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Modern Perspectives in Homologative Chemistry with or without External C1-
Donor Agents

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Dott. mag. Veronica Pillari

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Vittorio Pace Privatdoz. PhD

Abstract

This doctoral thesis presents innovative methodologies for the synthesis of complex organosulfur and spirocyclic compounds, focusing on overcoming long-standing challenges in homologation reactions and advancing sulfur-boron chemistry. The research explores a range of chemoselective strategies, which hold significant promise for both synthetic and medicinal chemistry. A central component of this work is the development of a two-step thiosulfonate homologation-nucleophilic substitution sequence, which allows for the efficient synthesis of unsymmetrical dithioacetals. The method employs chloromethyl lithium as the homologating agent, achieving high yields (up to 93%) with broad functional group tolerance. The successful synthesis of oxothioacetals ($R^1S-CH_2-OR^2$) further extends this approach, utilizing lithium halocarbenoids and external oxygen nucleophiles under optimized conditions. This process achieves high chemoselectivity, demonstrating compatibility with various phenols and alcohols and expanding the scope of sulfur electrophiles. A groundbreaking study delves into the synthesis of α,β -unsaturated aldehydes, through lithium halocarbenoid-mediated nucleophilic addition, enabling the transformation of spiro-epoxy oxindoles into α,β -unsaturated aldehydes via Meinwald rearrangement. This work includes extensive mechanistic studies, revealing the role of lithium carbenoids in facilitating epoxidation and cyclization reactions. Moreover, this chemoselective process showcases the potential of spirocyclic frameworks in expanding synthetic possibilities for bioactive compound development. Lastly, this thesis explores the possibility to realize multiple homologative events through the release of methylene units from the common solvent tetrahydrofuran. Though recently developed methodologies enable the single or double homologations of boron-nitrogen and boron oxygen linchpins (*i.e.* aza- and oxa-Matteson processes), the treatment of a thiol with THF in the presence of a suitable boron-centered Lewis acid, offers a convenient four-carbon homologation, thus forming under genuine regiocontrol ω -hydroxythioethers. Collectively, a challenging four-carbon homologation was accomplished without the aid of an external single carbon releasing agent.

Zusammenfassung

In dieser Dissertation werden innovative Methoden für die Synthese komplexer schwefelorganischer und spirozyklischer Verbindungen vorgestellt, wobei der Schwerpunkt auf der Überwindung langjähriger Herausforderungen bei Homologisierungsreaktionen und der Weiterentwicklung von Schwefel-Bor-Chemie liegt. Chemoselektiven Strategien, die sowohl für die synthetische als auch für die medizinische Chemie vielversprechend sind, sind Gegenstand der Forschung.

Ein zentraler Bestandteil dieser Arbeit ist die Entwicklung einer zweistufigen Thiosulfonat-Homologisierungs-Nukleophil-Substitutionssequenz, die eine effiziente Synthese von unsymmetrischen Dithioacetalen ermöglicht. Chlormethylithium wird dabei als Homologisierungsmittel verwendet, wobei hohe Ausbeuten (bis zu 93 %) bei breiter Toleranz gegenüber funktionellen Gruppen beobachtet wurde. Die erfolgreiche Synthese von Oxothioacetalen ($R^1S - CH_2 - OR^2$) erweitert diesen Ansatz, indem Lithiumhalogencarbanoide und externe Sauerstoffnukleophile unter optimierten Bedingungen eingesetzt werden. Mit diesem Verfahren wird eine hohe Chemoselektivität erreicht, die Kompatibilität mit verschiedenen Phenolen und Alkoholen nachgewiesen und der Anwendungsbereich von Schwefelelektrophilen erweitert.

Eine bahnbrechende Studie befasst sich mit der Synthese α,β -ungesättigter Aldehyde durch Lithiumhalogencarbenoid-vermittelte nukleophile Addition, die die Umwandlung von Spiro-Epoxy-Oxindolen in α,β -ungesättigte Aldehyde über Meinwald-Umlagerung ermöglicht. Diese Arbeit umfasst umfangreiche mechanistische Studien, die die Rolle der Lithium-Carbanoide bei Epoxidierungs- und Zyklisierungsreaktionen aufzeigen. Darüber hinaus ermöglicht dieser chemoselektive Prozess den Aufbau von spirozyklischen Gerüsten, was eine Erweiterung der synthetischen Möglichkeiten für die Entwicklung bioaktiver Verbindungen darstellt.

Schließlich wird in dieser Arbeit die Möglichkeit untersucht, durch die Freisetzung von Methyleneinheiten aus dem gängigen Lösungsmittel Tetrahydrofuran mehrfache Homologisierungen zu erreichen. Obwohl kürzlich entwickelte Methoden die Einzel- oder Doppelhomologisierungen von Bor-Stickstoff- und Bor-Sauerstoff-Verbindungen ermöglichen (d. h. Aza- und Oxa-Matteson-Prozesse), bietet die Behandlung eines Thiols mit THF in Gegenwart einer geeigneten Bor-zentrierten Lewis-Säure eine bequeme Vier-Kohlenstoff-Homologisierung, wodurch regiospezifisch ω -Hydroxythioether gebildet werden.

Abbreviation list

Ar	aryl
9-BBN	9-borabicyclo[3.3.1]nonano
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
bp	boiling point
<i>n</i> Bu	<i>n</i> -butyl
<i>t</i> Bu	<i>tert</i> -butyl
Bz	benzoyl
Cb	<i>N,N</i> -di(isopropyl)carbonyl
CCR	Corey–Chaykovsky reaction
CPBA	<i>meta</i> -chloroperoxybenzoic acid
CPME	cyclopentylmethyl ether
Cy	cyclohexyl
DABSO	1,4-diazabicyclo[2.2.2]octan bis(sulfur dioxide)
DBU	1,8-Diazabicyclo[5.4.0]undec-7-en
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano- <i>para</i> -benzoquinone
DES	deep eutectic solvent
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric rati
E	electrophile
EDG	electron donating group
ee	enantiomeric excess

equiv	equivalent(s)
er	enantiomeric ratio
Et	ethyl
EWG	electron withdrawing group
h	hour
Hal	halogen
Hex	hexane
HIV	anti-human immunodeficiency virus
HMDS	hexamethyldisilazane
HPLC	high performance liquid chromatography
HRMS	high-resolution mass spectrometry
Im	Imidazole
LA	Lewis acid
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
LTMP	lithium tetramethylpiperidide
M	molar
MAI	metal Assisted Ionization
MCF-7	Michigan cancer foundation-7
MCR	multicomponent reaction
MDM2	mouse double minute 2 homologs
Me	methyl
min	minute(s)
MOF	metal-organic framework
mp	melting point

Ms	methanesulphonyl
MTO	methyltrioxorhenium
N	normal
NBS	<i>N</i> -bromosuccinimide
NIS	<i>N</i> -iodosuccinimide
NMR	nuclear magnetic resonance
NOESY	nuclear overhauser effect spectroscopy
OTf	trifluoromethansulfonate
Nu	nucleophile
Ph	phenyl
PMI	process mass intensity
PMI RRC	PMI for reactants, reagents, and catalysts
<i>i</i> Pr	isopropyl
<i>n</i> Pr	<i>n</i> -propyl
Py	pyridine
<i>rac</i>	racemic
RAFT	reversible addition-fragmentation chain-transfer
rt	room temperature
<i>s</i> -Bu	<i>sec</i> -butyl
SN	nucleophilic substitution
SOM	small organic molecules
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBC	4- <i>tert</i> -butyl-cathecol
TBD	triazabicyclodecene
TBHP	<i>tert</i> -butyl-hydroperoxide

TBME	<i>tert</i> -butyl methyl ether
TFA	trifluoroacetic acid
TFAICs	Trifluoroacetimidoyl chlorides
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
TMSOI	trimethyl sulfoxonium iodide
Ts	tosyl (<i>p</i> -toluenesulfonyl)
UHP	urea-hydrogen peroxide

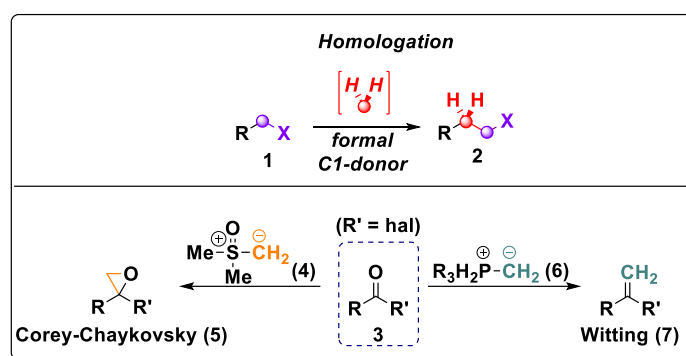
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1 Introduction

Homologation reactions encompass a sequential carbon unit addition to an existing molecular framework, offering synthetic chemists potent tools for elongating carbon chains and introducing diverse functional groups.¹⁻³ The choice of the homologation method relies on the desired carbon chain length and the functional groups present in the starting material.⁴⁻⁵ Among the well-known homologation reactions are the Arndt-Eistert,⁶⁻⁷ Wittig,⁸ and Johnson-Corey-Chaykovsky reactions,⁹⁻¹² and those involving organometallic reagents (Scheme 1. Examples of homologation reactions.).¹³⁻¹⁴



Scheme 1. Examples of homologation reactions.

**Readapted from Homologation Reactions: Reagents, Applications, and Mechanisms.¹⁵*

This thesis specifically focuses on the last category of homologation procedures, where organometallic reagents take center stage. Organometallic compounds, such as organolithium, organomagnesium, and organozinc,¹⁶ enable the introduction of carbon units into molecules *via* nucleophilic addition or metal-catalyzed cross-coupling reactions. For instance, organolithium reagents react with carbonyl compounds to form alcohols, which can undergo further transformations to yield longer carbon chains. In contrast, cross-coupling reactions like the Suzuki-Miyaura and Stille reactions find common use in synthesizing longer carbon chains.

These reactions involve coupling organometallic counterparts with suitable electrophiles, leading to the formation of carbon-carbon bonds. The Suzuki-Miyaura¹⁷⁻¹⁸ reaction employs organoboron compounds in conjunction with a palladium catalyst, while the Stille¹⁹ reaction utilizes organotin compounds as the nucleophilic partner, facilitating the construction of carbon-carbon bonds with a wide range of electrophiles.

Another significant organometallic homologation is the Negishi cross-coupling reaction,²⁰ which relies on an organozinc reagent and an organic halide or triflate in the presence of a palladium catalyst. This procedure has found extensive application in the synthesis of natural products and pharmaceuticals.

The core topic of this thesis revolves around organolithium and occasionally organomagnesium reagents, such as alkyl lithiums (*e.g.*, *n*-butyl lithium) and Grignard reagents,²¹ serving as nucleophilic partners with various electrophiles, including carbonyl compounds, halides, epoxides, and others, resulting in carbon skeleton elongation.

In summary, homologation reactions play a pivotal role in providing diverse possibilities for chemists to fine-tune the properties and enhance the biological activity of natural products, pharmaceuticals, agrochemicals, and more. The selective introduction of carbon units allows for modifications in potency, selectivity, and pharmacokinetic properties of drug candidates. Consequently, homologation reactions represent powerful tools to transform existing molecules into new products with desired properties.

1.1 Homologation reactions with carbenoids

Among the various synthetic tools available, homologation reactions *via* carbenoids have garnered significant attention due to their ability to introduce carbon-carbon bonds and expand molecular complexity. A metal carbenoid ($M-CH_2-X$) can be defined as a chemical species presenting a metal (M) and a late reactive element (X) linked to the same carbon atom.²²⁻²⁶ The presence of a highly electropositive metal (*e.g.*, Li) enhances the nucleophilic character of the resulting carbenoid, conferring a carbanion-like reactivity.

From an historical point of view, the term carbenoid was coined by the pioneers Closs and Moss, who defined these chemical entities as “*qualitatively analogous to carbenes without necessarily being free divalent carbon species*”.²⁷⁻²⁸

Indeed, as mentioned before, carbenoids show a dual character^{22, 29-30} depending on the nature of the metal linked: 1) the nucleophilic one, as a result of the ionic bond $M-CH_2$, in which the electrons reside mostly on the carbon atom; 2) the electrophilic one because of the breakage of the CH_2-X bond, which leaves a positive charge on the carbon atom, instead.³¹ Furthermore, other crucial factors need to be considered for the manipulation of carbenoids reactivity such as the nature of the metal, the halogen, and the substitution pattern (Figure 1).

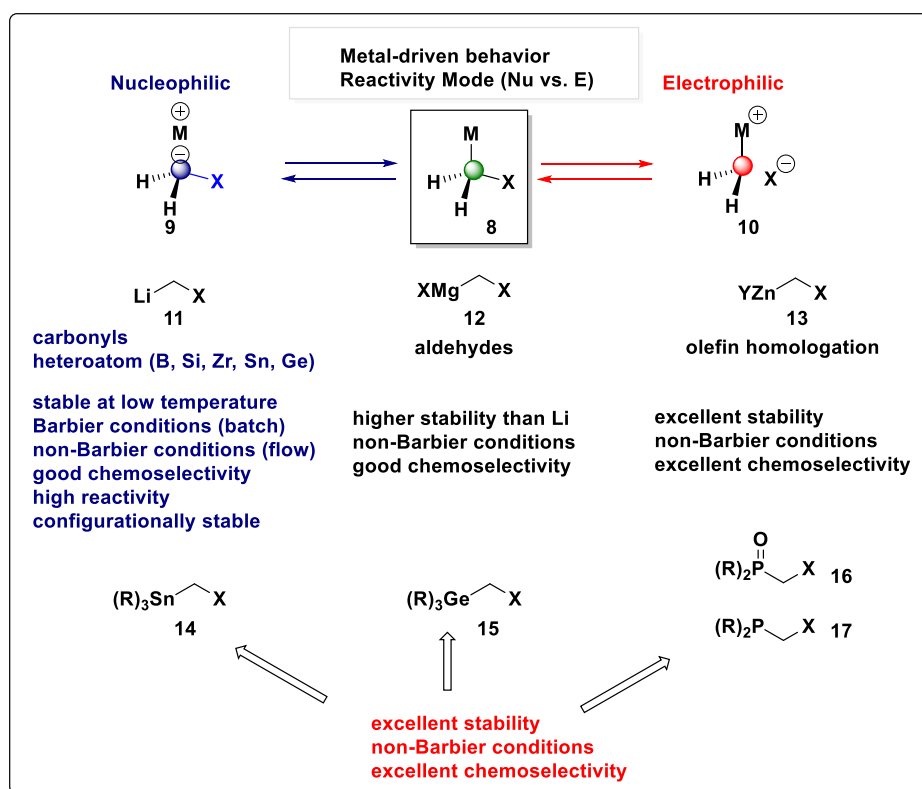


Figure 1. Reactivity mode (Nu vs. E) of carbenoids.

*Readapted from *Homologation Reactions: Reagents, Applications, and Mechanisms*.¹⁵

Due to the fragile chemical integrity of carbenoids (mainly the lithium ones), it is necessary to fine tune the reaction conditions, in order to avoid the rapid degradation of these species.³² By conducting homologations at low temperatures and eventually in Lewis base solvents and additives, this synthetic pattern has been proven to be successful and reliable, consistently delivering remarkable results.

In this thesis, the homologating potency of lithium halomethyl carbenoids (LiCH_2X) is extensively discussed, especially but not exclusively, with partners presenting sp^2 -hybridized carbon core, such as carbonyl-like derivatives (*e.g.*, ketone or aldehyde).

When delving into the cognitive journey of this chemistry, it is crucial to bear in mind a concept that proves and aids in handling these chemical entities: the distinction between carbenes and carbenoids and their intricate correlation. As elucidated by Closs in his studies on carbenoids, their principal differentiation lies in their capacity to induce stereocontrol in cyclopropanation reactions.²⁷⁻²⁸ Carbenes lack chirality, leading to racemic products upon insertion, whereas carbenoids can exhibit chirality depending on their substituents. The correlation between them is tied to carbenoids structure and their propensity to undergo Kirmse's α -elimination.³³ This degradative phenomenon arises from the internal coordination between the metal and the halogen, resulting in the formation of a free carbene and a metal (lithium) halide salt.

Another concept supporting the stereocontrol of carbenoids in reactions with nucleophilic counterparts, such as olefins, was introduced by Walborsky's through MAI (Metal Assisted Ionization) (Figure 2).³¹ Accordingly, the carbenoid behaves akin to a carbocation due to the lithium-assisted partial ionization of carbon-halogen (C-X) bond, while still maintaining its stereoconfiguration. Therefore, occasionally, this lithiated carbocationic center becomes a target for the nucleophile from the backside, leading to a product with an inverted configuration.

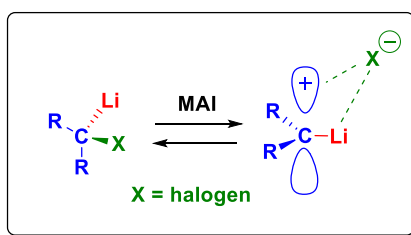


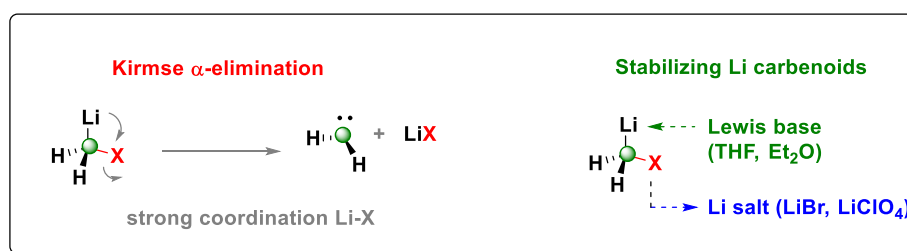
Figure 2. Metal Assisted Ionization (MAI).

*Readapted from *Homologation Reactions: Reagents, Applications, and Mechanisms*.¹⁵

Köbrich's seminal work has played a pivotal role in enabling modern chemists to acknowledge the inherent instability of lithium halomethyl carbenoids generated under non Barbier conditions.³⁴ Consequently, this understanding has facilitated the development of a procedure that effectively

modulates their stability. By employing Barbier conditions, wherein the electrophile is present in the reaction medium during carbenoid generation and conducting the reaction at low temperatures (-78 °C), an optional compromise between thermal stability and reactivity for this species can be achieved. Furthermore, employing lithium halide and Lewis basic ethereal solvents such as THF or diethyl ether, it becomes possible to prevent the α -elimination.

Indeed, as Villieras discovered in his studies,³⁵ the external addition of lithium halide (e.g., LiBr, LiClO₄) effectively prevents the undesired elimination reaction.³⁶ This prevention occurs due to the coordination of the halogen atom by the lithium halide, disrupting the internal interaction between Li and X, which is responsible for α -elimination reaction.³⁷ Regarding the use of Lewis basic ethereal solvents, also in this case there would be an additional coordinating interaction on carbenoid's lithium atom, enhancing the inhibitory effect on the elimination reaction and reinforcing its effective prevention (Scheme 2).

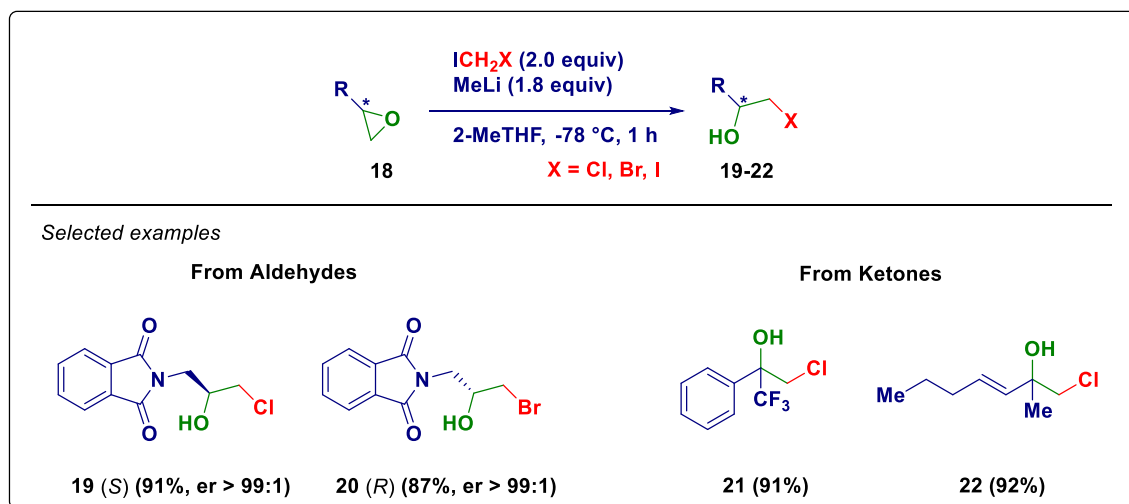


Scheme 2. Degradative α -elimination of carbenoids.

*Readapted from *Homologation Reactions: Reagents, Applications, and Mechanisms*.¹⁵

Nowadays, the most common lithiation agents, including MeLi, are readily purchased in the form of solutions complexed with LiBr.^{35, 38-42} Consequently, by adding this solution into the ethereal reaction medium (THF or diethyl ether) at low temperature (e.g., -78 °C, -65 °C), along with the presence of the electrophile (or nucleophile) and the carbon atom donor such as chloro-iodo-methane, the desired homologated product can be obtained without major complications.

In a noteworthy development in 2021, we made an exceptional utilization of the α -elimination reaction to achieve controlled ring-opening of epoxides **18**, resulting in the production of β -halohydrins (**19-22**).⁴³ In this study, being one of the published work further discussed later in the next chapters of this thesis, the eco-friendly solvent 2-MeTHF was employed (Scheme 3).⁴⁴⁻⁴⁵ However, this solvent triggered the degradation of lithium carbenoid due to the absence of the stabilizing effect typically provided by the classic THF. Additionally, the use of LiX-free MeLi, as lithium donor reagent, further contributed to the degradation. As well as it was effectively demonstrated that the α -elimination is a significant limitation for lithium carbenoid reactions and, indirectly, confirmed the existence of Kirmse's elimination.



Scheme 3. Pace's work exploiting the α -elimination as tool to achieve β -halohydrins.
 *Readapted from *Homologation Reactions: Reagents, Applications, and Mechanisms*.¹⁵

1.2 Lithium carbenoids synthetic pathways

Lithium carbenoids can be generated using well-established techniques commonly employed for preparing organolithium compounds.^{32, 46-50} Currently, the following methods are preferred: a) lithium-halide exchange using a suitable dihalomethane; b) lithium-sulfinyl exchange using a sulfoxide; c) lithium-tin exchange using a stannane. Lastly, the inherent acidity of dihalomethane protons ensures access to dihalomethyl carbenoids of the LiCHXY type through deprotonation with a lithium amide base (LiNR_2).

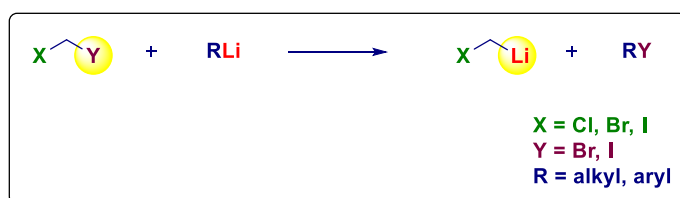
1.2.1 Metal-halide exchange

The most widely used method for generating halocarbenoids in homologation chemistry is lithium-halide exchange (Scheme 4). Unsaturated (XCH_2Y) or saturated (CH_2X_2) dihalomethanes can conveniently serve as pro-carbenoids for the desired lithium-halogen exchange. The choice of the specific carbenoid to be prepared can be predicted accurately since heavier halogens undergo exchange more rapidly. Iodine-containing halomethanes are particularly advantageous due to iodine's high reactivity towards metalation. However, in some cases, bromo-analogues, which are less prone to exchange,⁵¹ may be preferred to optimize costs, especially on an industrial scale.⁵²

Chloriodomethane (ICH₂Cl) is widely available at competitive prices, making it the reagent of choice for preparing LiCH₂Cl. Various aliphatic and aromatic organolithiums are effective for promoting the metal-halogen exchange, and there are no significant differences observed. However, considering the possible concurrent attack of the organolithium on the electrophile during carbenoid generation, the less nucleophilic MeLi can offer some advantages over *n*-BuLi. Additionally, the commercial availability of ethereal solutions of MeLi complexed with LiBr is particularly attractive and versatile, as it provides a convenient stabilizing element for the nascent carbenoid. The use of more basic *s*-BuLi and *t*-BuLi does not offer significant advantages over MeLi and *n*-BuLi and is now limited to specific cases or optimization studies.⁵³

In theory, the lithium-halogen exchange proceeds quantitatively, allowing for a 1:1 ratio between the dihalomethane and organolithium. However, it is preferable to use a slight excess (0.2-0.4 equiv) of dihalomethane to prevent the competing attack of the organolithium on the electrophile present in the reaction mixture.³⁶ This precaution is particularly relevant when titrated solutions of organolithiums are not used immediately. It is advisable to add the alkyllithium to the mixture of dihalomethane and electrophile slowly, ensuring prompt reaction of the carbenoid upon its formation.⁵³ Controlled addition of organolithium using a syringe pump is a convenient technique to ensure proper carbenoid formation.

Another critical consideration is the electrophilic reactivity of the homologating system, which must precisely yield the desired target structure. Highly reactive species may undergo attack by organolithium prior to carbenoid formation, compromising the chemocontrol of the process.³² Finally, it is important to acknowledge the formation of an electrophilic by-product (RY) during the generation of the carbenoid.⁵⁴ In subsequent sections of this chapter, we will explore the positive consequences of this by-product, which enable the design of more sophisticated homologation pathways.

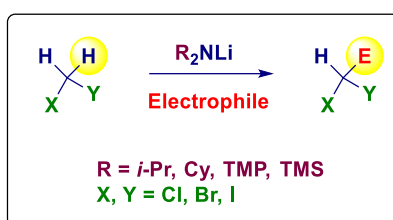


Scheme 4. Carbenoids generation through metal-halide exchange.

**Readapted from Homologation Reactions: Reagents, Applications, and Mechanisms.¹⁵*

1.2.2 Metal-proton exchange

The inherent acidity of dihalomethane protons, owing to the presence of two halogen atoms, allows for the successful generation of dihalomethyl lithium carbenoids through treatment with a lithium amide base (*e.g.*, LDA) (Scheme 5).⁵⁵⁻⁵⁹ These carbenoids serve as effective homologating reagents with two distinct halogens. Prominently, strict adherence to Barbier-type conditions is not necessary when utilizing dihalocarbenoids. While earlier studies by Nozaki⁵⁸⁻⁵⁹ and Barluenga⁵⁷ emphasized this aspect, more recent research by Bull⁶⁰⁻⁶¹ demonstrated that these carbenoids can be formed prior to their reaction with the electrophile. It can be postulated that Barbier-type conditions ensure the preservation of chemical integrity, rendering their use in batch-mode reactions non-detrimental.



Scheme 5. Carbenoids generation through metal-proton exchange.

*Readapted from *Homologation Reactions: Reagents, Applications, and Mechanisms*.¹⁵

Furthermore, the quantitative demonstration of the stability of different dihalocarbenoids, conferred by the nature of the halogens present, remains elusive. LiCHCl_2 and LiCHBr_2 are known to be less stable compared to LiCHI_2 , while mixed carbenoids such as LiCHClI , LiCHBrCl , and LiCHBrI are highly susceptible to degradative α -elimination.⁶²⁻⁶⁴ Notably, the introduction of LiCHF_2 by Pace and Luisi in 2019 merits special mention.⁶⁴ Like LiCH_2F , LiCHF_2 exhibits inherent instability, which can be effectively mitigated when generated in a mixture of THF and Et_2O .⁶⁵

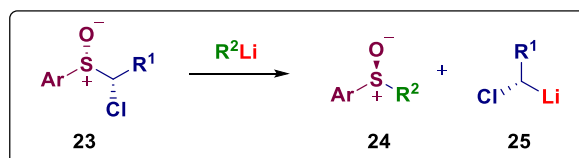
Collectively, the presence of two halogens moderates the nucleophilicity of dihalocarbenoids to some extent, relative to their monohalo analogues. Consequently, it is not surprising that certain electrophiles, which are not inherently reactive, may pose challenges in reactions with these reagents. The deprotonation strategy has also been employed to access trihalomethylcarbenoids from the corresponding haloforms. For instance, Molinski generated trichloromethyl lithium from chloroform and *n*-BuLi at -100°C .⁶⁶ However, trihalomethyl lithiums are highly unstable species even at very low temperatures, limiting their synthetic utility. Nonetheless, due to the lowered nucleophilicity conferred by the presence of three halogens, making them soft nucleophiles, they can participate in Michael additions by attacking the β -position of an unsaturated sultam.

1.2.3 Metal-sulfinyl exchange

The utilization of halomethyl-aryl sulfoxides as valuable starting materials for the generation of carbenoids through lithium-sulfinyl exchange has been well established (Scheme 6).⁶⁷⁻⁷¹ This approach, which has been extensively employed for generating organometallic species, provides an attractive alternative to the more commonly used halogen-lithium exchange.⁷²⁻⁷³ Pioneering work by Hoffmann validated this method for accessing chiral magnesium carbenoids, which are inherently less nucleophilic than their lithium analogues, thus limiting the scope of homologations.⁷⁴⁻⁷⁸

Building upon this, Blakemore identified the conditions to extend the application of sulfinyl exchange to lithium carbenoids, elucidating important aspects of the transformation.⁷⁰ Firstly, because of the exchange, a new sulfoxide is formed, characterized by the incorporation of the R residue delivered by the promoting organolithium reagent. Secondly, in the case of chiral sulfoxides, stereo-inversion occurs at the sulfur atom. Thirdly, the carbenoid generated exhibits high stereo-fidelity.

Unlike dihalomethanes, which are readily commercially available, sulfoxides typically need to be synthesized. The synthetic route usually involves the (asymmetric) oxidation of a thioether, followed by electrophilic halogenation at the α -position of sulfur.^{70, 79} Importantly, the formation of the exchange sulfoxide during carbenoid formation provides clear and unambiguous evidence of halomethyl lithium generation. While in the case of halogen/lithium interconversion, the exchange product (R-X) is also formed, its detection can be more challenging in reaction mixtures due to the higher volatility of these species compared to sulfoxides. Moreover, the presence of the chiral element in sulfoxides not only governs the stereochemistry of the final carbenoids but also facilitates derivatization at the sulfur-bearing carbon, offering a versatile pathway to access tertiary pro-nucleophiles. This represents a significant advantage over dihalomethanes, which would require more sophisticated approaches for desymmetrization.



Scheme 6. Carbenoids generation through metal-sulfinyl exchange.

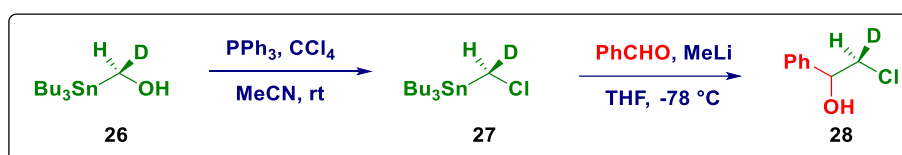
*Readapted from *Homologation Reactions: Reagents, Applications, and Mechanisms*.¹⁵

1.2.4 Lithium-Tin exchange

The concept of regarding lithium carbenoids of choice among organolithiums, inspired by Hoppe's work on α -oxygen substituted analogues,⁸⁰⁻⁸³ prompted Hammerschmidt to synthesize

configurationally stable monodeuterated chloromethylstannane (LiCDHCl) through a convenient tin-lithium exchange using a chiral stannane and MeLi .⁸⁴ The enantiopure chloromethylstannane-[D1] (**27**) was prepared from homochiral tributylstannyl-[D1]-methanol (**26**), followed by chlorination under Appel conditions (Scheme 7).⁸⁵ The choice of organolithium strongly influenced the success of the tin-lithium exchange, with MeLi yielding superior results compared to $n\text{-BuLi}$, which, due to its higher basicity, could lead to the formation of undesired side products. Mechanistically, the process involves the attack of the organolithium on the tin atom, forming a tin-ate complex, which subsequently undergoes a 1,2-metalate rearrangement to deliver the carbenoid.

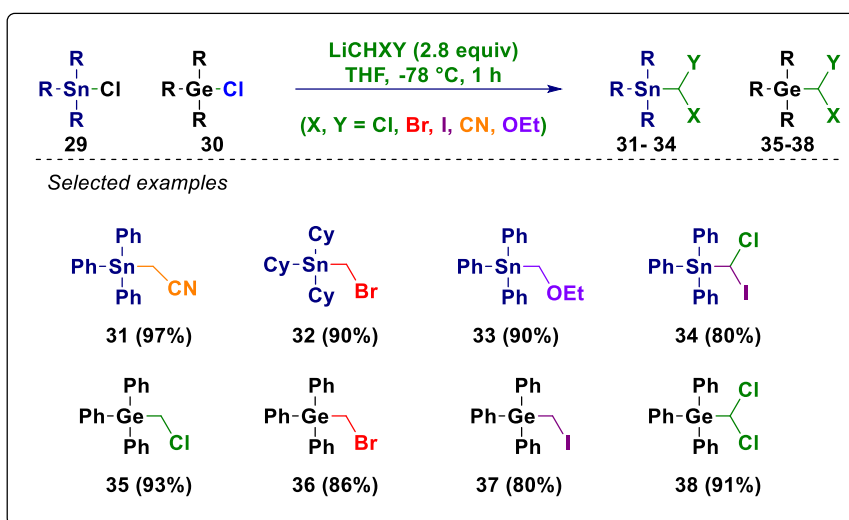
This explains why less sterically hindered stannanes (such as Me) facilitate the exchange and overall reactivity. However, the pronounced toxicity of trimethyltin donors discourages their widespread application in the synthesis of these analogues. The tin-lithium exchange performed at $-95\text{ }^{\circ}\text{C}$ demonstrated complete preservation of the chiral information of the carbenoid. Furthermore, when the reaction was conducted at $-78\text{ }^{\circ}\text{C}$ and the electrophile (benzaldehyde) was added after 30 seconds, the chemical stability of the carbenoid decreased but the chiral information was still maintained. This observation confirms that, at $-78\text{ }^{\circ}\text{C}$, the chiral carbenoid decomposes rather than racemizes. They investigated following the same rationale the configurational stability of LiCH_2Br ⁸⁶ and LiCH_2F ,⁸⁷ confirming the same results for this species.



Scheme 7. Carbenoids generation through lithium-tin exchange.

**Readapted from Homologation Reactions: Reagents, Applications, and Mechanisms.¹⁵*

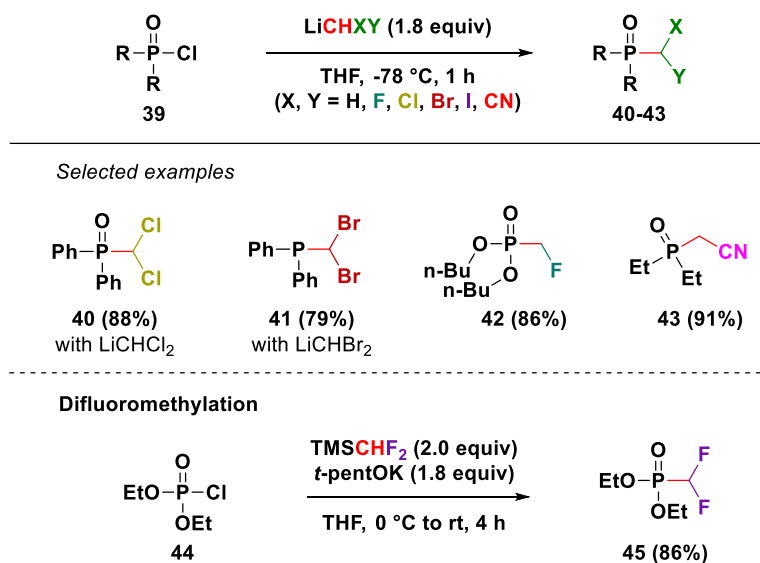
In light of the inherent stability conferred by the covalency of the C-Sn bond, as opposed to the ionic nature of the C-Li bond, Pace demonstrated the ability of lithium carbenoids (LiCHXZ ; X, Z = halogen, OR, CN) to act as donors of the CHXY unit to halostannanes **29** (or halogermanes **30**), generated through iodine-lithium exchange (Scheme 8).⁸⁸ This reaction, involving a formal nucleophilic substitution on the Sn or Ge center, allows for the synthesis of stable halomethyl-derivatives with remarkable stability (in comparison to their Li counterparts). These derivatives serve as valuable reservoirs. This direct and straightforward method enables the production of the desired compounds in a single synthetic step, representing a significant improvement over Hammerschmidt's two-step Appel-type protocol.⁸⁴



Scheme 8. Homologation of halo-stannanes and halo-germanes.

*Readapted from *Homologation Reactions: Reagents, Applications, and Mechanisms*.¹⁵

Remaining in transmetallation reactions domain, in 2021, Pace reported a one-step functionalization of various phosphorous electrophiles **39** (including phosphates, phosphinates, and phosphines) using α -substituted organolithium reagents (LiCHXY) to directly obtain geminal P-containing methanes (**40-43**) (Scheme 9).⁸⁹ The protocol was extended to access CHF_2 -analogues (**45**) by employing a formal equivalent of the difluoromethyl carbanion, generated from TMSCHF_2 and potassium *t*-pentoxide.⁹⁰⁻



Scheme 9. Functionalization of phosphorous electrophiles.

*Readapted from *Homologation Reactions: Reagents, Applications, and Mechanisms*.¹⁵

1.3 Carbenoids configurational stability

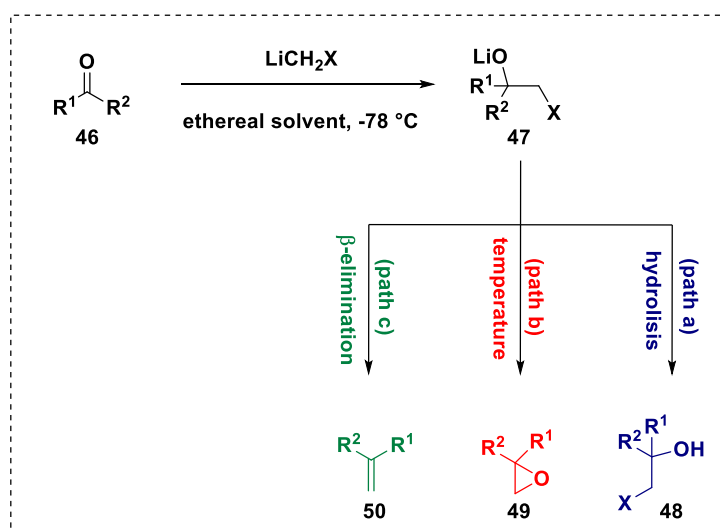
In 1994, Hoffmann and colleagues laid the foundation for evaluating the configurational stability of chiral organolithium compounds during their addition to aldehyde.⁹⁶ The test involved the kinetic resolution of α -bromo-, α -phenylseleno, and α -phenylthio-alkyl-lithium species, revealing that the addition of these compounds to a chiral aldehyde occurs more rapidly than the enantiomeric equilibration of the organolithium compounds. Subsequently, α -bromo-alkyllithium derivatives, which exhibited configurational stability at -110 °C, were generated through diastereoselective bromine/lithium exchange starting from dibromoalkanes. Trapping these derivatives with electrophiles yielded adducts in diastereomer ratios of up to 94:6.⁹⁷ Confirming these findings, Hammerschmidt discovered that homochiral chloromethylithium, prepared *via* tin-lithium exchange using the corresponding tributyl(chloro-[D1]methyl)stannane, demonstrated both microscopic and macroscopic configurational stability.^{84, 86-87}

The addition of chloromethylithium to benzaldehyde proceeded with retention of configuration, yielding up to 90% (microscopically) at -78 °C. However, the yield dropped to 54% (macroscopically) at -95 °C within 30 seconds, although an excellent enantiomeric excess of 98% was observed.⁸⁶ Notably, the presence of the halogen in these α -substituted organolithiums contributed to their configurational stability. Switching to thio-analogues led to significant epimerization of the corresponding reagents. On the other hand, iodo-[D1]methylithium, prepared similarly from tributyl-(iodo-[D1]methyl)stannanes (92% *ee*), was found to be configurationally labile during addition to benzaldehyde at all investigated temperatures (-95 °C to -30 °C).⁸⁷ The rate of disintegration of ICHDLi into deuterated carbene and LiI increased notably with temperature escalation.

1.4 Electrophilic partners of Lithium Carbenoids

1.4.1 Carbonyl adducts

Carbonyl compounds are commonly used in reactions involving nucleophilic lithium carbenoids. Early studies by researchers such as Cainelli,⁹⁸⁻⁹⁹ Villieras,³⁵ Matteson,⁴¹ Barluenga,¹⁰⁰ and Concellón¹⁰¹ demonstrated that the addition of a halomethyl lithium to an aldehyde or ketone (**46**) results in the formation of an isolable β -halohydrins **48** upon acidic quenching (Scheme 10, path a).



Scheme 10. General outcomes from homologation of carbonyl compounds with lithium carbenoids.

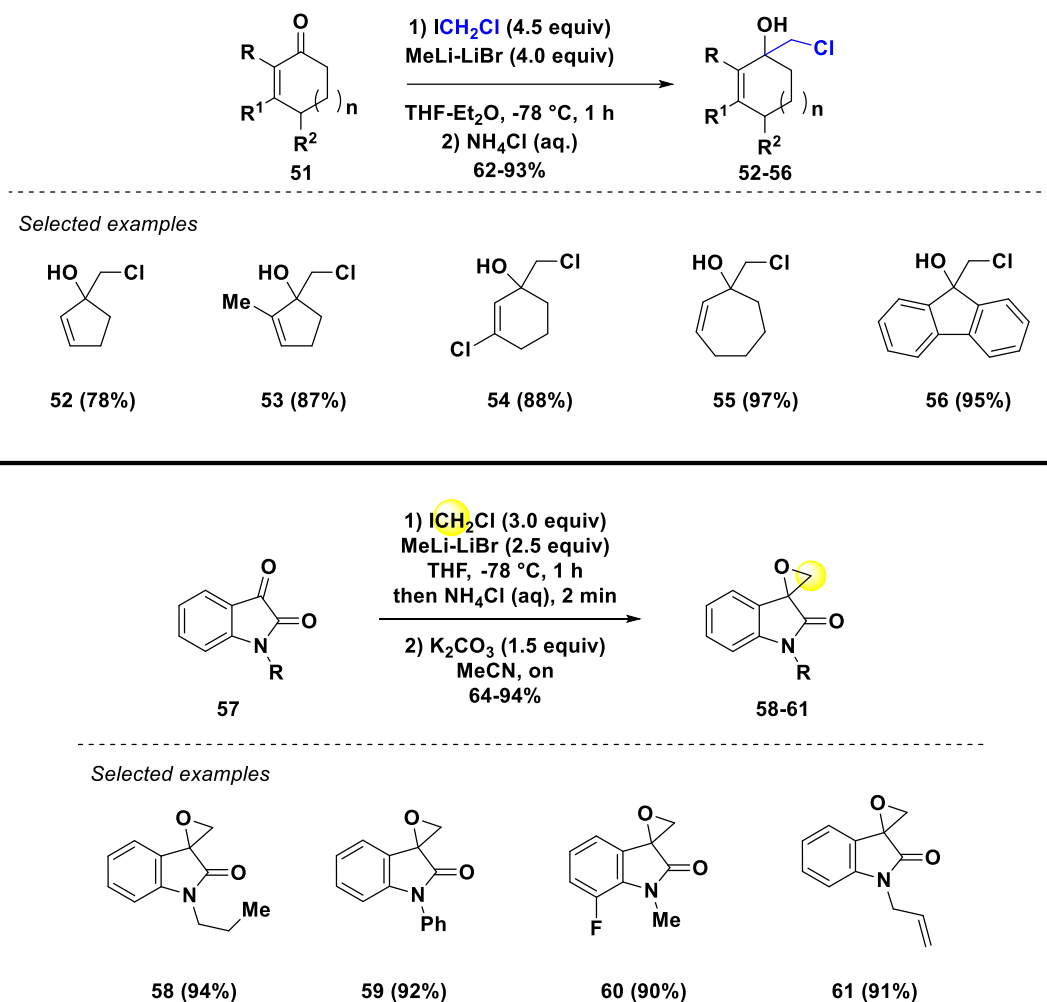
*Readapted from *Homologation Reactions: Reagents, Applications, and Mechanisms*.¹⁵

These β -halohydrins can be converted into epoxides **49** through base-assisted ring closure or by increasing the reaction temperature (Scheme 10, path b). This carbonyl homologation with halomethyl lithium provides an alternative to the Corey-Chaykovsky epoxidation with sulfur ylides.⁹⁹ Both reagents offer complementary approaches depending on the substrates and reaction conditions. Halolithiums and sulfur ylides act as carbanions with leaving groups, leading to cyclic systems through subsequent nucleophilic displacement events. Acidic quenching produces a halohydrin, while further lithiation triggers β -elimination to form a terminal olefin **50** (Scheme 10, path c).¹⁰²

Pace and colleagues achieved chemo-controlled homologation of unsaturated cyclic ketones **51** to obtain chloromethyl allylic alcohols **52-56** as exclusive products.¹⁰³ Lithium halocarbenoids exhibit excellent nucleophilic behavior, allowing selective 1,2-additions without unwanted 1,4-attacks that can occur with lithium carbenoids, resulting in cyclopropanes (Scheme 11).¹⁰⁴⁻¹⁰⁵

Similarly, functionalized isatins **57** can be transformed into spiro-epoxyoxindoles **58-61** through carbenoid nucleophilic addition to the highly electrophilic C3 carbon of the heterocycle¹⁰⁶⁻¹⁰⁷ (Scheme

11). In this case, the initially formed halohydrin is treated with a base to deliver the spiro-analogues with high yield and chemocontrol, even when starting materials contain sensitive groups.



Scheme 11. Homologation of cyclic ketones.

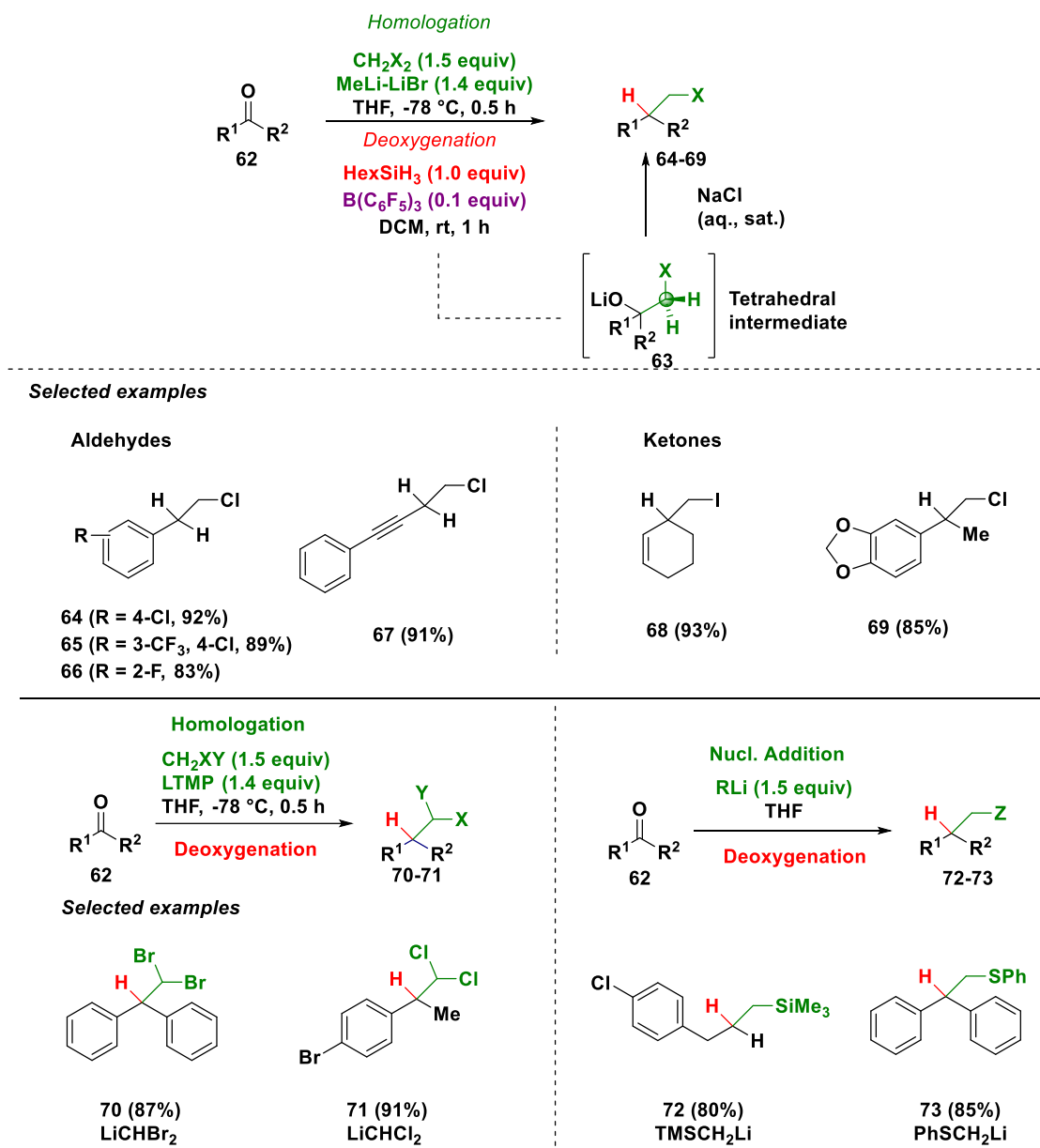
**Readapted from Homologation Reactions: Reagents, Applications, and Mechanisms.¹⁵*

The current state-of-the-art of carbenoid-mediated homologations demonstrates the effectiveness of sp^2 -hybridized carbon electrophiles for C1-insertion reactions.

However, achieving homologations with $LiCH_2X$ -type reagents for sp^3 -hybridized carbon analogues remains challenging due to unproductive polyhomologation events observed in early studies by Huisgen¹⁰⁸ and later confirmed by Hahn.¹⁰⁹

The Pace group overcame this issue by implementing a sequential carbonyl homologation/deoxygenation sequence using hydride sources and Lewis acids to remove the oxygen moiety.¹¹⁰ The process involved the generation of alkoxides from carbonyls through carbenoid

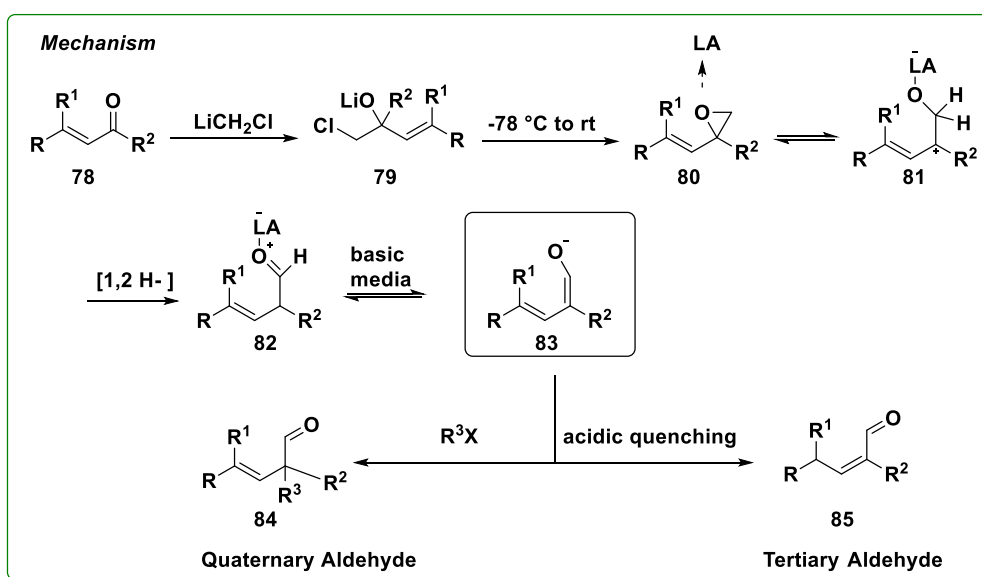
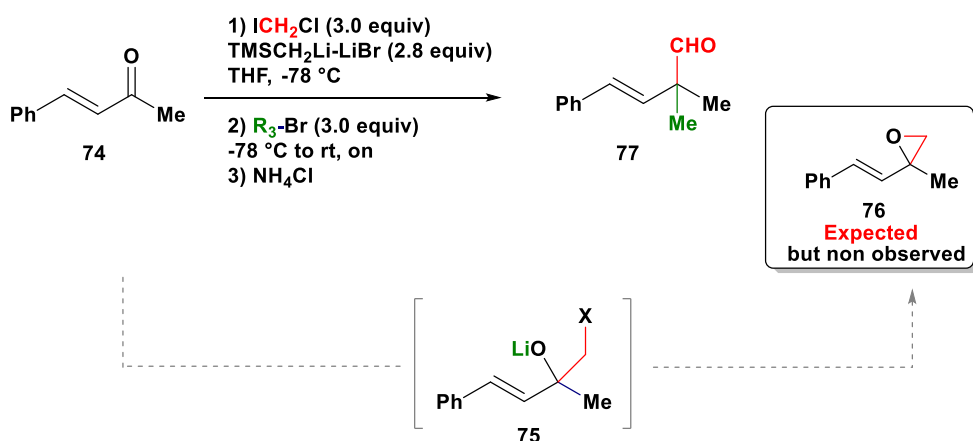
reactivity, followed by deoxygenation and further transformations.¹¹¹ The tactic is flexible and extends beyond carbenoids, as other carbanion-like species can serve as competent nucleophiles (Scheme 12).



Scheme 12. Homologation-deoxygenation of carbonyls and nucleophilic addition/deoxygenation with various carbanion-like reagents. *Readapted from *Homologation Reactions: Reagents, Applications, and Mechanisms*.¹⁵

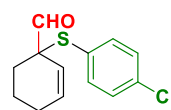
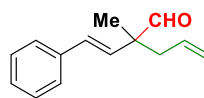
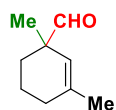
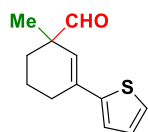
Pace and coworkers also observed unexpected outcomes when attempting to obtain vinyl epoxides⁵⁴ from α,β -unsaturated ketones **74** and LiCH_2Cl through thermal-mediated ring closure of β -haloalkoxides **75**.¹¹² Instead of the targeted epoxide **76**, fully α -substituted (homologated) aldehydes **77** were formed, along with non- α -functionalized β,γ -unsaturated aldehydes **85**, depending on the reaction conditions (Scheme 13). The presence of an additional carbon in the aldehyde indicated the occurrence of the homologation process, and the α -methyl group was attributed to the by-product

formed during carbenoid preparation. Different organolithiums did not result in quaternarization at the α -position of the aldehyde, suggesting that electrophilic species generated from MeI play a crucial role.



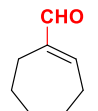
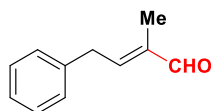
Selected examples

i) Use of MeLi-LiBr : formation of electrophilic MeI



ii) Use of $\text{TMSCH}_2\text{Li-LiBr}$: Possibility to Add a Second Electrophile

iii) Use of $\text{TMSCH}_2\text{Li-LiBr}$ and Acidic Quenching: Synthesis of α,β -Unsaturated Aldehydes



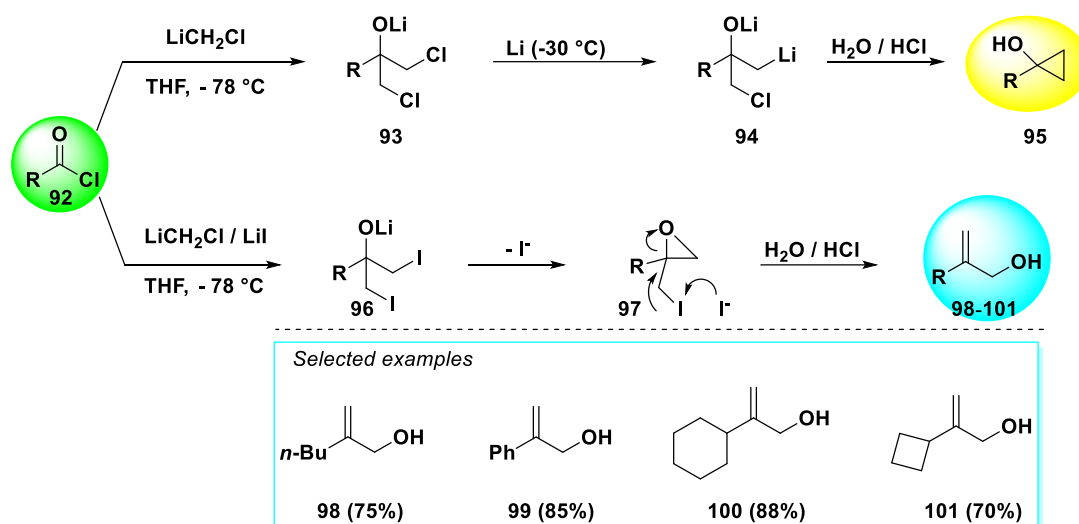
Scheme 13. Homologation of unsaturated ketones and scope of the reaction.

**Readapted from Homologation Reactions: Reagents, Applications, and Mechanisms.¹⁵*

Additionally, the presence of LiBr as a mild Lewis acid and an increase in temperature were found to be fundamental for the transformation. A mechanistic understanding of the process allowed the direct conversion of carbonyl compounds into homologated aldehydes fully functionalized at the α -position.¹¹³⁻¹¹⁴ By generating LiCH₂Cl from ICH₂Cl and MeLi-LiBr, cyclic and acyclic α -methyl aldehydes, including derivatives of natural products, were synthesized. TMSCH₂Li-LiBr was suitable for introducing different electrophiles at the α -position for subsequent transformations (Scheme 13). Reactive alkyl-type halides, even with sensitive groups, did not affect the chemoselectivity. Acidic quenching of the enolate yielded α,β -unsaturated aldehydes through spontaneous tautomerization of the less stable β,γ -unsaturated analogues.

1.4.2 Carboxylic acid chlorides

Barluenga and colleagues investigated the reactivity of carbenoids with carbonyl-like compounds¹¹⁵ and observed a unique behavior of carboxylic acid chlorides **92**.^{55, 102} By adjusting the reaction conditions (Scheme 14), these electrophiles can be conveniently used to prepare cyclopropanols **95** or allyl alcohols **98-101**. The carbenoids undergo two nucleophilic attacks on the acyl chloride, considering the instability of the intermediate ketone. Subsequent lithiation with Li metal leads to a dilithiated species **94** that, upon acidic treatment, serves as a precursor for 1,1-cyclopropanol **95**. Alternatively, in the presence of lithium iodide, an epiiodohydrin **97** is initially formed, and then LiI, acting as a base, facilitates elimination by attacking the iodine atom of the CH₂I fragment. This process ultimately yields an allylic alcohol **98-101**.

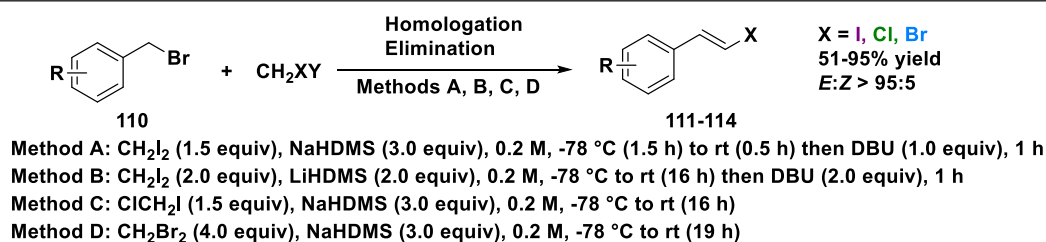
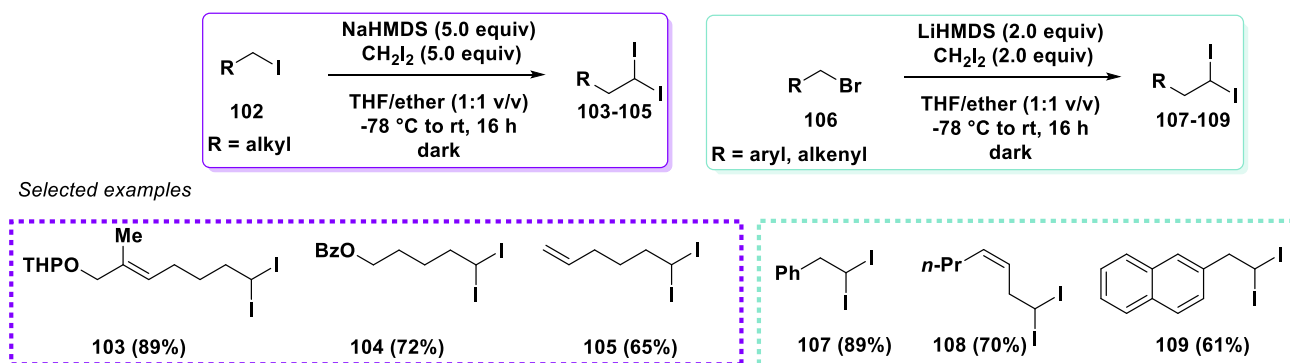


Scheme 14. Reaction between carbenoids and acyl chlorides resulting in cyclopropanols and allyl alcohols. *Readapted from *Homologation Reactions: Reagents, Applications, and Mechanisms*.¹⁵

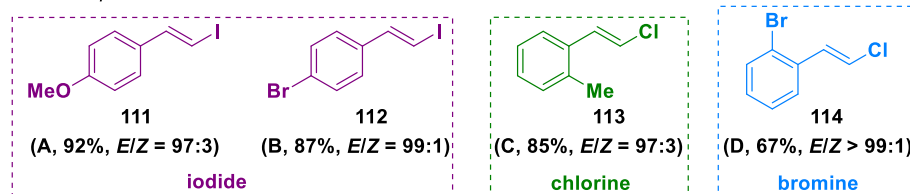
1.4.3 Homologation of benzyl halides

In 2008, Charette and colleagues developed a reliable and effective protocol for homologating haloalkanes using diiodomethyl carbenoids (Scheme 15).¹¹⁶⁻¹¹⁷ Iodoalkanes underwent smooth transformation with NaCHI_2 , resulting in valuable gem-diiodoalkanes in high yields. To maximize reaction yields, it was advantageous to generate the nucleophile by adding CH_2I_2 to a solution of NaHMDS in THF/diethyl ether. Benzyl and allyl bromides showed improved results with minimal formation of elimination products when using the analogous diiodomethyl lithium carbenoid (LiCHI_2), formed by deprotonating with LiHMDS (except for highly conjugated systems). It is noteworthy that both NaCHI_2 and LiCHI_2 could be effectively employed at $-78\text{ }^\circ\text{C}$, contrary to previous reports suggesting their instability even at temperatures below $-90\text{ }^\circ\text{C}$.¹¹⁸⁻¹¹⁹ The methodology demonstrated compatibility with functional groups such as ethers, hindered esters, and carbamates, without altering the geometry of stereo-defined olefins.

The group further envisioned the application of the strategy for the stereoselective synthesis of (*E*)- β -aryl vinyl halides by triggering subsequent elimination (Scheme 15).¹¹⁷ The use of the more basic NaCHI_2 favored the desired elimination, yielding the *E*-olefin as the predominant product (*E/Z* > 95:5). To ensure reproducibility, the addition of 1 equivalent of DBU prior to the work-up was recommended. For sensitive substrates, LiCHI_2 was more suitable but generally resulted in lower chemical yields. By using different dihalomethanes such as chloriodomethane and dibromomethane, the corresponding chloro- and bromo-alkenes were obtained without the need for external DBU addition.



Selected examples

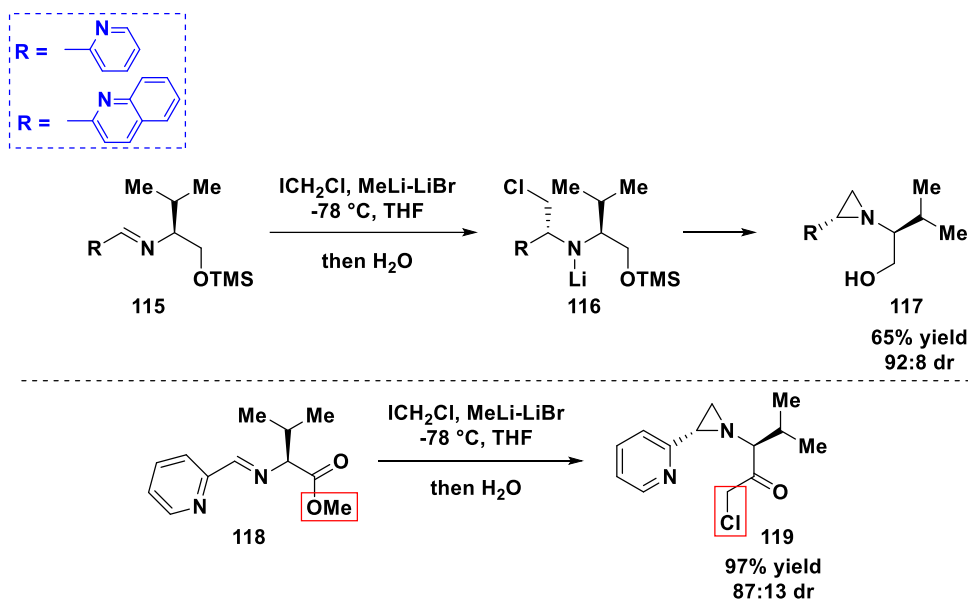


Scheme 15. Synthesis of gem-diiodoalkanes and (E)-β-aryl vinyl halides.

*Readapted from Homologation Reactions: Reagents, Applications, and Mechanisms.¹⁵

1.4.4 Imines

Imines serve as attractive platforms for homologation processes using lithium carbenoids to generate valuable materials such as β-haloamines and their cyclic analogues, aziridines. Savoia and colleagues proposed the use of chloromethyl lithium on an enantiopure imines **115** to prepare chiral substituted aziridines **117** with high yield and stereocontrol (Scheme 16).¹²⁰ This carbenoid exhibited favourable reactivity compared to the less nucleophilic zinc carbenoid (*i.e.*, ClCH₂ZnEt).¹²¹ By raising the temperature to 20 °C, a spontaneous ring closure occurred, leading to the formation of the desired aziridines. The presence of a pyridyl-type group (2-pyridine or 2-quinoline) was essential for reactivity as it chelated the incipient carbenoid, enhancing its nucleophilic character for attacking the relatively poor electrophilic imine carbon. The formation of aziridine did not occur when the imine lacked the 2-pyridine ring or had highly sterically hindered functionalities on the imine nitrogen. However, achieving chemocontrol was challenging in imines with additional electrophilic sites. For instance, the reaction performed on the (*S*)-valine methyl ester **118** derivative resulted in double addition to both sides (imine and ester), yielding the aziridine with an α-chloroketone motif **119** (Scheme 16).



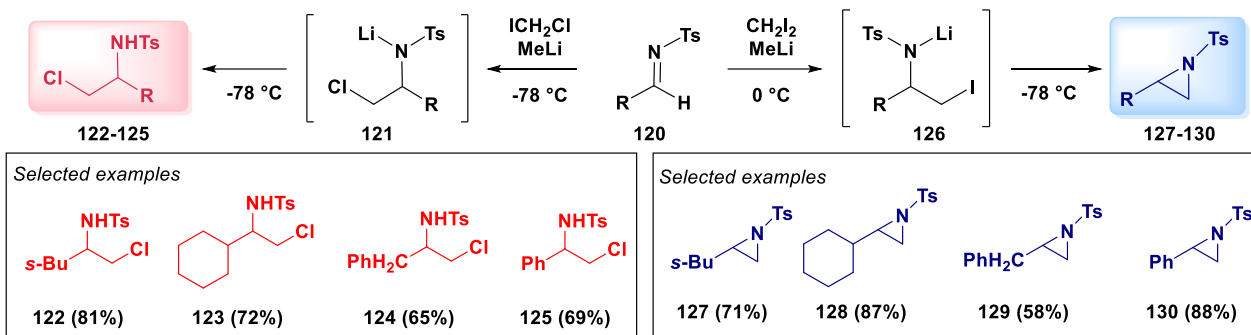
Scheme 16. Carbenoid-mediated aziridination by Savoia.

*Readapted from *Homologation Reactions: Reagents, Applications, and Mechanisms*.¹⁵

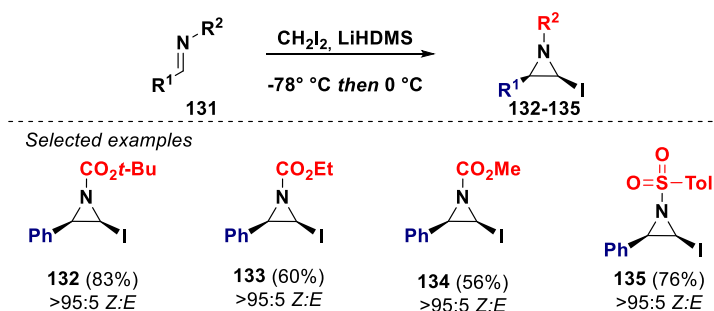
To enhance the electrophilicity of the azomethinic carbon and overcome the limited reactivity of *in situ* generated halomethyl lithium reagents towards poorly electrophilic compounds, Concellón and colleagues presented a strategy involving the installation of an electron-withdrawing group on the imine nitrogen (iodomethyl lithium with sulfonyl-protected imine) to prepare *N*-tosylaziridines **127-130** in one pot (Scheme 17 path a).¹²² However, the removal of tosyl-type protecting groups required harsh conditions, limiting the appeal of the synthetic sequence. Further investigations extended the protocol to *N*-sulfonyl protected imines **120** using chloromethyl lithium, resulting in β -chloroamines **122-125** after acidic work-up at -78°C . This approach allowed the isolation of intermediates and avoided the cyclization step to aziridines.¹²³

In another study, Bull and colleagues prepared *N*-Boc and *N*-Ts protected α -iodoaziridines **132-135** starting from the corresponding imines **131** using diiodomethyl lithium,⁶⁰⁻⁶¹ formed *via* deprotonation of diiodomethane with LiHDMS at -78°C , to obtain disubstituted aziridines with high *Z*-selectivity (Scheme 17 path b). The transformation could also be achieved using analogous magnesium carbenoids.

a) Concellón *et al.*



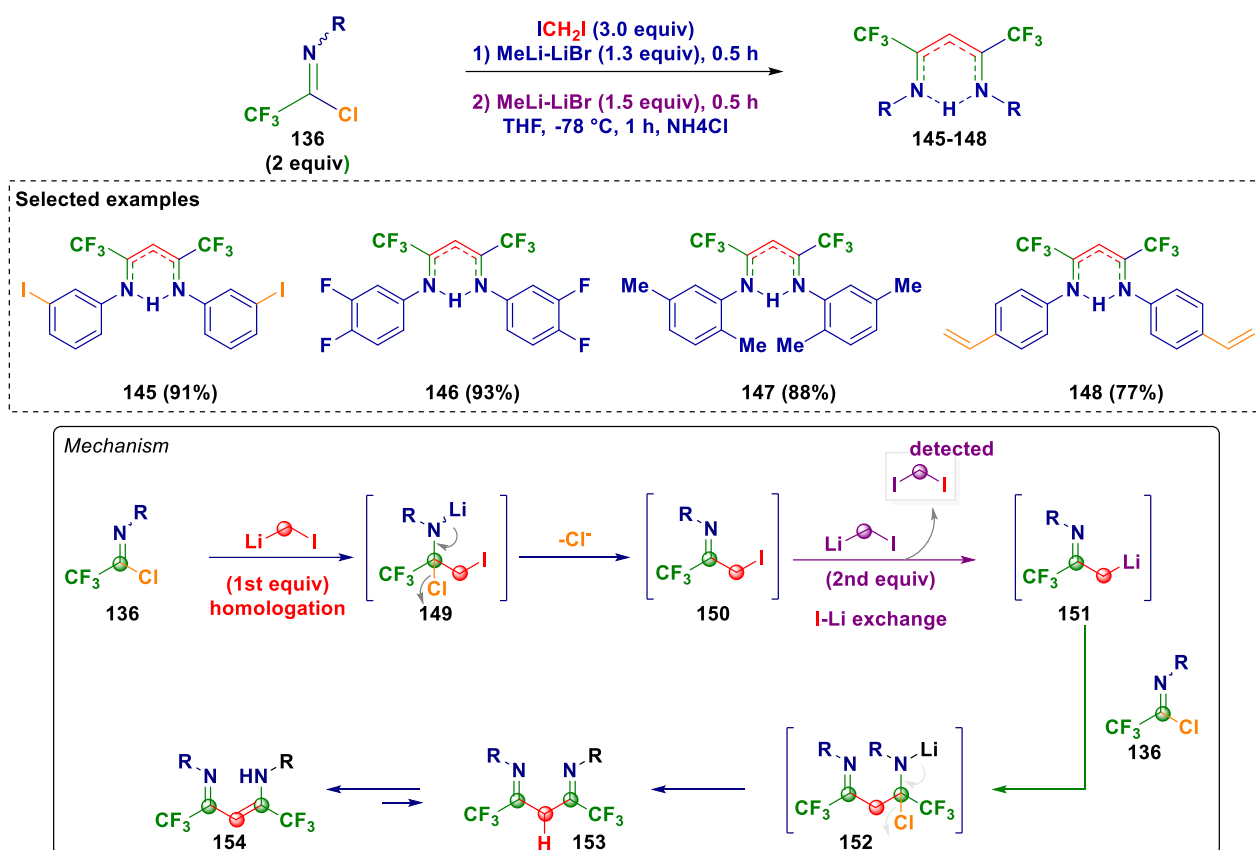
b) Bull *et al.*



Scheme 17. Synthesis of N-tosylaziridines and β -chloroamines by Concellón and of iodoaziridines by Bull.

*Readapted from *Homologation Reactions: Reagents, Applications, and Mechanisms*.¹⁵

Pace and coworkers reported the synthesis of unprecedented quaternary α -chloro **137-138** and α -halomethyl trifluoromethyl aziridines **139-140** using a telescoped carbenoid-mediated homologation of trifluoroacetimidoyl chlorides (**136**, TFAICs) (Scheme 18).¹²⁴ These electrophiles exhibited unique reactivity due to the excellent electrophilicity of the azomethinic carbon imparted by the electron-withdrawing trifluoromethyl group and the chlorine atom.¹²⁵ One C1 unit was inserted in the presence of 1.2 equiv of LiCH_2Cl ,¹²⁶ while increasing the stoichiometric loading up to 2.8 equiv resulted in a C1-C1 bis-homologation, furnishing gem-halomethyl-trifluoromethyl-aziridine (Scheme 18).¹²⁷⁻¹²⁸ The methodology demonstrated superb chemocontrol, selectively attacking the electrophilic TFAIC carbon in the presence of highly sensitive functionalities to organolithium reagents and tolerating nitrogen-containing substituents and unsaturated motifs.



Scheme 19. Synthesis of bis-trifluoromethyl-β-diketiminates and plausible mechanism.
 *Readapted from *Homologation Reactions: Reagents, Applications, and Mechanisms*.¹⁵

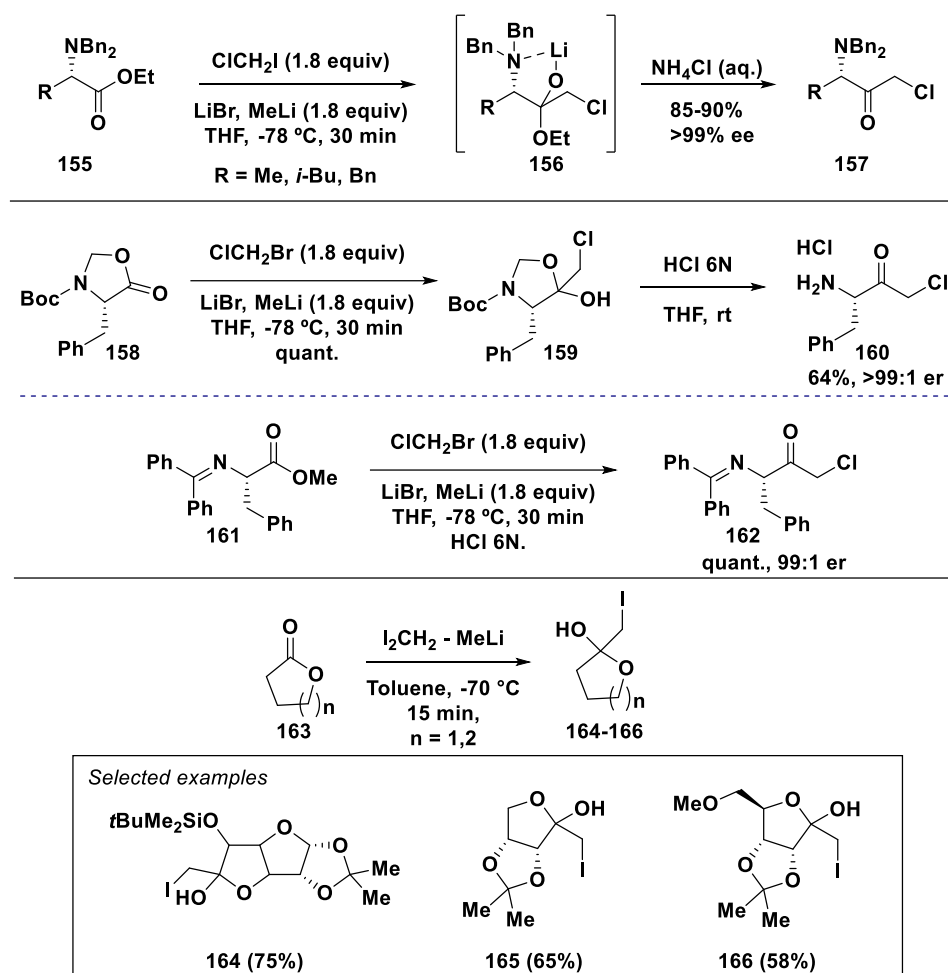
These studies highlight the versatile and valuable applications of lithium carbenoids in the homologation of imines, leading to the synthesis of various substituted aziridines and other compounds with high yield and stereocontrol.

1.4.5 Ester and Weinreb amides

Barluenga and colleagues have documented the homologation of esters **155** to access α – haloketones **157** through the addition of lithium carbenoids at -78°C under classical Barbier-type conditions (Scheme 20).^{56-57, 130-133} In this process, simple substrates may undergo polyaddition of the carbenoid, resulting in the formation of carbinols. However, the presence of a disubstituted α-amino group enables the internal coordination of the tetrahedral intermediate **156**, effectively preventing double addition. The stability of this intermediate is attributed to the electronegative halogen and oxygen atoms, which hinder the elimination of the alkoxide group.

Izawa's group studied the reactivity of esters and found that the presence of amino or amido groups with a hydrogen atom (i.e., non-fully substituted) inhibits the homologation reaction.¹³⁴⁻¹³⁸ In these cases, the basic carbenoid preferentially abstracts the hydrogen instead of attacking the ester

functionality. By employing *N*-protected 3-oxazolidin-5-ones **158** as suitable protecting groups, the chloromethylation of esters becomes feasible, leading to the desired chloroketone **160** upon acidic treatment. Additionally, they demonstrated the chemoselective chloromethylation of *N*-imine protected amino acid esters **161**, showcasing the low electrophilicity of the imine carbon and the steric hindrance (Scheme 20).



Scheme 20. Barluenga's, Izawa's and Morin's homologations of esters.

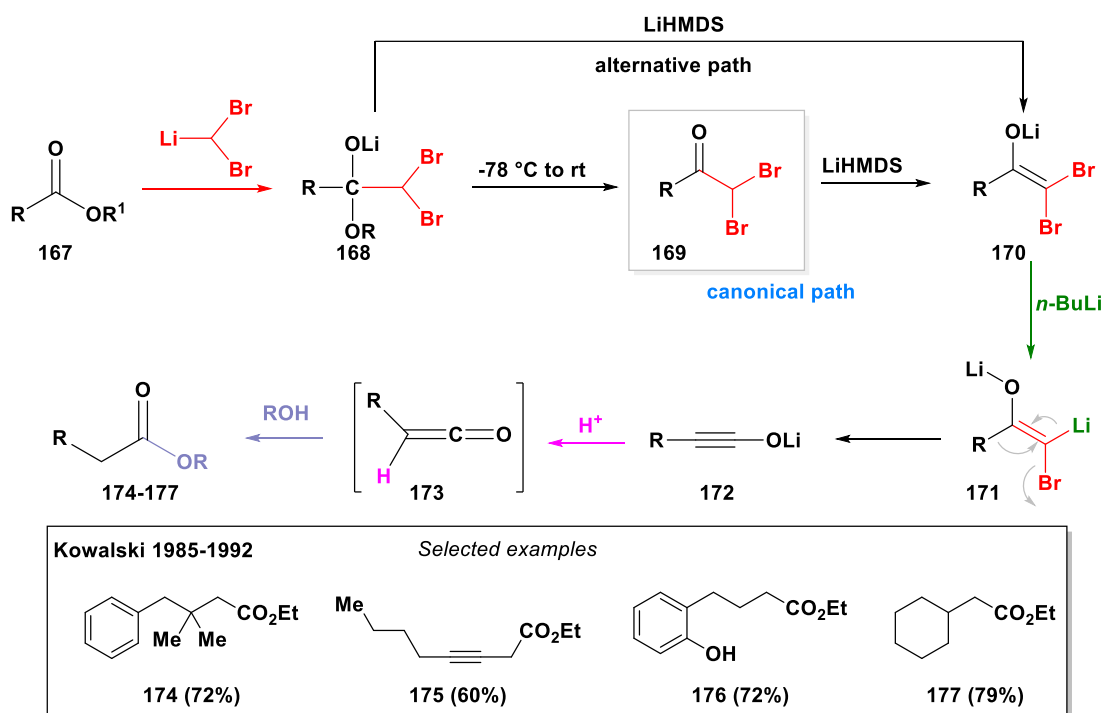
*Readapted from *Homologation Reactions: Reagents, Applications, and Mechanisms*.¹⁵

Hilpert and co-workers introduced an *in-situ* protection strategy for the (secondary) amide moiety using a labile *N*-trimethylsilyl amine, which can be easily removed during the work-up procedure.¹³⁹ This approach allows for the homologation of esters without affecting the ester moiety.

In 2000, Morin and co-workers, inspired by Barluenga's precedents,⁵⁷ achieved the homologation of various substituted lactones **163** using iodomethyl lithium (Scheme 20).¹⁴⁰⁻¹⁴¹ The use of toluene as the reaction medium proved beneficial, as it stabilized the carbenoid through coordination with the Lewis basic sites of the substrate, such as the lactone oxygen or neighboring oxygenated groups.

Kowalski and co-workers developed an alternative procedure in 1985 for homologating esters **167**, which serves as an alternative to the diazomethane-based Arndt-Eistert reaction.¹⁴²⁻¹⁴³ Unlike the

Barluenga-type ester reductive homologations that furnish α -haloketones, the Kowalski protocol delivers the elongated chain while leaving the ester moiety untouched. This method utilizes dibromomethyl lithium to form lithium ynolates as intermediates. After nucleophilic work-up, such as with R-OH, the homologated ester product (**174-177**) is obtained (Scheme 21).



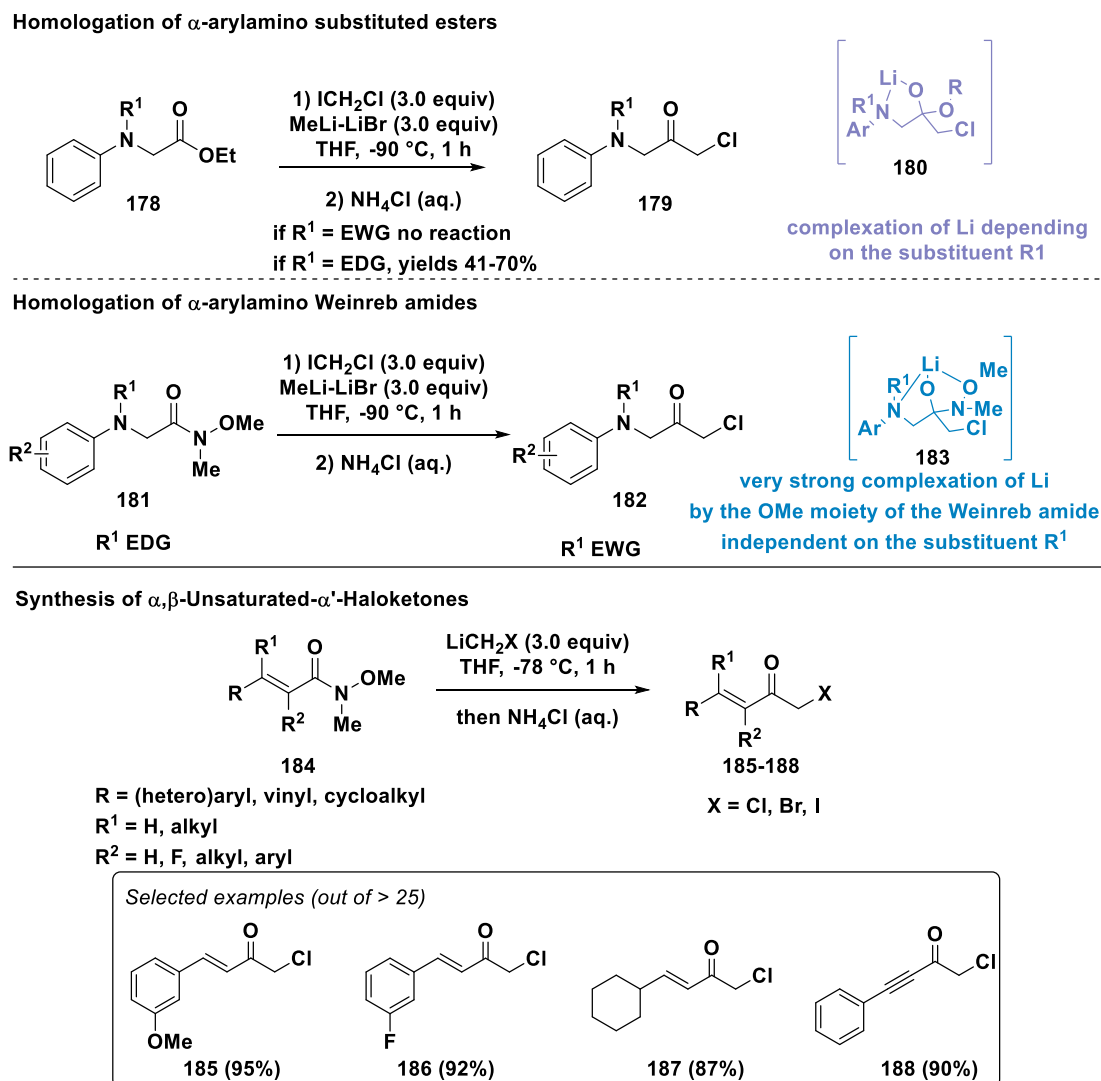
Scheme 21. Kowalski's protocol.

*Readapted from *Homologation Reactions: Reagents, Applications, and Mechanisms*.¹⁵

This reaction has a broad scope and is applicable to various carboxylic residues, including alkyl, alkenyl, alkynyl, and aryl groups. Lactones can also be used as substrates for this transformation. The presence of substitution elements is generally tolerated, and in the case of base-sensitive groups, their protection allows for safe conduct of homologation. This strategy has been extensively applied to access or functionalize complex structures, including natural products, and it is noteworthy that optically pure materials exhibit complete retention of stereochemistry.

The homologation of carboxylic acid derivatives under nucleophilic conditions with lithium carbenoids is influenced by the intrinsic stability of the tetrahedral intermediate formed during the process, as demonstrated by Pace in a comparative study between esters and Weinreb amides.¹⁴⁴ Experiments conducted on *N*-arylamino acetic acid derivatives (**178**) suggest that ester homologation proceeds only when an additional electron-donating group (EDG) is present on the nitrogen, enhancing the capability to coordinate the alkoxide's lithium. However, when the nitrogen's basicity is diminished by the presence of an electron-withdrawing group (EWG), the intermediate lacks sufficient stabilization, preventing homologative transformation (Scheme 22).

In contrast, the presence of a *N*-methoxy-*N*-methyl group in Weinreb amides (**181**) suppresses the substituent-dependent coordination of the tetrahedral intermediate. The inherent stability of the intermediate is provided by the methoxy group's complexation, allowing the reaction to proceed regardless of the substituent on the nitrogen.¹⁴⁵⁻¹⁴⁶ Furthermore, Weinreb amides selectively furnish α -haloketones,¹⁴⁷ in contrast to esters, whose homologation could introduce two C1 units, resulting in carbinols of limited synthetic interest (Scheme 22).

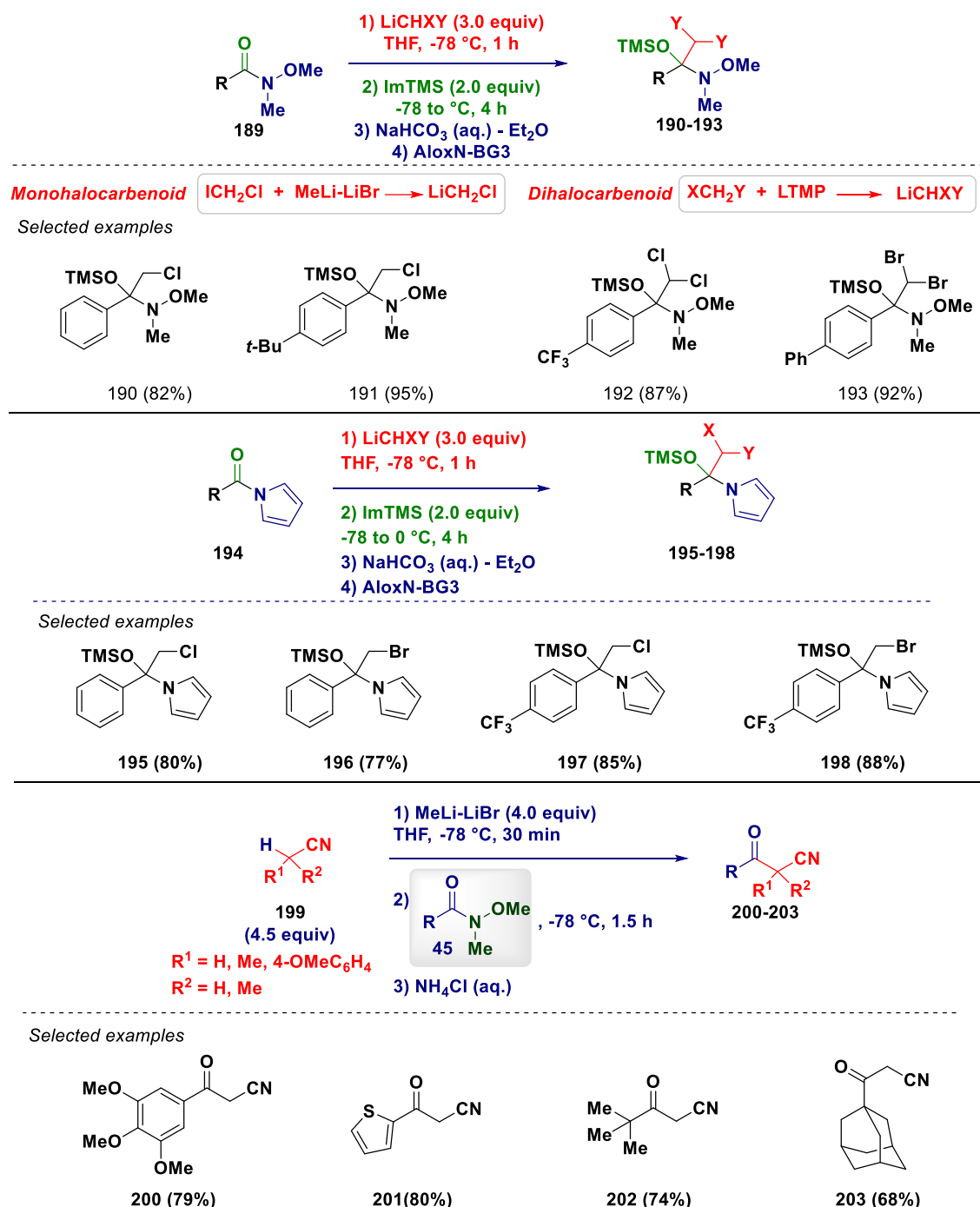


Scheme 22. Homologation of carboxylic acid derivatives under nucleophilic conditions with lithium carbenoids.

*Readapted from *Homologation Reactions: Reagents, Applications, and Mechanisms*.¹⁵

In 2017, Pace successfully isolated and characterized tetrahedral intermediates (**190-193**, **195-198**) formed upon the addition of lithium mono- and di-halocarbenoids to Weinreb amides **189** or *N*-acylpyrroles **194** as *O*-TMS-protected hemiaminals.⁶³ The use of TMS-imidazole (Im-TMS) as the silylating agent and deactivated neutral alumina as the stationary phase for chromatographic

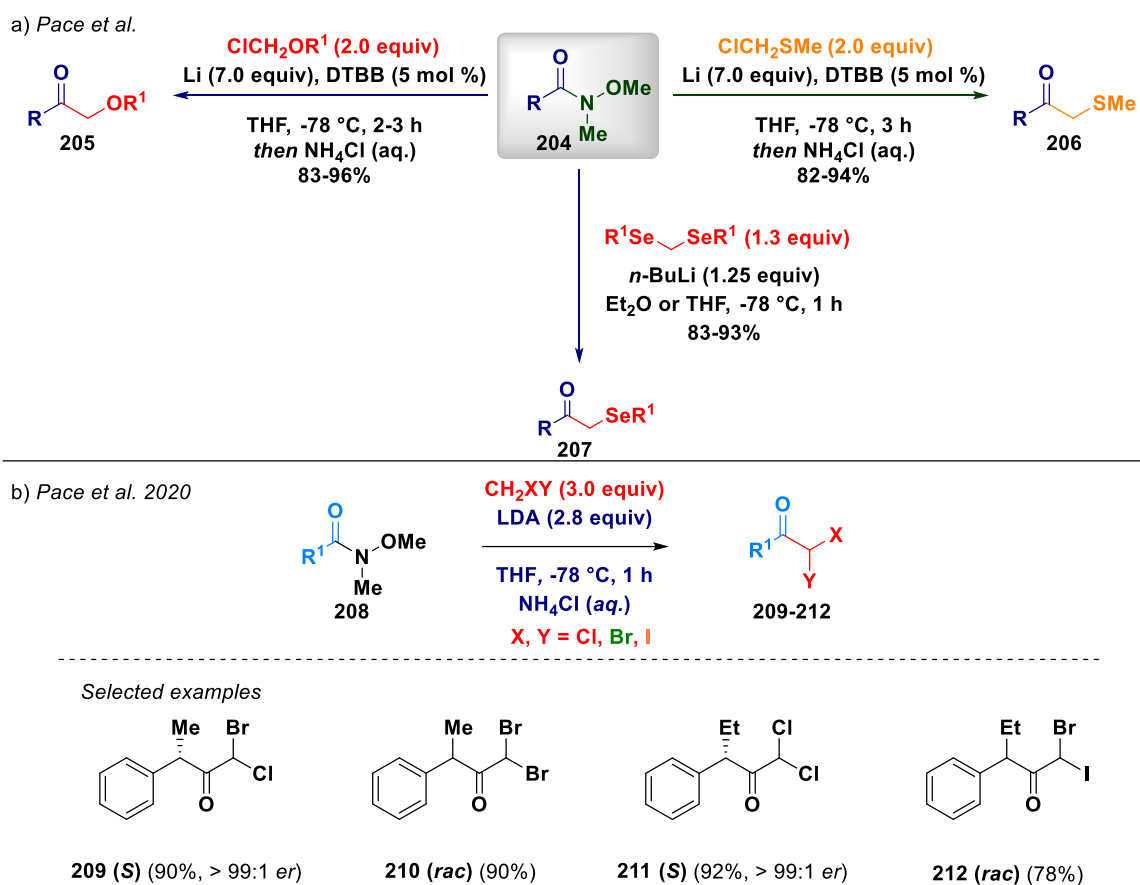
purification played a critical role in isolating these relatively unstable motifs (Scheme 23). The same protocol was also applied to *N*-acylpyrroles, generating tetrahedral intermediates under analogous reaction conditions (Scheme 23). Weinreb amides also react efficiently with nitrile-type carbanions generated *via* the deprotonation of the corresponding acetonitriles with MeLi-LiBr, yielding multi-substituted cyanomethylketones **200-203** with excellent chemoselectivity (Scheme 23).¹⁴⁸ Notably, the generation of these carbanions does not require Barbier-type conditions.



Scheme 23. Pace's homologation of Weinreb amides and *N*-acylpyrroles as *O*-TMS-protected hemiaminals, and of Weinreb amides with nitrile-type carbanions. *Readapted from *Homologation Reactions: Reagents, Applications, and Mechanisms*.¹⁵

Pace described the synthesis of α -oxyketones **205** and β -oxo thioethers **206** through the nucleophilic addition of $\text{LiCH}_2\text{OR}^{149}$ and $\text{LiCH}_2\text{SR}^{150}$ to Weinreb amides, respectively. α -Selenoketones **207** were also obtained *via* selenomethyl lithium reagents (LiCH_2SeR). The latter were prepared by lithium/selenium exchange starting from diselenoacetals (Scheme 24).¹⁵¹ Importantly, enantiopure Weinreb amides exhibited no racemization during these reactions.¹⁵²

In 2020, Pace and co-workers reported the selective transfer of variously functionalized dihalomethyl lithiums (LiCHBrCl , LiCHClI , LiCHBrI , LiCHCl_2 , LiCHBr_2 , LiCHI) to Weinreb amides **208**, allowing the synthesis of gem-dihaloketones **209-212** in a single step (Scheme 24).⁶⁴ The acylating agent properties of these amides, coupled with the availability of dihalomethanes as pronucleophiles, enable a straightforward route to the target compounds with full chemocontrol and no loss of stereochemical information. Additionally, the reaction exhibits tolerance toward sensitive functional groups such as esters, amides, halogens, olefins, etc., making this strategy flexible and tunable by the operator.



Scheme 24. Pace's protocol for synthesising α -oxo, α -thio, α -seleno methylketones and mixed chiral gem-dihaloketones.

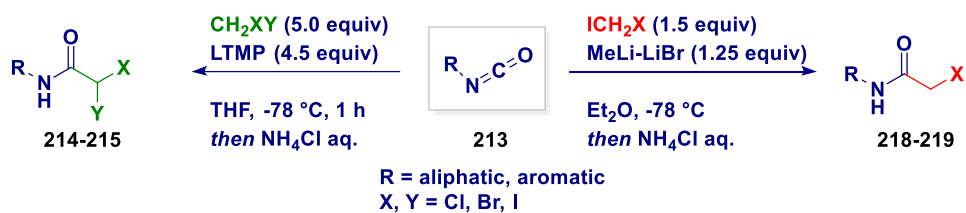
*Readapted from *Homologation Reactions: Reagents, Applications, and Mechanisms*.¹⁵

1.5 Homologation of heterocumulenes

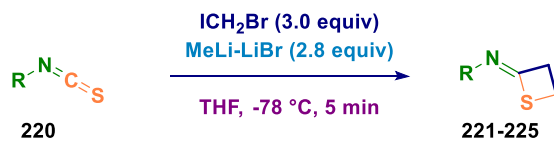
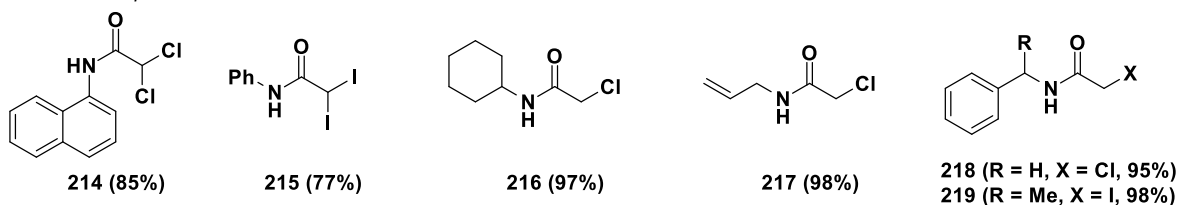
Heterocumulenes, due to the high electrophilicity of the *sp*-hybridized carbon¹⁵³⁻¹⁵⁴ atom, are excellent substrates for nucleophilic additions. This reactivity was first recognized in pioneering works by Gilman¹⁵⁵ and Bode¹⁵⁶. Interestingly, the electronic and steric effects of substituents on the nitrogen atom do not influence the nucleophilic attack of carbanion-like species, making the process efficient and reliable.

The Pace group applied this concept to selectively homologate isocyanates **213** to α -haloacetamides (**218-219**)¹⁵⁷ and α,α -dihaloacetamides (**214-215**)⁶² through the addition of monohalo- and dihalo-carbenoids. These carbenoids are conveniently generated via halogen/lithium exchange or deprotonation with a hindered lithium amide base (LTMP) (Scheme 25). It is worth noting the different behavior exhibited by isocyanates **213** and isothiocyanates **220** with monohalocarbenoids. The intermediate formed during the addition to isocyanates has tamed nucleophilicity, preventing ring-closure and producing α -haloamides upon acidic work-up. On the other hand, the intermediates formed upon the addition to isothiocyanates **220** are nucleophilic enough to trigger a cyclization to imino-thiirane **227**, which is then susceptible to a new homologation with a second equivalent of carbenoid. The resulting thioimide anion **228** undergoes another cyclization, ultimately yielding the thietane scaffold (**221-225**) with an *exo* imine-appendix (Scheme 25).¹⁵⁸ This tactic allows for the installation of an ethylene unit (-CH₂-CH₂-) into isothiocyanates **220** through the consecutive delivery of two methylene fragments furnished by the carbenoid bromomethyl lithium (LiCH₂Br).

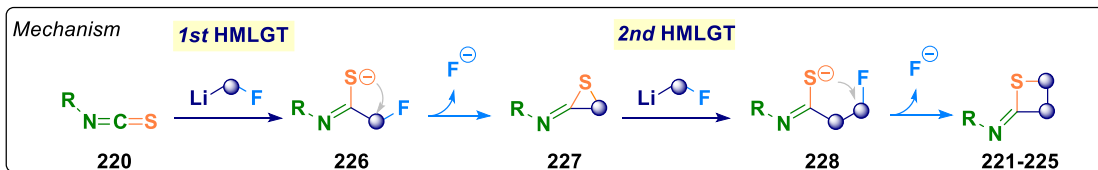
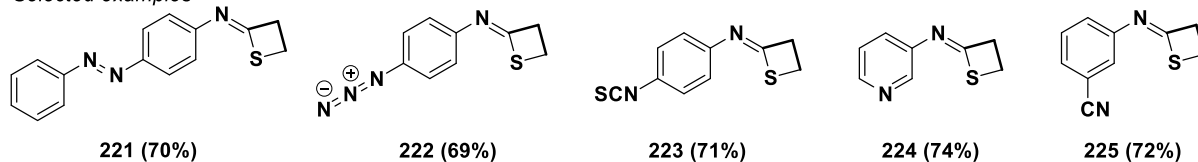
Notably, the entire process is completed within 5 minutes, which is compatible with the short existence of carbenoids. The reaction demonstrates a remarkable degree of chemoselectivity, as it can be successfully conducted even with isothiocyanates featuring additional sensitive functionalities such as halogens, seleno- and thio-ethers, amines, or electrophilic groups that could potentially attack the nucleophilic carbenoid (Scheme 25).



Selected examples



Selected examples



Scheme 25. Synthesis of α -haloamides and imino-thietanes, and general pathway of C2-homologation of isothiocyanates.
 *Readapted from Homologation Reactions: Reagents, Applications, and Mechanisms.¹⁵

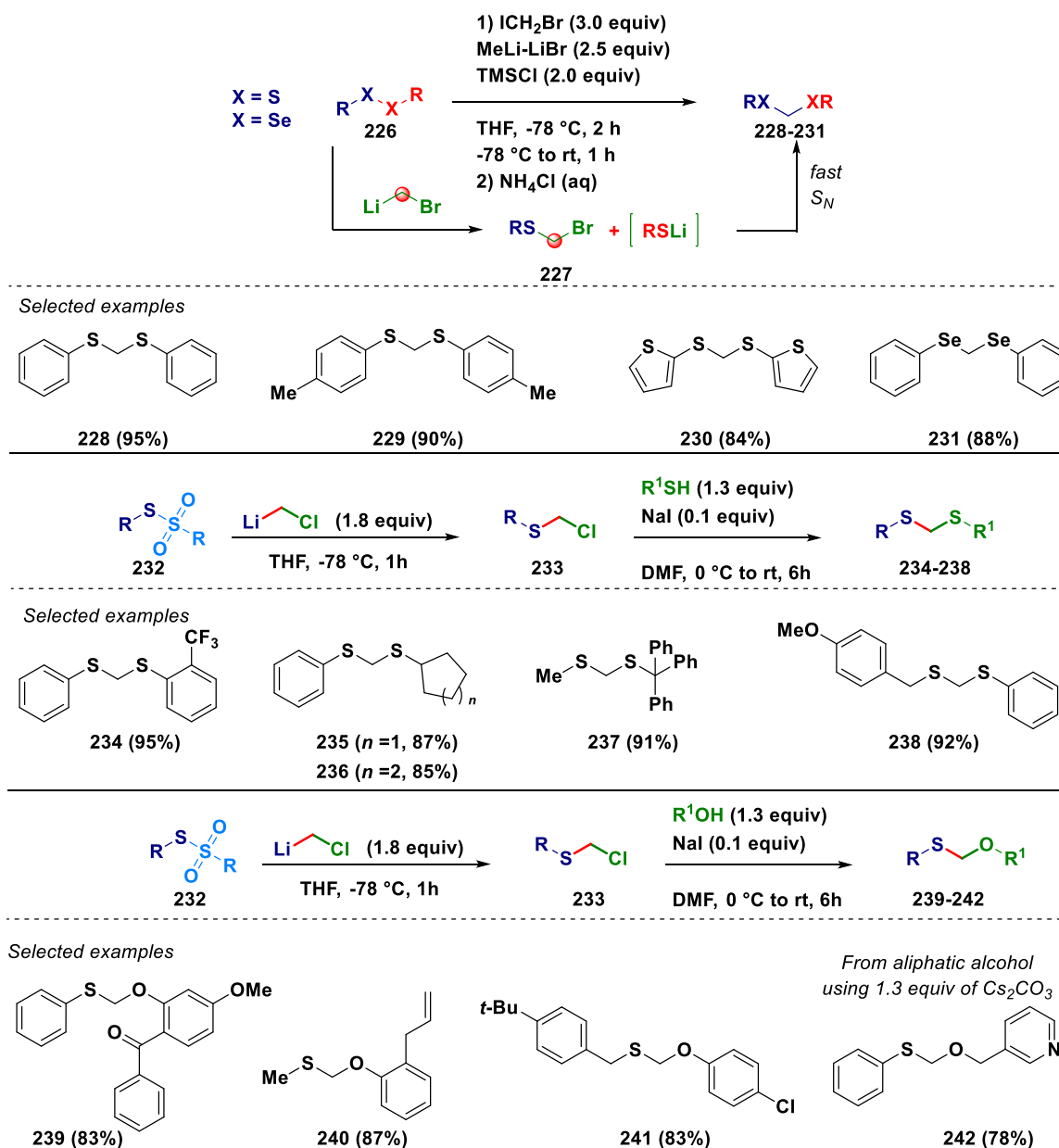
1.6 Homologation of heteroatom electrophiles

The Pace group utilized nucleophilic bromomethyl lithium for the chemoselective homologation of disulfides and diselenides **226** to dithioacetals and diselenoacetals **228-231**, respectively.¹⁵⁹ The addition of the halomethyl unit leads to the formation of a stable α -halomethyl thiosulfide intermediate (**227**), which undergoes a nucleophilic displacement by the mercapto anion (RS-) released during the initial homologation step (Scheme 26). Building upon previous findings that a lithium carbenoid (LiCH_2X) attacks a disulfide to form an α -chlorothioether and a mercapto anion, the Pace group reasoned that controlling the nucleophilicity of the released sulfur nucleophile could strategically prevent its attack to the symmetrical dithioacetal.

By carrying out the initial C1-homologation on an electrophilic sulfur platform, releasing a non-nucleophilic leaving group, the subsequent substitution with an externally added thiol allows for modular access to unsymmetrical dithioacetals.¹⁶⁰ Thiosulfonates **232** were judiciously selected as convenient sulfur electrophilic intermediates, ensuring the release of the non-reactive sulfonate group during the homologation event leading to the intermediate α -halothioether **233**. This enables the subsequent nucleophilic displacement with an externally added thiol, resulting in high yields and chemocontrol (Scheme 26).

Expanding the potential of the protocol, the Pace group further applied the consecutive C1-homologation/displacement for converting thiosulfonates **232** into *O,S*-oxothioacetals **239-242** upon treatment with alcohols.¹⁶¹ By installing the reactive CH_2Cl motif with the carbenoid, followed by nucleophilic displacement with ROH (aromatic or aliphatic), convenient access to the desired compounds was achieved. The methodology displayed genuine chemoselectivity even in the case of multi-functionalized systems (Scheme 26).

Regarding the last two cited Pace's publications, a more extensive discussion takes place in [Chapter 3](#) of this thesis.

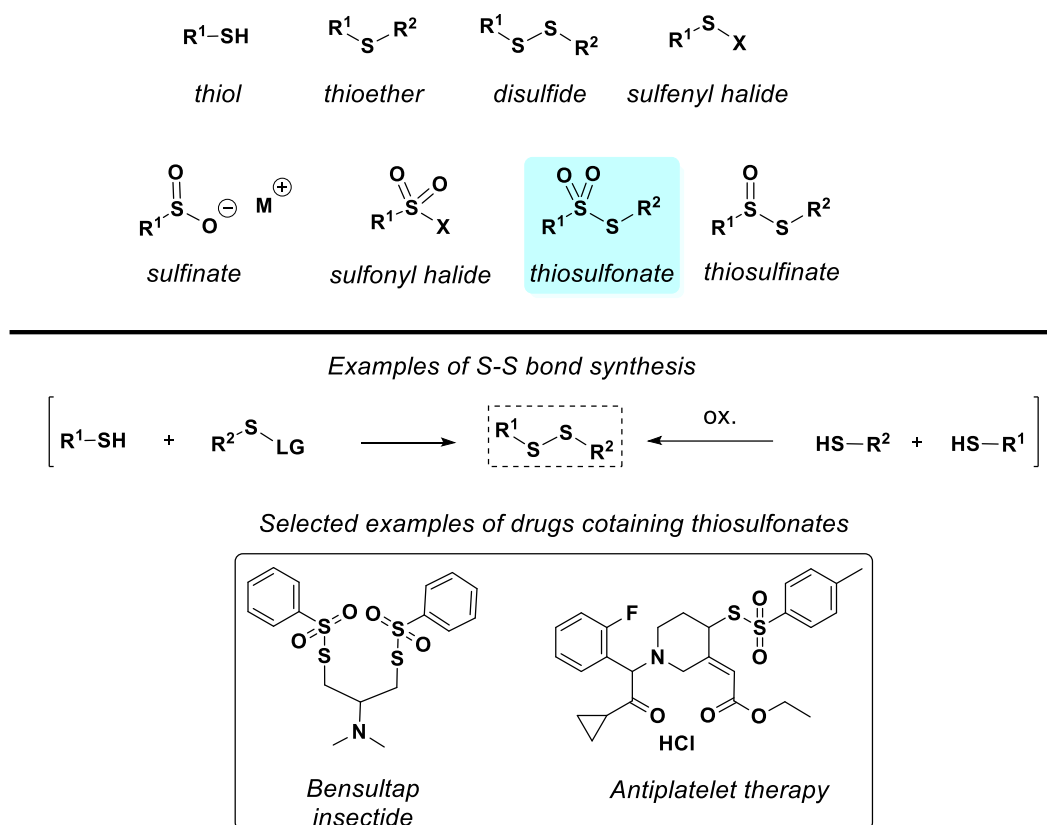


Scheme 26. Pace's protocol to synthesize disulfides, diselenides, unsymmetrical dithioacetals and oxothioacetals.

*Readapted from *Homologation Reactions: Reagents, Applications, and Mechanisms*.¹⁵

1.7 Organosulfur compounds: synthesis and application, an oversight

Organosulfur compounds have attracted significant attention in recent decades due to their wide-ranging applications in pharmaceuticals, agrochemicals, and other industries.¹⁶²⁻¹⁶⁸ The thioether functional group (and its oxidized forms) is frequently found in bioactive molecules, and disulfides, characterized by sulfur-sulfur (S-S) bonds, are particularly valuable (Scheme 27). Disulfides are critical in various fields: they stabilize protein structures through S-S bonds between cysteine residues, appear in multiple natural products,¹⁶⁹⁻¹⁷⁰ and serve as essential vulcanizing agents in industrial processes. Given their versatility, sulfur-sulfur bond-forming reactions are increasingly central to modern synthetic organic chemistry.^{164, 171-172}



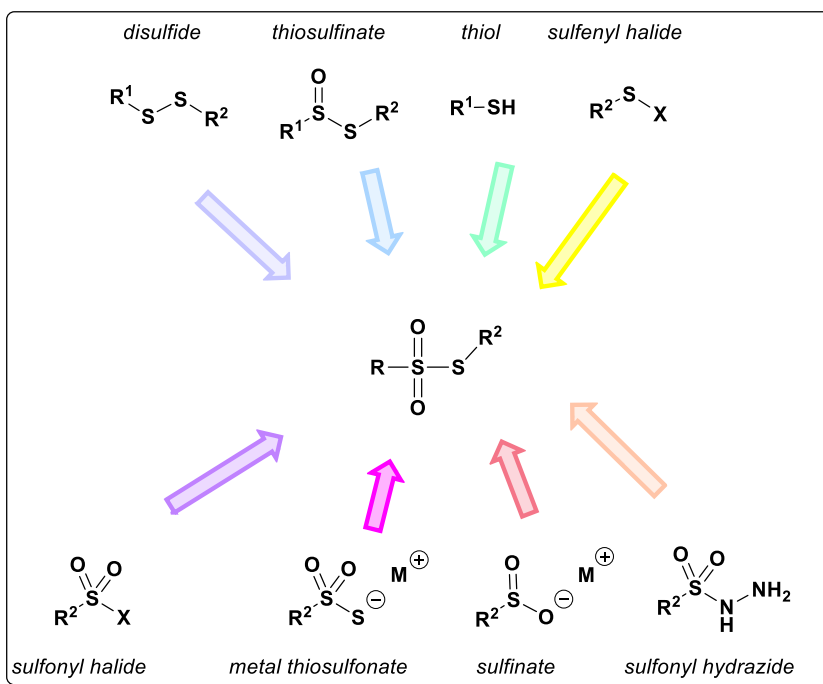
Scheme 27. Examples of organosulfur compounds and common protocols to synthesize S-S bonds. ¹⁷³⁻¹⁷⁶. *Readapted from *Thiosulfonates as emerging reactants: synthesis and applications*.¹⁷⁷

Historically, S-S bonds were synthesized through nucleophilic substitution reactions involving sulfenyl halides and thiols. However, oxidative coupling of thiols has become more common, although selectivity remains challenging. Among disulfide derivatives, thiosulfonates ($R_1SO_2SR_2$) are a unique class where one sulfur atom is linked to two oxygen atoms, distinguishing them as versatile compounds in synthesis. Thiosulfonates are stable yet highly reactive intermediates, participating as

both sulfenylating and sulfonylating agents based on reaction conditions. Additionally, they can generate sulfonyl and sulfenyl radicals through homolytic S-S bond cleavage, allowing them to participate in a range of radical-mediated and ionic reactions.

Despite their initial discovery in the 19th century by Weidmann and Lowig, thiosulfonates only garnered widespread interest in the mid-20th century when Small demonstrated their antimicrobial properties.¹⁷⁸ Today, only basic, unfunctionalized thiosulfonates, such as S-methyl methanethiosulfonate and S-phenyl benzenethiosulfonate, are commercially available, with more complex derivatives often requiring laboratory synthesis.

Thiosulfonate synthesis encompasses various methods, classified here based on the sulfur precursor used (Scheme 28).¹⁷⁷

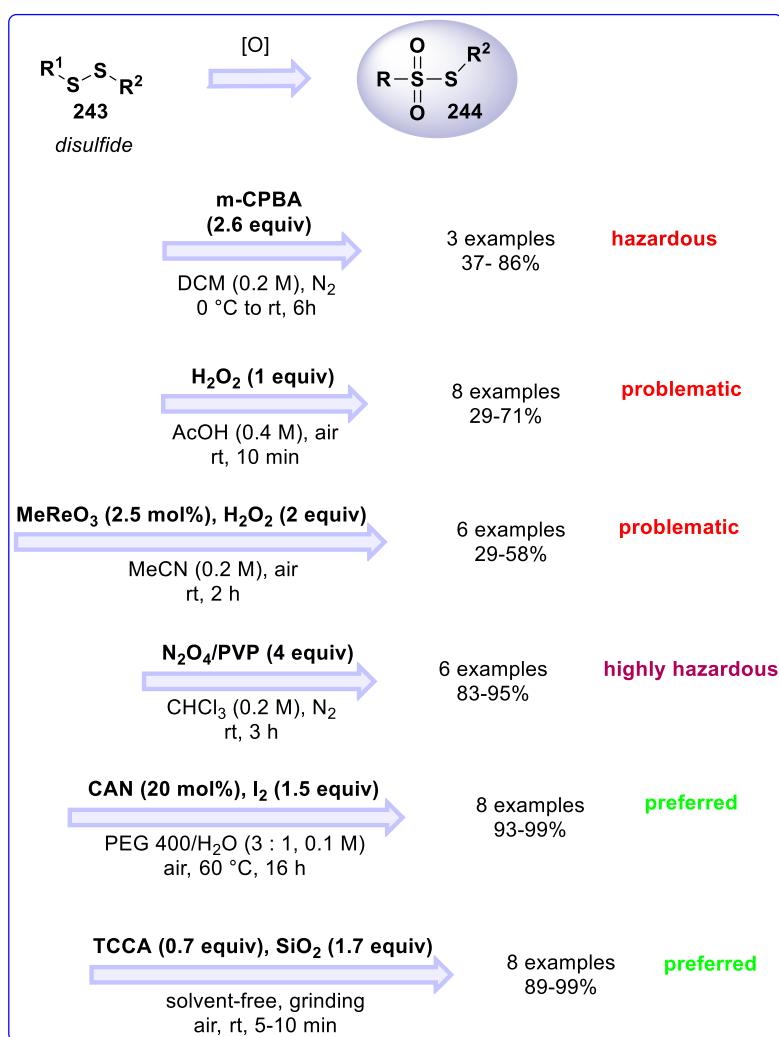


*Scheme 28. Classification of the synthetical pathways of thiosulfonates based on different sulfur precursors. *Readapted from Thiosulfonates as emerging reactants: synthesis and applications.¹⁷⁷*

1.7.1 Thiosulphonates synthetic methodologies

1.7.1.1 Using Disulfides

The direct oxidation of disulfides **243** remains a common route,¹⁷⁹⁻¹⁸⁴ yielding thiosulfonates **244** or other oxidation products, depending on the oxidant used. While some oxidants (e.g., *m*-CPBA, H₂O₂)^{182, 185-190} are widely used, others (e.g., N₂O₄ on polyvinylpyrrolidone)¹⁹¹ offer selective reactions but can be toxic or require high PMI due to solvent use. Catalysts like MTO¹⁹² and cyclic selenates¹⁹³ can improve selectivity but often increase PMI or toxicity (Scheme 29).¹⁹⁴⁻¹⁹⁵

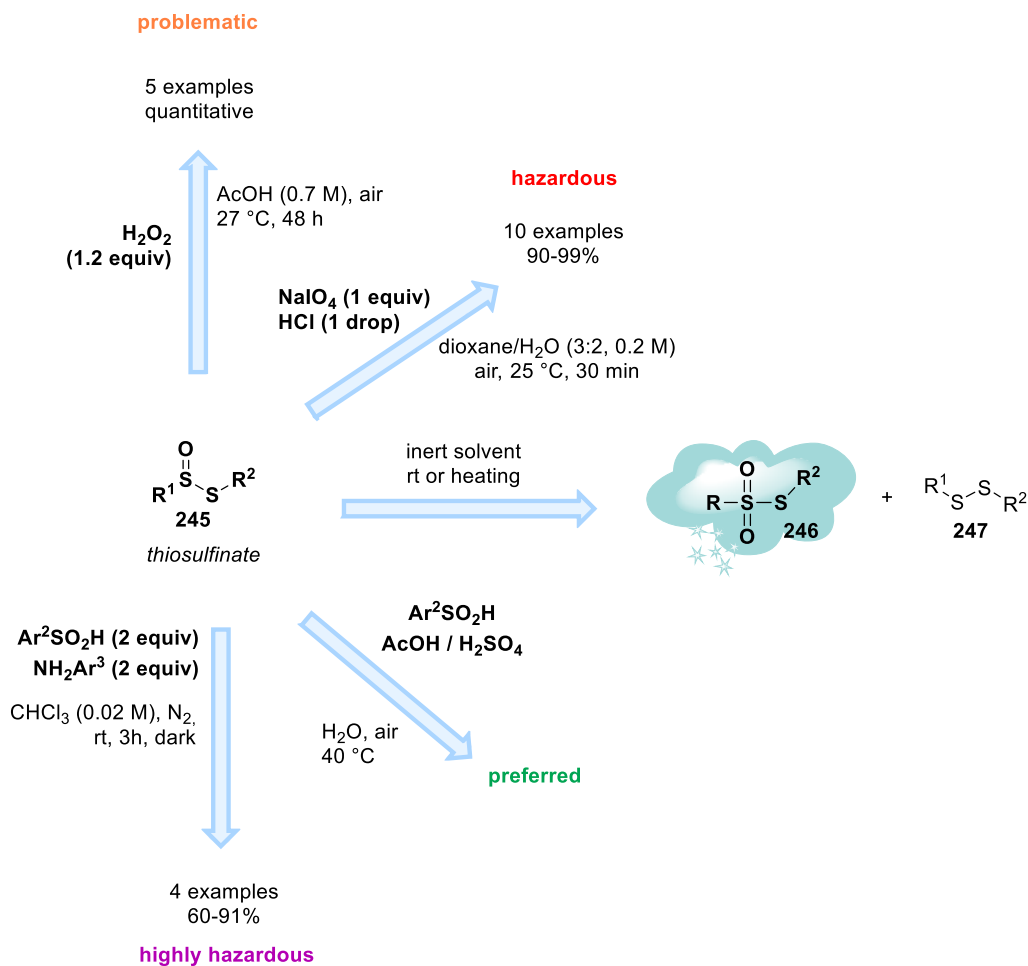


Scheme 29. Synthesis of thiosulfonates with disulfides.

*Readapted from Thiosulfonates as emerging reactants: synthesis and applications.¹⁷⁷

1.7.1.2 Using Thiosulfates

Oxidizing thiosulfates **245** provides a direct path to thiosulfonates **246**. Hydrogen peroxide in acetic acid yields high efficiency,¹⁹⁶⁻¹⁹⁷ whereas other oxidants like NaIO₄¹⁹⁸ offer selectivity with additional catalysts but may have environmental drawbacks due to solvent toxicity (Scheme 30).¹⁹⁹⁻²⁰²



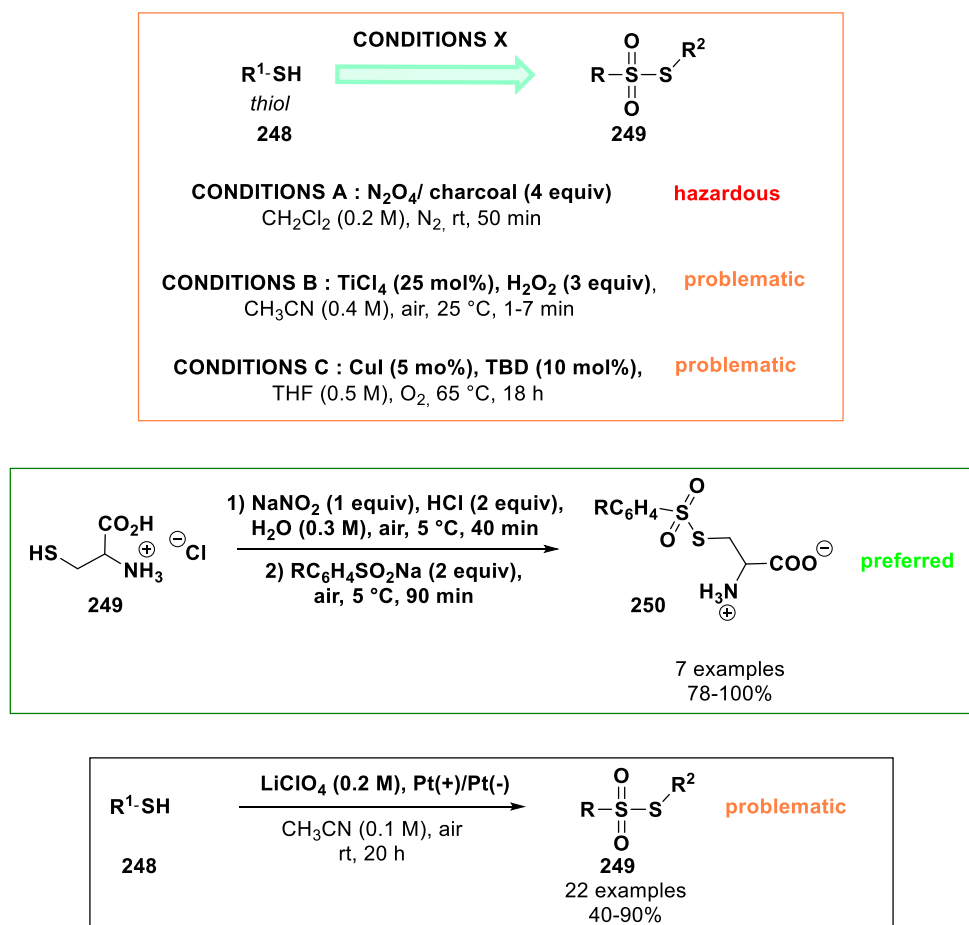
Scheme 30. Synthesis of thiosulfonates from thiosulfates.

*Readapted from Thiosulfonates as emerging reactants: synthesis and applications.¹⁷⁷

1.7.1.3 Using Thiols

Direct oxidative coupling of thiols **248** enables symmetrical thiosulfonate **249** formation, with methods involving oxidants like H₂O₂/TiCl₄²⁰³ and N₂O₄²⁰⁴ supported on charcoal.²⁰⁵ Despite high efficiency, some methods have high PMI due to excess oxidants or solvents.²⁰⁶ Recent work with

CuI/TBD²⁰⁷ and O₂ presents a more favourable PMI,²⁰⁸ offering lower toxicity. Alternative Reactions: Cross-dehydrogenative coupling using electrosynthesis demonstrates promise for green thiosulfonate synthesis but requires dilute conditions and thus a higher PMI than conventional methods (Scheme 31).²⁰⁹



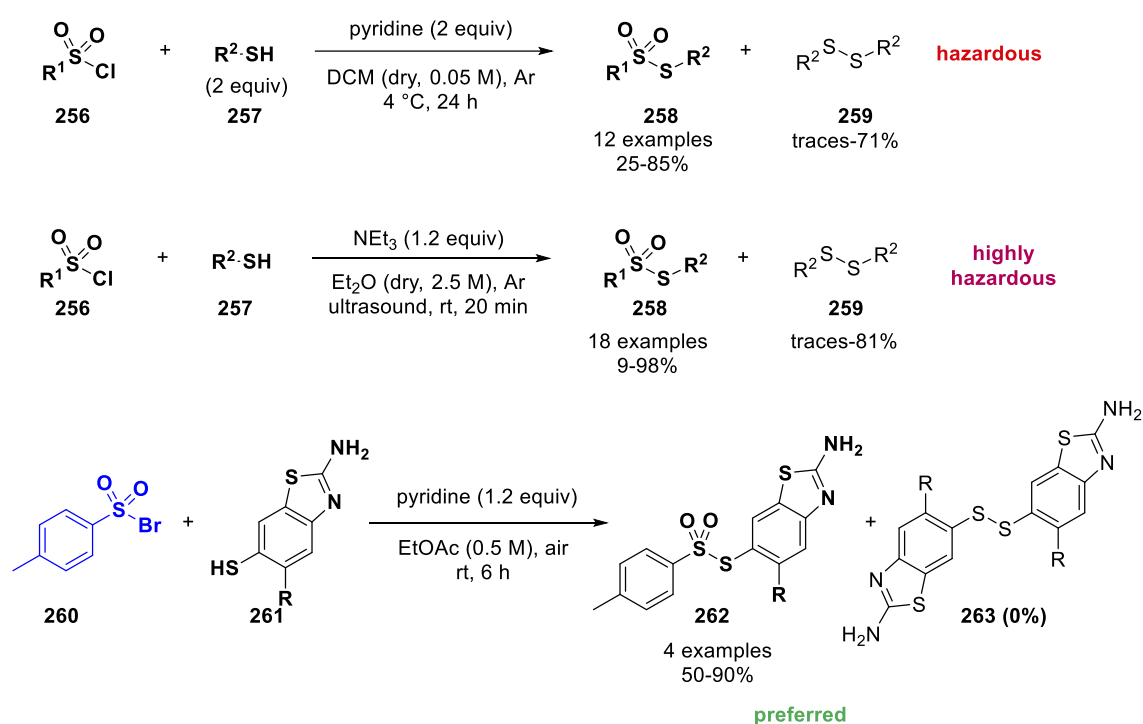
Scheme 31. Synthesis of thiosulfonates from thiols.
*Readapted from *Thiosulfonates as emerging reactants: synthesis and applications*.¹⁷⁷

1.7.1.4 Using Sulfenyl Halides

Sulfenyl chlorides (RSCI) serve as powerful sulfenylating agents for thiosulfonate synthesis. Prepared from disulfides **251** with chlorine or sulfonyl chloride,²¹⁰⁻²¹¹ or from thiols **252** with *N*-chlorosuccinimide **253**, sulfenyl chlorides are reactive and unstable, often necessitating *in situ* preparation. Various routes yield thiosulfonates **255** from sulfenyl chlorides and sulfinic acids/salts,²¹² with pyridine enhancing yields to over 80%.²¹³⁻²¹⁴ However, most methods require hazardous solvents like carbon tetrachloride, which inflates PMI and limits green potential (Scheme 32).²¹⁵⁻²¹⁶

1.7.1.5 Using Sulfonyl Halides

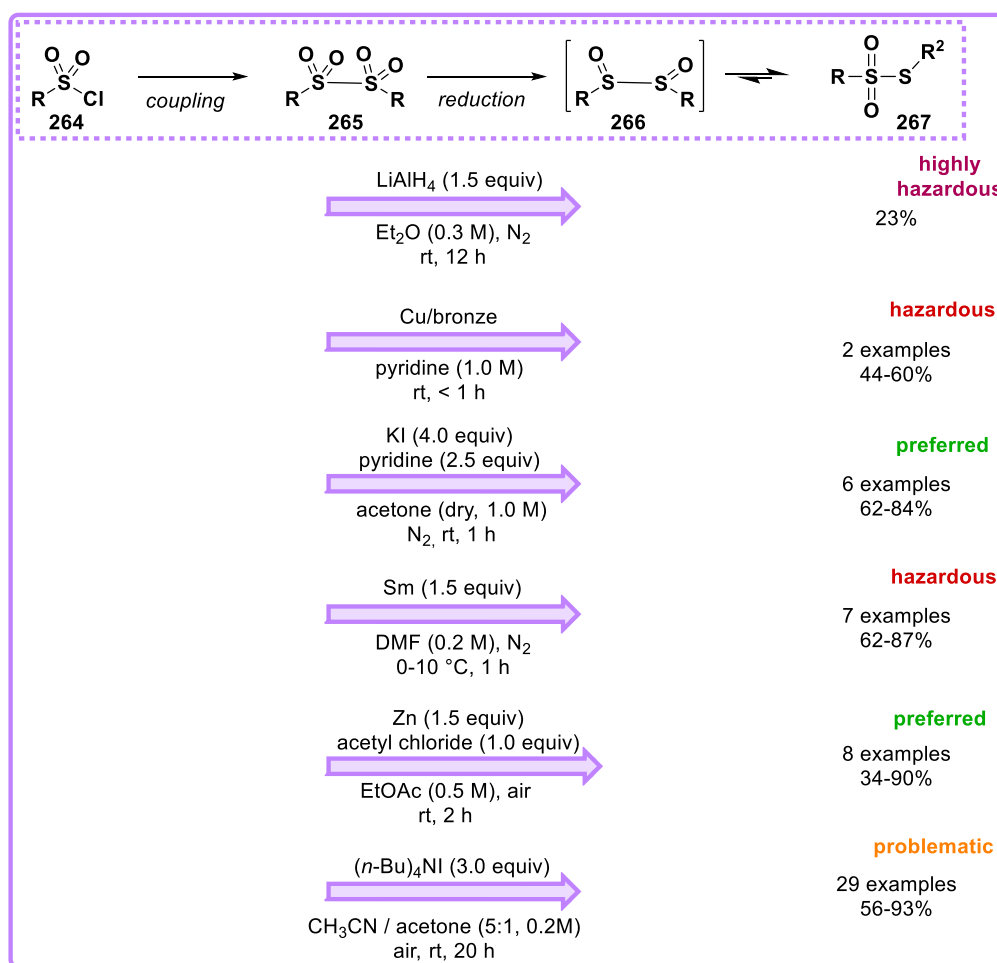
Sulfonyl chlorides **256** are cost-effective reagents for thiosulfonate **258** synthesis, but their reaction with thiols **257** often leads to disulfide byproducts **259**.²²¹⁻²²² Adjustments, like using excess thiol²²³ or alternative bases (e.g., triethylamine),²²⁴ can moderate yields and reduce toxicity, though hazardous solvents such as dichloromethane persist in use. Newer strategies employ tosyl bromide **260** with heteroaromatic thiols **261** to achieve thiosulfonates without protecting groups,²²⁵ and in situ reduction/coupling of sulfonyl chlorides with sulfonates avoids disulfide formation but involves chlorinated solvents, increasing PMI (Scheme 33).²²⁶



Scheme 33. Synthesis of thiosulfonates from sulfonyl halides 1.

*Readapted from *Thiosulfonates as emerging reactants: synthesis and applications*.¹⁷⁷

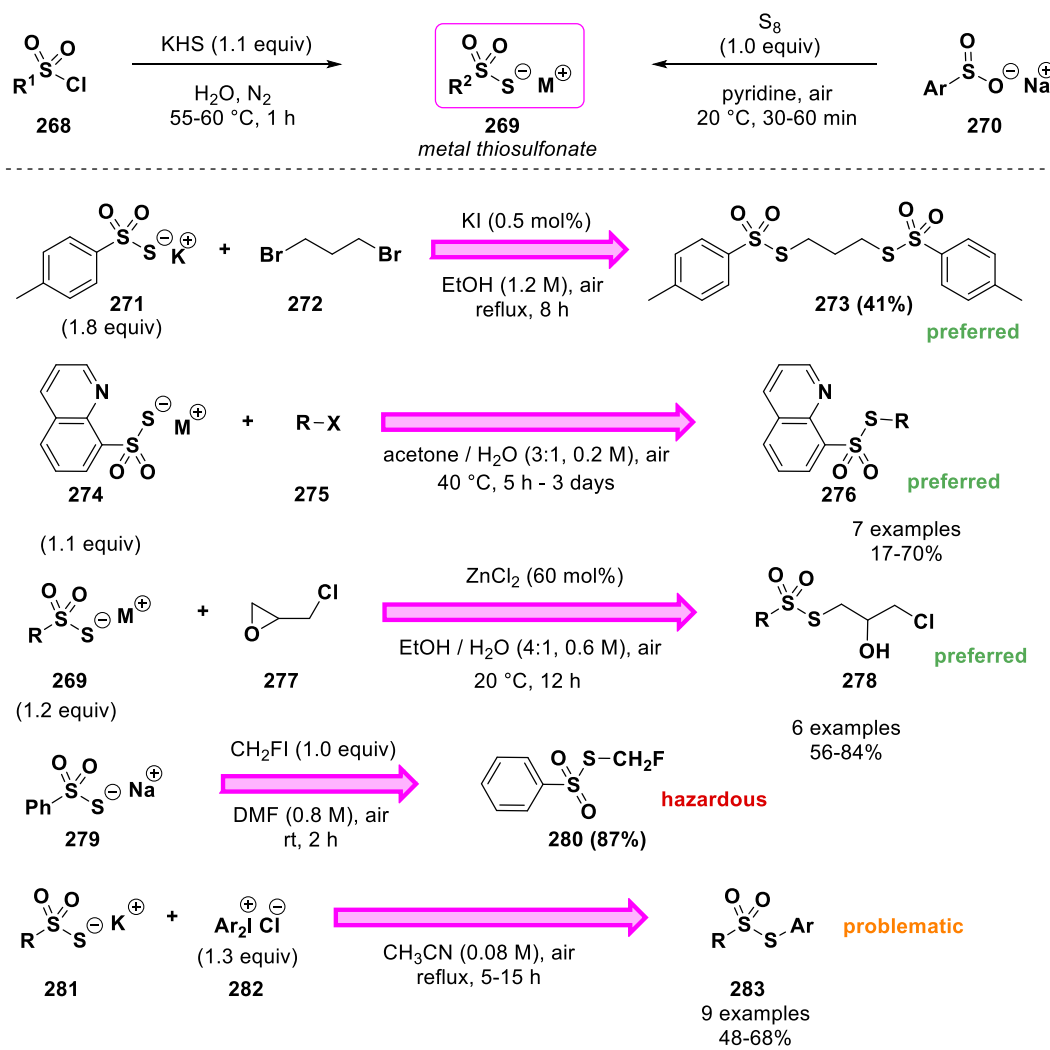
Reductive dimerization of sulfonyl chlorides **264** using agents like lithium aluminum hydride,²²⁷ copper,²²⁸ or samarium²²⁹ achieves symmetrical thiosulfonates **267** with varying green credentials depending on the solvents and reductants used.²³⁰⁻²³² Notable recent approaches (e.g., tetrabutylammonium iodide)²³³ provide high yields and lower PMI, making them attractive options, especially for heteroarenes (Scheme 34).



Scheme 34. Synthesis of thiosulfonates from sulfonyl halides 2.
 *Readapted from *Thiosulfonates as emerging reactants: synthesis and applications*.¹⁷⁷

1.7.1.6 Using Alkali Metal Thiosulfonates

Synthesis of unsymmetrical thiosulfonates can be achieved via nucleophilic substitution with alkali metal thiosulfonates **269** and alkyl halides.²³⁴⁻²⁴⁰ This substrate-specific method has been generalized with recent allylation approaches.²⁴¹ Preferred solvents (e.g., esters or alcohols)²⁴² improve green credentials, though the required alkali thiosulfonates must often be synthesized, commonly via reaction with sulfonyl chlorides²⁴³ or sodium sulfinates.²⁴⁴ Sulfonyl chloride routes are effective but increase PMI and toxicity due to corrosive reactants, whereas sulfinate routes are favoured when less toxic solvents are used (Scheme 35).



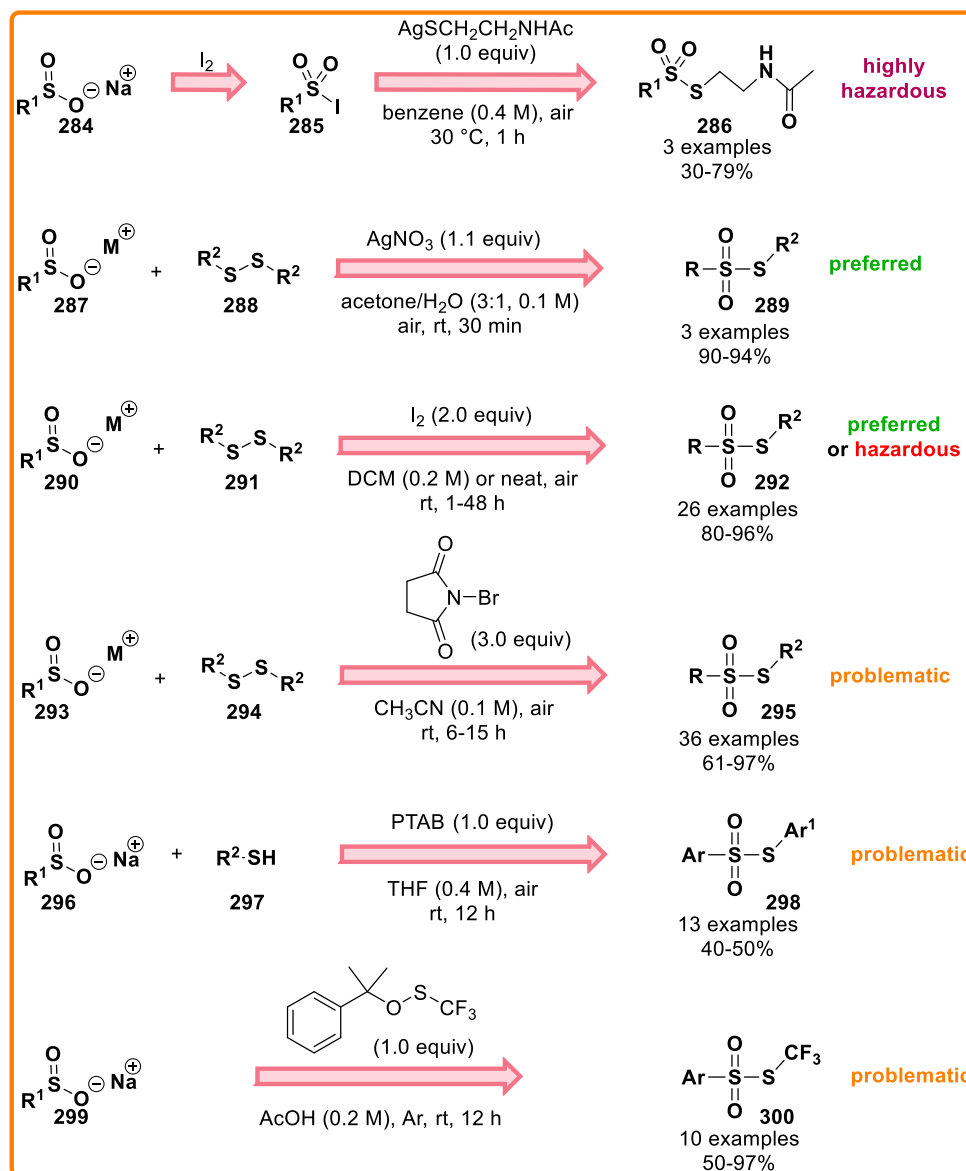
Scheme 35. Synthesis of thiosulfonates using alkali metal thiosulfonates.
 *Readapted from *Thiosulfonates as emerging reactants: synthesis and applications*.¹⁷⁷

Further advancements include reactions with oxiranes²⁴⁵ or arylation with iodonium salts,²⁴⁶ yielding functionalized thiosulfonates with applications in organic synthesis. The direct fluoromethylation of benzenethiosulfonates provides stable products,²⁴⁷ though the method's reliance on DMF impacts PMI. An alternative arylation approach employs diaryliodonium salts,²⁴⁸ though waste generation remains a consideration.

1.7.1.7 Using Alkali Metal Sulfonates

To avoid disulfide byproduct formation, alkali metal sulfonates (RSO_2M) are used for unsymmetrical thiosulfonate synthesis. The Field method involves transforming sulfonates into sulfonyl iodides (RSO_2I , **285**) with iodine,²⁴⁹ followed by nucleophilic substitution with silver thiolate, providing moderate

yields but using hazardous solvents. An alternative method activates disulfides with Lewis²⁵⁰ acids or oxidants like bromine or iodine for coupling with sulfonates,²⁵¹ significantly reducing PMI when performed solvent-free (Scheme 36).



Scheme 36. Synthesis of thiosulfonates with alkali metal sulfonates.

*Readapted from *Thiosulfonates as emerging reactants: synthesis and applications*.¹⁷⁷

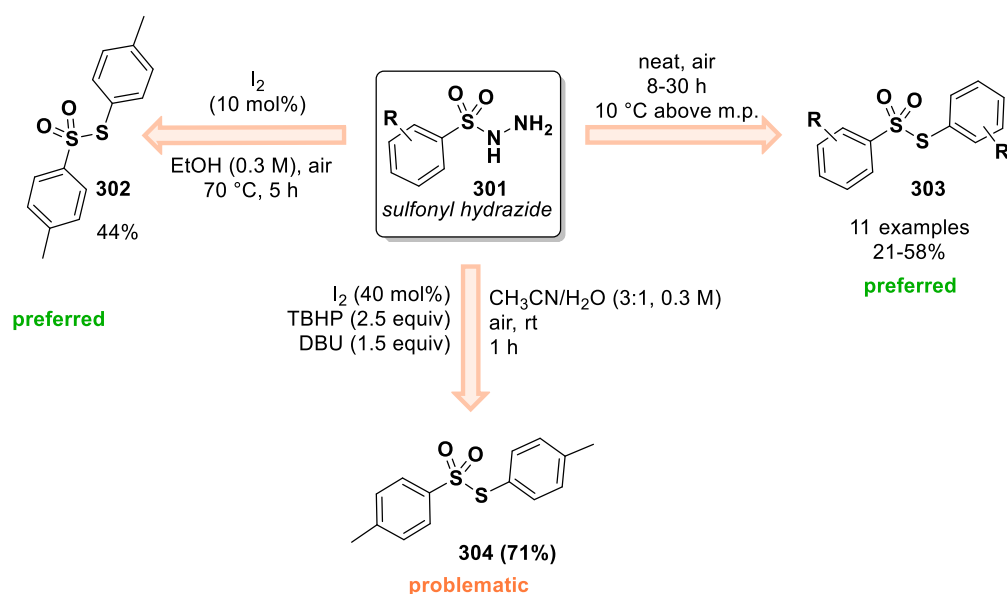
Additional strategies include using *N*-bromosuccinimide (NBS) to activate disulfides, yielding *N*-(organothio)succinimides that react with sulfonates.²⁵² The Abe²⁵³ group later adapted this to ionic liquids, which can be reused to improve green credentials. Transition metals (e.g., Cu, Fe)²⁵⁴⁻²⁵⁶

facilitate thiosulfonate formation from sulfinates and thiols, while the use of trimethyl phenylammonium tribromide (PTAB)²⁵⁷ offers a disulfide-free alternative.

Recent research on fluorinated thiosulfonates, such as SCF₃, has employed alkali metal sulfinates coupled with specialized fluorinated sulfonylating agents.²⁵⁸⁻²⁵⁹ Other advanced routes include glycosyl thiosulfonates²⁶⁰ and copper-catalyzed sulfonyl hydrazide cross-coupling,²⁶¹ though these approaches often generate halogenated waste or require toxic solvents, affecting overall sustainability.

1.7.1.8 Using Sulfonyl Hydrazides

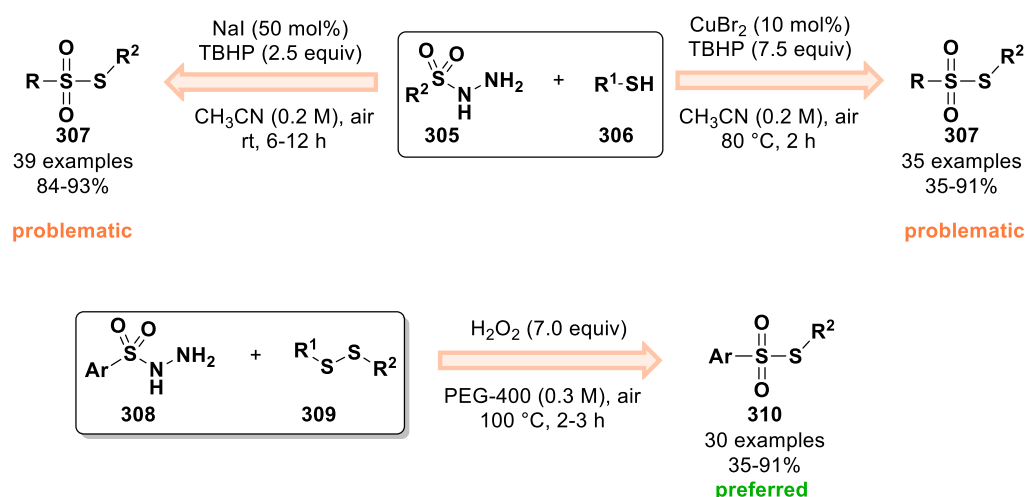
Sulfonyl hydrazides **301** provide a stable alternative for symmetrical thiosulfonate synthesis. Decomposition of sulfonyl hydrazides generates thiosulfonates in the absence of solvents,²⁶² but iodine²⁶³ or *tert*-butyl hydroperoxide can accelerate the reaction, increasing yield but introducing toxicity concerns.²⁶⁴ Radical mechanisms involving iodine or *N*-iodosuccinimide (NIS) offer more controlled pathways (Scheme 37).²⁶⁵



Scheme 37. Synthesis of thiosulfonates with sulfonyl hydrazide 1.

*Readapted from *Thiosulfonates as emerging reactants: synthesis and applications*.¹⁷⁷

Unsymmetrical thiosulfonates can be synthesized through cross-coupling of sulfonyl hydrazides with thiols or disulfides, catalyzed by copper²⁶⁶ or in transition-metal-free systems using *tert*-butyl hydroperoxide.²⁶⁷ Additionally, electrochemical methods using sulfonyl hydrazides minimize chemical oxidants, reducing PMIRRC.²⁶⁸ However, these require careful control over reaction conditions and solvents, impacting PMI (Scheme 38).²⁶⁹

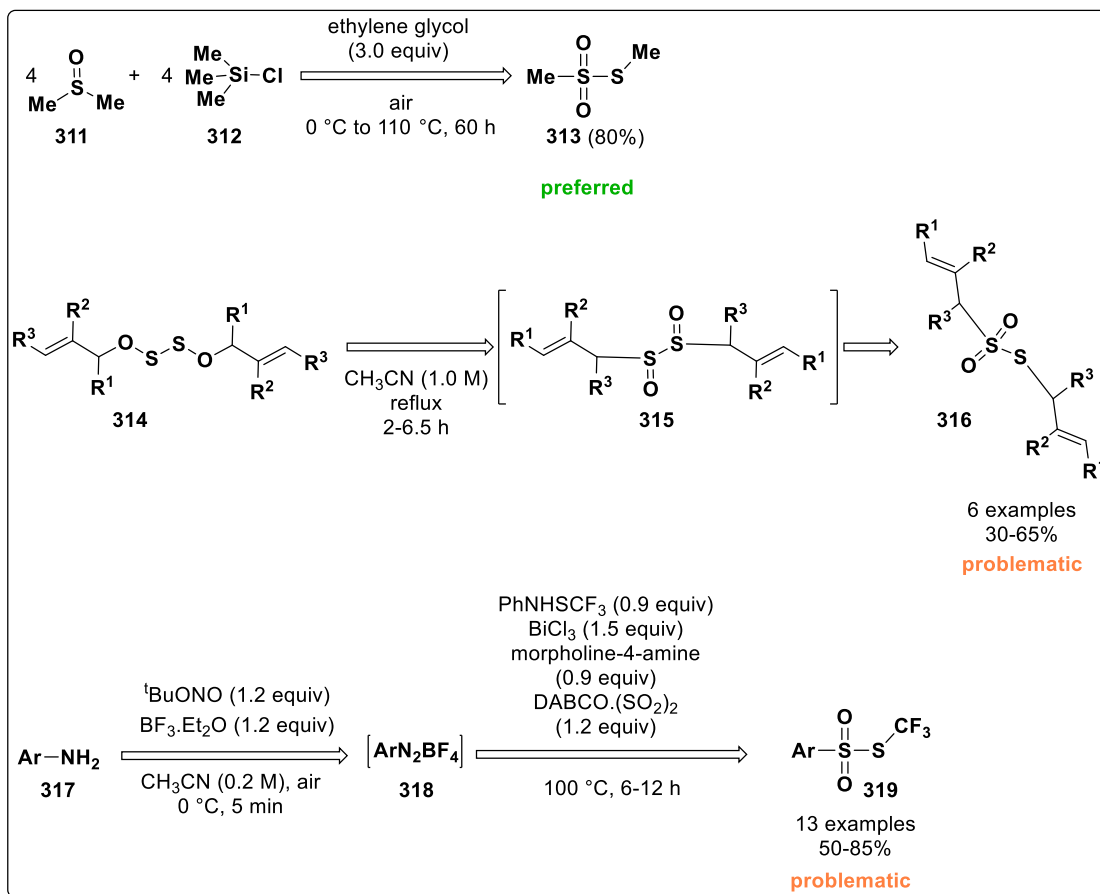


Scheme 38. Synthesis of thiosulfonates with sulfonyl hydrazide 2.

*Readapted from *Thiosulfonates as emerging reactants: synthesis and applications*.¹⁷⁷

1.7.1.9 Miscellaneous Strategies for Thiosulfonate Synthesis

Additional methods for thiosulfonate synthesis include using dimethylsulfoxide (DMSO, **311**) with chlorotrimethylsilane (**312**) and ethylene glycol, yielding *S*-methyl methanethiosulfonate (**313**) (the simplest thiosulfonate).²⁷⁰ Though efficient, this method's low atom economy and use of toxic reagents present limitations. Other pathways, like diallyloxydisulfides **314** refluxed in acetonitrile, offer low PMI but rely on toxic intermediates like disulfur dichloride (Scheme 39).²⁷¹⁻²⁷²



Scheme 39. Miscellaneous strategies for thiosulfonate synthesis.

*Readapted from *Thiosulfonates as emerging reactants: synthesis and applications*.¹⁷⁷

Recent one-pot approaches for fluorinated thiosulfonates **319** utilize reagents like DABSO as sulfonyl sources, allowing reaction with trifluoromethyl sulfenylating agents under mild conditions.²⁷³ However, the method's limited applicability to aromatic amines restricts its broader utility. For more comprehensive synthesis, alternate routes involving sulfonyl chlorides are recommended for applications requiring high sustainability.

1.7.2 Applicability of Thiosulphonates

Thiosulfonates are versatile in organic synthesis due to their reactivity with nucleophiles, electrophiles, and radicals. Key applications include:

Biological Activity: Thiosulfonates exhibit antimicrobial effects, functioning by blocking microbial enzymes through sulfenylation, and are useful in thiol protection, particularly for cysteine in peptides due to mild and selective conditions.²⁷⁴⁻²⁷⁵

Sulfenylation/Sulfonylation Reactions:

Sulfur Nucleophiles: Thiosulfonates facilitate unsymmetrical disulfide formation,²⁷⁶⁻²⁷⁷ and recent solvent-free methods using thiobenzoic acids enhance yields for various disulfides.²⁷⁸

Amine/Oxygen/Phosphor Nucleophiles:

Thiosulfonates yield sulfonamides and sulfenamides with amines, facilitated by NBS or copper catalysts, enabling applications in chiral catalyst synthesis.²⁷⁹⁻²⁸⁰

Carbon Nucleophiles:

Active methylene compounds and enolates undergo sulfenylation, producing key thioethers.²⁸¹⁻²⁸² Organometallic reagents,²⁸³ like lithium or Grignard reagents,²⁸⁴ further expand sulfur-carbon bond formation with high stereoselectivity in pharmaceutical synthesis (e.g., AZD4407).²⁸⁵

Cyanide and Aromatic Substitutions:

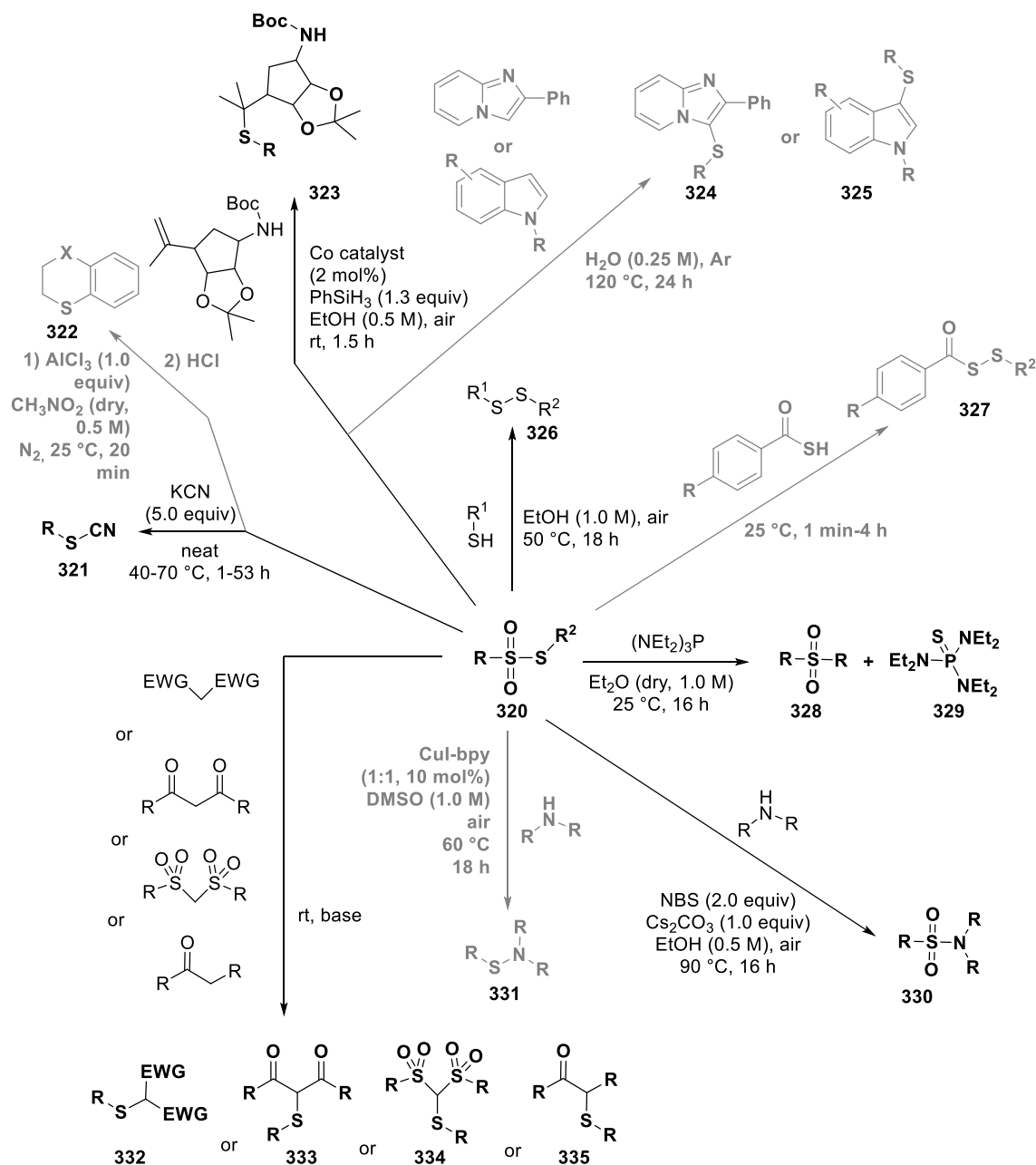
Cyanide reactions yield thiocyanates,²⁸⁶ while electrophilic aromatic substitution with aluminium trichloride forms benzo-1,4-dithiin derivatives.²⁸⁷

Alkene and Arene Sulfenylation:

Alkene Sulfenylation: Catalyzed by cobalt, thiosulfonates hydrosulfenylate alkenes.²⁸⁸

N-Heteroarene Sulfenylation: Thiosulfonates enable C3 sulfenylation of heteroarenes without a catalyst, relying on water for the dissociation into sulfinic and sulfonyl ions.²⁸⁹

These applications highlight thiosulfonates' broad utility in synthesis, from biochemically relevant transformations to complex organic molecules. Their multifunctional role supports diverse fields, including drug synthesis, catalyst preparation, and polymer chemistry, making them a valuable synthetic tool (Scheme 40).



Scheme 40. Examples of thiosulfonates applications 1.

*Readapted from *Thiosulfonates as emerging reactants: synthesis and applications*.¹⁷⁷

Thiosulfonates are highly versatile electrophiles, valuable for their ability to undergo diverse transformations with electrophiles, radicals, and nucleophiles. Here are the core applications (Scheme 41):

1.7.2.1 Reaction with Electrophiles

Thiosulfonates can act as electrophiles in reactions with alkyl bromides or epoxides, though their reaction typically involves an *in situ* transformation to nucleophilic sulfinates, which then react with electrophiles. For example, regioselective β -hydroxysulfones form *via* the ring-opening of epoxides by sulfinate anions, generated in situ from thiosulfonates.²⁹⁰

1.7.2.2 Radical Sulfenylation and Sulfonylation

Thiosulfonates decompose thermally or photochemically to produce sulfonyl and sulfenyl radicals, useful for radical trapping in cascade reactions.²⁹¹ Applications include radical carbonylation of allylsulfones, remote functionalization of aliphatic C-H bonds, and vinylsulfone formation.²⁹² Silver-catalyzed difluoromethylthiolation and trifluoromethylthiolation of alkenes also leverage thiosulfonate-derived radicals.²⁹³

1.7.2.3 Transition Metal-Catalyzed Cross-Coupling

Thiosulfonates facilitate cross-coupling to form C-S bonds in challenging C(sp³)-S coupling reactions.²⁹⁴⁻²⁹⁵ Nickel and copper catalysis enables the synthesis of various sulfides from alkyl or aryl halides and boronic acids,²⁹⁶⁻²⁹⁷ while Rhodium or Cu-TMEDA catalysis expands substrate compatibility.²⁹⁸⁻²⁹⁹

1.7.2.4 Reduction/Oxidation

Thiosulfonates are generally produced *via* disulfide oxidation but can also be reduced back to disulfides.³⁰⁰ Reactions with phosphine reagents or iodine enable deoxygenation to generate iodides or other sulfur-based products.³⁰¹⁻³⁰²

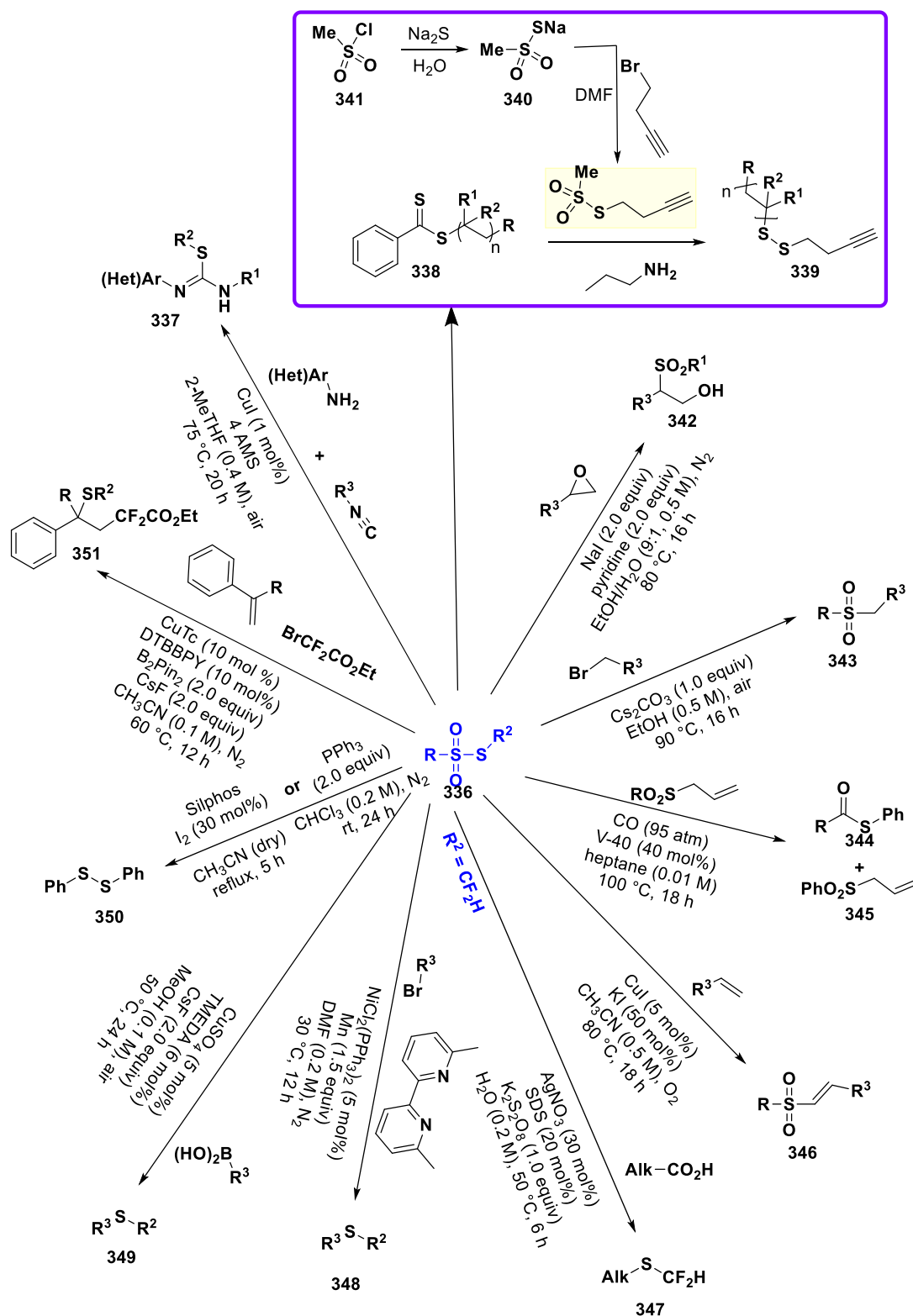
1.7.2.5 Multicomponent Reactions (MCRs)

Thiosulfonates enhance step economy in MCRs, commonly used in drug discovery. For example, they facilitate the copper-catalyzed synthesis of isothioureas and thiocarbamates from alkenes or isocyanides,³⁰³⁻³⁰⁵ leveraging radical and electrophilic reactions for efficient synthesis of complex frameworks.³⁰⁶⁻³⁰⁷

1.7.2.6 Polymer Chemistry

In polymer chemistry, thiosulfonates modify RAFT polymers to introduce functional end groups. They enable post-modification of polymer ends *via* aminolysis followed by thiol capping, allowing diverse

functional groups, such as acetylene, to be attached, and enabling further click-type modifications.³⁰⁸
 This approach has also been extended to copolymer formation with additional functional group modifications.³⁰⁹



Scheme 41. Examples of thiosulfonates applications 2.

*Readapted from *Thiosulfonates as emerging reactants: synthesis and applications*.¹⁷⁷

Thiosulfonates are valuable reagents for a wide array of synthetic applications. Their versatility in radical, nucleophilic, and electrophilic transformations, along with their use in MCRs and polymer modification, underscores their significance in synthetic organic chemistry. Their multifunctional behaviour supports developments in medicinal chemistry, materials science, and green chemistry through high-yield, sustainable transformations.

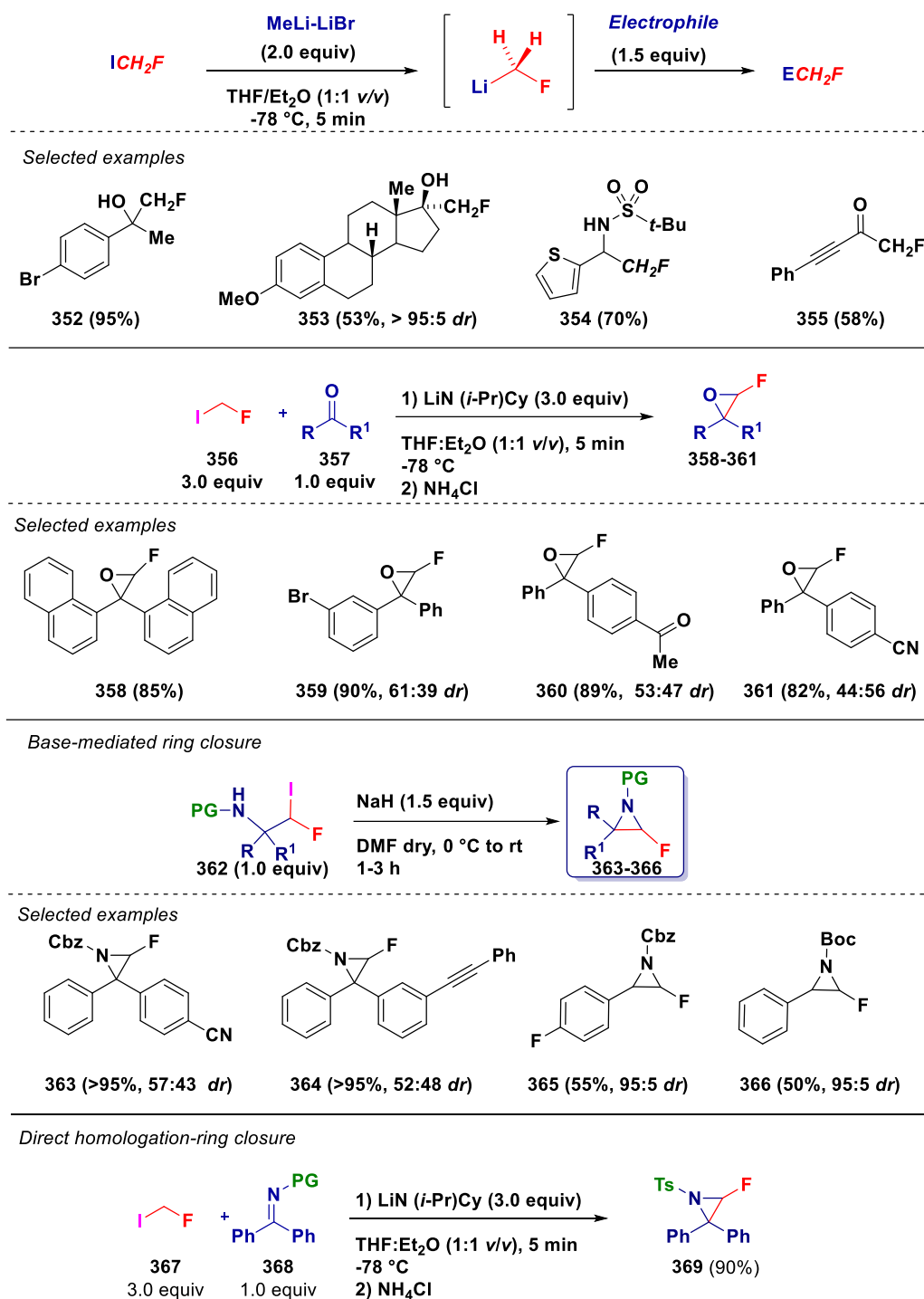
1.8 Fluoromethylating carbenoids

Direct introduction of CH₂F units into organic compounds simplifies access to fluoromethylated fragments, which have wide interest in the chemical community due to the influential role of fluorine in modulating crucial physical-chemical properties.³¹⁰⁻³¹⁴ However, fluorinated carbanions suffer from high kinetic and thermal instability, limiting the development of monofluoromethylating agents compared to difluoromethyl- and trifluoromethyl- methodologies.³¹⁵⁻³¹⁹

Previous strategies involved the installation of electron-withdrawing elements to stabilize monofluorinated organometallics.³¹⁵ Recently, the Pace and Luisi groups developed a fluoromethyl lithium reagent using fluoroiodomethane as a precursor,⁶⁵ allowing for versatile C1 transfer to electrophiles. The reagent exhibited excellent versatility and flexibility, reacting with various carbonyl compounds, nitriles, and unsaturated functionalities.³²⁰⁻³²⁴ Fluoroiodomethane shows notable dual reactivity with organolithium reagents. It allows for both an efficient iodine-lithium exchange and deprotonation to form the LiCHFI carbenoid.

Like other lithium dihalocarbenoids, treatment with a lithium amide base can effectively remove an acidic proton from FCH₂I, leading to carbenoid formation. LiCHFI is particularly intriguing, as it features a single carbon atom with four distinct substituents. Pace *et al.* highlighted its unique potential due to the differing reactivities of iodine and fluorine; specifically, under suitable conditions, iodine can facilitate nucleophilic displacement while fluorine remains in the molecule.

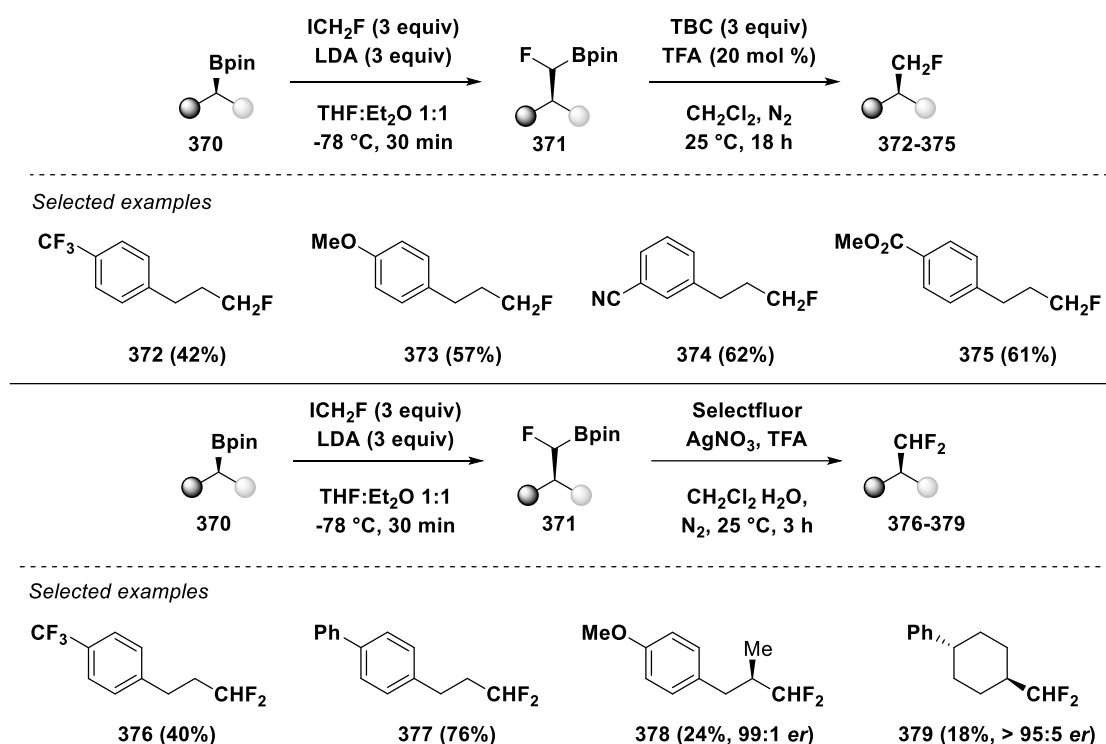
In 2019, LiCHFI was first applied in synthesis, specifically in a homologation and ring closure process for ketones and imines, yielding rare α -fluoroepoxides (**358-361**) and α -fluoroaziridines (**363-366**).^{127, 325} The conditions required to generate LiCH₂F, particularly using a THF/Et₂O solvent mixture, were successfully adapted for LiCHFI, thereby incorporating this carbenoid into synthetic chemistry. These developments provide valuable tools for the synthesis of fluoromethylated compounds (Scheme 42).



Scheme 42. Use of LiCH_2F with carbon electrophiles, and homologation of (aza)-carbonyl counterparts with LiCH_2F .
 *Readapted from *Homologation Reactions: Reagents, Applications, and Mechanisms*.¹⁵

Furthermore, Aggarwal's research group in 2020 demonstrated a divergent and stereospecific reaction of fluoroiodomethyl lithium with boronic esters **370**, leading to the formation of α -fluoro-boronic esters **371**.³²⁶ These intermediates could be readily converted into mono- (**376-379**) or difluoromethylated (**372-375**) derivatives through proto- or fluorodeboronation, respectively. The process involved a stereospecific Matteson-type homologation followed by the removal of the boron-centered functionality. By treating the α -fluoromethylboryl derivative with TFA and 4-*t*-Bu-cathecol

(TBC), alkylfluorides were obtained in high yields using a radical-mediated protodeboronation strategy previously developed by Renaud (Scheme 43).³²⁷ The same α -fluoromethylboryl intermediate could also undergo fluorodeboronation with Selectfluor and AgNO_3 , enabling the synthesis of difluoromethyl-congeners. Importantly, these homologation-protodeboronation and homologation-fluorodeboronation sequences demonstrated broad substrate scope, tolerating various electron-donating and electron-withdrawing groups on the aromatic ring of primary boronic esters without any undesired side reactions.

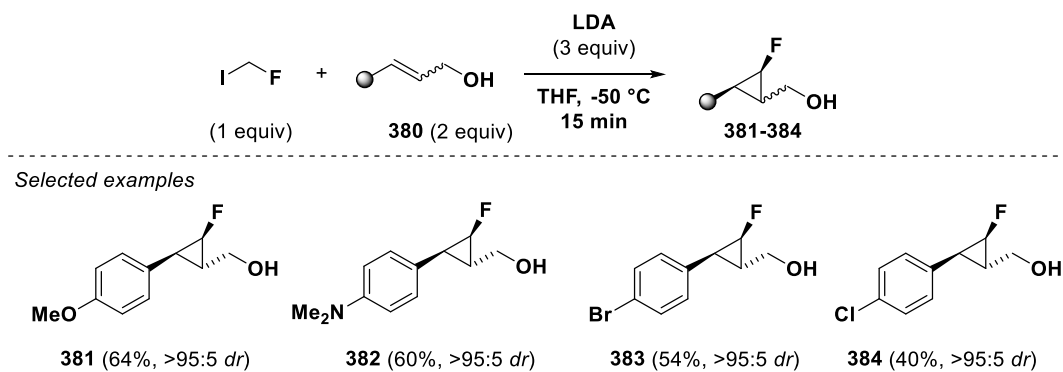


Scheme 43. Mono- and difluoromethylation of boronic esters.

*Readapted from *Homologation Reactions: Reagents, Applications, and Mechanisms*.¹⁵

1.9 Lithium carbenoid acting as electrophile

In a notable study, Luisi and colleagues reported a simple and highly selective method for the direct fluorocyclopropanation of allylic alcohols **380**.³²⁸ This transformative reaction exploited the unique electrophilic nature of fluoroiodomethyl lithium carbenoid, leading to rapid and efficient formation of cyclopropane products **381-384** with excellent stereochemistry. Computational modelling provided valuable insights into the observed stereochemical outcomes, confirming the feasibility of achieving chiral synthesis of cyclopropanes while maintaining the enantiopurity of the starting allylic alcohol (Scheme 44). This breakthrough approach offered a convenient and reliable strategy for accessing fluorinated cyclopropane derivatives.



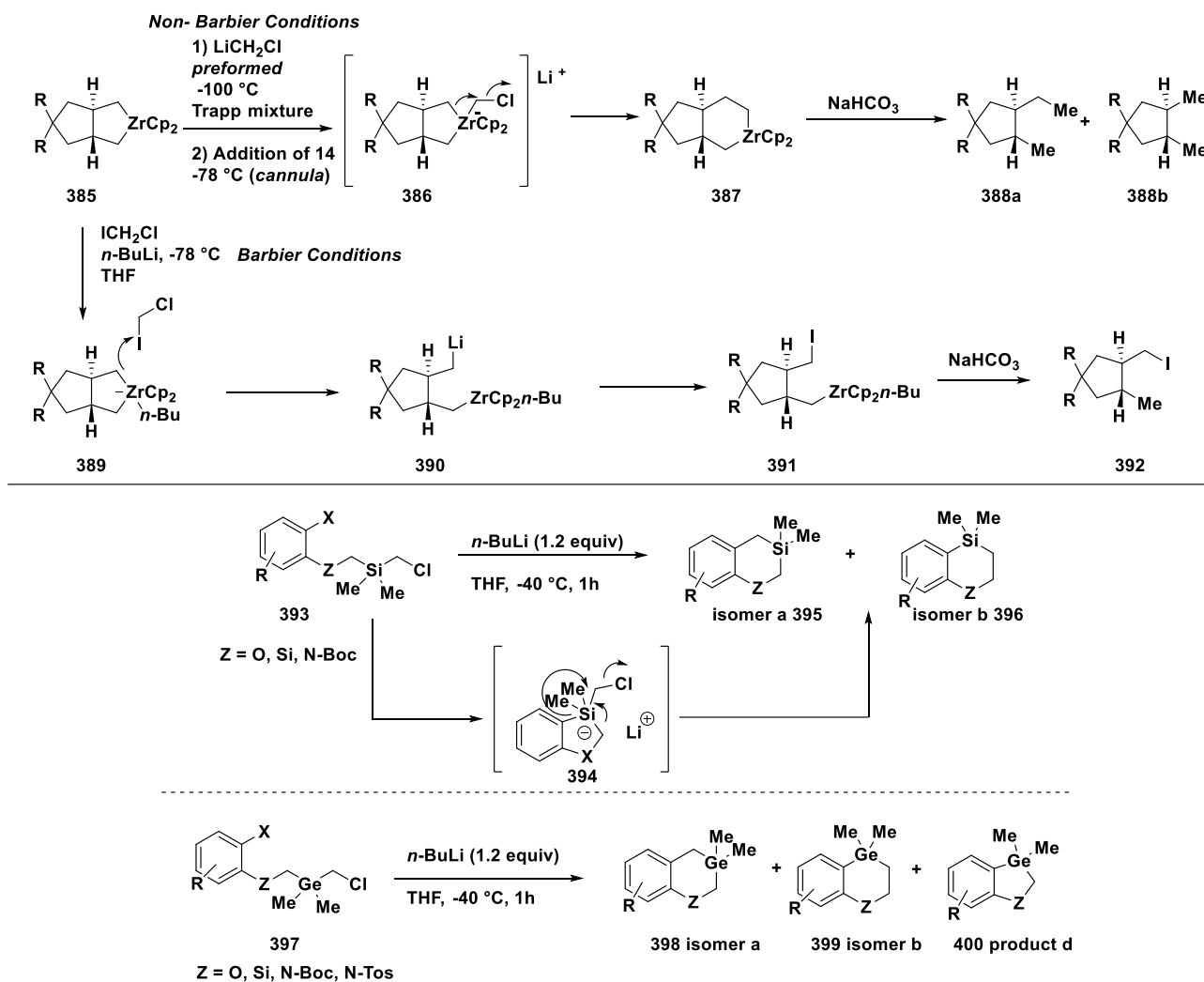
Scheme 44. Cyclopropanation of allylic alcohols with LiCHFI .

*Readapted from *Homologation Reactions: Reagents, Applications, and Mechanisms*.¹⁵

1.10 Homologation of heteroatom-centered cycles with lithium carbenoids

Whitby's 2004 study presented an exception to the conventional generation of chloromethylithium under Barbier-type conditions (Scheme 45).³²⁹ While investigating the insertion of a methylene carbenoid into a 5-membered zirconacycle **385**, the formation of an enlarged structure was expected. Surprisingly, employing a Barbier protocol led to the nucleophilic attack of *n*-BuLi on the zirconium center, forming the zirconate complex, which underwent iodine-metal exchange with ICH₂Cl. To address this issue, Whitby successfully generated the carbenoid from ICH₂Cl and *n*-BuLi in the Trapp mixture at -100 °C, allowing for desired homologation. This observation highlights the importance of the relative reactivity of the halomethane precursor and the electrophile in determining the outcome of the process.

In 2012, Maddaluno and colleagues reported the synthesis of silylated and germylated binuclear heterocycles through an innovative anionic rearrangement (Scheme 45).³³⁰⁻³³¹ The study emphasized the direct correlation between the electron density on the aromatic ring and the formation of a and b isomers. This methodology proved to be applicable to a broad range of substrates, including heterocyclic compounds, enabling the synthesis of heteroaromatic and silylated binuclear scaffolds with potential applications in medicinal chemistry and the discovery of new analogues.



Scheme 45. Whitby's and Maddaluno's homologations.

*Readapted from Homologation Reactions: Reagents, Applications, and Mechanisms.¹⁵

1.11 Heterocyclic “privileged scaffold”: spiro-epoxy oxindole

The term "spiro-epoxy oxindole" refers to a class of organic compounds characterized by a spiro (spiral) arrangement, an epoxy functional group, and an oxindole moiety. By breaking down these components:

Spiro: This refers to the arrangement of two or more molecular groups where they share a single atom in a cyclic structure, forming a spiral-like shape.³³²⁻³³³

Epoxy: It's a chemical functional group consisting of an oxygen atom bonded to two adjacent carbon atoms, forming a three-membered ring. It is highly reactive and can participate in various chemical reactions.³³⁴

Oxindole: This is a bicyclic compound containing both an indole ring and a lactam (cyclic amide) group. Oxindoles are commonly found in natural products and pharmaceutical compounds due to their diverse biological activities (Figure 3).³³⁵⁻³³⁶

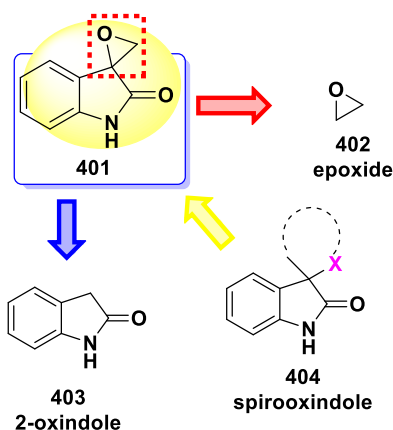


Figure 3. Structure of spiro-epoxy oxindole.

*Readapted from *Org. Biomol. Chem.*, 2020, 18, 8572.³³⁷

The combination of these three components, the spiro arrangement, epoxy functional group, and oxindole moiety, could create a molecule with potentially interesting chemical and biological properties. The exact characteristics, synthesis methods, and applications of specific spiro-epoxy oxindole compounds can vary widely based on their structure and intended purpose. These compounds might be studied for medicinal purposes, drug development, or as intermediates in organic synthesis.³³⁷

The spiro-epoxy oxindole frameworks present an effective structural platform for acquiring C3-functionalized oxindole derivatives, renowned for their susceptibility to nucleophiles due to inherent ring strain. This adaptable reactivity has enabled numerous synthetic transformations, facilitating the production of bioactive compounds and natural products. The 2-oxindole, recognized as a 'privileged scaffold' with abundant C3-substitutions, has garnered significant interest from synthetic and medicinal chemists due to its versatile reactivity.³³⁸ Over the past two decades, diverse 2-oxindole derivatives have emerged, showcasing substantial biological profiles, including anticancer,³³⁹⁻³⁴¹ antitubercular,³⁴² antimalarial,³⁴³ anti-human immunodeficiency virus (HIV),³⁴⁴ and MDM2 inhibitory properties.³⁴⁵

Isatin, serving as the primary building block for various C3-functionalized 2-oxindole derivatives, contains a prochiral center and a highly reactive carbonyl group at the C3 position, offering compelling applications in organic synthesis.³⁴⁶ Isatins undergo meticulous reactions, such as nucleophilic additions and diverse spiroannulations, to yield 2-oxindole derivatives.

Spirooxindoles attract substantial attention due to their challenging synthesis and potential biological applications.³⁴⁷⁻³⁴⁹ The steric strain induced by the spiro-carbon ensures the smooth conversion of spirooxindoles into 2-oxindole-bearing carbocyclic and heterocyclic rings.

Heterocycle fused three-membered ring systems chemistry significantly contributes to organic synthesis by harnessing their inherent ring strain into ring-opening/expansion reactions.³⁵⁰ Epoxides and their nitrogenous analogues, aziridines, are well-known for their reactivity and prevalence in bioactive small molecules and natural products, offering a rare combination of reactivity, atom economy, and synthetic applicability.³⁵¹

Epoxide- and aziridine-containing molecules serve as valuable entry points for simple and complex organic frameworks, imparting conformational rigidity to molecules and enabling interaction with specific biological targets.³⁵² The strategic fusion of epoxide/aziridine at the C3 position of the 2-oxindole moiety offers a promising approach for accessing spirooxindoles and 3,3-disubstituted oxindoles through ring-expansion/opening reactions.

This strategy not only showcases intriguing reactivity patterns but also holds promise for constructing complex frameworks with specific conformational properties, enhancing their interaction with biological targets.

This section aims to delve deeply into the chemistry of spiro-epoxy oxindoles. It will highlight advances in their synthetic strategies, reactivity profiles in ring-opening/expansion reactions, and their potential applications.

1.11.1 Synthesis approaches for spiro-epoxy indoles

This section aims to explore various synthetic strategies employed in the preparation of spiro-epoxy oxindoles, highlighting their utility in organic synthesis and drug discovery.

The synthesis of spiro-epoxy oxindoles can be accomplished through efficient methods such as the Darzens reaction and Corey-Chaykovsky epoxidation (Figure 4).³⁵³ These pathways offer facile access to this structural skeleton, leading to the formation of 3,3-disubstituted oxindoles and spiro-oxindoles, pivotal in the construction of complex natural products like brassinin, ($\pm$)-physovenine, and (+)-gliocladin C.³⁵⁴

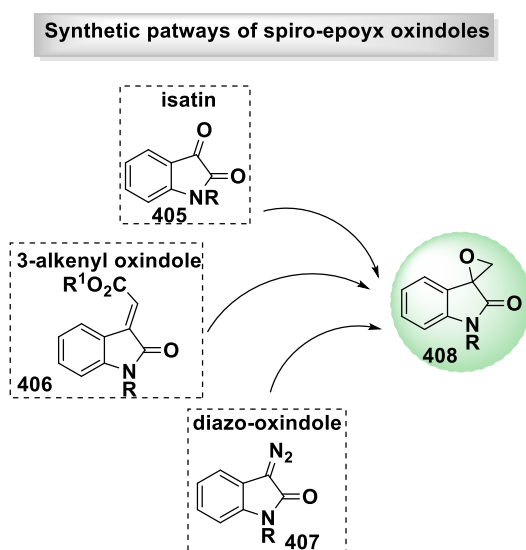


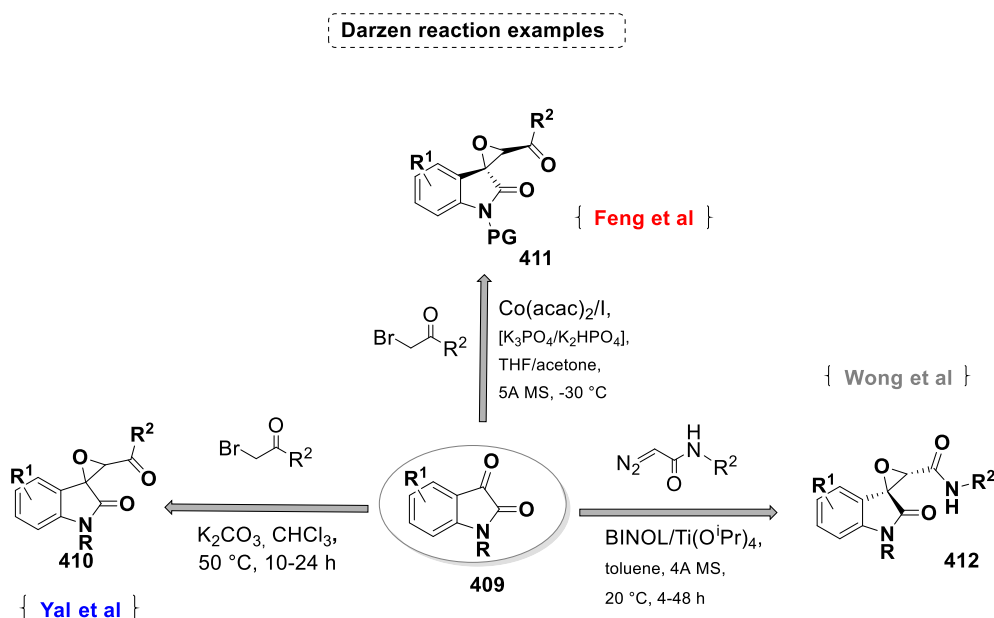
Figure 4. Synthetic pathways for spiro-epoxy oxindoles.

*Readapted from *Org. Biomol. Chem.*, 2020, 18, 8572.³³⁷

1.11.1.1 From Isatins

The Darzens reaction stands as a powerful non-oxidative method for epoxide preparation. Yan and colleagues effectively applied this method using isatins **409** and phenacyl bromides in the presence of a base, resulting in spiro-epoxy oxindole **410**.³⁵⁵ Intriguingly, the reaction with *N*-unsubstituted isatins and excess of phenacyl bromide yielded *N*-alkylated spiro-epoxy oxindole. Feng et al. reported an asymmetric variant of the Darzens reaction, utilizing a chiral *N,N*-dioxide I-Co(acac)₂ complex. This approach furnished optically active *trans*-spiro-epoxyoxindoles **411**. The stereochemistry of the

products significantly relied on the electronic nature of starting materials, influencing both yield and enantioselectivity. Wong et al. demonstrated an asymmetric Darzens reaction employing diazoacetamides with isatins **409**, yielding spiro-epoxy-oxindole **412** and producing nitrogen as the sole by-product (Scheme 46).³⁵⁶



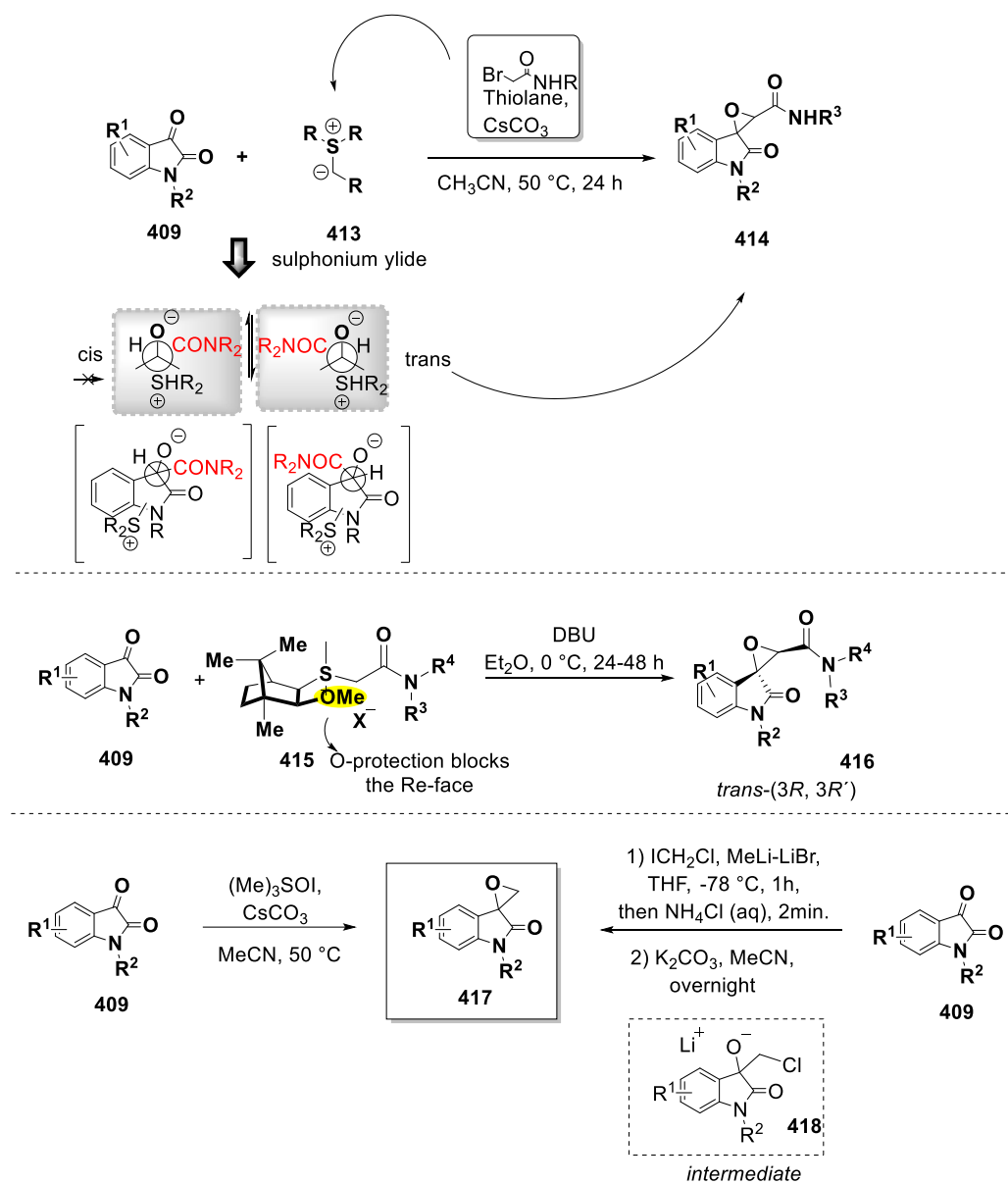
Scheme 46. Synthesis of spiro-epoxy oxindoles from isatin 1.

*Readapted from *Org. Biomol. Chem.*, 2020, 18, 8572.³³⁷

Sulphur ylides, versatile zwitterionic reagents, have been utilized by Schulz and co-workers to access spiro-epoxy oxindoles.³⁵⁷⁻³⁵⁸ The reaction involved in situ-generated sulphur ylides from α -bromo acetamides and isatin **409**. Thiolane in conjunction with a base converted α -bromo acetamides to sulphonium ylide, proceeding to an epoxidation reaction to furnish through the formation of transoid betaines. Lu and Xiao utilized camphor-derived chiral sulphur ylides to achieve spiro-epoxidation of isatin **409**, where a cisoid betaine intermediate underwent an intramolecular S_N2 substitution to produce *trans*-spiro-epoxy oxindole **416**.³⁵⁹

The Corey-Chaykovsky epoxidation emerged as a common method for constructing simple spiro-epoxy oxindoles. This approach involved trimethylsulfoxonium iodide and caesium carbonate to generate sulphur ylide, which subsequently reacted with isatin.³⁶⁰ Pace and colleagues utilized lithium halocarbenoids for synthesizing spiro-epoxy oxindoles from isatin **409**. The chloromethyl lithium carbenoid generated from MeLi–LiBr and chloriodomethane reacted with isatin **409** to produce a halohydrin intermediate, followed by ring closure to yield the desired spiro-epoxides (Scheme 47).¹⁰⁶

Epoxidation through Sulfur Ylides



Scheme 47. Synthesis of spiro-epoxy oxindoles from isatin 2.

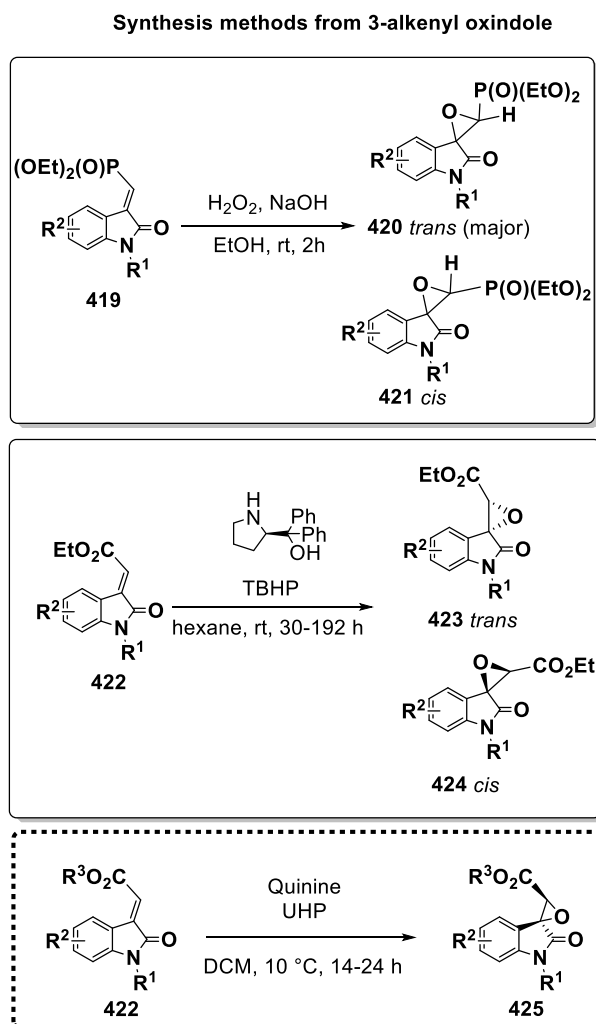
*Readapted from *Org. Biomol. Chem.*, 2020, 18, 8572.³³⁷

1.11.1.2 From 3-alkenyl oxindole

The 3-alkenyl oxindole, bearing an exocyclic double bond, serves as a feasible precursor for spiro-epoxides. However, an appropriate oxygen source and a base are imperative for the successful execution of the epoxidation process. Gasperi and colleagues pioneered the H₂O₂/NaOH-catalyzed

epoxidation of 3-(phosphoryl methylene) oxindoles **419**, leading to the generation of spiro-epoxy oxindole phosphonates **420-421**. Through nuclear overhauser effect spectroscopy (NOESY) analysis, the major isomer of the representative derivative was identified as *trans*.³⁶¹

Subsequently, the same research group introduced an asymmetric nucleophilic epoxidation reaction for 3-alkenyl oxindoles **422** using *tert*-butyl-hydroperoxide (TBHP) as the oxidant and (*S*)- α,α -diphenylprolinol III as a bifunctional organocatalyst.³⁶² This protocol represented an asymmetric catalytic adaptation of the Weitz–Scheffer epoxidation reaction,³⁶³ where the stereoselectivity of the resulting product relied heavily on both electronic and steric properties of substituents on the oxindole substrate (Scheme 48).



Scheme 48. Synthesis of spiro-epoxy oxindole from 3-alkenyl oxindole.

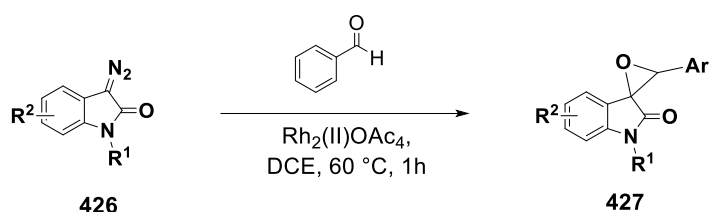
*Readapted from *Org. Biomol. Chem.*, 2020, 18, 8572.³³⁷

In 2013, Nair and co-workers outlined a quinine and urea-hydrogen peroxide (UHP)-mediated spiro-epoxidation method for 3-alkenyl oxindoles **422**. This protocol relied on quinine as a catalyst to ensure *trans*-diastereoselectivity (Scheme 48).³⁶⁴

1.11.1.3 From diazooxindoles

Muthusamy and colleagues introduced a straightforward method to produce aryl-substituted spiroepoxyoxindoles **427**. This synthesis involved the reaction of diazooxindoles **426** with aryl aldehydes in the presence of rhodium(II) acetate. Under optimized conditions, *N*-substituted diazooxindoles displayed favourable reactivity with aryl aldehydes carrying both electron-neutral and electron-withdrawing groups (Scheme 49).³⁶⁵

Synthesis of spiro-epoxyoxindole from diazooxindole



Scheme 49. Synthesis of spiro-epoxy oxindole from diazooxindole.

*Readapted from *Org. Biomol. Chem.*, 2020, 18, 8572.³³⁷

1.11.2 Reactivity of spiro-epoxy oxindoles

Reactions involving spiro-epoxy oxindoles, characterized by an epoxide ring housing two electrophilic centres (terminal and C3-spirocentre), exhibit remarkable reactivity towards diverse nucleophiles (Figure 5). The Hajra research group has been instrumental in advancing the chemistry of spiro-epoxy oxindoles, particularly in developing controlled ring-opening/expansion reactions, notably focusing on the C3-spirocentre. These efforts have yielded successful synthesis of natural products and their derivatives.³³⁷

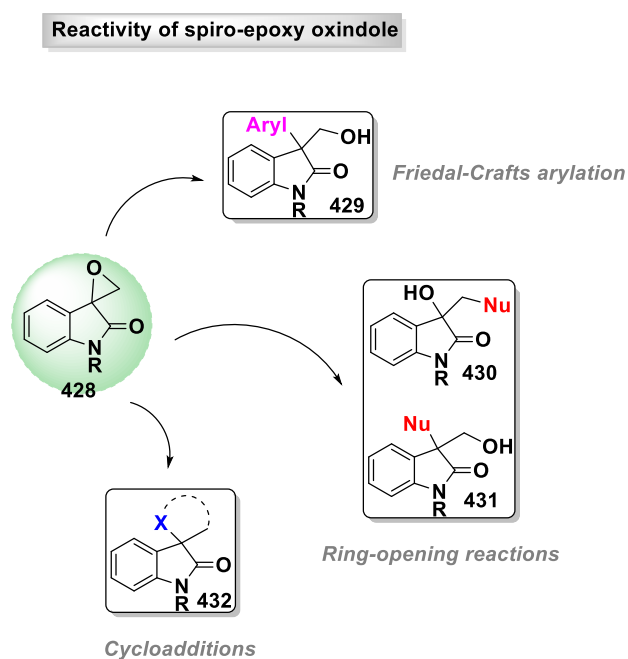


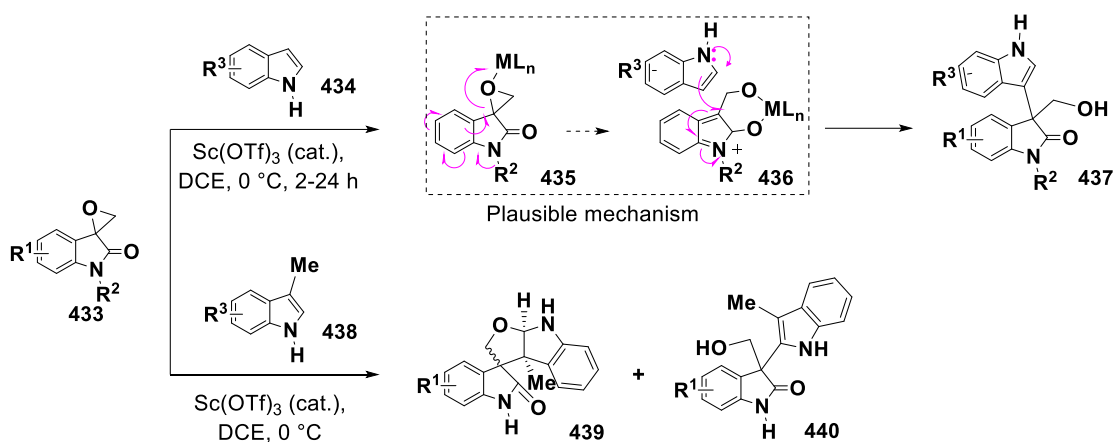
Figure 5. Reactions involving spiro-epoxy oxindoles.

*Readapted from *Org. Biomol. Chem.*, 2020, 18, 8572.³³⁷

Ring-opening reactions of spiro-epoxy oxindole

1.11.2.1 With C-nucleophiles

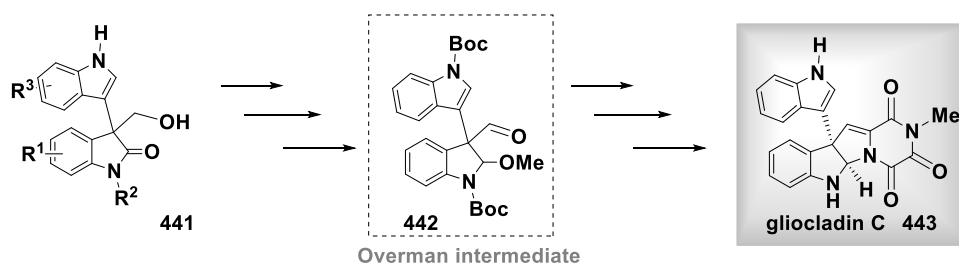
The nucleophilic ring-opening reactions of spiro-epoxy oxindole have been known since 2010, when Nair et al. disclosed their reactivity with aromatic/aliphatic nucleophiles at the terminal site.³⁶⁰ However, it was not until 2015 that the Hajra research group pioneered the nucleophilic ring-opening of spiro-epoxy oxindole with indole at the hindered site (Scheme 50). Since then, researchers have continuously explored the reactivity of spiro-epoxy oxindoles with various nucleophiles.



Scheme 50. Reaction with indole.
 *Readapted from *Org. Biomol. Chem.*, 2020, 18, 8572.³³⁷

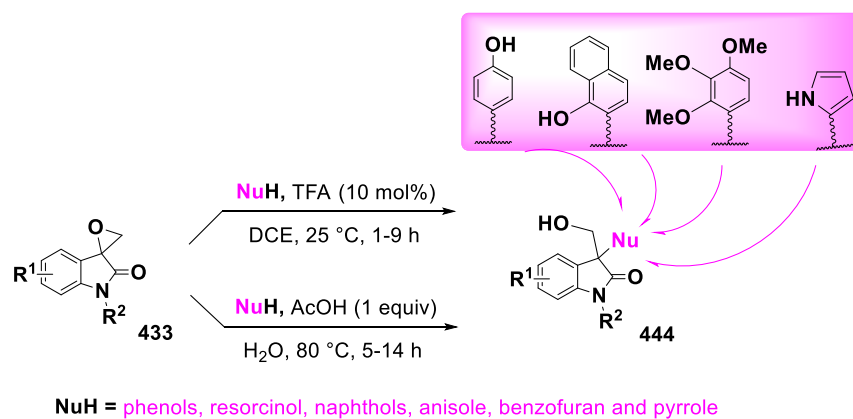
The application of a Friedel–Crafts-type regioselective spiro-epoxide ring-opening with indoles yielded 3-indolyl-3-hydroxymethyl oxindole **437** derivatives, which were further used in the formal total synthesis of (±)-gliocladin C **443** via the Overman intermediate (Scheme 51).³⁶⁶

Interestingly, reaction with 3-methyl indole **438** resulted in a mixture of spiro-tetrahydrofuranyl bisindole **439** alongside 2,3-bisindole **440**, forming a tricyclic tetrahydrofuranoindole core through a spiro-epoxide ring-opening followed by intramolecular cyclisation (Scheme 50).



Scheme 51. Synthesis of gliocladin C.
 *Readapted from *Org. Biomol. Chem.*, 2020, 18, 8572.³³⁷

The reactivity of spiro-epoxy oxindoles **433** was examined using various C-nucleophiles such as phenols, naphthols, anisole, pyrrole, and benzofuran. Regioselective Friedel–Crafts ring-opening processes produced 3,3-disubstituted oxindole derivatives **444**, while Lewis acid-catalysed epoxide ring-opening with electron-rich benzenoid arenes also demonstrated a regioselective mode (Scheme 52).³⁶⁷⁻³⁶⁸

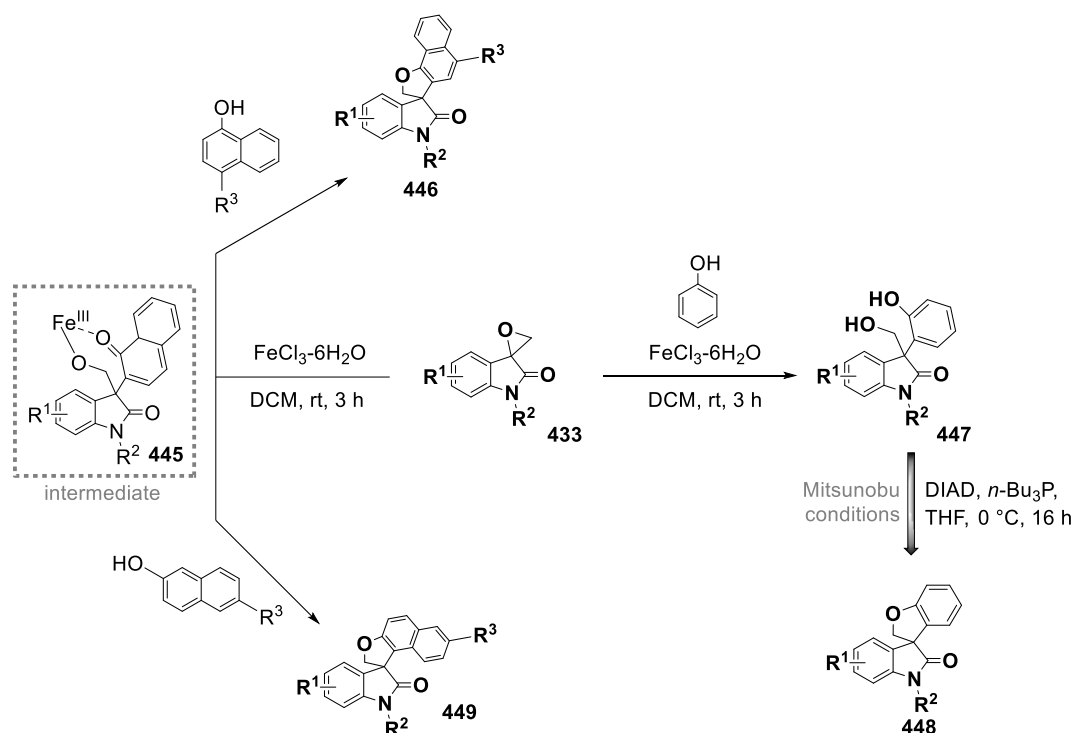


Scheme 52. Ring-opening reaction with carbon nucleophiles.

*Readapted from *Org. Biomol. Chem.*, 2020, 18, 8572.³³⁷

Additionally, Wei and co-workers introduced FeCl₃-catalysed Friedel–Crafts-type arylation using spiro-epoxy oxindoles and phenols, offering facile access to 3-aryl-3-hydroxymethyl oxindole. Further transformations of ring-opening adduct **447** into corresponding benzofuranyl spirooxindoles derivatives **448** were achieved under standard Mitsunobu conditions (Scheme 53).³⁶⁹

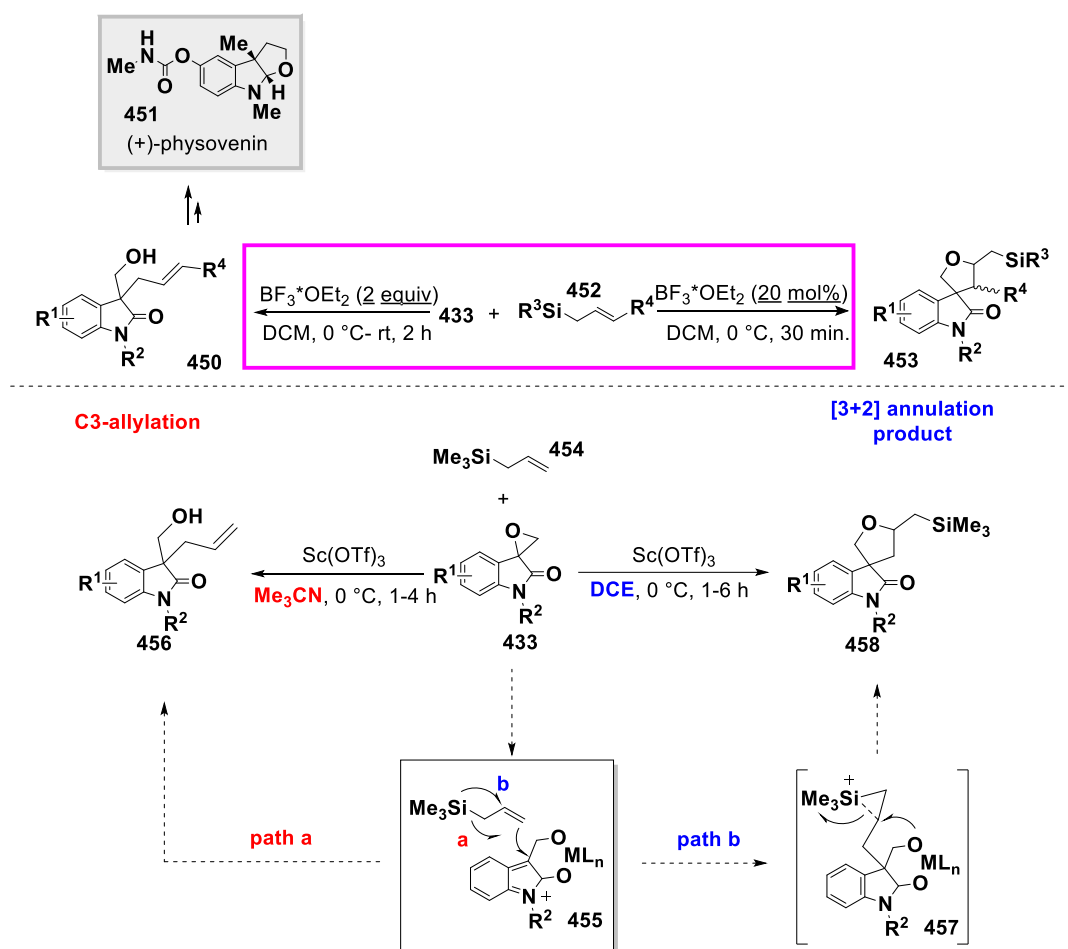
A tandem Friedel–Crafts arylation/*O*-cyclisation of spiro-epoxides with naphthols was disclosed; wherein the reaction proceeded *via* a spiro-cyclic intermediate **445**, culminating in the formation of naphthofuranyl-spirooxindoles **446** and **449**. This one-pot, two-step reaction was instrumental in the synthesis of the sodium channel Na_v1.7 inhibitor (±)-XEN402 on a gram scale (Scheme 53).



Scheme 53. Reactions of spiro-epoxy oxindole with phenol and naphthols.
 *Readapted from *Org. Biomol. Chem.*, 2020, 18, 8572.³³⁷

Subsequently, Hajra et al. unveiled a solvent-dependent dual reaction mechanism catalysed by Sc(OTf)₃, introducing a formal [3 + 2] cycloaddition and a notably selective Hosomi–Sakurai allylation using allyltrimethylsilane **454** as a carbon nucleophile. Within dichloroethane, the reaction pursued the [3 + 2] annulation route, yielding spirofuranooxindole derivatives **453**. In contrast, when conducted in acetonitrile, the reaction favoured Hosomi–Sakurai allylation, generating 3-allyl-3-(hydroxymethyl)-oxindoles **456**. The specific substitution pattern on spiro-epoxyoxindole significantly influenced the choice of Lewis acids in both reaction types.

Furthermore, the resulting C3-allylated products were strategically employed for the complete synthesis of (±)-*N*-methyl coerulescine and (±)-physovenine **451**. This solvent-dependent reaction's mechanism involved the formation of a reactive indolone intermediate. Direct allyl group addition to *via* C–Si bond cleavage led to the formation of a preferential allylation product (path a). However, the annulation reaction prevailed due to the β-silicon effect (path b) (Scheme 54).³⁷⁰

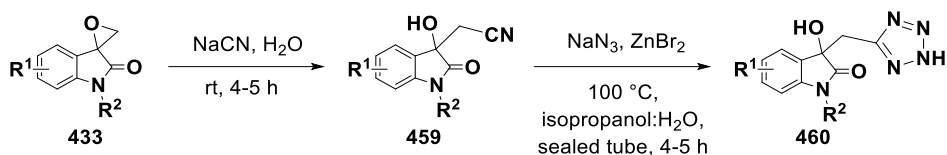


Scheme 54. [3+2] Cycloaddition and Hosomi-Sakurai allylation of spiro-epoxy oxindole.

*Readapted from *Org. Biomol. Chem.*, 2020, 18, 8572.³³⁷

In a similar vein, Kumar et al. reported a comparable ring-opening reaction utilizing allyltrimethylsilane. Unlike Hajra's findings, this reaction's outcome was contingent on the Lewis acid's stoichiometry. The Hosomi–Sakurai allylation reaction was promoted using 2-equivalents of $\text{BF}_3 \cdot \text{OEt}_2$ as the Lewis acid, while the [3 + 2] annulation product arose with 20 mol% of $\text{BF}_3 \cdot \text{OEt}_2$. Under optimized conditions, both reactions yielded the expected products **450** and **453**. Furthermore, 3-allyl-3-hydroxymethyl oxindole **450** served in the formal total synthesis of (±)-physovenine **451** (Scheme 54).³⁷¹

In 2015, Shankaraiah's group presented an H_2O -mediated nucleophilic spiro-ring opening employing NaCN. This straightforward method provided access to novel 3-hydroxy oxindole precursors **459**, incorporating nitrile functionality. Subsequently, these isatin hydroxy nitrile intermediates **459** were transformed into 3-hydroxy-3-tetrazolylmethyl oxindoles **460** via the azide-nitrile cycloaddition reaction (Scheme 55).



Scheme 55. H_2O -mediated nucleophilic spiro-ring opening employing NaCN.

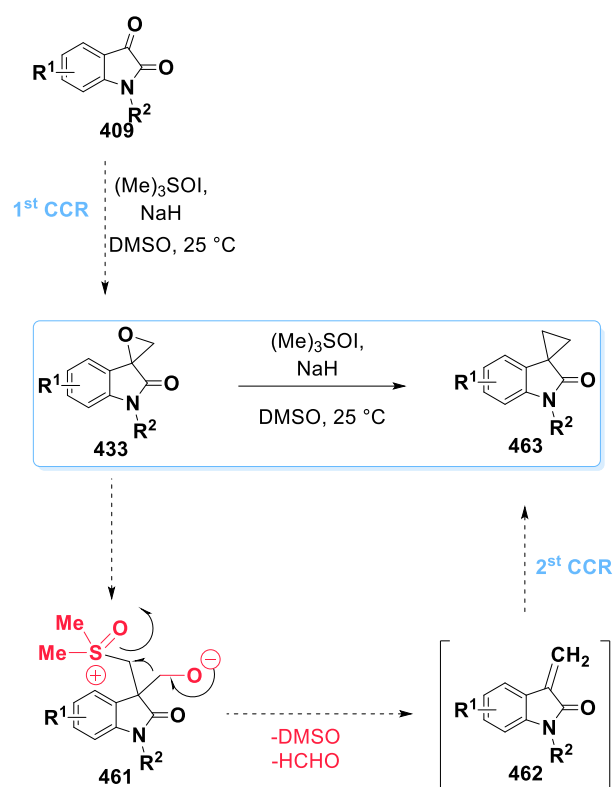
*Readapted from *Org. Biomol. Chem.*, 2020, 18, 8572.³³⁷

Remarkably, unlike reactions involving other C-nucleophiles, the interaction with the cyanide nucleophile targeted the less hindered site of the spiro-epoxide ring in a regiospecific manner. These modified 3-hydroxy oxindoles with the tetrazole motif exhibited significant cytotoxic activity, displaying an IC_{50} value of $4.26 \pm 0.09 \mu\text{M}$ on the human prostate cancer cell line (DU-145).³⁷²

In 2018, Hajra et al. detailed an intriguing transformation involving spiro-epoxy/aziridine oxindole into spirocyclopropyl oxindoles **463**.³⁷³ This process postulated that sulphur ylide, generated from trimethyl sulfoxonium iodide (TMSOI) and base, might initiate the opening of the spiro-epoxide ring from the hindered site, producing an alkoxide intermediate **461**. The subsequent retro-aldol reaction of intermediate **461**, followed by the elimination of dimethyl sulfoxide (DMSO) and formaldehyde (HCHO), led to the formation of the reactive 3-alkenyl oxindole **462**. Finally, the second Corey–Chaykovsky reaction (CCR) of **462**, in the presence of excess sulfur ylide, facilitated the generation of spirocyclopropyl oxindole **463** (Scheme 56).

Moreover, these biologically relevant spirocyclopropyl derivatives were directly derived from isatin *via* a domino CCR. The researchers also developed stereo-controlled reactions of the spiro-epoxy oxindoles, resulting in the creation of enantiopure all-carbon quaternary centered 2-oxindole derivatives.

Domino Corey-Chaykovsky reaction (CCR)

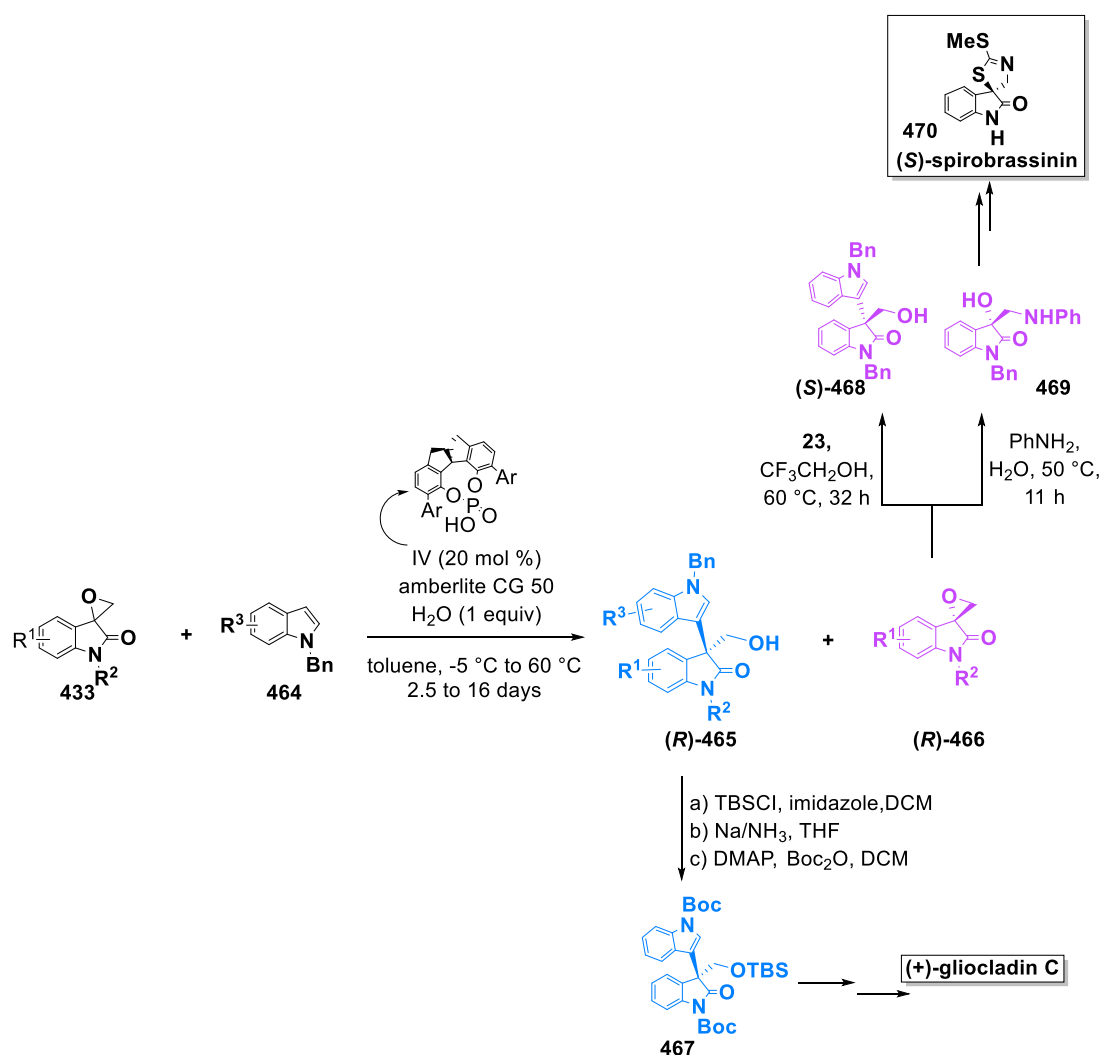


Scheme 56. Domino CCR.

*Readapted from *Org. Biomol. Chem.*, 2020, 18, 8572.³³⁷

Wang et al. demonstrated, for the first time, the chiral phosphoric acid IV-catalyzed kinetic resolution of racemic spiro-epoxy oxindoles **433** with indoles **464**.³⁵⁴ This reaction yielded the chiral Friedel–Crafts alkylation products, such as 3-indolyl-3-hydroxymethyl oxindole (*R*)-**465** with excellent enantioselectivity.

Additionally, up to 33–49% of the unreacted spiro-epoxy oxindoles (*R*)-**466** were recovered with an ee of 93–>99%. The synthetic potential of this reaction was demonstrated through the gram-scale synthesis of **467** followed by the synthesis of (+)-gliocladin C. Moreover, the reactivity of chiral spiro-epoxy oxindoles (*R*)-**466** was explored with indole and aniline, yielding the ring-opening products (*S*)-**468** and **469**, respectively. The ring-opening product **469** was utilized for the total synthesis of (*S*)-spirobrassinin.



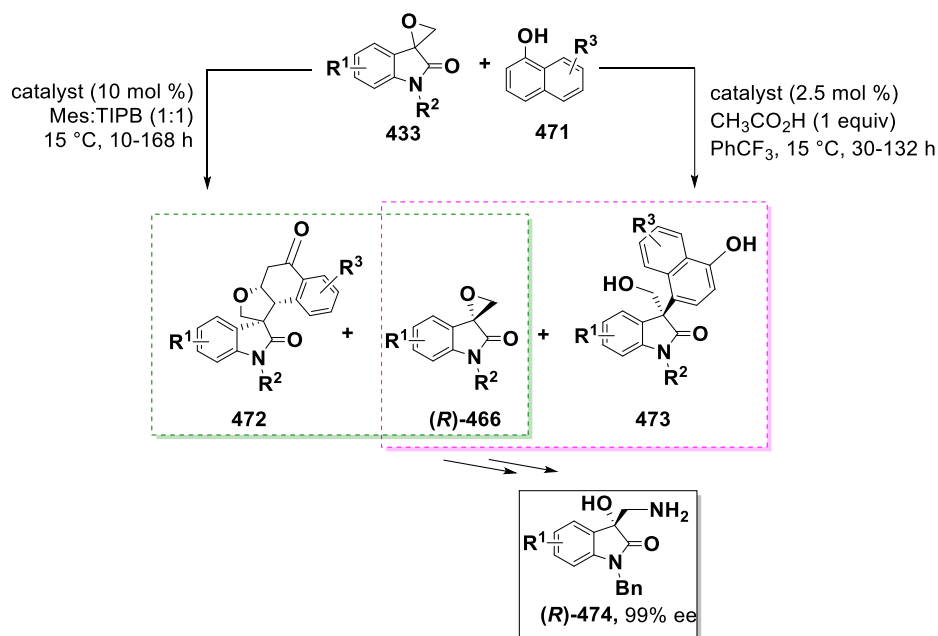
Scheme 57. Kinetic resolution of chiral spiro-epoxy oxindole with indoles.

*Readapted from *Org. Biomol. Chem.*, 2020, 18, 8572.³³⁷

Continuing this line of inquiry, Wang et al. also investigated the reactivity of 1-naphthols **471**, uncovering a polyphosphoric acid-catalyzed reaction of spiro-epoxides **433** with 1-naphthols **471**. Interestingly, this reaction underwent solvent-dependent asymmetric Friedel–Crafts alkylation and a dearomatisation/oxa-Michael reaction. Different solvent systems led to distinct product outcomes: tandem dearomatisation/oxa-Michael reaction to yield **472** in Mes:TIPB solvent, while Friedel–Crafts alkylation of **433** produced 3-naphthyl-3-hydroxymethyl oxindole **473** using fluorobenzene (Scheme 58).

Both reactions yielded resolved spiro-epoxides (*R*)-**466** in high enantioselectivity. These were further transformed into enantiopure azido alcohols via regio-stereoselective ring-opening by NaN₃, which were then reduced to 3-hydroxy-3-aminomethyl oxindole derivative **474**. The solvent-dependent

switchable chemoselectivity and simultaneous kinetic resolution of racemic spiro-epoxy oxindoles were notable features of this work (Scheme 58).³⁷⁴

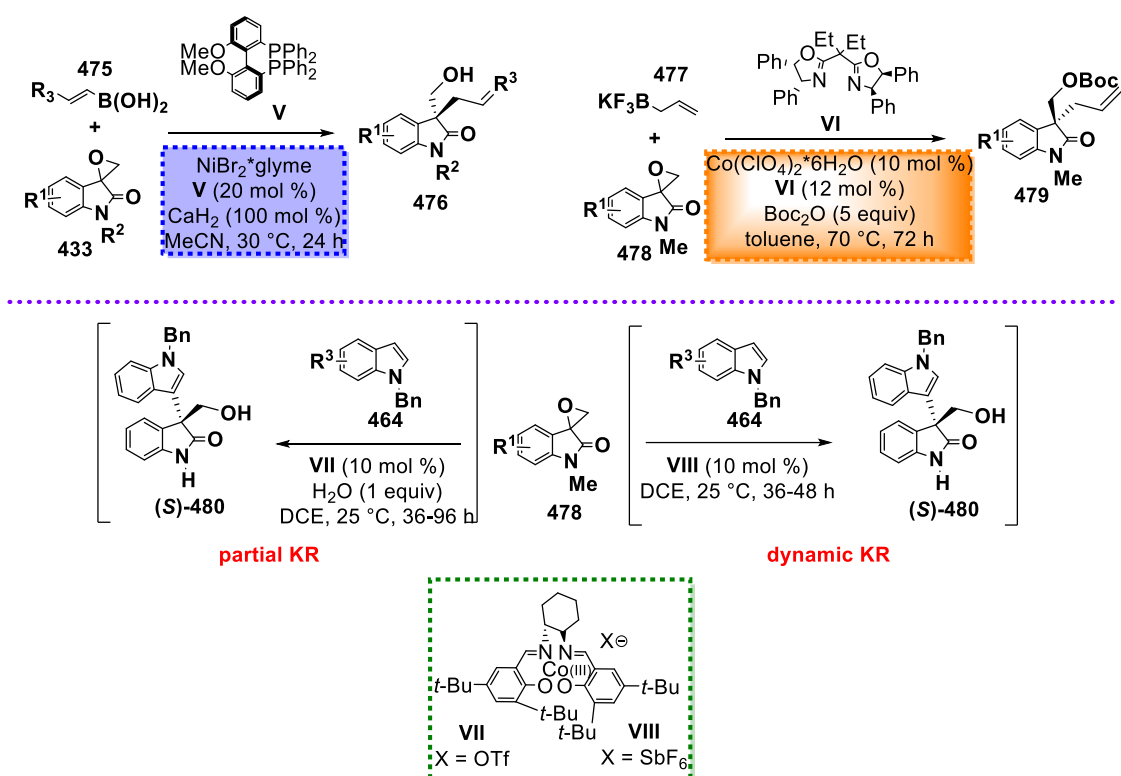


Scheme 58. Kinetic resolution of racemic spiro-epoxy oxindole with naphthols.

*Readapted from *Org. Biomol. Chem.*, 2020, 18, 8572.³³⁷

The Zhang research group established a Nickel-biphep-catalyzed cross-coupling of *N*-protected spiro-epoxy oxindoles **433** with alkenyl boronic acids **475**, yielding the 3-alkenyl-3-hydroxymethyl oxindoles **476**. This protocol was compatible with variously substituted 2-alkyl/aryl-vinyl boronic acids and spiro-epoxides bearing different electron-withdrawing, electron-releasing, and electron-neutral substituents.³⁷⁵

Furthermore, the Zhang group reported the asymmetric allylation reaction of **433**, producing enantiopure 3-allyl-3-(hydroxymethyl) oxindole **479**.³⁷⁶ This asymmetric spiro-epoxide ring-opening reaction was akin to Hajra's Sc(III)-catalyzed Hosomi–Sakurai allylation, albeit with very poor enantioselectivity (5% ee).³⁷⁰ The yield significantly improved when di-*tert*-butyl dicarbonate (Boc₂O) was used as an additive to trap the free hydroxyl group of the product *in situ*, preventing its coordination with the Co(II)/BOX-VI complex. During the substrate scope evaluation, it was observed that spiro-epoxy oxindoles with electron-releasing substituents delivered better yields and ee of the products compared to electron-withdrawing substituents. This asymmetric allylation operated through a stereoablative process, where Co(II) catalyzed the irreversible ring-opening of spiro-epoxides, followed by a Hosomi–Sakurai-type allylation (Scheme 59).



Scheme 59. Ni-Catalysed cross-coupling of alkenyl boronic acid, Co-(III)-catalysed asymmetric allylation and kinetic (partial and dynamic) resolution of **13**. *Readapted from *Org. Biomol. Chem.*, 2020, 18, 8572.³³⁷

Recently, the Hajra group unveiled a Co(III)salen-catalyzed asymmetric nucleophilic ring-opening reaction of unprotected spiro-epoxy oxindole **433** with indole **464**.³⁷⁷ Various counter-anions of Co(III)salen-complex were screened, with OTf and SbF₆ showcasing promising results.

When catalyst **VII** (X = OTf) was employed in the reaction, it resulted in the formation of the desired C-3 indolyl products (S)-**480** with yields ranging from 28% to 45%, accompanied by spiro-epoxy oxindole with enantiopurities in the range of 17–22%. This occurrence was labelled as a partial kinetic resolution. The presence of electron-releasing substituents on oxindole led to a higher reaction rate, yielding products in better quantities compared to electron-withdrawing substitutions.

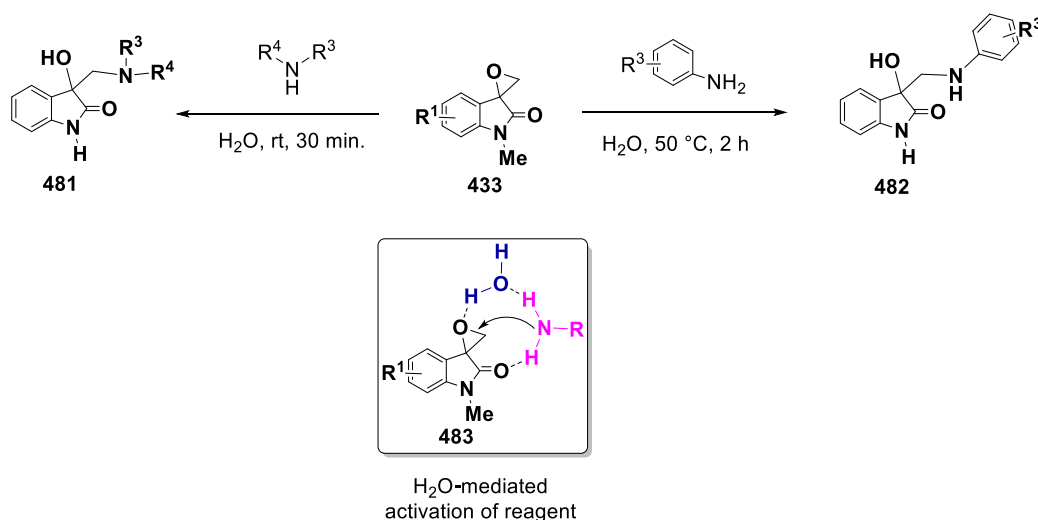
On the contrary, the use of catalyst **VIII** (X = SbF₆) led to a dynamic kinetic resolution phenomenon, exclusively yielding 3,3-bisindole methanols (S)-**480**. Extending the analysis of substrate scope revealed that various unprotected spiro-epoxides were compatible with indoles under optimized conditions, except for epoxides with 4- and/or 7-substituted oxindoles (Scheme 59).

The reduction in enantioselection for the unreacted spiro-epoxides was attributed to feedback inhibition—a phenomenon commonly observed in enzyme catalysis.³⁷⁸ This inhibition occurred after

a certain amount of product formation due to catalyst-product anchoring. Consequently, the C-3 indolylolation reaction of spiro-epoxy oxindole **433** was governed by an equilibrium between kinetic resolution and dynamic kinetic resolution.

1.11.2.2 With N-nucleophiles

Ring-opening reactions with *N*-nucleophiles have been a notable focus in several research endeavours. The Nair research group, in 2011, pioneered the nucleophilic ring-opening of spiro-epoxy oxindoles **433** utilizing aliphatic and aromatic amines. This mild, cost-effective aminolysis, conducted without a catalyst in water as a solvent, generated 3-hydroxy-3-aminomethyl oxindoles **481** and **482**. Unlike C-nucleophiles' ring-opening that occurs at the more hindered site, this reaction displayed regioselectivity at the less hindered site, facilitated by water enhancing the epoxide ring's electrophilicity through hydrogen bonding (Scheme 60).³⁶⁰



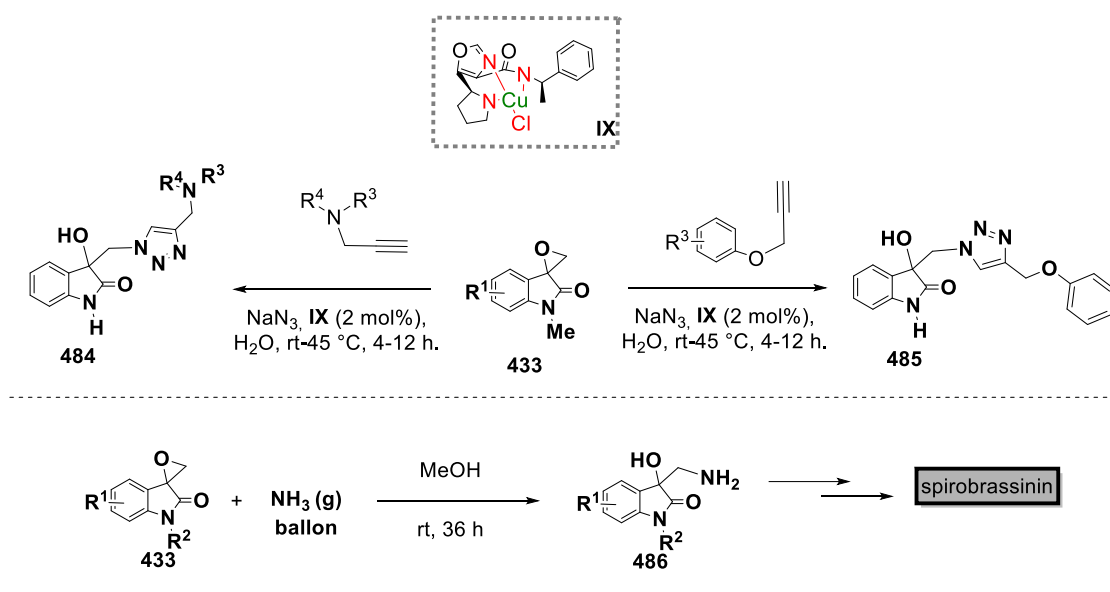
Scheme 60. Nair's ring-opening of spiro-epoxy oxindole with amines.

**Readapted from Org. Biomol. Chem., 2020, 18, 8572.³³⁷*

Shankaraiah's research group has actively contributed to ring-opening reactions of isatin spiro-epoxides, particularly with azide nucleophiles. In 2015, they introduced a Cu(I)-pyrrolidinyloxazole-carboxamide **IX** catalysed one-pot click reaction involving spiro-epoxides **433**, sodium azide, and variously substituted *N/O*-linked alkyne precursors. This method produced biologically important 3-hydroxy-3-triazolomethyl oxindoles **484** and **485** (Scheme 61).³⁷⁹

The Cu(I)-catalysed azide–alkyne cycloaddition, known as the 'click reaction,' is esteemed for synthesizing the 1,2,3-triazole moiety.³⁸⁰ The latter work identified an efficient 'pyrrolidinyl-oxazole-carboxamide' ligand that played a critical role in stabilizing the Cu(I)-center and enhancing catalytic activity. The regioselectivity in the azide nucleophile's ring-opening reaction with spiro-epoxides is attributed to increased electrophilicity of the epoxide ring mediated by water's hydrogen bonding.³⁸¹ Additionally, the azide's dipolar interaction with the amide carbonyl further stabilizes the reaction, allowing nucleophilic ring-opening from the less hindered site. The role of Cu(I) coordination with the epoxide ring's oxygen remains crucial in determining regioselectivity.

Later, the Nair research group also disclosed a similar copper iodide-catalyzed one-pot reaction.³⁸² Expanding on the knowledge of regiospecific spiro-epoxide ring-opening with azide nucleophiles, Shankaraiah's group accomplished the synthesis of 1,2,3-triazole-fused spiro-morpholinyl oxindoles *via* an intramolecular azide–alkyne cycloaddition reaction.^{383–389} These compounds, especially one with *N*-ethyl substitution, exhibited significant *in vitro* cytotoxicity, with an IC₅₀ value of 1.87 μM on an A549 (lung) cancer cell line.

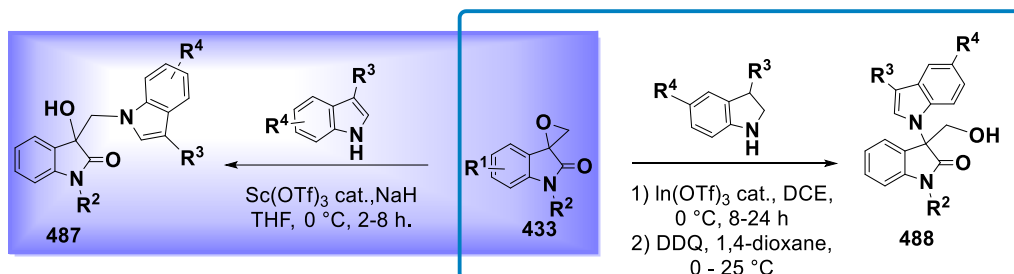


Scheme 61. Synthesis of *N*/*O*-linked 3-hydroxy-3-triazolylmethyl oxindoles and of 3-hydroxy-3-aminomethyl oxindole.

**Readapted from Org. Biomol. Chem., 2020, 18, 8572.*³³⁷

Recently, the Wang group accomplished a catalyst-free, regio- and stereoselective epoxide ring-opening using ammonia gas, enabling the facile production of 3-hydroxy-3-aminomethyl oxindoles **486**.³⁹⁰ This reaction exhibited better performance in methanol over water, albeit yielding a complex mixture. Under optimized conditions, both racemic and enantiopure spiro-epoxy oxindoles **433**, equipped with electron-donating or electron-withdrawing substituents, actively participated in

nucleophilic ring-opening reactions. However, tri- or tetra-substituted epoxides did not generate the desired products. This protocol's practical utility was demonstrated through the synthesis of spirobrassinin (Scheme 61).



Scheme 62. Lewis-acid-catalysed nucleophilic ring-opening reaction of spiro-epoxy oxindole with indoles.
*Readapted from *Org. Biomol. Chem.*, 2020, 18, 8572.³³⁷

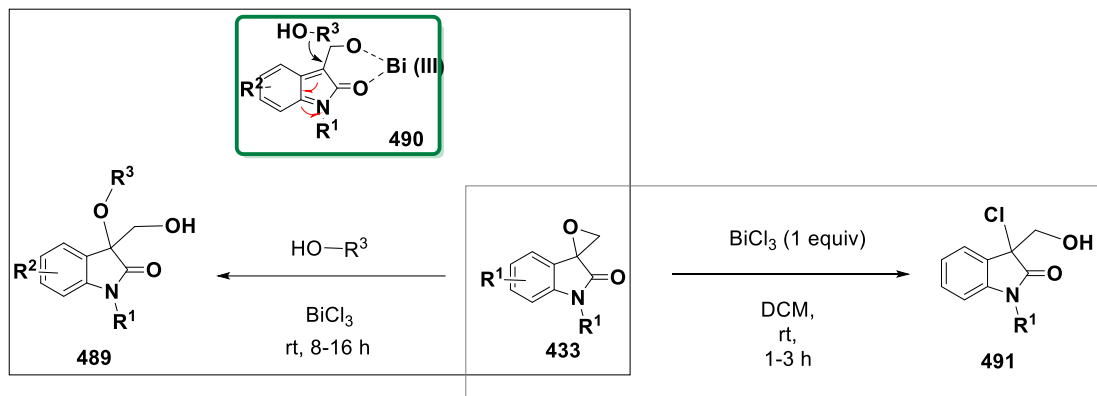
Typically, the Lewis acid-catalysed nucleophilic ring-opening of spiro-epoxide with indoles occurs at the more hindered site, specifically the C-3 quaternary centre of the oxindole ring, with the C-3 position of indole responsible for nucleophilic attack.³⁶⁶ However, the regio- and chemoselectivity in this ring-opening reaction was altered in the presence of a base.

In 2019, the Hajra group revealed the base-catalysed formation of C(3)–N(1') diindolylmethanes **487** by reacting spiro-epoxy oxindoles **433** with indoles.³⁹¹ Additionally, C(3)–N(1') heterodimeric bisindole **488** derivatives were obtained through direct insertion of an indole/tryptamine unit at the C3-spirocentre of oxindole. However, to bypass the involvement of the C3-carbon of indole during the regioselective ring-opening process, indoline was employed. The oxidant 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) facilitated the aromatization of the indoline ring (Scheme 62).

1.11.2.3 With O-nucleophiles

Ring-opening reactions with O-nucleophiles were explored by Suresh et al., who detailed a straightforward alcoholysis reaction of spiro-epoxy oxindoles. The process involved the use of various aliphatic alcohols and BiCl_3 to initiate the ring-opening of spiro-epoxides, resulting in the formation of 3-hydroxymethyl-3-alkoxy oxindoles **489**. However, attempts using bulky alcohols like *tert*-butyl alcohol and adamantyl alcohol failed to open the spiro-epoxide ring, leading instead to a

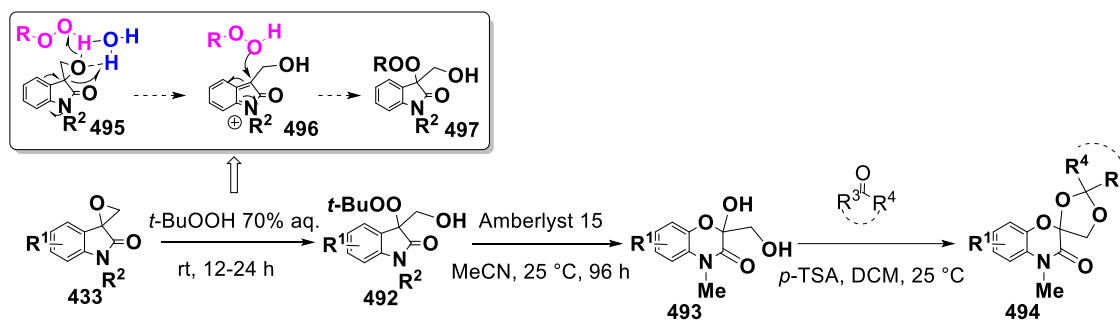
hydrochlorination reaction **491**, which was elucidated in further detail later in another work (Scheme 63).



Scheme 63. Alcoholysis and hydrochlorination of spiro-epoxy oxindole with O-nucleophiles.

*Readapted from *Org. Biomol. Chem.*, 2020, 18, 8572.³³⁷

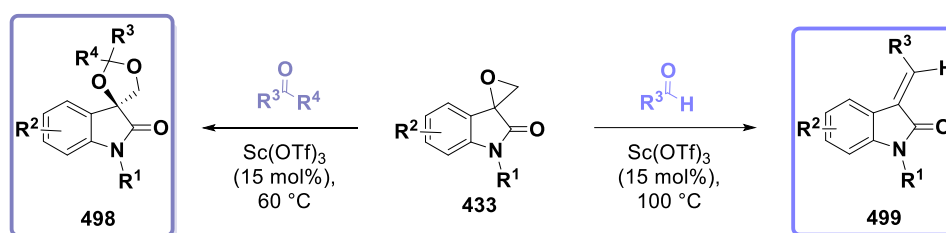
The mechanism underlying this reaction entailed the Bi(III)-mediated activation of the spiro-epoxy oxindole. This activation involved coordination with the carbonyl and oxygen of the epoxide ring, enabling the alcohol attack at the hindered site to generate the alkoxy product.³⁹² This intricate process was thoroughly explained in their study.



Scheme 64. Hajra's catalyst-free spiro-epoxide ring-opening reaction with TBHP.

*Readapted from *Org. Biomol. Chem.*, 2020, 18, 8572.³³⁷

Mechanistically, the Hajra group devised an efficient, catalyst-free spiro-epoxide ring-opening protocol employing TBHP (*tert*-butyl hydroperoxide).³⁹³ This protocol selectively produced 3-hydroxymethyl-3-*tert*-butylperoxy oxindoles **492**, which subsequently underwent rearrangement promoted by Amberlyst-15 to yield 2,2-disubstituted-1,4-benzoxazinones **493**. TBHP, along with water, activated the epoxide ring through hydrogen bonding, leveraging its mild acidity. This activation led to the formation of the indolone intermediate, which upon hydroperoxide nucleophilic attack, furnished the ring-opening product (Scheme 64).



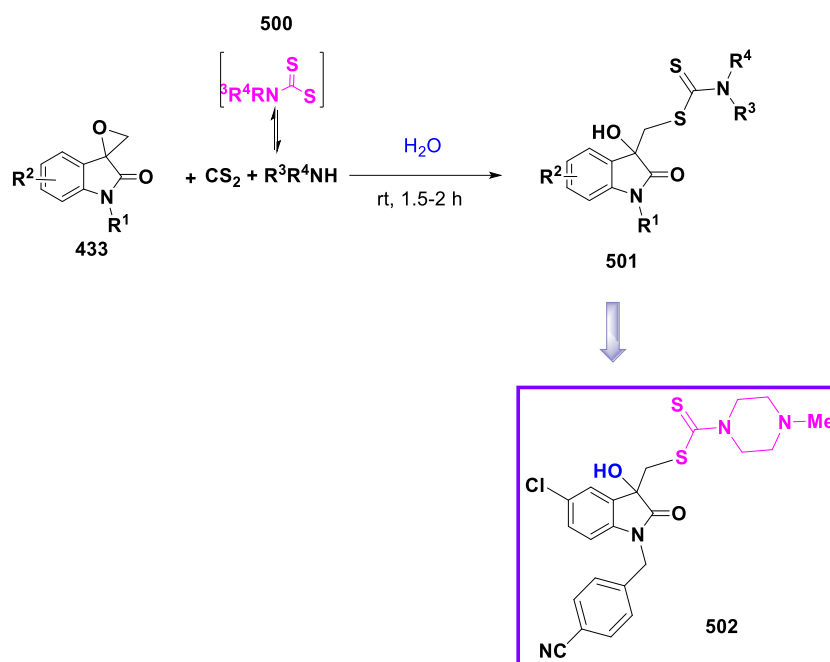
Scheme 65. Li's protocol involving ketones and aldehydes with $\text{Sc}(\text{OTf})_3$.

*Readapted from *Org. Biomol. Chem.*, 2020, 18, 8572.³³⁷

Li et al. revealed a reaction of compound **433** with ketones in the presence of $\text{Sc}(\text{OTf})_3$, resulting in the formation of spiro[[1,3]dioxolane-4,3'-indolin] derivatives **498**. Surprisingly, when aromatic aldehydes were substituted for ketones, the reaction underwent an unprecedented rearrangement, yielding 3-alkylidene oxindoles **499**. An array of cyclic and acyclic aliphatic ketones exhibited smooth reactivity under optimized conditions. However, acetophenone and benzophenone failed to yield the desired product. This reaction also displayed remarkable stereoselectivity, exclusively producing *E* isomers.³⁹⁴

1.11.2.4 With S-nucleophiles

Ring-opening reactions with S-nucleophiles were unveiled by Shankaraiah's research group in 2018, when they established an atom-economic, one-pot protocol to synthesize 3-hydroxy-oxindolino-dithiocarbamates **500** from the reaction of compound **433** with dithiocarbamates.³⁹⁵ This tandem reaction of secondary amines, CS_2 , and spiro-epoxides proceeded smoothly under a catalyst-free aqueous environment. Mechanistically, the reaction involved the *in situ* generation of the dithiocarbamate nucleophile from secondary amines and CS_2 (Scheme 66).

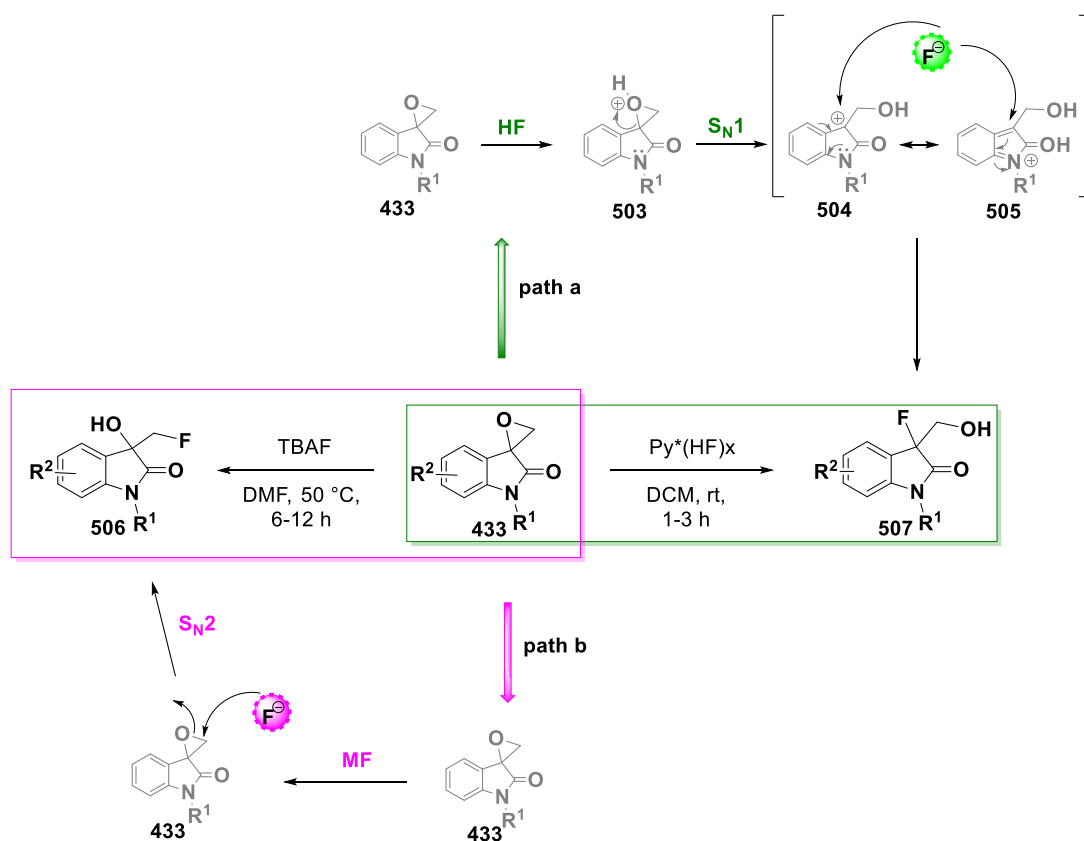


Scheme 66. Shankaraiah's ring-opening reaction of spiro-epoxy oxindole with S-nucleophile.
 *Readapted from *Org. Biomol. Chem.*, 2020, 18, 8572.³³⁷

The aqueous environment played a crucial role by mediating the activation of both reactants through hydrogen bonding, thereby enhancing the electrophilicity of the epoxide ring. Eventually, the activated dithiocarbamate underwent nucleophilic attack at the less hindered site of compound **433**, leading to the formation of the desired product. As part of the current ongoing research program aimed at discovering oxindole-based anticancer compounds,^{339, 396-398} evaluating these hybrids against various cancer cell lines. Compound **502** exhibited noteworthy in vitro cytotoxicity against breast cancer cells (MCF-7), demonstrating an IC₅₀ value of 2.1 ± 0.4 μM.

1.11.2.5 With halogen nucleophiles

Ring-opening reactions with halogen nucleophiles have seen recent advancements by Hajra et al., achieving nucleophilic fluorination of spiro-epoxy oxindoles under metal/catalyst-free conditions.³⁹¹ Notably, the regioselectivity during the ring-opening was reversed based on the fluorinating reagent used. Py·(HF)_x (Olah's reagent) mediated fluorination predominantly at the more hindered quaternary carbon of compound **433**, yielding 3-fluoro-3-hydroxymethyloxindoles **507** (Scheme 67).



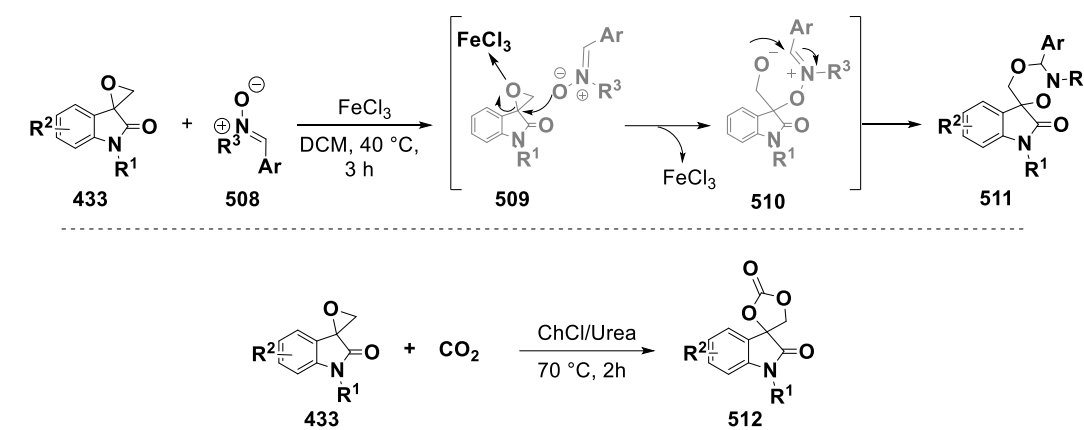
Scheme 67. Hajra's ring-opening reaction of spiro-epoxy oxindole with halogen nucleophiles.
 *Readapted from *Org. Biomol. Chem.*, 2020, 18, 8572.³³⁷

Conversely, tetrabutylammonium fluoride (TBAF)-promoted fluoride addition occurred at the less hindered site of the epoxide ring, resulting in the production of 3-fluoromethyl-3-hydroxyoxindoles **506**. The variation in regioselectivity was attributed to the nature of the fluorinating agents used, combined with the choice of solvent. Olah's reagent, being acidic, protonated the epoxide oxygen, favouring ring opening through the S_N1 mechanism, allowing fluoride ion attack at the C3 quaternary centre of the intermediate (path a). In contrast, in the absence of acidic conditions, fluoride ions directly attacked the primary sp^3 -carbon of epoxide **433** via an S_N2 pathway, leading to the formation of 3-fluoromethyl-3-hydroxyoxindole **506** (path b) (Scheme 67).

Additionally, Suresh et al. disclosed a $BiCl_3$ -catalyzed hydrochlorination reaction alongside their alcoholysis of spiro-epoxy oxindole **433**. In a water medium, $BiCl_3$ dissociates into bismuth oxychloride and two moles of hydrochloric acid. The *in situ* generated HCl acted as a nucleophile, favouring the regioselective ring-opening reaction to yield compound **491**.³⁹²

1.11.3 *Cyclo-addition reactions of spiro-epoxy oxindoles*

Cycloaddition reactions involving spiro-epoxy oxindole have seen recent innovations in different methodologies. Yu et al. reported a FeCl₃-catalyzed spiroannulation of spiro-epoxy oxindoles **433** with nitrones **508**, leading to the production of spiro[1,4,2-dioxazinan] oxindoles **511**. This reaction proceeded *via* a FeCl₃-mediated S_N2 ring-opening mechanism, involving the nitrone oxygen attacking the quaternary carbon of oxindole **509**. The subsequent intramolecular cyclization of intermediate **510** resulted in the desired spiro-product **511** (Scheme 68).³⁹⁹



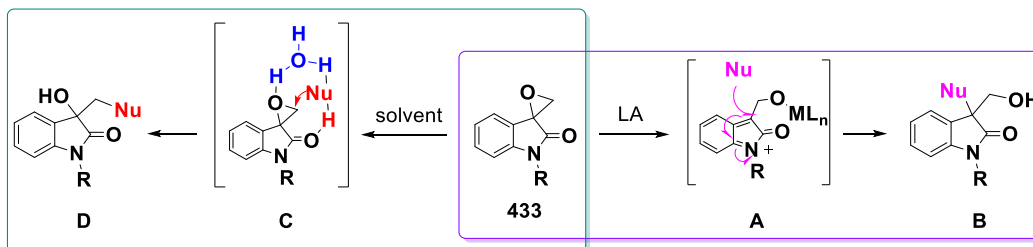
Scheme 68. Yu's spiroannulation and Tak's catalyst-free ring expansion.

*Readapted from *Org. Biomol. Chem.*, 2020, 18, 8572.³³⁷

Tak and colleagues developed a catalyst-free ring-expansion of spiro-epoxides with CO₂ using a deep eutectic solvent (DES) (Scheme 68).⁴⁰⁰ DES, known for its eco-friendliness and biodegradability, was easily synthesized by combining appropriate molar ratios of a hydrogen bond donor and acceptor.⁴⁰¹ The environmental impact of this protocol was measured by a low Sheldon E-factor of 90. Interestingly, the DES was recyclable, allowing up to four reaction cycles without significant yield loss. Similarly, Suresh et al. reported a similar ring-expansion reaction catalysed by a metal-organic framework (CoMOF-2) under ambient conditions.⁴⁰²

The regioselectivity of the spiro-epoxide ring-opening is influenced by several factors, including solvent, catalyst, and the type of nucleophiles used. Two key intermediates, A and B, have been proposed to determine the regioselectivity of the reaction. Lewis acids such as Sc(OTf)₃ and BF₃-OEt₂ facilitate the ring-opening from the more hindered site *via* the indolone intermediate A. Conversely, polar solvents such as water alter the regioselectivity by hydrogen bonding with the epoxide oxygen and the oxindole amide. Additionally, the reaction of carbon nucleophiles often requires a Lewis acid (except NaCN), leading to ring-opening from the more hindered site. On the other hand, most hetero

nucleophiles (N and S) can access the epoxide ring from the less hindered site without the need for a catalyst (Scheme 69).

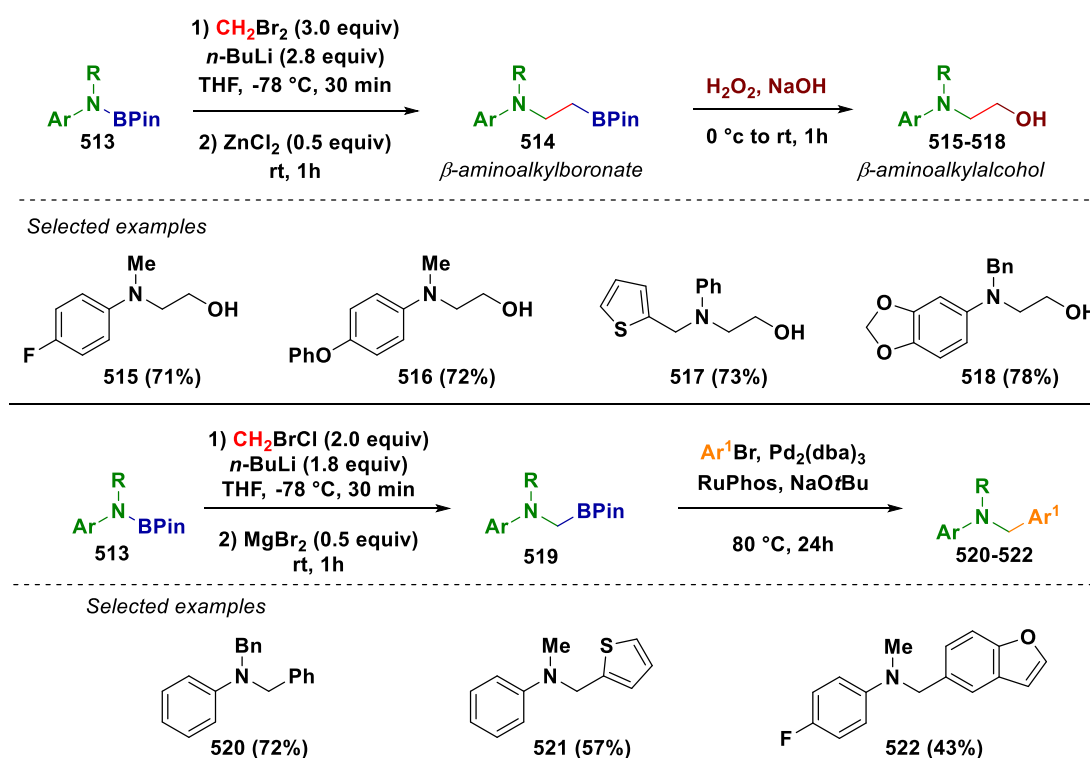


Scheme 69. Regioselectivity's variation in ring-opening reaction of spiro-epoxy oxindole.

*Readapted from *Org. Biomol. Chem.*, 2020, 18, 8572.³³⁷

1.12 Recent applications of lithium carbenoids in the homologation of boron electrophiles

Dong and colleagues recently published an intriguing study on the synthesis of α - and β -boron-substituted tertiary amines through Aza-Matteson reactions involving carbenoid insertions into aminoboranes **513** in a single step (Scheme 70).⁵¹ By optimizing the reaction conditions, they achieved selective carbon insertion into the N-B bonds of aminoboranes, simply by adjusting the leaving group in the carbenoid and the Lewis acid activator. The versatility of this methodology was demonstrated through the derivatization of complex amine-containing bioactive compounds. For the desired compounds requiring double insertion, bromomethyl lithium served as the carbenoid, and ZnCl₂ acted as the Lewis acid activator. To facilitate yield calculation, the β -aminoalkylboronates, which were challenging to isolate *via* chromatography, underwent in situ oxidation to the corresponding alcohols. The study encompassed a wide range of substrates, including complex biologically active molecules (Scheme 70). In the case of mono methylene insertion, chloromethyl lithium was utilized as the carbenoid, and MgBr₂ as the Lewis acid activator. Due to the instability of α -aminoalcohols resulting from the oxidative workup, the α -aminoboronates were converted to 1-arylmethyl amines via Suzuki coupling (Scheme 70).



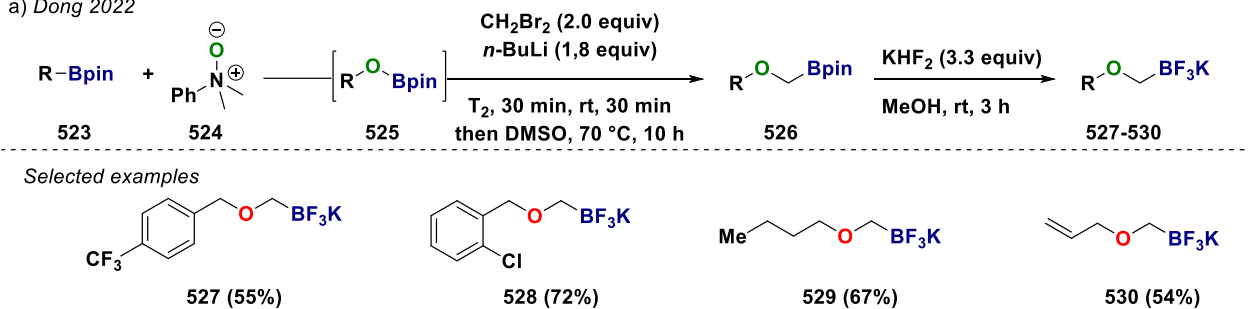
Scheme 70. Dong's double and mono-homologation of N-B functionalities.

*Readapted from *Homologation Reactions: Reagents, Applications, and Mechanisms*.¹⁵

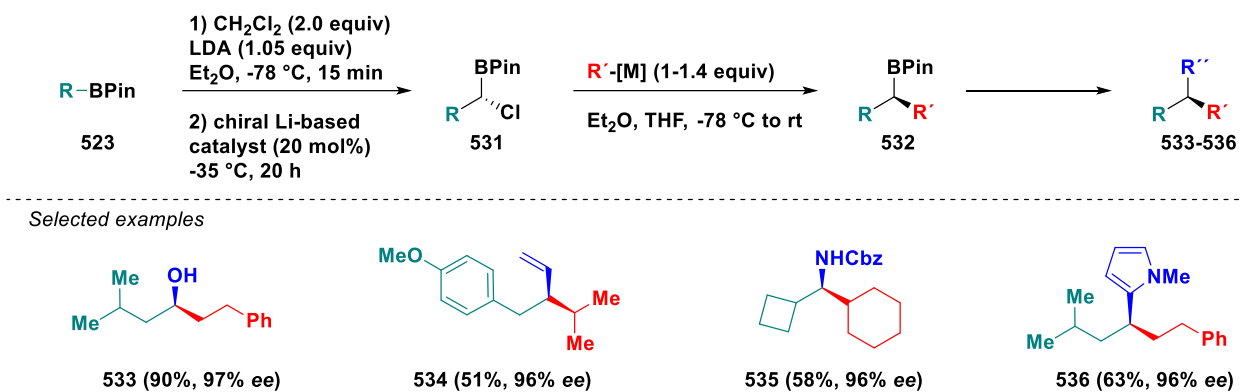
In 2022, the same research group reported a novel strategy for ether synthesis involving sequential oxygen insertion into the C-B bond of boronates ("O-insertion") and carbenoid insertion into the O-B bond of the resulting borate esters ("C-insertion"), referred to as the oxa-Matteson reaction.⁴⁰³ This approach enabled the sequential oxygen carbenoid insertion into various alkyl- and arylboronates, providing access to a broad range of boron-substituted ethers (Scheme 71). *N,N*-Dimethylaniline oxide **524** proved to be the most efficient reagent for the oxygen transfer into the C-B bond, ensuring complete conversion into the desired products. The carbenoid insertion was achieved using bromomethyl lithium, generated in situ from dibromomethane and *n*-BuLi, with THF and DMSO as co-solvents. The potential of the oxa-Matteson reaction was demonstrated through the synthesis of diverse functional ethers, the asymmetric synthesis of an acetyl-CoA-carboxylase inhibitor, and the programmable construction of polyethers (Scheme 71).

In 2021, Jacobsen and colleagues reported the enantioselective catalytic 1,2-boronate rearrangements for the preparation of α -chloro pinacol boronic **531** esters using dichloromethane and suitable boronic esters **523** (Scheme 71).⁴⁰⁴ These chiral building blocks underwent two sequential stereospecific transformations, leading to a wide variety of trisubstituted stereocenters. The lithium-isothiourethane-boronate complex was identified as a highly enantioselective catalyst (up to 94-95% *ee*) favoring a rearrangement *via* a dual-lithium-induced chloride abstraction (Scheme 71). The scope of the reaction was analyzed in terms of the preparation of α -chloro pinacol boronic esters. The synthetic utility of the prepared α -chloro pinacol boronic esters was demonstrated through a two-step procedure involving the 1,2-boronate rearrangement followed by a second enantiospecific rearrangement to achieve enantioenriched secondary boronic ester products using appropriate Grignard reagents. Furthermore, the secondary boronic ester products underwent further reactions, leading to a wide array of derivatives with diverse C-C, C-N, and C-O bonds in high yields. This latter pathway exploited previous carbon-boron transformations.

a) Dong 2022



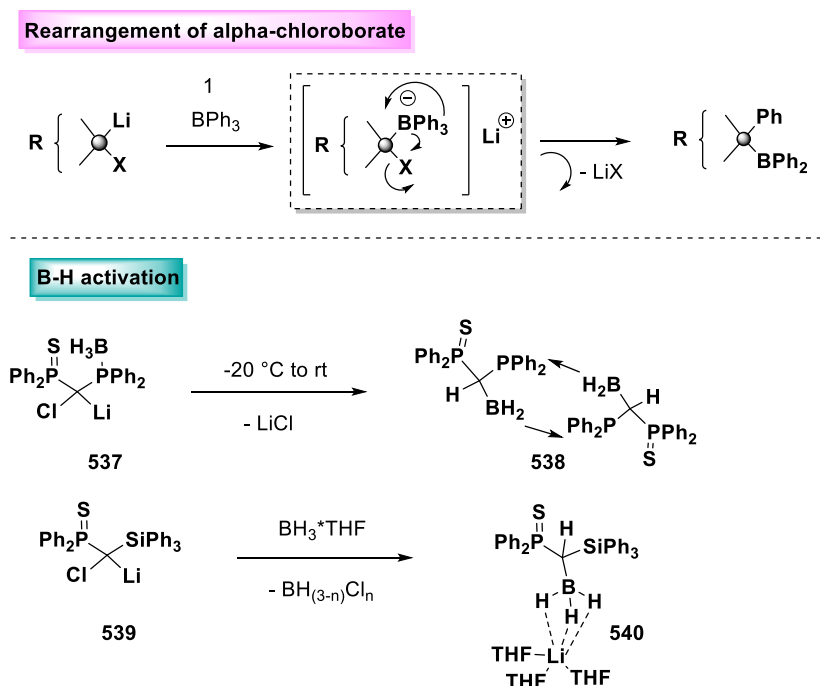
b) Jacobsen 2021



Scheme 71. Dong's sequential O-and-then-C insertion into C-B bonds and Jacobsen's 1,2-boronate rearrangements resulting in α -chloromethyl-pinacolboronates. *Readapted from Homologation Reactions: Reagents, Applications, and Mechanisms.¹⁵

1.13 Exploring Lithium-Boron chemistry: interactive protocols in contemporary synthesis

While carbenoids are largely employed in metalorganic synthesis, their reactivity towards main group element compounds and transition metals is less investigated. In the case of main group element chemistry, boron compounds are the most studied in the field of carbenoid chemistry.⁴⁰⁵ In the 1960s, Köbrich reported the homologation of triphenylborane via a 1,2-metalate rearrangement using Li/Cl carbenoids.⁴⁰⁶⁻⁴⁰⁷ This transformation's potential in organic synthesis has been recognized only recently, particularly with the use of boronates,⁴⁰⁸ diboranes, and silylboranes,⁴⁰⁹⁻⁴¹⁰ which allow for further functionalizations (Scheme 72). Researchers like Aggarwal and Blakemore have expanded the lithiation–borylation reaction, developing stereoselective procedures and iterative methods to build long alkyl chains.^{67-68, 411-415} Lithium carbamates and benzoates, due to their higher stability, have been more successfully employed in this chemistry.⁴¹⁶⁻⁴²⁰



Scheme 72. Köbrich's homologation of triphenylborane and Mezailles's B-H activation

Carbenoids have also been found to insert into the B–H bond of simple BH_3 Lewis base adducts. In 2013, Mézailles and So reported the phosphino-borane functionalized Li/Cl system **537**, which undergoes intramolecular B–H bond activation at temperatures above -20°C , forming a stabilized borane **538**.⁴²¹⁻⁴²² This reactivity was extended to intermolecular activation using $\text{BH}_3 \cdot \text{THF}$. Unlike other systems, the Li/Cl silyl substituted carbenoid **539** did not form an analogous borane but instead delivered a borate **540**.⁴²³ These reactions proceed via a stepwise mechanism involving nucleophilic

attack and H/Cl exchange, with the activation barrier determined by the stability of the Lewis base adduct (Scheme 72).

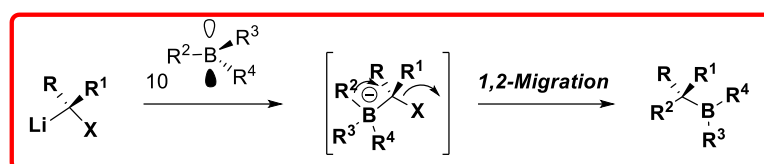
The formation of new carbon-carbon bonds with precise control over stereochemistry is a fundamental pursuit in synthetic organic chemistry, reflecting the field's constant quest for efficient methods with high selectivity. Particularly challenging is the selective incorporation of stereogenic elements into complex molecules, a task that continually evolves with advancements in synthesis methodologies.⁵⁰

The homologation of boronic esters using chiral organometallic reagents represents a powerful synthetic strategy in organic chemistry to reach the mentioned purpose. Two main classes of such reagents have emerged as particularly valuable: lithiated alkyl chlorides, derived from chloro sulfoxides, and lithiated carbamates/benzoates, obtained *via* asymmetric deprotonation of the corresponding alkyl carbamates/benzoates. Among these, lithiated carbamates and benzoates exhibit a broader substrate scope and are more readily accessible. This method enables the incorporation of primary alkyl substituents, where the β -carbon can be primary or secondary but not tertiary due to slow deprotonation kinetics. The resulting secondary boronic esters can either be isolated or used directly in subsequent homologation reactions, akin to a molecular assembly line process. Secondary alkyl carbamates can also be utilized, provided an anion-stabilizing group aids deprotonation.

This allows for the conversion of secondary benzylic, propargylic, or allylic alcohols into tertiary boronic esters with high enantioselectivity *via* their corresponding carbamates. Epoxides and aziridines, possessing good leaving groups at the anionic position, undergo borylation followed by stereospecific 1,2-migration, leading to a diverse array of secondary and tertiary boronic esters with varying functional groups. Addressing the limitation of obtaining simple chiral tertiary boronic esters from secondary alkyl carbamates would significantly expand the synthetic utility of this method. Furthermore, the ability of secondary and tertiary boronic esters to engage in cross-coupling reactions with aryl halides, such as the Suzuki reaction, would further enhance their versatility and applicability in organic synthesis. Following a more detailed exposition of the diverse homologating protocols of boronic esters using the organometallic reagents afore mentioned.⁴²⁴

1.13.1 *The reagent-controlled protocol*

One notable approach, pioneered by Matteson in the 1980s,^{39, 425} involves the homologation of boronic esters bearing a chiral diol. This method, conducted in a two-step sequence comprising the initial addition of dichloromethyl lithium followed by reaction with a Grignard reagent, exhibits exceptional levels of stereocontrol. Matteson's strategy employs a chiral auxiliary within the boronic ester's diol moiety, guiding subsequent transformations through substrate control. Alternatively, a reagent-controlled approach⁴²⁶ utilizes chiral organolithium reagents to generate a related chiral ate complex, which, through a 1,2-metallate rearrangement, evolves into the homologated chiral boronic ester. Leveraging readily available chiral organolithium reagents with high enantiomeric excess, this methodology has proven to be highly effective (Scheme 73).



Scheme 73. Lithiation-borylation with organo-lithiums. *Readapted from *Lithium-Boron chemistry: a synergistic strategy in moder chemistry*.⁴²⁴

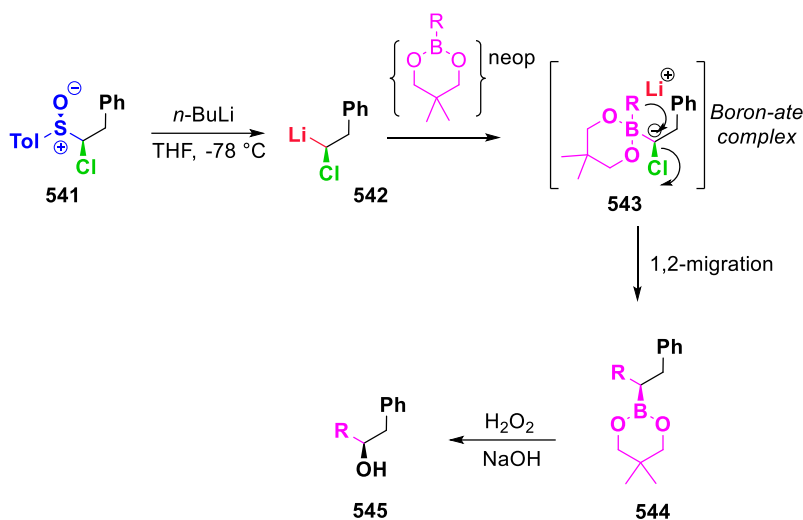
Central to achieving high stereocontrol is the complete retention of configuration during the 1,2-migration, wherein the migrating group adopts an antiperiplanar orientation to the leaving group. Additional factors influencing stereochemical outcomes include the configurational stability of the lithium carbenoid, stereospecific electrophilic substitution with boron, and the temperature dependence of the 1,2-metallate rearrangement to prevent over-homologation issues.

Significant differences exist between boranes and boronic esters in their reactivity and 1,2-metallate rearrangement kinetics. Boranes, being more electrophilic, readily form boron-ate complexes, particularly evident with stabilized organolithium reagents.⁴²⁷ Conversely, boronic ester-ate complexes exhibit slower 1,2-migration due to electron withdrawal by the oxygens, reducing boron's nucleophilicity and migration propensity.

For instance, sulfur ylides readily react with boranes but not boronic esters, highlighting these reactivity disparities. Subsequent sections will delve into the current landscape of reagent-controlled lithiation-borylation methodologies and their diverse applications in organic synthesis, categorized by the nature of the lithium carbenoid.

1.13.1.1 The α -halogen stabilized lithium carbenoids protocol

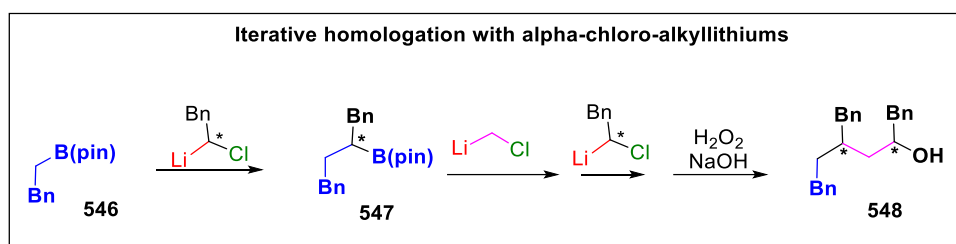
Halogen-lithium carbenoids²² are organometallic species known for their chemical and, if chiral, configurational stability under cryogenic conditions, typically at $-78\text{ }^{\circ}\text{C}$, making them valuable tools in asymmetric synthesis. Blakemore and colleagues⁶⁷ developed a stereospecific, reagent-controlled homologation of boronic esters using enantioenriched Li-Cl carbenoids. The carbenoid **542** was synthesized from enantioenriched α -chlorosulfoxide **541** *via* stereospecific sulfoxide-lithium exchange, employing the methodology pioneered by Hoffmann.⁷⁵ Due to the chemical instability of **542**, Barbier conditions were employed for its preparation. Consequently, the addition of *n*-BuLi to a mixture of neopentyl boronic ester and sulfoxide **541** at $-78\text{ }^{\circ}\text{C}$ yielded intermediate boron-ate complex **543**, which upon warming to $0\text{ }^{\circ}\text{C}$ underwent 1,2-rearrangement to furnish homologated boronic esters **544**. Subsequent oxidative workup afforded alcohols **545** in good yields and high levels of enantioselectivities (Scheme 74).



Scheme 74. Reagent-controlled homologation of boronic esters with enantioenriched Li-Cl carbenoids.

*Readapted from *Lithium-Boron chemistry: a synergistic strategy in modern chemistry*.⁴²⁴

This method marked the first asymmetric homologation of a boronic ester *via* reagent control. Furthermore, this approach was extended to more robust pinacol boronic esters.⁶⁸ While the substrate scope for boronic esters was broad, encompassing various primary and secondary aliphatic boronic esters, the scope for carbenoids was somewhat limited. Although a range of primary substrates showed efficacy, secondary and methyl substrates exhibited lower success rates.

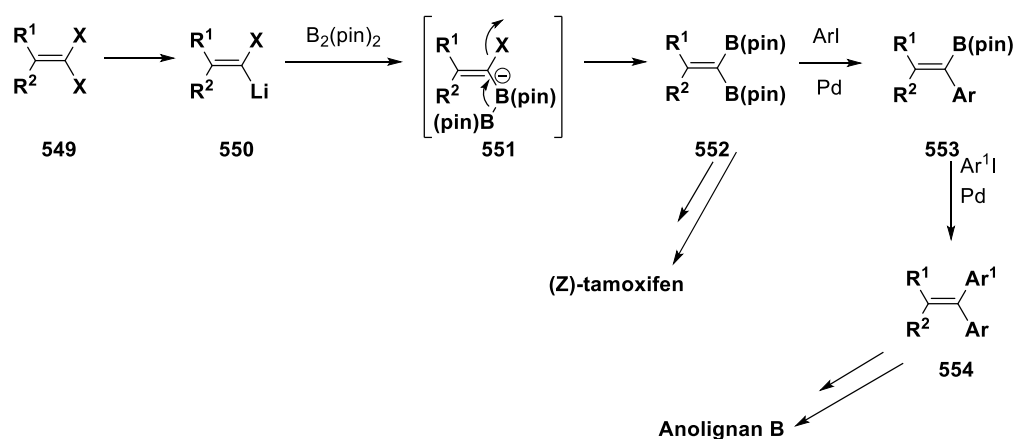


*Scheme 75. Blakemore's iterative homologation of pinacol boronic esters.
Readapted from Lithium-Boron chemistry: a synergistic strategy in moder chemistry.⁴²⁴

Subsequent reports from the same authors focused on the iterative homologation of boronic esters, demonstrating the potential of stereospecific, reagent-controlled homologations for the systematic assembly of enantioenriched products with precise control over both relative and absolute stereochemistry.

1.13.1.2 The alkylidene-type carbenoids protocol

Shimizu⁴²⁸ et al. have showcased the utility of alkylidene-type carbenoids in conjunction with diboron reagents. The process involves generating carbenoid **550** from 1,1-dihaloalkenes **549** or 1-haloalkenes, followed by the addition of bis(pinacolato)diboron [$B_2(\text{pin})_2$]. This sequence yields intermediate boron-ate complex **551**, which, upon 1,2-metalate rearrangement, affords diboryl compounds **552**. Further, palladium-catalyzed cross-coupling of diboryl compounds **552** with aryl iodides leads to the formation of (*E*)-alkenylboronates **553** as single diastereomers.⁴²⁹ Subsequent coupling with a different aryl iodide provides access to tetrasubstituted alkenes **554**. Notably, altering the order of adding the aryl iodides allows for the preparation of either diastereomers of **554**. This methodology finds application in a one-pot synthesis of (*Z*)-tamoxifen from diboryl compound **552** (Schema 76).



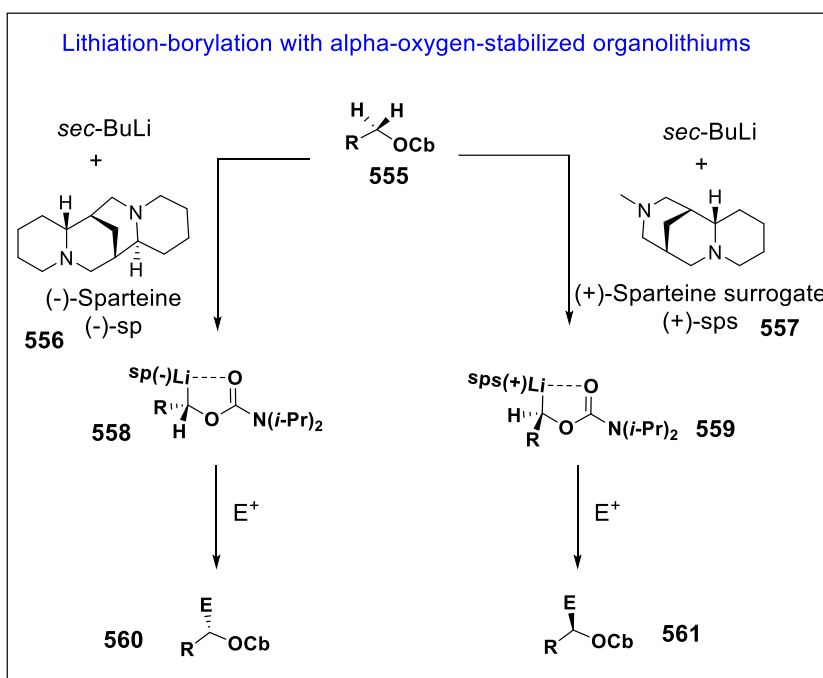
Scheme 76. Homologation of diboron reagents with alkylidene-type carbenoids.
 *Readapted from *Lithium-Boron chemistry: a synergistic strategy in moder chemistry*.⁴²⁴

Furthermore, treatment of diboron species with an excess of 1-bromo-1-lithioethene leads to the formation of 2,3-bis(pinacolatoboryl)-1,3-butadiene *via* a 1,2 migration of intermediate ate complex.⁴³⁰ Palladium-catalyzed cross-couplings of diborylbutadiene enable access to 2,3-difunctionalized 1,3-butadienes, a strategy employed in the synthesis of anolignan B.

1.13.1.3 The α -oxygen stabilized organolithium protocol

The utilization of α -oxy-stabilized organolithiums in reagent-controlled lithiation-borylation has become firmly established due to several key factors:

- As elucidated by Hoppe, their facile generation through stereoselective α -deprotonation with chiral bases like *sec*-BuLi·(–)-sparteine **556**.
- The resultant lithiated species (**558**, **559**) often exhibit configurational stability under cryogenic conditions.
- They demonstrate electrophilic substitution with a notable degree of stereoselectivity (**560**, **561**) (Scheme 77).



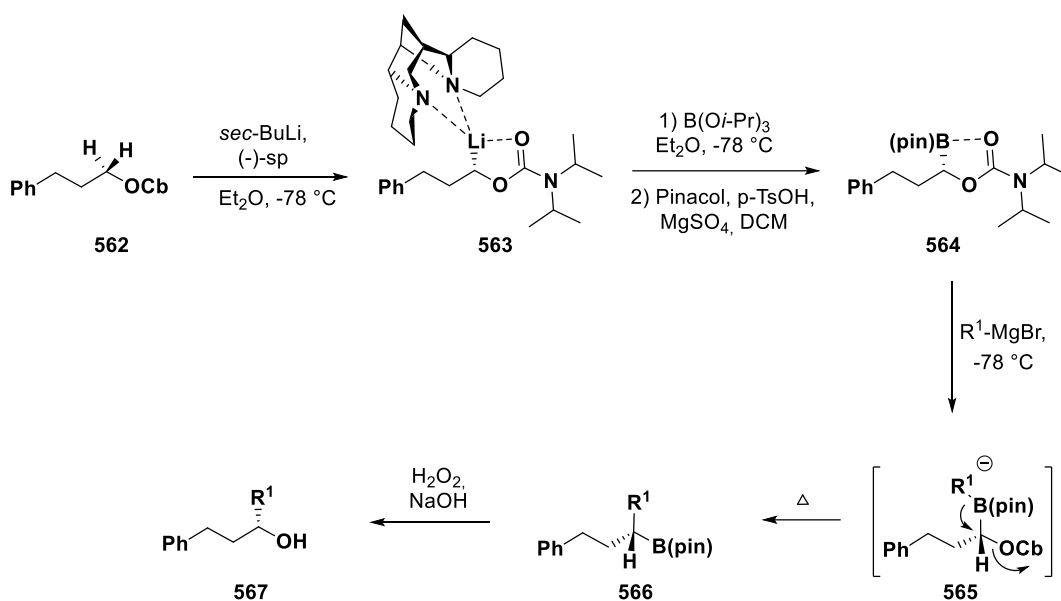
Scheme 77. Deprotonation and electrophilic quench of carbamates.

**Readapted from Lithium-Boron chemistry: a synergistic strategy in moder chemistry.⁴²⁴*

Furthermore, following the development of the (+)-sparteine surrogate by O'Brien and colleagues,⁴³¹⁻⁴³² it has become feasible to selectively deprotonate either the pro-S proton (using (-) - sparteine) or the pro-R proton (employing the (+)-sparteine surrogate).⁴³³⁻⁴³⁴

1.13.1.4 The α -lithiated primary carbamate protocol

Hoppe and colleagues extensively investigated the electrophilic trapping of chiral lithiated *N,N* - diisopropyl carbamates (OCb) and demonstrated their selective trapping by boron electrophiles, rendering them as chiral electrophiles in boron-based homologation protocols. Pinacol boronic ester **564** was prepared by trapping enantioenriched lithiated species **563** with triisopropoxyborate [B(Oi - Pr)₃], followed by esterification with pinacol, resulting in high yields and enantioselectivities. Subsequent addition of a Grignard reagent produced the 'boron-ate' complex **565**, which, upon warming in the presence of a Lewis acid, yielded boronic ester **566**. Oxidation of the homologated boronic esters led to highly enantioenriched secondary alcohols **567**.⁴³⁵⁻⁴³⁶ Kocienski⁴³⁷ and Aggarwal⁴³⁸ streamlined this process by directly trapping the lithium carbenoid with a boronic ester preloaded with the desired migrating group. Primary and secondary alkyl and phenyl boron substituents were effective as migrating groups, with both 9-BBN-based trialkyl boranes and pinacol boronic esters being viable options (Scheme 78).

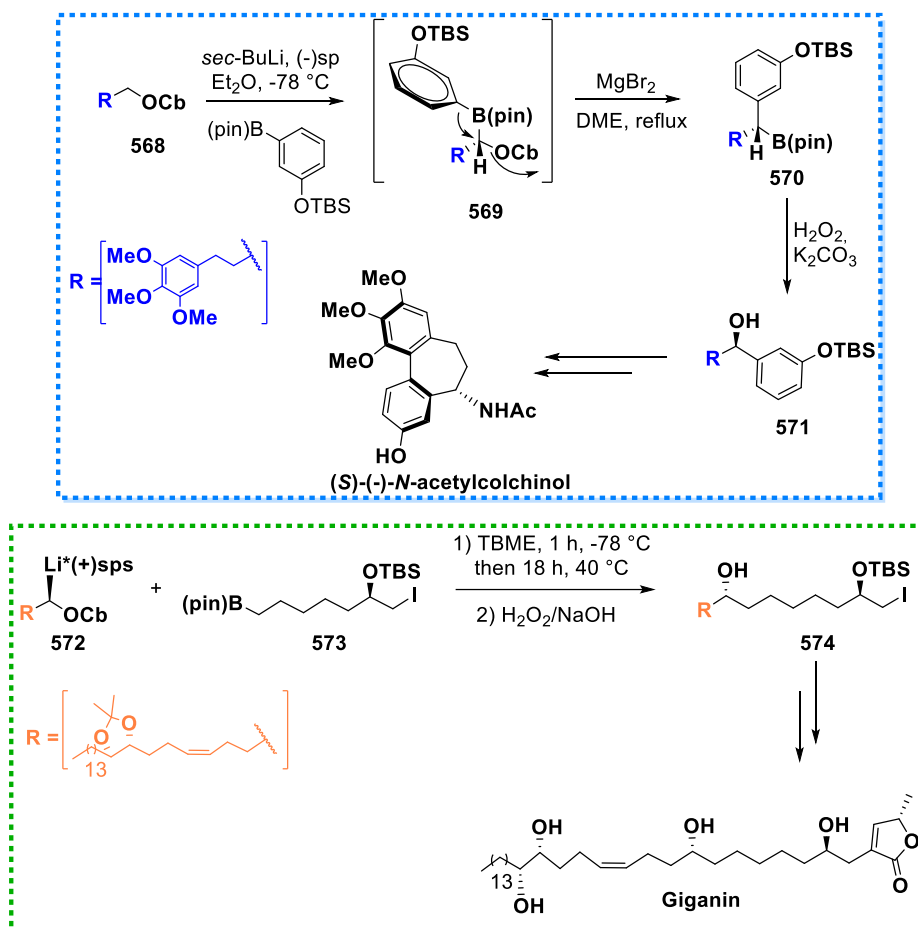


Scheme 78. Addition of Grignard reagents to α-O-boronic esters.

*Readapted from *Lithium-Boron chemistry: a synergistic strategy in modern chemistry*.⁴²⁴

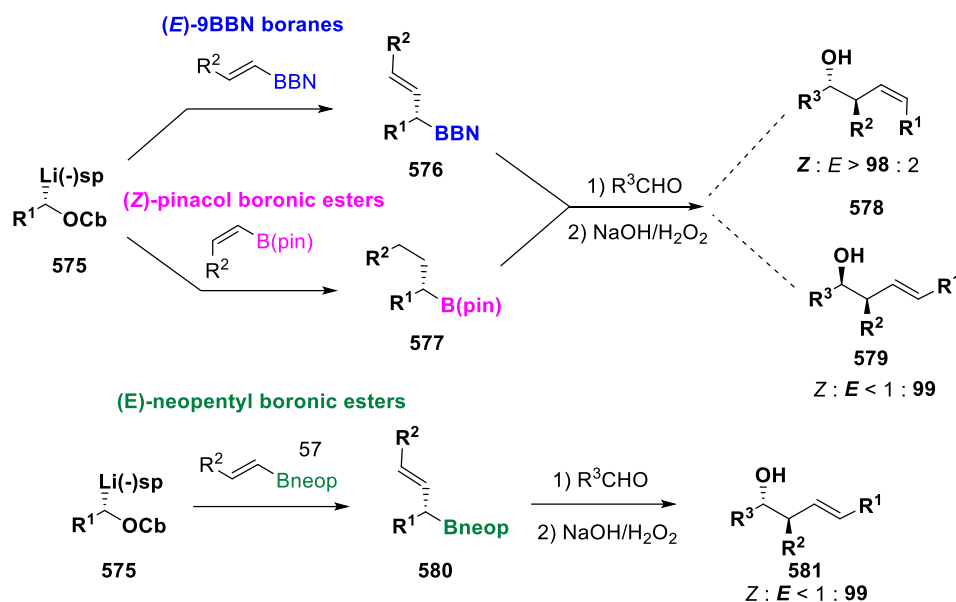
Notably, branching at the α-position of the carbamate was well tolerated, and masked alcohols could also be employed. Several key findings emerged from this investigation, including the slower migration of boronic ester-ate complexes compared to borane-ate complexes and the necessity of refluxing with the Lewis acid MgBr₂ to facilitate the effective rearrangement of arylboronic esters. Furthermore, MgBr₂ was found to enhance the enantioselectivity of the reaction with Ph-9-BBN borane. All reactions proceeded with retention of stereochemistry, and the carbamates remained configurationally stable under the reaction conditions, with the 1,2-metallate rearrangement being stereospecific.

The applicability of this reaction in the total synthesis of complex molecules was demonstrated by Kocienski in the total synthesis of (*S*)-(-)-*N*-acetylcolchinol and by Aggarwal in the total synthesis of giganin.⁴³⁹ The lithiation-borylation reaction was utilized as a key step in both syntheses, resulting in high yields and excellent levels of selectivity. Moreover, Aggarwal showcased the potential for multiple sequential homologations using this methodology in the synthesis of the insect pheromone (+) - faranal,⁴⁴⁰ highlighting its versatility and efficiency in complex molecule synthesis (Scheme 79).



Scheme 79. Total synthesis of (S)-(-)-N-acetylcolchinol and Giganin via lithiation-borylation.
 *Readapted from *Lithium-Boron chemistry: a synergistic strategy in modern chemistry*.⁴²⁴

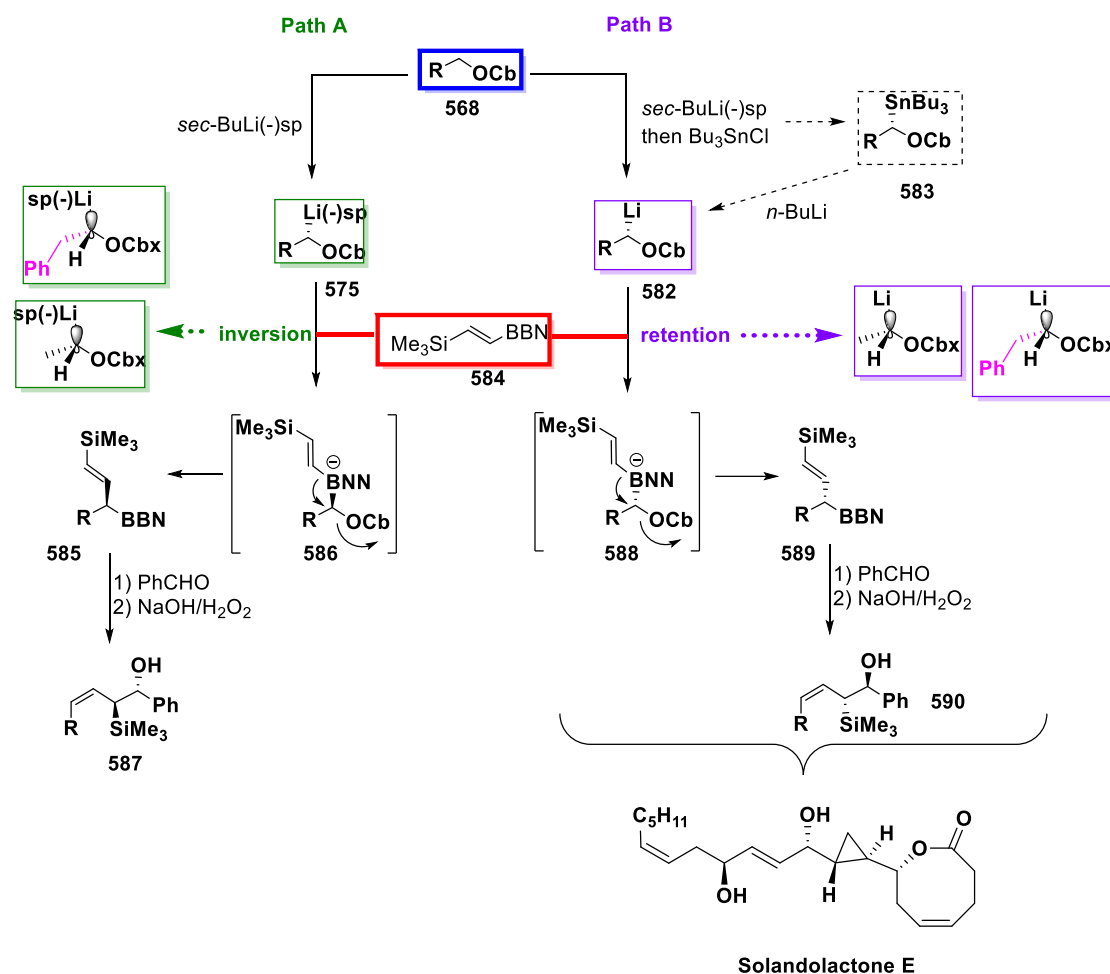
Apart from natural product synthesis, the homologation of organoborons with lithiated primary carbamates has found application in the synthesis of chiral allylboron reagents, crucial for asymmetric allylboration of aldehydes. Aggarwal's investigation⁴⁴¹ revealed that both the syn/anti and *E/Z* stereochemistry of the homoallylic products could be manipulated by the *E/Z* geometry of the boron reagent and the boron substituent's nature. Specifically, (*E*)-vinyl 9-BBN boranes yielded the *Z*-anti isomer **578**, (*Z*)-vinyl pinacol boronic esters provided the *E*-syn isomer **579**, while the less hindered (*E*)-vinyl neopentyl boronic ester afforded the *E*-anti isomer **581**. The substrate scope encompassed primary and secondary alkyl carbamates and primary alkyl allylic boranes. Reaction with benzaldehyde, cyclohexanecarboxyaldehyde, and *n*-butyraldehyde yielded good yields with excellent enantiomeric and diastereomeric ratios (Scheme 80).



Scheme 80. Synthesis of allylic boranes and boronic esters and their application in the allylboration of aldehydes.

*Readapted from *Lithium-Boron chemistry: a synergistic strategy in modern chemistry*.⁴²⁴

Exceptions were observed when both R¹ and R² were methyl, resulting in a low enantiomeric ratio of the major diastereomer. However, utilizing a diamine-free lithiated carbamate from tin-lithium exchange of the corresponding stannane allowed excellent enantioselectivities in such cases. This methodology was extended to create chiral allylsilanes, valuable reagents in asymmetric reactions. Aggarwal⁴²⁰ and collaborators utilized β -trimethylsilyl vinyl 9-BBN boranes to trap primary lithiated carbamates and produce allylboranes, which upon treatment with benzaldehyde yielded Z-configured anti- β -hydroxyallylsilanes. Interestingly, the enantioselectivity of the initial addition of the lithiated carbamate to the borane was influenced by the chelating diamine on the lithiated carbamate. Bulky diamines led to inversion, while diamine-free additions resulted in stereochemistry retention.



Scheme 81. Lithiation-borylation-allylboration of carbamates and its application in the synthesis of Solandolactone E.

*Readapted from *Lithium-Boron chemistry: a synergistic strategy in modern chemistry*.⁴²⁴

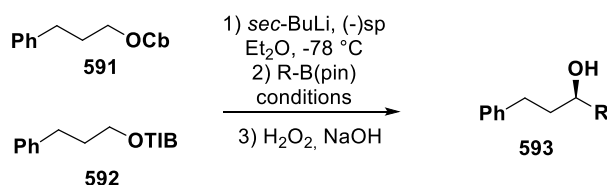
This methodology was applied to the total synthesis of decarestrictine D and solandelactone E. In the synthesis of solandelactone E,⁴⁴² enantioenriched stannane was utilized as a latent lithium carbenoid. Lithiation-borylation with borane, followed by treatment with aldehyde, afforded the product in 73% yield. Completion of the total synthesis involved epoxidation of the allylsilane and acid-catalyzed rearrangement, resulting in the natural product in 13 steps overall with high enantio- and diastereocontrol (Scheme 81).

1.13.1.5 The α -lithiated benzoate esters protocol

While lithiation-borylation utilizing lithiated carbamates has emerged as a valuable tool in asymmetric synthesis, certain boronic esters exhibit limited efficacy. Some boron substituents, such as methyl and phenyl groups, exhibit sluggish 1,2-metallate rearrangement kinetics. Substituting the carbamate functionality of the carbenoid with a more proficient leaving group has been identified as a strategy

to enhance the migration of these "difficult" substituents. Hindered benzoate esters possess several attributes conducive to their substitution for carbamates in lithiation-borylation: they are straightforward to prepare, readily lithiated at -78°C with similar selectivity levels, yield configurationally stable lithiated species, and the triisopropyl benzoate ester serves as an excellent leaving group.⁴⁴³ Selected examples comparing lithiation-borylation processes employing OCb carbamate **591** and 2,4,6-triisopropylbenzoyl chloride (TIBM) ester **592** are presented in Table 1. While both processes exhibit comparable enantioselectivities, TIB ester reactions often feature shorter reaction times and improved yields (Table 1).

Table 1. Comparison between carbamate and ester in lithiation-borylation.
 *Readapted from *Lithium-Boron chemistry: a synergistic strategy in moder chemistry*.⁴²⁴



Substrate	R	Conditions	Yield (%)	er
592	Me	A	76	96 : 4
591	Me	C	50	95 : 5
592	(CH ₂) ₂ CN	B	46	97 : 3
591	(CH ₂) ₂ CN	C	0	n.d.
592	(CH ₂) ₂ CO ₂ tBu	B	63	96 : 4
591	(CH ₂) ₂ CO ₂ tBu	C	35	93 : 7
592	Ph	A	79	96 : 4
591	Ph	C	88	99 : 1

Conditions:
A: 2-h reflux.
B: 16-h reflux.
C: 16-h reflux, MgBr₂, MeOH (2 equiv.).

1.13.1.6 The α -lithiated benzylic carbamates protocol

Although primary benzylic carbamates hold potential utility, their carbanions lack configuration stability (Figure 6). Conversely, carbanions derived from secondary benzylic carbamates exhibit

configuration stability and have been successfully trapped with a variety of electrophiles. Generally, electrophiles capable of lithium complexation, such as MeOH, esters, and carbonates, undergo reactions with retention of configuration. Conversely, electrophiles unable to form complexes with lithium, such as Me₃SiCl and Me₃SnCl, react with inversion. Boron-based electrophiles exhibit a similar behaviour trend: boronic esters, capable of lithium coordination, react with almost complete retention of configuration, while boranes react with nearly complete inversion.

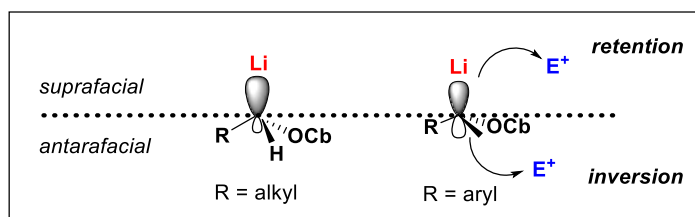


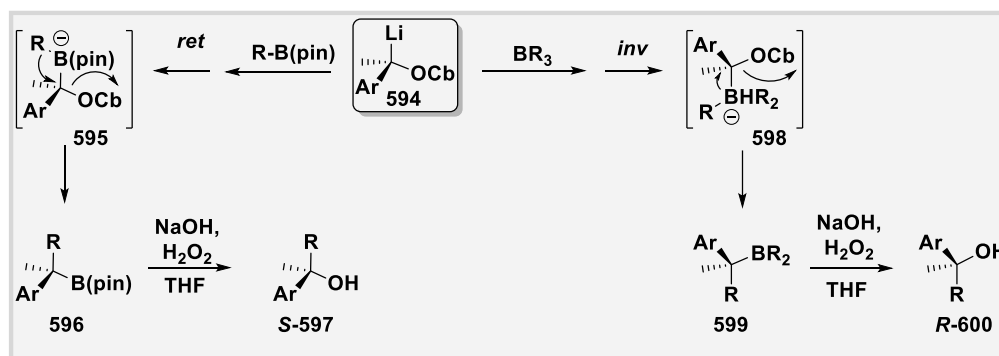
Figure 6. Comparison of electron density between lithiated benzylic carbamates and their alkyl counterparts.

**Readapted from Lithium-Boron chemistry: a synergistic strategy in modern chemistry.⁴²⁴*

This approach facilitates the synthesis of either enantiomer of tertiary alcohols from the same lithiated benzylic carbamate by employing either a boronic ester or the corresponding borane. The organoboron substrate scope is broad; primary and secondary boronic esters and boranes, as well as vinylic, allylic, aromatic, and heterocyclic boronic esters, are compatible (Table 2).^{412, 444} Electron-poor and electron-rich aromatic carbamates, as well as indenyl and tetralyl carbamates, are also effective. Addition of MgBr₂ in MeOH was found to maximize the enantiomeric ratio of product alcohols in cases where the 'ate' complex formation was reversible.

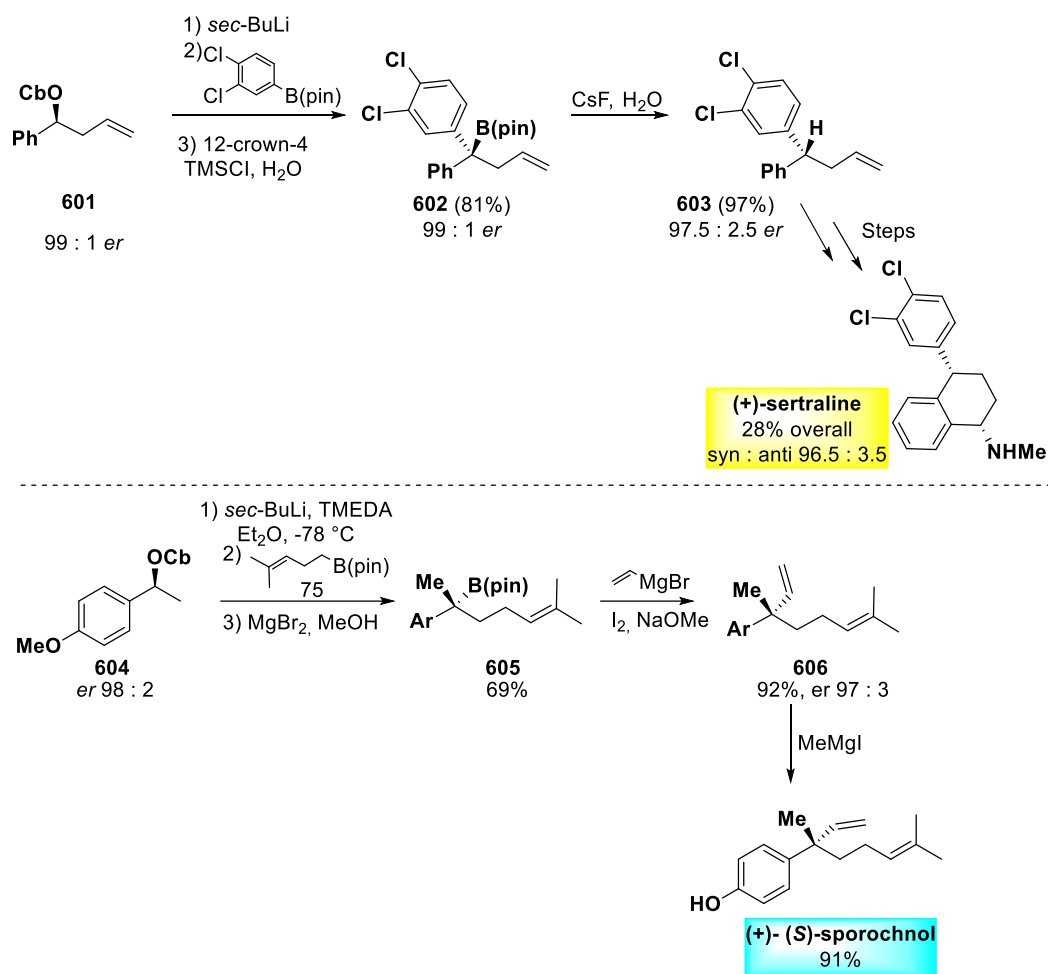
Table 2. Stereoselectivity in the lithiation-borylation of benzylic carbamate with boronic esters and boranes.

*Readapted from *Lithium-Boron chemistry: a synergistic strategy in modern chemistry*.⁴²⁴



Entry	Ar	Organoboron	Yield (%)	er (S:R)
1	Phenyl	EtB(pin)	95	1 : 99
2	Phenyl	BEt ₃	91	99 : 1
3	Phenyl	<i>i</i> Pr-9-BBN	91	98 : 2
4	Phenyl	CH ₂ =CH-B(pin)	95	1 : 99
5	Phenyl	CF ₃ -C ₆ H ₄ -B(pin)	92	99 : 1
6	Phenyl	2-furyl-B(pin)	94	98 : 2
7	Phenyl	1-Boc-2-indolyl-B(pin)	52	99 : 1
8		EtB(pin)	69	99 : 1
9		BEt ₃	90	5 : 95

The lithiation-borylation of benzylic carbamates found application in the total synthesis of the antidepressant escitalopram,⁴⁴⁵ demonstrating excellent enantioselectivity despite moderate yields. Tertiary boronic esters can be transformed into other functional groups, such as C-H, C-N, and C-C bonds.⁴⁴⁶ This strategy was utilized in several total syntheses, including (+)-sertraline and (+)-erogorgiaene. The lithiation-borylation between carbamates and boronic esters, followed by protodeboration, served as the key sequence in these syntheses, providing high yield and enantioselectivity (Scheme 82).⁴⁴⁷⁻⁴⁴⁸



Scheme 82. Synthesis of Sertraline via lithiation-borylation and of Sporochinol via lithiation-borylation-Zweifel olefination.

*Readapted from *Lithium-Boron chemistry: a synergistic strategy in modern chemistry*.⁴²⁴

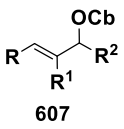
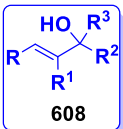
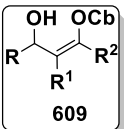
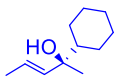
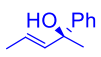
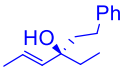
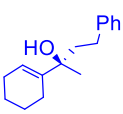
Moreover, the lithiation-borylation of benzylic carbamates offers the opportunity to create all-carbon quaternary stereocenters. For instance, subjecting tertiary boronic esters to Matteson homologation and Zweifel olefination resulted in highly enantioenriched all-carbon quaternary stereocenters, as demonstrated in the synthesis of (+)-sporochinol (Scheme 82).⁴⁴⁹⁻⁴⁵⁰

1.13.1.7 The α -lithiated allylic carbamates protocol

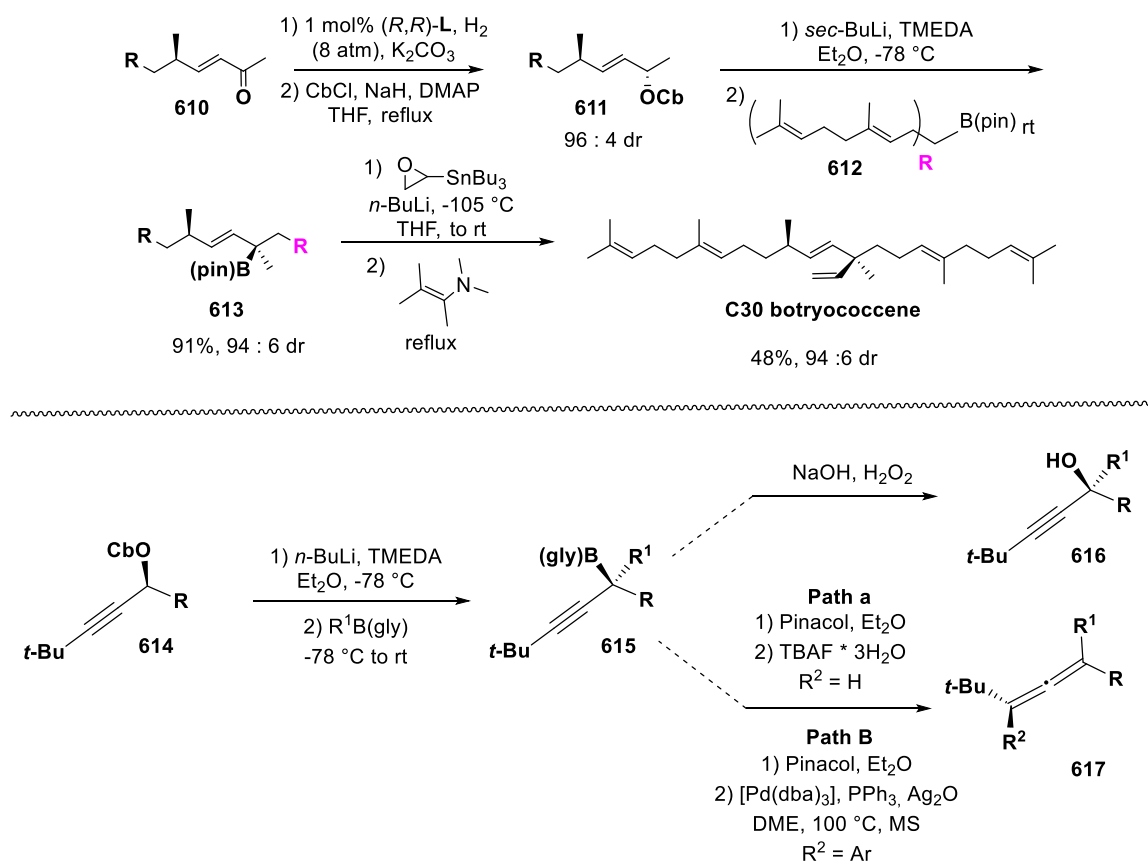
Unlike primary allylic carbamates, secondary allylic carbamates exhibit configuration stability, making them potential candidates for lithiation-borylation chemistry. However, Hoppe observed that trapping lithiated carbamates with various electrophiles often yielded mixtures of α - and γ -addition products.⁴⁵¹⁻⁴⁵² Nevertheless, reactions with boronic esters demonstrated excellent levels of

α - selectivity, likely due to precomplexation of the boronic ester oxygen with the lithium cation (Table 3).

Table 3. Lithiation-borylation of secondary allylic carbamates.
 *Readapted from *Lithium-Boron chemistry: a synergistic strategy in modern chemistry*.⁴²⁴

 607 1) sBuLi, TMEDA 2) R³-Bpin 3) NaOH/H₂O₂  608  609							
Entry	R	R ¹	R ²	R ³	608	608% (er)	609%
1	Me	H	Me	cHex		76 (99 : 1)	0
2	Me	H	Me	Ph		84 (98 : 2)	7
3	Me	H	Et	(CH ₂) ₂ Ph		83 (99 : 1)	<5
4	- (CH ₂) ₄ -		Me	(CH ₂) ₂ Ph		76 (72 : 28)	0

Aggarwal⁴⁵³ successfully employed this methodology in the synthesis of C30 botryococcene, a challenging synthetic target due to its remote stereocenters embedded in a heteroatom-free hydrocarbon. Both the boronic ester **612** and carbamate **611** essential for the key lithiation-borylation step were synthesized from geranyl chloride. The lithiation-borylation reaction proceeded with high yield and produced boronic ester **613** in a 94:6 diastereomeric ratio. Subsequent olefination resulted in complete stereo-retention, leading to the natural product in 13 steps with a 94:6 diastereomeric ratio (Scheme 83).

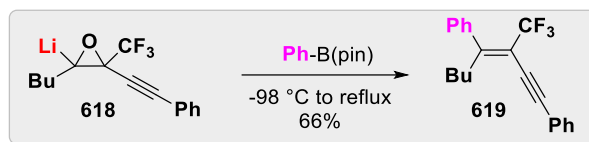


Scheme 83. Synthesis of C30 botryococcene via lithiation-borylation of allylic carbamate and synthesis of propargylic boronic esters. *Readapted from *Lithium-Boron chemistry: a synergistic strategy in modern chemistry*.⁴²⁴

Furthermore, propargylic carbamates **614** have been explored in lithiation-borylation,⁴⁵⁴ offering a route to enantioenriched propargyl tertiary alcohols **616** and tetrasubstituted allenes **617** (Scheme 83). While this extension has not yet been applied in target molecules, it presents an intriguing pathway for further exploration.

1.13.1.8 The α -lithiated epoxide protocol

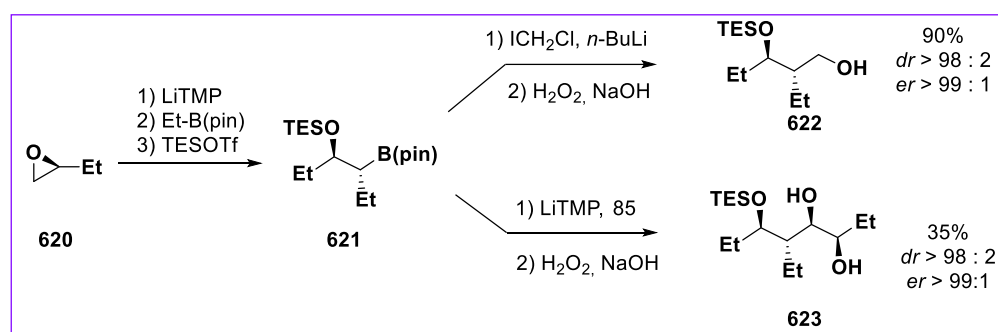
The lithiation of epoxides and subsequent stereospecific trapping with various electrophiles are extensively documented. While their application in lithiation-borylation could theoretically yield 1,3-diols, initial investigations into trapping lithiated epoxides with boron electrophiles by Shimizu suggested a different outcome (Scheme 84).⁴⁵⁵⁻⁴⁵⁶ It was observed that boron-ate complexes of lithiated epoxides underwent 1,2-metallate rearrangement followed by rapid elimination.



Scheme 84. 1,2-Metallate rearrangement-elimination of lithiated epoxide.

*Readapted from *Lithium-Boron chemistry: a synergistic strategy in modern chemistry*.⁴²⁴

However, in the absence of the anion-stabilizing Ph group, the elimination process is slowed down, allowing for the isolation of the boronic ester. For instance, lithiation of epoxide **620** with lithium tetramethylpiperidide (LTMP) followed by borylation with ethyl boronic acid pinacol ester led to the isolation of syn-diol **621** with complete diastereoselectivity after oxidation.⁴⁵⁷ Moreover, the intermediate alkoxyboronates proved to be versatile intermediates, enabling a second homologation to afford 1,2,4-triols **623** with excellent selectivity, while a Matteson homologation yielded 1,3-diols **622** without compromising enantiopurity (Scheme 85).



Scheme 85. Lithiation-borylation of epoxides using boronic esters.

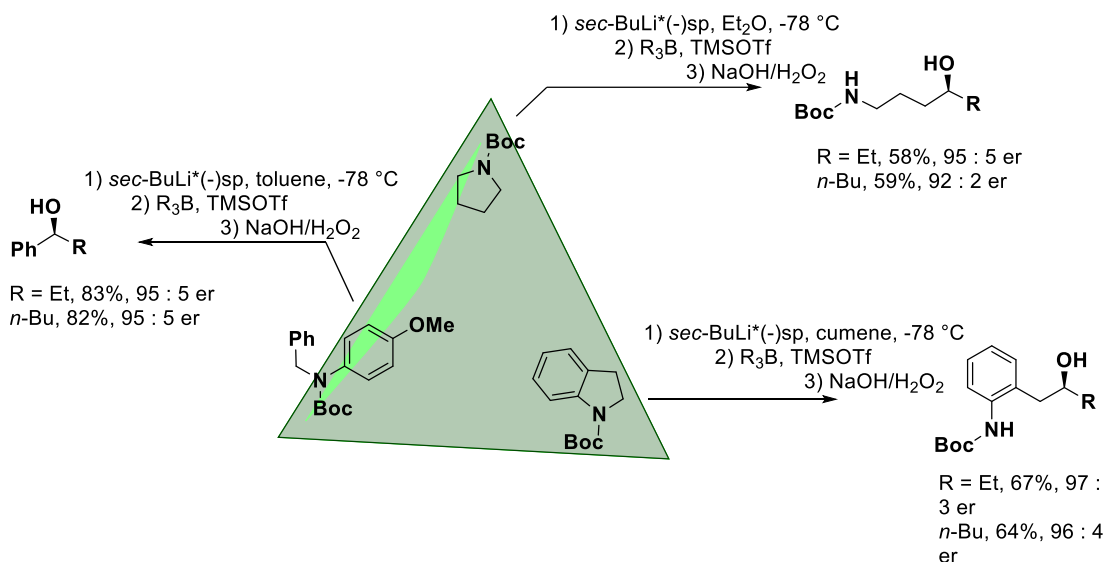
*Readapted from *Lithium-Boron chemistry: a synergistic strategy in modern chemistry*.⁴²⁴

In the case of styrene oxide, lithiation primarily occurred at the benzylic position. Trapping the organolithium species with a neopentyl boronic ester at low temperatures, followed by 1,2-metallate rearrangement and oxidation, yielded tertiary alcohols with good yield and exceptional enantiomeric ratio. However, the use of less reactive pinacol esters resulted in reduced enantioselectivity.

1.13.1.9 The α -nitrogen stabilized organolithium protocol

While oxygen carbamates are predominantly utilized in lithiation-borylation reactions, a few instances involving α -amino-stabilized organolithiums have been documented.⁴⁵⁸ For example, *N*-Boc pyrrolidine can undergo enantioselective lithiation using *sec*-BuLi(-)-sp, followed by borylation with

trialkylborane to yield chiral amino alcohols. Additionally, lithiated benzylamines and indolines have also been employed in lithiation-borylation reactions (Scheme 86).

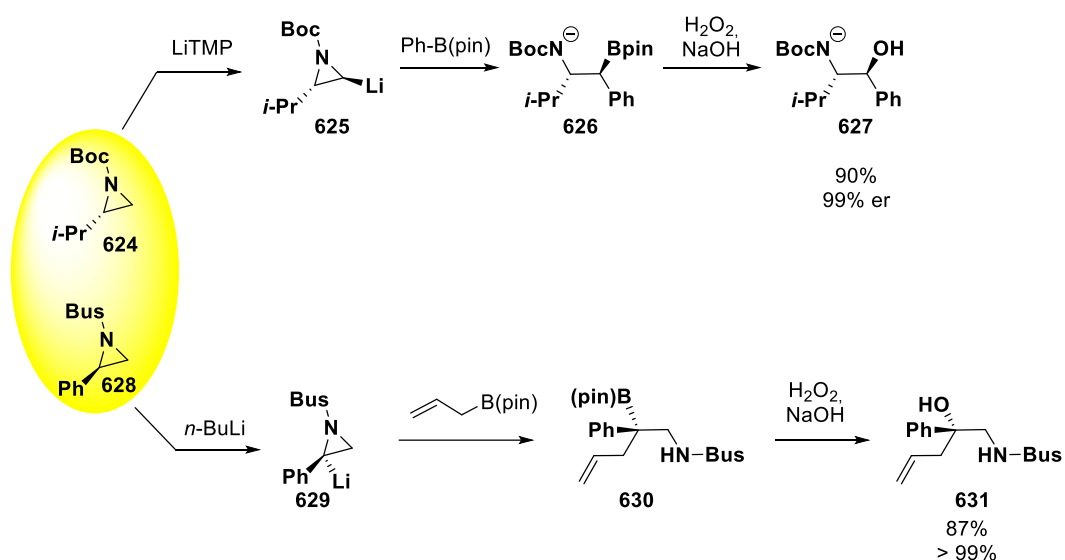


Scheme 86. Lithiation-borylation using α -N-organolithiums and boranes.
*Readapted from *Lithium-Boron chemistry: a synergistic strategy in modern chemistry*.⁴²⁴

However, due to the comparatively lower quality of nitrogen-based leaving groups compared to their oxygen counterparts, the scope of these reactions is typically restricted to the use of boranes exclusively.

1.13.1.10 The α -lithiated aziridine protocol

Similar to lithiation-borylation reactions involving epoxides, lithiation-borylation with aziridines results in the formation of β -amino alcohols.⁴⁵⁹ For instance, lithiation of *N*-Boc-protected aziridine **624** with LiTMP, followed by borylation and oxidation, yields the secondary amino alcohol **627** with high yield and enantiomeric ratio (Scheme 87).



Scheme 87. Lithiated aziridine's lithiation-borylation with boronic esters.
 *Readapted from *Lithium-Boron chemistry: a synergistic strategy in moder chemistry*.⁴²⁴

Expanding this methodology to phenylaziridines, which could potentially yield tertiary β -amino alcohols, pose a challenge when using *N*-Boc phenylaziridines. This led to the migration of the Boc protecting group to the benzylic position. However, this issue was resolved by substituting the protecting group with Bus (**628**), enabling the synthesis of tertiary alcohol **631** with excellent yield and enantiomeric ratio.

2 Aims and Objectives

The topics discussed in this thesis aim to design and develop new synthetic methodologies, with the focus on the active participation and involvement of organolithium reagents. As chemists, our most desirable goal is to give access to the rest of the community to new, highly reproducible, operationally feasible and high-yielding procedures, which can be exploited to obtain variously decorated organic molecules. In the next chapters published and unpublished works will be thoroughly reviewed, highlighting on one hand the pivotal role of lithium carbenoids in homologation reactions scenery and, on the other hand, how this unique class of metalorganic reagents approaches unexplored heteroatom-based partners. The synthesis of unsymmetrical thio-acetals, oxo-thioacetals, and halohydrins, along with unprecedented 3- formyl- 2- halomethyl- indoles and ω - mercapto- butan- 1- ols will be analysed. Each study will analyse different starting materials, and the structures mentioned above, which represent the final products. We will extensively discuss the optimization studies and fine tuning of the reaction conditions for each protocol, and ultimately, the scope of the reactions and the applicability of the methods to validate each procedure.

3 Result and Discussion

3.1 Straightforward Chemoselective Access to Unsymmetrical Dithioacetals through a Thiosulfonates Homologation-Nucleophilic Substitution Sequence

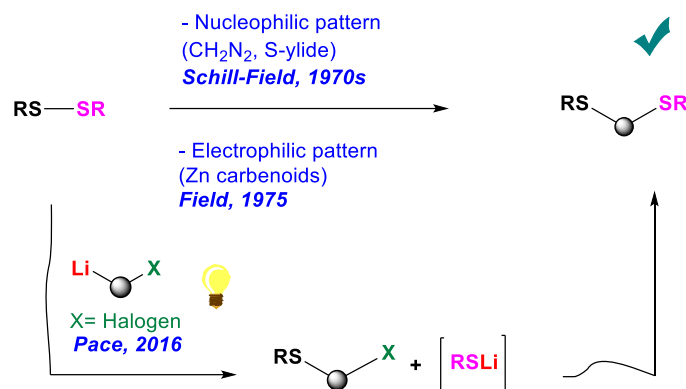
3.1.1 Introduction

Homologation chemistry provides a valuable approach to selectively introducing a methylene group (CH_2) into a given structure.^{1, 13, 460-462} This technique serves as the foundation for significant modifications of the organic framework, thus influencing critical physical-chemical parameters like lipophilicity and overall chemical reactivity, among others.⁴⁶³⁻⁴⁶⁵ Ideally, the homologation process would precisely deliver the methylene fragment between a pre-existing R-Y linkage.

In the current work an innovative synthetic methodology is presented, involving lithium carbenoids as methylene donor and yielding to the synthesis of unsymmetrical dithioacetals.

Dithioacetals ($\text{RS-CH}_2\text{-SR}$) are remarkable chemical entities that possess a multitude of versatile characteristics, rendering them pivotal across various domains in the field of chemical sciences.^{160, 466-469} The groundbreaking concept of *umpolung*, introduced by Corey and Seebach, enabled the transformation of a carbonyl group into a dithioacetal, thereby switching the reactivity of the conventional electrophilic carbon (CO) to a nucleophilic one (S-C-S).⁴⁷⁰⁻⁴⁷² This transformative strategy has found significant synthetic applications.

Additionally, to their synthetic significance, dithioacetals have recently emerged as favored structures for addressing the limitations of disulfides (Scheme 88). Overcoming the challenges posed by the susceptibility of disulfides to reducing and nucleophilic agents, which hinder their application in biological systems, has been elegantly achieved by replacing the delicate disulfide bridge with a more robust dithioacetal.⁴⁷³⁻⁴⁷⁴ Notably, this modification, as demonstrated by Cramer, not only enhances stability but also preserves the pharmacodynamic properties of resulting adducts. The strategic assembly of dithioacetals through homologative transformation of disulfides has proven to be a particularly feasible approach, facilitated by the straightforward insertion of the C1 unit between the two sulfur atoms.⁴⁷⁵



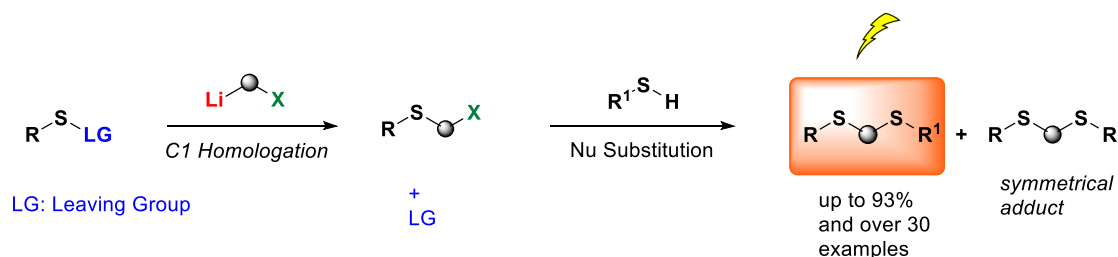
Scheme 88. Old and recent homologation process of disulfides resulting in symmetrical dithioacetals.

*Readapted from L. Ielo, V. Pillari, N. Gajic, W. Holzer and V. Pace, *Chem. Commun.*, 2020.¹⁶⁰

For decades, the successful realization of this strategy (by employing as methylene donor entities from both the nucleophilic, such as diazomethane⁴⁷⁶⁻⁴⁷⁷ and sulphur ylides,⁴⁷⁸ and electrophilic regimes, e.g., zinc carbenoids)⁴⁷⁹ was obscured by the inherent challenges in achieving satisfactory chemical yields. However, our group identified the nucleophilicity of the C1 carbenoid source as a critical parameter ensuring success. From our work emerged that highly nucleophilic bromomethyl lithium (LiCH₂Br) acts as a competent homologating agent (the most performing among the rest of the halogenated lithium carbenoids, Scheme 88), enabling the formation of symmetrical dithioacetals in a single operation under complete chemcontrol.¹⁵⁹

3.1.2 *Result and discussion*

Further investigational studies over this homologating strategy led to interesting advancements with the use of alternative C1 sources, such as CO₂,⁴⁸⁰ acetone under basic conditions,⁴⁸¹ and orthoesters,⁴⁸² each leading to the formation of symmetrical dithioacetals. However, the synthesis of unsymmetrical analogues (RS-CH₂-SR¹) has remained largely unexplored.



Scheme 89. General reaction's procedure of the presented work.

**Readapted from L. Ielo, V. Pillari, N. Gajic, W. Holzer and V. Pace, Chem. Commun., 2020.¹⁶⁰*

Conscious that the use of lithium carbenoids on disulfides would lead to the synthesis of symmetrical dithioacetals by forming an α -chlorothioether intermediate,^{13, 32, 54, 483-484} due to the high nucleophilicity of the sulphur nucleophile present in the starting material moiety (sulphide), we sought to overcome this obstacle by searching for alternative sulphenylating agents with lower nucleophilic leaving group, but still susceptible to the homologating event through lithium carbenoids. We were delighted to find out in thiosulfonate esters (for a detailed explanation of thiosulfonate's synthetic methodologies and applications see Section 1.7 of this thesis) the optimal electrophilic sulphur source, which in combination with an additive, external sulphur nucleophile (such as thiol or thiophenol), delivered the unsymmetrical dithioacetal in an outstanding 86% isolated yield. This process was further optimized to achieve a yield of up to 93% with the addition of a catalytic amount of NaI (entry 9 of the following optimization table, Table 4).

Table 4. Optimization table.

*Readapted from L. Ielo, V. Pillari, N. Gajic, W. Holzer and V. Pace, *Chem. Commun.*, 2020.¹⁶⁰

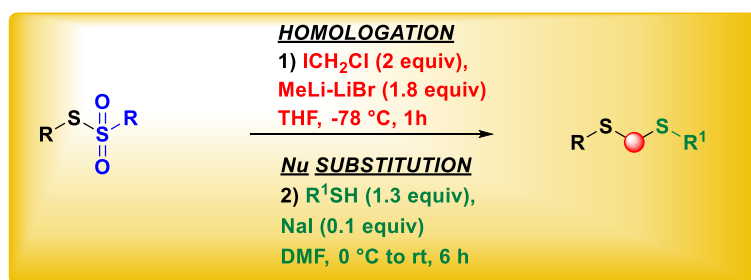
LG: Leaving Group

ENTRY	LG SUBSTRATE	LiCH ₂ X (X, equiv)	Solv., Temp (° C)	Ratio 634/635	Yield of 634 (%)
1	PhS	(Br, 1.8)	THF, -78 to rt	>1:99	-
2	PhS	(I, 1.8)	THF, -78 to rt	>1:99	-
3	PhS	(Cl, 1.8)	THF, -78 to rt	18:82	13
4	PhS	(Cl, 1.8)	DMF, -78 to rt	25:75	21
5	PhS	(Cl, 2.6)	DMF, -78 to rt	33:67	27
6	Cl	(Cl, 1.8)	DMF, -78 to rt	>99:1	37
7	PhN-Phth	(Cl, 1.8)	DMF, -78 to rt	>99:1	44
8	SO ₂ Ph	(Cl, 1.8)	DMF, -78 to rt	>99:1	86
9	SO₂Ph	(Cl, 1.8)	DMF, -78 to rt	>99:1	93
10	SO ₂ Ph	(Cl, 1.8)	DMF, 0	-	-
11	SO ₂ Ph	(ClCH ₂ MgCl-LiCl, 1.8)	DMF, -78 to rt	-	-
12	SO ₂ Ph	(Cl, 1.8)	DMF, -78 to rt	-	-

During the optimization studies we discovered that chloromethyl lithium was the best homologating carbenoid for this procedure. By dissolving the external thiol/thiophenol (the selected nucleophile) in DMF, a medium known for facilitating nucleophilic displacements on alkyl halide systems⁴⁸⁵ (in this case referring to the α -chlorothioether, **633** on the optimization Table 4), prior to its addition to the homologating reaction crude, led to a notable improvement in our results (entry 4, 8 Table 4).

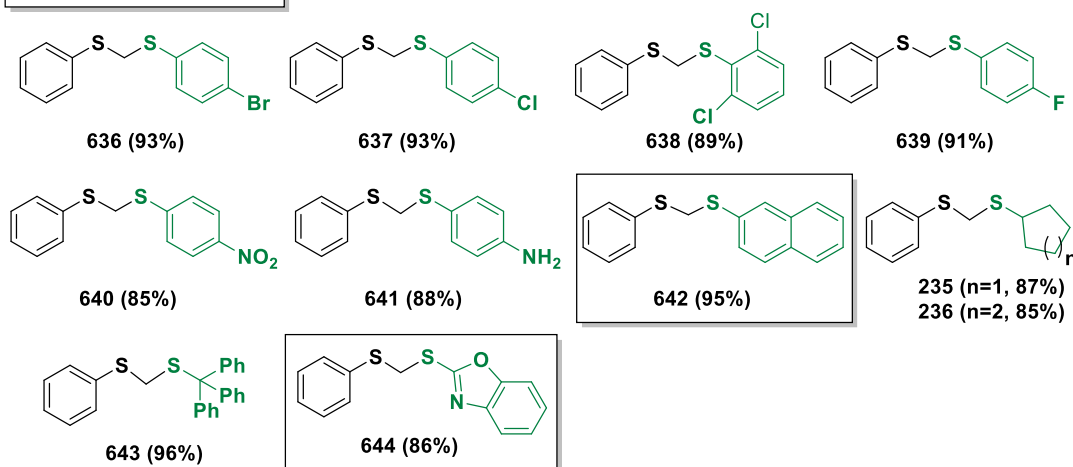
Several additional points deserve mention: removing the cooling bath and executing the displacement from 0 °C to room temperature was crucial for activating the benzenethiolate attack (entry 10, Table 4); the use of a weaker nucleophile, such as a Mg carbenoid, failed to trigger the homologation event, resulting in the full recovery of the thiosulfonate (entry 11, Table 4);⁴⁸⁶ the acidic quenching immediately after the homologation allowed us to obtain the α -chlorothioether as the sole product (entry 12, Table 4).

Lastly, the use of the reactive and easily accessible⁴⁸⁷⁻⁴⁸⁸ thiosulfonate did not entail any practical shortcomings commonly associated with sulfonylating agents, such as odour, toxicity, or low stability, ensuring excellent manipulability.

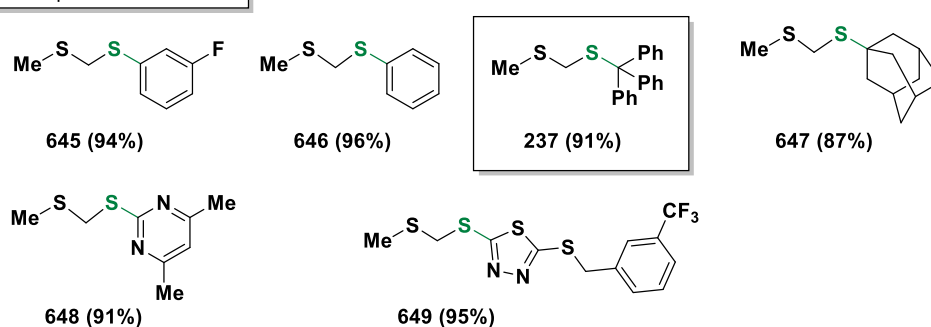


Selected examples:

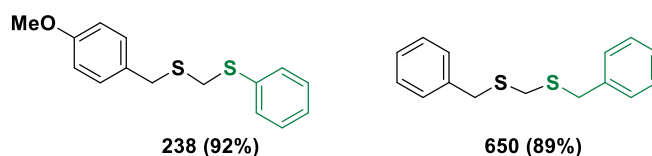
From aromatic thiosulfonates



From aliphatic thiosulfonates



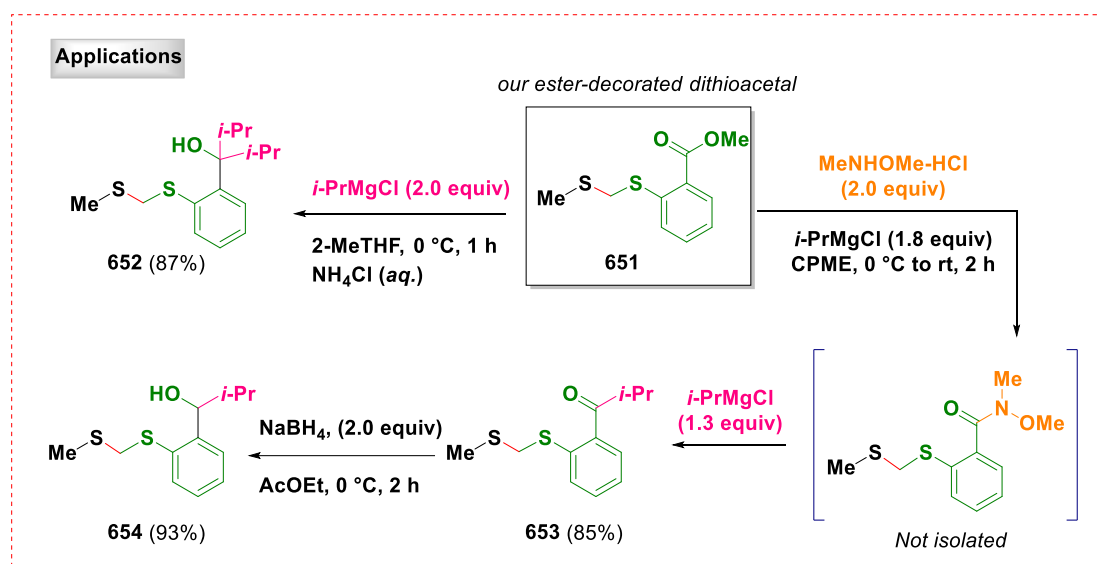
From benzyl thiosulfonates



Scheme 90. Scope of the homologation via lithium carbenoids - nucleophilic substitution of thiosulfonates yielding to unsymmetrical dithioacetals. *Readapted from L. Ielo, V. Pillari, N. Gajic, W. Holzer and V. Pace, *Chem. Commun.*, 2020.¹⁶⁰

With our optimized conditions in hand, we conducted an extensive study on the scope of our methodology, which demonstrated its wide tolerance towards functional groups potentially sensitive to the lithiating conditions. Various substituted halogenated thiophenols (e.g., 4-chloro, 4-bromo, 4-fluoro, 2,6-dichloro, 4-nitro, 4-amino, ecc.), aliphatic thiols (e.g., cyclopentyl, cyclohexyl), benzyl-type

thiols and various heteroaromatic thiophenols were used and successfully led to the synthesis of unsymmetrical dithioacetals, showcasing the versatility and applicability of our method. The X-ray analysis of selected representatives (entry 8, 12, and 15 scheme 90) revealed intriguing structural features of the constitutive RS-CH₂-SR¹ moiety of these compounds.



Scheme 91. Applicability of our methodology in tyrosinase inhibition.

*Readapted from L. Ielo, V. Pillari, N. Gajic, W. Holzer and V. Pace, *Chem. Commun.*, 2020.¹⁶⁰

To exploit the full potential of our procedure and establish a modular synthesis of dithioacetals with potential applications in tyrosinase inhibition,⁴⁸⁹ we conducted selected modifications on the ester-decorated analogue (Scheme 91). These modifications yielded promising results, indicating the practicality and effectiveness of our operationally simple and intuitive methodology.

3.1.3 Conclusion

In conclusion, a straightforward and effective approach for the preparation of rare unsymmetrical dithioacetals is fully presented and demonstrated, offering a practical and intuitive methodology with high yield and excellent chemo-control.

This brings us to our next research endeavour, where we extended our exploration into a related but distinct chemical territory. Just as dithioacetals offer an alternative to disulfides in certain applications, oxothioacetals represent an intriguing class of compounds with unique properties and applications. Our contribution to the field, therefore, revolves around a novel method for preparing oxothioacetals, specifically focusing on unsymmetrical oxothioacetals (RS-CH₂-OR).

3.1.4 Supporting information

Supporting information can be found at:

<https://doi.org/10.1039/D0CC04896H>

3.2 Consecutive C1-Homologation/Displacement Strategy for Converting Thiosulfonates into O, S-Oxothioacetals

3.2.1 Introduction

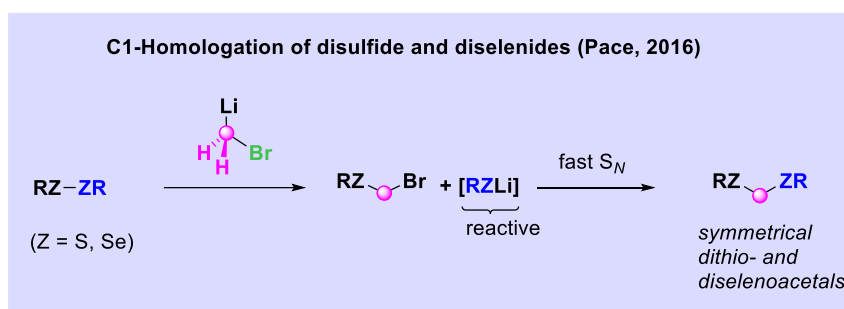
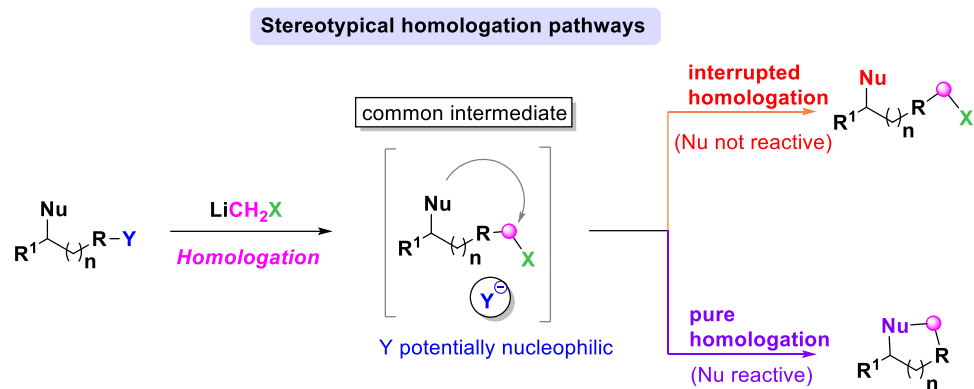
As mentioned previously, the homologation process consists in delivering the methylene fragment between a pre-existing R-Y linkage. Carbenoid reagents play a crucial role in releasing the methylene under a tuneable nucleophilic or electrophilic regime, primarily ruled by the nature of the metal.^{22-23, 29, 32, 36, 121, 490-493}

Two main interconnected mechanistic pathways can be envisioned for the reaction of a metal carbenoid (e.g., LiCH_2X – typically nucleophilic) with an electrophilic entity (R-Y)¹²⁷:

- the “*interrupted homologation*”, where the X element remains consistently in the final framework after forming the new R-CH₂X bond;^{103, 106, 157, 494-495}
- the pure homologation, leading to the homologue through an internal displacement of the X element, facilitated by the presence of an internal nucleophile.^{40, 42, 68, 70, 416, 449, 496-501}

As far as our understanding goes, conventional methods for conducting the C1-insertions have been mostly limited to X-Y systems (X, Y= carbon-carbon, carbon-heteroatom, heteroatom 1 – heteroatom 2),^{88, 329-330, 502} while analogous operations on homo-dimeric materials (X-X, X=heteroatom) are much less developed.

In this context, back in 2016, Pace’s group presented a direct procedure for converting disulfides and diselenides into symmetrical dithioacetals and diselenoacetals, respectively.¹⁵⁹⁻¹⁶⁰ This transformation, considered elusive for decades,^{476, 478-479} was effectively executed using the highly nucleophilic LiCH_2Br , which, upon attacking the di-chalcogen link, generated an intermediate α -halo thio- or seleno-ether. Subsequent internal nucleophilic displacement with the released anion during the homologation (RS- or RSe-) yielded the final homologated products (Scheme 92).

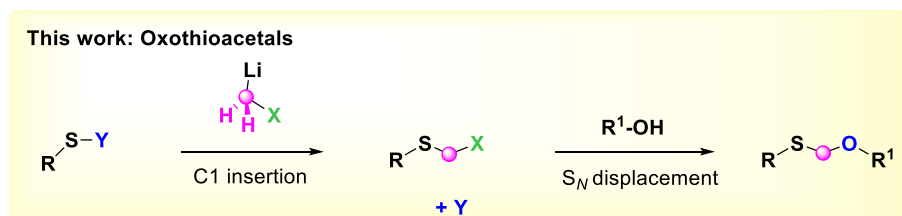


Scheme 92. Common homology pathways with carbenoids, and synthesis of dithio- and diseleno-acetals by Pace.

*Readapted from Adv. Synth. Catal. 2020, 362, 5444- 5449.¹⁶¹

3.2.2 Result and discussion

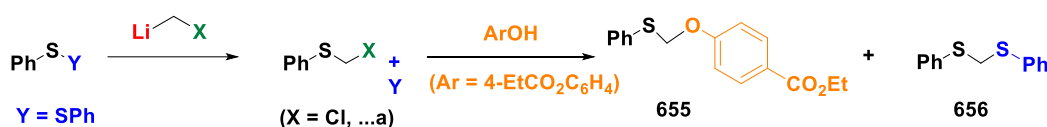
This successful endeavour encouraged us to investigate the possibility of employing an externally added (second) oxygen-centered nucleophile, thereby diversifying the strategy for a modular synthesis of oxothioacetals (Scheme 93).¹⁶¹



Scheme 93. General procedure for the present work.
**Readapted from Adv. Synth. Catal. 2020, 362, 5444– 5449.¹⁶¹*

We identified several critical points to be addressed during the protocol design. Firstly, the expelled leaving group (Y) on the sulfur electrophile should exhibit minimal nucleophilic behaviour to avoid any competitive phenomena with the external nucleophile. Secondly, the same Y group should confer strong electrophilic behaviour to the RS-platform to facilitate the attack of the nucleophilic carbenoid. Lastly, the oxygen-type reagent used for activating the displacement should be compatible with the adopted lithiating conditions, ensuring wide flexibility in incorporating substituents on the alcoholic partner.

Table 5. Optimization Table.
 *Readapted from Adv. Synth. Catal. 2020, 362, 5444- 5449.¹⁶¹



Entry	Y group	LiCH ₂ X (X, equiv)	Solv., Temp (° C)	Ratio 655/656	Yield of 655 (%)
1	PhS	(Br, 1.8)	THF, -78 to rt	>1:99	-
2	PhS	(I, 1.8)	THF, -78 to rt	>1:99	-
3	PhS	(Cl, 1.8)	THF, -78 to rt	7:93	4
4	PhS	(Cl, 1.8)	DMF, -78 to rt	11:88	7
5	Cl	(Cl, 1.8)	DMF, -78 to rt	>99:1	25
6	CN	(Cl, 1.8)	DMF, -78 to rt	>99:1	39
7	PhN-Phth	(Cl, 1.8)	DMF, -78 to rt	>99:1	48
8	PhN-Phth	(Cl, 2.8)	DMF, -78 to rt	>99:1	55
9	SO ₂ Ph	(Cl, 1.8)	DMF, -78 to rt	>99:1	78
10	SO₂Ph	(Cl, 1.8)	DMF, -78 to rt	>99:1	86
11	SO ₂ Ph	(Cl, 1.8)	DMF, -78 to rt	-	-

As prototype substrates we selected diphenyl disulfide (Y = SPh) and the ester-substituted phenol as the attacking nucleophile to gather preliminary information on the chemoselectivity. This decision was motivated by the inherent reactivity of carbenoids towards carboxylic derivatives, which could potentially lead to poor chemocontrol.^{147, 497} The introduction of the C1 unit in the form of LiCH₂Br predominantly resulted in the formation of dithioacetal (entry 1 Table 5), likely due to the higher nucleophilicity of the released mercapto anion compared to the electron-withdrawing group (EWG) substituted phenol.

Despite using LiCH₂I, which provides a more reactive methylene-iodide bond, there was no significant improvement (entry 2). However, a noticeable amount of the desired product was obtained in the presence of LiCH₂Cl (entry 3). Solubilizing the ester-substituted phenol in a polar solvent such as DMF before its addition to the homologation mixture proved beneficial, resulting in a detectable amount of the desired product (entry 4).

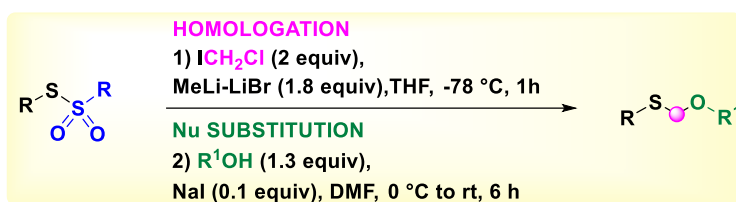
Raising the temperature from -78 °C to room temperature was essential for activating the phenoxide attack, as no reactivity was observed at lower temperatures. To moderate the nucleophilicity of the Y leaving group and enhance the sulfur electrophilicity, we explored different sulfenylating agents meeting these criteria. Chloro- (entry 5), cyano-phenylsulfide (entry 6), and *N*-phenylthiophtalimide (entry 7) effectively suppressed the formation of the symmetrical dithioacetal, although the chemical

yields did not exceed 55% even in the presence of substantial loadings of both carbenoid and the second nucleophile (entry 8).

Based on these initial experiments, it became evident that tempering the nucleophilicity of the Y group had to be appropriately complemented by a strong sulfur electrophilicity-enhancing component. Consequently, we focused on the *S*-thiosulfonate ester,¹⁷⁷ which, pleasingly, under the homologation/displacement conditions, was transformed into the desired compound in 78% isolated yield with excellent selectivity (entry 9). Furthermore, the Finkelstein reaction with the phenol benefited from the addition of a catalytic amount of NaI (0.1 equiv), resulting in an 86% isolated yield of **2** (entry 10).

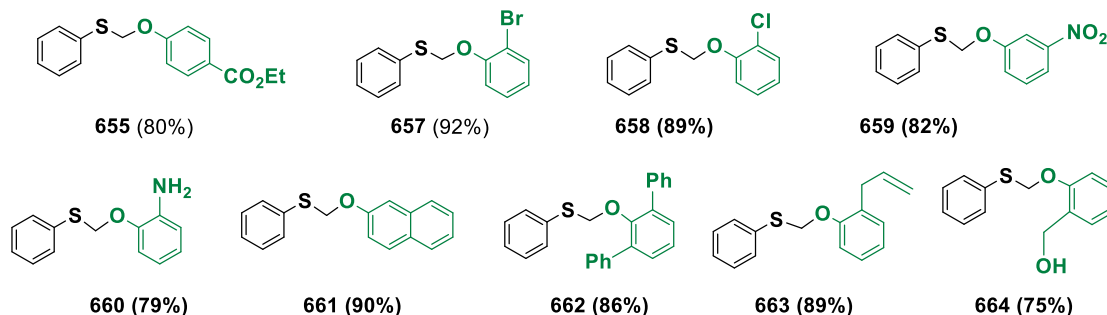
From a practical and environmental perspective, the use of the *S*-thiosulfonate is attractive due to its good manipulability and the avoidance of common drawbacks associated with sulfurating chemicals, such as odour, toxicity, and instability.⁴⁸⁷⁻⁴⁸⁸ It is worth noting that the overall process was positively influenced by the basic conditions, facilitated by the organolithium component of the mixture. Quenching the reaction with stoichiometric HCl (1 N) after completing the homologation and then adding the phenol allowed for the full recovery of the α -halothioether (entry 11).

With the optimized conditions in hand, we further explored the scope of the reaction.

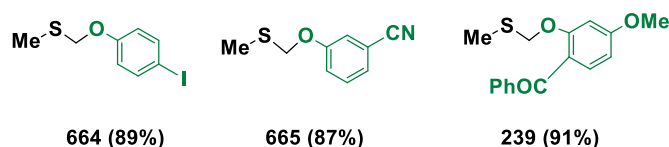


Selected examples:

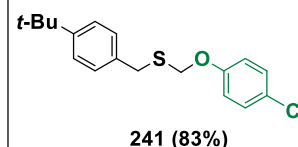
From aromatic thiosulfonates



From aliphatic thiosulfonates



From benzyl thiosulfonates



Scheme 94. Scope of the reaction.

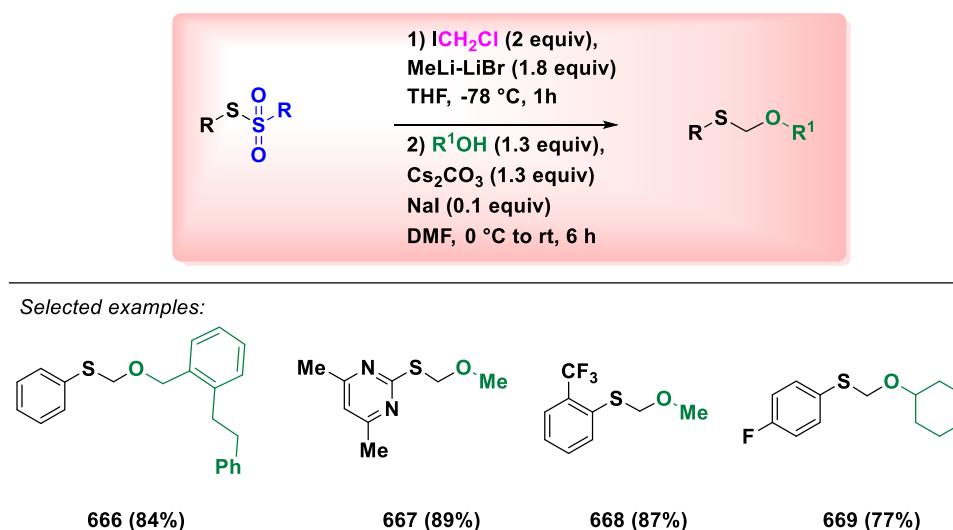
*Readapted from Adv. Synth. Catal. 2020, 362, 5444– 5449.¹⁶¹

The high chemoselectivity of the sequential process was evident not only in the case of an ester-substituted phenol (entry 3 in the scope scheme) but also in the case of a more reactive ketone-substituted system with a benzoyl group in the phenol *ortho* position (entry 14). The presence of potentially exchangeable halogens in the core of the phenol minimally affected the transformation, as evidenced in the cases of bromo or chloro and -iodo derivatives. The use of nitrogen-substituted phenol at different oxidation states proved to be fully compatible with the methodology, as indicated by the reluctant nitro compound (toward organolithium carbenoids).⁵⁰³ We were pleased to find that *o*-aminophenol was exclusively alkylated at the oxygen, leaving the nucleophilic amino group untouched.

Derivatives such as 2-naphthol and the sterically demanding 2,6-diphenylphenol further illustrated the versatility of the method. Moreover, the installation of a sensitive element such as a terminal olefin, was tolerated.⁵⁰⁴ The differential acidity between a phenol and a benzylic alcohol enabled the selective functionalization of the aromatic alcohol, leading to the preparation of the hydroxymethyl-containing scaffold.

The protocol was flexible enough to prepare *S*-alkyl type oxothioacetals starting from the corresponding thiosulfonates, as shown in the scope scheme where some examples are listed. With comparable efficiency, we could synthesize analogues embodying the sensitive functionalities on the aromatic nucleus, such as the highly reactive iodo compound. Like aromatic thiosulfonates, carboxylic, carbonyl, and alkenyl oxothioacetals were assembled without compromising the chemical integrity of these reactive handles.

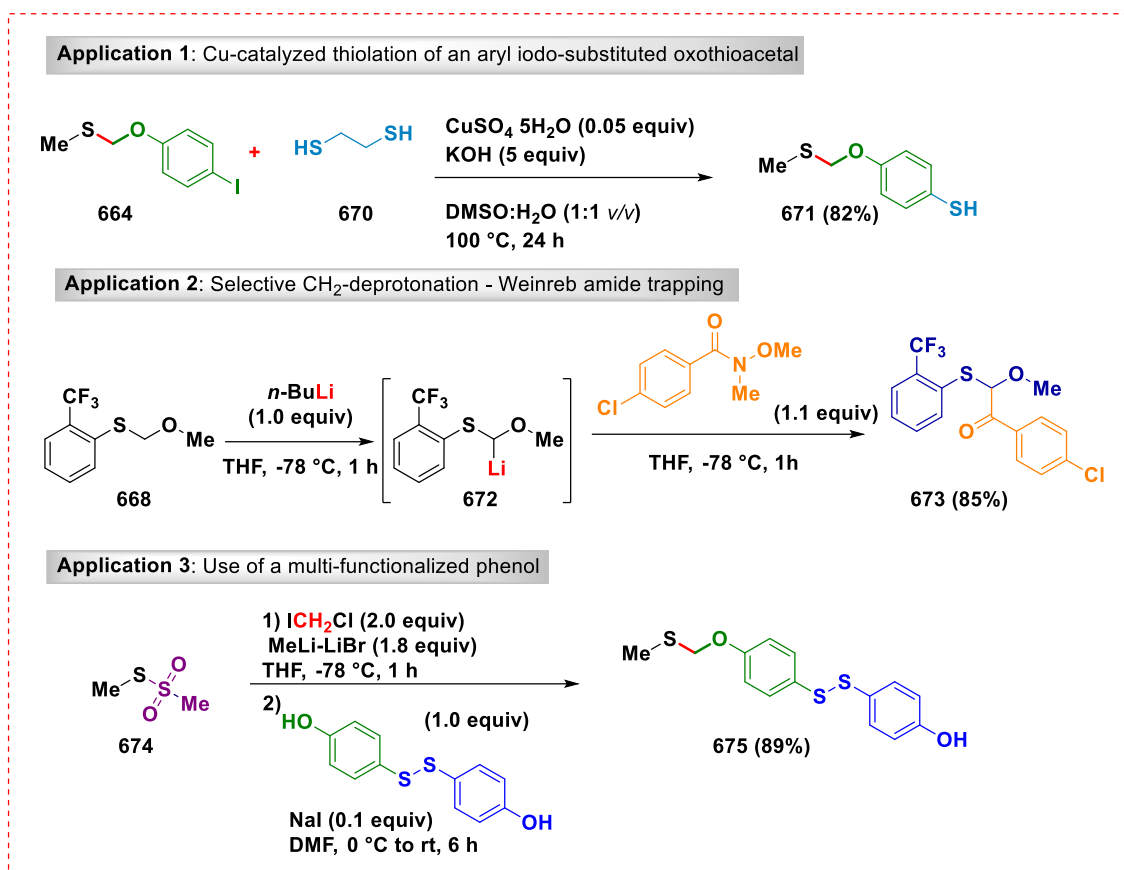
The chemoselective profile was further maintained when a nitrile-substituted phenol was used, which is particularly interesting given the well-established chemistry dealing with the addition of carbanion-like reagents to the CN group leading to ketones.⁵⁰⁵ Notably, a benzylic thiosulfonate smoothly underwent the sequential homologation/displacement (Scheme 94).



Scheme 95. Scope of the reaction with the addition of Cs₂CO₃.

Readapted from Adv. Synth. Catal.* **2020, *362*, 5444– 5449.¹⁶¹

To fully leverage the methodology, the use of aliphatic alcohols was also studied. Based on the evidence that a benzylic alcohol was not alkylated under the reaction conditions, we discovered that pre-treating the hydroxyl-derivative with stoichiometric Cs₂CO₃ in DMF at 0 °C (i.e., forming a cesium alkoxide) allowed us to address the limitation. As a result, corresponding analogues (from an *ortho*-substituted benzylic alcohol and from 3-pyridinylmethanol) were easily prepared in high yield. Similarly, upon the formation of cesium methoxide, a series of *O*-methylated oxothioacetals could be smoothly accessed. Despite the challenges posed by the poly-nitrogenated systems required for synthesizing the pyrimidinyl and the 1,3,4-thiodiazolyl analogues, no alkylating effect was observed with chloriodomethane, thus allowing the correct generation of the carbenoid (Scheme 95).



Scheme 96. Applicability of the developed synthetic methodology.

*Readapted from Adv. Synth. Catal. 2020, 362, 5444– 5449.¹⁶¹

To fully display the methodology's applicability, selective manipulations on specific synthesized frameworks were carried out to briefly screen their reactivity profile. The iodine-substituted derivative underwent a smooth I/S_H interchange under Chae's Cu-catalysed conditions⁵⁰⁶ with 1,2-ethanedithiol as the mercapto source, resulting in an oxothioacetal with a free thiol group.

The selective deprotonation of the oxothioacetal methylene of **668** with *n*-BuLi provided an intermediate oxo-thio geminal lithium anion, which was intercepted with a Weinreb amide giving a mixed oxo-thio ketone.^{149, 152}

Finally, we successfully employed a bis-disulfide-containing diphenol as the displacing alcohol for the tandem protocol, allowing the nucleophilic substitution to occur only on one of the phenolic groups with full retention of the labile S-S bond (Scheme 96).

3.2.3 Conclusion

In summary, we have developed a straightforward approach to preparing oxothioacetals from readily available thiosulfonates. The strategy relies on the selective installation of a halomethyl fragment using chloromethyl lithium. Key to the success of the methodology is the utilization of the thiosulfonate as a competent electrophilic sulfur platform, which upon the homologation event releases a non-nucleophilic (reactive) sulfinate species. The subsequent treatment of the (isolable) α -halothioether with a hydroxyl-containing nucleophile, whether (hetero)aromatic or aliphatic alcohols, triggers the displacement, thereby furnishing the desired oxothioacetals. We consistently observed high yields and chemoselectivity, demonstrating that reaction partners can incorporate sensitive groups without compromising their chemical integrity throughout the sequential process.

3.2.4 Supporting information

Supporting information can be found at:

<https://doi.org/10.1002/adsc.202000919>

3.3 Taking advantage of lithium monohalocarbenoid intrinsic α -elimination in 2-MeTHF: controlled epoxide ring-opening en route to halohydrins

3.3.1 *Introduction*

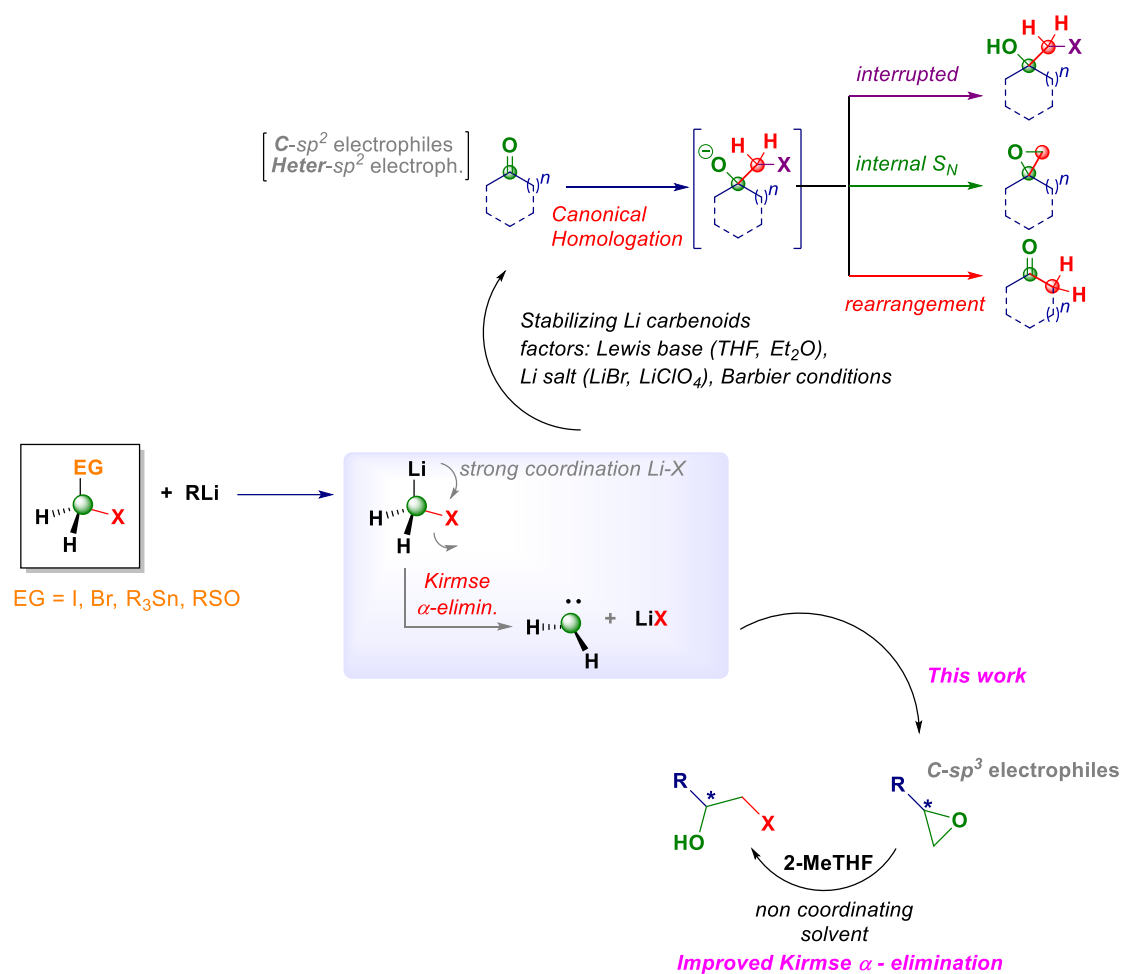
Lithium monohalocarbenoids (LiCH_2X , where X represents a halogen) have emerged as remarkably adaptable C1-synthons, facilitating a wide array of homologation processes across both nucleophilic and electrophilic realms.^{22, 32, 36, 491, 507}

It is pertinent to note that the action of lithium derivatives primarily occurs through the former mechanism. Thus, by releasing the CH_2X unit onto a suitable electrophilic platform, an extensive spectrum of beneficial synthetic transformations can be orchestrated.^{13, 127, 483} The coexistence of C–Li and C–X bonds on the same carbon atom significantly heightens the propensity for inducing the degradative Kirmse’s α -elimination phenomenon, owing to the robust Li–X internal coordination. This has always been the main reasons that renders the carbenoid unproductive for homologation purposes.^{423, 508-512}

Indeed, as highlighted in previous studies, the effective deployment of carbenoid chemistry in batch mode demands meticulous adherence to operational specifics,⁵³ notably including conducting the carbenoid generation under Barbier conditions to forestall degradation and employing coordinative solvents such as THF and diethyl ether in the presence of lithium halide salts to mitigate Kirmse’s α -elimination, leading to the formation of a free carbene and LiX species.³⁵ These delineated paradigms serve as essential guidelines for the effective application of carbenoid-mediated strategies within synthetic methodologies.^{54, 64, 484, 513}

Given our enduring engagement with this realm of chemistry over the years, it has piqued our curiosity to delve deeper into the potential synthetic implications underlying Kirmse’s elimination, a well-documented degradative impact on the chemical integrity of these C1-synthons (Scheme 97). A comprehensive examination of the current state-of-the-art pertaining to carbenoid-guided processes unequivocally highlights the privileged position of sp^2 -hybridized carbon electrophiles in effecting homologation-type transformations, alongside diverse heteroatoms, including but not limited to B^{39, 42, 73, 449, 514-515} and Sn.⁸⁸

Regrettably, the corresponding sp^3 -hybridized carbon electrophiles have proven elusive in their ability to achieve homologations with LiCH_2X , as evidenced in seminal works by Huisgen¹⁰⁸ and Hahn.¹⁰⁹ In consonance with these findings, our recent research has successfully documented the formal homologation of C–X functionalities via a sequential integration of the carbenoid into a carbonyl group, followed by Si–H-mediated deoxygenation.¹¹⁰



Scheme 97. General content of the current work.
 *Readapted from Org. Biomol. Chem., 2021, 19, 2038–2043.⁴³

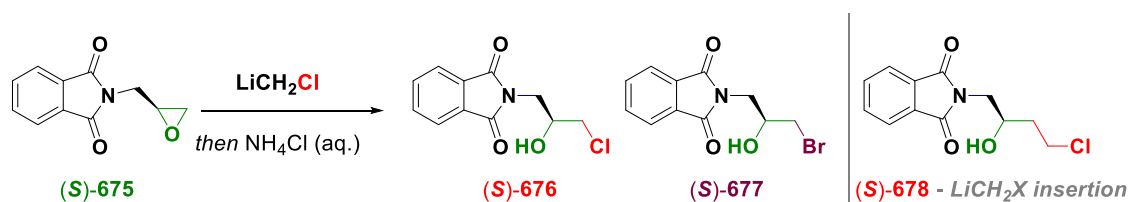
3.3.2 Result and discussion

In this study, we present the controlled ring-opening of epoxides using the lithium halide liberated during Kirmse's α -elimination, leading to the successful synthesis of β -halohydrins with high yield.⁴³

Central to the success of this method is the swift generation and subsequent degradation of the carbenoid in 2-MeTHF,^{44, 516-525} a green solvent increasingly gaining prominence in classical organic chemistry, biotransformations, polymerization, and extractive operations.⁵²⁶⁻⁵²⁸ This process ultimately culminates in the degradation of the monohalolithium carbenoid. We anticipate the distinctive regioselectivity of the transformation, harnessed through the formation of LiX, which assumes the dual role of a Lewis acid, facilitating C–O cleavage, and a source of the attacking halide.⁵²⁹⁻

530

Table 6. Optimization of the reaction.
*Readapted from Org. Biomol. Chem., 2021, 19, 2038–2043.⁴³



Entry	Solvent	LiCH_2Cl (equiv)	Ratio 676/677	Yield of (S)-676 (%)	er of (S)-676
1	THF	2.8	84:16	66	>99:1
2	THF	2.8	>99:1	74	>99:1
3	Et_2O	2.8	>99:1	78	>99:1
4	CPME	2.8	>99:1	81	98:2
5	TBME	2.8	>99:1	85	97:3
6	2-MeTHF	2.8	>99:1	93	>99:1
7	2-MeTHF	1.8	>99:1	91	>99:1
8	2-MeTHF	1.5	>99:1	77	>99:1
9	2-MeTHF	2.0	>99:1	87	>99:1
10	Toluene	2.0	>99:1	61	>99:1
11	2-MeTHF	2.0	>99:1	67	>99:1
12	2-MeTHF	2.0	>99:1	48	>99:1
13	2-MeTHF	2.0	>99:1	85	>99:1
14	2-MeTHF	2.0	>99:1	79	>99:1
15	2-MeTHF	2.0	-	-	-

To validate the stereochemical outcome of the process, we initiated our investigations with the enantiomerically pure epoxide-containing phthalimide (S)-675 as the starting material. LiCH_2Cl was

generated under established reaction conditions⁵⁴ from ICH₂Cl (in 3.0 equiv.) and MeLi–LiBr (in 2.8 equiv.) in THF at –78 °C. Surprisingly, rather than observing the anticipated nucleophilic attack leading to the homologated adduct (S)-**678**, we recovered a mixture of two enantiopure halohydrins [(S)-(**676**) and (S)-(**677**)] in an 84:16 ratio (entry 1 Table 6).

Notably, the subsequent HPLC analysis of both reaction products confirmed the complete preservation of the stereochemical information, thus proving our prior observations regarding the retention of configuration in reactions involving basic α -substituted methyllithiums.^{90, 149-151, 154, 157, 495, 531-534}

This initial experiment provided strong indications of the ring-opening of the epoxide with a LiX salt.⁵³⁵⁻⁵³⁶

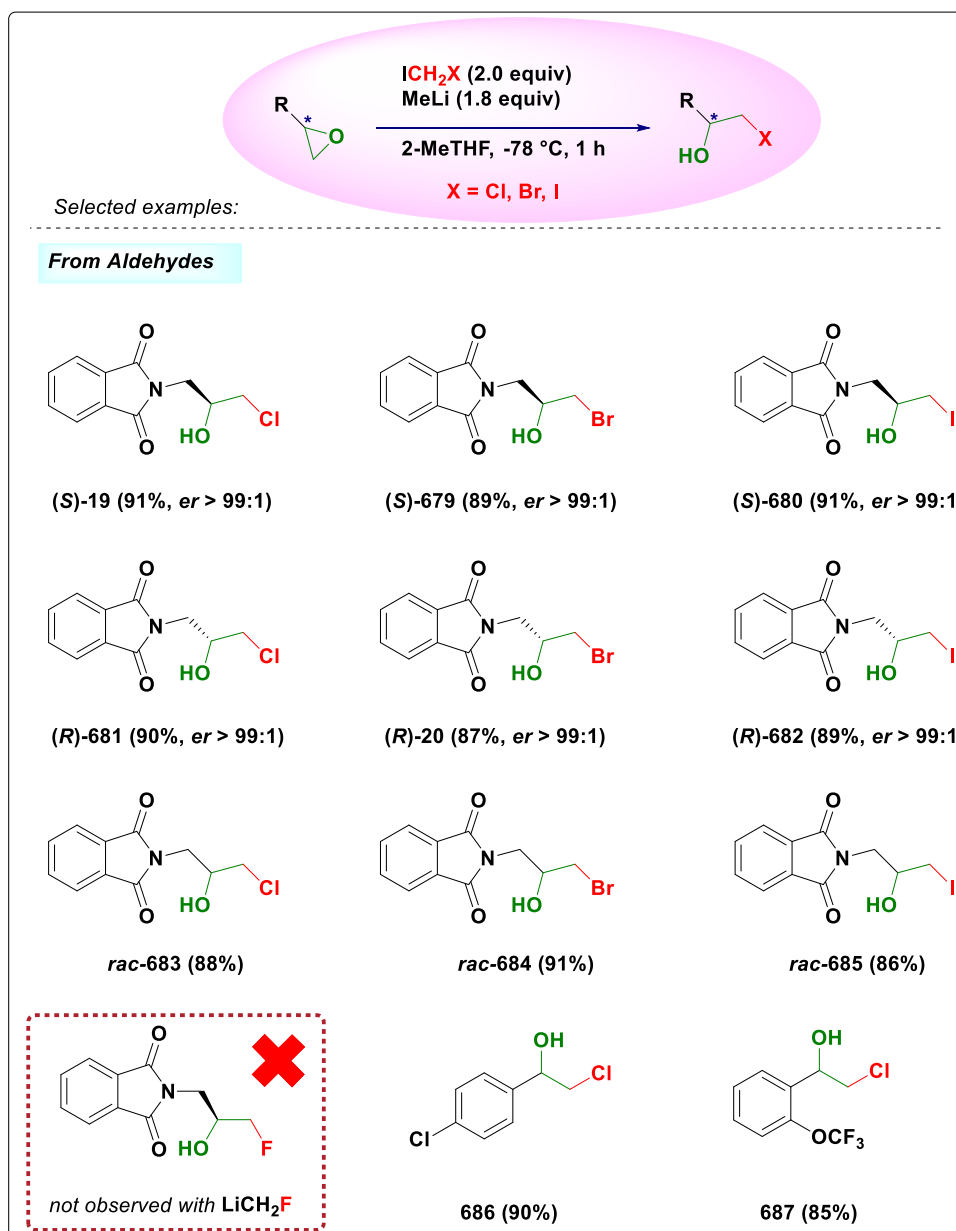
Furthermore, the simultaneous presence of the chloro (S)-(**676**) and bromo-(S)-(**677**) derivatives pointed towards a ring-opening mediated by two distinct species, respectively LiCl and LiBr. Supposedly, the formation of LiCl during Kirmse's α -elimination of the carbenoid led to the production of the chlorohydrin, while LiBr, complexing the metalating agent MeLi (*i.e.*, MeLi - LiBr complex in Et₂O), directly furnished the bromohydrin (S)-**677**. This hypothesis was supported by employing LiX-free MeLi (MeLi in Et₂O, 1.6 M), which resulted exclusively in the formation of the chlorohydrin (S)-**676**, thus confirming that LiCl (as a carbenoid degradation product) was responsible for the attack on the oxirane (these new conditions were used in all the entries of the optimization Table 6, but entry 1).

The choice of solvent emerged as a critical determinant in the process, as diminishing the medium-coordination effect on the carbenoid enabled an increase in the yield of the chlorohydrin, leading to a consequential positive modulating effect on Kirmse's elimination. This was evidenced by the increased formation of (S)-**676** when employing Et₂O (entry 3 Table 6), CPME⁵³⁷ (entry 4 Table 6), and TBME (entry 5 Table 6), and further maximized in 2-MeTHF (entry 6-15, excluding entry 10 of Table 6), resulting in an excellent yield of 93%.

Several additional factors emerged from the experimentation, including the optimal loading of carbenoid at 2.0 equiv (entries from 9 till 15 of Table 6), the negligible impact of the additive TMEDA (entry 9 of Table 6, with 2.0 equiv of it), the adverse effects of running the process in toluene (entry 10 of Table 6), and the influence of temperature variations on the effectiveness of the reaction (entry 11 of Table 6 was run at –40 °C, and entry 12 at –10 °C). Furthermore, the study revealed that the process remained independent of the pro-carbenoid source, as evidenced by comparable results obtained using a stannane (entry 13 of Table 6, by using (*n*-Bu)₃SnCH₂Cl) or a sulfoxide (entry 14 of

Table 6, employing PhS(O)CH₂Cl) for the corresponding metal exchange, albeit the procedure using ICH₂Cl yielded the most promising results.

Additionally, the presence of the other Kirmse's elimination product, CH₂ (free carbene), did not impede the overall transformation, while the adoption of non-Barbier-type conditions for carbenoid formation proved futile due to inadequate carbenoid generation (entry 15 of Table 6).



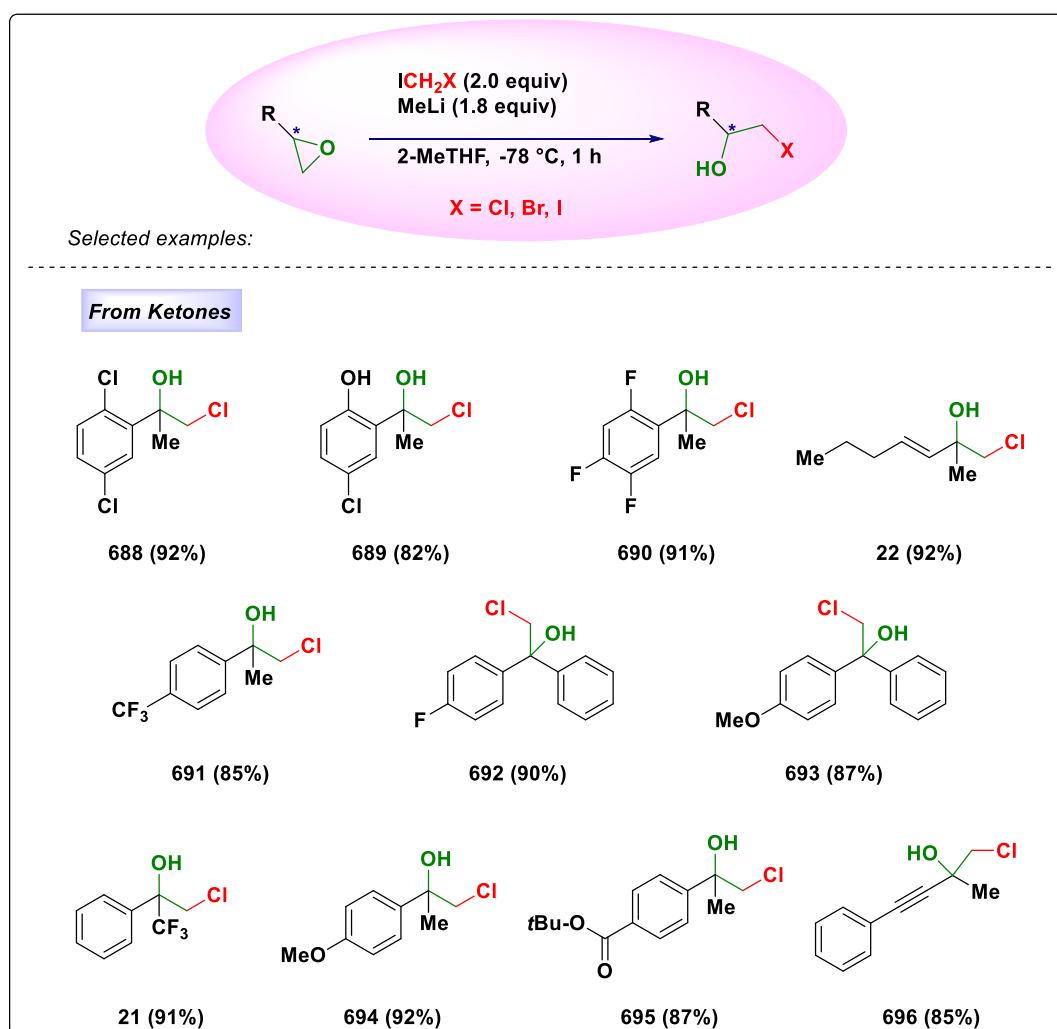
Scheme 98. Scope of the reaction using aldehydes.

*Readapted from *Org. Biomol. Chem.*, 2021, 19, 2038–2043.⁴³

With the establishment of the reaction conditions, an in-depth exploration of the scope of the reaction was initiated, encompassing the utilization of the *R* enantiomer of **675**, which yielded the

corresponding epimeric halohydrin (*R*)-**681** with comparable efficiency and enantiomeric purity. This flexibility was further underscored through the successful application of different halocarbenoids, such as LiCH_2Br and LiCH_2I , thereby attesting to the versatility of the methodology.

The extension of the procedure to the racemic derivative with the three distinct carbenoids confirmed the consistent yields obtained with the chiral platform. However, it is noteworthy that the methodology did not find applicability in the case of the LiF , which didn't produce any fluorohydrin (Scheme 98).^{65, 496, 538-539} Despite the appropriate generation of the unstable carbenoid, the degradation salt LiF appeared inadequate in promoting the ring opening.⁵⁴⁰ Epoxides derived from aldehydes and ketones, along with variously substituted aromatic rings, were found to be amenable substrates for the reaction, leading to the successful synthesis of diverse derivatives (Scheme 99).



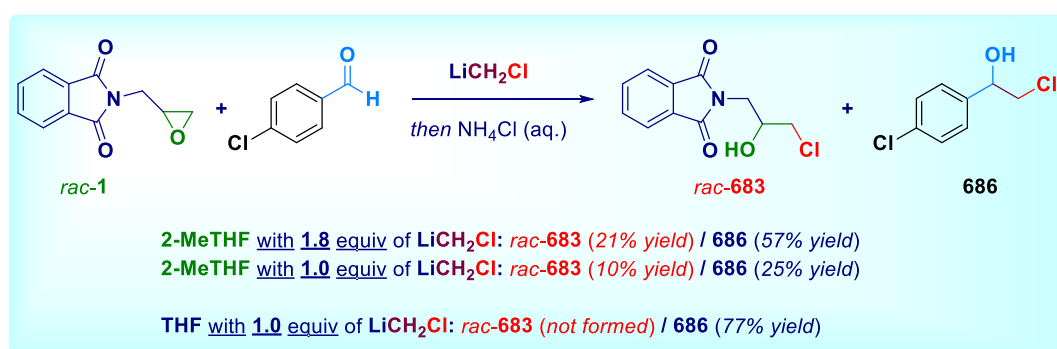
Scheme 99. Scope of the reaction using ketones.

*Readapted from *Org. Biomol. Chem.*, 2021, 19, 2038–2043.⁴³

The presence of sensitive functionalities did not constitute a limitation for the method, as exemplified by the smooth preparation of variously substituted β -chlorohydrins. Remarkably, even the presence of an acidic aromatic alcohol did not impede the process when deprotonation (using the same MeLi) was carried out prior to carbenoid formation.

Epoxides derived from benzo- or acetophenones also proved to be viable substrates, yielding the corresponding derivatives with high efficiency. The introduction of unsaturated fragments, including alkyne and alkene moieties, onto the epoxide core further validated the robustness of the process,¹⁰⁴⁻¹⁰⁵ as no cyclopropanation-like process was detected, thus affirming the hypothesis of the higher reactivity of the lithium halide salt (Scheme 99).

Determined to unravel the mechanistic pathway of the transformation, a mixture of racemic epoxide and an aromatic aldehyde was subjected to the reaction conditions.

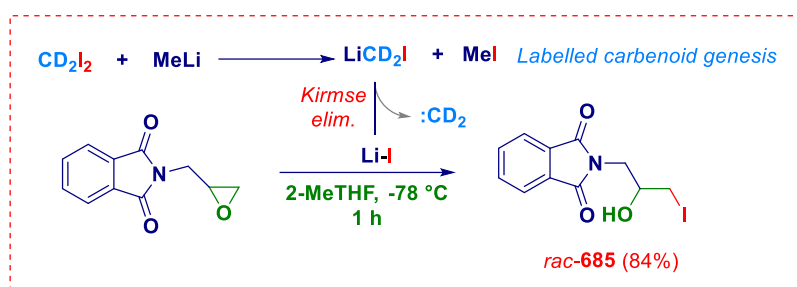


Scheme 100. Mechanism of the reaction.
*Readapted from Org. Biomol. Chem., 2021, 19, 2038–2043.⁴³

This resulted in the formation of two halohydrins, attributed to the attack of the carbenoid on the aldehyde (major compound) and the attack of the degradation product (LiCl) on the epoxide (minor compound). This observation can be rationalized by considering the higher electrophilicity of the carbonyl group in comparison to that of the epoxide, with the former facilitating the predominant nucleophilic addition on the carbonyl and the latter promoting the degradation of the carbenoid.

Notably, variations in the amount of LiCH₂Cl did not significantly alter the ratio of *rac*-683 and 686, indicating the tendency of the carbenoid to react with the more activated substrate (aldehyde) before its decomposition, leading to the attack of the degradation product (LiCl) on the epoxide.

Conversely, when the reaction was conducted in THF, optimal for stabilizing the carbenoid, the attack of 1 equiv. of LiCH₂Cl on the aldehyde was the predominant phenomenon, with minimal Kirmse's elimination taking place (Scheme 100).



Scheme 101. Confirmation of the reaction's mechanism using the labelled carbenoid LiCD_2I .
 *Readapted from *Org. Biomol. Chem.*, 2021, 19, 2038–2043.⁴³

Finally, as additional confirmation of the formation of LiX , an experiment employing the labelled carbenoid LiCD_2I was conducted, resulting in the formation of the iodohydrin *rac*-4 as the sole product. This observation further supported the hypothesis that the Kirmse's elimination of LiCD_2I yielded CD_2 and LiI , which was responsible for the ring opening of the epoxide (Scheme 101).

3.3.3 Conclusion

In conclusion, we have successfully developed a straightforward methodology for the efficient synthesis of various β -halohydrins (chloro, bromo, and iodo) through the amplified Kirmse's elimination of the corresponding lithium monohalocarbenoids, initiated from epoxides. This degradative process, conventionally deemed troublesome in canonical homologation chemistry, has been effectively harnessed in the environmentally benign and non-coordinating solvent 2-MeTHF. Consequently, the controlled formation of LiX salts is triggered, culminating in the ring-opening of the epoxides. The consistently high yield, complete retention of stereochemical information, and impeccable chemocontrol demonstrated by selectively synthesizing variously decorated motifs serve as compelling evidence of the potential of this operationally simple and intuitive methodology.

3.3.4 Supporting Information

Supporting information can be found at:

<https://doi.org/10.1039/D0OB02407D>

3.4 Sequential homologative-Meinwald rearrangement of epoxy-lactams to 3-formyl-2-halomethyl-indoles

3.4.1 Introduction

Spiro-epoxy oxindole as molecular structure (**428**), encapsulates a distinctive class of organic compounds characterized by a spiro arrangement (**432**), an epoxy functional group (**402**), and an oxindole moiety (**429,431** of Figure 7). This amalgamation of features gives rise to compounds exhibiting potentially fascinating chemical and biological properties (for further details on this class of organic compounds see [Section 1.11](#)).

Their 3,3'-spiro-cyclic structure exhibits heightened reactivity due to inherent ring strain. This characteristic has facilitated diverse synthetic pathways, enabling the creation of bioactive compounds and natural products.³⁵¹ Particularly within the domain of 2-oxindoles, a structurally versatile class vital in synthetic and medicinal chemistry, spiro-epoxy derivatives stand out due to their distinctive features and potential applications.

In recent years, spiro-epoxy oxindoles have attracted attention for their challenging synthesis and potential biological relevance.³⁴⁷⁻³⁴⁹ The inherent steric strain from their spiro-carbon arrangement allows smooth conversion into carbocyclic and heterocyclic rings containing 2-oxindole, thereby opening pathways to diverse molecular architectures.⁵⁴¹

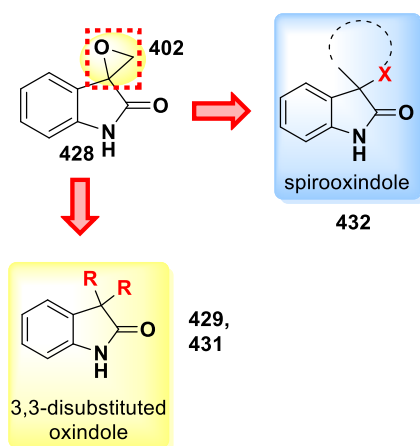
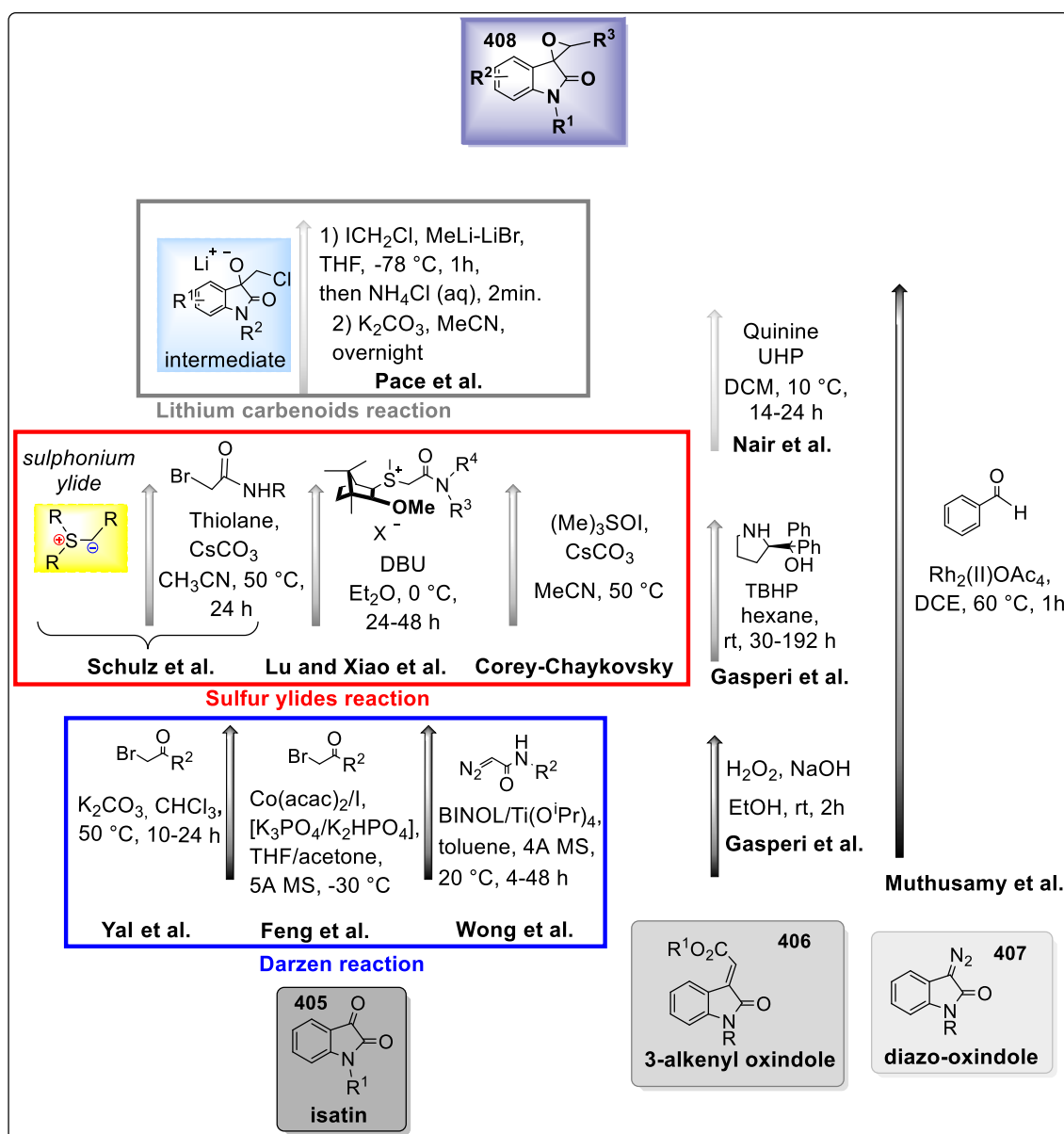


Figure 7. Structural architecture and reactivity of spiro-epoxy oxindole

By incorporating the epoxide moiety within the 2-oxindole scaffold presents a logical route to access spiro-oxindoles and 3,3-disubstituted oxindoles through controlled ring-expansion/opening

reactions.³⁵⁰ This approach demonstrates intriguing reactivity patterns and holds promise for constructing complex frameworks with specific conformational properties, enhancing their interaction with biological targets.³⁵²

The synthesis of spiro-epoxy oxindoles encompasses several efficient methods such as the Darzens reaction and Corey-Chaykovsky epoxidation (see [Section 1.11](#)),³⁵³ leading to three main synthetic pathways according to different starting materials: from isatin (**405**), from 3-alkenyl-oxindole (**406**) and from diazoxindole (**407**, Scheme 102). These pathways offer facile access to this structural skeleton, leading to the formation of pivotal compounds in the construction of complex natural products like brassinin, (±)-physovenine, and (+)-gliocladin C.⁵⁴²



Scheme 102. Synthetic pathways to spiro-epoxy oxindoles

The Darzens reaction, a potent non-oxidative method involving isatins (**405**) and phenacyl bromides with a base, stands as an effective approach for synthesizing spiro-epoxy oxindoles.³⁵⁵ It exhibits versatility in accessing various derivatives, showcasing potential in forming diverse architectures.

Asymmetric versions of the Darzens reaction have been developed, introducing enantioselectivity in the synthesis of spiro-epoxy oxindoles. Notably, this enhancement in stereochemistry was influenced by substituent electronic properties, fostering tailored synthesis of chiral spiro-epoxy oxindoles.³⁵⁶

Moreover, the utilization of sulphur ylides has facilitated the synthesis of spiro-epoxy oxindoles. This approach allows the construction of diverse trans-spiro-epoxides with varying substituents, where stereochemical outcomes depend on reaction conditions and isatin derivative properties.³⁵⁷⁻³⁵⁸

The incorporation of chiral sulphur ylides derived from camphor derivatives has enabled high enantioselectivity in spiro-epoxidation of isatins. Protection of functional groups has played a crucial role in enhancing enantioselectivity in this method.^{359, 543}

The Corey-Chaykovsky epoxidation method, involving trimethylsulfoxonium iodide and caesium carbonate, has proven effective in constructing simple spiro-epoxy oxindoles.³⁶⁰ Lithium halocarbenoids have also emerged as versatile reagents for this synthesis, exhibiting exclusive chemoselectivity as extensively discussed in the following pages.¹⁰⁶

Synthesis from 3-alkenyl oxindoles (**406**) via epoxidation reactions using various oxidants and asymmetric catalytic methodologies have been explored, providing access to diverse spiro-epoxy oxindoles.³⁶¹⁻³⁶⁴ Additionally, a facile approach using diazooxindoles (**407**, Scheme 102) demonstrated by Muthusamy, showcases the versatility of this method (see [Section 1.11](#) for extensive version of synthetic paths).³⁶⁵

Specifically for this project, we synthesised spiro-epoxy oxindoles with lithium carbenoids, starting from commercially available isatins (variously substituted on different positions of the heterocyclic ring) formerly *N*-functionalised.

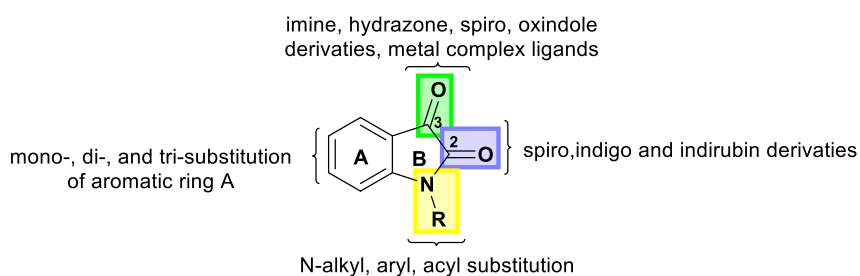


Figure 8. Isatin's structure analysis

Isatin, also known as indoline-2,3-dione and indanedione and indole quinone, is a natural product found in plants and metabolic derivatives of adrenaline in humans.³⁴⁶ It has a nitrogen atom at position 1 and two carbonyl groups at positions 2 and 3 respectively, showcasing two cyclic rings, one six-membered aromatic and one five-membered with anti-aromatic character (Figure 8).⁵⁴⁴

Originally obtained from the oxidation of indigo, its current structure was proposed by Kekule.^{346, 545} Isatin and its derivatives are commercially available and have been extensively studied for their synthesis and reactivity. They exhibit diverse reactions, including electrophilic aromatic substitution, N-substitutions, nucleophilic additions, chemoselective reductions, oxidations, ring-expansions, and spiro-annulations.⁵⁴⁶ Their unique potential as both electrophiles and nucleophiles, along with easy availability, makes them valuable building blocks in organic synthesis. Isatins have been utilized in synthesizing various heterocyclic frameworks with biological significance.⁵⁴⁷⁻⁵⁵²

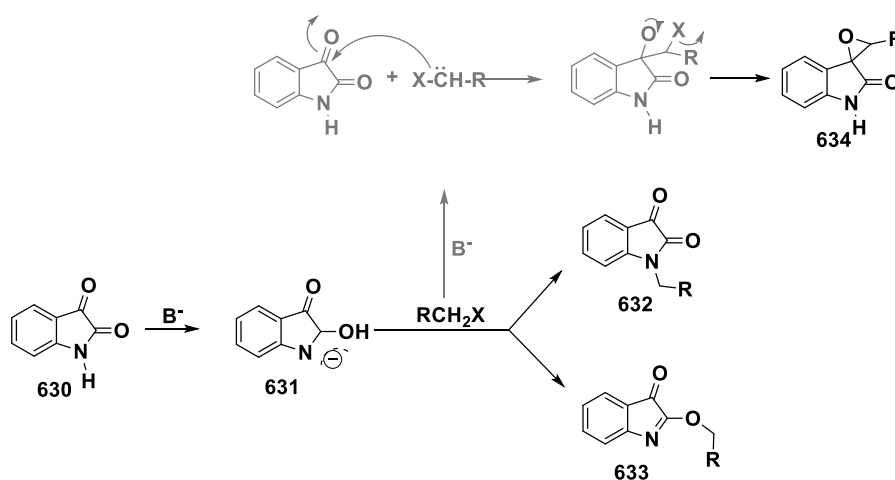
The reactive C-3 carbonyl group of isatins is a key prochiral center, leading to the formation of 2-oxindole derivatives through nucleophilic additions or spiroannulation. These 2-oxindoles, especially those spiro-fused to other cyclic frameworks, have gained significant interest in synthetic organic and medicinal chemistry. They are found in natural products with diverse bioactivities, making them valuable targets for research and synthesis. The architecture of spiro-cyclic frameworks, a challenging endeavour for synthetic organic chemists, has been extensively explored using isatins as precursors, either directly or via 3-substituted 2-oxindoles, enabling the design and synthesis of diverse spiro-cyclic frameworks.

3.4.2 Results and discussion

N-functionalization is pivotal preliminary step to fulfil the following interrupted homologation reactions with carbenoids, because substrates bearing acidic protons are reluctant to undergo carbenoid additions in the absence of a suitable protecting groups. Indeed, it is conceivable that the carbenoid, in presence of an unprotected isatin (**630**) would react as a base which deprotonate the nitrogen, whose N-Li amide intermediate (**631**) would be susceptible to chloromethylenic attack.

The N-protection is commonly performed with a base and an alkylating reagent. As mentioned in the work of Shmidt and coworkers,⁵⁵³ isatin's reactivity with alkylating agents with acidic methylenes can be insidious. Indeed, due to the ambident character of the anion of the amide, the use of alkali metal salts as bases leads mainly to N-alkyl derivatives (**632**),⁵⁵⁴ whereas the use of silver salts leads to O-alkylated regioisomers (**633**).⁵⁵⁵ Nevertheless, the formation of the epoxyoxindole is also often the main product when the alkylating agent has an acidic α -proton such as phenacyl and nitrobenzyl halides (**634**, Scheme 103).⁵⁵⁶⁻⁵⁵⁷

In summary, the course of this reaction depends on the acidity of the methylene attached to the halogen and the reaction conditions, such as the strength of the base, the nature of the solvent and the temperature.



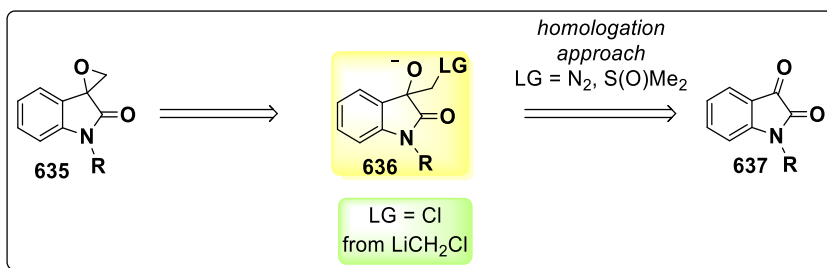
Scheme 103. N-protection reaction with base and alkylating agents and resulting outcomes.

As regards as the project discussed in this section, the N-protection of isatin is carried out in DMF with NaH at 10 °C. After 30 min, the corresponding benzyl halide is added to the mixture reaction and left to stir for 3 h at rt. Afterwards, the reaction mixture is poured into a crushed ice/water suspension and the resulting precipitate is filtered off, washed with cold water and light petroleum, and dried in

vacuo. All the N-functionalized isatins will be directly used for the epoxidation reaction with no further purification needed.⁵⁵⁸

The reason for choosing isatins as starting material lays on the fact that, from a retrosynthetic point of view, it is possible to access 3-spiroepoxy-2-oxindole (**636**) simply through homologation of N-functionalised isatins (**637**) via halolithium carbenoids nucleophilic addition-cyclization sequence (Scheme 104).

Indeed, in 2016, Prof. Pace and his team published a retrosynthetic approach involving the chemoselective addition of a lithium halocarbenoid to the electrophilic ketone moiety of isatin,¹⁰⁶ offering a simple and reliable route to access spiro-epoxyoxindoles. In the latter Pace et al selected the Weinreb amide-containing isatin as the model substrate.



Scheme 104. Rationale for choosing isatin as starting material.

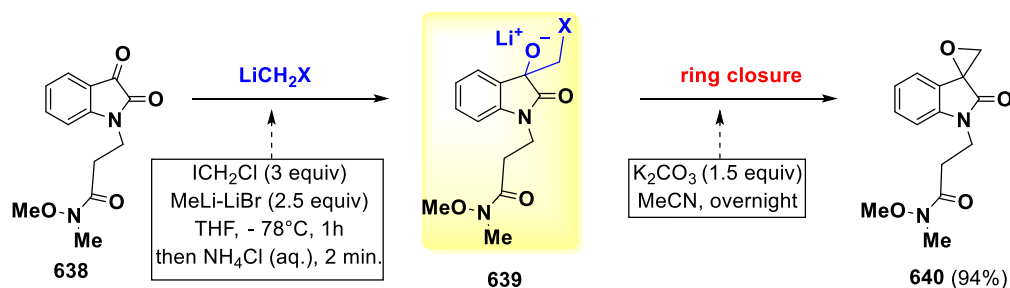
The retrosynthetic analysis of non-substituted analogues suggests the homologation of isatin as a straightforward approach. Previous approaches, such as diazomethane-based homologations⁵⁵⁹ and Corey–Chaykovsky epoxidation,^{9, 11} presented limitations. A unique strategy by Zhu and co-workers involved an intramolecular Friedel–Crafts process, but it provided only a single example of spiro-epoxyoxindole.⁵⁶⁰

To address these challenges, Pace and coworkers proposed an alternative route involving the chemoselective addition of a lithium halocarbenoid to the electrophilic ketone moiety of isatin at C-3. The choice of halocarbenoids is motivated by their versatility in homologation processes, even though certain considerations are required. The choice of the Weinreb amide-containing isatin (**638**, Scheme 105), instead, is intentional to further investigate the chemoselectivity⁵⁶¹⁻⁵⁶² of the process since the great affinity of carbenoids for Weinreb amide.^{147-148, 494}

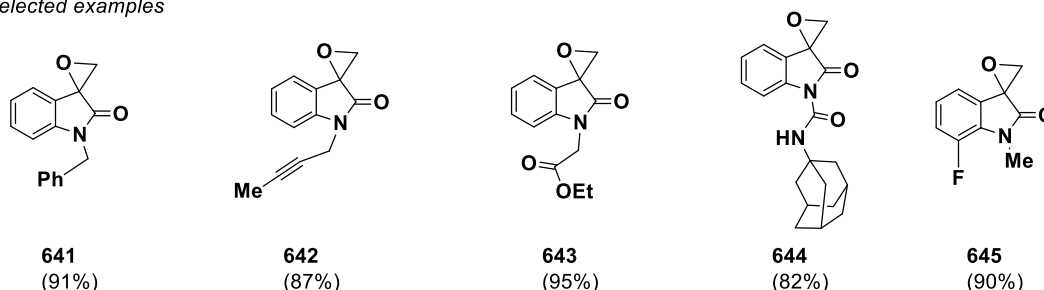
Key points for the success of halocarbonoids-based homologation are:

- the temperature at -78°C (in order to overcome the inherent electrophilicity of the reagent and avoid the degradative α -elimination event);⁵⁶³⁻⁵⁶⁵
- by adapting the standard Barbier-type conditions for the generation of chloromethyl lithium in THF;
- by quenching the homologation step with saturated aqueous ammonium chloride solution.

Thereafter, once the homologation step is completed, the cyclization phenomenon is triggered by redissolving in acetonitrile and adding potassium carbonate, and finally, by increasing the temperature up to room temperature overnight so that epoxidation product occurred (**640**, Scheme 105).



Selected examples



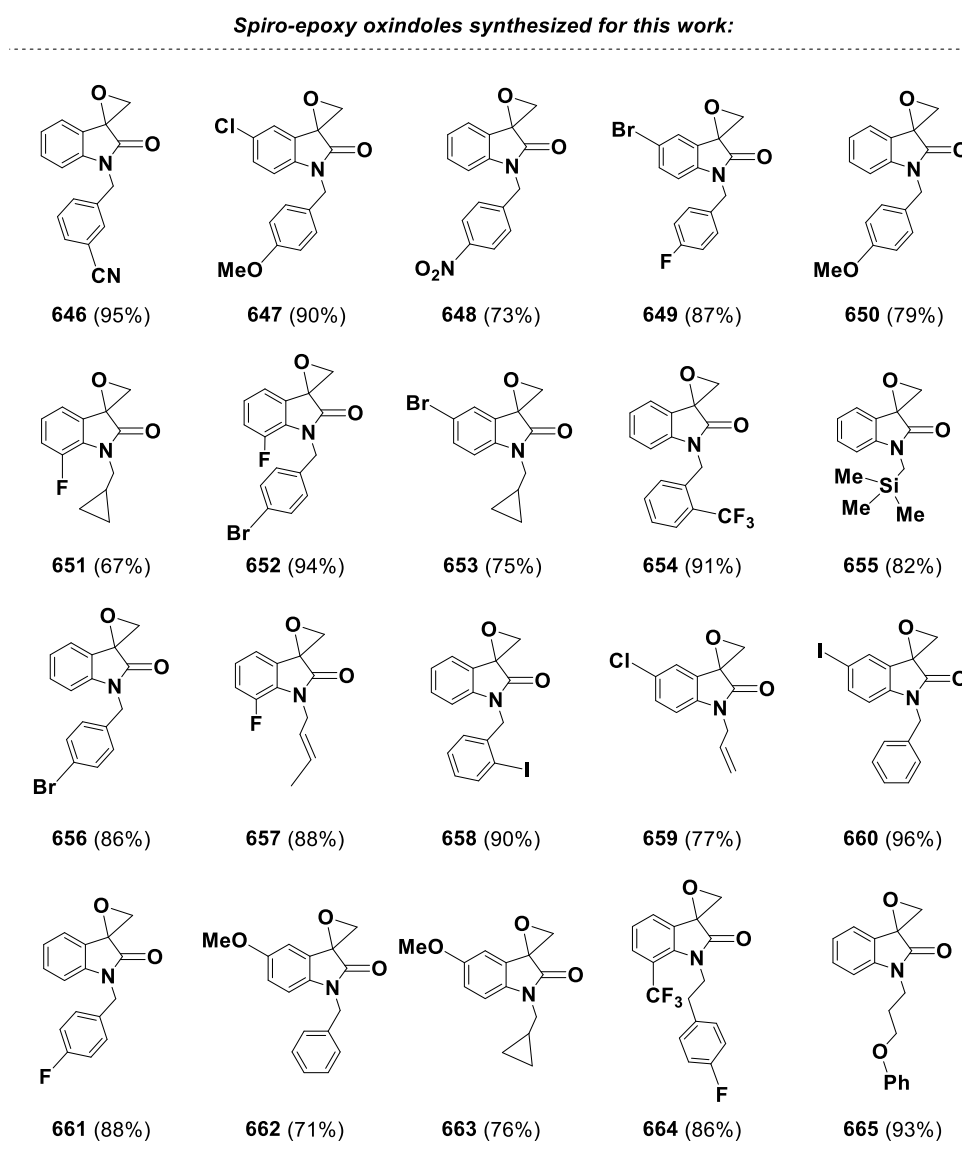
Scheme 105. Pace's spiro-epoxy oxindole's synthesis via LiCH_2X .

The results demonstrated effective epoxidation, with optimized conditions giving the desired product in an excellent yield of 94% (**640**, Scheme 105). Notably, the procedure maintained its features when scaled up to a 10 mmol scale. However, the desired epoxide proved to be highly unstable during chromatographic purifications, requiring specific measures for isolation and characterization.

With the optimized reaction conditions in hand, over 10 examples of spiro-epoxyoxindoles, bearing a wide range of functionalities both on the nitrogen and the aromatic ring of the isatin core, were synthesized. The versatility and chemoselectivity of this procedure were confirmed even in presence of sensitive substituents, such as aliphatic, aromatic, allylic, alkynyl moieties and esters, Weinreb

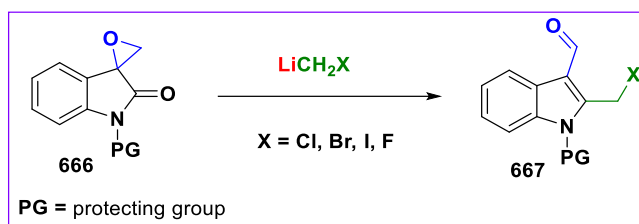
amide, nitrile, and halogens atom placed both on the aromatic ring and allylic moiety (**641** – **645** of Scheme 105).

Applying the same synthetic procedure, we successfully characterized a wide range of unprecedented spiro-epoxyoxindoles, whose reactivity will be explored in the current study (**646** – **665** of Scheme **106**). We were driven by our compelling thirst for discovery and knowledge about homologation events that would have occurred, relating such fascinating class of compounds to halolithium carbenoids. We chose as model substrate for this project N-benzyl spiro-epoxyoxindole, even though on the early-stage of reactivity's studies also N-methyl-spiro-epoxyoxindole was tested (**666** of Scheme 107 and Table 7). Following are represented some of the examples that were synthesized for this project, accompanied by their characterization, since the lack of such findings in literature so far.



Scheme 106. Unprecedented spiro-epoxy oxindoles synthesised through lithium carbenoids for this work.

We were surprisingly amazed by the results obtained from the preliminary attempt of homologation via classic lithium carbenoids mediated reaction, as shown in the following scheme.

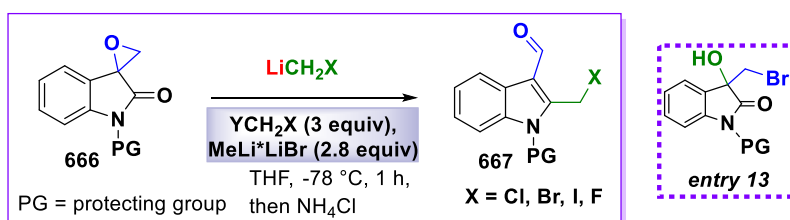


Scheme 107. This work's focus reaction.

We were expecting a ring-opening reaction, obviously, and a subsequent homologation at C3, but as illustrated in the above scheme, the homologation occurred at C2, while at C3 there will be a rearrangement of the oxirane in aldehyde, and later, a detailed mechanistic pattern that led us to the given structure will be further discussed (Scheme 107).

When we started the optimization studies on N-methyl epoxy-oxindole we observed good response by treating the starting material in Babier-type conditions, inert atmosphere (under argon), at -78 °C and by employing chloromethyl lithium as homologating agent, proceeding after 1 hour with acidic quenching (with NH₄Cl aqueous saturated solution). Then following work up and extraction with ethyl acetate or DCM, and as final step, chromatographic purification on silica gel were necessary to obtain the final isolated product in 80% yield (entry 1 of Table 7).

Table 7. Optimization table



Entry	Carbenoid or Nu	PG	Equivalents	Temperature	Solvent	Time	Yield [%]
1	LiCH ₂ Cl	Me	2.8	- 78 °C	THF	1 h	80
2	LiCH ₂ Br	Me	2.8	- 78 °C	THF	1 h	-
3	LiCH ₂ I	Me	2.8	- 78 °C	THF	1 h	-
4	LiCH ₂ F	Me	1	- 78 °C	THF:Et ₂ O	5 min.	20
5	LiCH ₂ Cl	Me	2.8	- 78 °C to rt	THF	24 h	10
6	I ₂ ZnCH ₂ I	Me	2.8	- 15 °C to rt	THF	24 h	8
7	<i>i</i> -PrMgCH ₂ I	Me	2.8	- 78 °C to rt	THF	24 h	-
8	LiCH ₂ Cl	Bn	2.8	- 78 °C	THF	1 h	95
9	LiCH ₂ F	Bn	1	- 78 °C	THF:Et ₂ O	5 min.	83
10	LiCH ₂ Br	Bn	2.8	- 78 °C	THF	1 h	58
11	LiCH ₂ I	Bn	2.8	- 78 °C	THF	1 h	50
12	LiBr	Bn	2.8	- 78 °C	THF	1 h	traces
13	LiBr	Bn	2.8	- 78 °C to rt	THF	24 h	40*

When we changed halogens atom on the carbenoid, no product was obtained in the case of bromomethyl lithium and iodomethyl lithium, and with fluoromethyl lithium the homologated aldehyde bearing compound was observed with a yield of 20% (entries 2, 3, and 4 of Table 7). By leaving the reaction to stir for 24 hours, and let it to reach room temperature before quenching, gave as result a lower yield (10%, entry 5 of Table 7). By using 2-Methyl THF, instead of THF; gave the same result as the latter case. Finally, by switching to a different metal on the carbenoid, such as Zn carbenoid and Mg one, the product occurred just in the former case with a very low yield (8%, entries 6 and 7 of Table 7).

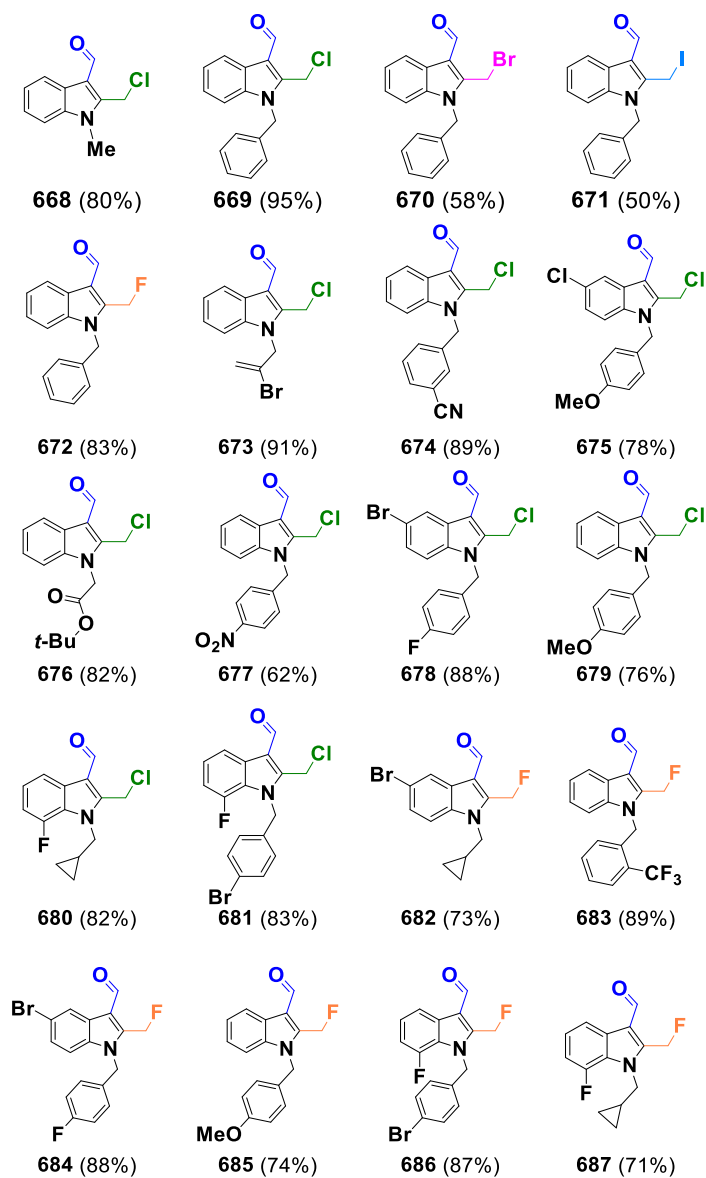
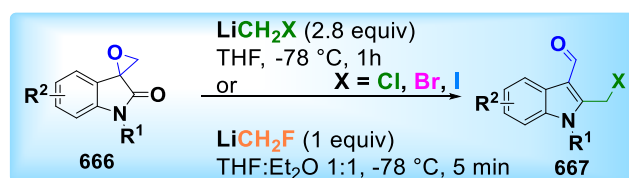
As matter of comparison, we applied the same optimization studies on a different N-functionalized epoxy-oxindole, namely the N-benzyl one, showcasing a higher reactivity. Indeed, higher yield was observed in standard conditions with chloromethyl lithium (95 %, entry 8) and fluoromethyl lithium (83%, entry 9), and with bromomethyl lithium and iodomethyl lithium the products were isolated in 58% and 50% yield respectively (entries 10 and 11 of Table 7).

Once established the optimized conditions and which one of the model substrates would be more suitable to be used, we further deepen the reactivity's studies on the N-benzyl stereotype. By treating the starting material with plain lithium bromide, in the standard reaction conditions, only traces of the aldehyde product were observed. Prolonging the reaction's time from 1 hour to 24 hours and let the reaction mixture to stir from -78 °C to rt yielded the ring-opening product in 40% (entries 12 and 13 of Table 7).

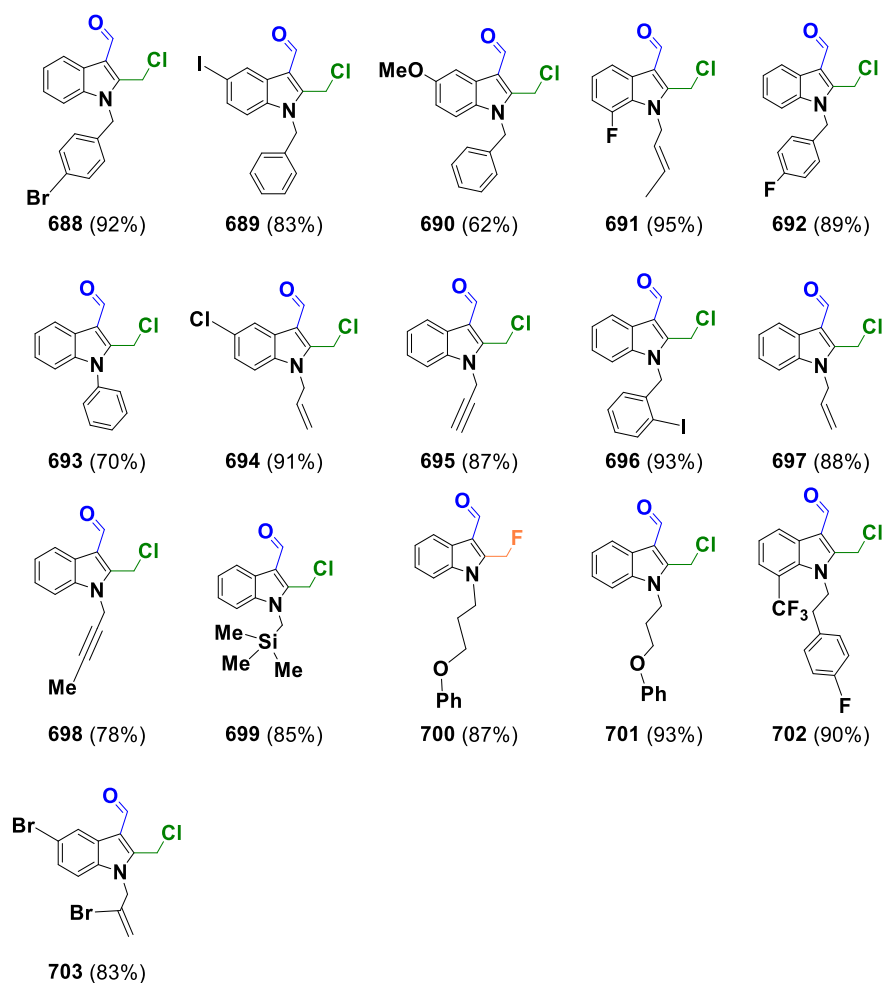
After completion of the optimization studies, two different procedures were adopted, depending on the halogen atom that we aimed to add to the starting material's skeleton. When performing the homologation with chloro-, bromo- and iodo- carbenoids the same reaction conditions used for N- methyl and N-benzyl epoxy-oxindoles, previously described, were adopted also with new and diversely functionalized starting materials. Pivotal points for the homologation reaction's success with these halogens are: complying to Barbier-type conditions that means generating the carbenoid in the starting material containing mixture, the number of equivalents (1 for the starting material, 3 for the halogenated carbon unit donor and 2.8 for the lithiating agent), the temperature (-78 °C), the solvent (just THF) and the time of the reaction (1h).

More attention, instead, is required in the case of homologation reaction with fluorinated carbenoids due to their extremely fragile nature and difficult handling. Also in this case, Barbier-type conditions are an indispensable parameter for the success of the homologating event, but some parameters need to be adapted to this very unique and delicate reagent: the numbers of the equivalents is different, slightly exceeding in starting material (1.5 equiv for the starting material, 1 equiv for the halogenated carbon unit donor and 2 equiv for the lithiating agent); the solvent in this case is a mixture in equal ratio of THF and Et₂O (1:1, v/v); the time is just 5 minutes, due to the high instability of the fluorinated carbenoid.

With these premises, the scope of the reaction was investigated and nearly 40 examples of unprecedented 2-halomethyl-1*H*-indole-3-carbaldehydes were synthetized, highly multi-functionalized either on the aromatic positions and on the nitrogen's protecting group.



Scheme 108. Scope of the reaction (first part)



Scheme 109. Scope of the reaction (second part)

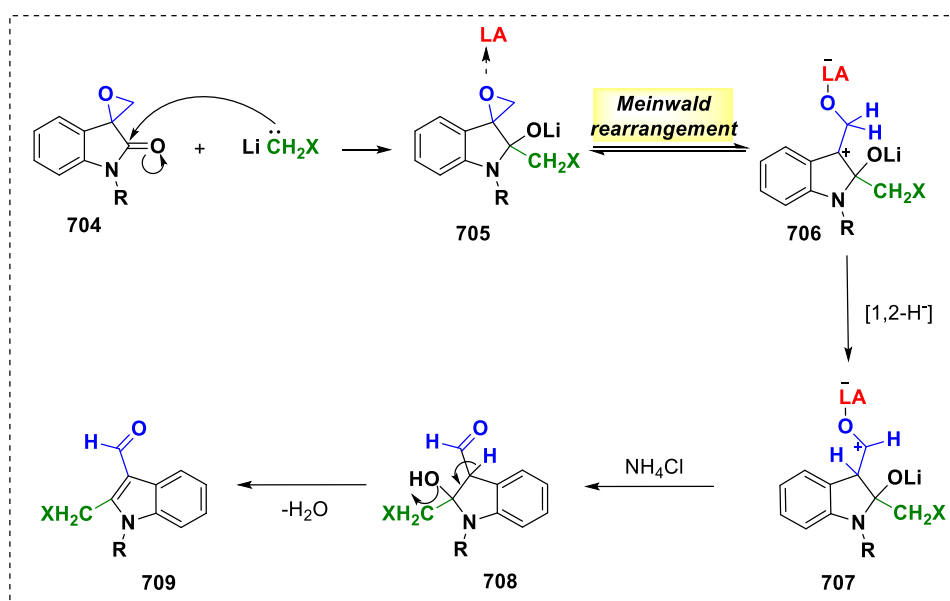
The chemo-selectivity is fully preserved in presence of aliphatic, aromatic, allylic and alkynyl moieties and was further enhanced in the case of esters, ethers, nitrile, nitro, and halogens substituents, such as bromines, iodine, fluorine and chlorines placed simultaneously on the aromatic rings and the allylic moieties, which did not influence even minimally the iodine-lithium exchange required to form the reactive carbenoid (**668** – **703** of Schemes 108 and 109).

Impressively, we successfully synthesized a considerable amount of multi-fluorinated compounds, proving how impactful this procedure can be for the whole synthetic chemist's community.

As mentioned before, from the mechanistic point of view, the final structure is the result of the lithium carbenoid's nucleophilic attack at the carbonyl in C2 (**705**, Scheme 110), yielding as intermediate the O-lithiated salt at C2 and the ring opening product at C3 (**706**), due to the presence of the Lewis acid (LiBr) in the reaction's mixture (additionally proved during the optimization studies, when running the

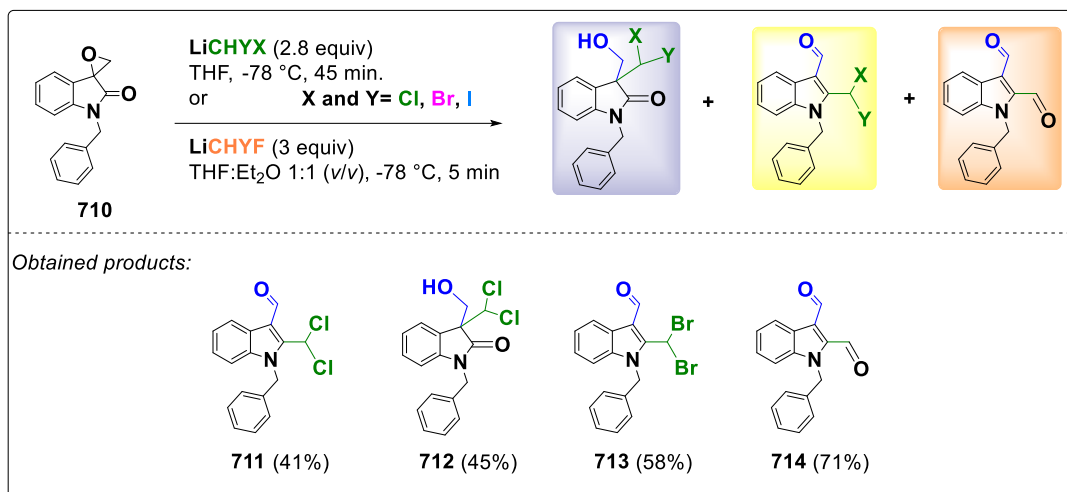
reaction just in presence of lithium bromide, the ring opening product was the only compound retrieved).

When the ring-opening sequence occurs, in what is known as Meinwald rearrangement (**705** and **706** of Scheme 110), concomitantly the formation of a shifting carbocation occurs (precisely 1,2-hydride shift, **707**), which brings to the α , β -unsaturated aldehyde (**709**) after acidic quenching and following water elimination (**708**).



Scheme 110. Mechanism of the reaction

To expand the overview of the addition of carbenoidic reagents to isatin derivatives, we approached the homologation via dihalomethylcarbenoids, by exploiting the deprotonation pathway as synthetic strategy of the carbenoid itself. As regards this matter, we observed very interesting results: on one hand, the ring opening products occurred, such as the examples with dichloromethylithium (**712**, Scheme 111); on the other hand, we observed the bis-halogenated homologated products at C2, with aldehyde at C3, *i.e.* the ones treated with dibromomethylithium (**713**) and dichloromethylithium (**711**). Nevertheless, the most interesting product was obtained in the reaction with fluoroiodomethylithium, where a bis-aldehyde bearing compound (**714** of Scheme 111), respectively at C2 and C3, was retrieved.



Scheme 111. Applicability of this protocol

3.4.3 Conclusions

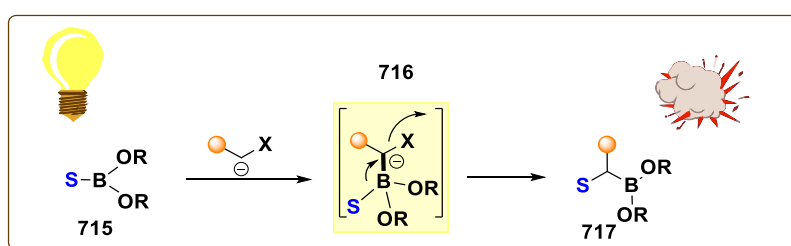
In conclusion, an outstanding chemoselective and innovative tactic yielding to unprecedented α , β -unsaturated aldehydes has been developed via nucleophilic addition of carbenoidic halomethyl lithium to various N-functionalized spiro-epoxyoxindoles. This method has shown a broad and excellent scope and its chemoselectivity is fully maintained, even in the presence of additional electrophilic functionalities such as ester, nitrile, exchangeable halogens, nitro, or acidic secondary lactam.

3.5 Regioselective Lewis-acid mediated opening of THF with sulfur nucleophiles: a convenient entry to ω -mercapto-butan-1-ols

3.5.1 *Introduction*

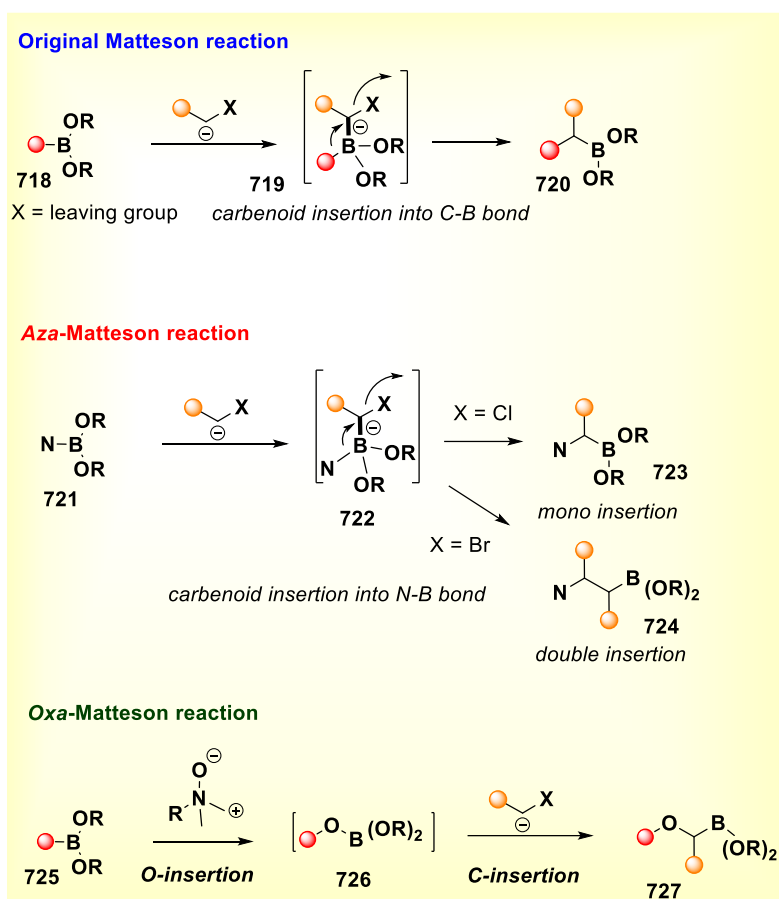
Crucial for the understanding of the work that will be discussed into this section, are two concepts: boron homologation reactions and the role of carbenoids in a broader scenario other than C-C bonds creation. As extensively formerly covered in the introduction chapter [Section 1.13](#) of this thesis, the typical boron homologation reaction is commonly identified with the Matteson reaction.^{39, 425, 566}

The latter involves formal carbenoid insertions into C-B bonds, demonstrating to be highly efficient for building SOMs (small organic molecules) with various and functionalized carbon scaffolds. Intriguing challenge for chemists is whether heteroatoms could be inserted in an iterative way, such as carbenoid can, exploiting the Matteson chain elongation. Following the inspirational work of G. Dong,⁵⁶⁷ who expanded the scope of Matteson reactions and introduced for the first time the so called *aza-Matteson*,^{51, 568} and *oxa-Matteson* reactions,⁴⁰³ we attempted to investigate the feasibility of a *thio-Matteson* reaction (Scheme 112).



Scheme 112. Initial idea for laying down the base for the current work

Conventionally, in a pure Matteson reaction, a carbanion bearing an α -leaving group, such as a carbenoid, attacks the electrophilic boron center (**718**, Scheme 113) to form a considerable stable borate intermediate (**719**, Scheme 113) at low temperature, causing with the increasing of the temperature, the carbon substituent on the borate to undergo a C-1,2-migration to replace the leaving group via the backside attack (**720** of Scheme 113).



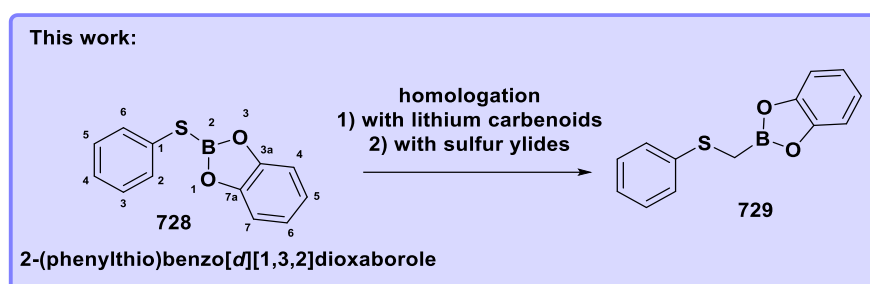
Scheme 113. Evolution of Matteson-type reactions

In the G. Dong's *aza-Matteson* homologation,⁵¹ published in 2021, the carbenoid was inserted into the N-B bonds of aminoboranes (**721**) and by changing the leaving groups and the Lewis acid activators, mono- and double-methylene insertions occurred resulting in diverse α - and β -boron-substituted tertiary amines (**723** and **724** of Scheme 113). Subsequently, the same research team developed, in a parallel study of 2022, a new ether synthesis strategy via sequential oxygen insertion into C-B bond of boronates (*O-insertion*, **725**) and a carbenoid insertion into the O-B bond of the resulting borate esters (*C-insertion*, **726**), originating the so called *oxa-Matteson* reaction.⁴⁰³

In a recent work, also published in 2023,⁵⁶⁸ Dong has presented the first programmable amine synthesis through iterative boron homologation in which the detailed sequential one-pot N- and C-insertion into C-B bonds was described. In the latter study, the challenging synthetic process that brings to the formation of aminoboranes by directly treating boronates with nitrenoids, merging nitrenoids and carbenoid insertion into one reaction vessel, was unravelled.

3.5.2 Results and Discussion

At the outset of our investigations, we considered to homologate a S-B bond in order to access a *gem*-borylated-sulfurated methane (**729** of Scheme 114); accordingly, 2-(phenylthio)benzo[d][1,3,2]dioxaborole⁵⁶⁹ (**728**, Scheme 114) – was individuated as the competent starting material for realizing homologation events with both carbenoid like reagents (*e.g.* LiCH₂X) and sulfur ylides (*e.g.* Me₃SI/base).



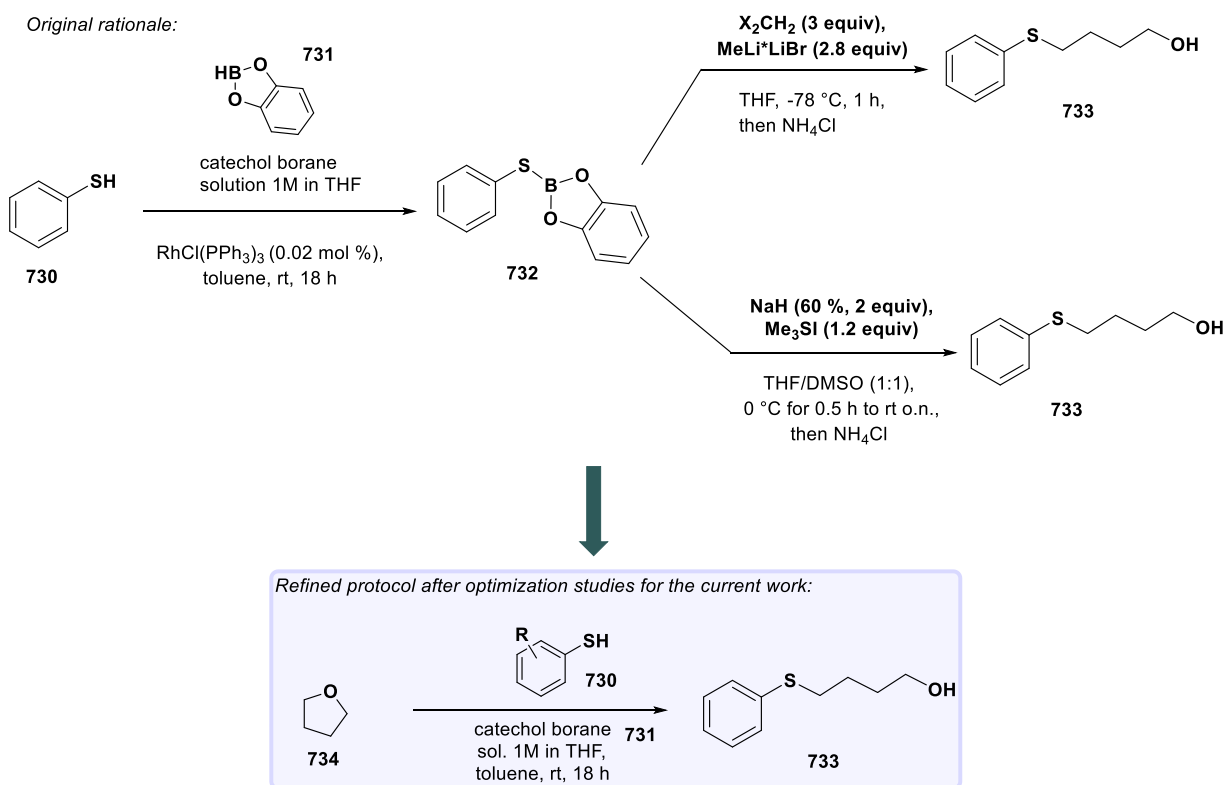
Scheme 114. Hypothetical homologation of S-B bond via carbenoid or sulfide regime

The initial experiments showed the formal impossibility to realize a single homologative event, since – regardless the releasing C1 units used - four methylene units were inserted within the S-B bond. In order to rationalize the unusual four-carbons homologation, the following points merit mention:

- no significant effect of stoichiometry was observed by varying the loading of C1 agents (entries 1-7 of Table 8);
- similarly, the outcome did not change when using distinct carbenoids (LiCH₂Cl, LiCH₂Br, LiCH₂I, including the less nucleophilic ClCH₂MgCl, entries 1, 2, 3, and 9^c of Table 8).

Of particular interest is the fact that the overall transformation was highly dependent on the structural characteristics of the boryl-manifold in the initial S-B material (**732** of Scheme 115 and Table 8).

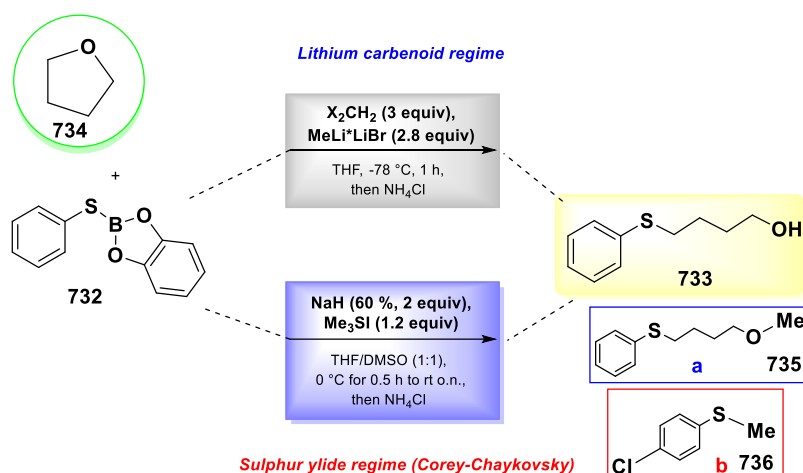
Indeed, in case of switching from the catechol- analogue to the pinacol- one, the transformation did not provide the four-membered analogue, but the mono-homologated product (entry 7^b of Table 8). Moreover, the presence of an aromatic functionality on sulfur was required, being an aliphatic analogue (benzyl) not reactive at all under the usual conditions (entries 12 and 13 of Table 8).



Scheme 115. Development and design of the synthetic protocol for this work

During the optimization studies of the original protocol, which is involving still the presence of lithium carbenoids or sulfur ylides in the reaction's scenery (Scheme 115), being for this reason split in two synthetic phases — the first one leading to the synthesis of the S-B compound (**732** of Scheme 115), while the second one represents the homologative event of the thiophenol- counterpart with the four methylenic units (**733** of Scheme 115) — we collected evidences that confirmed and proved the THF (**734** of Scheme 115) being the undiscussed and unexpected protagonist of this homologation reaction.

Table 8. Optimization Table



Entry	RS-B	RS-B	LiCH ₂ X [equiv]	Sulfur Ylide [equiv]	Yield [%]
1	PhS-	B-catechol	Br, 2.8	-	93
2	PhS-	B-catechol	Cl, 2.8	-	95
3	PhS-	B-catechol	I, 2.8	-	90
4	PhS-	B-catechol	-	1.2	85
5	PhS-	B-catechol	-	0.5	30
6 ^a	PhS-	B-catechol	-	10	90
7 ^b	PhS-	B-Pin	-	1.2	70*
8	PhS-	B-Pin	Br, 2.8	-	-
9 ^c	PhS-	B-catechol	-	-	80*
10	BnS-	B-catechol	Cl, 2.8	-	-
11	BnS-	B-catechol	-	1.2	-
12	RS- (R= aliph.)	B-catechol	Cl, 2.8	-	-
13	RS- (R= aliph.)	B-catechol	-	1.2	-

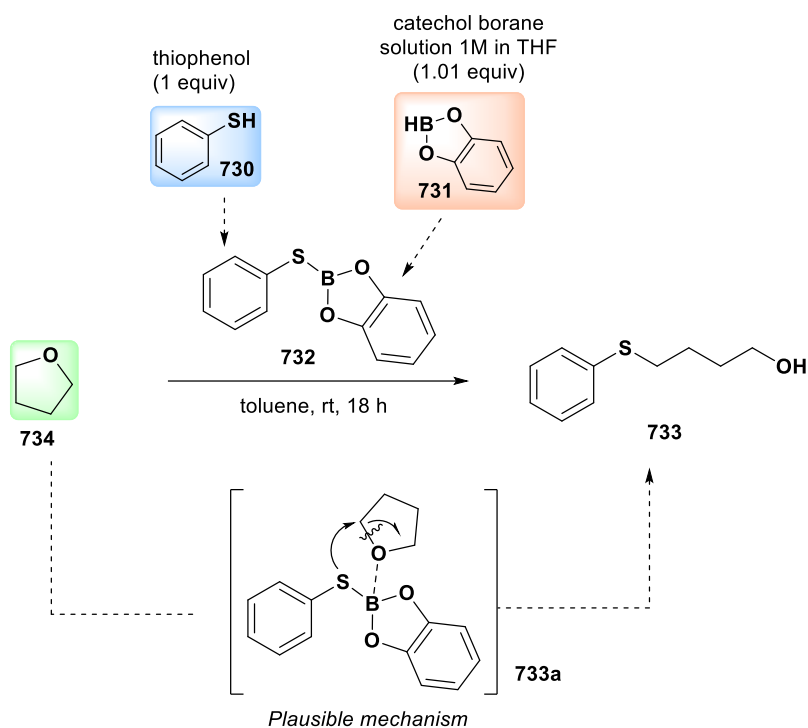
*a: 10 equiv of sulfur ylide resulted in the further methylation of O (see product a).

*b: in this case pinacol borane was used (resulting in the product b);

*c: homologation carried out by ClCH₂MgCl

These experimental evidences suggested us to individuate the possible interference of the practical procedure adopted for preparing the starting materials. In this sense, the use of different forms of catechol-borane appeared to completely modulate the outcome of the expected homologation. This is, employing a commercially available 1 M THF solution (**731** of Scheme 116), resulted in observing – at the end of the sequence – the four-carbon elongated system. Whereas – by simply repeating literature conditions based on the treatment with the neat reagent – no homologation at all was observed upon treatment with C1-reagents. Collectively, these results indicate the origin of the four

methylenes released by the same THF instead of consecutive homologative events. Accordingly, the Lewis acid character of the boron atom could justify the nucleophilic attack of the oxygen of THF and, therefore, inducing the C-O breaking event in the presence of mercaptanes (intermediate **733a** of Scheme 116).

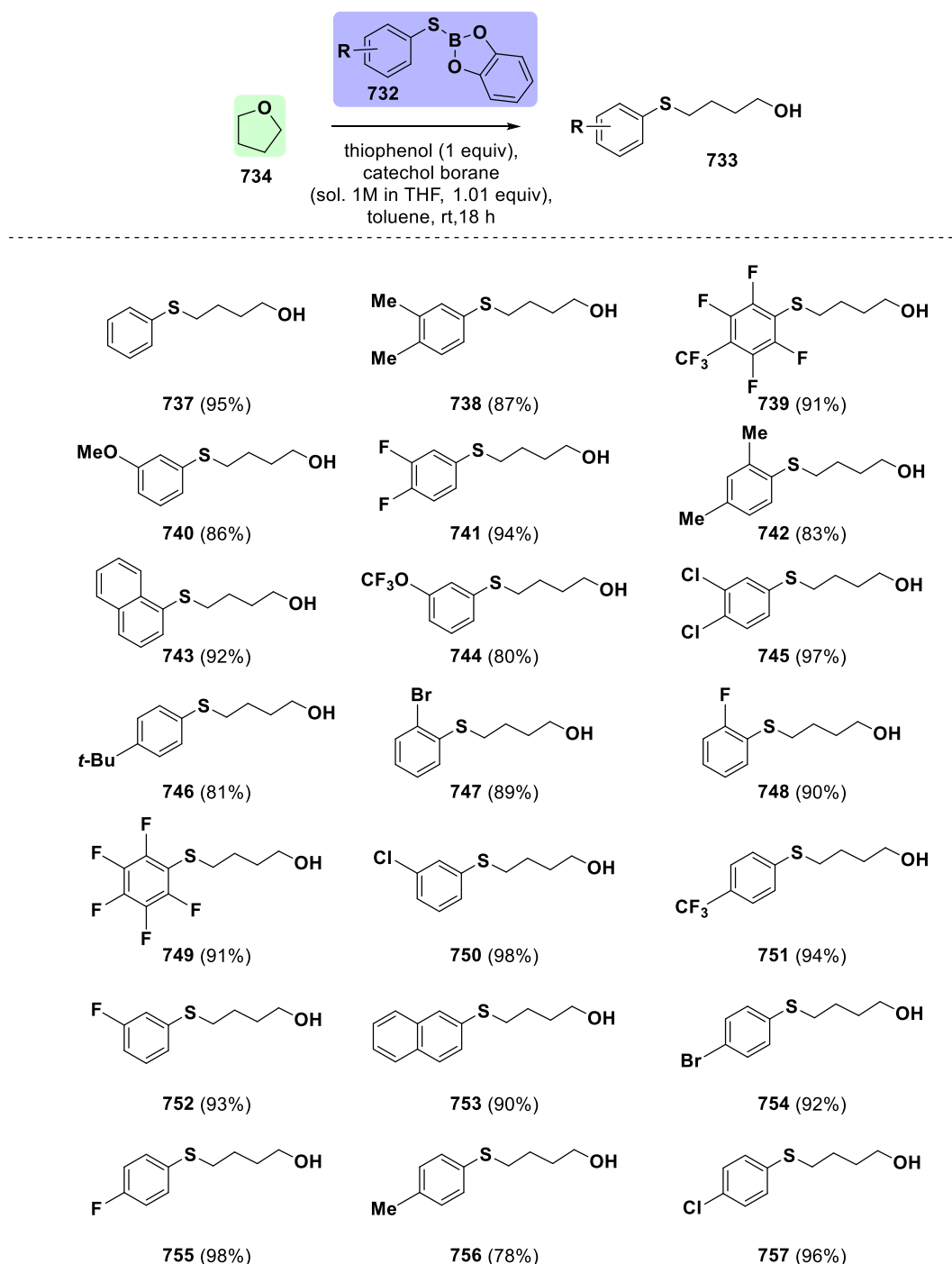


Scheme 116. Optimized reaction's regime and proposed mechanistic insight

In summa, the process – highlighting the powerful significance of THF as a reagent rather than a solvent – suggests that four-methylene homologative events can be better accomplished in the absence of prototypal C1-units.

All the starting materials were prepared from variously substituted thiophenols and catechol borane solution (1 M) in THF, which was the key element for the success of the reaction. The presence of THF, indeed, would justify the formation of such product, how clarified in the case where the starting material has been prepared with the pure catechol borane, demonstrating that the desired product was not retrieved.

With the optimized conditions in hand, we started the investigation to complete the scope of the reaction.



Scheme 117. Scope of the reaction

The protocol allowed us to prepare 20 examples, each one presenting different range of substitution on the aromatic ring of the thiophenol moiety. The chemoselectivity is fully preserved in presence of highly sensitive functionalities, such as bromine (**747** and **754** of Scheme 117), whose affinity for lithium carbenoids is well known. As overall consideration, the reaction is favoured with mild electron-releasing groups, such as methyl (mono or bis-methyl groups, both in position 3,4 and 2,4; **738**, **742** and **756**), O-methyl (**740**) and aliphatic substituents (*e.g.* the *t*-butyl one in position 4, **746**). The

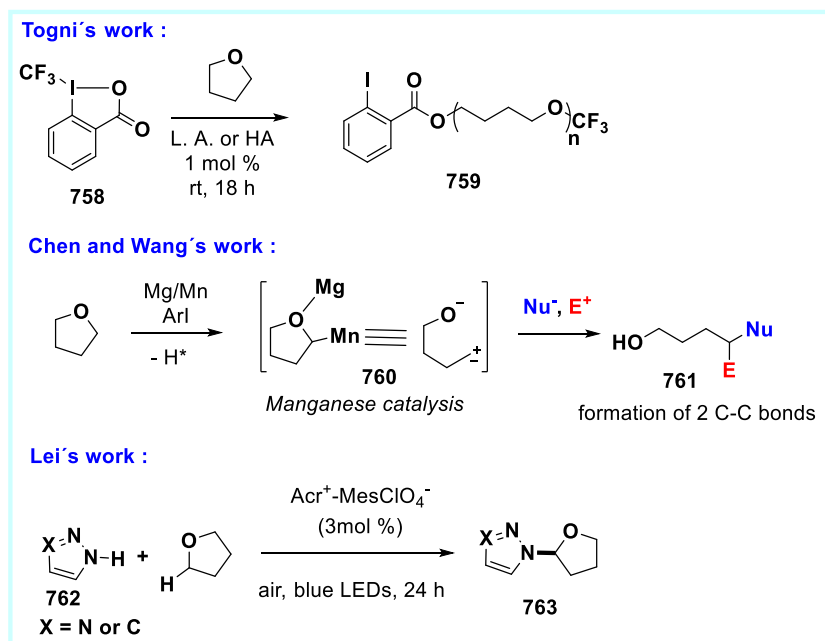
reaction is highly successful with fluorinated thiophenols, even the ones presenting high hindrance such as the one with penta-fluorothiophenol (**739** and **749** of Scheme 117). This approach was efficient also in the cases of 1- and 2-thionaphthol (**743** and **753** of Scheme 117).

Despite we didn't succeed in what was our premise at the beginning of this study, surprisingly new aspects and results have been discovered, which represent a step closer to uncover the mystery of *thio*-Matteson homologation. The role of THF was predominant as reagent rather than a common reaction mean, event that is not that commonly observed along homologation reactions scene. Indeed, literature databases have listed very few examples where THF is employed as reagent in organic chemistry reactions scene.

In 2010,⁵⁷⁰ Togni's and coworkers efforts' contribution highlighted the role of 1-Trifluoromethyl-1,2-benziodoxol-3-one (**758** of Scheme 118) in transferring an electrophilic CF₃ group to tetrahydrofuran (THF) in the presence of a Lewis or Bronsted acid. The CF₃-bearing initial reagent could transfer the CF₃ group to the oxygen atom of THF when activated by an acid, representing a novel approach since more traditional methods relied on nucleophilic trifluoromethylation. The final products, namely trifluoromethyl ethers (**759**), were the result of a ring-opening mechanism, being these conditions very significant because such transformation typically required harsh conditions and hazardous reagents.

In 2014,⁵⁷¹ Chen and Wang and coworkers discovered an alternative and enhanced use of Grignard reagents in THF. The discovery of organomagnesium compounds by V. Grignard has significantly advanced C–C bond formation in organic synthesis. Grignard reagents, particularly in ethereal solvents like diethyl ether and THF, are highly effective for adding to imines and nitriles, leading to a variety of amines and ketones. While THF is typically inert to organometallics at low temperatures, it can be deprotonated by strong organo-Li bases. As proved by earlier studies bimetallic reagents, such as sodium zincate, can metalate THF, a process previously limited to highly electropositive metals like lithium. More reactive bimetallic bases, such as Na/Mn or Na/Mg, have been shown to deprotonate and dismember THF into useful products.

This paper introduced a novel approach using a Mn/Mg bimetallic system and an aryl iodide to generate α -manganated THF (**760** of Scheme 118), which acted as a 1-butoxide. This facilitated the creation of geminal C–C bonds at the C-2 position of THF when reacted with Grignard reagents and imines/nitriles. The reaction efficiently produced 1,5-amino and keto alcohols (**761**), diverging from traditional Grignard additions.



Scheme 118. Other examples where THF is actively participating as reagent rather than mere solvent

Lastly, as shown in a remarkable work of Lei and coworkers, in 2017,⁵⁷² the THF can be exploited in developing new synthetic processes in green chemistry. They developed a mild and simple method for the catalytic oxidative amination of THF using visible-light catalysis, with molecular oxygen as an oxidant. This method efficiently tolerates various azoles (**762**), offering a green route to synthesize N-substituted azoles, which are valuable in agriculture, antifungal applications, and pharmaceuticals. Visible light photoredox catalysis has become a powerful tool in organic synthesis due to its mild conditions. Building on their interest in C–H activation, they report a metal-free catalytic oxidative amination of THF under visible-light irradiation using air as an oxidant. Using $\text{Acr}^+ - \text{Mes ClO}_4^-$ as a photocatalyst, they achieved a yield of 82% with 3-phenyl-1H-pyrazole as the model substrate (**763** of Scheme 118).

3.5.3 Conclusion

In this study, we explored the possibility of a *thio*-Matteson homologation reaction by investigating the S-B bond homologation of 2-(phenylthio)benzo[d][1,3,2]dioxaborole. Our findings indicate that thiobutanol is the sole product when the starting material is treated with either lithium carbenoids or sulfur ylides, under specific conditions. The homologation reaction depends critically on the presence of a catechol borane moiety and an aromatic thiophenol counterpart, as well as the presence of THF.

While our initial goal of achieving a *thio*-Matteson homologation was not fully realized, our study uncovered new aspects of the reaction mechanism, particularly the unique role of THF as a reagent.

In summary, although further studies are required to fully elucidate the mechanism and explore practical applications, our findings represent a significant step forward in understanding the *thio*-Matteson homologation and highlight the unique behaviour of THF in this new synthetic protocol.

4 Conclusion

Beyond its immediate synthetic utility, the insight gained from this research's work sets the foundation for further exploration in homologation chemistry. By expanding our understanding of homologation strategies and their applicability, we pave the way for future advancements in selective functionalization methodologies. Central to this thesis is the innovative application of lithium carbenoids as homologating agents, unlocking new pathways for the functionalization of heteroatom - containing electrophiles.

In this context, we successfully established a robust approach for the synthesis of rare unsymmetrical dithioacetals using lithium carbenoids as methylene donors, overcoming previous synthetic limitations. The strategic use of thiosulfonate esters in combination with an external sulfur nucleophile enabled a highly chemoselective transformation, expanding the synthetic accessibility of these valuable compounds. Furthermore, the extension of this methodology to oxothioacetals ($\text{RS}-\text{CH}_2-\text{OR}$) represents a major advancement, demonstrating broad functional group tolerance and significant potential for further applications, particularly in tyrosinase inhibition.

Moreover, this research also introduced a paradigm shift in lithium monohalocarbenoid chemistry by repurposing α -elimination—a traditionally undesired side reaction—into a synthetically valuable transformation. The selective synthesis of β -halohydrins was achieved through controlled epoxide ring-opening, with lithium halide salts (LiX) playing a dual role as both a Lewis acid and a nucleophilic halide source. This methodology proved highly versatile, accommodating a range of halocarbenoids and epoxide substrates while maintaining stereochemical integrity.

A further breakthrough was realized in the homologation of N-functionalized spiro-epoxyoxindoles, leading to the highly chemoselective synthesis of α,β -unsaturated aldehydes. The combination of homologation at the C2 position with a Meinwald rearrangement at C3 resulted in a unique and scalable approach to structurally complex aldehydes. By leveraging the reactivity of lithium halocarbenoids under optimized conditions, nearly 40 unprecedented 2-halomethyl-1*H*-indole-3-carbaldehydes were synthesized with high precision.

Finally, the investigation into the *thio*-Matteson homologation reaction uncovered a completely unexpected reactivity twist, wherein THF acted as both solvent and reactant, facilitating a four-carbon insertion process. This discovery highlights the untapped potential of common solvents in organic transformations and opens new avenues for further mechanistic exploration. The most striking finding of this study was the central role of THF, which acted not merely as a solvent but as a reagent, directly contributing the observed four methylene insertions. This was evidenced by the fact that employing a 1 M THF solution of catecholborane led to the expected transformation, whereas

using neat catecholborane resulted in no homologation at all. Our mechanistic hypothesis suggests that the Lewis acidic boron center facilitates nucleophilic attack by the sulfur of the thiophenol counterpart, triggering a C–O cleavage event and ultimately leading to the observed four-carbon homologation. While our initial goal of achieving a classical *thio*-Matteson reaction was not realized, this study has uncovered a novel reactivity paradigm that may pave the way for new synthetic strategies involving THF-mediated transformations.

Collectively, these findings provide valuable contributions to homologation chemistry, offering new tools for precise C1-insertion methodologies and expanding the synthetic utility of lithium carbenoids. Future studies will extend the applicability of these methodologies to broader classes of substrates, exploring new electrophilic/nucleophilic partners, and further elucidating the mechanistic intricacies of lithium carbenoid reactivity. By addressing longstanding challenges and introducing innovative solutions, this work reinforces the significance of homologation chemistry in modern organic synthesis and its potential impact on medicinal and material sciences.

5 Experimental part

5.1 Instrumentation and general analytical methods

Chemicals were supplied from different sources (SigmaAldrich, Acros, Alfa Aesar, Fluorochem and TCI Europe) and used without further purification. Solvents used in synthesis and chromatographic purification steps were distilled prior use (ethyl acetate, petrol ether, n-hexane, DCM), THF and 2-MeTHF used for synthesis were distilled over Na/benzophenone. All air moisture sensitive reactions were performed under inert atmosphere of argon. Sensitive reagents or solutions were transferred *via* syringe or cannula through rubber septa.

Thin layer chromatography (TLC) was carried out on aluminum sheets precoated with silica gel 60F²⁵⁴ (Merchery-Nagel, Merk); the spots were visualized by UV light ($\lambda = 254$ nm) and/or KMnO₄ (aq.) was used as revealing system.

Purification of compounds was performed by column chromatography on silica Gel 60 (0.04-0.063 mm).

Mass spectra were obtained on a Shimadzu QP 1000 instrument (EI, 70 eV) and on a Bruker maXis 4G instrument (ESI-TOF, HRMS).

NMR spectra were recorded on Bruker Avance III 200 MHz spectrometer (200 MHz for ¹H, 50 MHz for ¹³C), 400 MHz spectrometer (400 MHz for ¹H, 100 MHz for ¹³C, 40 MHz for ¹⁵N, 376 MHz for ¹⁹F. The center of the (residual) solvent signal was used as an internal standard which was related to TMS with δ 7.26 ppm (¹H in CDCl₃), 7.16 ppm (¹H in C₆D₆), 2.50 (¹H in DMSO-d₆), 2.05 ppm (¹H in Acetone-d₆), and δ 77.0 ppm (¹³C in CDCl₃), 128.06 (¹³C in C₆D₆), 29.8 (¹³C in Acetone-d₆). ¹⁵N NMR (gs-HMBC) spectra were referenced against neat, external nitromethane. ¹⁹F NMR spectra were referenced *via* the Ξ ratio (absolute referencing). Spin-spin coupling constants (*J*) are given in Hz.

In nearly all cases, full and unambiguous assignment of all resonances was performed by combined application of standard NMR techniques, such as APT, HSQC, HMBC, HSQCTOCSY, COSY and NOESY experiments.

Melting points were determined on a Reichert-Kofler hot-stage microscope and are uncorrected.

5.2 Supporting information for the [Section 3.4](#)

5.2.1 General procedures

5.2.1.1 General Procedure for the chemoselective addition of LiCH₂Cl to isatins and epoxide formation (General Procedure 1)

To a cooled (−78 °C) solution of the appropriate isatin (1.0 equiv) in dry THF (0.5 M concentration) was added chloriodomethane (3 equiv). After 2 min, an ethereal solution of MeLi–LiBr 2.2 M (2.5 equiv) was added dropwise over 5 min. The resulting solution was stirred for 1 hour at that temperature. After quenching with saturated aqueous NH₄Cl at −78 °C, the cooling bath was removed and, the mixture was stirred till it reached rt. After adding diethyl ether, the resulting organic phase was extracted, dried over Na₂SO₄ and, finally the solvent was removed under vacuum. The resulting crude mixture was re-dissolved in acetonitrile and potassium carbonate (1.5 equiv) was added. The suspension was stirred at rt overnight; then, water and diethyl ether were added and, after extracting the organic phase, drying over Na₂SO₄, and filtering the solvent was removed under vacuum. The resulting crude compounds were purified as reported below through neutral alumina chromatography (Brockmann degree IV).

5.2.1.2 Homologation reaction via LiCH₂Cl (General Procedure 2)

To a well stirred solution of spiro-epoxyoxindole (1 equiv) in dry tetrahydrofurane (THF) at −78 °C, chloriodomethane (3 equiv) was added under dry conditions, followed by the dropwise addition of methyllithium lithium bromide (MeLi·LiBr, 2.2 M, 2.8 equiv). After one hour, the reaction was quenched with a saturated aqueous solution of NH₄Cl. The extraction had been performed using ethereal solvent (Et₂O, 2 X 5 ml). The organic phase was dried over sodium sulphate (Na₂SO₄) and then after filtration it was dried under vacuum. The resulting crude aldehyde was purified as reported below through silica chromatography.

5.2.1.3 Homologation reaction via FCH₂Li (General Procedure.3)

After solubilizing the proper epoxide (1.5 equiv) in a mixture of THF:Et₂O (1:1, v/v), under inert atmosphere at -78 °C, fluoroiodomethane (1 equiv) was added and after 2 minutes MeLi·LiBr (2.0 equiv) was added dropwise. The reaction was kept stirring for 5 minutes at -78 °C and then was quenched with NH₄Cl (aq.). The work-up conditions and the purification were performed as described in the General Procedure 1.

5.2.1.4 Homologation reaction via BrCH₂Li (General Procedure 4)

The epoxide (1.0 equiv) was solubilized with dry THF and the temperature of -78 °C was reached. Then dibromomethane (3.0 equiv) was added to the solution under inert atmosphere. Immediately after, MeLi·LiBr (2.8 equiv) was added dropwise to the stirring mixture. One hour later, the reaction was quenched using NH₄Cl (aq.). For the work-up and purification conditions see General Procedure 1.

5.2.1.5 Homologation reaction via ICH₂Li (General Procedure 5)

To the stirring solution of epoxide (1.0 equiv) in dry THF at the temperature of -78 °C and inert atmosphere, diiodomethane (3.0 equiv) was added. Drop by drop addition of MeLi·LiBr (2.8 equiv) followed immediately after. The quenching of the reaction was performed after one hour, with NH₄Cl (aq.). For the work-up and purification conditions see General Procedure 1.

5.2.2 Characterization and spectral data of the compounds

5.2.2.1 CHARACTERIZATION OF SPIRO-EPOXYOXINDOLES

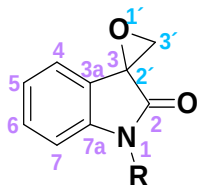
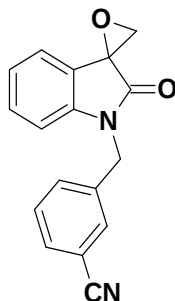


Figure 9. Numeration of the epoxyoxindole

Some of the epoxides were already characterized, therefore their characterization is not included in this work.

3-[(2-Oxospiro[indole-3,2'-oxirane])-1(2H)-yl] methyl] benzonitrile (**646**)



By following general procedure 1, starting from 3-[(2,3-dioxo-2,3-dihydro-1H-indol-1-yl)methyl]benzonitrile (500 mg, 1.9 mmol, 1.0 equiv), ICH_2Cl (1 g, 0.42 mL, 5.7 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M, 2.4 mL, 5.3 mmol, 2.8 equiv), after treatment with K_2CO_3 (395 mg, 2.9 mmol, 1.5 equiv) in acetonitrile (5 mL), compound **646** was obtained in 95% yield (499 mg) as brown-orange semisolid after column chromatography on neutral alumina (Brockmann degree IV) by using *n*-hexane / ethyl acetate (90 : 10) as eluent.

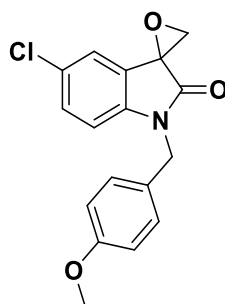
^1H NMR (400 MHz, CDCl_3) δ : 7.61 (m, 1H, Ph H-2), 7.59 (m, 2H, Ph H-4,6), 7.46 (m, 1H, Ph H-5), 7.31 (m, 1H, Ind H-6), 7.15 (m, 1H, Ind H-4), 7.10 (m, 1H, Ind H-5), 6.75 (m, 1H, Ind H-7), 5.03 – 4.95 (AB-system, $2J_{AB}$ =16.0 Hz, 2H, CH_2Ph), 3.67 – 3.51 (AB system, $2J_{AB}$ =6.6 Hz, 2H, CH_2 oxiran).

^{13}C NMR (100 MHz, CDCl_3) δ : 172.0 (Ind C-2), 143.6 (Ind C-7a), 137.0 (Ph C-3), 131.8 (Ph C-6), 131.7 (Ph C-4), 130.8 (Ph C-2), 130.5 (Ind C-6), 129.8 (Ph C-5), 123.4 (Ind C-5), 122.7 (Ind C-3a), 122.5 (Ind C-4), 118.3 (CN), 113.1 (Ph C-1), 109.4 (Ind C-7), 56.3 (Ind C-3), 54.4 (CH_2 oxiran), 43.5 (CH_2Ph).

^{15}N NMR (40 MHz, CDCl_3) δ : -241.8.

HRMS (ESI), m/z : calcd for $\text{C}_{17}\text{H}_{12}\text{N}_2\text{O}_2$: 277.0972 $[\text{M}+\text{H}]^+$; found: 277.0966.

5-chloro-1-[(4-methoxyphenyl)methyl]spiro[indole-3,2'-oxiran]-2(1H)-one (647)



By following general procedure 1, starting from 5-chloro-1-(4-methoxybenzyl)indoline-2,3-dione (500 mg, 1.7 mmol, 1.0 equiv), ICH_2Cl (877 mg, 0.36 mL, 5.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M, 2.1 mL, 4.6 mmol, 2.8 equiv), after treatment with K_2CO_3 (344 mg, 2.5 mmol, 1.5 equiv) in acetonitrile (5 mL), compound **647** was obtained in 90% yield (483 mg) as brown-orange semisolid after column chromatography on neutral alumina (Brockmann degree IV) by using *n*-hexane / ethyl acetate (90 : 10) as eluent.

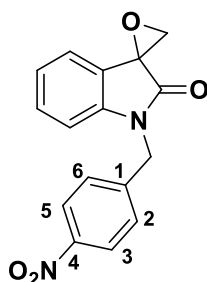
^1H NMR (400 MHz, CDCl_3) δ : 7.24 (m, 2H, Ph H-2,6), 7.23 (dd, $J=8.4, 2.1$ Hz, 1H, Ind H-6), 7.08 (d, $J=2.1$ Hz, 1H, Ind H-4), 6.86 (m, 2H, Ph H-3,5), 6.74 (d, $J=8.4$ Hz, 1H, Ind H-7), 4.89 (s, 2H, CH_2Ph), 3.78 (s, 3H, OCH_3), 3.65 – 3.45 (AB system, $2J_{AB}=6.7$ Hz, 2H, CH_2 oxiran).

^{13}C NMR (100 MHz, CDCl_3) δ : 171.3 (Ind C-2), 159.3 (Ph C-4), 142.7 (Ind C-7a), 130.2 (Ind C-6), 128.8 (Ph C-2,6), 128.5 (Ind C-5), 126.9 (Ph, C-1), 124.5 (Ind C-3a), 122.6 (Ind C-4), 114.3 (Ph C-3,5), 110.9 (Ind C-7), 56.1 (Ind C-3), 55.3 (OCH_3), 54.4 (CH_2 oxiran), 43.9 (CH_2Ph).

^{15}N NMR (40 MHz, CDCl_3) δ : -238.5.

HRMS (ESI), m/z : calcd for $\text{C}_{17}\text{H}_{14}\text{ClNO}_3$: 316.0735 $[\text{M}+\text{H}]^+$; found: 316.0735.

1-[(4-Nitrophenyl)methyl]spiro[indole-3,2'-oxiran]-2(1H)-one (648)



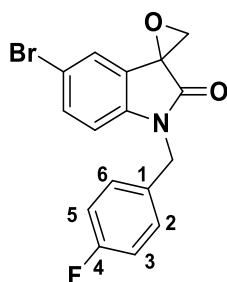
By following general procedure 1, starting from 1-(4-nitrobenzyl)indoline-2,3-dione (500 mg, 1.8 mmol, 1.0 equiv), ICH_2Cl (937 mg, 0.39 mL, 5.3 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M, 2.3 mL, 5.0 mmol, 2.8 equiv), after treatment with K_2CO_3 (367 mg, 2.7 mmol, 1.5 equiv) in acetonitrile (5 mL), compound **648** was obtained in 73% yield (389 mg) as brown-orange semisolid after column chromatography on neutral alumina (Brockmann degree IV) by using *n*-hexane / ethyl acetate (80 : 20) as eluent.

^1H NMR (400 MHz, CDCl_3) δ : 8.21 (m, 1H, Ph H-3,5), 7.50 (m, 1H, Ph H-2,6), 7.30 (m, 1H, Ind H-6), 7.16 (m, 1H, Ind H-4), 7.10 (m, 1H, Ind H-5), 6.74 (m, 1H, Ind H-7), 5.08 – 5.05 (2H, AB system, $2J_{AB}$ =16.3 Hz, CH_2Ph), 3.68 – 3.51 (2H, AB system, $2J_{AB}$ =6.7 Hz, CH_2 oxiran).

^{13}C NMR (100 MHz, CDCl_3) δ : 172.0 (Ind C-2), 147.7 (Ph C-4), 143.6 (Ind C-7a), 142.6 (Ph C-1), 130.5 (Ind C-6), 128.1 (Ph C-2,6), 124.2 (Ph C-3,5), 123.5 (Ind C-5), 122.7 (Ind C-3a), 122.6 (Ind C-4), 109.0 (Ind C-7), 56.3 (Ind C-3), 54.4 (CH_2 oxiran), 43.7 (CH_2Ph).

HRMS (ESI), m/z : calcd for $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_4$: 297.0870 $[\text{M}+\text{H}]^+$; found: 297.0870.

5-Bromo-1-(4-fluorobenzyl)spiro[indole-3,2'-oxirane]-2(1H)-one (649)



By following general procedure 1, starting from 5-bromo-1-(4-fluorobenzyl)indoline-2,3-dione (500 mg, 1.5 mmol, 1.0 equiv), ICH₂Cl (792 mg, 0.33 mL, 4.5 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M, 1.9 mL, 4.2 mmol, 2.8 equiv), after treatment with K₂CO₃ (310 mg, 2.2 mmol, 1.5 equiv) in acetonitrile (5 mL), compound **649** was obtained in 87% yield (454 mg) as brown-yellow semisolid after column chromatography on neutral alumina (Brockmann degree IV) by using *n*-hexane / ethyl acetate (90: 10) as eluent.

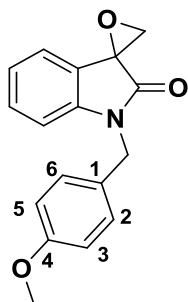
¹H NMR (400 MHz, CDCl₃) δ: 7.40 (dd, *J*=8.3, 2.0 Hz, 1H, Ind 6), 7.28 (m, 2H, Ph H-2,6), 7.23 (d, *J*=2.0 Hz, 1H, Ind H-4), 7.02 (m, 2H, Ph H-3,5), 6.67 (d, *J*=8.3 Hz, 1H, Ind H-7), 3.65 – 3.47 (d, *J*=6.7 Hz, 2H, CH₂ oxiran).

¹³C NMR (100 MHz, CDCl₃) δ: 171.3 (Ind C-2), 162.4 (d, *J*=247.0 Hz, Ph C-4), 143.0 (Ind C-7a), 133.1 (Ind C-6), 130.6 (d, *J*=3.3 Hz, Ph C-1), 129.2 (d, *J*=8.2 Hz, Ph C-2,6), 125.6 (Ind C-4), 124.9 (Ind C-3a), 115.9 (d, *J*=21.6 Hz, Ph C-3,5), 111.2 (Ind C-7), 56.0 (Ind C-3), 54.5 (CH₂ oxiran), 43.7 (CH₂Ph).

¹⁹F NMR (376 MHz, CDCl₃) δ; -113.8 (m, F-Ph).

HRMS (ESI), *m/z*: calcd for C₁₆H₁₁BrFNO₂: 348.0030 [M+H]⁺; found: 348.0030.

1-[(4-Methoxyphenyl)methyl]spiro[indole-3,2'-oxiran]-2(1H)-one (650)



By following general procedure 1, starting from 1-(4-methoxybenzyl)indoline-2,3-dione (500 mg, 1.9 mmol, 1.0 equiv), ICH_2Cl (990 mg, 0.41 mL, 5.6 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M, 2.4 mL, 5.2 mmol, 2.8 equiv), after treatment with K_2CO_3 (388 mg, 2.8 mmol, 1.5 equiv) in acetonitrile (5 mL), compound **650** was obtained in 79% yield (422 mg) as brown-red semisolid after column chromatography on neutral alumina (Brockmann degree IV) by using *n*-hexane / ethyl acetate (95: 5) as eluent.

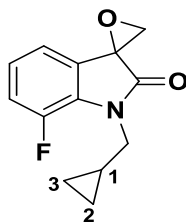
^1H NMR (400 MHz, CDCl_3) δ : 7.27 (m, 3H, Ph H-2,6, Ind H-6), 7.10 (m, 1H, Ind H-4), 7.04 (m, 1H, Ind H-5), 6.85 (m, 1H, Ph H-3,5), 6.84 (m, Ind H-7), 4.92 – 4.89 (AB-system $2J_{AB}=15.4$ Hz, 2H, CH_2Ph), 3.78 (s, 3H, OCH_3), 3.64 – 3.46 (d, $J=6.7$ Hz, 2H, CH_2 oxiran).

^{13}C NMR (100 MHz, CDCl_3) δ : 171.8 (Ind C-2), 159.2 (Ph C-4), 144.3 (Ind C-7a), 130.3 (Ind C-6), 128.8 (Ph C-2,6), 127.4 (Ph C-1), 122.8 (Ind C-5), 122.7 (Ind C-3a), 122.1 (Ind C-4), 114.2 (Ph C-3,5), 109.9 (Ind C-7), 56.4 (Ind C-3), 55.2 (OCH_3), 54.3 (CH_2 oxiran), 43.8 (CH_2Ph).

^{15}N NMR (40 MHz, CDCl_3) δ : -238.0.

HRMS (ESI), m/z : calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_3$: 282.1125 $[\text{M}+\text{H}]^+$; found: 282.1125.

1-(Cyclopropylmethyl)-7-fluorospiro[indole-3,2'-oxirane]-2(1H)-one (651)



By following general procedure 1, starting from 1-(cyclopropylmethyl)-7-fluoroindoline-2,3-dione (500 mg, 2.3 mmol, 1.0 equiv), ICH_2Cl (1207 mg, 0.50 mL, 6.8 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M, 2.9 mL, 6.4 mmol, 2.8 equiv), after treatment with K_2CO_3 (473 mg, 3.4 mmol, 1.5 equiv) in acetonitrile (5 mL), compound **651** was obtained in 67% yield (359 mg) as brown-yellow semisolid after column chromatography on neutral alumina (Brockmann degree IV) by using *n*-hexane / ethyl acetate (90:10) as eluent.

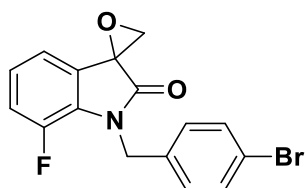
^1H NMR (400 MHz, CDCl_3) δ : 7.12 (m, 1H, Ind H-6), 7.02 (m, 1H, Ind H-5), 6.91 (dd, $J=8.3, 1.2$ Hz, 1H, Ind H-4), 3.78 (m, 2H, CH_2 -cyclopropyl), 3.60 – 3.43 (d, $J=6.7$ Hz, 2H, CH_2 oxiran), 1.27 (m, 1H, cyclopropyl H-1), 0.51 (m, 2H, cyclopropyl H-2,3), 0.43 (m, 2H, cyclopropyl H-2,3).

^{13}C NMR (100 MHz, CDCl_3) δ : 171.5 (Ind C-2), 147.6 (d, $J=244.6$ Hz, Ind C-7), 131.2 (d, $J=9.1$ Hz, Ind C-6), 125.9 (d, $J=3.6$ Hz, Ind C-3a), 123.4 (d, $J=6.5$ Hz, Ind C-5), 118.5 (d, $J=19.9$ Hz, Ind C-6), 118.0 (d, $J=3.3$ Hz, Ind C-4), 56.3 (d, $J=3.5$ Hz, Ind C-3), 54.7 (CH_2 oxiran), 47.0 (d, $J=4.4$ Hz, CH_2 -cyclopropyl), 10.7 (d, $J=3.6$ Hz, cyclopropyl C-1), 3.6 (cyclopropyl C-2,3).

^{19}F NMR (376 MHz, CDCl_3) δ : -134 (m).

HRMS (ESI), m/z : calcd for $\text{C}_{13}\text{H}_{12}\text{FNO}_2$: 234.0925 $[\text{M}+\text{H}]^+$; found: 234.0918.

1-[(4-Bromophenyl)methyl]-7-fluorospiro[indole-3,2'-oxiran]-2(1H)-one (652)



By following general procedure 1, starting from 1-(4-bromobenzyl)-7-fluoroindoline-2,3-dione (500 mg, 1.5 mmol, 1.0 equiv), ICH₂Cl (792 mg, 0.33 mL, 4.5 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M, 1.9 mL, 4.2 mmol, 2.8 equiv), after treatment with K₂CO₃ (310 mg, 2.2 mmol, 1.5 equiv) in acetonitrile (5 mL), compound **652** was obtained in 94% yield (491 mg) as brown-orange semisolid after column chromatography on neutral alumina (Brockmann degree IV) by using *n*-hexane / ethyl acetate (80 : 20) as eluent.

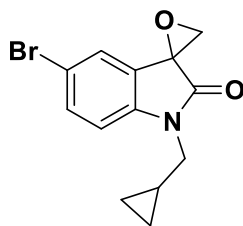
¹H NMR (400 MHz, CDCl₃) δ: 7.44 (m, 2H, Ph H-3,5), 7.25 (m, 2H, Ph H-2,6), 7.05 (m, 1H, Ind H-6), 7.02 (m, 1H, Ind H-5), 6.90 (dd, *J*=7.1, 1.4 Hz, 1H, Ind H-4), 5.04 (s, 2H, CH₂Ph), 3.64 – 3.45 (d, *J*=6.7 Hz, 2H, CH₂ oxiran).

¹³C NMR (100 MHz, CDCl₃) δ: 171.6 (Ind C-2), 147.6 (d, *J*=244.9 Hz, Ind C-7), 135.4 (Ph C-1), 131.8 (Ph C-3,5), 130.3 (d, *J*=9.3 Hz, Ind C-7a), 129.5 (d, *J*=1.8 Hz, Ph C-2,6), 125.7 (d, *J*=3.4 Hz, Ind C-3a), 123.9 (d, *J*=6.5 Hz, Ind C-5), 121.9 (Ph C-4), 118.6 (d, *J*=19.7 Hz, Ind C-6), 118.2 (d, *J*=3.3 Hz, Ind C-4), 56.2 (d, *J*=3.5 Hz, Ind C-3), 54.8 (CH₂ oxiran), 45.4 (d, *J*=4.6 Hz, CH₂Ph).

¹⁹F NMR (376 MHz, CDCl₃) δ; -133.1 (m).

HRMS (ESI), *m/z*: calcd for C₁₆H₁₁BrFNO₂: 348.0030 [M+H]⁺; found: 348.0030.

5-Bromo-1-(cyclopropylmethyl)spiro[indole-3,2'-oxirane]-2(1H)-one (653)



By following general procedure 1, starting from 5-bromo-1-(cyclopropylmethyl)indoline-2,3-dione (500 mg, 1.8 mmol, 1.0 equiv), ICH_2Cl (944 mg, 0.39 mL, 5.4 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M, 2.3 mL, 5.0 mmol, 2.8 equiv), after treatment with K_2CO_3 (370 mg, 2.7 mmol, 1.5 equiv) in acetonitrile (5 mL), compound **653** was obtained in 75% yield (397 mg) as brown-orange semisolid after column chromatography on neutral alumina (Brockmann degree IV) by using *n*-hexane / ethyl acetate (95: 5) as eluent.

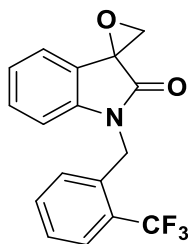
^1H NMR (400 MHz, CDCl_3) δ : 7.49 (dd, $J=8.3, 2.0$ Hz, 1H, Ind 6), 7.22 (d, $J=2.0$ Hz, 1H, Ind H-4), 6.88 (d, $J=8.3$ Hz, 1H, Ind C-7), 3.63 (m, 2H, NCH_2), 1.15 (m, 1H, cyclopropyl H-1), 0.55 (m, 2H, cyclopropyl H-2,3), 0.39 (m, 2H, cyclopropyl H-2,3).

^{13}C NMR (100 MHz, CDCl_3) δ : 171.1 (Ind C-2), 143.7 (Ind C-7a), 133.1 (Ind C-6), 125.5 (Ind C-4), 124.9 (Ind C-3a), 115.3 (Ind C-5), 110.7 (Ind C-7), 56.0 (Ind C-3), 54.3 (CH_2 oxiran), 45.0 (NCH_2), 9.5 (cyclopropyl C-1), 4.0 (cyclopropyl C-2,3).

^{15}N NMR (40 MHz, CDCl_3) δ : -237.2.

HRMS (ESI), m/z : calcd for $\text{C}_{13}\text{H}_{12}\text{BrNO}_2$: 294.0124 $[\text{M}+\text{H}]^+$; found: 294.0115.

1-[[2-(Trifluoromethyl)phenyl]methyl] spiro[indole-3,2'-oxiran]-2(1H)-one (654)



By following general procedure 1, starting from 1-(2-(trifluoromethyl)benzyl)indoline-2,3-dione (500 mg, 1.6 mmol, 1.0 equiv), ICH_2Cl (867 mg, 0.36 mL, 4.9 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M, 2.1 mL, 4.6 mmol, 2.8 equiv), after treatment with K_2CO_3 (340 mg, 2.5 mmol, 1.5 equiv) in acetonitrile (5 mL), compound **654** was obtained in 91% yield (465 mg) as brown-orange semisolid after column chromatography on neutral alumina (Brockmann degree IV) by using *n*-hexane / ethyl acetate (93: 7) as eluent.

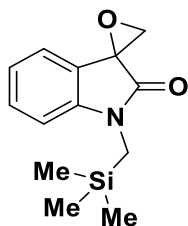
^1H NMR (400 MHz, CDCl_3) δ : 7.73 (m, 1H, Ph H-3), 7.45 (m, 1H, Ph H-5), 7.39 (m, 1H, Ph H-4), 7.26 (m, 1H, Ind H-6), 7.20 (m, 1H, Ph H-6), 7.17 (m, 1H, Ind H-4), 7.09 (m, 1H, Ind H-5), 6.65 (m, 1H, Ind C-7), 5.21 – 5.19 (AB-system $^2J_{AB}$ = 16.0 Hz, 2H, CH_2Ph), 3.70 – 3.54 (AB-system $^2J_{AB}$ = 6.7 Hz, 2H, CH_2 oxiran)

^{13}C NMR (100 MHz, CDCl_3) δ : 172.3 (Ind C-2), 143.8 (Ind C-7a), 133.5 (d, J =1.5 Hz, Ph C-1), 132.4 (q, J =5.8 Hz, Ph C-5), 130.6 (Ind C-6), 127.8 (q, J =30.8 Hz, Ph C-2), 127.6 (Ph C-4), 126.9 (Ph C-6), 126.3 (q, J =5.8 Hz, Ph C-3), 124.4 (q, J =273.8 Hz, CF_3), 123.3 (Ind C-5), 122.6 (Ind C-3a), 122.3 (Ind C-4), 109.8 (Ind C-7), 56.4 (Ind C-3), 54.4 (CH_2 oxiran), 40.7 (q, J =3.5 Hz, CH_2Ph)

^{19}F NMR (376 MHz, CDCl_3) δ : -60.1 (s, CF_3)

HRMS (ESI), m/z : calcd for $\text{C}_{17}\text{H}_{12}\text{F}_3\text{NO}_2$: 320.0893 $[\text{M}+\text{H}]^+$; found: 320.0884.

1-[(Trimethylsilyl)methyl]spiro[indole-3,2'-oxiran]-2-(1H)-one (655)



By following general procedure 1, starting from 1-((trimethylsilyl)methyl)indoline-2,3-dione (500 mg, 2.1 mmol, 1.0 equiv), ICH₂Cl (1133 mg, 0.47 mL, 6.4 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M, 2.7 mL, 6.0 mmol, 2.8 equiv), after treatment with K₂CO₃ (444 mg, 3.2 mmol, 1.5 equiv) in acetonitrile (5 mL), compound **655** was obtained in 82% yield (426 mg) as red-orange semisolid after column chromatography on neutral alumina (Brockmann degree IV) by using *n*-hexane / ethyl acetate (75 : 25) as eluent.

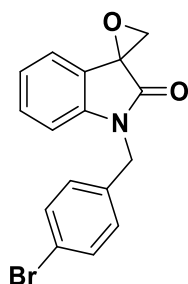
¹H NMR (400 MHz, CDCl₃) δ: 7.33 (Ind H-6), 7.06 (Ind H-4), 7.02 (Ind H-5), 6.84 (Ind H-7), 3.55 – 3.41 (2H, AB-system, *J* = 6.7 Hz), 3.24 (s, 2H, NCH₂Si(Me)₃), 0.1 (s, 9 H, Si(CH₃)₃)

¹³C NMR (100 MHz, CDCl₃) δ: 170.9 (Ind C-2), 145.4 (Ind C-7a), 130.1 (Ind C-6), 122.9 (Ind C-3a), 122.3 (Ind C-5), 121.8 (Ind C-4), 109.1 (Ind C-7), 56.0 (Ind C-3), 53.8 (Oxiran CH₂), 32.0 (NCH₂), -1.6 (3 Me)

¹⁵N NMR (40 MHz, CDCl₃) δ: -245.2

HRMS (ESI), *m/z*: calcd for C₁₃H₁₇NO₂Si: 248.1101 [M+H]⁺; found: 248.1108

1-(4-Bromobenzyl)spiro[indole-3,2'-oxiran]-2(1H)-one (656)



By following general procedure 1, starting from 1-(4-bromobenzyl)indoline-2,3-dione (500 mg, 1.6 mmol, 1.0 equiv), ICH_2Cl (837 mg, 0.35 mL, 4.7 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M, 2.0 mL, 4.4 mmol, 2.8 equiv), after treatment with K_2CO_3 (328 mg, 2.4 mmol, 1.5 equiv) in acetonitrile (5 mL), compound **656** was obtained in 86% yield (454 mg) as brown-orange semisolid after column chromatography on neutral alumina (Brockmann degree IV) by using *n*-hexane / ethyl acetate (90:10) as eluent.

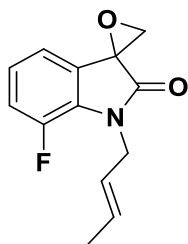
^1H NMR (400 MHz, CDCl_3) δ : 7.45 (m, 2H, Ph H-3,5), 7.28 (m, 1H, Ind H-6), 7.21 (m, 2H, Ph H-2,6), 7.12 (m, 1H, Ind H-4), 7.06 (m, 1H, Ind H-5), 6.77 (m, 1H, Ind H-7), 4.93–4.90 (AB system, 2H, J = 15.8 Hz, NCH_2Ph), 3.65–3.48 (AB system, 2H, J = 6.7 Hz, Oxiran CH_2)

^{13}C NMR (100 MHz, CDCl_3) δ : 171.9 (Ind C-2), 143.9 (Ind C-7a), 134.3 (Ph C-1), 132.0 (Ph C-3,5), 130.4 (Ind C-6), 129.1 (Ph C-2,6), 123.1 (Ind C-5), 122.6 (Ind C-3a), 122.3 (Ind C-4), 121.8 (Ph C-4), 109.7 (Ind C-7), 56.3 (Ind C-3), 54.3 (Oxiran CH_2), 43.7 (NCH_2Ph)

^{15}N NMR (40 MHz, CDCl_3) δ : -240.2

HRMS (ESI), m/z : calcd for $\text{C}_{16}\text{H}_{12}\text{BrNO}_2$: 330.0124 $[\text{M}+\text{H}]^+$; found: 330.0142

1-[(2E)-2-buten-1-yl]-7-fluorospiro[indole-3,2'-oxiran]-2(1H)-one (657)



By following general procedure 1, starting from (*E*)-1-(but-2-en-1-yl)-7-fluoroindoline-2,3-dione (500 mg, 2.3 mmol, 1.0 equiv), ICH₂Cl (1206 mg, 0.5 mL, 6.8 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M, 2.9 mL, 6.4 mmol, 2.8 equiv), after treatment with K₂CO₃ (473 mg, 3.4 mmol, 1.5 equiv) in acetonitrile (5 mL), compound **657** was obtained in 88% yield (472 mg) as brown-orange semisolid after column chromatography on neutral alumina (Brockmann degree IV) by using *n*-hexane / ethyl acetate (96: 4) as eluent.

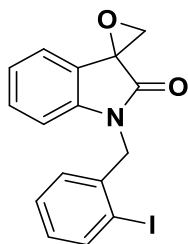
¹H NMR (400 MHz, CDCl₃) δ: 7.10 (ddd, 1H, *J* = 11.4, 8.4, 1.1 Hz, Ind H-6), 7.01 (ddd, 1H, *J* = 11.4, 7.3, 4.3 Hz, Ind H-5), 6.89 (dd, 1H, *J* = 7.3, 1.1 Hz, Ind H-4), 5.78 (m, 1H, CHCH₃), 5.57 (m, 1H, NCH₂CH), 4.44 (m, 2H, NCH₂), 3.60-3.42 (AB-system, 2H, *J* = 6.7 Hz, Oxiran CH₂), 1.68 (m, 3 H, CHCH₃)

¹³C NMR (100 MHz, CDCl₃) δ: 171.1 (Ind C-2), 147.7 (d, *J* = 245.4 Hz, Ind C-7), 130.9 (d, *J* = 9.3 Hz, Ind C-7a), 129.9 (Buten C-3), 125.9 (d, *J* = 3.7 Hz, Ind C-3a), 124.9 (Buten C-2), 123.5 (d, *J* = 6.4 Hz, Ind C-5), 118.5 (d, *J* = 19.7 Hz, Ind C-6), 117.9 (d, *J* = 3.2 Hz, Ind C-4), 56.3 (d, *J* = 3.3 Hz, Ind C-3), 54.6 (Oxiran CH₂), 44.0 (d, *J* = 4.5 Hz, Buten C-1), 17.7 (Buten C-4)

¹⁹F NMR (376 MHz, CDCl₃) δ: -133.9 (m)

HRMS (ESI), *m/z*: calcd for C₁₃H₁₂FNO₂: 234.0925 [M+H]⁺; found: 234.0929

1-(2-Iodobenzyl)spiro[indole-3,2'-oxiran]-2(1H)-one (658)



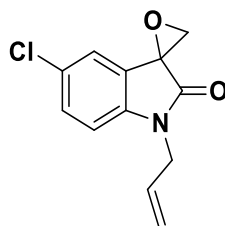
By following general procedure 1, starting from 1-(2-iodobenzyl)indoline-2,3-dione (500 mg, 1.4 mmol, 1.0 equiv), ICH_2Cl (729 mg, 0.30 mL, 4.1 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M, 1.8 mL, 3.9 mmol, 2.8 equiv), after treatment with K_2CO_3 (285 mg, 2.1 mmol, 1.5 equiv) in acetonitrile (5 mL), compound **658** was obtained in 90% yield (475 mg) as yellow-orange semisolid after column chromatography on neutral alumina (Brockmann degree IV) by using *n*-hexane / ethyl acetate (91:9) as eluent.

^1H NMR (400 MHz, CDCl_3) δ : 7.89 (m, 1H, Ph H-3), 7.28 (m, 1H, Ind H-6), 7.25 (m, 1H, Ph H-5), 7.16 (m, 1H, Ind H-4), 7.08 (m, 1H, Ind H-5), 7.04 (m, 1H, Ph H-6), 6.99 (m, 1H, Ph H-4), 6.70 (m, 1H, Ind H-7), 5.00 (s, 2H, CH_2Ph), 3.68- 3.52 (AB-system, $J = 6.7$ Hz, Oxiran CH_2)

^{13}C NMR (100 MHz, CDCl_3) δ : 172.0 (Ind C-2), 143.9 (Ind C-7a), 139.7 (Ph C-3), 136.7 (Ph C-1), 130.5 (Ind C-6), 129.4 (Ph C-4), 128.7 (Ph C-5), 127.1 (Ph C-6), 123.2 (Ind C-5), 122.6 (Ind C-3a), 122.3 (Ind C-4), 110.2 (Ind C-7), 97.6 (Ph C-2), 56.5 (Ind C-3), 54.3 (Oxiran CH_2), 49.4 (CH_2Ph)

HRMS (ESI), m/z : calcd for $\text{C}_{16}\text{H}_{12}\text{INO}_2$: 377.9985 $[\text{M}+\text{H}]^+$; found: 378.0003

1-Allyl-5-chlorospiro[indole-3,2'-oxiran]-2(1H)-one (659)



By following general procedure 1, starting from 1-allyl-5-chloroindoline-2,3-dione (500 mg, 2.3 mmol, 1.0 equiv), ICH₂Cl (1194 mg, 0.5 mL, 6.8 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M, 2.9 mL, 6.3 mmol, 2.8 equiv), after treatment with K₂CO₃ (468 mg, 3.4 mmol, 1.5 equiv) in acetonitrile (5 mL), compound **659** was obtained in 77% yield (417 mg) as brown-orange semisolid after column chromatography on neutral alumina (Brockmann degree IV) by using *n*-hexane / ethyl acetate (90:10) as eluent.

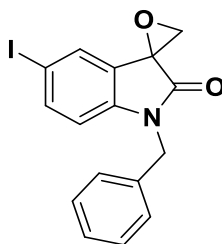
¹H NMR (400 MHz, CDCl₃) δ: 7.29 (dd, 1H, *J* = 8.4, 2.1 Hz, Ind H-6), 7.07 (d, 1H, *J* = 2.1 Hz, Ind H-4), 6.83 (d, 1H, *J* = 8.4 Hz, Ind H-7), 5.82 (m, 1H, allyl CH), 5.27 (m, 1H, allyl CHCH₂), 5.24 (m, 1H, allyl CHCH₂), 4.40 (m, 1H, NCH₂), 4.34 (m, 1H, NCH₂), 3.59 – 3.43 (AB system, 2H, *J* = 6.7 Hz, Oxiran CH₂)

¹³C NMR (100 MHz, CDCl₃) δ: 170.9 (Ind C-2), 142.7 (Ind C-7a), 130.6 (Allyl C-2), 130.1 (Ind C-6), 128.4 (Ind C-5), 124.4 (Ind C-3a), 122.6 (Ind C-4), 118.3 (Allyl C-3), 110.7 (Ind C-7), 56.0 (Ind C-3), 54.3 (Oxiran CH₂), 42.9 (Allyl C-1)

¹⁵N NMR (40 MHz, CDCl₃) δ: -243.1

HRMS (ESI), *m/z*: calcd for C₁₂H₁₀ClNO₂: 236.0473 [M+H]⁺; found: 236.0479

1-Benzyl-5-iodospiro[indole-3,2'-oxiran]-2(1H)-one (660)



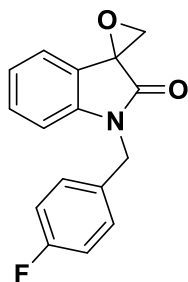
By following general procedure 1, starting from 1-benzyl-5-iodoindoline-2,3-dione (500 mg, 1.4 mmol, 1.0 equiv), ICH_2Cl (729 mg, 0.30 mL, 4.1 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M, 1.8 mL, 3.9 mmol, 2.8 equiv), after treatment with K_2CO_3 (285 mg, 2.1 mmol, 1.5 equiv) in acetonitrile (5 mL), compound **660** was obtained in 96% yield (507 mg) as yellow-orange semisolid after column chromatography on neutral alumina (Brockmann degree IV) by using *n*-hexane / ethyl acetate (87: 13) as eluent.

^1H NMR (400 MHz, CDCl_3) δ : 7.57 (dd, 1H, J = 8.3, 1.8 Hz, Ind H-6), 7.39 (d, 1H, J = 1.8 Hz, Ind C-4), 7.33 (m, 2H, Ph H-3,5), 7.30 (m, 3H, Ph H-2, 4,6), 6.58 (d, 1H, J = 8.3 Hz, Ind H-7), 4.96 – 4.93 (AB-system, 2H, J = 15.8 Hz, CH_2Ph), 3.65 – 3.46 (AB-system, 2H, J = 6.7 Hz, Oxiran CH_2)

^{13}C NMR (100 MHz, CDCl_3) δ : 171.1 (Ind C-2), 143.9 (Ind C-7a), 139.0 (Ind C-6), 134.8 (Ph C-1), 131.0 (Ind C-4), 129.0 (Ph C-3,5), 128.0 (Ph C-4), 127.4 (Ph C-2,6), 125.1 (Ind C-3a), 111.9 (Ind C-7), 85.3 (Ind C-5), 55.8 (Ind C-3), 54.4 (Oxiran CH_2), 44.4 (CH_2Ph)

HRMS (ESI), m/z : calcd for $\text{C}_{16}\text{H}_{12}\text{INO}_2$: 377.9985 $[\text{M}+\text{H}]^+$; found: 377.9996

1-[(4-Fluorophenyl)methyl]spiro[indole-3,2'-oxiran]-2(1H)-one (661)



By following general procedure 1, starting from 1-(4-fluorobenzyl)indoline-2,3-dione (500 mg, 2.0 mmol, 1.0 equiv), ICH₂Cl (1037 mg, 0.43 mL, 5.9 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M, 2.5 mL, 5.5 mmol, 2.8 equiv), after treatment with K₂CO₃ (406 mg, 2.9 mmol, 1.5 equiv) in acetonitrile (5 mL), compound **661** was obtained in 88% yield (474 mg) as brown-orange semisolid after column chromatography on neutral alumina (Brockmann degree IV) by using *n*-hexane / ethyl acetate (92: 8) as eluent.

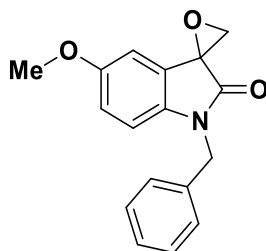
¹H NMR (400 MHz, CDCl₃) δ: 7.32 (m, 2H, Ph H-2,6), 7.28 (m, 1H, Ind H-6), 7.13 (m, 1H, Ind H-4), 7.06 (m, 1H, Ind H-5), 7.02 (m, 2H, Ph H-3,5), 6.80 (m, 1H, Ind H-7), 4.95 – 4.92 (AB-system, 2H, *J* =15.7 Hz, CH₂Ph), 3.65 – 3.48 (AB-system, 2H, *J* =6.7 Hz, Oxiran CH₂)

¹³C NMR (100 MHz, CDCl₃) δ: 171.9 (Ind C-2), 162.4 (d, *J* =246.4 Hz, Ph C-4), 144.0 (Ind C-7a), 131.1 (d, *J* =3.3 Hz, Ph C-1), 130.4 (Ind C-6), 129.2 (d, *J* =8.3 Hz, Ph C-2,6), 123.0 (Ind C-5), 122.7 (Ind C-3a), 122.3 (Ind C-4), 115.8 (d, *J* =21.6 Hz, Ph C-3,5), 109.7 (Ind C-7), 56.3 (Ind C-3), 54.3 (Oxiran CH₂), 43.6 (CH₂Ph)

¹⁹F NMR (376 MHz, CDCl₃) δ; -114.2 (m)

HRMS (ESI), *m/z*: calcd for C₁₆H₁₂FNO₂: 270.0925 [M+H]⁺ ; found: 270.0933

1-Benzyl-5-methoxyspiro[indole-3,2'-oxiran]-2(1*H*)-one (662)



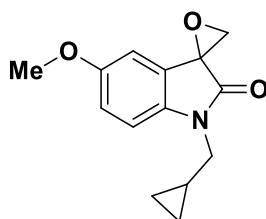
By following general procedure 1, starting from 1-benzyl-5-methoxyindoline-2,3-dione (500 mg, 1.9 mmol, 1.0 equiv), ICH_2Cl (990 mg, 0.41 mL, 5.6 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M, 2.4 mL, 5.2 mmol, 2.8 equiv), after treatment with K_2CO_3 (388 mg, 2.8 mmol, 1.5 equiv) in acetonitrile (5 mL), compound **662** was obtained in 71% yield (379 mg) as red-orange semisolid after column chromatography on neutral alumina (Brockmann degree IV) by using *n*-hexane / ethyl acetate (98:2) as eluent.

^1H NMR (400 MHz, CDCl_3) δ : 7.32 (m, 4H, Ph H-2,3,5,6), 7.28 (m, 1H, Ph H-4), 6.78 (dd, 1H, $J = 8.5, 2.6$ Hz, Ind H-6), 6.72 (d, 1H, $J = 2.6$ Hz, Ind H-4), 6.69 (d, 1H, $J = 8.5$ Hz, Ind H-7), 4.97- 4.92 (AB-system, 2H, $J = 15.7$ Hz, NCH_2Ph), 3.75 (s, 3H, OCH_3), 3.65 – 3.45 (AB-system, 2H, $J = 6.7$ Hz, Oxiran CH_2)

^{13}C NMR (100 MHz, CDCl_3) δ : 171.7 (Ind C-2), 156.2 (Ind C-5), 137.5 (Ind C-7a), 135.4 (Ph C-1), 128.8 (Ph C-3,5), 127.8 (Ph C-4), 127.4 (Ph C-2,6), 124.0 (Ind C-3a), 115.1 (Ind C-6), 110.5 (Ind C-7), 109.0 (Ind C-4), 56.7 (Ind C-3), 55.8 (OCH_3), 54.4 (Oxiran CH_2), 44.4 (NCH_2Ph)

HRMS (ESI), m/z : calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_3$: 282.1125 $[\text{M}+\text{H}]^+$; found: 282.1125.

1-(Cyclopropylmethyl)-5-methoxyspiro[indole-3,2'-oxiran]-2(1H)-one (663)



By following general procedure 1, starting from 1-(cyclopropylmethyl)-5-methoxyindoline-2,3-dione (500 mg, 2.2 mmol, 1.0 equiv), ICH_2Cl (1144 mg, 0.47 mL, 6.5 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M, 2.8 mL, 6.1 mmol, 2.8 equiv), after treatment with K_2CO_3 (448 mg, 3.2 mmol, 1.5 equiv) in acetonitrile (5 mL), compound **663** was obtained in 76% yield (410 mg) as red-orange semisolid after column chromatography on neutral alumina (Brockmann degree IV) by using *n*-hexane / ethyl acetate (99: 1) as eluent.

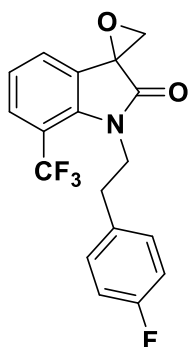
^1H NMR (400 MHz, CDCl_3) δ : 6.88 (m, 2H, Ind H-6,7), 6.69 (m, 1H, Ind H-4), 3.75 (s, 3H, OCH_3), 3.59 (m, 2H, NCH_2), 3.55-3.39 (AB-system, 2H, $J = 6.7$ Hz, Oxiran CH_2), 1.15 (m, 1H, CH cyclopropyl), 0.52 (m, 2H, CH_2 cyclopropyl), 0.37 (m, 2H, CH_2 cyclopropyl)

^{13}C NMR (100 MHz, CDCl_3) δ : 171.3 (Ind C-2), 156.0 (Ind C-5), 137.9 (Ind C-7a), 123.9 (Ind C-3a), 115.0 (Ind C-6), 109.7 (Ind C-7), 109.0 (Ind C-4), 56.5 (Ind C-3), 55.7 (OCH_3), 54.2 (Oxiran CH_2), 44.8 (NCH_2), 9.5 (CH cyclopropyl), 3.9 (2C, CH_2 cyclopropyl)

^{15}N NMR (40 MHz, CDCl_3) δ : -238.8

HRMS (ESI), m/z : calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_3$: 246.1125 $[\text{M}+\text{H}]^+$; found: 246.1120

1-[2-(4-Fluorophenyl)ethyl]-7-(trifluoromethyl)spiro[indole-3,2'-oxiran]-2(1H)-one (664)



By following general procedure 1, starting from 1-(4-fluorophenethyl)-7-(trifluoromethyl)indoline-2,3-dione (500 mg, 1.5 mmol, 1.0 equiv), ICH_2Cl (784 mg, 0.32 mL, 4.4 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M, 1.9 mL, 4.2 mmol, 2.8 equiv), after treatment with K_2CO_3 (307 mg, 2.2 mmol, 1.5 equiv) in acetonitrile (5 mL), compound **664** was obtained in 86% yield (453 mg) as orange semisolid after column chromatography on neutral alumina (Brockmann degree IV) by using *n*-hexane / ethyl acetate (97: 3) as eluent.

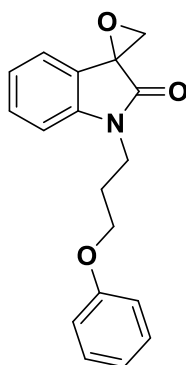
^1H NMR (400 MHz, CDCl_3) δ : 7.69 (m, 1H, Ind H-6), 7.27 (m, 1H, Ind H-4), 7.23 (m, 2H, Ph H-2,6), 7.18 (m, 1H, Ind H-5), 7.00 (m, 2H, Ph H-3,5), 4.11 (m, 2H, NCH_2), 3.62 – 3.46 (2H, J = 6.7 Hz, Oxiran CH_2), 2.92 (m, 2H, CH_2Ph)

^{13}C NMR (100 MHz, CDCl_3) δ : 172.9 (Ind C-2), 161.7 (d, J = 244.6 Hz, Ph C-4), 142.1 (q, J = 1.8 Hz, Ind C-7a), 133.4 (d, J = 3.2 Hz, Ph C-1), 130.4 (2C, d, J = 8.0 Hz, Ph C-2,6), 128.4 (q, J = 6.3 Hz, Ind C-6), 125.7 (Ind C-3a), 125.6 (Ind C-4), 123.4 (q, J = 271.6 Hz, CF_3), 122.4 (Ind C-5), 115.4 (2C, J = 21.3 Hz, Ph C-3,5), 113.3 (q, J = 33.0 Hz, Ind C-7), 55.0 (Oxiran CH_2), 54.8 (Ind C-3), 44.5 (q, J = 4.6 Hz, NCH_2), 33.2 (q, J = 2.4 Hz, CH_2Ph)

^{19}F NMR (376 MHz, CDCl_3) δ : -55.6 (s, CF_3), -116.3 (m, PhF)

HRMS (ESI), m/z : calcd for $\text{C}_{18}\text{H}_{13}\text{F}_4\text{NO}_2$: 352.0955 $[\text{M}+\text{H}]^+$; found: 352.0955

1-(3-Phenoxypropyl)spiro[indole-3,2'-oxiran]-2(1H)-one (665)



By following general procedure 1, starting from 1-(3-phenoxypropyl)indoline-2,3-dione (500 mg, 1.8 mmol, 1.0 equiv), ICH_2Cl (940 mg, 0.39 mL, 5.3 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M, 2.3 mL, 5.0 mmol, 2.8 equiv), after treatment with K_2CO_3 (368 mg, 2.7 mmol, 1.5 equiv) in acetonitrile (5 mL), compound **665** was obtained in 93% yield (494 mg) as brown-orange semisolid after column chromatography on neutral alumina (Brockmann degree IV) by using *n*-hexane / ethyl acetate (95: 5) as eluent.

^1H NMR (400 MHz, CDCl_3) δ : 7.31 (m, 1H, Ind H-6), 7.28 (m, 2H, Oph H-3,5), 7.11 (m, 1H, Ind H-4), 7.05 (m, 1H, Ind H-5), 6.99 (m, 1H, Ind H-7), 6.96 (m, 1H, Ph H-4), 6.89 (m, 2H, Ph H-2,6), 4.04 (m, 2H, PhOCH_2), 3.99 (m, 2H, NCH_2), 3.57-3.43 (2H, $J=6.7$ Hz, Oxiran CH_2), 2.20 (m, 2H, NCH_2CH_2)

^{13}C NMR (100 MHz, CDCl_3) δ : 171.8 (Ind C-2), 158.5 (Oph C-1), 144.5 (Ind C-7a), 130.4 (Ind C-6), 129.4 (2C, Oph C-3,5), 122.7 (Ind C-5), 122.6 (Ind C-3a), 122.2 (Ind C-4), 120.9 (Oph C-4), 114.4 (Oph C-2,6), 109.1 (Ind C-7), 64.8 (PhOCH_2), 56.3 (Ind C-3), 54.1 (Oxiran CH_2), 37.6 (NCH_2), 27.5 (NCH_2CH_2)

^{15}N NMR (40 MHz, CDCl_3) δ : -240.6

HRMS (ESI), m/z : calcd for $\text{C}_{18}\text{H}_{17}\text{NO}_3$: 296.1281 $[\text{M}+\text{H}]^+$; found: 296.1275

5.2.2.2 Characterisation of 1H-indole-3-carbaldehydes

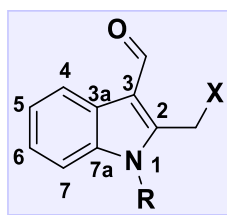
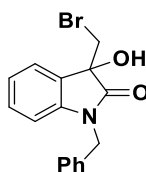


Figure 10. Numeration of the indole

1-Benzyl-3-(bromomethyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one (entry 13 of Table 7)



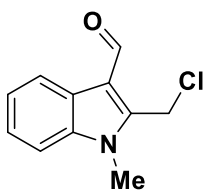
By following the general procedure, 1-benzylspiro[indole-3,2'-oxiran]-2(1H)-one (150 mg, 0.6 mmol, 1.0 equiv) was dissolved in dry THF (5 mL) and LiBr (solution 4.1 M, 0.73 mL, 3.0 mmol, 5.0 equiv) was added. The reaction was stirred at -78 °C and then left to stir over night till room temperature. The desired product was obtained in 40% yield (80 mg) as a white-greenish semi-solid after chromatography on silica gel (60 : 20 : 20, v/v/v, *n*-Hexane : EtOAc: DCM).

¹H NMR (400 MHz, CDCl₃) δ: 7.49 (m, 1H, Ind H-4), 7.32 (m, 4H, Ph H-2,3,5,6), 7.27 (m, 1H, Ph H-4), 7.26 (m, 1H, Ind H-6), 7.11 (m, 1H, Ind H-5), 6.75 (m, 1H, Ind H-7), 5.05 – 4.79 (AB system, *J*_{AB} = 15.7 Hz, 2H, CH₂Ph), 3.77 – 3.76 (AB system, *J*_{AB} = 10.2 Hz, 2H, CH₂Br).

¹³C NMR (100 MHz, CDCl₃) δ: 175.7 (Ind C-2), 143.0 (Ind C-7a), 135.0 (Ph C-1), 130.5 (Ind C-6), 128.8 (Ph C-3, 5), 127.8 (Ph C-4), 127.7 (Ind C-3a), 127.3 (Ph C-2,6), 124.1 (Ind C-4), 123.4 (Ind C-5), 109.8 (Ind C-7), 76.7 (Ind C-3), 44.1 (CH₂Ph), 34.9 (CH₂Br).

HRMS (ESI), *m/z*: calcd for C₁₆H₁₄BrNO₂: 332.0281 [M+H]⁺; found: 332.0281.

2- (Chloromethyl)-1-methyl-1*H*-indole-3-carbaldehyde (**668**)



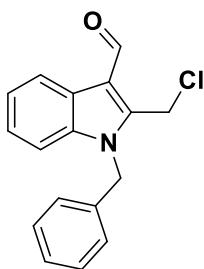
By following the General Procedure 2, 1-[(2*E*)-2-buten-1-yl]-7-fluorospiro[indole-3,2'-oxiran]-2(1*H*)-one (100 mg, 0.4 mmol, 1.0 equiv) was dissolved in dry THF (5 mL) and ClCH₂I (0.1 mL, 1.3 mmol, 3.0 equiv) was added. The reaction was stirred at -78 °C for 5 min, then MeLi x LiBr complex (2.2 M in diethyl ether, 0.5 mL, 1.0 mmol, 2.8 equiv) was added dropwise. The desired product **668** was obtained in 80% yield (66 mg) as dark green semi-solid after chromatography on silica gel (99:01, *v/v*, DCM : EtOAc).

¹H NMR (400 MHz, CDCl₃) δ: 10.31 (s, 1H, CHO), 8.24 (m, 1H, Ind H-4), 7.40 (m, 2H, Ind H-6,7), 7.34 (m, 1H, Ind H-5), 5.12 (s, 2H, CH₂Cl), 3.87 (s, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃) δ: 183.8 (CHO), 142.0 (Ind C-2), 137.4 (Ind C-7a), 125.5 (Ind C-3a), 124.5 (Ind C-6), 123.3 (Ind C-5), 121.0 (Ind C-4), 114.5 (Ind C-3), 109.9 (Ind C-7), 33.4 (CH₂Cl), 30.5 (NCH₃).

HRMS (ESI), *m/z*: calcd for C₁₁H₁₀ClNO: 208.0524 [M+H]⁺ ; found: 208.0525.

1-Benzyl-2-(chloromethyl)-1*H*-indole-3-carbaldehyde (669)



By following the General Procedure 2, 1-benzyl-spiro[indole-3,2'-oxiran]-2(1*H*)-one (300 mg, 1.3 mmol, 1.0 equiv) was dissolved in dry THF (5 mL) and ClCH₂I (0.3 mL, 4.0 mmol, 3.0 equiv) was added. The reaction was stirred at -78 °C for 5 min, then MeLi x LiBr complex (2.2 M in diethyl ether, 1.6 mL, 4.0 mmol, 2.8 equiv) was added dropwise. The desired product **669** was obtained in 95% yield (350 mg) as dark green semi-solid after chromatography on silica gel (80:20, *v/v*, *n*-Hexane : EtOAc).

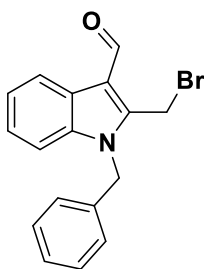
¹H NMR (400 MHz, CDCl₃) δ: 10.36 (s, 1H, CHO), 8.30 (m, 1H, Ind H-4), 7.33 (m, 1H, Ind H-5), 7.32 (m, 2H, Ind H-6,7), 7.31 (m, 2H, Ph H-3,5), 7.30 (m, 1H, Ph H-4), 7.05 (m, 2H, Ph H-2,6), 5.55 (s, 2H, CH₂Ph), 5.02 (s, 2H, CH₂Cl).

¹³C NMR (100 MHz, CDCl₃) δ: 184.0 (CHO), 142.1 (Ind C-2), 136.8 (Ind C-7a), 135.5 (Ph C-1), 129.1 (Ph C-3,5), 128.1 (Ph C-4), 126.0 (Ph C-2,6), 125.6 (Ind C-3a), 124.8 (Ind C-6), 123.4 (Ind C-5), 121.2 (Ind C-4), 115.0 (Ind C-3), 110.5 (Ind C-7), 47.0 (CH₂Ph), 33.4 (CH₂Cl).

¹⁵N NMR (40 MHz, CDCl₃) δ: - 235.3.

HRMS (ESI), *m/z*: calcd for C₁₇H₁₄ClNO: 284.0837 [M+H]⁺ ; found: 284.0840.

1-Benzyl-2-(bromomethyl)-1*H*-indole-3-carbaldehyde (670)



By following the General Procedure 4, 1-benzylspiro[indoline-3,2'-oxiran]-2-one (200 mg, 0.8 mmol, 1.0 equiv) was dissolved in dry THF and Br₂CH₂ (0.2 mL, 2.4 mmol, 3.0 equiv) was added. The reaction was stirred at -78 °C after MeLi x LiBr complex (2.2 M in diethyl ether, 1.0 mL, 2.2 mmol, 2.8 equiv) was added dropwise. The desired product **670** was obtained in 58% yield (152 mg) as brown solid (m.p. = 93.5 °C) after chromatography on silica gel (10:80:10 v/v/v, DCM : *n*- Hexane : EtOAc).

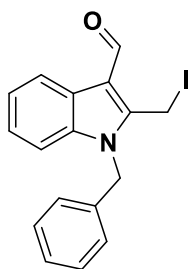
¹H NMR (400 MHz, CDCl₃) δ: 10.36 (s, 1H, CHO), 8.28 (m, 1H, Ind H-4), 7.33 (m, 1H, Ind H-5), 7.32 (m, 2H, Ind H-6,7), 7.31 (m, 2H, Ph H-3,5), 7.30 (m, 1H, Ph H-4), 7.06 (m, 2H, Ph H-2,6), 5.53 (s, 2H, CH₂Ph), 4.89 (s, 2H, CH₂Br).

¹³C NMR (100 MHz, CDCl₃) δ: 183.9 (CHO), 142.2 (Ind C-2), 137.3 (Ind C-7a), 135.4 (Ph C-1), 129.1 (Ph C-3,5), 128.1 (Ph C-4), 125.9 (Ph C-2, 6), 125.7 (Ind C-3a), 124.8 (Ind C-6), 123.4 (Ind C-5), 120.9 (Ind C-4), 114.6 (Ind C-3), 110.4 (Ind C-7), 46.9 (CH₂Ph), 19.3 (CH₂Br).

¹⁵N NMR (40 MHz, CDCl₃) δ: - 235.3.

HRMS (ESI), m/z: calcd for C₁₇H₁₄BrNO: 328.0331 [M+H]⁺; found: 328.0333.

1-Benzyl-2-(iodomethyl)-1*H*-indole-3-carbaldehyde (671)



By following the General Procedure 5, 1-benzyl-spiro[indole-3,2'-oxiran]-2(1*H*)-one (200 mg, 0.8 mmol, 1.0 equiv) was dissolved in dry THF (5 mL) and CH₂I₂ (0.2 mL, 2.4 mmol, 3.0 equiv) was added. The reaction was stirred at -78 °C for 5 min, then MeLi x LiBr complex (2.2 M in diethyl ether, 1.0 mL, 2.0 mmol, 2.8 equiv) was added dropwise. The desired product **671** was obtained in 50% yield (150 mg) as green semi-solid substance after chromatography on silica gel (60:20:20, v/v/v, *n*-Hexane : EtOAc: DCM).

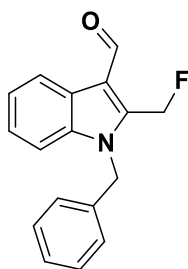
¹H NMR (400 MHz, CDCl₃) δ: 10.37 (s, 1H, CHO), 8.22 (m, 1H, Ind H-4), 7.32 (m, 1H, Ind H-5), 7.31 (m, 4H, Ind H-6,7, Ph H-3,5), 7.30 (m, 1H, Ph H-4), 7.05 (m, 2H, Ph H-2,6), 5.48 (s, 2H, CH₂Ph), 4.28 (s, 2H, CH₂I).

¹³C NMR (100 MHz, CDCl₃) δ: 183.9 (CHO), 143.9 (Ind C-2), 137.5 (Ind C-7a), 135.2 (Ph C-1), 129.2 (Ph C-3,5), 128.2 (Ph C-4), 126.1 (Ind C-3a), 125.9 (Ph C-2,6), 124.6 (Ind C-6), 123.4 (Ind C-5), 120.6 (Ind C-4), 113.6 (Ind C-3), 110.2 (Ind C-7), 46.9 (CH₂Ph), -9.8 (CH₂I).

¹⁵N NMR (40 MHz, CDCl₃) δ: - 235.7.

HRMS (ESI), m/z: calcd for C₁₇H₁₄INO: 376.0193 [M+H]⁺ ; found: 376.0196.

1-Benzyl-2-(fluoromethyl)-1H-indole-3-carbaldehyde (672)



By following the General Procedure 3, 1-benzylspiro[indoline-3,2'-oxiran]-2-one (160 mg, 0.6 mmol, 1.5 equiv) was dissolved in dry THF/Et₂O (1:1, v/v, 5 mL) and FCH₂I (0.03 mL, 0.4 mmol, 1.0 equiv) was added. The reaction was stirred at -78 °C for 5 min after MeLi x LiBr complex (2.2 M in diethyl ether, 0.4 mL, 0.8 mmol, 2.0 equiv) was added dropwise. The desired product **672** was obtained in 83% yield (133 mg) as green semi-solid after chromatography on silica gel (99 : 01, v/v, DCM : EtOAc).

¹H NMR (400 MHz, CDCl₃) δ: 10.35 (s, 1H, CHO), 8.36 (m, 1H, Ind H-4), 7.34 (m, 1H, Ind H-5), 7.33 (m, 2H, Ind H-6,7), 7.30 (m, 2H, Ph H-3,5), 7.29 (m, 1H, Ph H-4), 7.05 (m, 2H, Ph H-2,6), 5.82 (d, *J* = 48.2 Hz, 2 H, CH₂F), 5.52 (s, 2H, CH₂Ph).

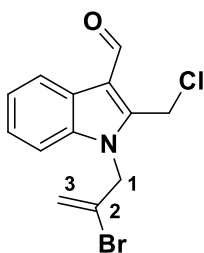
¹³C NMR (100 MHz, CDCl₃) δ: 184.2 (d, *J* = 1.7 Hz, CHO), 140.6 (d, *J* = 15.4 Hz, Ind C-2), 137.3 (d, *J* = 1.3 Hz, Ind C-7a), 135.6 (Ph C-1), 129.1 (Ph C-3,5), 128.0 (Ph C-4), 126.1 (d, *J* = 0.7 Hz, Ph C-2,6), 125.4 (d, *J* = 1.9 Hz, Ind C-3a), 125.0 (d, *J* = 1.5 Hz, Ind C-6), 123.4 (Ind C-5), 121.7 (Ind C-4), 116.3 (d, *J* = 4.4 Hz, Ind C-3), 110.6 (Ind C-7), 72.8 (d, *J* = 167.1 Hz, CH₂F), 47.6 (d, *J* = 2.7 Hz, CH₂Ph).

¹⁵N NMR (40 MHz, CDCl₃) δ: - 234.7.

¹⁹F NMR (376 MHz, CDCl₃) δ: - 208.3 (t, *J* = 48.2 Hz).

HRMS (ESI), *m/z*: calcd for C₁₇H₁₄FNO: 268.1132 [M+H]⁺ ; found: 268.1132 .

1-(2-Bromoprop-2-en-1-yl)-2-(chloromethyl)-1*H*-indole-3-carbaldehyde (673)



By following the General Procedure 2, 1-(2-bromoallyl)spiro[indoline-3,2'-oxiran]-2-one (280.12 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF (5 mL) and ClCH₂I (0.22 mL, 3.0 mmol, 3.0 equiv) was added. The reaction was stirred at -78 °C for 5 min, then MeLi x LiBr complex (2.2 M in diethyl ether, 1.27 mL, 2.8 mmol, 2.8 equiv) was added dropwise. The desired product **673** was obtained in 91% yield (284 mg) as light green solid (m.p. = 132 °C) after chromatography on silica gel (80:20 v/v, *n*-Hexane: EtOAc).

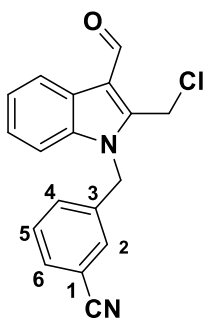
¹H NMR (400 MHz, CDCl₃) δ: 10.36 (s, 1H, CHO), 8.27 (m, 1H, Ind H-4), 7.37 (m, 3H, Ind H-5,6,7), 5.64 (m, 1H, propenyl H-3), 5.40 (m, 1H, propenyl H-3), 5.12 (m, 2H, propenyl H-1), 5.11 (s, 2H, CH₂Cl).

¹³C NMR (100 MHz, CDCl₃) δ: 184.1 (CHO), 141.6 (Ind C-2), 136.7 (Ind C-7a), 125.5 (propenyl C-2), 125.4 (Ind C-3a), 125.0 (Ind C-6), 123.7 (Ind C-5), 121.3 (Ind C-4), 118.6 (propenyl C-3), 115.2 (Ind C-3), 110.2 (Ind C-7), 50.9 (propenyl C-1), 33.2 (CH₂Cl).

¹⁵N NMR (40 MHz, CDCl₃) δ: -238.8.

HRMS (ESI), m/z: calcd for C₁₃H₁₁BrClNO: 311.9785 [M+H]⁺ ; found: 311.9790.

3-[[2-(Chloromethyl)-3-formyl-1H-indol-1-yl] methyl benzonitrile (**674**)



By following the General Procedure 2, 3-[[2-Oxospiro[indole-3,2'-oxirane]]-1(2H)-yl] methyl] benzonitrile (276.3 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF (5 mL) and ClCH₂I (0.22 mL, 3.0 mmol, 3.0 equiv) was added. The reaction was stirred at -78 °C for 5 min, then MeLi x LiBr complex (2.2 M in diethyl ether, 1.27 mL, 2.8 mmol, 2.8 equiv) was added dropwise. The desired product **674** was obtained in 89% yield (275 mg) as light green solid (m.p. = 169 °C) after chromatography on silica gel (60:40 v/v, *n*-Hexane: EtOAc).

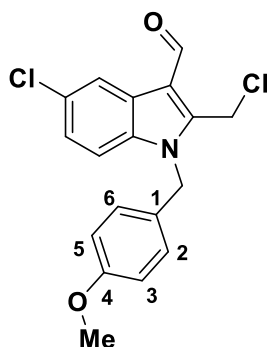
¹H NMR (400 MHz, CDCl₃) δ: 10.38 (s, 1H, CHO), 8.30 (m, 1H, Ind H-4), 7.60 (m, 1H, Ph H-6), 7.44 (m, 1H, Ph H-5), 7.37 (m, 1H, Ind H-5), 7.36 (m, 1H, Ph H-2), 7.33 (m, 1H, Ind H-6), 7.26 (m, 1H, Ph H-4), 7.20 (m, 1H, Ind H-7), 5.57 (s, 2H, CH₂Ph), 5.04 (s, 2H, CH₂Cl).

¹³C NMR (100 MHz, CDCl₃) δ: 184.0 (CHO), 141.4 (Ind C-2), 137.2 (Ph C-3), 136.8 (Ind C-7a), 131.9 (Ph C-6), 130.4 (Ph C-4), 130.0 (Ph C-5), 129.5 (Ph C-2), 125.7 (Ind C-3a), 125.2 (Ind C-6), 123.8 (Ind C-5), 121.4 (Ind C-4), 118.1 (CN), 115.3 (Ind C-3), 113.4 (Ph C-1), 110.1 (Ind C-7), 46.3 (CH₂Ph), 33.4 (CH₂Cl).

¹⁵N NMR (40 MHz, CDCl₃) δ: -239.0.

HRMS (ESI), m/z: calcd for C₁₈H₁₃ClN₂O: 309.0789 [M+H]⁺; found: 309.0785.

5-Chloro-2-(chloromethyl)-1-[(4-methoxyphenyl)methyl]-1*H*-indole-3-carbaldehyde (675)



By following the General Procedure 2, 5-Chloro-1-(4-methoxybenzyl)spiro[indol-3,2'-oxirane]-2(1*H*)-one (315.75 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF (5 mL) and ClCH₂I (0.22 mL, 3.0 mmol, 3.0 equiv) was added. The reaction was stirred at -78 °C for 5 min, then MeLi x LiBr complex (2.2 M in diethyl ether, 1.27 mL, 2.8 mmol, 2.8 equiv) was added dropwise. The desired product **675** was obtained in 78% yield (272 mg) as green solid (m.p. = 106 °C) after chromatography on silica gel (80:20 v/v, *n*-Hexane : EtOAc).

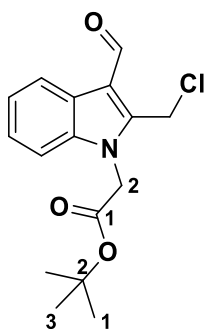
¹H NMR (400 MHz, CDCl₃) δ: 10.27 (s, 1H, CHO), 8.28 (m, 1H, Ind H-4), 7.25 (m, 1H, Ind H-6), 7.22 (m, 1H, Ind H-7), 6.97 (m, 2H, Ph H-2,6), 6.84 (m, 2H, Ph H-3,5), 5.44 (s, 2H, CH₂Ph), 4.98 (s, 2H, CH₂Cl), 3.77 (s, 3H, OCH₃).

¹³C NMR (100 MHz, CDCl₃) δ: 183.5 (CHO), 159.5 (Ph C-4), 143.1 (Ind C-2), 135.5 (Ind C-7a), 129.4 (Ind C-5), 127.3 (Ph C-2,6), 127.0 (Ph C-1), 126.4 (Ind C-3a), 125.2 (Ind C-6), 120.9 (Ind C-4), 114.6 (Ph C-3,5), 114.5 (Ind C-3), 111.6 (Ind C-7), 55.3 (OCH₃), 46.9 (CH₂Ph), 33.1 (CH₂Cl).

¹⁵N NMR (40 MHz, CDCl₃) δ: -233.8.

HRMS (ESI), *m/z*: calcd for C₁₈H₁₆ClNO₂: 348.0553 [M+H]⁺ ; found: 348.0558.

Tert-butyl [2-(chloromethyl)-3-formyl-1*H*-indol-1-yl]acetate (676)



By following the General Procedure 2, tert-butyl 2-(4-([2-oxospiro[indoline-3,2'-oxiran]-1-yl)methyl)phenyl)acetate (399.8 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF (5 mL) and ClCH₂I (0.22 mL, 3.0 mmol, 3.0 equiv) was added. The reaction was stirred at -78 °C for 5 min, then MeLi x LiBr complex (2.2 M in diethyl ether, 1.27 mL, 2.8 mmol, 2.8 equiv) was added dropwise. The desired product **676** was obtained in 82% yield (252 mg) as light green solid (m.p.= 120.5 °C) after chromatography on silica gel (80:10:10 v/v/v, *n*-Hexane : DCM: EtOAc).

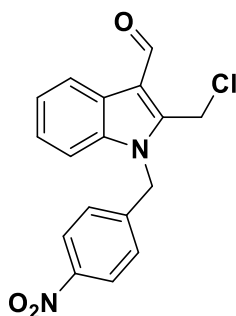
¹H NMR (400 MHz, CDCl₃) δ: 10.33 (s, 1H, CHO), 8.25 (m, 1H, Ind H-4), 7.37 (m, 1H, Ind H-6), 7.33 (m, 1H, Ind H-5), 7.30 (m, 1H, Ind H-7), 5.10 (s, 2H, CH₂Cl), 4.92 (s, 2H, CH₂CO₂*t*-Bu), 1.45 (s, 9H, *t*-Bu).

¹³C NMR (100 MHz, CDCl₃) δ: 184.0 (CHO), 166.1 (CO₂*t*-Bu), 141.8 (Ind C-2), 137.2 (Ind C-7a), 125.4 (Ind C-3a), 124.8 (Ind C-6), 123.5 (Ind C-5), 121.2 (Ind C-4), 115.1 (Ind C-3), 109.5 (Ind C-7), 83.7 (*t*-Bu C-2), 45.8 (NCH₂), 33.4 (CH₂Cl), 27.9 (*t*-Bu C-1,3,4).

¹⁵N NMR (40 MHz, CDCl₃) δ: -242.7.

HRMS (ESI), m/z: calcd for C₁₆H₁₈ClNO₃: 308.1048 [M+H]⁺; found: 308.1052.

2-(Chloromethyl)-1-[(4-nitrophenyl)methyl]-1*H*-indole-3-carbaldehyde (677)



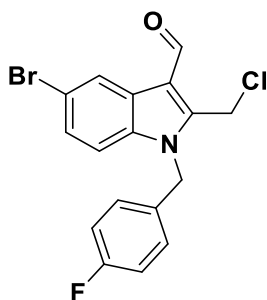
By following the General Procedure 2, 1-(4-Nitrobenzyl)spiro[indole-3,2'-oxirane]-2(1*H*)- one (296.28 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF (5 mL) and ClCH₂I (0.22 mL, 3.0 mmol, 3.0 equiv) was added. The reaction was stirred at -78 °C for 5 min, then MeLi x LiBr complex (2.2 M in diethyl ether, 1.27 mL, 2.8 mmol, 2.8 equiv) was added dropwise. The desired product **677** was obtained in 62% yield (204 mg) as dark green solid (m.p.= 180 °C) after chromatography on silica gel (60:20:20 v/v/v, *n*-Hexane : DCM : EtOAc).

¹H NMR (400 MHz, CDCl₃) δ: 10.38 (s, 1H, CHO), 8.31 (m, 1H, Ind H-4), 8.18 (s, 2H, Ph H-3,5), 7.37 (m, 1H, Ind H-5), 7.32 (m, 1H, Ind H-6), 7.21 (m, 2H, Ph H-2,6), 7.19 (m, 1H, Ind H-7), 5.63 (s, 2H, CH₂-Ph), 5.05 (s, 2H, CH₂Cl).

¹³C NMR (100 MHz, CDCl₃) δ: 184.0 (CHO), 147.8 (Ph C-4), 142.7 (Ph C-1), 141.5 (Ind C-2), 136.8 (Ind C-7a), 126.9 (Ph, C-2,6), 125.7 (Ind C-3a), 125.2 (Ind C-6), 124.4 (Ph C-3,5), 123.8 (Ind C-5), 121.4 (Ind C-4), 115.4 (Ind C-3), 110.1 (Ind C-7), 46.5 (CH₂-Ph), 33.3 (CH₂Cl).

HRMS (ESI), m/z: calcd for C₁₇H₁₃ClN₂O₃: 329.0687 [M+H]⁺ ; found: 329.0691.

5-Bromo-2-(chloromethyl)-1-[(4-fluorophenyl)methyl]-1*H*-indole-3-carbaldehyde (678)



By following the General Procedure 2, 5-Bromo-1-(4-fluorobenzyl)spiro[indole-3,2'-oxirane]-2(1*H*)-one (348.17 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF (5 mL) and ClCH_2I (0.22 mL, 3.0 mmol, 3.0 equiv) was added. The reaction was stirred at -78°C for 5 min, then MeLi x LiBr complex (2.2 M in diethyl ether, 1.27 mL, 2.8 mmol, 2.8 equiv) was added dropwise. The desired product **678** was obtained in 88% yield (335 mg) as dark green solid (m.p.= 114.5°C) after chromatography on silica gel (80:10:10 v/v/v, *n* - Hexane : DCM : EtOAc).

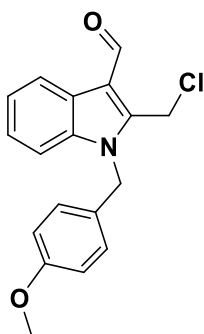
^1H NMR (400 MHz, CDCl_3) δ : 10.28 (s, 1H, CHO), 8.45 (m, 1H, Ind H-4), 7.40 (dd, 1H, $J = 8.8, 1.9\text{Hz}$, Ind H- 6), 7.13 (d, 1H, $J = 8.8\text{ Hz}$, H-7 Ind), 7.02 (m, 2H, Ph H-2,6), 7.00 (m, 2H, Ph H-3,5), 5.48 (s, 2H, CH_2Cl), 4.98 (s, 2H, $\text{CH}_2\text{-Ph}$).

^{13}C NMR (100 MHz, CDCl_3) δ : 183.7 (CHO), 162.6 (d, $J = 247.7\text{Hz}$, Ph C-4), 143.0 (Ind C-2), 135.9 (Ind C-7a), 130.9 (d, $J = 0.9\text{Hz}$, Ph C-1), 128.1 (Ind C-6), 127.9 (d, $J = 8.2\text{ Hz}$, Ph C-2,6), 127.1 (Ind C-3a), 124.2 (Ind C-4), 117.3 (Ind C-5), 116.4 (d, $J = 21.9\text{ Hz}$, Ph C-3,5), 114.7 (Ind C-3), 112.0 (Ind C-7), 46.8 ($\text{CH}_2\text{-Ph}$), 33.2 (CH_2Cl).

^{19}F NMR (376 MHz, CDCl_3) δ ; -113.3 (m).

HRMS (ESI), m/z : calcd for $\text{C}_{17}\text{H}_{12}\text{BrClFNO}$: 379.9848 $[\text{M}+\text{H}]^+$; found: 379.9845

2-(Chloromethyl)-1-[(4-methoxyphenyl)methyl]-1H-indole-3-carbaldehyde (679)



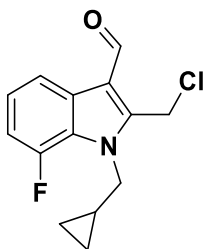
By following the General Procedure 2, 1-(4-Methoxybenzyl)spiro[indole-3,2'-oxirane]-2-(1H)-one (281.3 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF (5 mL) and ClCH_2I (0.22 mL, 3.0 mmol, 3.0 equiv) was added. The reaction was stirred at -78°C for 5 min, then MeLi x LiBr complex (2.2 M in diethyl ether, 1.27 mL, 2.8 mmol, 2.8 equiv) was added dropwise. The desired product **679** was obtained in 76% yield (238 mg) as brown semi-solid substance after chromatography on silica gel (80:10:10 v/v/v, *n*-Hexane : DCM: EtOAc).

^1H NMR (400 MHz, CDCl_3) δ : 10.34 (s, 1H, CHO), 8.28 (m, 1H, Ind H-4), 7.33 (m, 3H, Ind H-5,6,7), 7.00 (m, 2H, Ph H-2,6), 6.83 (m, 2H, Ph H-3,5), 5.48 (s, 2H, CH_2 -Ph), 5.02 (s, 2H, CH_2 -Cl), 3.77 (s, 3H, OCH_3).

^{13}C NMR (100 MHz, CDCl_3) δ : 184.1 (CHO), 159.5 (Ph C-4), 142.2 (Ind C-2), 137.3 (Ind C-7a), 125.7 (Ind C-3a), 127.6 (Ph C-2,6), 127.5 (Ph C-1), 124.9 (Ind C-6), 123.5 (Ind C-5), 121.3 (Ind C-4), 115.0 (Ind C-3), 114.6 (Ph C-3,5), 110.7 (Ind C-7), 55.4 (OCH_3), 46.8 (CH_2 -Ph), 33.6 (CH_2 -Cl).

HRMS (ESI), m/z : calcd for $\text{C}_{18}\text{H}_{16}\text{ClNO}_2$: 314.0942 $[\text{M}+\text{H}]^+$; found: 314.0938.

2-(Chloromethyl)-1-(cyclopropylmethyl)-7-fluoro-1H-indole-3-carbaldehyde (680)



By following the General Procedure 2, 1-(Cyclopropylmethyl)-7-fluorospiro[indole-3,2'-oxirane]-2(1H)-one (233.24 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF (5 mL) and ClCH_2I (0.22 mL, 3.0 mmol, 3.0 equiv) was added. The reaction was stirred at -78°C for 5 min, then MeLi x LiBr complex (2.2 M in diethyl ether, 1.27 mL, 2.8 mmol, 2.8 equiv) was added dropwise. The desired product **680** was obtained in 82% yield (218 mg) as dark green semi-solid substance after chromatography on silica gel (80:10:10 v/v/v, *n*-Hexane : DCM : EtOAc).

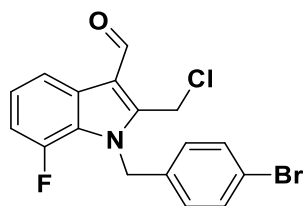
^1H NMR (400 MHz, CDCl_3) δ : 10.33 (s, 1H, CHO), 8.03 (dd, 1H, $J = 9.5, 4.7$ Hz, Ind H-4), 7.22 (m, 1H, Ind H-5), 7.04 (ddd, 1H, $J = 13.0, 8.0, 0.8$ Hz, Ind H-6), 5.10 (s, 2H, CH_2Cl), 4.36 (d, 2H, $J = 6.8$ Hz, CH_2 -cyclopropyl), 1.34 (m, 1H, cyclopropyl H-1), 0.61 (m, 2H, cyclopropyl H-2,3), 0.47 (m, 2H, cyclopropyl H-2,3).

^{13}C NMR (100 MHz, CDCl_3) δ : 184.1 (CHO), 149.8 (d, $J = 245.9$ Hz, Ind C-7), 142.9 (Ind C-2), 129.4 (d, $J = 3.9$ Hz, Ind C-3a), 125.0 (d, $J = 8.8$ Hz, Ind C-7a), 123.7 (d, $J = 6.8$ Hz, Ind C-5), 116.9 (d, $J = 3.9$ Hz, Ind C-4), 115.3 (d, $J = 1.2$ Hz, Ind C-3), 110.6 (d, $J = 18.7$ Hz, Ind C-6), 50.0 (d, $J = 5.8$ Hz, CH_2 -cyclopropyl), 33.2 ($\text{CH}_2\text{-Cl}$), 12.4 (d, $J = 2.0$ Hz, cyclopropyl C-1), 4.0 (d, 2C, $J = 1.5$ Hz, cyclopropyl C-2,3).

^{19}F NMR (376 MHz, CDCl_3) δ : -132.4 (m).

HRMS (ESI), m/z : calcd for $\text{C}_{14}\text{H}_{13}\text{ClFNO}$: 266.0742 $[\text{M}+\text{H}]^+$; found: 266.0740.

1-[(4-Bromophenyl)methyl]-2-(chloromethyl)-7-fluoro-1H-indole-3-carbaldehyde (681)



By following the General Procedure 2, 1-(4-Bromobenzyl)-7-fluorospiro[indole-3,2'-oxirane]-2(1H)-one (348.17 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF (5 mL) and ClCH₂I (0.22 mL, 3.0 mmol, 3.0 equiv) was added. The reaction was stirred at -78 °C for 5 min, then MeLi x LiBr complex (2.2 M in diethyl ether, 1.27 mL, 2.8 mmol, 2.8 equiv) was added dropwise. The desired product **681** was obtained in 83% yield (316 mg) as dark green solid (m.p. = 159 °C) after chromatography on silica gel (80:10:10 v/v/v, *n*-Hexane : DCM : EtOAc).

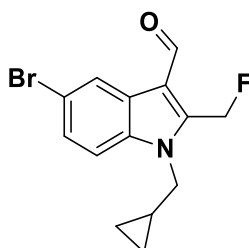
¹H NMR (400 MHz, CDCl₃) δ: 10.34 (s, 1 H, CHO), 8.06 (dd, 1H, *J* = 8.0, 0.6 Hz, Ind H-4), 7.44 (m, 2H, Ph H-3,5), 7.25 (m, 2H, Ph H-2,6), 7.02 (ddd, 1H, *J* = 12.7, 8.0, 0.8 Hz, Ind H-6), 6.91 (d, 1H, *J* = 8.5 Hz, Ind H-5), 5.66 (s, 2H, CH₂Ph), 4.97 (s, 2H, CH₂Cl).

¹³C NMR (100 MHz, CDCl₃) δ: 184.1 (CHO), 149.8 (d, *J* = 246.4 Hz, Ind C-7), 143.0 (Ind C-2), 135.6 (Ph C-1), 132.4 (Ph C-3,5), 129.2 (d, *J* = 3.7 Hz, Ind C-3a), 127.6 (Ph C-2,6), 125.1 (m, Ind C-7a), 124.1 (d, *J* = 6.6 Hz, Ind C-5), 122.2 (Ph C-4), 115.7 (Ind C-3), 111.0 (d, *J* = 18.1 Hz, Ind C-6), 48.8 (d, *J* = 7.2 Hz, CH₂Ph), 33.1 (CH₂Cl).

¹⁹F NMR (376 MHz, CDCl₃) δ; -133.9 (m).

HRMS (ESI), *m/z*: calcd for C₁₇H₁₂BrClFNO: 379.9848 [M+H]⁺ ; found: 379.9851.

5-Bromo-1-(cyclopropylmethyl)-2-(fluoromethyl)-1H-indole-3-carbaldehyde (682)



By following the General Procedure 3, 5-Bromo-1-(cyclopropylmethyl)spiro[indole-3,2'-oxirane]-2(1H)one (441.2 mg, 1.5 mmol, 1.5 equiv) was dissolved in dry THF/Et₂O (1:1, 5 mL, v/v) and FCH₂I (0.07 mL, 1.0 mmol, 1.0 equiv) was added. The reaction was stirred at -78 °C for 5 min. after MeLi x LiBr complex (2.2 M in diethyl ether, 0.9 mL, 2.0 mmol, 2.0 equiv) was added dropwise. The desired product **682** was obtained in 73% yield (340 mg) as light brown solid (m.p.= 106.5 °C) after chromatography on silica gel (20:70:10 v/v/v, DCM : n-Hexane : EtOAc).

¹H NMR (400 MHz, CDCl₃) δ: 10.23 (s, 1H, CHO), 8.46 (d, 1H, 1.9 Hz, Ind H-4), 7.44 (ddd, 1H, J =8.8, 1.9, 0.9 Hz, Ind H-6), 7.30 (d, 1H, J=8.8Hz, Ind H-7), 5.84 (d, 2H, J= 48.3 Hz, CH₂F), 4.14 (d, 2H, J=6.7 Hz, CH₂-cyclopropyl), 1.27 (m, 1H, cyclopropyl H-1), 0.63 (m, 2H, cyclopropyl H-2,3), 0.43 (m, 2H, cyclopropyl H-2,3).

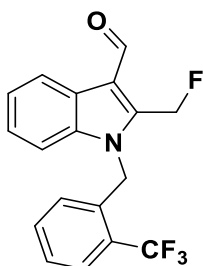
¹³C NMR (100 MHz, CDCl₃) δ: 183.7 (d, J=1.4 Hz, CHO), 141.0 (d, J= 15.9 Hz, Ind C-2), 135.7 (Ind C-7a), 127.6 (d, J=1.5 Hz, Ind C-6), 126.8 (d, J=1.8 Hz, Ind C-3a), 124.4 (Ind C-4), 116.8 (Ind C-5), 115.4 (d, J=4.2 Hz, Ind C-3), 112.0 (Ind C-7), 72.4 (d, J=168.0 Hz, CH₂F), 48.6 (d, J=2.0 Hz, CH₂cyclopropyl), 11.3 (d, J=0.7 Hz, cyclopropyl C-1), 4.4 (d, J=1.0 Hz, cyclopropyl C-2,3).

¹⁵N NMR (40 MHz, CDCl₃) δ: -228.8.

¹⁹F NMR (376 MHz, CDCl₃) δ: -207.2 (t, J=48.3 Hz, CH₂F).

HRMS (ESI), m/z: calcd for C₁₄H₁₃BrFNO: 310.0237 [M+H]⁺ ; found: 310.0242.

2-(Fluoromethyl)-1-{[2-(trifluoromethyl)phenyl]methyl}-1H-indole-3-carbaldehyde (683)



By following the General Procedure 3, 1-[2-(Trifluoromethyl)benzyl]spiro[indole-3,2'-oxirane]-2(1H)-one (478.9 mg, 1.5 mmol, 1.5 equiv) was dissolved in dry THF/Et₂O (1:1, v/v, 5 mL) and FCH₂I (0.07 mL, 1.0 mmol, 1.0 equiv) was added. The reaction was stirred at -78 °C for 5 min. after MeLi x LiBr complex (2.2 M in diethyl ether, 0.9 mL, 2.0 mmol, 2.0 equiv) was added dropwise. The desired product **683** was obtained in 89% yield (448 mg) as green solid (m.p.= 151 °C) after chromatography on silica gel (98:02, v/v, DCM : EtOAc).

¹H NMR (400 MHz, CDCl₃) δ: 10.38 (s, 1H, CHO), 8.38 (m, 1H, Ind H-4), 7.76 (m, 1H, Ph H-3), 7.39 (m, 1H, Ph H-4), 7.37 (m, Ind H-5), 7.32 (m, 2H, Ind H-6, Ph H-5), 7.19 (m, 1H, Ind H-7), 6.45 (m, 1H, Ph H-6), 5.83 (d, *J*=48.2 Hz, 2H, CH₂F), 5.71 (s, 2H, CH₂Ph).

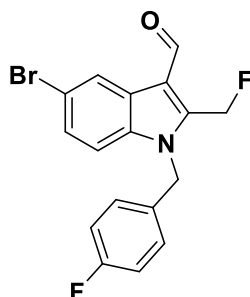
¹³C NMR (100 MHz, CDCl₃) δ: 184.2 (d, *J*=1.7 Hz CHO), 140.7 (d, *J*=15.7 Hz, Ind C-2), 137.0 (d, *J*=1.3 Hz, Ind C-7a), 134.3 (q, *J*=1.4, Ph C-1), 132.7 (q, *J*=1.2 Hz, Ph C-5), 127.9 (Ph C-4), 127.1 (q, *J*=31.0 Hz, Ph C-2), 126.34 (d, *J*=1.1 Hz Ph C-6), 126.29 (q, *J*=5.7 Hz, Ph C-3), 125.36 (d, *J*=1.8 Hz, Ind C-3a), 125.32 (Ind C-6), 124.3 (q, *J*=273.7 Hz, CF₃), 123.7 (d, *J*=1.5 Hz, Ind C-5), 121.9 (Ind C-4), 116.6 (d, *J*=4.4 Hz, Ind C-3), 110.3 (d, *J*=1.2 Hz, Ind C-7), 72.6 (d, *J*=167.7 Hz, CH₂F), 44.2 (m, CH₂Ph).

¹⁵N NMR (40 MHz, CDCl₃) δ: -239.3.

¹⁹F NMR (376 MHz, CDCl₃) δ: -60.6 (s, CF₃), -208.4 (t, *J*=48.2 Hz, CH₂F).

HRMS (ESI), *m/z*: calcd for C₁₈H₁₃F₄NO: 358.0825 [M+Na]⁺ ; found: 358.0835.

5-Bromo-2-(fluoromethyl)-1-[(4-fluorophenyl)methyl]-1*H*-indole-3-carbaldehyde (684)



By following the General Procedure 3, 5-Bromo-1-(4-fluorobenzyl)spiro[indole-3,2'-oxirane]-2(1*H*)-one (522.3 mg, 1.5 mmol, 1.5 equiv) was dissolved in dry THF/Et₂O (1:1, v/v, 5 mL) and FCH₂I (0.07 mL, 1.0 mmol, 1.0 equiv) was added. The reaction was stirred at -78 °C for 5 min. after MeLi x LiBr complex (2.2 M in diethyl ether, 0.9 mL, 2.0 mmol, 2.0 equiv) was added dropwise. The desired product **684** was obtained in 88% yield (481 mg) as green semi-solid substance after chromatography on silica gel (80:10:10, v/v/v, n-Hexane: DCM : EtOAc).

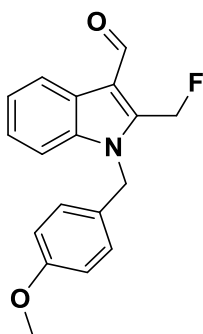
¹H NMR (400 MHz, CDCl₃) δ: 10.27 (d, *J*=5.6 Hz, 1H, CHO), 8.50 (m, 1H, Ind H-4), 7.40 (m, 1H, Ind H-6), 7.15 (dd, 1H, *J*=8.8, 3.1 Hz, Ind H-7), 7.02 (m, 2H, Ph C-2,6), 7.01 (m, 2H, Ph C-3,5), 5.80 (dd, 2H, *J*=48.0, 1.8 Hz, CH₂F), 5.45 (s, 2H, CH₂Ph).

¹³C NMR (100 MHz, CDCl₃) δ: 183.7 (CHO), 162.5 (d, *J*=247.6 Hz, Ph C-4), 141.3 (d, *J*=15.6 Hz, Ind C-2), 135.7 (Ind C-7a), 130.9 (d, *J*=3.1 Hz, Ph C-1), 128.2 (Ind C-6), 127.8 (d, *J*=8.2 Hz, Ph C-2,6), 126.8 (Ind C-3a), 124.6 (Ind C-4), 117.1 (Ind C-5), 116.2 (d, *J*=21.8 Hz, Ph C-3,5), 115.8 (d, *J*=4.2 Hz, Ind C-3), 111.9 (Ind C-7), 72.6 (d, *J*=168.0 Hz, CH₂F), 47.2 (CH₂-Ph).

¹⁹F NMR (376 MHz, CDCl₃) δ: -113.4 (m, F-Ph), -209.0 (dt, *J*_F= 48.0 Hz, *J*_d= 20.7 Hz, CH₂F).

HRMS (ESI), *m/z*: calcd for C₁₇H₁₂BrF₂NO: 364.0143 [M+H]⁺ ; found: 364.0158.

2-(Fluoromethyl)-1-[(4-methoxyphenyl)methyl]-1H-indole-3-carbaldehyde (685)



By following the General Procedure 3, 1-(4-Methoxybenzyl)spiro[indole-3,2'-oxirane]-2(1H)-one (421.95 mg, 1.5 mmol, 1.5 equiv) was dissolved in dry THF/Et₂O (1:1, v/v, 5 mL) and FCH₂I (0.07 mL, 1.0 mmol, 1.0 equiv) was added. The reaction was stirred at -78 °C for 5 min after MeLi x LiBr complex (2.2 M in diethyl ether, 0.9 mL, 2.0 mmol, 2.0 equiv) was added dropwise. The desired product **685** was obtained in 74% yield (330 mg) as dark green solid (m.p.= 103 °C) after chromatography on silica gel (10:80:10, v/v/v, DCM : *n*-Hexane : EtOAc).

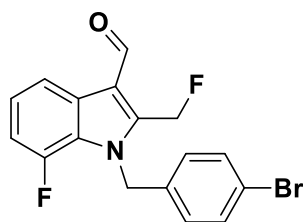
¹H NMR (400 MHz, CDCl₃) δ: 10.32 (d, 1H, *J*=1.8 Hz, CHO), 8.34 (m, 1H, Ind H-4), 7.33 (m, 3H, Ind H-5,6,7), 7.00 (m, 2H, Ph H-2,6), 6.82 (m, 2H, Ph H-3,5), 5.80 (dd, 2H, *J*=48.2, 1.8 Hz, CH₂F), 5.43 (d, 2H, *J*=1.5 Hz, CH₂-Ph), 3.75 (d, 3H, *J*=1.0 Hz, OCH₃).

¹³C NMR (100 MHz, CDCl₃) δ: 184.1 (CHO), 159.3 (Ph C-4), 140.7 (d, *J*=15.4 Hz, Ind C-2), 137.2 (Ind C-7a), 127.53 (Ph C-1), 127.45 (Ph C-2,6), 125.3 (Ind C-3a), 124.9 (Ind C-6), 123.3 (Ind C-5), 121.7 (Ind C-4), 116.2 (d, *J*=4.3 Hz, Ind C-3), 114.4 (Ph C-3,5), 110.6 (Ind C-7), 72.7 (d, *J*=167.0 Hz, CH₂F), 55.2 (OCH₃), 47.1 (d, *J*=2.3 Hz, CH₂-Ph).

¹⁹F NMR (376 MHz, CDCl₃) δ: -208.0 (t, *J*=48.2 Hz).

HRMS (ESI), *m/z*: calcd for C₁₈H₁₆FNO₂: 298.1238 [M+H]⁺ ; found: 298.1258.

1-[(4-Bromophenyl)methyl]-7-fluoro-2-(fluoromethyl)-1H-indole-3-carbaldehyde (686)



By following the General Procedure 3, 1-(4-bromobenzyl)-7-fluorospiro-[indole-3,2'-oxirane]-2(1H)-one (522.3 mg, 1.5 mmol, 1.5 equiv) was dissolved in dry THF/Et₂O (1:1, v/v, 5 mL) and FCH₂I (0.07 mL, 1.0 mmol, 1.0 equiv) was added. The reaction was stirred at -78 °C for 5 min after MeLi x LiBr complex (2.2 M in diethyl ether, 0.9 mL, 2.0 mmol, 2.0 equiv) was added dropwise. The desired product **686** was obtained in 87% yield (475 mg) as dark green solid (m.p. = 123 °C) after chromatography on silica gel (80:10:10 v/v/v, n-Hexane: DCM : EtOAc).

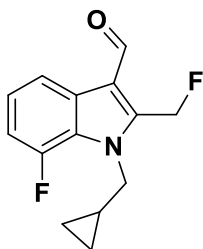
¹H NMR (400 MHz, CDCl₃) δ: 10.34 (s, 1H, CHO), 8.12 (d, 1H, *J* = 8.0Hz, Ind H-4), 7.43 (m, 2H, Ph H-3,5), 7.24 (td, 1H, *J_d* = 3.7Hz, *J_t* = 8.0Hz, Ind H-5), 7.02(dd, 1H, *J* = 12.6, 7.9 Hz, Ind H-6), 6.91 (m, 2H, Ph H-2,6), 5.80 (d, 2H, *J* = 48.1Hz, CH₂F), 5.64 (s, 2H, CH₂Ph).

¹³C NMR (100 MHz, CDCl₃) δ: 184.2 (CHO), 149.8 (dd, *J* = 246.6, 1.2 Hz, Ind C-7), 141.5(d, *J* = 15.6Hz, Ind C-2), 135.6 (Ph C-1), 132.2 (Ph C-3,5), 129.7 (d, *J* = 1.8Hz, Ph C-2,6), 125.2 (d, *J* = 9.2 Hz, Ind C-7a), 124.1 (d, *J* = 6.5 Hz, Ind C-5), 122.1 (Ph C-4), 121.7 (d, *J* = 3.4 Hz, Ind C-3a), 117.7 (d, *J* = 3.7 Hz, Ind C-4), 117.0 (d, *J* = 3.9Hz, Ind C-3), 111.1 (dd, *J* = 18.0, 1.1 Hz, Ind C-6), 72.6 (d, *J* = 168.0 Hz, CH₂F), 49.3 (dd, *J* = 6.8, 2.7 Hz, CH₂Ph).

¹⁹F NMR (376 MHz, CDCl₃) δ; -133.6 (m, Ind F-7), -208.8 (t, *J* = 48.1 Hz, CH₂F).

HRMS (ESI), *m/z*: calcd for C₁₇H₁₂BrF₂NO: 364.0143 [M+H]⁺ ; found: 364.0143.

1-(Cyclopropylmethyl)-7-fluoro-2-(fluoromethyl)-1H-indole-3-carbaldehyde (687)



By following the General Procedure 3, 1-(Cyclopropylmethyl)-7-fluorospiro[indole-3,2'-oxirane]-2(1H)-one (349.9 mg, 1.5 mmol, 1.5 equiv) was dissolved in dry THF/Et₂O (1:1, v/v, 5 mL) and FCH₂I (0.07 mL, 1.0 mmol, 1.0 equiv) was added. The reaction was stirred at -78 °C for 5 min after MeLi x LiBr complex (2.2 M in diethyl ether, 0.9 mL, 2.0 mmol, 2.0 equiv) was added dropwise. The desired product **687** was obtained in 71% yield (265 mg) as dark green semi-solid substance after chromatography on silica gel (10:80:10, v/v/v, DCM : *n*-Hexane : EtOAc).

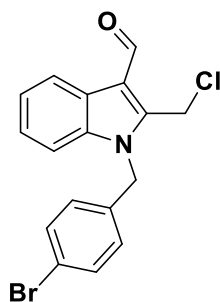
¹H NMR (400 MHz, CDCl₃) δ: 10.31 (s, 1H, CHO), 8.10 (d, 1H, *J* = 8.0 Hz, 1H, Ind H-4), 7.23 (m, 1H, Ind H-5), 7.05 (dd, 1H, *J* = 13.0, 7.9 Hz, 1H, Ind H-6), 5.86 (d, *J* = 48.4 Hz, 2H, CH₂F), 4.33 (d, *J* = 6.9 Hz, 2H, NCH₂-cyclopropyl), 1.35 (m, 1H, cyclopropyl H-1), 0.57 (m, 2H, cyclopropyl H-2,3), 0.46 (m, 2H, cyclopropyl H-2,3).

¹³C NMR (100 MHz, CDCl₃) δ: 184.3 (CHO), 149.8 (d, *J* = 247.3 Hz, Ind C-7), 141.3 (d, *J* = 15.8 Hz, Ind C-2), 129.1 (dd, *J* = 3.9, 1.9 Hz, Ind C-3a), 125.1 (d, *J* = 7.8 Hz, Ind C-7a), 123.7 (d, *J* = 6.7 Hz, Ind C-5), 117.6 (d, *J* = 3.5 Hz, Ind C-4), 116.8 (dd, *J* = 4.2, 1.3 Hz, Ind C-3), 110.7 (dd, *J* = 18.6, 1.2 Hz, Ind C-6), 72.4 (d, *J* = 168.0 Hz, CH₂F), 50.6 (dd, *J* = 5.6, 1.8 Hz, NCH₂-cyclopropyl), 12.3 (d, *J* = 2.0 Hz, cyclopropyl C-1), 3.9 (cyclopropyl C-2,3).

¹⁹F NMR (376 MHz, CDCl₃) δ: -132.3 (m, Ind F-7), -206.7 (t, *J* = 48.3 Hz, CH₂F).

HRMS (ESI), *m/z*: calcd for C₁₄H₁₃F₂NO: 250.1038 [M+H]⁺; found: 250.1042.

1-[(4-Bromophenyl)methyl]-2-(chloromethyl)-1*H*-indole-3-carbaldehyde (688)



By following the General Procedure 2, 1-(4-Bromobenzyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one (216 mg, 0.6 mmol, 1.0 equiv) was dissolved in dry THF (5 mL) and ClCH₂I (0.14 mL, 2.0 mmol, 3.0 equiv) was added. The reaction was stirred at -78 °C for 5 min, then MeLi x LiBr complex (2.2 M in diethyl ether, 0.83 mL, 1.8 mmol, 2.8 equiv) was added dropwise. The desired product **688** was obtained in 92% yield (200 mg) as dark green semi-solid after chromatography on silica gel (80:20, *v/v*, *n*-Hexane : EtOAc).

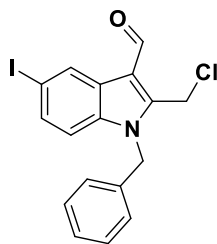
¹H NMR (400 MHz, CDCl₃) δ: 10.33 (s, 1H, CHO), 8.28 (m, 1H, Ind H-4), 7.43 (m, 2H, Ph H-3,5), 7.34 (m, 1H, Ind H-5), 7.31 (m, 1H, Ind H-6), 7.25 (m, 1H, Ind H-7), 6.92 (m, 2H, Ph H-2, 6), 5.47 (s, 2H, CH₂Ph), 5.01 (s, 2H, CH₂Cl).

¹³C NMR (100 MHz, CDCl₃) δ: 183.9 (CHO), 141.8 (Ind C-2), 136.9 (Ind C-7a), 134.5 (Ph C-1), 132.2 (Ph C-3, 5), 127.7 (Ph C-2, 6), 125.5 (Ind C-3a), 124.9 (Ind C-6), 123.5 (Ind C-5), 122.0 (Ph C-4), 121.2 (Ind C-4), 115.0 (Ind C-3), 110.3 (Ind C-7), 46.5 (CH₂Ph), 33.3 (CH₂Cl).

¹⁵N NMR (40 MHz, CDCl₃) δ: -236.5.

HRMS (ESI), *m/z*: calcd for C₁₇H₁₃BrClNO: 361.9942 [M+H]⁺; found: 361.9939.

1-Benzyl-2-(chloromethyl)-5-iodo-1*H*-indole-3-carbaldehyde (689)



By following the General Procedure 2, 1-benzyl-5-iodospiro[indole-3,2'-oxiran]-2(1*H*)-one (130 mg, 0.3 mmol, 1.0 equiv) was dissolved in dry THF (5 mL) and ClCH₂I (0.07 mL, 1.0 mmol, 3.0 equiv) was added. The reaction was stirred at -78 °C for 5 min, then MeLi x LiBr complex (2.2 M in diethyl ether, 0.43 mL, 1.0 mmol, 2.8 equiv) was added dropwise. The desired product **689** was obtained in 83% Yield (102 mg) as dark green semi-solid after chromatography on silica gel (80:20, *v/v*, *n*-Hexane : EtOAc).

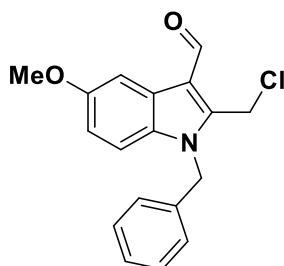
¹H NMR (400 MHz, CDCl₃) δ: 10.27 (s, 1H, CHO), 8.67 (d, *J* = 1.6 Hz, 1H, Ind H-4), 7.57 (dd, *J* = 8.7, 1.6 Hz, 1H, Ind H-6), 7.32 (m, 2H, Ph H-3,5), 7.30 (m, 1H, Ph H-4), 7.06 (d, *J* = 8.7 Hz, 1H, Ind H-7), 7.01 (m, 2H, Ph H-2, 6), 5.50 (s, 2H, CH₂Ph), 4.97 (s, 2H, CH₂Cl).

¹³C NMR (100 MHz, CDCl₃) δ: 183.5 (CHO), 142.6 (Ind C-2), 136.4 (Ind C-7a), 135.1 (Ph C-1), 133.3 (Ind C-6), 130.2 (Ind C-4), 129.2 (Ph C-3, 5), 128.3 (Ph C-4), 127.6 (Ind C-3a), 125.9 (Ph C-2, 6), 114.2 (Ind C-3), 112.3 (Ind C-7), 87.6 (Ind C-5), 47.2 (CH₂Ph), 33.0 (CH₂Cl).

¹⁵N NMR (40 MHz, CDCl₃) δ: -235.0.

HRMS (ESI), *m/z*: calcd for C₁₇H₁₃ClINO : 431.9623 [M+Na]⁺; found: 431.9633.

1-Benzyl-2-(chloromethyl)-5-methoxy-1*H*-indole-3-carbaldehyde (690)



By following the General Procedure 2, 1-benzyl-5-methoxyspiro[indole-3,2'-oxiran]-2(1*H*)-one (190 mg, 0.7 mmol, 1.0 equiv) was dissolved in dry THF (5 mL) and ClCH₂I (0.14 mL, 2.0 mmol, 3.0 equiv) was added. The reaction was stirred at -78 °C for 5 min, then MeLi x LiBr complex (2.2 M in diethyl ether, 0.85 mL, 1.8 mmol, 2.8 equiv) was added dropwise. The desired product **690** was obtained in 62% yield (136 mg) as dark green-brown semi-solid after chromatography on silica gel (99:01, v/v, DCM : EtOAc).

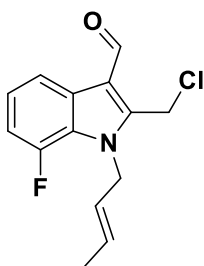
¹H NMR (400 MHz, CDCl₃) δ: 10.30 (s, 1H, CHO), 7.79 (d, *J* = 2.5 Hz, 1H, Ind H-4), 7.31 (m, 2H, Ph H-3, 5), 7.30 (m, 1H, Ph H-4), 7.18 (d, *J* = 9.0 Hz, 1H, Ind H-7), 7.04 (m, 2H, Ph H-2, 6), 6.94 (dd, *J* = 9.0, 2.5 Hz, 1H, Ind H-6), 5.50 (s, 2H, CH₂Ph), 4.97 (s, 2H, CH₂Cl), 3.90 (s, 3H, OCH₃).

¹³C NMR (100 MHz, CDCl₃) δ: 183.8 (CHO), 157.0 (Ind C-5), 142.3 (Ind C-2), 135.6 (Ph C-1), 132.1 (Ind C-7a), 129.1 (Ph C-3, 5), 128.1 (Ph C-4), 126.2 (Ind C-3a), 125.9 (Ph C-2, 6), 115.5 (Ind C-6), 114.9 (Ind C-3), 111.3 (Ind C-7), 102.5 (Ind C-4), 55.8 (OCH₃), 47.2 (CH₂Ph), 33.4 (CH₂Cl).

¹⁵N NMR (40 MHz, CDCl₃) δ: -235.7 .

HRMS (ESI), *m/z*: calcd for C₁₈H₁₆ClNO₂: 336.0762 [M+Na]⁺ ; found: 336.2526 .

1-[(2E)-But-2-en-1-yl]-2-(chloromethyl)-7-fluoro-1H-indole-3-carbaldehyde (691)



By following the General Procedure 2, 1-[(2E)-2-buten-1-yl]-7-fluorospiro[indole-3,2'-oxiran]-2(1H)-one (100 mg, 0.4 mmol, 1.0 equiv) was dissolved in dry THF (5 mL) and ClCH₂I (0.1 mL, 1.3 mmol, 3.0 equiv) was added. The reaction was stirred at -78 °C for 5 min, then MeLi x LiBr complex (2.2 M in diethyl ether, 0.5 mL, 1.0 mmol, 2.8 equiv) was added dropwise. The desired product 691 was obtained in 95% yield (101 mg) as dark green semi-solid after chromatography on silica gel (99:01, v/v, DCM : EtOAc).

¹H NMR (400 MHz, CDCl₃) δ: 10.30 (d, *J* = 0.6 Hz, 1H, CHO), 8.01 (dd, *J* = 8.0, 0.9 Hz, 1H, ind H-4), 7.21 (dt, *J_d* = 4.5 Hz, *J_t* = 8.0 Hz, 1H, Ind H-5), 7.02 (ddd, *J* = 12.7, 8.0, 0.9 Hz, 1H, Ind H-6), 5.68 (m, 1H, NCH₂CH=CHCH₃), 5.56 (m, 1H, NCH₂CH=CHCH₃), 5.05 (s, 2H, CH₂Cl), 5.00 (m, 2H, NCH₂CH=CHCH₃), 1.68 (dq, *J_d* = 6.4 Hz, *J_q* = 1.5 Hz, 3H, NCH₂CH=CHCH₃).

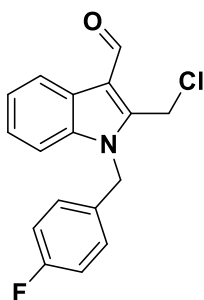
¹³C NMR (100 MHz, CDCl₃) δ: 183.8 (CHO), 149.7 (d, *J* = 246.6 Hz, Ind C-7), 142.9 (Ind C-2), 129.1 (NCH₂CH=CHCH₃), 129.0 (d, *J* = 4.0 Hz, Ind C-3a), 125.5 (NCH₂CH=CHCH₃), 124.6 (d, *J* = 9.2 Hz, Ind C-7a), 123.6 (d, *J* = 6.6 Hz, Ind C-5), 116.7 (d, *J* = 3.8 Hz, Ind C-4), 115.1 (Ind C-3), 110.4 (d, *J* = 18.3 Hz, Ind C-6), 47.5 (d, *J* = 6.7 Hz, NCH₂CH=CHCH₃), 32.8 (CH₂Cl), 17.6 (NCH₂CH=CHCH₃).

¹⁵N NMR (40 MHz, CDCl₃) δ: -235.4.

¹⁹F NMR (376 MHz, CDCl₃) δ: -113.7 (dd, *J* = 12.7, 4.4 Hz).

HRMS (ESI), *m/z*: calcd for C₁₄H₁₃ClFNO : 266.0742 [M+H]⁺; found: 266.0747.

2-(Chloromethyl)-1-[(4-fluorophenyl)methyl]-1H-indole-3-carbaldehyde (692)



By following the General Procedure 2, 1-(4-fluorobenzyl)spiro[indole-3,2'-oxiran]-2(1H)-one (100 mg, 0.4 mmol, 1.0 equiv) was dissolved in dry THF (5 mL) and ClCH₂I (0.1 mL, 1.3 mmol, 3.0 equiv) was added. The reaction was stirred at -78 °C for 5 min, then MeLi x LiBr complex (2.2 M in diethyl ether, 0.5 mL, 1.0 mmol, 2.8 equiv) was added dropwise. The desired product **692** was obtained in 89% yield (107 mg) as dark green semi-solid after chromatography on silica gel (99:01, v/v, DCM : EtOAc).

¹H NMR (400 MHz, CDCl₃) δ: 10.36 (s, 1H, CHO), 8.29 (m, 1H, Ind H-4), 7.34 (m, 1H, Ind H-5), 7.33 (m, 1H, Ind H-6), 7.29 (m, 1H, Ind H-7), 7.03 (m, 2H, Ph H-2,6), 7.02 (m, 2H, Ph H-3,5), 5.51 (s, 2H, CH₂Ph), 5.02 (s, 2H, CH₂Cl).

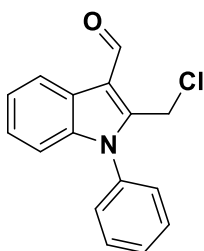
¹³C NMR (100 MHz, CDCl₃) δ: 184.0 (CHO), 162.4 (d, *J* = 247.3 Hz, Ph C-4), 141.8 (Ind C-2), 137.1 (Ind C-7a), 131.3 (d, *J* = 3.0 Hz, Ph C-1), 127.8 (d, *J* = 8.2 Hz, Ind C-2,6), 125.7 (Ind C-3a), 124.9 (Ind C-6), 123.5 (Ind C-5), 121.2 (Ind C-4), 116.1 (d, *J* = 21.8 Hz, Ph C-3,5), 115.1 (Ind C-3), 110.4 (Ind C-7), 46.5 (CH₂Ph), 33.4 (CH₂Cl).

¹⁵N NMR (40 MHz, CDCl₃) δ: -235.6.

¹⁹F NMR (376 MHz, CDCl₃) δ: -113.7 (m).

HRMS (ESI), *m/z*: calcd for C₁₇H₁₃ClFNO : 302.0742 [M+H]⁺; found: 302.0742.

2-(Chloromethyl)-1-phenyl-1*H*-indole-carbaldehyde (693)



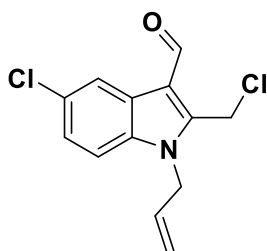
By following the General Procedure 2, 1-phenylspiro[indole-3,2'-oxiran]-2(1*H*)-one (100 mg, 0.4 mmol, 1.0 equiv) was dissolved in dry THF (5 mL) and ClCH₂I (0.1 mL, 1.3 mmol, 3.0 equiv) was added. The reaction was stirred at -78 °C for 5 min, then MeLi x LiBr complex (2.2 M in diethyl ether, 0.5 mL, 1.0 mmol, 2.8 equiv) was added dropwise. The desired product **693** was obtained in 70% yield (76 mg) as light green semi-solid after chromatography on silica gel (90:10, *v/v*, *n*-Hexane: EtOAc).

¹H NMR (400 MHz, C₆D₆) δ: 10.35 (s, 1H, CHO), 8.54 (m, 1H, Ind H- 4), 7.18 (m, 1H, Ind H- 5), 7.03 (m, 1H, Ind H-6), 7.01 (m, 3H, Ph H-3,4,5), 6.89 (m, 2H, Ph H-2,6), 6.79 (m, 1H, Ind H-7), 4.26 (s, 2H, CH₂Cl).

¹³C NMR (100 MHz, C₆D₆) δ: 183.7 (CHO), 142.6 (Ind C-2), 138.8 (Ind C- 7a), 135.4 (Ph C-1), 129.8 (Ph C-3,5), 129.3 (Ph C-4), 128.3 (Ph C-2,6), 125.9 (Ind C-3a), 125.0 (Ind C-6), 123.9 (Ind C-5), 121.9 (Ind C-4), 116.0 (Ind C-3), 111.3 (Ind C-7), 33.6 (CH₂Cl).

HRMS (ESI), *m/z*: calcd for C₁₆H₁₂ClNO : 270.0680 [M+H]⁺ ; found: 270.0685.

5-Chloro-2-(chloromethyl)-1-(prop-2-en-1-yl)-1H-indole-3-carbaldehyde (694)



By following the General Procedure 2, 1-allyl-5-chlorospiro[indole-3,2'-oxiran]-2(1H)-one (340 mg, 1.7 mmol, 1.0 equiv) was dissolved in dry THF (5 mL) and ClCH₂I (0.4 mL, 5.0 mmol, 3.0 equiv) was added. The reaction was stirred at -78 °C for 5 min, then MeLi x LiBr complex (2.2 M in diethyl ether, 2.2 mL, 4.7 mmol, 2.8 equiv) was added dropwise. The desired product **694** was obtained in 91% yield (415 mg) as light green semi-solid after chromatography on silica gel (95:05, *v/v*, *n*-Hexane: EtOAc).

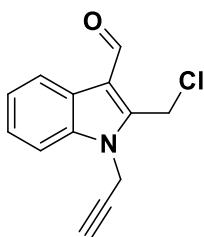
¹H NMR (400 MHz, CDCl₃) δ: 10.24 (s, 1H, CHO), 8.24 (m, 1H, Ind H-4), 7.28 (m, 1H, Ind H-6), 7.26 (m, 1H, Ind H-7), 5.99 (m, 1H, NCH₂CH=CH₂), 5.26 (m, *3J*_{HH} = 10.4 Hz, 1H, NCH₂CH=CH₂), 5.02 (s, 2H, CH₂Cl), 4.96 (m, *3J*_{HH} = 17.0 Hz, NCH₂CH=CH₂), 4.89 (m, 2H, NCH₂CH=CH₂).

¹³C NMR (100 MHz, CDCl₃) δ: 183.5 (CHO), 142.9 (Ind C-2), 135.1 (Ind C-7a), 131.3 (NCH₂CH=CH₂), 129.3 (Ind C-5), 126.3 (Ind C-3a), 125.0 (Ind C-6), 120.8 (Ind C-4), 117.9 (NCH₂CH=CH₂), 114.3 (Ind C-3), 111.4 (Ind C-7), 46.0 (NCH₂CH=CH₂), 32.9 (CH₂Cl).

¹⁵N NMR (40 MHz, CDCl₃) δ: - 236.5 .

HRMS (ESI), *m/z*: calcd for C₁₃H₁₁Cl₂NO: 268.0290 [M+H]⁺ ; found: 268.0293 .

2-(Chloromethyl)-1-(2-propyn-1-yl)-1H-indole-3-carbaldehyde (695)



By following the General Procedure 2, 1-(prop-2-yn-1-yl)-spiro[indole-3,2'-oxiran]-2(1H)-one (200 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF (5 mL) and ClCH₂I (0.2 mL, 3.1 mmol, 3.0 equiv) was added. The reaction was stirred at -78 °C for 5 min, then MeLi x LiBr complex (2.2 M in diethyl ether, 1.3 mL, 3.0 mmol, 2.8 equiv) was added dropwise. The desired product **695** was obtained in 87% yield (202 mg) as light blue semi-solid after chromatography on silica gel (99:01, v/v, DCM : EtOAc).

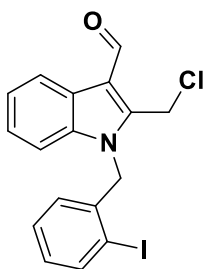
¹H NMR (400 MHz, CDCl₃) δ: 10.34 (s, 1H, CHO), 8.26 (m, 1H, Ind H-4), 7.51 (m, 1H, Ind H-7), 7.42 (m, 1H, Ind H-6), 7.36 (m, 1H, Ind H-5), 5.20 (s, 2H, CH₂Cl), 5.06 (d, *J* = 2.6 Hz, 2H, NCH₂CCH), 2.40 (t, *J* = 2.6 Hz, 1H, NCH₂CCH).

¹³C NMR (100 MHz, CDCl₃) δ: 184.0 (CHO), 141.2 (Ind C-2), 136.4 (Ind C-7a), 125.5 (Ind C-3a), 124.9 (Ind C-6), 123.6 (Ind C-5), 121.2 (Ind C-4), 115.3 (Ind C-3), 110.0 (Ind C-7), 76.3 (NCH₂CCH), 74.1 (NCH₂CCH), 33.2 (CH₂Cl), 33.0 (NCH₂CCH).

¹⁵N NMR (40 MHz, CDCl₃) δ: - 240.4

HRMS (ESI), *m/z*: calcd for C₁₃H₁₀ClNO: 232.0524 [M+H]⁺; found: 232.0522.

2-(Chloromethyl)-1-[(2-iodophenyl)methyl]-1*H*-indole-3-carbaldehyde (696)



By following the General Procedure 2, 1-(2-iodobenzyl)-spiro[indole-3,2'-oxiran]-2(1*H*)-one (300 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF (5 mL) and ClCH₂I (0.2 mL, 2.5 mmol, 3.0 equiv) was added. The reaction was stirred at -78 °C for 5 min, then MeLi x LiBr complex (2.2 M in diethyl ether, 1.1 mL, 2.3 mmol, 2.8 equiv) was added dropwise. The desired product **696** was obtained in 93% yield (381 mg) as dark green-blue semi-solid after chromatography on silica gel (90:10, *v/v*, *n*-Hexane : EtOAc).

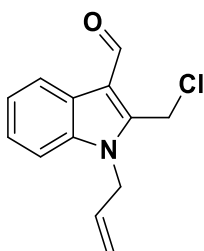
¹H NMR (400 MHz, CDCl₃) δ: 10.38 (s, 1H, CHO), 8.31 (m, 1H, Ind H-4), 7.93 (m, 1H, Ph H-3), 7.36 (m, 1H, Ind H-5), 7.31 (m, 1H, Ind H-6), 7.19 (m, 1H, Ind H-7), 7.14 (m, 1H, Ph H-5), 7.00 (m, 1H, Ph H-4), 6.28 (m, 1H, Ph H-6), 5.47 (s, 2H, CH₂Ph), 5.00 (s, 2H, CH₂Cl).

¹³C NMR (100 MHz, CDCl₃) δ: 184.0 (CHO), 142.0 (Ind C-2), 139.7 (Ph C-3), 137.3 (Ph C-1), 136.9 (Ind C-7a), 129.7 (Ph C-4), 128.9 (Ph C-5), 126.4 (Ph C-6), 125.6 (Ind C-3a), 125.0 (Ind C-6), 123.6 (Ind C-5), 121.3 (Ind C-4), 115.2 (Ind C-3), 110.4 (Ind C-7), 96.5 (Ph C-2), 52.4 (CH₂Ph), 33.3 (CH₂Cl).

¹⁵N NMR (40 MHz, CDCl₃) δ: -237.4.

HRMS (ESI), *m/z*: calcd for C₁₇H₁₃ClINO: 409.9803 [M+H]⁺; found: 409.9808.

2-(Chloromethyl)-1-(prop-2-en-1-yl)-1H-indole-3-carbaldehyde (697)



By following the General Procedure 2, 1-allyl-spiro[indole-3,2'-oxiran]-2(1H)-one (300 mg, 1.5 mmol, 1.0 equiv) was dissolved in dry THF (5 mL) and ClCH₂I (0.3 mL, 4.4 mmol, 3.0 equiv) was added. The reaction was stirred at -78 °C for 5 min, then MeLi x LiBr complex (2.2 M in diethyl ether, 1.9 mL, 4.2 mmol, 2.8 equiv) was added dropwise. The desired product **697** was obtained in 88% yield (308 mg) as dark green-blue semi-solid after chromatography on silica gel (90:10, *v/v*, *n*-Hexane : EtOAc).

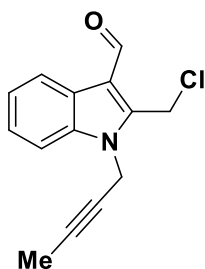
¹H NMR (400 MHz, CDCl₃) δ: 10.33 (s, 1H, CHO), 8.26 (m, 1H, Ind H-4), 7.36 (m, 2H, Ind H-6,7), 7.34 (m, 1H, Ind H-5), 6.01 (m, 1H, NCH₂CHCH₂), 5.25 (m, 1H, NCH₂CHCH₂), 5.07 (s, 2H, CH₂Cl), 4.99 (m, 1H, NCH₂CHCH₂), 4.92 (m, 2H, NCH₂CHCH₂).

¹³C NMR (100 MHz, CDCl₃) δ: 183.9 (CHO), 141.8 (Ind C-2), 136.8 (Ind C-7a), 131.7 (NCH₂CHCH₂), 125.6 (Ind C-3a), 124.6 (Ind C-6), 123.3 (Ind C-5), 121.1 (Ind C-4), 117.7 (NCH₂CHCH₂), 114.7 (Ind C-3), 110.4 (Ind C-7), 45.8 (NCH₂CHCH₂), 33.3 (CH₂Cl).

¹⁵N NMR (40 MHz, CDCl₃) δ: - 236.5.

HRMS (ESI), *m/z*: calcd for C₁₃H₁₂ClNO: 234.0680 [M+H]⁺; found: 234.0684.

1-(2-Butyn-1-yl)-2-(chloromethyl)-1*H*-indole-3-carbaldehyde (698)



By following the General Procedure 2, 1-(but-2-yn-1-yl)-spiro[indole-3,2'-oxiran]-2(1*H*)-one (250 mg, 1.2 mmol, 1.0 equiv) was dissolved in dry THF (5 mL) and ClCH₂I (0.3 mL, 3.5 mmol, 3.0 equiv) was added. The reaction was stirred at -78 °C for 5 min, then MeLi x LiBr complex (2.2 M in diethyl ether, 1.5 mL, 3.3 mmol, 2.8 equiv) was added dropwise. The desired product **698** was obtained in 78% yield (230 mg) as a white-greenish semi-solid after chromatography on silica gel (80:20, *v/v*, *n*-Hexane : EtOAc).

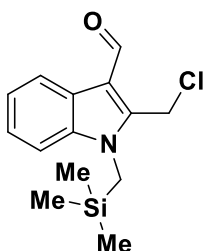
¹H NMR (400 MHz, CDCl₃) δ: 10.32 (s, 1H, CHO), 8.25 (m, 1H, Ind H-4), 7.50 (m, 1H, Ind H-7), 7.40 (m, 1H, Ind H-6), 7.34 (m, 1H, Ind H-5), 5.19 (s, 2H, CH₂Cl), 5.00 (q, *J* = 2.4 Hz, 2H, NCH₂CCCH₃), 1.79 (t, *J* = 2.4 Hz, 3H, NCH₂CCCH₃).

¹³C NMR (100 MHz, CDCl₃) δ: 183.2 (CHO), 141.4 (Ind C-2), 136.5 (Ind C-7a), 125.5 (Ind C-3a), 124.7 (Ind C-6), 123.4 (Ind C-5), 121.1 (Ind C-4), 115.0 (Ind C-3), 110.2 (Ind C-7), 82.1 (NCH₂CCCH₃), 71.9 (NCH₂CCCH₃), 33.4 (NCH₂CCCH₃), 33.3 (CH₂Cl), 3.5 (NCH₂CCCH₃).

¹⁵N NMR (40 MHz, CDCl₃) δ: - 236.9.

HRMS (ESI), *m/z*: calcd for C₁₄H₁₂ClNO: 246.0680 [M+H]⁺ ; found: 246.0679.

2-(Chloromethyl)-1-[(trimethylsilyl)methyl]-1*H*-indole-3-carbaldehyde (699)



By following the General Procedure 2, 1-((trimethylsilyl)methyl)spiro[indoline-3,2'-oxiran]-2-one (284 mg, 1.1 mmol, 1.0 equiv) was dissolved in dry THF (5 mL) and ClCH₂I (0.25 mL, 3.4 mmol, 3.0 equiv) was added. The reaction was stirred at -78 °C for 5 min, then MeLi x LiBr complex (2.2 M in diethyl ether, 1.5 mL, 3.2 mmol, 2.8 equiv) was added dropwise. The desired product **699** was obtained in 85% yield (262 mg) as a white-greenish semi-solid after chromatography on silica gel (90:5:5, *v/v/v*, *n*-Hexane : EtOAc : DCM).

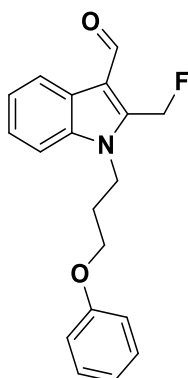
¹H NMR (400 MHz, CDCl₃) δ: 10.30 (s, 1H, CHO), 8.23 (m, 1H, Ind H-4), 7.33 (m, 2H, Ind H-6, 7), 7.31 (m, 1H, Ind H-5), 5.08 (s, 2H, CH₂Cl), 3.89 (s, 2H, NCH₂SiMe₃), 0.11 (s, 9H, SiMe₃).

¹³C NMR (100 MHz, CDCl₃) δ: 183.6 (CHO), 141.2 (Ind C-2), 137.0 (Ind C-7a), 125.8 (Ind C-3a), 124.0 (Ind C-6), 123.1 (Ind C-5), 120.8 (Ind C-4), 113.9 (Ind C-3), 110.8 (Ind C-7), 35.4 (NCH₂SiMe₃), 33.7 (CH₂Cl), -1.28 (SiMe₃).

¹⁵N NMR (40 MHz, CDCl₃) δ: - 235.9.

HRMS (ESI), *m/z*: calcd for C₁₄H₁₈ClNOSi: 280.0919 [M+H]⁺; found: 280.2639 .

2-(Fluoromethyl)-1-(3-phenoxypropyl)-1*H*-indole-3-carbaldehyde (700)



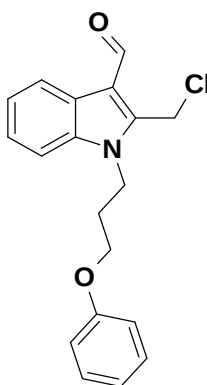
By following the General Procedure 3, 1-(3-phenoxypropyl)spiro[indoline-3,2'-oxiran]-2-one (325 mg, 1.1 mmol, 1.5 equiv) was dissolved in dry THF/Et₂O (1:1, v/v, 5 mL) and FCH₂I (0.05 mL, 0.7 mmol, 1.0 equiv) was added. The reaction was stirred at -78 °C for 5 min after MeLi x LiBr complex (2.2 M in diethyl ether, 0.4 mL, 1.5 mmol, 2.0 equiv) was added dropwise. The desired product **700** was obtained in 87% yield (298 mg) as green semi-solid after chromatography on silica gel (70 : 15 : 15, v/v/v, *n*-Hex : DCM : EtOAc).

¹H NMR (400 MHz, CDCl₃) δ: 10.30 (s, 1H, CHO), 8.32 (m, 1H, Ind H-4), 7.48 (m, 1H, Ind H-7), 7.35 (m, 1H, Ind H-6), 7.34 (m, 1H, Ind H-5), 7.31 (m, 2H, Ph H-3,5), 6.99 (m, 1H, Ph H-4), 6.90 (m, 2H, Ph H-2,6), 5.88 (d, J = 48.3 Hz, 2H, CH₂F), 4.54 (m, 2H, NCH₂), 3.97 (m, 2H, OCH₂), 2.36 (m, 2H, NCH₂CH₂).

¹³C NMR (100 MHz, CDCl₃) δ: 184.1 (CHO), 158.2 (1C, Oph C-1), 140.6 (d, J = 16.1 Hz, Ind C-2), 136.8 (Ind C-7°), 129.6 (2C, Oph C-3,5), 125.5 (Ind C-3°), 124.8 (Ind C-6), 123.4 (Ind C-5), 121.8 (Ind C-4), 121.3 (Oph C-4), 116.1 (d, J = 3.9 Hz, Ind C-3), 114.4 (2C, Oph C-2,6), 110.3 (Ind C-7), 72.5 (d, J = 166.7 Hz, CH₂F), 64.0 (OCH₂), 41.1 (NCH₂), 29.6 (NCH₂CH₂).

HRMS (ESI), m/z: calcd for C₁₉H₁₈FNO₂: 312.1394 [M+H]⁺; found: 312.1407.

2-(Chloromethyl)-1-(3-phenoxypropyl)-1*H*-indole-3-carbaldehyde (701)



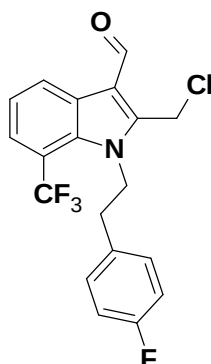
By following the General Procedure 2, 1-(3-phenoxypropyl)spiro[indoline-3,2'-oxiran]-2-one (429 mg, 1.5 mmol, 1.0 equiv) was dissolved in dry THF (5 mL) and ClCH₂I (0.32 mL, 4.4 mmol, 3.0 equiv) was added. The reaction was stirred at -78 °C for 5 min, then MeLi x LiBr complex (2.2 M in diethyl ether, 1.9 mL, 4.1 mmol, 2.8 equiv) was added dropwise. The desired product **701** was obtained in 93% yield (457 mg) as a white-greenish semi-solid after chromatography on silica gel (70:15:15, *v/v/v*, *n*-Hexane : EtOAc : DCM).

¹H NMR (400 MHz, CDCl₃) δ: 10.29 (s, 1H, CHO), 8.27 (m, 1H, Ind H-4), 7.45 (m, 1H, Ind H-7), 7.34 (m, 1H, Ind H-6), 7.33 (m, 1H, Ind H-5), 7.32 (m, 2H, Oph H-3,5), 7.01 (m, 1H, Oph H-4), 6.92 (m, 2H, Oph H-2,6), 5.10 (s, 2H, CH₂Cl), 4.53 (m, 2H, NCH₂), 3.96 (m, 2H, OCH₂), 2.38 (m, 2H, NCH₂CH₂).

¹³C NMR (100 MHz, CDCl₃) δ: 183.9 (CHO), 158.8 (Oph C-1), 142.2 (Ind C-2), 136.5 (Ind C-7a), 129.6 (Oph C-3,5), 125.7 (Ind C-3a), 124.5 (Ind C-6), 123.3 (Ind C-5), 121.3 (Oph C-4), 121.2 (Ind C-4), 114.6 (Ind C-3), 114.4 (Oph C-2,6), 110.3 (Ind C-7), 63.8 (OCH₂), 40.5 (NCH₂), 33.0 (CH₂Cl), 29.2 (NCH₂CH₂).

HRMS (ESI), *m/z*: calcd for C₁₉H₁₈ClNO₂: 328.1099 [M+H]⁺; found: 328.1097.

2-(Chloromethyl)-1-[2-(4-fluorophenyl)ethyl]-7-(trifluoromethyl)-1*H*-indole-3-carbaldehyde (702)



By following the General Procedure 2, 1-[2-(4-fluorophenyl)ethyl]-7-(trifluoromethyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one (174 mg, 0.5 mmol, 1.0 equiv) was dissolved in dry THF (5 mL) and ClCH₂I (0.11 mL, 1.5 mmol, 3.0 equiv) was added. The reaction was stirred at -78 °C for 5 min, then MeLi x LiBr complex (2.2 M in diethyl ether, 0.63 mL, 1.4 mmol, 2.8 equiv) was added dropwise. The desired product **702** was obtained in 90% yield (173 mg) as a white-greenish semi-solid after chromatography on silica gel (80:10:10, *v/v/v*, *n*-Hexane : EtOAc : DCM).

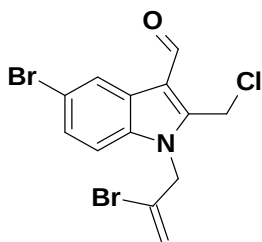
¹H NMR (400 MHz, CDCl₃) δ: 10.35 (s, 1H, CHO), 8.61 (d, *J* = 8.0 Hz, 1H, Ind H-4), 7.78 (d, *J* = 7.5 Hz, 1H, Ind H-6), 7.42 (m, 1H, Ind H-5), 7.11 (m, 2H, Ph H-2,6), 7.03 (m, 2H, Ph H-3,5), 4.87 (s, 2H, CH₂Cl), 4.63 (m, 2H, NCH₂), 3.05 (m, 2H, PhCH₂).

¹³C NMR (100 MHz, CDCl₃) δ: 183.8 (CHO), 162.0 (d, *J* = 246.0 Hz, Ph C-4), 144.3 (Ind C-2), 132.9 (d, *J* = 3.3 Hz, Ph C-1), 131.9 (q, *J* = 1.4 Hz, Ind C-7°), 130.3 (d, *J* = 8.0 Hz, Ph C-2,6), 128.5 (Ind C-3°), 125.9 (Ind C-4), 124.1 (q, *J* = 271.1 Hz, CF₃), 124.0 (q, *J* = 6.8 Hz, Ind C-6), 122.4 (Ind C-5), 115.9 (d, *J* = 21.3 Hz, Ph C-3,5), 115.3 (Ind C-3), 114.2 (q, *J* = 32.2 Hz, Ind C-7), 46.8 (q, *J* = 4.7 Hz, NCH₂), 36.0 (q, *J* = 3.0 Hz, CH₂Ph), 33.0 (CH₂Cl).

¹⁹F NMR (376 MHz, CDCl₃) δ: -55.3 (s, CF₃), -115.0 (m, PhF).

HRMS (ESI), *m/z*: calcd for C₁₉H₁₄ClF₄NO : 384.0773 [M+H]⁺; found: 384.0774.

5-Bromo-1-(2-bromo-2-propen-1-yl)-2-(chloromethyl)-1*H*-indole-3-carbaldehyde (703)



By following the General Procedure 2, 5-bromo-1-(2-bromoprop-2-en-1-yl)spiro[indole-3,2'-oxiran]-2(1*H*)-one (500 mg, 1.4 mmol, 1.0 equiv) was dissolved in dry THF (5 mL) and ClCH₂I (0.30 mL, 4.2 mmol, 3.0 equiv) was added. The reaction was stirred at -78 °C for 5 min, then MeLi x LiBr complex (2.2 M in diethyl ether, 1.8 mL, 3.9 mmol, 2.8 equiv) was added dropwise. The desired product **703** was obtained in 83% yield (455 mg) as a white-greenish semi-solid after chromatography on silica gel (80:10:10, *v/v/v*, *n*-Hexane : EtOAc : DCM).

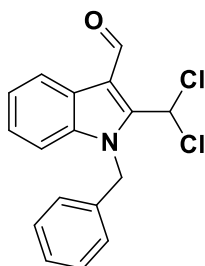
¹H NMR (400 MHz, CDCl₃) δ: 10.27 (s, 1H, CHO), 8.42 (1H, d, *J* = 1.5 Hz, Ind H-4), 7.45 (1H, dd, *J* = 8.7, 1.6 Hz, Ind H-6), 7.22 (1H, d, *J* = 8.7 Hz, Ind H-7), 5.66 (1H, m, NCH₂CBrCH₂), 5.44 (1H, m, NCH₂CBrCH₂), 5.08 (2H, s, NCH₂), 5.07 (2H, s, CH₂Cl).

¹³C NMR (100 MHz, CDCl₃) δ: 183.8 (CHO), 142.8 (Ind C-2), 135.5 (Ind C-7a), 128.2 (Ind C-6), 126.9 (Ind C-3a), 125.4 (NCH₂CBrCH₂), 124.3 (Ind C-4), 119.1 (NCH₂CBrCH₂), 117.4 (Ind C-5), 114.8 (Ind C-3), 111.9 (Ind C-7), 51.2 (NCH₂), 33.0 (CH₂Cl).

HRMS (ESI), *m/z*: calcd for C₁₃H₁₀ClBr₂NO: 389.8890 [M+H]⁺; found: 389.8888.

5.2.2.3 Application reaction's products

1-Benzyl-2-(dichloromethyl)-1*H*-indole-3-carbaldehyde (**711**)



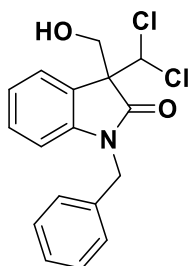
By following the general procedure for generation of the carbenoid via deprotonation, 1- benzylspiro[indole-3,2'-oxiran]-2(1*H*)-one (150 mg, 0.6 mmol, 1.0 equiv) was dissolved in dry THF (5 mL) and Cl₂CH₂ (0.11 mL, 1.8 mmol, 3.0 equiv) was added. The reaction was stirred at -78 °C for 5 min, afterwards LDA (lithium-diisopropyl amide, 0.23 mL, 1.7 mmol, 2.8 equiv) was added dropwise and, then after 45 minutes the reaction mixture was quenched with NH₄Cl. The desired product **711** was obtained in 41% yield (78 mg) as a white-greenish semi-solid after chromatography on silica gel (90 : 5 : 5 , v/v/v, *n*-Hexane : EtOAc: DCM).

¹H NMR (400 MHz, CDCl₃) δ: 10.46 (s, 1H, CHO), 8.15 (m, 1H, Ind H-4), 8.09 (s, 1H, CHCl₂), 7.33 (m, 1H, Ind H-5), 7.29 (m, 3H, Ph H-3,4,5), 7.26 (m, 1H, Ind H-6), 7.12 (m, 1H, Ind H-7), 7.08 (m, 2H, Ph H-2,6), 5.89 (s, 2H, CH₂Ph).

¹³C NMR (100 MHz, CDCl₃) δ: 184.5 (CHO), 140.1 (Ind C-2), 137.5 (Ind C-7a), 135.4 (Ph C-1), 128.8 (Ph C-3,5), 127.7 (Ph C-4), 126.2 (Ph C-2,6), 125.5 (Ind C-3a), 125.2 (Ind C-6), 123.7 (Ind C-5), 120.0 (Ind C-4), 111.9 (Ind C-3,7), 59.9 (CHCl₂), 49.0 (CH₂Ph).

HRMS (ESI), m/z: calcd for C₁₇H₁₃Cl₂NO: 318.0447 [M+H]⁺; found: 318.2423 .

1-Benzyl-3-(dichloromethyl)-3-(hydroxymethyl)-1,3-dihydro-2H-indol-2-one (712)



By following the general procedure for generation of the carbenoid via deprotonation, 1- benzylspiro[indole-3,2'-oxiran]-2(1H)-one (150 mg, 0.6 mmol, 1.0 equiv) was dissolved in dry THF (5 mL) and Cl_2CH_2 (0.11 mL, 1.8 mmol, 3.0 equiv) was added. The reaction was stirred at -78°C for 5 min, afterwards LDA (lithium-diisopropyl amide, 0.23 mL, 1.7 mmol, 2.8 equiv) was added dropwise, and lastly, left stirring for 45 min the reaction mixture was quenched with NH_4Cl . The desired product **712** was obtained in 45% yield (91 mg) as a white-greenish semi-solid after chromatography on silica gel (90 : 5 : 5 , v/v/v, *n*-Hexane : EtOAc: DCM).

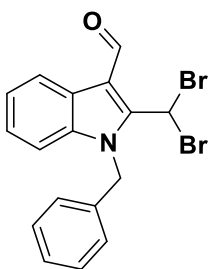
^1H NMR (400 MHz, CDCl_3) δ : 7.65 (m, 1H, Ind H-4), 7.31 (m, 4H, Ph H-2,3,5,6), 7.30 (m, 1H, Ind H-6), 7.27 (m, 1H, Ph H-4), 7.13 (m, 1H, Ind H-5), 6.79 (m, 1H, Ind H-7), 6.48 (s, 1H, CHCl_2), 5.06 – 4.84 (AB-system, $J_{AB} = 15.8$ Hz, 2H, CH_2Ph), 4.24 (brd, $J = 11.6$ Hz, 1H, CH_2OH), 3.87 (d, $J = 11.6$ Hz, 1H, CH_2OH), 2.94 (brs, 1H, OH).

^{13}C NMR (100 MHz, CDCl_3) δ : 175.4 (Ind C-2), 143.6 (Ind C-7a), 134.9 (Ph C-1), 129.8 (Ind C-6), 128.8 (Ph C-3,5), 127.8 (Ph C-4), 127.2 (Ph C-2,6), 125.1 (Ind C-4), 124.4 (Ind C-3a), 123.2 (Ind C-5), 109.7 (Ind C-7), 73.1 (CHCl_2), 65.4 (CH_2OH), 60.4 (Ind C-3), 44.0 (CH_2Ph).

^{15}N NMR (40 MHz, CDCl_3) δ : - 237.1.

HRMS (ESI), m/z : calcd for $\text{C}_{17}\text{H}_{15}\text{Cl}_2\text{NO}_2$: 336.0553 $[\text{M}+\text{H}]^+$; found: 336.0550.

1-Benzyl-2-(dibromomethyl)-1*H*-indole-3-carbaldehyde (713)



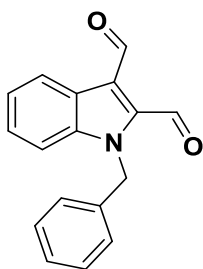
By following the general procedure for generation of the carbenoid via deprotonation, 1- benzylspiro[indole-3,2'-oxiran]-2(1*H*)-one (150 mg, 0.6 mmol, 1.0 equiv) was dissolved in dry THF (5 mL) and Br₂CH₂ (0.15 mL, 1.8 mmol, 3.0 equiv) was added. The reaction was stirred at -78 °C for 5 min, after LDA (lithium-diisopropyl amide, 0.23 mL, 1.7 mmol, 2.8 equiv) was added dropwise and quenched after 45 minutes with addition of NH₄Cl. The desired product **713** was obtained in 58% yield (142 mg) as a light blu-greenish semi-solid after chromatography on silica gel (80 : 10 : 10 , v/v/v, *n*-Hexane : EtOAc: DCM).

¹H NMR (400 MHz, CDCl₃) δ: 10.46 (s, 1H, CHO), 8.13 (m, 1H, Ind H-4), 8.02 (s, 1H, CHBr₂), 7.32 (m, 1H, Ind H-5), 7.30 (m, 3H, Ph H-3,4,5), 7.23 (m, 1H, Ind H-6), 7.11 (m, 2H, Ph H-2,6), 7.08 (m, 1H, Ind H-7), 5.90 (s, 2H, CH₂Ph).

¹³C NMR (100 MHz, CDCl₃) δ: 184.4 (CHO), 141.4 (Ind C-2), 137.7 (Ind C-7a), 135.1 (Ph C-1), 128.8 (Ph C-3,5), 127.7 (Ph C-4), 126.4 (Ph C-2,6), 125.3 (Ind C-3a), 125.2 (Ind C-6), 123.7 (Ind C-5), 120.0 (Ind C-4, br), 111.9 (Ind C-7), 48.6 (CH₂Ph), 24.9 (CHBr₂).

HRMS (ESI), m/z: calcd for C₁₇H₁₃Cl₂NO: 405.9437 [M+H]⁺; found: 405.9430 .

1-Benzyl-1*H*-indole-2,3-dicarbaldehyde (**714**)



By following the general procedure for synthesizing lithium carbenoid via deprotonation, 1 - benzylspiro[indoline-3,2'-oxiran]-2-one (200 mg, 0.8 mmol, 1 equiv) was dissolved in dry THF/Et₂O (1:1, v/v, 5 mL) and FCH₂I (0.16 mL, 2.4 mmol, 3.0 equiv) was added. The reaction was stirred at -78 °C for 5 min, afterwards LDA (lithium diisopropyl amide freshly prepared, 1.3 mL, 2.4 mmol, 3.0 equiv) was added dropwise and left to stir for 5 minutes, and lastly quenched with NH₄Cl. The desired product **714** was obtained in 71% yield (150 mg) as green semi-solid after chromatography on silica gel (80 : 10 : 10, v/v/v, *n* – Hex : DCM : EtOAc).

¹H NMR (400 MHz, CDCl₃) δ: 10.74 (s, 1H, CHO, Ind 3), 10.67 (s, 1H, CHO, Ind 2), 8.41 (m, 1H, Ind H-4), 7.48 (m, 2H, Ind H-6, 7), 7.41 (m, 1H, Ind H-5), 7.28 (m, 2H, Ph H-3, 5), 7.26 (m, 1H, Ph H-4), 7.09 (m, 2H, Ph H-2,6), 5.90 (s, 2H, CH₂Ph).

¹³C NMR (100 MHz, CDCl₃) δ: 185.0 (CHO, Ind 3), 182.9 (CHO, Ind 2), 138.9 (Ind C-7a), 136.2 (Ph C-1), 136.1 (Ind C-2), 128.9 (Ph C-3, 5), 128.1 (Ind C-6), 127.9 (Ph C-4), 126.5 (Ph C-2, 6), 125.1 (Ind C-3a), 124.7 (Ind C-5), 123.2 (Ind C-4), 122.8 (Ind C-3), 111.4 (Ind C-7), 48.7 (CH₂Ph).

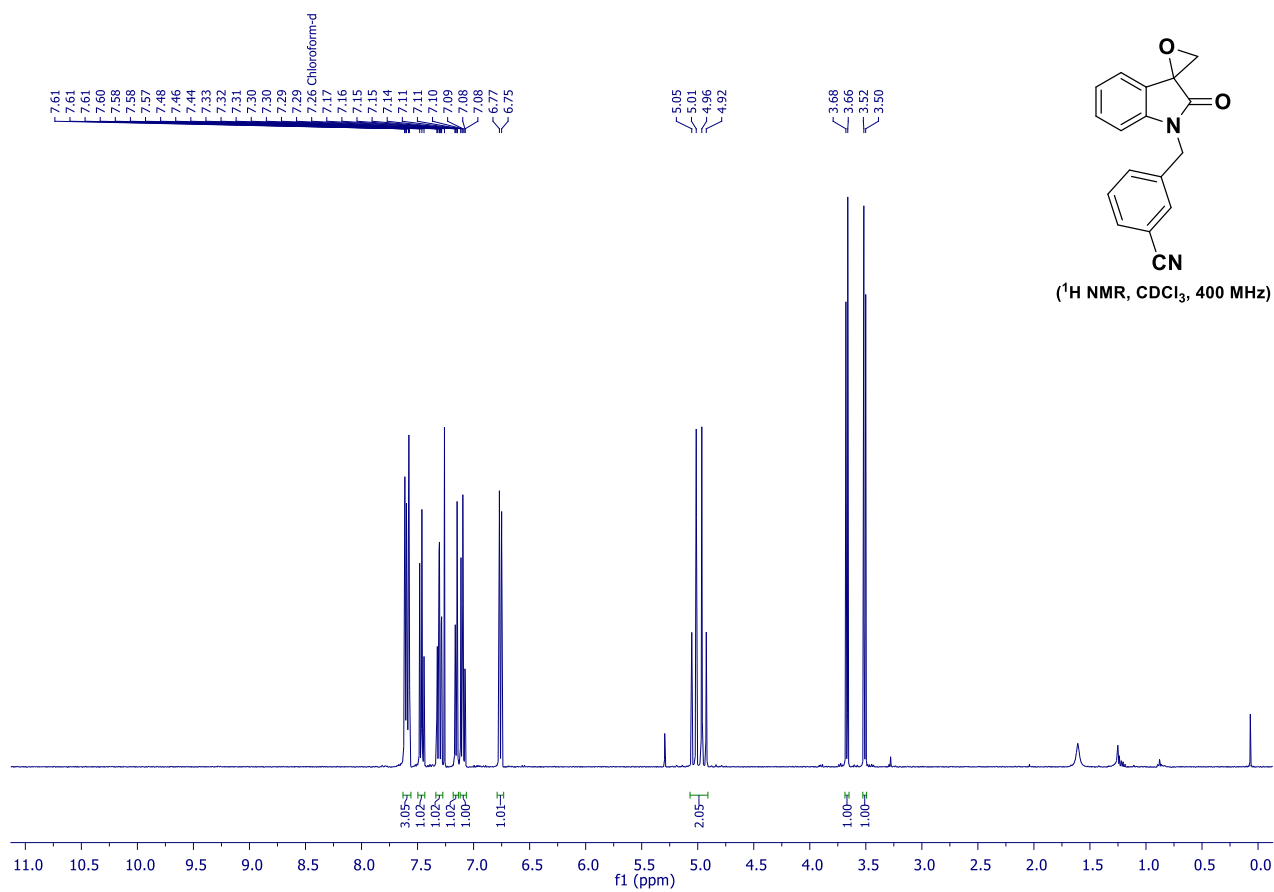
¹⁵N NMR (40 MHz, CDCl₃) δ: - 235.9.

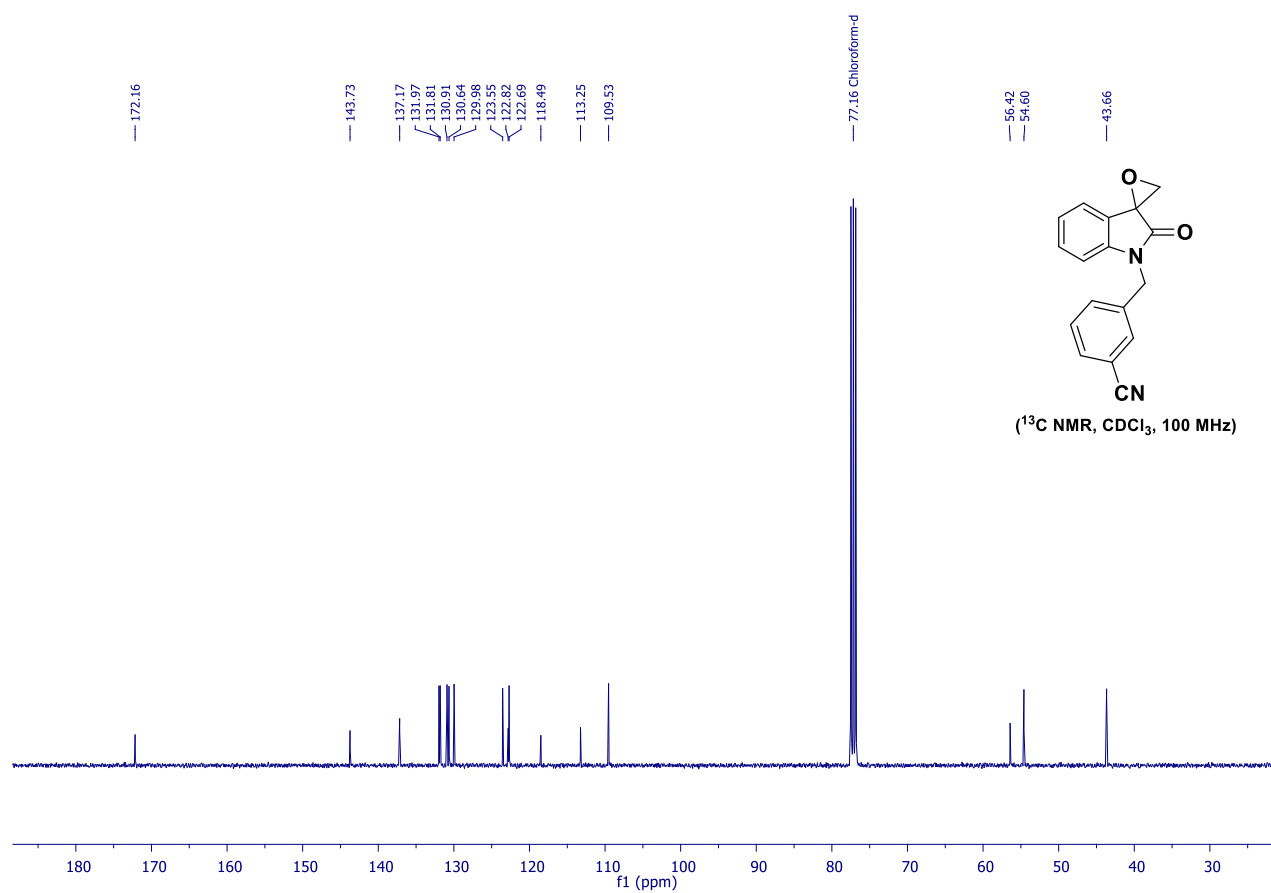
HRMS (ESI), *m/z*: calcd for C₁₇H₁₃NO₂: 264.1019 [M+H]⁺; found: 264.1019 .

5.2.3 Copies of ^1H and ^{13}C NMR spectra

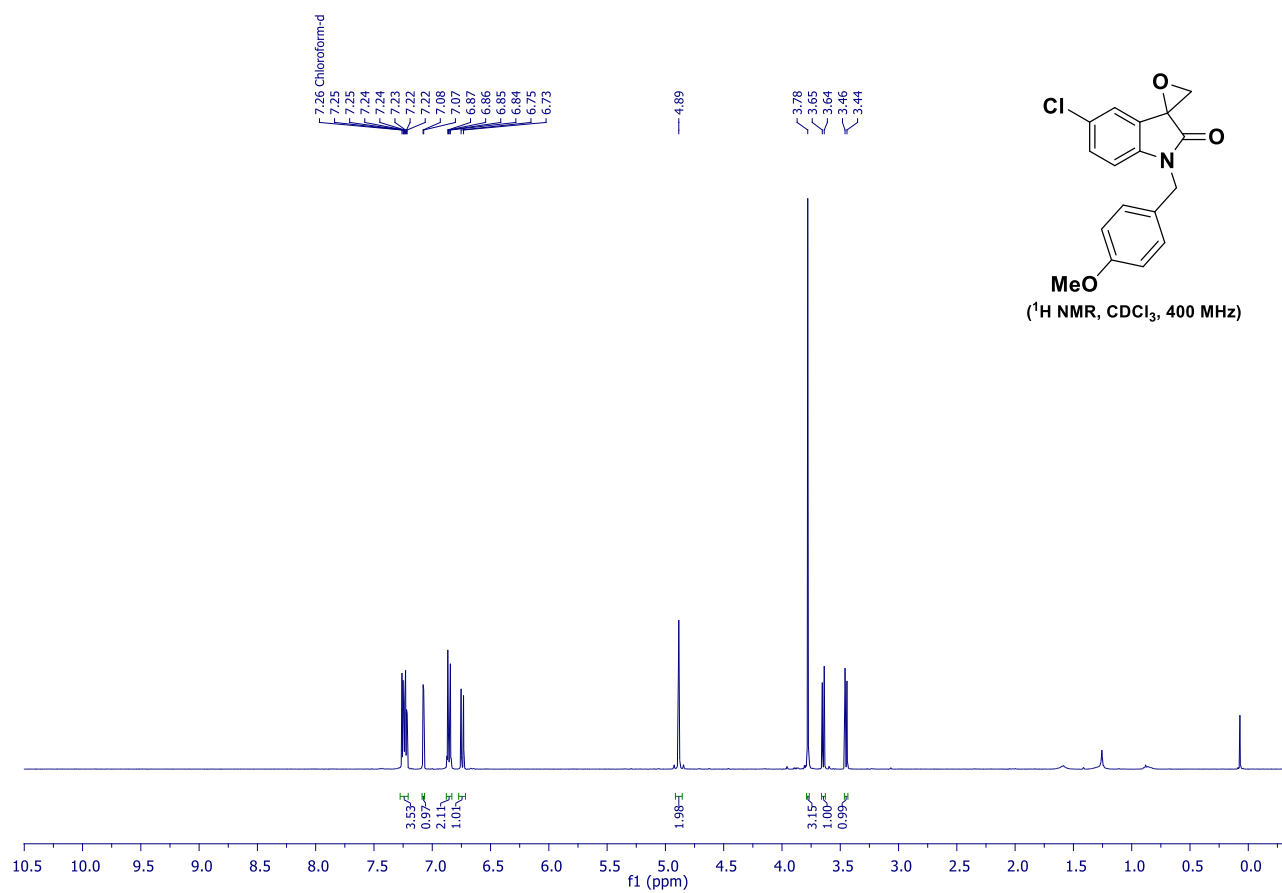
5.2.3.1 Spiro-epoxz oxindoles

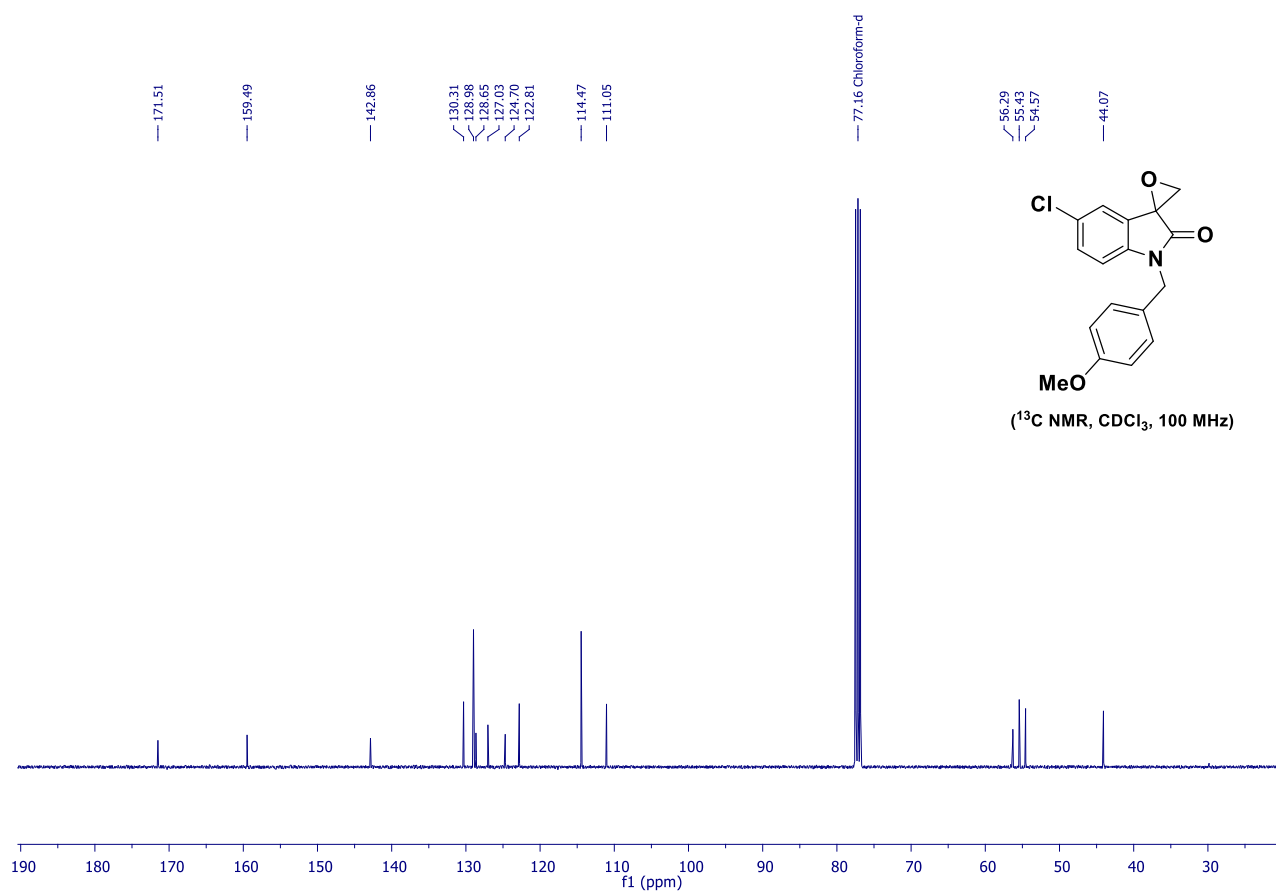
3-[(2-Oxospiro[indole-3,2'-oxirane])-1(2H)-yl] methyl] benzonitrile (646)



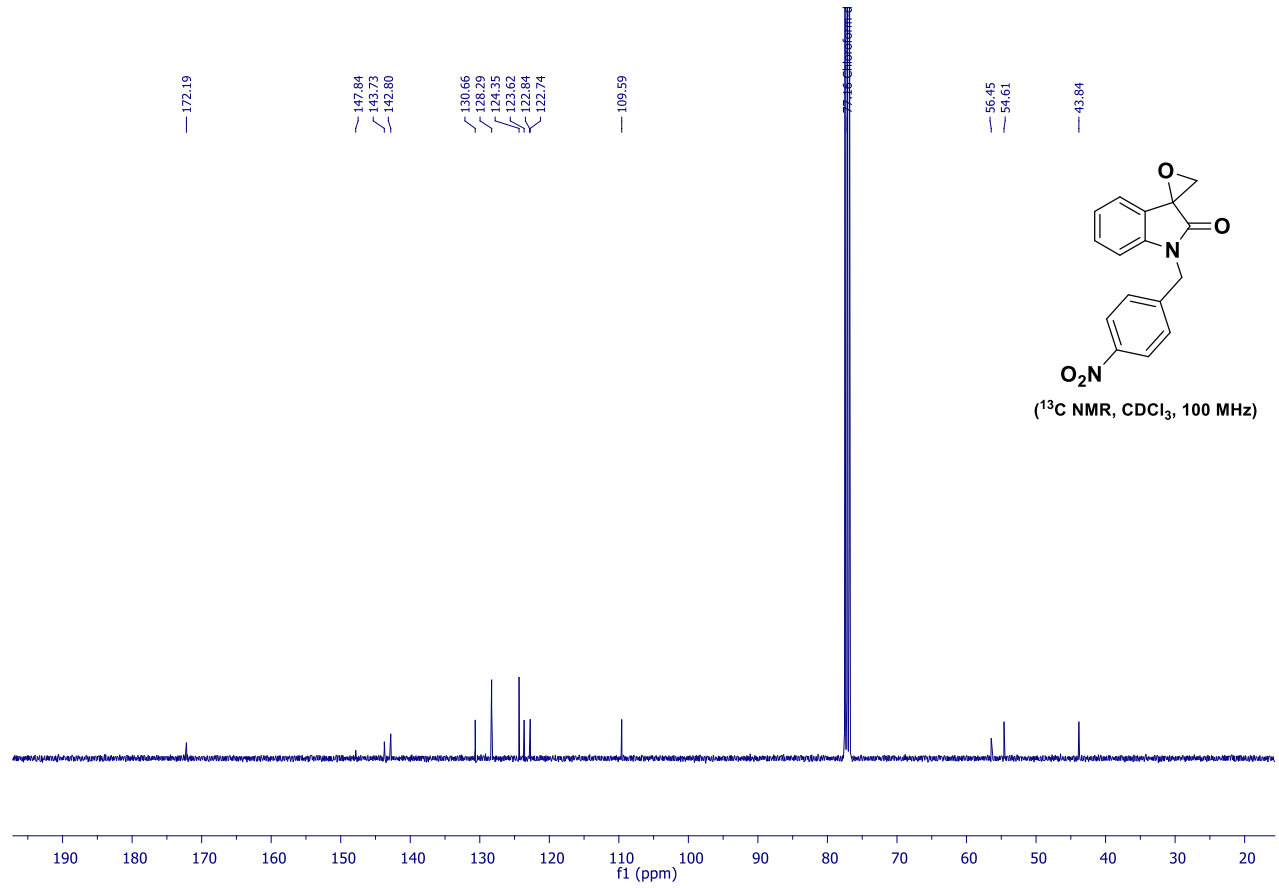
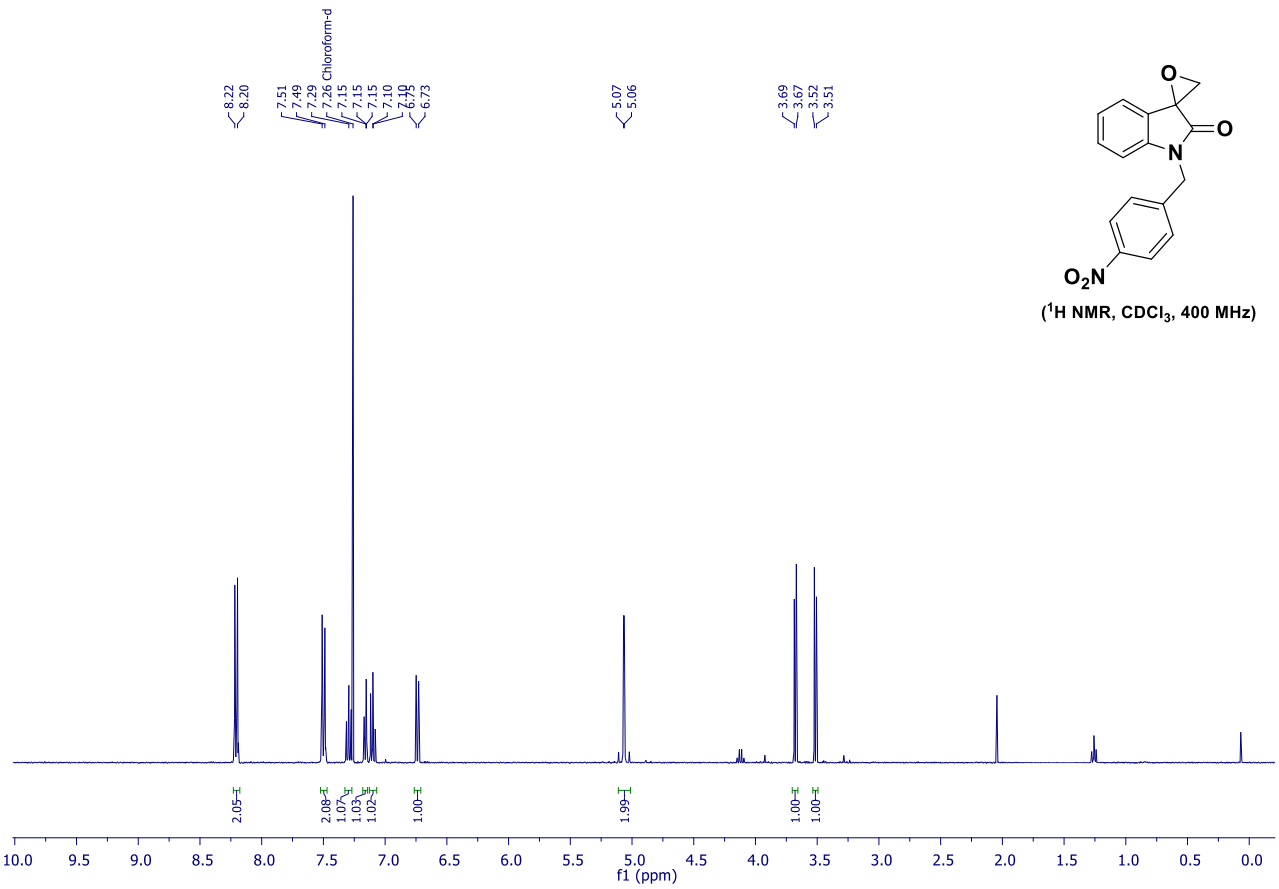


5-Chloro-1-(4-methoxybenzyl)spiro[indol-3,2'-oxirane]-2(1H)-one (647)

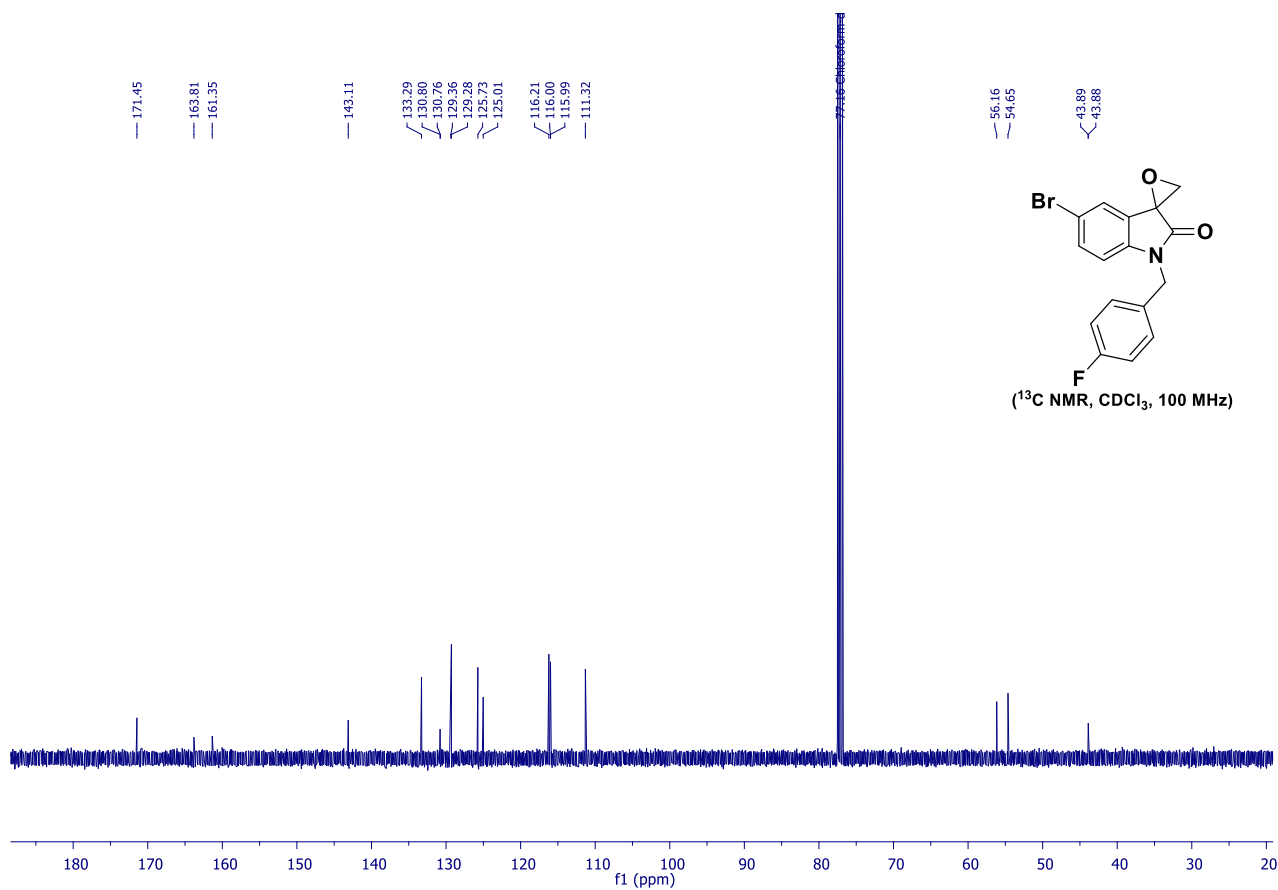
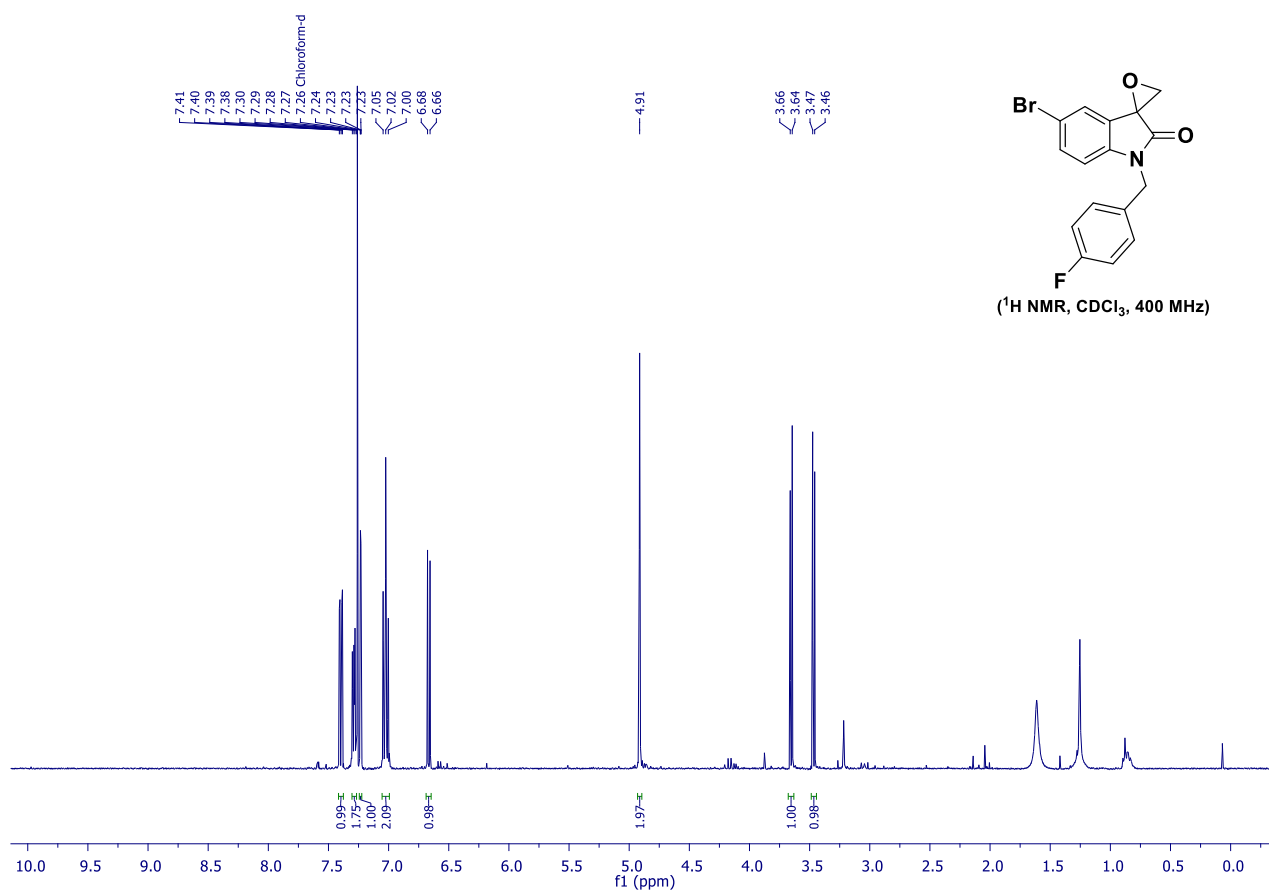


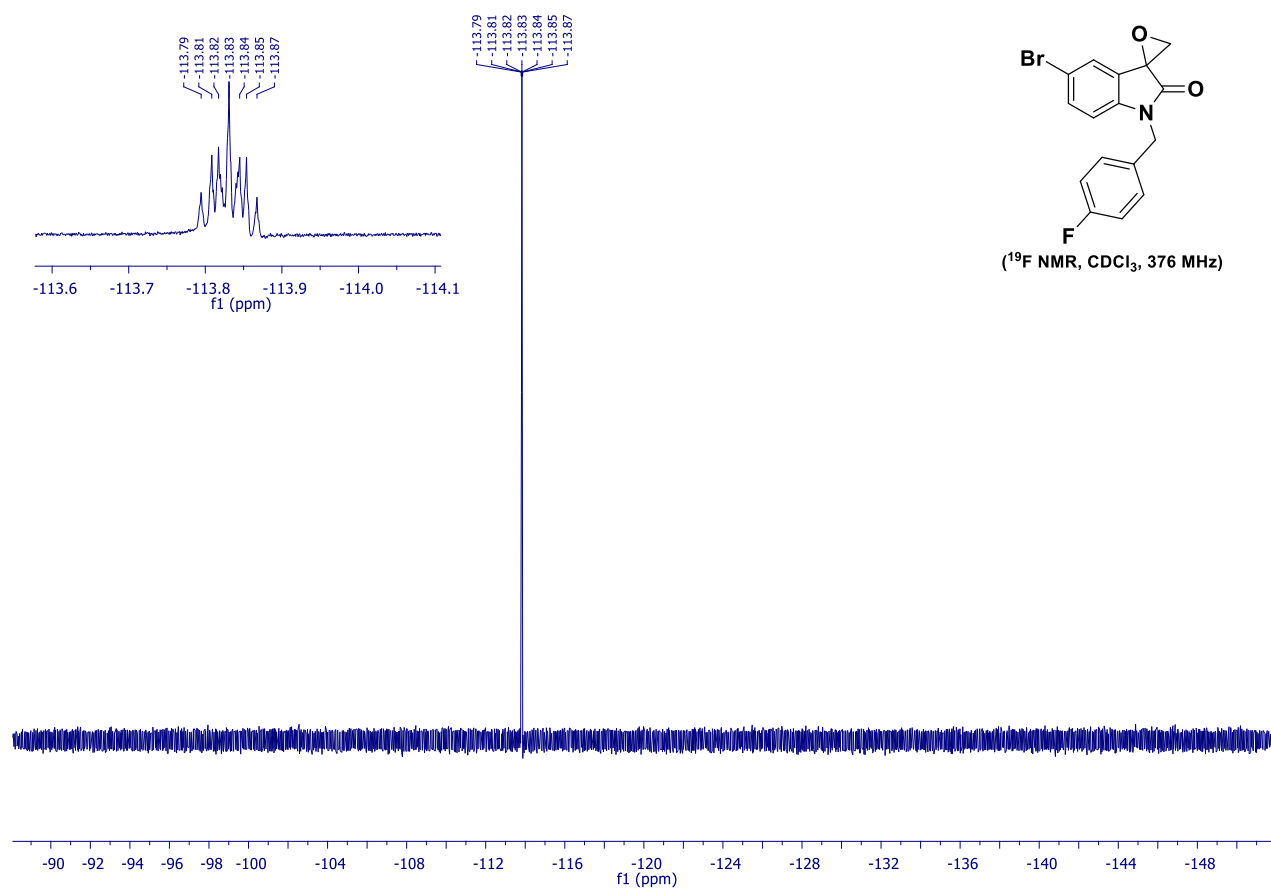


1-(4-Nitrobenzyl)spiro[indole-3,2'-oxirane]-2(1H)-one (648)

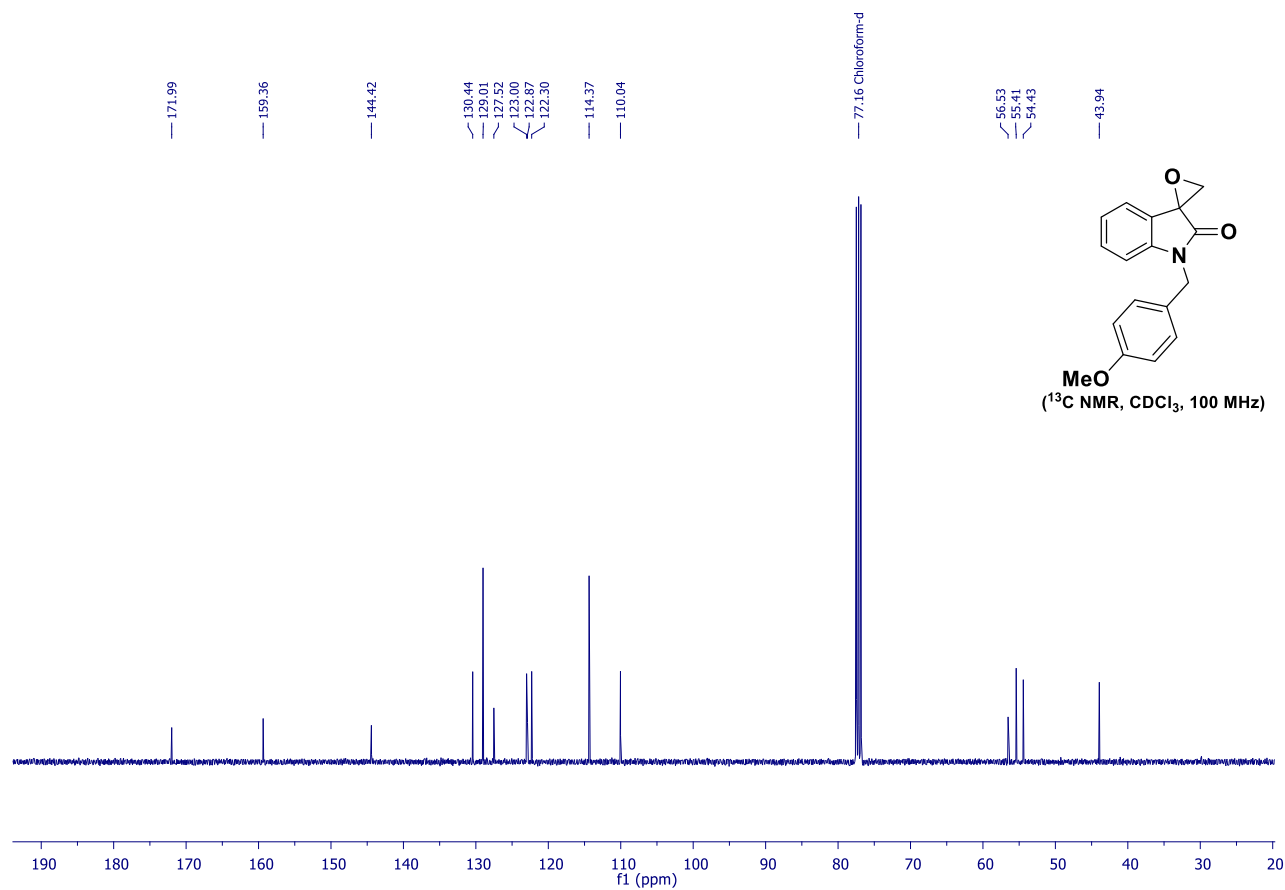
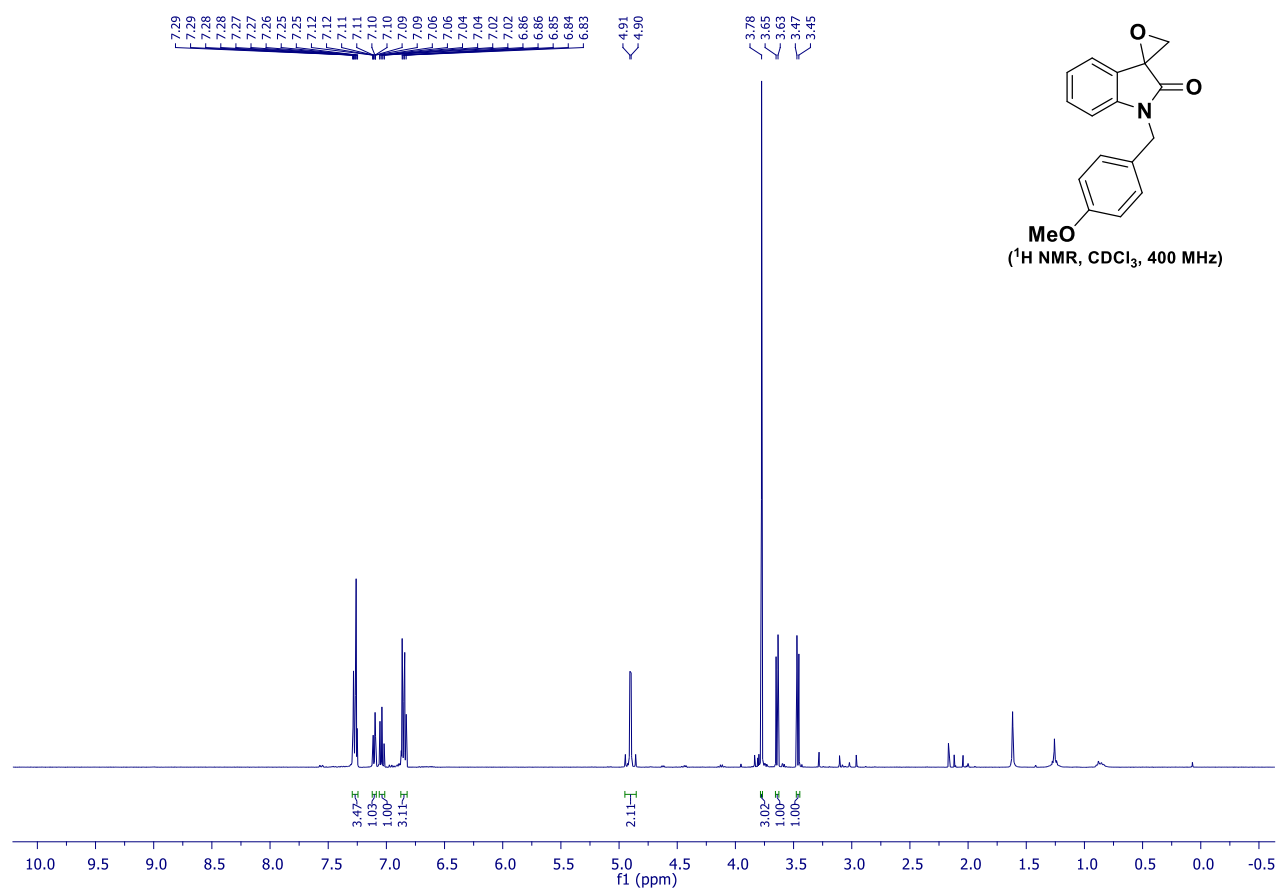


5-Bromo-1-(4-fluorobenzyl)spiro[indole-3,2'-oxirane]-2(1H)-one (649)

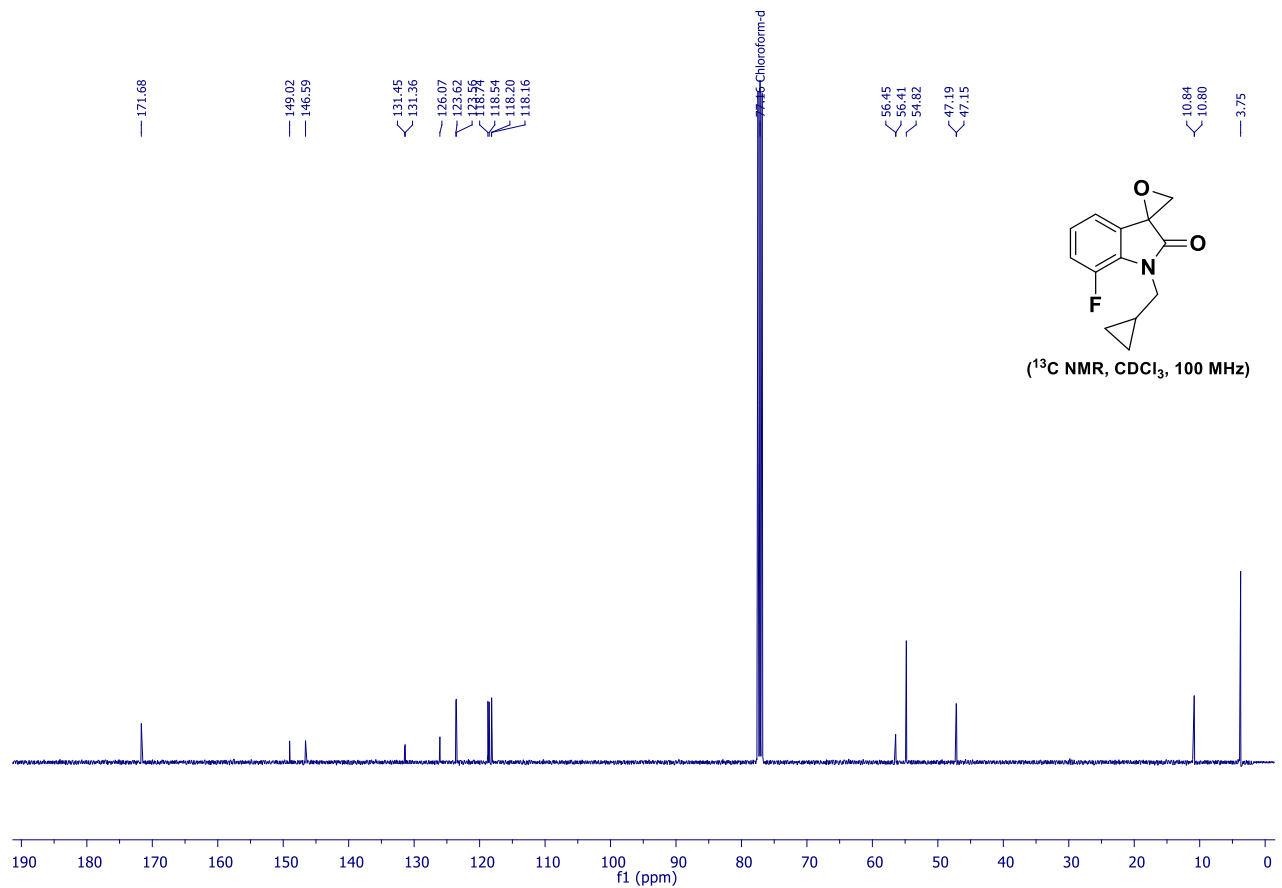
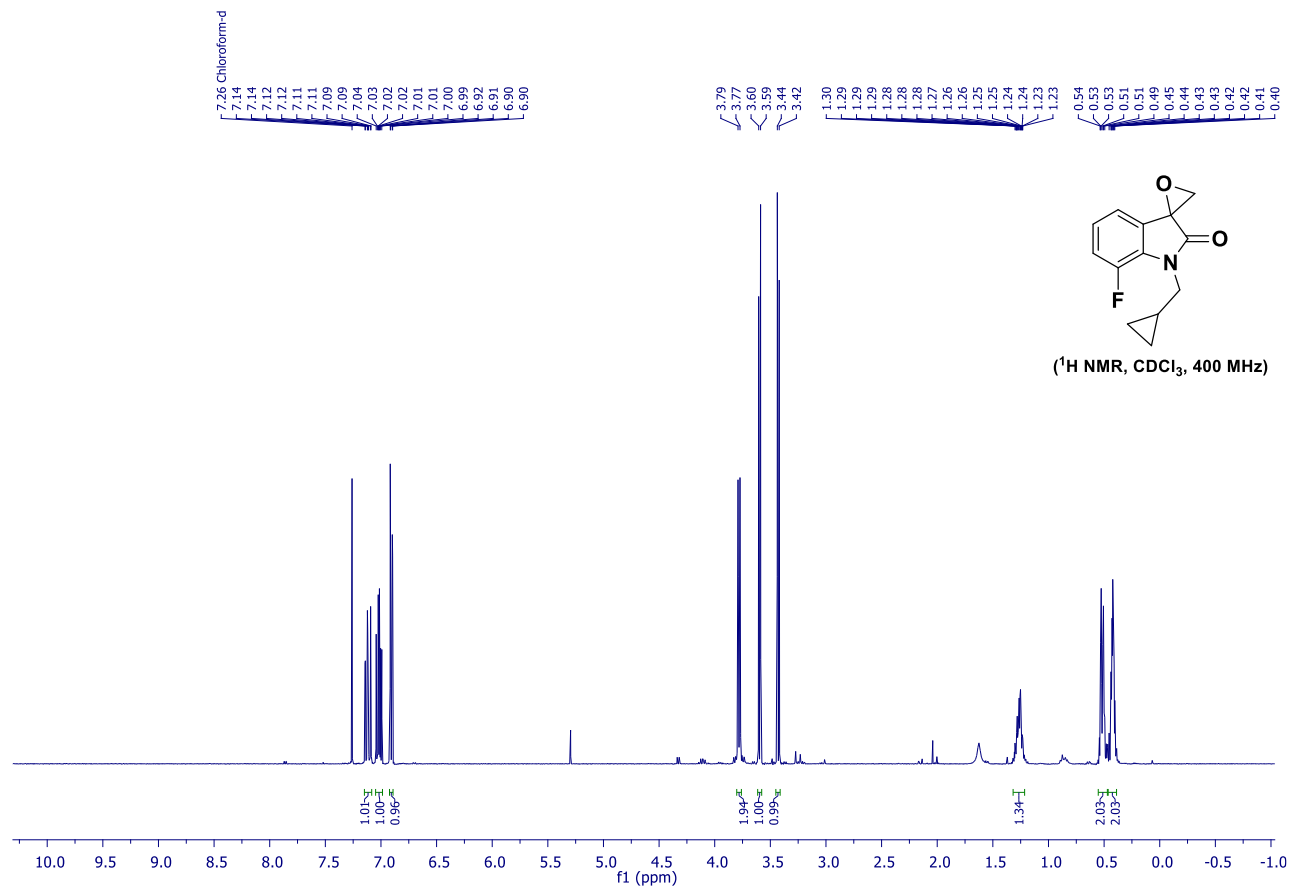


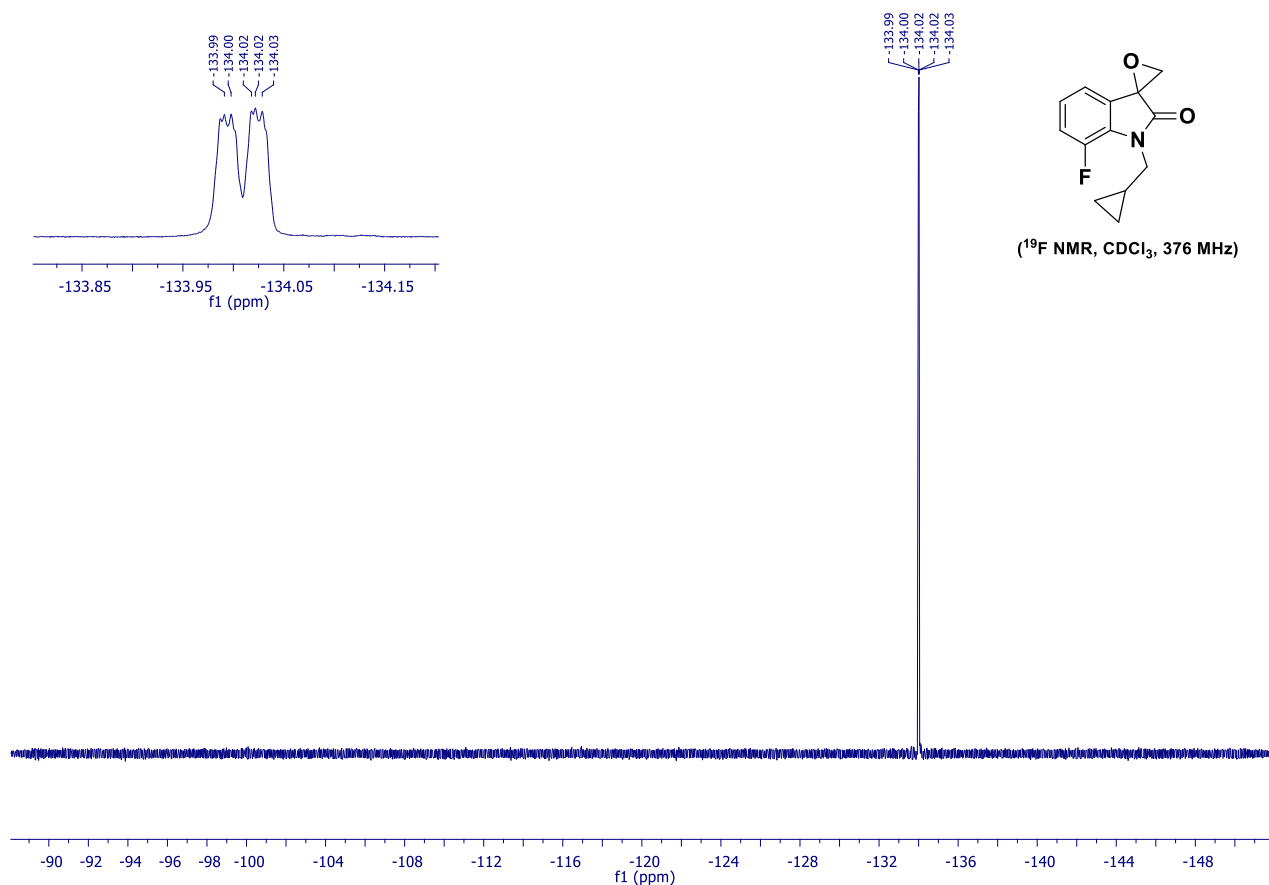


1-(4-Methoxybenzyl)spiro[indole-3,2'-oxirane]-2(1H)-one (650)

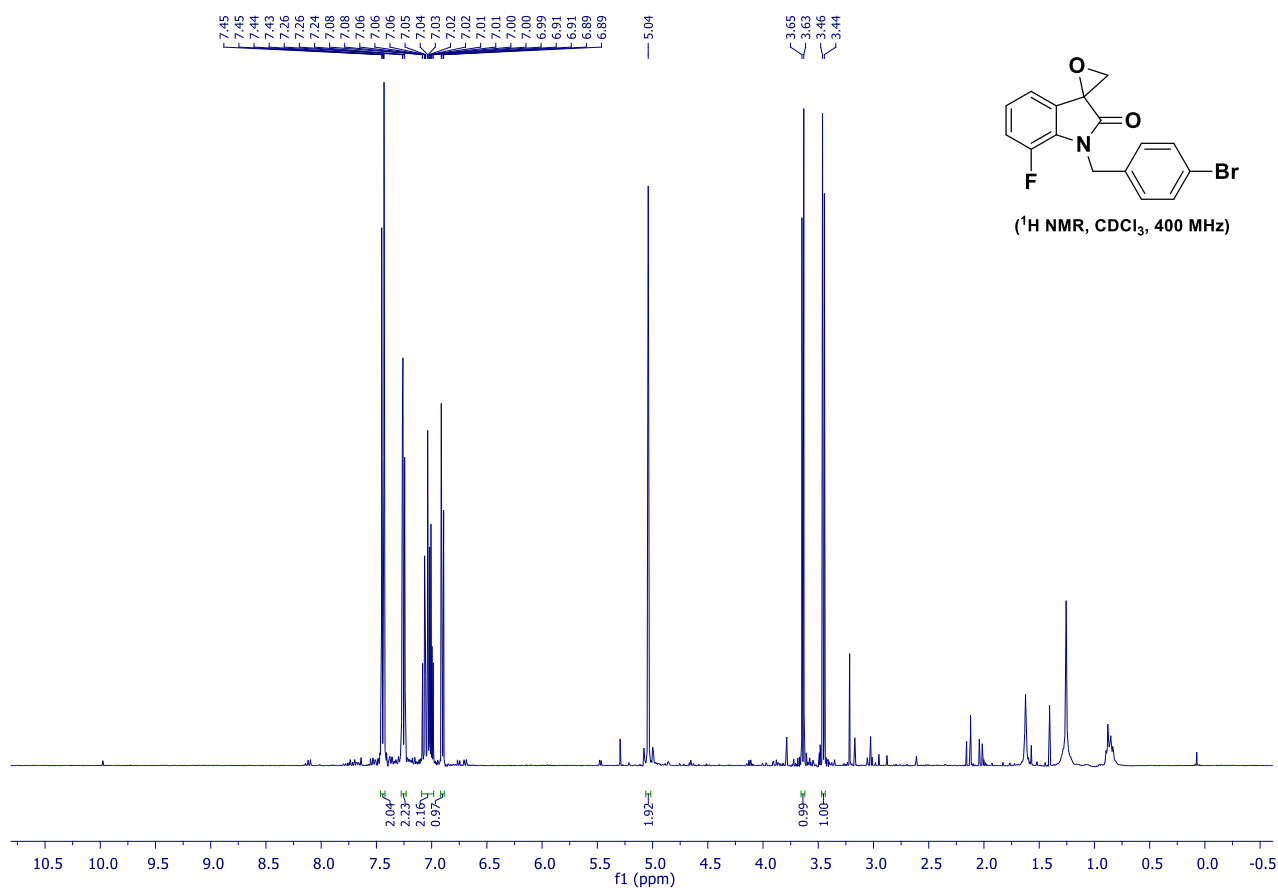


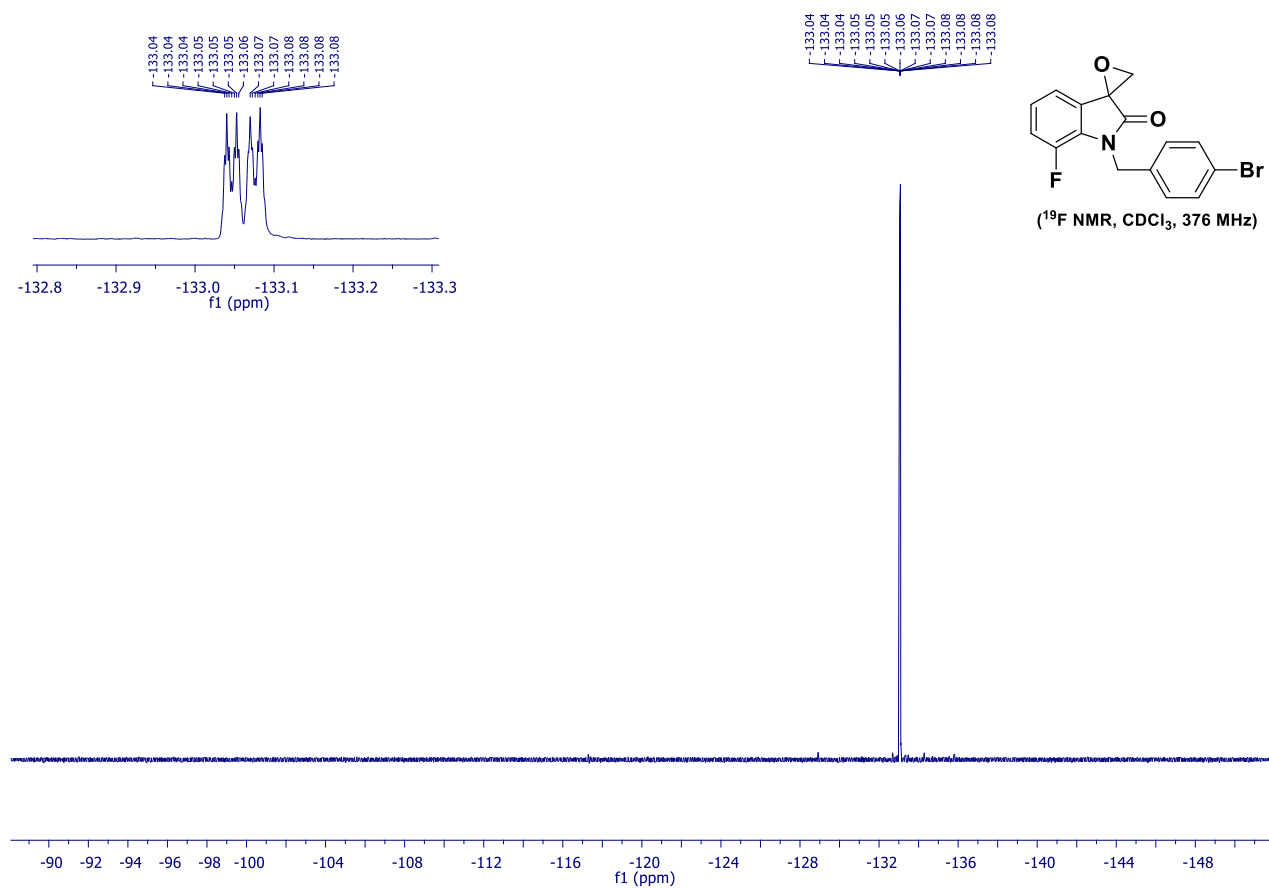
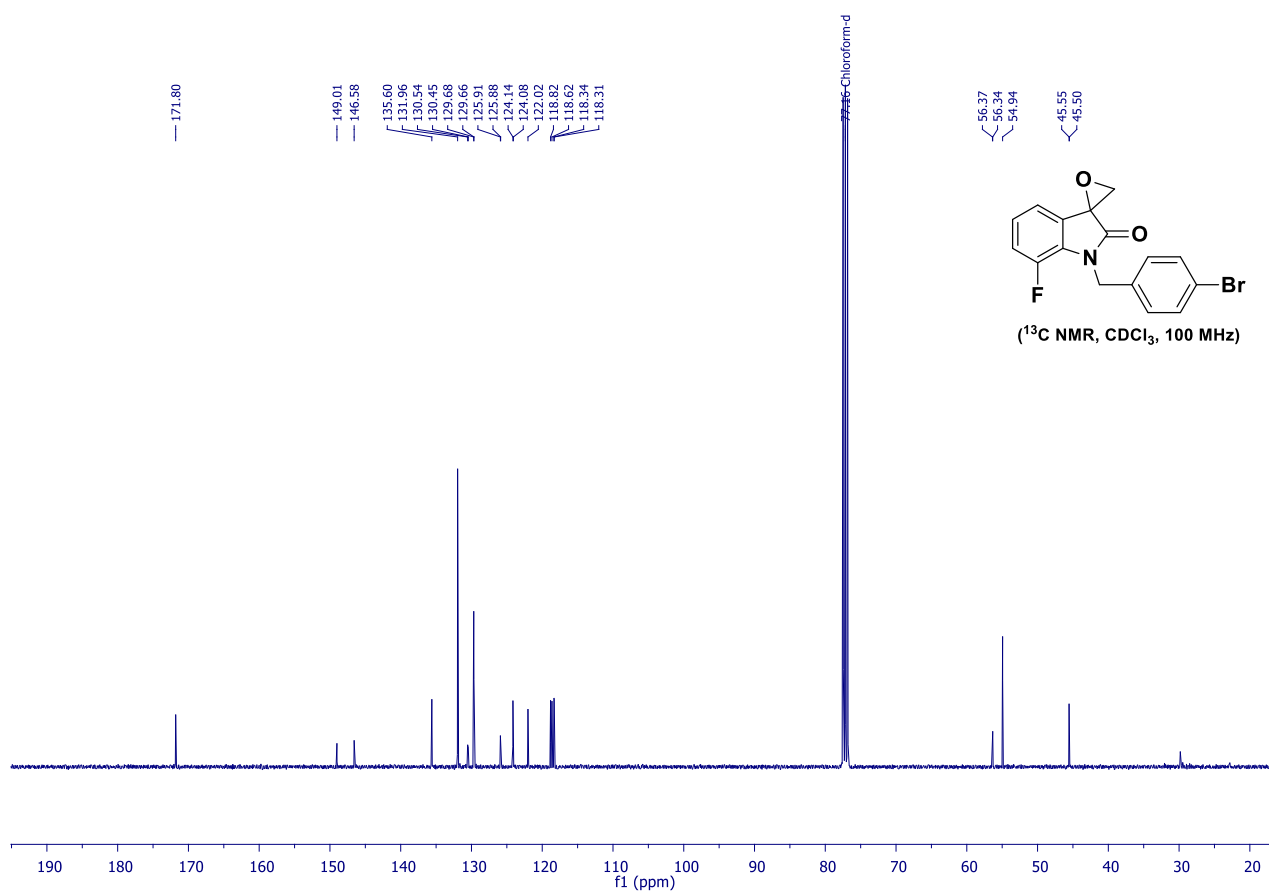
1-(Cyclopropylmethyl)-7-fluorospiro[indole-3,2'-oxirane]-2(1*H*)-one (651)



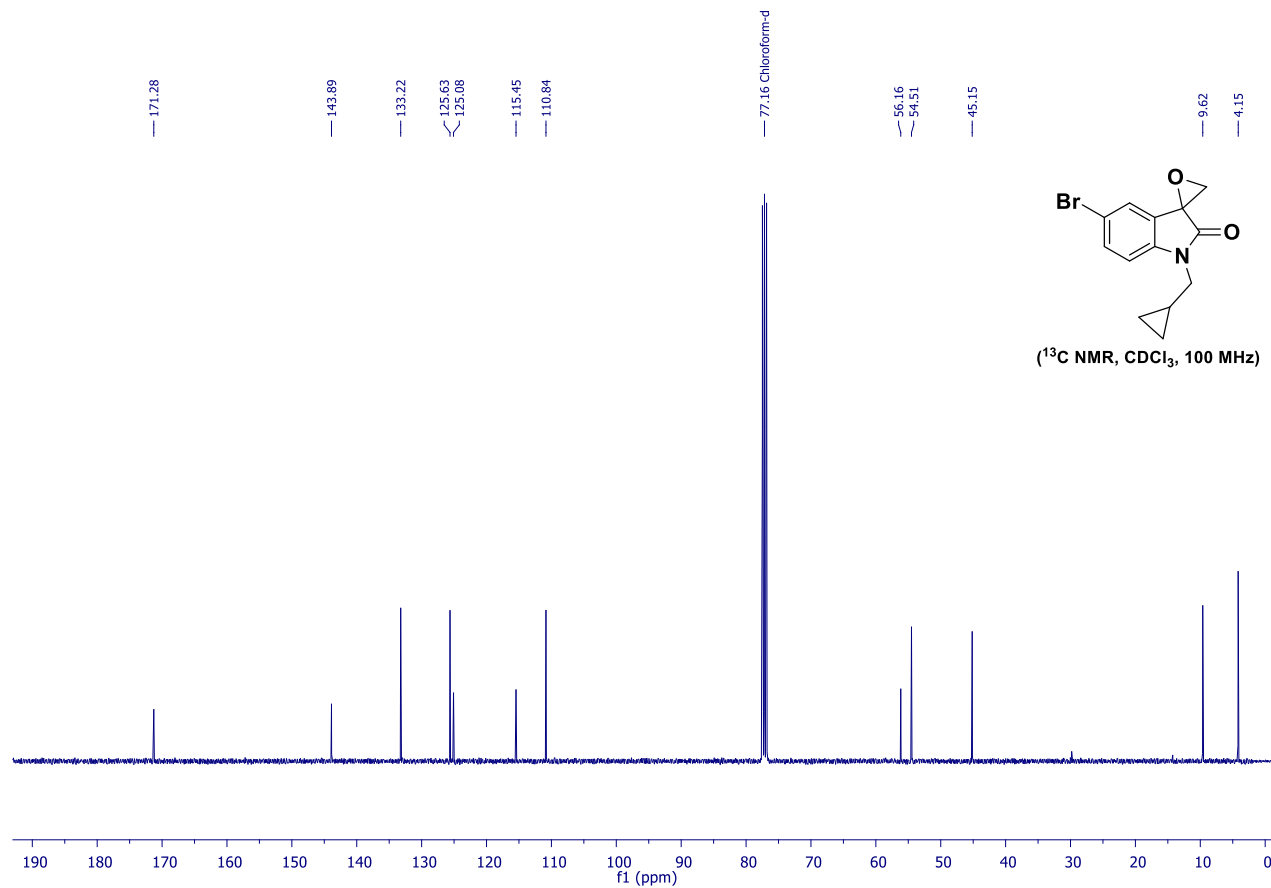
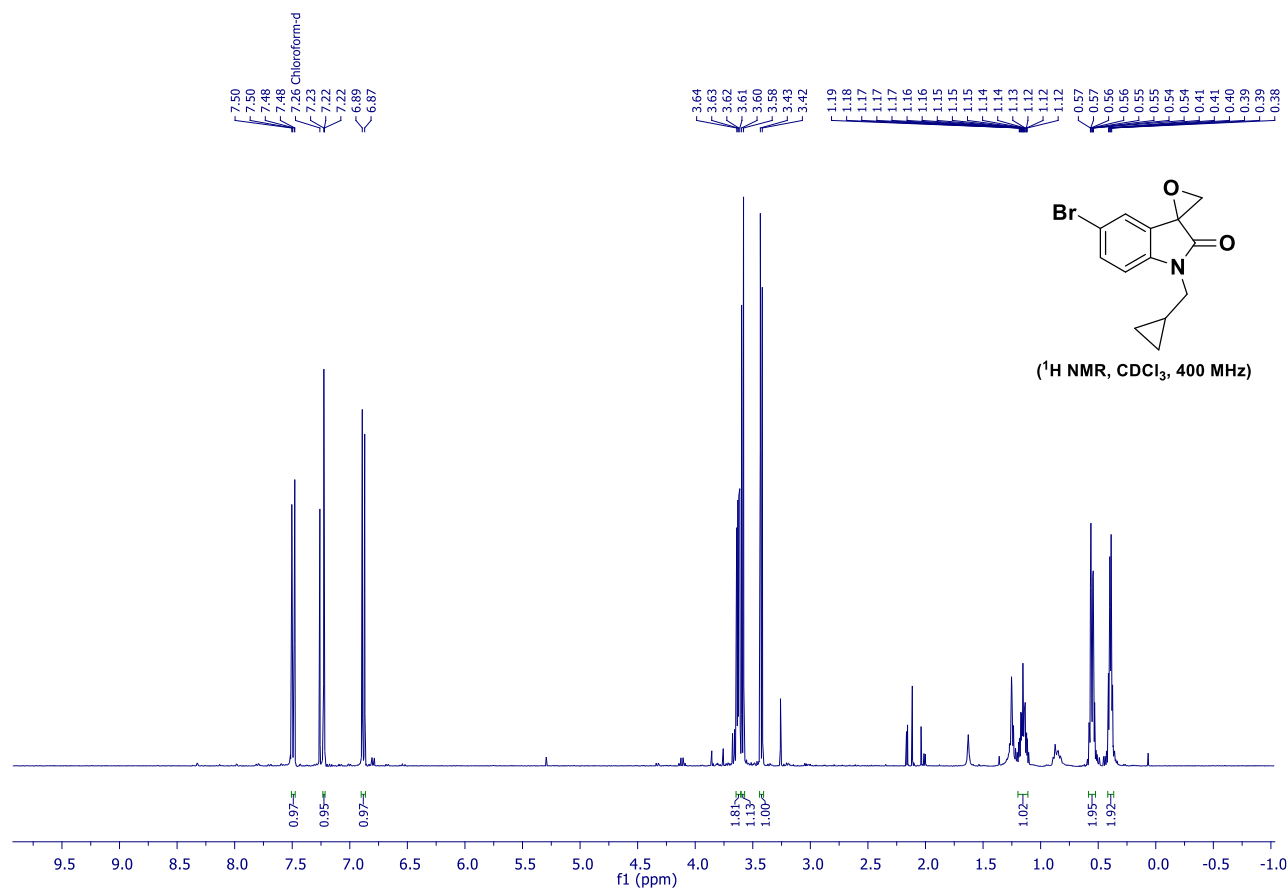


1-(4-Bromobenzyl)-7-fluorospiro[indole-3,2'-oxirane]-2(1H)-one (652)

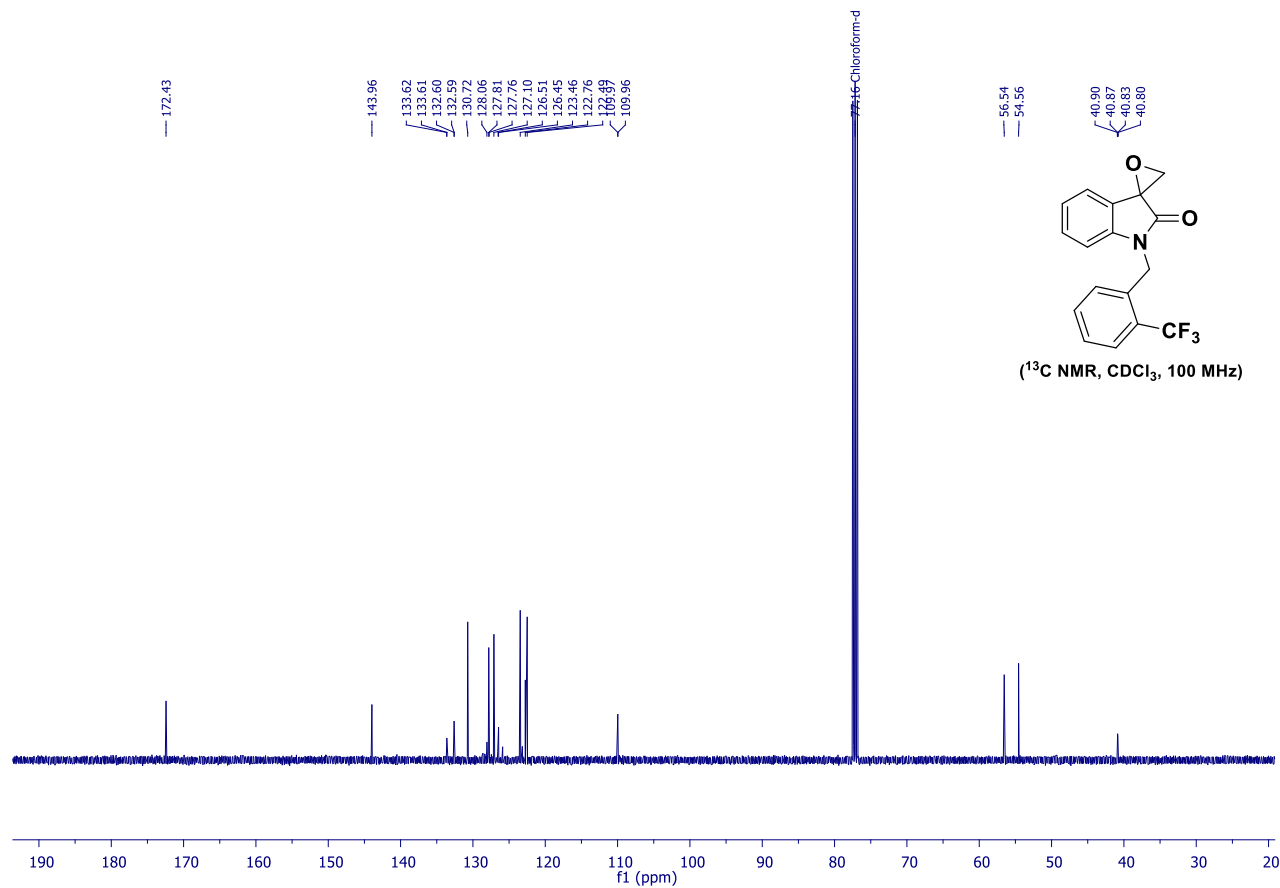
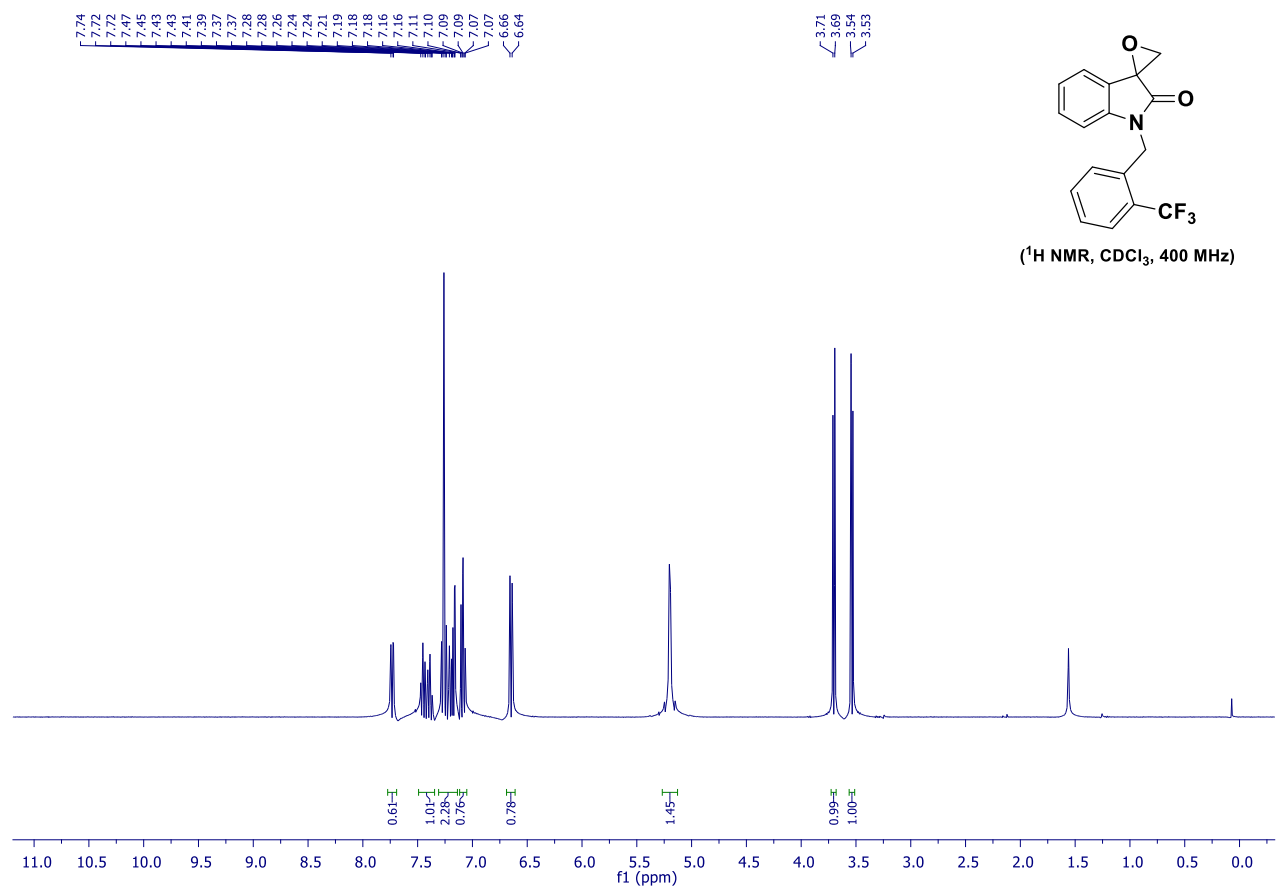


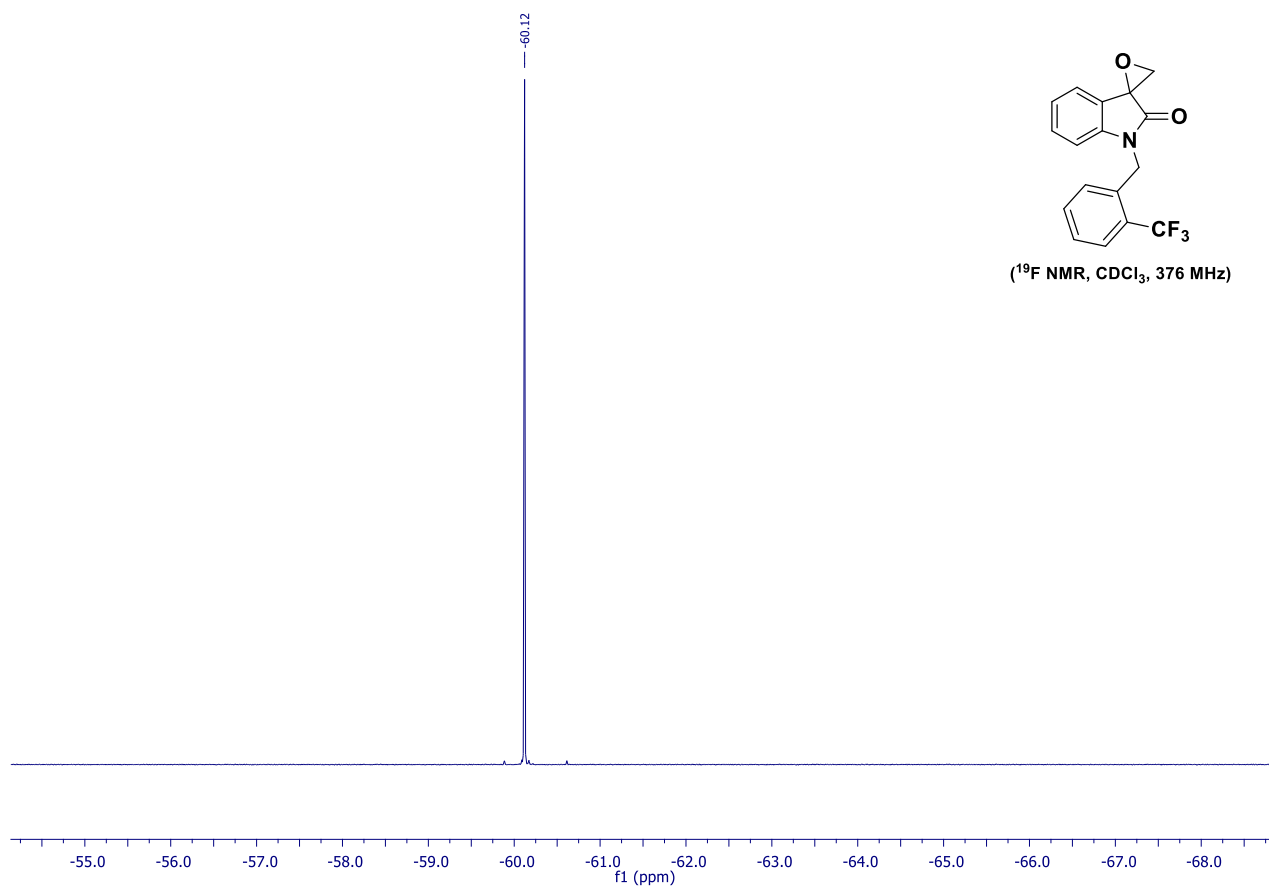


5-Bromo-1-(cyclopropylmethyl)spiro[indole-3,2'-oxirane]-2(1H)-one (653)

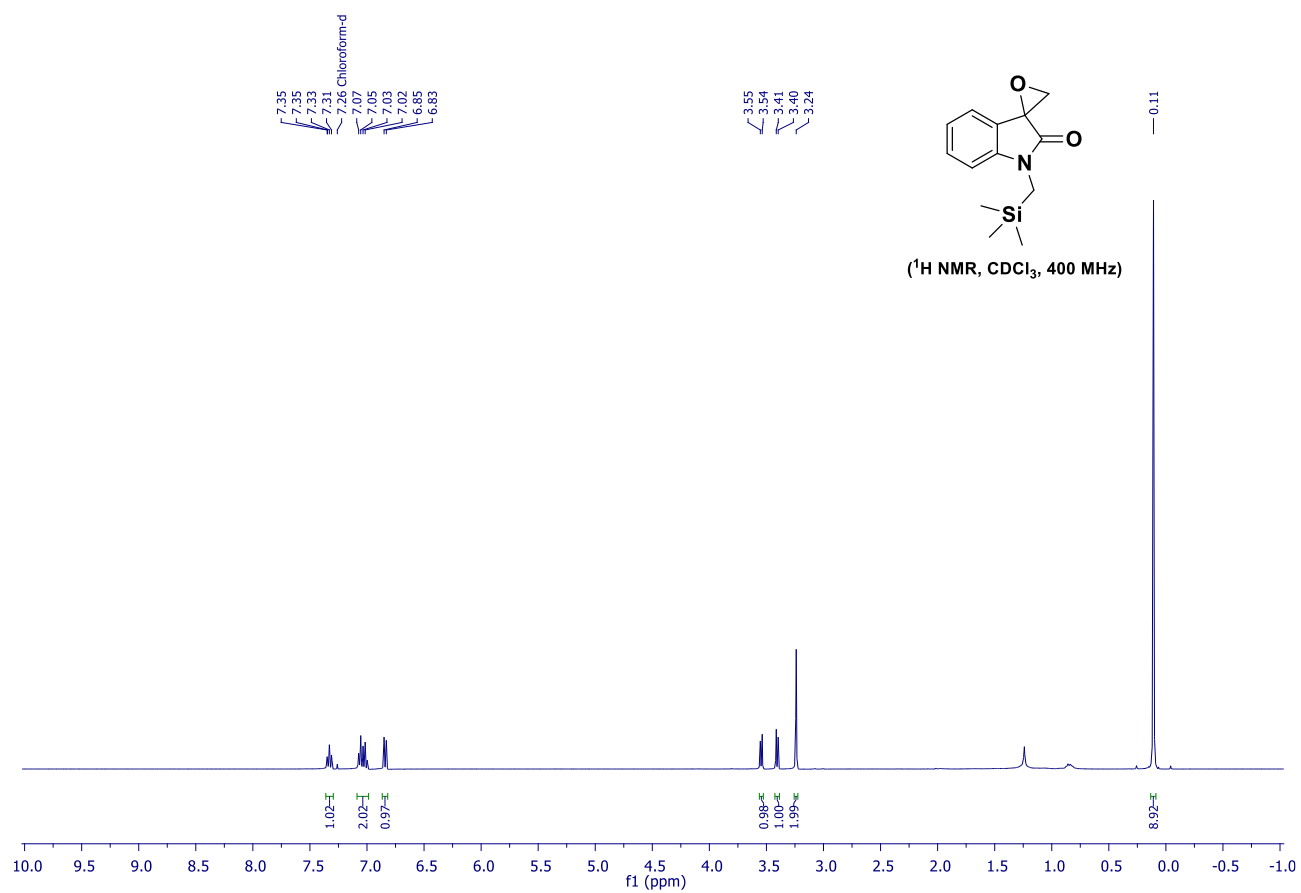


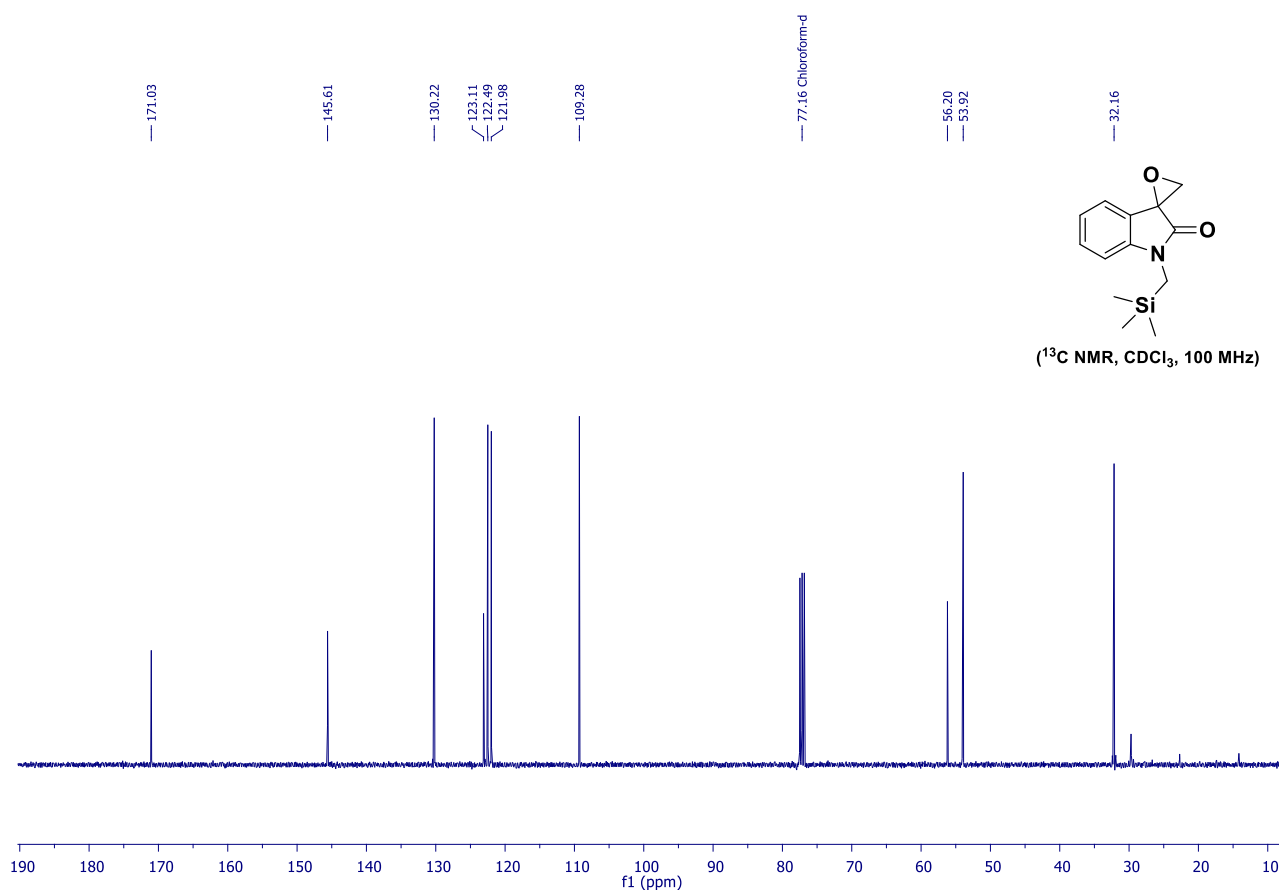
1-[2-(Trifluoromethyl)benzyl]spiro[indole-3,2'-oxirane]-2(1H)-one (654)



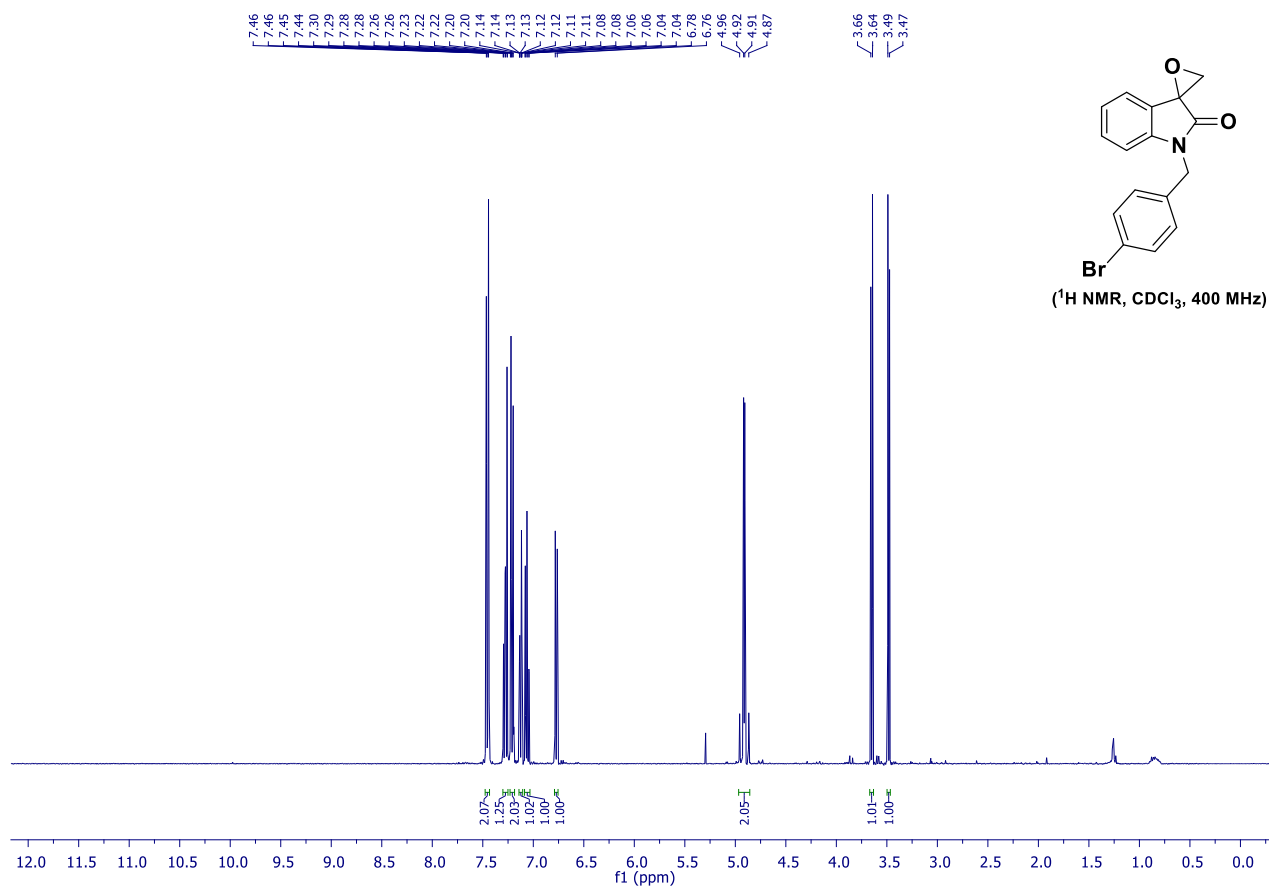


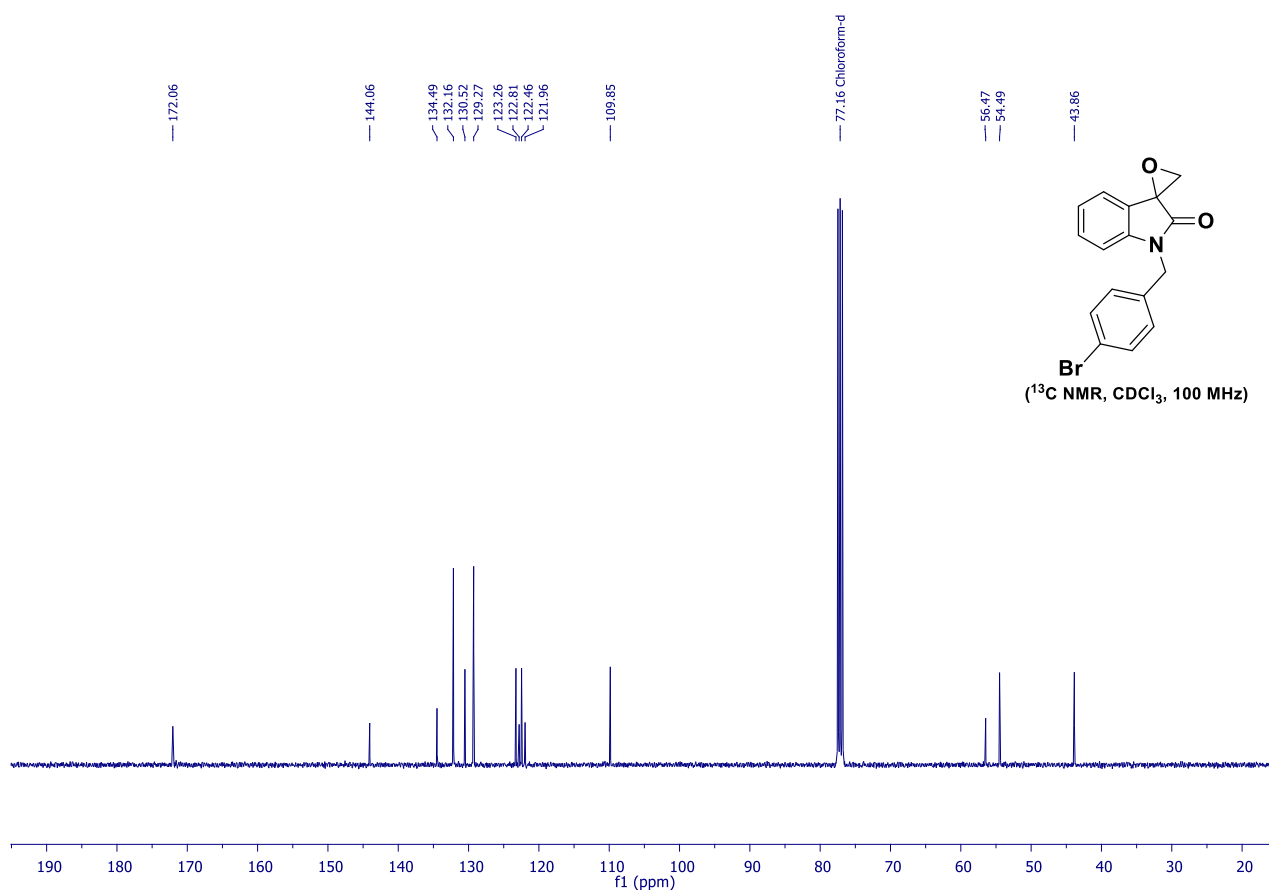
1-[(Trimethylsilyl)methyl]spiro[indole-3,2'-oxiran]-2-(1*H*)-one (655)



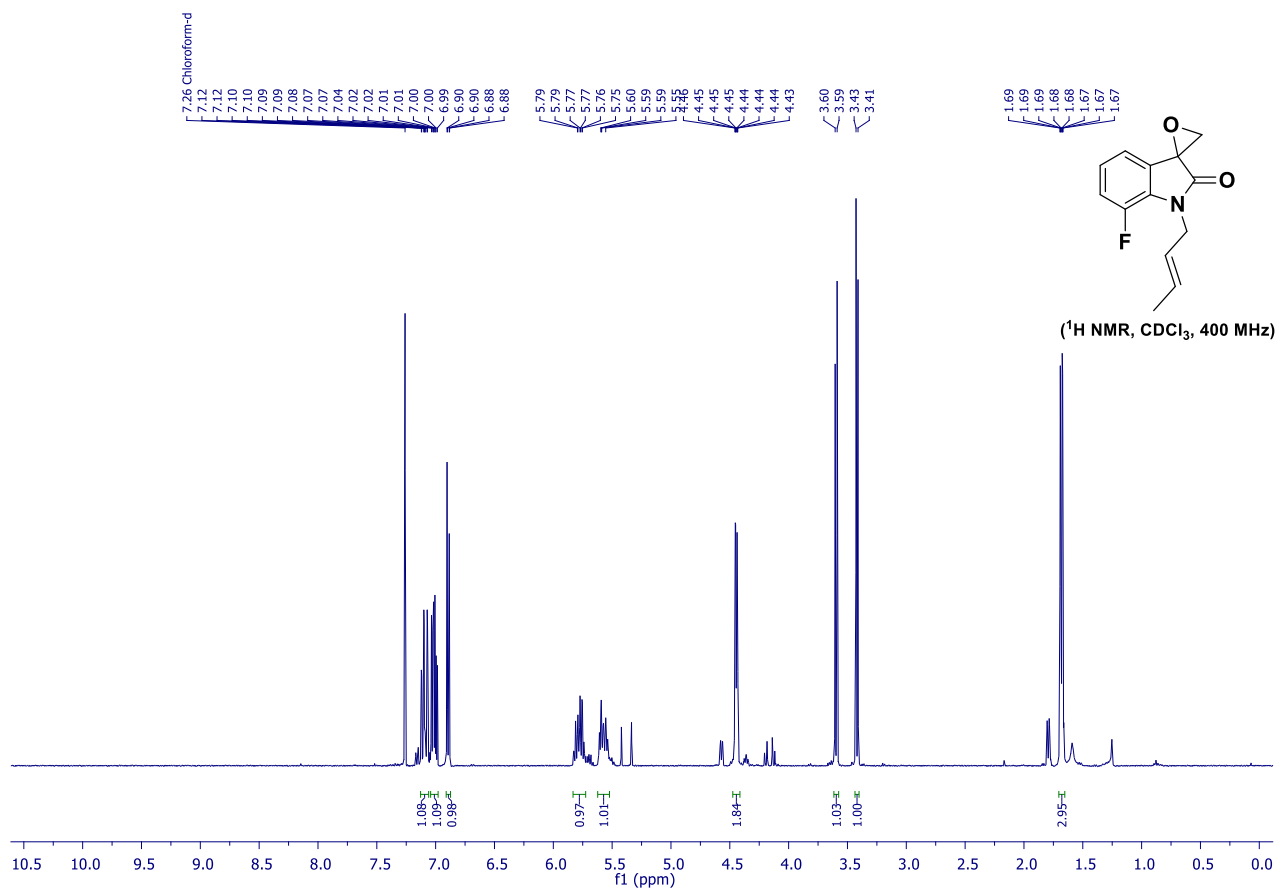


1-(4-Bromobenzyl)spiro[indole-3,2'-oxiran]-2(1H)-one (656)

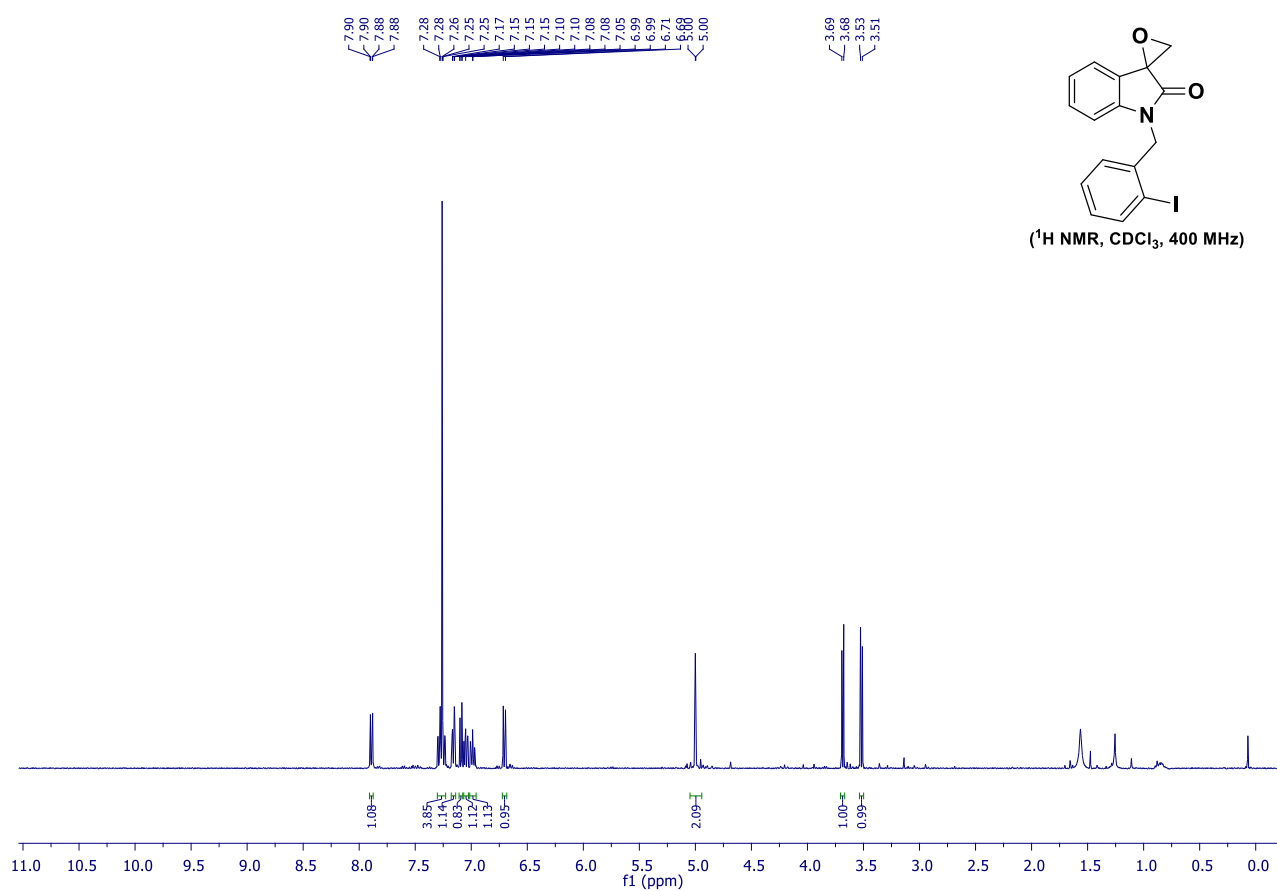


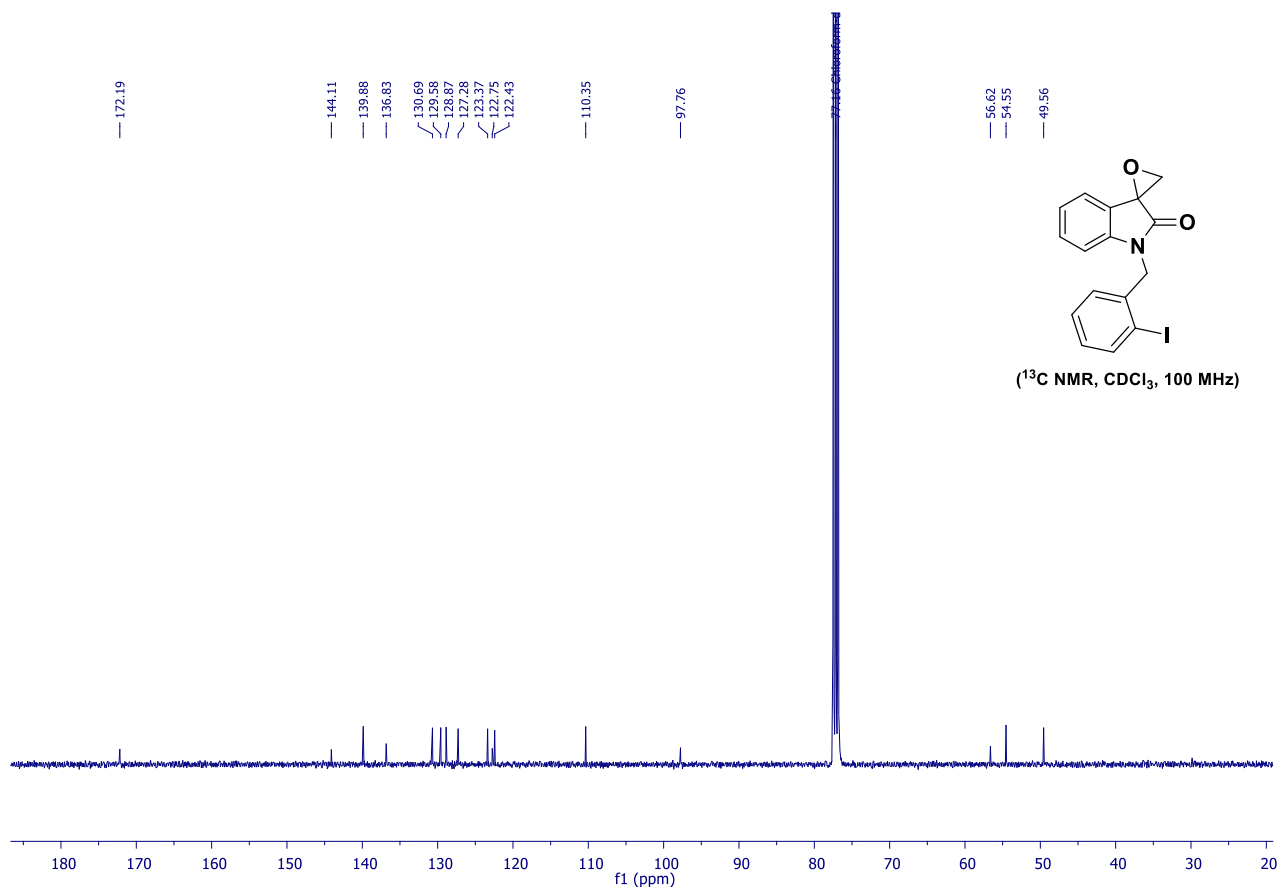


1-[(2E)-2-buten-1-yl]-7-fluorospiro[indole-3,2'-oxiran]-2(1H)-one (657)

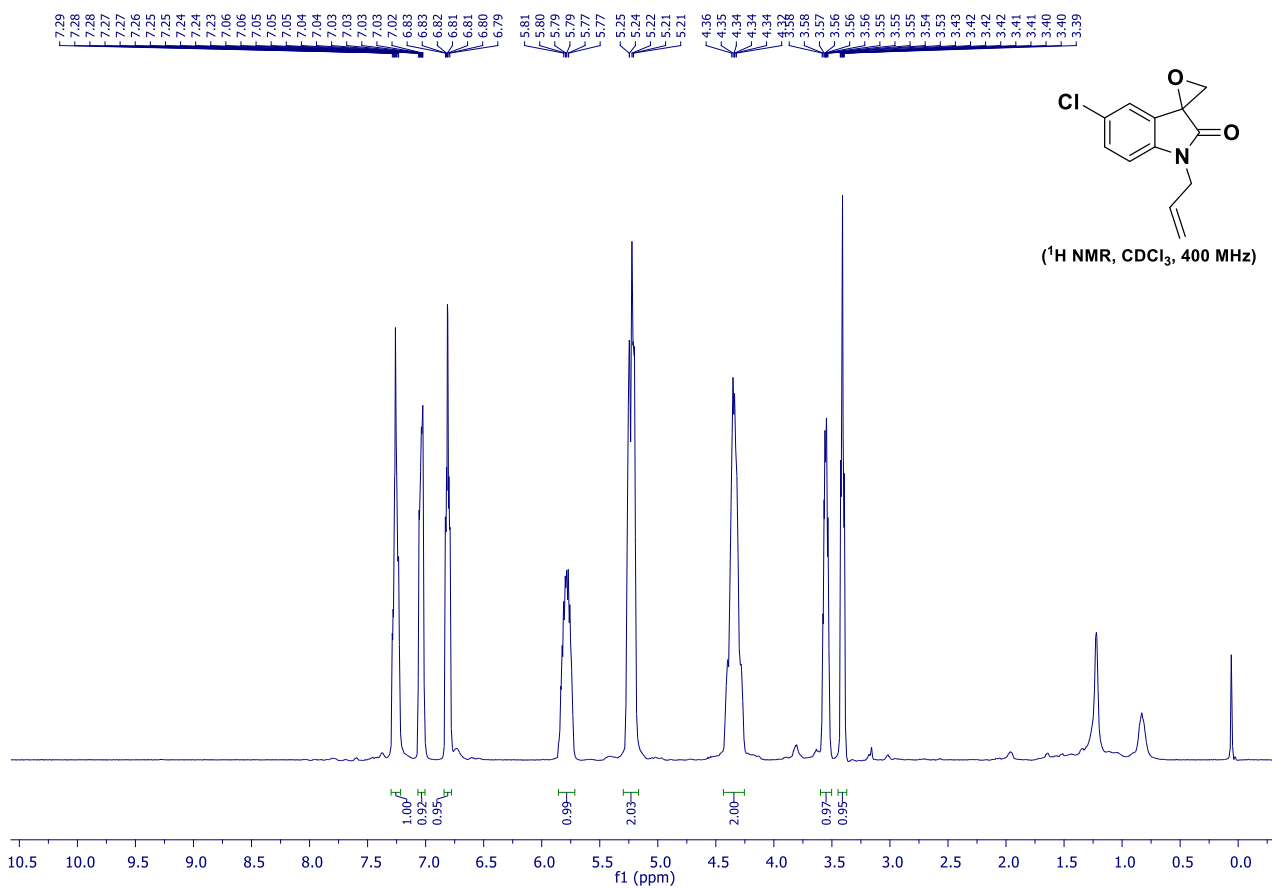


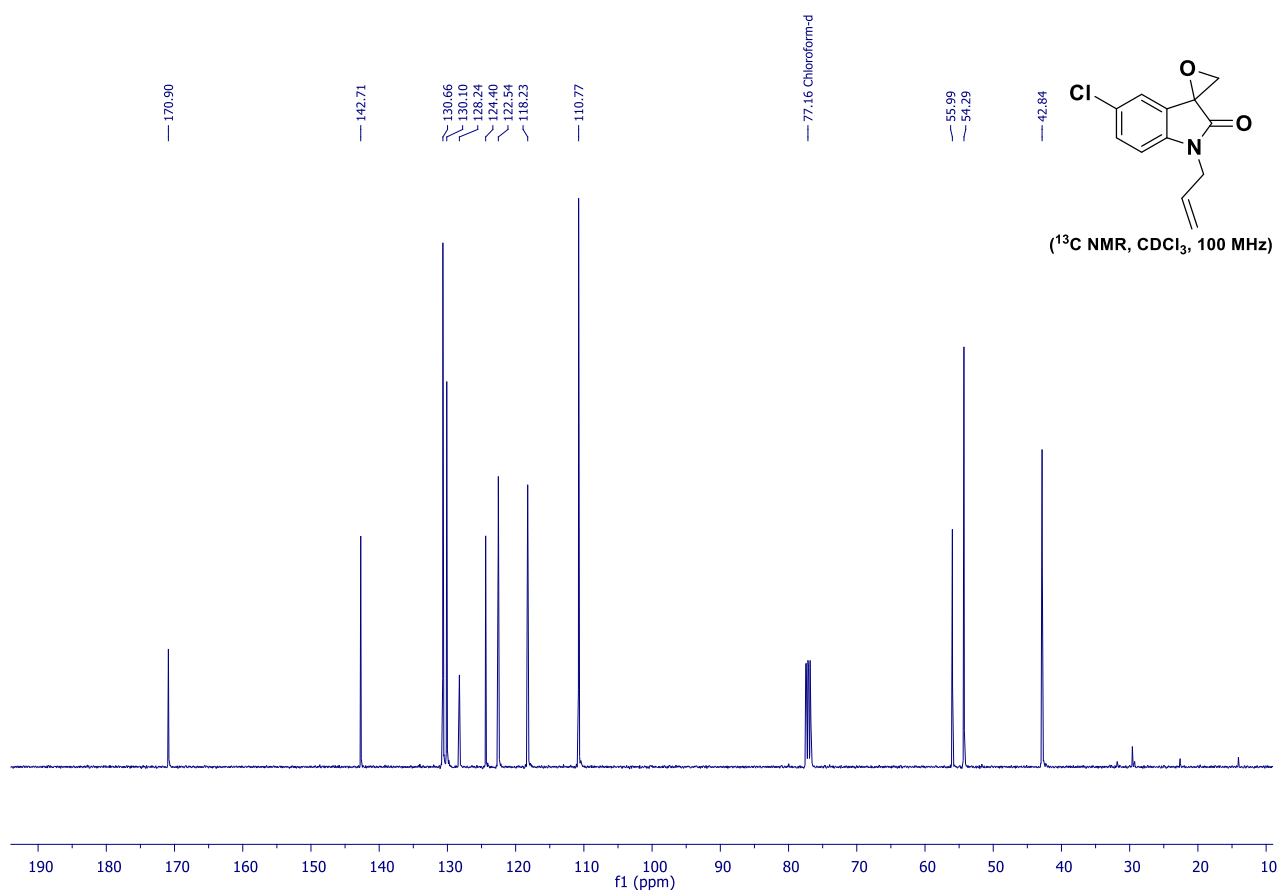
1-(2-Iodobenzyl)spiro[indole-3,2'-oxiran]-2(1H)-one (658)



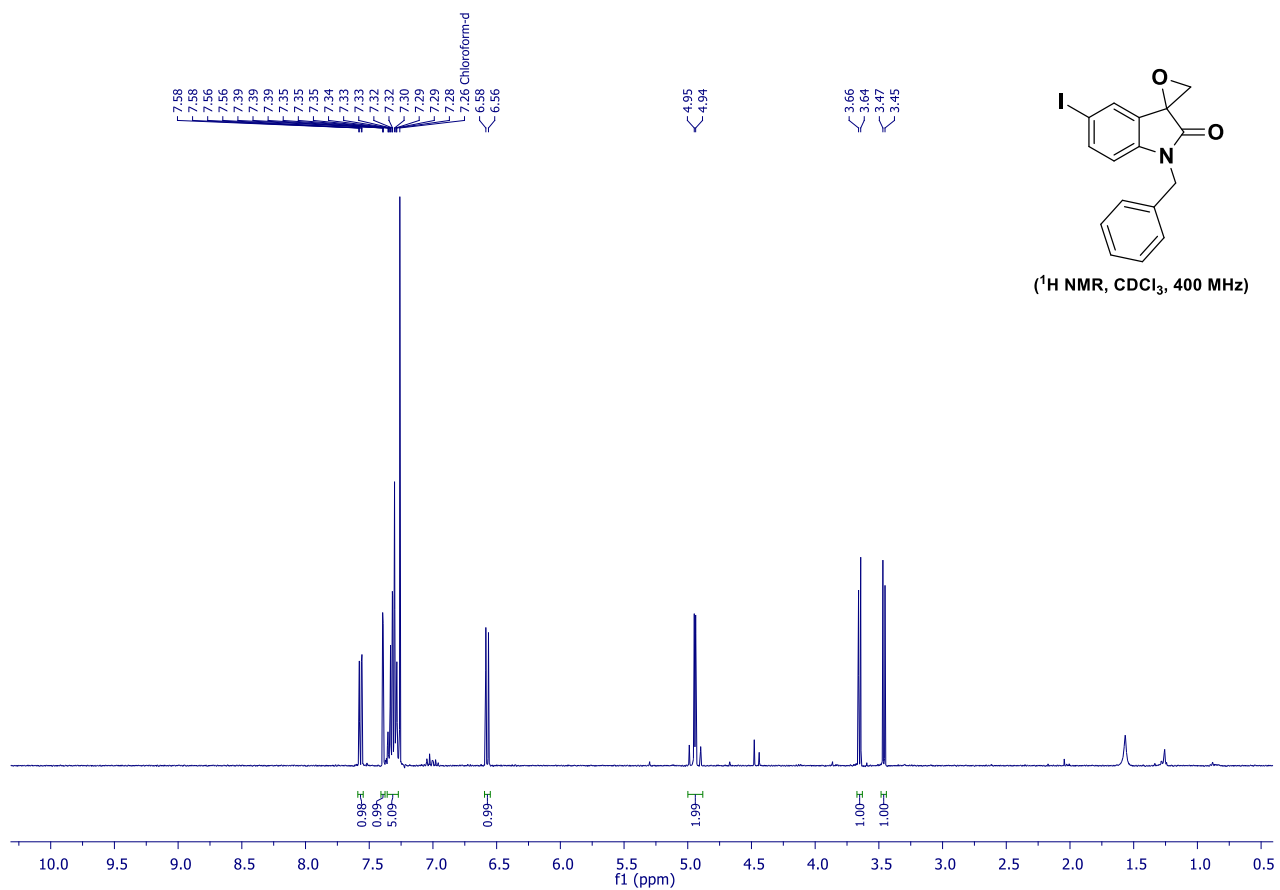


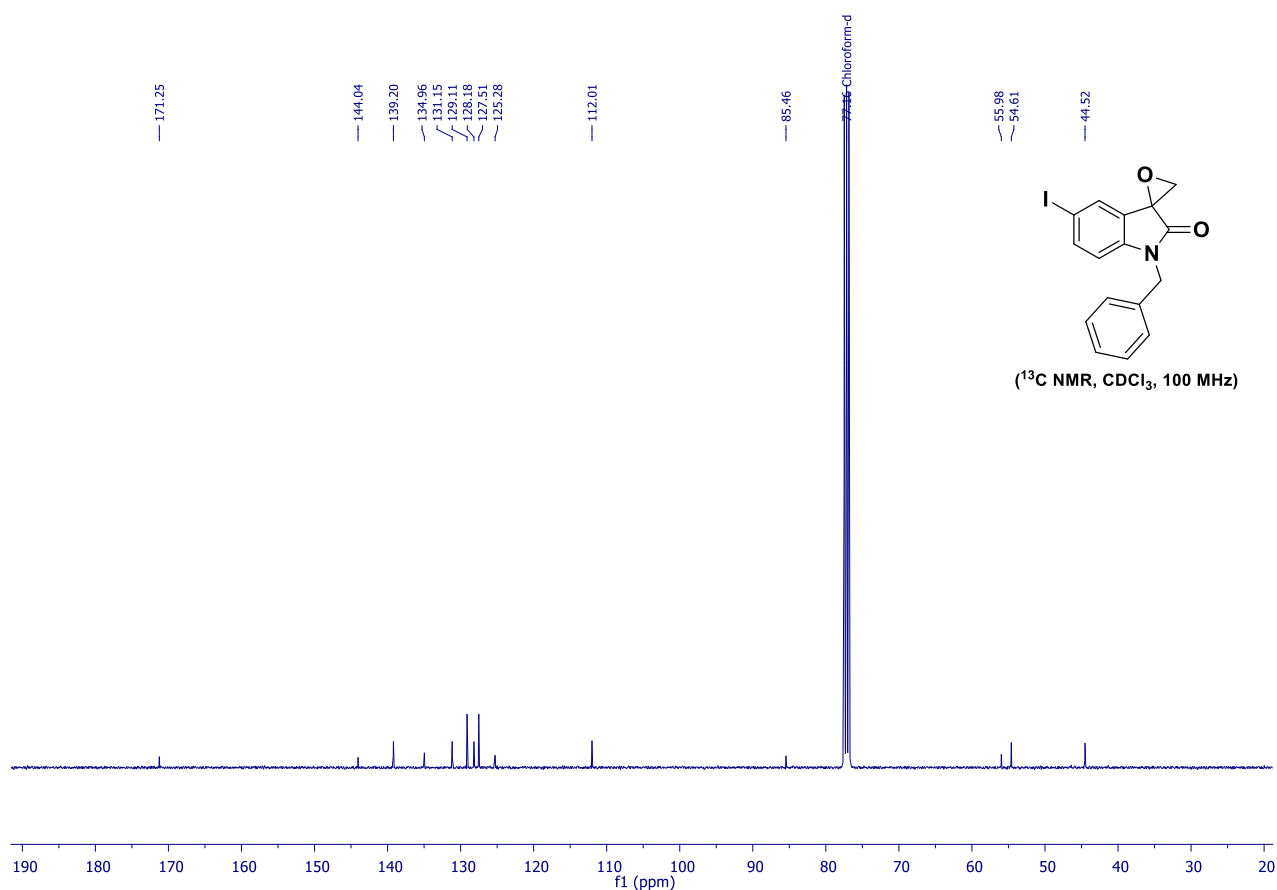
1-Allyl-5-chlorospiro[indole-3,2'-oxiran]-2(1H)-one (659)



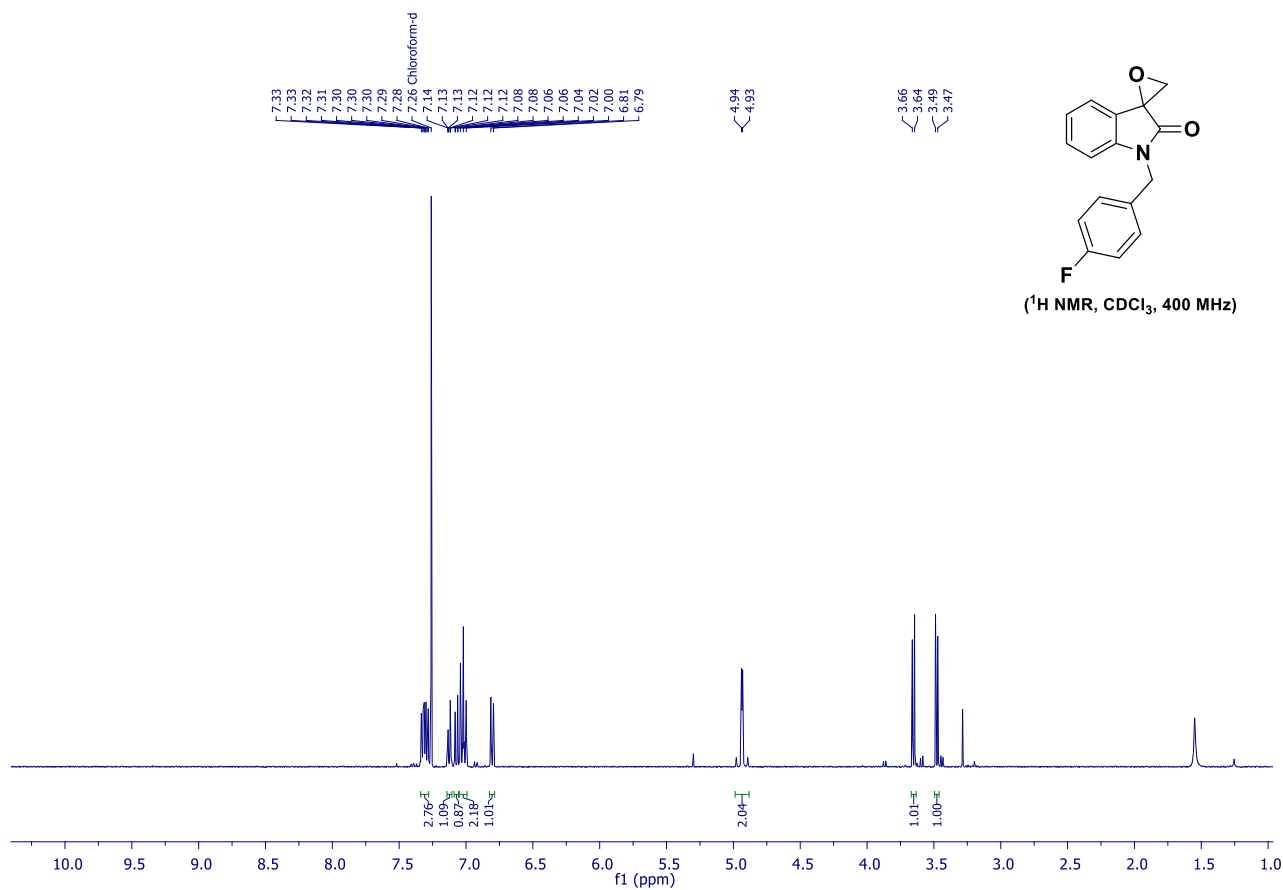


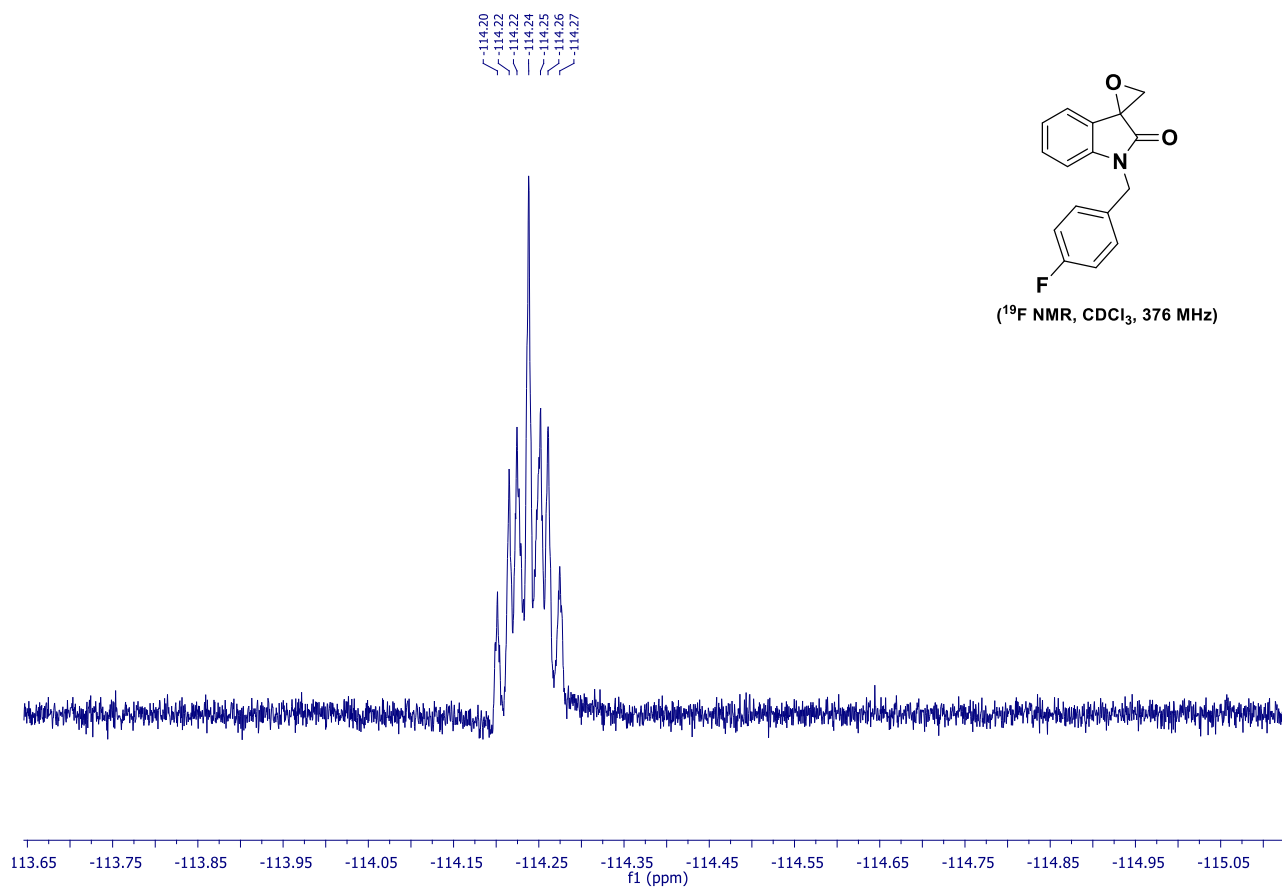
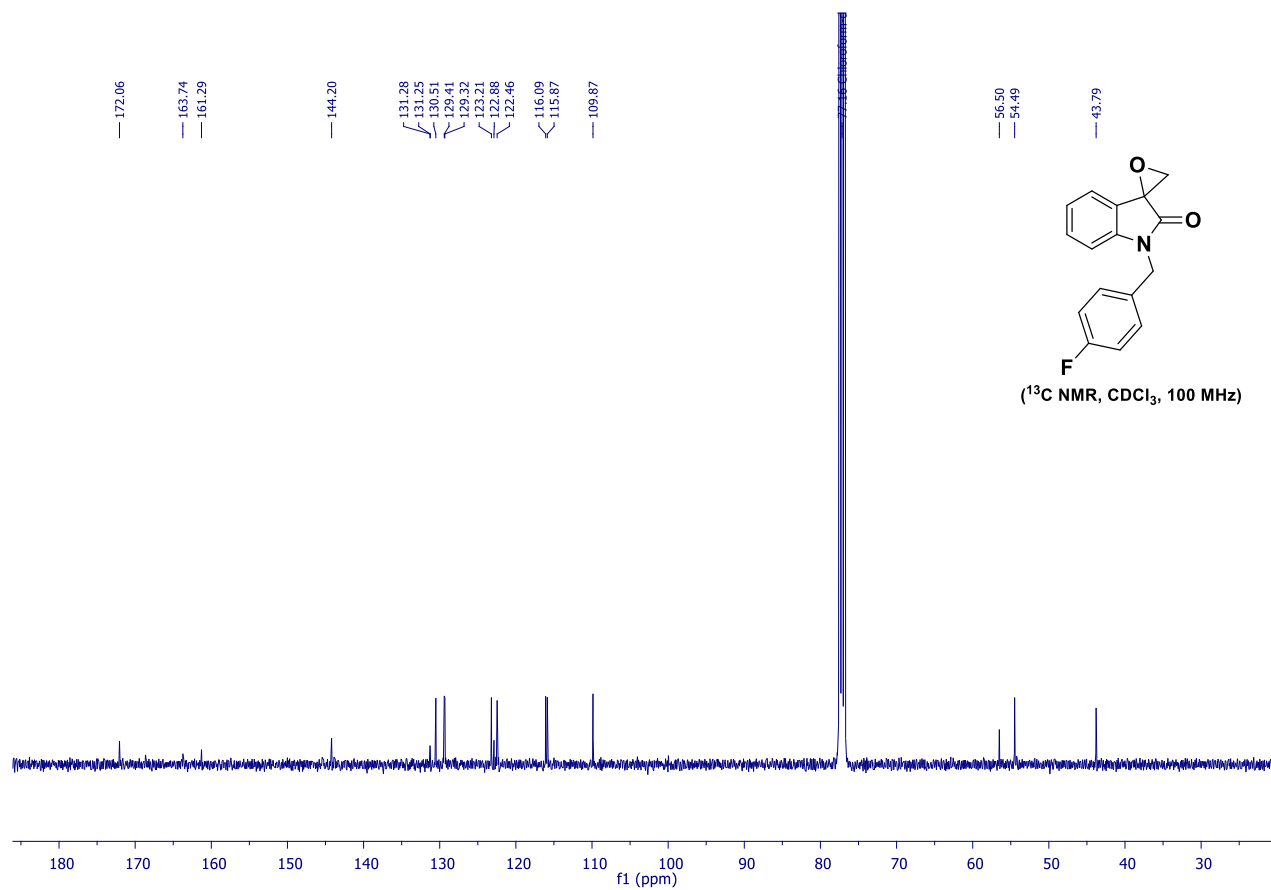
1-Benzyl-5-iodospiro[indole-3,2'-oxiran]-2(1H)-one (660)



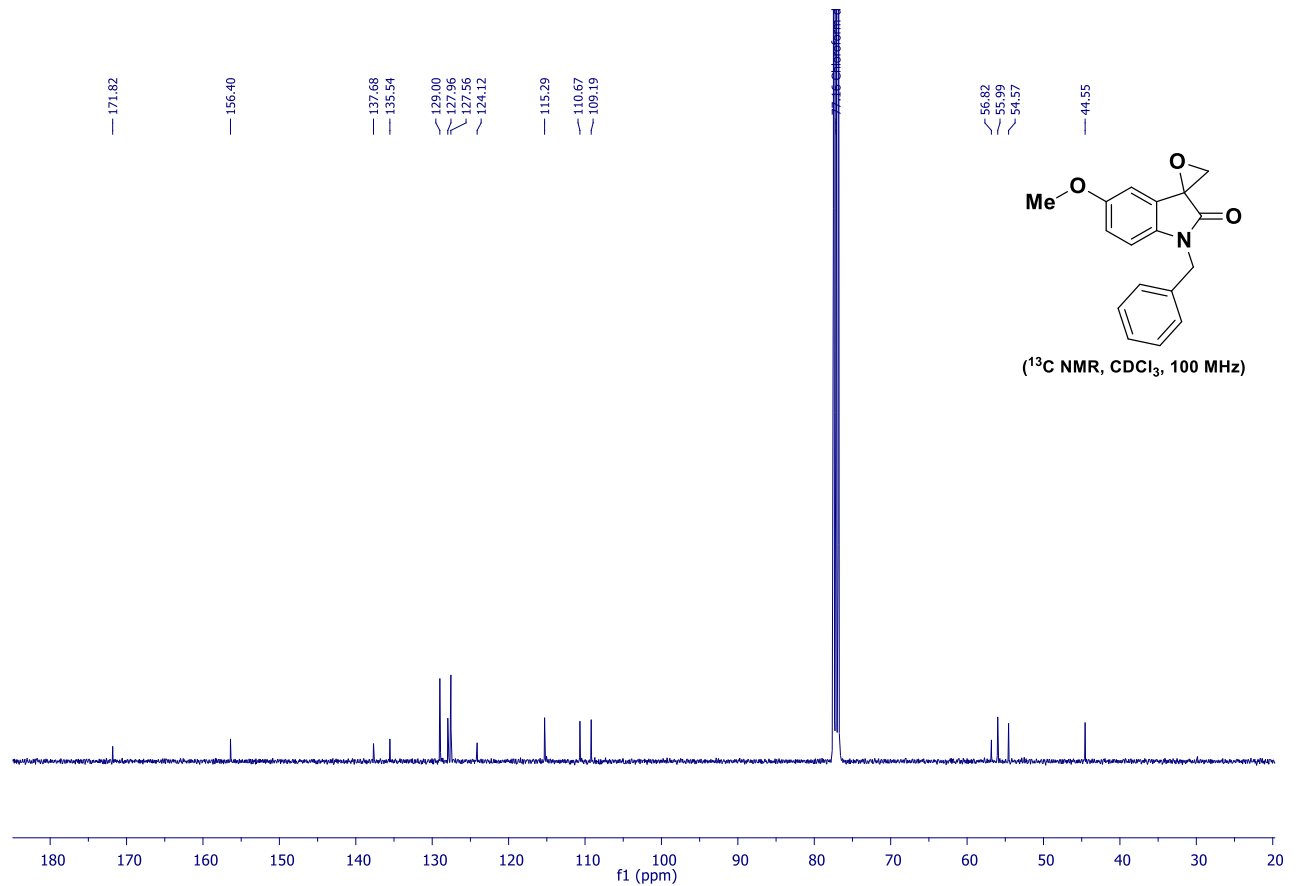
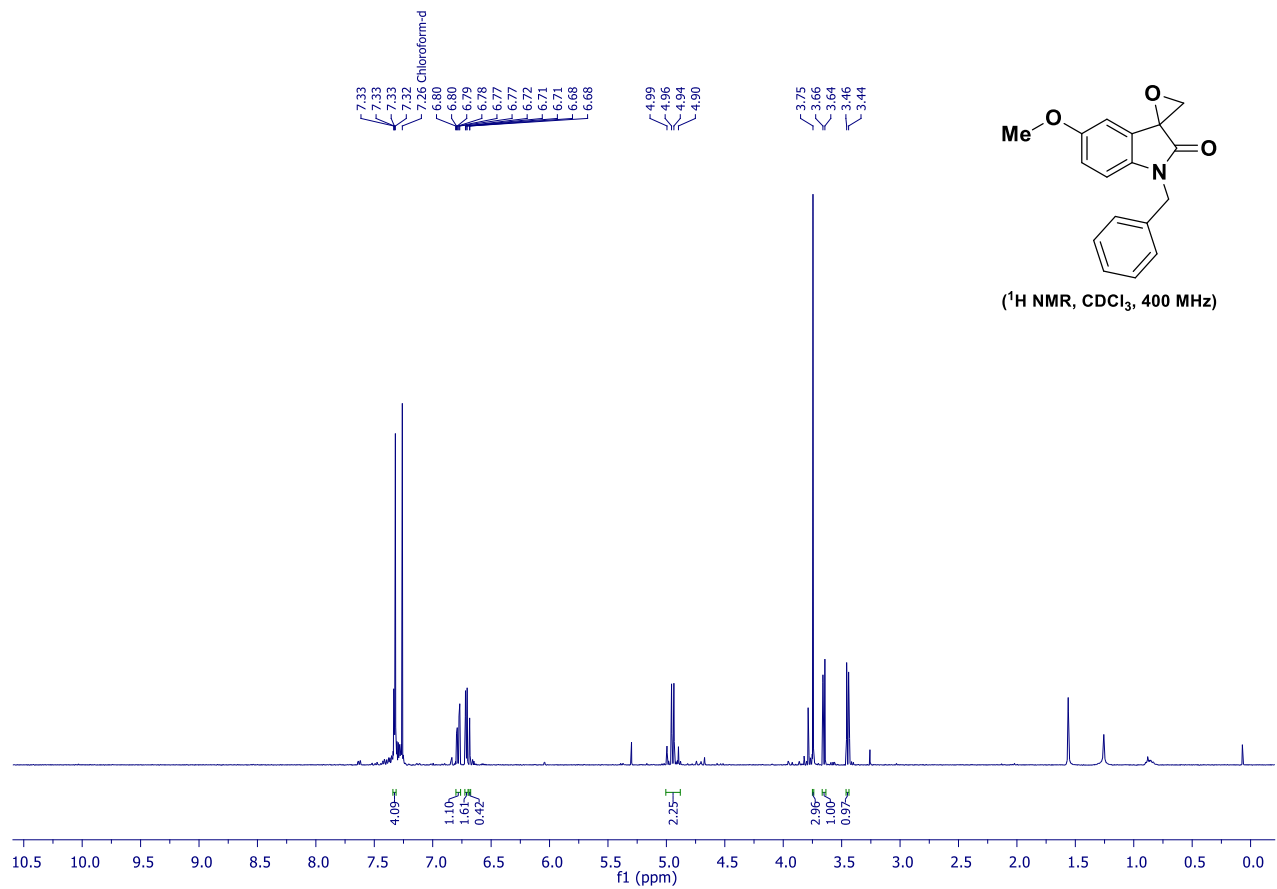


1-(4-Fluorobenzyl)spiro[indole-3,2'-oxiran]-2(1H)-one (661)

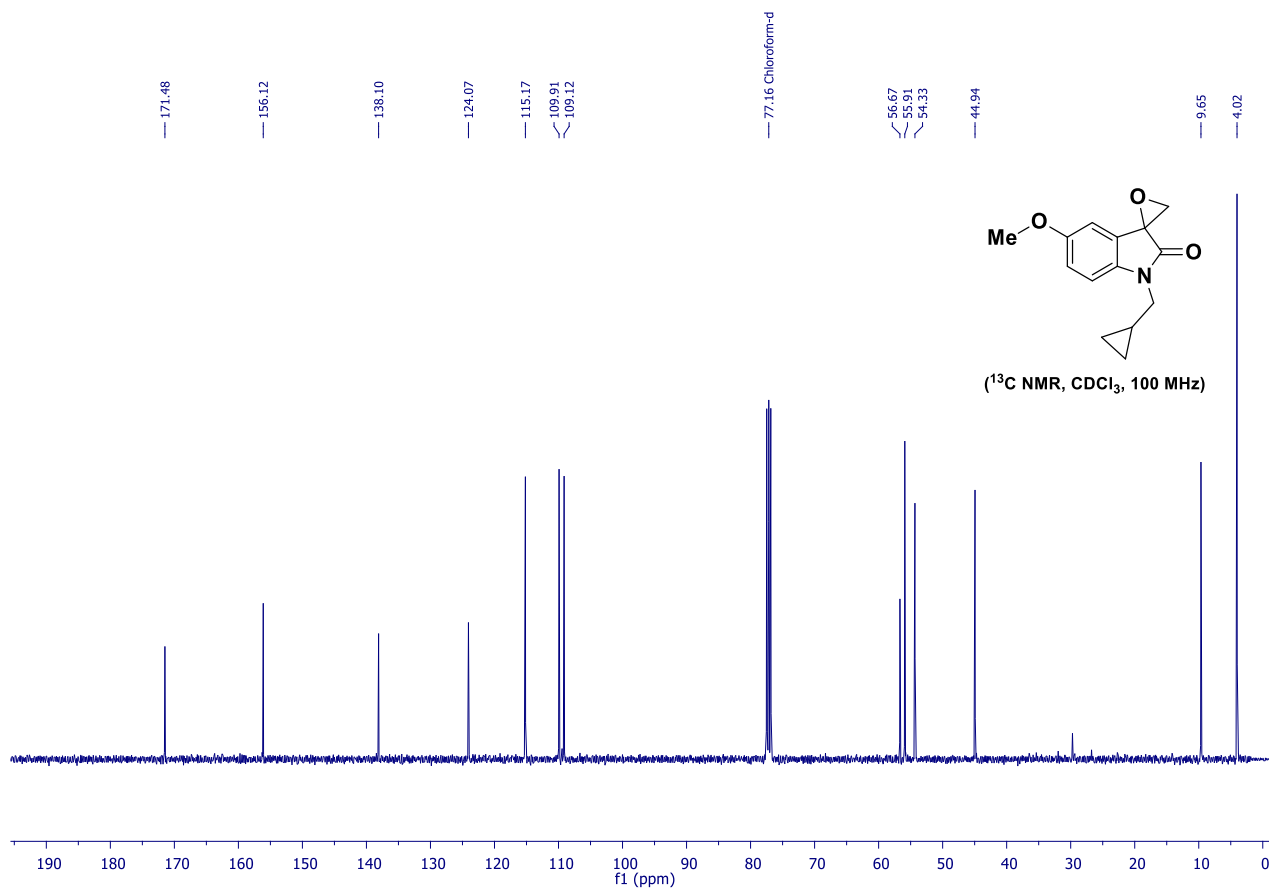
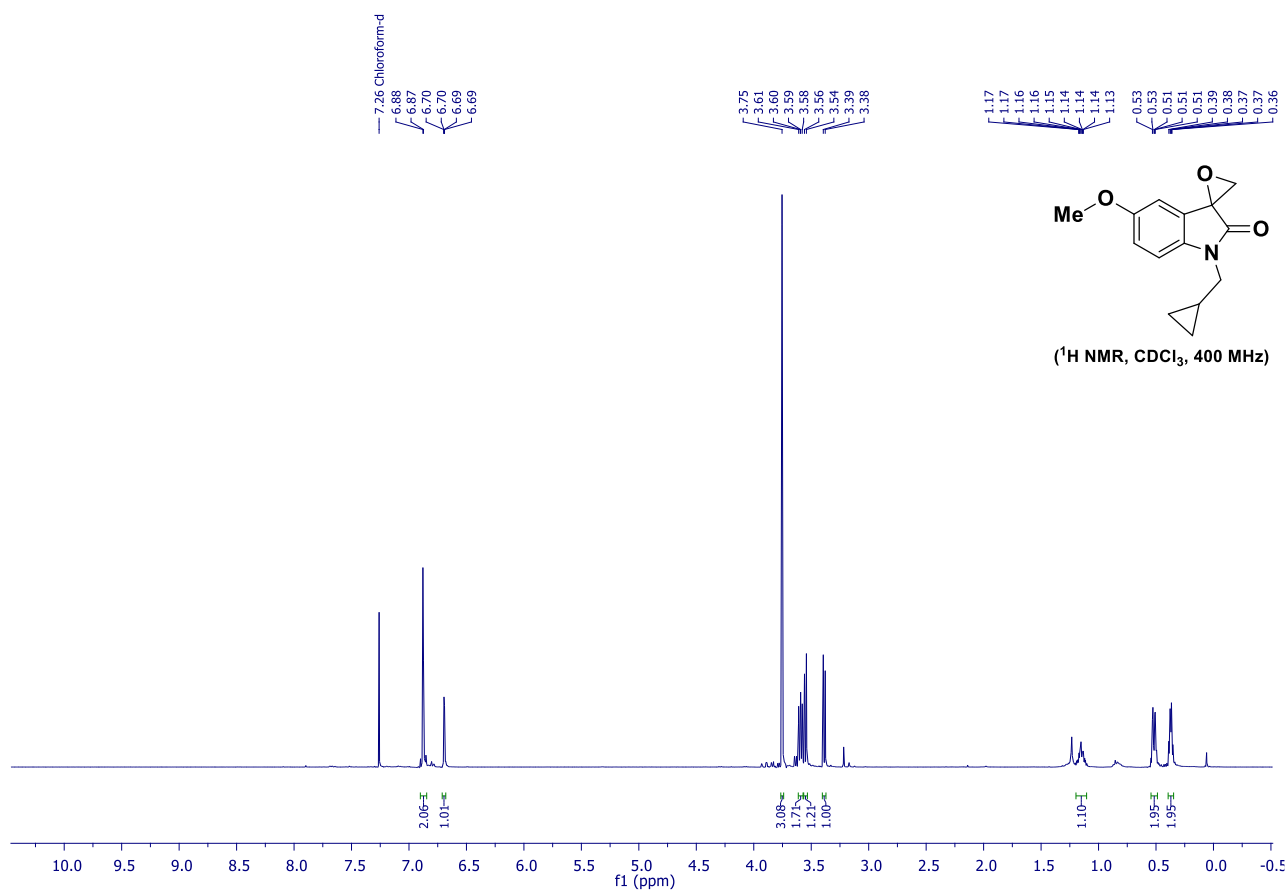




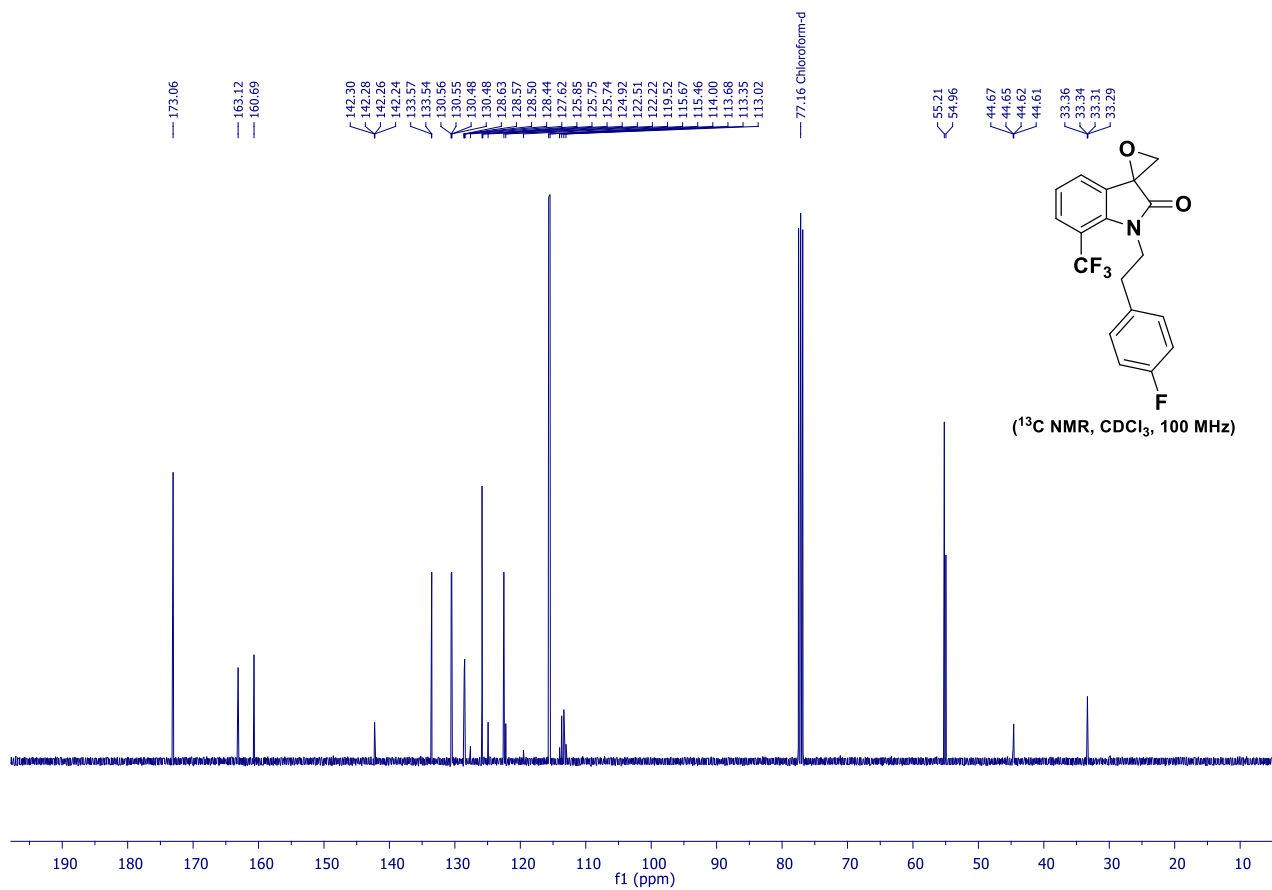
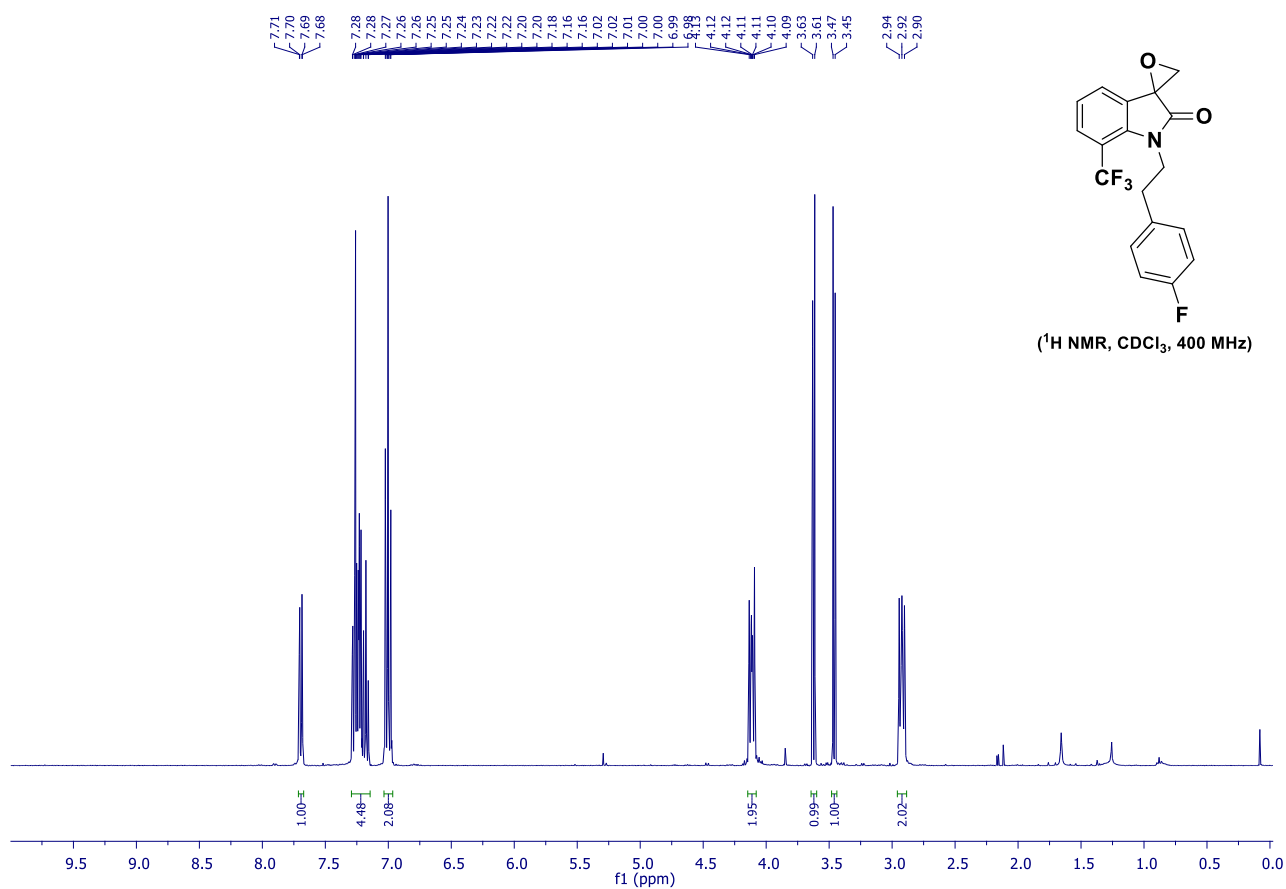
1-Benzyl-5-methoxyspiro[indole-3,2'-oxiran]-2(1*H*)-one (662)

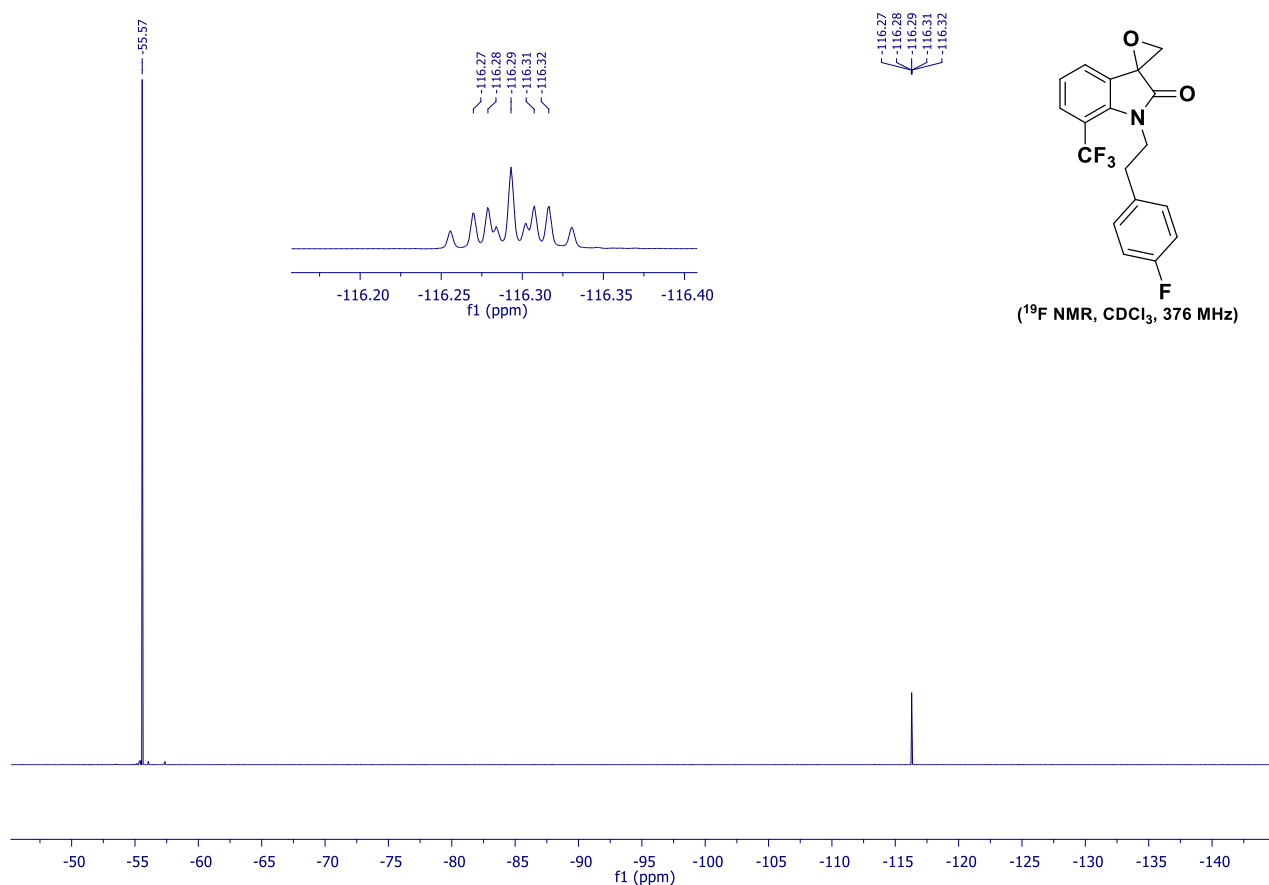


1-(Cyclopropylmethyl)-5-methoxyspiro[indole-3,2'-oxiran]-2(1H)-one (663)

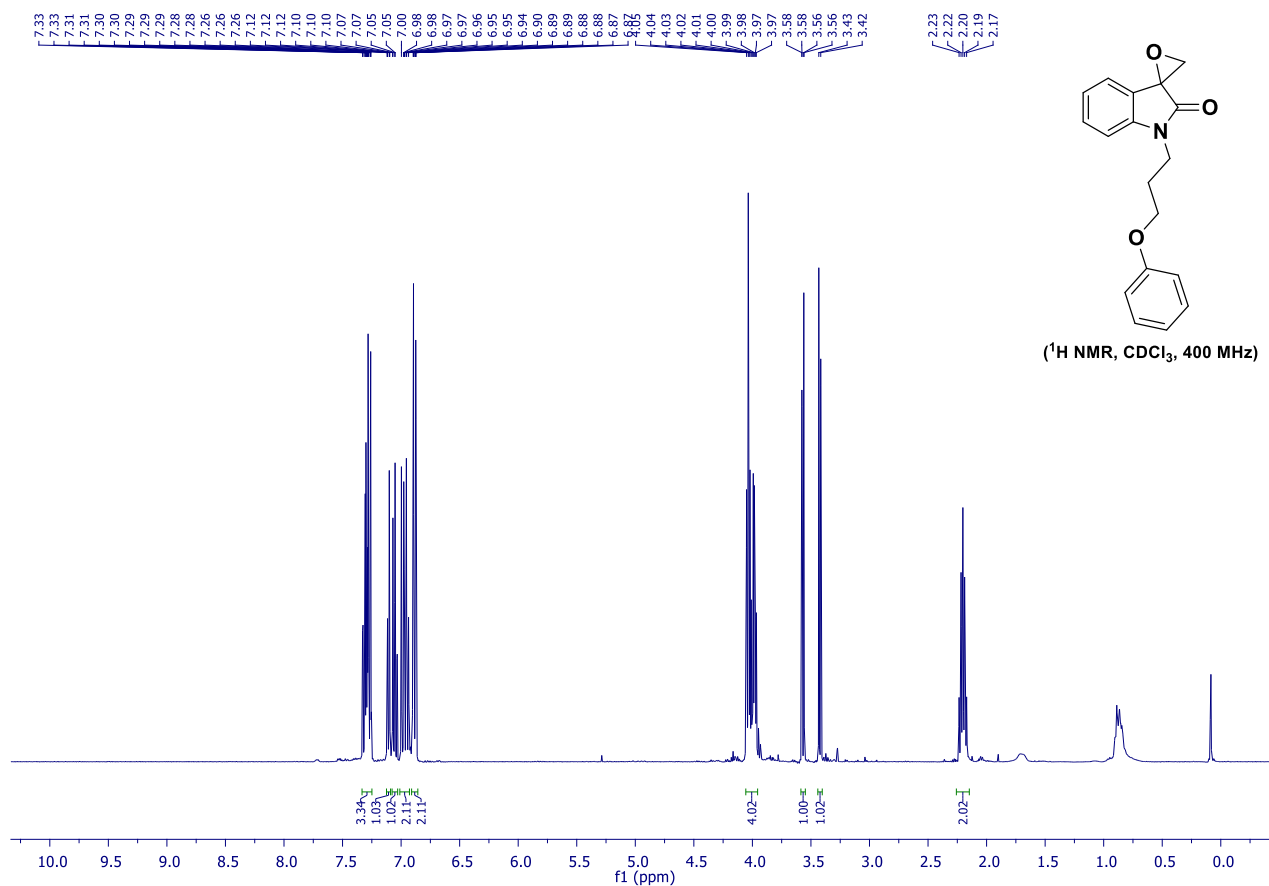


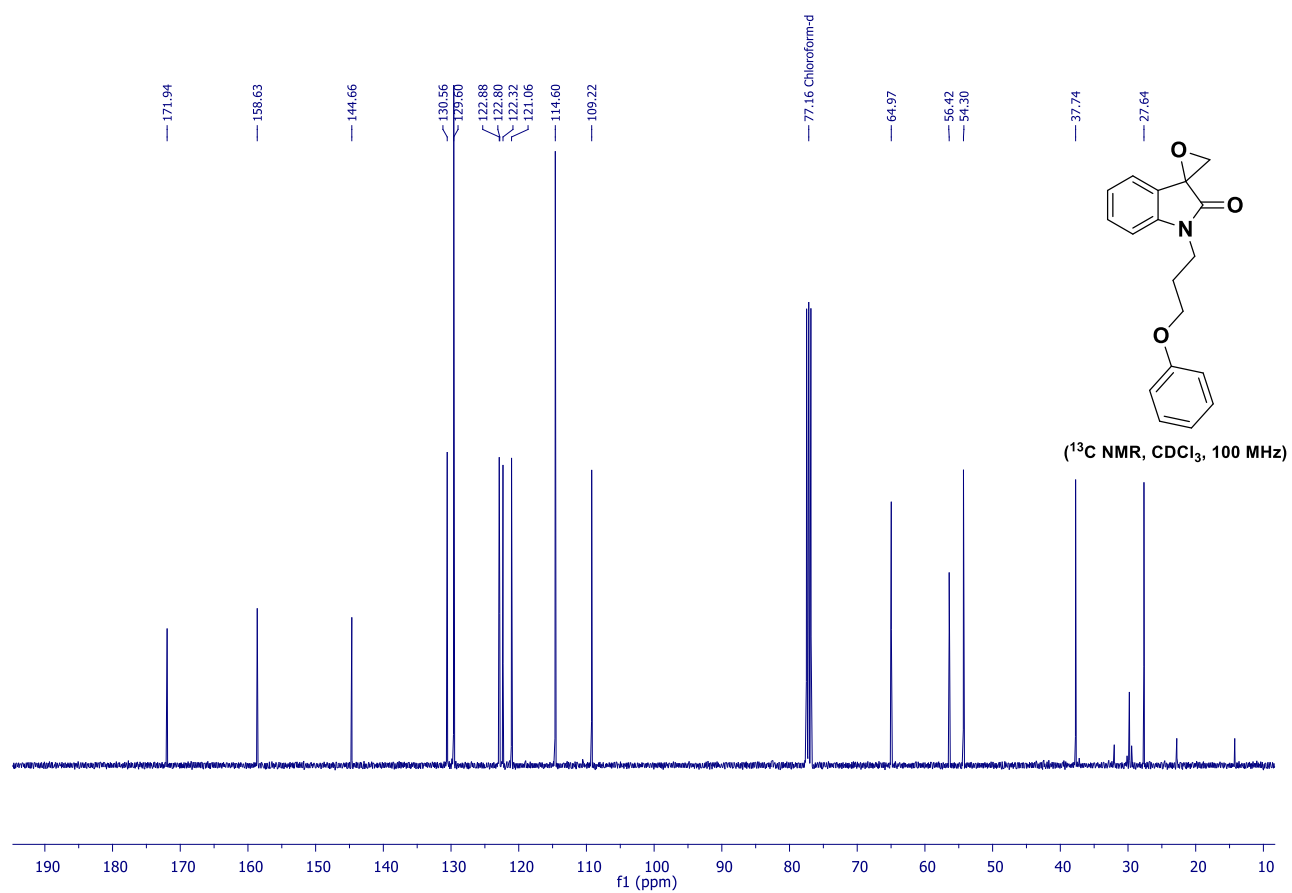
1-[2-(4-Fluorophenyl)ethyl]-7-(trifluoromethyl)spiro[indole-3,2'-oxiran]-2(1*H*)-one (664)





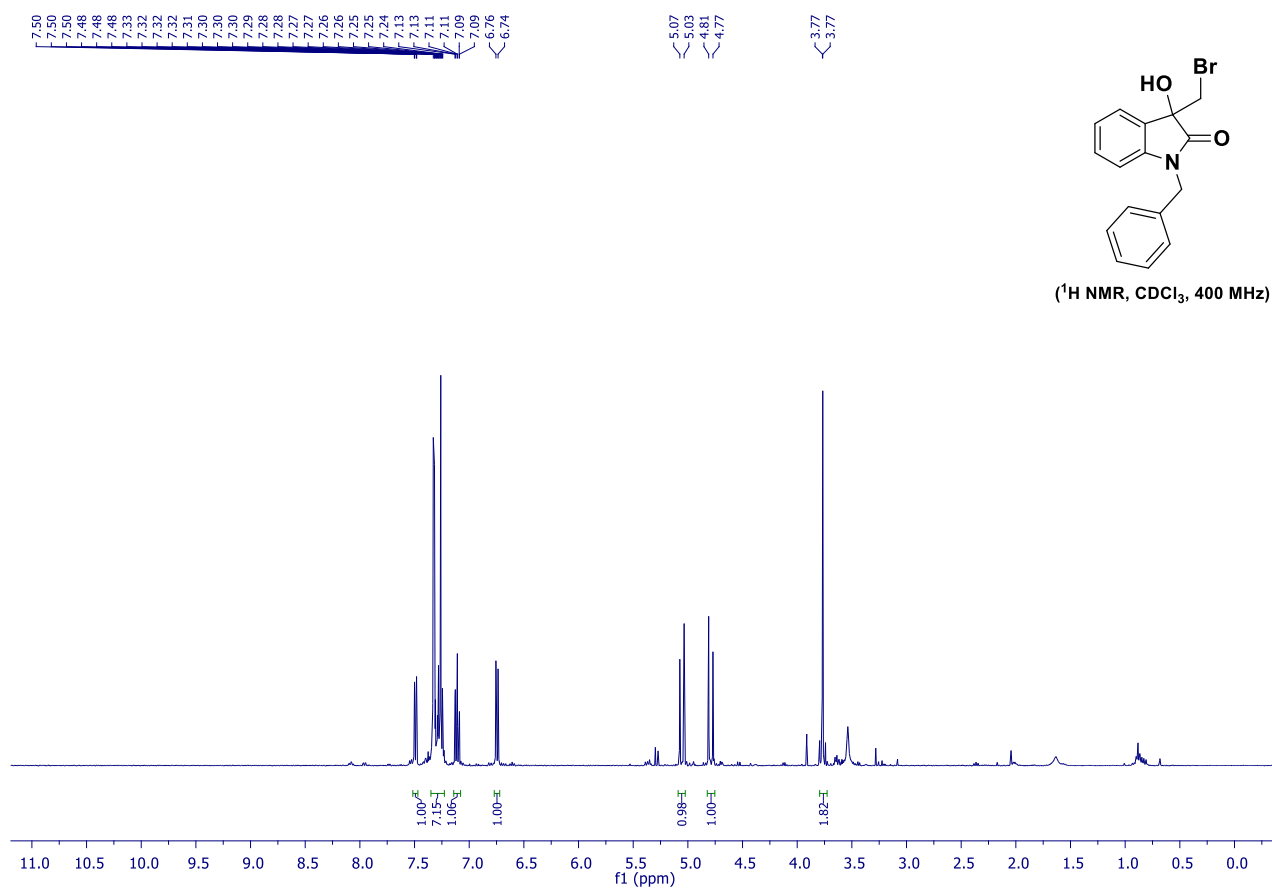
1-(3-Phenoxypropyl)spiro[indole-3,2'-oxiran]-2(1H)-one (665)

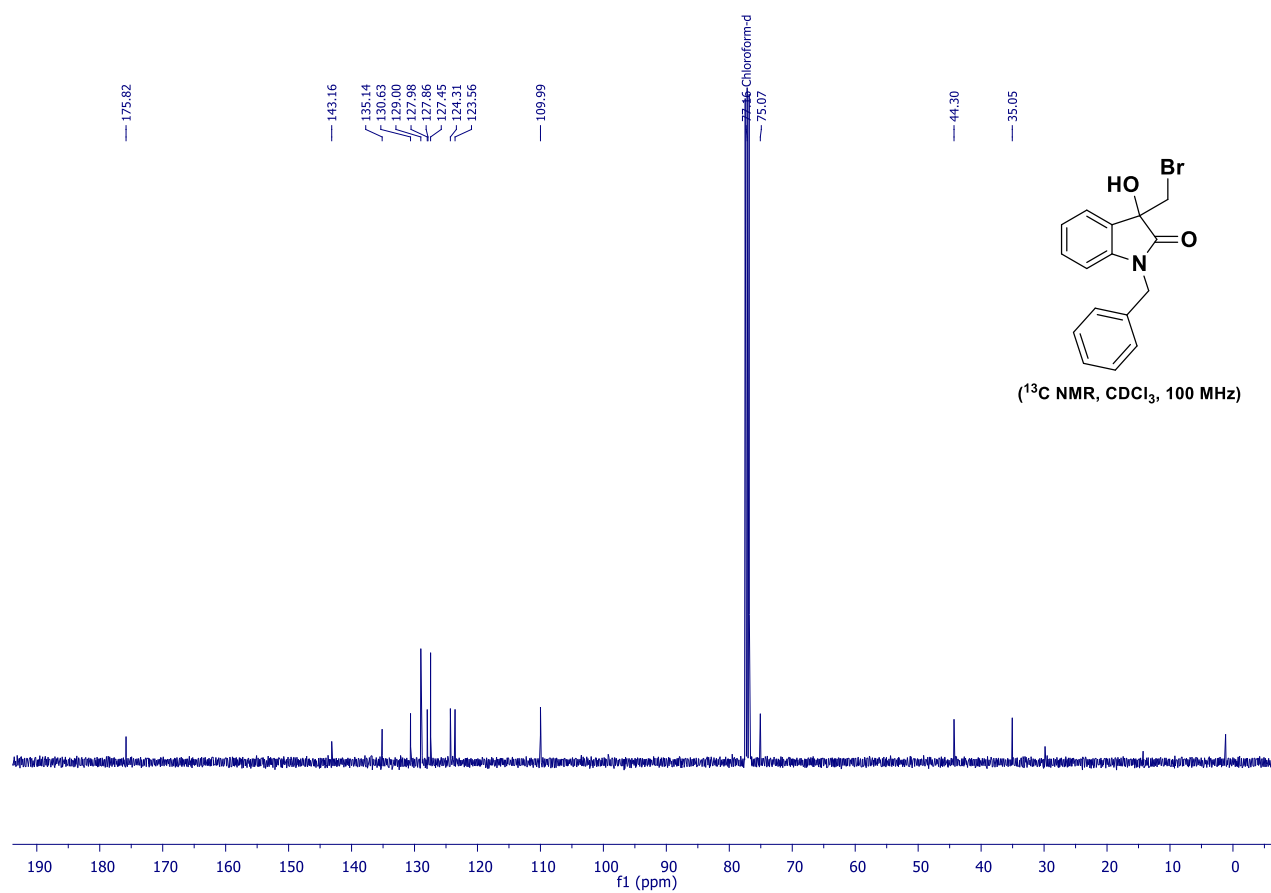




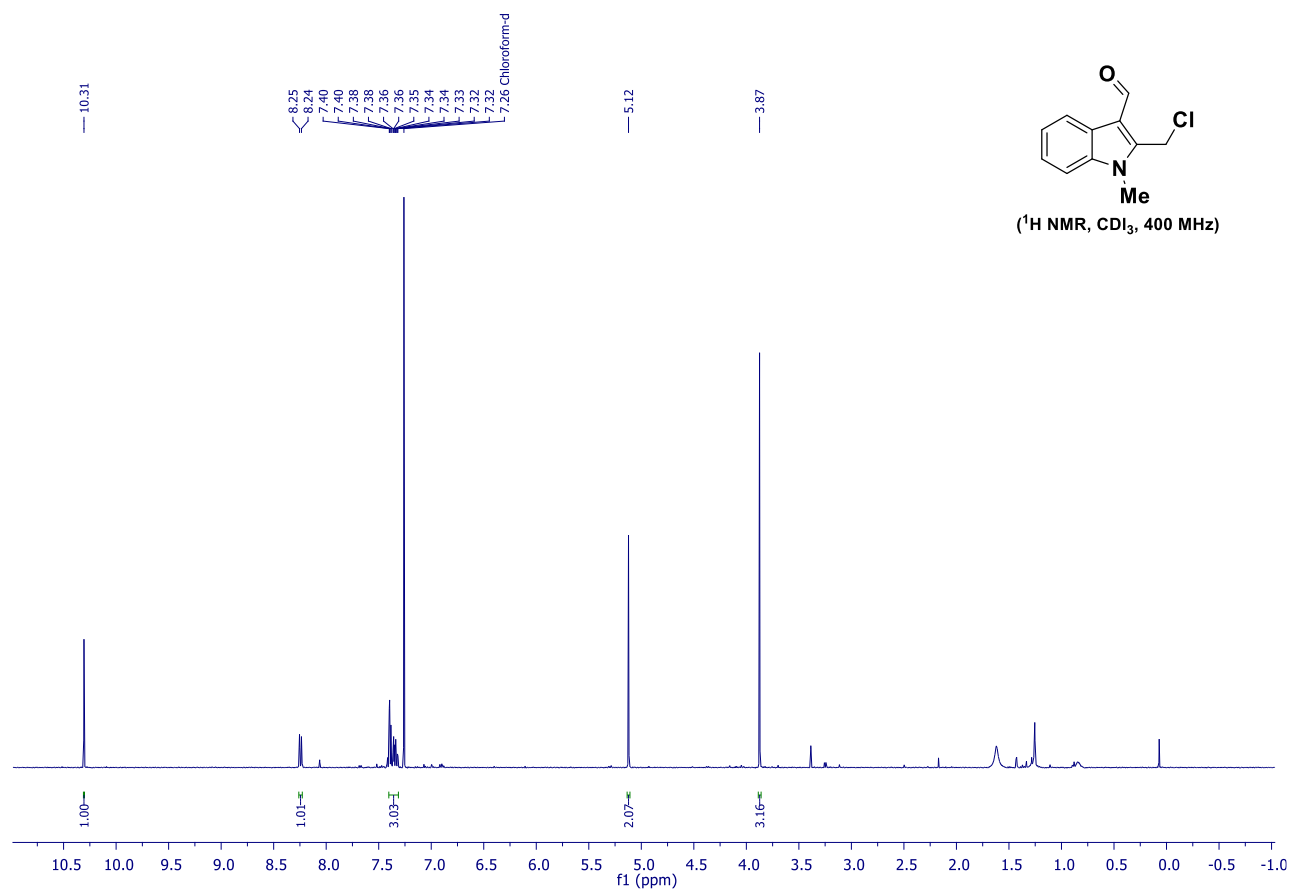
5.2.3.2 Carbaldehydes

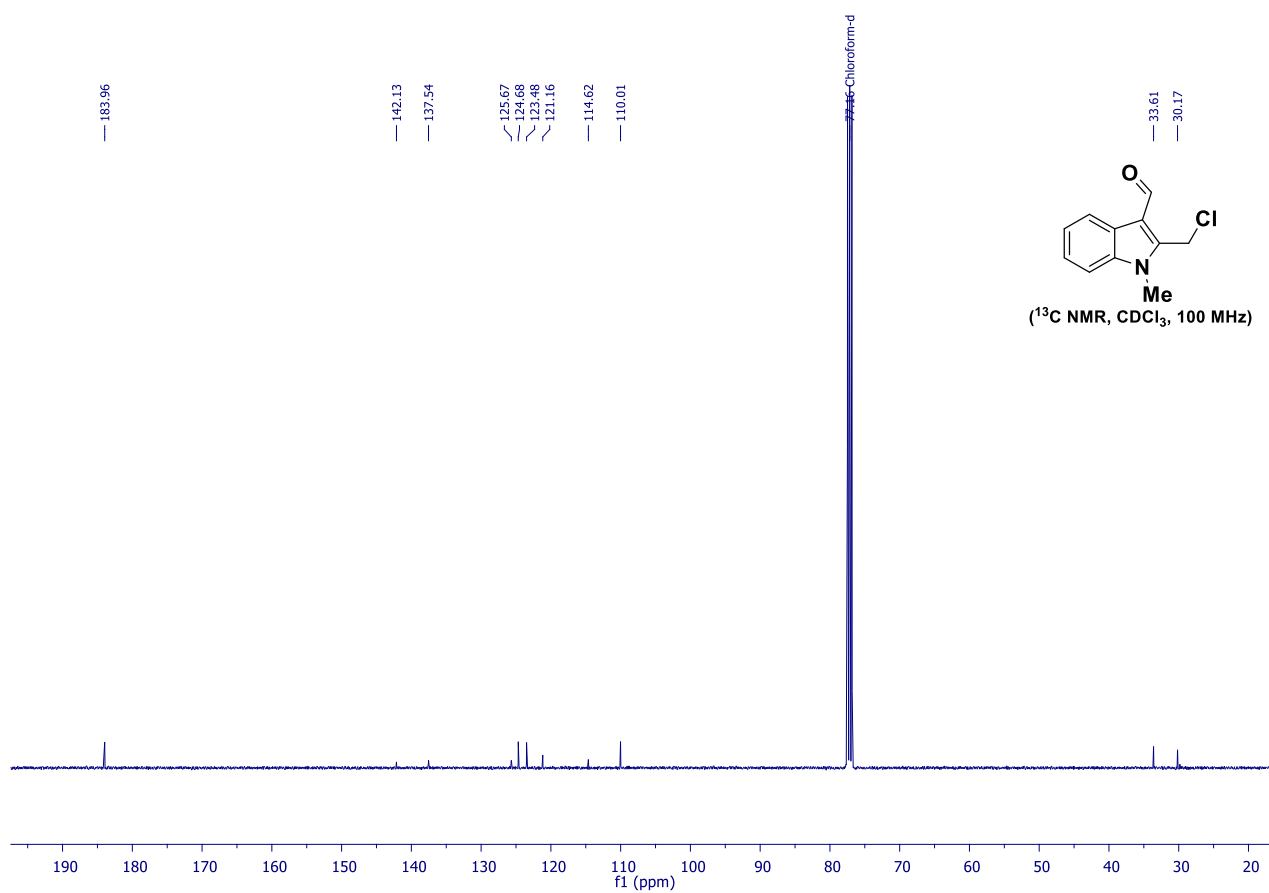
1-Benzyl-3-(bromomethyl)-3-hydroxy-1,3-dihydro-2H-indol-2-one (entry 13 of table 7)



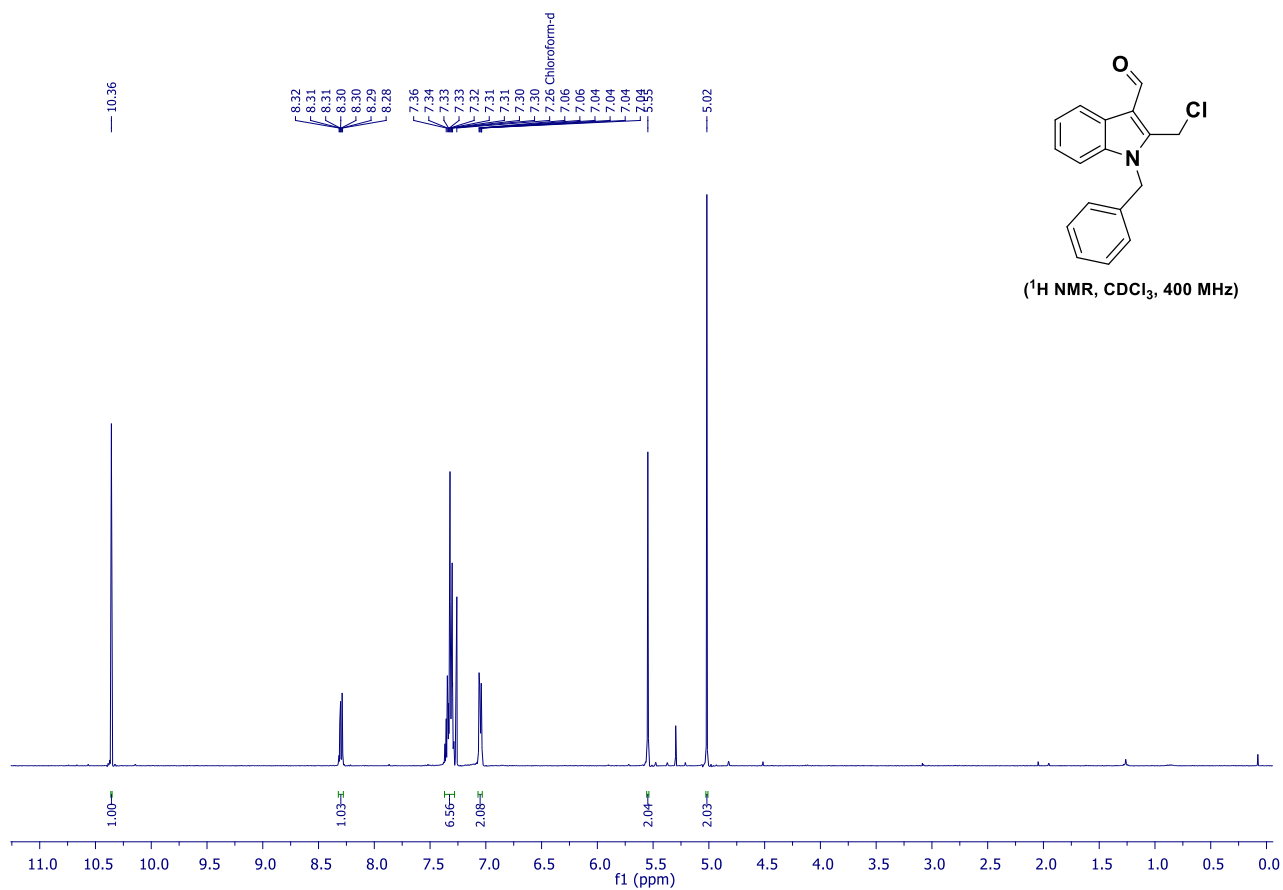


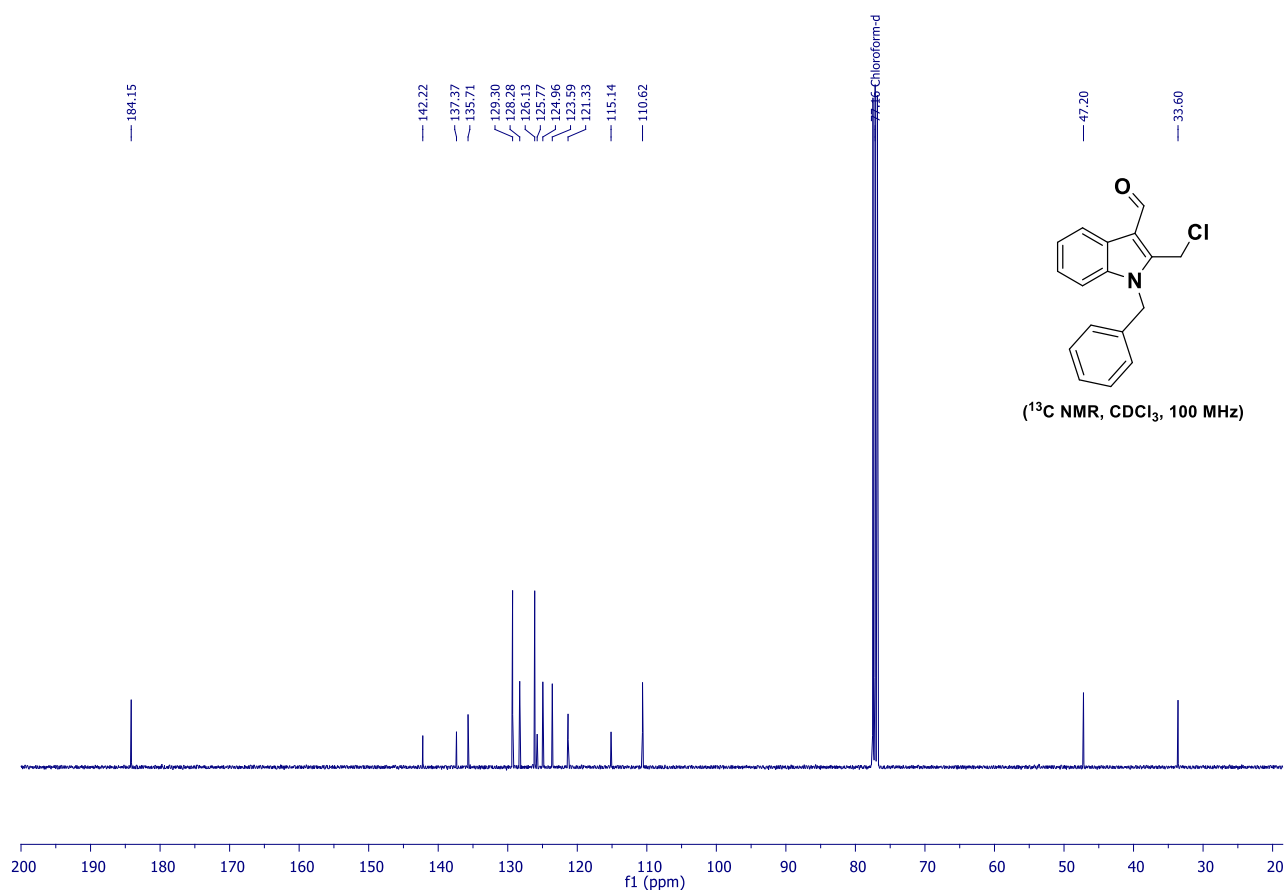
2- (Chloromethyl)-1-methyl-1H-indole-3-carbaldehyde (668)



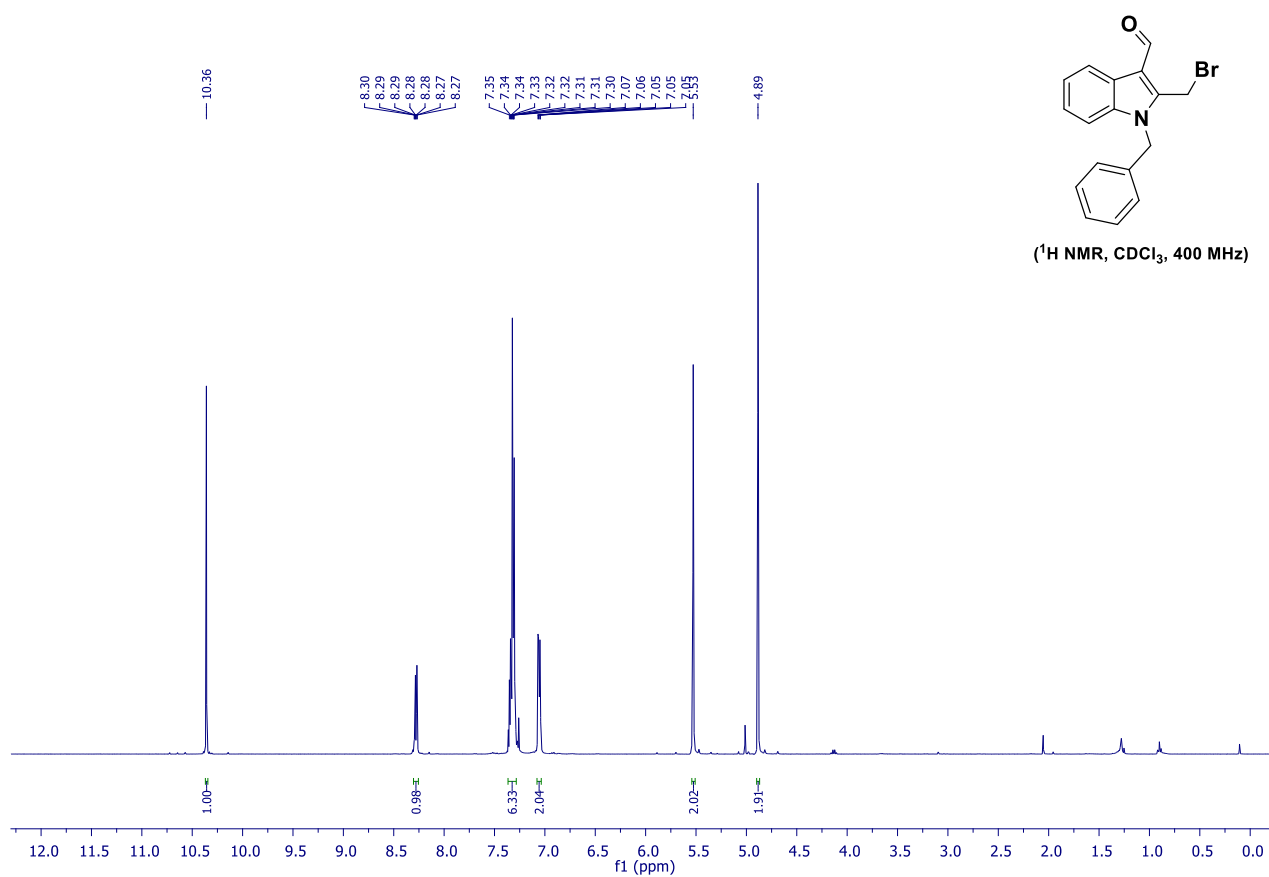


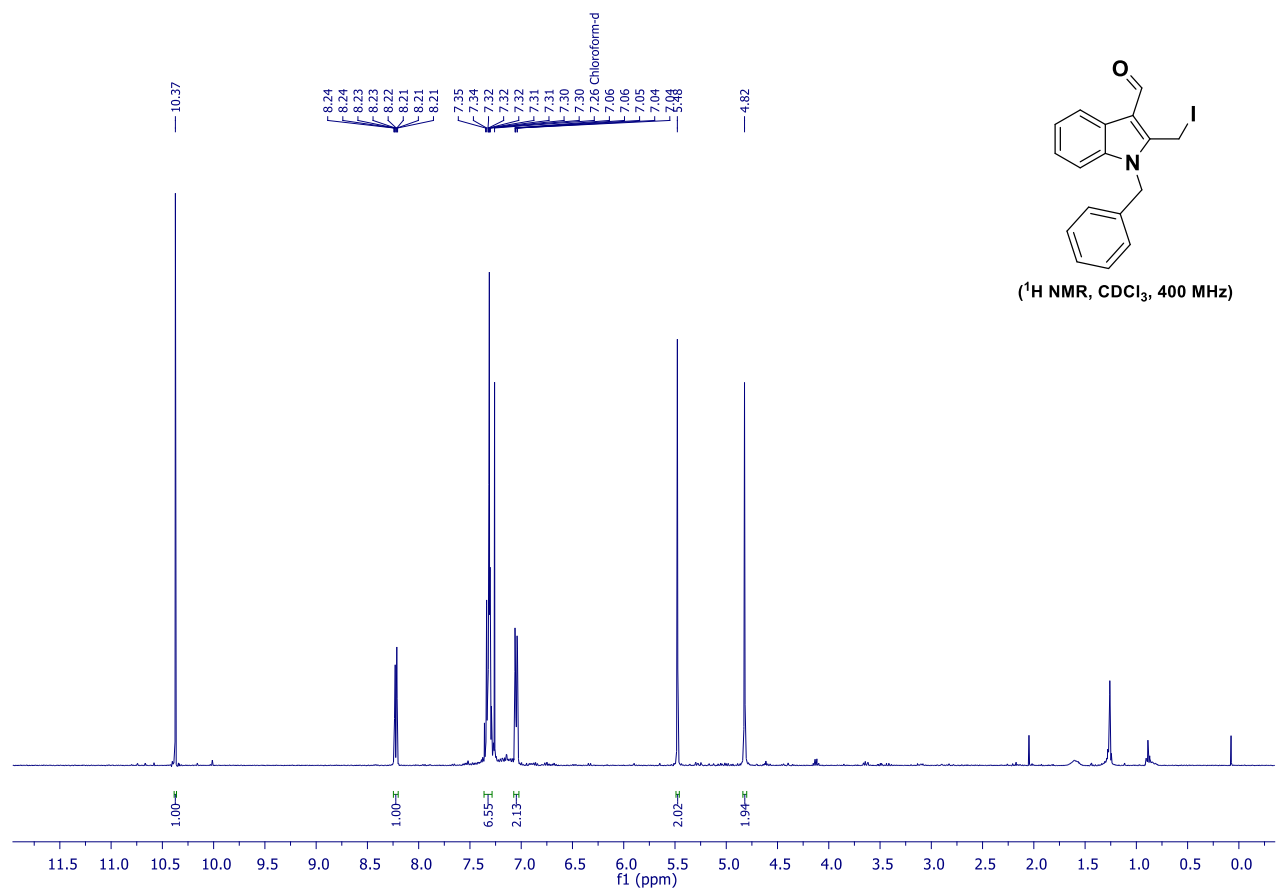
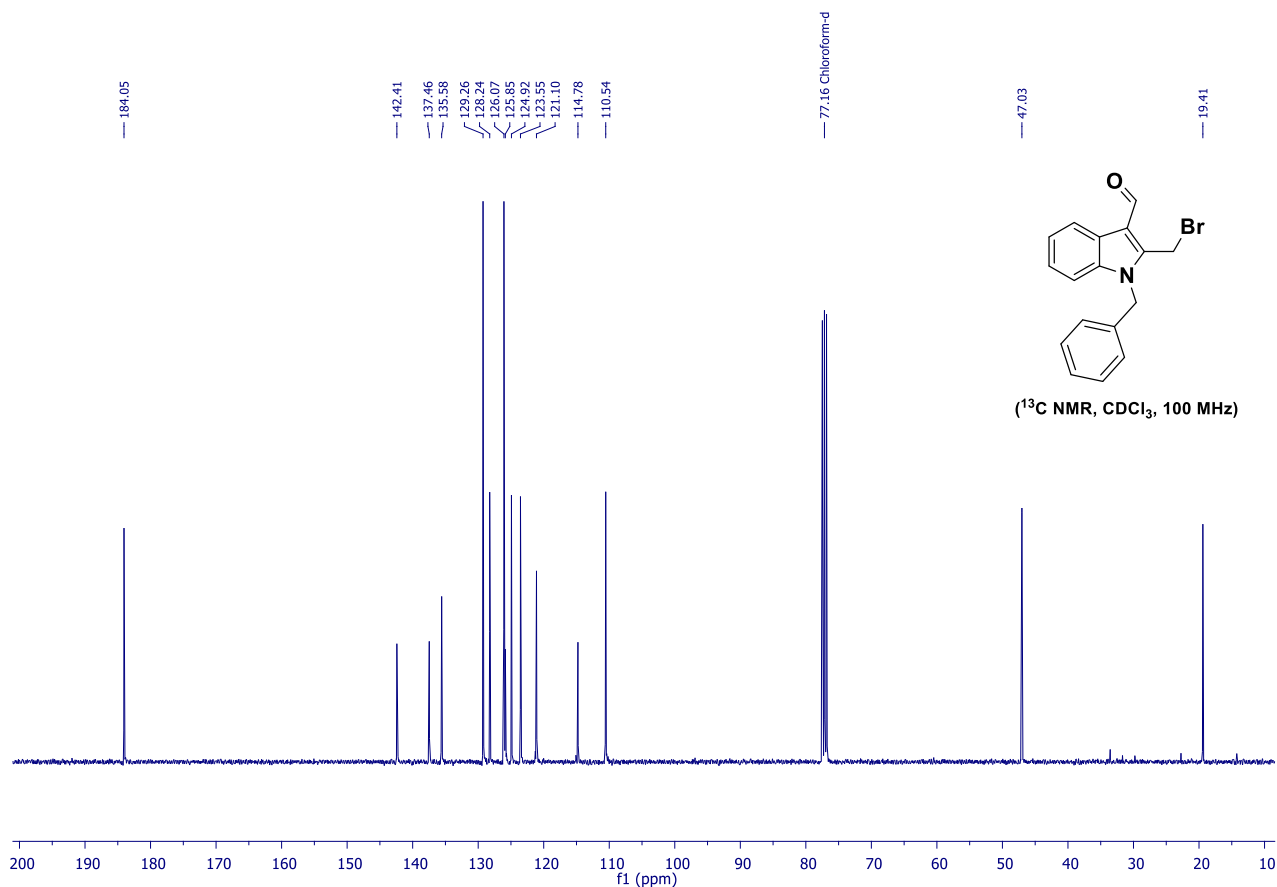
1-Benzyl-2-(chloromethyl)-1H-indole-3-carbaldehyde (669)

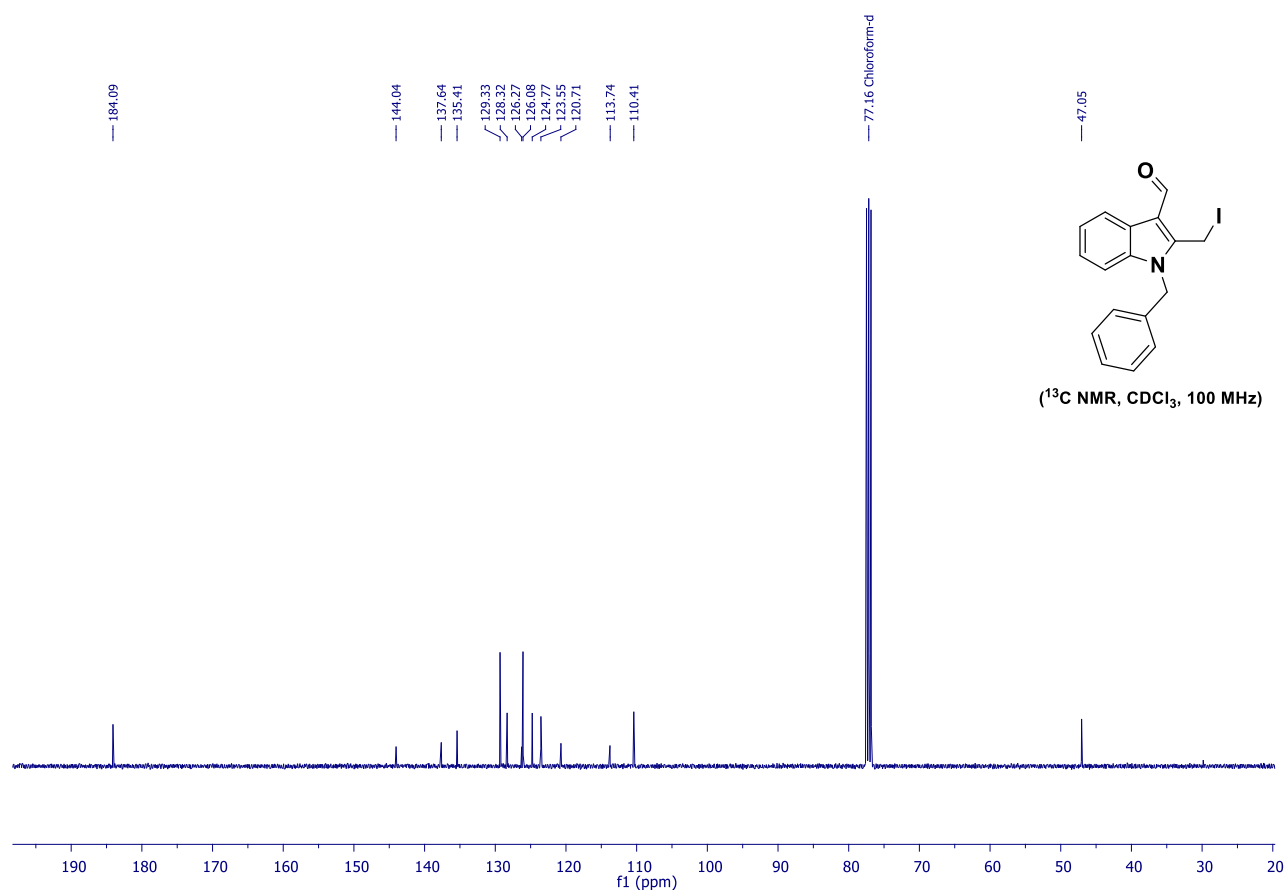




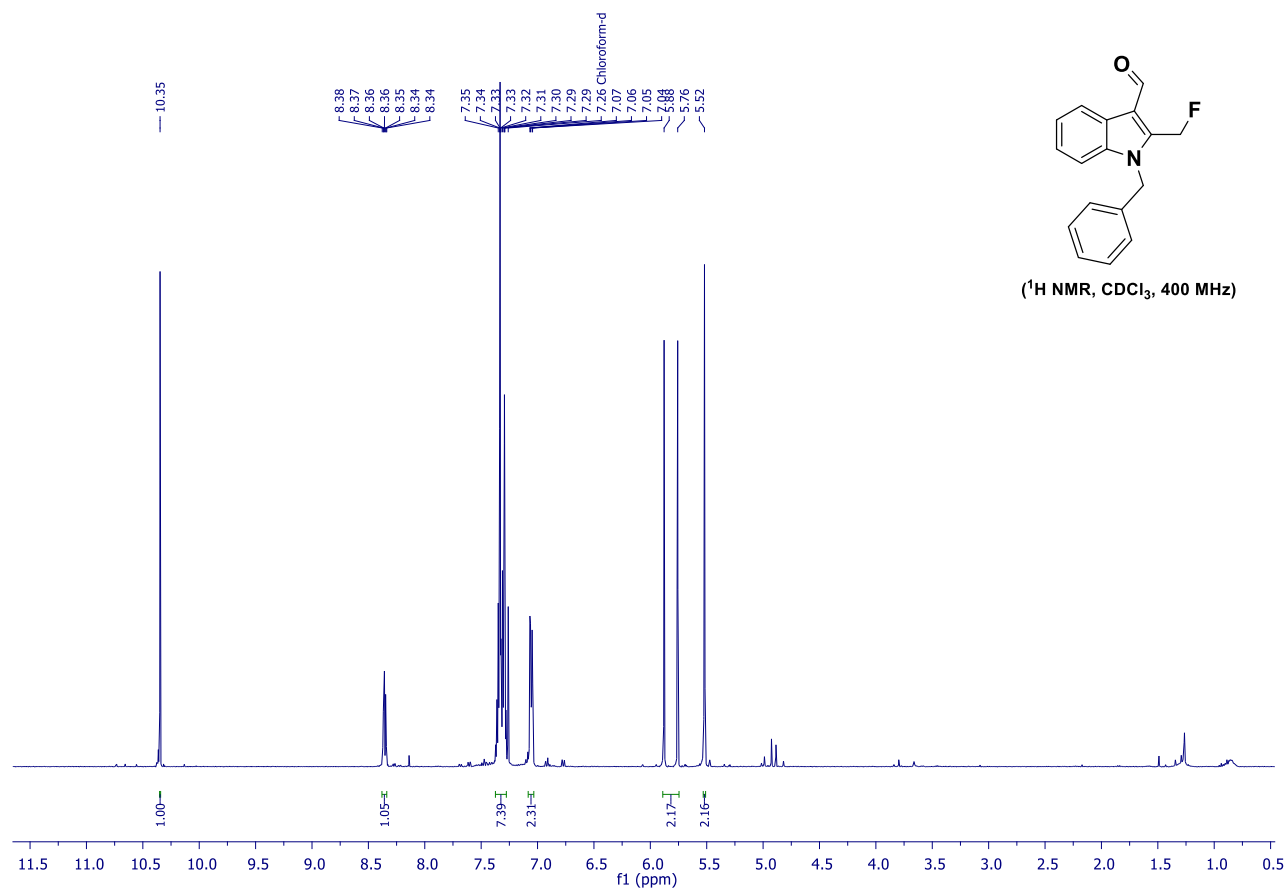
1-Benzyl-2-(bromomethyl)-1H-indole-3-carbaldehyde (670)

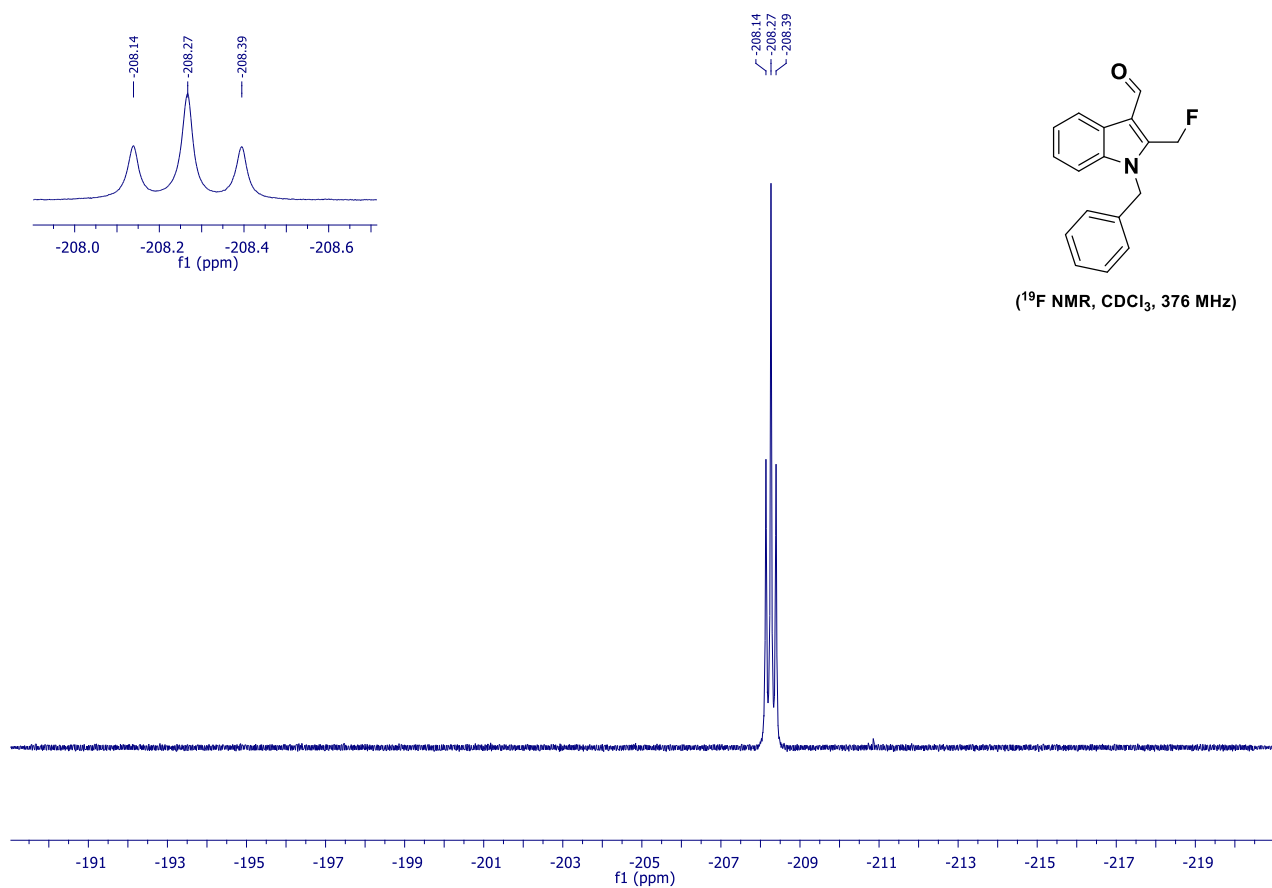
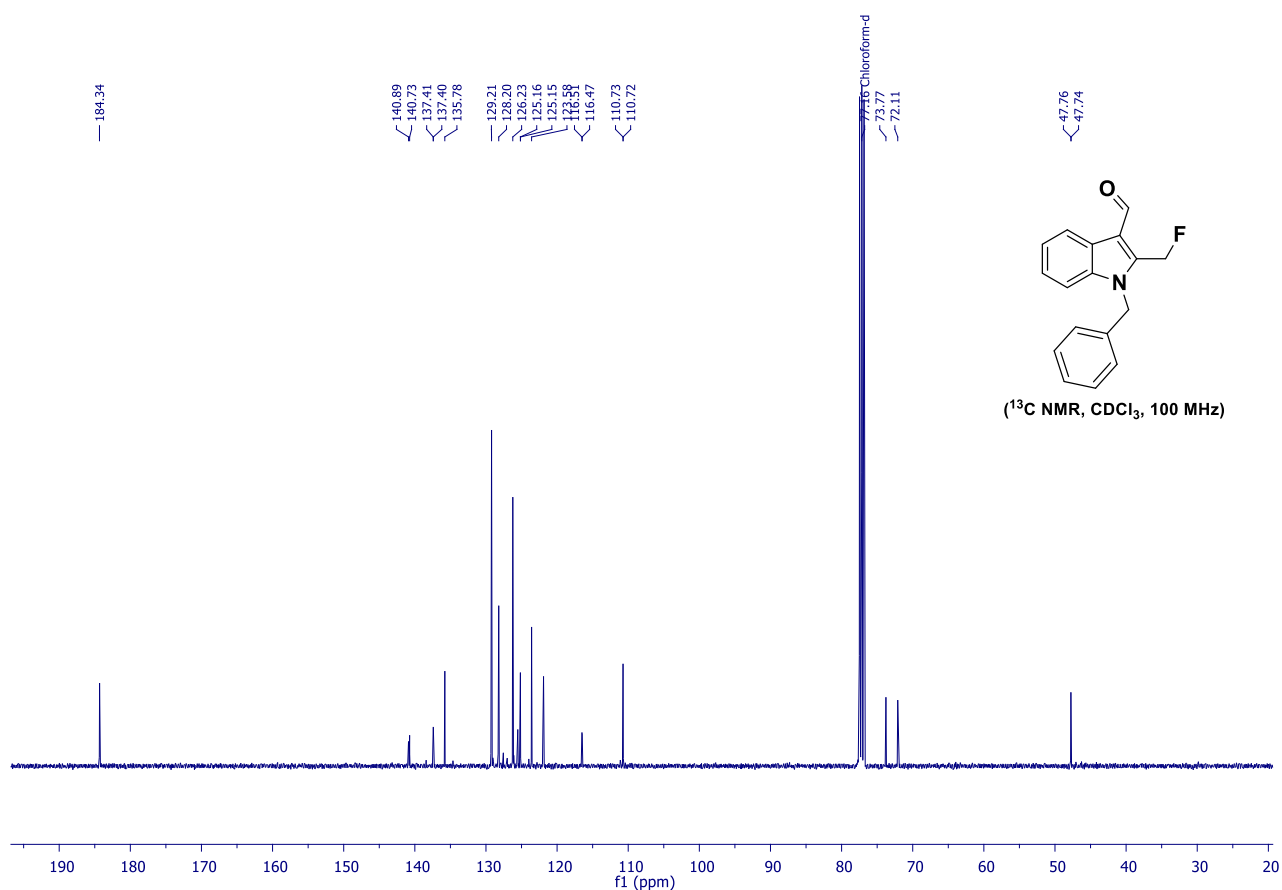




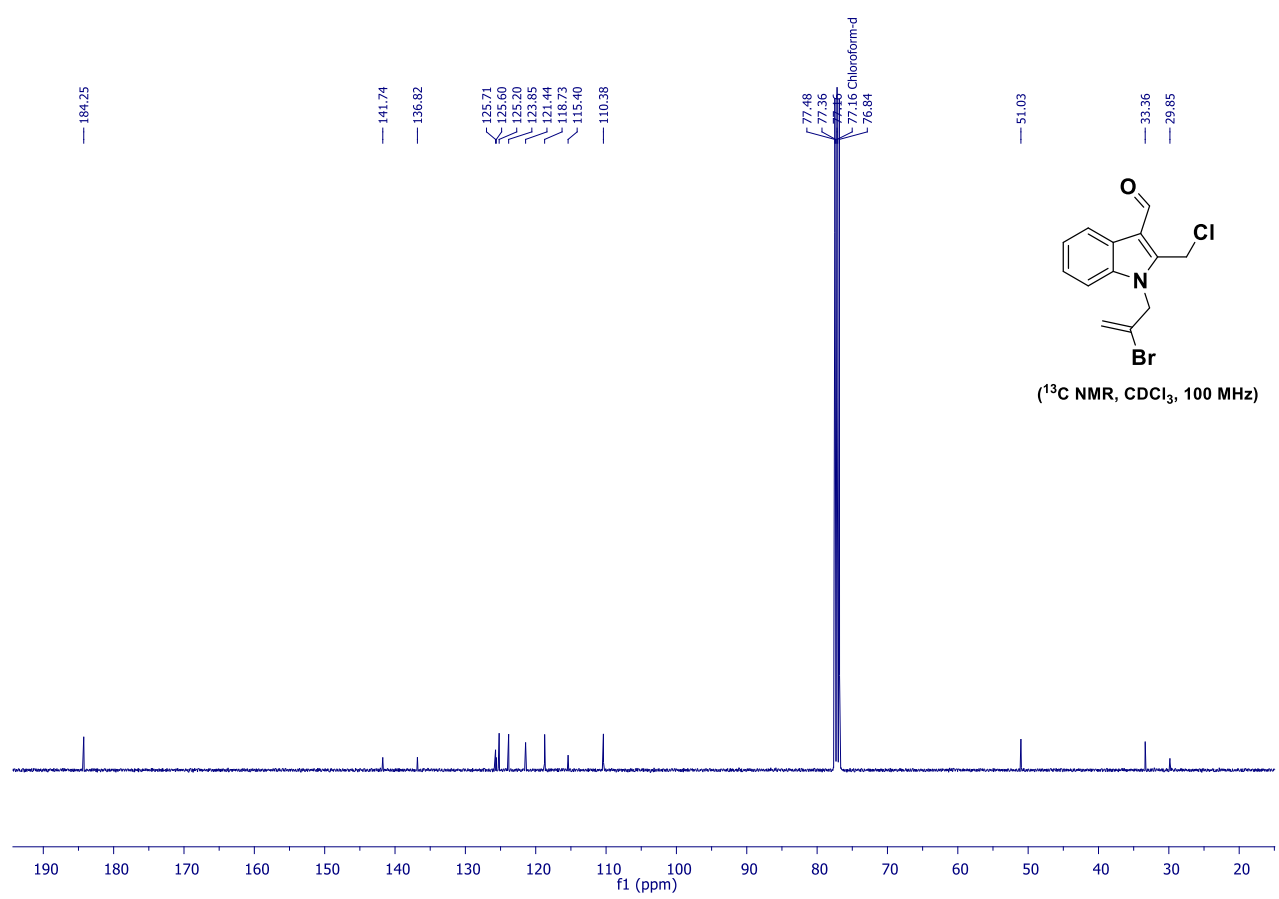
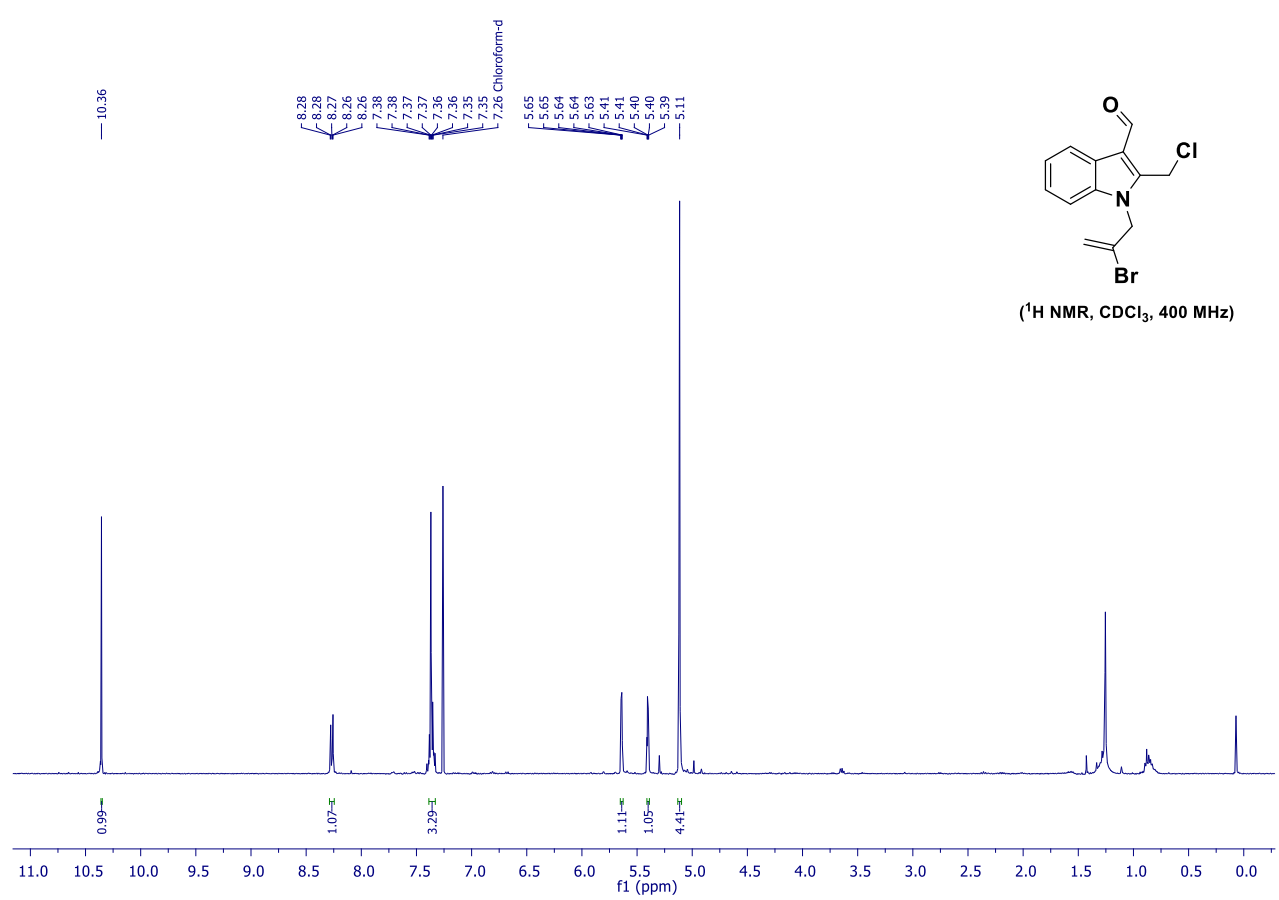


1-Benzyl-2-(fluoromethyl)-1H-indole-3-carbaldehyde (672)

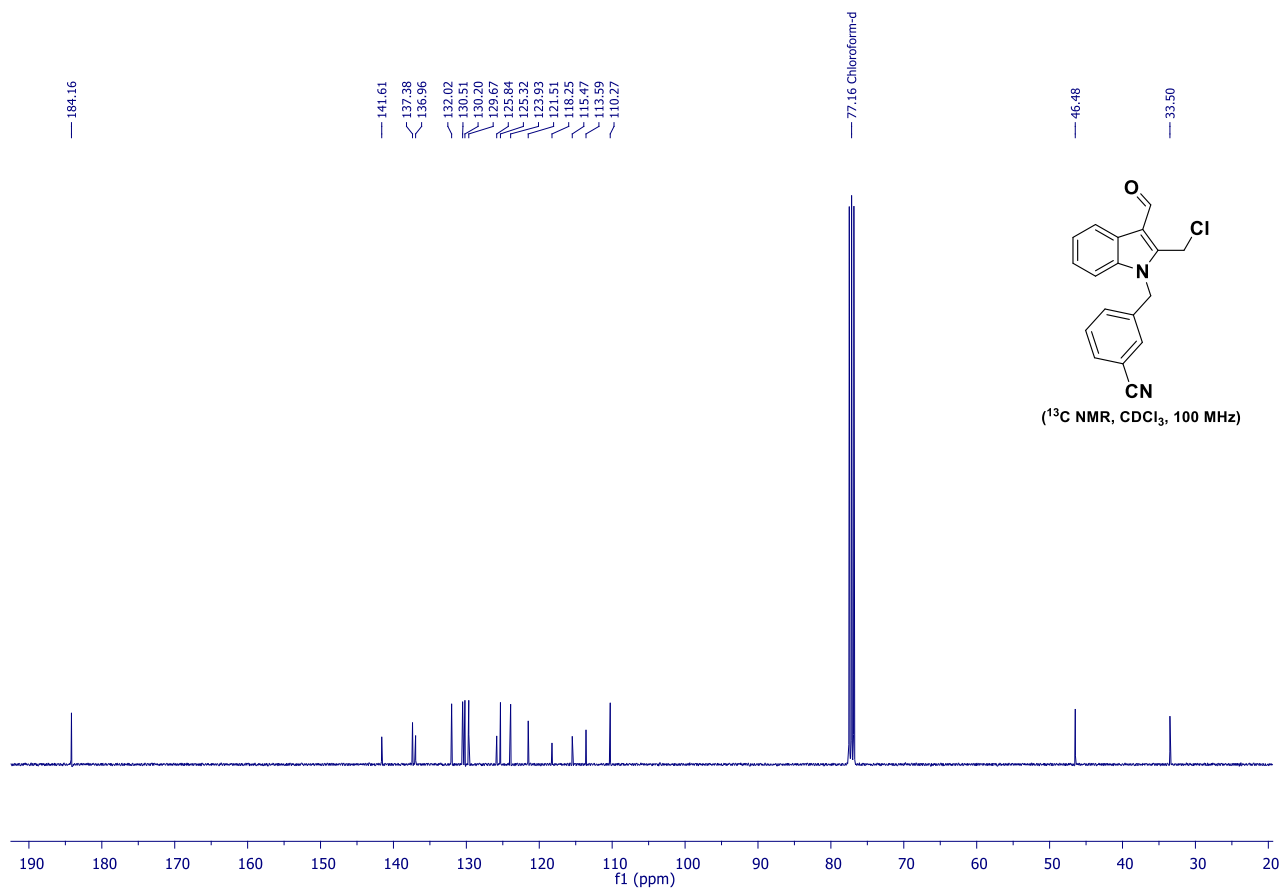
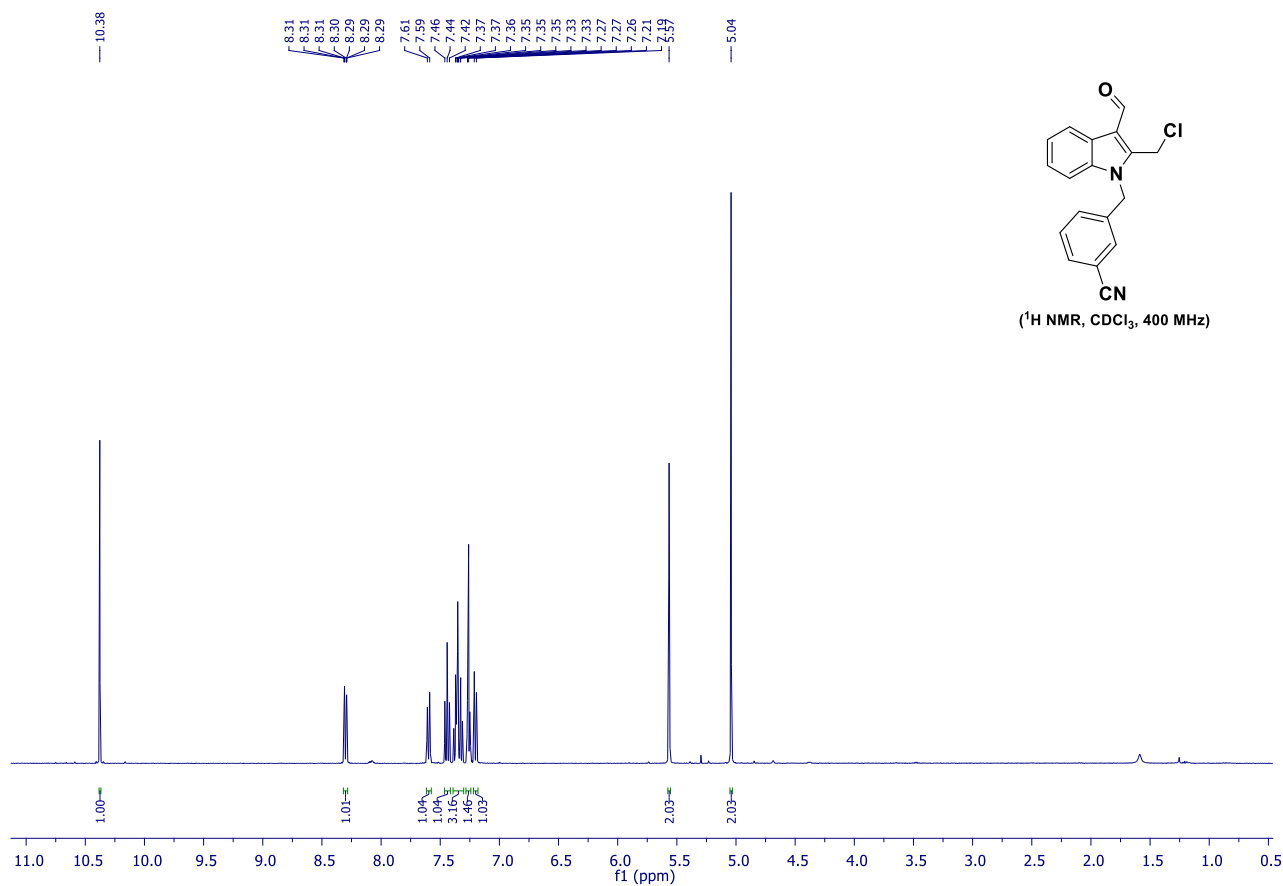




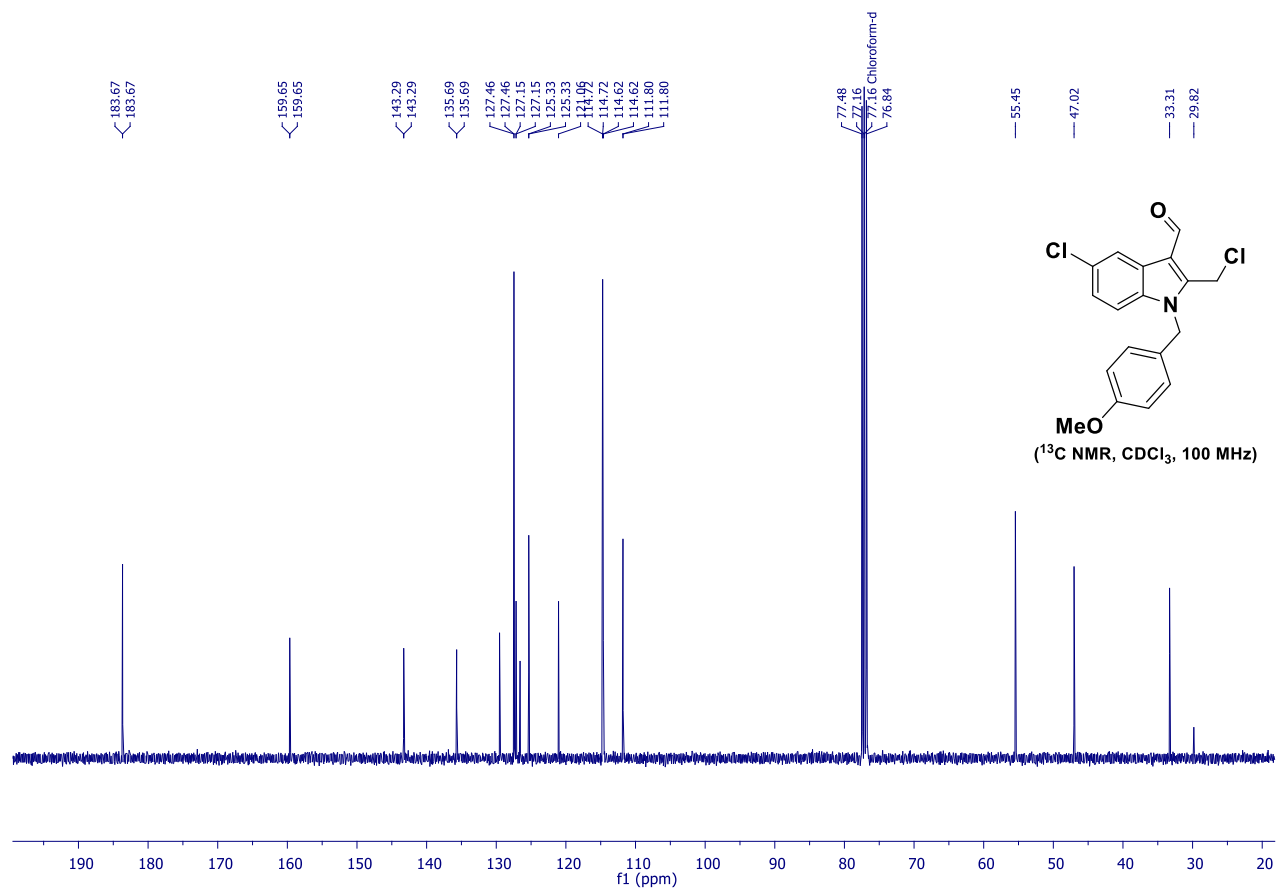
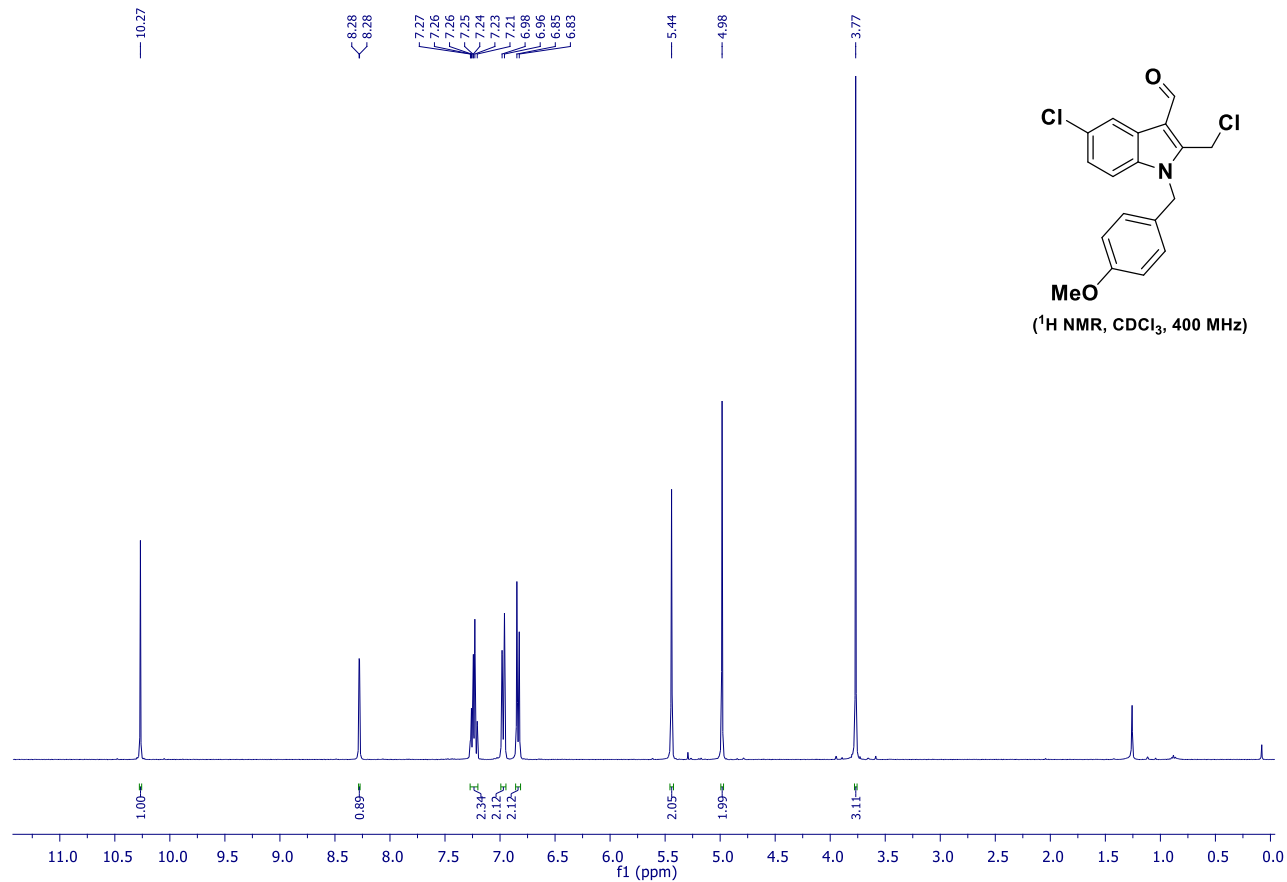
1-(2-Bromo-2-propen-1-yl)-2-(chloromethyl)-1H-indole-3-carbaldehyde (673)



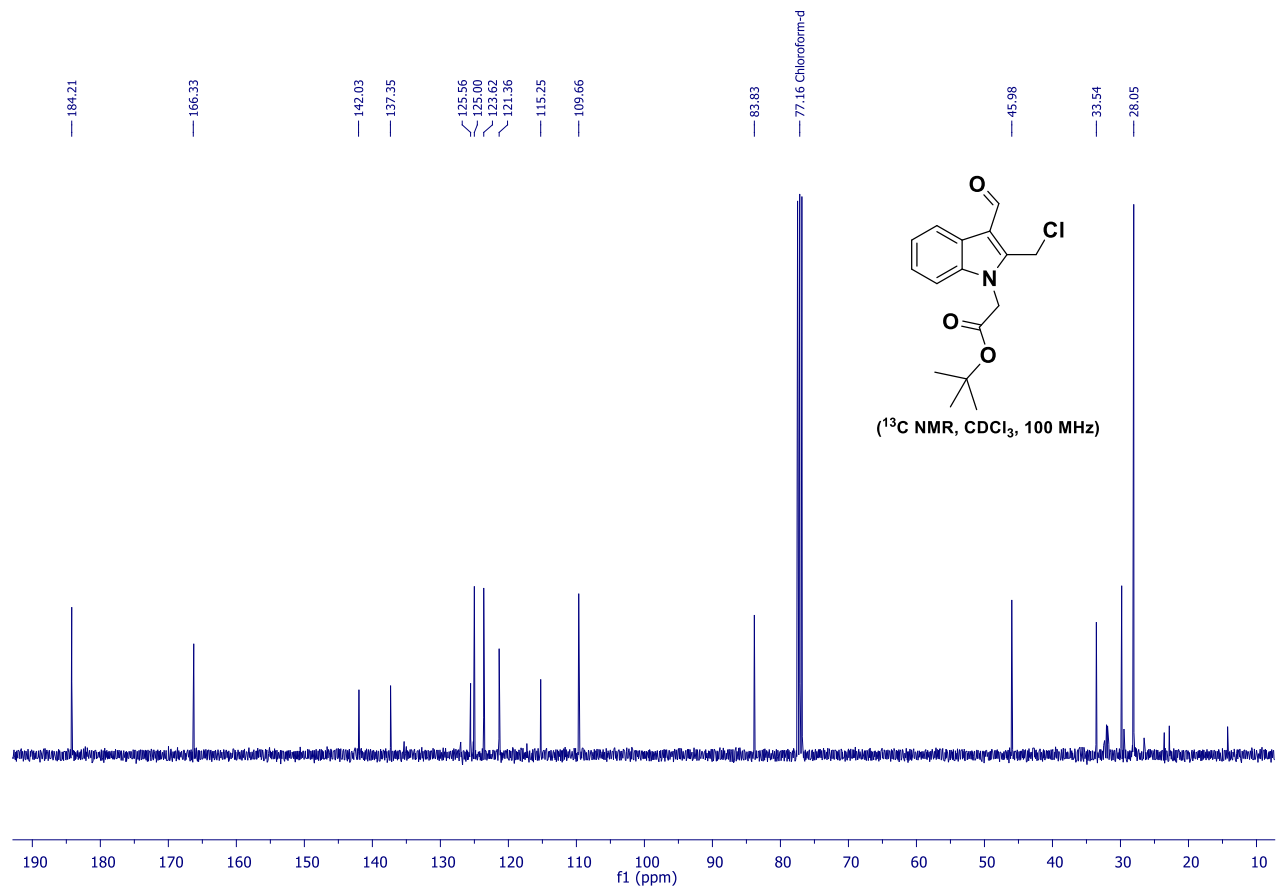
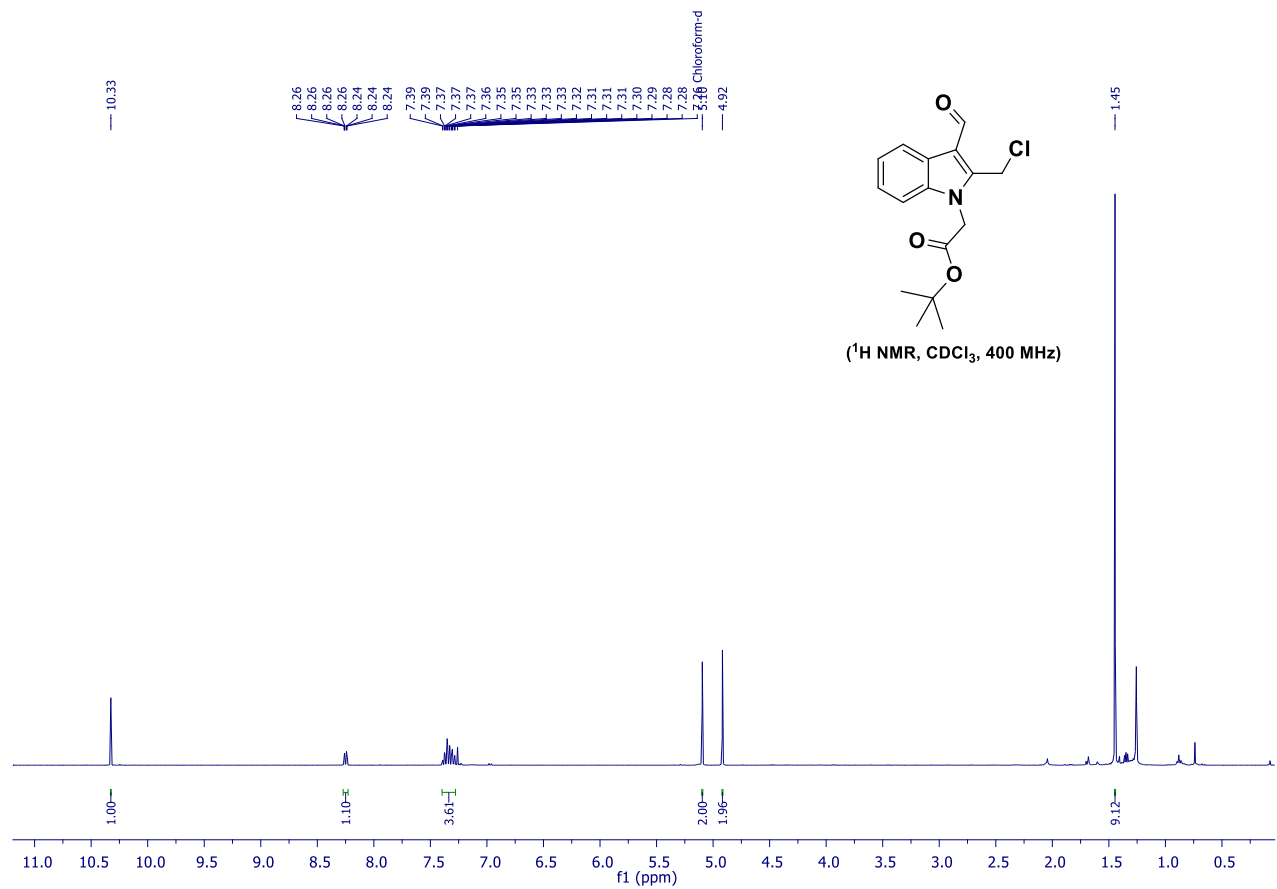
3-{[2-(Chloromethyl)-3-formyl-1H-indol-1-yl] methyl} benzonitrile (674)



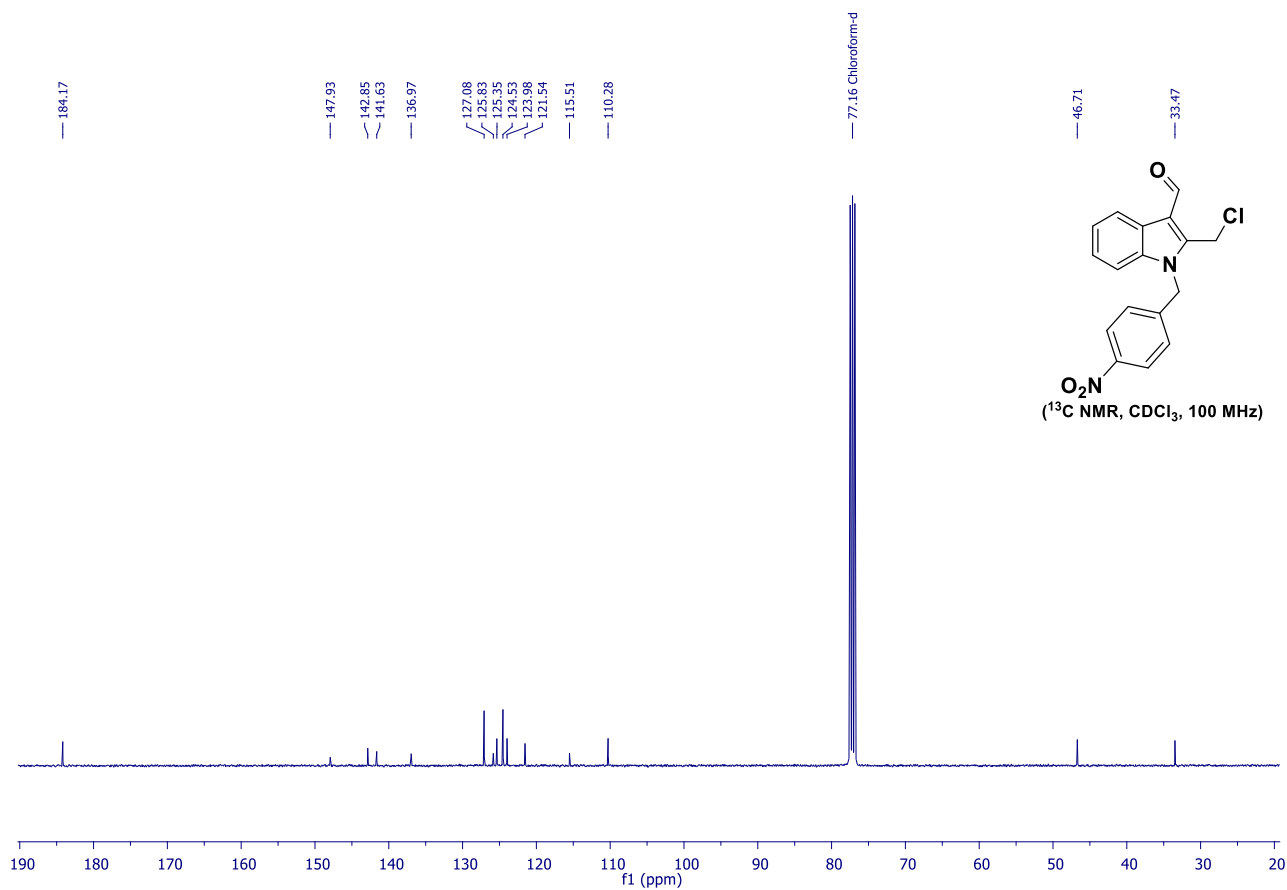
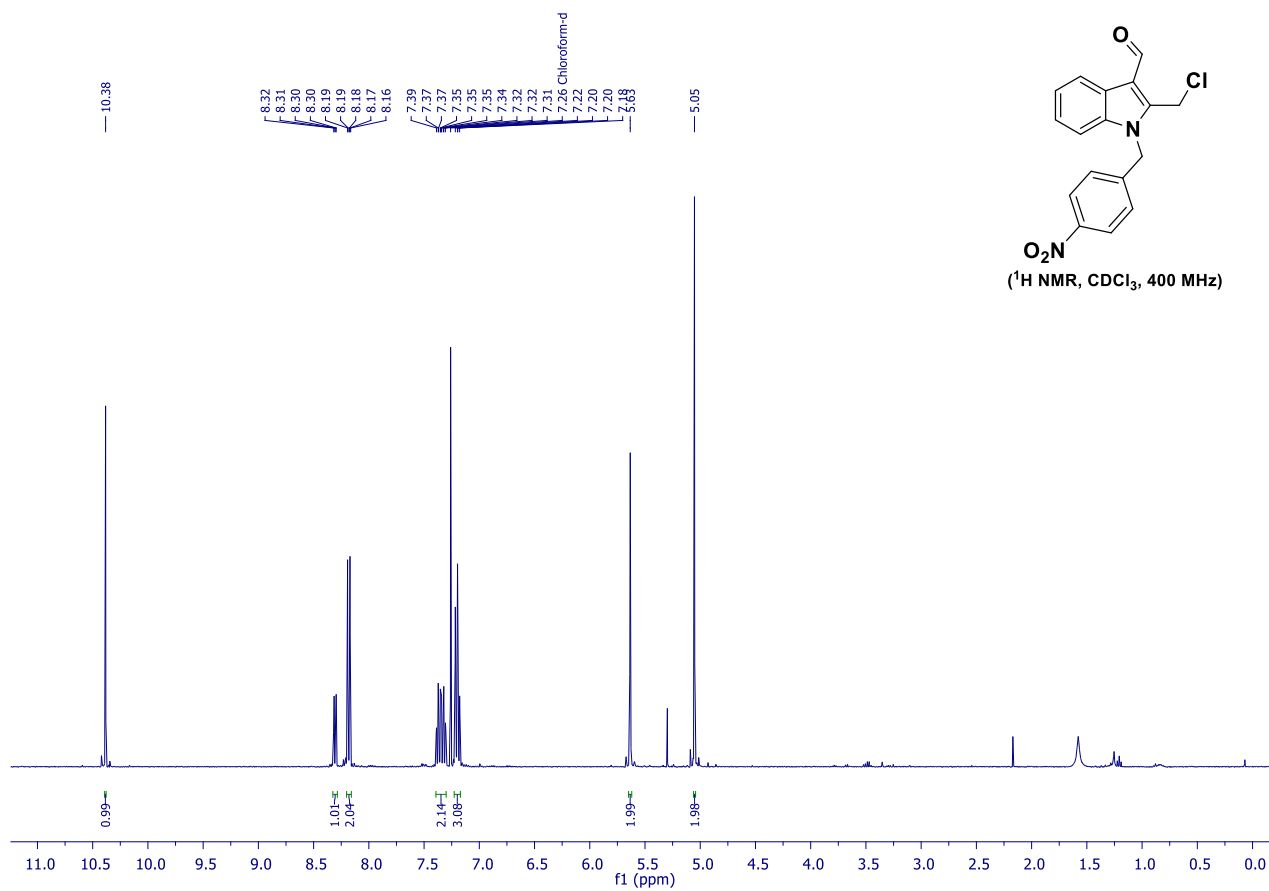
2-(Chloromethyl)-1-(4-methoxybenzyl)-1H-indole-3-carbaldehyde (675)



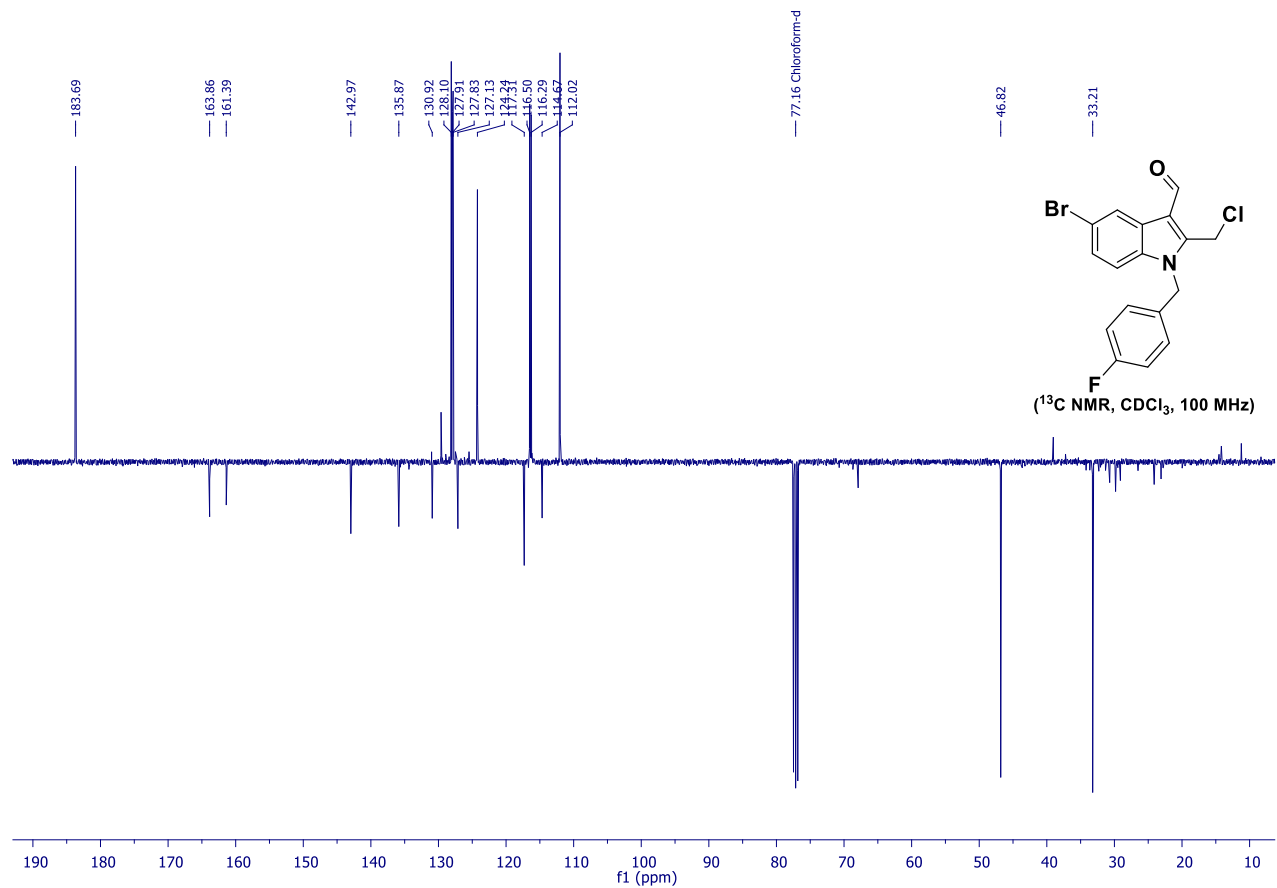
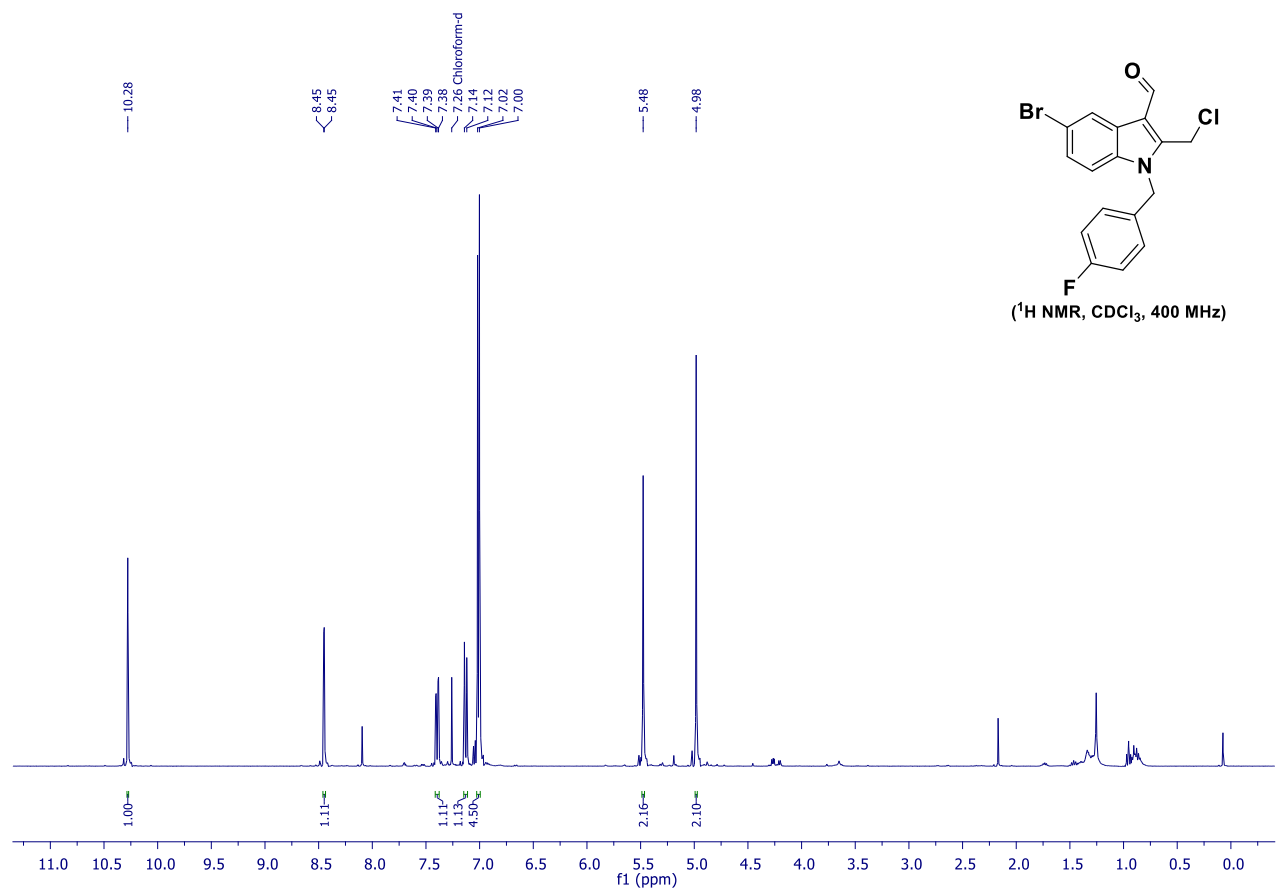
2-Methyl-2-propanyl [2-(chloromethyl)-3-formyl-1H-indol-1-yl] acetate (676)

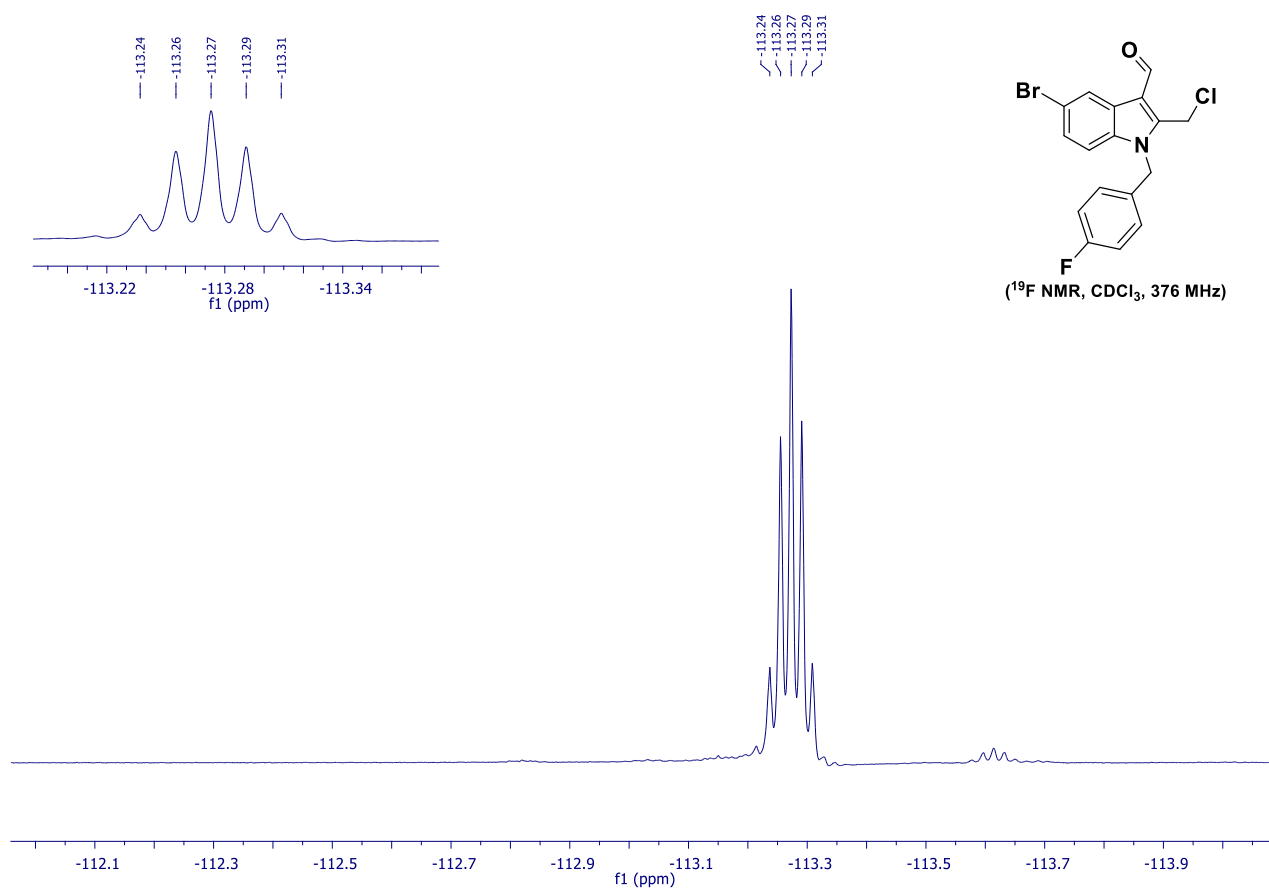


2-(Chloromethyl)-1-(4-nitrobenzyl)-1H-indol-3-carbaldehyde (677)

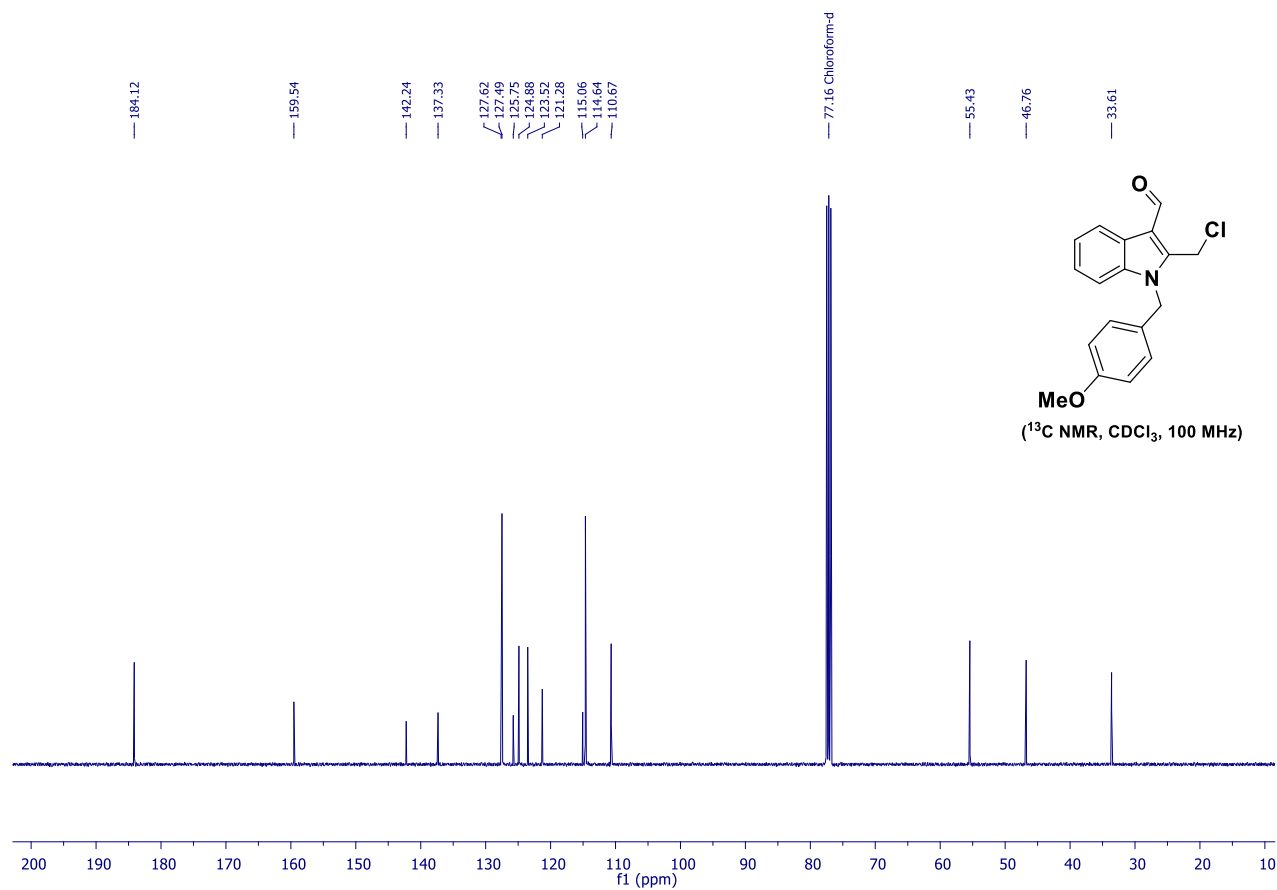
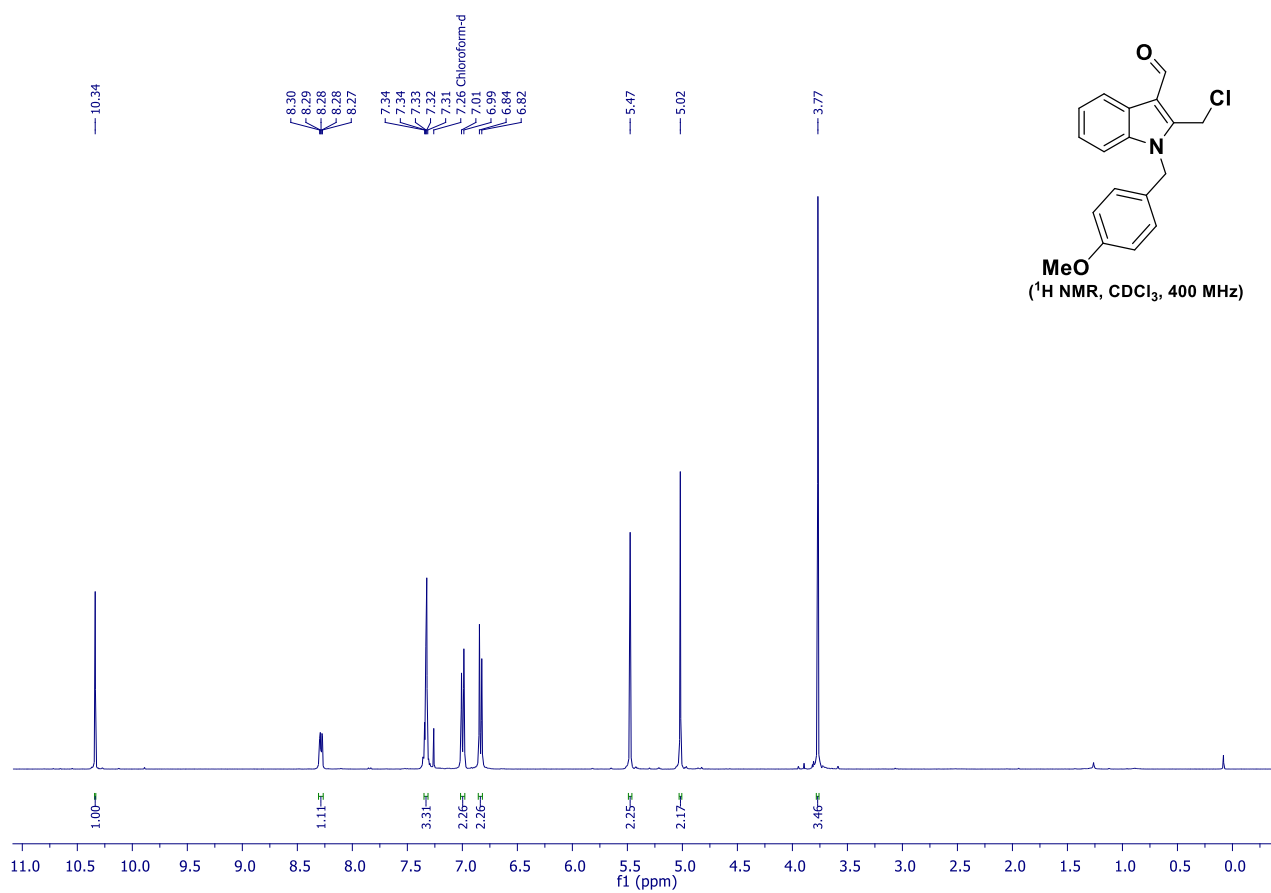


5-Bromo-2-(chloromethyl)-1-(4-fluorobenzyl)-1H-indole-3-carbaldehyde (678)

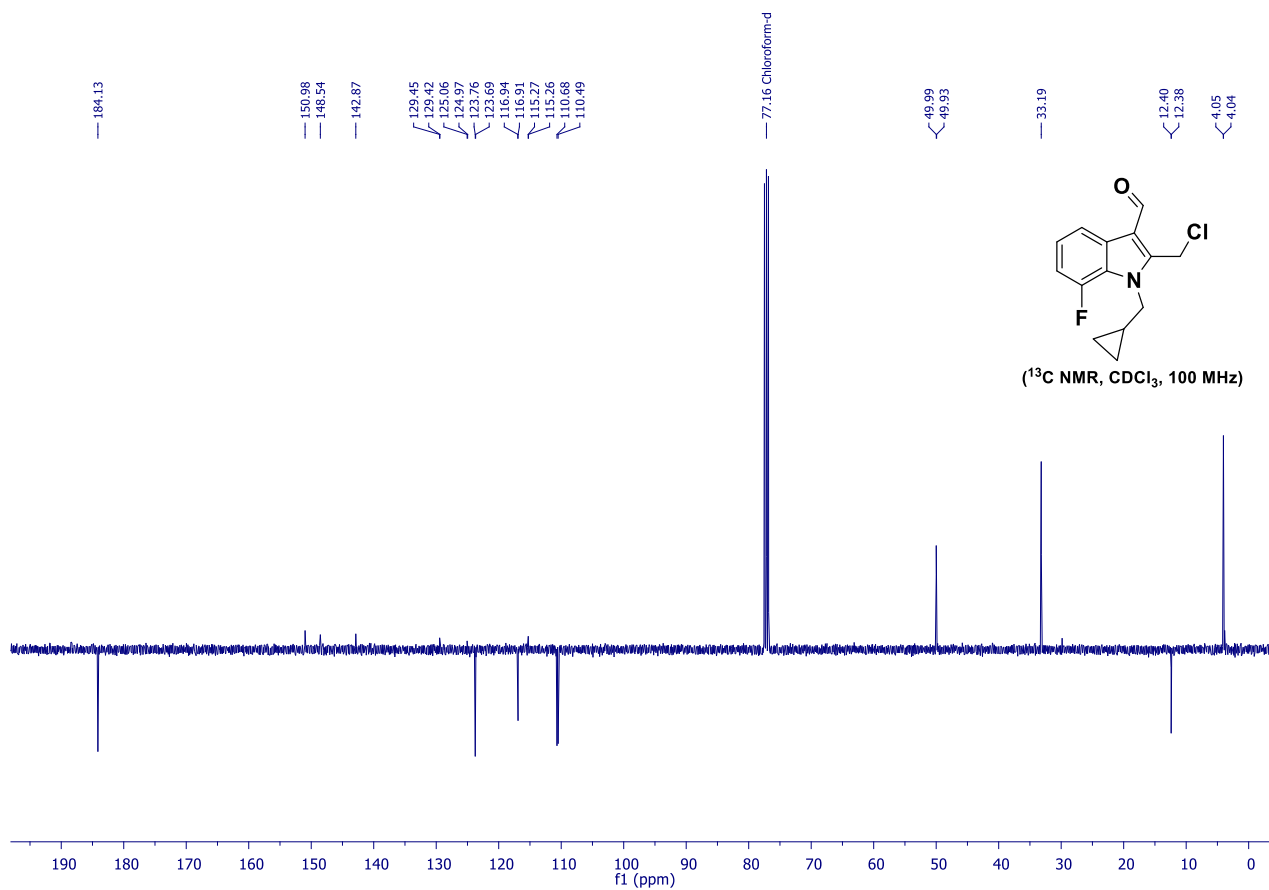
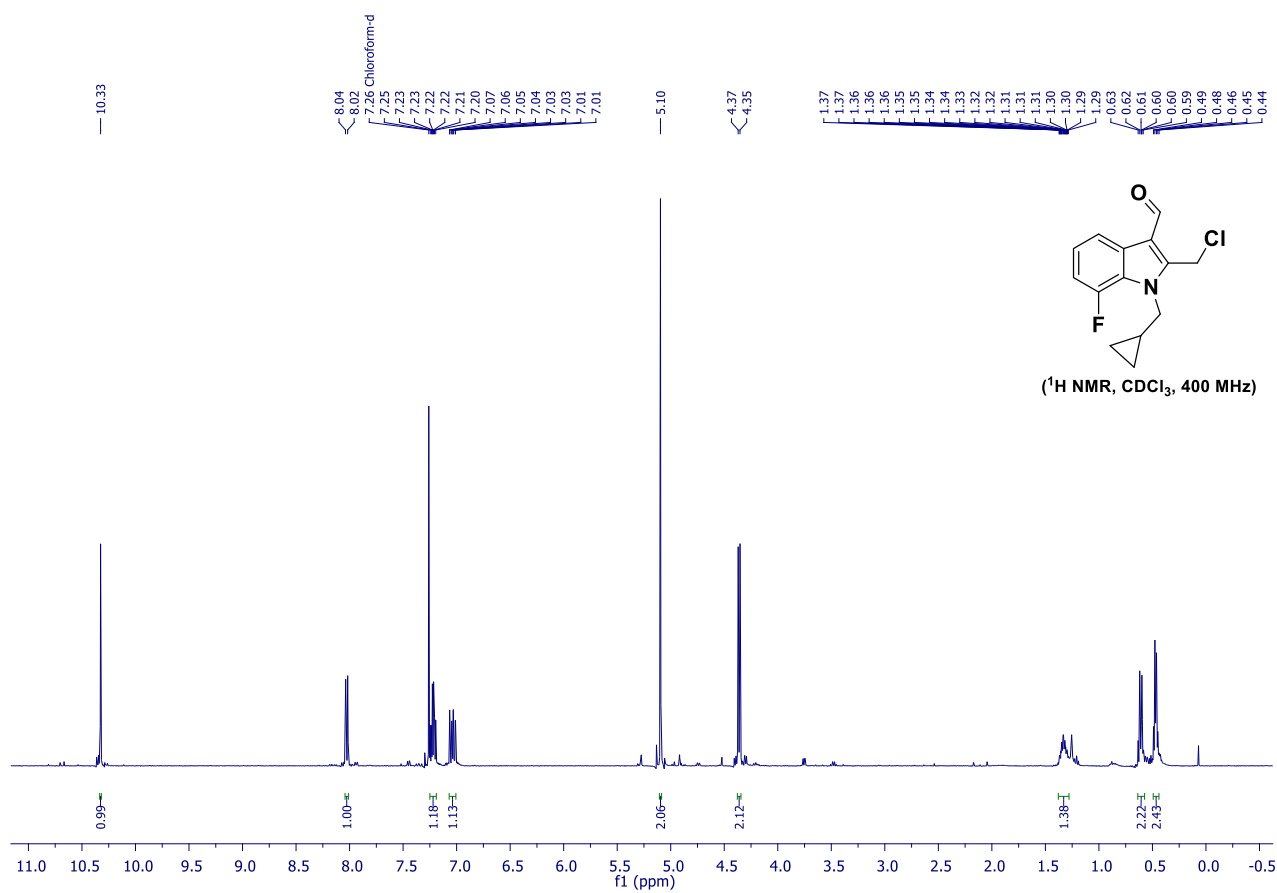


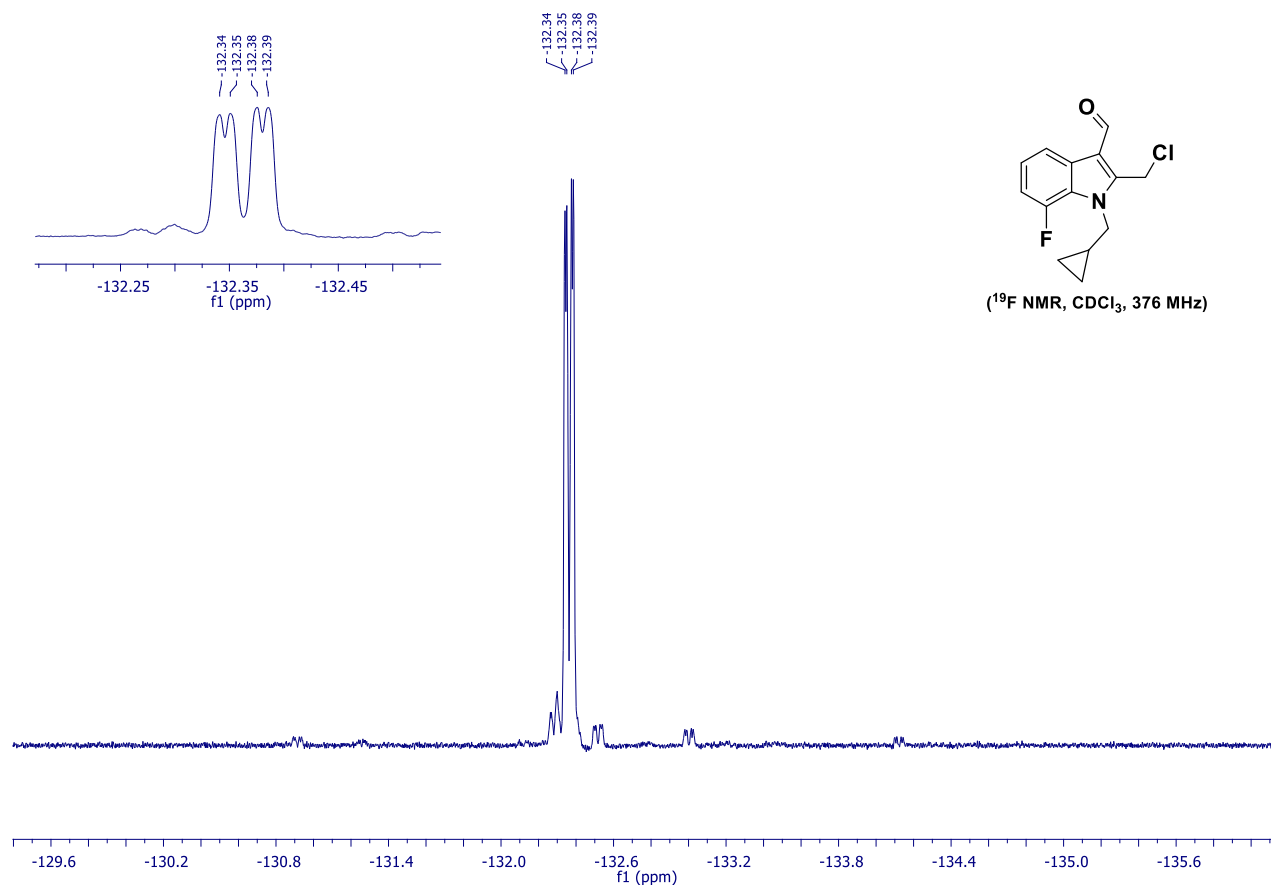


2-(Chloromethyl)-1-(4-methoxybenzyl)-1H-indole-3-carbaldehyde (679)

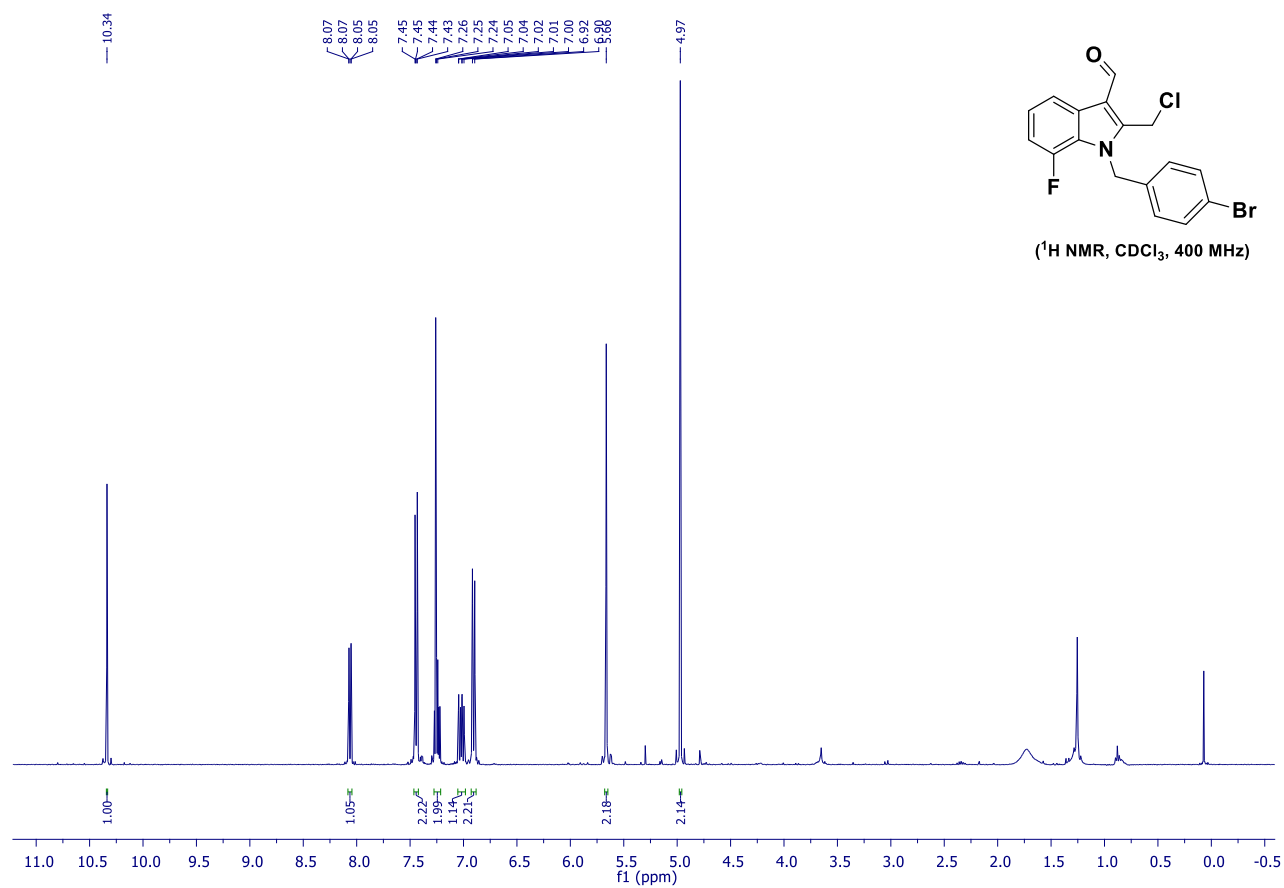


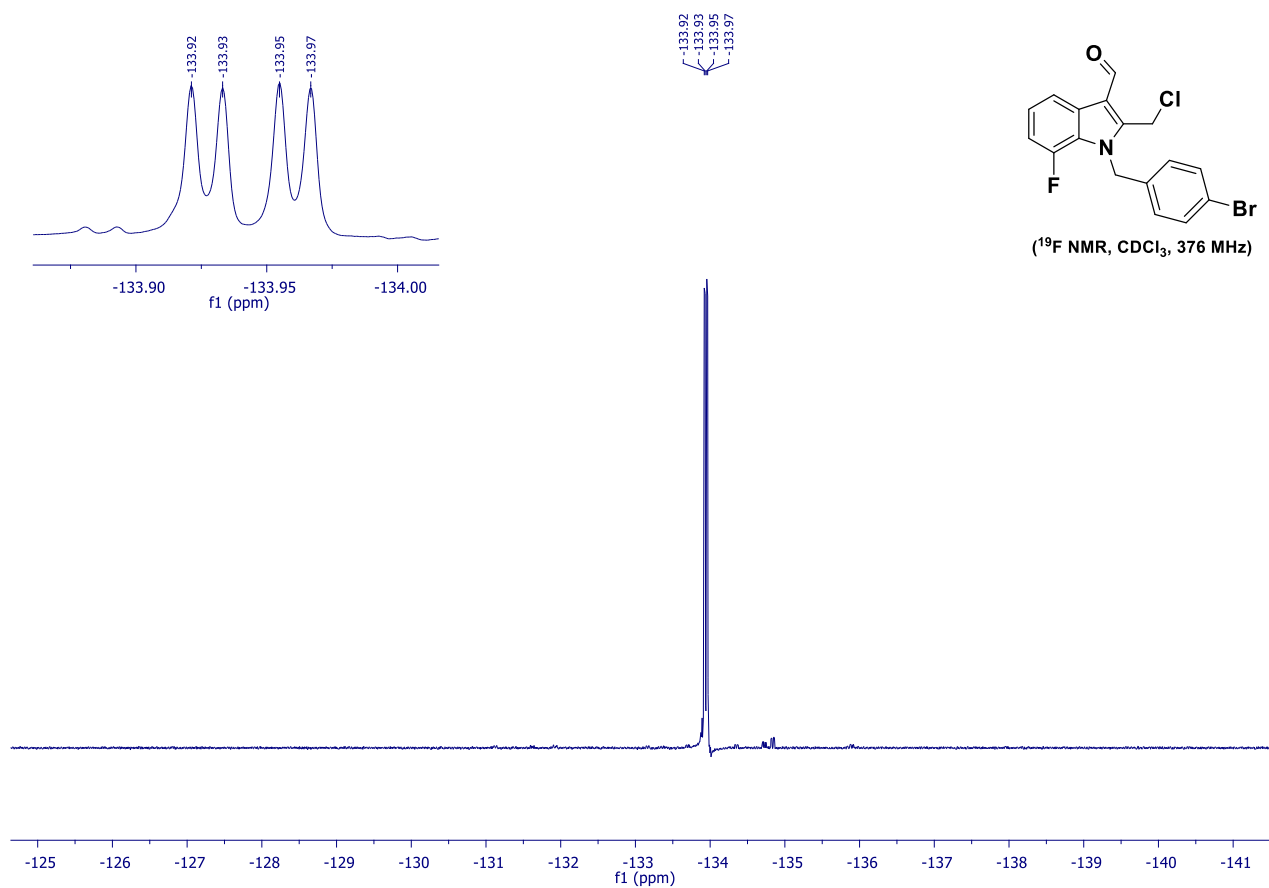
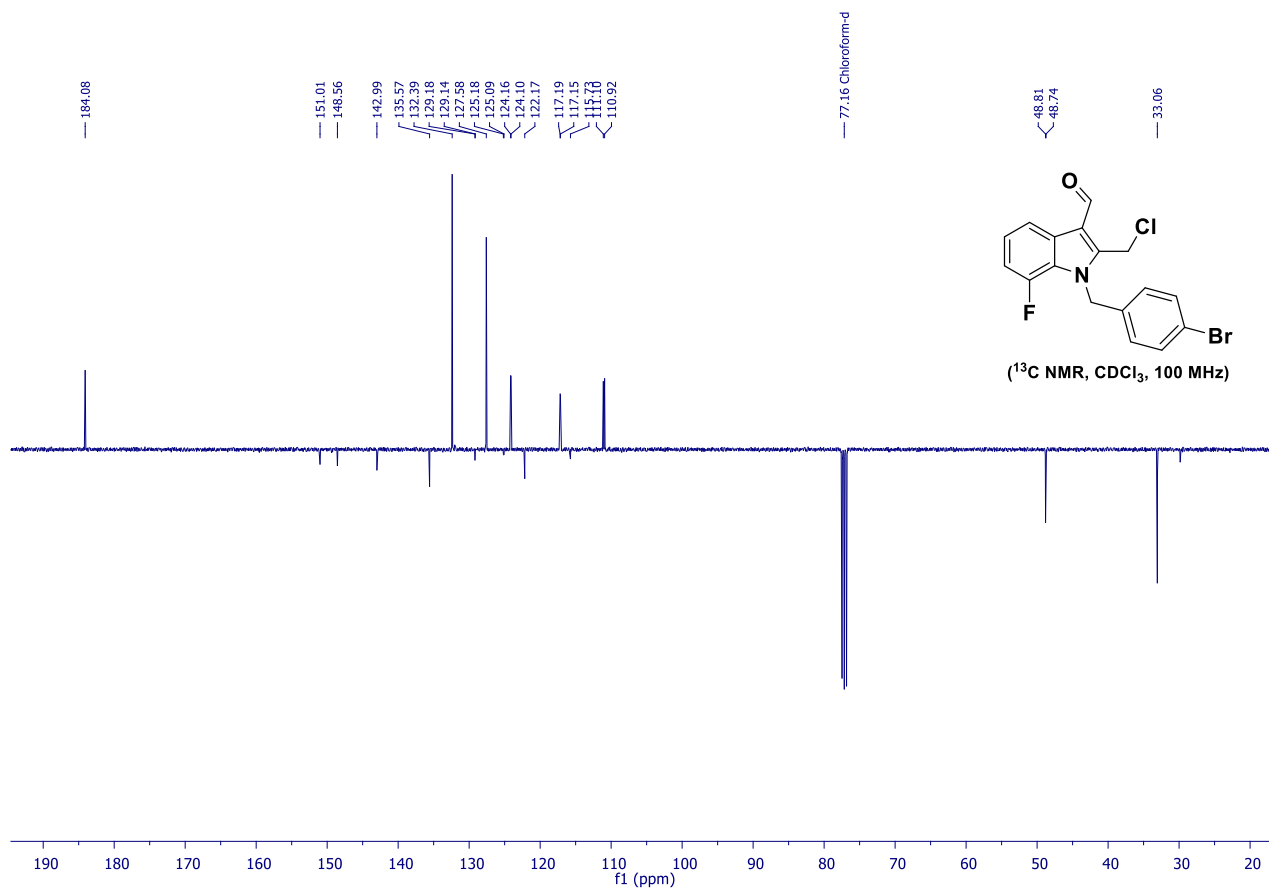
7-Fluoro-1-(cyclopropylmethyl)-2-(chloromethyl)-1H-indol-3-carbaldehyde (680)



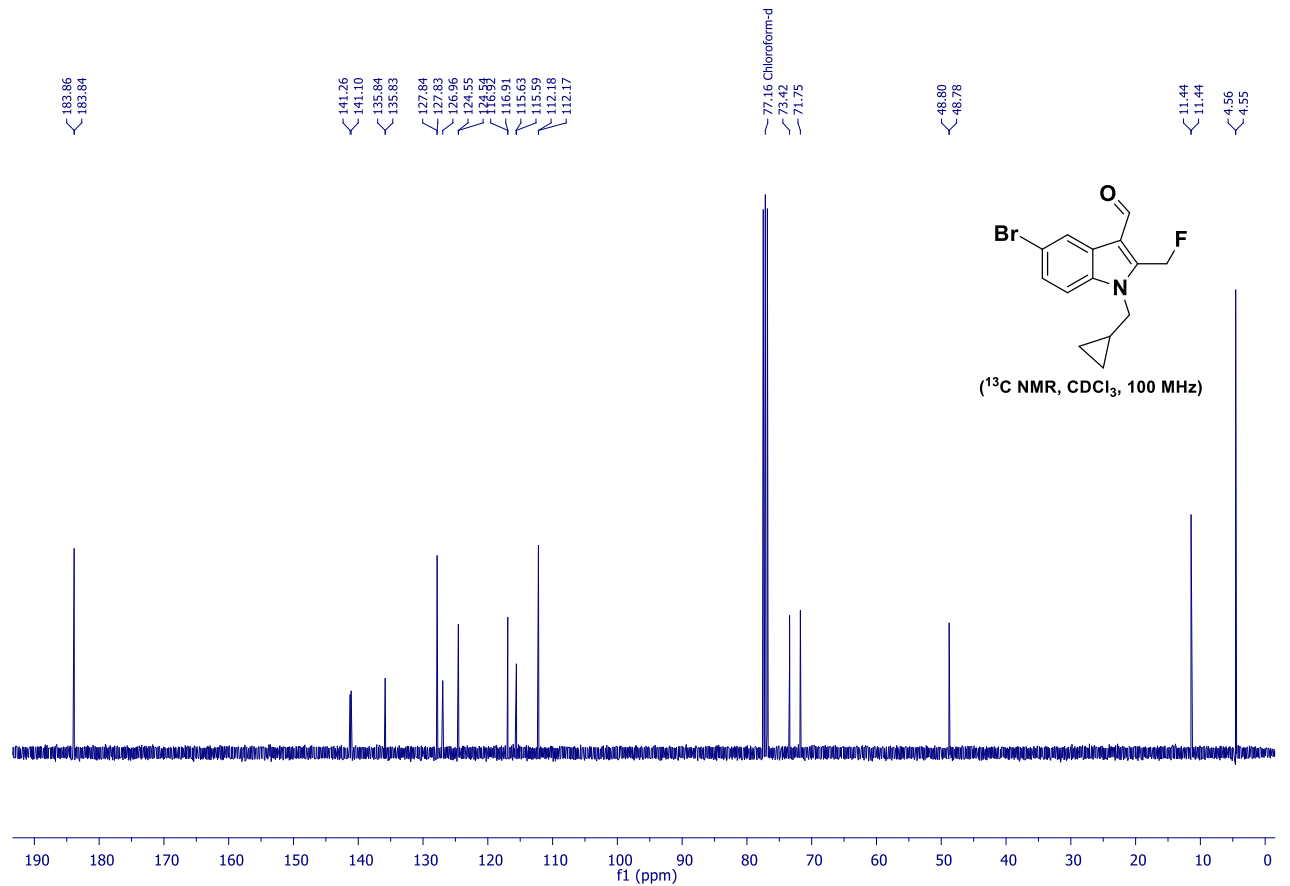
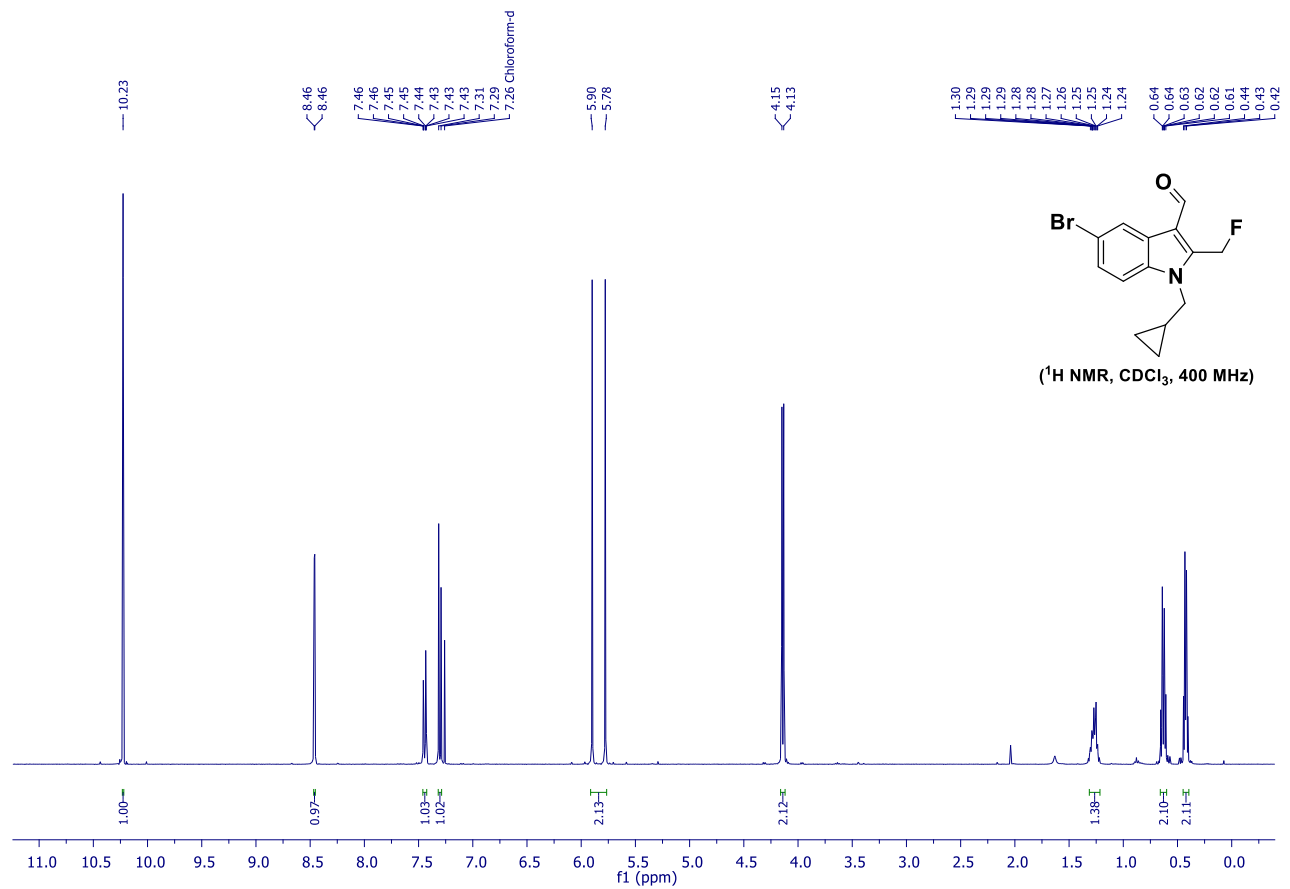


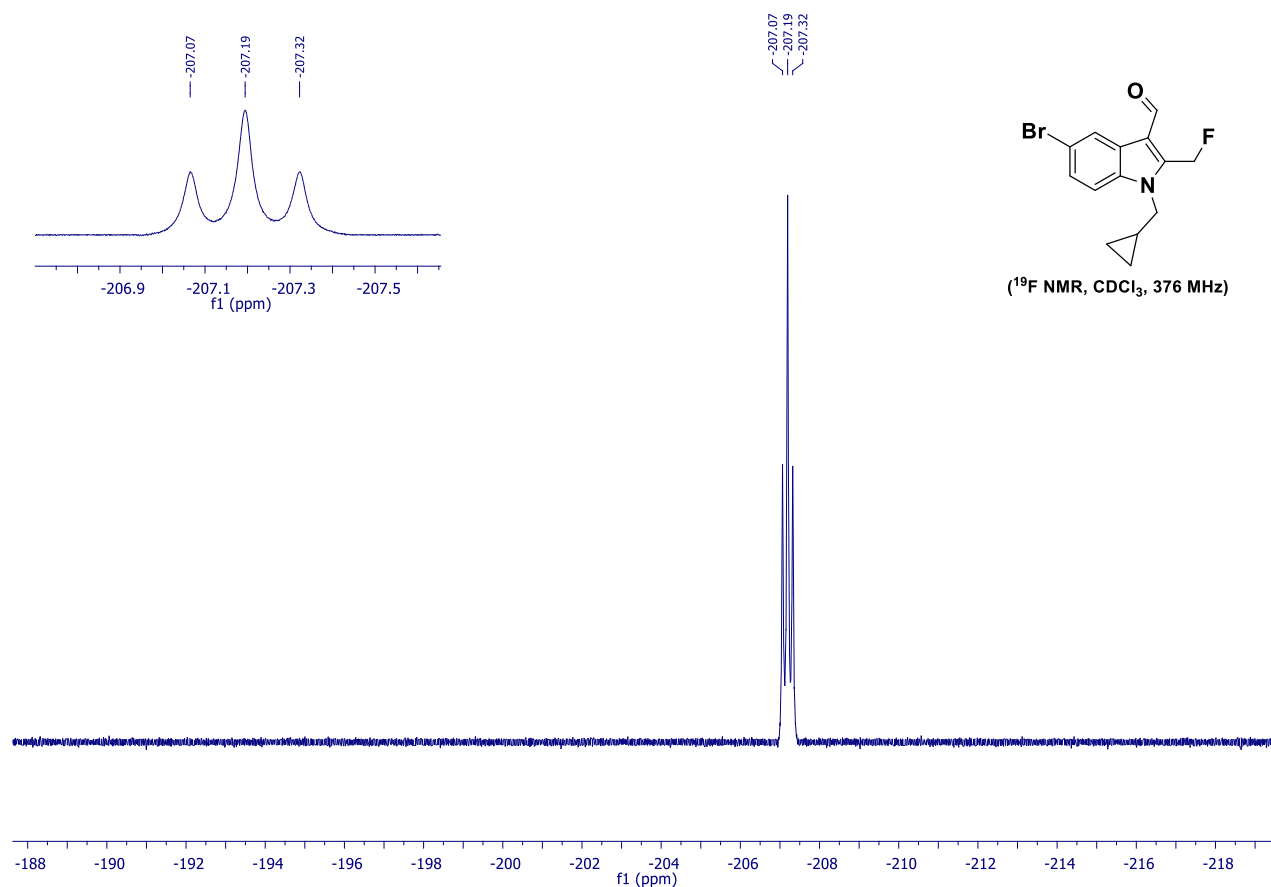
7-Fluoro-2-(chloromethyl)-1-(4-bromobenzyl)-1H-indole-3-carbaldehyde (681)



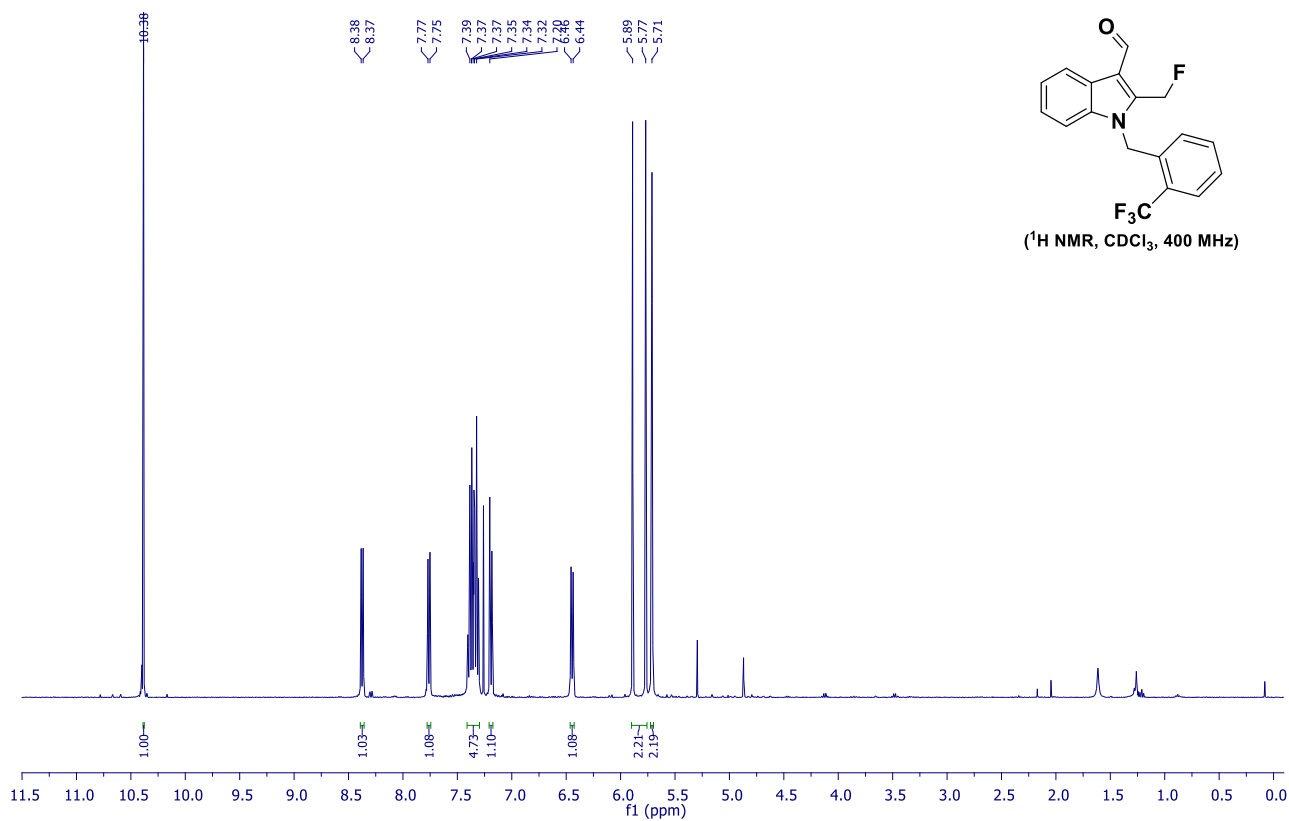


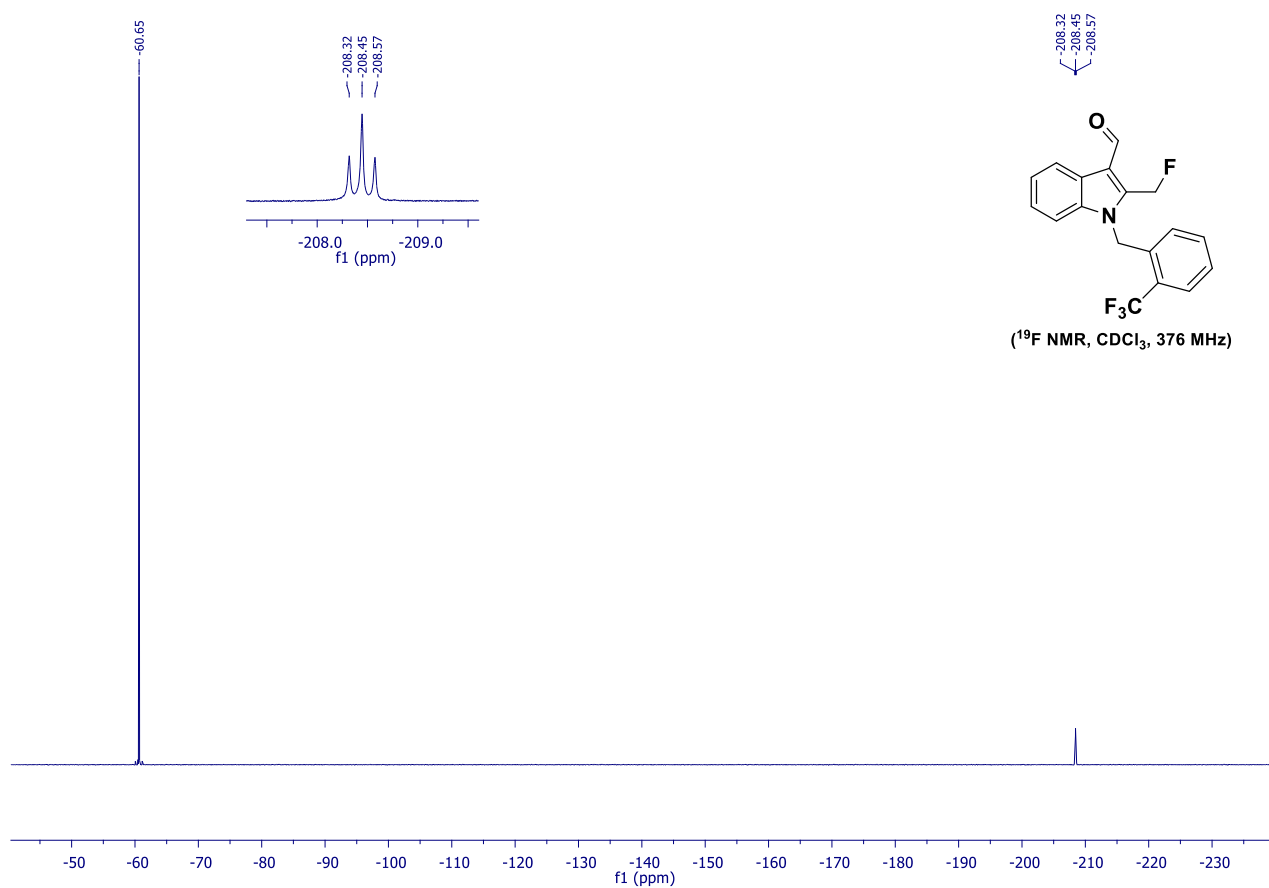
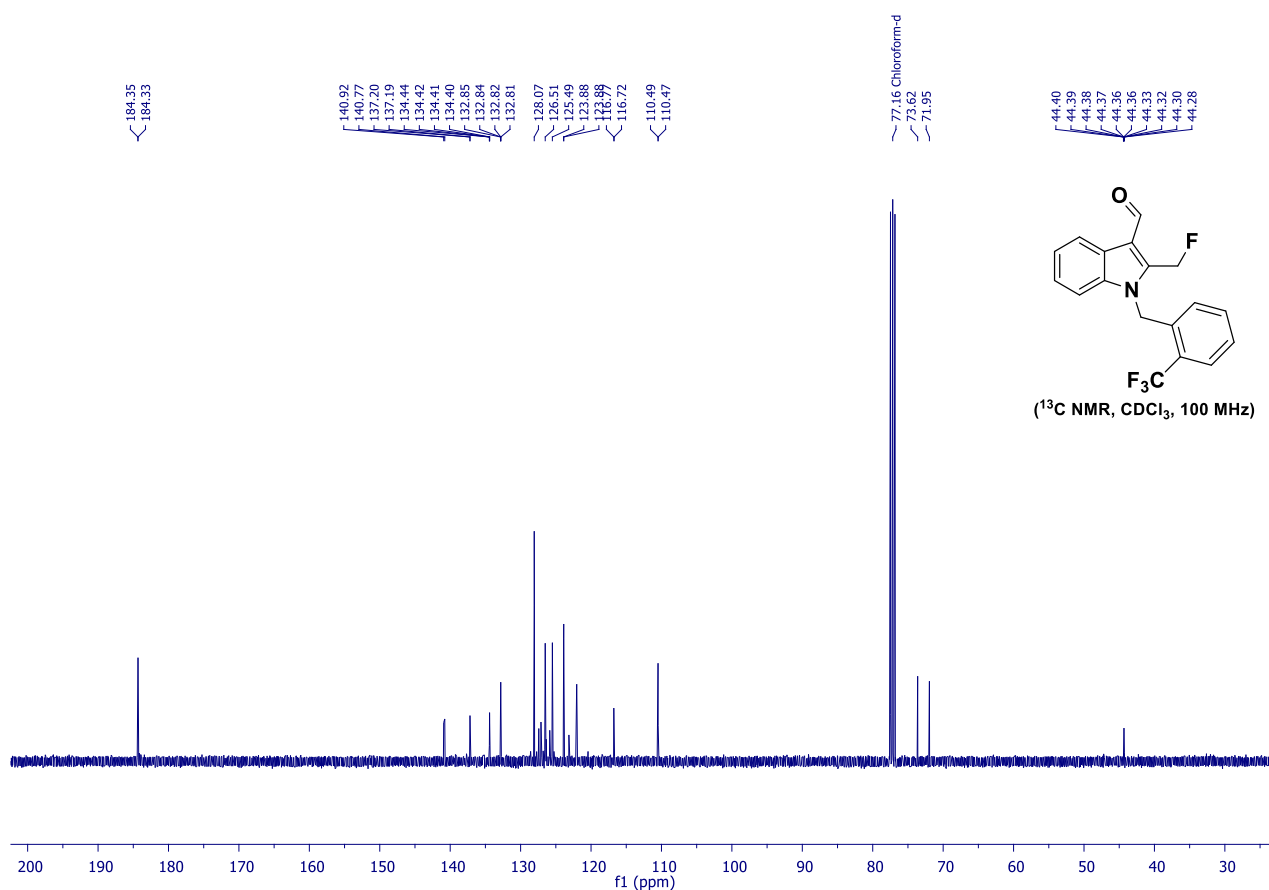
5-Bromo-1-(cyclopropylmethyl)-2-(fluoromethyl)-1H-indol-3-carbaldehyde (682)



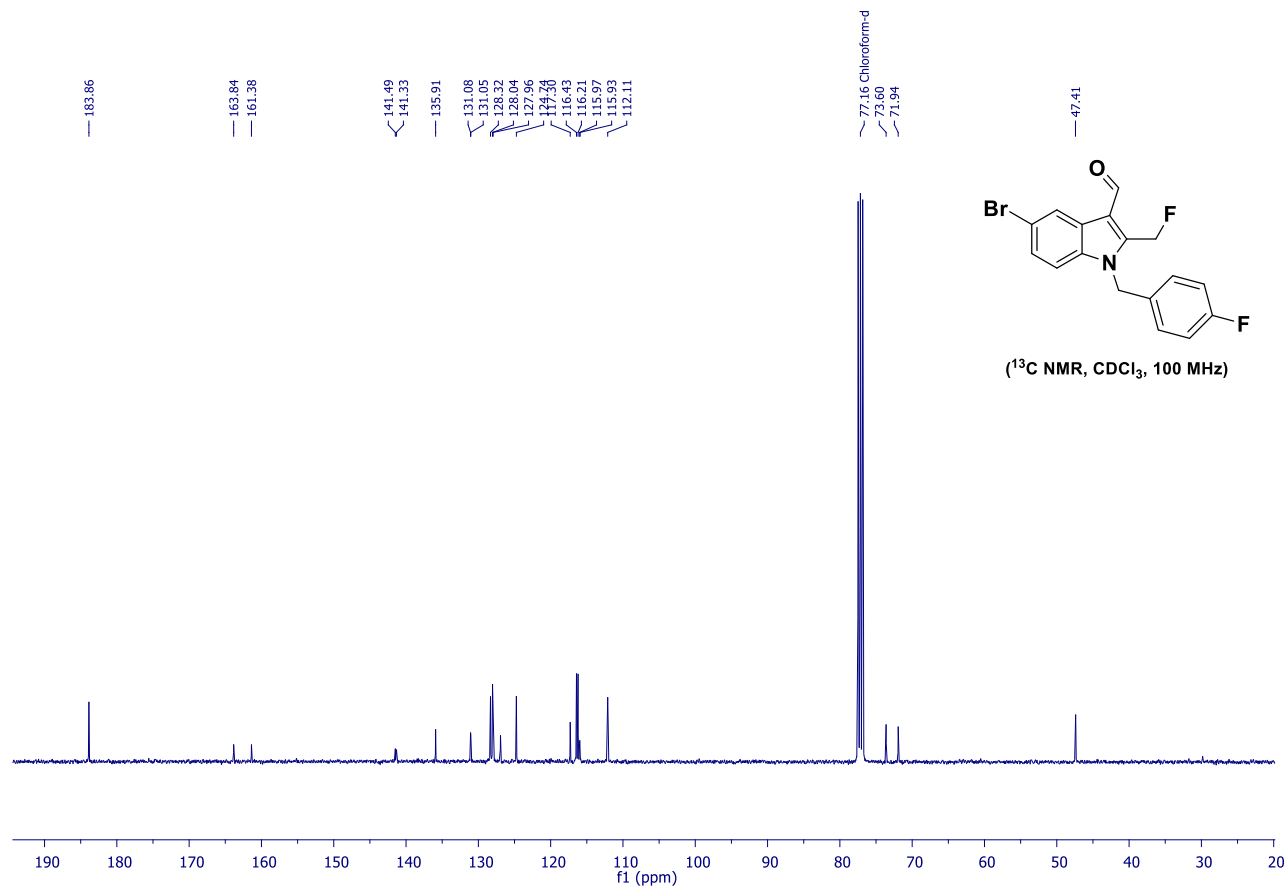
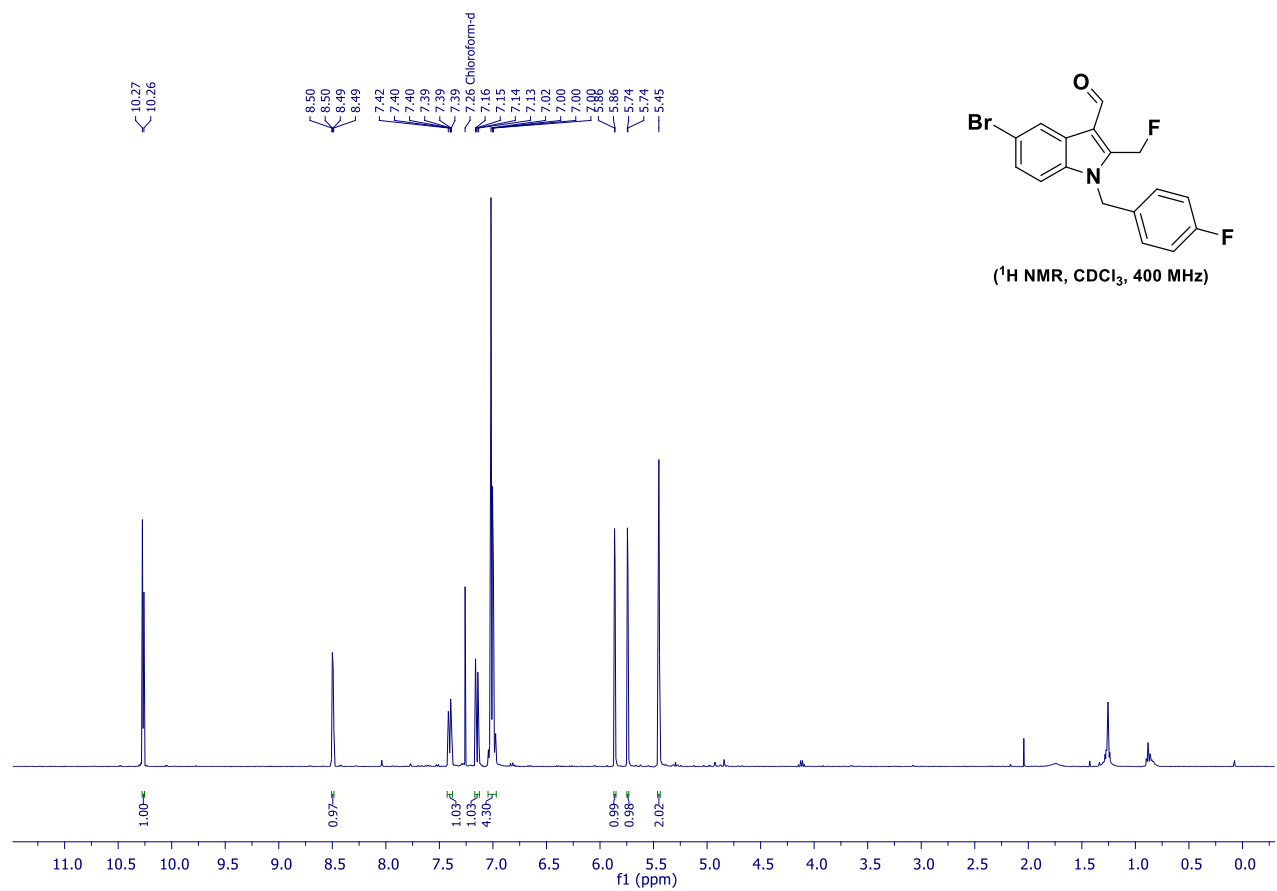


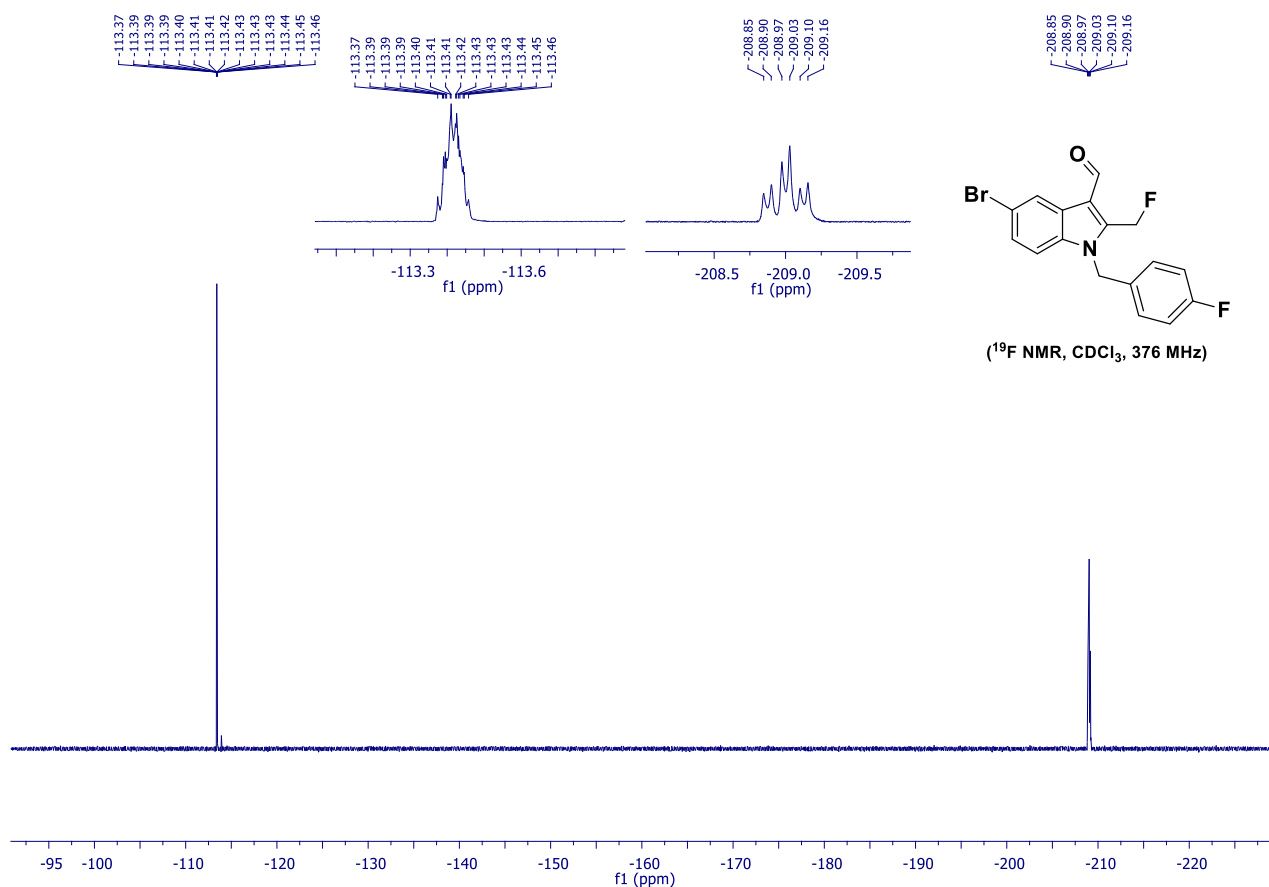
2-(Fluoromethyl)-1-[-2-(trifluoromethyl)benzyl]-1H-indole-3-carbaldehyde (683)



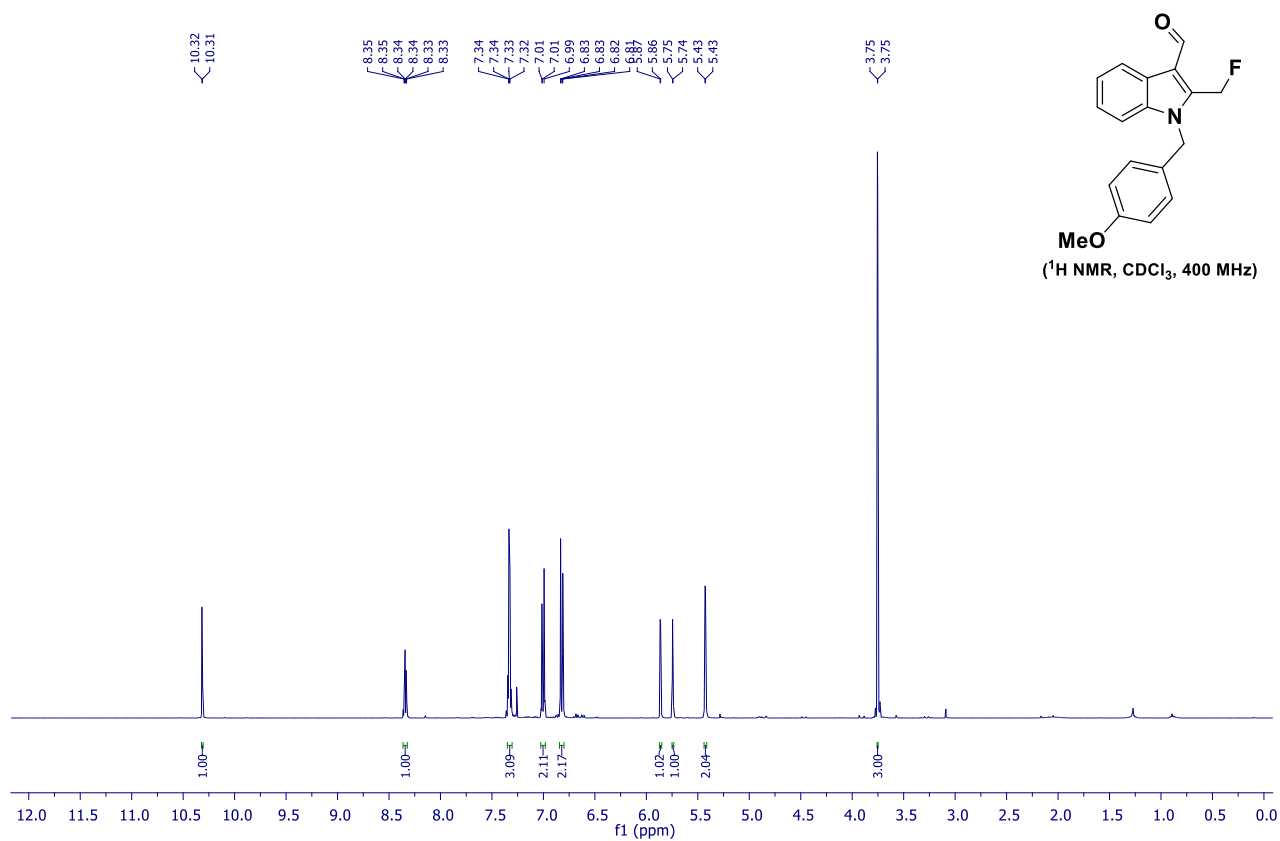


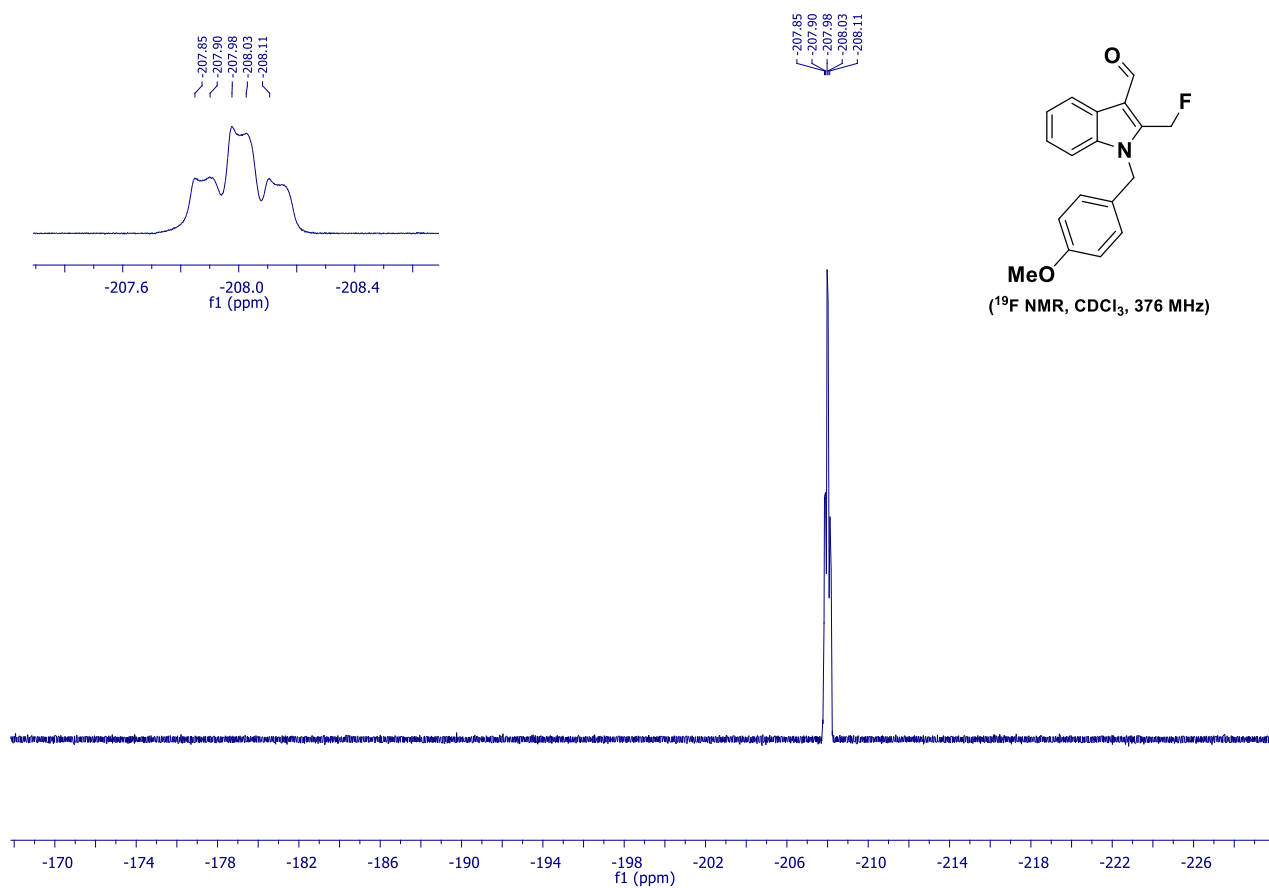
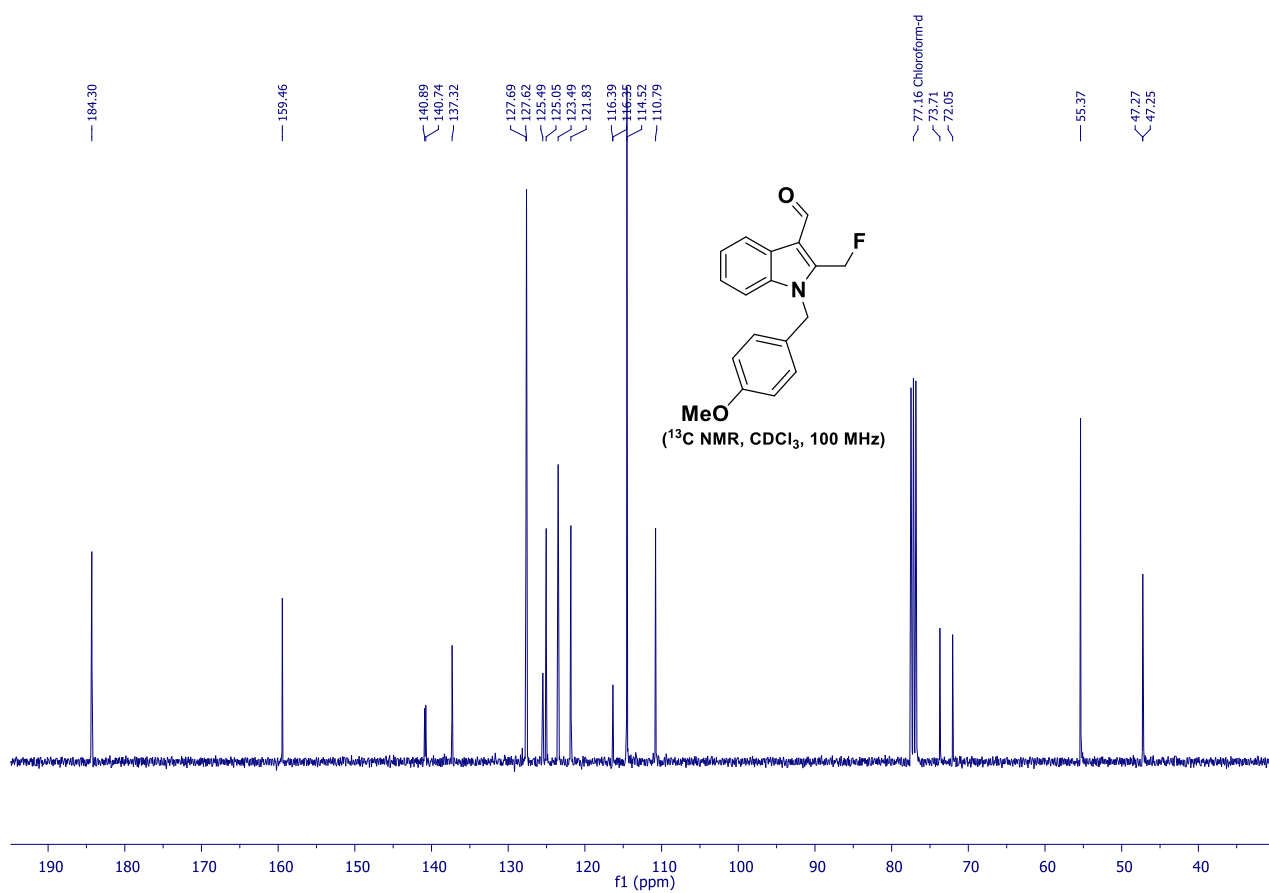
5-Bromo-1-(4-fluorobenzyl)-2-(fluoromethyl)-1H-indol-3-carbaldehyde (684)



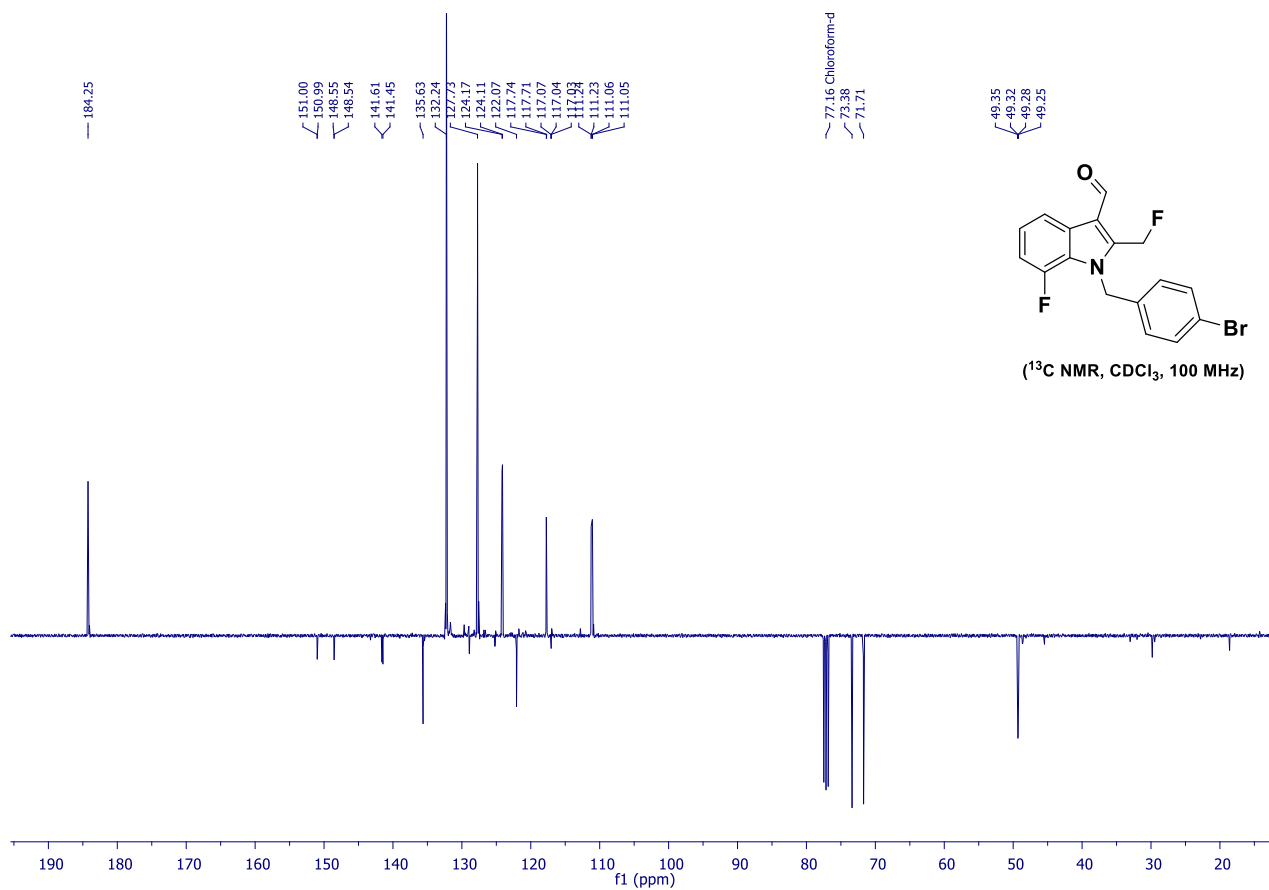
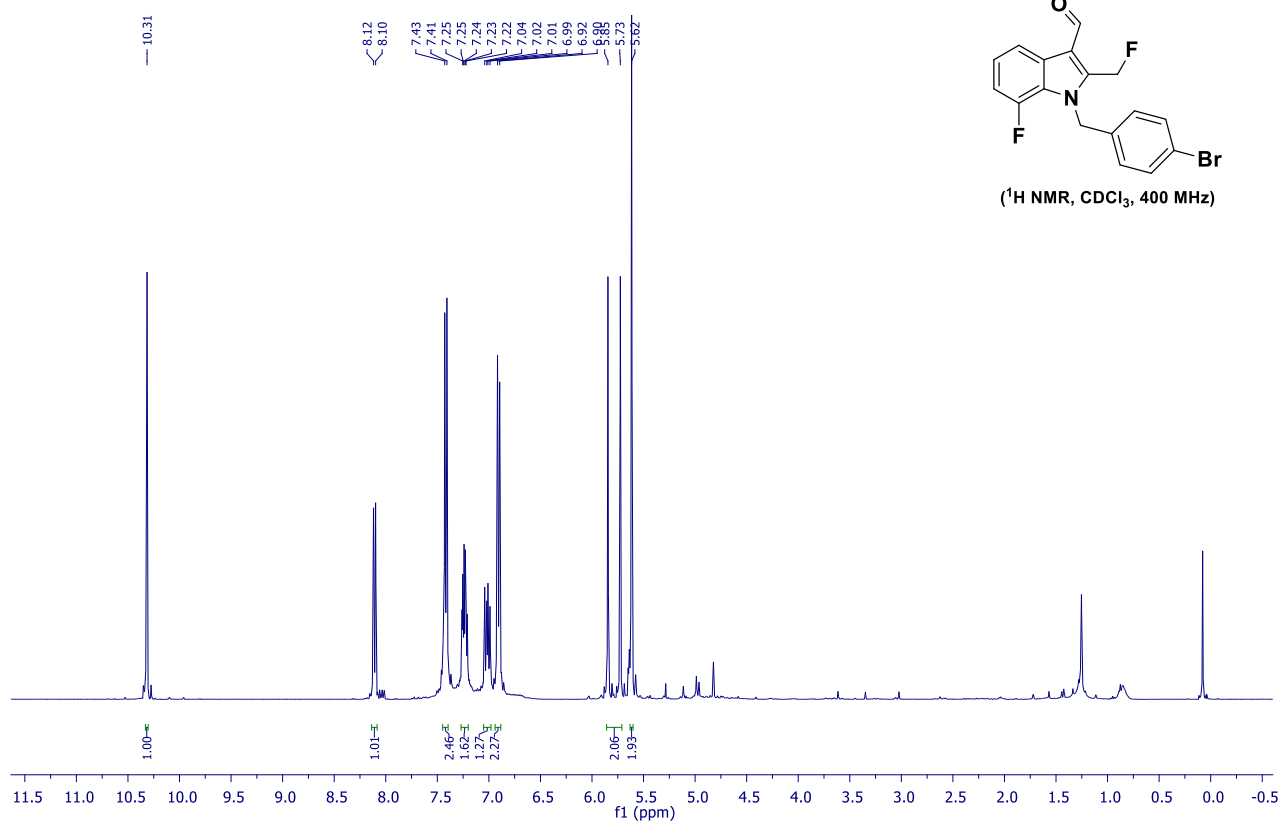


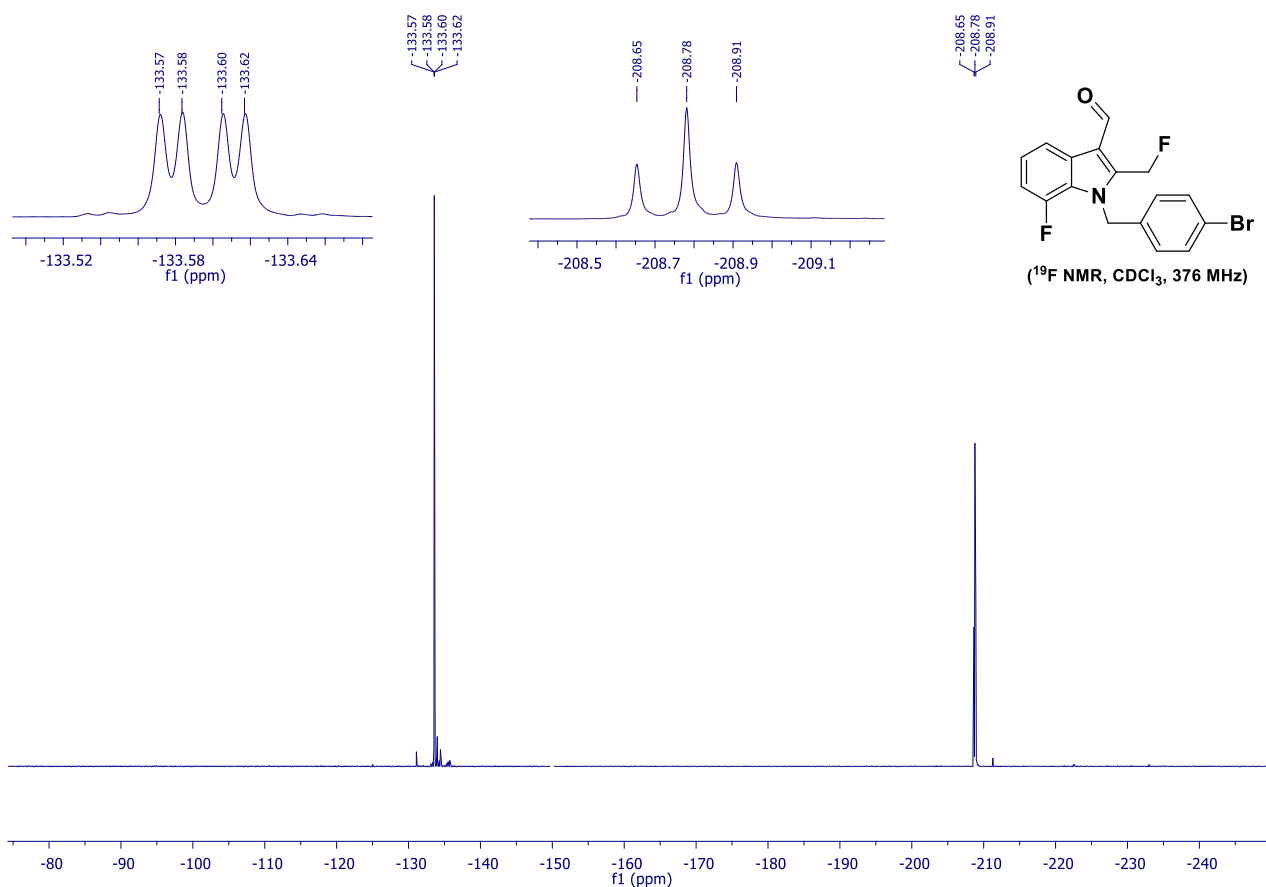
2-(Fluoromethyl)-1-(4-methoxybenzyl)-1H-indol-3-carbaldehyde (685)



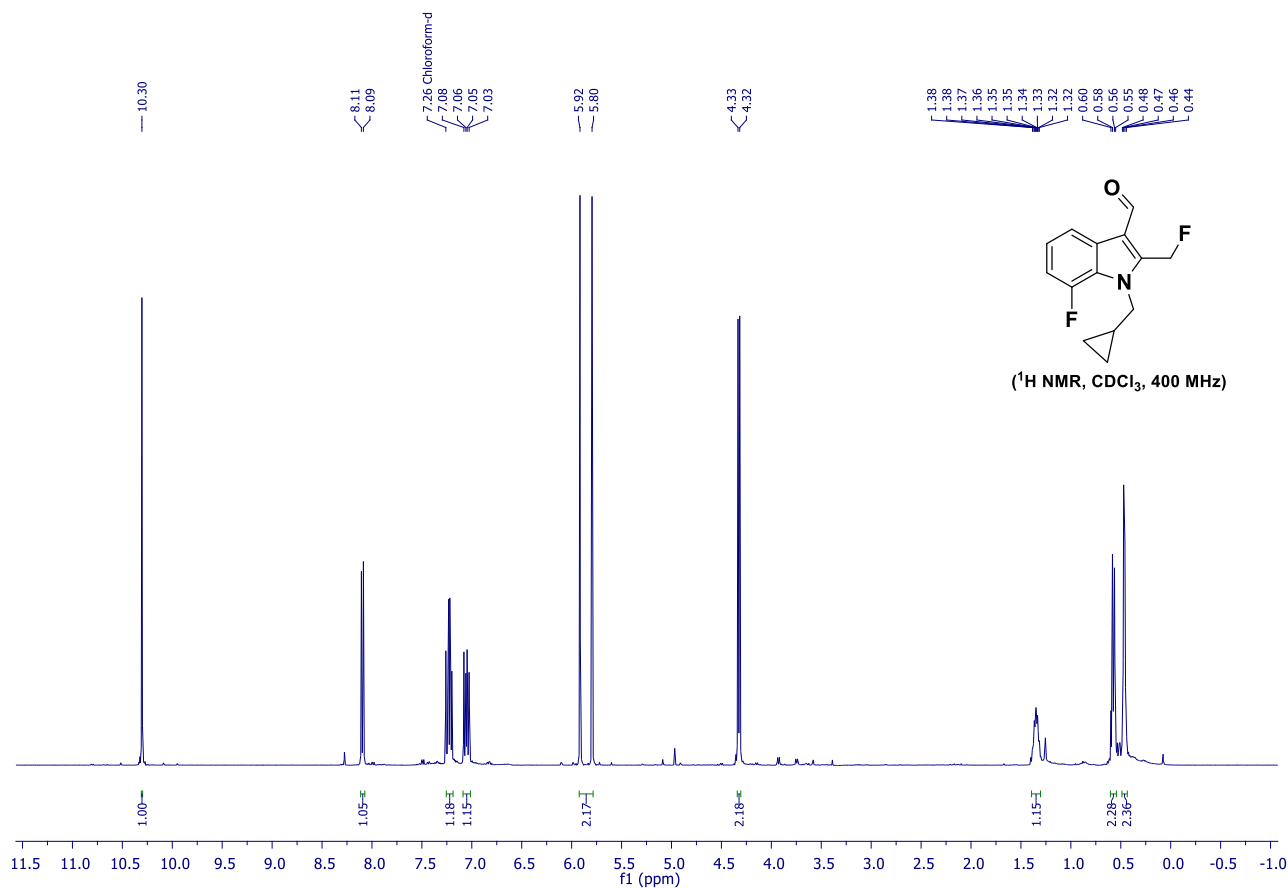


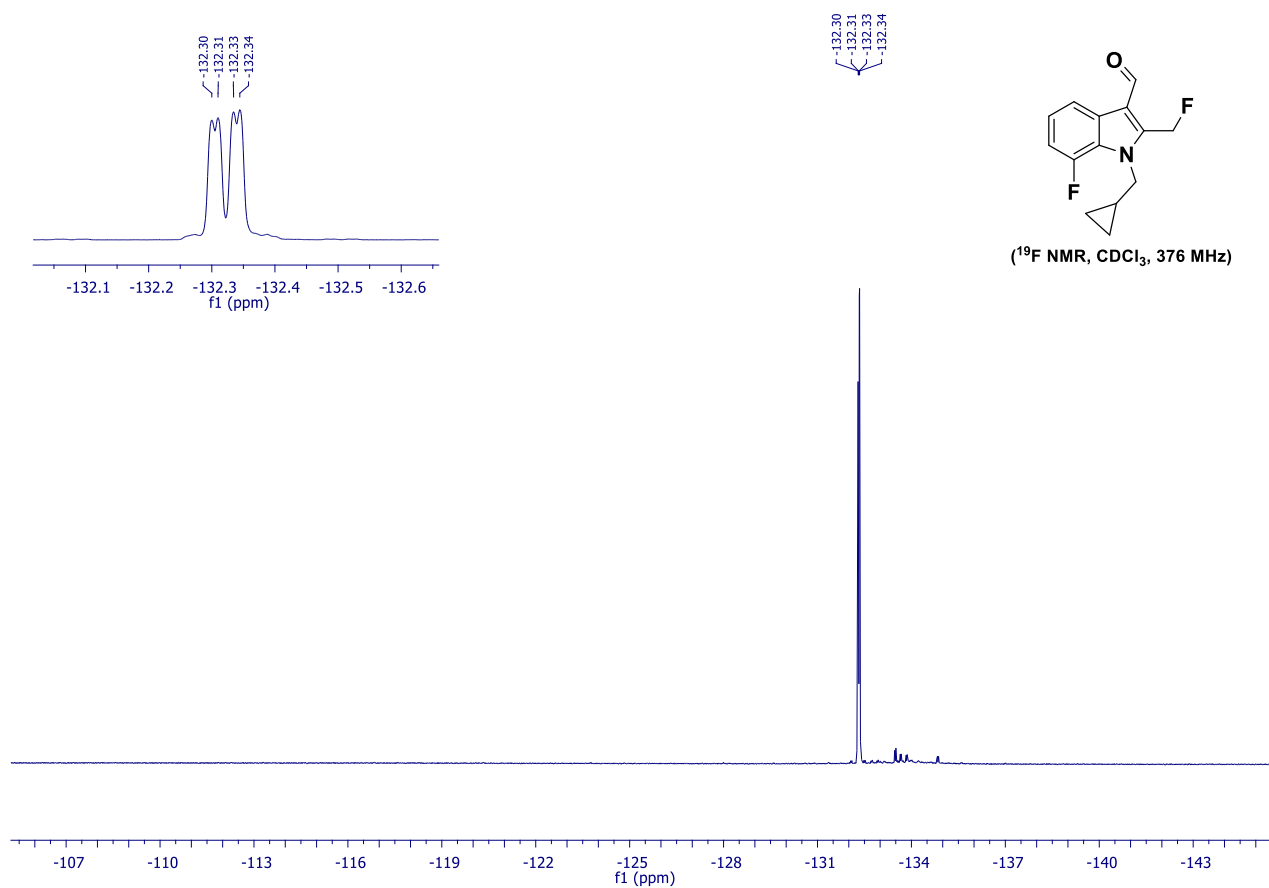
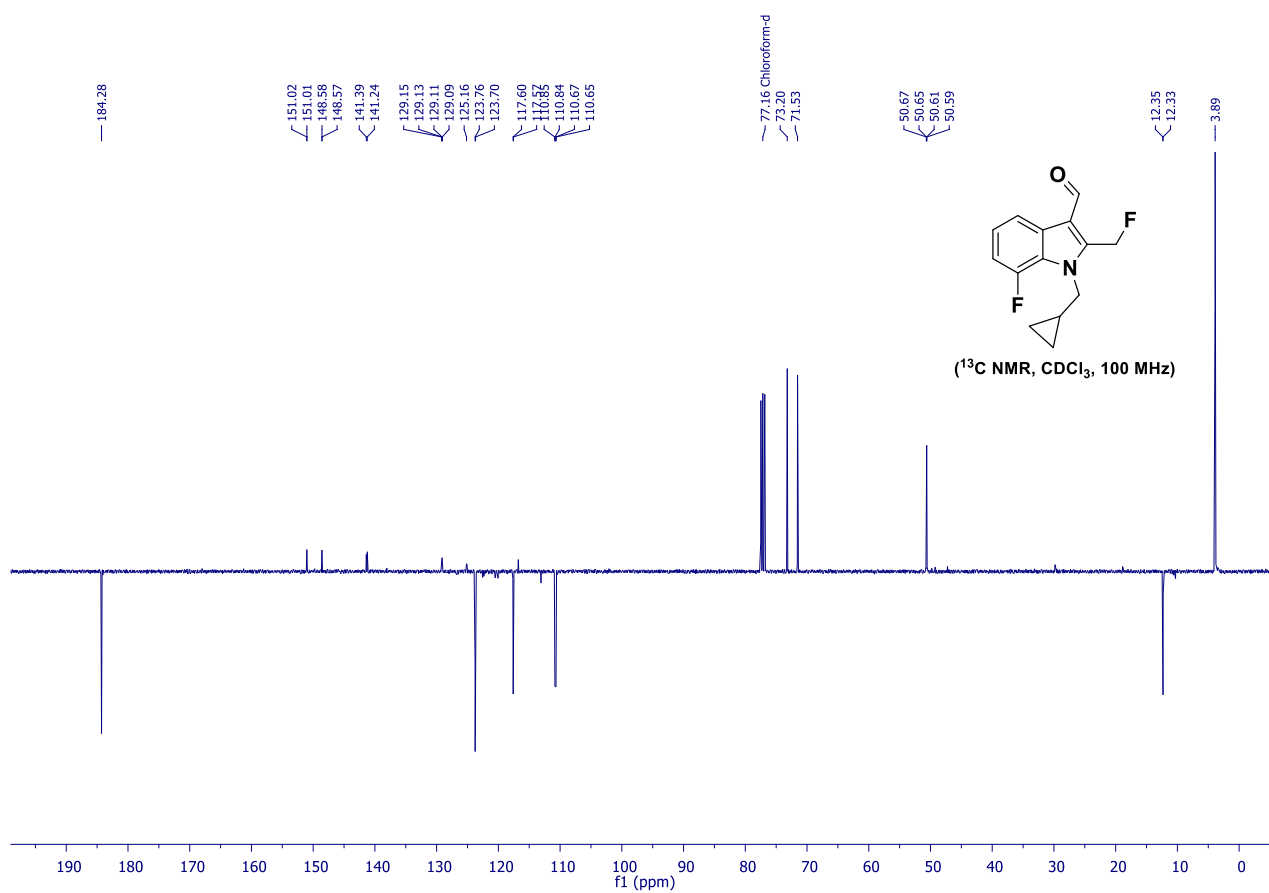
7-Fluoro-1-(4-bromoobenzyl)-2-(fluoromethyl)-1H-indol-3-carbaldehyde (686)

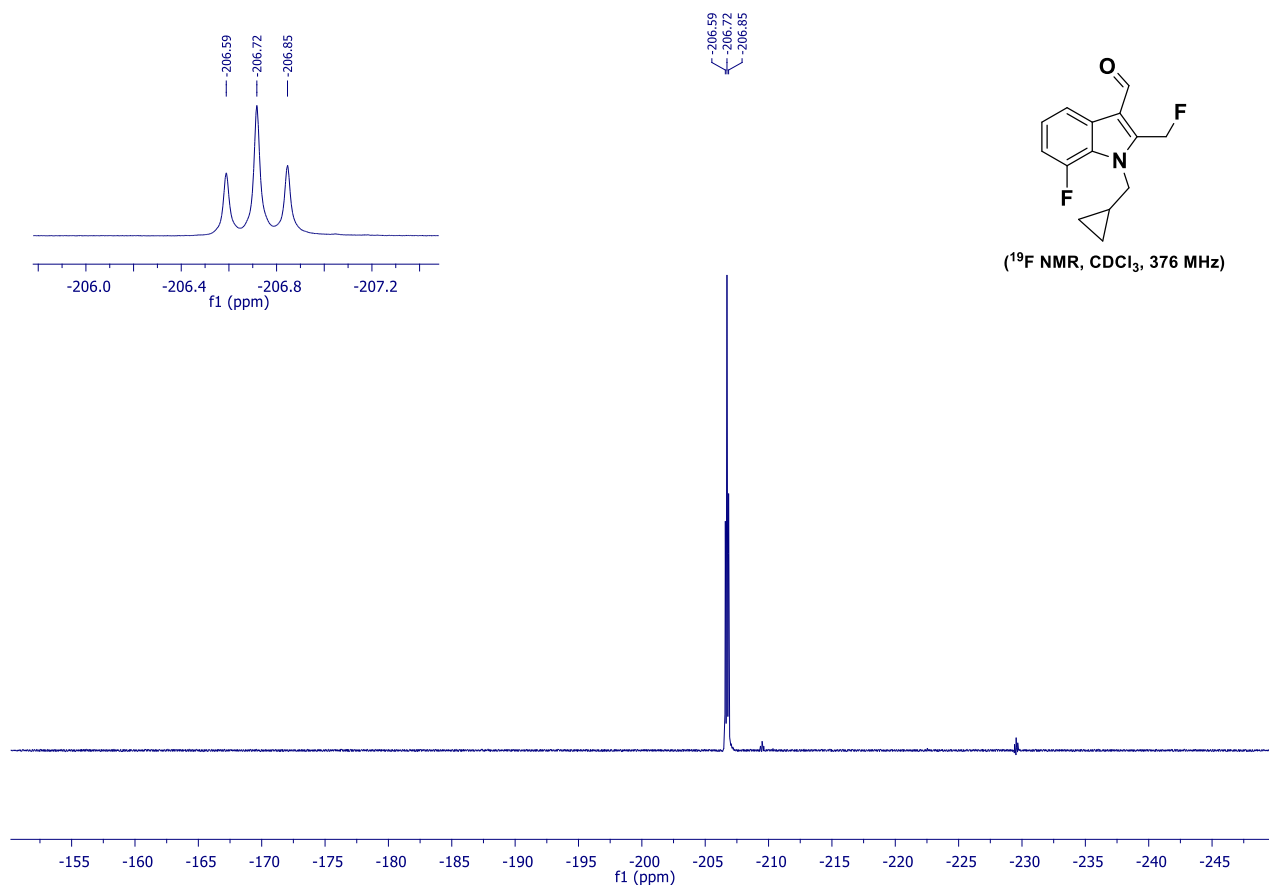




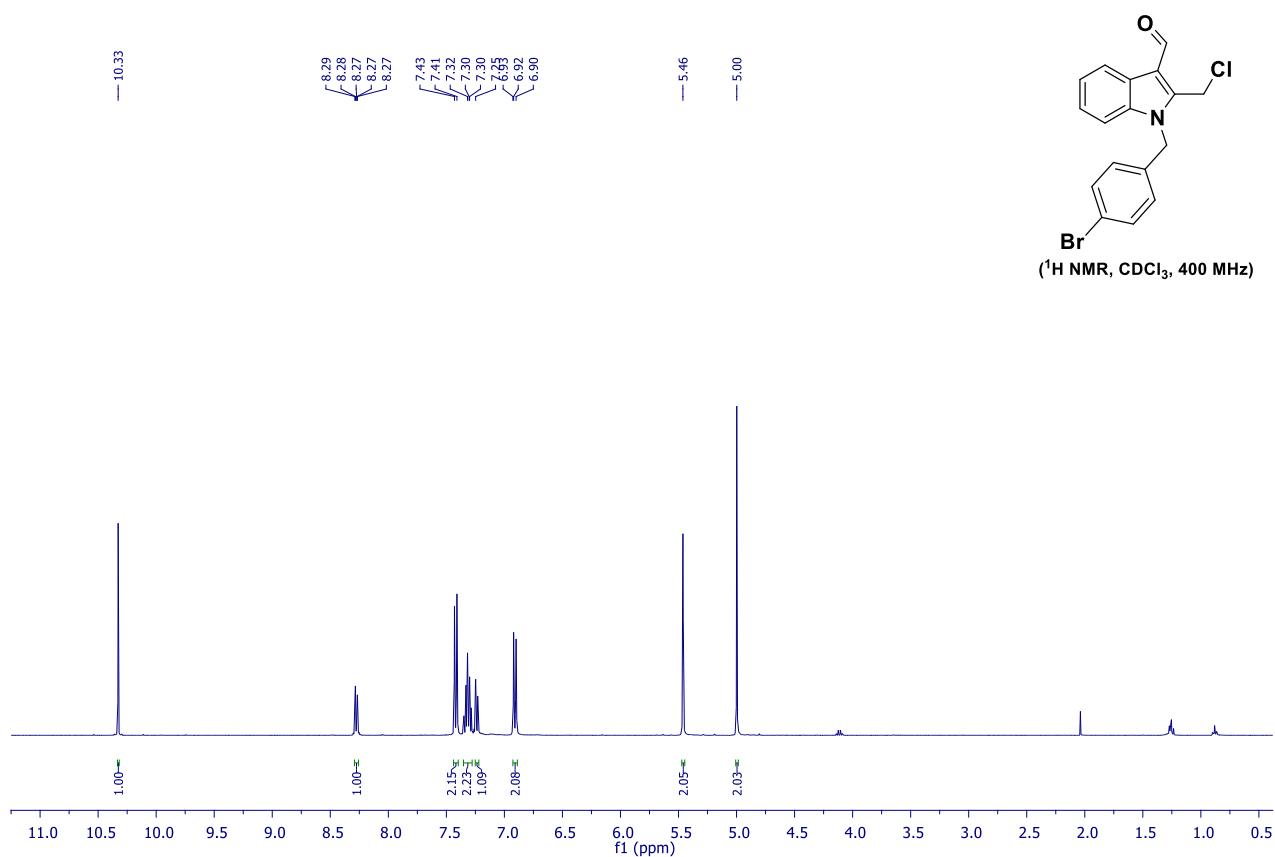
7-Fluoro-1-(cyclopropylmethyl)-2-(fluoromethyl)-1H-indol-3-carbaldehyde (687)

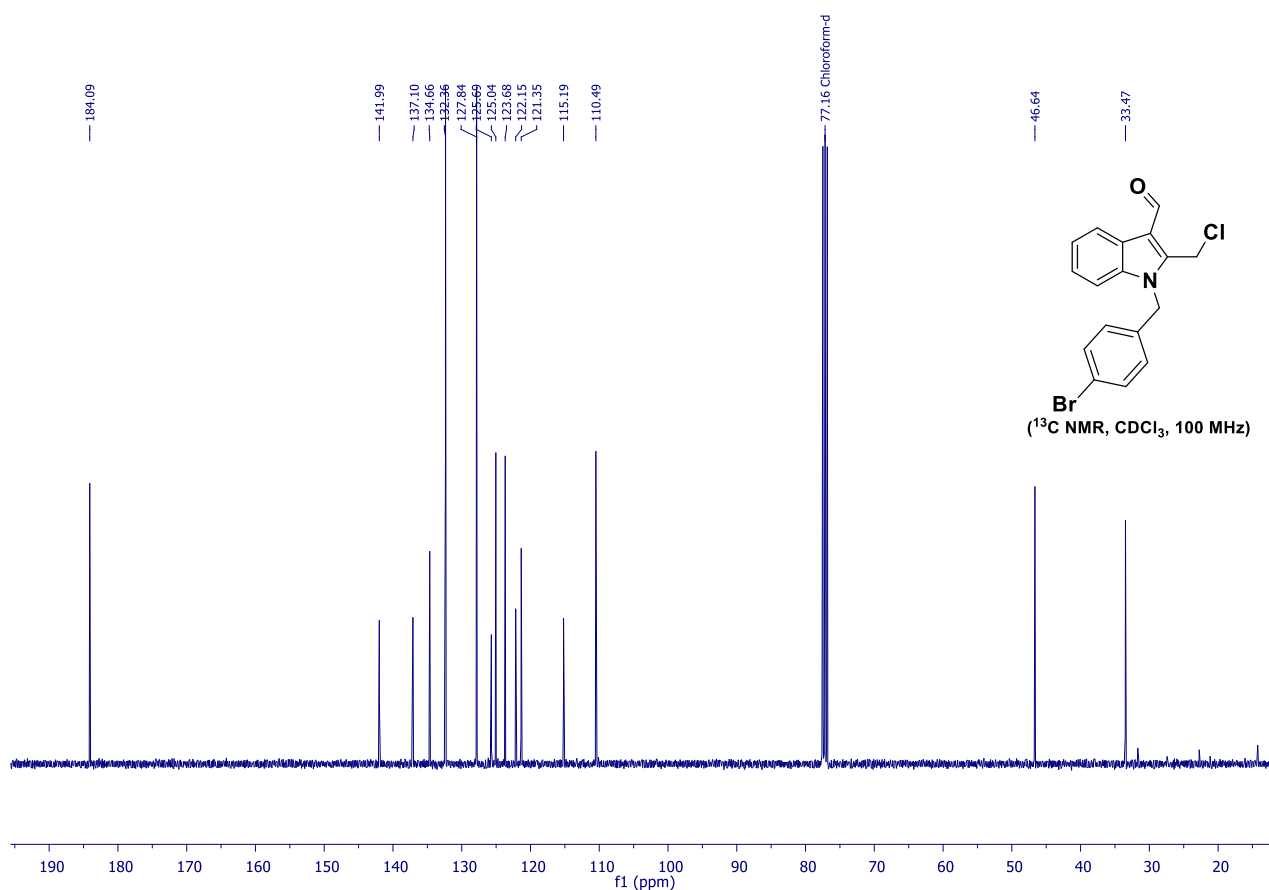




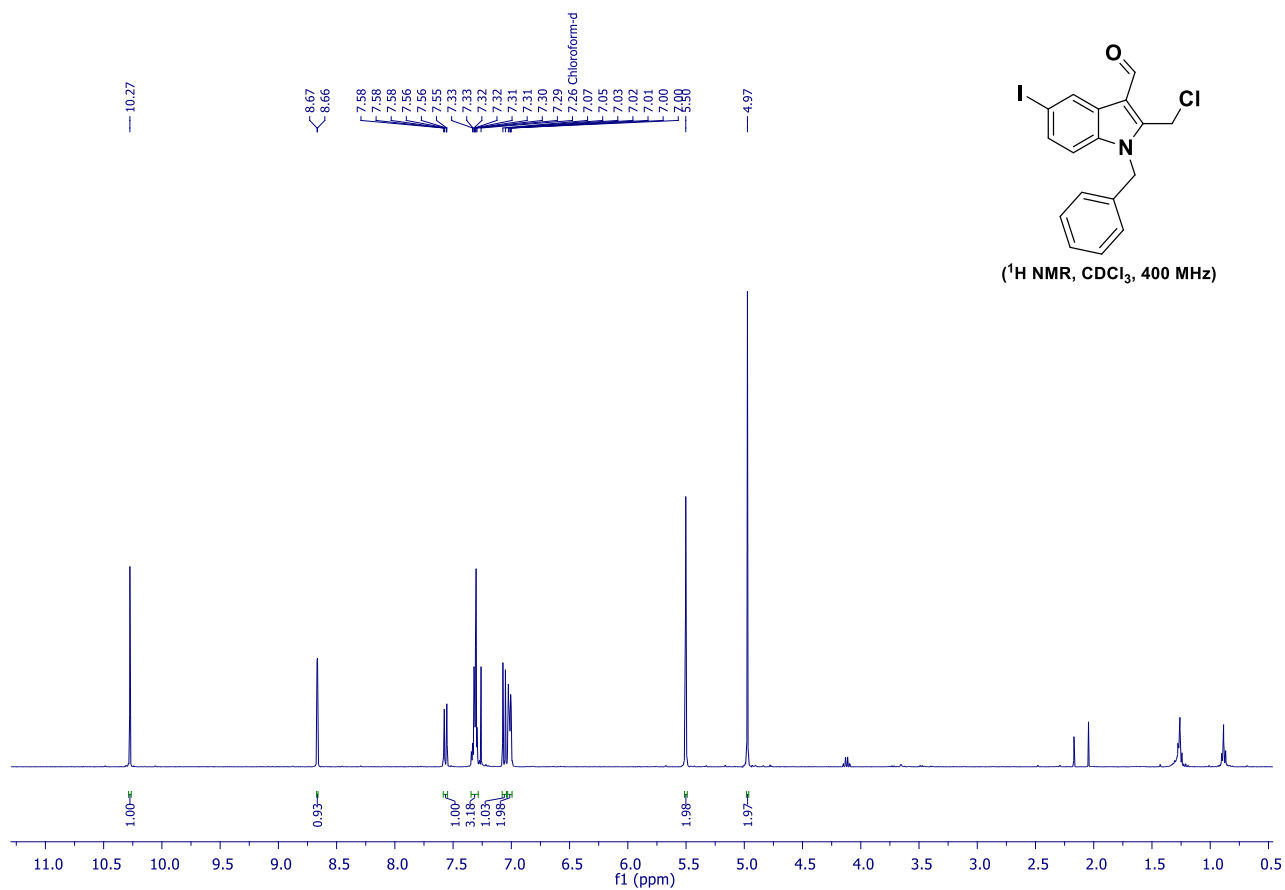


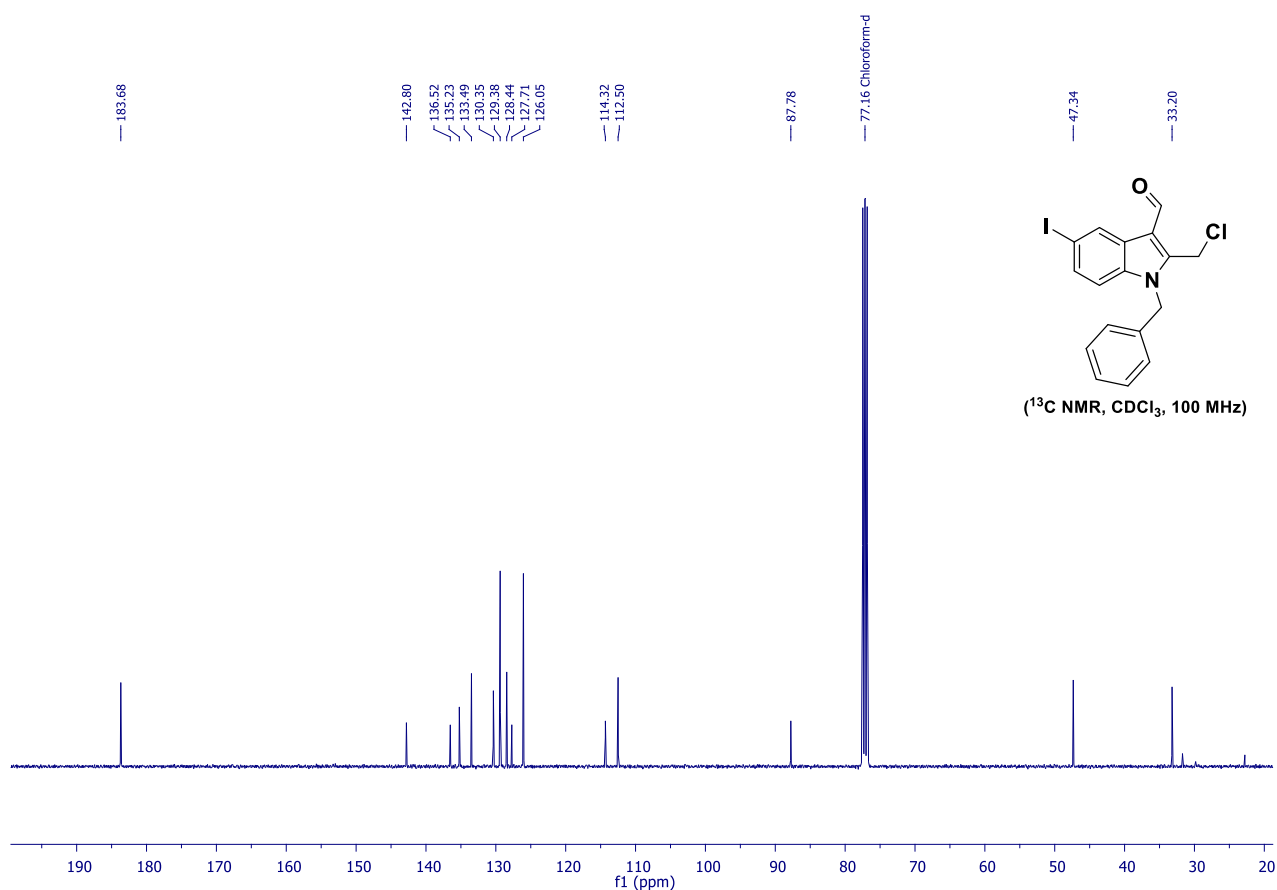
1-(4-Bromobenzyl)-2-(chloromethyl)-1H-indole-3-carbaldehyde (688)



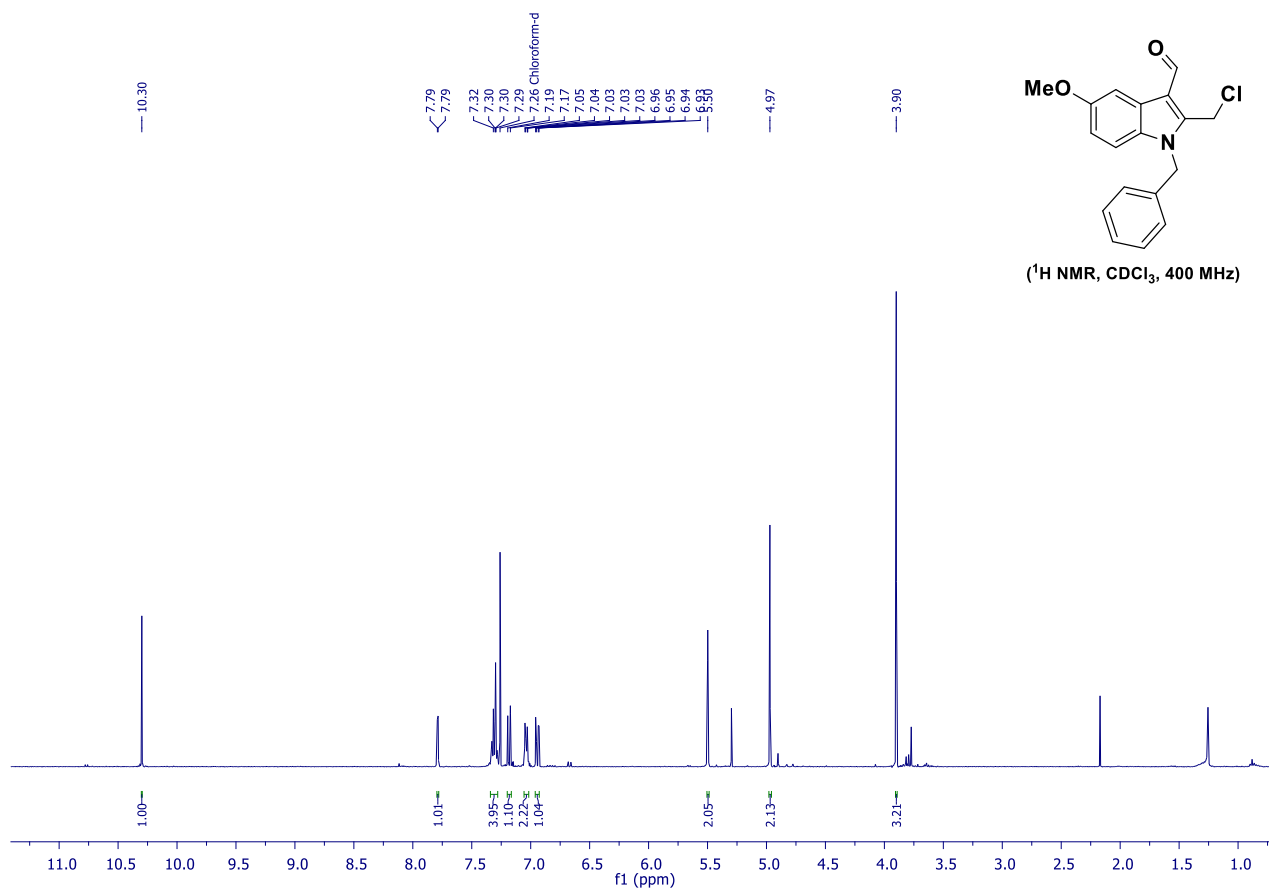


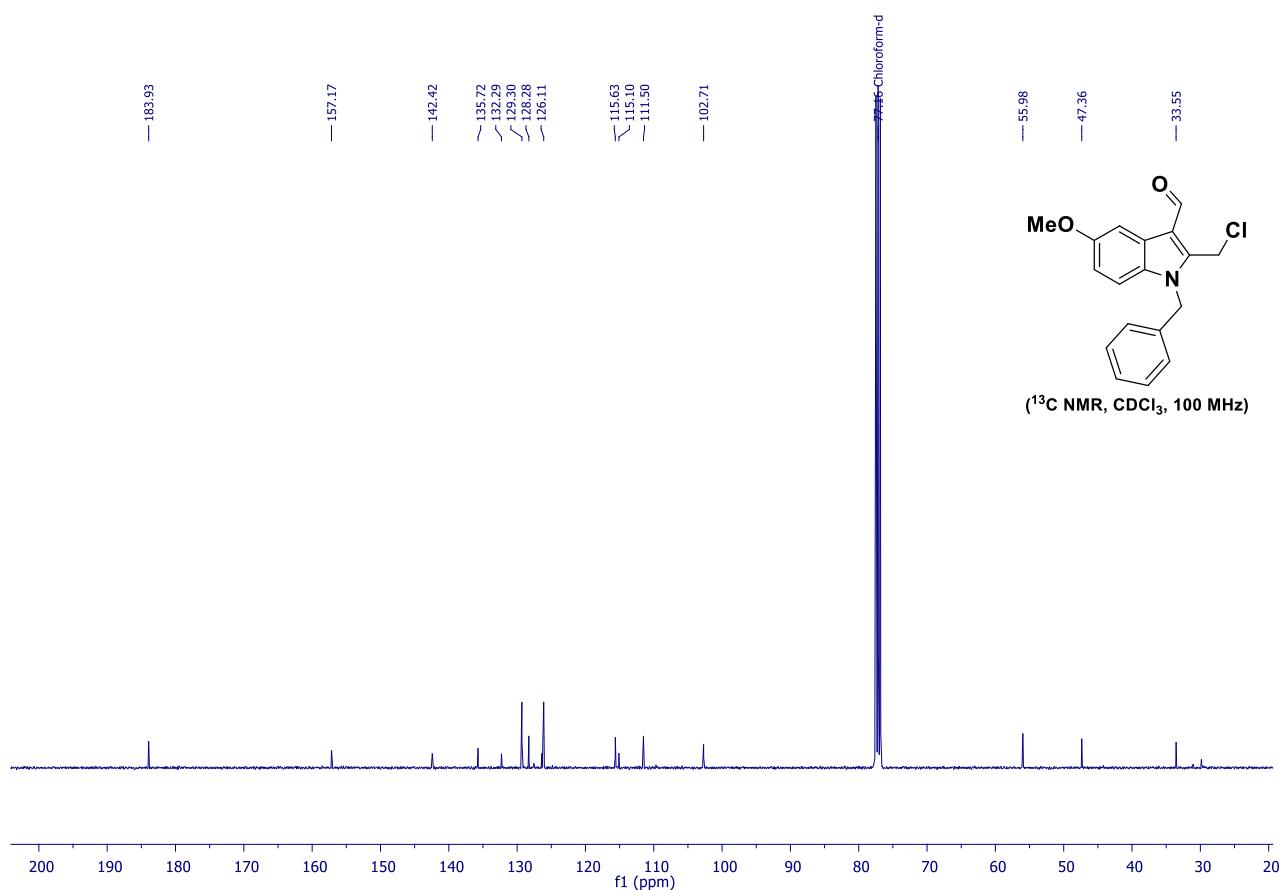
1- Benzyl -2-(chloromethyl)-5-iodo-1*H*-indole-3-carbaldehyde (689)



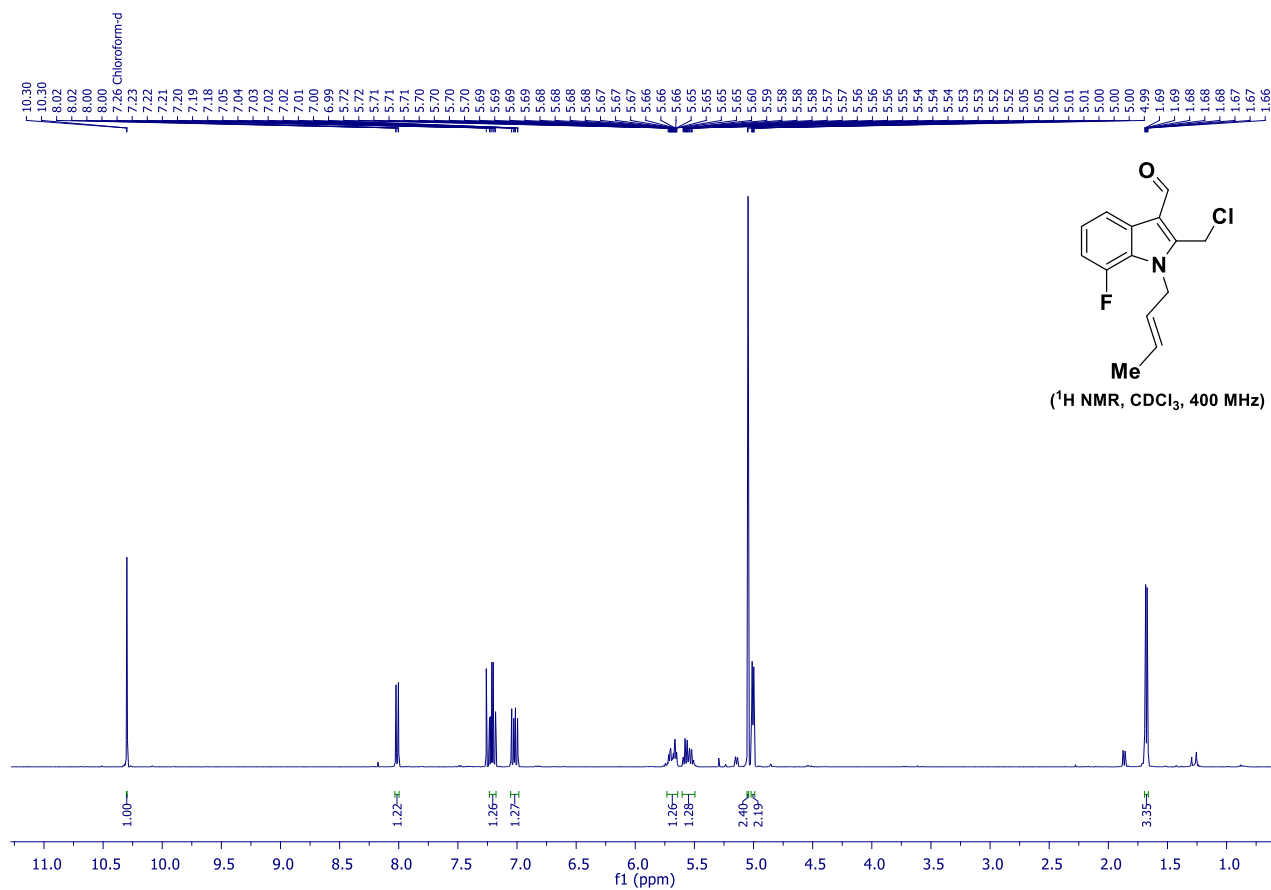


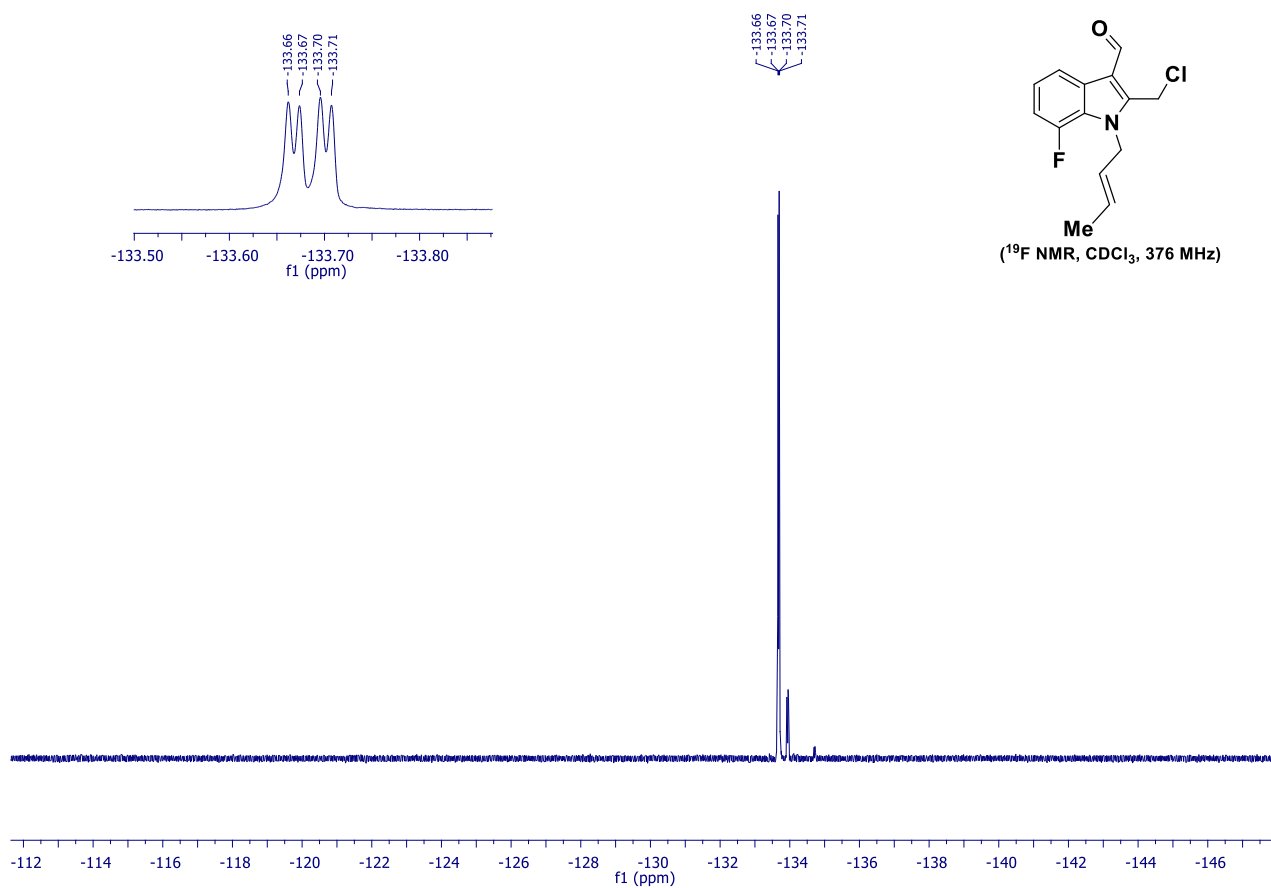
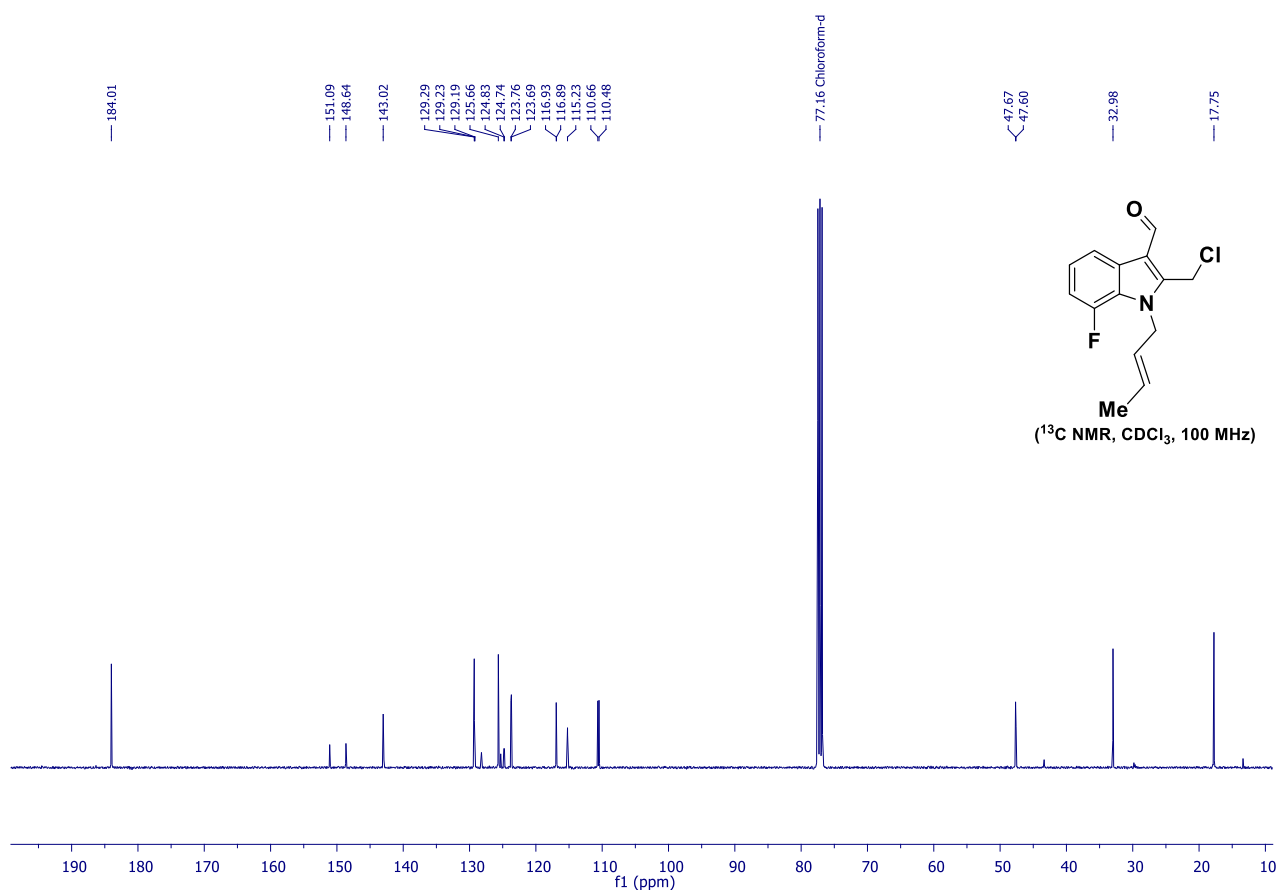
1-Benzyl-2-(chloromethyl)-5-methoxy-1H-indole-3-carbaldehyde (690)



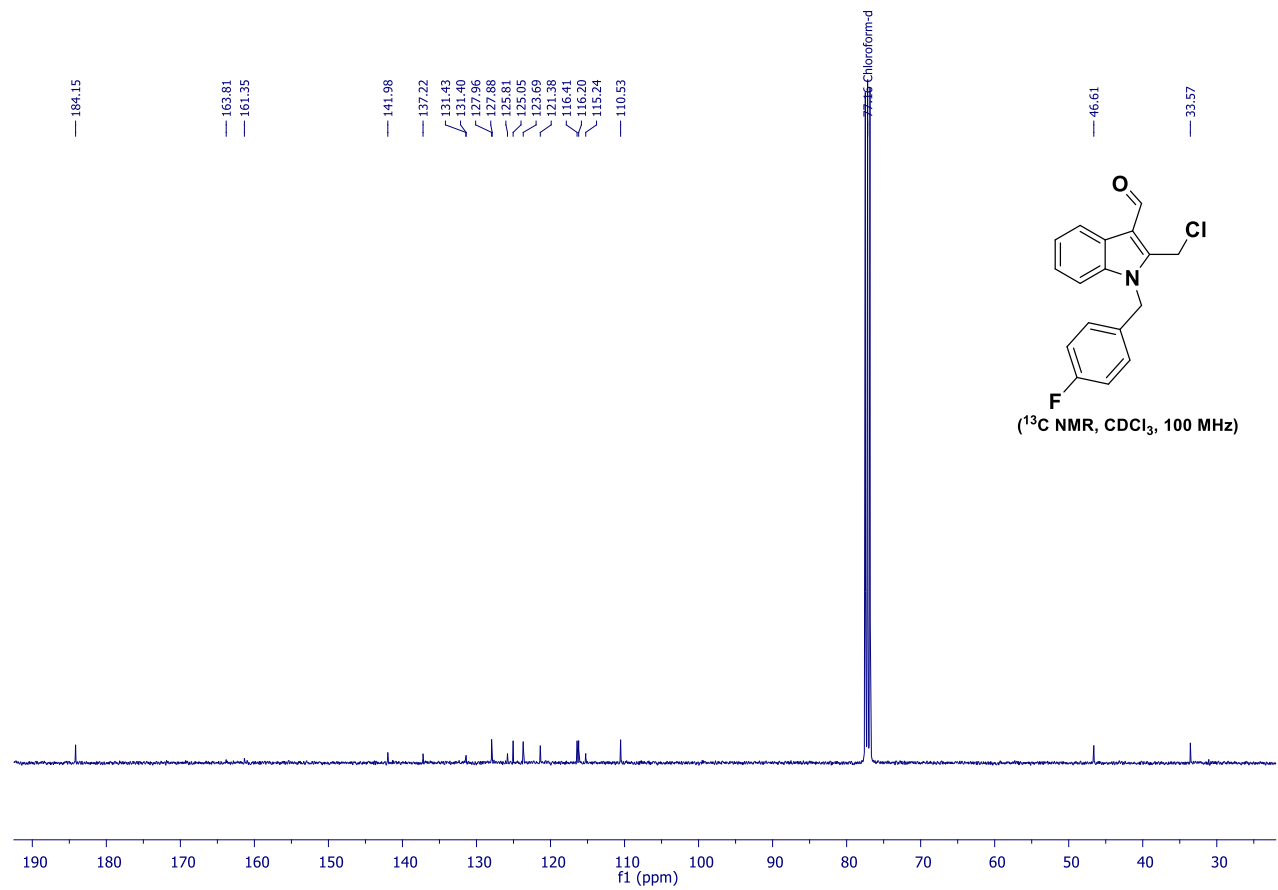
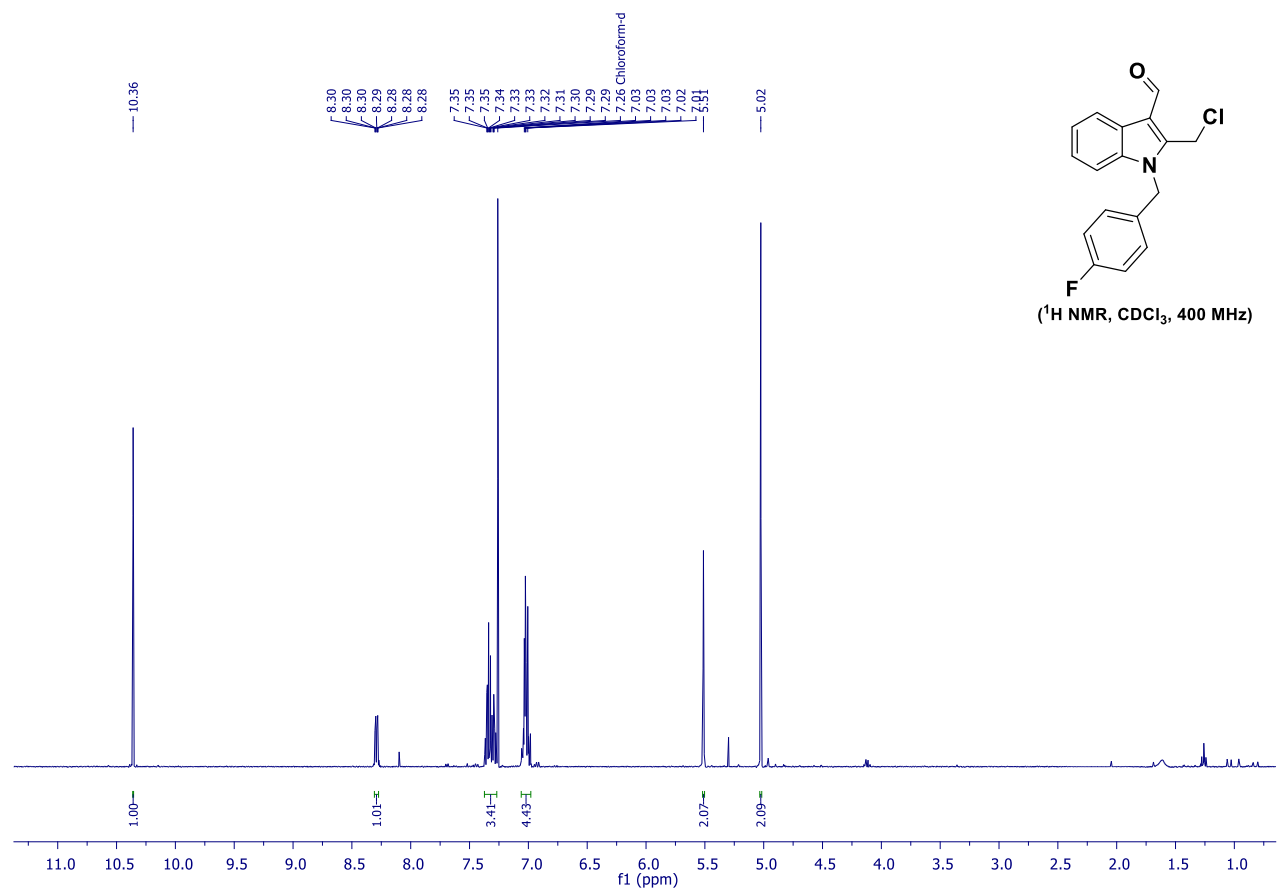


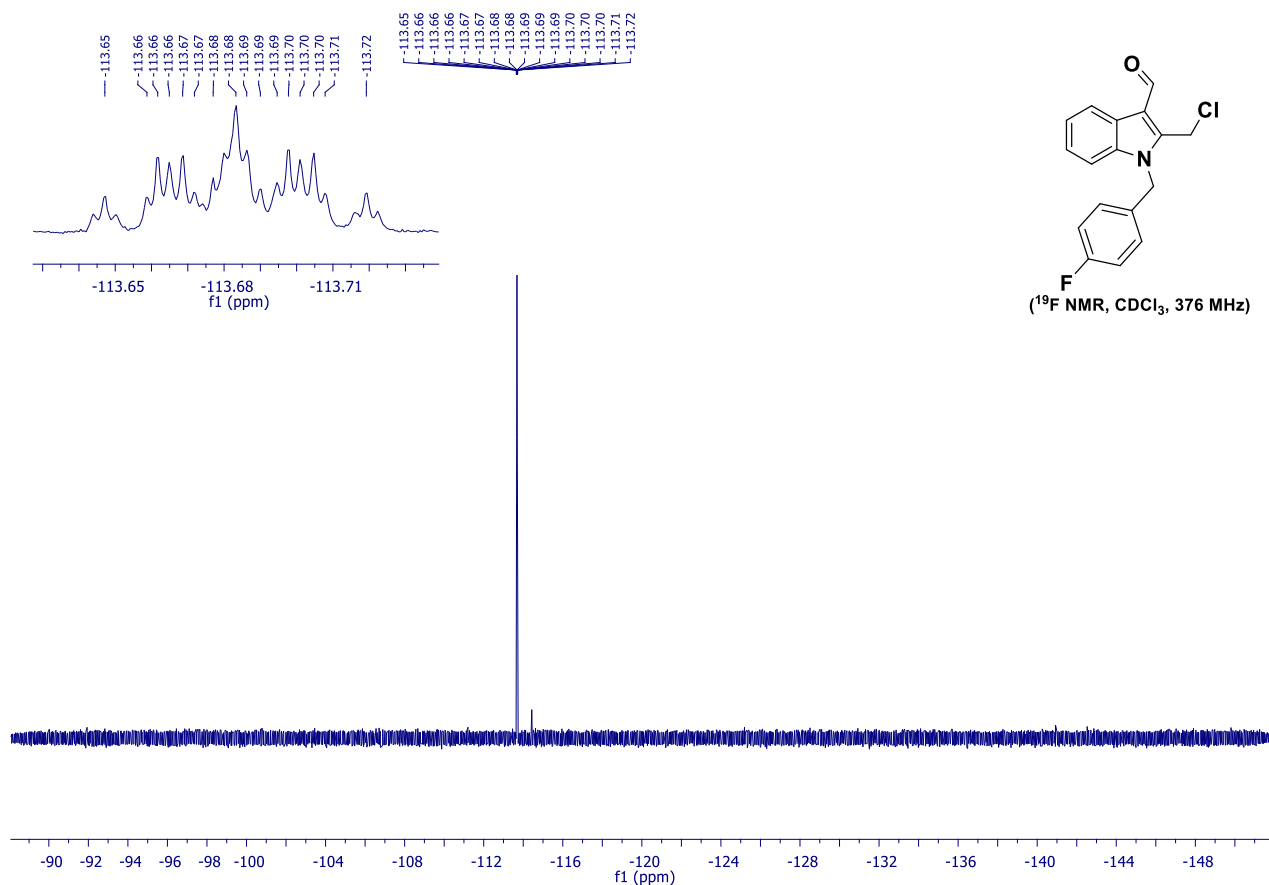
1-[(2E)-2-Buten-1-yl]-2-(chloromethyl)-7-fluoro-1H-indole-3-carbaldehyde (691)



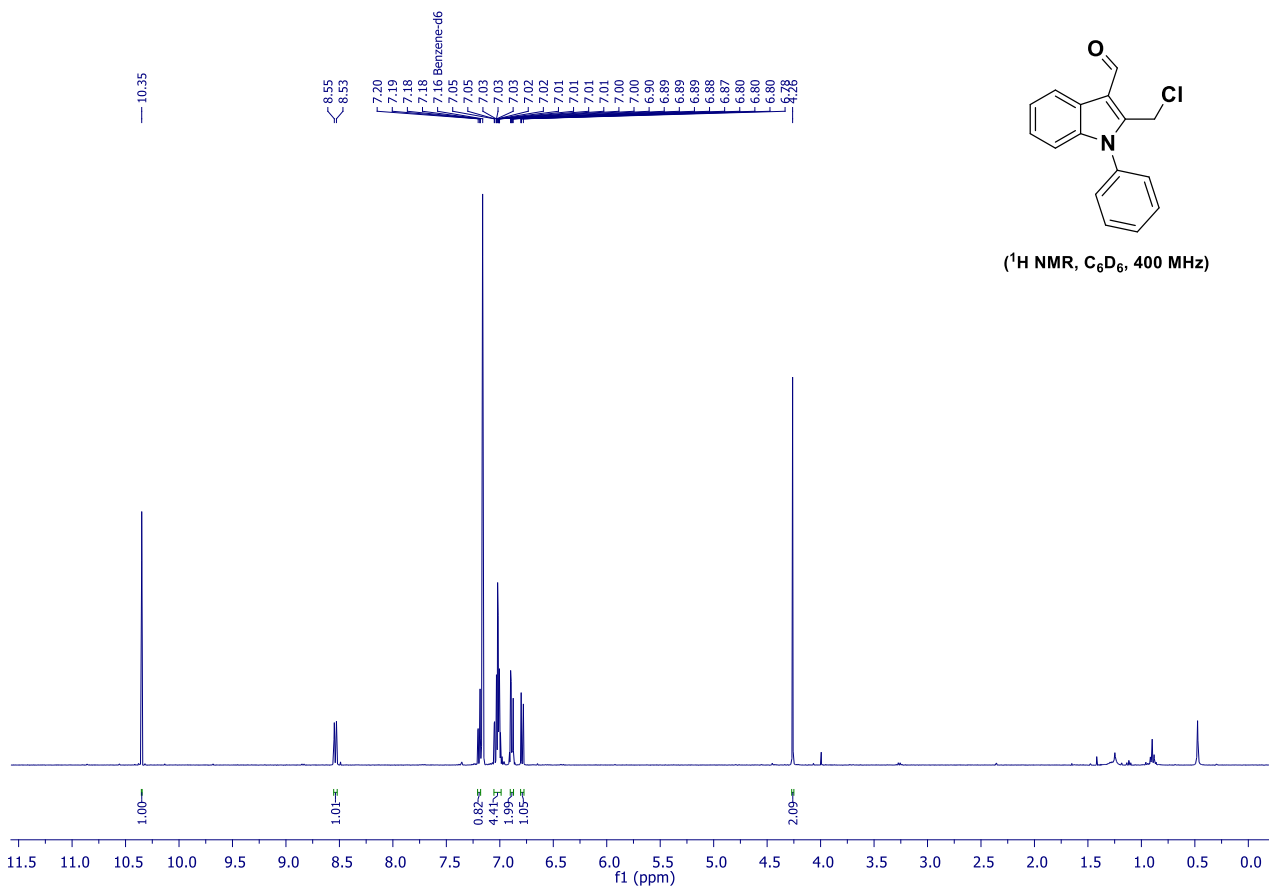


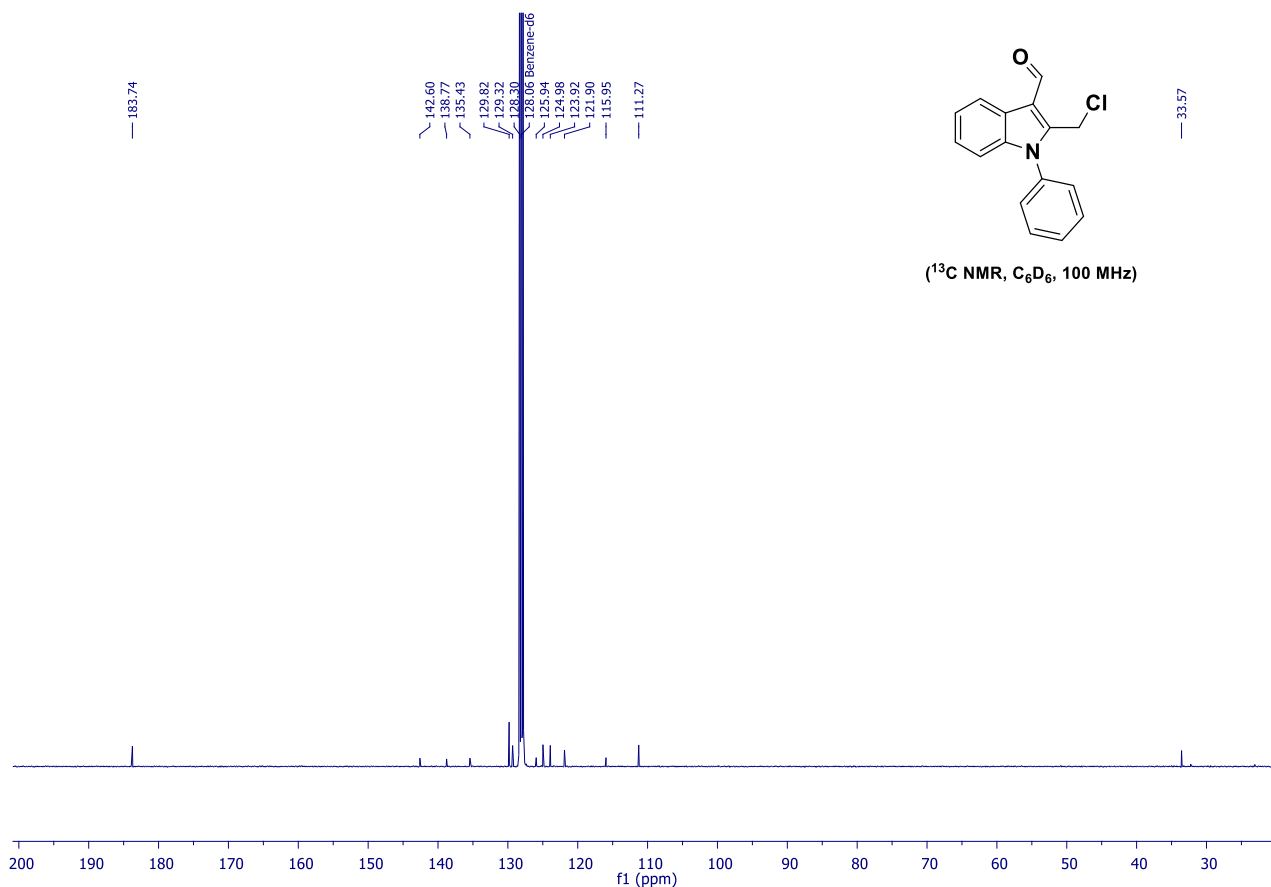
2-(Chloromethyl)-1-(4-fluorobenzyl)-1*H*-indole-3-carbaldehyde (692)



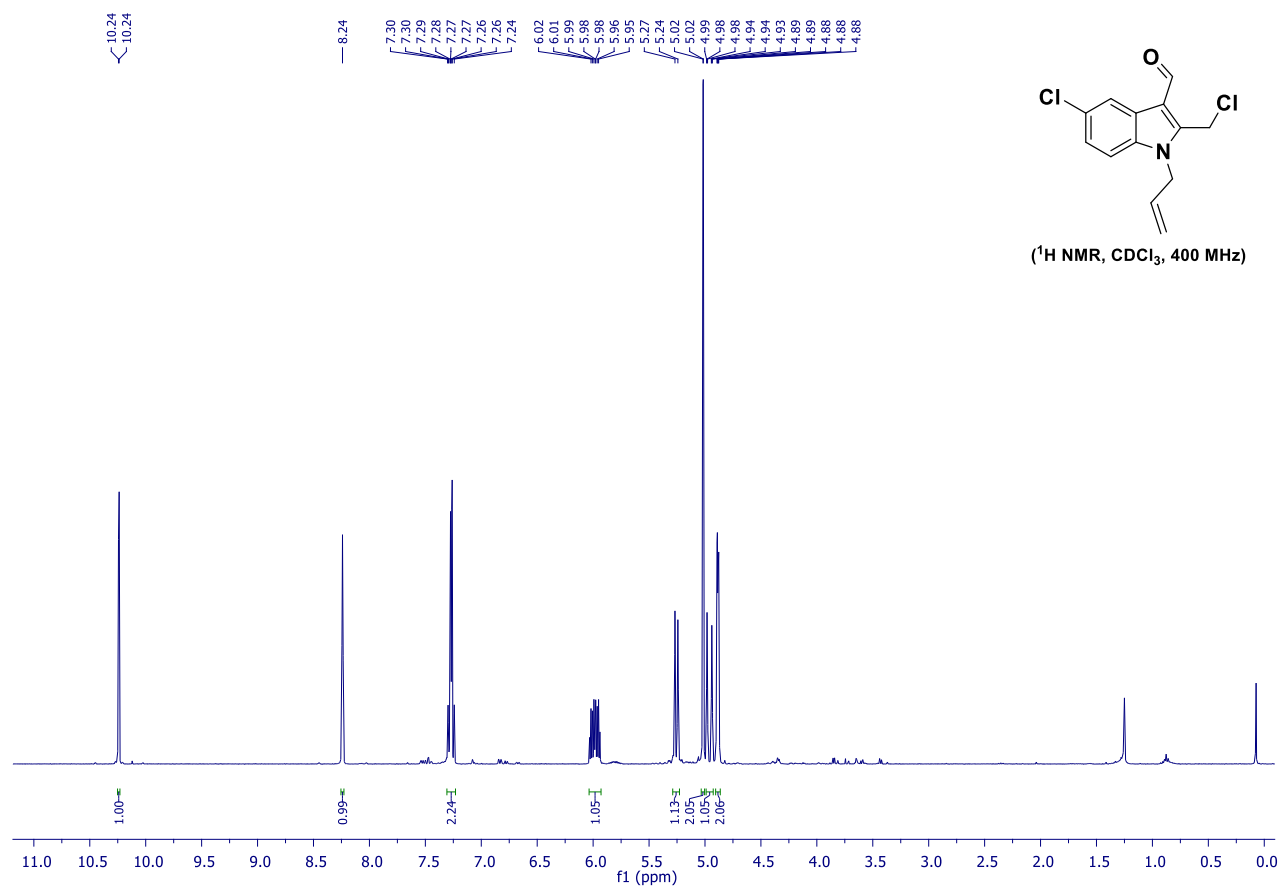


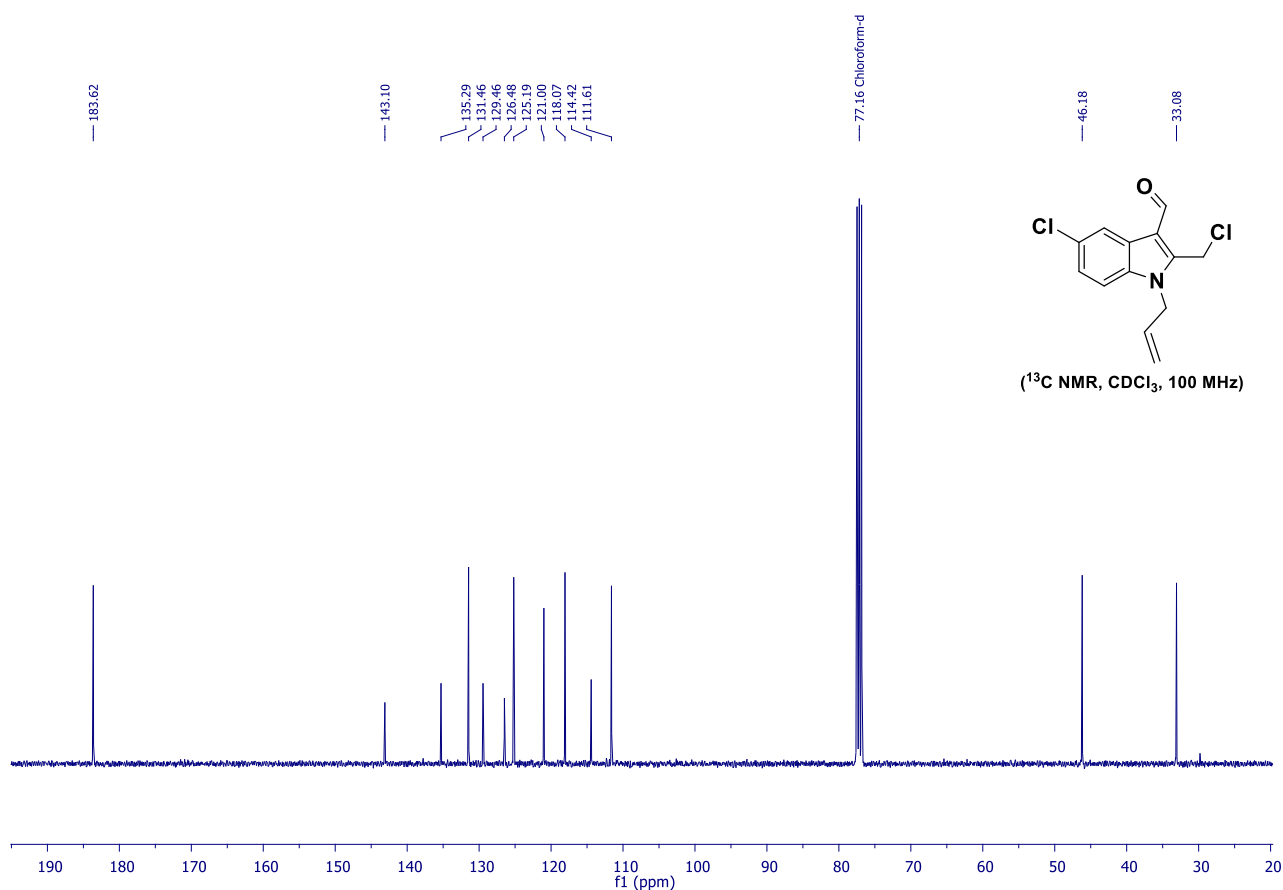
2-(Chloromethyl)-1-phenyl-1H-indole-carbaldehyde (693)



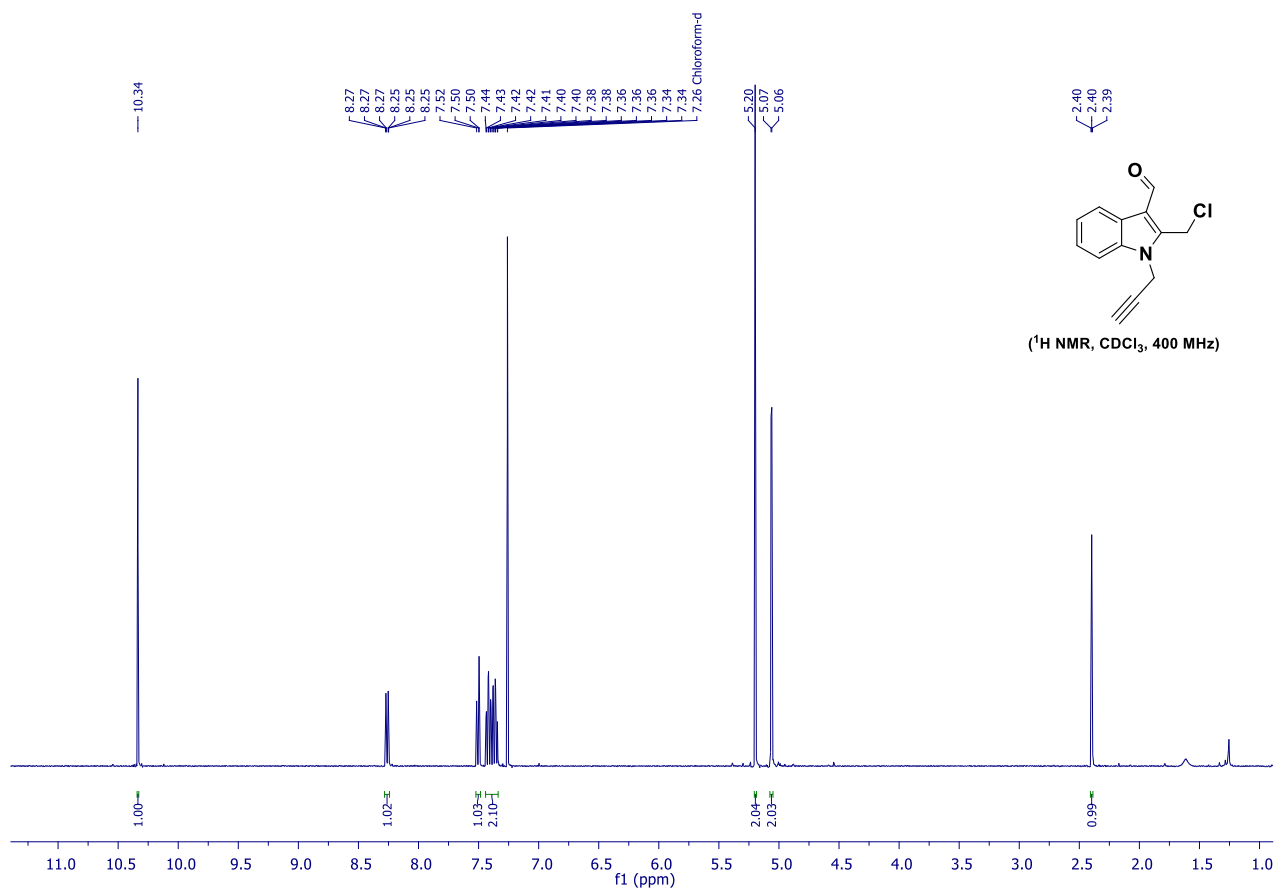


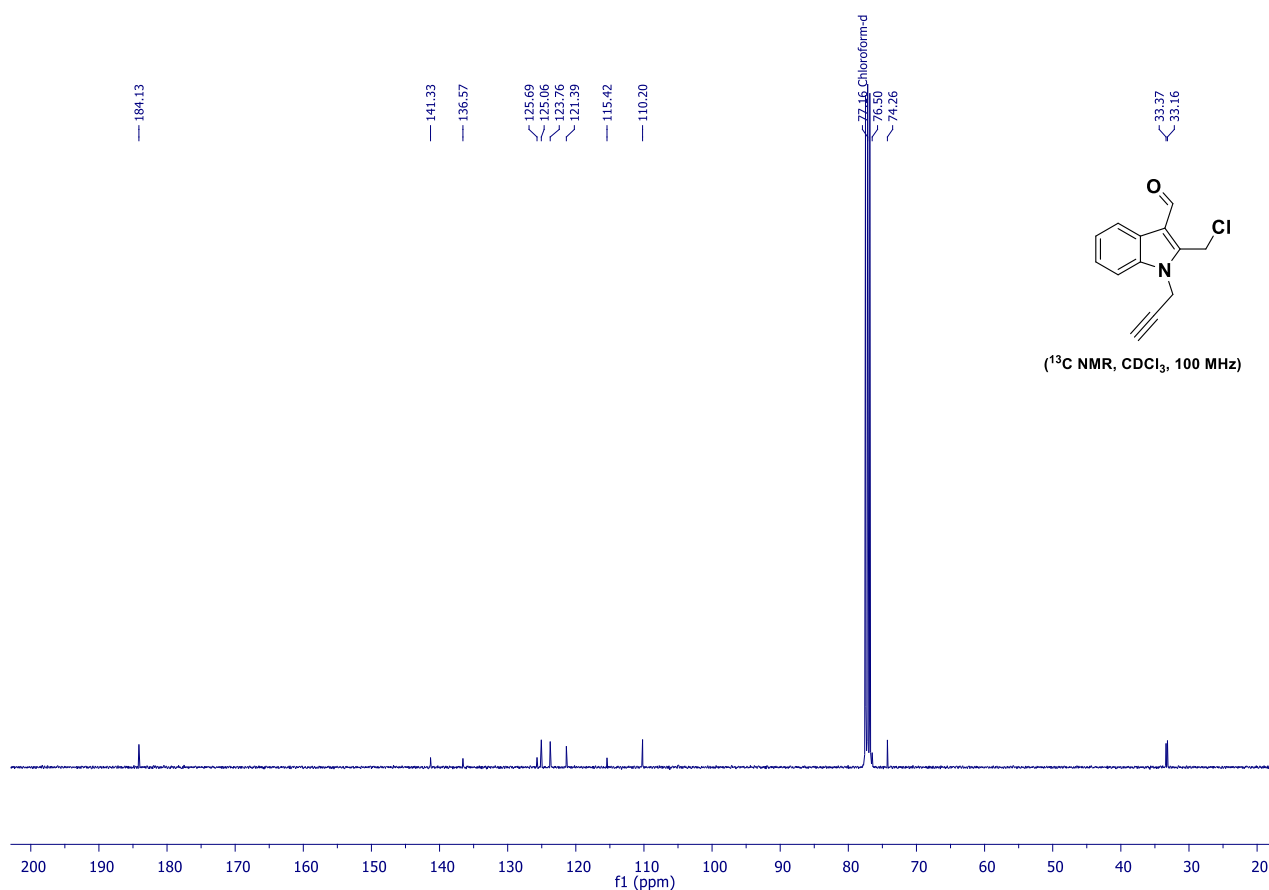
1-Allyl-5-chloro-2-(chloromethyl)-1H-indole-3-carbaldehyde (694)



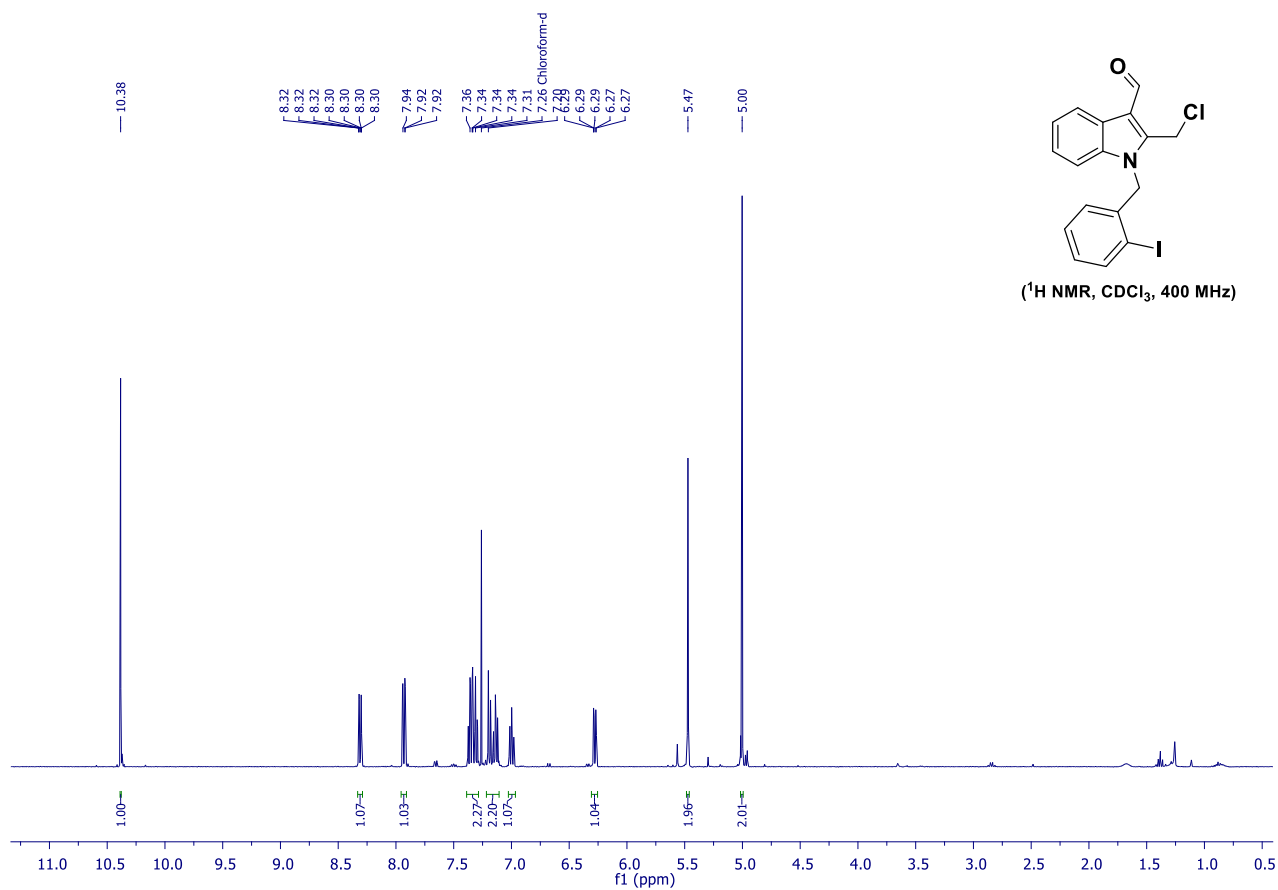


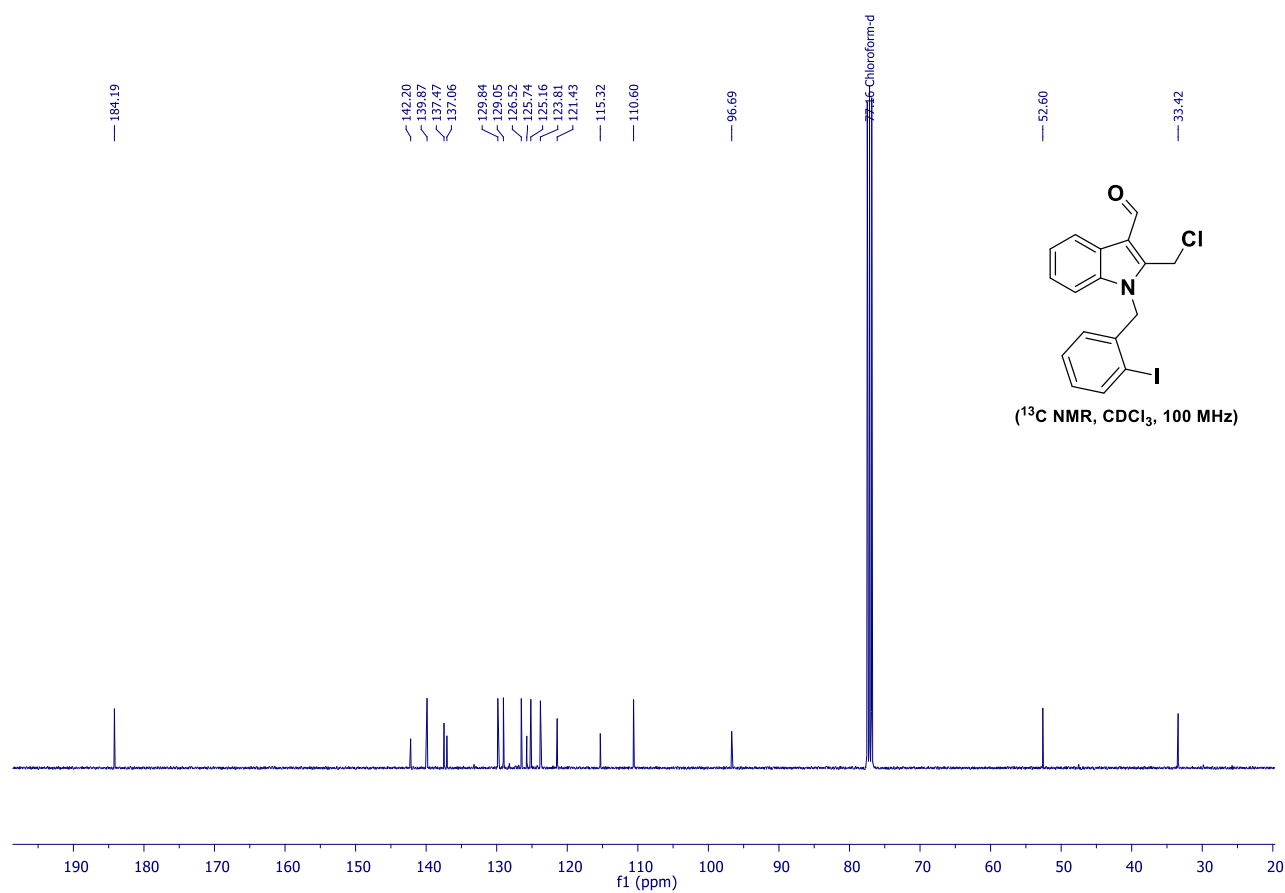
2-(Chloromethyl)-1-(2-propyn-1-yl)-1H-indole-3-carbaldehyde (695)



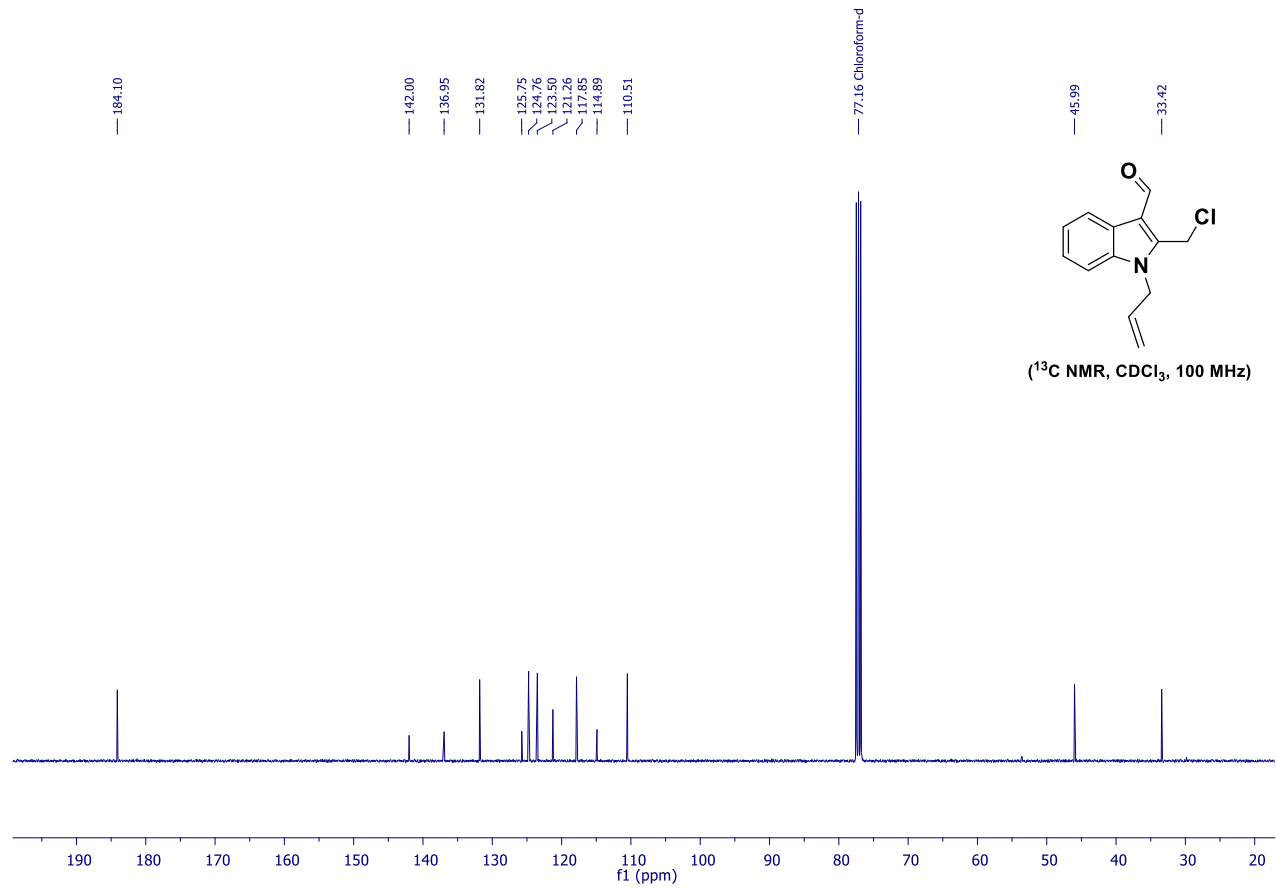
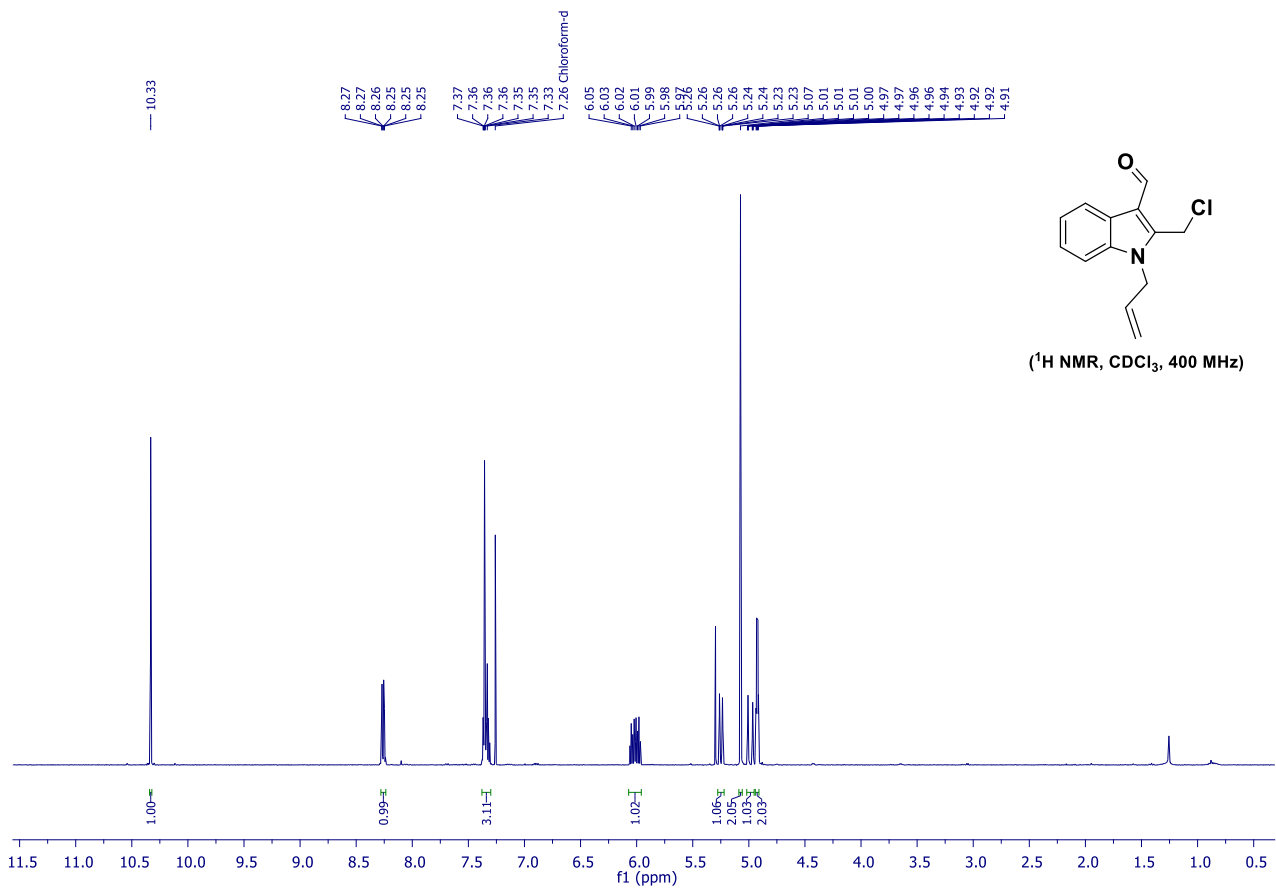


2-(Chloromethyl)-1-(2-iodobenzyl)-1H-indole-3-carbaldehyde (696)

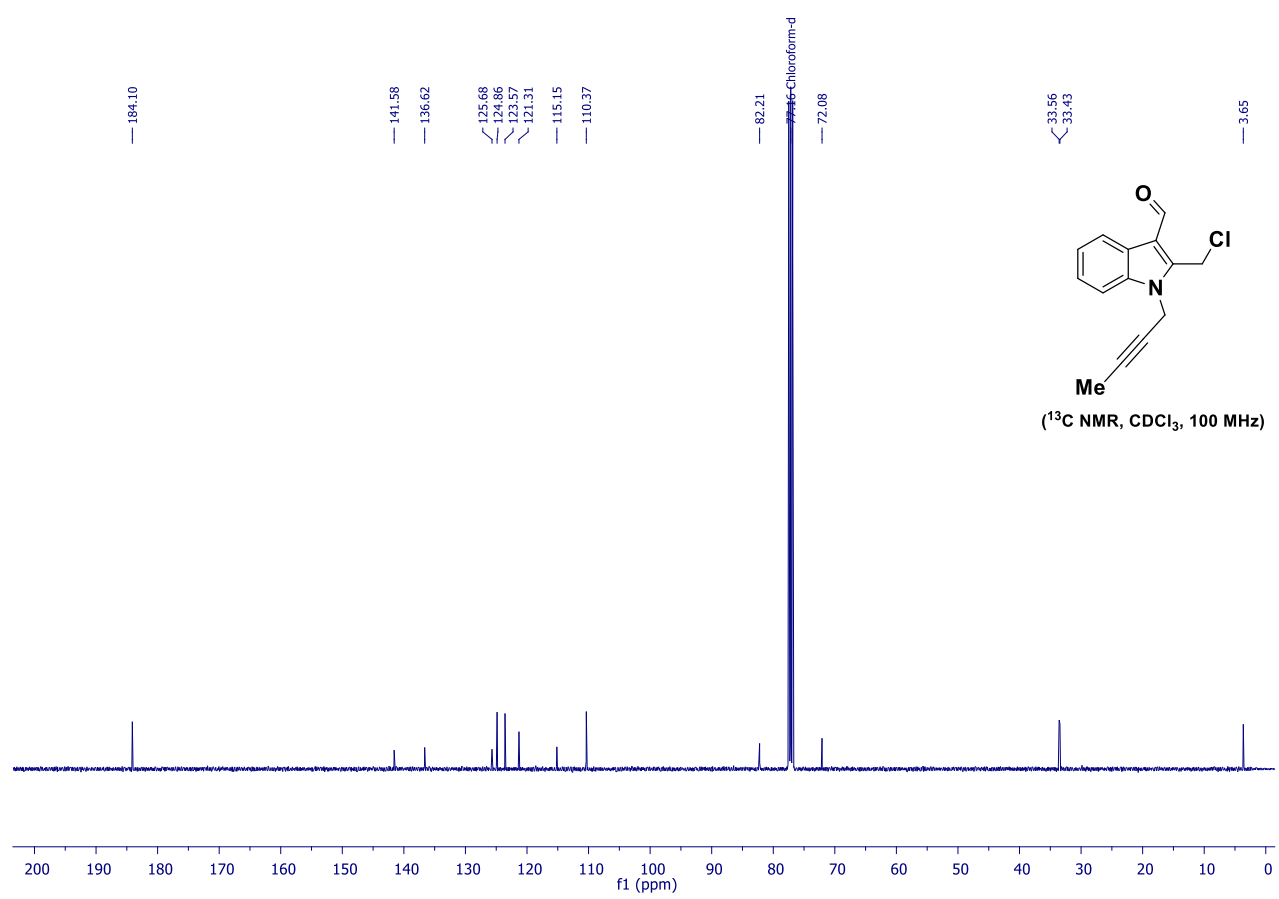
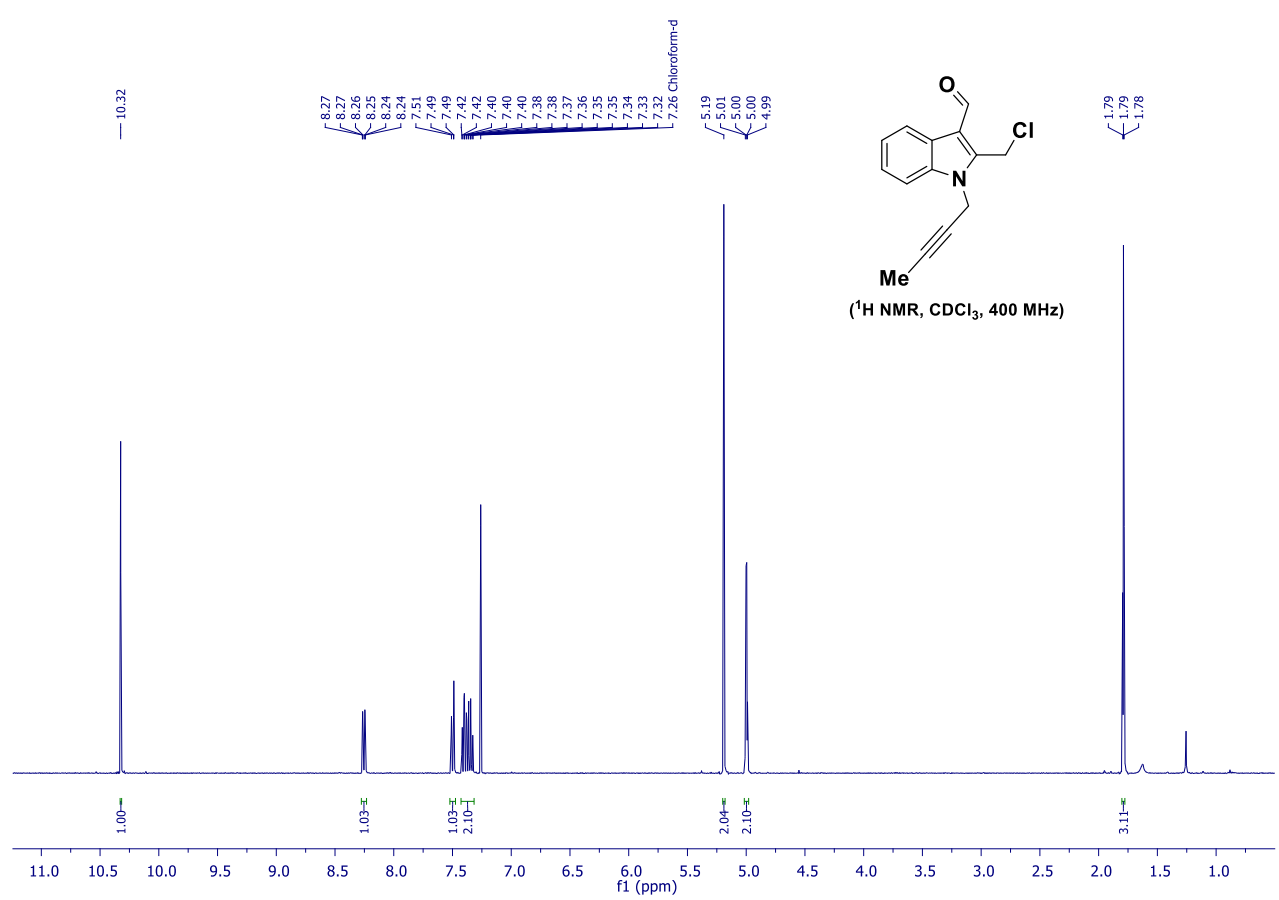




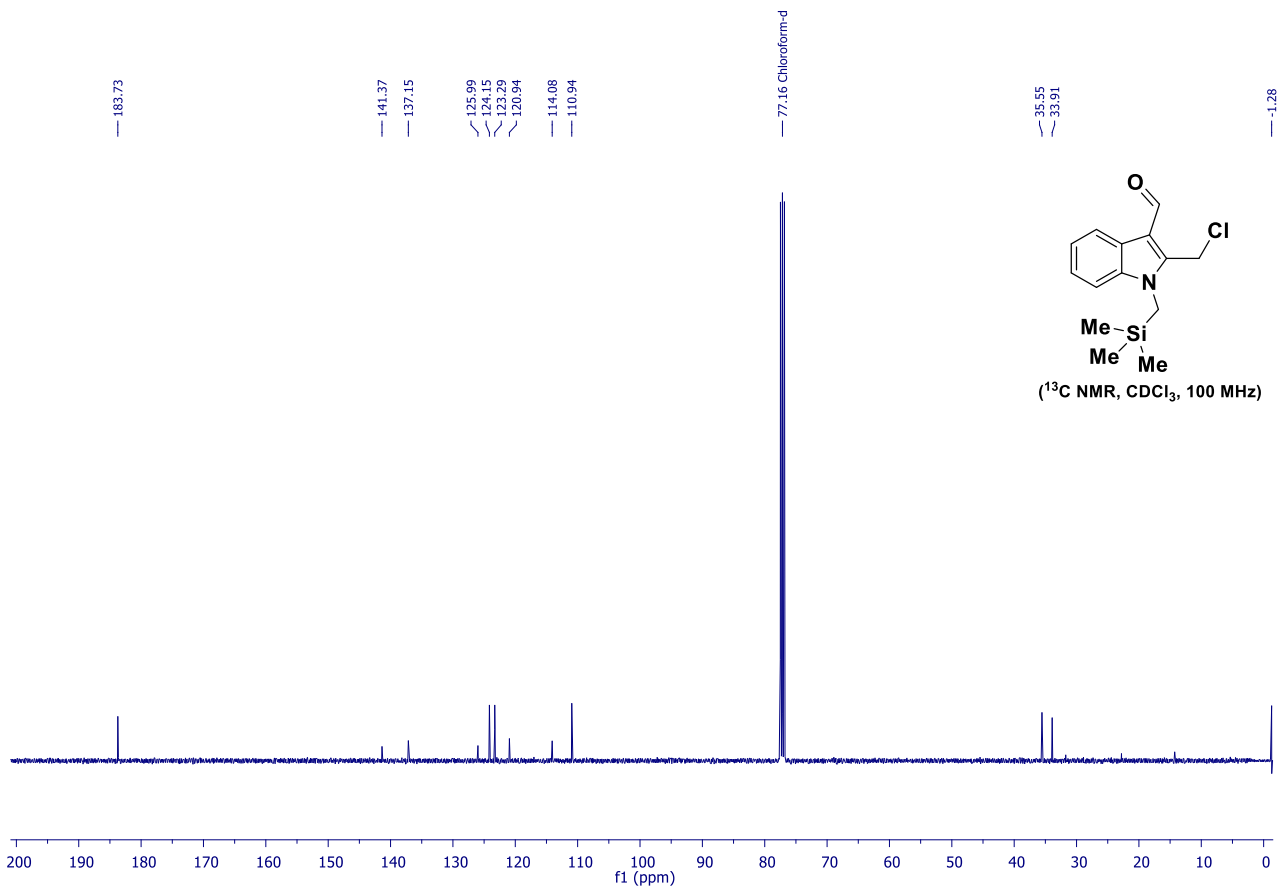
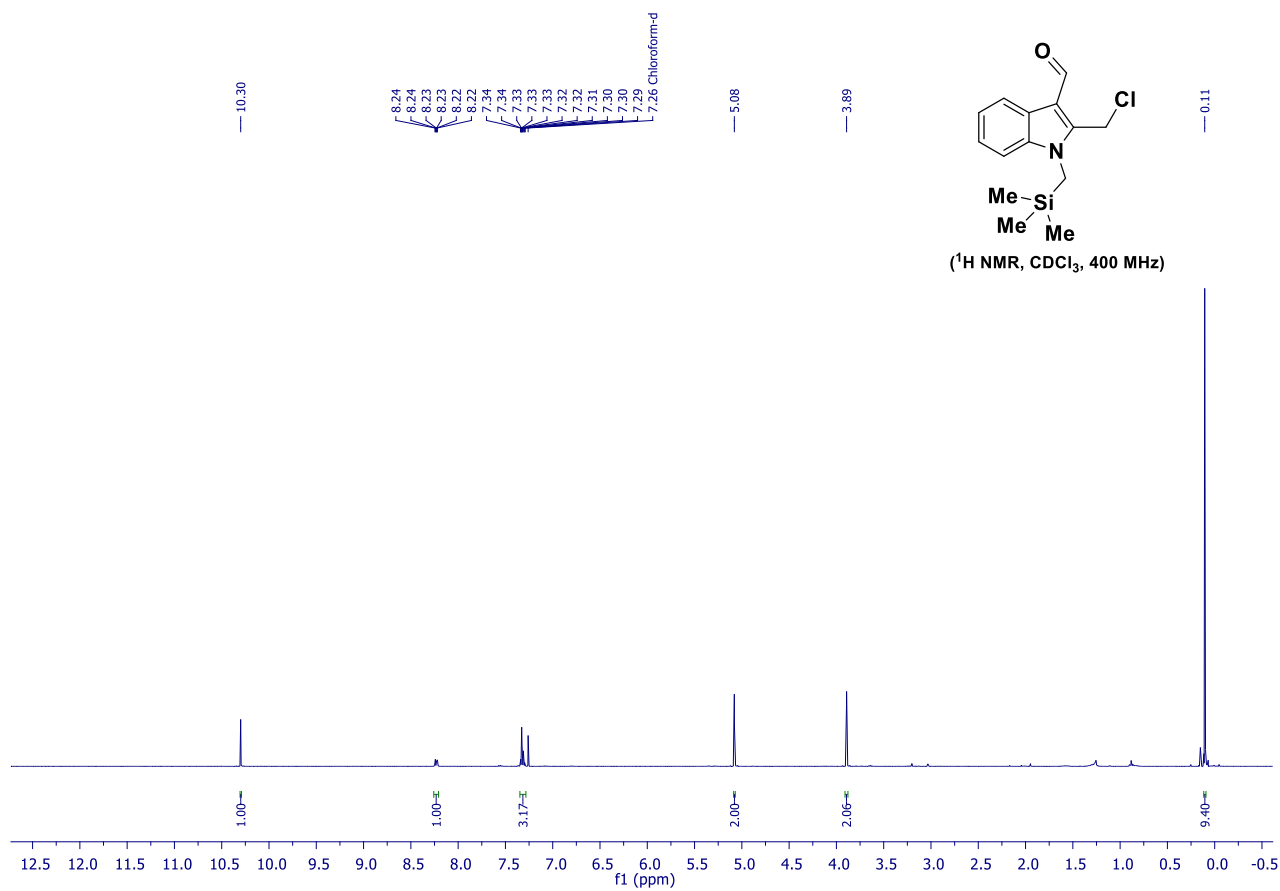
1-Allyl-2-(chloromethyl)-1*H*-indole-3-carbaldehyde (697)



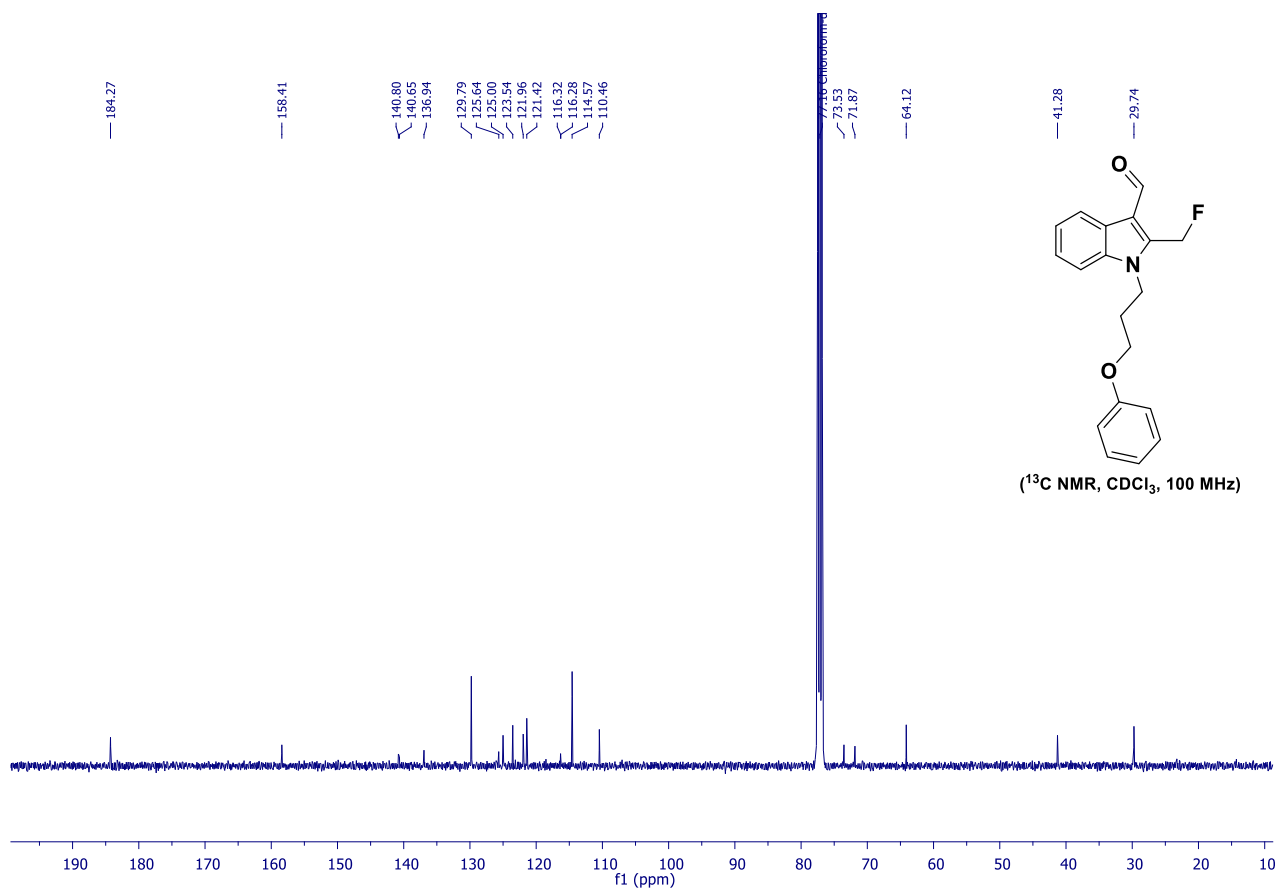
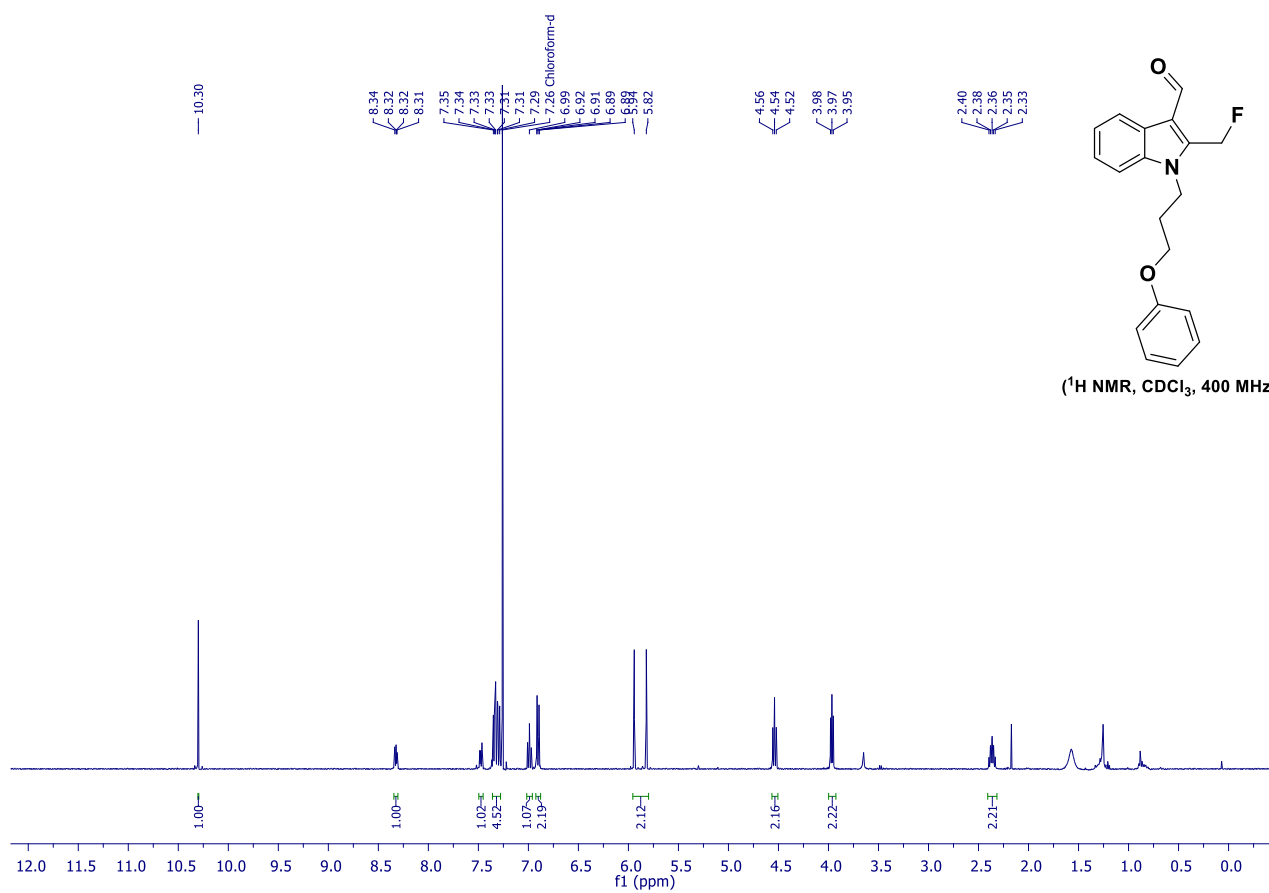
1-(2-Butyn-1-yl)-2-(chloromethyl)-1*H*-indole-3-carbaldehyde (698)

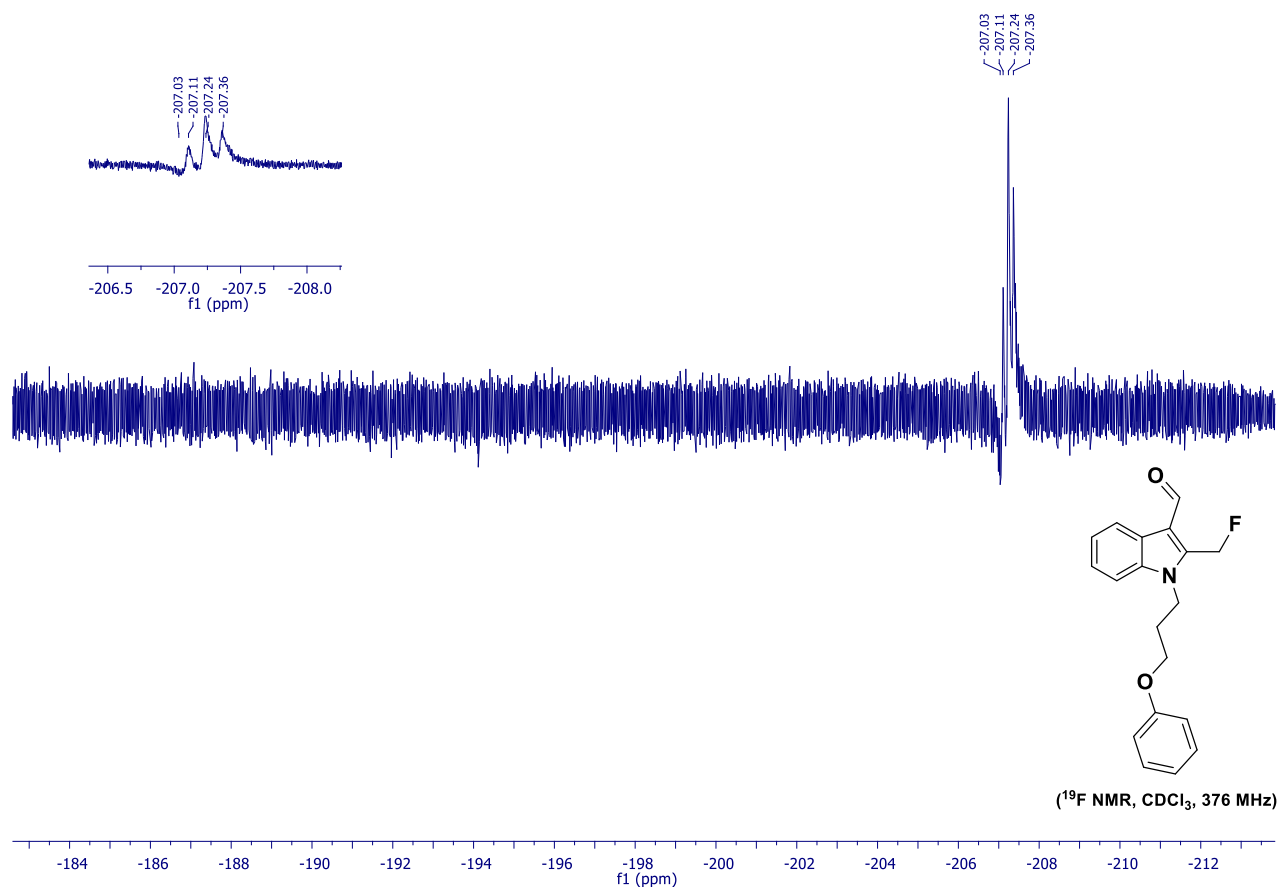


2-(Chloromethyl)-1-[(trimethylsilyl)methyl]-1*H*-indole-3-carbaldehyde (699)

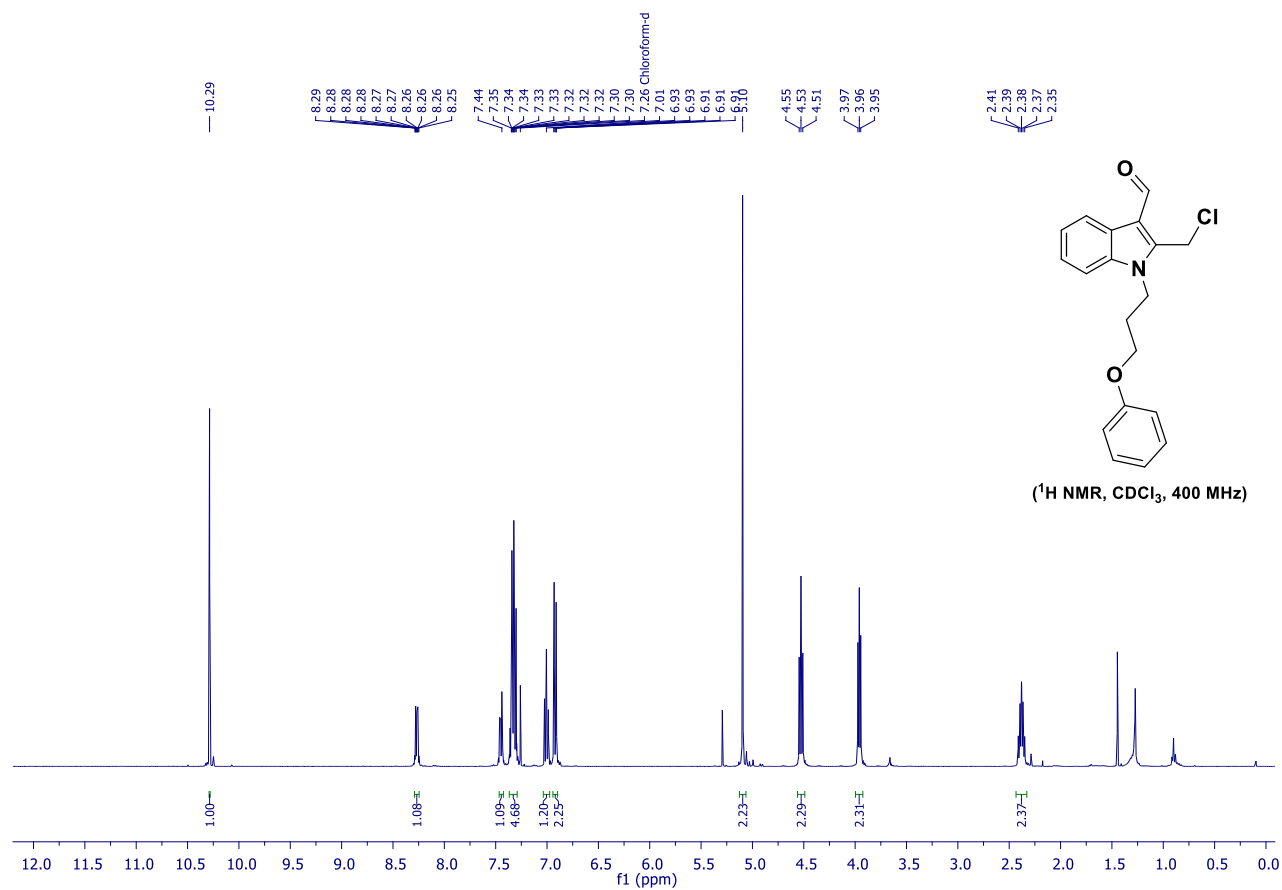


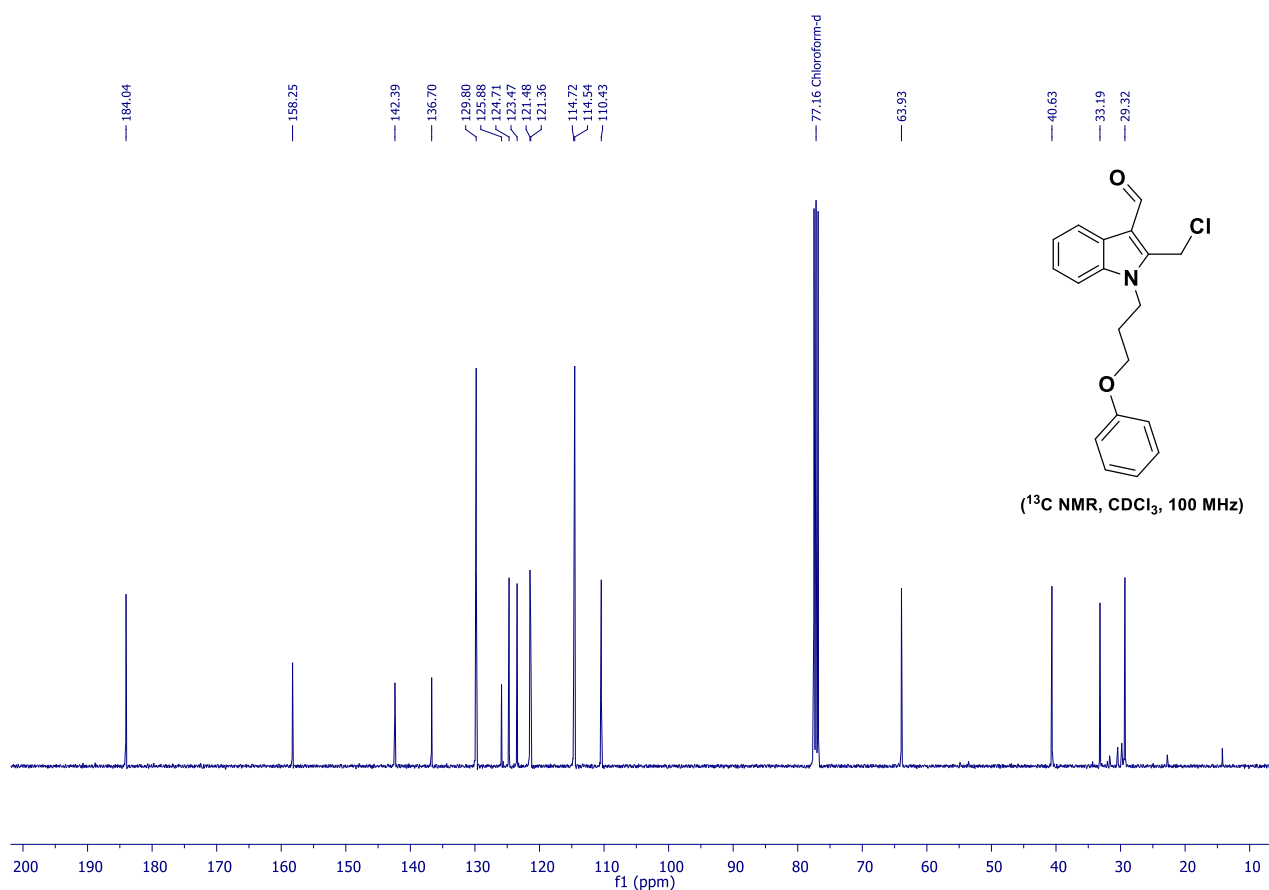
2-(Fluoromethyl)-1-(3-phenoxypropyl)-1H-indole-3-carbaldehyde (700)



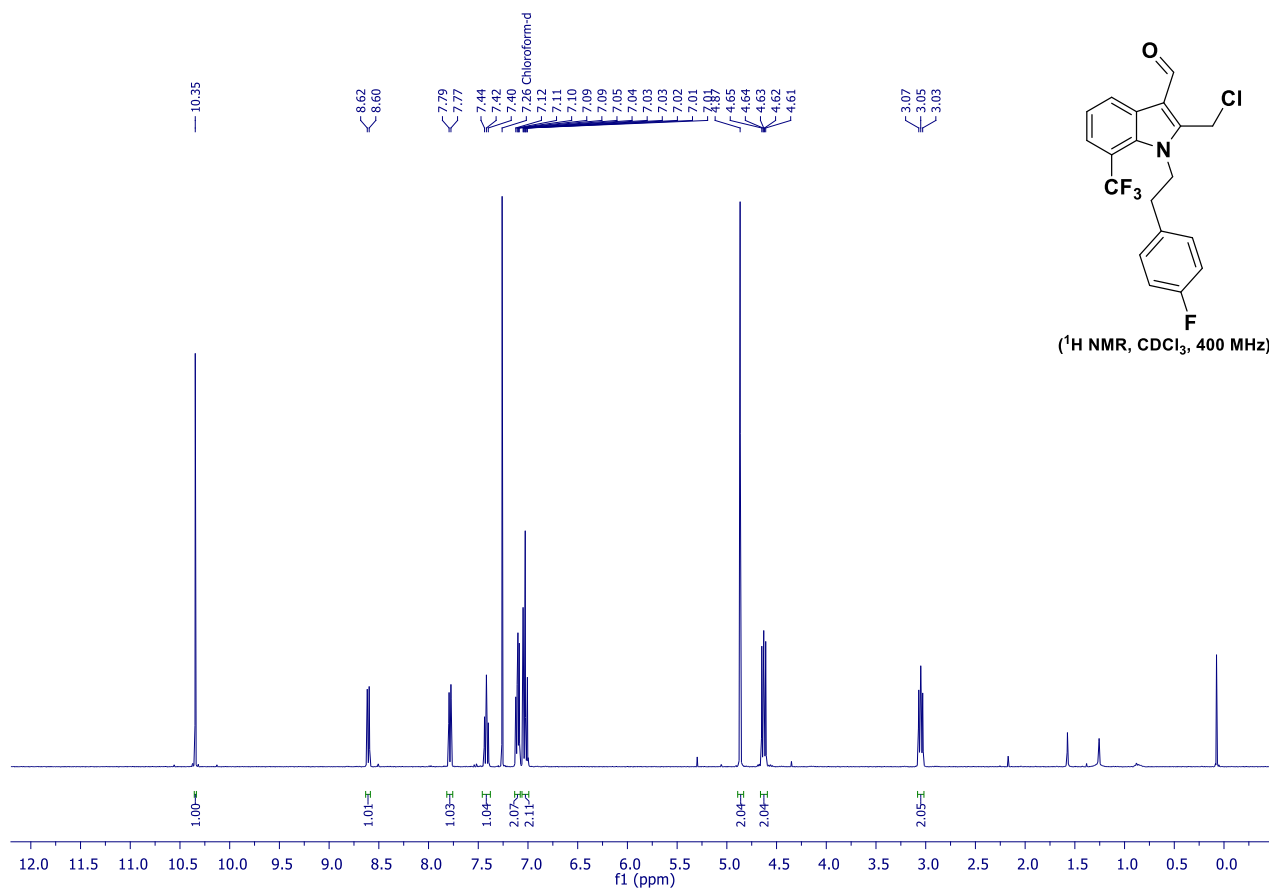


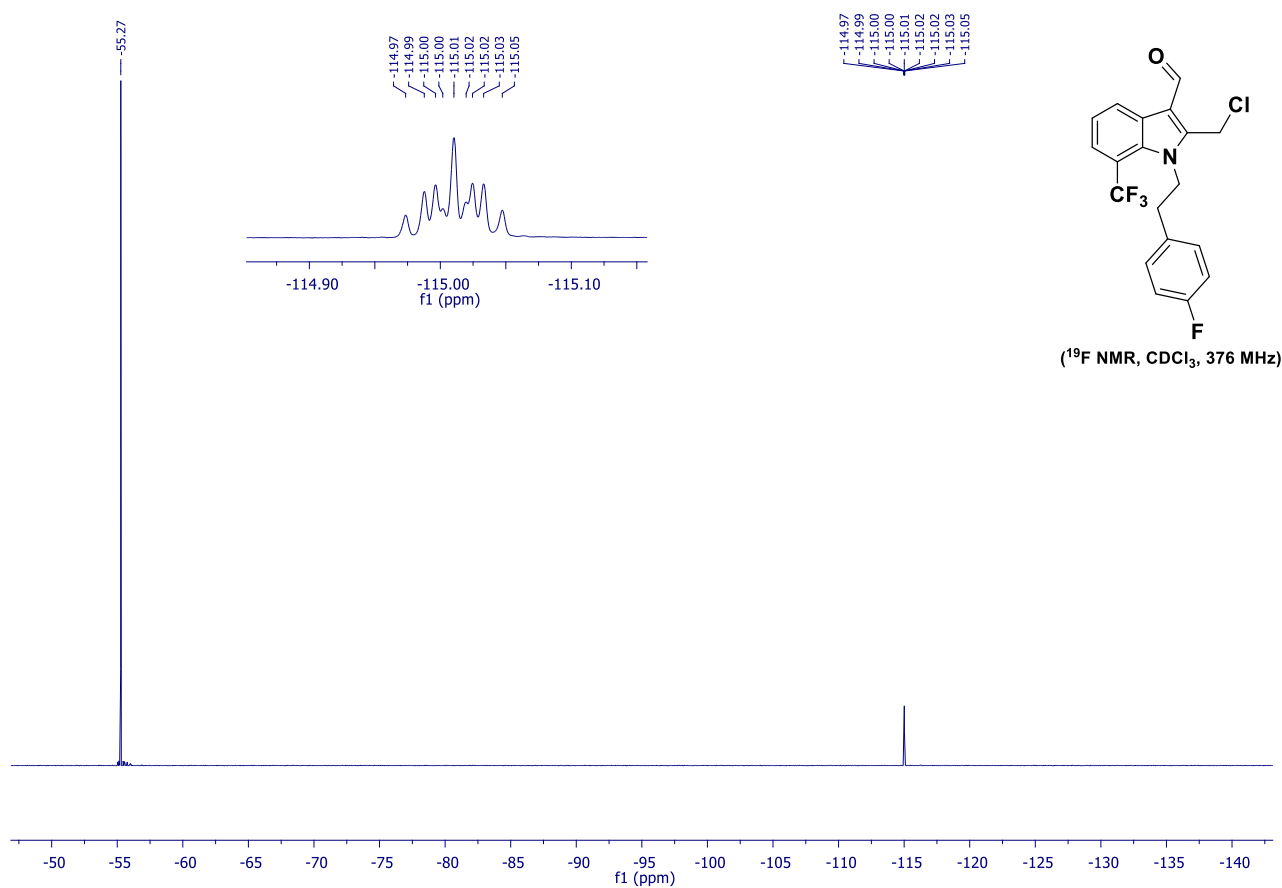
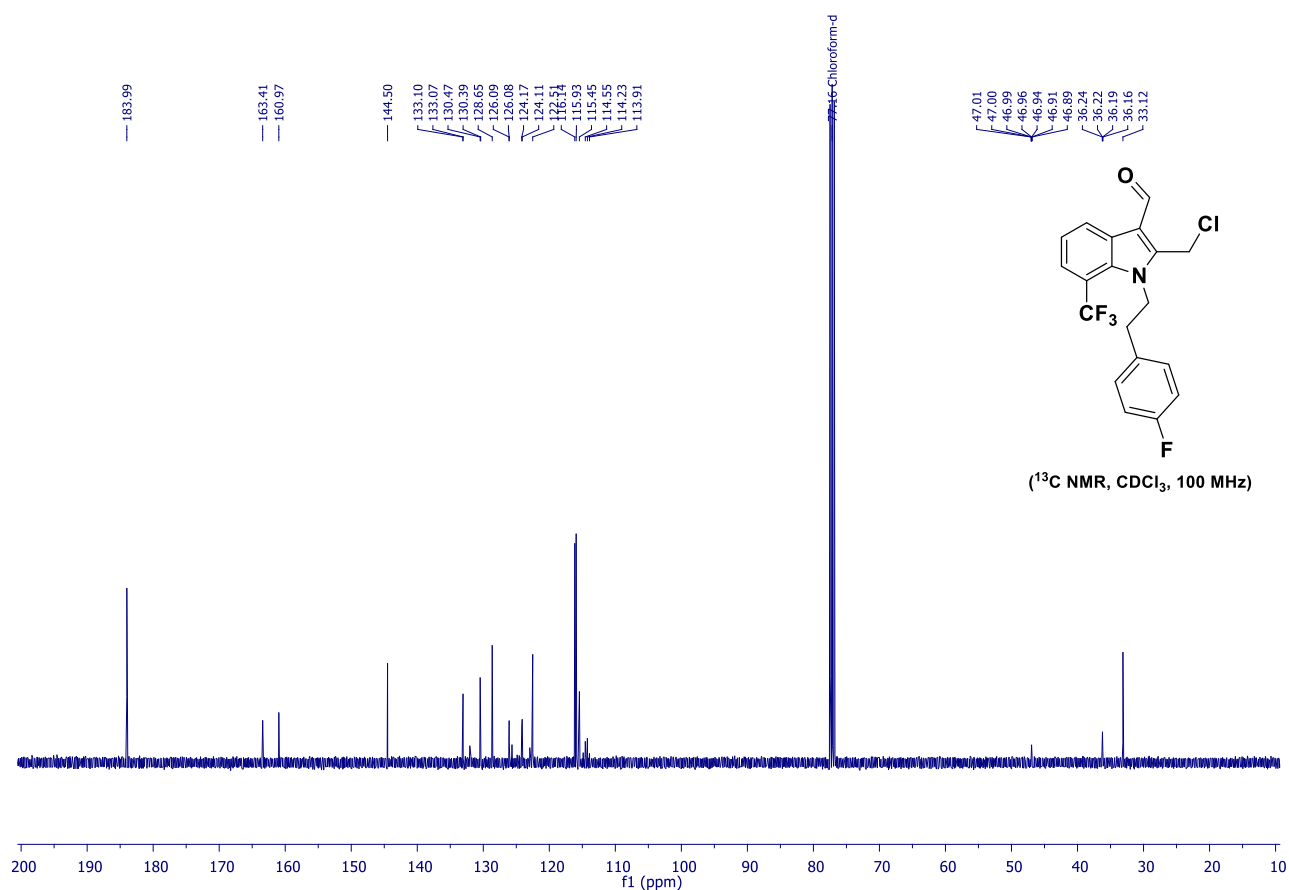
2-(Chloromethyl)-1-(3-phenoxypropyl)-1H-indole-3-carbaldehyde (701)



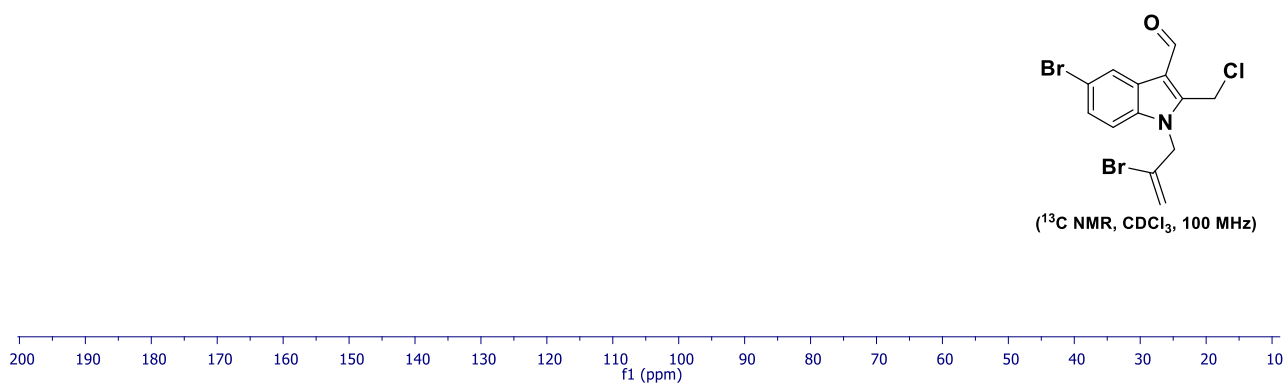
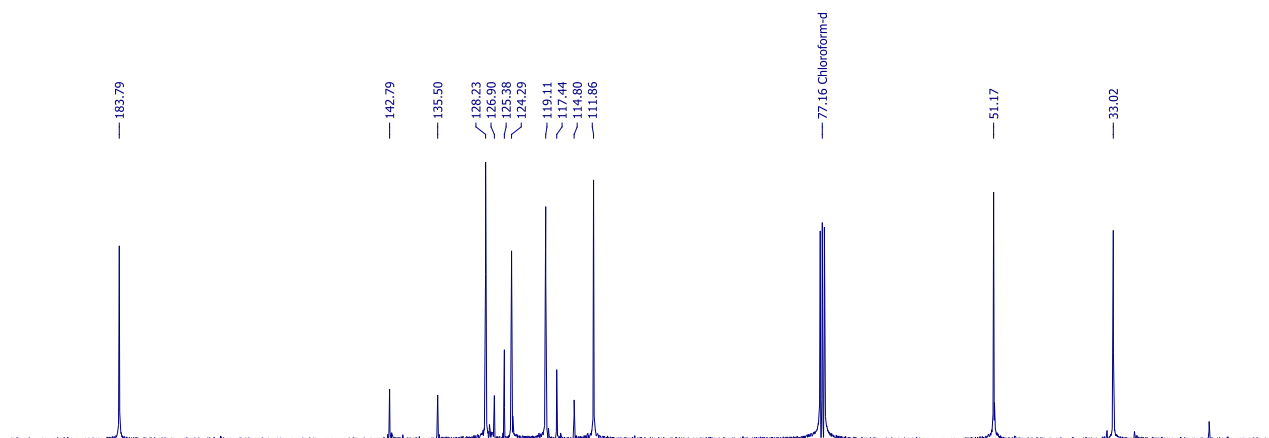
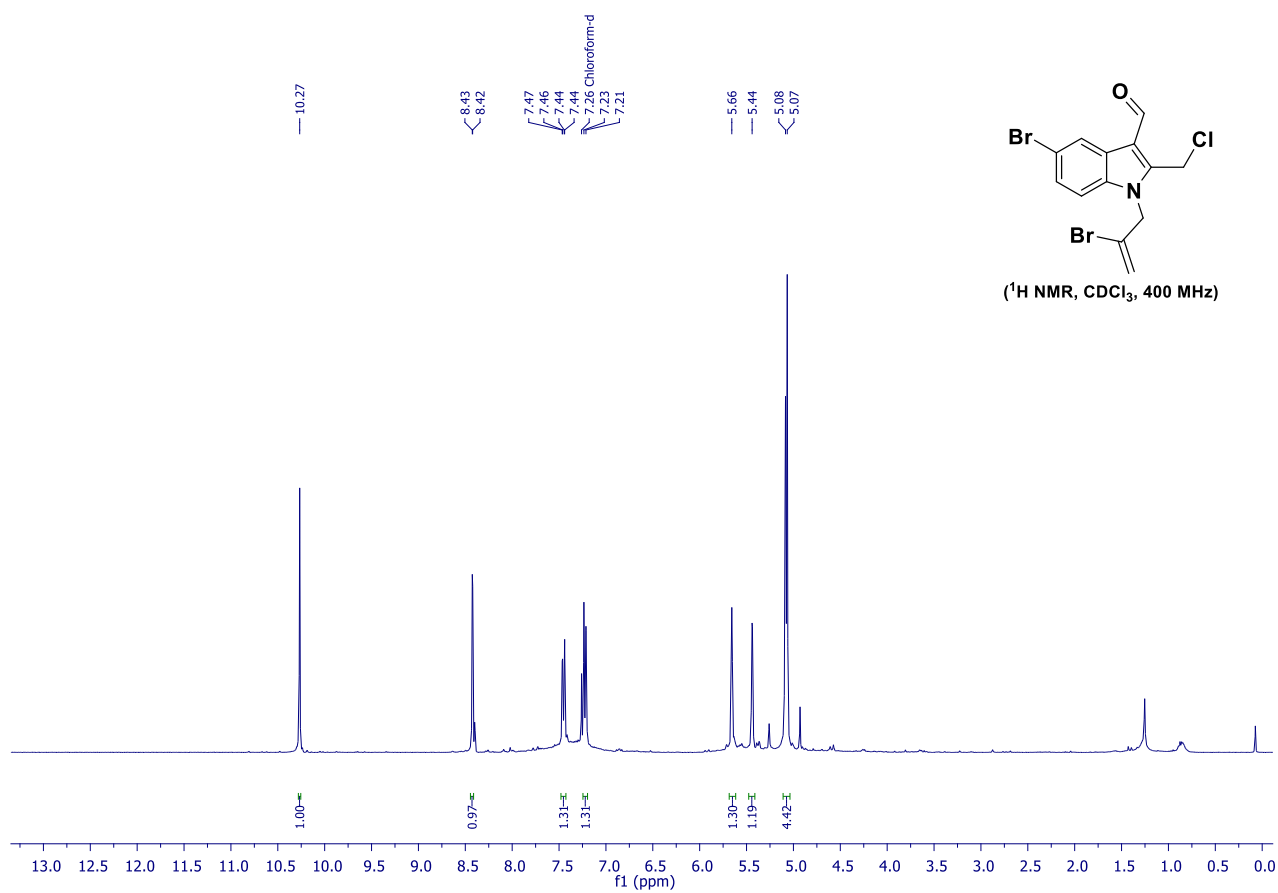


2-(Chloromethyl)-1-[2-(4-fluorophenyl)ethyl]-7-(trifluoromethyl)-1H-indole-3-carbaldehyde (702)

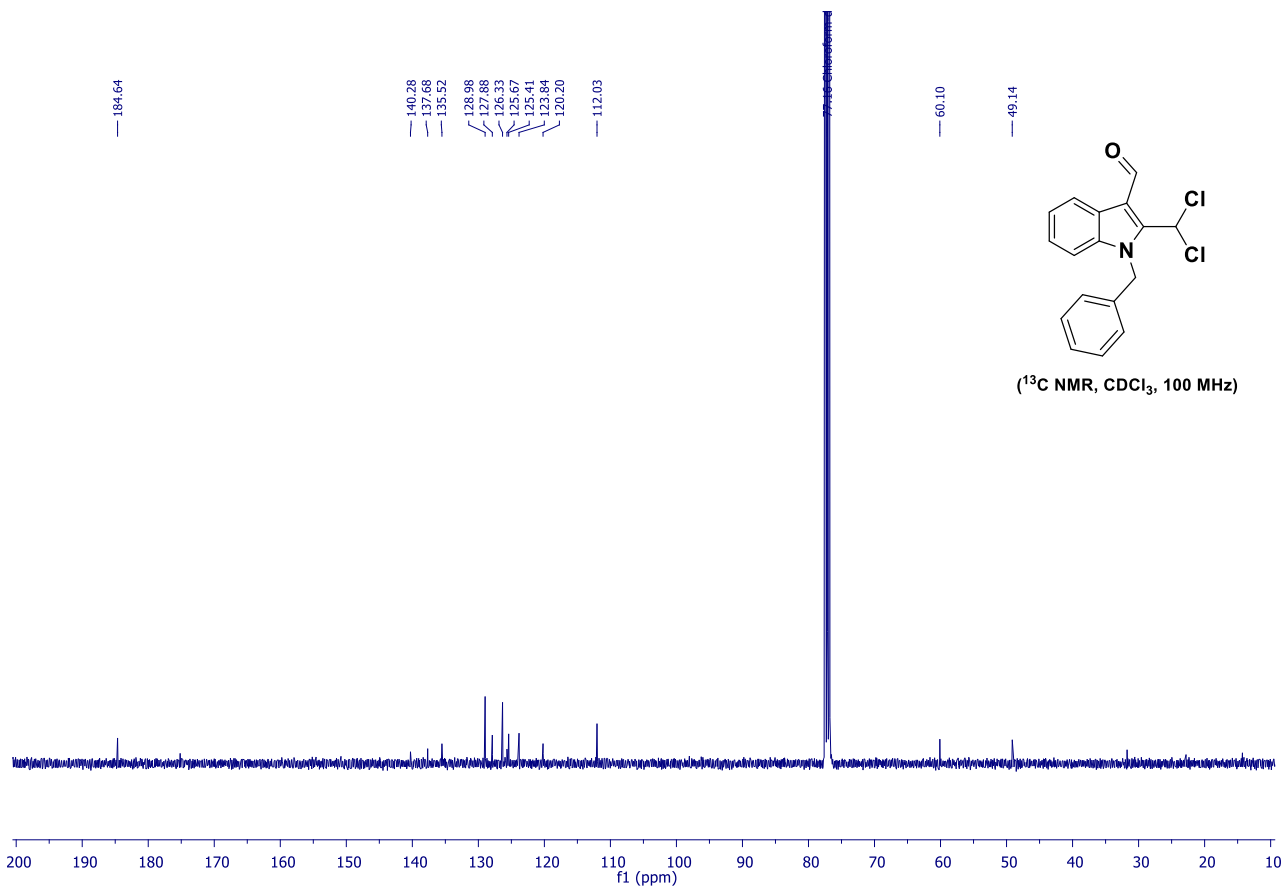
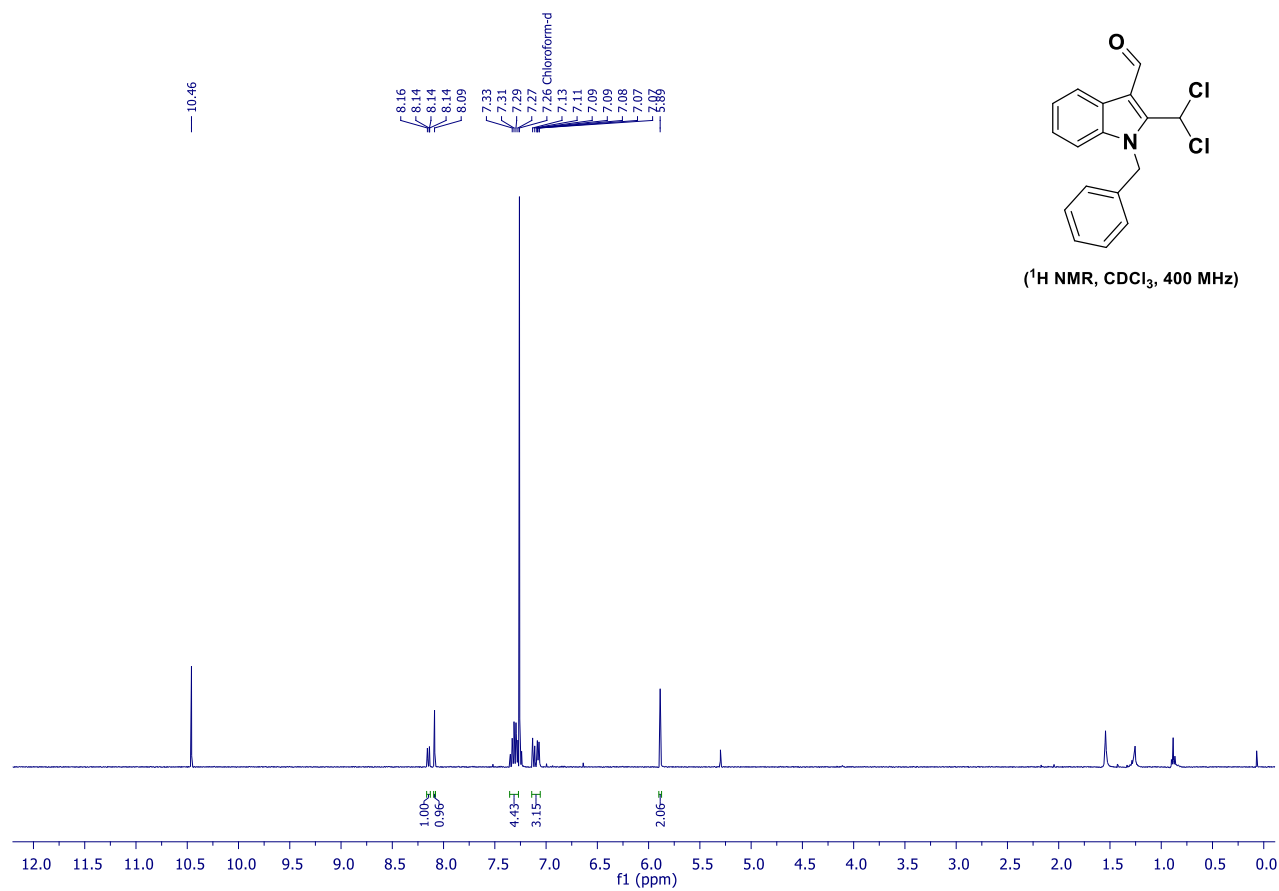




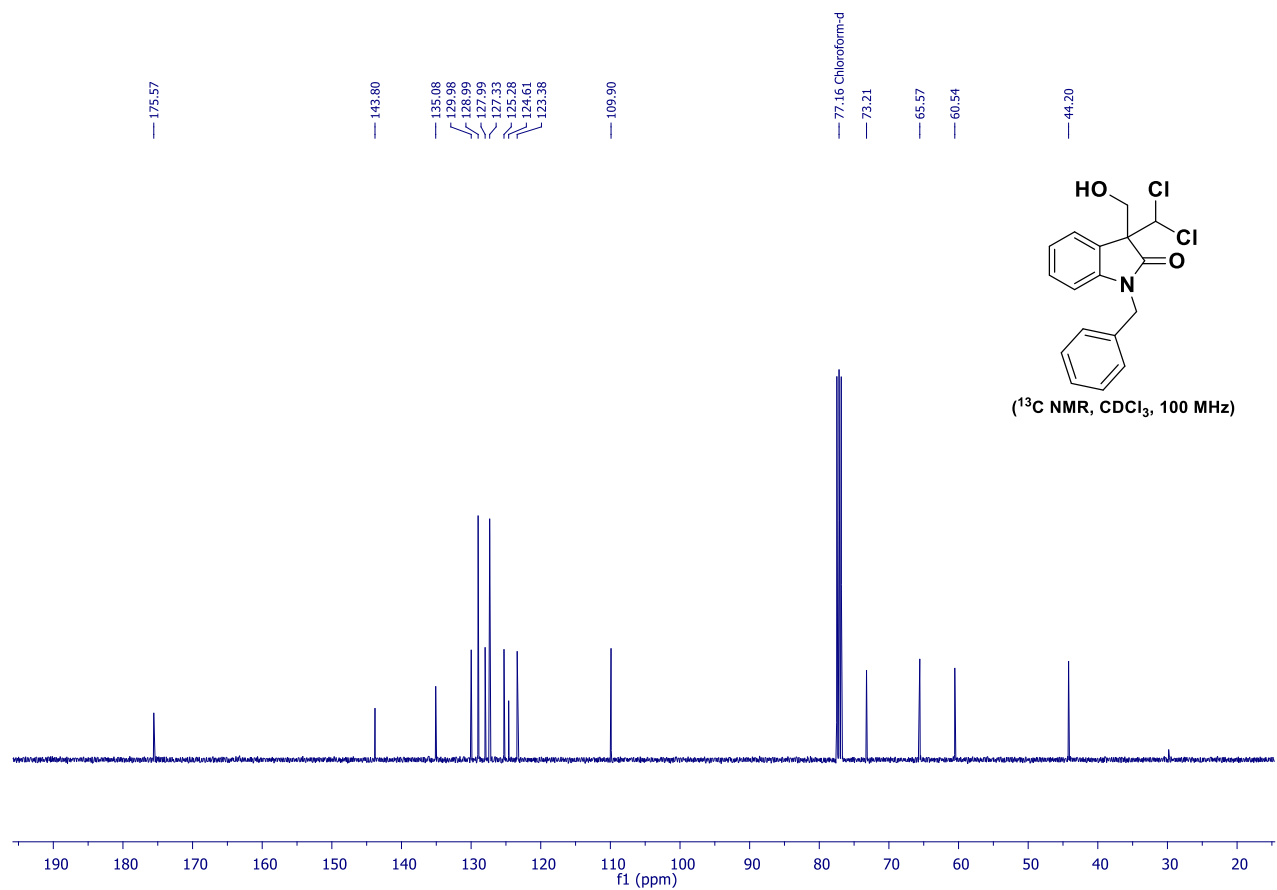
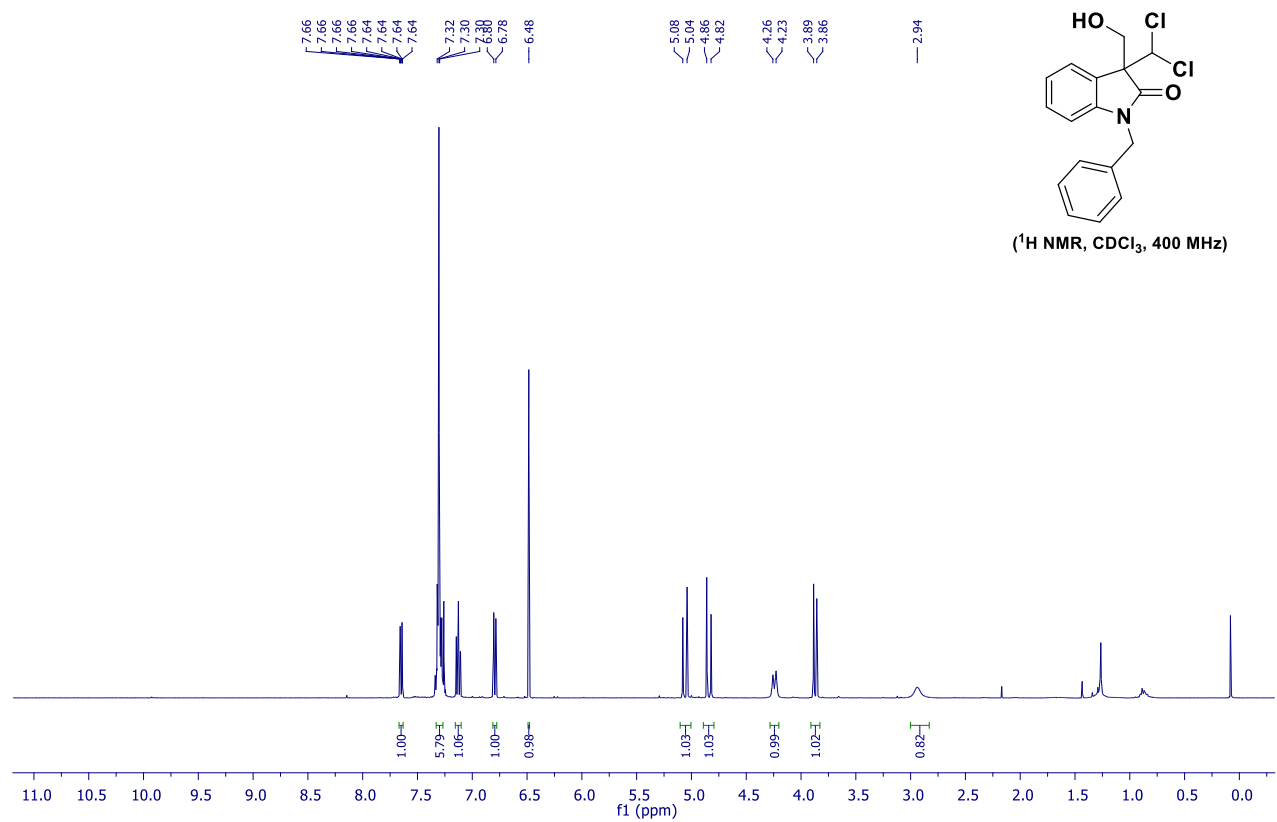
5-Bromo-1-(2-bromo-2-propen-1-yl)-2-(chloromethyl)-1*H*-indole-3-carbaldehyde (703)



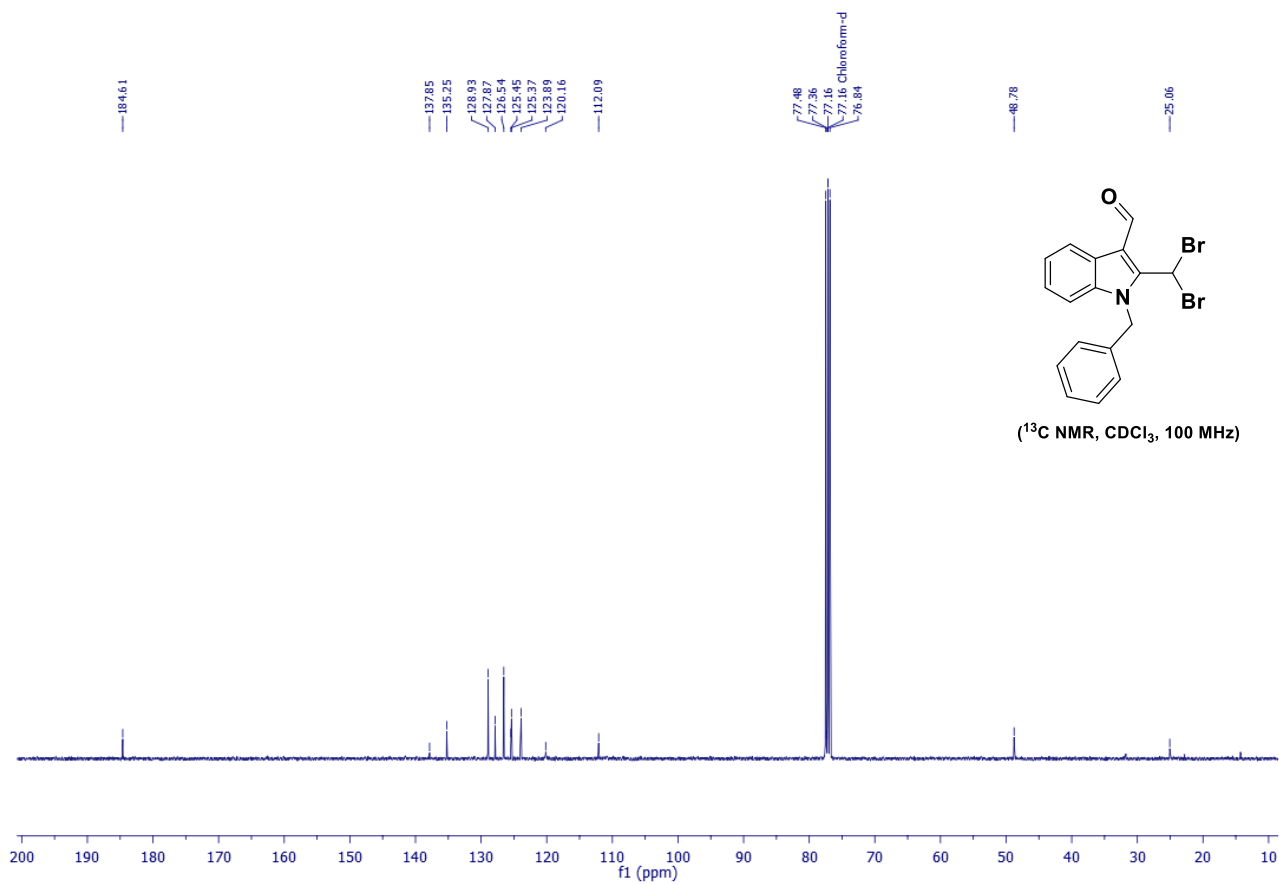
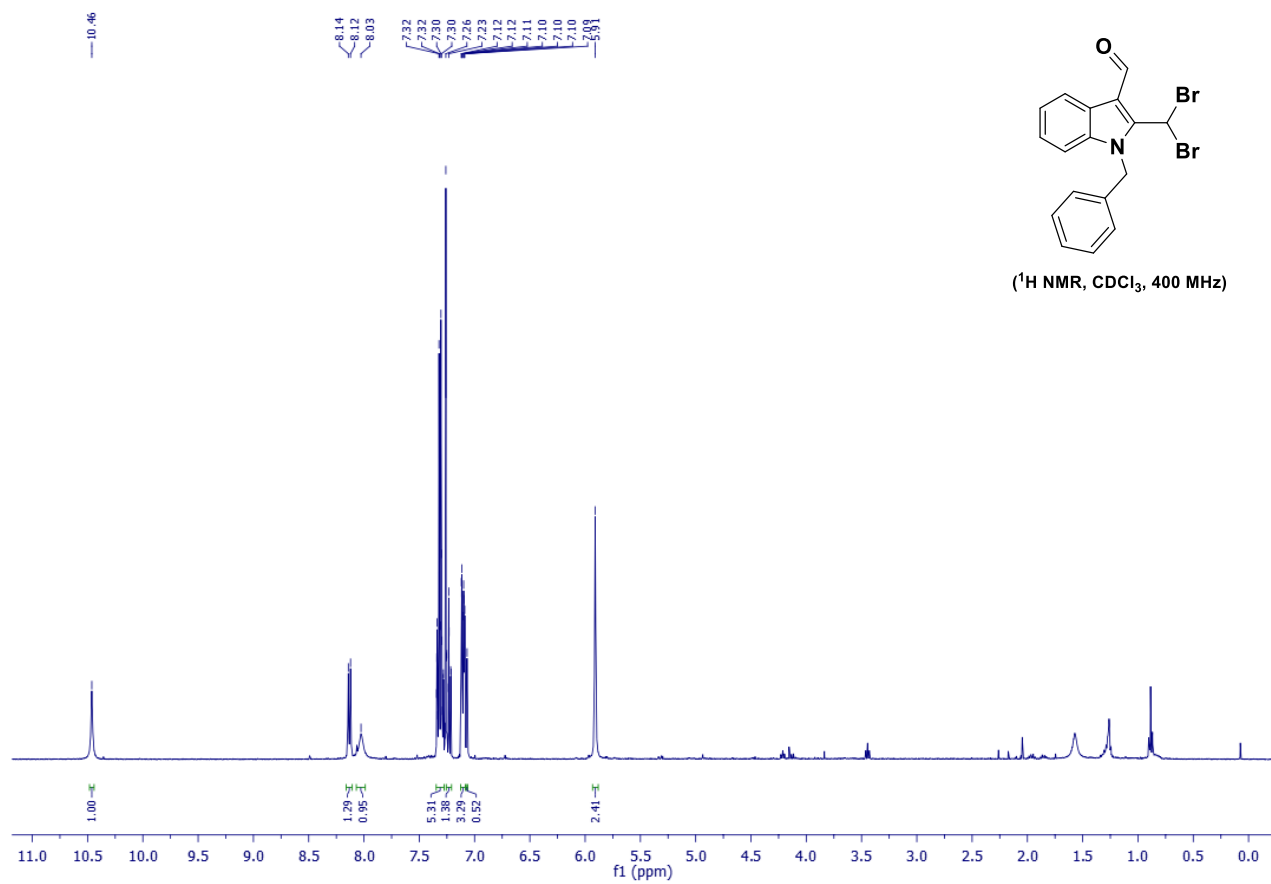
1-Benzyl-2-(dichloromethyl)-1*H*-indol-3-carbaldehyde (711)



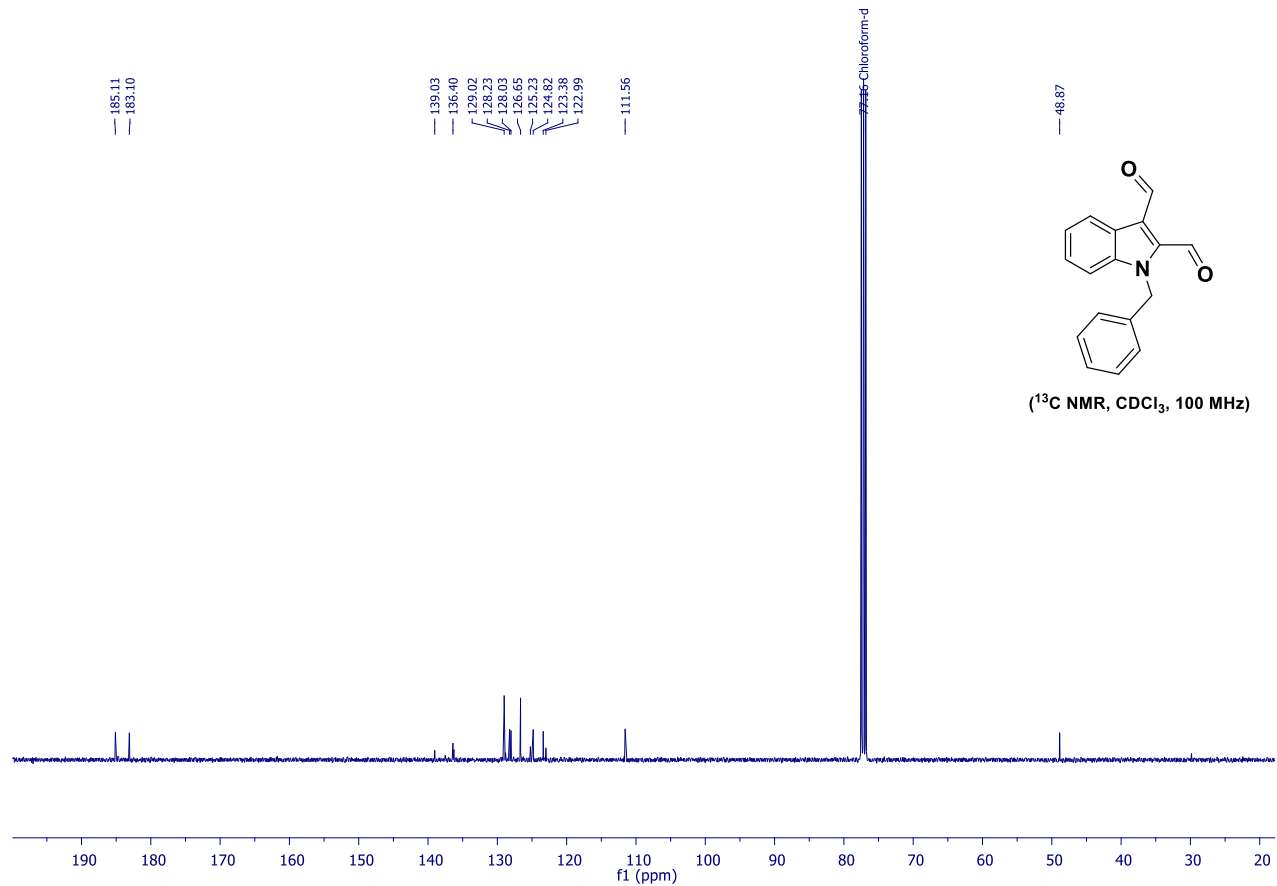
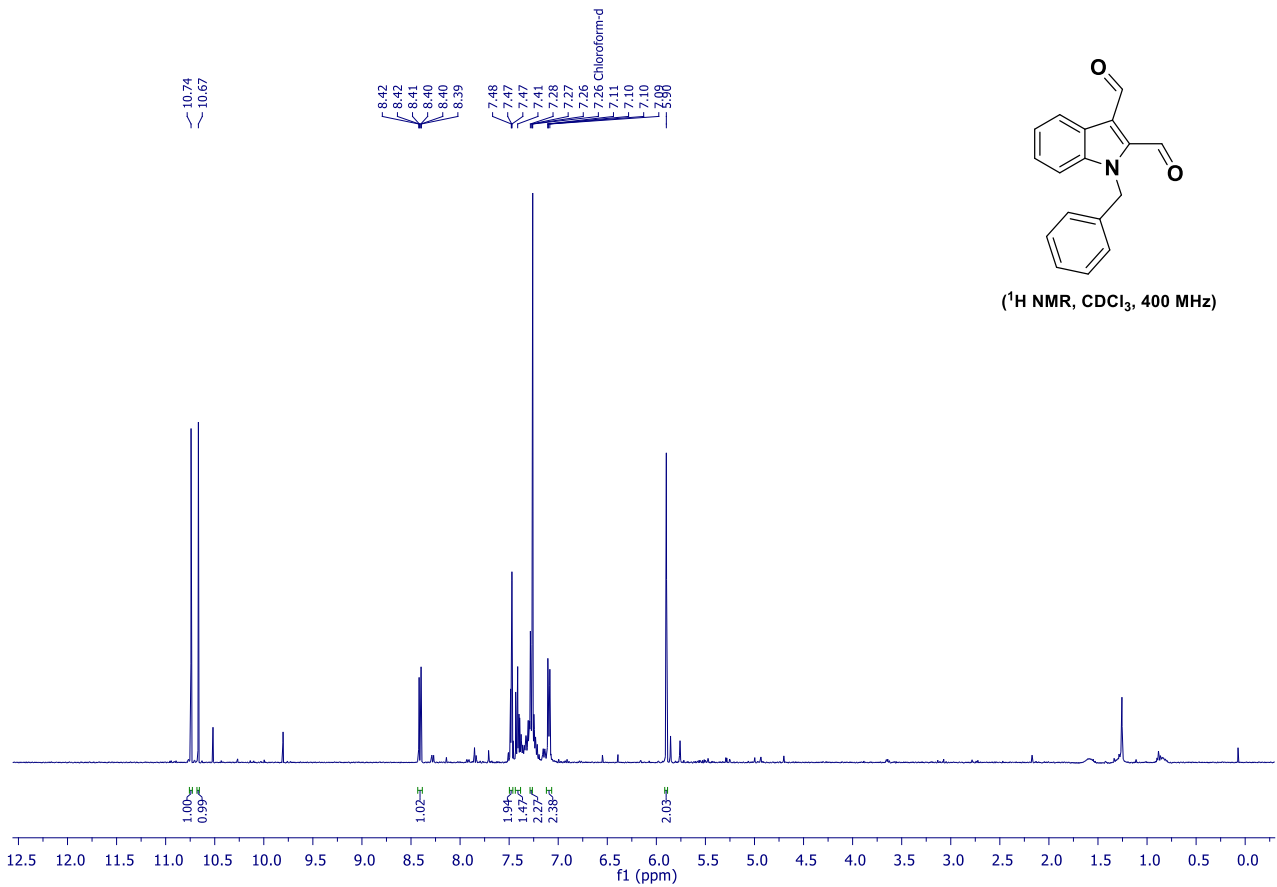
1-Benzyl-3-(dichloromethyl)-3-(hydroxymethyl)-1,3-dihydro-2H-indol-2-one (712)



1-Benzyl-2-(dibromomethyl)-1H-indole-3-carbaldehyde (713)



1-Benzyl-1*H*-indole-2,3-dicarbaldehyde (714)



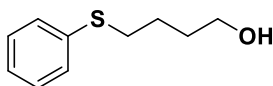
5.3 Supporting information for [Section 3.5](#)

5.3.1 *General procedures*

To a Toluene (2 mL) solution of the corresponding thiophenol (1 equiv) catecholborane solution in THF (1M, 1.01 equiv) is added. The reaction is allowed to proceed for 18 h, and then the solvent is removed under vacuum. The product is obtained as brown-yellowish oil after purification via chromatography on silica gel.

5.3.2 Characterization and spectral data of the compounds

4-(Phenylsulfanyl)butan-1-ol (**737**)



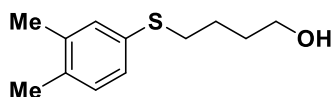
By following general procedure, starting from Thiophenol (300 mg, 0.28 mL, 2.7 mmol, 1.0 equiv), catecholborane solution in THF (1 M, 2.7 mL, 2.7 mmol, 1.01 equiv), in toluene (2 mL). The compound **737** was obtained in 95% yield (468 mg) as brown oil after chromatography on silica gel (98:2 v/v, dichloromethane/methanol).

¹H NMR (400 MHz, CDCl₃) δ : 7.25 (m, 2H), 7.20 (m, 2H), 7.09 (m, 1H), 3.59 (t, J = 6.0 Hz, 2H), 2.88 (t, J = 7.0 Hz, 2H), 1.65 (m, 4H).

¹³C NMR (100 MHz, CDCl₃) δ : 136.7, 129.3, 129.0, 126.0, 62.5, 33.6, 31.9, 25.6.

HRMS (ESI), m/z : calcd. for C₁₀H₁₄OS: 183.0838 [M+H]⁺; found: 183.0830

4-[(3,4-Dimethylphenyl)sulfanyl]butan-1-ol (**738**)



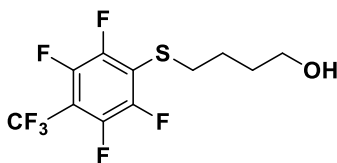
By following general procedure, starting from 3,4-Dimethylthiophenol (300 mg, 0.29 mL, 2.2 mmol, 1.0 equiv), catecholborane solution in THF (1M, 2.2 mL, 2.2 mmol, 1.01 equiv), in toluene (1 mL). The compound **738** was obtained in 87% yield (403 mg) as brown oil after chromatography on silica gel (98:2 v/v, dichloromethane/methanol).

¹H NMR (400 MHz, CDCl₃) δ: 7.15 (s, 1H), 7.10 (d, *J*=7.9 Hz, 1H), 7.05 (d, *J*= 7.8 Hz, 1H), 3.65 (t, *J*= 5.9 Hz, 2H), 2.91 (t, *J*= 6.8 Hz, 2H), 2.23 (d, *J*= 3.7 Hz, 6H), 1.74-1.67 (m, 4H).

¹³C NMR (100 MHz, CDCl₃) δ: 137.4, 135.0, 133.1, 131.5, 130.3, 127.6, 62.5, 34.4, 31.9, 25.8, 19.8, 19.4 .

HRMS (ESI), *m/z*: calcd. for C₁₂H₁₈NOS: 211.1151 [M+H]⁺; found: 211.1159.

4-[[2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl]sulfanyl]butan-1-ol (739)



By following general procedure, starting from 2,3,5,6-Tetrafluoro-4-(trifluoromethyl)-thiophenol (300 mg, 0.18 mL, 1.2 mmol, 1.0 equiv), catecholborane solution in THF (1 M, 1.2 mL, 1.2 mmol, 1.01 equiv), in toluene (2 mL). The compound **739** was obtained in 91% yield (352 mg) as brown oil after chromatography on silica gel (98:2 v/v, dichloromethane/methanol).

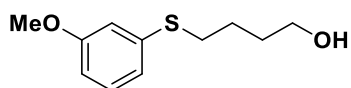
¹H NMR (400 MHz, CDCl₃) δ: 3.67 (m, 2H), 3.09 (t, *J*=6.5 Hz, 2H), 1.77-1.64 (m, 4H).

¹³C NMR (100 MHz, CDCl₃) δ: 148.4-147.9 (m), 146.0-145.2 (m), 143.2-142.6 (m), 122.5-122.1 (m), 121.1-120.7 (m), 119.6 (dt, *J*= 4.8, 1.8 Hz), 108.8-108.4 (m), 62.2 (s), 34.2 (t, *J*=3.9 Hz), 31.4 (s), 26.5 (s).

¹⁹F NMR (376 MHz, CDCl₃) δ: -56.3 (t, *J*=21.7 Hz, CF₃), -132.7(dt, *J*=15.1, 5.9 Hz), -140.5 (m).

HRMS (ESI), *m/z*: calcd. for C₁₁H₉F₇OS: 323.0335 [M+H]⁺; found: 323.0340.

4-[(3-Methoxyphenyl)sulfanyl]butan-1-ol (**740**)



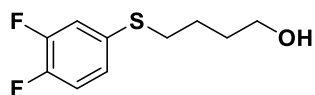
By following general procedure, starting from 3-Methoxythiophenol (300 mg, 0.26 mL, 2.1 mmol, 1.0 equiv), catecholborane solution in THF (1 M, 2.2 mL, 2.2 mmol, 1.01 equiv), in toluene (2 mL). The compound **740** was obtained in 86% yield (383 mg) as brown oil after chromatography on silica gel (98:2 v/v, dichloromethane/methanol).

¹H NMR (400 MHz, CDCl₃) δ: 7.19 (t, *J*=8.0 Hz, 1H), 6.92-6.86 (m, 2H), 6.71 (dd, *J*=8.2, 2.0 Hz, 1H), 3.80 (s, 3H), 3.67 (t, *J* = 5.8, 2H), 2.96 (t, *J* = 6.8 Hz, 2H), 1.80-1.66 (m, 4H) .

¹³C NMR (100 MHz, CDCl₃) δ: 160.1, 138.2, 129.8, 121.3, 114.6, 111.6, 62.5, 55.4, 33.5, 31.9, 25.7 .

HRMS (ESI), *m/z*: calcd. for C₁₁H₁₆O₂S: 213.0944 [M+H]⁺; found: 213.0940.

4-[(3,4-Difluorophenyl)sulfanyl]butan-1-ol (**741**)



By following general procedure, starting from 3,4-Difluorothiophenol (300 mg, 0.23 mL, 2.0 mmol, 1.0 equiv), catecholborane solution in THF (1 M, 2.1 mL, 2.1 mmol, 1.01 equiv), in toluene (2 mL). The compound **741** was obtained in 94% yield (410 mg) as brown oil after chromatography on silica gel (98:2 v/v, dichloromethane/methanol).

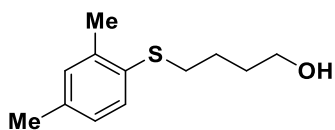
¹H NMR (400 MHz, CDCl₃) δ : 7.19-7.12 (m, 1H), 7.08 (dd, J =16.4, 7.1 Hz, 2H), 3.67 (m, 2H), 2.92 (t, J =6.6 Hz, 2H), 1.70 (m, 4H).

¹³C NMR (100 MHz, CDCl₃) δ : 149.7 (ddd, J = 134.8, 123.2, 12.9 Hz), 133.1 (dd, J = 5.8, 4.0 Hz), 126.0 (dd, J = 5.9, 3.6 Hz), 118.8 (d, J = 18.2 Hz), 117.8 (d, J = 17.4 Hz), 104.0, 62.4, 34.6, 31.6, 25.6 ..

¹⁹F NMR (376 MHz, CDCl₃) δ : -136.7 (m), -140.7 (m).

HRMS (ESI), m/z : calcd. for C₁₀H₁₂F₂OS: 219.0650 [M+H]⁺; found: 219.0642.

4-[(2,4-Dimethylphenyl)sulfanyl]butan-1-ol (**742**)



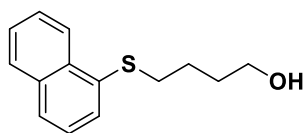
By following general procedure, starting from 2,4-Dimethylthiophenol (300 mg, 0.29 mL, 2.2 mmol, 1.0 equiv), catecholborane solution in THF (1 M, 2.2 mL, 2.2 mmol, 1.01 equiv), in toluene (2 mL). The compound **742** was obtained in 83% yield (384 mg) as brown oil after chromatography on silica gel (98:2 v/v, dichloromethane/methanol).

¹H NMR (400 MHz, CDCl₃) δ: 7.20 (d, *J* = 7.8 Hz, 1H), 7.00 (s, 1H), 6.97 (d, *J* = 7.9 Hz, 1H), 3.66 (m, 2H), 2.88 (m, 2H), 2.36 (s, 3H), 2.29 (s, 3H), 1.71 (m, 4H) .

¹³C NMR (100 MHz, CDCl₃) δ: 138.3, 136.0, 132.2, 131.2, 129.5, 127.3, 62.6, 33.6, 32.0, 25.6, 21.0, 20.5 .

HRMS (ESI), *m/z*: calcd. for C₁₂H₁₈OS: 211.1151 [M+H]⁺; found: 211.1156.

4-[(Naphthalen-1-yl)sulfanyl]butan-1-ol (**743**)



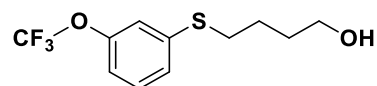
By following general procedure, starting from 1-Naphthalinethiol (300 mg, 0.26 mL, 1.9 mmol, 1.0 equiv), catecholborane solution in THF (1 M, 1.9 mL, 1.9 mmol, 1.01 equiv), in toluene (2 mL). The compound **743** was obtained in 92% yield (406 mg) as brown oil after chromatography on silica gel (98:2 v/v, dichloromethane/methanol).

¹H NMR (400 MHz, CDCl₃) δ: 8.41 (d, *J*=8.2 Hz, 1H), 7.85 (d, *J*=7.8 Hz, 1H), 7.73 (d, *J*= 8.1 Hz, 1H), 7.53 (dt, *J*= 14.8, 7.0 Hz, 3H), 7.41 (t, *J*=7.7 Hz, 1H), 3.65 (m, 2H), 3.01 (m, 2H), 1.73 (m, 4H). .

¹³C NMR (100 MHz, CDCl₃) δ: 134.1, 133.9, 133.1, 128.7, 128.1, 127.3, 126.5, 126.3, 125.7, 125.2, 62.5, 34.3, 31.9, 25.8 .

HRMS (ESI), *m/z*: calcd. for C₁₄H₁₆OS: 233.0995 [M+H]⁺; found: 233.0991.

4-{{3-(Trifluoromethoxy)phenyl}sulfanyl}butan-1-ol (**744**)



By following general procedure, starting from 3-Trifluoromethoxythiophenol (300 mg, 0.22 mL, 1.5 mmol, 1.0 equiv), catecholborane solution in THF (1 M, 1.6 mL, 1.6 mmol, 1.01 equiv), in toluene (2 mL). The compound **744** was obtained in 80% yield (320 mg) as brown oil after chromatography on silica gel (98:2 v/v, dichloromethane/methanol).

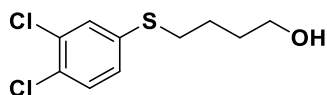
¹H NMR (400 MHz, CDCl₃) δ: 7.29 (d, *J*=7.9 Hz, 1H), 7.21 (d, *J*=8.0 Hz, 1H), 7.14 (s, 1H), 7.00 (dd, *J*=8.0, 0.9 Hz, 1H), 3.66 (t, *J*=6.1 Hz, 2H), 2.97 (t, *J*= 7.0 Hz, 2H), 1.81-1.66 (m, 4H).

¹³C NMR (100 MHz, CDCl₃) δ: 149.7 (d, *J* = 1.8 Hz), 139.6, 130.1, 126.7, 120.7, 120.6 (q, *J*=257.4 Hz), 118.0, 62.4, 33.2, 31.8, 25.4.

¹⁹F NMR (376 MHz, CDCl₃) δ: -57.8 (s).

HRMS (ESI), *m/z*: calcd. for C₁₁H₁₃F₃O₂S: 267.0661 [M+H]⁺; found: 267.0660.

4-[(3,4-Dichlorophenyl)sulfanyl]butan-1-ol (**745**)



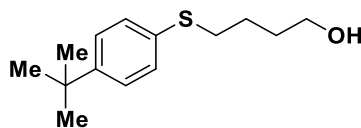
By following general procedure, starting from 3,4-Dichlorothiophenol (300 mg, 0.21 mL, 1.7 mmol, 1.0 equiv), catecholborane solution in THF (1 M, 1.7 mL, 1.7 mmol, 1.01 equiv), in toluene (2 mL). The compound **745** was obtained in 97% yield (414 mg) as brown oil after chromatography on silica gel (98:2 v/v, dichloromethane/methanol).

¹H NMR (400 MHz, CDCl₃) δ: 7.36 (s, 1H), 7.31 (d, *J*=8.4 Hz, 1H), 7.11 (dd, *J*=8.3, 0.9 Hz, 1H), 3.65 (t, *J*=5.6 Hz, 2H), 2.93 (t, *J*=6.7 Hz, 2H), 1.72-1.65 (m, 4H).

¹³C NMR (100 MHz, CDCl₃) δ: 137.3, 133.0, 130.6, 130.1, 129.8, 128.1, 62.3, 33.6, 31.7, 25.4.

HRMS (ESI), *m/z*: calcd. for C₁₀H₁₂Cl₂OS: 251.0059 [M+H]⁺; found: 251.0063.

4-[(4-*Tert*-butylphenyl)sulfanyl]butan-1-ol (**746**)



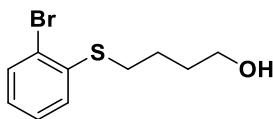
By following general procedure, starting from 4-*t*-Butylthiophenol (300 mg, 0.30 mL, 1.8 mmol, 1.0 equiv), catecholborane solution in THF (1 M, 1.8 mL, 1.8 mmol, 1.01 equiv), in toluene (2 mL). The compound **746** was obtained in 81% yield (348 mg) as brown oil after chromatography on silica gel (98:2 v/v, dichloromethane/methanol).

¹H NMR (400 MHz, CDCl₃) δ: 7.26-7.20 (m, 4H), 3.61 (t, *J*=5.8 Hz, 2H), 2.87 (t, *J*=6.8 Hz, 2H), 1.69-1.62 (m, 4H), 1.24 (s, 9H).

¹³C NMR (100 MHz, CDCl₃) δ: 149.4, 133.0, 129.6, 126.1, 62.6, 34.6, 34.1, 31.9, 31.4, 25.8 .

HRMS (ESI), *m/z*: calcd. for C₁₄H₂₂OS: 239.1464 [M+H]⁺; found: 239.1467.

4-[(2-Bromophenyl)sulfanyl]butan-1-ol (**747**)



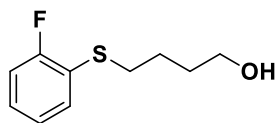
By following general procedure, starting from 2-Bromothiophenol (300 mg, 0.19 mL, 1.6 mmol, 1.0 equiv), catecholborane solution in THF (1 M, 1.6 mL, 1.6 mmol, 1.01 equiv), in Toluene (2 mL). The compound **747** was obtained in 89% yield (372 mg) as brown oil after chromatography on silica gel (98:2 v/v, dichloromethane/methanol).

¹H NMR (400 MHz, CDCl₃) δ: 7.57-7.52 (m, 1H), 7.30-7.24 (m, 2H), 7.03 (ddd, *J* = 8.1, 6.2, 2.8 Hz, 1H), 3.70 (t, *J* = 6.1 Hz, 2H), 2.99 (t, *J* = 7.0 Hz, 2H), 1.85-1.72 (m, 4H).

¹³C NMR (100 MHz, CDCl₃) δ: 138.3, 133.1, 130.2, 128.1, 127.8, 126.6, 62.4, 32.9, 31.9, 25.1.

HRMS (ESI), *m/z*: calcd. for C₁₀H₁₃BrOS: 260.9943 [M+H]⁺; found: 260.9946.

4-[(2-Fluorophenyl)sulfanyl]butan-1-ol (**748**)



By following general procedure, starting from 2- Fluorothiophenol (300 mg, 0.25 mL, 2.3 mmol, 1.0 equiv), catecholborane solution in THF (1 M, 2.4 mL, 2.4 mmol, 1.01 equiv), in toluene (2 mL). The compound **748** was obtained in 90% yield (415 mg) as brown oil after chromatography on silica gel (98:2 v/v, dichloromethane/methanol).

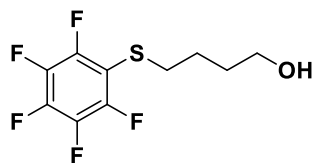
¹H NMR (400 MHz, CDCl₃) δ : 7.36 (tt, J =5.8, 2.8 Hz, 1H), 7.24-7.16 (m, 1H), 7.11-7.01 (m, 2H), 3.65 (dd, J =7.8, 4.1 Hz, 2H), 2.94 (dd, J =9.0, 4.8 Hz, 2H), 1.73-1.67 (m, 4H).

¹³C NMR (100 MHz, CDCl₃) δ : 161.6 (d, J =245.0 Hz), 132.2 (d, J =1.9 Hz), 128.4 (d, J =7.8 Hz), 124.5 (d, J =3.7 Hz), 123.4 (d, J =17.7 Hz), 115.8 (d, J =22.6 Hz), 62.5, 33.4 (d, J =2.5 Hz), 31.7, 25.7.

¹⁹F NMR (376 MHz, CDCl₃) δ : -109.6 (ddd, J =9.7, 7.5, 5.2 Hz).

HRMS (ESI), m/z : calcd. for C₁₀H₁₃FO: 201.0744 [M+H]⁺; found: 201.0750.

4-[(Pentafluorophenyl)sulfanyl]butan-1-ol (**749**)



By following general procedure, starting from 2,3,4,5,6-Pentafluorothiophenol (300 mg, 0.19 mL, 1.5 mmol, 1.0 equiv), catecholborane solution in THF (1 M, 1.5 mL, 1.5 mmol, 1.01 equiv), in toluene (2 mL). The compound **749** was obtained in 91% yield (372 mg) as brown oil after chromatography on silica gel (98:2 v/v, dichloromethane/methanol).

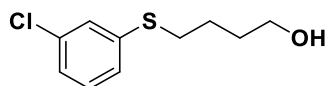
¹H NMR (400 MHz, CDCl₃) δ : 3.65 (t, J =5.9 Hz, 2H), 2.91 (t, J =6.8 Hz, 2H), 1.73-1.60 (m, 4H).

¹³C NMR (100 MHz, CDCl₃) δ : 147.7 (dddd, J = 245.4, 10.7, 8.4, 4.0 Hz), 142.7 (m), 140.1 (m), 139.1 (m), 136.6 (m), 62.3, 35.0, 31.3, 26.3.

¹⁹F NMR (376 MHz, CDCl₃) δ : -132.6 (m).

HRMS (ESI), m/z : calcd. for C₁₀H₉F₅OS: 273.0367 [M+H]⁺; found: 273.0371.

4-[(3-Chlorophenyl)sulfanyl]butan-1-ol (**750**)



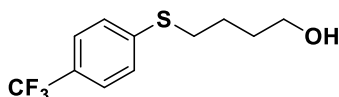
By following general procedure, starting from 3-Chlorothiophenol (300 mg, 0.24 mL, 2.1 mmol, 1.0 equiv), catecholborane solution in THF (1 M, 2.1 mL, 2.1 mmol, 1.01 equiv), in toluene (2 mL). The compound **750** was obtained in 98% yield (446 mg) as brown oil after chromatography on silica gel (98:2 v/v, dichloromethane/methanol).

¹H NMR (400 MHz, CDCl₃) δ: 7.35 (d, *J* = 7.8 Hz, 1H), 7.26 (m, 2H), 7.21 (m, 1H), 3.75 (t, *J* = 5.9 Hz, 2H), 3.04 (t, *J* = 6.9 Hz, 2H), 1.81 (m, 4H).

¹³C NMR (100 MHz, CDCl₃) δ: 139.1, 134.8, 130.0, 128.2, 126.8, 125.9, 62.4, 33.2, 31.8, 25.5.

HRMS (ESI), *m/z*: calcd. for C₁₀H₁₃ClOS: 217.0448 [M+H]⁺; found: 217.0442.

4-[[4-(Trifluoromethyl)phenyl]sulfanyl]butan-1-ol (**751**)



By following general procedure, starting from 4-Trifluoromethylthiophenol (300 mg, 0.23 mL, 1.7 mmol, 1.0 equiv), catecholborane solution in THF (1 M, 1.7 mL, 1.7 mmol, 1.01 equiv), in toluene (2 mL). The compound **751** was obtained in 94% yield (400 mg) as brown oil after chromatography on silica gel (98:2 v/v, dichloromethane/methanol).

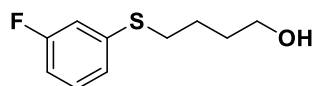
¹H NMR (400 MHz, CDCl₃) δ: 7.50 (d, *J*=8.2 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 3.68 (t, *J*=6.0 Hz, 2H), 3.01 (t, *J*=7.0 Hz, 2H), 1.74-1.66 (m, 4H).

¹³C NMR (100 MHz, CDCl₃) δ: 142.5 (d, *J* = 1.3 Hz), 127.5, 125.8 (q, *J* = 3.8 Hz), 124.3 (d, *J* = 271.7 Hz), 62.4, 32.4, 31.8, 25.4 .

¹⁹F NMR (376 MHz, CDCl₃) δ: -62.4 (s).

HRMS (ESI), *m/z*: calcd. for C₁₁H₁₃F₃OS: 251.0712 [M+H]⁺; found: 251.0719.

4-[(3-Fluorophenyl)sulfanyl]butan-1-ol (**752**)



By following general procedure, starting from 3-Fluorothiophenol (300 mg, 0.20 mL, 2.3 mmol, 1.0 equiv), catecholborane solution in THF (1 M, 2.4 mL, 2.4 mmol, 1.01 equiv), in toluene (2 mL). The compound **752** was obtained in 93% yield (428 mg) as brown oil after chromatography on silica gel (98:2 v/v, dichloromethane/methanol).

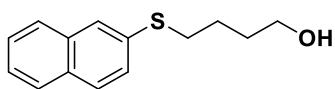
¹H NMR (400 MHz, CDCl₃) δ : 7.22 (ddd, J =9.1, 5.6, 2.5 Hz, 1H), 7.09-7.04 (m, 1H), 7.01 (ddd, J =9.6, 4.5, 2.7 Hz, 1H), 6.85 (td, J =8.4, 2.5 Hz, 1H), 3.68 (t, J =6.0 Hz, 2H), 2.97 (t, J =7.0 Hz, 2H), 1.79-1.67 (m, 4H).

¹³C NMR (100 MHz, CDCl₃) δ : 163.1 (d, J =247.8 Hz), 139.5 (d, J =7.8 Hz), 130.2 (m), 124.2 (d, J =2.9 Hz), 115.3 (d, J =23.1 Hz), 112.7 (d, J =21.2 Hz), 62.5, 33.2, 31.8, 25.5 .

¹⁹F NMR (376 MHz, CDCl₃) δ : -112.5 (m).

HRMS (ESI), m/z : calcd. for C₁₀H₁₃FOS: 201.0744 [M+H]⁺; found: 201.0750.

4-[(Naphthalen-2-yl)sulfanyl]butan-1-ol (**753**)



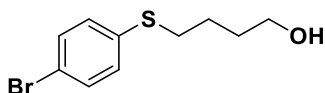
By following general procedure, starting from 2-Naphthalinethiol (300 mg, 1.9 mmol, 1.0 equiv), catecholborane solution in THF (1 M, 1.9 mL, 1.9 mmol, 1.01 equiv), in toluene (2 mL). The compound **753** was obtained in 90% yield (397 mg) as pink semi-solid after chromatography on silica gel (98:2 v/v, dichloromethane/methanol).

¹H NMR (400 MHz, CDCl₃) δ : 7.80-7.72 (m, 4H), 7.49-7.40 (m, 3H), 3.67 (t, J = 6.1 Hz, 2H), 3.06 (t, J = 7.0 Hz, 2H), 1.83-1.69 (m, 4H).

¹³C NMR (100 MHz, CDCl₃) δ : 134.3, 133.9, 131.9, 128.5, 127.8, 127.5, 127.2, 126.9, 126.7, 125.7, 62.5, 33.5, 31.9, 25.6 .

HRMS (ESI), m/z : calcd. for C₁₄H₁₆OS: 233.0995 [M+H]⁺; found: 233.0992.

4-[(4-Bromophenyl)sulfanyl]butan-1-ol (754)



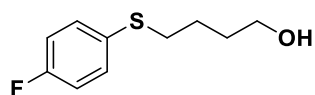
By following general procedure, starting from 4-Bromothiophenol (300 mg, 1.6 mmol, 1.0 equiv), catecholborane solution in THF (1 M, 1.6 mL, 1.6 mmol, 1.01equiv), in toluene (2 mL). The compound **794** was obtained in 92% yield (384 mg) as brown oil after chromatography on silica gel (98:2 v/v, dichloromethane/methanol).

¹H NMR (400 MHz, CDCl₃) δ: 7.39 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 8.2 Hz, 2H), 3.67 (m, 2H), 2.94 (t, *J* = 6.6 Hz, 2H), 1.73 (m, 4H).

¹³C NMR (100 MHz, CDCl₃) δ: 136.0, 132.1, 130.8, 119.8, 62.5, 33.7, 31.8, 25.5 . .

HRMS (ESI), *m/z*: calcd. for C₁₀H₁₃BrOS: 260.9943 [M+H]⁺; found: 260.9940.

4-[(4-Fluorophenyl)sulfanyl]butan-1-ol (**755**)



By following general procedure, starting from 4-Fluorothiophenol (300 mg, 0.25 mL, 2.3 mmol, 1.0 equiv), catecholborane solution in THF (1 M, 2.4 mL, 2.4 mmol, 1.01 equiv), in toluene (2 mL). The compound **755** was obtained in 98% yield (451 mg) as brown oil after chromatography on silica gel (98:2 v/v, dichloromethane/methanol).

¹H NMR (400 MHz, CDCl₃) δ: 7.36 (m, 2H), 7.02 (m, 2H), 3.68 (m, 2H),

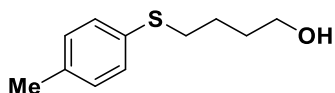
2.93 (m, 2H), 1.72 (m, 4H).

¹³C NMR (100 MHz, CDCl₃) δ: 162.7, 161.1, 134.4, 132.5, 132.4, 116.2, 116.0, 62.5, 35.0, 31.8, 25.7 . .

¹⁹F NMR (376 MHz, CDCl₃) δ: -108.7 (m), -115.8 (m).

HRMS (ESI), *m/z*: calcd. for C₁₀H₁₃FOS: 201.0744 [M+H]⁺; found: 201.0750.

4-[(4-Methylphenyl)sulfanyl]butan-1-ol (**756**)



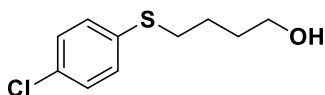
By following general procedure, starting from 4-Methylthiophenol (300 mg, 2.4 mmol, 1.0 equiv), catecholborane solution in THF (1 M, 2.4 mL, 2.4 mmol, 1.01 equiv), in toluene (2 mL). The compound **756** was obtained in 78% yield (367 mg) as brown oil after chromatography on silica gel (98:2 v/v, dichloromethane/methanol).

¹H NMR (400 MHz, CDCl₃) δ: 7.25 (d, J= 6.0 Hz, 2H), 7.10 (d, J= 8.0 Hz, 2H), 3.65 (m, 2H), 2.91 (t, J= 6.8 Hz, 2H), 2.32 (s, 3H), 1.70 (m, 4H).

¹³C NMR (100 MHz, CDCl₃) δ: 136.3, 132.8, 130.2, 129.8, 62.6, 34.4, 31.9, 25.7, 21.1 . .

HRMS (ESI), *m/z*: calcd. for C₁₁H₁₆OS: 197.0995 [M+H]⁺; found: 197.0990.

4-[(4-Chlorophenyl)sulfanyl]butan-1-ol (**757**)



By following general procedure, starting from 4-Chlorothiophenol (300 mg, 2.1 mmol, 1.0 equiv), catecholborane solution in THF (1 M, 2.1 mL, 2.1 mmol, 1.01 equiv), in toluene (2 mL). The compound **757** was obtained in 96% yield (437 mg) as brown oil after chromatography on silica gel (98:2 v/v, dichloromethane/methanol).

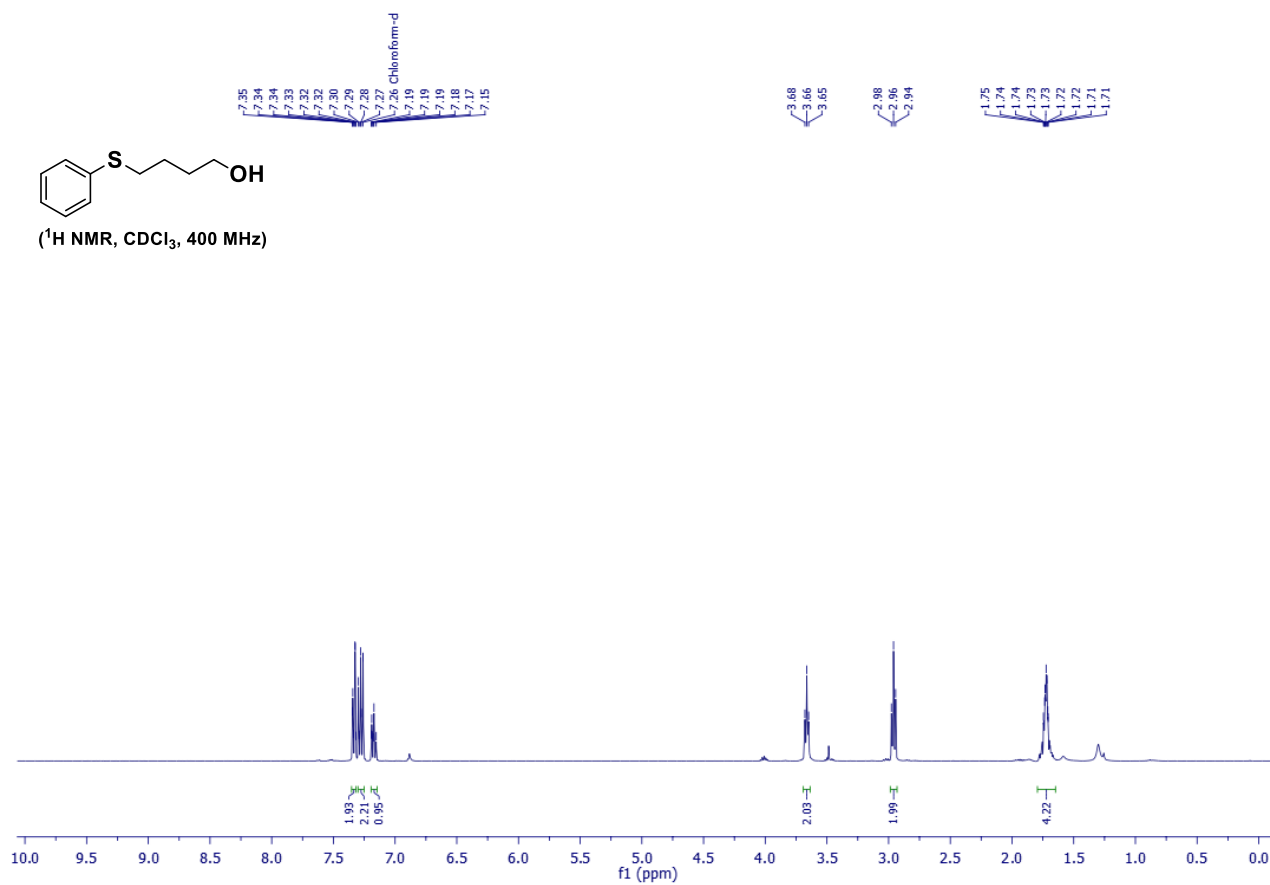
¹H NMR (400 MHz, CDCl₃) δ : 7.27 (d, *J* = 5.7 Hz, 4H), 3.67 (t, *J* = 5.9 Hz, 2H), 2.94 (t, *J* = 6.8 Hz, 2H), 2.32 (s, 3H), 1.71 (m, 4H).

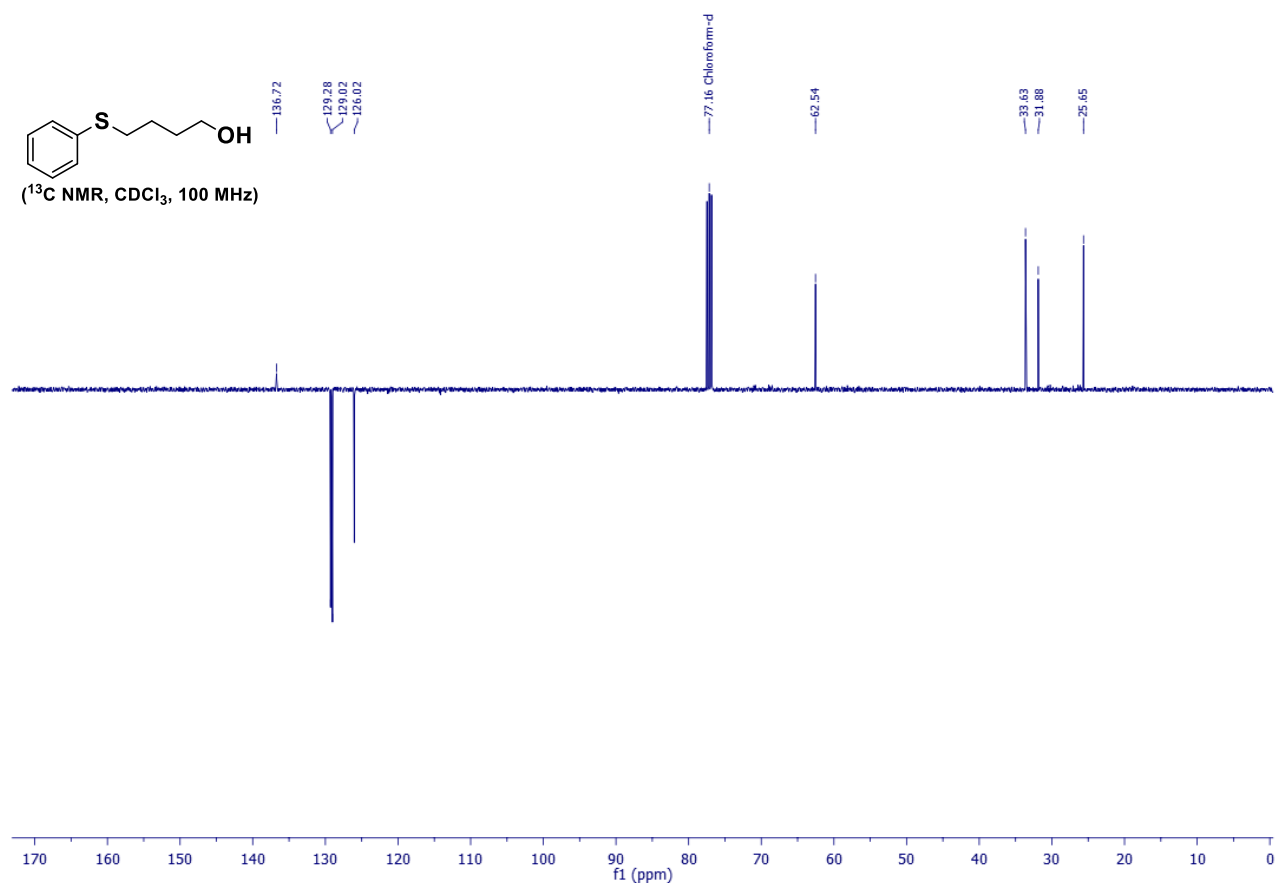
¹³C NMR (100 MHz, CDCl₃) δ : 135.3, 132.0, 130.6, 129.1, 62.4, 33.9, 31.8, 25.6.

HRMS (ESI), *m/z*: calcd. for C₁₀H₁₃ClOS: 217.0448 [M+H]⁺; found: 217.0443.

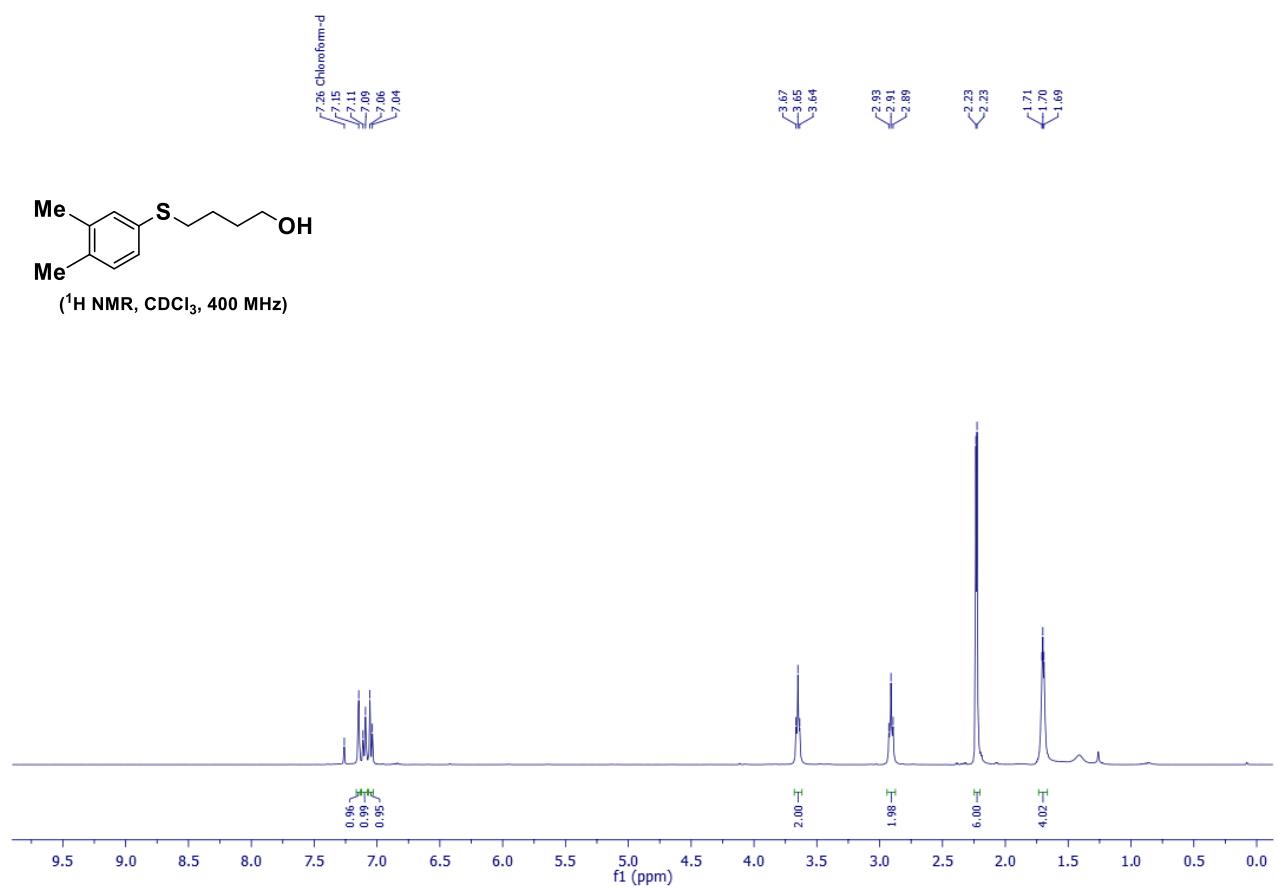
5.3.3 Copies of ^1H - and ^{13}C -NMR Spectra for all the compounds

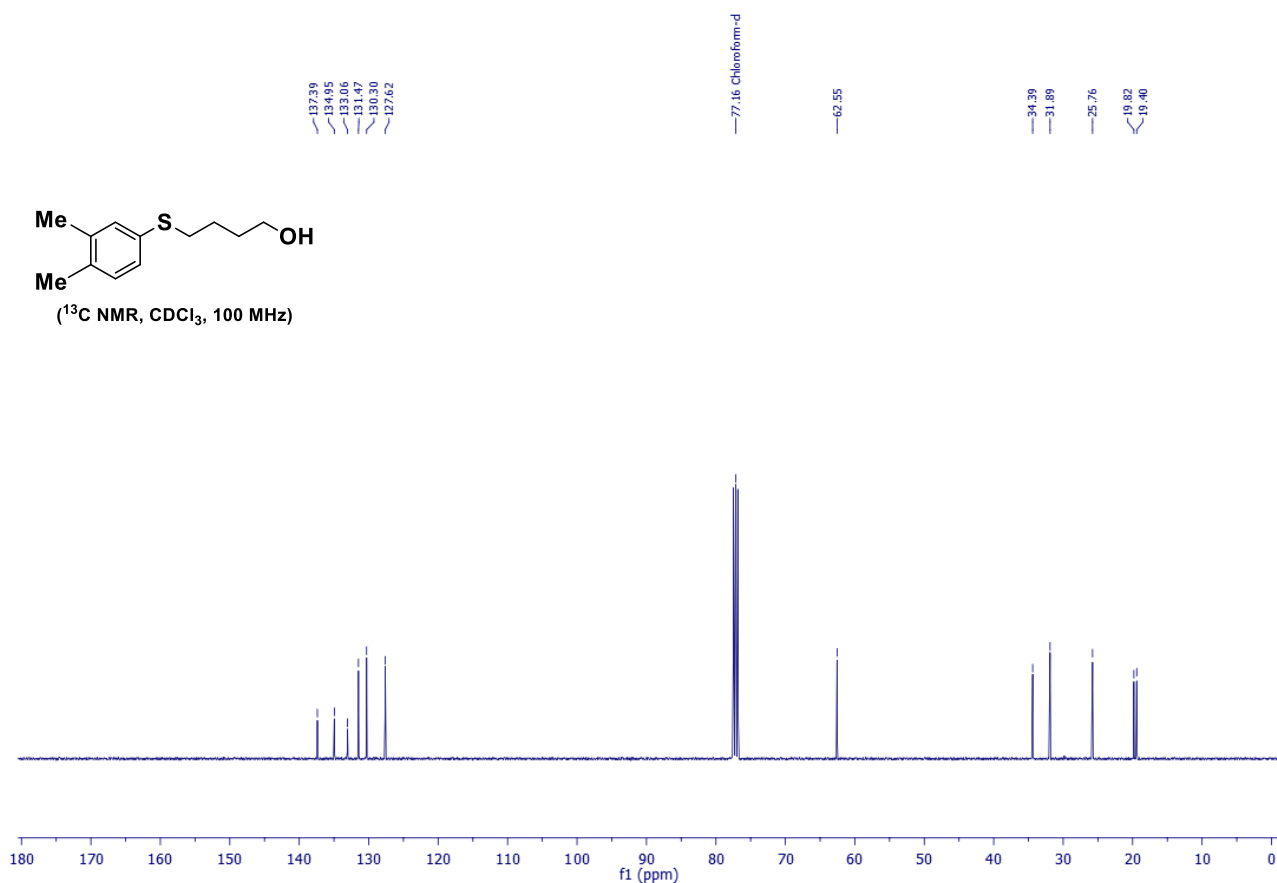
4-(Phenylsulfanyl)butan-1-ol (737)



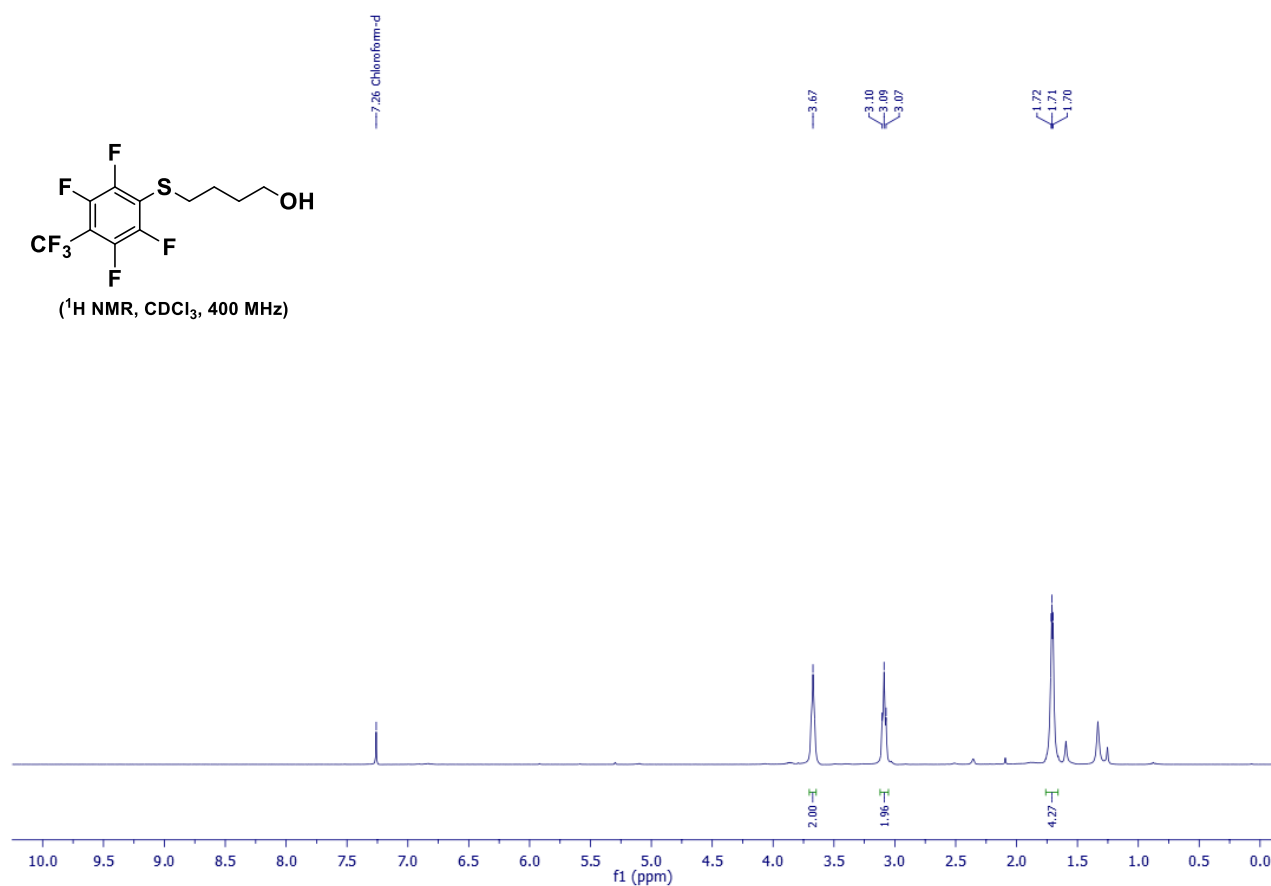


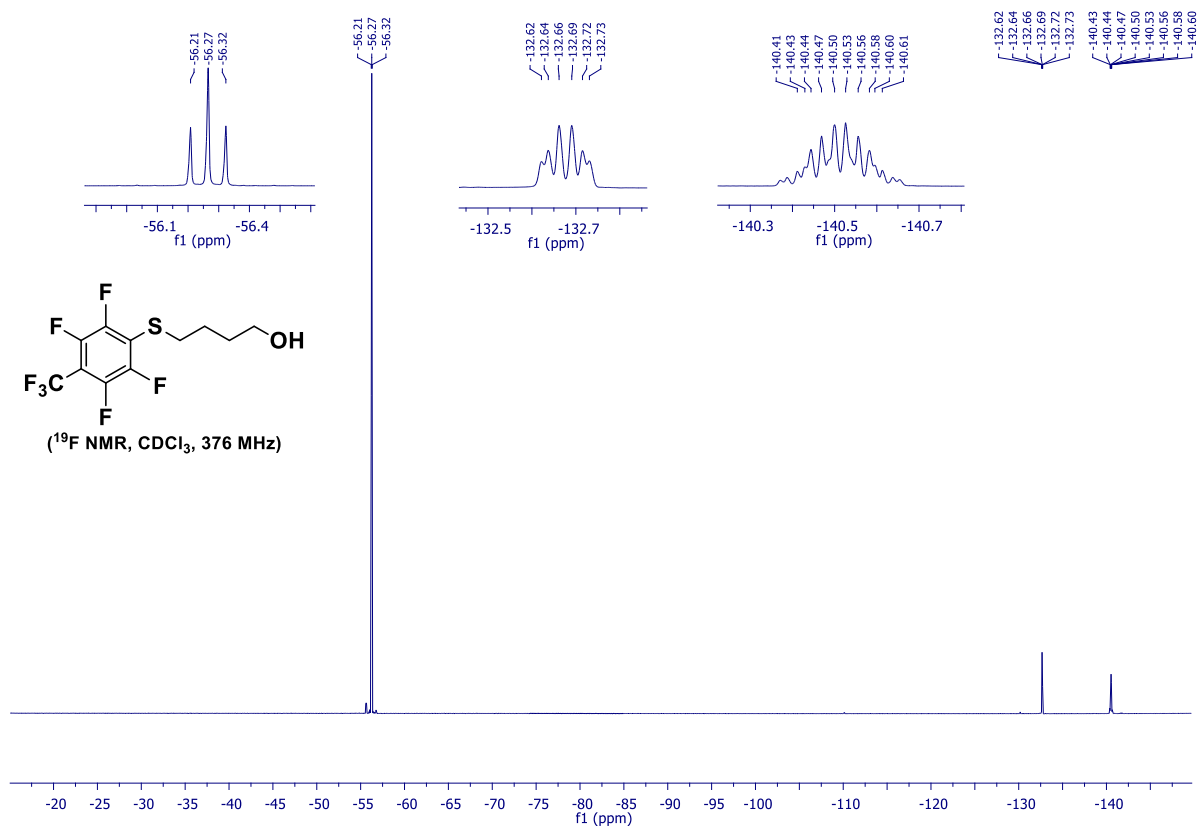
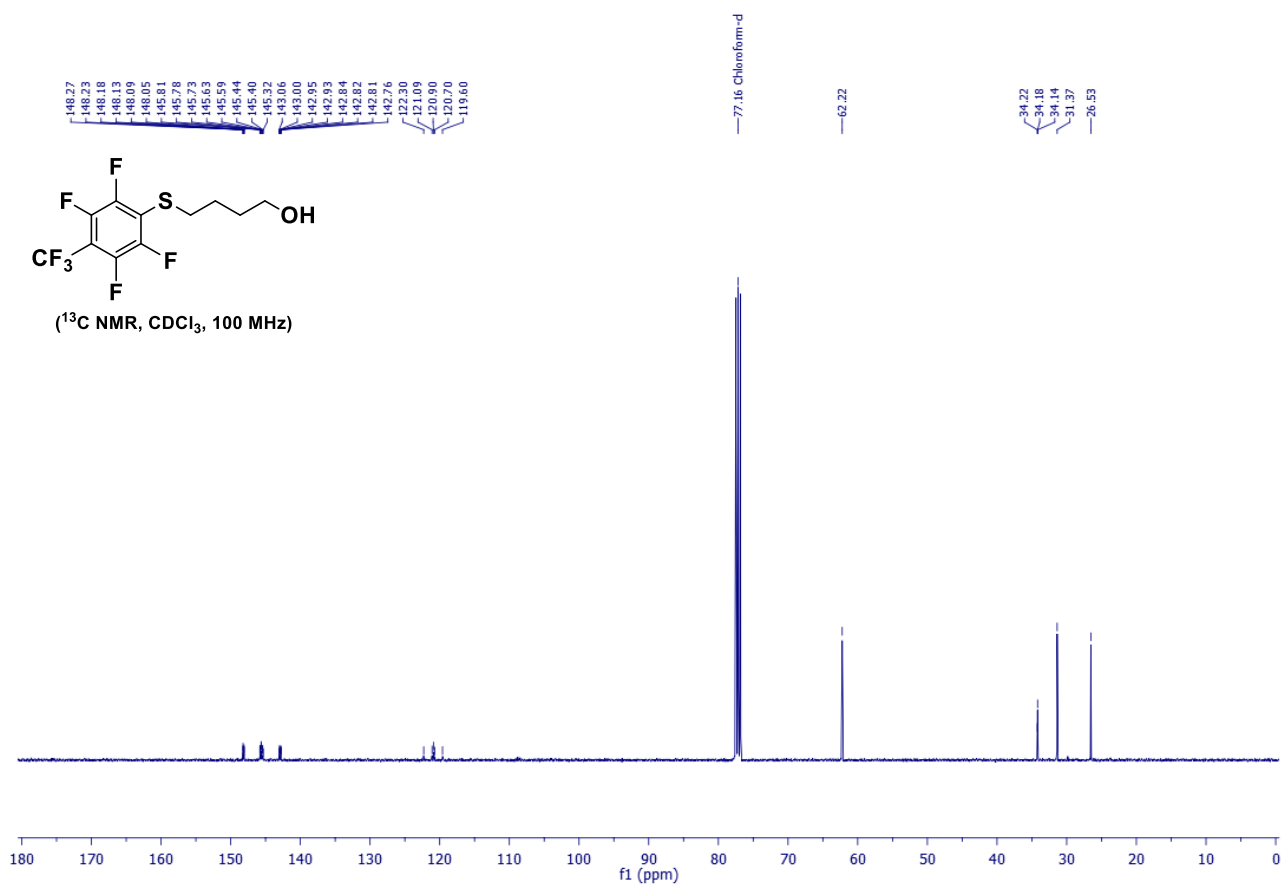
4-[(3,4-Dimethylphenyl)sulfanyl]butan-1-ol (738)



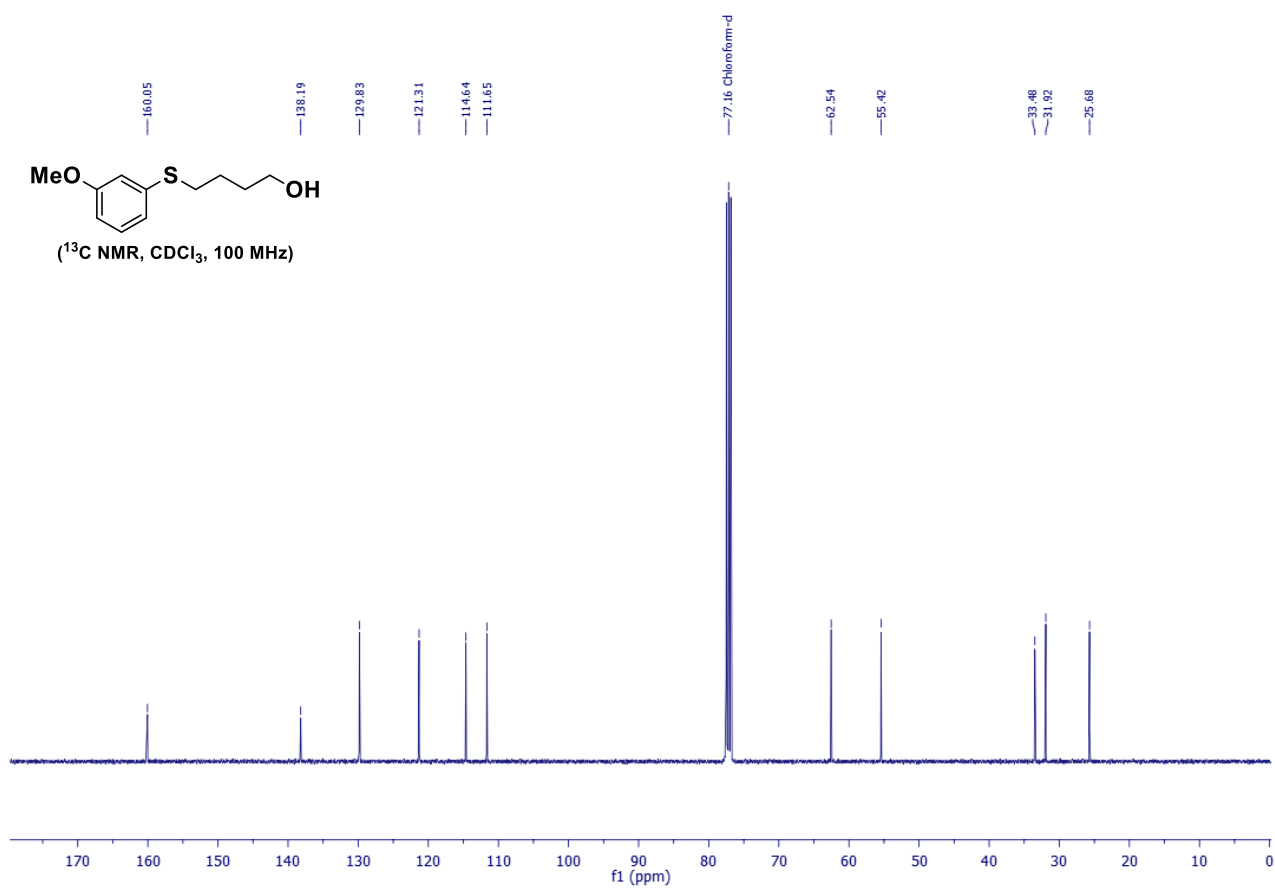
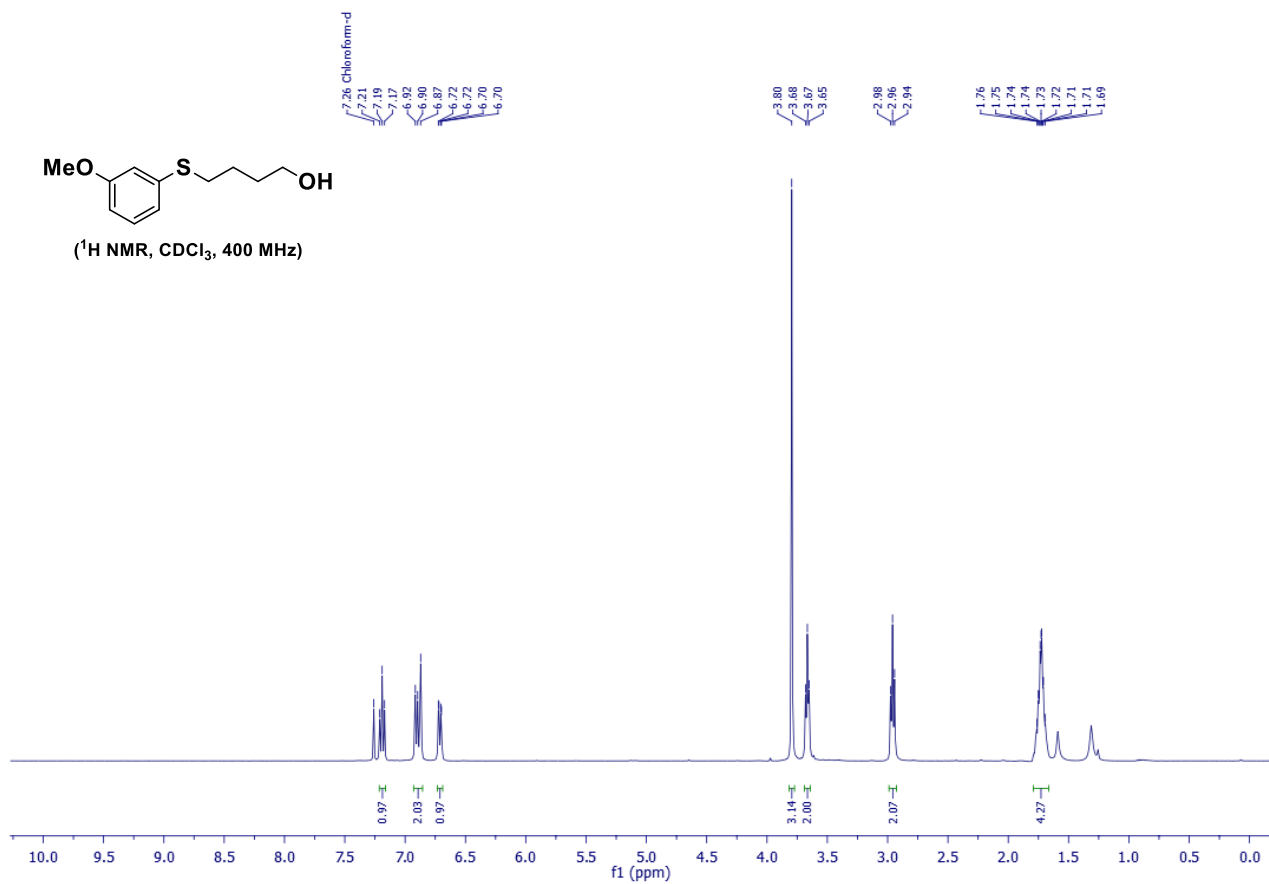


4-[[2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl]sulfanyl]butan-1-ol (739)

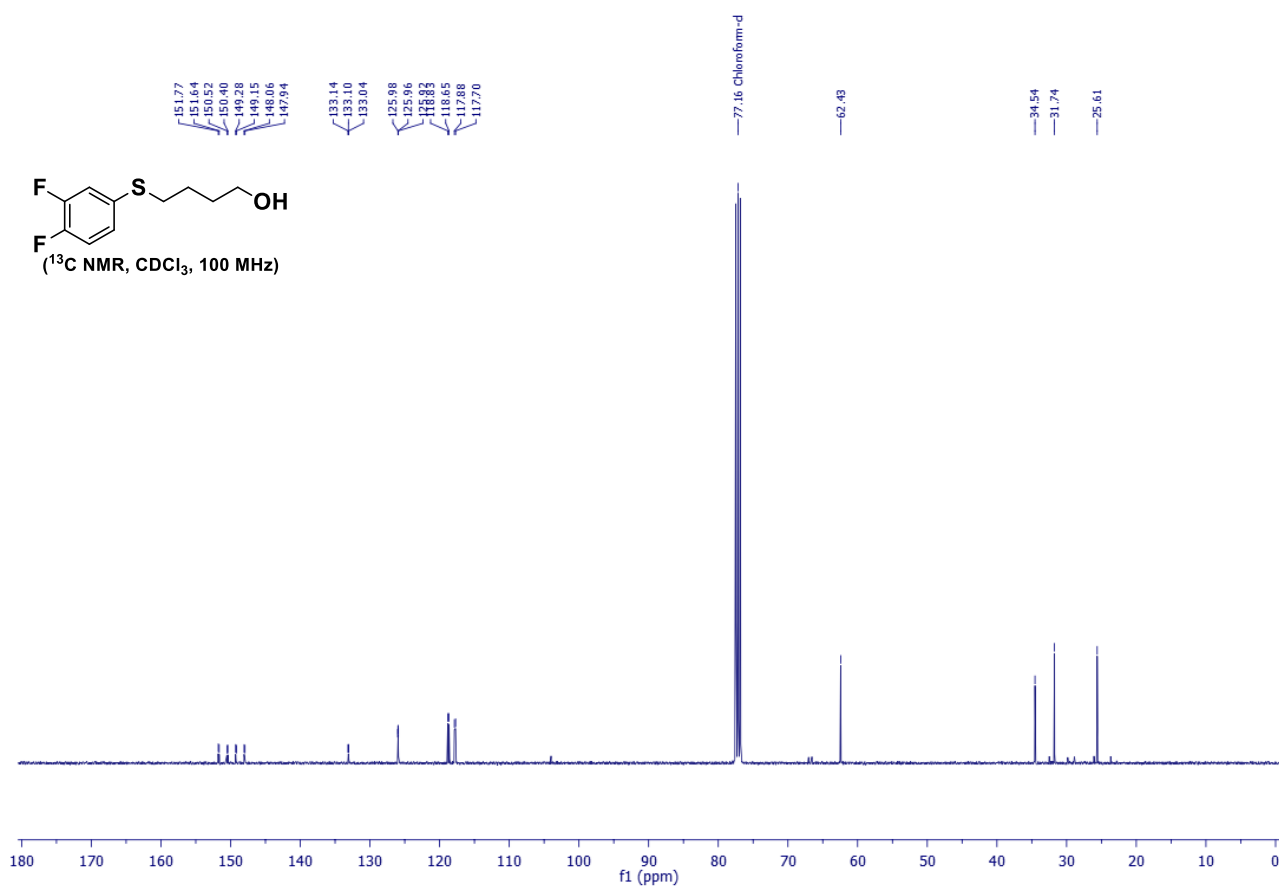
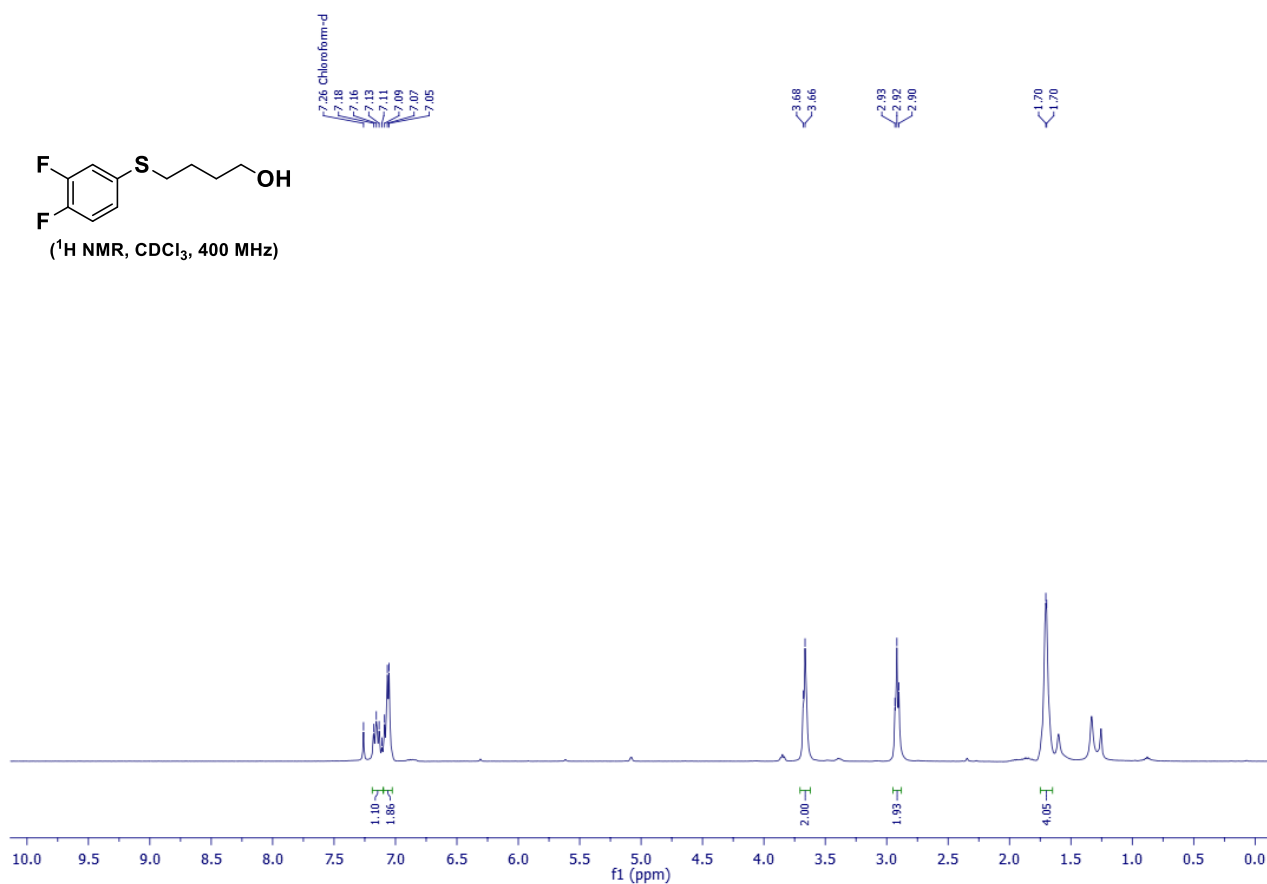
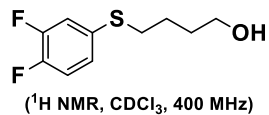


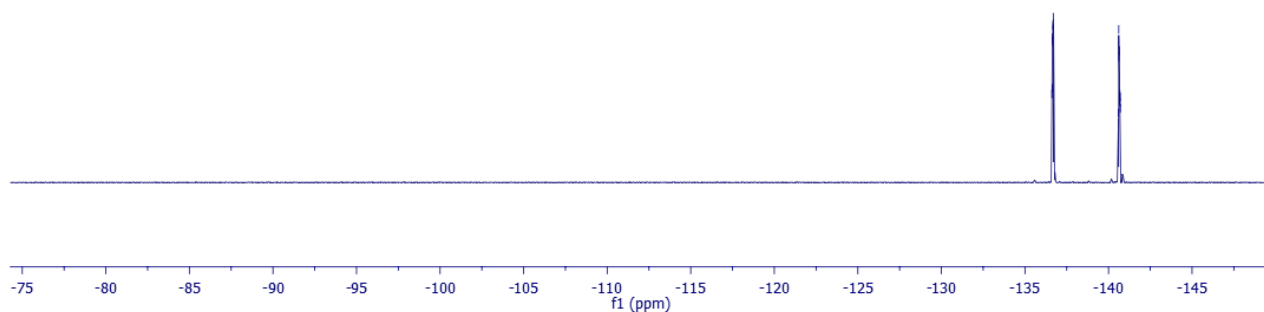
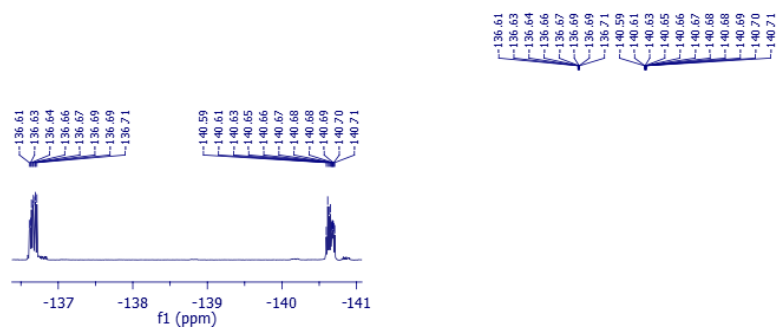


4-[(3-Methoxyphenyl)sulfanyl]butan-1-ol (740)

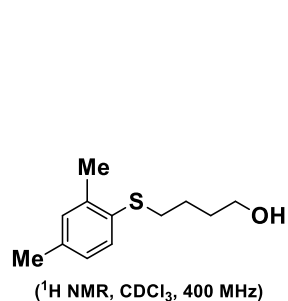


4-[(3,4-Difluorophenyl)sulfanyl]butan-1-ol (741)





4-[(2,4-Dimethylphenyl)sulfanyl]butan-1-ol (742)



7.26 Chloroform-d
 7.21
 7.19
 7.00
 6.98
 6.96

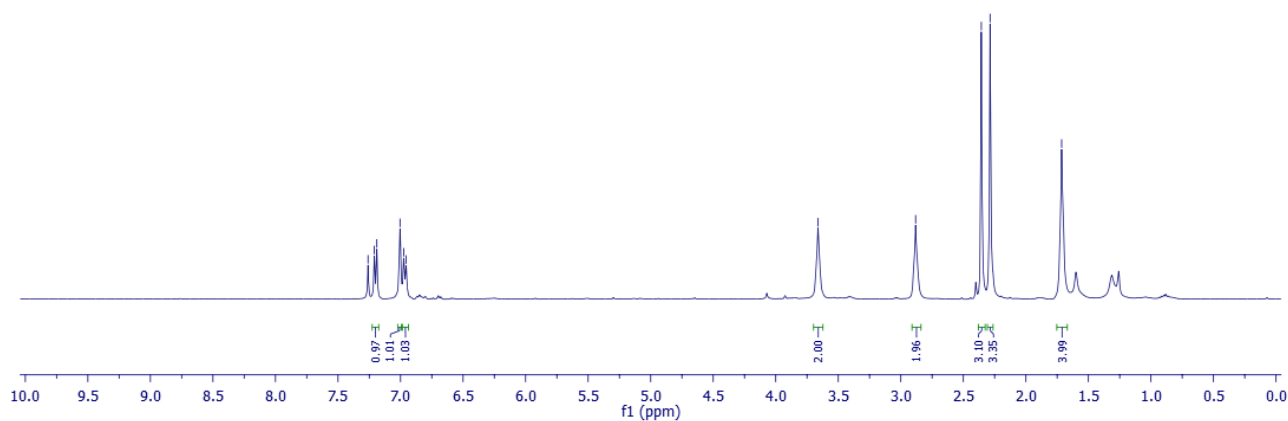
3.66

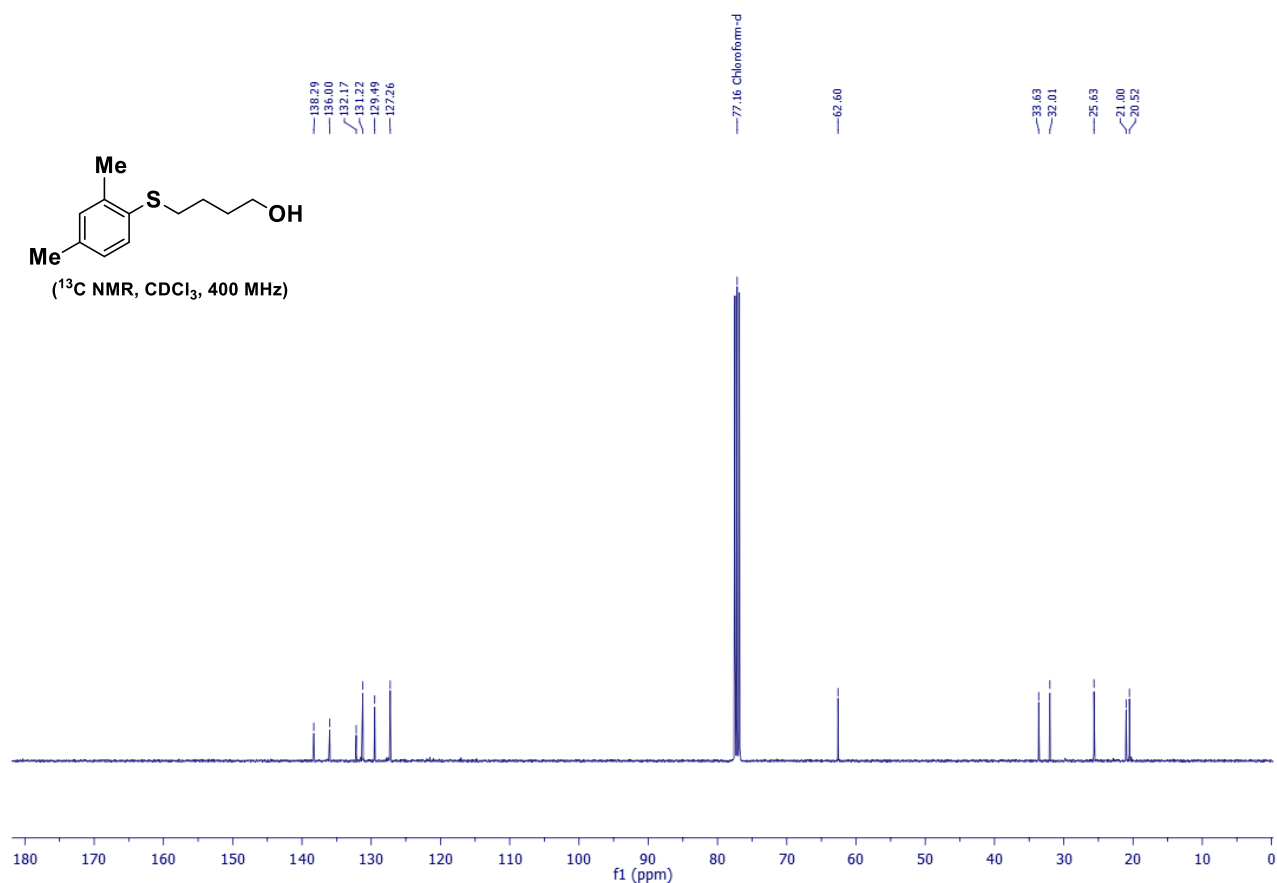
2.88

2.36

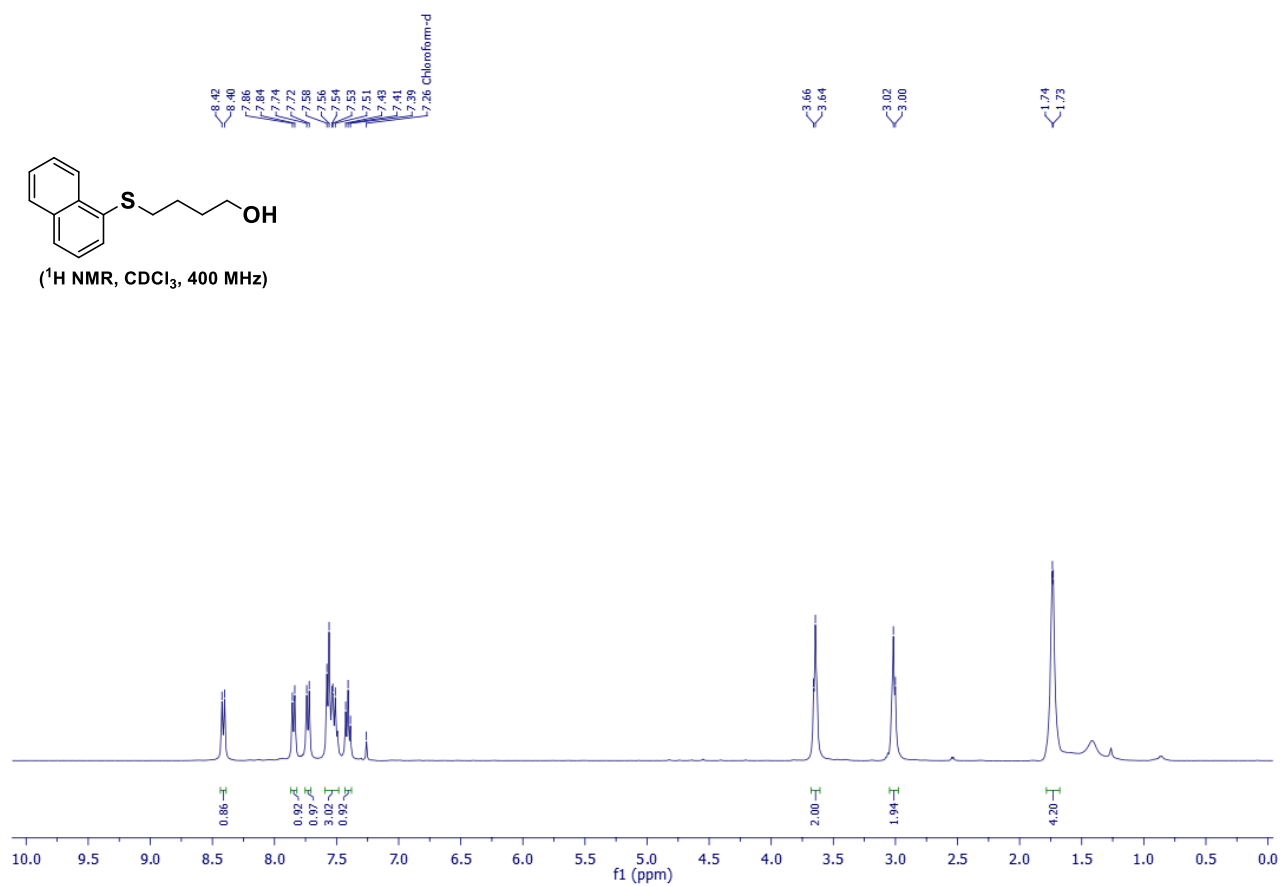
2.29

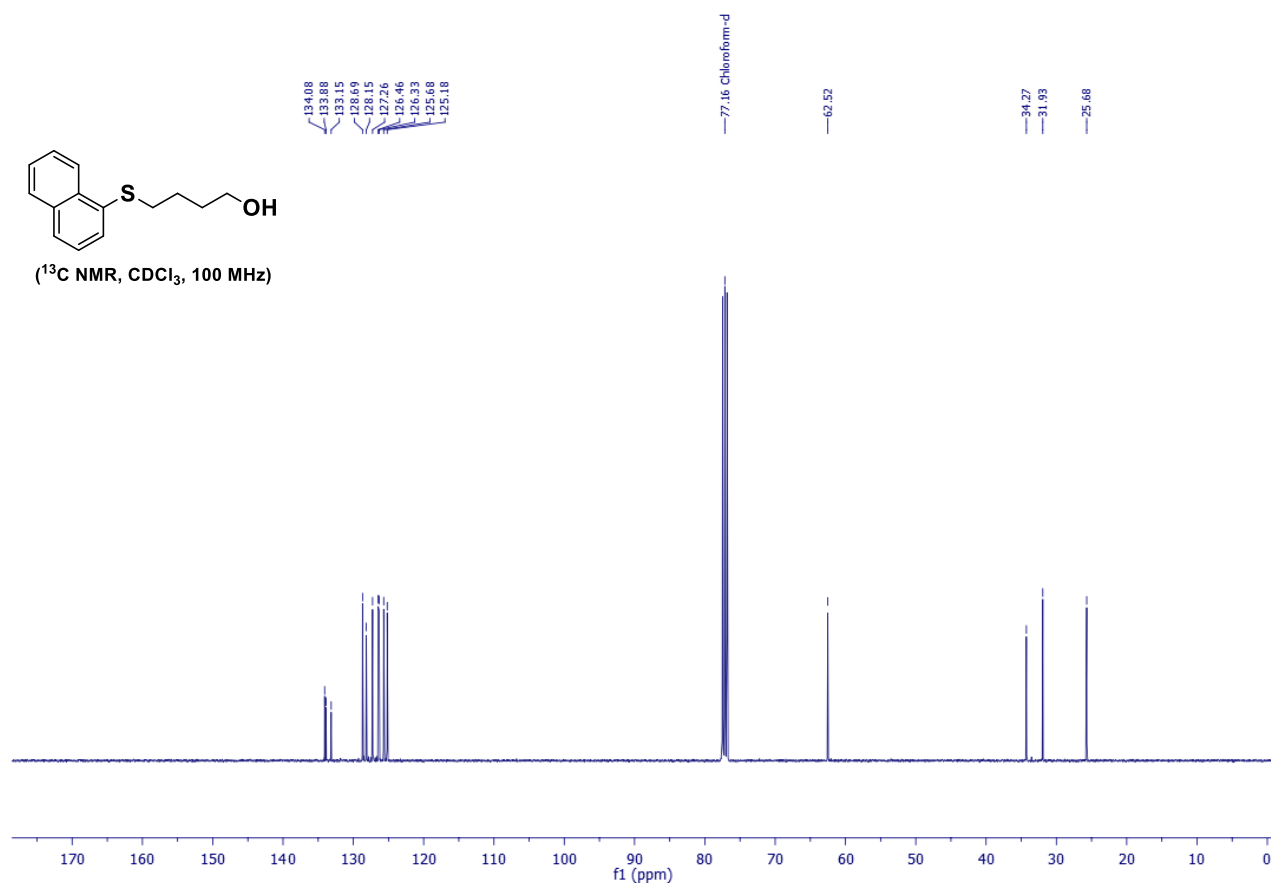
1.71



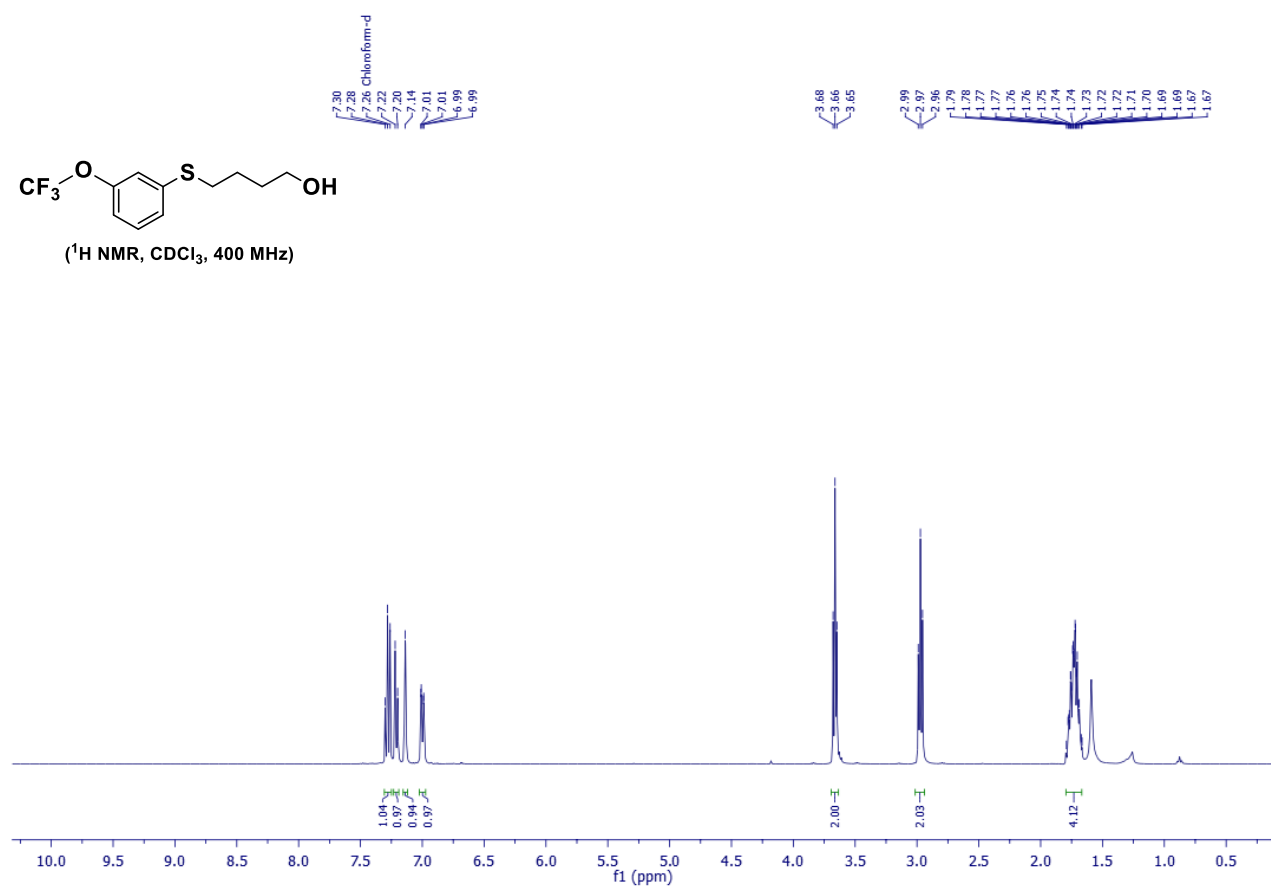


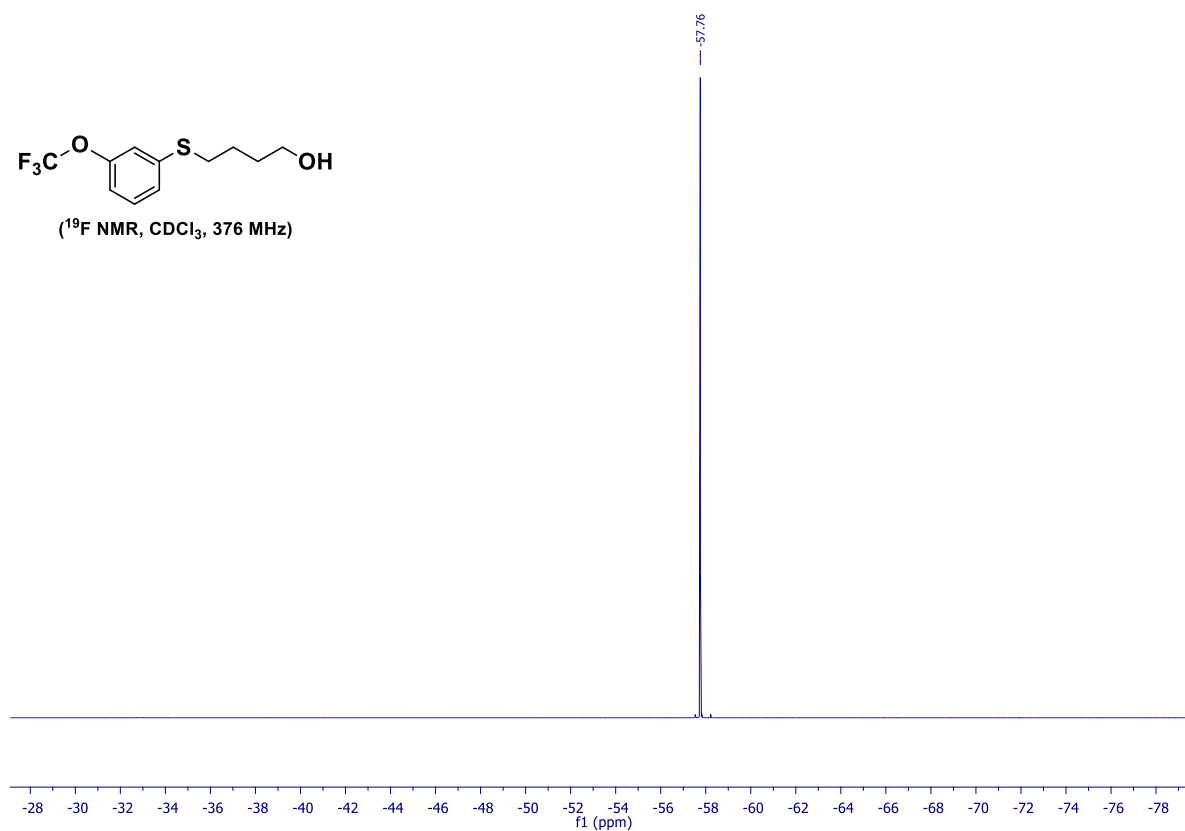
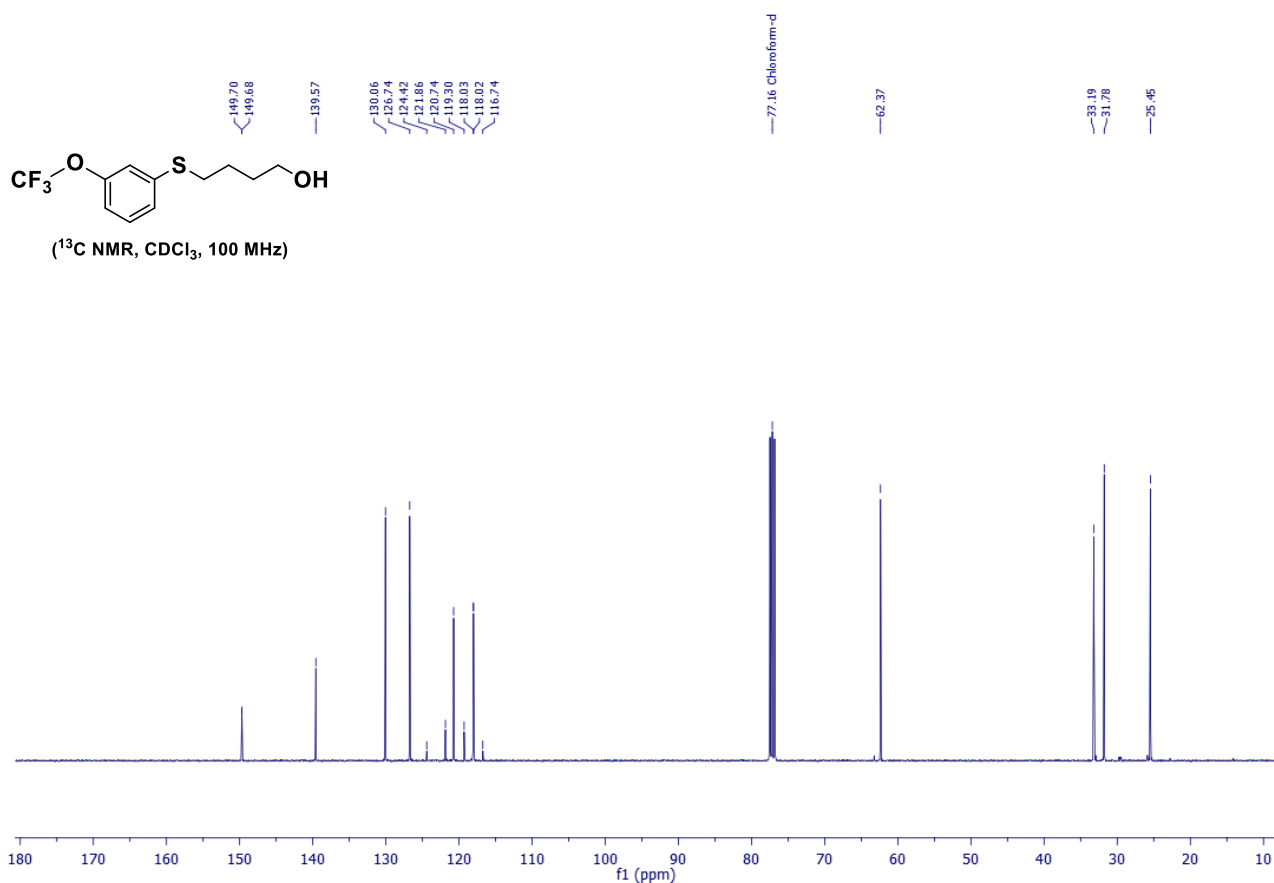
4-[(Naphthalen-1-yl)sulfanyl]butan-1-ol (743)



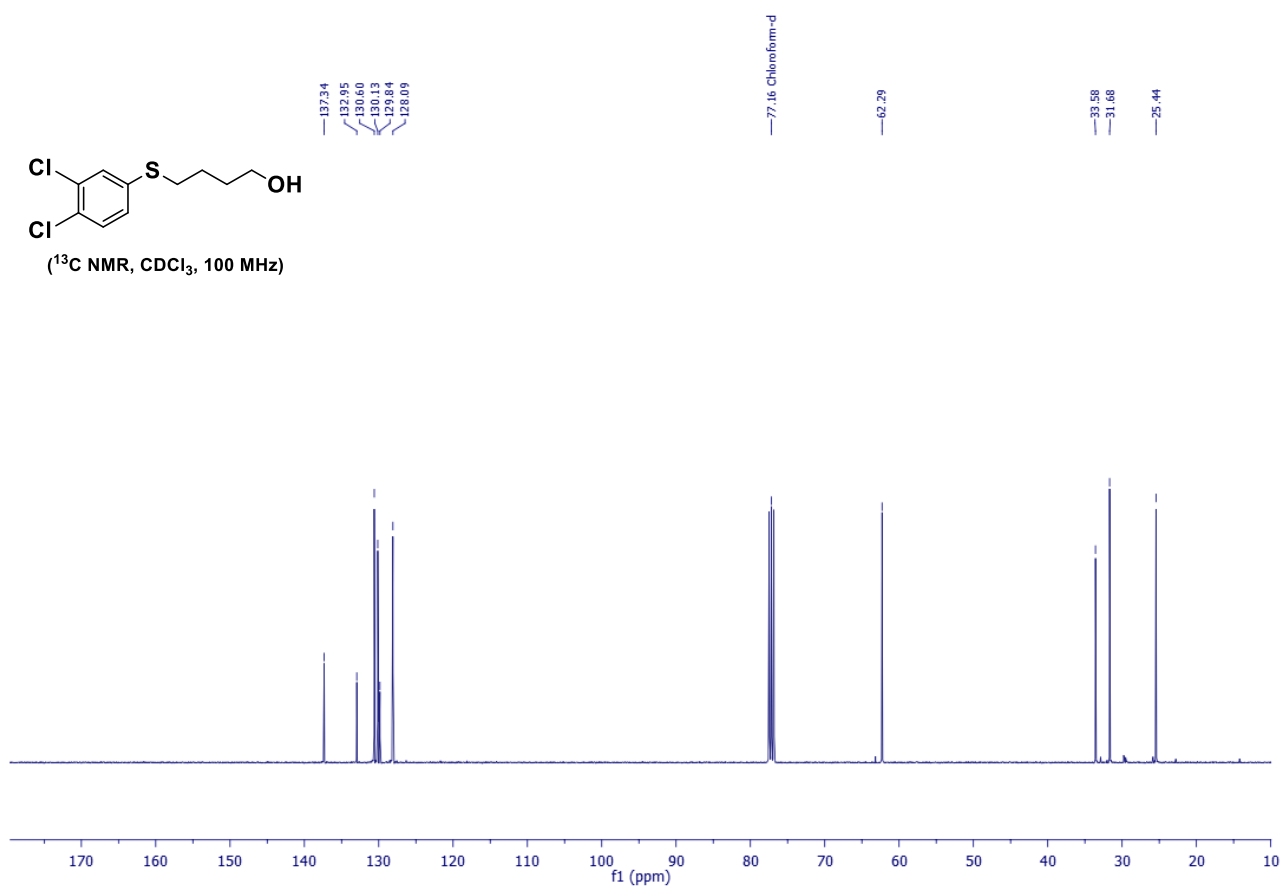
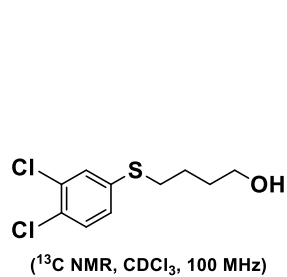
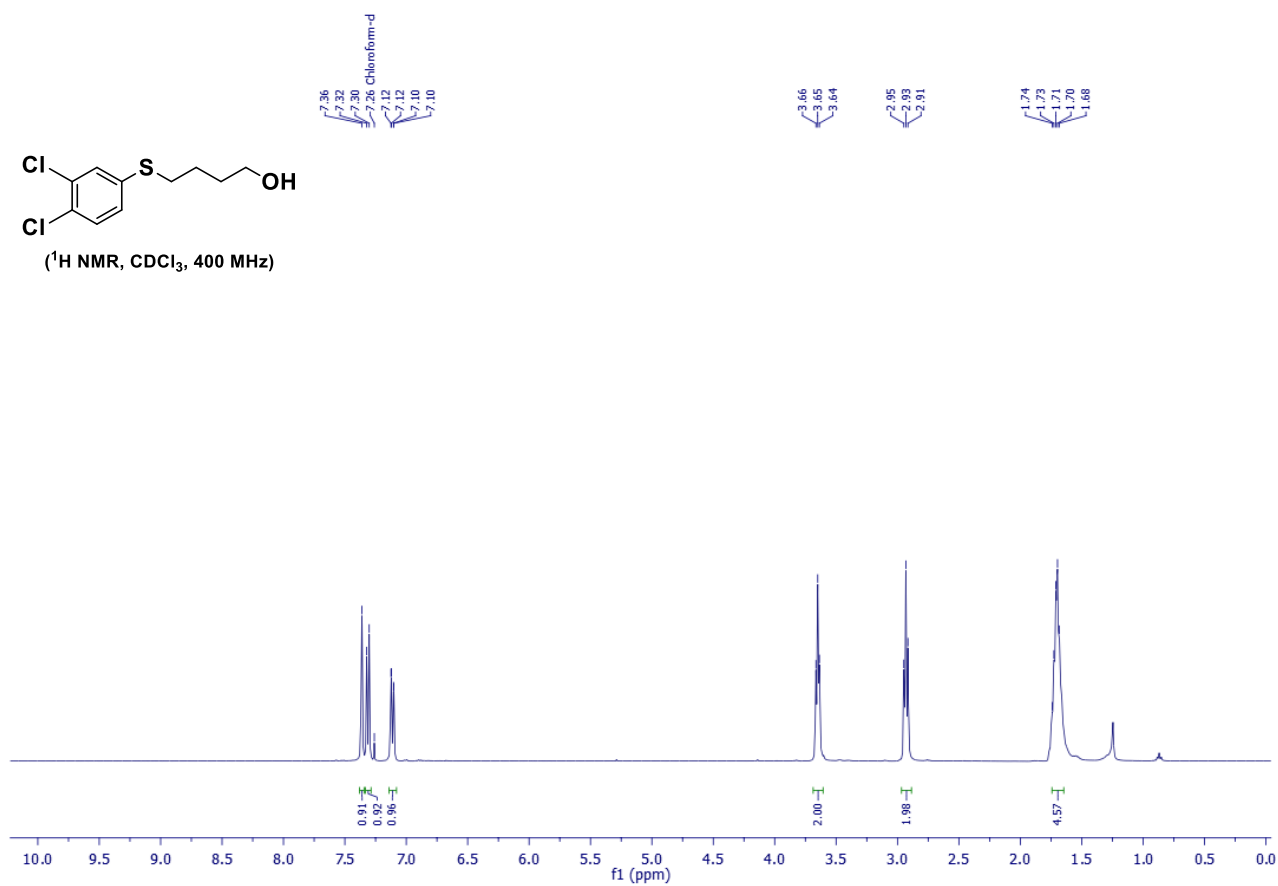
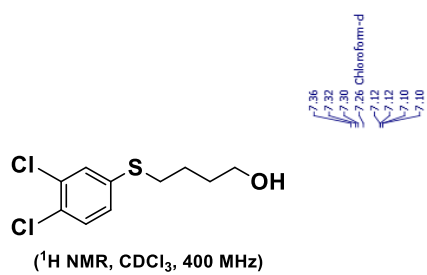


4-[[3-(Trifluoromethoxy)phenyl]sulfanyl]butan-1-ol (744)

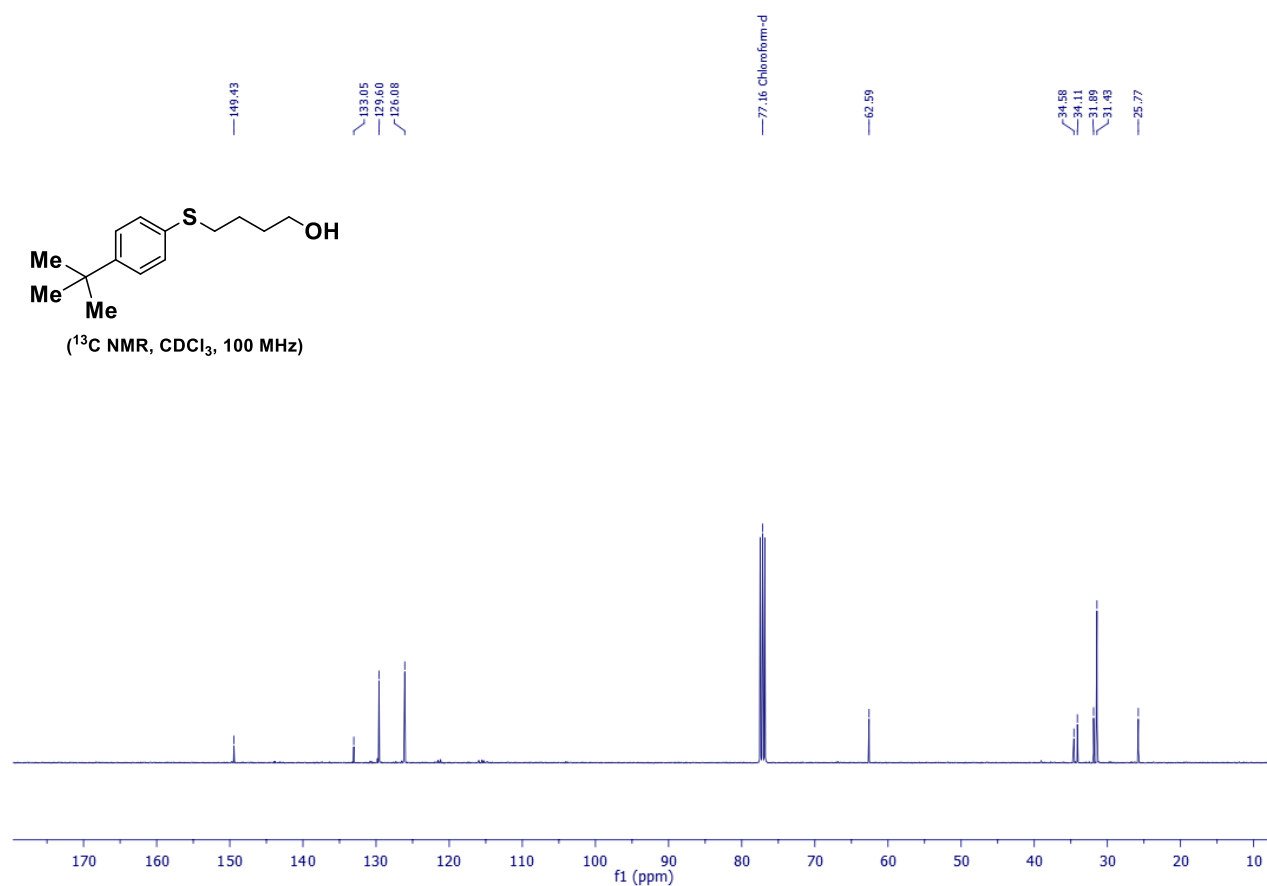
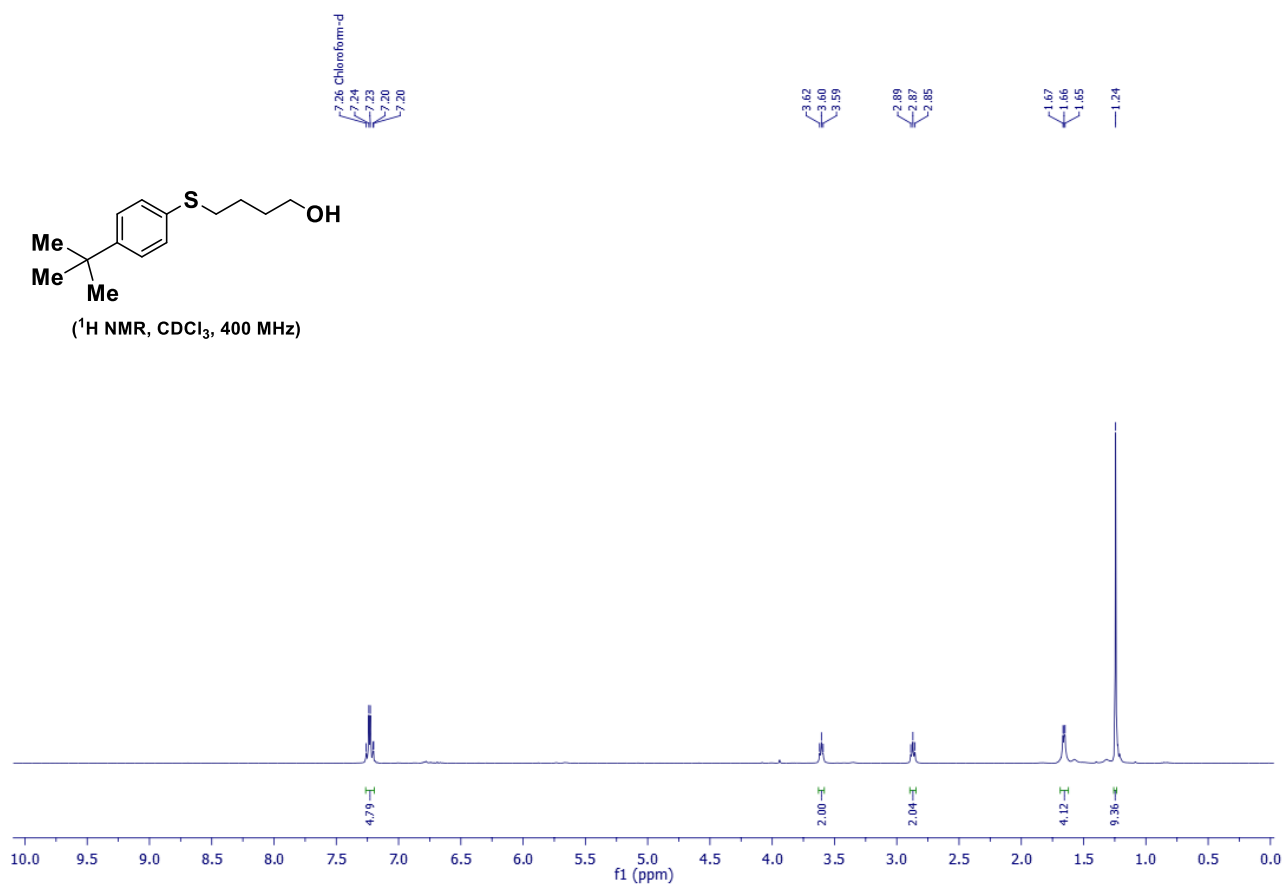




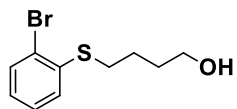
4-[(3,4-Dichlorophenyl)sulfanyl]butan-1-ol (745)



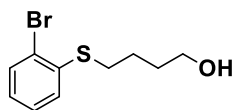
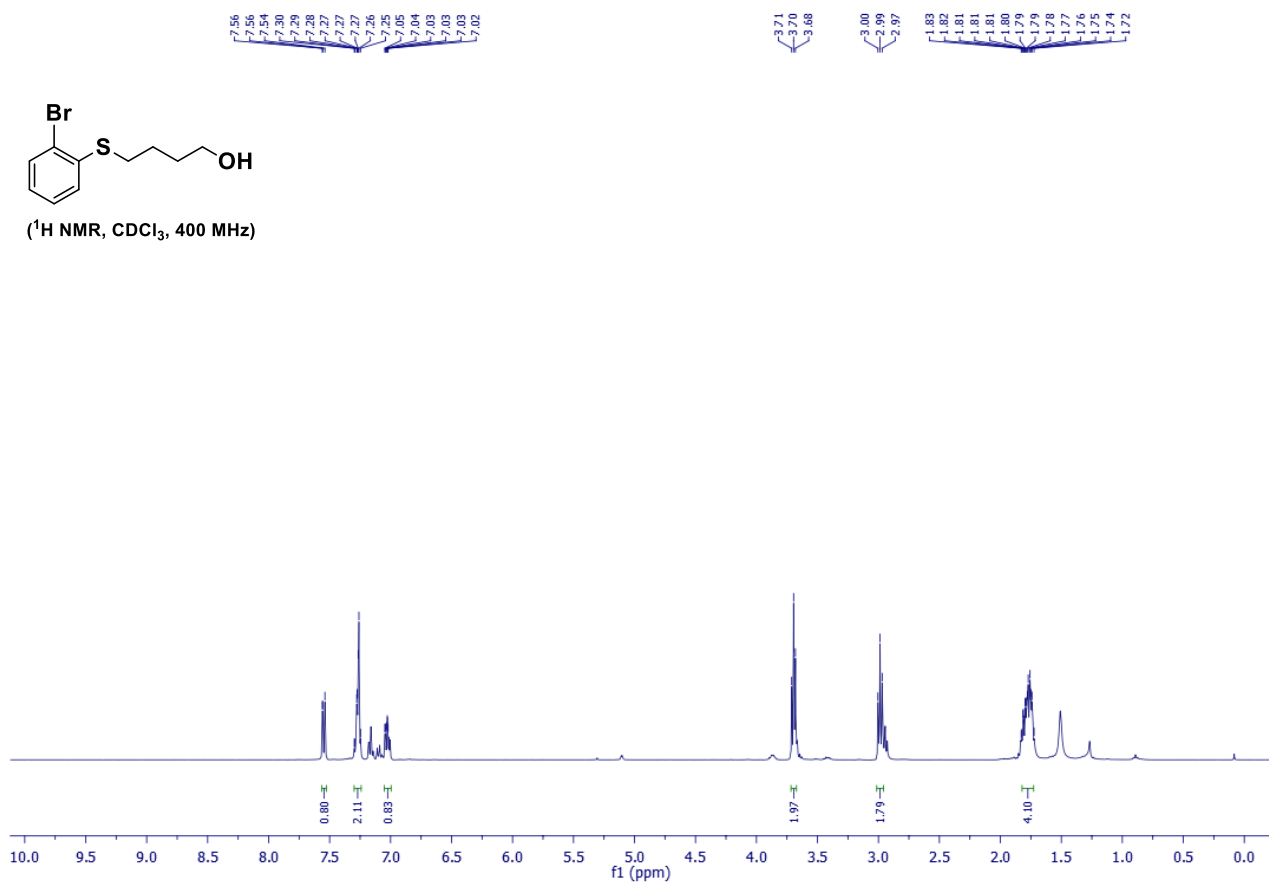
4-[(4-*Tert*-butylphenyl)sulfanyl]butan-1-ol (746)



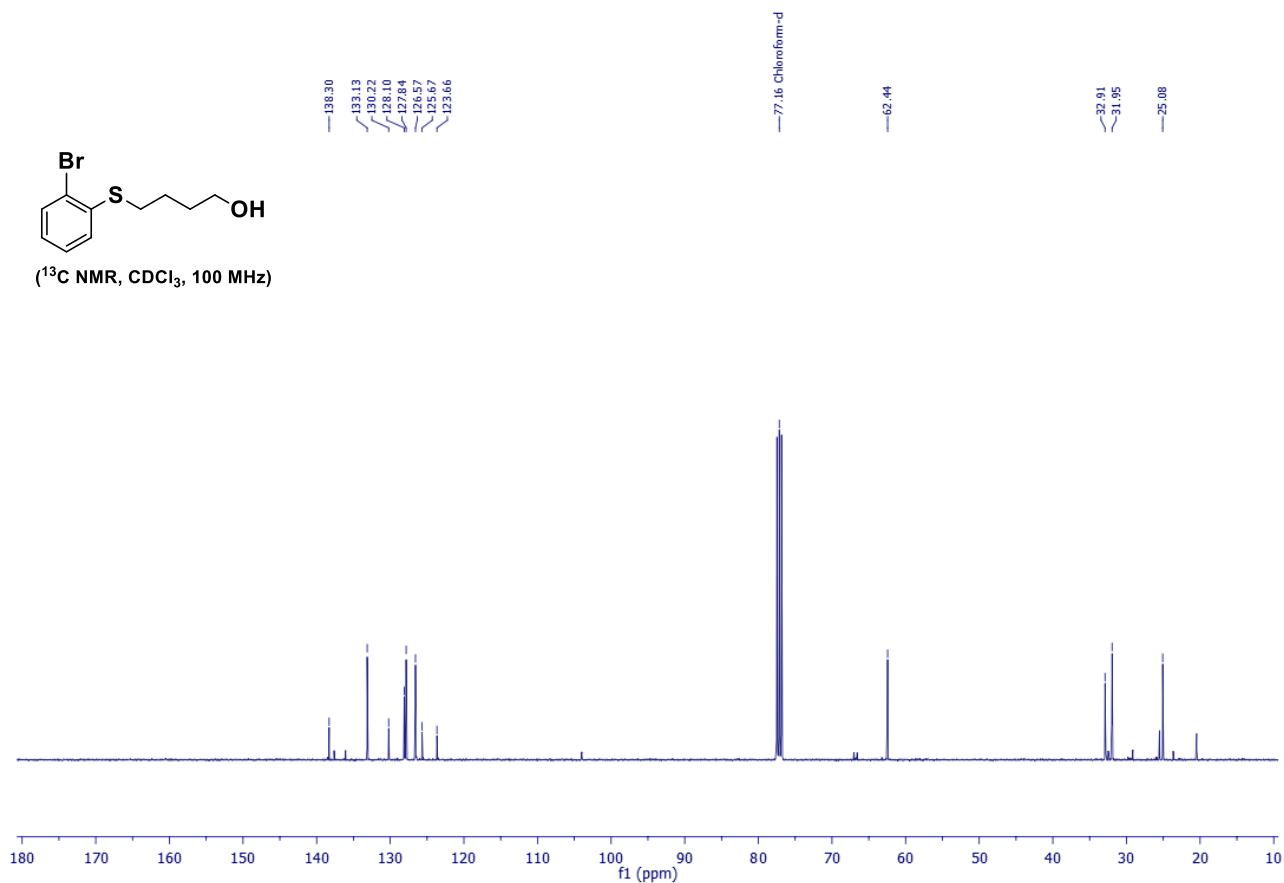
4-[(2-Bromophenyl)sulfanyl]butan-1-ol (747)



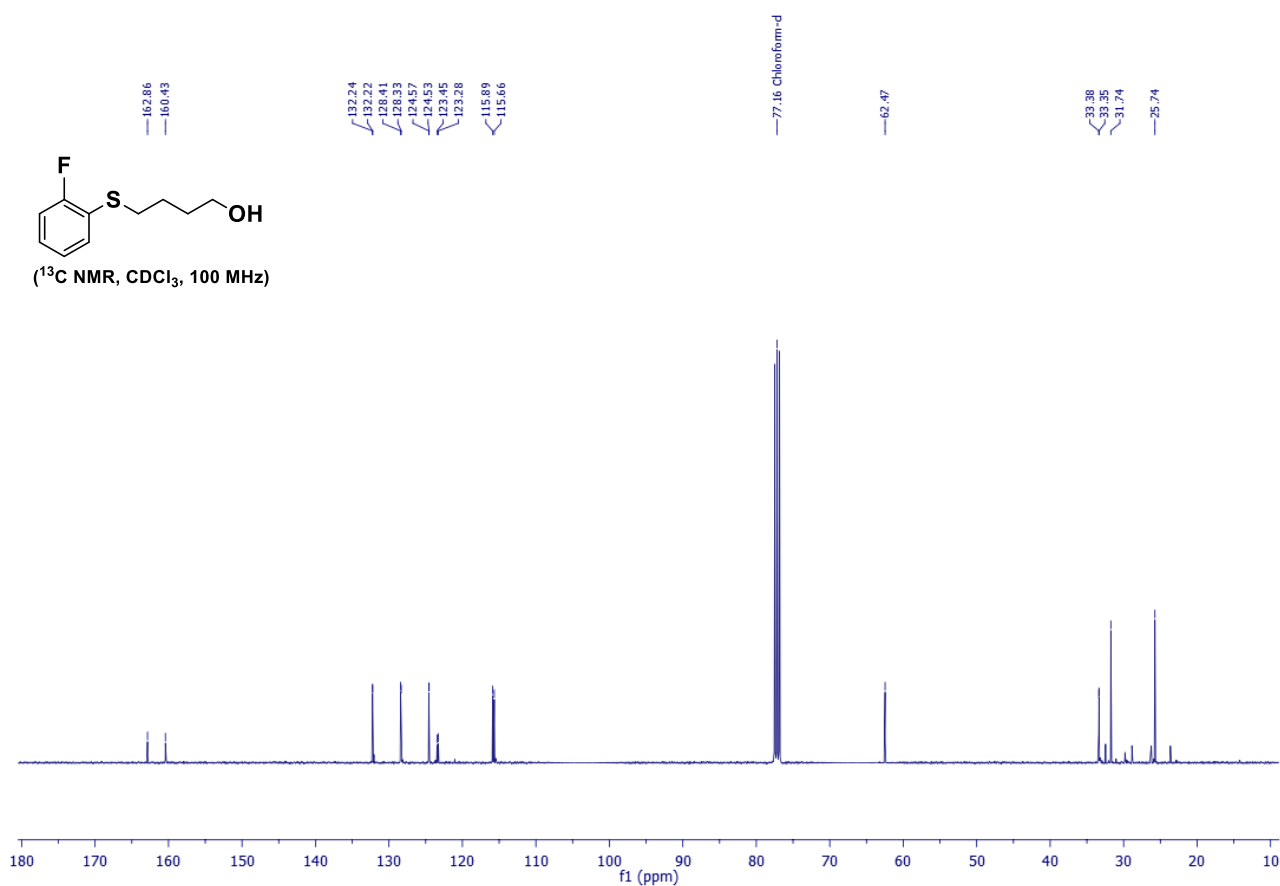
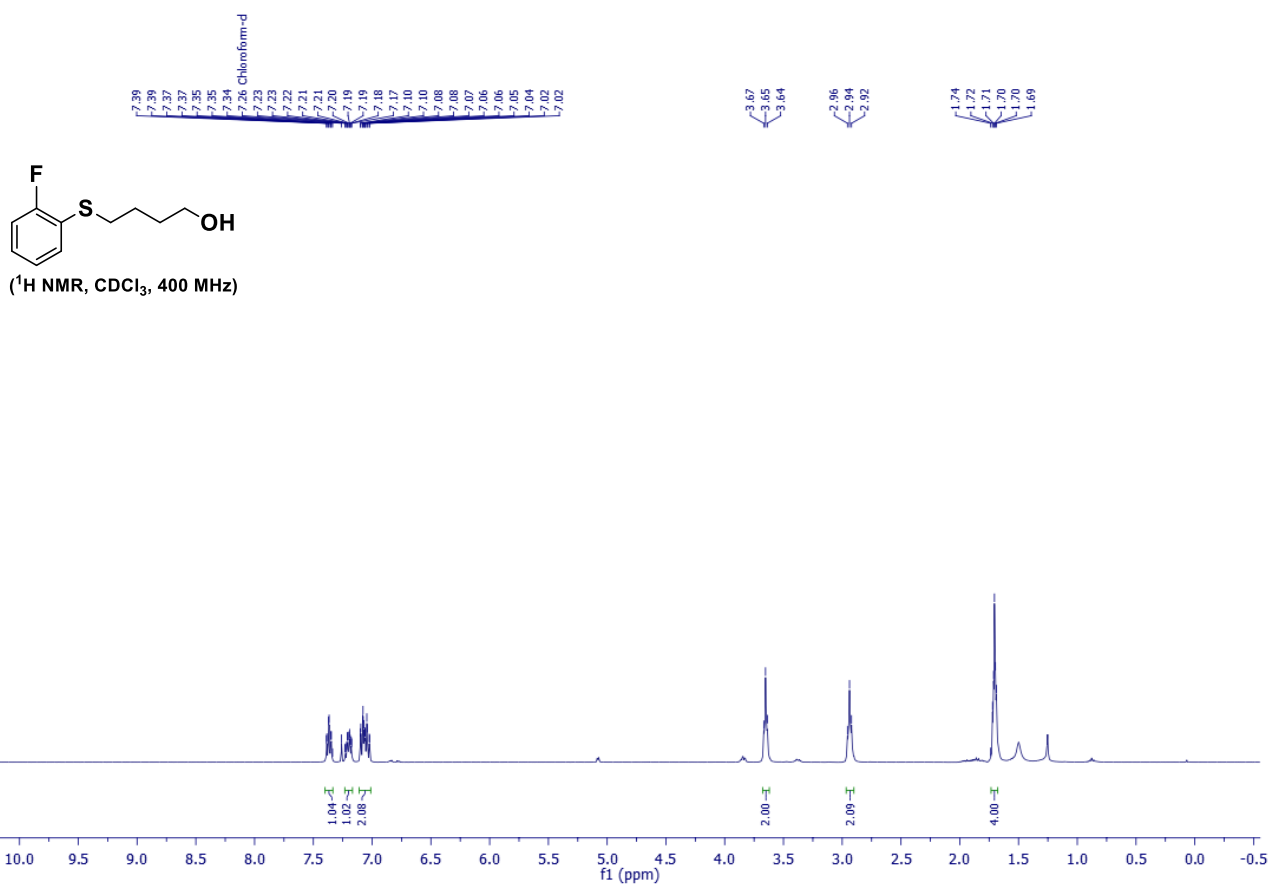
(¹H NMR, CDCl₃, 400 MHz)

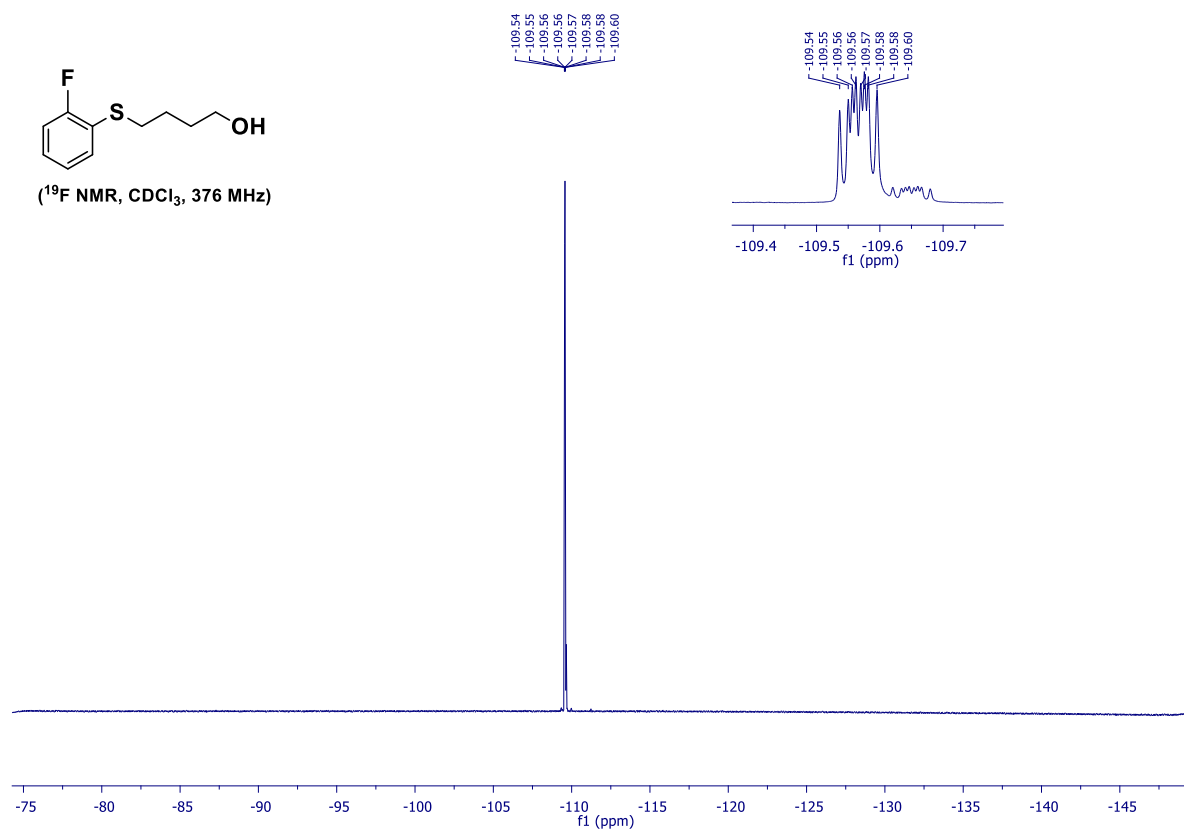


(¹³C NMR, CDCl₃, 100 MHz)

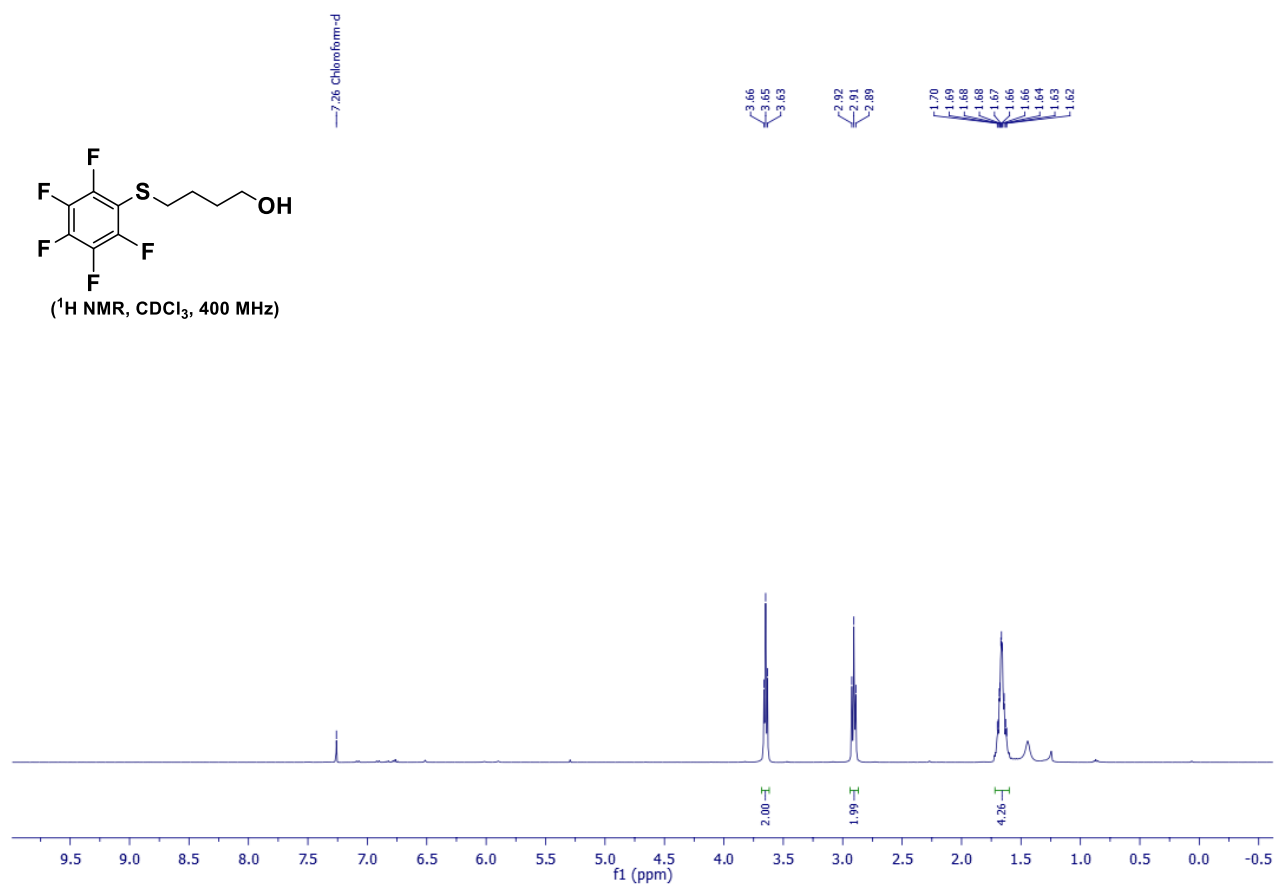


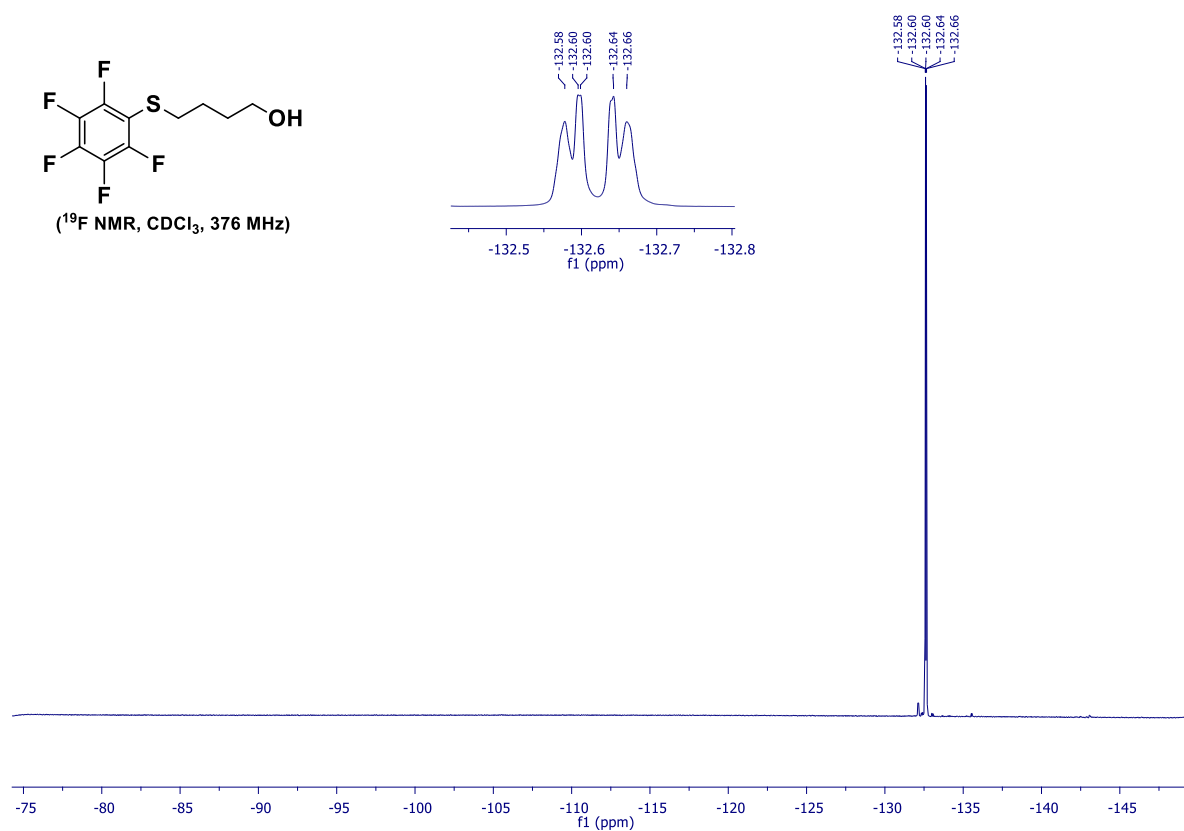
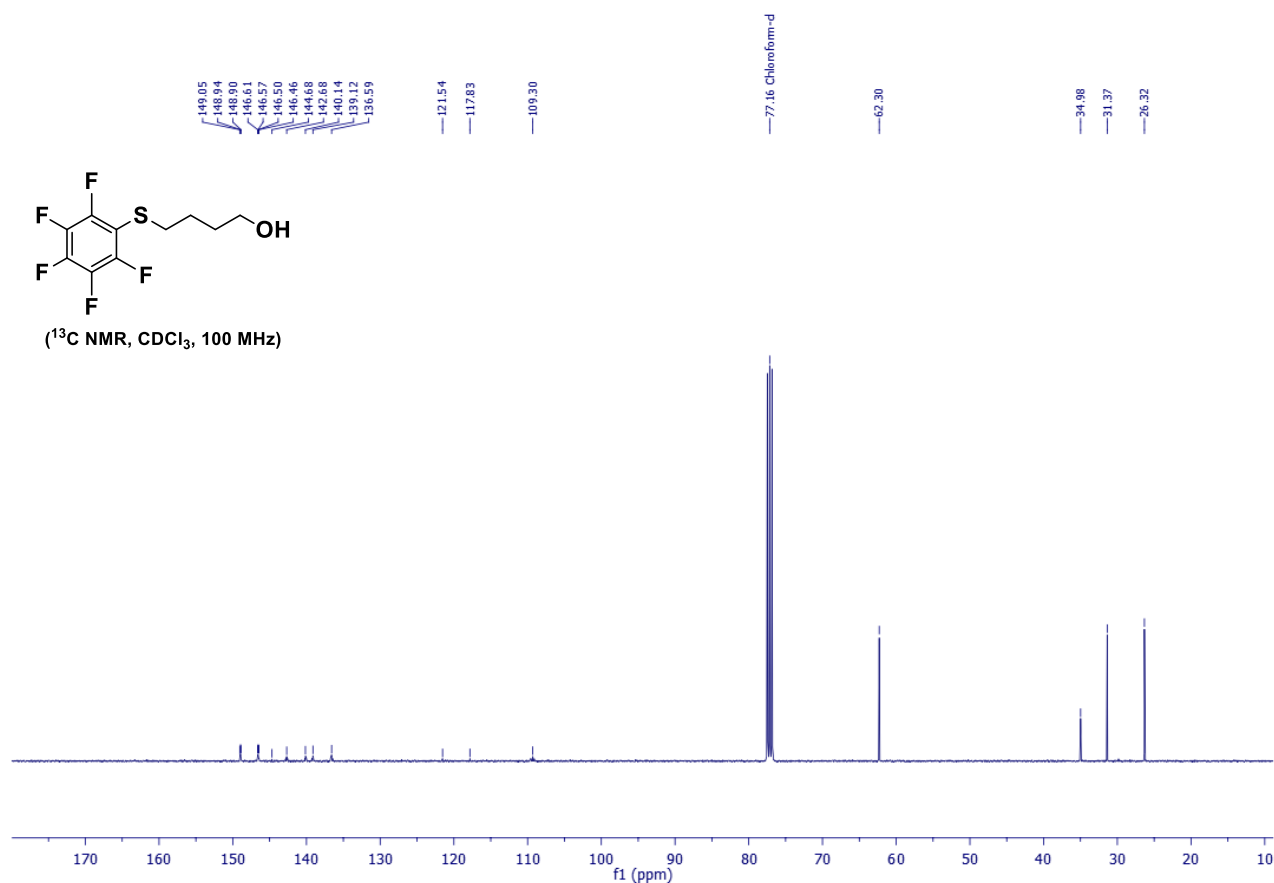
4-[(2-Fluorophenyl)sulfanyl]butan-1-ol (748)



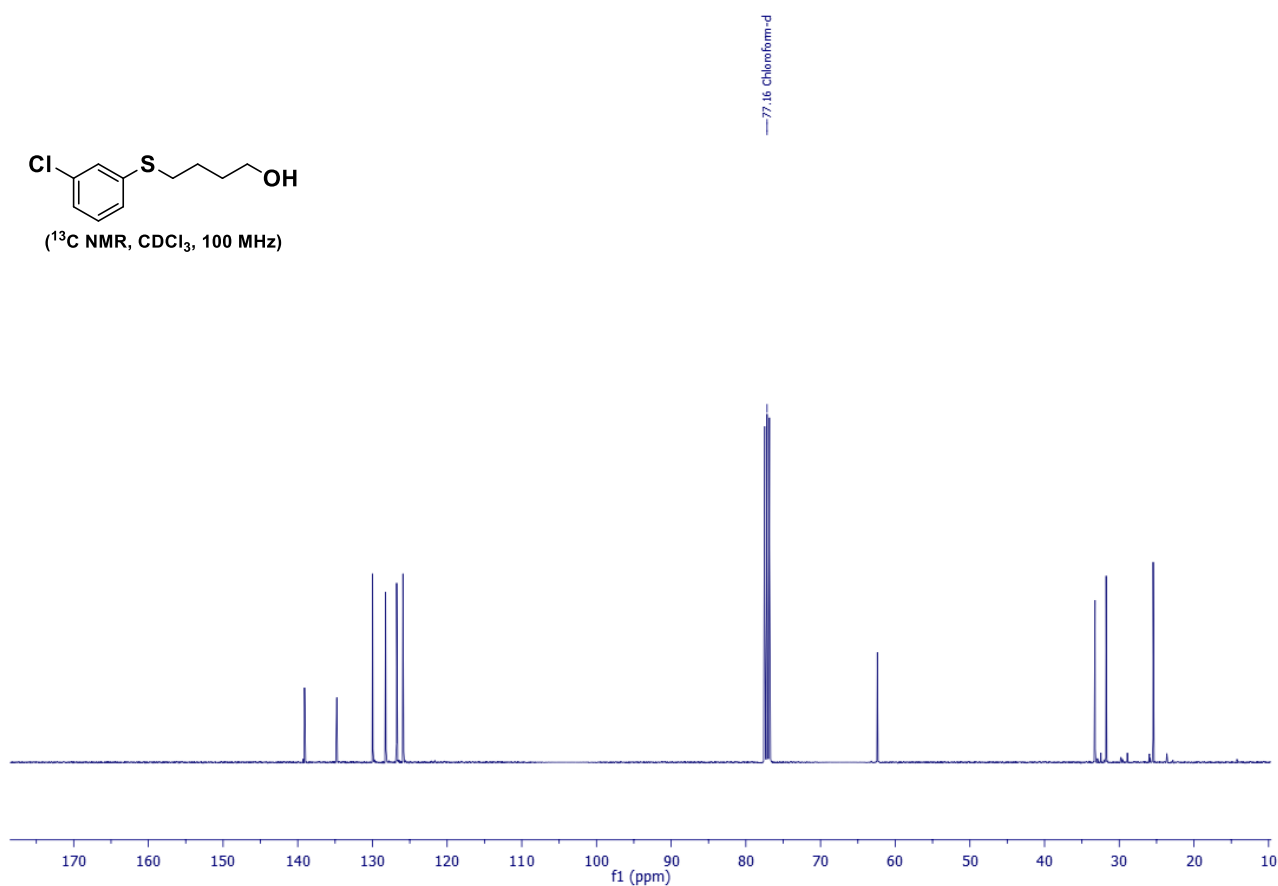
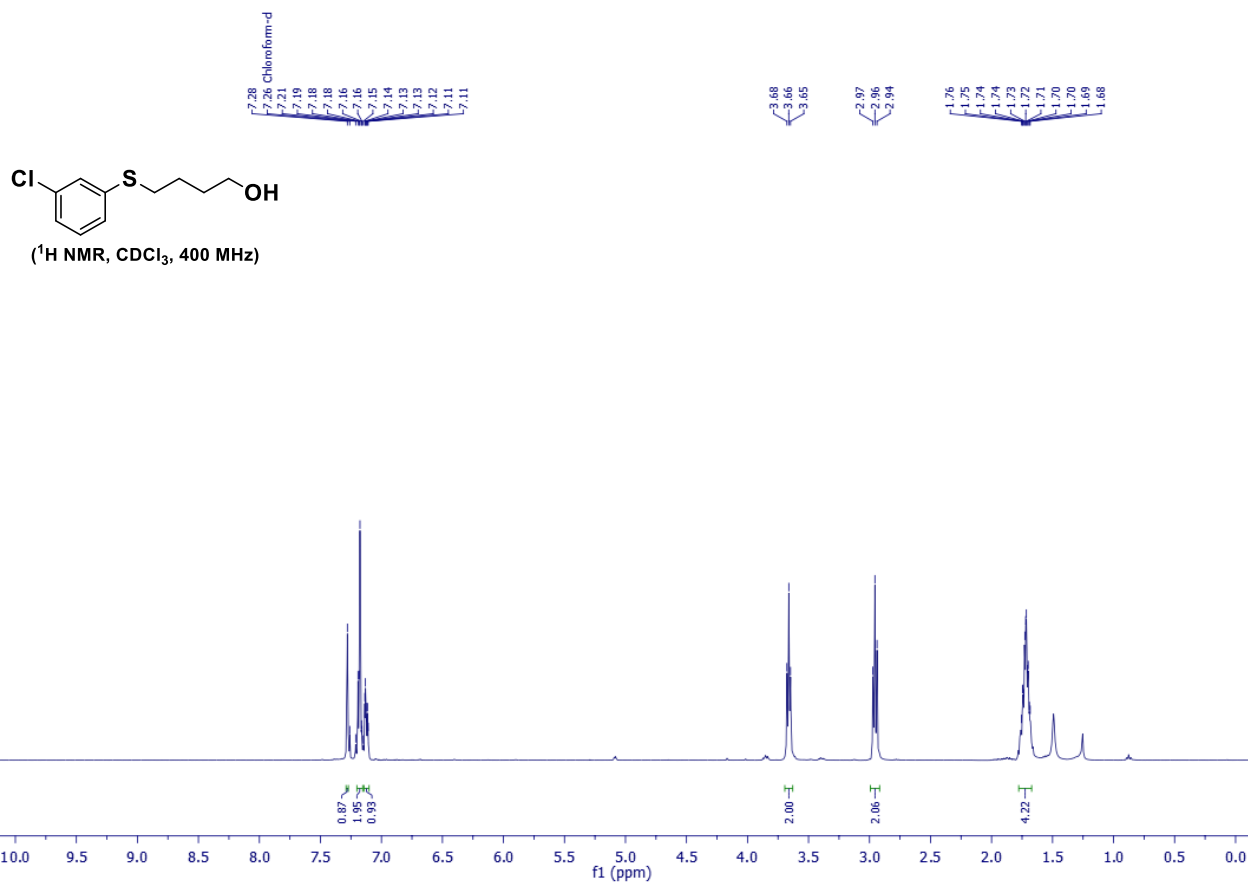


4-[(Pentafluorophenyl)sulfanyl]butan-1-ol (749)

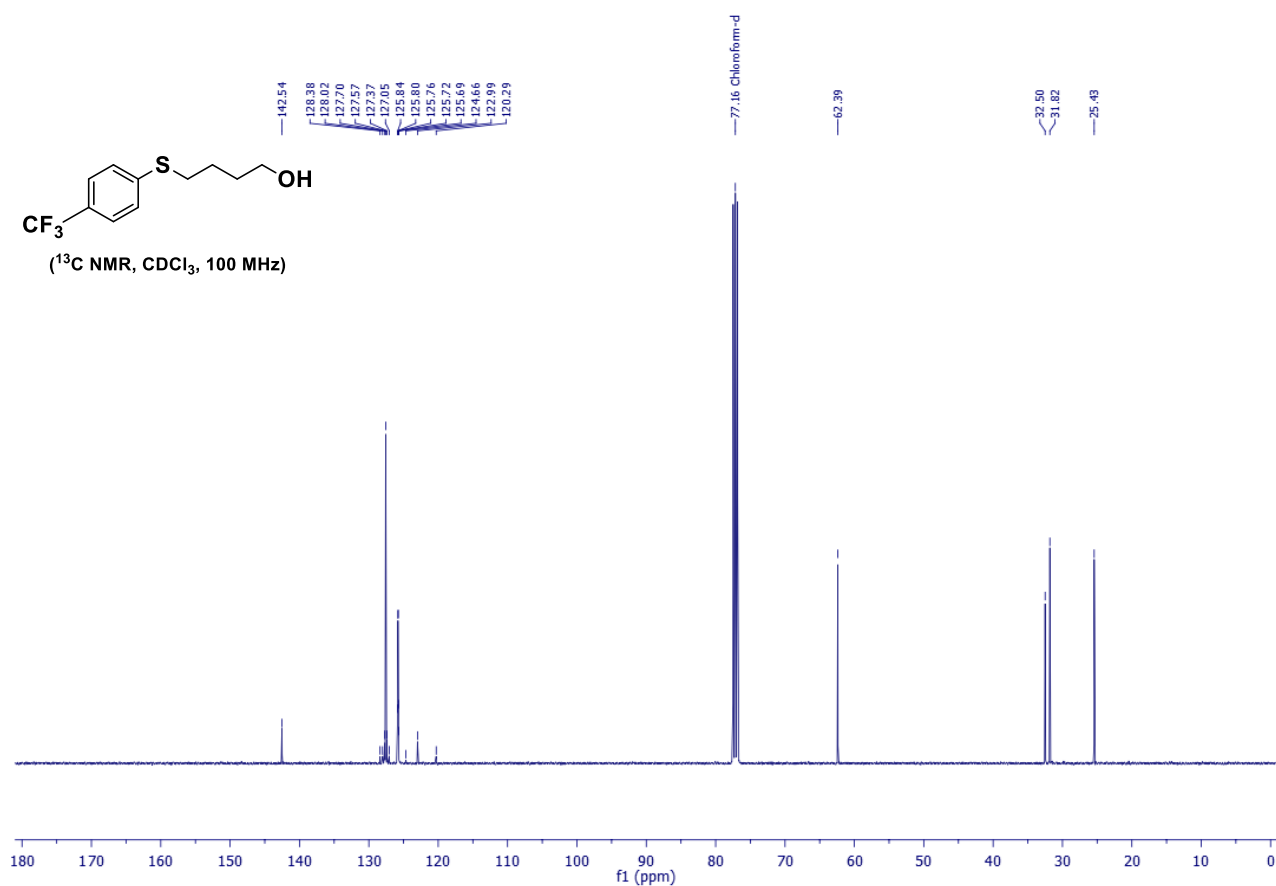
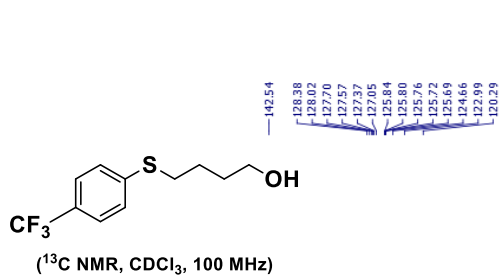
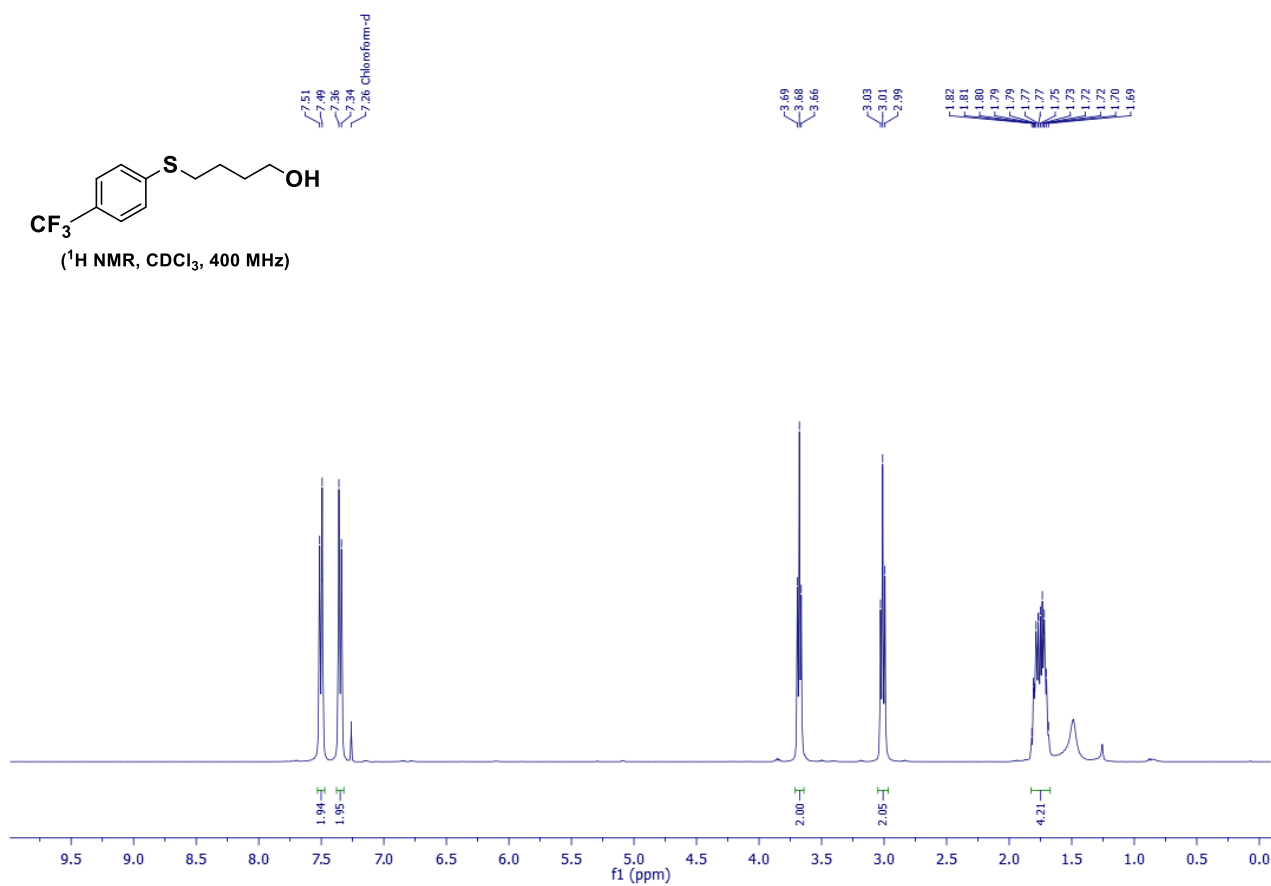
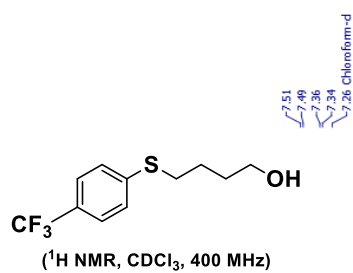


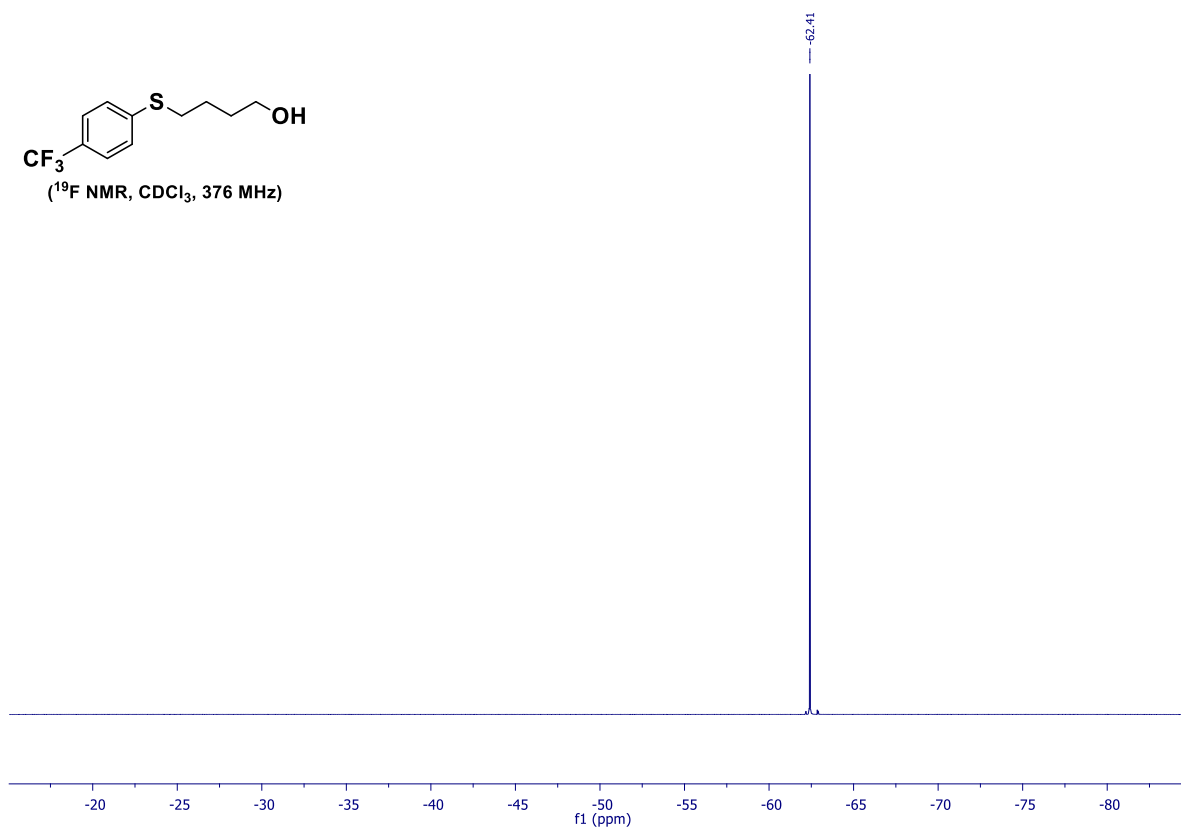
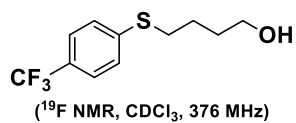


4-[(3-Chlorophenyl)sulfanyl]butan-1-ol (750)

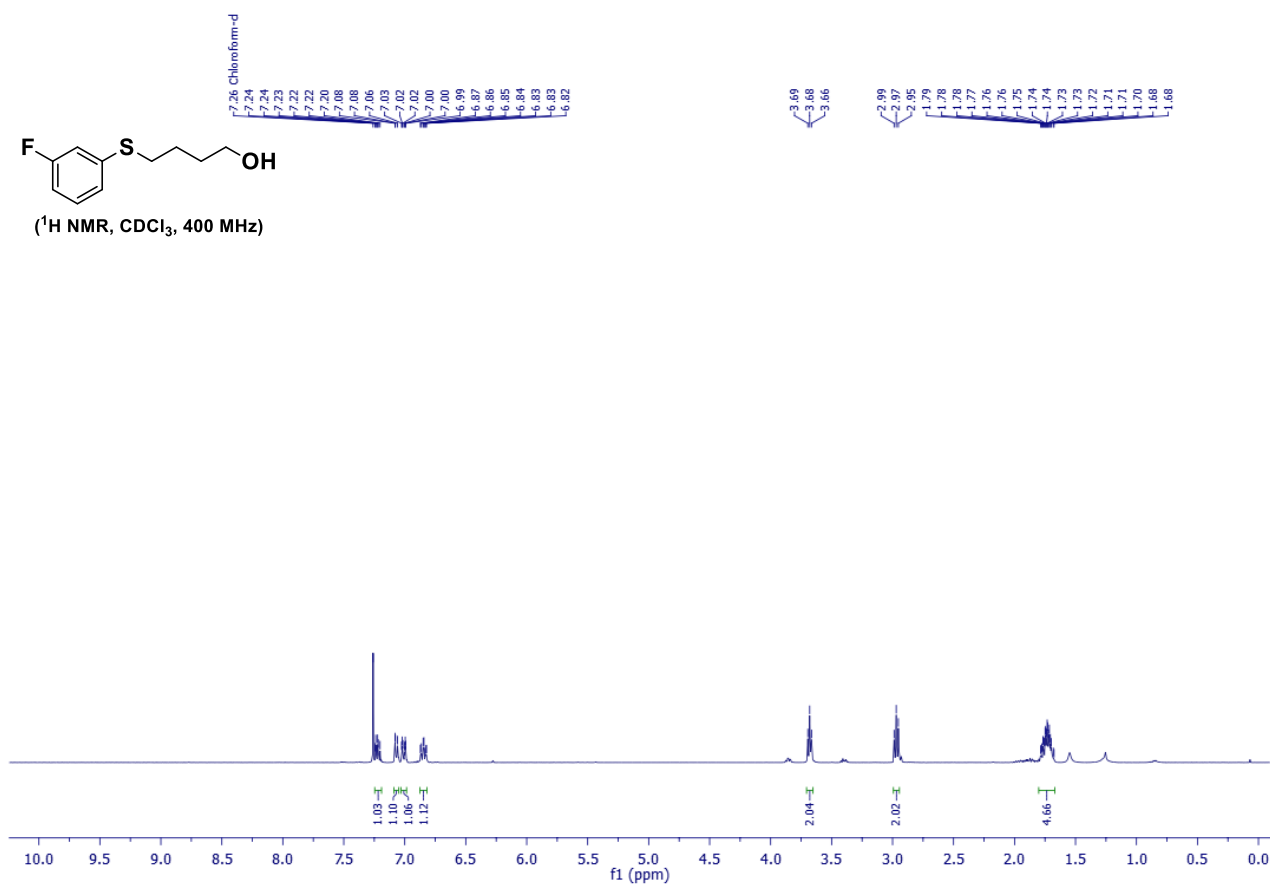
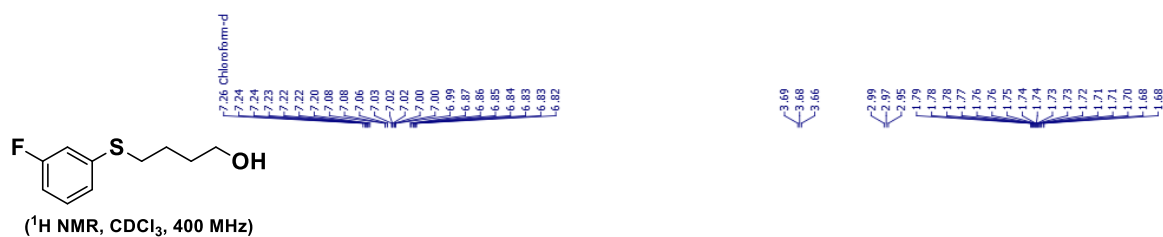


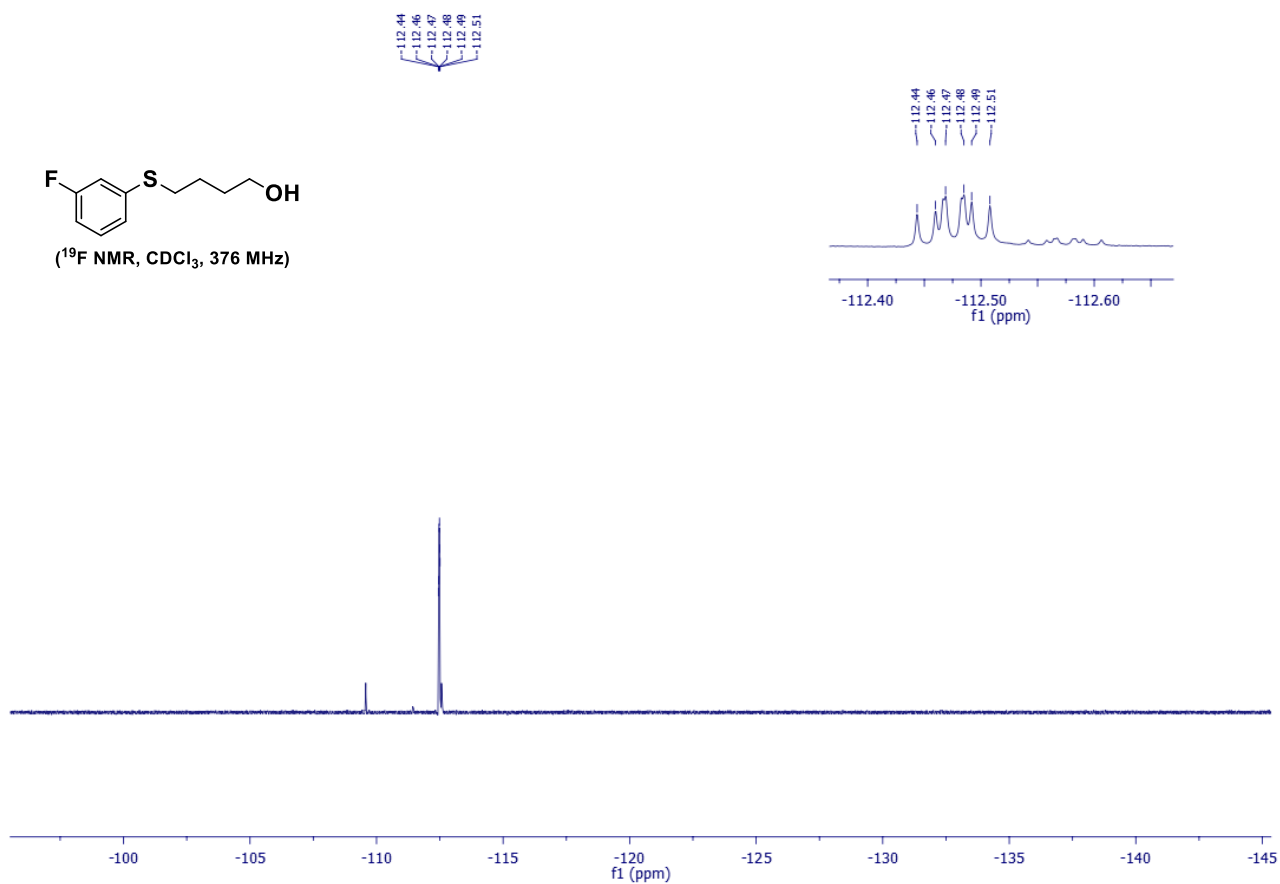
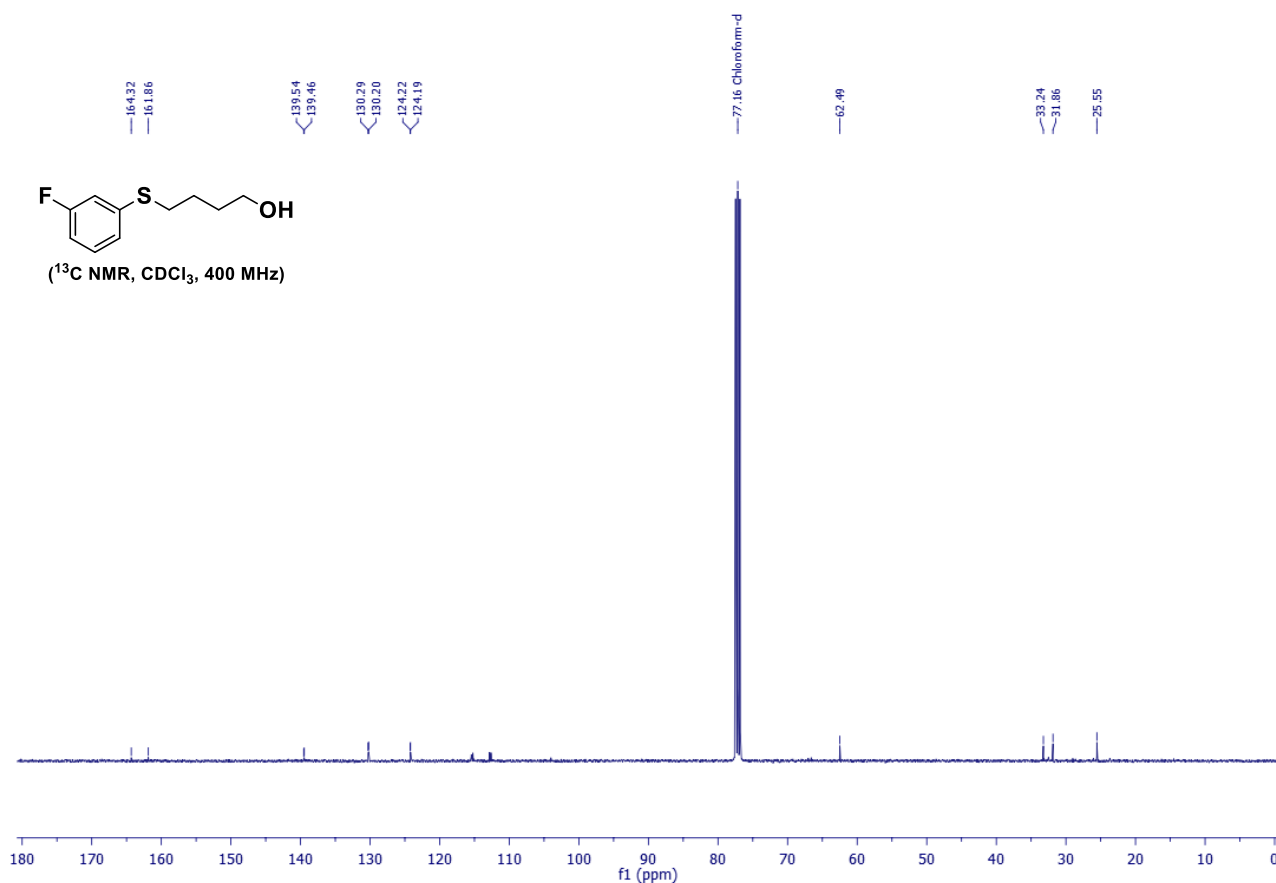
4-[[4-(Trifluoromethyl)phenyl]sulfanyl]butan-1-ol (751)



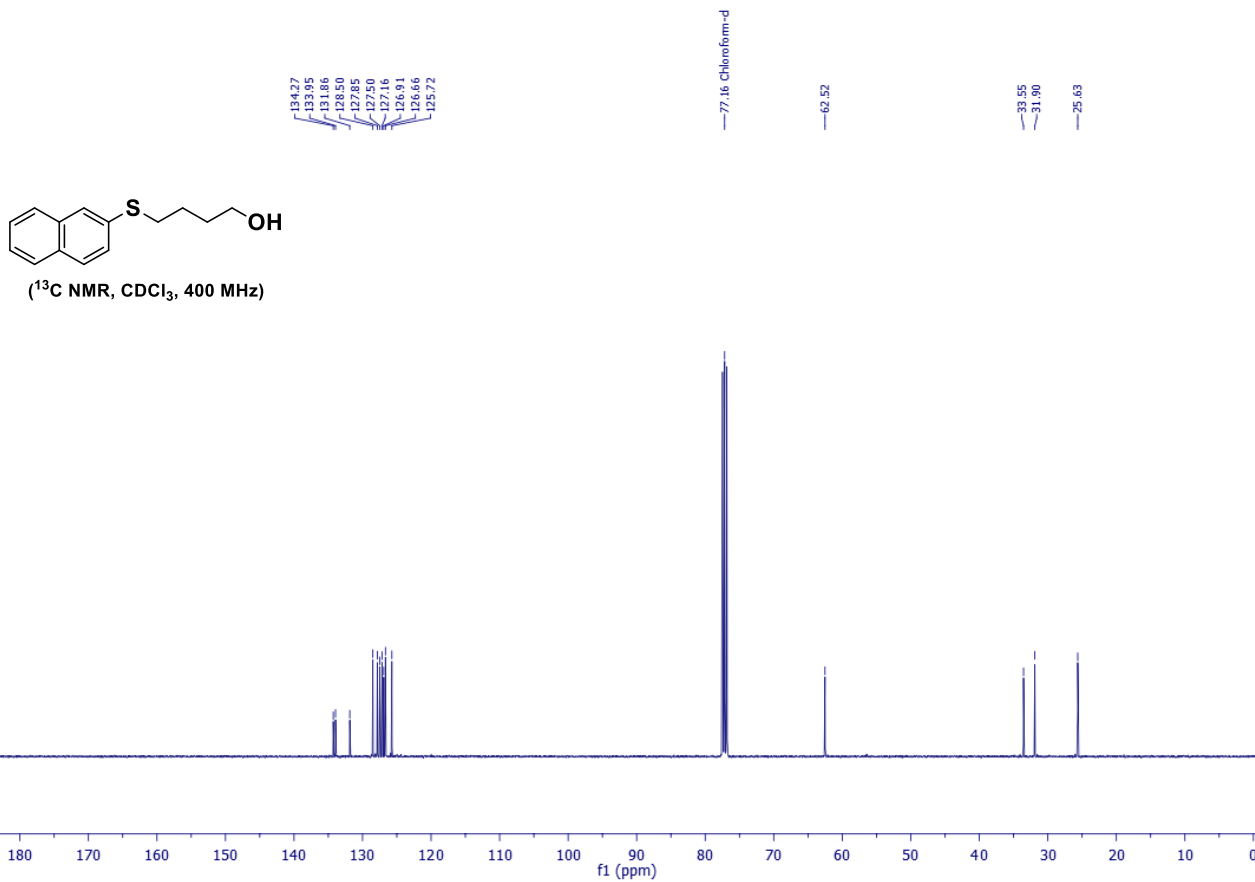
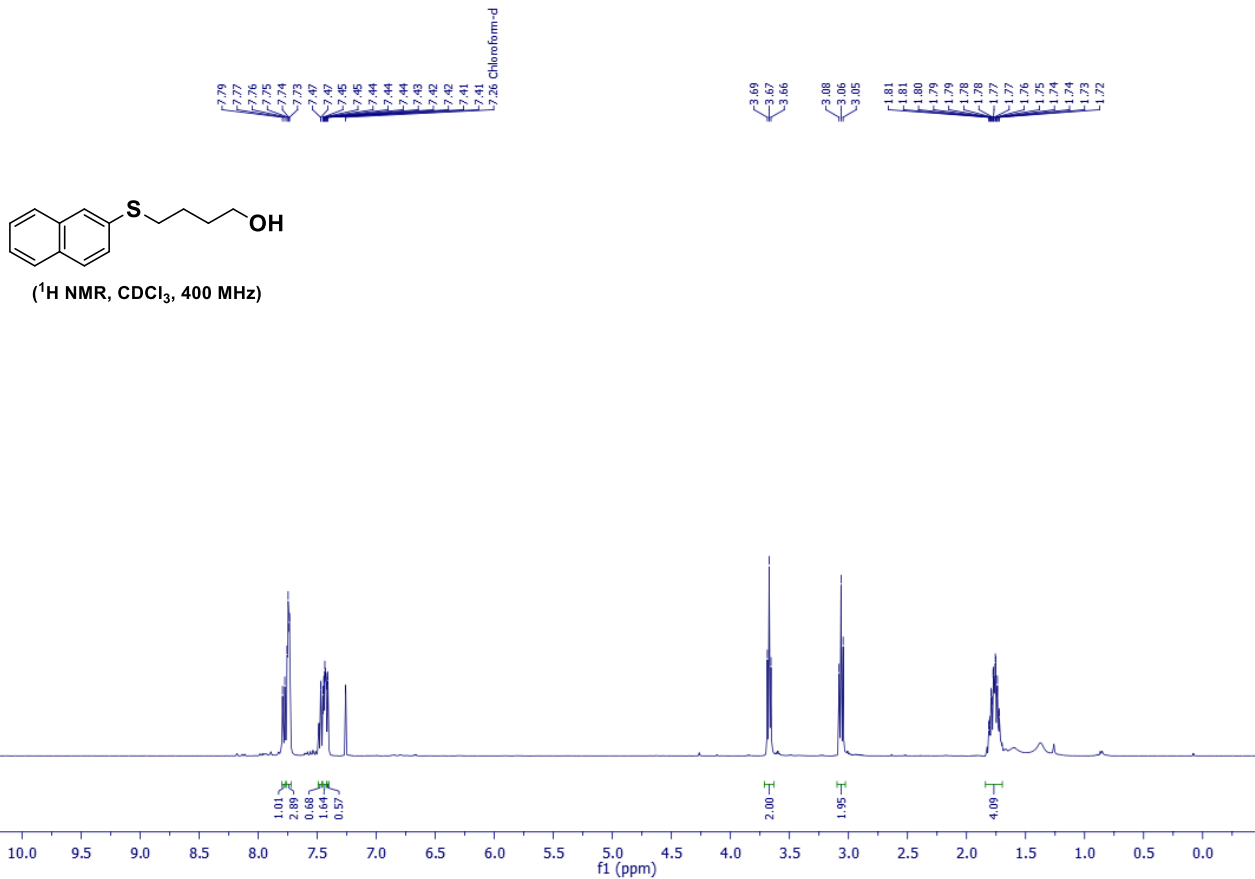


4-[(3-Fluorophenyl)sulfanyl]butan-1-ol (752)

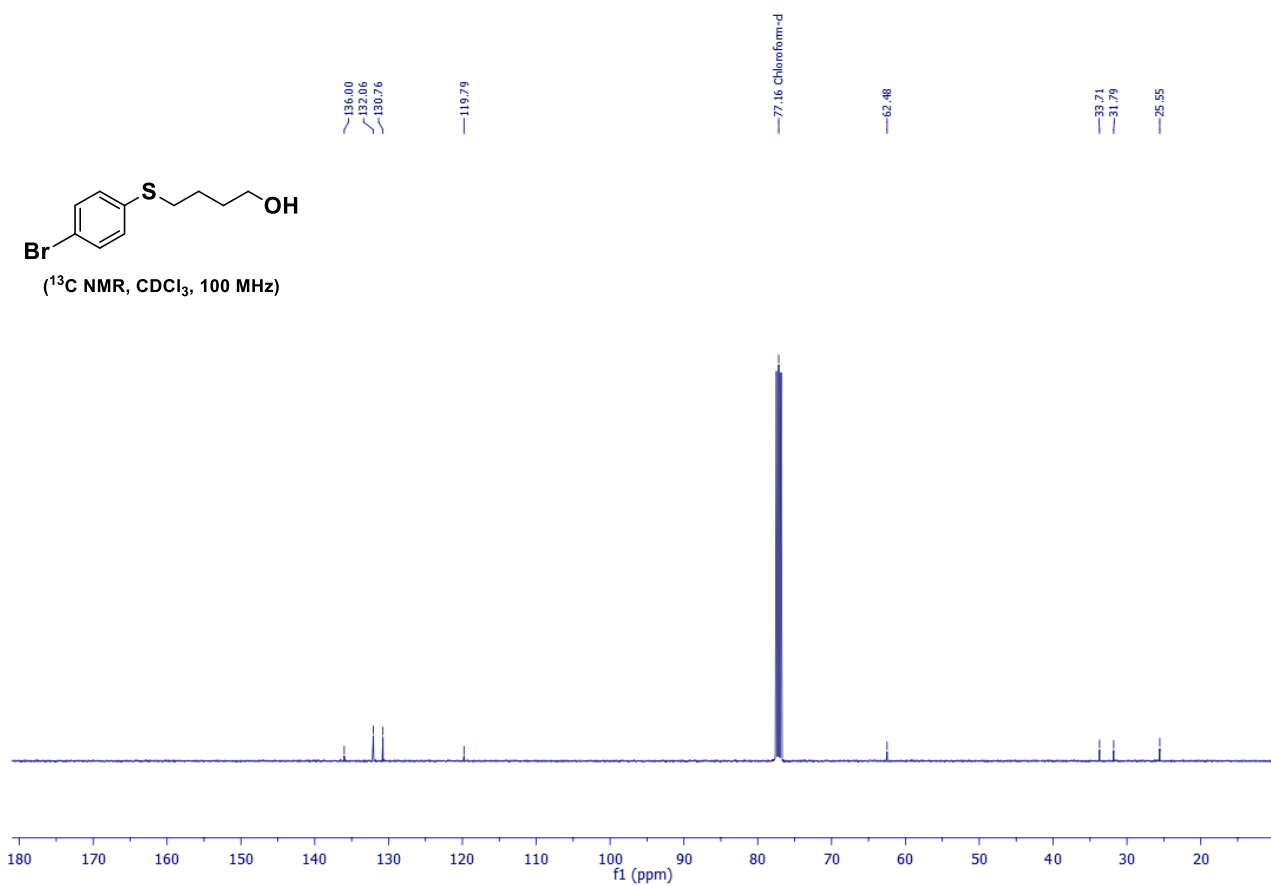
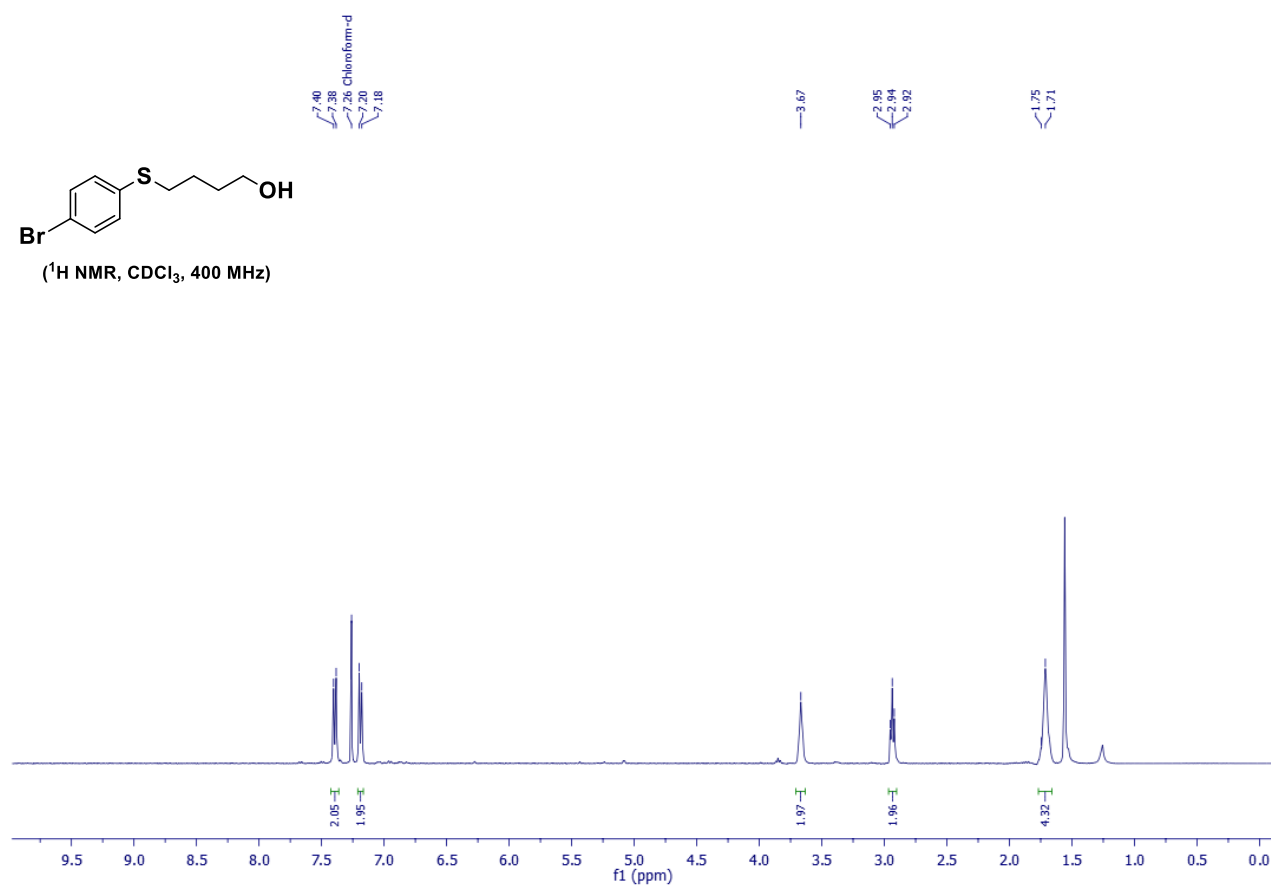




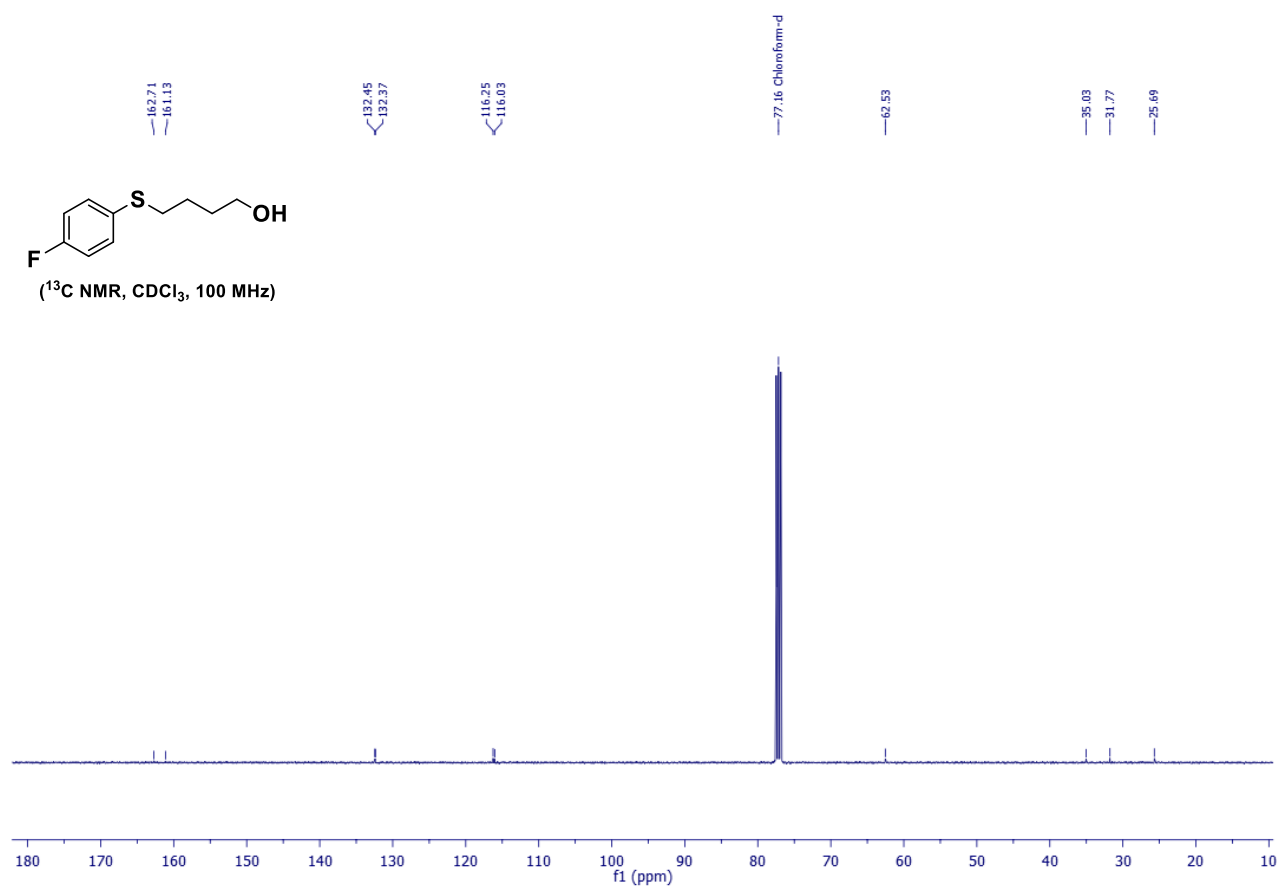
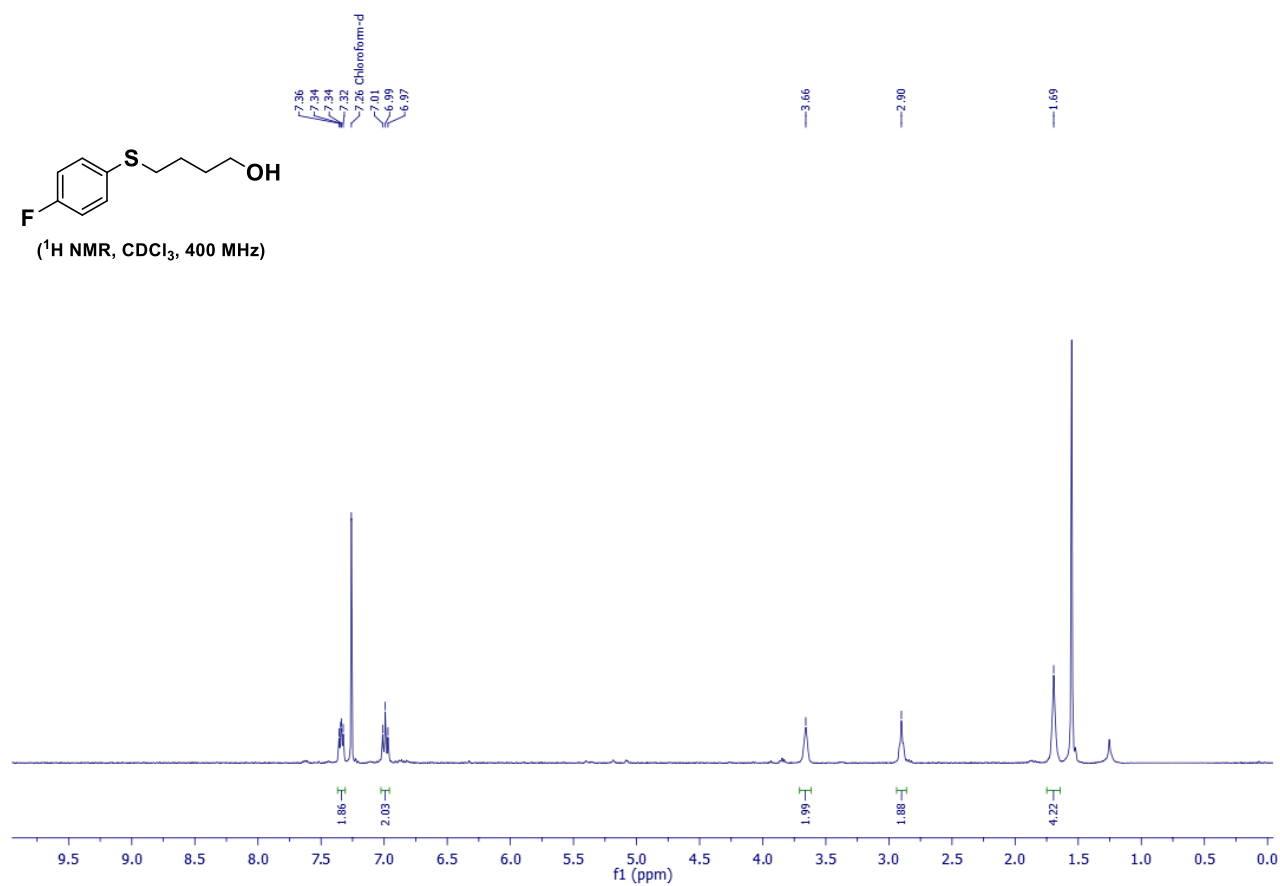
4-[(Naphthalen-2-yl)sulfanyl]butan-1-ol (753)

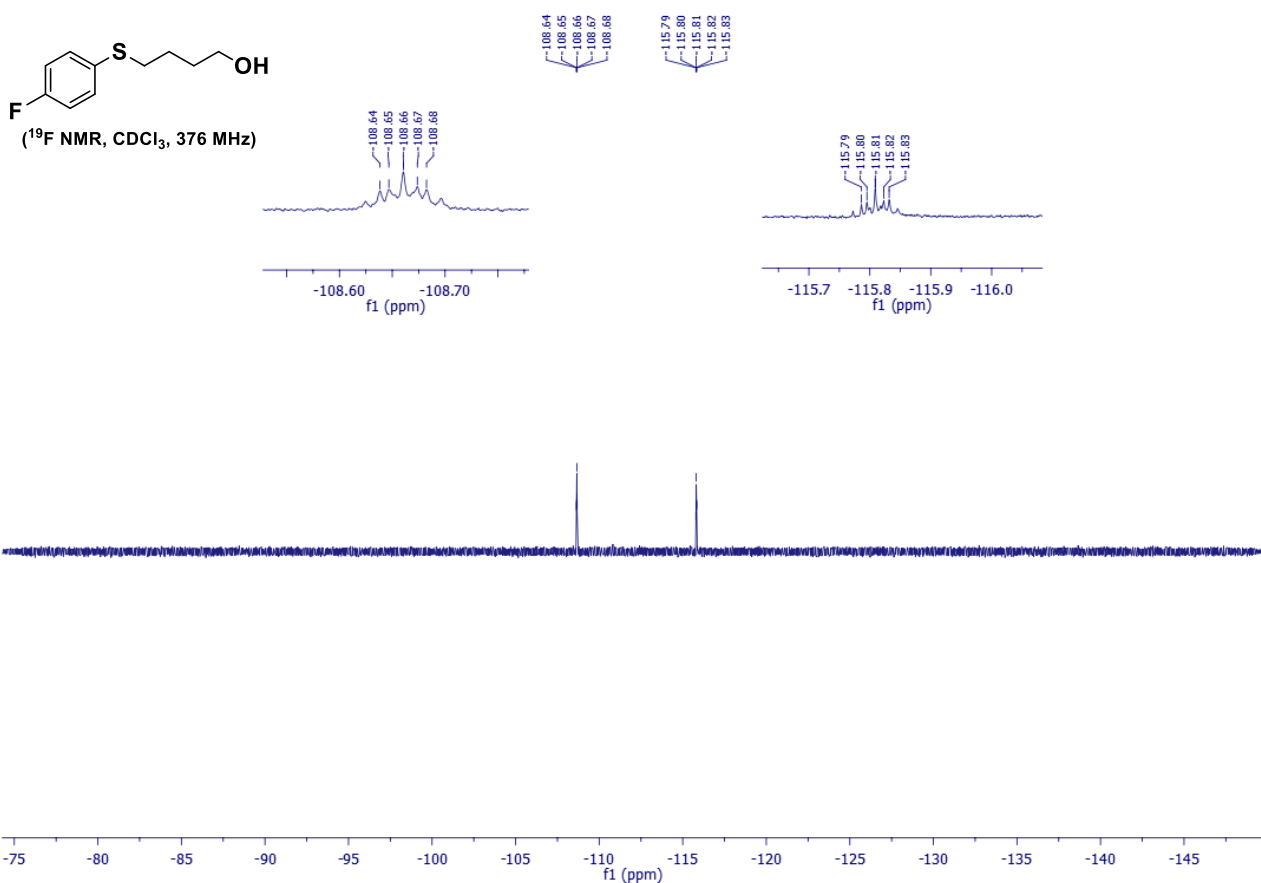


4-[(4-Bromophenyl)sulfanyl]butan-1-ol (754)

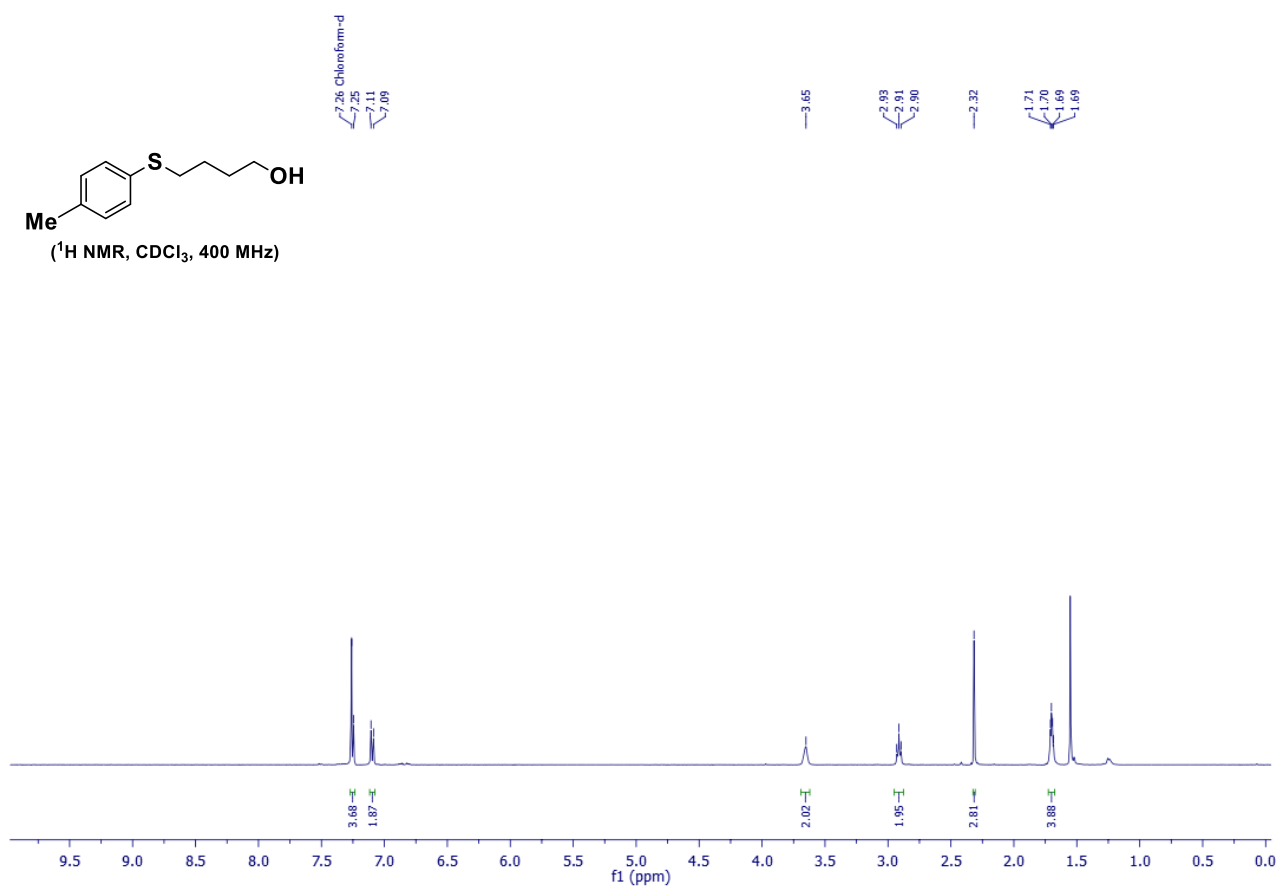


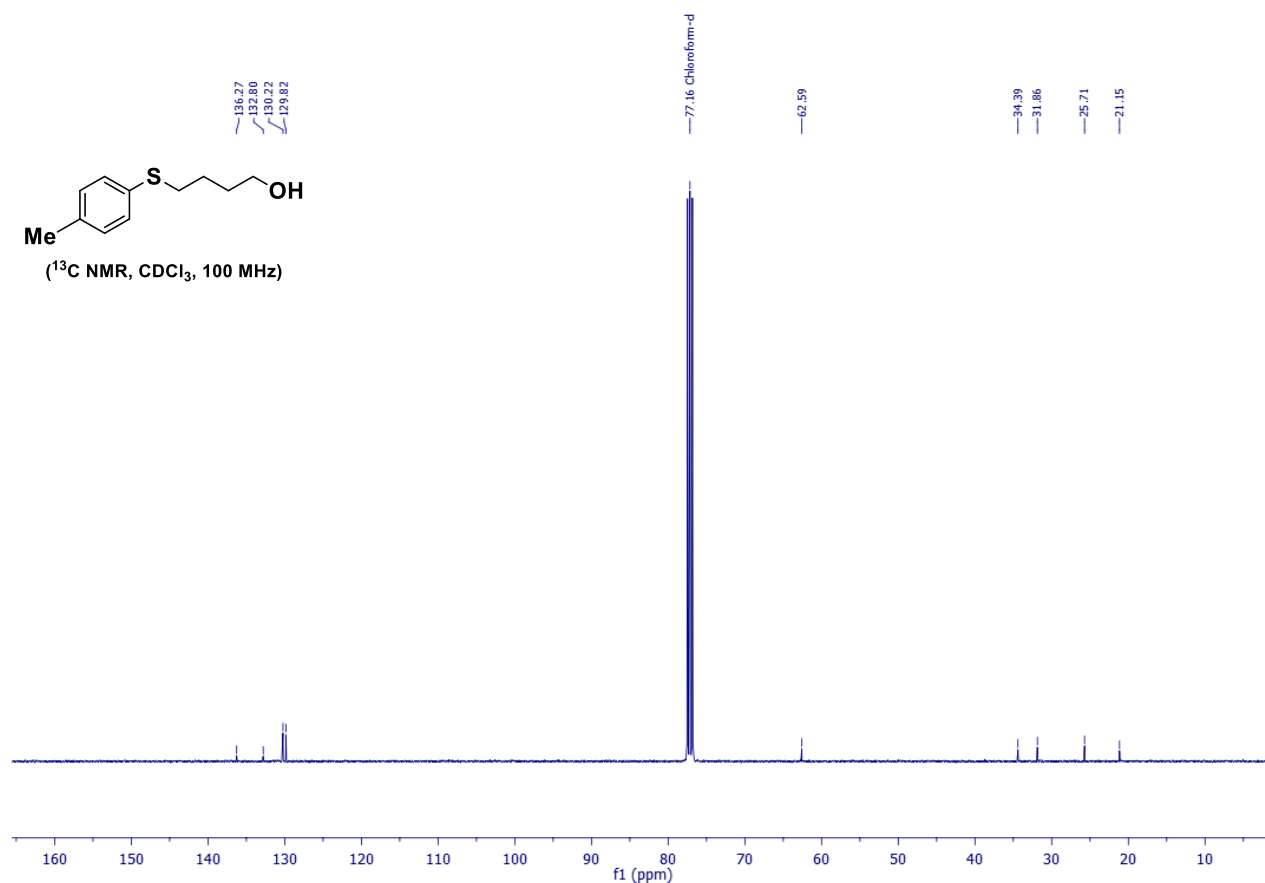
4-[(4-Fluorophenyl)sulfanyl]butan-1-ol (755)



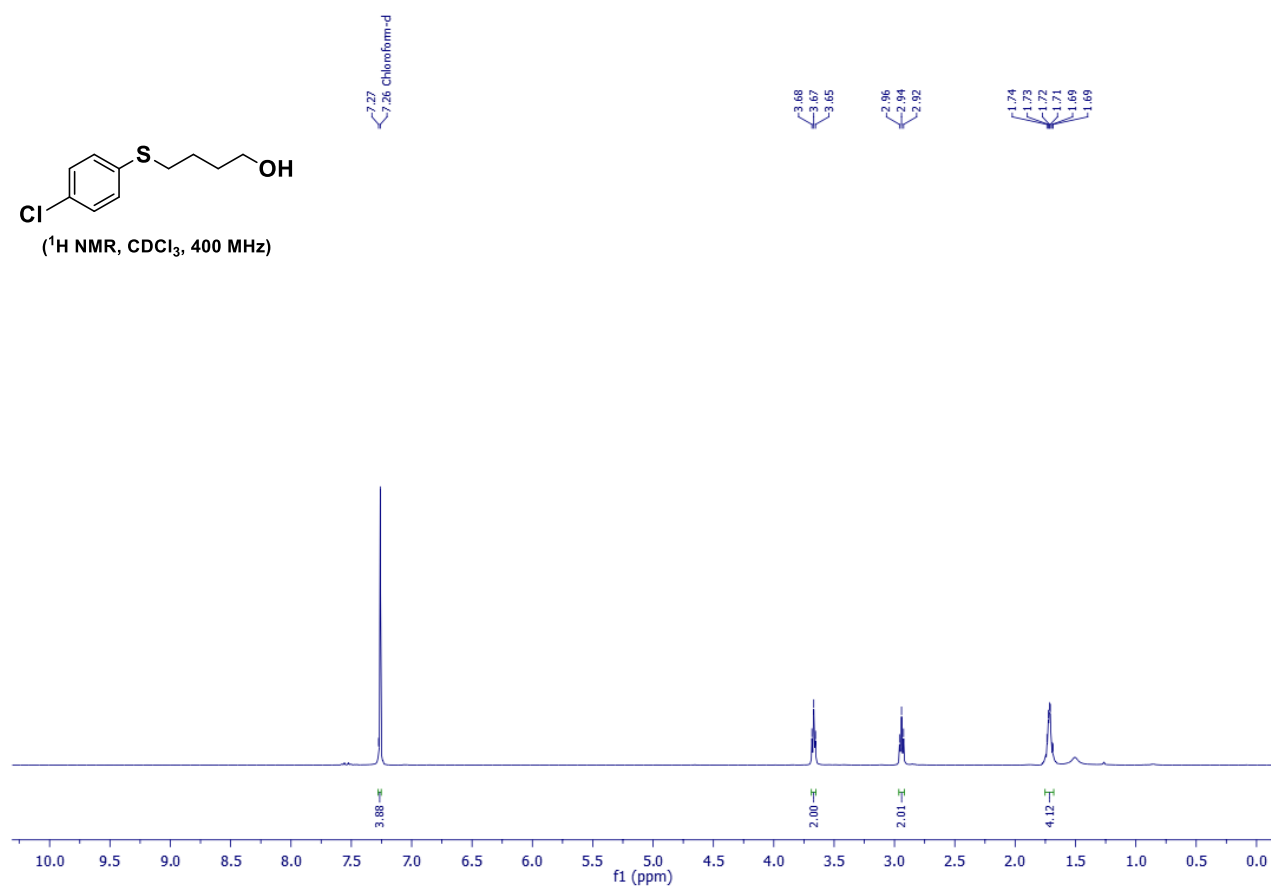


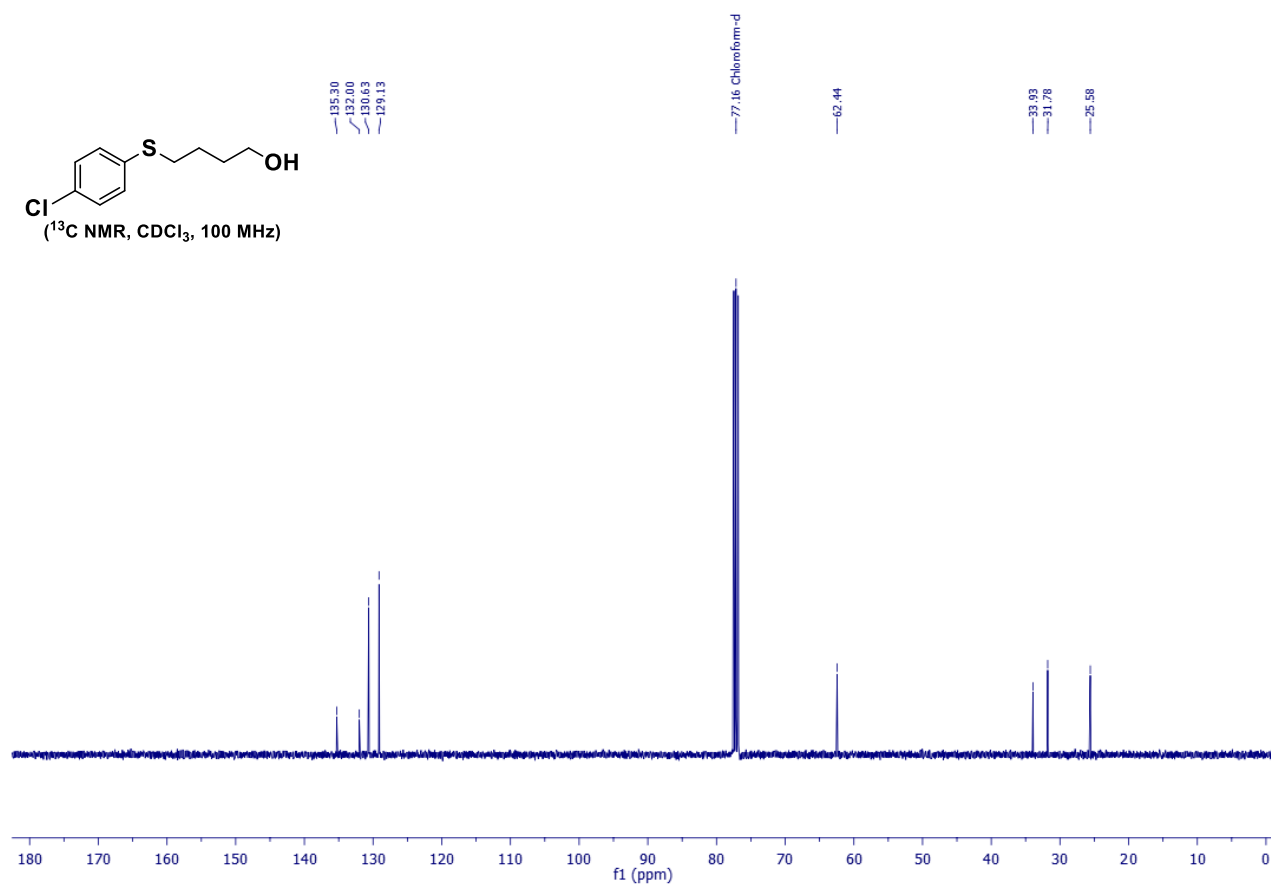
4-[(4-Methylphenyl)sulfanyl]butan-1-ol (756)





4-[(4-Chlorophenyl)sulfanyl]butan-1-ol (757)





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