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„ A Formal Fluorinative Homologation Strategy to Convert Carbonyl Platforms into Functionalized 1-Fluoro-2-Halo Skeletons "


verfasst von / submitted by

Szemerei Daniel Istvan Gabriel


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| Mitbetreut von / Co-Supervisor: | |

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# Abstract

The benefits of introducing a fluorine atom into the organic backbone of a pharmacophore are well understood and play an important role in medicinal chemistry in general. Fluorination strategies for medical targets have recently attracted much attention, because of the influence that a fluorine atom can exert on targets of medical importance, such as modulation of the lipophilicity, electronegativity, basicity and bioavailability, latter as a consequence of membrane permeability. In our case, we first performed a series of homologation reactions with the help of lithium carbenoids, followed by fluorination with deoxofluor. Through this two-phase reaction, we are able to generate our desired fluorinated compounds in a relatively fast and simple procedure. We were also able to obtain the compounds in good yields and with complete conversion.

Die Vorteile der Einführung eines Fluoratoms in das organische Grundgerüst eines Pharmakophores sind gut bekannt und spielen in der medizinischen Chemie im Allgemeinen eine wichtige Rolle. Fluorierungsstrategien für medizinische Targets haben in letzter Zeit viel Aufmerksamkeit auf sich gezogen. Da ein Fluoratom einen besonderen Einfluss auf Targets ausüben kann, welche von wesentlicher medizinischer Bedeutung sind, wie z. B. die Modulation der Lipophilie, Elektronegativität, Basizität und Bioverfügbarkeit, letztere als Folge der Membranpermeabilität. In unserem Fall haben wir zunächst eine Reihe von Homologierungsreaktionen mit Hilfe von Lithiumcarbenoiden durchgeführt, gefolgt von einer Fluorierung mit Deoxofluor. Durch diese Zweiphasenreaktion können wir unsere gewünschten fluorierten Verbindungen in einem relativ schnellen und einfachen Verfahren herstellen. Außerdem konnten wir die Verbindungen in guter Ausbeute und mit vollständiger Umwandlung erhalten.

# ACKNOWLEDGEMENT

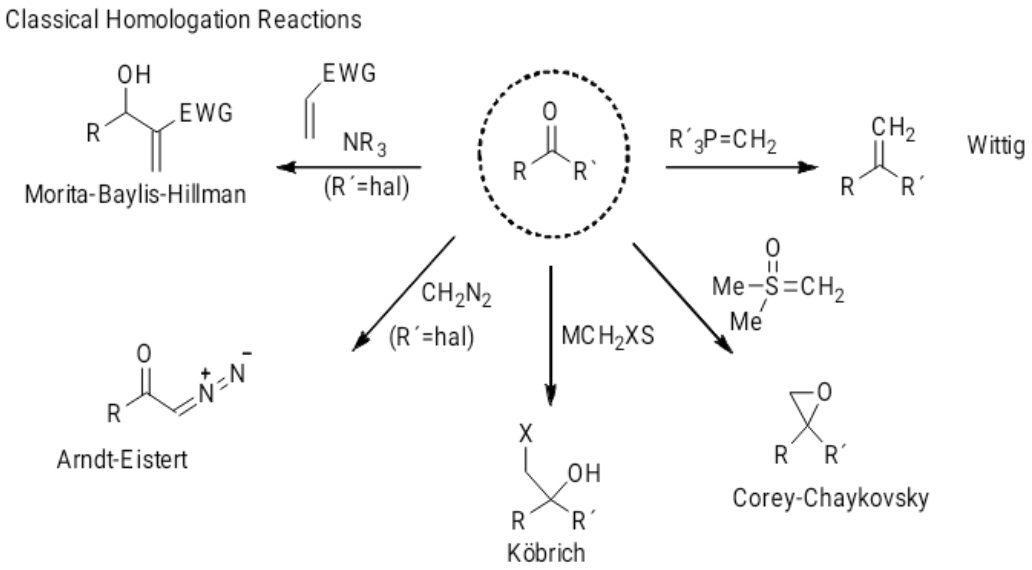
I would like to thank my major advisor, Prof. Dr. Vittorio Pace from the Department of Pharmaceutical Chemistry at the University of Vienna for his constant guidance and support. I also express my deepest gratitude to my family and friends for their unfailing support and continuous encouragement, especially to my daughter who was very patient with me and her playtime.

Thank you all very much!

Szemerei Daniel

# 1. Introduction

## 1.1 Homologation




*Scheme 1 Classical Homologation Reactions*

Homologation reactions are reactions, which make the expansion of the homologous series possible. This extension mostly occurs through the constant unit of the methylene group ($CH_2$). Generally speaking, the new linkage of carbon-carbon bonds is one of the main areas in organic chemistry. In view of this, the Arndt-Eistert homologation is a prototypical reaction in this field.

Diazomethane is used as a methylating reagent in the Arndt-Eistert homologation to extend carbon chains or a dipolar cycloaddition. The known toxicity and general safety deficiencies when using diazomethane, led to an increased search for reagents with a lower risk. Thanks to that effort, new ways were opened for the adaptation of similar reagents in different reactions, like Wittig, Corey-Chaykovsky or the Köbrich reaction (Scheme 1). [(1)]

## 1.2 Carbenoids

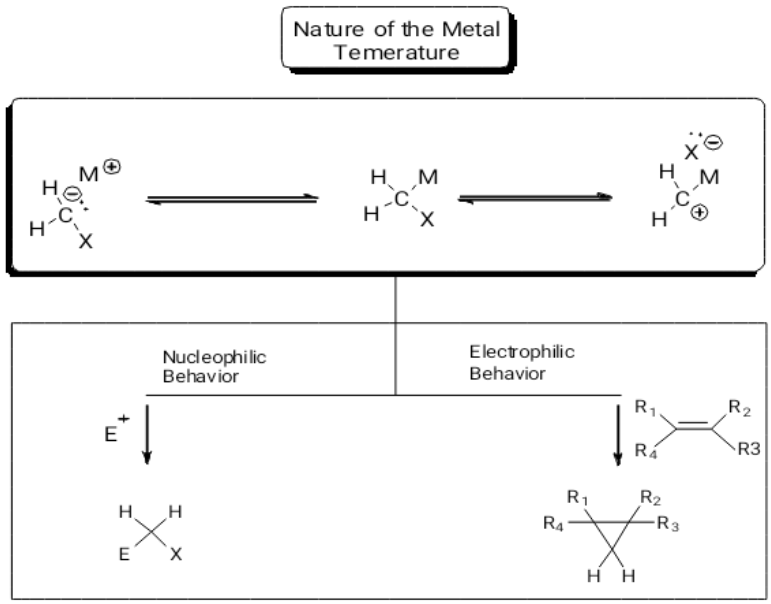
The term carbenoids was originally introduced by the chemists G.L. Closs and R.A. Moss, who defined them as "qualitatively analogous to carbenes without necessarily being a free divalent carbon species“. [1] [2]

The halocarbenoids are classical compounds for the addition of substituted methylenegroups to substrates with an electrophilic character. According to G.L Closs and R.A. Moss, these organometallic carbenoids are molecules with a metal atom (e.g. Li,Mg) and one or more electronegative elements (e.g. halogen) at the very same Carbon atom. [3]

Regarding the search for even better homologation reagents, the work of G. Köbrich and his team in particular, has demonstrated significant progress.[4] These findings also serve as a basis for understanding and advancing the synthetic chemistry with carbenoids.

It was observed that carbenoids can have an amphiphilic character. This behavior is dependent on the respective metal, electron-withdrawing atom at the functional carbon and the temperature. These basic influences determine whether the functional carbon behaves in a nucleophilic or a electrophilic mannere (Scheme 2).[5] It has been found that the reaction at low temperatures increases the nucleophilicity and again at high temperatures an electrophilic behavior is observed.

This behaviour also distinguishes the associated reaction categories: nucleophilic addition (Eventually followed by elimination) with the main metal lithium or magnesium, which have a particular nucleophilicity at the carbon atom. Otherwise metals such as zinc or rhodium show a more electrophilic behaviour for Cyclopropanation type reactions. [1]



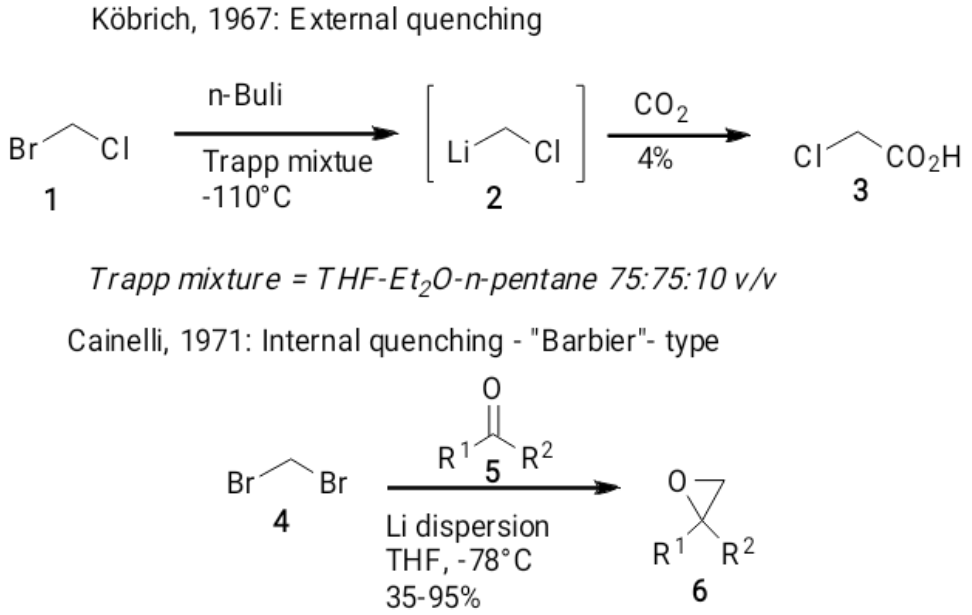

*Scheme 2 Reactivity properties of carbenoids*

# 1.3 Lithium carbenoids

The amphilicity of carbenoids, especially the lithium carbenoids was one of the primary focus points in the research of G. Köbrich and his coworkers. Lithium carbenoids have a wide range of applications in which they can incorporate methylene groups in the form of a nucleophile such as $LiCH_2X$ into a new scaffold. The challenge in using this reaction was to find the right balance between reactivity and stability. [(6)]

Very low temperatures were required to be able to work with them at all.

Köbrich reported at the time, that the production of chloromethyllithium **2** ($LiCH_2CL$) from bromochloromethane **1** and n-BuLi, followed by a carboxylation at -110°C to chloroacetatmethylester **3** , yielded the desired acetic acid, but only in a very poor yield (Scheme 3).




*Scheme 3 Initial consideration on a lithium carbenoid*

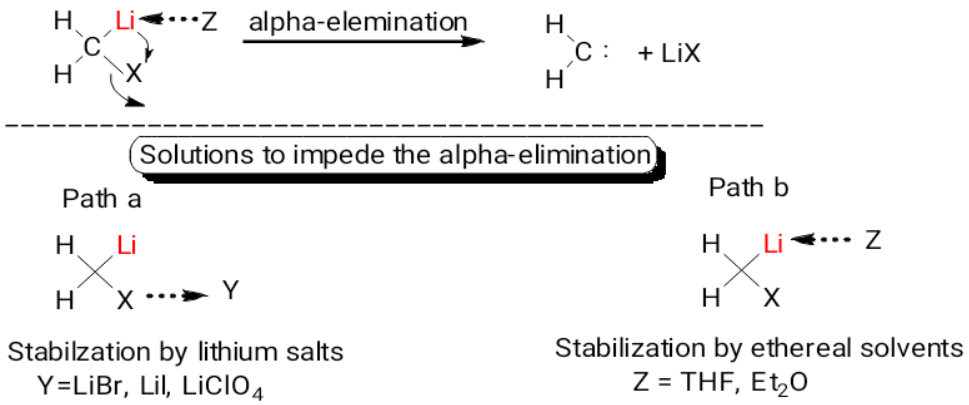
Later successes were achieved by G. Cainelli, who proved that monohalomethyllithium can also be produced at -78°C. However, this is only possible if the reaction is carried out according to the Barbier type protocol, [(7)] which meant that the electrophile had to be present in the reaction mixture before the carbenoid was produced. This electrophile prevents the decomposition of the carbenoid, as it can find an immediate reaction partner and thus react immediately to homologate a carbonyl **5** compound to the epoxide **6**. [(8)] Cainelli also showed that the production of carbenoids with pure lithium metal worked better than with the alkyllithium.

However, it was known that the carbenoids had a thermal instability.

The biggest problem in this case, was to find the optimum conditions for the stability and reactivity.

One of the most important findings of G. Köbrich is the alpha-elimination. This is an elimination where the leaving group and also the proton are located on the same atom. Since the carbenoid was useless for further reaction in this state, many important investigations were carried out that could contribute to a better stability of the carbenoid.

Through this search new conditions for preventing the alpha-elimination were found. According to Villieras and his co-workers, the internal Li-X coordination is disrupted by adding lithium halides to the reaction mixture. [9] [10] Moreover the presences of ethereal type solvents (Lewis Base) add an additional stabilizing effect, by coordinating the metal atom of the carbenoid (Scheme 4).




*Scheme 4 alpha-Elemination*

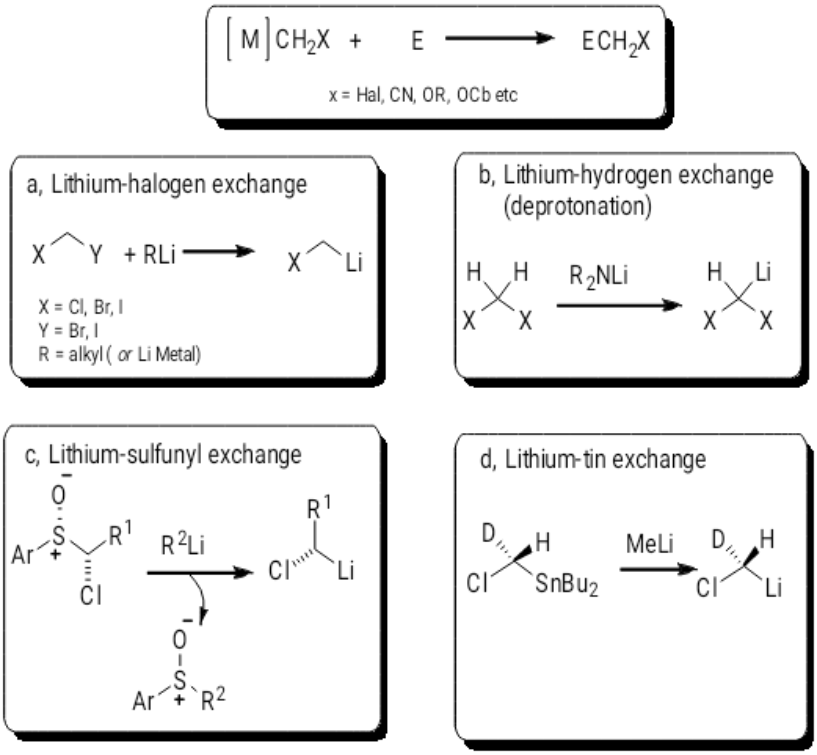
On the basis of this knowledge Barluenga and Matteson showed the wide range of these reactions. These were carried out at -78°C and let us assume that the thermal stability and good reactivity for carbenoids lies around this temperature. Those results showed us, that the stability of carbenoids can be influenced by various conditions. Especially the type of substitution, the metal/halogen combination, as well as the addition of lithium salts or Lewis-Base ethereal solvents.

In general, lithiumcarbenoids are produced in the following preparation methods:

a, Lithium - halogen exchange  b, Lithium - hydrogen exchange (i.e. deprotonation)

c, Lithium - sulfinyl exchange  d, Lithium - tin exchange

All these reactions should be carried out under Barbier-type conditions. This is considered to be ideal to reduce the activation of the degeneration pathways (Scheme 5). [11] [12]

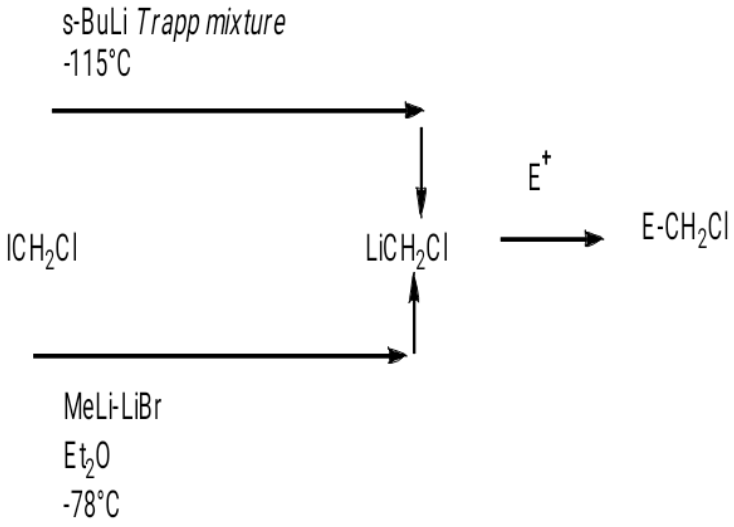



*Scheme 5 Different tactics for preparing lithium carbenoids*

## 1.3.1 Lithium halogen exchange

This method is one of the most common for preparing halo-carbenoids, which led to the good availability of the dihalomethane precursors. [11] At the beginning, this reaction was carried out in the Trapp mixture (THF-$Et_2O$-n-Pentane 75:75:10 v/v/v) with s-BuLi according to the studies of Villieras (Scheme 6). [9] [13] However, further studies have shown

that s-BuLi as lithium source works better for deprotonation reactions rather than for exchange reactions. This instead makes MeLi and n-BuLi the optimal lithium source (Scheme 6). [14]

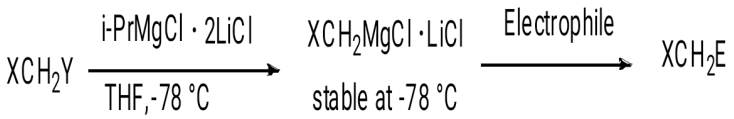



*Scheme 6 Lithium-iodine exchange in the presence of different alkyllithiums*

An excellent reagent for generating chloromethyllithium starting from chloroiodomethane is the MeLi-LiBr complex in $Et_2O$, that's why it became so widely commercially available in the last years [15]. According to the studies of Matterson [16], and also Pace who showed that this lithium bromide complex being present has a stabilizing effect on the carbenoid. Also the elimination of the concurrent attack of MeLi to an electrophilic substrate present in the reaction medium under Barbier-type conditions exhibits these stabilizing properties. [15] [17] This is particularly true for the production of chloromethyllithium starting from chloroiodomethane. [18] All in all, the process can be described as an in-situ generation of the carbenoid, followed by an immediate interaction with the electrophile. Lithium bromide also behaves as a mild Lewis acid,[17] which reduces the attack of the formed carbenoid on the electrophilic partner. The type of dihalomethane used as the carbenoid precursor also plays an important role in optimizing the efficiency of the reaction. [8] Due to the chemical simplicity, of iodine-containing molecules being easier to substitute, chloroiodomethane is naturally the first choice to use. [8] Nevertheless, there are efforts to use the cheaper

bromochloromethane instead of iodochloromethane. The envisaged advantages are mainly for industrial reasons for finding a cheaper precursor. [19] As a result, an alkyl or aryl-lithium reagent promotes a substitution on a dihalomethane to provide the corresponding lithium carbenoid. [6]

However, considering the residual possibility of competing attack of the alkyllithium to the electrophile and/or variations of its concentration, it is wise to employ a small excess (0.2–0.4 equiv.) of the dihalomethane and add the alkyllithium dropwise and very slow, to generate the halolithium carbenoid correctly. With this practical advice, both side processes may be advantageously avoided. [6] The counter part to the lithium reaction is the magnesium-iodine exchange which is based on the use of chloroiodomethane. [20] Further research of Knochel, Marek and their team showed the preparation of functionalized carbenoids from iodomethane. The better advantage compared to the lithium, is their higher stability. Because of that, they can be easily produced at -78°C and the electrophile can be added at a later stage (Scheme7). [21]

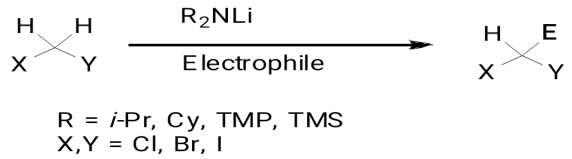



*Scheme 7 Formation of magnesium carbenoids via magnesium-iodine exchange under non-Barbier conditions*

Because of that, the magnesium carbenoids are suggested as a good alternative to the unstable lithium carbenoids. This claim is also true in the first place when a strong electrophile is used as a trapping reagent. But as Pace and his team have shown, less nucleophilic magnesium carbenoids do not react with weaker electrophiles, such as Weinreb-amides. Therefore, the use of lithium carbenoids in homologation reactions is necessary. [15] Furthermore, Clososki showed excellent chemoselectivities in the addition of magnesium carbenoids to aldehydes endowed with additional electrophilic functions such as esters, ketones or nitriles. [22] Lithium-halogen exchange also works through metalation with lithium metal, which is shown by the work of Cainelli. [21] It also should be mentioned

that Luche showed another way of lithiation with Lithium metal and sonication. In this case the unstable chloromethyllithium is produced at -15°C with ketones and at -50°C with aldehydes. Nevertheless, the comparative study of Beaulieu shows, that there were not really advantages between mechanical stirring or sonication for the generating of chloromethyllithium. [23]

## 1.3.2 Lithium -hydrogen exchange (i.e. deprotonation)




*Scheme 8 Lithiation via lithium-hydrogen*

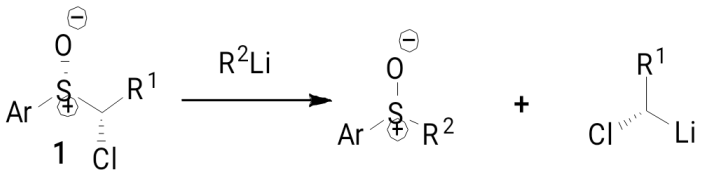
The production of monohalogen carbenoids by deprotonation is not really suitable for this purpose, because the lithium halogen exchange method has a clear advantage due to its particular speed and performance. [5] [24]

Among other things, this is also due to the very low temperatures (-115°C). Also the very basic s-BuLi performs a halogen exchange rather than the necessary deprotonation. [9] For the production of dihalomethylcarbonoids like (e.g. $LiCHCl_2$, $LiCHBr_2$, $LiCHI_2$), deprotonation is the reaction of choice (Scheme 8).

Lithium amide bases like LDA or LTMP can be used to abstract the proton and shouldn´t really affect the chemocontrol. Only one exception could be the isocyanates. They could react with lithium bases (LDA, LNCy2), who are less hindered because of their steric arrangement. [25] The use of Barbier-type conditions, as mentioned by Nozaki et al., is not required. In the case of $LiCHI_2$ like shown by Bull, it is easily formed before the reaction with the electrophile. Molinski reported another way producing trichloromethyllithium. This strategy uses chloroform and n-BuLi at -100°C *via* a deprotonation. In this case the carbenoid turns into a low nucleophilic reagent, which makes it more suitable for a Michael-type reaction with an unsaturated sultam. [8]

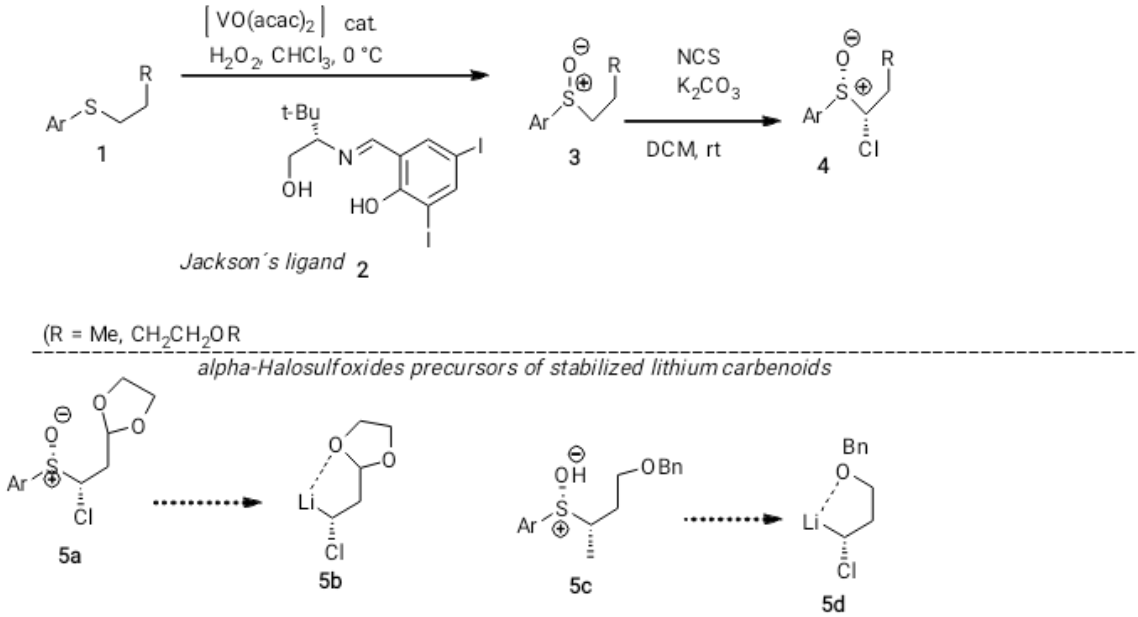
## 1.3.3 Lithium – sulfinyl exchange

According to Hoffman, another very useful alternative for the production of magnesium carbenoids is the magnesium-sulfinyl transformation instead of the conventional metal-halogen exchange. [26] Even at a temperature of -80°C, a sulfoxide and a Grignard reagent (e.g. i-PrMgCl) can react immediately to form a magnesium carbenoid. This species has been shown to have a particularly stable configuration even at temperatures below -60°C and for a period of over 30 min. This makes them especially suitable for asymmetric reactions. [20] [27] Blakemore and co-workers reported that lithium carbenoids can be prepared from certain halogenated arylsulfoxides. Unlike dihalomethanes, which are almost universally commercially available, the alpha-halogen sulfoxides must first be prepared. They can be easily prepared from thioethers ***1*** [28] by a two-step synthesis. First a asymmetric sulfoxidation, secondly followed by halogenation (Scheme 9).




*Scheme 9 Lithium carbenoids from halogenated arylsulfoxides*

To get there, the first step is over the vanadium-catalyzed Ellman-Bolm [29] enantioselective oxidation in the presence of the *Jackson´s tert-leucinol-derived ligand 2.* [13] The resulting sulfoxide ***3*** (up to 99:1 er) can be received by recrystallization. [28] The chlorsulfoxide ***4*** is than prepared by the Yamakawa chlorination. [30]

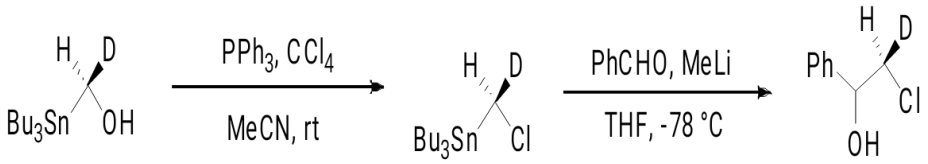



*Scheme 10 Blakemore´s sythesis of chiral halosulfoxide precursors of optically active lithium carbenoids*

It should be noted that chlorination occurs with a stereochemical reversion at the sulphur atom. The lithiation in this step can be done with either t-BuLi in toluene or PhLi in THF. These enantioenriched carbenoids, (**5a*, 5b***) which are created by P. R. Blakemore can be stabilized by internal coordination of Lithium with Lewis basic sites like acetals or ethers. (31)

### 1.3.4 Lithium – tin exchange

Another special discovery by Hammerschmidt and his team was the production of configuration-stable chloromethylstannanes, which are made from chiral stannan with MeLi. These special tin compounds, require the conversion of tributylstannylmethanol into the corresponding chloride and work well under appel conditions. [32]




*Scheme 11 Hammerschmidt´s preparation of chiral chloromethyllithium via tin-lithium exchange*

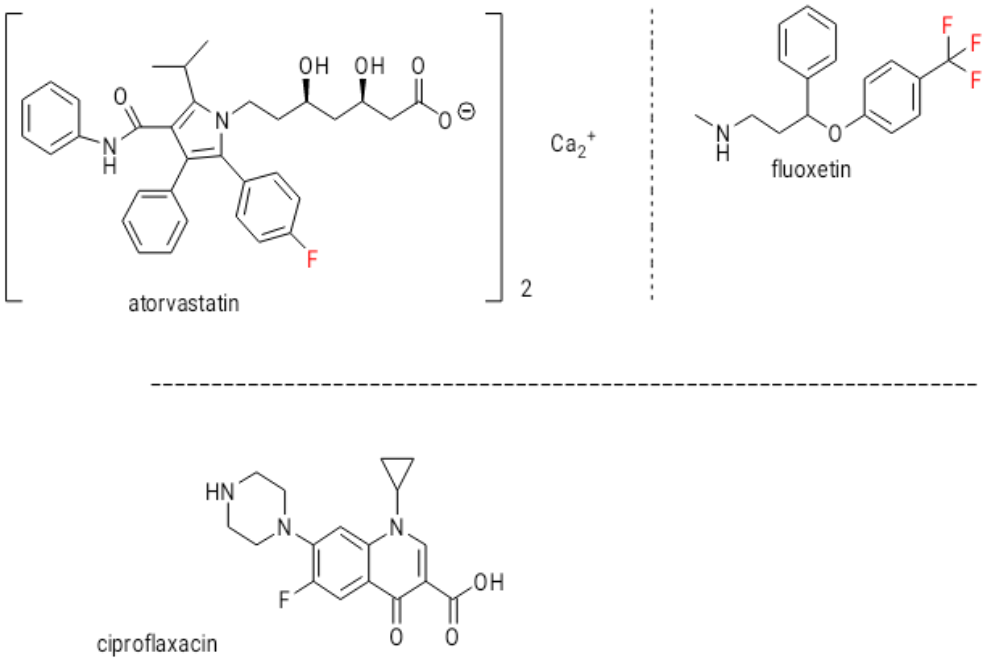
However, in the lithium-exchange reaction attention must be taken to the choice of lithium source. While MeLi achieves good results, the use of n-BuLi is less satisfactory. With n-BuLi, fewer clean reactions are observed with far more impurities. One possible reason, could be the less basicity of the MeLi compared to the n-BuLi. [8]

This work was a clear breakthrough for the work with chiral organo-lithium compounds, because it was possible to observe the configuration stability of halolithiumcarbenoids. [8]

## 1.4 Fluorination in medical chemistry

Introducing a fluorine atom into the organic backbone of a pharmacophore is coming along with a lot of benefits. These benefits are generally well known in pharmaceutical and in medicinal chemistry. [33] Just to name a few advantages the lipophilicity and electrostatic inter-actions are maybe the most well-known effects. These effects can significantly alter the biological properties of an organic molecule. Another important effect of fluorination in

medical chemistry is the possibility to influence the acidity and basicity of the compound, which can alter the binding affinity and bioavailability.[33] The substitution of hydrogen with fluorine on aromatic rings is a well-known strategy for slowing down oxidative metabolic processes by cytochrome P450 monooxygenases.[33] Fluorine substitution on aromatic rings is also known to increase binding affinity, as a result of increasing electrostatic interactions. The rapid progress and good understanding of the effects of fluorinated drugs has made it possible to develop a wide range of synthetic methods in organic fluorochemistry.




*Scheme 12 Examples of fluorinated drugs*

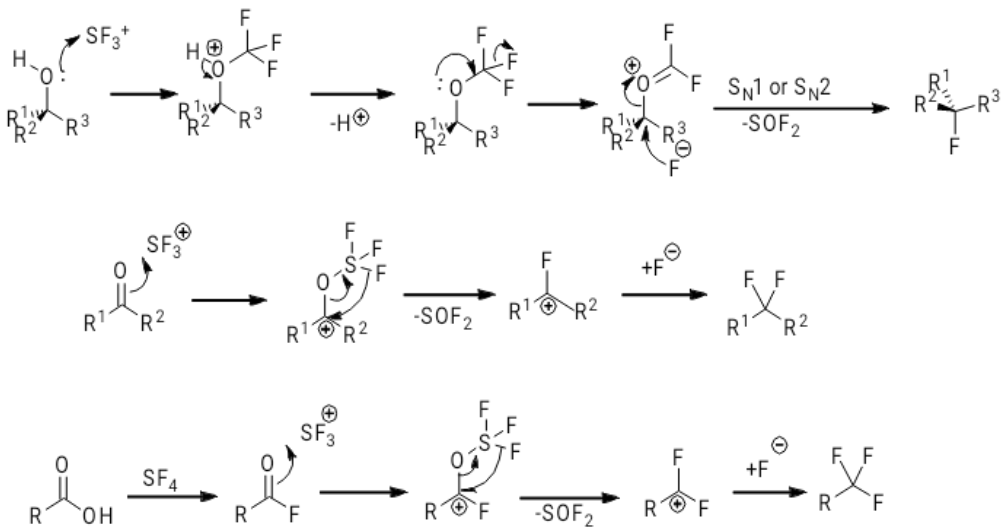
From a chemical point of view, fluorinated pharmacologically active drugs contain the fluorine atom in phenyl rings, heterocyclic rings, steroids and derivatives. Various synthetic strategies act, to introduce fluorine in the molecule with a synthetic late-stage strategy, such as substitutions on phenyl and heteroaromatic rings, and substitutions on sp3, sp2 and C-H bonds in aliphatic compounds.[33] A good method in the category of nucleophilic fluorination is the reaction with deoxofluor. In this reaction the integration of fluorine and the displacement of the oxygen is happening simultaneously. [8] This $S_N2$ reaction, with

reversal of the configuration, is preceded by the formation and simultaneous elimination of hydrogen-fluoride. However, there are still challenging issues in the field of late stage fluorination, with highly functionalized molecules.

## 1.4.2 Deoxoflurination.

Sulphur tetrafluoride so called $SF_4$ was discovered in 1929 by Joseph Fischer and Werner Jaenckner. It was successfully prepared from cobalt(III)-fluoride and Sulphur. [34]

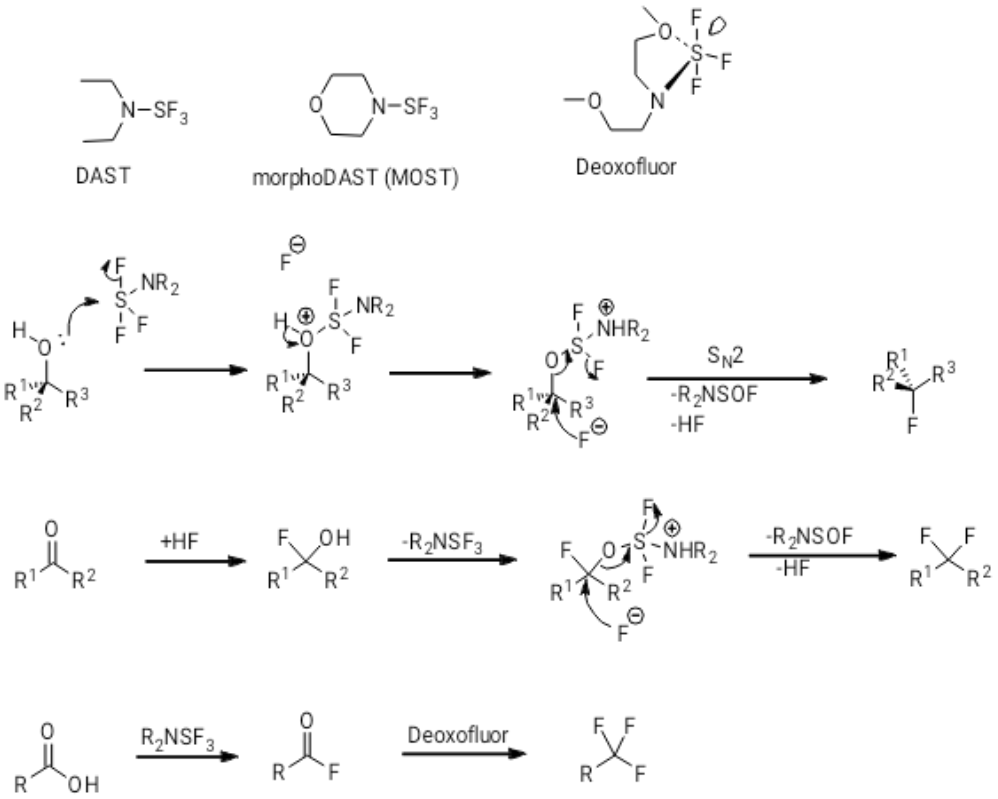
Almost three decades later in 1958, a group of scientist found out that it was possible to convert carbonyl and carboxyl groups in difluoromethylene and trifluoromethyl groups with the help of $SF_4$. This is why $SF_4$ became the parent compound in this type of reaction. Further in the 1960´s it was reported that $SF_4$ is even able to exchange a hydroxy group to fluorine. [35]




*Scheme 13 Mechanisms of deoxyfluorinations with $SF_4$. Exchanging OH for F has a strong tendency to shift towards $S_N1$-type substitution*

These reactions first had to be made under elaborate conditions. Later it became clear, that in the presence of major amounts of HF, carbonyl and carboxyl groups can also be transformed even at room temperature. [36] Nevertheless, there were problems just using the substance alone. $SF_4$ is a highly irritating, corrosive and toxic gas. It is tricky to handle and needs special equipment. That's why it ultimately led to further investigations to reach better alternatives. The substitution reaction which undergoes a $S_N1$ reaction can be observed in Scheme 13.

Towards the final use of Deoxofluor, [37] [38] Dialkylaminosulfur trifluorid DAST for short finds its way to effectively perform fluorinations and all this without the need of excessively high temperatures like with $SF_4$. For our needs it should be mentioned that OH→F exchange preforms very well at -78°C, and carbonyl→difluoromethylene transformations have a good activity at room temperature and some transformations like carboxyl→trifluoromethyl require temperatures up to 85°C. [38] [39] It is much easier to use, because it is liquid at room temperature and not that corrosive. Thank´s to that it can be used with normal laboratory glass. That´s why it became widely used. Nevertheless it also has its limitation in its thermolability with the decomposition and possibility of explosion at around 90°C. Like mentioned above this temperature is pretty close to the point where we like to perform our carboxyl→trifluoromethyl transformations. [40] [41] [42]



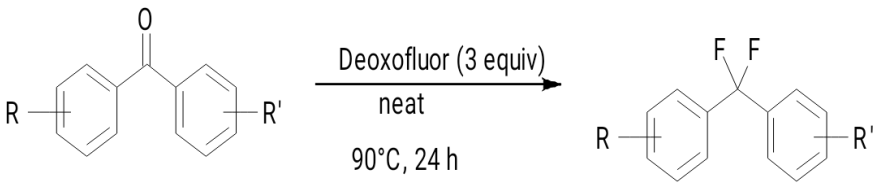

*Scheme 14 Mechanisms of deoxyfluorinations with dialkylaminosulfur trifluorides*

For these reasons, further research was carried out, especially on the decomposition pathway of DAST. The understanding of this pathway led to the development of morpholinosulphurtrifluoride, MOST for short. This provided a less dangerous alternative to DAST.

Last but not least more research paid off in the discover of Deoxofluor [bis(2 methoxyethyl)aminosulfur trifluoride] in 1999. The slower decomposition of deoxofluor not only made it much safer, but also the production of less heat proved to be an advantage especially for the use of larger, practical scales. In this way, using it to convert carboxyl groups in CF3, it must be heated for an extended period of time to temperatures around 85-90°C.

The good thermal stability of deoxofluor results in the influence of an ether oxygen from the side chain to the sulfur center with an electron deficiency. This performs with a good

kinetic stabilization. [43] All these reactions with deoxofluor are normally performed with an inert solvent, like methylene chloride and are leading to transform carboxylic acids to trifluormethyl derivates, aldehydes or ketones to gem-difluorides or just simple alcohols into alkyl fluorides. [44]



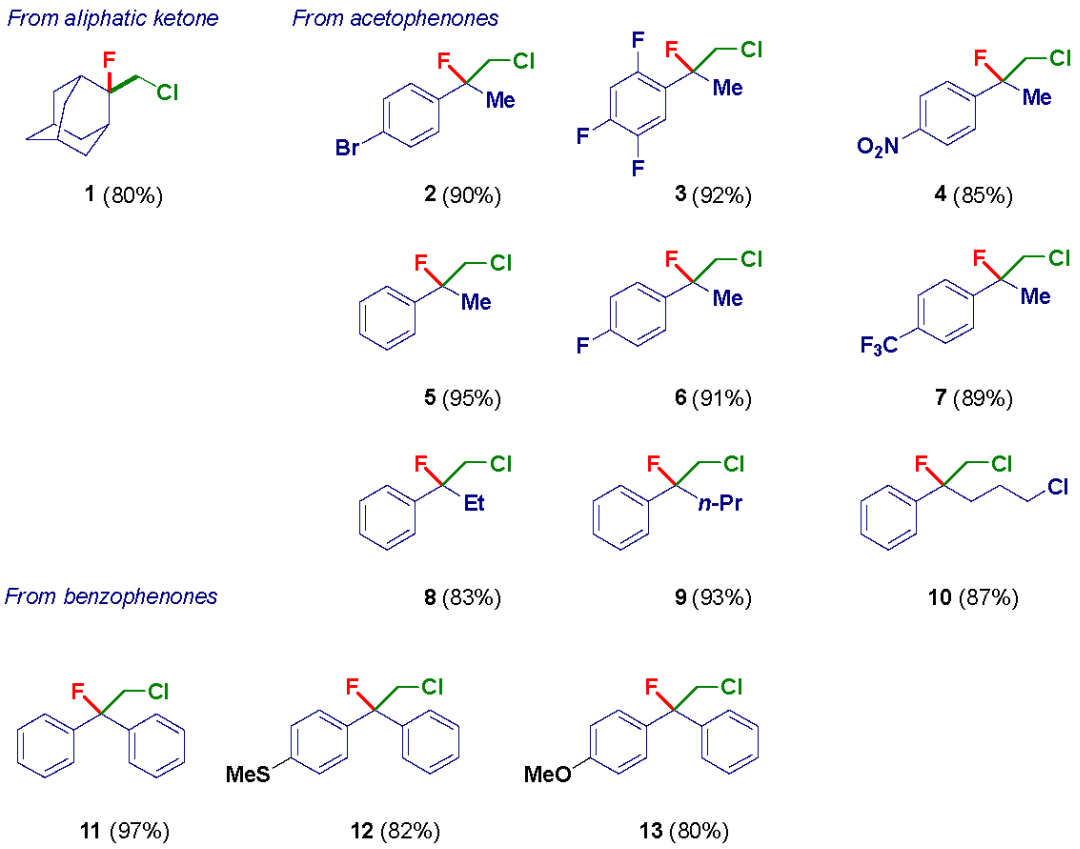

*Scheme 15 gem-Difluorination of benzophenones with Deoxofluor under neat conditions*

On the one hand we can see all the advantages like the one step fluorine integration in an organic framework and the easy production. On the other hand there are still some impairments like there were with $SF_4$. But because of the easy one step reaction for the integration of fluor and the above mentioned advantages, deoxofluor made its way to one of the more commonly used reagents.

# 2.Thesis project

The research team led by Vittorio Pace, had set itself the task of developing new synthetic methodologies for accessing various fluorinated compounds. Using the already optimized condition for the correct preparation of chlorolithium carbenoids, *via* lithium-halogen exchange using MeLi-LiBr and chloroiodomethane in dry THF at -78°C, a variety of halohydrines were obtained starting from the corresponding ketones. These species served as an intermediate for the subsequent functionalization on the $sp^3$ carbon upon treatment with deoxofluor. The substitution of the OH group of the halohydrines with the fluorine atom, operated by deoxofluor, led to our intended fluorinated compounds.

To examine the scope of the method we conducted the reaction on a variety of functionalized ketones. We observed excellent chemoselectivity, even with challenging substrates. A detailed overview of the scope of the reaction is shown in scheme 16. Finally, we were able to isolate the obtained compounds in very good yields and whenever additional purification was necessary it was carried out *via* column chromatography on grade IV neutral alumina to prevent any possible degradation.




Scheme 16. Scope of reactions

# 3. Conclusion

Due to the well-known instability of lithium carbenoids, they have always been a challenge in the field of organic chemistry and historically have caused limitations and leakage for new strategies in this area. Fortunately, the understanding of the mechanisms has led to far more versatile methods. After our optimization work, we were able to create our requested homologated-monofluorinated compound from a variety of different ketones. The scope of the reaction is shown in scheme 16.

We were able to demonstrate, that ketones containing electron-withdrawing as well as electron-donating substituents on the aromatic ring and various halogens in different positions (**2,3,6**) or even pseudo halogens performed an excellent reaction. Substrates with sterically hindered substituent (**1**) as well as in one case with methylthio functionality increasing the pi-orbital expansion on the ring and thus possibility of hindering the electrophilic ketone moiety did not influence the expected reaction (**12**). We succeeded

with the full implementation of the starting material and also without any detectable by-products.

# 4. Experimental section

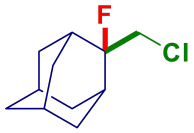
### Materials and methods

Melting Points were determined on a Reichert-Kofler hot-stage microscope and are uncorrected. Mass spectra were obtained on a Shimadzu QP 1000 instrument (EI, 70 eV) and on a Bruker maXis 4G instrument (ESI-TOF, HRMS). $^{1}H$, $^{13}C$ and $^{19}F$ NMR spectra were recorded at 297 K on a Bruker Avance III 400 spectrometer (400 MHz for $^{1}H$, 100 MHz for $^{13}C$, 40 MHz for $^{15}N$, 376 MHz for $^{19}F$) equipped with a directly detecting broadband observe (BBFO) probe, with a Bruker Avance III 500 spectrometer (500 MHz for $^{1}H$, 125 MHz for $^{13}C$) using a Prodigy cryoprobe, and with a Bruker DRX 200 spectrometer (200 MHz for $^{1}H$, 50 MHz for $^{13}C$) with a $^{1}H/^{13}C$ dual probe.
The centre of the solvent signal was used as an internal standard which was related to TMS with δ 7.26 ppm ($^{1}H$ in $CDCl_3$), δ 7.16 ppm ($^{1}H$ in $C_6D_6$), δ 77.00 ppm ($^{13}C$ in $CDCl_3$) and δ 128.06 ppm ($^{13}C$ in $C_6D_6$). Absolute referencing via Ξ ratio was usd for the $^{19}F$ NMR spectra. Spin-spin coupling constants (*J*) are given in Hz.
In nearly all cases, full and unambiguous assignment of all resonances was performed by combined application of standard NMR techniques, such as APT, HSQC, HMBC, HSQC-TOCSY, COSY and NOESY experiments.
All the reactions were carried out under inert atmosphere of argon. THF was distilled over Na/benzophenone. Chemicals were purchased from Sigma-Aldrich, Acros, Alfa Aesar and TCI Europe. Solutions were evaporated under reduced pressure with a rotary evaporator.
TLC was carried out on aluminium sheets precoated with silica gel 60F254 (Merchery-Nagel, Merk); the spots were visualised under UV light (λ = 254 nm).

#### General Procedure 1

To a solution of carbonyl compound (aldehyde or ketone, 1 equiv) in dry THF (3 mL) cooled at -78 °C, the dihalomethane carbenoids precursor was added (1.5 equiv) under Argon atmosphere. After 10 min, MeLi-LiBr 2.2 M solution in $Et_2O$ (1.4 equiv) was added dropwise during a period of 15 min and, then the stirring was continued for additional 0.5 h. Subsequently, a saturated (*aq.*) NaCl was added to the mixture and the cooling bath was removed; the organic phase was extracted with dichloromethane (3 x 3 mL) and, dried over anhydrous $Na_2SO_4$. The filtered solution (1.5 mL) was flushed under argon and Deoxofluor (4.2 equiv) was incorporated to it at room temperature, the reaction was stirred overnight. Finally, the mixture was quenched with saturated (*aq.*) $NH_4Cl$ (3 mL) and extracted with dichloromethane (3 mL). The organic layer was washed with saturated (*aq.*) NaCl (5 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure (bath: rt) to give the crude compound eventually purified as indicated below.

**2-(chloromethyl)-2-fluoroadamantane (1)**



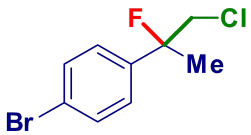

By following the **General procedure 1**, starting from adamantan-2-one (200 mg, 1.3 mmol, 1 equiv) in dry THF (3 mL), iodochoromethane (0.2 mL, 2.0 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in $Et_2O$ (0.9 mL, 1.9 mmol, 1.4 equiv), Deoxofluor 2.7 M solution in (2.1 mL, 5.6 mmol, 4.2 equiv), **compound 1** was obtained in 80% yield (216 mg) as colorless oil after column chromatography on neutral alumina grade IV (*n*-hexane/ ethyl acetate 8:2 as eluent).

**$^1$H NMR** (400 MHz, $C_6D_6$) δ: 4.30 (dd, 1H, $^2J_{H,H}$ = 11.9 Hz, $^3J_{H,H}$ = 27.7 Hz, $CH_2Cl$), 4.06 (dd, 1H, $^2J_{H,H}$ = 11.9 Hz, $^3J_{H,H}$ = 22.2 Hz, $CH_2Cl$), 2.22-1.34 (14H, Ad).

**$^{13}$C NMR** (100 MHz, $C_6D_6$) δ: 97.7 (d, 1C, $^1J_{C,F}$ = 181.8 Hz, CF), 63.9 (d, 1C, $^2J_{C,F}$ = 24.5 Hz, $CH_2Cl$),37.6-27.2 (9C, Ad).

**$^{19}$F NMR** (470 MHz, $C_6D_6$) δ: -151.1 (m, 1F, F-1).

**1-bromo-4-(1-chloro-2-fluoro-2-propanyl) benzene (2)**




By following the **General procedure 1**, starting from 4-Bromo acetophenon (200 mg, 1.0 mmol, 1 equiv) in dry THF (3 mL), iodochloromethane (0.1 mL, 1.7 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in $Et_2O$ (0.6 mL, 1.4 mmol, 1.4 equiv), Deoxofluor 2.7 M solution in (1.6 mL, 4.2 mmol, 4.2 equiv), **compound 2** was obtained in 90% yield (228 mg) as colorless oil without any further purification.

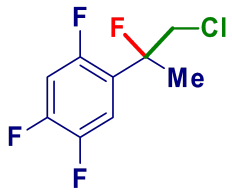
**$^1$H NMR** (400 MHz, $CDCl_3$) δ: 7.53 (m, 2H, Ph H-2,6), 7.26 (m, 2H, Ph H-3,5), 3.78 (dd, 1H, $^3J_{H,F}$ = 17.0 Hz, $^2J_{H,F}$ = 12.1 Hz, $CH_2Cl$), 3.73 (dd, 1H, $^3J_{H,F}$ = 20.5 Hz, $^2J_{H,F}$ = 12.1 Hz, $CH_2Cl$), 1.78 (d, 3H, $^3J_{H,F}$ = 22.1 Hz, $CH_3$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ: 140.4 (d, 1C, $^2J_{C,F}$ = 22.2 Hz, Ph C-4), 131.6 (d, 2C, $^4J_{C,F}$ = 1.2 Hz, Ph C-2,6), 126.3 (d, 2C, $^3J_{C,F}$ = 9.2 Hz, Ph C-3,5), 122.4 (d, 1C, $J_{C,F}$ = 1.7 Hz, Ph C-1), 95.3 (d, 1C, $^1J_{C,F}$ = 179.1 Hz, CF), 51.1 (d, 1C, $^2J_{C,F}$ = 28.7 Hz, $CH_2Cl$), 24.3 (d, 1C, $^2J_{C,F}$ = 24.3 Hz, $CH_3$).

**$^{19}$F NMR** (470 MHz, $CDCl_3$) δ: -150.0 (ddq, 1F, $^2J_{H,F}$ = 22.1 Hz, $^3J_{H,F}$ = 20.5 Hz, $^3J_{H,F}$ = 17.0 Hz, F-1).

**EI-MS m/z (%):** 251.0 ($M^+$, 30), 202.0 ($M^+$, 100), 122.0 ($M^+$, 99), 75.0 ($M^+$, 29).

**1-(1-chloro-2-fluoro-2-propanyl) -2,4,5-trifluorobenzene (3)**



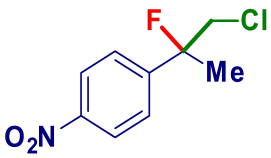

By following the **General procedure 1**, starting from 2,4,5-trifluoro acetophenon (200 mg, 1.5 mmol, 1 equiv) in dry THF (3 mL), iodochloromethane (0.1 mL, 1.7 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in $Et_2O$ (0.7 mL, 1.6 mmol, 1.4 equiv), Deoxofluor 2.7 M solution in (1.8 mL, 4.8 mmol, 4.2 equiv), **compound 3** was obtained in 92% yield (239 mg) as colorless oil without any further purification.

**$^1$H NMR** (400 MHz, $C_6D_6$) δ: 7.15 (m, 1H, Ph H-6), 6.25 (m, 1H, Ph H-3), 3.52-3.36 (m, 2H, $CH_2Cl$), 1.35 (dd, 3H, $^3J_{H,F}$ = 22.5 Hz, $^4J_{H,H}$ = 1.4 Hz, $CH_3$).

**$^{13}$C NMR** (100 MHz, $C_6D_6$) δ: 153.2, 150.0, 147.2 (dddd, 3C, Ph C-2,4,5), 125.4 (m, 1C, Ph C-1), 126.3 (d, 2C, $^3J_{C,F}$ = 9.2 Hz, Ph C-3,5), 122.4 (d, 1C, $J_{C,F}$ = 1.7 Hz, Ph C-1), 115.8 (dddd, 1C, $^2J_{C,F}$ = 21.4 Hz, $^3J_{C,F}$ = 16.6 Hz, $^3J_{C,F}$ = 5.5 Hz, $^3J_{C,F}$ = 1.4 Hz, Ph C-6), 106.2 (m, 1C, Ph C-3), 93.8 (ddt, 1C, $^1J_{C,F}$ = 183.1 Hz, $^3J_{C,F}$ = 4.9 Hz, $^3J_{C,F}$ = 0.6 Hz, CF), 49.2 (ddd, 1C, $^2J_{C,F}$ = 25.1 Hz, $^4J_{C,F}$ = 5.0 Hz, $^4J_{C,F}$ = 1.0 Hz, $CH_2Cl$), 23.6 (ddd, 1C, $^2J_{C,F}$ = 24.2 Hz, $^4J_{C,F}$ = 3.8 Hz, $^3J_{C,F}$ = 0.8 Hz, $CH_3$).

**$^{19}$F NMR** (470 MHz, $C_6D_6$) δ: -147.9, -141.6, -133,7, -117.2 (m, 4F, F-1, Ph F-2,4,5).

**1-(1-chloro-2-fluoro-2-propanyl)-4-nitrobenzene (4)**




By following the **General procedure 1**, starting from 4-Nitro acetophenon (200 mg, 1.2 mmol, 1 equiv) in dry THF (3 mL), iodochloromethane (0.1 mL, 1.8 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in $Et_2O$ (0.8 mL, 1.7 mmol, 1.4 equiv), Deoxofluor 2.7 M solution in (1.9 mL, 5.1 mmol, 4.2 equiv), **compound 4** was obtained in 85% yield (224 mg) as colorless oil without any further purification.

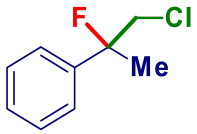
**$^1$H NMR** (400 MHz, $CDCl_3$) δ: 7.74 (m, 2H, Ph H-3,5), 6.65 (m, 2H, Ph H-2,6), 3.17-3.05 (m, 2H, $CH_2Cl$), 1.20 (d, 3H, $^3J_{H,F}$ = 21.9 Hz, $CH_3$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ: 147.9 (1C, Ph C-4), 147.7 (d, 1C, $^2J_{C,F}$ = 22.0 Hz, Ph C-1), 125.5 (d, 2C, $^3J_{C,F}$ = 9.5 Hz, Ph C-2,6), 123.6 (d, 2C, $^4J_{C,F}$ = 1.6 Hz, Ph C-3,5), 95.1 (d, 1C, $^1J_{C,F}$ = 181.5 Hz, CF), 50.5 (d, 1C, $^2J_{C,F}$ = 27.6 Hz, $CH_2Cl$), 24.3 (d, 1C, $^2J_{C,F}$ = 24.2 Hz, $CH_3$).

**$^{19}$F NMR** (470 MHz, $CDCl_3$) δ: -151.2 (m, 1F, F-1).

**EI-MS m/z (%):** 217.0 ($M^+$, 4), 168.0 ($M^+$, 100), 138.0 (M+, 20), 122.0 ($M^+$, 18), 110.0 ($M^+$, 50).

**(1-chloro-2-fluoro-2-propanyl) benzene (5)**

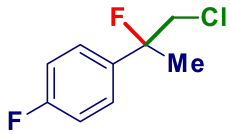



By following the **General procedure 1**, starting from acetophenon (200 mg, 1.7 mmol, 1 equiv) in dry THF (3 mL), iodochloromethane (0.2 mL, 2.5 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in $Et_2O$ (1.1 mL, 2.3 mmol, 1.4 equiv), Deoxofluor 2.7 M solution in (2.6 mL, 7.0 mmol, 4.2 equiv), **compound 5** was obtained in 95% yield (273 mg) as colorless oil without any further purification.
**$^1$H NMR** (400 MHz, $CDCl_3$) δ: 7.40 (m, 4H, Ph H-2,3,5,6), 7.36 (m, 1H, Ph H-4), 3.87-3.70 (m, 2H, $CH_2Cl$), 1.81 (d, 3H, $^3J_{H,F}$ = 22.2 Hz, $CH_3$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ: 141.4 (d, 1C, $^2J_{C,F}$ = 21.7 Hz, Ph C-1), 128.5 (d, 2C, $^4J_{C,F}$ = 1.4 Hz, Ph C-3,5), 128.2 (d, 1C, $^5J_{C,F}$ = 1.3 Hz, Ph C-4), 124.4 (d, 2C, $^3J_{C,F}$ = 9.1 Hz, Ph C-2,6), 95.5 (d, 1C, $^1J_{C,F}$ = 178.5 Hz, CF), 51.6 (d, 1C, $^2J_{C,F}$ = 28.4 Hz, $CH_2Cl$), 24.3 (d, 1C, $^2J_{C,F}$ = 24.4 Hz, $CH_3$).

**$^{19}$F NMR** (470 MHz, $CDCl_3$) δ: -150.4 (m, 1F, F-1).

**1-(1-chloro-2-fluoro-2-propanyl)-4-fluoro benzene (6)**



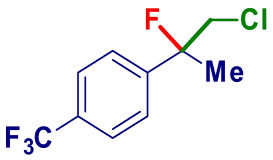

By following the **General procedure 1**, starting from 4-fluoro acetophenon (200 mg, 1.5 mmol, 1 equiv) in dry THF (3 mL), iodochloromethane (0.2 mL, 2.2 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in $Et_2O$ (0.9 mL, 2.0 mmol, 1.4 equiv), Deoxofluor 2.7 M solution in (2.3 mL, 6.1 mmol, 4.2 equiv), **compound 6** was obtained in 91% yield (251 mg) as colorless oil without any further purification.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ: 7.36 (m, 2H, Ph H-2,6), 7.08 (m, 2H, Ph H-3,5), 3.83-3.68 (m, 2H, $CH_2Cl$), 1.79 (d, 3H, $^3J_{H,F}$ = 22.2 Hz, $CH_3$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ: 162.5 (dd, 1C, $^1J_{C,F}$ = 247.2 Hz, $^5J_{C,F}$ = 1.7 Hz, Ph C-4), 137.2 (dd, 1C, $^2J_{C,F}$ = 22.2 Hz, $^4J_{C,F}$ = 3.2 Hz, Ph C-1), 126.4 (t, 2C, $^3J_{C,F}$ = 8.6 Hz, Ph C-2,6), 115.4 (dd, 2C, $^2J_{C,F}$ = 22.5 Hz, $^4J_{C,F}$ = 1.1 Hz, Ph C-3,5), 95.3 (d, 1C, $^1J_{C,F}$ = 178.4 Hz, CF), 51.4 (d, 1C, $^2J_{C,F}$ = 29.0 Hz, $CH_2Cl$), 24.4 (d, 1C, $^2J_{C,F}$ = 24.2 Hz, $CH_3$).

**$^{19}$F NMR** (470 MHz, $CDCl_3$) δ: -148.7 (m, 1F, F-1), -113.9 (m, 1F, Ph F-4).

**1-(1-chloro-2-fluoro-2-propanyl)-4-(trifluoromethyl) benzene (7)**



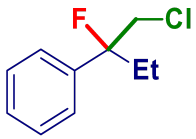

By following the **General procedure 1**, starting from 4-trifluoromethyl acetophenon (200 mg, 1.1 mmol, 1 equiv) in dry THF (3 mL), iodochloromethane (0.1 mL, 1.6 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in $Et_2O$ (0.8 mL, 1.5 mmol, 1.4 equiv), Deoxofluor 2.7 M solution in (1.7 mL, 4.5 mmol, 4.2 equiv), **compound 7** was obtained in 89% yield (228 mg) as colorless oil without any further purification.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ: 7.67 (m, 2H, Ph H-3,5), 7.51 (m, 2H, Ph H-2,6), 3.86-3.73 (m, 2H, $CH_2Cl$), 1.81 (d, 3H, $^{3}J_{H,F}$ = 24.3 Hz, $CH_3$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ: 145.2 (dq, 1C, $^{2}J_{C,F}$ = 22.1 Hz, $^{5}J_{C,F}$ = 1.3 Hz, Ph C-1), 130.5 (dq, 1C, $^{2}J_{C,F}$ = 32.7 Hz, $^{5}J_{C,F}$ = 1.2 Hz, Ph C-4), 125.5 (dq, 2C, $^{3}J_{C,F}$ = 3.8 Hz, $^{4}J_{C,F}$ = 1.2 Hz, Ph C-3,5), 125.0 (d, 2C, $^{3}J_{C,F}$ = 9.5 Hz, Ph C-2,6), 123.9 (q, 1C, $^{1}J_{C,F}$ = 272.2 Hz, $CF_3$), 95.3 (d, 1C, $^{1}J_{C,F}$ = 180.0 Hz, CF), 51.0 (dq, 1C, $^{2}J_{C,F}$ = 28.3 Hz, $^{7}J_{C,F}$ = 0.5 Hz, $CH_2Cl$), 24.6 (d, 1C, $^{2}J_{C,F}$ = 24.3 Hz, $CH_3$).

**$^{19}$F NMR** (470 MHz, $CDCl_3$) δ: -150.7 (m, 1F, F-1), -62.7 (m, 1F, $CF_3$).

**(1-chloro-2-fluoro-2-butanyl) benzene (8)**



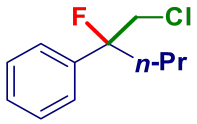

By following the **General procedure 1**, starting from propiophenone (200 mg, 1.5 mmol, 1 equiv) in dry THF (3 mL), iodochloromethane (0.2 mL, 2.2 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in $Et_2O$ (0.9 mL, 2.1 mmol, 1.4 equiv), Deoxofluor 2.7 M solution in (2.3 mL, 6.2 mmol, 4.2 equiv), **compound 8** was obtained in 83% yield (231 mg) as colorless oil without any further purification.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ: 7.10 (m, 4H, Ph H-2,3,5,6), 7.04 (m, 1H, Ph H-4), 3.42-3.37 (m, 2H, $CH_2Cl$), 2.00-1.55 (m, 2H, $CH_2CH_3$), 0.66 (t, 3H, $^{3}J_{H,H}$ = 7.4 Hz, $CH_3$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ: 140.2 (d, 1C, $^{2}J_{C,F}$ = 21.8 Hz, Ph C-1), 128.6 (d, 2C, $^{4}J_{C,F}$ = 1.9 Hz, Ph C-3,5), 128.0 (d, 1C, $^{5}J_{C,F}$ = 1.1 Hz, Ph C-4), 125.2 (d, 2C, $^{3}J_{C,F}$ = 10.0 Hz, Ph C-2,6), 98.0 (d, 1C, $^{1}J_{C,F}$ = 182.4 Hz, CHF), 50.8 (d, 1C, $^{2}J_{C,F}$ = 27.5 Hz, $CH_2Cl$), 30.3 (d, 1C, $^{2}J_{C,F}$ = 23.2 Hz, $CH_2CH_3$), 7.4 (d, 1C, $^{3}J_{C,F}$ = 4.5 Hz, $CH_2CH_3$).

**$^{19}$F NMR** (470 MHz, $CDCl_3$) δ: -164.4 (m, 1F, F-1).

**(1-chloro-2-fluoro-2-pentanyl) benzene (9)**



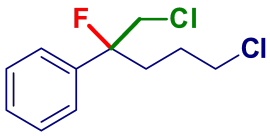

By following the **General procedure 1**, starting from 1-phenylbutan-1-one (200 mg, 1.4 mmol, 1 equiv) in dry THF (3 mL), iodochloromethane (0.2 mL, 2.0 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in $Et_2O$ (0.9 mL, 1.9 mmol, 1.4 equiv), Deoxofluor 2.7 M solution in (2.1 mL, 5.7 mmol, 4.2 equiv), **compound 9** was obtained in 93% yield (252 mg) as colorless oil without any further purification.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ: 7.40 (m, 2H, Ph H-3,5), 7.35 (m, 2H, Ph H-2,6), 7.34 (m, 1H, Ph H-4), 3.83 (d, 2H, $^3J_{H,H}$ = 19.7 Hz, $CH_2Cl$), 2.21-1.93 (m, 2H, $CH_2CH_3$), 1.41-1.16 (m, 2H, $CH_2CH_3$), 0.90 (t, 3H, $^3J_{H,H}$ = 7.4 Hz, $CH_3$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ: 140.1 (d, 1C, $^2J_{C,F}$ = 21.9 Hz, Ph C-1), 128.4 (d, 2C, $^4J_{C,F}$ = 1.8 Hz, Ph C-3,5), 127.9 (d, 1C, $^5J_{C,F}$ = 1.1 Hz, Ph C-4), 124.7 (d, 2C, $^3J_{C,F}$ = 10.0 Hz, Ph C-2,6), 97.7 (d, 1C, $^1J_{C,F}$ = 181.5 Hz, CHF), 50.9 (d, 1C, $^2J_{C,F}$ = 27.5 Hz, $CH_2Cl$), 39.3 (d, 1C, $^2J_{C,F}$ = 22.7 Hz, $CH_2CH_3$), 16.4 (d, 1C, $^3J_{C,F}$ = 3.6 Hz, $CH_2CH_3$), 14.1 (1C, $CH_3$).

**$^{19}$F NMR** (470 MHz, $CDCl_3$) δ: -162.0 (m, 1F, F-1).

**(1,5-dichloro-2-fluoro-2-pentanyl) benzene (10)**




By following the **General procedure 1**, starting from 4-chloro-1-phenylbutan-1-one (200 mg, 1.1 mmol, 1 equiv) in dry THF (3 mL), iodochloromethane (0.1 mL, 1.6 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in $Et_2O$ (0.7 mL, 1.5 mmol, 1.4 equiv), Deoxofluor 2.7 M solution in (1.7 mL, 4.6 mmol, 4.2 equiv), **compound 10** was obtained in 87% yield (224 mg) as colorless oil without any further purification.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ: 7.41 (m, 2H, Ph H-3,5), 7.35 (m, 1H, Ph H-4), 7.34 (m, 2H, Ph H-2,6), 3.84-3.79 (m, 2H, $CH_2Cl$), 3.50 (m, 2H, $CH_2CH_2Cl$), 2.40-2.15 (m, 2H, $CH_2CH_3$), 1.87-1.60 (m, 2H, $CH_2CH_2$).

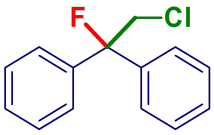
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ: 139.3 (d, 1C, $^2J_{C,F}$ = 21.8 Hz, Ph C-1), 128.6 (d, 2C, $^4J_{C,F}$ = 1.9 Hz, Ph C-3,5), 128.2 (d, 1C, $^5J_{C,F}$ = 1.0 Hz, Ph C-4), 124.7 (d, 2C, $^3J_{C,F}$ = 10.0 Hz, Ph C-2,6), 97.4 (d, 1C, $^1J_{C,F}$ = 182.4 Hz, CHF), 51.0 (d, 1C, $^2J_{C,F}$ = 27.6 Hz, $CH_2Cl$), 44.8 (1C, $CH_2Cl$), 34.3 (d, 1C, $^2J_{C,F}$ = 22.5 Hz, $CH_2CH_2$), 26.3 (d, 1C, $^3J_{C,F}$ = 3.1 Hz, $CH_2CH_2CH_2$).

**$^{19}$F NMR** (470 MHz, $CDCl_3$) δ: -162.6 (m, 1F, F-1).

**EI-MS m/z (%):** 185.0 ($M^+$, 87), 137.0 (M+, 13), 129.0 ($M^+$, 100).

**From Benzophenon**

**1,1'-(2-chloro-1-fluoro-1,1-ethanediyl) dibenzene (11)**



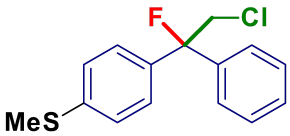

By following the **General procedure 1**, starting from benzophenone (200 mg, 1.1 mmol, 1 equiv) in dry THF (3 mL), iodochoromethane (0.1 mL, 1.6 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in $Et_2O$ (0.7 mL, 1.5 mmol, 1.4 equiv), Deoxofluor 2.7 M solution in (1.7 mL, 4.6 mmol, 4.2 equiv), **compound 11** was obtained in 97% yield (250 mg) as colorless oil after column chromatography on neutral alumina grade IV (*n*-hexane/ diethyl ether 9:1 as eluent).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ: 7.40 (m, 4H, Ph H-2,2,6,6), 7.39 (m, 4H, Ph H-3,3,5,5), 7.35 (m, 2H, Ph H-4,4), 4.24 (d, 2H, $^3J_{H,F}$ = 21.0 Hz, $CH_2Cl$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ: 140.4 (d, 2C, $^2J_{C,F}$ = 23.2 Hz, ph C-1,1), 128.5 (m, 2C, Ph C-4,4), 128.4 (d, 4C, $^4J_{C,F}$ = 0.8 Hz, ph C-3,3,5,5), 125.8 (d, 4C, $^3J_{C,F}$ = 7.8 Hz, ph C-2,2,6,6), 97.7 (d, 1C, $^1J_{C,F}$ = 182.4 Hz, CHF), 49.4 (d, 1C, $^2J_{C,F}$ = 25.6 Hz, $CH_2Cl$).

**$^{19}$F NMR** (470 MHz, $CDCl_3$) δ: -150.0 (t, $^3J_{H,F}$ = 21.0 Hz, 1F, F-1).

**1-(2-chloro-1-fluoro-1-phenylethyl)-4-(methylsulfanyl) benzene (12)**




By following the **General procedure 1**, starting from 4-(methylsulfanyl) benzophenone (200 mg, 0.9 mmol, 1 equiv) in dry THF (3 mL), iodochoromethane (0.1mL, 1.3 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in $Et_2O$ (0.6 mL, 1.2 mmol, 1.4 equiv), Deoxofluor 2.7 M solution in (1.4 mL, 3.7 mmol, 4.2 equiv), **compound 12** was obtained in 82% yield (202 mg) as colorless oil after column chromatography on neutral alumina grade IV (*n*-hexane/ diethyl ether 8:2 as eluent).

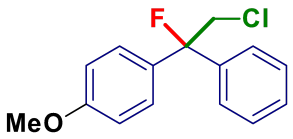
**$^1$H NMR** (400 MHz, $CDCl_3$) δ: 7.33-7.39 (m, 5H, Ph1 H-2,3,4,5,6), 7.30 (m, 2H, Ph2 H-2,6), 7.24 (m, 2H, Ph2 H-3,5), 4.21 (d, 2H, $^3J_{H,H}$ = 20.8 Hz, $CH_2F$), 2.48 (s, 3H, $SCH_3$).

**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ: 140.1 (d, 1C, $^2J_{C,F}$ = 23.2 Hz, ph1 C-1), 139.3 (d, 1C, $^5J_{C,F}$ = 1.8 Hz, ph2 C-4), 136.8 (d, 1C, $^2J_{C,F}$ = 23.6 Hz, $^3J_{C,F}$ = 2.7 Hz, ph2 C-1), 128.52 (d, 1C, $^5J_{C,F}$ = 1.7 Hz, Ph1 C-4), 128.46 (2C, Ph1 C-3,5), 126.4 (d, 2C, $^3J_{C,F}$ = 7.5 Hz, Ph2 C-2,6), 126.1 (2C, Ph2 C-3,5), 125.8 (d, 2C, $^3J_{C,F}$ = 7.6 Hz, Ph1 C-2,6), 97.6 (d, 1C, $^1J_{C,F}$ = 182.2 Hz, CHF), 49.3 (d, 1C, $^2J_{C,F}$ = 27.0 Hz, $CH_2Cl$), 15.4 (1C, $SCH_3$).

**$^{19}$F NMR** (470 MHz, $CDCl_3$) δ: -149.1 (t, $^3J_{H,F}$ = 20.8 Hz, 1F, F-1).

**HRMS (ESI)**, *m/z*: calcd. for $C_{15}H_{14}ClFSNa^+$: 303.0381 $[M+Na]^+$; found:241.0802.

**1-(2-chloro-1-fluoro-1-phenylethyl)-4-methoxybenzene (13)**




By following the **General procedure 1**, starting from 4-methoxybenzophenone (200 mg, 0.9 mmol, 1 equiv) in dry THF (3 mL), iodochoromethane (0.1 mL, 1.4 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in $Et_2O$ (0.6 mL, 1.3 mmol, 1.4 equiv), Deoxofluor 2.7 M solution in (1.5 mL, 4.0 mmol, 4.2 equiv), **compound 13** was obtained in 80% yield (200 mg) as colorless oil after column chromatography on neutral alumina grade IV (*n*-hexane/diethyl ether 8:2 as eluent).

**$^1$H NMR** (400 MHz, $CDCl_3$) δ: 7.39 (m, 4H, Ph1 H-2,3,5,6), 7.36 (m, 1H, Ph1 H-4), 7.31 (m, 2H, Ph2 H-2,6), 6.90 (m, 2H, Ph2 H-3,5), 4.24-4.19 (m, 2H, $CH_2Cl$), 3.81 (s, 3H, $OCH_3$).

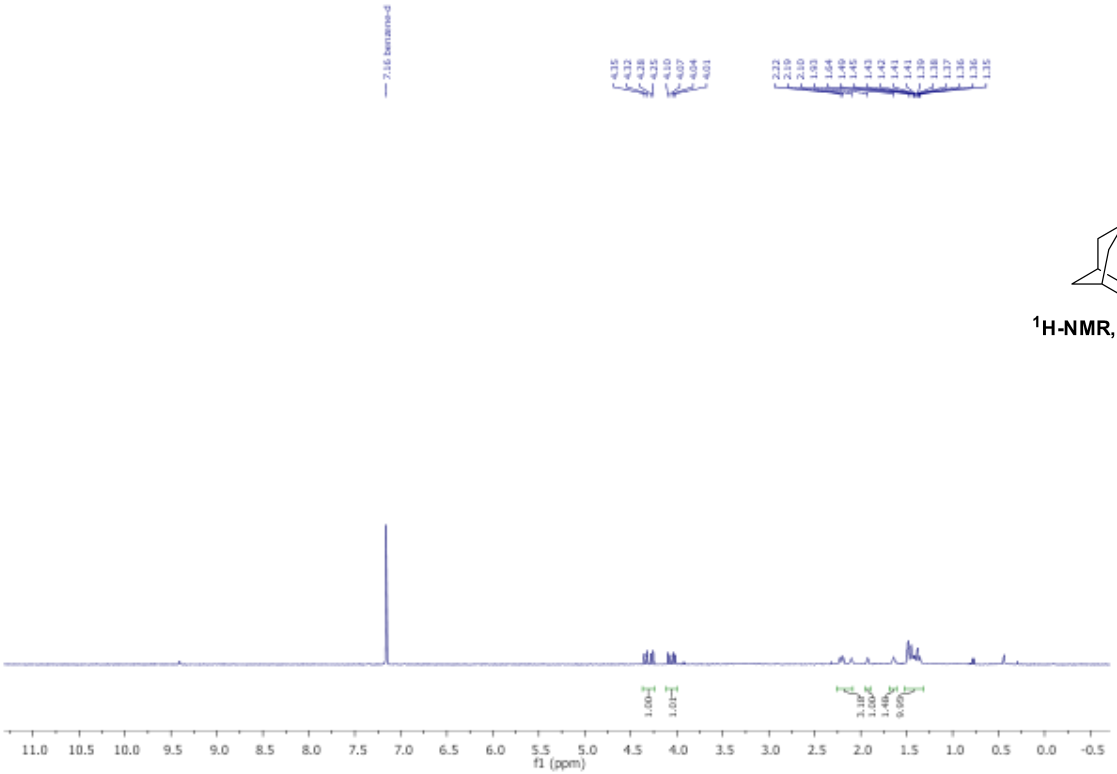
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ: 159.6 (d, 1C, $^5J_{C,F}$ = 1.8 Hz, ph2 C-4), 140.4 (d, 1C, $^2J_{C,F}$ = 23.3 Hz, ph1 C-1), 132.3 (d, 1C, $^3J_{C,F}$ = 23.7 Hz, ph2 C-1), 128.36 (d, 2C, $^4J_{C,F}$ = 0.6 Hz, ph1 C-3,5), 128.34 (1C, Ph1 C-4), 127.4 (d, 4C, $^3J_{C,F}$ = 7.2 Hz, Ph2 C-2,6, $^3J_{C,F}$ = 7.1 Hz, Ph1 C-2,6), 113.7 (2C, Ph2 C-3,5), 97.7 (d, 1C, $^1J_{C,F}$ = 181.5 Hz, CHF), 55.2 (1C, $OCH_3$), 49.5 (d, 1C, $^2J_{C,F}$ = 27.2 Hz, $CH_2Cl$).

**$^{19}$F NMR** (470 MHz, $CDCl_3$) δ: -147.3 (t, $^3J_{H,F}$= 20.7 Hz, 1F, F-1).

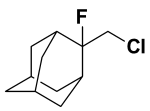
**EI-MS m/z (%):** 245.9 ($M^+$, 36), 244.0 ($M^+$, 100), 209.0 (M+, 59), 165.0 ($M^+$, 73).

### 1.1. $^{1}$H-, $^{13}$C- AND $^{19}$F-NMR SPECTRA FOR ALL THE COMPOUNDS

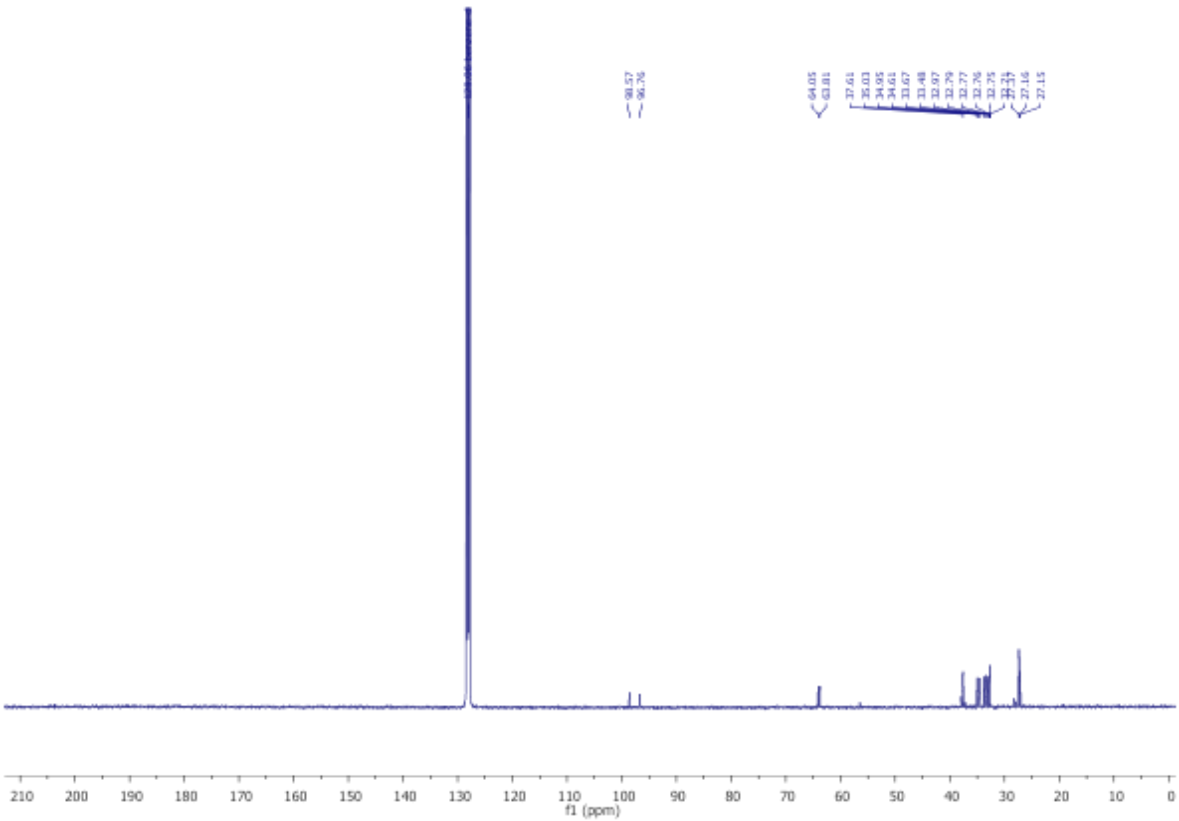
Compound 1

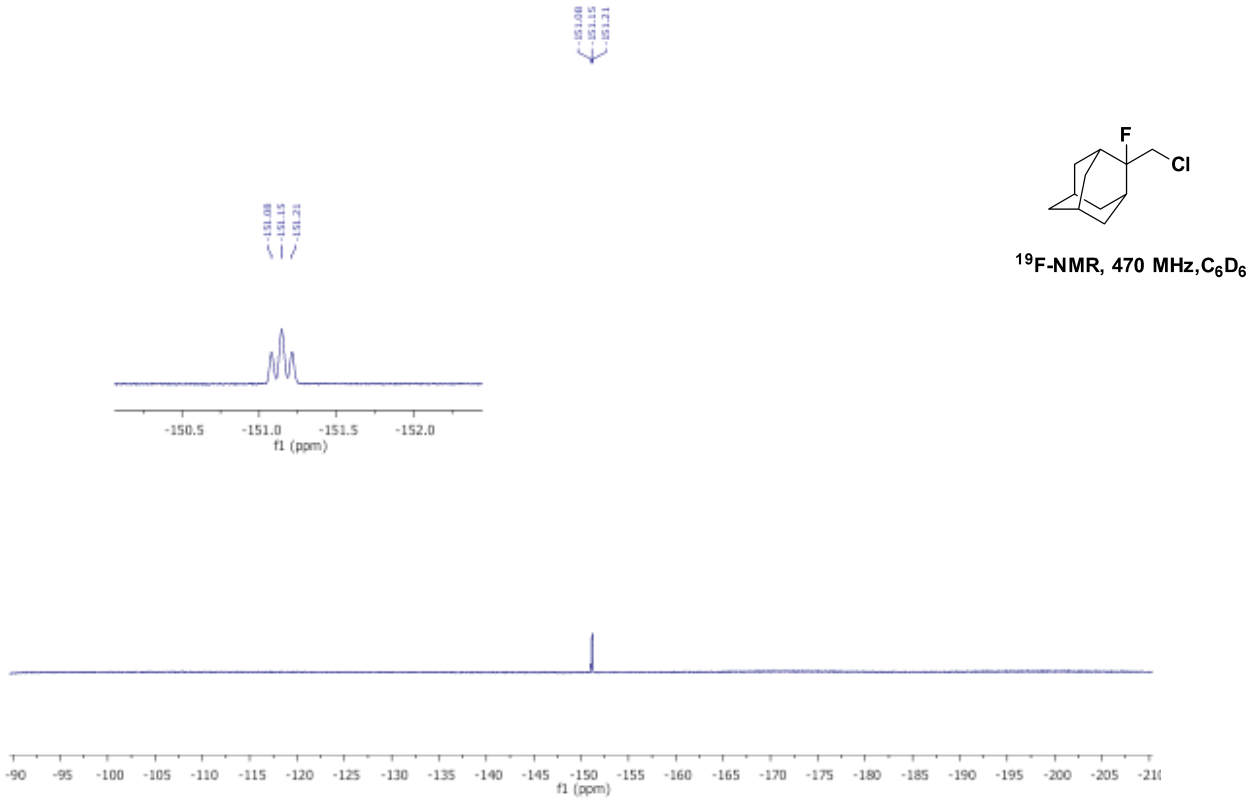



**$^{1}$H-NMR, 400 MHz,$C_6D_6$**



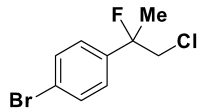

**$^{13}$C-NMR, 100 MHz,$C_6D_6$**


98.57
96.76
64.05
63.81
37.61
35.03
34.95
34.61
33.67
33.48
32.97
32.79
32.77
32.76
32.75
29.33
29.31
27.16
27.15
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

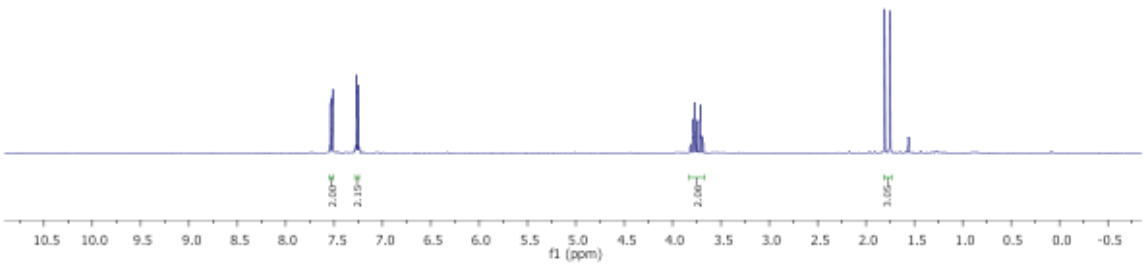


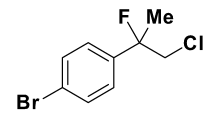

**$^{19}$F-NMR, 470 MHz,$C_6D_6$**

Compound 2

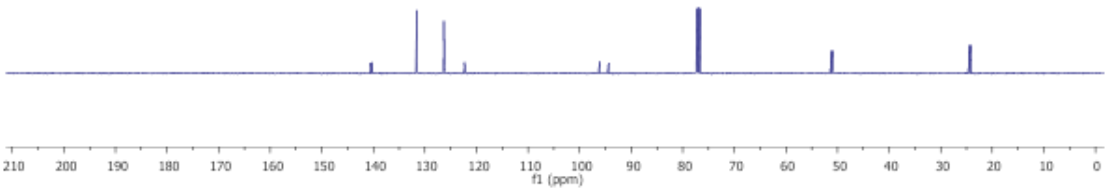


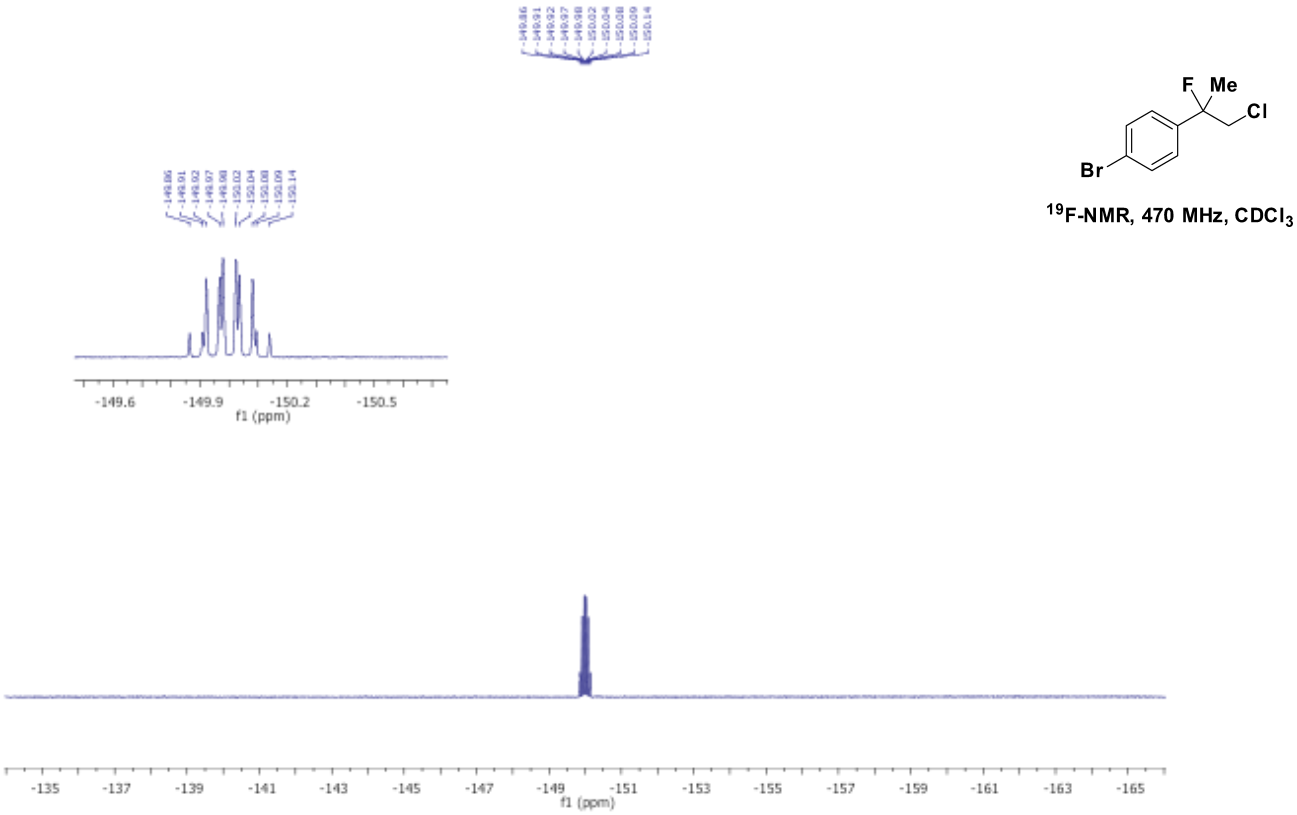

**1H-NMR, 400 MHz, CDCl3**



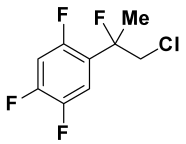

**$^{13}$C-NMR, 100 MHz, $CDCl_3$**



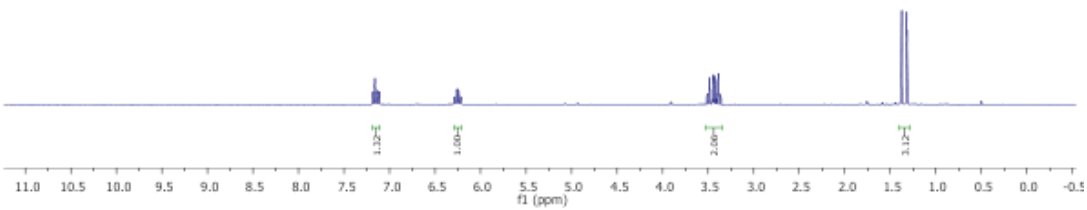


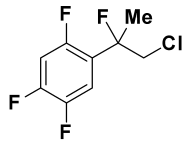

**$^{19}$F-NMR, 470 MHz, $CDCl_3$**

Compound 3

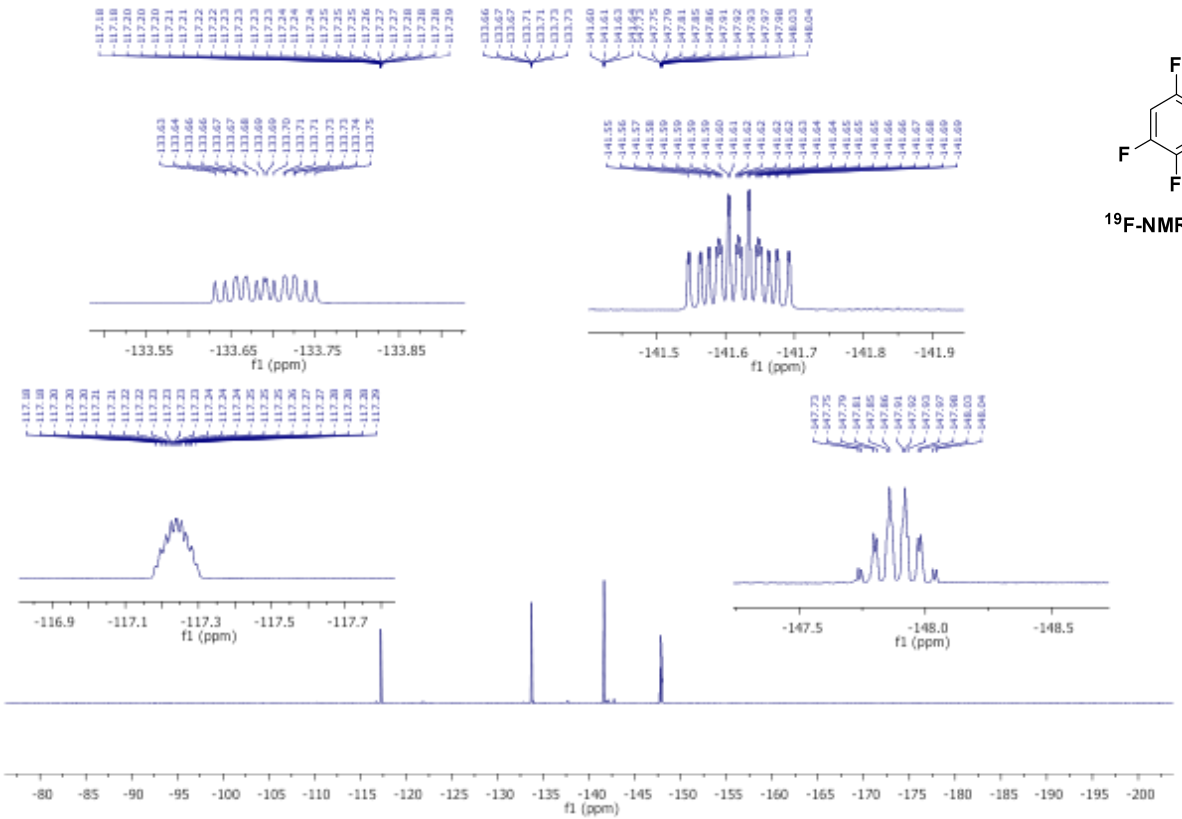


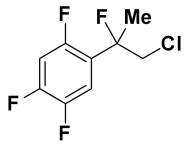

**$^{1}$H-NMR, 400 MHz,$C_6D_6$**





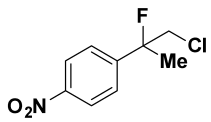

**$^{13}$C-NMR, 100 MHz,$C_6D_6$**



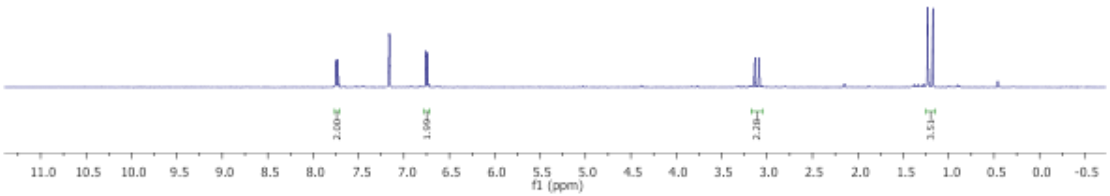



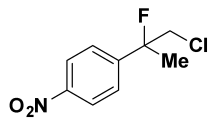

**$^{19}$F-NMR, 470 MHz,$C_6D_6$**

Compound 4

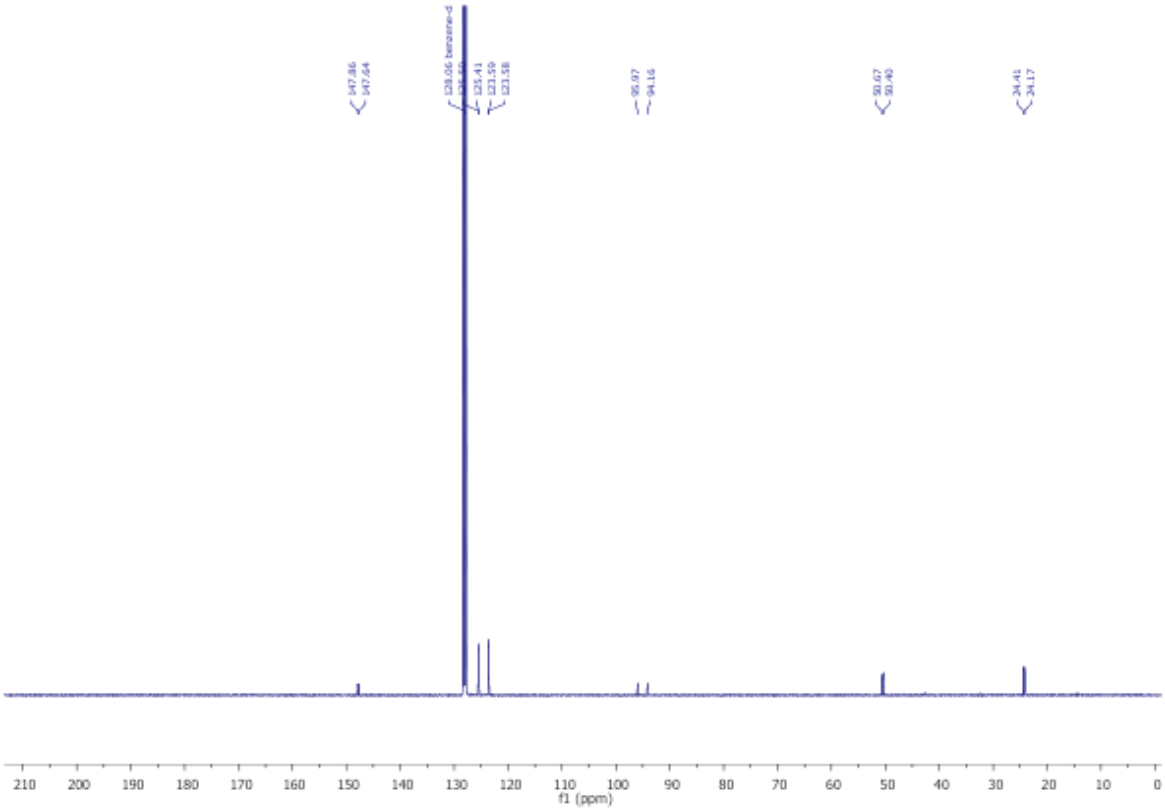


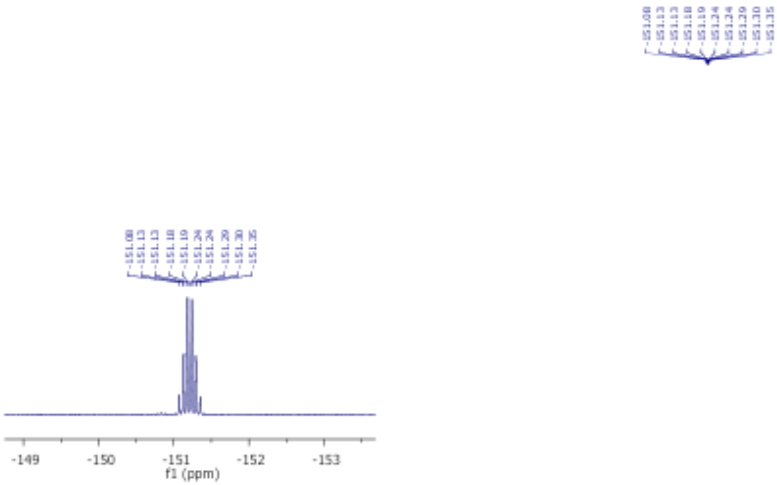

$^{1}$H-NMR, 400 MHz,$C_6D_6$



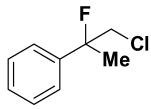

$^{13}$C-NMR, 100 MHz,$C_6D_6$


147.86
147.64
128.06 benzene-d
125.41
123.59
123.58
95.97
94.16
50.67
50.48
24.41
24.17
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

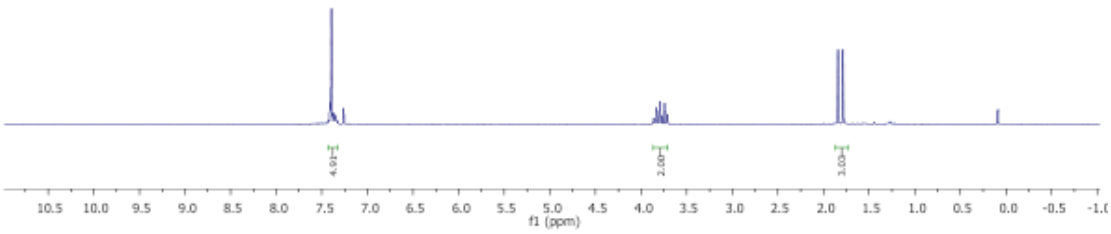


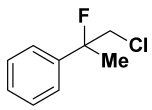

**$^{19}$F-NMR, 470 MHz,$C_6D_6$**

Compound 5

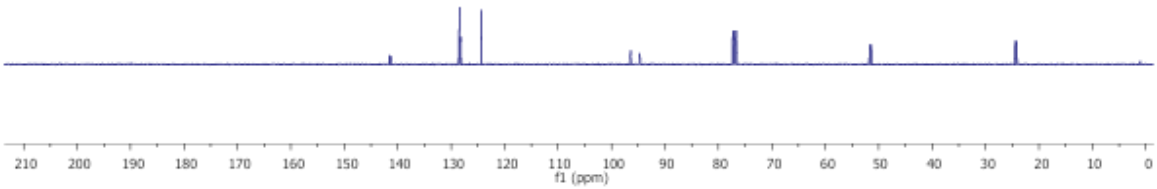


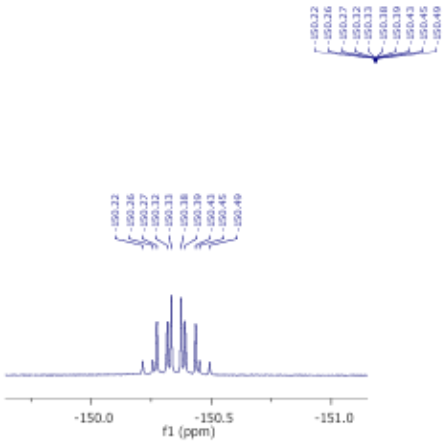

**1H-NMR, 400 MHz, CDCl3**

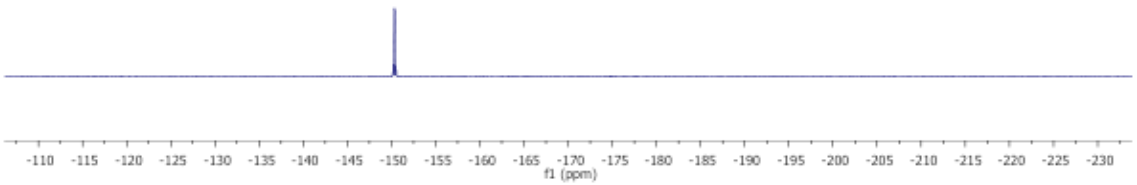


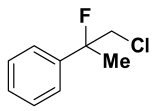




**$^{13}$C-NMR, 100 MHz, $CDCl_3$**



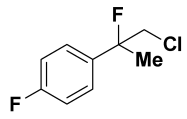


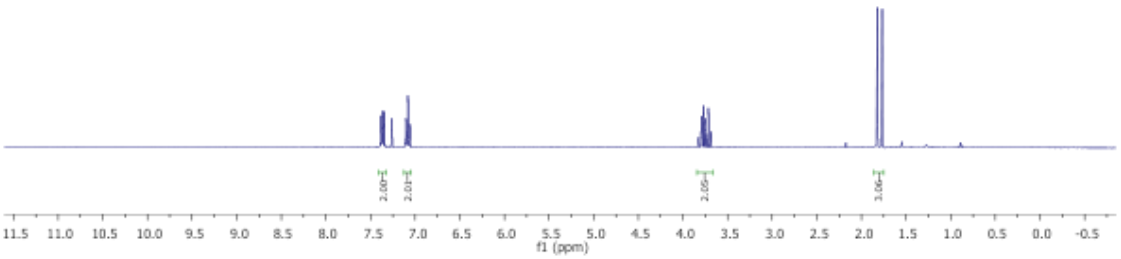



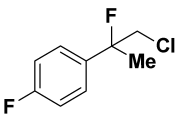

**$^{19}$F-NMR, 470 MHz, $CDCl_3$**

Compound 6

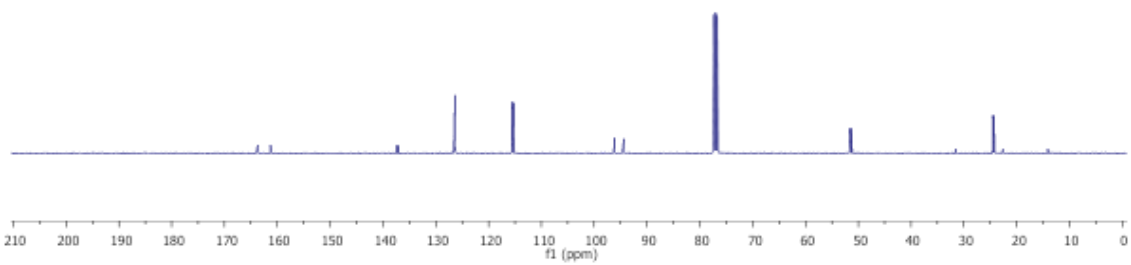


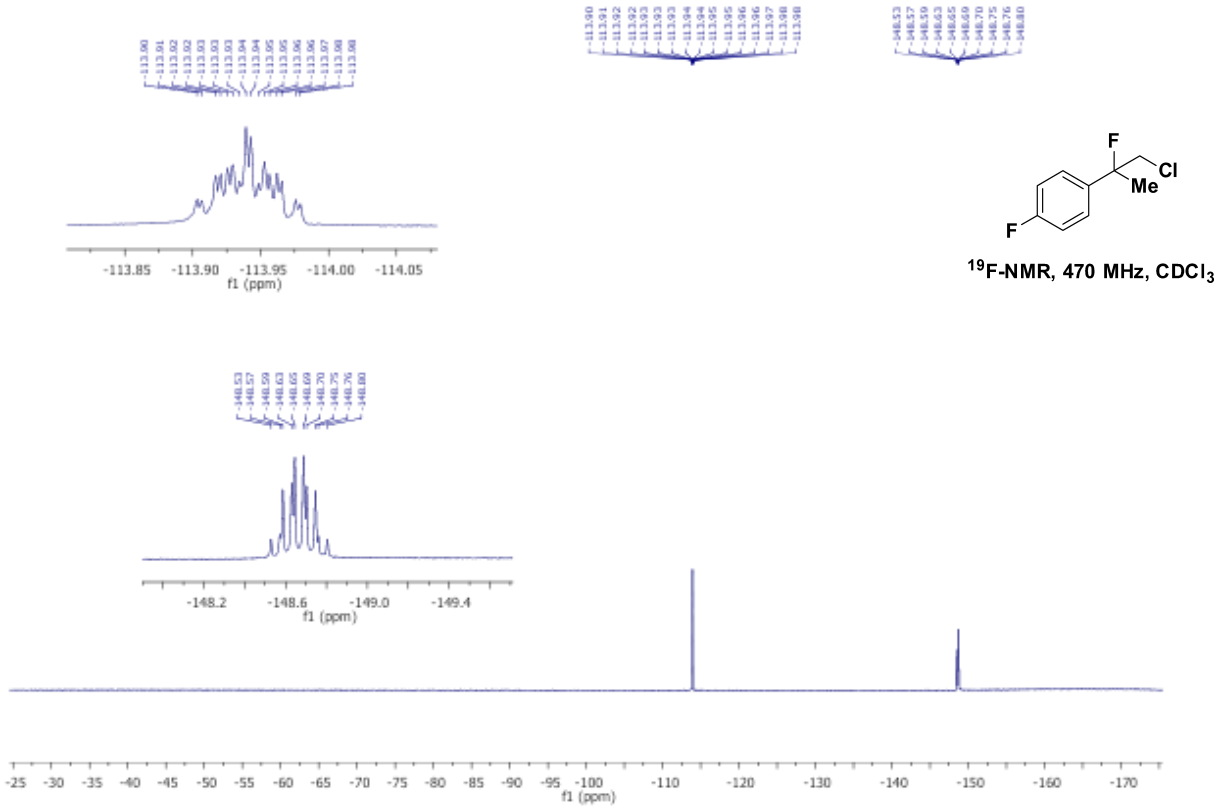

**1H-NMR, 400 MHz, CDCl3**



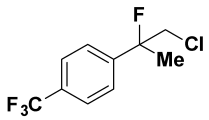

**$^{13}$C-NMR, 100 MHz, $CDCl_3$**



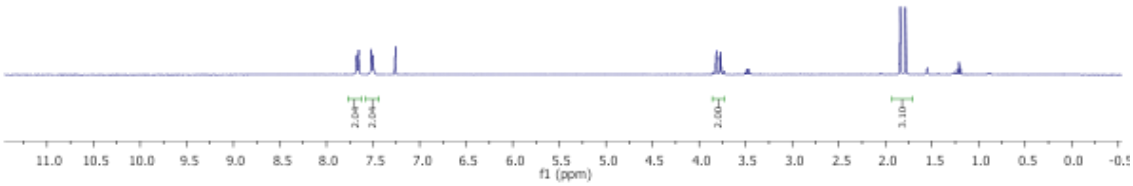


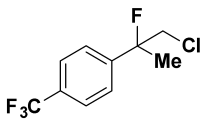

**$^{19}$F-NMR, 470 MHz, $CDCl_3$**

Compound 7

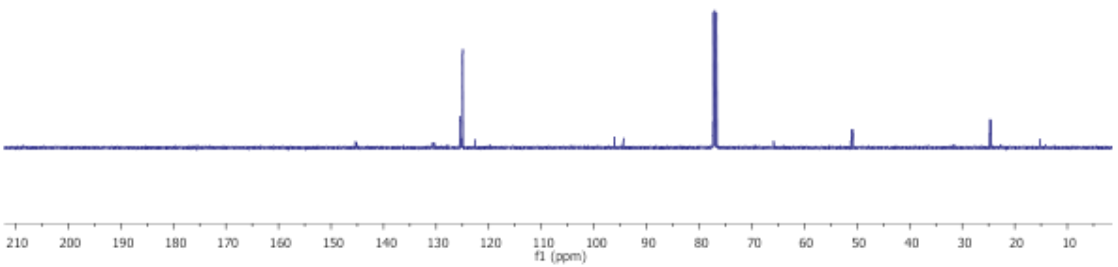


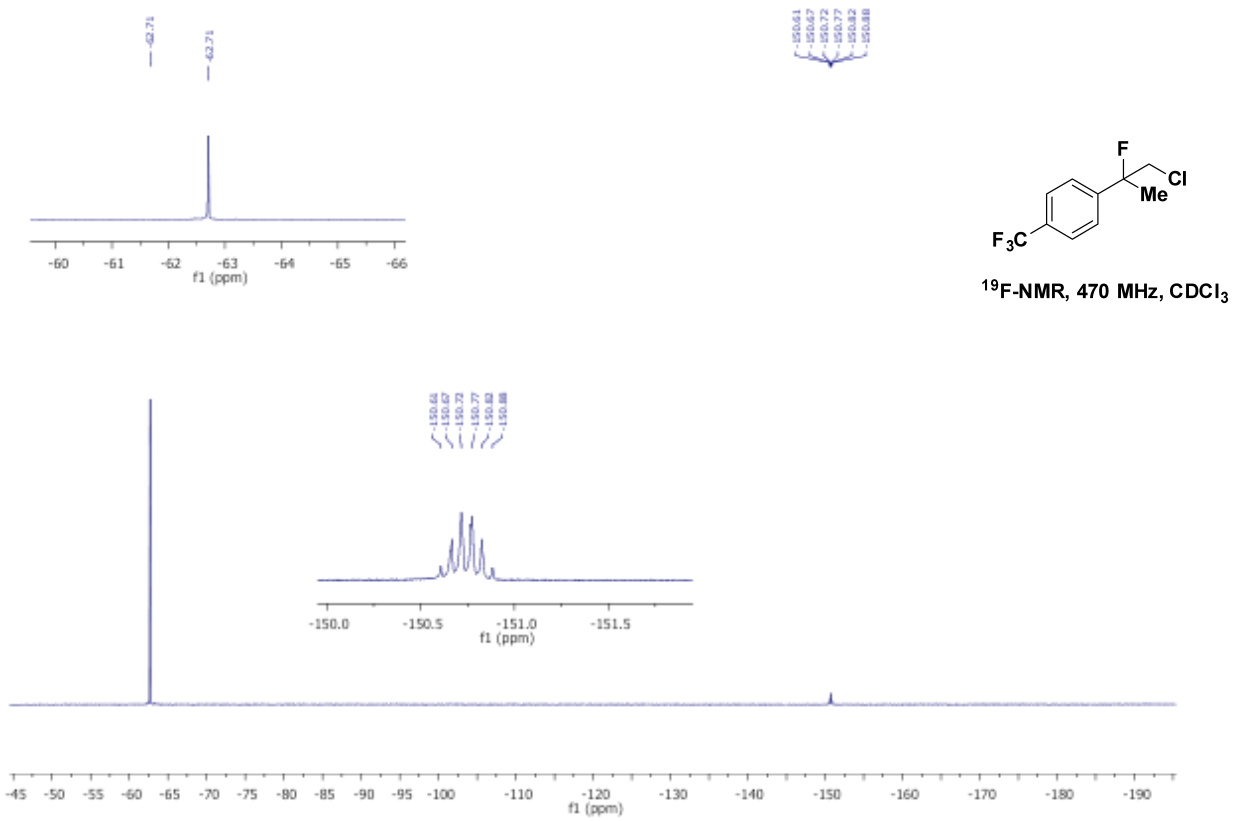

**1H-NMR, 400 MHz, CDCl3**



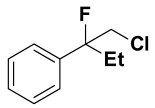

**$^{13}$C-NMR, 100 MHz, $CDCl_3$**



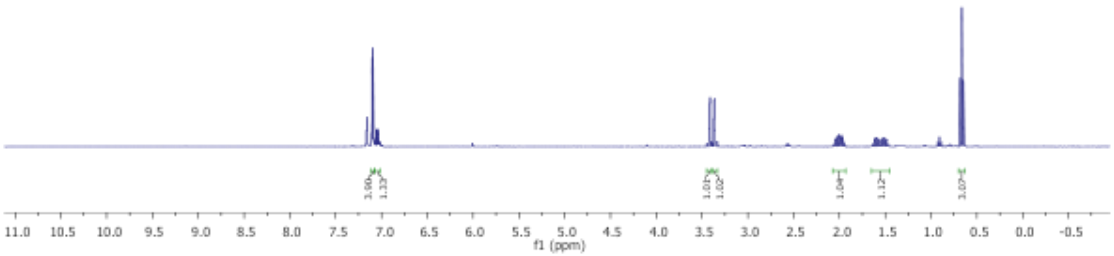


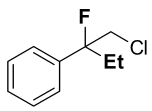

**$^{19}$F-NMR, 470 MHz, $CDCl_3$**

Compound 8

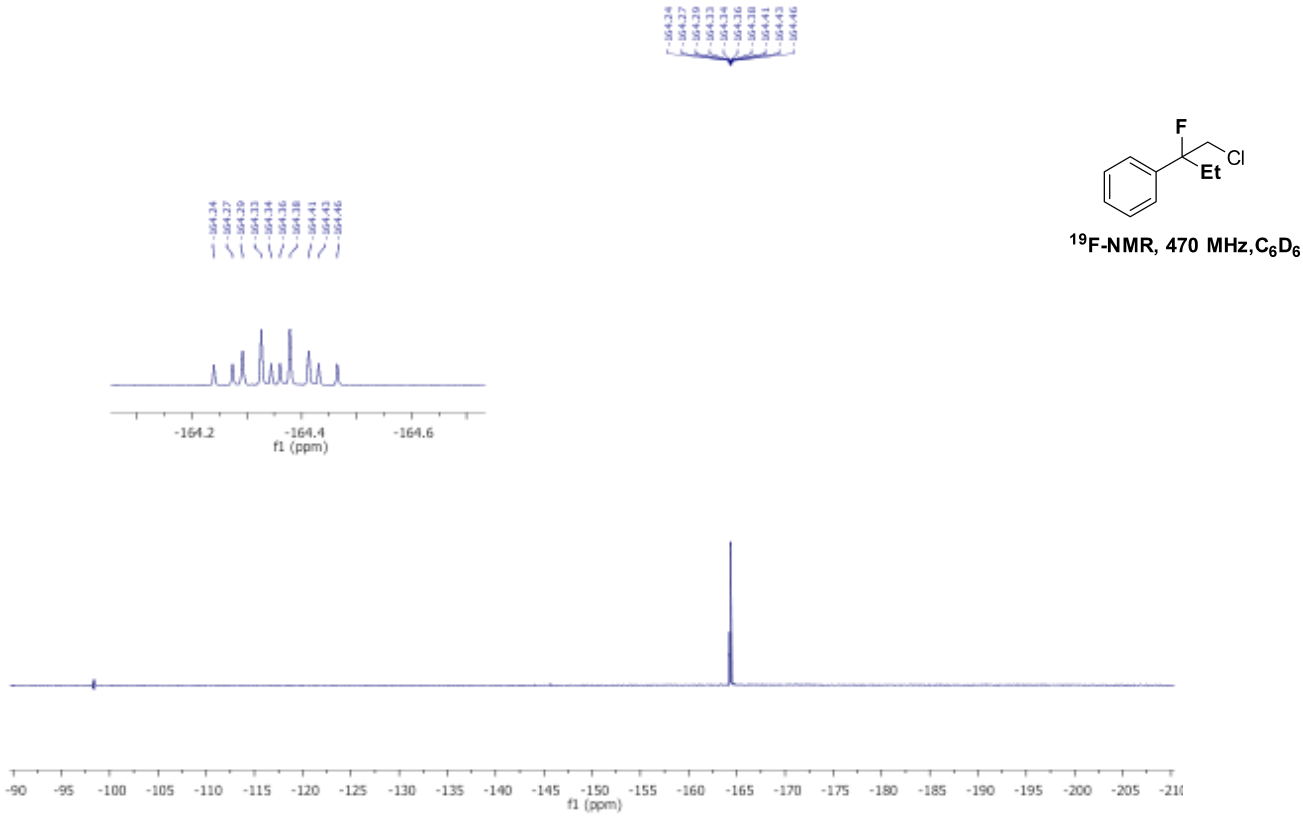



**1H-NMR, 400 MHz, $C_6D_6$**



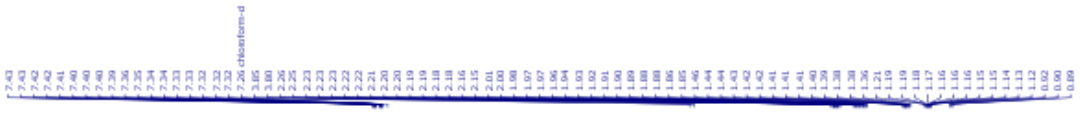



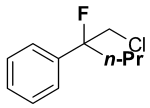

**$^{13}$C-NMR, 100 MHz,$C_6D_6$**



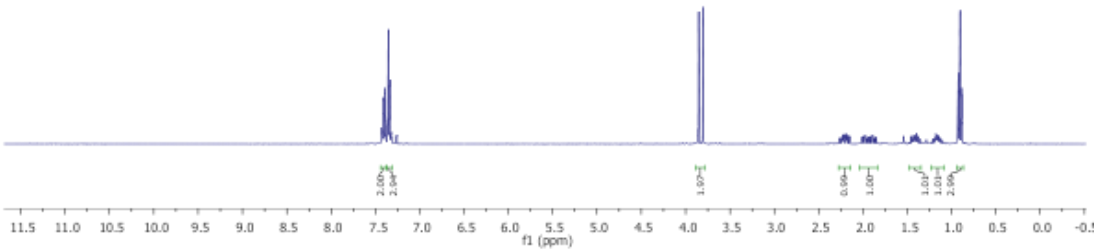

**$^{19}$F-NMR, 470 MHz, $C_6D_6$**

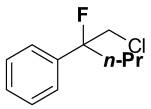
Compound 9



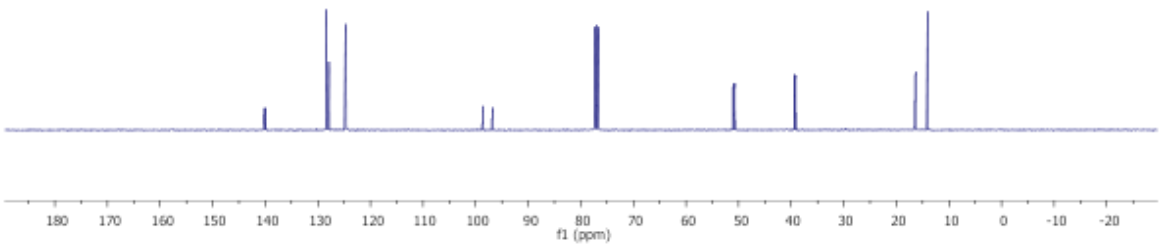


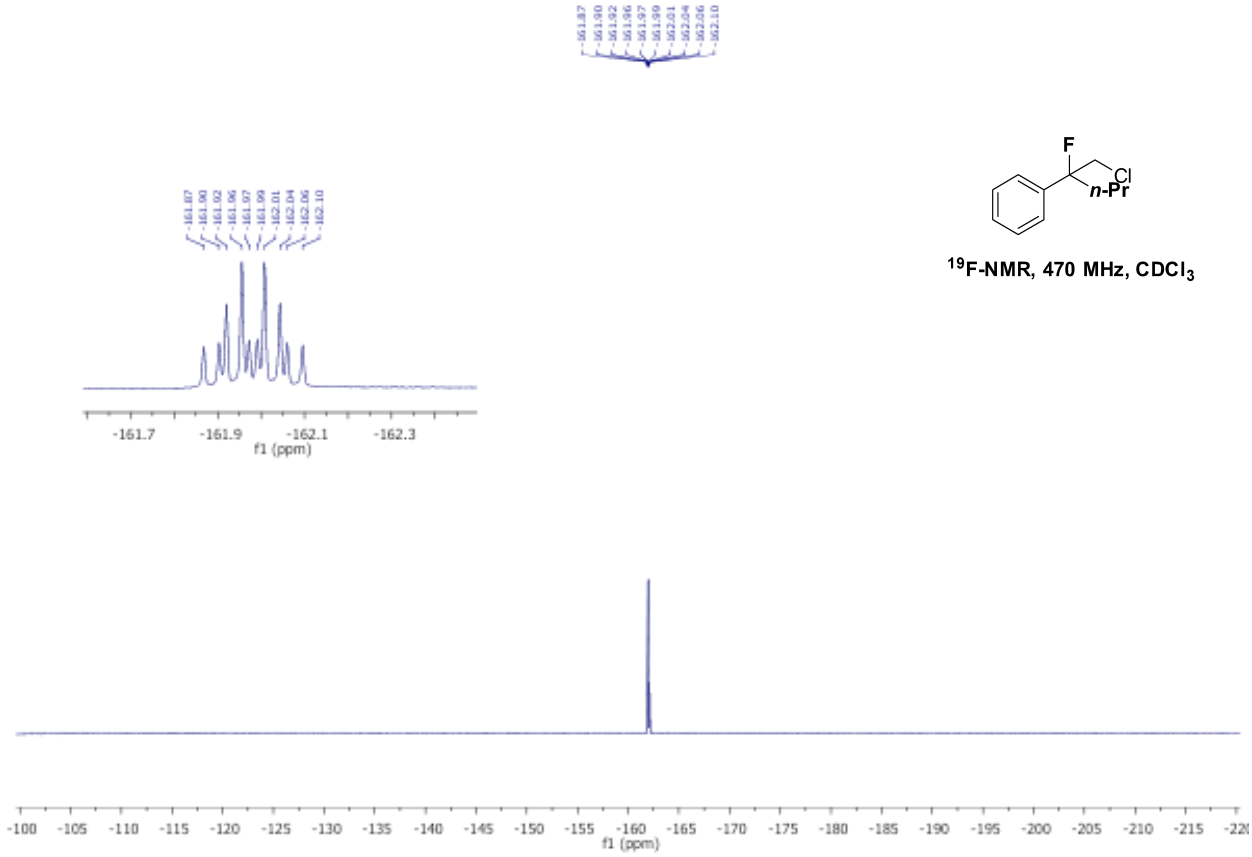

**$^{1}$H-NMR, 400 MHz, CDCl3**





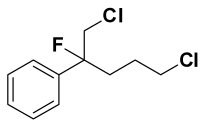

**$^{13}$C-NMR, 100 MHz, $CDCl_3$**



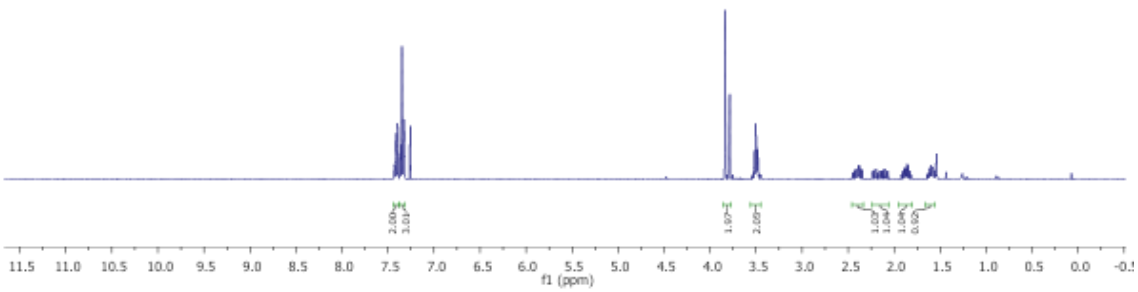


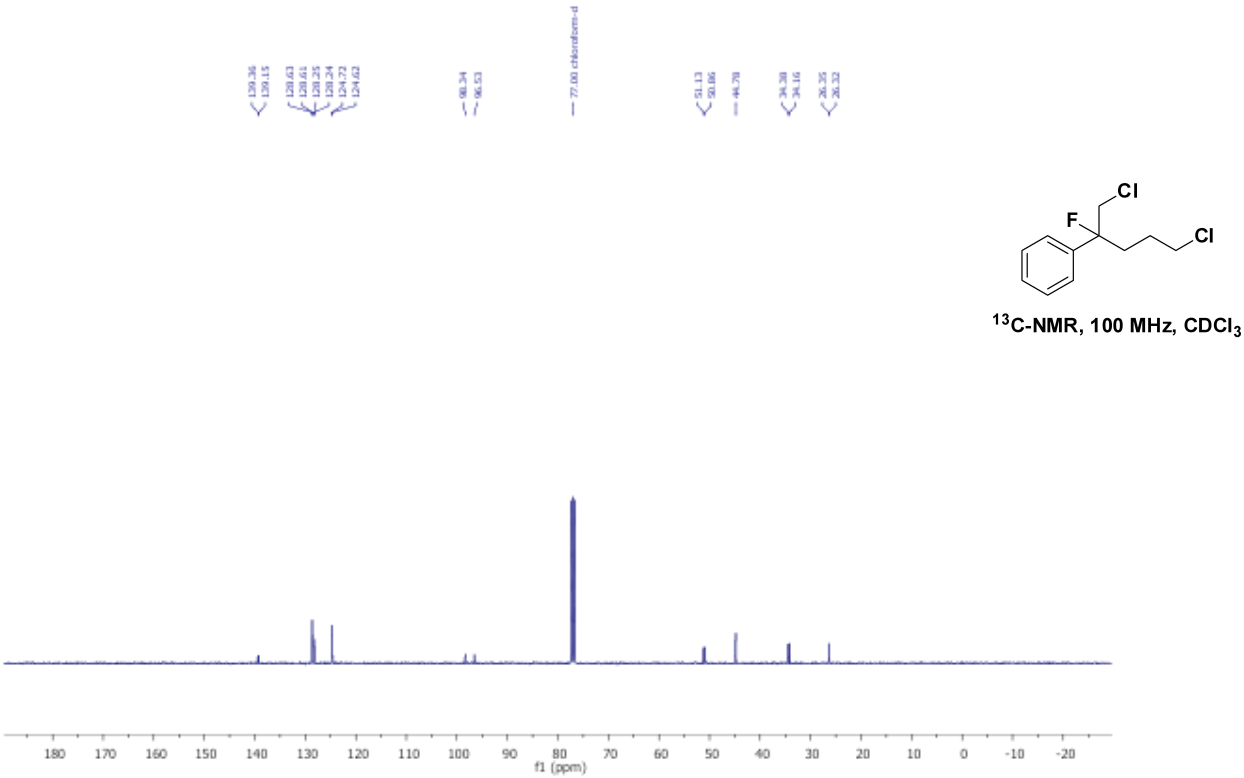

**$^{19}$F-NMR, 470 MHz, $CDCl_3$**

Compound 10

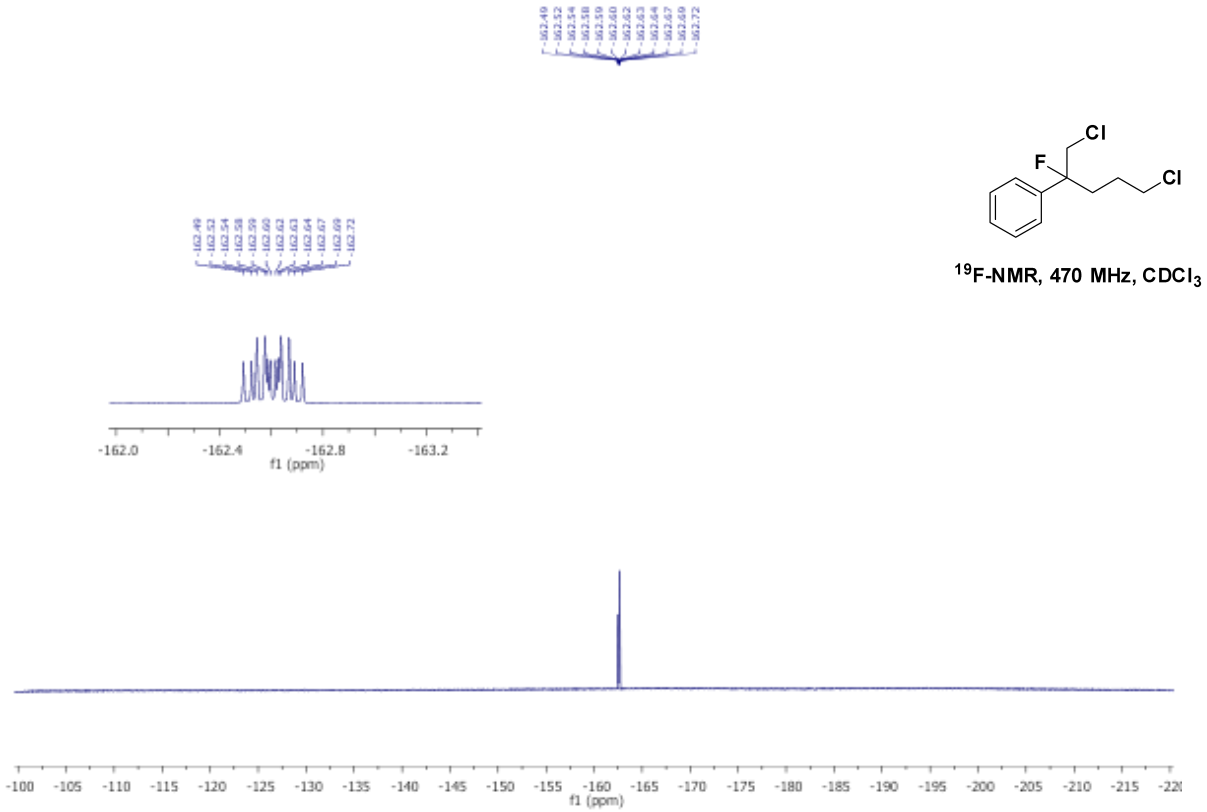



**$^{1}$H-NMR, 400 MHz, CDCl3**





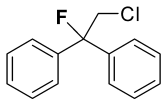

**$^{13}$C-NMR, 100 MHz, $CDCl_3$**



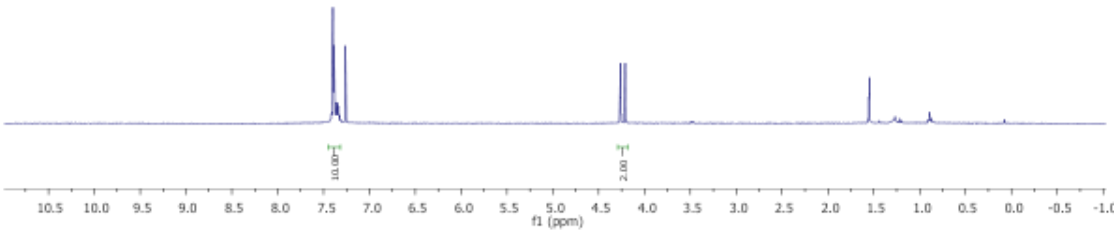

**$^{19}$F-NMR, 470 MHz, $CDCl_3$**

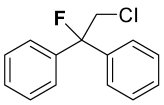
## From Benzophenones

Compound 11

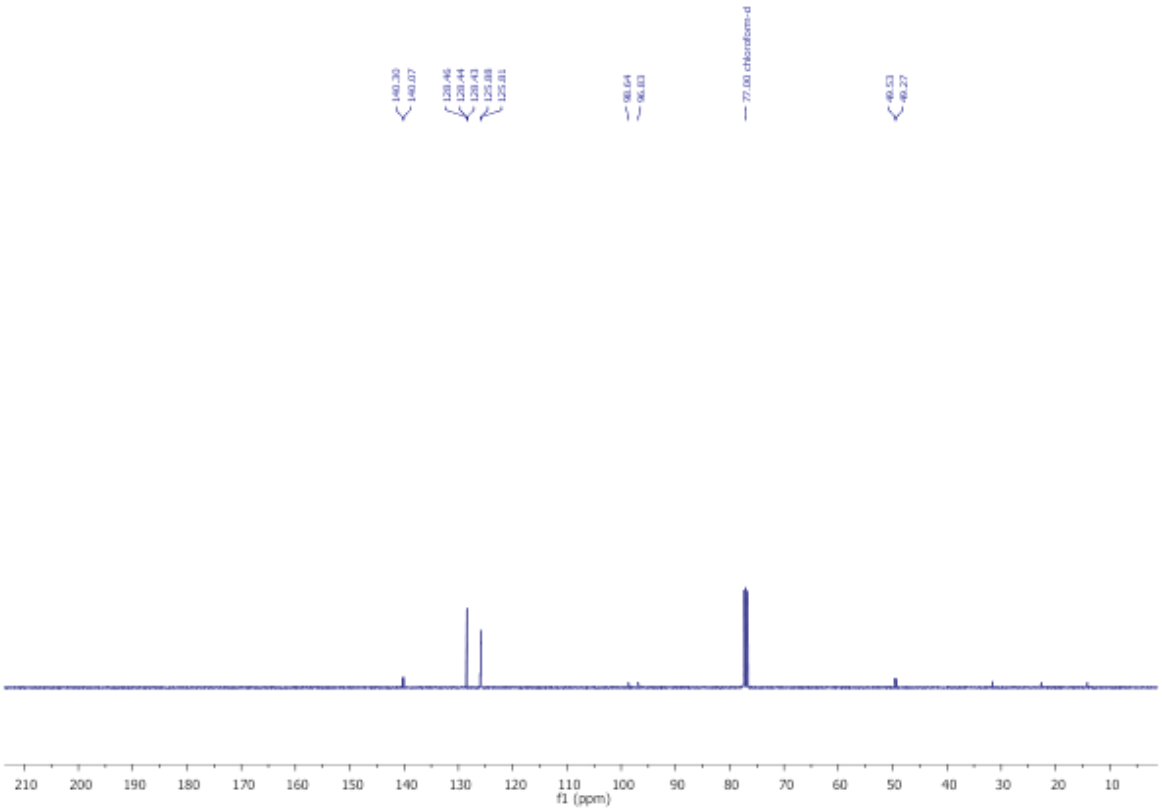


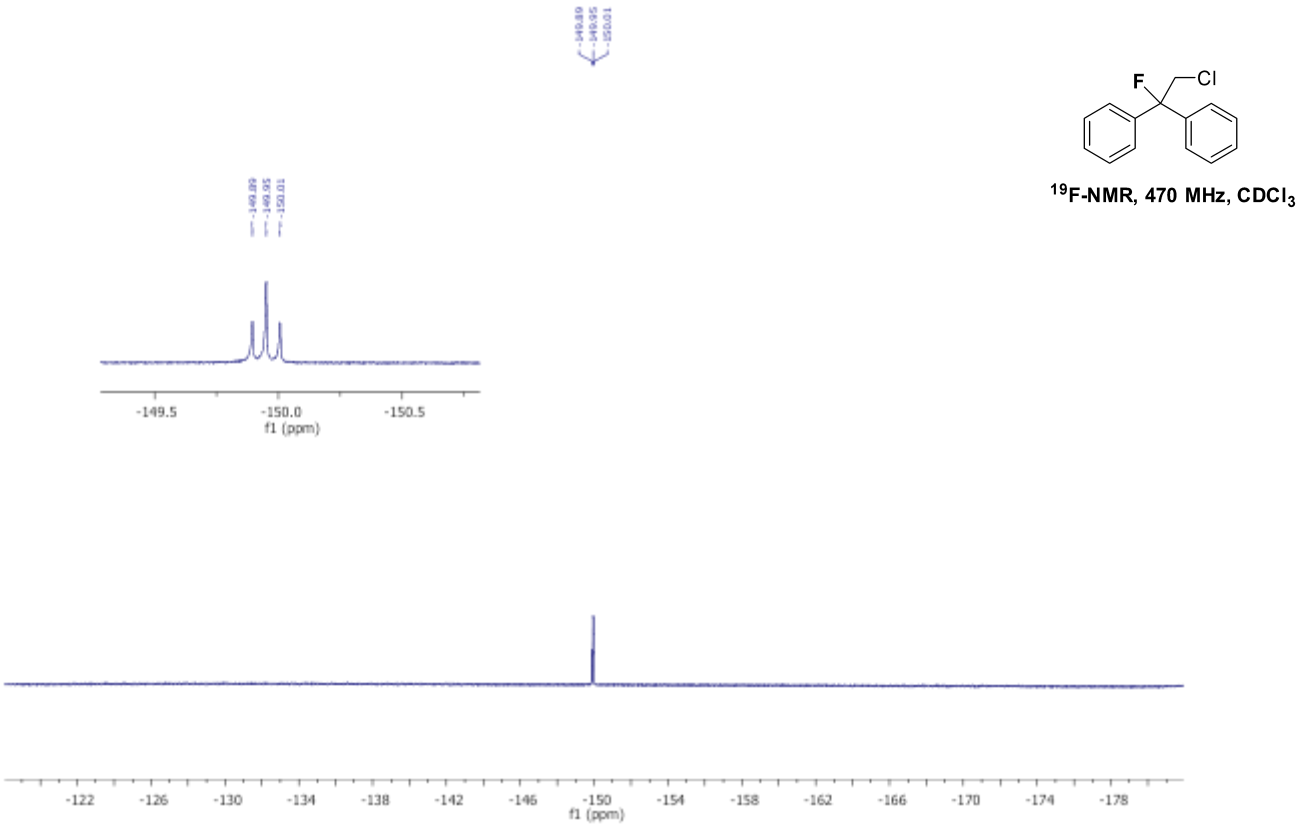

**$^{1}$H-NMR, 400 MHz, CDCl3**



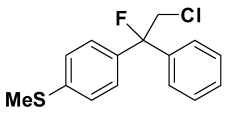

**$^{13}$C-NMR, 100 MHz, $CDCl_3$**


140.30
140.07
128.46
128.44
128.43
125.88
125.81
98.64
98.83
77.00 chloroform-d
49.53
49.27
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

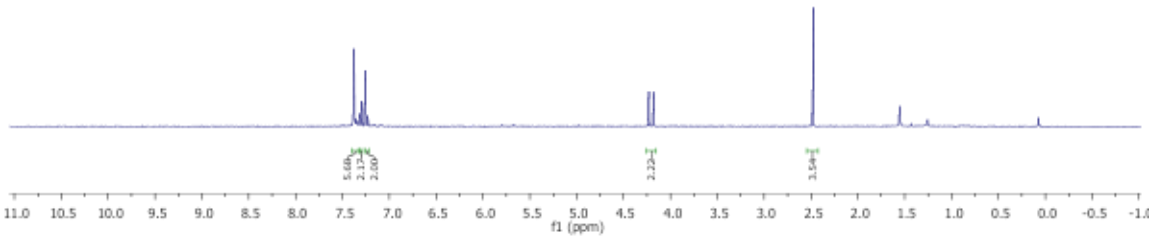


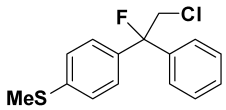

**$^{19}$F-NMR, 470 MHz, $CDCl_3$**

Compound 12

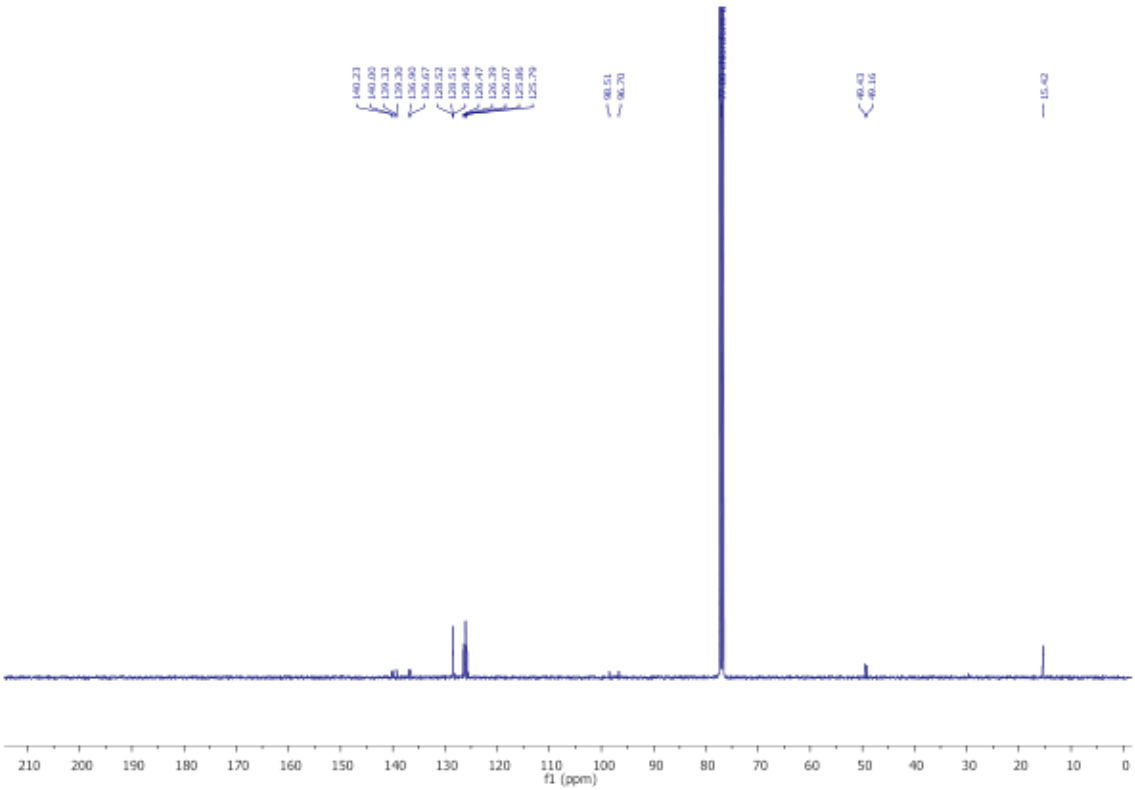


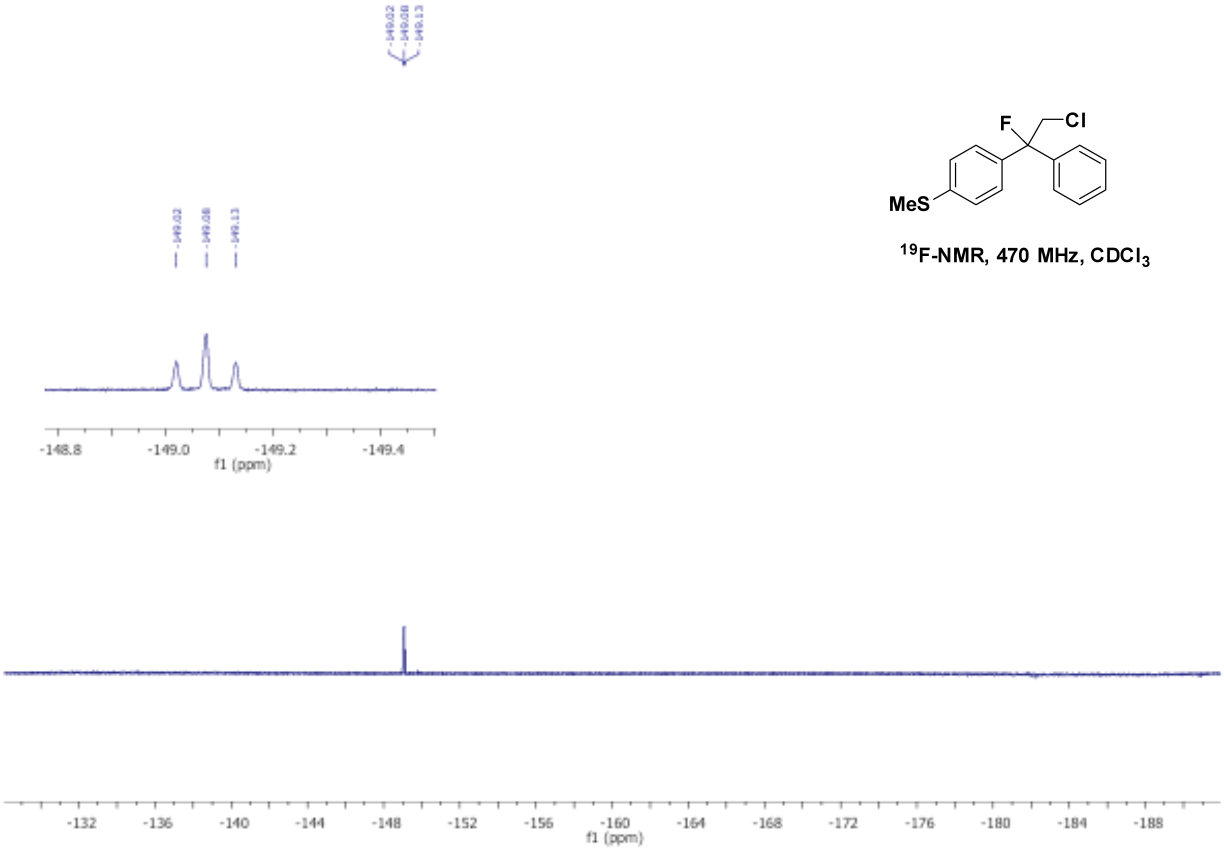

**$^{1}$H-NMR, 400 MHz, CDCl3**



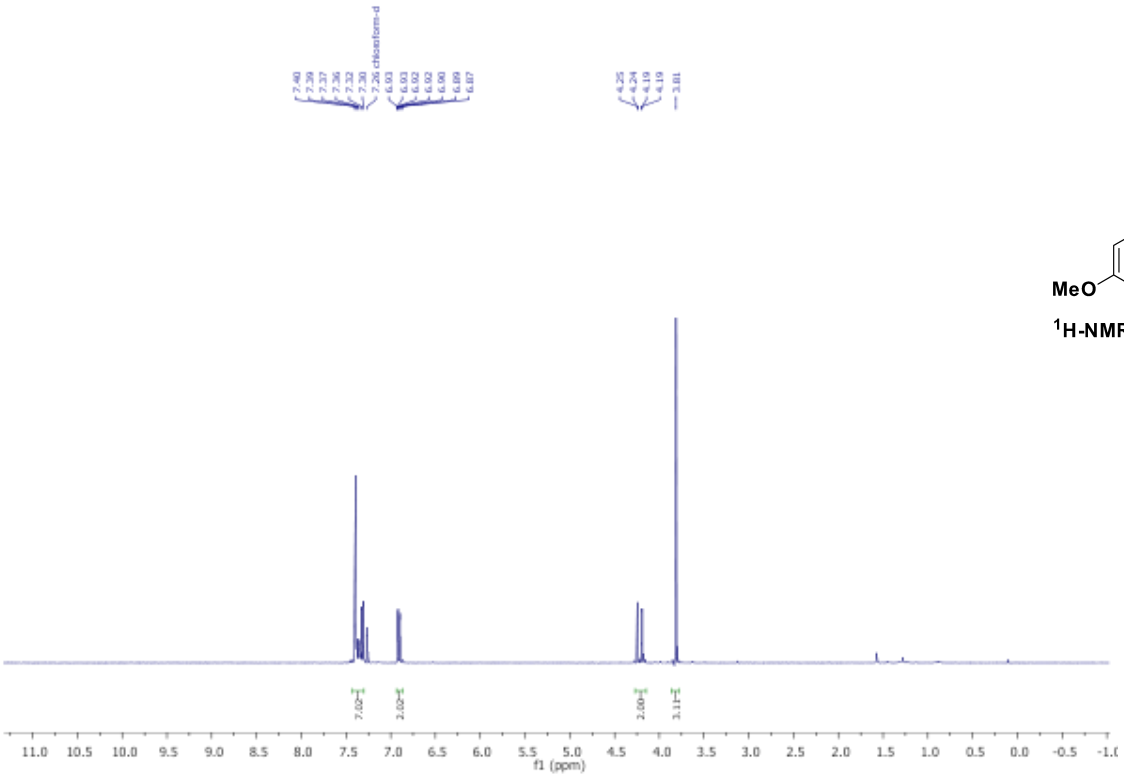

**$^{13}$C-NMR, 100 MHz, $CDCl_3$**

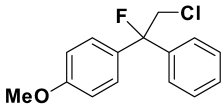

140.23
140.00
139.33
139.30
136.90
136.67
128.52
128.51
128.46
126.47
126.39
126.07
125.86
125.79
98.51
96.70
49.43
49.16
15.42
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



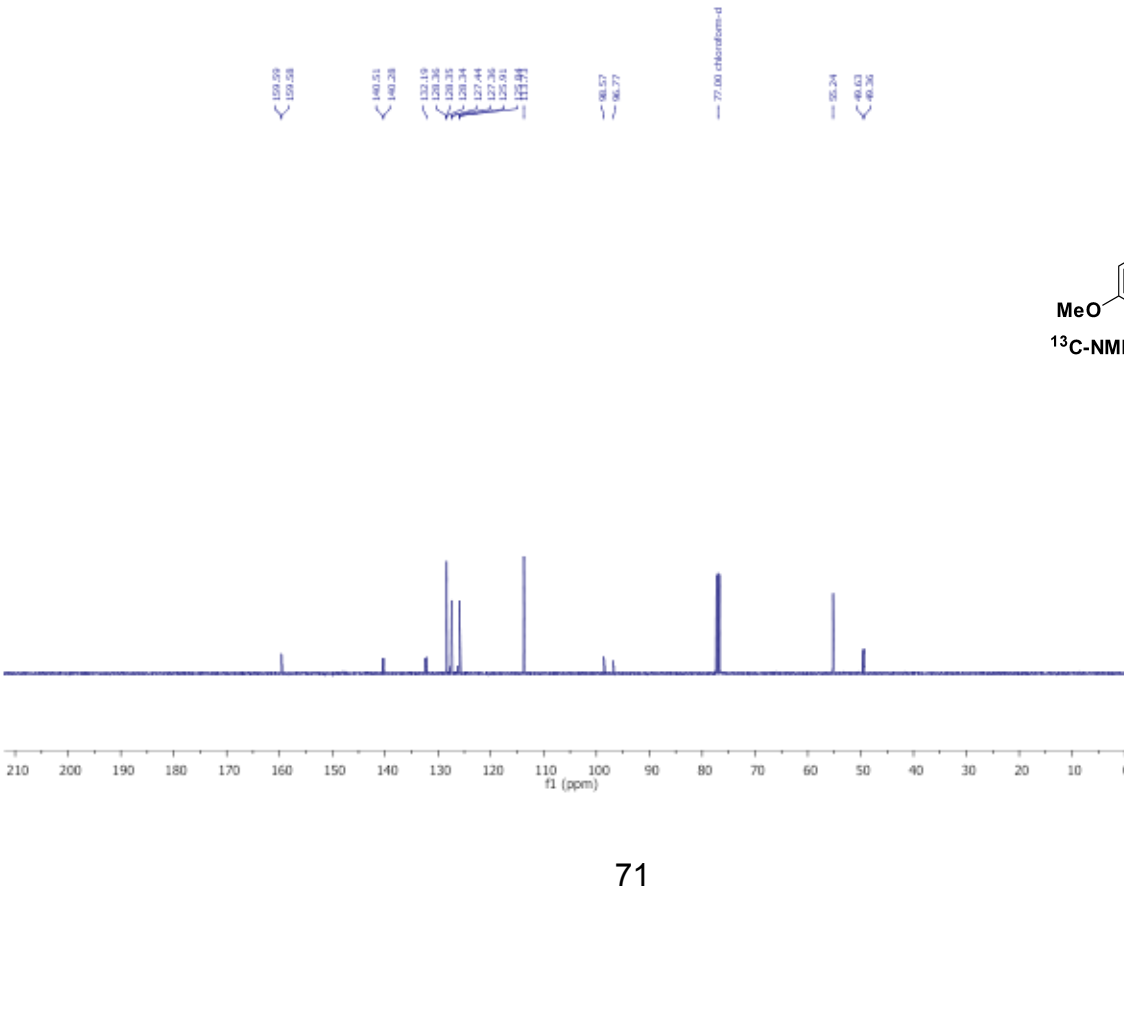

**$^{19}$F-NMR, 470 MHz, $CDCl_3$**

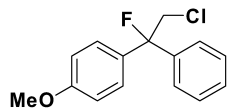
Compound 13



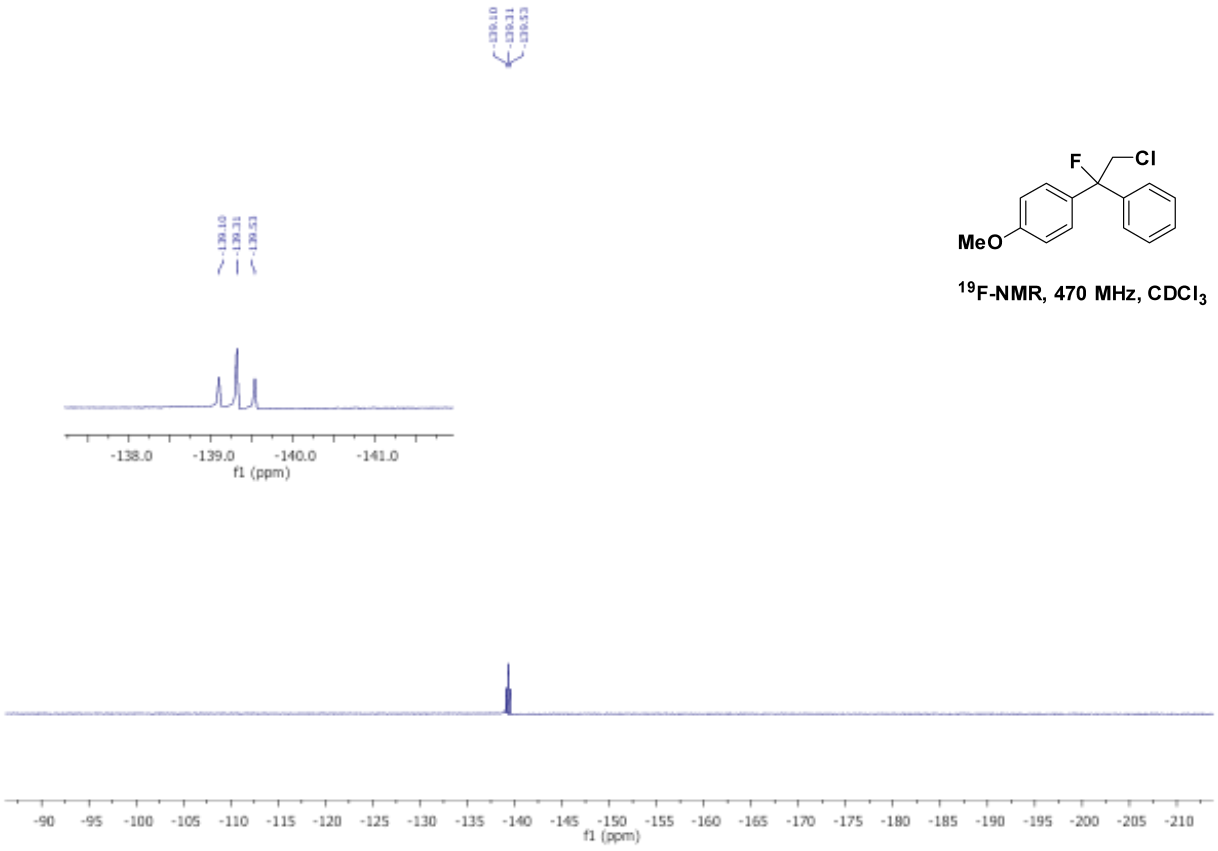



**$^{1}$H-NMR, 400 MHz, CDCl3**






**$^{13}$C-NMR, 100 MHz, $CDCl_3$**




**$^{19}$F-NMR, 470 MHz, $CDCl_3$**

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***List of Schemes***