INVESTIGATION OF NEW MECHANOCHEMICAL AND ORGANOFLUORINE SYNTHETIC METHODS

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A thesis presented for the award of degree of

Master of Philosophy (Chemistry)

of

Cardiff University

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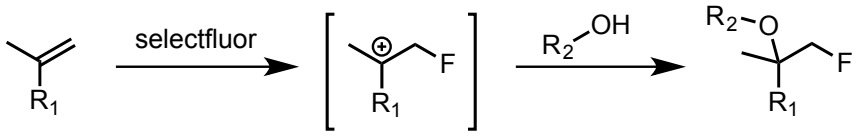
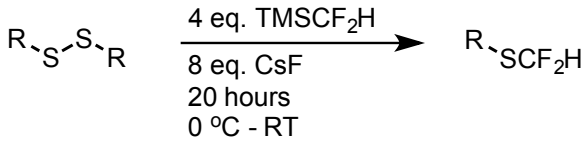
Abstract

Novel methods for the introduction of fluorine into organic molecules were investigated. The first method explored the use of mechanochemistry to introduce nucleophiles other than the solvent, acetonitrile, during a fluorous Ritter reaction. However, it was found that oxygen-based nucleophiles were able to attack the intermediate carbocation despite the presence of acetonitrile. A substrate scope of this oxy-fluorination reaction was investigated and moderate to good yields were achieved.



Scheme 1 The oxyfluorination of alkenes

The second method explored was the synthesis of difluoromethythioethers. It was discovered that disulfides could be used as precursers with difluoromethyltrimethylsilane ($TMSCF_2H$) as the difluoromethylating reagent. The reaction was optimised and substrate scope explored demonstrating a versatile method that could afford difluoromethylthioethers in good yields.



Scheme 2 Synthesis of difluoromethylthioethers using $TMSCF_2H$

Acknowledgements

Firstly, I must express my gratitude to Dr Duncan Browne for his constant support and guidance throughout this year and this project. Also for the opportunity to study in his group and for showing me how rewarding research can be.

I would also like to thank my labmates throughout the year for the fun times and making lab work that bit more exciting. A special mention to Christiane, Micol, Simon, Stephen, Alex and Laura.

Finally, I would like to thank my family for their help, support and encouragement during this year.

Some of the results presented in **Table 5** and **Table 6** were obtained by Alex Bukvic, a Pfizer summer student mentored by me. In addition, during the work on the synthesis of difluoromethylthioethers, a closely related paper was published on the same topic[1], in order to make more rapid progress several researchers contributed to the project. Owing to this, some of the optimisation reactions presented in **Table 7** and **Table 8** were performed in collaboration with Stephen Alston and Christiane Schotten. The non-commercially available thiols used were synthesised by Christiane Schotten.

Table of Contents

1 Mechanochemical Fluorination

1.1 Mechanochemistry

Mechanochemistry is the process of using mechanical energy to induce chemical transformations. This is usually performed by grinding, although other methods, such as ultrasound, have been used.[2] Here, I will focus on grinding as the mechanochemical method. It is not a new idea to grind materials together in order to change their properties and cause reactions is not a new idea. The first example was likely to be around the 4th century BC, making elemental mercury by grinding cinnabar with acetic acid in a copper vessel.[3] In the 1890s, it was shown that grinding metal halides could cause different outcomes to heating, causing decomposition instead of melting or sublimation.[3] These examples all made use of traditional grinding methods like a pestle and mortar. However, the pestle and mortar is not a reliable method, as individuals may have their own grinding technique as well as stamina and energy input. This can lead to reproducibility issues between operators. This led to the use of a ball mill for mechanochemistry. Ball mills were originally developed to grind powders to a certain particle size and are also used for grinding samples (hair, bones, etc.) for forensic analysis.

Figure 1: The MM400 mixer mill sold by Retsch

Figure 2 25 mL and 50 mL grinding jars, showing two different available sizes of milling balls.

Utilising the ball mill for mechanochemistry was developed in the late 1980s, as a method for making cocrystals which could not be made from solution.[4] The reactants are placed in the grinding jar with a ball bearing (typically stainless steel) as seen in **Figure 2**. The mill then shakes the jars in a shallow figure-of-eight motion at the programmed frequency. This causes the ball(s) to move and collide with the reactants and sides of the jar. These collisions release some of the kinetic energy of the ball as heat, with impact and shear forces on the reactant particles aiding reactivity. The exact mechanism of this is not well understood. Using physical models considering both the impact and sliding friction, it has been predicted that very localised hot spots are formed with temperatures exceeding 1000 ºC.[3] If such mechanisms were the main mechanism for reactivity in mechanochemical organic reactions extensive thermal decomposition should be observed. As it is not, it has been suggested that reactions involving the breaking of covalent bonds proceed via a bulk liquid eutectic state,[5] however this is not certain, and there are examples for which this is not the case.[6]

Organic reactions performed in ball mills are known[7] and these sometimes proceed with a shorter reaction time, give higher yields, or require milder reaction conditions compared to those carried out in batch by traditional solution-based methods. Another possible advantage of the use of ball milling is to aim for more sustainable and safer

chemistry by the ability to perform reactions without solvent present. If performing reactions by milling can be scaled up to batch sizes used in industry, and purification processes without consuming large quantities of solvents can be applied, then milling could have a real impact on the sustainability of chemical processes.
The main aim in this work, however, is to explore new reactivity that cannot occur in traditional batch reactions, but are enabled by milling. Reactions in which the solvent also acts as a reactant have been identified as a class of reactions that could provide increased reaction scope when milling conditions are applied, as the solvent would no longer be limiting the reactivity.

1.2 Fluorination

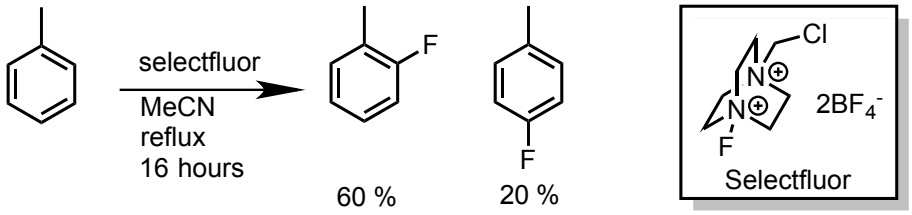
A large proportion of pharmaceuticals (approximately 15 - 20%) and agrochemicals (approximately 40%) currently on the market contain fluorine.[8] Fluorine substitution can be used to improve the efficacy of biologically active materials, by reducing their breakdown *in vivo*[9] and/or enhancing their performance or selectivity which leads to improved physicochemical properties.[10] The incorporation of fluorine can be used to affect a molecule's pKa, conformation, lipophilicity and solubility due to its high electronegativity.[11] These properties have an impact on the bioavailability of a molecule, which can then be tuned.

Consequently a large effort has been focused on methods for the introduction of fluorine into organic molecules.[12] Of particular interest is late-stage fluorination, where fluorine is introduced selectively during the late stages of a synthesis.[13] This enables the synthesis of fluorinated compounds when precursors containing fluorine are not readily available. During drug discovery it allows fine-tuning of a molecule's properties at a late stage without resorting to different starting materials for the synthesis. Another application for late-stage fluorination is the synthesis of PET imaging agents containing ^{18}F where time is of the essence due to its short half life. Short reaction times and rapid purification methods are important considerations.

The development of safe, easy to handle and selective reagents for fluorination of functionalised molecules is vital for the success of late-stage fluorination. Major

advances came with the development of N-F reagents. Selectfluor is such an example and its application in novel metal-free reaction manifolds was the focus of my efforts throughout this project.

1.3 Selectfluor

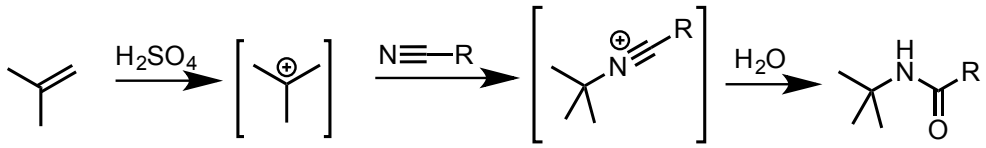


Scheme 3 An example of electrophilic fluorination by selectfluor[14]

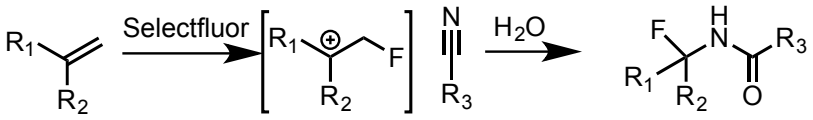
Selectfluor, sometimes known as F-TEDA-BF_4, is a commercially available source of electrophilic fluorine. It is now widely used due to being air and moisture stable, non-toxic, non-explosive and easier to handle than other F^+ sources such as F_2.[15] Reactions involving selectfluor are usually performed in acetonitrile due to its limited solubility in other common organic solvents.[16] Mechanochemistry allows solvent-free reactivity and could enable new reactivity of selectfluor by avoiding the fluorous Ritter reaction.

1.4 The fluorous Ritter reaction

The Ritter reaction is the protonation of an alkene to form a carbocation intermediate which is attacked by a nitrile (**Scheme 4**).[17] When an alkene attacks selectfluor (F^+) the carbocation can be intercepted by the solvent (acetonitrile) in a fluorous Ritter reaction (**Scheme 5**).[18–20] This reaction falls into a class of reactions in which the solvent can act as a reactant. As identified previously, these reactions could have an increased substrate scope if performed mechanochemically. Subjecting the fluorous Ritter reaction to solvent-free conditions could enable the carbocation to be attacked by a different nucleophile, instead of acetonitrile, or allow an elimination to take place.



Scheme 4: The Ritter reaction



Scheme 5: The fluorous Ritter reaction

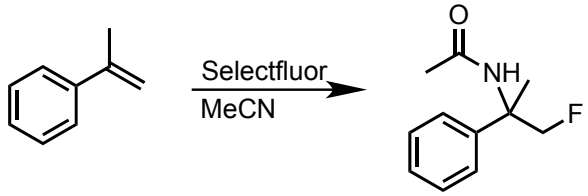
1.5 Results and discussion

Before performing the reaction mechanochemically, understanding its behaviour in a traditional batch reaction was important in order to make a valid comparison. Initial attempts used styrene as a substrate. These were unsuccessful, and it was expected that a substrate allowing a more stabilised carbocation to form in the α position may be more successful. The substrate was therefore changed to α-methystyrene, and a summary of the most important results is presented in **Table 1**. First, the reaction was performed at room temperature for 15 hours. However, no desired product was observed (**Table 1:** Summary of attempts at the fluorous Ritter reaction., entry 1). Increasing the ratio of selectfluor had no effect (entry 2). The fluorous Ritter reaction has been reported on heating[18] and so was attempted under reflux (entry 3). After confirming that the batch of selectfluor being used was not the problem and that it reacted as expected with dicarbonyls, other parameters (eg. dry conditions, other substrates) were screened, all without forming the fluoroamide. One report in the literature of the fluorous Ritter reaction used flow chemistry applying higher temperatures than reflux in acetonitrile.[21] In order to replicate the high temperatures the reaction was heated in a sealed tube to allow the solvent to be heated to above its boiling point. None of the desired product was observed, although the reaction mixture had many peaks in the ^{19}F NMR spectrum (entry 4). It is thought that the main product was polymerisation of the α-methystyrene. This fluorous Ritter reaction is reported using an indium catalyst, InF_3.[22] The reported conditions suggest that this reaction proceeds cleanly with 82% yield in 20 minutes, although no characterisation

data is reported for the product. On applying these conditions, no desired product was observed, and we were unable to reproduce the reported results.

Finally, several attempts were made mechanochemically (entry 6), and were also unsuccessful.

Table 1: Summary of attempts at the fluorous Ritter reaction.



entry	eq. MeCN	eq. selectfluor	conditions	^{19}F NMR conversion
1	310	1	RT, 15 hours	0%
2	310	3	RT, 24 hours	0%
3	310	1.1	Reflux, 24 hours	0%
4	310	1.2	1% acetic acid, 120 ^{o}C, sealed tube, 5 hours [21]	complex mixture
5	310	1.2	10% InF_3, RT, 22 hours [22]	complex mixture
6	1	1	milled (30 Hz, 60 mins)	0%

Fluorine NMR was chosen as a fast method to determine conversions. After the reaction was complete, a standard is added (in this case trifluorotoluene). The peaks in the ^{19}F NMR spectrum can then be integrated and the conversion measured by comparing the signal from the standard to the signal from the product.

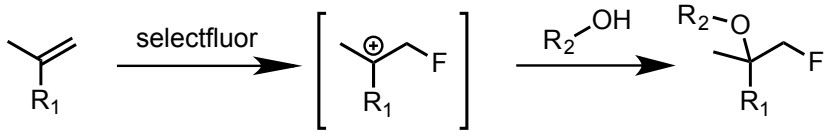
In some of the reaction mixtures, a side product was observed, and it was thought to be the addition of a hydroxyl group to the carbocation, possibly due to the presence of water from the air or the solvent. This suggested that other nucleophiles can attack the carbocation in the presence of acetonitrile. The addition of oxygen and fluorine atoms

in one step is an oxyfluorination reaction. As there are not many reported examples of this reaction in the literature it was decided to pursue this line of investigation further.

1.6 Oxyfluorination

The use of alcohols as nucleophiles in the fluorous Ritter reaction leads to the introduction of oxygen and fluorine atoms in one step and the formation of a quaternary centre in these examples. The use of methanol, water, acetate and fluoride as intercepting nucleophiles has been reported on a limited number of substrates (α-methystyrene and stilbene).[14] Other simple alcohols such as ethanol and isopropanol are reported to intercept the carbocation intermediate of benzocylenes.[23] However, there are relatively few examples and the substrate scope has not been fully investigated.

Since the original aim of this thesis was to enable new reactivity using mechanochemistry, the first reactions were performed in a ball mill. Phenol and α-methylstyrene were used as substrates and several conditions were screened (**Table 2**).

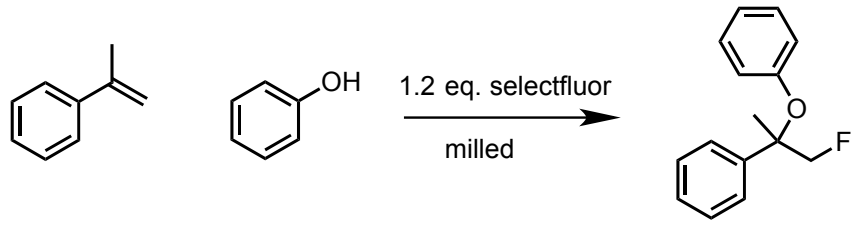


Scheme 6 The Oxyfluorination of alkenes using selectfluor and alcohols

Encouragingly, the first oxyfluorination reaction performed in the ball mill did produce the vicinal fluoroether, although with poor conversion of 11% (**Table 2**, entry 1). The use of a grinding agent was found to improve the conversion significantly to 29% (entry 3). A grinding agent helps mixing of the reagents in the ball mill and prevents the mixture sticking to the sides without taking part in the reaction itself. It is particularly useful when one or more reagents are liquids, as is the case here. A good grinding agent needs to be chemically inert and not affect the chemistry of the reaction being performed. Here, sodium chloride was used, as it has a high melting point and does not interfere with the reaction, although we were

checking for the formation of chlorinated products, which were not observed. The ratio of phenol and increasing the reaction time did not have a significant effect on the conversion (entry 4 and 7 respectively). However, reducing the frequency had a detrimental effect on the conversion (entry 5), as did using a larger ball (entry 8).
In summary, the highest conversions were achieved using a high frequency, smaller ball and using a grinding agent. The higher frequency allows for more energy to be transferred to the reagents. A smaller ball has lower momentum so can transfer less energy, but along with a grinding agent allows improved mixing.

Table 2 : Mechanochemical oxyfluorination of α-methylstyrene

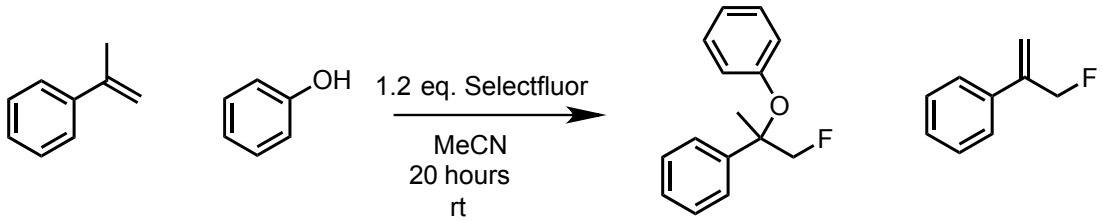


Entry	Eq. Phenol	Time	NaCl (grinding agent)	Conditions	^{19}F NMR conversion
1	1	90 mins	-	30 Hz, smaller ball	11%
2	1	90 mins	1.3 g	30 Hz, larger ball	21%
3	1	90 mins	2 g	30 Hz, smaller ball	29%
4	2	90 mins	2 g	30 Hz, smaller ball	30%
5	1	90 mins	2 g	15 Hz, smaller ball	20%
6	2	90 mins	2 g	15 Hz, smaller ball	11%
7	1	6 hours	2 g	30 Hz, smaller ball	33%
8	1	6 hours	2 g	30 Hz, larger ball	26%

In order to compare the mechanochemical reactions to solution based batch reactions, the reaction was repeated in acetonitrile (**Table 3**). This also allowed increased reaction time, as the ball mill cannot be run continuously for long periods. After monitoring the reactions by TLC for 8 hours, there was still starting material present.

After leaving them overnight, they were complete after 20 hours. While the reaction time did not have a large effect on this reaction in the ball mill, in solution the reaction continued for 20 hours. Also, in contrast to the mechanochemical reactions, the ratio of phenol had a significant effect on the reaction. This suggests that the limiting factor in the ball mill could have been degredation of one or more of the reagents, as the conversion remained almost unchanged after 90 minutes. The highest yields in batch solution were achieved with 2 equivalents of phenol. However, the conversion was not quantitative. It is known that under harsher conditions, selectfluor can fluorinate phenol and electron-rich aromatic rings.[24] Similar results were observed when pentanol was used instead of phenol, suggesting that fluorination of phenol was not the reason for non-quantitative conversion.

Table 3 : Effect of the amount of phenol in batch oxyfluorination reactions

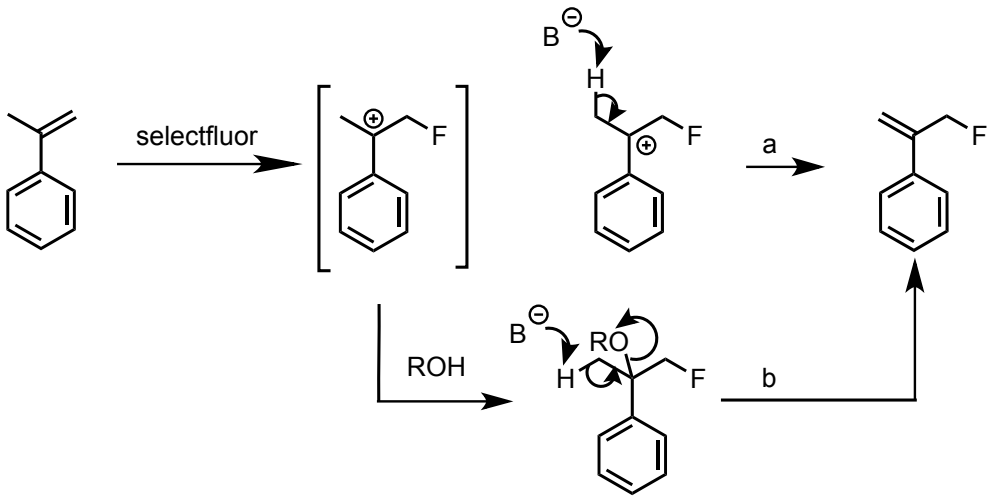


1 **2**

Eq. Phenol	^{19}F NMR conversion to 1
5	48%
2	62%
1	26%

Throughout these experiments, a side product was detected in the ^{19}F NMR spectrum with a peak at δ=-212 ppm. This was identified as elimination product **2** from ^{1}H NMR spectral data. The formation of this product can be understood as follows. After the addition of fluorine, a carbocation is formed. This can be intercepted by the nucleophile, to form the desired product, or deprotonation can occur, quenching the carbocation, and forming a new C=C double bond (Scheme 7a). An alternative possibility is that after addition of the nucleophile, forming the desired product **1**, elimination could still occur, with the -O^- species leaving (Scheme 7b). This would

depend on the leaving group ability of the -O^- species. This was tested by the addition of bases, and it was found that on the addition of triethylamine to the reaction mixture, the desired product was not formed, but the elimination product **2** was observed.



Scheme 7 Possible mechanisms for the formation of the elimination product. a) directly from the carbocation. b) after addition of the nucleophile

In order to explore the scope of the reaction further, other oxygen based nucleophiles were tested (**Table 4 :** Oxyfluorination of α-methylstyrene), and the reaction seems to be general for oxygen nucleophiles. However, the product from lower molecular mass nucleophiles could not be isolated due to volatility.

Table 4 : Oxyfluorination of α-methylstyrene

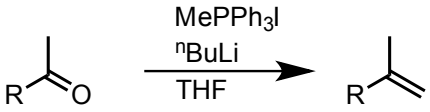
Nu	Isolated Yield
Phenol	54%
Pentanol	65%
iPrOH	56% [a]
KOAc	59% [a]

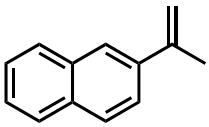
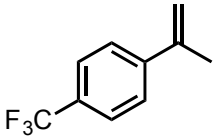
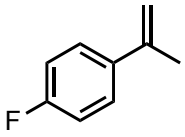
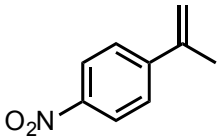
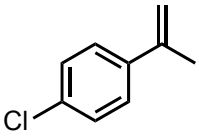
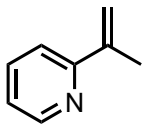
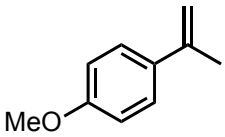
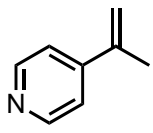
[a] ^{19}F NMR conversion

1.6.1 Synthesis of starting materials

In order to test the scope of this reaction, several different substrates were prepared by the Wittig methylenation reaction employing triphenylphosphonium iodide (**Table 5**).

Table 5 : Preparation of substrates by Wittig reaction



Product	Isolated Yield	Product	Isolated Yield
 **3**	74%	 **7**	32%
 **4**	71 %	 **8**	45%
 **5**	74%	 **9**	41%
 **6**	74%	 **10**	61%

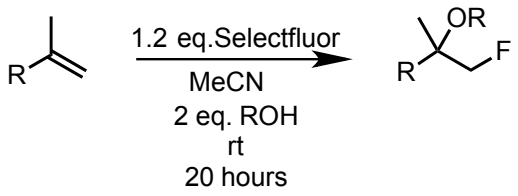
The substrate scope has so far been investigated using phenol and pentanol as the oxy-nucleophile (**Table 6**). Pleasingly, this reaction manifold seems to be applicable to many different α-methylstyrene derivatives except **10**. In almost all cases, the ratio of

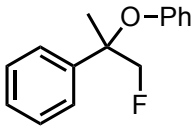
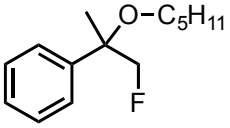
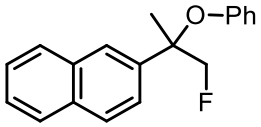
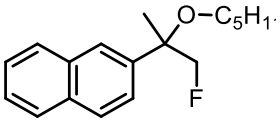
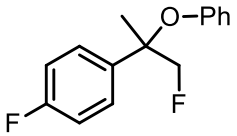
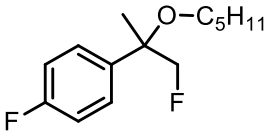
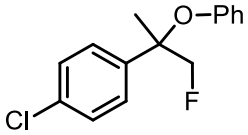
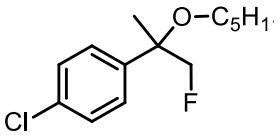
desired product to elimination product was higher using pentanol than phenol. This is particularly noticable in example **20**, with >98:2 selectivity for the desired product. Phenol has a lower pKa than pentanol, so pentanol is a better nucleophile due to more localised electron density on the oxygen atom. An alternative explanation is that, if the mechanism proceeds as shown in Scheme 7b, phenoxide is a better leaving group than pentanoxide. This trend was observed for all examples except products **21** and **22**.

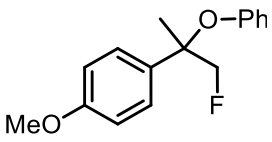
In general electron rich aromatic rings showed a higher conversion. This is particularly apparent on comparison between the electron donating methoxy group (products **19** & **20**) and the electron withdrawing nitro group (products **21** & **22**). Donating electron density into the aromatic ring also increases electron density in the alkene by conjugation. The more electron-rich the alkene, the more nucleophilic, thus the electron-donating derivatives are more susceptible to electrophilic attack of selectfluor.

Interestingly, the reaction failed on the pyridyl substrate (**10**, product **23**). This is possibly due to the lone pair on the nitrogen atom attacking selectfluor, bonding to the fluorine atom and forming a pyridinium salt. However, reported ^{19}F NMR shifts for derivatives used as fluorination reagents did not correspond to any observed peak in the crude spectrum.[25] Possibly this reaction may be achievable using higher molar equivalents of selectfluor.

Table 6 : Substrate scope for oxyfluorination of α-methylstyrene derivatives

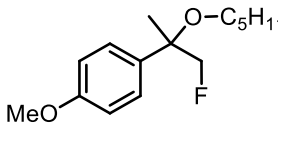


Product	^{19}F NMR conversion product: elimination Isolated Yield	Product	^{19}F NMR conversion product : elimination Isolated Yield
 **11**	62% 5 : 1 54%	 **12**	71% 9 : 1 65%
 **13**	45% 4 : 1 19% [a]	 **14**	67% 21 : 1 66%
 **15**	55% 5 : 1 55% [a]	 **16**	72% 9 : 1 64%
 **17**	51% 3 : 1 30% [a]	 **18**	53% 4 : 1 53% [a]



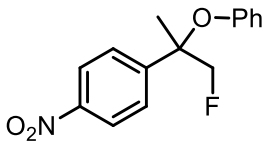
19

35%
6 : 1
12%[a]



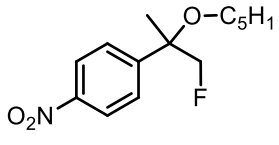
20

87%
>98 : 2
74%



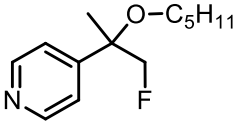
21

10%
3 : 1
72 hours



22

9%
2.5 : 1
36 hours

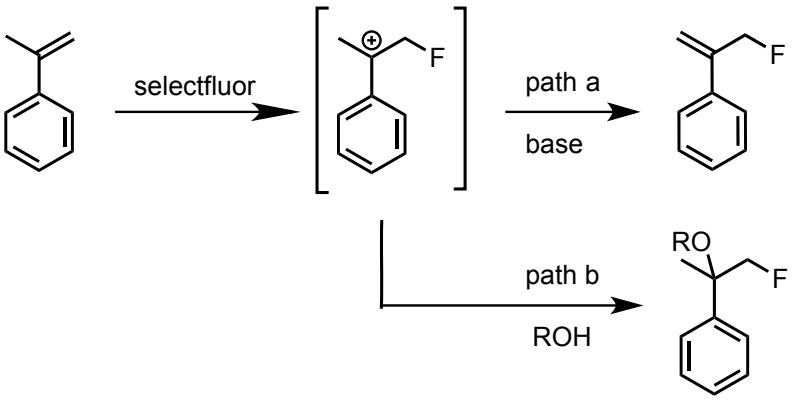


23

0%

[a]: A mixture of the desired product and elimination product was isolated.

In order to try and improve the selectivity, it was envisaged that changing the method of addition may affect the selectivity of the reaction. The two reactions involved are shown in Scheme 8. The rate of formation of the elimination product (path a) depends on the concentration of the carbocation intermediate and any species acting as a base, whereas the rate of formation of the desired product (path b) depends on the concentration of the carbocation intermediate and the oxy-nucleophile. It was therefore hypothesised that the selectivity could be improved by increasing the local concentration of the oxy-nucleophile. This could be achieved by slow addition of selectfluor, as this would ensure that as soon as a carbocation is formed, it is surrounded by a high local concentration of the oxy-nucleophile. Initial studies suggest that this is the case. Adding a solution of selectfluor via syringe pump over 20 hours to a solution of **3** and phenol increased the selectivity from 4 : 1 to 18 : 1.



Scheme 8 Possible reaction pathways from the carbocation intermediate. If the local concentration of alcohol around the carbocation is high, the selectivity for forming the fluoroether is improved.

Isolation of the products presented some difficulties. Firstly, some of the products were volatile and so were lost on removal of the solvent. The elimination product often had similar R_f to the desired product, so in some cases a mixture of both products were isolated.

1.7 Conclusions

The fluorous-Ritter reaction was investigated in solution and mechanochemically using α-methylstyrene, selectfluor and acetonitrile. Despite many attempts under different conditions the fluoroamide product was not observed. It was found that other oxygen-based nucleophiles could attack the intermediate carbocation in the presence of acetonitrile to form vicinal fluoroethers with a quaternary centre. The substrate scope of this oxy-fluorination reaction was investigated, with poor-excellent isolated yields. The selectivity depended on the oxy-nucleophile used, with a higher ratio of the desired fluoroether compared to the elimination product when using pentanol instead of phenol.

1.8 Future Work

Further investigation of the fluorous Ritter reaction is of interest, particularly to identify substrates for which it is efficient. One possible class of substrates is higher substituted alkenes, which would have more stabilised carbocations. Once an appropriate substrate has been identified, the use of mechanochemistry to enable the attack of other nucleophiles, possibly other nitriles could be investigated. This would be the first example of using mechanochemistry to achieve reactivity scope not possible under batch conditions.

The substrate scope of the oxyfluorination reaction could be extended further, and the screening for other nucleophiles is ongoing.

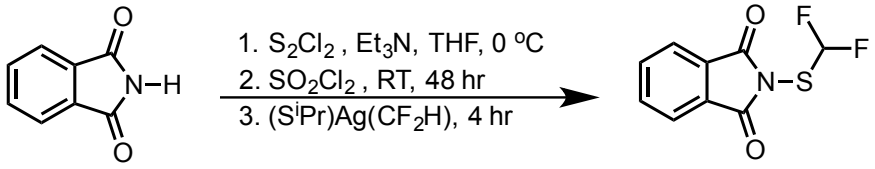
2 Synthesis of Difluoromethylthioethers

2.1 Introduction

2.1.1 Difluoromethylthioethers

The difluoromethyl group has interesting properties for the design of bioactive molecules, being a more lipophilic hydrogen bond donor than groups such as -OH and -NH.[26] The selective introduction of a trifluoromethyl group into functionalised molecules has been extensively studied.[27–33] The difluoromethyl group has received less attention. One method to further increase the lipophilicity and membrane permeability of a $-CF_3$ group further is to introduce a sulphur atom $-SCF_3$.[34] This is also likely to be the case for $-SCF_2H$ groups.

One of the most common methods of difluoromethylation involves using difluorocarbene. The most frequently used reagent to generate difluorocarbene, historically, was chlorodifluoromethane. However, this is an ozone depleting species so alternative methods are sought.[27] Nucleophilic difluoromethylation has been achieved using cadmium, zinc and copper based reagents[35,36], sulfones[37], phosphonates[38] and silanes[39].



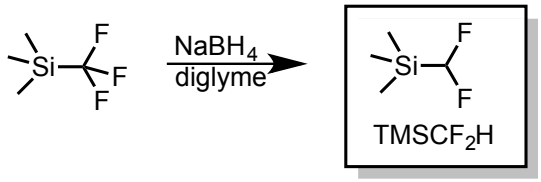
Scheme 9 Synthesis of N-difluoromethylthiophthalimide, as reported by Shen and coworkers.[40]

Until very recently, there were few reported syntheses of difluoromethyl thioethers.[1,40] Those that did exist were based on the insertion of the difluorocarbene into thiols. During the lifetime of the current project, Goossen and coworkers used organothiocyanates as substrates along with copper thiocyanates and $TMSCF_2H$.[1] Shen and coworkers developed a new reagent, N-difluoromethylthiophthalimide, for difluoromethylthiolation.[40] This reagent introduces the entire $-SCF_2H$ group so is quite

versatile, however it requires a three-step synthesis (Scheme 9). The synthesis of the silver reagent in the third step makes use of $TMSCF_2H$, which is the reagent used during this project.

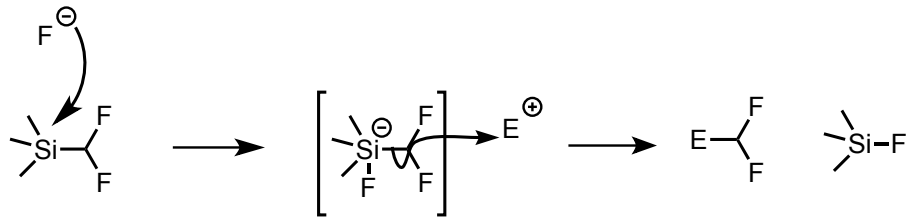
The inspiration for the reaction discovered here was from a reported method to synthesise trifluoromethyl thioethers. This used disulfides as the starting material and the Ruppert-Prakash reagent, trifluoromethyl trimethylsilane ($TMSCF_3$).[41] We envisaged that the difluoromethyl analogue ($TMSCF_2H$) may be used as a novel, metal-free, method to synthesise difluoromethyl thioethers.

2.1.2 Difluoromethyl trimethylsilane ($TMSCF_2H$)



Scheme 10 Synthesis of $TMSCF_2H$

$TMSCF_2H$ can be synthesised from the commercially available Ruppert-Prakash reagent ($TMSCF_3$) by reduction with sodium borohydride (Scheme 10).[42] Its use as a nucleophilic source of $-CF_2H$ was first demonstrated in 1995 where it was used to difluoromethylate aldehydes and ketones.[43] This required harsh conditions, so $TMSCF_2H$ was not investigated further during the following years.[44] In 2011, it was reported that using CsF as an additive, $TMSCF_2H$ could indeed be used at ambient temperatures to difluoromethylate aldehydes, ketones and imines.[45] This discovery reignited interest in $TMSCF_2H$ and its reactivity, mostly its addition to aromatic rings, has since been explored further as a nucleophilic source of $-CF_2H$.[46–48] In all its known reactions, the best conditions are in polar, aprotic solvents with activation by the addition of a fluoride source. This is probably due to the formation of the strong Si-F bond. This weakens the $Si-CF_2H$ bond, allowing the release of the nucleophilic "CF_2H^-" species (**Scheme 11**).



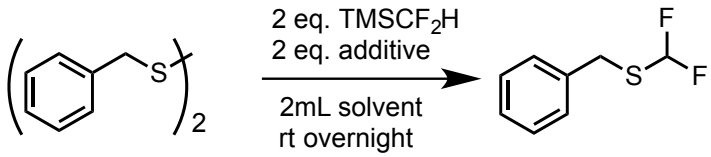
Scheme 11 Activation of $TMSCF_2H$ by a fluoride source

2.2 Results and discussion

2.2.1 Optimisation

Pleasingly, some conversion to the desired product was observed among the initial attempts at this reaction (**Table 7**), with the highest initial conversion using TBAF as fluoride source additive (entry 3). TBAF is supplied as a solution in THF so the choice of solvent is limited with this fluoride source. On changing the solvent CsF was able to give comparable conversions (entry 7). Strong bases, such as potassium tert-butoxide have been reported to activate silane reagents[45]. However, these did not increase the conversion in this reaction (entry 9). Copper (I) salts have been used to transfer the $-CF_2H$ group, so CuI was screened alongside other silane activating additives (entries 10 and 12), although to no effect. CsF having been identified as the most active additive, a solvent screen was performed. The solvent was found to have a significant effect on the conversion, with more polar solvents (e.g. DMSO, entry 13) generally being more successful than less polar solvents (e.g. THF, entry 1). The highest conversion was achieved using N-methylpyrrolidinone (NMP) (entry 14).

Table 7 A summary of optimisation results for difluoromethythiolation



Entry	Additive	Solvent	^{19}F NMR conversion
1	CsF	THF	1%
2	KF	THF	0%
3	TBAF	THF	14%
4	CsF	MeCN	10%
5	KF	MeCN	0%
6	CsF	DMF	5%
7	CsF	DMA	16%
8	KF	DMA	3%
9	tBuOK	THF	5%
10	CuI/ tBuOK	THF	4%
11	tBuOK	THF	6%
12	CuI/ CsF	THF	0%
13	CsF	DMSO	39%
14	CsF	NMP	63%

Having established the optimal solvent and additive, the effect of temperature and ratios of reagents were investigated (**Table 8**). It was found that heating the reaction had a detrimental effect on the conversion (entry 2), possibly due to degradation of one or more reagents. The optimal ratio was established as 4 equivalents $TMSCF_2H$

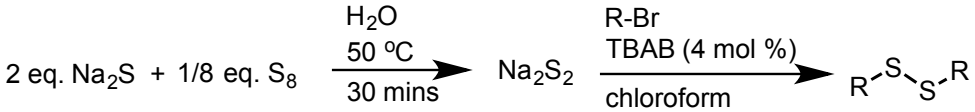
and 8 equivalents CsF (entry 5). With these optimised conditions in hand, the substrate scope was investigated.

Table 8 Effect of ratio of reactants and temperature on conversion

Entry	eq. $TMSCF_2H$	eq. CsF	T	^{19}F NMR conversion
1	2	2	0°C - rt	63%
2	2	2	60°C	36%
3	**4**	**2**	**0°C - rt**	**76%**
4	4	4	0°C - rt	73%
5	**4**	**8**	**0°C - rt**	**82%**
6	2	4	0°C - rt	52%

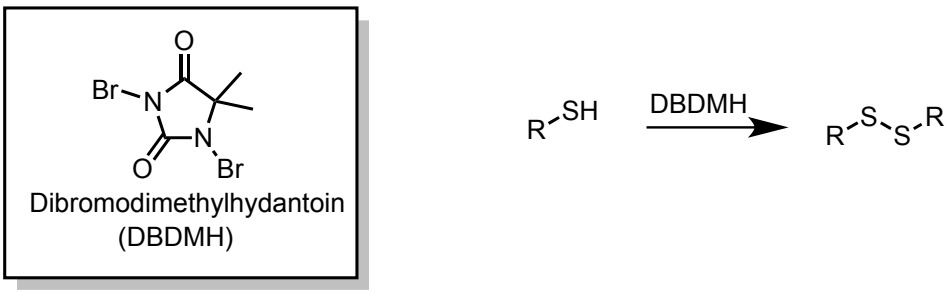
2.2.2 Synthesis of disulfides

In order to investigate the substrate scope, a simple method for the synthesis of disulfides was required. Initial attempts focused on a method reported by Sonavane et al. (**Scheme 12**) using alkyl bromides as the starting material for the synthesis of symmetrical disulfides.[49]



Scheme 12 Method for synthesis of disulfides

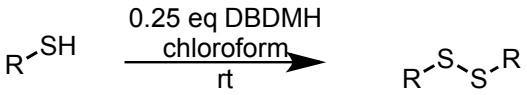
Following this procedure using 1-bromooctane, a mixture of the desired disulfide and the corresponding thioether were obtained in a ratio 1.5 : 1, respectively. These had very similar R_f values and were not easily separable. Modifying the procedure to only 1 eq. Na_2S improved this ratio significantly to 1:0.08. However, in order to obtain pure disulfide a different method was required.

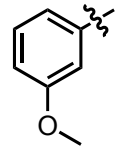
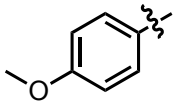
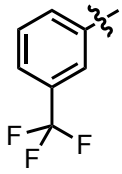
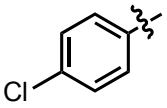
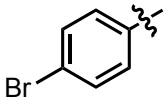
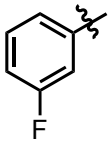
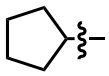
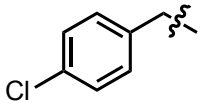
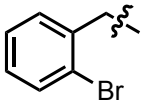
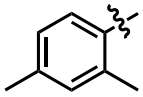
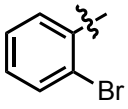
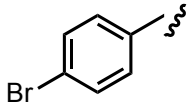


Scheme 13

A fast and simple method for the oxidation of thiols to disulfides (Scheme 13) using dibromodimethylhydantoin (DBDMH) was reported by Khazaei *et al*.[50] This method uses 1 equivalent of the oxidant. It was found that by reducing the ratio of DBDMH to 0.25 equivalents, the disulfides could be obtained in high purity without the need for column chromatography. This minor modification therefore allowed for the fast and simple preparation of several disulfides as starting materials for the substrate scope (**Table 9**).

Table 9 Synthesis of disulfides from thiols using DBDMH

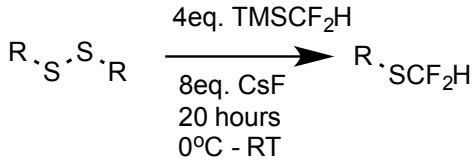


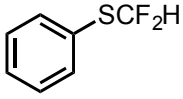
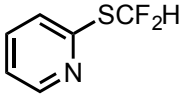
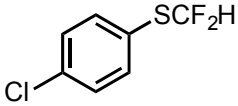
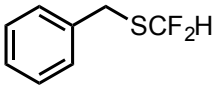
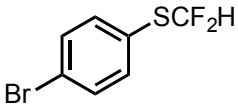
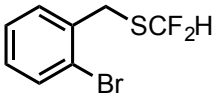
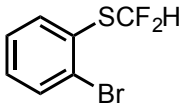
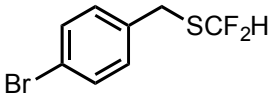
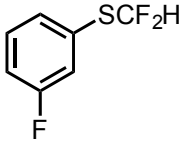
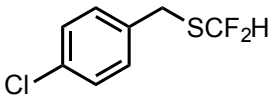
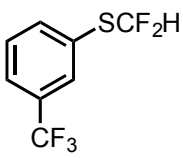
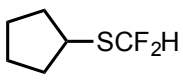
R	Isolated Yield	R	Isolated Yield
 **24**	97%	 **25**	87%
 **26**	89%	 **27**	91%
 **28**	92%	 **29**	88%
 **30**	89%	 **31**	93%
 **32**	82%	 **33**	90%
 **34**	93%	 **35**	80%
 **36**	98%		

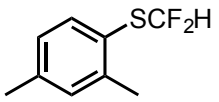
2.2.3 Substrate Scope

Having several disulfides in hand and optimal conditions for dibenzyl disulfide (**Table 8**, entry 5), the scope of the reaction was explored to see if it was generally applicable (**Table 10**).

Table 10 Substrate scope of the difluoromethylthiolation reaction

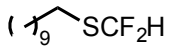


Product	Conversion	Product	Conversion
 **37**	72%	 **46**	49%
 **38**	99%	 **47**	82%
 **39**	59%	 **48**	61%
 **40**	56%	 **49**	70%
 **41**	100%	 **50**	53%
 **42**	88%	 **51**	34%



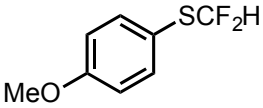
49%

43



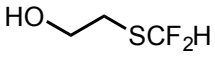
69%

52



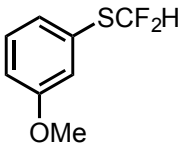
81%

44



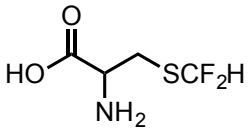
49%

53



97%

45



0%

54

Good conversions were achieved for many of the substrates. Aromatic and alkyl substrates were all successfully converted to their difluoromethylthioethers. It is notable that the more sterically demanding mono-ortho substituted rings do not show decreased conversions, such as **40**. The reaction conditions also tolerate heterocycles (**46**) and alcohols (**53**) which are both of interest to the pharmaceutical industry. The poorest conversion was from the cyclopentyl derivative, which could be due to increased steric demand around the reactive sulphur centre. The reaction was unsuccessful in the presence of a carboxylic acid group (**54**). Difluoromethane is observed as a sideproduct in some of the ^{19}F NMR spectra. This suggests that the -CF_2H group will readily accept a proton, even when conducting the reactions under dry conditions. This could explain why the reaction was unsuccessful with a carboxylic acid present, as this is a source of protons. The aromatic substrates were expected to have a higher conversion, as the thiolate leaving group would have its negative charge stabilised by conjugation. However, there is not a clear trend of higher conversion for the aromatic substituents, so maybe the leaving group is stabilised by other means, possibly by the polar solvent.

Isolation of the difluoromethylthioethers presented several difficulties. Many of the products were volatile and so were lost on removal of the solvent. Separation from the thiol side product was also difficult by chromatography due to very similar R_f values. Short-path distillation using a Kugelrohr apparatus was also attempted, and the pure difluoromethylthioether was not obtained. With such difficulties, the least volatile

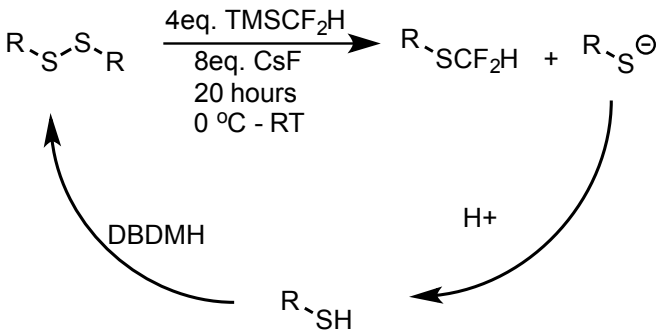
product (**39)** was isolated and characterised, and the yields for the other products determined using the characteristic -SC**F**$_2$H peak in the ^{19}F NMR spectrum.

2.3 Conclusion

A novel, metal-free method for the synthesis of difluoromethylthioethers has been developed using TMSCF$_2$H as a nucleophilic source of -CF$_2$H. Using disulfides as the substrates, its application to several examples has been demonstrated.

2.4 Future work

In order to make full use of both "halves" of the disulfide starting materials, methods for the recycling of the thiolate side product back to disulfides would increase the yield and atom economy of this process (Scheme 14).



Scheme 14 Recycling of side product via oxidation.

Further investigation of electrophilic substrates other than disulfidesis under investigation. This could demonstrate TMSCF$_2$H as a general nucleophilic source of difluoromethyl groups. Further investigation of the carbene reactivity observed with α-methylstyrene (**Error! Reference source not found.**) is of interest.

3 Experimental procedures for the synthesis of vicinal fluoroethers

3.1 General Methods

If not stated below, chemicals were commercially available and used without further purification.

Column chromatography was performed using 60 Å (40 - 64 micron) silica and solvent mixtures of petroleum ether (40 - 60 °C) and ethyl acetate.

^{1}H and ^{13}C NMR spectra were obtained on Bruker 400 Ultrashield™ or Bruker 500 MHz spectrometers with chloroform-d as deuterated solvent. These were performed without ^{19}F decoupling, so fluorine coupling is observed. ^{19}F NMR spectra were obtained using an Oxford Instruments 300 MHz spectrometer. The obtained chemical shifts δ are reported in ppm and are referenced to the residual solvent signal. Spin-spin coupling constants *J* are given in Hz.

High resolution mass spectral (HRMS) data were obtained on a Thermo Scientific LTQ Orbitrap XL by the EPSRC UK National Mass Spectrometry Facility at Swansea University or on a Waters MALDI-TOF mx.

Infrared spectra were recorded on a Shimadzu IR-Affinity-1S FTIR spectrometer.

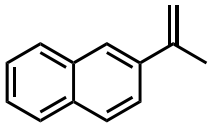
Melting points were measured using a Gallenkamp melting point apparatus and are reported uncorrected.

3.2 Synthesis of *α*-methylstyrene derivatives

An oven-dried flask was charged with methyltriphenylphosphonium iodide (4.04 g, 10 mmol) and dry THF (40 mL). The solution was cooled to -78 ºC and a solution of n-butyl lithium in hexanes* (2.05 M, 5.1 mL, 10.5 mmol) was added dropwise. The mixture was gently warmed to 0 ºC , stirred for 1 hour then again cooled to -78 ºC before acetophenone (10 mmol) was added dropwise. The mixture was allowed to warm slowly to room temperature and stirred until the reaction was complete by TLC. Diethyl ether (40 mL) was added and the mixture washed with saturated ammonium

chloride solution (3 x 40 mL), dried ($MgSO_4$), solvent evaporated and the crude product purified by flash column chromatography to yield the α-methylstyrene derivative.

*n-Butyl lithium solution was titrated before use: To a solution of menthol (0.200 g, 1.28 mmol) and 1,10-phenanthroline (25 mg) in THF (10 mL) was added dropwise n-butyl lithium in hexanes until a yellow colour persists. The concentration of the n-butyl lithium solution was determined as 2.05 M.



3

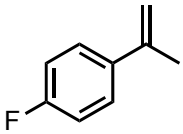
2-(prop-1-en-2-yl)naphthalene (74%) white solid (mp: 56-57 ºC, ethyl acetate)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 - 7.77 (m, 4H), 7.68 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.53 – 7.40 (m, 2H), 5.54 (s, 1H), 5.25 - 5.10 (m, 1H), 2.28 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.00, 143.40, 133.79, 133.20, 128.66, 128.11, 127.94, 126.55, 126.26, 124.69, 124.31, 113.46, 22.32.

IR: 1505, 1437, 1277, 1134, 883, 860, 824, 748, 473 cm^{-1}

HRMS (EI): [$C_{13}H_{12}$] calc. 168.0939, found 168.0940



4

1-fluoro-4-(prop-1-en-2-yl)benzene[52] (71%), colourless oil

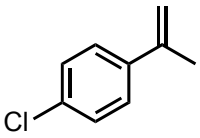
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.40 (m, 2H), 7.06 – 6.99 (m, 2H), 5.31 (s, 1H), 5.16 – 4.92 (m, 1H), 2.14 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.37 (d, J = 246.2 Hz), 142.33, 137.38, 127.16 (d, J = 7.8 Hz), 115.07 (d, J = 21.3 Hz), 112.37 (d, J = 1.4 Hz), 22.04.

^{19}F NMR (283 MHz, CDCl3) δ -115.26 (s).

IR: 1601, 1510, 1234, 1161, 841 cm^{-1}

HRMS (EI): [C_9H_9F] calc.136.0688, found 136.0687



5

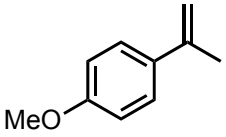
1-chloro-4-(prop-1-en-2-yl)benzene[53] (74%), colourless oil

^{1}H NMR (500 MHz, CDCl3) δ 7.44 (d, J = 8.6 Hz, 2H), 7.34 (d, J = 8.6 Hz, 2H), 5.41 (s, 1H), 5.19 – 5.12 (m, 1H), 2.18 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.56, 140.04, 133.63, 128.79, 127.26, 113.43, 22.18.

IR: 1495, 1117, 1094, 1013, 895 cm^{-1}

HRMS (EI): [C_9H_9Cl] calc. 152.0393, found 152.0392



6

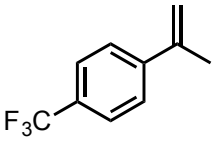
1-methoxy-4-(prop-1-en-2-yl)benzene[52] (74%), white solid (mp: 37-38 ºC, ethyl acetate)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.9 Hz, 2H), 6.87 (d, *J* = 8.9 Hz, 2H), 5.28 (s, 1H), 5.06 – 4.88 (m, 1H), 3.82 (s, 3H), 1.55 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.10, 142.60, 133.83, 126.60, 113.57, 110.65, 55.28, 21.89.

IR: 1603, 1508, 1439, 1287, 1244, 1182, 1030, 876, 835, 824, 677, 525, 486 cm^{-1}

HRMS (EI): [$C_{10}H_{12}O$] calc. 148.0888, found 148.0886



7

1-(prop-1-en-2-yl)-4-(trifluoromethyl)benzene (32%), yellow oil

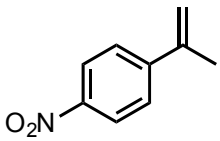
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (q, *J* = 8.6 Hz, 4H), 5.44 (s, 1H), 5.20 (d, *J* = 1.4 Hz, 1H), 2.18 – 2.17 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.81, 142.25, 129.38 (q, *J* = 32.5 Hz), 125.78, 125.17 (q, *J* = 3.7 Hz), 123.17, 114.52, 21.62.

^{19}F NMR (283 MHz, $CDCl_3$) δ -62.36 (s).

IR: 1331, 1171, 1132, 1069, 847 cm^{-1}

HRMS (EI): [$C_{10}H_9F_3$] calc. 186.0656, found 186.0655



8

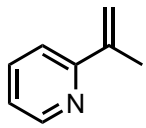
1-nitro-4-(prop-1-en-2-yl)benzene[54] (45%), orange solid (mp: 51-52 °C, ethyl acetate)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 9.0 Hz, 2H), 7.59 (d, *J* = 9.0 Hz, 2H), 5.52 (s, 1H), 5.37 – 5.22 (m, 1H), 2.40 – 2.02 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.00, 148.06, 141.98, 126.66, 124.04, 116.85, 22.03.

IR: 1593, 1504, 1339, 1319, 1103, 912, 854, 746, 712 cm^{-1}

HRMS (EI): [$C_9H_9NO_2$] calc. 163.0633, found 163.0631



9

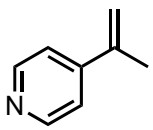
2-(prop-1-en-2-yl)pyridine[55] (61%), colourless oil

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, *J* = 4.8 Hz, 1H), 7.62 (ddd, *J* = 8.0, 7.5, 1.9 Hz, 1H), 7.46 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.13 (ddd, *J* = 7.4, 4.8, 0.9 Hz, 1H), 5.84 (dd, *J* = 1.5, 0.8 Hz, 1H), 5.39 – 5.24 (m, 1H), 2.20 (dd, *J* = 1.4, 0.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.32, 148.88, 143.26, 136.17, 122.03, 119.69, 115.55, 20.41.

IR: 1585, 1564, 1468, 1431, 903, 802, 746 cm^{-1}

HRMS (EI): [C_8H_9N] calc. 119.0735, found 119.0733



10

4-(prop-1-en-2-yl)pyridine[55] (41%), colourless oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 6.2 Hz, 2H), 7.32 (d, *J* = 6.2 Hz, 2H), 5.56 (s, 1H), 5.26 (s, 1H), 2.16 – 2.10 (m, 3H).

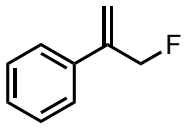
^{13}C NMR (101 MHz, $CDCl_3$) δ 150.06, 148.72, 141.37, 120.42, 116.33, 21.27.

IR: 1597, 1410, 993, 908, 833 cm^{-1}

HRMS (EI): [C_8H_9N] calc. 119.0735, found 119.0738

3.3 Synthesis of vicinal fluoroethers

To a solution of the α-methylstyrene derivative (1 mmol) and selectfluor (0.425 g, 1.2 mmol) in acetonitrile (10 mL) the alcohol nucleophile (2 mmol) was added. The mixture was stirred at room temperature for the appropriate time, monitored by TLC. Trifluoroethanol (0.024 mL, 0.33 mmol) was added as a standard and the conversion determined by ^{19}F NMR spectroscopy. The crude mixture was purified by flash column chromatography to yield the vicinal fluoroether. Fluoroethers **13**, **15**, **17**, **18** and **19** were obtained as mixtures with the elimination side product. The ratio was determined using the characteristic peak in the ^{19}F NMR spectrum, having isolated and characterised elimination product **2**.



2

(3-fluoroprop-1-en-2-yl)benzene[56] (10%), colourless oil

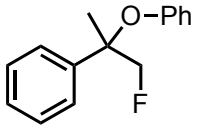
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.4 Hz, 2H), 7.27 (m, 3H), 5.53 (s, 1H), 5.34 (s, 1H), 5.16 (d, *J* = 47.1 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.05 (d, *J* = 14.6 Hz), 137.33 (d, *J* = 2.1 Hz), 128.61, 128.25, 125.96, 115.37 (d, *J* = 10.6 Hz), 84.39 (d, *J* = 169.1 Hz).

^{19}F NMR (283 MHz, $CDCl_3$) δ -212.72. (proton decoupled)

IR: 3059, 1705, 1497, 1018, 988, 910, 775, 702 cm^{-1}

HRMS (p NSI): $[C_9H_9F + H]^+$ calcd. 137.0761, found 137.0757



11

(1-fluoro-2-phenoxypropan-2-yl)benzene (54%), colourless oil

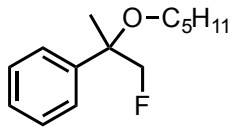
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.0 Hz, 2H), 7.42 (m, 3H), 7.17 (t, *J* = 7.7 Hz, 2H), 6.96 (t, *J* = 7.3 Hz, 1H), 6.76 (d, *J* = 7.7 Hz, 2H), 4.51 (ddd, *J* = 56.6, 47.8, 9.4 Hz, 2H), 1.82 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.41, 141.25 (d, *J* = 3.6 Hz), 129.22, 128.94, 128.35, 126.59, 122.12, 120.39, 89.46 (d, *J* = 184.6 Hz), 81.30 (d, *J* = 18.2 Hz), 19.73 (d, *J* = 4.0 Hz).

^{19}F NMR (283 MHz, $CDCl_3$) δ -220.07 (t, *J* = 48.0 Hz).

IR:3061, 2988, 2947, 1597, 1449, 1287, 1140, 1071, 1022, 760 cm^{-1}

HRMS (EI): $[C_{15}H_{15}OF]^+$ calcd. 230.1107, found 230.1110



12

(1-fluoro-2-(pentyloxy)propan-2-yl)benzene (65%), colourless oil

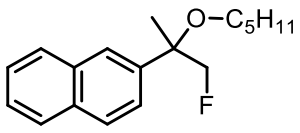
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.29 (m, 5H), 4.39 (ddd, *J* = 56.7, 47.9, 9.3 Hz, 2H), 3.25 (ddt, *J* = 69.7, 8.6, 6.9 Hz, 2H), 1.67 (d, *J* = 2.2 Hz, 3H), 1.60 (d, *J* = 7.1 Hz, 2H), 1.38 – 1.23 (m, 4H), 0.96 – 0.84 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.59 (d, *J* = 3.9 Hz), 128.65, 127.99, 126.87, 89.51 (d, *J* = 181.3 Hz), 78.16 (d, *J* = 18.0 Hz), 63.22, 30.25, 28.59, 22.85, 20.21, 14.33.

^{19}F NMR (283 MHz, $CDCl_3$) δ -221.55 (t, *J* = 47.8 Hz).

IR: 2934, 2872, 1448, 1233, 1152, 1077, 1020, 761, 701 cm^{-1}

HRMS (nESI): $[C_{14}H_{21}OF + NH_4]^+$ calcd. 242.1915, found 242.1917



14

2-(1-fluoro-2-(pentyloxy)propan-2-yl)naphthalene (66%), colourless oil

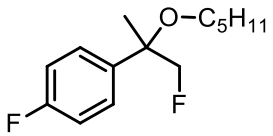
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 9.7, 6.9 Hz, 4H), 7.66 – 7.48 (m, 3H), 4.52 (ddd, *J* = 56.6, 47.8, 9.3 Hz, 2H), 3.52 – 3.08 (m, 2H), 1.80 (d, *J* = 2.1 Hz, 3H), 1.72 – 1.59 (m, 2H), 1.35 (dd, *J* = 7.4, 3.7 Hz, 4H), 0.93 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.06, 139.03, 133.21, 132.92, 128.21, 128.14, 127.57, 126.20, 125.91, 124.52, 89.07 (d, *J* = 181.0 Hz), 78.00 (d, *J* = 18.2 Hz), 63.14, 30.07, 28.41, 22.59, 20.27 (d, *J* = 4.1 Hz), 14.05.

^{19}F NMR (283 MHz, $CDCl_3$) δ -221.74 (t, *J* = 47.8 Hz).

IR: 1080, 1059, 1018, 856, 818, 746, 476 cm^{-1}

HRMS (EI): [$C_{18}H_{23}OF$] calc. 274.1733, found 274.1726



16

1-fluoro-4-(1-fluoro-2-(pentyloxy)propan-2-yl)benzene (64%), colourless oil

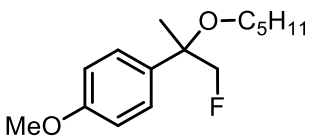
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 8.9, 5.4 Hz, 2H), 7.05 (t, *J* = 8.8 Hz, 2H), 4.34 (ddd, *J* = 54.3, 47.8, 9.3 Hz, 2H), 3.21 (ddt, *J* = 78.9, 8.6, 6.8 Hz, 2H), 1.63 (d, *J* = 2.2 Hz, 3H), 1.61 – 1.54 (m, 2H), 1.29 (dd, *J* = 7.4, 3.5 Hz, 4H), 0.88 (ddd, *J* = 7.2, 3.5, 1.5 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.31 (d, *J* = 246.3 Hz), 137.30, 128.35 (d, *J* = 8.0 Hz), 115.15 (d, *J* = 21.2 Hz), 89.04 (d, *J* = 181.1 Hz), 77.44 (d, *J* = 18.3 Hz), 62.88, 29.94, 28.32, 22.51, 20.10 (d, *J* = 3.9 Hz), 13.97.

^{19}F NMR (283 MHz, $CDCl_3$) δ -114.85 – -115.00 (m), -221.53 (t, *J* = 47.9 Hz).

IR: 1508, 1229, 1092, 1022, 1013, 835 cm^{-1}

HRMS (pNSI): [$C_{14}H_{20}OF_2 + NH_4$] calc. 260.182, found 260.1822



20

1-(1-fluoro-2-(pentyloxy)propan-2-yl)-4-methoxybenzene (74%), colourless oil

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 2H), 6.94 – 6.86 (m, 2H), 4.34 (ddd, *J* = 56.7, 48.0, 9.2 Hz, 2H), 3.82 (s, 3H), 3.42 – 2.97 (m, 2H), 1.83 – 1.48 (m, 5H), 1.40 – 1.18 (m, 4H), 0.94 – 0.81 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.50, 133.60 (d, *J* = 4.0 Hz), 128.29, 114.09, 89.80 (d, *J* = 181.2 Hz), 77.96 (d, *J* = 18.1 Hz), 63.18, 55.66, 30.41, 28.76, 23.00, 20.24 (d, *J* = 3.9 Hz), 14.49.

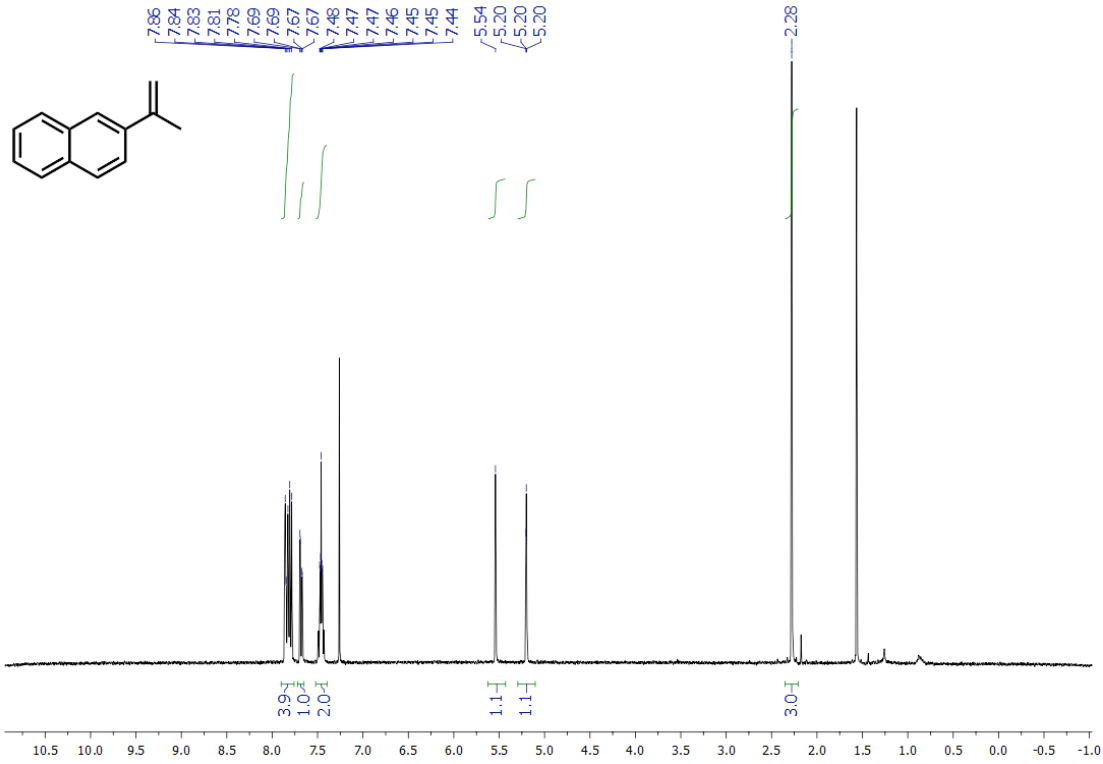
^{19}F NMR (283 MHz, $CDCl_3$) δ -220.97 (t, *J* = 48.1 Hz).

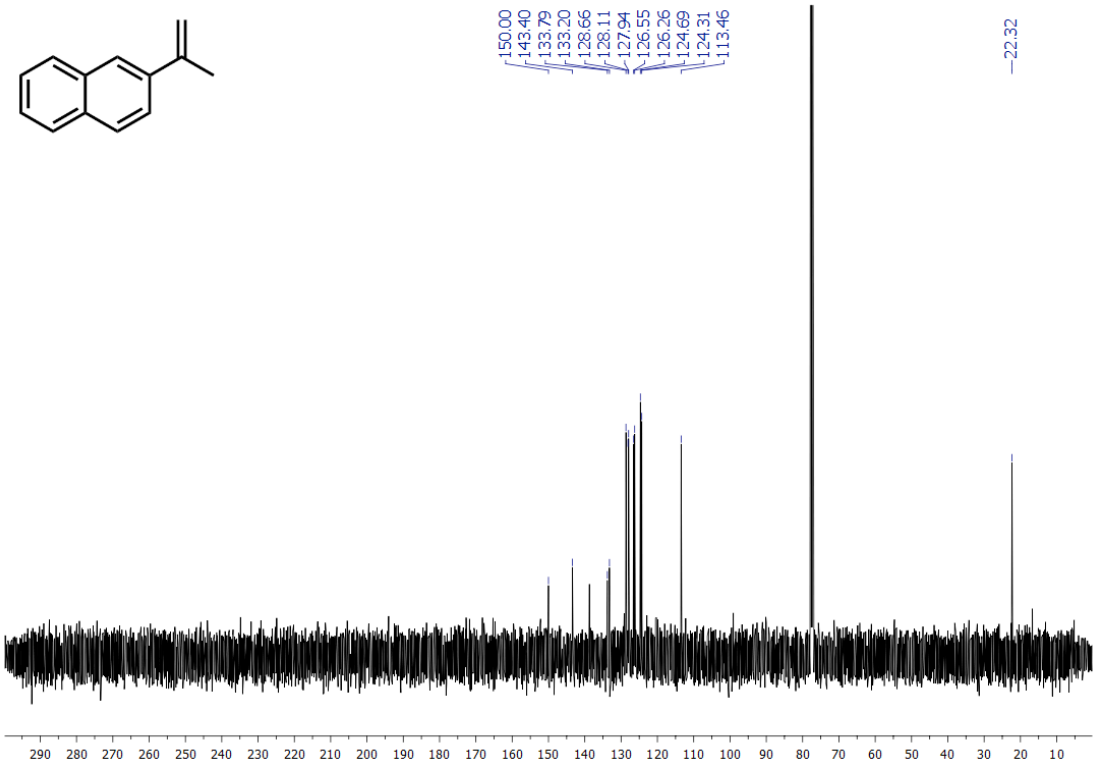
IR:2934, 1611, 1510, 1250, 1179, 1032, 1018, 829, 598 cm^{-1}

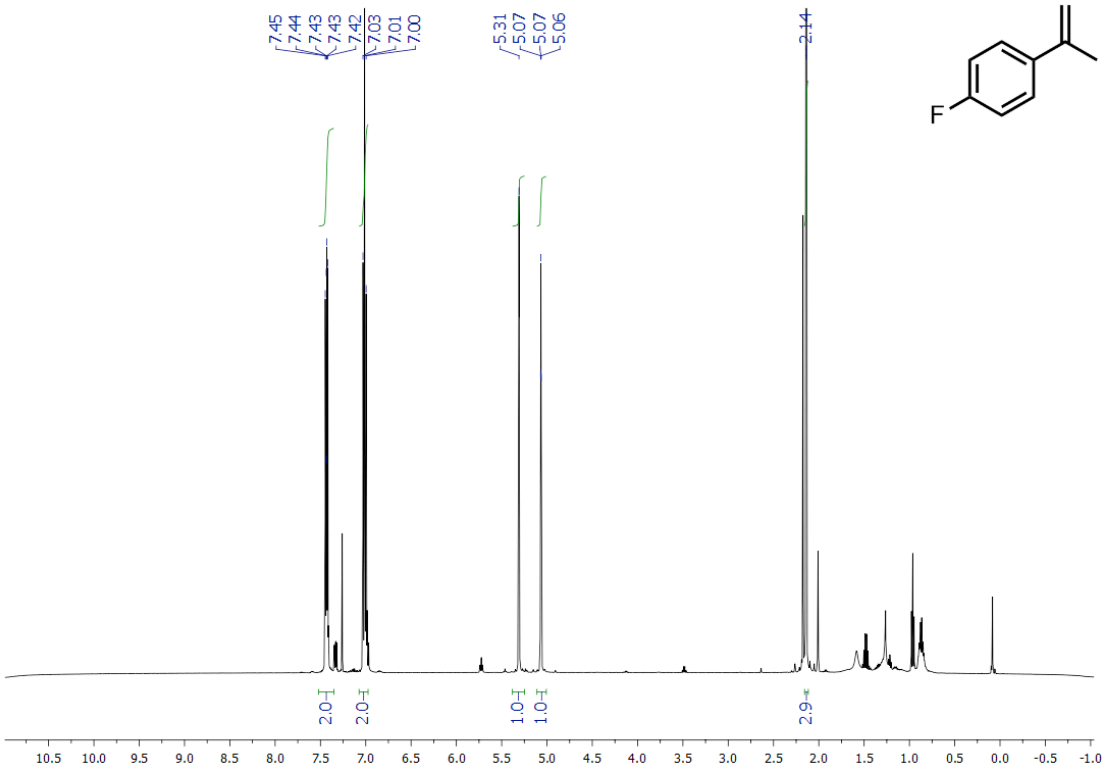
HRMS (p NSI): [$C_{15}H_{23}O_2F$ + K] calc. 293.1314, found 293.1316

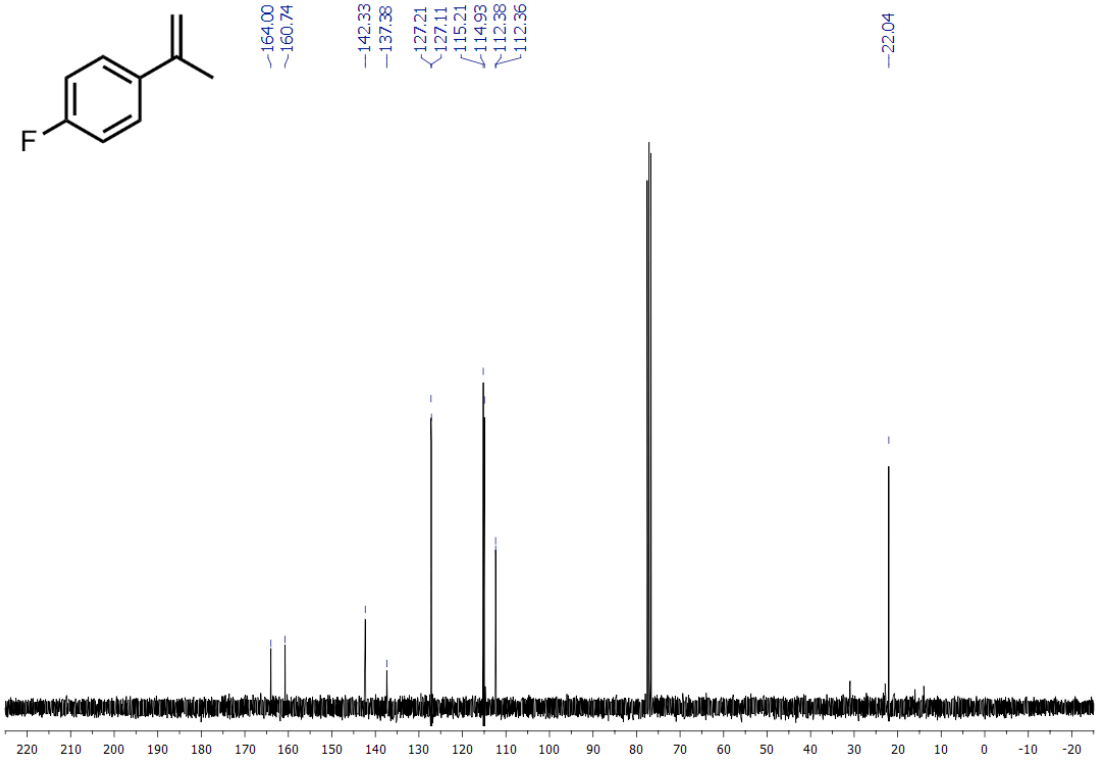
3.4 Spectroscopic data

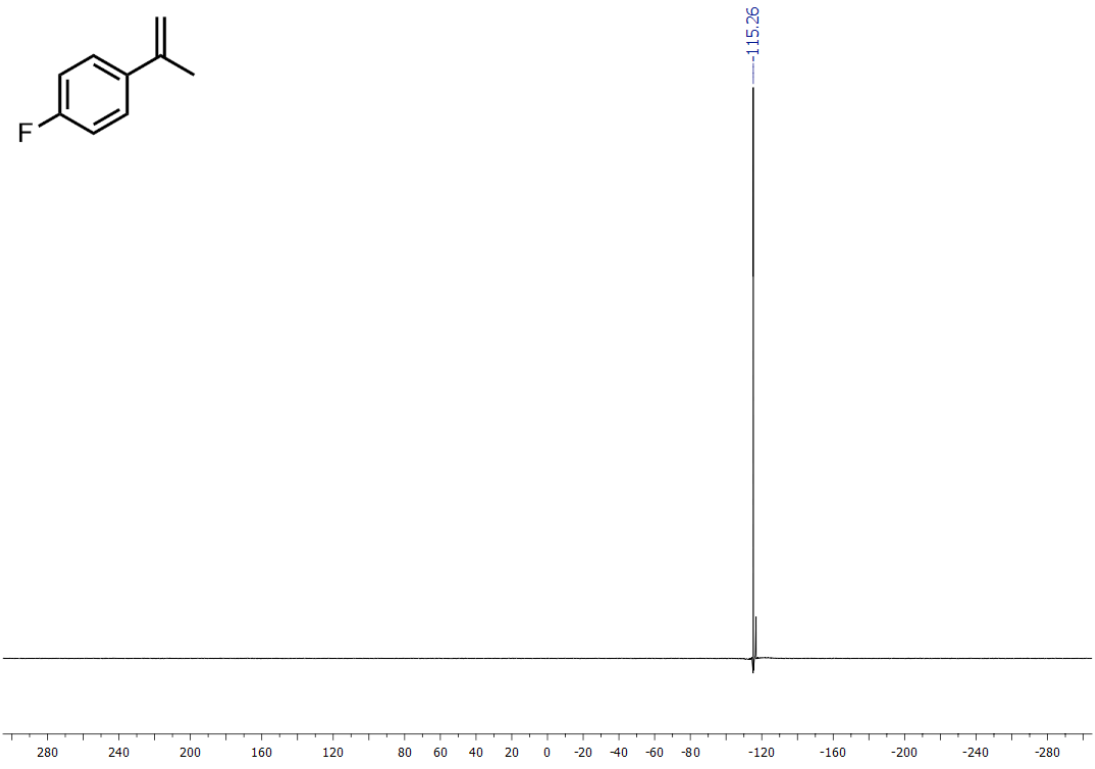
3.4.1 α-methylstyrene derivatives

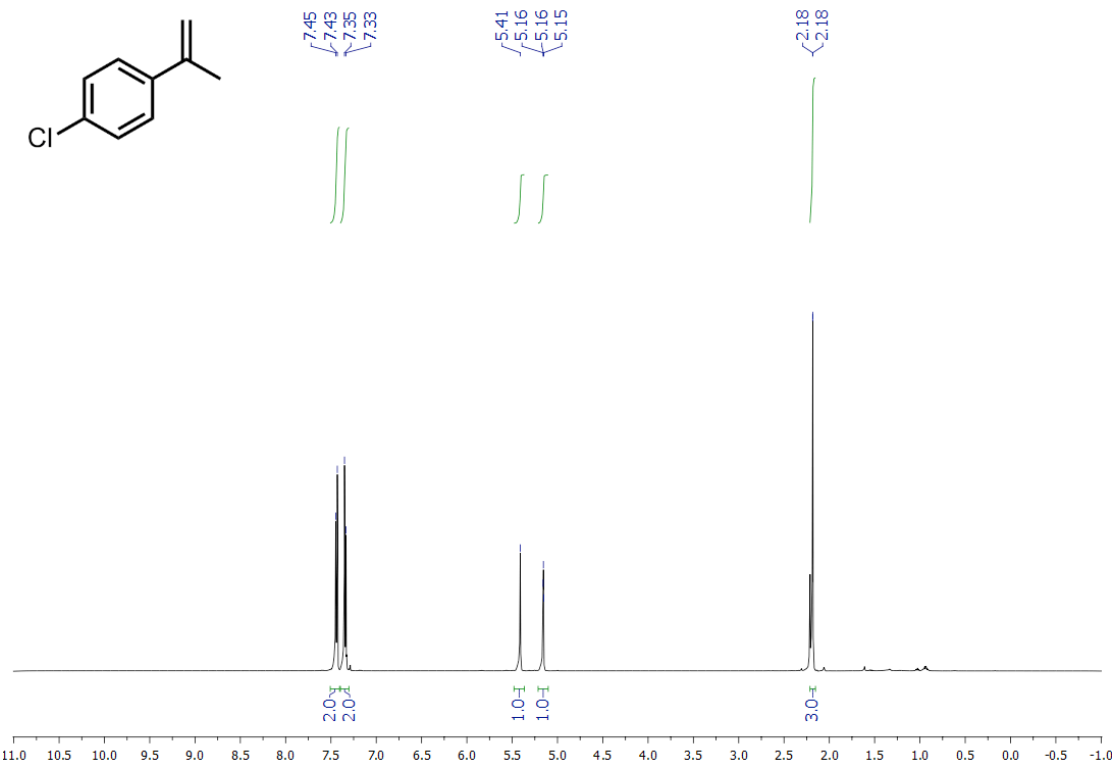





7.45
7.44
7.43
7.43
7.42
7.03
7.01
7.00
5.31
5.07
5.07
5.06
2.14
F
2.0
2.0
1.0
1.0
2.9


164.00
160.74
142.33
137.38
127.21
127.11
115.21
114.93
112.38
112.36
22.04
F


F
-115.26
280
240
200
160
120
80
60
40
20
0
-20
-40
-60
-80
-120
-160
-200
-240
-280


Cl
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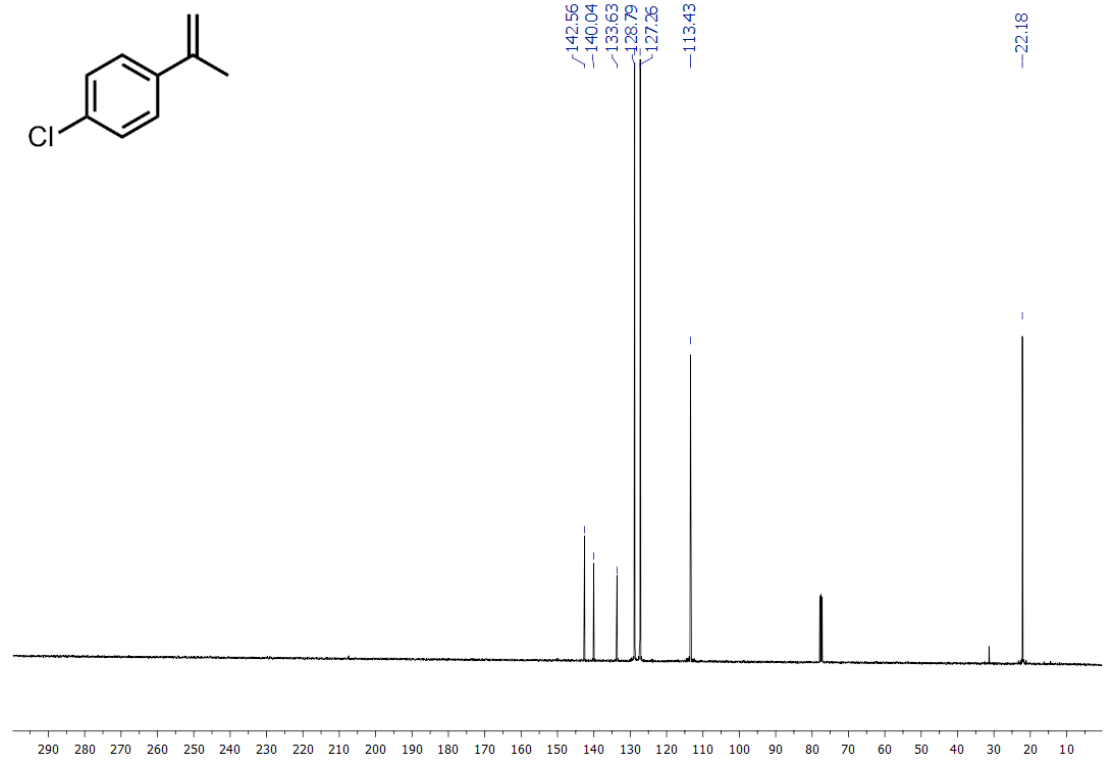
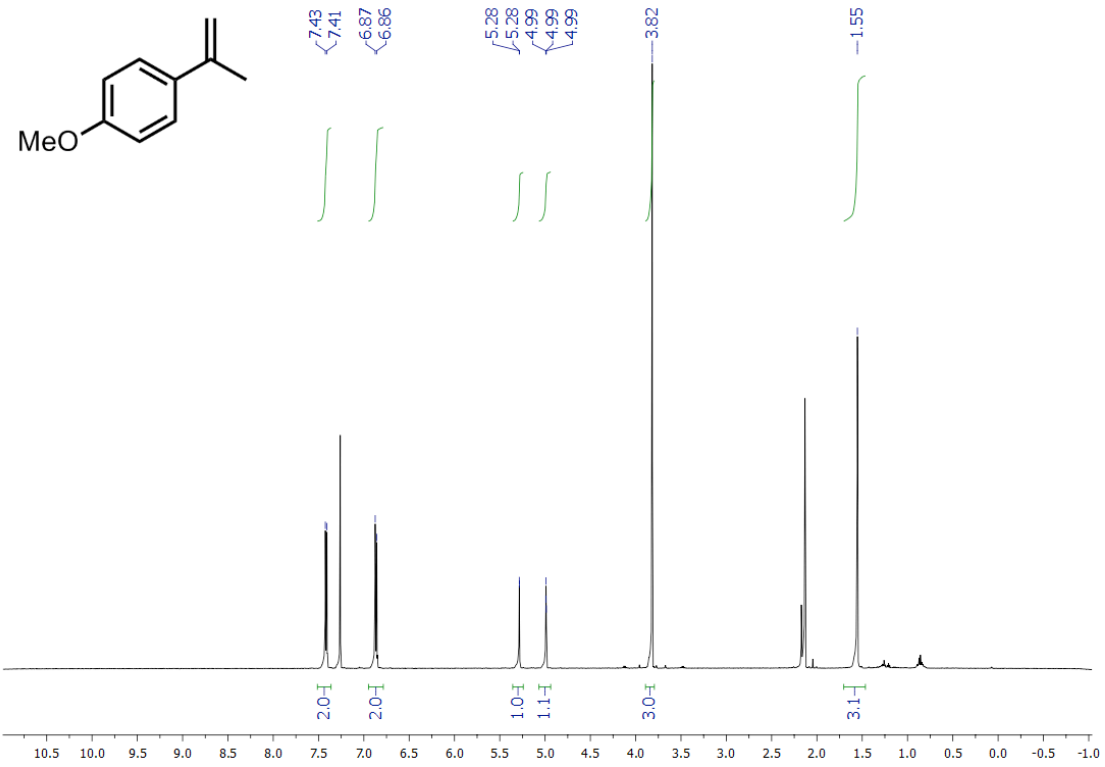
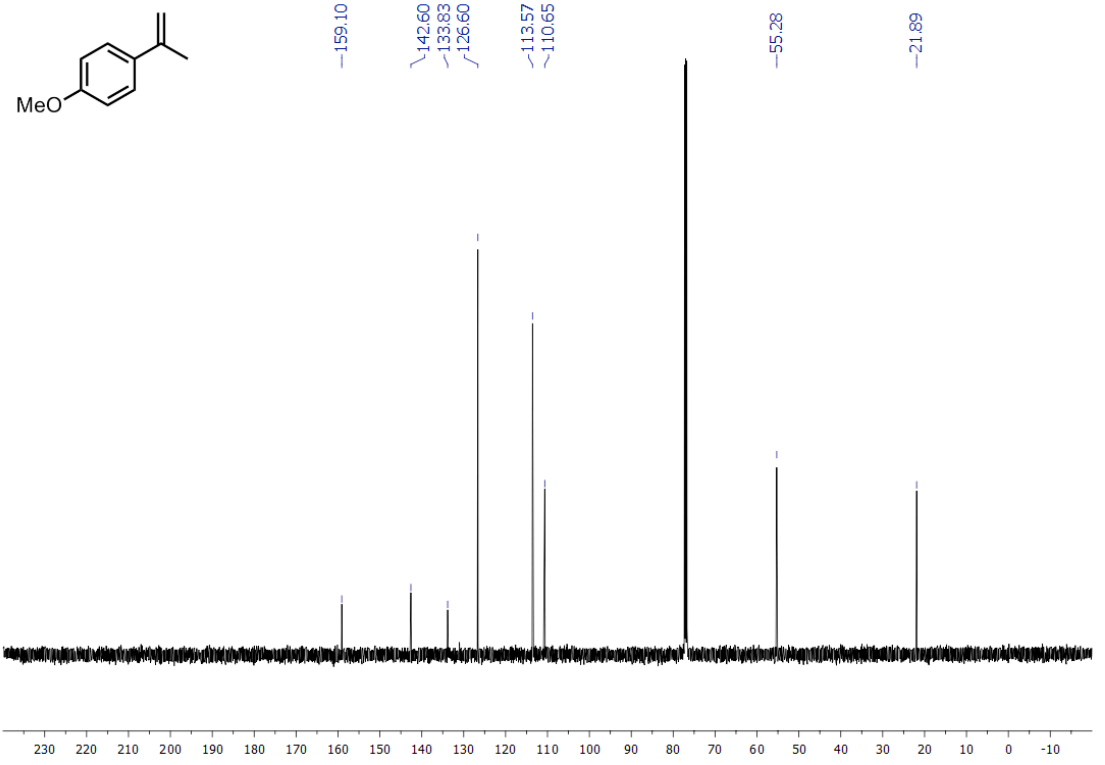
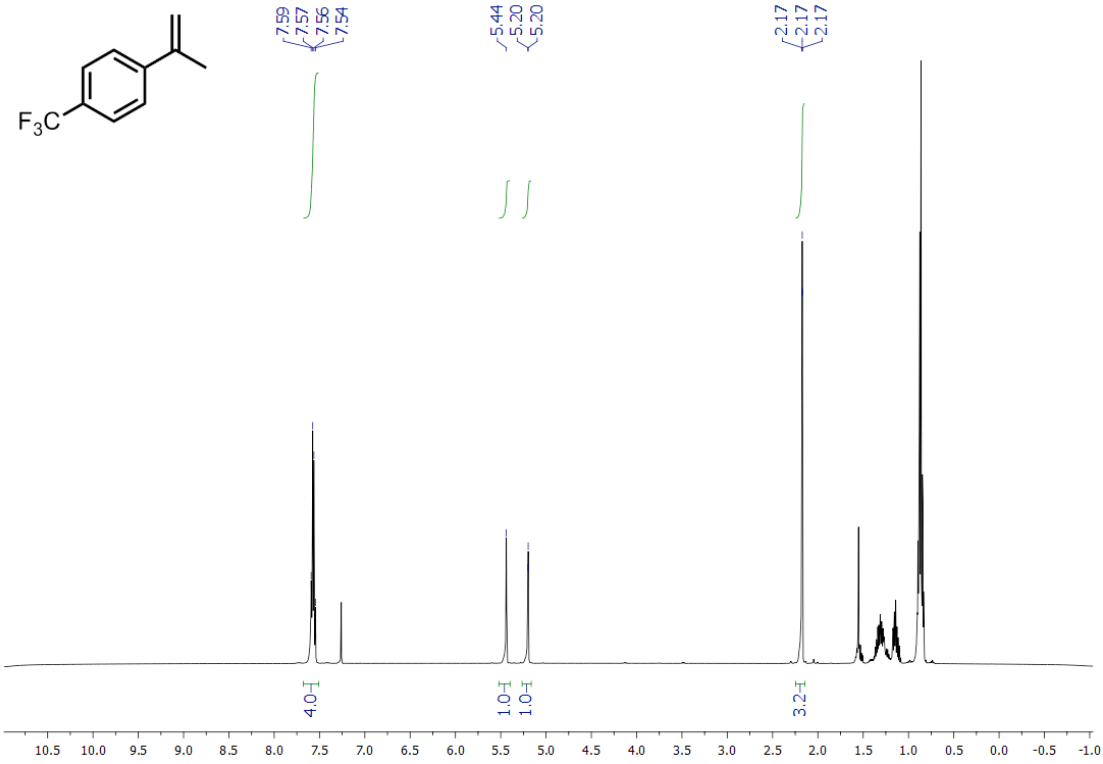
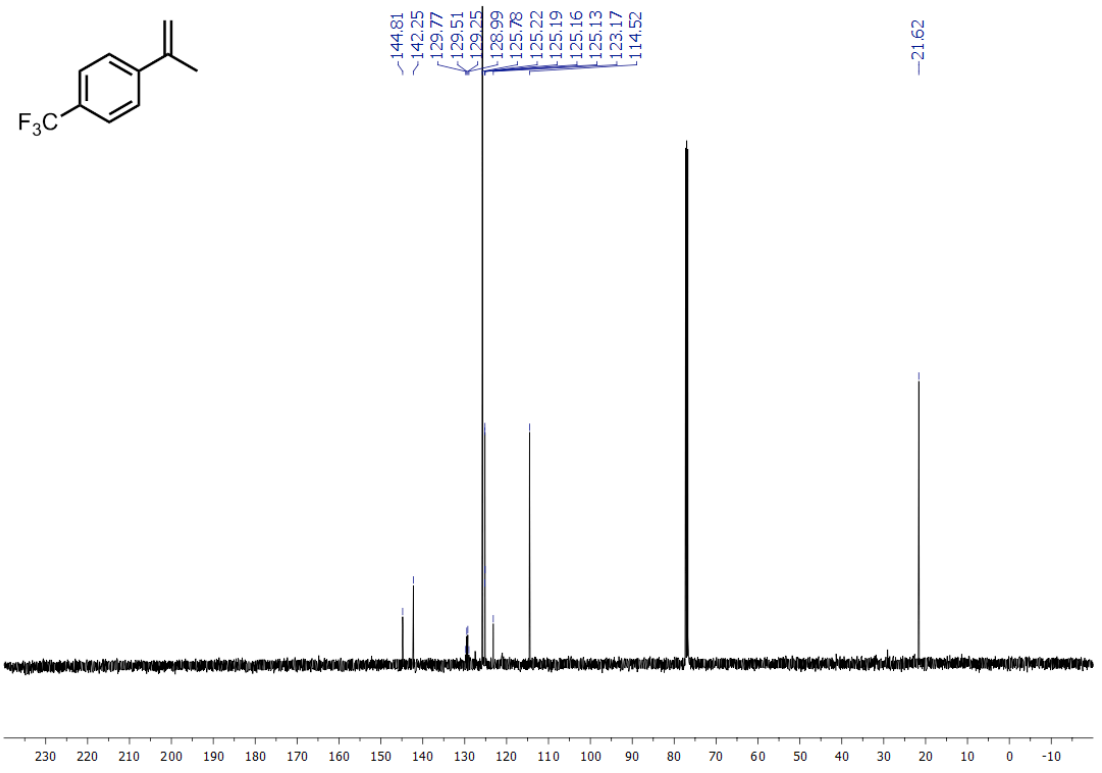
7.43
7.35
7.33
5.41
5.16
5.16
5.15
2.18
2.18
2.0
2.0
1.0
1.0
3.0
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0

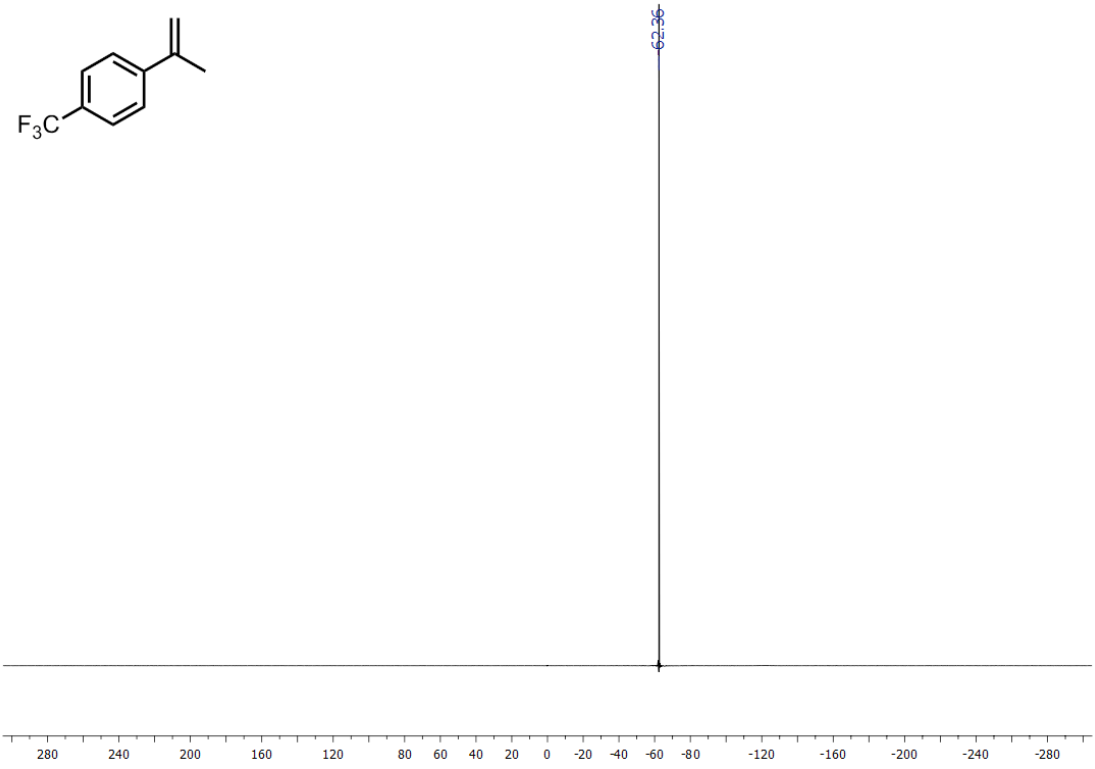

Cl
142.56
140.04
133.63
128.79
127.26
113.43
22.18
290 280 270 260 250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

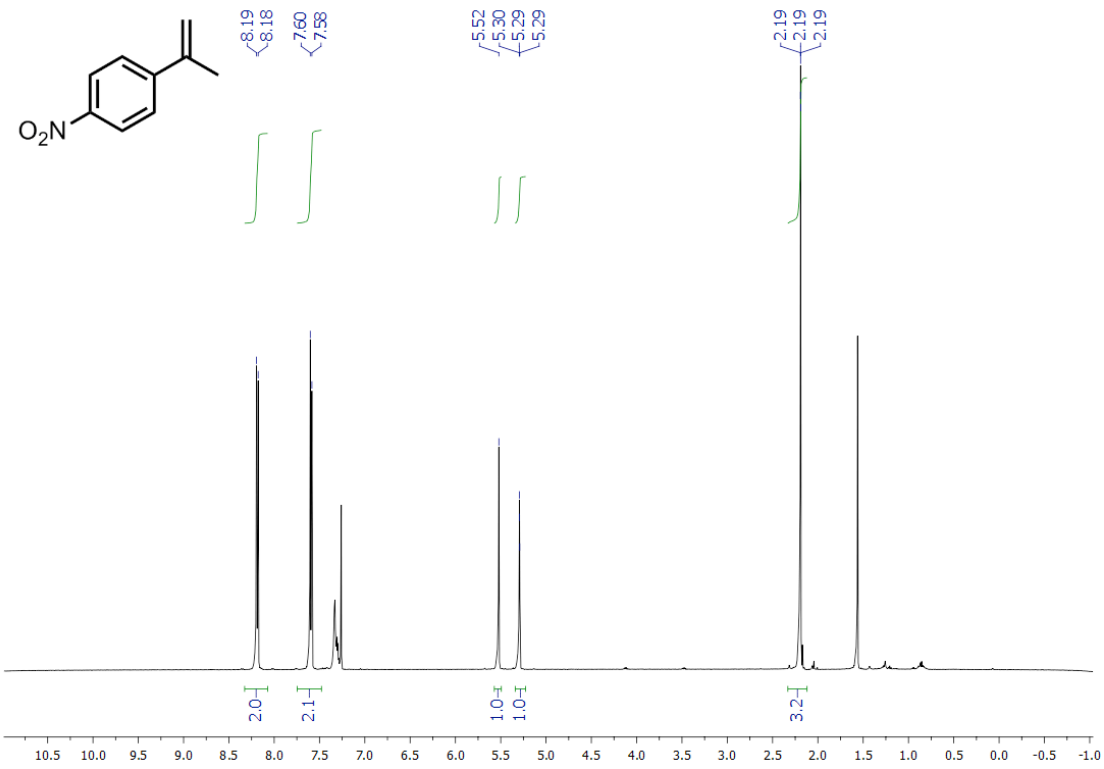

MeO
7.43
7.41
6.87
6.86
5.28
5.28
4.99
4.99
4.99
3.82
1.55
2.0
2.0
1.0
1.1
3.0
3.1
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0

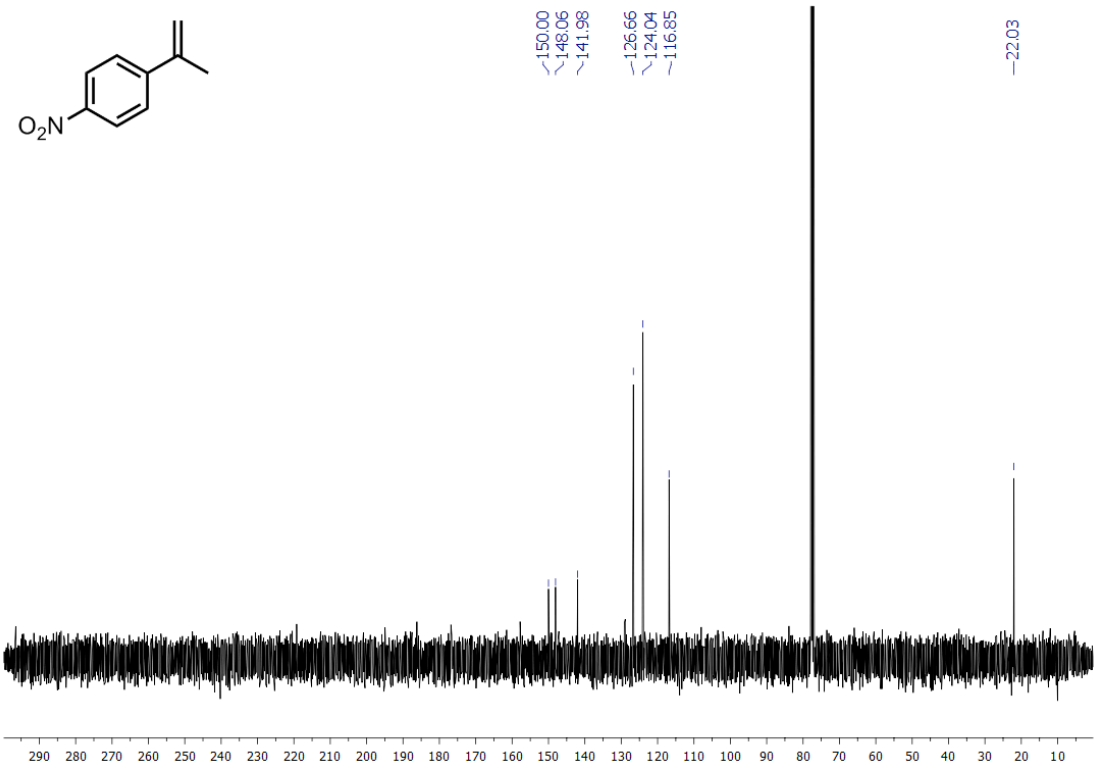

MeO
159.10
142.60
133.83
126.60
113.57
110.65
55.28
21.89
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


F3C
7.59
7.57
7.56
7.54
5.44
5.20
5.20
2.17
2.17
2.17
4.0
1.0
1.0
3.2
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0


F3C
144.81
142.25
129.77
129.51
129.25
128.99
125.78
125.22
125.19
125.16
125.13
123.17
114.52
21.62
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


F3C
-62.36
280
240
200
160
120
80
60
40
20
0
-20
-40
-60
-80
-120
-160
-200
-240
-280


O2N
8.19
8.18
7.60
7.58
5.52
5.30
5.29
5.29
2.19
2.19
2.19
2.0
2.1
1.0
1.0
3.2
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0


O2N
150.00
148.06
141.98
126.66
124.04
116.85
22.03
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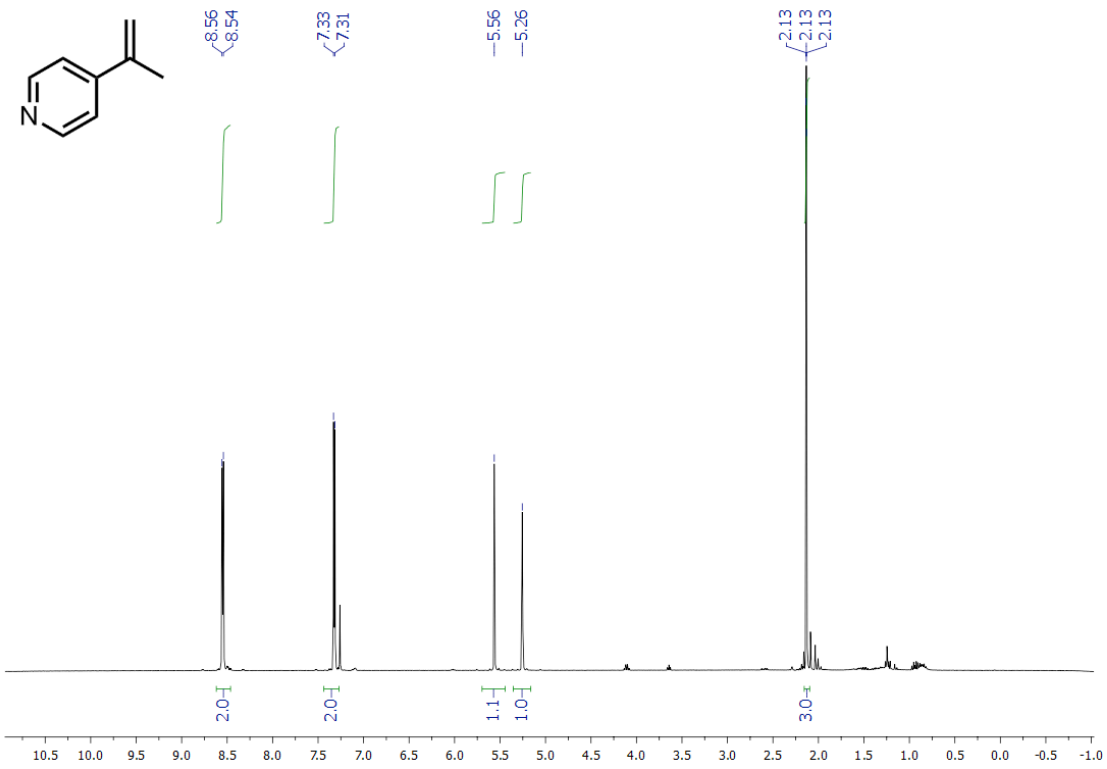
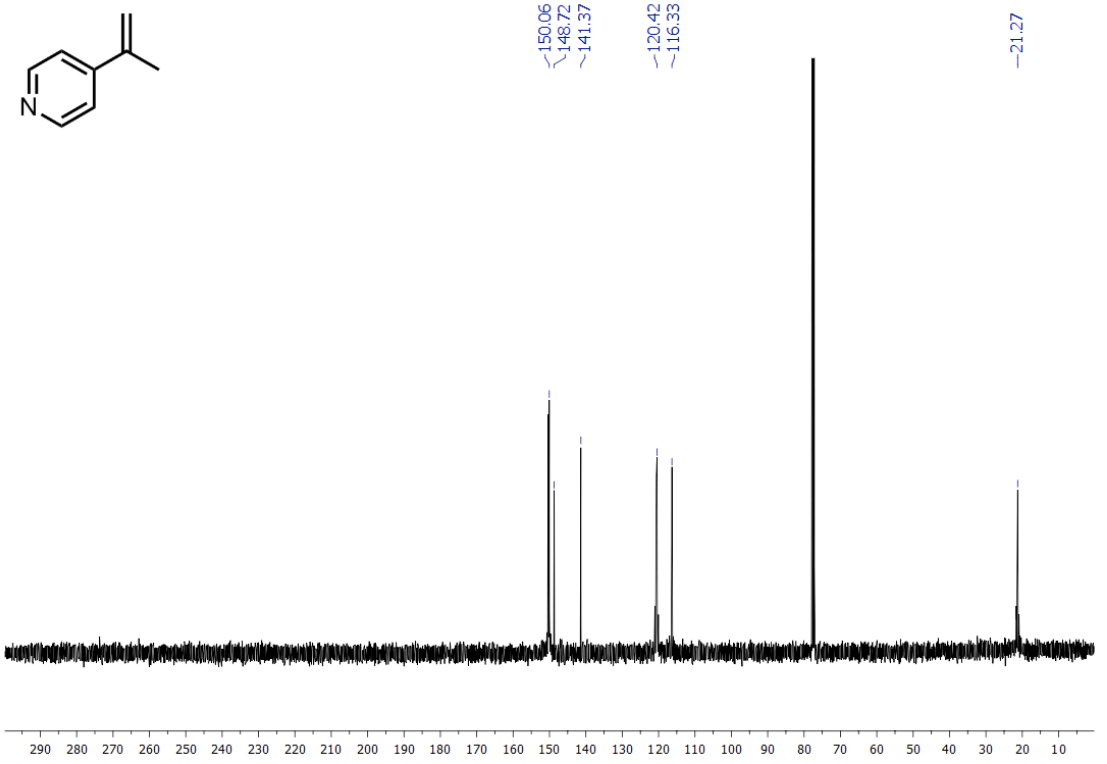
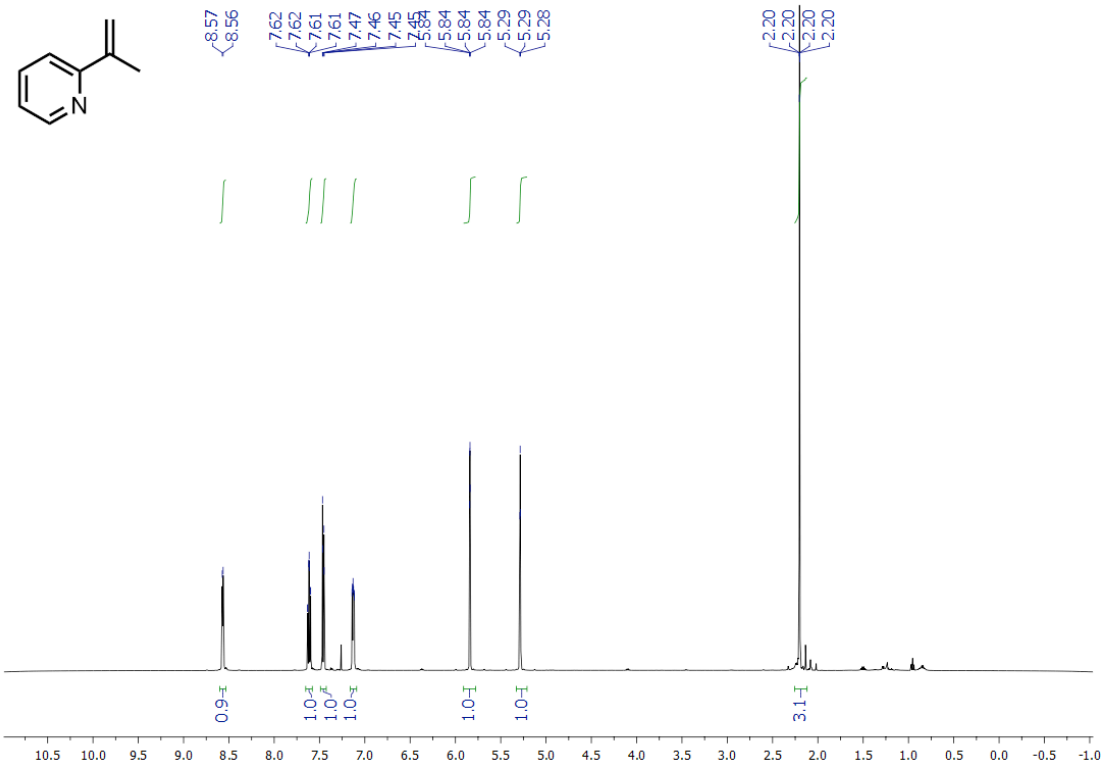
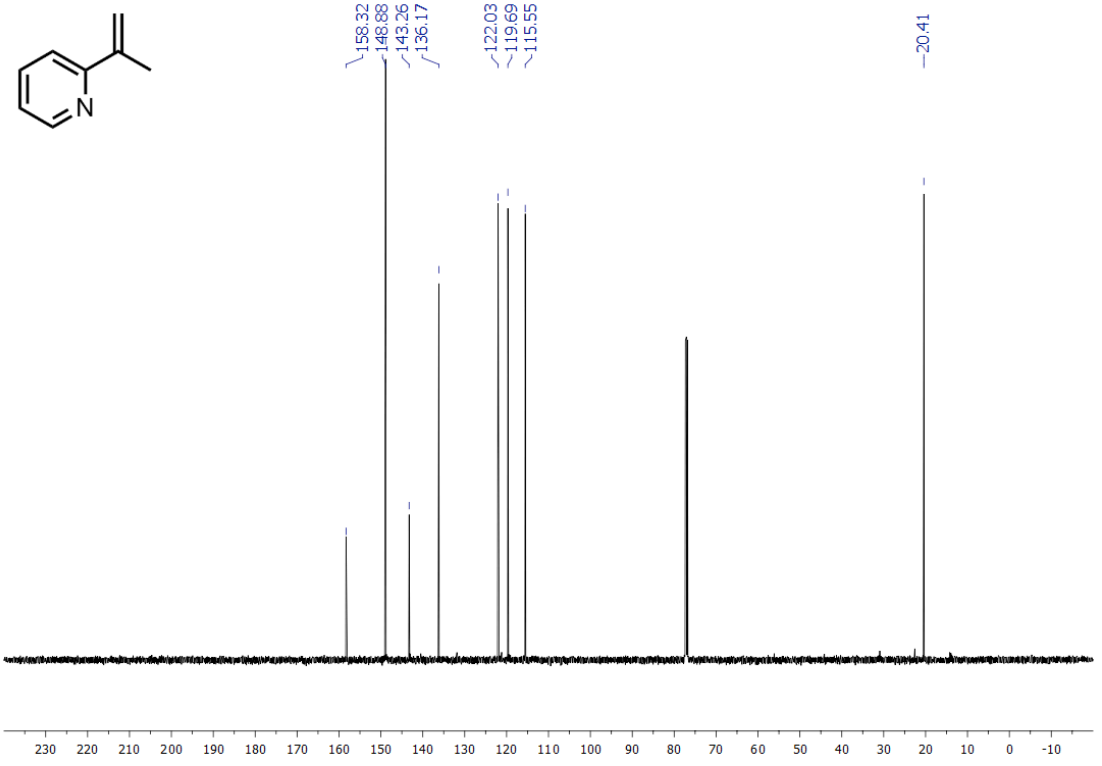
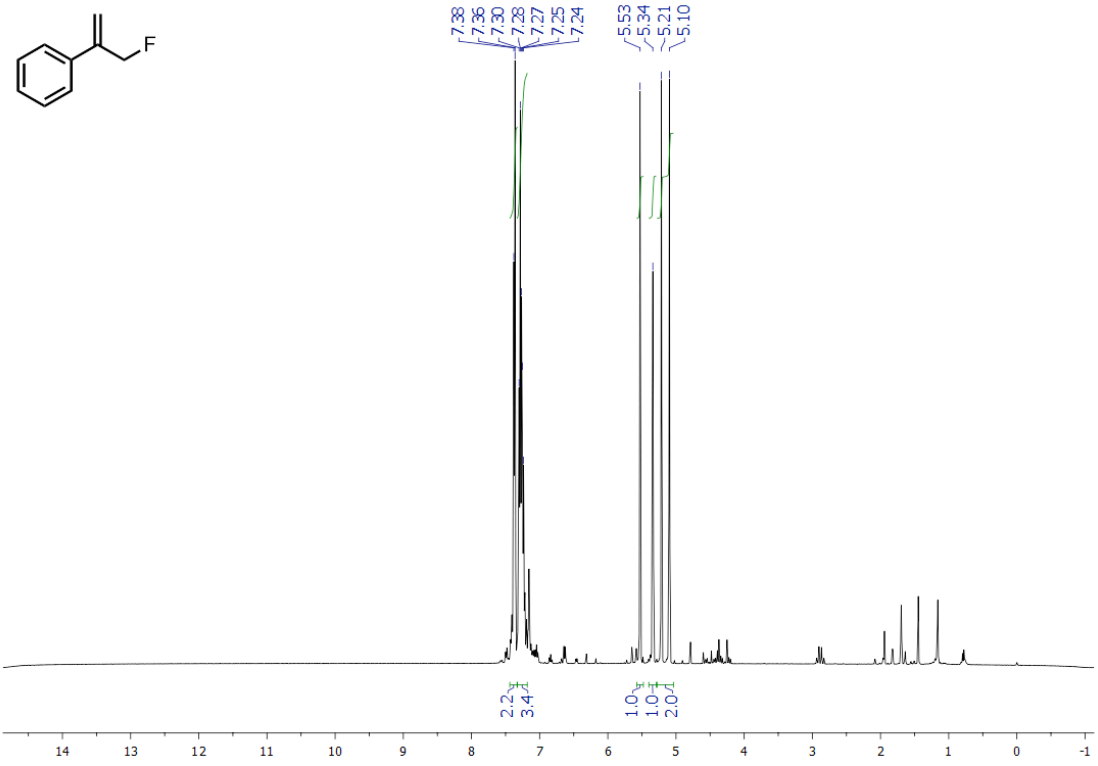

8.56
8.54
7.33
7.31
5.56
5.26
2.13
2.13
2.13
2.0
2.0
1.1
1.0
3.0
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0

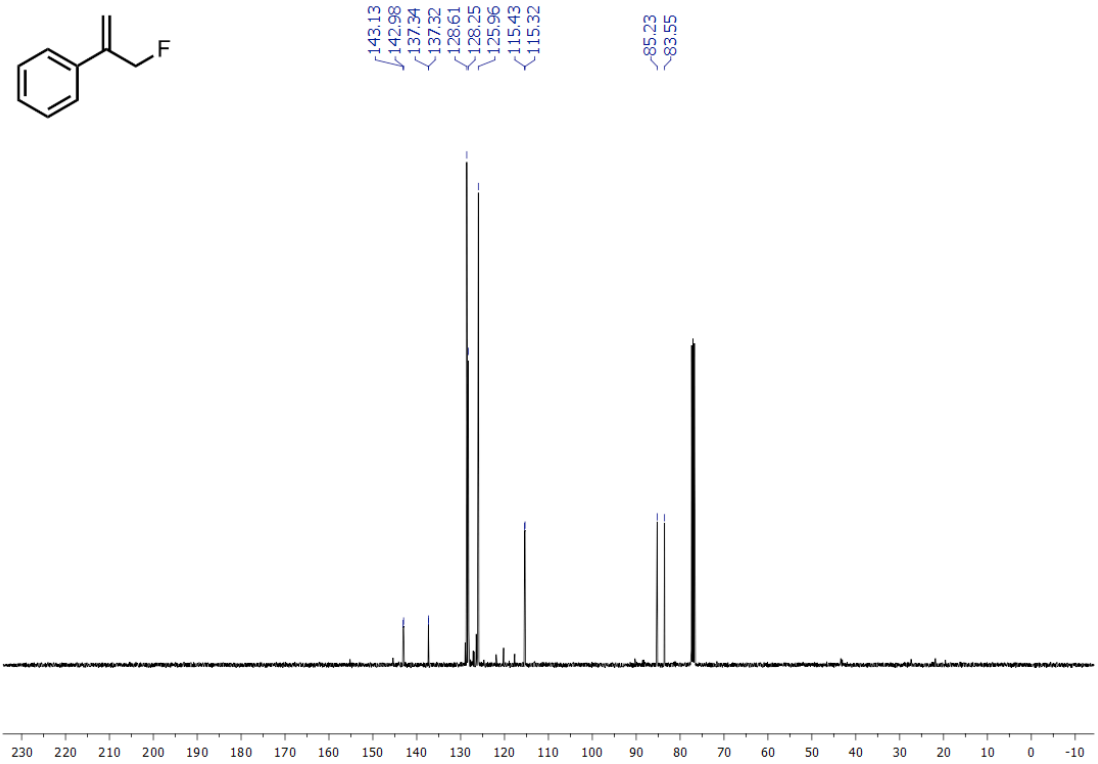

150.06
148.72
141.37
120.42
116.33
21.27
290 280 270 260 250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

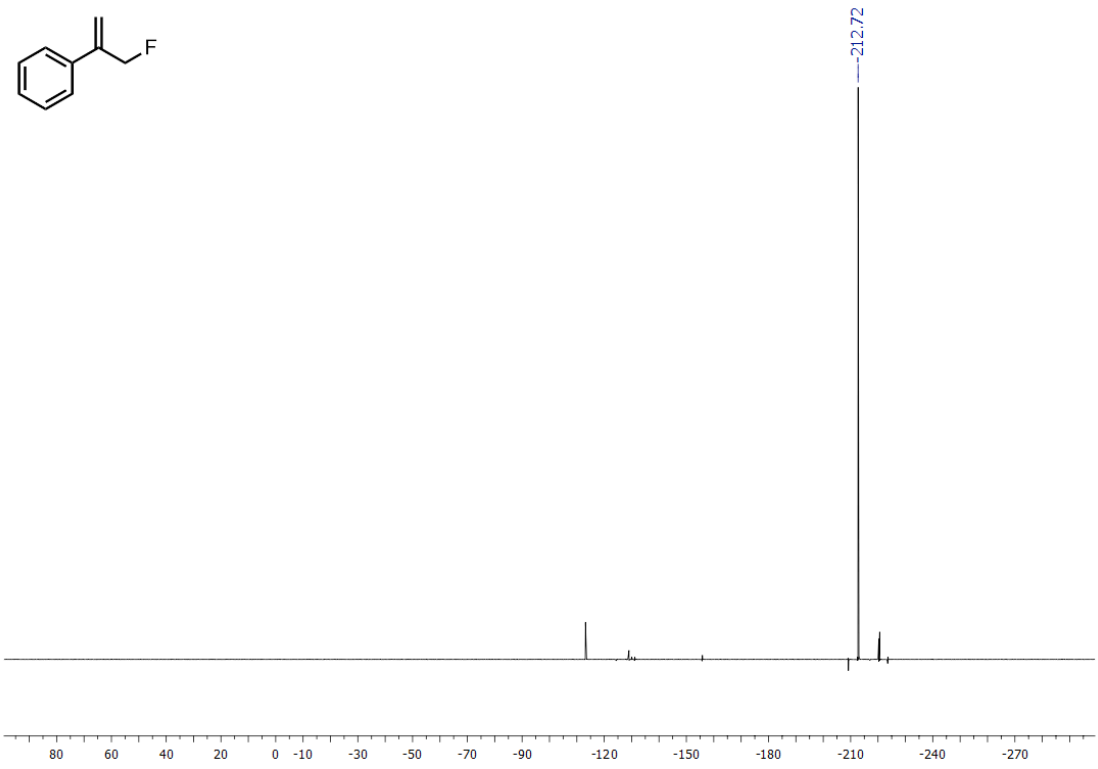

8.57
8.56
7.62
7.62
7.61
7.61
7.47
7.46
7.45
5.84
5.84
5.84
5.29
5.28
2.20
2.20
2.20
2.20
0.9
1.0
1.0
1.0
1.0
1.0
3.1
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0


158.32
148.88
143.26
136.17
122.03
119.69
115.55
20.41
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

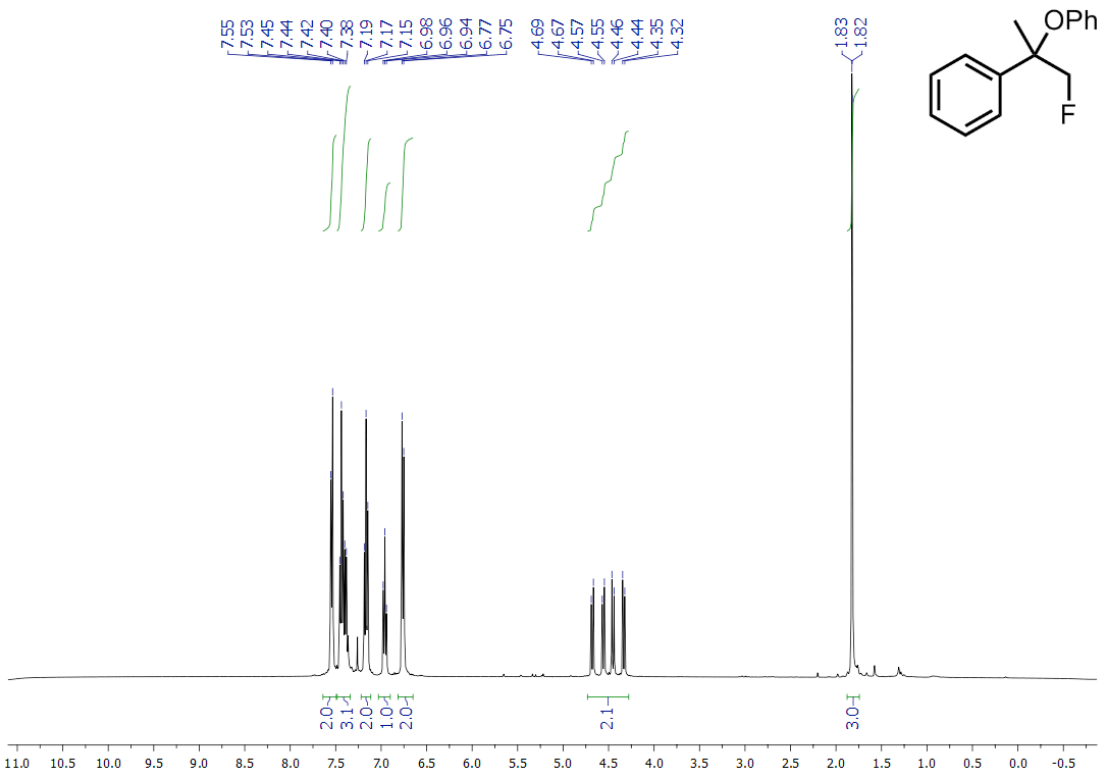
3.4.2 Elimination side product

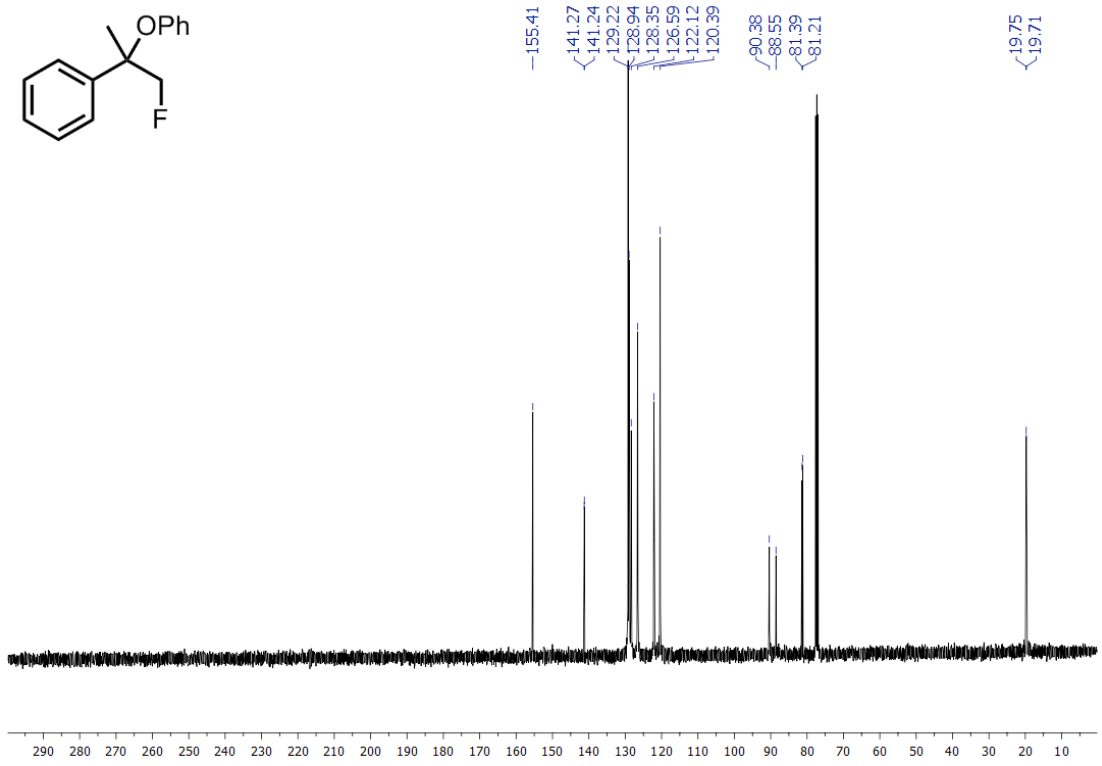


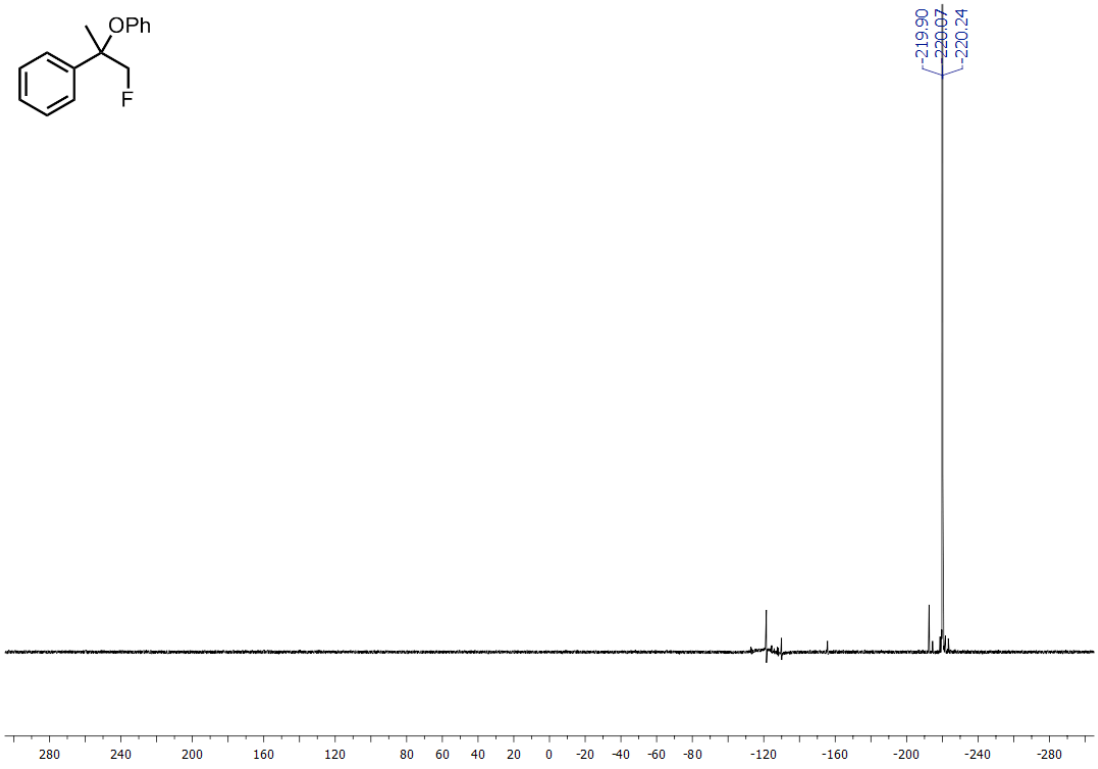



F
-212.72
80
60
40
20
0
-10
-30
-50
-70
-90
-120
-150
-180
-210
-240
-270

3.4.3 Vicinal fluoroethers






OPh
F
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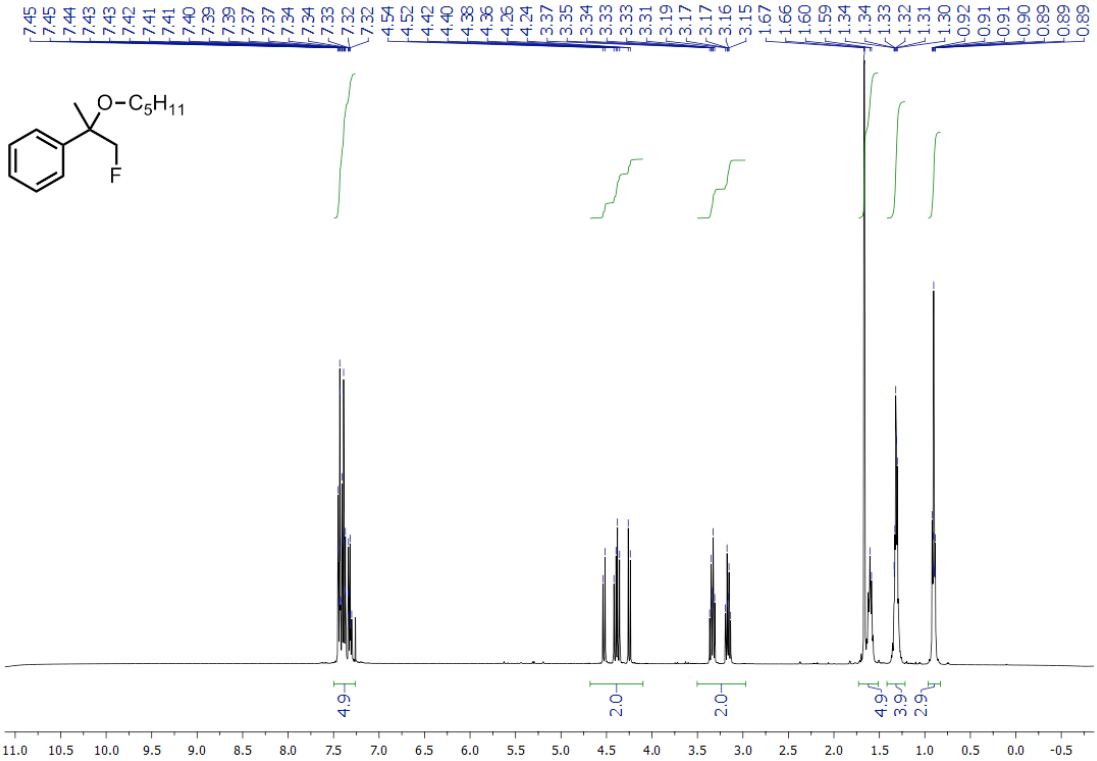
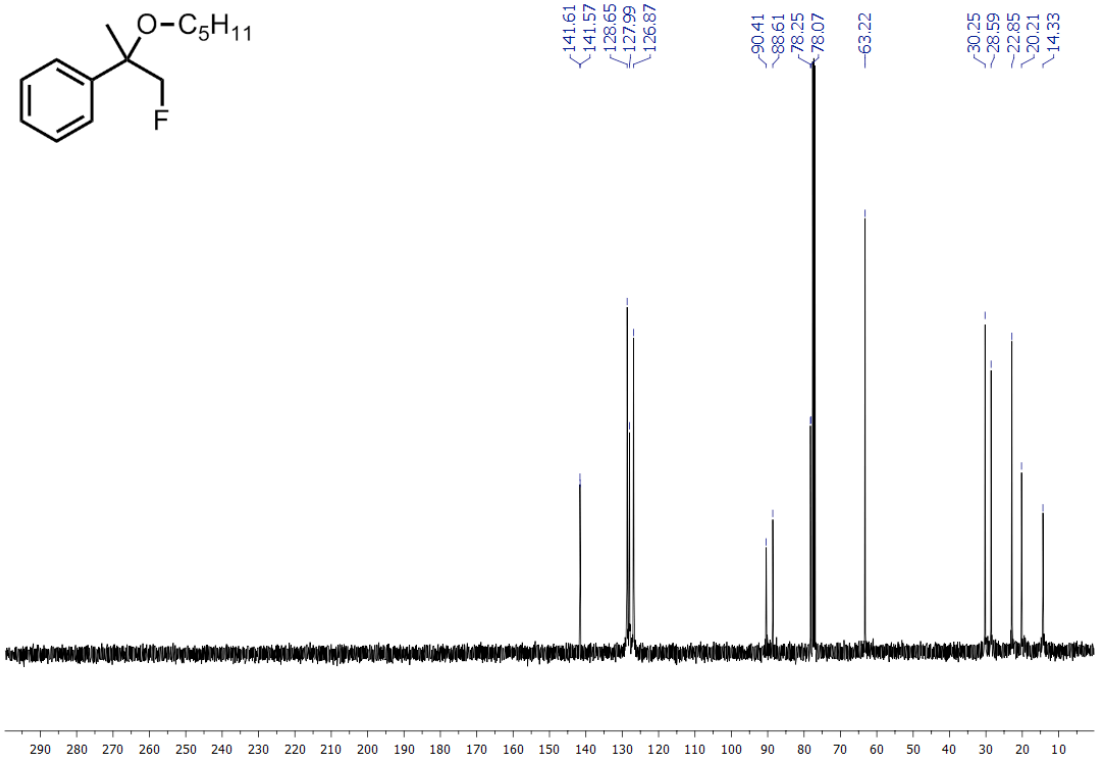
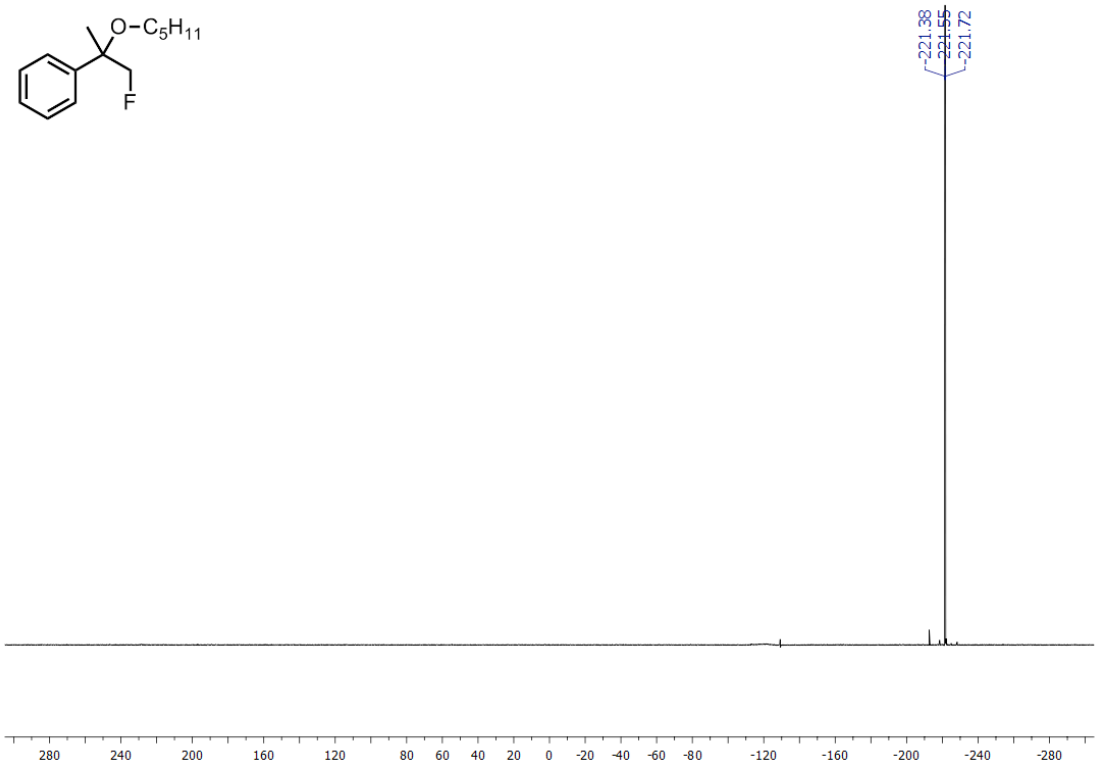
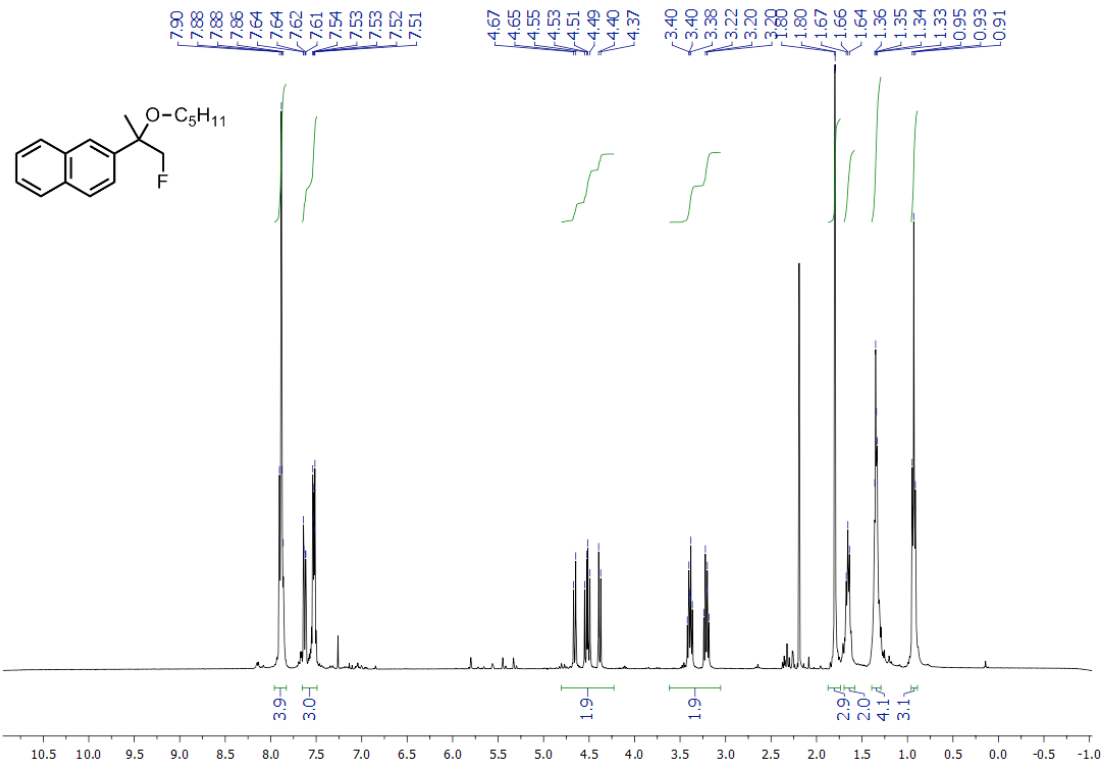
-220.07
-220.24
280
240
200
160
120
80
60
40
20
0
-20
-40
-60
-80
-120
-160
-200
-240
-280


7.45 7.45 7.44 7.43 7.43 7.42 7.41 7.41 7.40 7.39 7.39 7.37 7.37 7.34 7.34 7.33 7.32 7.32
4.54 4.52 4.42 4.40 4.38 4.36 4.26 4.24 3.37 3.35 3.34 3.33 3.33 3.31 3.19 3.17 3.17 3.16 3.15
1.67 1.66 1.60 1.59 1.34 1.34 1.33 1.32 1.31 1.30 0.92 0.91 0.91 0.90 0.89 0.89 0.89
O-C5H11
F
4.9 2.0 2.0 4.9 3.9 2.9
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5


O-C5H11
F
141.61 141.57 128.65 127.99 126.87
90.41 88.61 78.25 78.07 63.22
30.25 28.59 22.85 20.21 14.33
290 280 270 260 250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10


O–C5H11
F
-221.38
-221.55
-221.72
280
240
200
160
120
80
60
40
20
0
-20
-40
-60
-80
-120
-160
-200
-240
-280


7.90
7.88
7.88
7.86
7.64
7.64
7.62
7.61
7.54
7.53
7.53
7.52
7.51
4.67
4.65
4.55
4.53
4.51
4.49
4.40
4.37
3.40
3.40
3.38
3.22
3.20
3.20
1.80
1.80
1.67
1.66
1.64
1.36
1.35
1.34
1.33
0.95
0.93
0.91
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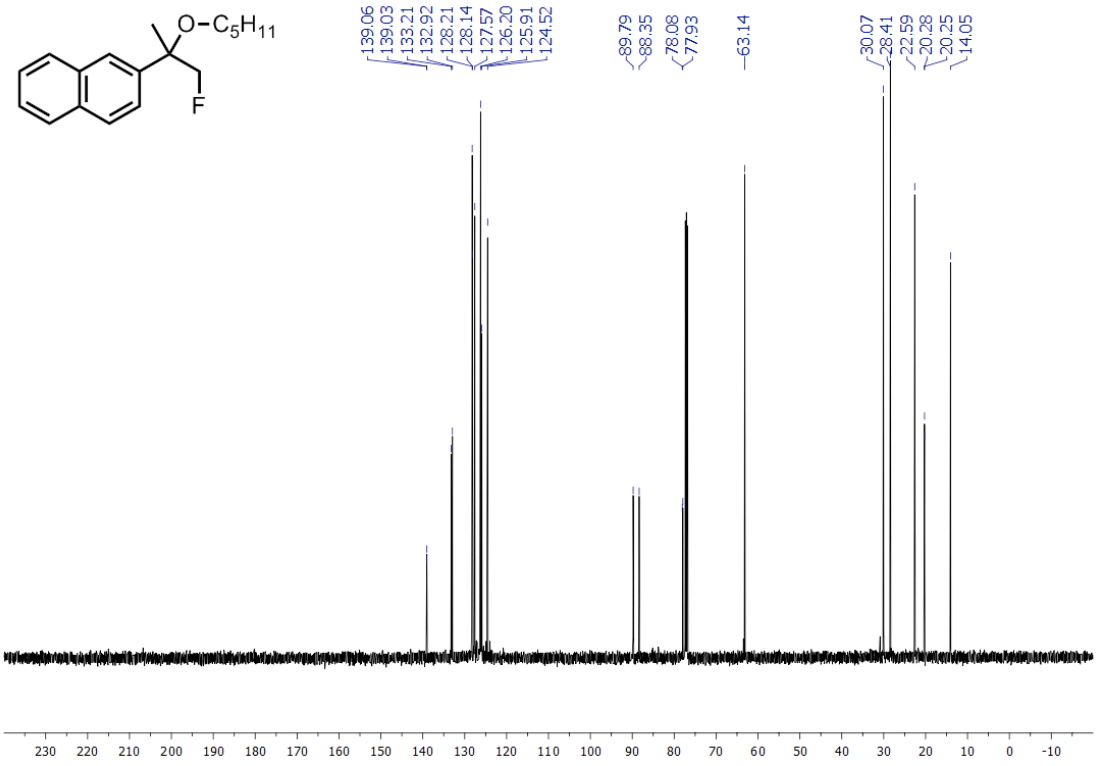
3.0
1.9
1.9
2.9
2.0
4.1
3.1
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0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139.03
133.21
132.92
128.21
128.14
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126.20
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124.52
89.79
88.35
78.08
77.93
63.14
30.07
28.41
22.59
20.28
20.25
14.05
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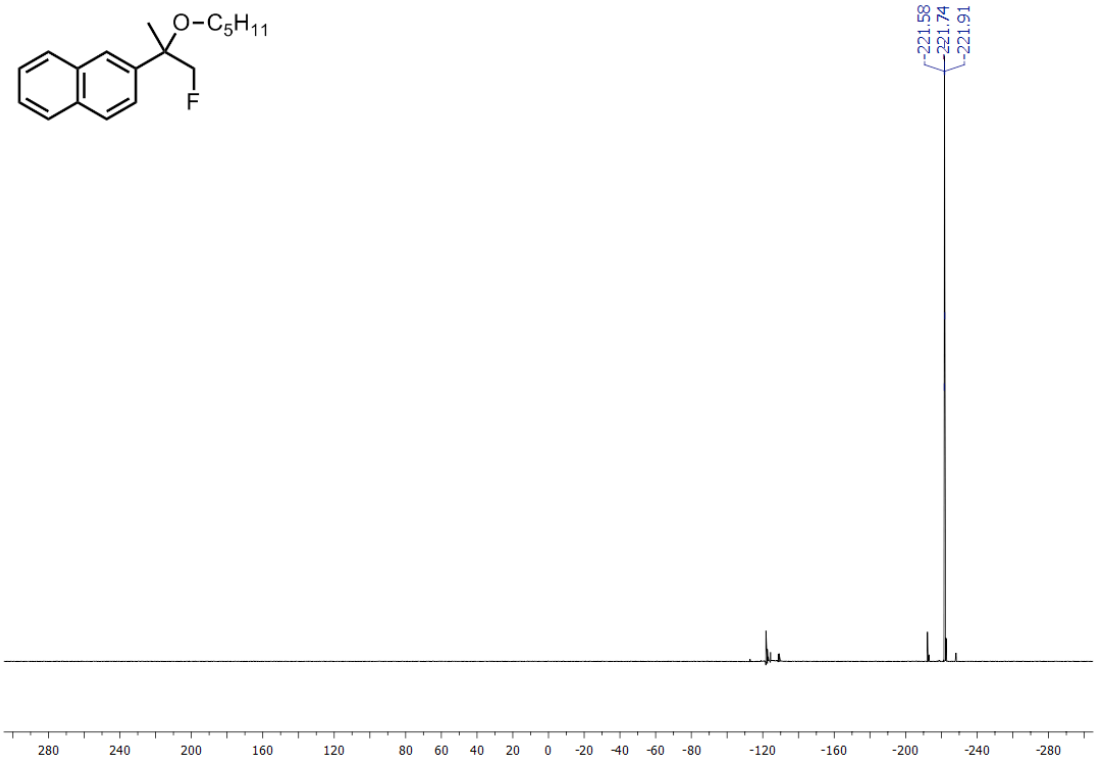
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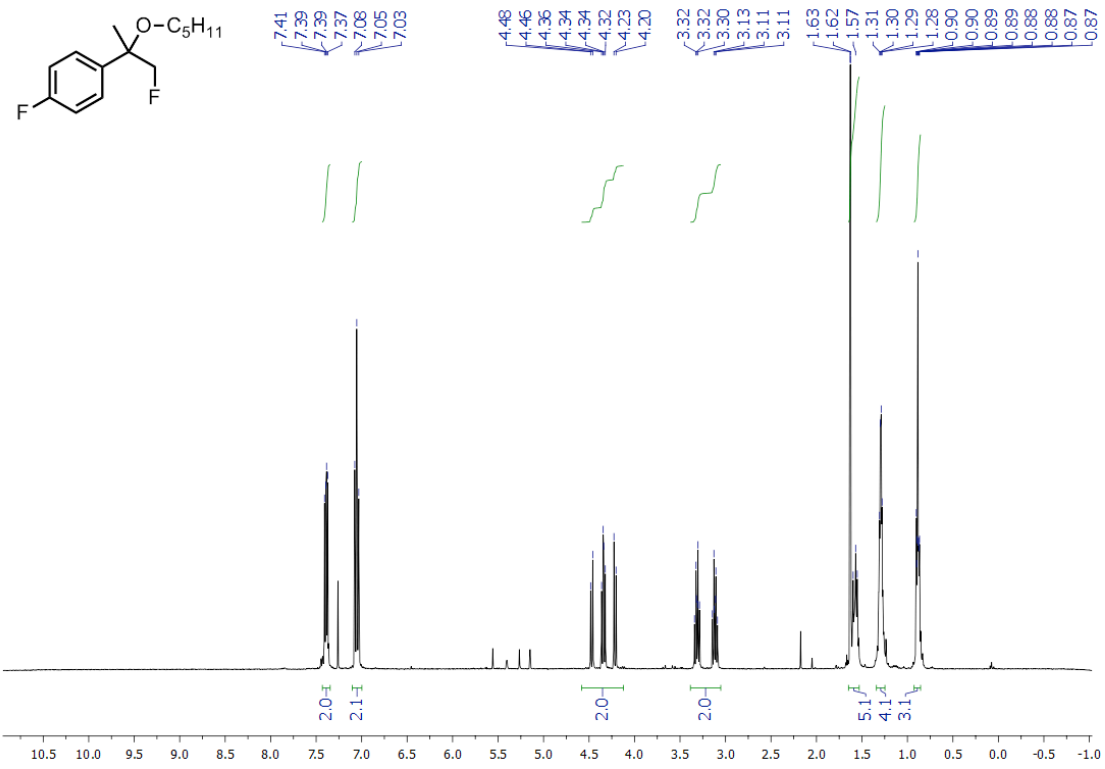
-80
-120
-160
-200
-240
-280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F
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7.39
7.37
7.08
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7.03
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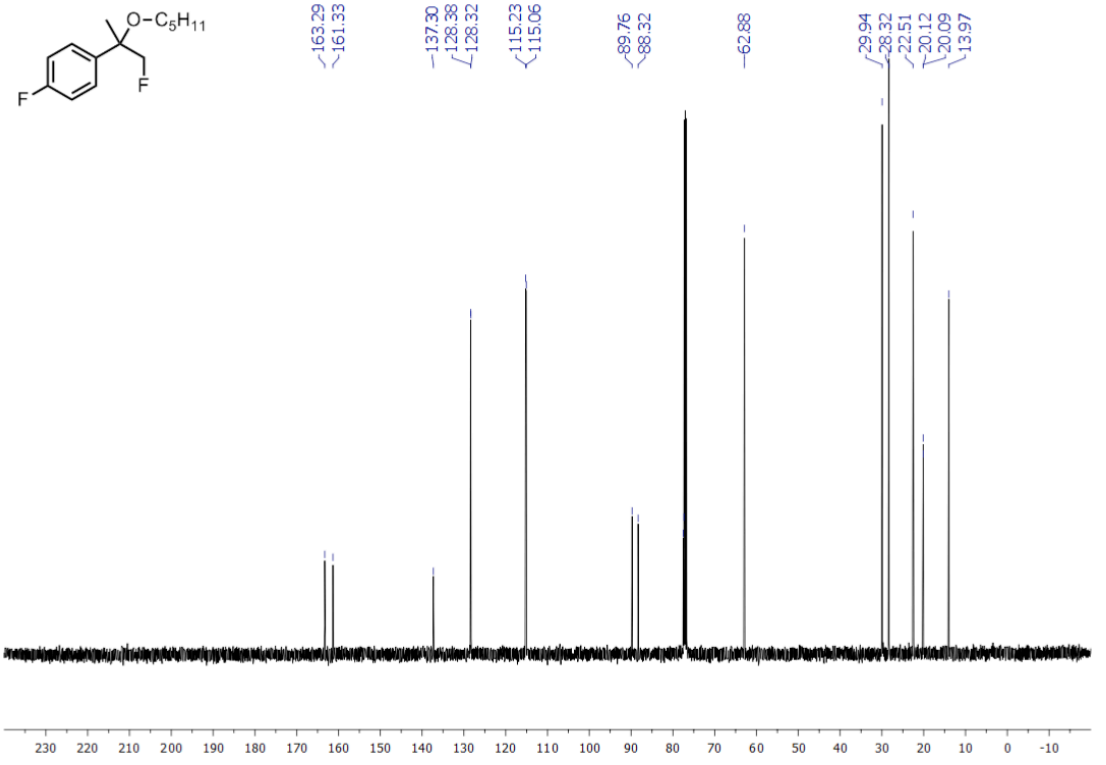
4.46
4.36
4.34
4.34
4.32
4.23
4.20
3.32
3.32
3.30
3.13
3.11
3.11
1.63
1.62
1.57
1.31
1.30
1.29
1.28
0.90
0.90
0.89
0.89
0.88
0.88
0.87
0.87
2.0
2.1
2.0
2.0
5.1
4.1
3.1
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0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115.06
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62.88
29.94
28.32
22.51
20.12
20.09
13.97
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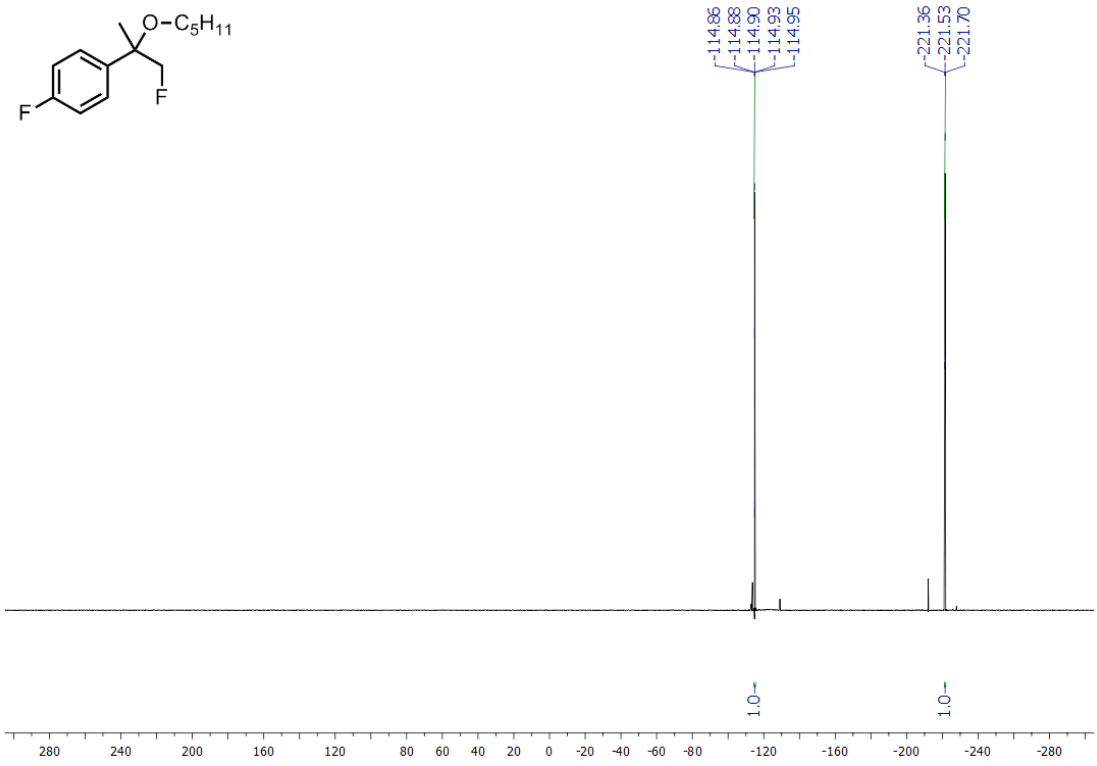
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1.0
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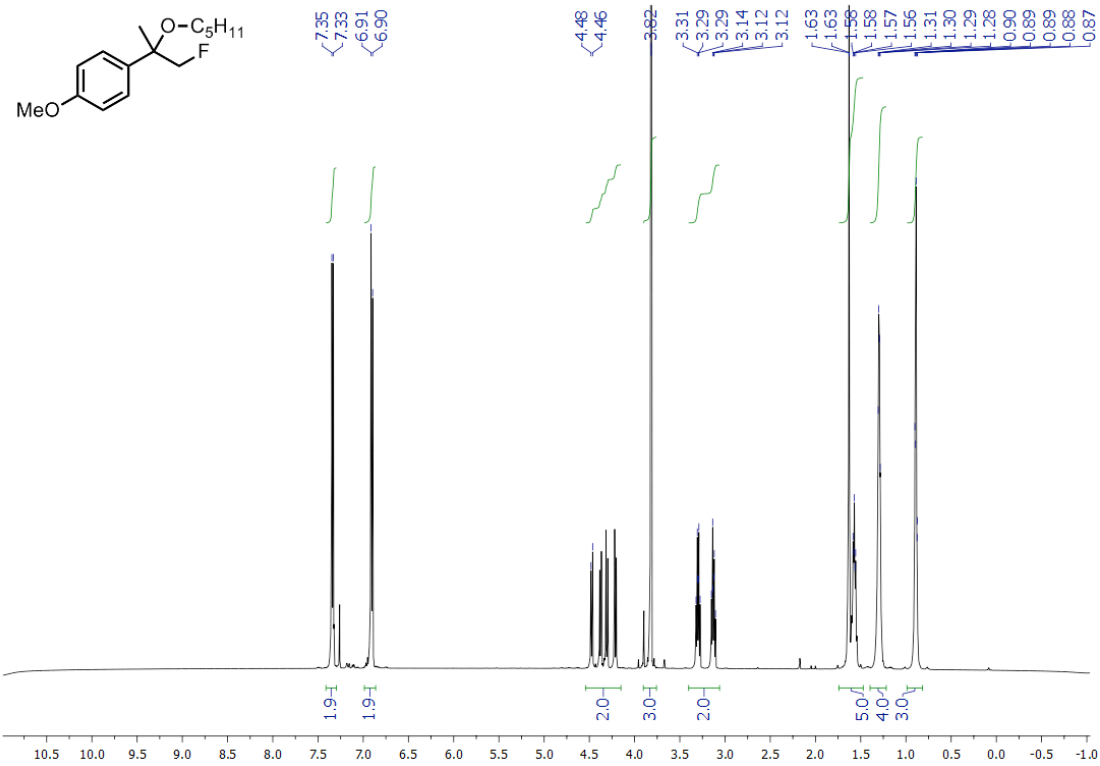
40
20
0
-20
-40
-60
-80
-120
-160
-200
-240
-280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3.14
3.12
3.12
1.63
1.63
1.58
1.58
1.57
1.56
1.31
1.30
1.29
1.28
0.90
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0.88
0.87
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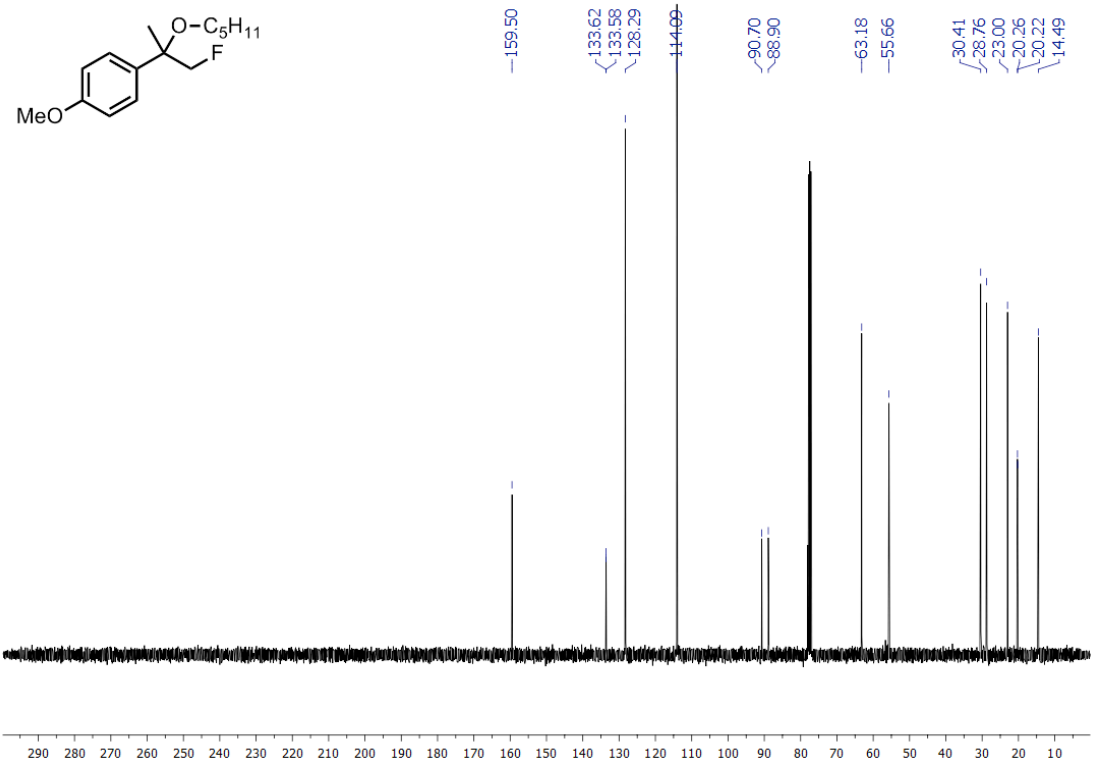
3.0
2.0
5.0
4.0
3.0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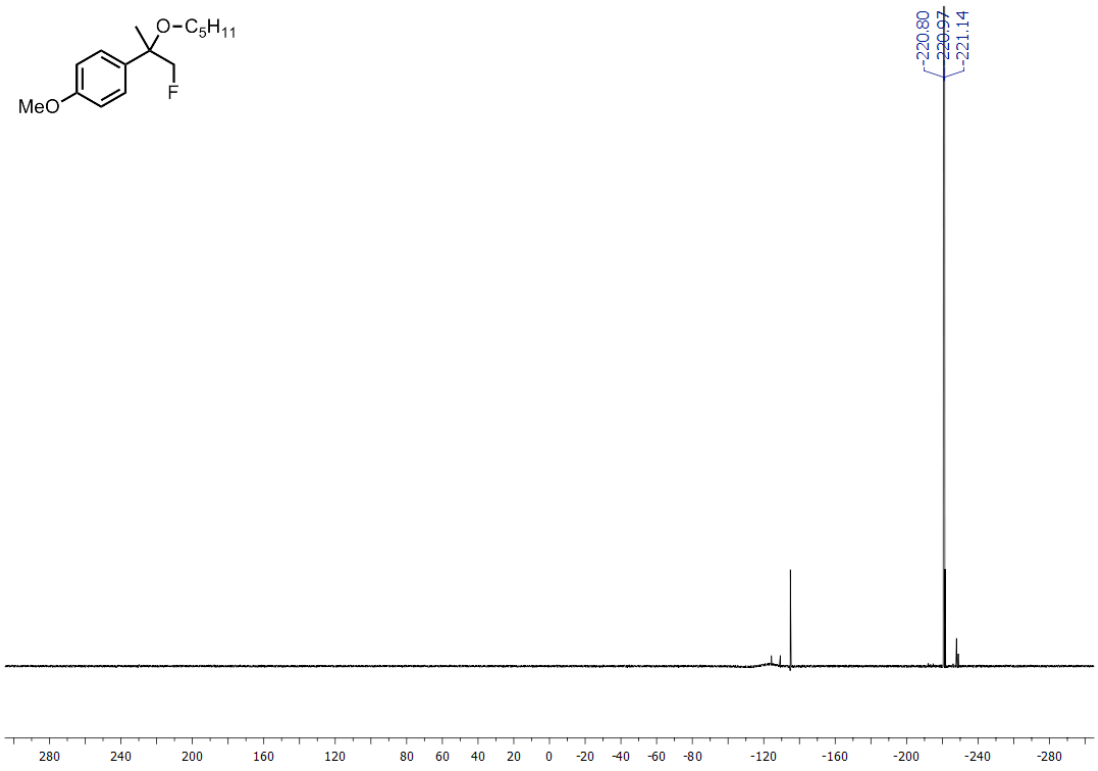
28.76
23.00
20.26
20.22
14.49


O–C5H11
MeO
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280
240
200
160
120
80
60
40
20
0
-20
-40
-60
-80
-120
-160
-200
-240
-280

4 Experimental procedures for the synthesis of Difluoromethylthioethers

4.1 General Methods

Reactions were performed in oven-dried glassware under a nitrogen atmosphere.
Caesium fluoride was dried at 200 °C, 5 mbar for 12 h prior to use. N-Methyl-2-pyrrolidone (NMP) was dried over oven-dried molecular sieves (4 Å) prior to use. Diglyme was distilled from calcium hydride before use. If not stated below, chemicals were commercially available and used without further purification.
^{1}H and ^{13}C NMR spectra were obtained on Bruker 400 Ultrashield™ and Bruker 500 MHz spectrometers with chloroform-d as deuterated solvent. These were performed without ^{19}F decoupling, so fluorine coupling is observed. ^{19}F NMR spectra were obtained using an Oxford Instruments 300 MHz spectrometer. The obtained chemical shifts δ are reported in ppm and are referenced to the residual solvent signal. Spin-spin coupling constants J are given in Hz.
High resolution mass spectral (HRMS) data were obtained on a Thermo Scientific LTQ Orbitrap XL by the EPSRC UK National Mass Spectrometry Facility at Swansea University or on a Waters MALDI-TOF mx.
Infrared spectra were recorded on a Shimadzu IR-Affinity-1S FTIR spectrometer
Melting points were measured using a Gallenkamp apparatus and are reported uncorrected.
The microwave used for the synthesis of thiols was a CEM Discover SP.

4.2 Synthesis of difluoromethyltrimethylsilane ($TMSCF_2H$)

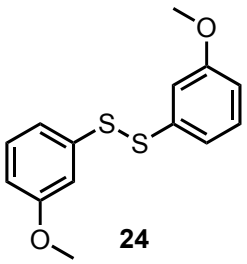
Following a known procedure[42] trimethylsilanetrifluoromethane (24.0 g, 169 mmol) was added slowly over 20 min to an icecold solution of sodium borohydride (2.22 g, 59 mmol, 0.43 eq) in dry diglyme (50 mL). After 2 h the ice bath was removed and the reaction stirred for another 18 h. The reaction mixture was distilled twice at

atmospheric pressure (set temperature 170 °C and 90 °C) to yield 13.1 g (62%, 105.4 mmol) of $TMSCF_2H$.

^1H NMR (400 MHz, $CDCl_3$) δ 5.84 (t, J = 46.2 Hz, 1H), 0.17 (s, 9H).
^{13}C NMR (300 MHz, $CDCl_3$) δ 124.06 (t, J = 253.7 Hz), -5.35 (s).
^{19}F NMR (283 MHz, $CDCl_3$) δ -139.79 (d, J = 46.0 Hz).
IR: 1256, 1080, 991, 862 cm^{-1}

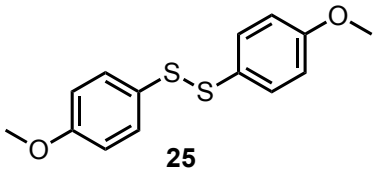
4.3 Synthesis of disulfides

Standard procedure for the synthesis of disulfides from the corresponding thiol:
Following a modified literature procedure[50], a suspension of 1,3-dibromo-5,5-dimethylhydantoin (1.073 g, 3.75 mmol) in chloroform (10 mL) was added dropwise to a solution of the thiol (15 mmol) in chloroform (5 mL). The suspension was stirred at room temperature for 1 h and then washed with a saturated $NaHCO_3$ solution (2 x 15 mL) and brine (15 mL). The organic layer was dried over anhydrous $MgSO_4$ and solvent removed under reduced pressure to yield the corresponding disulfide.



24

Bis(3-methoxyphenyl)disulfide[57] (2.040 g, 97%, 7.3 mmol), colourless oil
^1H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.22 (m, 2H), 7.19 – 7.10 (m, 4H), 6.89 – 6.75 (m, 2H), 3.82 (s, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 160.49, 138.71, 130.38, 119.97, 113.55, 112.95, 55.75
IR: 2932, 2924, 1568, 1468, 1221, 851, 766 cm^{-1}
HRMS (EI): [$C_{14}H_{14}O_2S_2$] calc. 278.0435, found 278.0434



25

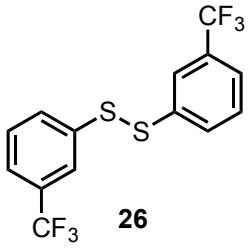
Bis(4-methoxyphenyl)disulfide[57] (1.815 g, 87%, 6.5 mmol) , brown oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.9 Hz, 4H), 6.88 (d, *J* = 8.9 Hz, 4H), 3.84 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.33, 133.13, 128.83, 115.04, 55.75

IR: 2932, 2832, 1587, 1485, 1171, 1028, 817, 520 cm^{-1}

HRMS (EI): [$C_{14}H_{14}O_2S_2$] calc. 278.0435, found 278.0438



26

Bis(3-(trifluoromethyl)phenyl)disulfide[58] (2.382 g, 89%, 6.7 mmol), yellow oil

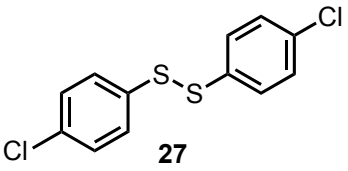
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 2H), 7.67 (d, *J* = 7.8 Hz, 2H), 7.51 (d, *J* = 7.8 Hz, 2H), 7.45 (t, *J* = 7.8 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.14, 132.12 (q, *J* = 32.7 Hz), 131.05, 130.15, , 124.72 (dd, *J* = 6.5, 3.7 Hz), 124.6 - 124.8 (m).

^{19}F NMR (283 MHz, $CDCl_3$) δ -63.14 (s).

IR: 1317, 1119, 1098, 791, 692 cm^{-1}

HRMS (EI): [$C_{14}H_8S_2F_6$] calc353.9972, found 353.9973



27

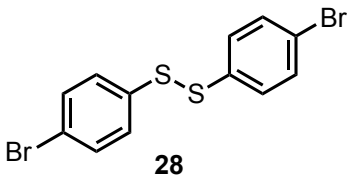
Bis(4-chlorophenyl)disulfide[57] (1.944 g, 91%, 6.8 mmol), white solid (mp: 74-75 ºC, chloroform)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.6 Hz, 4H), 7.33 (d, *J* = 8.6 Hz, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.54, 134.05, 129.75, 129.72

IR: 1468, 1377, 810, 486 cm^{-1}

HRMS (EI): [$C_{12}H_8S_2Cl_2$] calc 285.9444, found 285.9446



28

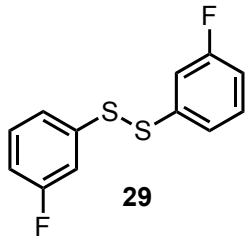
Bis(4-bromophenyl)disulfide[57] (2.601 g, 92%, 6.9 mmol), white solid (mp: 91-93 ºC, chloroform)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.6 Hz, 4H), 7.38 (d, *J* = 8.6 Hz, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.14, 132.66, 129.79, 121.96.

IR: 1464, 1377, 1067, 810, 494 cm^{-1}

HRMS (EI): [$C_{12}H_8S_2Br_2$] calc. 373.8434, found 373.8436



29

Bis(3-fluorophenyl)disulfide (1.680 g, 88%, 6.6 mmol), colourless oil

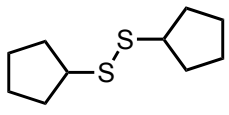
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.10 (m, 6H), 6.88 – 6.80 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.49 (d, *J* = 249.5 Hz), 139.18 (d, *J* = 7.1 Hz), 130.95 (d, *J* = 8.4 Hz), 123.04 (d, *J* = 3.0 Hz), 114.80 (d, *J* = 21.4 Hz), 114.39 (d, *J* = 24.2 Hz).

^{19}F NMR (283 MHz, $CDCl_3$) δ -111.40 (s).

IR: 1578, 1470, 1213, 872, 772, 673, 494 cm^{-1}

HRMS (EI): [$C_{12}H_8F_2S_2$] calc. 254.0036, found 254.0036



30

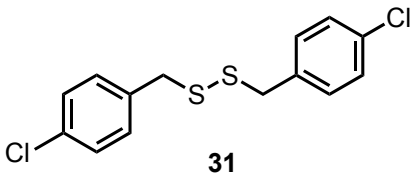
Dicyclopentyldisulfide (1.411 g, 89%, 6.7 mmol), colourless oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.28 (dq, *J* = 7.1, 5.5 Hz, 2H), 2.10 – 1.86 (m, 4H), 1.84 – 1.49 (m, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 50.80, 33.53, 25.13

IR: 2955, 2862, 1443, 1235, 481 cm^{-1}

HRMS (EI): [$C_{10}H_{10}S_2$] calc. 202.0850, found 202.0850



31

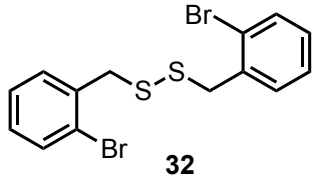
Bis(4-chlorobenzyl)disulfide[59] (2.199 g, 93%, 7.0 mmol), white solid (mp: 62-63 ºC, chloroform)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.4 Hz, 4H), 7.16 (d, *J* = 8.4 Hz, 4H), 3.57 (s, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.24, 133.82, 131.11, 129.12, 42.87

IR: 1489, 1088, 1015, 837, 505, 494 cm^{-1}

HRMS (EI): [$C_{14}H_{12}S_2Cl_2$] calc. 313.9757, found 313.9760



32

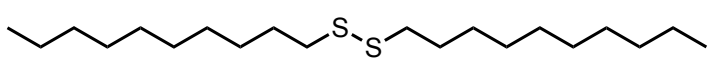
Bis(2-bromobenzyl)disulfide[60] (1.164 g, 82%, 2.88 mmol), white solid (mp: 86-87 ºC, chloroform)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.9 Hz, 2H), 7.21 – 7.16 (m, 4H), 7.11 – 7.02 (m, 2H), 3.71 (s, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.08, 133.51, 132.11, 129.60, 127.82, 125.01, 44.14

IR: 1435, 1026, 756 648, 571, 440 cm^{-1}

HRMS (EI): [$C_{14}H_{12}S_2Br_2$] calc. 401.8747, found 401.8752



33

Didecyldisulfide[60](1.238 g, 90%, 3.6 mmol), colourless oil

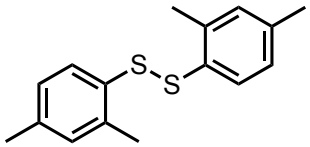
1,3-dibromo-5,5-dimethylhydantoin (0.574 g, 2 mmol) was added slowly to a solution of 1-decanethiol (1.394 g, 8 mmol) in chloroform (8 mL). The suspension was stirred at room temperature for 2 h, filtered and the solvent removed under reduced pressure to yield didecyldisulfide.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.80 – 2.65 (m, 4H), 1.71 (dt, *J* = 14.9, 7.2 Hz, 4H), 1.48 – 1.20 (m, 28H), 0.92 (t, *J* = 6.9 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 39.61, 32.35, 30.01, 29.97, 29.77, 29.70, 29.66, 28.98, 23.13, 14.57.

IR: 2922, 2847, 1454, 762 cm^{-1}

HRMS (EI): [$C_{20}H_{42}S_2$] calc. 346.2728, found 346.2727



34

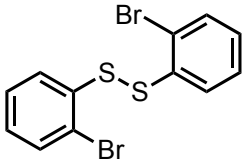
Bis(2,4-dimethylphenyl)disulfide (1.932 g, 93%, 7.0 mmol), yellow oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.9 Hz, 2H), 7.07 (s, 2H), 7.01 (d, *J* = 7.5 Hz, 2H), 2.45 (s, 6H), 2.37 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.69, 138.27, 132.75, 131.69, 130.85, 127.83, 21.48, 20.63

IR: 1472, 1045, 806, 546 cm^{-1}

HRMS (EI): [$C_{16}H_{18}S_2$] calc. 274.0850, found 274.0852



35

Bis(2-bromophenyl)disulfide(0.895 g, 80%, 2.4 mmol), white solid (mp: 95-96 ºC, chloroform)

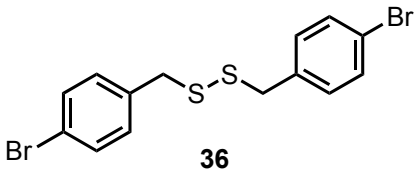
A suspension of 1,3-dibromo-5,5-dimethylhydantoin (0.429 g, 1.5 mmol) in chloroform (5 mL) was added dropwise to a solution of 2-bromothiophenol (1.126 g, 6 mmol) in chloroform (3 mL). The suspension was stirred at room temperature for 1 h and then washed with a saturated $NaHCO_3$ solution (2 x 15 mL) and brine (15 mL). The organic layer was dried over anhydrous $MgSO_4$ and solvent removed under reduced pressure to yield Bis(2-bromophenyl)disulfide.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (m, 4H), 7.23 – 7.15 (m, 2H), 7.00 (td, J = 7.8, 1.4 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.52, 133.35, 128.66, 128.37, 127.28, 121.43

IR: 1420, 1011, 733, 648 cm^{-1}

HRMS (EI): [$C_{12}H_8S_2Br_2$] calc. 373.8434, found 373.8437



36

Bis(4-bromobenzyl)disulfide (0.9703 g, 98%, 2.4 mmol) , colourless oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.41 (m, 4H), 7.13 – 7.05 (m, 4H), 3.55 (s, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.46, 131.79, 131.14, 121.63, 42.71.

IR: 1481, 1065, 1011, 826, 802, 494, 401 cm^{-1}.

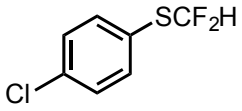
HRMS calcd for $C_{14}H_{11}Br_2S_2$ [M-H]$^+$: 400.8663, found: 400.8657.

4.4 Synthesis of difluoromethyl thioethers

Standard procedure for the synthesis of difluoromethyl thioethers from the corresponding disulfide:

An oven-dried flask was charged with caesium fluoride (0.608 g, 4 mmol) and the disulfide (0.5 mmol) and flushed with nitrogen. N-Methyl-2-pyrrolidone (1 mL) was added and the solution cooled to 0 ºC. Difluoromethyltrimethylsilane (0.248 g, 4 mmol) was added dropwise. The suspension was stirred at 0 °C for 1 h and then at rt for a further 19 h. Trifluorotoluene (0.041 mL, 0.33 mmol) was added as a standard

and conversion determined by ^{19}F-NMR spectroscopy using the integration of the doublet at δ= -94 ppm. The NMP was removed by a manual counter-current extraction with diethyl ether (4 x 10 mL) and water (4 x 10 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography.



38

(4-chlorophenyl)(difluoromethyl)sulfane (0.065 g, 0.33 mmol, 67%), colourless oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 6.81 (t, *J* = 56.6 Hz, 1H).

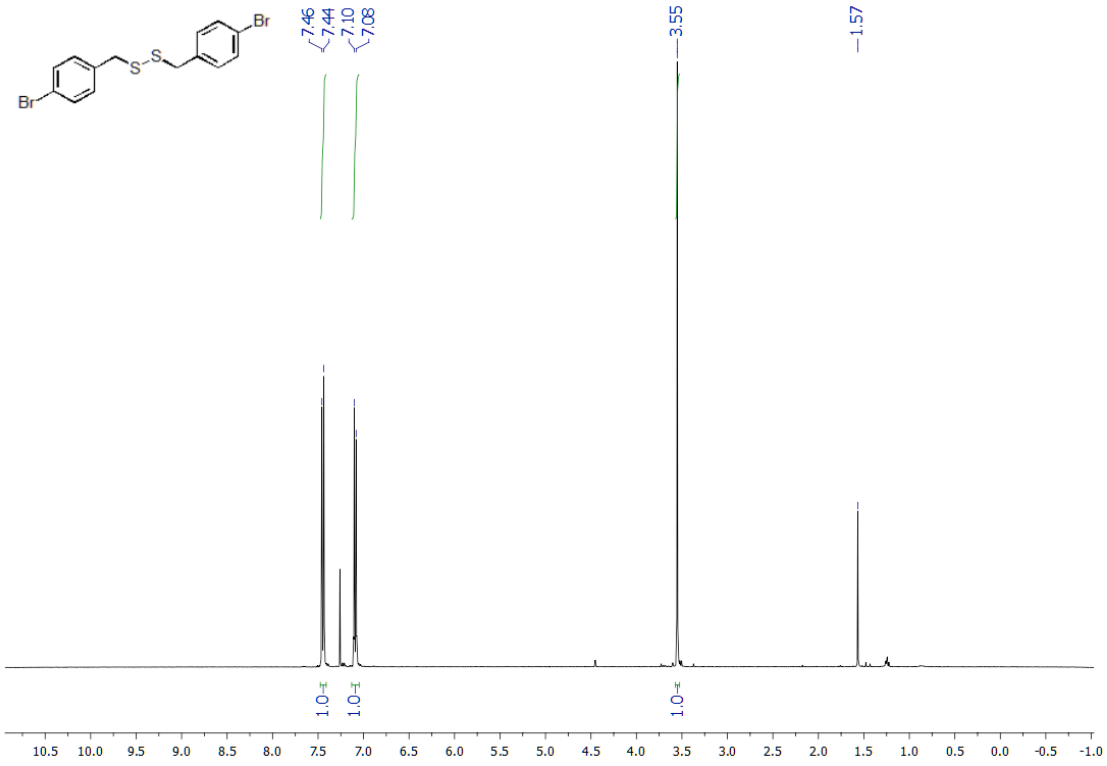
^{13}C NMR (126 MHz, $CDCl_3$) δ 136.70, 136.53, 129.60, 124.29, 120.36 (t, *J* = 275.8 Hz).

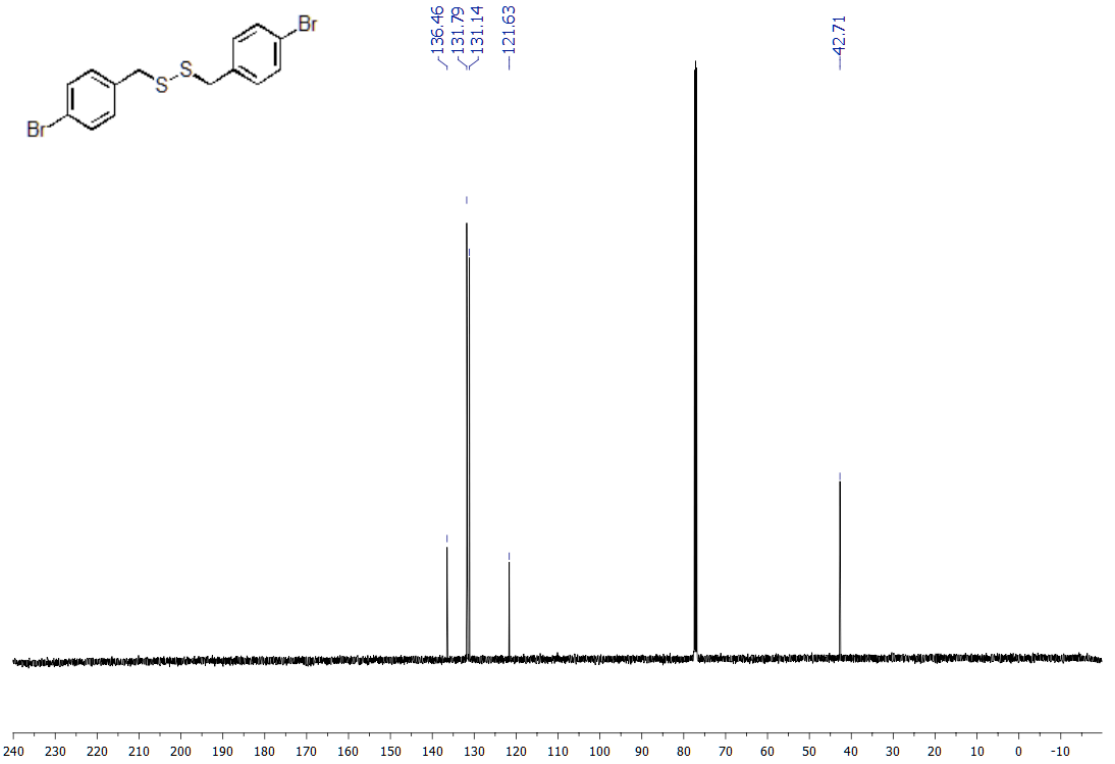
IR: 2361, 1574, 1477, 1319, 1296, 1065, 1038, 907, 826, 733, 501 cm^{-1}.

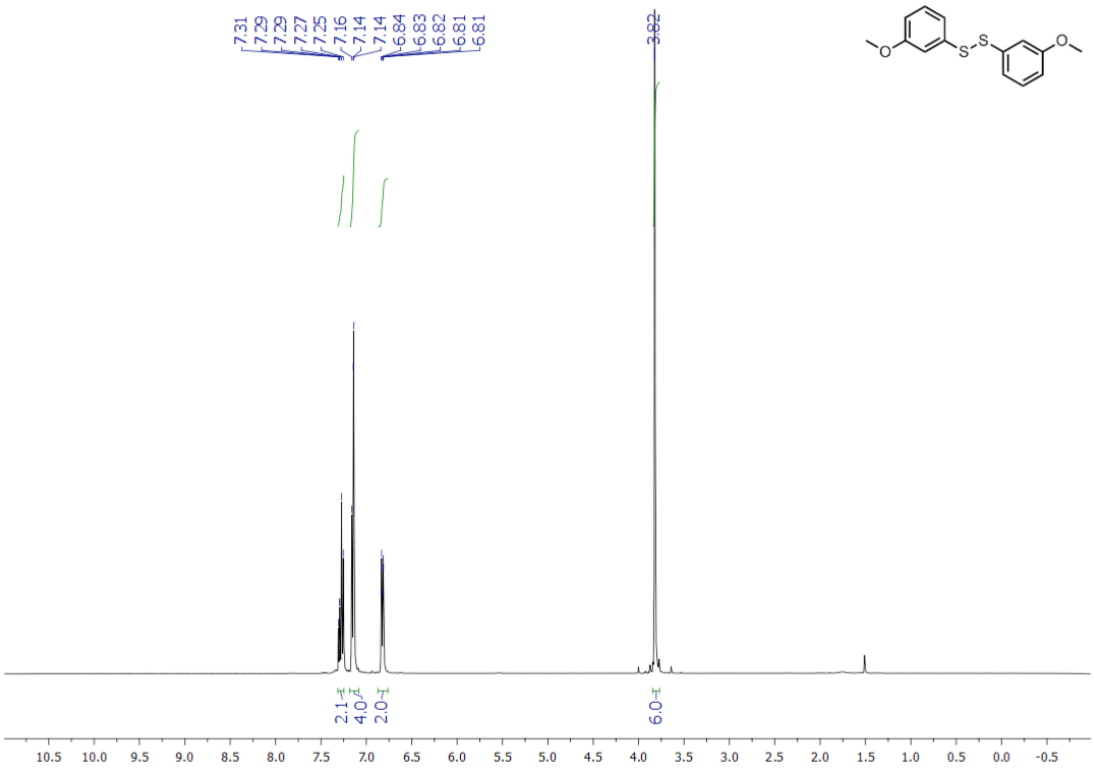
HRMS (ASAP+): $[C_7H_5F_2SCl]^+$ calcd. 193.9769, found: 193.9771.

4.5 Spectroscopic Data

4.5.1 Disulfides



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7.14
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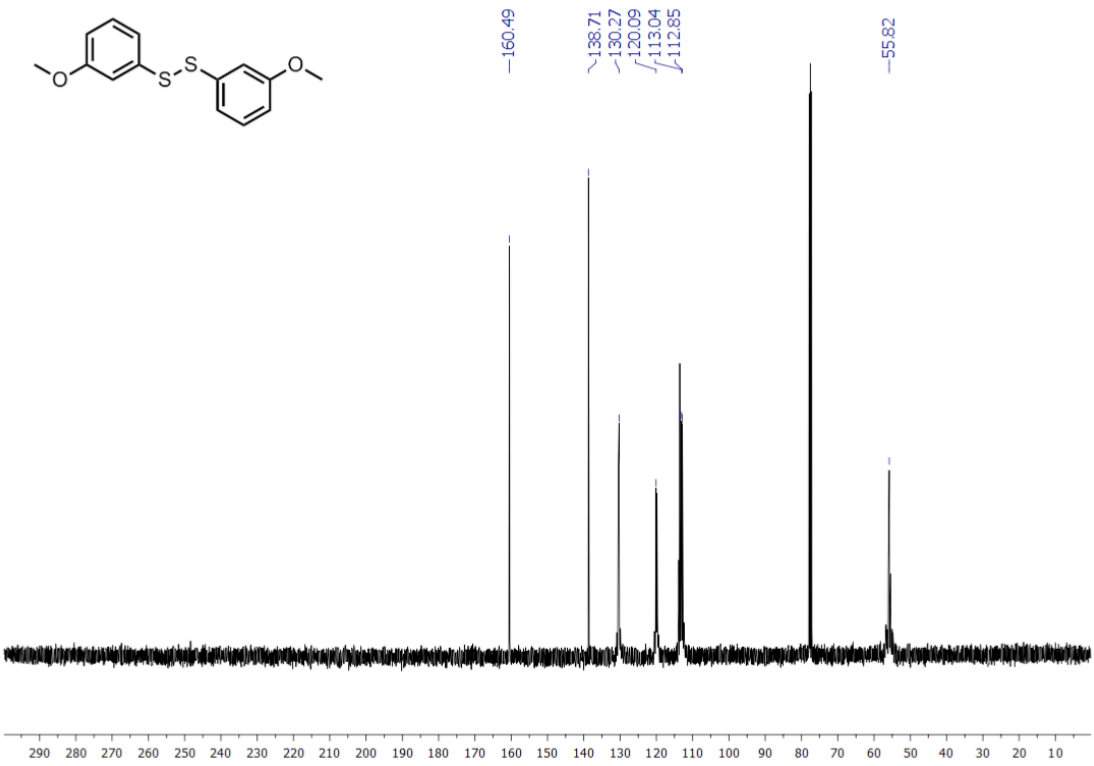
6.83
6.82
6.81
6.81
3.82
2.1
4.0
2.0
6.0
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5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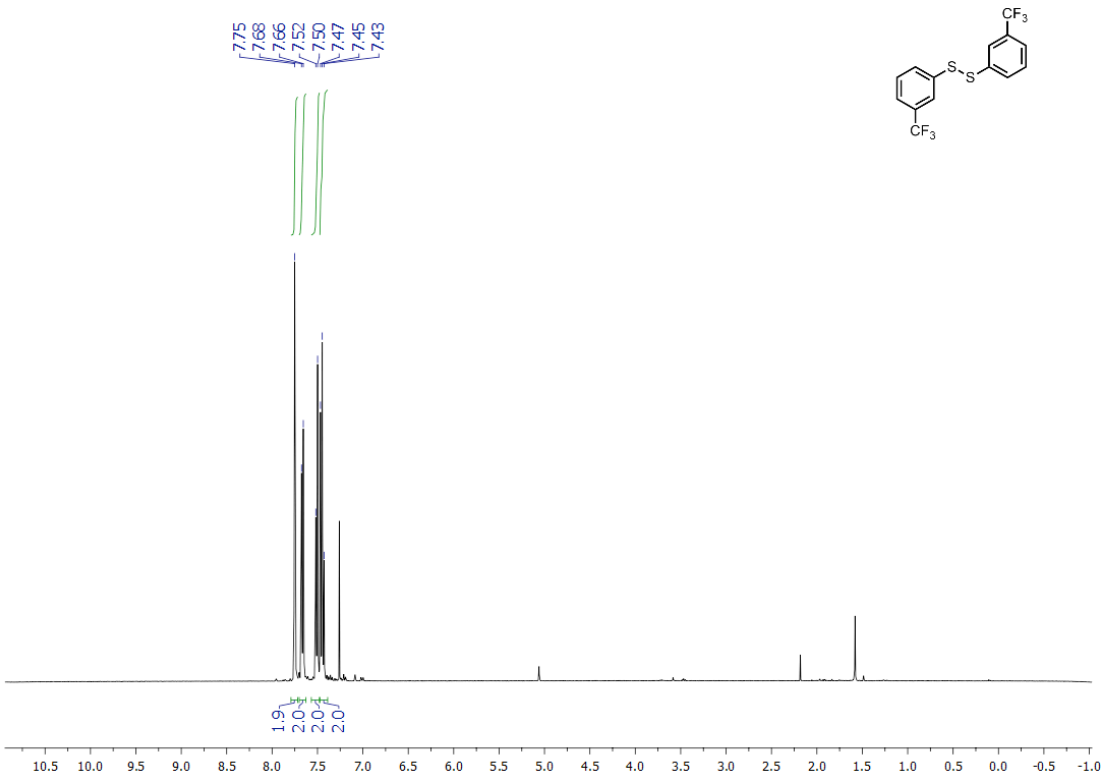
138.71
130.27
120.09
113.04
112.85
55.82
290 280 270 260 250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10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7.47
7.45
7.43
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S
CF3
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2.0
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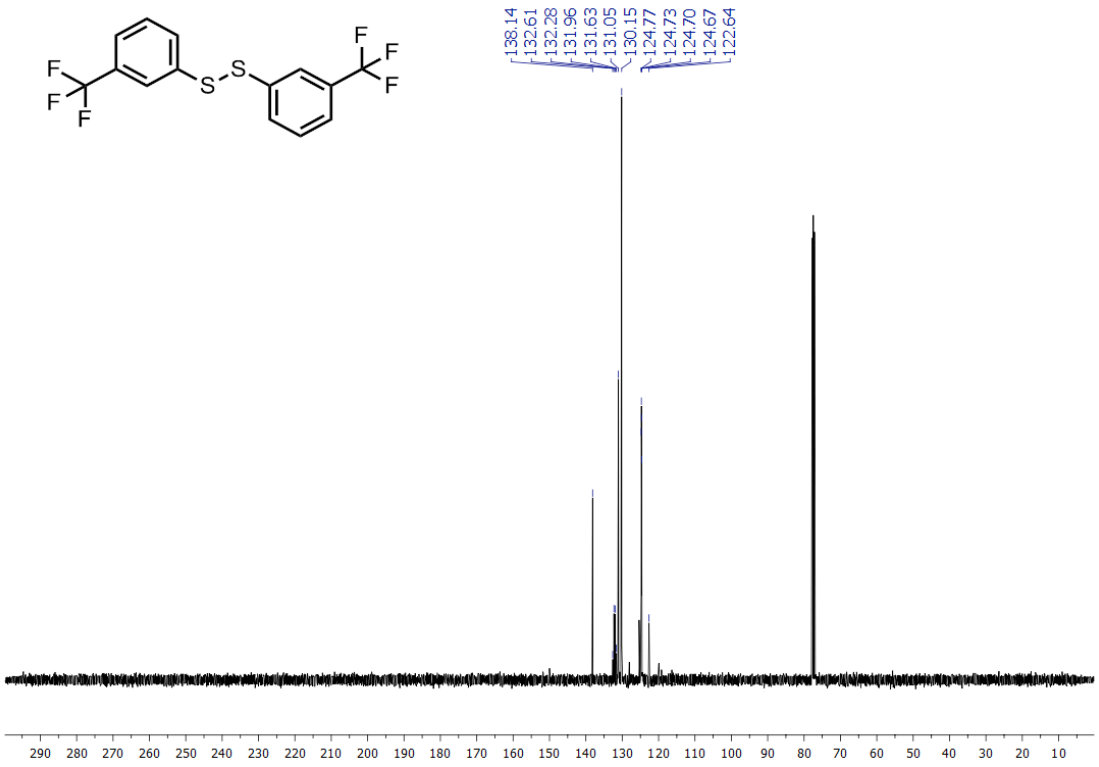
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S
F
F
F
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131.05
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124.70
124.67
122.64
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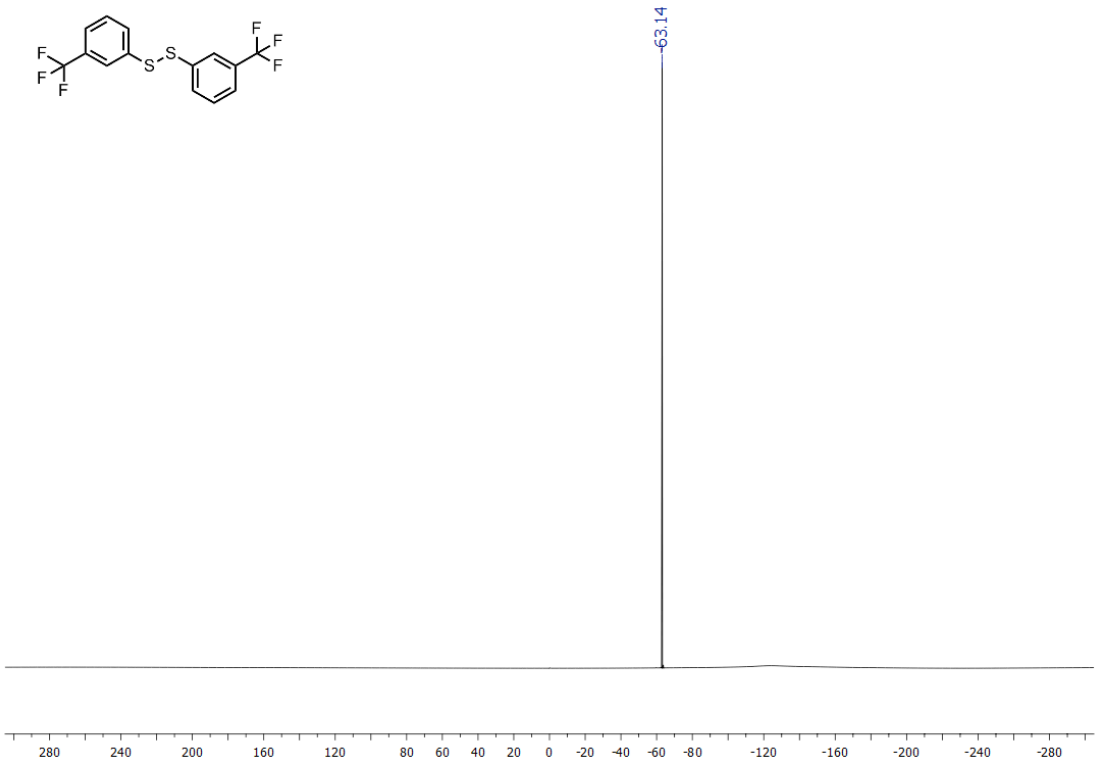
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F
F
S
S
F
F
F
-63.14
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240
200
160
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40
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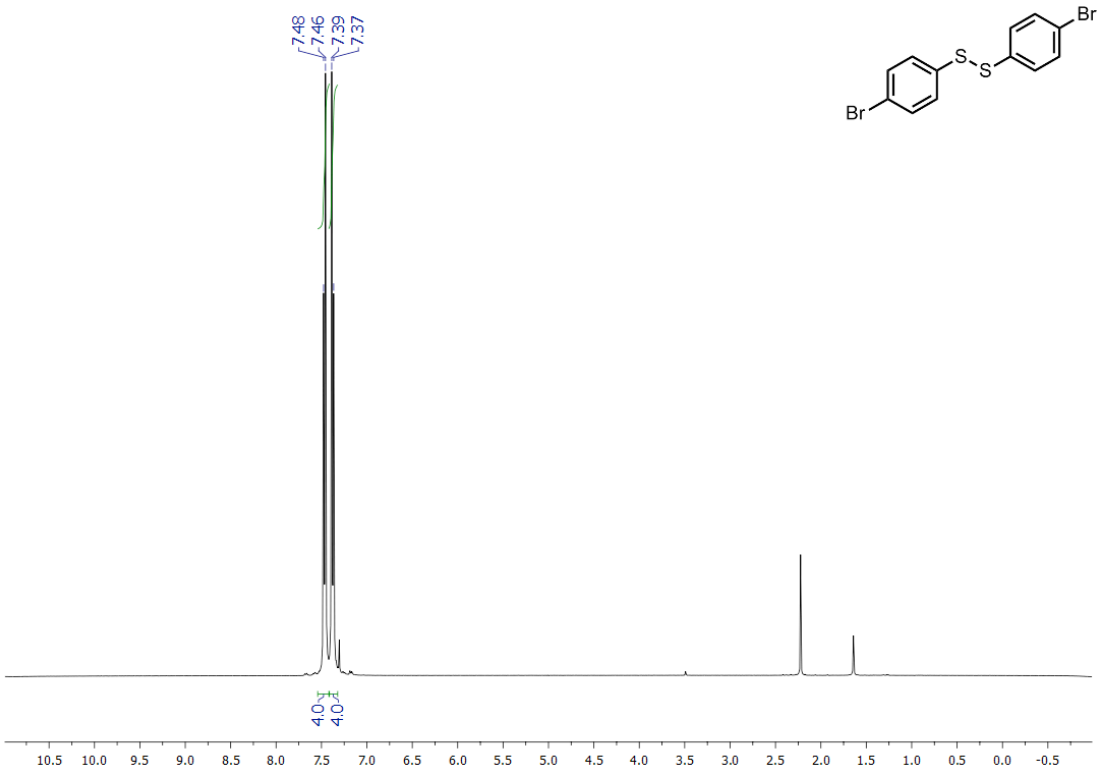
0
-20
-40
-60
-80
-120
-160
-200
-240
-280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S
S
Br
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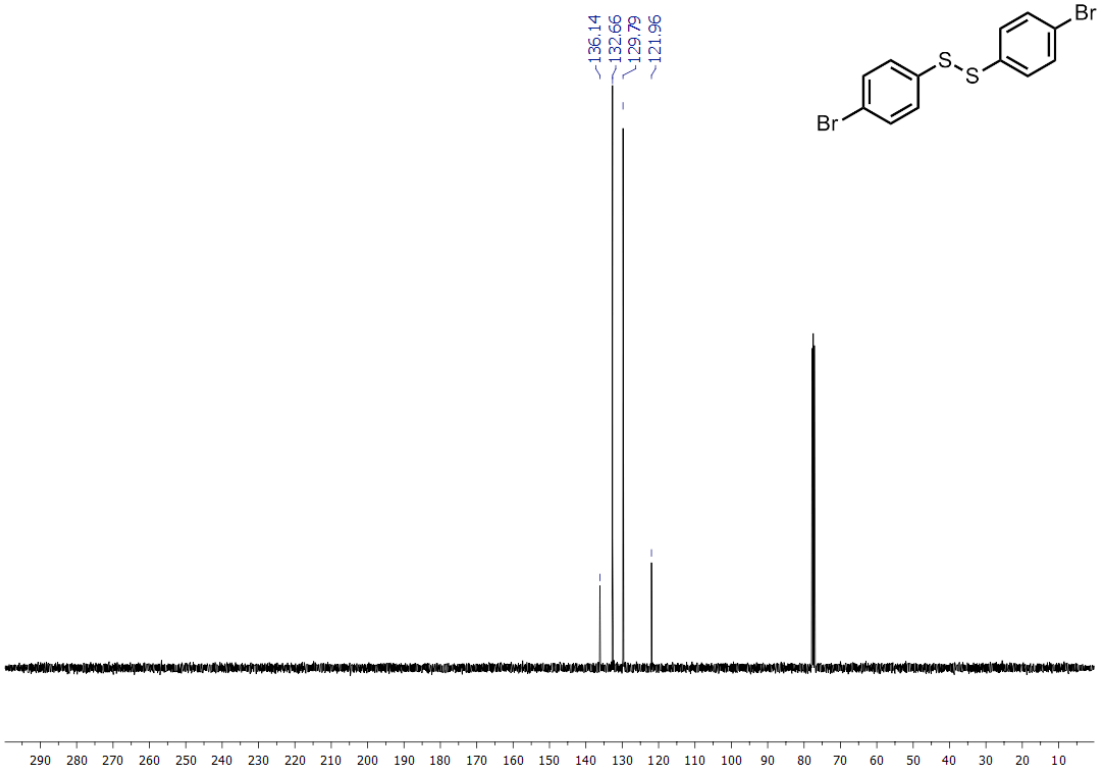
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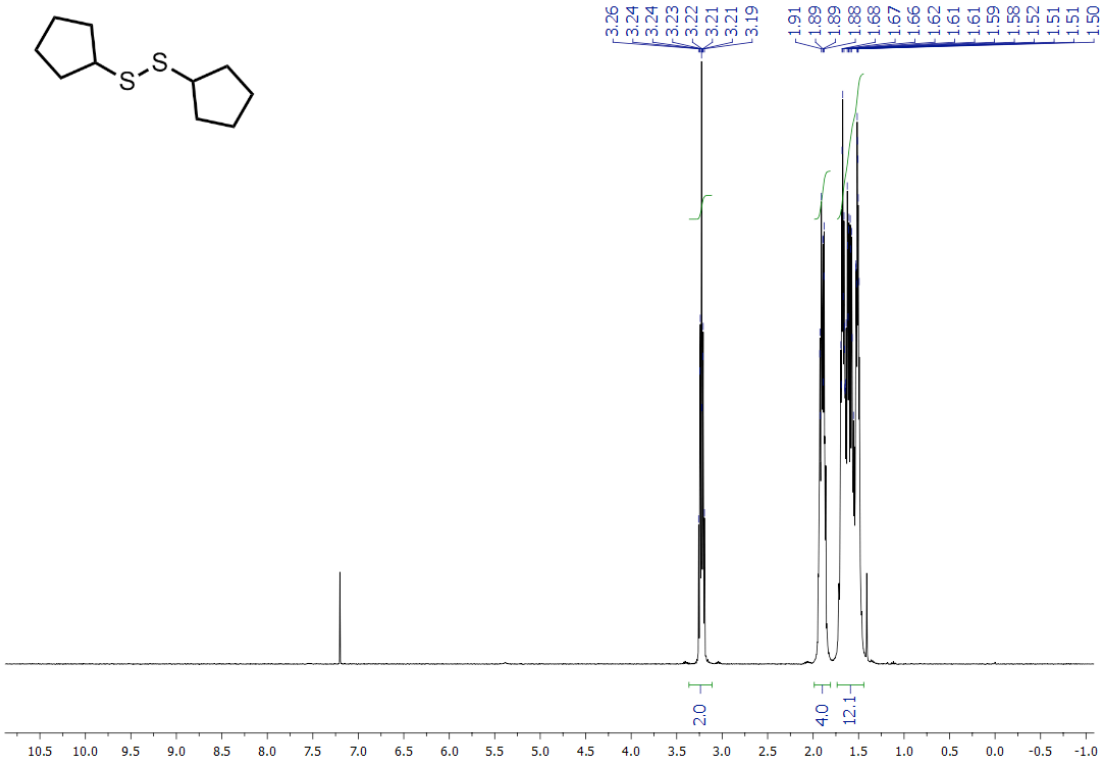
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1.62
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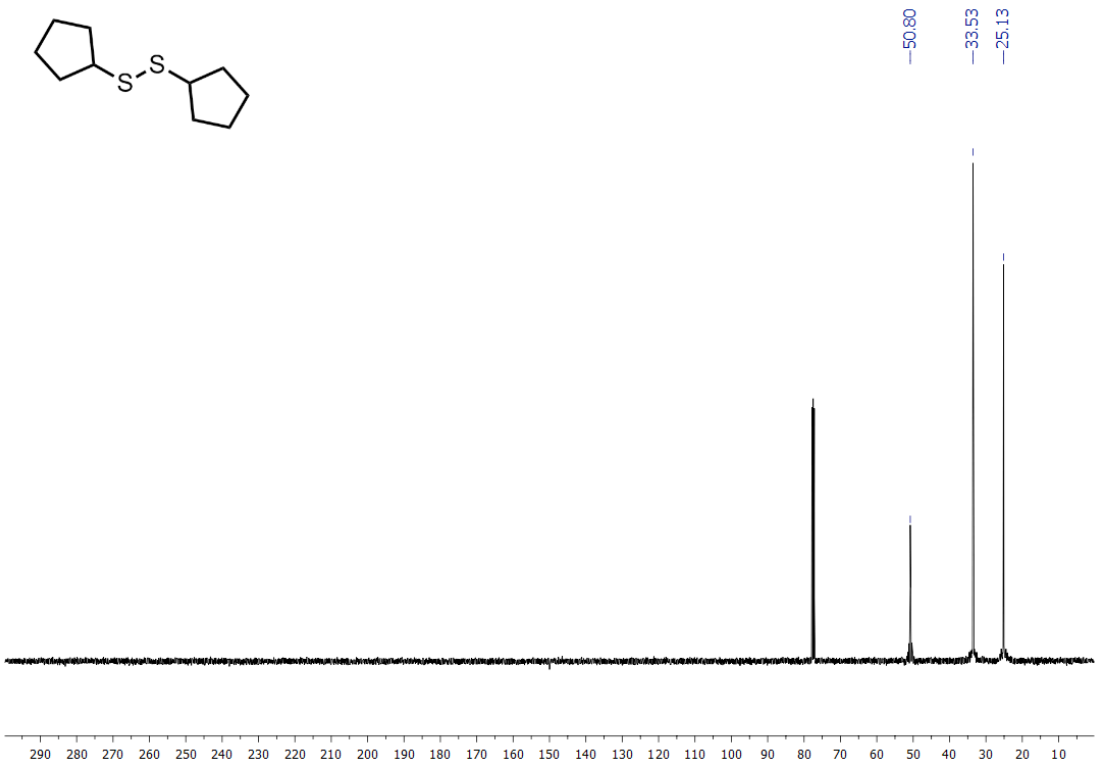
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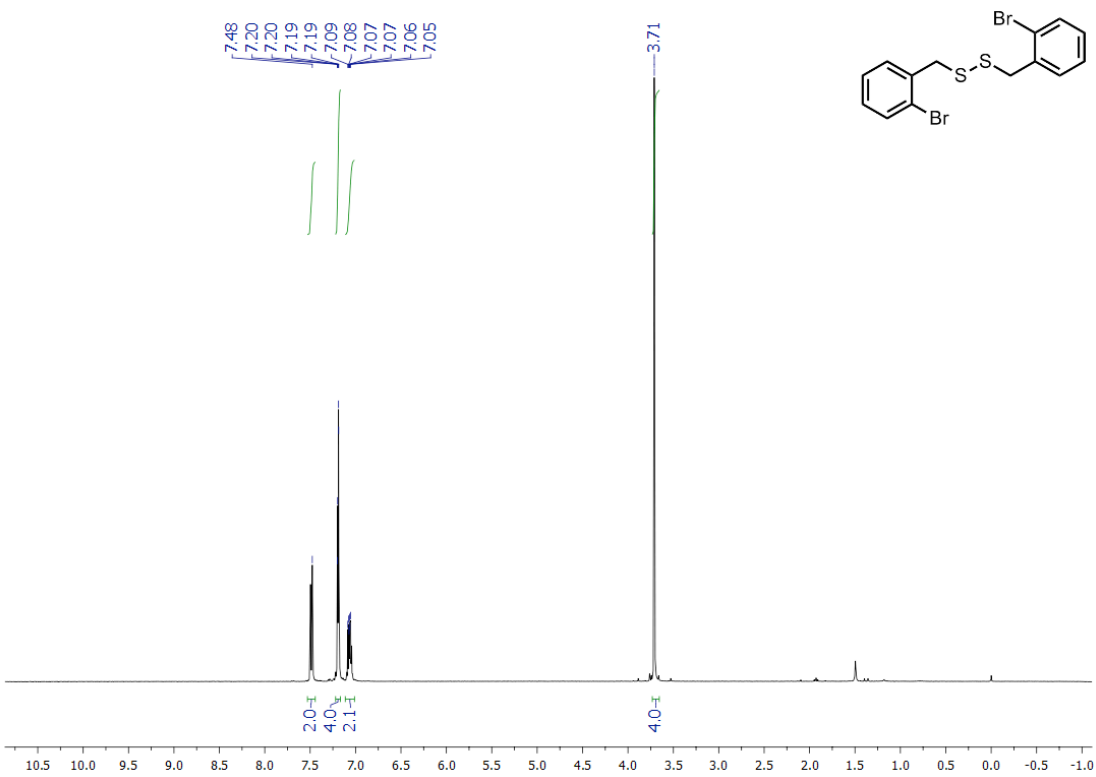
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7.05
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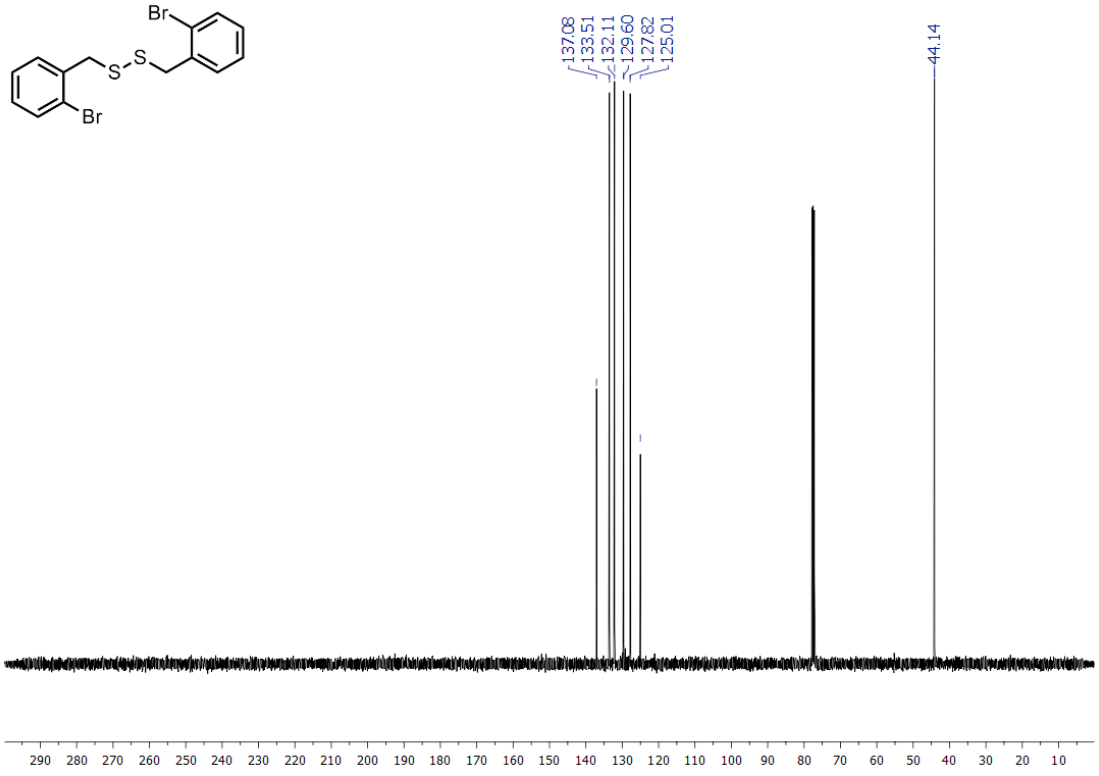
S
S
Br
2.0
4.0
2.1
4.0
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0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Br
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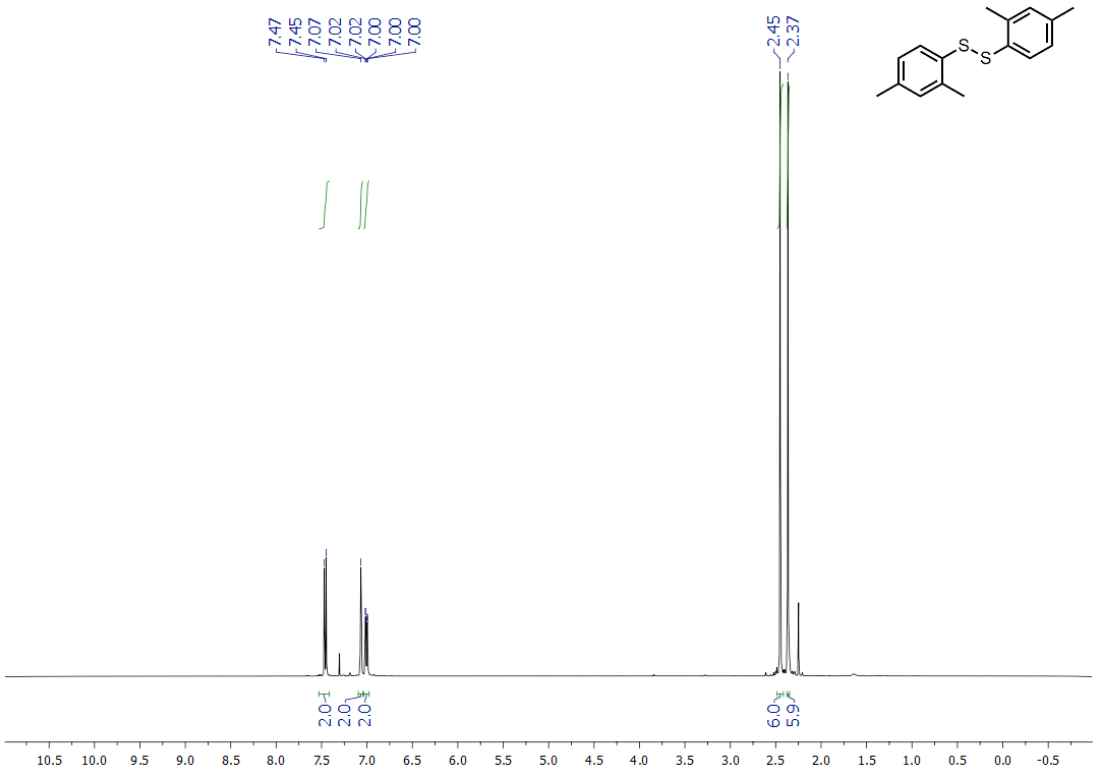
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7.00
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2.0
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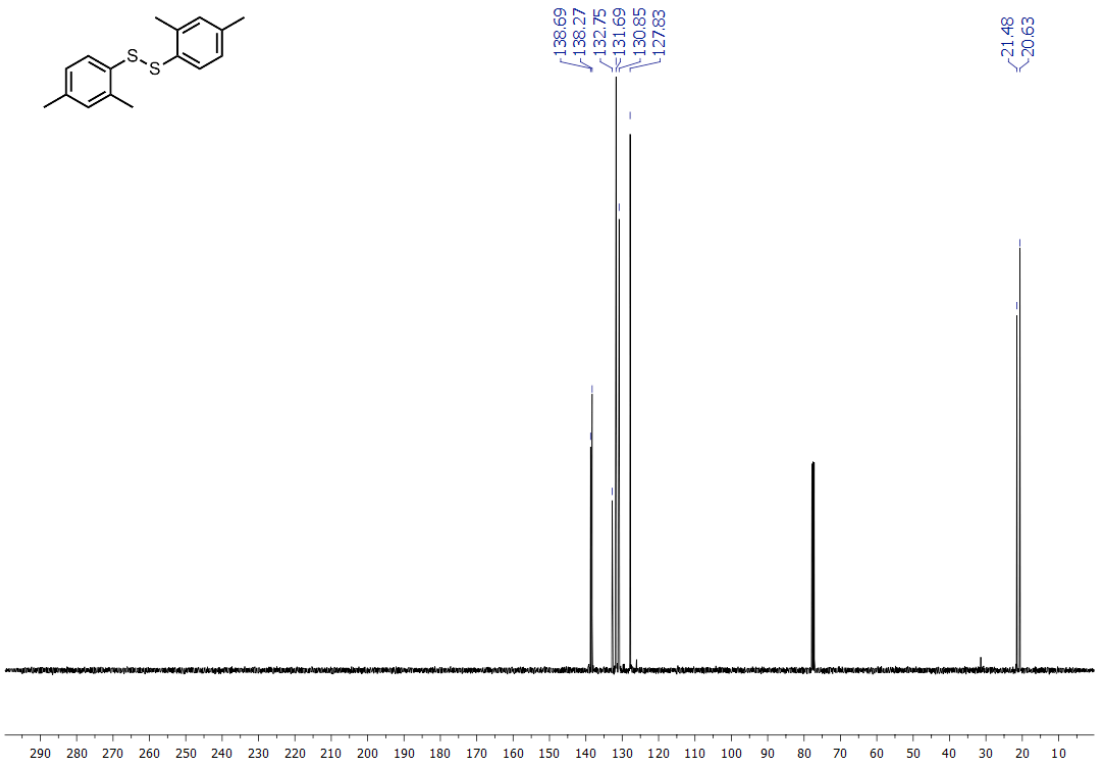
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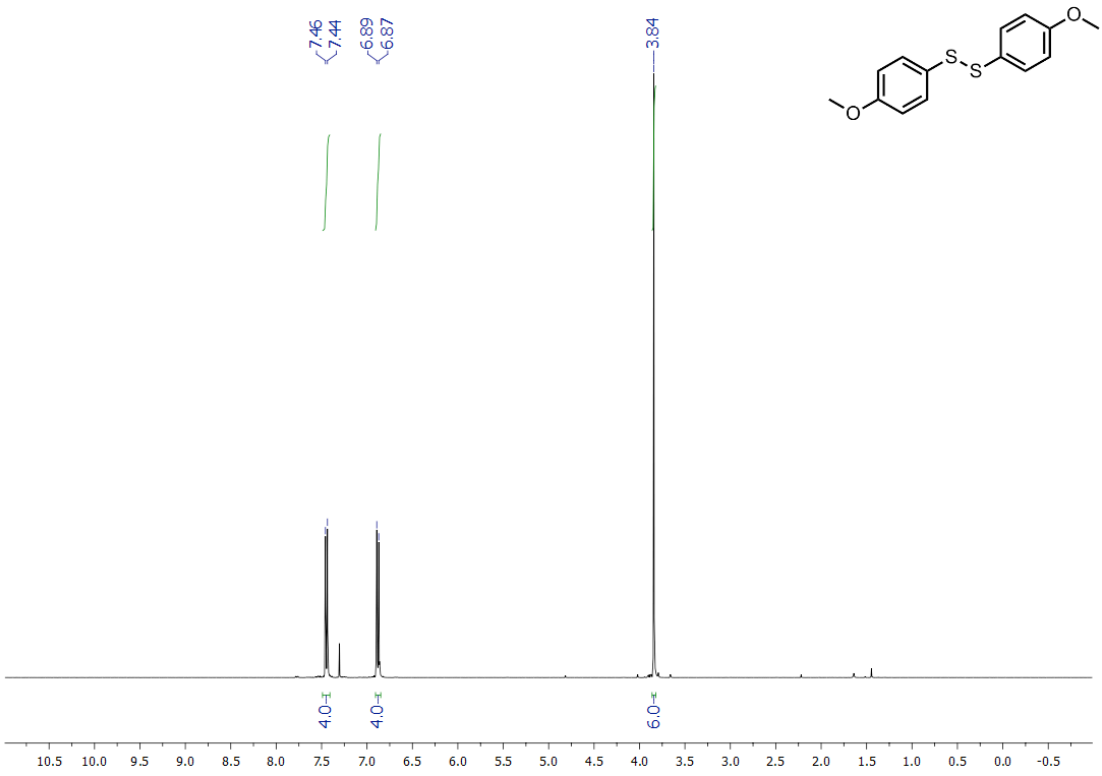
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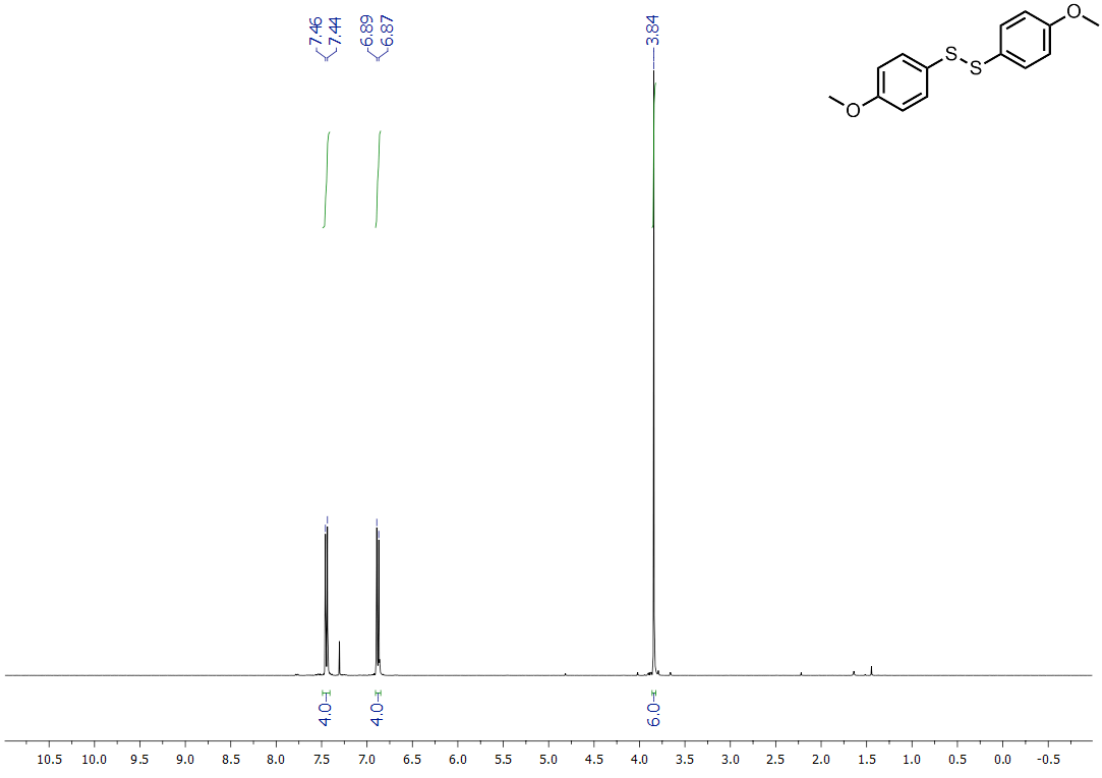
O
O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6.87
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4.0
6.0
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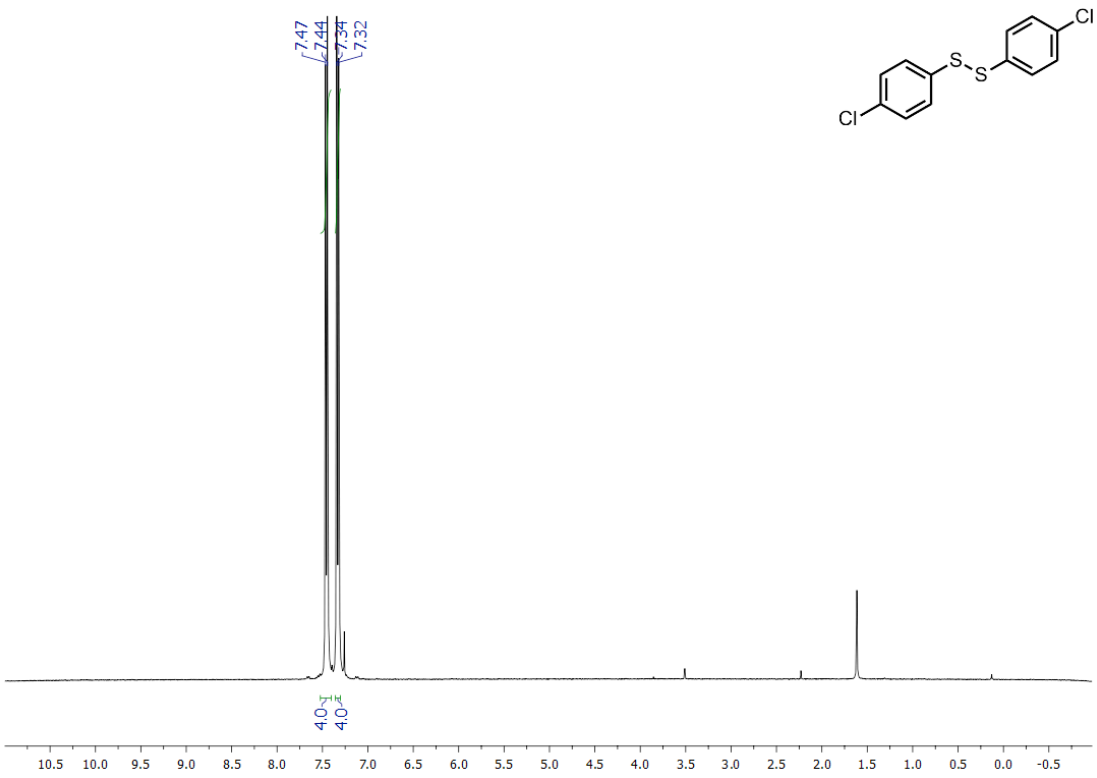
O
O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4.00
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S
Cl
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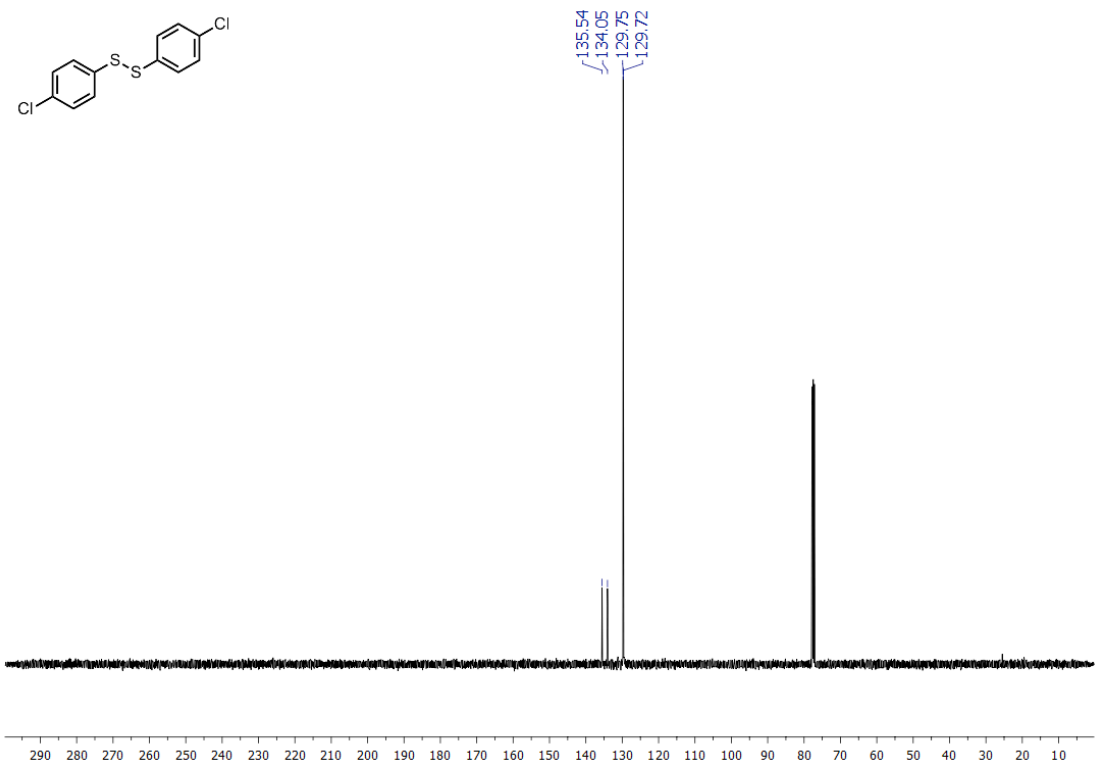
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S
Cl
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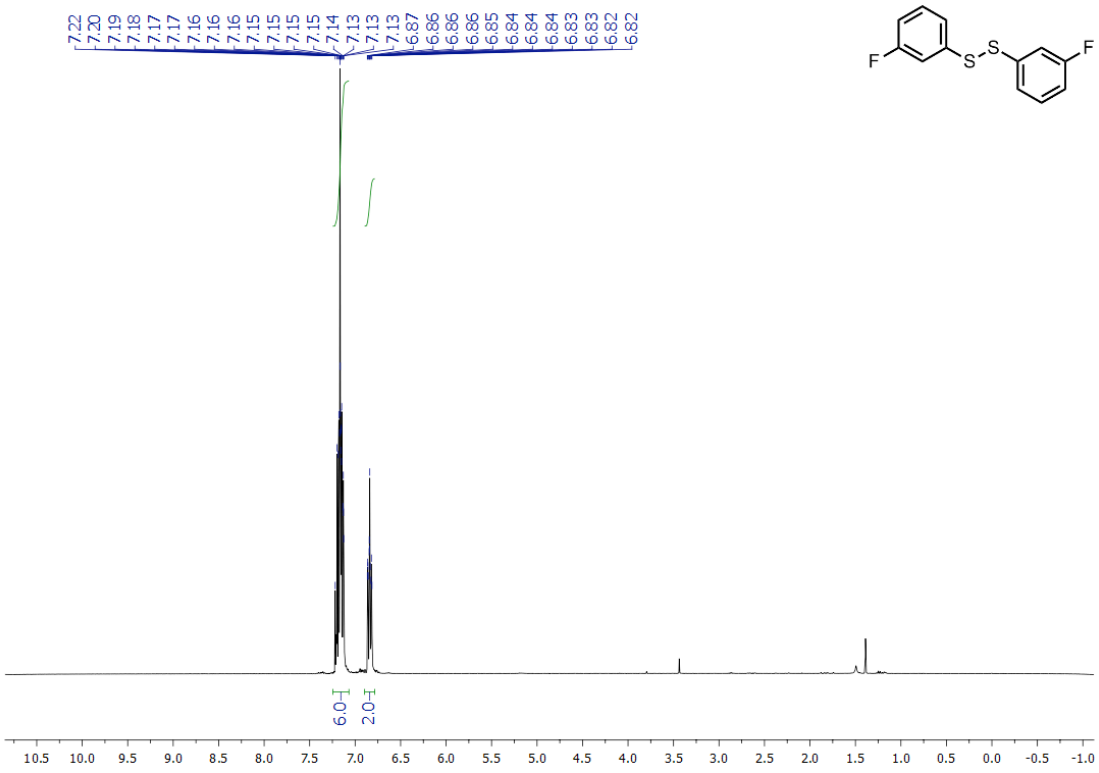
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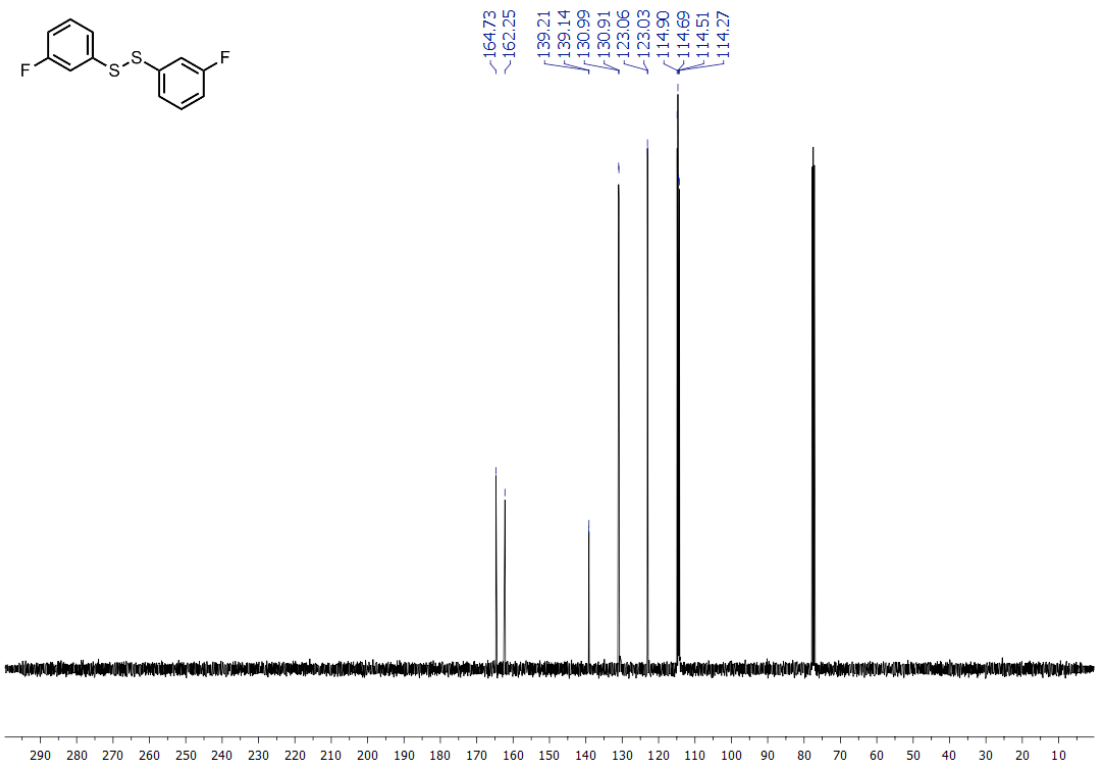
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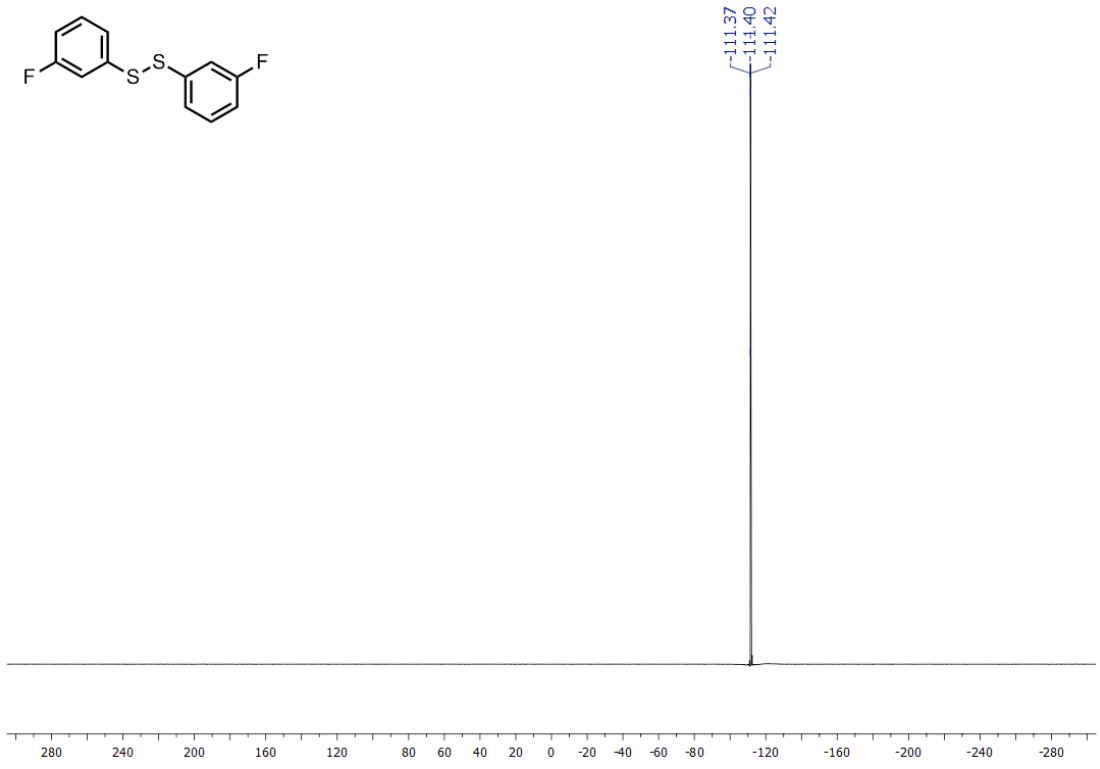
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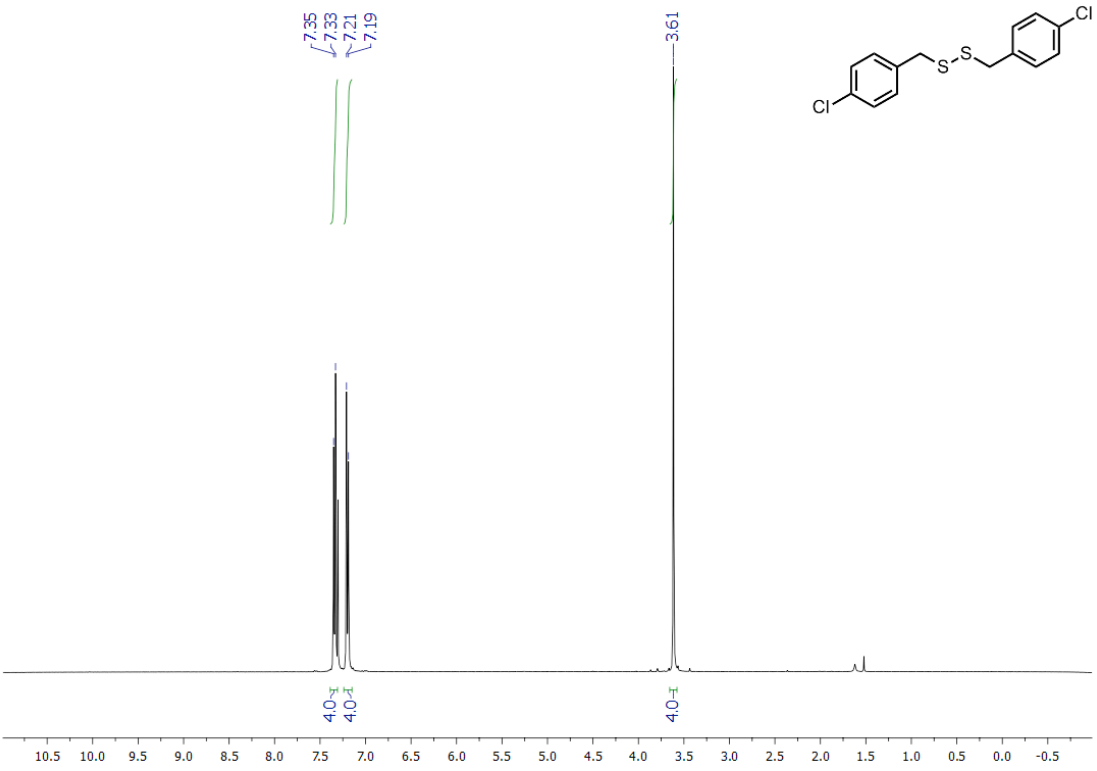
-280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S
Cl
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4.0
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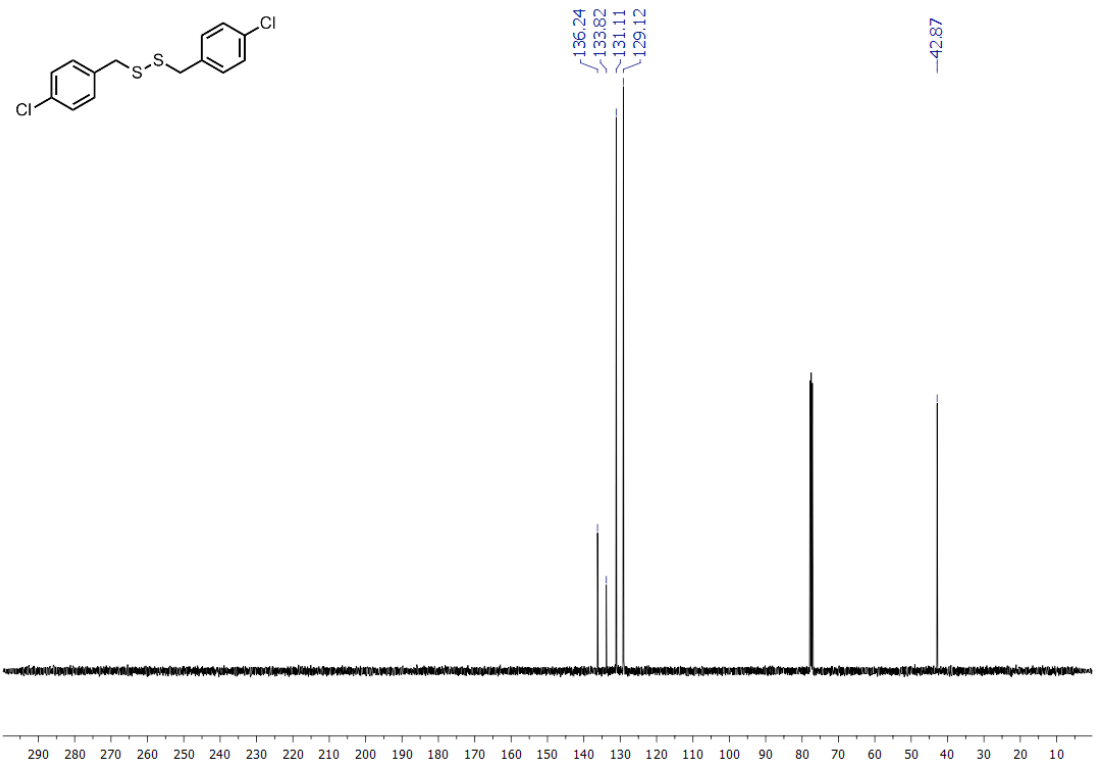
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S
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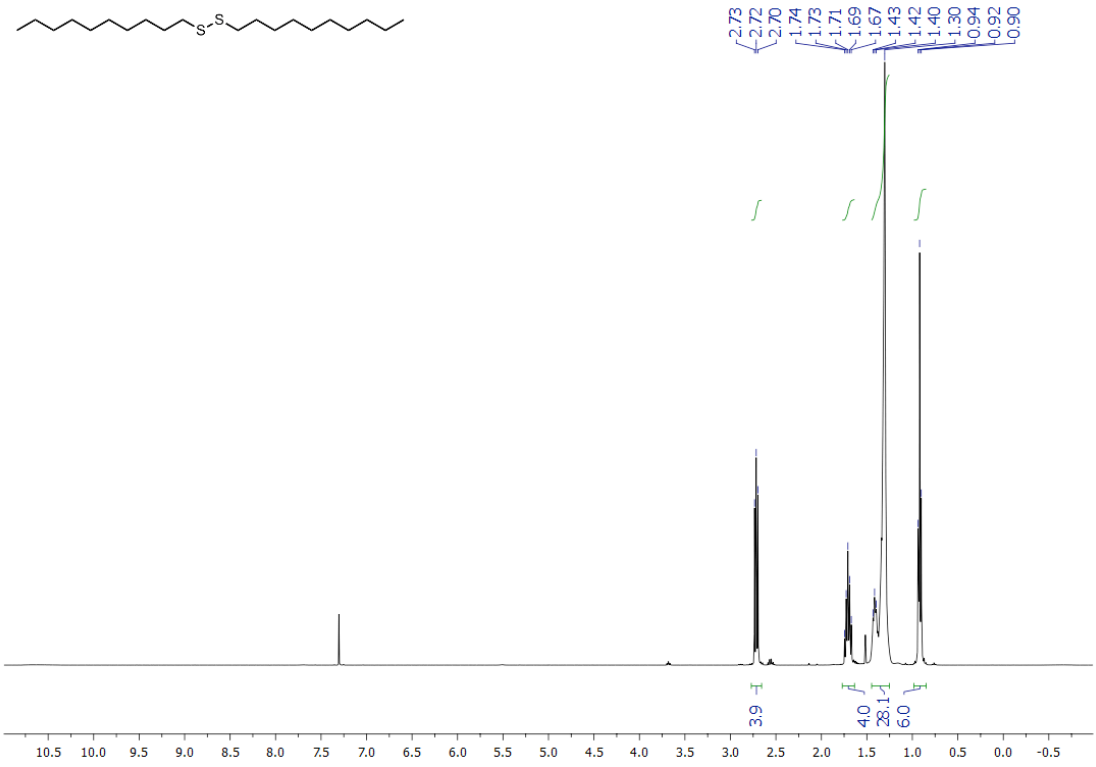
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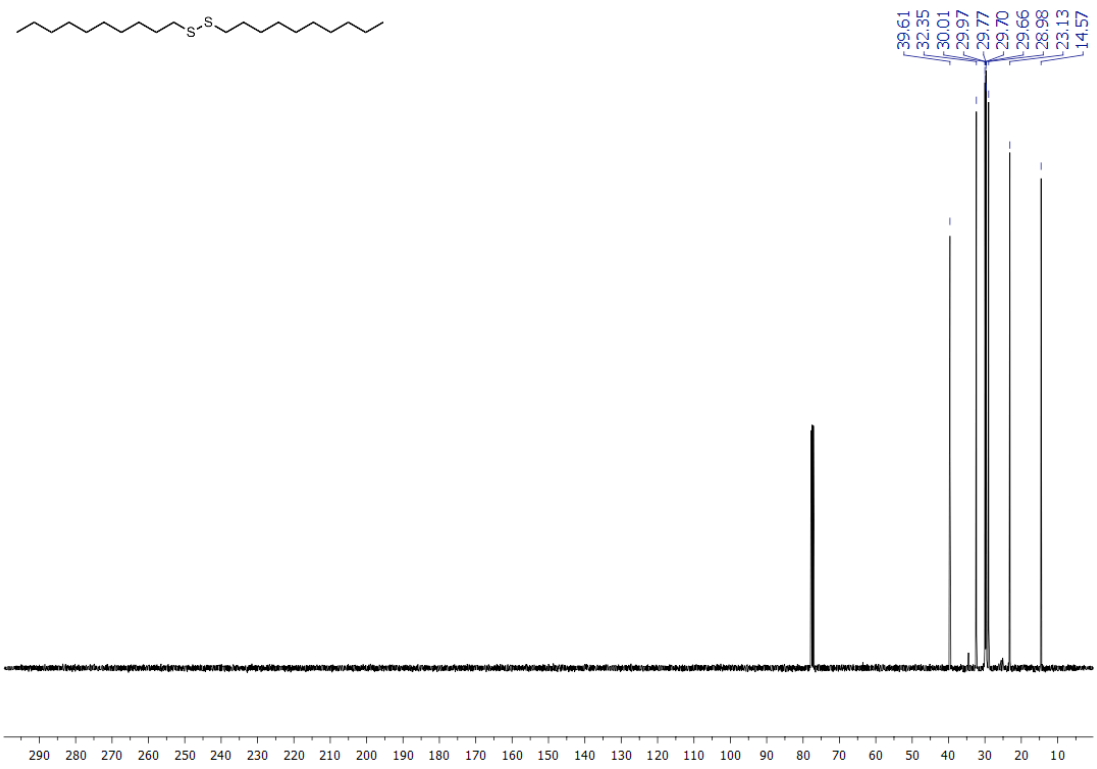
0.92
0.90
3.9
4.0
28.1
6.0
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5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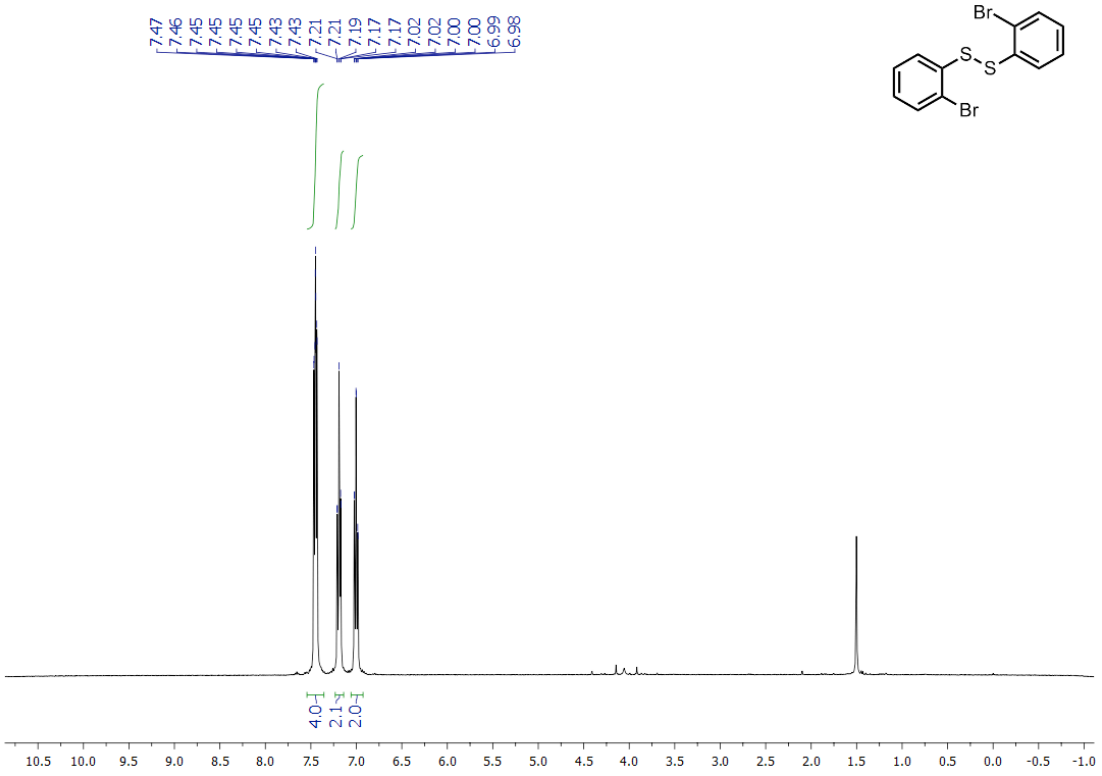
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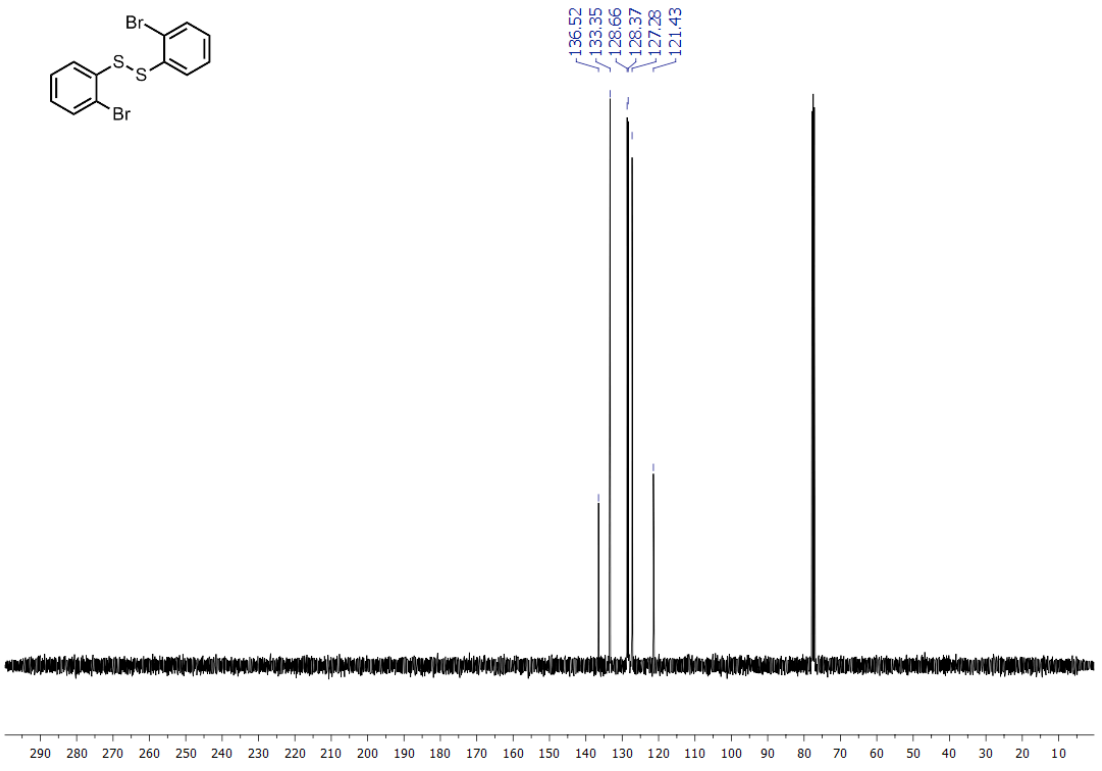
7.02
7.02
7.00
7.00
6.99
6.98
Br
S
S
Br
4.0
2.1
2.0
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0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Br
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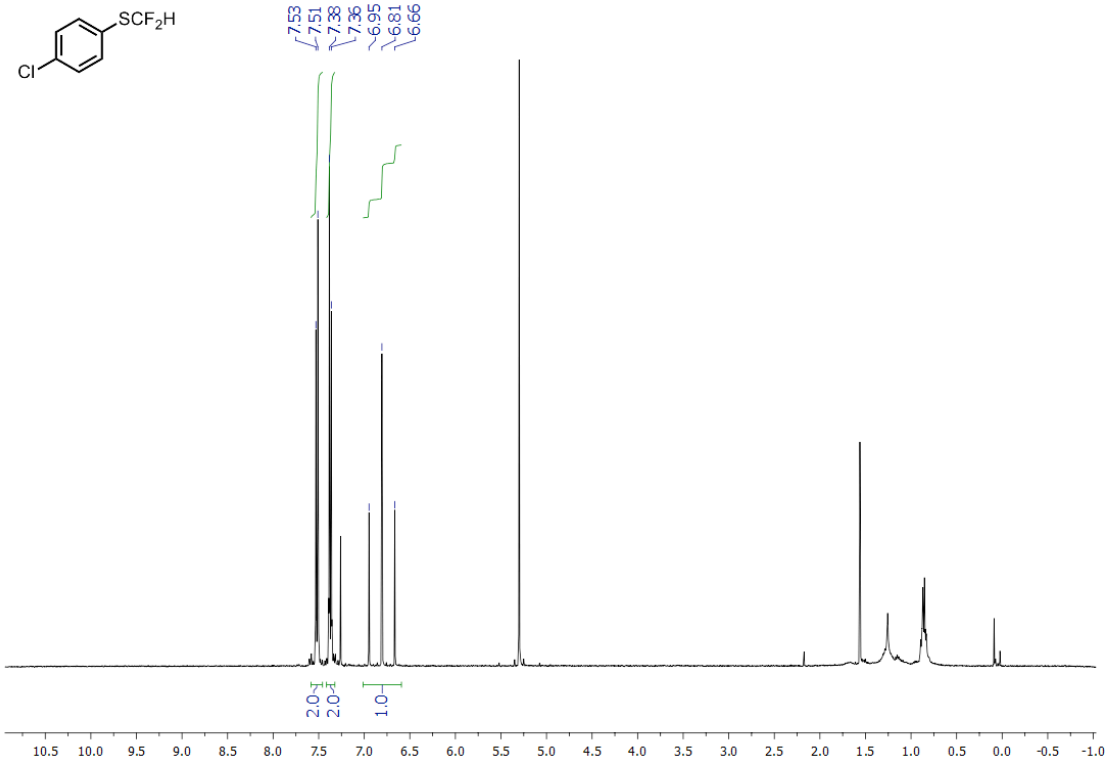
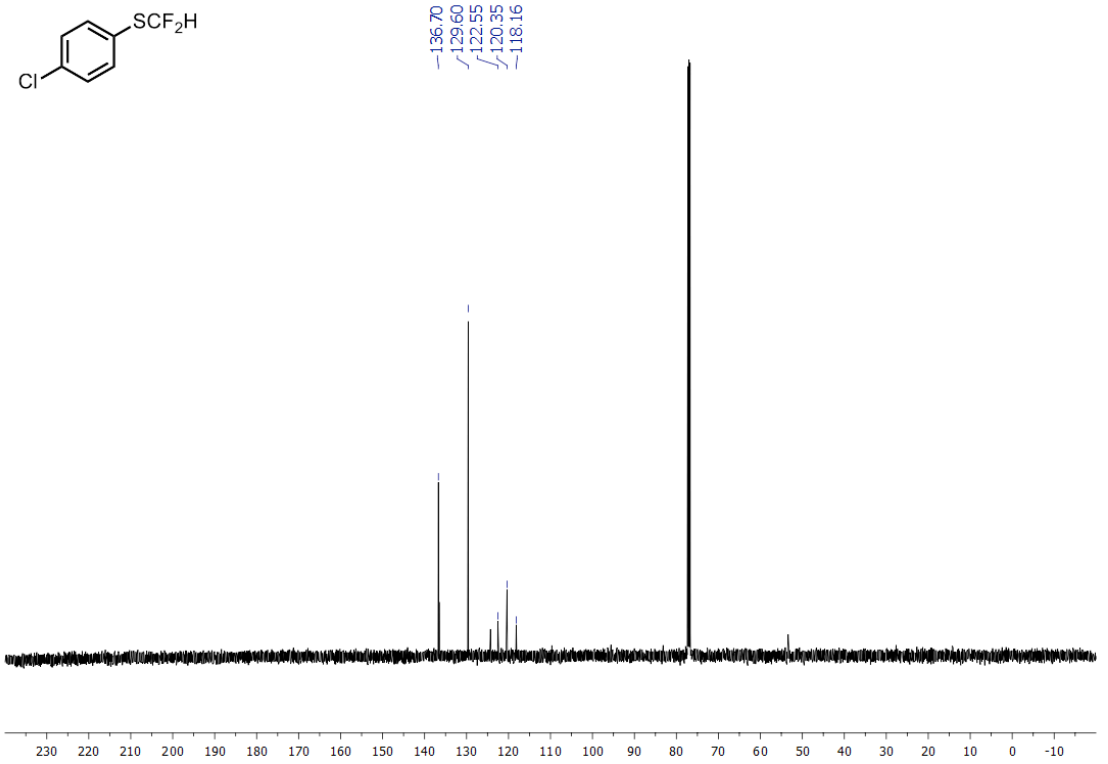
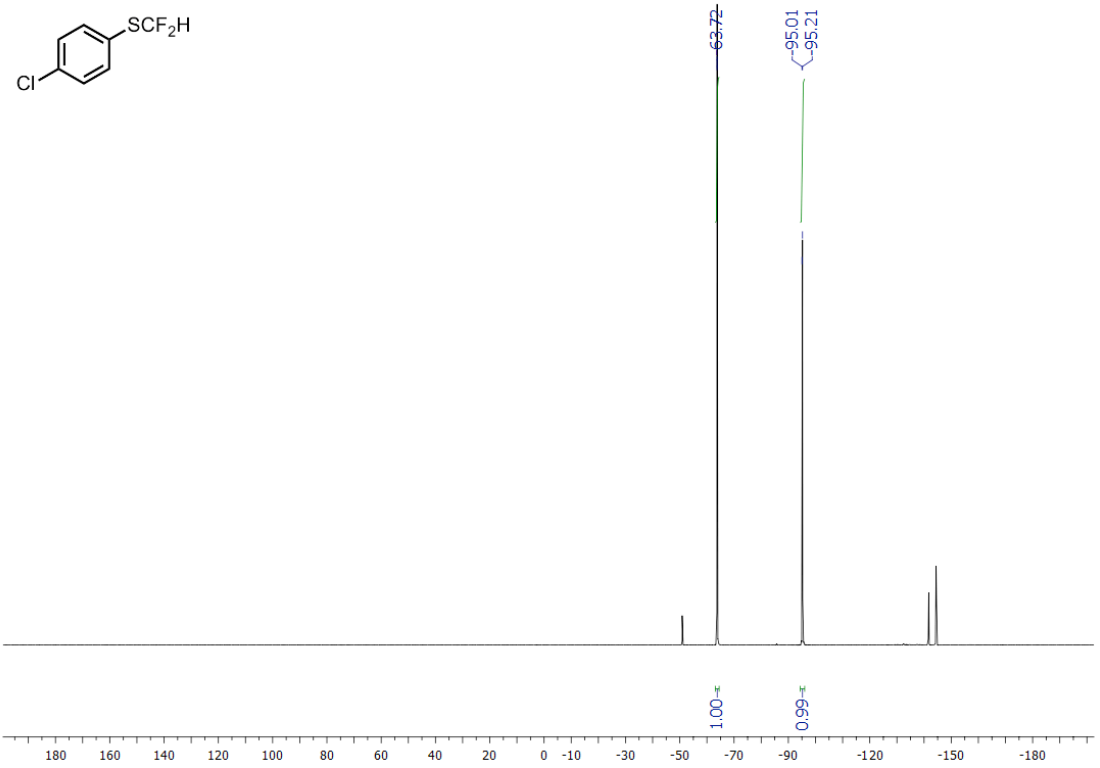
4.5.2 Difluoromethylthioethers



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1.00
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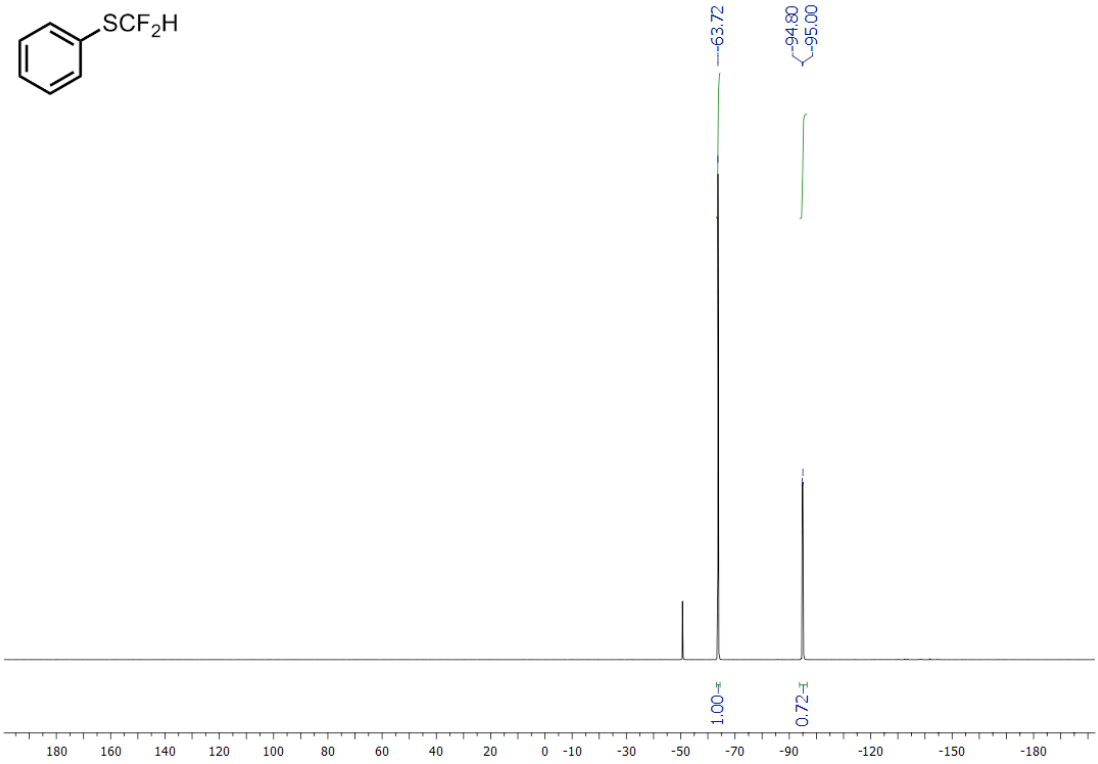
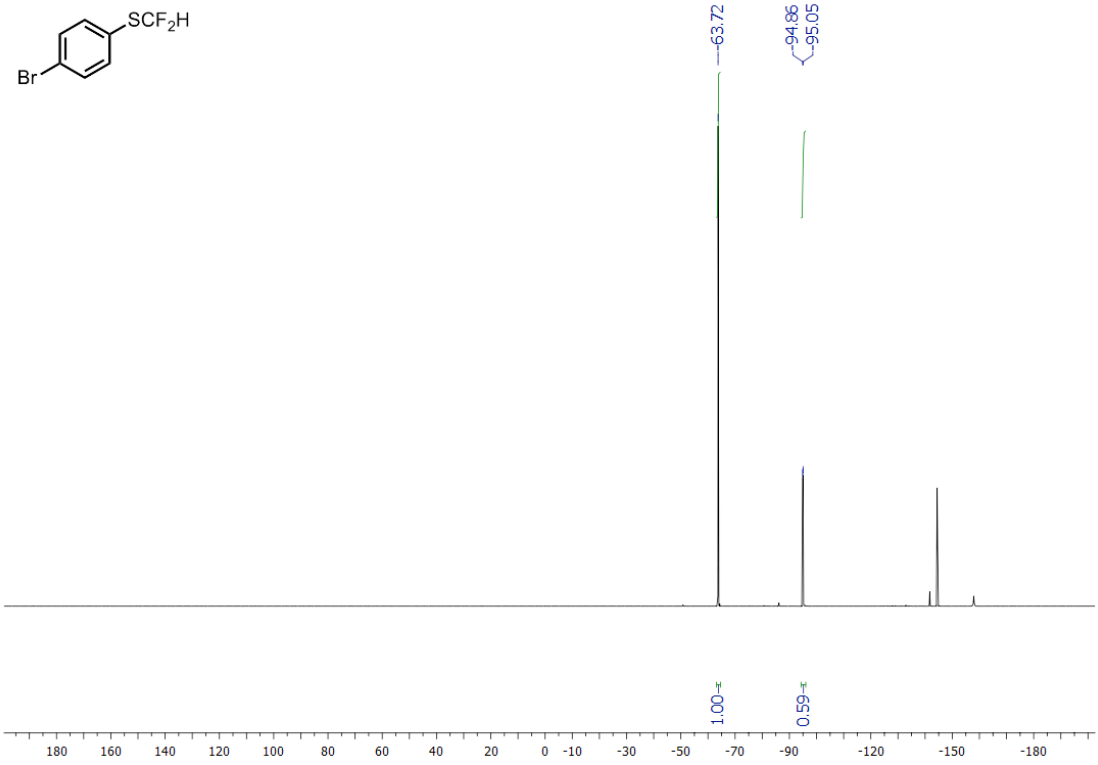
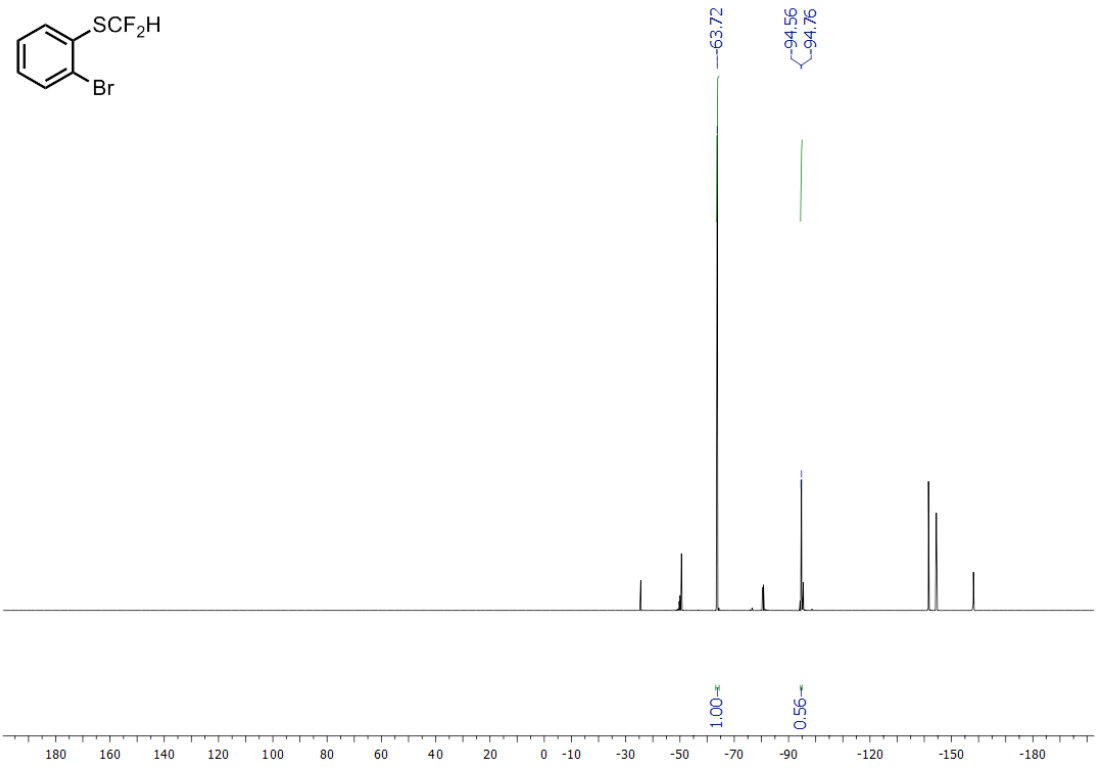
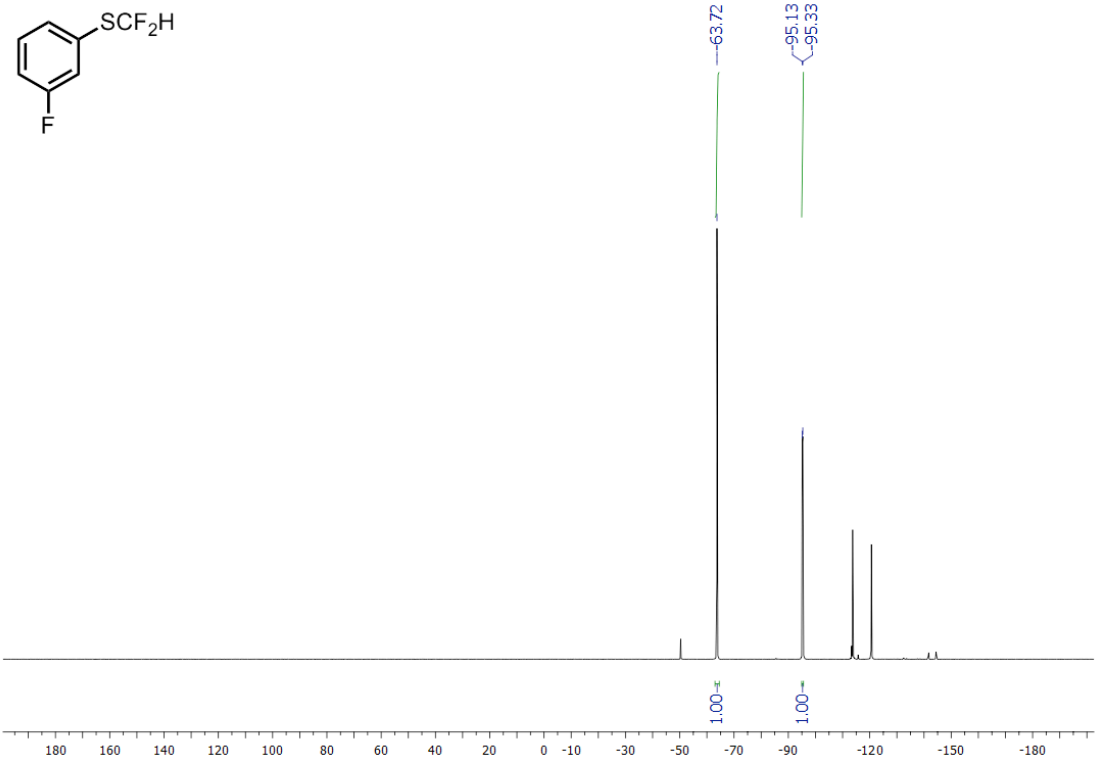
140
120
100
80
60
40
20
0
-10
-30
-50
-70
-90
-120
-150
-180

^{19}F NMR spectra of crude reaction mixtures with trifluorotoluene standard to determine conversion.






SCF2H
Br
-63.72
-94.56
-94.76
1.00
0.56
180 160 140 120 100 80 60 40 20 0 -10 -30 -50 -70 -90 -120 -150 -180


SCF2H
F
-63.72
-95.13
-95.33
1.00
1.00
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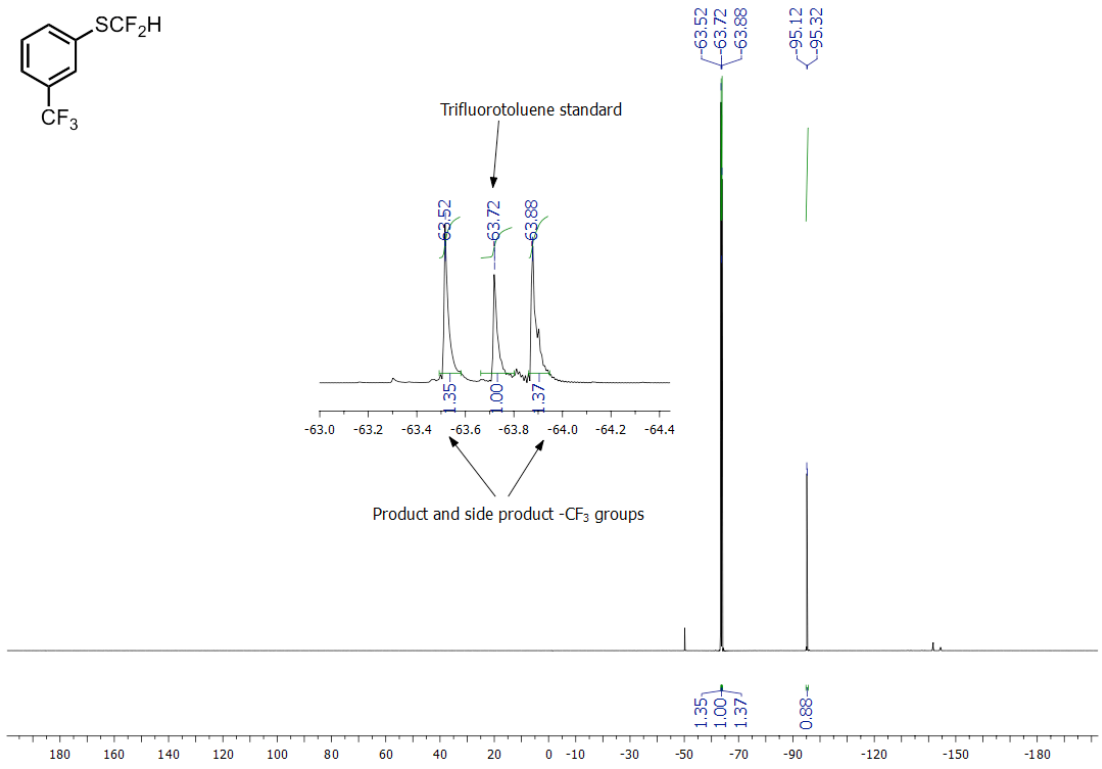
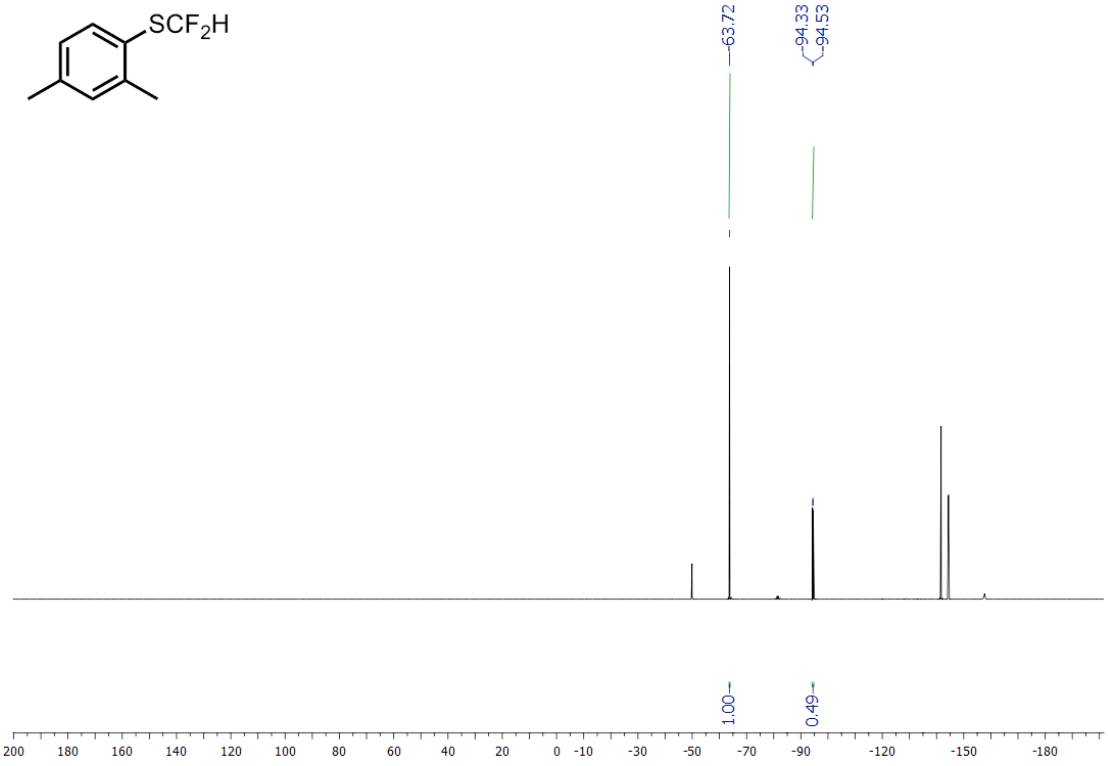
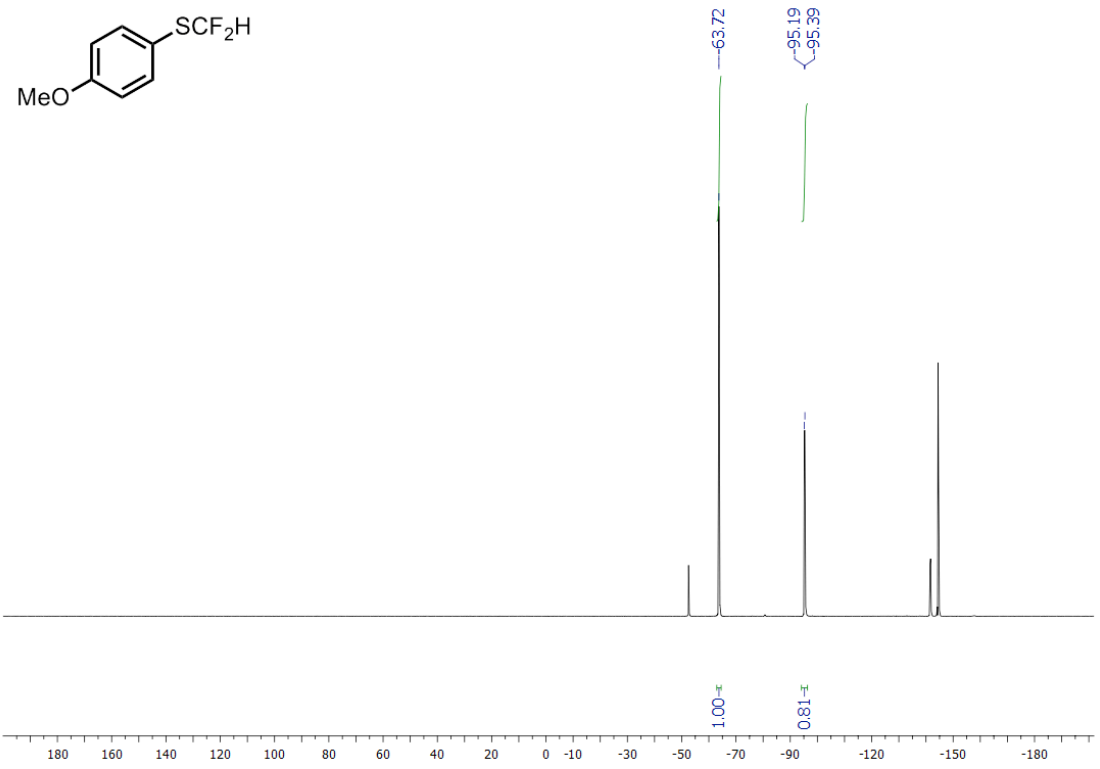

SCF2H
CF3
Trifluorotoluene standard
-63.52
-63.72
-63.88
1.35
1.00
1.37
-63.0
-63.2
-63.4
-63.6
-63.8
-64.0
-64.2
-64.4
Product and side product -CF3 groups
-63.52
-63.72
-63.88
-95.12
-95.32
1.35
1.00
1.37
0.88
180
160
140
120
100
80
60
40
20
0
-10
-30
-50
-70
-90
-120
-150
-180


SCF2H
-63.72
-94.33
-94.53
1.00
0.49
200
180
160
140
120
100
80
60
40
20
0
-10
-30
-50
-70
-90
-120
-150
-180


SCF2H
MeO
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-95.19
-95.39
1.00
0.81
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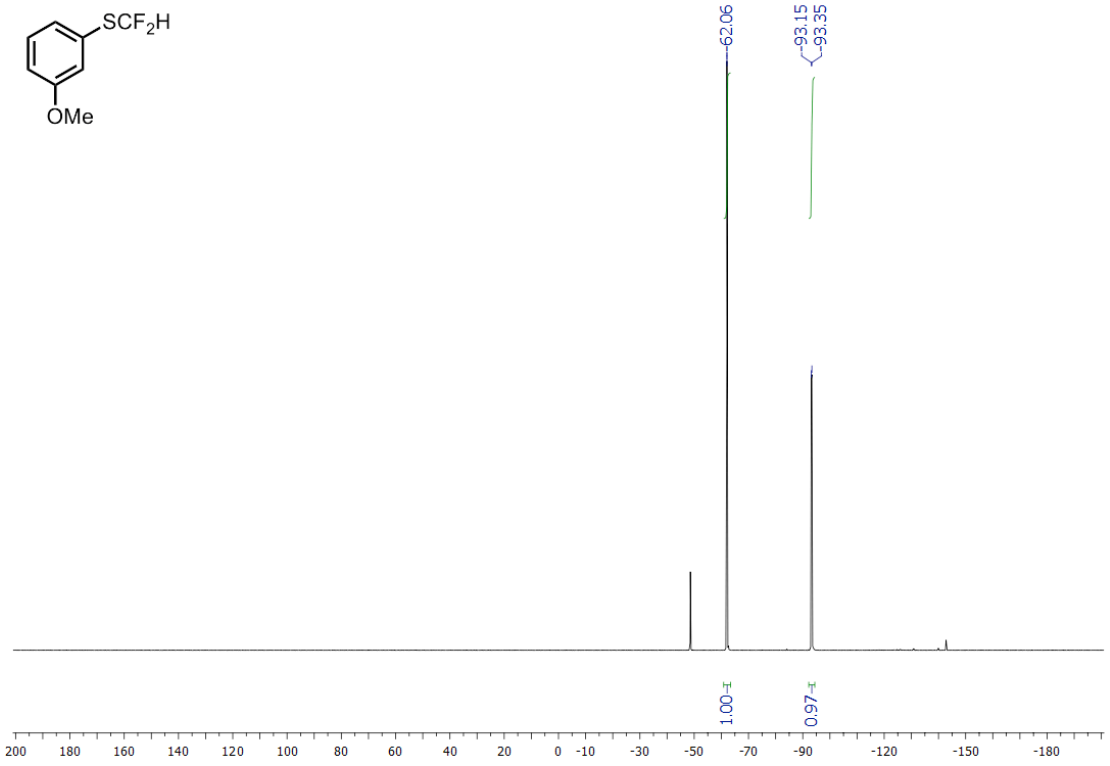
SCF2H
OMe
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-93.15
-93.35
1.00
0.97
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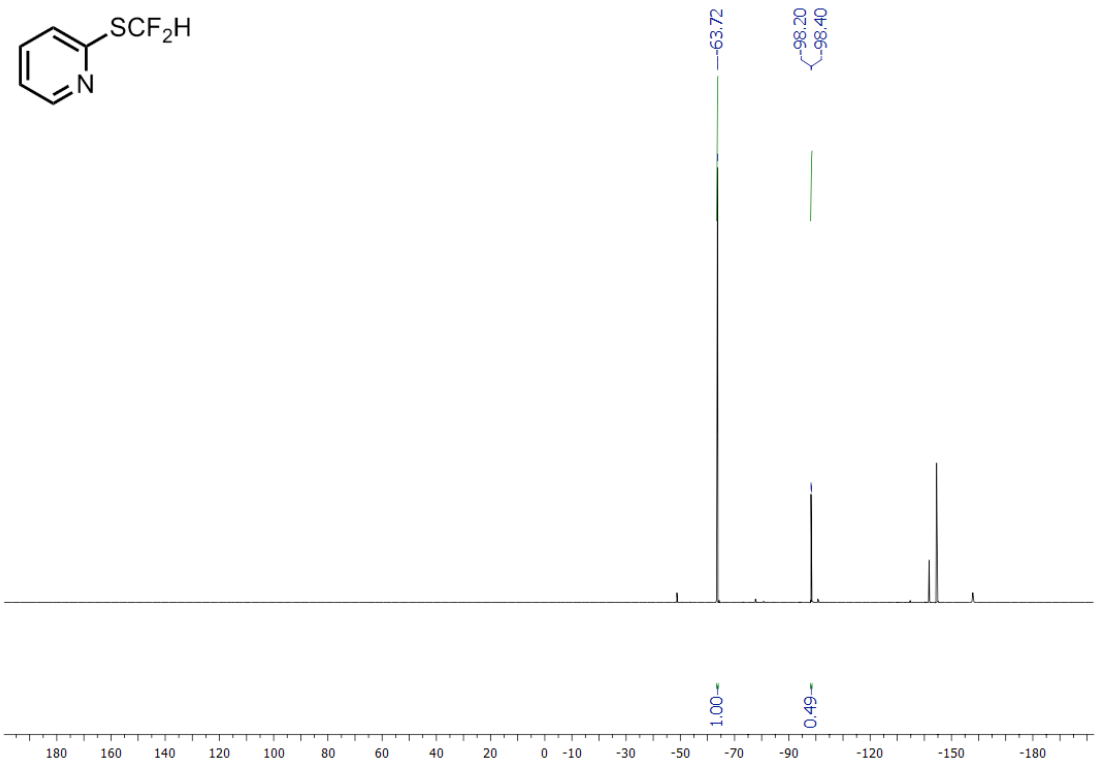
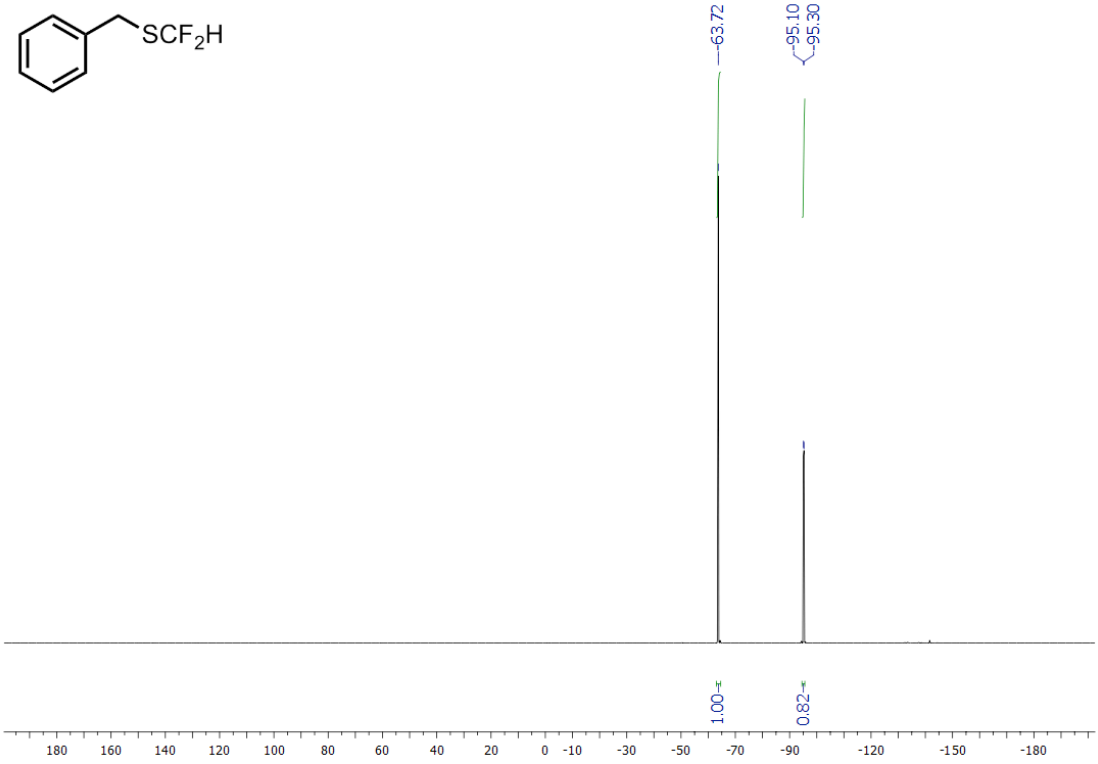

SCF2H
N
-63.72
-98.20
-98.40
1.00
0.49
180 160 140 120 100 80 60 40 20 0 -10 -30 -50 -70 -90 -120 -150 -180


SCF2H
-63.72
-95.10
-95.30
1.00
0.82
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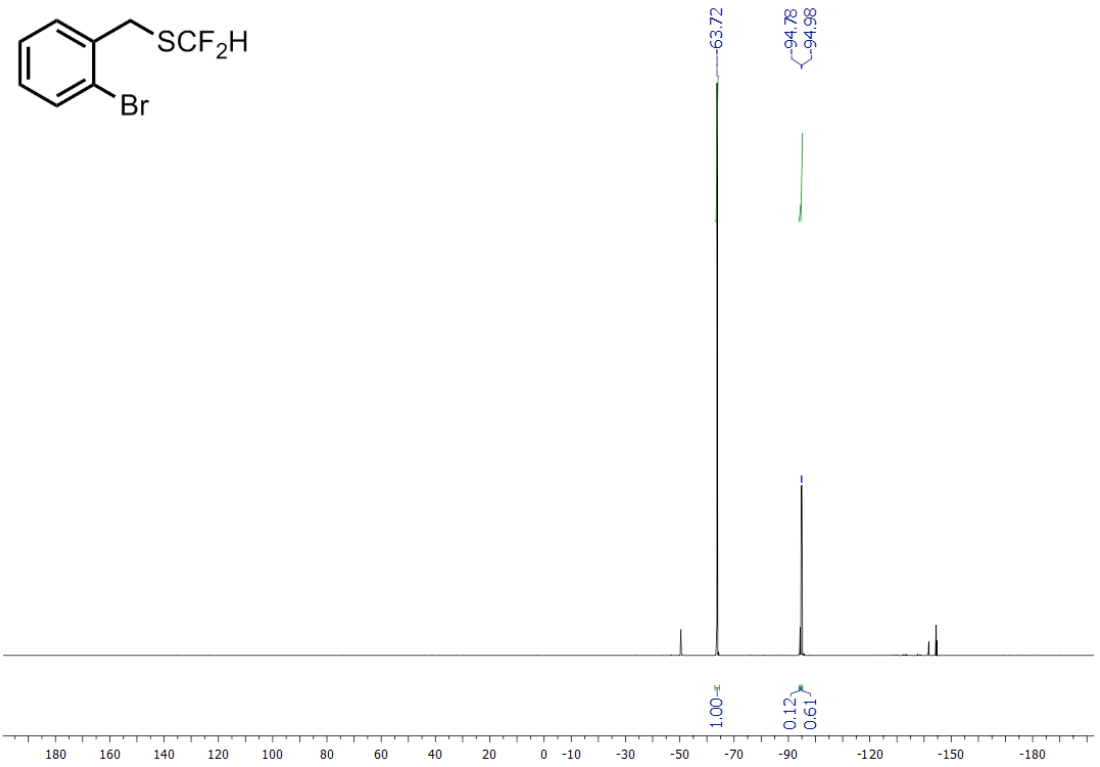
SCF2H
Br
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-94.78
-94.98
1.00
0.12
0.61
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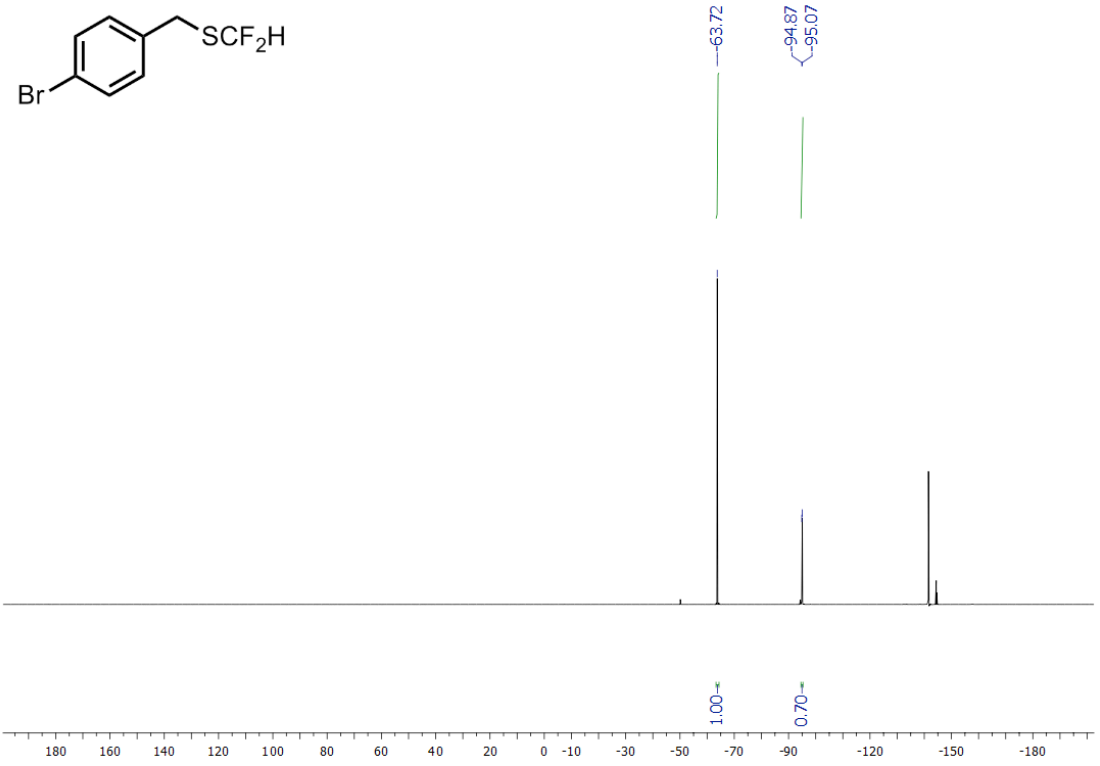
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Br
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-95.07
1.00
0.70
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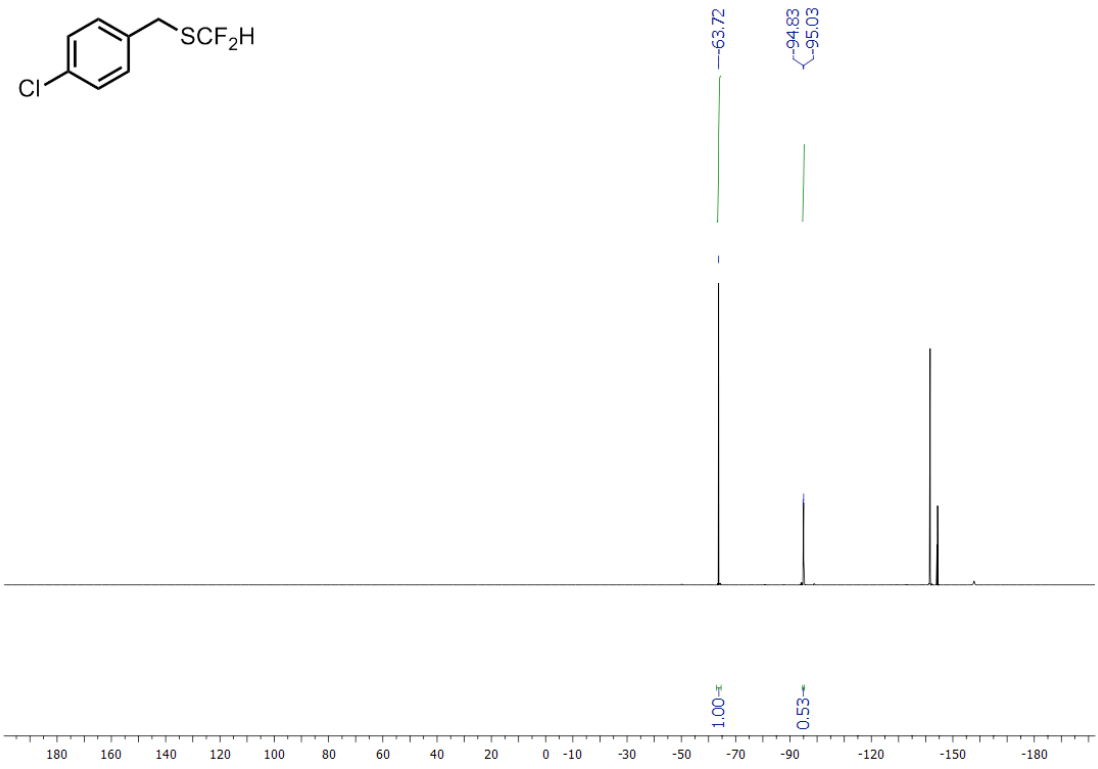
Cl
SCF2H
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1.00
0.53
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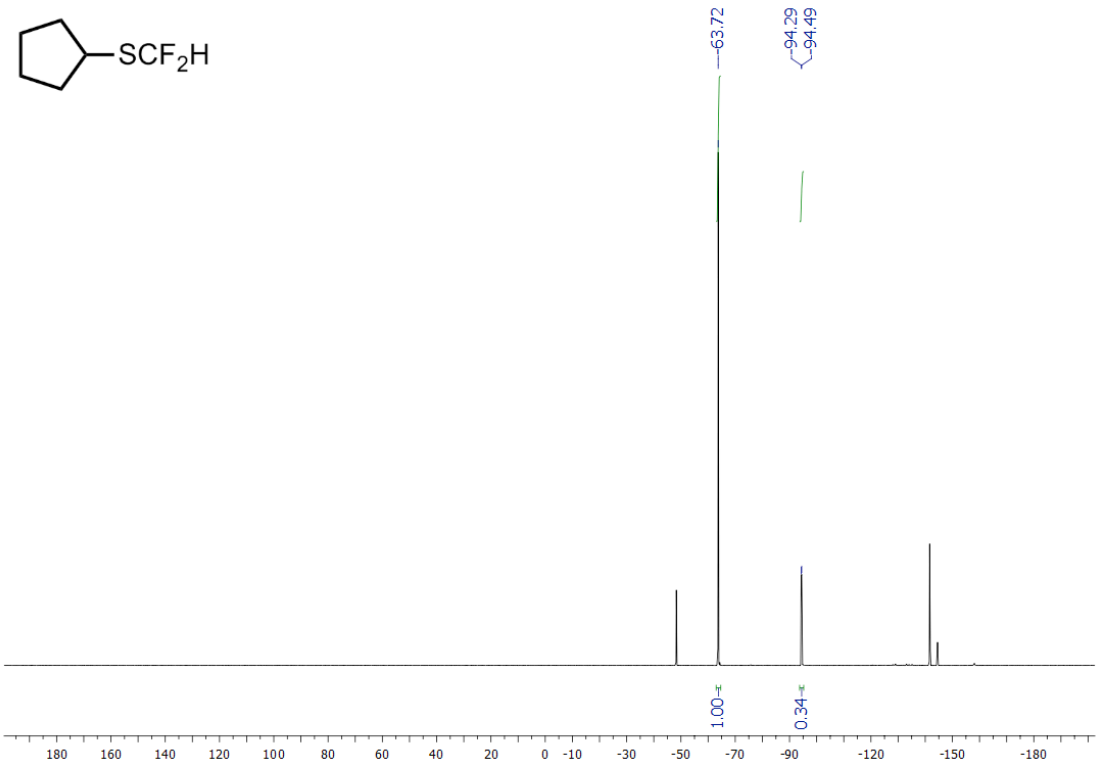
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-94.29
-94.49
1.00
0.34
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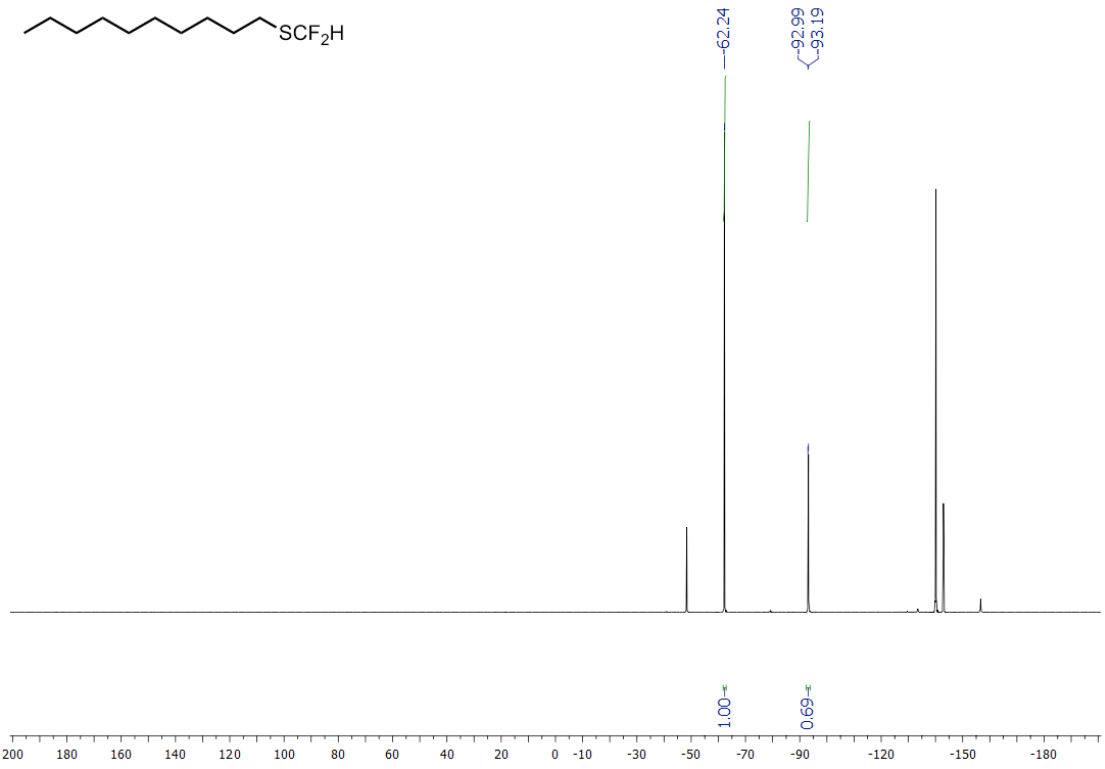
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-92.99
-93.19
1.00
0.69
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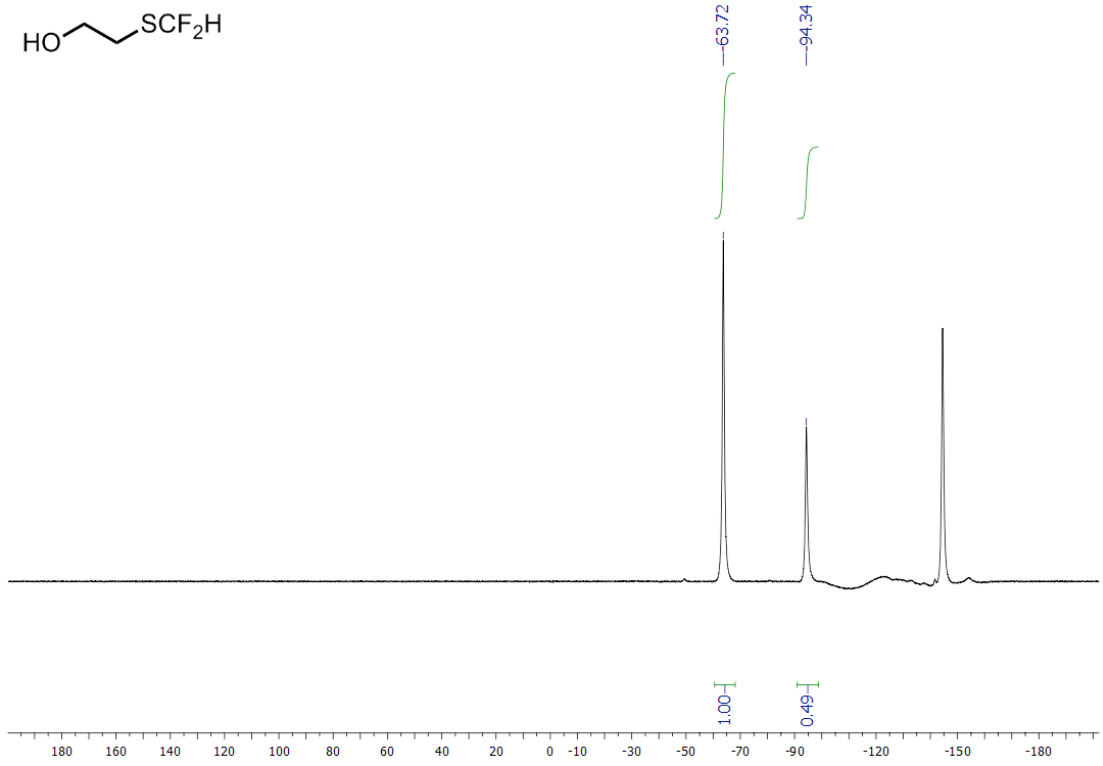
HO
SCF2H
-63.72
-94.34
1.00
0.49
180 160 140 120 100 80 60 40 20 0 -10 -30 -50 -70 -90 -120 -150 -180

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