universität wien

MASTERARBEIT / MASTER'S THESIS

Titel der Masterarbeit / Title of the Master's Thesis

"Conjunctive homologation - fluorination of aldehydes: a straightforward access to 1-halo-2-fluoroethanes"

verfasst von/ submitted by

Senem Yilmaz-Simsek, BSc

angestrebter akademischer Grad/ in partial fulfilment of the requirements for the degree of

Magistra pharmaciae (Mag.pharm.)

Wien, 2021/ Vienna, 2021

Studienkennzahl lt. Studienblatt / degree programme code as it appears on the student record sheet:	UA 066 605
Studienrichtung lt. Studienblatt / degree programme as it appears on the student record sheet:	Masterstudium Pharmazie
Betreut von / Supervisor:	Vittorio Pace, Privatdoz. PhD

ACKNOWLEDGEMENT

First of all, I would like to express my gratitude to Prof. Dr. Vittorio Pace from the Department of Pharmaceutical Chemistry at the University of Vienna, who gave me the opportunity to work in a chemistry laboratory for my thesis.

During my work in the laboratory, my co-supervisor Dott.mag. Margherita Miele always supported me. I would like to thank her for her mentoring, patience, help and the great time we spent together, moreover, for the friendship that has developed during this time.

Last but not least, I have to express my deep gratefulness to my husband, my family and my friends who have always motivated and supported me both during my studies and during the time for the Master thesis, who believed in me and never doubted me. I could not have achieved this success without them.

Thank you all very much!

Senem Yilmaz-Simsek

TABLE OF CONTENTS

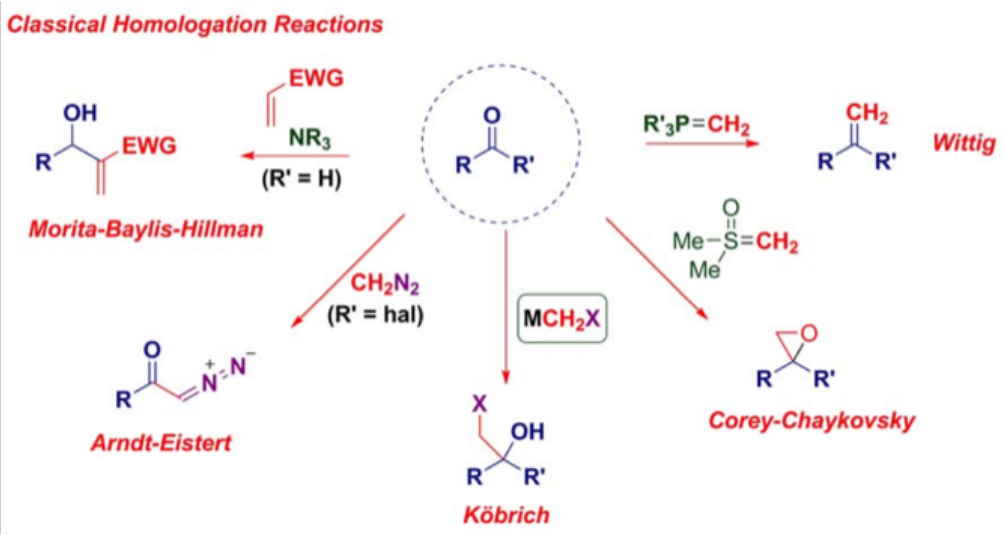
ABSTRACT

In recent decades, the importance of fluorine and techniques of fluorination in drug research has been growing continously. Due to their properties concerning the chemical structure and the reactivity, they have been eliciting interest and attraction from pharmaceutical chemists increasingly. In the first step of this thesis, aldehydes are homologated using lithium carbenoids. Lithium carbenoids are versatile gadgets for homologation reactions because of their chemical ambiphilicity. Subsequently, these compounds become fluorinated with Deoxofluor. On the basis of this two-phased procedure, fluorinated molecules can be obtained in a fast and easy way, moreover, producing high yield under full conversion.

Die Bedeutung von Fluor und Techniken der Fluorierung in der Arzneimittelforschung hat in den letzten Jahrzehnten immer mehr zugenommen. Aufgrund ihrer Eigenschaften bezüglich der chemischen Struktur und der Reaktivität gewinnen sie zunehmend an Interesse und Aufmerksamkeit unter pharmazeutischen Chemikern. Im ersten Schritt dieser Arbeit werden Aldehyde mit Lithiumcarbenoide homologiert. Lithiumcarbenoide sind aufgrund ihrer chemischen Ambiphilie vielseitige Hilfsmittel für Homologationsreaktionen. Anschließend werden diese Verbindungen mit Deoxofluor fluoriert. Mit diesem zweistufigen Verfahren lassen sich fluorierte Moleküle schnell und einfach, zudem in hoher Ausbeute und unter vollständiger Umsetzung erhalten.

1. INTRODUCTION

1.1. CARBENOIDS



Scheme 1 *Classical Homologation Reactions*

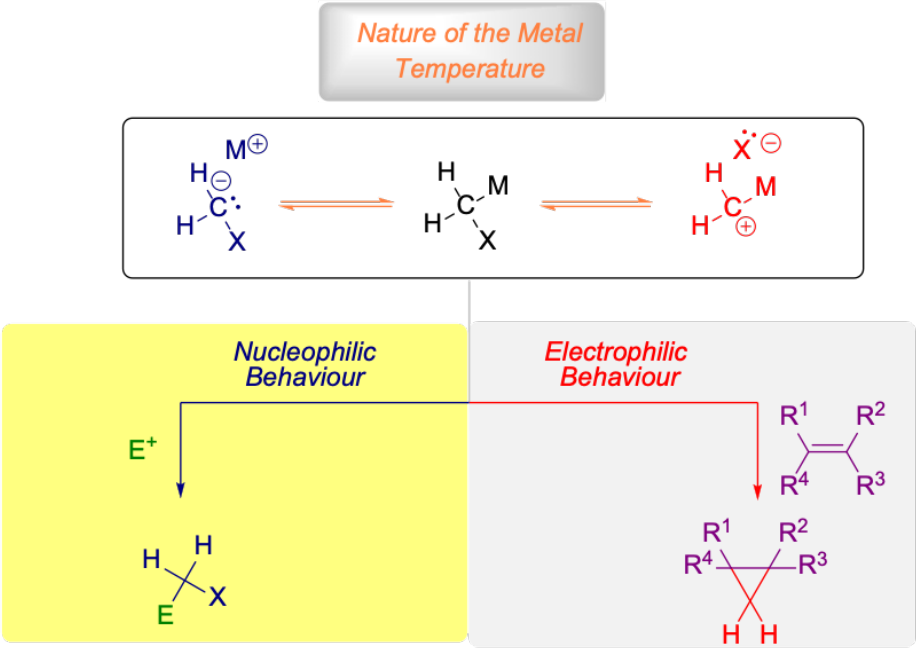
Homologation reactions are a very common method to extend compounds with carbon atoms. Typical examples of homologation reactions are the carbon chain extension or the ring expansion of carbonyl compounds (*Scheme 1)*.[1, 5]

The Arndt-Eistert reaction which is interceded by the diazomethane is the experimental model for homologation reactions. It revealed the access to a new domain of integrating reagents with a comparable nucleophilic character.[2]

Methylating agents are highly useful synthetic gadgets in homologation reactions for integrating methylene units, for instance CH_2, into preformed compounds. One outstanding example of methylating agents are the carbenoidic reagents.[1]

The fathers of this area of research G. L. Closs and R. A. Moss coined the expression carbenoid and characterize them as ‘‘qualitatively analogous to those of carbenes without necessarily being free divalent carbon species’’.[1, 16] Therefore, organometallic molecules which consist of a metal atom, for instance Li or Mg, and of at least one electronegative element, for example halogen, are defined as carbenoids under the condition that these are related to the same carbon.[1]

In the 1960s, Gert Köbrich and his team achieved major progresses concerning working with carbenoids. Due to the simultaneous existence of an electron-donating and electron-withdrawing substituent at the carbon center, carbenoids show a characteristic ambiphilic behavior and react both as electrophilic and nucleophilic species.[1] Nevertheless, their manner of reaction is determined by the following circumstances: the type of the metal and the temperature.[2] At low temperatures, carbenoids act nucleophile whereas at higher temperatures, they attain an electrophilic character *(Scheme 2)*.[1]



Scheme 2 *Reactivity properties of carbenoids*

One cause for this peculiar behaviour is the configuration which can occur in two contrary ionization forms. One structure has a negative charged carbon atom so that it turns nucleophilic, whereas the other has a positive charged by which the molecule turns electrophilic.[1]

Another reason is that the metal atom and the electronegative element are coupled with the same carbon atom of the carbenoid.[2]

Under these terms, carbenoids can participate in two distinct reaction types:

- nucleophilic additions (eventually followed by elimination)
- cyclopropanation-type processes[1]

It is worth considering that carbenoids of lithium and magnesium behave as carbanions due to their outstanding nucleophilic character whereas carbenoids of zinc and rhodium show an electrophilic reaction due to their lower nucleophilic character.[1]

1.2. LITHIUM CARBENOIDS

Lithium carbenoids represent the prototype of carbenoids because of their chemical ambiphilicity by the divalent carbon and simultaneously maintain the shut valence shell configuration.
On the basis of the results of the research of G. L. Closs, G. Köbrich and their co-workers, lithium carbenoids can be set in a wide range of chemical reactions such as cyclopropanation under the condition of the prosperous handling of their reactivity and tendency to decay.[3]

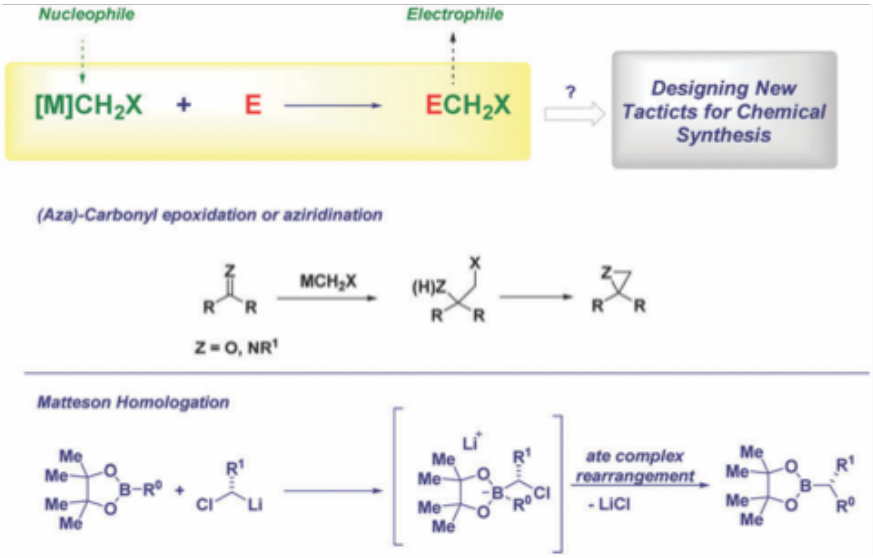
The field of chemistry can benefit from the miscellaneousness of lithium carbenoids in the integration of methylene groups such as a CH_2 group in form of a nucleophile as $LiCH_2X$, which in the further phases of the synthesis sequence acts like an electrophile.[2]

The epoxidation or aziridination of carbonyls or imines or the Matteson homologation of boronic esters with (eventually) chiral carbenoids are typical examples for this kind of reactions. During the epoxidation or aziridination of carbonyls or imines, a construct of three constituents arises as the key precursor alkoxide or amide offends the electrophilic halomethyl group. Otherwise, the ate complex rearrangement eliminates the halide whereby the homologated configuration comes into being.
As a result, with the help of this electrophilic CH_2X group it renders possible to investigate this field further.[2]

Correspondingly, the methodology of improved procedures depends on the following points:

- formation of the nucleophilic reagent

- awareness of mechanistic issues that could have a critical impact on the processes *(Scheme 3)*[2]



Scheme 3 *Handling the integration of a CH2X group*

Through borylation of the lithium in lithium carbenoids, lithium carbamates and benzoates, it is possible to deal with the stereochemistry along the carbon chain and to construct various stereo centers. Moreover, it is more feasible to have control over the configuration in these centers.[2]

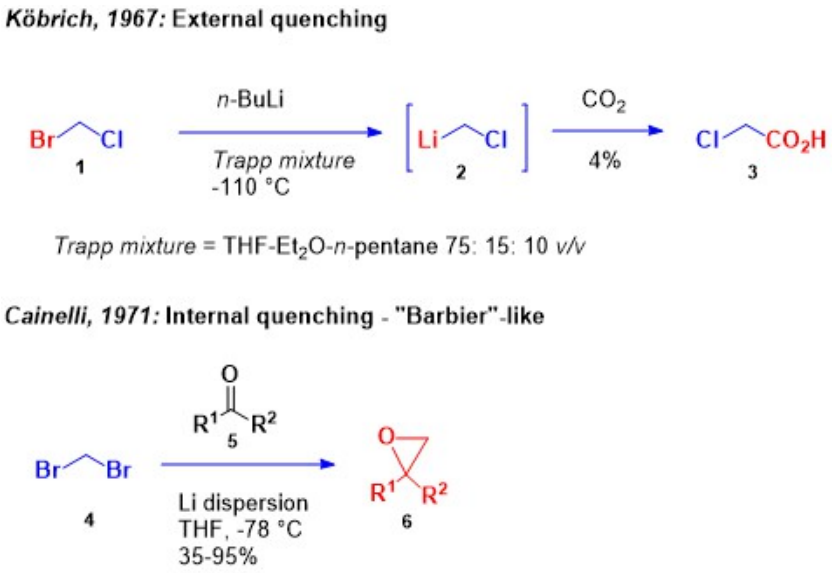
Scheme 4 *Aggarwal's assembly-line synthesis of (+)-kalkitoxin*

Based on this factor, V. K. Aggarwal and coworkers figured with the brief synthesis of (+)-kalkitoxin out that the "purification between several homologations could be avoided ". Thereby the entire reaction could be remarkably enhanced *(Scheme 4)*.[2]

In addition to controlling the stereochemistry, it is sufficient to decay the surplus carbenoid in order to proceed to the subsequent process of the homologation by raising the temperature.[2]

1.3. THE LIMITED STABILITY OF LITHIUM CARBENOIDS

One limitation of carbenoids is their thermal instability. To be able to work with them, low temperatures in the reaction medium are needed. G. Köbrich was apparently the first scientist who disputed about the thermal instability of carbenoids and achieved a reaction with bromochlormethane **1** and *n*-Butyllithium (*n*-BuLi) at a temperature of - 110 °C to gain methyl chloroacetate **3** where chloromethyllithium ($LiCH_2Cl$) **2** was produced as an intermediate product *(Scheme 5)* .[4,5]



Scheme 5 *Initial consideration on a lithium carbenoid generation*

About more than ten years later, G. Cainelli achieved to provide monohalomethyllithiums indeed at - 78 °C by working under Barbier-type conditions, i. e. the electrophile should be in the synthesis milieu before the generation of the carbenoid. An electrophile in the reaction medium prevents the formed carbenoid from its immediate decomposition, moreover, it could be applied to transform a carbonyl compound **5** into an epoxide **6** *(Scheme 5).*[5]

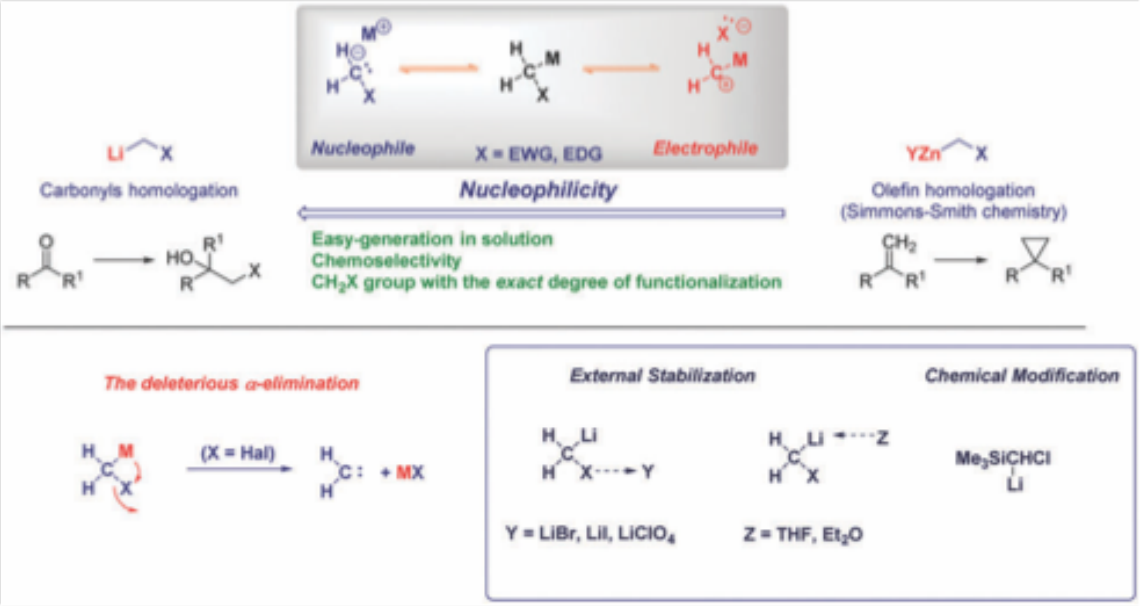
As reported by G. Cainelli, the generation of the carbenoid works better per metalation with lithium metal than per a synthesis with an alkyllithium.

Additionally, this method can be used as an alternative to the Corey–Chaykovsky epoxidation.[5]

Another weak point of carbenoids is the lability.[2] G. Köbrich noticed that the intramolecular organisation of the metal atom and the halogen initiates the so-called Kirmse's alpha-elimination which results in the end in a free carbene and a metal halide.[2,5,6] In this condition, the carbenoid is of no avail for homologation reactions.[6]

Therefore, this incident cuts back on the handling of carbenoids. Thus, the groundwork and the stabilization of the carbenoids is of vital importance to be able to work with them.[2]

J. Villieiras and J. Barluenga theorised that the elimination or the reduction of this intamolecular organisation could help to increase the stability of the carbenoids.[7]
Thus, they tried to disturb this coordination to avoid the alpha-elimination by using lithium halides and ethereal solvents and achieved it *(Scheme 6).*[2]



Scheme 6 *Characteristic traits of carbenoids*

The addition of a lithium salt fixes the alpha-monohaloalkyllithium due to accepting electrons. As a result, the interaction between Li and X is decreased which actually causes the alpha-elimination.[7]

Putting basic solvents as for example THF or diethyl ether into the reaction medium maintains the carbenoid by enlarging their nucleophilic character. Solvents like HMPA, on the other hand, are facilitating the alpha-elimination.[7]

Furthermore, by using a specific precursor such as dihalomethane, stannane, or sulfoxide and working under Barbier-type conditions, it is possible to balance out this intramolecular lability and form a functional carbenoid.[6]

According to P. Magnus, integrating a compound which involves silicon into the halocarbenoid configuration can also solve the problem with the stability of the carbenoids. However, contrary to the other stabilization methods, a further step to eliminate the silicone must be included.[2]

Consequently, Barbier-type conditions enable to prepare these compounds, moreover, to let these interact with the correspondent electrophile.[2]

Lithium carbenoids can be considered as the prototypical formation of organolithium reagents.[5]

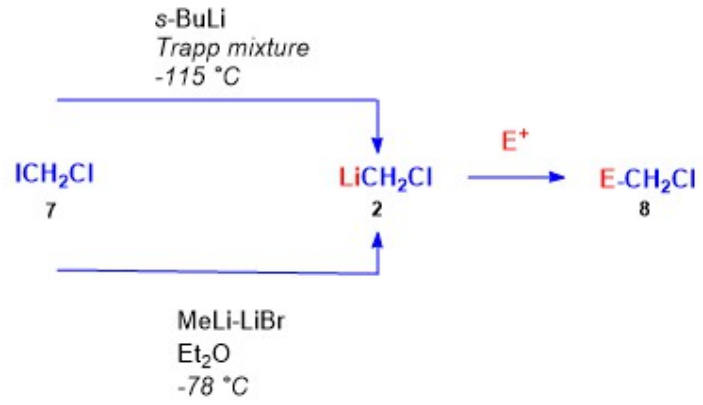
The listed processes below are generally used to obtain these organometallic compounds:

- lithiation via lithium–halogen exchange
- lithiation via lithium–hydrogen exchange (i.e., deprotonation)
- lithiation via lithium–sulfinyl exchange
- lithiation via lithium–tin exchange.[5]

1.1.1. Lithiation via Lithium-Halogen Exchange

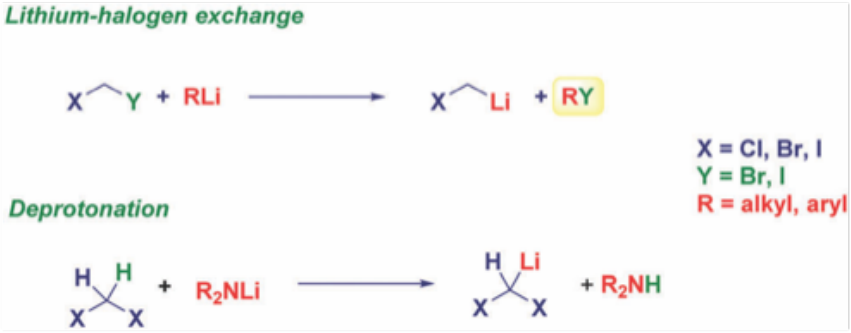
The most frequent mechanism to provide halocarbenoids for synthetic utilities is the metal-halogen exchange in form of an oxidative addition on a dihalomethane.[2] One reason is that the work steps are quite simple. Furthermore, the dihalomethane precursor is accessible in big amounts.[8]

G. Köbrich and his coworkers failed generating carbenoids because they used *n*-Butyllithium solutions in hexane or pentane which do not supply the essential salt. Therefore, J. Villieiras achieved success in the exchange reaction by using secondary Butyllithium in the so-called Trapp mixture of THF: Et2O: pentane at a ratio of 75:15:10 at - 110 °C *(Scheme 7).*[5,7]



Scheme 7 *Lithium-iodine exchange in the presence of different alkyllithiums*

Nevertheless, it turned out later that this lithium base is suitable for operating deprotonations (*Scheme 8)*[2] and not exchange reactions.[5]



Scheme 8 *Generation of lithium carbenoids via lithium-halogen and lithium-hydrogen exchange*

Therefore, the best resources of Lithium have highlighted MeLi and *n*-BuLi. As a result, the MeLi-LiBr complex in Et_2O is used nowadays to form chloromethyllithium from chloroiodomethane **7** *(Scheme 7).*[5]

In compromise with the prior researches of D. S. Matteson, V. Pace proved that the lithium bromide both leads to stability of the carbenoid "through the above-discussed coordinative effect" and eradicates "the competing attack of MeLi to a given electrophilic substrate present in the reaction medium under Barbier conditions". In addition to this, lithium bromide has a lenient Lewis acid effect that makes it easier for the generated carbenoid to offend the electrophilic compound. The formation of the carbenoid takes place in situ which is succeeded by the interaction with the electrophile.[5]

The type of the dihalomethane that serves as the precursor for the formation of the carbenoids has an impact on the success of the reaction.[5] Larger halogens are substituted before any other. Thus, molecules which imply iodo facilitate the groundwork of carbenoids.[2] Chloroiodomethane is the first reagent that comes into question. Nevertheless, there are attempts to put bromochloromethane in place of chloroiodomethane because of the lower costs.[5]
As a result, an alkyl or aryl-lithium reagent encourages the substitution on XCH_2I (Br) to provide the appropriate lithium carbenoid.[2]

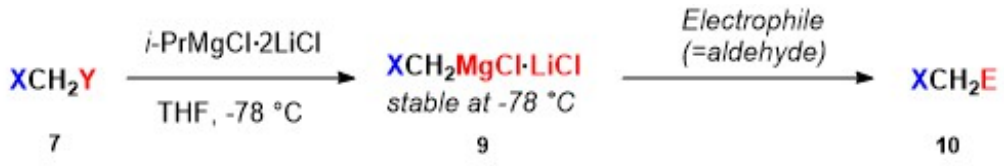
Furthermore, a factor that should be paid attention to is the metal-halogen exchange. It takes place at such speed that the nucleophilic organolithium compound cannot react with the electrophile, which is by that time current in the synthesis milieu, in that short time span.
As a matter of fact, the use of Lithium-bromide results in lower appearances of alike unrequested incidences during the formation of a carbenoid.[2]

The stoichiometric ratio of 1:1 between the dihalomethane and organolithium compound could be enough for the exchange reaction. However, to foreground the tendency of the alkyllithium to perform a potential competing attack to the electrophilic partner and/or alterations of its concentration, it is more promising and rational to increase the dihalomethane by 0.2–0.4 equivalent.[5] It should be considered that the organolithium reagent should be added slowly to the reaction medium to assure the formation, stability and reactivity of the required lithium carbenoid.[1]

In addition to this, when carbenoids are participating in syntheses, the halomethyl precursor as well as the resource for lithium are necessary in greater quantity than actually required. This is important to get over the restricting instability after their formation at - 78 °C.[1]

P. Knochel, I. Marek and co-workers accomplished to generate functionalised magnesium halocarbenoids beginning from iodomethanes and *i*-PrMgCl in a composition of THF and NBP (N-butylpyrrolidone). Their generation can be count as secure at a temperature of - 78 °C due to their greater stability. Furthermore, the addition of the electrophilic partner takes place at a subsequential phase of the synthesis.[5]

Basing on this scheme, G. C. Clososki treated ICH_2Cl **7** with *i*-$PrMgCl_2LiCl$ to obtain the carbenoid $ClCH_2MgClLiCl$ via magnesium–iodine exchange. This once again confirms the fact that the formation of the carbenoid happens before being captured with aldehydes *(Scheme 9).*[5]



Scheme 9 *Formation of magnesium carbenoids via magnesium-iodine exchange under non-Barbier conditions*

Magnesium carbenoids seem to be an impressive option next to the lithium carbenoids which are not stable, but only as long as a potent electrophilic partner interacts with the magnesium carbenoid. V. Pace and co-workers affirmed this by demonstrating reactions with low electrophilic compounds, as for example Weinreb amides. These interacted with lithium carbenoids but not with the low nucleophilic magnesium carbenoids.[5]

Nonetheless, the homologation reactions of aldehydes adorned with further electrophilic components such as esters, ketones, or nitriles with magnesium carbenoids are presented with superior chemoselectivity by G. C. Clososki.[5]

As explained above in chapter „The Limited Stability of Carbenoids", the generation of the lithium carbenoid via lithium-halogen exchange is also possible via metalation which has been reported by G. Cainelli.[5]

1.3.1. Lithiation via Lithium-Hydrogen Exchange

Although it is suspected that the lithium-halogen exchange runs at a higher speed due to an associated electron transfer, it appears that the deprotonation of very acidic compounds by alkyl lithiums is more rapid than the bromine-lithium exchange.[9] Therefore, it is not possible to obtain monohalolithiumcarbenoids via the lithium-halogen exchange.[10] Another reason is that at temperatures of - 115 °C, the very basic *s*-BuLi accomplishes the metal-halogen exchange and not the deprotonation of a dihalomethane.[5]

Dihalomethanes are due to the electron-withdrawing halogens acid. Therefore, during the lithium-proton exchange the proton can be removed conveniently from the dihalomethane by using a lithium amide base, as for instance LDA and LTMP.[2] In favour of formation of dihalomethylcarbenoids, as for example $LiCHCl_2$, $LiCHBr_2$, or $LiCHI_2$, starting from the appropriate dihalomethanes is a common technique *(Scheme 10).*[5]

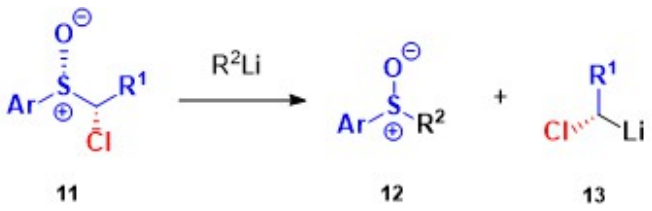
Scheme 10 *Lithation via lithium-hydrogen exchange*

H. Nozaki and co-workers stressed the importance of working under Barbier-type conditions. On the other hand, J. A. Bull argued that this was not really necessary because he showed that LiCHI may be generated before the interaction with the electrophilic partner.[5]

T. F. Molinski achieved producing trichloromethyllithium via deprotonation starting from chloroform and *n*-BuLi at a temperature of - 100 °C. The three chlorine atoms turn this carbenoid into a low nucleophilic compound which can undergo a Michael-type reaction with an unsaturated sultam.[5]

1.3.2. Lithiation via Lithium-Sulfinyl Exchange

R. W. Hoffmann asserts that it is possible to obtain magnesium carbenoids via the magnesium–sulfinyl exchange instead of the metal-halogen exchange. At a temperature of - 80 °C, a sulfoxide and a Grignard reagent — generally *i*-PrMgCl — react and end up building a magnesium carbenoid that is stable both configurationally and thermic at lower temperatures longer than 30 min.[5]



Scheme 11 *Lithium carbenoids from halogenated arylsulfoxides*

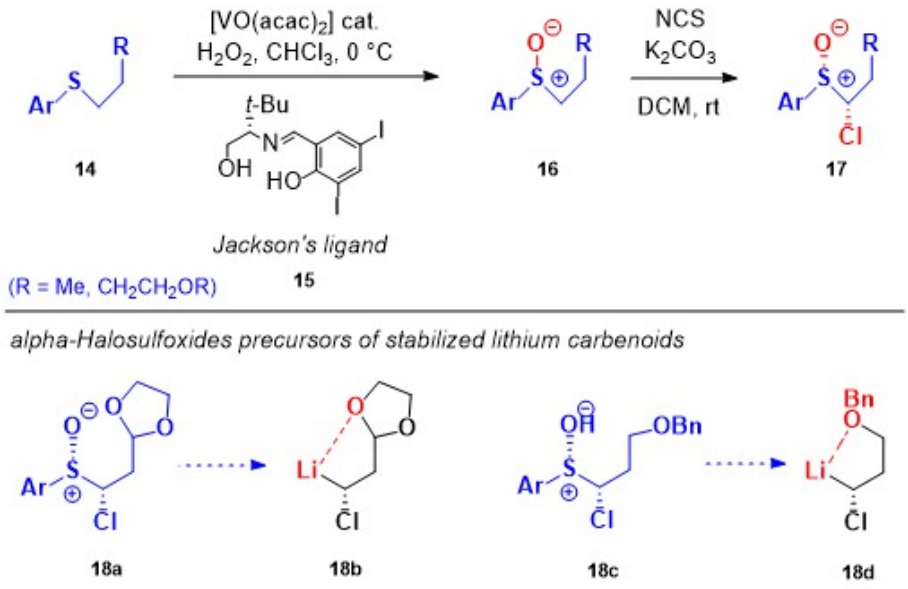
In the year 2006, F. Hammerschmidt and P. R. Blakemore revealed that the lithium-sulfoxide exchange or the lithium-tin exchange leads to enantioenriched alpha-chloroalkyllithiums, which are stable for a longer time than previously assumed at - 78 °C.[3] Through this discovery, they succeeded to form lithium carbenoids **13** from a halogenated arylsulfoxide **11** using the same procedure R. W. Hoffmann did *(Scheme 11).*[5]

During the metal-sulfoxide exchange, the wanted alpha-chloroalkyllithium compounds are formed from the corresponding alpha-chlorosulfoxide precursors which are generated from thioethers **14** by a two-step sequence of sulfoxidation followed by chlorination.

The first step of these sequences is represented by the vanadium-catalyzed Ellman–Bolm enantioselective oxidation with the application of the corresponding enantiomer of Jackson's tert-leucinol derived ligand **15** (*Scheme 12).*[3,5] Then, the required optically pure sulfoxide (up to 99:1 er) is gathered through recrystallizations.[5]

Afterwards, the Yamakawa's nonracemizing chlorination results in the chlorosulfoxide **17**. There are two things that should be mentioned here:

- K_2CO_3 in the synthesis milieu decreases the speed of the chlorination to block the racemization.
- The chlorination takes place with a stereochemical inversion at sulfur.[3]



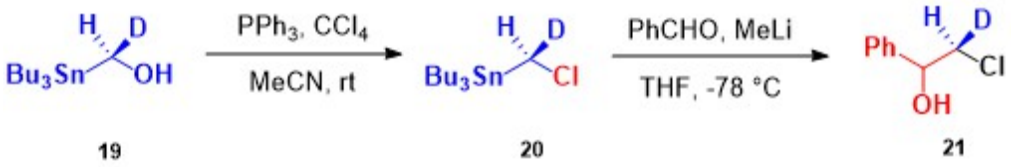
Scheme 12 *Blakemore's synthesis of chiral halosulfoxide precursors of optically active lithium carbenoids*

To obtain the lithium carbenoid via the lithium-sulfoxide exchange between the basic chloroalkyllithium and the acidic chlorosulfoxide, *t*-BuLi in Toluene or Ph-Li in THF are used as solvents.[3]

It should be noted as a final remark that P. R. Blakemore created enantioenriched carbenoids (**18b**, **18d**) that can be secured through inner configuration of lithium with Lewis basic functionalities like ethers or acetals.[5]

1.3.3. Lithiation via Lithium-Tin Exchange

In 2008, F. Hammerschmidt and co-workers found a method to form configurationally stable chloromethyllithiums of a chiral stannane **20** and Methyllithium. For this, the homochiral tributylstannyl- [D1]-methanol **19** must convert into the chloromethylstannane-[D1] **20**, which serves as a precursor *(Scheme 13).*[5]



19 20 21

Scheme 13 *Hammerschmidt's preparation of chiral chloromethyllithium via tin-lithium exchange*

It is possible to obtain the chloromethylstannane-[D1] **20** in an enantiopure form under Appel conditions. Nevertheless, the kind of the alkyllithium that is used, has an impact on this synthesis because the use of *n*-BuLi in the lithium-tin exchange leads to contaminated reactions and to unrequested by-products whereas the treatment with Methyllithium makes for fulfilling outcomes. The reduced basicity of Methyllithium could be a potential cause for this.[5]

1.4. FLUORINATION

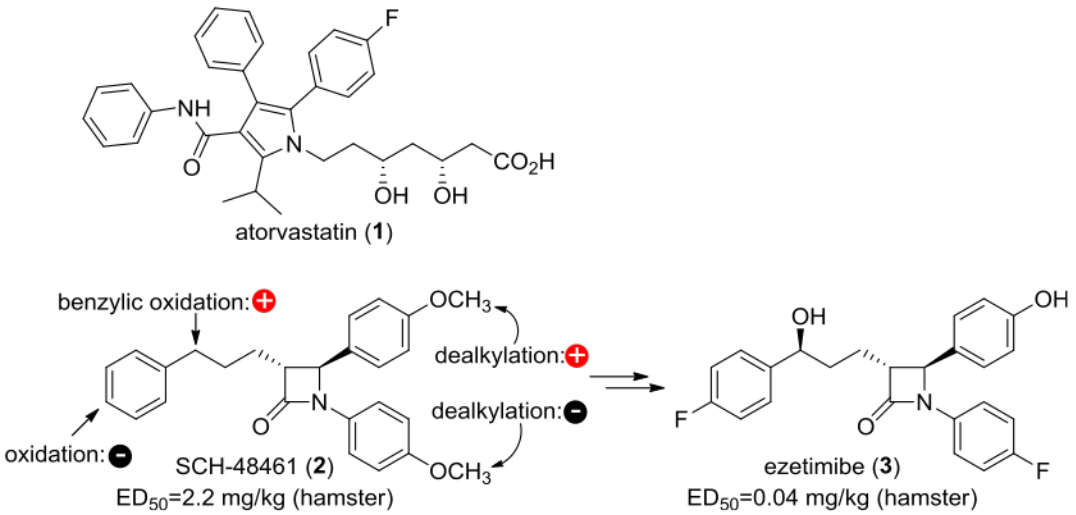
The conceivable opportunities that the fluorine atom and the carbon-fluorine bonding reveal has grown the interest and attention to integrate fluorine into the structure of organic compounds in the last decades. This usage is popularized by the particular features of the fluorine atom and its bonding to the carbon atom, such as the high electronegativity of fluorine which leads to the instance that C-F bondings are polar whereas C-H bondings are non-polar. As a result, C-F bondings renders dipole-dipole and dipole-charge reciprocation possible which improves linkings. Nonetheless, the bonding between the fluorine atom and the carbon atom is as well non-polarizable so that it is a poor H-bonding acceptor. Due to this fact, solvation through water is not really actual.[11]

In sum, both outcomes cause polar hydrophobicity that has an impact on the lipophilic behaviour of the compound. Both lipophilicity as well as bioavailability are essential criteria in medicinal chemistry. The second can also be affected from pKa values of close functional groups determined by the high electronegativity of fluorine.[11] Furthermore, fluorination also elevates the receptor binding affinity of compounds via polar intermolecular interactions.[12]

The bondings between the carbon atom and the fluorine atom are more intense than between the carbon atom and the hydrogen atom that can have a positive effect by enlarging the metabolic stability.[11]

It is substantial to mention that the size of the fluorine atom resides between those of the hydrogen atom and the hydroxy group which results in the isosteria of fluorine with these molecules. Due to that effect, the conformation of the compounds is relatively untouched after fluorination despite which the fluorination is able to cause modifications because of stereoelectronic effects.[11]

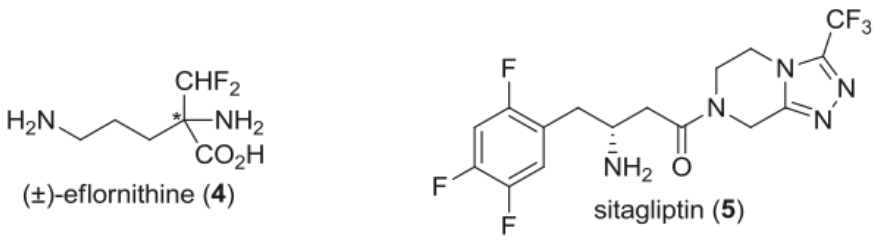
Regarding all the facts and outcomes mentioned above, the percentage of fluorinated drug molecules is growing. A few examples of this can be seen in *Scheme 14*.[11]



Scheme 14 *Examples of fluorinated drugs*

Further examples are amino acids, which benefit from fluorination. Fluorinated amino acid derivates can be easily integrated into proteins devoid of constructural modifications. Furthermore, these molecules can be analysed with techniques like ^{19}F NMR and enzyme mechanisms. However, studies of peptide-based drugs can take advantage from fluorinated amino acids too due to the conformational modifications and limits caused by fluorination. "Namely, fluorine prefers gauche arrangement relative to vicinal highly electronegative heteroatoms and antiperiplanar arrangement relative to vicinal oxo groups." For obtaining particular secondary configurations or side-chain conformations, these properties can be harnessed.[11]

In *Scheme 15*, some fluorinated amino acid drugs are illustrated to demonstrate the importance of such compounds in pharmaceutical chemistry.[11]



Scheme 15 *Fluorinated amino acid drugs*

1.4.1. Techniques of Fluorination

Fluorinated compounds have risen in importance in the recent years and therefore also methods of fluorination. One of the beneficial techniques of avail is deoxyfluorination. Deoxyfluorination is a subtype of nucleophilic fluorination where the integration of fluorine and the displacement of oxygen proceeds at the same time.[11] During this process hydrogen fluoride is formed and eliminated. Afterwards, the reaction takes course through the S_N2 pathway with inversion of configuration.[13]

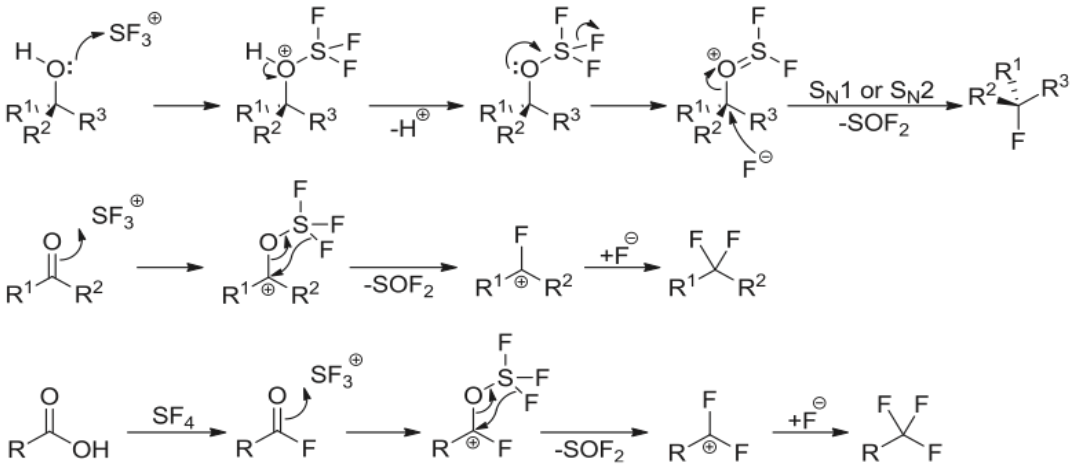
Nevertheless, there are still difficulties concerning fluorination, particularly in incorporating fluorine into highly-functionalised frameworks usual for late-stage fluorination.[11]

1.5. DEOXOFLUOR

1.5.1. SF_4 - The Mother Compound of Fluorination

In the year of 1958, scientists explored that SF_4 is able to convert carbonyl and carboxyl groups into difluoromethylene and trifluoromethyl groups. This is how the history of sulfur fluoride deoxyfluorinating reagents began.

Two years later, it was declared that SF_4 can substitute a hydroxy group with fluorine via S_N1 reaction mechanism *(Scheme 16).*[11]



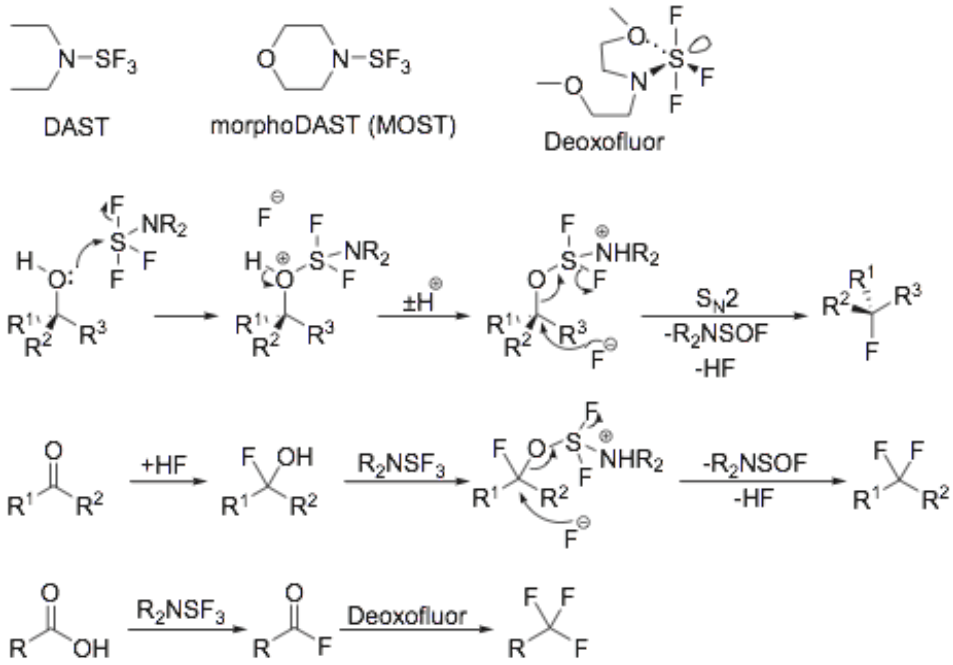
Scheme 16 *Mechanisms of deoxyfluorinations with SF_4. Exchanging OH for F has a strong tendency to shift towards S_N1-type substitution*

However, there were complications and struggles when working with this compound. Under standard conditions, SF_4 is a corrosive gas, moreover, it is toxic. Furthermore, particular apparatuses such as autoclave or fluoropolymer vessel are necessary. These circumstances led to deeper investigation into superior variants.[11]

1.5.2. Dialkylaminosulfur trifluorides - The Next Generation

In the 1970s dialkylaminosulfur trifluorides were discovered as the following generation of deoxyfluorinating reagents. Compared to SF_4, these substances do not need increased temperatures to effectively conduct fluorinations. The replacement of a hydroxy group with fluorine is possible at - 78 °C, carbonyl groups can be remodeled into difluoromethylene at room temperature even though a few compounds demand temperatures about 80-85 °C. In addition, these reagents are simpler to work with because they are fluid at room temperature and do not require particular material.[11]

The most common and conveniently available compound of this family for deoxyfluorination is diethylaminosulfur trifluoride or the so-called DAST. However, the problem here is that DAST is thermic labile. Temperatures about 90 °C lead to explosion. On the one hand this fact narrows the commercial-scale use of DAST, on the other hand it is not appropriate to insert it for conversion of carboxyl groups into trifluoromethyl that demands long heating near the degradation temperature of DAST.[11]



Scheme 17 *Mechanisms of deoxyfluorinations with dialkylaminosulfur trifluorides*

In the year 1989, scientists analysed the thermic stability of dialkylaminosulfur trifluorides and discovered that their degradation takes place in two phases. The first one consists of a tardy dissociation of R_2NSF_3 to SF_4 and $(R_2N)_2SF_2$ at a temperature of 90 °C. This leads to the development of explosive bis(dialkylamino)sulfur difluorides. At particularly high concentration, this compound induces detonations of the total reaction medium.[11]

R_2NSF_3 derivatives from six-membered cyclic amines such as piperidine and morpholine presented higher thermic stability. Therefore, the morpholinosulfur trifluoride or so-called Morph-DAST or MOST, which has been known for longer time, has established itself as a more secure variant to DAST *(Scheme 17)*.[11]

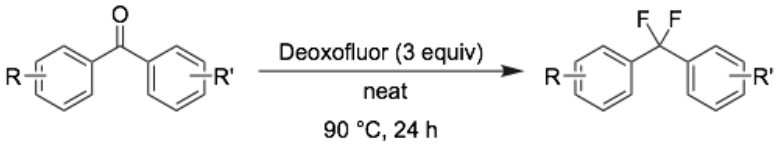
1.5.3. And Finally: Deoxofluor

After years of study and experimentation, an even more secure recent reagent was configured in 1999: Deoxofluor [bis(2-methoxyethyl)aminosulfur trifluoride].

The degradation of this compound is tardier than DAST, moreover, it causes not that high temperatures. Therefore, Deoxofluor lends itself to a large-scale application and is used for the selective fluorination of organic molecules.[11,14] Compared to DAST, Deoxofluor is also able to convert a carboxyl group into a CF_3 part but this procedure demands heating the acyl fluoride at temperatures of 85-90 °C in Deoxofluor as a solvent for extended periods.[11]

The arrangement of an ether oxygen atom of the side chain to the electron-poor sulfur center redounds to kinetic stabilization and subsequently to thermic stability of Deoxofluor.[11]

Deoxofluor is capable of transforming alcohols to alkyl fluorides, aldehydes or ketones to gem-difluorides *(Scheme 18)*, and carboxylic acids to trifluoromethyl derivatives. These syntheses are commonly performed with an appropriate inert solvent, for example methylene chloride.[14]
Since Deoxofluor makes the integration of one or more fluorine atoms into organic compounds possible in a single step reaction, it is an advantageous reagent.[15]



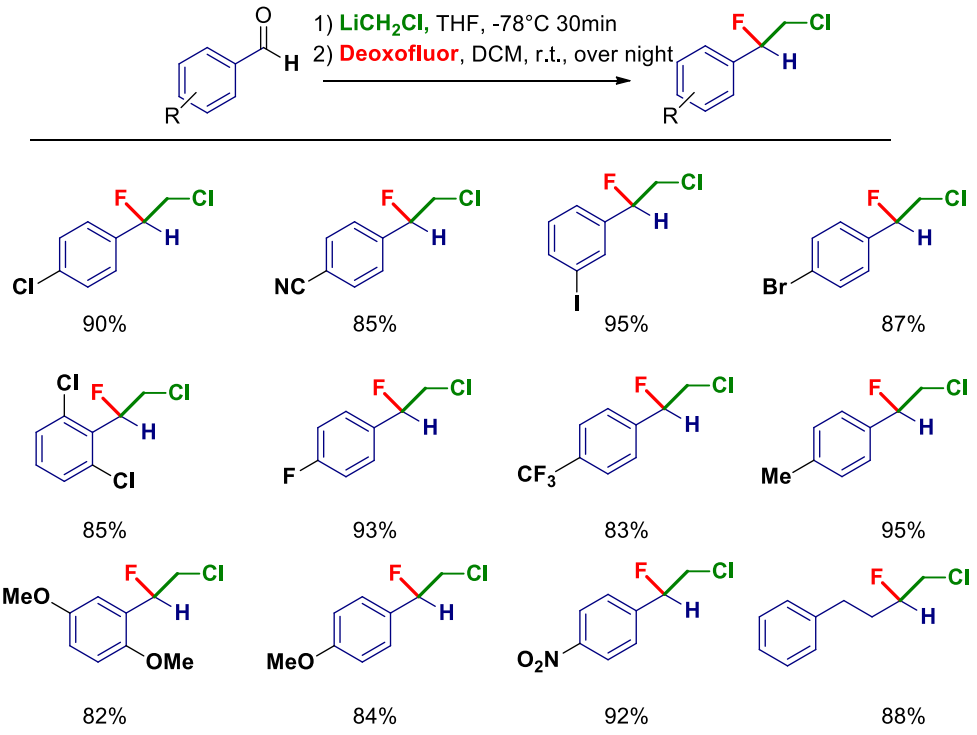
Scheme 18 *gem-Difluorination of benzophenones with Deoxofluor under neat conditions*

Nevertheless, there are still some detriments concerning R_2NSF_3 substances. First of all, they are like SF_4 sensitive to humidity. On the one hand, their formation is simple because SF_4 is implemented with dialkylaminotrimethylsilane in an apolar organic solvent, on the other hand vacuum distillation is necessary to make the crude product clean. This is not just hazardous but also raises the end price of the substance.[11]

Lastly, it should be mentioned that almost all reactions of fluorination run an S_N2 trail, whereas substances which are able to build stable carbocations prefer the S_N1 reaction mechanism.[11]

2. WORK PROJECT

The research group of Prof. Vittorio Pace, with whom I worked for my thesis, developed a new synthetic procedure to obtain fluorinated compounds. First, we formed lithium carbenoids starting from a dihalomethane with a MeLi-LiBr solution in dry THF via the lithium-halogen exchange reaction. This was followed by the fluorination with Deoxofluor at room temperature allowing us to obtain the desired fluorinated compounds in high yields and good chemoselectivity even in presence of a variety of sensitive groups. Once the optimal reaction conditions were established, we studied the scope of the method *(Scheme 19)*. The reaction was performed on a wide range of variously functionalized aldehydes. The compounds, when necessary, were purified by column chromatography on neutral alumina grade IV to avoid the possible decomposition, and isolated in good yields.



Scheme 19 *Scope of the reaction*

3. CONCLUSION

We demonstrated that a variety of substituted aldehydes react at the optimized condition to give the desired homologated-monofluorinated products with full conversion of the starting material and without any possible fluorinated byproduct. Electro-withdrawing (10) and electro-donating (1) groups were effectively tolerated under the reaction conditions. The presence of cyan, nitro or fluorine did not influence the outcome of the reaction. The reaction works well on substrate with functionalities in para, meta, and ortho positions. The procedure is versatile on both aromatic and aliphatic substrates.

4. EXPERIMENTAL SECTION

4.1. 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 used 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).

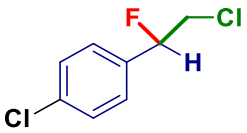
4.2. GENERAL PROCEDURES

4.2.1. General Procedure 1

To a solution of carbonyl compound (aldehyde, 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 into 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 eventually purify the crude compound as indicated below.

4.3. SPECTRAL AND CHARACTERIZATION DATA

1-chloro-4-(2-chloro-1-fluoroethyl) benzene (1)



By following **General procedure 1**, starting from 4-chlorobenzaldehyde (200 mg, 1.4 mmol, 1 equiv) in dry THF (3 mL), iodochoromethane (0.16 mL, 2.1 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, 5.9 mmol, 4.2 equiv), the **compound 1** was obtained in 90 % yield (248 mg) as colorless oil after column chromatography on neutral alumina grade IV (*n*-hexane/ethyl ether 5:5 as eluent).

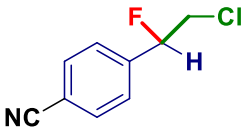
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.72 (m, 2H, Ph H-2,6), 7.49 (m, 2H, Ph H-3,5), 3.56 (m, 2H, CH_2I), 5.68 (m, 1H, CHF), 3.83 (m, 1H, CH_2), 3.78 (m, 1H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.5 (d, 1C, $^2J_{C,F}$ = 20.5 Hz, Ph C-4), 132.5 (Ph C-2,6), 126.4 (d, 2C, $^3J_{C,F}$ = 7.5 Hz, Ph C-3,5), 118.2 (CN), 113.1 (d, 1C, $^5J_{C,F}$ = 1.5 Hz, Ph C-1), 91.7 (d, $^1J_{C,F}$ = 181.0 Hz, CHF), 46.1 (d, 1C, $^2J_{C,F}$ = 27.7 Hz, CH_2Cl).

^{19}F NMR (470 MHz, $CDCl_3$) δ: -181.8 (m, 1F, F-1).

EI-MS m/z (%): 192.0 (M^+, 20), 194.0 (M^++2, 13), 143.0 (M^+, 100), 107.0 (M^+, 22), 51.1 (M^+, 12).

4-(2-chloro-1-fluoroethyl)benzonotrile (2)



By following **General procedure 1**, starting from 4-cyanobenzaldehyde (200 mg, 1.5 mmol, 1 equiv) in dry THF (3 mL), iodochoromethane (0.17 mL, 2.3 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (1.0 mL, 2.1 mmol, 1.4 equiv), Deoxofluor 2.7 M solution in (2.4 mL, 6.3 mmol, 4.2 equiv), the **compound 2** was obtained in 85 % yield (238 mg) as colorless oil after column chromatography on neutral alumina grade IV (*n*-hexane/ethyl ether 5:5 as eluent).

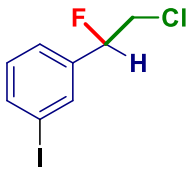
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.72 (m, 2H, Ph H-2,6), 7.49 (m, 2H, Ph H-3,5), 3.56 (m, 2H, CH_2I), 5.68 (m, 1H, CHF), 3.83 (m, 1H, CH_2), 3.78 (m, 1H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.5 (d, 1C, $^2J_{C,F}$ = 20.5 Hz, Ph C-4), 132.5 (Ph C-2,6), 126.4 (d, 2C, $^3J_{C,F}$ = 7.5 Hz, Ph C-3,5), 118.2 (CN), 113.1 (d, 1C, $^5J_{C,F}$ = 1.5 Hz, Ph C-1), 91.7 (d, $^1J_{C,F}$ = 181.0 Hz, CHF), 46.1 (d, 1C, $^2J_{C,F}$ = 27.7 Hz, CH_2Cl).

^{19}F NMR (470 MHz, $CDCl_3$) δ: -181.8 (m, 1F, F-1).

EI-MS m/z (%): 183.0 (M^+, 60), 185.0 (M^++2, 21), 133.9 (M^+, 100), 107.0 (M^+, 71), 51.1 (M^+, 20).

1-(2-chloro -1-fluoroethyl)-3-iodo benzene (3)



By following **General procedure 1**, starting from 3-iodobenzaldehyde (200 mg, 0.9 mmol, 1 equiv) in dry THF (3 mL), iodochoromethane (0.1 mL, 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 (1.3 mL, 3.6 mmol, 4.2 equiv), the **compound 3** was obtained in 95 % yield (233 mg) as colorless oil without any further purification.

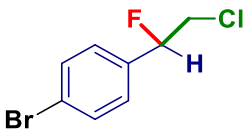
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32 (m, 1H, Ph H-4), 7.30 (m, 1H, Ph H-2), 6.74 (m, 1H, Ph H-6), 6.48 (m, 1H, Ph H-5), 4.89 (ddd, 1H, $^2J_{H,F}$ = 47.0 Hz, $^3J_{H,H}$ = 7.6 Hz, $^3J_{H,H}$ = 3.6 Hz, CHF), 3.13-2.88 (m, 2H, CH_2Cl).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.2 (d, 1C, $^2J_{C,F}$ = 20.4 Hz, Ph C-1), 138.2 (d, 1C, $^5J_{C,F}$ = 1.4 Hz, Ph C-4), 134.9 (d, 1C, $^3J_{C,F}$ = 7.0 Hz, Ph C-2), 130.3 (Ph C-5), 125.0 (d, 1C, $^3J_{C,F}$ = 6.9 Hz, Ph C-6), 94.5 (Ph C-3), 91.7 (d, 1C, $^1J_{C,F}$ = 180.6 Hz, CHF), 46.5 (d, 1C, $^2J_{C,F}$ = 27.1 Hz, CH_2Cl).

^{19}F NMR (470 MHz, $CDCl_3$) δ: -180.4 (ddd, 1F, $^2J_{H,F}$ = 47.0 Hz, $^1J_{C,F}$ = 25.4 Hz, $^2J_{C,F}$ = 16.8 Hz, F-1).

EI-MS m/z (%): 284.0 (M^+, 85), 186.0 (M^++2, 31), 235.0 (M^+, 100), 108.0 (M^+, 99), 50.0 (M^+, 28).

1-bromo-4-(2-chloro -1-fluoroethyl) benzene (4)



By following **General procedure 1**, starting from 4-bromobenzaldehyde (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), the **compound 4** was obtained in 87 % yield (224 mg) as colorless oil after column chromatography on neutral alumina grade IV (*n*-hexane/ethyl ether 9:1 as eluent).

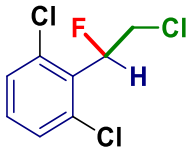
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.55 (m, 2H, Ph H-2,6), 7.24 (m, 2H, Ph H-3,5), 5.57 (ddd, 1H, $^{2}J_{H,F}$ = 46.6 Hz, $^{3}J_{H,H}$ = 7.1 Hz, $^{3}J_{H,H}$ = 4.3 Hz, CHF), 3.85-2.68 (m, 2H, CH_2Cl).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.6 (d, 1C, $^{2}J_{C,F}$ = 20.5 Hz, Ph C-4), 131.9 (2C, Ph C-2,6), 27.4 (d, 2C, $^{3}J_{C,F}$ = 6.8 Hz, Ph C-3,5), 123.3 (d, 1C, $^{5}J_{C,F}$ = 2.2 Hz, Ph C-1), 91.3 (d, 1C, $^{1}J_{C,F}$ = 179.1 Hz, CHF), 46.4 (d, 1C, $^{2}J_{C,F}$ = 28.4 Hz, CH_2Cl).

^{19}F NMR (470 MHz, $CDCl_3$) δ: -178.8 (ddd, 1F, $^{2}J_{H,F}$ = 46.6 Hz, $^{1}J_{C,F}$ = 23.4 Hz, $^{2}J_{C,F}$ = 16.1 Hz, F-1).

EI-MS m/z (%): 237.0 (M^+, 58), 239.0 (M^++2, 14), 189.0 (M^+, 100), 108.0 (M^+, 89), 51.0 (M^+, 30).

1,3-dichloro-2-(2-chloro -1-fluoroethyl) benzene (5)



By following **General procedure 1**, starting from 2,6-dichlorobenzaldehyde (200 mg, 1.1 mmol, 1 equiv) in dry THF (3 mL), iodochoromethane (0.13 mL, 1.7 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), the **compound 5** was obtained in 85 % yield (221 mg) as colorless oil after column chromatography on neutral alumina grade IV (*n*-hexane as eluent).

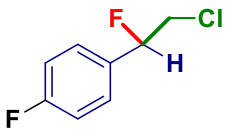
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 (m, 2H, Ph H-4,6), 7.25 (m, 1H, Ph H-5), 6.29 (ddd, 1H, $^{2}J_{H,F}$ = 46.0 Hz, $^{3}J_{H,H}$ = 8.7 Hz, $^{3}J_{H,H}$ = 4.8 Hz, CHF), 4.27 (m, 1H, CH_2Cl), 3.90 (ddd, 1H, $^{3}J_{H,F}$ = 24.1 Hz, $^{2}J_{H,H}$ = 11.9 Hz, $^{3}J_{H,H}$ = 4.8 Hz, CH_2Cl).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.0 (d, 2C, $^{3}J_{C,F}$ = 3.1 Hz, Ph C-1,3), 130.9 (d, 1C, $^{2}J_{C,F}$ = 18.4 Hz, Ph C-2), 130.8 (d, 1C, $^{5}J_{C,F}$ = 1.5 Hz, Ph C-5), 129.5 (d, 2C, $^{4}J_{C,F}$ = 1.1 Hz, Ph C-4,6), 90.0 (d, 1C, $^{1}J_{C,F}$ = 182.9 Hz, CHF), 42.9 (d, 1C, $^{2}J_{C,F}$ = 23.2 Hz, CH_2Cl).

^{19}F NMR (470 MHz, $CDCl_3$) δ: -183.5 (dddq, 1F, $^{2}J_{H,F}$ = 46.0 Hz, $^{3}J_{H,F}$ = 34.3 Hz, $^{3}J_{H,F}$ = 24.1 Hz, $^{2}J_{C,F}$ = 10.1 Hz, $^{5}J_{C,F}$ = 1.1 Hz, F-1).

EI-MS m/z (%): 227.0 (M^+, 30), 229.0 (M^++2, 10), 177.0 (M^+, 100), 107.0 (M^+, 26), 50.0 (M^+, 10).

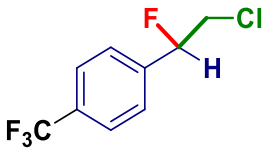
1-(2-chloro -1-fluoroethyl)-4-fluorobenzene (6)



By following **General procedure 1**, starting from 4-fluorobenzaldehyde (200 mg, 1.6 mmol, 1 equiv) in dry THF (3 mL), iodochoromethane (0.18 mL, 2.4 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (1.0 mL, 2.2 mmol, 1.4 equiv), Deoxofluor 2.7 M solution in (2.4 mL, 6.7 mmol, 4.2 equiv), the **compound 6** was obtained in 93 % yield (265 mg) as colorless oil without any further purification.

^{1}H NMR (400 MHz, C_6D_6) δ: 6.68 (m, 2H, Ph H-2,6), 6.65 (m, 2H, Ph H-3,5), 5.03 (ddd, 1H, $^2J_{H,F}$ = 46.8 Hz, $^3J_{H,H}$ = 7.5 Hz, $^3J_{H,H}$ = 3.9 Hz, CHF), 3.22 (m, 1H, CH_2Cl), 3.08 (m, 1H, CH_2Cl).
^{13}C NMR (100 MHz, C_6D_6) δ: 163.3 (dd, 1C, $^1J_{C,F}$ = 247.5 Hz, $^5J_{C,F}$ = 1.9 Hz, Ph C-4), 132.8 (dd, 1C, $^2J_{C,F}$ = 20.7 Hz, $^4J_{C,F}$ = 3.3 Hz, Ph C-1), 128.0 (m, 2C, Ph C-2,6), 115.6 (d, 2C, $^2J_{C,F}$ = 21.7 Hz, Ph C-3,5), 92.2 (d, 1C, $^1J_{C,F}$ = 178.9 Hz, CHF), 46.6 (d, 1C, $^2J_{C,F}$ = 28.2 Hz, CH_2Cl).
^{19}F NMR (470 MHz, C_6D_6) δ: -177.0 (m, 1F, F-1), -112.4 (m, 1F, F-4).

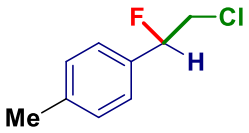
1-(2-chloro -1-fluoroethyl)-4-(trifluoromethyl) benzene (7)



By following **General procedure 1**, starting from 4-(trifluoromethyl)benzaldehyde (200 mg, 1.2 mmol, 1 equiv) in dry THF (3 mL), iodochoromethane (0.12 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), the **compound 7** was obtained in 83 % yield (216 mg) as colorless oil after column chromatography on neutral alumina grade IV (*n*-hexane as eluent).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69 (m, 2H, Ph H-3,5), 7.50 (m, 2H, Ph H-2,6), 5.68 (ddd, 1H, $^2J_{H,F}$ = 46.5 Hz, $^3J_{H,H}$ = 6.6 Hz, $^3J_{H,H}$ = 4.7 Hz, CHF), 3.89-3.73 (m, 2H, CH_2Cl).
^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.4 (d, 1C, $^2J_{C,F}$ = 20.5 Hz, Ph C-1),131.4 (q, 1C, $^2J_{C,F}$ = 32.0 Hz, Ph C-4), 126.1 (d, 2C, $^3J_{C,F}$ = 7.2 Hz, Ph C-2,6), 125.7 (d, 2C, $^4J_{C,F}$ = 3.7 Hz, Ph C-3,5), 123.8 (q, 1C, $^1J_{C,F}$ = 272.2 Hz, CF_3), 92.0 (d, 1C, $^1J_{C,F}$ = 180.1 Hz, CHF), 46.4 (d, 1C, $^2J_{C,F}$ = 27.7 Hz, CH_2Cl).
^{19}F NMR (470 MHz, $CDCl_3$) δ: -180.9 (ddd, 1F, $^2J_{H,F}$ = 46.5 Hz, $^3J_{H,F}$ = 22.6 Hz, $^2J_{C,F}$ = 17.7 Hz, F-1), -62.8 (s, 1F, CF_3).
EI-MS m/z (%): 249.0 (M^+, 100), 207.0 (M^+, 19), 177.0 (M^+, 15), 165.0 (M^+, 39).

1-(2-chloro -1-fluoroethyl)-4-methylbenzene (8)



By following **General procedure 1**, starting from 4-methylbenzaldehyde (200 mg, 1.7 mmol, 1 equiv) in dry THF (3 mL), iodochoromethane (0.18 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, 6.9 mmol, 4.2 equiv), the **compound 8** was obtained in 95% yield (273 mg) as colorless oil without any further purification.

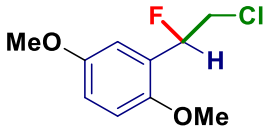
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.26 (m, 2H, Ph H-2,6), 7.23 (m, 2H, Ph H-3,5), 5.57 (ddd, 1H, $^2J_{H,F}$ = 47.1 Hz, $^3J_{H,H}$ = 7.8 Hz, $^3J_{H,H}$ = 3.9 Hz, CHF), 3.89-3.67 (m, 2H, CH_2Cl), 2.38 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.2 (d, 1C, $^5J_{C,F}$ = 1.9 Hz, Ph C-4), 133.6 (d, 1C, $^2J_{C,F}$ = 20.2 Hz, Ph C-1), 129.4 (2C, Ph C-3,5), 125.8 (d, 2C, $^3J_{C,F}$ = 6.4 Hz, Ph C-2,6), 93.0 (d, 1C, $^1J_{C,F}$ = 177.6 Hz, CHF), 46.8 (d, 1C, $^2J_{C,F}$ = 28.7 Hz, CH_2Cl), 21.2 (1C, CH_3).

^{19}F NMR (470 MHz, $CDCl_3$) δ: -176.9 (m, 1F, F-1).

EI-MS m/z (%): 172.0 (M^+, 5), 174.0 (M^++2, 16), 122.9 (M^+, 100), 103.0 (M^+, 42), 91.0 (M^+, 16), 77.0 (M^+, 32).

2-(2-chloro -1-fluoroethyl)-1,4-dimethoxybenzene (9)



By following **General procedure 1**, starting from 2,5-dimethoxybenzaldehyde (200 mg, 1.2 mmol, 1 equiv) in dry THF (3 mL), iodochoromethane (0.13 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, 5.0 mmol, 4.2 equiv), the **compound 9** was obtained in 82 % yield (216 mg) as colorless oil after column chromatography on neutral alumina grade IV (*n*-hexane/ethyl ether 8:2 as eluent).

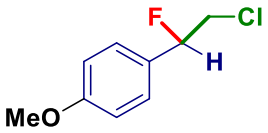
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.00 (d, 1H, $^4J_{H,H}$ = 2.9 Hz, Ph H-1,3), 6.86 (dd, 1H, $^3J_{H,H}$ = 9.0 Hz, $^4J_{H,H}$ = 2.9 Hz, Ph H-5), 6.81 (dd, 1H, $^3J_{H,H}$ = 9.0 Hz, $^5J_{H,F}$ = 1.1 Hz, Ph H-6), 5.91 (ddd, 1H, $^2J_{H,F}$ = 47.2 Hz, $^3J_{H,H}$ = 7.7 Hz, $^3J_{H,H}$ = 2.6 Hz, CHF), 3.86 (ddd, 1H, $^3J_{H,F}$ = 29.0 Hz, $^2J_{H,H}$ = 12.1 Hz, $^3J_{H,H}$ = 2.6 Hz, CH_2Cl), 3.80 (s, 3H, C_1OCH_3), 3.79 (s, 3H, C_4OCH_3), 3.73 (ddd, 1H, $^3J_{H,F}$ = 19.3 Hz, $^2J_{H,H}$ = 12.1 Hz, $^3J_{H,H}$ = 7.7 Hz, CH_2Cl).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.7 (1C, Ph C-4), 149.6 (d, 1C, $^3J_{C,F}$ = 5.6 Hz, Ph C-1), 125.9 (d, 1C, $^2J_{C,F}$ = 20.4 Hz, Ph C-2), 114.6 (1C, Ph C-5), 112.1 (d, 1C, $^3J_{C,F}$ = 10.7 Hz, Ph C-3), 111.4 (1C, Ph C-6), 89.0 (d, 1C, $^1J_{C,F}$ = 177.7 Hz, CHF), 55.81 (1C, C_1OCH_3), 55.79 (1C, C_4OCH_3), 46.2 (d, 1C, $^2J_{C,F}$ = 25.2 Hz, CH_2Cl).

^{19}F NMR (470 MHz, $CDCl_3$) δ: -189.5 (dddd, 1F, $^2J_{H,F}$ = 47.2 Hz, $^3J_{H,F}$ = 29.0 Hz, $^2J_{C,F}$ = 19.3 Hz, $^5J_{H,F}$ = 1.0 Hz, F-1).

EI-MS m/z (%): 218.0 (M^+, 13), 220.0 (M^++2, 5), 169.0 (M^+, 100), 121.0 (M^+, 99), 91.0 (M^+, 84), 77.0 (M^+, 58).

1-(2-chloro -1-fluoroethyl)-4-methoxybenzene (10)



By following **General procedure 1**, starting from 4-methoxybenzaldehyde (200 mg, 1.5 mmol, 1 equiv) in dry THF (3 mL), iodochoromethane (0.16 mL, 2.2 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (1.0 mL, 2.1 mmol, 1.4 equiv), Deoxofluor 2.7 M solution in (2.3 mL, 6.3 mmol, 4.2 equiv), the **compound 10** was obtained in 84 % yield (233 mg) as colorless oil after column chromatography on neutral alumina grade IV (*n*-hexane/ethyl ether 8:2 as eluent).

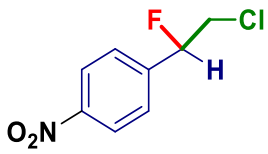
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 (m, 2H, Ph H-2,6), 6.93 (m, 2H, Ph H-3,5), 5.54 (ddd, 1H, $^2J_{H,F}$ = 46.9 Hz, $^3J_{H,H}$ = 7.9 Hz, $^3J_{H,H}$ = 4.1 Hz, CHF), 3.84 (ddd, 1H, $^3J_{H,F}$ = 14.5 Hz, $^2J_{H,H}$ = 12.1 Hz, $^3J_{H,H}$ = 7.9 Hz, CH_2Cl), 3.82 (s, 3H, OCH_3), 3.71 (ddd, 1H, $^3J_{H,F}$ = 25.3 Hz, $^2J_{H,H}$ = 12.1 Hz, $^3J_{H,H}$ = 7.9 Hz, CH_2Cl).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.3 (d, 1C, $^5J_{C,F}$ = 1.8 Hz, Ph C-4), 128.6 (d, 1C, $^2J_{C,F}$ = 20.6 Hz, Ph C-1), 127.4 (d, 2C, $^3J_{C,F}$ = 6.1 Hz, Ph C-2,6), 114.1 (2C, Ph C-3,5), 92.9 (d, 1C, $^1J_{C,F}$ = 176.9 Hz, CHF), 55.3 (1C, OCH_3), 46.7 (d, 1C, $^2J_{C,F}$ = 29.6 Hz, CH_2Cl).

^{19}F NMR (470 MHz, $CDCl_3$) δ: -189.5 (ddd, 1F, $^2J_{H,F}$ = 46.9 Hz, $^3J_{H,F}$ = 25.1 Hz, $^3J_{H,F}$ = 14.4 Hz, F-1).

EI-MS m/z (%): 169.0 (M^+, 100), 134.0 (M^+, 33), 121.0 (M^+, 18), 91.0 (M^+, 22), 77.0 (M^+, 17).

1-(2-chloro -1-fluoroethyl)-4-nitrobenzene (11)



By following **General procedure 1**, starting from 4-nitrobenzaldehyde (200 mg, 1.3 mmol, 1 equiv) in dry THF (3 mL), iodochoromethane (0.15 mL, 2.0 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (0.8 mL, 1.9 mmol, 1.4 equiv), Deoxofluor 2.7 M solution in (2.0 mL, 5.5 mmol, 4.2 equiv), the **compound 11** was obtained in 92% yield (247 mg) as colorless oil without any further purification.

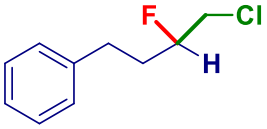
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69 (m, 2H, Ph H-3,5), 6.58 (m, 2H, Ph H-2,6), 4.89 (ddd, 1H, $^2J_{H,F}$ = 46.7 Hz, $^3J_{H,H}$ = 6.4 Hz, $^3J_{H,H}$ = 4.4 Hz, CHF), 3.11-2.95 (m, 2H, CH_2Cl).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.4 (1C, Ph C-4), 142.8 (d, 1C, $^2J_{C,F}$ = 20.4 Hz, Ph C-1), 126.4 (d, 2C, $^3J_{C,F}$ = 7.4 Hz, Ph C-2,6), 123.6 (2C, Ph C-3,5), 91.4 (d, 1C, $^1J_{C,F}$ = 181.3 Hz, CHF), 46.1 (d, 1C, $^2J_{C,F}$ = 26.7 Hz, CH_2Cl).

^{19}F NMR (470 MHz, $CDCl_3$) δ: -182.3 (m, 1F, F-1).

EI-MS m/z (%): 203.0 (M^+, 5), 154.0 (M^+, 100), 138.0 (M^+, 14), 124.0 (M^+, 75), 108.0 (M^+, 44).

(4-chloro -3-fluorobuthyl) benzene (12)



By following **General procedure 1**, starting from 3-phenylpropanal (200 mg, 1.5 mmol, 1 equiv) in dry THF (3 mL), iodochoromethane (0.16 mL, 2.2 mmol, 1.5 equiv), MeLi-LiBr 2.2 M solution in Et_2O (1.0 mL, 2.1 mmol, 1.4 equiv), Deoxofluor 2.7 M solution in (2.3 mL, 6.3 mmol, 4.2 equiv), the **compound 12** was obtained in 88% yield (245 mg) as colorless oil after column chromatography on neutral alumina grade IV (*n*-hexane as eluent).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31 (m, 2H, Ph H-3,5), 7.22 (m, 1H, Ph H-4), 7.21 (m, 2H, Ph H-2,6), 4.64 (m, 1H, $^2J_{H,F}$ = 47.8 Hz, CHF), 3.67 -3.59 (m, 2H, CH_2Cl), 2.85-2.73 (m, 2H, C-3H_2), 2.17-1.88 (m, 2H, C-2H_2).

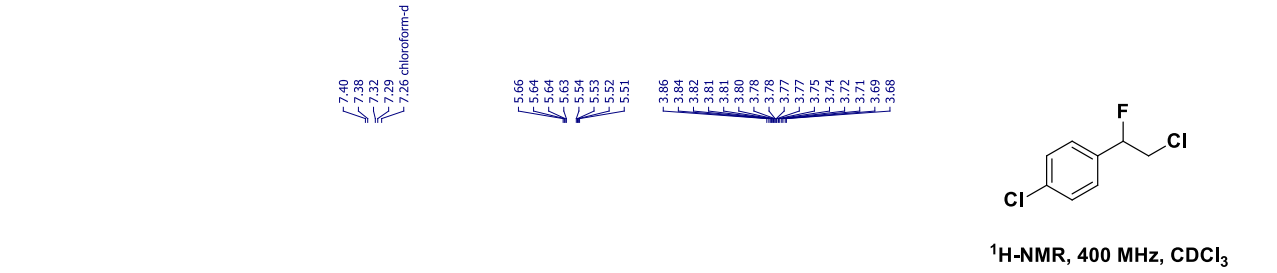
^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.6 (1C, Ph C-1), 128.6 (2C, Ph C-3,5), 128.4 (2C, Ph C-2,6), 126.2 (1C, Ph C-4), 91.4 (d, 1C, $^1J_{C,F}$ = 175.4 Hz, CHF), 45.7 (d, 1C, $^2J_{C,F}$ = 25.4 Hz, CH_2Cl), 34.1 (d, 1C, $^2J_{C,F}$ = 20.7 Hz, CH_2), 30.9 (d, 1C, $^3J_{C,F}$ = 4.2 Hz, CH_2).

^{19}F NMR (470 MHz, $CDCl_3$) δ: -183.6 (m, 1F, F-1).

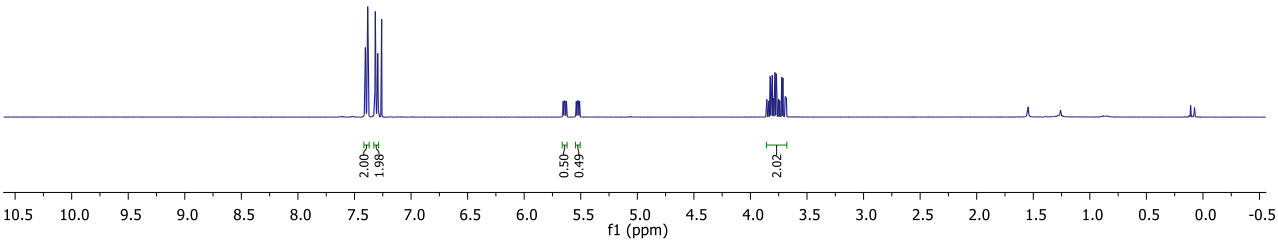
EI-MS m/z (%): 186.0 (M^+, 4), 105.0 (M^+, 8), 91.0 (M^+, 100).

4.4. ^{1}H-, ^{13}C- AND ^{19}F-NMR SPECTRA FOR ALL THE COMPOUNDS

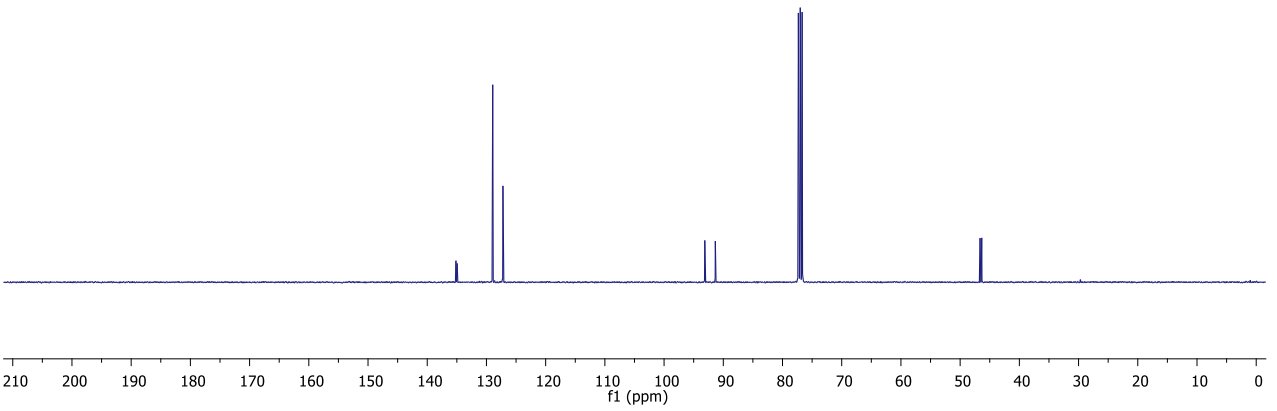
Compound 1

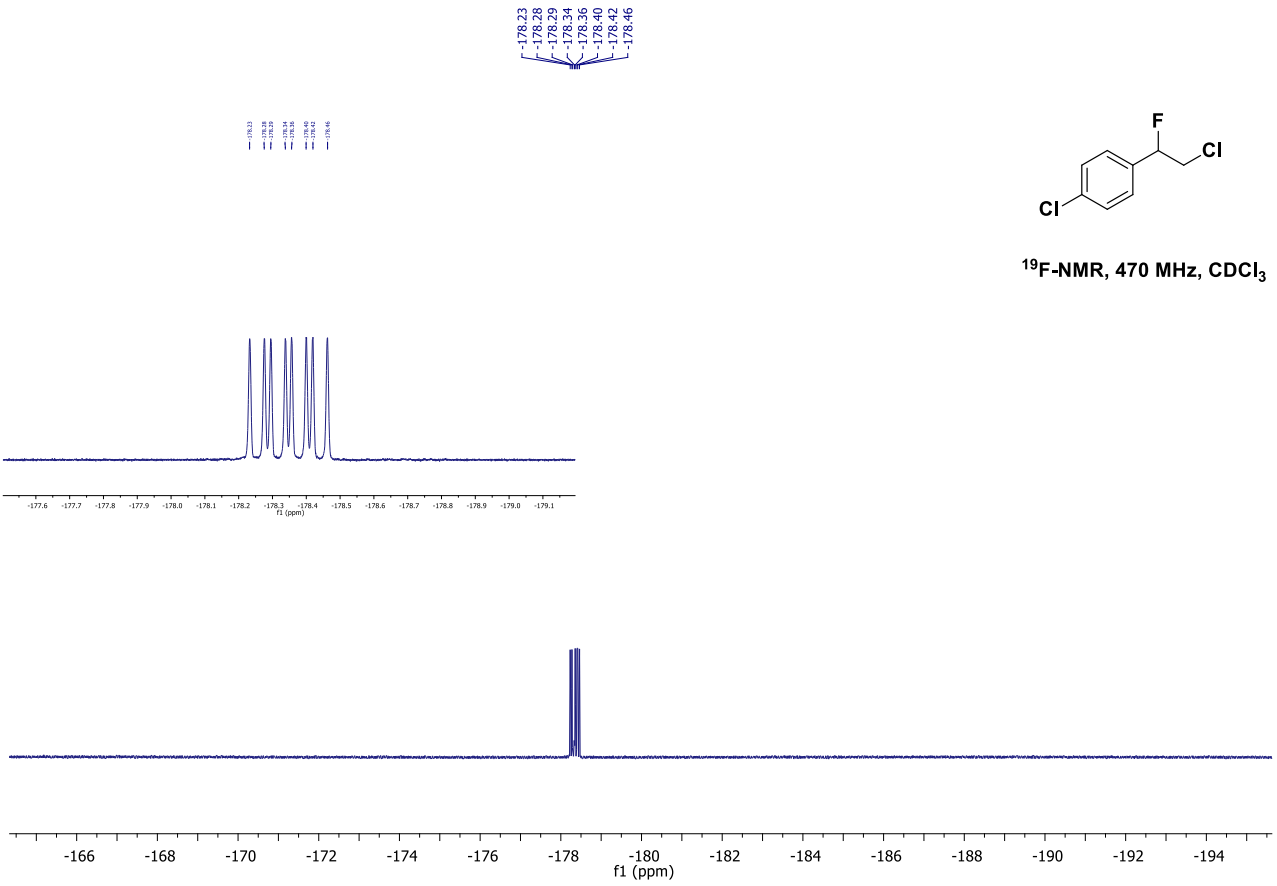


^{1}H-NMR, 400 MHz, $CDCl_3$



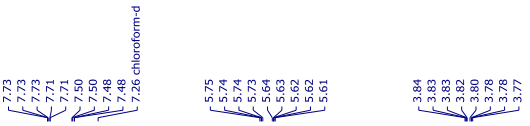
^{13}C-NMR, 100 MHz, $CDCl_3$

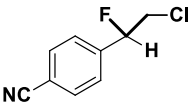




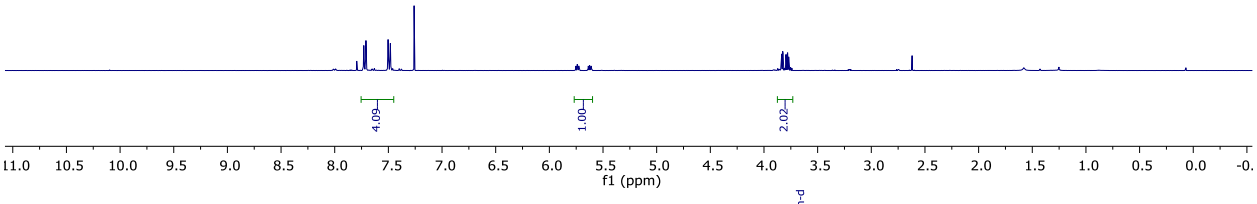
^{19}F-NMR, 470 MHz, $CDCl_3$

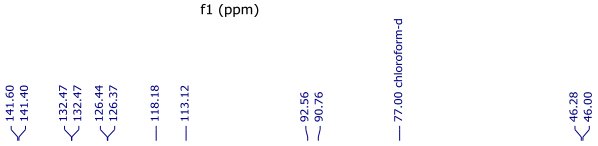
Compound 2

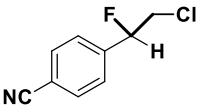




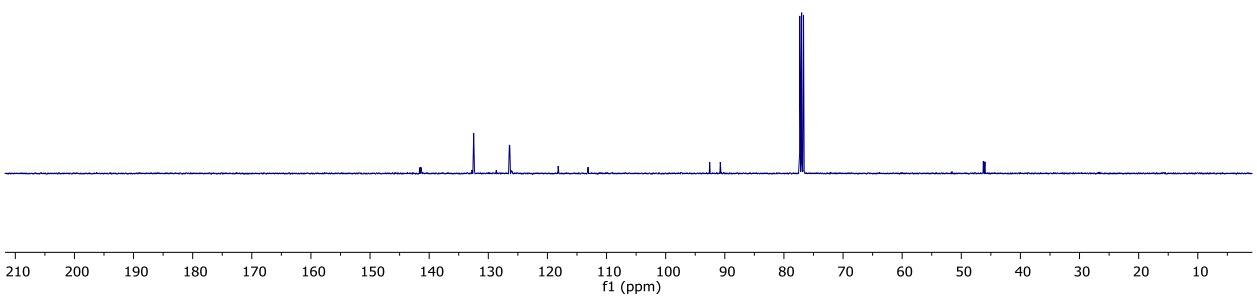
^{1}H-NMR, 400 MHz, $CDCl_3$

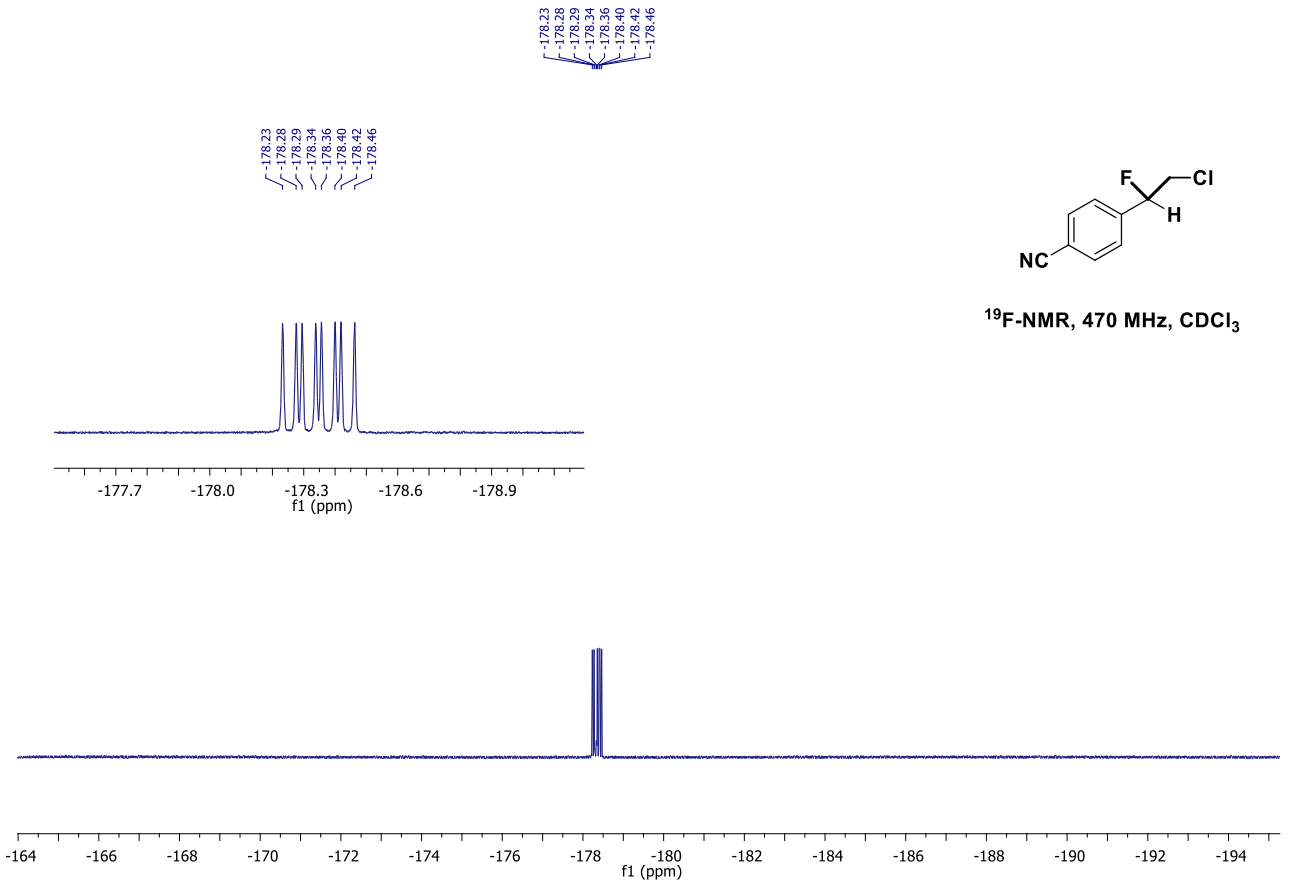






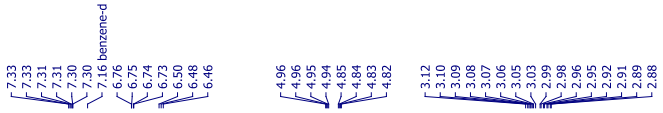
^{13}C-NMR, 100 MHz, $CDCl_3$

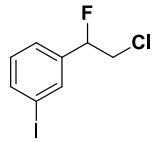




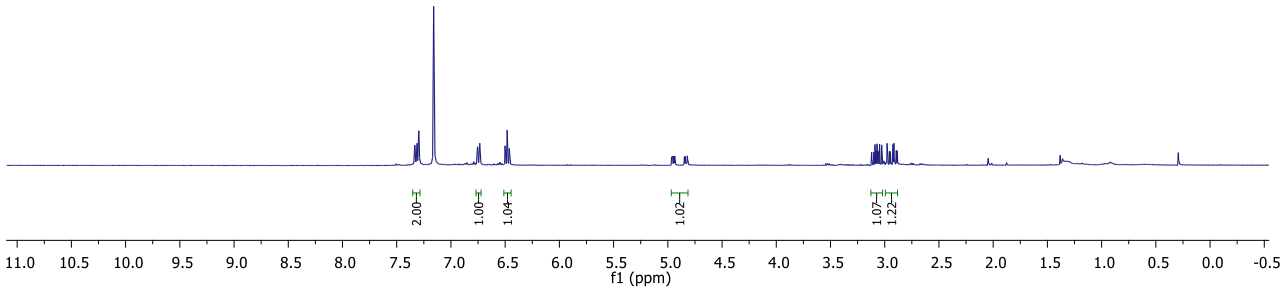
^{19}F-NMR, 470 MHz, $CDCl_3$

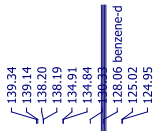
Compound 3

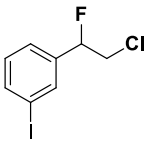




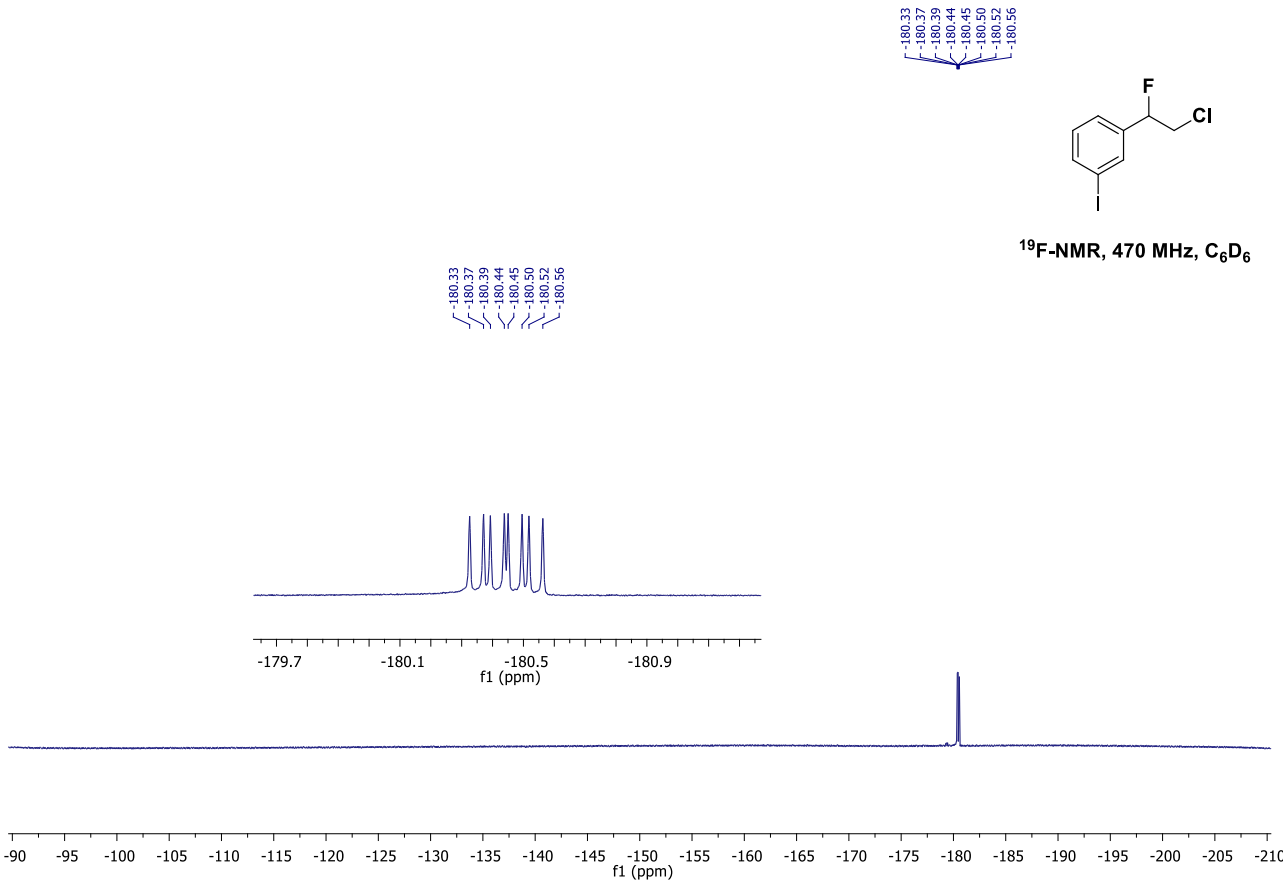
^{1}H-NMR, 400 MHz, C_6D_6



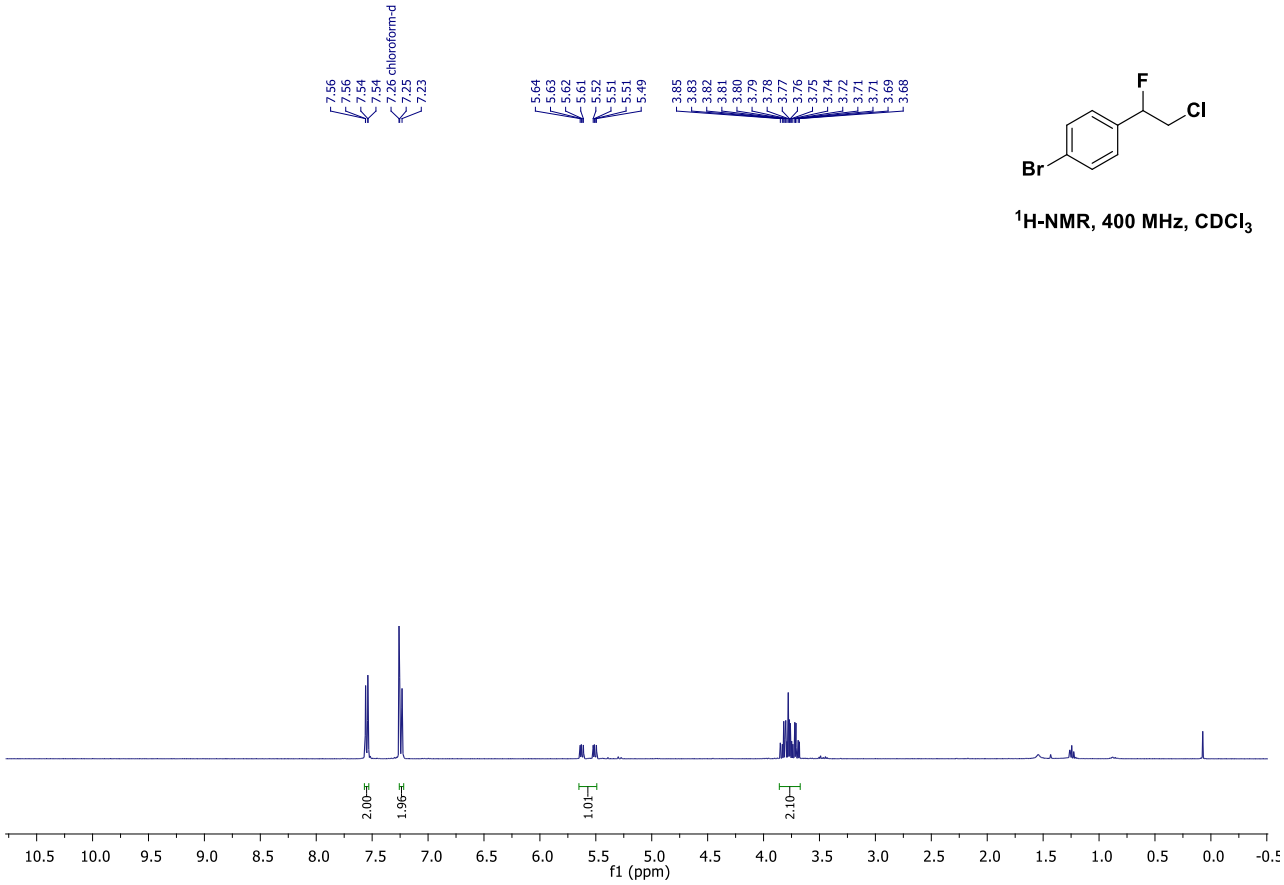




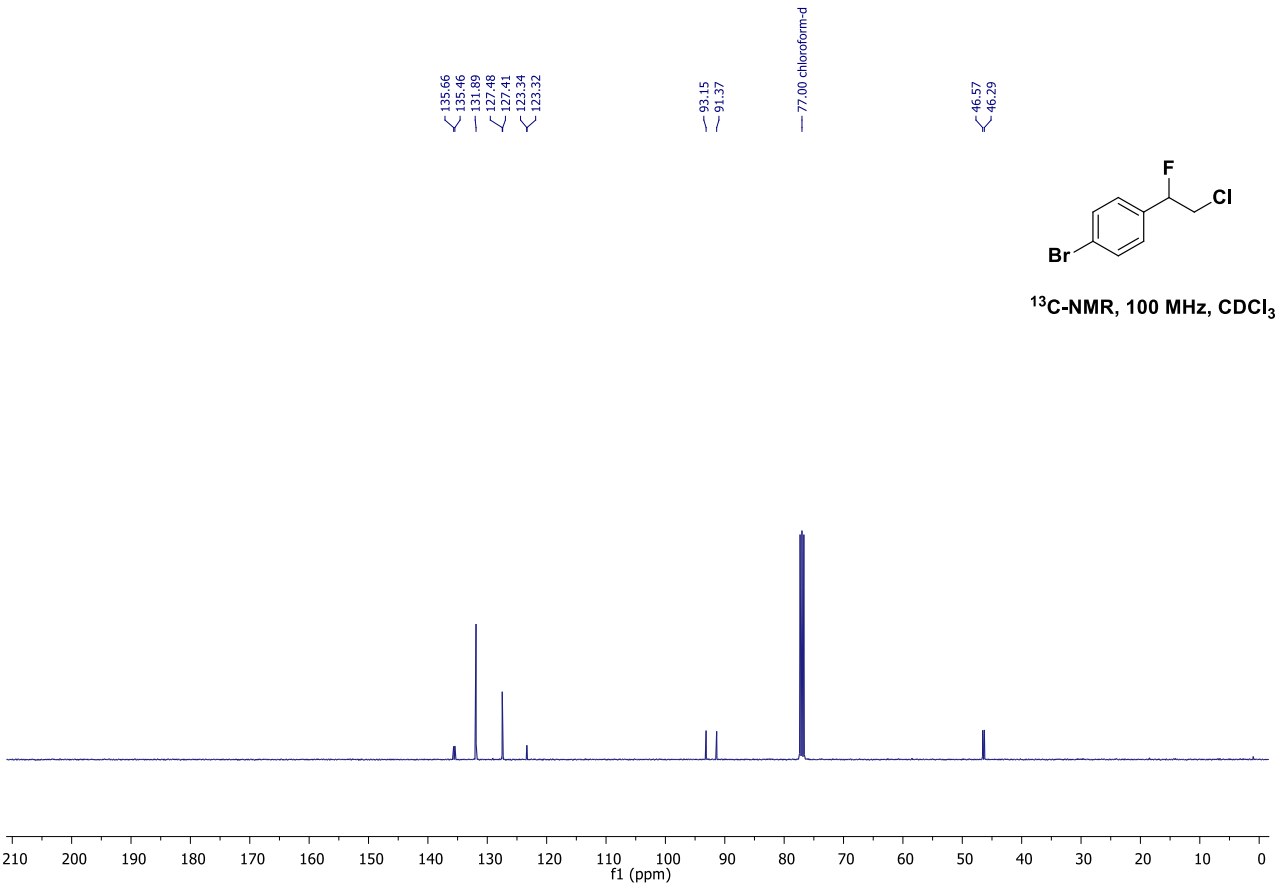
^{13}C-NMR, 100 MHz, C_6D_6


-180.33
-180.37
-180.39
-180.44
-180.45
-180.50
-180.52
-180.56
F
Cl
I
19F-NMR, 470 MHz, C6D6
-179.7
-180.1
-180.5
-180.9
f1 (ppm)
-90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160 -165 -170 -175 -180 -185 -190 -195 -200 -205 -210
f1 (ppm)

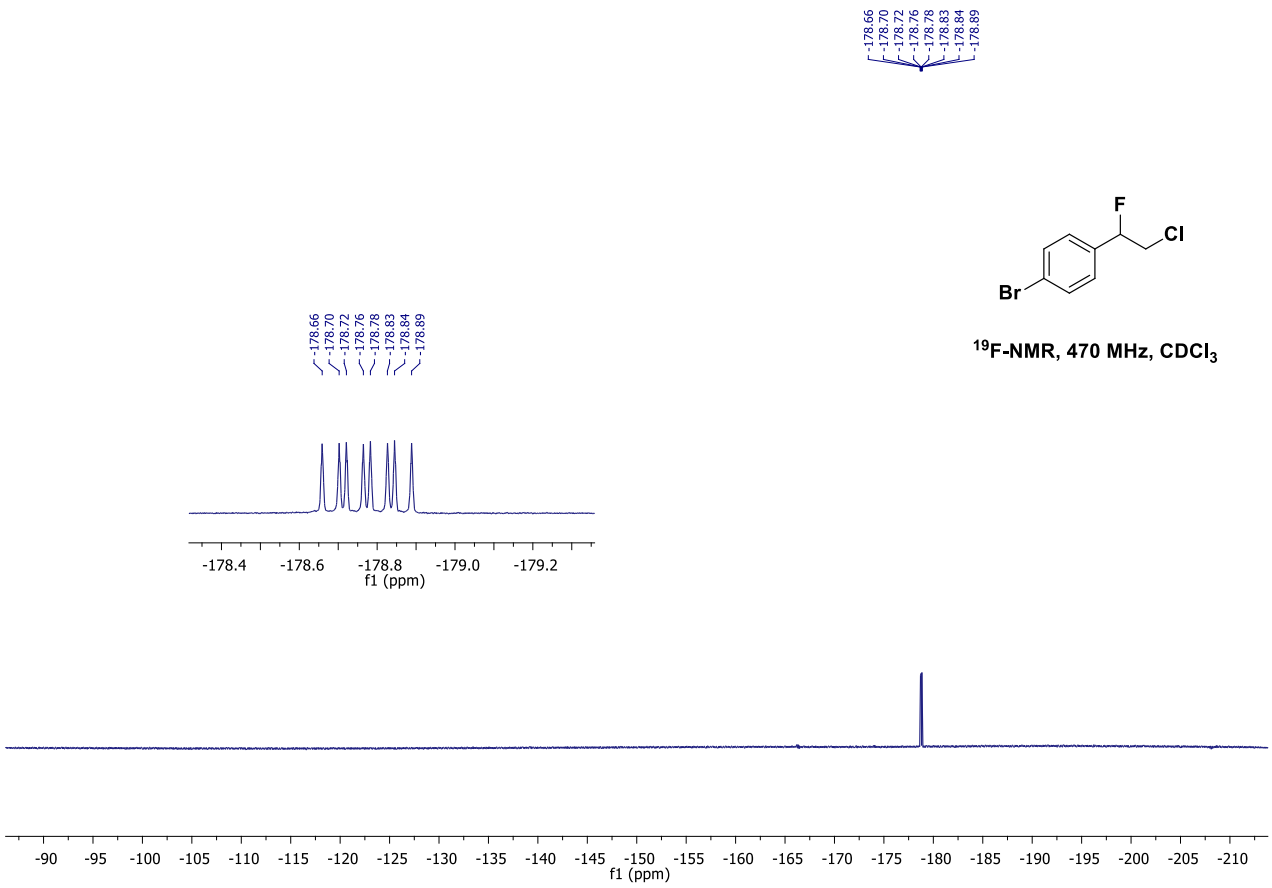
Compound 4



^{1}H-NMR, 400 MHz, $CDCl_3$

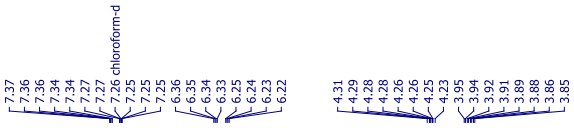


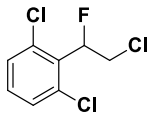
^{13}C-NMR, 100 MHz, $CDCl_3$



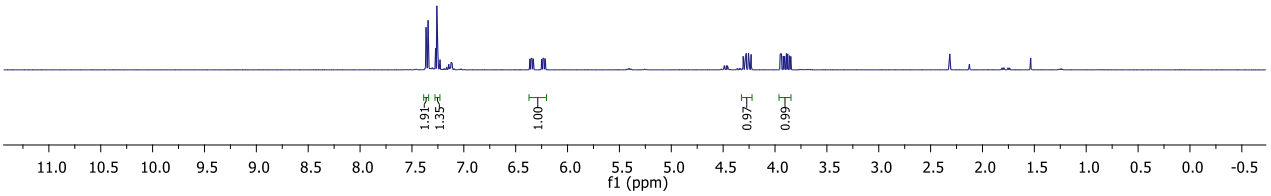
^{19}F-NMR, 470 MHz, $CDCl_3$

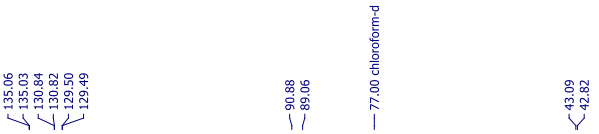
Compound 5

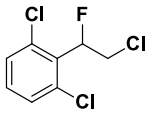




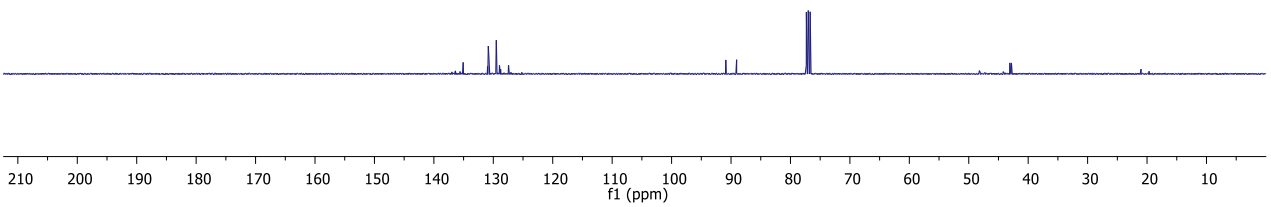
^{1}H-NMR, 400 MHz, $CDCl_3$

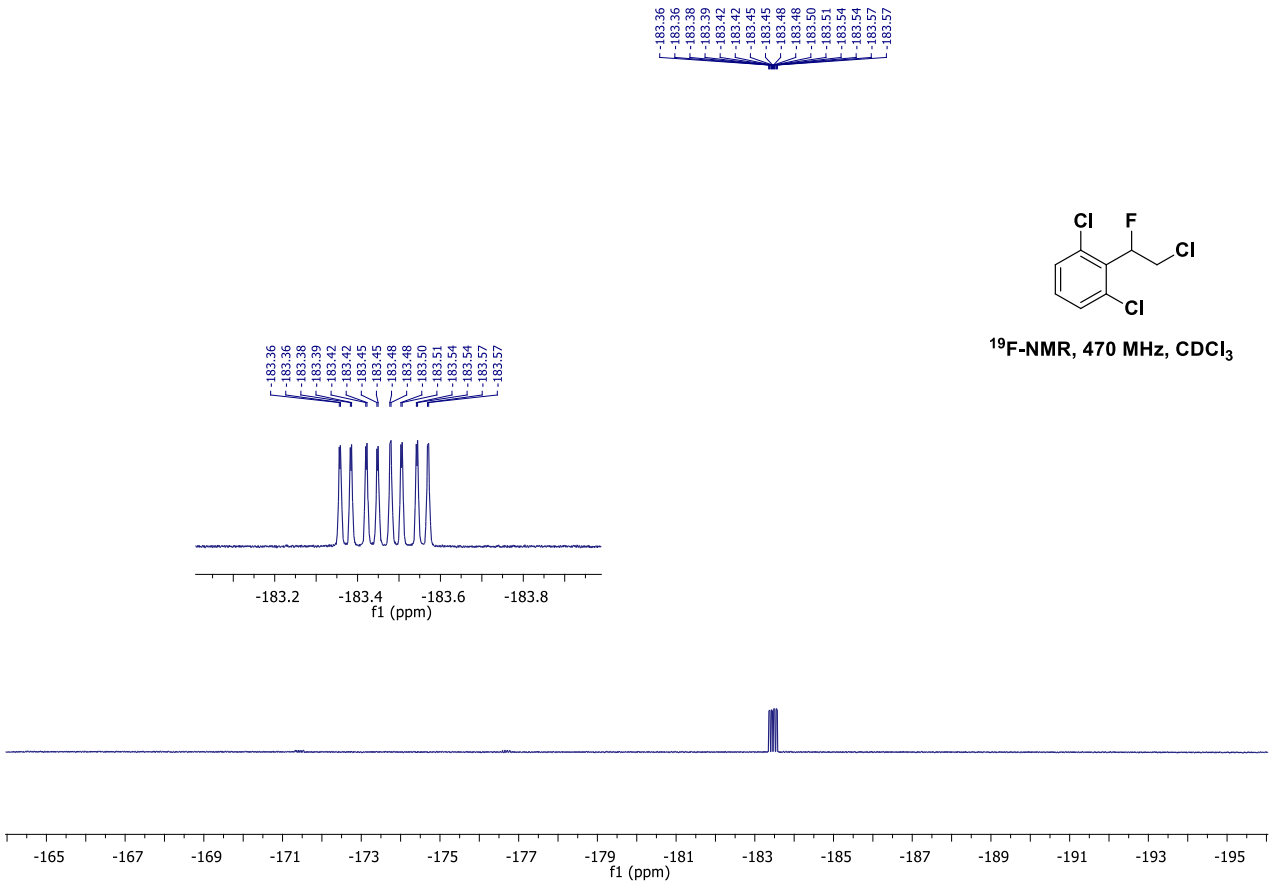






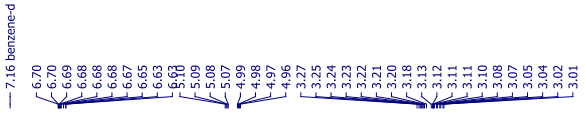
^{13}C-NMR, 100 MHz, $CDCl_3$

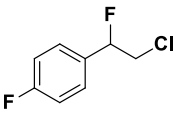




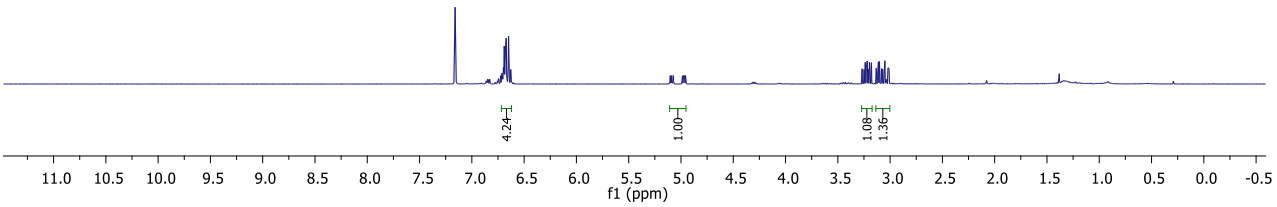
^{19}F-NMR, 470 MHz, $CDCl_3$

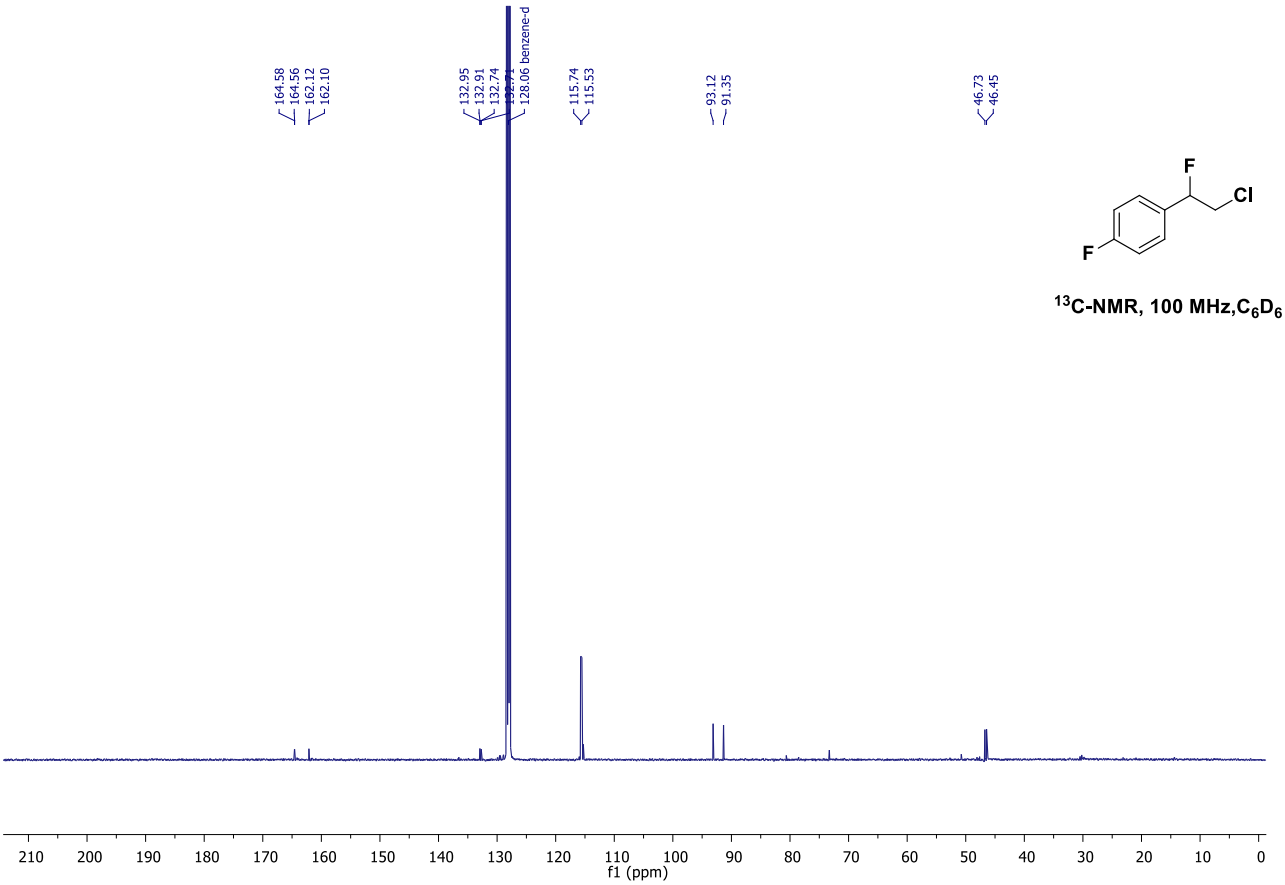
Compound 6



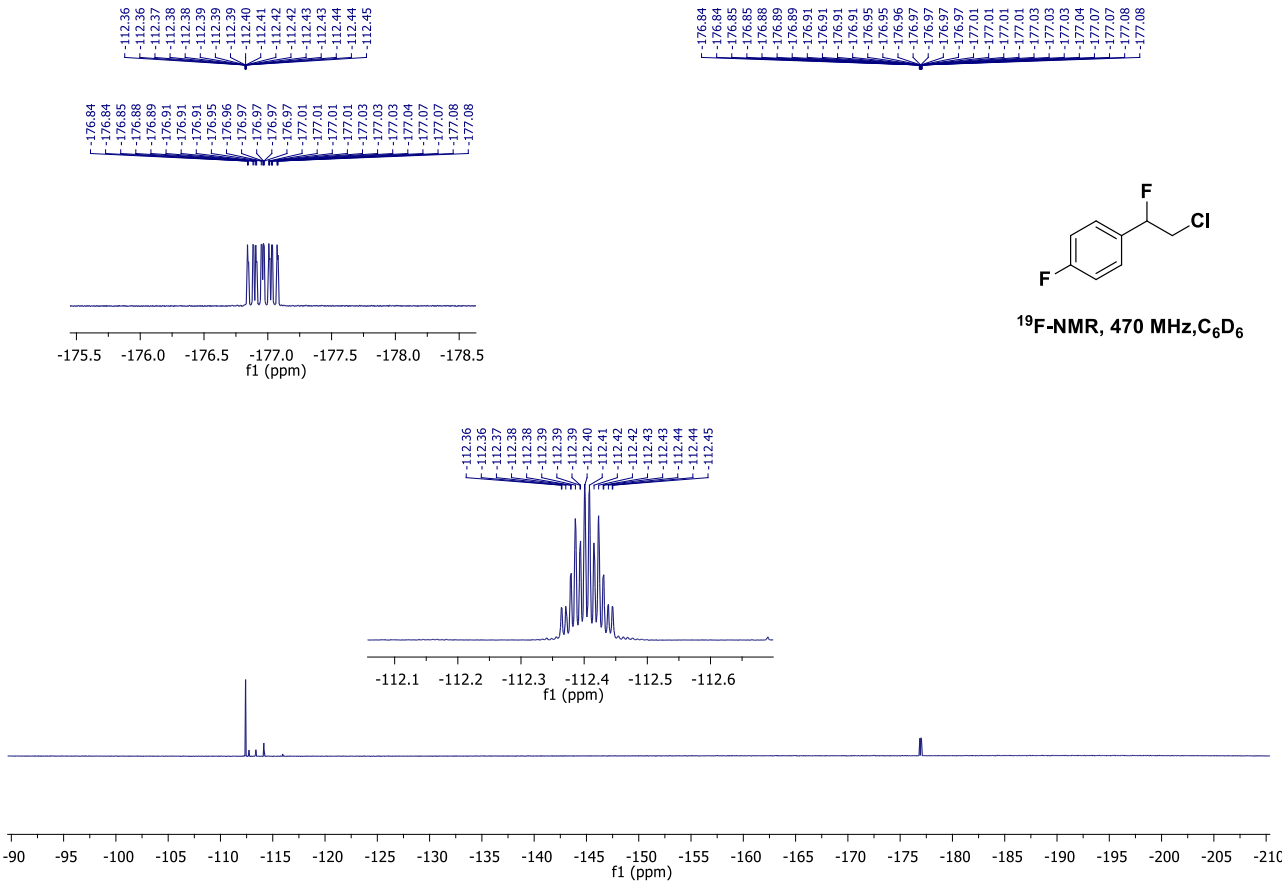


^{1}H-NMR, 400 MHz,C_6D_6



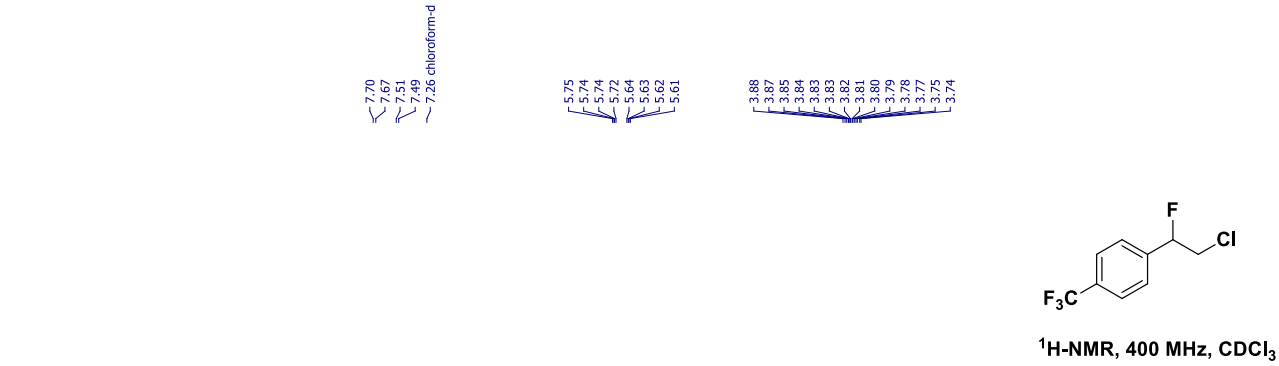


^{13}C-NMR, 100 MHz,C_6D_6

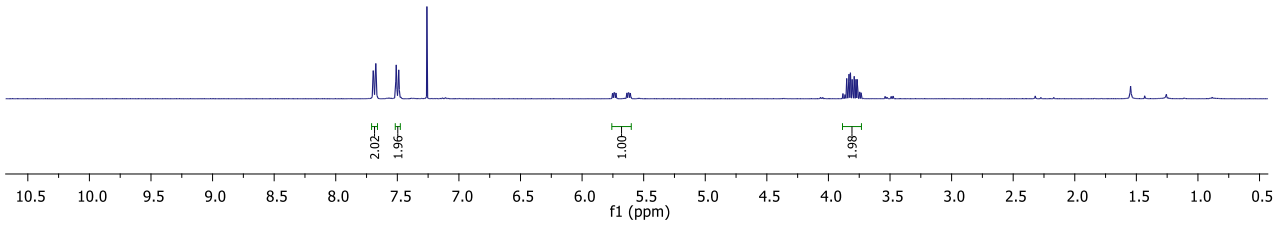


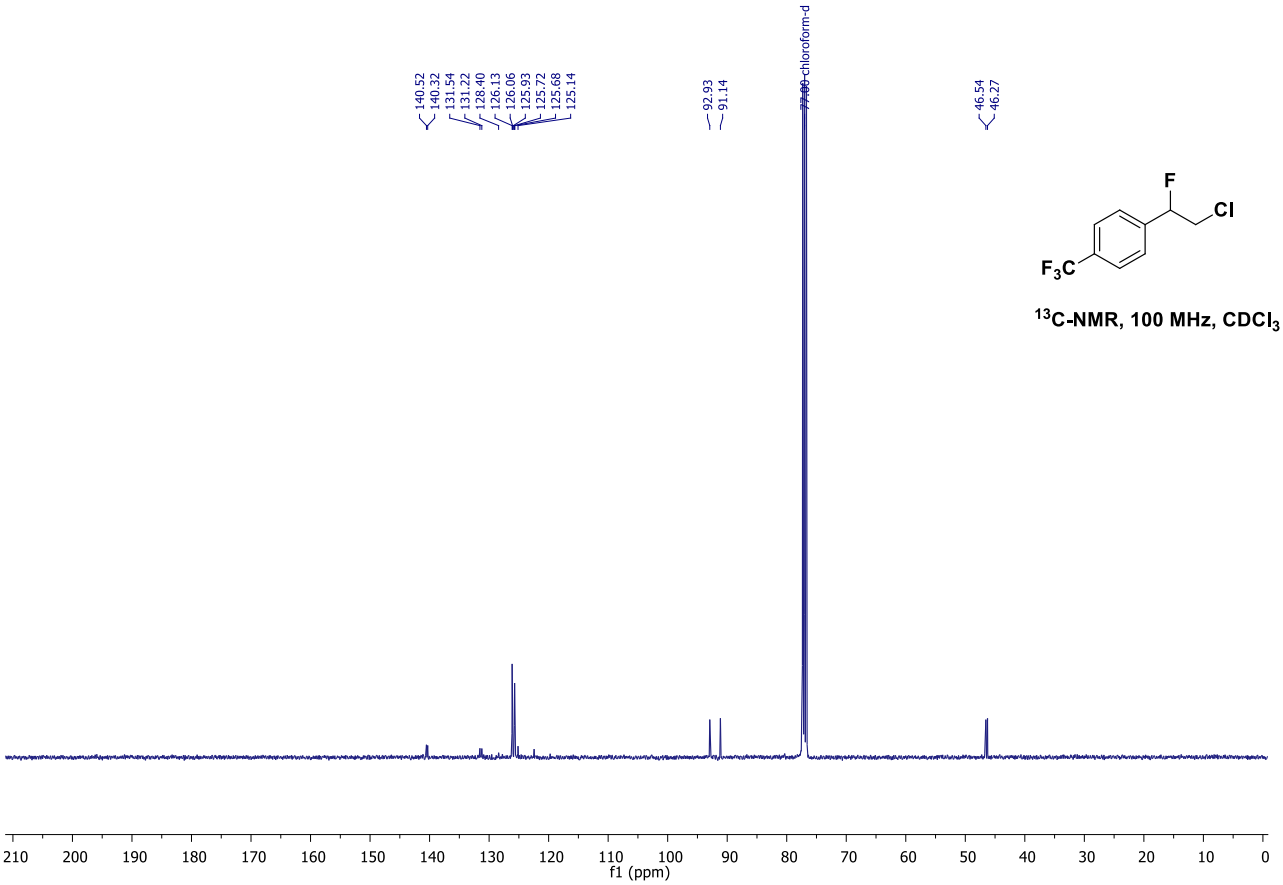
^{19}F-NMR, 470 MHz,C_6D_6

Compound 7

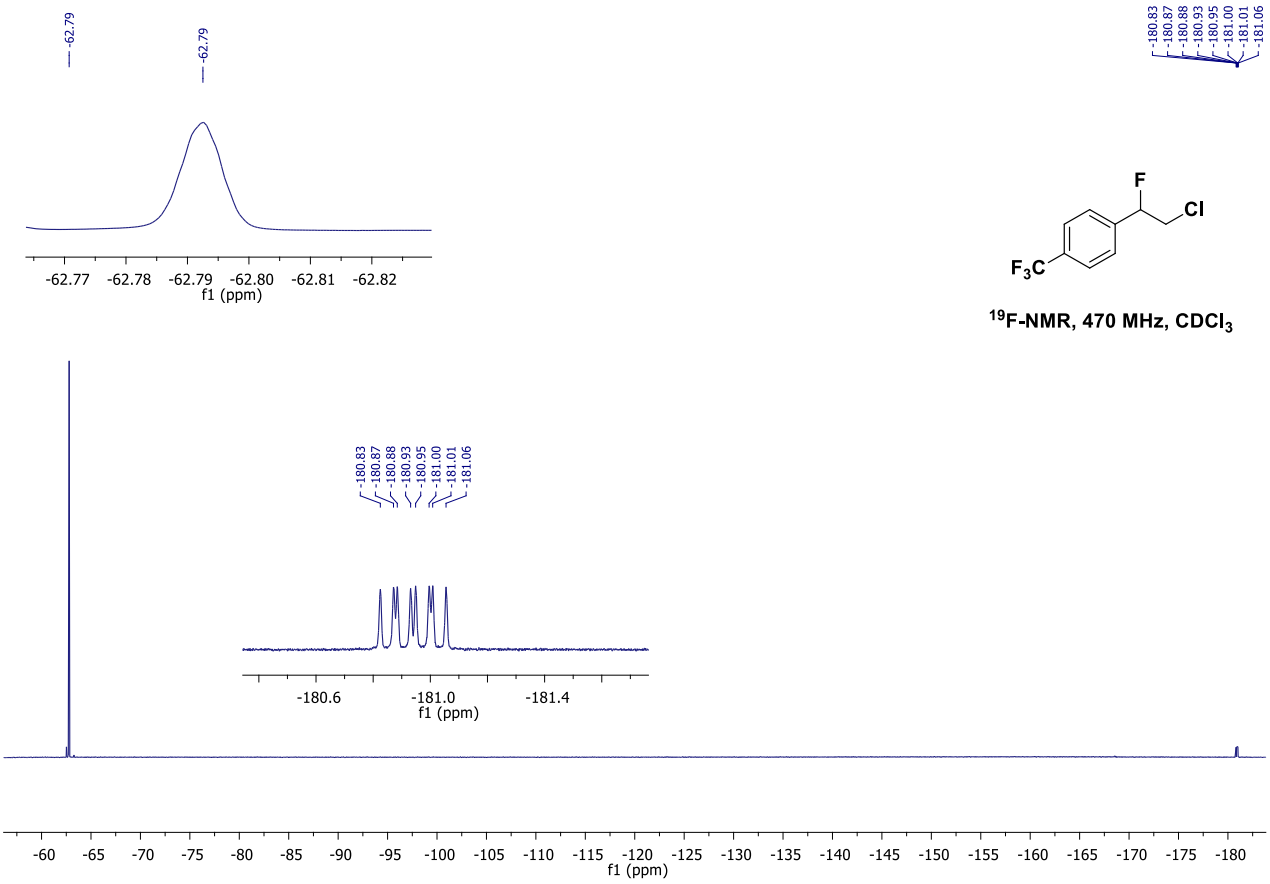


^{1}H-NMR, 400 MHz, $CDCl_3$

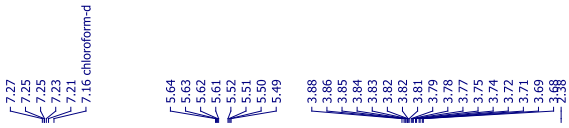


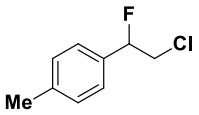


^{13}C-NMR, 100 MHz, $CDCl_3$

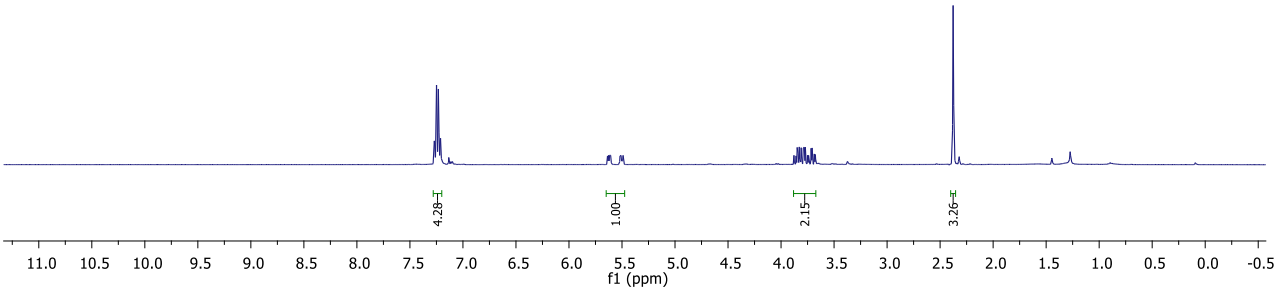

-62.79
-62.79
-62.77 -62.78 -62.79 -62.80 -62.81 -62.82
f1 (ppm)
-180.83
-180.87
-180.88
-180.93
-180.95
-181.00
-181.01
-181.06
F
Cl
F3C
19F-NMR, 470 MHz, CDCl3
-180.6 -181.0 -181.4
f1 (ppm)
-60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160 -165 -170 -175 -180
f1 (ppm)

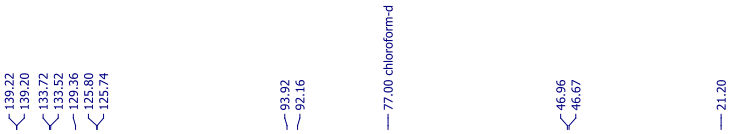
Compound 8

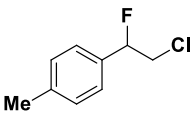




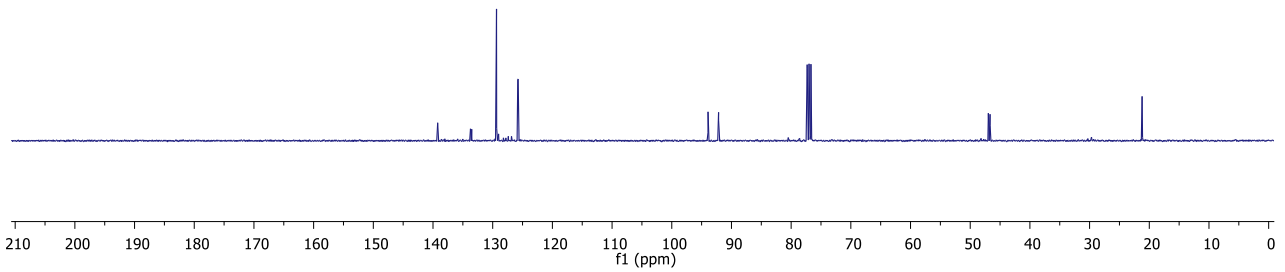
^{1}H-NMR, 400 MHz, $CDCl_3$

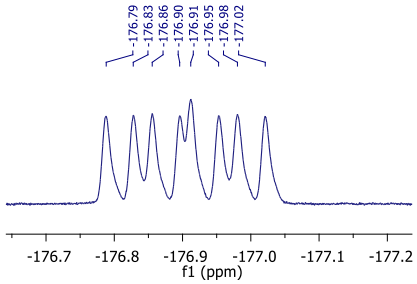


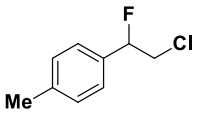




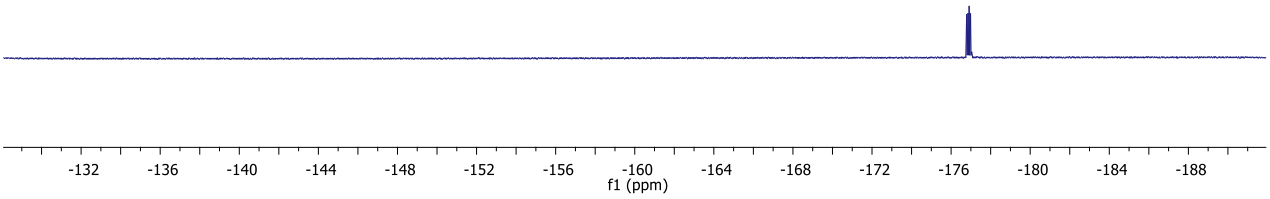
^{13}C-NMR, 100 MHz, $CDCl_3$



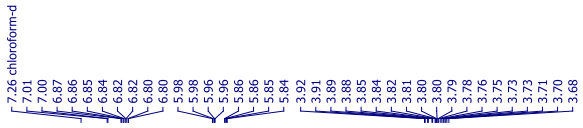


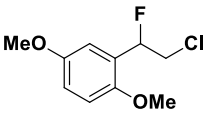


^{19}F-NMR, 470 MHz, $CDCl_3$

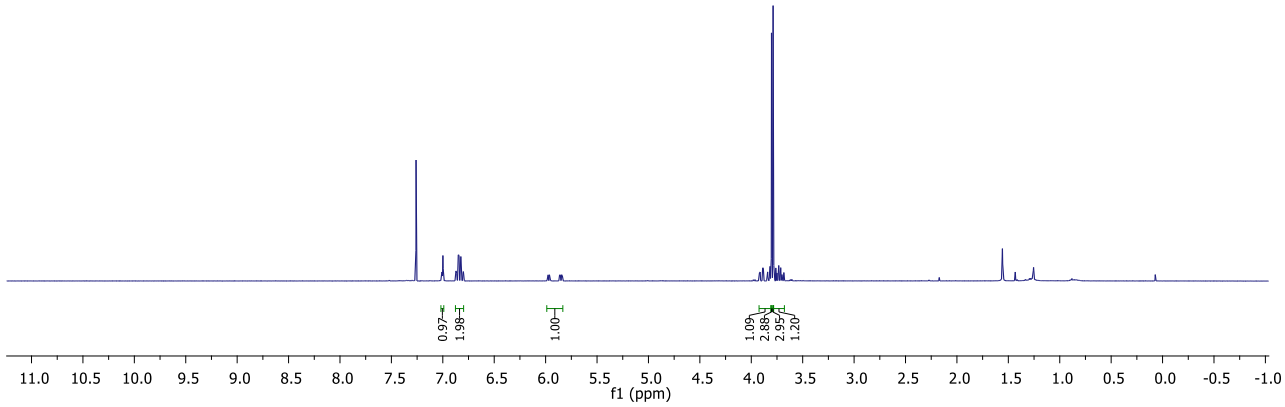


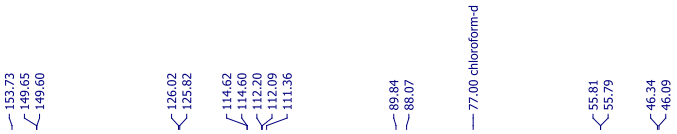
Compound 9

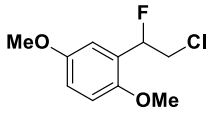




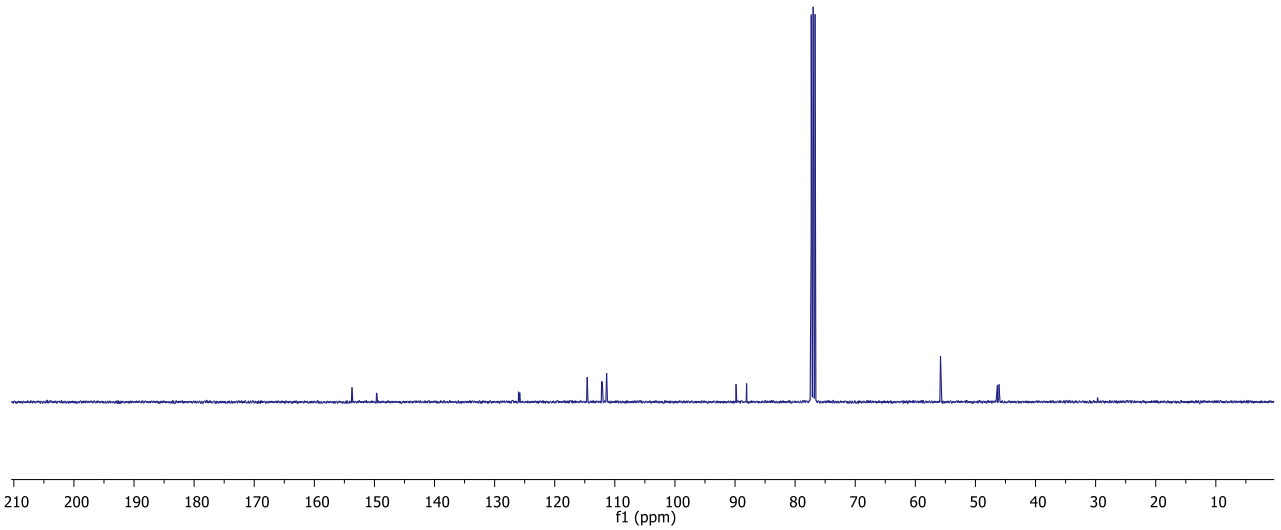
^{1}H-NMR, 400 MHz, $CDCl_3$

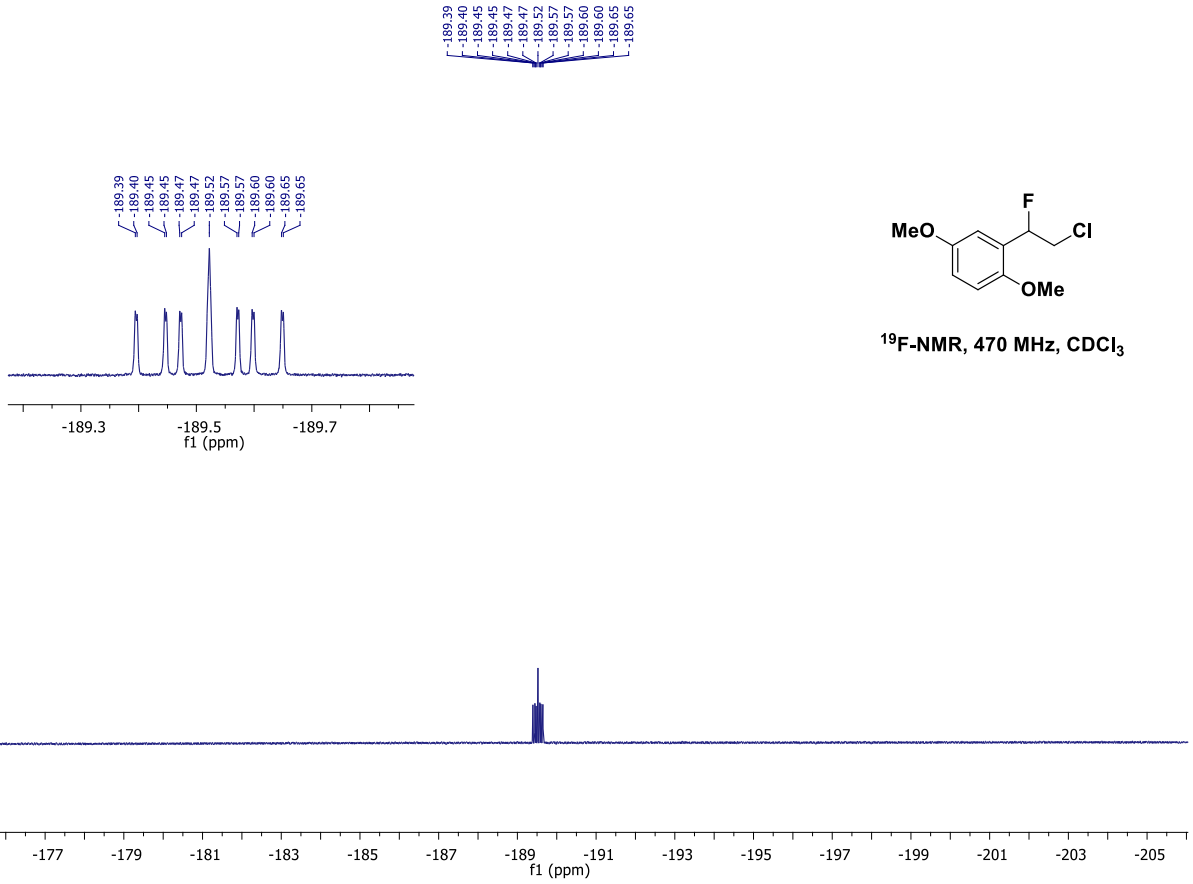






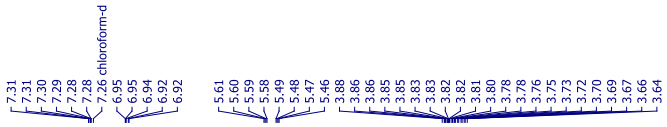
^{13}C-NMR, 100 MHz, $CDCl_3$

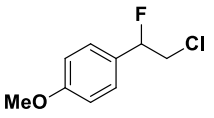




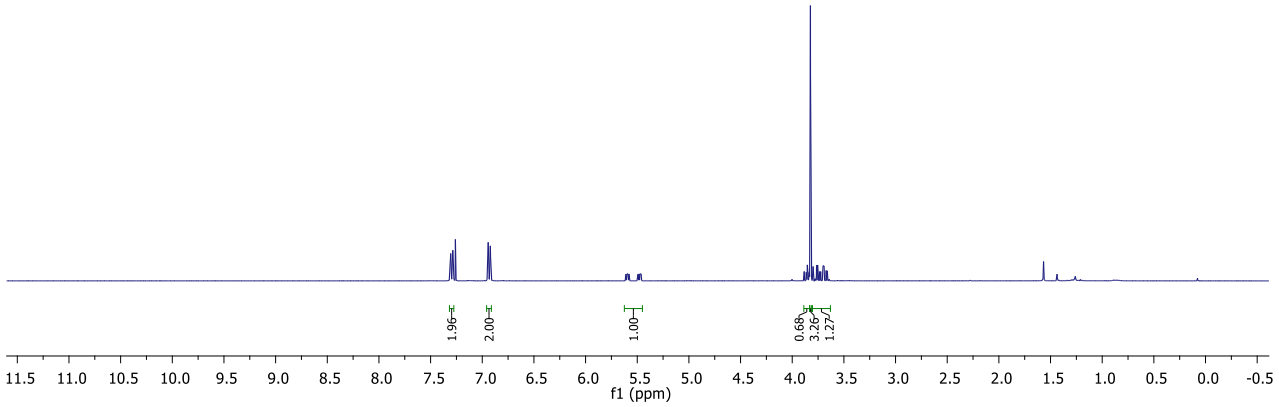
^{19}F-NMR, 470 MHz, $CDCl_3$

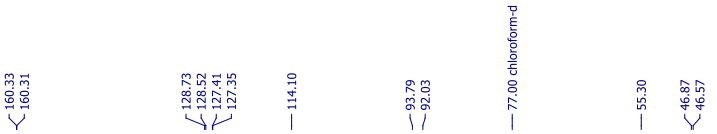
Compound 10

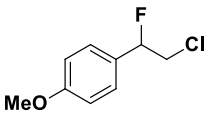




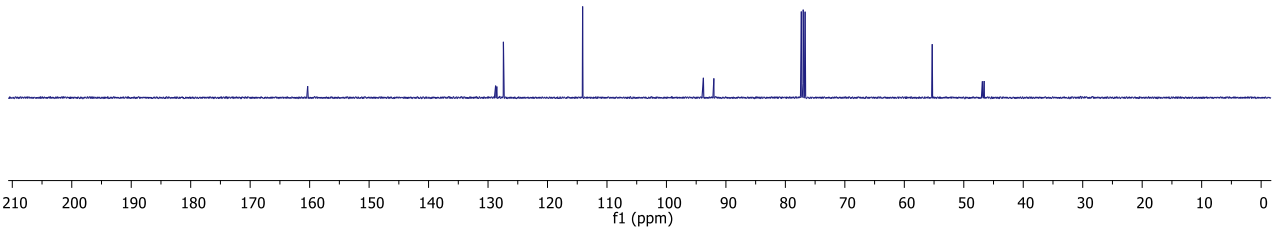
1H-NMR, 400 MHz, CDCl3

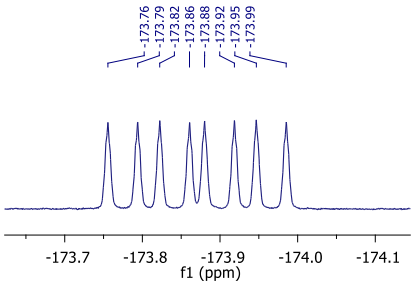


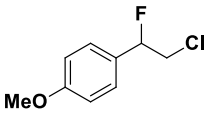




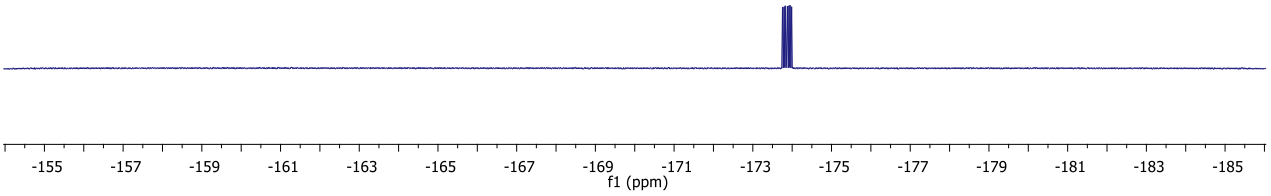
^{13}C-NMR, 100 MHz, $CDCl_3$



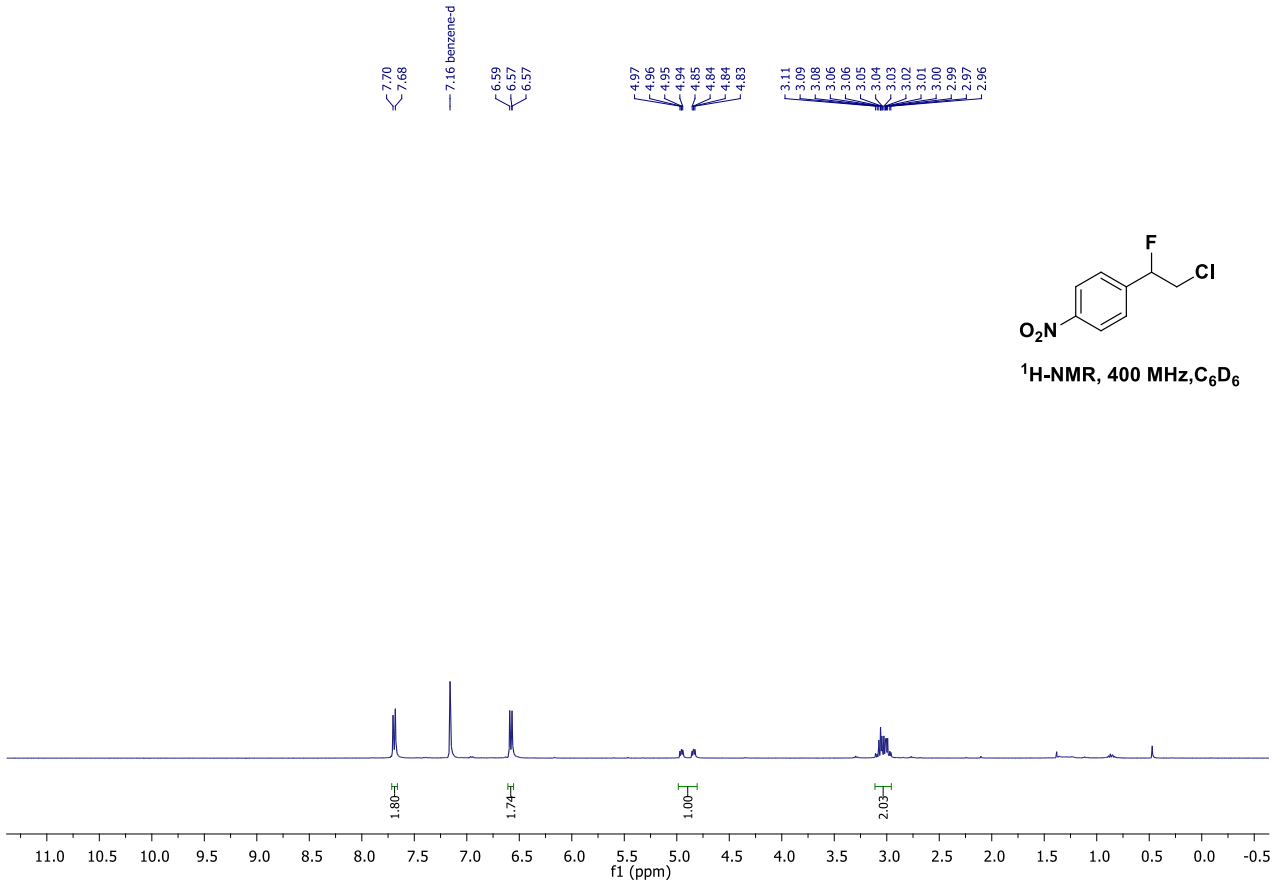


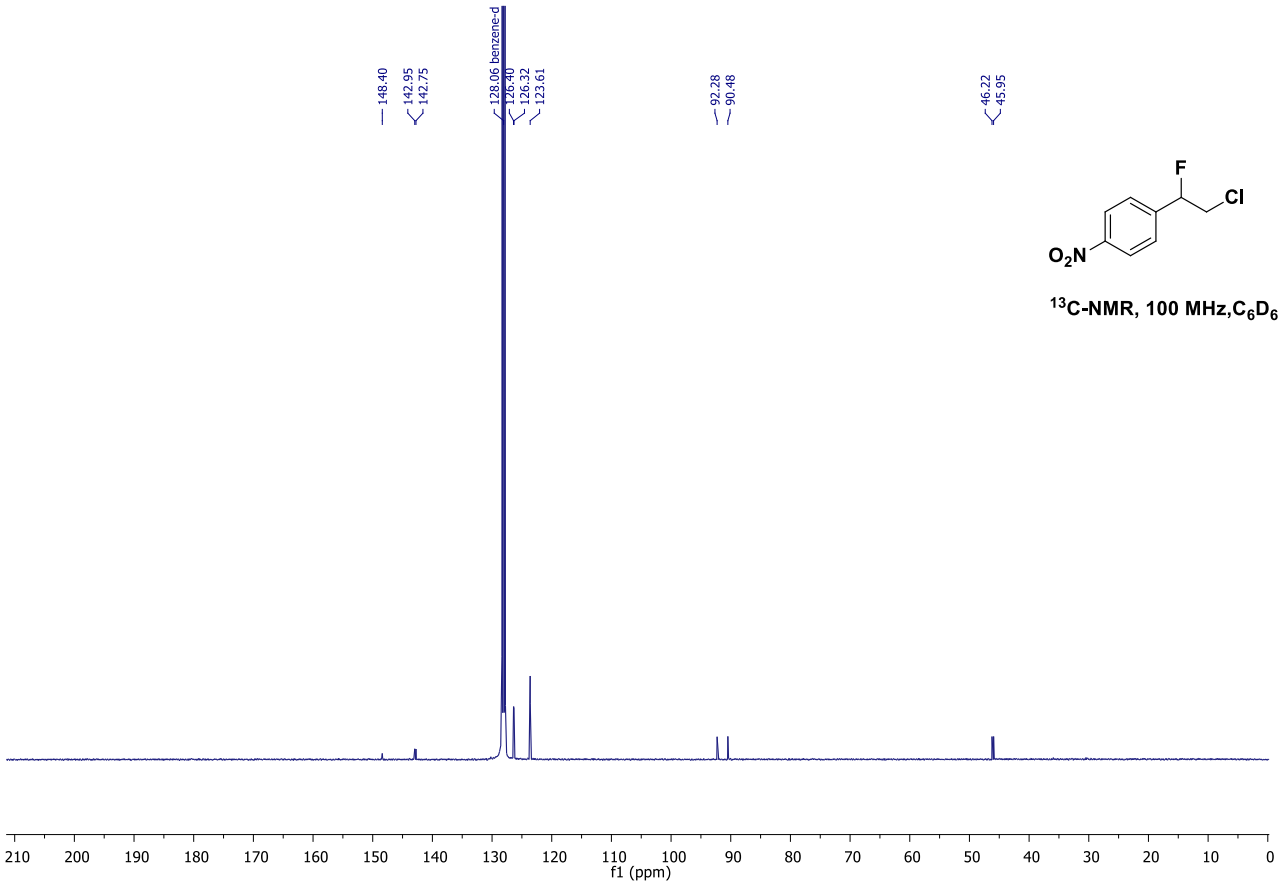


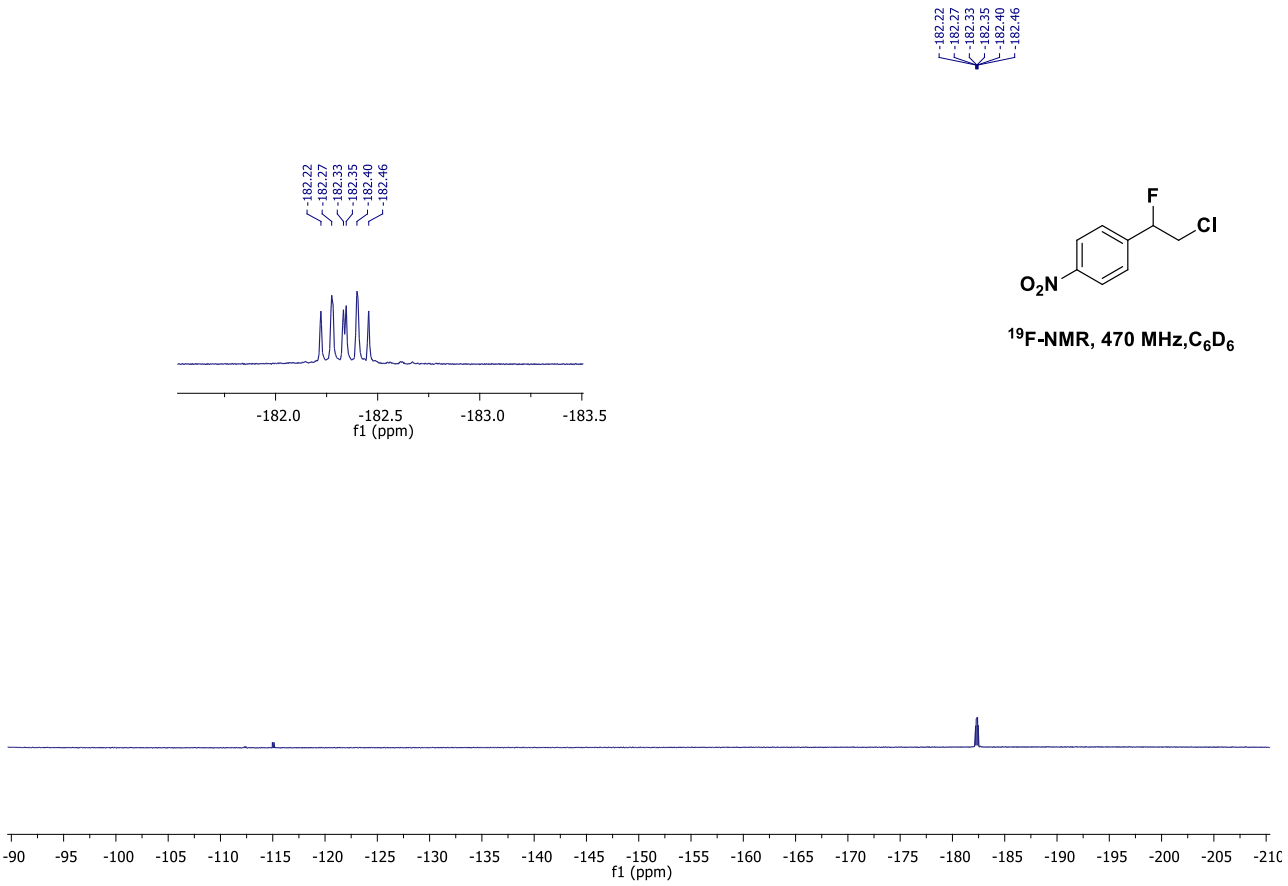
^{19}F-NMR, 470 MHz, $CDCl_3$



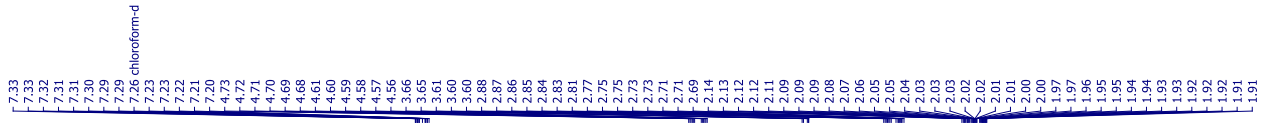
Compound 11

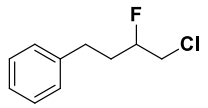

7.70
7.68
7.16 benzene-d
6.59
6.57
6.57
4.97
4.96
4.95
4.94
4.85
4.84
4.84
4.83
3.11
3.09
3.08
3.06
3.06
3.05
3.04
3.03
3.02
3.01
3.00
2.99
2.97
2.96
F
Cl
O2N
1H-NMR, 400 MHz,C6D6
1.80
1.74
1.00
2.03
f1 (ppm)


148.40
142.95
142.75
128.06 benzene-d
125.40
126.32
123.61
92.28
90.48
46.22
45.95
F
Cl
O2N
13C-NMR, 100 MHz,C6D6
f1 (ppm)

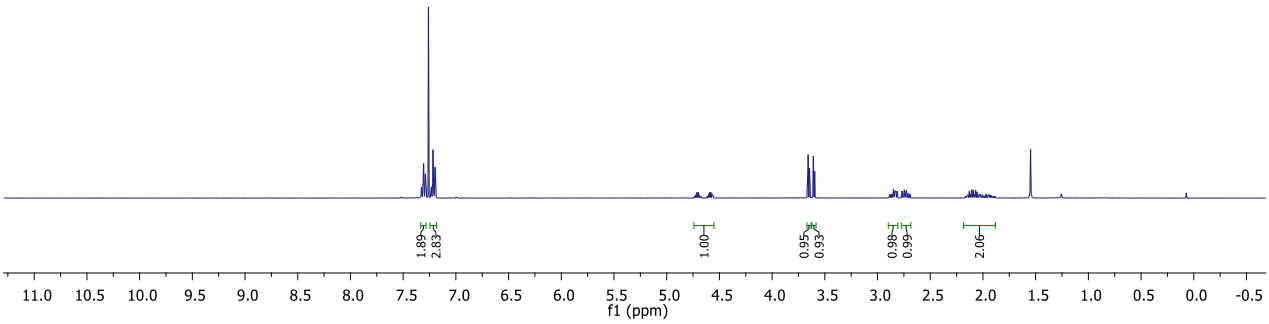

-182.22
-182.27
-182.33
-182.35
-182.40
-182.46
F
Cl
O_2N
^{19}F-NMR, 470 MHz,C_6D_6
-182.0
-182.5
-183.0
-183.5
f1 (ppm)
-90
-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
-155
-160
-165
-170
-175
-180
-185
-190
-195
-200
-205
-210
f1 (ppm)

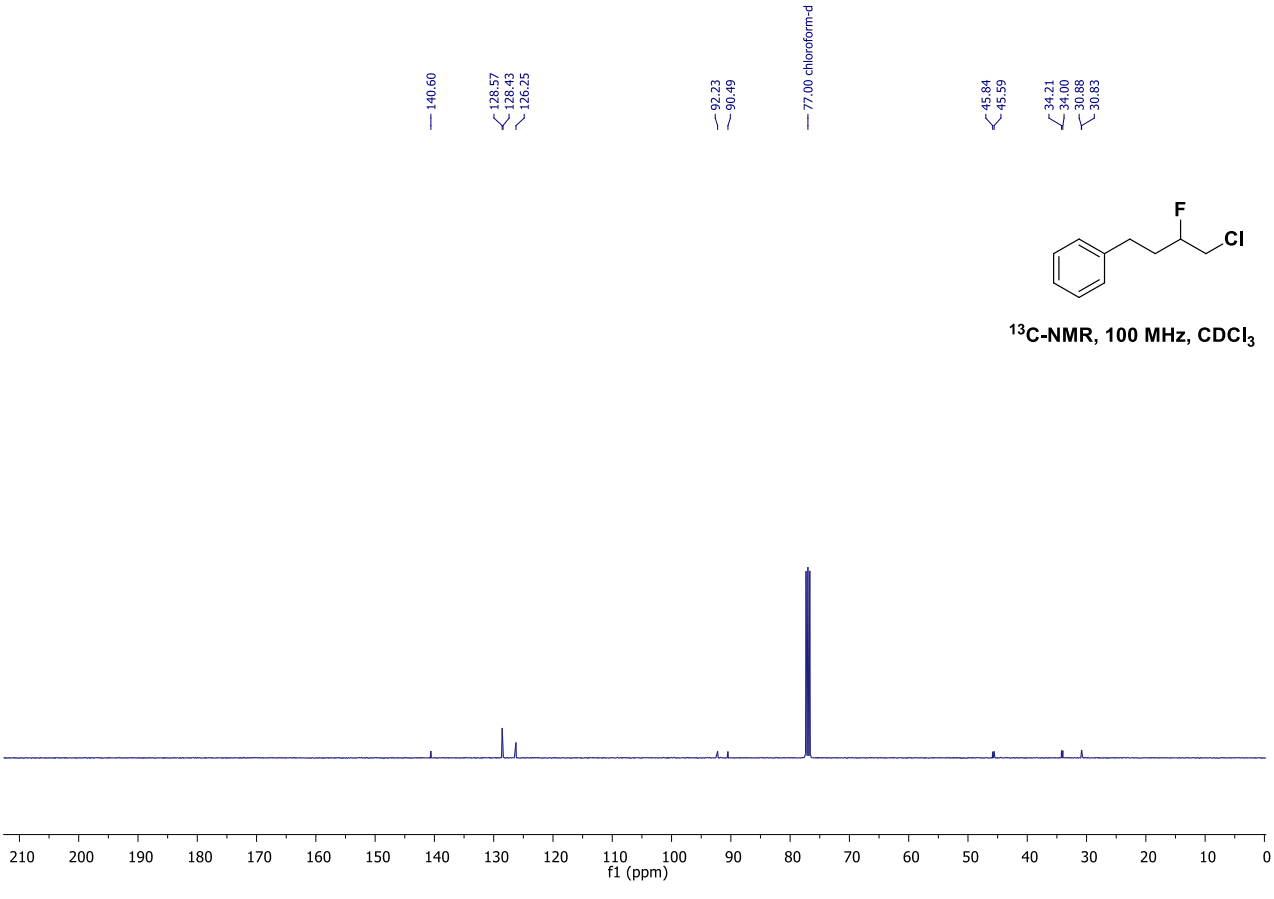
Compound 12



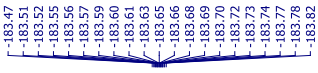


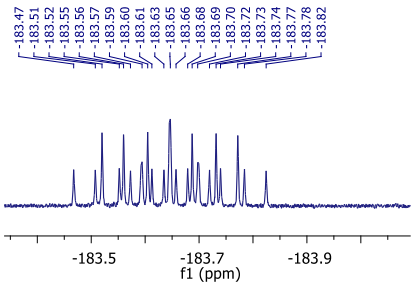
1H-NMR, 400 MHz, CDCl3

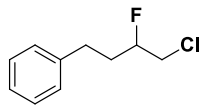




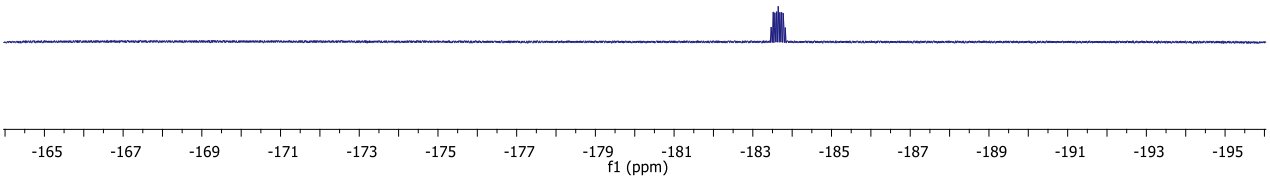
^{13}C-NMR, 100 MHz, $CDCl_3$







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



5. REFERENCES

1. Monticelli S., Rui M., Castoldi L., Missere G., Pace V. A practical guide for using lithium halocarbenoids in homologation reactions. *Chemical Monthly.* 2018; 149(7):1285–1291. doi:https://doi.org/10.1007/s00706-018-2232-9

2. Castoldi L., Monticelli S., Senatore R., Ielo L., Pace V. Homologation chemistry with nucleophilic alpha-substituted organometallic reagents: chemocontrol, new concepts and (solved) challenges. *Chem. Commun*. 2018; 54(50):6692-6704. doi: 10.1039/c8cc02499e

3. Emerson C. R., Zakharov L. N., Blakemore P. R. Investigation of Functionalized alpha-Chloroalkyllithiums for a Stereospecific Reagent-Controlled Homologation Approach to the Analgesic Alkaloid (-)-Epibatidine. *Chem. Eur. J*. 2013; 19(48):16342-16356. doi:10.1002/chem.201302511

4. Köbrich G., Fischer R. H. Stabile Carbenoide-XXX: Chlormethyllithium und Bromchlormethyllithium. *Tetrahedron*. 1968; 24(11):4343-4346. doi:https://doi.org/10.1016/0040-4020(68)88194-3

5. Pace V., Holzer W., De Kimpe N. Lithium Halomethylcarbenoids: Preparation and Use in the Homologation of Carbon Electrophiles. *Chem. Rec*. 2016; 16:2061-2076. doi:10.1002/tcr.201600011

6. Ielo L., Miele M., Pillari V., Senatore R., Mirabile S., Gitto R., Holzer W., Alcántara A. R., Pace V. Taking advantage of lithium monohalocarbenoid intrinsic alpha-elimination in 2-MeTHF: controlled epoxide ring-opening en route to halohydrins. *Org. Biomol. Chem*. 2021; 19(9):2038-2043. doi:10.1039/d0ob02407d

7. Tarhouni R., Kirschleger B., Rambaud M., Villieras J. Monohalomethyllithium XCH_2Li: Stabilization of a potential synthetic reagent. *Tetrahedron Letters*. 1984; 25(8):835-838. doi:https://doi.org/10.1016/S0040-4039(01)80040-X

8. Clayden J. Organolithiums: selectivitiy for synthesis. Elsevier. 2002; Vol. 23

9. Beak P., Chen C.-W. Relative Rates of Deprotonation and of Bromine-Lithium Exchange by Organolithium Reagents: Interpretation of Some Deceptive Results. *Tetrahedron Letters*. 1985; 26(41):4979-4980. doi:https://doi.org/10.1016/S0040-4039(01)80830-3

10. Boultwood T., Affron D. P., Trowbridge A. D., Bull J. A. Synthesis of cis-C-Iodo-N-Tosyl-Aziridines using Diiodomethyllithium: Reaction Optimization, Product Scope and Stability, and a Protocol for Selection of Stationary Phase for Chromatography. *J. Org. Chem*. 2013; 78(13):6632-6647. doi:dx.doi.org/10.1021/jo400956x

11. Remete A. M., Nonn M., Fustero S., Fülöp F., Kiss L. Synthesis of fluorinated amino acid derivatives through late-stage deoxyfluorinations. *Tetrahedron*. 2018; 74(44):6367-6418. doi:https://doi.org/10.1016/j.tet.2018.09.021

12. Wang Z., Hunter L. Synthesis of difluorinated beta- and gamma-amino acids: Investigation of a challenging deoxyfluorination reaction. *Journal of Fluorine Chemistry*. 2012; 143:143-147. doi:http://dx.doi.org/10.1016/j.jfluchem.2012.06.016

13. Khalil A., Bayach I., Mathé C. A synergistic synthetic and computational insights towards anomerization of N-nitro pyrimidine nucleosides using fluorinating agents. *Journal of Fluorine Chemistry*. 2020; 233(2); 109504. doi:https://doi.org/10.1016/j.jfluchem.2020.109504

14. Chang Y., Tewari A., Adi A.-I., Bae C. Direct nucleophilic fluorination of carbonyl groups of benzophenones and benzils with Deoxofluor. *Tetrahedron*. 2008; 64(42):9837-9842. doi:10.1016/j.tet.2008.08.009

15. Singh R. P., Shreeve J. M. Nucleophilic fluorination of amino alcohols and diols using Deoxofluor. *Journal of Fluorine Chemistry*. 2002; 116(1):23-26. doi:https://doi.org/10.1016/S0022-1139(02)00065-9

16. Closs G. L., Moss R. A. *J. Am. Chem. Soc*. 1964; 86, page 4042

6. LIST OF SCHEMES