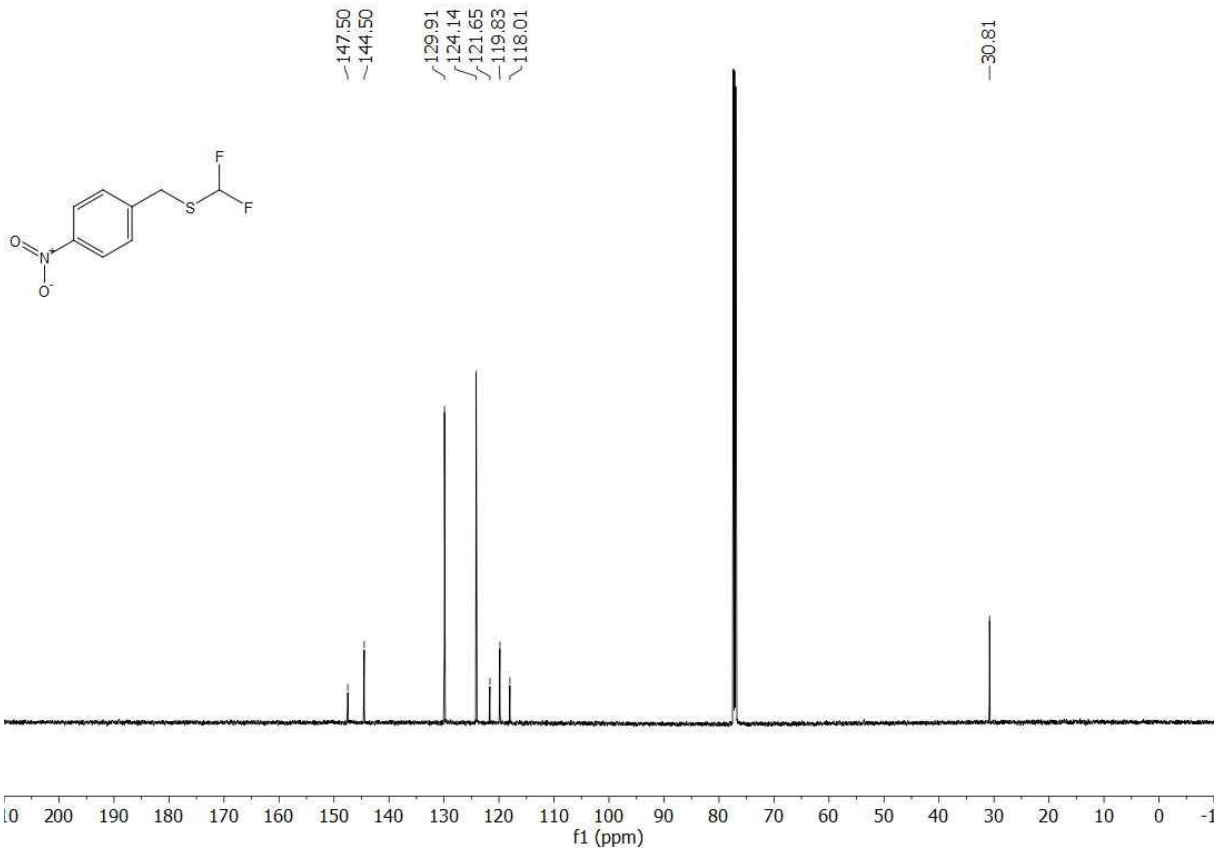



166.80
141.84
129.64
129.04
121.90
120.09
118.28
52.30
31.42
31.39
31.37
F
F
S
O
O
f1 (ppm)

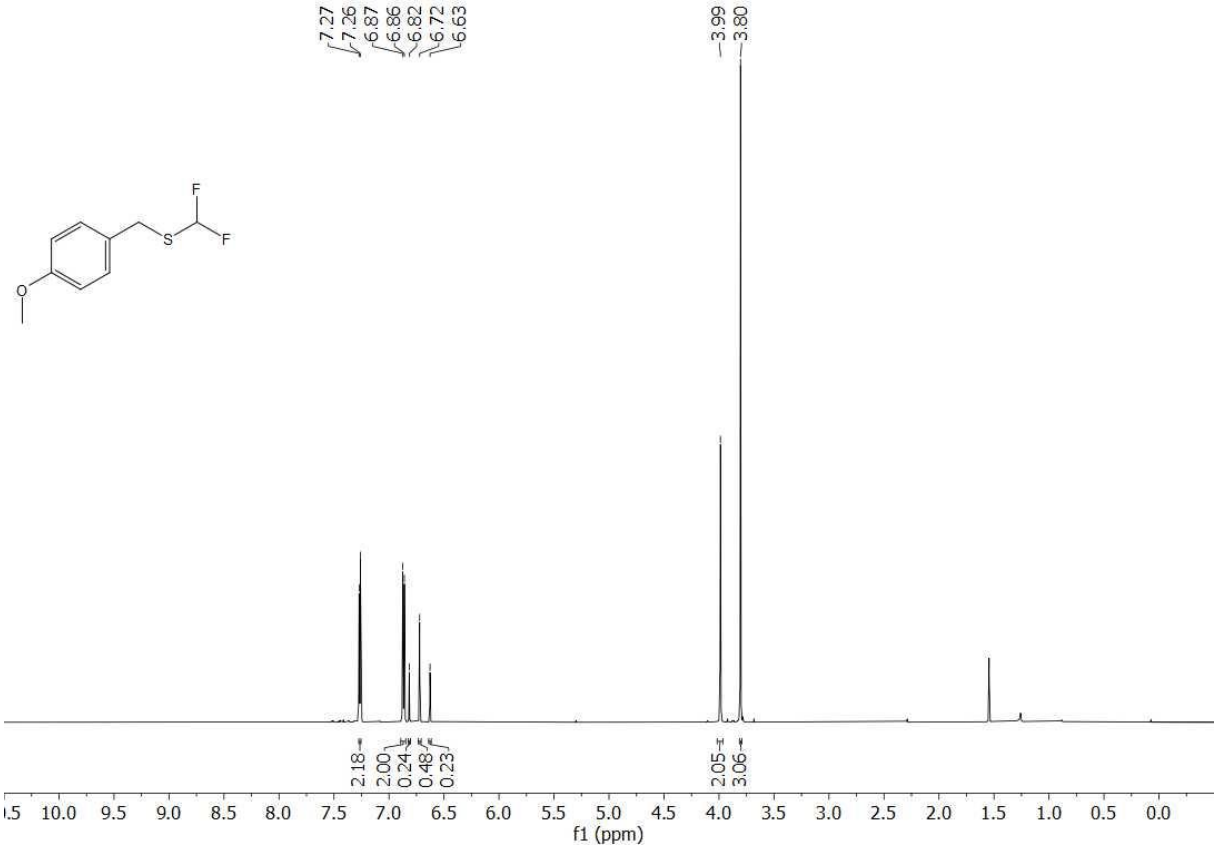
(difluoromethyl)(4-nitrobenzyl)sulfane **2f**

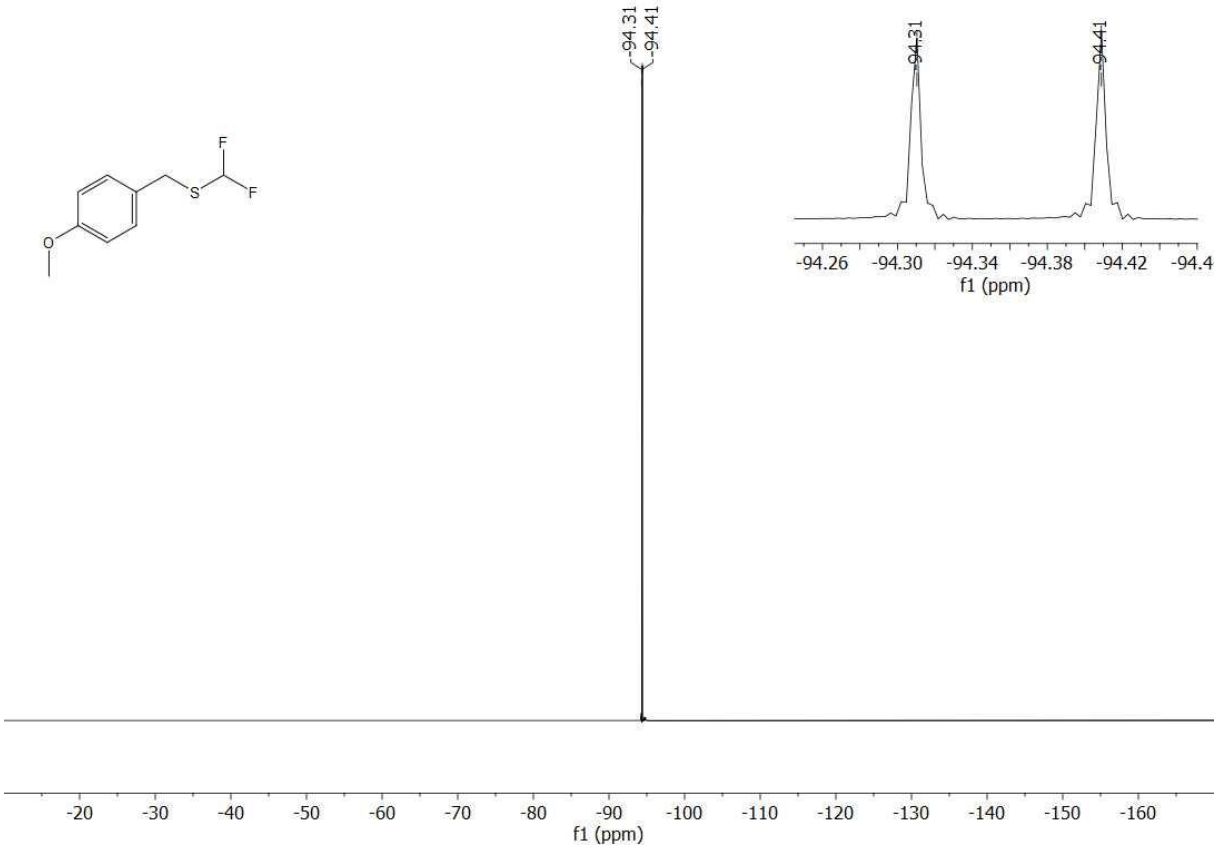


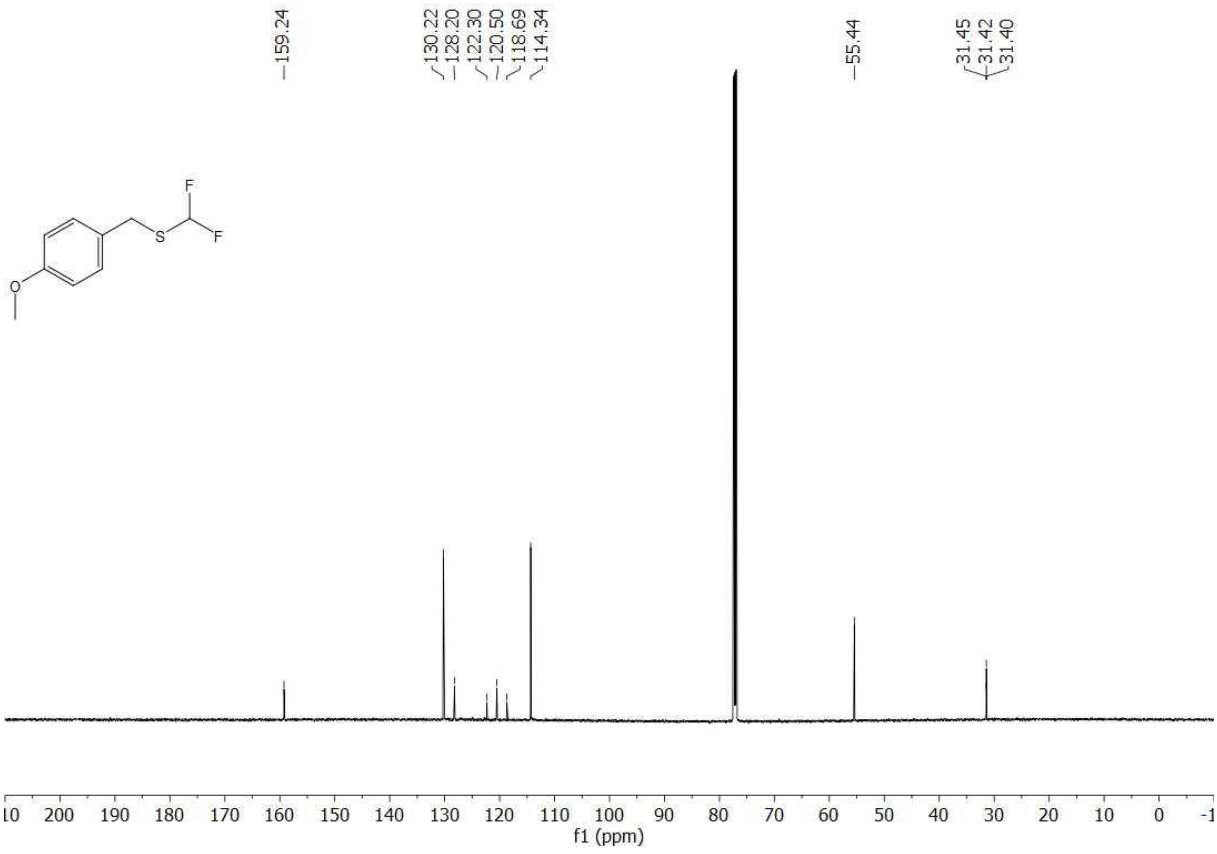



147.50
144.50
129.91
124.14
121.65
119.83
118.01
30.81
F
S
F
O
N+
O-
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

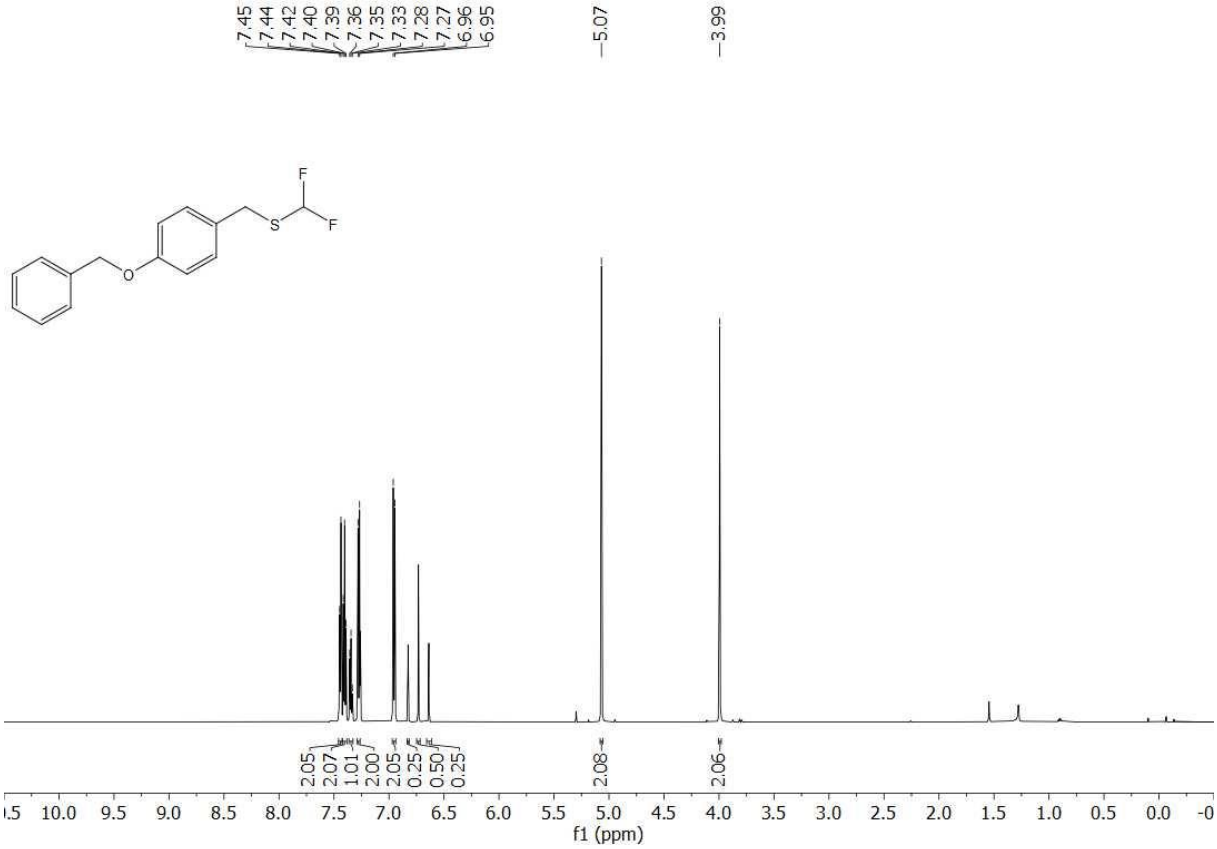
(difluoromethyl)(4-methoxybenzyl)sulfane **2g**

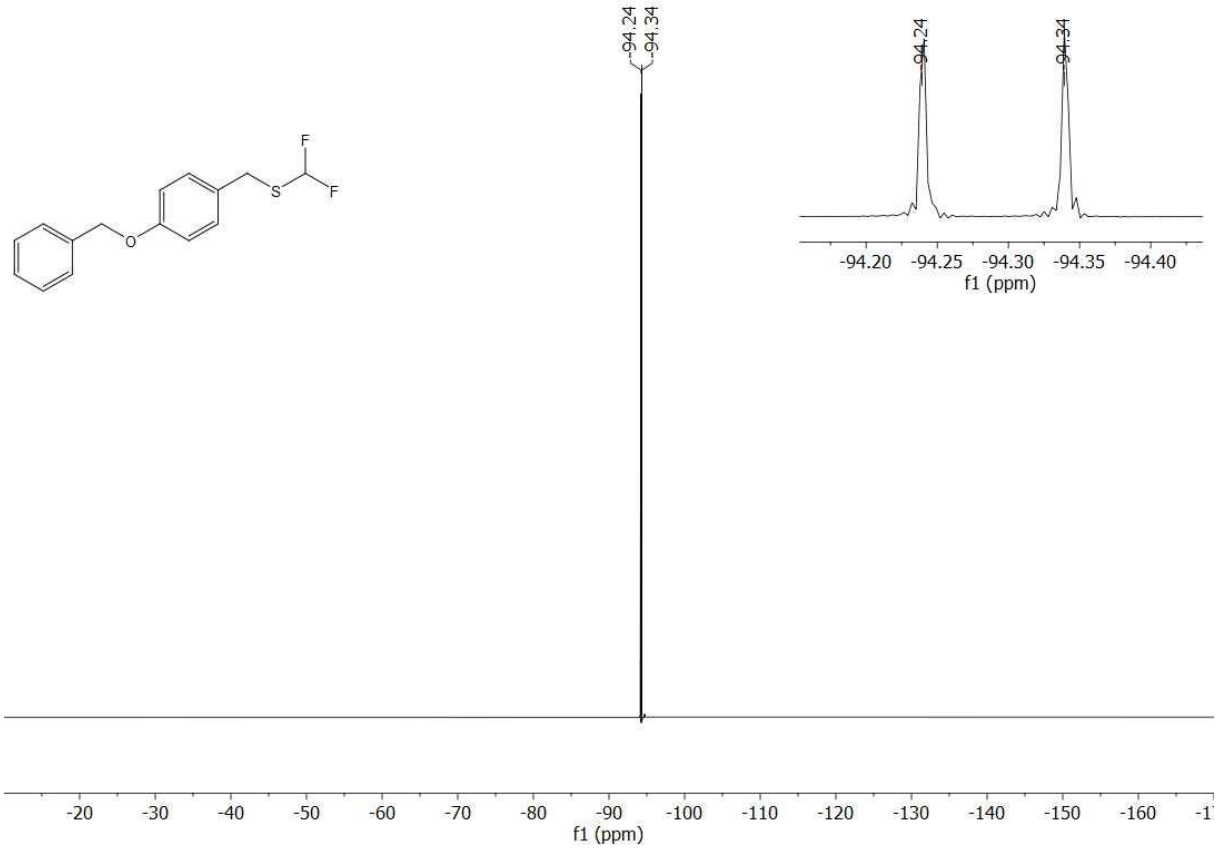


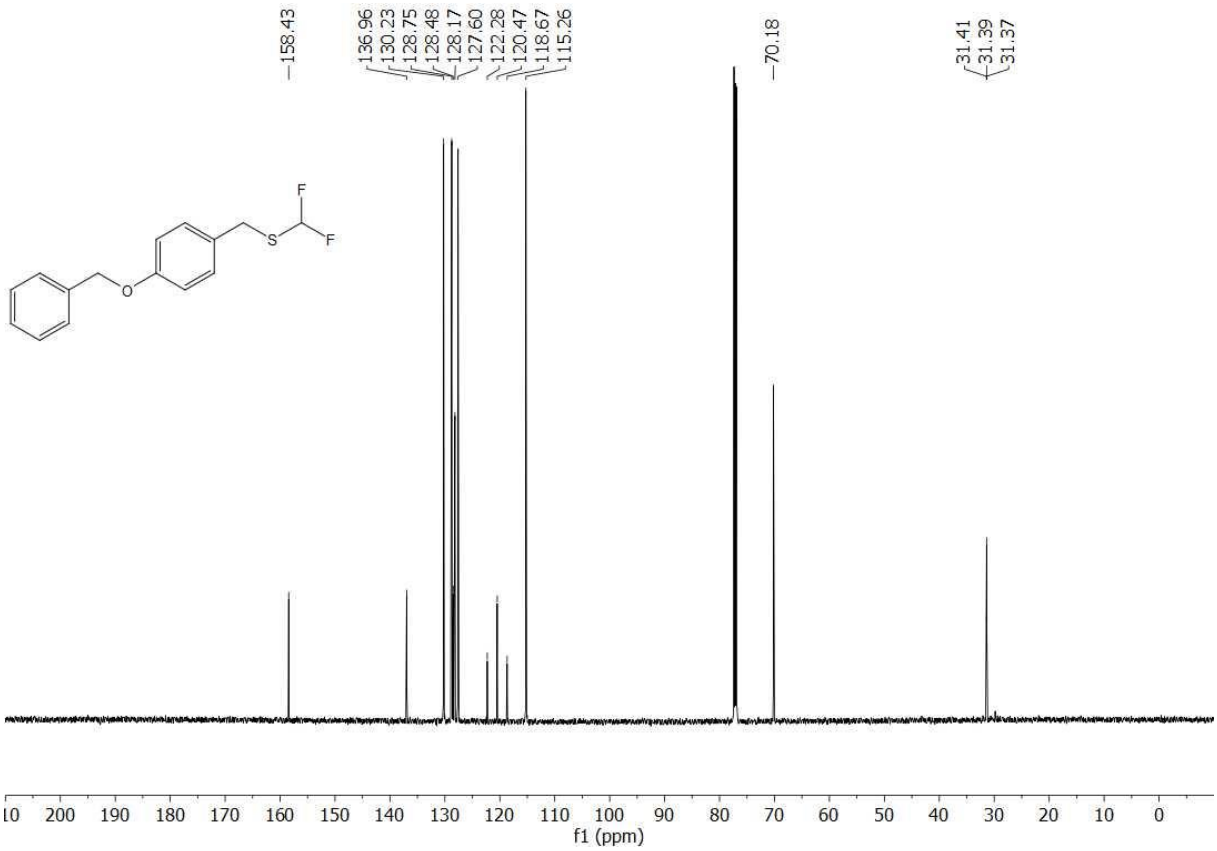



159.24
130.22
128.20
122.30
120.50
118.69
114.34
55.44
31.45
31.42
31.40
F
S
F
O
f1 (ppm)

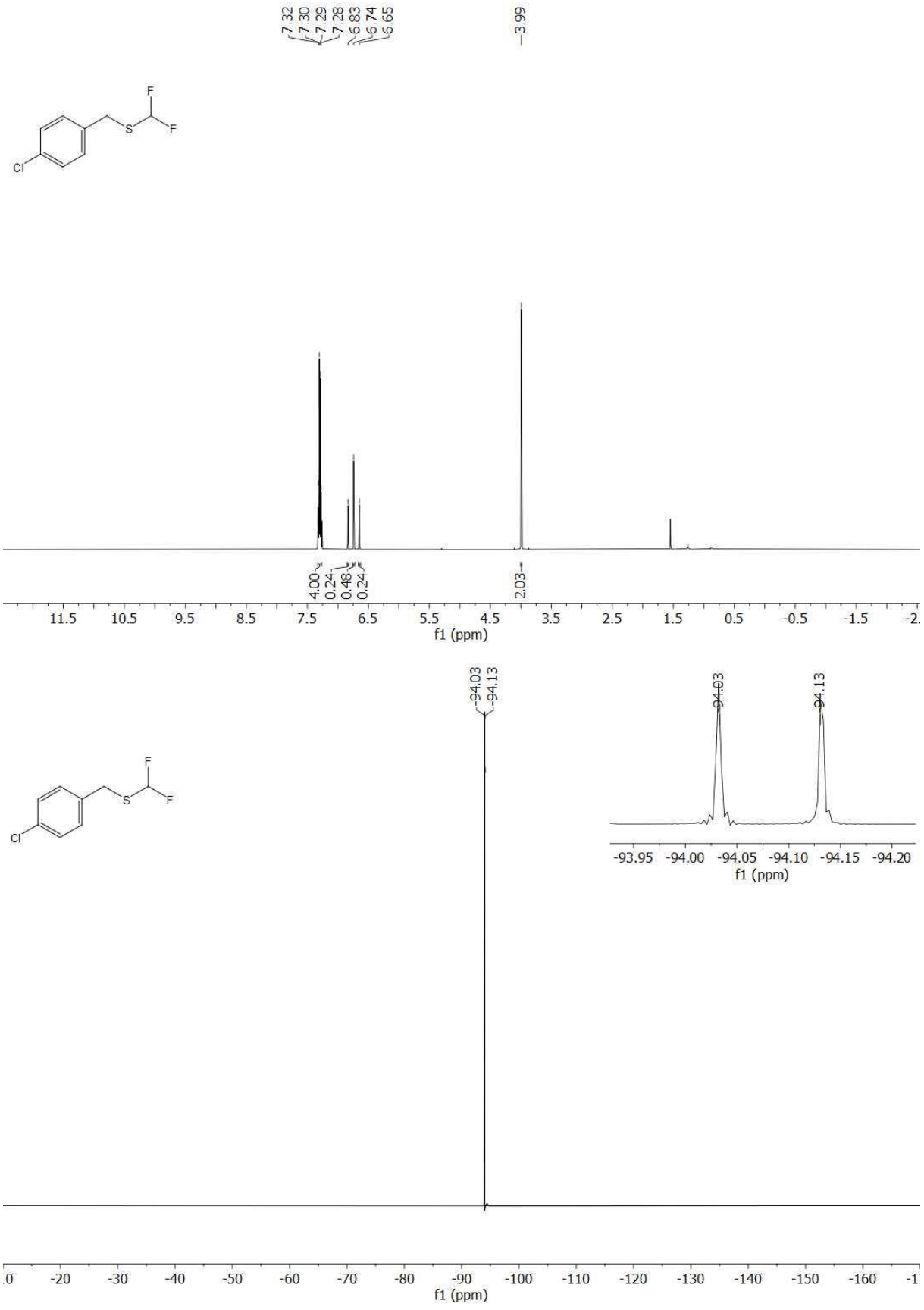
4-(benzyloxy)benzyl)(difluoromethyl)sulfane **2h**

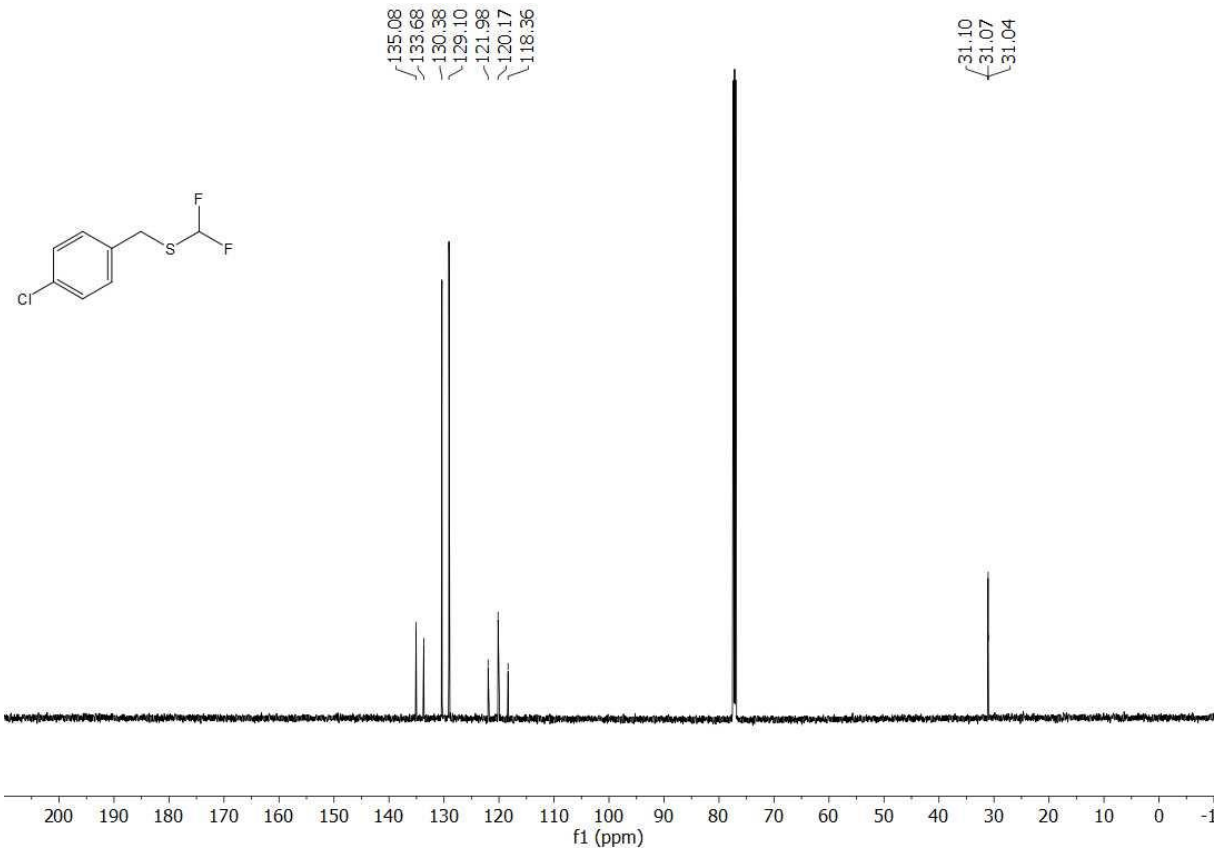




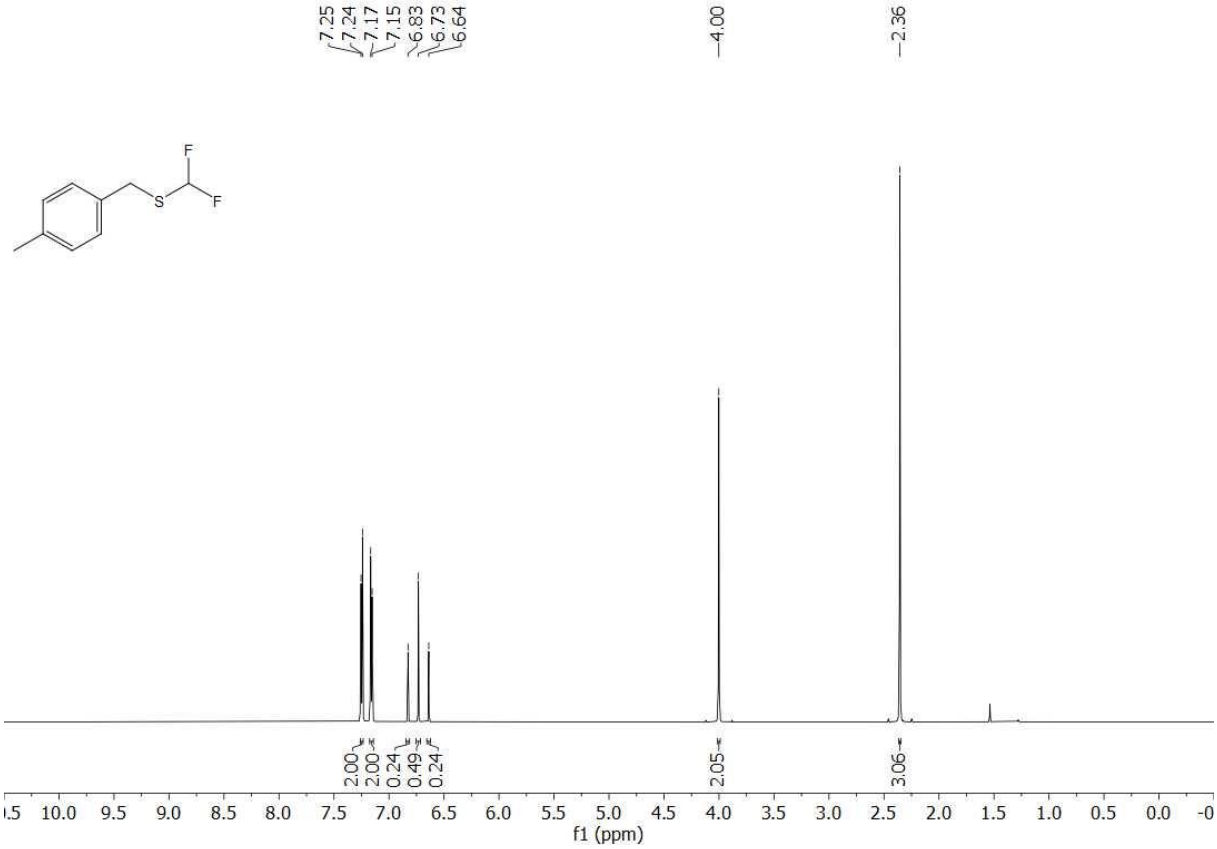

158.43
136.96
130.23
128.75
128.48
128.17
127.60
122.28
120.47
118.67
115.26
70.18
31.41
31.39
31.37
F
S
F
O
f1 (ppm)

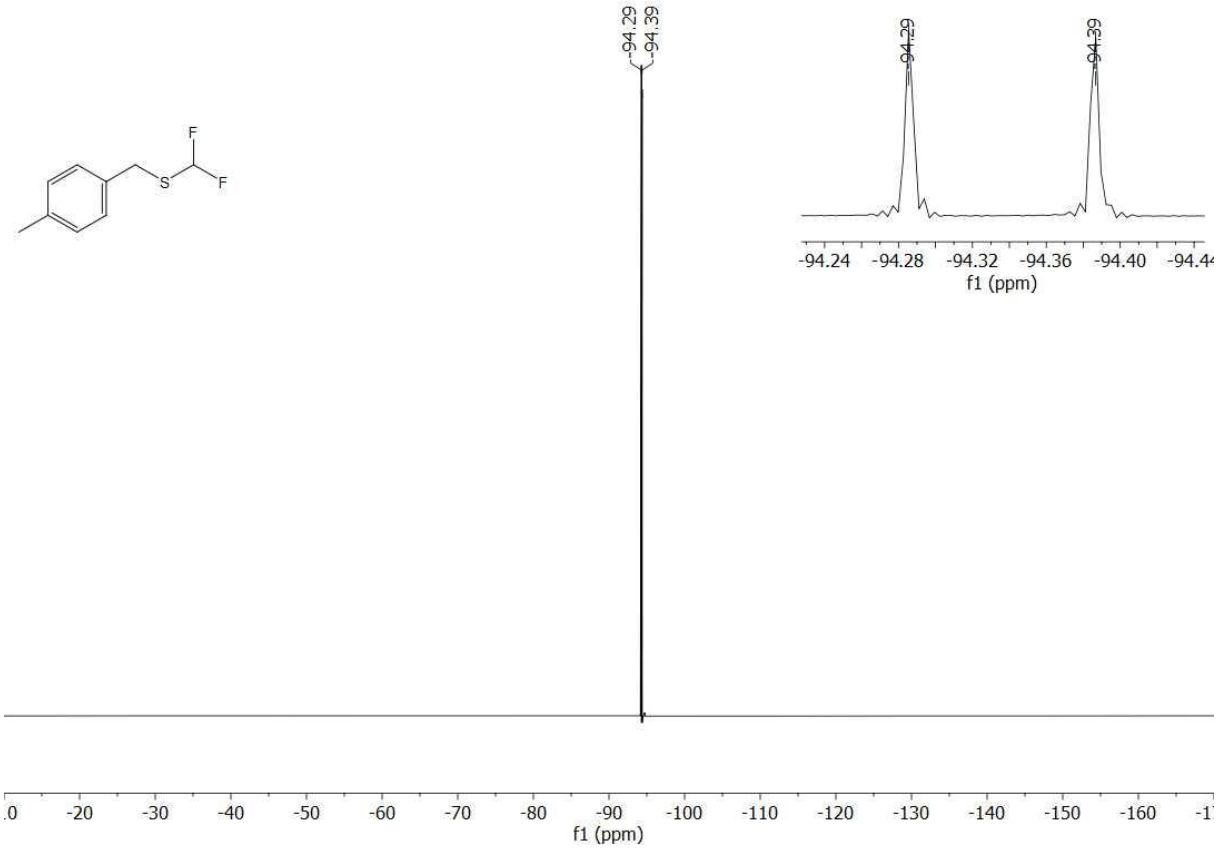
(4-chlorobenzyl)(difluoromethyl)sulfane **2i**

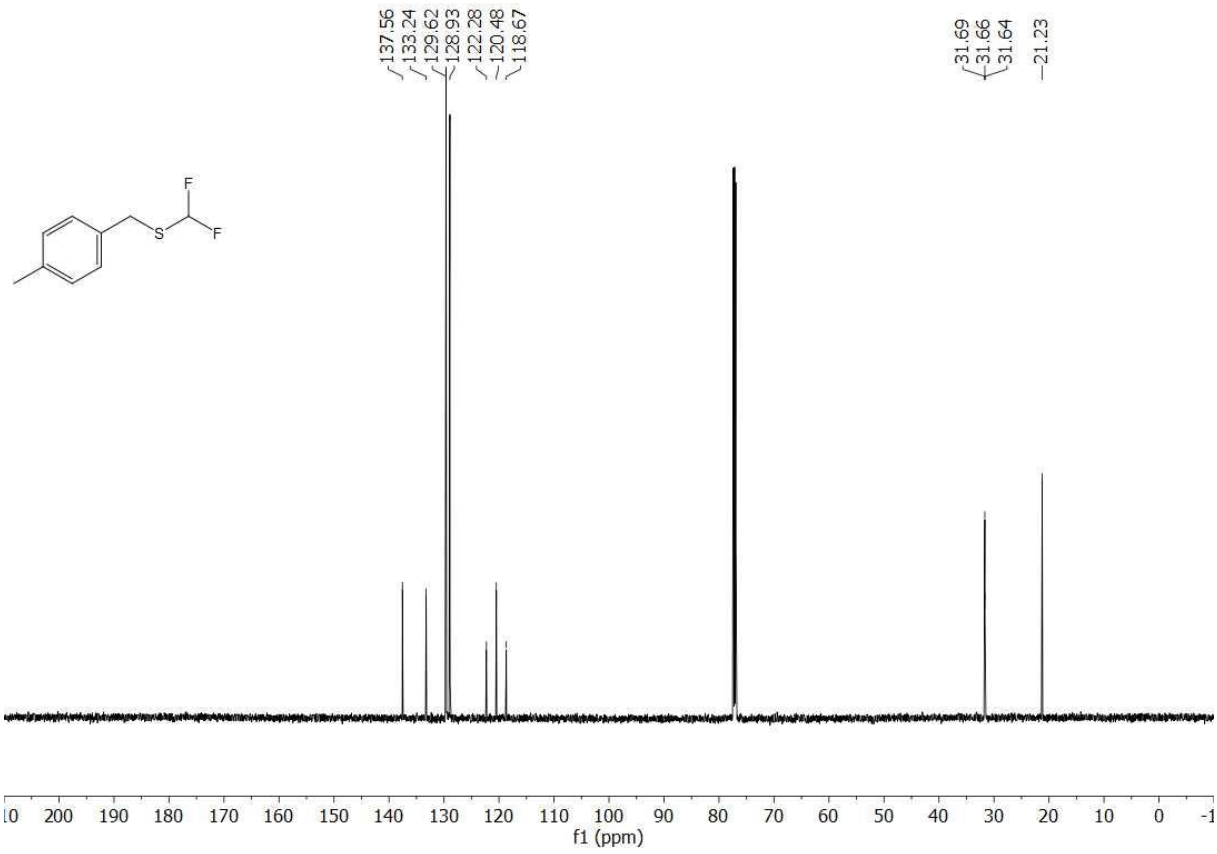



135.08
133.68
130.38
129.10
121.98
120.17
118.36
31.10
31.07
31.04
F
S
F
Cl
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

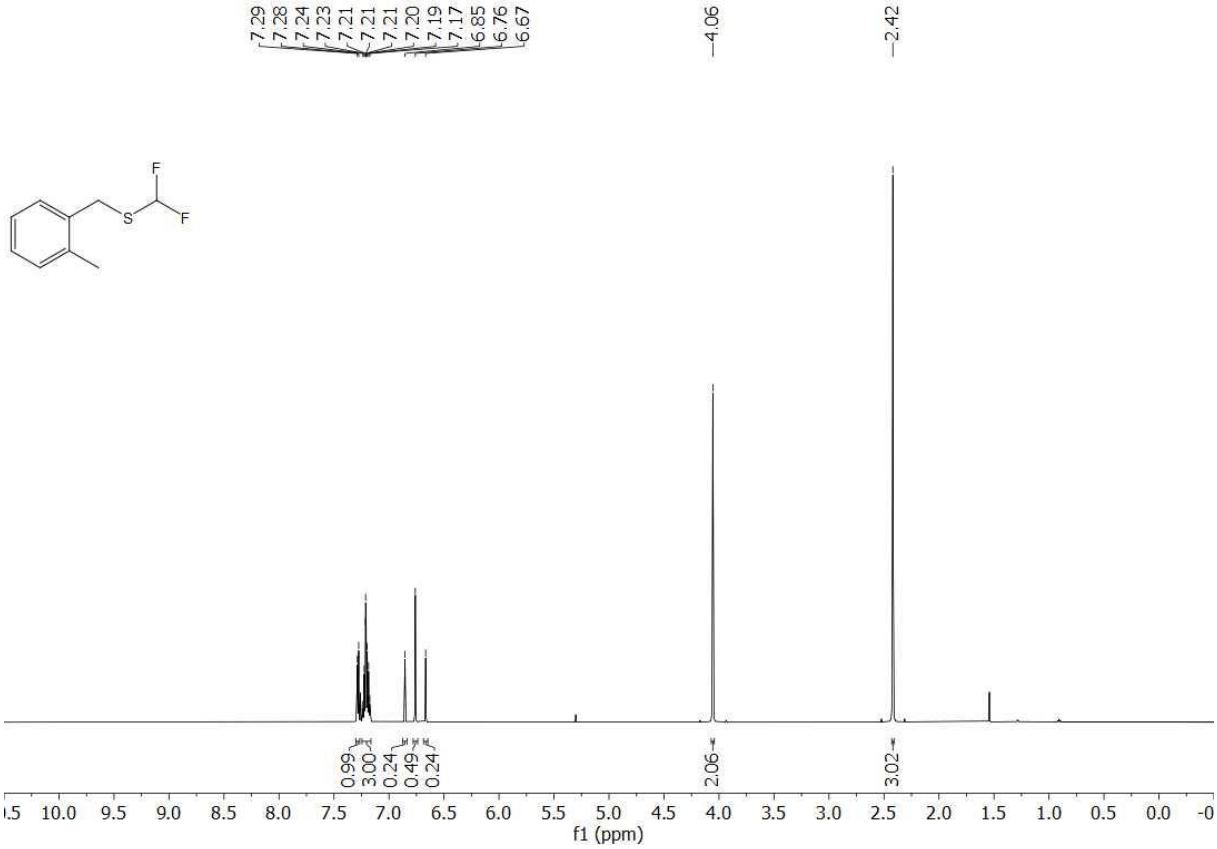
(difluoromethyl)(4-methylbenzyl)sulfane **2j**

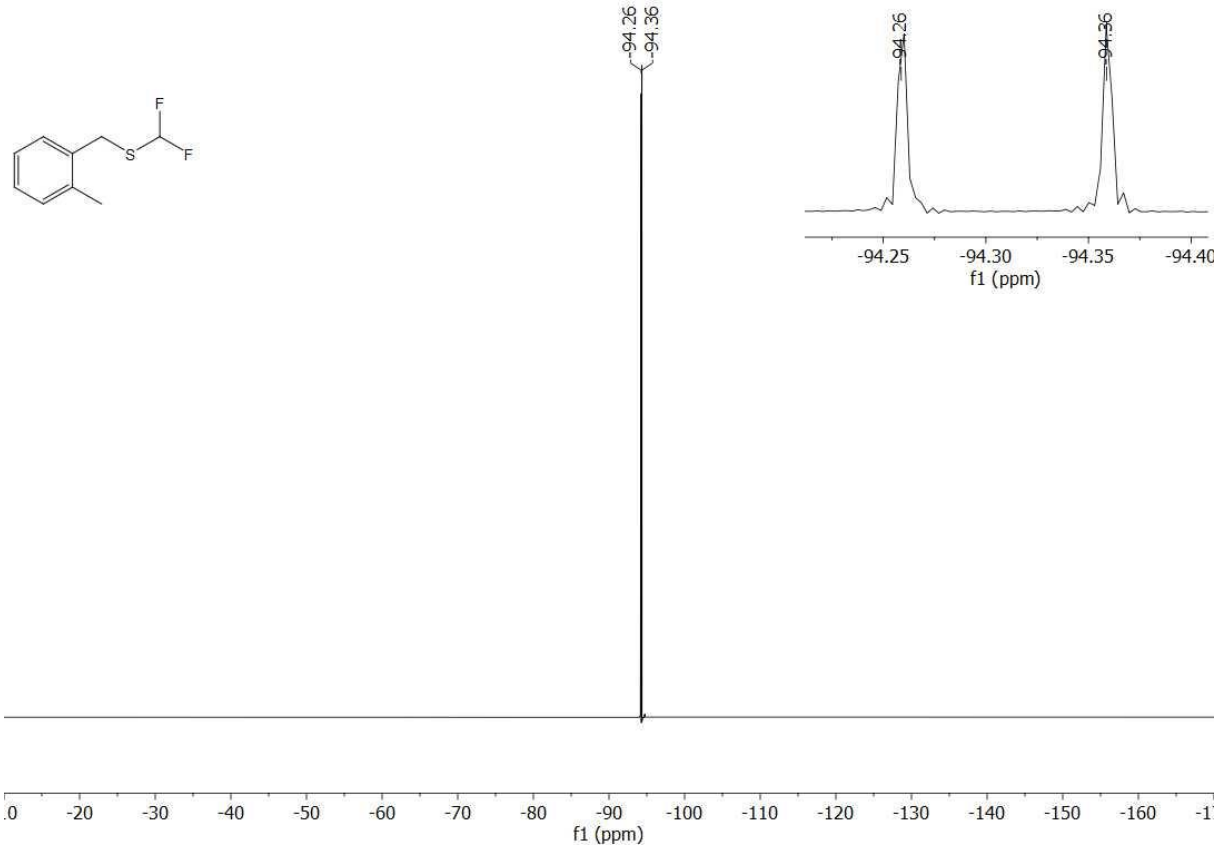


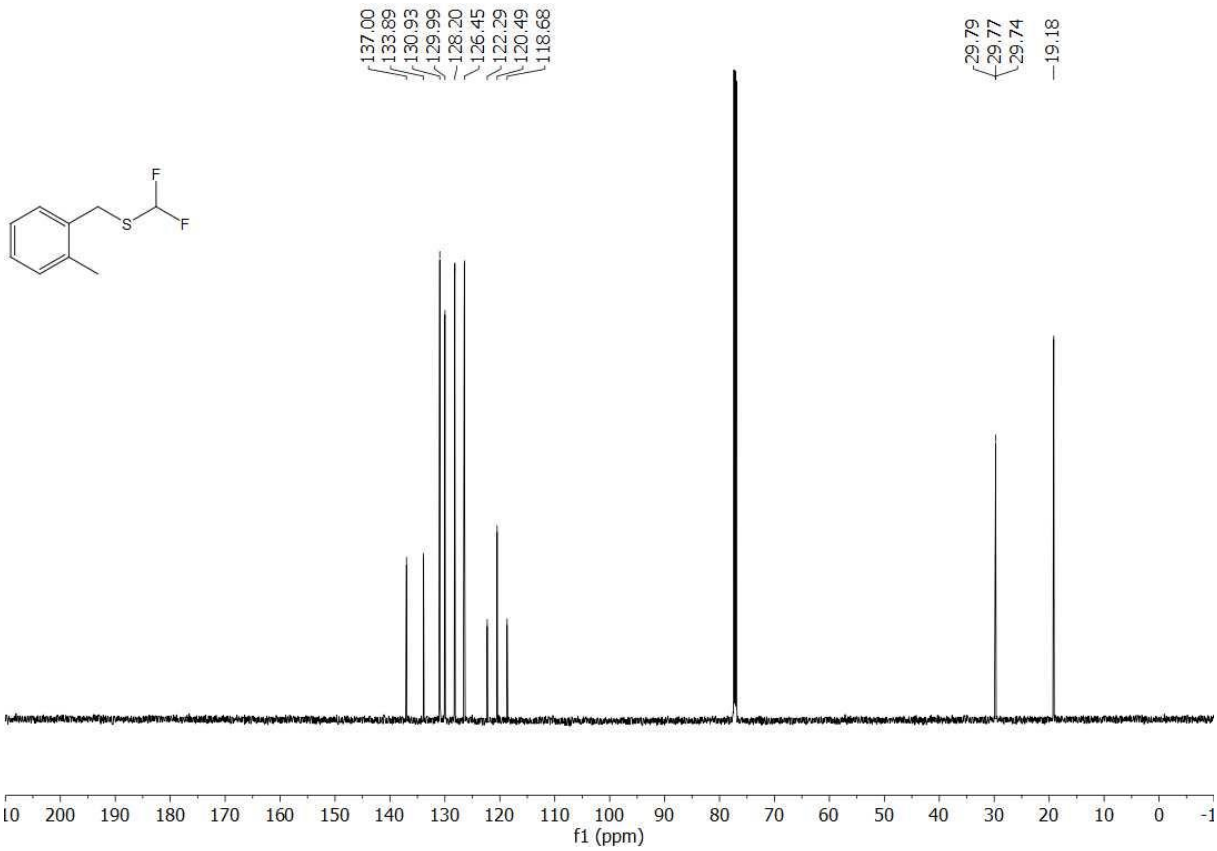



137.56
133.24
129.62
128.93
122.28
120.48
118.67
31.69
31.66
31.64
21.23
F
S
F
f1 (ppm)

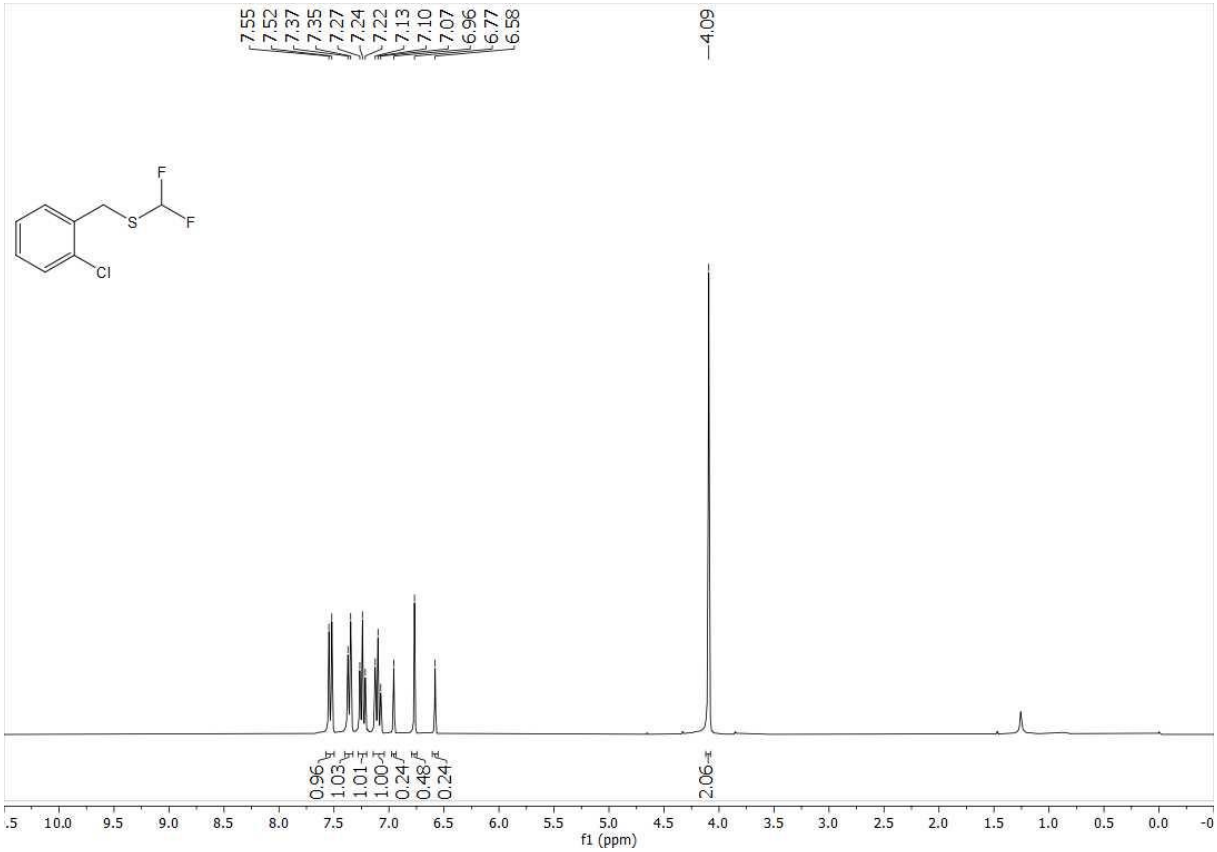
(difluoromethyl)(2-methylbenzyl)sulfane **2k**

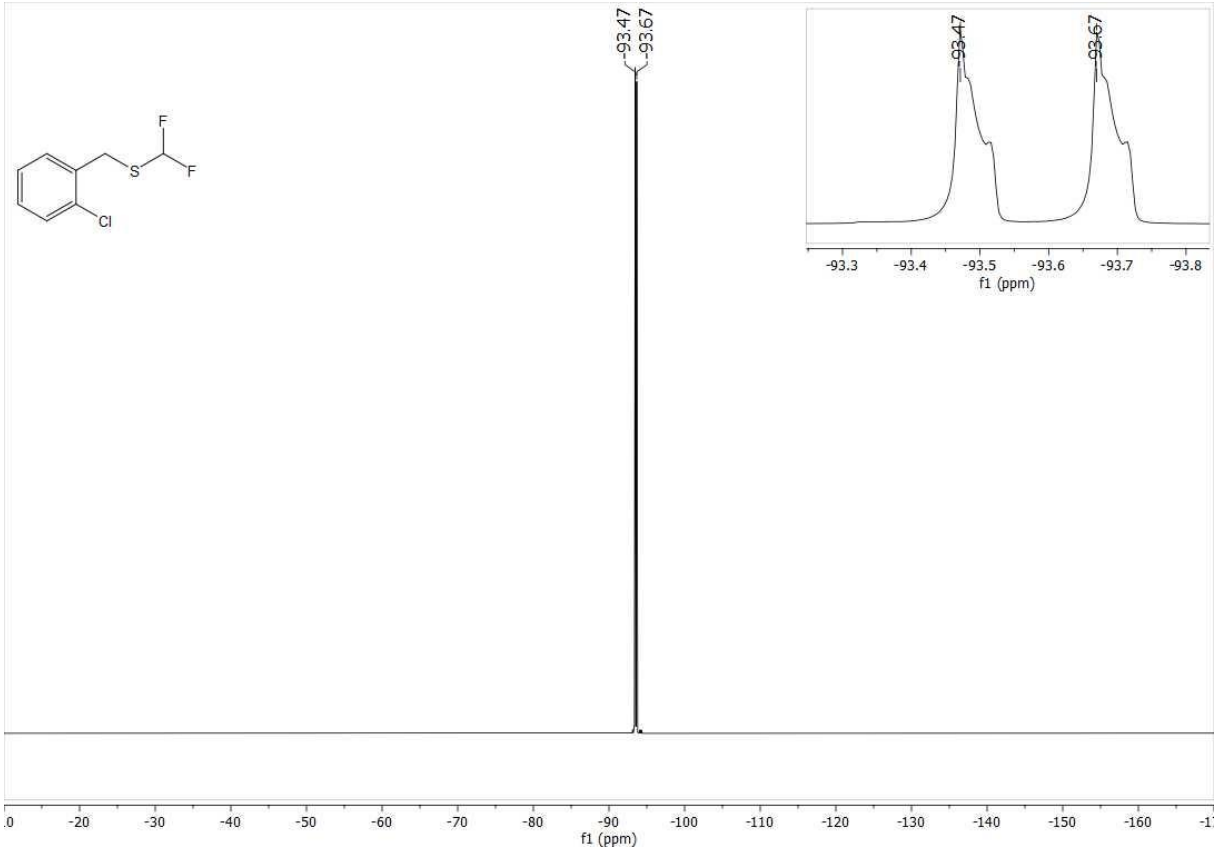


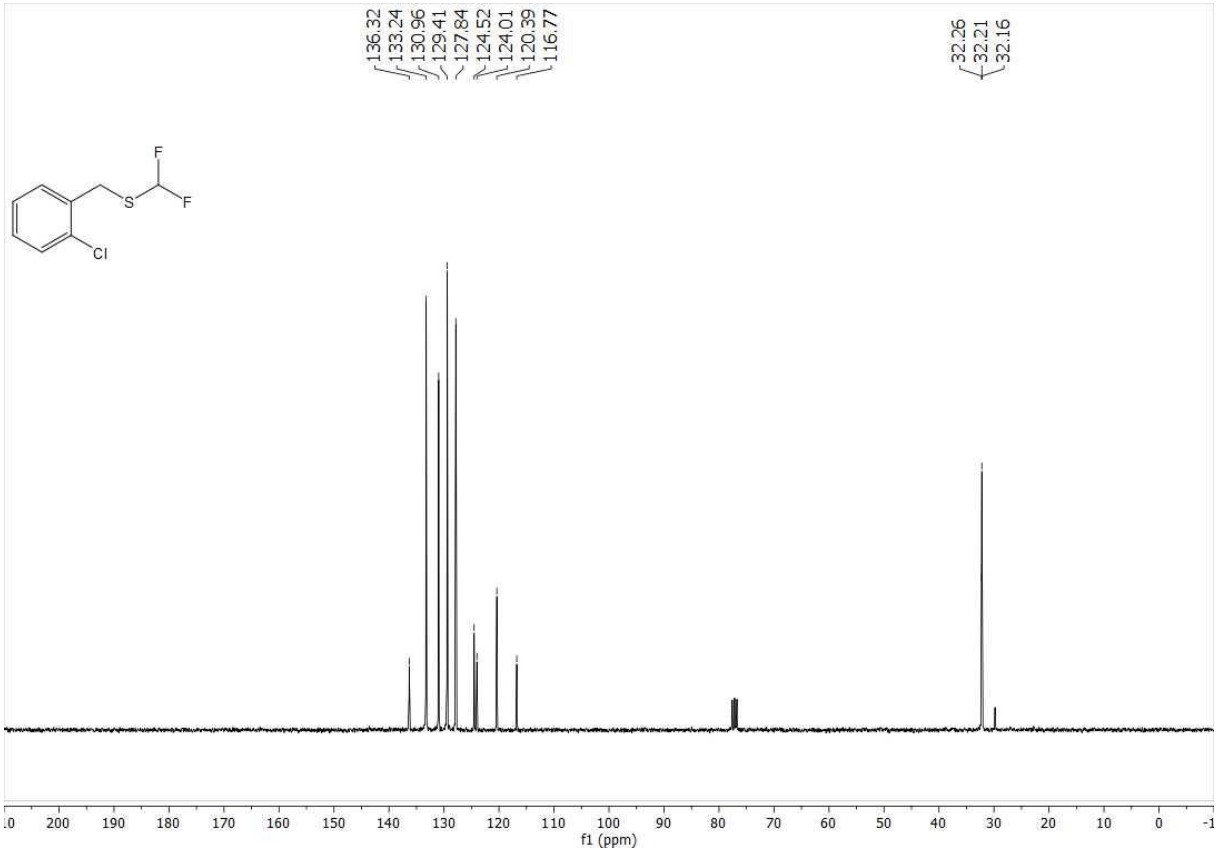



137.00
133.89
130.93
129.99
128.20
126.45
122.29
120.49
118.68
29.79
29.77
29.74
19.18
F
S
F
f1 (ppm)

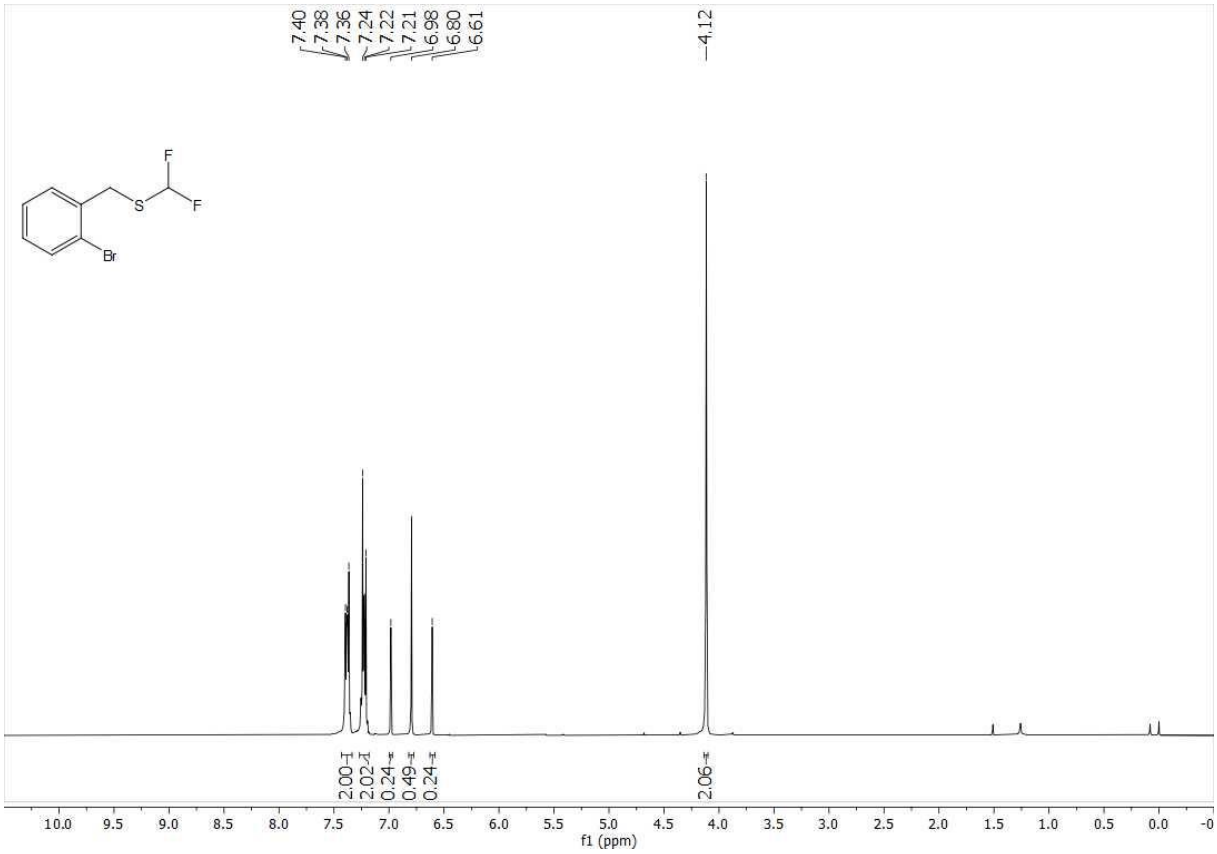
(difluoromethyl)(2-chlorobenzyl)sulfane **2l**

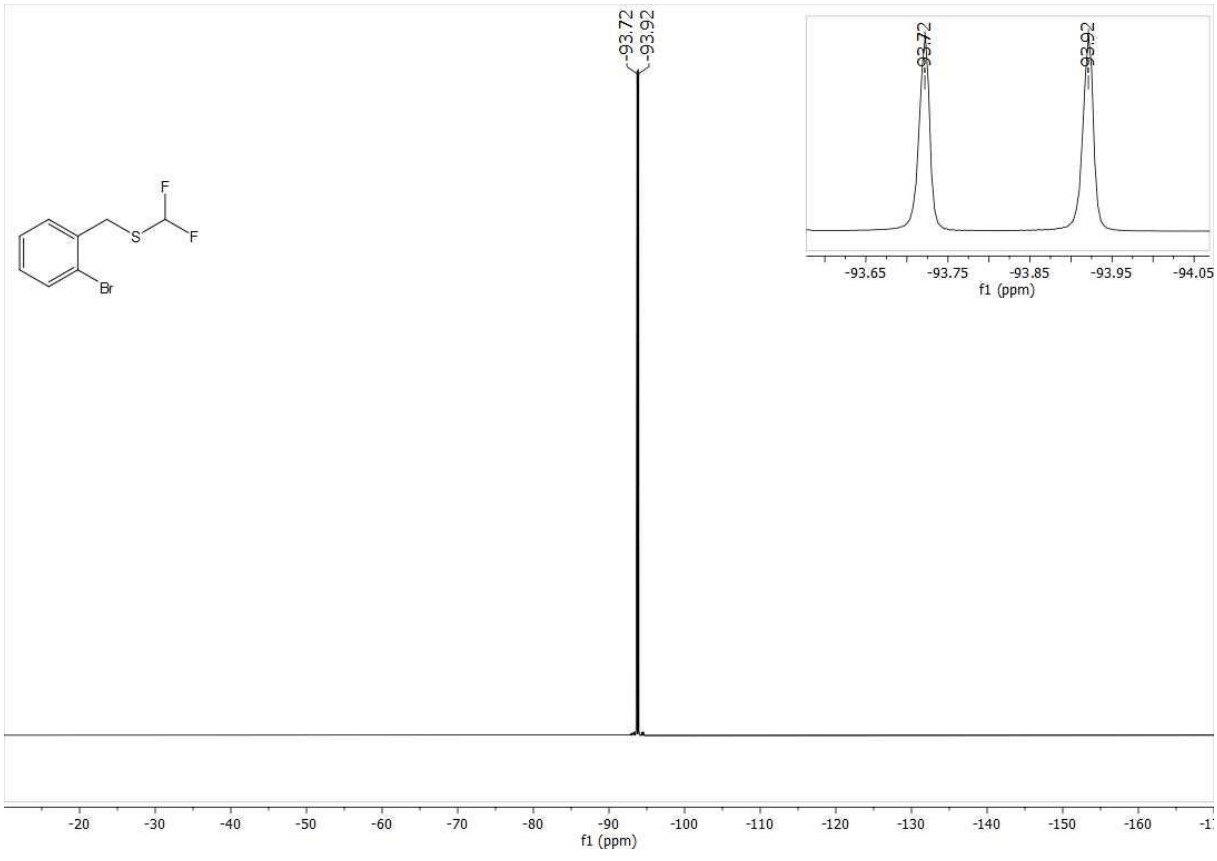


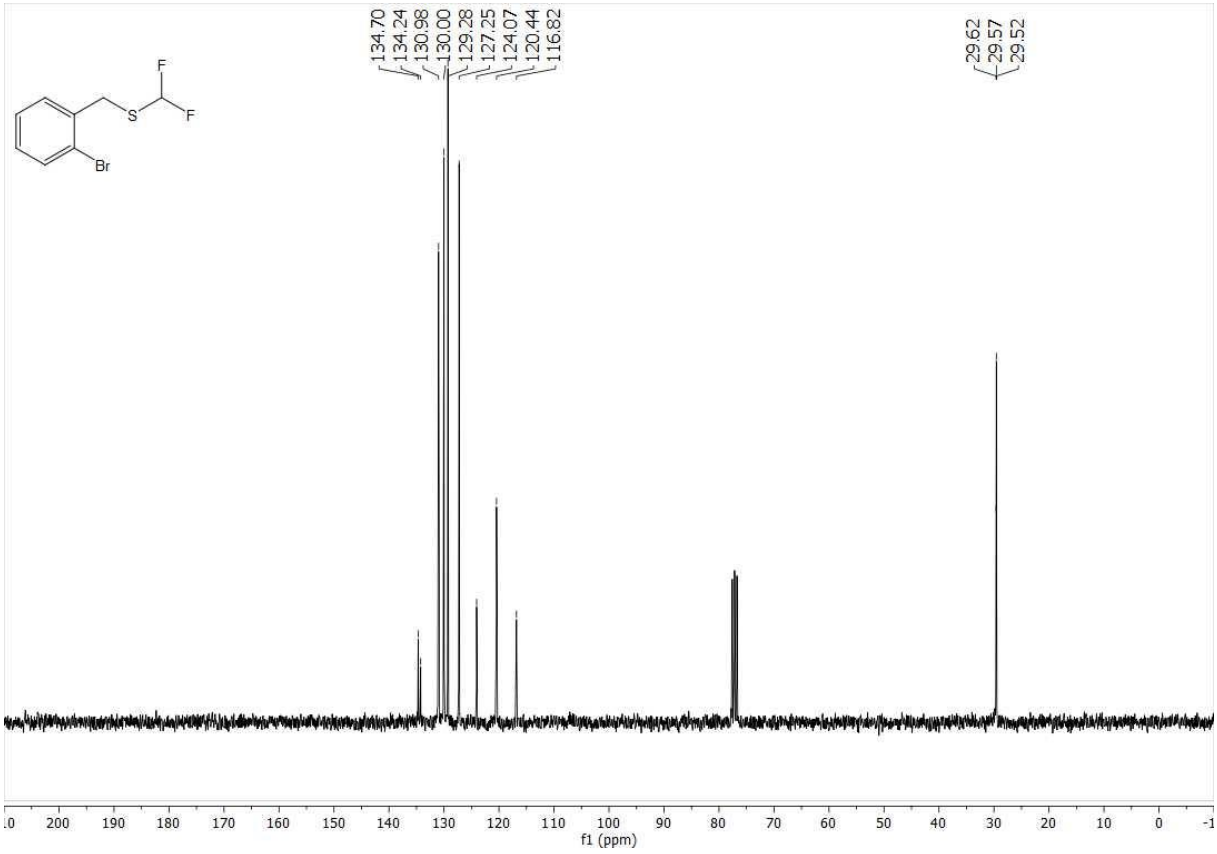



136.32
133.24
130.96
129.41
127.84
124.52
124.01
120.39
116.77
32.26
32.21
32.16
F
S
F
Cl
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

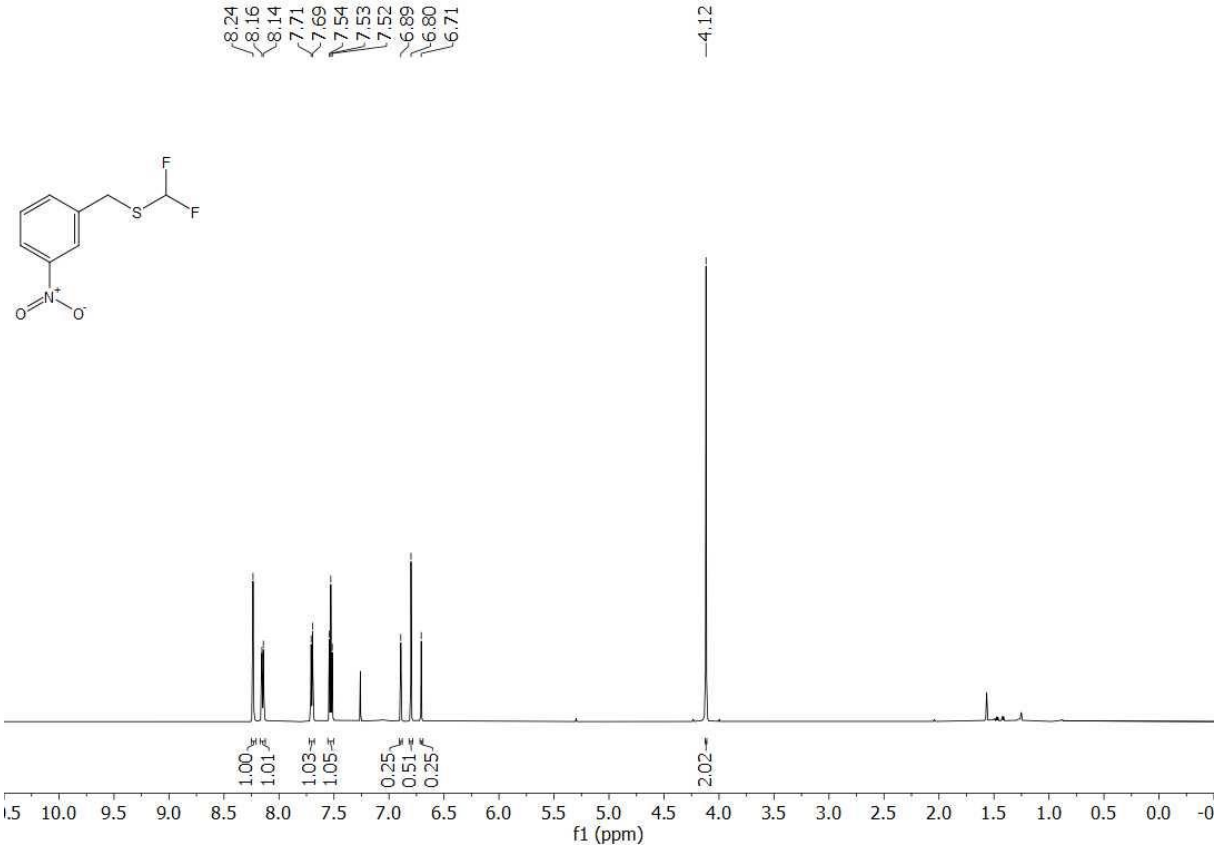
(difluoromethyl)(2-bromobenzyl)sulfane **2m**

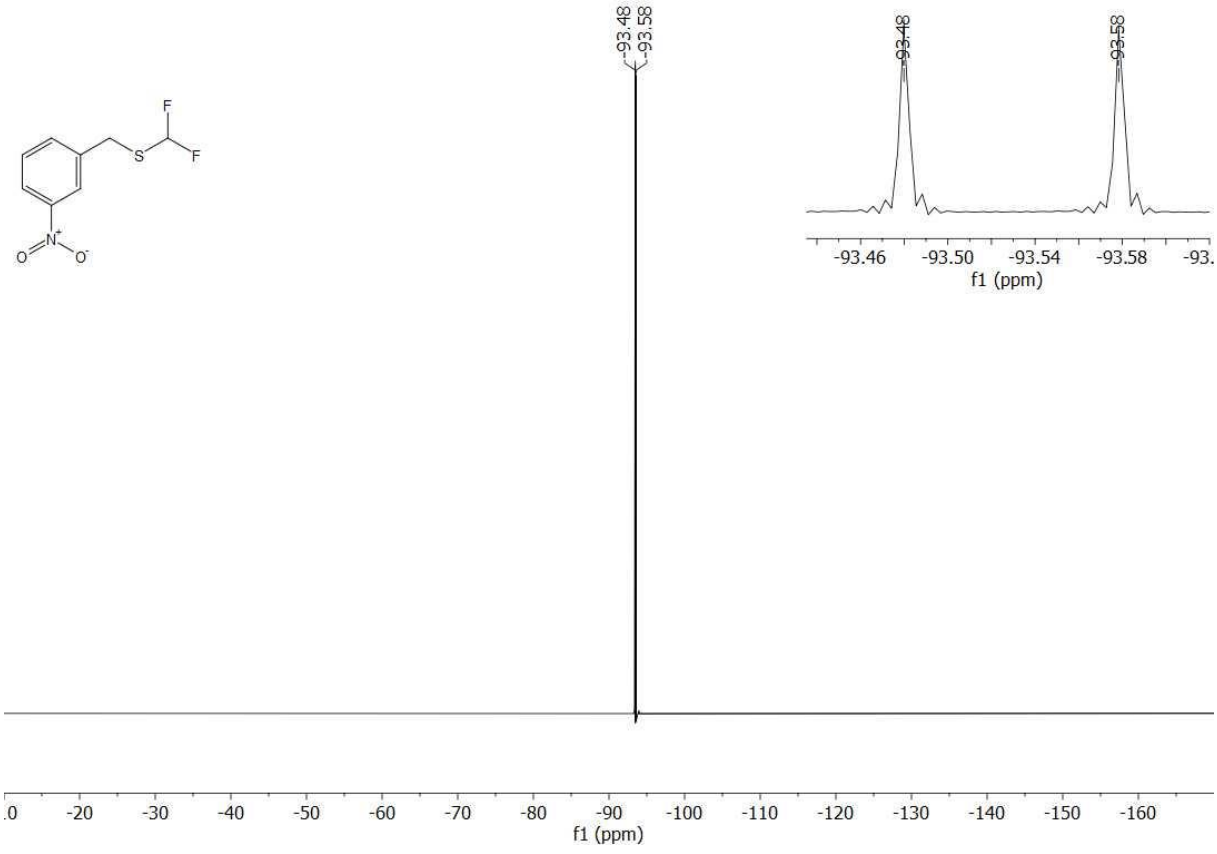


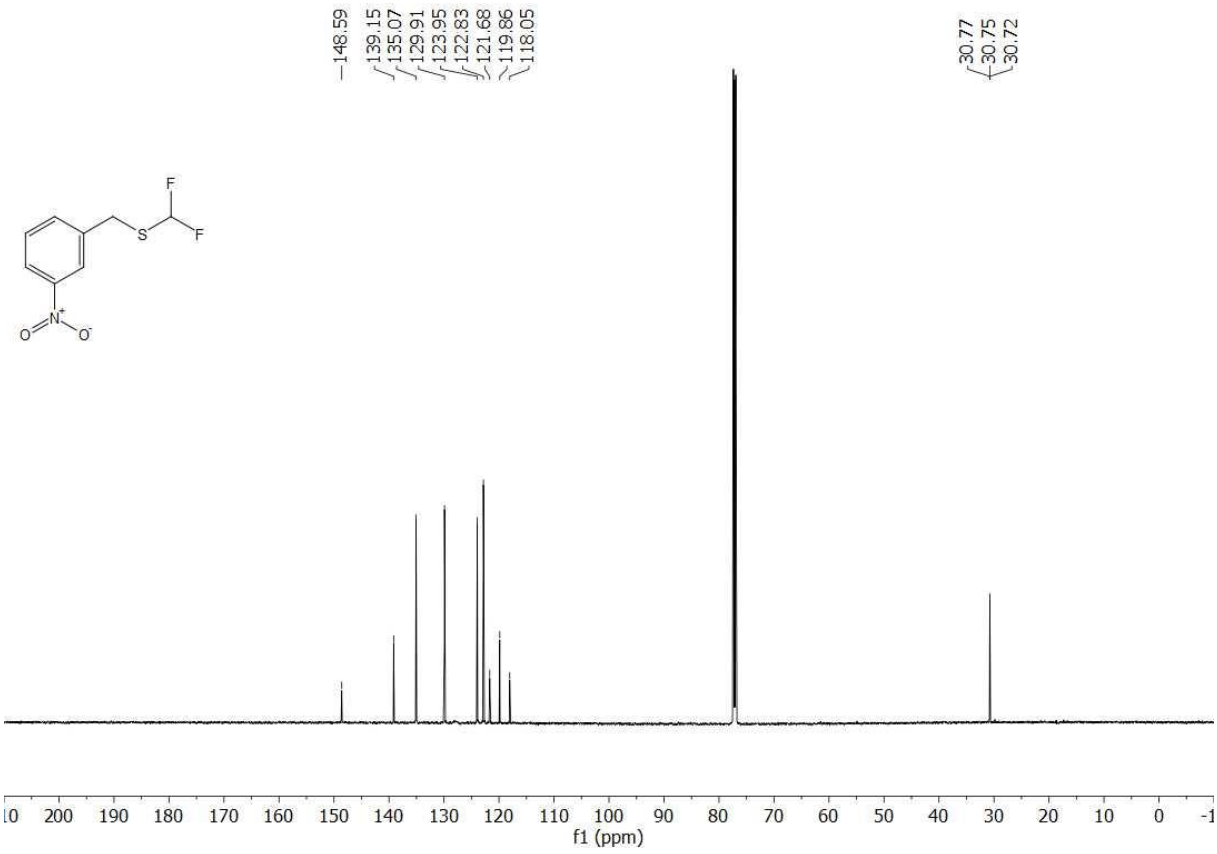



134.70
134.24
130.98
130.00
129.28
127.25
124.07
120.44
116.82
29.62
29.57
29.52
F
S
F
Br
f1 (ppm)

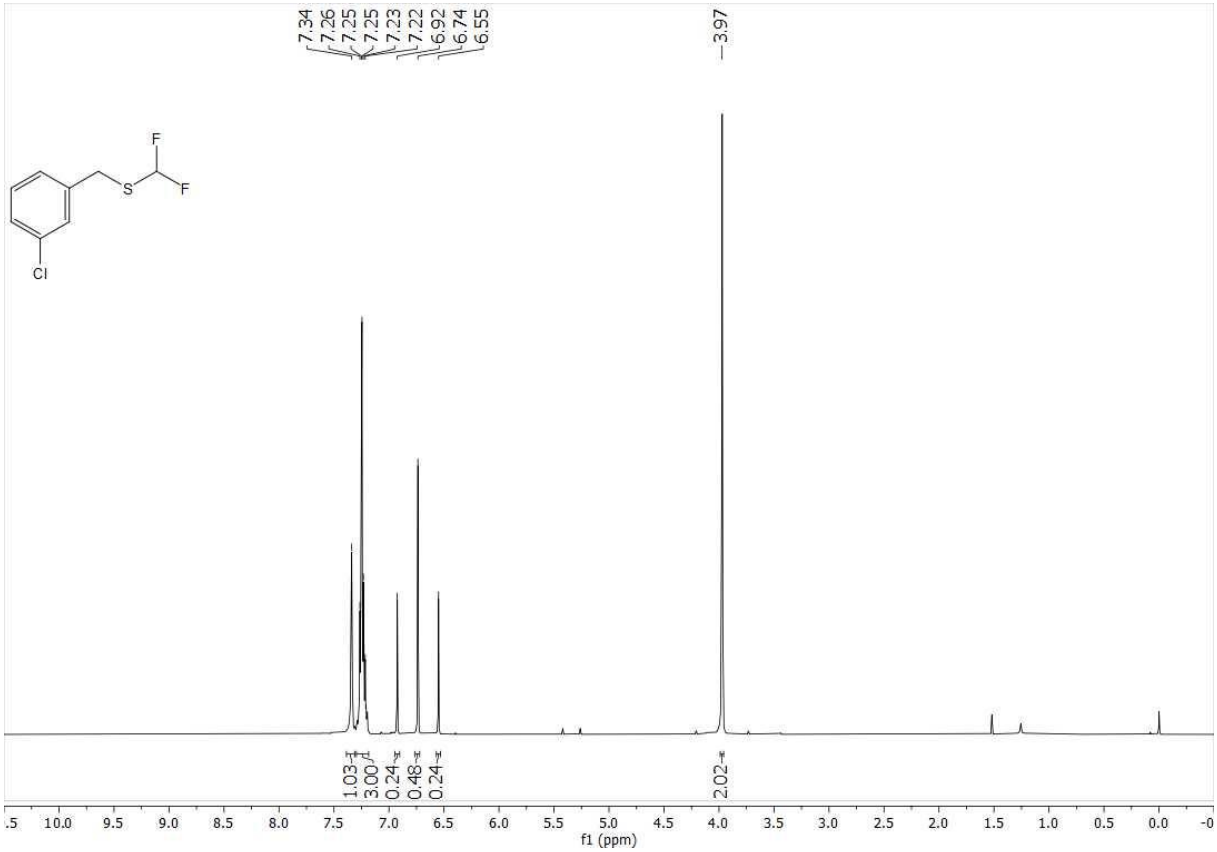
(difluoromethyl)(3-nitrobenzyl)sulfane **2n**

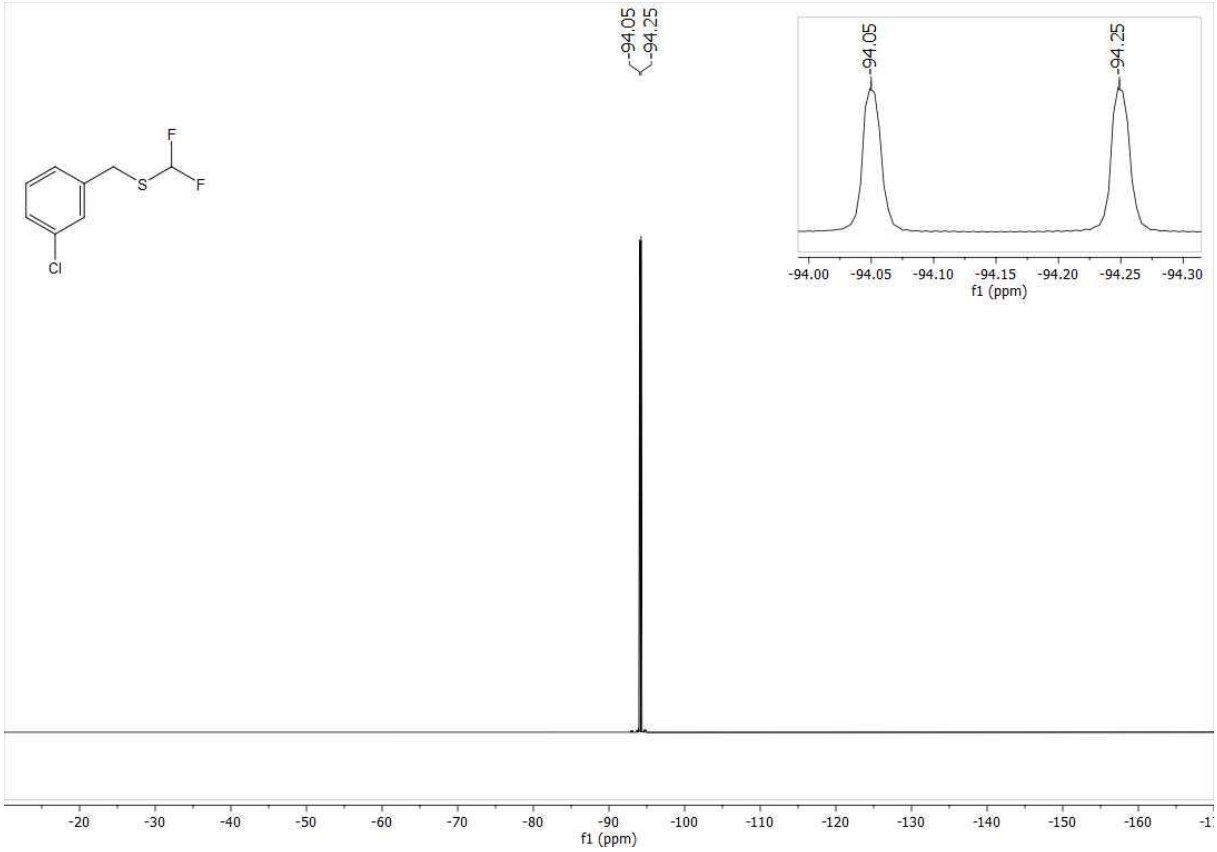


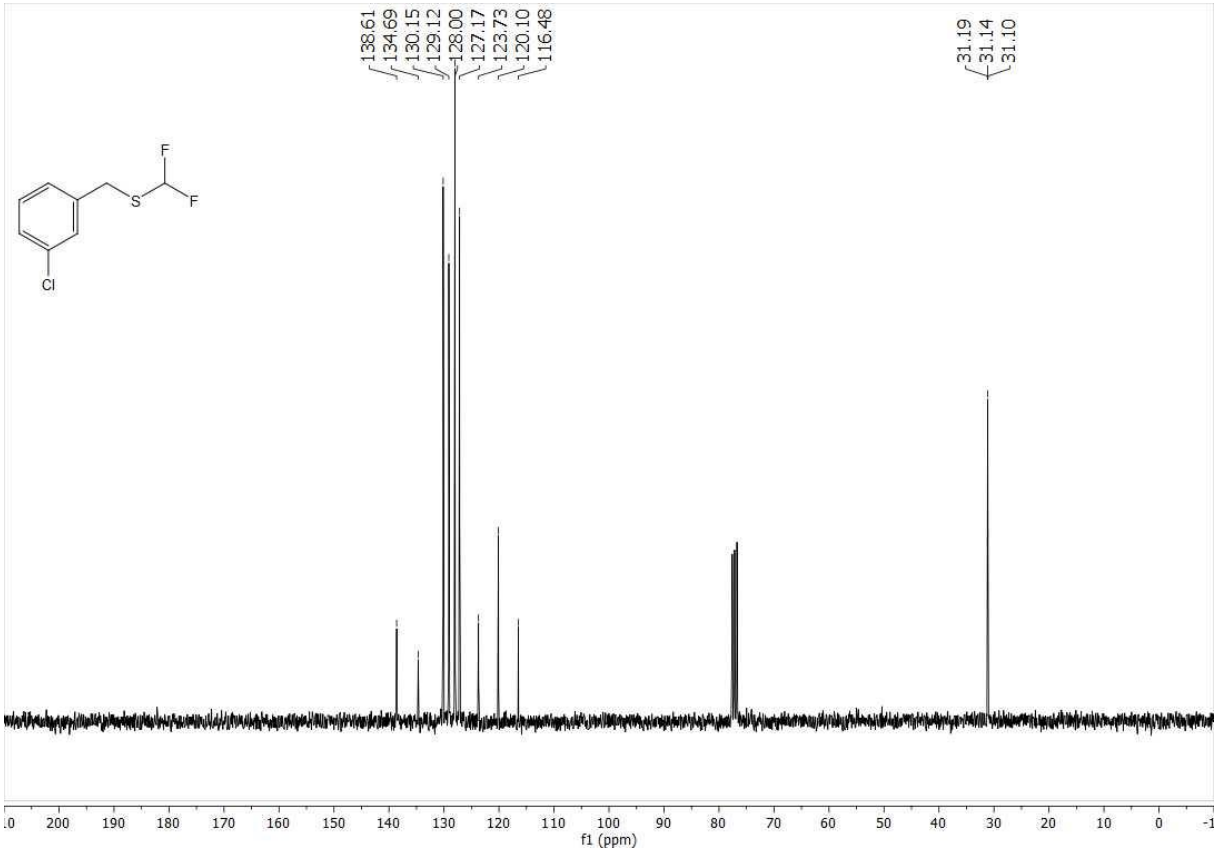



148.59
139.15
135.07
129.91
123.95
122.83
121.68
119.86
118.05
30.77
30.75
30.72
F
S
F
O
N+
O-
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

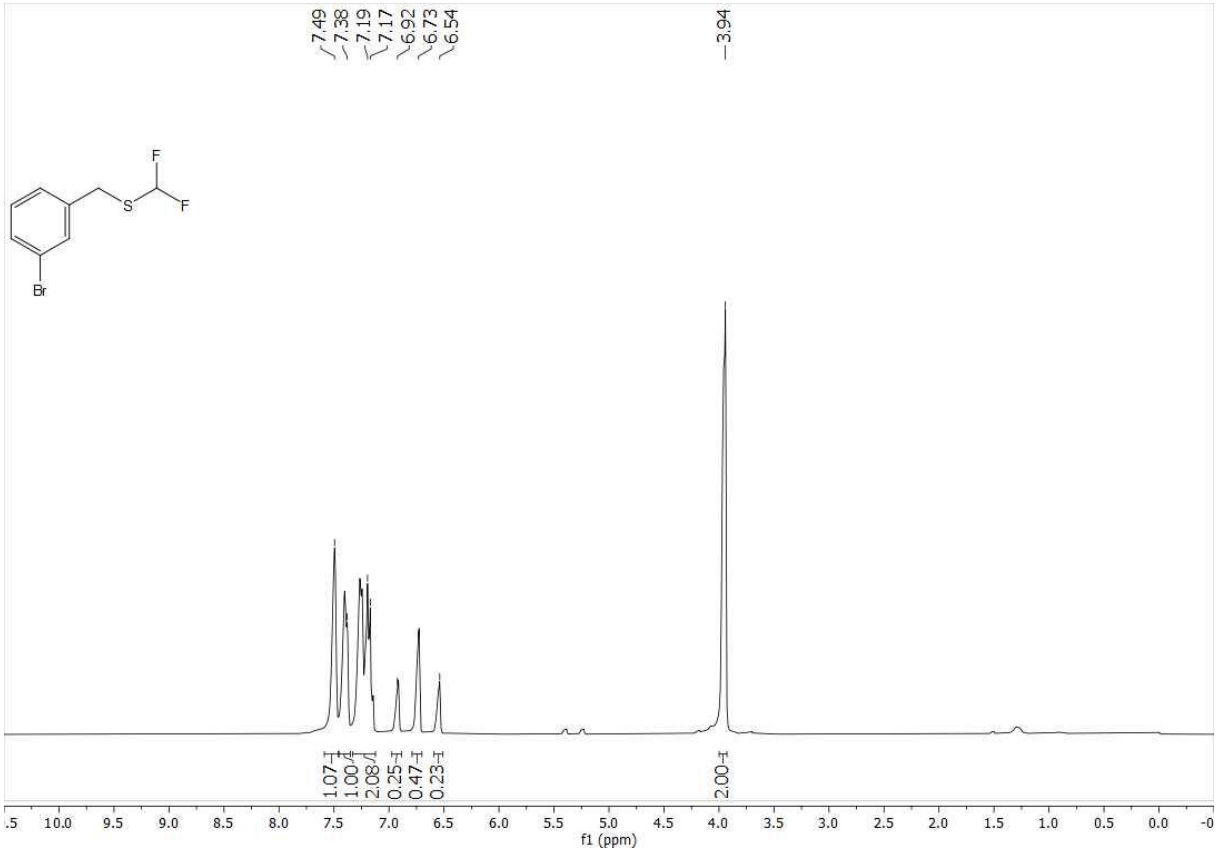
(difluoromethyl)(3-chlorobenzyl)sulfane **2o**

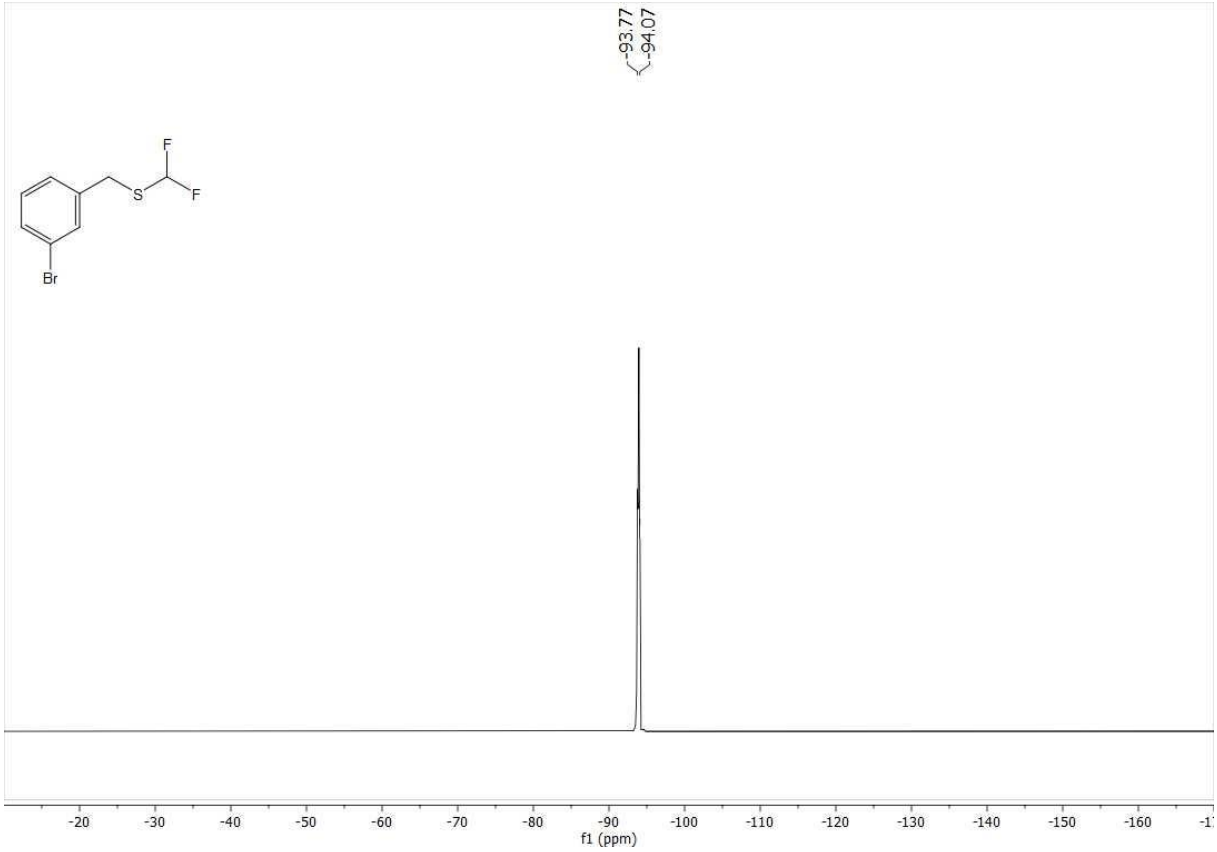


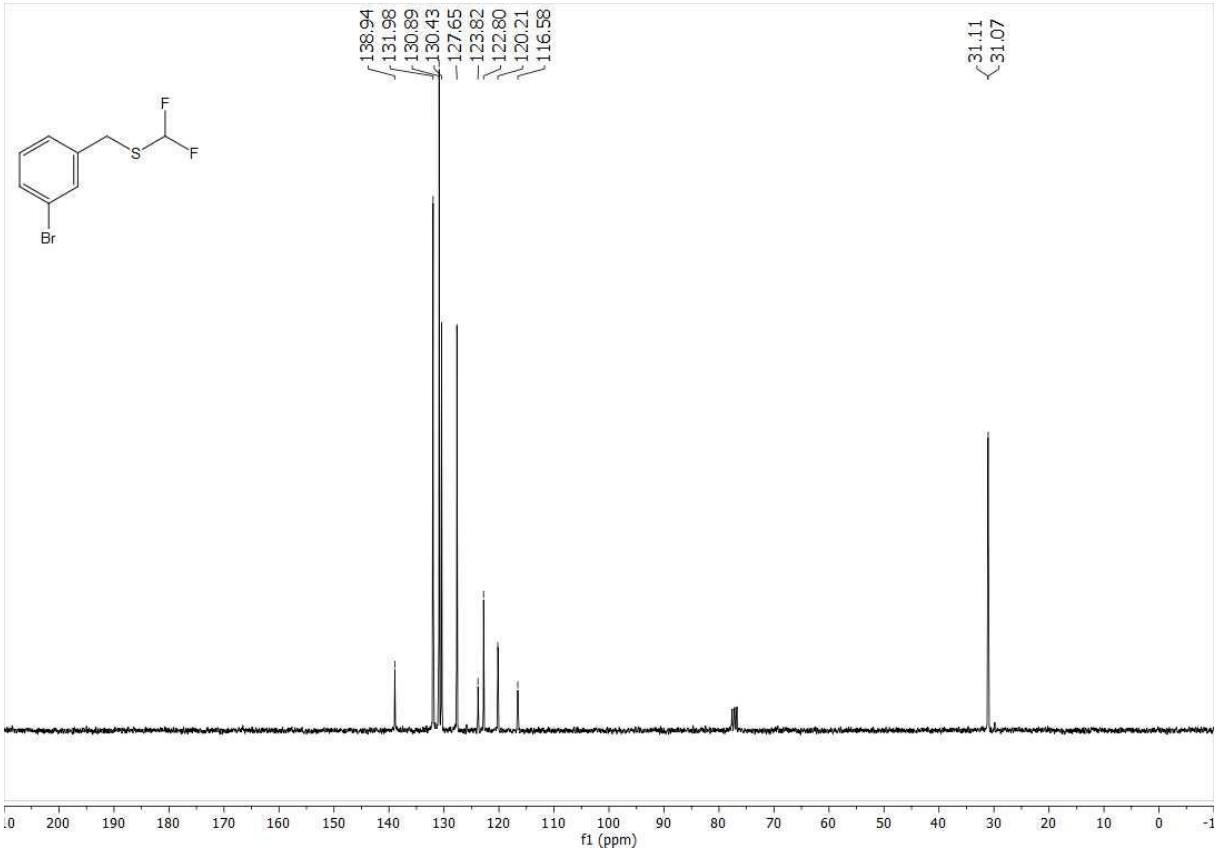



138.61
134.69
130.15
129.12
128.00
127.17
123.73
120.10
116.48
31.19
31.14
31.10
F
S
F
Cl
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

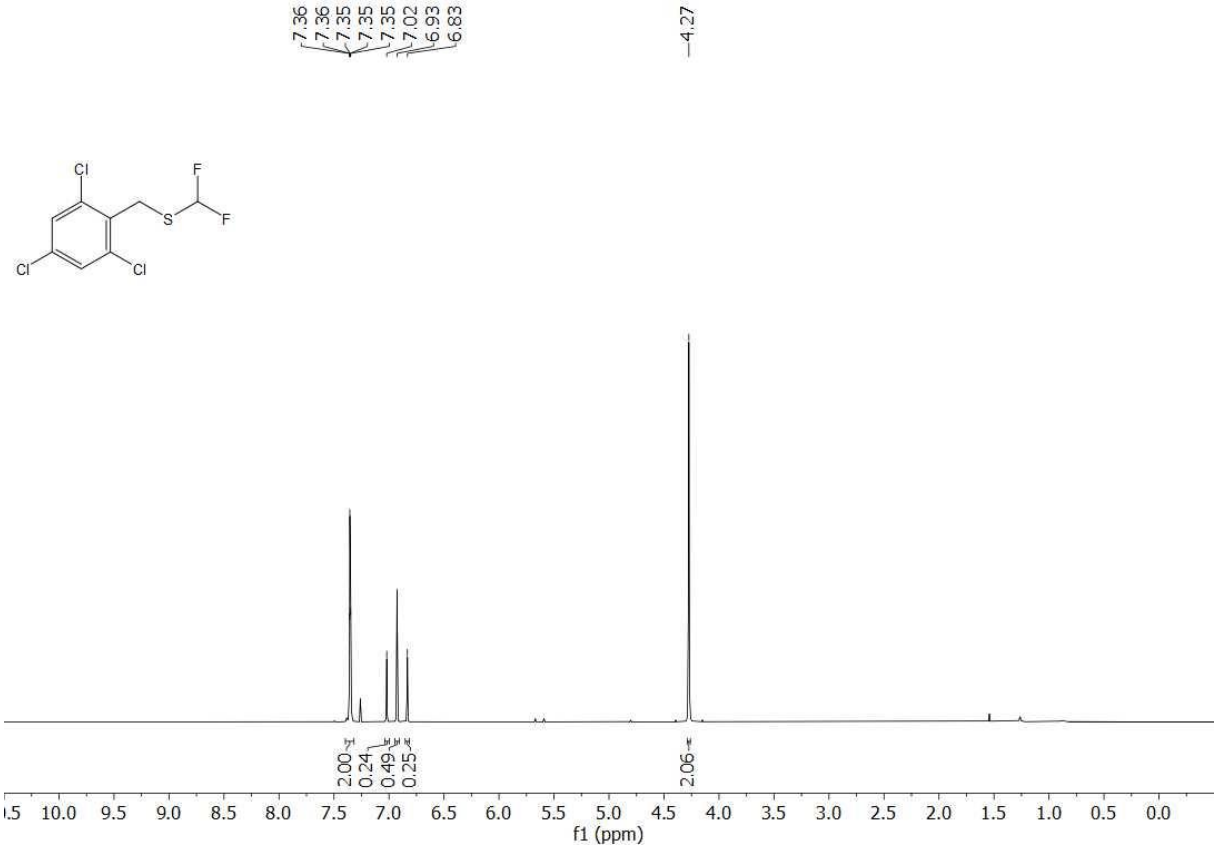
(difluoromethyl)(3-bromobenzyl)sulfane **2p**

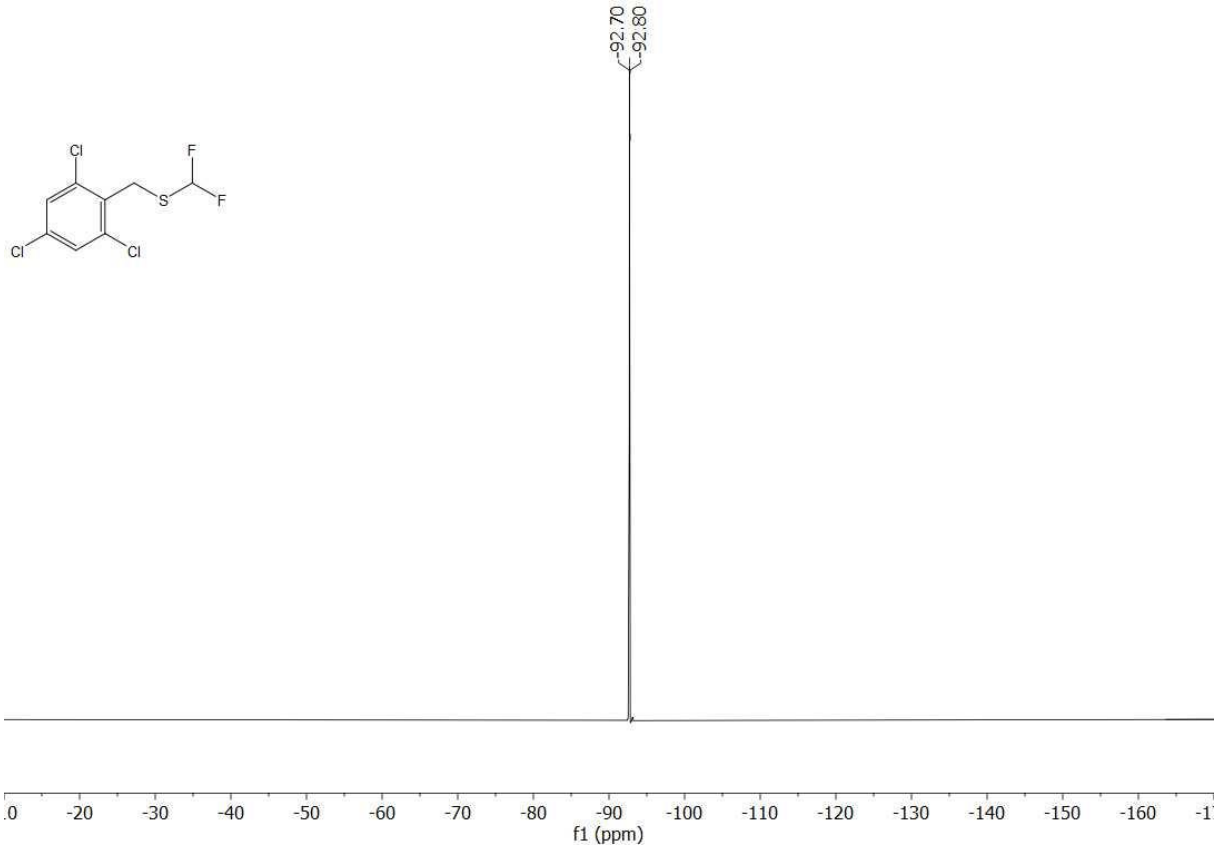


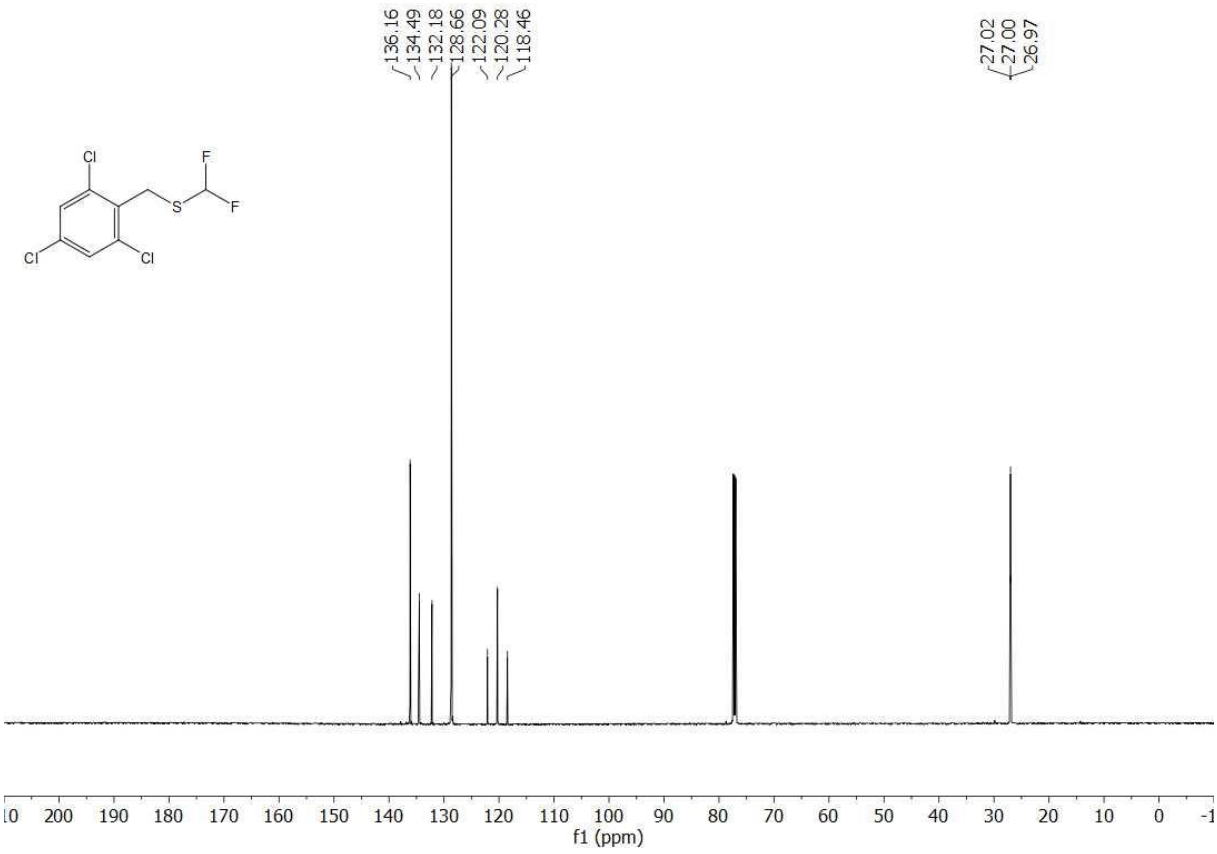



138.94
131.98
130.89
130.43
127.65
123.82
122.80
120.21
116.58
31.11
31.07
F
S
F
Br
f1 (ppm)

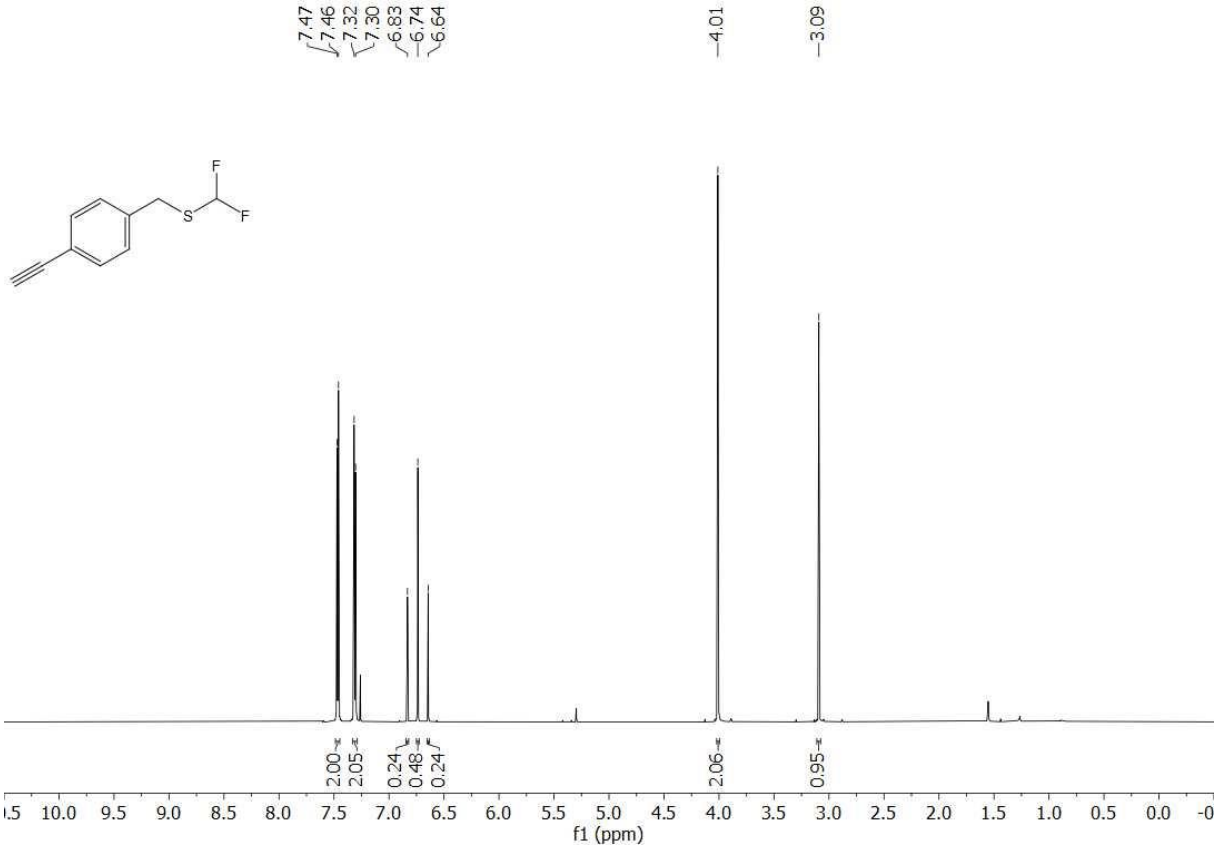
(difluoromethyl)(2,4,6-trichlorobenzyl)sulfane **2q**

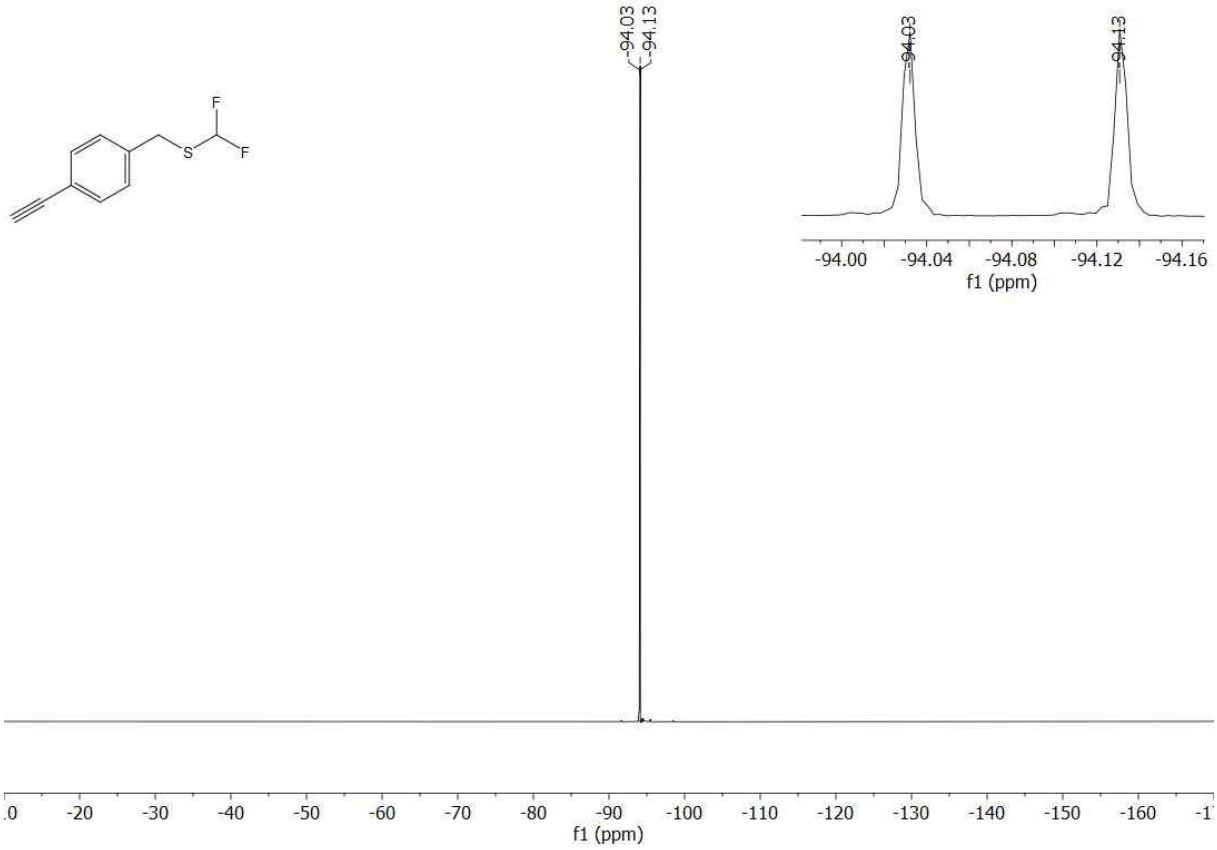


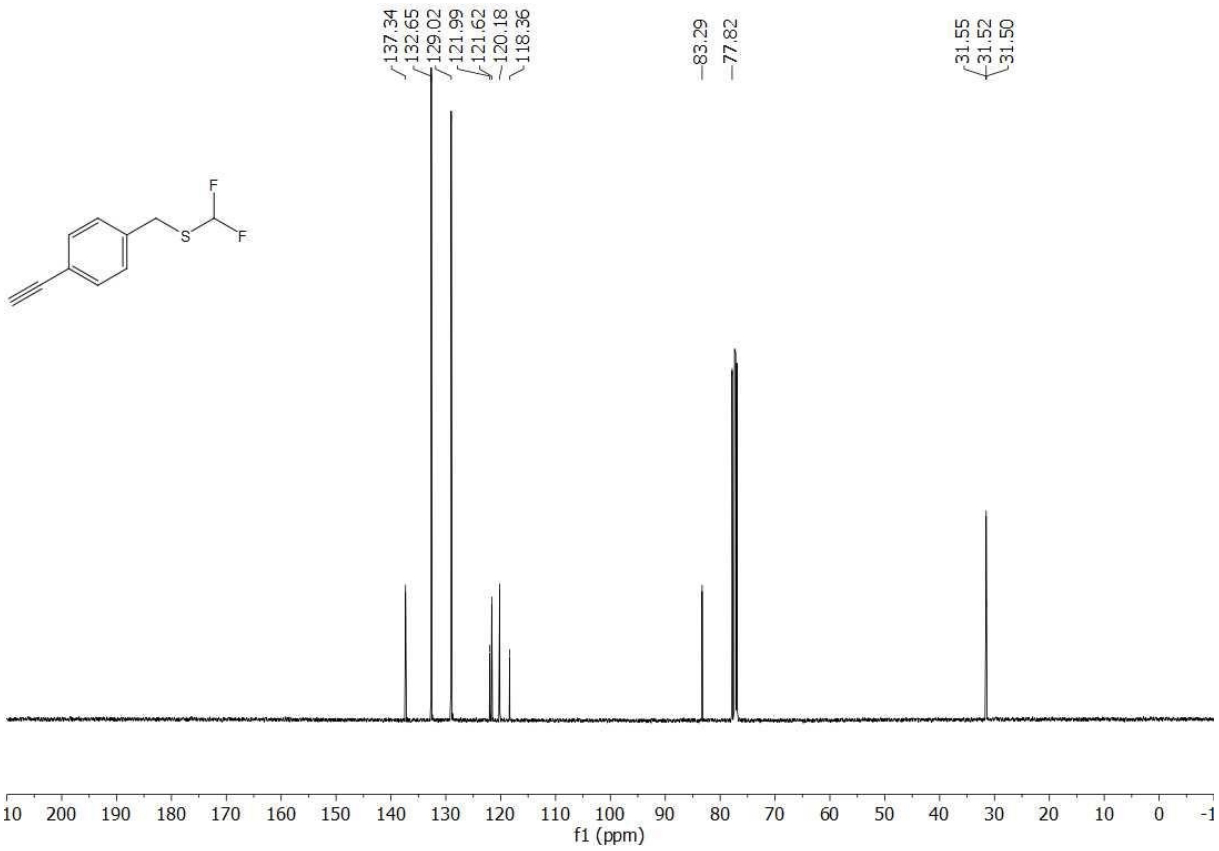



136.16
134.49
132.18
128.66
122.09
120.28
118.46
27.02
27.00
26.97
Cl
F
S
F
Cl
Cl
f1 (ppm)

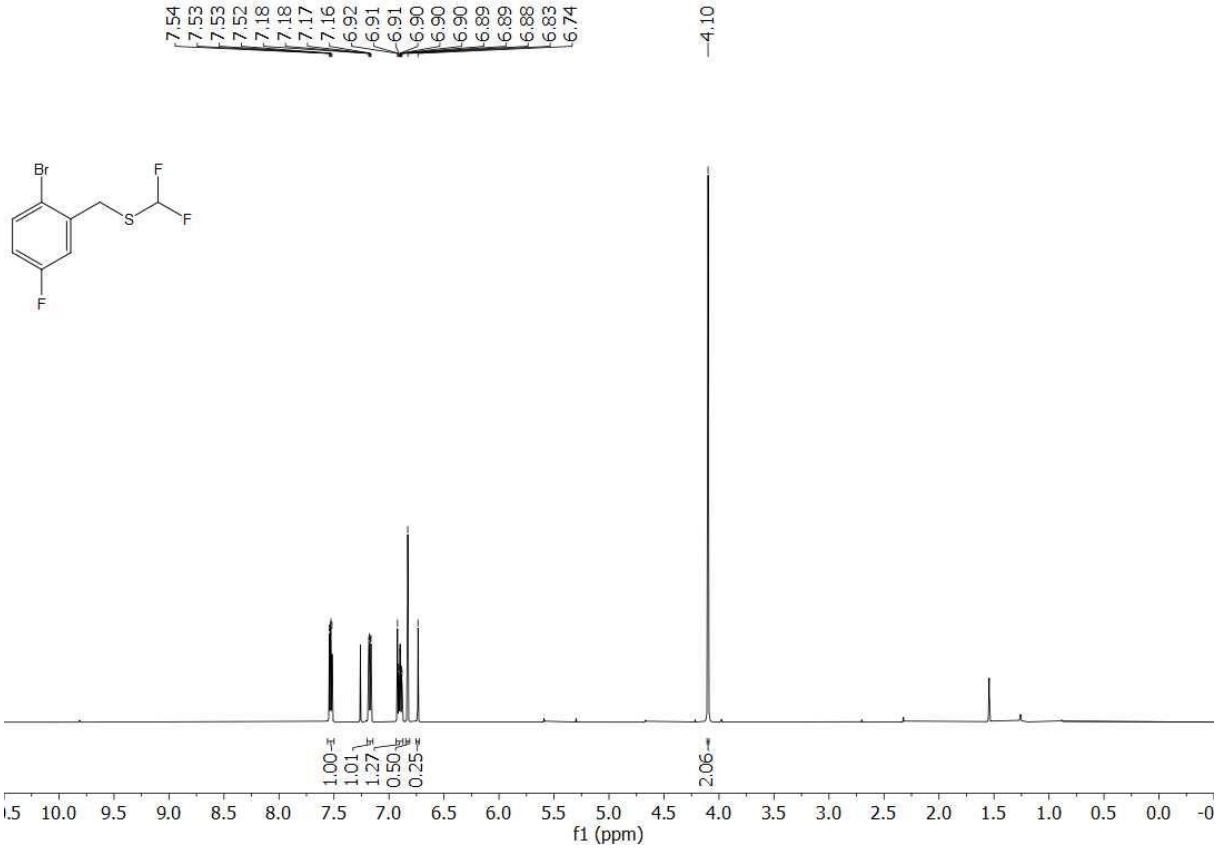
(difluoromethyl)(4-ethynylbenzyl)sulfane **2r**

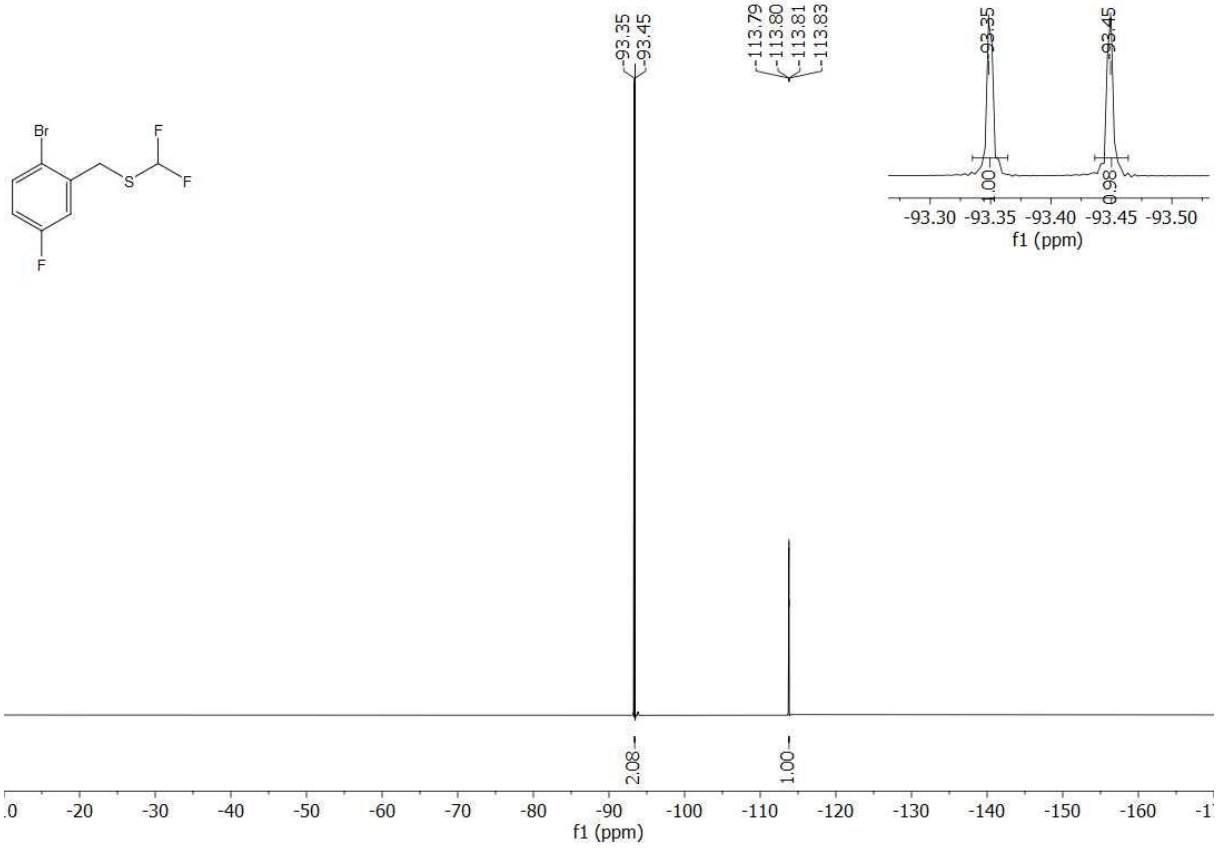


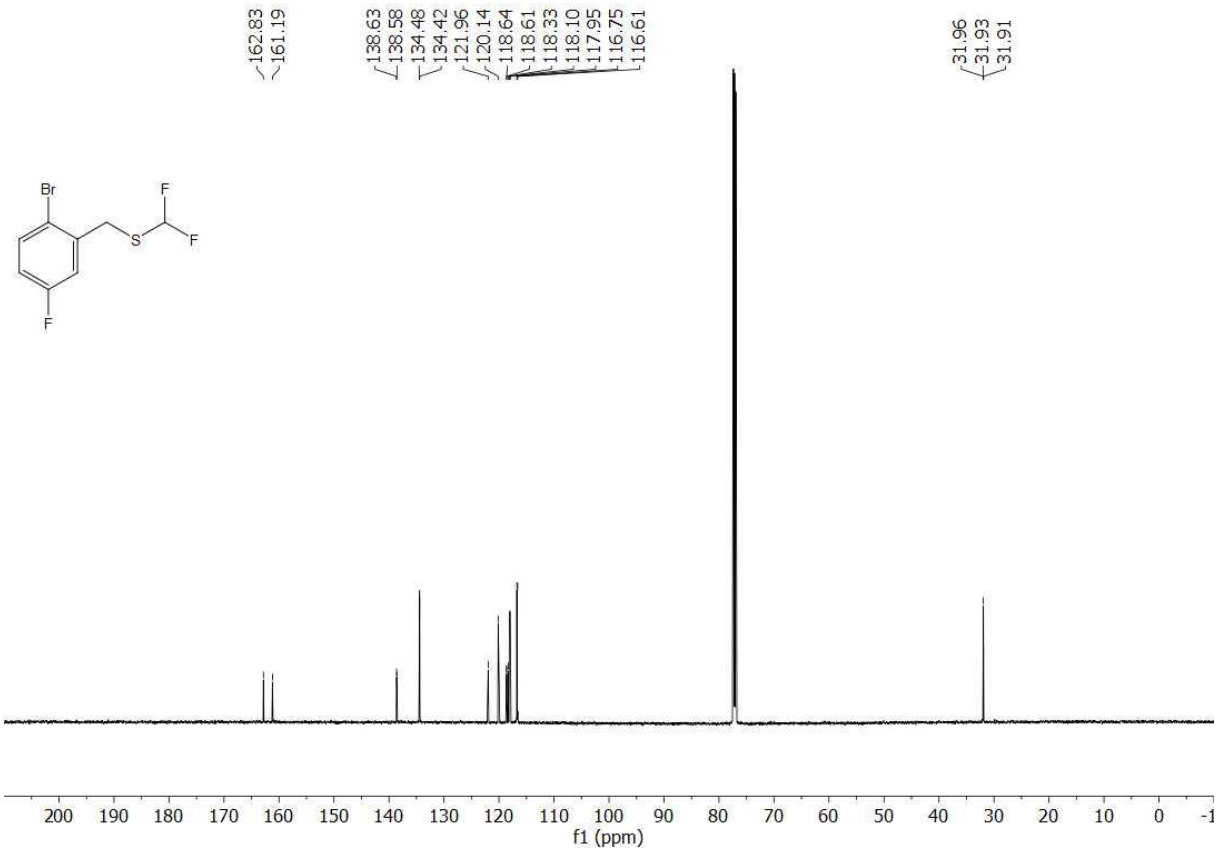



137.34
132.65
129.02
121.99
121.62
120.18
118.36
83.29
77.82
31.55
31.52
31.50
F
S
F
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

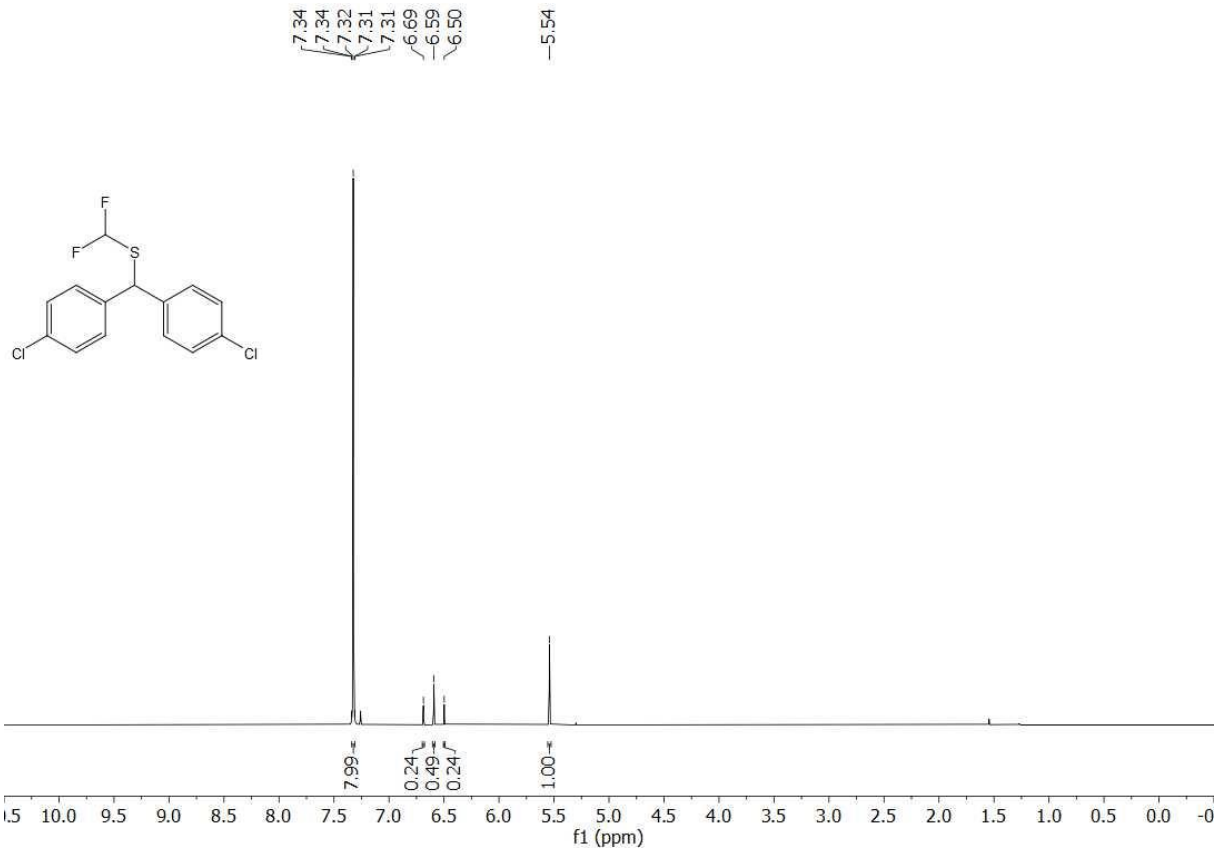
(2-bromo-5-fluorobenzyl)(difluoromethyl)sulfane **2s**

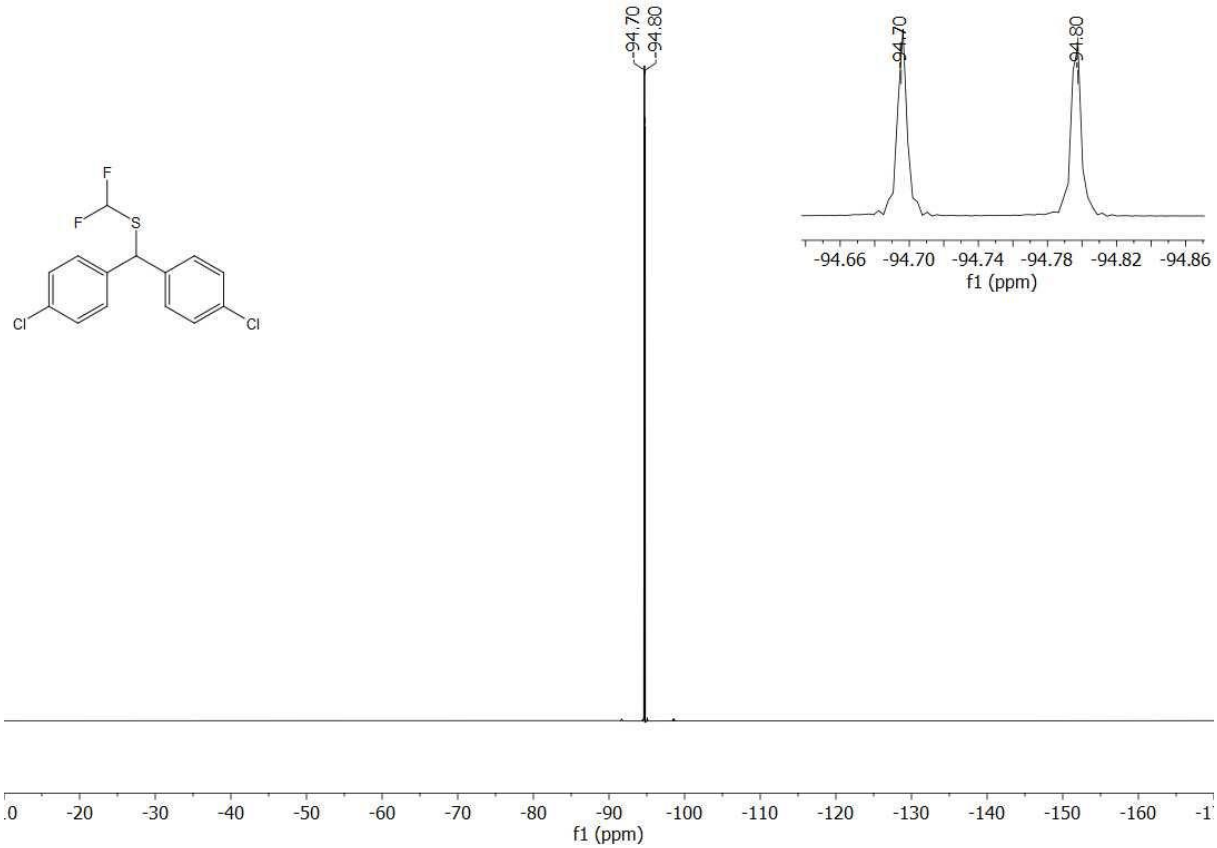


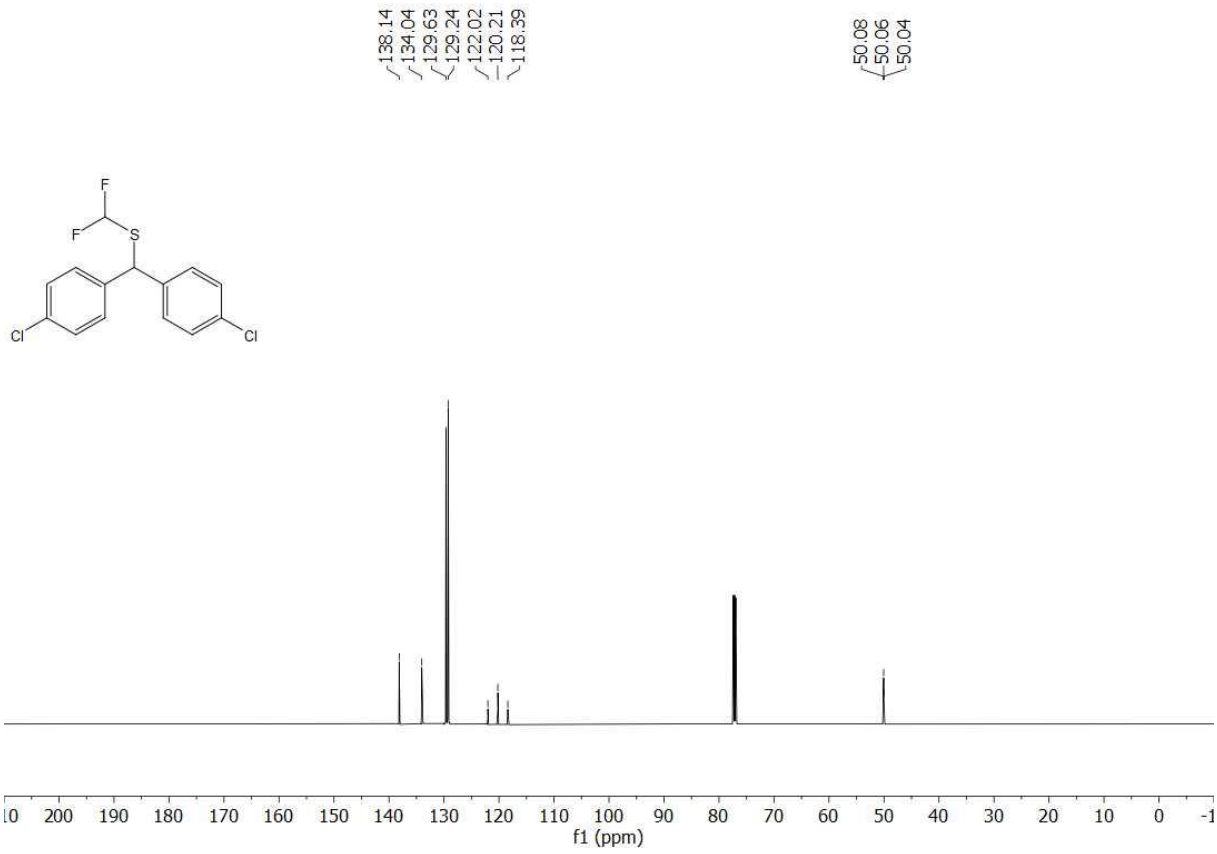



162.83
161.19
138.63
138.58
134.48
134.42
121.96
120.14
118.64
118.61
118.33
118.10
117.95
116.75
116.61
31.96
31.93
31.91
Br
F
S
F
F
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

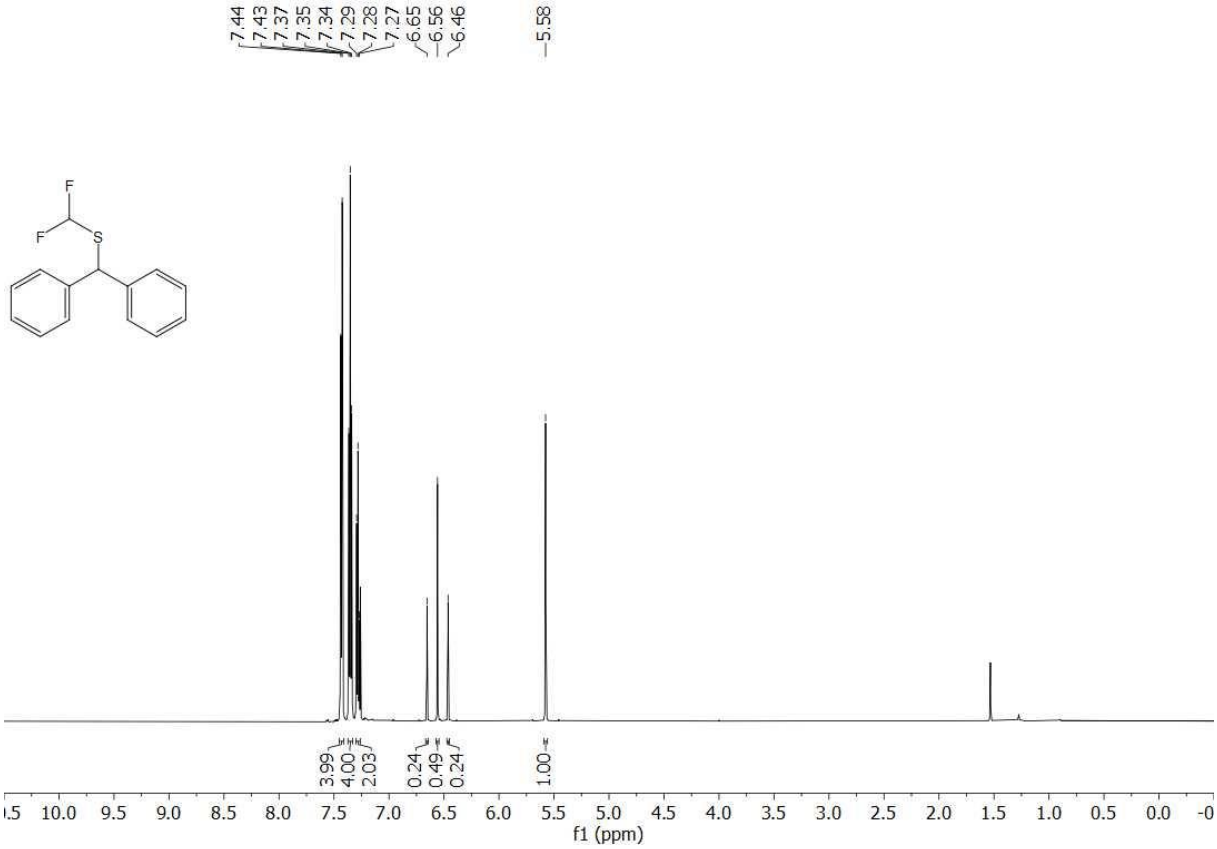
(bis(4-chlorophenyl)methyl)(difluoromethyl)sulfane **2t**

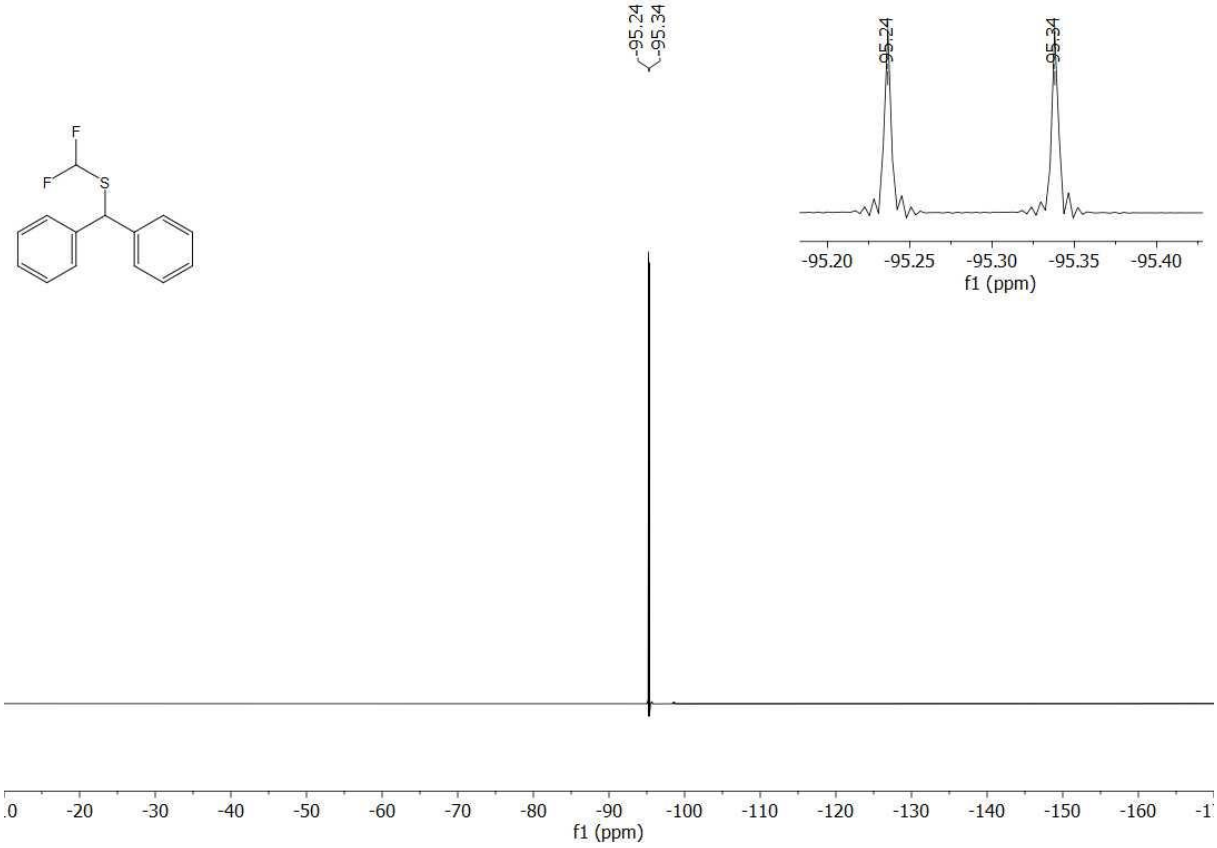


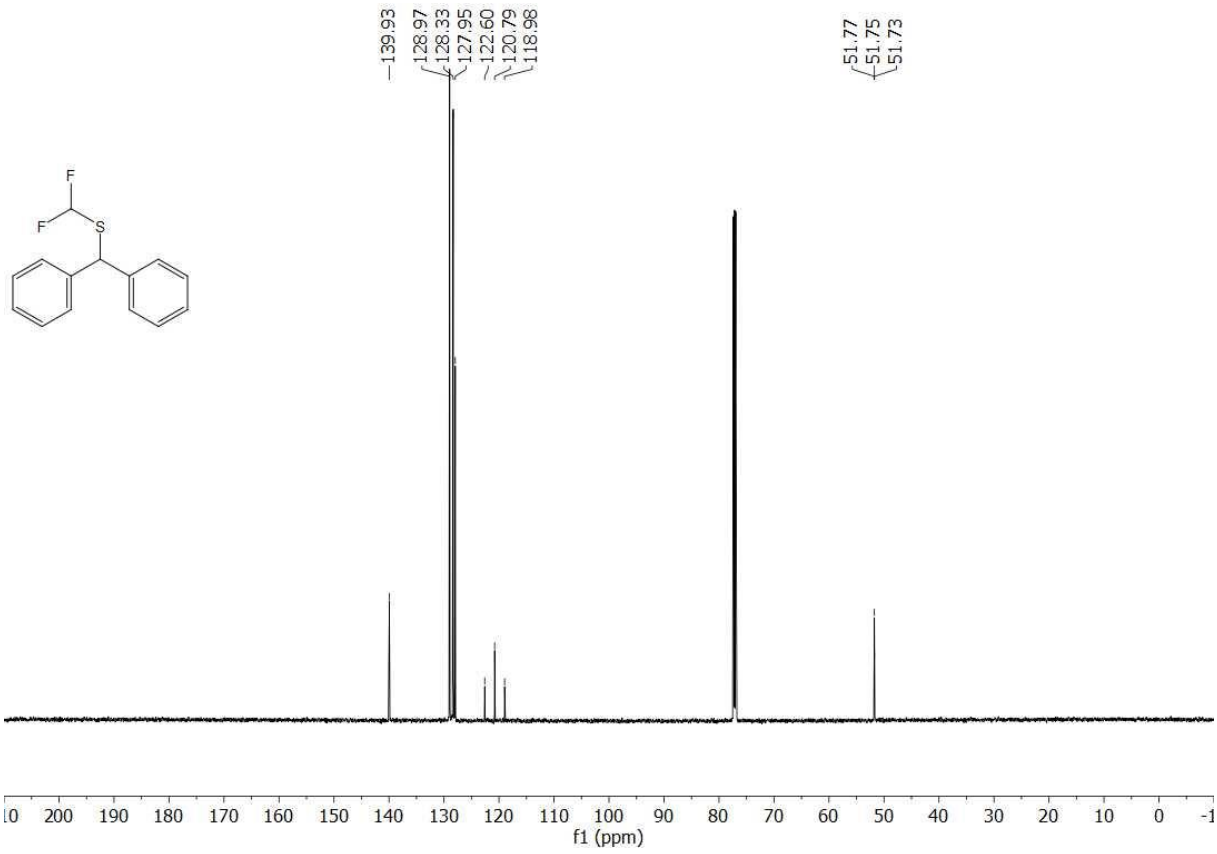



138.14
134.04
129.63
129.24
122.02
120.21
118.39
50.08
50.06
50.04
F
F
S
Cl
Cl
f1 (ppm)

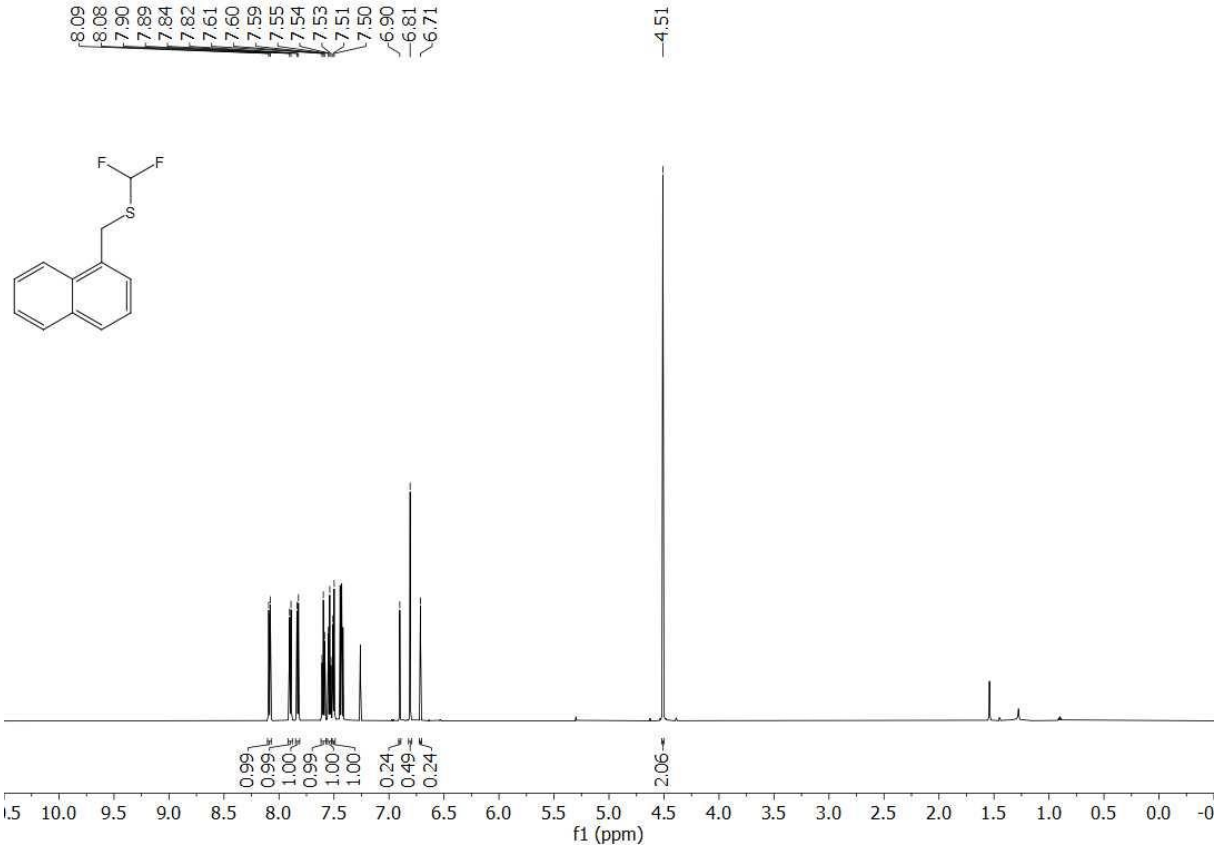
benzhydryl(difluoromethyl)sulfane **2u**

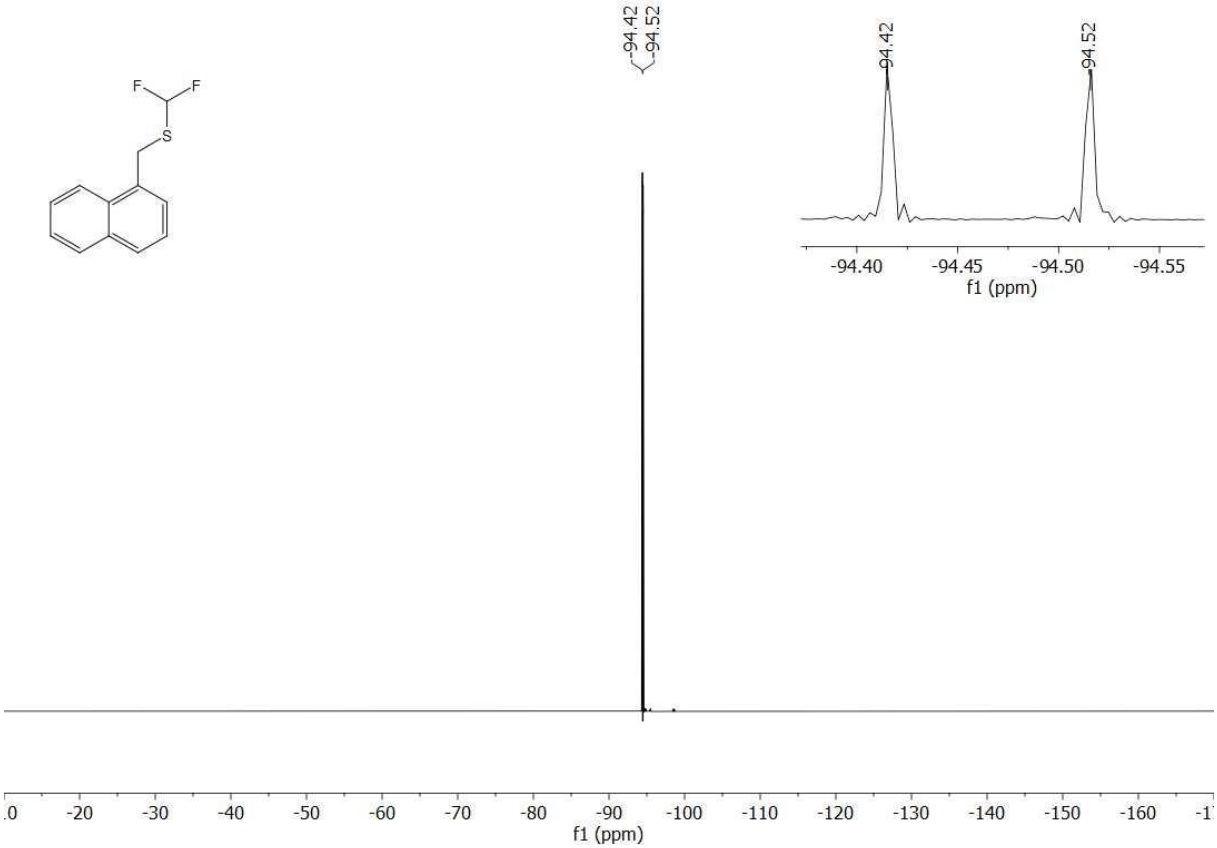


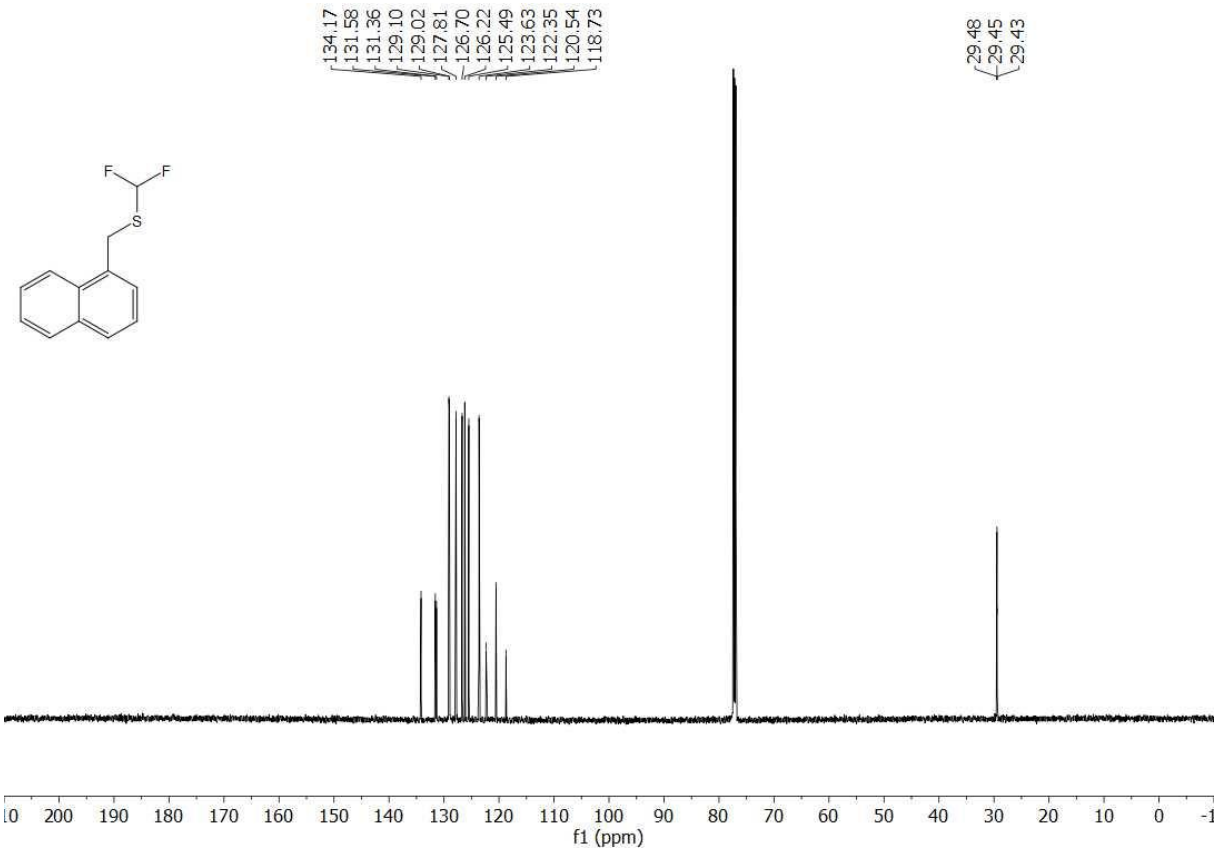



139.93
128.97
128.33
127.95
122.60
120.79
118.98
51.77
51.75
51.73
F
F
S
f1 (ppm)

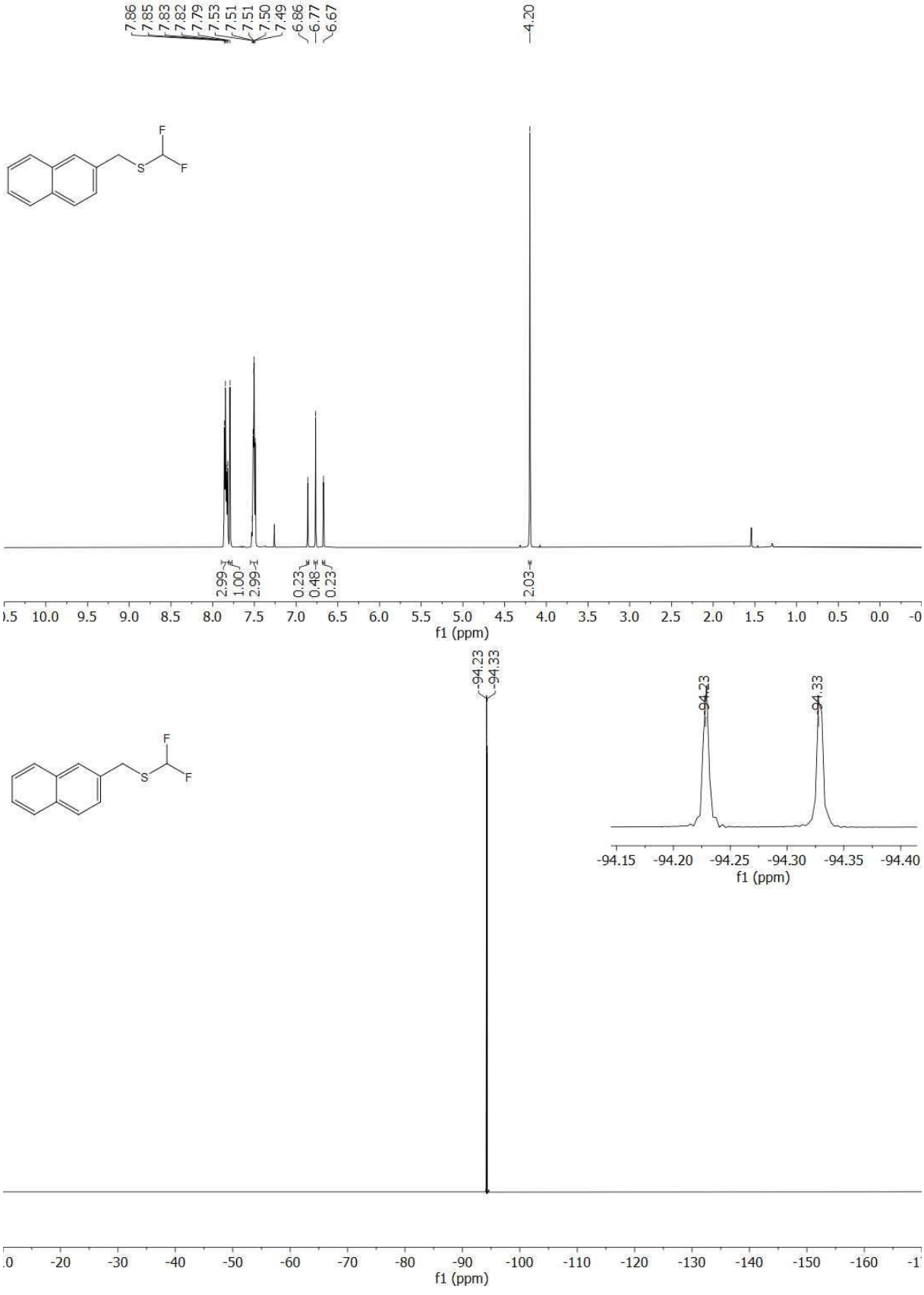
(difluoromethyl)(naphthalen-1-ylmethyl)sulfane **2v**

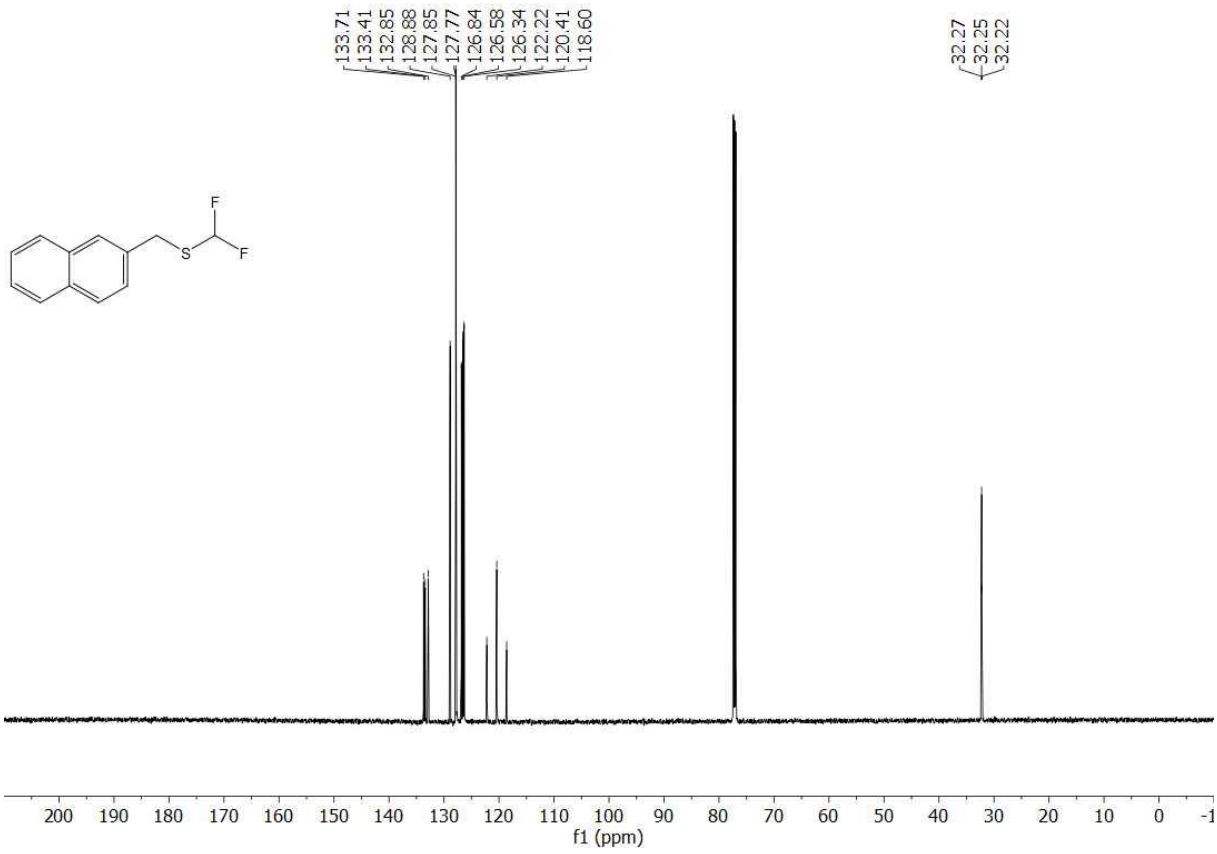




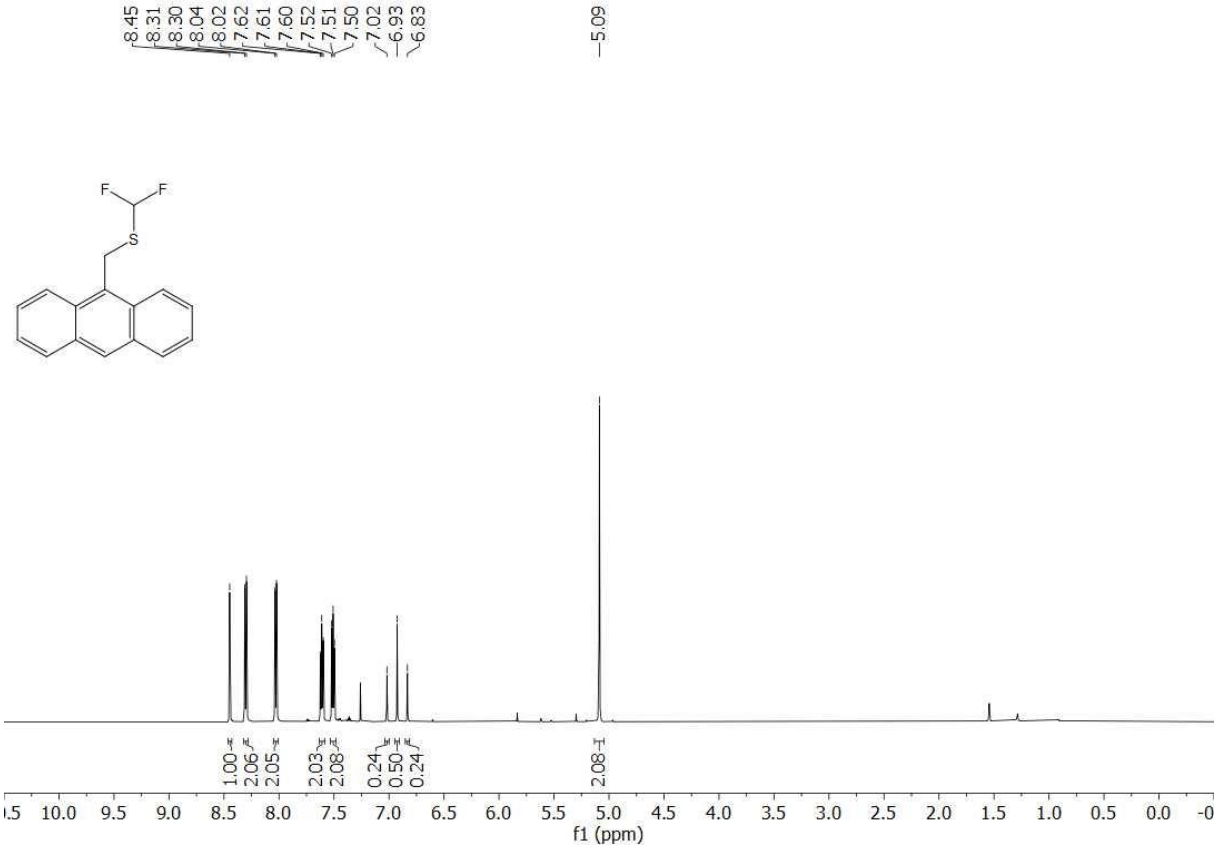

134.17
131.58
131.36
129.10
129.02
127.81
126.70
126.22
125.49
123.63
122.35
120.54
118.73
29.48
29.45
29.43
F
F
S
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

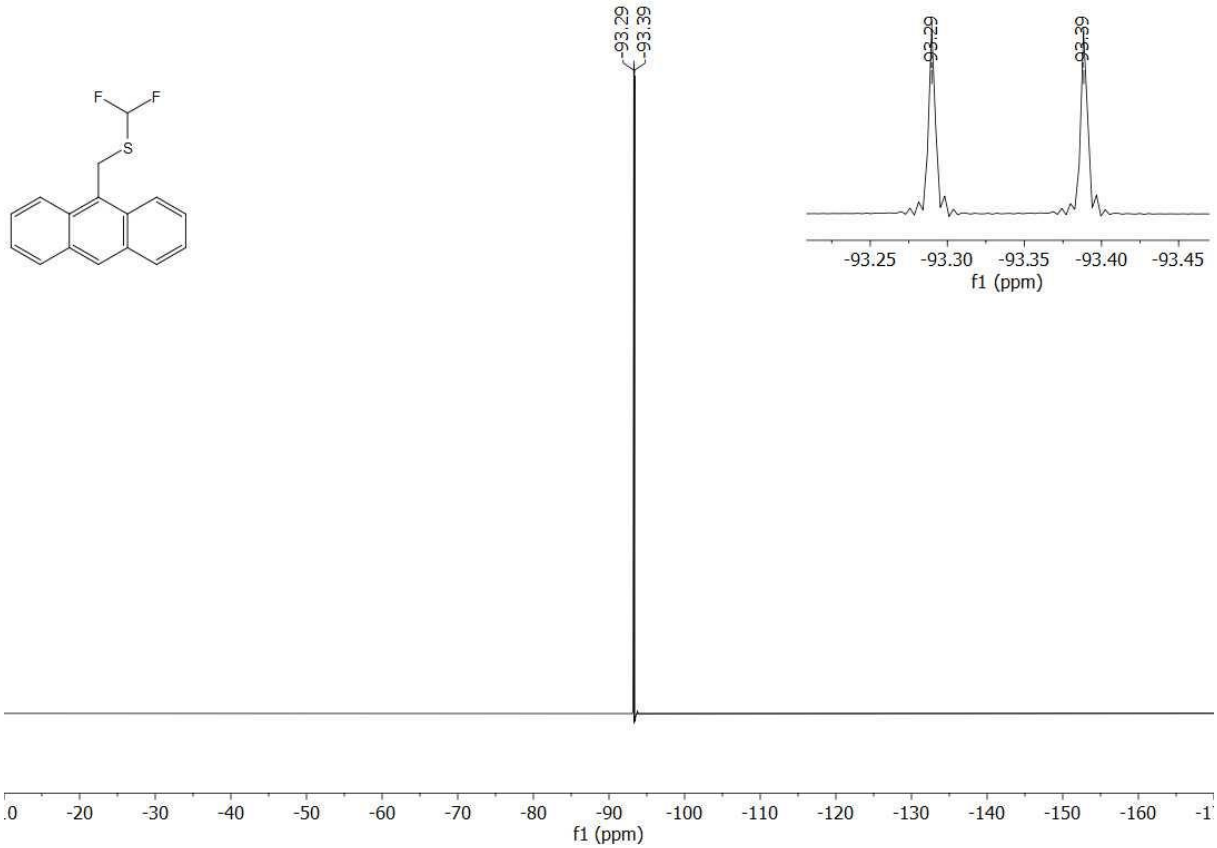
(difluoromethyl)(naphthalen-2-ylmethyl)sulfane **2w**

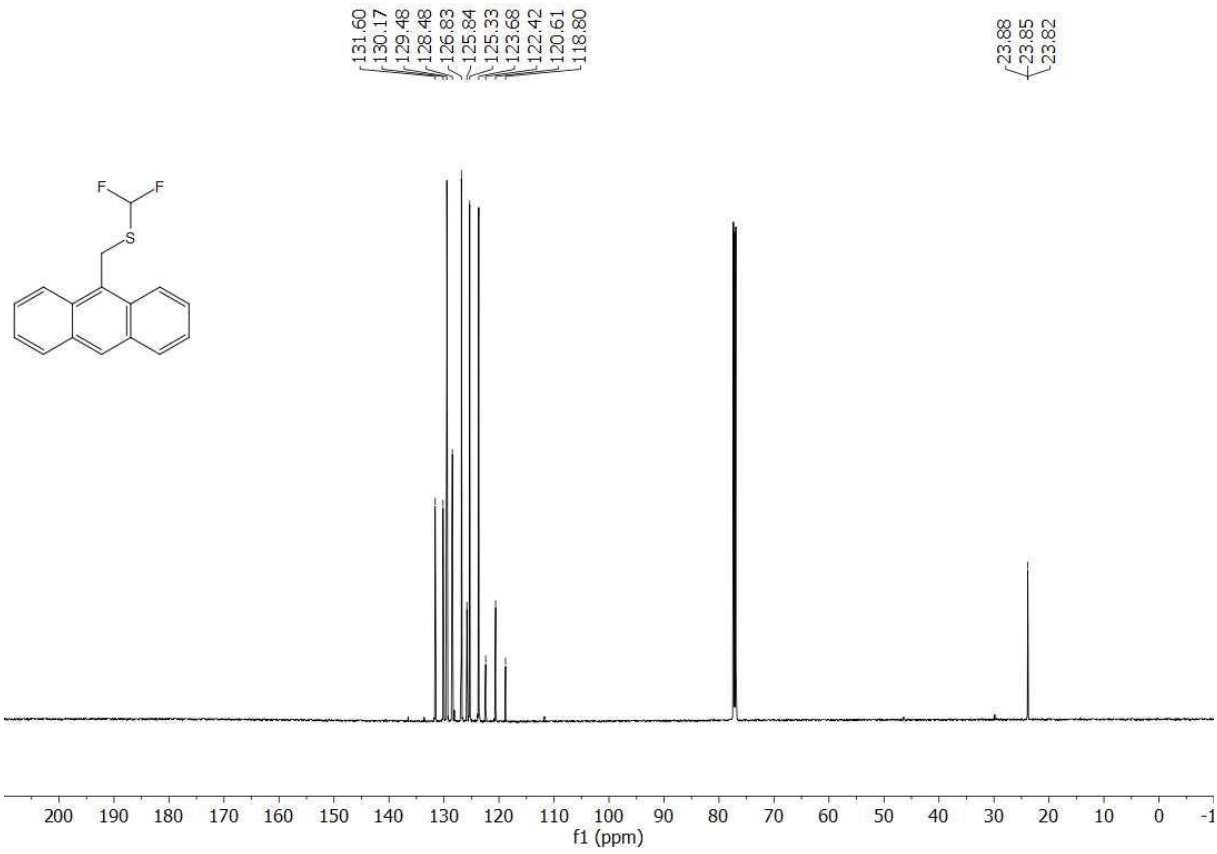



133.71
133.41
132.85
128.88
127.85
127.77
126.84
126.58
126.34
122.22
120.41
118.60
32.27
32.25
32.22
F
S
F
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

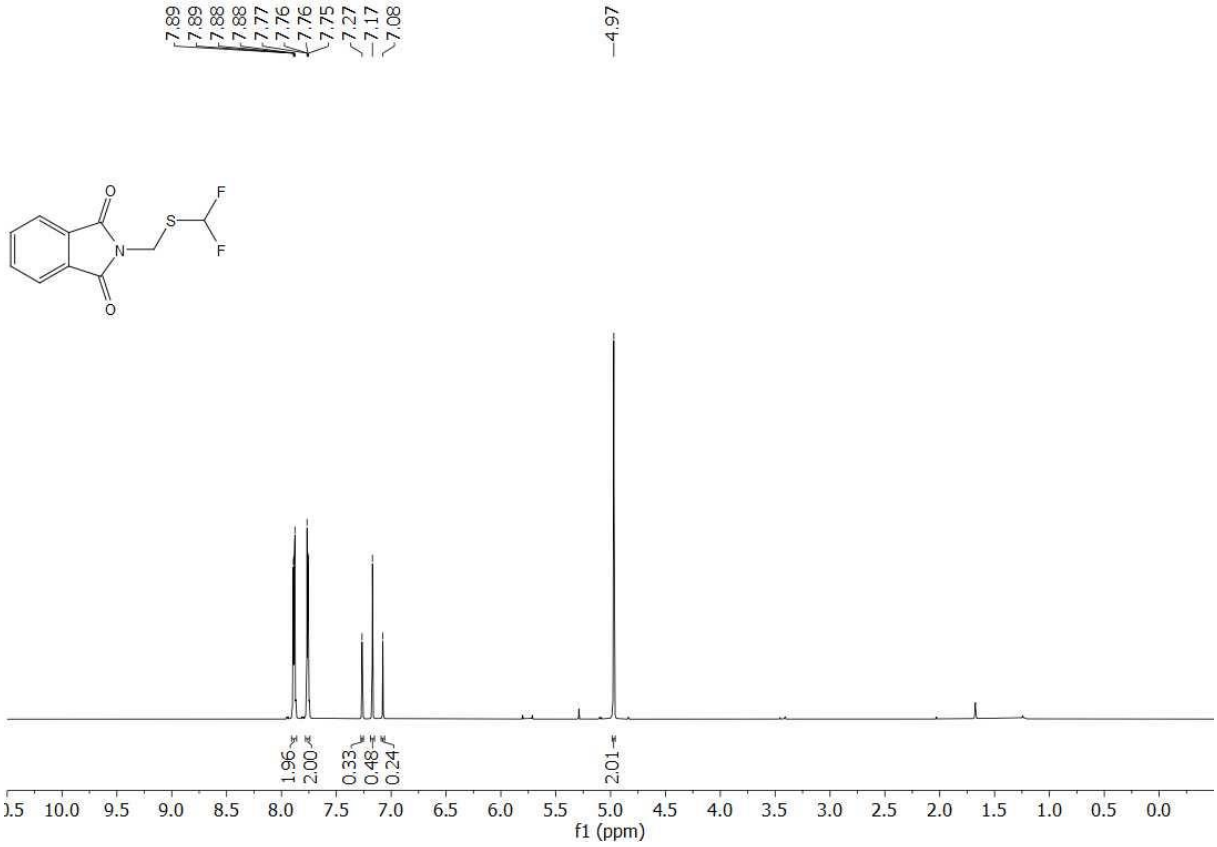
(anthracen-9-ylmethyl)(difluoromethyl)sulfane **2x**

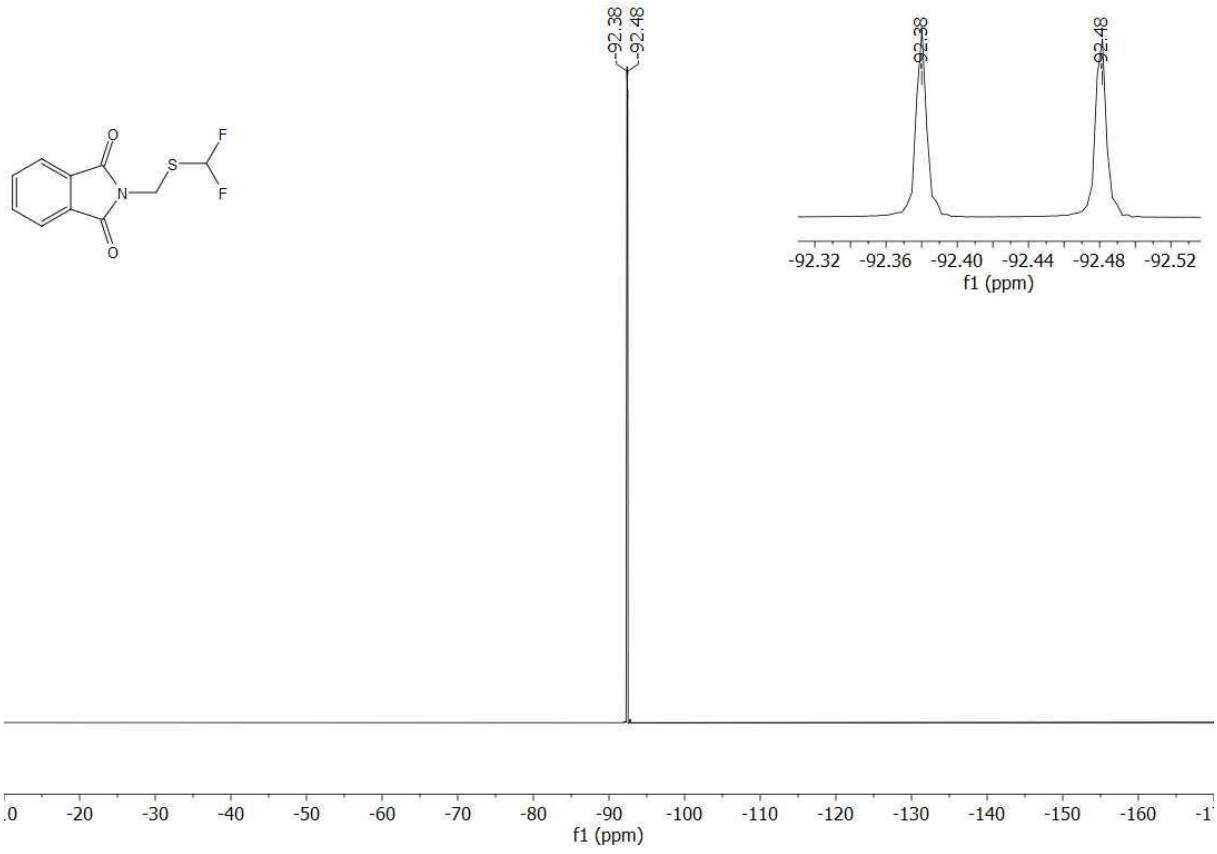


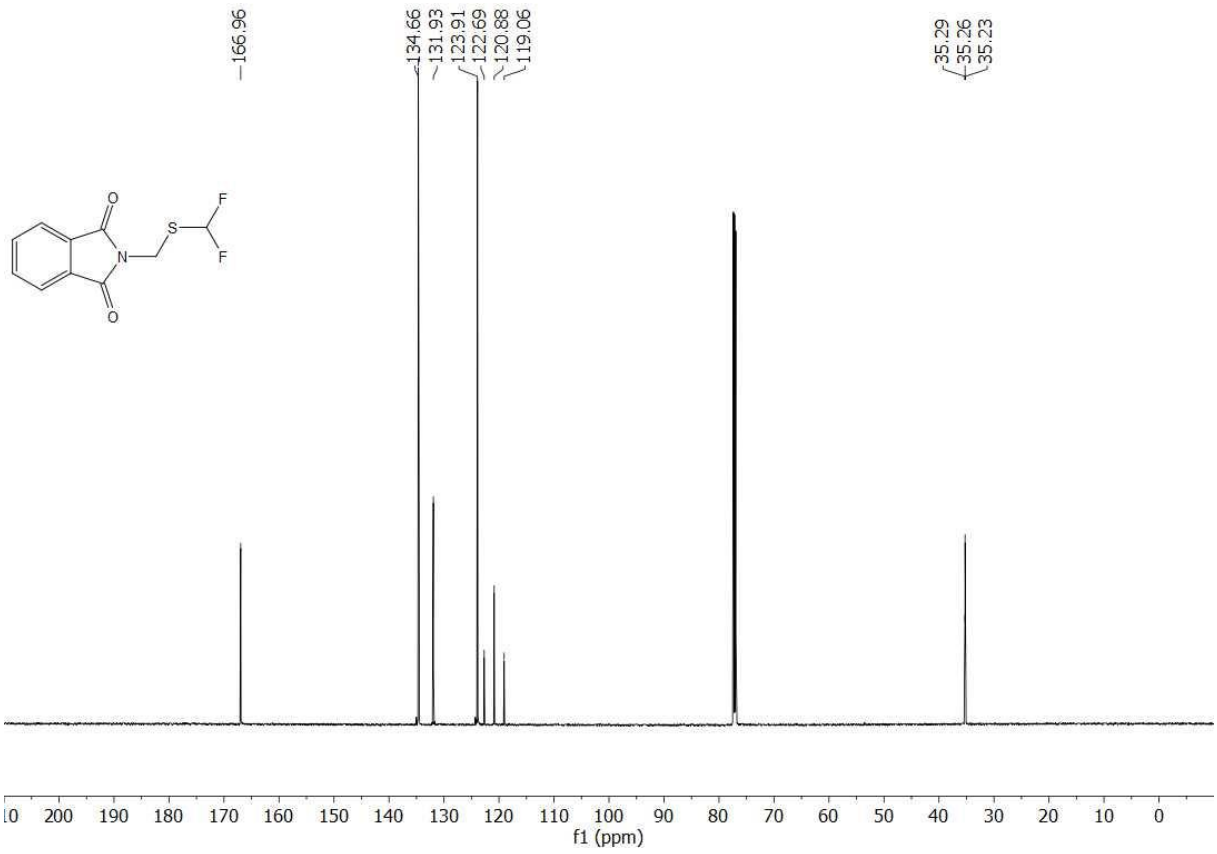



131.60
130.17
129.48
128.48
126.83
125.84
125.33
123.68
122.42
120.61
118.80
23.88
23.85
23.82
F
F
S
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

2-(((difluoromethyl)thio)methyl)isoindoline-1,3-dione **2y**






166.96
134.66
131.93
123.91
122.69
120.88
119.06
35.29
35.26
35.23
O
N
O
S
F
F
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)