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Dott. Giovanna Parisi

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Dipartimento di Chimica

Processi Chimici Avanzati CHIM/06

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Recent Advances in α-Heterosubstituted Organometallic Reagents: Design and Applications in Synthesis

Coordinatore:

Ch.mo Prof. Pietro Favia

Supervisori:

Ch.mo Prof. Renzo Luisi

Ch.mo Prof. Vittorio Pace

Dottoranda:

Giovanna Parisi

Anno Accademico 2016-2017

Abstract

My PhD thesis is the result of the work carried out at the Department of Pharmacy - Drug Sciences of University of Bari, Italy, and the Department of Pharmaceutical Chemistry, University of Vienna, Austria, in the period 2014-2017.

The present dissertation is focused on two main topics: the first section is the core of my Organic Chemistry project and will highlight the synthetic versatility of previously undisclosed fluoro lithium carbenoids, whereas the second part will concern the functionalization of four- and six- membered heterocycles. These two topics converge in a single goal, which is the possibility to apply organometallic chemistry for the synthesis of pharmacologically active substances.

During my PhD experience I had the possibility to get in touch with several aspects of this intriguing chemistry; in particular I improved my skills as an organolithium and organometallic reagents I learnt how to develop a research project, aimed to discovering new pharmaceutical entities. Moreover, during the period spent at University of Vienna in Pace's research group, I had the opportunity to explore the medicinal chemistry field working at the synthesis of new pharmacologically active compounds as P-GP modulator and colic acid derivatives.

Key for success of my PhD studies has been the synergetic collaborations between both research groups, culminated in publications in high impact international journals.

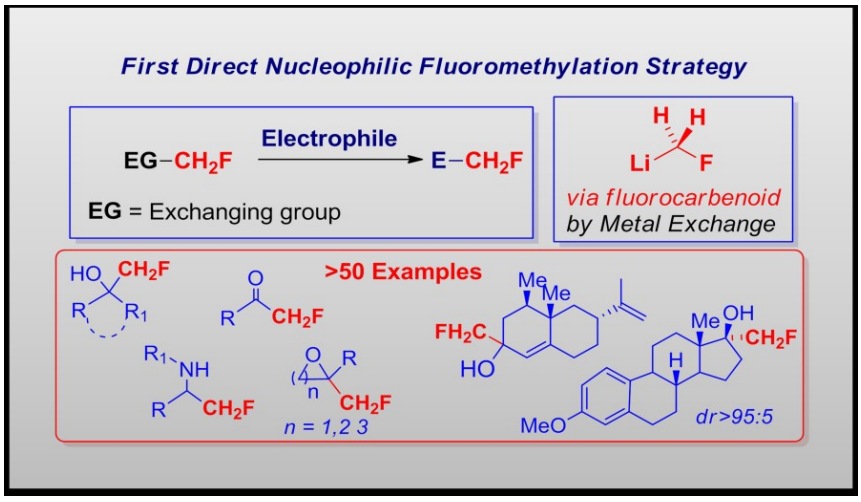
The following sections highlight the two main topics of my PhD research project.

1. Fluoro carbenoids as useful synthetic agents.

In the last decades, lithium organometallics attracted enormous interest both in synthetic and medicinal chemistry field as well as in industrial environment. Special mention deserves the chemistry of carbenoids which have become useful reagents for the direct introduction of CH_2X-type functionalities into an organic array.

Moreover, the introduction of a fluorine atom into a pharmaceutical molecules can induce significant changes in their chemical, physical and biological properties. These effects provides an increase of molecular lipophylicity, and thereby improves the drugs bioavailability. In this context, the first direct and straightforward direct nucleophilic fluoromethylation based on fluorocarbenoids has been developed: we demonstrate the versatility of $LiCH_2F$ as a unique homologating agent enabling – *through a single operation* – the formation of a new C-C bond featuring the exact degree of fluorination.

Interestingly, after a careful study of the reaction conditions, we were able to generate the fluoromethyllithium (FML) and use it with different electrophiles. This protocol can be conveniently applied for the synthesis of fluorinated compounds now difficult to prepare in a single synthetic step. The results have been recently published in *J. Am. Chem. Soc.*, **2017**, *139* (39), 13648–13651. DOI: 10.1021/ jacs.7b07891.



Graphical Abstract of Fluoro carbenoids topic.

2. Lithiation of four- and six-membered cyclic sulfones.

During my experience at the University of Vienna, I completed a project started at the University of Bari concerning the study of the reactivity of small sulfur-bearing heterocycles such as thietane 1,1-dioxide and the corresponding homologue tetrahydro-2H-thiopyran 1,1-dioxide.

The interest towards sulfone is tied up by the biological activities of molecules featuring this kind of heterocycles in their structures. In fact, a wide range of drugs that find application as antibacterial, antifungal, antiviral, anthelmintic agents, anticonvulsant, antiallergic, anti-HIV, contain such heterocyclic cores. However, despite the importance for the pharmaceutical industry, strategies for the functionalization of cyclic sulfones are so far little explored.

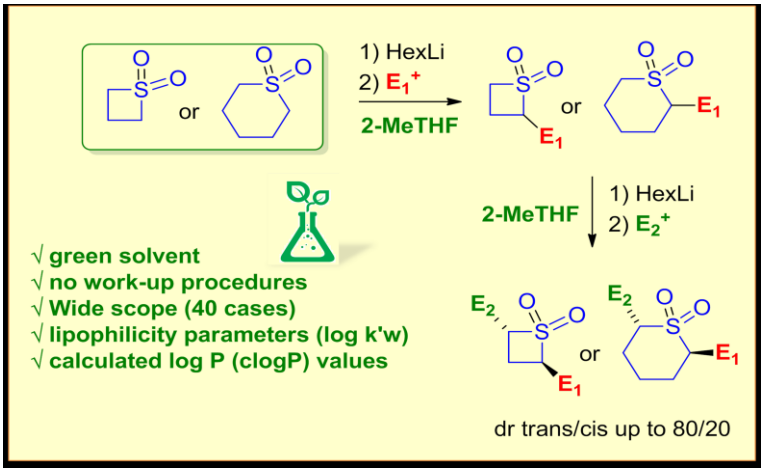
For this reason, the regioselective mono and doubly functionalization of thietane 1,1-dioxide and tetrahydro-*2H*-thiopyran 1,1-dioxide was investigated using a lithiation/electrophile trapping strategy. The protocol has been effective to a plethora of electrophiles with a good functional groups tolerance leading to a new series of substituted cyclic sulfones.

The synthetic protocol was quite sustainable; in fact, the reaction did not required an aqueous work-up procedure, and could be performed with a safer lithiating agent such as HexLi and, in a renewable eco-friendly solvent such as 2-MeTHF.

The reactivity of lithiated four- and six-membered cyclic sulfones was also tested in more challenging reactions such as the direct C2 arylation and fluorination.

For representative substituted cyclic sulfones, the lipophilicity was measured by RP-HPLC, which significantly encodes solvophobic and silanophilic interactions of the analytes.

The results obtained were recently published in *Org. Biomol. Chem.;* **2017**, 15, 5000-5015, DOI: 10.1039/c7ob00846e.



Graphical Abstract of sulfone heterocycles topic.

Riassunto

La mia tesi di dottorato è il risultato del lavoro svolto presso il Dipartimento di Farmacia - Scienze del Farmaco dell' Università di Bari e il Dipartimento di Chimica Farmaceutica dell' Università di Vienna, Austria, nel periodo 2014-2017.

La tesi si focalizza su due argomenti principali: la prima parte, che rappresenta il fulcro del mio progetto di ricerca, metterà in evidenza la versatilità sintetica dei fluoro litio carbenoidi, mentre la seconda parte riguarderà la funzionalizzazione di eterocicli a quattro e a sei termini. Questi due argomenti convergono in un unico obiettivo, ovvero la possibilità di applicare la chimica organometallica per la sintesi di sostanze farmacologicamente attive.

Durante la mia esperienza di dottorato ho avuto la possibilità di entrare in contatto con diversi aspetti di questa chimica intrigante; in particolare ho migliorato le mie conoscenze sulla chimica degli organometalli ed ho imparato a sviluppare un progetto di ricerca finalizzato alla scoperta di nuove entità farmaceutiche.

Inoltre, durante il periodo trascorso presso l'Università di Vienna nel gruppo di ricerca del Prof. Dr. Pace, ho avuto l'opportunità di esplorare il campo della chimica farmaceutica lavorando alla sintesi di nuovi composti farmacologicamente attivi come potenziali modulatori della Glicoproteina-P e derivati dell'acido colico.

La chiave del successo dei miei studi di dottorato è stata la collaborazione sinergica tra i due gruppi di ricerca, culminata in pubblicazioni effettuate su riviste internazionali ad alto impatto.

I paragrafi seguenti descrivono brevemente i due temi principali del mio progetto di ricerca.

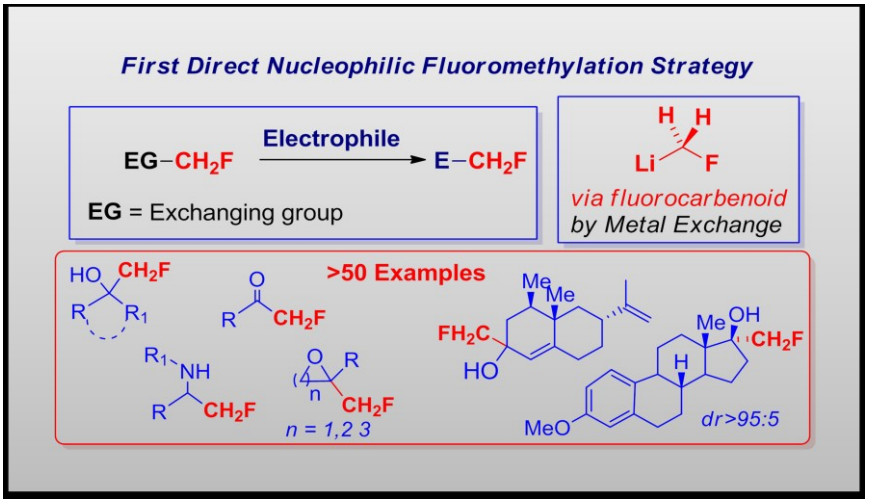
1. Fluoro carbenoidi come utili agenti sintetici.

Nell' ultimo decennio, gli agenti organolitio hanno richiamato un enorme interesse sia in campo sintetico e chimico che in ambito industriale. Una menzione speciale deve essere fatta alla chimica dei carbenoidi i quali sono utilizzati come utili reagenti per l'introduzione diretta di funzionalità di tipo CH_2X in un composto organico.

Tuttavia, l'introduzione di un atomo di fluoro in molecole farmacologicamente attive può indurre modifiche significative nelle loro proprietà chimiche, fisiche e biologiche. Questi effetti inducono un aumento della lipofilicità molecolare e quindi migliora la biodisponibilità del farmaco. In questo contesto, abbiamo sviluppato la prima diretta e robusta fluorometilazione nucleofilica basata sui fluorocarbonoidi: abbiamo dimostrato la versatilità

del $LiCH_2F$ come unico agente omologante che consente - attraverso un solo *step* di reazione- la formazione di un nuovo legame C-C con l'esatto grado di fluorurazione.

È interessante notare che, dopo un attento studio delle condizioni di reazione, siamo riusciti a generare il fluorometillitio (FML) e utilizzarlo con diversi elettrofili. Questo protocollo può essere convenientemente applicato per la sintesi di composti fluorurati difficili da preparare in un'unica operazione sintetica. I risultati sono stati recentemente pubblicati in *J. Am. Chem. Soc.*, **2017**, 139 (39), 13648-13651. DOI: 10.1021 / jacs.7b07891.



Riepilogo grafico:fluoro carbenoidi

2. Litiazione di solfoni ciclici a quattro e a sei termini.

Durante la mia esperienza presso l'Università di Vienna, ho completato un progetto iniziato presso l'Università di Bari riguardante lo studio della reattività di piccoli eterocicli solforati come il tietano 1,1-diossido e il corrispondente omologo tetraidro-*2H*-tiopirano 1,1-diossido.

L'interesse verso questi composti è legato alle attività biologiche delle molecole che presentano questi tipi di eterocicli nelle loro strutture. Infatti, un'ampia gamma di farmaci che trovano applicazione come antibatterici, antifungini, antivirali, agenti antielmintici, anticonvulsivanti, antiallergici, anti-HIV, contengono tali nuclei solforati. Tuttavia, nonostante l'interesse farmaceutico, strategie per la funzionalizzazione di solfoni ciclici sono ancora poco esplorati.

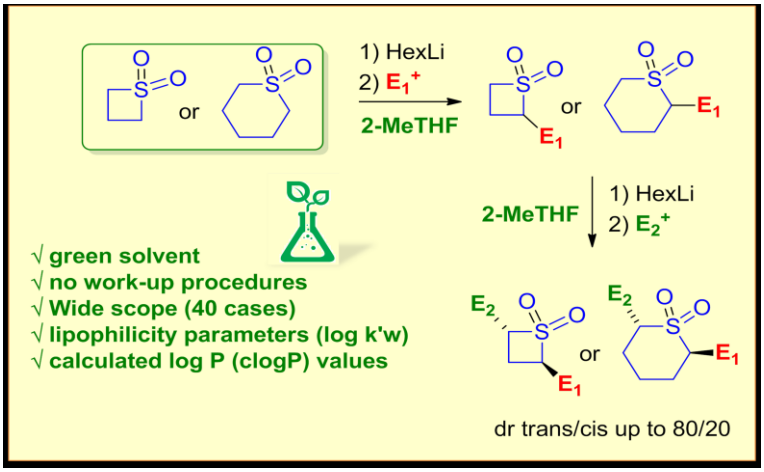
Per questo motivo ho investigato la mono e la doppia funzionalizzazione regioselettiva del tietano e del tiopirano 1,1-diossido usando come strategia sintetica la litiazione seguita da una successiva cattura con elettrofilo dell'intermedio litiato. Il protocollo si è rivelato efficace per una vasta gamma di elettrofili mostrando una buona tolleranza ai gruppi funzionali permettendo cosi la sintesi di una nuova serie di solfoni ciclici sostituiti.

L'approccio sintetico è eco-sostenibile; infatti, la reazione non richiede un trattamento acquoso del crudo di reazione e può essere eseguita con un agente organolitio più sicuro come HexLi e in un solvente eco-compatibile come il 2-MeTHF.

La reattività di questi solfoni ciclici a quattro e a sei termini è stata esplorata anche in reazioni più difficili come l'arilazione e la fluorurazione diretta al carbonio-2.

Per alcuni solfoni rappresentativi è stata valutata la lipofilicità mediante RP-HPLC, che codifica in modo significativo interazioni solvofobiche tra gli analiti.

I risultati ottenuti sono stati recentemente pubblicati in *Org. Biomol. Chem* .; **2017**, 15, 5000-5015, DOI: 10.1039 / c7ob00846e.



Riepilogo grafico: litiazione di solfoni ciclici

Abstrakt

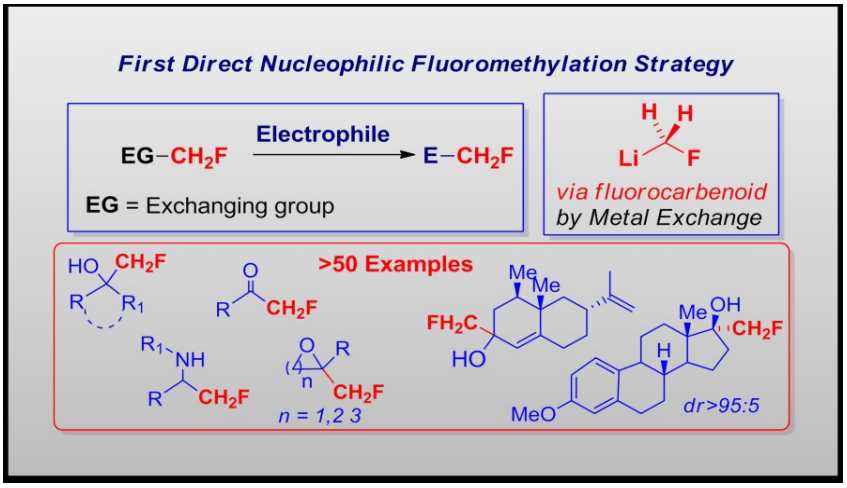
Meine doktorarbeit ist der ergebniss einer kollaboration zwischen dem Department für Pharmazeutische Chemie der Universität Bari, Italien, und der Fakultät für Lebenswissenschaften an der Universität Wien, Österreich im zeitraum von 2014 bis 2017. Das haupttheme meiner dissertation war die organometallische synthese von pharmazeutisch relevanten stoffklassen unter verwendung von Fluoro Lithium Carbenoids und der funktionalisierung von 4- und 6-Heterozyklen. Während meiner doktorarbeit hatte ich die möglichkeit mein theoretisches und praktische wissen im umgang mit organolithium und organometallischen.

Reagenzien zu erweitern und zu vertiefen und wissenschaftliche fragestellungen zu entwickeln. Weiters wurde mir durch meinen aufenthalt in der arbeitsgruppe von Vittorio Pace die Möglichkeit gegeben, tieferen einblick in die medizinische chemie anhand der synthese von neuen, pharmazeitische relevanten molekülen als P-GP Molulatoren und Colic Acid Derivaten zu erhalten. Entscheidend für den positiven abschluss meiner synthetischen arbeit war die gute und synergetische kollaboration der beiden arbeitsgruppen welche in Publikationen in mehreren high-impact Journals kummulierte.

1. Fluorkarbenoide als nützliche synthetische mittel.

In den letzten zehn jahren haben Lithium-Spezies sowohl im bereich der synthese und der medizinischen chemie als auch im industriellen umfeld enormes Interesse geweckt. Besondere erwähnung verdient die chemie der carbenoide, die zu nützlichen reagentien für die direkte einführung von CH_2X-funktionalitäten in ein organisches molekül geworden sind. Darüber hinaus kann die einführung eines fluoratoms in pharmazeutische moleküle signifikante veränderungen in ihren chemischen, physikalischen und biologischen eigenschaften hervorrufen. Diese effekte führen zu einer erhöhung der molekularen lipophilie und verbessern dadurch die bioverfügbarkeit der wirkstoffe. In diesem zusammenhang wurde die erste direkte und direkte fluorophile fluormethylierung auf der basis von fluorcarbenoiden entwickelt: wir demonstrieren die vielseitigkeit von $LiCH_2F$ als einzigartigem homologationsmittel, das durch einen einzigen vorgang die bildung einer neuen C-C bindung mit genauem fluorierungsgrad ermöglicht. Interessanterweise konnten wir nach sorgfältiger untersuchung der reaktionsbedingungen das fluormethyllithium (FML) generieren und mit verschiedenen elektrophilen verwenden. Dieses protokoll kann bequem für die synthese von fluorierten verbindungen angewendet werden, die in einem einzigen syntheseschritt schwierig

herzustellen sind. Die ergebnisse wurden kürzlich in *J. Am. Chem. Chem. Soc*., **2017**, 139 (39), 13648-13651. DOI: 10.1021/jacs.7b07891.



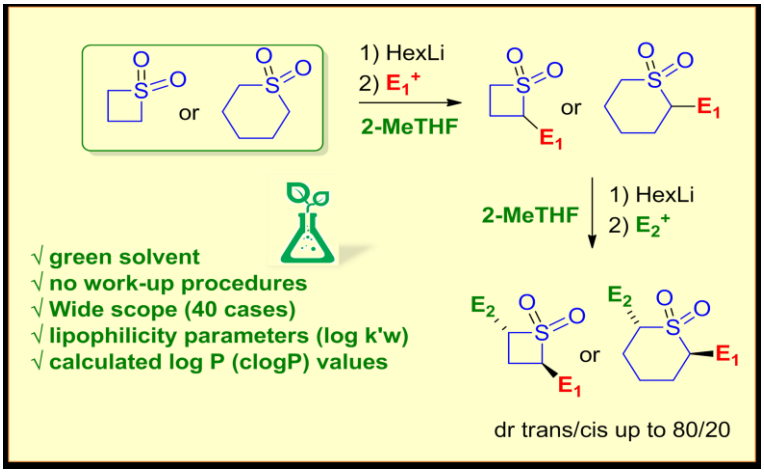
Grafische Abstrakte: Fluorkarbenoide

2. Lithiation von vier- und sechsgliedrigen cyclischen Sulfonen. Während meiner erfahrung an der Universität Wien habe ich ein projekt abgeschlossen, das an der Universität Bari zur untersuchung der reaktivität kleiner schwefelhaltiger heterocyclen wie Thietan-1,1-dioxid und des entsprechenden homologen tetrahydro-2H-thiopyran 1,1-Dioxid begann. Das interesse an sulfonen ist durch die biologischen aktivitäten von molekülen gebunden, die diese art von heterocyclen in ihren strukturen aufweisen. In der tat enthalten eine vielzahl von arzneimitteln, die als antibakterielle, antimykotische, antivirale, anthelminthische mittel, Antikonvulsiva, Antiallergika, Anti-HIV-Mittel Anwendung finden, solche heterocyclischen Kerne. Trotz der bedeutung für die pharmazeutische industrie sind strategien zur funktionalisierung von cyclischen sulfonen bislang wenig erforscht. Aus diesem grund wurde die regioselektive Mono- und Doppelfunktionalisierung von Thietan-1,1-dioxid und Tetrahydro-2H-thiopyran-1,1-dioxid mit einer lithiierung/elektrophil-trapping-strategie untersucht. Das protokoll war für eine vielzahl von elektrophilen mit einer guten toleranz gegenüber funktionellen gruppen wirksam, was zu einer neuen reihe von substituierten cyclischen Sulfonen führte. Das synthetische protokoll war ziemlich nachhaltig; In der Tat erforderte die reaktion kein wässriges aufarbeitungsverfahren und konnte mit einem sichereren lithiierungsmittel wie HexLi und in einem erneuerbaren umweltfreundlichen lösungsmittel wie 2-MeTHF durchgeführt werden.

Die reaktivität von lithiierten vier- und sechsgliedrigen cyclischen sulfonen wurde auch in anspruchsvolleren reaktionen wie der direkten C2-Arylierung und fluorierung getestet.

Für repräsentative substituierte cyclische sulfone wurde die lipophilie durch RP-HPLC gemessen, die signifikant die solvophoben und silanophilen wechselwirkungen der analyten codiert.

Die Ergebnisse wurden kürzlich in Org veröffentlicht *Org. Biomol. Chem.*; **2017**, 15, 5000-5015, DOI: 10.1039/c7ob00846e.



Grafische Abstrakte: lithiation von cyclischen sulfonen

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Chapter 2 - LITHIATION OF CYCLIC SULFONES

Chapter 1

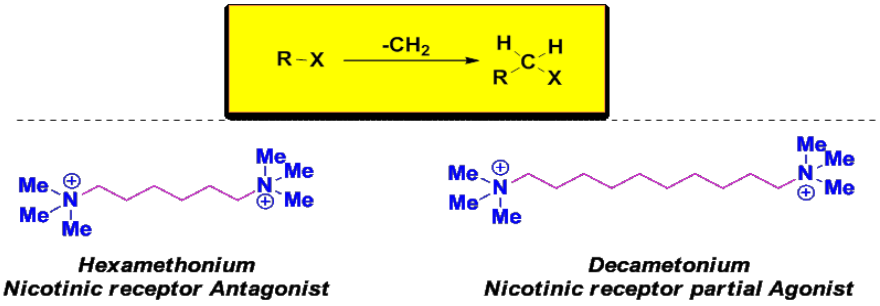
1. Introduction

1.1 General overview of carbenoids like useful synthetic reagents.

Carbenoid chemistry continues to attract great interest within the synthetic community mainly because of their potential in homologation processes.

In pharmaceutical chemistry, homologation reactions represent potent and versatile tools for the synthesis of compounds with potential biological activity.

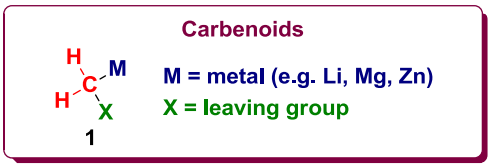
In fact, the precise introduction of the methylene group into bioactive molecules often results in significant changes in their biological properties; for example, hexamethonium and decametonium, both nicotinic receptor ligands with antagonist and agonist action respectively, differ only for a constant unit, constituted by the methylenic (CH_2) group.



Scheme 1. *Representative example of biologically active compounds.*

In the *portfolio* of homologating agents a central role is played by the so-called carbenoidic reagents[1] (in particular α-halomethyllithiums), among which the exceptional highly reactive fluoro-containing carbenoids[1a] constitute the one of the topic of interest of the presented thesis. Carbenoids **1** are versatile species employed in modern organic synthesis which contain an electronegative element, such as a halogen, and a metal atom (*e.g.* Li, Mg) linked to the same carbon (Scheme 2).

The term carbenoid was first introduced by Closs and Moss in 1964 to describe compounds ‘‘*which exhibit reactions qualitatively similar to those of carbenes without necessarily being free divalent carbon species*’’.[2]



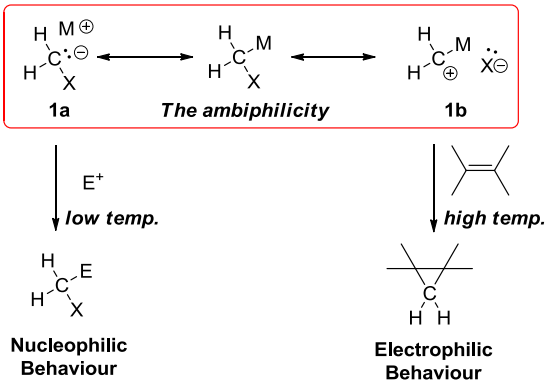
Scheme 2. *Definition of carbenoids.*

In the 1960s Köbrich[3] observed that carbenoids showed a dual reactivity, namely nucleophilic and electrophilic; this special feature is due to the presence of an electron-donating and electron-withdrawing functionality bonded to the carbon centre.

In fact, the ambiphilic behaviour of carbenoid reagents can be explained by the mesomeric structures of **1**.

As shown in *Scheme 3,* the extreme ionization of the polar bonds leads to the liberation of a carbanionic species in which the negative charge is localized at carbon and thus, it becomes nucleophilic (**1a**). Instead, when the extreme ionization of the polar bonds leads to the formation of carbocation species a positive charge is localized at carbon and it becomes electrophilic **1b.**

For this reason, they exhibit both nucleophilic and electrophilic reactivity that, in principle, can be tuned by the experimental reaction conditions: at low temperature the nucleophilicity behaviour comes into play, while at higher temperatures the electrophilic behaviour is predominant.



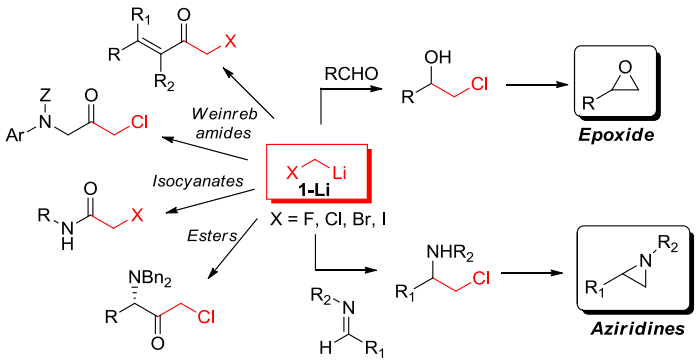
Scheme 3. *Structural features of carbenoids: ambiphilicity and reactivity profile.*

Lithium or magnesium carbenoids, because of their higher nucleophilicities mainly react as carbanions,[1b] while zinc or rhodium carbenoids tend to feature as electrophiles as a consequence of the decreased nucleophilicities.[1a,4]

Given these premises, it's clear that one of the main advantages is the possibility to place a functionalized carbon atom, using a single synthetic operation, susceptible to further elaboration.

Reactive species as halomethyllithium **1-Li**, have been extensively employed in homologation processes of carbonyl derivates such as aldehydes, ketones, imines, acyl halides, esters, Weinreb amides and isocyanates.[5, 6] Moreover, the direct introduction of a halomethyl unit

into carbonyl compound gives α-halo alcohols which are potential precursors of epoxides while the addition to imines gives amines, possible precursors of aziridines (Scheme 4).



Scheme 4. *Synthetic use of halocarbenoids in homologation type reactions.*

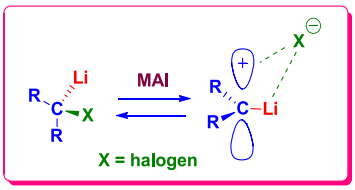
1.2 Carbenoids nature: configurational stability and thermal instability.

The first report on the configurational and thermal instability of carbenoids dates back to seminal work by Köbrich; he reported that the epimers of 7-chloro-7-lithionorcarane rearranged only slowly at -80 °C at a rate similar to their decomposition, probably due to the strained cyclopropane ring resisting inversion of configuration at the carbanionic centre.[7]

It is worth to highlight that, this finding was also in agreement that a variety of *R*-bromo and *R*-chloro cyclopropyllithiums were configurationally stable below -78 ˚C, but started to epimerize above that temperature.[8]

Walborsky and co-workers reported a study on the mechanism and the stereochemistry of the reaction of chiral lithium carbenoids (*e.g.* cyclopropyl and vinyl lithium analogues) with nucleophilic partners.[9] In order to get insight into the stereochemical outcome of the reaction on such carbenoid reagents, the concept of "metal-assisted ionization" (MAI) was introduced (Scheme 5).

According to these authors, because of a lithium-assisted partial ionization of the C-Hal bond, the carbenoid reacts as carbocation, but still conserving its stereo configuration as a consequence of the constant coordination of lithium to the halogen (Scheme 5). Thus, the lithiated carbocationic centre could be attacked by the nucleophile from the backside generating a product that often, but not always, shows an inversion of configuration.



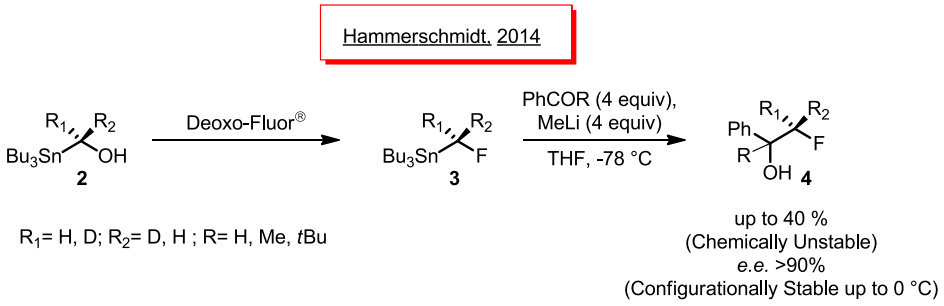
Scheme 5. *Metal-assisted ionization (MAI) in Li-X carbenoid.*

Nevertheless, enantiomeric α-halolithium compounds are not deeply studied compared to α-oxygen and α-nitrogen-functionalized lithium carbenoids which are configurationally stable below -78 ˚C.[10]

However, the studies reported to date are pleasingly surprising and encouraging for stereoselective reactions. In this context, Hoffmann and co-workers demonstrated that R-bromoalkyllithiums generated by halogen-lithium exchange from geminal dihalides could generate products with high diastereoselectivity.[11] Moreover, they reported that acyclic R-bromoalkyllithiums were configurationally stable at -110 °C in the absence of their dibromo precursors.[12]

Very interestingly, Hammerschmidt and co-workers have underlined the excellent configurationally stability of enantiomerically enriched chloromethyllithium-[D1] - [13] generated by tin-lithium exchange. However, their chemical stability was considerably limited even at low temperatures (-78 ˚C), thus indicating the employment of Barbier-type conditions optimal for carrying out analogous processes. In particular they showed that, when the reaction was conducted at this temperature after an external quenching of 30 seconds with benzaldehyde as electrophile, a decrease of the chemical stability of the carbenoid was noticed, even if the chiral information was preserved. It is then clear that the chiral carbenoid at -78 °C decomposes rather than racemizes.

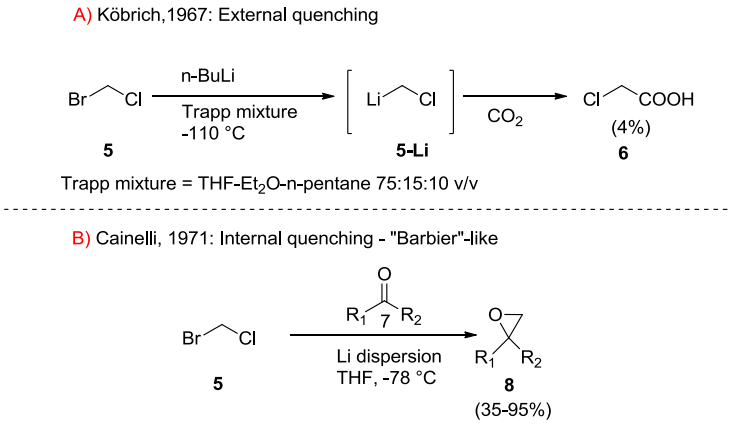
The same group also briefly reported analogous transformations involving $LiCH_2F$ and $LiCH_2I$.[14] In particular, they showed that fluoromethyllithium **3-Li** was configurationally stable in a wide range of temperatures ranging from -95˚C to 0˚C (Scheme 6). However this synthetic approach could not be used for synthetic applications because the carbenoids were too chemical unstable even at these very low temperatures. As a consequence, the preparative use was limited to simple models involving benzaldehyde as the electrophilic partner, thus leaving fully undisclosed the potentialities of the technique.



***Scheme 6**. Conversion of fluoromethylstannane **3** to fluoromethyllithium **3-Li** and its trapping with benzaldehyde/ketones.*

This result clearly manifests that the Achilles' heel of carbenoids is the pronounced thermal instability. In this sense, seminal observations carried out by Köbrich were fully confirmed: chloromethylithium - **5-Li** - generated at -110°C from bromochloromethane **5** and *n*-BuLi could be only minimally carbonated (4% yield) under external trapping conditions to give the desired chloroacetic acid **6** (Scheme 7a).[3,15] This illustrative example clearly highlights the different chemical reactivity of lithium carbenoids compared to other nucleophilic organometallic compounds whose employment in carbonation processes has been successfully demonstrated by Grignard in late 1800s.[16]

In order to avoid instantaneous decomposition, Cainelli proposed the generation of the carbenoid reagent in the presence of the electrophile.[17] Following this so-called Barbier-type protocol, monohalomethylithiums can be prepared at -78°C and could be advantageously used to homologate a carbonyl compound **7** to epoxide **8** (Scheme 7b). According to Canelli, the ideal way to generate carbenoid is the metallation with lithium metal, rather than by reaction with alkyllithium.



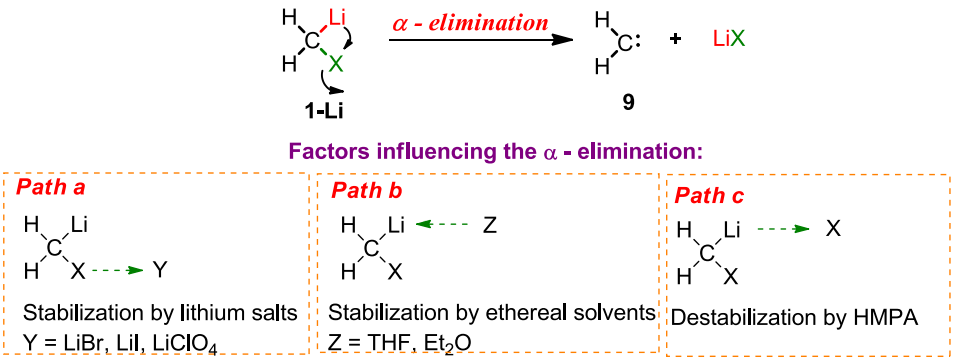
***Scheme** 7. First investigation on lithium carbenoids formation.*

In 1984, Villieras showed the utility of adding to the reaction mixture lithium halides, which by through the coordination to the halogen atom of the carbenoid, destroy the internal Li-X interaction causing the α-elimination of the carbenoid to the free carbene (Scheme 8, path a).[18,19]

Furthermore, the use of Lewis basic ethereal-type solvents stabilizes the carbenoid because they allow to disaggregate organolithium species in solution (Scheme 8, path b).

Indeed, adding a polar solvent such as hexamethylphosphoramide (HMPA) the oxygen atom of this solvent allows to break the C-Li bond by coordination and it actives the degradative α-

elimination (Scheme 8, path c). The control of parameters affecting the stabilization of the carbenoid is a key step in order to achieve useful synthetic applications.



Scheme 8. *Degradative α-elimination process of carbenoid and possible factors to stabilize it.*

Finally, in the broad context of thermal stability of carbenoidic species it is very significant the employment of microreactor technologies allowing to perform external trapping (e.g. it constitutes an admirable and effective alternative to usual Barbier-type conditions, considered nowadays the method of choice for the generation of the carbenoids)[1e] even at higher temperatures as reported by Luisi.[20] Very recently, he reported the efficacy of microflow systems for generating the thermolabile species $LiCH_2Cl$ **5-Li** followed by external trapping with electrophiles at much higher temperatures (up to -20 °C) than in batch-mode (Figure 1). The methodology works quite well with a wide range of electrophiles included Weinreb amides, imines, carbonyl compounds and isocyanates.

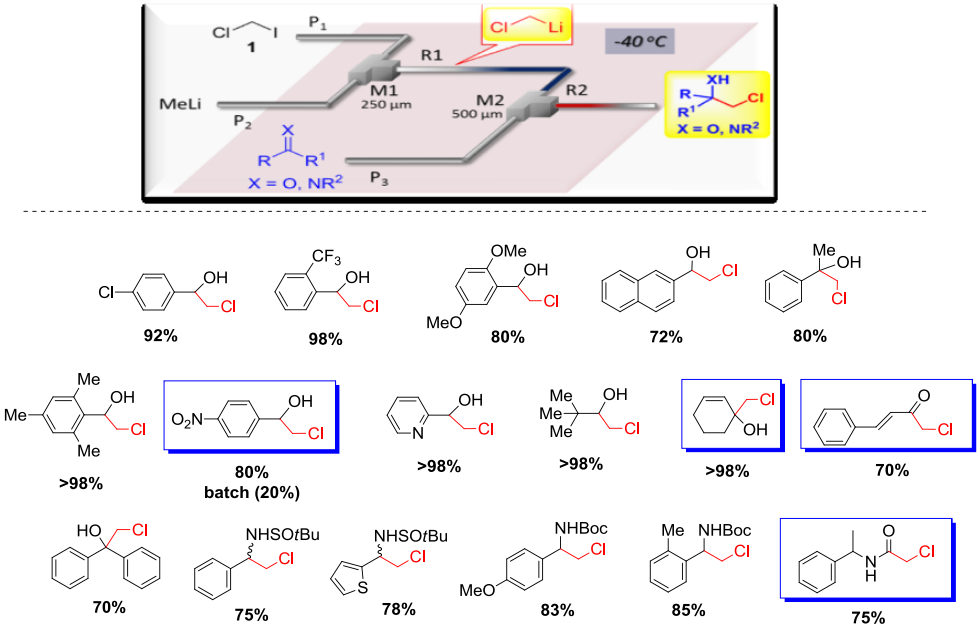
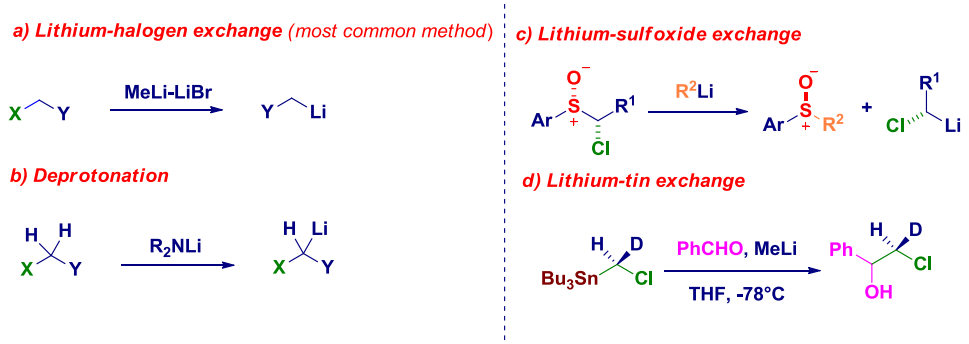


Figure 1. *Generation and trapping of chloromethyllithium through microreactor technologies.*

1.3 Synthetic strategies for the generation of Halocarbenoids.

The preparation of lithium carbenoids may be considered as normal generation of organolithium species.[21,22] The methods for their formation can be classified into these categories: a) lithiation through lithium-halogen exchange; b) lithiation through lithium-hydrogen exchange (i.e. deprotonation); c) lithiation through lithium-sulfinyl exchange; d) lithiation through lithium-tin exchange (Scheme 9).



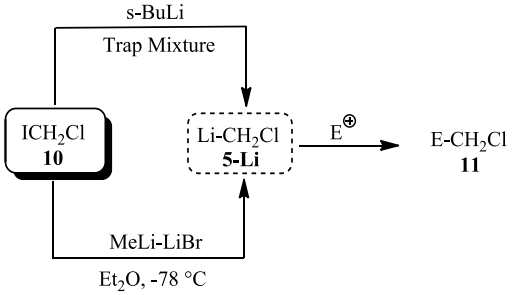
Scheme 9. *Generation of carbenoids: common method.*

In the literature there is a broad prevalence of synthetic processes *via* lithium-halogen exchange because of the easy operational procedures required and the large commercial availability of the dihalomethane precursors (almost all purchasable from standard chemical providers).[19]

In seminal investigations by Villieras, *sec*-BuLi was used to perform the exchange reaction in the so-called Trapp mixture (THF-Et_2O-*n*-pentane, 75:15:10 *v/v*)[23] at -115 °C.[16]

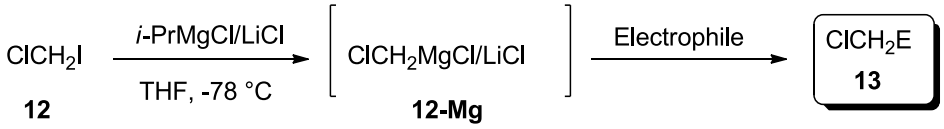
However this lithium reagent, as noticed in more recent reports, is the base of choice for accomplishing deprotonations rather than exchange reactions[24] and thus, MeLi and *n*-BuLi have come out as the best lithium sources.[6 a-c, 25]

Recently, the commercially available MeLi-LiBr complex in Et_2O has been demonstrated to be an excellent reagent for producing chloromethyllithium **5-Li** starting from chloroiodomethane **10** (Scheme 10).[5e-h]



Scheme 10. *Lithium-iodine exchange in the presence of different alkyllithiums.*

In agreement with previous studies by Matteson,[26] Pace and co-workers reported that the presence of lithium bromide not only enhances the stability of the carbenoid by means of the above showed coordinative effect but, also suppresses the competing attack of MeLi to a given electrophilic partner present in the reaction mixture under Barbier- conditions.[24a, 24c, 27]
Furthermore, lithium bromide behaves as a mild Lewis acid,[26b] thus promoting the attack of the formed carbenoid to the electrophilic substrate. Interestingly, the mild Lewis acid activity of LiBr can be advantageously employed for triggering a Meinwald type rearrangement. In 2017 Pace documented a one-pot conversion of α,β-unsaturated ketones to homologated fully substituted quaternary aldehydes *via* a single synthetic operation constituted by: i) $LiCH_2X$ homologation; ii) Meinwald-type vinyl-epoxide enolate transposition and iii) electrophilic trapping.[5v]
A final consideration regarding the stoichiometric ratio between dihalomethane and organolithiums species is that the exchange reaction can be assumed to proceed quantitatively thus, a ratio of 1:1 may be sufficient for the synthetic application. Considering the competitive attack of alkyllithium to electrophile and/or fluctuation of its concentrations it is useful a slight excess of dihalomethane (0.2-0.4 equiv). Because of thermal instability of lithium carbenoids that decomposes instantaneously, alkyllithium **1-Li** reagents is slowly added to precooled reaction medium contaning electrophile and dihalomethane.
Knochel, Marek *et al.* reported the formation of analogous magnesium carbenoids starting from iodomethanes and *i*-PrMgCl in a mixture of THF and *N*-butylpyrrolidone.[28]
Because of their higher stability compared to their lithium counterparts, they can be safely prepared at -78 °C and, the electrophile can be added in the reaction medium subsequently. This protocol was utilized by Clososki to obtain carbenoid $ClCH_2MgCl \cdot LiCl$ **12-Mg**, through magnesium-iodine exchange on ICH_2Cl **12** with *i*-PrMgCl · LiCl (Scheme 11).[29]
Clososki reported excellent chemoselectivities after addition of magnesium carbenoids to aldehydes bearing additional electrophilic moieties such as esters, ketones or nitriles.[28b]
It is clear that magnesium carbenoids represents a good alternative to lithium ones almost exclusively in reactions involving the use of strong electrophiles (e.g. aldehyde). Otherwise, the use of the more nucleophilic lithium carbenoids should be preferred.[24b]



Scheme 11. *Magnesium-iodine exchange under non-Barbier conditions to prepare magnesium carbenoids.*

Because of the excellent performance of the lithium-halogen exchange and the high rate that characterizes the latter process, deprotonation has not been employed for the formation of monohalolithium carbenoids. This is due to the fact that the sec-BuLi performs the halogen exchange rather than the deprotonation on a dihalomethane even at cryogenic temperature (-115 °C).[16]

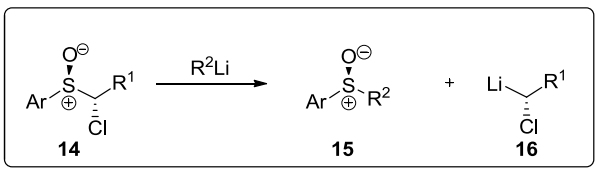
The deprotonation becomes the method of choice to prepare dihalomethylcarbenoids from the corresponding dihalomethanes, the proton of which can be easily extracted by reaction with a lithium amide base such as LDA, $LNCy_2$, LTMP or LHDMS. Generally, the nature of the amide base does not influence in a dramatic way the chemoselectivity of the process, except in the case of isocyanates, which may react with less sterically hindered lithium bases (e.g. LDA, $LNCy_2$).[24d]

Deprotonation can also be used to prepare trichloromethyllithium from chloroform and *n*-BuLi at -110 °C as reported by Molinski[30] and, because of the presence of three chlorine atoms in this carbenoid makes it a weak nucleophile that, unusually, reacts in a Michael-type addition with an unsatured sultam.

Among synthetic strategies to generate carbenoids, it is important to highlight metal-sulfinyl exchange reaction. In this context, Hoffmann reported the formation of magnesium carbenoids starting from magnesium-sulfinyl exchange.[31]

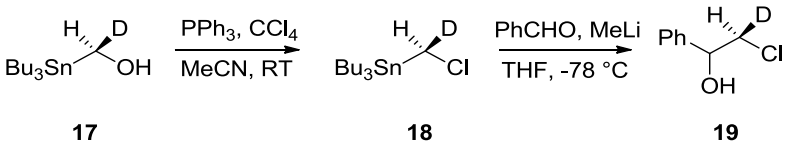
Magnesium carbenoids are generated from sulfoxide with a Grignard reagent (usually *i*-PrMgCl) at -80 ˚C. They are characterized by configurational stability, useful for asymmetric synthesis.[32,33]

In Blakemore's works, published in 2006, lithium carbenoids **16** are generated from analogous halogenated arylsulfoxides **14** (Scheme 12).[34]



Scheme 12. *Lithiation using lithium-sulfinyl exchange starting from halogenated arylsulfoxides*

As a valid alternative to generate chiral chloromethyllithium, reported by Hammerschmidt in 2008 [35], is starting from reaction of chiral stannane **18** with MeLi. The enantiopure chloromethylstannane-[D1] is synthesized as carbenoid precursor from treatment of homochiral tributylstannyl-[D1]-methanol **17** (Scheme 13).



17 **18** **19**

Scheme 13. *Tin-lithium exchange to generate chiral chloromethyllithium.*

Using Appel conditions[36] the tributylstannymethanol **17** is converted into the corresponding chloride **18**. This approach is highly responsive to the type of alkyllithium used. Indeed MeLi, maybe for its lower basicity, is more satisfactory than *n*-BuLi in the tin-lithium exchange.

2. The Research

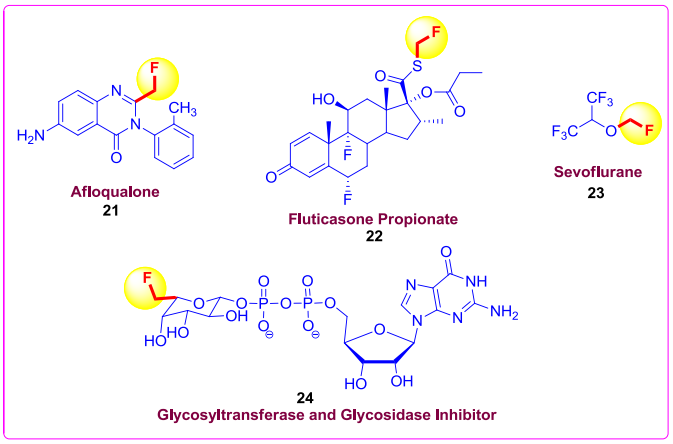
2.1. General context of α-fluoroalkyllithium carbenoid in synthetic and medicinal chemistry.

In the context of halomethyl carbenoids a very intriguing challenge is represented by $LiCH_2F$ **20-Li**. Indeed, despite its structure, aggregation, solvation and addition to alkenes have been calculated extensively,[1a, 1c] α-fluoroalkyllithiums are still experimentally unknown compounds as a consequence of the well known instability of these species.[12]

Fluorine, called "*a small atom with a big ego*",[37] is considered an isostere of hydrogen, in fact the simple replacement of hydrogen atoms by fluorine in organic compounds can modulate important physical and chemical properties, including the lipophilicity, the stability, and the bioavailability.[38]

For this reason, fluorinated compounds show higher tendency to penetrate cells membranes at physiological pH value,[39] increased binding affinity to proteins likely because of attractive polar interaction and improved metabolic stability by impeding reducing oxidative eliminative metabolism. Fluorinated molecules can also be used as transition-state inhibitors[40] and radiotracers for positron emission tomography (PET).[37]

Nowadays the efficient and selective incorporation of fluorine atom(s) or fluorine-containing moieties into organic molecules to modulate their biological properties has become a routine and powerful strategy in drug design.[41] GABAergic drug Afloqualone **21**, corticosteroid Fluticasone Propionate **22**, general anaesthetic Sevoflurane **23** are just some successful examples of fluorine-containing drugs (Scheme 14).



Scheme 14. *Examples of fluorine-containing drugs.*

2.2. State-of-the-art: What about Fluoroalkylation?

Despite the large interest in medicinal chemistry, fluorination methods are still a challenging topic due to the high electronegativity and high hydration energy of fluorine, in fact, fluorinated substitution show a very different reactivity respect to non-fluorinated analogs.[42]

Concerned to nucleophylic fluoroalkylation reactions, Hu reported the concept of "*Negative Fluorine Effect"* (NFE) with the aim to explain the influence of fluorine atom on a carbanion center.[43,44] The authors suggested that this effect was induced by two factors: 1) metal-assisted α-elimination which is the cause of the thermal instability of fluoroanion; 2) fluorine atoms could be influence the nucleophilicity behaviour of fluorinated carbanions. Moreover, it was possible to modulate the course of a fluoroalkylation reactions just changing: -the number of fluorine atoms linked on the atom carbon; -the nature of neighbouring groups; -the metal counterion (M^+).

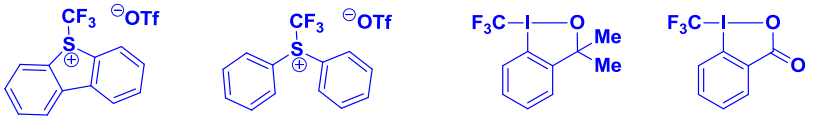
In the past, a variety of methods for the introduction of a fluoroalkyl group such as -CF_3, -CF_2H, or -CF_2R into an organic compound have been developed. It is common to classify di and tri fluoromethylation reactions in the following categories: a) nucleophilic fluoroalkylation; b) electrophilic fluoroalkylation; c) radical fluoroalkylation; d) transition metal-mediatedfluoroalkylation.

Nevertheless, compared to di- and tri- fluoroalkylation reactions, the introduction of methyl group containing a single fluorine (-CH_2F) into organic compound is still a challenging topic due to the high instability of this specie.

2.2.1 Electrophilic Trifluoromethylation.

Molecules containing trifluoromethyl groups exhibit improved molecular properties and the anticancer agent *Fludelone* is a great example of how this substitution can increase the metabolic stability leaving unaltered the cytotoxic potency.[45]

Among the reagents widely used as electrophilic trifluoromethylating reagents, manageable and cheaper crystalline compounds, such as S-(trifluoromethyl)dibenzothiophenium salts **26**,[46] S-trifluoromethyldiarylsulfonium salts **27**[47] and Togni reagents **28**, **28-II**[48] have allowed the functionalization of a good range of substrates (Scheme 15).



S-trifluoromethyldiarylsulfonium salts
26-27

Togni reagent
28

Togni reagent II
28-II

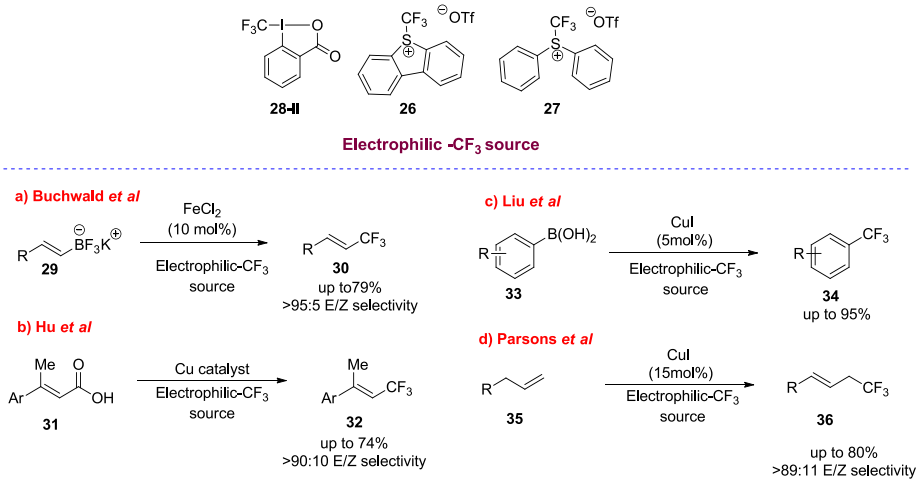
Scheme 15. *Electrophilic trifluoromethylating reagents.*

In particular, it has been reported that through a radical mechanism, the reaction of **28-II** and potassium alkenyl trifluoroborates **29** in presence of iron as catalyst affords the corresponding trifluoromethylated alkenes **30** in good yield and very high stereoselectivity (> 95:5 *E/Z* selectivity, Scheme 16a).[49] Recently, Hu and co-workers reported a facile transformation of α-β unsaturated carboxylic acid **31** into trifluoromethylated alkene **32** using Togni Reagent II **28-II** and copper as catalyst.[50] The force point of this approach was the possibility to convert, after saponification, α-β unsaturated esters and carboxylic acid derivatives into unsaturated trifluoromethylated compound with good stereoselectivity (Scheme 16b).

The synthesis of trifluoromethylated *sp* center has been developed using copper catalysis by oxidation with the electrophilic -CF_3 reagents listed above. As described by Liu *et al.*,[51] these reagents, in particular diaryltrifluoromethylsulfonium salts **26-27**, have been employed for the trifluoromethylation of a broad range of aryl and alkenylboronic acid **33** using low loading of the copper catalyst (Scheme 16c).

Nevertheless, Togni reagent **28** is considered a novel electrophilic trifluoromethylating reagent that enables the functionalization on sp^3 carbon centers of aldehydes, ketone, β-keto esters and terminal alkenes.

In 2011, Parsons and co-workers,[52] reported that it was possible to functionalize unactivated terminal olefins **35** through a C-H activation of the allylic position followed by the oxidation with **28-II** in the presence of catalytic amount of Cu^I salts. This direct trifluoromethylation leads to allylic products **36** with a > 90:10 E/Z selectivity just using mild reaction conditions without the pre-functionalization of the olefin (Scheme 16d).



Scheme 16. *Selected methods for electrophilic trifluoromethylation.*

2.2.2. Nucleophilic trifluoromethylation.

As a method for the direct nucleophilic trifluoromethylation (Trifluoromethyl)trimethylsilane (Me_3Si-CF_3), also called Ruppert-Prakash reagent,[53] represents the most popular nucleophilic trifluoromethylating reagent used in addition and cross-coupling reactions.

This stable organosilane readily reacts with a fluoride ion to release the trifluoromethyl anion species. This active species shows nucleophilic behaviour and reacts with carbonyl compounds to proceed with the trifluoromethylation.

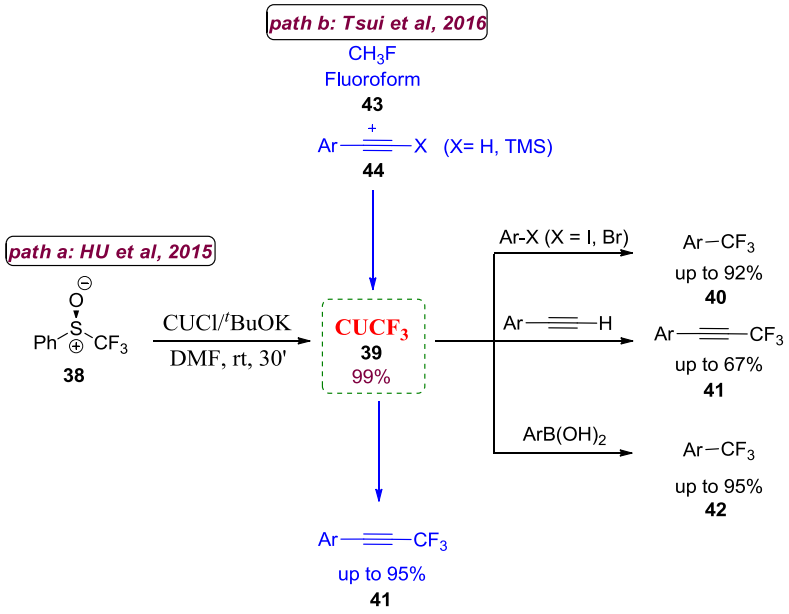
In the past years, the copper-mediated trifluoromethylation has received attention from chemists due to its efficiency and the low cost of copper.[54] Among trifluoromethylating agents, several methods were developed for the generation of practical and air-stable trifluoromethylcopper **39** ("$CuCF_3$"), which has been successfully used in the trifluoromethylation of different functional groups such as α-haloketones, arylboronic acids aryl/ vinyl halides and arenediazonium salts.

In 2015, Hu reported that phenyl trifluoromethyl sulfoxide **38** ($PhSOCF_3$) can be employed as -CF_3 source (Scheme 17, path a).[55] In particular when **38** was added into a mixture of CuCl (0.3 mmol) and t- BuOK (2 equiv) in DMF at room temperature for 30 min, $CuCF_3$ **39** was performed in quantitative yield. With optimal conditions in hand, the reactivity of **38** was compared with the ability of phenyl trifluoromethyl sulfone ($PhSO_2CF_3$) to generate $CuCF_3$. This study has shown that **38** was more reactive of phenyl trifluoromethyl sulfone probably for steric reasons.

$CuCF_3$ reagent **39**, in this way synthesized, has been employed both for the trifluoromethylation of aryl halides **40**, without the use of additional ligands, and in the

oxidative cross-coupling of terminal alkynes or arylboronic acids, afforded the expected products **41-42** in good yields.

Following the previous studies, Tsui and co-workers used non-toxic gas fluoroform **43** (CF_3H) as $CuCF_3$ precursor. Fluoroform has the advantages of being cheaper, atom economic, no-ozone depleter and readily available. In fact Tsui's aim was to prepare **39** in large quantities and employ it in trifluoromethylation reactions of terminal and TMS protected alkynes **44** (Scheme 17, path b).[56]



Scheme 17. *Selected methods for nucleophilic trifluoromethylation.*

2.2.3. Electrophilic Difluoromethylation.

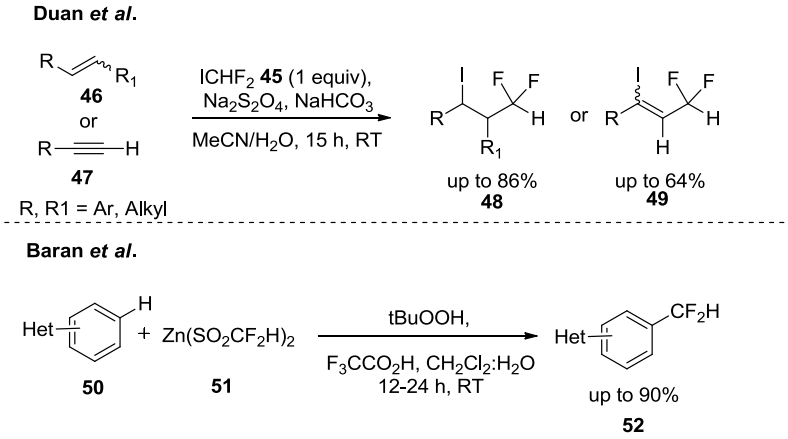
In medicinal chemistry compounds containing $-CF_2$ group have attracted interest owing their intrinsic properties and their widespread biological applications.[57]

Despite its importance, difluoromethylation approach is still undeveloped respect to trifluoromethylation, probably due to the poor stability of $-CF_2$ moiety. Among electrophilic difluoromethylation approaches, those involving radicals and carbenes as intermedietes are the most studied.

In the past decades, radical difluoromethylation of alkenes and alkynes has been developed by Duan's group.[58] According to their report, difluoroiodomethane **45** ($ICHF_2$) was selected as radical source in the presence of sodium dithionite as a radical initiator. In these reaction conditions the radical addition of **45** across alkenes **46** and alkynes **47** occurred with good yields (Scheme 18).

Later, approaches for the difluoromethylation of alkenes have been reported starting from different reagents such as halodifluoro sulfonyl reagents, [59] halodifluoro sulfonamide reagents[56c] and halodifluoro sulfanyl reagents[60] using a right radical initiators.

In 2012, Baran and co-workers[61] documented the discovered of a new reagent for the direct difluoromethylation of heterocycles *via* radical process (Scheme 18). The difluoromethyl radical source used was $Zn(SO_2CF_2H)_2$ **51**; this precursor was air-stable, easy to handle and provides the functionalization of a wide range of heteroarenes. The reaction took place under open-flask conditions and the radical intermediate generated preferably reacts with the electron-poor centers of arenes, obviously for the electrophilic behaviour of difluoromethyl radicals.

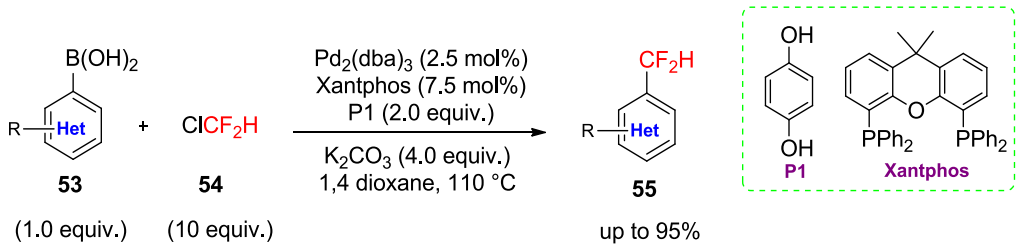


Scheme 18. *Selected methods for radical electrophilic difluoromethylation.*

Halocarbenes, such as difluorocarbenes, are useful and stable species that readily reacts with a larger variety of substrates including electron-rich and electron-poor sites. In the literature different electrophilic difluoromethylation strategies are reported involving difluorocarbene as intermediate; in 2016 Zhang *et al,* [62] published an elegant example of a straightforward transition-metal-mediated direct difluoromethylation of aromatics compounds *via* carbene process. The key point of this study was the use of cheaper and atom economy Chlorodifluoromethane **54** ($ClCF_2H$) as difluoromethyl source. The latter, was used in the past for the difluoromethylation of O, S, N, P and C nucleophiles under basic conditions but these strategies were circumscribed to particular substrates.[63]

Nevertheless, the study developed by Zhang's group was a palladium-catalysed difluoromethylation of a plethora of heteroarylboronic acids **53** under mild reaction conditions; mechanism studies have highlighted that a palladium difluorocarbene pathway took place in the cross-coupling reaction. These strategies open the door to the synthesis of

new difluoromethylated biological active compounds such as indometacin derivate, fluoxetine derivative, loratadine derivative (Scheme 19).



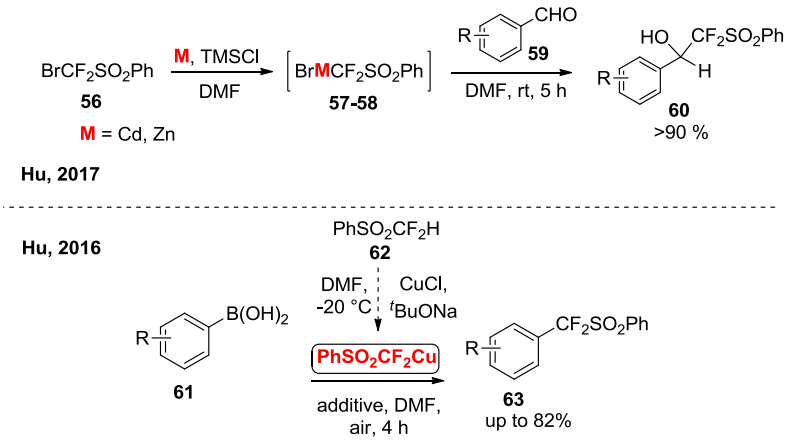
Scheme 19. *Pd-catalysed cross-coupling of $ClCF_2H$ with arylboronic and heteroarylboronic acids and esters.*

2.2.4. Nucleophilic difluoromethylation.

Nucleophilic difluoromethylation received significant attention by scientists because it is considered an alternative and method to prepare difluoromethylated compounds. For several years, $TMSCF_2H$ was employed as useful difluoromethanide anion (CF_2H) precursor in nucleophilic addition of different electrophiles like aldehydes, ketones and imines.[64]

However, difluoromethyl pronucleophiles such as sulfone, sulfoxide and phosphonate were used to form new C_{sp3}-CF_2X bonds; in 2017 Hu and co-workers, [65] reported that (phenylsulfonyl)difluoromethylzinc **57** and (phenylsulfonyl)difluoromethylcadmium **58** can be used as important reagents for nucleophilic addition to aldehydes **59** under mild reaction conditions (Scheme 20). Moreover, they underlined that phenylsulfonyl group (SO_2Ph) play a crucial role during the reaction because improve the stability of difluoromethyl organometallic reagents.

The same group developed a protocol for the introduction of -CF_2H group into sp^2 carbons via a transition-metal-assisted.[66] In particular difluoromethyl phenyl sulfone **62** can be cross-coupled with arylboronic acids **61** in the presence of copper chloride to afford corresponding product with good yields. With this method, a wide range of arylboronic acids containing either electro-withdrawing groups (EWG) or electro-donating groups (EDG) at the ortho-position were efficiently converted into the desired difluoroalkylated products; meta- and para-substituted arylboronic acids were tolerate. The protocol works with good yield also with various N-, O- and S-containing heterocyclic arylboronic acids (Scheme 20).



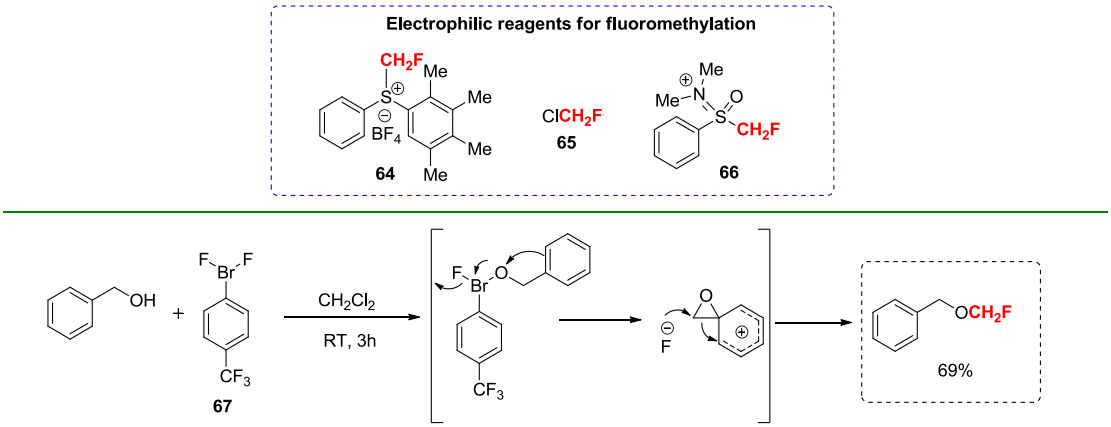
Scheme 20. *Selected methods for nucleophilic difluoromethylation.*

2.2.5. Electrophilic Fluoromethylation.

Electrophilic methods for fluoromethylation are considerably more developed: in fact, chlorofluoromethane **65**, [67] *N*-dimethyl-S-fluoromethyl-S-phenylsulfoximinium **66**, [68] aryl difluoro-λ3-bromane **67** [69] and fluoromethylsulfonium compound **64** [70] could be efficiently employed as alkylation reagents (see Scheme 21). In this case, the introduction of fluoromethyl groups through an SN_2 reaction with fluoromethyl halide reagents is more challenging than methylation with methyl halide reagents because the transition state involves the formation of a partial positive charge on the penta-coordinate carbon atom functionalized with the electronegative fluorine. Reactive nucleophiles and fluoromethylating reagents with good leaving groups are thus required for electrophilic fluoromethylation. The fluoromethylation of phenols, thiophenols, as well as of imidazole and indole can be accomplished with chlorofluoromethane **65** as the alkylating reagent, as described by Hu and co-workers.[65]

It should be highlighted that monofluoromethylated amines, ethers, and sulfides can be unstable due to the hyper conjugation of the lone pairs of electrons with the s*C-F orbitals, which results in elongation of the C-F bond and can leads to fluoride extrusion.

Another approach for the synthesis of fluoromethylated ethers involves the oxidative rearrangement of benzyl alcohols induced by aryl difluoro-λ3-bromane **67** [68] through participation of the phenyl group in the aryl carbon-oxygen bond-forming step in the synthesis of aryl α-fluoromethyl ethers (Scheme 21).



Scheme 21. *Oxidative rearrangement of benzyl alcohol to monofluoro-methylphenol with aryl dif luoro- λ 3-bromane.*

The fluoromethylsulfonium reagent **64** developed by Prakash, Olah *et al*. can allow the fluoromethylation of tertiary amines, imidazoles, phosphines and even carbon-based nucleophiles,[68] but the electrophilic fluoromethylation of carbon nucleophiles is limited to methyne nucleophiles containing mesomeric stabilizing groups: in the case of the corresponding methylene nucleophiles, the reaction products are susceptible to hydrogen fluoride elimination.[68]

2.2.6. Nucleophilic Fluoromethylation.

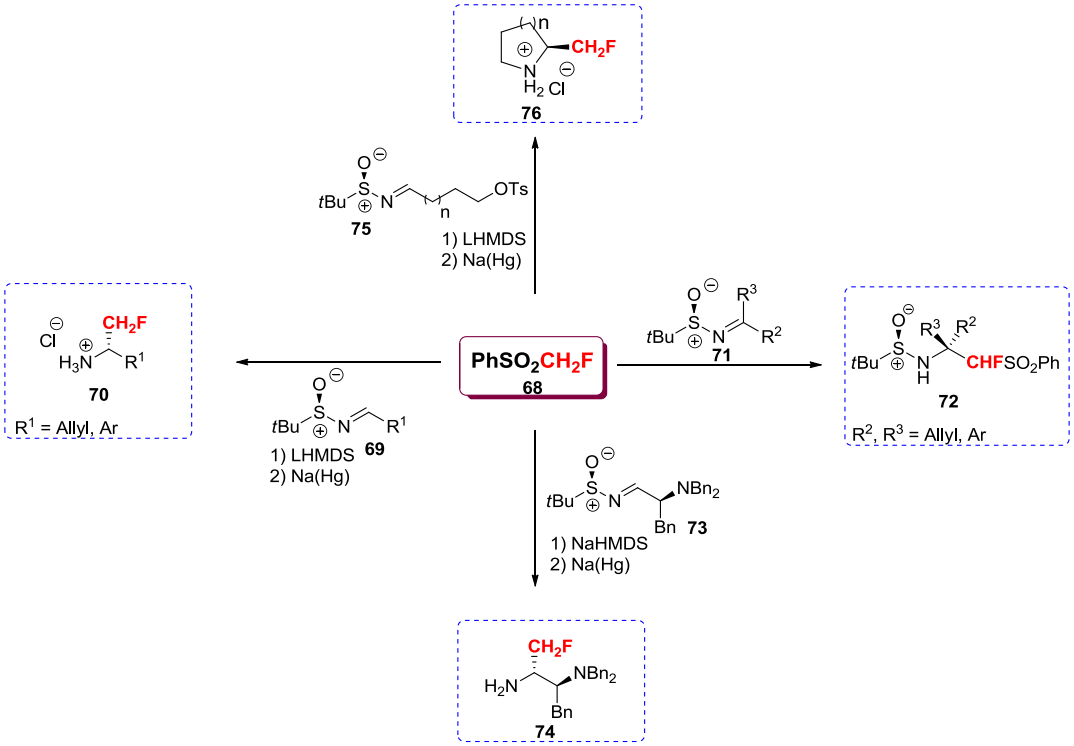
For long time, the direct nucleophilic monofluoromethylation (i.e. the transfer of a "CH_2F" fragment to a carbon electrophile) has not been object of investigations,[71] since many α-fluorinated carbanions are kinetically unstable due to 1,1-elimination to form carbenes. Nowadays, the intrinsic chemical instability of fluoromethyl carbanion has been overcome with the presence of a strong EWG group that stabilized the intermediate. Conceptually, a selective nucleophilic monofluoromethylation could be accomplished through two main strategies: a) the direct transfer of a "CH_2F" moiety; b) the transfer of the fluorinated group linked to a suitable auxiliary requiring removal at the end of the sequence.[43]

In this context, Hu and co-workers reported the first highly stereoselective monofluoromethylation of chiral *N*-tertbutanesulfinaldimines **69**[72] and ketimines **71**,[73] as well as of chiral α-amino *N*-(tert-butylsulfinyl)aldimines **73**[74] using fluoromethyl phenyl sulfone **68** ($PhSO_2CH_2F$) as a novel nucleophilic fluoromethide (Scheme 22).

The reaction has been shown to be highly stereoselective and convenient for the synthesis of enantiomerically pure α-monofluoromethyl amines. The same methodology can also be used

to synthesize homochiral α-monofluoromethylated cyclic secondary amines **76** by using tosylate (OTs) bearing (R)-(*tert*-butanesulfinyl)imine precursors **75** (Scheme 22).[69]

Crucial for the successful outcome of the reaction were: a) the presence of the stabilizing phenylsulfonyl group ($PhSO_2$-); b) the imine nitrogen must be substituted with a strong electron-withdrawing group (*t*-BuSO-) which *per se* requires harsh conditions for the removal.



Scheme 22. *Addition of monofluoromethyl pronucleophiles to chiral N-(tertbutylsulfinyl)aldimines and ketimines. LHMDS = lithium hexamethyldisilazide; NaHMDS = Sodium hexamethyldisilazane.*

Evidently, due to the asymmetry of the sulfur atom in the sulfinyl group, it acts as the stereochemical inductor for the whole process. Though effective, the limitations of this procedure appear clear: a) it prefers aldimines as the nuclophilic partners for the transfer and, b) the deprotection step is particularly critical because of the use of amalgam Na(Hg) and 4 N HCl, which in turn can compromise the chemo efficiency in the case of a multi-decorated electrophile.

Very recently, Hu's developed a new strategy for the direct monofluoromethylation of O-, S-, N-, and P-nucleophiles starting from fluorinated sulfoximines and sulfoximinium salts as fluoroalkylating agents **77**.[75] The reaction was effective with different structurally phenols, thiophenol and diphenylphosphine that were successfully monofluoromethylated by *N*-tosyl-S-fluoromethyl-S-phenylsulfoximine ($PhSO(NTs)CH_2F$) to give the expected

monofluorinated products in very good yields. Afterwards, the use of a radical scavengers into the reaction mixtures provided the implication of a radical ($S_{RN}1$) mechanism involving an SET process. Unfortunately, such methodology was not suitable for C-nucleophiles thus, leaving undisclosed the development of a direct C-CH_2F bond formation strategy (see Scheme 23).[76]

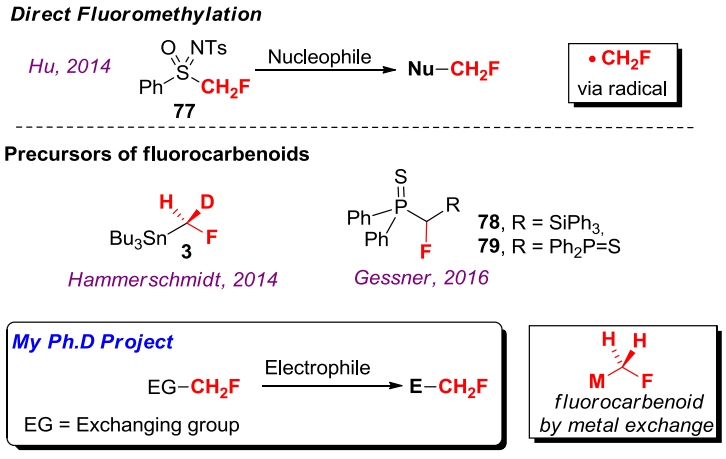
In this context, the availability of a reagent able to introduce directly the CH_2F group is highly desirable. Conceptually, fluorocarbenoid (M-CH_2F) represent a straightforward synthetic tactic to install, through a single synthetic operation, the fragment -CH_2F (contemporaneous fluorination / carbon-carbon bond formation) on an electrophilic substrate.

Gessner synthesized and characterized alkali metal fluorine carbenoids, in particular Li, Na and K fluorocarbenoids, stabilized by EWG group such as triphenylsilane **78** ($SiPh_3$) and diphenylphosphine sulfide **79** (Ph_2P=S), (see Scheme 23). [77]

NMR study and experimental calculations have highlighted that lithium carbenoids are less stable than their Na and K congeners due to different strengths of the M–F interactions.

In such an interesting report, the author textually stated: "*.. Li/F systems are still regarded as the "beast" in carbenoid chemistry. This is due to their extreme sensitivity and reactivity connected with the facile LiF elimination typically at temperatures as low as –78 °C. Hence, applications are extremely limited*".[76]

Moreover, the important contributions by Hammerschmidt 's group demonstrated that although $LiCH_2F$ can be generated through tin-lithium exchange with an excellent degree of stereostability, the tremendous chemical instability it suffers do not enable application in synthetic sequence even at very low temperatures (Scheme 23).[12]



Scheme 23. *State-of-the-Art of monofluoromethylations.*

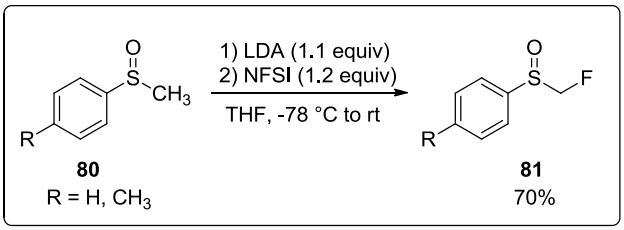
However, it should be highlighted that Hammerschmidt seminal work is exclusively based on the use of fluoro-[D1]methyllithium and thus, more intriguing and challenging, functionalized secondary and tertiary fluoro-lithiums (non incorporating deuterium) have not yet been reported.

Moved by this challenge, and inspired by Hammerschimdt's report, we embarked in a research endeavour aimed at exploiting the reactivity of Mg, and Li fluoromethyl carbenoids.

3. PhD Project

3.1 Development of a straightforward direct nucleophilic fluoromethylation strategy.

As a first step of our investigation we aimed to generate α-fluoromethyl carbenoid through metal-sulfinyl exchange, as reported by Hoffman[30] and Blakemore,[24] with particular emphasis on the nature of the metal (Mg or Li), and to trap it with a strong electophile such as benzaldeyde under different reaction conditions (e.g. organometallic species, temperatures and solvents). In other word, we tried to generate fluorocarbenoid intermediate starting from α-fluoro sulfoxide as a precursor. At the beginning we synthesized fluoromethyl phenyl sulfoxide **81** starting from commercial methylphenyl sulfoxide **80**, lithium diisopropylamide (LDA) as base and *N*-Fluorobenzenesulfonimide (NFSI) as the electrophilic fluorinating agent (Scheme 24).

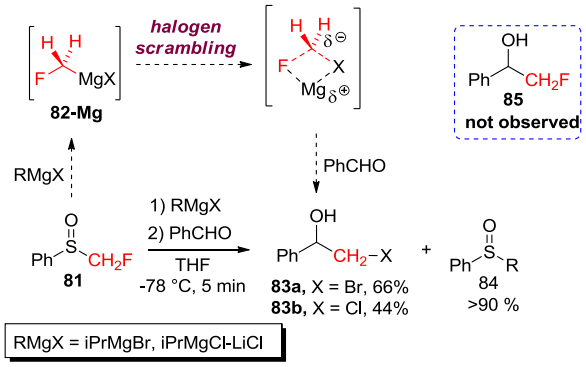


Scheme 24. *Synthesis of Fluorinated Sulfoxides.*

With α-fluoro sulfoxides in hand we focused our attention on the sulfoxide-metal exchange reaction; we started using *i*-PrMgBr as metallating agent, benzaldeyde as electrophile at -78 °C with an external queching after 5 minutes(Table 1, entry 2).

Surprisingly we didn't observe the generation of the desired fluorohydrine **85** but during the reaction took place an halogen scrambling between fluorine/bromine atoms when *i*-PrMgBr were involved as the metallating agent afforded bromohydrine **83a** as unique product of the reaction (Scheme 25).

When *i*-PrMgCl/LiCl was used as metallating agent, the product of the reaction was the corresponding chlorohydrine **83b** (Table 1, entry 4). Notably, (Isopropylsulfinyl)benzene **84** derived from the nucleophilic attack of the Grignard reagent to the sulfinyl centre, was isolated in a quantitative amount from the crude. This results suggests that the carbenoidic species should be formed in a first step of the reaction and, the halogen scrambling might occur in a second time likely by activation of the C-F bond caused by the mild Lewis acidity of Mg.



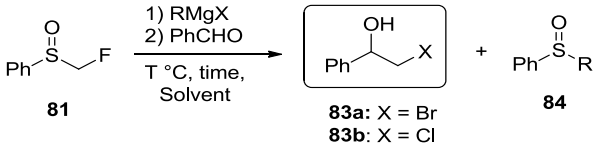
Scheme 25. *The unexpected case of* α-Fluoro sulfoxides*. A halogen scrambling mechanism was proposed.*

To confirm this intuition and obtain mechanistic insight into this unexpected behaviour, we carried out a reaction without using Grignard reagents, but only in the presence of Magnesium bromide ethyl etherate $MgBr_2 \cdot O(C_2H_5)_2$. No reaction we observed and this result helped us to understand that the F-Br exchange did not occur on the substrate but only on the fluorocarbenoid. Nevertheless, our hypothesis was supported by an excellent example reported by Charette and co-workers of an analogous F/I halogen scrambling with electrophilic Zinc fluorocarbenoids.[78]

This outcome is in agreement with the well known thermodynamic stability and kinetic inertness of the carbon-fluorine bond, that had severely limited previous attempts of replacement of fluorine by chorine, bromine or iodine.[25-26]

With the aim of reducing the rate of the halogen scrambling we tried to stabilize the carbenoidic intermediates using different reaction conditions.

Only starting material was recovered from the reaction when toluene, diethylether or a MeTHP:Et_2O (mixture 1:3) were used as reaction solvents (Table 1, entry 6,7,8). Lowering temperature to -110 °C, did not allow to generate the desired fluorohydrine **85** and it was observed also a decrease of the yield of bromohydrine **83b** (Table 1, entry 1). Finally we tried to trap fluorocarbenoid using Barbier condition but also in these cases only starting material was recovered from the reaction (Table 1, entry 9).



81 **83a:** X = Br **83b**: X = Cl **84**

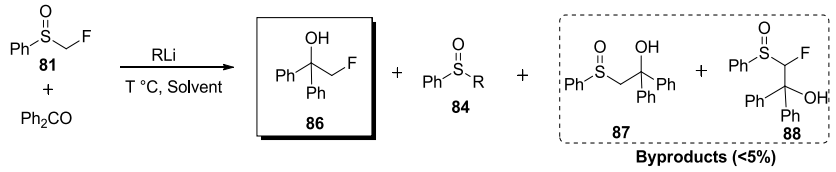
Entry	Solvent	T °C	time	RMgX	Ratio[a]	Products[b]	Transmet.[f]	Decompos.[g]
1	THF	-110	5'	*i*-PrMgBr	1.2/1.1/1	**83a** (40%)	45%	5%
2	THF	-78	5'	*i*-PrMgBr	1.2/1.1/1	**83a** >95%	29%	
3	THF	-78	1'	*i*-PrMgBr	1.2/1.1/1	**83a** (60%)	70%	10%
4	THF	-78	15'	*i*-PrMgCl/LiCl	1.2/1.1/1	**83b** (44%)[c]	>95%	50%
5	THF	-78	5'	MeMgBr	1.2/1.1/1	NR	-	-
6	Toluene	-78	5'	*i*-PrMgBr	1.2/1.1/1	NR	-	-
7	Et_2O	-78	5'	*i*-PrMgBr	1.2/1.1/1	NR	-	-
8	MeTHP:Et_2O (1:3)	-78	5'	*i*-PrMgBr	1.2/1.1/1	-	70%	70%
9	THF	-110	-[d]	*i*-PrMgBr	1.2/1.1/1	NR	-	-

[a] Ratio of **81**/RMgX/PhCHO; [b] Product ratio established by ^{1}H MNR of the crude reaction mixture; [c] The product was chlorohydrine **83b**; [d] Internal quenching conditions; [e] Entry 2 total Mg/SO exchange maximum yield of **83a**; [f] Calculated by ^{1}H NMR of the crude mixture on the basis of amount of byproduct **84**; [g] Calculated by ^{1}H NMR of the crude mixture on the basis of product **83a-b**/**2** difference.

Table 1. *Optimization study of fluoro methyl phenyl sulfoxide with Grignard reagent.*

In the light of the results obtained, we explored the formation of fluorocarbenoid changing the metallating agents; in particular we used MeLi or MeLi-LiBr instead of *i*-PrMgBr . With the aim to evaluate the chemical stability of fluoromethyllithium **82-Li**, a screening of the reaction conditions was conducted.

As shown in Table 2 entry 8, after different trials, we got the best result using MeLi-LiBr, Benzophenone as electrophiles and a mixture of solvents THF:Et_2O (1:1) at -98 °C. In these conditions, it was possible to trap fluorocarbenoid **82-Li** in 23 % yield. The reaction worked with lower yield using different mixtures of solvents such as MeTHF:Et_2O or MeTHF:Et_2O (Table 2, entry 9,10). No reaction was observed when Toluene, Et_2O and CPME were choosed as reaction solvents (Table 2, entry 4, 6 and 7). Then, when p-clorobenzaldehyde was used as electrophile we found a lower yield (17%, table 2, entry 12).



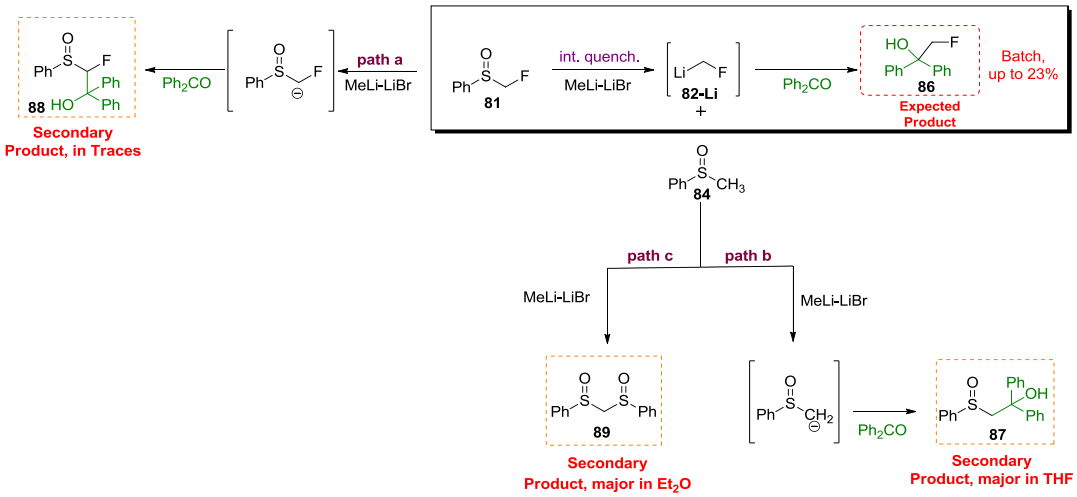
Entry	Solvent	T °C	RLi	Ratio[a]	Product[b] 86	Transmetal.[f]	Decomp.[g]
1	THF	-78	MeLi	1.2:1.1:1	< 5%	32%	30%
2	THF	-78	MeLi	1:3:2	< 5%	>95%	>95%
3	THF	-98	MeLi	1:3:2	< 5%	>95%	>95%
4	Toluene	-78	MeLi	1:3:2	NR	>95%	>95%
5	THF	-98	MeLi/LiBr	1:3:2	20%[e]	94%	74%
6	Et_2O	-98	MeLi/LiBr	1:3:2	NR	>95%	>95%
7	CPME	-98	MeLi/LiBr	1:3:2	< 5%	>95%	>95%
8	THF:Et_2O(1:1)	-98	MeLi/LiBr	1:3:2	23%	50%	27%
9	MeTHP:Et_2O(1:1)	-98	MeLi/LiBr	1:3:2	21%	36%	15%
10	MeTHF:Et_2O(1:1)	-98	MeLi/LiBr	1:3:2	17%	36%	19%
11	THF:Et_2O(1:1)	-110	MeLi/LiBr	1:3:2	22%	46%	24%
12	THF:Et_2O(1:1)	-98	MeLi/LiBr	1:3:2	17%	23%[c]	6%
13	THF:Et_2O(1:1)	-98	*n*-HexLi	1:3:2	14%[d]	>95%	81%
14	THF	-78	PhLi	1:3:2	10%[d]	>95%	85%

[a] Ratio of **1**/RLi/Ph_2CO; [b] Product ratio established by ^{1}H MNR of the crude reaction mixture; [c] Benzaldehyde was used as the electrophile; [d] Complex reaction mixture, only signals of **86** were considered; [e] Byproduct **87** was obtained with 44% yield. [f] Calculated by ^{1}H NMR of the crude mixture on the basis of amount of byproduct **84**; [g] Calculated by ^{1}H NMR of the crude mixture on the basis of product **86**/**2** difference.

Table 2. *Optimization study of fluoro methyl phenyl sulfoxide with organolithium reagents.*

Notably, (methylsulfinyl)benzene **84** derived from the nucleophilic attack of the organolithium reagent to the sulfinyl centre, wasn't isolated in a quantitative amount from the crude of the reaction; this result suggests side take place leading to by products. As shown in Scheme 25, part of the starting material was subjected to deprotonation by MeLi-LiBr leading to the formation of **88**. Both diasteroisomers of **88** were separated by chromatography and characterized (path a, scheme 26).

Moreover, in the presence of an excess of base (methylsulfinyl)benzene, derived from the nucleophilic attack of the organolithium reagent to the sulfinyl centre, undergoes to two reactions: a) the deprotonation and subsequent trapping with benzophenone giving **87** (path b, scheme 26); b) the deprotonation and subsequent homologation with the starting material giving **89** (path c, scheme 26). Anyway, these reactions took place using THF or Et_2O as unique solvents of the reaction, in particular **87** is major in THF, **89** is major in Et_2O. Nevertheless, we are able to limit the formation of these secondary products using the mixtures solvents THF: Et_2O (1:1).



***Scheme 26**. Rationale mechanism of the formation of collateral products resulting from the reaction between **81** and **84**.*

Taking into consideration the well-established applicability reported by Pace *et al* of dihalomethanes as carbenoid precursors [79] we deemed the commercially available fluoroiodomethane **90** a convenient source for the MCH_2F reagent.[80]

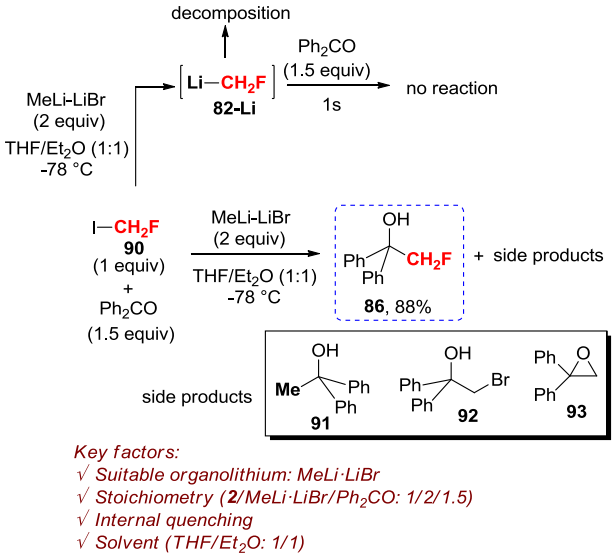
In striking contrast to sulfoxide **81**, both *i*-PrMgCl·2LiCl and *i*-PrMgBr were ineffective to promote the metalation of **90** and, only the attack of the Grignard to the electrophile was observed. After extensive reaction tuning, fluoroiodomethane **90** was identified as the optimal substrate for lithiation.

At the beginning, the reactions were carried out using THF as solvent and benzophenone as electrophile under Barbier-like condition.[15,30] With the purpose to minimize degradative α-elimination of fluoromethyllithium, according to pioneering studies by Villieras[16] and recent findings by Pace,[24,26] we used MeLi-LiBr as metallating agent. The thermal instability of fluorocarbenoids **82-Li** has been kept under control running the reaction at low temperature (-78 ˚C).

As shown in *Table 3* entry 1, using 1:3:2 as stoichiometric ratio between **90**, base and electrophile, we were able to trap fluorocarbenoid **82-Li** with a good yield (73%). This result helped us to understand that the temperature of -78 °C represented a perfect compromise for reactivity and stability of such carbenoidic species .

From a careful analysis of ^{1}H NMR spectra of the crude of the reaction, were found that fluorohydrine **86** was not the unique product of the reaction; bromohydrine **92** and epoxide **93** were side products of the reaction with variable yields. We thought that also in this case, the formation of these side products, was a consequence of a halogen scrambling induced by LiBr. This scrambling led to the formation of bromohydrine **92** that under basic condition cyclized to form the epoxide **93**. The amounts of **92** and **93** were strictly dependent on the reaction conditions, and possibly on the chemical stability of **82-Li**.

As expected, lithium fluorocarbenoid **82-Li** was found extremely reactive, fully decomposing under external trapping conditions, even when the electrophile was added after only 1 second (Scheme 27).



Scheme 27. *Reactivity of fluoroiodomethane **90**.*

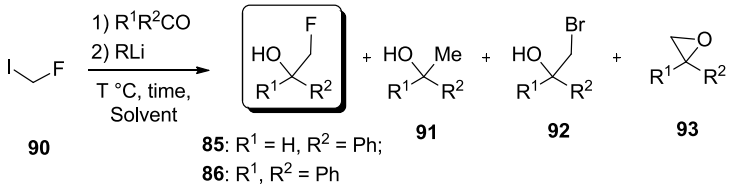
Starting from these preliminary results, in order to limit the inevitable direct attack of the base to the electrophile and thus limit the amount of **91**, the stoichiometric ratio of the reaction was controlled. In this sense, using less equivalents of the reagents (1:2:1.5 instead of 1:3:2) the formation of side product **91** was tamed and the reaction gave the expected fluorohydrine **86** with a comparable yield (Table 3, entry 3).

Nevertheless, the influence of the reaction solvent was investigated; the use of toluene, cyclopentyl methyl ether or Et_2O as reaction solvents proved to be ineffective (Table 3, entry

6,7,8). Instead, the use of a 1:1 *v/v* mixture of THF/Et_2O as the medium increase the yield of desired fluorohydrine up to 88%, while decrease the yield of epoxide **93** up to 10% (Table 3, entry 4). This result suggests that the solvent plays an important role on the ambiphilicity of carbenoids. In fact, the use of THF as unique solvent of the reaction exalts the electrophilic nature of carbenoidic species promoting the direct insertion of a carbene into the C=O of the electrophile.

Higher temperatures, exalted the decomposition of **82-Li**. In fact, increasing temperature up to -40 °C - under internal quenching conditions - epoxide **93** was formed in 23% yield, whereas **86** in 72% yield (Table 3, entry 2).

Moreover, in striking contrast to sulfoxide **81**, both *i*-PrMgCl·2LiCl and *i*-PrMgBr were ineffective to promote the metalation of **90** and, only the attack of the Grignard to the electrophile was observed (Table 3, entry 17-19).



					Products[b]		
Entry	**Solvent**	**T °C**	**RLi**	**Ratio[a]**	**4**	**9**	**10**
1	THF	-78	MeLi/LiBr	1/3/2	**86**, 73%	<5%	21%
2	THF	-40	MeLi/LiBr	1/3/2	**86**, 72%	<5%	23%
3	THF	-78	MeLi/LiBr	1/2/1.5	**86**, 73%	<5%	23%
4	THF:Et_2O(1:1)	-78	MeLi/LiBr	1/2/1.5	**86**, 88%	<5%	10%
5	THF:Et_2O(1:1)	-78	MeLi/LiBr	1/2/1.1	**86**, 57%	8%	34%
6	Et_2O	-78	MeLi/LiBr	1/2/1.5	No Reaction	-	-
7	CPME	-78	MeLi/LiBr	1/2/1.5	No Reaction	-	-
8	Toluene	-78	MeLi/LiBr	1/2/1.5	**86**, <5%	-	-
9	Toluene/Et_3N	-78	MeLi/LiBr	1/2/1.5	**86**, <5%	-	-
10	THF:Et_2O(1:1)	-78	MeLi	1/2/1.5	**85**, 15%	-	<5%
11	THF:Et_2O(1:1)	-78	MeLi	1/2/1.5	**86**, 31%	-	-
12	THF:Et_2O(1:1)	-40	MeLi	1/2/1.5	**85**, 22%	-	-
13	THF:Et_2O(1:1)	-78	PhLi	1/2/1.5	**86**, 25%	-	-
14	THF:Et_2O(1:1)	-78	PhLi/LiCl	1/2/1.5	**86**, 8%	<5%[c]	-
15	THF:Et_2O(1:1)	-78	TMSMeLi	1/2/1.5	**86**, 38%	<5%	-
16	THF:Et_2O(1:1)	-78	MeLi/LiBr	1/2/1.5	No Reaction	-[d]	-
17	THF:Et_2O(1:1)	-78	*i*PrMgCl/LiCl	1/2/1.5	No Reaction	-	-
18	THF:Et_2O(1:1)	-78	MeMgBr	1/2/1.5	No Reaction	-	-
19	THF:Et_2O(1:1)	-78	*i*PrMgBr	1/2/1.5	No Reaction	-	-

[a] Ratio of **90**/RLi/Electrophile; [b] Product ratio established by ^{1}H MNR of the crude reaction mixture by using mesitylene or hexafluorobenzene as internal standards; [c] the product was chlorohydrine 8**3b**; [d]External quenching conditions after 1 second.

Table 3. *Optimization reaction of fluoroiodometane* ***90*** *with organolithium reagents.*

3.2 Application of the optimal conditions

After realizing reliable optimization investigation, the reactivity of such fluorocarbenoids with different functional groups was evaluated. Remarkably, our protocol can be conveniently applied to a wide range of electrophiles. In fact, the methodology has been extended to a plethora of electrophiles such as aldehydes, ketones, Weinreb amides, α,β unsaturated ketones.

As show in *Scheme 28*, the protocol worked quite well when aromatic and heteroaromatic aldehydes were used as electrophiles; the corresponding fluorohydrine **86o-u** were obtained in good yields in almost all cases, with exception of **86p** (due to its volatility) where chemocontrol in the presence of a nitrile electrophilic functionality was fully preserved.

A wide range of β-fluoro alcohols **86a-z** were obtained in good to excellent yields and high chemocontrol, as showcased by adducts **86c, 86o** and **86f-i** featuring additional potentially exchangeable halogens.[81] Methodology may be used towards carbocyclic and heterocyclic enolizable ketones provide the corresponding fluoromethylated products **86j-n** in very good yields.

The reaction proceeded with stereocontrol in the case of a small-size cyclic ketone, obtaining fluoro alcohol **86l** in 94% yield and 90:10 diastereomeric ratio. Fluorohydrins **86t-z** were furnished when α,β-Unsaturated carbonyls were employed as electrophiles; these latter, reacted chemoselectively preserving the integrity of the double bond.

Surprisingly, the use of chromanone, led to both 1,2- and 1,4-addition products **86aa** and **94**, but **86aa** was found highly unstable on silica gel during the purification and only adduct **94** was isolated in 50% yield.[26a]

The direct access to α-fluorinated ketones **95a-l** were possible using soft electrophiles such as Weinreb amides which have proved excellent acylating agents for $LiCH_2F$.

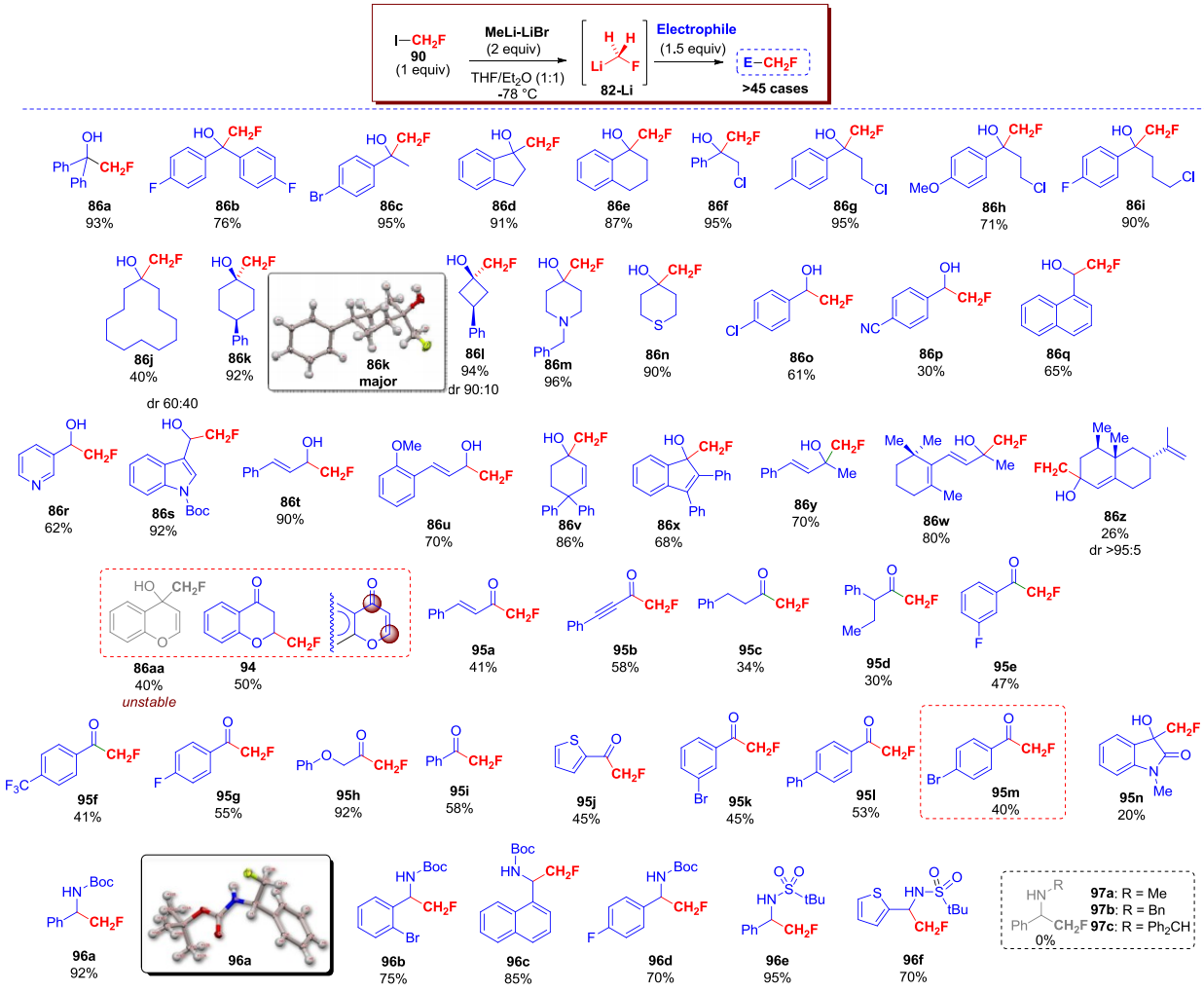
Unsaturated motifs such as alkene and alkynes were perfectly tolerated in terms of chemocontrol (*i.e.* **96a,b**), as well as heterocycles and halogenated aromatics (*i.e.***96j,k**). A special ketone, such as isatine, was fluoromethylated giving adduct **95n** in lower yield 20% yield due to its low solubility in the reaction medium.

An important result was the possibility to apply this straightforward protocol for the synthesis of β-fluoroamine **96a-f** and this represent a significant advancement for its synthesis compared to the usually employed one consisting of various steps.[82]

When the reactions were carried out with imines having an electron donating group (EDG) linked to nitrogen such as *N*-alkyl or *N*-benzyl imines (*i.e* **97a-c**) the desired products wasn't

observed; in fact, the process requires imines bearing *N*-electron-withdrawing groups such as Boc, t-BuSO, t-BuSO$_2$ (Scheme 28).

It is worthy to highlight that the structures of compounds fluoroalcohol-**86k** and β-fluoroamine-**96a** were ascertained by single crystal X-ray analysis.

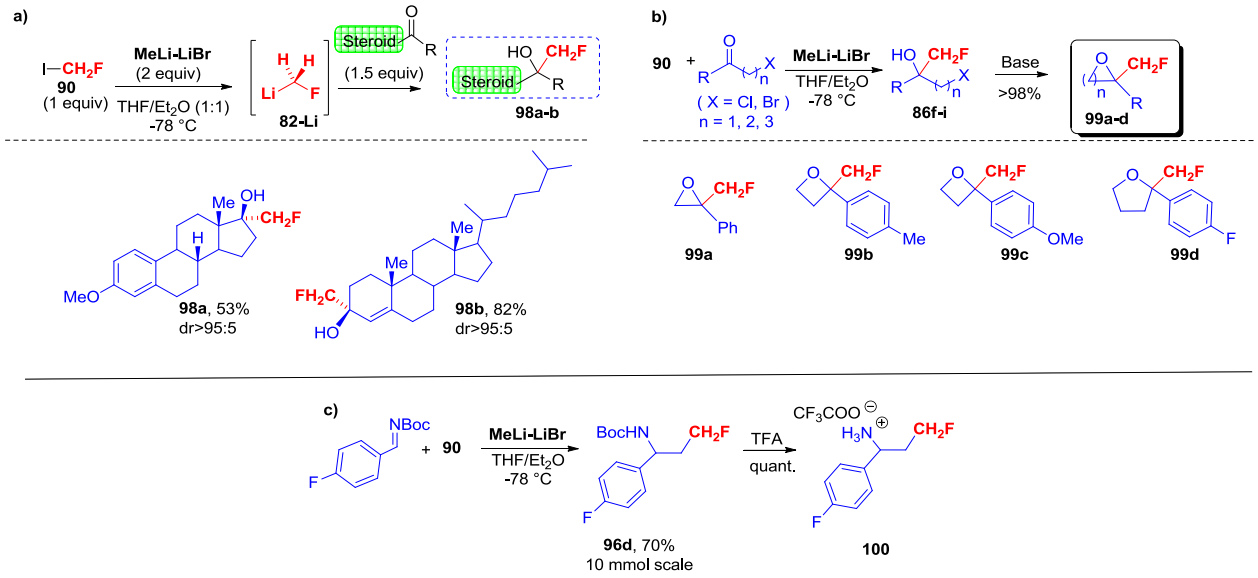


Scheme 28. *Scope of the direct nucleophilic fluoromethylation strategy.*

Finally, the so developed method has been applied to the synthesis of a privileged scaffold of pharmaceutical relevance such as 3-*O*-methylestrone and 4-colesten-3-one. Nuclear Overhauser Spectroscopy (Noesy-2D) have highlight that the reaction of the fluorocarbenoid **82-Li** occurred with high stereoselectivity, furnishing **98a,b** as single stereoisomers (Scheme 29a).

Another challenging goal was to synthesize in just two steps α-fluoromethylated oxygenated heterocycles such as epifluorohydrine **99a**, fluoromethylated oxetanes **99b,c** and tetrahydrofuran **99d** through the chemoselective intramolecular cyclization (Scheme 29b).

To conclude, given the importance of β-fluoro amines, a 10 mmol preparation of **100** was achieved using a two steps sequence based on the direct fluoromethylation of N-Boc imine, followed by acidic removal of the Boc group (Scheme 29c).



Scheme 29. Further applications of the direct fluoromethylation strategy.

4. Conclusion

The first direct nucleophilic fluoromethylation of organic compounds was disclosed. In particular the reactivity and the stability of fluoromethyllithium has been study.

A preliminary study performed on α-fluorosulfoxides highlighted that, when a Grignard reagent was used as a metalleting agent, an unexpected halogen scrambling caused the formation of chloro- and bromohydrins instead of the expected fluorohydrin when benzaldehyde was added. This type of halogen scrambling seemed to occur only on the carbenoidic intermediate and not on the starting material, and was probably due to the Lewis acidic feature of Mg. The use of an organolithium such as MeLi as metalleting reagent was definitely unsuccessful due to uncontrollable side reactions that took place during the reaction.

The employment of a cheaper, readily available fluoroiodomethane (ICH_2F) was of great importance because, in striking contrast to sulfoxide, immediately turned out to be a convenient source of MCH_2F.

After a scrupulous screening of the reaction conditions, a robust strategy for the direct introduction of a fluoromethyl group into an organic compound has been developed. The straightforward and versatile protocol has been applied towards *c.a* 50 examples of electrophiles; fluoro alchols, β-fluoro amine, α-fluorinated ketones has been synthesized in high yields and good chemoselectivity.

We believe that the present work open the doors to an incredible possibilities for the medicinal chemistry; in fact, the strategy may be used for fluoromethylation of important biologically and complex scaffolds such as steroids.

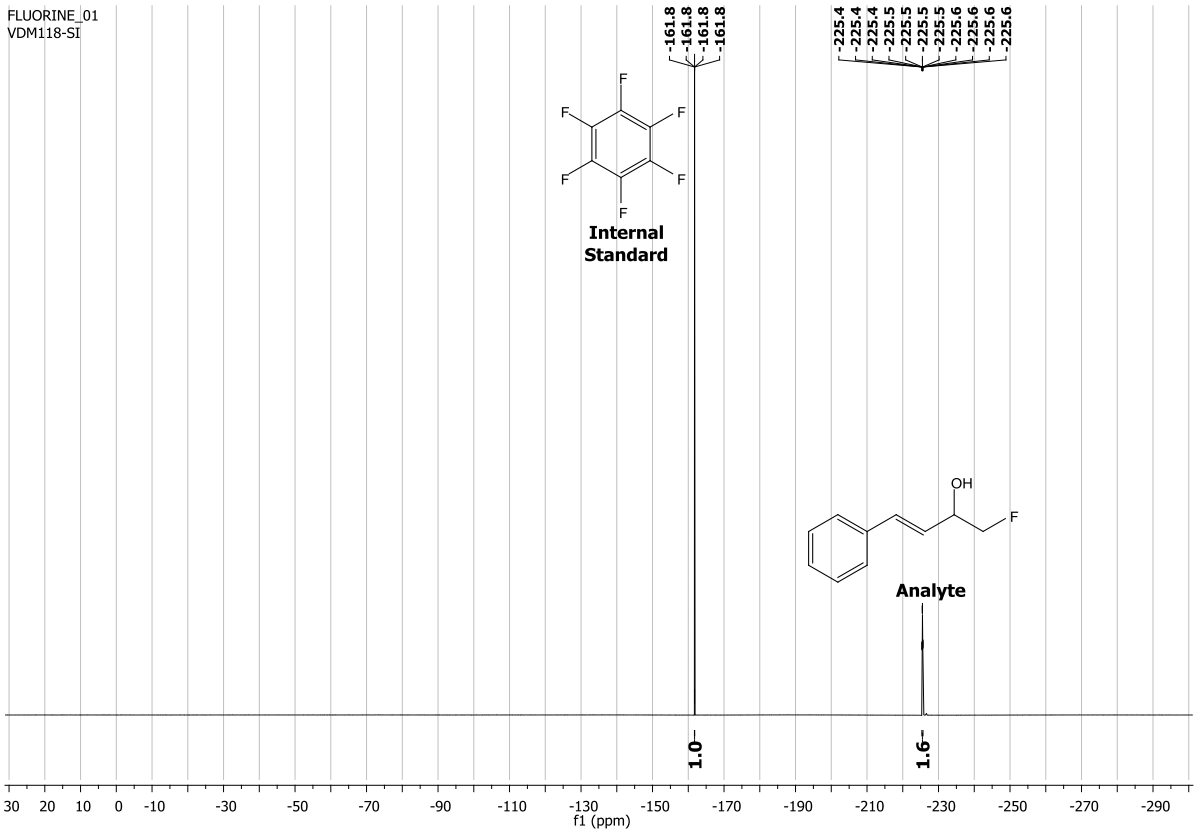
5. Experimental Section

Within this experimental section the characterization data of coumponds **86a-z**, **94**, **95a-n**, **96f-n**, **98a-b**, **99a-d** and **100** were reported. The copies of ^{1}H NMR, ^{13}C NMR, HSQC, COSY of such compounds are available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b07891.

5.1 Material and methods

THF, 2MeTHF and Et_2O were freshly distilled under a nitrogen atmosphere over Na/benzophenone, toluene was freshly distilled under a nitrogen atmosphere over CaH_2. MeLi/LiBr was purchased as diethyl ether solution and the title established by titration method. Fluoroiodomethane was purchased by ABCR Gmbh company. All other chemicals were commercially available and used without further purification. For the ^{1}H, ^{13}C NMR, ^{19}F NMR spectra (^{1}H NMR 400, 500, 600 MHz, ^{13}C NMR 100, 125, 150 MHz, ^{19}F NMR 376 MHz), $CDCl_3$, methanol-d_4 and toluene-d_8 were used as the solvents. MS-ESI analyses were performed on LC/MSD trap system VL. Melting points were uncorrected. GC-MS spectrometry analyses were carried out on a gas chromatograph (dimethylsilicon capillary column, 30 m, 0.25 mm i.d.) equipped with a mass selective detector operating at 70 eV (EI). The high resolution mass spectrometry (HRMS) analyses were performed using a Bruker microTOF QII mass spectrometer equipped with an electrospray ion source (ESI) operated in positive ion mode. The sample solutions (CH_3OH) were introduced by continuous infusion with a syringe pump at a flow rate of 180 μL min^{-1}. The instrument was operated with end-plate offset and capillary voltages set to −500 V and −4500 V respectively. The nebulizer pressure was 0.4 bar (N_2), and the drying gas (N_2) flow rate was 4.0 L min^{-1}. The capillary exit and skimmer voltages were 90 V and 30 V respectively. The drying gas temperature was set at 180°C. The calibration was carried out with a sodium formate solution (10 mM NaOH in isopropanol/water 1:1 (+0.2% HCOOH) and the software used for the simulations was Bruker Daltonics Data Analysis (version 4.0). For flash chromathography silica Gel 60, 0.04-0.063 mm particle size was used. All reactions involving air-sensitive reagents were performed under argon in oven-dried glassware using syringe septum cap technique.

5.2 ^{19}F NMR yield determination of Fluoromethylated compounds using Hexafluorobenzene as internal standard.



The molar amount of analyte can be calculated from the molar amount of internal standard (IS) and the molar ratio:

$$nA = nIS \times rA/IS$$

(eq.1)

The ratio between analyte and internal standard is:

$$rA/IS = \frac{1.6}{1/6} = 10$$

The sample contains 12.6 mg internal standard (Hexafluorobenzene):

$$nIS = \frac{12.6\ mg}{186.05\ {}^{mg}/_{mmol}} = 0.068\ mmol$$

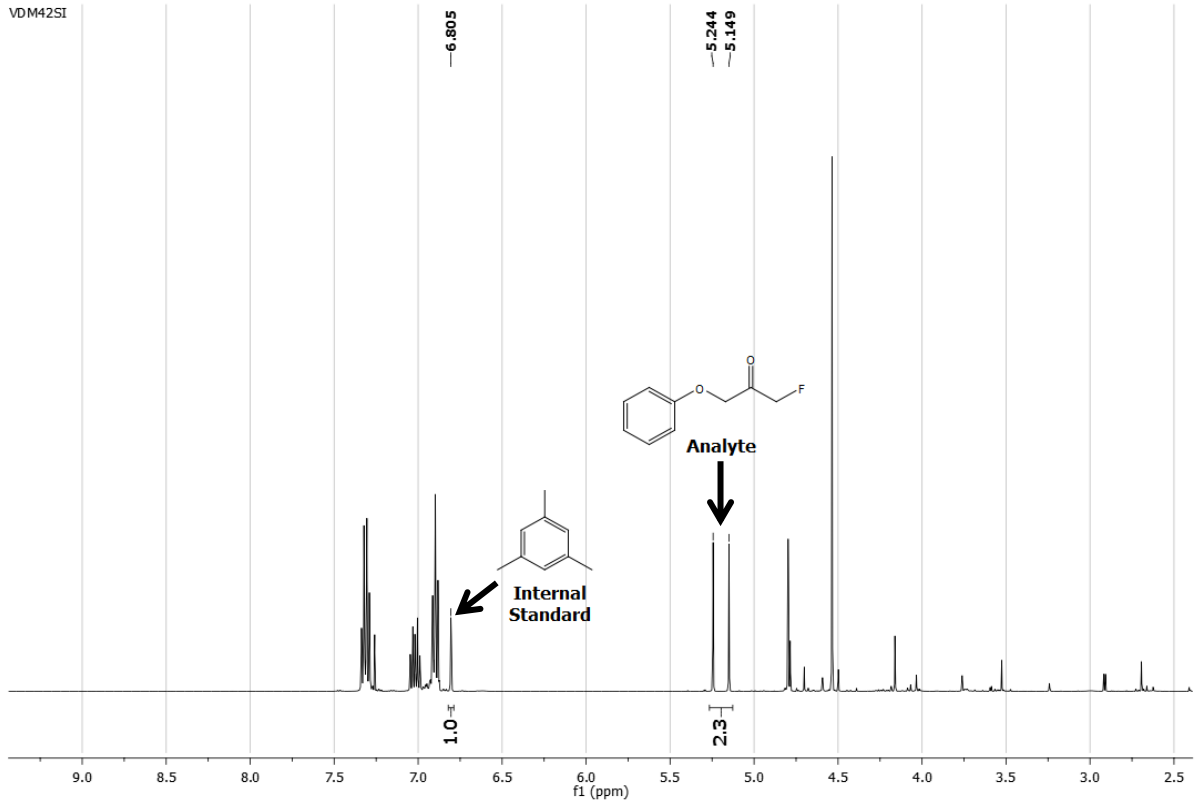
Inserting into **eq.1** above gives:

$$nA = 0.068 \times 10 = 0.680\ mmol$$

The sample is the crude reaction mixture in which the theoretical yield of analyte is expected to be 0.750 mmol, therefore the NMR yield is:

$$\% = \frac{0.680\ mmol}{0.750\ mmol} \times 100 = 91$$

5.3 ^{1}H NMR yield determination of Fluoromethylated compounds using Mesitylene as internal standard.



The molar amount of analyte can be calculated from the molar amount of internal standard (IS) and the molar ratio:

$$nA = nIS \times rA/IS$$

(eq.1)

The ratio between analyte and internal standard is:

$$rA/IS = \frac{2.3/2}{1/3} = 3.48$$

The sample contains 10 mg internal standard (Mesytilene):

$$nIS = \frac{10\ mg}{120.19\ {}^{mg}/_{mmol}} = 0.083\ mmol$$

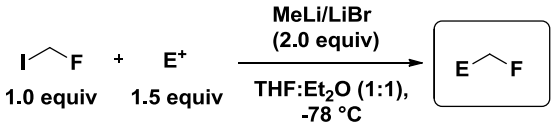
Inserting into **eq.1** above gives:

$$nA = 0.083 \times 3.48 = 0.289\ mmol$$

The sample is the crude reaction mixture in which the theoretical yield of analyte is expected to be 0.312 mmol, therefore the NMR yield is:

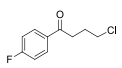
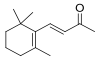
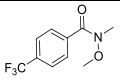
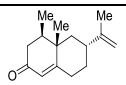
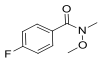
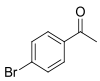
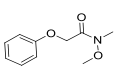
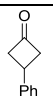
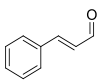
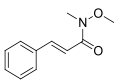
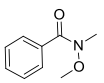
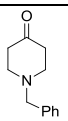
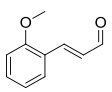
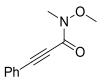
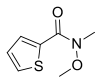
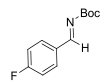
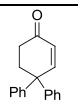
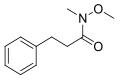
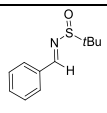
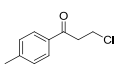
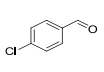
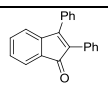
$$\% = \frac{0.289\ mmol}{0.312\ mmol} \times 100 = 92$$

5.4 General fluoromethylation procedure by lithiation/electrophile trapping sequence of FCH_2I.

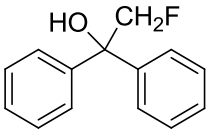


To a stirred solution of electrophile (1.5 mmol, 1.5 equiv) in dry mixture of THF : Et_2O (16 mL, 1:1, v/v) cooled at -78°C, fluoroiodomethane (159.92 mg, 0.67 mL, 1.0 mmol, 1.0 equiv) was added. Then, a solution of MeLi-LiBr complex (1.5M in Et_2O, 1.33 mL, 2.0 mmol, 2.0 equiv) was added dropwise. After stirring for 5 min at -78 ˚C, the reaction mixture was quenched with saturated aqueous NH_4Cl (1mL). The mixture was poured into water (10mL) and extracted with Et_2O (3x10 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated under vacuum. Flash chromatography on the crude afforded fluoro compounds **86a-z**, **94**, **95a-m, 96a-f, 98b**. In the synthetic procedure of compounds **95n** and **98a**, the reaction was run in dry THF (16 mL) .

Table S1. Employed electrophiles

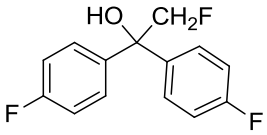
Electrophile	Prod	Electrophile	Prod	Electrophile	Prod	Electrophile	Prod	Electrophile	Prod	Electrophile	Prod
	**86a**		**86i**		**86q**		**86y**		**95f**		**95n**
	**86b**		**86j**		**86r**		**86z**		**95g**		**96a**
	**86c**		**86k**		**86s**		**94**		**95h**		**96b**
	**86d**		**86l**		**86t**		**95a**		**95i**		**96c**
	**86e**		**86m**		**86u**		**95b**		**95j**		**96d**
	**86f**		**86n**		**86v**		**95c**		**95k**		**96e**
	**86g**		**86o**		**86w**		**95d**		**95l**		**96f**
	86h		**86p**		**86x**		**95e**		**95m**		

2-fluoro-1,1-diphenylethanol (86a)



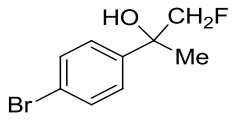
Column chromatography on silica gel (Hexane/AcOEt 90:10), colorless oil, 88% (186 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.95 (bs, 1H, OH), 4.87 (d, $^{2}J_{HF}$ = 48.0 Hz, 2H, CH_2F), 7.28-7.44 (m, 10 H, Ar*H*). ^{13}C NMR (126 MHz, $CDCl_3$), δ 77.9 (d, $^{2}J_{CF}$ = 18.9 Hz, *C*CH_2F), 87.4 (d, $^{1}J_{CF}$ = 180.2 Hz, *C*H_2F), 126.6 (d, $^{4}J_{CF}$ = 1.1 Hz, Ar*C*H), 127.9 (Ar*C*H), 128.4 (Ar*C*H), 142.4 (d, $^{3}J_{CF}$ = 2.46 Hz, Ar*C*). ^{19}F NMR (470 MHz, $CDCl_3$) δ -218.88 (t, $^{2}J_{HF}$ = 47.7 Hz). FT-IR (NaCl, cm^{-1}) υ 3564, 3029, 2967, 1491, 1449, 1171, 996, 696. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{14}H_{13}FO$ 239.0843, found 239.0849.

2-fluoro-1,1-bis(4-fluorophenyl)ethanol (86b)



Column chromatography on silica gel (Hexane/AcOEt 90:10), colorless oil, 76% (192 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.96 (d, *J* = 2.4 Hz, 1H, OH), 4.72-4.88 (d, $^{2}J_{HF}$ = 47.9 Hz, 2H, CH_2F), 7.01-7.06 (m, 4H, Ar*H*), 7.35-7.4 (m, 4H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 86.0 (*C*CH_2F), 87.2 (d, $^{1}J_{CF}$ = 180.9 Hz, *C*H_2F), 115.27 (d, $^{4}J_{CF}$ = 21.5 Hz, Ar*C*H), 128.5 (Ar*C*H), 128.6 (Ar*C*H), 138.1 (Ar*C*), 160.65 (Ar*C*), 163.9 (Ar*C*). ^{19}F NMR (282 MHz, $CDCl_3$) δ -114.33 (ddd, *J* = 13.8, 6.8, 4.2 Hz), -217.92 (t, $^{2}J_{HF}$ = 47.7 Hz, CH_2F). FT-IR (NaCl, cm^{-1}) υ 555, 592, 680, 833, 994, 1089, 1162, 1224, 1509, 1601, 1900, 2971, 3466, 3571. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{14}H_{11}F_3NaO$ 275.0654; found 275.0653.

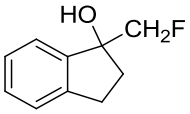
2-(4-bromophenyl)-1-fluoropropan-2-ol (86c)



Column chromatography on silica gel (Hexane/AcOEt 90:10), colorless oil, 95% (291 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.57 (d, *J* = 1.9 Hz, 3H, CH_3), 2.37 (s, OH, 1H), 4.43-4.50 (double AB system, *J* = 47.5, 9.3 Hz, 2H, CH_2F), 7.35-7.37 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.49-7.51 (d, *J* = 8.5 Hz, 2H, Ar*H*). ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.3 (d, $^{3}J_{CF}$ = 3.7 Hz, *C*H_3), 73.5 (d, $^{2}J_{CF}$= 18.8 Hz, *C*OH), 89.2 (d, $^{1}J_{CF}$ = 177.6 Hz,*C*H_2F), 121.7 (Ar*C*), 127.0 (Ar*C*H),

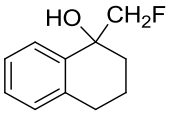
131.5 (Ar*C*H), 142.1 (d, $^{3}J_{CF}$ = 4.0 Hz, Ar*C*). ^{19}F NMR (470 MHz, $CDCl_3$) δ -223.15 (t, J_{HF} = 47.7 Hz). FT-IR (NaCl, cm^{-1}) υ 823, 1008, 1020, 1398, 1490, 1591, 1721, 2982, 3401, 3583. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_9H_{10}BrClNaO$ 270.9496; found 270.9501.

1-(fluoromethyl)-2,3-dihydro-1*H*-inden-1-ol (86d)



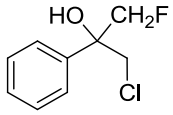
Column chromatography on silica gel (Hexane/AcOEt 90:10), yellow oil, 91% (151 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.09-2.19 (m, 1H, CH_2CH_2C), 2.41-2.46 (m, 2H, CH_2CH_2C + OH), 2.84-2.90 (m, 1H, CH_2CH_2C), 3.06-3.09 (m, 1H, CH_2CH_2C), 4.38-4.56 (double AB system, *J* = 48.5, 9.3 Hz, 2H, CH_2F) (m, 2H, CH_2F), 7.24-7.41 (m, 4H, Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.4 (CH_2CH_2C), 36.4 (d, $^{3}J_{CF}$ = 3.1 Hz, CH_2CH_2C), 82.6 (d, $^{2}J_{CF}$ = 18.6 Hz, CCH_2F), 86.8 (d, $^{1}J_{CF}$ = 176.2 Hz, CH_2F), 123.6 (Ar*C*H), 125.1 (Ar*C*H), 126.9 (Ar*C*H), 129.1 (Ar*C*H), 143.0 (d, $^{3}J_{CF}$ = 3.9 Hz, Ar*C*), 143.5 (Ar*C*); ^{19}F NMR (470 MHz, $CDCl_3$) δ -223.99 (td, *J* = 47.8, 17.6 Hz); FT-IR (NaCl, cm^{-1}) υ 728, 1098, 1264, 1458, 2924, 3400; (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{10}H_{11}FONa$ 189.0686; found 189.0690.

1-(fluoromethyl)-1,2,3,4-tetrahydronaphthalen-1-ol (86e)



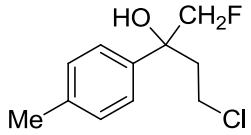
Column chromatography on silica gel (Hexane/AcOEt 90:10), yellowish oil, 87% (157 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.82-1.89 (m, 2H, $CH_2CH_2CH_2C$), 1.92-1.98 (m, 1H, $CH_2CH_2CH_2C$), 2.05-2.06 (m, 1H, OH), 2.24-2.27 (m, 1 H, $CH_2CH_2CH_2C$), 2.74-2.89 (m, 2H, $CH_2CH_2CH_2C$), 4.46 (d, $^{2}J_{HF}$ = 48.0 Hz, 2H, CH_2F), 7.11-7.14 (m, 1H, Ar*H*), 7.22-7.23 (m, 2H, Ar*H*), 7.53-7.55 (m, 1H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9 ($CH_2CH_2CH_2C$), 29.5 ($CH_2CH_2CH_2C$), 33.0 (d, $^{3}J_{CF}$ = 3.7 Hz $CH_2CH_2CH_2C$), 72.2 (CCH_2F), 87.5 (d, $^{1}J_{CF}$ = 179.0 Hz, CH_2F), 126.4 (Ar*C*H), 126.8 (Ar*C*H), 128.1 (Ar*C*H), 129.0 (Ar*C*H), 136.6 (Ar*C*), 137.7 (Ar*C*); ^{19}F NMR (470 MHz, $CDCl_3$) δ -222.9 (t, $^{2}J_{HF}$ = 48.1 Hz); FT-IR (NaCl, cm^{-1}) υ 761, 1020, 1335, 1453, 1489, 1604, 1926, 2938, 3401; (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{11}H_{13}FONa$ 203.0843; found 203.0844.

1-chloro-3-fluoro-phenylpropan-2-ol (86f)



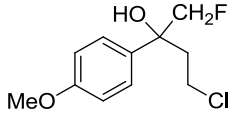
Column chromatography on silica gel (Hexane/AcOEt 90:10), colourless oil, 95% (179 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.79 (s, OH, 1H), 3.97 (dd, *J* = 52.9, 11.6 Hz, 2H, C*H*$_2$Cl), 4.51-4.70 (double AB system, *J* = 48.5, 9.3 Hz, 2H, C*H*$_2$F), 7.38 (dd, *J* = 20.0, 7.3 Hz, 1H, Ar*H*) 7.52 (d, *J* = 7.8 Hz, 2H, Ar*H*). ^{13}C NMR (126 MHz, $CDCl_3$) δ 49.9 (*C*H$_2$Cl), 74.86 (d, $^{2}J_{CF}$ = 18.1 Hz, *C*CH$_2$F), 85.8 (d, $^{1}J_{CF}$ = 180.0 Hz, *C*H$_2$F), 125.5 (Ar*C*H), 128.52 (d, $^{4}J_{CF}$ = 23.1 Hz, Ar*C*H), 139.2 (Ar*C*). ^{19}F NMR (470 MHz, $CDCl_3$) δ -224.72 (t, J_{HF} = 47.2 Hz). FT-IR (NaCl, cm^{-1}) υ 699, 1025, 1073, 1266, 1449, 1721, 2960, 3438, 3545. HRMS (ESI-TOF) m/z [M+Na]$^{+}$ calcd for $C_9H_{10}ClFNaO$ 211.0304; found 211.0296.

4-chloro-1-fluoro-2-(p-tolyl)butan-2-ol (86g)



Column chromatography on silica gel (Hexane/AcOEt 90:10), colorless oil, 95% (205 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29-2.50 (m, 2H, C*H*$_2$CH$_2$Cl), 2.35 (s, C*H*$_3$), 2.56 (d, *J* = 1.6 Hz, 1H, OH), 3.25-3.34 (m, 1H, CH$_2$C*H*$_2$Cl), 3.54-3.63 (m, 1H, CH$_2$C*H*$_2$Cl), 4.31-4.59 (double AB system, ddd, $^{2}J_{HF}$ = 48.2 Hz, $^{2}J_{HF}$ = 16.9 Hz, J_{HH} = 9.0 Hz, 2H, C*H*$_2$F), 7.20 (d, *J* = 8.3 Hz, 2H, Ar*H*), 7.31 (d, *J* = 6.6 Hz, 2H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$), δ 21.0 (*C*H$_3$), 39.6 (*C*H$_2$CH$_2$Cl), 40.8 (CH$_2$*C*H$_2$Cl), 75.6 (*C*CH$_2$F), 89.0 (d, $^{1}J_{CF}$ = 177.6 Hz, *C*H$_2$F), 125.1 (Ar*C*H), 129.4 (Ar*C*H), 136.80 (d, $^{3}J_{CF}$ = 4.4 Hz, Ar*C*), 137.7 (Ar*C*). ^{19}F NMR (282 MHz, $CDCl_3$), δ -224.40 (t, $^{2}J_{HF}$ = 47.9 Hz). FT-IR (NaCl, cm^{-1}) υ 733, 838, 918, 1040, 1178, 1265, 1513, 1615, 2836, 2959, 3469, 3556. HRMS (ESI-TOF) m/z [M+Na]$^{+}$ calcd for $C_{11}H_{14}ClFNaO$ 239.0609; found 239.0614.

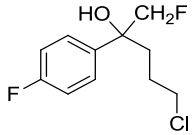
4-chloro-1-fluoro-2-(4-methoxyphenyl)butan-2-ol (86h)



Column chromatography on silica gel (Hexane/AcOEt 90:10), colorless oil, 71% (165 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30-2.50 (m, 2H, C*H*$_2$CH$_2$Cl), 2.61 (d, *J* = 1.7 Hz, 1H, OH), 3.28-3.35 (m, 1H, CH$_2$C*H*$_2$Cl), 3.53-3.62 (m, 1H, CH$_2$C*H*$_2$Cl), 3.81 (s, 3H, OC*H*$_3$), 4.31-4.59 (double AB system, ddd, $^{2}J_{HF}$ = 47.2 Hz, $^{2}J_{HF}$ = 16.3 Hz, J_{HH} = 9.3 Hz, 2H, C*H*$_2$F) 6.90-6.95

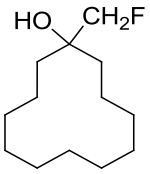
(d, J = 8.9 Hz, 2H, Ar*H*), 7.32-7.37 (d, J = 9.0 Hz, 2H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$), δ 39.6 (*C*H_2CH_2Cl), 40.8 (CH_2*C*H_2Cl), 55.3 (O*C*H_3), 75.5 (d, $^{2}J_{CF}$ = 18.3 Hz, *C*CH_2F), 89.0 (d, $^{1}J_{CF}$ = 178.0 Hz, *C*H_2F), 114.0 (Ar*C*H),126.5 (Ar*C*H), 131.8 (d, $^{3}J_{CF}$ = 4.5 Hz, Ar*C*) , 159.2 (Ar*C*). ^{19}F NMR (282 MHz, $CDCl_3$), δ -223.83 (t, $^{2}J_{HF}$ = 47.9 Hz). FT-IR (NaCl, cm^{-1}) υ 597, 729, 832, 910, 1033, 1180, 1250, 1513, 1611, 2838, 2957, 3467, 3553. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{11}H_{14}ClFNaO_2$ 255.0559; found 255.0562.

5-chloro-1-fluoro-2-(4-fluorophenyl)pentan-2-ol (86i)



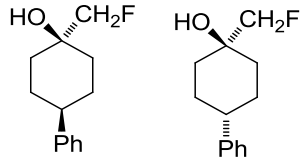
Column chromatography on silica gel (Hexane/AcOEt 90:10), colorless oil, 90% (211 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50-1.62 (m, 1H, $CH_2CH_2CH_2Cl$), 1.77-1.91 (m, 1H, $CH_2CH_2CH_2Cl$), 1.95-2.12 (m, 2H, $CH_2CH_2CH_2Cl$), 2.41 (d, J = 1.9 Hz, 1H, OH), 3.47-3.52 (m, 2H, CH_2Cl), 4.35-4.57 (double AB system, ddd, $^{2}J_{HF}$ = 48.2 Hz, $^{2}J_{HF}$ = 16.9 Hz, J_{HH} = 9.0 Hz, 2H, CH_2F), 7.00-7.13 (m, 2H, Ar*H*), 7.37-7.46 (m, 2H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$), δ 26.2 ($CH_2CH_2CH_2Cl$), 34.5 (d, $^{3}J_{CF}$ = 2.9 Hz, $CH_2CH_2CH_2Cl$), 45.2 (CH_2Cl), 75.6 (d, $^{2}J_{CF}$ = 18.4 Hz *C*CH_2F), 89.2 (d, $^{1}J_{CF}$ = 177.3 Hz, *C*H_2F), 115.4 (d, J_{CF} = 21.4 Hz, Ar*C*H), 127.2 (d, J_{CF} = 8.1 Hz, Ar*C*H), 136.5 (d, $^{3}J_{CF}$ = 3.6 Hz, Ar*C*), 162.2 (d, $^{1}J_{CF}$ = 246.4 Hz, Ar*C*). ^{19}F NMR (282 MHz, $CDCl_3$), δ -115.09 (ArC*F*), -224.68 (t, $^{2}J_{HF}$ = 47.8 Hz, CH_2F). FT-IR (NaCl, cm^{-1}) υ HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{11}H_{13}BrClFNaO$ 316.9715; found 316.9720.

1-(fluoromethyl)cyclododecanol (86j)



Column chromatography on silica gel (Hexane/AcOEt 90:10), white solid, mp= 67-69 °C, 40% (86 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37-1.59 (m, 22H), 1.77 (s, 1H, OH), 4.22 (d, $^{2}J_{HF}$ = 47.9 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$), δ 18.9, 2.9, 22.4, 26.0, 26.3, 30.0 (d, $^{3}J_{CF}$ = 4.6 Hz, CH_2CCH_2F), 74.8 (d, $^{2}J_{CF}$ = 16.8 Hz, *C*CH_2F), 88.7 (d, $^{1}J_{CF}$ = 172.2 Hz, *C*H_2F); ^{19}F NMR (470 MHz, $CDCl_3$), δ -231.75 (t, J_{HF} = 47.9 Hz). FT-IR (KBr, cm^{-1}) υ 1026, 1098, 1443, 1471, 1723, 2848, 2930, 3400; (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{13}H_{25}FONa$ 239.1782; found 239.1787.

1-(fluoromethyl)-4-phenylcyclohexanol (86k)[83]



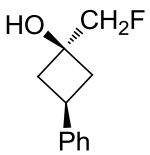
Cis-minor Trans-major

Separable mixture of diastereoisomers. Column chromatography on silica gel (Hexane/AcOEt 90:10), white solid, mp= 91-93 °C, 92 % (191 mg), *dr* = 60:40.

(***Trans***)-**Major:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43-1.70 (m, 2H C*H*$_2$COH, 2H C*H*$_2$CHAr), 1.90-2.02 (m, 2H C*H*$_2$COH, 2H C*H*$_2$CHAr), 2.14 (d, *J* = 1.5 Hz, 1H, OH), 2.58-2.67 (m, 1H, C*H*Ar), 4.52 (d, $^{2}J_{HF}$= 47.8 Hz, 2H, C*H*$_2$F), 7.18-7.33 (m, 5H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$), δ 30.8 (*C*H$_2$CHAr), 34.0 (d, $^{3}J_{CF}$ = 5.2 Hz, *C*H$_2$COH), 43.1 (*C*HAr), 71.1 (d, $^{2}J_{CF}$ = 17.7 Hz, *C*CH$_2$F), 86.5 (d, $^{1}J_{CF}$ = 172.3 Hz, *C*H$_2$F), 126.2 (Ar*C*H), 126.7 (Ar*C*H), 128.4 (Ar*C*H), 146.8 (Ar*C*). ^{19}F NMR (282 MHz, $CDCl_3$), δ -234.03 (tt, J_{HF} = 47.9, 4.4 Hz). FT-IR (KBr, cm^{-1}) υ 535, 700, 760, 902, 975, 1025, 1098, 1141, 1199, 1449, 1494, 1600, 2864, 2935, 3351. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{13}H_{17}FNaO$ 231.1156; found 231.1157.

(***Cis***)-**Minor:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44-1.60 (m, 2H), 1.76-1.94 (m, 6H), 2.17 (s, 1H, OH), 2.46-2.55 (m, 1H, C*H*Ar), 4.24 (d, $^{2}J_{HF}$ = 47.8 Hz), *7*.18-7.34 (m, 5H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$), δ 28.3 (*C*H$_2$CHAr), 32.9 (d, $^{3}J_{CF}$= 3.7 Hz, *C*H$_2$COH), 44.0 (*C*HAr), 69.9 (d, $^{2}J_{CF}$= 17.7 Hz, *C*CH$_2$F), 90.9 (d, $^{1}J_{CF}$ = 172.3 Hz, *C*H$_2$F); 126.1 (Ar*C*H), 126.8 (Ar*C*H), 128.4 (Ar*C*H), 146.9 (Ar*C*); ^{19}F NMR (282 MHz, $CDCl_3$), -229.85 (t, J_{HF} = 47.9 Hz); FT-IR (KBr, cm^{-1}) υ 658, 700, 758, 911, 976, 1015, 1034, 1450, 1493, 1601, 1709, 2861, 2930, 3026, 3414, 3563. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{13}H_{17}FNaO$ 231.1156; found 231.1157.

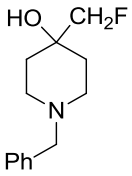
1-(fluoromethyl)-3-phenylcyclobutanol (86l)



Column chromatography on silica gel (Hexane/AcOEt 90:10), white solid, mp= 70-73 °C, 94% (169 mg), *dr* = 90:10. (**Cis**)-**Major:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.23-2.87 (m, 2H, C*H*$_2$COH), 2.46 (s, 1H, OH), 2.62-2.67 (m, 2H, C*H*$_2$COH), 3.03-3.10 (m, 1H, C*H*Ar), 4.54 (d, $^{2}J_{HF}$ = 47.9 Hz, 2H, C*H*$_2$F), 7.21-7.26 (m, 3H, ArH), 7.31-7.34 (m, 2H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$), δ 30.2 (*C*HAr), 39.5 (d, $^{3}J_{CF}$ = 6.3 Hz, *C*H$_2$COH), 69.7 (d, $^{2}J_{CF}$ = 19.0 Hz,

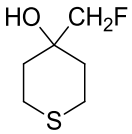
CCH_2F), 87.5 (d, $^1J_{CF}$ = 171.6 Hz, *C*H_2F), 126.3 (Ar*C*H), 126.5 (Ar*C*H) , 128.4 (Ar*C*H), 144.3 (Ar*C*). ^{19}F NMR (470 MHz, $CDCl_3$), δ -227.9 (tt, J_{HF} = 48.0, 3.8 Hz). FT-IR (KBr, cm^{-1}) υ 759, 1015, 1228, 1289, 1429, 1602, 2950, 2973, 3271; HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{11}H_{13}FNaO$ 203.0843; found 203.0845.

1-benzyl-4-(fluoromethyl)piperidin-4-ol (86m)



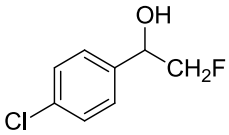
Column chromatography on silica gel (Hexane/AcOEt 60:40), yellowish oil, 96% (214 mg). ^1H NMR (500 MHz, $CDCl_3$) δ 1.60-1.62 (m, 2H, C$H_2$$CH_2$N), 1.67-1.73 (m, 2H, C$H_2$$CH_2$N), 2.41-2.45 (m, 2H, CH_2CH_2N), 2.64-2.67 (m, 2H, CH_2CH_2N), 3.14 (bs, 1H, OH), 3.56 (s, 2H, CH_2Ph), 4.16-4.26 (d, $^2J_{HF}$ = 47.7 Hz, 2H, CH_2F), 7.24-7.26 (m, 1H, Ar*H*), 7.29-7.34 (m, 4H, Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 32.3 (*C*$H_2$$CH_2$N), 48.5 ($CH_2$*C*$H_2$N), 62.9 (*C*$H_2$Ph), 68.8 (d, $^2J_{CF}$ = 18.0 Hz, *C*CH_2F), 89.9 (d, $^1J_{CF}$ = 172.4 Hz, *C*H_2F), 127.2 (Ar*C*H), 128.3 (Ar*C*H), 129.3 (Ar*C*H), 137.8 (Ar*C*); ^{19}F NMR (470 MHz, $CDCl_3$), δ -230.70 (m); FT-IR (KBr, cm^{-1}) υ 733, 910, 1036, 1305, 1454, 2247, 2816, 3029, 3391; (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{13}H_{19}FNO$ 224.1445; found 224.1459.

4-(fluoromethyl)tetrahydro-2H-thiopyran-4-ol (86n)



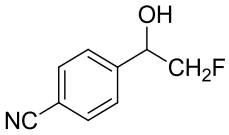
Column chromatography on silica gel (Hexane/AcOEt 90:10), colorless oil, 90 % (135 mg). ^1H NMR (300 MHz, $CDCl_3$) δ 1.70-1.80 (m, 2H), 1.90-2.00 (m, 2H), 2.40-2.50 (m, 2H), 3.00-3.10 (m, 2H), 4.17 (d, $^2J_{HF}$ = 47.6 Hz, 2H, CH_2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.3, 33.8, 69.4 (d, $^2J_{CF}$ = 17.4 Hz, *C*CH_2F), 90.1 (d, $^1J_{CF}$= 172.8 Hz, *C*H_2F). ^{19}F NMR (282 MHz, $CDCl_3$), δ -232.89 (t, J_{HF} = 47.7 Hz). FT-IR (NaCl, cm^{-1}) υ 732, 919, 977, 1030, 1248, 1276, 1429, 1458, 1612, 2849, 2919, 3400. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_6H_{11}FNaO_2$ 173.0407; found 173.0407.

(4-chlorophenyl)-2-fluoroethanol (86o)



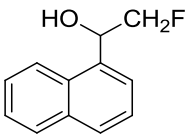
Column chromatography on silica gel (Hexane/AcOEt 90:10), colorless oil, 61% (106 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.51 (bs, 1H, OH), 4.32-4.56 (double ddd, J = 47.2 Hz, J = 9.6 Hz, J = 8.2, J = 3.3 Hz, 2H, CH_2F), 4.99-5.04 (m, 1H, C*H*OH), 7.32-7.38 (m, 4H, Ar*H*). ^{13}C NMR (126 MHz, $CDCl_3$) δ 72.3 (d, $^{2}J_{CF}$ = 20.1 Hz, *C*HOH), 86.9 (d, $^{1}J_{CF}$ = 174.9 Hz, *C*H_2F), 127.7 (Ar*C*H), 128.8 (Ar*C*H), 134.2 (Ar*C*), 136.5 (d, $^{3}J_{CF}$ = 8.1 Hz, Ar*C*). ^{19}F NMR (470 MHz, $CDCl_3$) δ -221.27 (ddd, J_{HF} = 48.2, 46.7, 13.9 Hz). FT-IR (NaCl, cm^{-1}) υ 1012, 1101, 1454, 1495, 2893, 3406, HRMS (ESI-TOF) m/z $[M-H]^-$ calcd for C_8H_8ClFO 173.0175; found 173.0170.

4-(2-fluoro-1-hydroxyethyl)benzonitrile (86p)



Column chromatography on silica gel (Hexane/AcOEt 90:10), colorless oil, 30% (49 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.59-2.61 (dd, J = 3.4, 1.2 Hz, 1H, OH), 4.29-4.64 (double ddd, J = 47.2 Hz, J = 9.6 Hz, J = 8.2, J = 3.3 Hz, 2H, CH_2F), 5.05-5.14 (m, C*H*OH), 7.52-7.54 (m, 2H, Ar*H*), 7.67-7.70 (m, 2H, Ar*H*). ^{13}C NMR (126 MHz, $CDCl_3$), δ 72.2 (d, $^{2}J_{CF}$ = 20.4 Hz, *C*HOH), 86.5 (d, $^{1}J_{CF}$ = 175.7 Hz, *C*H_2F), 112.3 (Ar*C*), 118.5 (*C*N) ,127.0 (Ar*C*H), 132.4 (Ar*C*H). ^{19}F NMR (470 MHz, $CDCl_3$), δ -222.51 (td, J_{HF} = 47.2, 14.4 Hz). FT-IR (NaCl, cm^{-1}) υ 1092, 1409, 1609, 2230, 3417; HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for C_9H_8FNNaO 188.0482; found 188.0481.

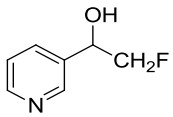
2-fluoro-1-(naphthalen-1-yl)ethanol (86q)



Column chromatography on silica gel (Hexane/AcOEt 90:10), white solid, mp= 68-70 °C, 65% (123 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.65 (dd, J = 3.0, 1.1 Hz, 1H, OH), 4.43-4.83 (double ddd, J = 47.2 Hz, J = 9.8 Hz, J = 8.5, J = 2.8 Hz, 2H, CH_2F), 5.80-5.89 (m, 1H, C*H*OH), 7.49-7.59 (m, 3H, Ar*H*), 7.74-7.76 (m, 1H, Ar*H*), 7.83-7.91 (m, 2H, Ar*H*), 8.04-8.07 (m, 1H, Ar*H*), ^{13}C NMR (75 MHz, $CDCl_3$), δ 69.9 (d, $^{2}J_{CF}$ = 20.1 Hz, *C*HOH), 86.9 (d, $^{1}J_{CF}$ =

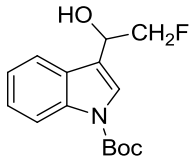
174.7 Hz, *C*CH_2F), 122.4 (Ar*C*H), 124.1 (Ar*C*H), 125.5 (Ar*C*H), 125.8 (Ar*C*H), 126.5 (Ar*C*H), 128.9 (Ar*C*H), 129.1 (Ar*C*H), 130.4 (Ar*C*), 133.5 (d, $^3J_{CF}$ = 8.6 Hz, Ar*C*), 133.7 (Ar*C*).^{19}F NMR (470 MHz, $CDCl_3$), δ -218.90 (ddd, J_{HF} = 49.0, 47.6, 14.3 Hz). FT-IR (KBr, cm^{-1}) υ 493, 562, 776, 799, 889, 1013, 1082, 1103, 1168, 1511, 2954, 3050, 3390. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for C12H11FNaO 213.0686; found 213.0687.

2-fluoro-1(pyridin-3yl)ethanol (86r)



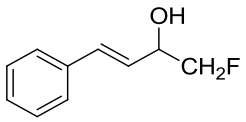
Column chromatography on silica gel (Hexane/AcOEt 60:40), yellowish oil, 62% (87 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.45 (bs, 1H, OH), 4.39-4.59 (double ddd, *J* = 47.7 Hz, *J* = 9.6 Hz, *J* = 8.2, *J* = 2.8 Hz, 2H, C*H*$_2$F), 5.03-5.08 (m, 1H, C*H*CH_2F), 7.30-7.33 (m, 1H, Ar*H*), 7.76-7.78 (d, *J* = 7.9 Hz, 1H, Ar*H*), 8.53-8.55 (d, *J* = 4.7 Hz, 1H, Ar*H*), 8.59 (s, 1H, Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 70.7 (d, $^2J_{CF}$ = 20.6 Hz, *C*HCH_2F), 86.6 (d, $^1J_{CF}$ = 175.2 Hz, *C*H_2F), 123.6 (Ar*C*H), 134.1 (d, $^3J_{CF}$ = 7.8 Hz, Ar*C*), 134.2 (Ar*C*H), 148.0 (Ar*C*H), 149.6 (Ar*C*H); ^{19}F NMR (470 MHz, $CDCl_3$) δ -222.3 (td, *J* = 47.6, 15.2 Hz, CH_2F); FT-IR (NaCl, cm^{-1}) υ 727, 1016, 1096, 1264, 1428, 1597, 2922, 3195; (ESI-TOF) m/z $[M+H]^+$ calcd for C_7H_9FNO 142.0663; found 142.0665.

***tert*-butyl 3-(2-fluoro-1-hydroxyethyl)-*1H*-indole-1-carboxylate (86s)**



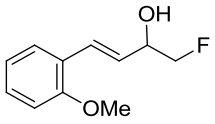
Column chromatography on silica gel (Hexane/AcOEt 90:10), colorless oil, 92% (257 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.67 (s, 9H, C(C*H*$_3$)$_3$), 2.65 (bs, 1H, OH), 4.58-4.74 (m, 2H, C*H*$_2$F), 5.26-5.31 (m, 1H, C*H*OH), 7.24-7.36 (m, 2H, Ar*H*), 7.62-7.64 (m, 2H, C*H*=C + Ar*H*), 8.15-8.17 (m, 1H, Ar*H*). ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.2 (C(*C*H_3)$_3$), 67.1 (d, $^2J_{CF}$ = 21.3 Hz, *C*HOH), 84.0 (*C*$(CH_3)_3$), 86.2 (d, $^1J_{CF}$ = 174.1 Hz, *C*H_2F), 115.4 (Ar*C*H), 117.9 (d, $^3J_{CF}$ = 8.9 Hz, *C*=CH), (Ar*C*H), 122.8 (Ar*C*H), 123.7 (*C*H=C), 124.8 (Ar*C*H), 128.3 (Ar*C*), 135.6 (Ar*C*), 149.5 (*C*=O). ^{19}F NMR (470 MHz, $CDCl_3$) δ -221.9 (td, J_{HF} = 47.5, 15.2 Hz). FT-IR (NaCl, cm^{-1}) υ 747, 1016, 1158, 1372, 1453, 1733, 2252, 2980, 3443. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{15}H_{18}FNNaO_3$ 302.1163; found 302.1169.

(E)-1-fluoro-4-phenylbut-3-en-2-ol (86t)



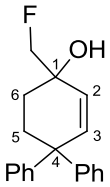
Column chromatography on silica gel (Hexane/AcOEt 90:10), waxy solid, 90% (149 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.24 (d, *J* = 3.8 Hz, 1H, OH), 4.32-4.58 (double ddd, *J* = 47.2 Hz, *J* = 9.3 Hz, *J* = 7.8, *J* = 3.3 Hz, 2H, C*H*$_2$F), 4.59-4.67 (m, 1H, C*H*CH$_2$F), 6.17 (dd, *J* = 16.0, 6.3 Hz, 1H, ArCH=C*H*), 6.75 (d, *J* = 16.0 Hz, 1H, ArC*H*=CH), 7.26-7.40 (m, 5H, Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 71.5 (d, $^{2}J_{CF}$ = 20.2 Hz, *C*HCH$_2$F), 86.1 (d, $^{1}J_{CF}$ = 173.5 Hz, *C*H$_2$F), 125.2 (d, $^{3}J_{CF}$ = 8.5 Hz, ArCH=*C*H), 126.6 (Ar*C*H), 128.8 (Ar*C*H), 128.6 (Ar*C*H), 133.1 (d, $^{4}J_{CF}$ = 1.3 Hz, Ar*C*H=CH), 136.1 (Ar*C*); ^{19}F NMR (470 MHz, $CDCl_3$) δ -225.75 (td, *J* = 47.5, 16.1 Hz, CH$_2$F); (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{10}H_{11}FONa$ 189.0686; found 189.0690.

(E)-1-fluoro-4-(2-methoxyphenyl)but-3-en-2-ol (86u)



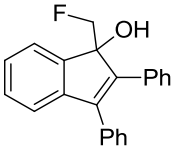
Column chromatography on silica gel (Hexane/AcOEt 90:10), yellowish oil, 70% (137 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.17 (s, 1H, OH), 3.85 (s, 3H, OC*H*$_3$), 4.32-4.56 (double ddd, *J* = 47.2 Hz, *J* = 9.6 Hz, *J* = 8.2, *J* = 3.3 Hz, 2H, C*H*$_2$F), 4.60-4.63 (m, 1H, C*H*CH$_2$F), 6.17-6.22 (dd, *J* = 16.1, 6.5 Hz, 1H, ArCH=C*H*), 6.87-6.89 (d, *J* = 8.3 Hz, 1H, Ar*H*), 6.91-6.94 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.03-7.07 (d, *J* = 16.1 Hz, 1H, ArC*H*=CH), 7.22-7.25 (m, 1H, Ar*H*), 7.41-7.43 (dd, *J* = 7.6, 1.4 Hz, 1H, Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 55.4 (O*C*H$_3$), 71.9 (d, $^{2}J_{CF}$ = 20.0 Hz, *C*HCH$_2$F), 86.2 (d, $^{1}J_{CF}$ = 173.3 Hz, *C*H$_2$F), 110.9 (Ar*C*H), 120.6 (Ar*C*H), 125.1 (Ar*C*), 125.9 (d, $^{3}J_{CF}$ = 8.5 Hz, ArCH=*C*H), 127.1 (Ar*C*H), 128.2 (d, $^{4}J_{CF}$ = 1.3 Hz, Ar*C*H=CH), 129.2 (Ar*C*H), 156.9 (Ar*C*OCH$_3$); ^{19}F NMR (470 MHz, $CDCl_3$) δ -225.67 (td, *J* = 49.5, 16.1 Hz, CH$_2$F); FT-IR (NaCl, cm^{-1}) υ 727, 1099, 1247, 1264, 1408, 2918, 3435; (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{11}H_{13}FO_2Na$ 219.0792; found 219.0798.

1-(fluoromethyl)-4,4-diphenyl-2-cyclohexen-1-ol (86v)



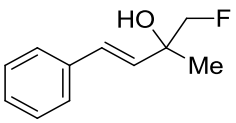
Column chromatography on neutral alumina gel Brockmann grade II (Hexane/AcOEt 85:15), colorless oil, 86%, 0.243 g. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.73 (m, 2H, *c*Hex*H*-6), 2.24 (br s, 1H, O*H*), 2.33 (m, 1H, *c*Hex*H*-5), 2.58 (m, 1H, *c*Hex*H*-5), 4.28-4.33 (double AB system, $^{2}J_{HF}$ = 47.7 Hz, $^{2}J_{HH}$ = 9.1 Hz, 2H, CH_2F), 5.91 (d, ^{3}J =10.2 Hz, 1H, *c*Hex*H*-2), 6.37 (d, ^{3}J = 10.2 Hz, 1H, *c*Hex*H*-3), 7.20-7.33 (m, 10H, 2Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5 (d, $^{3}J_{CF}$ = 3.6 Hz, *c*Hex*C*-6), 32.0 (*c*Hex*C*-5), 48.9 (*c*Hex*C*-4), 69.1 (d, $^{2}J_{CF}$ = 18.3 Hz, *c*Hex*C*-1), 88.3 (d, $^{1}J_{CF}$ = 175.9 Hz, *C*H_2F), 126.2 (Ar*C*-4), 126.2 (Ar*C*-4), 127.2 (d, $^{3}J_{CF}$ = 5.8 Hz, *c*Hex*C*-2), 127.6 (Ar*C*-2,6), 127.8 (Ar*C*-2,6), 128.2 (Ar*C*-3,5), 128.2 (Ar*C*-3,5), 139.6 (d, $^{4}J_{CF}$ = 1.3 Hz, *c*Hex*C*-3), 146.7 (Ar*C*-1), 147.7 (Ar*C*-1). ^{19}F NMR (376 MHz, $CDCl_3$) δ -229.1 (m, CH_2F). HRMS (ESI) m/z $[M\text{-}Na]^+$ calcd for $C_{19}H_{19}FNaO$ 305.1312; found 305.1320.

1-(fluoromethyl)-2,3-diphenyl-1H-inden-1-ol (86w)



Column chromatography on neutral alumina gel Brockmann grade II (Hexane/AcOEt 88:12), yellow solid (mp 103-107 °C) 68%, 0.215 g. ^{1}H NMR (400 MHz, C_6D_6) δ 4.56-4.19 (double AB system, $^{2}J_{HF}$ = 47.7 Hz, $^{2}J_{HH}$ = 9.1 Hz, 2H, CH_2F), 6.95-7.13 (m, 8H, Ar*H*), 7.19-7.22 (m, 1H, Ar*H*), 7.28-7.31 (m, 2H, Ar*H*), 7.49-7.52 (m, 3H, Ar*H*). ^{13}C NMR (100 MHz, C_6D_6) δ 84.6 (d, $^{2}J_{CF}$ = 19.2 Hz, *C*-OH), 86.4 (d, $^{1}J_{CF}$ = 179.7 Hz, *C*H_2F), 121.2 (Ar*C*H), 124.0 (Ar*C*H), 124.0 (Ar*C*H), 127.0 (Ar*C*H), 127.9 (Ar*C*H), 128.4 (Ar*C*H) 128.9 (Ar*C*H), 129.2 (Ar*C*H), 129.6 (Ar*C*H), 129.8 (Ar*C*H). 134.9 (Ar*C*), 134.9 (Ar*C*), 135.0 (Ar*C*), 142.1 (Ar*C*), 143.0 (Ar*C*), 143.5 (Ar*C*), 146.2 (Ar*C*). ^{19}F NMR (376 MHz, C_6D_6) δ -227.3 (t, $^{2}J_{FH}$ = 47.5 Hz, CH_2F). HRMS (ESI) m/z $[M\text{-}Na]^+$ calcd for $C_{22}H_{17}FNaO$ 339.1156; found 339.1159.

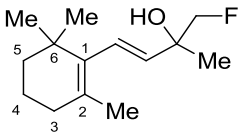
(3E)-1-fluoro-2-methyl-4-phenyl-3-buten-2-ol (86x)



Column chromatography on neutral alumina gel Brockmann grade II (Hexane/AcOEt 88:12), colorless oil, 70%, 0.126 g. ^{1}H NMR (400 MHz, C_6D_6) δ 1.11 (dd, $^{4}J_{HF}$ = 2.1 Hz, *J* = 1.0 Hz,

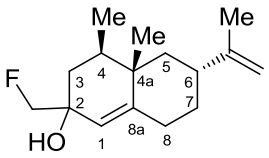
3H, CH_3), 1.64, (br s, 1 H, O*H*), 3.92-3.98 (double AB system, $^2J_{HF}$ = 47.2 Hz, $^2J_{HH}$ = 9.0 Hz, 2H, CH_2F), 6.02 (d, *J* = 16.1 Hz, 1H, Ar-CH=C*H*), 6.67 (d, *J* = 16.1 Hz, 1H, Ar-C*H*=CH), 7.05 (m, 1H, Ar*H*-4), 7.12 (m, 2H, Ar*H*-3,5), 7.21 (m, 2H, Ar*H*-2,6). ^{13}C NMR (100 MHz, C_6D_6) δ 23.9 (d, $^3J_{CF}$ = 3.7 Hz, *C*H$_3$), 72.3 (d, $^2J_{CF}$ = 18.8 Hz, *C*-OH), 88.9 (d, $^1J_{CF}$ = 177.7 Hz, *C*H$_2$F), 127.0 (Ar*C*-2,6), 127.9 (Ar*C*-4), 128.8 (Ar*C*-3,5), 130.1 (d, $^4J_{CF}$ = 1.7 Hz, Ar-*C*H=CH), 131.9 (d, $^3J_{CF}$ = 4.0 Hz, Ar-CH=*C*H), 137.1 (Ar*C*-1). ^{19}F NMR (376 MHz, C_6D_6) δ -224.3 (qt, $^4J_{FH}$ = 2.1 Hz, $^2J_{FH}$ = 48.1 Hz, CH$_2$*F*). HRMS (ESI) m/z [M-Na]$^+$ calcd for $C_{11}H_{13}FNaO$ 203.0843; found 203.0846.

(3E)-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1-fluoro-2-methyl-3-buten-2-ol (86y)



Column chromatography on neutral alumina gel Brockmann grade II (Hexane/AcOEt 9:1), colorless oil, 80%, 0.181 g. ^{1}H NMR (400 MHz, C_6D_6) δ 1.03 (s, 6H, 6-*Me*$_2$), 1.12 (d, $^4J_{HF}$ = 2.1 Hz, 3H, *CH*$_3$), 1.42-1.46 (m, 2H, *c*Hex*H*-5), 1.53-1.60 (m, 2H, *c*Hex*H*-4), 1.62 (br s, 1H, O*H*), 1.66 (s, 3H, 2-*Me*), 1.90 (m, 2H, *c*Hex*H*-3), 3.95-3.99 (double AB system, $^2J_{HF}$ = 48.2 Hz, $^2J_{HH}$ = 8.9 Hz, 2H, CH_2F), 5.37 (d, ^3J = 16.2 Hz, 1H, *c*Hex-CH=C*H*), 6.24 (d, ^3J = 16.2 Hz, 1H, *c*Hex-C*H*=CH). ^{13}C NMR (100 MHz, C_6D_6) δ 19.7 (*c*Hex*C*-4), 21.5 (2-*Me*), 23.9 (d, $^3J_{CF}$ = 3.7 Hz, *C*H$_3$), 28.86 (6-*Me*)28.89 (6-*Me*), 32.9 (*c*Hex*C*-3), 34.2 (*c*Hex*C*-6), 39.7 (*c*Hex*C*-5), 72.3 (d, $^2J_{CF}$ = 18.9 Hz, *C*-OH), 89.1 (d, $^1J_{CF}$ = 177.1 Hz, *C*H$_2$F), 127.8 (d, $^4J_{CF}$ = 1.7 Hz, *cHex*-*C*H=CH), 128.5 (*c*Hex*C*-2), 136.4 (d, $^3J_{CF}$ = 4.0 Hz, *c*Hex-CH=*C*H), 137.3 (*c*Hex*C*-2). ^{19}F NMR (376 MHz, C_6D_6) δ -224.2 (qt, $^4J_{FH}$ = 2.1 Hz, $^2J_{FH}$ = 48.2 Hz, CH$_2$*F*). HRMS (ESI) m/z [M-Na]$^+$ calcd for $C_{14}H_{23}FNaO$ 249.1625; found 249.1627.

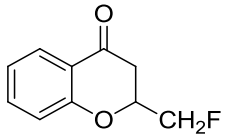
(4R, 4aS, 6R)-2-(fluoromethyl)-6-isopropil-4,4a-dimethyl-2,3,4,4a,5,6,7,8-octahydro-2-naphtenol (86z)



Column chromatography on neutral gel alumina Brockmann grade II (Hexane/AcOEt 88:12), light yellow oil, 26%, 0.066 g, isolated as single diastereoisomer, stereochemistry at C2 not assigned. ^{1}H NMR (400 MHz, C_6D_6) δ 0.72 (s, 3H, 4a-*Me*), 0.75 (d, *J* = 6.9 Hz, 3H, 4-*Me*), 0.99 (m, 1H, *H*-5), 1.16 (m, 1H, *H*-7), 1.36 (m, 2H, *H*-3), 1.62 (m, 3H, C*H*$_3$C=CH$_2$), 1.67 (m, 1H, *H*-7), 1.80 (m, 1H, *H*-4), 1.83 (m, 1H, *H*-5), 1.95 (m, 1H, *H*-8), 2.11 (m, 1H, *H*-6), 2.12

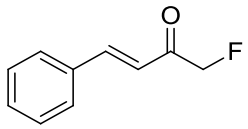
(m, 1H, *H*-8),), 3.98-4.01 (double AB system, $^{1}J_{HF}$ = 48.0 Hz, $^{2}J_{HH}$ = 8.8 Hz, 2H, CH_2F), 4.78 (m, 2H, C=CH_2), 5.21 (s, 1H, *H*-1). ^{13}C NMR (100 MHz, C_6D_6) δ 15.3 (4-*Me*), 16.9 (4a-*Me*), 20.9 (*C*H_3C=CH_2), 32.8 (*C*-8), 32.8 (*C*-7), 36.0 (d, $^{4}J_{CF}$ = 1.0 Hz, *C*-4), 36.6 (d, $^{3}J_{CF}$ = 2.7 Hz, *C*-3), 38.7 (*C*-4a), 41.0 (*C*-6), 44.7 (*C*-5), 69.3 (d, $^{2}J_{CF}$ = 15.4 Hz, *C*-OH), 89.6 (d, $^{1}J_{CF}$ = 176.1 Hz, *C*H_2F),109.2 (C=*C*H_2), 121.4 (d, $^{3}J_{CF}$ = 5.0 Hz, *C*-1), 149.4 (*C*-8a), 149.9 (C=*C*H_2). ^{19}F NMR (376 MHz, C_6D_6) δ -227.0 (t, $^{2}J_{FH}$ = 48.0 Hz, CH_2F). HRMS (ESI) m/z $[M-Na]^+$ calcd for $C_{16}H_{25}FNaO$ 275.1782; found 275.1777; α_D = +110.

2-(fluoromethyl)chroman-4-one (94)



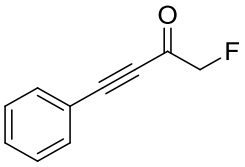
Column chromatography on silica gel (Hexane/AcOEt 90:10), yellowish oil, 50% (90 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.67-2.70 (dd, *J* = 16.9, 2.8 Hz, 1H, CH_2CO), 2.94 (dd, *J* = 16.8, 13.2 Hz, 1H, CH_2CO), 4.58-4.80 (m, 3H, CH_2F, C*H*CH_2F), 7.03-7.07 (m, 2H, Ar*H*), 7.51 (m, 1H, Ar*H*), 7.90 (dd, *J* = 7.8, 1.4 Hz, 1H, Ar*H*). ^{13}C NMR (126 MHz, $CDCl_3$) δ 38.1 (d, $^{3}J_{CF}$ = 5.4 Hz, *C*H_2CO), 76.0 (d, $^{2}J_{CF}$ = 20.2 Hz, *C*HCH$_2$F), 83.6 (d, $^{1}J_{CF}$ = 175.8 Hz, *C*H_2F), 118.0 (Ar*C*H), 121.8 (Ar*C*H), 127.0 (Ar*C*H), 136.3 (Ar*C*H), 160.9 (Ar*C*), 191.0 (*C*=O). ^{19}F NMR (470 MHz, $CDCl_3$) δ -230.2 (m); FT-IR (NaCl, cm^{-1}) υ 763, 1121, 1228, 1307, 1464, 1608, 1694, 2918. HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{10}H_9FO_2$ 181.0659; found 181.0654.

(3E)-1-fluoro-4-phenyl-3-buten-2-one (95a)



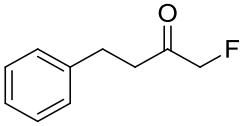
Column chromatography on silica gel (Hexane/AcOEt 98:2), light yellow solid (mp 28-31 °C), 41%, 0.067 g. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.04 (d, $^{2}J_{HF}$ = 47.6 Hz, 2H, CH_2F), 7.03 (dd, ^{3}J = 16.1 Hz, $^{4}J_{HF}$ = 3.1 Hz, 1H, C*H*-C=O), 7.42 (m, 2H, Ar*H*-3,5), 7.43 (m, 1H, Ar*H*-4), 7.60 (m, 2H, Ar*H*-2,6), 7.76 (d, ^{3}J = 16.1 Hz, 1H, Ar-C*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 84.8 (d, $^{1}J_{CF}$ = 184.6 Hz, *C*H_2F), 119.8 (*C*H-C=O), 128.7 (Ar*C*-2,6), 129.0 (Ar*C*-3,5), 131.2 (Ar*C*-4), 134.1 (Ar*C*-1), 145.1 (d, $^{4}J_{CF}$ = 3.5 Hz, Ar-*C*H), 194.8 (d, $^{2}J_{CF}$ = 18.7 Hz, *C*=O). ^{19}F NMR (376 MHz, $CDCl_3$) δ -228.7 (dt, $^{2}J_{FH}$ = 47.6 Hz, $^{4}J_{FH}$ = 3.1 Hz, CH_2F). HRMS (ESI), m/z $[M-Na]^+$ calcd for $C_{10}H_9FNaO$ 187.0530; found 187.0527.

1-fluoro-4-phenyl-3-butyn-2-one (95b)



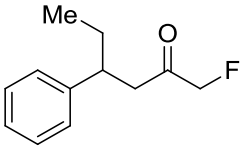
Column chromatography on silica gel (Hexane/AcOEt 97:3), light yellow solid (mp 30-32 °C, Lit. 39-39.5 °C),[84] 58%, 0.094 g. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.00 (d, $^{2}J_{HF}$ = 47.1 Hz, 2H, CH_2F), 7.41 (m, 2H, Ar*H*-3,5), 7.50 (m, 1H, Ar*H*-4), 7.61 (m, 2H, Ar*H*-2,6). ^{13}C NMR (100 MHz, $CDCl_3$) δ 84.5 (*C*-C=O), 84.8 (d, $^{1}J_{CF}$ = 188.4 Hz, *C*H_2F), 96.1 (d, $^{4}J_{CF}$ = 2.2 Hz, Ar-*C*), 119.1 (Ar*C*-1), 128.7 (Ar*C*-3,5), 131.4 (Ar*C*-4), 133.3 (Ar*C*-2,6), 181.6 (d, $^{2}J_{CF}$ = 22.6 Hz, *C*=O). ^{19}F NMR (376 MHz, $CDCl_3$) δ -224.8 (t, $^{2}J_{FH}$ = 47.1 Hz, CH_2*F*). HRMS (ESI) m/z [M-Na]$^{+}$ calcd for $C_{10}H_7FNaO$ 185.0373; found 185.0372.

1-fluoro-4-phenyl-2-butanone (95c)



Column chromatography on silica gel (Hexane/AcOEt 98:2), light yellow oil, 34.2%, 0.057 g. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.88 (m, 2H, CH_2-C=O), 2.95 (m, 2H, Ar-CH_2), 4.77 (d, $^{2}J_{HF}$ = 47.6 Hz, 2H, CH_2F), 7.20 (m, 2H, Ar*H*-2,6), 7.21 (m, 1H, Ar*H*-4), 7.29 (m, 2H, Ar*H*-3,5). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.7 (Ar-*C*H_2), 39.9 (*C*H_2-C=O), 85.1 (d, $^{1}J_{CF}$ = 185.1 Hz, *C*H_2F), 126.3 (Ar*C*-4), 128.3 (Ar*C*-2,6), 128.6 (Ar*C*-3,5), 140.4 (Ar*C*-1), 206.2 (d, $^{2}J_{CF}$ = 19.5 Hz, *C*=O). ^{19}F NMR (376 MHz, $CDCl_3$) δ -227.6 (tt, $^{2}J_{FH}$ = 47.7 Hz, $^{4}J_{FH}$ =2.5 Hz, CH_2*F*). HRMS (ESI) m/z [M-Na]$^{+}$ calcd for $C_{10}H_{11}FNaO$ 189.0686; found 189.0688.

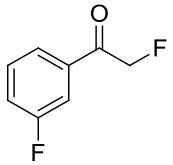
1-fluoro-3-phenyl-2-pentanone (95d)



Column chromatography on silica gel (Hexane/AcOEt 97:3), light yellow oil, 30%, 0.054 g. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, *J* = 7.4 Hz, 3H, CH_3), 1.77 (m, 1H, CH_2), 2.10 (m, 1H, CH_2), 3.77 (m, 1H, C*H*), 4.77 (d, $^{2}J_{HF}$ = 47.5 Hz, 2H, CH_2F), 7.22 (m, 2H, Ar*H*-2,6), 7.27 (m, 1H, Ar*H*-4), 7.33 (m, 2H, Ar*H*-3,5). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9 (*C*H_3), 24.8 (d, $^{4}J_{CF}$ = 1.2 Hz, *C*H_2), 55.7 (d, $^{3}J_{CF}$ = 1.0 Hz, *C*H), 84.1 (d, $^{1}J_{CF}$ = 186.0 Hz, *C*H_2F), 127.5 (Ar*C*-4), 128.4 (Ar*C*-2,6), 129.0 (Ar*C*-3,5), 137.3 (Ar*C*-1), 205.8 (d, $^{2}J_{CF}$ = 17.5 Hz, *C*=O). ^{19}F NMR

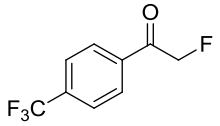
(376 MHz, $CDCl_3$) δ -227.6 (dt, $^2J_{FH}$ = 47.5 Hz, $^4J_{FH}$ = 3.2 Hz, CH_2F). HRMS (ESI) m/z [M-Na]$^+$ calcd for $C_{11}H_{13}FNaO$ 203.0843; found 203.0844.

2-fluoro-1-(3-fluorophenyl)ethanone (95e)



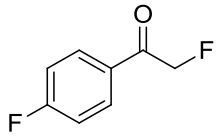
Column chromatography on silica gel (Hexane/Et_2O 9:1), light yellow oil, 46.5 %, 0.073 g. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49 (d, $^2J_{HF}$ = 46.8 Hz, 2H, CH_2F), 7.32 (m, 1H, Ar*H*-4), 7.48 (m, 1H, Ar*H*-5), 7.61 (m, 1H, Ar*H*-2), 7.66 (m, 1H, Ar*H*-6). ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.6 (d, $^1J_{CF}$ = 183.5 Hz, *C*H_2F), 114.8 (dd, $^2J_{CF}$ = 22.6 Hz, $^4J_{CF}$ = 2.9 Hz, Ar*C*-2), 121.2 (d, $^2J_{CF}$ = 21.4 Hz, Ar*C*-4), 123.6 (t, $^4J_{CF}$ = 3.0 Hz, Ar*C*-6), 130.7 (d, $^3J_{CF}$ = 7.7 Hz, Ar*C*-5), 135.6 (d, $^3J_{CF}$ = 6.5 Hz, Ar*C*-1), 162.8 (d, $^1J_{CF}$ = 249.0 Hz, Ar*C*-3), 192.4 (dd, $^2J_{CF}$ = 15.9 Hz, $^4J_{CF}$ = 2.2 Hz, *C*=O). ^{19}F NMR (376 MHz, $CDCl_3$) δ -230.2 (t, $^2J_{FH}$ = 46.8 Hz, CH_2F), -110.8 (m, Ar-*F*). HRMS (ESI) m/z [M-Na]$^+$ calcd for $C_8H_6F_2O$ 179.0279; found 179.0283.

2-fluoro-1-[4-(trifluoromethyl)phenyl]ethanone (95f)



Column chromatography on silica gel (Hexane/AcOEt 95:5), light yellow solid (mp 29-32 °C, Lit. 35-36 °C),[85] 40.6 %, 0.084 g. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.52 (d, $^2J_{HF}$ = 46.9 Hz, 2H, CH_2F) 7.77 (m, 2H, Ar*H*-3,5), 8.02 (m, 2H, Ar*H*-2,6). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 83.7 (d, $^1J_{CF}$ = 184.3 Hz, *C*H_2F), 123.3 (q, $^1J_{CF}$ = 272.9 Hz, *C*F_3), 126.0 (q, $^3J_{CF}$ = 3.7 Hz, Ar*C*-3,5), 128.5 (d, $^4J_{CF}$ = 3.1Hz, Ar*C*-2,6), 135.3 (q, $^2J_{CF}$ = 32.9 Hz, Ar*C*-4), 136.4 (Ar*C*-1), 192.9 (d, $^2J_{CF}$ = 16.4 Hz, *C*=O). ^{19}F NMR (376 MHz, $CDCl_3$) δ -229.6 (t, $^2J_{FH}$ = 46.9 Hz, CH_2F), -63.3 (s, CF_3). HRMS (ESI) m/z [M-Na]$^+$ calcd for $C_9H_6F_4O$ 229.0247; found 229.0242.

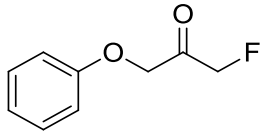
2-fluoro-1-(4-fluorophenyl)ethanone (95g)



Column chromatography on silica gel (Hexane/AcOEt 97:3), yellow solid (mp 33-38 °C, Lit. 49-51 °C),[8] 55%, 0.086 g. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48 (d, $^2J_{HF}$ = 47.0 Hz, 2H, CH_2F) 7.18 (m, 2H, Ar*H*-3,5), 7.96 (m, 2H, Ar*H*-2,6). ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.6 (d, $^1J_{CF}$ = 183.4 Hz, *C*H_2F), 116.2 (d, $^2J_{CF}$ = 22.0 Hz, Ar*C*-3,5), 130.3 (d, $^3J_{CF}$ = 3.0 Hz, Ar*C*-1), 130.8

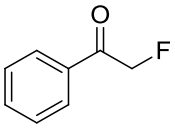
(dd, $^{3}J_{CF}$ = 9.4 Hz, $^{4}J_{CF}$ = 3.2 Hz, Ar*C*-2,6), 166.3 (d, $^{1}J_{CF}$ = 256.7 Hz, Ar*C*-4), 192.1 (d, $^{2}J_{CF}$ = 15.9 Hz, *C*=O). ^{19}F NMR (376 MHz, $CDCl_3$) δ -229.2 (t, $^{2}J_{FH}$ = 47.0 Hz, CH_2F), -102.8 (m, Ar-*F*). HRMS (ESI) m/z $[M-Na]^+$ calcd for $C_8H_6F_2NaO$ 179.0279; found 179.0285.

1-fluoro-3-phenoxypropan-2-one (95h)



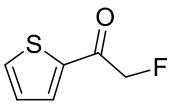
Column chromatography on silica gel (Hexane/AcOEt 90:10), colorless oil, 92% (160 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.81 (s, 2H, CH_2OAr), 5.21 (d, $^{2}J_{HF}$ = 47.2 Hz, 2H, CH_2F), 6.91 (d, *J* = 7.9 Hz, 2H, Ar*H*), 7.03 (t, *J* = 7.4 Hz, 1H, Ar*H*), 7.32 (dd, *J* = 8.6, 7.5 Hz, 2H, Ar*H*). ^{13}C NMR (126 MHz, $CDCl_3$) δ 71.2 (*C*H_2OAr), 84.5 (d, $^{1}J_{CF}$ = 182.7 Hz, *C*H_2F), 114.5 (Ar*C*H), 122.2 (Ar*C*H), 129.8 (Ar*C*H), 157.3 (Ar*C*), 201.8 (d, $^{2}J_{CF}$ = 17.4 Hz, *C*=O). ^{19}F NMR (470 MHz, $CDCl_3$) δ -236.46 (t, $^{2}J_{HF}$ = 47.2 Hz). FT-IR (NaCl, cm^{-1}) υ 754, 1068, 1430, 1495, 1598, 1748, 2854, 2925, 3064. HRMS (ESI-TOF) m/z $[M-H]^-$ calcd for $C_9H_9FO_2$ 167.0514; found 167.0511.

2-fluoro-1-phenylethanone (95i)



Column chromatography on silica gel (Hexane/AcOEt 98:2), light yellow oil, 58%, 0.079 g. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52 (d, $^{2}J_{HF}$ = 46.9 Hz, 2H, CH_2F), 7.49 (m, 2H, Ar*H*-3,5), 7.62 (m, 1H, Ar*H*-4), 7.89 (m, 2H, Ar*H*-2,6). ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.5 (d, $^{1}J_{CF}$ = 182.6 Hz, *C*H_2F), 127.8 (d, $^{4}J_{CF}$ = 2.6 Hz, Ar*C*-2,6), 128.9 (Ar*C*-3,5), 133.7 (Ar*C*-1), 134.1 (Ar*C*-4), 193.4 (d, $^{2}J_{CF}$ = 15.5 Hz, *C*=O). ^{19}F NMR (376 MHz, $CDCl_3$) δ -230.8 (t, $^{2}J_{FH}$ = 46.9 Hz, CH_2F). HRMS (ESI) m/z $[M-Na]^+$ calcd for C_8H_7FNaO 161.0373; found 161.0376.

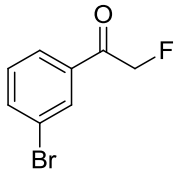
2-fluoro-1-(2-thienyl)ethanone (95j)



Column chromatography on neutral alumina gel Brockmann grade II (Hexane/AcOEt 98:2), brownish solid (mp: 49-52 °C, Lit. 58.6-60.1 °C),[86] 42%, 0.060 mg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33 (d, $^{2}J_{HF}$ = 47.2 Hz, 2H, CH_2F), 7.18 (dd, ^{3}J = 4.9 Hz, ^{3}J = 3.9 Hz, 1H, Th*H*-4), 7.75 (ddd, ^{3}J = 4.9 Hz, ^{4}J = 1.1 Hz, *J* = 0.6 Hz, 1H, Th*H*-5), 7.88 (ddd, ^{3}J = 3.9 Hz, ^{4}J = 1.1 Hz, *J* = 1.1 Hz, 1H, Th*H*-3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.9 (d, $^{1}J_{CF}$ = 185.3), 128.4 (d,

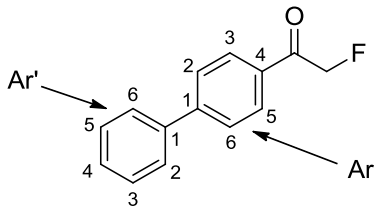
$^{5}J_{CF}$ = 1.2 Hz, Th*C*-4), 133.2 (d, $^{4}J_{CF}$ = 6.6 Hz, Th*C*-3), 134.9 (d, $^{5}J_{CF}$ = 1.6 Hz, Th*C*-5), 140.0 (d, $^{3}J_{CF}$ = 2.7 Hz, Th*C*-2), 187.2 (d, $^{2}J_{CF}$ = 18.3 Hz, *C*=O). ^{19}F NMR (376 MHz, $CDCl_3$) δ -226.6 (t, $^{2}J_{FH}$ = 47.2 Hz, CH_2F). HRMS (ESI) m/z $[M\text{-}Na]^+$ calcd for C_6H_5FNaOS 166.9937; found 166.9934.

1-(3-bromophenyl)-2-fluoroethanone (95k)



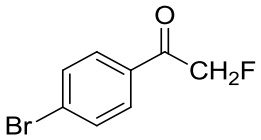
Column chromatography on silica gel (Hexane/AcOEt 99:1), white solid (mp 41-44°C)[87], 64%, 0.138 g. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48 (d, $^{2}J_{HF}$ = 46.9 Hz, 2H, CH_2F), 7.38 (m, 1H, Ar*H*-5), 7.75 (m, 1H, Ar*H*-4), 7.82 (m, 1H, Ar*H*-6), 8.03 (m, 1H, Ar*H*-2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.3 (d, $^{1}J_{CF}$ = 183.9 Hz, *C*H_2F), 123.2 (Ar*C*-3), 126.4 (d, $^{4}J_{CF}$ = 2.9 Hz, Ar*C*-6), 130.4 (Ar*C*-5), 130.9 (d, $^{4}J_{CF}$ = 3.0 Hz, Ar*C*-2), 135.3 (Ar*C*-1), 136.9 (Ar*C*-4), 192.3 (d, $^{2}J_{CF}$ = 16.2 Hz, *C*=O). ^{19}F NMR (376 MHz, $CDCl_3$) δ -230.0 (t, $^{2}J_{FH}$ = 46.9 Hz, CH_2F). HRMS (ESI) m/z $[M\text{-}Na]^+$ calcd for $C_8H_6BrFNaO$ 238.9478; found 238.9478.

1-(4-biphenyl)-2-fluoroethanone (95l)



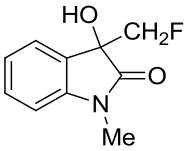
Column chromatography on silica gel (Hexane/AcOEt 98:2), light yellow solid (mp 130-134°C, Lit. 131.5–132.4 °C),[9] 53%, 0.154 g. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (d, $^{2}J_{HF}$ = 47.0 Hz, 2H, CH_2F), 7.42 (m, 1H, Ar'*H*-4),7.49 (m, 2H, Ar'*H*-3,5), 7.63 (m, 2H, Ar'*H*-2,6), 7.72 (m, 2H, Ar*H*-2,6), 7.98 (m, 2H, Ar*H*-3,5). ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.6 (d, $^{1}J_{CF}$ = 182.8 Hz, *C*H_2F), 127.3 (Ar'*C*-2,6), 127.5 (Ar*C*-2,6), 128.5 (Ar*C*-3,5), 128.5 (Ar'*C*-4), 129.0 (Ar'*C*-3,5), 132.4 (Ar*C*-4), 139.6 (Ar'*C*-1), 146.9 (Ar*C*-1), 193.0 (d, $^{2}J_{CF}$ = 15.7 Hz, *C*=O). ^{19}F NMR (376 MHz, $CDCl_3$) δ -230.2 (t, $^{2}J_{FH}$ = 47.0 Hz, CH_2F). HRMS (ESI), m/z $[M\text{-}Na]^+$ calcd for $C_{14}H_{11}FNaO$ 237.0686; found 237.0683.

1-(4-bromophenyl)-2-fluoroethanone (95m)



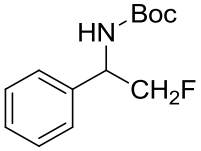
Column chromatography on silica gel (Hexane/AcOEt 90:10), yellow oil, 36% (77 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.47 (d, $^{1}J_{HF}$ = 46.9 Hz, 2H, CH_2F), 7.65 (d, ^{2}J = 8.7 Hz, 2H, Ar*H*), 7.78 (d, *J* = 8.4 Hz, 2H, Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 83.6 (d, $^{1}J_{CF}$ = 183.9 Hz, *C*H_2F), 129.46 (d, $^{4}J_{CF}$ = 3.2 Hz, Ar*C*H), 132.3 (Ar*C*H), 192.68 (d, $^{2}J_{CF}$ = 16.0 Hz, *C*=O); ^{19}F NMR (470 MHz, $CDCl_3$) δ -229.57 (t, $^{2}J_{HF}$ = 47.0 Hz); FT-IR (NaCl, cm^{-1}) υ 727, 1099, 1264, 1454, 1643, 2908, 3427. (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_8H_6BrFONa$ 238.9478; found 238.9481.

3-(fluoromethyl)-3-hydroxy-1-methylindolin-2-one (95n)



Column chromatography on silica gel (Hexane/AcOEt 90:10), waxy solid, 20% (39 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.00 (s, 1H, OH), 3.22 (s, 3H, NCH_3), 4.59 (d, $^{2}J_{HF}$ = 47.0 Hz, 2H, CH_2F), 6.88 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.14 (t, *J* = 7.6 Hz, 1H, Ar*H*), 7.39 (t, *J* = 7.8 Hz, 1H, Ar*H*), 7.45 (d, *J* = 7.4 Hz, 1H, Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.4 (N*C*H_3), 84.7 (d, $^{1}J_{CF}$ = 180.9 Hz, *C*H_2F), 108.7 (Ar*C*H), 123.4 (Ar*C*H), 124.6 (Ar*C*H), 130.7 (Ar*C*H), 143.9 (Ar*C*); ^{19}F NMR (470 MHz, $CDCl_3$) δ -230.10 (t, $^{2}J_{HF}$ = 46.9 Hz); (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{10}H_{10}FNO_2Na$ 218.0588; found 218.0592.

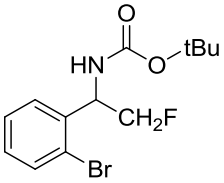
***tert*-butyl (2-fluoro-1-phenylethyl)carbamate (96a)[88]**



Column chromatography on silica gel (Hexane/AcOEt 90:10), white solid, mp 109-111 °C, 92% (220 mg), rotamers mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (s, 9H, C(CH_3)$_3$), 4.53-4.71 (m, 2H, CH_2F), 4.91-4.96 (m, 1H, C*H*NH), 5.15 (bs, 1H, N*H*), 7.29-7.38 (m, 5H, Ar*H*). ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.3 (C(*C*H_3)$_3$), 54.4 (*C*HNH), 80.0 (*C*(CH$_3$)$_3$), 85.0 (d, $^{1}J_{CF}$ = 175.9 Hz, *C*H_2F), 126.8 (Ar*C*H), 127.9 (Ar*C*H), 128.7 (Ar*C*H), 138.3 (Ar*C*), 155.1 (*C*=O). ^{19}F NMR (470 MHz, $CDCl_3$) δ -226.4 (m). FT-IR (KBr, cm^{-1}) υ 699, 1013, 1172, 1283, 1518,

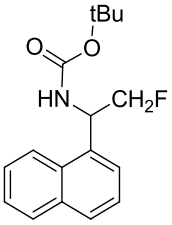
1682, 2938, 3009, 3388. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{13}H_{18}FNO_2Na$ 262.1214; found 262.1213.

***tert*-butyl (1-(2-bromophenyl)-2-fluoroethyl)carbamate (96b)**



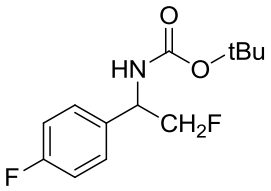
Column chromatography on silica gel (Hexane/AcOEt 90:10), white solid, 75% (238 mg), rotamers mixture. ^{1}H NMR (500 MHz, CD_3OD, selected data for major rotamer) δ 1.43 (s, 9H, C(C*H*$_3$)$_3$), 4.30-4.61 (m, 2H, C*H*$_2$F), 5.25-5.36 (m, 1H, C*H*NH), 7.20 (t, $^3J_{HH}$ = 7.9 Hz, 1H, Ar*H*), 7.36 (t, $^3J_{HH}$ = 7.5 Hz, 1H, Ar*H*), 7.43 (dd, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.5 Hz, 1H, Ar*H*), 7.43 (dd, $^3J_{HH}$ = 7.9, $^4J_{HH}$ = 1.4 Hz, 1H, Ar*H*). ^{13}C NMR (126 MHz, CD_3OD, selected data for major rotamer) δ 27.3 (C(*C*H$_3$)$_3$), 54.4 (*C*HNH), 78.3 (*C*(CH$_3$)$_3$), 82.8 (d, $^1J_{CF}$ = 175.9 Hz, *C*H$_2$F), 122.8 (Ar*C*), 127.5 (Ar*C*H), 128.0 (Ar*C*H), 129.1 (Ar*C*H), 132.6 (Ar*C*H), 138.6 (Ar*C*), 155.2 (*C*=O). ^{19}F NMR (470 MHz, CD_3OD) δ -223.5 (td, J_{HF} = 47.2, 19.5 Hz). FT-IR (KBr, cm^{-1}) υ 747, 1016, 1170, 1276, 1527, 1683, 2500, 2987, 3366; HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{13}H_{17}BrFNO_2Na$ 340.0319; found 340.0322.

***tert*-butyl (2-fluoro-1-(naphthalen-1-yl)ethyl)carbamate (96c)**



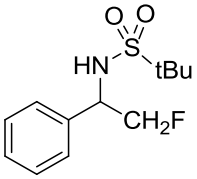
Column chromatography on silica gel (Hexane/AcOEt 90:10), white solid, mp = 116-119 °C, 85% (246 mg), rotamers mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (s, 9H, C(C*H*$_3$)$_3$), 4.68-4.89 (m, 2H, C*H*$_2$F), 5.25 (bs, 1H, N*H*), 5.79-5.83 (m, 1H, C*H*CH$_2$F), 7.45-7.58 (m, 4H, Ar*H*), 7.83 (d, *J* = 8.1 Hz, 1H, Ar*H*), 7.89 (d, *J* = 8.1 Hz, 1H, Ar*H*), 8.10 (d, *J* = 8.4 Hz, 1H, Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$), 28.3 (C(*C*H$_3$)$_3$), 50.3 (*C*HCH$_2$F), 80.1 (*C*(CH$_3$)$_3$), 84.32 (d, $^1J_{CF}$ = 176.3 Hz, *C*H$_2$F), 122.0 (Ar*C*), 123.9 (d, $^3J_{CF}$ = 2.1 Hz, Ar*C*), 125.2 (Ar*C*H), 125.9 (Ar*C*H), 126.7 (Ar*C*H), 128.7 (Ar*C*H), 129.0 (Ar*C*H), 130.9 (Ar*C*H), 133.8 (Ar*C*),133.9 (Ar*C*H), 155.1 (*C*=O). ^{19}F NMR (470 MHz, $CDCl_3$), δ -224.3, -221.9 (m, rotamers mixture); FT-IR (KBr, cm^{-1}) υ 773, 1069, 1164, 1254, 1528, 1681, 2980, 3356; HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{17}H_{20}FO_2Na$ 312.1370; found 312.1373.

***tert*-butyl (2-fluoro-1-(4-fluorophenyl)ethyl)carbamate (96d)**



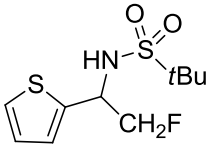
Column chromatography on silica gel (Hexane/AcOEt 90:10), colorless oil, 70% (180 mg), rotamers mixture. ^{1}H NMR (500 MHz, CD_3OD) δ 1.41 (s, 9H, C(C*H*$_3$)$_3$), 4.40-4.57 (m, 2H, C*H*$_2$F), 4.91 (overlapping D_2O, 1H, C*H*NH), 7.07-7.11 (m, 2H, Ar*H*), 7.36-7.40 (m, 2H, Ar*H*). ^{13}C NMR (126 MHz, CD_3OD), δ 28.7 (C(*C*H$_3$)$_3$), 55.6 (d, ^{2}J = 19.6 Hz, C*H*NH), 80.6 (*C*(CH$_3$)$_3$), 85.6 (d, $^{1}J_{CF}$ = 176.1 Hz, *C*H$_2$F), 116.20 (d, $^{2}J_{CF}$ = 21.7 Hz, Ar*C*H), 129.90 (d, $^{3}J_{CF}$ = 8.2 Hz, Ar*C*H), 157.8 (Ar*C*), 162.7 (*C*=O), 164.7 (d, $^{1}J_{CF}$ = 248.2 Hz Ar*C*F). ^{19}F NMR (470 MHz, CD_3OD), δ -117.5 (s, ArC*F*), -223.0 (m, CH$_2$*F*). FT-IR (NaCl, cm^{-1}) υ 548, 834, 865, 1002, 1060, 1171, 1224, 1252, 1368, 1513, 1606, 1679, 2982, 3318, 3382. HRMS (ESI-TOF) m/z [M+Na]$^{+}$ calcd for $C_{13}H_{17}F_2NNaO_2$ 280.1120; found 280.1121.

***N*-(2-fluoro-1-phenylethyl)-2-methylpropane-2-sulfonamide (96e)**



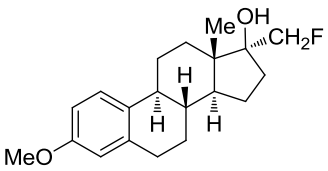
Modification of the general procedure. The crude mixture of *tert*-butyl sulfinamide was subjected to oxidation by treatment with 1.2 eq of *m*-chloroberbenzoic acid in 10 mL of CH_2Cl_2 at 25 °C for 24h. The reaction mixture was quenched with sat. $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography on SiO2, 10–40% EtOAc in hexane, to provide **14e** as white solid, mp 148-149 °C, 95% (246 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (s, 9H, C(C*H*$_3$)$_3$), 4.50-4.72 (m, 2H, C*H*$_2$F), 4.75-4.83 (m, 1H, C*H*NH), 4.93 (bs, 1H, N*H*), 7.32-7.34 (m, 2H, Ar*H*), 7.37-7.40 (m, 3H, Ar*H*). ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.1 (C(*C*H$_3$)$_3$), 58.2 (d, $^{2}J_{CF}$ = 19.2 Hz, *C*HNH), 60.2 (*C*(CH$_3$)$_3$), 86.0 (d, $^{1}J_{CF}$ = 177.7 Hz, *C*H$_2$F), 126.8 (Ar*C*H), 128.3 (Ar*C*H), 128.9 (Ar*C*H), 137.8 (d, $^{3}J_{CF}$ = 3.6 Hz, Ar*C*). ^{19}F NMR (470 MHz, $CDCl_3$) δ -224.5 (td, J_{HF} = 47.1, 20.9 Hz). FT-IR (KBr, cm^{-1}) υ 709, 1032, 1113, 1132, 1302, 1458, 1637, 1718, 2978, 3289, 3427. HRMS (ESI-TOF) m/z [M-H]$^{-}$ calcd for $C_{12}H_{18}FNO_2S$ 258.0970; found 258.0966.

***N*-(2-fluoro-1-(thiophen-2-yl)ethyl)-2-methylpropane-2-sulfonamide (96f)**



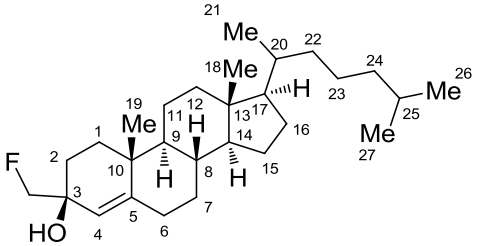
Modification of the general procedure. The crude mixture of *tert*-butyl sulfinamide was subjected to oxidation by treatment with 1.2 eq of m-chloroberbenzoic acid in 10 mL of CH_2Cl_2 at 25 °C for 24h. The reaction mixture was quenched with sat. $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography on SiO_2, 10–40% EtOAc in hexane, to provide the **14f** white solid, 70% (186 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (s, 9H, C(C*H*$_3$)$_3$), 4.55 (d, *J* = 9.3 Hz, 1H, NH), 4.63-4.81 (m, 2H, C*H*$_2$F), 4.99-5.07 (m, 1H, C*H*CH$_2$F), 7.00-7.01 (m, 1H, Ar*H*), 7.07-7.08 (m, 1H, Ar*H*), 7.28-7.29 (m, 1H, Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.1 (C(*C*H$_3$)$_3$), 54.2 (d, $^2J_{CF}$ = 20.1 Hz, *C*HCH$_2$F), 60.4 (*C*(CH$_3$)$_3$), 85.7 (d, $^1J_{CF}$ = 177.8 Hz, *C*H$_2$F), 125.5 (Ar*C*H), 125.7 (Ar*C*H), 127.2 (Ar*C*H), 140.70 (d, $^3J_{CF}$ = 3.0 Hz, Ar*C*); ^{19}F NMR (470 MHz, $CDCl_3$) δ -225.51 (td, J_{HF} = 46.9, 22.2 Hz, CH_2F); FT-IR (KBr, cm^{-1}) υ 727, 1029, 1126, 1296, 1435, 2919, 3273; (ESI-TOF) m/z [M+H]$^+$ calcd for $C_{10}H_{16}FNO_2S_2Na$ 288.0499; found 288.0506.

3-Methoxy-17β-fluoromethyl-Δ$^{1.3.5}$(10)-oestratrien-17α-ol (98a)



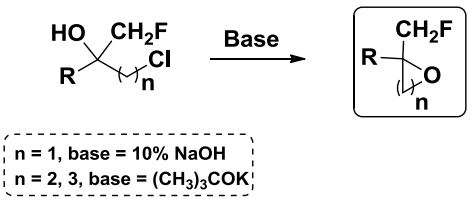
Column chromatography on silica gel (Hexane/AcOEt 90:10), dr>95/5, white solid, 50% (159 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (s, 3H, C*H*$_3$), 1.21-1.54 (m, 6H), 1.66-1.69 (m, 1H), 1.78-1.80 (m, 3H), 1.88-1.91 (m, 1H), 2.15-2.21 (m, 2H), 2.30-2.33 (m, 1H), 2.85-2.88 (m, 2H), 3.79 (s, 3H, OC*H*$_3$), 4.29 (dd, *J* = 48.0, 9.3 Hz, 1H, C*H*$_2$F), 4.60 (dd, *J* = 47.5, 9.3 Hz, 1H, C*H*$_2$F), 6.63 (s, 1H, Ar*H*), 6.71 (d, *J* = 8.5 Hz, 1H, Ar*H*), 7.20 (d, *J* = 8.6 Hz, 1H, Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.1 (*C*H$_3$), 23.1, 26.2, 27.5, 29.8, 32.4 (d, *J* = 2.7 Hz), 33.0 (d, *J* = 5.3 Hz), 39.3, 43.7, 45.9, 50.6, 55.2 (O*C*H$_3$), 82.5 (d, $^2J_{CF}$ = 15.7 Hz, *C*CH$_2$F), 87.0 (d, $^1J_{CF}$ = 171.3 Hz), 111.5 (Ar*C*H), 113.8 (Ar*C*H), 126.3 (Ar*C*H), 132.3 (Ar*C*), 137.9 (Ar*C*), 157.5 (Ar*C*); ^{19}F NMR (470 MHz, $CDCl_3$) δ -223.35 (t, $^2J_{HF}$ = 47.7 Hz); FT-IR (KBr, cm^{-1}) υ 727, 1017, 1099, 1263, 1408, 1453, 1502, 1609, 2925, 3436; (ESI-TOF) m/z [M+Na]$^+$ calcd for $C_{20}H_{27}FO_2Na$ 341.1887; found 341.1889. α_D = +2.01 (c = 0.5, $CHCl_3$)

3-(fluoromethyl)cholest-4-en-3-ol (98b)



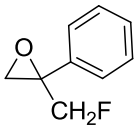
Column chromatography on neutral alumina gel Brockmann grade II (Hexane/AcOEt 9:1), white solid (mp 98-102 °C), dr > 95/5, 82%, 0.343 g. ^{1}H NMR (400 MHz, C_6D_6) δ 0.61 (m, 1H, *H*-9), 0.66 (s, 3H, *H*-18 = 13-*Me*), 0.85 (m, 1H, *H*-14), 0.77 (m, 1H, *H*-7), 0.90 (s, 3H, *H*-19 = 10-*Me*), 0.94 (d, *J* = 6.6 Hz, 6H, 25-*Me*$_2$), 1.02 (d, *J* = 6.6 Hz, 3H, *H*-21 = 20-*Me*), 1.02 (m, 1H, *H*-15), 1.07 (m, 2H, *H*-24), 1.09 (m, 1H, *H*-17), 1.10 (m, 1H, *H*-22), 1.13 (m, 1H, *H*-1), 1.22 (m, 1H, *H*-11), 1.25 (m, 1H, *H*-23), 1.27 (m, 1H, *H*-16), 1.28 (m, 1H, *H*-20), 1.30 (m, 1H, *H*-11), 1.44 (m, 1H, *H*-8), 1.45 (m, 1H, *H*-1), 1.45 (m, 1H, *H*-22), 1.45 (m, 1H, *H*-23), 1.53 (m, 1H, *H*-15), 1.56 (m, 1H, *H*-2), 1.56 (d, *J* = 6.6 Hz, 1H, *H*-25), 1.60 (m, 1H, *H*-7), 1.85 (m, 1H, *H*-2), 1.85 (m, 1H, *H*-16), 1.92 (m, 1H, *H*-6), 1.99 (m, 2H, *H*-12), 2.07 (m, 1H, *H*-6), 4.07-4.17 (double AB-system, $^{2}J_{HF}$ = 48.4 Hz, $^{2}J_{HH}$ = 9.1 Hz, 1H, C*H*$_2$F), 5.12 (m, 1H, *H*-4). ^{13}C NMR (100 MHz, C_6D_6) δ 12.3 (*C*-18), 18.9 (*C*-19), 19.0 (*C*-21), 21.5 (*C*-11), 22.8 (25-*Me*), 23.0 (25-*Me*), 24.4 (*C*-23), 24.5 (*C*-15), 28.4 (*C*-25), 28.6 (*C*-16), 28.9 (d, $^{3}J_{CF}$ = 3.2 Hz, *C*-2), 32.7 (*C*-6), 33.4 (*C*-7), 35.0 (*C*-1), 36.2 (*C*-8), 36.2 (*C*-20), 36.7 (*C*-22), 37.8 (*C*-10), 40.0 (*C*-24), 40.2 (*C*-12), 42.8 (*C*-13), 54.6 (*C*-9), 56.3 (*C*-14), 56.7 (*C*-17), 70.7 (d, $^{2}J_{CF}$ =18.6 Hz, *C*-3), 87.3 (d, $^{1}J_{CF}$ = 178.0 Hz, *C*H$_2$F), 121.3 (d, $^{3}J_{CF}$ = 5.8 Hz, *C*-4), 150.0 (d, $^{4}J_{CF}$ = 1.7 Hz, *C*-5).). ^{19}F NMR (376 MHz, C_6D_6) δ -226.3 (dt, $^{4}J_{FH}$ =1.6 Hz, $^{2}J_{FH}$ = 48.4 Hz, CH$_2$*F*). HRMS (ESI) m/z [M-Na]$^{+}$ calcd for $C_{28}H_{47}FNaO$ 441.3503; found 441.3501. α_D = +69.6 (*c* 0.24, $CHCl_3$).

5.5 General procedure for the synthesis of fluoromethylated heterocycles.



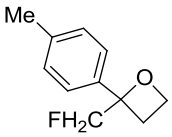
To a stirred solution of compounds **86f-i** (1.0 mmol, 1.0 equiv) in THF (10 ml), NaOH 10% aqueous solution or potassium *tert*-butoxide (3.0 mmol, 3.0 equiv), was added. The solution was allowed to stir at room temperature for two hours. The colour of solution changed to yellow. After this time, a saturated aqueous solution of NH_4Cl (1mL) was added, then the mixture was poured into water (10mL) and extracted with Et_2O (3x10 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated under vacuum to give fluorinated heterocycles in almost quantitative yield as a clear yellow oil.

2-(fluoromethyl)-2-phenyloxirane (99a)



Column chromatography on silica gel (Hexane/Et_2O 90:10), colorless oil, 98% (149 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.88-2.90 (m, 1H, CH_2O), 3.19-3.20 (dd, *J*= 5.2, 1.3 Hz, 1H, CH_2O), 4.66-4.88 (double AB-system, $^2J_{HF}$ = 48.4 Hz, $^2J_{HH}$ = 9.1 Hz, 1H, CH_2F), 7.34-7.40 (m, 3H, Ar*H*), 7.43-7.44 (m, 2H, Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 52.9 (d, $^3J_{CF}$ = 6.0 Hz, *C*H_2O), 84.5 (d, $^1J_{CF}$ = 176.4 Hz, *C*H_2F), 126.1 (Ar*C*H), 128.3 (Ar*C*H), 128.5 (Ar*C*H), 136.0 (Ar*C*). ^{19}F NMR (470 MHz, $CDCl_3$) δ -225.2 (td, J_{HF} = 47.4, 4.3 Hz). FT-IR (NaCl, cm^{-1}) υ 697, 1018, 1100, 1265, 1450, 1720, 2917. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd C_9H_9FNaO 175.0530; found 175.0532.

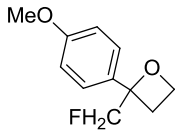
2-(fluoromethyl)-2-(p-tolyl)oxetane (99b)



Column chromatography on silica gel (Hexane/AcOEt 90:10), colorless oil , 90 % (162 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3H, CH_3), 2.69-2.76 (m, 1H, CH_2CH_2O), 3.16-3.26 (m, 1H, CH_2CH_2O), 4.28-4.67 (m, 4H, CH_2O, CH_2F), 7.23-7.24 (m, 4H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$), δ 21.1 (*C*H_3), 29.4 (d, $^3J_{CF}$ = 4.0 Hz, *C*H_2CH_2O), 65.8 (*C*H_2O), 86.8 (d, $^1J_{CF}$ =

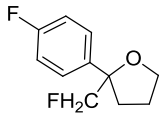
181.3 Hz,*C*CH_2F), 88.71 (d, $^2J_{CF}$ = 18.8 Hz, *C*CH_2F), 124.4 (Ar*CH*), 129.1 (Ar*CH*), 137.4 (Ar*C*), 138.9 (d, $^3J_{CF}$ = 6.3 Hz, Ar*C*). ^{19}F NMR (282 MHz, $CDCl_3$), δ -222.34 (t, J_{HF} = 48.7 Hz). FT-IR (NaCl, cm^{-1}) υ 815, 960, 1016, 1236, 1267, 1445, 1513, 1614, 1910, 2889, 2967. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{11}H_{13}FNaO$ 203.0843; found 203.0849.

2-(fluoromethyl)-2-(4-methoxyphenyl)oxetane (99c)



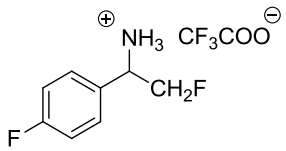
Column chromatography on silica gel (Hexane/AcOEt 90:10), white solid, 95% (186 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.68-2.73 (m, 1H, C*H*$_2$$CH_2O$), 3.17-3.22 (m, 1H, C*H*$_2$$CH_2O$), 3.82 (s, OC*H*$_3$), 4.29-4.44 (double AB system, $^2J_{HF}$ = 48.7 Hz, $^3J_{HH}$ = 10.5 Hz, 2H, C*H*$_2$F), 4.49-4.53 (m, 1H, C*H*$_2$O), 4.63-4.67 (m, 1H, C*H*$_2$O), 6.92-6.93 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.26-7.28 (d, *J* = 8.6 Hz, 2H, Ar*H).* ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.3 (d, $^3J_{CF}$ = 3.8 Hz, *C*H_2CH_2O), 55.3 (O*C*H_3), 65.7 (*C*H_2O), 86.8 (d, $^2J_{CF}$ = 18.9 Hz, *C*CH_2F), 87.2 (d, $^1J_{CF}$ = 180.1 Hz, *C*H_2F), 113.8 (Ar*C*H), 125.8 (Ar*C*H), 133.87 (d, $^3J_{CF}$ = 6.2 Hz, Ar*C*), 159.1 (Ar*C).* ^{19}F NMR (470 MHz, $CDCl_3$), δ -222.0 (t, J_{HF} = 48.3 Hz). FT-IR (KBr, cm^{-1}) υ 584, 815, 956, 1017, 1251, 1457, 1514, 1613, 1726, 2898, 2962. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{11}H_{13}FNaO_2$ 219.0792; found 219.0795.

2-(fluoromethyl)-2-(4-fluorophenyl)tetrahydrofuran (99d)



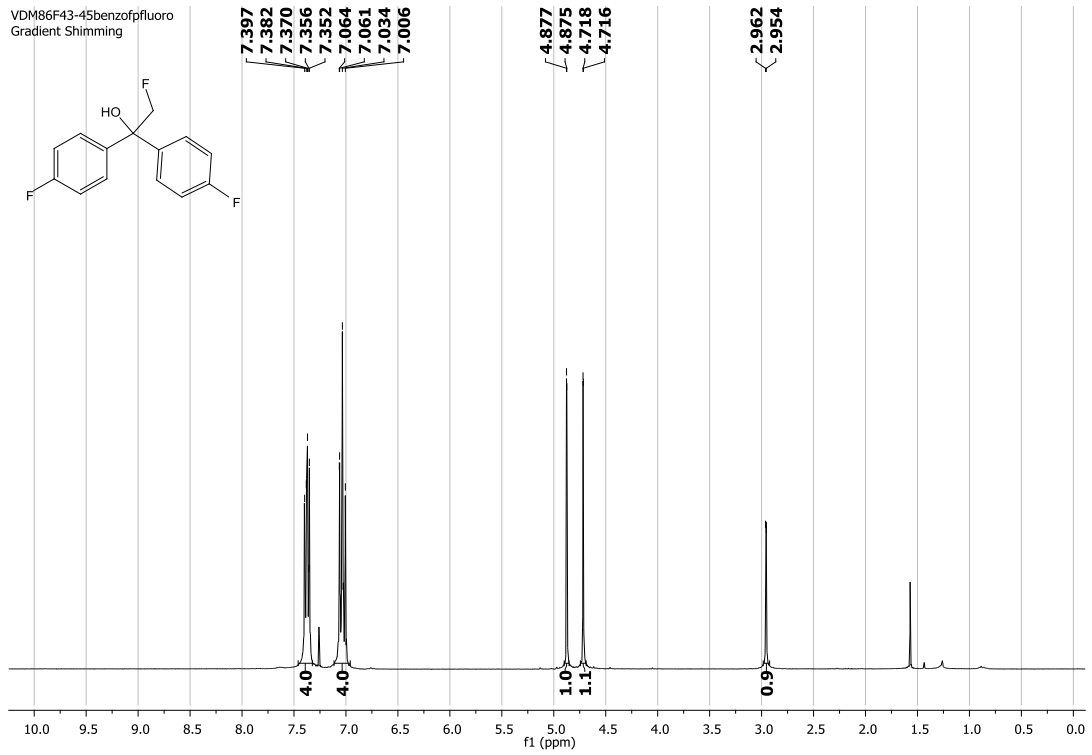
Column chromatography on silica gel (Hexane/AcOEt 90:10), yellowish oil, 98% (194 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.82-1.93 (m, 1H, C*H*$_2$$CH_2O$), 1.97-2.17 (m, 2H, C*H*$_2$$CH_2O$, C*H*$_2$CO), 2.35-2.43 (m, 1H, C*H*$_2$CO), 3.89-3.96 (m, 1H, C*H*$_2$O), 4.02-4.09 (m, 1H, C*H*$_2$O), 4.24-4.47 (d, $^2J_{HF}$ = 47.6 Hz, 2H, C*H*$_2$F), 6.99-7.07 (m, 2H, Ar*H*), 7.36-7.43 (m, 2H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$), δ 25.9 (*C*H_2CH_2O), 34.1 (d, $^3J_{CF}$ = 2.7 Hz, *C*H_2CO), 68.6 (*C*H_2O), 85.1 (d, $^2J_{CF}$ = 18.2 Hz, *C*CH_2F), 87.4 (d, $^1J_{CF}$ = 181.5 Hz, *C*H_2F), 115.0 (d, *J* = 21.3 Hz, Ar*C*H), 127.4 (d, J_{CF} = 8.0 Hz, Ar*C*H), 138.5 (Ar*C*), 162.1 (d, $^1J_{CF}$ = 245.6 Hz, Ar*C*). ^{19}F NMR (282 MHz, $CDCl_3$), δ -115.7 (m, Ar*F*), -220.6 (t, J_{HF} = 48.0 Hz, CH_2F). FT-IR (NaCl, cm^{-1}) υ 531, 562, 730, 813, 836, 1031, 1071, 1159, 1224, 1457, 1508, 1604, 2877, 2953, 2979. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{11}H_{12}F_2NaO$ 221.0748; found 221.0754.

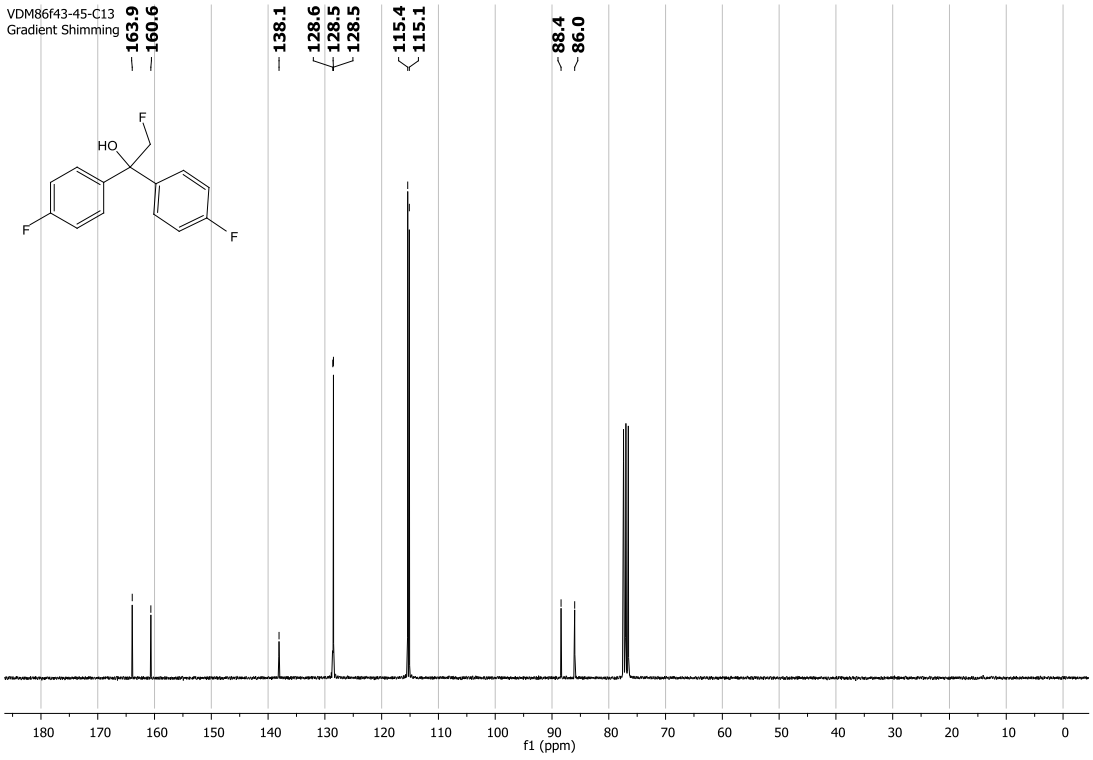
(2-fluoro-1-(4-fluorophenyl)ethyl)ammonium trifluoroacetate (100)

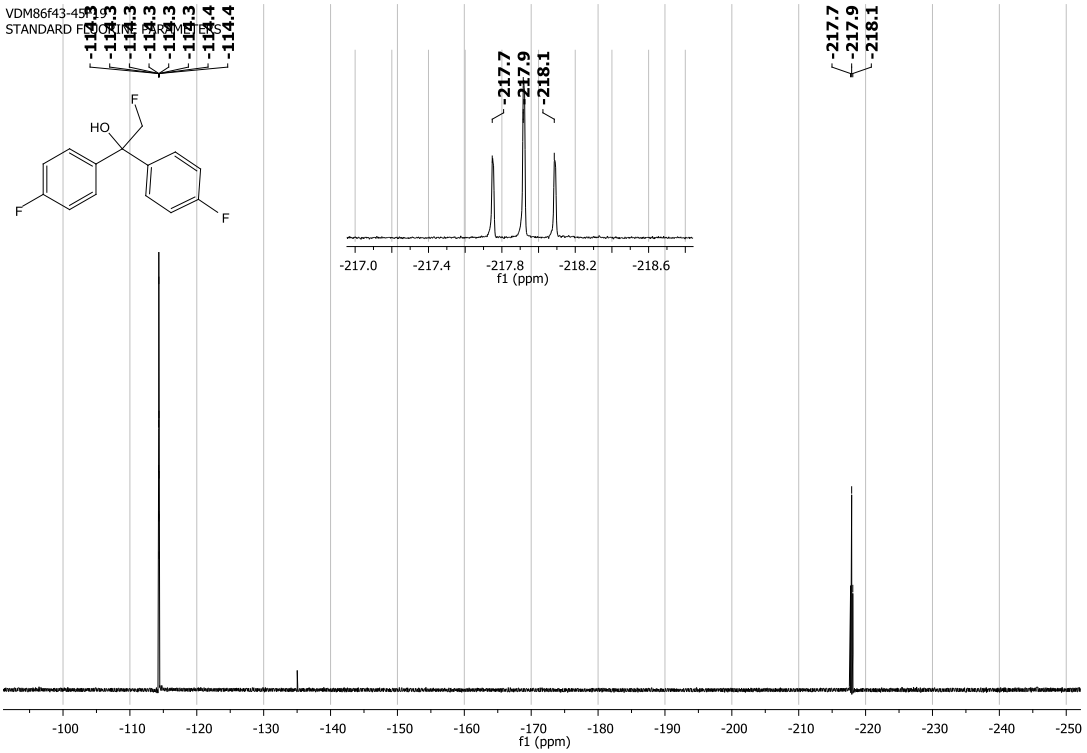


To a solution of carbamate **96d** (1 mmole, 157 mg) at room temperature in 2 mL of CH_2Cl_2 was added trifluoroacetic acid (3 eq, 0.3 mL). After stirring for 30 min, the solvent was removed in vacuo to give the title product (270 mg, 99% yield), as waxy solid. ^{1}H NMR (500 MHz, CD_3OD) δ 4.67-4.83 (m, 3H, C*H*$_2$F and C*H*NH), 7.22 (t, *J* = 8.7 Hz, 2H, Ar*H*), 7.51 (dd, *J* = 8.8, 5.1 Hz, 2H, Ar*H*). ^{13}C NMR (126 MHz, CD_3OD), δ 53.9 (d, ^2J = 19.2 Hz, C*H*NH), 82.8 (d, $^1J_{CF}$ = 176.1 Hz, *C*H$_2$F), 115.9 (d, $^2J_{CF}$ = 22.2 Hz, Ar*C*H), 128.5 (m, Ar*C*H), 129.6 (d, *J* = 8.6 Hz, Ar*C*H), 160.8 (CF3*C*O), 164.7 (d, *J* = 248.1 Hz, Ar*C*F). ^{19}F NMR (470 MHz, CD_3OD), δ –77.1 (s, C*F*$_3$), 113.4 (s, ArC*F*), 225.8 (m, CH$_2$*F*). HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_8H_{10}F_2N$ 158.0776; found 158.0786.

5.6 Copies of NMR spectra of rappresentative fluoro compounds.






VDM86f43-45-1-19
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-113.3
-113.3
-114.3
-114.3
-113.3
-113.3
-114.3
-114.4
-114.4
F
HO
F
F
-217.7
-217.9
-218.1
-217.0
-217.4
-217.8
-218.2
-218.6
f1 (ppm)
-217.7
-217.9
-218.1
-100
-110
-120
-130
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-150
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-170
-180
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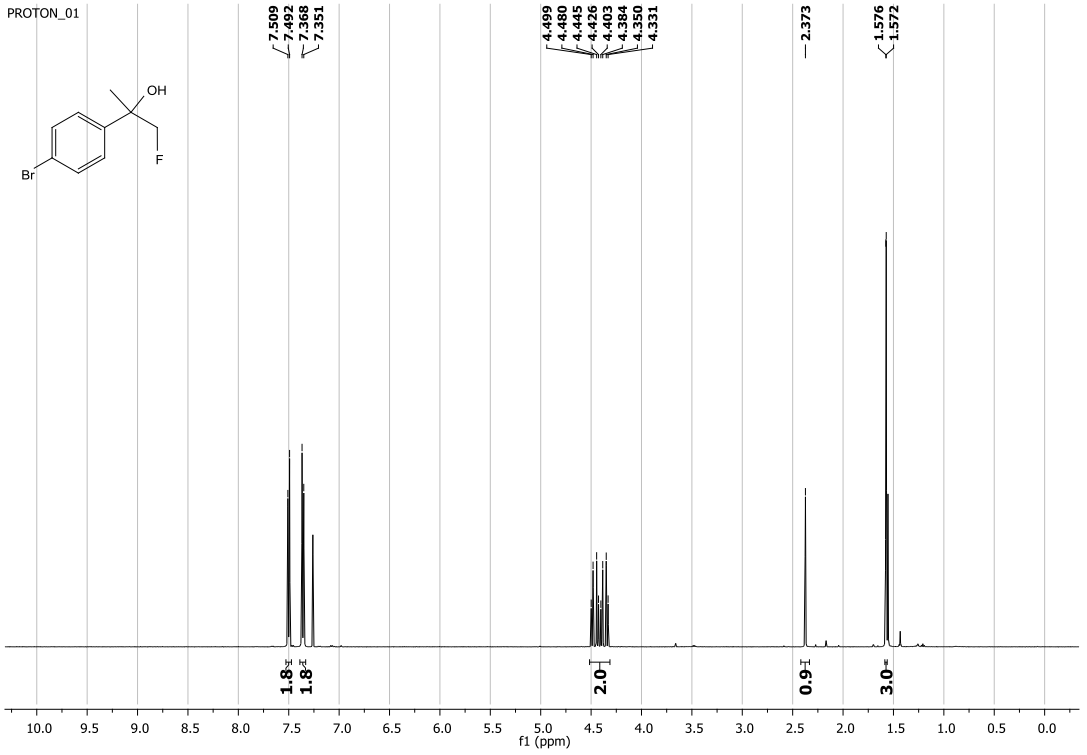
-210
-220
-230
-240
-250
f1 (ppm)


PROTON_01
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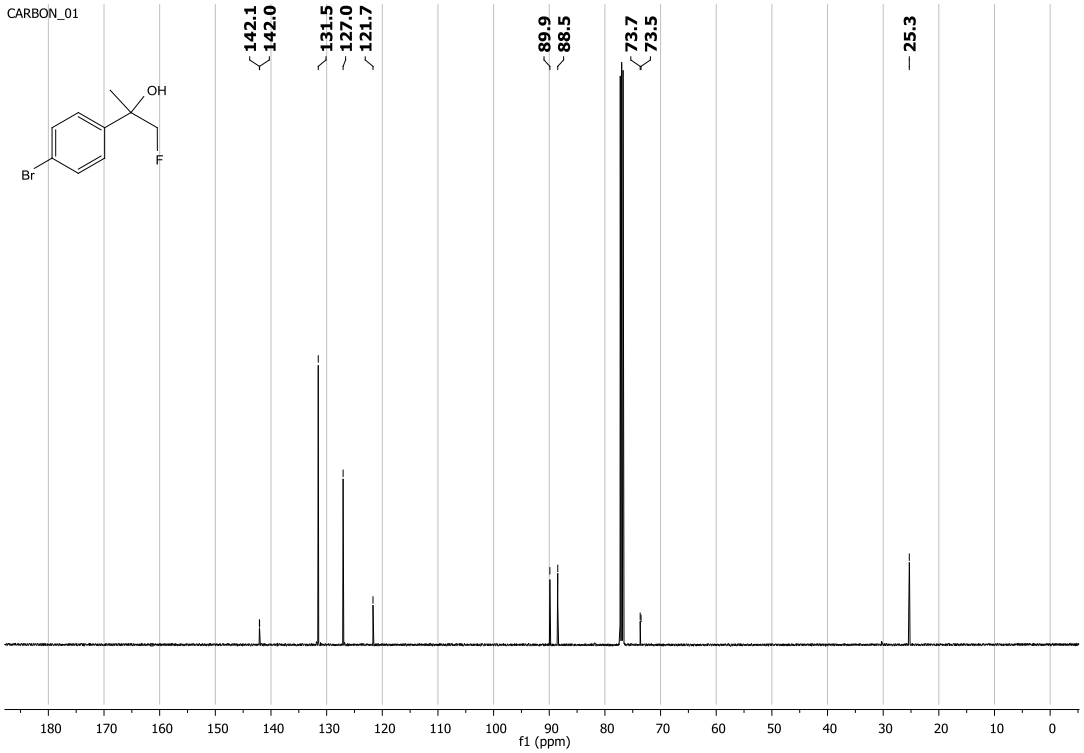
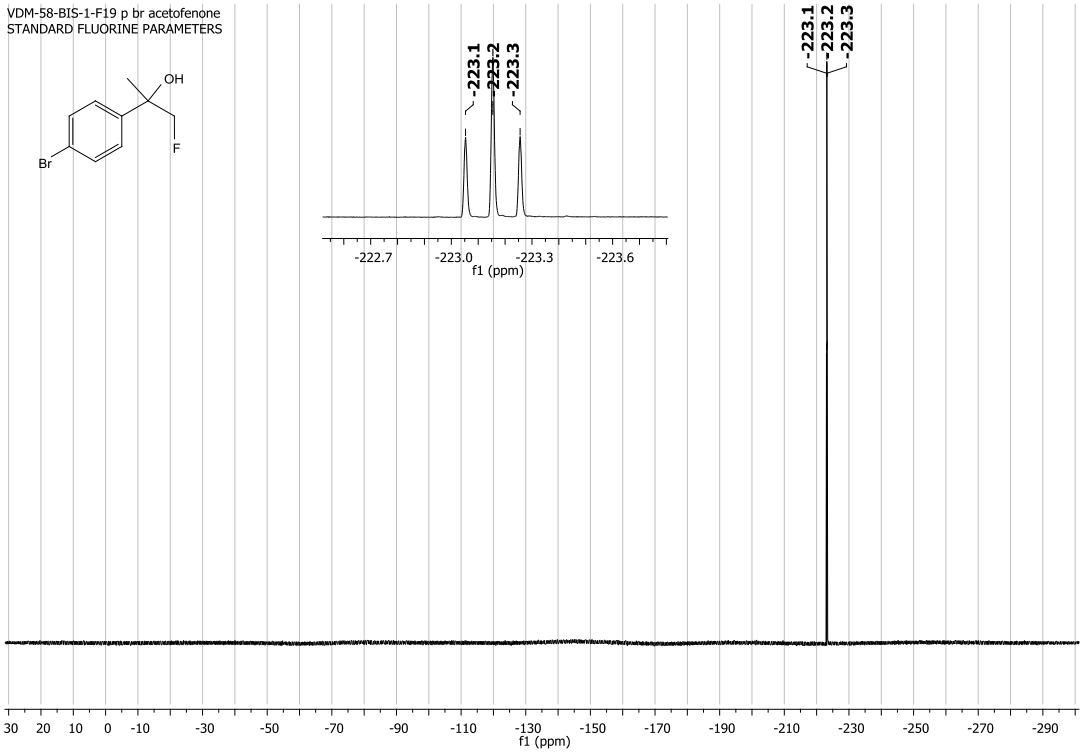
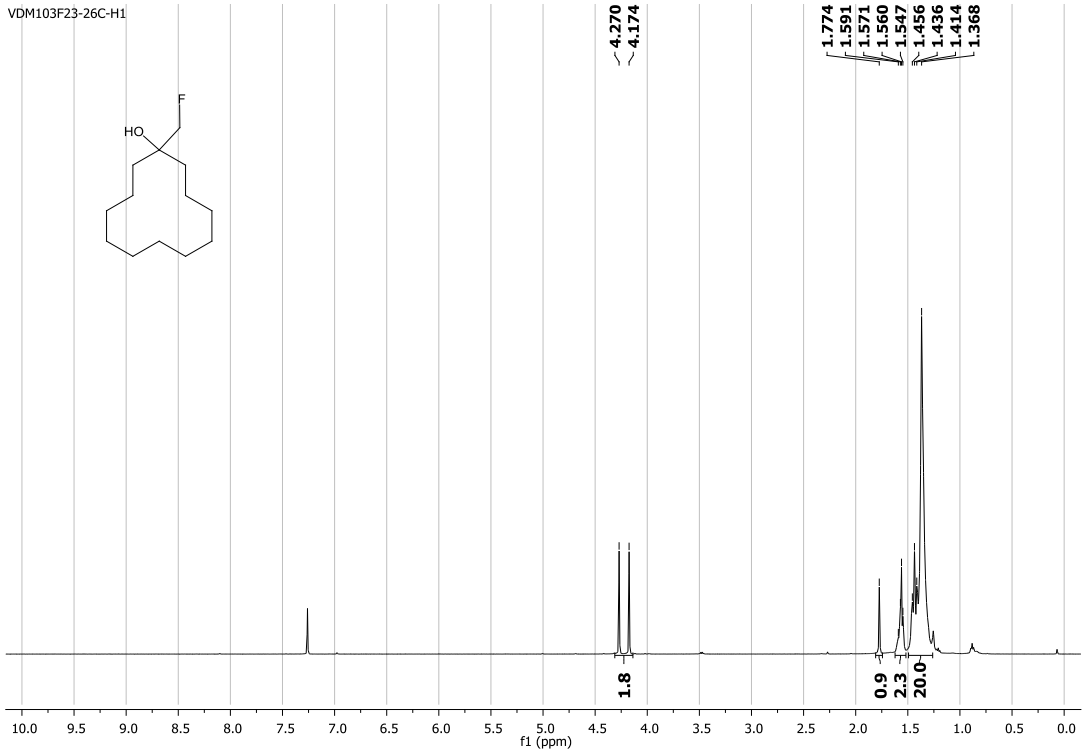
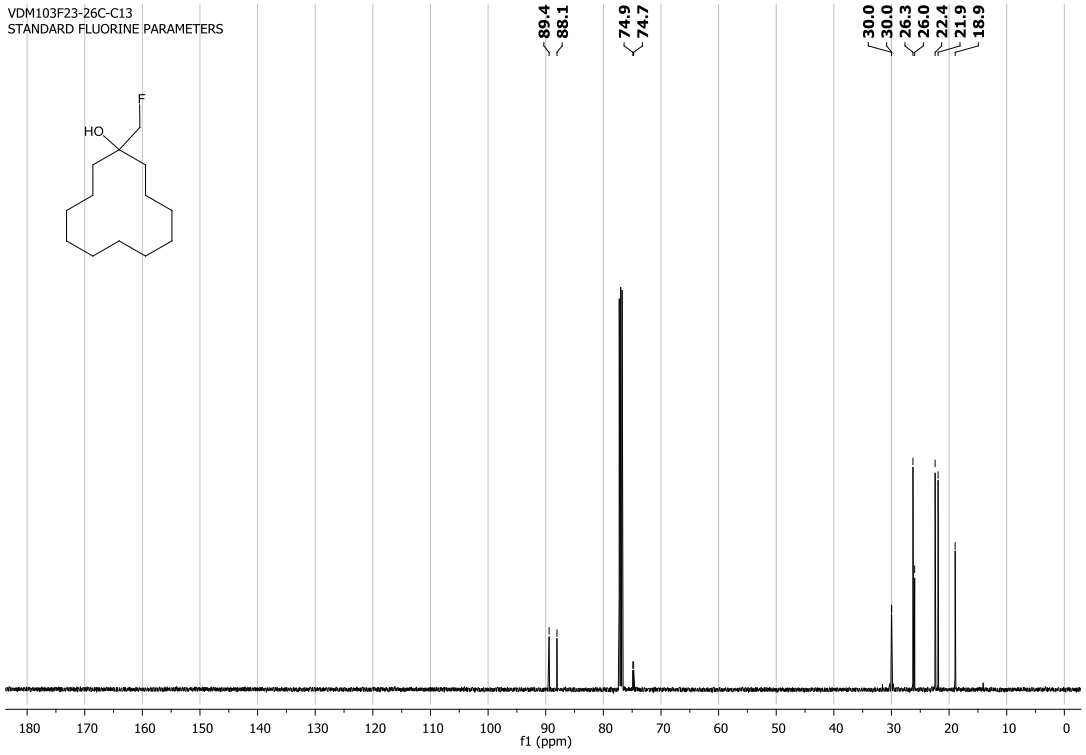
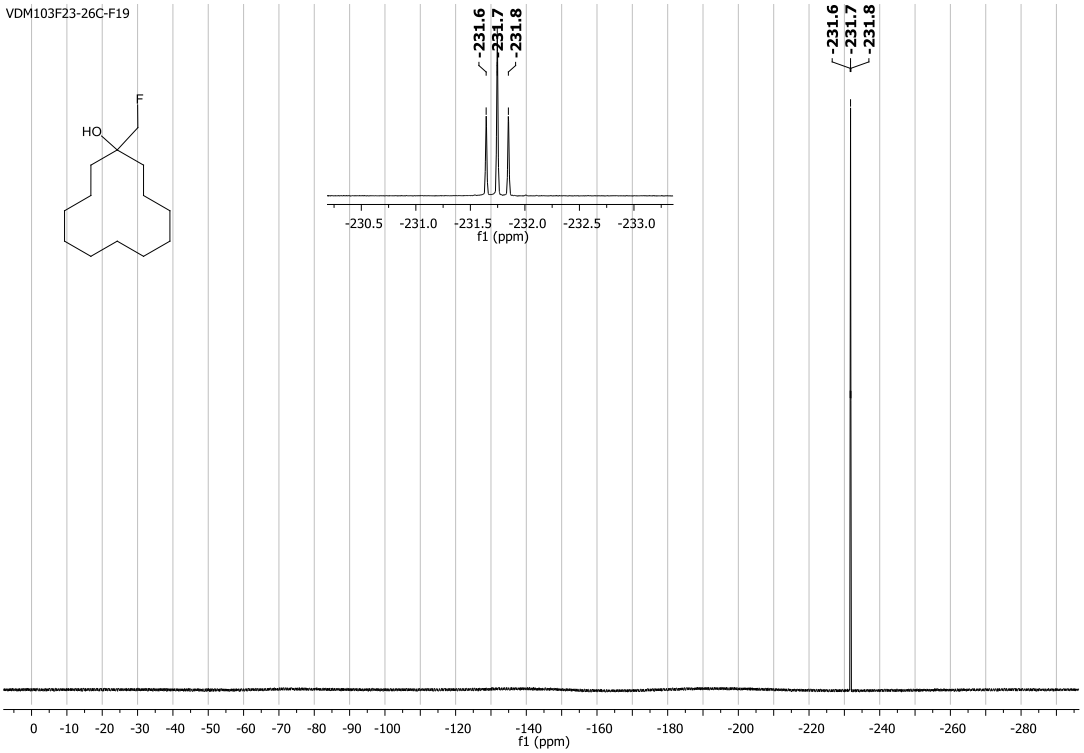
Br
F
7.509
7.492
7.368
7.351
4.499
4.480
4.445
4.426
4.403
4.384
4.350
4.331
2.373
1.576
1.572
1.8
1.8
2.0
0.9
3.0
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

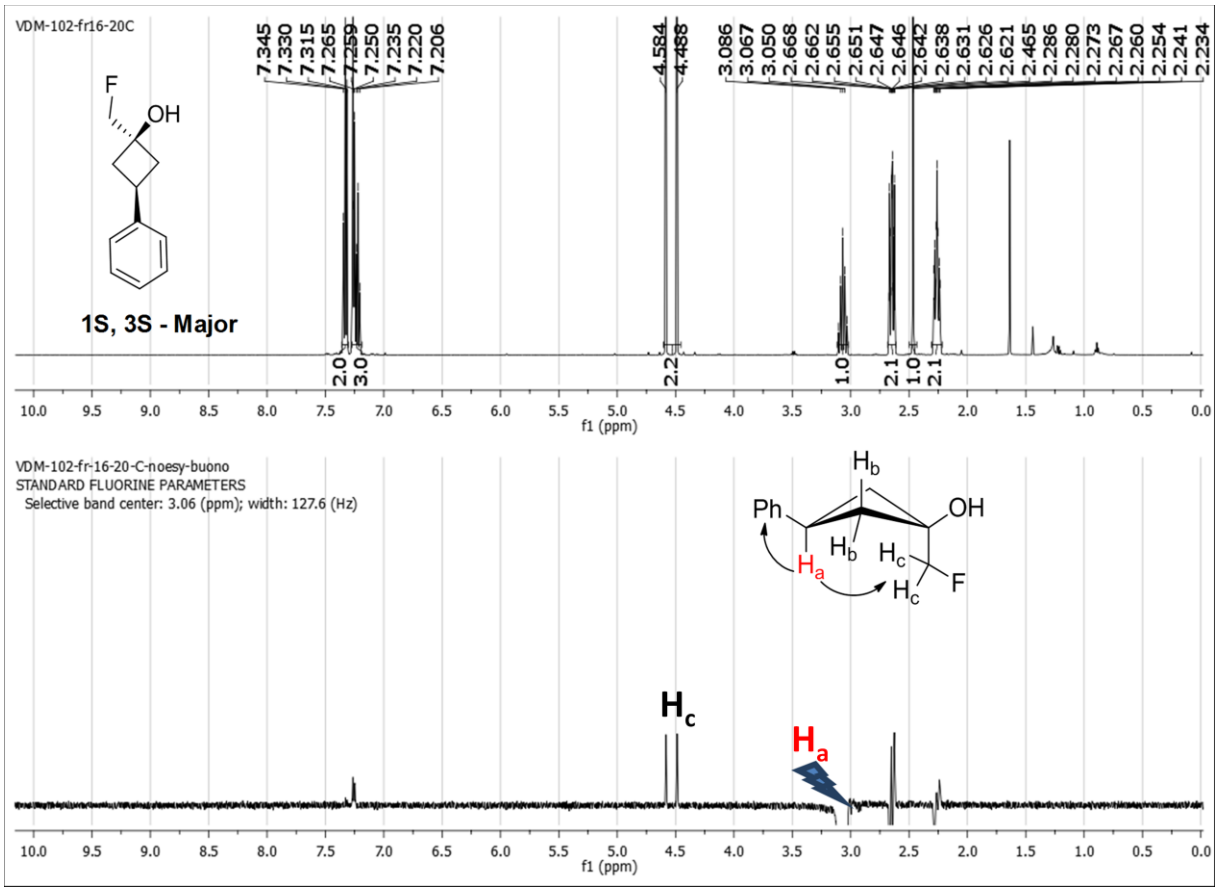

CARBON_01
142.1
142.0
131.5
127.0
121.7
89.9
88.5
73.7
73.5
25.3
OH
Br
F
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

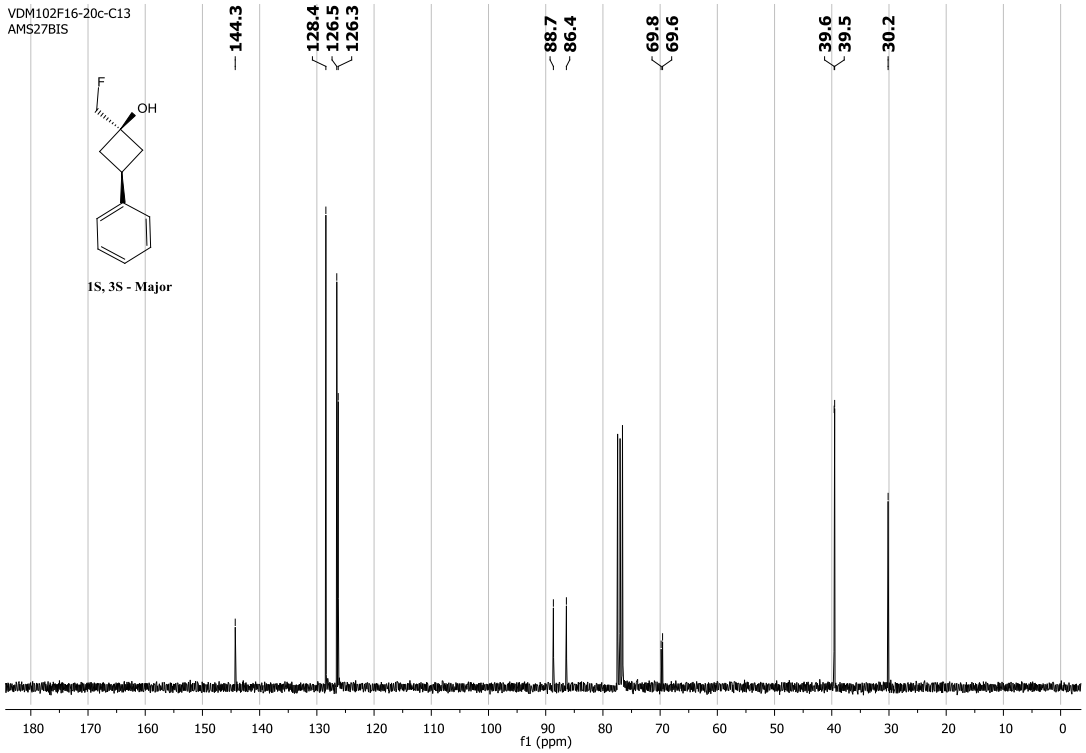

VDM-58-BIS-1-F19 p br acetofenone
STANDARD FLUORINE PARAMETERS
OH
Br
F
-223.1
-223.2
-223.3
-222.7 -223.0 -223.3 -223.6
f1 (ppm)
-223.1
-223.2
-223.3
30 20 10 0 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190 -210 -230 -250 -270 -290
f1 (ppm)

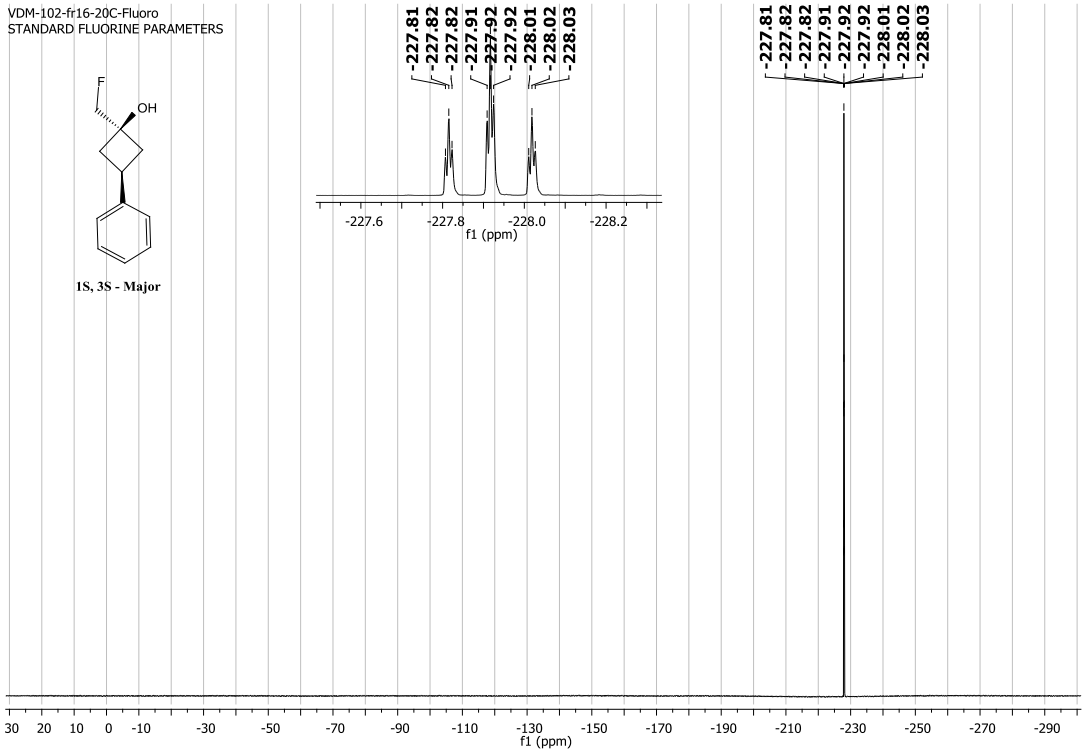

VDM103F23-26C-H1
F
HO
4.270
4.174
1.774
1.591
1.571
1.560
1.547
1.456
1.436
1.414
1.368
1.8
0.9
2.3
20.0
f1 (ppm)

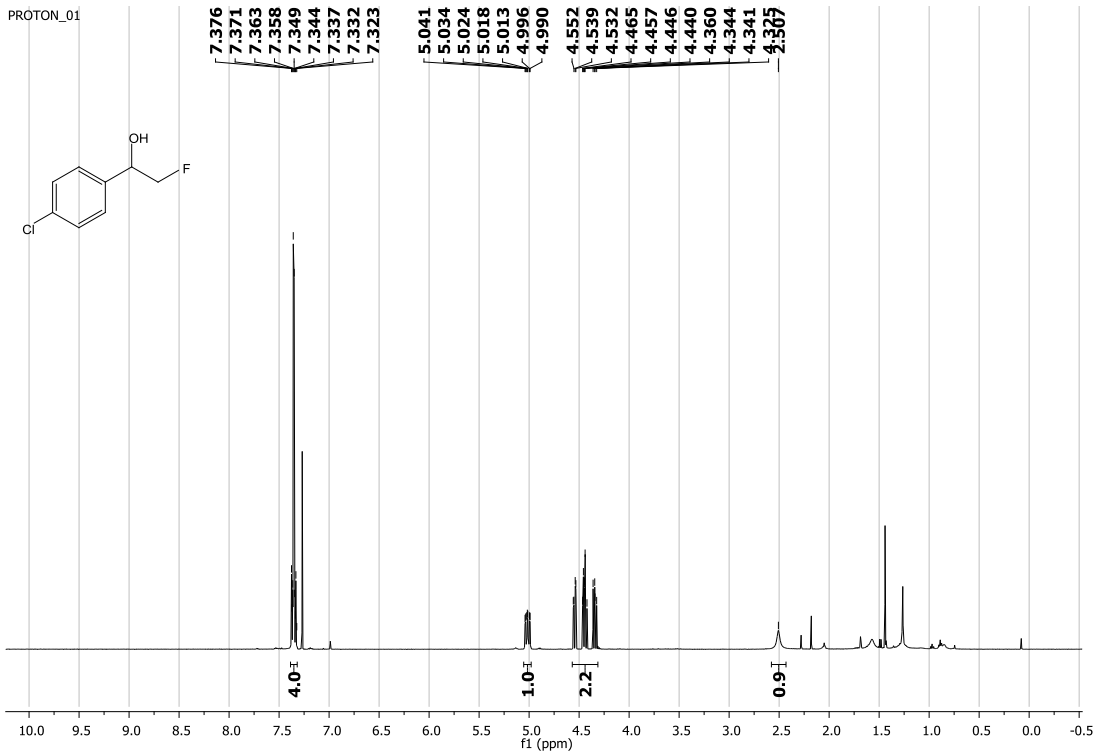

VDM103F23-26C-C13
STANDARD FLUORINE PARAMETERS
F
HO
89.4
88.1
74.9
74.7
30.0
30.0
26.3
26.0
22.4
21.9
18.9
f1 (ppm)


VDM103F23-26C-F19
HO
F
-231.6
-231.7
-231.8
-230.5
-231.0
-231.5
-232.0
-232.5
-233.0
f1 (ppm)
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-120
-140
-160
-180
-200
-220
-240
-260
-280
f1 (ppm)


VDM-102-fr16-20C
F
OH
1S, 3S - Major
7.345
7.330
7.315
7.265
7.259
7.250
7.235
7.220
7.206
4.584
4.488
3.086
3.067
3.050
2.668
2.662
2.655
2.651
2.647
2.646
2.642
2.638
2.631
2.626
2.621
2.465
2.286
2.280
2.273
2.267
2.260
2.254
2.241
2.234
2.0
3.0
2.2
1.0
2.1
1.0
2.1
f1 (ppm)
VDM-102-fr-16-20-C-noesy-buono
STANDARD FLUORINE PARAMETERS
Selective band center: 3.06 (ppm); width: 127.6 (Hz)
Ph
OH
F
Hb
Ha
Hc
Hc
Ha
f1 (ppm)


VDM102F16-20c-C13
AMS27BIS
144.3
128.4
126.5
126.3
88.7
86.4
69.8
69.6
39.6
39.5
30.2
F
OH
1S, 3S - Major
f1 (ppm)


VDM-102-fr16-20C-Fluoro
STANDARD FLUORINE PARAMETERS
-227.81
-227.82
-227.82
-227.91
-227.92
-227.92
-228.01
-228.02
-228.03
F
OH
1S, 3S - Major
f1 (ppm)


PROTON_01
7.376
7.371
7.363
7.358
7.349
7.344
7.337
7.332
7.323
5.041
5.034
5.024
5.018
5.013
4.996
4.990
4.552
4.539
4.532
4.465
4.457
4.446
4.440
4.360
4.344
4.341
4.325
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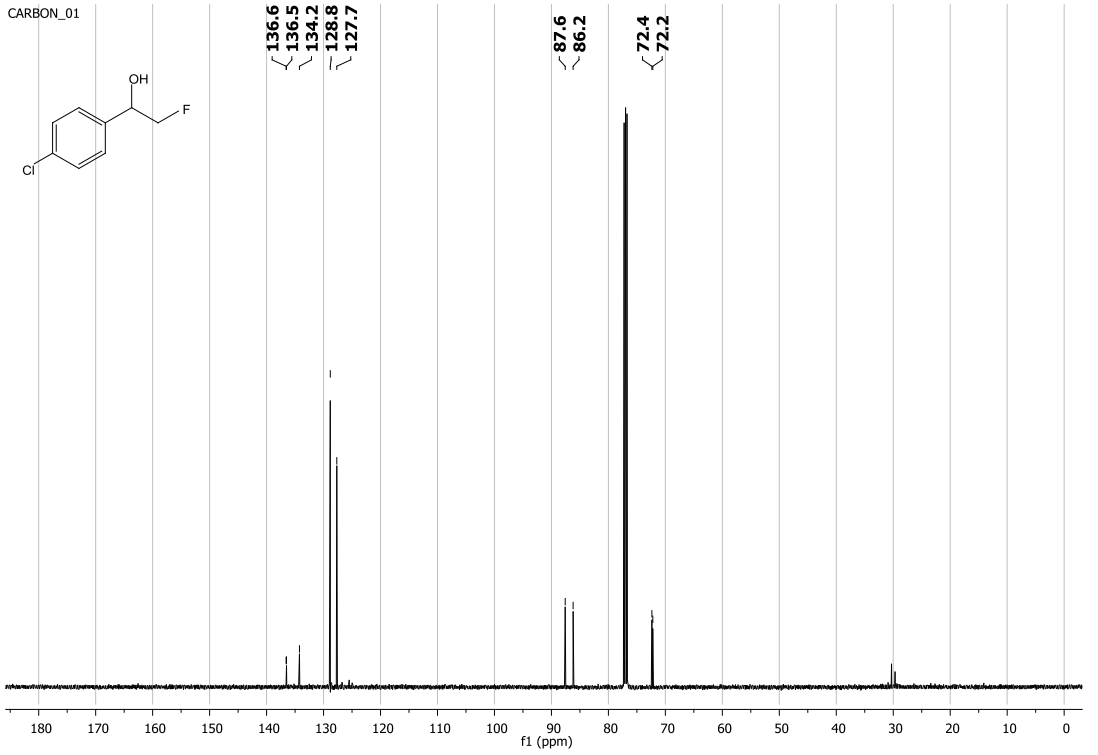
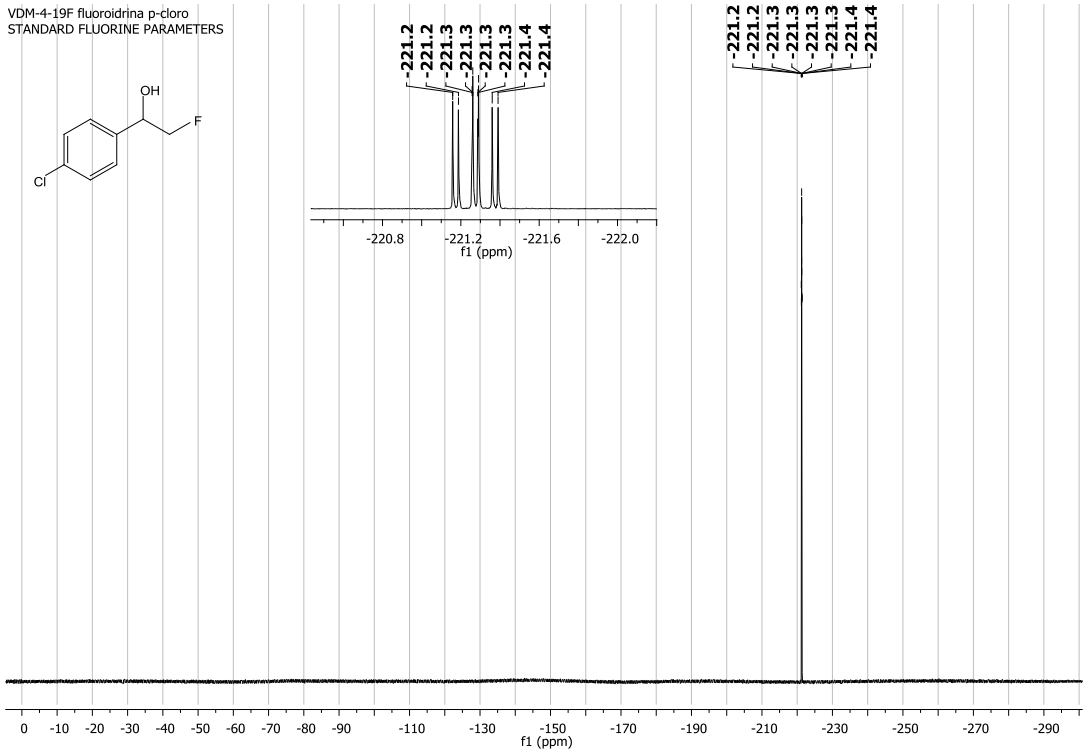
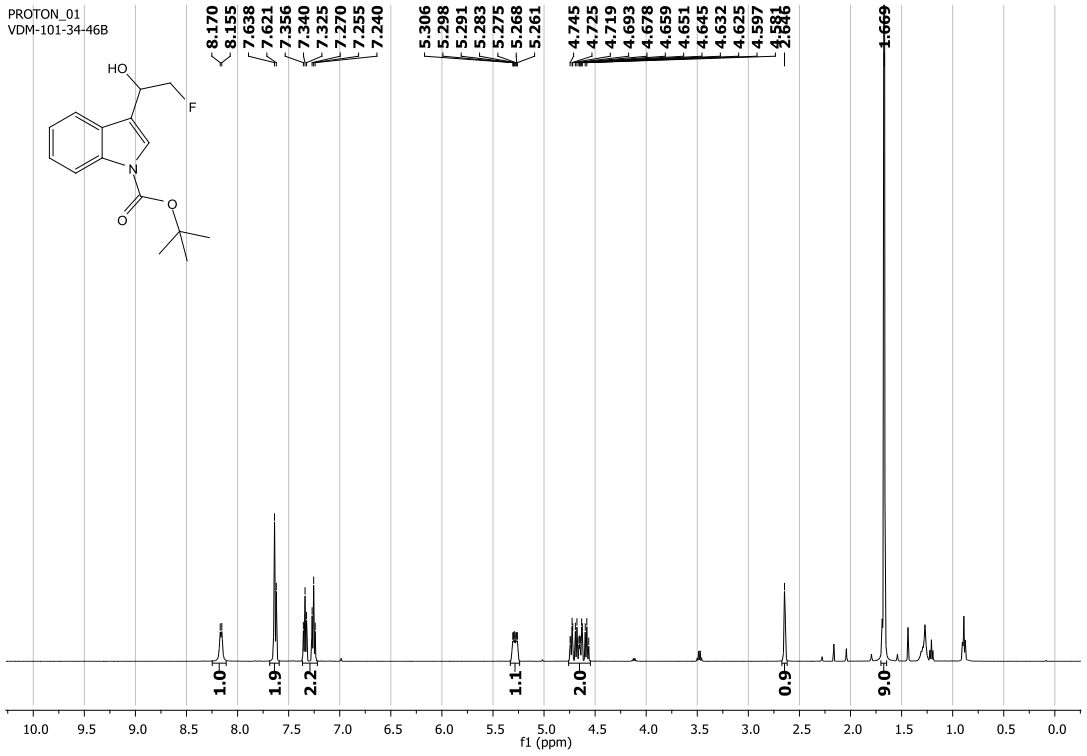
OH
F
Cl
4.0
1.0
2.2
0.9
f1 (ppm)


CARBON_01
136.6
136.5
134.2
128.8
127.7
87.6
86.2
72.4
72.2
OH
F
Cl
f1 (ppm)


VDM-4-19F fluoroidrina p-cloro
STANDARD FLUORINE PARAMETERS
OH
F
Cl
-221.2
-221.2
-221.3
-221.3
-221.3
-221.3
-221.4
-221.4
-220.8
-221.2
-221.6
-222.0
f1 (ppm)
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -110 -130 -150 -170 -190 -210 -230 -250 -270 -290
f1 (ppm)


PROTON_01
VDM-101-34-46B
HO
F
N
O
O
8.170
8.155
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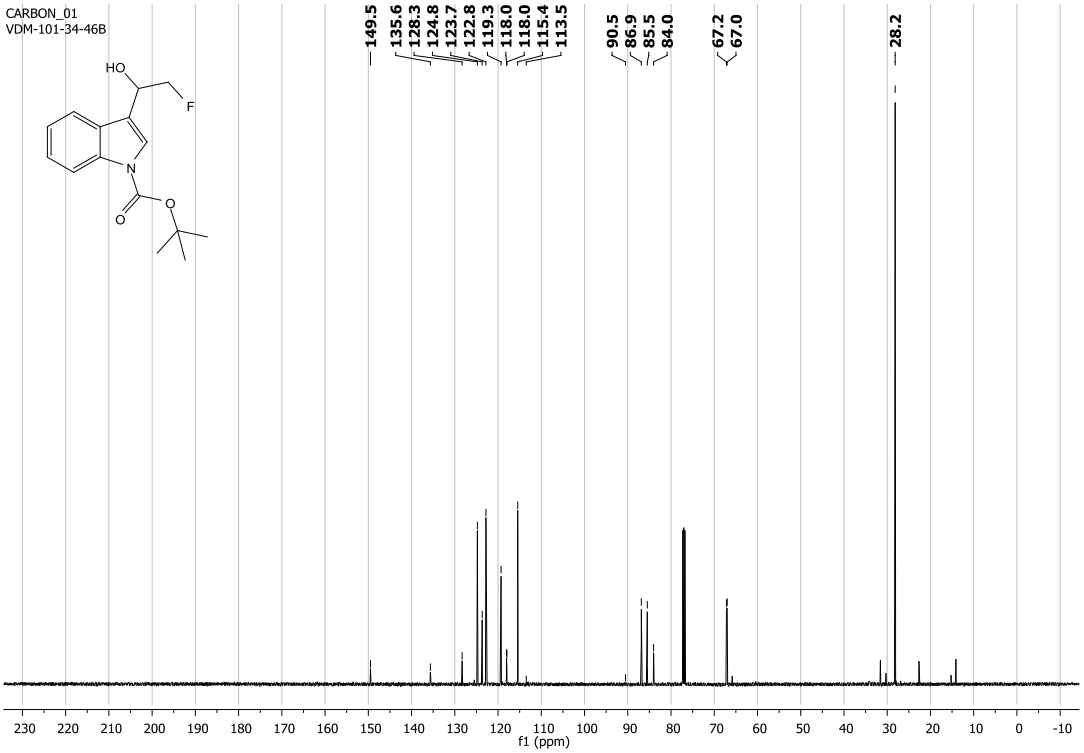
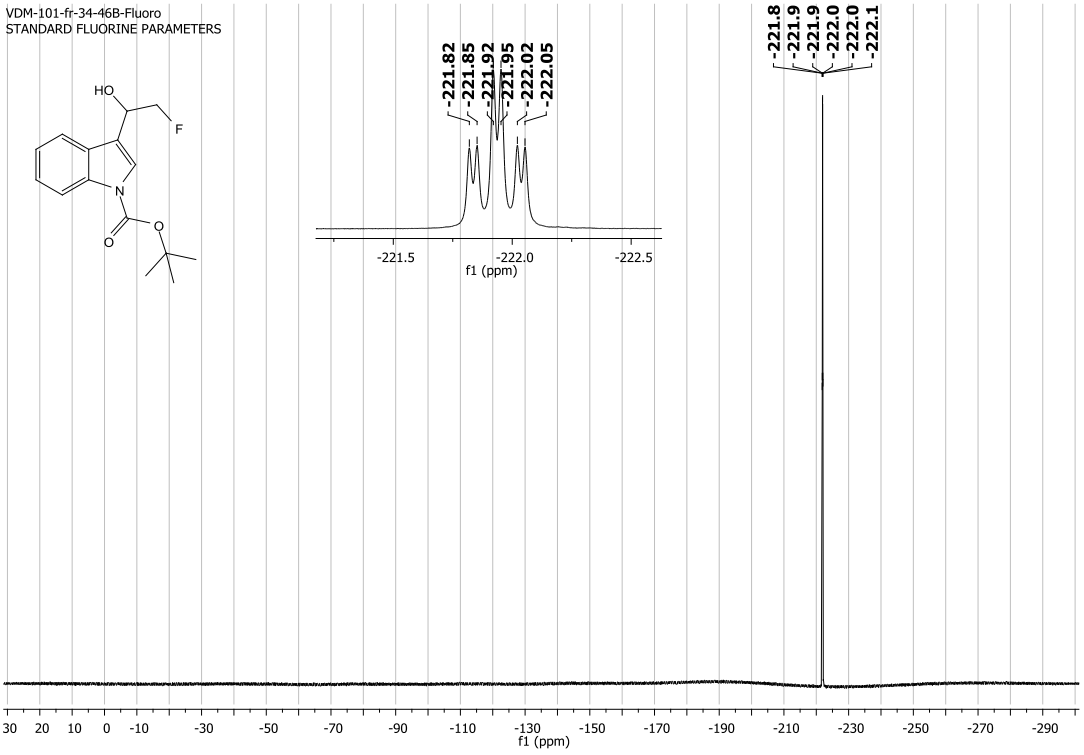
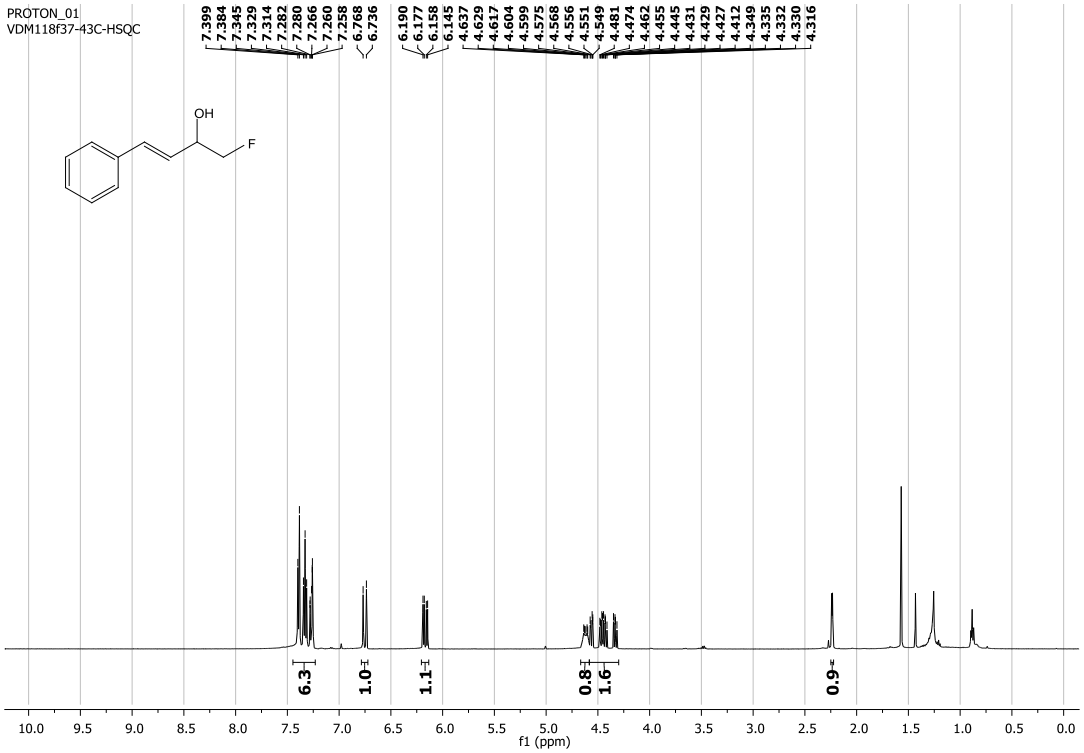
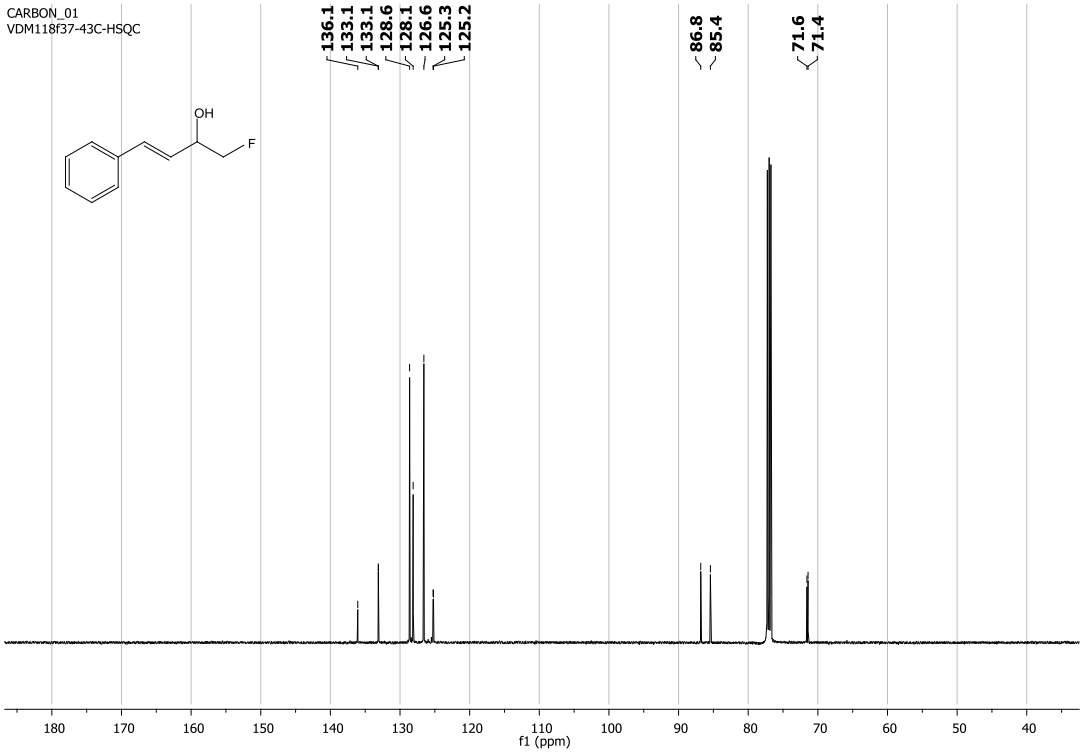
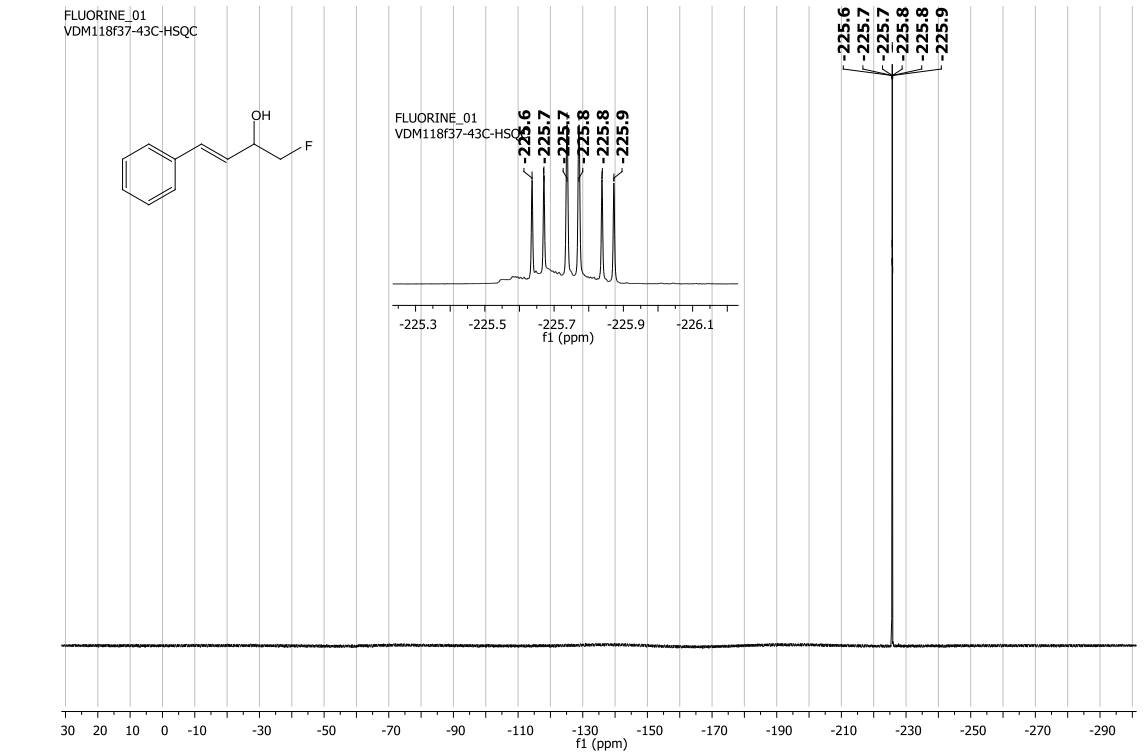
7.621
7.356
7.340
7.325
7.270
7.255
7.240
5.306
5.298
5.291
5.283
5.275
5.268
5.261
4.745
4.725
4.719
4.693
4.678
4.659
4.651
4.645
4.632
4.625
4.597
1.669
1.0
1.9
2.2
1.1
2.0
0.9
9.0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

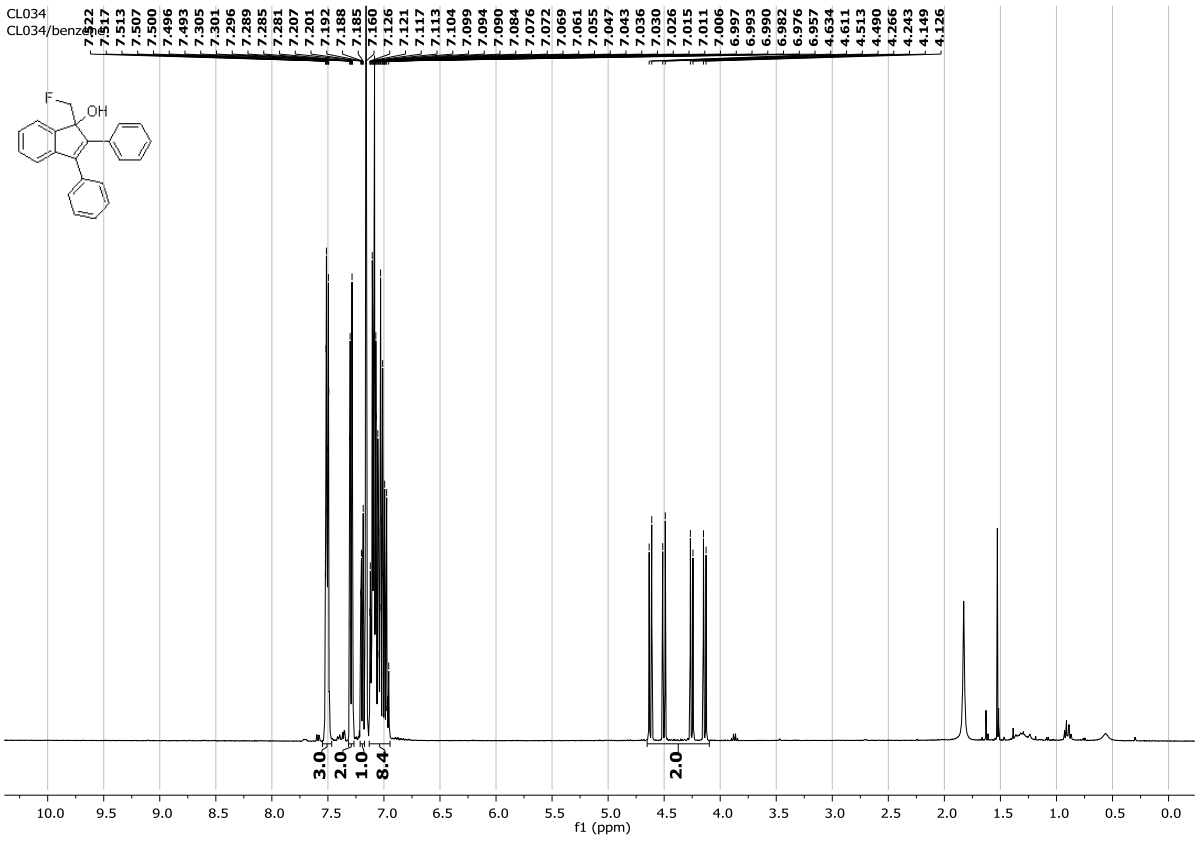

CARBON_01
VDM-101-34-46B
HO
F
N
O
O
149.5
135.6
128.3
124.8
123.7
122.8
119.3
118.0
118.0
115.4
113.5
90.5
86.9
85.5
84.0
67.2
67.0
28.2
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

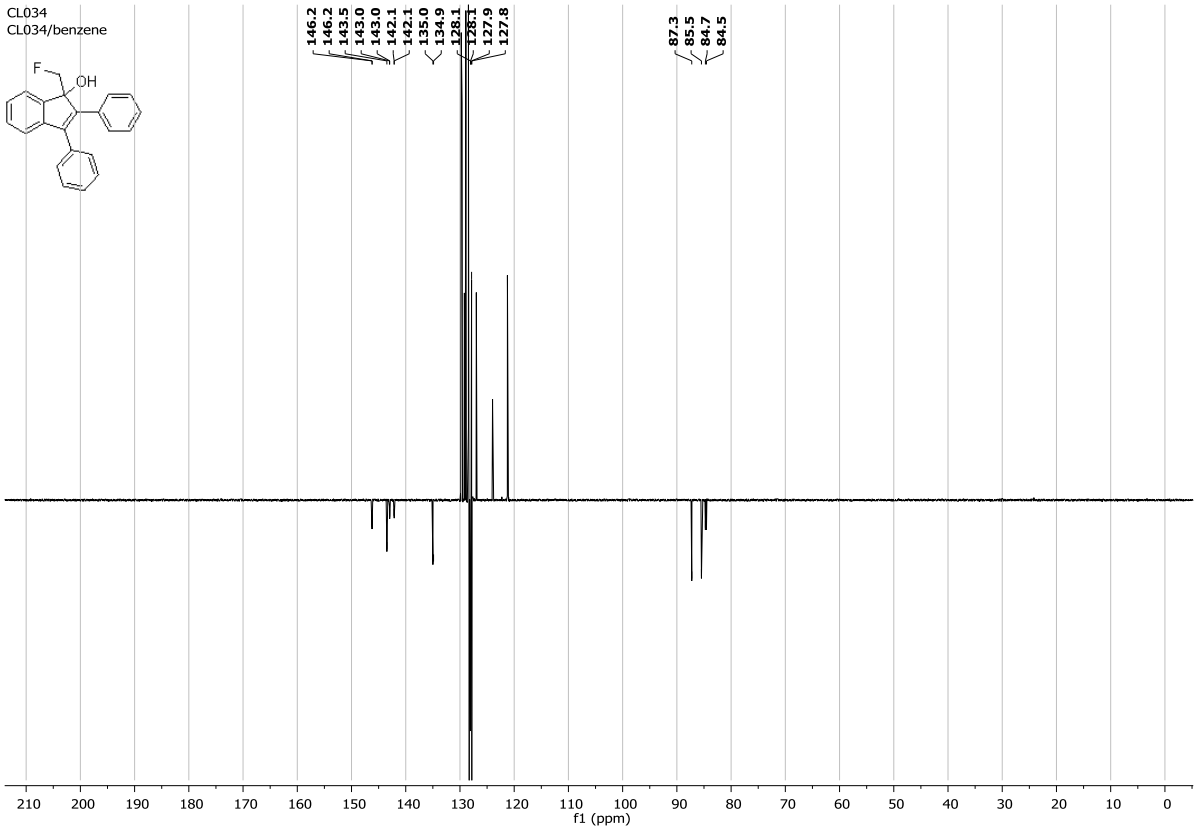

VDM-101-fr-34-46B-Fluoro
STANDARD FLUORINE PARAMETERS
HO
F
N
O
O
-221.82
-221.85
-221.92
-221.95
-222.02
-222.05
-221.5
-222.0
-222.5
f1 (ppm)
-221.8
-221.9
-221.9
-222.0
-222.0
-222.1
30 20 10 0 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190 -210 -230 -250 -270 -290
f1 (ppm)

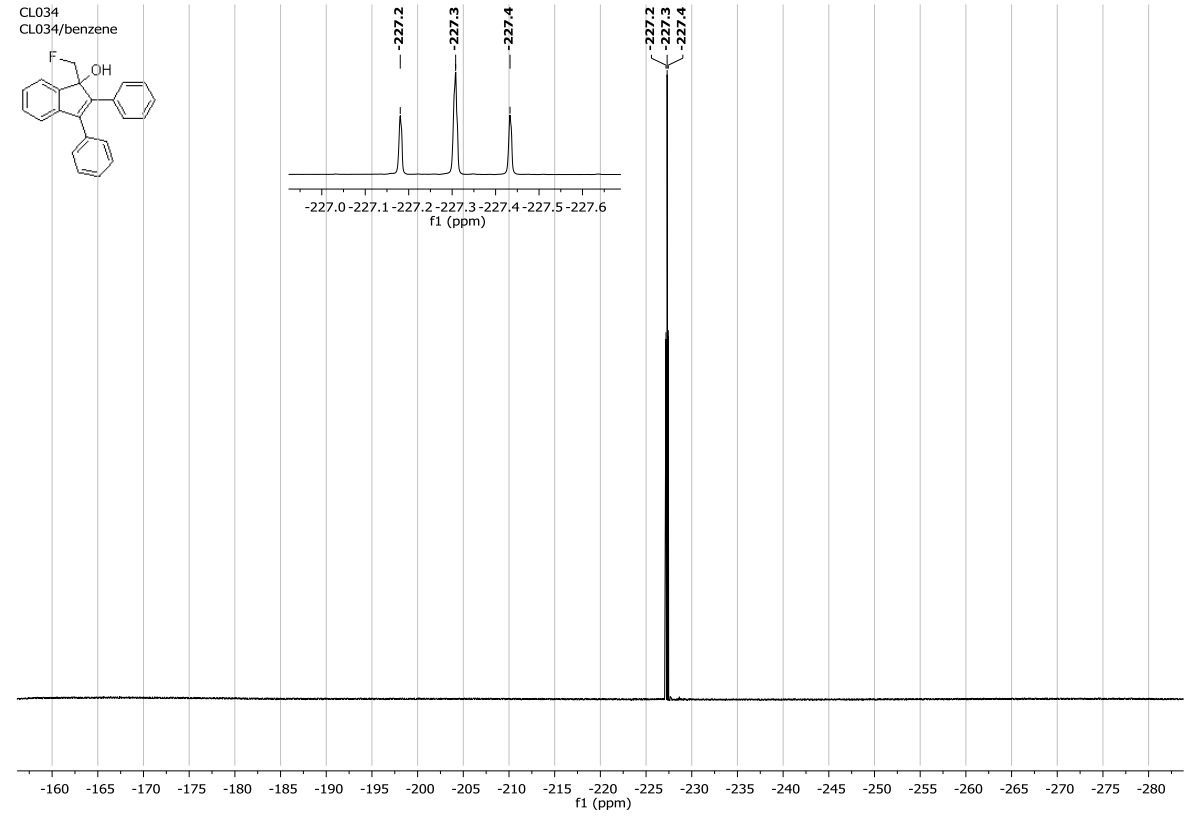

PROTON_01
VDM118f37-43C-HSQC
7.399
7.384
7.345
7.329
7.314
7.282
7.280
7.266
7.260
7.258
6.768
6.736
6.190
6.177
6.158
6.145
4.637
4.629
4.617
4.604
4.599
4.575
4.568
4.556
4.551
4.549
4.481
4.474
4.462
4.455
4.445
4.431
4.429
4.427
4.412
4.349
4.335
4.332
4.330
4.316
OH
F
6.3
1.0
1.1
0.8
1.6
0.9
f1 (ppm)

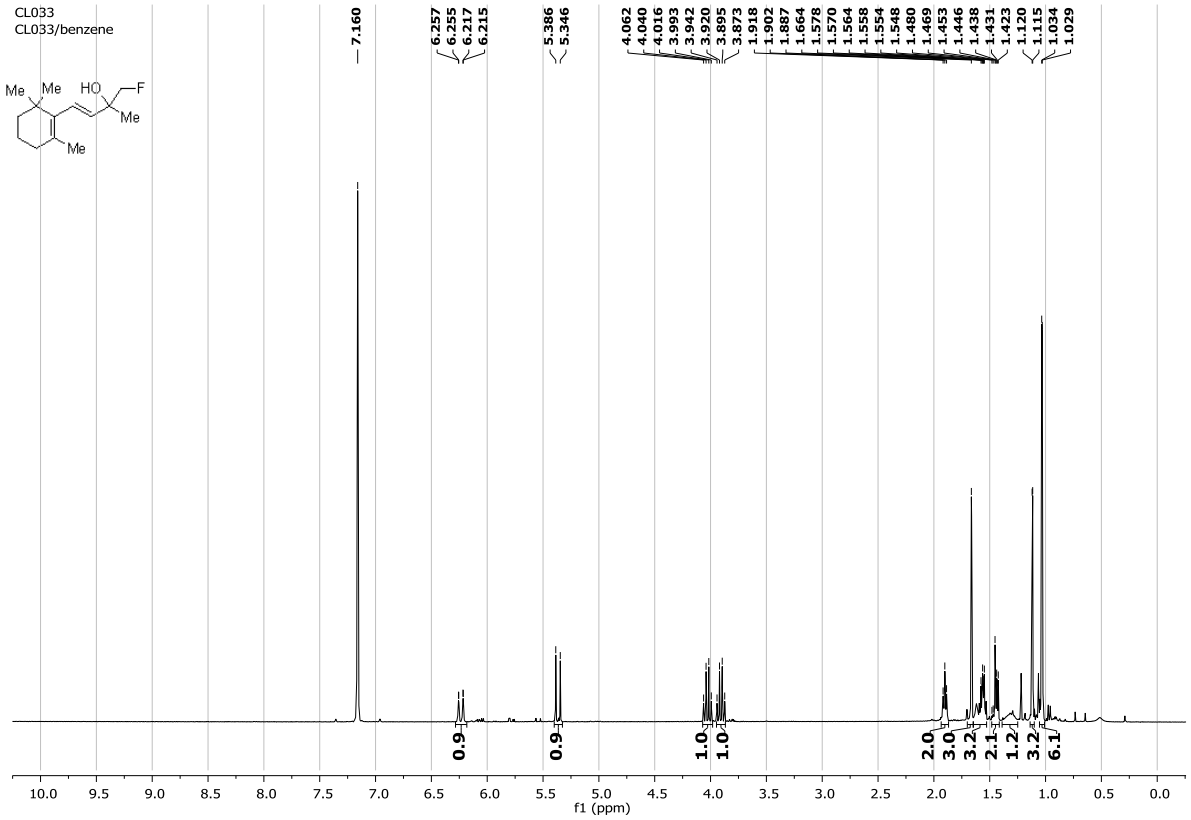

CARBON_01
VDM118f37-43C-HSQC
136.1
133.1
133.1
128.6
128.1
126.6
125.3
125.2
86.8
85.4
71.6
71.4
OH
F
f1 (ppm)

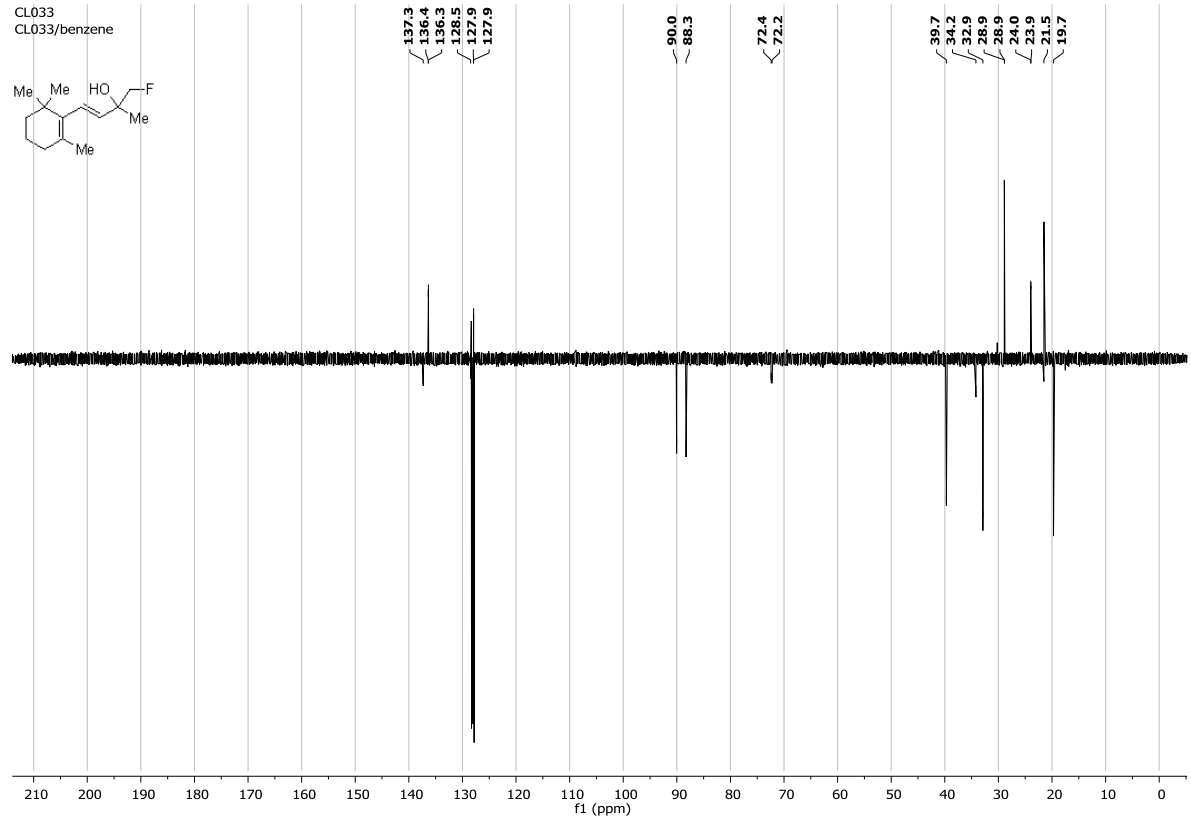

FLUORINE_01
VDM118f37-43C-HSQC
OH
F
-225.6
-225.7
-225.7
-225.8
-225.8
-225.9
-225.3
-225.5
-225.7
-225.9
-226.1
f1 (ppm)
30 20 10 0 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190 -210 -230 -250 -270 -290
f1 (ppm)

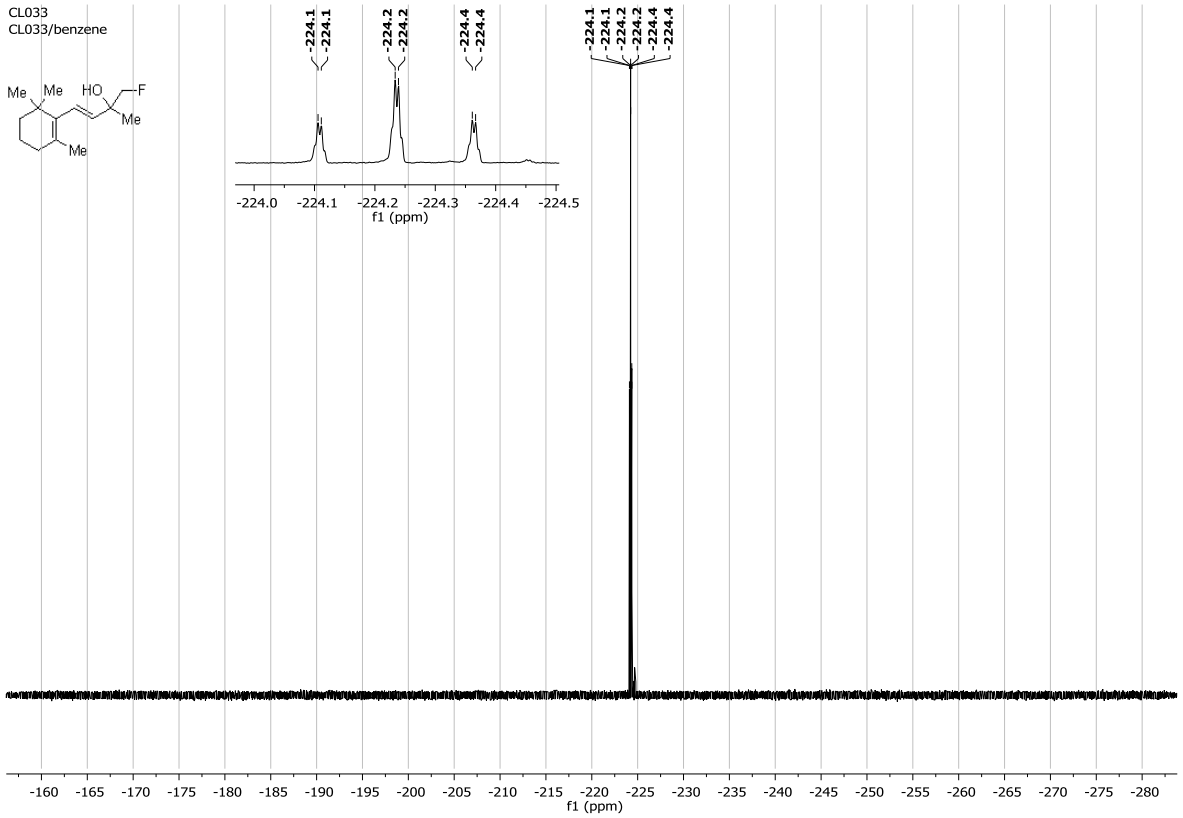

CL034
CL034/benzene
F
OH
3.0
2.0
1.0
8.4
2.0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

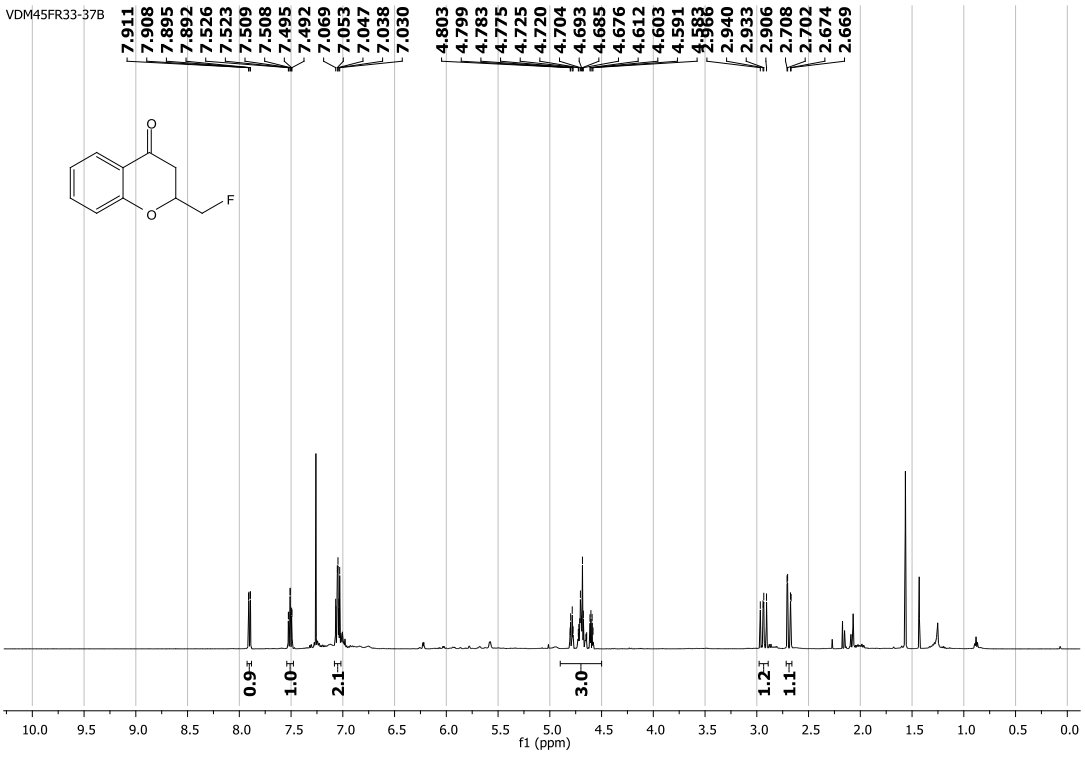

CL034
CL034/benzene
F
OH
146.2
146.2
143.5
143.0
143.0
142.1
142.1
135.0
134.9
128.1
128.1
127.9
127.8
87.3
85.5
84.7
84.5
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

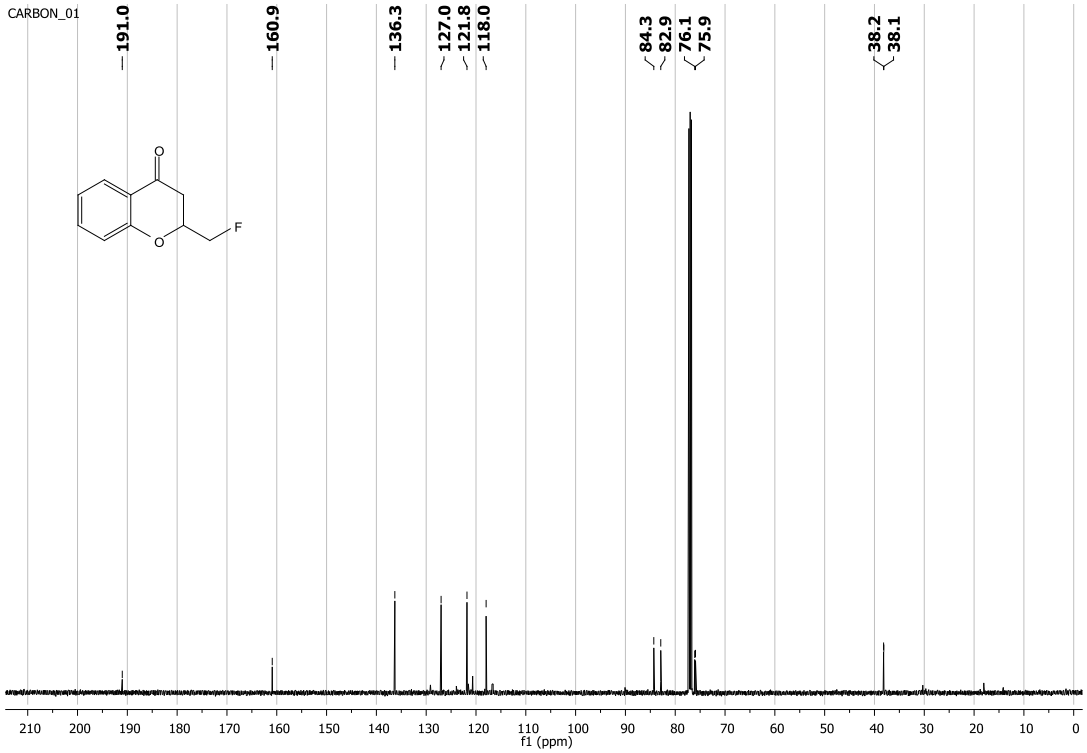

CL034
CL034/benzene
F
OH
-227.2
-227.3
-227.4
-227.0 -227.1 -227.2 -227.3 -227.4 -227.5 -227.6
f1 (ppm)
-227.2
-227.3
-227.4
-160 -165 -170 -175 -180 -185 -190 -195 -200 -205 -210 -215 -220 -225 -230 -235 -240 -245 -250 -255 -260 -265 -270 -275 -280
f1 (ppm)

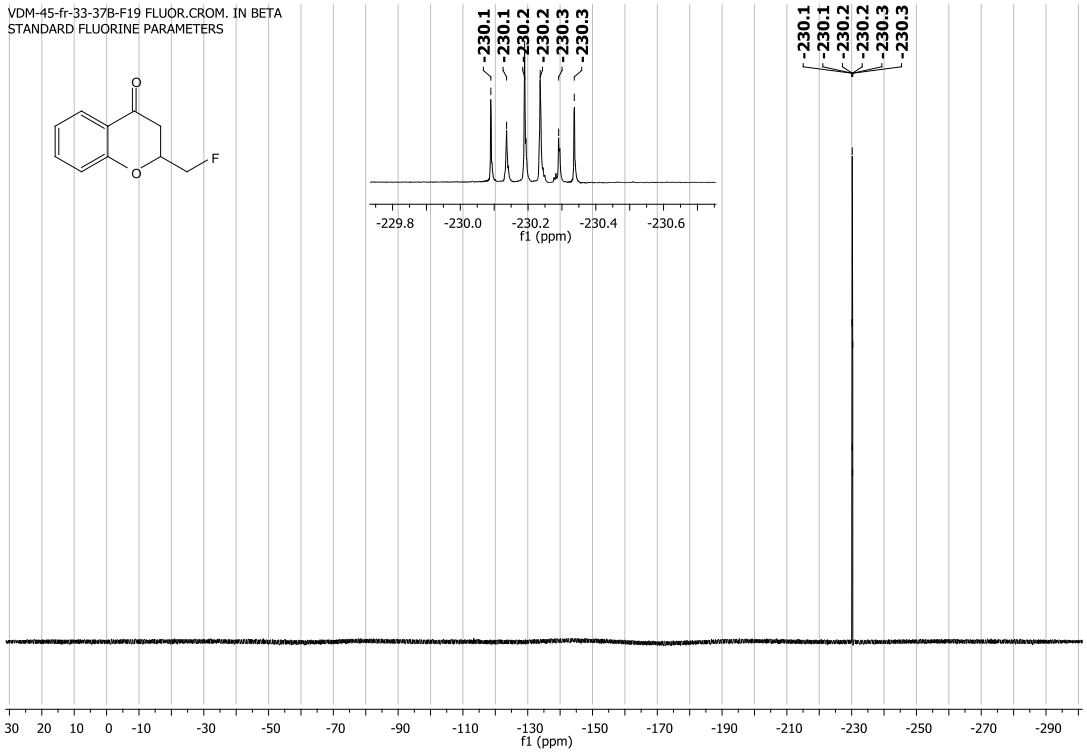

CL033
CL033/benzene
Me
Me
HO
F
Me
Me
7.160
6.257
6.255
6.217
6.215
5.386
5.346
4.062
4.040
4.016
3.993
3.942
3.920
3.895
3.873
1.918
1.902
1.887
1.664
1.578
1.570
1.564
1.558
1.554
1.548
1.480
1.469
1.453
1.446
1.438
1.431
1.423
1.120
1.115
1.034
1.029
0.9
0.9
1.0
1.0
2.0
3.0
3.2
2.1
1.2
3.2
6.1
f1 (ppm)

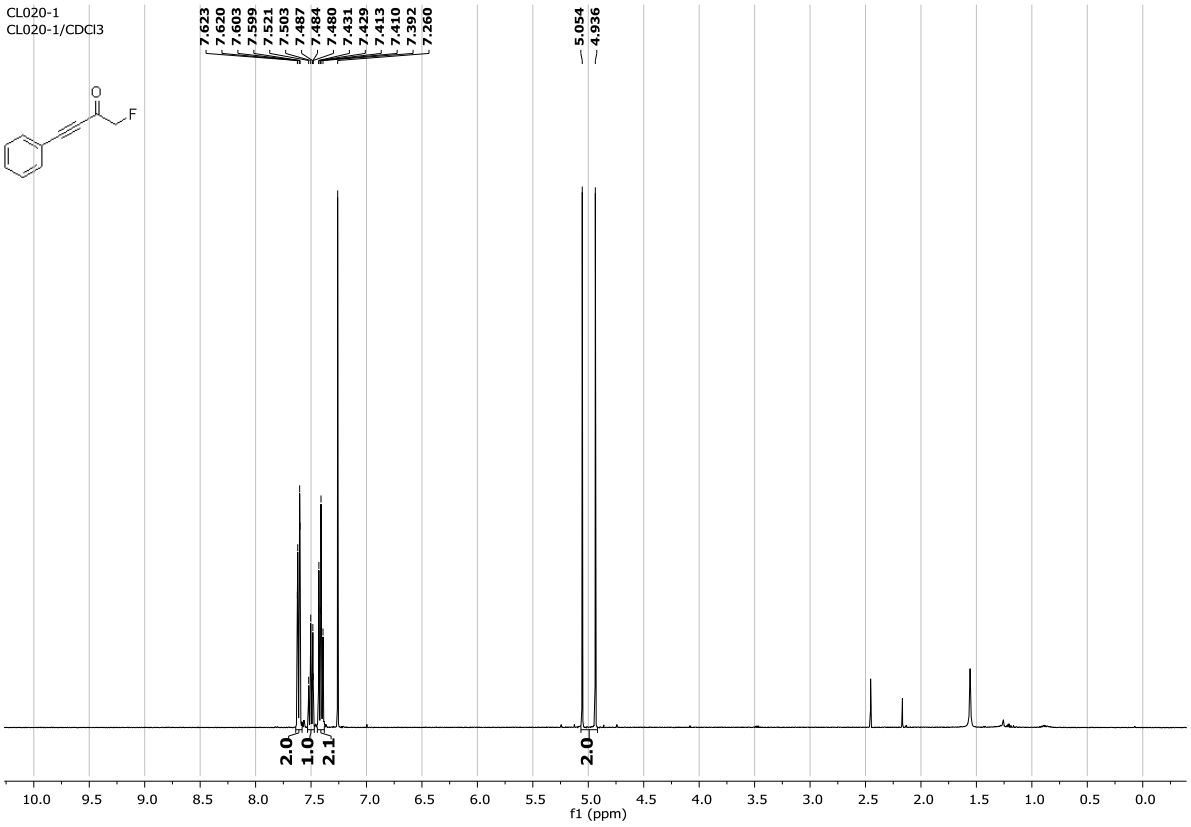

CL033
CL033/benzene
Me
Me
HO
F
Me
Me
137.3
136.4
136.3
128.5
127.9
127.9
90.0
88.3
72.4
72.2
39.7
34.2
32.9
28.9
28.9
24.0
23.9
21.5
19.7
f1 (ppm)

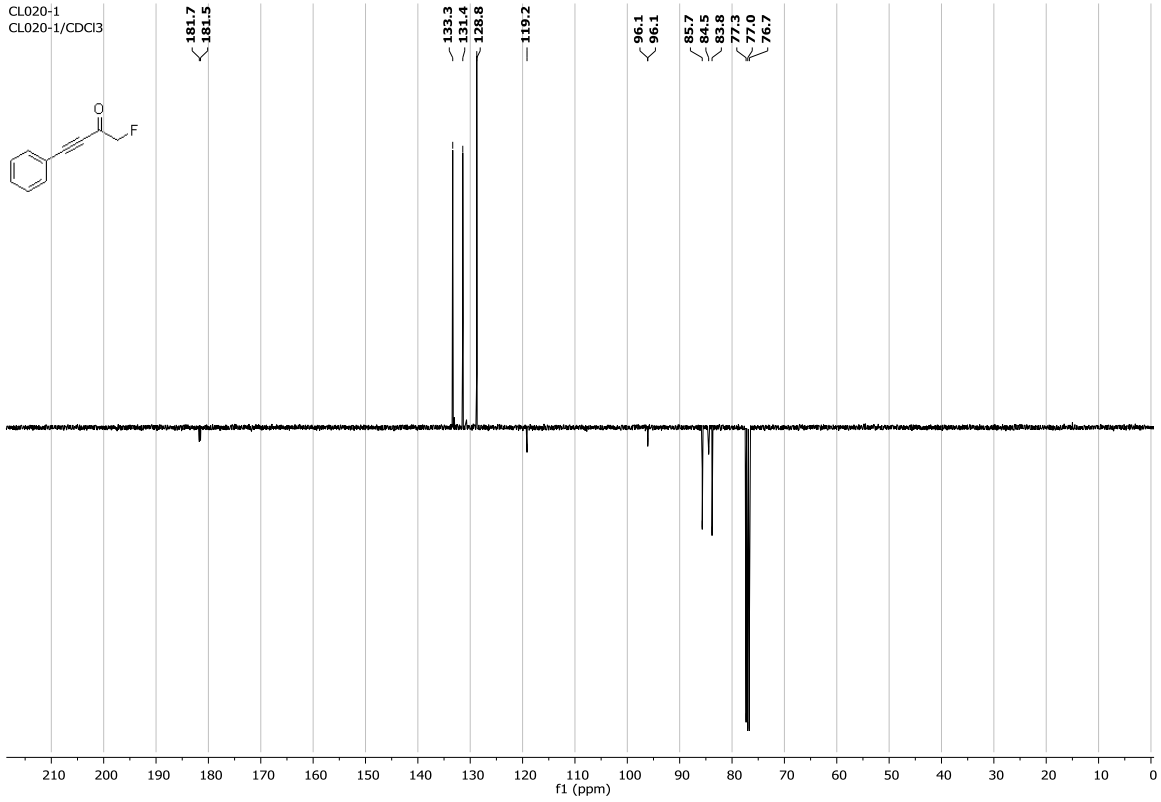

CL033
CL033/benzene
Me
Me
HO
F
Me
Me
-224.1
-224.1
-224.2
-224.2
-224.4
-224.4
-224.0
-224.1
-224.2
-224.3
-224.4
-224.5
f1 (ppm)
-160
-165
-170
-175
-180
-185
-190
-195
-200
-205
-210
-215
-220
-225
-230
-235
-240
-245
-250
-255
-260
-265
-270
-275
-280
f1 (ppm)

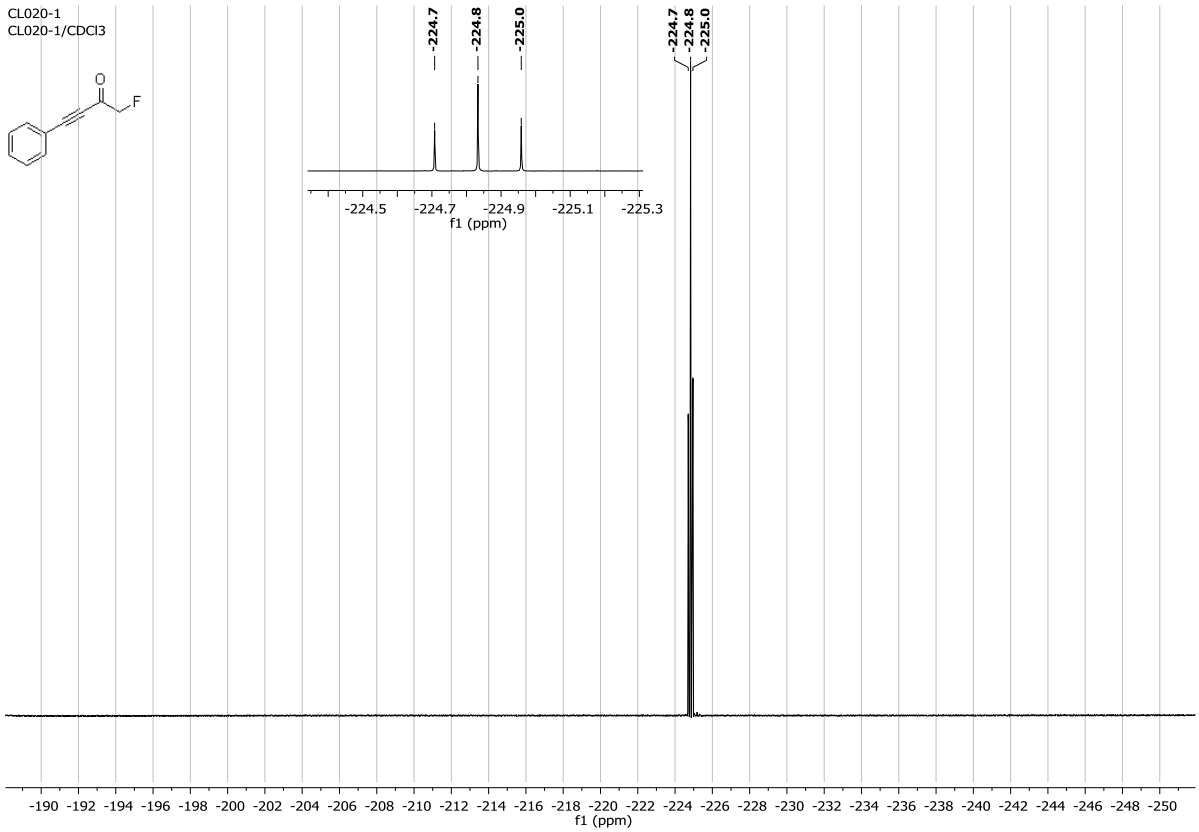

VDM45FR33-37B
7.911
7.908
7.895
7.892
7.526
7.523
7.509
7.508
7.495
7.492
7.069
7.053
7.047
7.038
7.030
4.803
4.799
4.783
4.775
4.725
4.720
4.704
4.693
4.685
4.676
4.612
4.603
4.591
2.940
2.933
2.906
2.708
2.702
2.674
2.669
O
O
F
0.9
1.0
2.1
3.0
1.2
1.1
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

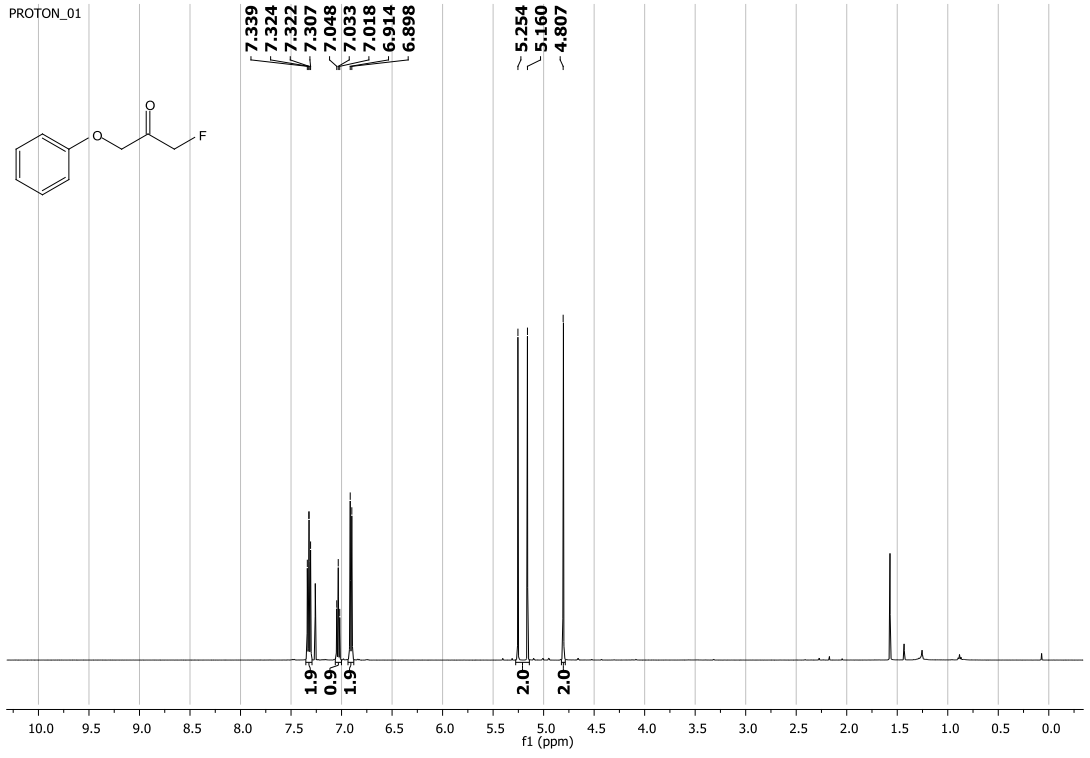

CARBON_01
191.0
160.9
136.3
127.0
121.8
118.0
84.3
82.9
76.1
75.9
38.2
38.1
O
O
F
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

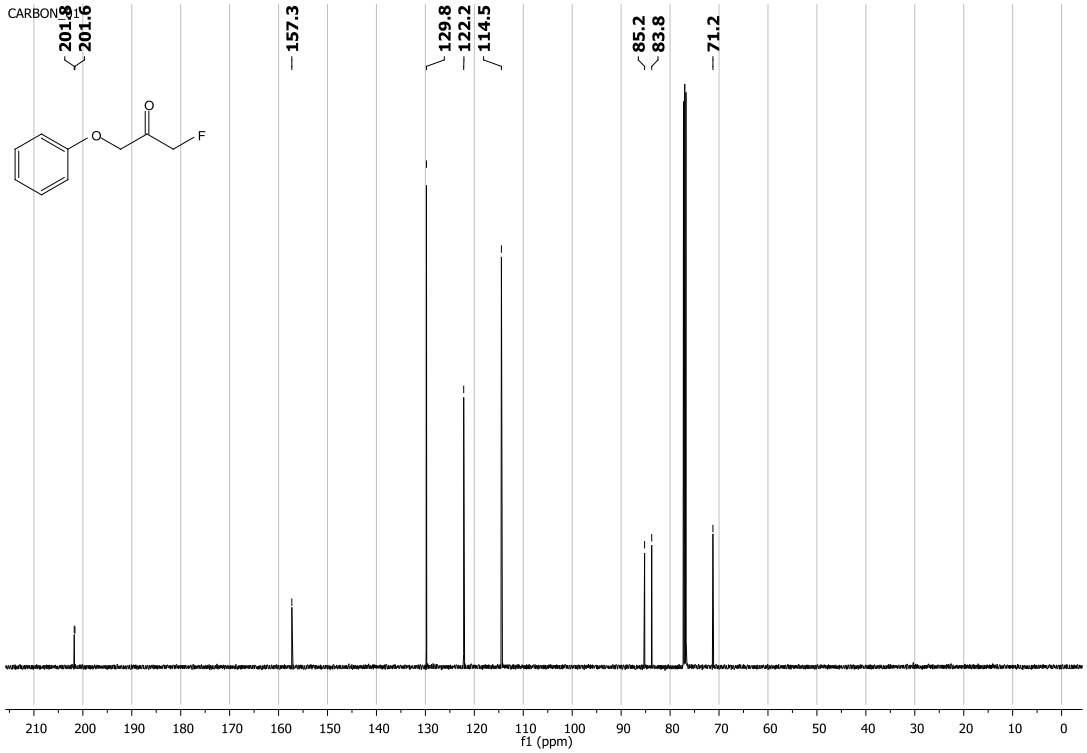

VDM-45-fr-33-37B-F19 FLUOR.CROM. IN BETA
STANDARD FLUORINE PARAMETERS
-230.1
-230.1
-230.2
-230.2
-230.3
-230.3
-230.1
-230.1
-230.2
-230.2
-230.3
-230.3
O
O
F
-229.8 -230.0 -230.2 -230.4 -230.6
f1 (ppm)
30 20 10 0 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190 -210 -230 -250 -270 -290
f1 (ppm)

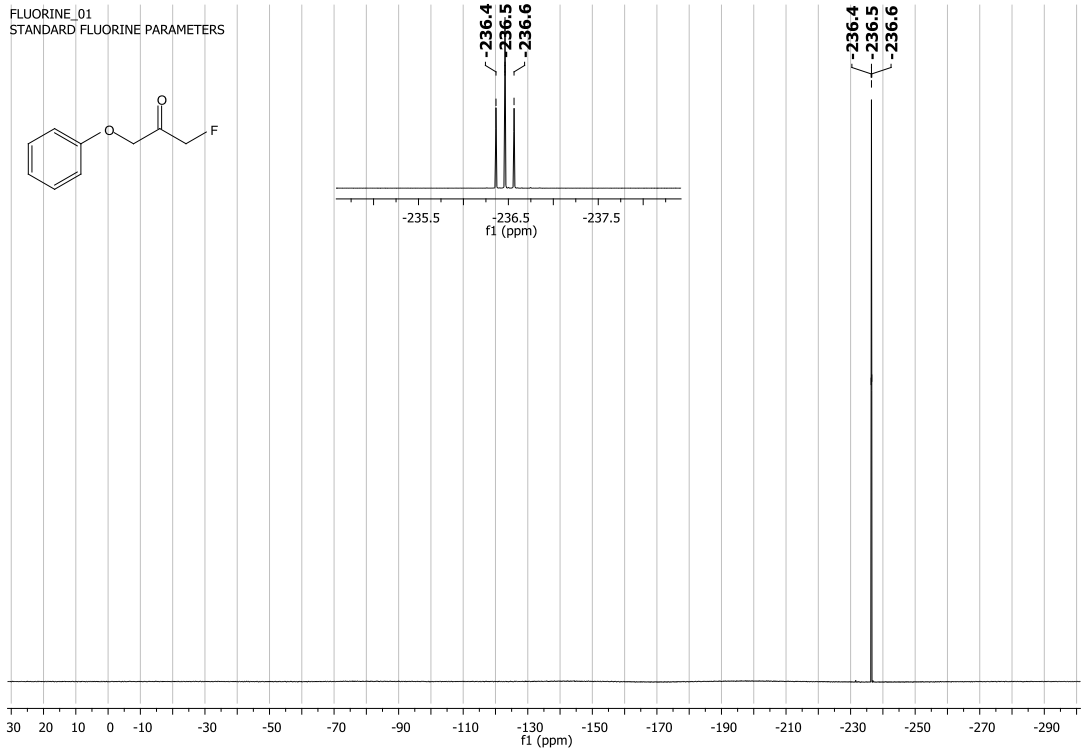

CL020-1
CL020-1/CDCl3
7.623
7.620
7.603
7.599
7.521
7.503
7.487
7.484
7.480
7.431
7.429
7.413
7.410
7.392
7.260
5.054
4.936
2.0
1.0
2.1
2.0
O
F
f1 (ppm)

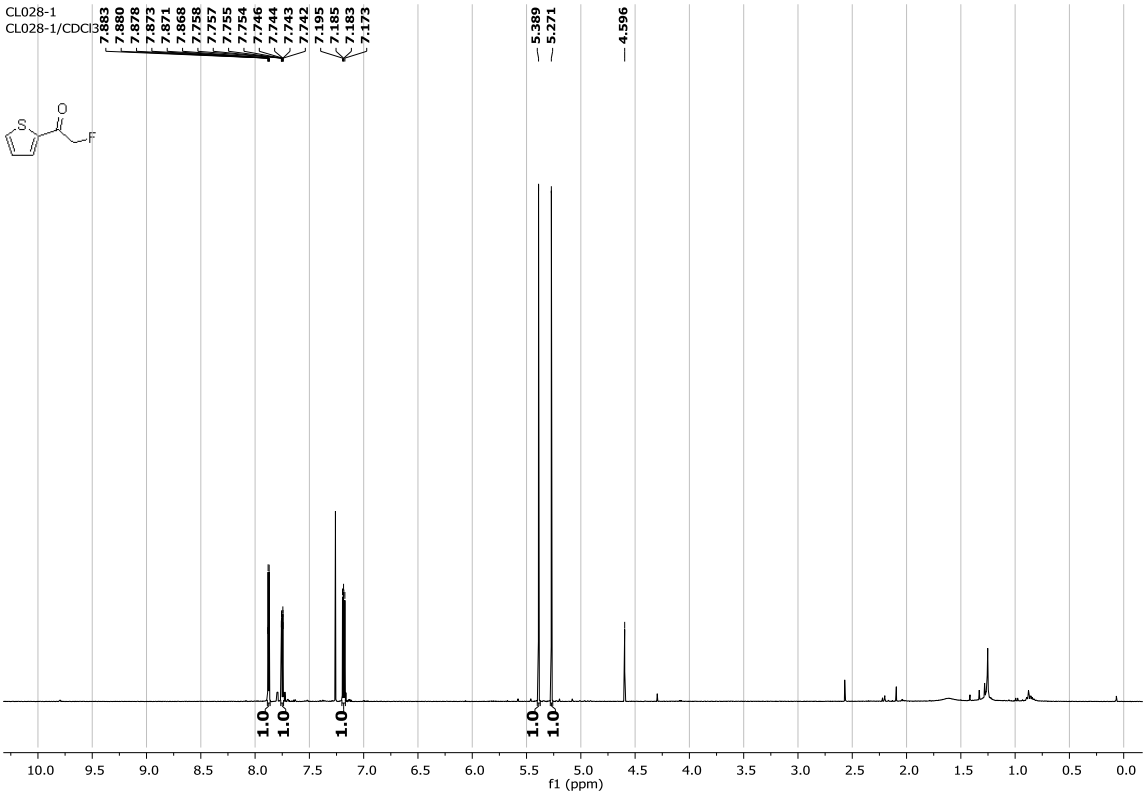

CL020-1
CL020-1/CDCl3
181.7
181.5
133.3
131.4
128.8
119.2
96.1
96.1
85.7
84.5
83.8
77.3
77.0
76.7
O
F
f1 (ppm)

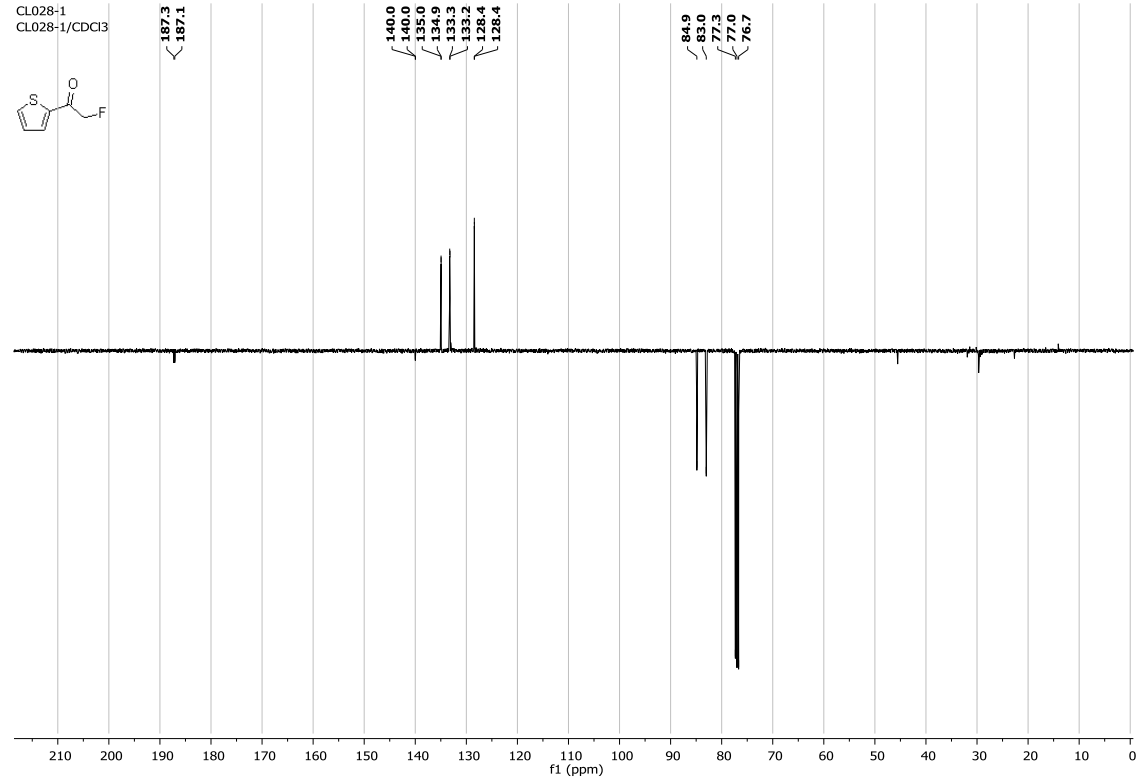

CL020-1
CL020-1/CDCl3
O
F
-224.7
-224.8
-225.0
-224.5
-224.7
-224.9
-225.1
-225.3
f1 (ppm)
-190 -192 -194 -196 -198 -200 -202 -204 -206 -208 -210 -212 -214 -216 -218 -220 -222 -224 -226 -228 -230 -232 -234 -236 -238 -240 -242 -244 -246 -248 -250
f1 (ppm)

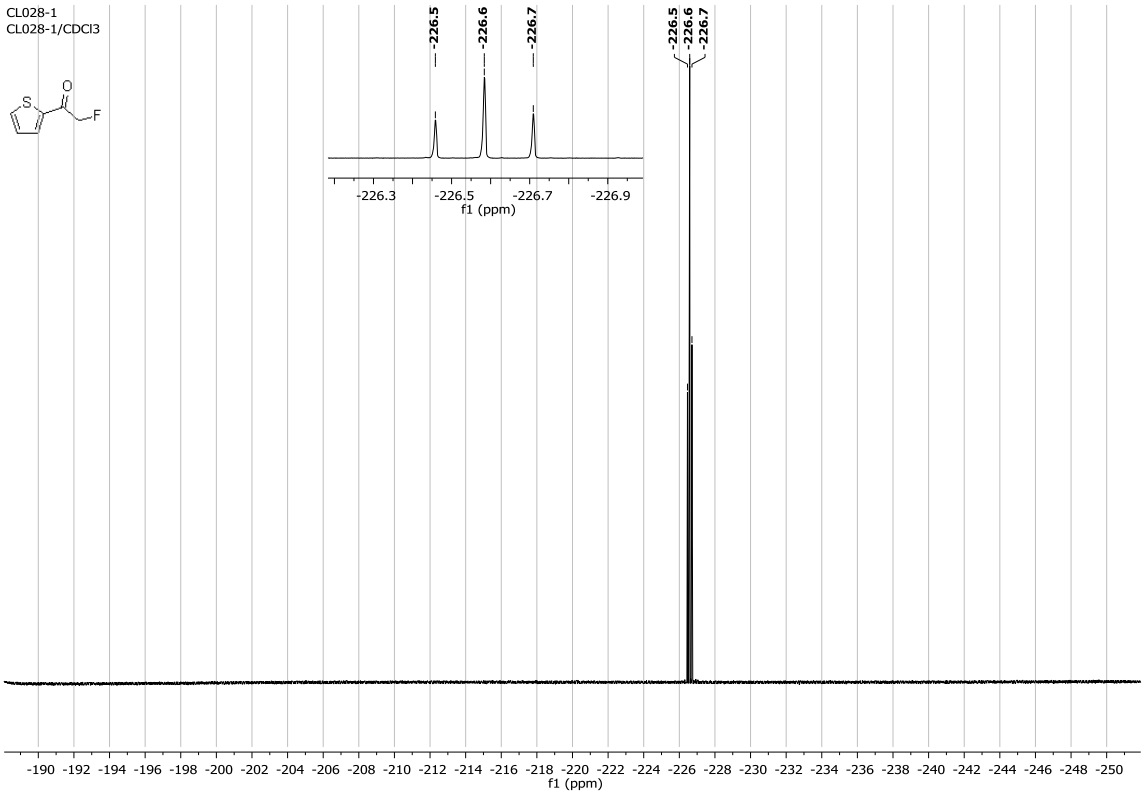

PROTON_01
O
O
F
7.339
7.324
7.322
7.307
7.048
7.033
7.018
6.914
6.898
5.254
5.160
4.807
1.9
0.9
1.9
2.0
2.0
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

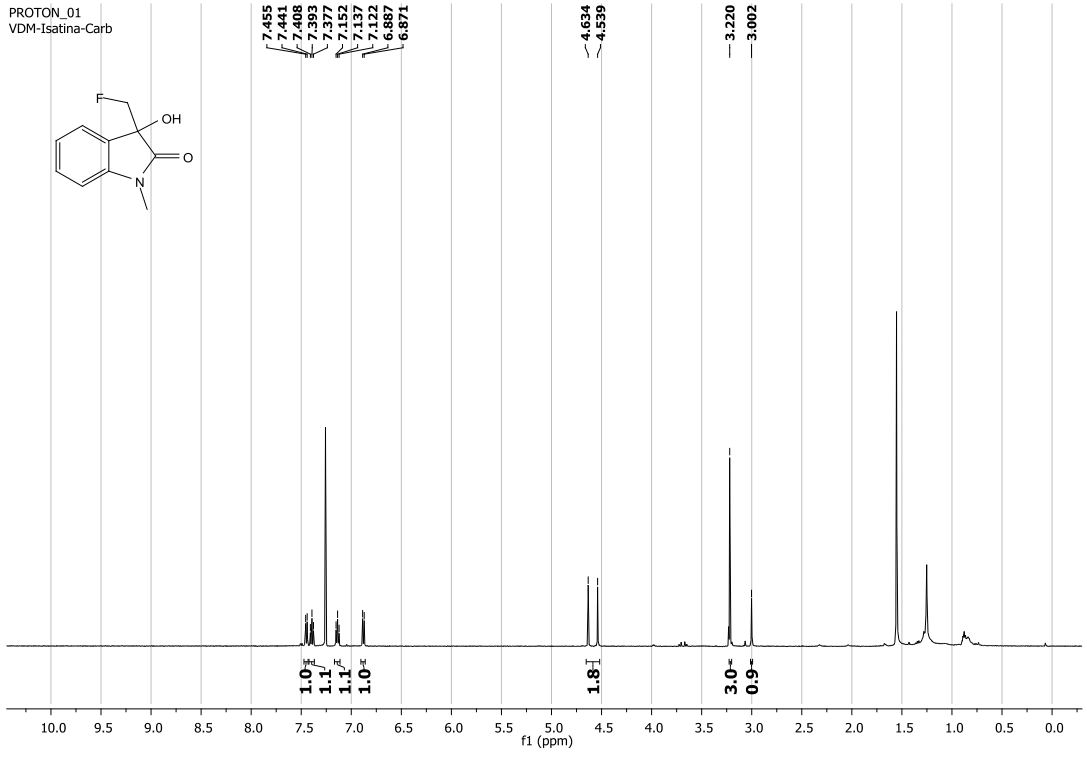

CARBON_01
201.8
201.6
157.3
129.8
122.2
114.5
85.2
83.8
71.2
O
O
F
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

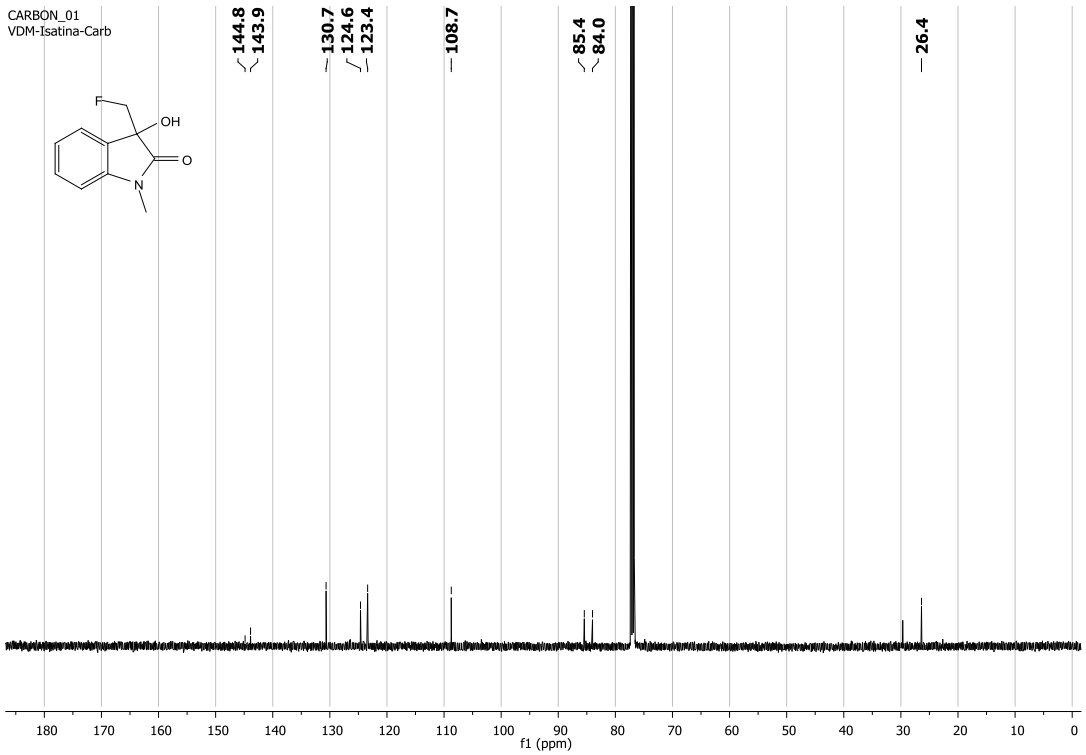

FLUORINE_01
STANDARD FLUORINE PARAMETERS
-236.4
-236.5
-236.6
O
O
F
-235.5
-236.5
-237.5
f1 (ppm)
30 20 10 0 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190 -210 -230 -250 -270 -290
f1 (ppm)

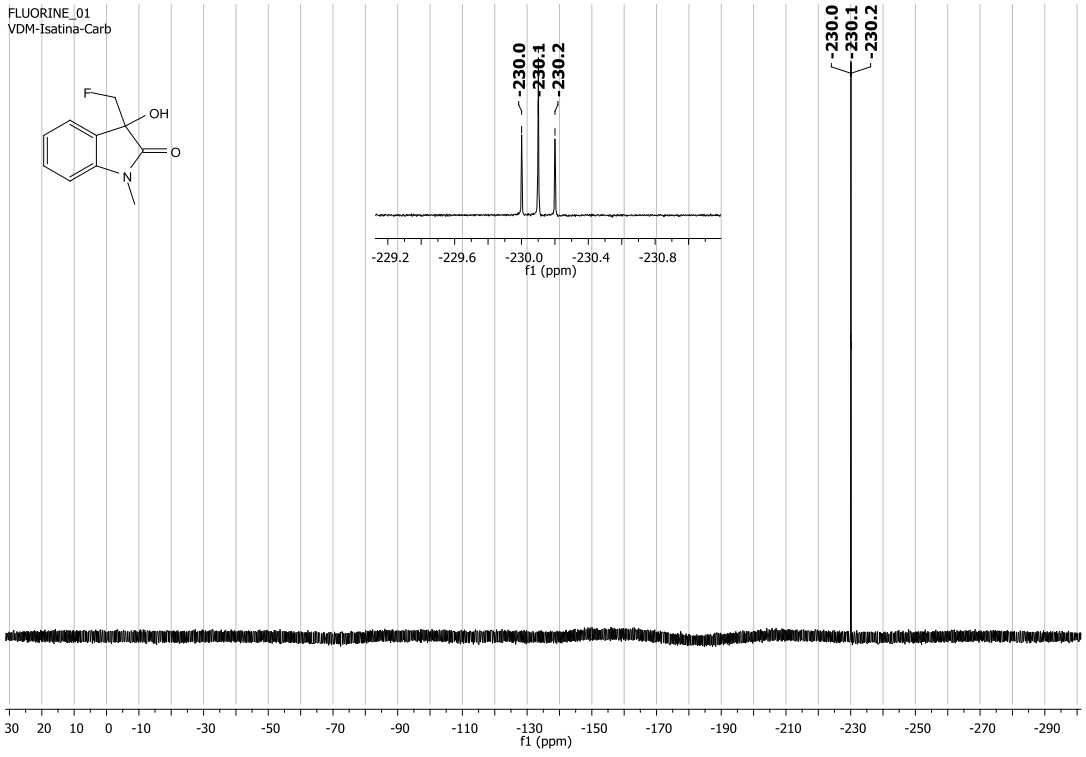

CL028-1
CL028-1/CDCl3
7.883
7.880
7.878
7.873
7.871
7.868
7.758
7.757
7.755
7.754
7.746
7.744
7.743
7.742
7.195
7.185
7.183
7.173
5.389
5.271
4.596
1.0
1.0
1.0
1.0
1.0
f1 (ppm)

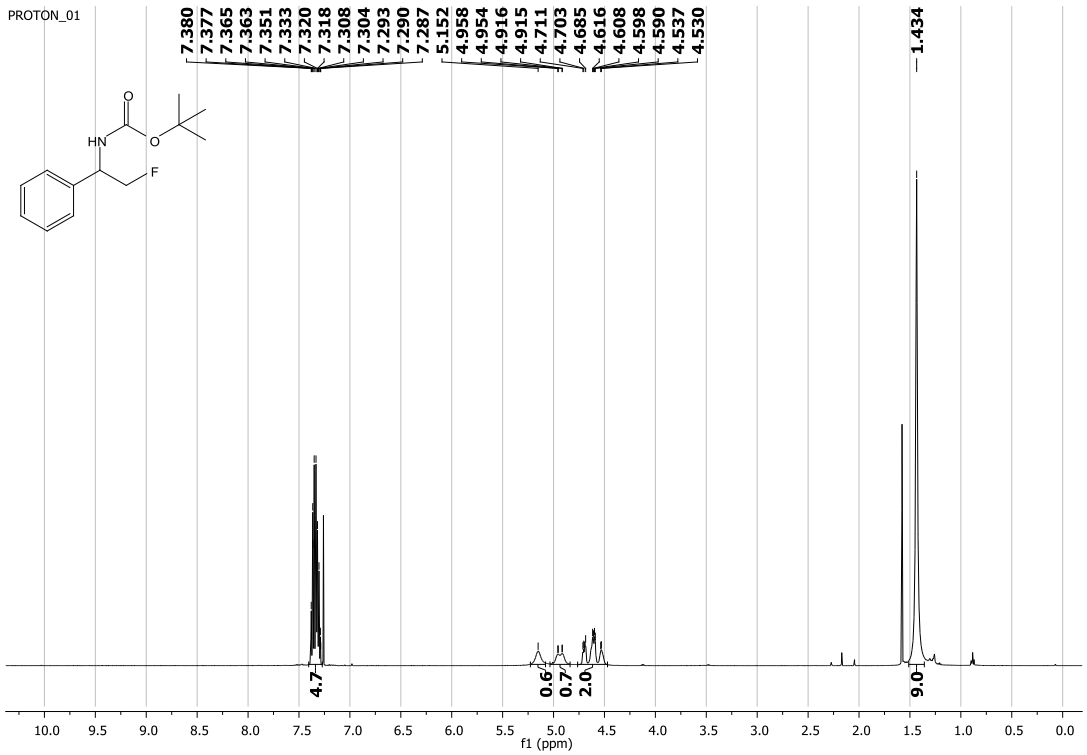

CL028-1
CL028-1/CDCl3
187.3
187.1
140.0
140.0
135.0
134.9
133.3
133.2
128.4
128.4
84.9
83.0
77.3
77.0
76.7
f1 (ppm)

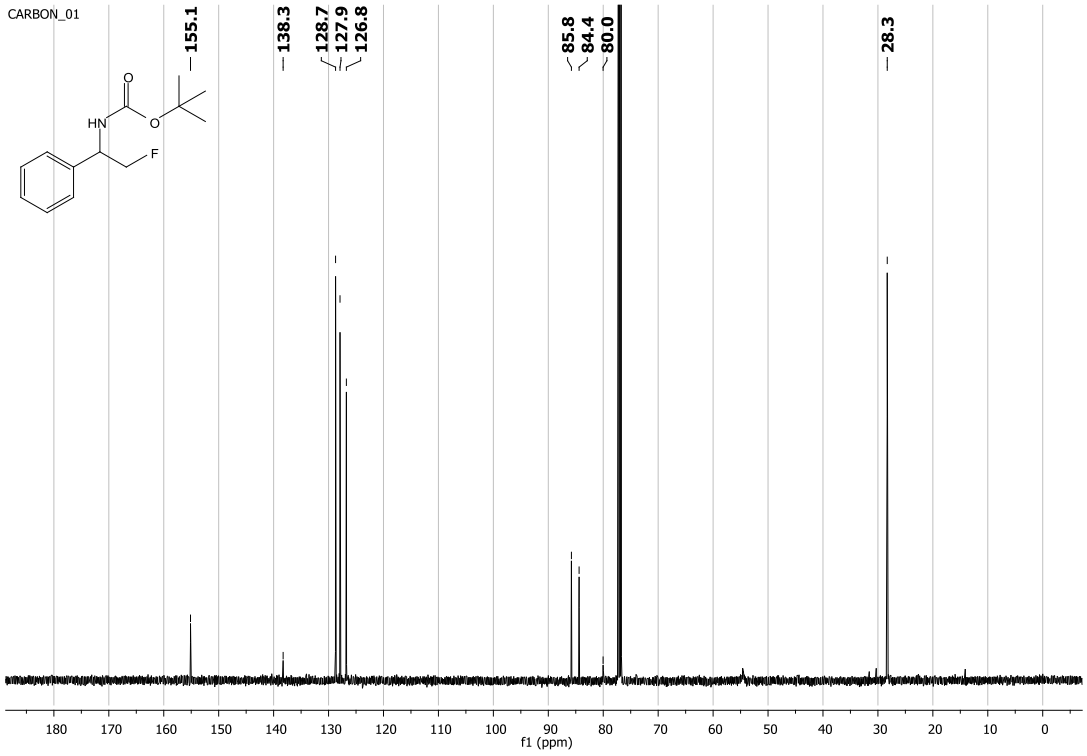

CL028-1
CL028-1/CDCl3
-226.5
-226.6
-226.7
-226.3
-226.5
-226.7
-226.9
f1 (ppm)
-190 -192 -194 -196 -198 -200 -202 -204 -206 -208 -210 -212 -214 -216 -218 -220 -222 -224 -226 -228 -230 -232 -234 -236 -238 -240 -242 -244 -246 -248 -250
f1 (ppm)

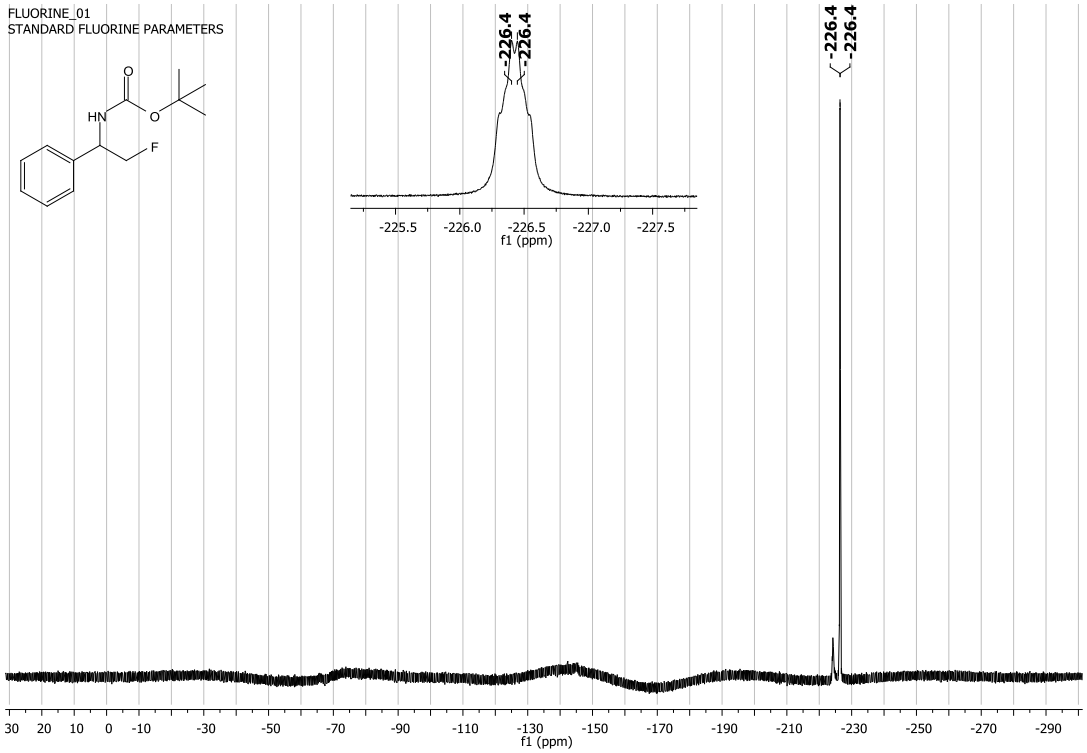

PROTON_01
VDM-Isatina-Carb
7.455
7.441
7.408
7.393
7.377
7.152
7.137
7.122
6.887
6.871
4.634
4.539
3.220
3.002
1.0
1.1
1.1
1.0
1.8
3.0
0.9
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

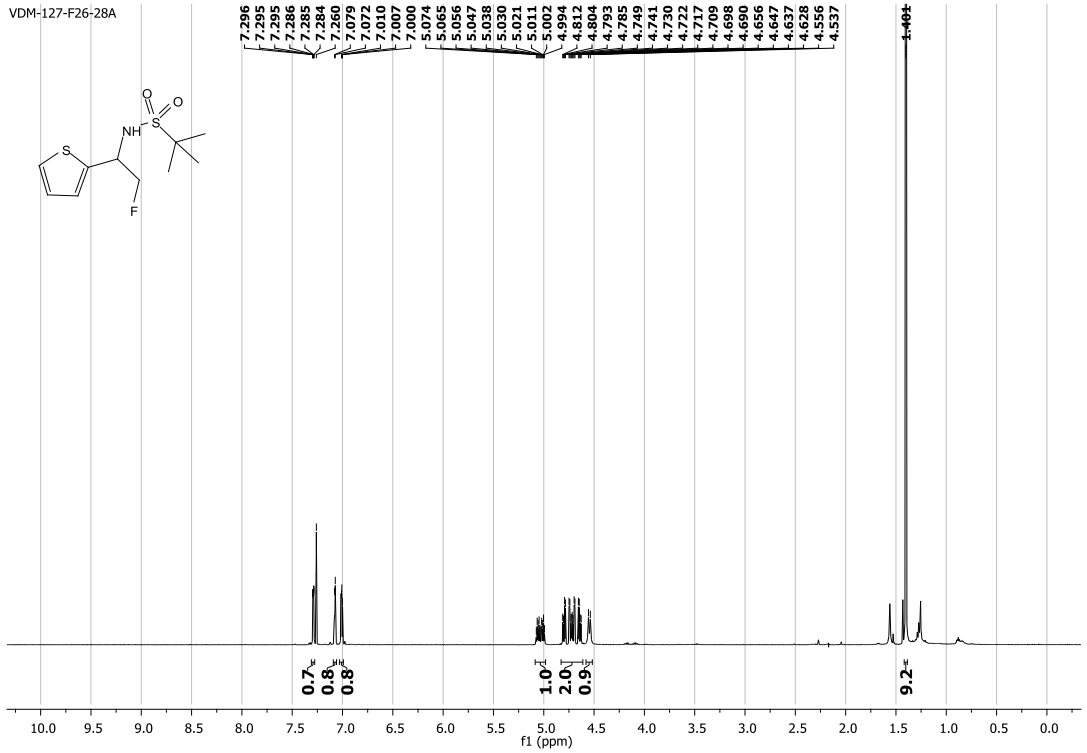

CARBON_01
VDM-Isatina-Carb
144.8
143.9
130.7
124.6
123.4
108.7
85.4
84.0
26.4
F
OH
O
N
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

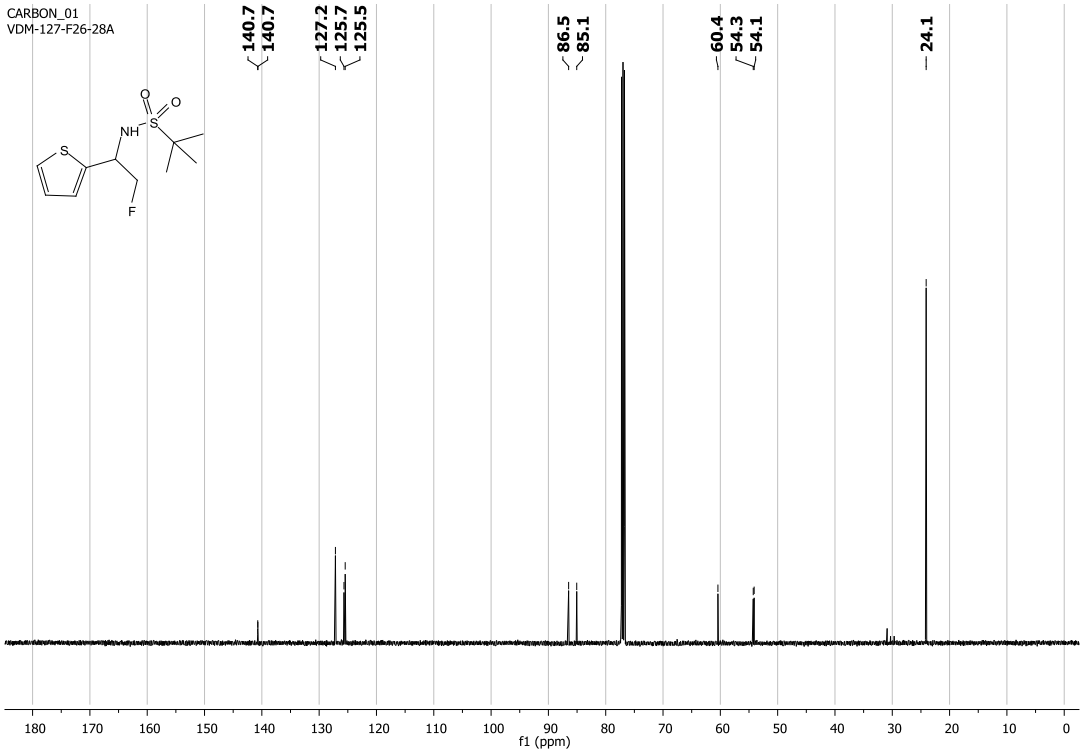

FLUORINE_01
VDM-Isatina-Carb
-230.0
-230.1
-230.2
F
OH
O
N
-229.2 -229.6 -230.0 -230.4 -230.8
f1 (ppm)
30 20 10 0 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190 -210 -230 -250 -270 -290
f1 (ppm)

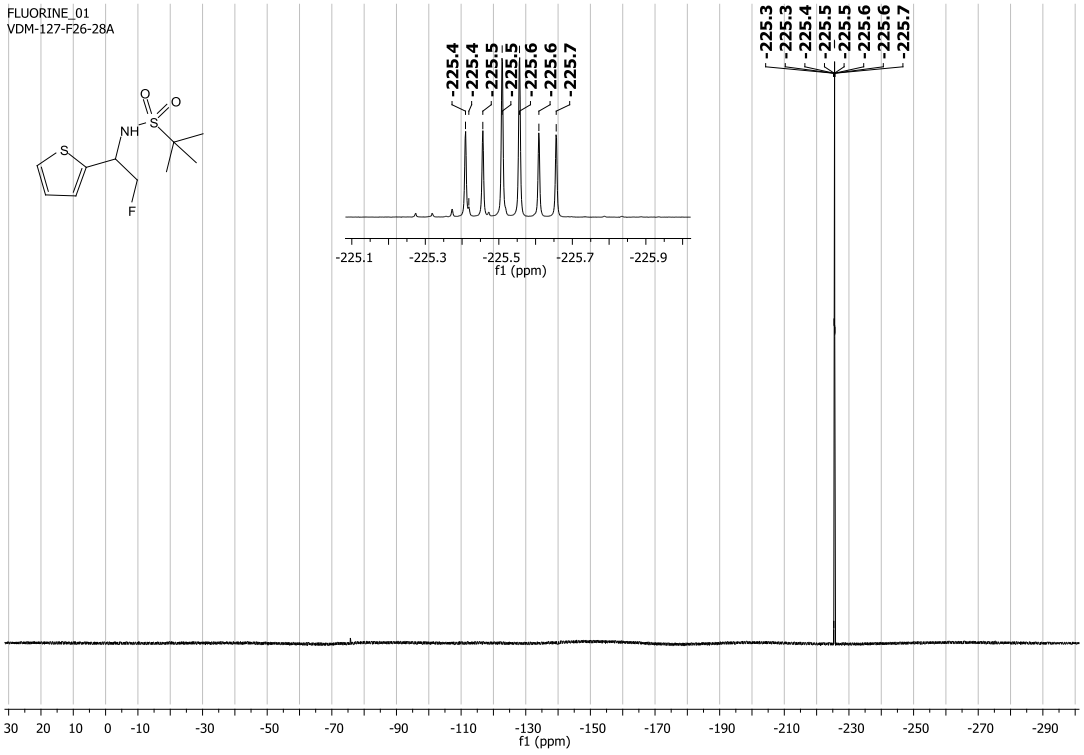

PROTON_01
7.380
7.377
7.365
7.363
7.351
7.333
7.320
7.318
7.308
7.304
7.293
7.290
7.287
5.152
4.958
4.954
4.916
4.915
4.711
4.703
4.685
4.616
4.608
4.598
4.590
4.537
4.530
1.434
4.7
0.6
0.7
2.0
9.0
f1 (ppm)

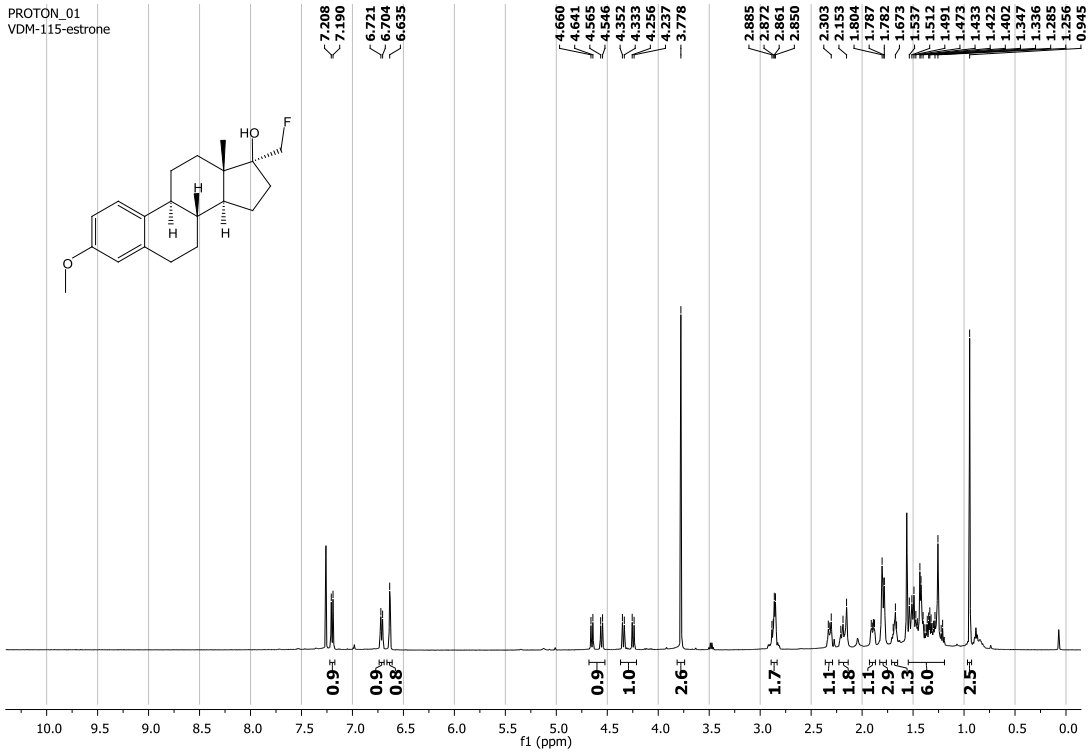

CARBON_01
155.1
138.3
128.7
127.9
126.8
85.8
84.4
80.0
28.3
f1 (ppm)

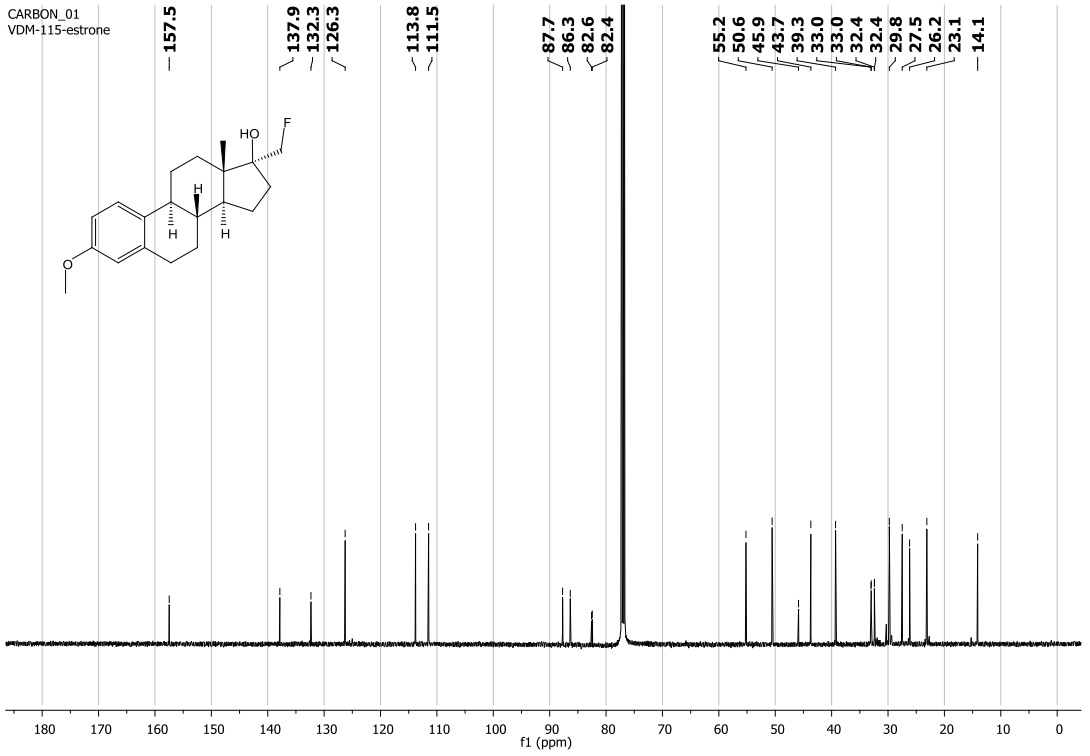

FLUORINE_01
STANDARD FLUORINE PARAMETERS
-226.4
-226.4
-226.4
-226.4
f1 (ppm)
f1 (ppm)

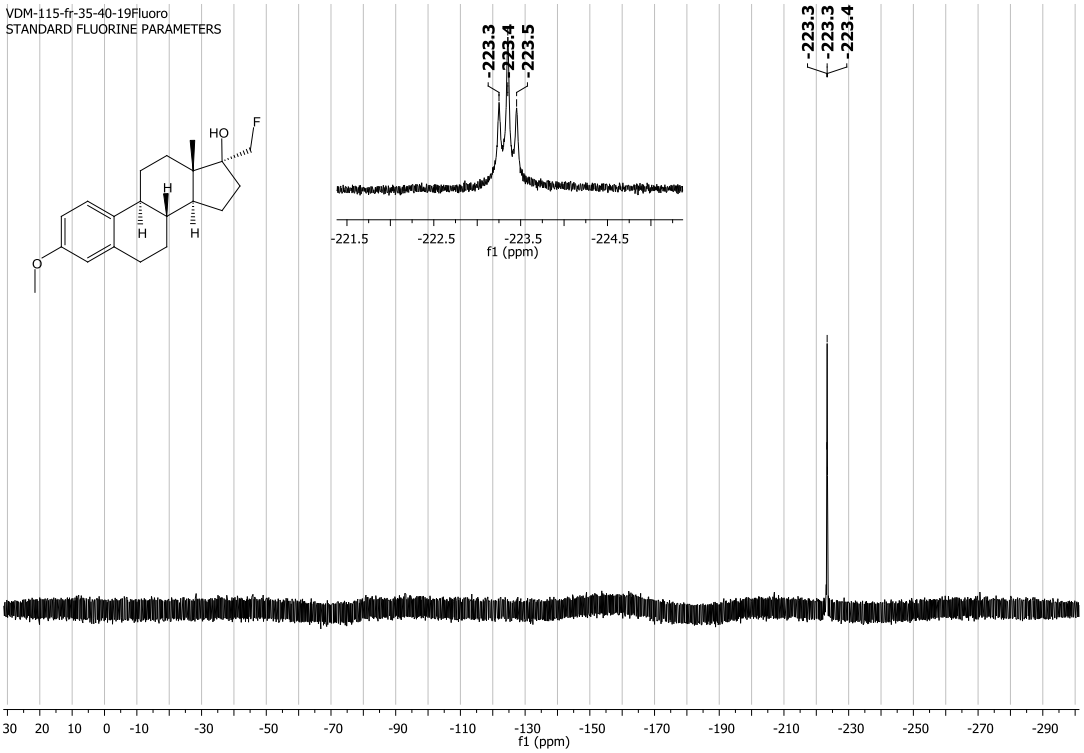

VDM-127-F26-28A
7.296
7.295
7.295
7.286
7.285
7.284
7.260
7.079
7.072
7.010
7.007
7.000
5.074
5.065
5.056
5.047
5.038
5.030
5.021
5.011
5.002
4.994
4.812
4.804
4.793
4.785
4.749
4.741
4.730
4.722
4.717
4.709
4.698
4.690
4.656
4.647
4.637
4.628
4.556
4.537
1.401
0.7
0.8
0.8
1.0
2.0
0.9
9.2
f1 (ppm)


CARBON_01
VDM-127-F26-28A
140.7
140.7
127.2
125.7
125.5
86.5
85.1
60.4
54.3
54.1
24.1
f1 (ppm)


FLUORINE_01
VDM-127-F26-28A
-225.4
-225.4
-225.5
-225.5
-225.6
-225.6
-225.7
-225.3
-225.3
-225.4
-225.5
-225.5
-225.6
-225.6
-225.7
f1 (ppm)


PROTON_01
VDM-115-estrone
7.208
7.190
6.721
6.704
6.635
4.660
4.641
4.565
4.546
4.352
4.333
4.256
4.237
3.778
2.885
2.872
2.861
2.850
2.303
2.153
1.804
1.787
1.782
1.673
1.537
1.512
1.491
1.473
1.433
1.422
1.402
1.347
1.336
1.285
1.256
0.945
HO
F
H
H
H
O
0.9
0.9
0.8
0.9
1.0
2.6
1.7
1.1
1.8
1.1
2.9
1.3
6.0
2.5
f1 (ppm)


CARBON_01
VDM-115-estrone
157.5
137.9
132.3
126.3
113.8
111.5
87.7
86.3
82.6
82.4
55.2
50.6
45.9
43.7
39.3
33.0
33.0
32.4
32.4
29.8
27.5
26.2
23.1
14.1
HO
F
H
H
H
O
f1 (ppm)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H
H
H
O
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-223.5
-223.3
-223.3
-223.4
-221.5
-222.5
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f1 (ppm)
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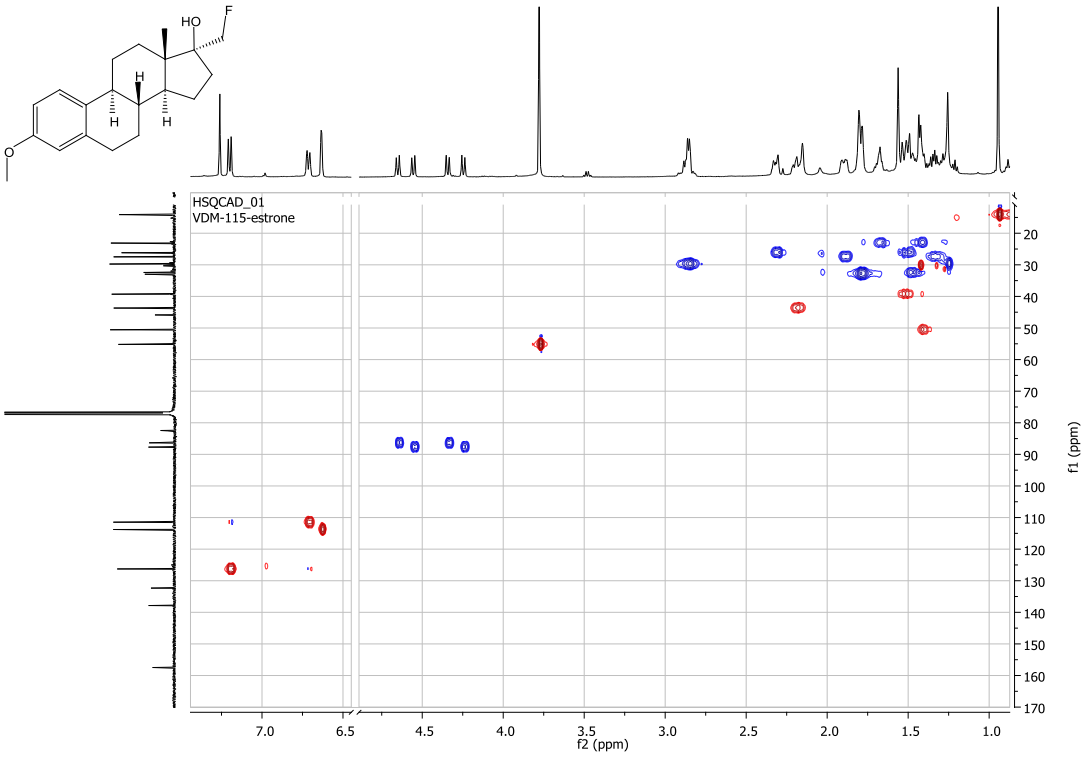
f1 (ppm)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H
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O
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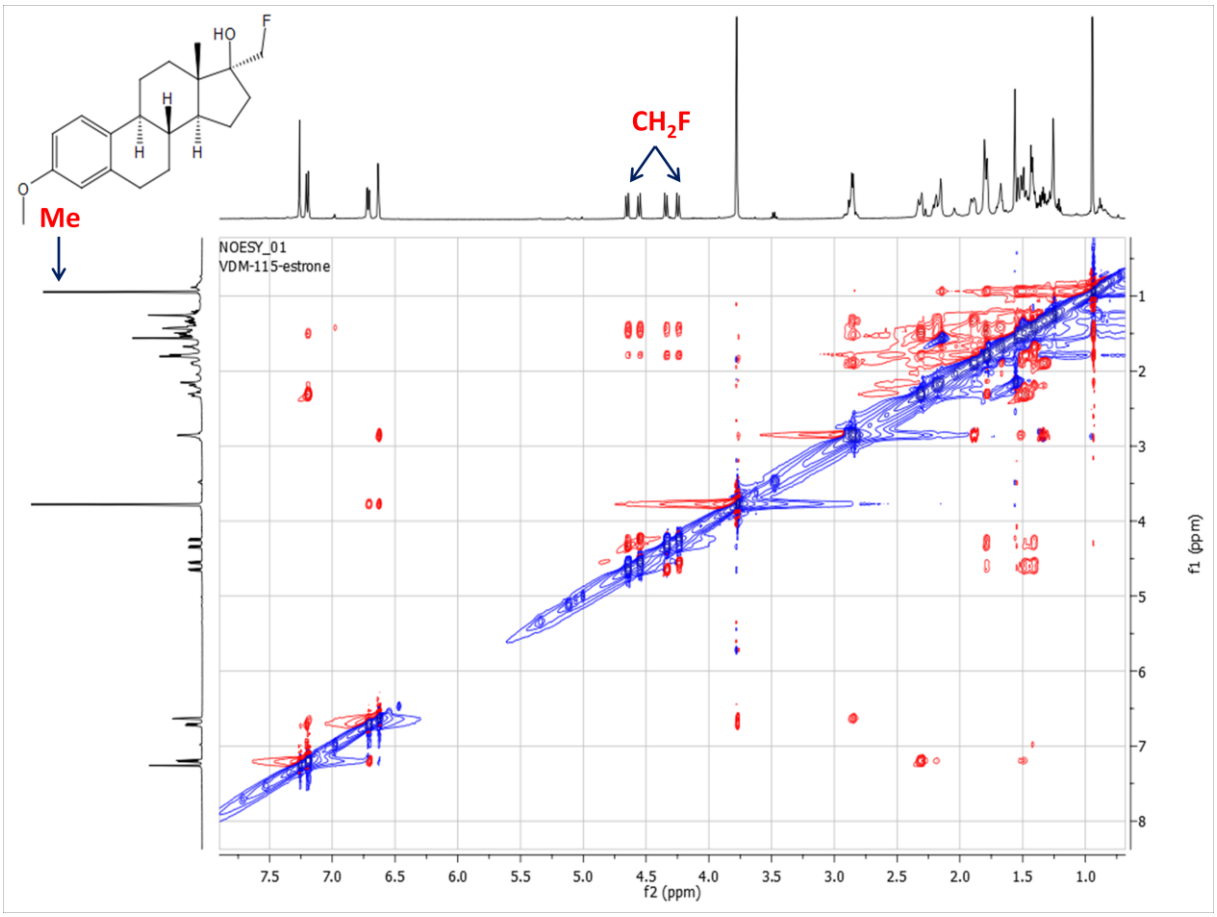
f1 (ppm)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VDM-115-estrone
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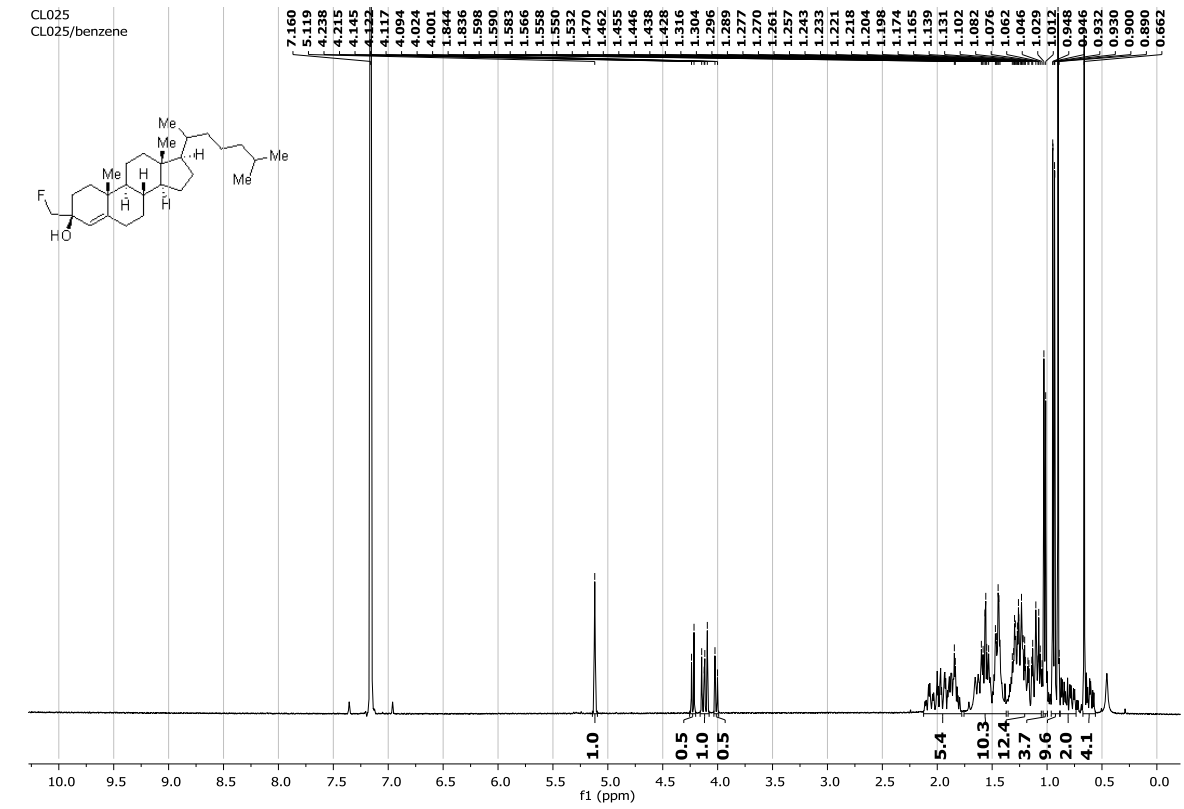
f1 (ppm)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Me
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Me
H
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F
HO
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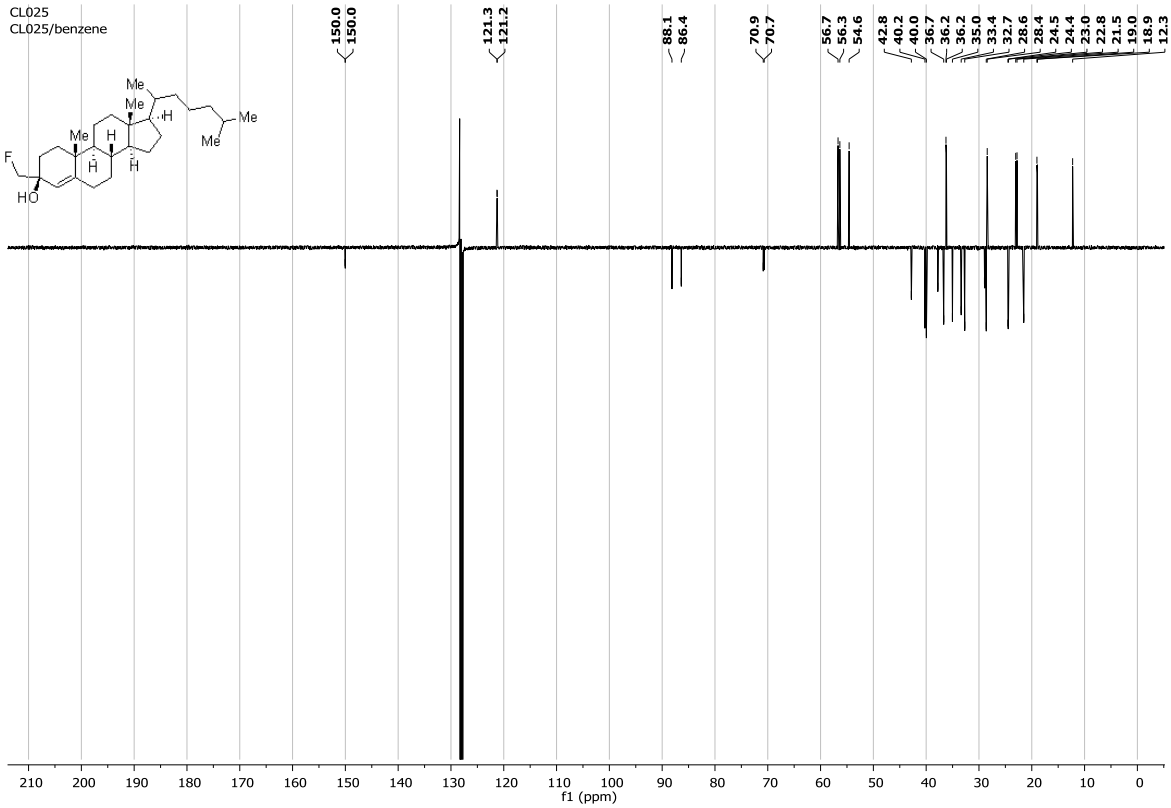
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40.2
40.0
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36.2
36.2
35.0
33.4
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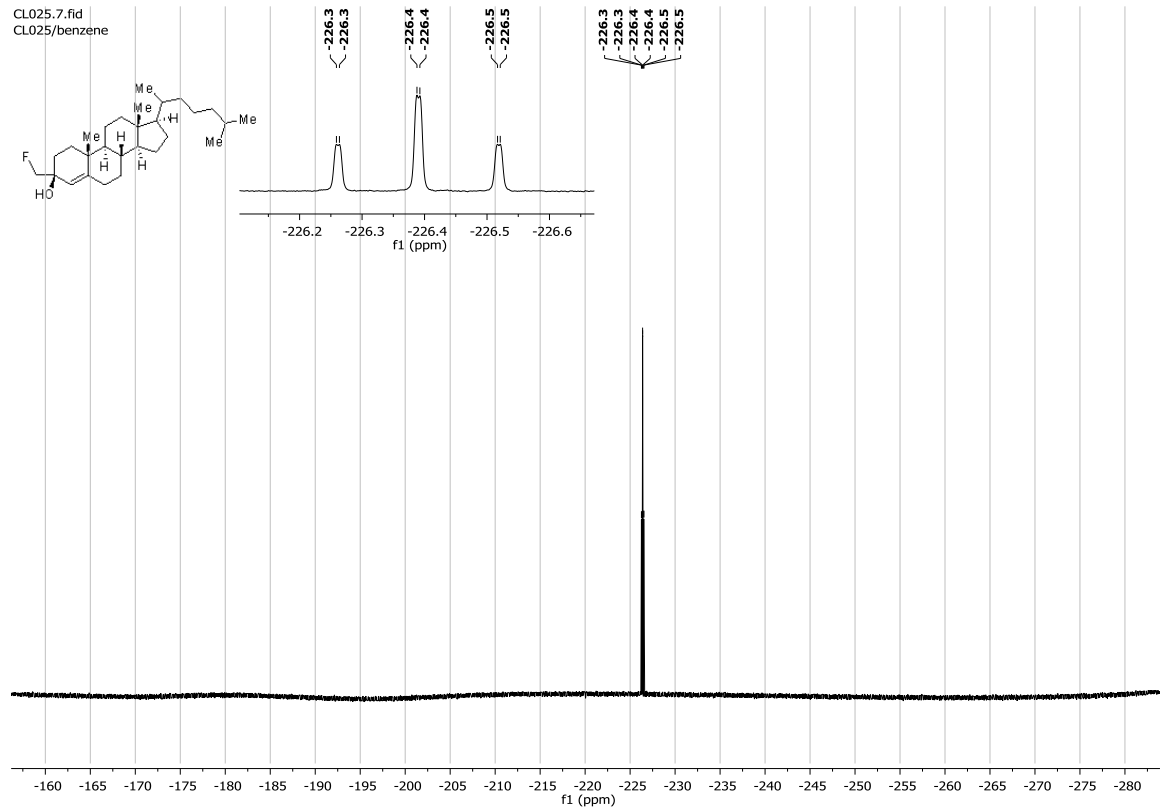
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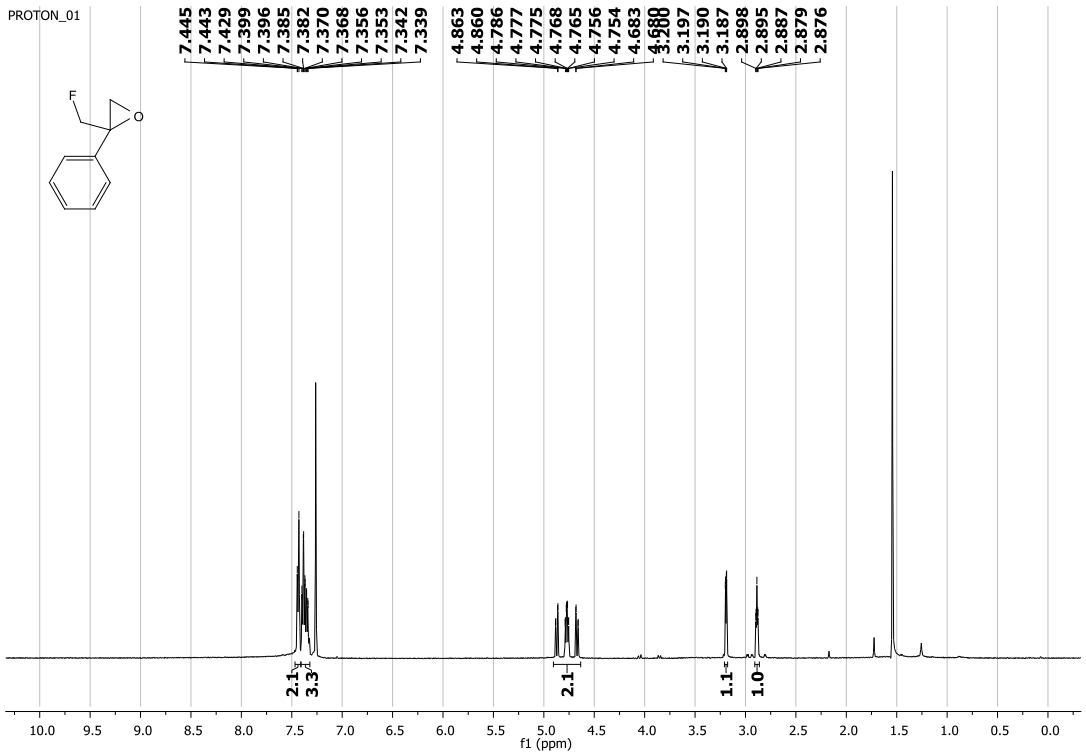
f1 (ppm)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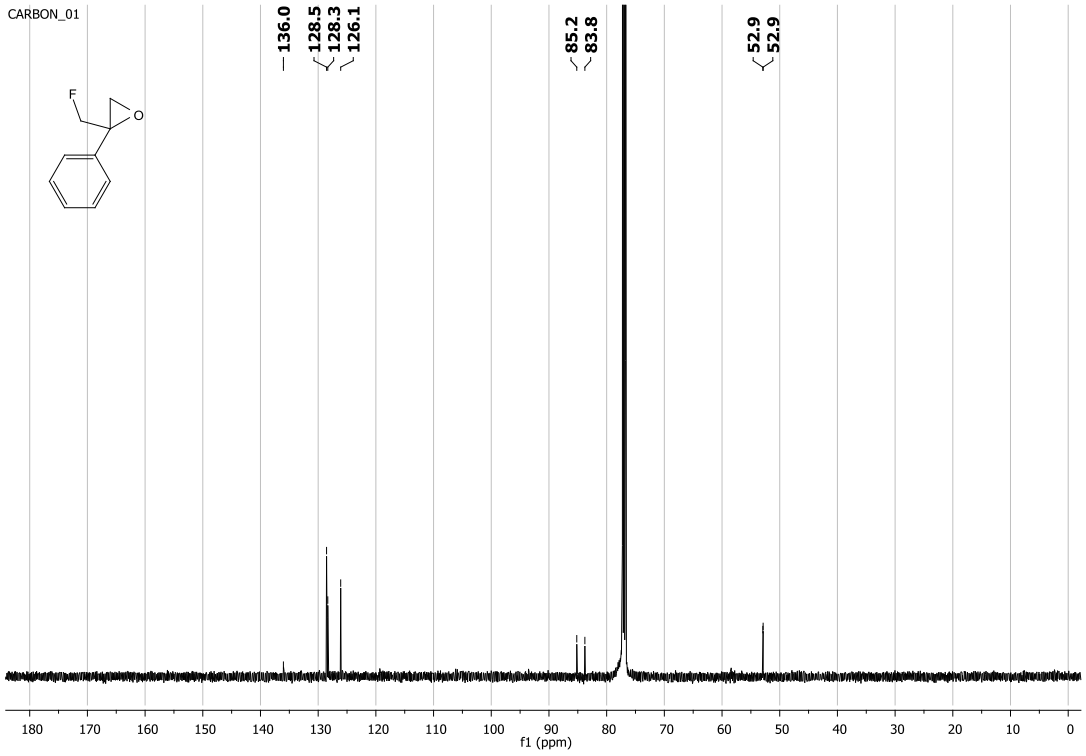
f1 (ppm)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F
O
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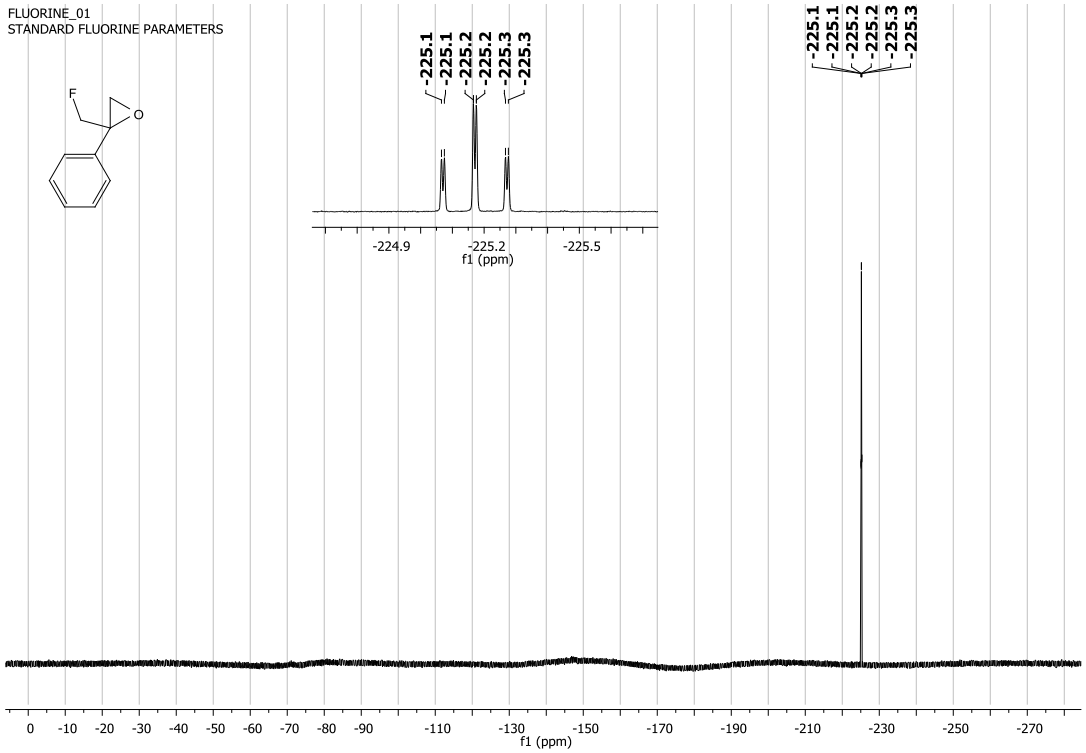
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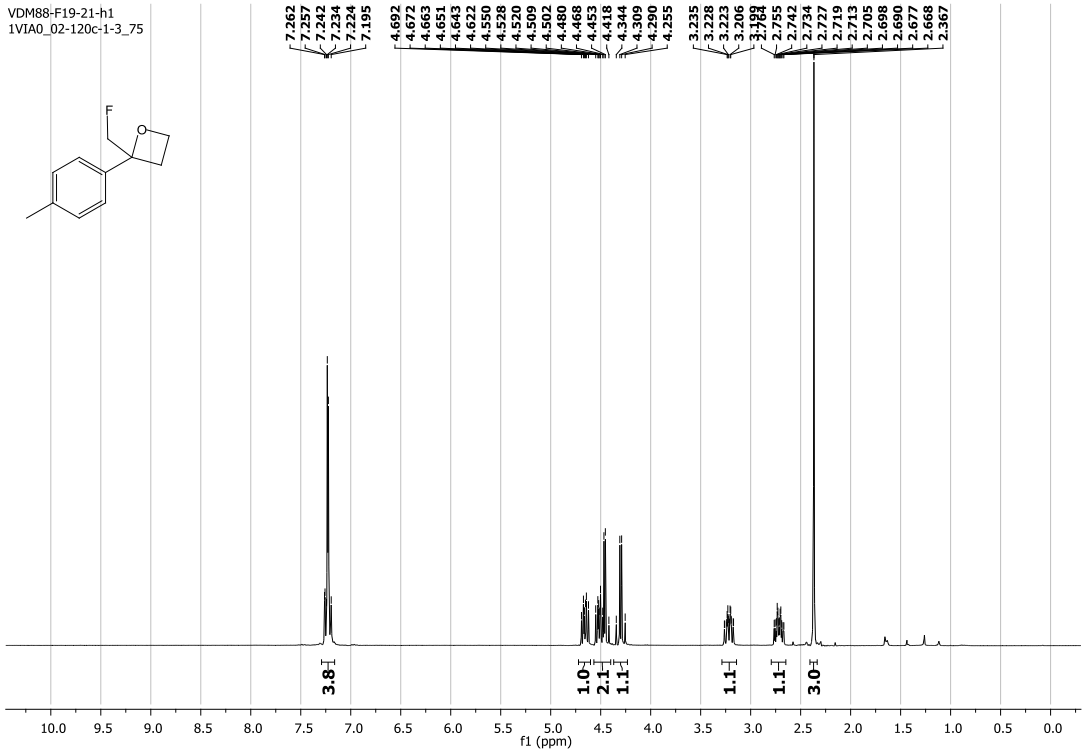
f1 (ppm)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4.509
4.502
4.480
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4.453
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3.228
3.223
3.206
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2.677
2.668
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3.0
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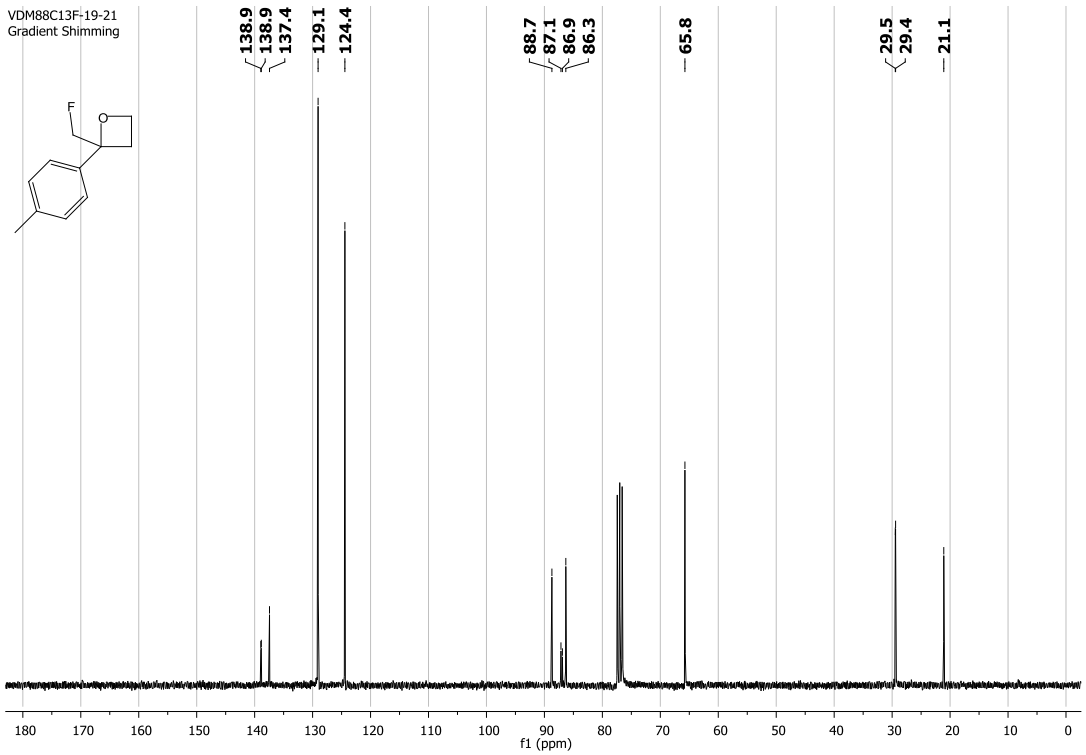
f1 (ppm)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F
O
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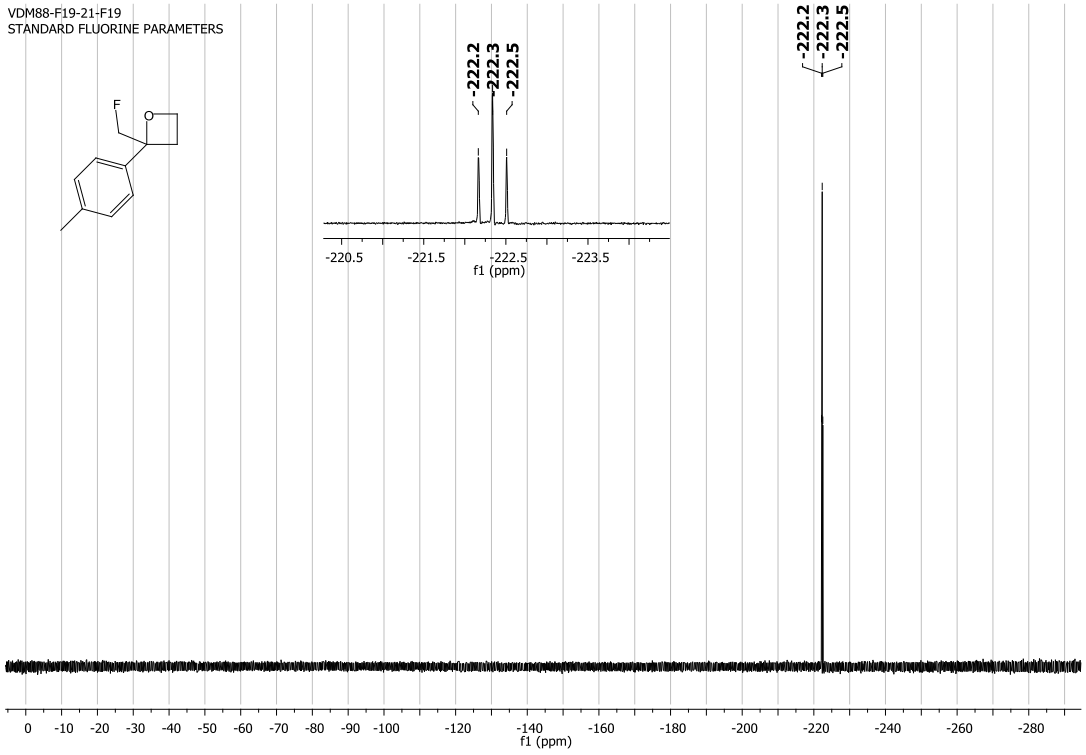
f1 (ppm)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STANDARD FLUORINE PARAMETERS
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-222.3
-222.5
F
O
-220.5 -221.5 -222.5 -223.5
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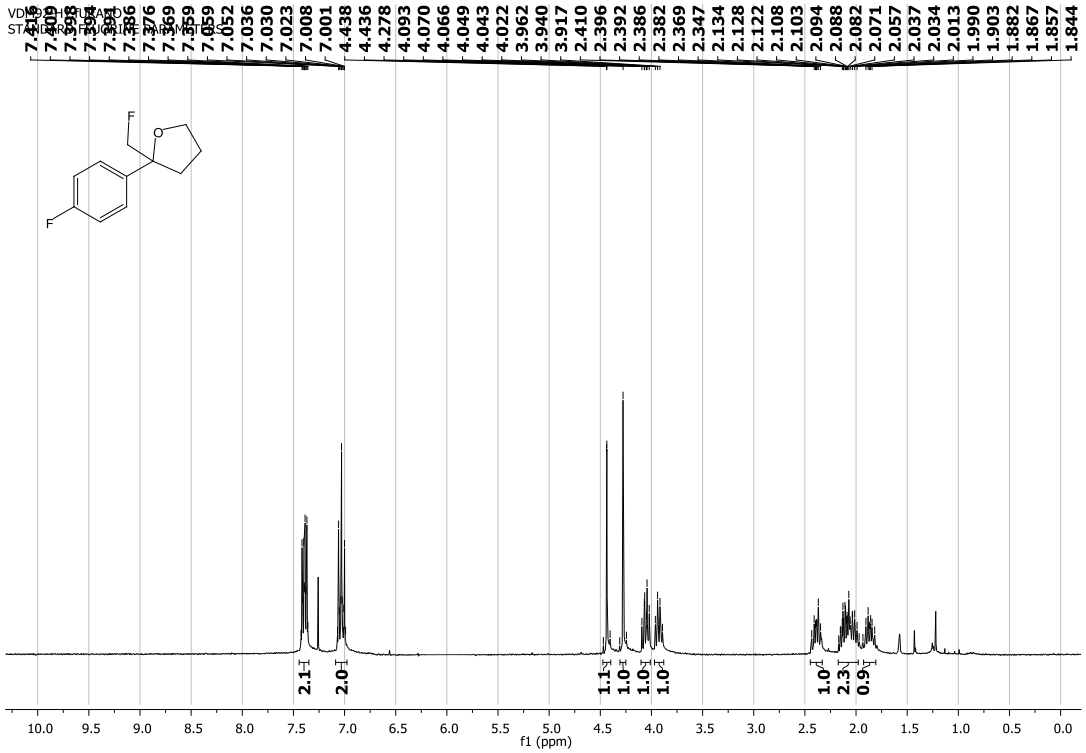
f1 (ppm)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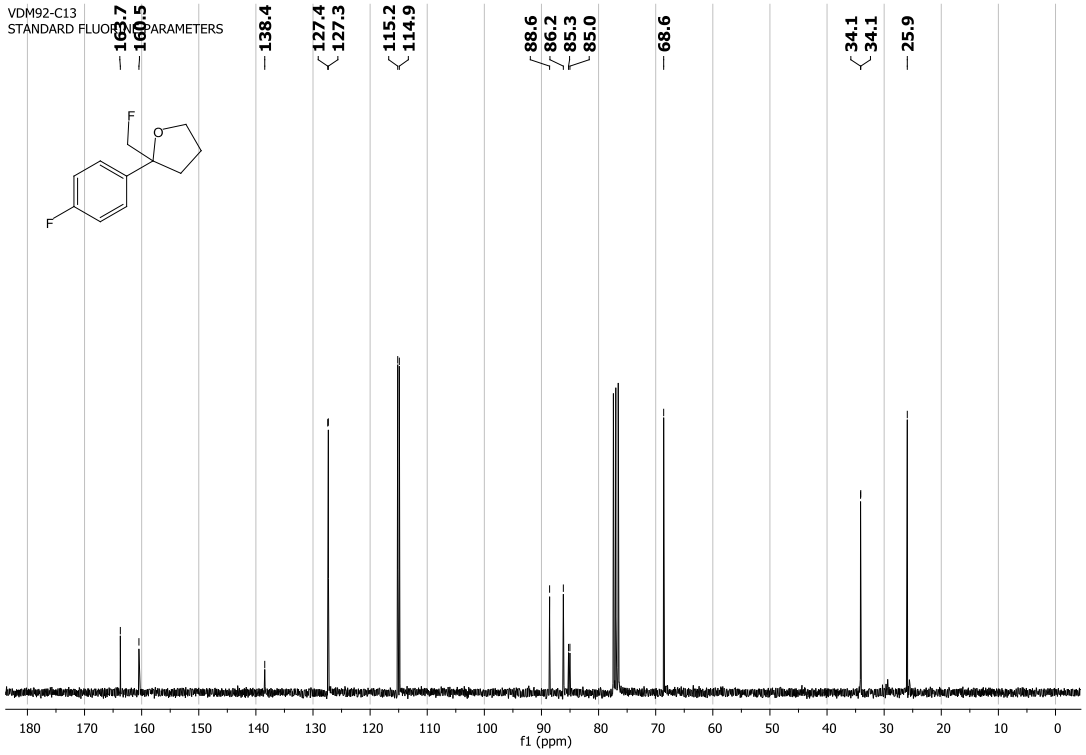
f1 (ppm)


VDM92-C13
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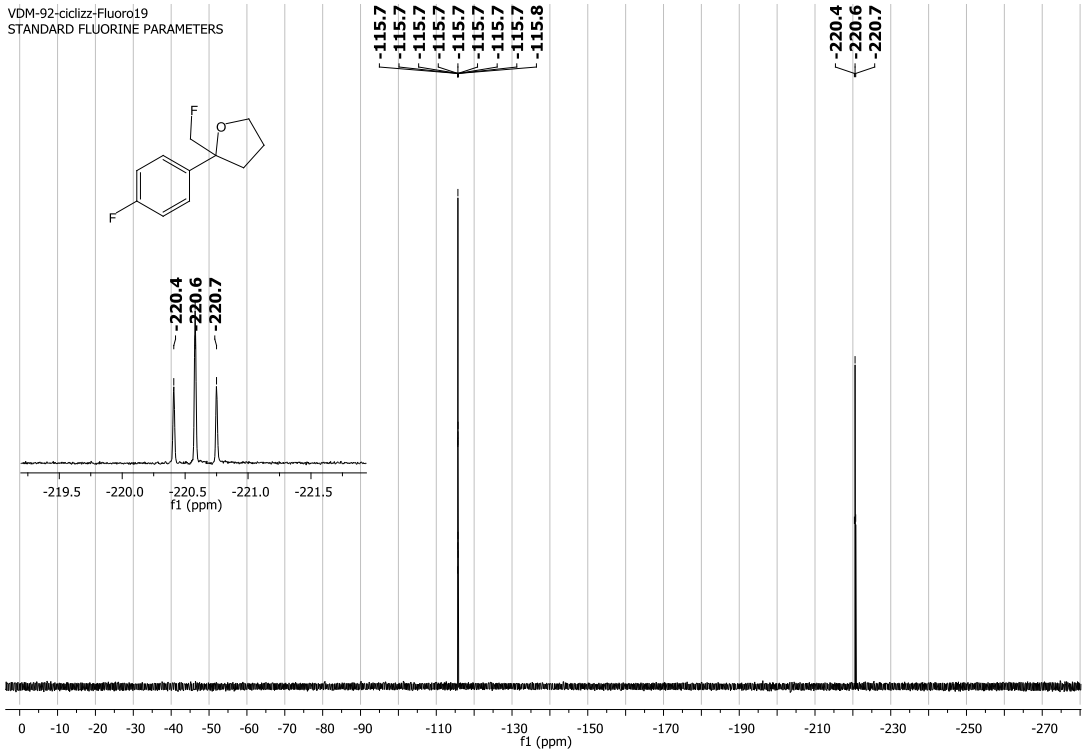
O
F
f1 (ppm)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f1 (ppm)
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-20
-30
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-110
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-170
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-210
-230
-250
-270
f1 (ppm)

Chapter 2

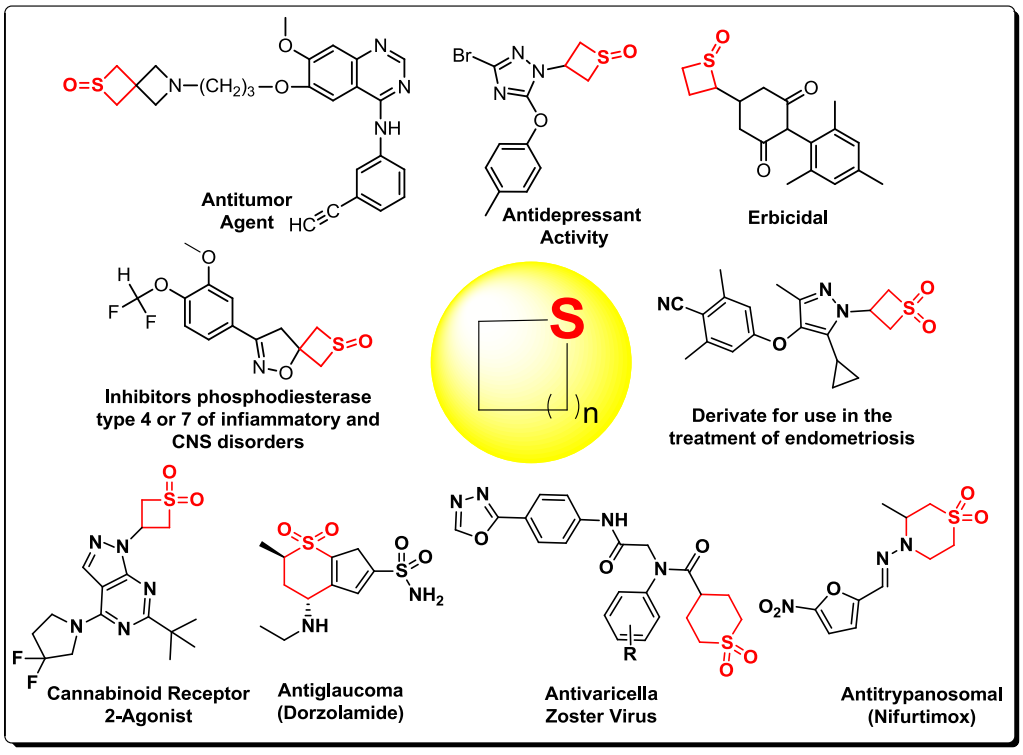
1. Introduction

1.1 Four-membered heterocycles (FMHs) as important scaffolds in Medicinal Chemistry.

Heterocyclic compounds, represent one of the most extensive classes in organic chemistry. Nowadays, the investigation of new synthetic strategies that lead to the synthesis and the functionalization of FMHs is an important topic in medicinal chemistry and biochemistry due to their biological activity.

The interest towards sulfur-bearing FMHs is dictated by the biological activities of molecules including this kind of heterocycles in their structures.

It is well recognized that, a large number of drugs used for a wide range of diseases contain such heterocyclic core that have application as antibacterial, antifungal, antiviral, anthelmintic agents, anticonvulsant, antiallergic, anti-HIV etc etc (Scheme 1).[89]



Scheme 1. *Examples of biologically active molecules contains sulfur-bearing heterocycles core.*

2. The Research

2.1 State of the Art: functionalization of four-membered ring thietane.

In the last decades, Luisi's research group focused the attention on the study of the reactivity of small heterocycles such as aziridines, azetidines and thietanes with the purpose to develop a novel approaches aimed at exploiting the corresponding species.[90] In particular, in striking contrast to nitrogen-bearing heterocycles, thietanes received less attention from the scientific community and the scarcely presence in the literature of synthetic strategies for the metalation and functionalization of these important systems is the obvious proof.

In 1982 Neville Jones *et al*, developed a strategies for the synthesis of functionalized cyclopropanes through an anionic rearrangement of lithiated diastereoisomeric 2,3- and 3-substituted thietane 1-oxides **1**. The authors confirmed an influence of the starting thietane 1-oxide **1** on the stereochemistry of the final cyclic products and a *syn*-lithiation to the sulfinyl oxygen was proposed; nevertheless, the possibility to trap the lithiated intermediate was not reported.

Starting from this isolated example, in 2014 Luisi and co-workers, reported the direct single and double metalation/functionalization of thietane 1-oxide **1**.[91] The previous evidences obtained with aziridine and azetidine rings in regioselective lithiation reactions, highlighted a dynamics – reactivity relationship related to both ring substitution and ring puckering due to the non-planar arrangement of the cycle.[92]

Computational studies showed that for the starting material **1** two limit situations can occur: 1) S=O group extends along an equatorial position **1eq**; 2) the S=O group extends along an axial position **1ax** (Figure 1).

^{1}H NMR simulation studies confirmed that the thermodynamically favoured conformer, and hence more stable, showed a pseudo-equatorial oxygen in fact at low temperature **1** exist with a preferential conformation **1eq** (Figure 1).

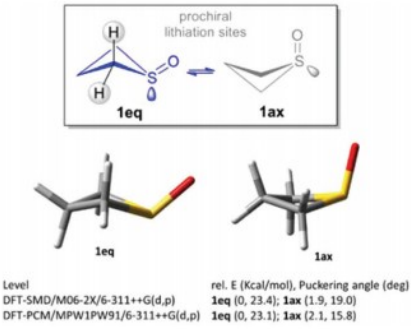


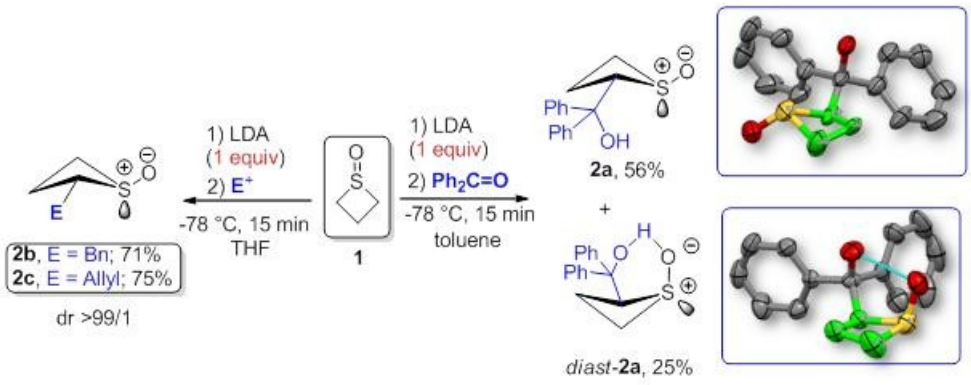
Figure 1. *Ring puckering of **1** and optimized structures of conformers **1ax** and **1eq***

After a precise screening of the reaction conditions, it has been found that the use of this direct approach, based on the functionalization of the simple and readily available thietane 1-oxide **1**, several C2-substituted thietane 1-oxides could be obtained. In fact, using lithium diisopropylamide (LDA) as base, THF or Toluene as solvent (depending on the solubility of the electrophile) with an external quenching after 15 minutes, several C2-substituted thietane 1-oxides were effectively trapped with electrophiles.

Being **1** a prochiral substrate, the C2 functionalization led to two diastereoisomeric adducts **2** and diast-**2**.

The diasteroisomeric ratio was strictly dependent on different factors such as the solvent and the nature of the electrophile. In fact, when benzophenone was used as electrophile, the reaction proceeded with a *cis* selectivity due to the formation of an intramolecular hydrogen bond between the oxygen atom of the S=O group and hydrogen atom of hydroxyalkyl moiety of the molecule. The stereochemical preference was confirmed by single crystal X-ray analysis of conformer **2a** and diast-**2a.** (Scheme 2).

Nevertheless, with the exception of diast-**2a**, when the reaction was performed with other electrophiles such as allyl- and benzyl bromide, only *trans* stereoisomers **2b** and **2c** were obtained. This result confirmed that, in the absence of hydroxyalkyl group in the molecule, no trace of the *cis* diasteroisomer was detected and so *dr* was always larger than 99% (Scheme 2).

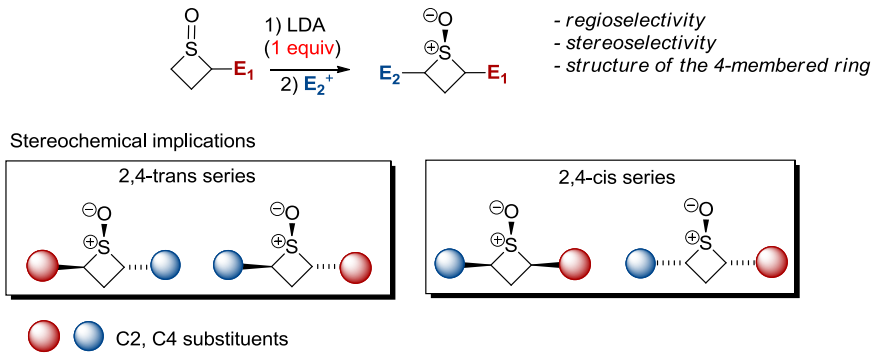


Scheme 2. *Synthesis of C2-Functionalized Thietane 1-Oxides* ***1.***

Driven from these preliminary results, a double substitution on the C2 and C4 carbons was attempted. The screening of the reaction conditions emphasized that the use of 2 equiv of LDA allowed to obtain C2 and C4 doubly substituted thietane 1-oxide via a stepwise lithiation/trapping mechanism, as diastereomeric mixture.

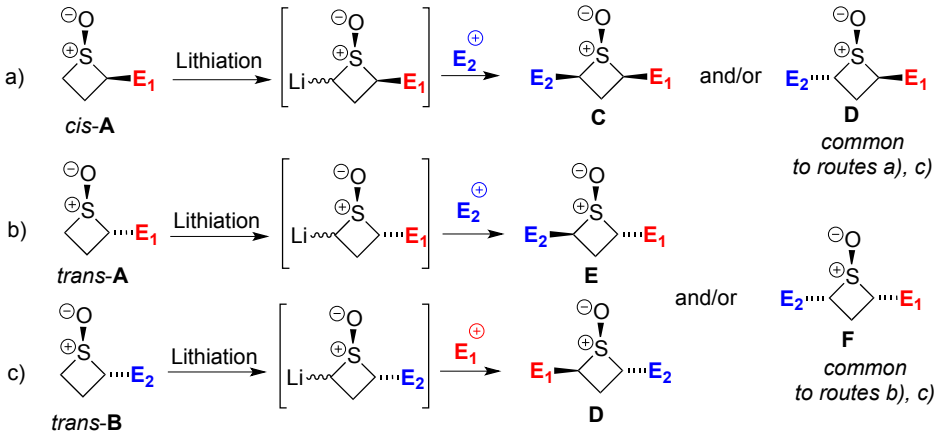
This evidence suggested us that a non symmetric functionalization of C2-disubstituted thietane-1-oxides could be possible in order to obtain different C2,C4-disubstituted-thietane-1-oxides.[93]

We immediately realized the power of this strategy because it would allow to obtain, in a simple and direct way, whichever required diasteroisomers with any combination of functionalization (Scheme 3).



Scheme 3. *Non symmetric double functionalization of thietane-1-oxides.*

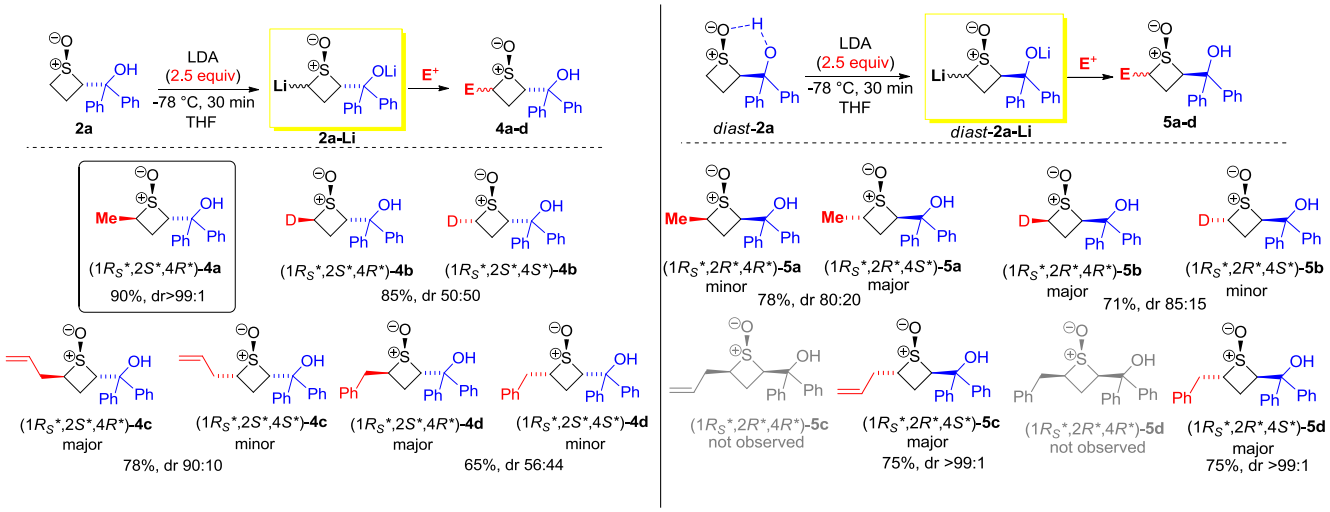
As show in the *Scheme 4*, a judicious choice of the starting material was important in order to obtain all four possible C2,C4-disubstituted diasteroisomers. However, when the electrophile used for the first C2-functionalization was not able to form an intramolecular hydrogen bond, only thietane **2** is made available and thus only three of four combinations are possible. (Scheme 4).



Scheme 4. *Stereochemical implications in the synthesis of all the four possible diasteroismers.*

At the beginning, the reactivity of both stereoisomers **2** and diast-**2a** in the lithiation reaction have been investigated. When **2** was lithiated by using 2.5 equiv of LDA at -78 °C in THF, the trapping of the intermediate successfully occurs with different electrophiles leading to

disubstituted thietanes **4a-d** like a mixtures of two diasteroisomers. Nevertheless, NMR studies confirmed that the electrophiles preferentially were introduced in *syn* oriantation to the sulfur oxygen giving to the relative stereochemistry ($1R_S$*,2S*,4R*) for the main stereoisomer. Afterwards, the same reaction conditions has been used for the lithiation of *diast*-**2a** and, also in this case, diasteroisomeric mixtures of disubstituted thietanes **5a-d** were obtained mainly with a *trans* stereoselectivity with all electrophiles except to deuterium that gave the *cis* stereoselectivity (Scheme 5).

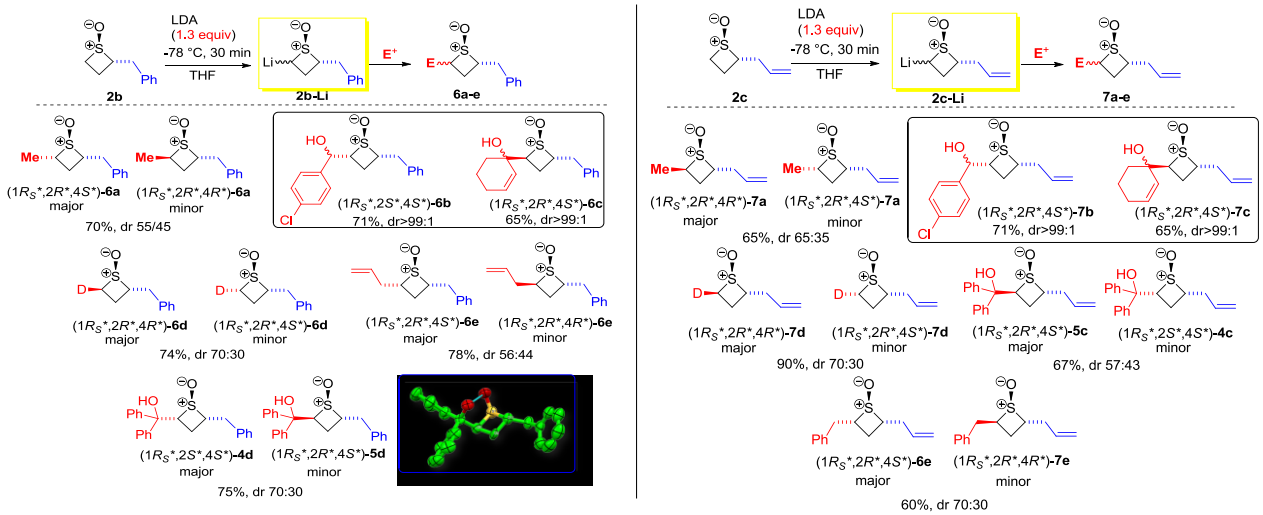


Scheme 5. *Lithiation/substitution of thietanes* ***2a*** *and diast-****2a****.*

When the reactivity of **2b** and **2c** were investigated, it was found that by using 1.3 equiv. of LDA at -78 °C in THF as medium, the lithiated intermediates **2b-Li** and **2c-Li** could be trapped with several electrophiles leading to C2, C4 disubstituted thietanes **6a-e** and **7a-e** respectively as diasteroisomeric mixtures (Scheme 6). From this study emerged a modest stereoselectivity when MeI, MeOD, AllylBr or BnBr are used as electrophiles; while *dr* was always larger than 99% when both lithiated intermediates **2b-Li** and **2c-Li** were trapped with p-chlorobenzaldehyde and cyclohexenone.

It is worth noting that, in the reaction of **2c-Li** with benzophenone produce the same stereoisomers seen in the lithiation/allylation of **2a** and *diast*-**2a**.

All this complex stereochemical study has been carried out with the essential aid of *X-Ray* analysis and 2D NMR techniques.



Scheme 6. *Lithiation/substitution of thietanes* ***2b*** *and* ***2c****.*

Further, starting from this *scenario*, we tried to fill a gap on the reactivity and stereoselectivity of other sulfur-bearing heterocycles such as thietane 1,1-dioxide and the corresponding six-membered homologue tetrahydro-2H-thiopyran 1,1-dioxide.

Following, the results of this investigation, as well as a preliminary study on the lipophilicity of the newly synthesized cyclic sulfone derivatives, is reported.

3. My Ph.D Project

3.1 A Greener and Efficient Access to Substituted Four- and Six-membered Sulfur-bearing Heterocycles.

Sulfones represent a versatile class of organic compounds with relevant synthetic and biological utilities. Several scaffolds with cyclic sulfone unit, show particular features that allow an efficient design of potential drugs. Moreover, being a strong H-bond acceptor, sulfone moiety it is considered as a carbonyl group bioisostere that enforces interaction of the drug with potential biological target.

Inter alia, an huge number of pharmaceutical and natural product have sulfur-bearing heterocycles; antiglaucoma agent Dorzolamide, antitrypanosomal drug Nifurtimox (Lampit®) are just some successful examples of sulfur-containing drugs.

Despite the importance for the pharmaceutical industry, strategies for the synthesis of substituted cyclic sulfones are undeveloped; in particular, several studies on the reactivity of sulfolane (*i.e.* five-membered cyclic sulfones) have been carried out,[94] while the metalation and the functionalization of thiethane and tetrahydro-*2H*-thiopyrane 1,1 -dioxide have been less explored.

The few examples on the metalation and functionalization of thietane 1,1-dioxide at the α position, rely only on the α-bromination and α-chlorination reactions.[95]

In 2010, Velàsquez and co-workers reported that a lithiation of four-, five-, and six-membered cyclic sulfones followed by a trapping with a sulfynylimine was possible but with low stereoselectivity.[96]

Nevertheless, the aim of Velàsquez's work was to obtaining some protease inhibitors for pharmaceutical application therefore, information about the reactivity and the stability of these cyclic sulfones needed to be addressed.

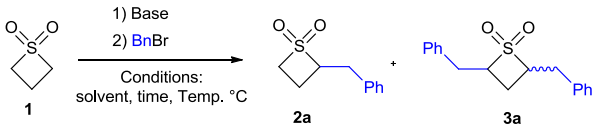
On the basis of these investigations, and the lack into the literature of a systematic study, we decided to investigate the regio- and stereoselectivity in the metalation reactions of thietane 1,1-dioxide, in comparison with six-membered homologues such as tetrahydro-*2H*-thiopyran 1,1-dioxide.

At the beginning, we explored the reactivity in the lithiation reactions of thietane 1,1-dioxide **8** under several reaction conditions and using benzyl bromide (BnBr) as model electrophile (Table 1).

The cyclic α-sulfonyl carbanion is likely stabilized by sulfone moiety and the proton in α-position to sulphur atom is sufficiently acid to be removed by using bases such as lithium diisopropylamine (LDA) and *n*-hexyllithium (HexLi).

As shown in the *Table 1*, entries 1 and 2, a mixture of C2 mono-, and C2, C4 di-substituted derivatives **8a** and **9a** respectively has been obtained when LDA was used as base of the reaction either in a polar medium such as THF or a less polar one such as toluene.

In order to perform a selective mono lithiation and obtaining **8a** as the sole product of the reaction, we tried to use tetramethylethylenediamine (TMEDA) as co-solvent. Unfortunately, a 75:25 mixture of **8a** and **9a** was obtained with a good overall yield (Table 1, entry 5).



Entry	Base (equiv)	BnBr(equiv)	Solvent	Time	Temp. (°C)	Ratio **2a/3a**	Yield (%)
1	LDA (1.1)	1	THF	15 min	-78	57:43[b]	70[e]
2	LDA (1.1)	1	Toluene	15 min	-78	86:14[d]	77[e]
3	HexLi (1.1)	1	Toluene[a]	15 min	-78	75:25[c]	80[e]
4	HexLi (1.1)	1	2-MeTHF	5 min	-78	100/0	75[f]
5	HexLi (2.5)	2.5	2-MeTHF	10 min	-78	0/100	60[f]
6	HexLi (2.5)	2.5	2-MeTHF	2 min	-50	0/100	22[f]
7	HexLi (2.5)	2.5	2-MeTHF	2 min	-20	0/100	20[f]
8	HexLi (2.5)	2.5	2-MeTHF	2 min	-10	0/100	15[f]
9	HexLi (2.5)	2.5	2-MeTHF	1 min	-20	0/100	22[f]
10	HexLi (2.5)	2.5	2-MeTHF	1 sec	-20	0/100	14[f]

[a]TMEDA (1.1 equiv.) was employed as a co-solvent. [b]Ratio of disubstituted thietanes **9a** trans/cis (25/75) as ascertained by ^{1}H NMR. [c]Ratio of disubstituted thietanes **9a** trans/cis (>99:1) as ascertained by ^{1}H NMR. [d]Ratio of disubstituted thietanes **9a** trans/cis (54/46) as ascertained by ^{1}H NMR. Stereochemistry assigned on the basis of the chemical equivalence of the ring protons. [e]Established by ^{1}H NMR. [f]Yield of the isolated product.

Table 1. Optimization of the lithiation/trapping of thietane 1,1-dioxide **8**.

Surprisingly, more selective reaction in favour of compound **8a** was observed when 2-MeTHF was choose as reaction solvent (Table 1, entry 4); in fact, by using HexLi (1.1 equiv.) as base and 2-MeTHF as solvent at -78°C the C2 mono-substituted lithiated intermediate could be trapped with an external quenching after 5 minutes in good yield.

The use of 2-MeTHF render the whole synthetic process appealing from an eco-compatible perspective. In fact, 2-MeTHF is obtained from renewable resources such as corncobs and bagasse and represent a truly green alternative to tetrahydrofuran[97] and dichloromethane in biphasic reactions.[98] Although it is an ether-type solvent, it resembles toluene in terms of

physical properties and for its features and benefits, this solvent is widely used for synthetic organic transformations[99] and bio catalysis.[100]

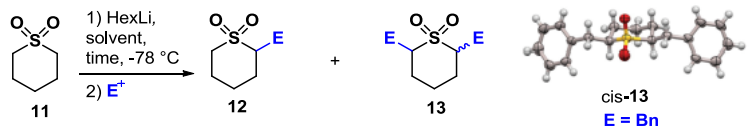
At this point, in order to evaluated the chemical stability of lithiated thietane, we attempted the reaction at higher temperatures. Surprisingly, in the range between -10 and -50 °C, the unique product of the reaction was the C2, C4 di-substituted derivative **9a** but with low yields (Table 1, entries 6-10). It was evident that the temperature was a crucial parameter for the stability of the lithiated intermediate.

For this reason, with the aim to found a right compromise between stability and efficiency, we decided to change the lithiation time and go down with the temperature until -78 °C. As show in Table 1 entry 5, by using HexLi (2.5 equiv.) as base, 2-MeTHF as solvent at -78°C the C2, C4 di-substituted lithiated thietane has been trap with an external quenching after 10 minutes leading to derivate **9a** as a single trans stereoisomer in 60% yield.

In striking contrast to thietane 1,1 dioxide **8**, the corresponding six-membered homologue tetrahydro-2H-thiopyran 1,1-dioxide **11**, subjected to a lithiathion/trapping sequence gave both mono- and di-substituted derivatives **12a** and **13a**.

Also in this case, with the purpose to compare the results with those obtained with **8**, benzyl bromide and HexLi were choose as model elecrophile and base respectively.

The screening of the reaction conditions highlight that the use of HexLi (1.1 equiv) as base and a lithiation time of 10 minutes, allowed to obtain a mixture 90:10 respectively of **12a-13a**, C2 mono- substituted and C2, C6 di-substituted **13a** (Table 2, entry 1); moreover changing stoichiometry of the reaction and the lithiation time, afforded **13a** as the main reaction product (Table 2, entry 3).



Entry	HexLi (equiv)	Electrophile	Solvent	Time (min)	Ratio **12a/13a**	Yield (%)
1	1.1	BnBr (1.0 equiv)	2-MeTHF	10	90/10[e]	50[b]
2	2.5	BnBr (2.5 equiv)	THF	10	87/13[e]	80[c]
3	2.5	BnBr (2.5 equiv)	2-MeTHF	30	10/90[e]	60[b]
4	2.5	Weinreb amide[d]	2-MeTHF	30	85/15[f]	80[c]

[a]Yield of the isolated major adduct .[b]Yield of the isolated product. [c]Ascertained by ^{1}HNMR.[d] 4-*t*-Butyl-*N*-methoxy-*N*-methyl-benzamide (2.5 equiv.).[e] The C2,C6 disubstituted derivative**13a** was obtained as an 80 : 20 cis:trans mixture. [f]The C2,C6 disubstituted derivative was not isolated.

***Table 2**. Optimization of the lithiation/trapping of tetrahydro-2H-thiopyran 1,1-dioxide **11**.*

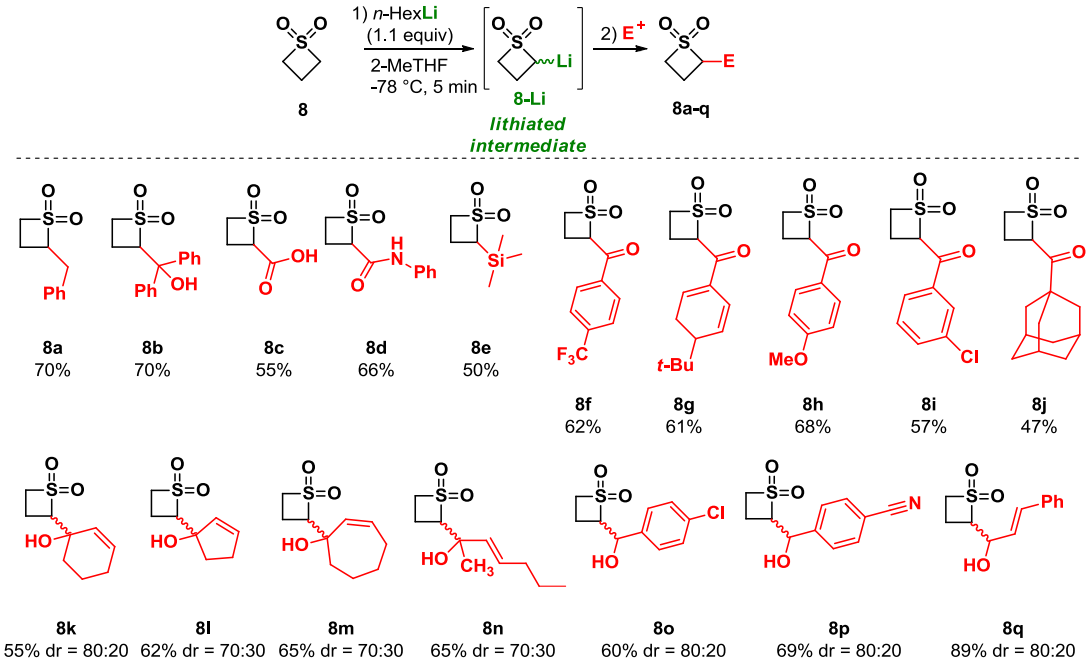
These evidences suggested that, a selective C2 functionalization was hard to achieve probably due to a competing double H-abstraction; moreover the studies conducted on **11** underline that the smaller heterocycle show a more regioselective lithiation, and so the four- and six-membered rings behave differently.

In fact, for the six-membered rings it seems that the regioselectivity of the lithiation reaction was depending from the nature of the solvent and from the electrophile chosen (Table 2, entries 3-4).

An interesting aspect that raised during the optimization study, was related to the ease of the process and its sustainability. In fact, the process did not required an aqueous work-up procedure for obtaining the crude of the reaction,[101] and can be conducted with a safer base like HexLi and, as mentioned before, in a more sustainable solvent such as 2-MeTHF.

3.2. Application of the strategy

The optimized protocol was employed for the trapping with a plethora of electrophiles. As show in the *Scheme 7*, trapping of lithiated thietane **8-Li** efficiently occurred with carbonyl compounds such as aldehydes or ketones, Weinreb amides, isocyanates, silyl and benzylhalides, carbon dioxide, leading to C2-functionalized thietanes **8a-q**. These latter adducts were obtained in good yields and with a reasonable stereoselectivity in the reaction of prochiral electrophiles as in the case of **8k-q** (Scheme 7).

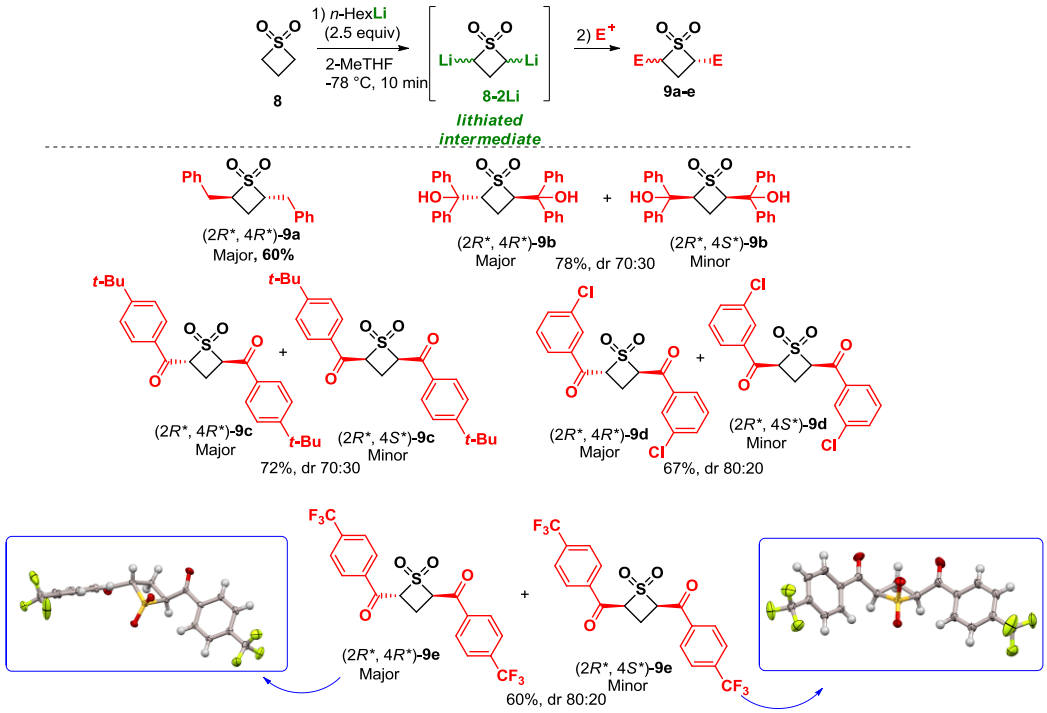


***Scheme** 7. Mono-functionalization of thietane 1,1-dioxide **8**.*

Driven from the optimal conditions reported in the Table 1 entry 5, a double functionalization at the two α-positions (C2 and C4) of the thietane was carried out.

The trapping of the intermediate **8-Li** successfully occurs via lithiation/trapping mechanism with several electrophiles such as benzylbromide, benzophenone and Weinreb amide. The reaction leading to **9a-e** as products, in good yield and with acceptable trans stereoselectivity that can be rationalized considering the steric hindrance (Scheme 8).

The structures and stereochemistry for the major and the minor stereoisomers (2R*,4R*)-**9e** and (2R*,4S*)-**9e** respectively were ascertained by single crystal X-ray analysis.



Scheme 8. *Double functionalization of thietane 1,1-dioxide* ***8***.

With the aim to obtain mechanistic insight on the intermediacy of **8-2Li**, and exclude a sequential lithiation process, a lithiation/deuteration experiment has been conducted on thietane **8**. In particular, thietane sulfone **8** was reacted with 1.5 equiv of HexLi under the optimized conditions and quenched with a deuterium source (CD_3OD) after 10 minutes of lithiation time at -78 °C.[13] Under these conditions it was expected that the first equivalent of base generated the monolithiated intermediate, and that the remaining 0.5 equiv of base generated the di-lithiated intermediate (0.5 equiv).

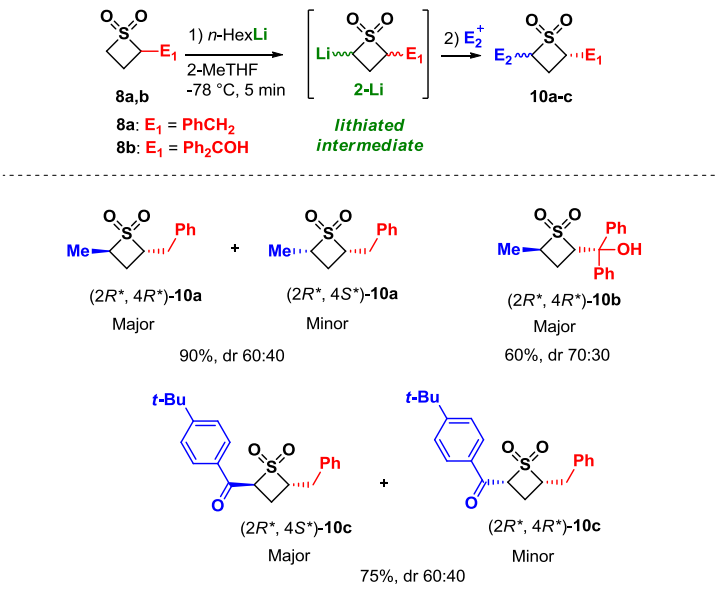
According to expectations, NMR and HRMS analyses, upon deuteration, an almost 1:1 mixture of mono deuterated and di-deuterated thietane was observed. These evidences helped us to understand that probably the double functionalization at C2 and C4 carbons of **8** occurs following a double lithiated intermediate such as **8-2Li** (see the Experimental section).

Subsequently, we turned out our attention on the possibility to introduce different substituents at C2 and C4 carbon atoms of the ring through a non-symmetric approach.

As reported in Scheme 9, starting from compounds **8a-b,** non symmetrically substituted C2, C4 di-functionalized thietanes **10a-c** were obtained in good yields through a lithiation/trapping sequence with different electrophiles, such as MeI, BnBr, benzophenone and 4-tert-Butyl-N-methoxy-N-methyl-benzamide.

All products were obtained as a diasteroisomeric mixtures and Noesy experiments highlighted that the trans isomers was preferred in alkylation reactions (as for (2R*,4R*)-**10a** and

(2R*,4R*)-**10b**), while the cis stereoisomer was the major one in acylation reactions (as for (2R*,4R*)-**10c**).



Scheme 9. *C2,C4 double functionalization of mono substituted thietane 1,1-dioxides* ***8a-b***.

Nevertheless, further lithiation/deuteration experiments performed on (2R*,4R*)-**9a**, and on the diastereomeric mixture of keto thietane sulfones (2R*,4R*)- and (2R*,4S*)-**9d** emphasized that likely kinetic products are observed under the reaction conditions.[13]

In particular, in the case of enolizable keto-substituted thietane sulfones, the trans stereoisomers are probably also the thermodynamic products (Scheme 8).

However, as reported in the sperimental section of this thesis, these kinds of compounds, in protic solvents such as MeOH, undergo a very fast epimerization that could alter the final diastereomeric ratio.[13]

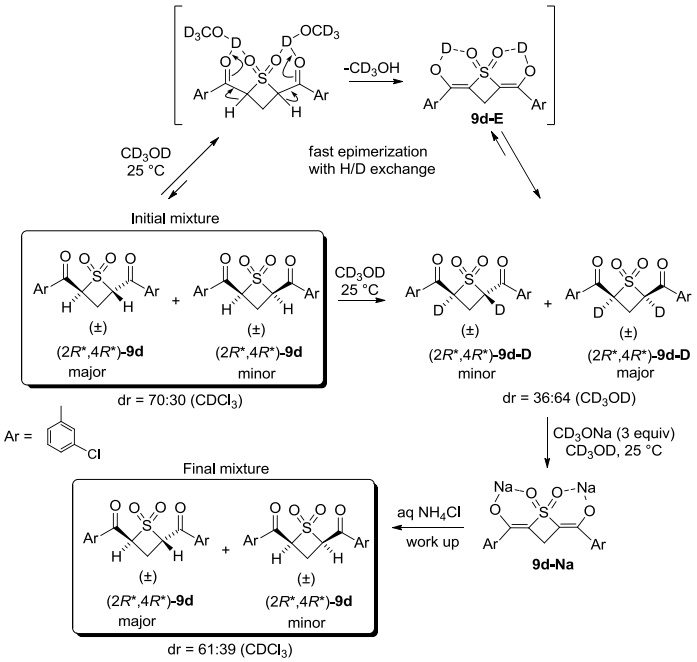
However, in order to explain the observed diastereoselectivity in the reactions of **8-2Li** with Weinreb amides an ^{1}H NMR experiment has been runned.

As show in the Scheme 10, when a 70:30 diastereomeric mixture of (2R*,4R*)-**9d** and (2R*,4S*)-**9d** was solubilized in CD_3OD and analyzed by ^{1}H NMR, an opposite stereochemical preference was observed; in particular a fast H/D exchange occured at 25 °C leading to the formation of (2R*,4R*)-**9d-D** and (2R*,4S*)-**9d-D** in 36:64 diastereomeric ratio respectively.

Upon addition of CD_3ONa (3 equiv), to the NMR tube containing the (2R*,4R*)-**9d-D** and (2R*,4S*)-**9d-D** diastereomeric mixture, led to the formation of the corresponding di-enolate **9d-Na** as main species. Addition of an aqueous solution of ammonium chloride followed by

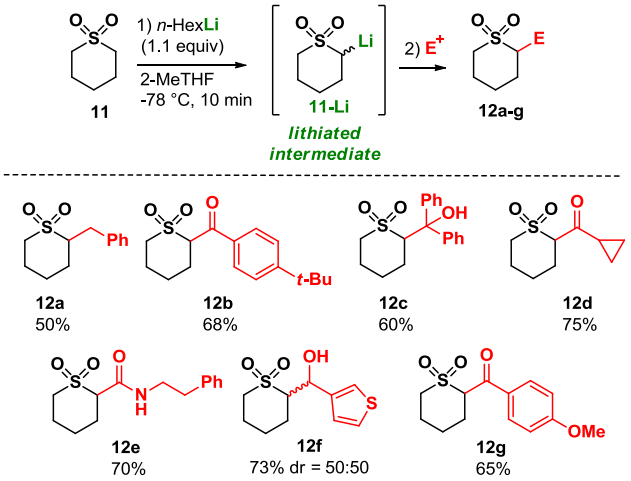
work-up with AcOEt furnished again a mixture of (2R*,4R*)-**9d** and (2R*,4S*)-**9d** but with a 61:39 diastereomeric ratio respectively (Scheme 10).

This experiment help us to understand that these kinds of compounds, in a protic solvent as MeOH, ungergo a very fast epimerization that could be explained assuming an enolization of keto thietane. Moreover, this very fast H/D exchange could alter the final diastereomeric ratio.



Scheme 10. *Evaluation of diastereomeric distribution for di-substituted keto-thietane* ***9d****.*

For sake of comparison, the lithiation/trapping of six-membered heterocycle tetrahydro-2H-thiopyran 1,1-dioxide **11** was further investigated (Table 2). With the best conditions in hand (see table 2, entry 1), the trapping of the lithiated specie **11-Li** effectively occurs leading to C2 mono-substituted thiopyran 1,1-dioxide **12a-g** in good yield (Scheme 11). When a prochiral aldehyde was used as elctrophile, a 1:1 mixture of diastereoisomers was observed for adduct **12f** (Scheme 11).



Scheme 11. *C2 functionalization of tetrahydro-2H-thiopyran 1,1-dioxide* ***11****.*

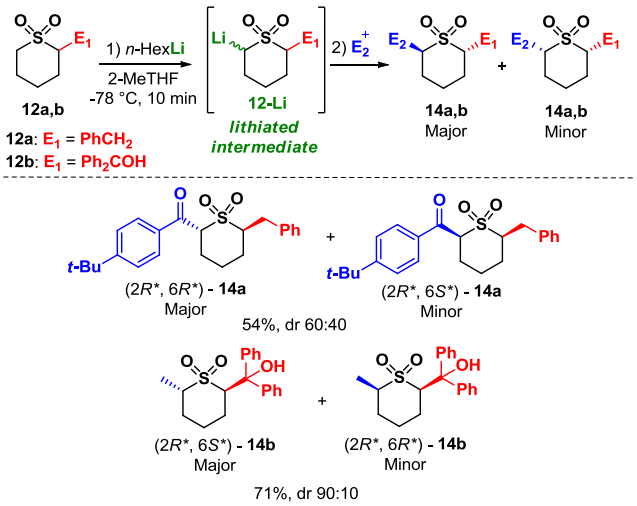
Subsequently, a non-symmetrical double functionalization of C2-substituted thiopyrans **12a,b** was investigated.

From a stereochemical point of view, the experiments carried out have disclosed that the reaction stereoselectivity was electrophile-dependent after introducing the second electrophile (Scheme 12).

In fact, compounds **14a,b** were obtained in modest yields but with a variable degree of stereoselectivity depending on the electrophile.

Moreover, in contrast to thietane 1,1-dioxide **8**, when the reaction was run with MeI, *cis* stereoisomer (2R*,6R*)-**14b** was the major product observed with a high diasteroisomeric ratio (90:10); while by using Weinreb amide as electrophile the *trans* stereoisomer (2R*,6R*)-**14a** was the main one with modest diasteroisomeric selectivity (dr 60:40) (Scheme 12).

The different stereochemical preference observed in the double (C2, C6) functionalization of thiopyrans, with respect to the four-membered ring, could be explained considering a different thermodynamic stability of the C2, C6 di-substituted derivatives.



Scheme 12. *C2, C6 di-functionalization of tetrahydro-2H-thiopyran 1,1-dioxide.*

It is likely that in thiopyrans, the stereoisomer that sets the two substituents in a di-equatorial fashion is preferred, just as seen with **13a** (Table 2), where *X-ray analysis* is available, and (2R*,6R*)-**14b** where a higher stereoselectivity is observed.

In the case of acylated thiapyrans such as **14a**, it is reasonable to assume that an epimerization occurs according to what observed in the case of keto thietane **9d**.

Finally, with the aim of investigating the synthetic utility of these species both thietane 1,1-dioxide **8** and tetrahydro-*2H*-thiopyran 1,1 dioxide **11** were used as starting material in more relevant reactions such as C2 arylation and fluorination (Scheme 13a and b).

It should be noted that, a direct α-arylation on both cyclic sulfones **8** and **11** effectively occurs through Li/Cu transmetalation and by using an aryliodonium salt such as Ph_2IPF_6 as the arylating agent. The corresponding products **15a,b** were obtained in modest yield (Scheme 13a).

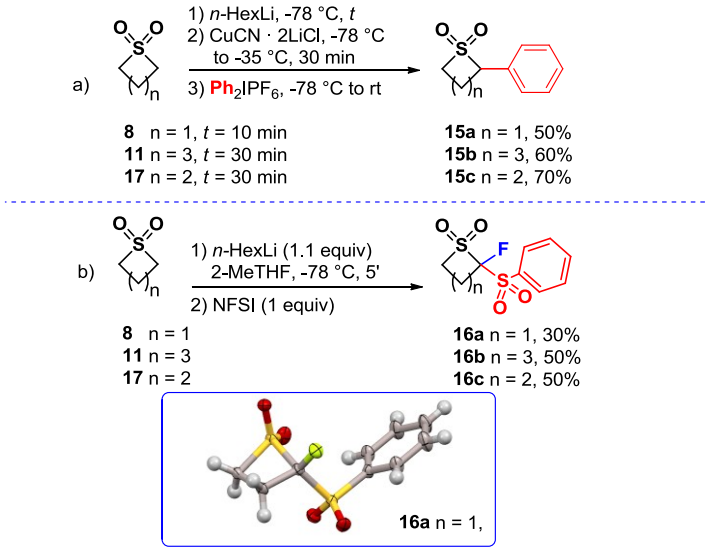
Surprisingly, the lithiation of four- and six-membered cyclic sulfones **8** and **11** followed by subsequent trapping with *N*-fluorodibenzenesulfonimide (NFSI) as the fluorinating agent led to products **16a,b** (Scheme 13b).

We tried to explain this unusual behaviour supposing that the introduction of the fluorine at C2 renders the remaining proton very acidic so as to be removed under the basic reaction conditions, allowing a further sulfonylation.

Finally, these new transformations were also tested on five membered sulfolane that has been already studied in lithiation trapping reactions.[102]

We were glad to find that under the developed reaction conditions (Scheme 13) sulfolane **17** furnished either the C2-arylated product **15c** or the α,α di-functionalized fluorinated

derivative **16c**. In the case of **16a**, the structure of this unusual fluoro-sulfonylated derivative was confirmed by single crystal *X-ray analysis*.[103]



Scheme 13. *a) C2-arylation of cyclic sulfones; b) C2-fluorination of cyclic sulfones.*

After investigating the reactivity of cyclic sulfones, the lipophilicity of 24 selected derivatives, including C2-mono- and C2,C4-difunctionalized four-membered (2-MTE and 2,4-DTE respectively) and C2-mono- and one C2,C6-difunctionalized six-membered (2-MTHTP and 2,6-DTHTP respectively) cyclic sulfones, was assessed through reversed-phase high performance liquid chromatography (RP-HPLC).

Lipophilicity is an important molecular property that influence absorption, distribution, metabolism, excretion and toxicity (ADMET) of a potential drug substance, and therefore its determination has relevance in the drug discovery process.[104,105]

In the last years, RP-HPLC has been widely employed as a useful method for evaluating drug lipophilicity at the early stages of drug discovery. [106]

In this study, the relative lipophilicity of cyclic sulfone derivatives was measured by previously reported RP-HPLC methods.[107]

An alkyl modified C18 column was used as the stationary phase and capacity factors (k') of each compound were determined at different MeOH/aqueous buffer (pH 5) mobile phase v/v compositions (0.05-increments of MeOH volume fraction, ranging between 0.7 and 0.3). For all the examined compounds the log k' values increased linearly ($r^2 \geq 0.98$) with the decreasing MeOH volume fraction, and the linear relationships were extrapolated to a 100% aqueous mobile phase to yield log k'_w values. Lipophilicity data were also estimated using two

well-known computational tools (BioLoom software, vers. 1.7 and ACDLabs software, release 10.0) for calculating 1-octanol–water partition coefficients (clog *P*).

Experimental and calculated lipophilicity parameters are listed in Table 3 and in the ESI reported in the experimental section).

2-monofunctionalized thietane 1,1-dioxides (2-MTE)											
Cmpd	**8a**	**8d**	**8f**	**8h**	**8i**	**8j**	**8k**	**8o**	**8p**	**15a**	**16a**
clogP[a]	0.54	-0.22	1.08	0.29	0.85	1.18	0.29	0.38	-0.90	0.21	0.81
log k'_w[b]	1.97	1.44	2.94	1.89	2.50	3.34	2.19	2.02	0.95	1.47	2.12
2,4-difunctionalized thietane 1,1-dioxides (2,4-DTE)											
Cmpd	**9a**			**9d**			**9e**			**10c**	
clogP[a]	2.48			3.25			3.70			3.98	
log k'_w[b]	3.71			4.38			5.38			5.01	
2-monofunctionalized tetrahydro 2H-thiopyran 1,1-dioxides (2-MTHTP)											
Cmpd	**12a**	**12b**	**12c**	**12e**	**12f**	**12g**	**13a**	**15b**	**16b**		
clogP[a]	1.66	3.01	2.22	1.14	0.43	1.40	3.60	1.33	1.64		
log k'_w[b]	2.62	3.90	3.20	2.18	1.48	2.19	4.25	1.91	2.20		

[a]*n*-Octanol/water partition coefficient calculated by CLOGP software ver. 4.73 (Biobyte, Claremont, CA, USA). [b]RP-HPLC capacity factor extrapolated at 100% water volume fraction in aqueous mobile phase.

Table 3. *Lipophilicity parameters of thietane and tetrahydro-2H-thiopyran 1,1-dioxide derivatives.*

The comparison between the chromatographic parameters and *in silico* lipophilicity descriptors showed that a better linear relationship, which holds up over a range of about 5 log *P* units, exists between log k'_w and clog *P* calculated by using Bio-Loom software, as shown by the following equation:

$$\log k'w = 0.84\ (\pm 0.06) clog\ P + 1.51\ (\pm 0.12) \qquad (1)$$

$$n = 24, r^2 = 0.885, s = 0.411, F = 168$$

where *n* represents the number of data points, r^2 is the coefficient of determination (squared correlation coefficient), *s* is the standard deviation of the regression equation, and *F* is the statistical significance of fit; 95% confidence intervals of the regression coefficients are given in parentheses.

A closer look at the scatter plot relating log k'_w and clog *P* (Fig. 2) points out that there are two groups of points lying on two almost parallel lines.

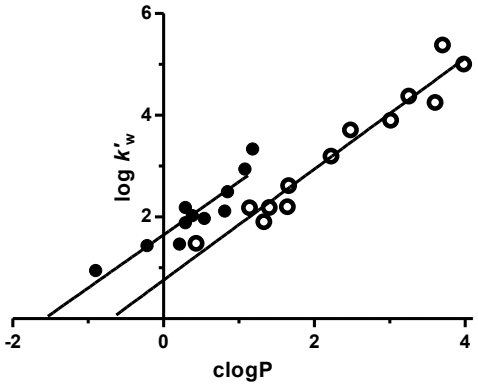


Figure 2. Graphical comparison between RP-HPLC lipophilicity parameter log k'_w and clog P calculated by the Bio-Loom software. (●) 2-Monofunctionalized thiethane 1,1-dioxide derivatives (2-MTE); (○) 2,4-difunctionalized thiethane 1,1-dioxide (2,4-DTE), and 2-mono- (2-MTHTP) and 2,6-difunctionalized tetrahydro-2*H*-thiopyrane 1,1-dioxide (2,6-DTHTP) derivatives.

The separate regression analysis yielded the following linear equations, one gathering all the 2-MTE derivatives (eqn (2)) and the other gathering the 2,4-DTE, 2-MTHTP and 2,6-DTHTP derivatives (eqn (3)):

$$\log k'w = 1.04\ (\pm 0.15) clog\ P + 1.65\ (\pm 0.10) \quad (2)$$

$$n = 11, r^2 = 0.846, s = 0.281, F = 49.3$$

$$\log k'w = 1.09\ (\pm 0.075) clog\ P + 0.76\ \ (\pm 0.19) \quad (3)$$

$$n = 13, r^2 = 0.951, s = 0.294, F = 211.6$$

The slope value (sensitivity) close-to-one in both eqn (2) and (3) suggests that the solvophobic interactions involved inthe octanol–water partitioning have similar effects on the RP-HPLC retention of the cyclic sulfone derivatives. In contrast, the positive intercept values (+1.65 and +0.76 in eqn (2) and (3), respectively) can be attributed to the so-called 'silanophilic' interactions with free silanol groups on the silica-based C18 stationary phase, which results in increased log k'_w values.

Silanophilic interactions in RP-HPLC retention mechanisms mainly depend upon polarity, and electrostatic and H-bonding interactions of the analytes, which are in turn negatively affected by the reduction (due to the surrounding substitution degree, steric restriction to solvation, etc.) of the surface area available to polar groups of the analytes to bind free silanols.[108]

With the cyclic sulfones examined herein, it appeared that the degree of silanophilic interactions, accounted for by the intercept values in eqn (2) and (3), correlate with the cycle size (four- vs.six-membered cycles), degree of functionalization (mono-vs. di-functionalized derivatives) and polar/H-bonding features of the substituents in α to the H-bond acceptor SO_2 group.

4. Conclusion

In conclusion, a greener and efficient access to substituted four- and six-membered sulfur-bearing heterocycles in lithiation/electrophilic trapping sequences has been disclosed. This investigation realizes that, the stereoselective functionalization of thietane 1,1-dioxide and the corresponding homologue tetrahydro-*2H*-thiopyran is feasible with good electrophiles tolerance.

Mono (C2 substituted) and doubly (C2,C4 or C2,C6 disubstituted) functionalized cyclic sulfones have been obtained from the readily available starting material by using the corresponding organometallic intermediates that reacted with electrophiles leaving intact the 4- and 6-membered rings.

One of the strengths of this approach was related to the ease of the process and its eco-compatibility. In fact, the process did not required an aqueous work-up procedure for obtaining the crude of the reaction, and can be conducted with a safer base asHexLi and, in a more eco-friendly solvent such as 2-MeTHF.

Concerning the mechanism of the lithiation reaction, deuteration experiments conducted on thietane 1,1-dioxide, showed that a double lithiathion at C2 and C4 carbons occurs, excluding in this way a sequential lithiation.

It is worth pointing out that, this protocol, was compatible with transmetallation with CuCN-2LiCl and C_{sp}^2 cross coupling reaction.

Moreover, attempts for electrophilic fluorination at the C2, resulted in an unexpected concomitant arylsulfonylation.

For representative substituted cyclic sulfones, the lipophilicity was measured by RP-HPLC, which significantly encodes solvophobic and silanophilic interactions of the analytes. A high linear correlation, with a slope close to 1.0, was observed between the experimental chromatographic parameter log k'_w and in *silico* lipophilicity descriptor clog *P*. A systematic difference in absolute values between the two parameters has to be most likely attributed to silanophilic interactions mainly involving the H-bond acceptor SO_2 group. The results obtained in this reactivity and quantitative structure-property relationship study can be useful, not only in understanding the RP-HPLC retention of cyclic sulfones, but also in assessing lipophilicity profiles of sulfonyl-containing bioactive substances in early drug discovery programs.

5. Experimental Section

Within this experimental section the characterization data of coumponds **86a-q**, **9a-e**, **10a-c**, **12a-g**, **14a-b**, **15a-c** and **16a-c** were reported. The copies of ^{1}H NMR, ^{13}C NMR, HSQC, COSY of such compounds are available free of charge on the http://www.rsc.org/suppdata/c7/ob/c7ob00846e/c7ob00846e1.pdf

5.1 Material and methods

THF and 2-MeTHF was freshly distilled under a nitrogen atmosphere over Na/benzophenone. N,N,N',N'-tetramethylethylenediamine (TMEDA) was distilled over finely powdered CaH_2, hexyllithium was purchased as hexane solution and was filtered on celite before using and title established by titration method1. All the other chemicals were commercially available and used without further purification.

Magnetic Resonance spectra were recorded using Varian 500 MHz, and Bruker 400 and 600 MHz spectrometers. For the ^{1}H, ^{13}C NMR spectra (^{1}H NMR 400, 500, 600 MHz, ^{13}C NMR 100, 125, 150 MHz), $CDCl_3$, methanol-d_4 and toluene-d_8 were used as the solvents. MS-ESI analyses were performed on LC/MSD trap system VL.

Melting points were uncorrected. GC-MS spectrometry analyses were carried out on a gas chromatograph (dimethylsilicon capillary column, 30 m, 0.25 mm i.d.) equipped with a mass selective detector operating at 70 eV (EI). Analytical thin layer chromatography (TLC) was carried out on precoated 0.25 mm thick plates of Kieselgel 60 F254; visualization was accomplished by UV light (254 nm) or by spraying a solution of 5 % (w/v) ammonium molybdate and 0.2 % (w/v) cerium(III) sulfate in 100 ml 17.6 % (w/v) aq. sulphuric acid and heating to 200 °C for some time until blue spots appear. Infra-red spectra of the compounds were recorded neat, as film, as KBr disc as indicated, by a Perkin-Elmer 283 spectrometer. For flash chromathography silica Gel 60, 0.04-0.063 mm particle size was used. CHN analyses were performed on a EuroEA 3000 analyzer. The high resolution mass spectrometry (HRMS) analyses were performed using a Bruker microTOF QII mass spectrometer equipped with an electrospray ion source (ESI) operated in positive ion mode.

The sample solutions (CH_3OH or CH_3OH + 0.1%v/v HCOOH) were introduced by continuous infusion at a flow rate of 180 mL $min^{-1}$with the aid of a syringe pump.

The instrument was operated with end-plate offset and capillary voltages set to –500 V and –4500 V respectively. The nebulizer pressure was 0.4 bar (N_2), and the drying gas (N_2) flow rate was 4.0 L min-1. The capillary exit and skimmer 1 voltages were 90 V and 30 V, respectively. The drying gas temperature was set at 180 °C.

The calibration was carried out with sodium formate: a solution made up of 10 µl of 98% formic acid, 10 µl of sodium hydroxide (1.0 M), 490 µl of i-propanol and 490 µl of deionized water. The software used for the simulations was Bruker Daltonics DataAnalysis (version 4.0). All reactions involving air-sensitive reagents were performed under argon in oven-dried glassware using syringe septum cap technique.

5.2 General procedure for lithiation/electrophilic trapping sequence on C2-substituted thietane 1,1-dioxide.

To a stirred solution of thietane 1,1-dioxide commercially available (1.0 mmol, 1.0 equiv) in dry 2-MeTHF (10 mL) cooled at -78°C, a solution of n-HexLi (2.5M in hexane, 1.1 equiv) was added dropwise. After stirring for 5 min. at -78°C, the electrophile (1 equiv) was added neat if liquid and in 1.0 mL of solvent if solid. After the reaction was complete, as ascertained by GC or TLC, the reaction mixture was quenched with saturated aqueous NH_4Cl (0.1mL) and directly filtered over Na_2SO_4 and concentrated in vacuo. Flash chromatography on silica gel (Hexane/AcOEt) afforded the thietane 1,1-dioxide substitute.

2-benzylthietane 1,1-dioxide-8a.

Column chromatography on silica gel (Hexane/AcOEt 70:30), white solid, mp 67-70 °C, 70% (142 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.84-1.90 (m, 1H), 2.23-2.29 (m, 1H), 3.03 (dd, J = 14.6, 7.8 Hz, 1H), 3.43 (dd, J = 14.6, 7.8 Hz, 1H), 3.92-4.04 (m, 2H), 4.59 (m, 1H), 7.23-7.26 (m, 3H), 7.31-7.34 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.0, 35.2, 61.8, 79.0, 127.0, 128.7, 128.9, 136.4. FT-IR (KBr, cm^{-1}) υ 613, 700, 757, 1121, 1161, 1294, 2922. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{10}H_{12}O_2SNa$ 219.0450; found 219.0456.

(1,1-dioxido-2-thietanyl)-(diphenyl)methanol-8b.

Column chromatography on silica gel (Hexane/AcOEt 70:30), white solid, mp 143-146 °C, 70% (160 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80-1.89 (m, 1H), 2.36-2.46 (m, 1H), 3.91-3.96 (m, 2H), 4.03 (s, 1H, OH), 5.36 (t, *J* = 9.3 Hz, 1H), 7.12-7.32 (m, 8H), 7.46-7.48 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 8.8, 62.5, 72.8, 84.4, 125.4, 126.0, 127.4, 128.2, 128.8, 142.8, 144.8. FT-IR (KBr, cm^{-1}) υ 511, 546, 698, 800, 1123, 1152, 1250, 1449, 1490, 2965, 3011, 3029, 3063, 3090, 3489. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{16}H_{16}O_3SNa$ 311.0712; found 311.0717.

1,1-dioxido-2-thietanyl-carboxylic acid-8c.

White solid, mp 143-146 °C, 55% (85 mg). ^{1}H NMR (600 MHz, CD_3OD) δ 2.28-2.32 (m, 1H), 2.39-2.44 (m, 1H), 4.05-4.13 (m, 1H), 4.16-4.21 (m, 1H), 5.23 (m, 1H). ^{13}C NMR (150 MHz, CD_3OD) δ 9.5, 63.8, 79.5, 165.8. FT-IR (KBr, cm^{-1}) υ 584, 607, 804, 1136, 1180, 1303, 1387, 1449, 1633, 1732, 2974. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_4H_6O_4SNa$ 172.9879; found 172.9888.

***N*-phenyl-2-thietanecarboxamide 1,1-dioxide-8d.**

Column chromatography on silica gel (Hexane/AcOEt 70:30), white solid, mp 150-152 °C, 66% (150 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32-2.42 (m, 1H), 2.68-2.77 (m, 1H), 4.12-4.31 (m, 2H), 5.12-5.16 (m, 1H), 7.12-7.16 (m, 1H), 7.29-7.33 (m, 2H), 7.53-7.55 (m, 2H), 8.33 (bs, 1H, NH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 10.1, 65.0, 80.6, 120.3, 125.2, 129.1, 137.0, 160.6. FT-IR (KBr, cm^{-1}) υ 604, 620, 689, 753, 1136, 1302, 1315, 1539, 1599, 1688, 3368. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{10}H_{11}NO_3SNa$ 248.0532; found 248.0533.

(1,1-dioxido-2-thietanyl)(trimethyl)silane-8e.

Column chromatography on silica gel (Hexane/AcOEt 70:30), yellow oil, 50% (90 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.22 (s, 9H), 1.88-1.97 (m, 1H), 2.15-2.24 (m, 1H), 3.98-4.06 (m, 2H), 4.12-4.21 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ -2.9, 7.7, 65.8, 69.9. FT-IR (NaCl, cm^{-1}) υ 608, 840, 1126, 1304, 2957. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_6H_{14}O_2SSiNa$ 201.0376; found 201.0376.

(1,1-dioxido-2-thietanyl)[4-(trifluoromethyl)phenyl]methanone-8f.

Column chromatography on silica gel (Hexane/AcOEt 60:40), white solid, mp 108-110 °C, 62% (173 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30-2.39 (m, 1H), 2.94-3.04 (m, 1H), 4.15-4.34 (m, 2H), 5.91-5.96 (m, 1H), 7.80-7.82 (m, 2H), 8.15-8.17 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 7.6, 64.4, 82.4, 123.3 (d, J = 272.9 Hz), 126.3 (q, J = 3.7 Hz), 129.0, 135.6 (q, J = 33.0 Hz), 137.9, 186.5. ^{19}F NMR (377 MHz, $CDCl_3$) δ -63.3 (s). FT-IR (KBr, cm^{-1}) υ 587, 864, 1065, 1122, 1171, 1314, 1688. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{11}H_9F_3O_3SNa$ 301.0117; found 301.0119.

(1,1-dioxido-2-thietanyl)[4-(2-methyl-2-propanyl)phenyl] methanone-8g.

Column chromatography on silica gel (Hexane/AcOEt 60:40), white solid, mp 98-101 °C, 61% (161 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 9H), 2.23-2.33 (m, 1H), 2.94-3.03 (m, 1H), 4.12-4.29 (m, 2H), 5.91-5.95 (m, 1H), 7.54-7.57 (m, 2H), 7.97-8.00 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 7.6, 31.0, 35.3, 64.1, 82.2, 126.2, 128.7, 132.8, 158.7, 186.6**.** FT-IR (KBr, cm^{-1}) υ 593, 722, 753, 805, 1133, 1313, 1686. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{14}H_{18}O_3SNa$ 289.0869; found 289.0869.

(1,1-dioxido-2-thietanyl)(4-methoxyphenyl)methanone-8h.

Column chromatography on silica gel (Hexane/AcOEt 60:40), white solid, mp 137-140 °C, 68% (153 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23-2.32 (m, 1H), 2.95-3.01 (m, 1H), 3.89 (s, 3H), 4.11-4.26 (m, 2H), 5.87-5.91 (m, 1H), 6.99-7.02 (m, 2H), 8.01-8.04 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 7.7, 55.6, 64.1, 82.1, 114.4, 128.5, 131.1, 164.9, 185.3. FT-IR (KBr, cm^{-}

^{1}) υ 577, 788, 843, 1016, 1132, 1175, 1313, 1594, 1662, 2923. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{11}H_{12}O_4SNa$ 263.0349; found 263.0349.

(3-chlorophenyl)(1,1-dioxido-2-thietanyl)methanone-8i.

Column chromatography on silica gel (Hexane/AcOEt 60:40), white solid, mp 93-95 °C, 57% (140 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27-2.37 (m, 1H), 2.93-3.02 (m, 1H), 4.15-4.22 (m, 1H), 4.26-4.32 (m, 1H), 5.87-5.91 (m, 1H), 7.48-7.52 (m, 1H), 7.62-7.65 (m, 1H), 7.90-7.93 (m, 1H), 8.02-8.03 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 7.7, 64.4, 82.2, 126.7, 128.6, 130.5, 134.6, 135.7, 136.8, 186.2. FT-IR (KBr, cm^{-1}) υ 593, 722, 753, 805, 1133, 1313, 1686. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{10}H_9ClO_3SNa$ 266.9853; found 266.9855.

adamantan-1-yl(1,1-dioxido-2-thietanyl)methanone-8j.

Column chromatography on silica gel (Hexane/AcOEt 60:40), white solid, mp 95-97 °C, 47% (127 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.69-1.78 (m, 6H), 1.80-1.93 (m, 6H), 2.01-2.10 (m, 4H), 2.64-2.73 (m, 1H), 4.06-4.16 (m, 2H), 5.54-5.58 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 7.6, 27.6, 36.3, 37.3, 46.0, 64.4, 80.1, 202.5. FT-IR (KBr, cm^{-1}) υ 589, 1130, 1167, 1308, 1698, 2903. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{14}H_{20}O_3SNa$ 291.1025; found 291.1025.

1-(1,1-dioxido-2-thietanyl)-2-cyclohexen-1-ol-8k.

Column chromatography on silica gel (Hexane/AcOEt 60:40), white solid, mp 57-62 °C, 55% (112 mg) Dr = 80:20. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38-1.43 (m, 1H minor) 1.54-1.88 (m, 3H major + 3H minor), 1.94-2.21 (m, 4H major + 3H minor), 2.34-2.48 (m, 1H minor + 1H major), 3.13 (s, 1H major + 1H, minor), 3.96-4.05 (m, 2H major + 2H minor), 4.39-4.45 (m, 1H minor + 1H major), 5.48 (d, J = 10.0 Hz, 1H, major), 5.89-5.93 (m, 2H minor + 1H minor). ^{13}C NMR (101 MHz, $CDCl_3$) δ 8.2 (minor), 8.6 (major), 18.1 (minor), 18.3 (major), 24.9 (minor), 24.9 (major), 33.1 (minor), 35.7 (major), 63.2 (major), 63.2 (minor), 69.3 (minor), 69.6 (major), 85.6 (major), 86.1 (minor), 126.6 (major), 129.2 (minor), 131.7 (minor), 132.6 (major). FT-IR (KBr, cm^{-1}) υ 506, 729, 1104, 1123, 1307, 1408, 2927, 3517. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_9H_{14}O_3SNa$ 225.0556; found 225.0556.

1-(1,1-dioxido-2-thietanyl)-2-cyclopenten-1-ol-8l.

Column chromatography on silica gel (Hexane/AcOEt 75:25), colorless oil, 62% (120 mg), D_r 75:25. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81-1.88 (m, 1H, minor), 1.93-2.02 (m, 1H, minor), 2.09-2.40 (m, 5H, major), 2.17- 2.45 (m, 3H, minor), 2.51-2.60 (m, 1H, minor), 2.54-2.63 (m, 1H, major), 3.10 (s, 1H, OH, minor), 3.11 (s, 1H, OH, major), 3.97-4.07 (m, 2H, minor), 3.97-4.01 (m, 2H, major), 4.37-4.41 (m, 1H, minor), 4.42-4.46 (dd, J = 10.0, 7.6 Hz, 1H,

major), 5.68-5.70 (dt, d = *J* = 5.7 Hz, t = *J* = 2.2 Hz, 1H, major), 5.92 (dt, d = *J* = 5.6 Hz, t = *J* = 2.2 Hz, 1H, minor), 6.03 (dt, d = *J* = 5.6 Hz, t = *J* = 2.4 Hz, 1H, minor), 6.02-6.04 (m, 1H, major). ^{13}C NMR (101 MHz, $CDCl_3$) δ 9.0 (minor), 9.6 (major), 30.5 (minor), 31.4 (major), 36.1 (minor), 37.7 (major), 63.4 (minor), 63.5 (major), 84.0 (minor), 84.4 (major), 85.6 (major), 85.6 (minor), 131.4 (major), 133.4 (minor), 135.9 (minor), 136.9 (major). FT-IR (NaCl, cm^{-1}) υ 518, 727, 1119, 1264, 1408, 2851, 2919. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_8H_{12}NaO_3S$ 211.0399; found 211.0398.

1-(1,1-dioxido-2-thietanyl)-2-cyclohepten-1-ol-8m.

Column chromatography on silica gel (Hexane/AcOEt 70:30), white solid, mp 61-64 °C, 65% (140 mg) D_r 70:30. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50-1.72 (m, 5H, minor), 1.47-1.57 (m, 1H, major), 1.64-1.77 (m, 2H, major), 1.89-1.97 (m, 1H, minor), 1.91-2.03 (m, 2H, major), 2.06-2.15 (m, 3H, major), 2.08-2.16 (m, 2H, minor), 2.18-2.27 (m, 1H, major), 2.26-2.42 (m, 2H, minor), 2.39-2.49 (m, 1H, major), 3.10 (bs, 1H, OH, major), 3.33 (bs, 1H, OH, minor), 3.90-4.03 (m, 2H, major), 3.92-4.06 (m, 2H, minor), 4.64-4.69 (m, 1H, minor), 4.69-4.73 (m, 1H, major), 5.43 (td, t = *J* = 1.7 Hz, d = J_{cis} = 11.9 Hz, 1H, major), 5.77 (ddd = *J* = 11.9, 7.4, 5.0 Hz, 1H, major), 5.82 (d = *J* = 11.9 Hz, 1H, minor), 5.91 (ddd = *J* = 11.9, 6.6, 5.6 Hz, 1H, minor). ^{13}C NMR (101 MHz, $CDCl_3$) δ 8.3 (minor), 8.6 (major), 23.9 (minor), 24.6 (major), 27.0 (major), 27.0 (minor), 27.7 (major), 27.8 (minor), 35.8 (minor), 39.1 (major), 62.8 (minor), 62.9 (major), 74.8 (minor), 75.9 (major), 82.5 (major), 85.3 (minor), 132.1 (major), 133.3 (minor), 134.2 (major), 135.8 (minor). FT-IR (KBr, cm^{-1}) υ 800, 1128, 1292, 1307, 1650, 2941, 3514. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{10}H_{16}O_3SNa$ 239.0712; found 239.0713.

(3*E*)-2-(1,1-dioxido-2-thietanyl)-3-hepten-2-ol-8n.

Column chromatography on silica gel (Hexane/AcOEt 60:40), colorless oil, 65% (145 mg), D_r 70:30. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.4 Hz, 3H, major), 0.90 (t, *J* = 7.4 Hz, 3H, minor), 1.19 (s, 3H, minor), 1.35-1.42 (m, 2H, major), 1.39-1.45 (m, 2H, minor), 1.56 (s, 3H, major), 1.98-2.09 (m, 3H, major), 2.02-2.08 (m, 2H, minor), 2.12-2.19 (m, 1H, minor), 2.24-2.33 (m, 1H, major), 2.39-2.49 (m, 1H, minor), 3.20 (bs, 1H, OH, major), 3.36 (bs, 1H, OH, minor), 3.88-4.04 (m, 2H, minor), 3.93-3.97 (m, 2H, major), 4.34 (dd, *J* = 10.0, 8.2 Hz, 1H, major), 4.49 (t, *J* = 9.4 Hz, 1H, minor), 5.24 (dt, d = *J* = 15.7 Hz, t = *J* = 1.3 Hz, 1H, major), 5.67 (dt, d = *J* = 15.7 Hz, t = *J* = 1.3 Hz, 1H, minor), 5.74 (dt, d = *J* = 15.7 Hz, t = *J* = 6.7 Hz, 1H, major), 5.81 (dt, d = *J* = 15.7 Hz, t = *J* = 6.7 Hz, 1H, minor). ^{13}C NMR (101 MHz, $CDCl_3$) δ 8.8 (minor), 8.9 (major), 13.5 (major), 13.5 (minor), 22.2 (minor), 22.2 (major),

26.0 (minor), 28.1 (major), 34.2 (major), 34.2 (minor), 62.6 (minor), 62.7 (major), 71.8 (major), 72.0 (minor), 85.6 (minor), 85.7 (major), 130.7 (minor), 131.3 (major), 131.6 (major), 133.7 (minor). FT-IR (NaCl, cm^{-1}) υ 730, 974, 1122, 1309, 1458, 2960, 3522. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{10}H_{18}O_3SNa$ 241.0869; found 241.0873.

(4-chlorophenyl)(1,1-dioxido-2-thietanyl)methanol-8o.

Column chromatography on silica gel (Hexane/AcOEt 60:40), white solid, mp 123-125 °C, 60% (149 mg) D_r 80:20. ^1H NMR (400 MHz, $CDCl_3$) δ 1.80-1.90 (m, 1H, minor), 1.97-2.08 (m, 1H, minor), 1.97-2.07 (m, 1H, major), 2.36-2.45 (m, 1H, major), 3.10 (bs, 1H, OH, minor), 3.32 (bs, 1H, OH, major), 3.96-4.02 (m, 2H, minor), 4.02-4.07 (m, 2H, major), 4.52-4.57 (m, 1H, major), 4.60-4.66 (m, 1H, minor), 5.08 (d, *J* = 9.0 Hz, 1H, minor), 5.44 (d, *J* = 3.0 Hz, 1H, major), 7.30-7.37 (m, 4H, major), 7.32-7.36 (m, 4H, minor). ^{13}C NMR (101 MHz, $CDCl_3$) δ 7.5 (major), 10.8 (minor), 62.1 (minor), 63.6 (major), 68.6 (major), 72.4 (minor), 82.8 (major), 83.1 (minor), 126.9 (major), 127.9 (minor), 129.0 (major), 129.2 (minor), 134.1 (major), 134.7 (minor), 137.5 (major), 137.5 (minor). FT-IR (KBr, cm^{-1}) υ 585, 782, 802, 1125, 1190, 1305, 1490, 3506. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{10}H_{11}ClO_3SNa$ 269.0010; found 269.0009.

4-[(1,1-dioxido-2-thietanyl)(hydroxyl)methyl]benzonitrile-8p.

Column chromatography on silica gel (Hexane/AcOEt 60:40), white solid mp 104-106 °C, 69% (164 mg), D_r 80:20. ^1H NMR (400 MHz, $CDCl_3$) δ 1.96-2.06 (m, 2H minor + 1H major), 2.32-2.42 (m, 1H, major), 3.49 (bs, OH, 1H), 4.03-4.11 (m, 2H major + 2H minor), 4.53-4.59 (m, 1H, major), 4.62-4.66 (m, 1H, minor), 5.15 (d, *J* = 9.0 Hz, 1H, minor), 5.49 (m, 1H, major), 7.50-7.53 (m, 2H major + 2H minor), 7.66-7.68 (m, 2H major + 2H minor). ^{13}C NMR (101 MHz, $CDCl_3$) δ 7.5 (major), 10.7 (minor), 62.4 (minor), 63.8 (major), 68.6 (major), 72.3 (minor), 82.3 (major), 82.7 (minor), 112.1 (major), 112.7 (minor), 118.2 (minor), 118.4 (major), 126.4 (major), 127.2 (minor), 132.6 (major), 132.8 (minor), 144.2 (minor), 144.3 (major). FT-IR (KBr, cm^{-1}) υ 563, 590, 784, 1124, 1292, 1605, 3449. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{11}H_{11}NO_3SNa$ 260.0352; found 260.0354.

(2*E*)-1-(1,1-dioxide-2-thietanyl)-3-phenyl-2-propen-1-ol-8q.

Column chromatography on silica gel (Hexane/AcOEt 50:50), white solid, mp 114-118 °C, 89% (238 mg), D_r 80:20. ^1H NMR (400 MHz, $CDCl_3$) δ 1.96-2.34 (m, 2H, minor), 2.12-2.22 (m, 1H, major), 2.33-2.42 (m, 1H, major), 2.95 (bs, 1H, OH, minor), 3.08 (bs, 1H, OH, major), 3.97-4.12 (m, 2H, minor), 4.04-4.08 (m, 2H, major), 4.46-4.51 (m, 1H, major), 4.47-4.60 (m, 1H, minor), 4.70-4.76 (m, 1H, minor), 5.03-5.05 (m, 1H, major), 6.07 (dd, *J* = 15.9,

5.5 Hz, 1H, major), 6.21 (dd, *J* = 15.9, 5.5 Hz, 1H, minor), 6.74 (d, *J* = 15.9 Hz, 1H, minor), 6.76 (dd, *J* = 15.9, 1.5 Hz, 1H, major), 7.27-7.40 (m, 5H, major), 7.29-7.44 (m, 5H, minor). ^{13}C NMR (101 MHz, $CDCl_3$) δ 7.8 (major), 10.4 (minor), 62.7 (minor), 64.0 (major), 68.2 (major), 71.9 (minor), 81.5 (major), 82.2 (minor), 125.7 (major), 126.1 (minor), 126.6 (major), 126.7 (minor), 128.2 (major), 128.4 (minor), 128.7 (minor), 128.7 (major), 132.3 (major), 133.5 (minor), 135.7 (minor), 135.9 (major). FT-IR (KBr, cm^{-1}) υ 749, 1129, 1302, 1640, 1722, 3457. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{12}H_{14}O_3SNa$ 261.0556; found 261.0560.

5.3 General procedure for lithiation-electrophile trapping sequence on C2,C2'-substituted thietane-1,1- dioxide.

To a stirred solution of thietane 1,1-dioxide (1.0 mmol, 1.0 equiv) in dry 2-MeTHF (10 mL) cooled at -78°C, a solution of *n*-HexLi (2.5M in hexane, 2.5 equiv) was added dropwise. After stirring for 10 min. at -78°C, the electrophile (2.5 equiv) was added neat if liquid and in 1.0 mL of solvent if solid. After the reaction was complete, as ascertained by GC or TLC, the reaction mixture was quenched with saturated aqueous NH_4Cl (0.1mL) and directly filtered over Na_2SO_4 and concentrated in vacuo. Flash chromatography on silica gel (Hexane/AcOEt) afforded the thietane 1,1-dioxide disubstitute.

2,4-dibenzylthietane 1,1-dioxide-9a.

Column chromatography on silica gel (Hexane/AcOEt 80:20), white solid, mp 78-81 °C, 60% (174 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97 (t, *J* = 8.1 Hz, 2H), 2.97 (dd, *J* = 14.6, 9.6 Hz, 1H), 3.44 (dd, *J* = 14.6, 6.9 Hz, 1H), 4.44-4.52 (m, 2H), 7.19-7.31 (m, 10H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.9, 35.4, 75.7, 127.1, 128.7, 128.9, 136.3. FT-IR (KBr cm^{-1}) υ 699, 744, 1163, 1303, 1454, 1495, 2925. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{17}H_{18}O_2SNa$ 309.0922; found 309.0920.

(1,1-dioxido-2,4-thietanediyl)bis(diphenyl)methanol-9b.

Column chromatography on silica gel (Hexane/AcOEt 80:20), white solid, mp 218-223 °C, 78% (370 mg), D_r 70:30. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60-1.64 (m, 1H, minor), 2.19 (t, *J* = 9.0 Hz, 2H, major), 3.09-3.13 (m, 1H, minor), 3.90 (s, 2H, minor), 3.96 (s, 2H, major), 5.20 (t, *J* = 9.9 Hz, 2H, minor), 5.36 (t, *J* = 8.9 Hz, 2H, major), 7.17-7.20 (m, 2H major + 2H minor), 7.24-7.38 (m, 16H major + 16H minor), 7.49-7.51 (m, 2H, major), 7.57-7.58 (m, 2H, minor). ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.5 (major), 12.8 (minor), 79.7 (minor), 82.6 (major), 125.3 (minor), 125.4 (major), 125.8 (major), 126.0 (minor), 127.3 (major), 127.4 (minor), 128.1 (major), 128.2 (minor), 128.4 (minor), 128.5 (major), 128.7 (minor), 128.8 (major), 142.7 (major), 143.0 (minor), 144.8 (minor), 145.0 (major). FT-IR (KBr, cm^{-1}) υ 528, 698, 1101, 1265, 1449, 2853, 2965, 3027, 3495. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for for $C_{29}H_{26}O_4SNa$ 493.1444; found 493.1446.

(1,1-dioxido-2,4-thietanediyl)bis[4-(2-methyl-2-propanyl)phenyl] methanone-9c.

Column chromatography on silica gel (Hexane/AcOEt 80:20), colorless oil, 72% (310 mg), D_r 70:30. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 18H, minor), 1.35 (s, 18H, major), 2.39 (dt, d =

J = 12.7 Hz, t = *J* = 9.7 Hz, 1H, minor), 3.06 (t, *J* = 8.2 Hz, 2H, major), 3.81 (dt, d = *J* = 12.7 Hz, t = *J* = 9.7 Hz, 1H, minor), 5.94 (t, *J* = 9.7 Hz, 2H, minor), 5.98 (t, *J* = 8.2 Hz, 2H, major), 7.48-7.56 (m, 4H minor + 4H major), 7.92-8.02 (m, 4H major + 4H minor). ^{13}C NMR (101 MHz, $CDCl_3$) δ 10.0 (major), 10.1 (minor), 31.0 (major), 31.0 (minor), 35.3 (minor), 35.4 (major), 79.3 (minor), 81.0 (major), 126.2 (minor), 126.2 (major), 128.6 (minor), 128.8 (major), 132.8 (minor), 158.7 (minor), 158.9 (major), 185.4 (minor), 186.7 (major). FT-IR (NaCl, cm^{-1}) υ 545, 991, 1125, 1325, 1603, 1677, 2961. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{25}H_{30}O_4SNa$ 449.1757; found 449.1756.

(1,1-dioxido-2,4-thietanediyl)bis[(3-chlorophenyl)methanone]-9d.

Column chromatography on silica gel (Hexane/AcOEt 80:20), yellow solid, mp 122-125 °C, 67% (254 mg), D_r 80:20. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (dt, d = *J* = 12.8 Hz, t = *J* = 9.7 Hz, 1H, minor), 3.08 (t, *J* = 8.1 Hz, 2H, major), 3.76-3.80 (dt, d = *J* = 12.8 Hz, t = *J* = 9.5 Hz, 1H, minor), 5.93 (t, *J* = 9.6 Hz, 2H, minor), 5.95 (t, *J* = 8.1 Hz, 2H, major), 7.51 (t, *J* = 7.9 Hz, 2H minor + 2H major), 7.62-7.65 (m, 2H minor + 2H major), 7.85-7.87 (dt, *J* = 7.8, 1.7, 1.0 Hz, 2H, major), 7.90-7.93 (dt, *J* = 7.8, 1.7, 1.0 Hz, 2H, minor), 8.02 (t, *J* = 1.9 Hz, 2H, major), 8.04 (t, *J* = 1.9 Hz, 2H, minor). ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.1 (minor), 10.2 (major), 79.5 (minor), 81.1 (major), 126.6 (minor), 126.8 (major), 128.6 (minor), 128.7 (major), 130.6 (major), 134.8 (minor), 134.8 (major), 135.8 (minor), 135.8 (major), 136.7 (minor), 136.7 (major), 184.9 (minor), 186.1 (major). FT-IR (KBr, cm^{-1}) υ 767, 777, 1162, 1320, 1425, 1687, 3068. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{17}H_{12}Cl_2O_4SNa$ 404.9726; found 404.9724.

(1,1-dioxido-2,4-thietanediyl)bis{[4-(trifluoromethyl)phenyl]} methanone-9e.

Column chromatography on silica gel (Hexane/AcOEt 80:20), yellow solid, mp 180-183 °C, 60% (277 mg), D_r 80:20. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45-2.53 (dt, d = *J* = 12.8 Hz, t = *J* = 9.7 Hz, 1H, minor), 3.13 (t, *J* = 8.1Hz, 2H, major), 3.80-3.85 (dt, d = *J* = 12.8 Hz, t = *J* = 9.4 Hz, 1H, minor), 5.99 (t, *J* = 9.5 Hz, 2H, minor), 6.01 (t, *J* = 8.1Hz, 2H, major), 7.81-7.84 (m, 4H minor + 4H major), 8.12-8.18 (m, 4H major + 4H, minor). ^{13}C NMR (101 MHz, $CDCl_3$) δ 9.9 (minor), 10.0 (major), 79.7 (minor), 81.3 (major), 123.2 (d, $^1J_{C,F}$ = 273.1 Hz, major), 126.4 (q, $^3J_{C,F}$ = 3.7 Hz, major), 128.9 (minor), 129.1 (major), 136.1 (q, $^2J_{C,F}$ = 33.0 Hz, major), 137.7 (major), 185.0 (minor), 186.3 (major). ^{19}F (377 MHz, $CDCl_3$) δ -63.4(s). FT-IR (KBr, cm^{-1}) υ 809, 859, 1070, 1128, 1169, 1333, 1692, 2957. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{19}H_{12}F_6O_4SNa$ 473.0253; found 473.0255.

5.4 General procedure for lithiation/electrophile trapping sequence on C2'-substituted thietane-1,1- dioxide.

To a stirred solution of thietane 1,1-dioxide 2-substituted (1.0 mmol, 1.0 equiv) in dry 2-MeTHF (10 mL) cooled at -78°C, a solution of *n-Hex*Li (2.5M in hexane, 1.1 equiv) was added dropwise. After stirring for 5 min. at -78°C, the electrophile (1 equiv) was added neat if liquid and in 1.0 mL of solvent if solid. After the reaction was complete, as ascertained by GC or TLC, the reaction mixture was quenched with saturated aqueous NH_4Cl (0.1mL) and directly filtered over Na_2SO_4 and concentrated in vacuo. Flash chromatography on silica gel (Hexane/AcOEt) afforded the thietane 1,1-dioxide 2,4-disubstitute.

2-benzyl-4-methylthietane 1,1-dioxide-10a.

Column chromatography on silica gel (Hexane/AcOEt 70:30), yellow oil, >99%, D_r = 60:40. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33-1.41 (m, 1H, minor), 1.43 (d, *J* = 7.0 Hz, 1H, minor), 1.46 (d, *J* = 7.2 Hz, 3H, major), 1.83 (ddd, *J* = 12.0, 9.9, 5.5 Hz, 1H, major), 2.03 (ddd, *J* = 12.0, 9.9, 7.1 Hz, 1H, major), 2.34-2.41 (m, 1H, minor), 2.91-2.98 (m, 2H), 3.36 (ddd, *J* = 14.6, 7.9 Hz, 1H, minor), 3.42 (dd, *J* = 14.6, 7.4 Hz, 1H, major), 4.13-4.26 (m, 2H), 4.33-4.41 (m, 1H, minor), 4.42-4.50 (m, 1H, major), 7.18-7.23 (m, 6H), 7.27-7.29 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.2 (minor), 14.8 (major), 22.9 (major), 23.9 (minor), 34.8 (minor), 35.3 (major), 69.2 (minor), 70.0 (major), 75.7 (minor), 76.1 (major), 127.0 (minor), 127.0 (major), 128.6 (minor), 128.7 (minor), 128.7 (major), 128.9 (major), 136.5 (minor). FT-IR (KBr, cm^{-1}) υ 511, 546, 698, 800, 1123, 1152, 1250, 1449, 1490, 2965, 3011, 3029, 3063, 3090, 3489. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{17}H_{18}O_3SNa$ 325.0869; found 325.0872.

(4-methyl-1,1-dioxido-2-thietanyl)(diphenyl)methanol-10b.

Column chromatography on silica gel (Hexane/AcOEt 70:30), white solid, mp 143-146 °C, 60%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.51 (d, *J* = 7.0 Hz, 3H), 1.51-1.57 (m, overlapping d at 1.51, 1H), 2.56-2.61 (m, 1H), 4.27-4.33 (m, 1H), 5.33-5.36 (m, 1H), 7.20-7.22 (m, 1H), 7.28-7.39 (m, 7H), 7.53-7.54 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.1, 18.5, 70.9, 82.0, 125.4, 126.0, 127.3, 128.1, 128.4, 128.8, 143.2, 145.0. FT-IR (KBr, cm^{-1}) υ 511, 546, 698, 800, 1123, 1152, 1250, 1449, 1490, 2965, 3011, 3029, 3063, 3090, 3489. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{17}H_{18}O_3SNa$ 325.0869; found 325.0872.

(4-benzyl-1,1-dioxido-2-thietanyl)[4-(2-methyl-2-propanyl)phenyl] methanone-10c.

Column chromatography on silica gel (Hexane/AcOEt 80:20), white solid, mp 96-99 °C, 75% (270 mg), D_r 60:40. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 9H, minor), 1.35 (s, 9H, major)

1.96-2.03 (m, 1H, minor), 2.30-2.37 (m, 1H, major), 2.68-2.75 (m, 1H, major), 2.97-3.05 (m, 1H, minor), 3.079 (m, 1H, major), 3.127 (m, 1H, minor), 3.41 (dd, *J* = 14.5, 7.7 Hz, 1H, major), 3.51 (dd, *J* = 14.5, 7.5Hz, 1H, minor), 4.62-4.75 (m, 1H major + 1H minor), 5.74 (t, *J* = 9.2 Hz, 1H, major), 5.81 (ddd, *J* = 9.8, 4.7, 1.3Hz, 1H, minor), 7.25-7.28 (m, 3H minor + 3H major), 7.32-7.35 (m, 2H minor + 2H major), 7.53-7.57 (m, 2H minor + 2H major), 7.94-7.96 (m, 2H, minor), 8.01-8.03 (m, 2H, major). ^{13}C NMR (101 MHz, $CDCl_3$) δ 15.5 (major), 15.8 (minor), 31.0 (major), 35.1 (major), 35.3 (major), 35.4 (minor), 77.5 (major), 78.6 (major), 79.0 (minor), 79.3 (minor), 126.1 (minor), 126.2 (major), 127.2 (major), 127.2 (minor), 128.6 (major), 128.7 (minor), 128.7 (minor), 128.8 (major), 128.9 (major), 132.9 (major), 133.0 (minor), 135.8 (minor), 136.1 (major), 158.5 (minor), 158.6 (major), 186.4 (major), 187.1 (minor). FT-IR (KBr, cm^{-1}) υ 545, 700, 1129, 1312, 1685, 2959. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{21}H_{24}O_3SNa$ 379.1338; found 379.1345.

5.5 General procedure for lithiation/electrophile trapping sequence on C2-substituted tetrahydro-2*H*-thiopyran 1,1-dioxide.

To a stirred solution of tetrahydro-2*H*-thiopyran 1,1-dioxide (1.0 mmol, 1.0 equiv) in dry 2-MeTHF (10 mL) cooled at -78°C, a solution of *n*-HexLi (2.5M in hexane, 1.1 equiv) was added dropwise. After stirring for 10 min. at -78°C, the electrophile (1 equiv) was added neat if liquid and in 1.0 mL of solvent if solid. After the reaction was complete, as ascertained by GC or TLC, the reaction mixture was quenched with saturated aqueous NH_4Cl (0.1mL) and directly filtered over Na_2SO_4 and concentrated in vacuo. Flash chromatography on silica gel (Hexane/AcOEt) afforded the tetrahydro-2*H*-thiopyran 1,1-dioxide substitute.

2-benzyltetrahydro-2*H*-thiopyran 1,1-dioxide-12a.

Column chromatography on silica gel (Hexane/AcOEt 70:30), white solid, mp 111-114 °C, 50% (114 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27-1.35 (m, 1H), 1.67-1.83 (m, 2H), 1.88-1.93 (m, 1H), 2.04-2.09 (m, 2H), 2.65 (dd, *J* = 13.5, 11.1 Hz, 1H), 2.88-3.05 (m, 2H), 3.10-3.16 (m, 1H), 3.52 (dd, *J* = 13.5, 2.7 Hz, 1H), 7.17-7.19 (m, 2H), 7.23-7.26 (m, 1H), 7.30-7.33 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 23.8, 24.3, 28.6, 30.8, 51.9, 63.0, 126.9, 128.7, 129.3, 136.5. FT-IR (KBr, cm^{-1}) υ 473, 707, 760, 1127, 1282, 2927. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{12}H_{16}O_2SNa$ 247.0763; found 247.0762.

(1,1-dioxidotetrahydro-2*H*-thiopyran-2-yl)[4-(2-methyl-2-propanyl)phenyl]methanone-12b.

Column chromatography on silica gel (Hexane/AcOEt 80:20), white solid, mp 151-154 °C 68% (200 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 9H), 1.59-1.67 (m, 1H), 1.86-1.95 (m, 1H), 2.15-2.20 (m, 2H), 2.32-2.46 (m, 2H), 3.03-3.10 (m, 1H), 3.59-3.65 (m, 1H), 4.87-4.90 (m, 1H), 7.51-7.53 (m, 2H), 7.91-7.93 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.3, 24.2, 28.3, 31.1, 35.3, 51.4, 64.9, 125.9, 128.9, 133.2, 158.4, 192.0. FT-IR (KBr, cm^{-1}) υ. 548, 926, 1118, 1270, 1324, 1677, 2866, 2967. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{16}H_{22}O_3SNa$ 317.1182; found 317.1183.

(1,1-dioxidotetrahydro-2*H*-thiopyran-2-yl)(diphenyl)methanol-12c.

Column chromatography on silica gel (Hexane/AcOEt 80:20), white solid, mp 98-102 °C 60% (195 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39-1.51 (m, 1H), 1.87-1.98 (m, 2H), 2.02-2.09 (m, 2H), 2.20-2.30 (m, 1H), 2.98-3.06 (m, 2H), 4.09 (dd, *J* = 12.2, 3.2 Hz, 1H), 4.65 (bs, 1H, OH), 7.18-7.23 (m, 2H), 7.30-7.34 (m, 4H), 7.50-7.53 (m, 2H), 7.63-7.66 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.0, 24.2, 26.7, 55.2, 67.3, 79.1, 124.9, 125.6, 127.0, 127.3,

127.9, 128.5, 143.9, 144.5. FT-IR (KBr, cm^{-1}) υ 693, 747, 1130, 1265, 1318, 1448, 2927, 3454. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{18}H_{20}O_3SNa$ 339.1025; found 339.1028.

cyclopropyl(1,1-dioxidotetrahydro-2*H*-thiopyran-2-yl)methanone-12d.

Column chromatography on silica gel (Hexane/AcOEt 60:40), white solid, mp 110-113 °C 75% (155 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 1.03-1.24 (m, 4H), 1.51-1.56 (m, 1H), 1.85-1.92 (m, 1H), 2.08-2.11 (m, 2H), 2.26-2.32 (m, 3H), 2.96-3.03 (m, 1H), 3.24-3.30 (m, 1H), 4.13 (ddd, *J* = 8.2, 4.5, 1.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.9, 21.6, 22.1, 24.2, 27.1, 52.4, 71.3, 201.5. FT-IR (KBr, cm^{-1}) υ. 550, 1120, 1677, 2788, 2967. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_9H_{14}O_3SNa$ 225.0556; found 225.0559.

***N*-(2-phenylethyl)tetrahydro-2*H*-thiopyran-2-carboxamide 1,1-dioxide-12e.**

Column chromatography on silica gel (Hexane/AcOEt 70:30), white solid, mp 50-53 °C, 70% (200 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 1.46-1.53 (m, 1H), 1.90-1.96 (m, 1H), 2.04-2.10 (m, 2H), 2.15-2.24 (m, 1H), 2.31-2.39 (m, 1H), 2.86 (t, *J* = 7.1 Hz, 2H), 2.89-3.01 (m, 1H), 3.08-3.14 (m, 1H), 3.50-3.67 (m, 3H), 6.74 (bs, NH, 1H), 7.21-7-25 (m, 3H), 7.29-7.33 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 22.7, 24.1, 27.9, 35.4, 41.2, 52.1, 65.6, 126.5, 128.6, 128.8, 138.5, 163.0. ^{15}N δ -263.3. FT-IR (KBr, cm^{-1}) υ 702, 746, 917, 1129, 1192, 1290, 1318, 1557, 1651, 3314. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{14}H_{19}NO_3SNa$ 304.0978; found 304.0973.

(1,1-dioxidotetrahydro-2*H*-thiopyran-2yl)(3-thienyl)methanol-12f.

Column chromatography on silica gel (Hexane/AcOEt 70:30), white solid, mp 105-108 °C 73% (183 mg), D_r = 50:50. ^1H NMR (400 MHz, $CDCl_3$) δ 1.31-1.41 (m, 2H), 1.50-1.66 (m, 3H), 1.73-1.79 (m, 1H), 1.85-1.98 (m, 2H), 2.02-2.14 (m, 6H), 2.17-2.26 (m, 1H), 2.97-3.00 (m, 4H), 3.15-3.30 (m, 3H), 5.36 (d, *J* = 9.1 Hz, 1H, minor), 5.89 (s, 1H, major), 6.99 (dd, *J* = 4.9, 1.3 Hz, 1H, major), 7.10 (dd, *J* = 5.0, 1.3 Hz, 1H, minor), 7.28 (dd, *J* = 3.0, 1.3 Hz, 1H, minor), 7.30 (dd, *J* = 3.0, 1.3 Hz, 1H, major), 7.33 (dd, *J* = 4.9, 3.0 Hz, 1H, major), 7.35 (dd, *J* = 5.0, 3.0 Hz, 1H, minor). ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.4 (major), 23.5 (minor), 23.8 (minor), 24.0 (major), 24.2 (major), 27.5 (minor), 52.3 (minor), 53.0 (major), 65.4 (major), 66.4 (major), 67.3 (minor), 68.1 (minor), 121.8 (major), 123.3 (minor), 124.9 (major), 125.6 (minor), 126.4 (major), 126.8 (minor), 140.0 (minor), 140.8 (major). FT-IR (KBr, cm^{-1}) υ 616, 790, 1129, 1281, 1637, 2925, 3418. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{10}H_{14}O_3S_2Na$ 269.0277; found 269.0281.

(1,1-dioxidotetrahydro-2*H*-thiopyran-2yl)(4-methoxyphenyl) methanone-12g.

Column chromatography on silica gel (Hexane/AcOEt 70:30), white solid, mp 161-163 °C 65% (179 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60-1.65 (m, 1H), 1.90-1.97 (m, 1H), 2.14-2.18 (m, 2H), 2.36-2.40 (m, 2H), 3.03-3.08 (m, 1H), 3.57-3.63 (m, 1H), 3.89 (s, 3H), 4.84 (td, *J* = 5.3, 2.0 Hz, 1H), 6.95-6.98 (m, 2H), 7.95-7.98 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.4, 24.1, 28.3, 51.5, 55.6, 64.8, 114.1, 128.8, 131.5, 164.5. FT-IR (KBr, cm^{-1}) υ 713, 827, 934, 1132, 1174, 1270, 1316, 1663, 2933. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{13}H_{16}O_4SNa$ 291.0662; found 291.0669.

5.6 General procedure for lithiation-electrophile trapping sequence on C2,C2'-substituted tetrahydro-2*H*-thiopyran 1,1-dioxide.

To a stirred solution of tetrahydro-2*H*-thiopyran 1,1-dioxide (1.0 mmol, 1.0 equiv) in dry 2-MeTHF (10 mL) cooled at -78°C, a solution of *n*-HexLi (2.5M in hexane, 2.5 equiv) was added dropwise. After stirring for 30 min at -78°C, the electrophile (2.5 equiv) was added neat if liquid and in 1.0 mL of solvent if solid. After the reaction was complete, as ascertained by GC or TLC, the reaction mixture was quenched with saturated aqueous NH_4Cl (0.1mL) and directly filtered over Na_2SO_4 and concentrated in vacuo. Flash chromatography on silica gel (Hexane/AcOEt) afforded the tetrahydro-2*H*-thiopyran 1,1-dioxide disubstitute.

2,6-dibenzyltetrahydro-2*H*-thiopyran 1,1-dioxide-13a.

Column chromatography on silica gel (Hexane/AcOEt 80:20), white solid, mp 179-181 °C 60% (190 mg), Dr = 80:20. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13-1.26 (m, 1H, major), 1.57-1.63 (m, 2H, minor), 1.70-1.80 (m, 3H major + 2H minor), 1.85-1.90 (m, 2H, major), 1.98-2.06 (m, 2H, minor), 2.71 (dd, *J* = 13.6, 11.0 Hz, 2H, major), 2.79 (dd, *J* = 13.5, 12.0 Hz, 2H, minor), 2.97-3.05 (m, 2H, major), 3.16-3.22 (m, 2H, minor), 3.53 (dd, *J* = 13.5, 3.2 Hz, 2H, minor) 3.58 (dd, *J* = 13.6, 3.2 Hz, 2H, major), 7.20-7.22 (m, 4H major + 4H minor), 7.23-7.29 (m, 2H major + 2H minor), 7.30-7.36 (m, 4H major + 4H minor). ^{13}C NMR (101 MHz, $CDCl_3$) δ 18.6 (minor), 24.4 (major), 27.1 (minor), 29.0 (major), 30.9 (major), 31.7 (minor), 60.4 (minor), 63.6 (major), 126.9 (major), 127.0 (minor), 128.7 (major), 128.8 (minor), 129.2 (minor), 129.4 (major), 136.8 (minor), 136.8 (major). FT-IR (KBr, cm^{-1}) υ 491, 700, 756, 1114, 1307, 1455, 1722, 2934 HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{19}H_{22}O_2SNa$ 337.1233; found 337.1230.

5.7 General procedure for lithiation/electrophile trapping sequence on C2'-substituted tetrahydro-2*H*-thiopyran 1,1-dioxide.

To a stirred solution of tetrahydro-2*H*-thiopyran 1,1-dioxide 2-substituted (1.0 mmol, 1.0 equiv) in dry 2-MeTHF (10 mL) cooled at -78 °C, a solution of *n*-HexLi (2.5M in hexane, 1.1 equiv) was added dropwise. After stirring for 10 min at -78 °C, the electrophile (1 equiv) was added neat if liquid and in 1.0 mL of solvent if solid. After the reaction was complete, as ascertained by GC or TLC, the reaction mixture was quenched with saturated aqueous NH_4Cl (0.1mL) and directly filtered over Na_2SO_4 and concentrated in vacuo. Flash chromatography on silica gel (Hexane/AcOEt) afforded the tetrahydro-2*H*-thiopyran 1,1-dioxide 2,4-disubstitute.

(6-benzyl-1,1-dioxidotetrahydro-2*H*-thiopyran-2-yl)[4-(*tert*-butyl) phenyl]methanone-14a.

Column chromatography on silica gel (Hexane/AcOEt 80:20), white solid, mp 149-152 °C, 72% (235 mg), Dr = 60:40. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24-1.30 (m, 2H), 1.35 (s, 9H major + 9H minor), 1.42-1.49 (m, 1H), 1.61-1.66 (m, 1H, major), 1.72-2.00 (m, 5H), 2.08-2.13 (m, 1H, minor), 2.24-2.27 (m, 1H, major), 2.49-2.56 (m, 1H, major), 2.60-2.66 (m, 1H, minor), 2.69 (dt, *J* = 9.3, 8.4 Hz, 1H, major + 1H, minor), 3.15-3.21 (m, 1H, minor), 3.56 (dd, *J* = 13.5, 3.1 Hz, 1H, major + 1H, minor), 3.91 (ddd, *J* = 11.4, 7.3, 3.4 Hz, 1H, major), 4.87 (dd, *J* = 12.6, 2.9 Hz, 1H, minor), 4.99 (dd, *J* = 5.3, 2.7 Hz, 1H, major), 7.20-7.35 (m, 5H, major + 5H, minor), 7.51-7.53 (m, 2H, major + 2H, minor), 7.89 (d, *J* = 8.5 Hz, 2H, major), 8.02 (d, *J* = 8.5 Hz, 2H, minor). ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.6 (minor), 23.8 (major), 28.2 (minor), 28.6 (major), 28.8 (major), 28.8 (minor), 30.7 (major), 30.9 (minor), 31.0 (major), 31.0 (minor), 35.3 (major), 35.2 (minor), 61.1 (major), 64.6 (major), 65.5 (minor), 67.0 (minor), 125.7 (minor), 126.0 (major), 126.9 (major), 127.0 (minor), 128.7 (major), 128.8 (major), 128.8 (minor), 129.4 (minor), 129.5 (minor), 129.5 (major), 132.8 (major), 134.0 (minor), 136.4 (major), 136.4 (minor), 158.1 (minor), 158.4 (major), 189.0 (minor), 192.9 (major). FT-IR (KBr, cm^{-1}) υ 511, 701, 1119, 1269, 1301, 1602, 1674, 2952, 3453. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{23}H_{28}O_3SNa$ 407.1651; found 407.1653.

2-(hydroxydiphenylmethyl)-6-methyltetrahydro-2*H*-thiopyran 1,1-dioxide-14b.

Column chromatography on silica gel (Hexane/AcOEt 80:20), white solid, mp 159-164 °C, 71% (235 mg), Dr = 90:10. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (d, *J* = 6.8 Hz, 3H, major), 1.42 (d, *J* = 7.1 Hz, 3H, minor), 1.50-1.54 (m, 1H, major), 1.59-1.67 (m, 1H, minor), 1.73-1.79 (m, 1H, minor), 1.77-1.90 (m, 2H, major), 1.83-1.91 (m, 2H, minor), 1.93-2.01 (m, 2H,

major), 2.11-2.21 (m, 2H, minor), 2.24-2.33 (m, 1H, major), 3.00-3.06 (m, 1H, major), 3.16-3.22 (m, 1H, minor), 4.05 (dd, *J* = 12.6, 3.1 Hz, 1H, major), 4.19 (dd, *J* = 10.9, 3.8 Hz, 1H, minor), 4.50 (bs, 1H, minor), 4.79 (s, 1H, major), 7.18-7.23 (m, 2H, minor), 7.18-7.24 (m, 2H, major), 7.29-7.33 (m, 4H, minor), 7.30-7.34 (m, 4H, major), 7.46-7.48 (m, 2H, minor), 7.53-7.54 (m, 2H, major), 7.60-7.62 (m, 2H, minor), 7.63-7.65 (m, 2H, major). ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.3 (major), 12.7 (minor), 19.0 (minor), 24.6 (major), 25.8 (minor), 27.1 (major), 29.4 (minor), 32.2 (major), 57.7 (minor), 60.3 (major), 64.6 (minor), 67.4 (major), 79.2 (minor), 79.2 (major), 124.9 (major), 125.0 (minor), 125.6 (minor), 125.6 (major), 126.9 (minor), 127.0 (major), 127.3 (minor), 127.3 (major), 127.9 (major), 128.0 (minor), 128.4 (minor), 128.5 (major), 144.0 (major), 144.2 (minor), 144.6 (major), 145.1 (minor). FT-IR (KBr, cm^{-1}) υ 571, 695, 964, 1132, 1273, 1449, 1637, 2863, 2972, 3492. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{19}H_{22}O_3SNa$ 353.1182; found 353.1183.

5.8 General procedure for direct α-arylation of thietane-1,1-dioxide and tetrahydro-2*H*-thiopyran 1,1-dioxide.

To a stirred solution of thietane 1,1-dioxide (1.0 mmol, 1.0 equiv) in dry THF (10 mL) cooled at -78°C, a solution of *n*-HexLi (2.5M in hexane, 1.1 equiv) was added dropwise. After stirring for 15 or 30 min at -78°C, anhydrous Copper(I) cyanide di(lithium chloride) complex solution (CuCN 2LiCl, 1 equiv) was added in one portion. The mixture was allowed to warm to -35 °C, stirred for 15 min at this temperature. Diphenyliodonium hexafluorophoshate (1 equiv) was added, in one portion, resulting in the immediate formation of a bright yellow mixture. The reaction was maintained at -35 °C for 15 min then allowed to slowly to warm to room temperature. After stirring for 4 hour to rt, the reaction mixture was quenched with saturated aqueous NH_4Cl (0.1mL) and the organic layer was separated, and the acqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent evaporated under vacuum.

2-phenylthietane 1,1-dioxide-15a.

Flash chromatography on silica gel (Hexane/AcOEt 70:30) afforded 2-phenylthietane 1,1-dioxide, yellow solid, mp 81-84°C, 50% (111 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36-2.47 (m, 1H), 2.54-2.62 (m, 1H), 3.98-4.20 (m, 2H), 5.45-5.49 (m, 1H), 7.38-7.44 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 15.0, 62.1, 82.3, 128.5, 128.9, 129.2, 130.8. FT-IR (KBr, cm^{-1}) υ 583, 704, 734, 769, 1125, 1189, 1301, 1455, 1492, 2360, 2920. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_9H_{10}O_2SNa$ 205.0294; found 205.0296.

2-phenyltetrahydro-2*H*-thiopyran 1,1-dioxide-15b.

The solid was washed two times with diethyl ether and one time with distilled hexane afforded 2-phenyltetrahydro-2*H*-thiopyran 1,1-dioxide as white solid, mp 84-87°C, 60% (126 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.55-1.65 (m, 1H), 2.04-2.09 (m, 2H), 2.17-2.24 (m, 2H), 2.46-2.54 (m, 1H), 3.02-3.08 (m, 1H), 3.23 (dtd, J = 14.1, 3.5, 1.4 Hz, 1H), 4.02 (dd, J = 13.0, 3.0 Hz, 1H), 7.38-7.44 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.6, 25.2, 31.0, 52.7, 67.6, 128.6, 129.0, 129.9, 130.4. FT-IR (KBr, cm^{-1}) υ 697, 727, 1124, 1281, 1446, 1493, 2862, 2935. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{11}H_{14}O_2SNa$ 233.0607; found 233.0609.

2-phenyltetrahydrothiophene 1,1-dioxide-15c.

Columnchromatography on silica gel (hexane/AcOEt 60:40), colorlessoil, 70%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.19–2.27 (m, 1H), 2.34–2.39 (m, 1H), 2.45–2.49 (m,1H), 2.51–2.58 (m, 1H), 3.14–3.20 (m, 1H), 3.28–3.32 (m, 1H), 4.15–4.19 (dd, J = 12.2, 7.2 Hz, 1H), 7.39–7.41 (m,

5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.8, 28.7, 50.6, 66.7, 128.8 , 129.0, 129.1, 130.3; FT-IR (NaCl, cm^{-1}) ν 594, 724, 1132, 1189, 1301, 1449, 1493, 2359, 2921; HRMS (ESI-TOF)m/z $[M + Na]^+$calcd for $C_{10}H_{12}NaO_2S$ 219.0450; found 219.0459.

5.9 General procedure for fluorination on C2-substituted thietane-1,1- dioxide and tetrahydro-2*H*-thiopyran 1,1-dioxide.

To a stirred solution of thietane-1,1- dioxide or tetrahydro-2*H*-thiopyran 1,1-dioxide (1.0 mmol, 1.0 equiv) in dry 2-MeTHF (10 mL) cooled at -78°C, a solution of *n*-HexLi (2.5M in hexane, 1.1 equiv) was added dropwise. After stirring for 10 min at -78°C, the electrophilic fluorinated reagent *N*-Fluorobenzenesulfonimide (NFSI, 1 equiv) was added in 2.0 mL of solvent. The reaction was maintained at -78°C for 15 min then allowed to slowly to warm to room temperature. After the reaction was complete, as ascertained by GC or TLC, the reaction mixture was quenched with saturated aqueous NH_4Cl (0.1mL), directly filtered over Na_2SO_4 and concentrated in vacuo. Flash chromatography on silica gel (Hexane/AcOEt) afforded the thietane-1,1- dioxide or tetrahydro-2*H*-thiopyran 1,1-dioxide substitute.

2-fluoro-2-(phenylsulfonyl)thietane 1,1-dioxide-16a

Column chromatography on silica gel (Hexane/AcOEt 60:40), yellowish solid, mp 130-132 °C, 30% (85 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50-2.65 (m, 1H), 3.23-3.32 (m, 1H), 4.06-4.27 (m, 2H), 7.62-7.66 (m, 2H), 7.78-7.80 (m, 1H), 8.07-8.10 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.9 (d, J = 20.6 Hz), 61.2 (d, J = 5.0 Hz), 125.6 (d, J = 298 Hz), 129.5, 130.8, 133.1, 136.0. ^{19}F NMR (377 MHz, $CDCl_3$) δ -128.99 (ddd, J = 21.6, 8.0, 1.8 Hz). FT-IR (KBr, cm^{-1}) υ 557, 720, 1153, 1328, 1448, 2854, 2926, 3049. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_9H_9FO_4S_2Na$ 286.9818; found 286.9822.

2-fluoro-2-(phenylsulfonyl)tetrahydro-2*H*-thiopyran 1,1-dioxide-16b.

Column chromatography on silica gel (Hexane/AcOEt 60:40), yellowish solid, mp 114-117, 50% (146 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.77-1.85 (m, 1H), 1.99-2.12 (m, 2H), 2.1-2.23 (m, 1H), 2.65-2.72 (m, 1H), 2.80-2.92 (m, 1H), 3.18-3.31 (m, 2H), 7.58-7.61 (m, 2H), 7.74-7.77 (m, 1H), 8.02-8.04 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.5 (d, J = 4.1 Hz), 23.6, 29.3 (d, J = 18.2 Hz), 51.9, 111.8 (d, J = 251 Hz), 129.0, 131.1 (d, J = 1.2 Hz), 134.8, 135.5. ^{19}F NMR (470 MHz, $CDCl_3$) δ -150.4 (m). FT-IR (KBr, cm^{-1}) υ 582, 867, 1160, 1328, 1451, 2862, 2926, 3444. HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{11}H_{13}FO_4S_2Na$ 315.0131; found 315.0148.

2-Fluoro-2-(phenylsulfonyl)tetrahydrothiophene 1,1-dioxide-10c.

Column chromatography on silica gel (hexane/AcOEt 60:40), yellow oil, 50%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.23–2.39 (m, 2H), 2.52–2.61 (m, 1H), 3.04–3.17 (m, 1H), 3.23–3.32 (m, 2H), 7.61–7.64 (t, J = 7.6 Hz, 2H), 7.7–7.78 (t, J = 7.4 Hz, 1H), 8.06–8.07 (d, J = 7.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 16.3 28.8 (d, $^2J_{CF}$ = 19.5 Hz), 50.9, 111.4 (d, J = 267.8 Hz),

129.2, 130.9, 113.8, 135.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ −142.53 (dd, J_{HF} = 28.4, 21.2 Hz); FT-IR (NaCl, cm^{-1}) ν 572, 887, 1156, 1 328 1450, 2860, 2926, 3060; HRMS(ESI-TOF) m/z $[M + Na]^+$calcd for $C_{10}H_{11}FNaO_4S_2$ 300.9975; found 300.9980.

Chapter 3

Addendum: use of organometallic chemistry for pharmaceutical application.

One of the most intriguing aspects to mention is that organometallic chemistry can be extended to various substrates and therefore finds wide application for the synthesis of pharmaceuticals and total synthesis of complex natural products.

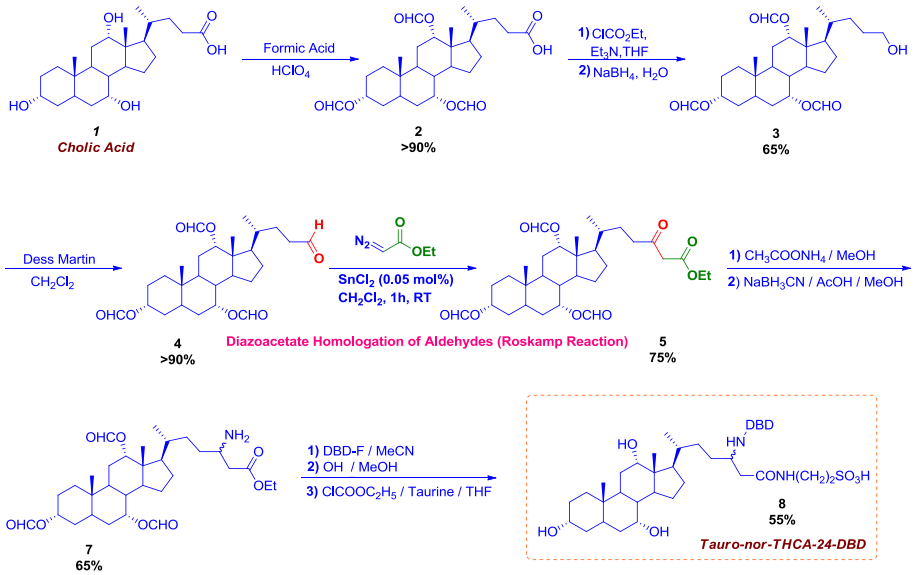
During my permanence at University of Vienna in Pace's research group, I had the opportunity to approach the pharmaceutical chemistry field working at the synthesis of new pharmacologically active compounds as P-GP modulator and colic acid derivatives.

As show in *Scheme 1*, for the synthesis of colic acid derivate, the target was Tauro-nor-THCA-24-DBD **8**. Conventional chemistry has been used for the first steps of the synthesis; nevertheless several hurdles occurred during the conversion of aldehyde intermediate **4** in the corresponding β-keto esters **5**.

In this context, organometallic chemistry has been the keystone to the problem. In fact, the breakthrough was to use an homologation reaction discovered by Roskamp and co-workers in 1989,[109] that is very useful in synthesizing β-keto esters from aldehydes and diazoacetate, using various Lewis acids as catalysts such as BF_3, $SnCl_2$, $GeCl_2$.

The mild conditions and the selectivity are the two most strengths of this reaction; in fact no more than one hour at room temperature was required to convert with good yield the aldehyde **4** into the desiderated product **8** by using ethyl diazoacetate and $SnCl_2$ as catalyst (Scheme 1).

The mechanism proposed, provide the formation of an electrophilic tin-carbenoid specie that allow an CH-insertion mechanism.



Scheme 1. *Total Synthesis of Tauro-nor-THCA-24-DBD* ***8****.*

The use of organometallic reagents was also crucial for the synthesis of important P-glycoprotein modulator.

P-glycoprotein (Pg-P) is an important protein of the cell membrane that have the function to extrude, through cytoplasm, many foreign substances out of cells. For this reason, this protein play an important protective role at the level of the blood-brain barrier (BBB) and in other biological district deputies to the exchange and the transport of xenobiotics.

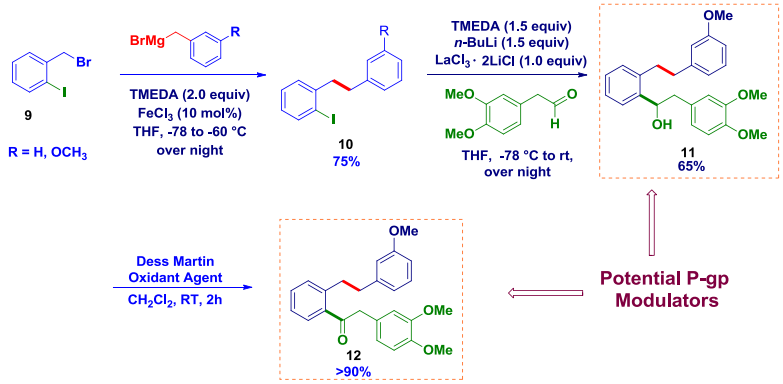
In the last years, pharmaceutical studies have highlight that the Pg-P activity and its numerical expression are correlated with both the onset and the progression of neurodegenerative disease such as Alzheimer. Nevertheless, in order to previous diagnosis of neurodegenerative pathology, it is important to *in vivo* monitor the activity of this membrane protein.

In this context, in collaboration with Hecker's research group, the synthesis of potential Pg-P modulators used as PET radio tracing has been explored.

As show in *Scheme 2,* the targets **11** and **12** has been quickly synthesized in just two and three steps respectively by using organometallic chemistry. At the beginning, an iron-catalyzed Kumada coupling in the presence of tetramethylethylenediamine (TMEDA) has been employed in order to obtain the intermediate **10**.[110]

Subsequently, an homologation reaction through a lithium/iodide exchange mechanism in presence of aldehyde as electrophile was attempted in order to synthesized the first target **11**. Unfortunately, the reaction doesn't lead to the expected product because lithium intermediate, through a single electron transfer mechanism (SET), reduced the aldehyde to benzylic alcol subtracting in this way the electrophile from the reaction. For this reason, we thought to use lanthanum(III) chloride bis(lithium chloride) complex in order to inhibit the nucleophilicity of the intermediate and to favour the nucleophilic addition.

Later, the hydroxyalkyl moiety of **11** was converted into the corresponding ketone **12** by using Dess-Martin periodinane as oxidant reagent.



Scheme 2. *Total Synthesis of Potential Pg-P Modulators* ***11*** *and* ***12.***

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