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NEW PERSPECTIVES AND APPLICATIONS IN ORGANOLITHIUM CHEMISTRY: HALOCARBENOIDS AND REDUCTIVE LITHIATION

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SASSARI, ITALY, NOVEMBRE, 2014

To my beloved and deeply respected grandfather Mamuye Biru.

ይህ የጥናት ምርምር ዉጤት መታሰቢያነቱ በጣም ለማከብረዉ እና ለምወደው አያቴ ማሙዬ ብሩ ይሁንልኝ።

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New Perspectives and Applications in Organolithium Chemistry: Halocarbenoids and Reductive Lithiation

Abstract

We report on the employment of 2-methyltetrahydrofuran and cyclopentyl methyl ether as alternative green solvents for the efficient generation of radical anions of Polycyclic Aromatic Hydrocarbons and their employment in the generation of organolithium reagents. 2-MeTHF was successfully employed as a solvent in the reductive lithiation of the benzylic C–O bond of phthalan, of the aromatic C–Cl bond of 4-chlorobenzyl methyl ether, and of the C–N bond of *N*-phenylaziridine. Results obtained with *N*-phenylaziridine show that such a PAH mediated reductive lithiation of is strongly dependant on the solvent employed.

We next investigated the reactivity of Weinreb amides with cyanomethyllithiums to access β-oxonitriles. Such a transformation occurs in the presence of primary, secondary and tertiary nitrile-containing carbanions. The study of the previously undisclosed ^{15}N- and ^{17}O-NMR data was correlated with analogous substrates thus, highlighting the spectroscopic effect of the β-oxonitrile group. Subsequently, the homologation of isocyanates with lithium carbenoids to reach α-halo or α,α-dihaloamides was realized: the protocol is high-yielding and no lose of optical purity was noticed in the presence of chiral materials. Finally, we studied the homologation of isatins derivatives with lithium carbenoids to access spiro-epoxyoxindoles.

Keywords: reductive lithiation, green solvents, 2-methyltetrahydrofuran and cyclopentyl methyl ether, halocarbenoids, cyanomethyllithiums, homologation.

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List of Abbreviations

2,2-BP	2,2'-bipyridine
2-MeTHF	2-Methyltetrahydrofuran
2-PP	2-phenylpyridine
bPh	biphenyl
CA	Catalytic Amount
CPME	Cyclopentyl Methyl Ether
DBB	Di-tert Butylbiphenyl
DMAN	1-dimethylaminonaphthalene
DMB	2,3-dimethylbutadiene
DME	1,2-dimethoxyethane
E_{act}	Activation Energy
ET	Electron Transfer
HIV	Human Immunodeficiency Virus
HMBC	Heteronuclear Multiple Bond Correlation
HMPA	Hexamethylphosphoramide
HRMS	High Resolution Mass Spectrometry
HSQC	Heteronuclear Single Quantum Coherence
LDA	Lithium Diisopropylamide
LDBB	4,4'-di-*tert*-butylbiphenylide
LDMAN	lithium 1-dimethylaminonaphthalenide
LiHDMS	Lithium bis(trimethylsilyl)amide
$LNCy_2$	Lithium dicyclohexylamide
LTA	Lithium *t*-amoxide
LTMP	Lithium Tetramethylpiperidide
NBP	*N*-butylpyrrolidone
n-BuLi	*n*-Butyllithium
PAH	Polynuclar Aromatic Hydrocarbons
PAR	Preformed Radical Anion
Qun	Quinoline
SA	Stoichiometric Amount
SET	Single Electron Transfer
THF	Tetrahydrofuran
TMS	Tetramethylsilane
VOC	Volatile Organic Compound

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Chapter 1

Studies on Reductive Lithiation

1.1 Introduction

1.1.1 Organolithium Compounds and Reductive Lithiation

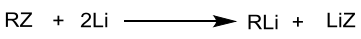
"Chemistry has a central role in science and synthesis has a central role in chemistry" Ryoji Noyori.[1] Chemical synthesis is the foundation of many aspects of society, from consumer healthcare and medicines, to transportation and communication.[2] The synthesis of organic compounds is one of the most important and creative pursuits in modern science, requiring not only technical expertise, but also imagination, intuition and individual judgment.[3] The use of metals in synthetic organic chemistry has become a general tool for the construction of complex organic chemistry and its contribution lead synthesis to an extraordinary level of sophistication.[4] With their versatile structure and bonding and reactions organolithiums are the most fascinating organometallic reagents for the construction of a wide variety of organic compounds.[5]

Following the seminal work of Schlenk and Holtz,[6] this powerful synthetic tool, shows a tremendous progress and advancement in both preparation and application.[5a,7] Even the problem associated with them (the need of very mild reaction conditions and physicochemical properties) has been changed due to the availability of various safe handling, chemical utilization protocols and improvement in laboratory facilities and techniques.[8]

Due to strongly polarized carbon-lithium bond organolithium species can be applied as nucleophiles in addition and substitution reactions, and as lithiating reagents in proton or halogen exchange reactions.[9] Their application is vital in polymerization[10] to macromolecular architectures,[11] deprotonation[12] and asymmetric synthesis in the pharmaceutical industry.[13]

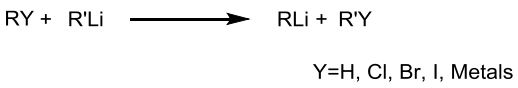
Organolithium species can be generated by two major pathways; one is the *de novo* preparation of C-Li bonds in which the lithium metal undergoes reductive insertion into an organic

compound (Scheme 1.1) with the leaving group Z = (halogens (Cl, Br, I), chalcogens (O, S, Se, Te), metalloids (Hg, Sn), carbon (in particular triarylmethyl or CN units) and hydrogen.



Scheme 1.1: *de novo* preparation of C-Li bonds.

The other method involves construction of new C-Li bonds using another organolithium reagent (Scheme 1.2). The second method can be sub classified as: deprotonation, halogen lithium exchange, transmetallation, carbolithiation of carbon-carbon unsaturated bond and Shapiro reactions.[4,14]

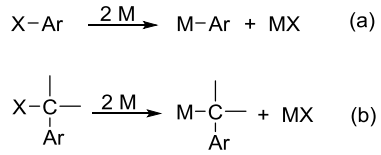


Scheme 1.2: New C-Li bonds via another organolithum reagent.

Among the two major methods, the *de novo* pathway is the most straightforward and often the most rational approach;[15] as such it is the method of choice for the industrial production of typical organolithium compounds.[8] For instance, today the organic synthesis[13] and polymer industries equally share the annual usage of *n*-butyllithium, estimated at 2000−3000 tons per year.[16] The preparation of *n*-butyllithium or other simple, unfunctionalized organolithiums required the corresponding alkyl halides (usually chlorides)[17] and a slight molar excess of lithium metal under specified temperature and conditions. This procedure is called reductive metalation.[14] Nevertheless, reductive metalation using lithium metal causes several problems which limit the exponential production of organolithium reagents.

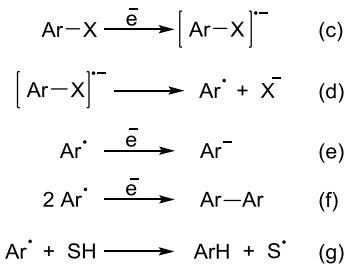
1.1.2 Limitation and Mechanistic Explanation of Reductive Lithiation

For explanation purpose, due to the availability of numerous literature[18] and in the connection to our study, we considered the metal mediated reductive cleavage of benzylic carbon - heteroatom and aromatic carbon-heteroatom bonds (Scheme 1.3 **(a)** and **(b)**).



Scheme 1.3: Metal mediated reductive cleavage of benzylic/aromatic carbon - heteroatom bond.

The presence of an aromatic ring moiety plays an important role in the electron transfer mechanism from the metal to the substrate. Within the general frame of Dissociative Electron Transfer reactions [19], the mechanism usually considered for the cleavage of a carbon leaving group bond involve a Single Electron Transfer (SET) from the metal to the scissile bond followed by (or contemporary to) a fragmentation step leading to the formation of a carbon radical; the last one is further reduced to the corresponding organometal in a successive SET step.[18,20] Consider the following two Schemes (1.4 and 1.5) in which the SET mechanism and the corresponding secondary reactions are described.

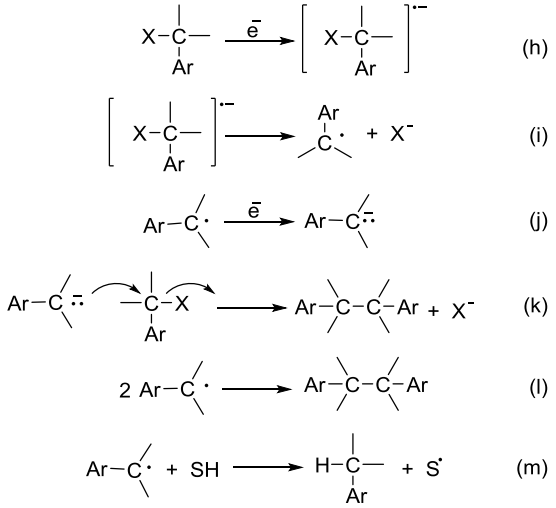


Scheme 1.4: Metal mediated reductive cleavage of aromatic carbon - heteroatom bond and associated reactions.

As illustrated in these Schemes, secondary reactions are possible in both cases. In the case of aromatic carbon - heteroatom system, the main ones are represented by eqs. (**f**) and (**g**) (Scheme 1.4). Reaction path (**f**) and (**g**) showed that the intermediate radical can undergo a coupling reaction

(**f**) and/or could abstract an hydrogen atom from some components of the reaction system (SH, e.g., the solvent), thus affording the corresponding hydrocarbon derivatives and a resulting radical (S˙).

These secondary reactions are also observed in the case of benzylic carbon- heteroatom system, reaction path (**l**) and (**m**) (Scheme-1.5). In addition, benzylic carbon- heteroatom systems can undergo further reaction between the reactive organometallic nucleophile and the unreacted electrophilic starting material, (**k**) which will end up with formation of dimeric reaction products.[18]

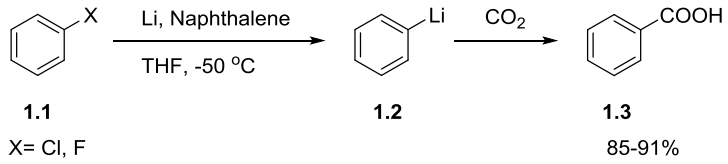


Scheme 1.5: Metal mediated reductive cleavage of carbon – heteroatom.

As such we can summarize the limitations[21] of reductive lithiation as: i) requirement of relatively low reaction temperatures, ii) the newly formed organolithium species can attack the un-reacted starting materials as explained in path (**k**) (e.g Wurtz-type products in the case of allyl and benzylic lithiation), iii) unwanted reaction with solvent as explained in path **(g)**, iv) difficulties to prepare less stable or functionalized organolithium, v) the nature of lithium metals affects the overall yield (e.g. lithium dispersion, lithium with high or low content of sodium, or activated lithium). The most exercised and promising technical strategy to overcome these problems is called Polynuclar Aromatic Hydrocarbons (PAH) mediated reductive lithiation.

1.1.3 PAH - Mediated Reductive Lithiation Overview

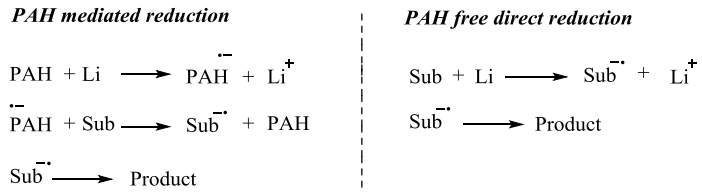
The 1867 Berthelot fusing of metallic potassium with naphthalene,[22] the 1914 Wilhelm Schlenk preparation of the dianion of sodium antheracene,[23] the 1960 Normant and Angelo report on the possibility of using radical-anions for metallation[24] and the 1963 John J. Eisch demonstration of the first attempt of cleavage reactions using 2: 1 lithium-biphenyl adduct[25] are the historical traces of PAH-mediated lithiation. Following these milestone works, in 1972 Screttas[26] (Scheme 1.6) reported the first naphthalene ($C_{10}H_8$) mediated reductive lithiation of an aryl halide (1.1) to generate the corresponding lithiated organolithium compound (**1.2**), successfully trapped by applying CO_2 as an electrophile to get the carboxylic acid derivative (**1.3**). In this case, Screttas stated that the organolithium compound (**1.2**) was formed with the highest yield when the stoichiometry of the reaction was lithium naphthalenide : aryl halide = 2/1.[26a]



Scheme 1.6: $C_{10}H_8$ mediated reductive lithiation of aryl halide.

It was suggested that the reductive cleavage occurred since lithium metal reacted with the PAH ($C_{10}H_8$) to generate the corresponding radical anion (or the dianion); the last one acts as a homogeneous shuttle to transfer electrons from the metal to the substrate. The radical anion of the substrate then undergoes cleavage of the carbon-leaving group, thus leading to the formation of an organolithium intermediate, eventually trapped with an electrophile.

As a result of this initial work several investigations have been done and reported. A recent paper suggested an answer to the question why arene mediated electron transfer from metal (Li) is faster than the unmediated direct reduction (Scheme 1.7).



Scheme 1.7: Schematic representation of PAH mediated vs unmediated electron transfer reaction[27]

A quantitative electron transfer kinetic study revealed that the use of mediators in lithium reductions offers a very large rate increase over the un-mediated route. In particular it was found that reductions of a mediator (PAH) such as 4,4'-di-*tert*-butylbiphenyl (DBB) occurred with a small reorganization energy (i.e., the energy required to conform bonding and solvent conditions of reactants to bonding and solvent conditions of products) leading to two steps with a relatively low activation energy (E_{act}) of a little over one-half of the direct, slow, un-mediated electron transfer from lithium, as summarized in Figure 1.1, where both the substantial reorganization energies for the Li/Li+ and Sub/Sub$^{\bullet-}$ couples are combined to give one large activation energy.[27]

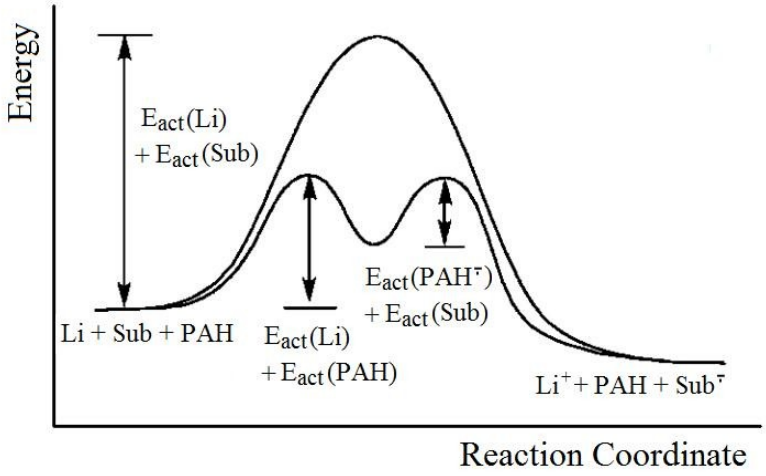


Figure 1.1: Schematic energy diagram for direct and mediated lithium reductions, adapted from ref.[27]

Having this and based on several additional findings,[17,20] the efficiency of PAH-promoted reaction depends on i) the type of methods used two generate radical-anion/dianion, ii) the nature of

electron shuttles or mediators, and iii) the type of solvent used to generate and solubilize the radical anions, iv) miscellaneous factors (e.g., reaction temperature and the form of the metal).

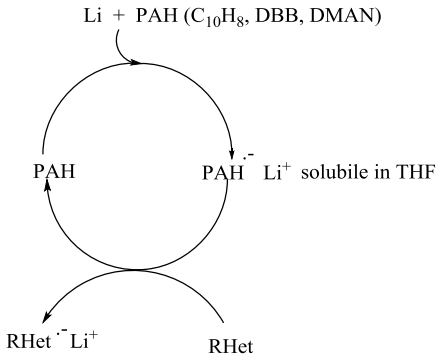
1.1.4 Methods Used to Generate Radical-Anion (or Dianions)

There are two major techniques of performing radical-anion induced reductive lithiations that can be used for activation of lithium metal and production of organolithium species. These methods are classified as:

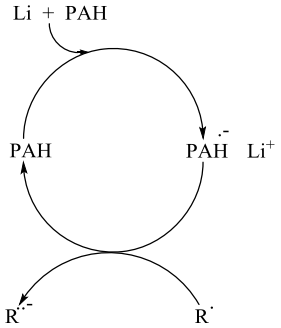
i) Stoichiometric amount PAH-promoted lithiation (SA):[28] In the SA method, also described as PAR (preformed radical anion) by Cohen,[29] both lithium and PAH are used in stochiometric amounts with respect to the substrate. Within this methodology, the PAH is first reacted with the metal to afford the corresponding radical anion; this step is followed by addition of a titred solution of $PAH^{\cdot -}$ to the substrate (or *vice versa*), thus affording the radical anion of the substrate. Thereafter, the last one undergoes the cleavage step followed by further reduction to an organolithiium derivative. THF has been reported as the solvent of choice for this reaction. Removal of the stoichiometric amount of the mediator[30] is the most encountered drawback of SA method.[4,31] To overcome this problem the CA method developed as an outstanding and dominant alternative.

ii) *Catalytic amount PAH-promoted lithiation (CA)*:[32] This process requires catalytic amount of PAH[20] and an excess of lithium metal. Also in this protocol, THF is the solvent most commonly employed. In this case, the radical anion of the PAH acts as an electron shuttle, from the metal to the substrate, being continuously regenerated in the reaction mixture. In some instances, formation of PAH dianions,[33] with a stronger reducing power with the respect to the corresponding radical anion, has been invoked to account for better yields and shorter reaction times observed in comparison with the SA method.[33]

As such in CA method, PAH reacts quickly with lithium metal or other alkali metal to form the corresponding radical anion or dianion in THF. The resulting strongly colored radical-anion (or dianion), which is soluble in THF (Scheme 1.8), is able to function as an effective homogeneous electron transfer agent.



Scheme 1.8: Scheme 1.8: Reduction of carbon-heteroatom bond in the presence of a polycyclic aromatic hydrocarbon; $C_{10}H_8$ = naphthalene; DBB = 4,4'-di-*tert*-butylbiphenyl; DMAN = 1-dimethylaminonaphthalene



Scheme 1.9: Reduction of carbon radical in the presence of a polycyclic aromatic hydrocarbon.

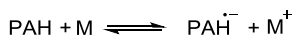
Radical anions of PAH are effective agent to overcome the associated secondary reactions observed in reductive metalation (Scheme 1.4 and 1.5). Indeed, such a homogeneous electron transfer reagent will facilitate both the reduction of the substrate to the corresponding radical anion (Scheme 1.8), as well as the subsequent reduction of the intermediate radical to the corresponding organolithium derivative (Scheme 1.9).[32b,32c,34] The mechanistic aspect and methodology development of these two methods have been investigated with different authors specially with pioneers M. Screttas, M. Yus[33], U. Azzena[32a] and T. Cohen.[35] The chemical reactivity, the physical

behavior, the x-ray[36] and the spectroscopic data of radical anions and dianions have been investigated.

Reactivity based mechanistic investigations on dianions[37] and radical anions[38] show that, their reactivity is dependent on the starting material and the solvent.[39] As an example, voltammetric[40] studies in THF demonstrated that the electro-generated radical anion of anthracene effectively mediated the reduction of organic substrates at -78 ^{o}C, whereas the more reactive dianion was quickly protonated thus resulting useless as an ET reagent. According to this finding it can be rationalized that the use of the dianion of anthracene to bring about a mediated two-electron process appears to be synthetically of no use since it is a too basic species, so that attempts of mediation at the dianion level led to the abstraction of protons from the solvent in preference to the reduction.

1.1.5 The Nature of Mediators

Polynuclar aromatic hydrocarbons (PAH) have mediator role in alkali metal based reduction as homogeneous electron-transfer reagents via the generation of either their radical anions or dianions. The PAH provide its conjugate system as an electron shuttle and the electron donated by the metal is believed to occupy the lowest unoccupied π^* orbital of the mediator.[22] Measurements of equilibrium constants for the reaction between alkali metals (Li, Na, K or Cs) and aromatic hydrocarbons ($C_{10}H_8$ or biphenyl) showed that such a constant is highly dependent on the nature of the metal, and the higher values, within a given solvent and at a given temperature, were obtained with the smallest cation because of the higher heat of salvation, i.e., $Li^+ > Na^+ > K^+ > Cs^+$ (Scheme 1.10).[22]



Scheme 1.10: Representation of an equilibrium reaction between a metal (M) and a PAH

Following Screttas's $C_{10}H_8$ (**1.4**) work, in 1980 Freeman and Hutchinson proposed 4,4'-di-*tert*-butylbiphenyl (**1.10**, DBB) as an alternative and versatile mediator.[34] Almost at the same time T. Cohen reported 1-dimethylaminonaphthalene (**1.7**, DMAN)[35] as an efficient electron shuttle. Additionally, different polymer supported versions of them were proposed as a storehouse of electrons,[42] but the most exercised and applicable mediators in reductive lithiation are summarized in figure 1.2. Accordingly, the radical anion of $C_{10}H_8$, DMAN and DBB are named as lithium naphthalenide (**1.5**), lithium 1-dimethylaminonaphthalenide (**1.8**, LDMAN) and lithium 4,4'-di-*tert*-butylbiphenylide (**1.11**, LDBB). While experimental evidences on the formation of the dianion of $C_{10}H_8$ (**1.6**)[33] are available, it is worth noting that, to the best of my knowledge, there are no experimental evidences on the actual formation and employment of dianions **1.9** and **1.12**.

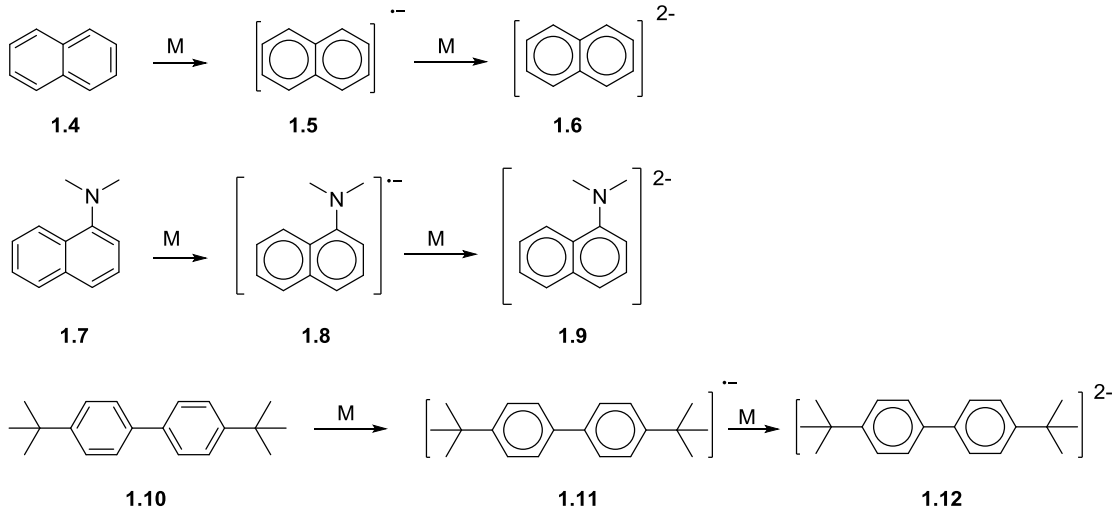


Figure 1.2: Chemical structure of common mediators, radical anion and dianion.

To measure the efficiency of mediators in single electron transfer process, different approaches were recently proposed by Donohoe and coworkers.[40,43] Their study demonstrated that the efficiency of mediators or searching of new mediators can be achieved by computational methods, e.g., evaluating a characteristic related to the overlapping between the of the conjugate π system such as the dihedral angle between the aromatic rings in the case of alkyl-substituted

biphenyl derivatives; or by electrochemical studies (voltammetric analysis), as exemplified by a comparison of DBB and $C_{10}H_8$, showing that DBB is more efficient due to its lower (more negative) reduction potential.[34,44]

1.1.6 The Effect of Solvent on PAH Mediated Reductive Lithiation

The early work of Shatenshtein [45] and coworkers described the effect of solvents on the generation of radical anions and the kinetic effect on the reduction process. Higher solubilities and faster kinetics can often be achieved by performing reductive lithiation reactions in relatively polar ethereal solvents. The cyclic ether THF has long been routinely used in the formation and reactions of different organolithium derivatives. According to Wittig[46] and Gilman[47] detailed investigation of organometallic-induced ether cleavage, THF can undergo reverse [3+2] cycloaddition and ring opening according to mechanisms which will be later described in some details (see Schemes 1.13 and 1.14).

Moreover, it was recently demonstrated the ability of LiDBB to promote the reductive cleavage of the carbon – oxygen bond of THF either under ultrasonic irradiation[48] as well as under "silent"[49] reaction conditions, thus leading to the formation 4-lithiobutoxide, a strongly basic reagent. According to these findings, different groups investigated the possibility to substitute THF with less problematic solvents. After several attempts to generate lithium radical anions of several PAH's in solvents like Et_2O or 1,2-dimethoxyethane (DME), T. Cohen et al. successfully employed dimethyl ether (Me_2O) in the generation of LiDMAN[50] ; it is however worth noting that this solvent has a particularly low boiling point and no further application has been reported.

Additionally, several practical and environmental drawbacks of THF should be taken into considerations. Indeed, THF is considered as a Volatile Organic Compound (VOC), has a strong tendency to form peroxides, and is completely soluble in H_2O, thus leading to laborious work-up

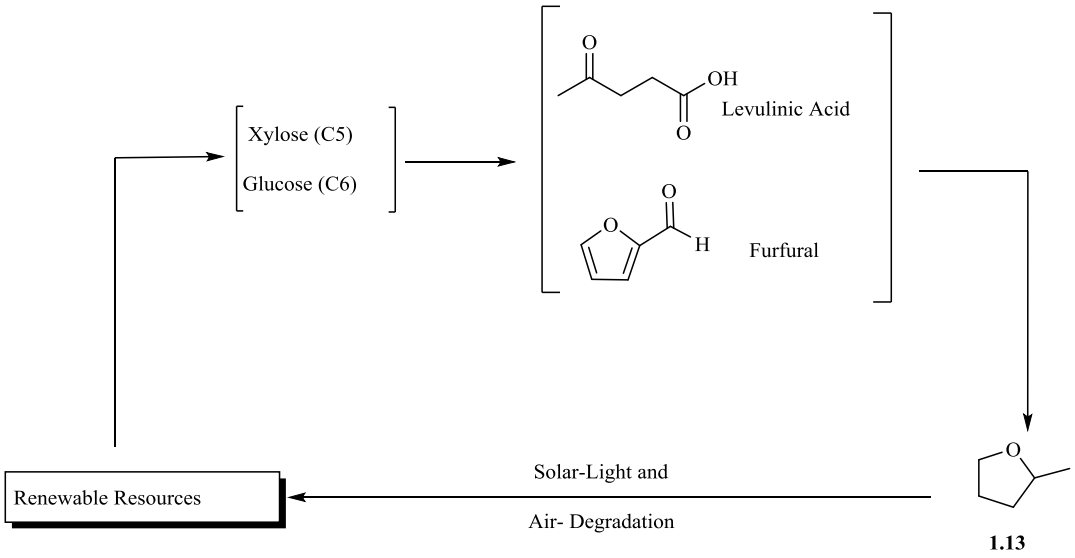
procedures and rendering its purification and recovery particularly difficult.[51] As such the need of convenient and green solvents for reductive lithiation remains as a major homework.

Replacing hazardous chemicals with environmentally more friendly alternatives is currently a matter of intense research, aligned with the "Green Chemistry" philosophy.[52] Green chemistry for chemical synthesis addresses our future challenges in working with chemical processes and products by inventing novel reactions that can maximize the desired products and minimize by-products, designing new synthetic Schemes, simplifying operations in chemical productions,[53] and seeking solvents and reagents that are inherently environmentally and ecologically benign.[54]

The adjective "sustainable" or "green" is used to describe different types of solvents including the ones that are produced from biomass feedstock and eco-friendly petrochemical based solvents that are non-toxic and/or biodegradable. The seven classes of solvents generally claimed as green solvents according to various criteria includes: water, supercritical fluids, bio-sourced solvents, ionic liquids, fluorinated solvents, liquid polymers, eco-friendly solvents.[55] Based on pioneer reports of alternative solvents for organometallic chemistry,[56] according to environmental assessment methods (environmental, health, safety, i.e., EHS, and life-cycle assessment)[55b] and GSK's solvent selection guide,[57] we select 2-MeTHF and CPME as preliminary candidates as alternative solvent for reductive lithiation.

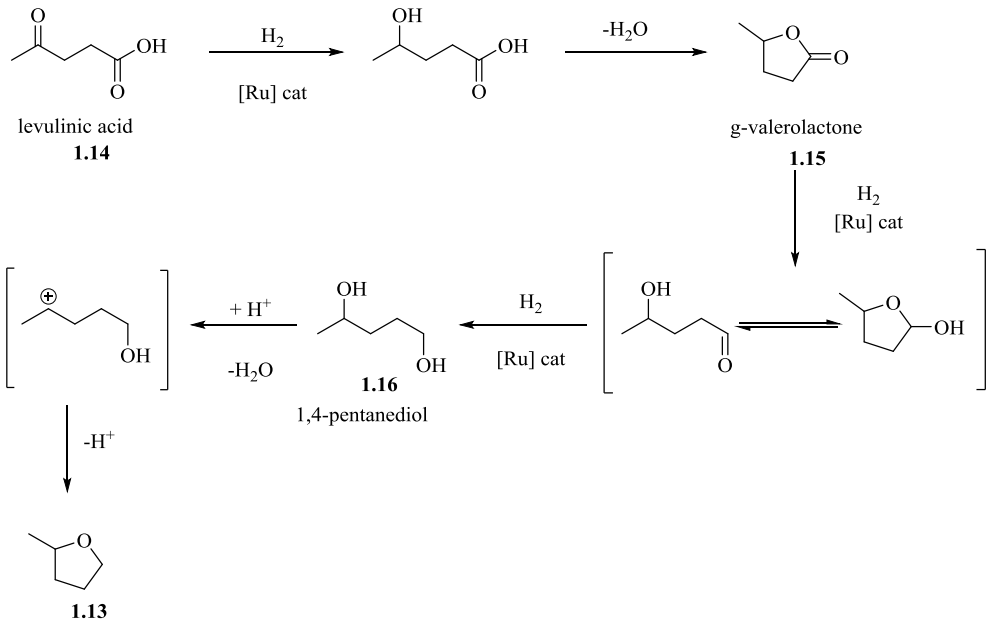
1.1.6.1 2-Methyltetrahydrofuran (2-MeTHF)

For the quest of eco-friendly solvents,[58] biomass-derived chemicals – satisfying the 7th principle of Green Chemistry (Fig. 1.3),[52] are very promising and emerging alternatives.[59] In this respect, 2-MeTHF can be produced from renewable resources using substrates like furfural or levulinic acid.[60] Moreover, when accidentally spoiled into the environment, 2-MeTHF (**1.13)** is abiotically degraded by solar light and air, thus providing an interesting environmental footprint (bio-based and ease of degradation) (Scheme 1.11).



Scheme 1.11: Conceptual cycle for the production / degradation of 2-MeTHF, adapted from ref.[54]

Novel synthetic strategies to produce 2-MeTHF focuses on more selective catalysts or on process development concepts, again using raw materials like furfural,[61] and levulinic acid.[62] For instance, the design of flexible multifunctional catalytic systems based on a series of reductions-dehydrations steps, allows the biomass transformation into a set of useful intermediates, including 2-MeTHF (**1.13**), starting from levulinic acid (**1.14**). Other interesting chemicals, *e.g.* γ-valerolactone (**1.15**) or 1,4-pentanediol (**1.16**) were produced as well (Scheme 1.12).[62]



Scheme 1.12: Novel catalytic routes to 2-MeTHF starting from levulinic acid.[62]

Based on that, 2-MeTHF is generally considered a worth option, with an increasing use in industrial pilot plants.[63] Apart from its rapid (bio)degradation in the environment (10th and 12th Principles of Green Chemistry),[52] preliminary data on 2-MeTHF toxicology allows its employment in the development of pharmaceutical process as well.[64] A confirmation of this with more in-depth studies would align 2-MeTHF with the 4th and 5th Principles of Green Chemistry (Fig.1.3).[52]

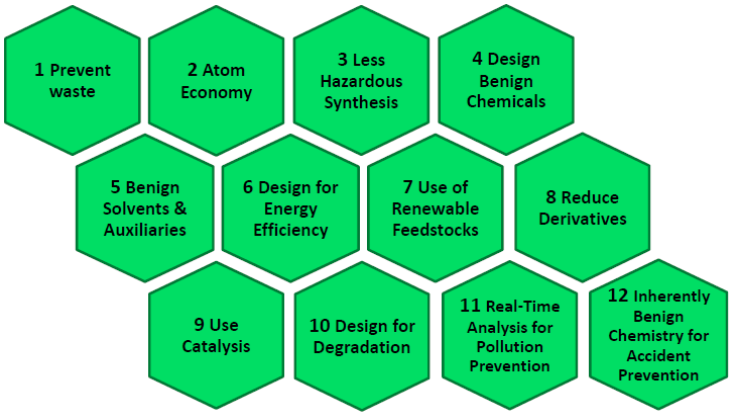
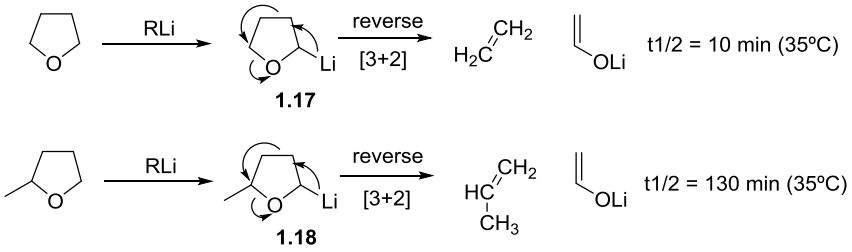


Figure 1.3: The 12 principles of green chemistry.

Stability of 2-MeTHF under acidic conditions: Water-miscible cyclic ether-based solvents (*e.g.* THF) are relatively unstable in aqueous acidic conditions, being degraded by ring-opening. Herein, replacing THF with 2-MeTHF is an asset due to the low miscibility of 2-MeTHF with water,[56a] what creates a biphasic system and preserves 2-MeTHF from the acidic hydrolytic action. As a result, THF degrades 9-fold faster than 2-MeTHF in the presence of 2N HCl at 60 ºC.[56a] However, 2-MeTHF can undergo ring-opening reactions under Lewis acid mediated reaction conditions.[65]

Stability of 2-MeTHF under basic conditions and its use in organometallic chemistry: Ethereal solvents, or ether-containing solvent mixtures, constitute the indispensable media for virtually all organometallic reactions.[66] A reason for this is the Lewis basic behaviour, which modulates the reactivity of organometallic species by disaggregating them. Solvents behaving like Lewis bases

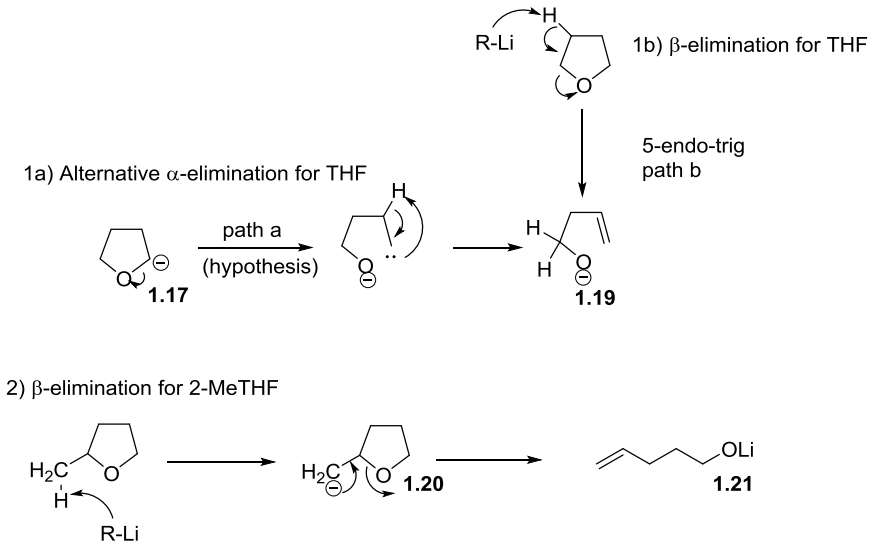
will increase the reactivity of organolithiums by becoming an integral part of the organolithium aggregate. THF has been the most widely employed solvent for such reactions, due to the extraordinary ligand properties for lithium.[67] However, ether-based solvents also tend to react with organometallics, thus precluding their use at relatively high temperatures and in some cases limiting them to 0 ºC or below.[68,15] For THF the main pathway involves the deprotonation at C-2 to afford the lithiated intermediate **1.17**, undergoing a reverse [3+2] cycloaddition with formation of ethylene and the enolate of acetaldehyde, the so-called "α-cleavage". The half-life for this reaction of THF in the presence of *n*-BuLi is only 10 min at 35 ºC. Conversely, the methyl group in 2-MeTHF decreases its polarity, and thus the aforementioned α-cleavage is considerably reduced, with a half-life of 130 min at 35 ºC (Scheme 1.13).[68a]



Scheme 1.13: Comparison of the classical α-cleavage for THF and 2-MeTHF.[68a]

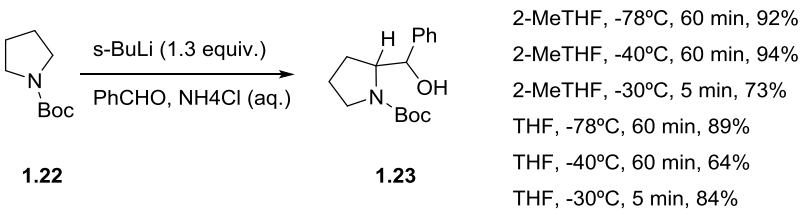
Moreover, in the presence of organolithiums, THF may decompose into lithium-but 3-en-1-oxide (**1.19**) either *via* an alternative α-elimination of (**1.17**) (Scheme 1.14, path 1.a) or *via* the (disfavored) *5-endo-trig* reverse cyclization initiated by deprotonation at C-3 (Scheme 1.14, path 1.b).[69] Conversely, the main decomposition pathway associated to 2-MeTHF is the β-cleavage, which involves the abstraction of a β-proton from the external methyl group to produce (**1.21**) *via* the unstable carbanion (**1.20**) (Scheme 1.14, path 2). Notably, this reaction presents a $t_{1/2}$ = 70 min at 35 ºC, not affecting the outcome of organometallic reactions, often proceeding at higher rates[68a].

In addition, a recent study shows that ring-opening of 2-methyltetrahydrofuran can occur via hydrodeoxygenation over a Ni_2P/SiO_2 catalyst at 0.5 MPa.[70]



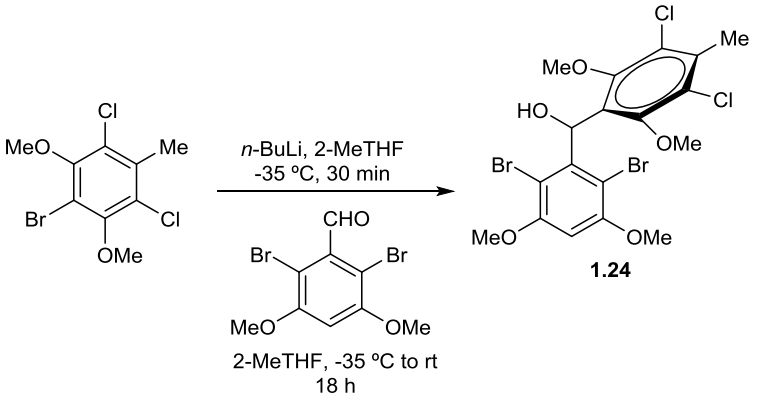
Scheme 1.14: 1a, b: Alternative α-elimination and β-elimination observed for THF[69]; 1b: β-elimination observed for 2-MeTHF.[68a,68b]

Selected examples illustrates the efficiency of 2-MeTHF as a solvent in organometallic chemistry. Remarkably, the employment of 2-MeTHF in the presence of organolithium reagents (Scheme 1.15) resulted in an effective protocol for the diamine-free lithiation – trapping of *N*-Boc pyrrolidine affording the desired product in better yield than in THF.[71]



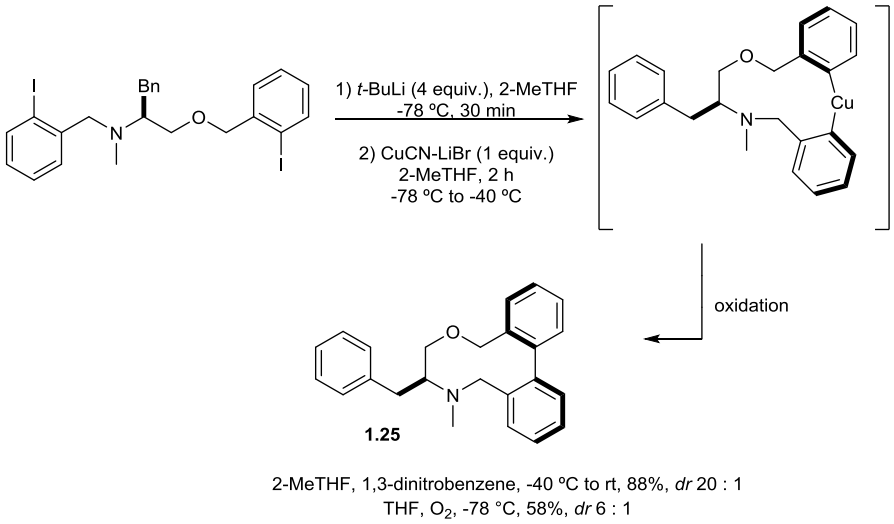
Scheme 1.15: Solvent effect in diamine free lithiation and trapping of *N*-Boc heterocycles.

Under similar conditions, the preparation of alcohol (**1.24**), a key-intermediate in the total synthesis of the marine antibiotic Pestalone, was accomplished by bromine-lithium exchange.



Scheme1.16. Preparation of the key-intermediate for the total synthesis of Pestalone by Li/Br exchange.[72]

As an additional example, a very good diastereoselectivity was achieved during the preparation of a complex biaryl structures, such as (**1.25**), via sequential lithium/iodine exchange reaction, transmetallation, oxidation (Scheme 1.17).[73]



Scheme 1.17: Synthesis of biaryl systems *via* sequential transmetallation-oxidation.[74]

In addition to its employment in organolithium chemistry, 2-MeTHF was recently employed as a particularly effective solvent for a number of different reactions. Indeed, it is worth mentioning that a recent investigation of solvent effect on a series of Grignard-type reactions indicated 2-MeTHF has consistently either out-performed or performed in an equivalent manner to typical reaction solvents such as Et_2O and THF.[75] Further examples include the scale-up of Grignard

reactions of industrial interest,[76] the chemoselective protection of anilines,[77] the formation of C-C and C-heteroatom bond,[78] its employment as a solvent in organocatalysis,[79] in biomass processing,[80] in biocatalysis processes,[81] in boronic acid formation,[82] iron-catalyzed alkylation of carboxamides[83] for photoluminescence measurement,[84] ruthenium-catalyzed olefin metathesis [85] and nickel-catalyzed amination[86]. Although the formation of peroxides (comparable with THF) remains as a significant drawback, all these characteristics highlight 2-MeTHF as a promising solvent for PAH-mediated reductive lithiation.

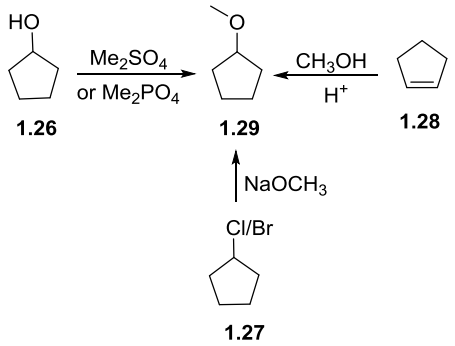
1.1.6.2 Cyclopentyl Methyl Ether (CPME)

To overcome the drawbacks associated with other ethereal solvents, CPME emerged in 2005 as an alternative solvent from Zeon Corporation.[87] CPME is a non-symmetric aliphatic ether having a cyclopentyl group. It has several unique features (Table 1.1) attributed to its structure, including relatively high boiling point, low formation of peroxides,[88] relatively high stability under acidic and basic conditions, low solubility in water coupled with a narrow range of explosion limits that render CPME an interesting alternative to other ethereal solvents.[89]

Table 1.1: Physical properties of CPME, 2-MeTHF and other ethers[90]

	Unique features	CPME	2-MeTHF	THF	MTBE
(1)	Solubility of solvent in water (23 ºC) [g/100g]	1.1	14	Infinite	4.8
	Solubility of water in solvent (23 ºC) [g/100g]	0.3	4.4	Infinite	1.5
(2)	Peroxide formation	Slower	Faster	Faster	Slower
(3)	Stability to acids	More stable	Less stable	Unstable	Unstable
(4)	Boling point [ºC]	106	80	66	55
	Melting point [ºC]	<-140	-136	-108.5	-108.7
(5)	Latent heat of vaporization (bp) [Kcal/kg]	69.2	89.7	98.0	81.7
(6)	Azeotropic temperature with water [ºC]	836.3	71	64	52.9
	Azeotropic composition (solvent/water) [wt%]	83.7/16.3	89.4/10.6	93.3/6.7	96.5/3.5
(7)	Dielectric constant (25 ºC)	4.76	7.0	7.4	2.6
	Dipole moment [D]	1.27	-	1.7	1.4

Zeon manufactured CPME (Scheme 1.18) via acid catalyzed addition of MeOH to cyclopentene[90-91] (**1.28**) with a 100% atom economy. Additionally, some more synthetic pathways have been reported to prepare CPME (**1.29**). These includes: methylation of cyclopentanol (**1.26**) via nucleophilic substitution reaction[92] or from halo-cyclopentane (**1.27**) with sodium methoxide.[93]

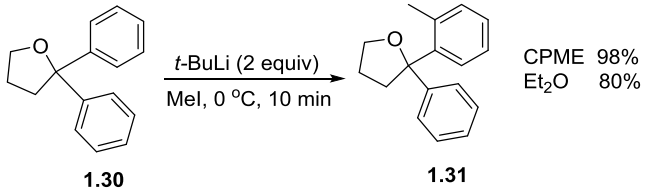


Scheme 1.18: Synthesis of cyclopentyl methyl ether.

Interestingly, CPME solutions of several reagents are now commercially available. For instance, lithium t-amoxide (LTA) and sodium t-amoxide (NTA) in CPME are available from

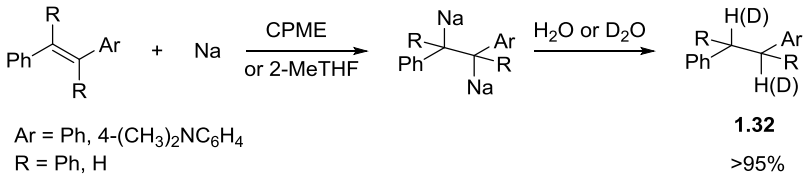
Rockwood Lithium. CPME shows better solubility than THF and 2-MeTHF for NTA. In addition, some Grignard reagents in CPME are available from Pentagon Chemical Specialties and Acros Organics, including methylmagnesium bromide, phenylmagnesium bromide and phenylmagnesium chloride.

The good characteristics of CPME as a solvent in reactions that involve the use of organometallic reagents are confirmed by numerous examples. Recently, regioselective desymmetrization of diaryltetrahydrofurans (**1.30**) via directed *ortho*-lithiation [94] has been achieved with CPME and trapping with electrophile gave better yield comparing to Et_2O.



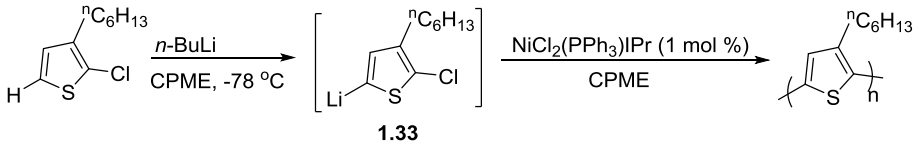
Scheme 1.19: Directed *ortho*-lithiation of diaryltetrahydrofuran derivative.

Interestingly, the generation in CPME (and 2-MeTHF as well), as a green alternative to THF, of selected 1,2-diaryl-1,2-disodioethanes (**1.32**) as well as their employment as single-electron transfer reagents[56b] was recently investigated.



Scheme 1.20: Reductive metalation of 1,2-diarylethenes.

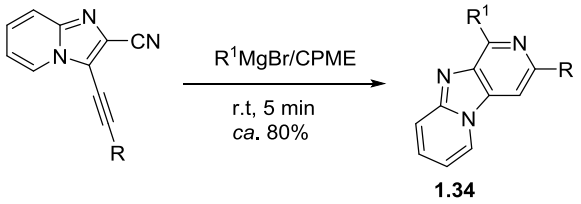
Recently, improved polydispersity indexes were achieved by CPME on the Murahashi Coupling polymerization of lithiated hetero arenes (**1.33**) via nickel(II)-catalyzed polycondensation.[95]



IPr = 1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene

Scheme 1.21: Murahashi coupling polymerization

CPME proved to be a good solvent to assemble dipyrido[1,2-*a*;3′4′-*d*]imidazole (**1.34**) by employing a Grignard reagent-promoted 6-*endo*-dig cyclization of a nitrile.[96]



1.34

Scheme 1.22: Grignard reagent-promoted 6-*endo*-dig cyclization.

Additional applications includes its employment as a solvent in catalytic enantioselective addition of thioacids to trisubstituted nitroalkenes,[97] in the dehydration of lignocellulosic pentoses to furfural,[98] C–H bond functionalization of tetrahydroisoquinolines,[99] palladium-catalysed bond formation,[100] synthesis of 1-haloethenamides,[101] aza-Michael reaction,[102] reactions in biphasic solvent systems,[103] and many others.

To the best of my knowledge, there is no report concerning the employments of CPME or 2-MeTHF as solvents in reductive metalation besides the above described generation of *vic*-1,2-diaryl-1,2-disodioethanes by the reaction of Na metal with 1,2-diarylethenes.[56b]

1.1.7 Miscellaneous Factors Affecting PAH Mediated Reductive Lithiations

Temperature has a major role on PAH mediated reductive lithiations. For instance SA derived LDBB is unstable above 0 °C[20b], LDMAN decomposes above -45 °C[104] and CA derived lithium naphthalenide (**1.5**) is stable at room temperature.[105] Meanwhile the form of the metal is an

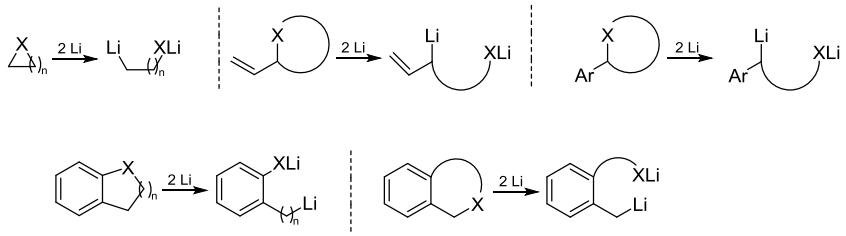
important parameter to control the efficiency of the reductive lithiation. Among the different forms of the commercially available metal (granular, ingot, ribbon, wire, and so on) dispersions in mineral oil (~25 or 30% by weight) were reported to be highly effective, due to reactivity and handling advantages.[106] Recently, Screttas *et. al.* reported a new protocol for the preparation of a highly reactive variety of lithium metal in the form of spherules. These were prepared by vigorously stirring Li chips in mineral oil/cholesterol at high temperatures. Using Et_2O as a solvent, this highly reactive form of lithium was successfully employed in the first direct preparation of room-temperature-stable dilithioarenes.[107]

1.1.8 Application of Meditated Reductive Lithiations

Mediated reductive lithiation procedure established itself in the last decades as an alternative and a complement to different applications. The distinct advantage of this method have been shown in synthetic organic chemistry, nanoparticle preparation or activation of metal (Sn [108], Ni[109],Mn[110],Zn[111],Cu [112]), nanotubes[113], hydrogen storage[114] and others methodologies.[20b]

In synthetic organic chemistry PAH mediated reductive lithiation has been demonstrated to be one of the most versatile methods known for generating organolithiums. Its advancement has been intensively studied in terms of chemo- regio- and stereo-selectivities as well as mildness of reaction conditions, strongly expanding the number of precursors. As a result of these, the role of mediators as homogeneous ET reagents for the reductive cleavage of functional groups is widely employed in synthetic organic chemistry. Typically PAH mediated bond cleavages of carbon-carbon, carbon-oxygen, carbon-nitrogen, carbon-fluorine, carbon-sulfur, nitrogen-sulfur, nitrogen-nitrogen, nitrogen-oxygen bonds have been reported.[20,50] In addition to the preparation of α, β, γ, δ and ε functionalized organolitiums, the synthesis of several poly-lithium was also described.[20]

Moreover, the enormous role of this reaction in the reductive ring opening and functionalization of heterocycles was reported (Scheme 1.23).[115]



Scheme 1.23: Reductive lithiation of different classes of heterocyclic compounds; X = NR, O, S; n = 1,2.

In this dissertation, special attention was given to the reductive lithiation of phatalan, 4-chlorobenzyl methyl ether and *N*-phenylaziridine,, i.e., to the reductive lithiation of a benzylic carbon – oxygen bond, of an aromatic carbon-chlorine bond, and of a carbon-nitrogen bond within a strained heterocycle. The present work was performed to study: (i) the generation of radical anions and/or dianions of known and new PAH mediators in 2-MeTHF and CPME as alternative green solvents, as well as, (ii): reductive lithiation reactions on the above mentioned starting materials by employing both SA and CA protocols.

1.2 Results and Discussion

1.2.1 Generation of Homogeneous Electron Transfer Agents in 2-MeTHF and CPME

As explained in the introduction part, the reductive metallation reactions constitutes an important class of transformation for the generation of polar organometallic reagents, especially organolithium reagents, in the presence of PAH mediators. The effectiveness of these synthetic reactions relies on the possibility to operate the reactions of electron transfer from the alkali metal to the substrate under homogeneous conditions.

For this reason, we envisaged the potential application of both 2-MeTHF and CMPE for the generation of radical anions and/or dianions. Based on the formation of intense and characteristic colors of radical anion and/or dianion solutions, we initially performed a series of visualizing color tests employing, as possible electron shuttles, the compounds reported in Figure 1.4 in addition to DBB and $C_{10}H_8$ (Figure 1.2). It is worth mentioning that besides aromatic and heteroaromatic compounds, we investigated also the employment of a conjugated diene, 2,3-dimethylbutadiene (DMB) as an electron shuttle.

CA reactions were run under dry Ar by adding 2 mmol (10 mol%) of the PAH to a vigorously stirred suspension of 20 mg atom of Li metal in 10 mL of the solvent, at rt; SA reactions were run under similar conditions with 4 mmol of PAH and 4 mg atom of Li metal (Table 1.2 and 1.3).

(Table 1.2 and 1.3), putting particular emphasis on the employment of basic heterocyclic derivatives (**1.35**-**1.37**), due to the possibility of an easily recovery from the reaction mixtures with acidic-basic extractions.

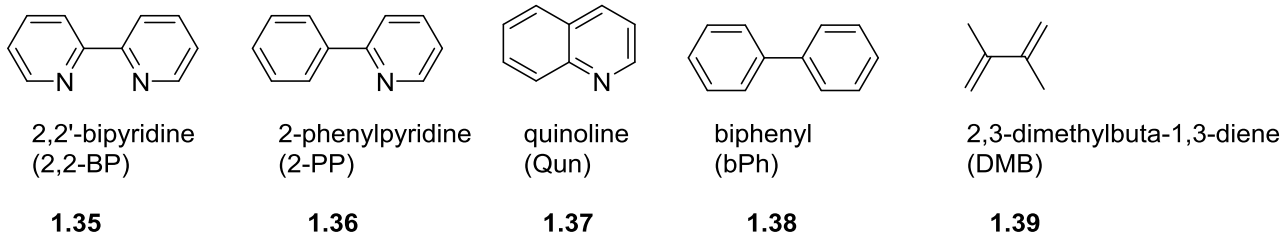


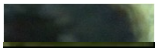
Figure 1.4: Chemical structure (with abbreviations) of mediators used for investigation in addition to Figure 1.2.

The results reported in Table 1.2 and 1.3 shows that the possibility to generate highly visible colored species, which may be radical anions and/or dianions (in CA case) or radical anions (SA case). As explained in the introduction, these colored reactive species act as homogeneous electron transfer agent. These findings supported the idea to employ CPME and 2-MeTHF as green and convenient ethereal solvents for PAH-mediated reductive metallation reaction.

Table 1.2: Radical anion and/or dianion generation using catalytic amounts of electron shuttle and lithium metal.

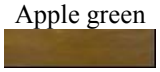
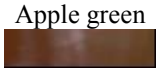
Solvent	Metal	Electron shuttle	Color change and time			
			Start time(s)	Beginning	On progress	After an hour
2-MeTHF	Li dispersion	DBB	30	Apple green	Deep green	Darkgreen
		bPh	30	Blue green	Dark green	Dark green
		$C_{10}H_8$	30	Apple green	dark-green	Dark purple
		2-PP	180	Blue brown	Blue green	Dark green
		DMB	600	Sand	Apple green	Apple green
		Qun	60	Apple green	Apple green	Apple green
		DMAN	30	Purple	Dark blue	blue green
		2,2-BP	40	Blue green	Dark green	Dark green
CPME	Li dispersion	DBB		NC[a]	NC[a]	NC[a]
		bPh	1500	Apple green	Olive	Reddish-brown
		$C_{10}H_8$	30	Royal Purple	Royal Purple	Dark purple
		2-PP	150	Apple green	Light brown	Reddish-brown
		DMB		NC[a]	NC[a]	NC[a]
		2,2-BP	150	Deep green	Light green	Dark green

Table 1.2 (*continued*): Radical anion and/or dianion generation using catalytic amounts of electron shuttle and lithium metal.

Solvent	Metal	Electron shuttle		Color change and time		
			Start time (s)	Beginning	On progress	After an hour
2-MeTHF	Li ribbon	DBB		NC[a]	NC[a]	NC[a]
		bPh	720	 Green	 Blue green	 Dark green
		$C_{10}H_8$	600	 Apple green	 Purple	 Dark purple
		2-PP	150	 Blue brown	 Dark blue	 Dark green
		DMB	600	 Yellow green	 Yellow green	 Yellow green

[a]NC= No visible color change occurred.

Table 1.3: Radical anion generation using stoichiometric amounts of electron shuttle and lithium metal.

Solvent	Metal	Electron shuttle	Color change and time			
			Start time (s)	Beginning	On progress	After 4 hours
CPME	Li dispersion	DBB		NC[a]	NC[a]	NC[a]
		bPh	460	 Apple green	 Olive	 Reddish brown
		$C_{10}H_8$	120	 Apple green	 Royal purple	 Dark purple
		2-PP	240	 Apple green	 Green	 Green
		DMB	1800	 Yellow green	 Deep yellow	 Deep yellow
		2,2-BP	65	 Violet	 Dark green	 Dark green
2-MeTHF	Li dispersion	DBB	30	 Deep green	 Blue-greenish	 Dark blue-green
		bPh	60	 Blue green	 Blue green	 Blue green
		$C_{10}H_8$	30	 Dark green	 Dark green	 Dark purple
		2-PP	30	 Brown to violet	 Dark green	 Dark green
		DMB	13	 Yellow green	 Yellow green	 Yellow green
		2,2-BP	10	 Violet	 Dark green	 Dark green

[a]NC= No visible color change occurred.

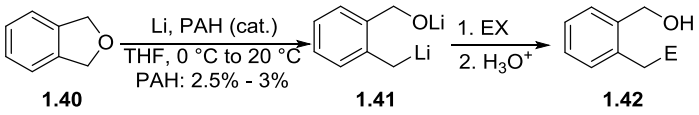
In this preliminary investigation, the result from CA method (Table 1.2) confirmed that lithium metal in the form of dispersion or ribbon gives similar results although, in several experiments with different mediators, the employment of Li dispersion led to a faster color formation.

It is however worth noting that employing CMPE as a solvent, no color change was observed either in the presence of catalytic or stoichiometric amounts of DBB or DMB. These observations strongly indicate 2-MeTHF as the solvent of choice to investigate electron transfer reactions in the presence of the above mentioned PAH. This may be due to the lower polarity of CPME, as indicated by the corresponding dielectric constant values at 25 °C: 2 -MeTHF, ε = 7.00; CPME, ε = 4.76 (Table 1.1).[90]

Taking into account the problem of removal of PAH after reductive lithiation[30] and to obey the principles of green chemistry concerning atom economy as well as the prevention of waste formation,[116] nitrogen containing electron shuttles (2,2-BP (**1.35**), 2-PP (**1.36**) and Qun (**1.37**)) appeared to be particularly interesting mediators, due to their possible easy recovery as a result of their basicities.

1.2.2 Reductive Lithiation of Phthalan

Phthalan (**1.40**) also known as isocoumaran or 1,3-dihydro-2-benzofuran, is a versatile substrate for reductive lithiation studies. As demonstrated in a number of interesting articles, reaction of phthalan with Li and a catalytic amount of DBB or $C_{10}H_8$ led to a highly regioselective cleavage of the arylmethyl carbon-oxygen bond, with formation of a stable dilithium intermediate (**1.41**) (Scheme 1.24).[32a,117]



Scheme 1.24: Reductive lithiation of phthalan, and reaction with electrophiles. EX = H_2O, D_2O, alkyl halides, ketones, aldehydes, CO_2; yields 54 - > 95%; PAH: DBB or $C_{10}H_8$.[32a,117]

This intermediate is suitable to be transformed into a wide range of derivatives (**1.42**). As such we considered this substrate as a candidate to check the possible application of 2-MeTHF in reductive lithiation.

For comparison reasons all reactions were conducted in the presence of catalytic or stoichiometric amounts of PAH (Table 1.4 and 1.5). Additionally few experiments with sub-stoichiometric amounts of a PAH (i.e., with 2 equivalents of Li and 1 equivalent of a PAH) will be also reported (see below). As preliminary results, we observed that no reaction took place when phthalan was treated with Li metal in the absence of any PAH.

1.2.2.1 Reductive Lithiation of Phthalan by CA Method

The reduction of **1.40**, taken as a model compound, was carried out under Ar with different electron shuttles in 2-MeTHF at 0 °C under CA reaction conditions (3 mol% PAH and 5 equiv of Li as a 30% dispersion). The results are reported in Table 1.4, while Figure 1.5 reports the main reaction products obtained in our experiments.

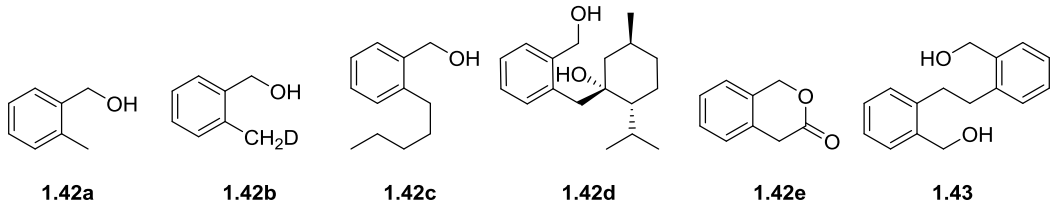


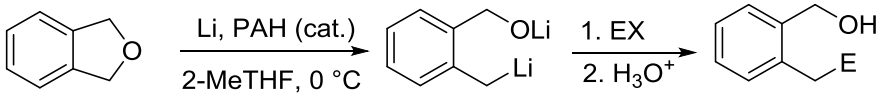
Figure 1.5: Reaction products obtained by the reductive lithiation of phthalan (**1.40**).

The reductive cleavage of **1.40** with Li metal and DBB shows that, besides the expected 2-(methylphenyl)methanol (**1.42a**, E = H), a side product, i.e., 1,2-bis(2-hydroxymethyl)diphenyl-

ethane (**1.43**, Figure 1.5) was obtained (Table 1.4, entries 1 and 2), most probably due to dimerization of an intermediate benzylic radical (see Scheme 1.5, equation l).[117b]

Better results were obtained in the presence of catalytic amounts of 2-PP; indeed, under these conditions, exclusive formation of **1.42a** occurred via intermediate formation of the corresponding carbanions, as evidenced upon D_2O quenching of the reduction mixtures (Table 1.4, entry 3).

Table 1.4: Reductive lithiation of **1.40** by CA method in 2-MeTHF[a]



1.40 **1.41** **1.42a-e**

Entry	PAH	Time (h)	Electrophile (EX)	Product	Yield (%)[b]
1	DBB	6	H_2O (D_2O)	**1.42a** (**1.42b**)	91(95)[c]
2	DBB	12	H_2O (D_2O)	**1.42a** (**1.42b**)	92 (96)[d]
3	2-PP	6	H_2O (D_2O)	**1.42a** (**1.42b**)	>99 (98)
4	2-PP	12	H_2O (D_2O)	**1.42a** (**1.42b**)	95 (>99)
5	2,2-BP	12	H_2O (D_2O)	**1.42a** (**1.42b**)	97 (89)
6	Qun	6	H_2O (D_2O)	**1.42a** (**1.42b**)	70 (57)
7	$C_{10}H_8$	12	H_2O (D_2O)	**1.42a** (**1.42b**)	17 (35)
8	DMB	6	H_2O	**1.42a**	NR[d]
9	2-PP	12	*n*-Butyl bromide	**1.42c**	82[e]
10	2,2-BP	12	(-)-Menthone	**1.42d**	39[e,f]
11	2-PP	12	(-)-Menthone	**1.42d**	41[e,f]
12	2-PP	12	CO_2	**1.42e**	90[e]

[a] All reactions were performed with 3 mol% PAH and 5 equiv of Li (30% dispersion). [b]Yields were determined by ^{1}H-NMR spectroscopic analyses of crude reaction mixtures. [c]9% of compound **1.43** was also detected. [d]8% of compound **1.43** was also detected. [d]NR = No reaction was observed. [e]Isolated yield after flash chromatography. [f]As a single diastereoisomer.

While satisfactory results were obtained employing 2,2-BP as a catalyst (Table 1.4, entry 5), reductions run in the presence of Qun, $C_{10}H_8$ and DMB led to relatively low or no conversion of the starting material (Table 1.4, entries 6-8).

Interestingly, quenching the reduction mixtures generated in the presence of catalytic amounts of 2,2-BP and 2-PP with different electrophiles, *i.e.*, *n*-butyl bromide, (-)-menthone and CO_2, afforded reaction products **1.42c-e** in satisfactory yields (Table 1.4, entries 9-12 and Figure 1.5). It is worth mentioning that, according an analogous procedure performed in THF, compound **1.42d** was isolated as a single stereoisomer.[117c]

Moreover, it should be considered that mediators 2,2-BP and 2-PP were quantitatively recovered from quenched reduction mixtures by a simple acid-base extraction technique, thus facilitating the purification and characterization of the reaction products. Recovered basic PAH were identical (^{1}H- and ^{13}C-NMR spectra) to the corresponding starting materials. These findings are particularly encouraging due to the possibility to recycle the recovered PAH catalysts, and certainly deserve further studies.

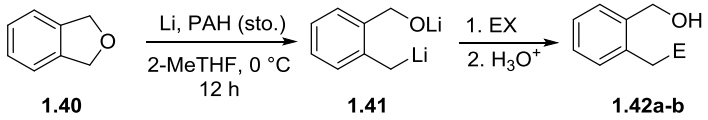
1.2.2.2 Reductive Lithiation of Phthalan by SA Method

To get more information on the feasibility to employ 2-MeTHF as an alternative to THF in reductive lithiation reactions, we next investigated the reductive cleavage of **1.40** under SA reaction conditions. The reduction of this model compound was carried out under Ar with different electron shuttles in 2-MeTHF at 0 °C by applying 2.2 equiv of PAH and of Li (30% dispersion) unless otherwise indicated. The results are reported in Table 1.5.

At variance with what observed under CA reaction conditions, H_2O and D_2O quenching experiments (Table 1.5, entries 1 and 2) evidenced that DBB mediated reaction led to the formation of compounds **1.42a** and **1.42b** without any evidence for the formation of the dimeric product **1.43**.

Most probably, the presence of a pre-formed stoichiometric amount of the homogeneous reducing agent speeds up further reduction of the intermediate benzylic radical to the corresponding carbanion, thus avoiding the coupling reaction. Furthermore, D_2O quenching evidenced the almost quantitative formation of the intermediate organometal **1.41** (Table 1.5, entry 1).

Table 1.5: Reductive lithiation of **1.40**[a] by SA method in 2-MeTHF



1.40 **1.41** **1.42a-b**

Entry	Mediator	Electrophile	Product	Yield [b]
1	DBB	H_2O (D_2O)	**1.42a** (**1.42.b**)	100 (97)
2	2,2-BP	H_2O	**1.42a**	NR[c]
3	2-PP	H_2O	**1.42a**	8
4	2-PP	H_2O (D_2O)	**1.42a** (**1.42.b**)	42 (62)[d]
5	$C_{10}H_8$	H_2O	**1.42a**	NR[c,e]
6	DMB	H_2O	**1.42a**	NR[c,e]

[a]All reactions were performed with 2.2 equiv of PAH and Li (30% dispersion) unless and otherwise indicated. [b]Yields were determined by ^{1}H-NMR spectroscopic analyses of crude reaction mixtures. [c]NR = No appreciable reaction observed. [d]Reaction performed in the presence of 2 equiv Li and 1 equiv of PAH. [e] Minor amounts of unidentified by products also formed.

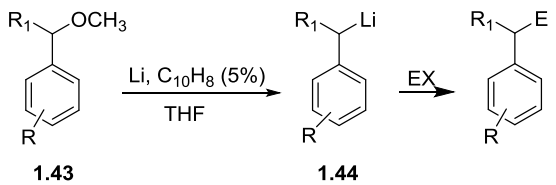
At odds with the above reported result, as well as with what observed under CA conditions, the employment of stochiometric amounts of 2,2-BP, led to the quantitative recovery of the starting material (Table 1.5, entry 2), while a very low conversion was observed in the presence of the other nitrogen containing PAH, i.e., 2-PP (Table 1.5, entry 3). Quite interestingly, however, reduction of

1.40 with 2 equiv of Li metal and 1 equiv of 2-PP (sub-stoichiometric reaction conditions) led to the formation of 42% of the desired product, with evidences for the intermediate formation of the corresponding organometal (Table 1.5, entry 3). While it is relatively easy to consider that the reducing power of the radical anions of the aza-substituted PAH are lower than the reducing power of the radical anion of DBB, the result obtained under sub-stoichiometric conditions is somewhat puzzling. Although further work is certainly necessary to shed light on such a behavior, it could be hypothesized that the reactivity evidenced in the presence of a sub-stoichiometric amount of 2-PP is due to some sort of activation of the surface of the metal, leading to the reductive metalation reaction.

Finally, attempts to employ 2.2 equiv of Li in the presence of stoichiometric amounts of either $C_{10}H_8$ or DMB as mediators were unsuccessful, leading to the recovery of the starting material together with minor amounts of unknown by-products (entry 5 and 6 Table 1.5).

1.2.3 Reductive Lithiation of 4-chlorobenzyl Methyl Ether

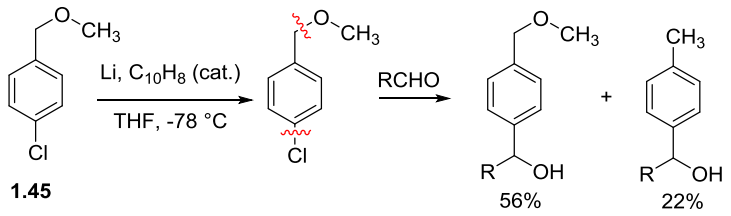
As mentioned in the introduction, the reductive cleavage of benzyl carbon - oxygen bonds is one of the most effective methods to generate benzyllithium derivatives. For instance, reductive lithiation of substituted benzyl methyl ethers **1.43** was developed as a straightforward approach to the generation of the corresponding carbanions **1.44** under mild reaction conditions (Scheme 1.25).



1.43 **1.44**

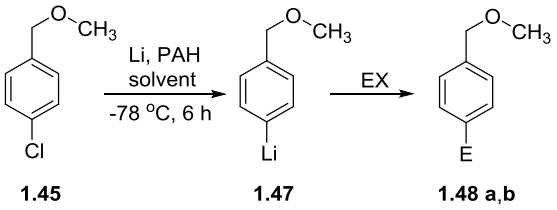
Scheme 1.25: Some examples of reductive lithiation of methyl benzyl ethers and trapping with electrophiles. R = H, 4-CH_3O, 3-CH_3O, 2-CH_3O, 3,5- (CH_3O), 2,4-$(CH_3)_2N$, 4-CH_3, 4-F; R_1 = H, CH_3; EX = H_2O, D_2O, CH_3I, PhCHO, $(CH_3)_3CCHO$; yields 67 - > 95%.[118]

However, reductive lithiation of 4-chlorobenzyl methyl ether, **1.45**, was reported to afford a preferential, although not exclusive, reductive cleavage of the aromatic carbon - chlorine bond (Scheme 1.27). Indeed, a reaction run employing THF as a solvent at -80 °C with an excess of Li metal and a catalytic amount of $C_{10}H_8$, followed by quenching with an aldehyde, led to the recovery of two alcohols, showing a competition between the cleavages of the aromatic carbon – chlorine bond and the benzylic carbon – oxygen bond (Scheme 1.26).[119]



Scheme 1.26: Reactivity of 4-chlorobenzyl methyl ether, **1.45**, under reductive lithiation reaction conditions; R = $(CH_3)_3C$.

One of the most important advantages of PAH mediated reductive lithiation is the possibility to achieve selectivity by an appropriate choice of reaction parameters. As such we decided to investigate this reaction under catalytic reaction condition by employing an excess of lithium and a catalytic amount (3% mol) of PAH (Table 1.6, Scheme 1.27).



Scheme 1.27: Reactivity of 4-chlorobenzyl methyl ether, **1.45**, under reductive lithiation reaction conditions; solvent: 2-MeTHF or THF; PAH = 2-PP or $C_{10}H_8$; EX = H_2O or CO_2; **1.48 a**, E = H; **1.48 b**, E = COOH.

We started our investigation by applying the nitrogen containing electron shuttle 2-PP. The results show that 2-PP did not mediate any bond cleavage under the reaction conditions diagrammatically depicted in Scheme 1.25 (Table 1.6, entries 1 and 2).

Interestingly, changing the mediator from 2-PP to $C_{10}H_8$ and employing 2-MeTHF as a solvent, led to complete conversion of the starting material, and an intermediate organometal was trapped employing CO_2 as an electrophile, thus evidencing a highly selective reductive cleavage of the carbon – chlorine bond (Table 1.6, entry 3).

Table 1.6: Reductive lithiation of **1.45**

Entry	Reaction conditions	Solvent	EX	Product	%Yield [a]
1	8 equiv Li, 3% 2-PP	2-MeTHF	H_2O	1.48a	NR[b]
2	10 equiv Li, 3% 2-PP	2-MeTHF	H_2O	1.48a	NR[b]
3	9 equiv Li, 5% $C_{10}H_8$	2-MeTHF	CO_2	1.48b	78.5
4	9 equiv Li, 5% $C_{10}H_8$	THF	CO_2	1.48b	76.6

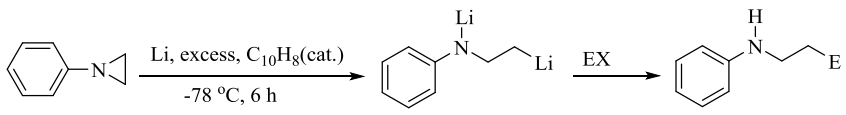
[a] Isolated yield, [b] NR = No appreciable reaction observed.

Quite surprisingly, however, a comparable results was obtained turning the solvent from 2-MeTHF to THF (Table 1.6, entry 4). Indeed, in both solvents trapping of the generated organolithium intermediate **1.47** afforded comparable yields of the corresponding carboxylic acid, **1.48b**. Accordingly, a comparison with the literature result reported above[119] strongly suggests that the observed chemoselectivity is due to the nature of the electrophile. Indeed, it can be considered that reaction of the intermediate organometal **1.47** with CO_2 led to the formation of the corresponding, probably insoluble, lithium carboxylate, thus preventing any further electron transfer from the reducing agent, thus avoiding competitive cleavage of the benzylic carbon – oxygen bond.

As a preliminary conclusion, we can consider that the employment of 2-MeTHF as a solvent, although not representing an improvement in terms of chemoselectivity, represents an interesting and efficient greener alternative to THF in the reductive lithiation of aromatic carbon – chlorine bonds.

1.2.4 Reductive Lithiation of *N*-phenylaziridine

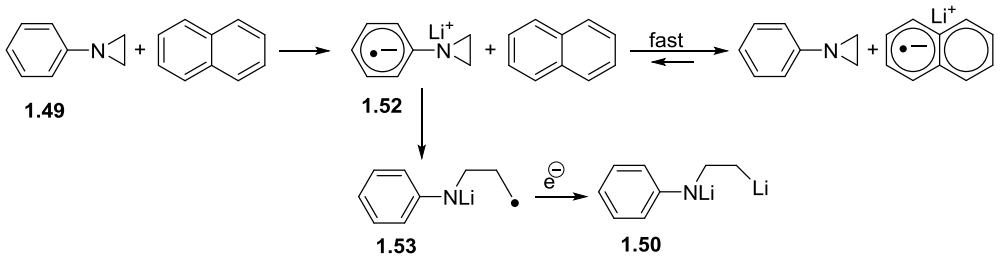
The C-N bond reductive cleavage of *N*-phenylaziridine is one of the controversial point for the comparison of CA and SA methods. First Yus and co-workers demonstrated that the ring strained, three-membered *N*-phenylaziridine, **1.49**, underwent effective cleavage of an aliphatic carbon–nitrogen bond only under CA reaction conditions, i.e., in the presence of excess lithium and a catalytic amount of $C_{10}H_8$ in THF at –78 °C (Scheme 1.28), but not under SA reaction conditions, at least at a reaction temperature useful to allow the preparation of the corresponding organolithium intermediate **1.50**.[39,41a]



1.49 **1.50** **1.51**

Scheme 1.28: Reductive lithiation of *N*-phenylaziridine in CA method and trapping with electrophiles. EX= H_2O. D_2O, Me_2S_2, Bu-*t*CHO. and others. Yields 66 - 93%. [41a]

On the other hand, in a successive paper, T. Cohen and co-workers claimed that $C_{10}H_8$ behaves as an inhibitor, rather than an effective catalyst, in the reductive lithiation of the same starting material.[41b] Their hypothesis was tested by attempting reductive cleavage of **1.49** with lithium in the absence of $C_{10}H_8$. Such a reaction afforded the desired open chain reaction product in quantitative yield. Additional experiments from the same authors demonstrated that the higher the concentration of $C_{10}H_8$ added to the reduction mixtures, the lower the rate of ring cleavage reaction.[41b,119]



Scheme 1.29: Hypothesis based mechanistic explanation for the inhibitory activity of $C_{10}H_8$[41b]

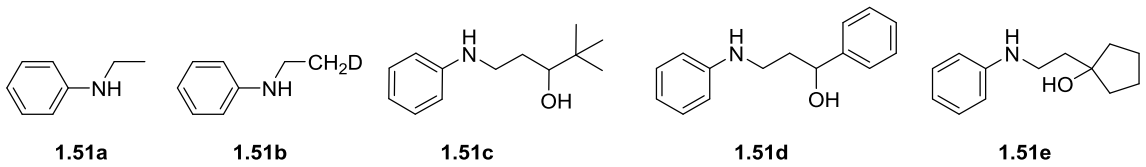
Accordingly, they proposed that the radical anion of *N*-phenylaziridine, **1.52**, forms more rapidly than Li naphthalenide (**1.5**) on the surface of the metal. However, Li naphthalenide should be thermodynamically more stable than **1.52**, thus leading, in the presence of $C_{10}H_8$, to a rapid electron transfer and to the recovery of the starting material, as diagrammatically depicted in (Scheme 1.29).[41b,119]

Considering the above two controversial points, we decided to perform additional reactions on *N*-phenylaziridine, to check its behavior under reductive lithiation reaction conditions in 2-MeTHF. Additionally, such a substrate offered us the possibility to check the effectiveness of 2-MeTHF as a solvent in the reductive cleavage of a strained carbocyclic carbon – nitrogen bond, i.e., of a third kind of carbon-heteroatom bond, thus widening the scope of our investigation.

1.2.4.1 Reductive Lithiation of *N*-phenylaziridine, 1.49, in 2-MeTHF

At variance with the above reported results, the reaction of *N*-phenylaziridine, **1.49**, run with an excess of lithium powder in the absence of any PAH did not led to cleavage of the desired reductive cleavage reaction (Table 1.7, entry 1). Much better results were obtained running the reductive cleavage reactions with an excess of lithium and catalytic (0.025 equiv) to sub-stoichiometric (1 equiv) amount of $C_{10}H_8$. Interestingly, quenching these reactions with D_2O evidenced the intermediate formation of diorganometal **1.50** (Table 1.7, entries 2 and 3). Under

these conditions, such an intermediate was successfully trapped with different electrophiles (Table 1.7, entries 4-6, and Figure 1.6).

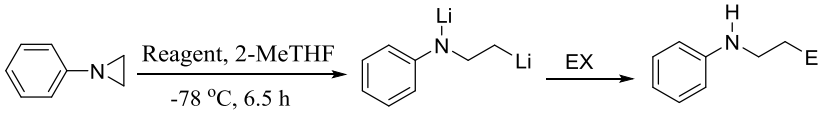


1.51a **1.51b** **1.51c** **1.51d** **1.51e**

Figure 1.6: Reaction products obtained by the reductive lithiation of *N*-phenylaziridine (**1.49**).

Quite surprisingly, in view of the above mentioned literature results, the reductive cleavage reaction proceeded, although to a very low extent, also in the presence of 2.2 equiv of preformed Li naphthalenide (Tab. 1.7, entry 7).

Table 1.7: Reductive lithiation of *N*-phenylaziridine, **1.49**, in 2-MeTHF.



1.49 **1.50** **1.51 a-e**

Entry	Reagent	EX	Product	Yield (%)[a]
1	10 equiv Li	H_2O	**1.51a**	NR[b]
2	10.0 equiv Li, 0.025 equiv $C_{10}H_8$	H_2O (D_2O)	**1.51a** (**1.51b**)	91 (95)
3	10.0 equiv Li, 1.0 equiv $C_{10}H_8$	H_2O (D_2O)	**1.51a** (**1.51b**)	99 (>95)
4	10.0 equiv Li, 1.0 equiv $C_{10}H_8$	$(CH_3)_3CCHO$	**1.51c**	59[c]
5	10.0 equiv Li, 1.0 equiv $C_{10}H_8$	PhCHO	**1.51d**	87[c]
6	10.0 equiv Li, 1.0 equiv $C_{10}H_8$	$(CH_2)_4CO$	**1.51e**	37[c]
7	2.2 equiv Li, 2.2 equiv $C_{10}H_8$	H_2O	**1.51a**	23

[a]Yields were determined by ^{1}H-NMR spectroscopic analyses of crude reaction mixtures. [b] NR = No appreciable reaction observed. [c]Isolated yield.

1.2.5. Conclusions

In this work we performed a preliminary investigation on the possibility to employ 2-MeTHF or CPME as low impact alternatives to THF in reductive lithiation reactions. Due to the importance of generating radical anions and/or dianions of polycyclic aromatic hydrocarbons to be employed as homogeneous electron transfer reagents in these reactions, we first performed a series of colorimetric tests to evidence the formation of these intermediates in the above mentioned solvents. According to these tests, 2-MeTHF appeared as the most promising one, and we concentrated our work on the possibility to employ it as solvent in this kind of reactions.

Reductive lithiation of the benzylic carbon – oxygen bond of phthalan was accomplished employing the so-called catalytic protocol, i.e., by employing as a reducing agent an excess of the metal in the presence of catalytic amounts of a PAH. As an additional bonus, we were able to demonstrate that this reaction occur employing 2-phenylpyridine (2-PP) or 2,2'-bipyridine (2,2-BP) as electron shuttles, thus allowing easy recovery of these basic polycyclic heteroaromatics.

According to an analogous protocol, we were able to perform the reductive lithiation of the aromatic carbon – chlorine bond of 4-chlorobenzyl methyl ether, thus generating the corresponding 4-methoxymethyl-substituted aryllithium derivative.

Finally, we investigated the reactivity under reductive lithiation reaction conditions in 2-MeTHF of *N*-phenylaziridine. A comparison of our results with previous literature reports show that PAH mediated reductive lithiation of *N*-phenylaziridine is strongly dependant on the solvent employed. Indeed, whilst this compound is reported to quantitatively react in THF in the absence of any PAH and that the employment of an electron shuttle such as $C_{10}H_8$ could behave as an inhibitor of the reductive lithiation reaction, we detected a relatively different reactivity of this substrate (no reaction in the absence of any PAH, quantitative ring-opening reductive cleavage in the presence of catalytic or sub-stochiometric amounts of $C_{10}H_8$) in 2-MeTHF.

Although the above mentioned results indicates that 2-MeTHF can be employed as a green alternative to THF in the reductive lithiation of different carbon – heteroatom bonds (benzylic carbon – oxygen; aromatic carbon – chlorine; strained heterocyclic carbon – nitrogen), thus leading to the formation of functionalized as well as non functionalized organometals, further work is evidently necessary to verify its wider applicability as a solvent for this type of reactions.

1.3 Experimental Part

1.3.1 Instrumentation and General Analytical Methods

Boiling and melting points are uncorrected; the air bath temperature on bulb-to-bulb distillation are given as boiling points. Starting materials were of the highest commercial quality and were purified by distillation or recrystallization immediately prior to use. Li as a 30% dispersion in mineral oil was washed three times with the appropriate anhydrous solvent immediately prior to use. Li wire was cut under inert solvent (isooctane). D_2O was 99.8% isotopic purity. THF and 2-MeTHF were distilled from Na/K alloy under N_2 immediately prior to use. CPME was distilled from Na metal under N_2 immediately prior to use. All the reactions were performed under an argon atmosphere in two-necked Schlenk tubes kept in a desiccator and, prior to use, ventilated two times under vacuum and two times under argon. Standard precautions against moisture were taken. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Ascend 400 spectrometer (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) or on a Bruker Avance III 400 spectrometer (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR) in $CDCl_3$ solutions (unless otherwise indicated) at 25 °C using as an internal standard TMS or the centre of the (residual) solvent signal which was related to TMS with δ = 7.26 (^{1}H, $CDCl_3$), δ 77.0 (^{13}C, $CDCl_3$). Deuterium incorporation was calculated by monitoring the ^{1}H NMR spectra of crude reaction mixtures and comparing the integration of the signal corresponding to protons in the arylmethyl position with that of known signals. Coupling constants are reported in Hz. Abbreviations: *s*, singlet, *br s*, broadened singlet, *d*, doublet, *t*, triplet, *q*, quadruplet, *m*, multiplet. The error in the integration of the areas under the NMR peaks is estimated at 5%. Resonances of the CHD protons are usually shifted 0.02-0.04 ppm (δ) upfield relative to the resonances of the corresponding CH_2 protons; the resonances of the arylmethyl CHD carbons appear as triplet (J = 18-20 Hz) shifted 0.3-0.5 ppm (δ) upfield relatively to the corresponding arylmethyl CH_2 carbons. Flash chromatography was performed on Merck silica gel 60 (40-63 μm) using EtOAc–hexane mixtures as eluant, unless otherwise specified. TLC

analyses were performed on Macherey-Nagel silica gel pre-coated plastic sheets (0.20 mm) and spots were visualized under UV light (λ = 254 nm) and/or cerium molybdate stain (Hanessian's stain)[120] was used as the developing system.

1.3.2 General Procedure for Color Test Reactions under CA Conditions

To a 50 ml two-necked Schlenk tube, equipped with a stirring bar and argon inlet, was added Li (20.0 mg atoms, 140 mg of wire or 470 mg of a 30% dispersion in mineral oil) in Ar atmosphere. When using the dispersion, it was washed (3 × 10 ml) with the corresponding anhydrous solvent (Table 1.2) within the Schlenk tube. 10 ml of 2-MeTHF or CPME were added, followed by the appropriate electron transfer agent (0.2 mmol) (Table 1.2). The reaction mixture was stirred at 0 °C for about 1 h and color changes were recorded and captured by photograph camera. After 1 h the reaction mixture was quenched by slow dropwise addition of cold ethanol (10 mL).

1.3.3 General Procedure for Color Test Reactions under SA Conditions

To a 50 ml two-necked Schlenk tube, equipped with a stirring bar and argon inlet was added Li (4.0 mg atoms, 92 mg of a 30% dispersion in mineral oil) in Ar atmosphere. Then it was washed (3 × 10 ml) with the corresponding anhydrous solvent (Table 1.3). 10 ml of 2-MeTHF or CPME were added, followed by the appropriate electron transfer agent (4 mmol) (Table 1.3). The reaction mixture was stirred at 0 °C for about 4 h and color changes were recorded and captured by photograph camera. After 4 h the reaction mixture was quenched by slow dropwise addition of cold ethanol (10 mL).

1.3.4 Reductive Lithiation of Phthalan

1.3.4.1 General Procedure for Reductive Lithiation of Phthalan under CA Conditions

Li metal (12.5 mg atom, 87 mg, 290 mg of a 30% wt. dispersion in mineral oil, 5 equiv) was placed under Ar in a two-necked Schlenk tube equipped stirring bar and Ar inlet, washed with anhydrous 2-MeTHF (3 × 10 mL), and suspended in 10 mL of 2-MeTHF. Then the appropriate electron transfer agent (0.4 mmol, 3 mol%,) (see Table 1.4) was added to the reaction mixture and the mixture was stirred until the reported (see Table 1.2) color was observed. After the reaction mixture was cooled to 0 °C, a solution of phthalan (0.30 g, 2.5 mmol) dissolved in 5 ml of 2-MeTHF was added. After stirring for the reported time (Table 1.4), the reactions were quenched as described below.

Quenching with H_2O was realized by adding 10 mL of the electrophile (caution!) to the reduction mixture chilled at 0 °C. The cold bath was removed, the mixture stirred at r.t. for several minutes, then extracted with 2-MeTHF (3 × 10 mL). The organic phases were collected, washed with brine (10 mL), dried (Na_2SO_4) and the solvent evaporated to afford a crude mixture which was analyzed by ^1H NMR spectroscopy.

D_2O quenching was performed by dropwise adding the electrophile (1 mL), to the reduction mixture chilled at 0 °C and stirring the resulting mixture for several minutes at rt before aqueous work up as described above.

Quenching with *n*-butyl bromide was performed by dropwise adding the electrophile (1.2 equiv, 3 mmol, 0.41 g, 0.32 mL), dissolved in 2-MeTHF (3 mL), to the reduction mixture chilled at 0 °C. Quenching with (-)-menthone (1.2 equiv, 3 mmol, 0.46 g, 0.52 mL) was performed analogously. The resulting mixtures were vigorously stirred and slowly allowed to reach r.t., followed by aqueous work up as described above.

Quenching with CO_2 was performed by bubbling the gaseous reagent through the reduction mixture chilled at 0 °C during 30 minutes, followed by addition of H_2O (10 mL). The organic phase

was extracted with 1N NaOH (2 × 10 mL), the aqueous phases were collected, acidified with *conc.* HCl and extracted with 2-MeTHF (3 × 10 mL). The organic phases were collected, washed with brine (10 mL), dried (Na_2SO_4) and the solvent evaporated to afford the crude compound.

Compounds **1.42a**, **1.42b** and **1.43** were recognized by comparison with authentic samples. Compounds **1.42c-e** were purified and characterized as described below.

1.3.4.2 General Procedure for Reductive Lithiation of Phthalan under SA Conditions

Li metal (5.5 mg atom, 38.2 mg, 130 mg of a 30% wt. dispersion in mineral oil) was placed in a two-necked Schlenk tube equipped with stirring bar and Ar inlet, washed with 2-MeTHF (3 × 10 mL), and suspended in 10 mL of 2-MeTHF. After the appropriate electron transfer agent (5.5 mmol, or 2.75 mmol, see Table 1.5) was added, the reaction mixture was stirred until the reported color observed (see Table 1.3). Then the reaction mixture was cooled to 0 °C and allowed to stir at that temperature for about 4 h. After 4 h a solution of phthalan (0.30 g, 2.5 mmol), dissolved in 5ml of 2-MeTHF was added dropwise, and the resulting mixture stirred at the same temperature during 12 h, after which time it was quenched by slow dropwise addition of H_2O (10 mL) or D_2O (1 mL), and elaborated as described in general procedure 3.4.1. Crude products were characterized by ^1H NMR spectroscopy.

1.3.4.3 General Procedure to Recover 2,2-BP and 2-PP

Organic solutions of crude reaction mixtures obtained according to the general procedure described in 3.4.1, were transferred into a 50 mL Erlemeyer flask equipped with a stirring bar and chilled to 0 °C. These organic solutions were extracted with 1N aqueous HCl (3 × 5 mL), and the aqueous phases were collected, washed with the organic solvent (5 ml), chilled again to 0 °C and basified under vigorous stirring by slow addition of solid NaOH pellets. The resulting mixtures were extracted with Et_2O (3 x 5 mL), dried (K_2CO_3) and the solvent evaporated.

1.3.4.4 Characterization of Reaction Products

(2-Methylphenyl)methanol, 1.42a[117b]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.34 (m, 1H), 7.24-7.17 (m, 3H), 4.68 (s, 2H), 2.36 (s, 3H), 1.90 (br s, 1H).

(2-Deuteromethylphenyl)methanol, 1.42b[117b]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.34 (m, 1H), 7.23-7.16 (m, 3H), 4.70 (s, 2H), 2.35-2.34 (m, 2H), 1.66 (br s, 1H).

1,2-Bis[2-(hydroxymethyl)phenyl]ethane, 1.43[117b]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.28 (m, 4H), 7.25 – 7.23 (m, 4H), 4.63 (s, 4H), 3.02 (s, 4H), 2.84 (br s, 1H).

(2-Pentylphenyl)methanol, 1.42c[117b]

Yield 365 mg (82%); purified by kugelrohr distillation; white to yellow oil. **^{1}H NMR** (400MHz, $CDCl_3$): δ 7.37 (m, 1H, Ph H-6), 7.23 (m, 1H, Ph H-4), 7.21 (m, 1H, Ph H-5), 7.20 (m, 1H, Ph H-3), 4.73 (s, 2H, C$\underline{H}_2$OH), 2.67 (m, 2H, Ph 2-CH_2), 1.82 (br s, 1H, OH), 1.59 (m, 2H, Ph 2-$CH_2C\underline{H}_2$), 1.36 (m, 4H, C$\underline{H}_2C\underline{H}_2CH_3$), 0.90 (m, 3H, $CH_2C\underline{H}_3$). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 141.0 (Ph C-2), 138.2 (Ph C-1), 129.4 (Ph C-3), 128.1 (Ph C-6), 127.9 (Ph C-4), 126.0 (Ph C-5), 63.1 (CH_2OH), 32.3 (Ph 2-$\underline{C}H_2$), 31.9 ($\underline{C}H_2CH_2CH_3$), 31.0 (Ph 2-$CH_2\underline{C}H_3$), 22.6 ($CH_2\underline{C}H_2CH_3$), 14.0 (CH_3).

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methyl-1-[(2-hydroxymethylphenyl)methyl]cyclohexanol, 1.42d[117c,121]

Yield 283 mg (41%); purified by flash chromatography (AcOEt/hexane = 2:8, colorless oil. **^{1}H NMR** (400MHz, $CDCl_3$): δ 7.35 (m, 1H, Ph H-3), 7.25 (m, 1H, Ph H-5), 7.24 (m, 1H, Ph H-4), 7.16

(m, 1H, Ph H-6), 4.79 (d, *J* = 11.8 Hz, 1H, C$\underline{H}_2$OH), 4.64 (br s, 1H, CH_2OH), 4.39 (d, *J* = 11.8 Hz, 1H, C$\underline{H}_2$OH), 3.60 (d, *J* = 13.9 Hz, 1H Ph 2-CH_2), 2.42 (d, *J* = 13.9 Hz, 1H, Ph 2-CH_2), 2.42 (m, 1H, Cyclohexane 2-CH), 1.77 (m, 1H, Cyclohexane H-4), 1.62 (m, 1H, Cyclohexane H-3), 1.48 (m, 1H, Cyclohexane H-6), 1.42 (m, 1H, Cyclohexane H-5), 1.41 (m, 1H, Cyclohexane H-3), 1.25 (m, 1H, Cyclohexane H-2), 1.00 (d, *J* = 6.9 Hz, 3H, Cyclohexane 2-CH(C$\underline{H}_3$)$_2$), 1.00 (m, 1H, Cyclohexane H-6), 0.99 (d, *J* = 6.9 Hz, 3H, Cyclohexane 2-CH(C$\underline{H}_3$)$_2$), 0.90 (m, 1H, Cyclohexane H-4), 0.82 (d, *J* = 6.4 Hz, 3H, Cyclohexane 5-CH_3).**^{13}C NMR** (100 MHz, $CDCl_3$): δ 140.4 (Ph C-2), 136.0 (Ph C-1), 132.9 (Ph C-6), 130.6 (Ph C-3), 127.3 (Ph C-5), 126.8 (Ph C-4), 74.5 (Cyclohexane C-1), 63.2 (CH_2OH), 51.0 (Cyclohexane C-2), 46.7 (Cyclohexane C-6), 42.4 (Ph 1-$\underline{C}$H), 34.8 (Cyclohexane C-4), 27.9 (Cyclohexane C-5), 25.8 (Cyclohexane 2-$\underline{C}$H), 23.8 (Cyclohexane 2-CH($\underline{C}H_3$)$_2$), 22.3 (Cyclohexane 5-$\underline{C}H_3$), 18.0 (Cyclohexane 2-CH($\underline{C}H_3$)$_2$).

Isochroman-3-one, **1.42e**[117b]

Yield 333 mg, 90%; Purified by flash chromatography (AcOEt/hexane = 1:1); mp 80-81 °C (CH_3OH/H_2O) light yellow to white solid (Ref.[117b] mp 80-81 °C CH_3OH/H_2O). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.39 – 7.27 (m, 2H), 7.26 – 7.22 (m, 2H), 5.32 (s, 2H), 3.72 (s, 2H).**^{13}C NMR** (101 MHz, $CDCl_3$): δ 170.7, 131.5, 131.0, 128.8, 127.4, 127.1, 124.7, 70.1, 36.2.

1.3.5 Reductive Lithiation of 4-chlorobenzyl methyl ether

1.3.5.1 Synthesis of 4-chlorobenzyl Methyl Ether, 1.45[122]

In a 250 mL two-necked flask of, equipped with a reflux condenser, Ar inlet, dropping funnel with magnetic stirring, were placed 1.40 g of 60% suspension of NaH in mineral oil (35.0 mmol, 1.25 equiv). The mineral oil was removed by washing the suspension with anhydrous THF (3 × 10 mL) and decanting the solvent. The resulting slurry was suspended in anhydrous THF (50

mL) and chilled to 0 °C, and a solution containing 4.0 g (28 mmol) of 4-chlorobenzyl alcohol in THF (30 ml) was added dropwise. The reaction mixture was stirred at room temperature for 1 h and 30 min or until the evolution of H_2 ceased, then chilled again to 0 °C before slowly adding a solution of CH_3I (4.97 g, 2.2 mL, 35 mmol, 1.25 equiv) dissolved in dry THF(15 mL). The resulting mixture was allowed to warm up to room temperature and vigorously stirred during 24 h, then chilled to 0 °C and quenched by slow dropwise addition of H_2O (20 mL). The resulting mixture was evaporated under reduced pressure, and extracted with Et_2O (3 × 25 ml). The organic phases were combined, dried over $CaCl_2$, filtered, and the solvent removed by evaporation. The residue was purified by distillation at reduced pressure (111-112 °C at 30 mmHg) to afford 3.90 g (24.9 mmol, 89% yield) of colorless oil, which was characterized as follows: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.40 (s, 3H), 4.41 (s, 2H), 7.28–7.46 (m, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 58.4, 74.1, 128.9, 129.3, 133.7, 137.2.

1.3.5.2 General procedure for reductive lithiation of 4-chlorobenzyl methyl ether, 1.45

In a 50 mL two-necked flask, equipped with a reflux condenser, Ar inlet, dropping funnel and magnetic stirrer, were placed 20 (8 equiv, 140 mg) to 25 (10 equiv, 175 mg) mg atom of Li metal in the form of a 30% dispersion in mineral oil. The mineral oil was removed by washing the suspension with the corresponding anhydrous solvent (THF or 2-MeTHF, 3 × 10 mL) and decanting the solvent. The resulting slurry was suspended in the anhydrous solvent (10 mL) and the appropriate electron transfer agent (2-PP, 3 mol%; $C_{10}H_8$, 5 mol%) was added to the reaction vigorously stirred reaction mixture. After the reaction mixture was cooled to -78 °C, a solution of 4-chlorobenzyl methyl ether (0.19 g, 2.5 mmol), dissolved in the corresponding solvent (5 mL) was added dropwise ,and the mixture was stirred at the same temperature during 6 h.

Quenching with H_2O was realized by adding 10 mL of the electrophile (*caution!*). The cold bath was removed, the mixture stirred at r.t. for several minutes, then extracted with Et_2O (3 × 10 mL). The organic phases were collected, washed with brine (10 mL), dried (Na_2SO_4) and the solvent evaporated to afford a crude mixture which was analyzed by ^1H NMR spectroscopy.

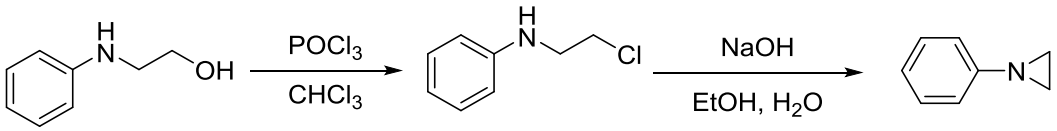
Quenching with CO_2 was performed by bubbling the gaseous reagent through the reduction mixture chilled at 0 °C during 30 minutes, followed by addition of H_2O (10 mL). The organic phase was extracted with 1N NaOH (2 × 10 mL), the aqueous phases were collected, acidified with *conc.* HCl and extracted with Et_2O (3 × 10 mL). The organic phases were collected, washed with brine (10 mL), dried (Na_2SO_4) and the solvent evaporated to afford the crude compound.

4-(Methoxymethyl)benzoic acid ,1.48b[123]

Yield 326 mg, 78.5%; purified by recrystallization from water; light yellow solid, mp 120-122 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 4.54 (s, 2H), 3.43 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.3, 144.5, 130.4, 128.4, 127.3, 74.0, 58.5.

1.3.6 Reductive lithiation of *N*-phenylaziridine

1.3.6.1 Synthesis of N- *N*-phenylaziridine, 1.49 [119,124]



a) *N*-(2-Chloroethyl)aniline: 27.6 g of 2-Anilinoethanol (25.2 mL, 200 mmol) was dissolved in 17.2 mL of concentrated hydrochloric acid and the solution was evaporated under

diminished pressure. The resulting 2-anilinoethanol hydrochloride was dissolved in 35.0 mL of chloroform, the solution was cooled in ice, and fresh phosphorus oxychloride 59.2 g (36 mL, 386 mmol) was slowly added. The resulting mixture was stirred at rt during 30 min then under reflux for 1 h. The resulting solution was evaporated *in vacuo*, and then absolute ethanol (50 mL) was added to it. The suspension was cooled for one day, then filtered to afford colorless crystals of *N*-(2-chloroethyl)aniline hydrochloride (29.41 g, 153 mmol, 76.5%). This compound was used in the next step without further characterization.

b) *N*-Phenylaziridine 1.49: A solution of 100 mL of 3.00 N sodium hydroxide and 100 mL of ethanol was placed in a 500 mL three-necked flask equipped with a stirrer, condenser and dropping funnel and the flask was immersed in a water bath held at 50 °C. To this was added dropwise and with stirring 20.0 g (104 mmol) *N-(*2-chloroethyl)aniline hydrochloride dissolved in 100 mL ethanol. After the addition was complete the temperature of the water bath was raised to 85 °C for one hour. Next, ethanol was removed by distillation, the residue was cooled to room temperature and extracted with ether (3 × 30 mL). The ethereal solution was dried over K_2CO_3, filtered and distilled until the temperature reached 82 °C. The residue was subjected to vacuum distillation. A fraction (64-65 °C at 4 mmHg) of 11 g *N*-phenylaziridine **1.49** (72%) was obtained, and was characterized as follows:

***N*-Phenylaziridine 1.49**[41b]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 – 7.20 (m, 2H), 7.05 – 6.94 (m, 3H), 2.11 (s, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): 154.8, 128.6, 122.0, 120.6, 27.3.

1.3.6.2 General procedure for reductive lithiation of *N*-phenylaziridine by the CA method:

Li metal (10 or 20 equiv, 20 or 40 mg atom) in the form of a 30% wt. dispersion in mineral oil, was placed under Ar in a two-necked Schlenk tube equipped stirring bar and argon inlet, washed with 2-MeTHF (3 × 10 mL) and finally suspended in the same anhydrous solvent (10 mL). The appropriate amount of $C_{10}H_8$ (Table 1.7) was added to the suspension and the mixture was stirred until the reported color started to develop (Table 1.2). The mixture was then chilled to -78 ^{o}C and *N*-phenylaziridine (238 mg, 2.0 mmol), dissolved in 2-MeTHF (2 mL) was added under Ar and stirring was continued at the same temperature during 6.5 h.

Quenching with H_2O was realized by adding 10 mL of the electrophile (*caution!*) to the reduction mixture. The cold bath was removed, the mixture stirred at r.t. for several minutes, then extracted with 2-MeTHF (3 × 10 mL). The organic phases were collected, washed with brine (10 mL), dried (K_2CO_3) and the solvent evaporated to afford a crude mixture which was analyzed by ^{1}H NMR spectroscopy.D_2O quenching was performed by dropwise adding the electrophile (1 mL), to the reduction mixture, and the cooling bath was removed and the mixture allowed to stir during 30 minutes before adding H_2O (10 mL), followed by work up as described above.

Pivaldehyde, benzaldehyde and cyclopentanone (4 mmol, 2 equiv), were dissolved in 2-MeTHF) and drpwise added to the reduction mixture chilled at -78 °C. After 30 minutes stirring at the same temperature, the cooling bath was removed and the mixture allowed to stir ultil reaching room temperature. Finally, H_2O (10 mL) was added, followed by work up as described above. Reaction products were purified and characterized as described below.

***N*-Ethylaniline, 1.51a[41b]**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 – 7.16 (m, 2H), 6.75– 6.71 (m, 1H), 6.65– 6.63 (m, 2H), 3.56 (s, 1H), 3.18 (q, J = 7.1 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H).

***N*-(ethyl-2-d)aniline, 1.51b[41b]**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 – 7.22 (m, 2H), 6.80 – 6.76 (m, 1H), 6.69 – 6.67 (m, 2H), 3.59 (br s, 1H), 3.21 (t, *J* = 7.0 Hz, 2H), 1.30 (ddd, *J* = 8.9, 4.4, 1.9 Hz, 2H).

1-Anilino-4,4-dimethyl-3-pentanol, 1.51c[39]

Yield 245 mg (59%): Purified by flash chromatography (AcOEt/hexane = 2:8), mp 65-67 °C, **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.19 (dd, *J* = 8.5, 7.4 Hz, 2H), 6.73 (t, *J* = 7.3 Hz, 1H), 6.68 – 6.63 (m, 2H), 3.41 (dd, *J* = 10.5, 1.8 Hz, 1H), 3.31 (td, *J* = 6.5, 1.6 Hz, 2H), 1.86 (dtd, *J* = 14.3, 6.3, 1.8 Hz, 1H), 1.59 (m, 1H), 0.92 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 148.3, 129.2, 117.7, 113.3, 79.4, 43.0, 34.9, 30.7, 25.5.

3-anilino-1-phenyl-1-propanol, 1.51d[41b]

Yield 396 mg, (87%); Purified by flash chromatography (AcOEt/hexane = 2:8), mp 61-63 °C, yellow to white solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42 – 7.28 (m, 5H), 7.18 (m, 2H), 6.73 (t, *J* = 7.3 Hz, 1H), 6.63 (dd, *J* = 8.6, 1.0 Hz, 2H), 4.91 (dd, *J* = 7.6, 5.0 Hz, 1H), 3.30 (t, *J* = 6.4 Hz, 2H), 2.13 – 2.01 (m, 2H). **^{13}C NMR** (400 MHz, $CDCl_3$): δ 148.3, 144.4, 129.2, 128.6, 127.7, 125.7, 117.8, 113.4, 73.7, 41.7, 38.2.

1-(2-(phenylamino)ethyl)cyclopentan-1-ol, 1.51e

Yield 152 mg, (37%); Purified by flash chromatography (AcOEt/hexane = 3:7), mp 80-82 °C, yellow solid.**^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.20 (d, *J* = 15.7 Hz, 2H), 6.78 – 6.59 (m, 3H), 3.57 (s, 1H), 3.35 (t, *J* = 6.7 Hz, 1H), 3.18 (q, *J* = 7.1 Hz, 2H), 1.92 (t, *J* = 6.7 Hz, 1H), 1.90 – 1.50 (m, 4H), 1.28 (t, *J* = 7.1 Hz, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.2, 129.2, 118.0, 113.5, 82.6, 41.5, 40.0, 29.7, 23.6.

1.3.6.3 General Procedure for the Reductive Lithiation of *N*-Phenylaziridine by the SA method:

Li metal (2.2 equiv, 4.4 mg atom, 30 mg, in the form of 100 mg of a 30% wt. dispersion in mineral oil) was placed under Ar in a two-necked Schlenk tube equipped with stirring bar and argon inlet, washed with 2-MeTHF (3 × 10 mL), and finally suspended in the same anhydrous solvent (10 mL). $C_{10}H_8$ (2.2 equiv, 4.4 mmol, 560 mg) was added to the suspension and the mixture was stirred until the reported color started to develop (Table 1.3). Then the reaction mixture was cooled to 0 °C and was allowed to stir at that temperature for about 4 h. The mixture was then chilled to -78 ^{o}C and *N*-phenylaziridine (238 mg, 2.0 mmol), dissolved in 2-MeTHF (2 mL) was added under Ar at the same temperature. After the mixture had been stirred for 6.5 h, the reaction mixture was quenched with H_2O (10 mL) and worked pout as reported above and the crude reaction product analyzed by ^{1}H NMR spectroscopy.

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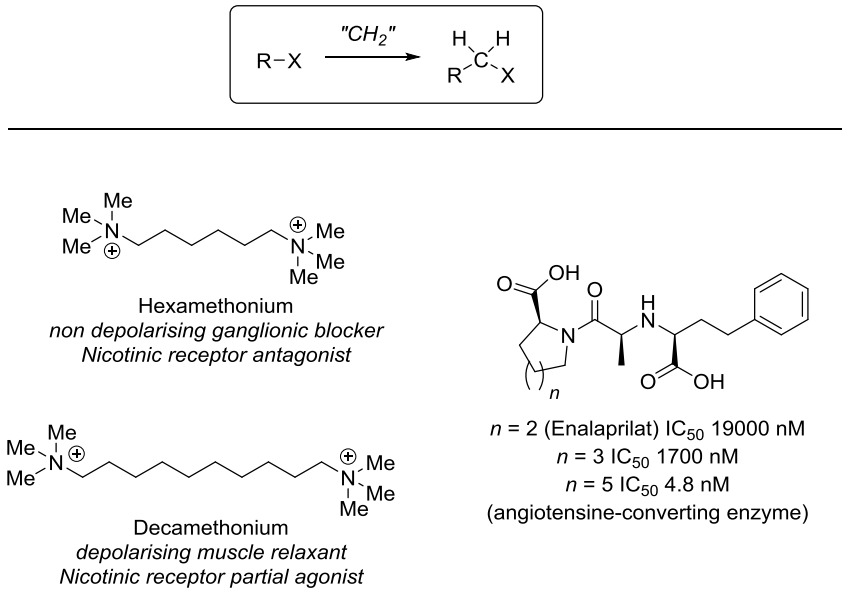
Chapter 2

Studies on Lithium Halocarbenoids

2.1 Introduction

2.1.1 Homologation Reactions in Organic Chemistry

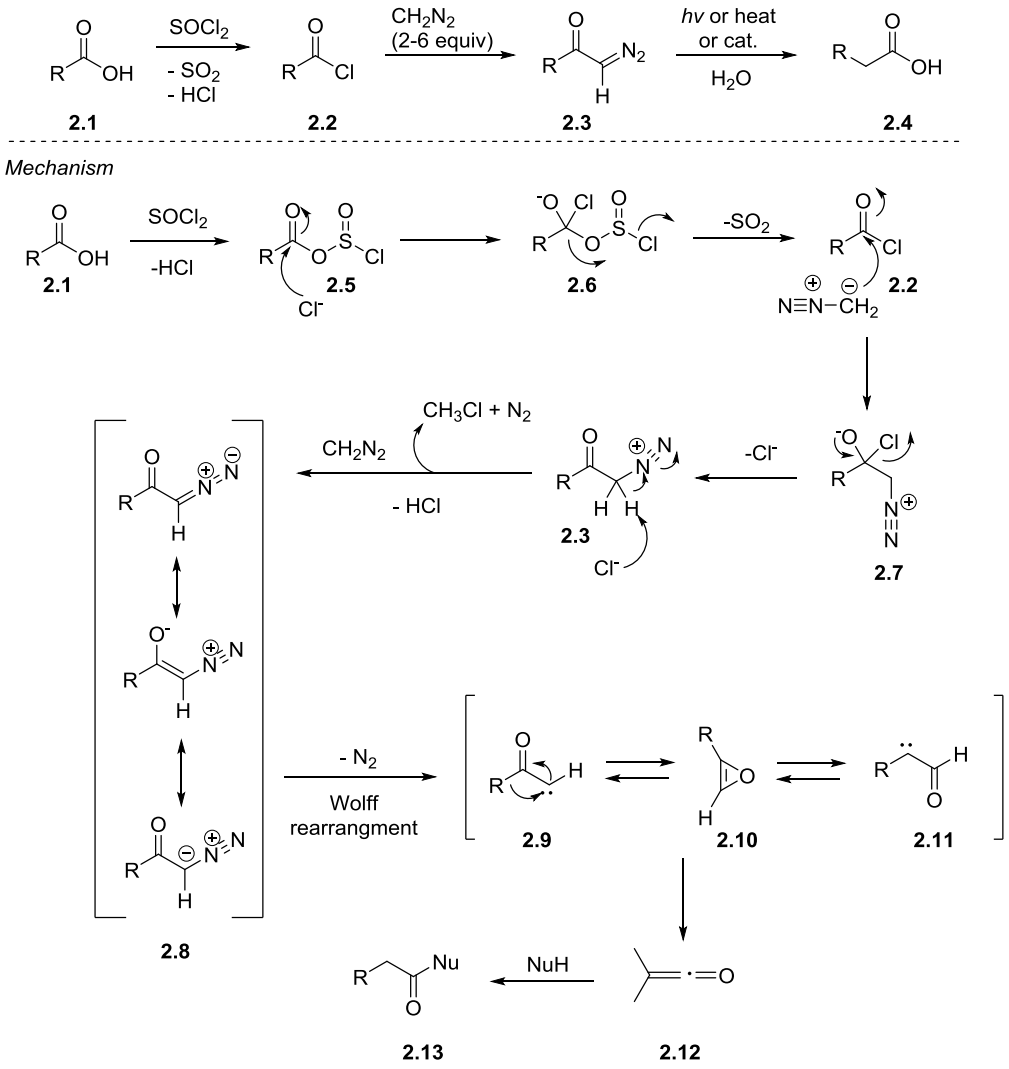
Efficient functional group transformations have been the goal of organic chemists for many years.[1] Reports have appeared on atom economy and towards the ideal synthesis highlighting these goals.[2] The addition of a one carbon unit to a given reactant with the final result to obtain the next member of an homologous series is defined homologation.[3] In other words, within a homologous series compounds differ from each other by a constant unit. A pivotal role in synthetic chemistry is played by homologations which add a methylene fragment "CH_2" to an existent carbon-(hetero)atom bond. Homologation chemistry has important applications in medicinal chemistry since the (progressive) introduction of methylene fragments might significantly modify bioactivity (Scheme 2.1).



Scheme 2.1: Concept of homologation and examples of homologues with different bioactivity.

2.1.1.1 Arndt-Eistert homologation

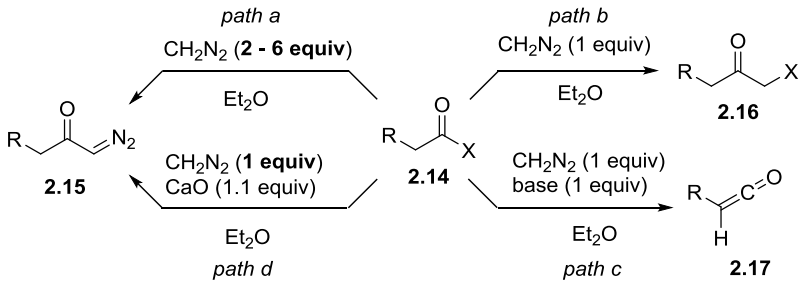
From an historical perspective, the Arndt-Eistert homologation is considered the milestone in the field.[4] In fact, the conversion of a carboxylic acid to its homolog in three stages *via* an α-diazomethylketone is one of the first examples of homologation reactions and, still nowadays it is often employed for synthetic purposes. It is the best preparative method for the chain elongation of carboxylic acids (Scheme 2.2).



Scheme 2.2: Arndt-Eistert homologation

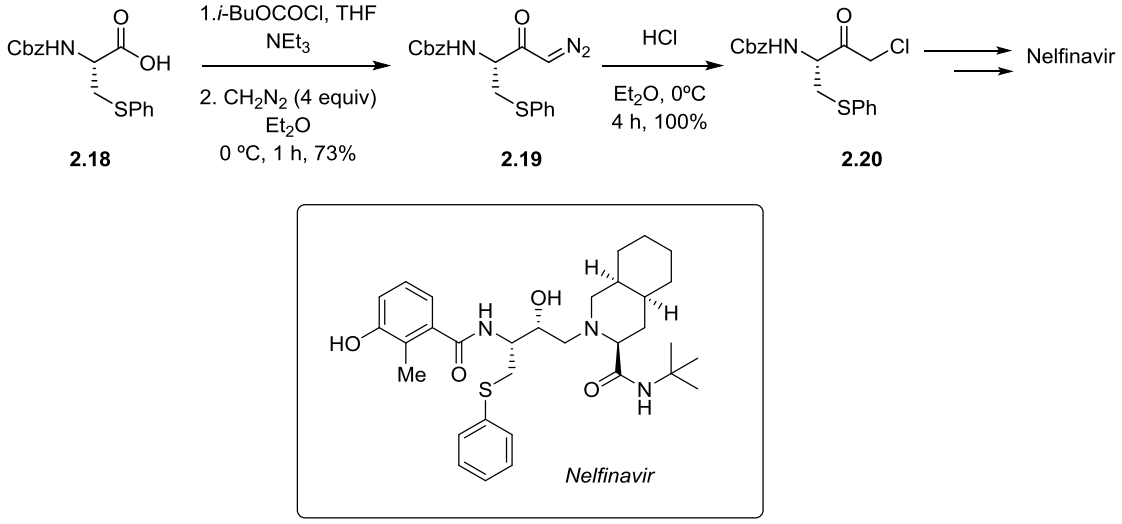
In the first step, the carboxylic acid **2.1** is converted to an acid chloride **2.2**, which reacts with diazomethane to afford the α-diazomethylketone **2.3**. Subsequent Wolff rearrangement[5] provides the homologated carboxylic acid. Classically, a silver catalyst is used to mediate the Wolff rearrangement, although heat, photolysis or other metals (Pt, Cu) can be employed. In the presence of water the homologated acid **2.4** is isolated; however, on addition of alternative nucleophiles, other products can be produced. The whole transformation can rationalized as follows. Exposure of carboxylic acid **2.1** to thionyl chloride (or analogous reagent) produces acid chloride **2.2**, and in the process SO_2 and HCl are produced. Displacement of chloride moiety by diazomethane furnishes diazoketone **2.3**. Classically, a silver catalyst was employed to mediate the Wolff rearrangement, although the role of the catalyst is poorly understood. Loss of nitrogen from diazoketone **2.3** gives a carbene **2.9**, which can interconvert *via* a 1,2-oxygen shift, with oxirene **2.10** as an intermediate. A rapid [1,2]-shift affords ketene **2.12**, which reacts readily with nucleophiles to give homologated acid derivative **2.13**.

Since HCl is a by-product of this reaction, *at least* two equivalents of diazomethane must be used to prevent side products like chloroketones (Scheme 2.3 – *path a*). In fact the formed diazoketone would react immediately with the released acid thus, giving the corresponding chloroketone (Scheme 2.3 – *path b*). However, the well known safety issues associated to the use of this reagent render this strategy not particularly attractive.[6] Scott and Minton reported a modification whereby triethylamine is added to capture the released HCl.[7] Although effective in some instance, the method cannot be applied to acid chlorides bearing acidic protons which will be easily abstracted to obtain a ketene (Scheme 2.3 – *path c*).[8] In 2010 Pace and De Kimpe designed an effective protocol which enables the Arndt-Eistert synthesis with minimal (stoichiometric) loading of diazomethane: the key to achieve this challenging objective is the use of the innocuous calcium oxide as acid scavenger (Scheme 2.3 – *path d*).[4d]



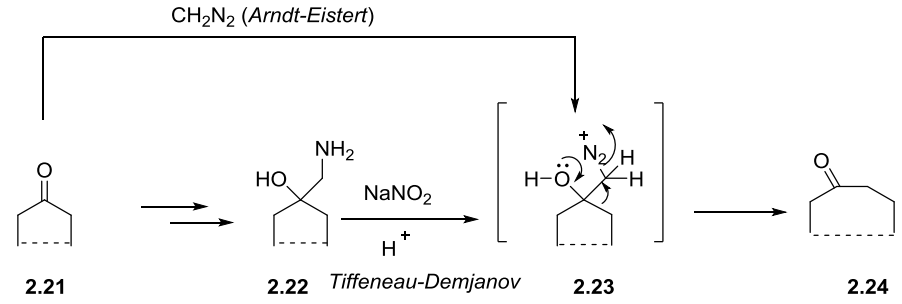
Scheme 2.3: Alternative protocol for Arndt-Eistert homologation.

Arndt-Eistert chemistry is still a valuable method to access pharmaceutical synthons, as for example showed by a key intermediate (**2.20**) for the synthesis of the HIV inhibitor Nelfinavir, which were prepared through this tactic with a large amount of diazomethane (Scheme 2.4).[9]



Scheme 2.4: Application of the Arndt-Eistert homologation to the synthesis of a medicinal relevant scaffold.

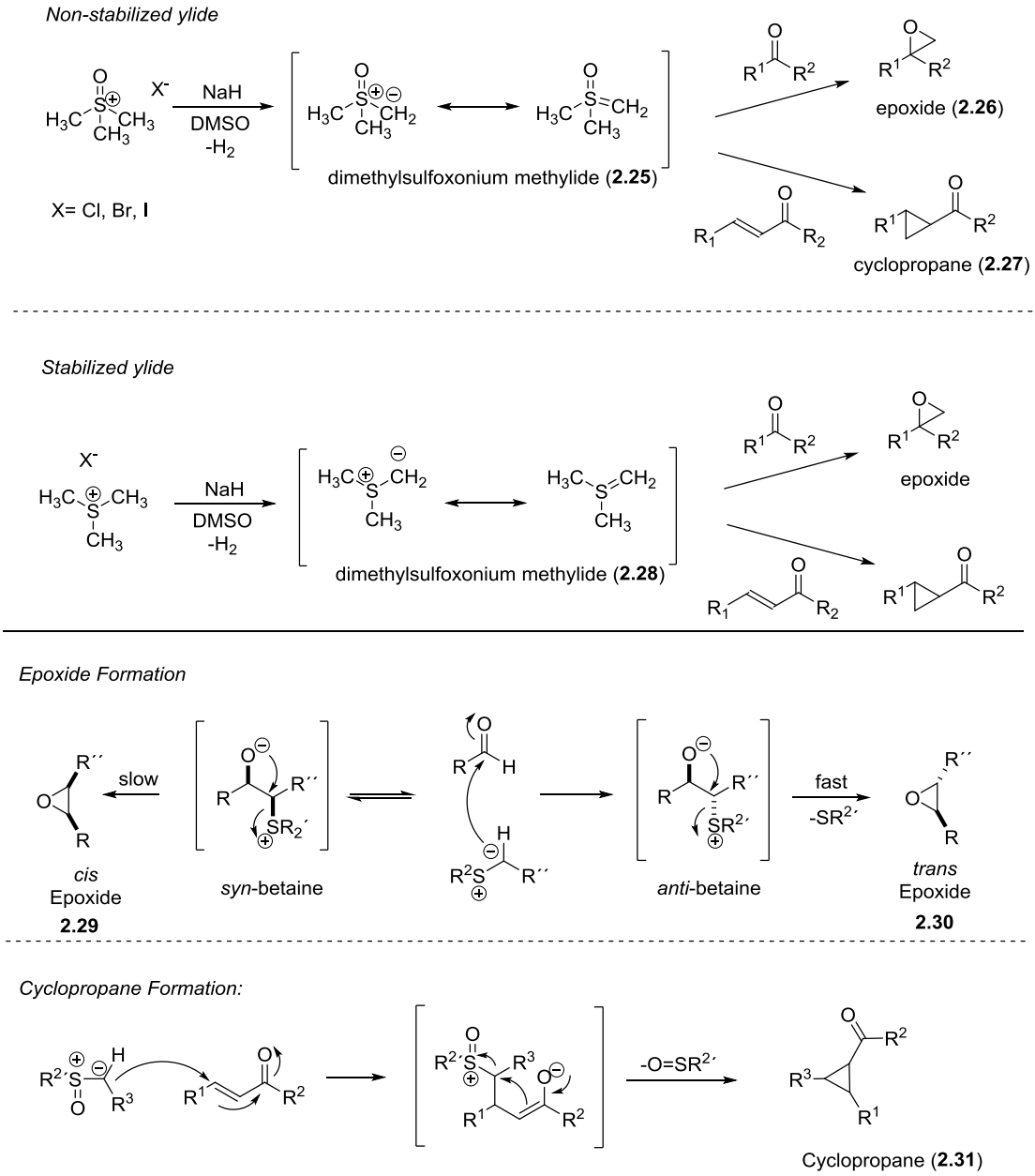
The addition of diazomethane to a cyclic ketone **2.21** generates the tetrahedral intermediate **2.23** which upon expulsion of nitrogen, affords the homologated structure **2.24**. The same process takes place when β-amino cyclic alcohol (**2.22**) is treated with sodium nitrite in acidic medium thus, generating the diazo group on a preformed aminomethyl group. This transformation known as the Tiffeneau-Demjanov[10] ring-expansion is an alternative to the classical Arndt-Eistert (Scheme 2.5).



Scheme 2.5: Homologation of a cyclic ketone *via* Tiffeneau-Demjanov and Arndt-Eistert chemistries.

2.1.1.2 Corey-Chaykovsky Homologation

In 1962, E. J. Corey and M. Chaykovsky deprotonated trimethylsulfoxonium halides using powdered sodium hydride under nitrogen at room temperature to form a reactive compound, dimethylsulfoxonium methylide (**2.25**).[11] When simple aldehydes and ketones were mixed with **2.25**, the formation of epoxides (**2.26)** was observed (Scheme 2.6). Likewise, the reaction of dimethylsulfonium methylide (**2.28**) with aldehydes and ketones also resulted in epoxide formation. Compounds **2.25** and **2.28** are both sulfur ylides and are prepared by the deprotonation of the corresponding sulfonium salts.[12] When **2.25** is reacted with α,β-unsaturated carbonyl compounds, a conjugate addition take place to produce a cyclopropane (**2.27**) as the major product. Sulfur ylide **2.28** is more reactive and less stable than **2.25**, so it is usually generated and used at low temperature. The reaction of substituted sulfur ylides with aldehydes is stereoselective, leading predominantly to *trans* epoxides. Asymmetric epoxidations are also possible using chiral sulfides.[13] The use of various substituted sulfur ylides allows the transfer of substituted methylene units to carbonyl compounds (isopropylidene or cyclopropylidene fragments) to prepare highly substituted epoxides. Since the *S*-alkylation of sulfoxides is not a general reaction, it is not practical to obtain the precursor salts in the trialkylsulfoxonium series. This shortcoming limits the corresponding sulfur ylides to the unsubstituted methylide.



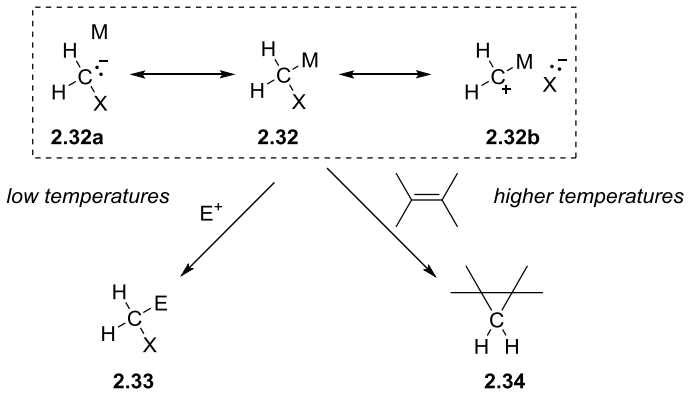
Scheme 2.6: Corey-Chaykovsky homologation.

2.1.2 Carbenoids as Homologating Agents: Historical Perspective and General Considerations

In the plethora of homologating agents a prominent role is played by the so-called carbenoidic reagents.[14] The term *carbenoid* dates back a seminal work by the pioneers of the fields, Closs and Moss.[15] According to these Authors, organometallic compounds containing a metal atom (*e.g.* Li, Mg) and at least one electronegative element (*e.g.* halogen) linked at the same carbon, have

been refereed as carbenoids, thus considering their carbene-like features (Scheme 2.7). In fact, such species show a reactivity profile "*qualitatively analogous to those of carbenes without necessarily being free divalent carbon species*."[15] A significant advancement in the field originated from the work of G. Köbrich and coworkers in the 1960s.[16] These milestones still represent the key concepts in carbenoid chemistry and put the bases for the rational design and understanding of reactions involving these versatile synthetic tools.

The concomitant presence of an electron-donating and electron-withdrawing substituent at the carbon center determines the so-called ambiphilicity of these reagents. Thus, carbenoids display a dual reactivity ranging from a nucleophilic to an electrophilic one. Depending on the experimental conditions, they may selectively exhibit one of these two properties: it is normally accepted that the nucleophilic behavior is shown at low temperatures, while their electrophilicity comes into play at higher temperatures (Scheme 2.7). This key characteristic of carbenoid reagents can be explained taking into consideration the mesomeric structures, which in principle could provide two different ionization forms. In one hand a negative charge is localized at the carbon (*i.e.* it becomes nucleophilic, **2.32a**), while in the other the carbon brings a positive charge (*i.e.* it becomes electrophilic, **2.32b**).



Scheme 2.7: Ambiphilicity and reactivity profile of carbenoids.

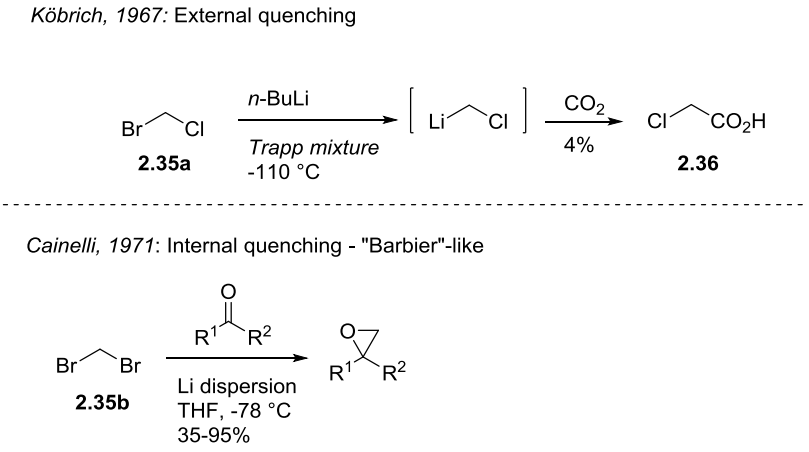
Given these premises, one may individuate two different reactions' categories in which carbenoids are involved: *i*) nucleophilic additions (eventually followed by elimination – *i.e.* acyl nucleophilic substitutions); *ii*) cyclopropanation-type processes. It is important to stress that carbenoids of lithium and magnesium, because of their excellent nucleophilicities, do react according to classical carbanionic processes;[14d] on the other hand, less nucleophilic carbenoids such as zinc or rhodium exhibit preferentially an electrophilic behavior.[14c,17]

As a consequence, it appears clear the versatility of these *chameleon-like* reagents in carbon-carbon bond formations: effectively, one of the main advantages they possess is the possibility to install with a single synthetic operation a functionalized carbon atom susceptible of further elaboration (*e.g.* an halomethyl function which may undergo subsequent transformations on the reactive methylenic carbon).[18]

2.1.3 The Big Drawback: Thermal Instability and Literature Debate Regarding the Decomposition Temperature.

It was clear from the beginning of their more than 50-years history that carbenoid reagents were thermolabile. The first drawback chemists had to overcome was determining the optimal conditions enabling a good compromise between stability and reactivity. In this context seminal studies have been performed by Köbrich who reported that at -110 °C the generation of chloromethyllithium ($LiCH_2Cl$) from bromochloromethane and *n*-BuLi, followed by carbonation provided the desired chloroacetic acid in only 4% yield (Scheme 2.8).[16,19] This first example manifests clearly the different chemical profile of carbenoids compared to other nucleophilic organometallic species which have been carbonated in excellent yields since standpoints works by Grignard in late XIX century.[20] The constitutive presence of the halogen atom, which *per se*, differentiates an organometallic entity from a carbenoid, deeply modifies the resultant structure.

Cainelli showed that monohalomethyllithiums can be efficiently prepared even at -78 °C when reactions were carried out according to a Barbier-type protocol.[21] Effectively, the generation of the carbenoid reagent in the presence of the electrophile, avoided its instantaneous decomposition and, as such it could be used to homologate the carbonyl of a ketone into the corresponding halohydrin, which in turn, cyclizes to give the final epoxyde. According to Cainelli, the carbenoid is best formed *via* metallation with lithium metal, rather than by reaction with an alkyllithium. As it can be seen, this strategy represents an useful alternative to the above seen Corey-Chaykovsky epoxydation.[11-12,12e]

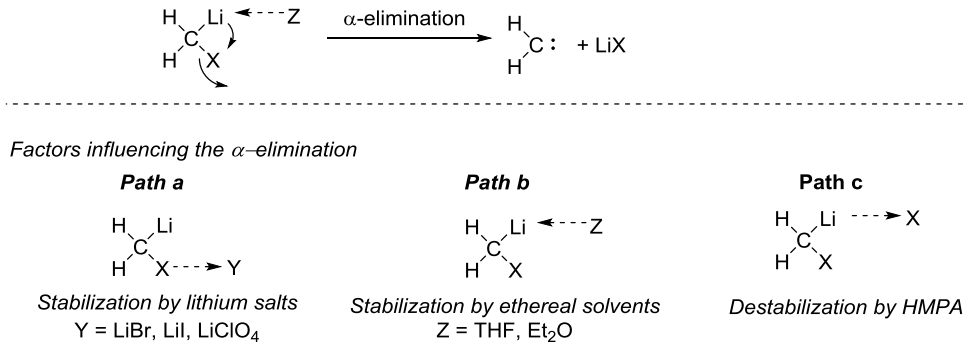


Scheme 2.8: Initial considerations on lithium carbenoids generation.

In fact, shortly after the same Köbrich recognized the main degradation pathway operating in carbenoid chemistry:[22] the so-called α-elimination to a free divalent carbene and to a metal halide.[23] Interestingly, Köbrich focused his investigations also on dihalomethyl- and trihalomethyllithiums reaching the conclusions that these species could be significantly more stable than the monohalocarbenoids.

Although Cainelli's study is important for establishing the correct generation of carbenoids through Barbier conditions,[21] it is worth noting that further studies did not agree in fixing an univocal temperature to which reactions involving these species could be successfully carried out.

As an example, a more recent report by Villieras and coworkers published in 1984,[24] was in substantial agreement with Köbrich,[16] thus, emphasizing the requirement of temperatures below -115 °C in order to suppress the undesired α-elimination. Remarkably, they demonstrate the usefulness of adding to the reaction mixture lithium halides, which through the coordination to the halogen atom of the carbenoid, disrupt the internal Li-X interaction responsible for α-elimination with consequent decomposition of the carbenoid to the free carbene.[24-25]



Scheme 2.9: Degradation pathway of carbenoid and possible points of interaction to suppress it.

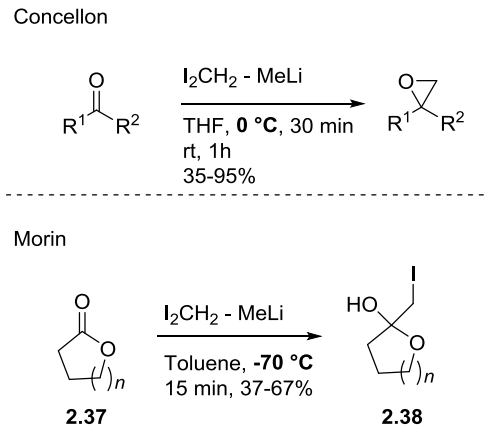
An additional stabilizing effect on the carbenoid is guaranteed by the use of Lewis basic ethereal-type solvents which coordinate the metal atom of the carbenoid (Scheme 2.9). Indeed, it is possible to affirm that stabilization of monohalolithium carbenoids may take place at two different sites: 1) the halogen responsible of the coordination with a lithium salt (Scheme 2.9 – *path a*) and, 2) the lithium atom which could be coordinated with the ethereal-type solvent (Scheme 2.9 – *path b*). Additionally, the use of this kind of solvents contributes to disaggregate organolithiums species, as uniformly encountered in organolithium chemistry. The peculiarity of monohalolithium carbenoids is even clearer when a polar solvent like hexamethylphosphoramide (HMPA) is added to the reaction mixture (Scheme 2.9 – *path c*). The oxygen atom of this solvent strongly coordinates the lithium atom of the carbenoid thus, enabling the breaking of the carbon-lithium bond and, as a consequence, the activation of the degradative α-elimination process. It must be mentioned that the

latter solvent has an opposite effect on dihalolithium carbenoids which in its presence do behave as powerful nucleophiles. As a consequence, the control of parameters affecting the stabilization of the carbenoids is a key step in order to achieve useful synthetic transformations.

Thus, it becomes evident that the electrophilicity of these species is responsible for the decomposition. This concept has also been evidenced through NMR spectroscopy: Seebach confirmed the exhibition of electrophilic properties of the carbenoid carbon atom by comparing spectra recorded at low temperatures of alkyl dihalides and of the corresponding lithiated species.[26] Invariably, the exchange of hydrogen or halogen by lithium causes deshielding of the ^{13}C-signal by up to 289 and 434 ppm, respectively, and decrease of ^{1}J (^{1}H, ^{13}C) and ^{1}J (^{13}C,^{13}C) couplings with the C-atom of up to 104 and 30 Hz, respectively. The ^{1}J (^{6}Li, ^{13}C) and ^{1}J (^{7}Li, ^{13}C) coupling of *ca.* 17 and 45 Hz, respectively, obtained is independent of the substitution pattern of the C-skeleton and of the particular halogen atom. In other words the C-X bond is elongated as a consequence of the metalation, which enhances its *p* character; at the same time, the *s* character is increased as well. This particular hybridridization of the carbenoid carbon atom has been definitively experimentally ascertained by X-ray analysis.[14c,27]

Further studies in late 1980s and early 1990s by Matteson[28] and Barluenga[29] point out the feasibility of reactions at -78 °C and thus, it can be definitively assumed that such temperature is a good compromise between thermal stability and reactivity of carbenoids. This temperature is considered the optimal one for generating both chloromethyllithium and bromomethyllithium. Although some more recent report deals with the formation of chloromethyllithium at slightly higher temperatures (-65 °C),[30] it is remarkable the preparation of iodomethyllithium at 0 °C as firstly evidenced by Concellón in 2001 (see also later).[31] Unfortunately, there is no literature agreement with this finding, as for example stressed by Morin who found the employment of a temperature of – 70 °C mandatory in order to accomplish chemistry involving this species (Scheme 2.10).[32] This author in the course of investigations aimed at iodomethylate lactones **2.37** observed a

prominent role played by toluene as the reaction medium. In fact, by following the classical procedure in the presence of THF, only minimal amounts of the desired compounds were noticed. The use of toluene resulted beneficial because the stabilization of the carbenoid is assured by its coordination with the Lewis basic sites of the substrate (*i.e.* the oxygen of the lactone and the eventually oxygenated neighboring groups). In this particular iodomethyllithium-based homologation of lactones, the stabilization of the carbenoid by means of an ethereal solvent seems to be not large enough, given the high density of additional oxygenated functionalities present on the substrates. This explanation is also consistent with previous studies by Barluenga involving unfunctionalized (*i.e.* without additional oxygenated groups) lactones which could be easily homologated with dihalomethyllithiums in diethyl ether.[29a]



Scheme 2.10: Employment of iodomethyllithium at 0 °C and -70 °C.

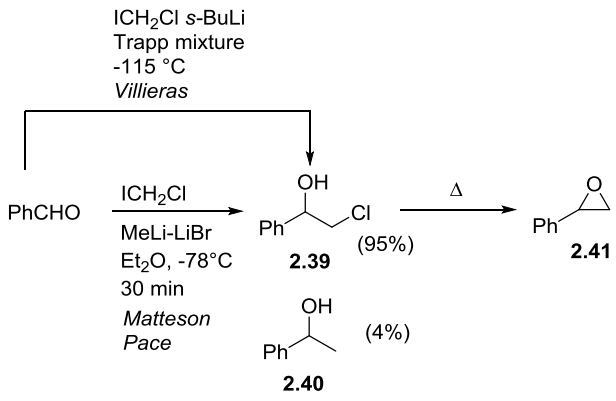
2.1.4 Generation of Monohalolithium carbenoids

As mentioned before there is a substantial agreement in the literature regarding the proper formation and utilization of monohalolithium carbenoids.[14d,33] The requirement for Barbier-type conditions is considered the method of choice to carry out reactions involving these species in order to minimize the activation of degradation pathways. Effectively, the formation of lithium

carbenoids may be regarded as a classical organolithium reagents' formation:[34] the most common methods employed to prepare these species are equally efficient for the preparation of carbenoids. It is widely accepted classifying them in the following categories: a) lithiation *via* lithium-halogen exchange; b) lithiation *via* lithium-hydrogen exchange (*i.e.* deprotonation); c) lithiation *via* lithium-sulfoxide exchange; d) lithiation *via* lithium-tin exchange.

2.1.4.1 Lithiation *via* Lithium-Halogen Exchange

In the literature there is a large predominance of preparative methods through a lithium-halogen exchange because of the easy operational details required and the widely availability of the dihalomethane precursors (almost all purchasable from standard chemical suppliers).[34a] In initial studies by Villieras, *s*-BuLi[24] was employed to accomplish the exchange reaction in the so-called Trapp mixture (THF–Et_2O– *n*-pentane, 75:15:10 v/v)[35] at -115 °C. However this lithium base, as showed in more recent studies, is the choice for performing deprotonations rather than exchange reactions[36] and thus, MeLi and *n*-BuLi have emerged as the optimal lithium sources.[29b] In recent years the commercially available MeLi-LiBr complex in Et_2O has become the first choice as indicated by Pace and coworkers in a series of studies aimed at definitely ascertain the correct use of monohalolithium carbenoids in synthesis (Scheme 2.11).[37]



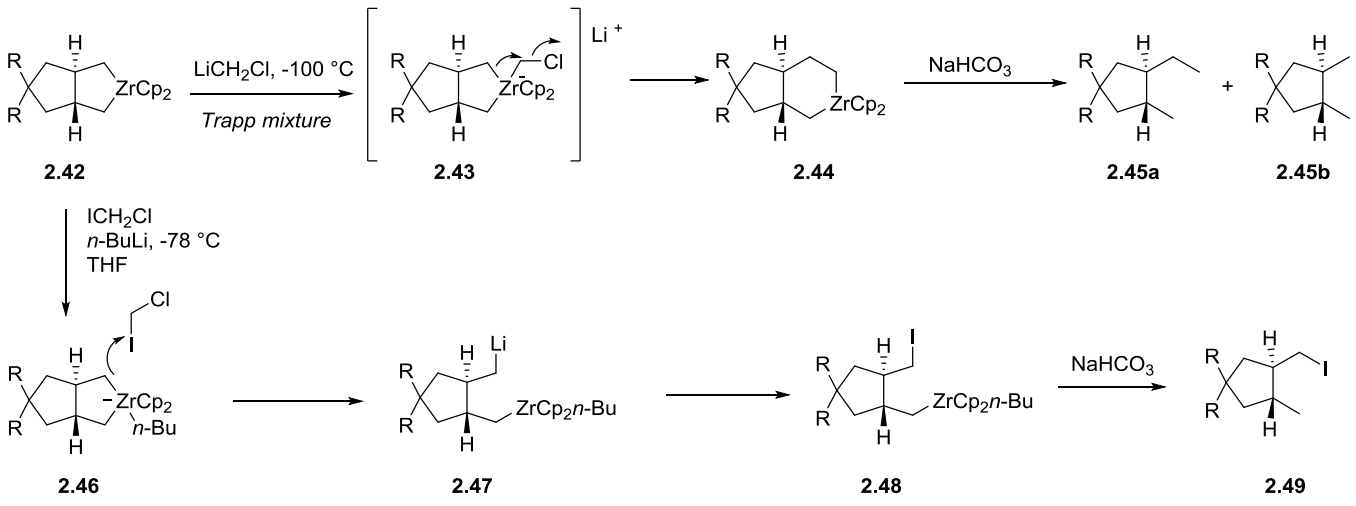
Scheme 2.11: Lithium-iodine exchange in the present of different alkyllithiums.

In agreement with previous work by Matteson,[28a] Pace showed that the presence of lithium bromide[38] not only stabilizes the carbenoid through the above seen coordinative effect but, also eliminates the competing attack of MeLi to a given electrophilic substrate present in the reaction medium under Barbier conditions.[37a,37c,39] The overall procedure can be considered as *in situ* generation of the carbenoid, followed by the immediate capture by the electrophile present therein. Moreover, lithium bromide exerts a mild Lewis acid effect through the coordination to oxygen's carbonyl lone pairs thus, facilitating the attack of the formed carbenoid to the electrophilic partner. The nature of the 1,1-dihalomethane selected as carbenoid precursor plays a critical role to maximize the effectiveness of a process. Because of the easier exchange carried out on a iodo-containing halomethane,[34a] it is not surprising that iodochloromethane is the first option to be considered. However, as it will be shown there is still a big interest (mainly at industrial level) to replace it with the cheaper bromochloromethane.[40] A final consideration concerning the stoichiometric ratio between dihalomethane and organolithiums reagent: in principle, the exchange reaction proceeds quantitatively so, a ratio of 1:1 may suffice for the synthetic purpose. However, considering the residual possibility of competing attack of the alkyllithium to the electrophile and/or variations of its title, it is wise to employ a small excess (0.2-0.4 equiv) of dihalomethane. With this practical shrewdness both side processes maybe advantageously avoided.[18]

Given the exceptional instability of lithium carbenoids, which means in other words, that it is simply destroyed immediately after its formation, it is recommended to add the alkyllithium species to the cooled solution containing the electrophile and the dihalomethane very slowly (*e.g.* within 10-30 min). In this way the operator can be sure of the proper generation and reaction of the sensitive halolithium.

An important exception to the generation of chloromethyllithium under Barbier-type conditions has been described by Whitby in 2004 (Scheme 2.12).[41] During the study on the

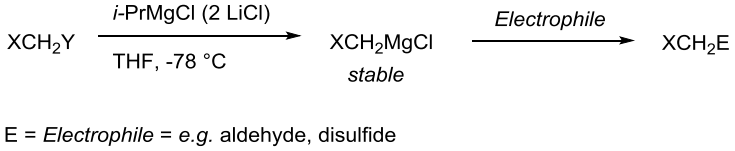
insertion of a methylene carbenoid into the 5-membered zyrconacycle **2.42**, he expected the formation of the enlarged structure **2.44**. However, through the use of a Barbier protocol the highly nucleophilic *n*-BuLi attacked the zirconium centre to form the zirconate complex **2.46**, which undergoes iodine-metal exchange with ICH_2Cl, either directly, or *via* the lithiated species **2.47**. This assumption is also based on previous work by Negishi who reported a similar ring opening of zirconacyclopentanes with alkyllithium reagents.[42] However, the fate of $LiCH_2Cl$ remains unclear though the insertion into the Zr-*n*-Bu bond is plausible. To overcome this drawback, Whitby generated the carbenoid from ICH_2Cl and *n*-BuLi in the Trapp mixture at -100 °C.[41] To this medium was cannulated the cold solution (-78 °C) of the zyrconacycle **2.42** and the homologation could be performed in the desired way. The Whitby's procedure is probably one of the few examples from the recent literature which claims that the lithium carbenoid can be generated prior to its trapping with an electrophile.[43]



Scheme 2.12: Whitby's homologation of zirconacycles under non-Barbier conditions.

It is important noting that the analogous magnesium-iodine exchange carried out on chloroiodomethane represents a method to prepare magnesium halocarbenoids.[44] Knochel, Marek

and coworkers reported the preparation of functionalized carbenoids starting from iodomethanes and *i*-PrMgCl in a mixture of THF and NBP (*N*-butylpyrrolidone).[45] Because of their higher stability compared to lithium counterparts, they can be safely generated at -78 °C and, the electrophile is added at a later stage of the reaction. Notably, the procedure has been extended by Clososki to the preparation of the carbenoid $ClCH_2MgCl{\cdot}LiCl$ (*via* magnesium-iodine exchange on ICH_2Cl with *i*-PrMgCl·LiCl).[46] In Clososki's work it is reaffirmed the needing to prepare the carbenoid prior to the electrophilic trapping, since under Barbier-type conditions reaction proceeds with low conversion (Scheme 2.13).



Scheme 2.13: Generation of magnesium carbenoids *via* magnesium-iodine exchange under non-Barbier conditions.

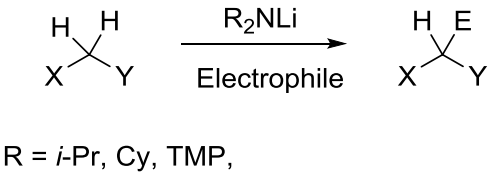
At first sight, one may conclude that magnesium carbenoids are highly effective alternative to instable lithium ones. This conclusion is certainly true if an exceptional electrophile is used as the trapping reagent (*e.g.* aldehyde): however, as shown very recently by Pace and coworkers, less nucleophilic magnesium carbenoids do not react with weaker electrophiles such as Weinreb amides for which it becomes mandatory to use lithium carbenoids in homologation processes.[37a]

The lithium-halogen exchange maybe realized also by metalation with lithium metal as shown above in the seminal work of Cainelli.[47] Subsequently, Luche demonstrated the better performance of the lithiation with Li shot when sonication (60 W energy) was applied.[48] The following aspects should be highlighted: *i*) the instable chloromethyllithium is generated at unusual high temperatures (-15 °C in the case of ketones and -50 °C in the case of aldehydes); *ii*) the exact role of sonication in this Barbier-type reaction is unclear as observed more recently by Beaulieu.[30]

In fact, sound-induced cavitation is known to increase surface areas through pitting and to remove oxide layers from metal surfaces. Additionally, the effects of sonication such as localized high pressures and temperatures may aid in surmounting energy barriers in chemical processes. However, Beaulieu's comparative study between generating chloromethyllithium (from $BrCH_2Cl$ and Li shot) under mechanical stirring or sonochemical conditions revealed their substantial analogy and thus, there is no apparent advantage of employing the latter protocol.[30]

2.1.4.2 Lithiation *via* Lithium-Hydrogen Exchange

Due to the excellent performance of the lithium-halogen exchange and the rapidity that characterizes the process, the deprotonation has not been applied for the generation of monohalolithium carbenoids. This is because also the very basic *s*-BuLi at very low temperature -115 °C in the Trapp mixture carries out the exchange of the halogen rather than a deprotonation on a dihalomethane, as reported by Villieras.[24] The deprotonation turns into the preferred method to generate dihalomethylcarbenoids (*e.g.* $LiCHCl_2$, $LiCHBr_2$ and $LiCHI_2$) from the corresponding dihalomethanes whose proton can be conveniently abstracted by treatment with a lithium amide base such as LDA, $LNCy_2$, LTMP or LiHDMS (Scheme 2.14).



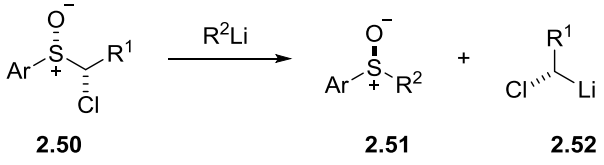
Scheme 2.14: Lithiation via lithium-hydrogen exchange.

Since seminal studies by Nozaki *et al.*, it is preferable to perform the reaction under Barbier-type conditions;[49] however, it is not a strict requirement as very recently observed by Bull in the case of $LiCHI_2$ which could be easily formed prior to the reaction with the electrophile.[50]

Deprotonation can also be used to form trichloromethyllithium from chloroform and *n*-BuLi at -100 °C as reported by Molinski:[43] the presence of three chlorine atoms in this carbenoid makes it a soft nucleophile that, singularly, can react in a Michael fashion with an unsaturated sultam. The overall procedure allows to prepare it at -100 °C prior to capture with the electrophilic partner. In general the nature of the base amide does not affect dramatically the chemocontrol of the reaction, except in the case of isocyanates, which as will be discussed in this dissertation tend to react with less sterically hindered lithium bases (*e.g.* LDA, $LNCy_2$).

2.1.4.3 Lithiation Via Lithium-Sulfoxide Exchange

As an useful alternative to the metal-halogen exchange, Hoffmann reported that magnesium carbenoids can be generated through magnesium-sulfoxide interconversion.[51] Thus, treatment of a sulfoxide with a Grignard reagent (usually *i*-PrMgCl) results in the formation of a magnesium carbenoid instantaneously even at -80 °C. Such species is found to be stable at lower than -60 °C for over 30 min. Remarkably, they also present configurational stability which renders them particularly attractive for asymmetric synthesis.[44,52] In 2006 Blackemore and coworkers reported that also lithium carbenoids **2.52** can be generated in an analogous manner from a given halogenated arylsulfoxide **2.50** (Scheme 2.15).[53]

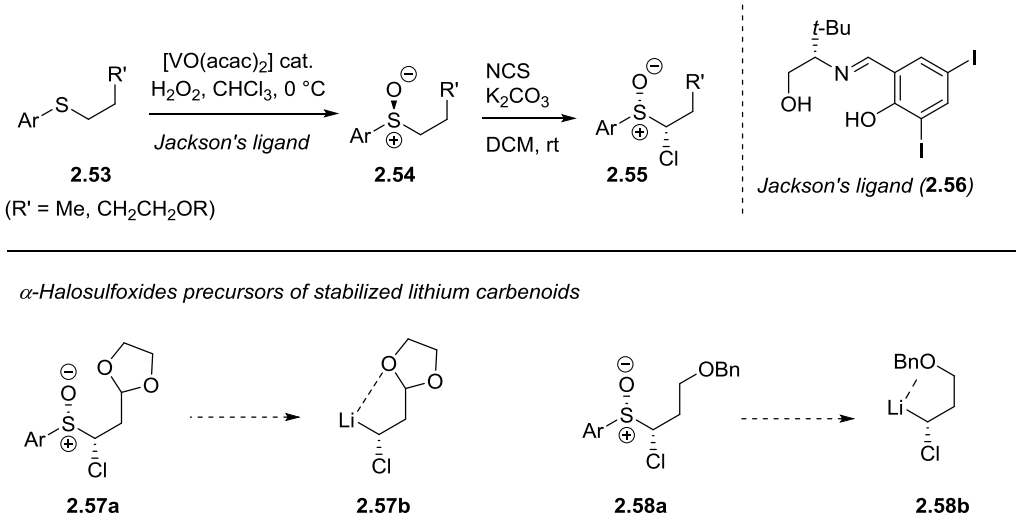


2.50 **2.51** **2.52**

Scheme 2.15: Lithium carbenoids from halogenated arylsulfoxide.

Key feature of the method are: a) the aryl group (typically *p*-tolyl) remains attached to the sulfoxide, while the R^2 group from the organolithium reagent replaces the non-aromatic group on

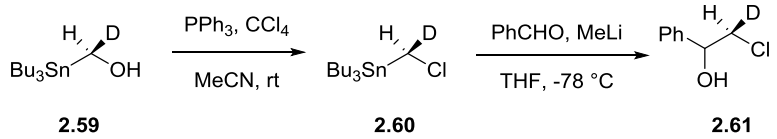
the sulfoxide R^1 (**2.51**); b) the process takes place with inversion of stereochemistry at sulfur. However, the stereofidelity is highly dependent on the particular carbenoid generated and, unfortunately cannot be predicted rationally. Compared to dihalomethanes which are almost all commercially available, α-halosulfoxides need to be prepared. They are readily accessible from thioethers[53a] **2.53** by a two-step sequence of asymmetric sulfoxidation followed by halogenations (Scheme 2.16). The crucial step for their synthesis is represented by the asymmetric sulfide-sulfoxide oxidation:[54] a valuable solution is the vanadium-catalyzed Ellman-Bolm[55] enantioselective oxidation in the presence of Jackson's *tert*-leucinol derived ligand (**2.56**).[56] The desired optically pure sulfoxide (up to 99:1 *er*) can be simply obtained after successive recrystallizations.[53a,53b] Then, Yamakawa's asymmetric chlorination under heterogeneous conditions[57] affords the chlorinated sulfoxide **2.55** with stereochemical inversion at sulfur. The lithiation step can be conducted either with *t*-BuLi in toluene and PhLi in THF. Importantly, Blackemore designed complex functionalized enantioenriched carbenoids which can be stabilized by internal coordination of lithium with Lewis basic sites such as ethers or acetals.



Scheme 2.16: Blakemore's synthesis of chiral halosulfoxides precursors of optically active lithium carbenoids.

2.1.4.4 Lithiation *via* Lithium-Tin Exchange

In 2008 Hammerschmidt and coworkers reported an effective synthesis of configurationally stable chloromethyllithiums generated upon treatment of a chiral stannane **2.60** with MeLi.[58] The enantiopure chloromethylstannane-[D_1] had to be synthesized as a precursor from homochiral tributylstannyl-[D_1]-methanol **2.59** (Scheme 2.17). This was first performed with the unlabeled compound to evaluate the feasibility of the approach and to optimize the conditions and yields. Transformation of tributylstannylmethanol into the corresponding chloride **2.60** worked cleanly with under Appel conditions[59] including in the case of enantiopure labeled material. It is important to note that this procedure is highly sensitive to the nature of the alkyllithium employed. In fact, MeLi gives highly satisfactory results in the tin-lithium exchange compared to *n*-BuLi which provides less clean reactions with considerable formation of undesired impurities. A possible reason of the success of MeLi is its lower basicity compared to *n*-BuLi. Hammerschmidt's work is a milestone in chiral organolithiums species since for the first time could be ascertained both the microscopic (configurational) and macroscopic stability of a halocarbenoid. By realizing the tin-lithium exchange at -95 °C he could observe preservation of the chiral information contained in the carbenoid. More importantly, when reaction was performed at -78 °C by adding the electrophile (benzaldehyde) after 30 s, the chemical stability of the carbenoid was diminished but still the chiral information was retained. This fact indicates that the chiral carbenoid at -78 °C decomposes rather than racemizes.



2.59 **2.60** **2.61**

Scheme 2.17: Hammerschmidt's preparation of chiral chloromethyllithium *via* tin-lithium exchange.

Later on, the same group demonstrated an analogous outcome for reactions involving chiral iodomethyllithium and fluoromethyllithium.[60] In this latter study, $LiCH_2F$ could be used for

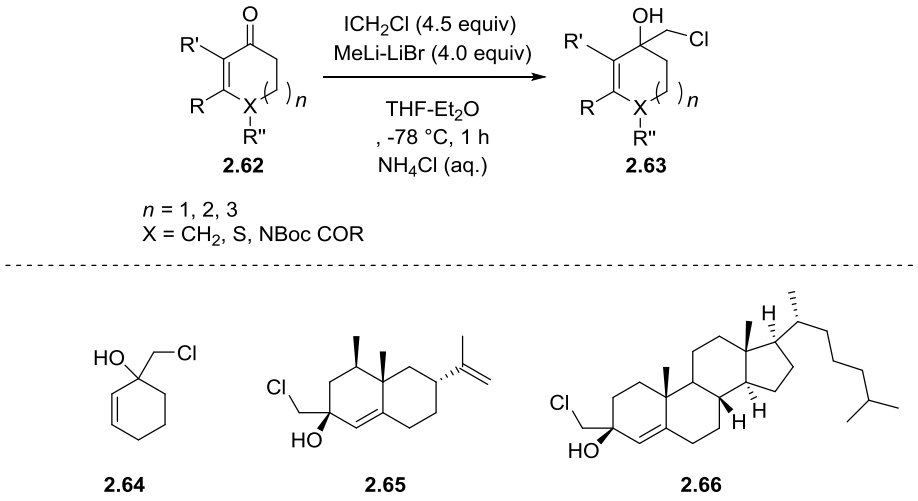
synthetic purposes for the first time. However, its highly chemical instability accounted for requiring temperatures below –95 °C: even at this cryogenic temperature chemical yields were only moderate. It should be underlined the configurationally stability of this carbenoid in a wide range of temperatures ranging from -95 °C to 0 °C: *i.e.* although it is very labile, it is completely configurationally stable.

2.1.5 Electrophilic Partners for Carbenoids

2.1.5.1 Carbonyls Adducts

As noted in the previous paragraph concerning the formation of carbenoid reagents, carbonyl compounds have been extensively employed as electrophilic counterparts for reactions involving carbenoid species. As independently shown by Cainelli,[21,47] Villieras[24] and Matteson[28] in seminal studies and later confirmed by others such as Barluenga,[29b] Concellón[31] or Lautens,[61] the addition of an halomethyllithium to an aldehyde or a ketone produces an isolable halohydrin, that in turn can be transformed into an epoxyde by ring-closure through the simple increase of temperature (to rt) or through a base assisted process. The scope of the method is broad and can be applied even to challenging substrates such as unsaturated cyclic ketones as very recently noted by Pace and coworkers (Scheme 2.18).[39] In Pace's work, chloromethyllithium carbenoid has been chemoselectively added to cyclic enones **2.62** (5, 6 and 7-membered systems) to access chloromethyl allylic alcohols. Under the optimized reaction conditions neither concomitant ($n+1$) homologation nor conjugate addition or Simons-Smith-like cyclopropanation[17] takes place. The presence of LiBr is estimated to have a dual role, namely as a carbenoid stabilizer and mild Lewis acid activator of the C=O group. The addition of the carbenoid to complex cyclic enones isolated in natural products proceeds with excellent diastereoseletivity. It is worth mentioning the prominent

role played by the heteroatom present at the β-position of the cyclic enone since its mesomeric effect determines the exact position to which the reagent attacks the backbone.

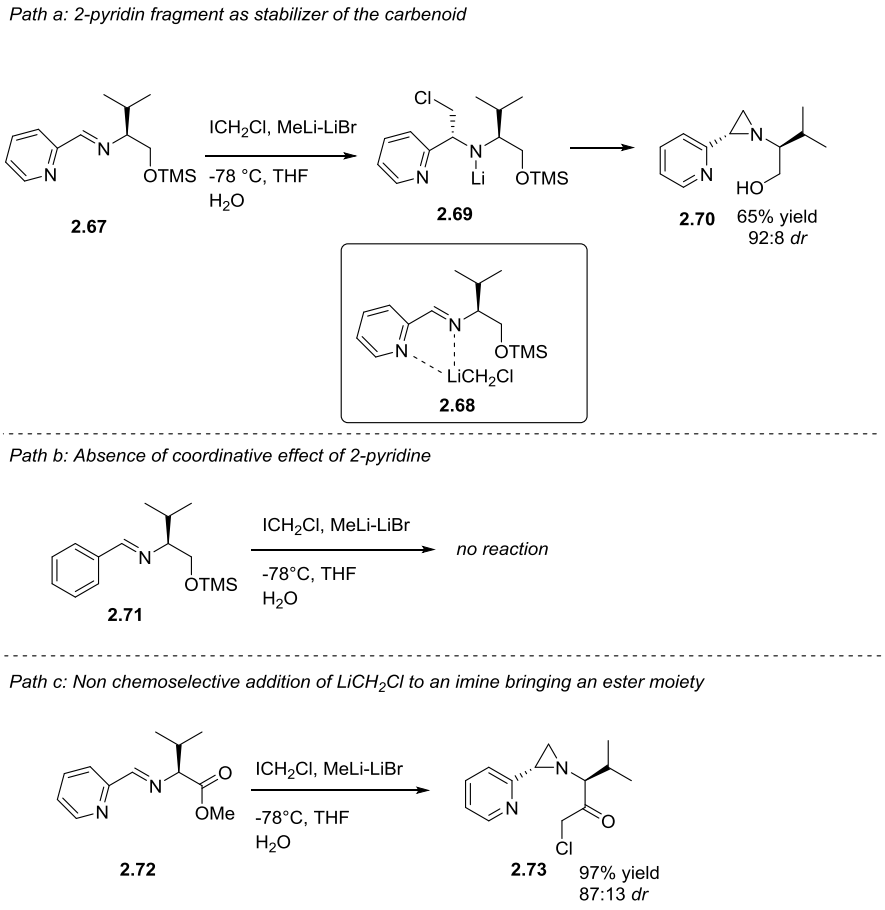


Scheme 2.18: Pace's addition of chloromethyllithium to cyclic enones.

2.1.5.2 Imines

In 2006 Savoia and coworkers described the addition of chloromethyllithium to the imine **2.67** derived from 2-pyridinecarboxaldehyde and (*S*)-valinol to reach upon raising of temperature aziridine compound **2.70** (Scheme 2.19).[62] Excellent yield and high stereocontrol (*dr* 92:8) were achieved by using an excess of carbenoid. $LiCH_2Cl$ resulted the optimal reagent for the homologation compared to unreactive organometallics (*i.e.* less nucleophilic zinc carbenoids, $ClCH_2ZnEt$), or compounds which addition resulted in complex mixtures ($LiCH_2I$). The main requisite for the successful aziridination is the presence of a 2-pyridinimine fragment which chelates the formed carbenoid and enhances its nucleophilic behavior thus, enabling the attack to the poor electrophilic azomethinic carbon (*path a*). Authors remark that in the absence of the coordinative nitrogen of the pyridine at the 2-position no reactivity is observed (*path b*). By raising temperature up to 20 °C a spontaneous ring-closure takes place with formation of the desired

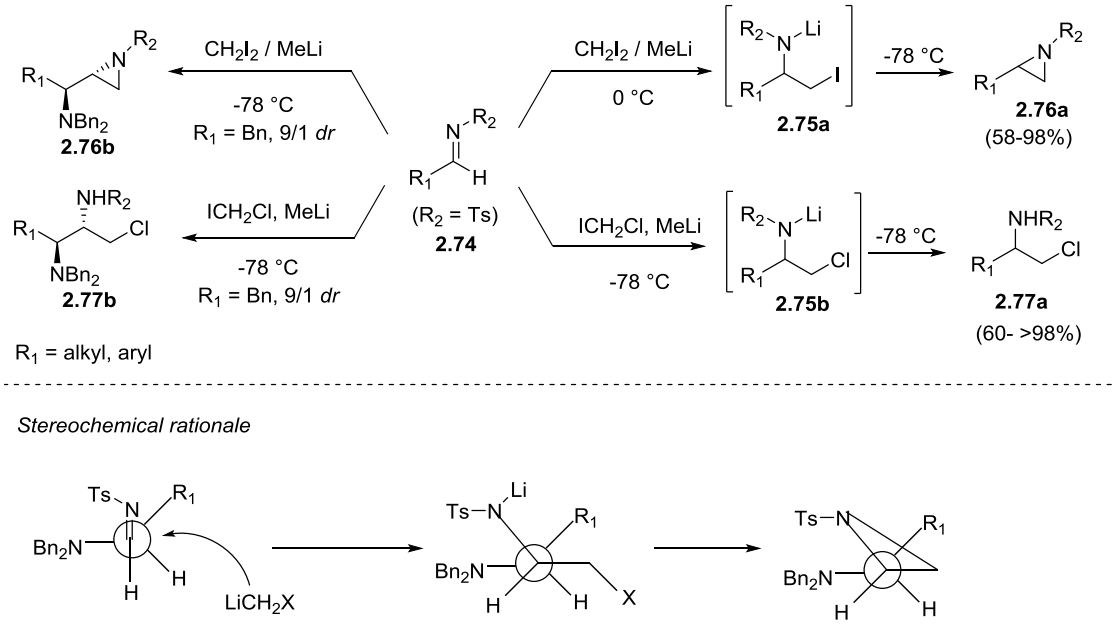
aziridine. Additional critical points of the procedures are: a) highly sterically hindered substituents on the imine nitrogen inhibits the reaction; b) chemocontrol is particularly difficult in imines bringing additional electrophilic sites. In fact, in the presence of an ester moiety (**2.72**) it is not possible to chemoselectively obtain the addition on the imine but, rather addition occurs to both carbonyl-type moieties giving **2.73** (*path c*).



Scheme 2.19: Savoia's carbenoid-mediated 2-aziridination of 2-pyridinimines.

Subsequently, Concellón and coworkers in 2008 reported the addition of iodomethyllithium to sulfonyl-protected imines (Scheme 2.20).[63] In this study it is demonstrated that the protecting group enhances the electrophilicity of the azomethinic carbon through an electron-withdrawing

effect. Although chloromethyllithium can also be successfully added, reactions are slightly less efficient: these Authors remark the possibility to generate iodomethyllithium from diiodomethane and MeLi at 0 °C. The procedure is particularly attractive since *N*-tosylaziridines **2.76a-b** are prepared in short reaction times in a single experimental operation. One may argue that removal of tosyl-type protecting groups requires harsh conditions (*e.g.* Li-naphthalenide, see chapter 1). Nowadays removal of analogous groups maybe conveniently achieved under milder conditions with SmI_2 as recently reported by Procter.[64]



Scheme 2.20: Divergent access to aziridines or β-chloroamines by Concellón.

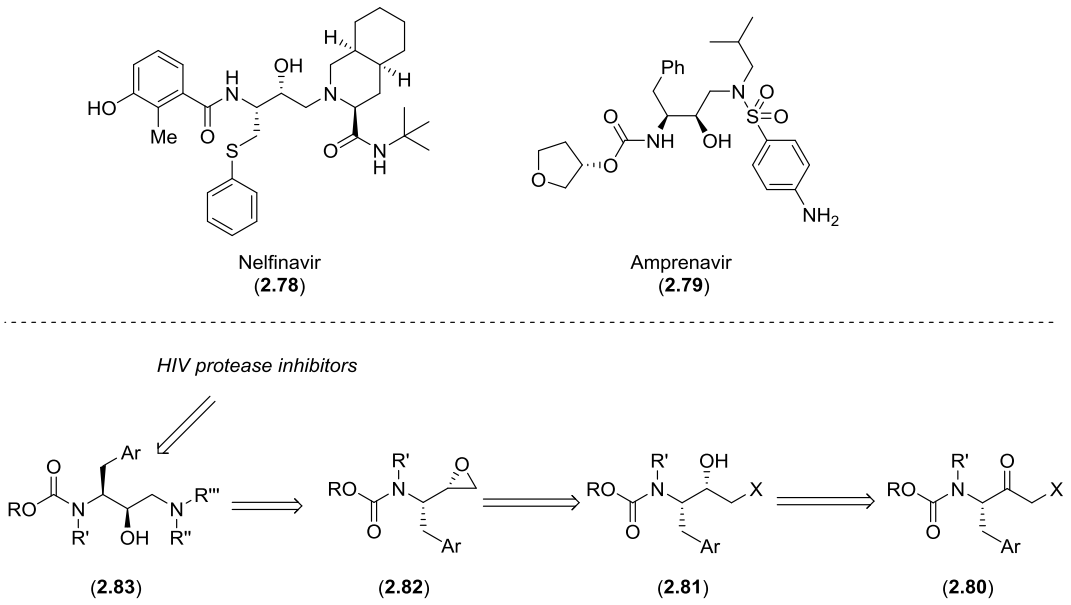
Further work followed by the same laboratories showed that the addition of chloromethyllithium to *N*-sulfonyl protected imines affords β-chloroamines **2.77a-b** upon simple acidic work-up.[65] Evidently, the possibility to isolate and thus, to impede the cyclization step to the aziridine, complements the synthetic strategy. The divergent synthesis of aziridines with $LiCH_2I$ and of β-chloroamines with $LiCH_2Cl$ found its rationale by assuming an addition process of the carbenoids to the imine forming an iodated or chlorinated lithium amide. The so obtained iodo-

(**2.75a**) intermediate undergoes a spontaneous heterocyclization to give the corresponding aziridines **2.76a**; in contrast, no ring-closure is noticed in the case of the chloro lithiated intermediate **2.75b** at -78 °C and, the corresponding β-chloroamine **2.77a** is produced. Notably, the bulky dibenzylamino group on the nitrogen's imine deeply influences the stereochemical outcome of the whole addition. Assuming that the addition mode of the carbenoid happens under nonchelation control, the energetically more favored transition state has the larger substituent (*i.e.* dibenzylamino group) *anti* to the attack of the halomethyllithium.

2.1.5.3 Esters, Weinreb Amides and Isocyanates

α-haloketones are privileged prochiral building blocks in synthetic medicinal chemistry for the preparation of HIV protease inhibitors (*e.g.* Nelfinavir (**2.78**), amprenavir (**2.79**)] (Scheme 2.21). [40b,66] In fact, the enantioselective reduction of the carbonyl of haloketone **2.80** leads to the homochiral aminohalohydrin **2.81,**[67] which is the direct precursor of the enantiopure epoxide **2.82**. This oxirane, may be opened by an amine nucleophile, thus providing the 1,3-diaminopropan-2-ol fragment **2.83**, that represents the common feature of such class of inhibitors (Scheme 2.21)[9,40a,68].

The particular route: ketone reduction - ring closure - epoxide opening deserves some comments: although in principle, the nucleophilic displacement may be carried out on the aminohalohydrin (**2.81**), it is preferred the reaction on the epoxide for two main reasons: a) the reactivity of the latter is evidently enhanced compared to the former as a consequence of the ring-strain b) epoxides are easily chemoselectively obtained by base-promoted cyclization of the aminohalohydrin[69].

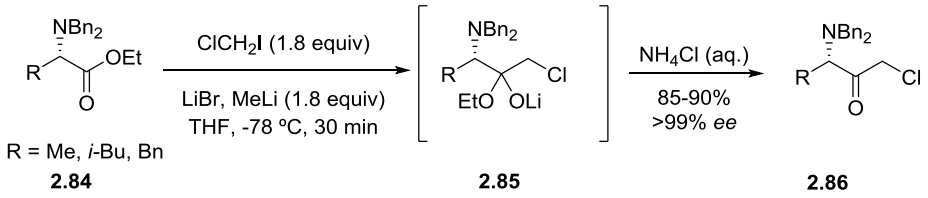


Scheme 2.21: Examples and retrosynthesis of HIV protease inhibitors starting from α-amino-α'-halomethylketones.

Extensive surveys on the synthesis and pharmaceutical employment of such compounds as HIV protease inhibitors have been recently published.[40b,66b] However, to understand in depth the importance of carbenoids in halomethylketones chemistry, a brief overview of the synthesis of these compounds is given. This is also to demonstrate the effectiveness of carbenoid chemistry in medicinal chemistry processes: the possibility to install in a single synthetic operation a functionalized carbon atom ("CH_2X" unit) is undoubtedly what renders this chemistry fascinating and, though obvious limitations such as thermal instability of the species must be taken into account, the advantages it offers compared to procedures involving non easily controlled halogenations, are by far numerous.

Barluenga pioneered in early 1990s the homologation of esters **2.84** to access α-haloketones **2.86** by means of addition of carbenoids at -78 °C formed under classical Barbier-type conditions (Scheme 2.22).[29b,29c] The reaction is highly innovative since it allows to realize a *single* addition of the nucleophilic carbenoid to esters, a class of electrophiles that usually reacts with organometallics to give carbinols *via* the double addition of the nucleophile used.[29b,29c] According to Barluenga the

tetrahedral intermediate **2.85** is stable under the reaction conditions and thus, it does not permit the double addition of the organometallic species, even when they are used in excess. The explanation provided for this non common stability of a tetrahedral intermediate[70] is the presence of the electronegative halogen and oxygen substituents that thwarted the elimination of the alkoxyde group. As observed in the case of the addition to imines,[63,65] the addition of $LiCH_2Cl$ proceeds under non-chelation control.



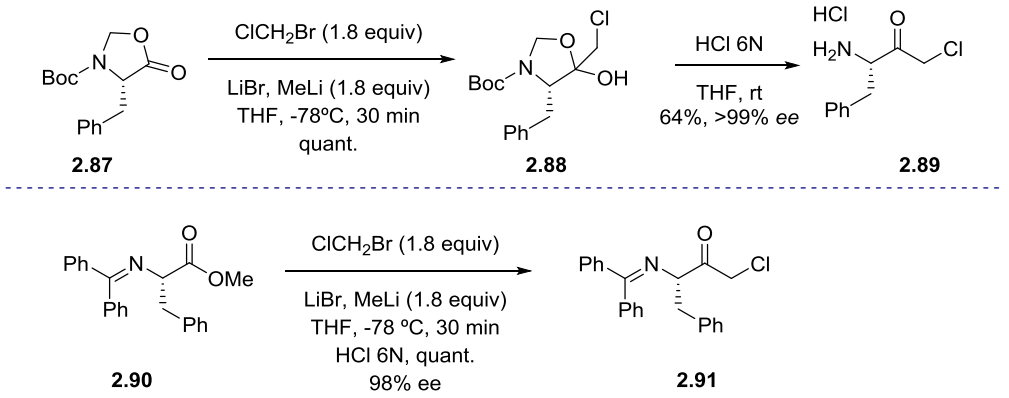
R = Me, *i*-Bu, Bn

2.84 **2.85** **2.86**

Scheme 2.22: Barluenga's homologation of esters to α-haloketones.

Further insights into the homologation of esters to α-haloketones came from chemists operating at Ajinomoto Co. leaded by K. Izawa.[71] The industrial team demonstrated that the process cannot occur in the presence of amino or amido groups whose nitrogen bears an hydrogen atom: evidently, the carbenoid abstracts this acidic proton rather than attacking the electrophile such as an ester. To overcome this drawback the Japanese team introduced the employment of *N*-protected 3-oxazolidin-5-ones **2.87** which can be easily chloromethylated to afford the intermediate **2.88**, which in turn can be transformed into the desired chloroketone **2.89** upon acidic treatment (Scheme 2.23). In agreement with Barluenga's study,[29b,29c] the reaction proceeded with full preservation of the optical purity. Analogous problems associated with homologation of esters with carbenoids have also been observed by Hilpert who proposed the temporary protection of a (secondary) amide moiety with the trimethylsilyl (TMS) group prior to homologation.[72] Izawa's group also reported the chemoselective chloromethylation of *N*-imine protected amino acids esters **2.90**:[71b] at first sight, it seems to be not in full agreement with Savoia's work who noticed a difficult control of the

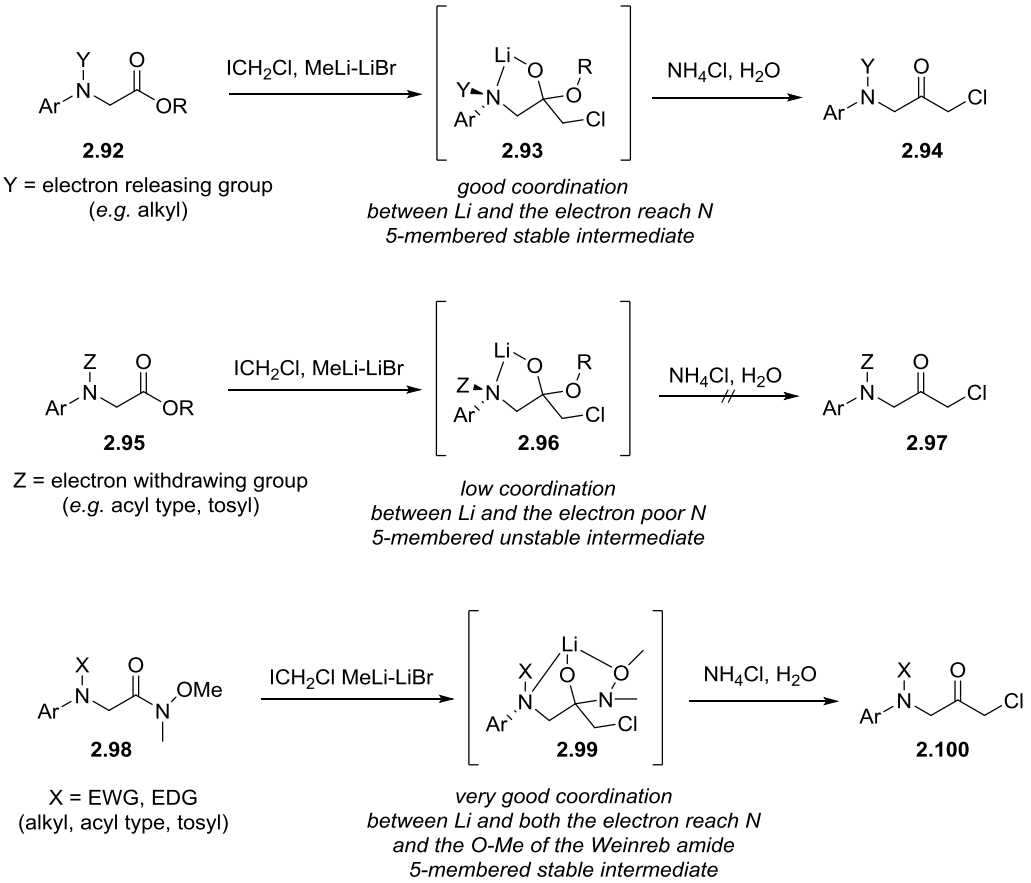
addition of carbenoids to imino esters.[62] However, imine **2.90** used by Izawa is derived from acetophenone and, as a consequence its pronounced bulkiness accounts for thwarting the addition to the azomethinic position.



Scheme 2.23: Izawa's homologation of lactones and imino-esters to access α-amino-α'-chloroketones.

Almost ten years later, Pace and coworkers[37c] revisited the homologation of carboxylic acid derivatives during studies focused at preparing particular aminoketones such as α-arylamino-α'-chloroacetones. In a comparative study between esters and Weinreb amides[73] used as placeholders for the homologation, the stabilization of the putative tetrahedral intermediate generated through the addition of the carbenoid has been postulated to constitute the main factor governing the process (Scheme 2.24). This conclusion arises from the different behavior that *N*-arylamino acetic acid derivatives shows in the reaction: based on the experimental evidence that in the case of an ester the homologation is possible exclusively in the case of the presence of an additional EDG on the nitrogen, these researchers focused their attention on the factors governing the stability of the tetrahedral adducts. When an EDG is present, the intermediate **2.93** can be sufficiently stabilized by the relatively basic nitrogen and thus, the reaction proceeds. However, when the basicity of the nitrogen is diminished by the presence of an EWG the intermediate **2.96** is not stabilized and thus, the transformation does not take place.

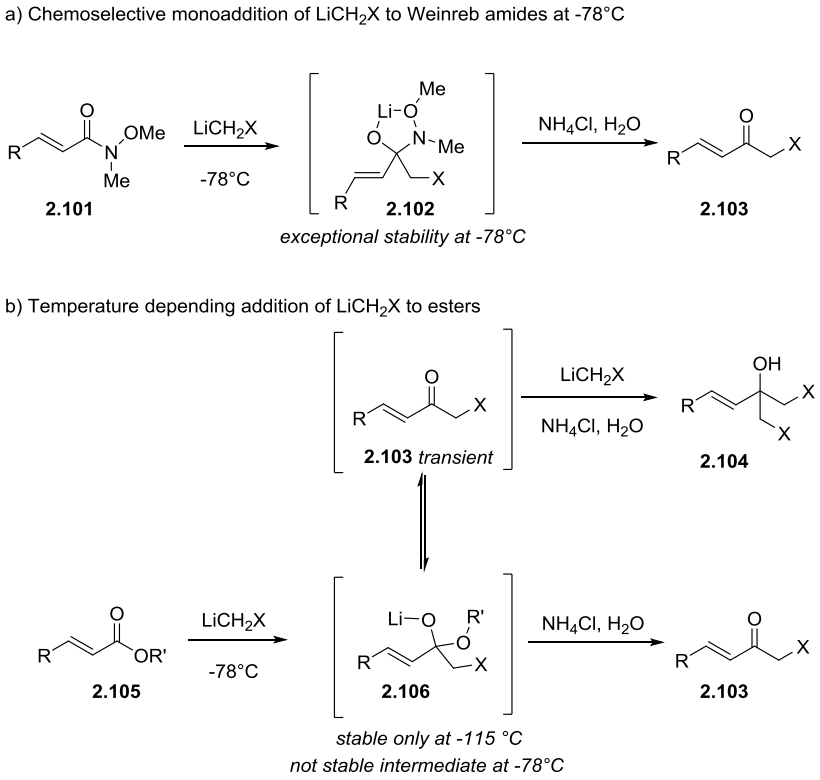
However, if the transformation is carried out on a particular class of substrates like the corresponding *N*-methoxy-*N*-methyl amides, the transformation takes place regardless the nature of the substituent on the nitrogen. This result derives from the exceptional stability of the chelated 5-membered tetrahedral intermediate **2.99** originated from the addition of organometallics reagents to them. In the particular case of α-amino Weinreb amides discussed by Pace, the additional presence of this fragment is responsible for the success of the transformation: in fact, the basicity of the nitrogen becomes non critical for the stability of the intermediate, which *perse* is chelated with the methoxy group of the Weinreb amide.



Scheme 2.24: Pace's mechanistic explanation of the different behaviour of esters and Weinreb amides towards lithium carbenoid-mediated homologation.

This explanation is also in agreement with chemistry developed in Barluenga's laboratories[29b,29c] reporting the addition-elimination pathway for *N,N*-dibenzyl protected esters (seen above – Scheme 2.22), which evidently are electron-donating functionalities.

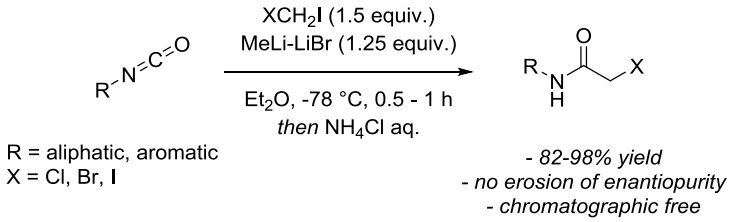
Pace also demonstrated the performance of Weinreb amides in homologation of α,β-unsaturated substrates (**2.101**) which underwent double addition when reactions were carried out on esters.[37a] To rationalize the chemoselectivity, they assumed the exceptional stability at -78 °C of the intermediate **2.102** offered by the *N*-methoxy group of the Weinreb amide, which evidently hinders a second addition of $LiCH_2X$ (Scheme 2.25, *path a*). As a consequence of the high stability of intermediate **2.102**, the desired α-haloketone **2.103** is formed only after acidic hydrolysis. By contrast, the addition of the carbenoid to an ester **2.105** results in the formation of a tetrahedral intermediate **2.106** (not stable at -78 °C), which is in equilibrium with the transient α-haloketone **2.103**, the latter more susceptible to a second attack of the carbenoid (compared to the starting ester), and thus providing the carbinol **2.104** (Scheme 2.25, *path b*). This explanation is in line with the finding that by running the halomethylation of esters at -115 °C, the major product is the α-haloketone. Thus, it is conceivable that the tetrahedral intermediate **2.106** formed through mono addition to an ester, is only stable (thus, thwarting the second addition) at that very low temperature, but not at -78 °C.



Scheme 2.25: Temperature-based mechanistic explanation of the different behavior towards halomethylithium reagents of Weinreb amides (*path a*) and esters (*path b*).

The importance of Weinreb amides as placeholders for the addition of functionalized organometallics such as the carbenoid cyanomethyllithium will be presented in this doctoral thesis.

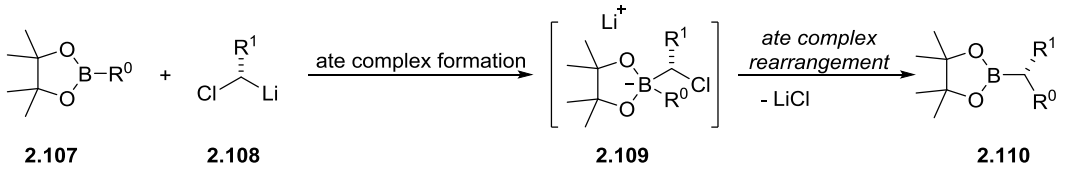
The portfolio of electrophilic partners of carbenoids includes also isocyanates: the same group of Pace in 2013 designed an effective synthesis of α-haloamides through the addition of lithium carbenoids to this class of cumulene-type materials (Scheme 2.26).[37b] The method is high-yielding and usually no purification is required. In the course of this dissertation the results arising from the treatment of isocyanates with dihalocarbenoids will be object of discussion. Furthermore, the preservation of the chiral information contained in optically pure isocyanates will be presented for both dihalo- and monohalocarbenoids.



Scheme 2.26: Homologation of isocyanates to α-haloacetamides

2.1.6 Non-Carbon Electrophiles: the Matteson Homologation of Boronic Esters.

In 1980 Matteson discovered that boronic esters can be homologated with lithium halocarbenoids.[74] As depicted in Scheme 2.27 – the mechanism for the transformation involves the addition of the nucleophile to the electrophilic boron atom of **2.107** to form an *ate* complex **2.109** which by raising of the temperature rearranges into the homologated structures **2.110**. This seminal concept opened the field of modern organoboron chemistry in which outstanding works by Aggarwal[36a,75] and Blackemore[53,76] also demonstrated the non-erosion of chiral information contained in chiral carbenoids.

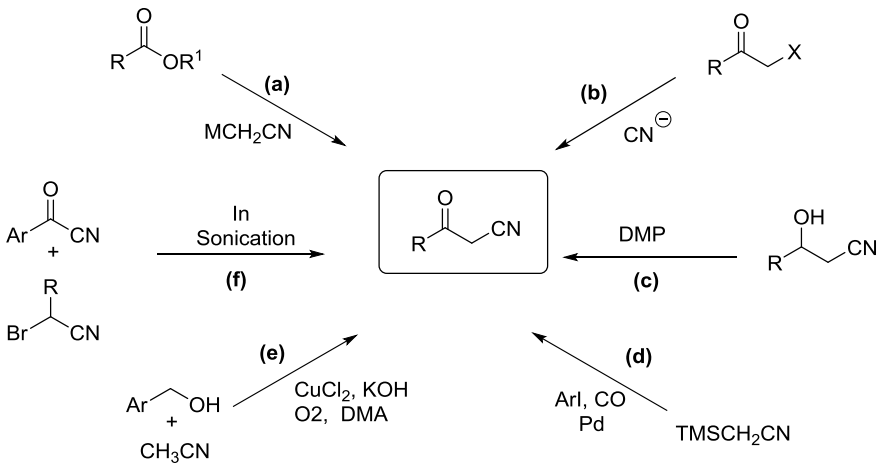


Scheme 2.27: Blakemore's application of Matteson homologation with chiral lithium carbenoids.

2.2 Results and Discussion

2.2.1 Synthesis of β-oxonitriles via the addition of Cyanomethyllithium to Weinreb Amides

β-Oxonitriles, also referred as α-cyanoketones, are valuable synthons in organic synthesis because of the multiple manipulations that both the carbonyl and the nitrile functionalities can undergo.[77] In this sense, they represent useful building blocks for the construction of biologically active heterocycles such as HIV inhibitors[78] or anti-inflammators.[79] Moreover, stereoselective reductions of the ketone moiety would afford enantiopure β-hydroxynitriles[80] that are versatile scaffolds in the synthesis of important drugs such as the antidepressants (*S*)-fluoxetine[81] (Prozac®) and (*S*)-duloxetine[82] (Cymbalta®). Thus, the synthesis of this motif has been object of several studies during the years and a closer examination allows to include them in the following main categories (Scheme 2.28): a) homologation of a given carbonyl precursor (*i.e.* ester) with a metalated cyanomethyl carbanion (MCH_2CN, M = Li, MgHal, K, Na, Sm);[83] b) nucleophilic substitution with the highly toxic cyanide anion on an α-haloketone;[84] c) oxidation of a cyanohydrin;[85] d) Pd-catalysed carbonylation of aryl iodides and $TMSCH_2CN$[86] or unactivated nitriles;[87] e) Cu-catalysed oxidative coupling of aromatic alcohols and CH_3CN;[88] f) In-mediated coupling of bromoacetonitriles with acyl cyanides;[89] g) *C*-arylation of resin-bound cyanoacetates.[90]



Scheme 2.28: Synthetic routes to access β-oxonitriles.

Historically, the homologation strategies have constituted the method of choice because of the conceptually simplicity of the process and the easy availability of the required reagents (a carboxylic acid derivative and CH_3CN). However, this significant advantage compared to other procedures, has been limited severely by the lack of general applicability to sensitive carboxylic esters and by non-uniform efficiency in terms of reaction yields. Recently, Trenkle and co-workers reported that by deprotonating acetonitrile with KO*t*-amyl, reaction yields can be improved, though the scope is rather limited in terms of both esters and substituted acetonitriles:[83c] in particular, disubstituted ones (*i.e* R^1R^2CHCN) have not been employed. Moreover, the higher reactivity displayed in Pd-catalysed carbonylations by aryl iodides compared to aliphatic counterparts renders it applicable only to the synthesis of aromatic α-cyanoketones.[86] An analogous limitation affects the oxidative coupling strategy recently described by Liu and co-workers.[88]

Considering the exceptional nucleophilic properties of metalated nitriles,[91] as highlighted in a series of illuminating works by Fleming and collaborators,[77c,83j,91b,92] we decided to investigate the reaction by considering simultaneously the effects of *i*) the electrophilic carboxylic derivative used for the homologation and *ii*) the nature of the metalated nitrile. Recently our group demonstrated that Weinreb amides,[73,93] due to the stability of the tetrahedral intermediate generated upon reaction with an organometallic reagent, are well-suited placeholders[37a,37c] for reactions involving α-halosubstituted organolithiums reagents (*e.g.* $LiCH_2X$, X = Cl, Br, I).[14a,14c,18,33,34c,37b,39,94] In fact, the simple switching to these easily-prepared substrates allows to maximize reactions' efficiency compared to the corresponding esters or acid halides.

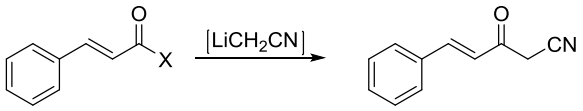
In this part of the dissertation, a versatile, chemoselective, high-yielding access to (α-substituted) α-cyanoketones through the generation of lithiated acetonitriles followed by the trapping with variously functionalized Weinreb amides is presented. We also report previously undisclosed ^{15}N- and ^{17}O-NMR data for selected examples of this class of structures.

Commercially available methyl cinnamate (**2.111a**) was reacted with 4 equiv of $LiCH_2CN$ (generated from CH_3CN (4.5 equiv) and *n*-BuLi (4.0 equiv) giving the desired α'-cyano-α,β-unsaturated ketone **2.112** in 66% yield (Table 2.1, entry 1). Surprisingly, in contrast with our previous findings dealing with halomethylation of Weinreb amides,[37a,37c] we found that lowering the loading of $LiCH_2CN$ to 1.5 equiv, an increase of **2.112** was noticed (Table 2.1, entries 2-3). Moreover, the addition of this lithiated species did not give any corresponding carbinol product (as we observed in the case of $LiCH_2Cl$)[37a] resulting from the double addition to the ester. Further optimization revealed that MeLi-LiBr was the best base to accomplish CH_3CN deprotonation compared to other ones such as simple MeLi, *s*-BuLi, LDA, LTMP, LHDMS or $LiNH_2$ (Table 2.1, entries 4-9). Considering MeLi-LiBr the optimal base for generating the reacting lithiated acetonitrile, we tested the corresponding Weinreb amide **2.111b**: pleasingly, **2.112** could be obtained in an excellent 86% isolated yield after simple washing (brine) work-up thus, without needing to perform chromatographic purification (Table 2.1, entry 10). Increasing the temperature up to 0 °C causes a dramatic decrease of yields and the formation of significant amounts of impurities difficult to remove by chromatography (Table 2.1, entries 11-12). The use of diethyl ether does not affect the reaction at much extent (Table 2.1, entry 13), while performing the process in *tert*-butyl methyl ether (MTBE) or 2-methyltetrahydrofuran (2-MTHF)[95] significantly drops the yields (Table 2.1, entries 14-15).

Based on previous work by Fleming, Knochel and co-workers,[83j,92b] who reported the generation of $LiCH_2CN$ from ICH_2CN and *n*-BuLi *via* iodine-metal exchange for reactions with ketones, we attempted the reaction with **2.111b**. However, the desired cyanoketone **2.112** could only be detected by ^{1}H-NMR analysis of the reaction crude, either generating the anion followed by trapping (after 1 or 5 min, Table 2.1, entries 16-17) with **2.111b** and running reaction in the presence of the same electrophile (Table 2.1, entry 18). These results suggest that the outcome of cyanomethylation reactions may be dependent on the nature of the electrophile[96] and, as such, less

reactive substrates (*i.e.* Weinreb amides compared to aldehydes or ketones previously used[83j,92b]) are not suitable for the purpose.

Table 2.1: Reaction optimization.



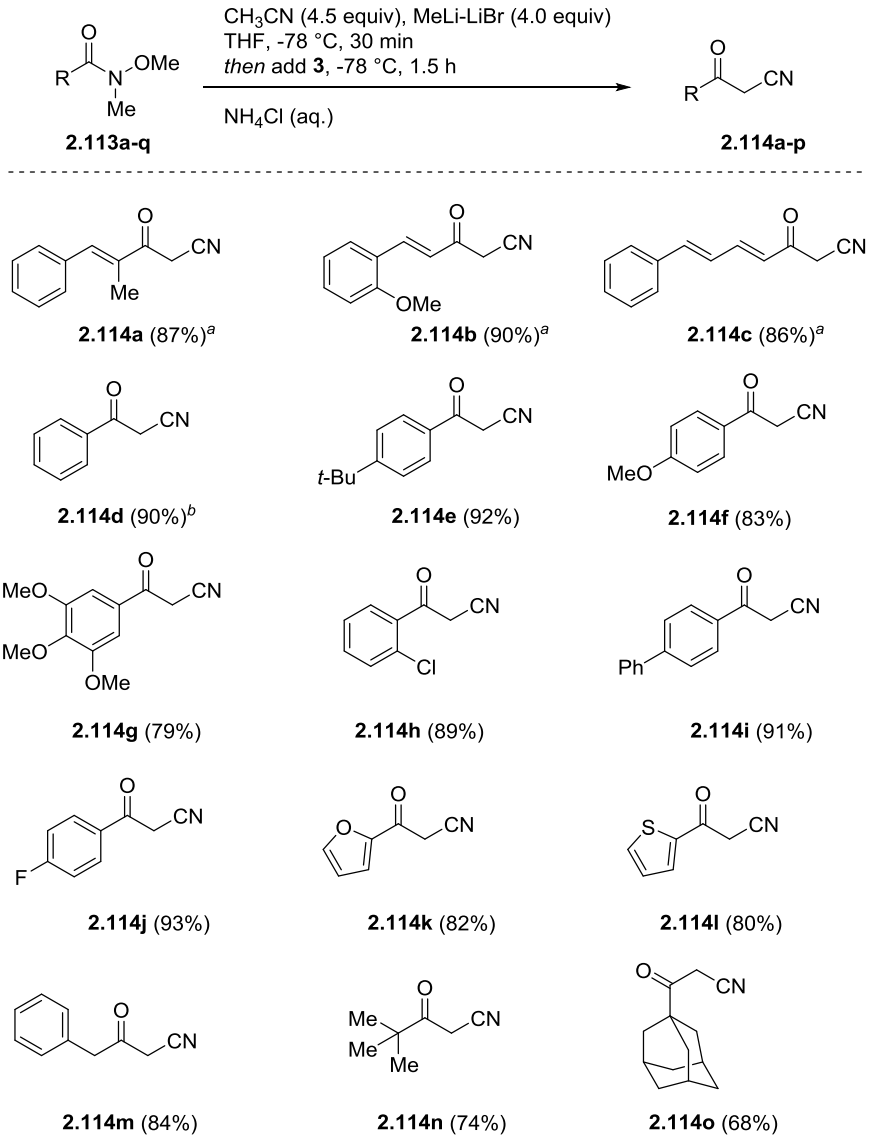
X= OMe (**2.111a**)
X= N(OMe)Me (**2.111b**)

2.112

Entry	Substrate	Metal reagent	[$LiCH_2CN$] equiv	Solvent / Temp. (° C)	Yield of **2.112** (%) [a]
1	**2.111a**	*n*-BuLi	4.0	THF / -78	66
2	**2.111a**	*n*-BuLi	2.0	THF / -78	68
3	**2.111a**	*n*-BuLi	1.5	THF / -78	69
4	**2.111a**	MeLi-LiBr	1.5	THF / -78	71
5	**2.111a**	*s*-BuLi	1.5	THF / -78	62
6	**2.111a**	LDA	1.5	THF / -78	66
7	**2.111a**	LTMP	1.5	THF / -78	61
8	**2.111a**	LHDMS	1.5	THF / -78	66
9	**2.111a**	$LiNH_2$	1.5	THF / -78	47
10	**2.111b**	MeLi-LiBr	1.5	THF / -78	86
11	**2.111b**	MeLi-LiBr	1.5	THF / -40	65
12	**2.111b**	MeLi-LiBr	1.5	THF / 0	44
13	**2.111b**	MeLi-LiBr	1.5	Et_2O / -78	83
14	**2.111b**	MeLi-LiBr	1.5	MTBE / -78	71
15	**2.111b**	MeLi-LiBr	1.5	MTHF / -78	68
16	**2.111b**	*n*-BuLi [b]	1.5	THF / -78	11 [c]
17	**2.111b**	*n*-BuLi [d]	1.5	THF / -78	12 [c]
18	**2.111b**	*n*-BuLi [e]	1.5	THF / -78	7[c]

[a] Isolated yields. [b] **2.111b** was added after 1 min from the end of the addition of *n*-BuLi to ICH_2CN. [c] NMR yields (1,3,5-trimethoxybenzene as internal standard). [d] **2.111b** was added after 5 min from the end of the addition of *n*-BuLi to ICH_2CN. [e] **2.111b** was present at the beginning of the addition of *n*-BuLi to ICH_2CN (*i.e.* "Barbier-type" condition).

Subsequently, different α,β-unsaturated Weinreb amides were subjected to the optimal reaction conditions for cyanomethylation (Scheme 2.29). Substitution across the olefinic double bond is tolerated, as ketone **2.114a** was obtained in high yield. Interestingly, the protocol works well also in the case of vinyl-homologue **2.114c**. However, the employment of such conditions (1.5 equiv of $LiCH_2CN$) to non-α,β-unsaturated Weinreb amides resulted in lower conversion: pleasingly, we found beneficial to use an excess of $LiCH_2CN$ (4.0 equiv) to obtain **2.114d** in 90% yield (*vs.* 75% yield with 1.5 equiv of $LiCH_2CN$). These results point out to a comparatively high electrophilicity of the α,β-unsaturated systems although, in the mean time, strongly suggest that a higher loading of the cyanomethylating reagent may interfere with the olefinic double bond, thus resulting in decreased yields. Aromatic substrates are well-suitable for the transformation (**2.114d-2.114j**): however, slightly decrements were observed for strong electron-donating substituted ones (**2.114f-g**), compared to analogues with a weak electron-donor (**2.114e**), or with electron-withdrawing functionalities (**2.114h-j**). No deleterious effects were noticed in the presence of an halogen substituent (**2.114h**, **2.114j**) or, when heteroaromatic nuclei (**2.114k-l**) were installed into the core of the reagent. Aliphatic substrates react efficiently even in the presence of pronounced steric congestion as in the case of a *tert*-butyl group (**2.114n**) and an adamantyl moiety (**2.114o**). Pleasingly, the use of a Weinreb amide bearing acidic hydrogens performs equally very well: no side reactions derived from acidic-base equilibria promoted by the basic homologating reagent could be observed in the case of **2.114m**.

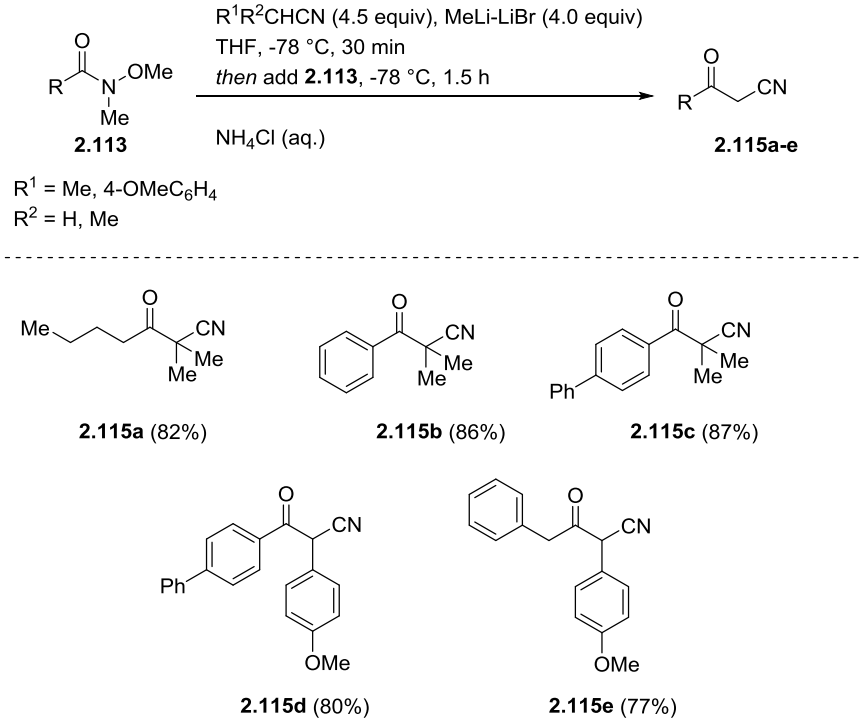


[a] $LiCH_2CN$ (1.5 equiv); [b] 75% yield when 1.5 equiv of $LiCH_2CN$ were employed

Scheme 2.29: Scope of the cyanomethylation reaction.

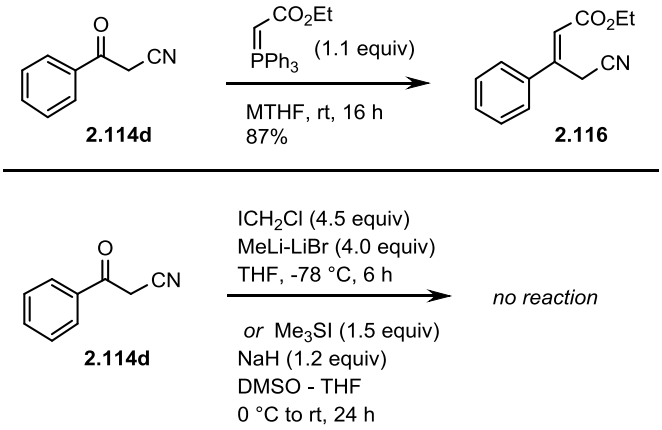
With the aim to expand the synthetic portfolio of the transformation, we focused on the employment of substituted acetonitriles. Upon forming the lithiated species under the usual conditions, a series of α,α-dimethyl-α-cyanoketones could be obtained in very good yields with aliphatic or aromatic Weinreb amides (**2.115a-c**, Scheme 2.30). This approach shows how the easy generation of the functionalised lithiated acetonitrile may be considered the method of choice for

accessing such particular cyanoketones. In fact, previously reported syntheses through the direct α-methylation of the parent benzoylacetonitrile[97] or, the electrophilic addition of chlorosulfonyl isocyanate to ketones in the presence of DMF,[98] or the NaCN treatment of aroylhydrazones under PTC conditions[99] lack of general applicability and their potential is somewhat limited by almost uniformly modest yields. Analogously, the protocol allows the addition of a lithiated α-arylacetonitrile in high yields (**2.115d** and **2.115e**, Scheme 2.30).



Scheme 2.30: Synthesis of α-mono and α,α-disubstituted cyanoketones from functionalized acetonitrile derivatives.

Inspired by our interest towards homologation chemistry,[37,39] we evaluated the reactivity of cyanoketone **2.114d** with a stabilized phosphorous ylide. Thus, β-cyanomethyl-β-phenyl ethyl acrylate **2.116** was easily obtained in high yield (Scheme 2.31). Surprisingly, neither a lithium carbenoid nor a sulphur ylide (Corey-Chaykovsky),[11,12b] that are well-known reagents for carbonyl epoxidations, did react with substrate **2.114d**.



Scheme 2.31: Attempted homologations with an α-cyanoketone.

Finally, due to the very limited availability of ^{15}N- and ^{17}O-NMR data for ß-oxonitriles,[100] we herein provide the ^{15}N NMR chemical shifts (of C≡N) and ^{17}O NMR chemical shifts (of C=O) of selected representatives (Table 2.2). Moreover, in Table 2.2 are also reported the corresponding data we measured for some related structures to gain information on how minimal changes on the structure are reflected on spectroscopic data (**R1**-**R10**) (Fig. 2.1).

Table 2.2: ^{17}O and ^{15}N shifts for selected cyanoketones and correlation with various α-substituted ketones.

Entry	Compound	^{17}O (δ, ppm)	^{15}N (δ, ppm)
1	**2.114d**	542	-126.0
2	**2.114f**	521[a]	-126.7
3	**2.114j**	536	-125.6
4	**2.114k**	510[b]	-126.9
5	**2.114n**	560	-127.8
6	**2.114o**	561	-127.5
7	**R1**	541	-
8	**R2**	532	-
9	**R3**	538	-
10	**R4**	546	-
11	**R5**	525	-
12	**R6**	527	-
13	**R7**	540	-
14	**R8**	556	-
15	**R9**	574	-
16	**R10**	-	-135.3

[a] OMe: 65 ppm. [b] Furan-O: 239 ppm.

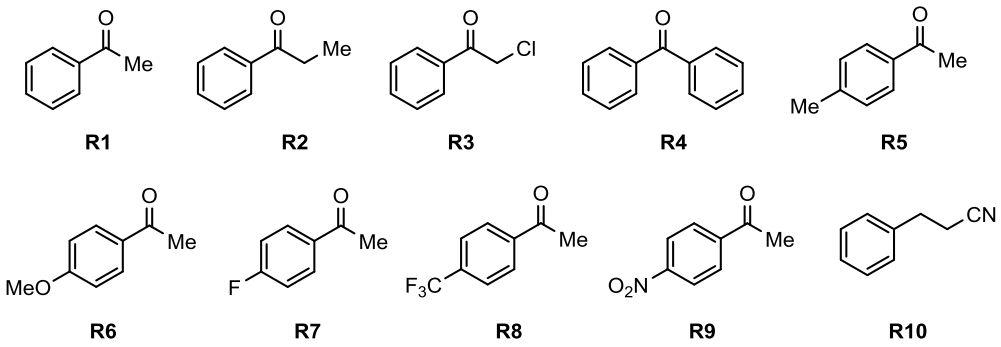


Figure 2.1: Reference compounds.

The ^{15}N NMR chemical shifts of the nitrile-N of compounds **2.114** are very consistent and located in the range between -126.0 and -127.8 ppm. Removal of the carbonyl oxygen atom of **2.114d** (**2.114d** → **R10**) results in an upfield shift of 9.3 ppm in compound **R10** (entry 16).

The ^{17}O NMR chemical shifts of the carbonyl-O in β-cyanoketones **2.114** are markedly influenced by the second substituent attached to the carbonyl moiety. Compounds carrying a (cyclo)aliphatic rest (**2.114n**: 560, **2.114o**: 561 ppm) show somewhat larger shifts, whereas congeners with aromatic (**2.114d**: 542, **2.114f**: 521, **2.114j**: 536 ppm) or heteroaromatic substituents (**2.114k**: 510 ppm) exhibit smaller ones, obviously depending in addition on the electron donating properties of the (hetero)aromatic moiety. A similar trend regarding the influence of substituents attached to the phenyl ring of related acetophenones can be read off from the data of **R1**-**R9**, which are incorporated in Table 2 for comparison purposes. Expectedly, substitution of the nitrile moiety in **2.114d** by hydrogen (**R1**), methyl (**R2**) or chlorine (**R3**) has a comparably smaller effect on the ^{17}O chemical shift of C=O.

2.2.3 Use of Isocyanates as Placeholders for the Synthesis of Halomethylated Amides

α-Haloamides and α,α-dihaloamides are versatile scaffolds in organic synthesis. In particular, the presence of the halogen atom(s) renders these structures valuable as alkylating units

for a wide range of organic transformations such as the preparation of lactams, or α,β-unsaturated amides.[101] Moreover, they constitute useful synthons for accessing lanthanide-based macrocycles of biological interest used as contrast agents.[102] Analogously, the corresponding α,α-dihaloamides found various applications in synthesis:[103] *e.g.* as materials for the obtainment of α-halogenated lactams.[104] Importantly, the α,α-dihaloamide moiety is found in biologically active compounds such as the broad-spectrum bacteriostatics analogues of chloramphenicol[105] or anticancer agents related to *N*-phenyl dichloroacetamide.[106] (Figure 2.2)

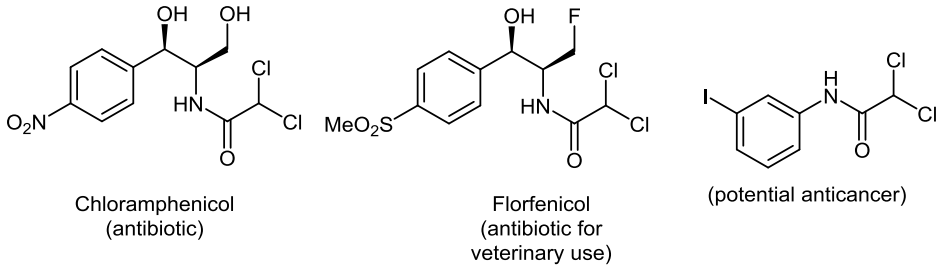
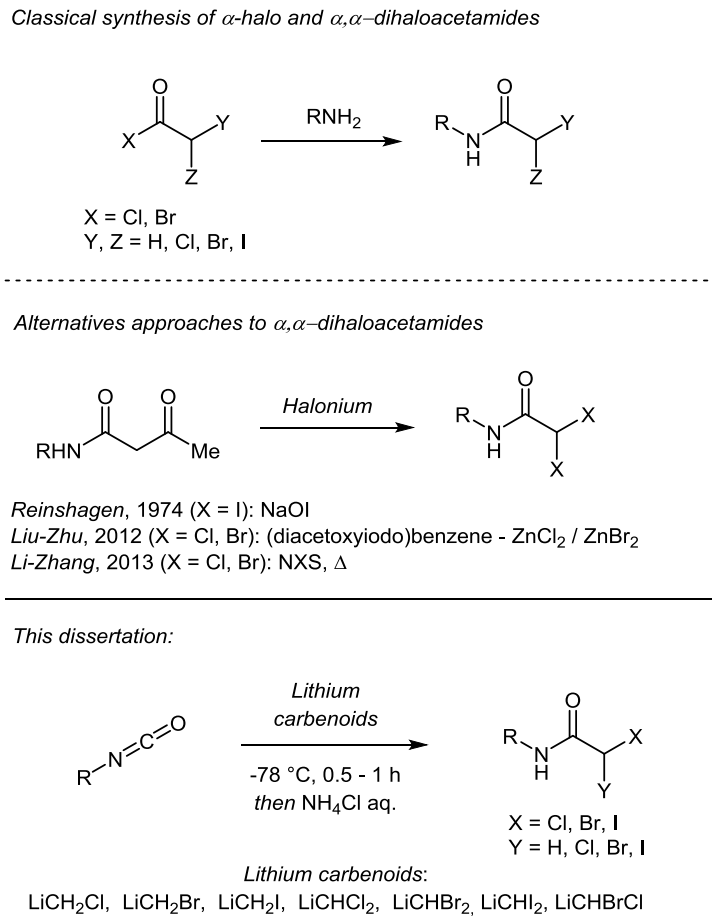


Figure 2.2: Versatility of haloamides in medicinal chemistry.

The classical approach to the synthesis of the aforementioned structures involves the reaction of an α-halo or α,α-dihalocarboxylic acid derivative (acyl halide or ester) with an amine.[102b,107] Unfortunately, the efficiency of the procedure depends on the nucelophilicity of the amine and thus, sterically hindered or less nucleophilic amines still remain challenging materials.[37a,108] It should be observed that this tactic requires the use of not always commercially available substrates such as α-iodoacetyl, α,α-dibromoacetyl or α,α-diodoacetyl halides. Thus, further halogen substitutions should be performed in order to reach the desired target.[109] Moreover, more complex routes involving tandem electrophilic α,α-dihalogenations-deacylations of acetoacetanilide derivatives have been reported (*e.g.* Reinshagen,[110] Liu-Zhu[111] and Li-Zhang[112]). (Scheme 2.32)



Scheme 2.32: Synthetic Routes to α-halo and α,α-dihaloacetamides.

Very recently Bode and coworkers re-explored the potential of the underestimated reaction of isocyanates with Grignard reagents to access sterically hindered and electron-deficient secondary amides with high efficiency.[113] Though there are precedents in the literature using various organometallic reagents such as organolithiums,[114] organomagnesiums,[115] organocopper species,[116] organomanganese[117] or organostannanes,[118] it seems that such a tactic has not been fully exploited as a versatile tool for amides synthesis. Inspired by this precedent[119] and by our own interest in designing transformations involving the use of lithium carbenoid reagents (*e.g.* $LiCH_2X$, LiCHXY),[37a,37c,39] we wondered if isocyanates could be valuable electrophilic reagents susceptible of homologation with such nucleophilic lithium species. Whenever successful the method could be

applied to the one-pot preparation of α-haloacetamides or α,α-dihaloacetamides starting from widely available materials as isocyanates.

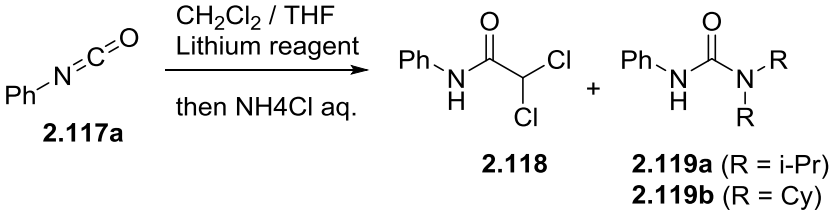
As outlined in the Introduction, Pace and coworkers discovered the homologation of isocyanates with carbenoids[37b]and, in this dissertation subsequent investigation concerning the feasibility of the reaction with polihalocarbenoids will be showed.

According to the literature, the most common method to form these species is based on the deprotonation of a dihalomethane with a lithium amide base.[29a,49,120] The reaction between phenylisocyanate **2.117a** and the putative dihalomethyllithium was selected as the model reaction for screening (Table 2.3). By using the conditions developed for the corresponding α-halomethylation (1.5 equiv CH_2Cl_2 and 1.25 equiv of lithium reagent) in the presence of LDA, only urea **2.119a** was obtained in 84% yield with only minimal amount (6%) of the desired dichloroamide **2.118** (entry 1). Modifications of the stoichiometry, reaction time or the solvent did not have beneficial effects (entries 2-4). When the formation of the carbenoid was attempted in the absence of the electrophile, no reaction was observed at all, suggesting that its decomposition took place (entry 5). By switching to lithium *N,N*-dicyclohexylamide, introduced by Nozaki for the generation of dihalocarbenoids,[49] a similar competing attack of the base to the isocyanate to give urea **2.119b** was observed (entry 6). Because the formation of ureas through the addition of lithium amide bases is known in the literature,[121] we consider that their attack to the isocyanate is faster than the deprotonation of CH_2Cl_2 and thus, to the formation and reaction of dichloromethylithium with the electrophile. Running the reaction at lower temperature (-100 °C) did not modify the reactivity profile (entry 7). Attempts to dichloromethylate **2.117a** adapting Izawa's procedure[122] for esters in the presence of MeLi-LiBr, resulted equally in the formation of amide **7** (entry 8).

Pleasingly, the use of the more sterically hindered base lithium 2,2,6,6-tetramethylpiperidide proved to be effective in avoiding the formation of urea compounds, thus allowing the chemoselective obtainment of dichloroacetamide **2.118** as indicated by ^{1}H-NMR analysis of the

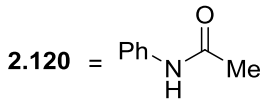
crude (entry 9). Because of the lower nucleophilicity of dichloro methylithiums compared to the corresponding monochloro ones, we found the use of an excess (5 equiv of CH_2Cl_2 and 4.5 equiv LTMP) beneficial to maximize the yield up to 87% (entries 9-12).

Table 2.3: Reaction optimization for the dichloromethylation of PhNCO.

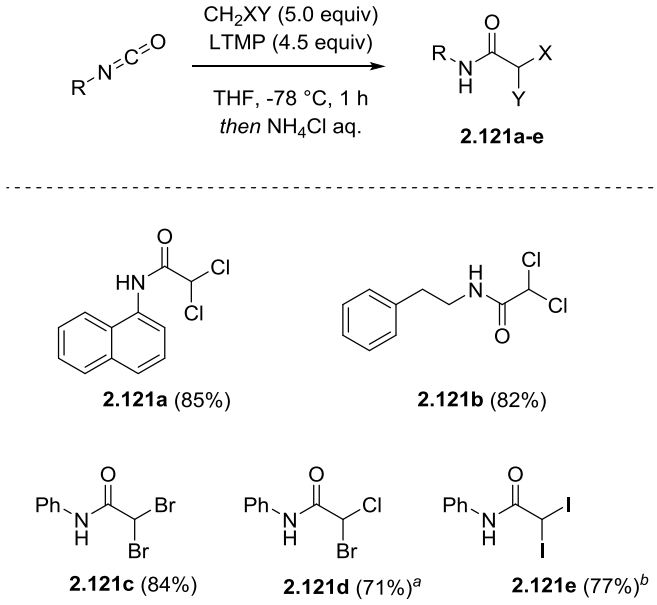


Entry	Li Reagent (equiv)	CH_2Cl_2 (equiv)	Reaction time (h)	Yield of **2.118** (%)[a]	Yield of **2.119** (%)[a]
1	LDA (1.25)	.5	1	6	(**2.119a**) 84
2	LDA (4.5)	5.0	1	9	(**2.119a**) 82
3	LDA (4.5)	5.0	3	11	(**2.119a**) 79
4[b]	LDA (4.5)	5.0	1	8	(**2.119a**) 86
5[c]	LDA (4.5)	5.0	1	-	-
6	$LiNCy_2$ (4.5)	5.0	1	12	(**2.119b**) 78
7[d]	$LiNCy_2$ (4.5)	5.0	1	14	(**2.119b**) 75
8[e]	MeLi-LiBr (4.5)	5.0	1	-	-
9	LTMP (4.5)	5.0	1	87	-
10	LTMP (3.0)	5.0	1	76	-
11	LTMP (2.0)	5.0	1	71	-
12	LTMP (6.0)	8.0	1	84	-

Reactions were performed at –78 °C otherwise indicated. [a] Isolated yield. [b] Reaction run in Et_2O. [c] **2.117a** was added after 1 min from the end of the addition of LDA. [d] Reaction run at -100 °C. [e] Amide **2.120** was obtained in 86% yield.



The dichloromethylation could be efficiently applied to various isocyanates (aromatic and aliphatic) providing compound **2.121a** and **2.121b** in very good yields (Scheme 2.33). Analogously, the LTMP-assisted procedure could be employed for generating dibromo compound **2.121c** from CH_2Br_2 and, the particularly challenging bromochloro derivative **2.121d** from $BrCH_2Cl$ albeit in somewhat lower yield. Finally, by employing Bull's protocol[50,123] for the generation of diiodomethyllithium from CH_2I_2 and LHMDS we were able to prepare diiodoacetamide **2.121e**. It should be observed that $LiCHI_2$ could be preformed prior to the addition of the isocyanate thus, indicating the higher stability of this carbenoid compared to the others employed in this study which required the contemporaneous presence of the same isocyanates. It should be stressed that compound **2.121e** has been previously synthesized by Reinshagen through a complex procedure involving the degradation of acetoacetanilide with NaOI.[110]

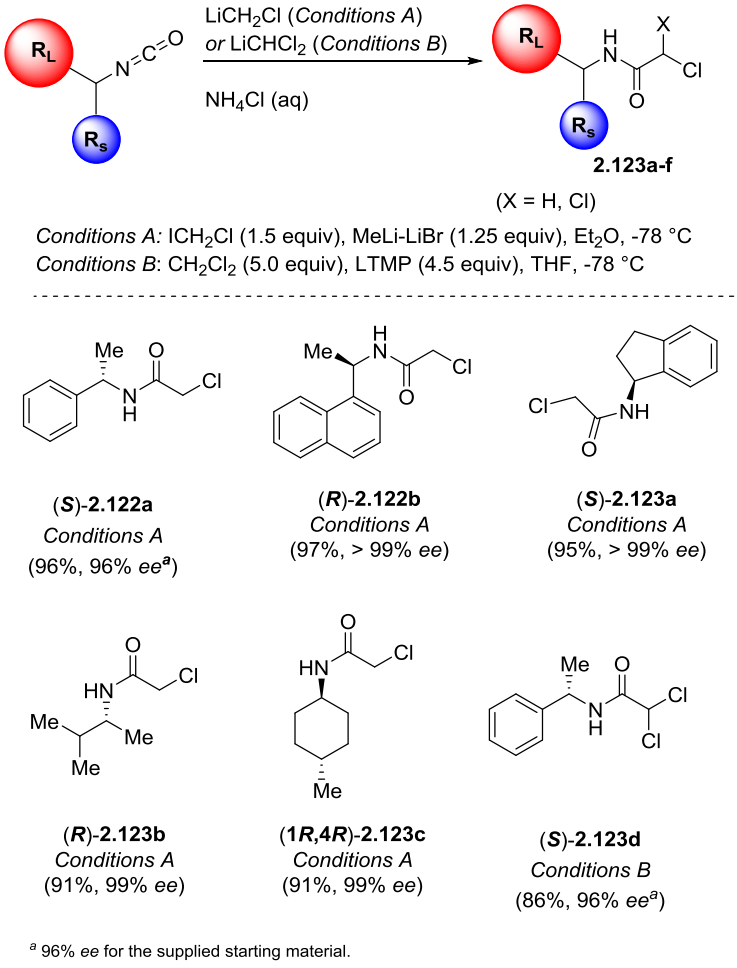


[a] Reaction time 3 h. [b] CH_2I_2 (4.4 equiv), LHDMS (4.0 equiv), THF-Et_2O (3:1 v/v), -78 °C, overnight

Scheme 2.33: Synthesis of α,α'-dihaloamides from isocyanates and dihalocarbenoids.

In order to gain full insights into the transformation, we finally studied its adaptability to optically active isocyanates (Scheme 2.34). Full preservation of the chiral information was

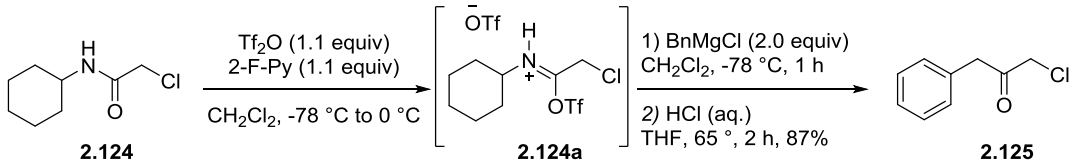
evidenced both in the case of the addition of $LiCH_2Cl$ (*S*)-**2.122a**, (*R*)-**2.122b**, **2.123a-c** and $LiCHCl_2$ (**2.123d**).



Scheme 2.34: Halo- and dihalomethylations on chiral isocyanates.

Because of our interest in α-halo ketone compounds synthesis,[4d,37a,37c,85,124] we were attracted by a recent report by Charette and coworkers[125] dealing with the full chemoselective access to ketones from secondary amides *via* the formation of a highly electrophilic imidoyl triflate ion **2.124a**.[93,126] Pleasingly, upon activation of inert amide **2.124** under such conditions, followed by the addition of benzylmagnesium chloride and acidic hydrolysis, α-haloketone **2.125** was obtained in an excellent 87% yield (Scheme 2.35). This example broadens the scope of such a

powerful strategy in allowing the addition of organometallics also to substrates bearing reactive chloromethyl functionalities. Interestingly, such a tactic allows to simplify considerably the access to ketone **2.125** compared to former techniques as the Villieras' direct addition of chloromethyllithium to an ester which had to be performed at – 115 °C.[24]



Scheme 2.35: Addition of BnMgCl to an α-chloroamide *via* activation as imidoyl triflate.

Finally, due to the lack of available information regarding ^{15}N-NMR data of α-chloroamides synthesized in the course of this work, we report in Table 2.4 the ^{15}N chemical shifts of the amidic nitrogen for selected examples.

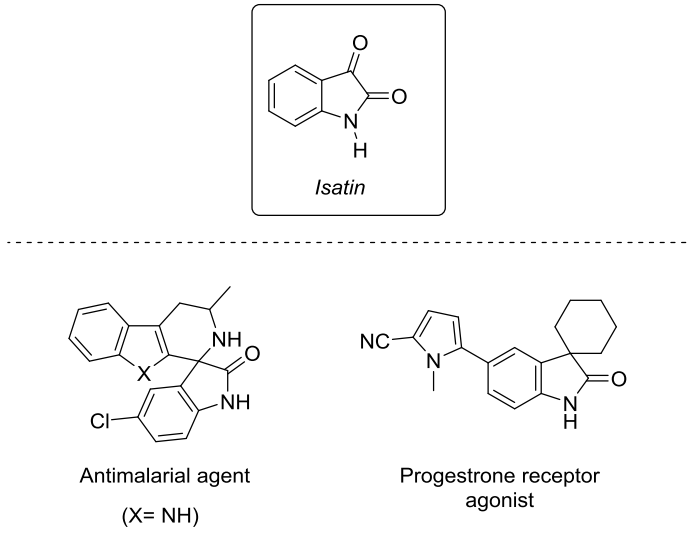
Table 2.4. ^{15}N-NMR data for selected synthesized compounds.[a]

Compound	^{15}N (δ, ppm)
2.119b	-276.1
2.121a	-266.4
2.121b	-273.5
2.121c	-258.3
2.121d	-259.2
2.121e[b]	-260.3
2.123a	-253.9
2.123b	-256.0
2.123c	-252.7
2.123d	-257.3

[a] Measurements were realized in $CDCl_3$ referencing against external nitromethane. [b] DMSO-d_6 was used as the solvent.

2.2.3 Reaction of Isatins With Carbenoids

The isatin core (indole-1*H*-2,3-dione) is a structural motif first isolated in plants of genus *Isatis*, *Calanthe discolor* and *Couropita guianensis*.[127] Its outstanding importance in chemistry is a consequence of the fact that can be found in several natural products, synthetically-prepared biologically active compounds or even as metabolite of epinephrine in humans. Such a versatility of the isatin core is mainly attributed to the exceptional electrophilicity of the C-3 (ketone carbonyl) which enables functionalizations to access privileged scaffolds including spiro-fused heterocyclic and carbocyclic rings (*e.g.* 2-oxindoles).[127b,128] The synthetic portfolio displayed by isatins is not limited to the reactivity at C-3 but, encompasses also classical aromatic chemistry (electrophilic substitution) and lactam-type one thus, conferring a complex scenario in terms of chemoselectivity (Scheme 2.136).[129]



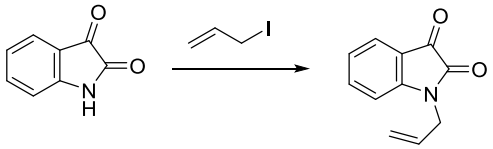
Scheme 2.36: The isatin motif in medicinal chemistry.

As such, the synthesis of isatins has been an attractive and challenging topic for the synthetic community: historically, the so-called Sandmeyer method represented the most commonly used.[127a] It involves the reaction of an aniline with chloral hydrate and hydroxylamine

hydrochloride which provides an isonitrosoacetanilide precursor of the isatin. Unfortunately, when the procedure is applied to the synthesis of *N*-alkylisatins, reactions proceed with low efficiency.

Because of the limited cost of commercially available isatins, we decided to functionalize its secondary lactam-type amide through an alkylation strategy involving the use of an heterogeneous base. Previous work by Pace showed that aminic and amidic nitrogens maybe alkylated in the presence of the heterogeneous base KF supported onto Celite or aluminium oxide.[130] Thus, upon screening a series of conditions (Table 2.5) for the model reaction between isatin and allyl iodide, we found optimal utilizing KF-Celite in the ecofriendly solvent 2-MeTHF. Reactions carried out in this solvent proceeded in almost quantitative yield and analytical pure substances were recovered after removal of the base by filtration under vacuum and additional washing with 2-MeTHF. Although reaction in CPME gave a lower yield (Table 2.5, entry 5), it proved to be ideal for recrystallizing the *N*-functionalized isatin.

Table 2.5: Optimization of the *N*-allylation reaction.

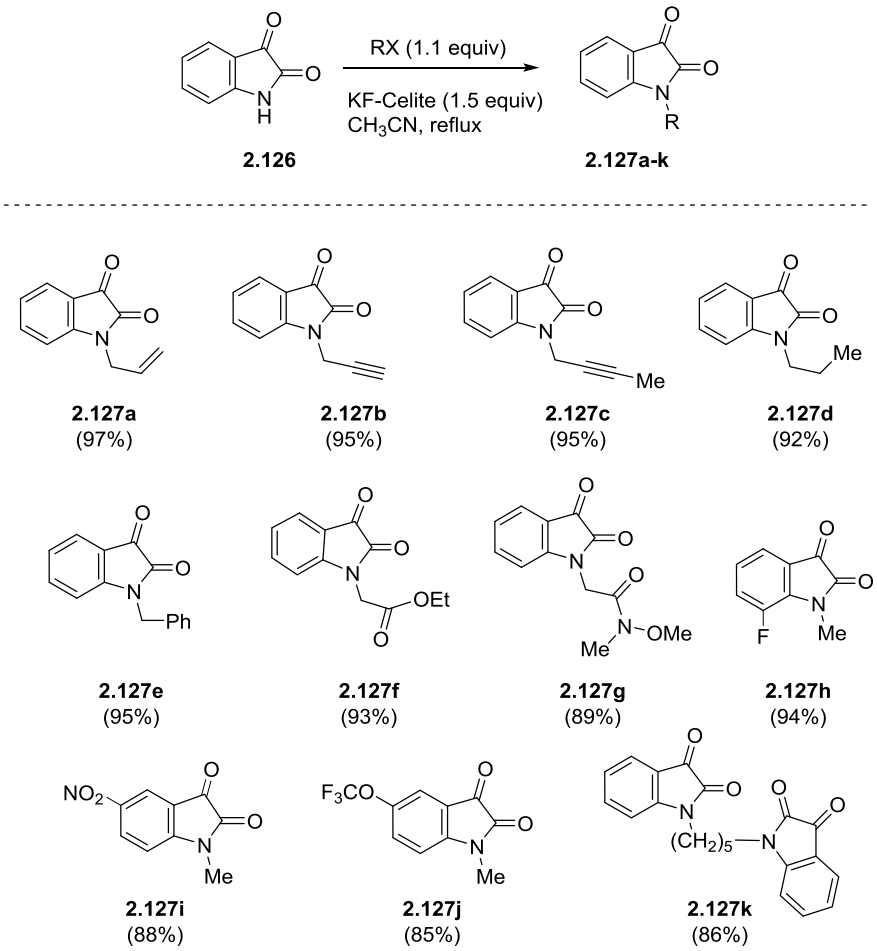


2.126 **2.127a**

Entry	Solvent	Base	Base equiv	Temperature (°C)	Reaction time (h)	Yield of **1.127a** (%) [a]
1	2-MeTHF	KF-Celite	1.5	83	2	97
2	2-MeTHF	KF-Celite	1.0	83	4	88
3	2-MeTHF	KF-Celite	2.5	83	1	96
4	2-MeTHF	KF-Celite	1.5	rt	6	85
5	CPME	KF-Celite	1.5	90	4	81
6	DMF	KF-Celite	1.5	90	3	91
7	CH_3CN	KF-Celite	1.5	83	3	93
8	1,4-dioxane	KF-Celite	1.5	90	6	74
9	Acetone	KF-Celite	1.5	55	5	88
10	CH_2Cl_2	KF-Celite	1.5	45	8	47
11	AcOEt	KF-Celite	1.5	77	8	55
12	Toluene	KF-Celite	1.5	90	12	41
13	2-MeTHF	KF-Al_2O_3	1.5	83	6	84
14	2-MeTHF	K_2CO_3	1.5	83	6	89
15	2-MeTHF	K_3PO_4	1.5	83	6	84

[a] Isolated yield.

The method was then extended to a broad series of alkylating agents incorporating sensitive moieties such as esters, Weinreb amides or propargyl groups (**2.127a-k**, Scheme 2.37). The use of 0.5 equiv of 1,5-dibromopentane resulted in the formation of the bis-isatin analogue incorporating the pentamethylenic spacer. Analogously, the procedure did not lose its effectiveness in tha case of isatins bringing substituents on the aromatic core.



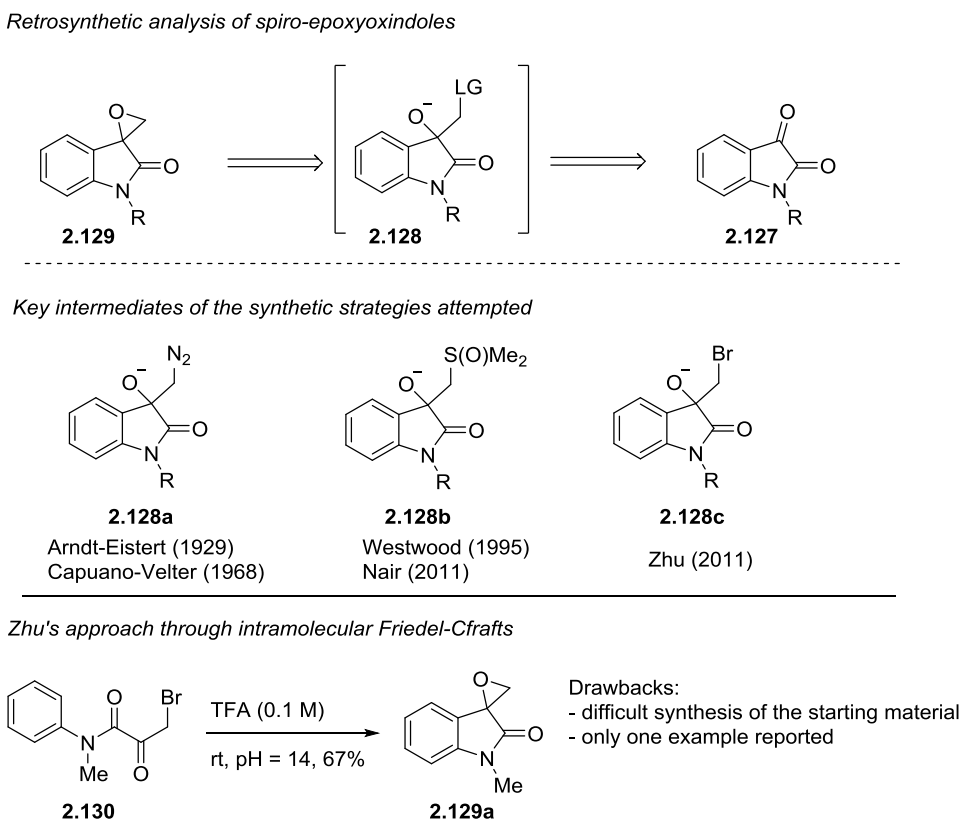
Scheme 2.37: *N*-functionalization of isatines derivatives.

With a reliable method to access the starting materials, we then turned our attention towards the halomethylation reaction in order to access spiro-epoxyoxindole (Scheme 2.38). From a synthetic standpoint they can be considered the products of a formal epoxydation carried out on the isatine (1*H*-indole-2,3-dione) core: as such, the installation of an oxirane ring at C-3 will provide a tricyclic spiro-skeleton. Despite the availability of the methods seen above to access such substituted spiroepoxyoxyindoles, we were impressed by the substantial lack of general approaches to reach simple ones.

However, the challenge seems to be known by organic chemists since seminal studies on diazomethane-assisted homologations by the pionners of the field Arndt and Eistert who paved the

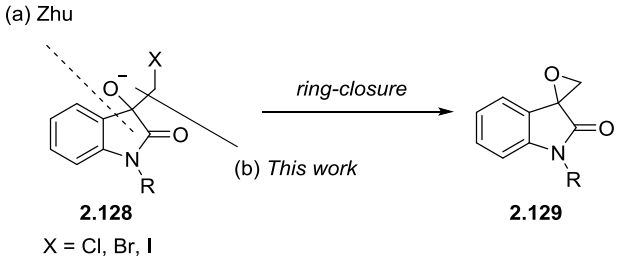
field without reporting details on the process (Scheme 2.38).[4a] Curiously, 40 years later also Capuano and Welter reported the reaction albeit no data regarding reaction yields were disclosed.[131]

Almost contemporaneously, Stevens and co-workers demonstrated the substantial feasibility of the process via Corey-Chaykovsky chemistry,[132] a result which was more recently confirmed by Westwood *et al.*,[133] reporting for the first time the exact reaction yields for the process (25-57%) and the difficult chemocontrol achievable in reactions involving the use of diazomethane. Again, very recently Nair applied Corey-Chaykosky homologation to access some secondary or tertiary-type isatins without disclosing experimental details of the process.[134] Finally, Zhu reported a synthesis of a single spiro-epoxyoxindole **2.129a** through an intramolecular Friedel-Craft reaction starting from an α-oxo-*N*-anilide **2.130** assisted by trifluoroacetic acid.[135]



Scheme 2.38. Context of isatin-derivatives formal epoxydation at C-3

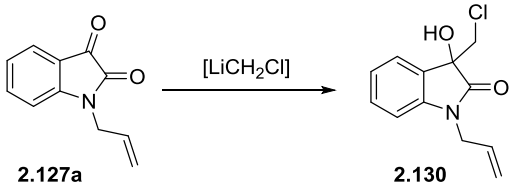
These precedents stimulated us to revisit this apparently simple but, stimulating chemistry from a different perspective involving carbenoids as homologating agents. Our assumption was motivated on the experimental evidence that among the above seen strategies, the Zhu's one appeared the more reliable.[135] Thus, the tactic of constructing the same type of tetrahedral intermediate through a different disconnection approach was investigated. In fact, our envisaged tactic differed from Zhu's one for the formal mechanism conducting to intermediate **2.128c**: in the latter case, as specified above, it was the result of a Friedel-Crafts process (*path a*) while, in our intention it had to be formed through the addition of a carbenoid to the C-3 of the isatin (*path b*) (Scheme 2.39). Our assumption was motivated by the experimentally evidence that this kind of intermediates (like **2.128**) have been successful in forming the desired epoxyde. Thus, we deemed appropriate investigating how it could be formed through a different homologation of the isatin core at C-3.



Scheme 2.39: Synthetic plan to reach the key tetrahedral intermediate precursor of the epoxyde.

N-allylisatin (**2.127a**) was selected as the model substrate for optimization studies (Table 2.6). By using the standard Barbier-type conditions for the generation of the carbenoid chloromethyllithium (1.3 equiv) in THF, we observed 73% conversion as judged by the ^{1}H-NMR of the reaction crude (Table 2.6, entry 1). Further optimization followed and, we found that the use of 2.5 equiv of carbenoid generated from 3.0 equiv of chloroiodomethane and 2.5 equiv of MeLi-LiBr maximized the conversion (94%, Table 2.6, entry 3). In order to isolate and fully characterize the formed chlorohydrin, purification by chromatography on silica gel was attempted.

Table 2.6. Optimization of chloromethylation and purification of *N*-allylisatin.



2.127a **2.130**

Entry	ICH_2Cl (equiv)	MeLi-LiBr (equiv)	Conversion (%) [a]	Stationary phase for chromatography	Isolated Yield of **2.130** (%)
1	1.5	1.3	73	-	-
2	2.0	1.8	78	-	-
3	3.0	*2.5*	94	SiO_2	14
4	3.0	2.5	94	SiO_2 (+2% TEA)	16
5	3.0	2.5	94	SiO_2 (+5% TEA)	15
6	3.0	2.5	94	SiO_2 (+1% TMSCl)	8
7	3.0	2.5	94	SiO_2 (+3% TMSCl)	10
8	3.0	2.5	94	Al_2O_3 neutral (IV deg)	86
9	3.0	2.5	94	Al_2O_3 acidic (IV deg)	24
10	3.0	2.5	94	Al_2O_3 basic (IV deg)	31

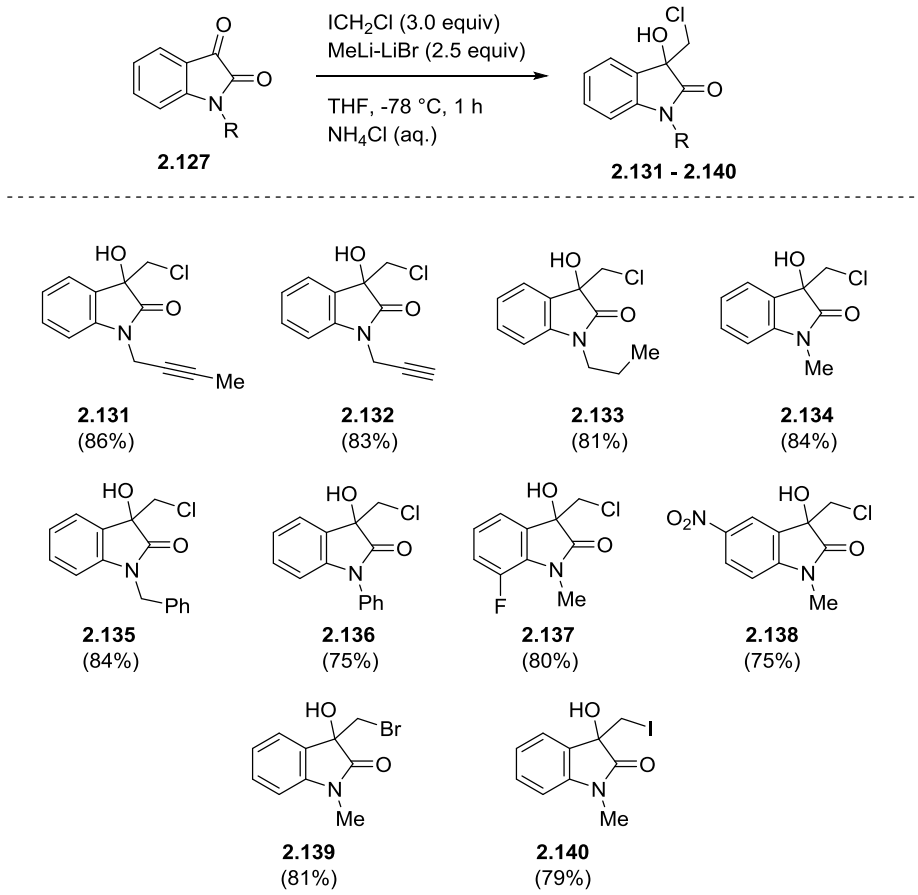
[a] Yields were determined by ^{1}H-NMR spectroscopic

Unfortunately only 14% of the desired product could be obtained (Table 2.6, entry 3): evidently, the sensitive chlorohydrin underwent degradation processes in the presence of the stationary phase. Regrettably, the degradation products could not be recovered from the column even after washing with pure acetone. The fate of the chlorohydrin during chromatography could not be modified by deactivating the silica with triethylamine (2-5%) or TMSCl (1-3%) (entries 4-7). The deleterious action of silica gel on halogenated compounds is a known drawback, as for example noticed by Bull the case of iodoaziridines[50,123] and by Pace for haloketones.[37c] In both circumstances by switching to a different phase such as alumina benefited the purification: in a

comparative study between the three different forms of this stationary phase (acidic, neutral and basic), Bull concluded that the basic form is the most suitable for the purification of iodoaziridines,[50,123] while Pace showed the effectiveness of using the neutral form for purifying sensitive chloroketones.[37c] Remarkably, the commercially available alumina for chromatography (usually referred as Brockamnn degree I) - regardless its nature - is too active and, therefore to avoid complete retention of the products into the column, it is recommended to deactivate them with a known volume of water. Thus, the use of neutral alumina Brockamnn degree IV (obtained by adding 10% w/w of water to alumina followed by homogenization of the mixture) was attempted.

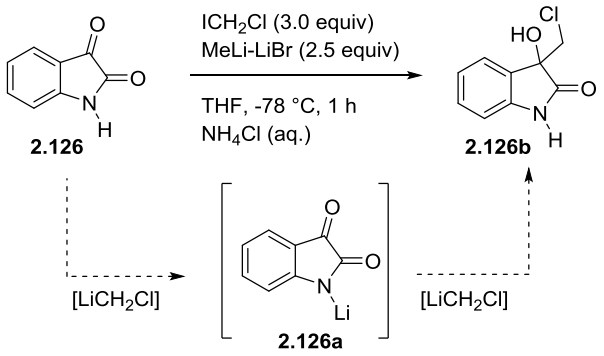
Pleasingly, the crude reaction mixture could be efficiently purified and the desired chlorohydrin **2.130** was obtained in an excellent 86% (entry 8) yield thus, confirming the pivotal role played by the choice of neutral alumina as the stationary phase. For completeness also the other forms (acidic and basic, Brockmannn degree IV) were tested: both gave not satisfactory results since the model chlorohydrin could be isolated in only 24% and 31% yield, respectively (Table 2.6, entries 9-10).

With the development of a robust method to ensure the successful purification of the materials, we then turned our focus towards the scope of the protocol (Scheme 2.40). Pleasingly, the reaction allows the chemoselectivity installation of the halomethylenic fragment into different isatins including those ones bearing sensitive groups such as unsaturated carbon chains (**2.131** – **2.132**), aryl (**2.136**), fluoro (**2.137**) or nitro (**2.138**). The protocol tolerates also the use of different halomethyllithiums, such as $LiCH_2Br$ and $LiCH_2I$, to give the corresponding bromo- and iodohydrins (**2.139** and **2.149**).



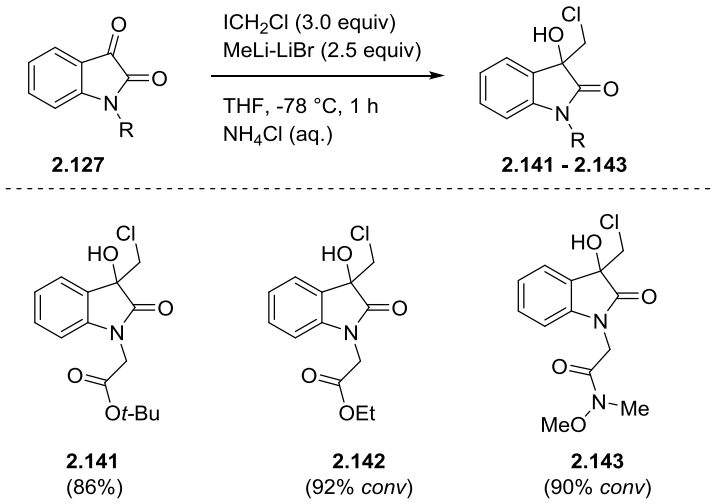
Scheme 2.40: Halomethylation of *N*-substituted isatins.

It is worth highlighting the success noted in the reaction involving the simple isatin **2.126** (Scheme 2.41): as mentioned in the introduction of the chapter, substrates bearing acidic protons are reluctant to undergo carbenoid additions in the absence of protection group.[71a,72] However, this particular example demonstrates that these processes are rather substrate-controlled and, it is conceivable that the carbenoid first abstracts the proton giving a lithiated lactam **2.126a** which in turn undergoes the addition to afford the chloromethylated compound **2.126b**.



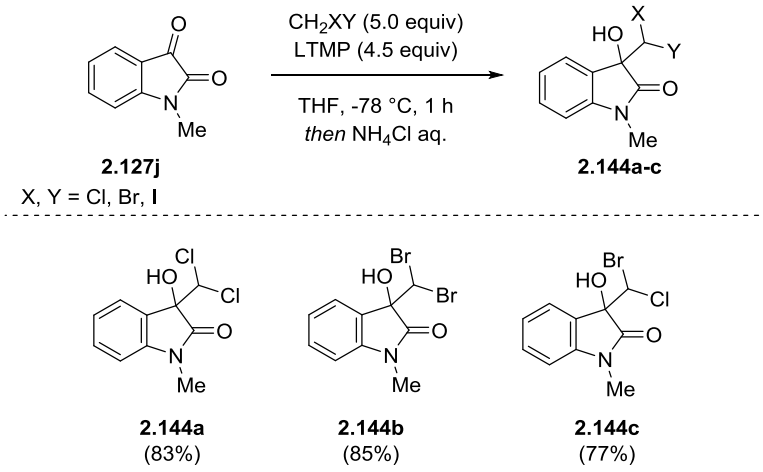
Scheme 2.41: Case of the simple isatin.

Of outstanding significance is the chemoselectivity observed in the case of multi-electrophilic substrates which undergo the addition exclusively to the C-3 carbon of the isatin core (Scheme 2.42). Whenever this excellent chemoselectivity could be easily postulated in the case of a sterically hindered ester like **2.141**, it is quite surprising in the case of an ethyl ester (**2.142**) or even with a Weinreb amide (**2.143**), which, as discussed earlier, represent suitable partners for reactions involving carbenoids. The same outcome was also noticed by running the reactions in the presence of an additional excess of carbenoid (up to 5.0 equiv). Unfortunately, the purification of compounds **2.142** and **2.143** resulted particularly tricky in neutral alumina: the ^{1}H-NMR of the crudes indicated in both cases a conversion > 90% and, therefore we decided to use them directly for the following step.



Scheme 2.42: Chemoselective addition to isatins showing an additional electrophilic moiety.

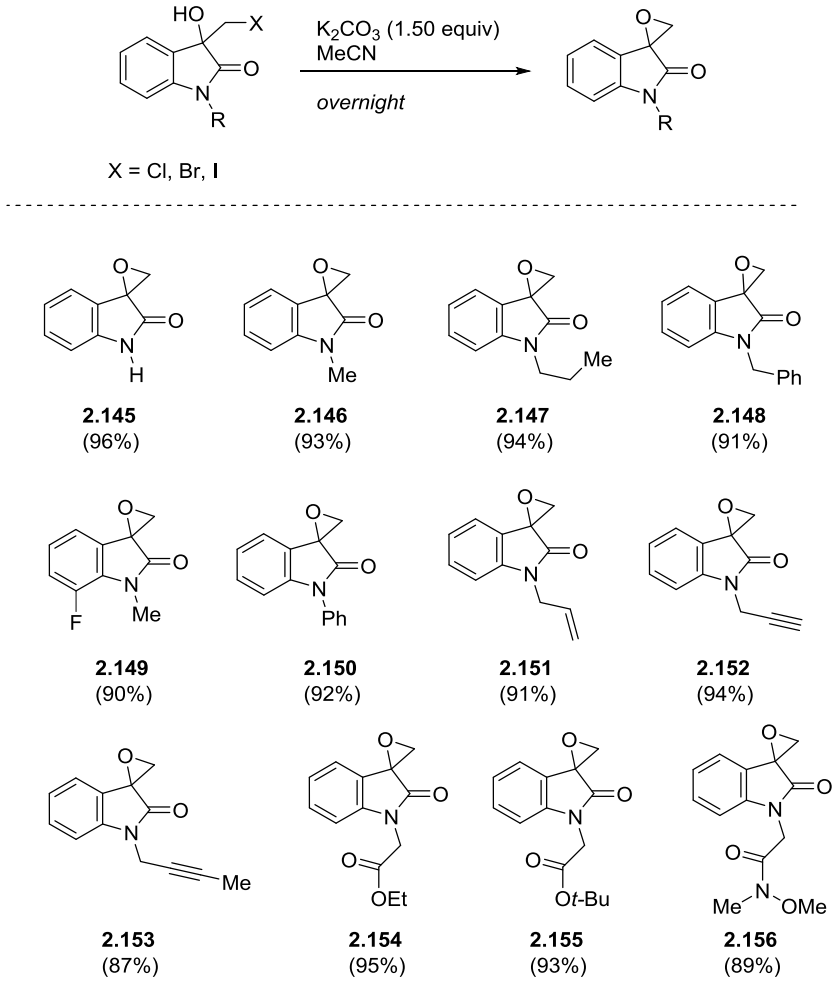
Based on the previously developed method for the employment of dihalocarbenoids, we also evaluated the installation of these synthons into the isatins (Scheme 2.43). The reactions smoothly yielded the desired dihaloalcohols, which again were purified on neutral alumina.



Scheme 2.43: Dihalomethylation of *N*-methylisatin.

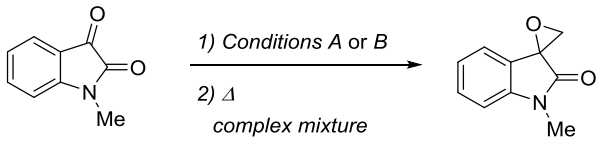
Based on literature precedents regarding the ring-closure of halohydrins to epoxides,[29b,29c,31,69,136] we selected potassium carbonate to accomplish the reaction (Scheme 2.44). Pleasingly, through the simple stirring of the halohydrin at rt with potassium carbonate (1.50 equiv)

in dry acetonitrile, the desired epoxydes (**2.145**-**2.156**) were recovered in > 90% yield, upon flash-chromatography on a plug of neutral alumina (Brockmannn degree IV).



Scheme 2.44: Ring-closure of halohydrins to the corresponding epoxides.

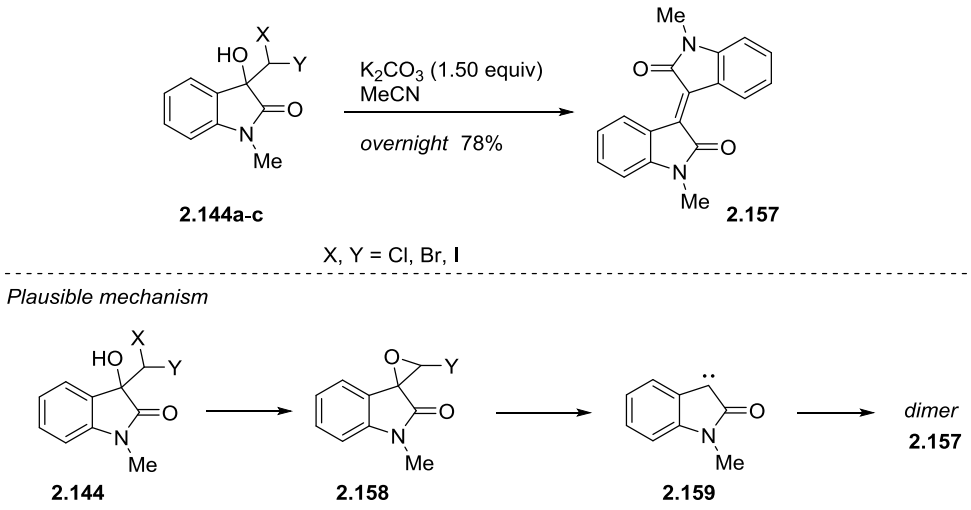
Because of the possible limited stability of some epoxyde, in some circumstances they could not been isolated and fully characterized. In a comparison study between the herein proposed two-steps access to epoxydes from isatins and known procedures[28,31] involving the one-step carbenoid addition / ring-closure, we ascertained the latter to be not suitable for the purpose since only complex mixtures were recovered (Scheme 2.45).



Conditions A: ICH_2Cl (3.0 equiv) - MeLi-LiBr (2.5 equiv) - THF, -78 °C, 1 h (Matteson)
Conditions B: I_2CH_2 (2.0 equiv) - MeLi (3.0 equiv) - THF 0 °C, 30 min (Concellon)

Scheme 2.45: Attempted one-pot homologation / ring closure.

With much of our surprise the treatment of dihalogenated alcohols 2.**144a-c** under the usual conditions (K_2CO_3, acetonitrile) afforded as a single compound the isoindigo **2.157**, as evidenced by fully and unambiguously NMR and HRMS analyses. This particular behavior can be rationalized by assuming the formation of an unstable haloepoxide intermediate, which then affords the free carbene species, susceptible of dimerization to give the isoindigo.



Scheme 2.46: Isoindigo formation from dihaloalcohols.

2.2.4 Conclusions

In this part of dissertation realized at the University of Vienna, an in-depth study on carbenoid chemistry has been realized. The following main achievements have been reached:

- Given the excellent nucleophilicities of nitrile-type carbanions and the unique acylating properties of Weinreb amides, we have developed a simple, efficient, protocol for the synthesis of variously functionalised α-cyanoketones. Key features of the method are: a) uniformly high yields, without necessity to purify by chromatography, depending neither on the substituted acetonitrile structure nor on the Weinreb amide used; b) possibility to access polysubstituted cyanomethylketones by simply selecting the proper R^1R^2CLiCN carbanion; c) excellent chemoselectivity found in particular systems such as α,β-unsaturated Weinreb amides.
- We have demonstrated the effectiveness of the homologation of readily available isocyanates with lithium carbenoid (monohalo and dihalo) reagents to produce the corresponding secondary amide adducts through a simple nucleophilic addition. The method is particularly attractive compared to usual procedures to prepare these substrates because: 1) it does not rely on the nucleophilicity of the amine as occurs in the case of condensation with haloacetyl halides; 2) the sterically hindrance on the isocyanate does not affect at all the overall transformation; 3) the protocol can be smoothly adapted to the synthesis of the desired haloamides by properly selecting the isocyanate and the carbenoid; 4) with chiral isocyanates no erosion of the optical purity of reaction products was observed.
- The chemoselective homologation of isatin analogues at the C-3 carbon has been performed with lithium mono- and dihalocarbenoids. The reaction takes place smoothly and upon purification on deactivated alumina the corresponding halo- or dihalo- tertiary alcohols are obtained. The subsequent potassium carbonate-mediate cyclization affords the desired spiro-

epoxyindolones in almost quantitative yield in the case of monohaloalcohol precursors. The reaction on dihaloalcohol precursors leads to the formation of an isoindigo structure presumably derived from a free carbene species generated in the course of the reaction.

2.3 Experimental Part

2.3.1 Instrumentation and General Analytical Methods

Melting points were determined on a Reichert–Kofler hot-stage microscope and are uncorrected. Mass spectra were obtained on a Shimadzu QP 1000 instrument (EI, 70 eV) and on a Bruker maXis 4G instrument (ESI-TOF, HRMS). IR spectra were recorded on a Perkin-Elmer FTIR 1605 spectrophotometer. ^{1}H, ^{13}C, ^{15}N, ^{19}F and ^{17}O NMR spectra were recorded with a Bruker Avance III 400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C, 40 MHz for ^{15}N, 376 MHz for ^{19}F, 54 MHz for ^{17}O) or a Bruker Avance 500 spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C, 50 MHz for ^{15}N, 470 MHz for ^{19}F) at 297 K using a "directly" detecting broadband observe (BBFO) probe. The center of the solvent signal was used as an internal standard which was related to TMS with δ 7.26 ppm (^{1}H in $CDCl_3$) and δ 77.0 ppm (^{13}C in $CDCl_3$). ^{15}N NMR spectra (gs-HMBC, gs-HSQC) were referenced against neat, external nitromethane, ^{19}F NMR spectra by absolute referencing via Ξ ratio. ^{17}O NMR spectra were taken from approximately 1M solutions and are referenced against external H_2O (0 ppm). For the latter 10 000 to 300 000 scans were accumulated (pulse width 90°, acquisition time 0.15 s, relaxation delay 0.2 s, spectral width 500-600 ppm) and Fourier transformed after a 200-250 Hz line broadening by exponential multiplication. To decrease acoustic ringing a pre-scan delay DE = 100 μs was used in the pulse sequence. Spin-spin coupling constants (*J*) are given in Hz. In some cases, full and unambiguous assignment of all resonances was performed by combined application of standard NMR techniques, such as APT, HSQC, HMBC, COSY and NOESY experiments. Chiral HPLC was carried out with Chiralcel OD-H, or Chiralpak IA columns, as indicated. IR absorption spectra were recorded as NaCl pellets on a Shimadzu FT-IR 8400S (E41107) instrument. Spectra analyses were performed with the software Shimadzu IRsolution (Version 1.21, 2005). Elementary microanalyses were carried out using a Leco® CHNS 932 equipment.

Light petroleum refers to the fraction with boiling point 40–65 °C. All the reactions were carried out under inert atmosphere of nitrogen. Acetonitrile derivatives were purified immediately before their use by distillation. Dihalomethanes used as carbenoids precursors and amine bases (*i*-Pr_2NH and 2,2,6,6-tetramethylpiperidine) were distilled immediately before use. THF was distilled over Na / benzophenone. Chemicals were purchased from Sigma-Aldrich, Acros, Alfa Aesar and TCI Europe. Starting Weinreb amides were prepared according to our previously reported method.[73c] Solutions were evaporated under reduced pressure with a rotary evaporator and the residue was chromatographed on a silica gel column using ethyl acetate / hexanes mixture as the eluent unless otherwise specified. TLC was carried out on aluminium sheets precoated with silica gel 60F254 (Macherey-Nagel, Merk); the spots were visualised under UV light (λ = 254 nm) and/or $KMnO_4$ (aq.) was used as revealing system.

2.3.2 General Procedures for the Cyanomethylation of Weinreb amides

2.3.2.1 Cyanomethylation of α,β-unsaturated Weinreb amides (General Procedure 1)

To a solution of dry acetonitrile derivative (2.0 equiv) in anhydrous THF cooled at -78 °C, MeLi-LiBr (1.5 M in Et_2O, 1.5 equiv) was added dropwise during 5 min and, the resulting mixture was stirred for 30 min. Then, a solution of Weinreb amide (1.0 equiv) in THF was added and the stirring was continued for additional 1.5 h at – 78 °C. A solution of saturated aqueous NH_4Cl was added and after removing of the cooling-bath the system was allowed to reach rt. After extracting with diethyl ether, two additional washings with brine followed. Finally, the organic phase was dried over Na_2SO_4 and, the pure cyanoketones were recovered upon removal of the solvent under vacuum.

2.3.2.2 Cyanomethylation of NON α,β-unsaturated Weinreb amides (General Procedure 2)

To a solution of dry acetonitrile derivative (4.5 equiv) in anhydrous THF cooled at -78 °C, MeLi-LiBr (1.5 M in Et_2O, 4.0 equiv) was added dropwise during 5 min and the resulting mixture was stirred for 30 min. Then, a solution of Weinreb amide (1.0 equiv) in THF was added and, the stirring was continued for additional 1.5 h at – 78 °C. A solution of saturated aqueous NH_4Cl was added and after, removing of the cooling-bath, the system was allowed to reach rt. After extracting diethyl ether, two additional washings with brine followed. Finally, the organic phase was dried over Na_2SO_4 and the pure cyanoketones were recovered upon removal of the solvent under vacuum.

(4*E*)-3-oxo-5-phenyl-4-pentenenitrile (2.112)

By following the general procedure 1, starting from (2*E*)-*N*-methoxy-*N*-methyl-3-phenylacrylamide **2.111b** (0.191 g, 1.0 mmol, 1.0 equiv), CH_3CN (0.08 g, 0.1 mL, 2.0 mmol, 2.0 equiv) and MeLi-LiBr (1.0 mL, 1.5 mmol, 1.5 equiv) in THF, β-oxonitrile **2.112** was obtained in 86% yield (0.147 g) as a yellow solid, mp**:** 97 °C (lit.,[137] 97-98 °C).

IR (NaCl, ν_{max}, cm^{-1}): 2253, 1792, 1683, 1608, 1470, 1379.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68 (d, ^3J = 16.0 Hz, 1H, PhC<u>H</u>=CH) 7.58 (m, 2H, Ph H-2, 6), 7.45 (m, 1H, Ph H-4), 7.44 (m, 2H, Ph H-3,5), 6.86 (d, ^3J = 16.0 Hz, 1H, PhCH=C<u>H</u>), 3.73 (s, 2H, CH_2CN). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 186.3 (C=O), 146.5 (Ph<u>C</u>H=CH), 133.3 (Ph C-1), 131.6 (Ph C-4), 129.1 (Ph C-3,5), 128.8 (Ph C-2,6), 122.4 (PhCH=<u>C</u>H), 114.0 (CN), 30.8 (<u>C</u>H_2CN). **^{15}N NMR** (40 MHz, $CDCl_3$) δ: -126.6 (CN).

Anal. Calcd for $C_{11}H_9NO$.Calcd: C, 77.17; H, 5.30; N, 8.18. **Found**: C, 77.31; H, 5.37; N, 8.29.

(4*E*)-4-methyl-3-oxo-5-phenyl-4-pentenenitrile (2.114a)

By following the general procedure 1, starting from (2*E*)-*N*-methoxy-*N*,2-dimethyl-3-phenylacrylamide (0.205 g, 1.0 mmol, 1.0 equiv), CH_3CN (0.08 g, 0.1 mL, 2.0 mmol, 2.0 equiv)

and MeLi-LiBr (1.0 mL, 1.5 mmol, 1.5 equiv) in THF, β-oxonitrile **2.114a** was obtained in 87% yield (0.161 g) as a yellow solid, mp**:** 80°C.

IR (NaCl, ν_{max}, cm^{-1}): 2253, 1793, 1684, 1469, 1382.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44 (s, 1H, C<u>H</u>=CCO), 7.43 (m, 4H, Ph H-2,3,5,6), 7.40 (m, 1H, Ph H-4), 3.97 (s, 2H, CH_2CN), 2.10 (s, 3H, CH=CC<u>H</u>$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 189.1 (C=O), 141.8 (<u>C</u>H=CCO), 135.4 (CH=<u>C</u>CO), 134.6 (Ph C-1), 129.9 (Ph C-2,6), 129.4 (Ph C-4), 128.6 (Ph C-3,5), 114.3 (CN, ^{2}J(CN,CH_2) = 10.3 Hz), 28.6 (<u>C</u>H_2CN, ^{1}J(CH_2) = 134.6 Hz), 13.1 (CH=C<u>C</u>H_3, ^{1}J(CH_3) = 129.0 Hz, ^{3}J(CH_3,=CH) = 8.0 Hz). **^{15}N NMR** (40 MHz, $CDCl_3$) δ: -127.4 (CN).

Anal. Calcd for $C_{12}H_{11}NO$.Calcd.: C, 77.81; H, 5.99; N, 7.56. **Found**: C, 77.97; H, 6.08; N, 7.70.

(4*E*)-5-(2-methoxyphenyl)-3-oxo-4-pentenenitrile (2.114b)

By following the general procedure 1, starting from (2*E*)-*N*-methoxy-3-(2-methoxyphenyl)-*N*-methylacrylamide (0.221 g, 1.0 mmol, 1.0 equiv), CH_3CN (0.08 g, 0.1 mL, 2.0 mmol, 2.0 equiv) and MeLi-LiBr (1.0 mL, 1.5 mmol, 1.5 equiv) in THF, β-oxonitrile **2.114b** was obtained in 85% yield (0.171 g) as a yellow semi-solid mass.

IR (NaCl, ν_{max}, cm^{-1}): 3076, 2258, 1691.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.97 (d, *J* = 16.2Hz, 1H, Ph-C<u>H</u>=CH), 7.54 (m, 1H, Ph H-6), 7.42 (m, 1H, Ph H-4), 6.99 (m, 1H, Ph H-5), 6.94 (m, 1H, Ph H-3), 6.94 (d, *J* = 16.2Hz, 1H, Ph-CH=C<u>H</u>), 3.91 (s, 3H, OCH_3), 3.74 (s, 2H, CH_2CN). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 186.9 (C=O), 158.9 (Ph C-2), 141.9 (Ph-<u>C</u>H=CH), 133.0 (Ph C-4), 129.4 (Ph C-6), 123.2 (Ph-CH=<u>C</u>H), 122.3 (Ph C-1), 120.9 (Ph C-5), 114.2 (CN), 111.1 (Ph C-3), 55.6 (OCH3), 30.5 (<u>C</u>H_2CN).

Anal. Calcd for $C_{12}H_{11}NO_2$.Calcd.: C, 71.63; H, 5.51; N, 6.96. **Found**: C, 71.77; H, 5.62; N, 7.10.

(4*E*,6*E*)-3-oxo-7-phenyl-4,6-heptadienenitrile (2.114c)

By following the general procedure 1, starting from (2*E*,4*E*)-*N*-methoxy-*N*-methyl-5-phenyl-2,4-pentadienamide (0.217 g, 1.0 mmol, 1.0 equiv), CH_3CN (0.08 g, 0.1 mL, 2.0 mmol, 2.0 equiv) and MeLi-LiBr (1.0 mL, 1.5 mmol, 1.5 equiv) in THF, β-oxonitrile **2.114c** was obtained in 90% yield (0.177 g) as a brown solid, mp**:** 69-70 °C.

IR (NaCl, ν_{max}, cm^{-1}): 2253, 1792, 1467, 1379.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46 (dd, *J* = 15.2, 10.9 Hz, 1H, H-5), 7.49 (m, 2H, Ph H-2,6), 7.37 (m, 3H, Ph H-3,4,5), 7.06 (d, *J* = 15.6 Hz, 1H, H-7), 6.91 (dd, *J* = 15.6, 10.9 Hz, 1H, H-6), 6.41 (d, *J* = 15.2 Hz, 1H, H-4), 3.64 (s, 2H, CH_2CN). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 186.2 (C=O), 146.4 (C-5), 144.5 (C-7), 135.4 (Ph C-1), 129.9 (Ph C-4), 128.9 (Ph C-3,5), 127.6 (Ph C-2,6), 125.7 (C-6), 125.4 (C-4), 114.1 (CN), 30.6 ($\underline{C}H_2CN$).

Anal. Calcd for $C_{13}H_{11}NO$.Calcd: C, 79.16; H, 5.62; N, 7.10. **Found**: C, 79.29; H, 5.71; N, 7.19.

2-oxo-3-phenylpropanenitrile (2.114d)

By following the general procedure 2, starting from *N*-methoxy-*N*-methylbenzamide (0.165 g, 1.0 mmol, 1.0 equiv), CH_3CN (0.18 g, 0.24 mL, 4.5 mmol, 4.5 equiv) and MeLi-LiBr (2.7 mL, 4.0 mmol, 4.0 equiv) in THF, β-oxonitrile **2.114d** was obtained in 90% yield (0.130 g) as a light yellow solid, mp**:** 80-82 °C (lit.,[86b] 81 °C).

IR (NaCl, ν_{max}, cm^{-1}): 3070, 2253, 1696, 1605, 1002.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.91 (m, 2H, Ph H-2,6), 7.66 (m, 1H, Ph H-4), 7.52 (m, 2H, Ph H-3,5), 4.10 (s, 2H, CH_2CN). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 187.1 (C=O), 134.7 (Ph C-4), 134.2 (Ph C-1), 129.1 (Ph C-3,5), 128.4 (Ph C-2,6), 113.8 (CN), 29.4 ($\underline{C}H_2CN$). **^{15}N NMR** (40 MHz, $CDCl_3$) δ: -126.0 (CN). **^{17}O NMR** (54 MHz, $CDCl_3$) δ: 542 (C=O).

Anal. Calcd for C_9H_7NO.Calcd: C, 74.47; H, 4.86; N, 9.65. **Found**: C, 74.61; H, 4.94; N, 9.80.

3-[4-(2-methyl-2-propanyl)phenyl]-3-oxopropanenitrile (2.114e)

By following the general procedure 2, starting from 4-*tert*-butyl-*N*-methoxy-*N*-methylbenzamide (0.221 g, 1.0 mmol, 1.0 equiv), CH_3CN (0.18 g, 0.24 mL, 4.5 mmol, 4.5 equiv) and MeLi-LiBr (2.7 mL, 4.0 mmol, 4.0 equiv) in THF, β-oxonitrile **2.114e** was obtained in 92% yield (0.185 g) as a white solid, mp**:** 75°C (lit.,[86a] 74-77°C).

IR (NaCl, ν_{max}, cm^{-1}): 3076, 2258, 1700.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85 (m, 2H, Ph H-2,6), 7.53 (m, 2H, Ph H-3,5), 4.06 (s, 2H, CH_2CN) 1.34 (s, 9H, $C(CH_3)_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 186.6 (C=O), 158.8 (Ph C-4), 131.7 (Ph C-1), 128.5 (Ph C-2,6), 126.1 (Ph C-3,5), 113.9 (CN), 35.3 ($\underline{C}(CH_3)_3$), 30.9 ($C(\underline{C}H_3)_3$), 29.2 ($\underline{C}H_2CN$, $^1J(CH_2)$ = 134.3 Hz, $^2J(CN,CH_2)$ = 10.2 Hz). **^{15}N NMR** (40 MHz, $CDCl_3$) δ: -126.5 (CN).

Anal. Calcd for $C_{13}H_{15}NO$.Calcd.: C, 77.58; H, 7.51; N, 6.96. **Found**: C, 77.72; H, 7.65; N, 7.06.

3-(4-methoxyphenyl)-3-oxopropanenitrile (2.114f)

By following the general procedure 2, starting from *N*,4-dimethoxy-*N*-methylbenzamide (0.195 g, 1.0 mmol, 1.0 equiv), CH_3CN (0.18 g, 0.24 mL, 4.5 mmol, 4.5 equiv) and MeLi-LiBr (2.7 mL, 4.0 mmol, 4.0 equiv) in THF, β-oxonitrile **2.114f** was obtained in 83% yield (0.145 g) as a white solid, mp**:** 119-120°C (lit.,[86b] 123-126 °C).

IR (NaCl, ν_{max}, cm^{-1}): 3081, 2250, 1701, 1602, 1524,999. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.89 (m, 2H, Ph H-2,6), 6.97 (m, 2H, Ph H-3,5), 4.02 (s, 2H, CH_2CN), 3.89 (s, 3H, OCH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 185.4 (C=O), 164.7 (Ph C-4), 130.9 (Ph C-2,6), 127.2 (Ph C-1), 114.3 (Ph C-3,5), 114.1 (CN), 55.6 (OCH3, $^1J(OCH_3)$ = 144.9 Hz), 29.0 ($\underline{C}H_2CN$, $^1J(CH_2)$ = 134.2 Hz, $^2J(CN,CH_2)$ = 10.2 Hz). **^{15}N NMR** (40 MHz, $CDCl_3$) δ: -126.7 (CN). **^{17}O NMR** (54 MHz, CD_3CN) δ: 521 (C=O), 65 (OCH_3).

Anal. Calcd for $C_{10}H_9NO_2$.Calcd.: C, 68.56; H, 5.18; N, 8.00. **Found**: C, 68.69; H, 5.26; N, 8.12.

3-oxo-3-(3,4,5- trimethoxyphenyl)propanenitrile (2.114g)

By following the general procedure 2, starting from *N*,3,4,5-tetramethoxy-*N*-methylbenzamide(0.225 g, 1.0 mmol, 1.0 equiv), CH_3CN (0.18 g, 0.24 mL, 4.5 mmol, 4.5 equiv) and MeLi-LiBr (2.7 mL, 4.0 mmol, 4.0 equiv) in THF, β-oxonitrile **2.114g** was obtained in 79% yield (0.186 g) as a white solid, mp**:** 129-130°C.

IR (NaCl, ν_{max}, cm^{-1}): 3077, 2253, 1706, 1598, 1520.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.15 (s, 2H, Ph H-2,6), 4.05 (s, 2H, CH_2CN), 3.94 (s, 3H, Ph 4-OCH_3), 3.92 (s, 6H, Ph 3,5-OCH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 185.8 (C=O), 153.3 (Ph C-3,5) 144.1 (Ph C-4), 129.2 (Ph C-1), 113.8 (CN), 106.1 (Ph C-2,6), 61.0 (Ph C-4-O$\underline{C}H_3$), 56.4 (Ph C-3,5-O$\underline{C}H_3$), 29.2 ($\underline{C}H_2CN$). **^{15}N NMR** (40 MHz, $CDCl_3$) δ: -126.0 (CN).

Anal. Calcd for $C_{12}H_{13}NO_4$.Calcd.: C, 61.27; H, 5.57; N, 5.95. **Found**: C, 61.40; H, 5.69; N, 6.09.

3-(2-chlorophenyl)-3-oxopropanenitrile (2.114h)

By following the general procedure 2, starting from 2-chloro-*N*-methoxy-*N*-methylbenzamide (0.200 g, 1.0 mmol, 1.0 equiv), CH_3CN (0.18 g, 0.24 mL, 4.5 mmol, 4.5 equiv) and MeLi-LiBr (2.7 mL, 4.0 mmol, 4.0 equiv) in THF, β-oxonitrile **2.114h** was obtained in 89% yield (0.160 g) as a yellow solid, mp**:** 51-54 °C (lit.,[84c] 50-54°C).

IR (NaCl, ν_{max}, cm^{-1}): 3082, 2256, 1698, 1002.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63 (m, 1H, Ph H-6), 7.51 (m, 1H, Ph H-4), 7.47 (m, 1H, Ph H-3), 7.40 (m, 1H, Ph H-5), 4.15 (s, 2H, CH_2CN). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 189.4 (C=O), 135.6 (Ph C-1), 133.7 (Ph C-4), 131.7 (Ph C-2), 131.0 (Ph C-3), 130.4 (Ph C-6), 127.5 (Ph C-5), 113.3 (CN), 32.9 ($\underline{C}H_2CN$). **^{15}N NMR** (40 MHz, $CDCl_3$) δ: -126.5 (CN).

Anal. Calcd for C_9H_6ClNO.Calcd.: C, 60.19; H, 3.37; N, 7.80. **Found**: C, 60.30; H, 3.48; N, 7.89.

3-(4-biphenylyl)-3-oxopropanenitrile (2.114i)

By following the general procedure 2, starting from *N*-methoxy-*N*-methyl-4-phenylbenzamide (0.241 g, 1.0 mmol, 1.0 equiv), CH_3CN (0.18 g, 0.24 mL, 4.5 mmol, 4.5 equiv) and MeLi-LiBr (2.7 mL, 4.0 mmol, 4.0 equiv) in THF, β-oxonitrile **2.114i** was obtained in 91% yield (0.201 g) as a yellow solid, mp**:** 112 °C (lit.,[138] 112-113 °C).

IR (NaCl, ν_{max}, cm^{-1}): 3078, 2252, 1703, 1595, 996.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (m, 2H, Ph H-2,6), 7.74 (m, 2H, Ph H-3,5), 7.63 (m, 2H, Ph′ H-2,6), 7.49 (m, 2H, Ph′ H-3,5), 7.43 (m, 1H, Ph′ H-4), 4.11 (s, 2H, CH_2CN). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 186.6 (C=O), 147.5 (Ph C-4), 139.2 (Ph′ C-1), 132.9 (Ph C-1), 129.1 (Ph C-2,6, Ph′ C-3,5), 128.7 (Ph′ C-4), 127.7 (Ph C-3,5), 127.3 (Ph′ C-2,6), 113.8 (CN), 29.4 ($\underline{C}H_2CN$).

Anal. Calcd for $C_{15}H_{11}NO$.Calcd.: C, 81.43; H, 5.01; N, 6.33. **Found**: C, 81.52; H, 5.12; N, 6.43.

3-(4-fluorophenyl)-3-oxopropanenitrile (2.114j)

By following the general procedure 2, starting from 4-fluoro-*N*-methoxy-*N*-methylbenzamide (0.183 g, 1.0 mmol, 1.0 equiv), CH_3CN (0.18 g, 0.24 mL, 4.5 mmol, 4.5 equiv) and MeLi-LiBr (2.7 mL, 4.0 mmol, 4.0 equiv) in THF, β-oxonitrile **2.114j** was obtained in 93% yield (0.152 g) as a light yellow solid, mp**:** 85-86°C (lit.,[86b] 84-86 °C).

IR (NaCl, ν_{max}, cm^{-1}): 3078, 2252, 1703, 1595, 996.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96 (m, 2H, Ph H-2,6), 7.20 (m, 2H, Ph H-3,5), 4.08 (s, 2H, CH_2CN). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 185.6 (C=O), 166.6 (Ph C-4, $^1J_{C,F}$= 258.1 Hz), 131.3 (Ph C-2,6, $^3J_{C,F}$= 9.7 Hz), 130.7 (Ph C-1, $^4J_{C,F}$= 3.0 Hz), 116.4 (Ph C-3,5 $^2J_{C,F}$= 22.2 Hz), 113.6 (CN), 29.4 ($\underline{C}H_2CN$). **^{15}N NMR** (40 MHz, $CDCl_3$) δ: -125.6 (CN). **^{17}O NMR** (54 MHz, $CDCl_3$) δ: 536. **^{19}F NMR** (376 MHz, $CDCl_3$) δ: -101.6 (m).

Anal. Calcd for C_9H_6FNO.Calcd.: C, 66.26; H, 3.71; N, 8.59. **Found**: C, 66.38; H, 3.79; N, 8.71.

3-(2-furyl)-3-oxopropanenitrile (2.114k)

By following the general procedure 2, starting from *N*-methoxy-*N*-methyl-2-furancarboxamide (0.155 g, 1.0 mmol, 1.0 equiv), CH_3CN (0.18 g, 0.24 mL, 4.5 mmol, 4.5 equiv) and MeLi-LiBr (2.7 mL, 4.0 mmol, 4.0 equiv) in THF, β-oxonitrile **2.114k** was obtained in 82% yield (0.099 g) as a light yellow solid, mp**:** 69 °C (lit.,[139] 66-68 °C).

IR (NaCl, ν_{max}, cm^{-1}): 2247, 1699, 998.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65 (d, *J* = 1.6 Hz, 1H, Furyl H-5), 7.36 (d, *J* = 3.6 Hz, 1H, Furyl H-3), 6.62 (dd, *J* = 3.6, 1.6 Hz, 1H, Furyl H-4), 3.98 (s, 2H, CH_2CN). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 175.8 (C=O), 150.3 (Furyl C-2), 147.8 (Furyl C-5), 119.3 (Furyl C-3), 113.4 (CN), 113.3 (Furyl C-4), 28.8 ($\underline{C}H_2CN$, $^1J(CH_2)$=135.6 Hz). **^{15}N NMR** (40 MHz, $CDCl_3$) δ: -126.9 (CN). **^{17}O NMR** (54 MHz, $CDCl_3$) δ: 510 (C=O), 239 (Furane-O).

Anal. Calcd for $C_7H_5NO_2$.Calcd.: C, 62.22; H, 3.73; N, 10.37. **Found**: C, 62.35; H, 3.81; N, 10.46.

3-oxo-3-(2-thienyl)propanenitrile (2.114l)

By following the general procedure 2, starting from *N*-methoxy-*N*-methyl-2-thiophenecarboxamide(0.171 g, 1.0 mmol, 1.0 equiv), CH_3CN (0.18 g, 0.24 mL, 4.5 mmol, 4.5 equiv) and MeLi-LiBr (2.7 mL, 4.0 mmol, 4.0 equiv) in THF, β-oxonitrile **2.114l** was obtained in 80% yield (0.120 g) as a yellow solid, mp**:** 133 °C (lit.,[86b] 131-135 °C).

IR (NaCl, ν_{max}, cm^{-1}): 3079, 2254, 1691.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79 (dd, *J* = 4.9, 1.1 Hz, 1H, Th H-5), 7.78 (dd, *J* = 3.9, 1.1 Hz, 1H, Th H-3), 7.20 (dd, *J* = 4.9, 3.9 Hz, 1H, Th H-4), 4.01 (s, 2H, CH_2CN). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 179.5 (C=O), 140.8 (Th C-2, ^2J(C-2,H-3) = 7.0 Hz, ^3J(C-2,H-4) = 9.0 Hz, ^3J(C-2,H-5) = 5.9 Hz), 136.3 (Th C-5, ^1J(C-5,H-5) = 186.4 Hz, ^2J(C-5,H-4) = 7.2 Hz, ^3J(C-5,H-3) = 10.9 Hz), 133.7 (Th C-3, ^1J(C-3,H-3) = 167.8 Hz, ^2J(C-3,H-4) = 5.5 Hz, ^3J(C-3,H-5) = 9.3 Hz), 128.7 (Th C-4,

^{1}J(C-4,H-4) = 171.6 Hz, ^{2}J(C-4,H-3) = 4.1 Hz, ^{3}J(C-4,H-5) = 4.1 Hz), 113.4 (CN, ^{2}J(CN,CH_2) = 10.3 Hz), 29.5 ($\underline{C}H_2CN$, ^{1}J(CH_2) = 135.0 Hz).

Anal. Calcd for C_7H_5NOS.Calcd.: C, 55.61; H, 3.33; N, 9.26; S, 21.21. **Found**: C, 55.71; H, 3.41; N, 9.40; S, 21.12.

3-oxo-4-phenylbutanenitrile (2.114m)

By following the general procedure 2, starting from *N*-methoxy-*N*-methyl-2-phenylacetamide(0.179 g, 1.0 mmol, 1.0 equiv), CH_3CN (0.18 g, 0.24 mL, 4.5 mmol, 4.5 equiv) and MeLi-LiBr (2.7 mL, 4.0 mmol, 4.0 equiv) in THF, β-oxonitrile **2.114m** was obtained in 84% yield (0.134 g) as a yellow solid, mp**:** 30 °C (lit.,[140] 29 °C).

IR (NaCl, ν_{max}, cm^{-1}): 2248, 1702.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 (m, 2H, Ph H-3,5), 7.31 (m, 1H, Ph H-4), 7.20 (m, 2H, Ph H-2,6), 3.82 (s, 2H, Ph-C$\underline{H}_2$), 3.48 (s, 2H, CH_2CN). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 195.6 (C=O), 131.9 (Ph C-1), 129.3 (Ph C-2,6), 129.0 (Ph C-3,5), 127.7 (Ph C-4), 113.7 (CN), 48.9 (Ph-$\underline{C}$H), 31.2 ($\underline{C}H_2CN$). **^{15}N NMR** (40 MHz, $CDCl_3$) δ: -126.8 (CN) **^{17}O NMR** (54 MHz, $CDCl_3$) δ: 574 (C=O).

Anal. Calcd for $C_{10}H_9NO$.Calcd.: C, 75.45; H, 5.70; N, 8.80. **Found**: C, 75.55; H, 5.82; N, 8.94.

4,4-dimethyl-3-oxopentanenitrile (2.114n)

By following the general procedure, starting from *N*-methoxy-*N*,2,2-trimethylpropanamide(0.145 g, 1.0 mmol, 1.0 equiv), CH_3CN (0.18 g, 0.24 mL, 4.5 mmol, 4.5 equiv) and MeLi-LiBr (2.7 mL, 4.0 mmol, 4.0 equiv) in THF, β-oxonitrile **2.114n** was obtained in 74% yield (0.092 g) as a light brown solid, mp: 70 °C (lit.,[137] 70 °C).

IR (NaCl, ν_{max}, cm^{-1}): 2252, 1699.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.64 (s, 2H, CH_2CN), 1.18 (s, 9H, $C(CH_3)_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 202.8 (C=O), 114.1 (CN), 44.5 ($\underline{C}(CH_3)_3$), 27.4 ($\underline{C}H_2CN$, ^{1}J(CH_2) = 134.1 Hz), 26.0

($C(\underline{C}H_3)_3$, $^1J(CH_3)$ = 127.6 Hz). **^{15}N NMR** (40 MHz, $CDCl_3$) δ: -127.8 (CN). **^{17}O NMR** (54 MHz, $CDCl_3$) δ: 560 (C=O).

Anal. Calcd for $C_7H_{11}NO$.Calcd.: C, 67.17; H, 8.86; N, 11.19. **Found**: C, 67.29; H, 8.97; N, 11.31.

3-(adamantan-1-yl)-3-oxopropenenitrile (2.114o)

By following the general procedure 2, starting from *N*-methoxy-*N*-methyl-1-adamantanecarboxamide (0.223 g, 1.0 mmol, 1.0 equiv), CH_3CN (0.18 g, 0.24 mL, 4.5 mmol, 4.5 equiv) and MeLi-LiBr (2.7 mL, 4.0 mmol, 4.0 equiv) in THF, β-oxonitrile **2.114o** was obtained in 68% yield (0.138 g) as a white solid, mp: 112 °C.

IR (NaCl, ν_{max}, cm^{-1}): 2249, 1703, 998.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.58 (s, 2H, CH_2CN), 2.08 (m, 3H, Adamant H-3,5,7), 1.82 (d, *J* = 2.8 Hz, 6H, Adamant H-2,8,9), 1.76 (m, 3H, Adamant H-4,6,10) 1.68 (m, 3H, Adamant H-4, 6, 10). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 202.2 (C=O), 114.1 (CN), 46.8 (Adamant C-1), 37.9 (Adamant C-2,8,9), 36.1 (Adamant C-4,6,10), 27.6 (Adamant C-3,5,7), 27.0 ($\underline{C}H_2CN$). **^{15}N NMR** (40 MHz, $CDCl_3$) δ: -127.5 (CN). **^{17}O NMR** (54 MHz, $CDCl_3$) δ: 561 (C=O).

Anal. Calcd for $C_{13}H_{17}NO$.Calcd.: C, 76.81; H, 8.43; N, 6.89. **Found**: C, 76.92; H, 8.52; N, 6.99.

2,2-dimethyl-3-oxoheptanenitrile (2.115a)

By following the general procedure 2, starting from *N*-methoxy-*N*-methylpentanamide (0.145 g, 1.0 mmol, 1.0 equiv), $(CH_3)_2CCN$ (0.31 g, 0.4 mL, 4.5 mmol, 4.5 equiv) and MeLi-LiBr (2.7 mL, 4.0 mmol, 4.0 equiv) in THF, β-oxonitrile **2.115a** was obtained in 82% yield (0.125 g) as a light yellow oil.

IR (NaCl, ν_{max}, cm^{-1}): 2253, 1709.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.77 (t, *J* = 7.3 Hz, 2H, CH_2CO), 1.59 (m, 2H, $C\underline{H}_2CH_2CO$), 1.47 (s, 6H, $C(C\underline{H}_3)_2$), 1.32 (m, 2H, $C\underline{H}_2CH_3$), 0.91 (t, *J* = 7.4 Hz, 3H, $CH_2C\underline{H}_3$). **^{13}C NMR** (100 MHz,

$CDCl_3$) δ: 204.3 (C=O), 122.0 (CN), 43.5 (<u>C</u>$(CH_3)_2$), 38.3 (<u>C</u>H_2CO), 25.6 (<u>C</u>H_2CH_2CO), 23.8 (C(<u>C</u>$H_3)_2$), 22.0 (<u>C</u>H_2CH_3), 13.7 (CH_2<u>C</u>H_3).

Anal. Calcd for $C_9H_{15}NO$.Calcd.: C, 70.55; H, 9.87; N, 9.14. **Found**: C, 70.77; H, 10.01; N, 9.28.

2, dimethyl-3-oxo-3-phenylpropanenitrile (2.115b)

By following the general procedure 2, starting from *N*-methoxy-*N*-methylbenzamide(0.165 g, 1.0 mmol, 1.0 equiv), $(CH_3)_2CCN$(0.31 g, 0.4 mL, 4.5 mmol, 4.5 equiv) and MeLi-LiBr (2.7 mL, 4.0 mmol, 4.0 equiv) in THF, β-oxonitrile **2.115b** was obtained in 86% yield (0.149 g) as a light yellow oil.

IR (NaCl, ν_{max}, cm^{-1}): 3081, 2260, 1713, 1523, 1491, 1001.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 (m, 2H, Ph H-2,6), 7.58 (m, 1H, Ph H-4), 7.47 (m, 2H, Ph H-3,5), 1.69 (s, 6H, C(C<u>H</u>$_3)_2$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 193.7 (C=O), 133.6 (Ph C-4), 133.4 (Ph C-1), 129.2 (Ph C-2,6), 128.5 (Ph C-3,5), 122.4 (CN), 40.6 (<u>C</u>CN), 25.4 (C(<u>C</u>$H_3)_2$). **^{15}N NMR** (40 MHz, $CDCl_3$) δ: -129.0 (CN).

Anal. Calcd for $C_{11}H_{11}NO$.Calcd.: C, 76.28; H, 6.40; N, 8.09. **Found**: C, 76.39; H, 6.54; N, 8.22.

3-(4-biphenylyl)-2,2-dimethyl-3-oxopropanenitrile (2.115c)

By following the general procedure 2, starting from *N*-methoxy-*N*-methyl-4-phenylbenzamide (0.241 g, 1.0 mmol, 1.0 equiv), $(CH_3)_2CCN$ (0.31 g, 0.4 mL, 4.5 mmol, 4.5 equiv) and MeLi-LiBr (2.7 mL, 4.0 mmol, 4.0 equiv) in THF, β-oxonitrile **2.115c** was obtained in 87% yield (0.217 g) as a white solid, mp: 96-97 °C.

IR (NaCl, ν_{max}, cm^{-1}): 3081, 2260, 1713, 1523, 1491, 1001.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.26 (m, 2H, Ph H-2,6), 7.73 (m, 2H, Ph H-3,5), 7.64 (m, 2H, Ph′ H-2,6), 7.49 (m, 2H, Ph′ H-3,5), 7.42 (m, 1H, Ph′ H-4), 1.76 (s, 6H, (C<u>H</u>$_3)_2$C). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 193.3 (C=O), 146.5 (Ph C-4), 139.4 (Ph′ C-1), 132.1 (Ph C-1), 130.1 (Ph C-2,6),

129.0 (Ph′ C-3,5), 128.5 (Ph′ C-4), 127.3 (Ph C-3,5, Ph′ C-2,6), 122.7 (CN), 40.7 (CCN), 25.6 ($C(CH_3)_2$). **^{15}N NMR** (40 MHz, $CDCl_3$) δ: -130.3 (CN).

Anal. Calcd for $C_{17}H_{15}NO$.Calcd.: C, 81.90; H, 6.06; N, 5.62. **Found**: C, 82.12; H, 6.18; N, 5.74.

3-(4-biphenylyl)-2-(4-methoxyphenyl)-3-oxopropanenitrile (2.115d)

By following the general procedure 2, starting from *N*-methoxy-*N*-methyl-4-phenylbenzamide (0.241 g, 1.0 mmol, 1.0 equiv), 4-Methoxyphenylacetonitrile (0.66 g, 0.36 mL, 4.5 mmol, 4.5 equiv) and MeLi-LiBr (2.7 mL, 4.0 mmol, 4.0 equiv) in THF, β-oxonitrile **2.115d** was obtained in 80% yield (0.261 g) as a pink solid, mp: 108 °C.

IR (NaCl, ν_{max}, cm^{-1}): 3083, 2256, 1708, 997.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01 (m, 2H, Ph H-2,6), 7.67 (m, 2H, Ph H-3,5), 7.59 (m, 2H, Ph′ H-2,6), 7.47 (m, 2H, Ph′ H-3,5), 7.41 (m, 1H, Ph′ H-4), 7.38 (m, 2H, Ph′′ H-2, 6), 6.92 (m, 2H, Ph′′ H-3, 5), 5.59 (s, 1H, -HCCN), 3.79 (s, 3H, OCH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 188.6 (C=O), 160.1 (Ph′′ C-4), 147.0 (Ph C-4), 139.2 (Ph′ C-1), 132.2 (Ph C-1), 129.8 (Ph C-2,6), 129.5 (Ph′′ C-2,6), 129.0 (Ph′ C-3,5), 128.6 (Ph′ C-4), 127.5 (Ph C-3,5), 127.2 (Ph′ C-2,6), 122.2 (Ph′′ C-1), 116.8 (CN), 115.1 (Ph ′′ C-3,5), 55.3 (OCH_3) 46.0 (-CHCN). **^{15}N NMR** (40 MHz, $CDCl_3$) δ: -127.1 (CN).

Anal. Calcd for $C_{22}H_{17}NO_2$.Calcd.: C, 80.71; H, 5.23; N, 4.28. **Found**: C, 80.84; H, 5.32; N, 4.36.

2-(4-methoxyphenyl)-3-oxo-4-phenylbutanenitrile (2.115e)

By following the general procedure, starting from *N*-methoxy-*N*-methyl-2-phenylacetamide(0.179 g, 1.0 mmol, 1.0 equiv), 4-methoxyphenylacetonitrile (0.66 g, 0.36 mL, 4.5 mmol, 4.5 equiv) and MeLi-LiBr (2.7 mL, 4.0 mmol, 4.0 equiv) in THF, β-oxonitrile**6e** was obtained in 77% yield (0.204 g) as a viscous yellow oil.

IR (NaCl, ν_{max}, cm^{-1}): 2261, 1702.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31 (m, 3H, Ph H-3,4,5), 7.24 (m, 2H, Ph′ H-2,6), 7.07 (m, 2H, Ph H-2,6), 6.94 (m, 2H, Ph′ H-3,5), 4.73 (s, 1H, CHCN), 3.83 and 3.76, (AB-System, ^{2}J = 15.9 Hz, 2H, $COC\underline{H}_2$), 3.82 (s, 3H, OCH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 196.6 (C=O), 160.2 (Ph′ C-4), 132.1 (Ph C-1), 129.5 (Ph′ C-2,6), 129.4 (Ph C-2,6), 128.8 (Ph C-3,5), 127.5 (Ph C-4), 121.3 (Ph′ C-1), 116.3 (CN), 115.0 (Ph′ C-3,5), 55.3 (OCH_3), 49.0 ($\underline{C}HCN$), 46.3 (CH_2). **^{15}N NMR** (40 MHz, $CDCl_3$) δ: -126.3 (CN).

Anal. Calcd for $C_{17}H_{15}NO_2$.Calcd.: C, 76.96; H, 5.70; N, 5.28. **Found**: C, 77.10; H, 5.81; N, 5.40.

Synthesis of ethyl (2*E*)-4-cyano-3-phenyl-2-butenoateEthyl (2.116)

To a solution of cyanoketone **2.114d** (145 mg, 1.0 mmol, 1.0 equiv) dissolved in dry 2-MeTHF (2 mL) was added (carbethoxymethylene)triphenylphosphorane (383 mg, 1.1 mmol, 1.1 equiv) and the resulting mixture was stirred for 16 h at rt. Then, a saturated solution of NH_4Cl (aq) was added and the organic phase directly extracted in 2-MeTHF, dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure and purification of the crude through silica gel chromatography (petroleum ether – ethyl acetate, 95:5), compound **7** was obtained as a yellowish oil (187 mg, 87% yield).

IR (NaCl, ν_{max}, cm^{-1}): 2250, 1711, 1490, 998.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.50 – 7.33 (m, 5H, Ph-H), 5.78 (s, 1H, alkene-H), 4.13 (q, *J* = 7.1 Hz, 2H, $OC\underline{H}_2$), 3.89 (s, 2H, $C\underline{H}_2CN$), 1.19 (t, *J* 39.3, 13.9.

Anal. Calcd for $C_{13}H_{13}NO_2$.Calcd: C, 72.54; H, 6.09; N, 6.51. **Found**: C, 72.71; H, 6.22; N, 6.35.

2.3.3 General procedure for Dichloromethylation of Phenyl Isocyanate with Lithium Diisopropylamide and Lithium Dicyclohexylamide (General Procedure 3)

A 1.5 M MeLi–LiBr solution (3.0 mL, 4.5 mmol, 4.5 equiv) was added dropwise to a precooled solution of the corresponding amine (4.5 equiv) in THF (4 mL) at 0 °C.32f The generated

lithium amide was transferred to a cooled (–78 °C) solution of phenyl isocyanate (0.11 mL, 119 mg, 1.0 mmol, 1.0 equiv) and CH_2Cl_2 (425 mg, 0.32 mL, 5.0 mmol, 5.0 equiv) in dry THF (1 M concentration) over 5 min. The resulting solution was stirred for 1 h at this temperature, and then sat. aq NH_4Cl was added (2 mL/mmol substrate). After removal of the cooling bath, the mixture was stirred till it reached r.t. and then extracted with additional Et_2O (2 × 5 mL) and washed with 3 M HCl and brine. The organic phase was dried (anhyd Na_2SO_4), filtered, and, after removal of the solvent under reduced pressure, afforded a mixture of compounds **2.118** and **2.119a** or **2.119b (Table 2.3).**

2,2-Dichloro-*N*-phenylacetamide (**2.118**)

Yield: 177 mg (87%); white solid; mp 106–107 °C (Lit.,[141] 109 °C).

IR (NaCl): 1673, 1601, 1498 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (br s, 1 H, NH), 7.56 (m, 2 H, $H2_{Ph}$, $H6_{Ph}$), 7.39 (m, 2 H, $H3_{Ph}$, $H5_{Ph}$), 7.21 (m, 1 H, $H4_{Ph}$), 6.05 (s, 1 H, Cl_2CH). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 161.7 (C=O), 136.2 ($C1_{Ph}$), 129.2 ($C3_{Ph}$, $C5_{Ph}$), 125.7 ($C4_{Ph}$), 120.2 ($C2_{Ph}$, $C6_{Ph}$), 66.9 (Cl_2CH). ^{15}N NMR (40 MHz, $CDCl_3$): δ = –259.3 (NH).

1,1-Diisopropyl-3-phenylurea (**2.119a**)

Yield: 189 mg (86%); white solid; mp 112–114 °C (Lit.,[142] 114–116 °C).

IR (NaCl): 1632, 1521, 1445, 1332, 1247 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (m, 2 H, $H2_{Ph}$, $H6_{Ph}$), 7.28 (m, 2 H, $H3_{Ph}$, $H5_{Ph}$), 7.01 (m, 1 H, $H4_{Ph}$), 6.18 (br s, 1 H, NH), 3.99 (sept, *J* = 6.9 Hz, 2 H, $CHMe_2$), 1.34 [br s, 12 H, $CH(CH_3)_2$]. **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 154.6 (C=O), 139.3 ($C1_{Ph}$), 128.9 ($C3_{Ph}$, $C5_{Ph}$), 122.6 ($C4_{Ph}$),

119.7 ($C2_{Ph}$, $C6_{Ph}$), 45.4 ($CHMe_2$), 21.5 [$CH(CH_3)_2$]. **^{15}N NMR** (40 MHz, $CDCl_3$): δ = –276.4 (PhNH), –268.2 (*i*-PrN).

Anal. Calcd for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found: C, 70.93; H, 9.31; N, 12.86.

1,1-Dicyclohexyl-3-phenylurea (2.119b)

Yield: 234 mg (78%); white solid; mp 170–171 °C.

IR (NaCl): 1635, 1520 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (m, 2 H, $H2_{Ph}$, $H6_{Ph}$), 7.27 (m, 2 H, $H3_{Ph}$, $H5_{Ph}$), 7.00 (m, 1 H, $H4_{Ph}$), 6.25 (br s, 1 H, NH), 3.48 (m, 2 H, $H1_{Cy}$), 1.84 (m, 4 H, $H3_{Cy}$, $H5_{Cy}$), 1.76 (m, 8 H, $H2_{Cy}$, $H6_{Cy}$), 1.68 (m, 2 H, $H4_{Cy}$), 1.35 (m, 4 H, $H3'_{Cy}$, $H5'_{Cy}$), 1.14 (m, 2 H, $H4'_{Cy}$). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 154.9 (C=O), 139.4 ($C1_{Ph}$), 128.8 ($C3_{Ph}$, $C5_{Ph}$), 122.5 ($C4_{Ph}$), 119.6 ($C2_{Ph}$, $C6_{Ph}$), 55.4 ($C1_{Cy}$), 31.9 ($C2_{Cy}$, $C6_{Cy}$), 26.4 ($C3_{Cy}$, $C5_{Cy}$), 25.5 ($C4_{Cy}$). **^{15}N NMR** (40 MHz, $CDCl_3$): δ = –276.1 (NH), CyN not found.

Anal. Calcd for $C_{19}H_{28}N_2O$: C, 75.96; H, 9.39; N, 9.32. **Found**: C, 76.09; H, 9.48; N, 9.40.

2.3.4 General Procedure for Chemoselective Addition of Lithium Polyhalocarbenoids to Isocyanates (General Procedure 4)

A 1.5 M MeLi–LiBr solution (3.0 mL, 4.5 mmol, 4.5 equiv) was added dropwise to a precooled solution of 2,2,6,6-tetramethylpiperidine (0.77 mL, 636 mg, 4.5 mmol, 4.5 equiv) in THF (4 mL) at 0 °C. The generated LTMP was transferred to a cooled (–78 °C) solution of the isocyanate (1.0 equiv) and dihalomethane (5.0 equiv) in dry THF (1 M concentration) over 5 min. The resulting solution was stirred for 1 h at this temperature, and then sat. aq NH_4Cl was added (2 mL/mmol substrate). After removal of the cooling bath, the mixture was stirred until it reached r.t. and then extracted with additional Et_2O (2 × 5 mL) and washed with 3 M HCl and brine. The organic phase was dried (anhyd Na_2SO_4), filtered and, after removal of the solvent under reduced

pressure; the so-obtained crude mixture was subjected to chromatography (silica gel) to afford pure dihaloamides.

2,2-Dichloro-*N*-(1-naphthyl)acetamide (2.121a)

By following general procedure 4, starting from 1-naphthyl isocyanate (0.14 mL, 169 mg, 1.0 mmol) and CH_2Cl_2 (425 mg, 0.32 mL, 5.0 mmol) in THF (1 mL) with chromatography (silica gel, petroleum ether–EtOAc, 8:2, Rf = 0.4) gave **2.121a** (216 mg, 85%) as a colorless solid; mp 135–137 °C.

IR (NaCl): 1675, 1605 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.59 (br s, 1 H, NH), 7.90 (m, 1 H $H5_{Naphth}$), 7.88 (m, 1 H, $H2_{Naphth}$), 7.86 (m, 1 H, $H8_{Naphth}$), 7.78 (m, 1 H, $H4_{Naphth}$), 7.58 (m, 1 H, $H7_{Naphth}$), 7.54 (m, 1 H, $H6_{Naphth}$), 7.49 (m, 1 H, $H3_{Naphth}$), 6.17 (s, 1 H, $CHCl_2$). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 162.6 (C=O), 134.0 ($C4a_{Naphth}$), 130.4 ($C1_{Naphth}$), 128.9 ($C5_{Naphth}$), 127.2 ($C8a_{Naphth}$), 127.1 ($C4_{Naphth}$), 126.9 ($C7_{Naphth}$), 126.4 ($C6_{Naphth}$), 125.6 ($C3_{Naphth}$), 121.2 ($C2_{Naphth}$), 120.2 ($C8_{Naphth}$), 67.1 ($CHCl_2$). ^{15}N NMR (40 MHz, $CDCl_3$): δ = –266.4 (NH).

Anal. Calcd for $C_{12}H_9Cl_2NO$: C, 56.72; H, 3.57; N, 5.51. **Found**: C, 56.81; H, 3.60; N, 5.58.

2,2-Dichloro-*N*-(2-phenylethyl)acetamide (2.121b)

By following general procedure 4, starting from phenethyl isocyanate (0.14 mL, 147 mg, 1.0 mmol) and CH_2Cl_2 (425 mg, 0.32 mL, 5.0 mmol) in THF (1 mL) with chromatography (silica gel, petroleum ether–EtOAc, 8:2, Rf = 0.45) gave **2.121b** (190 mg, 82%) as a colorless solid; mp 67–68 °C.

IR (NaCl): 1667, 1598, 1454 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (m, 2 H, $H3_{Ph}$, $H5_{Ph}$), 7.26 (m, 1 H, $H4_{Ph}$), 7.22 (m, 2 H, $H2_{Ph}$, $H6_{Ph}$), 6.57 (br s, 1 H, NH), 5.89 (s, 1 H, Cl_2CH), 3.59 (m, 2 H, $NHCH_2$), 2.88 (t, *J* = 7.0 Hz, 2 H, $PhCH_2$). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 164.0 (C=O), 138.0 ($C1_{Ph}$), 128.8 ($C2_{Ph}$, $C6_{Ph}$), 128.7 ($C3_{Ph}$, $C5_{Ph}$), 126.8 ($C4_{Ph}$), 66.4 (Cl_2CH), 41.5 ($NHCH_2$), 35.2 ($PhCH_2$). **^{15}N NMR** (40 MHz, $CDCl_3$): δ = –273.5 (NH).

Anal. Calcd for $C_{10}H_{11}C_{l2}NO$: C, 51.75; H, 4.78; N, 6.03. **Found**: C, 51.87; H, 4.90; N, 6.13.

2,2-Dibromo-*N*-phenylacetamide (2.121c)[112]

By following general procedure 4, starting from phenyl isocyanate (0.11 mL, 119 mg, 1.0 mmol) and CH_2Br_2 (869 mg, 0.35 mL, 5.0 mmol) in THF (1 mL), with chromatography (silica gel, petroleum ether–EtOAc, 8:2, Rf = 0.45) gave **2.121c** (246 mg, 84%) as a colorless solid; mp 115–117 °C.

IR (NaCl): 1670, 1601, 1497 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (br s, 1 H, NH), 7.55 (m, 2 H, $H2_{Ph}$, $H6_{Ph}$), 7.38 (m, 2 H, $H3_{Ph}$, $H5_{Ph}$), 7.20 (m, 1 H, $H4_{Ph}$), 5.94 (s, 1 H, Br_2CH). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 162.1 (C=O), 136.5 (C1Ph), 129.2 ($C3_{Ph}$, $C5_{Ph}$), 125.6 ($C4_{Ph}$), 120.1 ($C2_{Ph}$, $C6_{Ph}$), 36.7 (Br_2CH). ^{15}N NMR (40 MHz, $CDCl_3$): δ = –258.3 (NH).

Anal. Calcd for $C_8H_7Br_2NO$: C, 32.80; H, 2.41; N, 4.78. **Found**: C, 32.91; H, 2.48; N, 4.85.

2-Bromo-2-chloro-*N*-phenylacetamide (2.121d)[143]

By following general procedure 4, starting from phenyl isocyanate (0.11 mL, 119 mg, 1.0 mmol) and $ClCH_2Br$ (647 mg, 0.33 mL, 5.0 mmol) in THF (1 mL), with chromatography (silica gel,

petroleum ether–EtOAc, 8:2, Rf = 0.40) gave **2.121d** (176 mg, 71%) as a clear yellowish solid; mp 100–102 °C.

IR (NaCl): 1672, 1600, 1527, 1490 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (br s, 1 H, NH), 7.55 (m, 2 H, $H2_{Ph}$, $H6_{Ph}$), 7.38 (m, 2 H, $H3_{Ph}$, $H5_{Ph}$), 7.20 (m, 1 H, $H4_{Ph}$), 6.04 (s, 1 H, BrClCH). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 162.0 (C=O), 136.3 ($C1_{Ph}$), 129.2 ($C3_{Ph}$, $C5_{Ph}$), 125.6 ($C4_{Ph}$), 120.1 ($C2_{Ph}$, $C6_{Ph}$), 52.2 (BrClCH). **^{15}N NMR** (40 MHz, $CDCl_3$): δ = –259.2 (NH).

Anal. Calcd for $C_8H_7BrClNO$: C, 38.67; H, 2.84; N, 5.64. **Found**: C, 38.75; H, 2.90; N, 5.71.

2,2-Diiodo-*N*-phenylacetamide (2.121e)[110]

A 1 M LHDMS solution in THF (2 mL, 2.0 mmol, 4.0 equiv) in THF–Et_2O (3:2, 6 mL) was stirred at –78 °C for 10 min, then CH_2I_2 (0.18 mL, 589 mg, 2.2 mmol, 4.4 equiv) in THF (1.5 mL) was added dropwise to the mixture in the dark. After 20 min at –78 °C, phenyl isocyanate (0.06 mL, 60 mg, 0.50 mmol, 1.0 equiv) added dropwise to the mixture over 5 min. The reaction was then stirred overnight from –78 °C to r.t. The reaction was then quenched by the addition of sat. aq NH_4Cl. The aqueous solution was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layers were dried

(Na_2SO_4), and the solvent was removed under reduced pressure. Purification by flash chromatography (silica gel, petroleum ether–EtOAc, 8:2, Rf = 0.25) gave **2.121e** (298 mg, 77%) as a colorless solid; mp 163–165 °C.

IR (NaCl): 3081, 1671, 1602 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.32 (br s, 1 H, NH), 7.52 (m, 2 H, $H2_{Ph}$, $H6_{Ph}$), 7.33 (m, 2 H, $H3_{Ph}$, $H5_{Ph}$), 7.09 (m, 1 H, $H4_{Ph}$), 5.64 (s, 1 H, I_2CH). **^{13}C NMR** (126 MHz, DMSO-d_6): δ =

165.2 (C=O), 138.0 ($C1_{Ph}$), 128.9 ($C3_{Ph}$, $C5_{Ph}$), 124.0 ($C4_{Ph}$), 119.3 ($C2_{Ph}$, $C6_{Ph}$), –33.6 (I_2CH). **^{15}N NMR** (40 MHz, DMSO-d_6): δ = –260.3 (NH).

Anal. Calcd for $C_8H_7I_2NO$: C, 24.83; H, 1.82; N, 3.62. **Found**: C, 24.92; H, 1.86; N, 3.68.

2.3.5 General Procedure for the Chemoselective Addition of Li Carbenoids to Isocyanates (General Procedure 5)

To a cooled (–78 °C) solution of isocyanate (1.0 equiv) in dry Et_2O (1 M concentration) was added the dihalomethane derivative (1.5 equiv). After 2 min, an ethereal solution of 1.5 M MeLi–LiBr (1.25 equiv) was added dropwise over 5 min. The resulting solution was stirred for 1 h at that temperature. Sat. aq NH_4Cl was added (2 mL/mmol substrate) and the cooling bath was removed, the mixture was stirred till it reached r.t., and then it was extracted with additional Et_2O (2 × 5 mL) and washed with water (5 mL) and brine (10 mL). The organic phase was dried (anhyd Na_2SO_4), filtered, and the solvent removed under reduced pressure to give pure samples of haloacetamides.

2-Chloro-*N*-cyclohexylacetamide (**2.124**)[37b]

By following the general procedure 5, starting from cyclohexyl isocyanate (0.47 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in Et_2O gave **2.124** (647 mg, 97%) as a white solid; mp 113 °C.

IR (NaCl): 3241, 1651, 1567, 1223 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.40 (br s, 1 H), 3.96 (s, 2 H), 3.73–3.69 (m, 1 H), 1.87–1.84 (m, 2 H), 1.65–1.63 (m, 2 H), 1.5–1.53 (m, 1 H), 1.33–1.29 (m, 2 H), 1.16–1.13 (m, 3 H).**^{13}C NMR** (126 MHz, $CDCl_3$): δ = 164.8, 48.6, 42.7, 32.8, 25.4, 24.7.

Anal. Calcd for $C_8H_{14}ClNO$: C, 54.70; H, 8.03; N, 7.97. Found: C, 54.83; H, 8.14; N, 8.12.

Synthesis of Optically Active Halomethylamides

(*S*)-2-Chloro-*N*-(1-phenylethyl)acetamide (*S*-2.122a)[37b]

By following the general procedure 5, starting from (*S*)-methylbenzyl isocyanate (96 % ee purity) (0.56 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol) and MeLi-LiBr (3.04 mL, 4.56 mmol) in Et_2O, α-chloroacetamide ***S*-2.122a** was obtained in 96% yield (721 mg) as a white solid. Mp 100 °C.

IR (NaCl): 3260, 2974, 1652, 1542, 1230, 907 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30–7.18 (m, 5 H), 6.74 (s, 1 H), 5.05 (quint., *J* = 7.0 Hz, 1 H), 3.98 (m, 2 H), 1.46 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 165.0, 144.2, 128.8, 127.3, 125.8, 49.3, 42.7, 21.7.

Anal. Calcd for $C_{10}H_{12}ClNO$: C, 60.76; H, 6.12; N, 7.09. **Found**: C, 60.89; H, 6.29; N, 7.24.

HPLC (column: Chiralpak IA; *n*-hexane–*i*-PrOH, 95:5; 1 mL/min, 28 °C): t_R = 8.714 min [(*R*)-enantiomer, minor], 11.194 min [(*S*)-enantiomer, major]. Racemic sample: t_R = 9.173 min [(*R*)-enantiomer], 11.219 min [(*S*)-enantiomer]. $[\alpha]_D^{20}$ –56 (*c* 2, $CHCl_3$).

(*R*)-2-chloro-*N*-(1-(naphthalen-1-yl)ethyl)acetamide (*R*-2.122b)[37b]

By following the general procedure 5, starting from (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate (> 99 % *ee* purity, 0.75 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol) and MeLi-LiBr (3.04 mL, 4.56 mmol) in Et_2O, α-chloroacetamide ***R*-2.122b** was obtained in 96% yield (913 mg) as a white solid. Mp 140 °C.

IR (NaCl): 3284, 1649, 1537, 1231 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 8.5 Hz, 1H), 7.92 (d, *J* = 8.6 Hz, 1H,), 7.86 (d, *J* = 7.6 Hz, 1H), 7.56 (m, 4H), 6.81 (s, 1H), 4.15 (s, 2H), 1.74 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 164.4, 137.0, 133.5, 130.5, 128.5, 128.2, 126.2, 125.5, 124.8, 122.6, 122.1, 44.8, 42.2, 20.4.

Anal. Calcd for $C_{14}H_{14}ClNO$: C, 67.88; H, 5.70; N, 5.65. **Found**: C, 67.99; H, 5.87; N, 5.82.

HPLC (column: Chiralcel OD-H; *n*-hexane–*i*-PrOH, 80:20; 1 mL/min, 28 °C) t_R = 6.393 min [(*R*)-enantiomer, major], 11.586 min [(*S*)-enantiomer, minor]. Racemic sample: t_R = 6.481 min [(*R*)-enantiomer], 11.586 min [(*S*)-enantiomer]; $[\alpha]_D^{20}$ +68 (*c* 1.8, $CHCl_3$).

2-Chloro-*N*-[(1*S*)-2,3-dihydro-1*H*-inden-1-yl]acetamide (*S*-2.123a)

By following the general procedure 5, starting from (1*S*)-1-indanyl isocyanate (320 mg, 2.0 mmol), ICH_2Cl (529mg, 0.22 mL, 3.0 mmol) and MeLi-LiBr (1.60 mL, 2.4 mmol) in Et_2O, compound ***S*-2.123a** was obtained in 95% yield (398 mg) and > 99% *ee*. as a white solid. mp 148-150 °C.

IR (NaCl): 1655, 1590, 1472 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (m, 1 H, $H7_{indenyl}$), 7.27 (m, 2 H, $H4_{indenyl}$, $H5_{indenyl}$), 7.25 (m, 1 H, $H6_{indenyl}$), 6.79 (br s, 1 H, NH), 5.49 (q, *J* = 7.9 Hz, 1 H, $H1_{indenyl}$), 4.12 and 4.09 (AB-system, 2 J = 15.2 Hz, 2 H, CH_2Cl), 3.02 (m, 1 H, $H3_{indenyl}$), 2.90 (m, 1 H, $H3'_{indenyl}$), 2.63 (m, 1 H, $H2_{indenyl}$), 1.86 (m, 1 H, $H2'_{indenyl}$). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 165.7 (C=O), 143.4 ($C3a_{indenyl}$), 142.2 ($C7a_{indenyl}$), 128.2 ($C5_{indenyl}$), 126.9 ($C6_{indenyl}$), 124.9 (C4indenyl), 123.9 ($C7_{indenyl}$), 55.0 ($C1_{indenyl}$), 42.6 ($ClCH_2$), 33.8 ($C2_{indenyl}$), 30.2 ($C3_{indenyl}$). **^{15}N NMR** (40 MHz, $CDCl_3$): δ = –253.9 (NH).

Anal. Calcd for $C_{11}H_{12}ClNO$: C, 63.01; H, 5.77; N, 6.68. **Found**: C, 63.08; H, 5.83; N, 6.78.

HPLC (column: Chiralpak IC; isohexane–*i*-PrOH, 95:5; 0.5 mL/min, 23 °C): t_R = 26.039 min [(*R*)-enantiomer, minor], 27.725 min [(*S*)-enantiomer, major]. Racemic sample: t_R = 26.031 min [(*R*)-enantiomer], 27.573 min [(*S*)-enantiomer]; $[\alpha]_D^{20}$ –21.4 (*c* 0.07, CH_2Cl_2).

2-Chloro-*N*-[(2*R*)-3-methyl-2-butanyl]acetamide (*R*-2.123b)

By following the general procedure 5, starting from (2*R*)-3-methylbutan-2-yl isocyanate (0.26 mL, 226 mg, 2.0 mmol), ICH_2Cl (529 mg, 0.22 mL, 3.0 mmol), and MeLi–LiBr (1.60 mL, 2.4 mmol) in Et_2O gave ***R*-2.123b** (298 mg, 91%) as a white solid; 99% ee; mp 42–44 °C.

IR (NaCl): 1652, 1595, 1468, 998 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.41 (br s, 1 H, NH), 4.03 (s, 2 H, $ClCH_2$), 3.86 (m, 1 H, $NHCHCH_3$), 1.72 (m, 1 H, CH_3CHCH_3), 1.10 (d, *J* = 6.8 Hz, 3 H, $NHCHCH_3$), 0.902 (d, *J* = 6.8 Hz, 3 H, CH_3CHCH_3), 0.898 (d, *J* = 6.8 Hz, 3 H, CH_3CHCH_3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 165.0 (C=O), 50.5 (CH_3CHNH), 42.8 ($ClCH_2$), 32.8 (CH_3CHCH_3), 18.35 (CH_3CHCH_3), 18.31 (CH_3CHCH_3), 17.3 ($NHCHCH_3$). **^{15}N NMR** (40 MHz, $CDCl_3$): δ = –256.0 (NH).

Anal. Calcd for $C_7H_{14}ClNO$: C, 51.38; H, 8.62; N, 8.56. **Found**: C, 51.45; H, 8.73; N, 8.62.

Chiral GC [Varian 3800 Gas Chromatographer, CP Chiralsil-DEX CB (25 m × 0.32 mm × 0.25 mm) capillary column; 90–170 °C]: t_R = 6.359 min [(*S*)-enantiomer, minor], 6.539 min [(*R*)-enantiomer, major]. Racemic sample: t_R = 6.326 min [(*S*)-enantiomer], 6.544 min [(*R*)-enantiomer]; $[\alpha]_D^{20}$ –20.5 (c 1, CH_2Cl_2).

2-Chloro-*N*-((1*R*, 4*R*)-4-methylcyclohexyl)acetamide (*trans* 2.123c)

By following the general procedure 5, starting from trans-4-methylcyclohexyl isocyanate (0.27 mL, 278 mg, 2.0 mmol), ICH_2Cl (529 mg, 0.22 mL, 3.0 mmol), and MeLi–LiBr (1.60 mL, 2.4 mmol) in Et_2O gave *trans*-**2.123c** (345 mg, 91%) as a white solid; 99% ee; mp 98–100 °C.

IR (NaCl): 1661, 1475, 1421 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.36 (br s, 1 H, NH), 4.00 (s, 2 H, $ClCH_2$), 3.70 (m, 1 H, $H1_{Cy}$), 1.95 (m, 2 H, $H2_{Cy}$, $H6_{Cy}$), 1.72 (m, 2 H, $H3_{Cy}$, $H5_{Cy}$), 1.33 (m, 1 H, $H4_{Cy}$), 1.18 (m, 2 H, $H2'_{Cy}$, $6'_{Cy}$), 1.04 (m, 2 H, H3′Cy, $H5'_{Cy}$), 0.88 (d, *J* = 6.5 Hz, 3 H, CH3). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 164.9 (C=O), 48.9 ($C1_{Cy}$), 42.7 (CH_2Cl), 33.6 ($C3_{Cy}$, $C5_{Cy}$), 32.8 ($C2_{Cy}$, $C6_{Cy}$), 31.8 ($C4_{Cy}$), 22.1 (CH_3). **^{15}N NMR** (40 MHz, $CDCl_3$): δ = –252.7 (NH).

Anal. Calcd for $C_9H_{16}ClNO$: C, 56.99; H, 8.50; N, 7.38. **Found**: C, 57.10; H, 8.61; N, 7.46.

Chiral GC [Varian 3800 Gas Chromatographer, CP Chiralsil-DEXCB (25 m × 0.32 mm × 0.25 mm) capillary column; 90–170 °C]: t_R = 12.447 min (cis-isomer, minor), 13.027 min (*trans*-isomer, major).Racemic sample: t_R = 12.447 min (*cis*-isomer), 12.932 min (*trans*-isomer). $[\alpha]_D^{20}$ +5.9 (c 0.01, CH_2Cl_2).

2,2-Dichloro-*N*-[(1*S*)-1-phenylethyl]acetamide (*S*-2.123d)

By following the general procedure 4, starting from (1*S*)-α-methylbenzyl isocyanate (0.14 mL, 147 mg, 1.0 mmol, 96% ee) and Cl_2CH_2 (647 mg, 0.33 mL, 5.0 mmol) gave (*S*)- **2.123d** (199 mg, 86%) as a colorless solid; 96% ee; mp 134–136 °C.

IR (NaCl): 1659, 1593, 1470 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (m, 2 H, $H3_{Ph}$, $H5_{Ph}$), 7.33 (m, 2 H, $H2_{Ph}$, $H6_{Ph}$), 7.30 (m, 1 H, $H4_{Ph}$), 6.73 (br s, 1 H, NH), 5.91 (s, 1 H, Cl_2CH), 5.09 (m, 1 H, $NHCHCH_3$), 1.57 (d, *J* = 6.9 Hz,

3 H, NHCHCH$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 163.2 (C=O), 141.7 ($C1_{Ph}$), 128.9 ($C3_{Ph}$, $C5_{Ph}$), 127.8 ($C4_{Ph}$), 126.0 ($C2_{Ph}$, $C6_{Ph}$), 66.4 (Cl_2CH), 49.8 (NHCHCH$_3$), 21.3 (NHCHCH$_3$). **^{15}N NMR** (40 MHz, $CDCl_3$): δ = –257.3 (NH).

Anal. Calcd for $C_{10}H_{11}Cl_2NO$: C, 51.75; H, 4.78; N, 6.03. **Found**: C, 51.83; H, 4.86; N 6.10.

HPLC (Chiralpak IA; isohexane–*i*-PrOH, 95:5; 0.5 mL/min, 23 °C): t_R = 13.920 min [(*S*)-enantiomer, major], 15.337 min [(*S*)-enantiomer, minor]. Racemic sample: t_R = 13.824 min [(*S*)-enantiomer], 15.338 min, [(*R*)-enantiomer]. $[\alpha]_D^{20}$ +44.5 (c 0.1, CH_2Cl_2).

2.3.6. Synthesis of Ketone 2.125 according to Charette's Procedure[125]

To a solution of chloroacetamide **2.124** (200 mg, 1.04 mmol, 1.0 equiv) in dry CH_2Cl_2 (26 mL, concentration 0.044 M), was added 2-fluoropyridine (62 mg, 0.11 mL, 1.26 mmol, 1.1 equiv) and the resulting solution was cooled at –78 °C and stirred for 2 min. Tf_2O (354 mg, 0.21 mL, 1.26 mmol, 1.1 equiv) was added dropwise at this temperature and the mixture was then stirred for 10 min. The solution was warmed at 0 °C and the reaction was stirred for 20 min. The reaction was then cooled at –78 °C and a solution of 2.0 M BnMgCl in THF (1.04 mL, 2.08 mmol, 2.0 equiv) was added dropwise over 10 min and stirred for a further 50 min. The reaction was quenched with 0.5 M HCl (8 mL) and THF (8 mL). The biphasic system was warmed at 65 °C leaving the flask open for 2 h. After extraction of the organic phase with additional CH_2Cl_2 (10 mL), the combined extracts were dried (Na_2SO_4), filtered, and the solvent removed under reduced pressure to give crude **2.125**. Chromatography (silica gel, petroleum ether–EtOAc, 95:5) gave pure chloro ketone **2.125**[24] (152 mg, 87%) as a yellow oil.

IR (NaCl): 3082, 1737, 992, 897 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.23 (m, 5 H), 4.13 (s, 2 H), 3.91 (s, 2 H).**^{13}C NMR** (125 MHz, $CDCl_3$): δ = 199.1, 132.8, 129.4, 128.9, 127.5, 47.7, 46.8.

Anal. Calcd for C_9H_9ClO: C, 64.11; H, 5.38. **Found**: C, 64.29; H, 5.53.

2.3.7 General procedure for the preparation of N-substituted isatins (General Procedure 6)

To a solution of the isatin derivative (2.0 mmol, 1.0 equiv) in 2-MeTHF, was added KF-Celite (1.5 equiv, 3.0 mmol, 0.349 g, 50% w/w) and the reaction mixture was stirred for 5 min at rt. Then the alkylating agent (2.0 mmol, 1.0 equiv) was added dropwise and, the mixture refluxed for 2 h. Subsequently, the reaction mixture was allowed to cool to rt and then, filtered, washed thoroughly with 2MeTHF (20 mL) and the filtrate evaporated under vacuum. Analytical pure sample were recrystallyzed from CPME.

1-allyl-1*H*-indole-2,3-dione (2.127a)[144]

By following general procedure 6, starting from 1*H*-indole-2,3-dione (0.294 g, 2.0 mmol, 1.0 equiv), 3-bromo-1-propene (0.242 g, 2.0 mmol, 1.0 equiv) and KF-Celite (1.5 equiv, 3.0 mmol, 0.349 g , 50% w/w) in 2-MeTHF, compound **2.127a** was obtained in 95% yield (0.355 g) as a red solid; mp 71-72 °C.

^{1}H NMR (400MHz, $CDCl_3$):δ 7.59 (m, 1H, Indole H-4), 7.56 (m, 1H, Indole H-6), 7.11 (m, 1H, Indole H-5), 6.89 (d, *J* = 7.9 Hz, 1H, Indole H-7), 5.83 (m, 1H, C<u>H</u>=CH_2), 5.31(m, 1H, CH=C<u>H</u>$_2$), 5.28 (m, 1H, CH=C<u>H</u>$_2$), 4.35 (s, 2H, C<u>H</u>$_2$CH). **^{13}C NMR** (100 MHz, $CDCl_3$):δ 183.2 (Indole C-3), 157.8 (Indole C-2), 150.8 (Indole C-7a), 138.3 (Indole C-6), 130.3 (<u>C</u>H=CH_2), 125.3 (Indole C-4), 123.7 (Indole C-5), 118.6 (CH=<u>C</u>H_2), 117.5 (Indole C-3a), 110.9 (Indole C-7), 42.4 (NCH_2). **^{15}N NMR** (40MHz, $CDCl_3$): δ -245.6 (Indole N-1).

1-(2-propyn-1-yl)-1*H*-indole-2,3-dione (2.127b)[145]

By following general procedure 6, starting from 1*H*-indole-2,3-dione (0.294 g, 2.0 mmol, 1.0 equiv), 3-bromo-1-propyne (0.238 g, 2.0 mmol, 1.0 equiv) and KF (1.5 equiv, 3.0 mmol, 0.349

g , 50% w/w KF-Celite) in 2-MeTHF, compound **2.127b** was obtained in 92% yield (0.340 g) as an orange solid; mp 138-140 °C.

^{1}H NMR (400MHz, DMSO-d_6): δ 7.71 (m, 1H, Indole H-6), 7.58 (m, 1H, Indole H-4), 7.23 (m, 1H, Indole H-7), 7.17 (m, 1H, Indole H-5), 4.54 (d, *J* = 2.5 Hz, 2H, NCH_2), 3.34 (t, *J* = 2.5 Hz, 1H, C<u>C</u>H). **^{13}C NMR** (100 MHz, DMSO-d_6): δ 182.5 (Indole C-3), 157.3 (Indole C-2), 149.4 (Indole C-7a), 138.1 (Indole C-6), 124.5 (Indole C-4), 123.6 (Indole C-5), 117.6 (Indole C-3a), 111.2 (Indole C-7), 77.3 (<u>C</u>CH), 74.9 (C<u>C</u>H), 29.0 (NCH_2). **^{15}N NMR** (40MHz, DMSO-d_6):δ -247.7 (Indole N-1).

1-(2-butyn-1-yl)-1*H*-indole-2,3-dione (2.127c)

By following general procedure 6, starting from 1*H*-indole-2,3-dione (0.294 g, 2.0 mmol, 1.0 equiv), 1-bromo-2-butyne (0.266 g, 2.0 mmol, 1.0 equiv) and KF-Celite (1.5 equiv, 3.0 mmol, 0.349 g , 50% w/w KF-Celite) in 2-MeTHF, compound **2.127c** was obtained in 95% yield (0.378 g) as anorange solid; mp 112-113 °C.

^{1}H NMR (400MHz, $CDCl_3$):δ 7.63 (m, 1H, Indole H-6), 7.62 (m, 1H, Indole H-4), 7.15 (m, 1H, Indole H-5), 7.11 (m, 1H, Indole H-7), 4.47 (q, *J* = 2.4 Hz, 2H, NCH_2), 1.79 (t, *J* = 2.4 Hz, 3H, CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$):δ 183.0 (Indole C-3), 157.2 (Indole C-2), 150.0 (Indole C-7a), 138.3 (Indole C-6), 125.3 (Indole C-4), 123.9 (Indole C-5), 117.6 (Indole C-3a), 111.2 (Indole C-7), 81.1 (CH_2<u>C</u>), 71.0 (<u>C</u>CH_3), 29.9 (<u>C</u>H_2C), 3.4 (C<u>C</u>H_3).

^{15}N NMR (40MHz, $CDCl_3$):δ -246.2 (Indole N-1).

HRMS (ESI), *m/z*: calcd. for $C_{12}H_9NNaO_2$222.0525$[M+Na]^+$; found 222.0526.

1-propyl-1*H*-indole-2,3-dione (2.127d)[146]

By following general procedure 6, starting from 1*H*-indole-2,3-dione (0.294 g, 2.0 mmol, 1.0 equiv), 1-bromopropane (0.246 g, 2.0 mmol, 1.0 equiv) and KF-Celite (1.5 equiv, 3.0 mmol, 0.349 g , 50% w/w KF-Celite) in 2-MeTHF, compound **2.127d** was obtained in 97% yield (0.366 g) as a red solid; mp 72-72 °C.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.58 (m, 1H, Indole H-4), 7.57 (m, 1H, Indole H-6), 7.09 (m, 1H, Indole H-5), 6.89 (d, *J* = 8.3 Hz, 1H, Indole H-7), 3.68 (m, 2H, NCH_2), 1.73 (m, 2H, $C\underline{H}_2CH_3$), 0.98 (t, *J* = 7.4 Hz, 3H, $CH_2C\underline{H}_3$). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 183.6 (Indole C-3), 158.1 (Indole C-2), 151.0 (Indole C-7a), 138.3 (Indole C-6), 125.4 (Indole C-4), 123.5 (Indole C-5), 117.5 (Indole C-3a), 110.1 (Indole C-7), 41.7 ($\underline{C}H_2CH_2$), 20.6 ($\underline{C}H_2CH_3$), 11.3 ($CH_2\underline{C}H_3$). **^{15}N NMR** (40MHz, $CDCl_3$):δ -242.2 (Indole N-1).

1-benzyl-1*H*-indole-2,3-dione (2.127e)[146]

By following general procedure 6, starting from 1*H*-indole-2,3-dione (0.294 g, 2.0 mmol, 1.0 equiv), (bromomethyl)benzene (0.342 g, 2.0 mmol, 1.0 equiv) and KF-Celite (1.5 equiv, 3.0 mmol, 0.349 g , 50% w/w KF-Celite) in 2-MeTHF, compound **2.127e** was obtained in 98% yield (0.466 g) as anorange solidmp 121-123 °C.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.59 (m, 1H, Indole H-4), 7.48 (m, 1H, Indole H-6), 7.33 (m, 4H, Ph H-2,3,5,6), 7.29 (m, 1H, Ph H-4), 7.08 (m, 1H, Indole H-5), 6.78 (d, *J* = 8.0 Hz, 1H, Indole H-7), 4.92 (s, 2H, $C\underline{H}_2Ph$). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 183.2 (Indole C-3), 158.2 (Indole C-2), 150.6 (Indole C-7a), 138.3 (Indole C-6), 134.4 (Ph C-1), 129.0 (Ph C-3,5), 128.1 (Ph C-4), 127.4 (PhC-2,6), 125.3 (Indole C-4), 123.8 (Indole C-5), 117.6 (Indole C-3a), 111.0 (Indole C-7), 44.0 ($\underline{C}H_2Ph$). **^{15}N NMR** (40MHz, $CDCl_3$):δ -242.2 (Indole N-1).

Ethyl(2,3-dioxo-2,3-dihydro-1*H*-indol-1-yl)acetate (2.127f)

By following general procedure 6, starting from 1*H*-indole-2,3-dione (0.294 g, 2.0 mmol, 1.0 equiv), ethyl bromoacetate (0.334 g, 2.0 mmol, 1.0 equiv) and KF-Celite (1.5 equiv, 3.0 mmol, 0.349 g , 50% w/w KF-Celite) in 2-MeTHF, compound **2.127f** was obtained in 97% yield (0.738 g) as an orange solid; mp 91-92 °C.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.62 (m, 1H, Indole H-4), 7.58 (m, 1H, Indole H-6), 7.14 (m, 1H, Indole H-5), 6.78 (m, 1H, Indole H-7), 4.47 (s, 2H, NCH_2), 4.23 (q, *J* = 7.1 Hz, 2H, $C\underline{H}_2CH_3$), 1.27 (t, *J* = 7.1 Hz, 3H, $CH_2C\underline{H}_3$). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 182.4 (Indole C-3), 166.7 (O=$\underline{C}$O), 158.0 (Indole C-2), 150.3 (Indole C-7a), 138.4 (Indole C-6), 125.5 (Indole C-4), 124.1 (Indole C-5), 117.6 (Indole C-3a), 110.1 (Indole C-7), 62.1 ($\underline{C}H_2CH_3$), 41.2 (NCH_2), 14.0 (CH_3).**^{15}N NMR** (40MHz, $CDCl_3$): δ-251.5 (Indole N-1).

2-(2,3-dioxo-2,3-dihydro-1*H*-indol-1-yl)-*N*-methoxy-*N*-methylacetamide (2.127g)

By following general procedure 6, starting from 1*H*-indole-2,3-dione (0.294 g, 2.0 mmol, 1.0 equiv), 2-chloro-*N*-methoxy-*N*-methylacetamide (0.276 g, 2.0 mmol, 1.0 equiv) and KF-Celite (1.5 equiv, 3.0 mmol, 0.349 g , 50% w/w KF-Celite) in 2-MeTHF, compound **2.127g** was obtained in 93% yield (0.462 g) as a red solid; mp 130-131 °C.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.60 (m, 1H, Indole H-4), 7.55 (m, 1H, Indole H-6), 7.11 (m, 1H, Indole H-5), 6.80 (m, 1H, Indole H-7), 4.66 (s, 2H, NCH_2), 3.82 (s, 3H, OCH_3), 3.22 (s, 3H, $NC\underline{H}_3$).**^{13}C NMR** (100 MHz, $CDCl_3$):δ 186.5 (O=$\underline{C}$N), 182.8 (Indole C-3), 158.4 (Indole C-2), 150.9 (Indole C-7a), 138.3 (Indole C-6), 125.3 (Indole C-4), 123.8 (Indole C-5), 117.6 (Indole C-3a), 110.5 (Indole C-7), 61.7 (OCH_3), 32.4 ($\underline{C}H_3N$).**^{15}N NMR** (40MHz, $CDCl_3$):δ -251.8 (Indole N-1), -195.3 (O=C$\underline{N}$).

HRMS (ESI), *m/z*: calcd. for $C_{12}H_{12}KN_2O_4$ 287.0429$[M+K]^+$; found 287.0432.

7-fluoro-1-methyl-1*H*-indole-2,3-dione (2.127h)

By following general procedure 6, starting from 7-fluoro-1*H*-indole-2,3-dione (0.330 g, 2.0 mmol, 1.0 equiv), iodomethane (0.284 g, 2.0 mmol, 1.0 equiv) and KF-Celite (1.5 equiv, 3.0 mmol, 0.349 g , 50% w/w KF-Celite) in 2-MeTHF, compound **2.127h** was obtained in 89% yield (0.412 g) as a red solid; mp 120-122 °C.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.42 (d, J = 7.4 Hz, 1H, Indole H-4), 7.34 (m, 1H, Indole H-6), 7.07 (m, 1H, Indole H-5), 3.46 (d "through-space-coupling", J = 2.9 Hz, 3H, NCH_3). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 182.4 (Indole C-3), 157.9 (Indole C-2), 148.2 (^{1}J = 248.0 Hz, Indole C-7), 137.5 (d, J = 8.7 Hz, Indole C-7a), 126.4 (d, J = 19.6 Hz, Indole C-6), 124.6 (d, J = 5.8 Hz, Indole C-5), 121.2 (d, J = 3.4 Hz, Indole C-4), 120.0 (d, J = 2.7 Hz, Indole C-3a), 29.1 (d, J = 5.5 Hz, CH_3). **^{15}N NMR** (40MHz, DMSO-d_6):δ -256.9 (Indole N-1).

1-methyl-5-nitro-1*H*-indole-2,3-dione (2.127i)[147]

By following general procedure 6, starting from 5-nitro-1*H*-indole-2,3-dione (0.384 g, 2.0 mmol, 1.0 equiv), iodomethane (0.284 g, 2.0 mmol, 1.0 equiv) and KF-Celite (1.5 equiv, 3.0 mmol, 0.349 g , 50% w/w KF-Celite) in 2-MeTHF, compound **2.127i** was obtained in 92% yield (0.380 g) as a brown solid; mp 132-134 °C.

^{1}H NMR (400MHz, DMSO-d_6): δ 8.53 (dd, ^{3}J = 8.8 Hz,^{4}J = 2.4 Hz, 1H, Indole H-6), 8.22 (d, ^{4}J = 2.4 Hz, 1H, Indole H-4), 7.35 (d, ^{3}J = 8.8 Hz, 1H, Indole H-7), 3.21 (s, 3H, C$\underline{H}_3$).

^{13}C NMR (100 MHz, DMSO-d_6):δ 181.2 (Indole C-3), 158.9 (Indole C-2), 155.6 (Indole C-7a), 142.0 (Indole C-5), 133.0 (Indole C-6), 118.9 (Indole C-4), 117.8 (Indole C-3a), 110.9 (Indole C-7), 26.5 (CH_3). **^{15}N NMR** (40MHz, DMSO-d_6):δ -248.2 (Indole N-1), -8.1 (NO_2).

1-methyl-5-(trifluoromethoxy)-1*H*-indole-2,3-dione (2.127j)[148]

By following general procedure 6, starting from 5-(trifluoromethoxy)-1*H*-indole-2,3-dione (0.462 g, 2.0 mmol, 1.0 equiv), iodomethane (0.284 g, 2.0 mmol, 1.0 equiv) and KF-Celite (1.5 equiv, 3.0 mmol, 0.349 g , 50% w/w KF-Celite) in 2-MeTHF, compound **2.127j** was obtained in 95% yield (0.466 g) as an orange solid; mp 47-49 °C.

^{1}H NMR (400MHz, DMSO-d_6): δ 7.69 (dd, ^{3}J = 8.6 Hz,^{4}J = 1.7 Hz, 1H, Indole H-6), 7.56 (d, ^{4}J = 1.7 Hz, 1H, Indole H-4), 7.24 (d, J = 8.6 Hz, 1H, Indole H-7), 3.14 (s, 3H, C$\underline{H}_3$). **^{13}C NMR** (100 MHz, DMSO-d_6):δ 182.33 (Indole C-3), 158.3 (Indole C-2), 150.1 (Indole C-7a), 143.8 (q, J = 2.1 Hz, Indole C-5), 130.6 (Indole C-6), 119.8 (q, J = 256.4 Hz, OCF_3), 118.4 (Indole C-3a), 117.5 (Indole C-4), 111.9 (Indole C-7), 26.2 (CH_3). **^{15}N NMR** (40MHz, DMSO-d_6):δ -253.0 (Indole N-1). **^{19}F NMR** (376 MHz, $CDCl_3$):δ -57.56 (CF_3).

1,1'-(1,5-pentanediyl)bis(1*H*-indole-2,3-dione) (2.127k)

By following general procedure 6, starting from 1*H*-indole-2,3-dione (0.294 g, 2.0 mmol, 1.0 equiv), 1,5-dibromopentane (0.230 g, 1.0mmol, 0.5 equiv) and KF-Celite (1.5 equiv, 3.0 mmol, 0.349 g , 50% w/w KF-Celite) in 2-MeTHF, compound **2.127k** was obtained in 86% yield (0.624 g) as an orange solid; mp 145-147 °C.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.59 (m, 2H, Indole H-6,6′), 7.58 (d, J = 7.5 Hz, 2H, Indole H-4,4′), 7.10 (m, 2H, Indole H-5,5′), 6.92 (d, J = 8.2 Hz, 2H, Indole H-7,7′), 3.71 (t, J = 7.2 Hz, 4H, H-1,1′), 1.78 (m, 4H, H-2,2′), 1.46 (m, 2H, H-3). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 183.4 (Indole C-3,3′), 158.2 (Indole C-2, 2′), 150.7 (Indole C-7a, 7a′), 138.5 (Indole C-4,4′), 125.4 (Indole C-6,6′), 123.7 (Indole C-5,5′), 117.5 (Indole C-3a,3a′), 110.1 (Indole C-7,7′), 39.7 (C-1,5), 26.6 (C-2,4), 23.8 (C-3). **^{15}N NMR** (40MHz, $CDCl_3$):δ -242.7 (2N, Indole N-1).

HRMS (ESI), *m/z*: calcd. for$C_{21}H_{18}N_2NaO_4$385.1164 $[M+Na]^+$; found 385.1159.

2.3.8 General Procedure for the Chemoselective Addition of Li Carbenoids to isatins (General Procedure 7)

To a cooled (–78 °C) solution of isatin (1.0 equiv) in dry THF (0.5 M concentration) was added the dihalomethane derivative (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 h at that temperature. After quenching with saturated aqueous NH_4Cl at – 78°C, the cooling bath was removed and, the mixture was stirred till it reached rt. Work-up continued through extraction with Et_2O (3 × 5 mL) and washing with water (5 mL) and brine (10 mL). The organic phase was dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. The crude product was purified by liquid chromatography on neutral alumina (Brockmann grade IV) with the specified eluent to give analytically pure samples of halohaydrins.

3-(chloromethyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one (2.126b)

By following general procedure **7**, starting from 1*H*-indole-2,3-dione (0.147 g, 1.0mmol, 1.0 equiv), $ClCH_2I$ (0.22 ml, 0.530 g, 1.5 mmol, 3.0 equiv) and MeLi-LiBr (1.14 ml, 2.2 M, 2.5 mmol, 2.5 equiv) in THF, after column chromatography in neutral alumina (Brockmann grade IV) eluting with hexane/ethyl acetate 8:2, compound **2.126b** was obtained in 87% yield (0.172 g) as a white solid; mp 178-180 °C.

^{1}H NMR (400MHz, DMSO-d_6): δ 10.42 (s, 1H, NH), 7.38 (m, 1H, Indole H-4), 7.24 (m, 1H, Indole H-6), 6.99 (m, 1H, Indole H-5), 6.82 (m, 1H, Indole H-7), 6.54 (br s, 1H, OH), 3.87 and 3.74 (AB-System, $^2J_{AB}$ = 10.4 Hz, 2H, CH_2Cl). **^{13}C NMR** (100 MHz, DMSO-d_6):δ 176.6 (Indole C-2), 142.5 (Indole C-7a), 129.7 (Indole C-6), 129.3 (Indole C-3a), 124.5 (Indole C-4), 121.7 (Indole C-5), 109.7 (Indole C-7), 75.0 (Indole C-3), 46.4 ($\underline{C}H_2Cl$).

^{15}N NMR (40MHz, $CDCl_3$):δ -246.2 (Indole N-1).

HRMS (ESI), *m/z*: calcd. for$C_9H_8ClNNaO_2$220.0136 $[M+Na]^+$; found 220.0133.

1-allyl-3-(chloromethyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one (2.130)

By following general procedure 7, starting from 1-allyl-1*H*-indole-2,3-dione(0.094 g, 0.5 mmol, 1.0 equiv), $ClCH_2I$ (0.11 ml, 0.265 g, 1.5 mmol, 3.0 equiv) and MeLi-LiBr (0.57 ml, 2.2 M, 1.25 mmol, 2.5 equiv) in THF, after column chromatography in neutral alumina (Brockmann grade IV) eluting with hexane/ethyl acetate 8:2, compound **2.130** was obtained in 80% yield (0.095 g) as a white to yellow solid; mp 98-100 °C.

^{1}H NMR (400MHz, C_6D_6):δ 7.27 (d, J = 7.3 Hz, 1H, Indole H-4), 6.96 (m, 1H, Indole H-6), 6.82 (m, 1H, Indole H-5), 6.37 (d, J = 7.8 Hz, 1H, Indole H-7), 5.41 (m, 1H, C$\underline{H}$=CH_2), 4.99 (d,^3J = 17.2 Hz, 1H, CH=C$\underline{H}_{2(trans)}$), 4.85 (d,^3J = 10.4 Hz, 1H, CH=C$\underline{H}_{2(cis)}$), 4.23 (s, 1H, OH), 4.03,3.71 (m, ^2J = 16.5 Hz,1H, NCH_2), 3.81 and 3.67 (AB-System, $^2J_{AB}$ = 10.7 Hz, 2H, CH_2Cl). **^{13}C NMR** (100 MHz, C_6D_6):δ 176.1 (Indole C-2), 143.7 (Indole C-7a), 131.1 (C$\underline{H}$=CH_2), 130.1 (Indole C-6), 128.3* (Indole C-3a), 124.7 (Indole C-4), 123.3 (Indole C-5), 117.3 (CH=C$\underline{H}_2$), 109.6 (Indole C-7), 76.1 (Indole C-3), 47.0 (CH_2Cl),42.3 ($\underline{N}$CH), (*via HMBC). **^{15}N NMR** (40MHz, C_6D_6):δ -244.6 (Indole N-1).

HRMS (ESI), *m/z*: calcd. for$C_{12}H_{12}ClNNaO_2$260.0449 $[M+Na]^+$; found 260.0449.

1-(2-butyn-1-yl)-3-(chloromethyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one (2.131)

By following general procedure **7**, starting from 1-(2-butyn-1-yl)-1*H*-indole-2,3-dion (0.100 g, 0.5 mmol, 1.0 equiv), $ClCH_2I$ (0.11 ml, 0.265 g, 1.5 mmol, 3.0 equiv) and MeLi-LiBr (0.57 ml, 2.2 M, 1.25 mmol, 2.5 equiv) in THF, after column chromatography in neutral alumina (Brockmann grade IV) eluting with hexane/ethyl acetate 8:2, compound **2.131** was obtained in 86% yield (0.107 g) as a white solid; mp 102-103 °C.

^{1}H NMR (400MHz, C_6D_6):δ 7.27(m, 1H, Indole H-4), 7.03 (m, 1H, Indole H-6), 6.82 (m, 1H, Indole H-5), 6.74 (m, 1H, Indole H-7), 4.14 and 4.02 (AB-System, $^{2}J_{AB}$ = 17.5 Hz, ^{5}J = 2.4 Hz, 2H, NCH_2), 3.64 and 3.60 (AB-System, $^{2}J_{AB}$ = 11.0 Hz, 2H, CH_2Cl), 1.26 (t, ^{5}J = 2.4 Hz, 1H, CH_3). **^{13}C NMR** (100 MHz, C_6D_6): δ175.1 (Indole C-2), 143.0 (Indole C-7a), 130.2 (Indole C-6), 128.4 (Indole C-3a), 124.8 (Indole C-4), 123.4 (Indole C-5), 109.8 (Indole C-7), 80.3 ($\underline{C}CCH_3$), 75.9 (Indole C-3), 72.5 ($\underline{C}CH_3$), 47.3 (CH_2Cl), 29.7 ($\underline{C}H_2CC$), 3.0 ($C\underline{C}H_3$).

^{15}N NMR (40MHz, $CDCl_3$):δ -245.4 (Indole N-1).

HRMS (ESI), *m/z*: calcd. for$C_{13}H_{12}ClKNO_2$288.0188 $[M+K]^+$; found 288.0186.

3-(chloromethyl)-3-hydroxy-1-(2-propyn-1-yl)-1,3-dihydro-2*H*-indol-2-one (2.132)

By following general procedure **7**, starting from 1-(2-propyn-1-yl)-1*H*-indole-2,3-dione(0.093 g, 0.5 mmol, 1.0 equiv), $ClCH_2I$ (0.11 ml, 0.265 g, 1.5 mmol, 3.0 equiv) and MeLi-LiBr (0.57 ml, 2.2 M, 1.25 mmol, 2.5 equiv) in THF, after column chromatography in neutral alumina (Brockmann grade IV) eluting with hexane/ethyl acetate 8:2, compound **2.132** was obtained in 83% yield (0.098 g) as a yellow solid; mp 88-90 °C.

^{1}H NMR (400MHz, C_6D_6):δ 7.22 (m, 1H, Indole H-4), 6.99 (m, 1H, Indole H-6), 6.80 (m, 1H, Indole H-5), 6.63 (m, 1H, Indole H-7), 4.03 and 3.86 (AB-System, $^{2}J_{AB}$ = 17.8 Hz,^{4}J = 2.5 Hz, 2H, NCH_2), 3.57 and 3.53 (AB-System, $^{2}J_{AB}$ = 10.9 Hz, 2H, CH_2Cl), 3.40 (brs, 1H, OH), 1.65 (t, ^{4}J = 2.5 Hz, 1H, $CC\underline{H}$). **^{13}C NMR** (100 MHz, C_6D_6): δ174.9 (Indole C-2), 142.5 (Indole C-7a), 130.2 (Indole C-6), 128.4 (Indole C-3a), 124.8 (Indole C-4), 123.5 (Indole C-5), 109.6 (Indole C-7), 76.8 ($\underline{C}CH$), 75.7 (Indole C-3), 72.6 ($C\underline{C}H$), 47.3 (CH_2Cl), 29.1 ($\underline{C}H_2CCH$).

HRMS (ESI), *m/z*: calcd. for$C_{12}H_{10}ClNNaO_2$258.0292 $[M+Na]^+$; found 258.0293.

3-(chloromethyl)-3-hydroxy-1-propyl-1,3-dihydro-2*H*-indol-2-one (2.133)

By following general procedure **7**, starting from 1-propyl-1*H*-indole-2,3-dione(0.095 g, 0.5 mmol, 1.0 equiv), $ClCH_2I$ (0.11 ml, 0.265 g, 1.5 mmol, 3.0 equiv) and MeLi-LiBr (0.57 ml, 2.2 M, 1.25 mmol, 2.5 equiv) in THF, after column chromatography in neutral alumina (Brockmann grade IV) eluting with hexane/ethyl acetate 8:2, compound **2.133** was obtained in 81% yield (0.097 g) as an yellow solid; mp 110-111 °C.

^{1}H NMR (400MHz, C_6D_6): δ 7.31 (m, 1H, Indole H-4), 6.99 (m, 1H, Indole H-6), 6.83 (m, 1H, Indole H-5), 6.31 (m, 1H, Indole H-7), 4.80 (s, 1H, OH), 3.90 and 3.74 (AB-System, $^2J_{AB}$ = 10.7 Hz, 2H, CH_2Cl), 3.70 (m, 1H, NCH_2), 3.12 (m, 1H, NCH_2), 1.34 (m, 2H, $C\underline{H}_2CH_3$), 0.68 (t, *J* = 7.4 Hz, 3H, $CH_2C\underline{H}_3$). **^{13}C NMR** (100 MHz, C_6D_6): δ 176.7 (Indole C-2), 144.0 (Indole C-7a), 130.1 (Indole C-6), 128.8 (Indole C-3a), 124.8 (Indole C-4), 123.2 (Indole C-5), 109.0 (Indole C-7), 76.2 (Indole C-3), 47.0 (CH_2Cl), 41.7 (NCH_2), 20.8 ($\underline{C}H_2CH_3$), 11.3 ($CH_2\underline{C}H_3$). **^{15}N NMR** (40MHz, C_6D_6):δ -240.9 (Indole N-1).

HRMS (ESI), *m/z*: calcd. for$C_{12}H_{14}ClNNaO_2$262.0605 $[M+Na]^+$; found 262.0607.

3-(chloromethyl)-3-hydroxy-1-methyl-1,3-dihydro-2*H*-indol-2-one (2.134)

By following general procedure **7**, starting from 1-methyl-1*H*-indole-2,3-dione (0.161 g, 1.0 mmol, 1.0 equiv), $ClCH_2I$ (0.22 ml, 0.529 g, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (1.14 ml, 2.2 M, 2.5 mmol, 2.5 equiv) in THF, after column chromatography in neutral alumina (Brockmann grade IV) eluting with hexane/ethyl acetate 8:2,compound **2.134** was obtained in 84% yield (0.178 g) as an yellow solid; mp 136-138 °C.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.4 Hz, 1H, Indole H-4), 7.38 (m, 1H, Indole H-6), 7.14 (m, 1H, Indole H-5), 6.87 (d, *J* = 7.8 Hz, 1H, Indole H-7), 4.24 (brs, 1H, OH), 3.86 and 3.84 (AB-System, $^2J_{AB}$ = 11.0 Hz, 2H, CH_2Cl), 3.20 (s, 3H, CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 175.8

(Indole C-2), 143.7 (Indole C-7a), 130.4 (Indole C-6), 127.6 (Indole C-3a), 124.3 (Indole C-4), 123.4 (Indole C-5), 108.7 (Indole C-7), 75.5 (Indole C-3), 47.1 ($\underline{C}H_2Cl$), 26.4 (CH_3). **^{15}N NMR** (40MHz, $CDCl_3$):δ -252.2 (Indole N-1).

HRMS (ESI), *m/z*: calcd. for $C_{10}H_{10}ClNNaO_2$234.0297 $[M+Na]^+$; found 234.0292.

1-benzyl-3-(chloromethyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one (2.135)

By following general procedure **7**, starting from 1-benzyl-1*H*-indole-2,3-dione(0.119 g, 0.5 mmol, 1.0 equiv), $ClCH_2I$ (0.11 ml, 0.265 g, 1.5 mmol, 3.0 equiv) and MeLi-LiBr (0.57 ml, 2.2 M, 1.25 mmol, 2.5 equiv) in THF, after column chromatography in neutral alumina (Brockmann grade IV) eluting with hexane/ethyl acetate 8:2, compound **2.135** was obtained in 84% yield (0.121 g) as an yellow solid; mp 87-88 °C.

^{1}H NMR (400MHz, C_6D_6):δ 7.24 (m, 1H, Indole H-4), 7.12 (m, 2H, Ph H-2,6), 7.00 (m, 2H, Ph H-3,5),6.94 (m, 1H, Ph H-4), 6.83 (m, 1H, Indole H-6), 6.76 (m, 1H, Indole H-5), 6.33 (m, 1H, Indole H-7), 4.70 and 4.32 (AB-System, $^2J_{AB}$ = 15.8 Hz, 2H, $C\underline{H}_2Ph$), 4.09 (s, 1H, OH), 3.83 and 3.68 (AB-System, $^2J_{AB}$ = 10.7 Hz, 2H, CH_2Cl). **^{13}C NMR** (100 MHz, C_6D_6):δ 176.5 (Indole C-2), 143.7 (Indole C-7a), 135.7 (Ph C-1), 130.2 (Indole C-6), 129.0 (Ph C-3,5), 128.4 (Indole C-3a), 127.8 (Ph4), 127.4 (Ph C-2,6), 124.7 (Indole C-4), 123.4 (Indole C-5), 109.8 (Indole C-7), 76.1 (Indole C-3),47.0 (CH_2Cl), 43.9 ($\underline{C}H_2Ph$). **^{15}N NMR** (40MHz, C_6D_6):δ -241.8 (Indole N-1).

HRMS (ESI), *m/z*: calcd. for$C_{16}H_{14}ClNNaO_2$310.0605 $[M+Na]^+$; found 310.0608.

3-(chloromethyl)-3-hydroxy-1-phenyl-1,3-dihydro-2*H*-indol-2-one (2.136)

By following general procedure **7**, starting from 1-phenyl-1*H*-indole-2,3-dione(0.112 g, 0.5 mmol, 1.0 equiv), $ClCH_2I$ (0.11 ml, 0.265 g, 1.5 mmol, 3.0 equiv) and MeLi-LiBr (0.57 ml, 2.2 M, 1.25 mmol, 2.5 equiv) in THF, after column chromatography in neutral alumina (Brockmann grade

IV) eluting with hexane/ethyl acetate 8:2, compound **2.136** was obtained in 75% yield (0.102 g) as a yellow solid; mp 83-84 °C.

^{1}H NMR (400MHz, C_6D_6):δ 7.23 (m, 1H, Indole H-4), 7.18 (m, 2H, Ph H-2,6), 7.07 (m, 2H, Ph H-3,5), 6.99 (m, 1H, Ph H-4), 6.88 (m, 1H, Indole H-6), 6.81 (m, 1H, Indole H-5), 6.50 (m, 1H, Indole H-7), 3.63 and 3.54 (AB-System, $^{2}J_{AB}$ = 10.7 Hz, 2H, CH_2Cl), 2.83 (s, 1H, OH). **^{13}C NMR** (100 MHz, C_6D_6):δ 174.9 (Indole C-2), 144.7 (Indole C-7a), 134.5 (Ph C-1), 130.3 (Indole C-6), 129.7 (Ph C-3,5),128.1 (Ph C-4), 127.9 (Indole C-3a), 126.7 (Ph C-2,6), 124.9 (Indole C-4), 123.6 (Indole C-5), 109.9 (Indole C-7), 75.7 (Indole C-3), 47.5 ($\underline{C}H_2Cl$).

3-(chloromethyl)-7-fluoro-3-hydroxy-1-methyl-1,3-dihydro-2*H*-indol-2-one (2.137)

By following general procedure **7**, starting from 7-fluoro-1-methyl-1*H*-indole-2,3-dione(0.090 g, 0.5 mmol, 1.0 equiv), $ClCH_2I$ (0.11 ml, 0.265 g, 1.5 mmol, 3.0 equiv) and MeLi-LiBr (0.57 ml, 2.2 M, 1.25 mmol, 2.5 equiv) in THF, after column chromatography on neutral alumina (Brockmann grade IV) eluting with hexane/ethyl acetate 8:2, compound **2.137** was obtained in 80% yield (0.092 g) as a white solid; mp 110-111 °C.

^{1}H NMR (400MHz, C_6D_6): δ 6.92 (dd, $^{3}J_{\text{Ind H-4,Ind H-5}}$ = 7.3 Hz, $^{4}J_{\text{Ind H-4,Ind H-6}}$ = 1.1 Hz, 1H, Indole H-4), 6.63 (ddd, $^{3}J_{\text{Ind H-6,Ind F-7}}$ = 11.5 Hz, $^{3}J_{\text{Ind H-6,Ind H-5}}$ = 8.5 Hz, $^{4}J_{\text{Ind H-6,Ind H-4}}$ = 1.1 Hz, 1H, Indole H-6), 6.52 (ddd, $^{3}J_{\text{Ind H-5,Ind H-6}}$ = 8.5 Hz, $^{3}J_{\text{Ind H-5,Ind H-4}}$ = 7.3 Hz, $^{4}J_{\text{Ind H-5,Ind F-7}}$ = 4.5 Hz, 1H, Indole H-5), 3.57 and 3.49 (AB-System, $^{2}J_{AB}$ = 10.8 Hz, 2H, CH_2Cl), 3.50 (brs, 1H, OH), 2.89 (d"through space", $J_{\text{CH3,Ind F-7}}$ = 2.8 Hz, 3H, $C\underline{H}_3$). **^{13}C NMR** (100 MHz, C_6D_6): δ 175.4 (Indole C-2), 148.0 (d, ^{1}J = 243.6 Hz, Indole C-7), 131.1 (d, J = 3.0 Hz, Indole C-3a), 130.9 (d, J = 8.1 Hz, Indole C-7a), 123.8 (d, J = 6.2 Hz, Indole C-5), 120.4 (d, J = 3.3 Hz, Indole C-4), 118.2 (d, J = 19.3 Hz, Indole C-6), 75.7 (d, J = 2.7 Hz, Indole C-3), 47.1 (CH_2Cl), 28.3 (d, J = 5.6 Hz, CH_3). **^{15}N NMR** (40MHz, C_6D_6):δ -257.2 (Indole N-1).

^{19}F NMR (376 MHz, C_6D_6):δ -136.5 (ddq,$^3J_{\text{Ind F-7,Ind H-6}}$ = 11.5 Hz, $^4J_{\text{Ind F-7,Ind H-5}}$ = 4.5 Hz, $J_{\text{Ind F-7,CH3}}$ = 2.8 Hz,Indole C 7-F).

HRMS (ESI), *m/z*: calcd. for$C_{10}H_9ClFNNaO_2$252.0198 $[M+Na]^+$; found 252.0201.

3-(chloromethyl)-3-hydroxy-1-methyl-5-nitro-1,3-dihydro-2*H*-indol-2-one (2.138)

By following general procedure **7**, starting from 1-methyl-5-nitro-1*H*-indole-2,3-dione(0.103 g, 0.5 mmol, 1.0 equiv), $ClCH_2I$ (0.11 ml, 0.265 g, 1.5 mmol, 3.0 equiv) and MeLi-LiBr (0.57 ml, 2.2 M, 1.25 mmol, 2.5 equiv) in THF, after column chromatography on neutral alumina (Brockmann grade IV) eluting with hexane/ethyl acetate 8:2, compound **2.138** was obtained in 75% yield (0.096 g) as an yellow solid; mp 169-170 °C.

^{1}H NMR (400MHz, DMSO-d_6): δ 8.36 (m, 1H, Indole H-4), 8.34 (m, 1H, Indole H-6), 7.28 (m, 1H, Indole H-7), 6.99 (s, 1H, OH), 4.15 and 3.85 (AB-System, $^2J_{AB}$ = 10.6 Hz, 2H, CH_2Cl), 3.21 (s, 3H, CH_3) **^{13}C NMR** (100 MHz, DMSO-d_6): δ 175.5 (Indole C-3), 149.9 (Indole C-7a), 142.8 (Indole C-5), 129.7 (Indole C-3a), 127.1 (Indole C-6), 119.8 (Indole C-4), 109.1 (Indole C-3a), 74.6 (Indole C-3), 45.6 (CH_2Cl), 26.5 (CH_3). **^{15}N NMR** (40MHz, DMSO-d_6):δ -247.3 (Indole N-1), -11.1 (NO_2).

HRMS (ESI), *m/z*: calcd. for$C_{10}H_9ClN_2NaO_4$279.0143$[M+Na]^+$; found 279.0142.

3-(bromomethyl)-3-hydroxy-1-methyl-1,3-dihydro-2*H*-indol-2-one (2.139)[135]

By following general procedure **7**, starting from 1-methyl-1*H*-indole-2,3-dione (0.161 g, 1.0 mmol, 1.0 equiv), $BrCH_2I$ (0.23 ml, 0.663 g, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (1.14 ml, 2.2 M, 2.5 mmol, 2.5 equiv) in THF, after column chromatography on neutral alumina (Brockmann grade IV) eluting with hexane/ethyl acetate 1:1, compound **2.139** was obtained in 81% yield (0.207 g) as a yellow solid; mp 116-117 °C.

^{1}H NMR (400MHz, DMSO-d_6): δ 7.43 (m, 1H, Indole H-4), 7.35 (m, 1H, Indole H-6), 7.08 (m, 1H, Indole H-5), 7.01 (m, 1H, Indole H-7), 6.68 (s,1H, OH), 3.78 and 3.63 (AB-System, $^{2}J_{AB}$ = 9.7 Hz, 2H, CH_2Br), 3.11 (s, 3H, CH_3). **^{13}C NMR** (100 MHz, DMSO-d_6): δ 174.9 (Indole C-2), 143.8 (Indole C-7a), 129.8 (Indole C-6), 129.0 (Indole C-3a), 123.9 (Indole C-4), 122.4 (Indole C-5), 108.6 (Indole C-7), 74.5 (Indole C-3), 34.9 (CH_2Br), 25.9 (CH_3). **^{15}N NMR** (40MHz, DMSO-d_6): δ -252.6 (Indole N-1).

HRMS (ESI), *m/z*: calcd. for $C_{10}H_{10}BrNNaO_2$277.9792 $[M+Na]^+$; found 277.9787.

3-hydroxy-3-(iodomethyl)-1-methyl-1,3-dihydro-2*H*-indol-2-one (2.140)

By following general procedure **7**, starting from 1-methyl-1*H*-indole-2,3-dione (0.161 g, 1.0 mmol, 1.0 equiv), CH_2I_2 (0.24 ml, 0.804 g, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (1.14 ml, 2.2 M, 2.5 mmol, 2.5 equiv) in THF,after column chromatography in neutral alumina (Brockmann grade IV) eluting with hexane/ethyl acetate 1:1, compound **2.140** was obtained in 79% yield (0.238 g) as an yellow solid; mp 125-127°C.

^{1}H NMR (400MHz, DMSO-d_6): δ 7.41 (m, 1H, Indole H-4), 7.34 (m, 1H, Indole H-6), 7.07 (m, 1H, Indole H-5), 7.01(m, 1H, Indole H-7), 6.65 (s, 1H, OH), 3.54 and 3.38 (AB-System, $^{2}J_{AB}$ = 9.5 Hz, 2H, CH_2I), 3.11 (s, 3H, CH_3).**^{13}C NMR** (100 MHz, DMSO-d_6): δ 175.0 (Indole C-2), 143.6 (Indole C-7a), 129.8 (Indole C-6), 129.6 (Indole C-3a), 123.6 (Indole C-4), 122.3 (Indole C-5), 108.5 (Indole C-7), 74.3 (Indole C-3), 25.9 (CH_3), 9.2 ($\underline{C}H_2I$). **^{15}N NMR** (40MHz, DMSO-d_6): δ -252.9 (Indole N-1).

HRMS (ESI), *m/z*: calcd. for $C_{10}H_{10}INNaO_2$325.9653 $[M+Na]^+$; found 325.9648.

2-methyl-2-propanyl[3-(chloromethyl)-3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate (2.141)

By following general procedure **7**, starting from 2-methyl-2-propanyl (2,3-dioxo-2,3-dihydro-1*H*-indol-1-yl)acetate (0.131 g, 0.5 mmol, 1.0 equiv), $ClCH_2I$ (0.11 ml, 0.265 g, 1.5 mmol, 3.0 equiv) and MeLi-LiBr (0.57 ml, 2.2 M, 1.25 mmol, 2.5 equiv) in THF, after column chromatography in neutral alumina (Brockmann grade IV) eluting with hexane/ethyl acetate 8:2, compound **2.141** was obtained in 86% yield (0.134 g) as a yellow thick oil.

^{1}H NMR (400MHz, C_6D_6):δ 7.28 (m, 1H, Indole H-4), 6.94 (m, 1H, Indole H-6), 6.79 (m, 1H, Indole H-5), 6.31 (m, 1H, Indole H-7), 4.09,3.95 (AB-System, $^2J_{AB}$ = 17.4 Hz, 2H, NCH_2), 3.70 and 3.66 (AB-System, $^2J_{AB}$ = 11.0 Hz, 2H, CH_2Cl),3.64 (br s, 1H, OH),1.20 (s, 9H, $C(CH_3)_3$). **^{13}C NMR** (100 MHz, C_6D_6):δ 175.7 (Indole C-2), 166.4 ($CH_2\underline{C}$=O), 143.3 (Indole C-7a), 130.1 (Indole C-6), 128.4 (Indole C-3a), 125.0 (Indole C-4), 123.3 (Indole C-5), 108.6 (Indole C-7), 82.3 ($\underline{C}(CH_3)_3$), 75.6 (Indole C-3), 47.5 ($\underline{C}H_2Cl$), 42.2 ($N\underline{C}H_2$), 27.8 ($C(\underline{C}H_3)_3$). **^{15}N NMR** (40MHz, C_6D_6):δ -249.9 (Indole N-1).

HRMS (ESI), *m/z*: calcd. for$C_{15}H_{18}ClNNaO_4$334.0817 $[M+Na]^+$; found 334.0813.

2.3.9 General Procedure for Chemoselective Addition of Lithium Polyhalocarbenoids to Isatins (General Procedure 8)

A 2.2 M MeLi–LiBr solution (2.05 mL, 4.5 mmol, 4.5 equiv) was added dropwise to a precooled solution of 2,2,6,6-tetramethylpiperidine (0.77 mL, 636 mg, 4.5 mmol, 4.5 equiv) in THF (4 mL) at 0 °C. The generated LTMP was transferred to a cooled (–78 °C) solution of the isatin (1.0 equiv) and dihalomethane (5.0 equiv) in dry THF (0.5 M concentration) over 5 min. The resulting solution was stirred for 1 h at this temperature, and then sat. aq NH_4Cl was added (2 mL/mmol substrate). After removal of the cooling bath, the mixture was stirred until it reached r.t. and then

extracted with additional Et_2O (2 × 5 mL) and washed with 3 M HCl and brine. The organic phase was dried (anhyd Na_2SO_4), filtered and, after removal of the solvent under reduced pressure; the so-obtained crude mixture was subjected to chromatography (neutral alumina) to afford pure isatin halohydrine.

3-(dichloromethyl)-3-hydroxy-1-methyl-1,3-dihydro-2*H*-indol-2-one (2.144a)

By following general procedure **8**, starting from 1-methyl-1*H*-indole-2,3-dione (0.161 g, 1.0 mmol, 1.0 equiv), CH_2Cl_2 (0.29 ml, 0.382 g, 3.0 mmol, 3.0 equiv), LTMP [generated at 0 °C from TMP (0.77 mL, 636 mg, 4.5 mmol, 4.5 equiv) and MeLi-LiBr (2.05 ml, 2.2 M, 4.5 mmol, 4.5 equiv)] in THF, after column chromatography in neutral alumina (Brockmann grade IV) eluting with hexane/ethyl acetate 8:2, compound **2.144a** was obtained in 83% yield (0.204 g) as an white solid; mp 166-168 °C.

^{1}H NMR (400MHz, C_6D_6): δ 7.57 (m, 1H, Indole H-4), 6.97 (m, 1H, Indole H-6), 6.79 (m, 1H, Indole H-5), 6.13 (m, 1H, Indole H-7), 5.87 (s, 1H, $CHCl_2$) 3.25 (s, 1H, OH),2.48 (s, 3H, CH_3). **^{13}C NMR** (100 MHz, C_6D_6):δ 173.7* (Indole C-2), 145.0* (Indole C-7a), 130.8 (Indole C-6), 126.0 (Indole C-4), 125.6* (Indole C-3a), 123.1 (Indole C-5), 108.6 (Indole C-7), 78.2* (Indole C-3), 74.9 ($CHCl_2$), 25.8 (CH_3), (**via* HMBC). **^{15}N NMR** (40MHz, C_6D_6):δ -253.5 (Indole N-1).

HRMS (ESI), *m/z*: calcd. for $C_{10}H_9Cl_2NNaO_2$267.9903 $[M+Na]^+$; found 267.9906.

3-(dibromomethyl)-3-hydroxy-1-methyl-1,3-dihydro-2*H*-indol-2-one (2.144b)

By following general procedure **8**, starting from 1-methyl-1*H*-indole-2,3-dione (0.161 g, 1.0 mmol, 1.0 equiv), CH_2Br_2 (0.31 ml, 0.782 g, 3.0 mmol, 3.0 equiv), LTMP [generated at 0 °C from TMP (0.77 mL, 636 mg, 4.5 mmol, 4.5 equiv) and MeLi-LiBr (2.05 ml, 2.2 M, 4.5 mmol, 4.5 equiv)] in THF,after column chromatography in neutral alumina (Brockmann grade IV) eluting with

hexane/ethyl acetate 8:2, compound **2.144b** was obtained in 85% yield (0.285 g) as an white solid; mp 159-161 °C.

^{1}H NMR (400MHz, C_6D_6): δ 7.68 (m, 1H, Indole H-4), 6.98 (m, 1H, Indole H-6), 6.81 (m, 1H, Indole H-5), 6.15 (m, 1H, Indole H-7), 5.81 (s, 1H, $CHBr_2$) 3.43 (brs, 1H, OH), 2.51 (s, 3H, CH_3). **^{13}C NMR** (100 MHz, C_6D_6):δ 173.6 (Indole C-2), 144.9 (Indole C-7a), 130.8 (Indole C-6), 126.4 (Indole C-4), 125.6 (Indole C-3a), 123.0 (Indole C-5), 108.6 (Indole C-7), 77.7 (Indole C-3), 48.5 ($CHBr_2$), 25.8 (CH_3). **^{15}N NMR** (40MHz, C_6D_6):δ -253.7 (Indole N-1).

HRMS (ESI), *m/z*: calcd. for $C_{10}H_9Br_2NNaO_2$355.8892 $[M+Na]^+$; found 355.8893.

3-(bromo(chloro)methyl)-3-hydroxy-1-methyl-1,3-dihydro-2*H*-indol-2-one (2.144c)

By following general procedure 8, starting from 1-methyl-1*H*-indole-2,3-dione (0.161 g, 1.0 mmol, 1.0 equiv), CH_2BrCl (0.29 ml, 0.582 g, 3.0 mmol, 3.0 equiv), LTMP [generated at 0 °C from TMP (0.77 mL, 636 mg, 4.5 mmol, 4.5 equiv) and MeLi-LiBr (2.05 ml, 2.2 M, 4.5 mmol, 4.5 equiv)] in THF, after column chromatography in neutral alumina (Brockmann grade IV) eluting with hexane/ethyl acetate 8:2, compound **2.144c** was obtained in 77% yield (0.223 g) as an white solid; mp 148-150 °C.

^{1}H NMR (400MHz, C_6D_6): δ 7.64 (m, 1H, Indole H-4), 6.98 (m, 1H, Indole H-6), 6.82 (m, 1H, Indole H-5), 6.14 (m, 1H, Indole H-7), 5.96 (s, 1H, CHBrCl) 3.75 (br s, 1H, OH), 2.49 (s, 3H, CH_3). **^{13}C NMR** (100 MHz, C_6D_6):δ 173.8 (Indole C-2), 144.9 (Indole C-7a), 130.8 (Indole C-6), 126.1 (Indole C-3a), 125.9 (Indole C-4), 123.1 (Indole C-5), 108.6 (Indole C-7), 78.2 (Indole C-3), 63.0 (CHBrCl), 25.8 (CH_3). **^{15}N NMR** (40MHz, C_6D_6):δ -253.1 (Indole N-1).

HRMS (ESI), *m/z*: calcd. for $C_{10}H_9ClBrNNaO_2$311.9397 $[M+Na]^+$; found 311.9402.

2.3.10 General Procedure for Preparation of Isatin Epoxides

(General Procedure 9)

The halohydrin derived from isatin (1.0 equiv) were dissolved in anhydrous acetonitrile and, to this mixture was added dry potassium carbonate (1.5 equiv). The resulting suspension was kept stirring at rt overnight; then the acetonitrile evaporated *in vacuo* and 5 mLwater was added and the organic phase was extracted with diethyl ether (3 x 10 mL). The crude compounds were purified as reported below through neutral alumina chromatography (Brockmann degree IV).

Spiro[indole-3,2'-oxiran]-2(1*H*)-one (2.145)

By following general procedure 9, starting from 3-(chloromethyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one(0.100 g, 0.51 mmol, 1.0 equiv) and K_2CO_3 (0.106 g, 0.77 mmol, 1.5 equiv) in ACN, compound **2.145** was obtained in 96% yield (0.079 g) as an orange solid; mp 92-94 °C**.**

^{1}H NMR (400MHz, DMSO-d_6):δ 7.29 (m, 1H, Indole H-6), 7.13 (m, 1H, Indole H-4), 6.98 (m, 1H, Indole H-5), 6.93 (m, 1H, Indole H-7), 6.30-4.30 (verybroad s, 1H, NH), 3.55 and 3.33 (AB-System, $^2J_{AB}$ = 6.6 Hz, 2H, CH_2O). **^{13}C NMR** (100 MHz, DMSO-d_6):δ 172.9 (Indole C-2), 144.0 (Indole C-7a), 130.3 (Indole C-6), 123.0 (Indole C-3a), 122.6 (Indole C-4), 121.7 (Indole C-5), 110.6 (Indole C-7), 56.3 (Indole C-3), 53.2 ($\underline{C}H_2O$). **^{15}N NMR** (40MHz, C_6D_6):δ -241.8 (Indole N-1).

HRMS (ESI), *m/z*: calcd. for $C_9H_7NNaO_2$ 184.0369 $[M+Na]^+$; found 184.0367.

1-methylspiro[indole-3,2'-oxiran]-2(1*H*)-one (2.146)[135]

By following general procedure 9, starting from 3-(chloromethyl)-3-hydroxy-1-methyl-1,3-dihydro-2*H*-indol-2-one(0.106 g, 0.5 mmol, 1.0 equiv) and K_2CO_3 (0.104 g, 0.75 mmol, 1.5 equiv) in ACN, compound **2.146** was obtained in 93% yield (0.081 g) as a yellow solid; mp 65-67 °C.

^{1}H NMR (400MHz, C_6D_6):δ 6.96 (m, 1H, Indole H-6), 6.73 (m, 1H, Indole H-5), 6.69 (m, 1H, Indole H-4), 6.16 (“d”, *J* = 7.9 Hz, 1H, Indole H-7), 3.28 (d, *J* = 6.9 Hz, 1H, CH_2O), 2.75 (d, *J* = 6.9 Hz, 1H, CH_2O), 2.54 (s, 3H, CH_3).**^{13}C NMR** (100 MHz, C_6D_6):δ 171.1 (Indole C-2), 145.6 (Indole C-7a), 130.0 (Indole C-6), 123.3 (Indole C-3a), 122.3 (Indole C-5), 122.1 (Indole C-4), 108.6 (Indole C-7), 56.3 (Indole C-3), 53.7 ($\underline{C}H_2O$), 25.8 (CH_3). **^{15}N NMR** (40MHz, C_6D_6):δ -253.0 (Indole N-1).

HRMS (ESI), *m/z*: calcd. for $C_{10}H_9NNaO_2$ 198.0525 $[M+Na]^+$; found 198.0524.

1-propylspiro[indole-3,2'-oxiran]-2(1*H*)-one (2.147)

By following general procedure 9, starting from 3-(chloromethyl)-3-hydroxy-1-propyl-1,3-dihydro-2*H*-indol-2-one(0.101 g, 0.42 mmol, 1.0 equiv) and K_2CO_3 (0.087 g, 0.63 mmol, 1.5 equiv) in ACN, compound **2.147** was obtained in 94% yield (0.080 g) as a dark yellow oil.

^{1}H NMR (400MHz, C_6D_6):δ 7.36 (m, 1H, Indole H-6), 7.11 (m, 1H, Indole H-4), 7.06 (m, 1H, Indole H-5), 6.93 (m, 1H, Indole H-7), 3.74 (m, 1H, NCH_2), 3.58 and 3.43 (AB-System, $^{2}J_{AB}$ = 6.7 Hz, 2H, CH_2O), 3.17 (m, 1H, NCH_2), 1.74 (m, 2H, $C\underline{H}_2CH_3$), 0.99 (t, *J* = 7.4 Hz, 3H, $CH_2C\underline{H}_3$). **^{13}C NMR** (100 MHz, C_6D_6):δ 171.6 (Indole C-2), 144.6 (Indole C-7a), 130.3 (Indole C-6), 122.8 (Indole C-3a), 122.5 (Indole C-5), 122.2 (Indole C-4), 109.1 (Indole C-7), 56.3 (Indole C-3), 54.1 (CH_2O), 42.1 (NCH_2), 20.8 ($\underline{C}H_2CH_3$), 11.3 ($CH_2\underline{C}H_3$). **^{15}N NMR** (40MHz, C_6D_6):δ -239.0 (Indole N-1).

HRMS (ESI), *m/z*: calcd. for $C_{12}H_{13}NNaO_2$ 226.0838 $[M+Na]^+$; found 226.0836.

1-benzylspiro[indole-3,2'-oxiran]-2(1*H*)-one (2.148)

By following general procedure 9, starting from 1-benzyl-3-(chloromethyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one(0.100 g, 0.35mmol, 1.0 equiv) and K_2CO_3 (0.072 g, 0.52mmol, 1.5 equiv) in ACN, compound **2.148** was obtained in 91% yield (0.080 g) as a white solid; mp 99-101 °C. **^{1}H NMR** (400MHz, C_6D_6):δ 7.08 (m, 2H, Ph H-2,6), 6.99 (m, 2H, Ph H-3,5), 6.98 (m, 1H, Ph H-4), 6.84 (m, 1H, Indole H-6), 6.69 (m, 1H, Indole H-4), 6.67 (m, 1H, Indole H-5), 6.36 (m, 1H, Indole H-7), 4.58 and 4.47 (AB-System, $^2J_{AB}$ = 15.8 Hz, 2H, C$\underline{H}_2$Ph), 3.34 (d, *J* = 6.9 Hz, 1H, CH_2O), 2.77 (d, *J* = 6.9 Hz, 1H, CH_2O). **^{13}C NMR** (100 MHz, C_6D_6):δ 171.6 (Indole C-2), 144.8 (Indole C-7a), 136.2 (Ph C-1), 130.1 (Indole C-6), 129.0 (Ph C-3,5), 127.8* (Ph 4), 127.5 (Ph C-2,6), 123.4 (Indole C-3a), 122.6 (Indole C-5), 122.3 (Indole C-4), 109.7 (Indole C-7), 56.4 (Indole C-3), 53.9 (CH_2O), 44.1 ($\underline{C}H_2$Ph) (**via* HSQC). **^{15}N NMR** (40MHz, C_6D_6):δ -240.9 (Indole N-1).

HRMS (ESI), *m/z*: calcd. for $C_{16}H_{13}NNaO_2$ 274.0838 $[M+Na]^+$; found 274.0837.

7-fluoro-1-methylspiro[indole-3,2'-oxiran]-2(1*H*)-one (2.149)

By following general procedure 9, starting from 3-(chloromethyl)-7-fluoro-3-hydroxy-1-methyl-1,3-dihydro-2*H*-indol-2-one(0.100 g, 0.44 mmol, 1.0 equiv) and K_2CO_3 (0.090 g, 0.65 mmol, 1.5 equiv) in ACN, compound **2.149** was obtained in 90% yield (0.076 g) as a yellow solid. **^{1}H NMR** (400MHz, C_6D_6): δ 6.62 (ddd, $^3J_{\text{Ind H-6,Ind F-7}}$ = 11.6 Hz, $^3J_{\text{Ind H-6,Ind H-5}}$ = 8.4 Hz, $^4J_{\text{Ind H-6,Ind H-4}}$ = 1.1 Hz, 1H, Indole H-6), 6.45 (ddd, $^3J_{\text{Ind H-5,Ind H-6}}$ = 8.4 Hz, $^3J_{\text{Ind H-5,Ind H-4}}$ = 7.4 Hz, $^4J_{\text{Ind H-5,Ind F-7}}$ = 4.3 Hz, 1H, Indole H-5), 6.35 (dd, $^3J_{\text{Ind H-4,Ind H-5}}$ = 7.4 Hz, $^4J_{\text{Ind H-4,Ind H-6}}$= 1.1 Hz, 1H, Indole H-4), 3.22 and 2.68 (AB-System, $^2J_{AB}$ = 6.9 Hz, 2H, CH_2O), 2.89 (d, $J_{\text{CH3,Ind F-7}}$ = 2.8 Hz, 3H, CH_3). **^{13}C NMR** (100 MHz, C_6D_6): δ 170.7 (Indole C-2), 148.0 (d, ^1J = 243.3 Hz, Indole C-7), 132.0 (d, *J* = 8.9 Hz, Indole C-7a), 126.4 (d, *J* = 3.7 Hz, Indole C-3a), 122.9 (d, *J* = 6.4 Hz, Indole C-5), 117.88 (d, *J* = 19.3 Hz, Indole C-6), 117.85 (d, *J* = 3.3 Hz, Indole C-4), 56.0 (d, *J* = 3.6 Hz, Indole C-3), 54.2 (CH_2O), 28.5 (d, *J* = 5.5 Hz, CH_3). **^{15}N NMR** (40MHz, C_6D_6):δ -256.4 (Indole N-1). **^{19}F NMR**

(376 MHz, C_6D_6):δ -137.1 (ddq, $^3J_{\text{Ind F-7,Ind H-6}}$ = 11.6 Hz, $^4J_{\text{Ind F-7,Ind H-5}}$ = 4.4 Hz, $J_{\text{Ind F-7,CH3}}$ = 2.8 Hz,Indole C 7-F).

HRMS (ESI), *m/z*: calcd. for $C_{10}H_8FNNaO_2$ 216.0431 $[M+Na]^+$; found 216.0428.

1-phenylspiro[indole-3,2'-oxiran]-2(1*H*)-one (2.150)

By following general procedure 9, starting from 3-(chloromethyl)-3-hydroxy-1-phenyl-1,3-dihydro-2*H*-indol-2-one(0.100 g, 0.37 mmol, 1.0 equiv) and K_2CO_3 (0.076 g, 0.55 mmol, 1.5 equiv) in ACN, compound **2.150** was obtained in 92% yield (0.081 g) as a white solid; mp 92-94 °C.

^{1}H NMR (400MHz, C_6D_6):δ 7.01 (m, 2H, Ph H-2,3,5,6), 6.91 (m, 1H, Ph H-4), 6.80 (m, 1H, Indole H-6), 6.68 (m, 1H, Indole H-4), 6.67 (m, 1H, Indole H-5), 6.45 (m, 1H, Indole H-7), 3.25 (d, *J* = 6.8, Hz, 1H, CH_2O), 2.71 (d, *J* = 6.8, Hz, 1H, CH_2O). **^{13}C NMR** (100 MHz, C_6D_6):δ 170.6 (Indole C-2), 145.6 (Indole C-7a), 134.9 (Ph C-1), 130.1 (Indole C-6), 129.6 (Ph C-3,5), 128.0 (Ph C-4), 126.6 (Ph C-2,6), 123.3 (Indole C-3a), 123.0 (Indole C-5), 122.5 (Indole C-4), 110.0 (Indole C-7), 56.3 (Indole C-3), 54.3 ($\underline{C}H_2O$).

HRMS (ESI), *m/z*: calcd. for $C_{15}H_{11}NNaO_2$ 260.0682 $[M+Na]^+$; found 260.0680.

1-allylspiro[indole-3,2'-oxiran]-2(1*H*)-one (2.151)

By following general procedure 9, starting from 1-allyl-3-(chloromethyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one(0.100 g, 0.42 mmol, 1.0 equiv) and K_2CO_3 (0.087 g, 0.63 mmol, 1.5 equiv) in ACN, compound **2.151** was obtained in 91% yield (0.077 g) as a yellow solid; mp 65-67 °C.

^{1}H NMR (400MHz, C_6D_6):δ 7.35 (m, 1H, Indole H-6), 7.12 (m, 1H, Indole H-4), 7.08 (m, 1H, Indole H-5), 6.92 (m, 1H, Indole H-7), 5.86 (m, 1H, $C\underline{H}_a=CH_2$), 5.29 (m, 1H, $CH=C\underline{H}_{2(trans)}$), 5.26 (m, 1H, $CH=C\underline{H}_{2(cis)}$), 4.43 (m, ^2J = 16.3 Hz, 1H, NCH_2),4.38 (m, ^2J = 16.3 Hz, 1H, $NC\underline{H}_2$), 3.61 and 3.45 (AB-System, $^2J_{AB}$ = 6.7 Hz, 2H, CH_2O).

^{13}C NMR (100 MHz, C_6D_6):δ 171.5 (Indole C-2), 144.3 (Indole C-7a), 131.0 (<u>C</u>H=CH_2), 130.3 (Indole C-6), 122.8 (Indole C-5), 122.6 (Indole C-3a), 122.2 (Indole C-4), 118.1 (CH=<u>C</u>H_2), 109.8 (Indole C-7), 56.3 (Indole C-3), 54.2 (CH_2O), 42.8 (N<u>C</u>H_2). **^{15}N NMR** (40MHz, C_6D_6):δ -242.5 (Indole N-1).

HRMS (ESI), *m/z*: calcd. for $C_{12}H_{11}NNaO_2$224.0682 $[M+Na]^+$; found 224.0681.

1-(2-propyn-1-yl)spiro[indole-3,2'-oxiran]-2(1*H*)-one (2.152)

By following general procedure 9, starting from 3-(chloromethyl)-3-hydroxy-1-(2-propyn-1-yl)-1,3-dihydro-2*H*-indol-2-one(0.100 g, 0.42 mmol, 1.0 equiv) and K_2CO_3 (0.088 g, 0.64mmol, 1.5 equiv) in ACN, compound **2.152** was obtained in 94% yield (0.079 g) as a yellow solid; mp 110-112 °C.

^{1}H NMR (400MHz, C_6D_6):δ6.98 (m, 1H, Indole H-6), 6.71 (m, 1H, Indole H-5), 6.63 (m, 1H, Indole H-4), 6.61 (m, 1H, Indole H-7), 4.24 (dd, ^2J = 17.8 Hz, ^4J = 2.5 Hz, 1H, NCH_2),3.65 (dd, ^2J = 17.8 Hz, ^4J = 2.5 Hz, 1H, NCH_2), 3.16 and 2.61 (AB-System, $^2J_{AB}$ = 6.8 Hz, 2H, CH_2O), 1.66 (t, ^4J = 2.5 Hz, 1H, CC<u>H</u>).

^{13}C NMR (100 MHz, C_6D_6): δ 170.4 (Indole C-2), 143.7 (Indole C-7a), 130.0 (Indole C-6), 123.3 (Indole C-3a), 122.8 (Indole C-5), 122.2 (Indole C-4), 109.6 (Indole C-7), 77.1 (<u>C</u>CH), 72.4 (C<u>C</u>H), 56.2 (Indole C-3), 53.9 (CH_2O), 29.2 (NCH_2). **^{15}N NMR** (40MHz, C_6D_6):δ -247.2 (Indole N-1).

HRMS (ESI), *m/z*: calcd. for $C_{12}H_9NNaO_2$ 222.0525 $[M+Na]^+$; found 222.0523.

1-(2-butyn-1-yl)spiro[indole-3,2'-oxiran]-2(1*H*)-one (2.153)

By following general procedure 9, starting from 1-(2-butyn-1-yl)-3-(chloromethyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one(0.100 g, 0.40mmol, 1.0 equiv) and K_2CO_3 (0.083 g,

0.60mmol, 1.5 equiv) in ACN, compound **2.153** was obtained in 87% yield (0.074 g) as a white solid; mp 115-117 °C.

^{1}H NMR (400MHz, C_6D_6):δ 7.01 (m, 1H, Indole H-6), 6.73 (m, 1H, Indole H-5), 6.72 (m, 1H, Indole H-7), 6.67 (m, 1H, Indole H-4), 4.33 (qd, ^2J = 17.6 Hz, ^5J = 2.5 Hz, 1H, NCH_2), 3.85 (qd, ^2J = 17.6 Hz, ^5J = 2.5 Hz, 1H, NCH_2), 3.20 and 2.65 (AB-System, $^2J_{AB}$ = 6.8 Hz, 2H, CH_2O), 1.28 (t, ^5J = 2.5 Hz, 3H, CH_3). **^{13}C NMR** (100 MHz, C_6D_6): δ 170.4 (Indole C-2), 144.2 (Indole C-7a), 130.0 (Indole C-6), 123.4 (Indole C-3a), 122.6 (Indole C-5), 122.2 (Indole C-4), 109.7 (Indole C-7), 80.0 ($CH_2\underline{C}$), 72.8 ($\underline{C}CH_3$), 56.3 (Indole C-3), 53.9 (CH_2O), 29.8 (NCH_2), 3.0 (CH_3). **^{15}N NMR** (40MHz, C_6D_6):δ -244.7 (Indole N-1).

HRMS (ESI), *m/z*: calcd. for $C_{13}H_{11}KNO_2$ 252.0421 $[M+K]^+$; found 252.0420.

ethyl 2-(2-oxospiro[indole-3,2'-oxiran]-1(2*H*)-yl)acetate (2.154)

By following general procedure 9, starting from ethyl [3-(chloromethyl)-3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate(0.120 g, 0.42 mmol, 1.0 equiv) and K_2CO_3 (0.087 g, 0.63 mmol, 1.5 equiv) in ACN, compound **2.154** was obtained in 95% yield (0.099 g) as a yellowsolid; mp 65-66 °C.

^{1}H NMR (400MHz, C_6D_6):δ 6.94 (m, 1H, Indole H-6), 6.72 (m, 1H, Indole H-5), 6.67 (m, 1H, Indole H-4), 6.27 (m, 1H, Indole H-7), 4.32 and 3.79 (AB-System, $^2J_{AB}$ = 17.6 Hz, 2H, NCH_2), 3.78 (q, *J* = 7.1 Hz, 2H, $C\underline{H}_2CH_3$), 3.24 and 2.67 (AB-System, $^2J_{AB}$ = 6.8 Hz, 2H, CH_2O), 0.79 (s, 3H, $CH_2C\underline{H}_3$). **^{13}C NMR** (100 MHz, C_6D_6):δ 171.5 (Indole C-2), 167.3 ($CH_2\underline{C}$=O), 144.5 (Indole C-7a), 130.1 (Indole C-6), 123.3 (Indole C-3a), 122.8 (Indole C-5), 122.4 (Indole C-4), 108.8 (Indole C-7), 61.5 ($\underline{C}H_2CH_3$), 56.3 (Indole C-3), 54.0 ($\underline{C}H_2O$), 41.6 ($N\underline{C}H_2$), 13.9 ($CH_2\underline{C}H_3$).

HRMS (ESI), *m/z*: calcd. for $C_{13}H_{13}NNaO_4$ 270.0737 $[M+Na]^+$; found 270.0735.

2-methyl-2-propanyl(2-oxospiro[indole-3,2'-oxiran]-1(2*H*)-yl)acetate (2.155)

By following general procedure 9, starting from 2-methyl-2-propanyl [3-(chloromethyl)-3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-1-yl]acetate(0.150 g, 0.48mmol, 1.0 equiv) and K_2CO_3 (0.100 g, 0.72mmol, 1.5 equiv) in ACN, compound **2.155** was obtained in 93% yield (0.122 g) as a yellow solid; mp 61-62 °C.

^{1}H NMR (400MHz, C_6D_6):δ 6.94 (m, 1H, Indole H-6), 6.71 (m, 1H, Indole H-5), 6.67 (m, 1H, Indole H-4), 6.32 (m, 1H, Indole H-7), 4.28 and 3.80 (AB-System, $^2J_{AB}$ = 17.5 Hz, 2H, NCH_2), 3.24 and 2.66 (AB-System, $^2J_{AB}$ = 6.8 Hz, 2H, CH_2O), 1.21 (s, 9H, $C(CH_3)_3$). **^{13}C NMR** (100 MHz, C_6D_6):δ 171.5* (Indole C-2), 166.5 ($CH_2\underline{C}$=O), 144.7 (Indole C-7a), 130.0 (Indole C-6), 123.3* (Indole C-3a), 122.7 (Indole C-5), 122.4 (Indole C-4), 108.8 (Indole C-7), 82.1 ($\underline{C}(CH_3)_3$), 56.3* (Indole C-3), 53.9 ($\underline{C}H_2O$), 42.4 ($N\underline{C}H_2$), 27.8 ($C(\underline{C}H_3)_3$); (* via HMBC).

HRMS (ESI), *m/z*: calcd. for $C_{15}H_{17}NNaO_4$ 298.1050 $[M+Na]^+$; found 298.1046.

N-methoxy-N-methyl-2-(2-oxospiro[indole-3,2'-oxiran]-1(2*H*)-yl)acetamide (2.156)

By following general procedure 9, starting from 2-[3-(chloromethyl)-3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-1-yl]-*N*-methoxy-*N*-methylacetamide(0.150 g, 0.5 mmol, 1.0 equiv) and K_2CO_3 (0.104 g, 0.75 mmol, 1.5 equiv) in ACN, compound **2.156** was obtained in 89% yield (0.117 g) as a yellow solid; mp 135-137 °C.

^{1}H NMR (400MHz, C_6D_6):δ 6.98 (m, 1H, Indole H-6), 6.74 (m, 1H, Indole H-5), 6.71 (m, 1H, Indole H-4), 6.48 (m, 1H, Indole H-7), 4.60 and 3.99 (AB-System, $^2J_{AB}$ = 17.2 Hz, 2H, NCH_2), 3.25 and 2.68 (AB-System, $^2J_{AB}$ = 6.8 Hz, 2H, CH_2O), 2.97 (s, 3H, OCH_3), 2.68 (s, 3H, NCH_3). **^{13}C NMR** (100 MHz, C_6D_6):δ 171.8 (Indole C-2), 167.4* ($CH_2\underline{C}$=O), 145.2 (Indole C-7a), 130.0 (Indole C-6), 123.3 (Indole C-3a), 122.6 (Indole C-5), 122.3 (Indole C-4), 109.4 (Indole C-7), 60.9

(OCH_3), 56.5 (Indole C-3), 54.0 ($\underline{C}H_2O$), 41.4 (NCH_2), 32.0 (broad, NCH_3); *(*via* HMBC). **^{15}N NMR** (40MHz, C_6D_6):δ -196.3 (O=CN).

HRMS (ESI), *m/z*: calcd. for $C_{13}H_{11}NNaO_2$ 285.0846 $[M+Na]^+$; found 285.0851.

(3*E*)-1-methyl-3-(1-methyl-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)-1,3-dihydro-2*H*-indol-2-one (2.157)

By following general procedure 9, starting from **2.144a** or **2.144b** or **2.144c**, (0.100 g, 0.35 mmol, 1.0 equiv) and K_2CO_3 (0.072 g, 0.52 mmol, 1.5 equiv) in ACN, compound **2.157** was obtained in 91% yield (0.080 g) as a white solid; mp 99-101 °C.

Purple solid; mp 273-275 °C

^{1}H NMR (400MHz, C_6D_6):δ 9.80 (m, 2H, Indole H-4,4′), 7.01 (m, 2H, Indole H-6,6′), 6.95 (m, 2H, Indole H-5,5′), 6.12 (m, 2H, Indole H-7,7′), 2.63 (s, 6H, CH_3,CH_3′). **^{13}C NMR** (100 MHz, C_6D_6):δ 167.9 (Indole C-2,2′), 145.7 (Indole C-7a,7a′), 133.7 (Indole C-3,3′), 132.2 (Indole C-6,6′), 130.7 (Indole C-4,4′), 122.35 (Indole C-3a,3a′), 122.32 (Indole C-5,5′), 107.5 (Indole C-7,7′), 25.5 (CH_3,CH_3′). **^{15}N NMR** (40MHz, C_6D_6):δ -252.9 (Indole N-1,1′).

HRMS (ESI), *m/z*: calcd. for $C_{18}H_{14}N_2NaO_2$313.0947 $[M+Na]^+$; found 313.0951.

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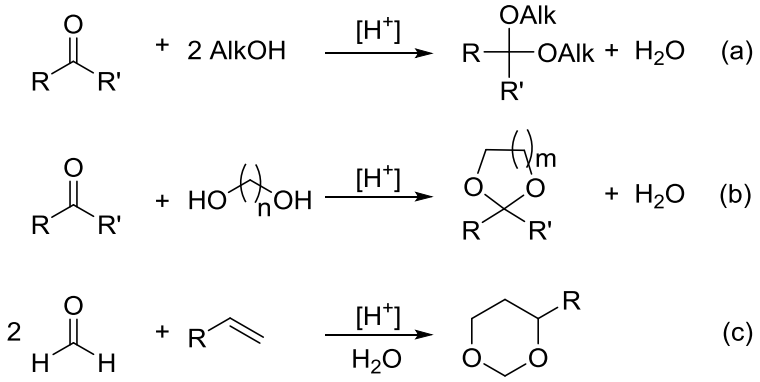
Appendix

Acetalization Reaction in Green and Convenient Solvents

A.1.1 Introduction

The process of formation of masked carbonyl derivatives from ketones or aldehydes with alcohols or with alkenes (Prins reaction, path c, Scheme A.1.1)[1] in the presence of acidic catalysts is known as acetalization and the resulting product is called an acetal (Scheme A.1.1). Acetals have fundamental applications in the chemical industry as intermediates or final compounds.[2] For instance, additives in diesel,[3] as low-toxicity solvents in different areas (injectable preparations, paints, plastifying agents, insecticide delivery systems),[4] in insecticides,[5] in cosmetics,[6] in detergents[7] or as additives in foods and beverages.[8] In addition, acetalization of carbonyl compounds with alcohols is one of the most useful methods for protecting carbonyl compounds in organic synthesis from the attack of nucleophiles, oxidants, and basic reagents, especially in the case of carbohydrate and steroid chemistry.[9]



Scheme A.1.1: Acetalization reaction of a carbonyl compound. R, R' = alkyl, aryl, H; usually n = 2 or 3; usually m = 1 or 2.

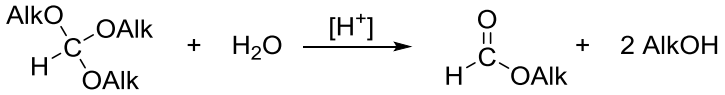
Acetalization of carbonyl compounds with alcohols is a well known reversible reaction that reaches equilibrium[10] with the formation of the corresponding acetal and water. To drive the

reaction towards completion by shifting the equilibrium, the formed water must be removed, either by physical[11] or chemical techniques.[12]

Considering catalytic activation of this reversible reaction, several catalysts have been reported. Among these: H_2SO_4,[13] HCl, trifluoroacetic acid, *p*-toluenesulfonic acid,[14] solid acids,[15] functionalized silica,[16] polymer-bound metal complexes,[15] acid free organocatalysts,[17] metal catalysts,[18] Lewis acids,[19] and zeolite clay,[20] are some of the reported examples. In general terms, the aldehydes undergo acetalization reaction in the presence of weak acids, while the less electrophilic ketones require stronger acids, often used in higher concentrations.

A.1.2 The role of Azeotropic Distillation on Acetalization Reactions

Water can be removed using additional reagents such as the orthoesters; under acidic conditions, these compounds consumes water by turning into one mole of ester and two moles of alcohols (Scheme A.1.2). As an alternative, acetalization can be driven to completion when water is removed from the reaction system by azeotropic distillation or trapped with drying agents.



Scheme A.1.2: Acid catalyzed reaction of an alkyl orthoester with water.

Azeotropes are mixtures of two or more solvents that behave as a single solvent maintaining a constant composition at their boiling points.[21] A positive azeotrope has a boiling point lower than the boiling points of any of its constituents (e.g. 78.2 °C for the azeotrope EtOH/H_2O, with bp EtOH = 78.4 °C and bp H_2O = 100 °C; weight percentage composition of the distillate: EtOH = 95.6, H_2O = 4.4), while a negative azeotrope has a boiling point greater than the boiling points of its constituents (e.g. 121 °C for the azeotrope HNO_3/H_2O, with bp HNO_3 = 78.4 °C and bp H_2O = 100

°C; weight percentage composition of the distillate: HNO_3 = 68, H_2O = 32). The Dean-Stark apparatus (Figure A.1.1) is designed to collect water produced in a reaction and removed as a positive azotrope by co-distillation with an immiscible solvent of lower density.[22] Since this procedure does not require additional reagents, such as an orthoformate, it can be considered as a green alternative from an economical and environmental point of view.

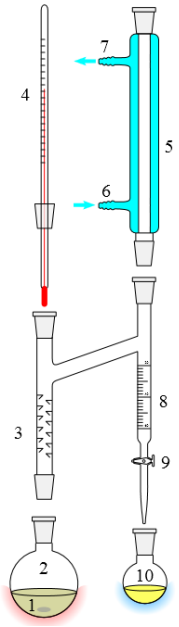


Figure A.1.1: Apparatus Dean-Stark: 1: Magnetic stirrer; 2: Reaction flask; 3: fractionation Column; 4: Thermometer; 5: Condenser; 6 and 7: Cooling liquid circulation; 8: Burette for the separation and collection of the reaction water; 9: Tap; 10: Water collecting vessel.

However, it should be considered that the procedure for azeotropic removal of water is usually accomplished using toluene as an organic solvent (to form the azeotrope in water with a boiling temperature of 84 °C and a weight percentage composition of the distillate: toluene = 79.8, H_2O = 20.2). This solvent is obtained from the petroleum industry and is commonly used in the synthesis of chemicals or as a solvent in different industrial processes. Toluene exerts toxic properties and detrimental health effects, especially on the nervous system, the liver and on the auditive function.[23] As an alternative, benzene was reported in the older literature as an efficient

solvent to perform acetalization reactions, as it forms a positive azeotrope with water having a boiling temperature of 69 °C with a 8.9 weight percentage composition of H_2O in the distillate. However, due to its well known highly toxic profile, it is recommended to ban such a solvent both from industrial as well as from laboratories procedures. Accordingly, both of these solvents are considered incompatible with synthetic procedures with a low environmental impact.

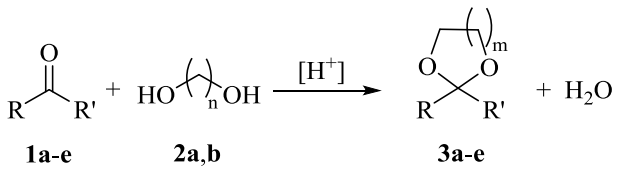
As mentioned in chapter 1, besides their robustness towards acids, both CPME and 2-MeTHF form positive azeotropes with H_2O (2-MeTHF/H_2O, bp 71 °C, % of H_2O in azeotrope = 10.6 w/w; CPME/H_2O, bp 83 °C, % of H_2O in azeotrope = 16.3 w/w) thus resulting, due to their high hydrophobicities, easy to recover and dry.

These last characteristics prompted us to evaluate their employment as alternatives to the solvents with a higher environmental impact mentioned above in reactions run under azeotropic distillation conditions, focusing our attention on the synthesis of cyclic acetals such as 1,3-dioxanes and 1,3-dioxolanes.[24]

A.1.2 Results and Discussion

A.1.2.1 Reactions of Acetals Formation

The reactions were run using a mild excess (10 mol%) of the diol (1,3-propandiol or 1,2-ethandiol) in the presence of NH_4Cl or Et_3NHCl (3 mol%) employed as acid catalysts. The choice of the catalysts is based on their easy availability and low cost, as well as to their easy of handling and reduced toxicity comparing with stronger acids (Scheme A.1.3).



1a-e **2a**,**b** **3a-e**

Scheme A.1.3: Synthesis of 1,3-dioxanes and dioxolanes, **3a-e**, under Dean-Stark reaction conditions. **1a**, **3a**: R = Ph, R' = H; **1b**, **3b**: R = 4-$(CH_3O)C_6H_4$, R' = H; **1c**, **3c**: R = 4-ClC_6H_4, R' = H; **1d**, **3d**: R = 2-$(C_2H_5)C_5H_{10}$, R' = H; **1e**, **3e**: R = C_6H_5, R' = CH_3; **2a**, n = 2; **2b**, n = 3; **3a**, **3b**, **3e**: m = 2; **3c**, **3d**: m = 1).

These catalysts (Table A.1.1) proved insoluble in the employed solvents, a characteristic which allowed the elaboration of the reaction mixtures by mere filtration on K_2CO_3. This effortless procedure has the great advantage to avoid an aqueous work up as well as to minimize the amount of solvent necessary for the elaboration of the reaction mixture.

Table A.1.1 reports the results obtained in the acetalization of aldehydes **1a-d** and a ketone, **1e** (Scheme A.1.4).

Taken together, these results demonstrate the effectiveness of both solvents in the synthesis of dioxanes and dioxolanes. An as interesting result, it is worth mentioning the highly efficient synthesis of dioxolane **3d** (Table A.1.1, entries 5 and 6), which is a product used in the fragrance industry[25]. Nonetheless, it is evident that reactions run in CPME are more rapid than similar reactions run in 2-MeTHF (Table A.1.1, entries 5 versus entry 6, and entry 7 versus entry 9), and

much more efficient in the acetalization of the aromatic ketone (Table A.1.1, entry 7 versus entry 9). These results are probably due by the higher boiling point of the CPME/H_2O azeotrope, as well as to the higher percentage of H_2O azeotropically removed by CPME (azeotrope 2-MeTHF / H_2O, bp 71 ° C, 10.6% by weight of H_2O in the distillate; azeotrope CPME / H_2O, bp 83 ° C, 16.3 wt% of H_2O in the distillate).

Table A.1.1: Acid-catalyzed reactions of aldehydes and ketones, **1**, with 1,3-propanediol, **2a**, or 1,2-ethanediol, **2b**

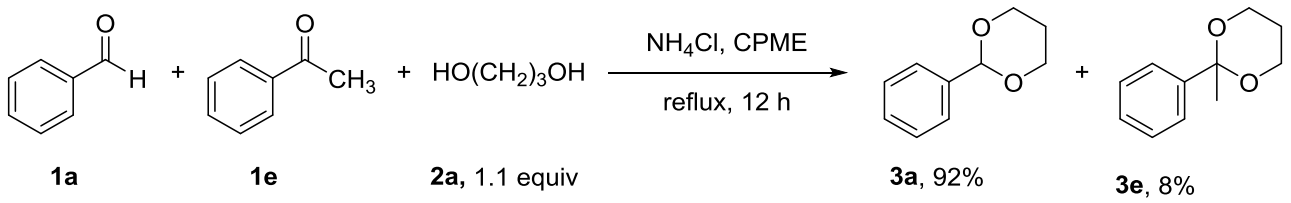
Entry	Substrate	Diol	Acid (mol%)	Solvent	Time (h)	Product (%)[a] **1** : **3**
1	**1a**	**2a**	NH_4Cl (3)	CPME	12	2 : 98
2	**1b**	**2a**	NH_4Cl (3)	CPME	12	9 : 91
3	**1c**	**2b**	NH_4Cl (3)	CPME	4	16 : 84
4	**1c**	**2b**	NH_4Cl (3)	CPME	12	8 : 92
5	**1d**	**2b**	NH_4Cl (3)	CPME	2	2 : 98
6	**1d**	**2b**	NH_4Cl (3)	2-MeTHF	12	2 : 98
7	**2e**	**2a**	NH_4Cl (3)	CPME	12	30 : 70
8	**1e**	**2a**	Et_3NHCl (3)	CPME	12	26 : 74
9	**1e**	**2a**	NH_4Cl (3)	2-MeTHF	12	75 : 25

[a]Determined by ^{1}H-NMR analyses of crude reaction mixtures. No other product, unless starting materials was identified to a considerable extent.

Additionally, it is worth mentioning that under similar reaction conditions, benzaldehyde, **1a**, show a higher conversion with respect to a ketone with a comparable structure such as acetophenone, **1e** (Table A.1.1, entry 1 versus entries 7 and 8).

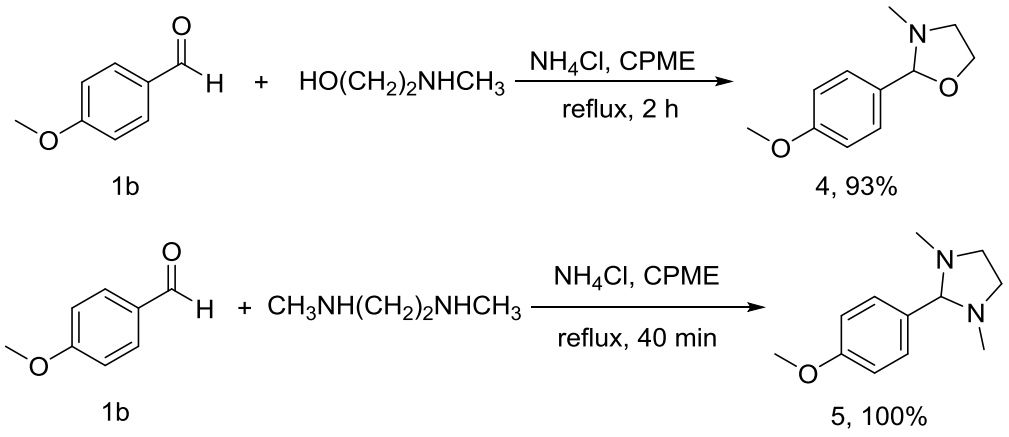
Considering the electrophilicity of the respective carbonyls, the different reactivities of aldehydes and ketones in this system is such to allow almost quantitative and highly selective

conversion of benzaldehyde, **1a**, into the corresponding acetal, **3a**, even in the presence of equimolar amounts of acetophenone, **1e**, and 1,3-propanediol, **2a**, as diagrammatically reported in Scheme A.1.4.



Scheme A.1.4: Chemoselective protection of benzaldehyde, **1a**, in the presence of equimolar amounts of acetophenone, **1e**, and 1,3-propanediol, **2a**.

Finally, we successfully extended the above reported procedure to the preparation of 2-(4-methoxyphenyl)-3-methyloxazolidine, **4**, and of 2-(4-methoxyphenyl)-1,3-dimethylimidazolidine, **5**. Interestingly, these products were obtained with higher yields and shorter reaction times compared to those necessary to obtain the corresponding dioxane **3b**. These results are very likely attributable to the increased reactivity of the dinucleophiles employed for the latter synthesis (Scheme A.1.5).



Scheme A.1.5: Synthesis of oxazolidine **4** and imidazolidine **5**.

A.1.3 Conclusions

We tested the possibility of using either CPME or 2-MeTHF in the synthesis of dioxanes, dioxolanes, oxazolidines and imidazolidines under azeotropic distillation reaction conditions. Apart from the use of green solvents, the reduced environmental impact of this procedure is emphasized by the employment of almost stoichiometric reaction conditions. In this regard, it should be remembered that a large number of methods recently proposed for the acetal preparation includes the use of an excess of the alcohol component compared to the carbonyl one, with excesses ranging from 1:2 up to 1:10,[26] or alternatively, an excess of dehydrating agents, such as orthoformiates[18,27] (Scheme A.1.2).

However, it is clear that this reaction should be further developed, mainly for what concerns the conversion of the less reactive carbonyl compounds, such as aromatic ketones. For this purpose, it will certainly be worth checking the possible use of different catalysts, making use of solid catalysts with higher acidities such as, for example, some zeolites.[26a]

Finally, it is worth mentioning that it was possible to realize a 60-70% mass recovery of 2-MeTHF and CPME by submitting the solvents, collected by evaporation of reaction mixtures, to aqueous washings followed by drying over KOH and distillation (see Experimental part).

A.1.4 Experimental Part

A.1.4.1 General Remarks

Starting materials, including solvents, were of the highest commercial quality and were employed as received. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ with a Bruker Ascend 400 spectrometer in $CDCl_3$ solutions with $SiMe_4$ as internal standard.

A.1.4.2 General Procedure for the Protection Reactions of Carbonyl Compounds

In a 50 mL flask fitted with a Dean-Stark distiller and bubble condenser provided with a calcium chloride valve, the starting product (80 mmol) was dissolved in 20 mL of solvent together with a small excess of the appropriate nucleophile (diol, diamine or amino alcohol, 88 mmol) and the catalyst (3 mol %). The reaction mixture was heated with an oil bath under vigorous stirring and allowed to reflux for the indicated time (Table A.1.1), then cooled to room temperature and filtered directly over potassium carbonate (1.0 g), stirred for 15 min and filtered again. The solvent was evaporated at reduced pressure and the crude product thus obtained analyzed by means of ^{1}H NMR spectroscopy. Reaction products were identified by comparison with literature data and/or with authentic samples synthesized according to literature procedures.[28]

2-Phenyl-1,3-dioxane, 3a[28a]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51-7.45 (m, 2H, 2 × ArH), 7.40-7.29 (m, 3H), 5.51 (s, 1H), 4.31-4.23 (m, 2H), 4.05-3.94 (m, 2H), 2.32-2.14 (m, 1H), 1.49-1.40 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 138.7, 128.8, 128.3, 126.0, 101.7, 67.4, 25.8.

2-(4-Methoxyphenyl)-1,3-dioxane, 3b[28b]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.38 (m, 2H, 2 × ArH), 6.91-6.86 (d, 2H, 2 × ArH), 5.46 (s, 1H, ArCH), 4.25 (dd, J = 12.0, 4.0 Hz, 2 H, CH_2-O), 3.97 (td, J = 12.0, 1.6 Hz, 2H, 2 × CHO), 3.80

(s, 3H, CH_3O), 2.28-2.15 (m, 1 H, CH_2), 1.43 (d, *J* =16.0 Hz, 1 H, CH_2); **^{13}C NMR** ($CDCl_3$, 75 MHz); δ 159.8, 131.2, 127.2, 113.5, 101.4, 67.2, 55.1, 25.6; mp 46-47 °C (CPME/heptane).

2-(4-Chlorophenyl)-1,3-dioxolane, 3c[28c]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.37 (m, 2H, 2 × ArH), 7.36-7.33 (m, 2H, 2 × ArH), 5.78 (s, 1H), 4.15-3.98 (m, 4H, 2 × CH_2O). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 136.5, 135.0, 128.5, 127.9, 103.0, 65.3.

2-(Heptan-3-yl)-1,3-dioxolane, 3d[28d]

Purified by fractional distillation, bp 105 °C/30 mmHg (Ref.[28d]. bp 206 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.78 (d, *J* = 3.6 Hz, 1H, CH), 3.99-3.89 (m, 2H 2 × CH), 3.89-3.79 (m, 2H 2 × CH), 1.56-1.25 (m, 9H), 096-0.85 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 106.7, 64.8, 42.9, 29.4, 28.2, 23.1, 21.7, 14.1, 11.5.

2-Metil-2-fenil-1,3-dioxane, 3e[28e]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.36 (m, 5H, 5 × ArH), 3.82-3.75 (m, 4H, 2 × CH_2O), 2.18-2.06 (m, 1H, CH), 1.51 (s, 3H, CH_3), 1.27-1.22 (m, 1H, CH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 141.6, 129.1, 128.0, 127.2, 100.9, 61.6, 32.8, 25.9.

2-(4-Methoxyphenyl)-3-methyloxazolidine, 4[28f]

Purified by fractional distillation, bp 175 °C/30 mmHg (Ref.[28f]. bp 133-136 °C/3 mmHg);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.36 (m, 2H, 2 × ArH), 6.92-6.88 (m, 2H, 2 × ArH), 4.58 (s, 1H, ArCH), 4.09 (dd, 1H, *J* = 8.8, 7.6 Hz, CHO), 4.00 (td, 1H, J = 7.6, 2.4, Hz, CHO), 3.81 (s, 3H, OCH_3), 3.37-3.27 (m, 1H, CHN), 2.68 (1H, q, *J* = 8.8 Hz, CHN), 2.26 (s, 3H, CH_3N); **^{13}C NMR** (400 MHz, $CDCl_3$): 160.1; 131.1, 128.9, 113.7, 98.1, 65.2, 55.3, 54.7, 38.1.

2-(4-Methoxyphenyl)-1,3-dimethylimidazolidine, 5[28g]

^{1}H NMR (400 MHz, $CDCl_3$): 7.38-7.33 (m, 2H, 2 × ArH), 6.92-6.86 (m, 2H, 2 × ArH), 3.81 (s, 3H, OCH_3), 3.44-3.34 (m, 2H, 2 × CHN), 2.59-2.49 (m, 2H, 2 × CHN), 2.16 (s, 6H, 2 × NCH_3).

A.1.4.3 Recovery of Organic Solvents

CPME and 2-MeTHF were recovered *via* evaporation of the reaction mixtures obtained as described above. Evaporations were realized employing a rotatory evaporator operating *in vacuo* (*ca.* 30 mmHg), by gently warming (30 – 35 °C) the boiling flask with a water bath, condensing the vapor phase with efficient cooling (4 °C) and chilling the condensate-collecting flask with an ice-water bath. The organic solvent recovered from several runs (at least 100 ml) was dried (KOH) and distilled at atmospheric pressure under dry N_2, usually leading to 60-70% mass recovery of the starting material. Recovered solvents, as analyzed and characterized by ^{1}H and ^{13}C NMR, were identical to commercial samples.

A.1.5 References

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Supporting Information

S.1.1 Copies of ^{1}H, ^{13}C NMR Spectras for Chapter 1

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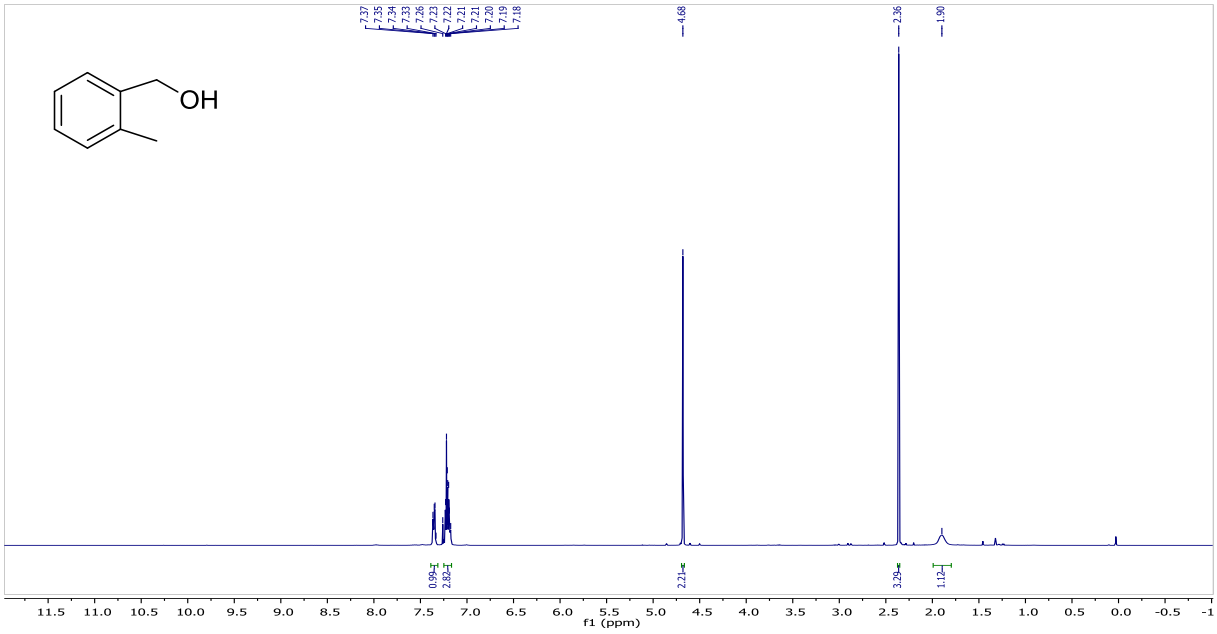

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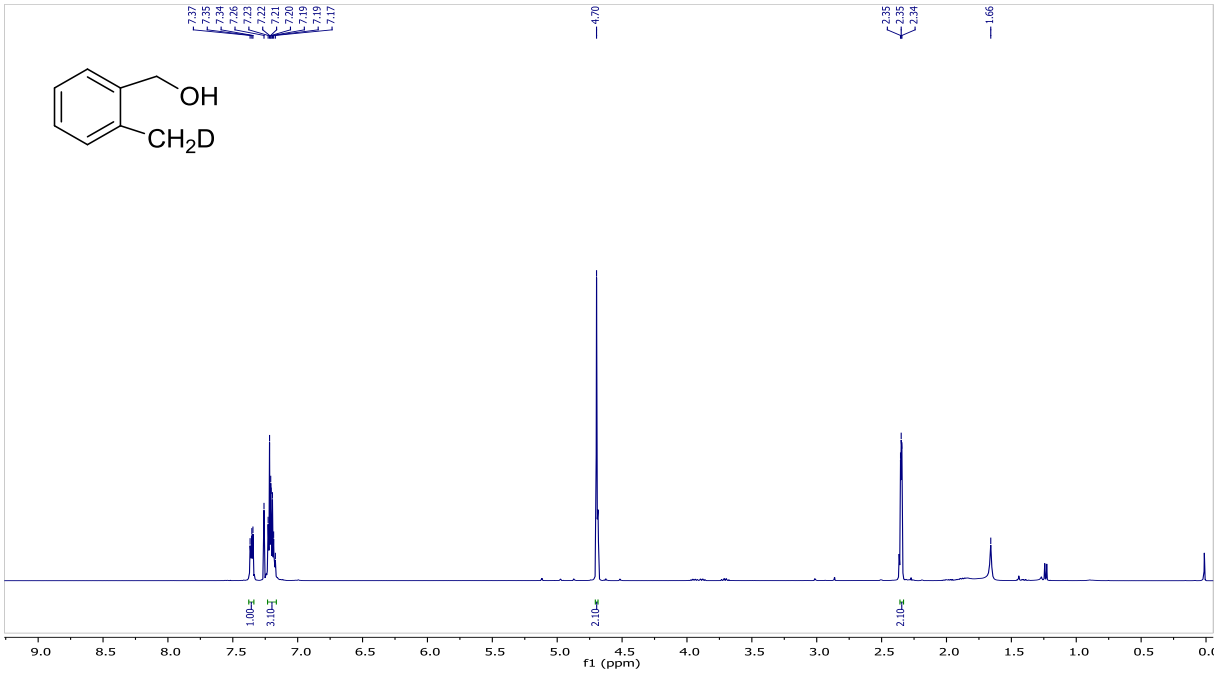

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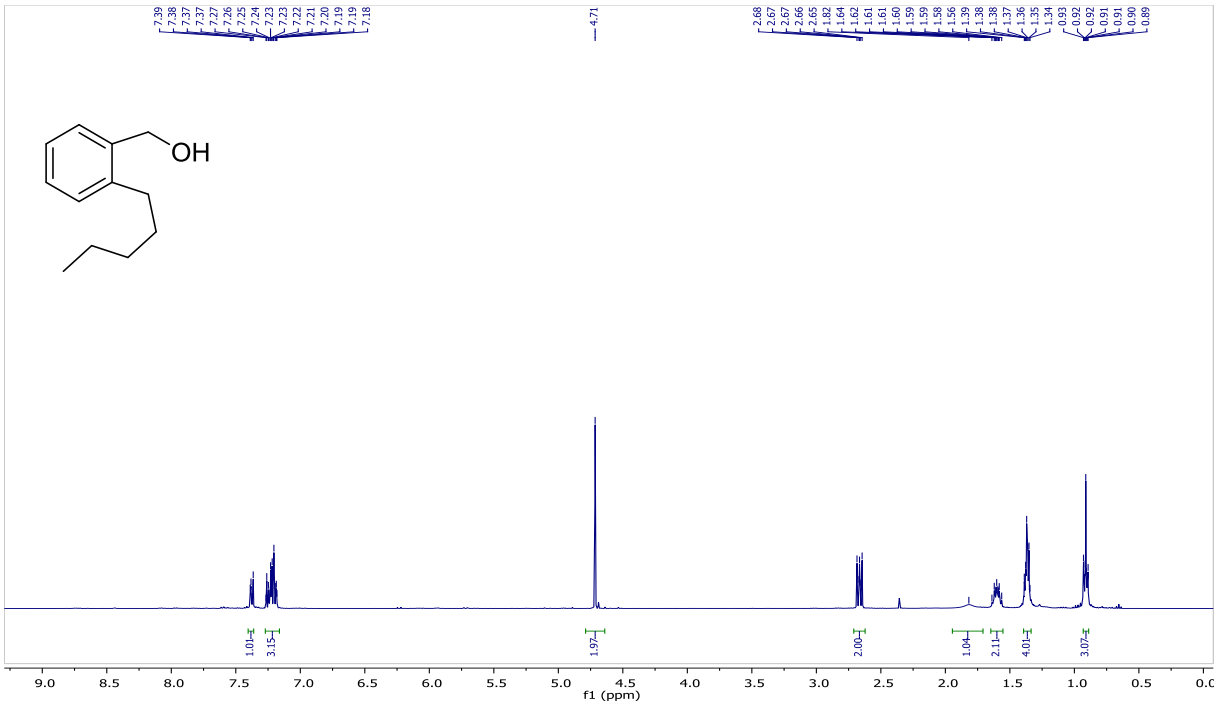

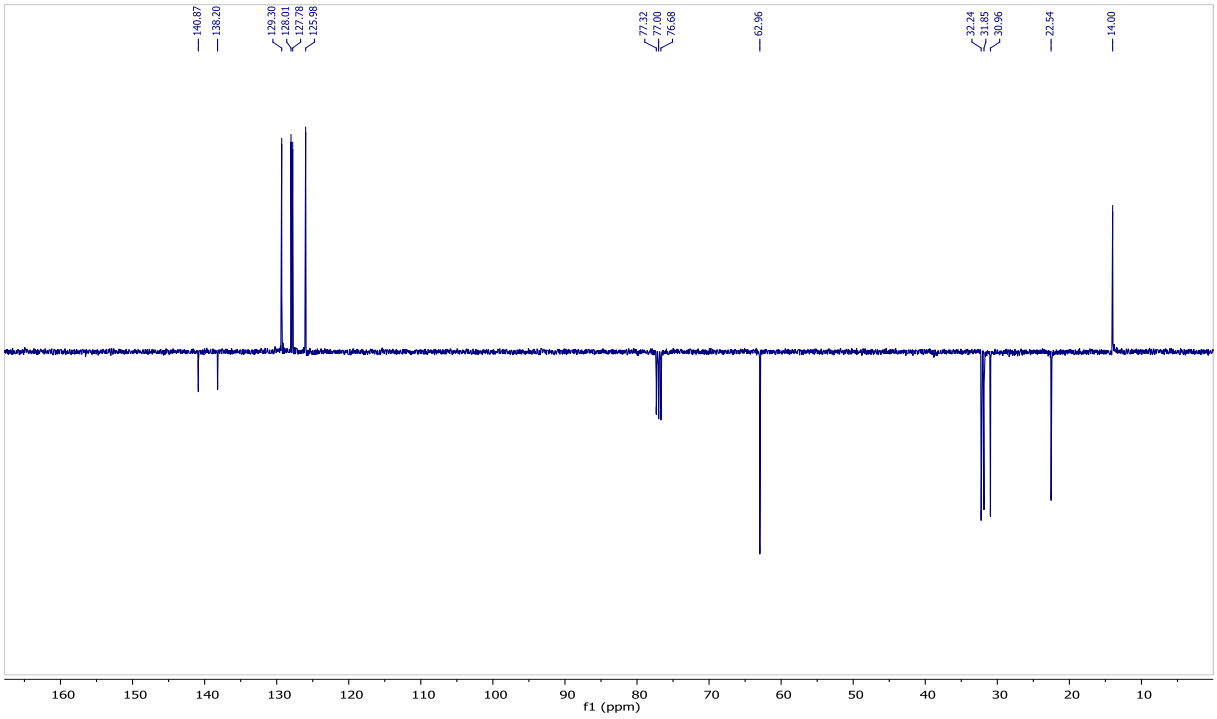

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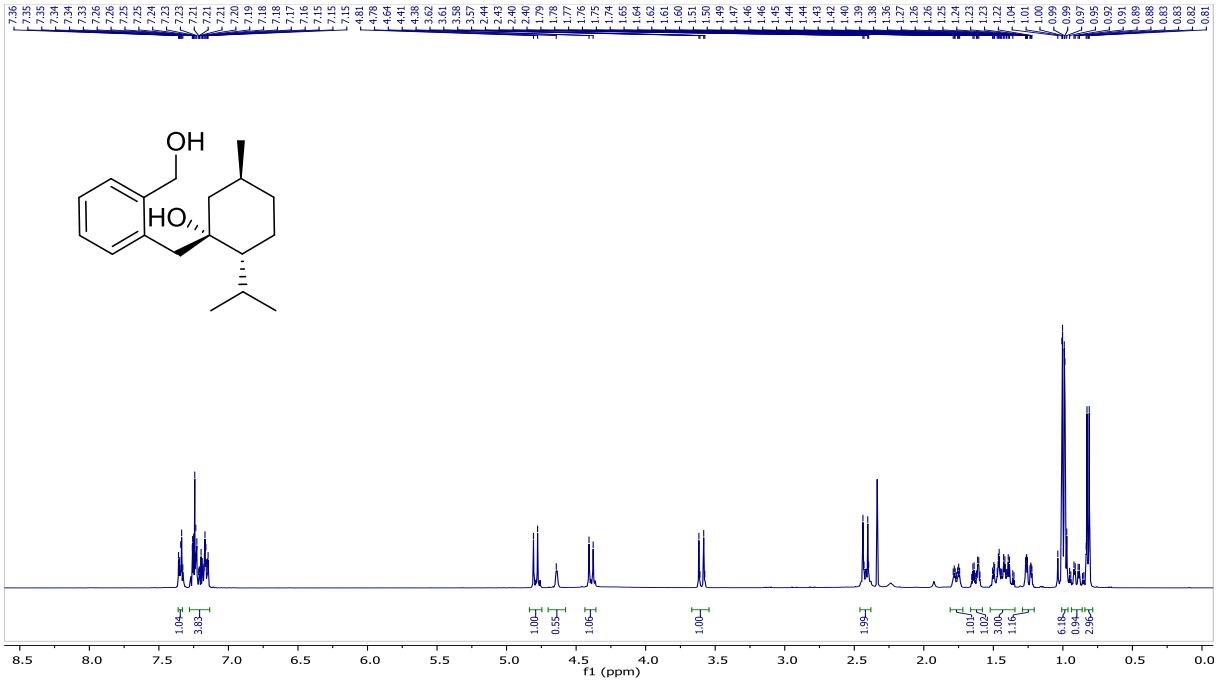
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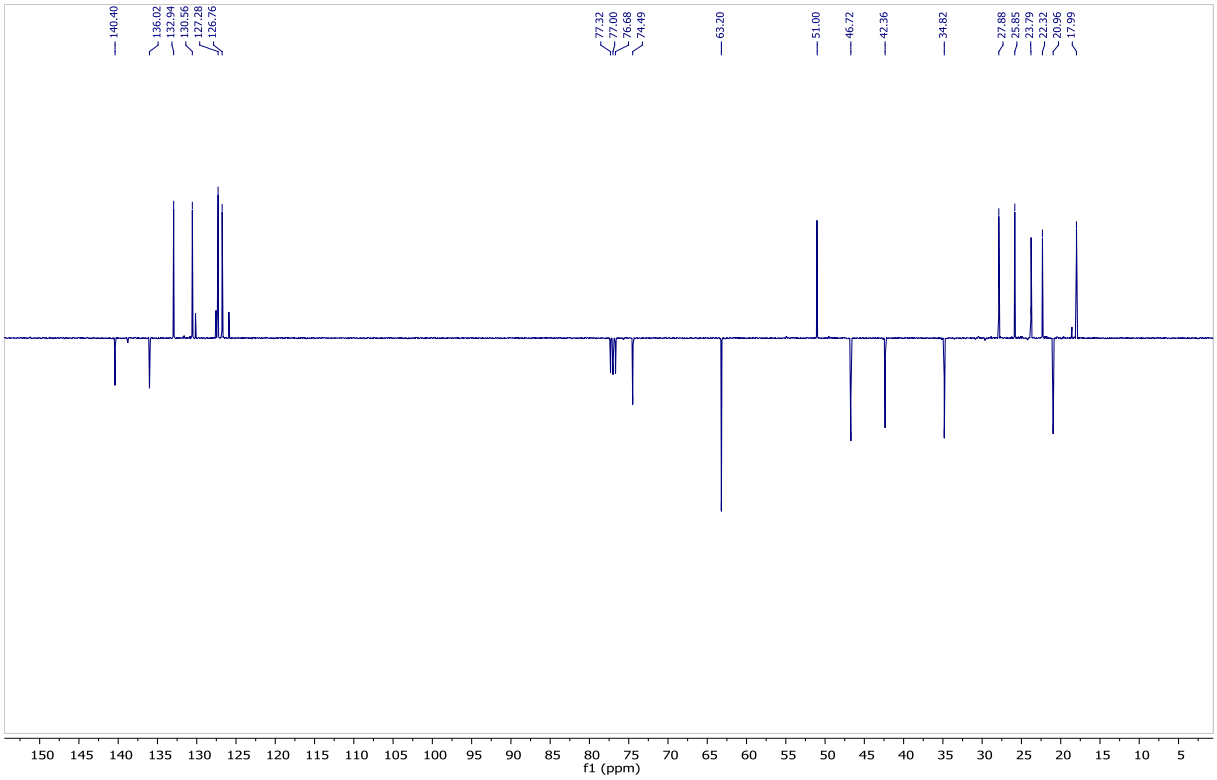
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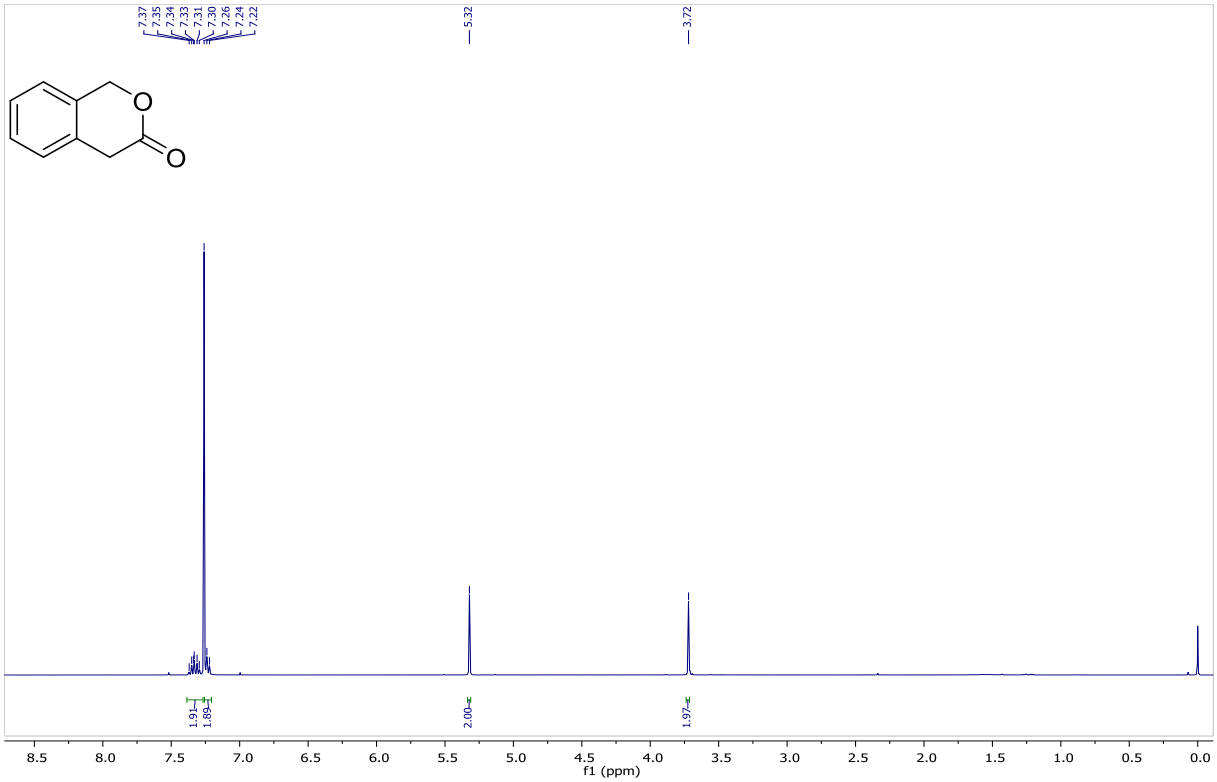
22.32
20.96
17.99
f1 (ppm)

1.42e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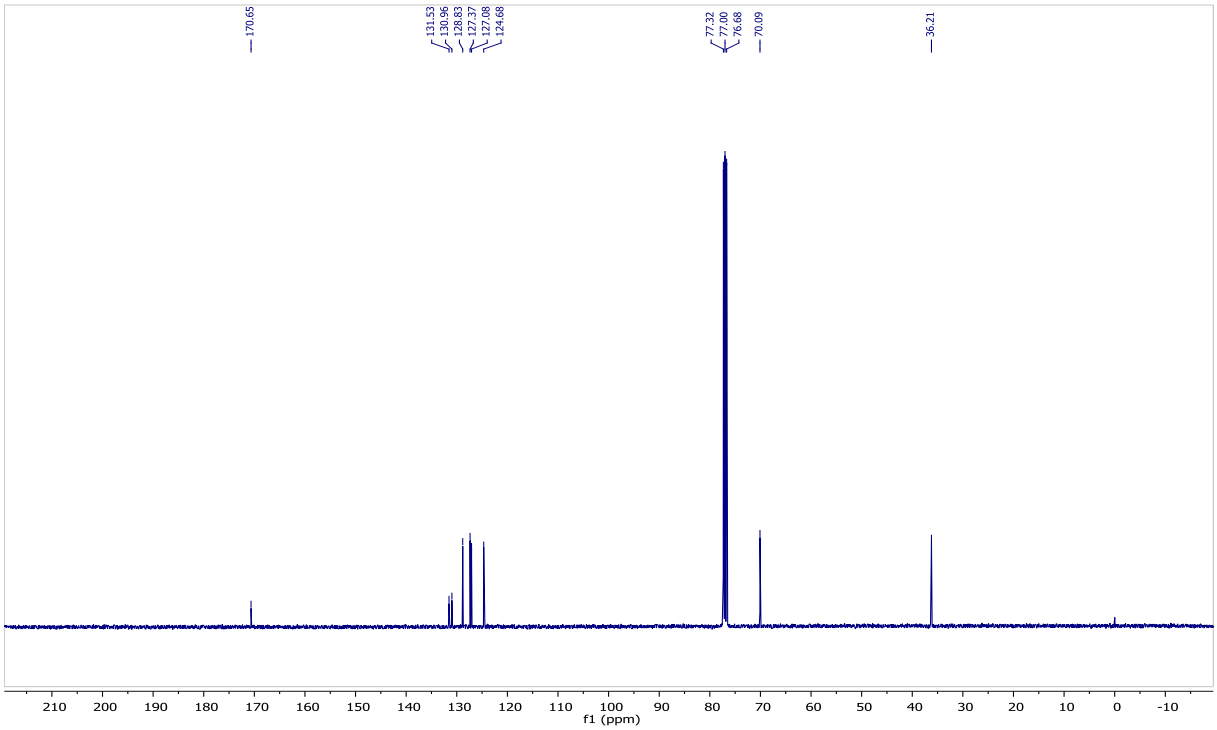
f1 (ppm)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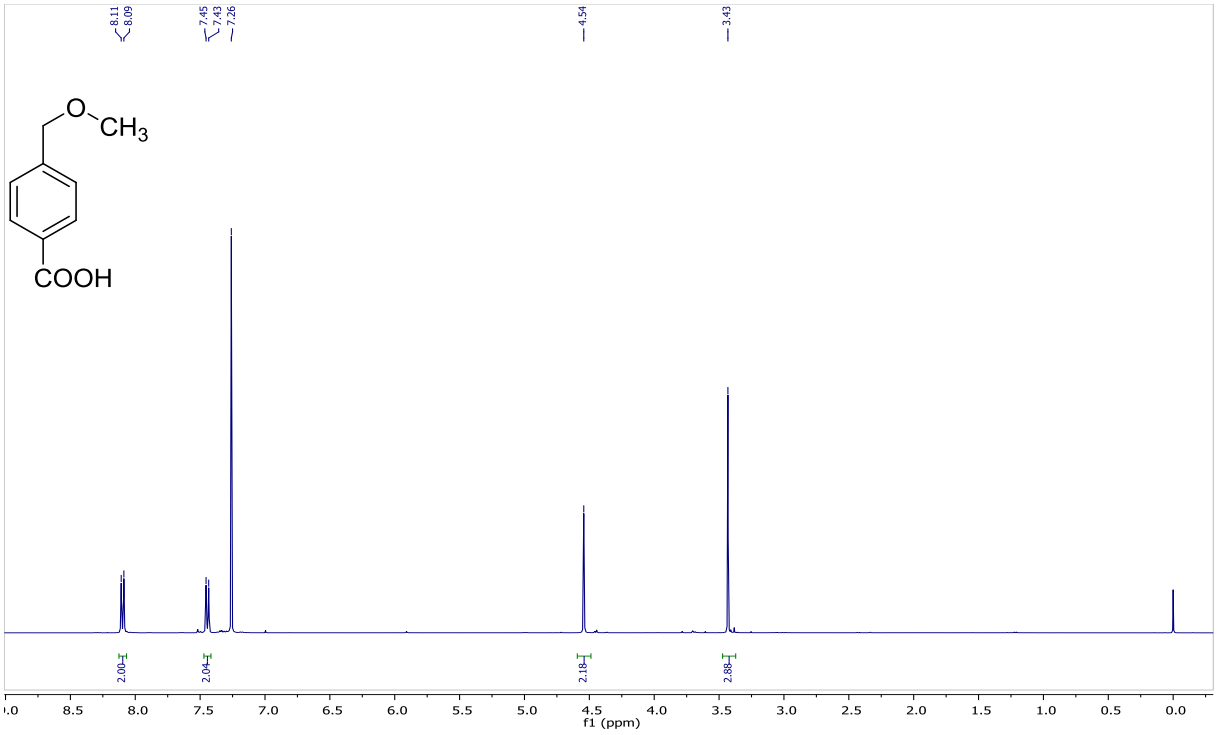
1.48b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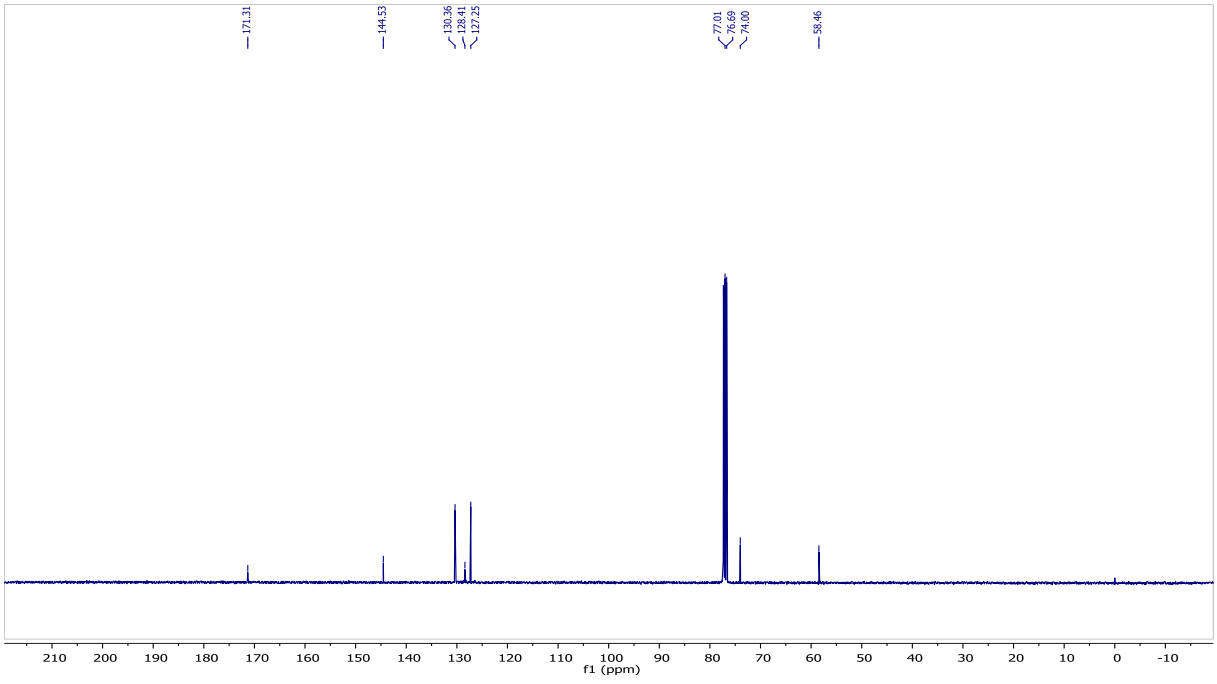
f1 (ppm)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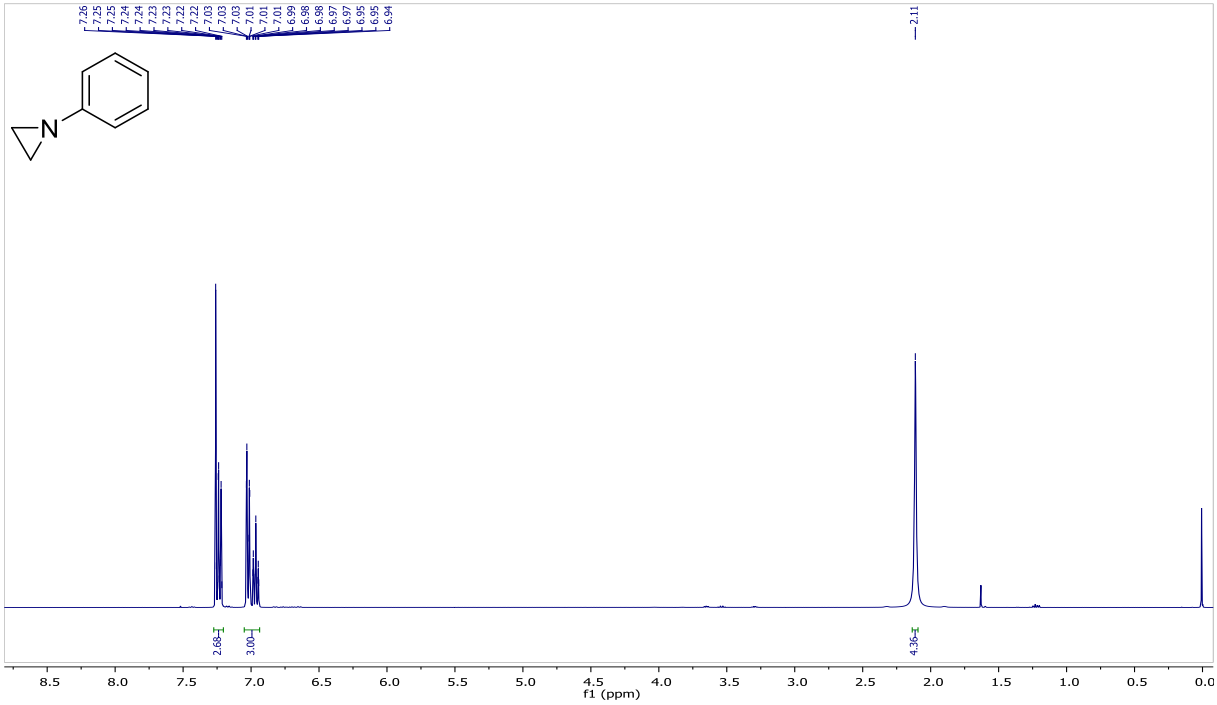
1.49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6.98
6.97
6.97
6.95
6.95
6.94
2.11
N
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3.00
4.36
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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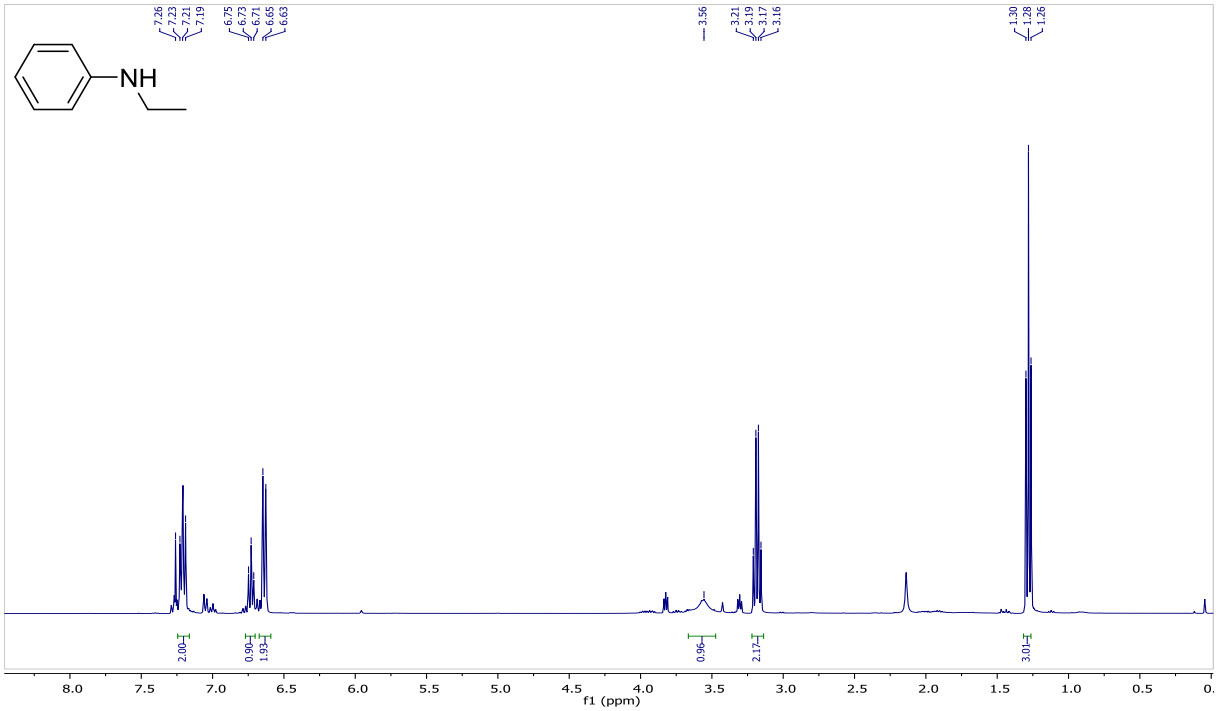
f1 (ppm)

1.51a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3.01
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7.0
6.5
6.0
5.5
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1.0
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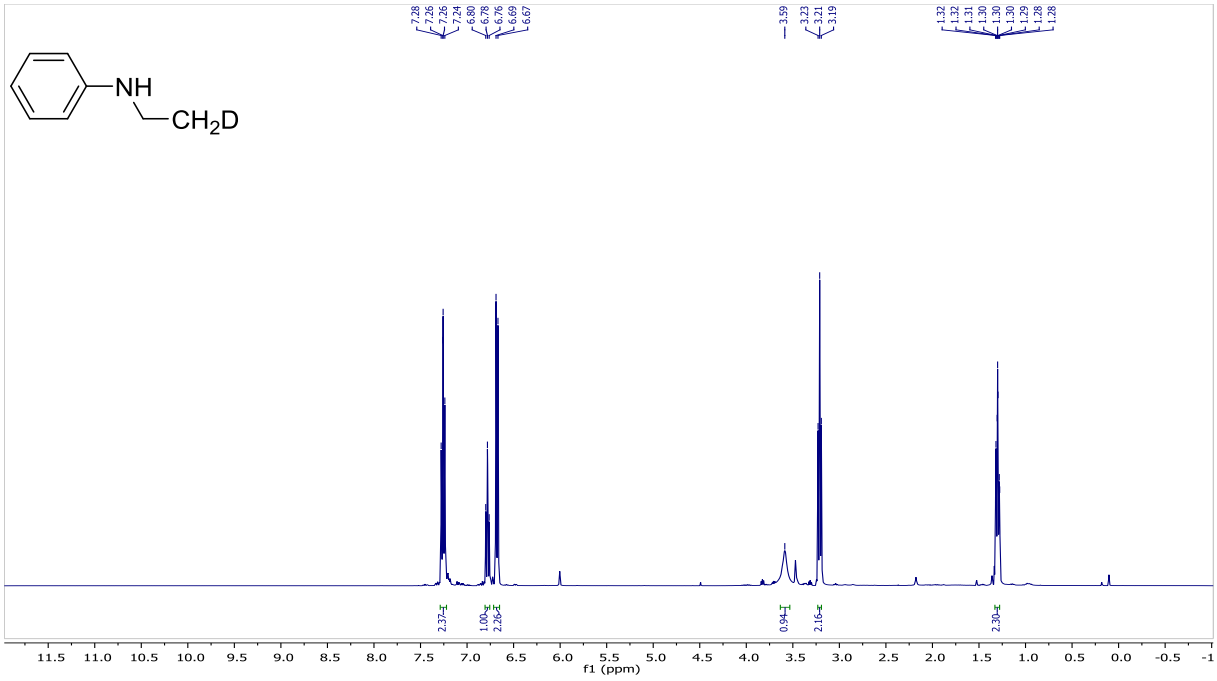
f1 (ppm)

1.51b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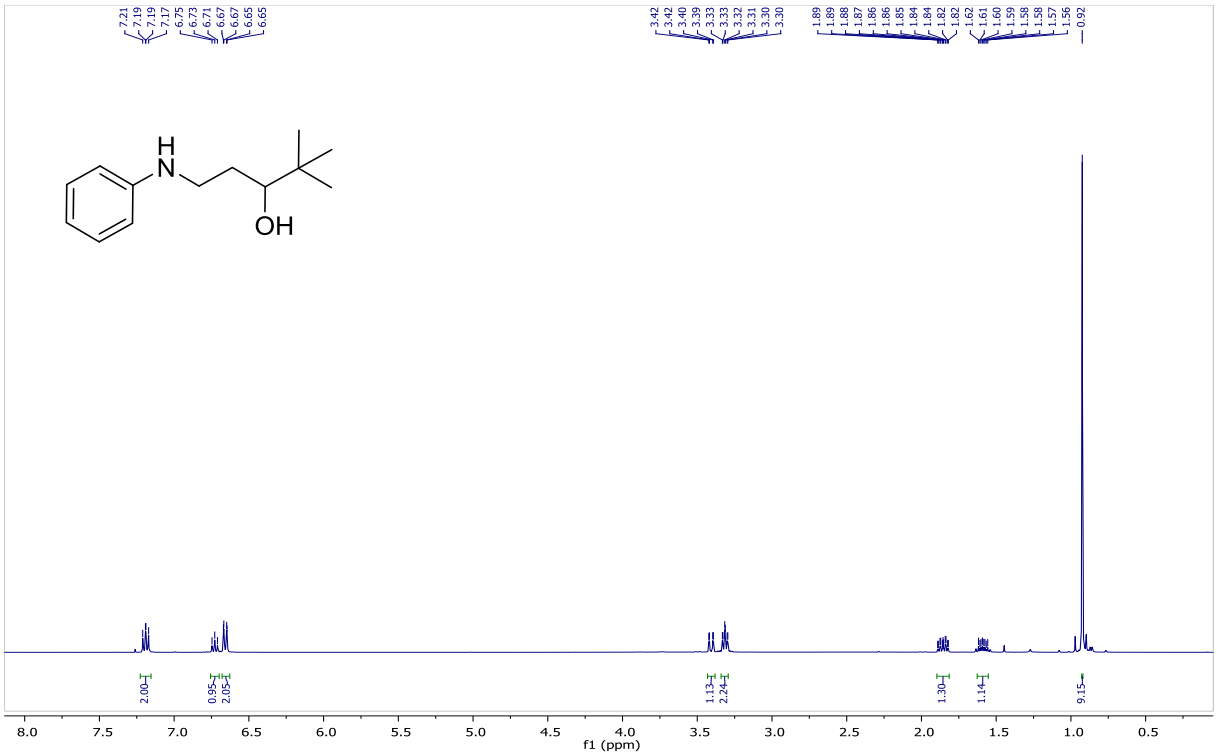
3.21
3.19
1.32
1.32
1.31
1.30
1.30
1.30
1.29
1.28
1.28
2.37
1.00
2.26
0.94
2.16
2.30
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

1.51c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3.39
3.33
3.33
3.32
3.31
3.30
3.30
1.89
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1.88
1.87
1.86
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1.85
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1.61
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1.59
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1.58
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N
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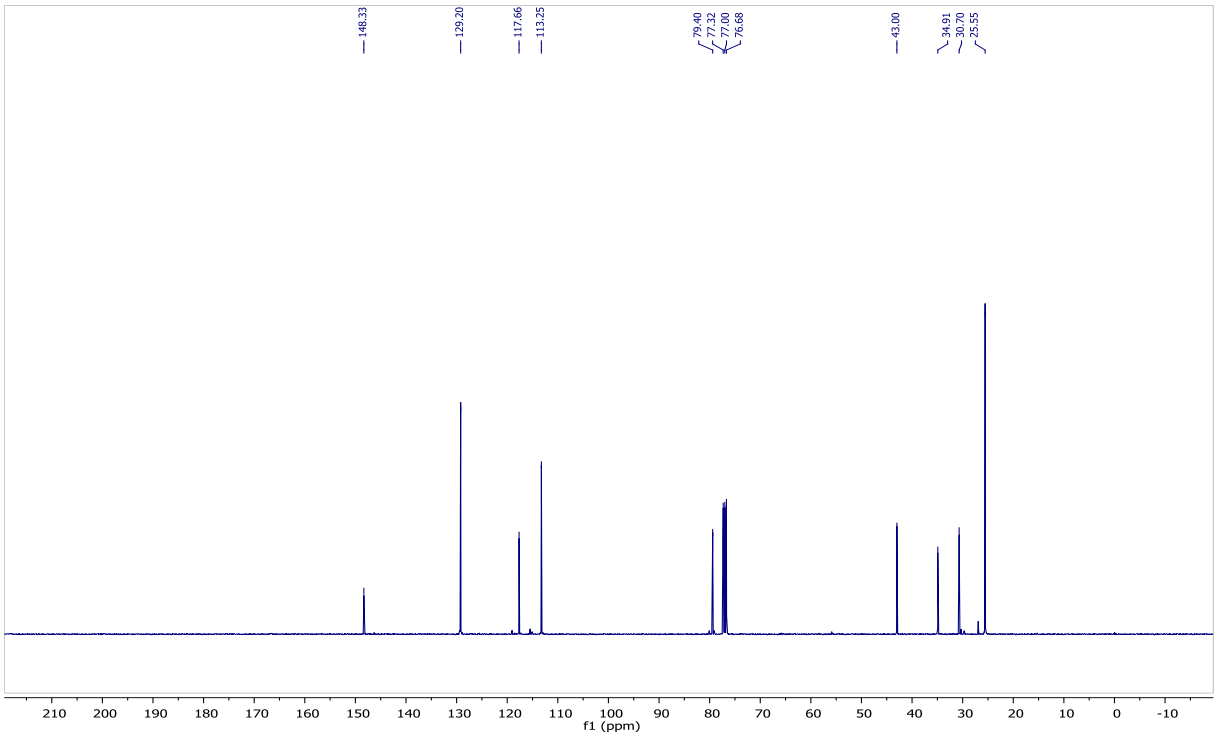
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200
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180
170
160
150
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f1 (ppm)

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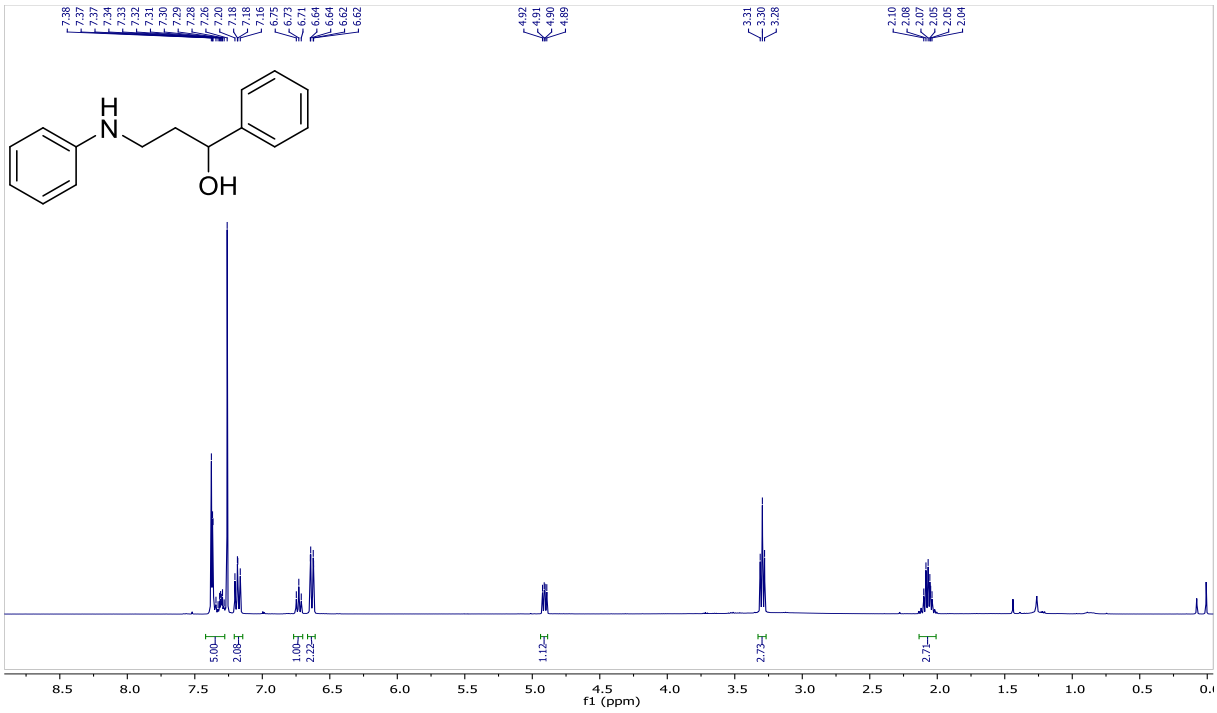
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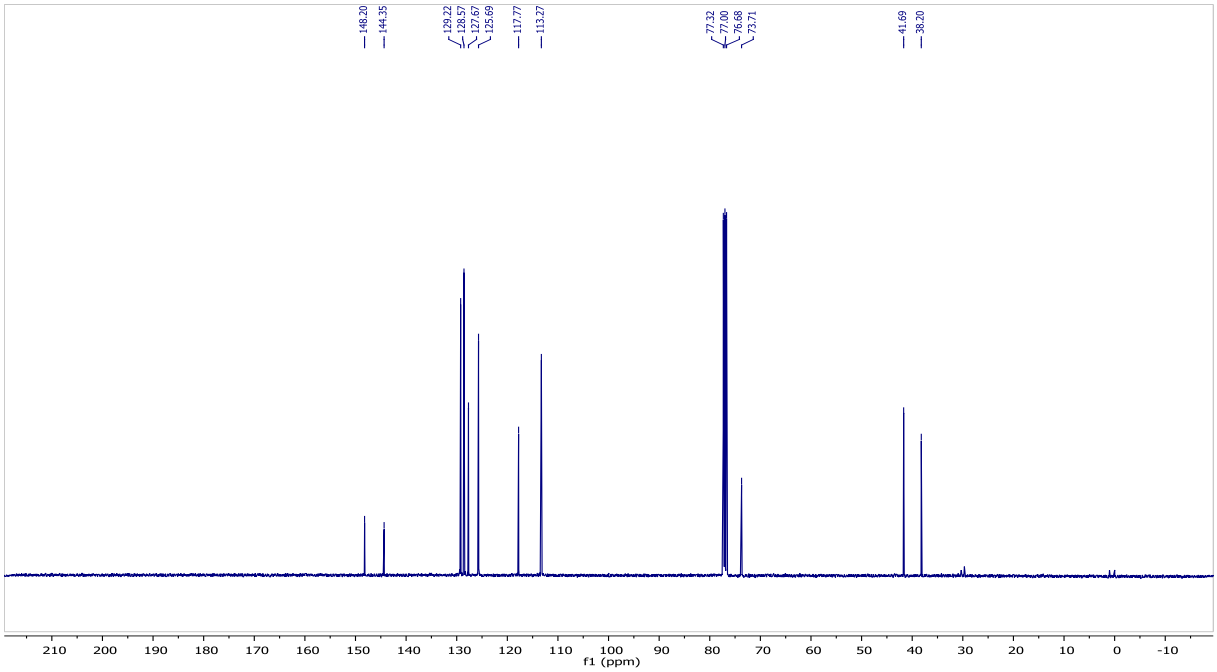
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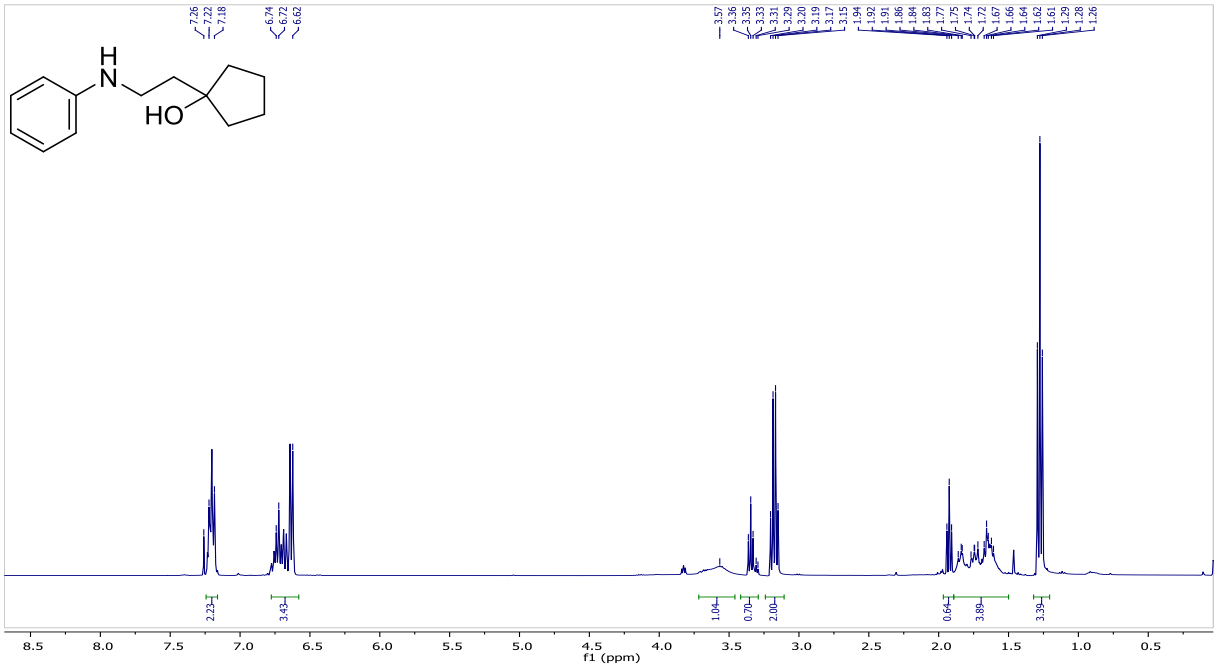
38.20
f1 (ppm)

1.51e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3.20
3.19
3.17
3.15
1.94
1.92
1.91
1.86
1.84
1.83
1.77
1.75
1.74
1.72
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1.66
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1.62
1.61
1.29
1.28
1.26
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N
HO
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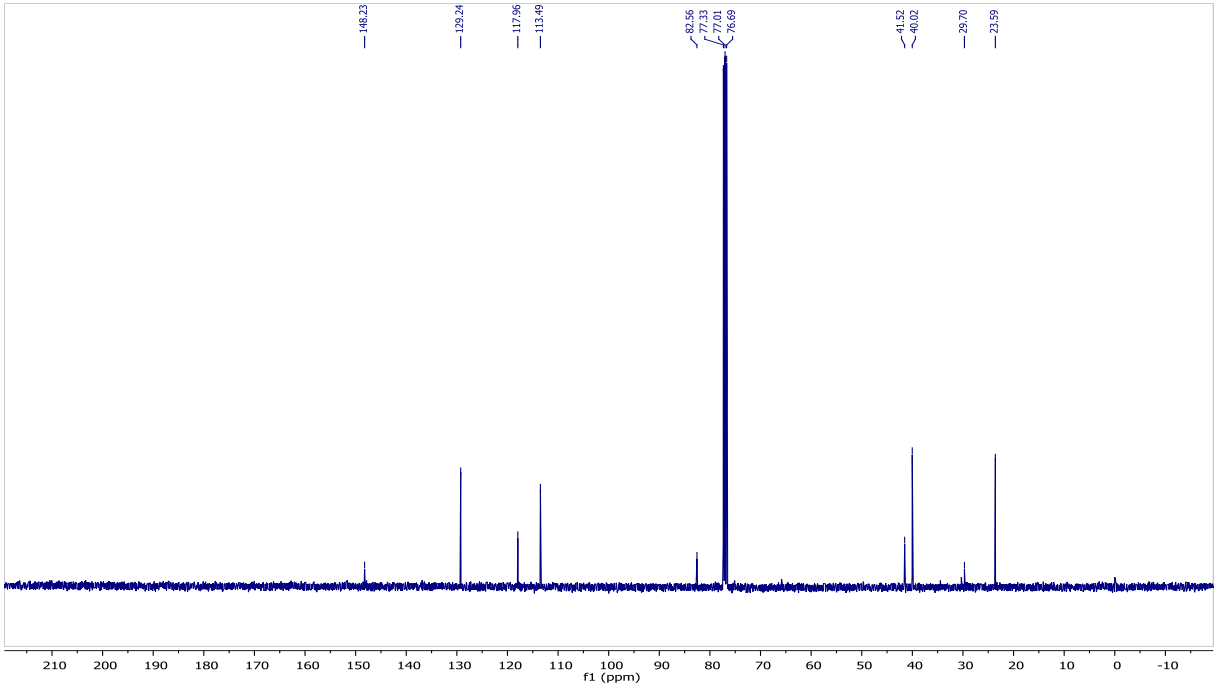
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100
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80
70
60
50
40
30
20
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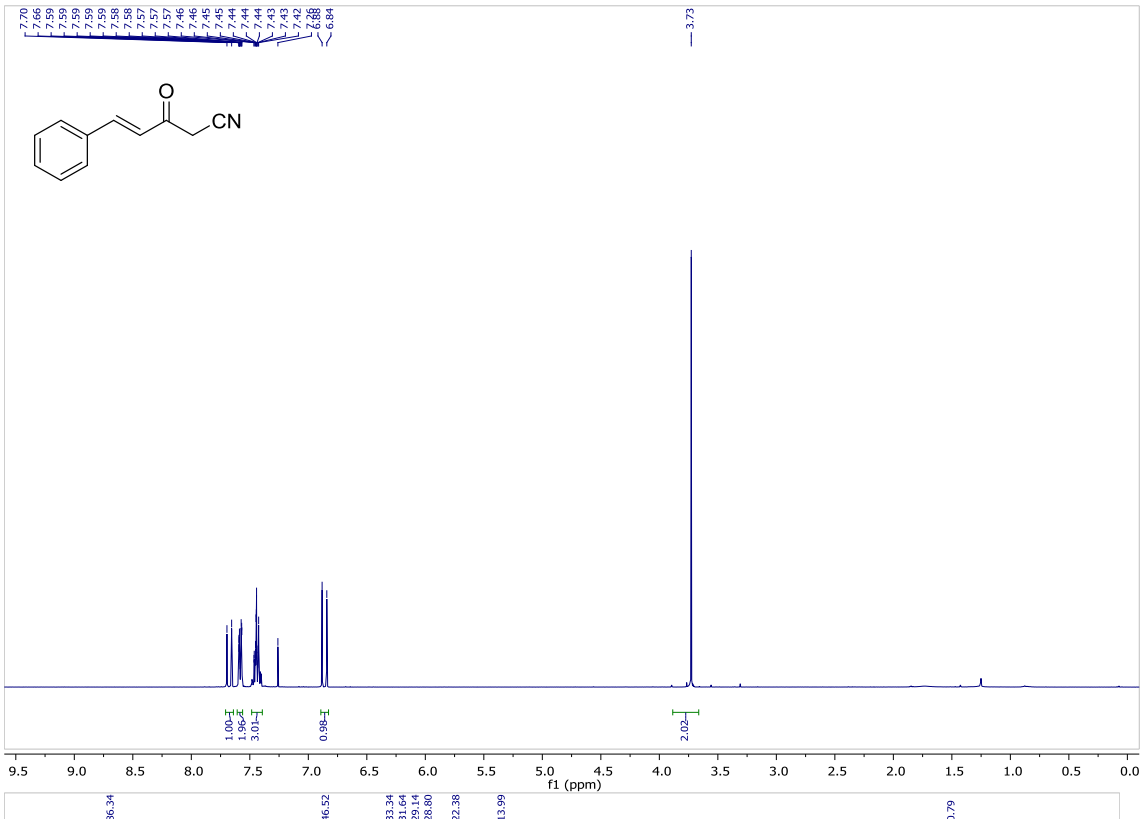
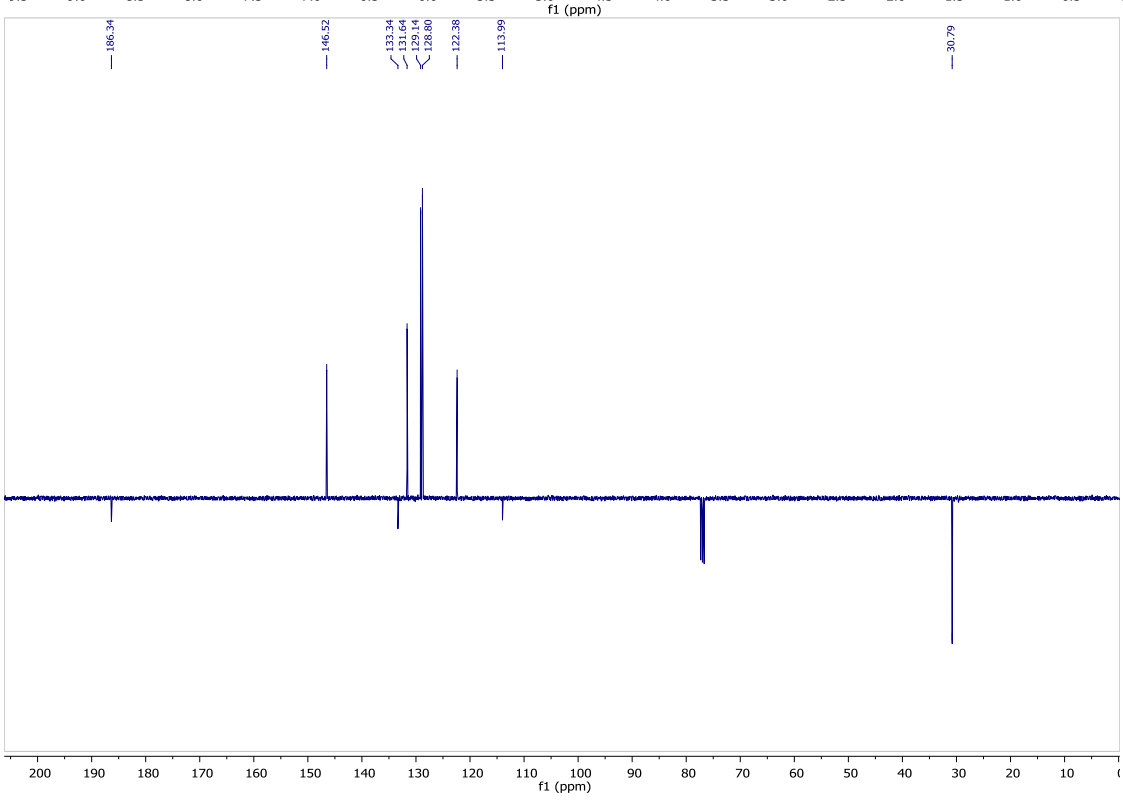
f1 (ppm)

S.2 Copies of ^{1}H, ^{13}C, ^{19}F and NMR Spectras for Chapter 2

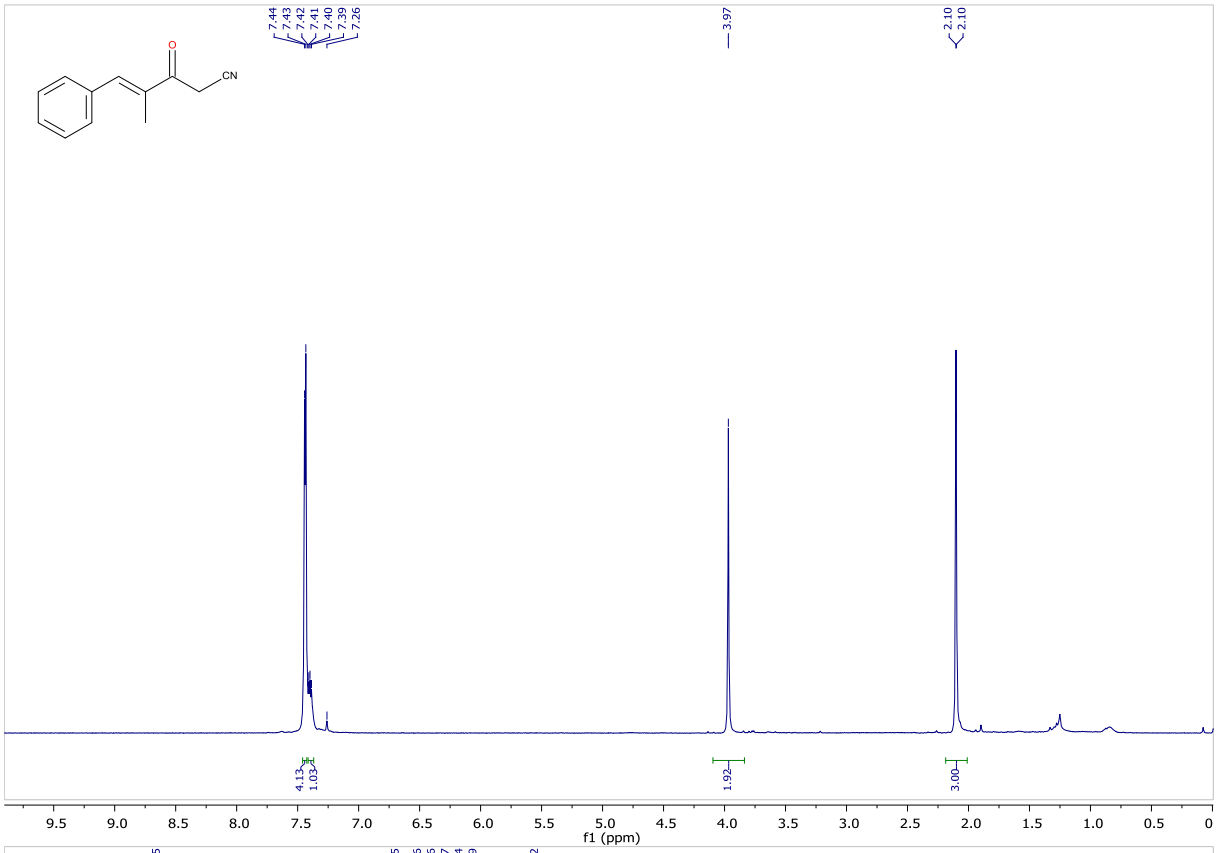
S.2.1 Cyanoketone Derivatives

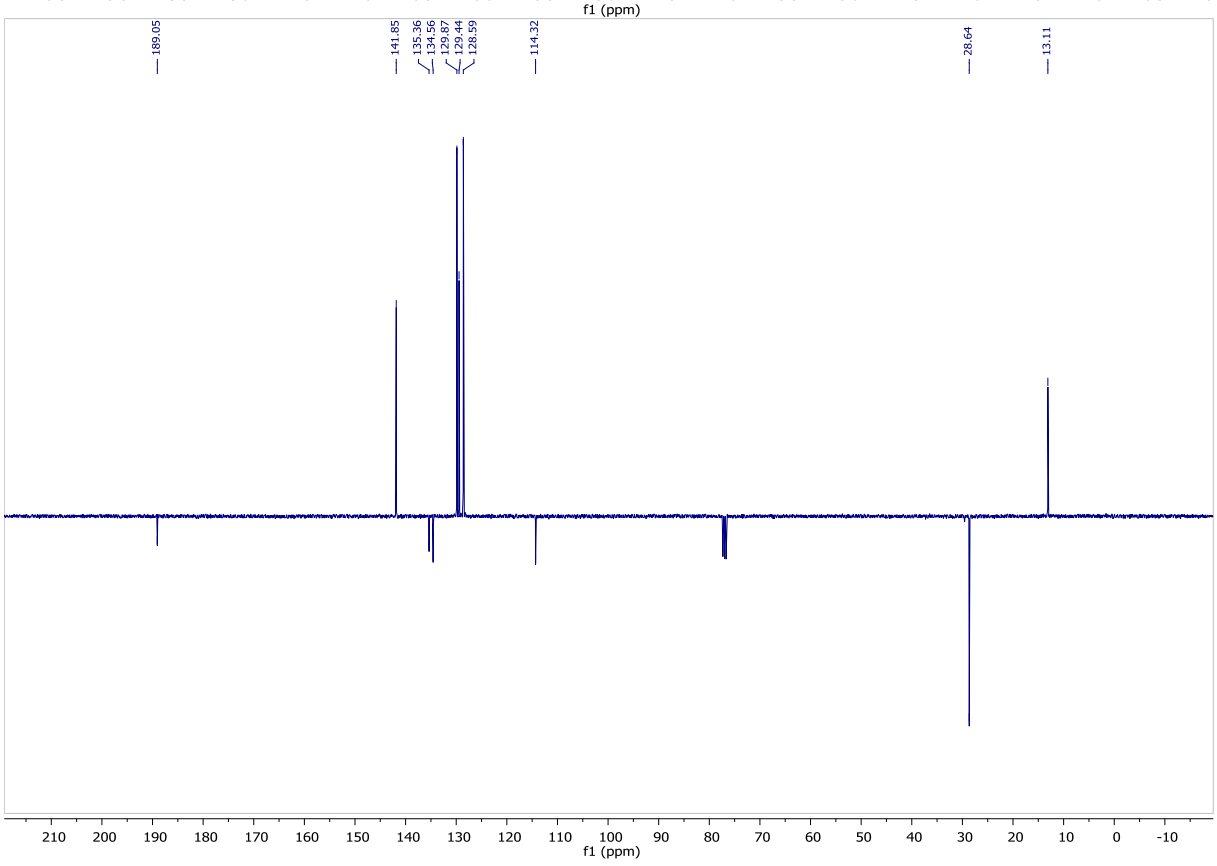
2.112



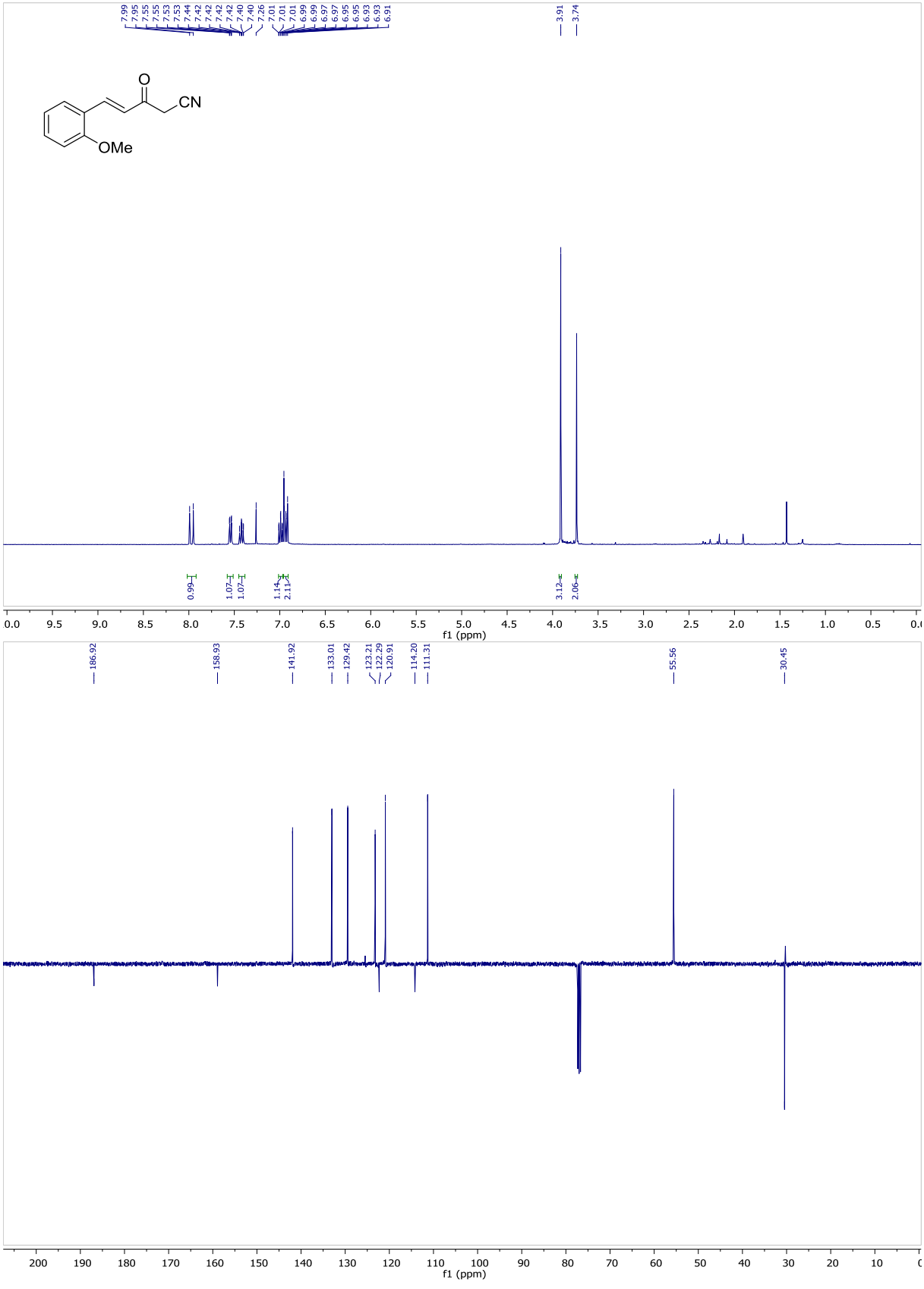


2.114a

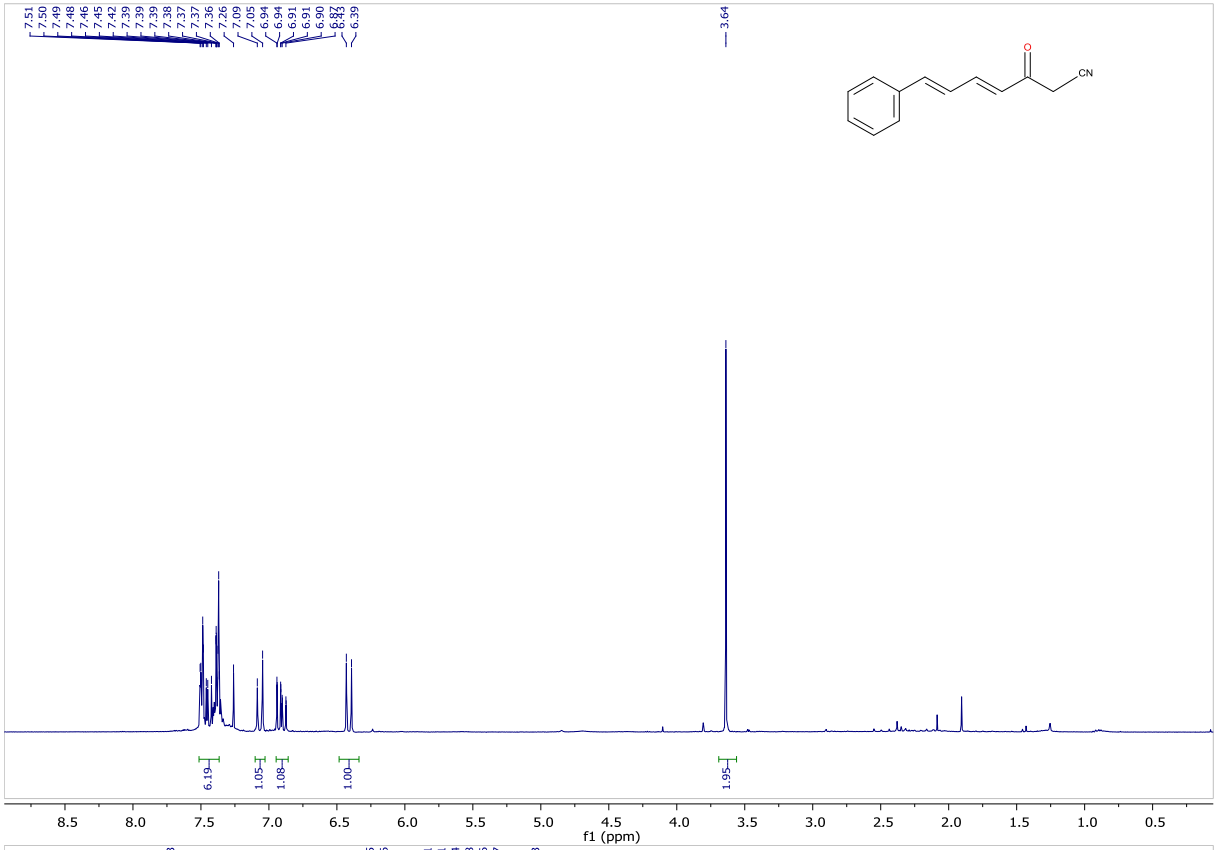

7.44
7.43
7.42
7.41
7.40
7.39
7.26
3.97
2.10
2.10
O
CN
4.13
1.03
1.92
3.00
f1 (ppm)

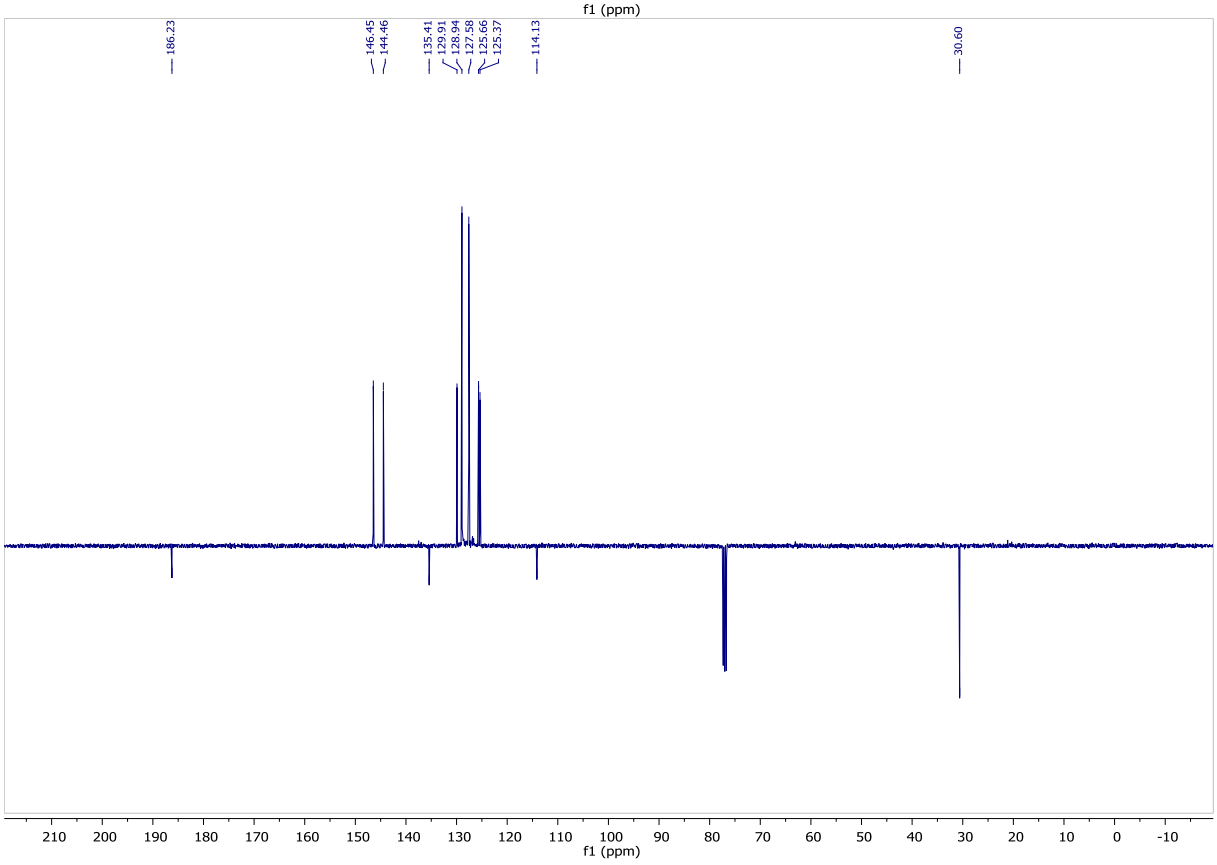

189.05
141.85
135.36
134.56
129.87
129.44
128.59
114.32
28.64
13.11
f1 (ppm)

2.114b

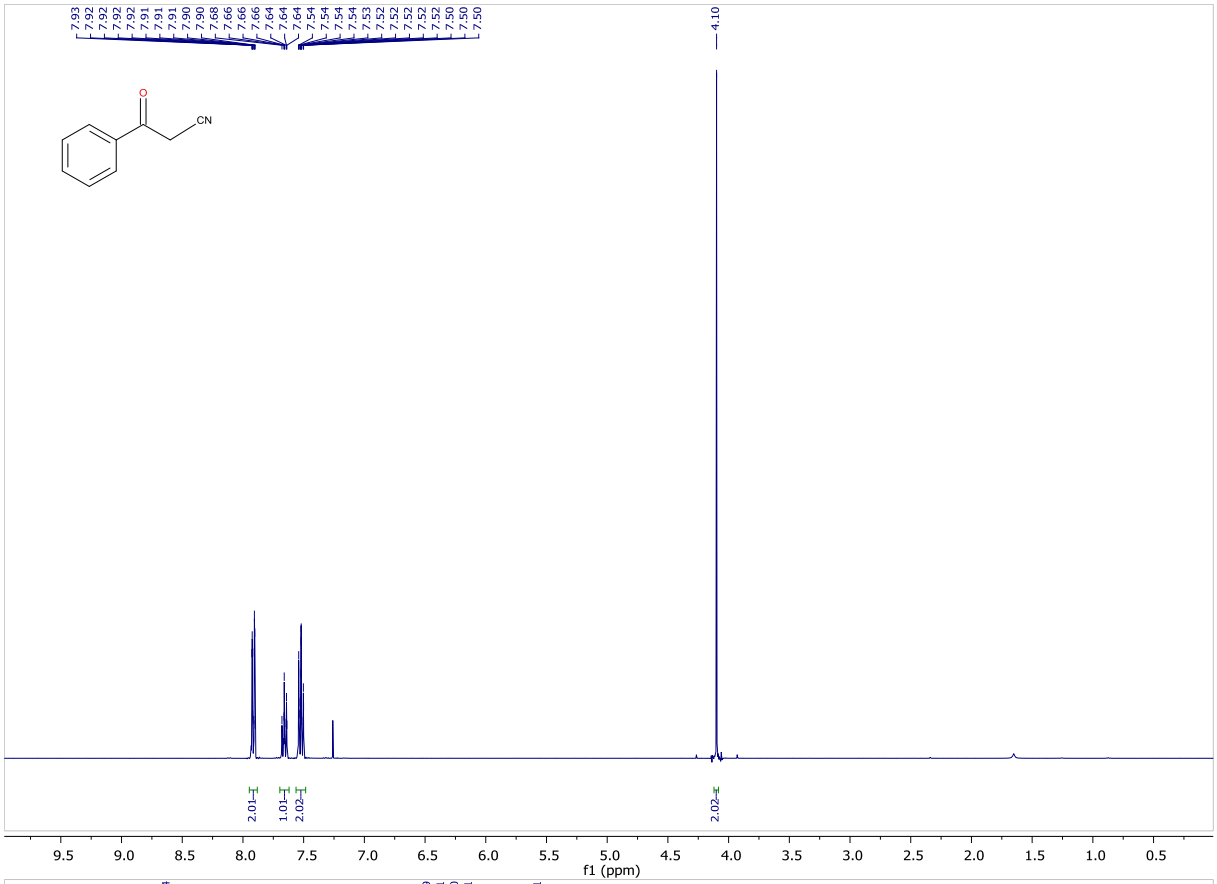

O
CN
OMe
7.99
7.95
7.55
7.55
7.53
7.53
7.44
7.42
7.42
7.42
7.42
7.40
7.40
7.26
7.01
7.01
7.01
6.99
6.99
6.99
6.97
6.97
6.95
6.95
6.93
6.93
6.91
3.91
3.74
0.99
1.07
1.07
1.14
2.11
3.12
2.06
f1 (ppm)
186.92
158.93
141.92
133.01
129.42
123.21
122.29
120.91
114.20
111.31
55.56
30.45
f1 (ppm)

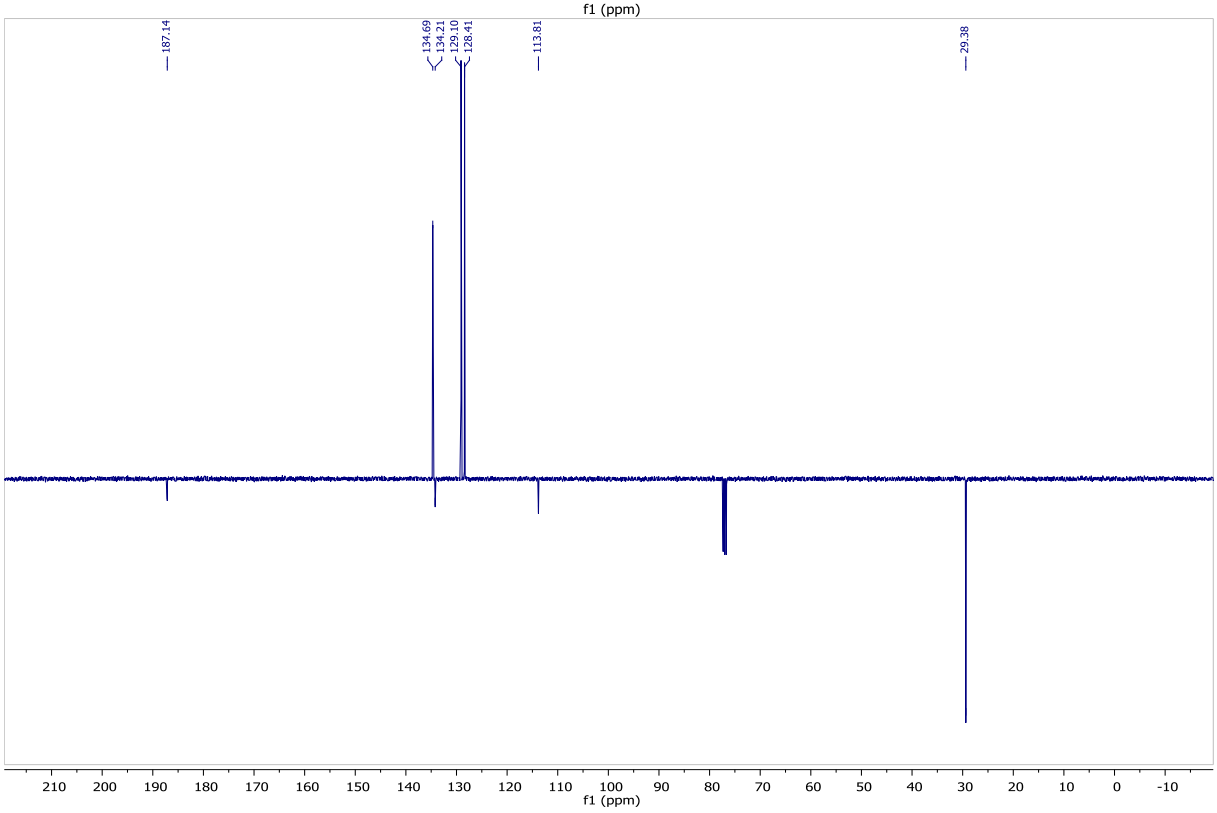
2.114c


7.51
7.50
7.49
7.48
7.46
7.45
7.42
7.39
7.39
7.39
7.38
7.37
7.37
7.36
7.26
7.09
7.05
6.94
6.94
6.91
6.91
6.90
6.39
3.64
O
CN
6.19
1.05
1.08
1.00
1.95
f1 (ppm)

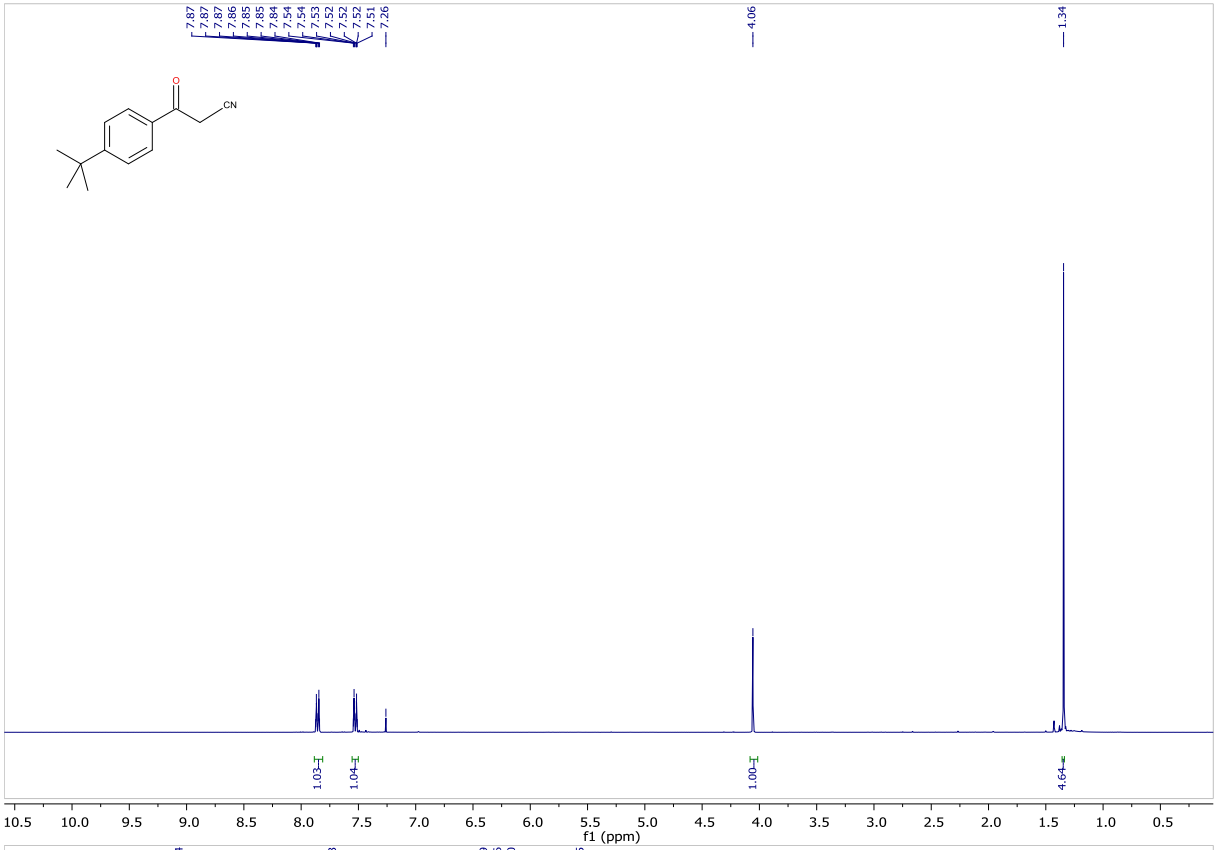

186.23
146.45
144.46
135.41
129.91
128.94
127.58
125.66
125.37
114.13
30.60
f1 (ppm)

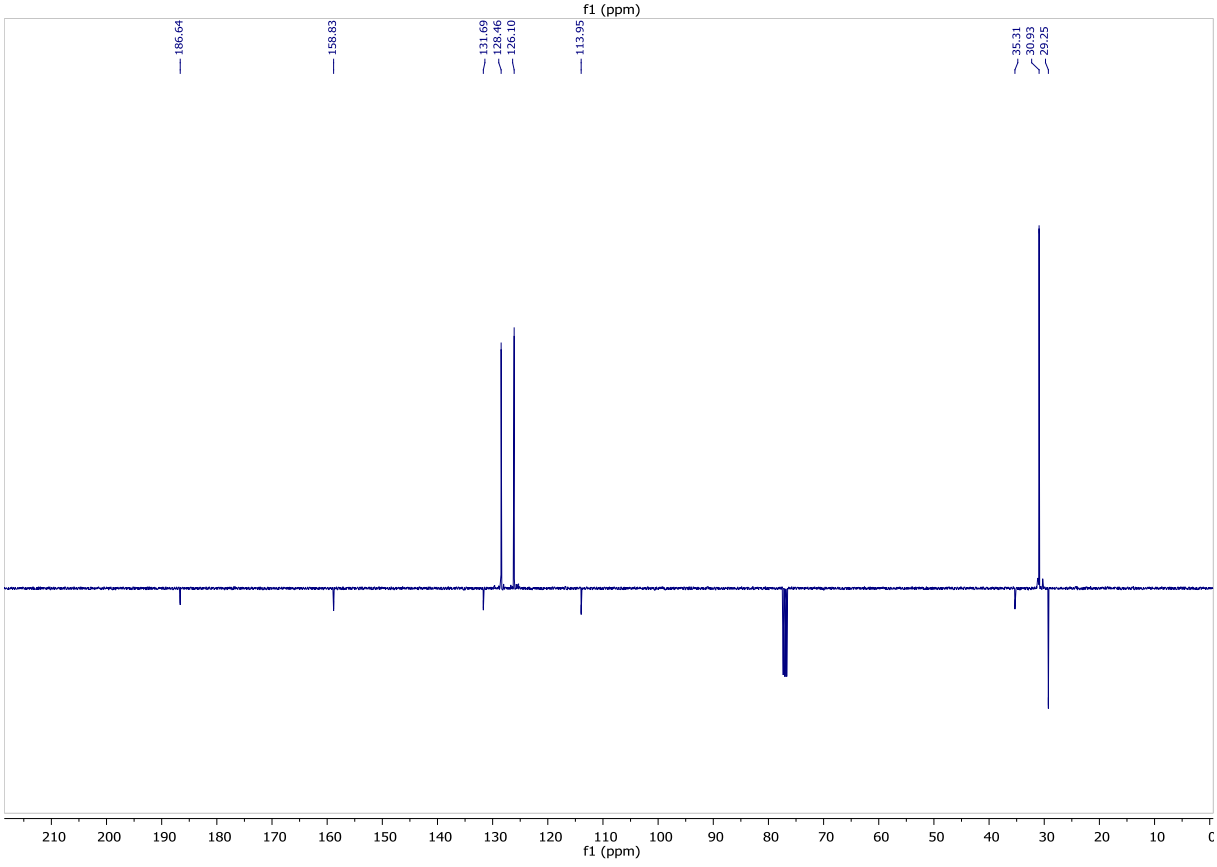
2.114d


7.93
7.92
7.92
7.92
7.92
7.91
7.91
7.91
7.90
7.90
7.68
7.66
7.66
7.66
7.64
7.64
7.64
7.54
7.54
7.54
7.53
7.52
7.52
7.52
7.52
7.52
7.50
7.50
7.50
4.10
O
CN
2.01
1.01
2.02
2.02
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

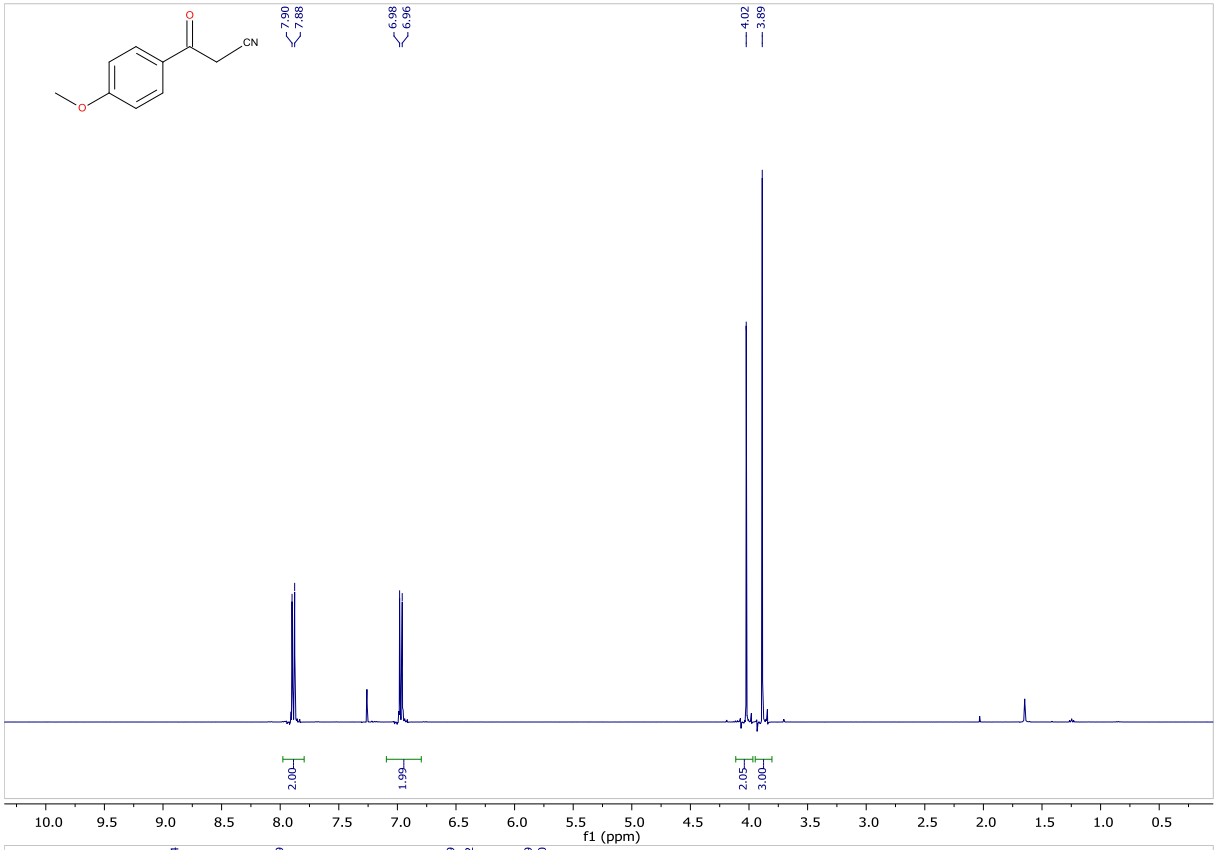

187.14
134.69
134.21
129.10
128.41
113.81
29.38
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

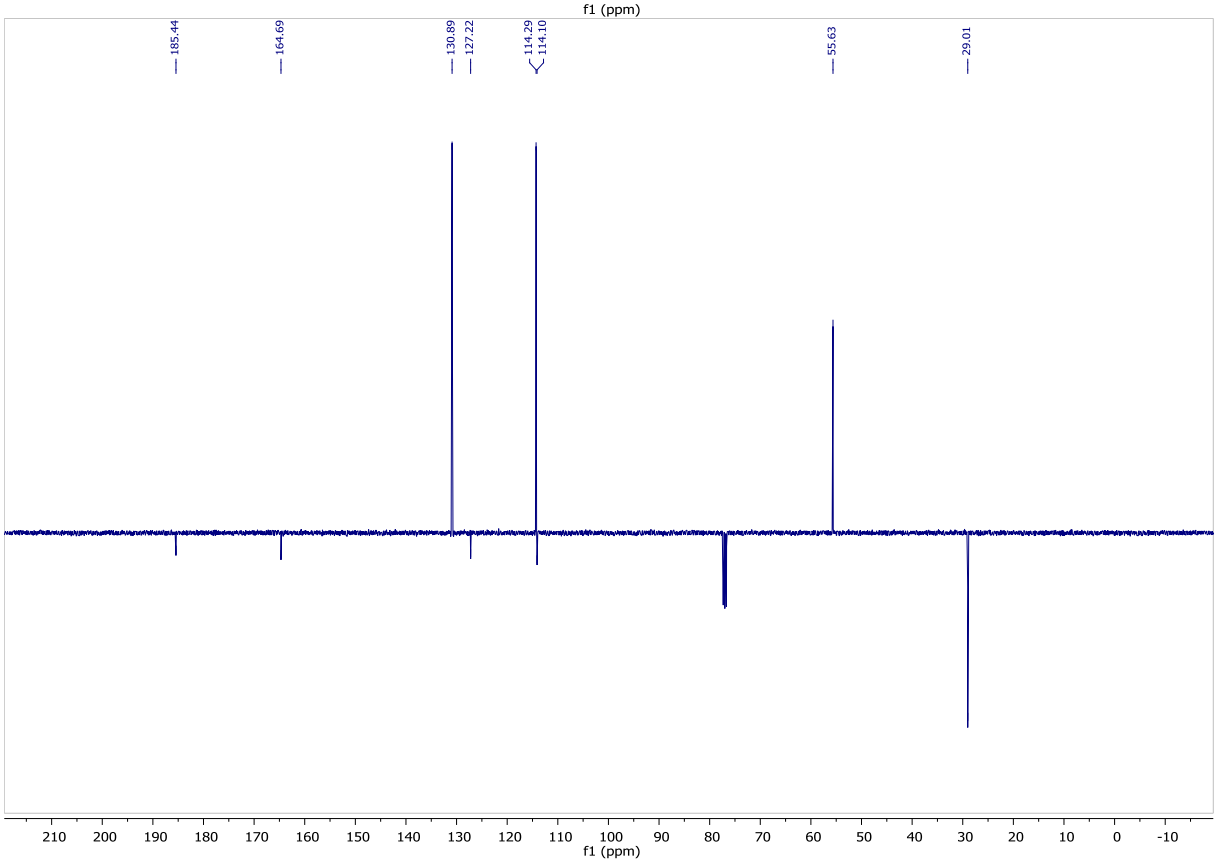
2.114e


7.87
7.87
7.87
7.86
7.85
7.85
7.84
7.54
7.54
7.53
7.52
7.52
7.52
7.51
7.26
4.06
1.34
O
CN
1.03
1.04
1.00
4.64
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

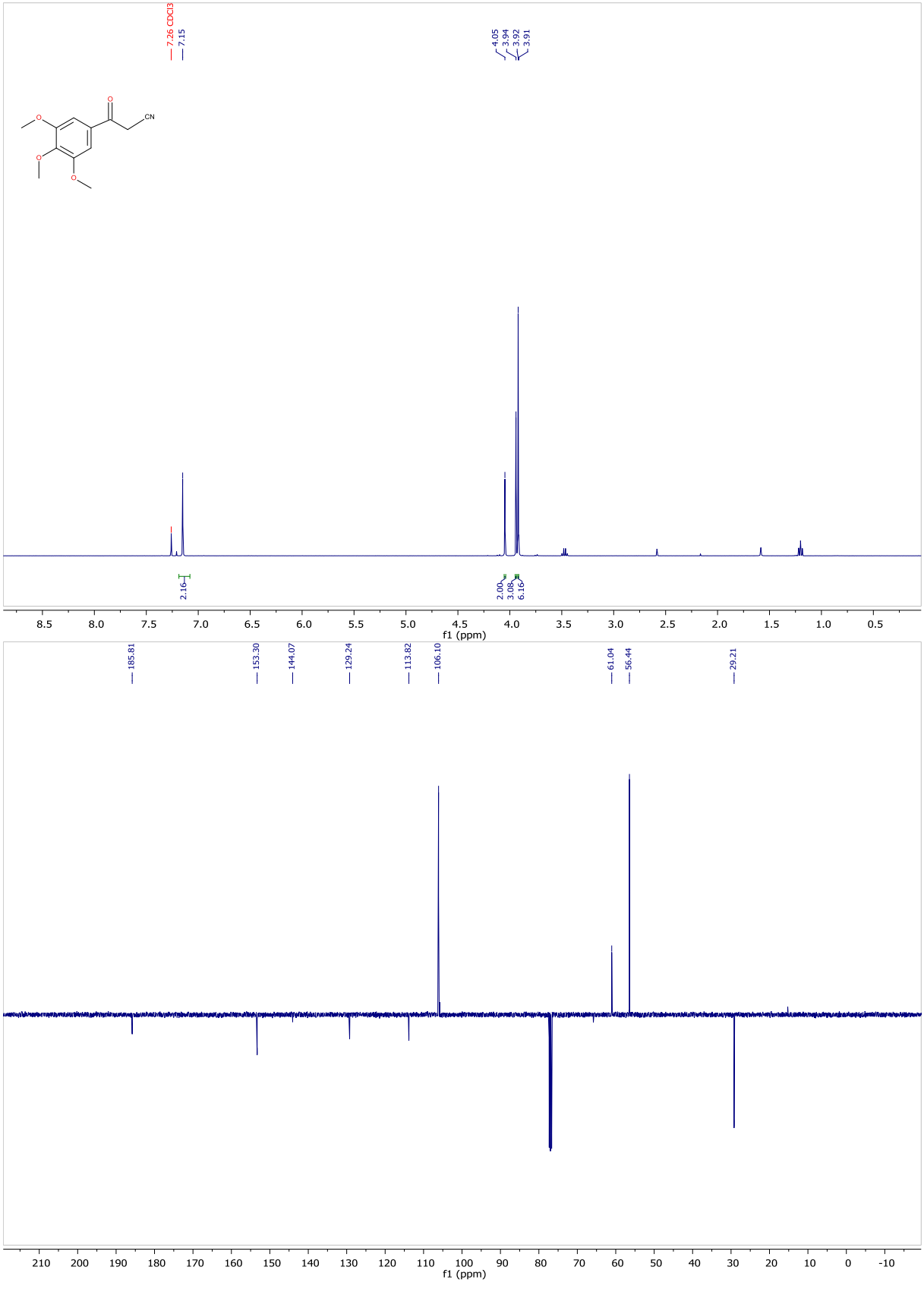

186.64
158.83
131.69
128.46
126.10
113.95
35.31
30.93
29.25
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

2.114f

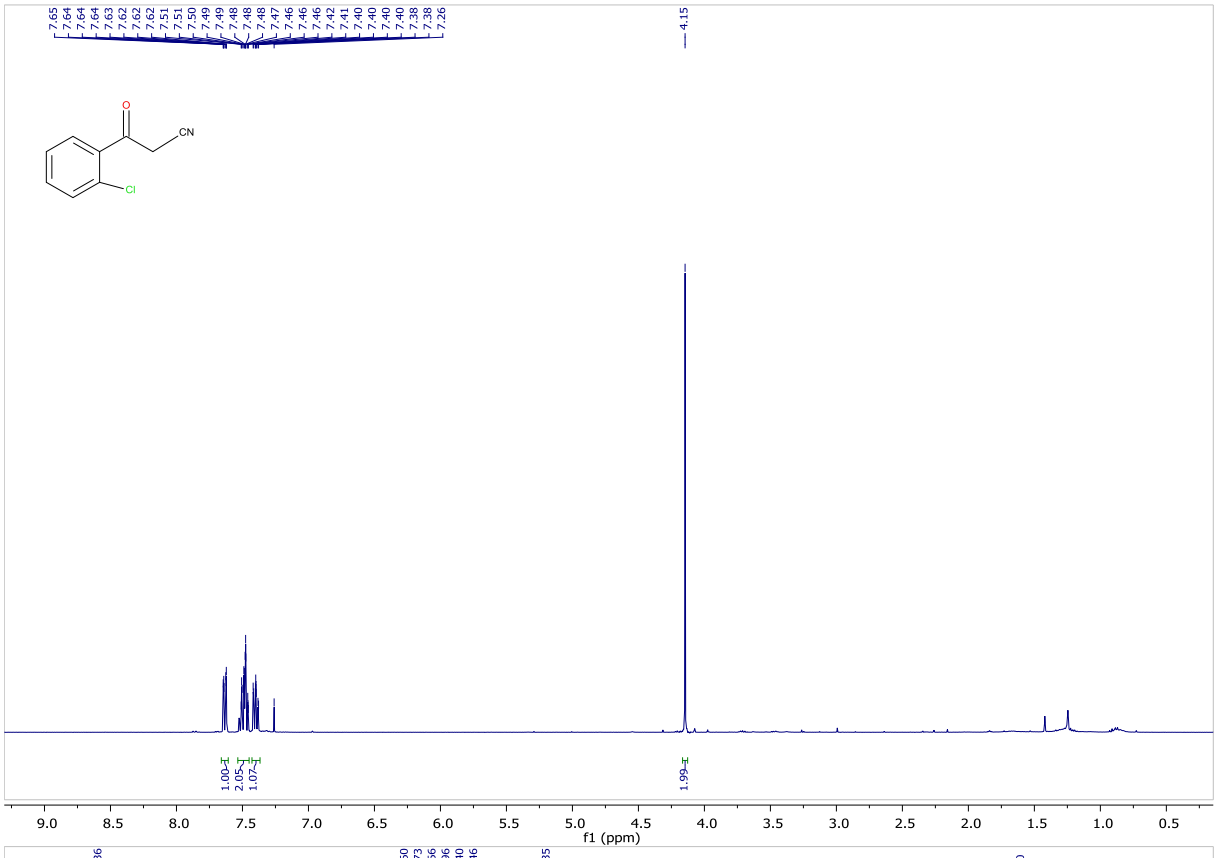

O
CN
O
7.90
7.88
6.98
6.96
4.02
3.89
2.00
1.99
2.05
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

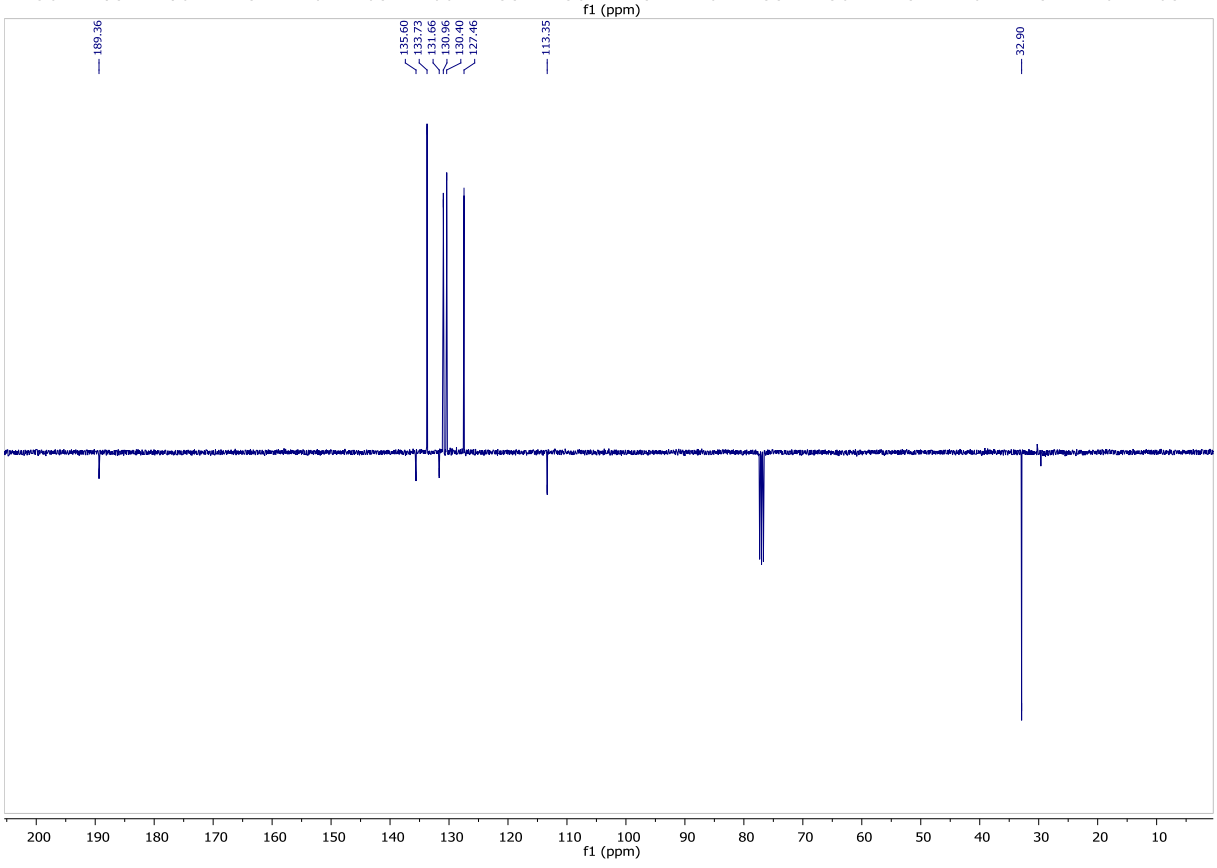

185.44
164.69
130.89
127.22
114.29
114.10
55.63
29.01
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

2.114g

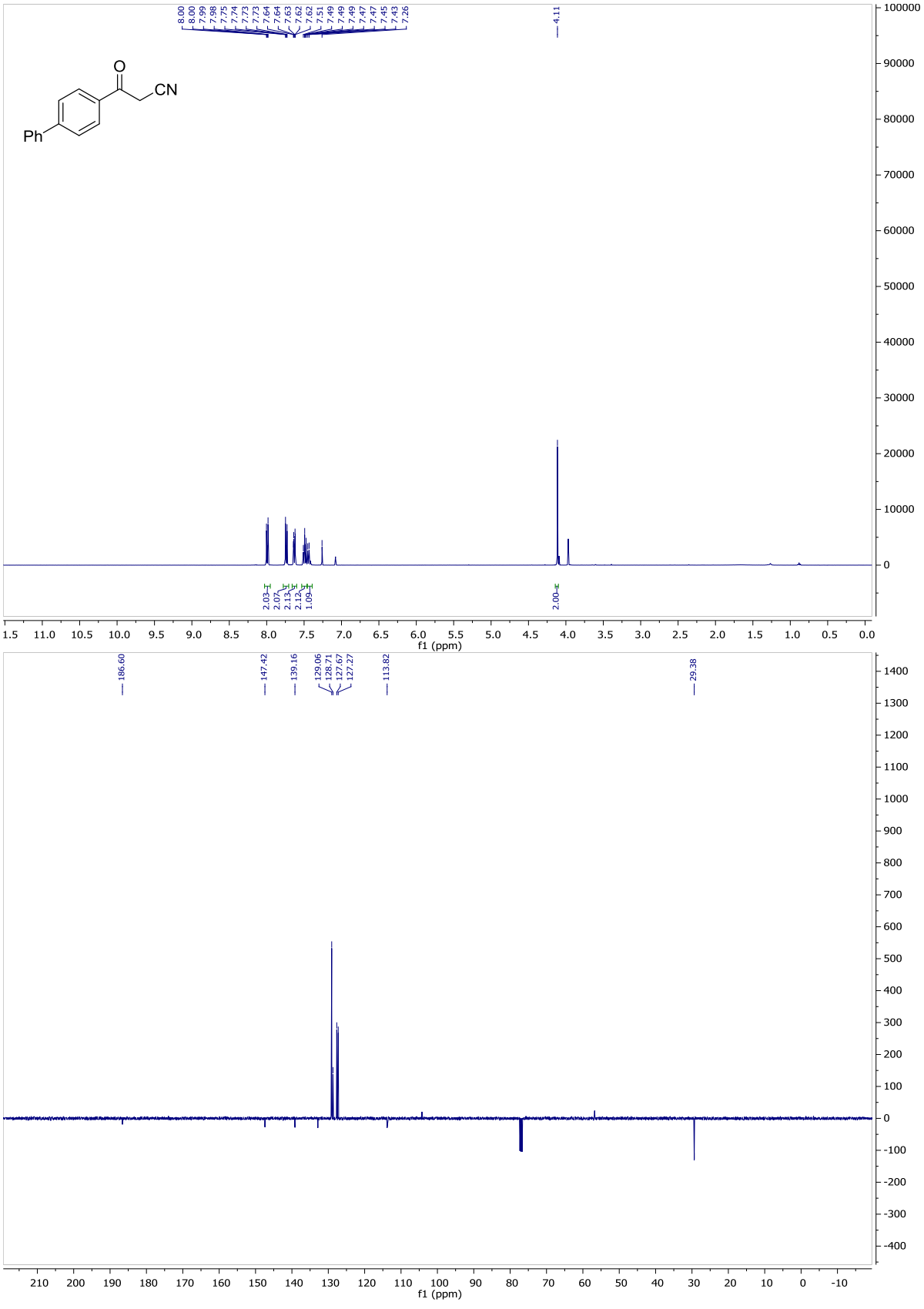

7.26 CDCl3
7.15
4.05
3.94
3.92
3.91
O
CN
O
O
O
2.16
2.00
3.08
6.16
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
185.81
153.30
144.07
129.24
113.82
106.10
61.04
56.44
29.21
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

2.114h

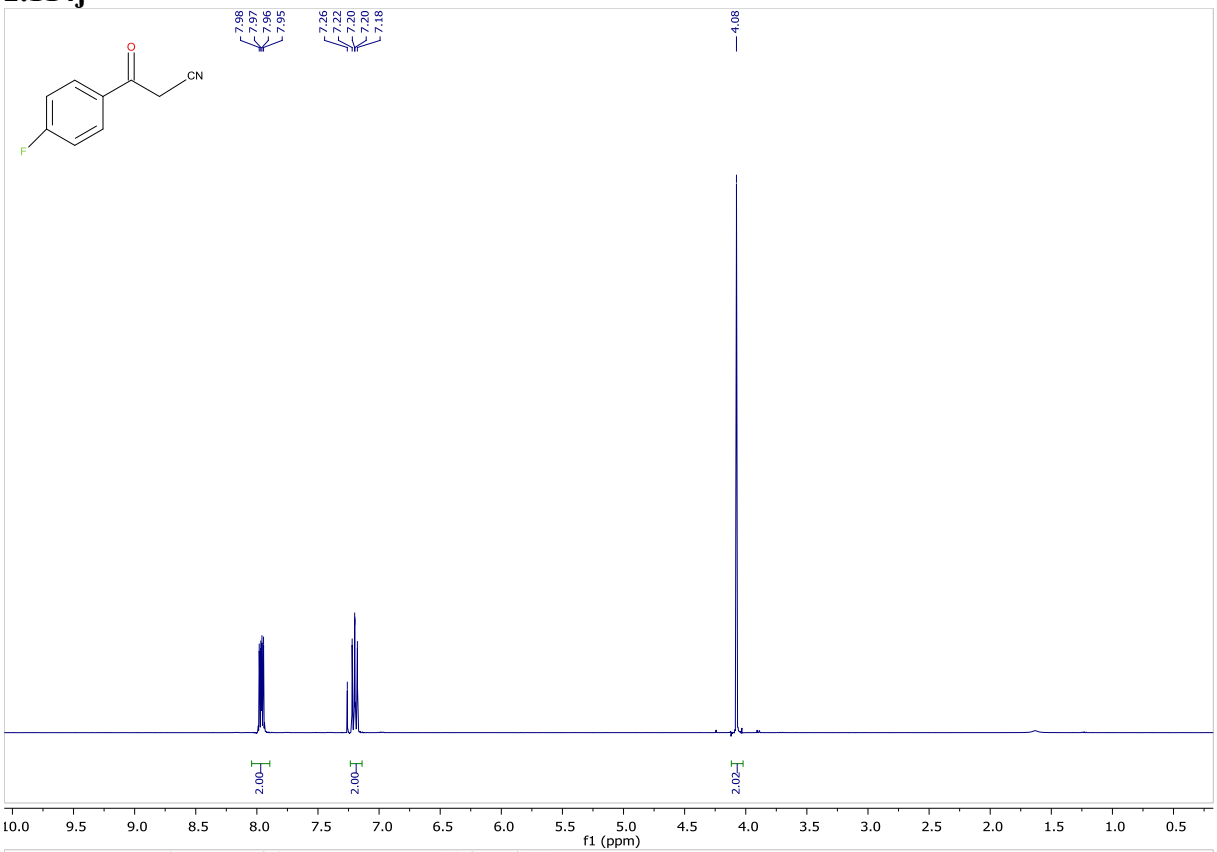

7.65
7.64
7.64
7.64
7.63
7.62
7.62
7.62
7.51
7.51
7.50
7.49
7.49
7.48
7.48
7.48
7.47
7.46
7.46
7.46
7.42
7.41
7.40
7.40
7.40
7.40
7.38
7.38
7.26
4.15
O
CN
Cl
1.00
2.05
1.07
1.99
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

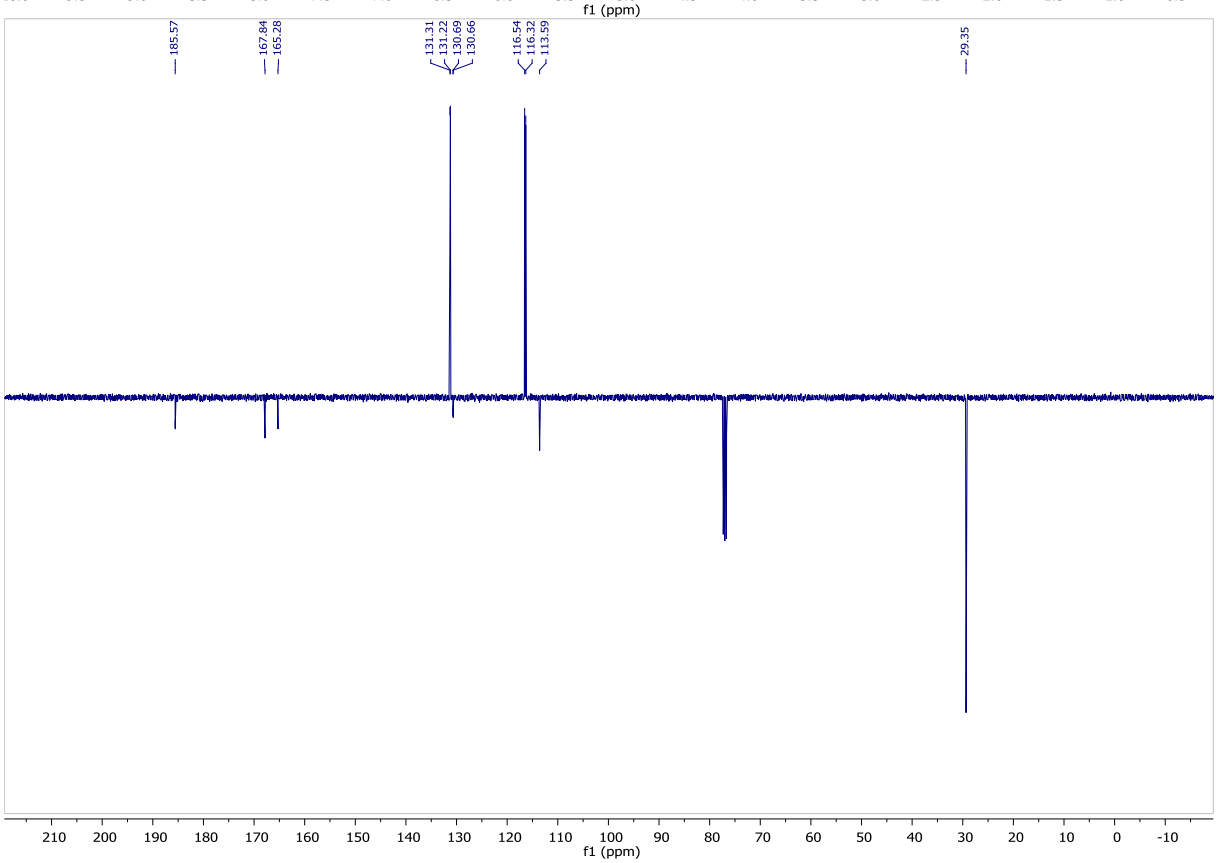

189.36
135.60
133.73
131.66
130.96
130.40
127.46
113.35
32.90
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

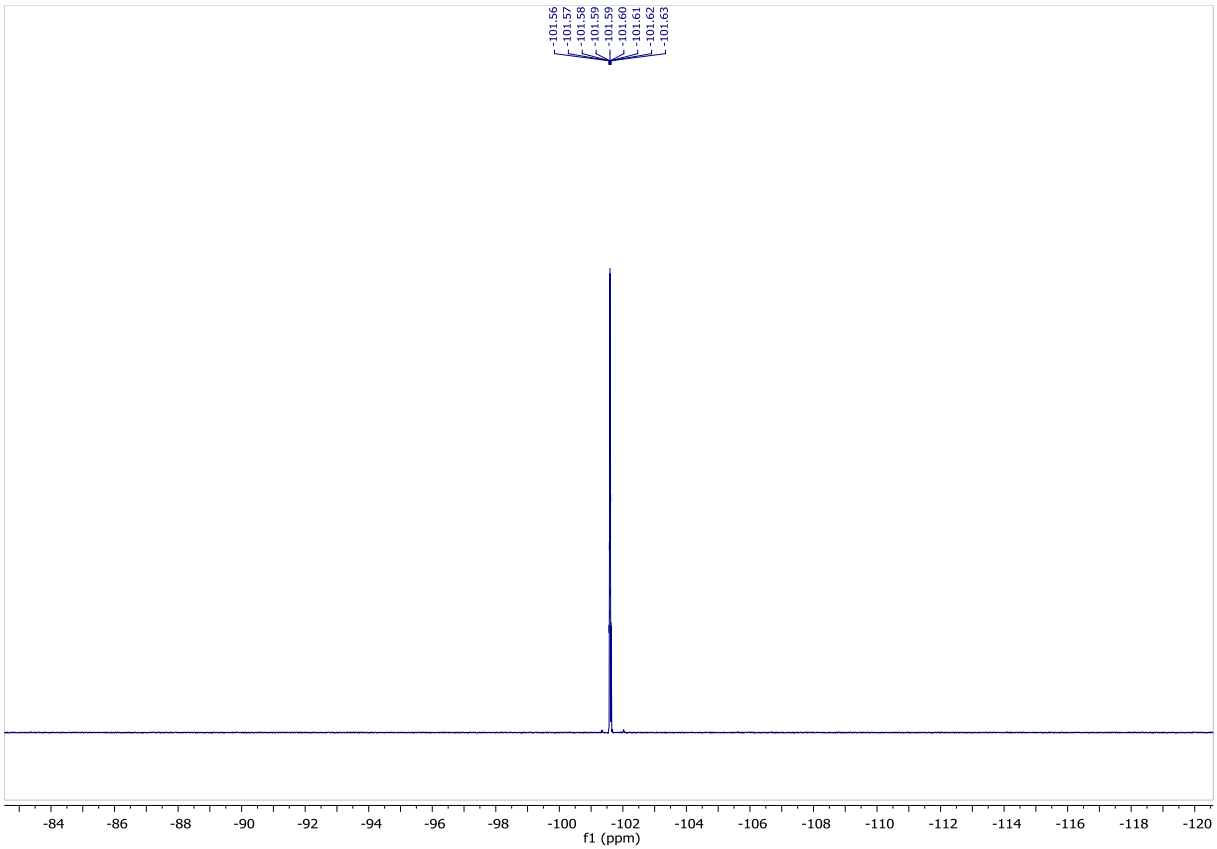
2.114i


8.00
8.00
7.99
7.98
7.75
7.74
7.73
7.73
7.64
7.64
7.63
7.62
7.62
7.51
7.49
7.49
7.47
7.47
7.45
7.43
7.26
4.11
O
CN
Ph
2.03
2.07
2.13
2.12
1.09
2.00
f1 (ppm)
186.60
147.42
139.16
129.06
128.71
127.67
127.27
113.82
29.38
f1 (ppm)

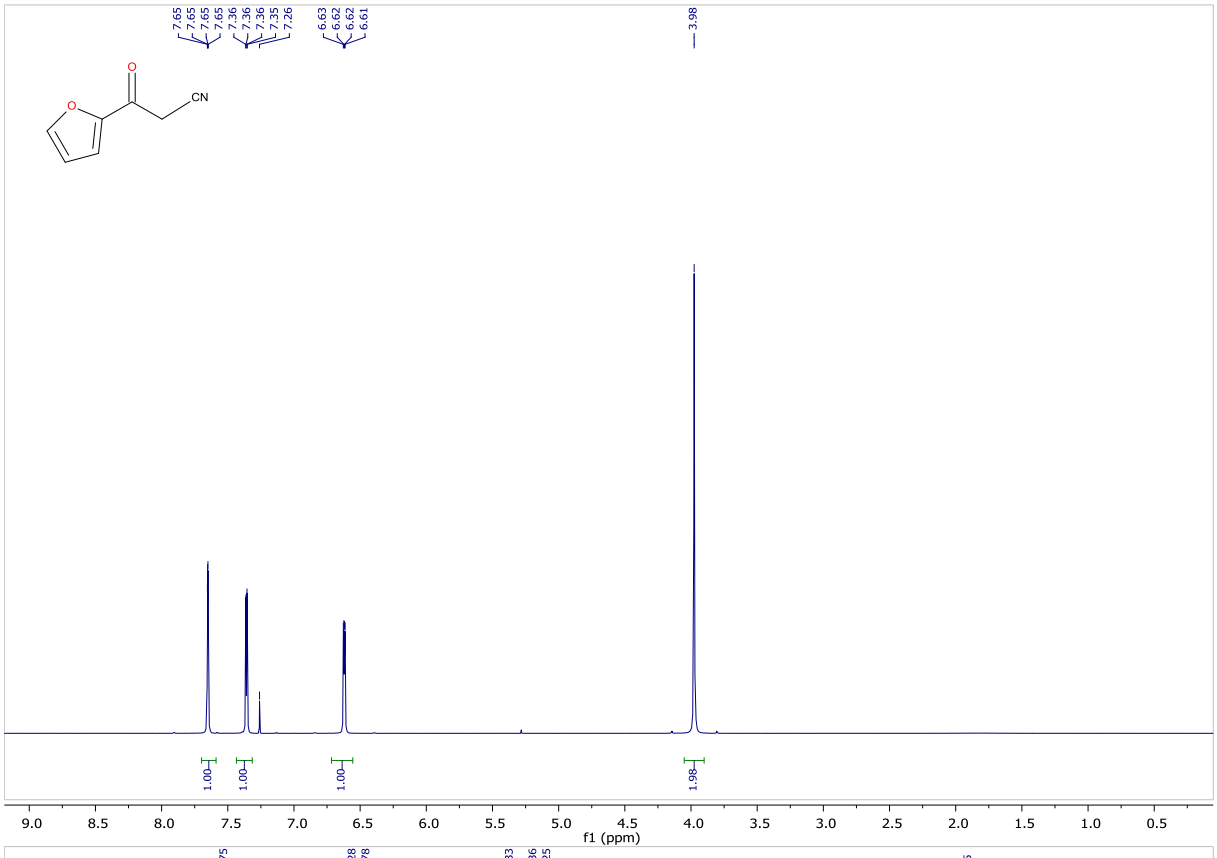
2.114j

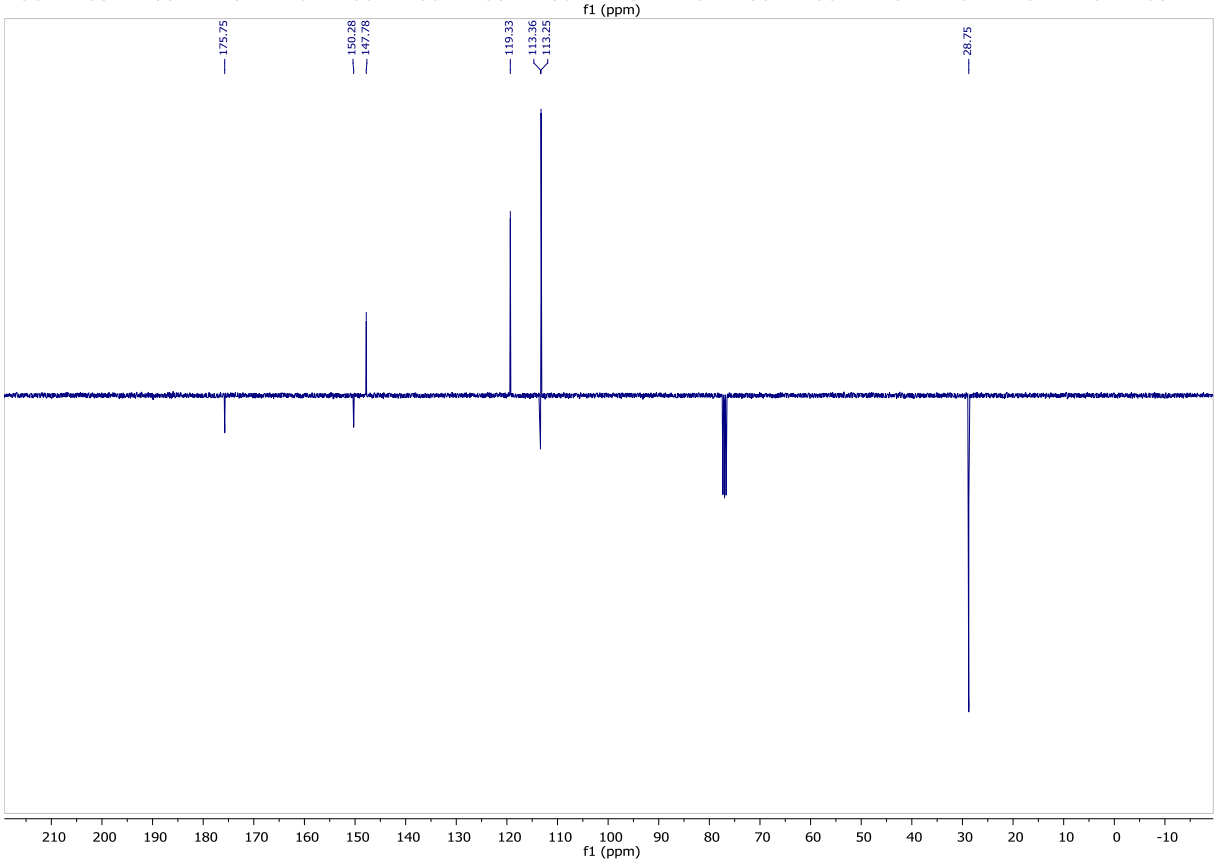

7.98
7.97
7.96
7.95
7.26
7.22
7.20
7.20
7.18
4.08
O
CN
F
2.00
2.00
2.02
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


185.57
167.84
165.28
131.31
131.22
130.69
130.66
116.54
116.32
113.59
29.35
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

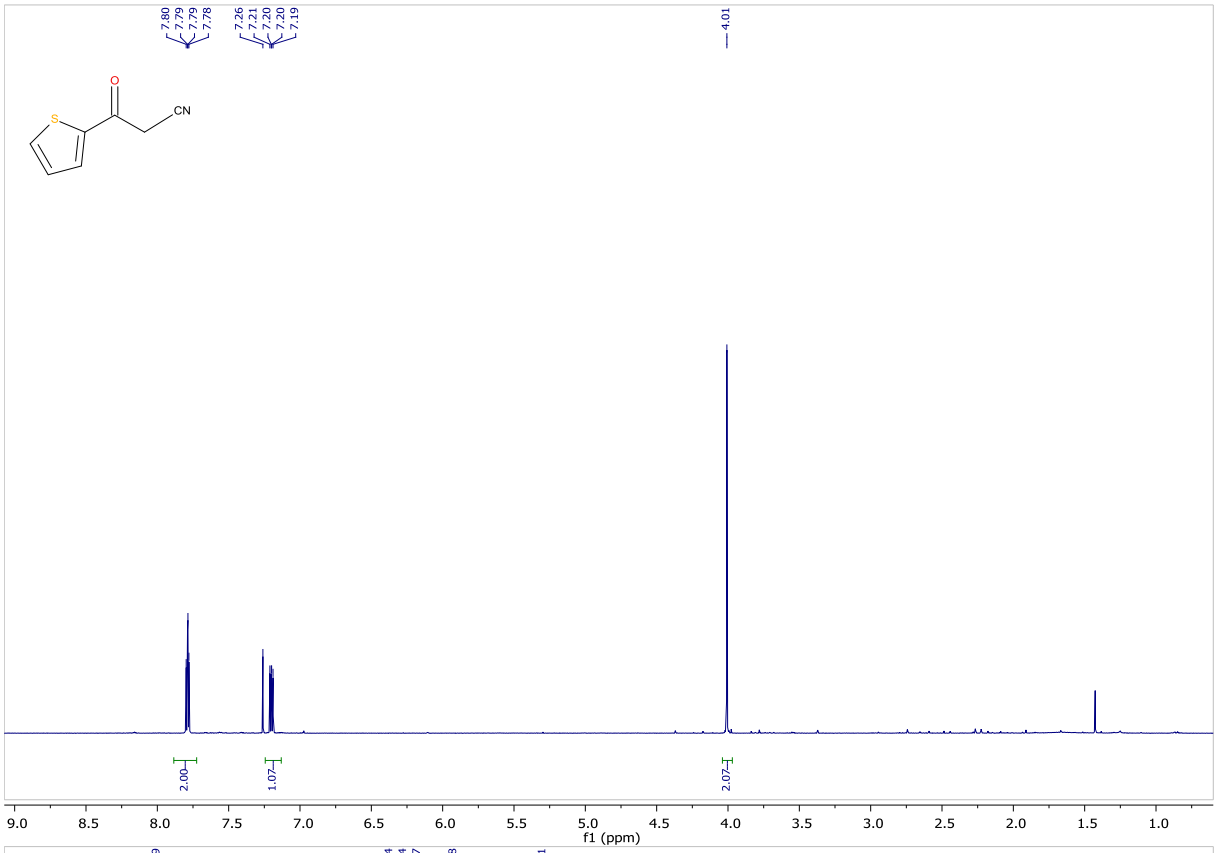

-101.56
-101.57
-101.58
-101.59
-101.59
-101.60
-101.61
-101.62
-101.63
-84
-86
-88
-90
-92
-94
-96
-98
-100
-102
-104
-106
-108
-110
-112
-114
-116
-118
-120
f1 (ppm)

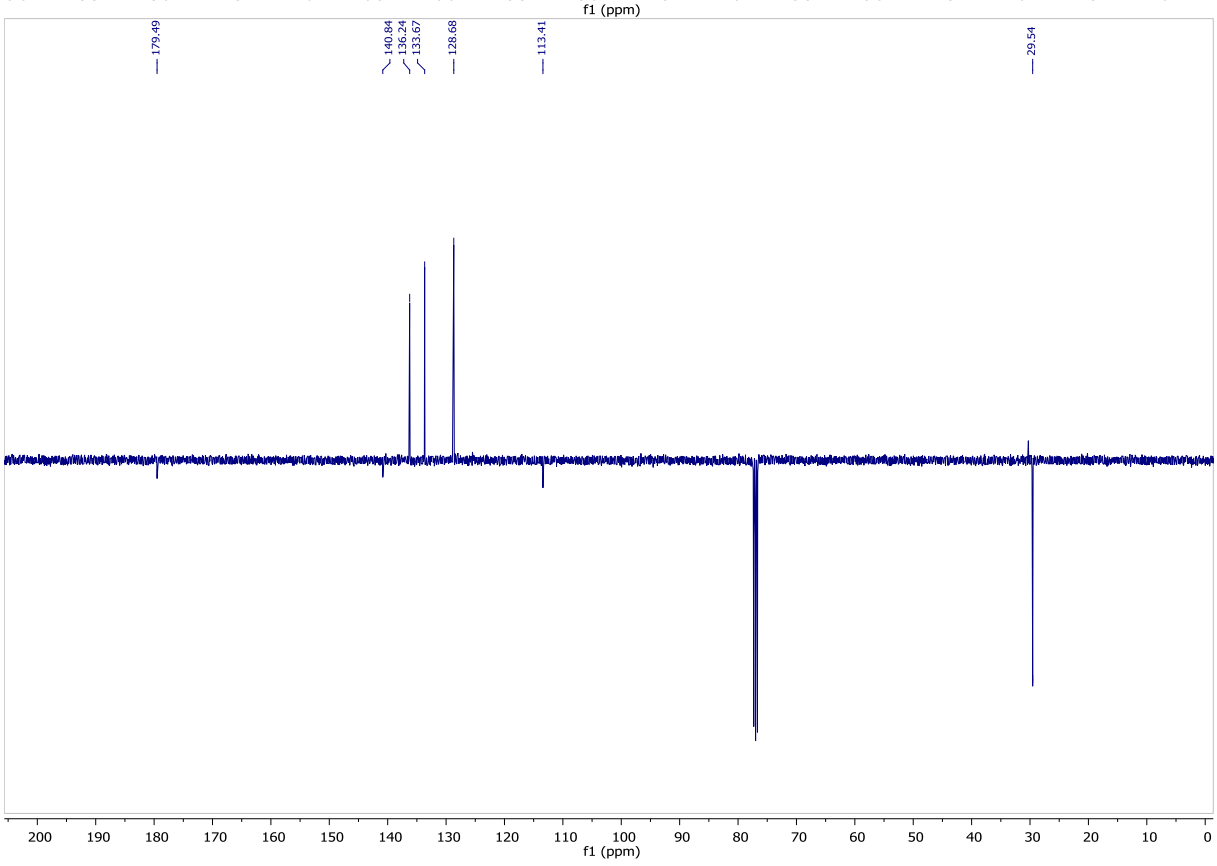
2.114k


7.65
7.65
7.65
7.65
7.36
7.36
7.36
7.35
7.26
6.63
6.62
6.62
6.61
3.98
O
O
CN
1.00
1.00
1.00
1.98
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

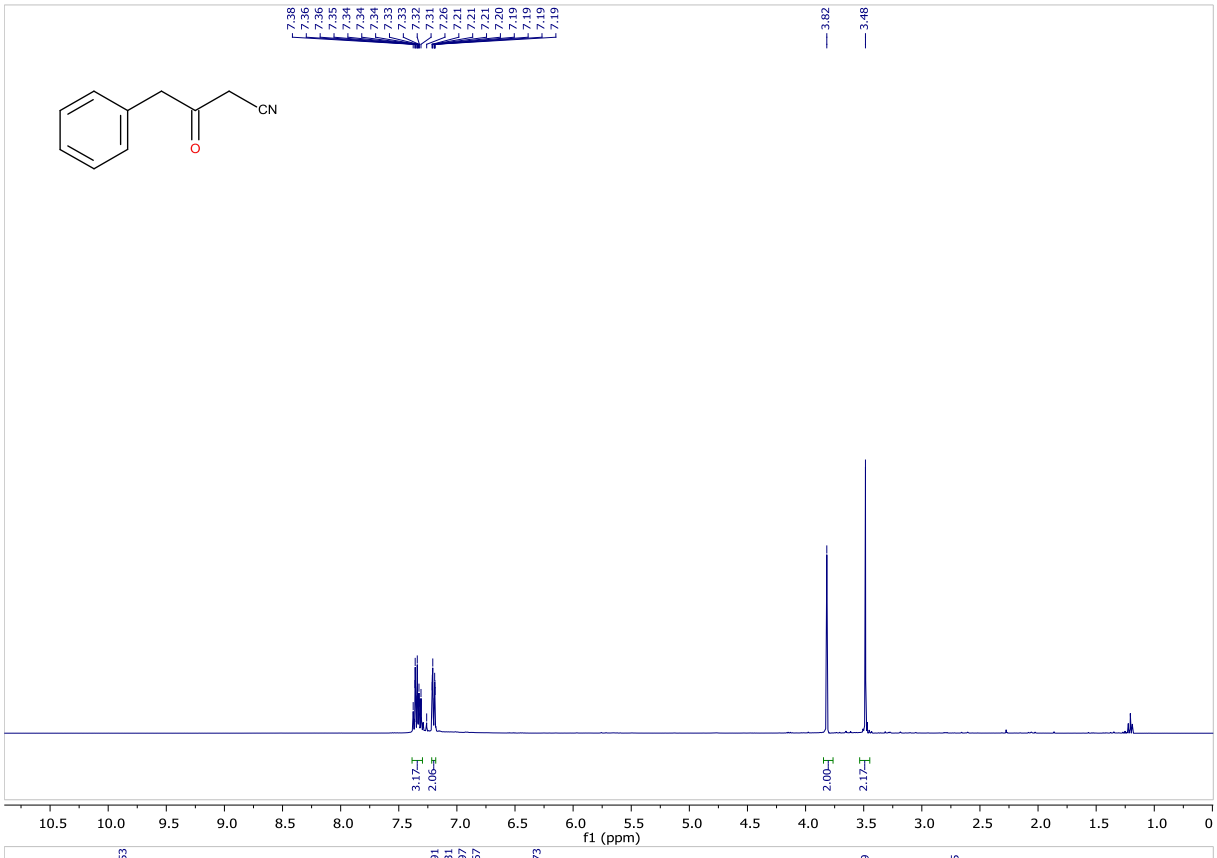

175.75
150.28
147.78
119.33
113.36
113.25
28.75
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

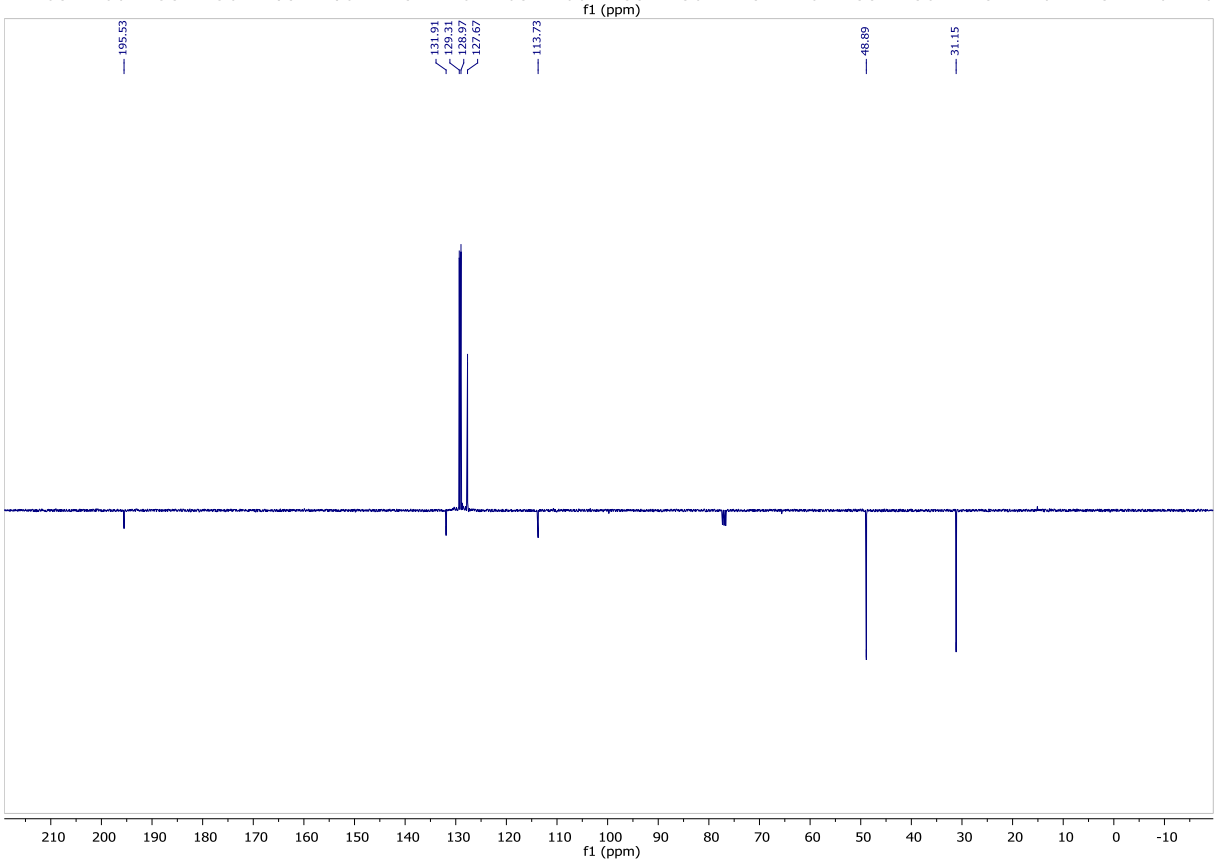
2.114l


7.80
7.79
7.79
7.78
7.26
7.21
7.20
7.20
7.19
4.01
O
S
CN
2.00
1.07
2.07
f1 (ppm)

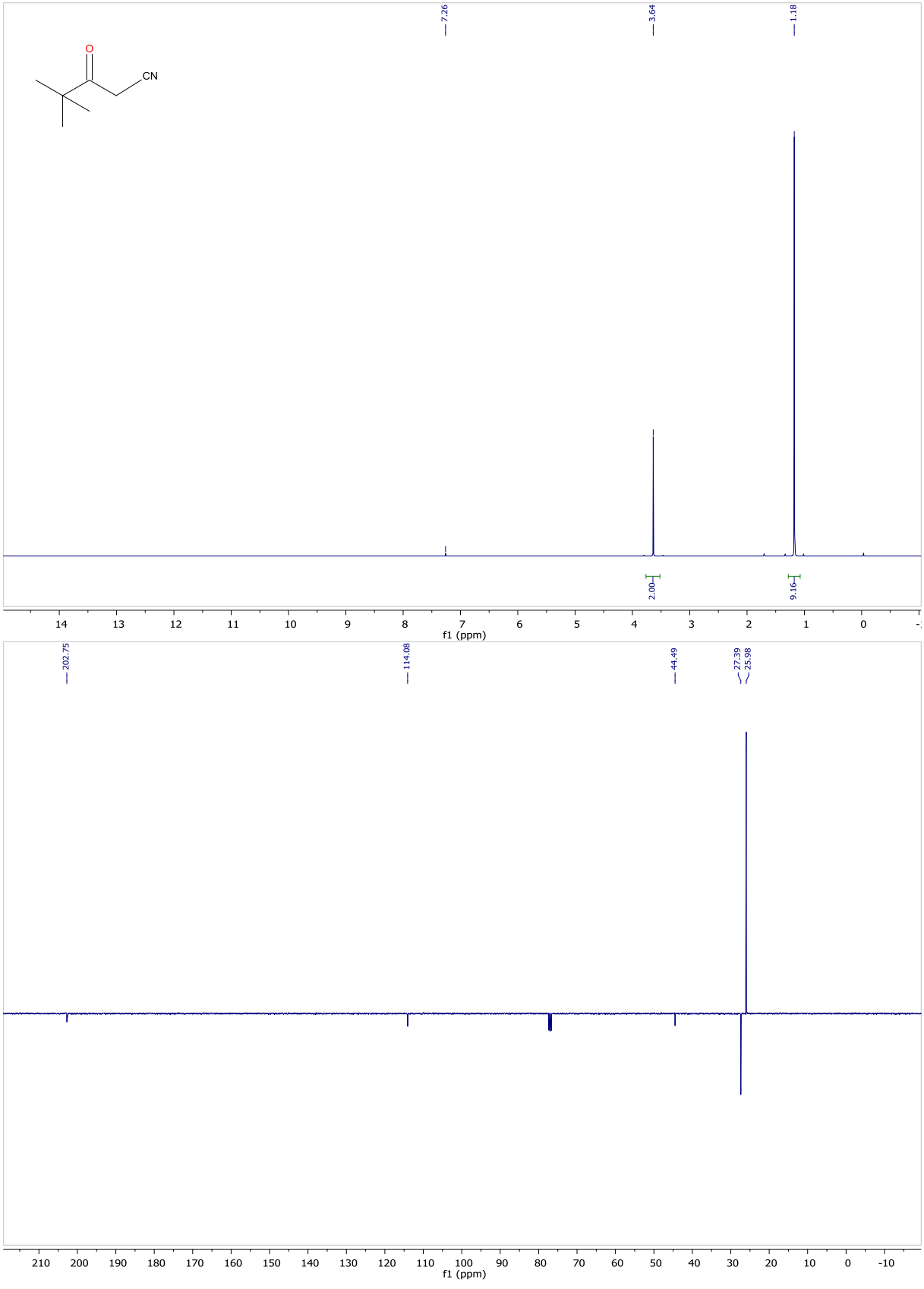

179.49
140.84
136.24
133.67
128.68
113.41
29.54
f1 (ppm)

2.114m

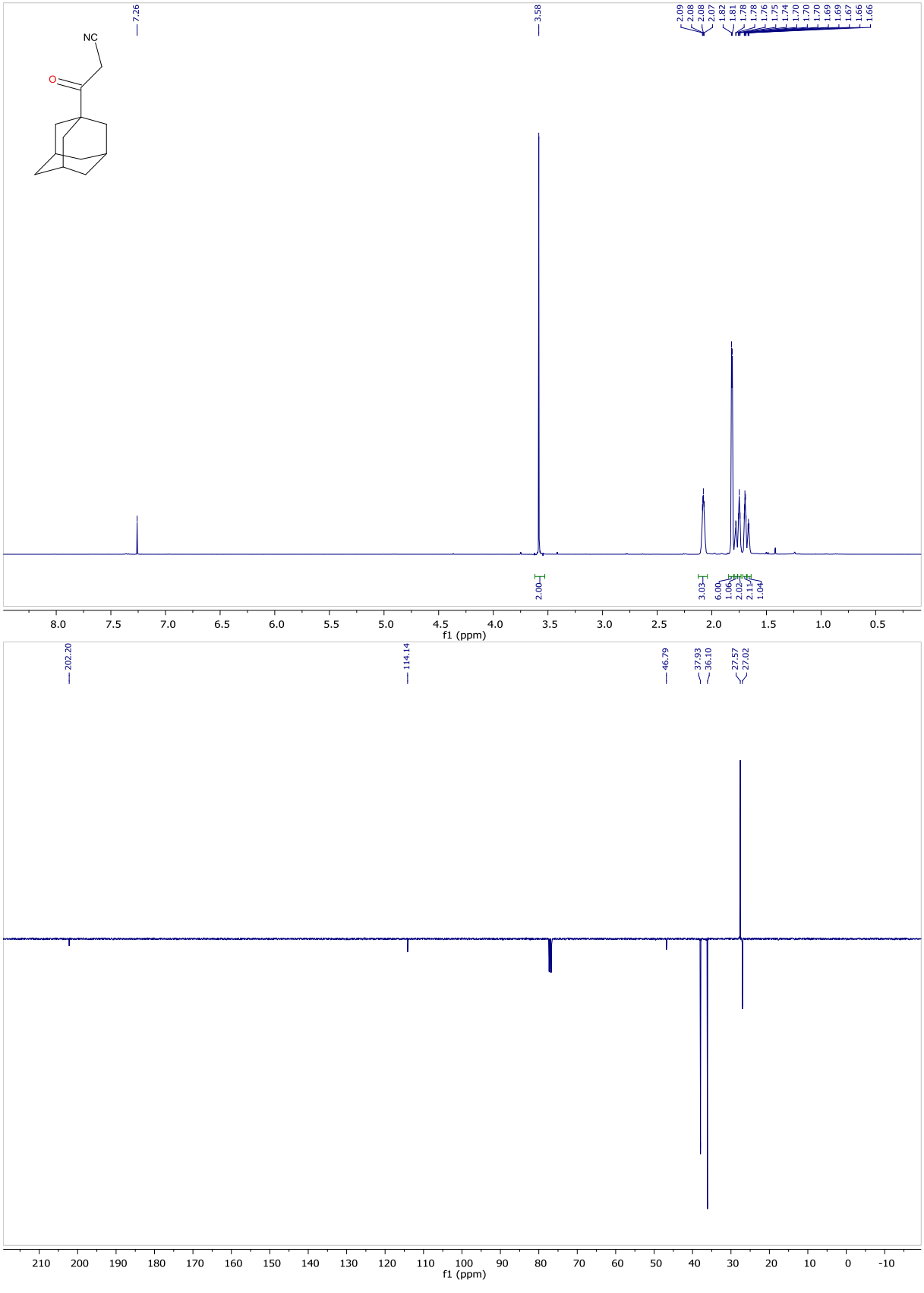

7.38
7.36
7.36
7.35
7.34
7.34
7.34
7.33
7.33
7.32
7.31
7.26
7.21
7.21
7.21
7.20
7.19
7.19
7.19
7.19
3.82
3.48
CN
O
3.17
2.06
2.00
2.17
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0
f1 (ppm)


195.53
131.91
129.31
128.97
127.67
113.73
48.89
31.15
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

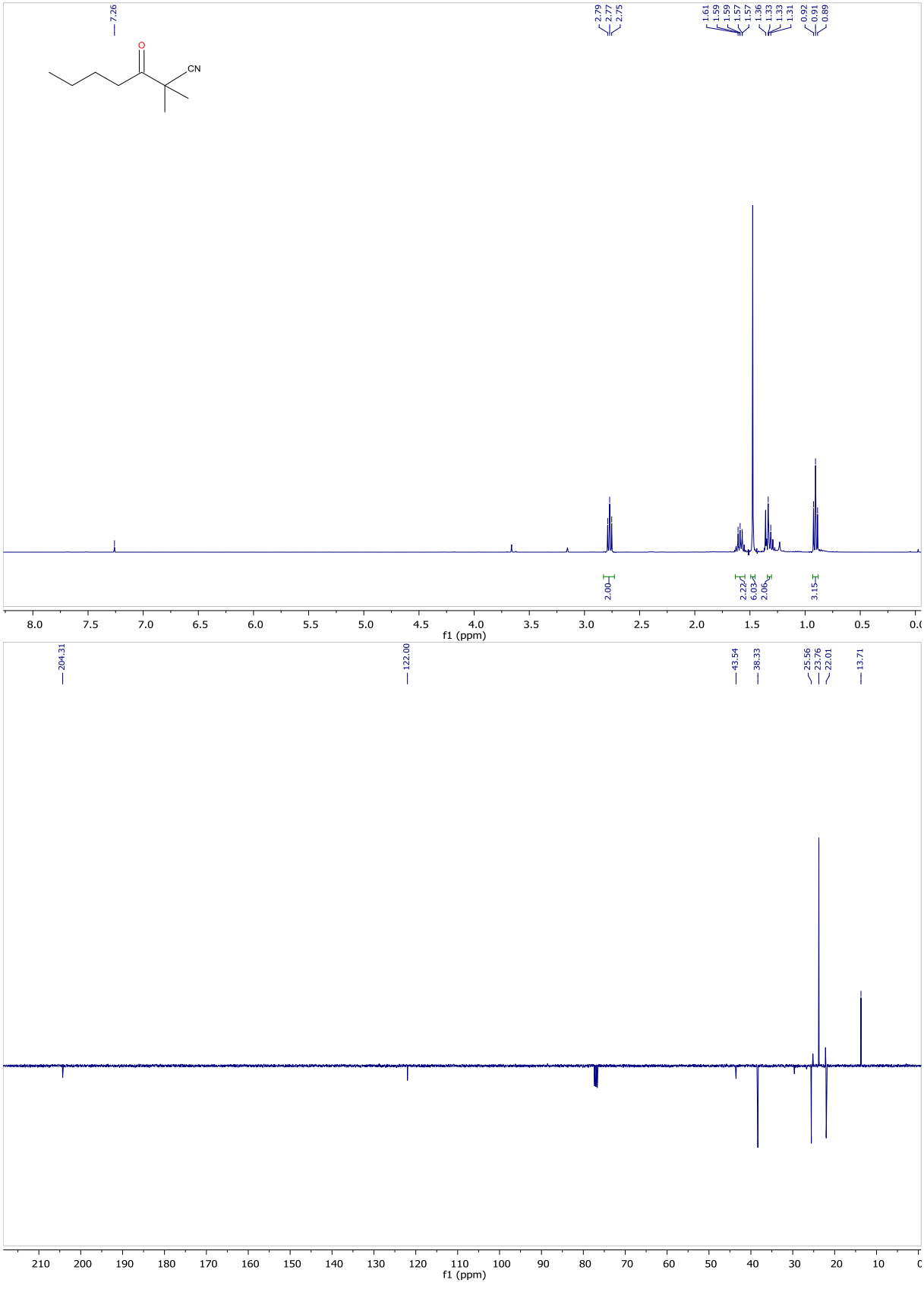
2.114n


O
CN
7.26
3.64
1.18
2.00
9.16
f1 (ppm)
202.75
114.08
44.49
27.39
25.98
f1 (ppm)

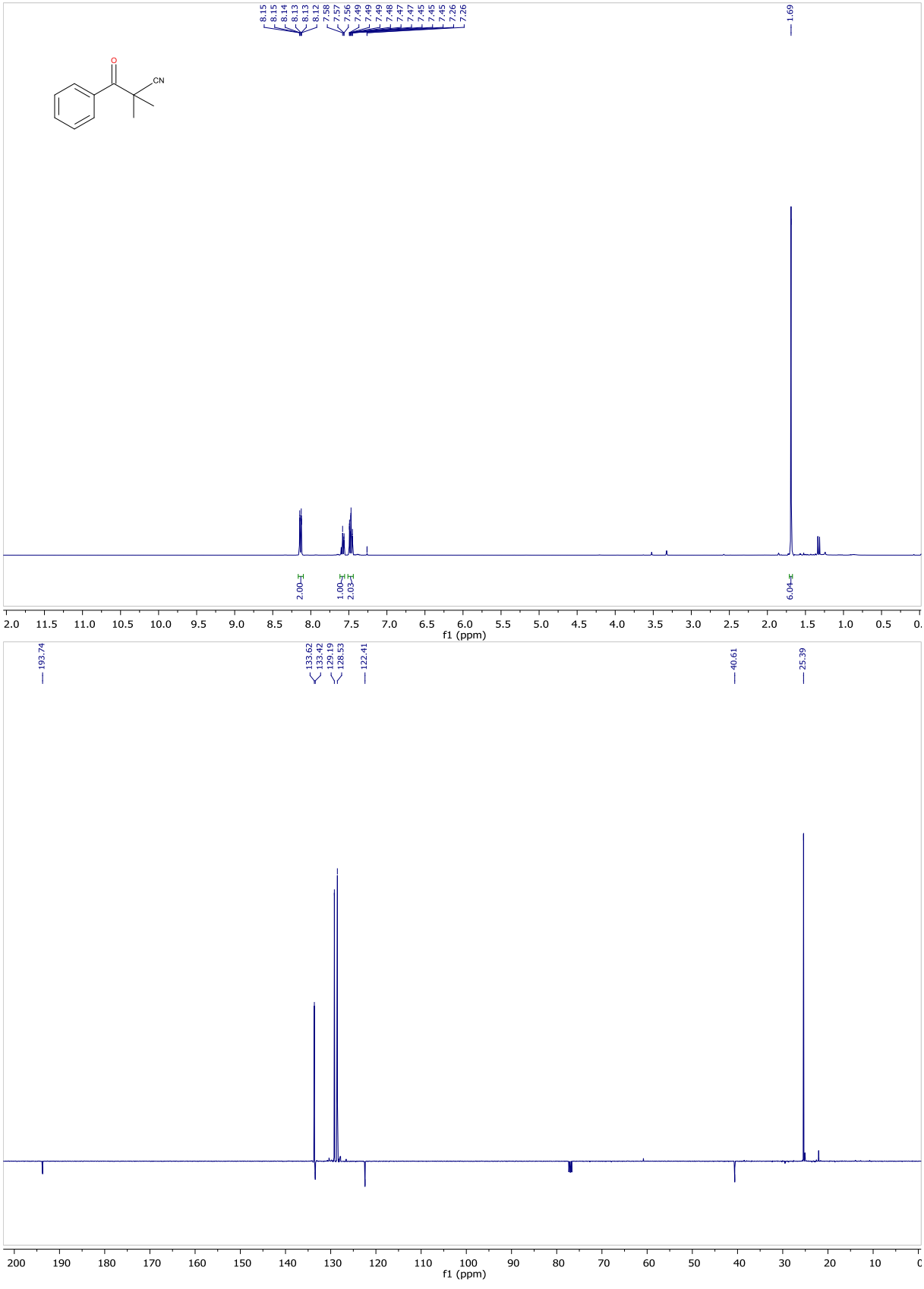
2.114o


NC
O
7.26
3.58
2.09
2.08
2.08
2.07
1.82
1.81
1.78
1.78
1.76
1.75
1.74
1.70
1.70
1.70
1.69
1.69
1.67
1.66
1.66
2.00
3.03
6.00
1.06
2.02
2.11
1.04
f1 (ppm)
202.20
114.14
46.79
37.93
36.10
27.57
27.02
f1 (ppm)

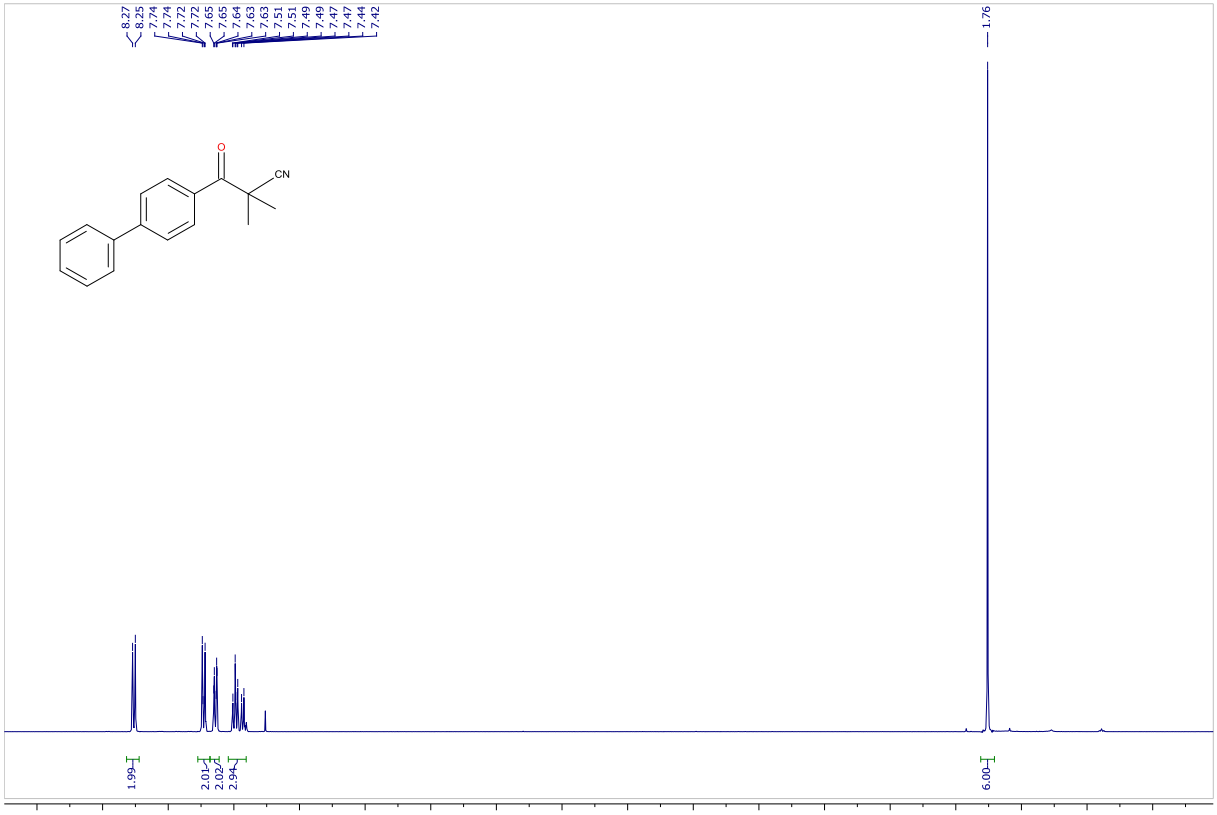
2.115a

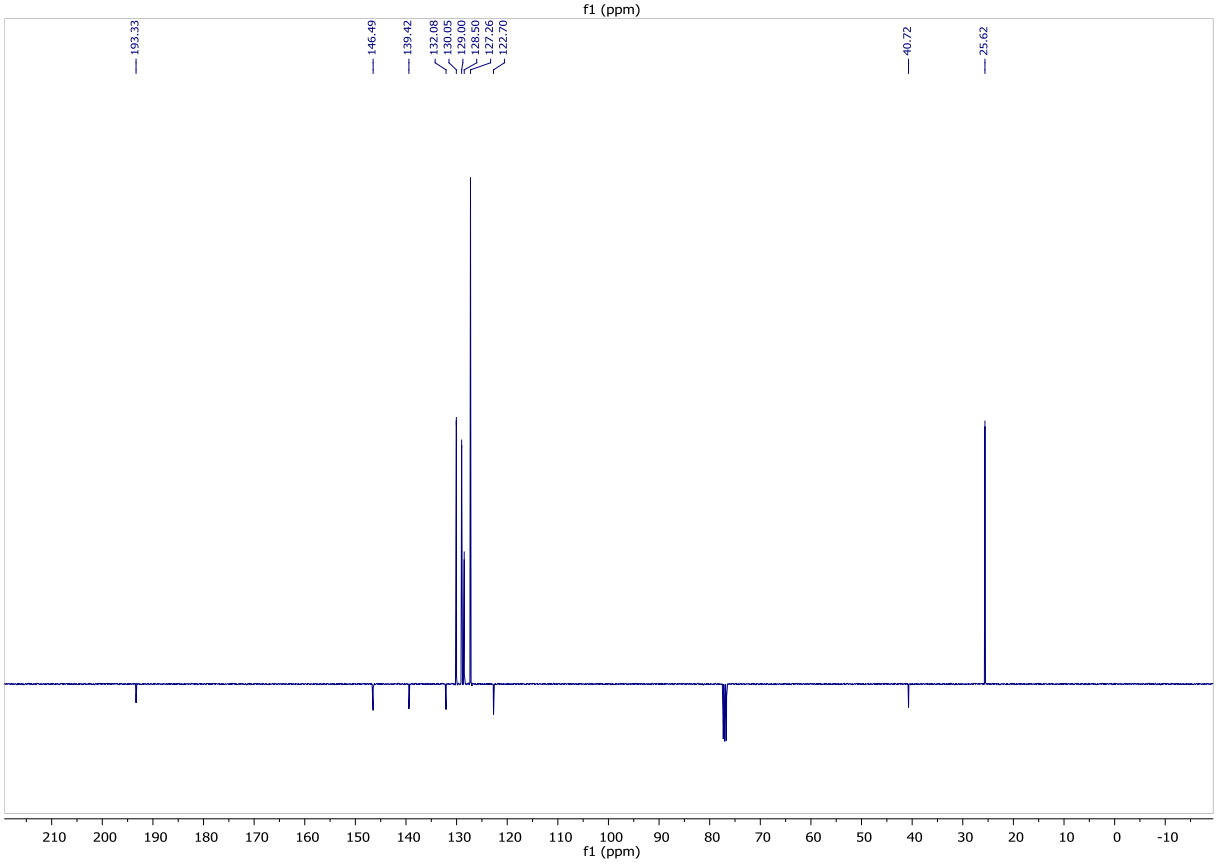

7.26
2.79
2.77
2.75
1.61
1.59
1.59
1.57
1.57
1.36
1.33
1.33
1.31
0.92
0.91
0.89
O
CN
2.00
2.22
6.03
2.06
3.15
f1 (ppm)
204.31
122.00
43.54
38.33
25.56
23.76
22.01
13.71
f1 (ppm)

2.115b

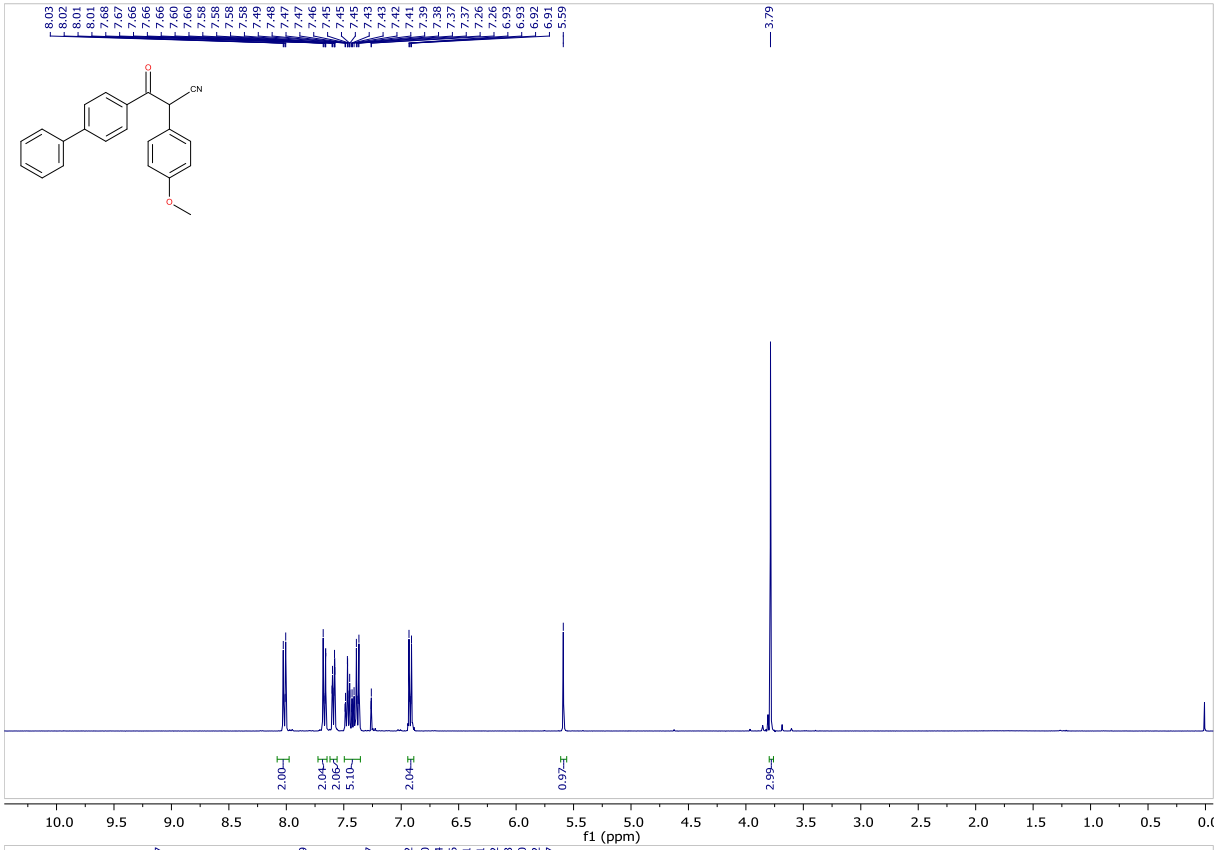

8.15
8.15
8.14
8.13
8.13
8.12
7.58
7.57
7.56
7.49
7.49
7.49
7.48
7.47
7.47
7.45
7.45
7.45
7.26
7.26
1.69
O
CN
2.00
1.00
2.03
6.04
f1 (ppm)
193.74
133.62
133.42
129.19
128.53
122.41
40.61
25.39
f1 (ppm)

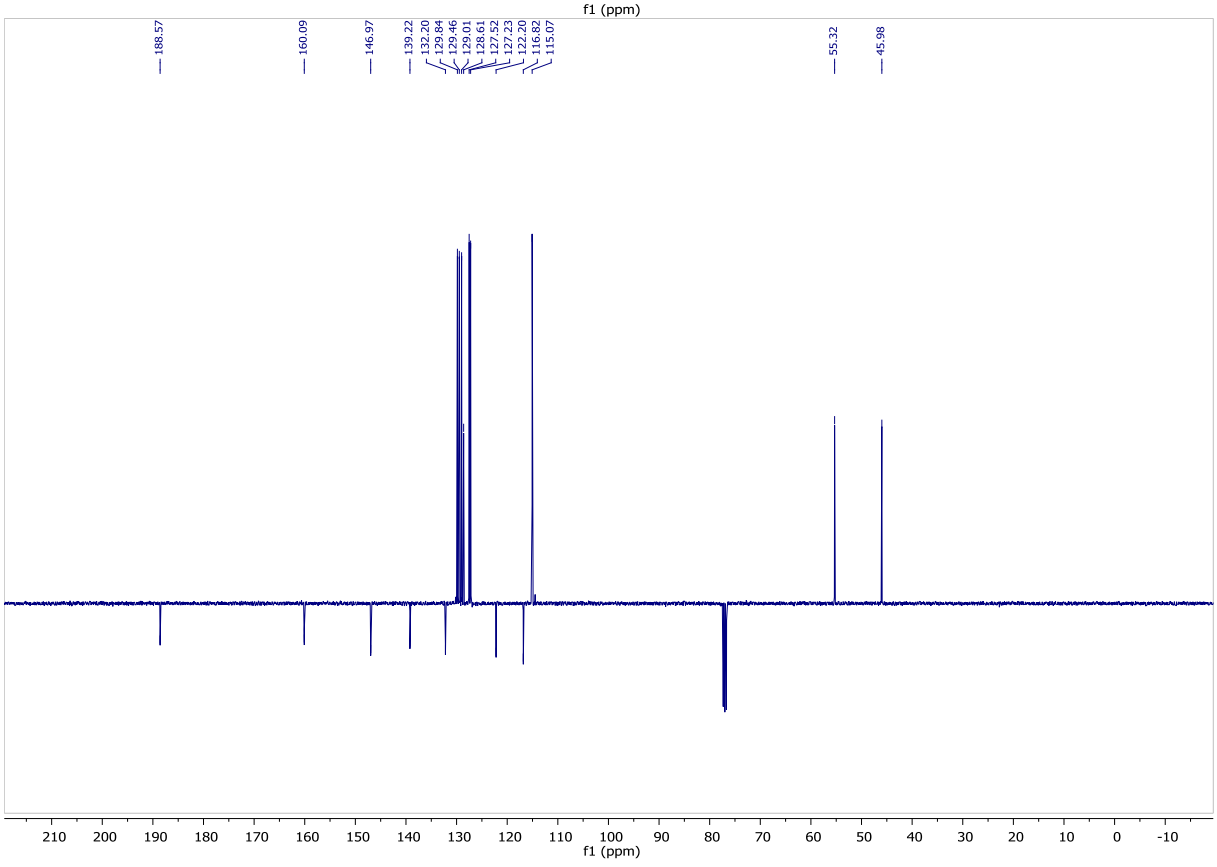
2.115c


8.27
8.25
7.74
7.74
7.72
7.72
7.65
7.65
7.64
7.63
7.63
7.51
7.51
7.49
7.49
7.47
7.47
7.44
7.42
1.76
O
CN
1.99
2.01
2.02
2.94
6.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

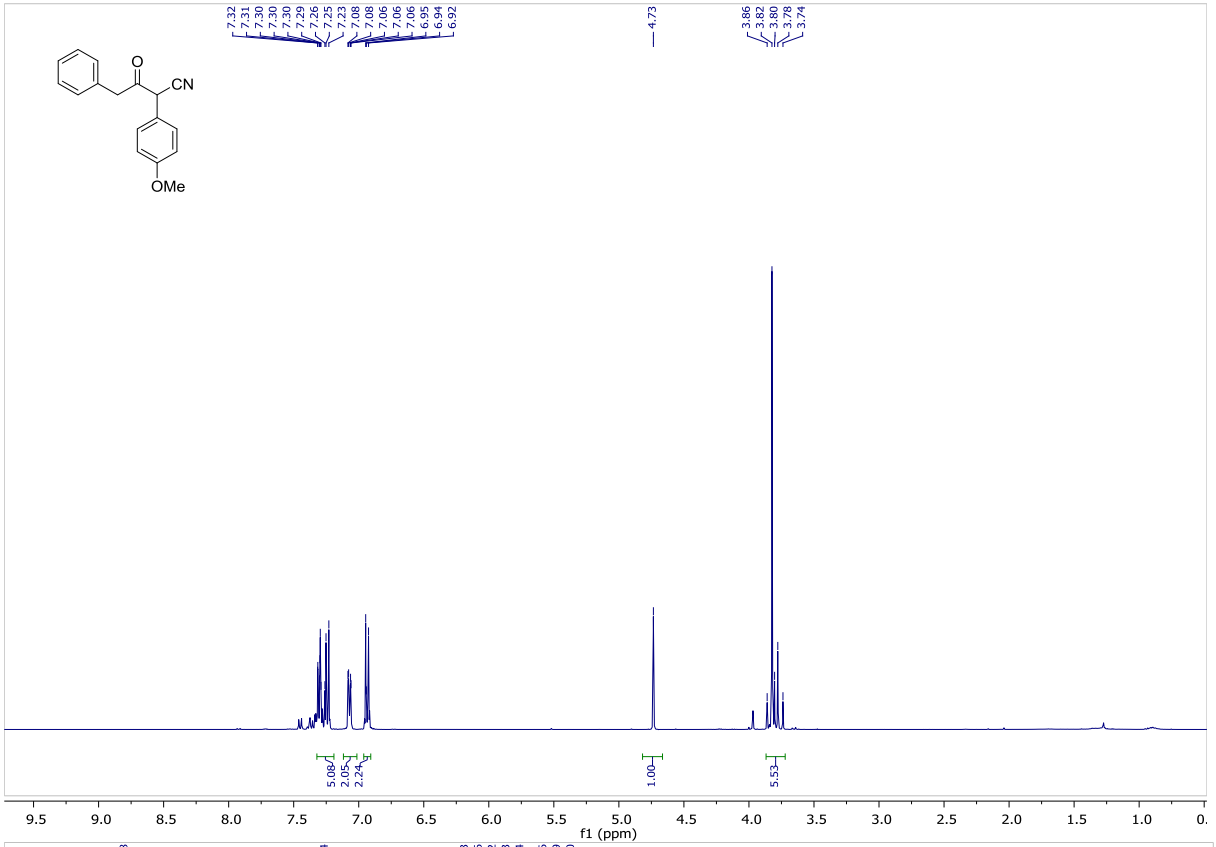

193.33
146.49
139.42
132.08
130.05
129.00
128.50
127.26
122.70
40.72
25.62
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

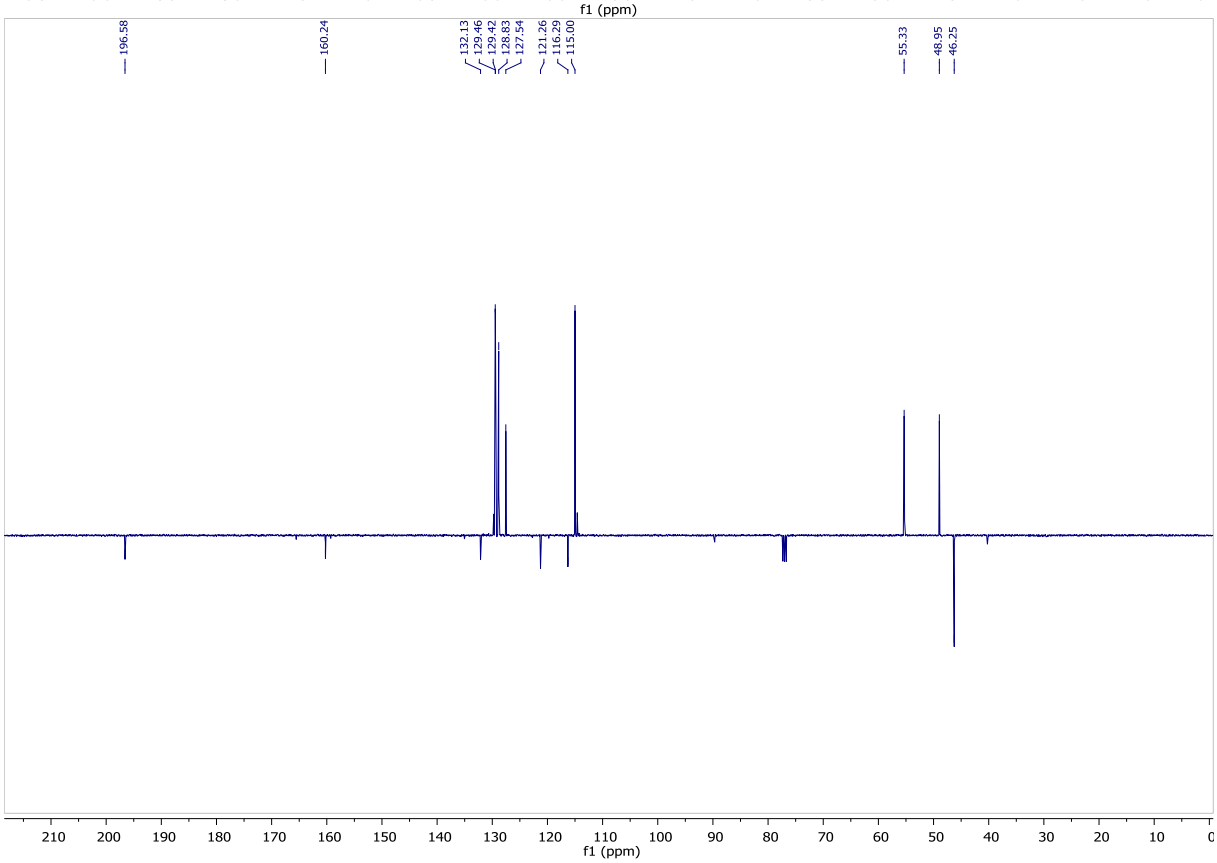
2.115d


8.03
8.02
8.01
8.01
7.68
7.67
7.66
7.66
7.60
7.60
7.58
7.58
7.58
7.49
7.48
7.47
7.47
7.46
7.45
7.45
7.45
7.43
7.43
7.42
7.41
7.39
7.38
7.37
7.37
7.26
6.93
6.93
6.92
6.91
5.59
3.79
O
CN
O
2.00
2.04
2.06
5.10
2.04
0.97
2.99
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

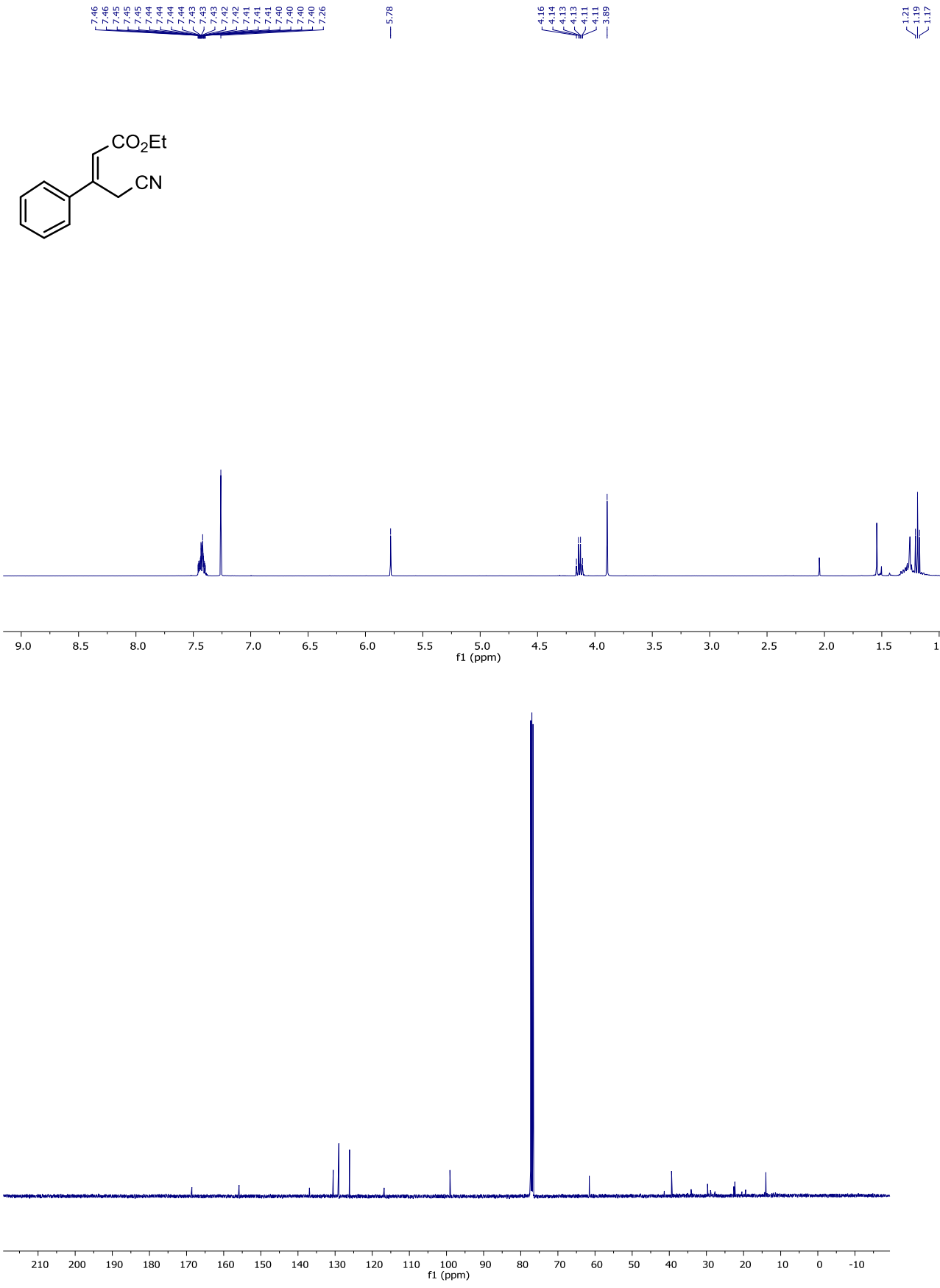

188.57
160.09
146.97
139.22
132.20
129.84
129.46
129.01
128.61
127.52
127.23
122.20
116.82
115.07
55.32
45.98
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

2.115e


7.32
7.31
7.30
7.30
7.30
7.29
7.25
7.23
7.08
7.08
7.06
7.06
7.06
6.95
6.94
6.92
4.73
3.86
3.82
3.80
3.78
3.74
O
CN
OMe
5.08
2.05
2.24
1.00
5.53
f1 (ppm)

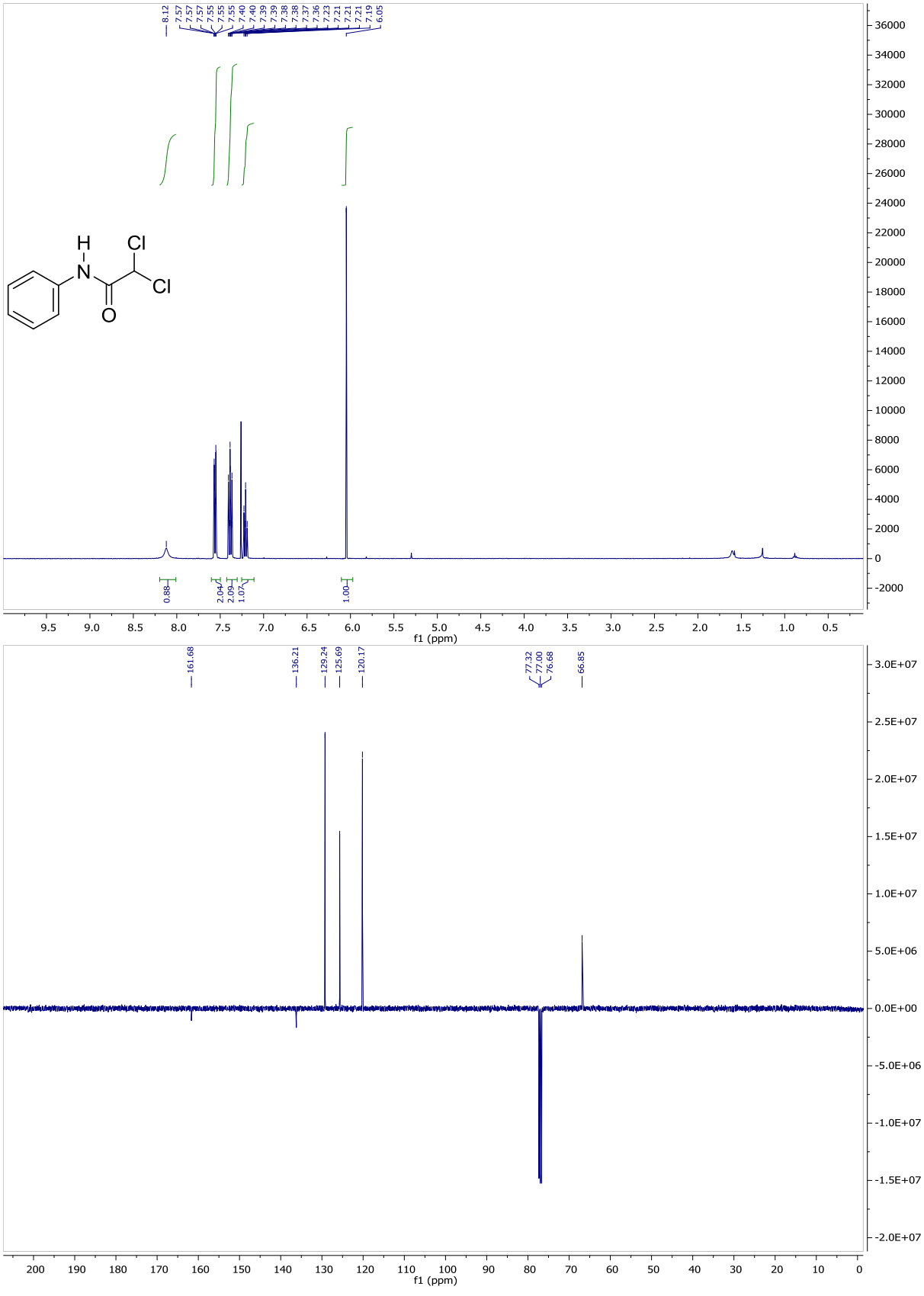

196.58
160.24
132.13
129.46
129.42
128.83
127.54
121.26
116.29
115.00
55.33
48.95
46.25
f1 (ppm)

2.116

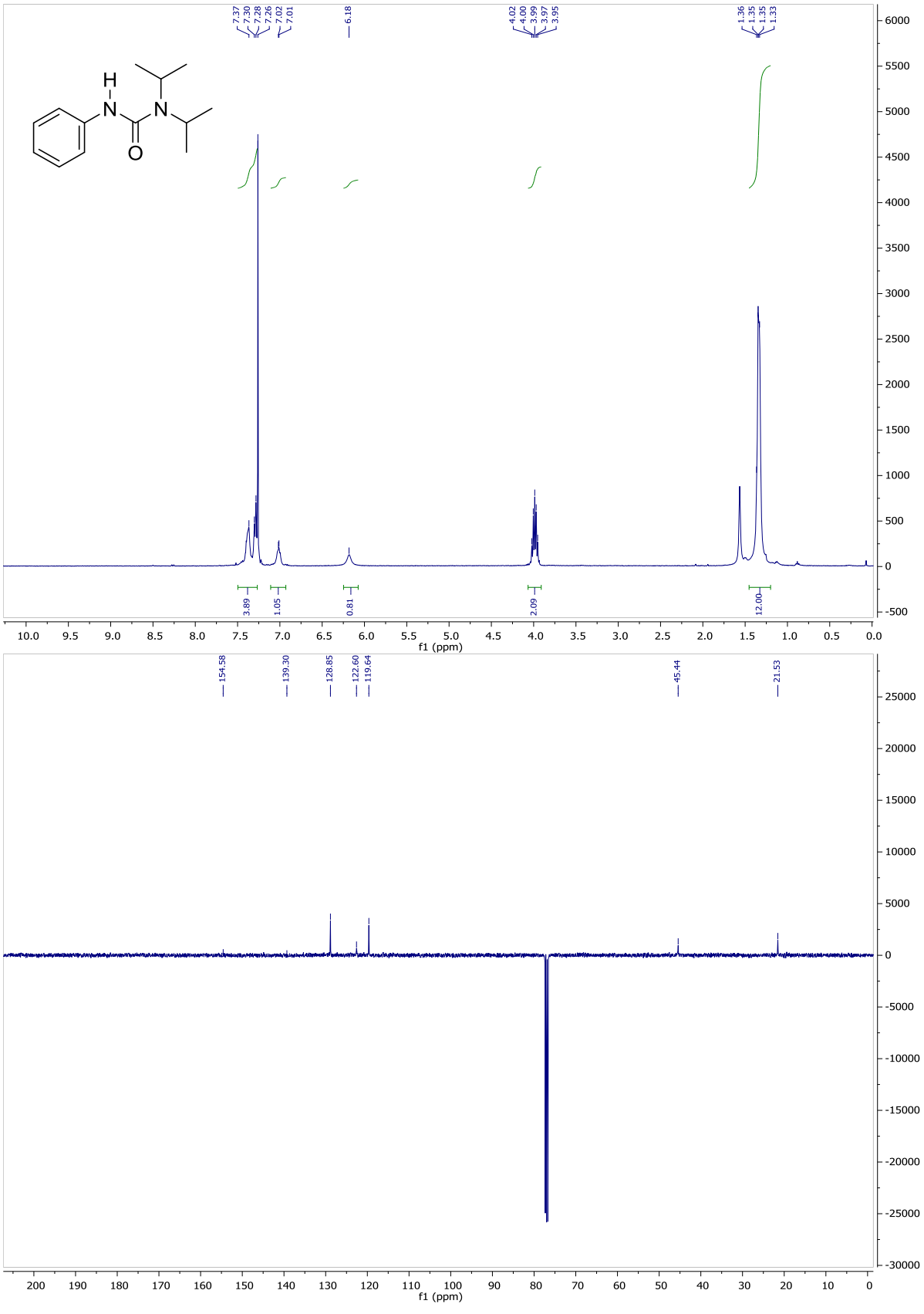

7.46
7.46
7.45
7.45
7.45
7.44
7.44
7.44
7.44
7.43
7.43
7.43
7.42
7.42
7.41
7.41
7.41
7.40
7.40
7.40
7.40
7.26
5.78
4.16
4.14
4.13
4.13
4.11
4.11
3.89
1.21
1.19
1.17
CO2Et
CN
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

S.2.2 Halo/Dihalo-acetamide Derivatives

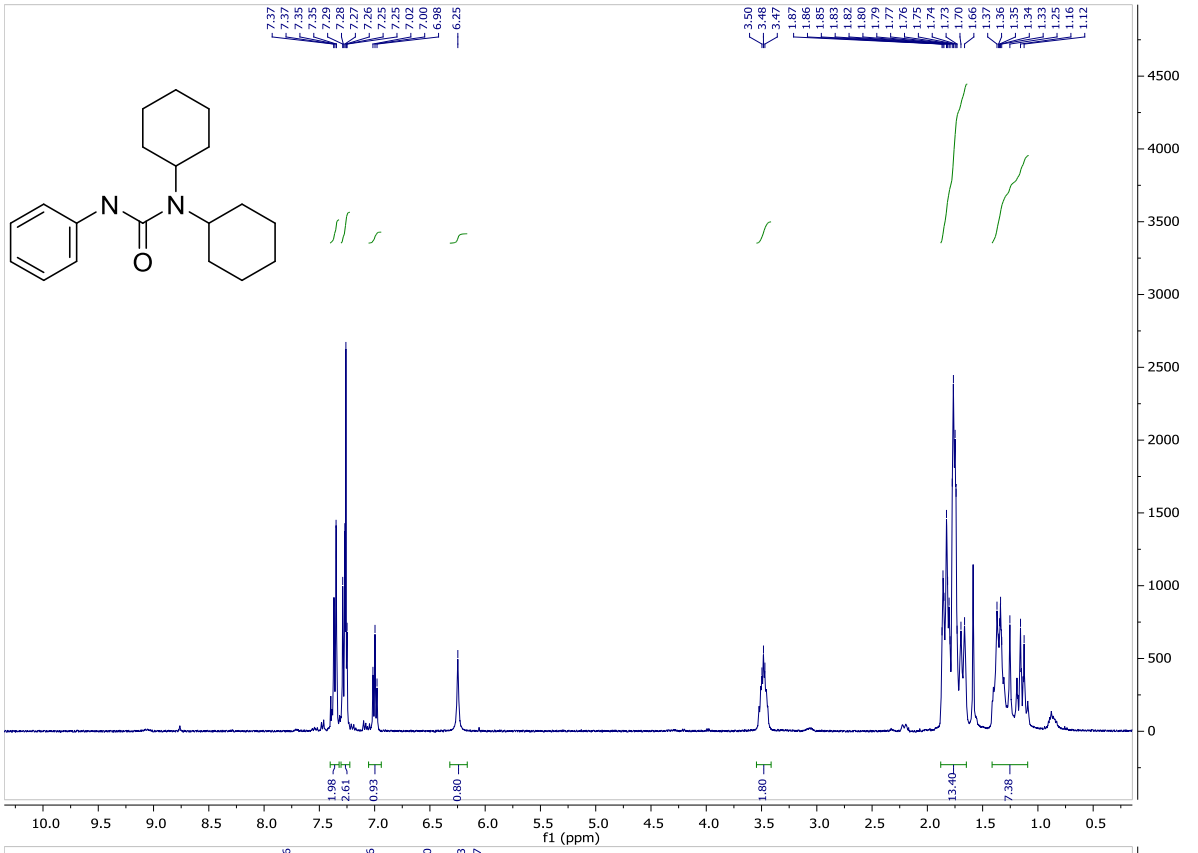
2.118

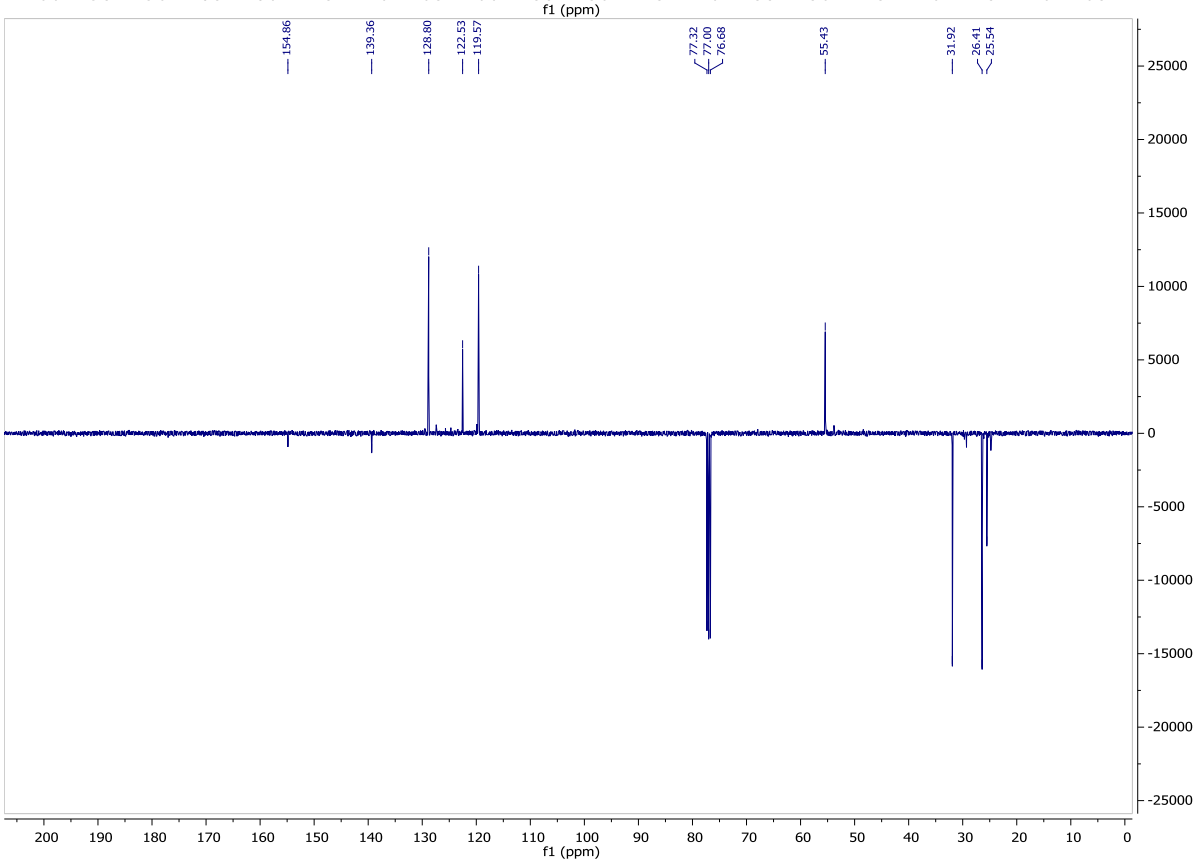


2.119a

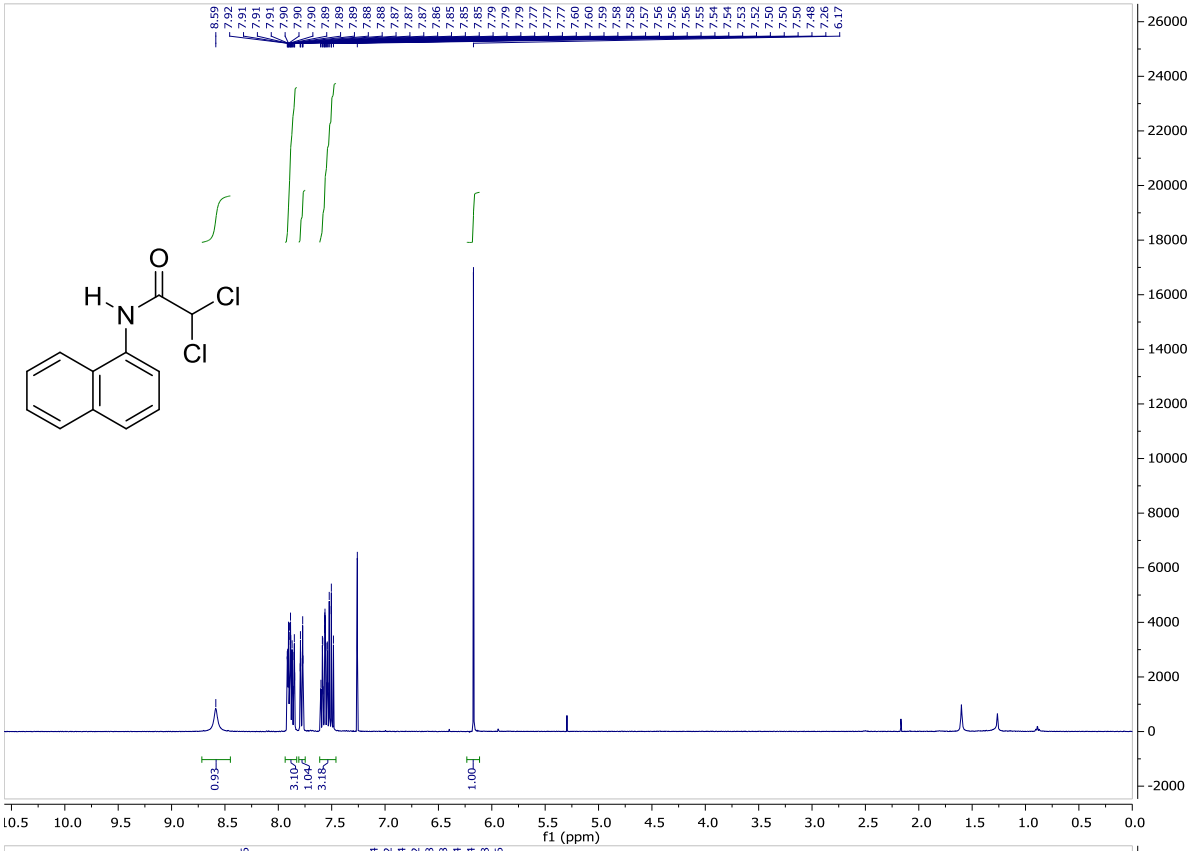

7.37
7.30
7.28
7.26
7.02
7.01
6.18
4.02
4.00
3.99
3.97
3.95
1.36
1.35
1.35
1.33
3.89
1.05
0.81
2.09
12.00
f1 (ppm)
154.58
139.30
128.85
122.60
119.64
45.44
21.53
f1 (ppm)

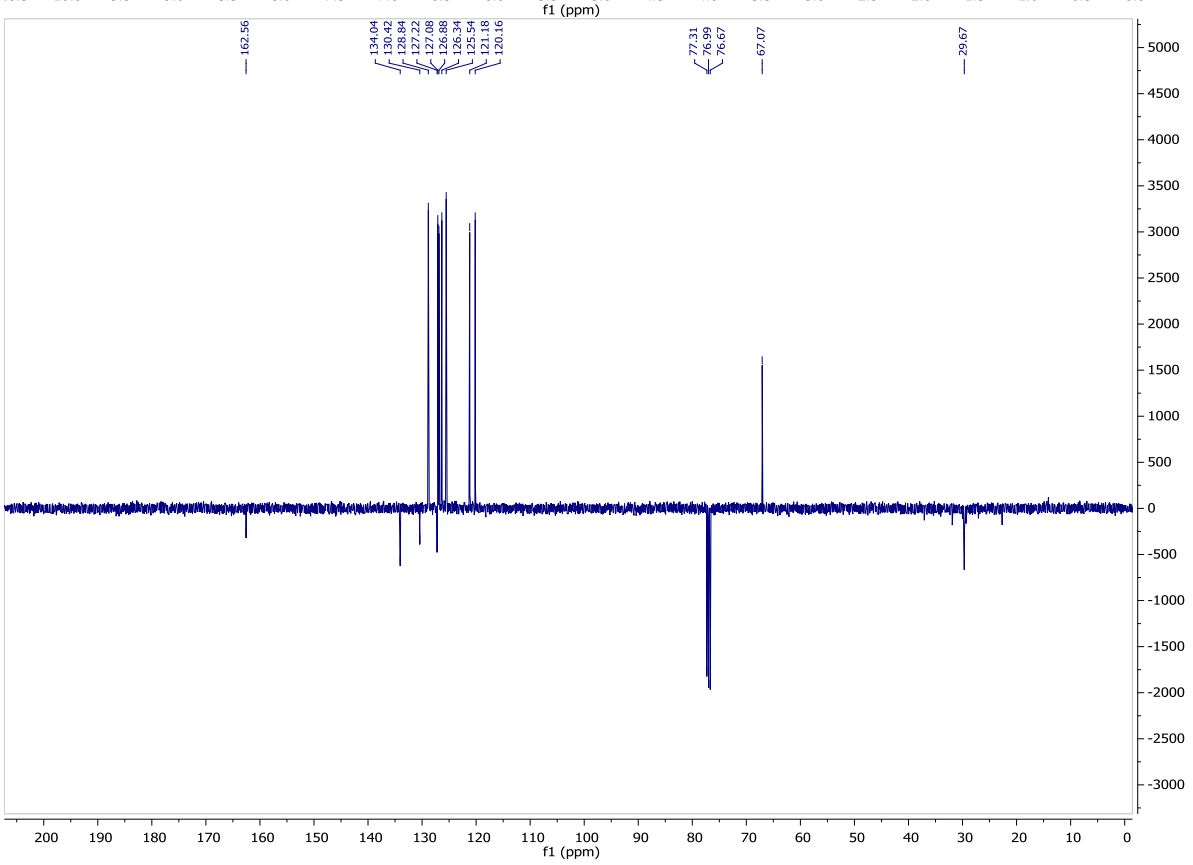
2.119b


7.37
7.37
7.35
7.35
7.29
7.28
7.27
7.26
7.25
7.25
7.02
7.00
6.98
6.25
3.50
3.48
3.47
1.87
1.86
1.85
1.83
1.82
1.80
1.79
1.77
1.76
1.75
1.74
1.73
1.70
1.66
1.37
1.36
1.35
1.34
1.33
1.25
1.16
1.12
1.98
2.61
0.93
0.80
1.80
13.40
7.38
f1 (ppm)

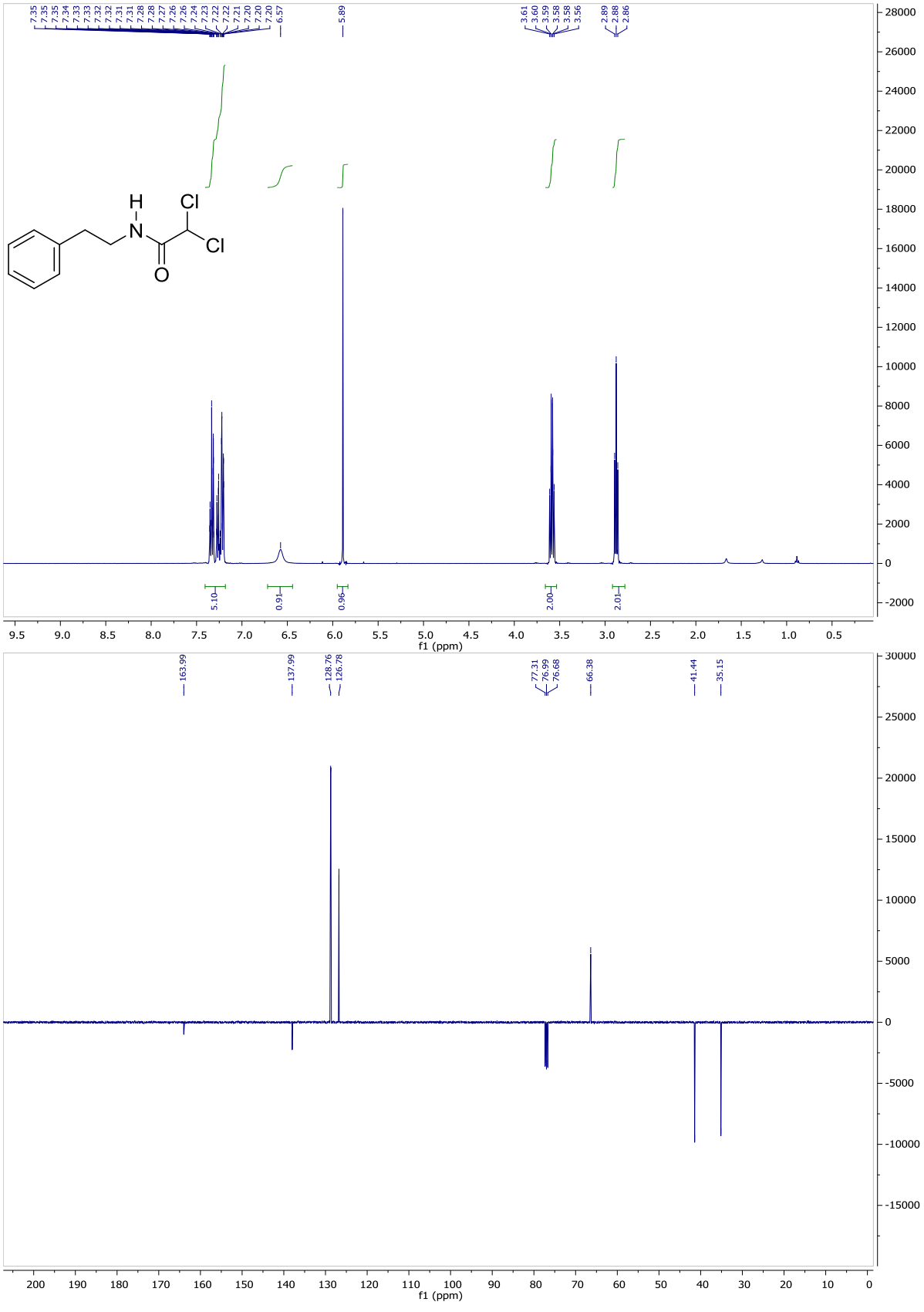

154.86
139.36
128.80
122.53
119.57
77.32
77.00
76.68
55.43
31.92
26.41
25.54
f1 (ppm)

2.121a

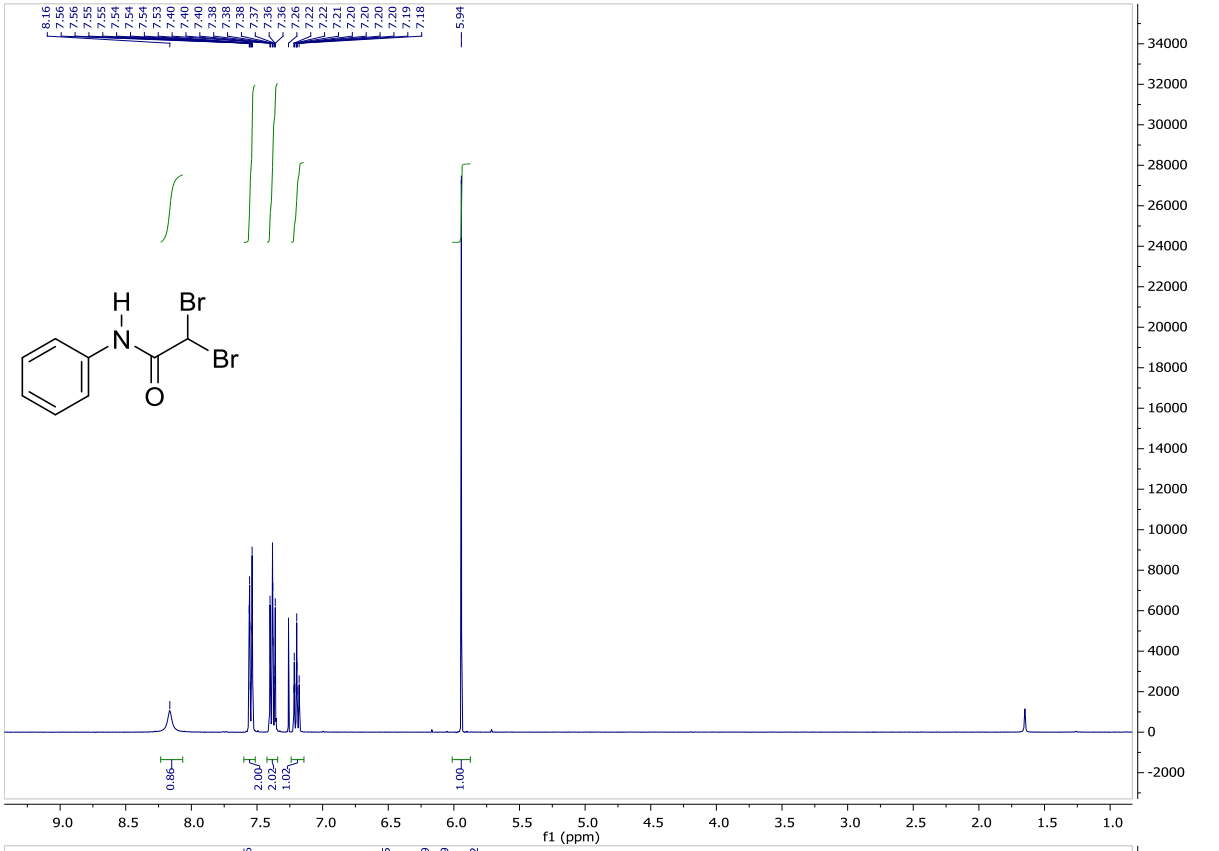

8.59
7.92
7.91
7.91
7.91
7.90
7.90
7.90
7.89
7.89
7.89
7.88
7.88
7.88
7.87
7.87
7.87
7.87
7.86
7.85
7.85
7.85
7.79
7.79
7.79
7.77
7.77
7.77
7.60
7.60
7.59
7.58
7.58
7.57
7.56
7.56
7.56
7.55
7.54
7.54
7.53
7.52
7.50
7.50
7.50
7.48
7.26
6.17
O
H
N
Cl
Cl
0.93
3.10
1.04
3.18
1.00
f1 (ppm)

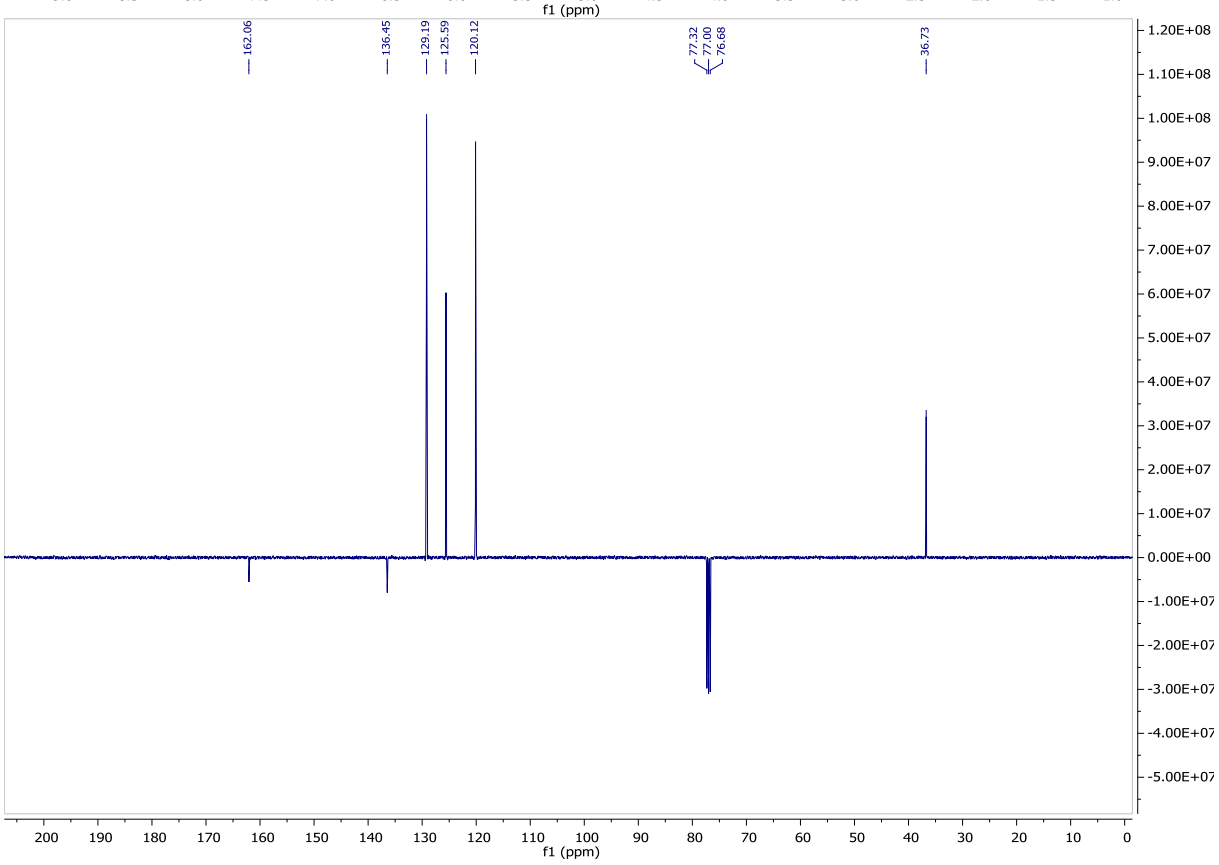

162.56
134.04
130.42
128.84
127.22
127.08
126.88
126.34
125.54
121.18
120.16
77.31
76.99
76.67
67.07
29.67
f1 (ppm)

2.121b

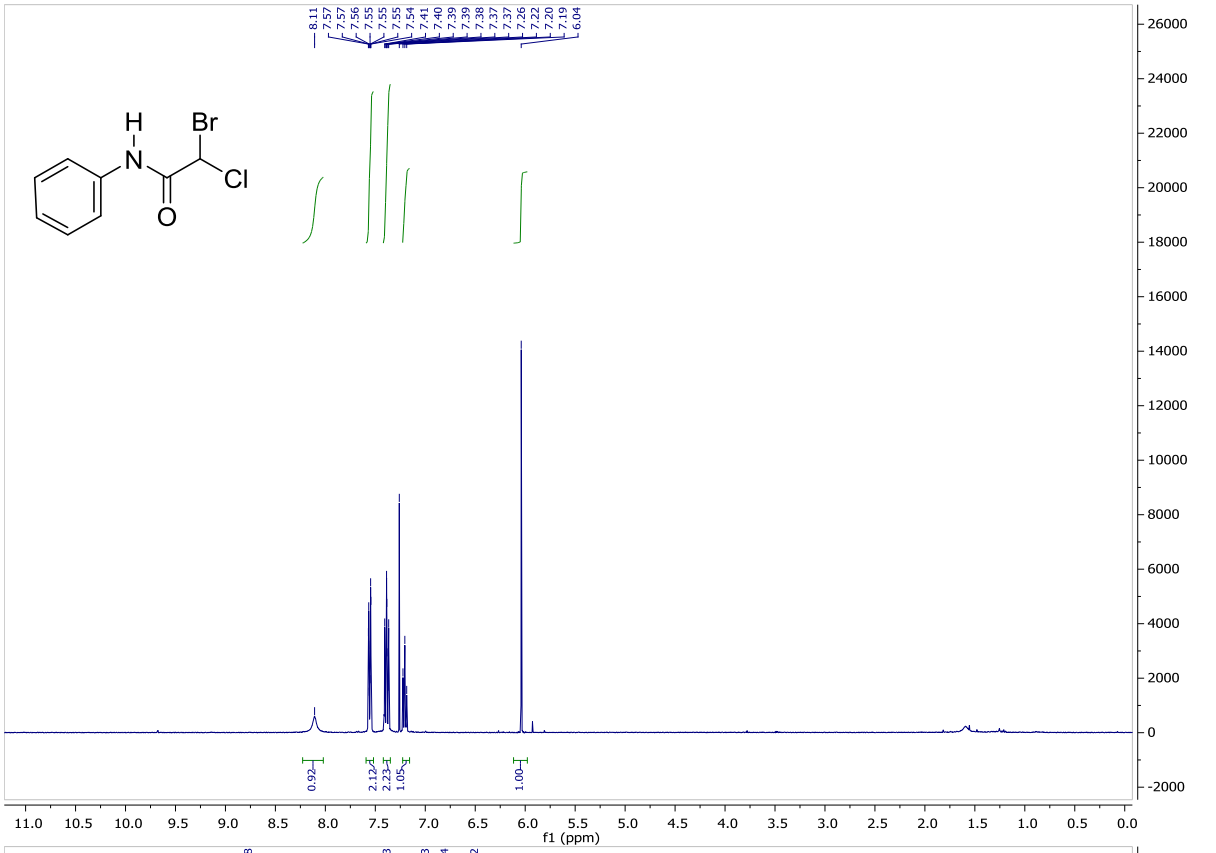

7.35 7.35 7.35 7.34 7.33 7.33 7.32 7.32 7.31 7.31 7.28 7.28 7.27 7.26 7.26 7.24 7.23 7.22 7.22 7.21 7.20 7.20 7.20 6.57
5.89
3.61 3.60 3.59 3.58 3.58 3.56
2.89 2.88 2.86
H
N
Cl
Cl
O
5.10
0.91
0.96
2.00
2.01
f1 (ppm)
163.99
137.99
128.76
126.78
77.31
76.99
76.68
66.38
41.44
35.15
f1 (ppm)

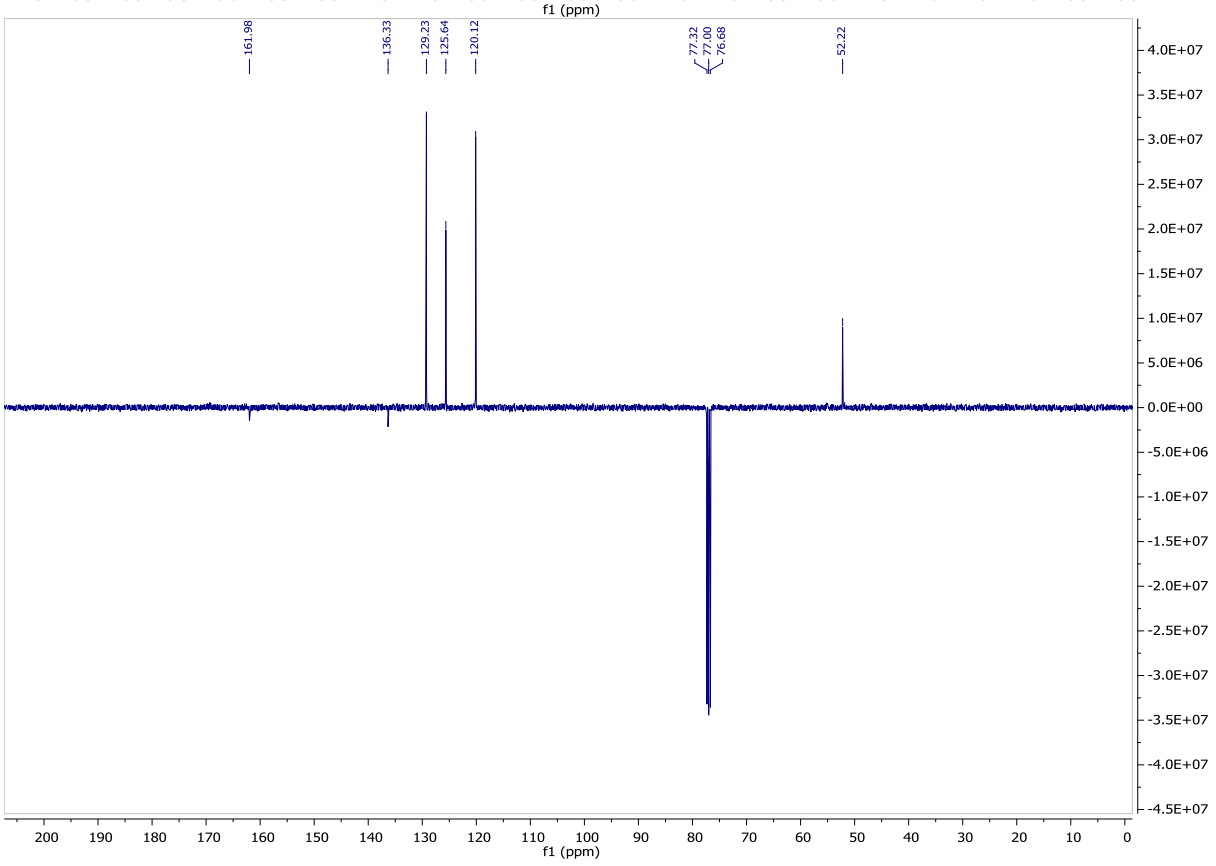
2.121c


8.16
7.56
7.56
7.56
7.55
7.55
7.54
7.54
7.54
7.53
7.40
7.40
7.40
7.38
7.38
7.38
7.37
7.36
7.36
7.26
7.22
7.22
7.21
7.20
7.20
7.20
7.20
7.19
7.18
5.94
H
N
Br
Br
O
0.86
2.00
2.02
1.02
1.00
f1 (ppm)

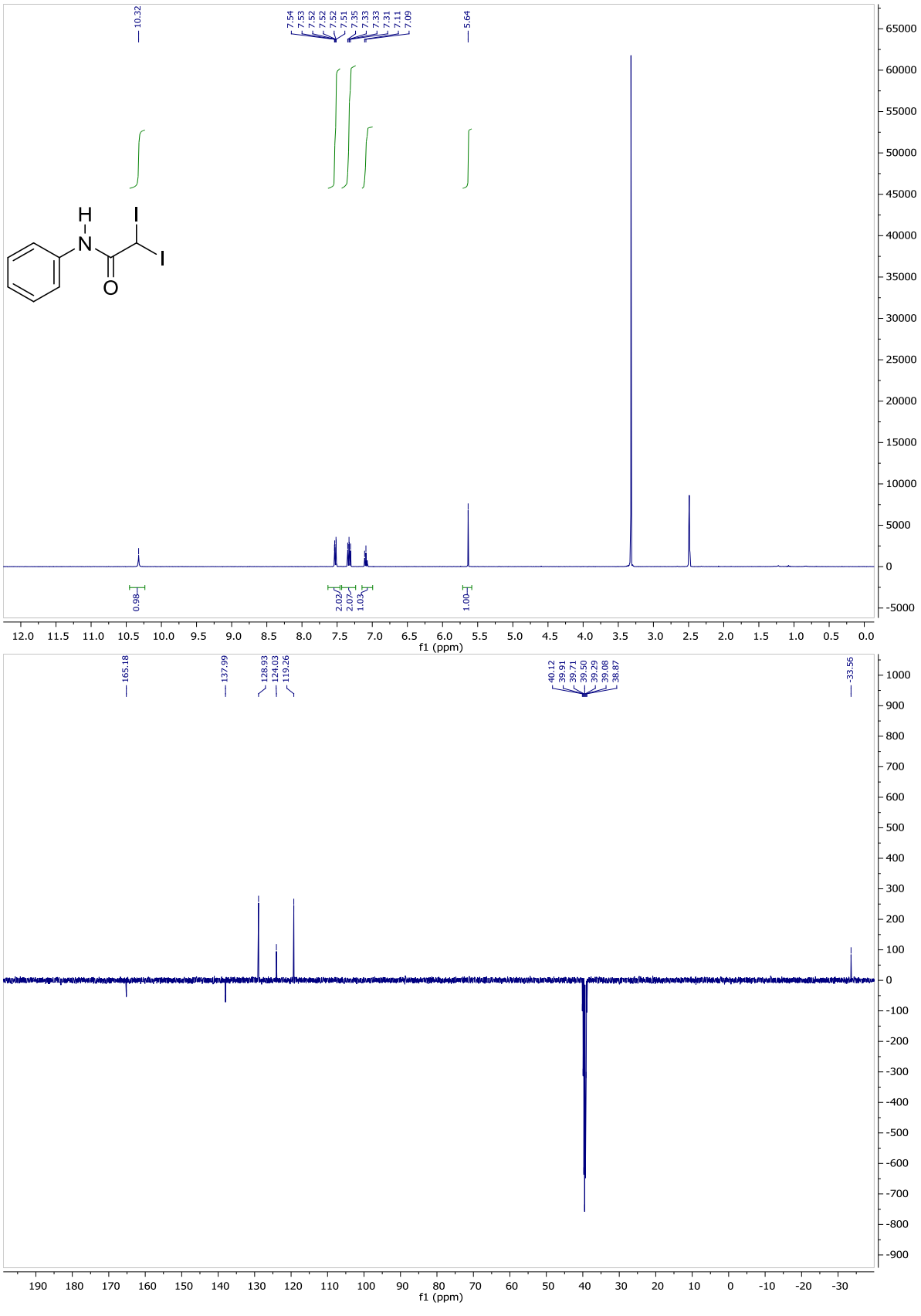

162.06
136.45
129.19
125.59
120.12
77.32
77.00
76.68
36.73
f1 (ppm)

2.121d

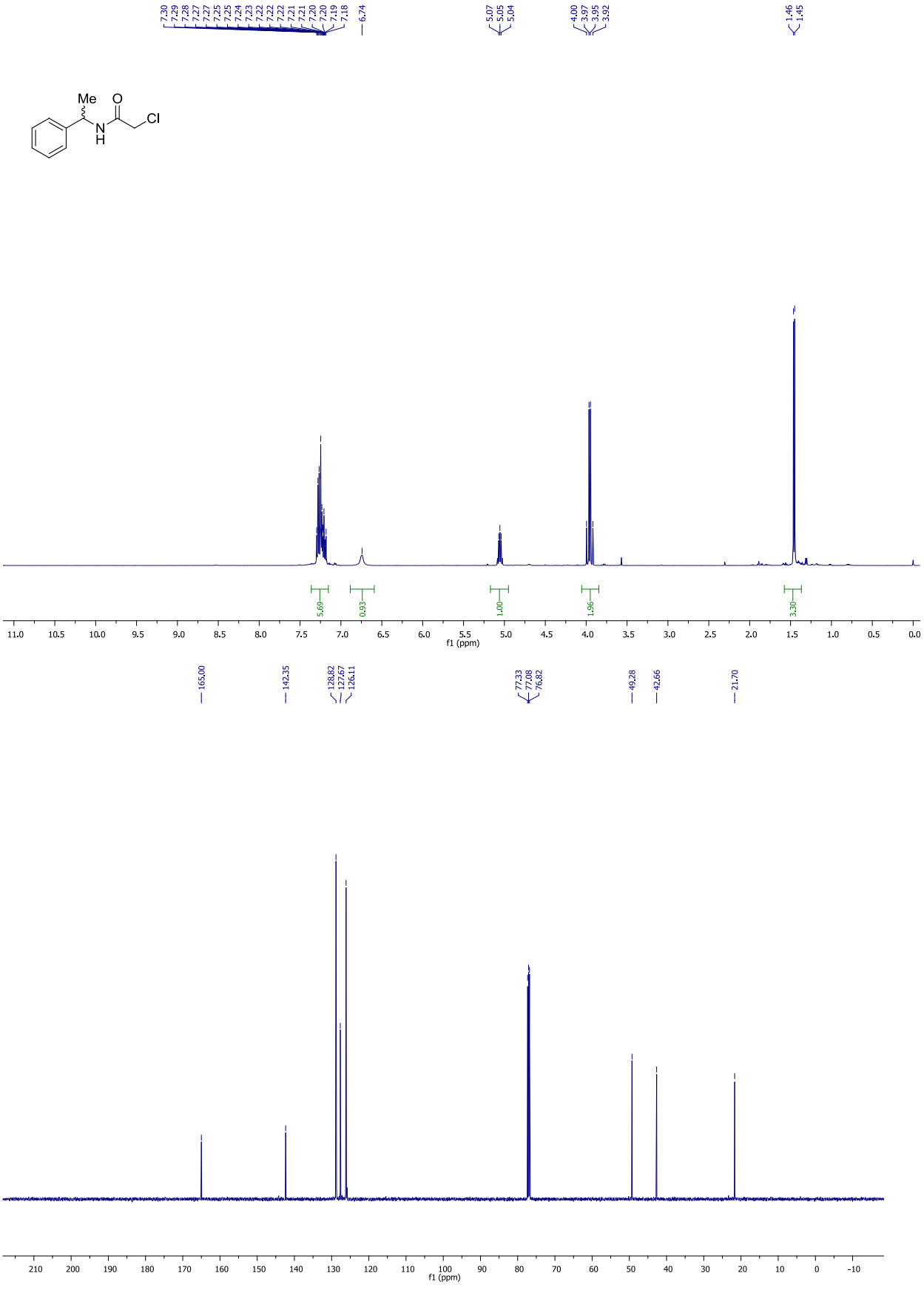

8.11
7.57
7.56
7.55
7.55
7.54
7.41
7.40
7.39
7.38
7.37
7.26
7.22
7.20
7.19
6.04
H
N
Br
Cl
O
0.92
2.12
2.23
1.05
1.00
f1 (ppm)


161.98
136.33
129.23
125.64
120.12
77.32
77.00
76.68
52.22
f1 (ppm)

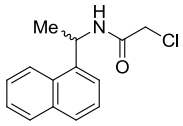
2.121e


10.32
7.54
7.53
7.52
7.52
7.52
7.51
7.35
7.33
7.33
7.31
7.11
7.09
5.64
H
N
O
I
I
0.98
2.02
2.07
1.03
1.00
f1 (ppm)
165.18
137.99
128.93
124.03
119.26
40.12
39.91
39.71
39.50
39.29
39.08
38.87
33.56
f1 (ppm)

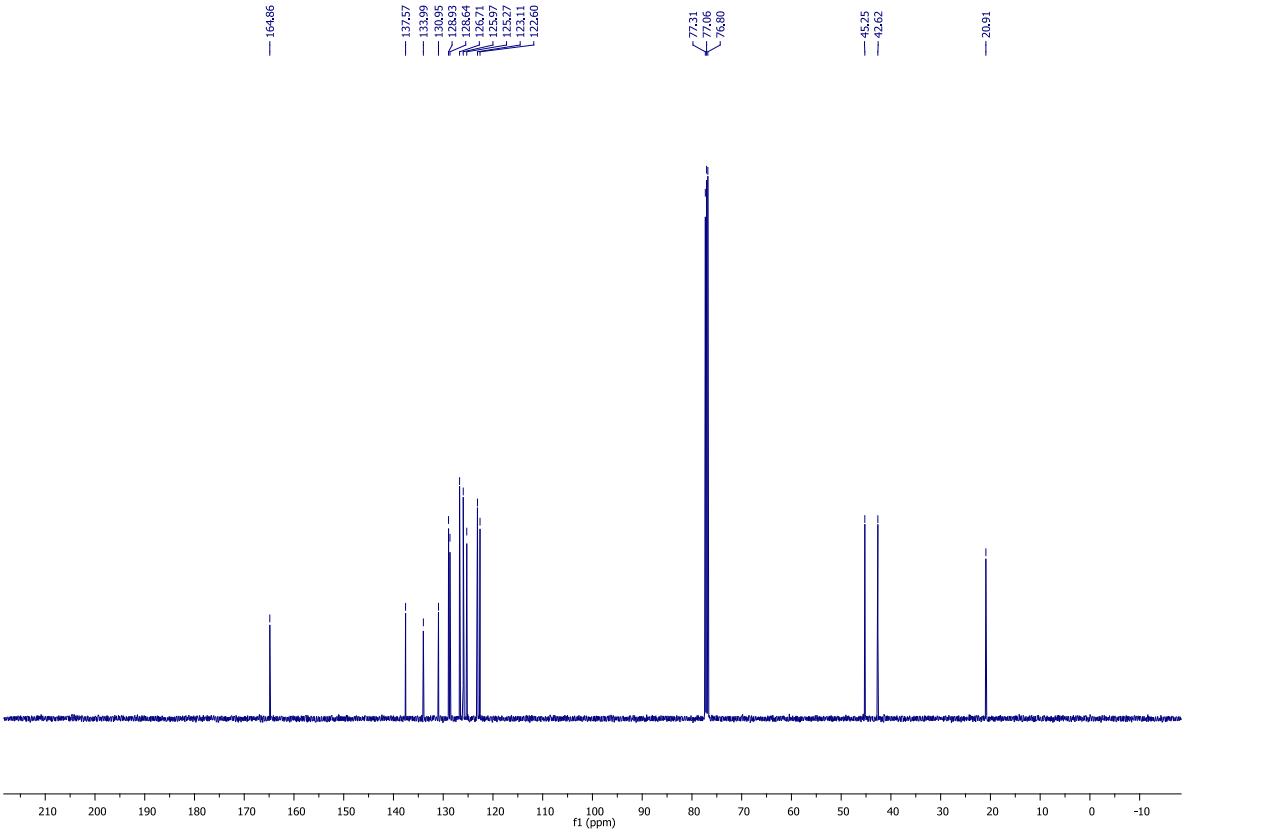
2.122a


7.30
7.29
7.28
7.27
7.27
7.25
7.25
7.24
7.23
7.22
7.22
7.22
7.21
7.21
7.20
7.20
7.19
7.18
6.74
5.07
5.05
5.04
4.00
3.97
3.95
3.92
1.46
1.45
Me
O
N
H
Cl
5.69
0.93
1.00
1.96
3.30
f1 (ppm)
165.00
142.35
128.82
127.67
126.11
77.33
77.08
76.82
49.28
42.66
21.70
f1 (ppm)

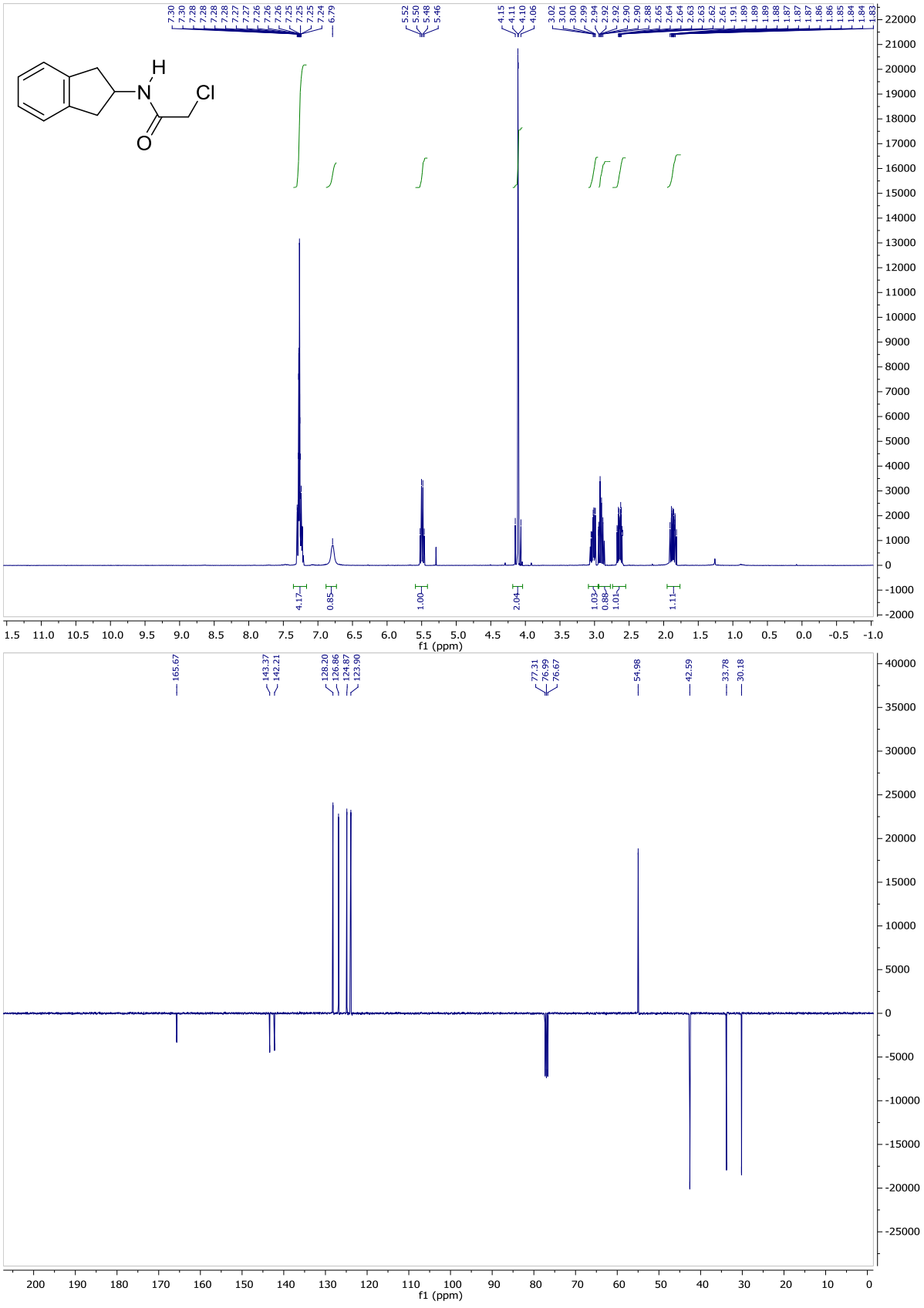
2.122b


Me
H
N
O
Cl

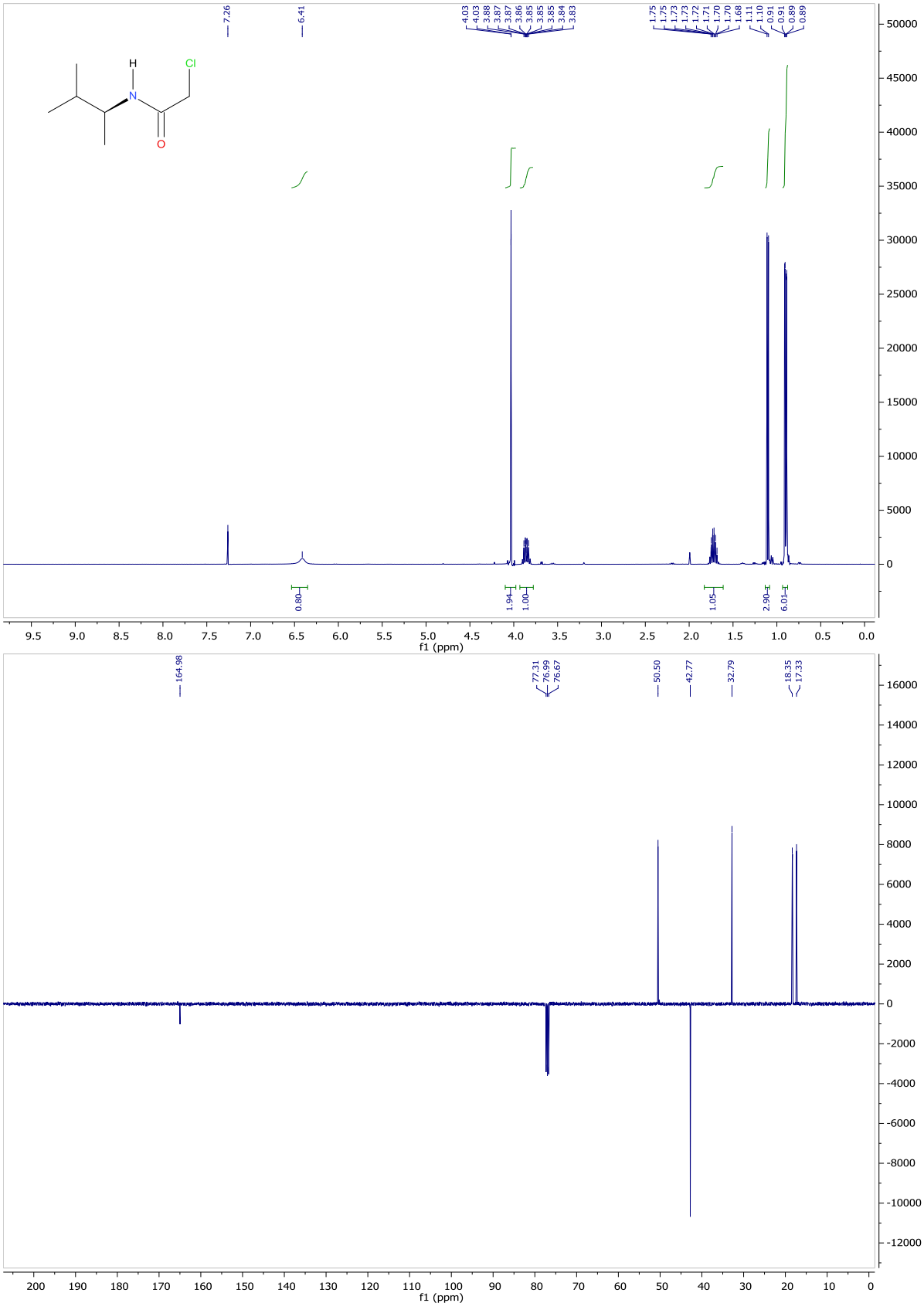
8.00
7.98
7.73
7.39
7.17
6.74
6.73
5.89
5.88
5.86
5.85
5.83
4.02
3.99
3.96
3.93
1.63
1.61
f1 (ppm)


164.86
137.57
133.99
130.95
128.93
128.64
126.71
125.97
125.27
123.11
122.60
77.31
77.06
76.80
45.25
42.62
20.91
f1 (ppm)

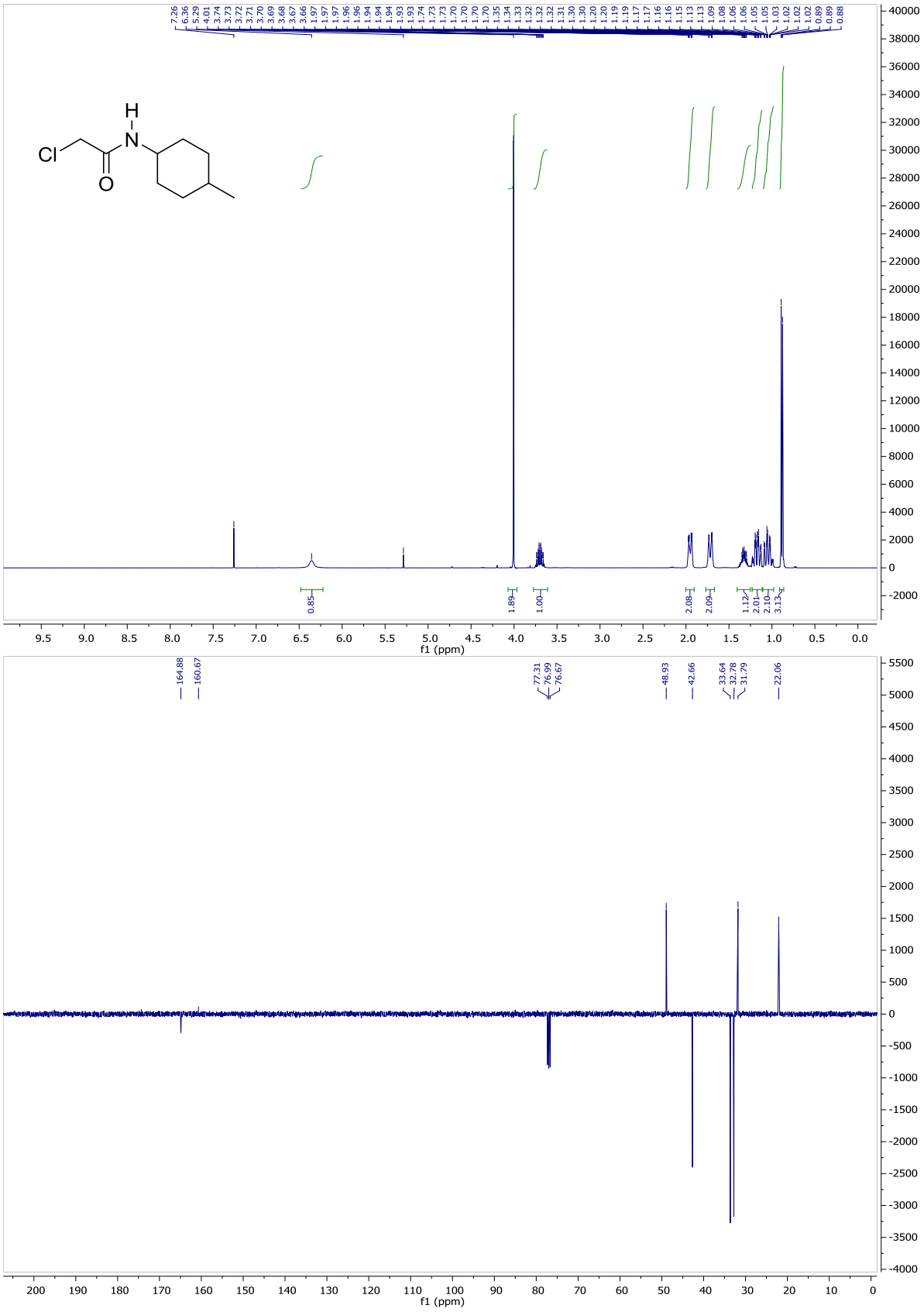
2.123a



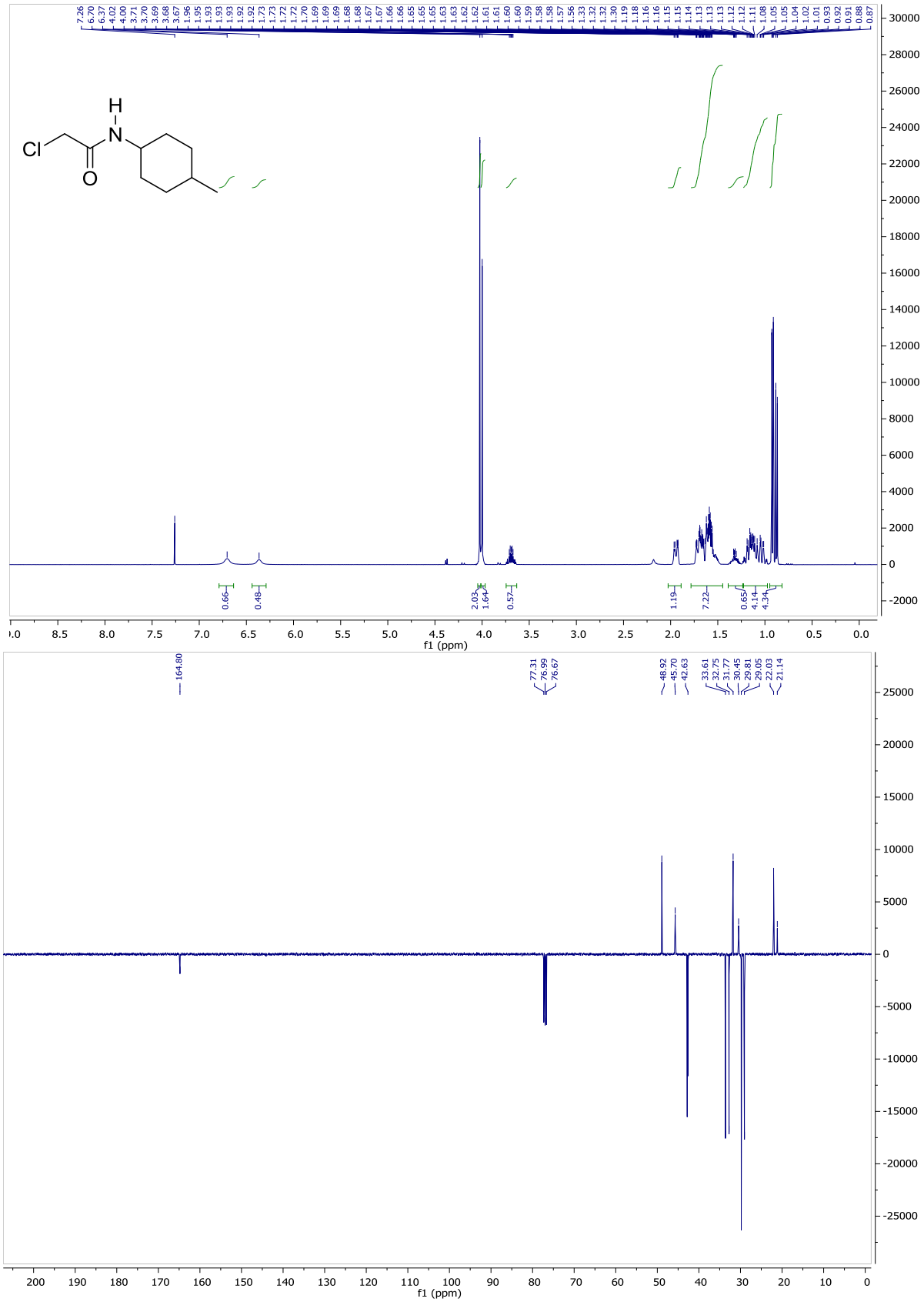
2.123b


7.26
6.41
4.03
4.03
3.88
3.87
3.87
3.86
3.85
3.85
3.85
3.84
3.83
1.75
1.75
1.73
1.73
1.72
1.71
1.70
1.70
1.68
1.11
1.10
0.91
0.91
0.89
0.89
H
N
Cl
O
0.80
1.94
1.00
1.05
2.90
6.01
f1 (ppm)
164.98
77.31
76.99
76.67
50.50
42.77
32.79
18.35
17.33
f1 (ppm)

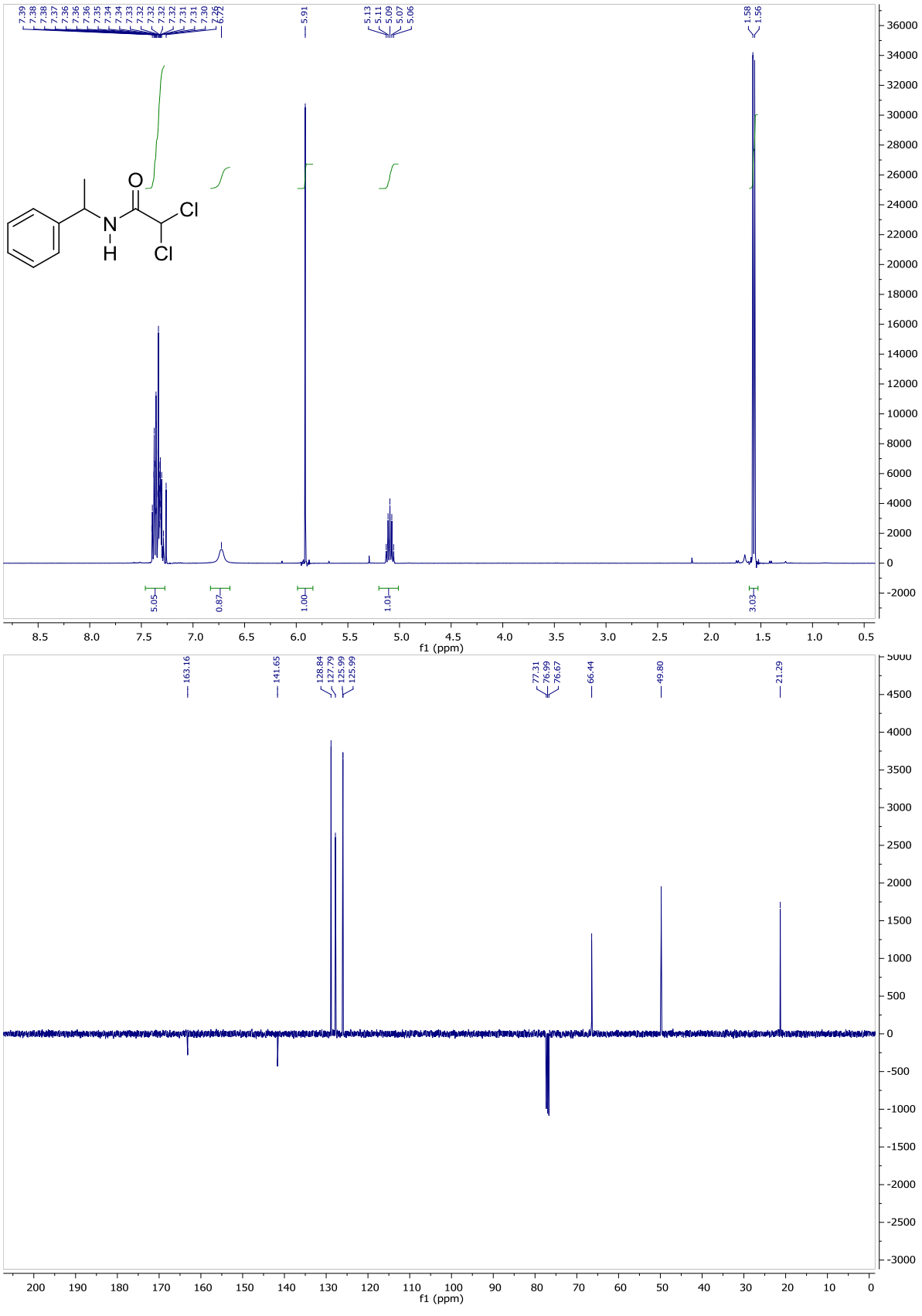
***Trans*-2.123c**


7.26 6.36 5.29 4.01 3.74 3.73 3.72 3.71 3.70 3.69 3.68 3.67 3.66 1.97 1.97 1.97 1.96 1.96 1.94 1.94 1.94 1.93 1.93 1.74 1.73 1.73 1.70 1.70 1.70 1.70 1.35 1.34 1.33 1.32 1.32 1.32 1.31 1.30 1.30 1.20 1.20 1.19 1.19 1.17 1.17 1.16 1.16 1.15 1.13 1.13 1.09 1.08 1.06 1.06 1.05 1.05 1.03 1.02 1.02 1.02 0.89 0.89 0.88
H
N
Cl
O
0.85 1.89 1.00 2.08 2.09 1.12 2.01 2.10 3.13
f1 (ppm)
164.88 160.67 77.31 76.99 76.67 48.93 42.66 33.64 32.78 31.79 22.06
f1 (ppm)

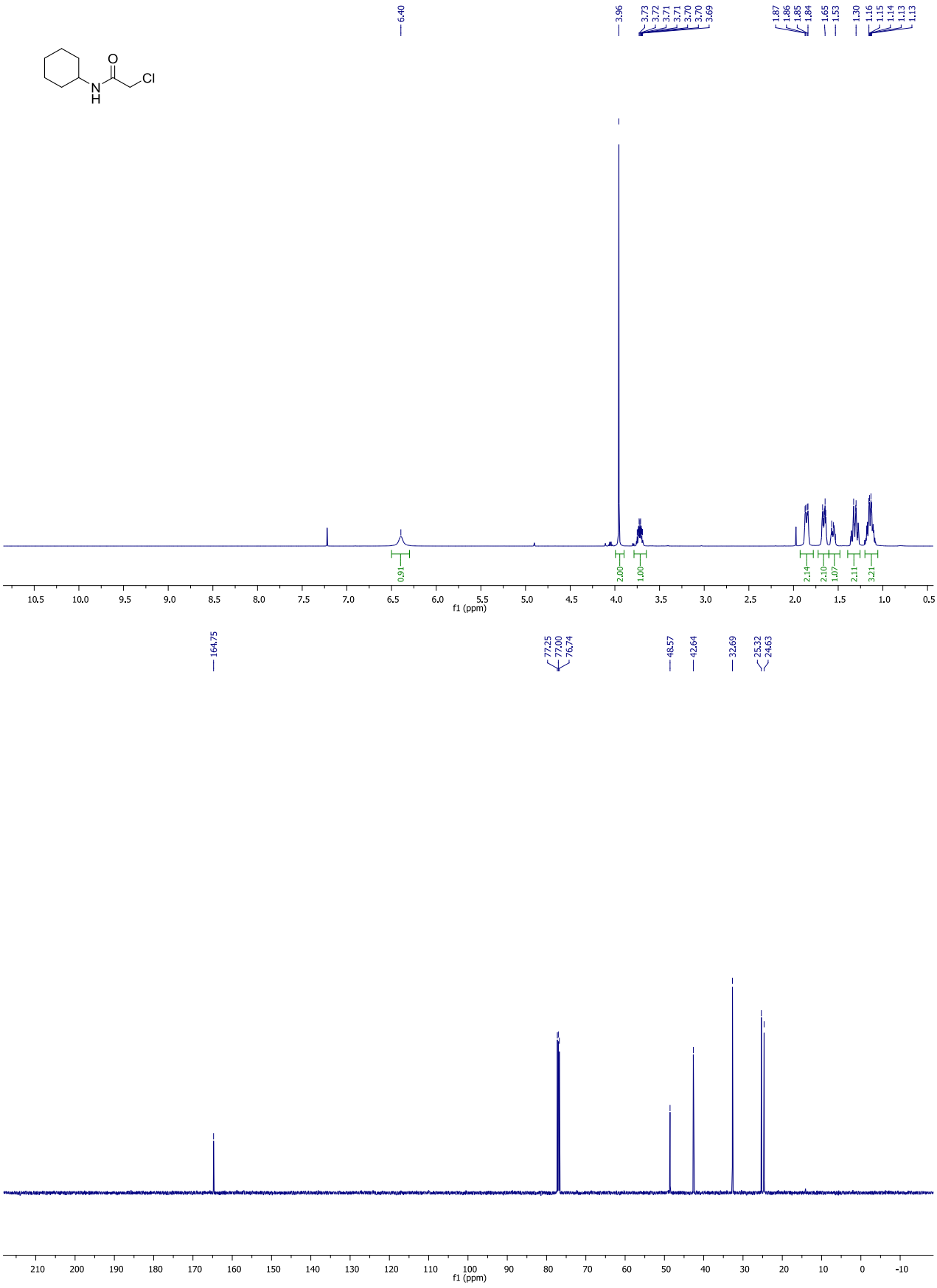
***cis/trans*- 2.123c**



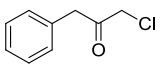
2.123d


7.39
7.38
7.38
7.37
7.36
7.36
7.36
7.35
7.34
7.34
7.33
7.32
7.32
7.32
7.32
7.31
7.31
7.30
7.26
6.72
5.91
5.13
5.11
5.09
5.07
5.06
1.58
1.56
O
N
H
Cl
Cl
5.05
0.87
1.00
1.01
3.03
f1 (ppm)
163.16
141.65
128.84
127.79
125.99
125.99
77.31
76.99
76.67
66.44
49.80
21.29
f1 (ppm)

2.124


6.40
3.96
3.73
3.72
3.71
3.71
3.70
3.70
3.69
1.87
1.86
1.85
1.84
1.65
1.53
1.30
1.16
1.15
1.14
1.13
1.13
O
N
H
Cl
0.91
2.00
1.00
2.14
2.10
1.07
2.11
3.21
f1 (ppm)
164.75
77.25
77.00
76.74
48.57
42.64
32.69
25.32
24.63
f1 (ppm)

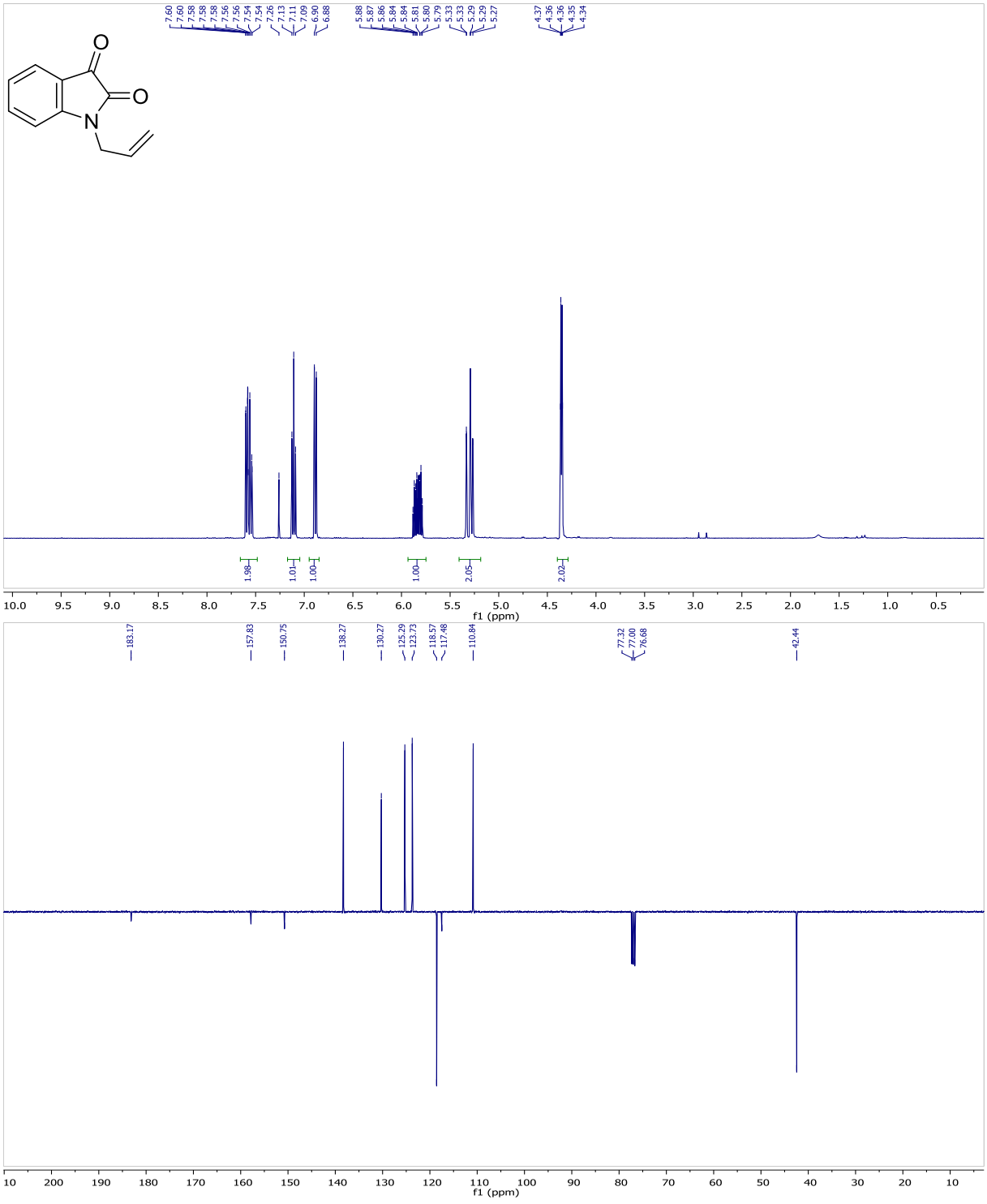
2.125


Cl
O

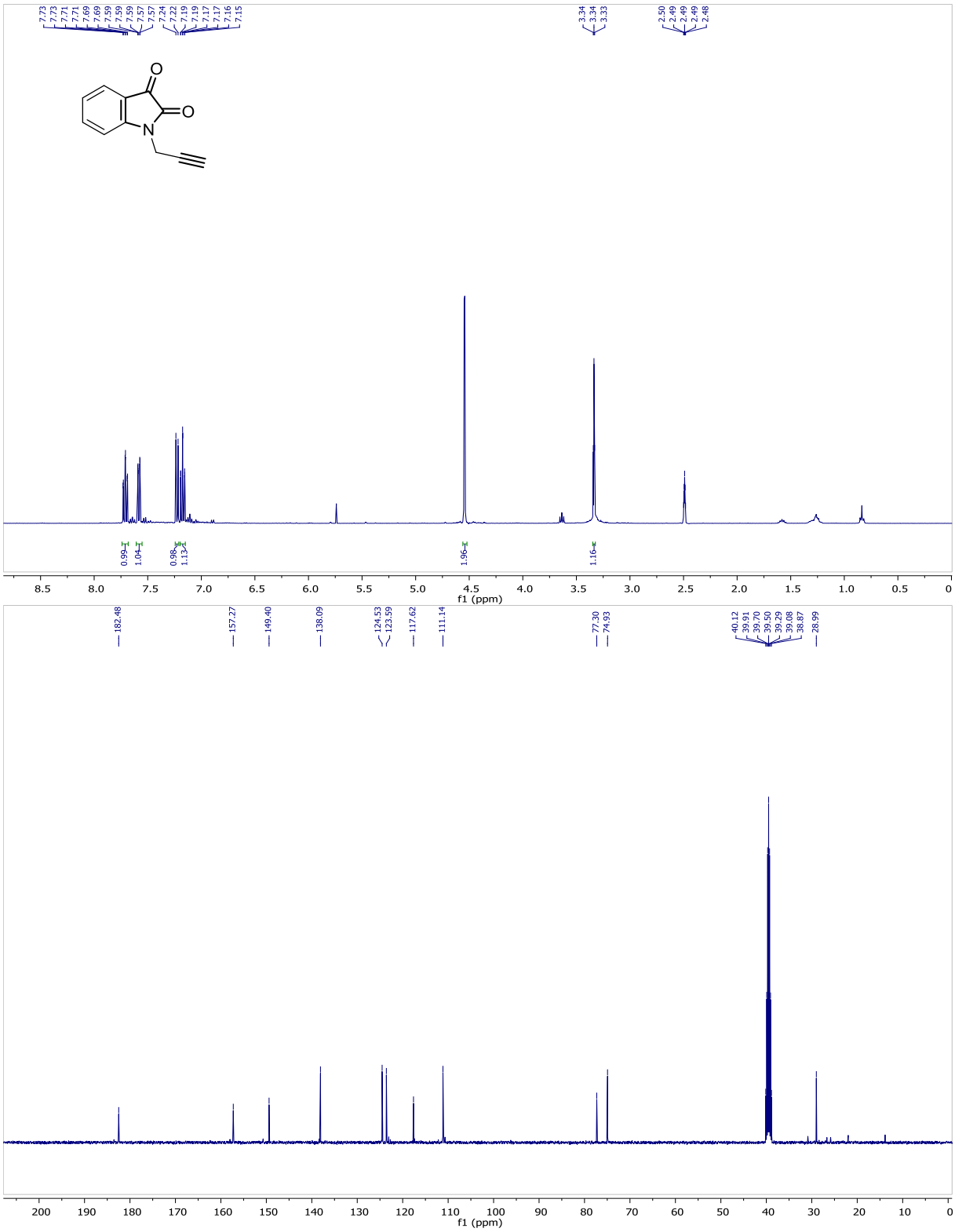
7.38
7.36
7.36
7.35
7.35
7.32
7.32
7.31
7.27
7.25
7.25
7.23
4.13
3.91
3.77
1.18
2.00
1.98
f1 (ppm)
199.92
132.79
129.42
128.95
127.52
77.25
77.00
76.75
47.68
46.85
f1 (ppm)

S.2.3 Isatin Derivatives

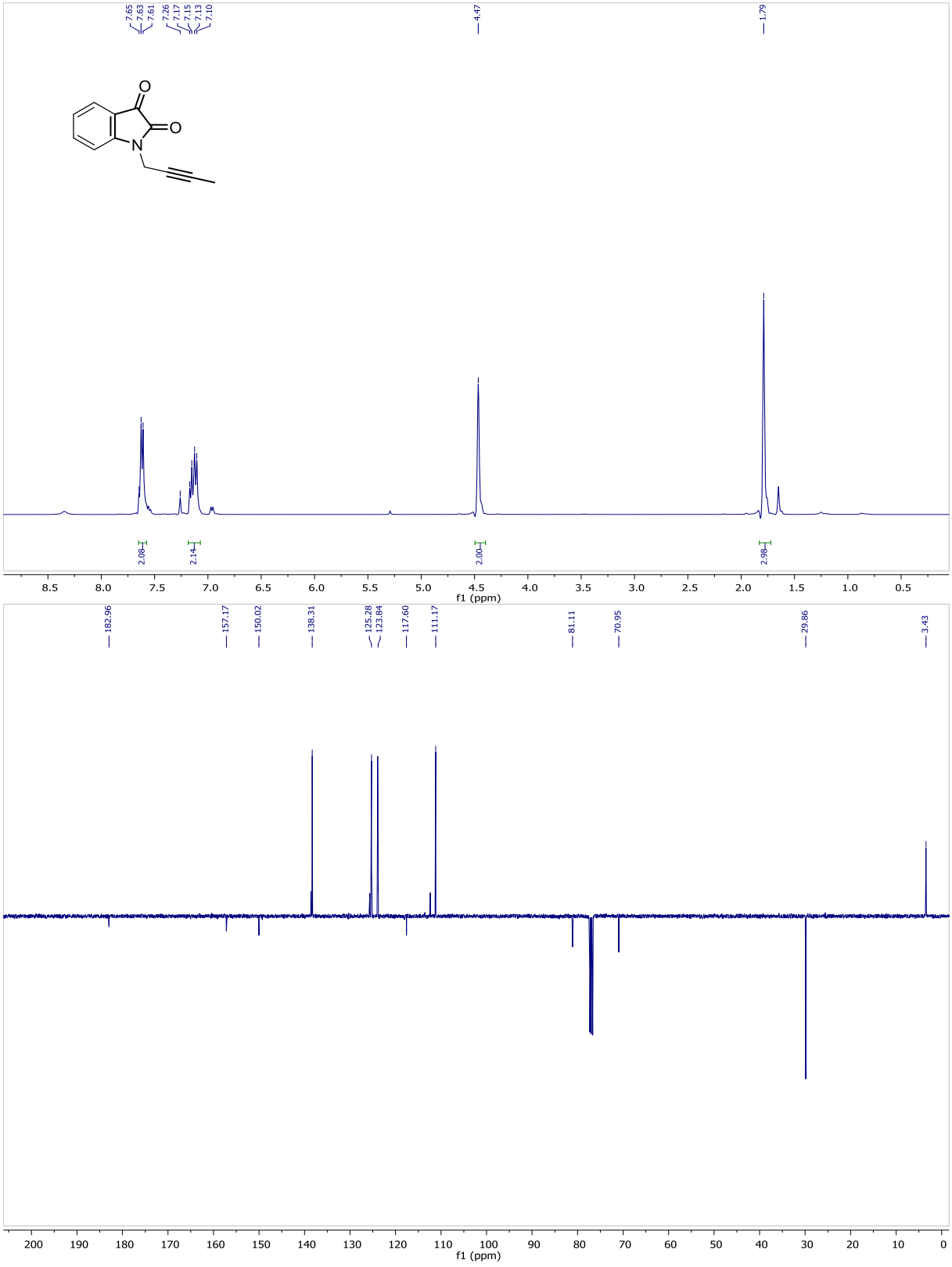
2.127a



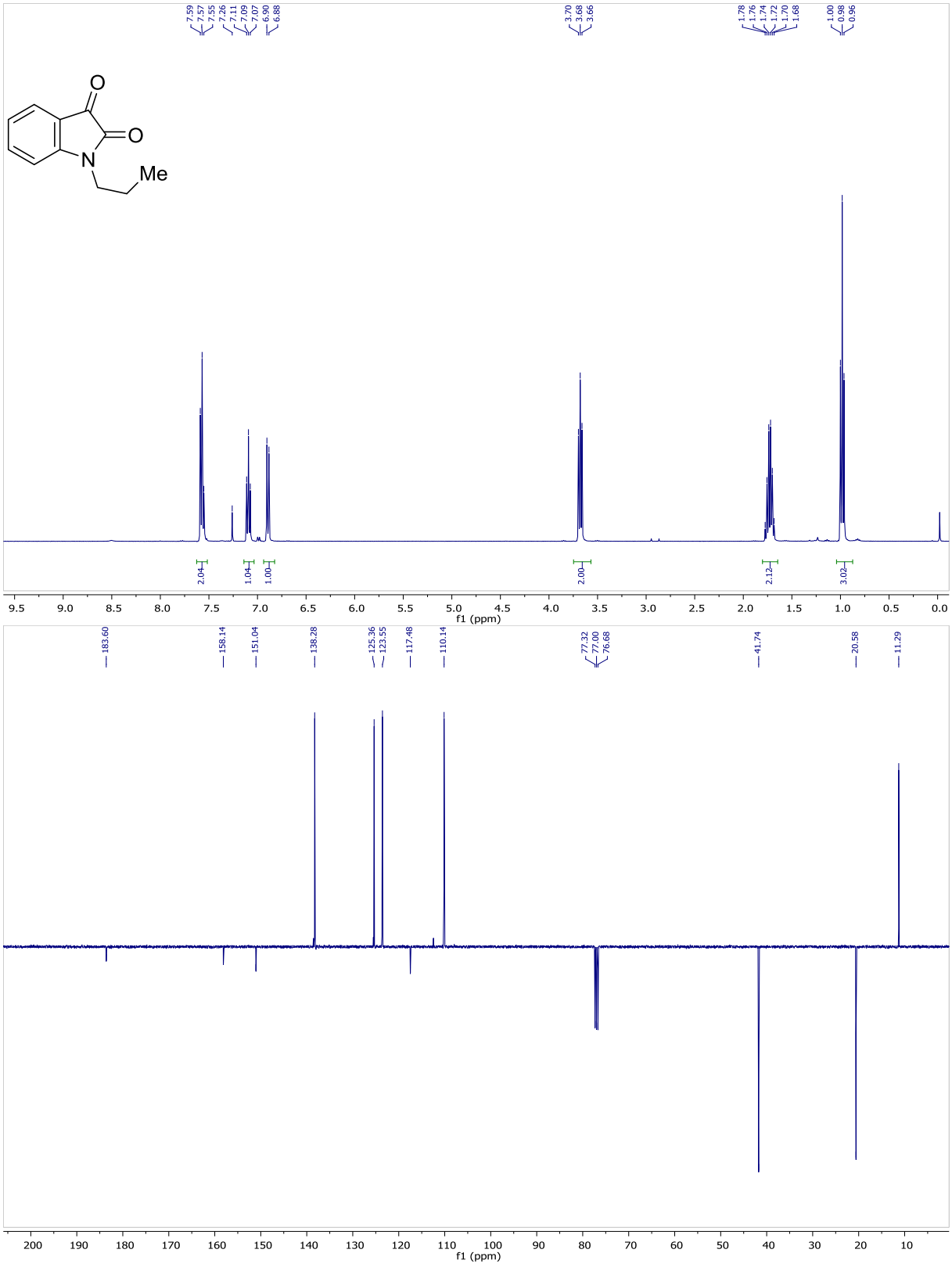
2.127b


7.73
7.73
7.71
7.71
7.69
7.69
7.59
7.59
7.59
7.57
7.57
7.24
7.22
7.19
7.19
7.17
7.17
7.16
7.15
3.34
3.34
3.33
2.50
2.49
2.49
2.49
2.48
O
O
N
0.99
1.04
0.98
1.13
1.96
1.16
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)
182.48
157.27
149.40
138.09
124.53
123.59
117.62
111.14
77.30
74.93
40.12
39.91
39.70
39.50
39.29
39.08
38.87
28.99
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

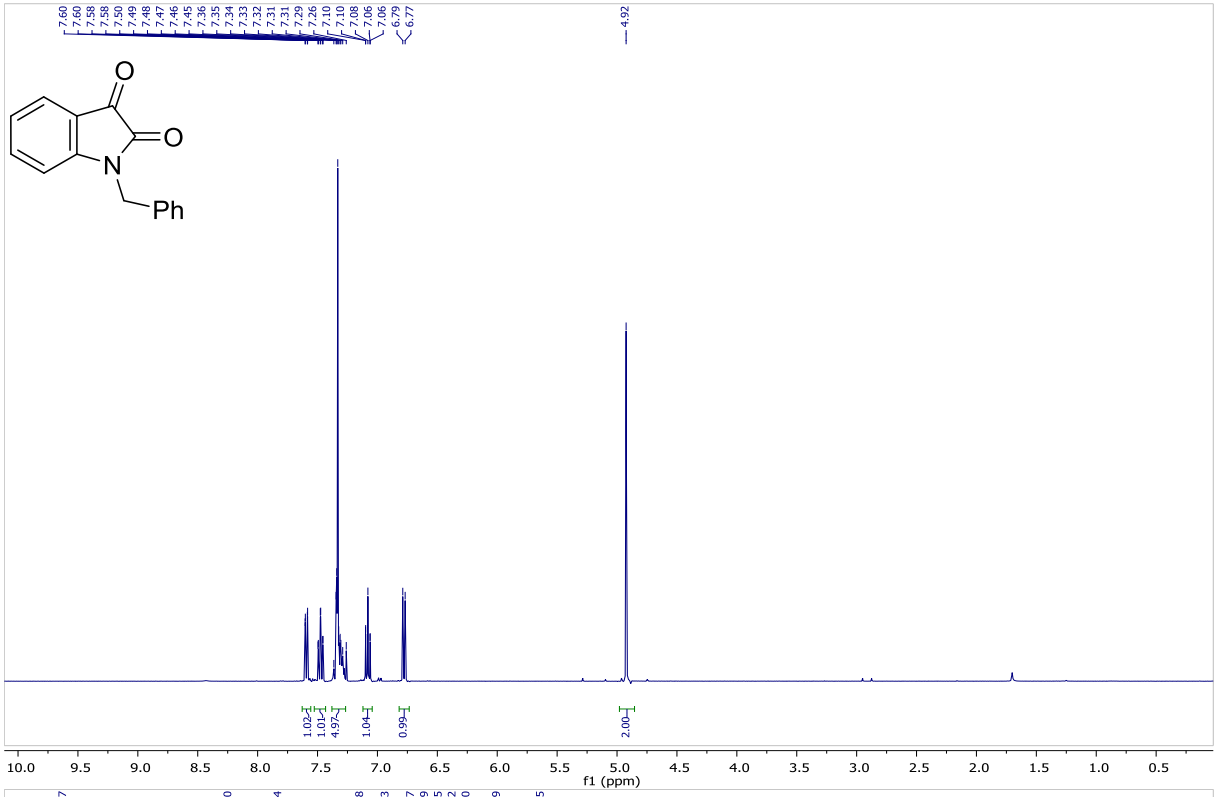
2.127c

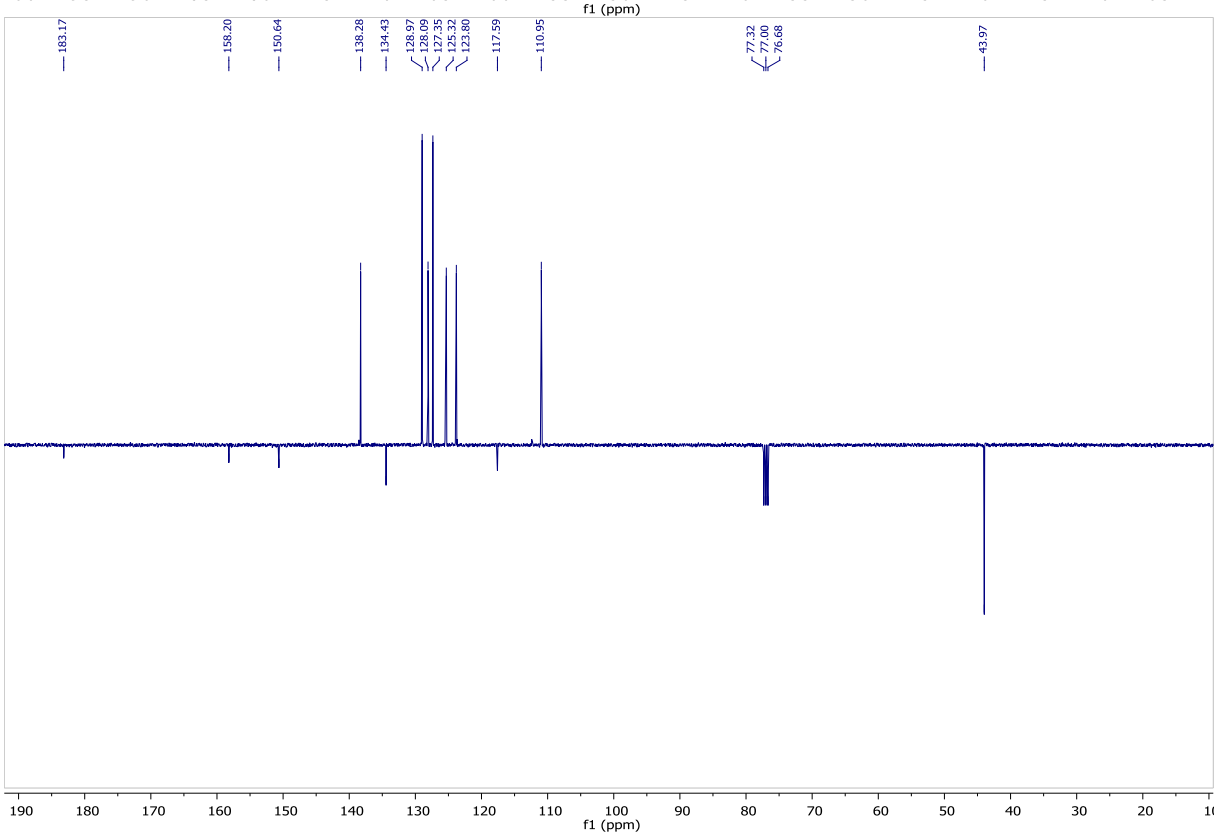

7.65
7.63
7.61
7.26
7.17
7.15
7.13
7.10
4.47
1.79
O
O
N
2.08
2.14
2.00
2.98
f1 (ppm)
182.96
157.17
150.02
138.31
125.28
123.84
117.60
111.17
81.11
70.95
29.86
3.43
f1 (ppm)

2.127d

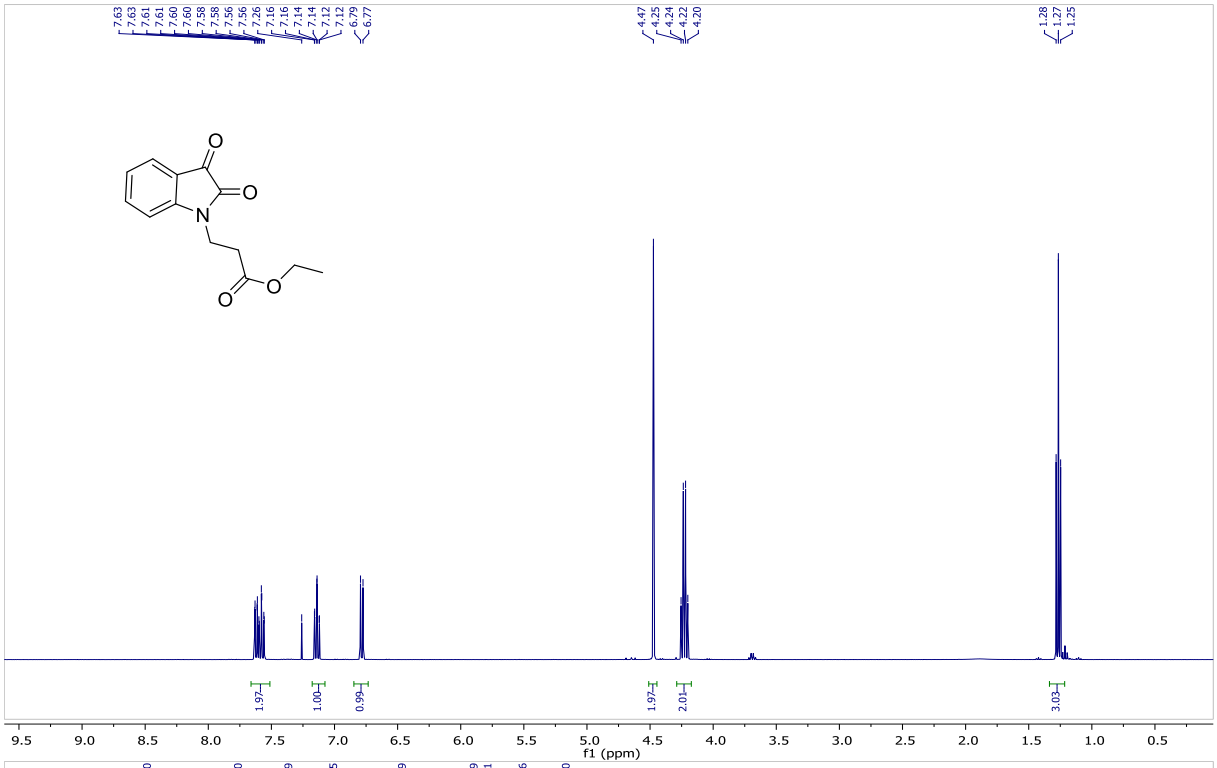

7.59
7.57
7.55
7.26
7.11
7.09
7.07
6.90
6.88
3.70
3.68
3.66
1.78
1.76
1.74
1.72
1.70
1.68
1.00
0.98
0.96
O
O
N
Me
2.04
1.04
1.00
2.00
2.12
3.02
f1 (ppm)
183.60
158.14
151.04
138.28
125.36
123.55
117.48
110.14
77.32
77.00
76.68
41.74
20.58
11.29
f1 (ppm)

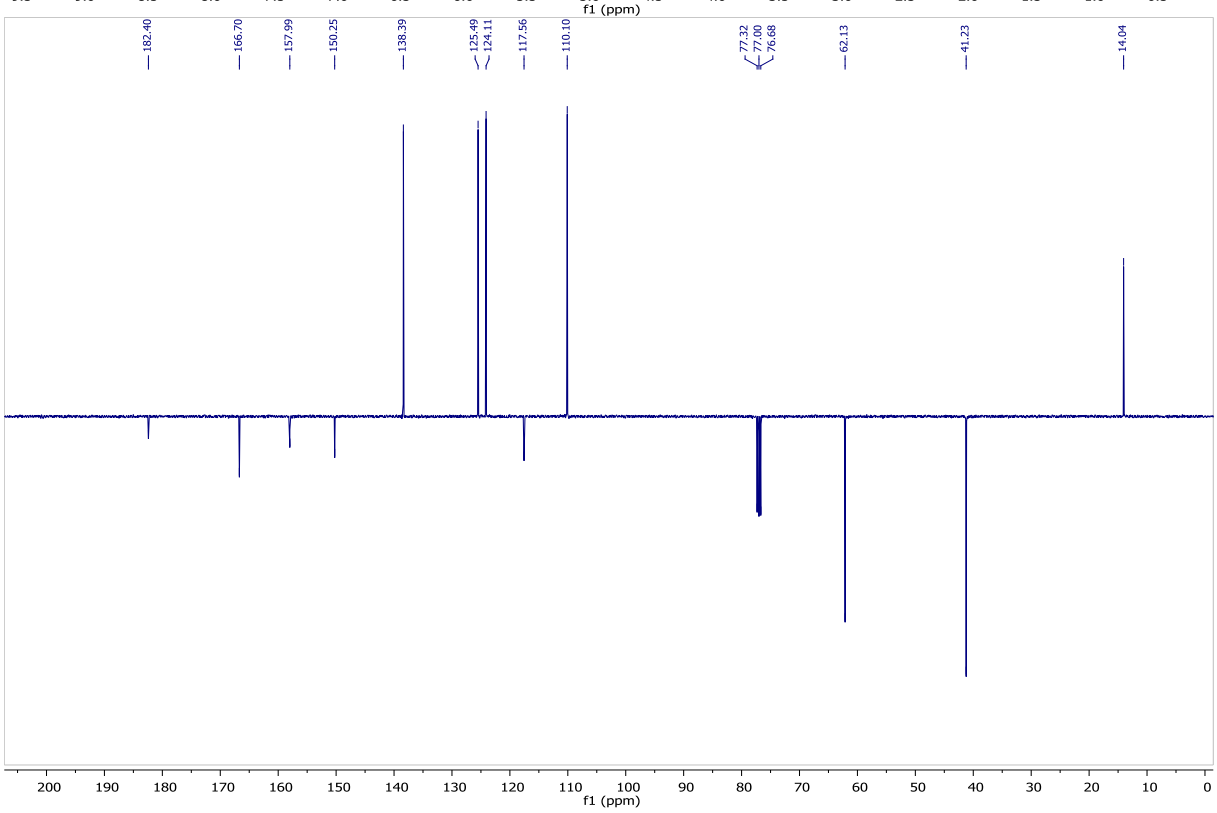
2.127e


7.60
7.60
7.58
7.58
7.50
7.48
7.47
7.46
7.45
7.36
7.35
7.34
7.33
7.32
7.31
7.31
7.29
7.26
7.10
7.08
7.06
7.06
6.79
6.77
4.92
O
O
N
Ph
1.02
1.01
4.97
1.04
0.99
2.00
f1 (ppm)

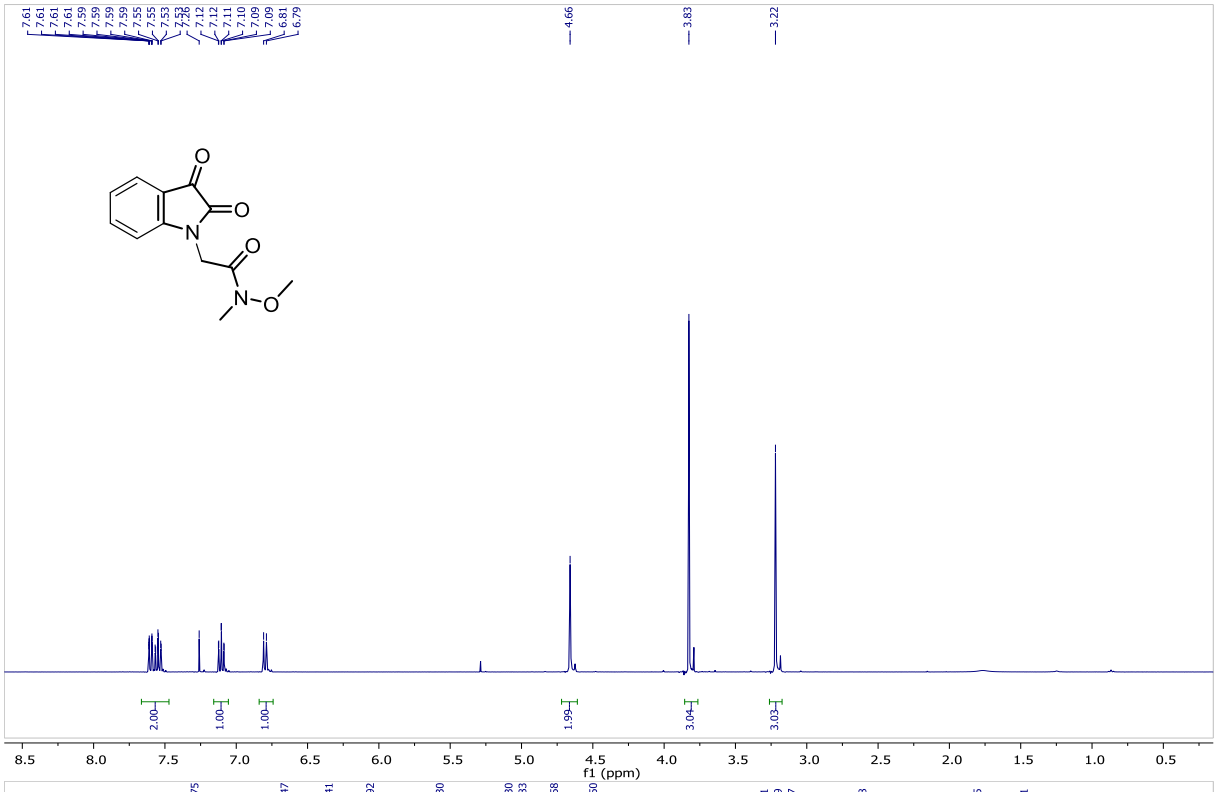

183.17
158.20
150.64
138.28
134.43
128.97
128.09
127.35
125.32
123.80
117.59
110.95
77.32
77.00
76.68
43.97
f1 (ppm)

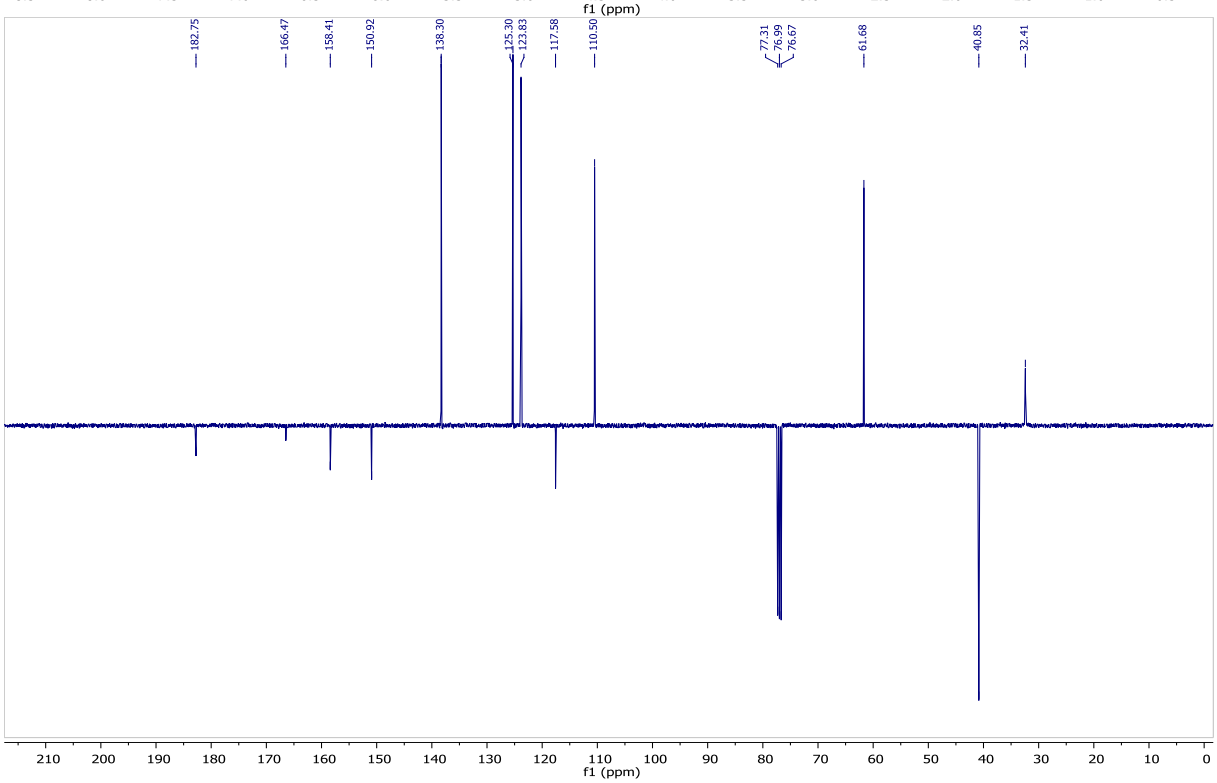
2.127f


7.63
7.63
7.61
7.61
7.60
7.60
7.58
7.58
7.56
7.56
7.26
7.16
7.14
7.14
7.12
7.12
6.79
6.77
4.47
4.25
4.24
4.22
4.20
1.28
1.27
1.25
O
O
N
O
O
1.97
1.00
0.99
1.97
2.01
3.03
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

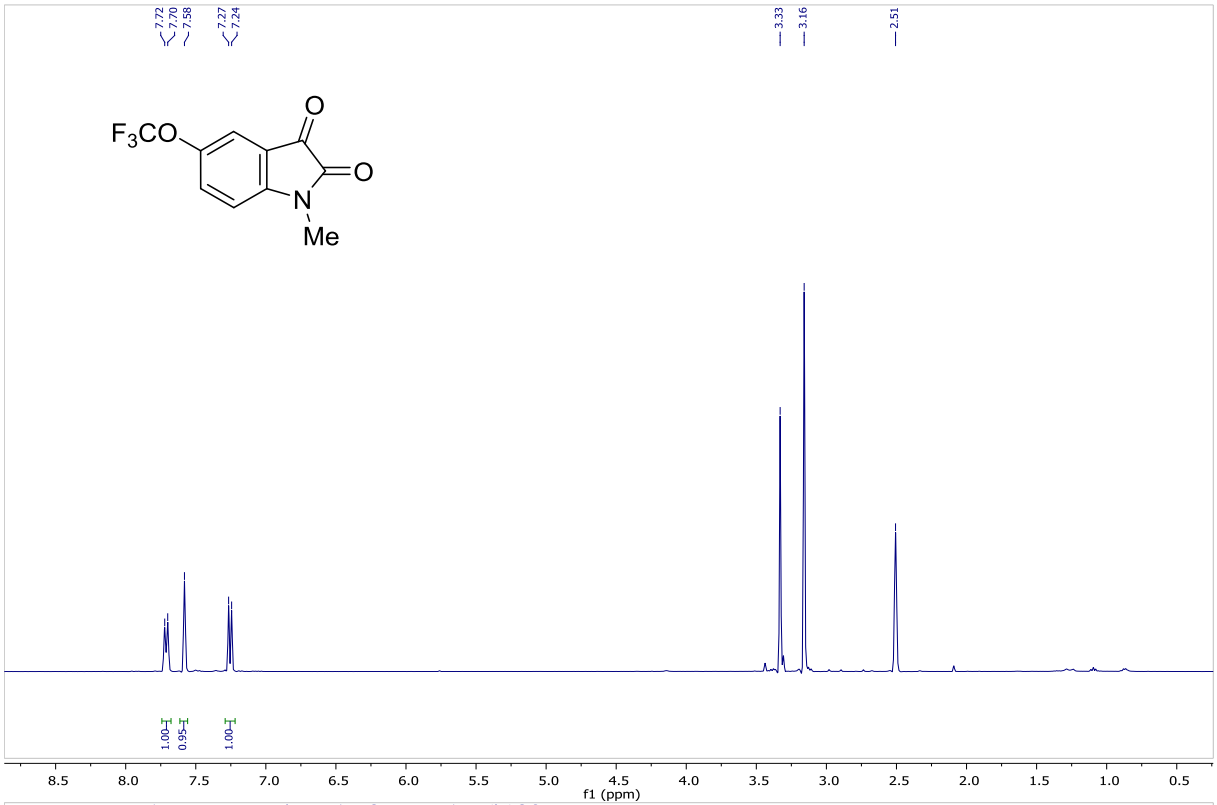

182.40
166.70
157.99
150.25
138.39
125.49
124.11
117.56
110.10
77.32
77.00
76.68
62.13
41.23
14.04
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

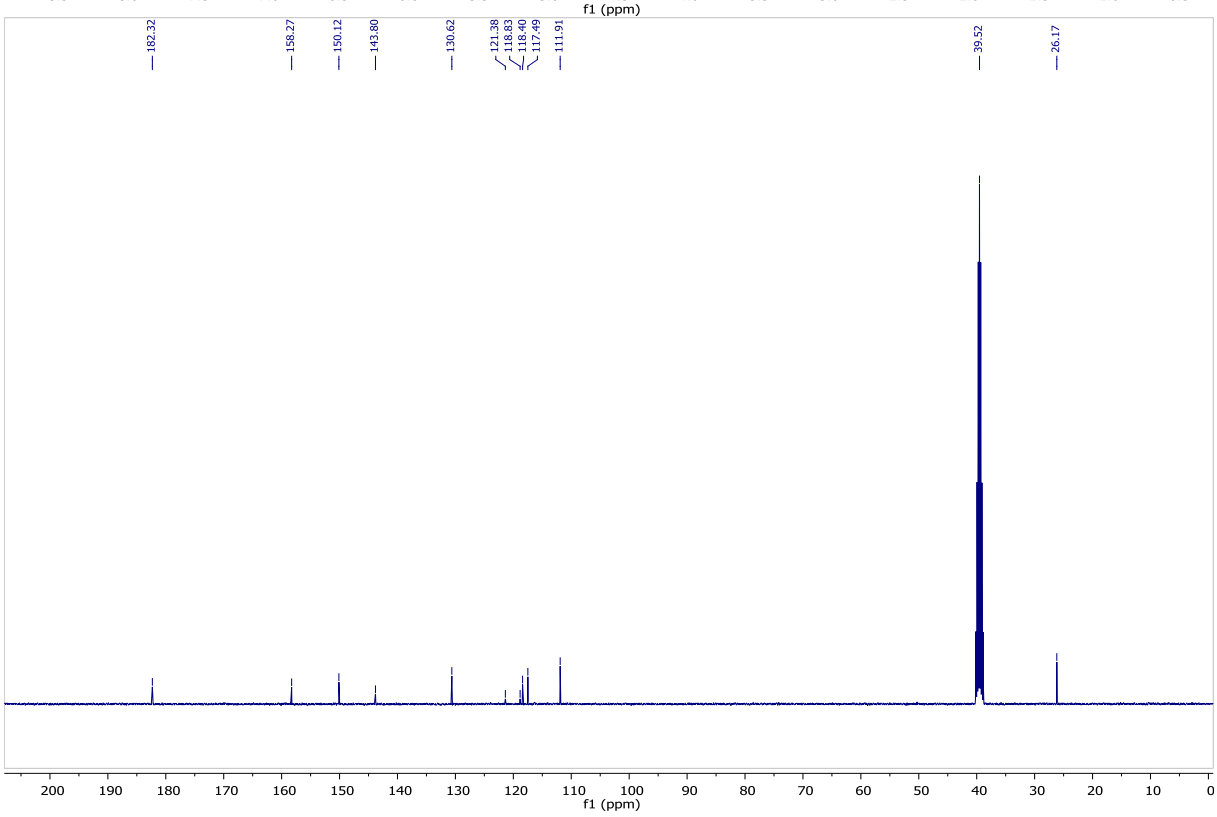
2.127g


7.61
7.61
7.61
7.61
7.59
7.59
7.59
7.59
7.59
7.55
7.55
7.53
7.53
7.12
7.12
7.11
7.10
7.09
7.09
6.81
6.79
4.66
3.83
3.22
O
O
N
O
N
O
2.00
1.00
1.00
1.99
3.04
3.03
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

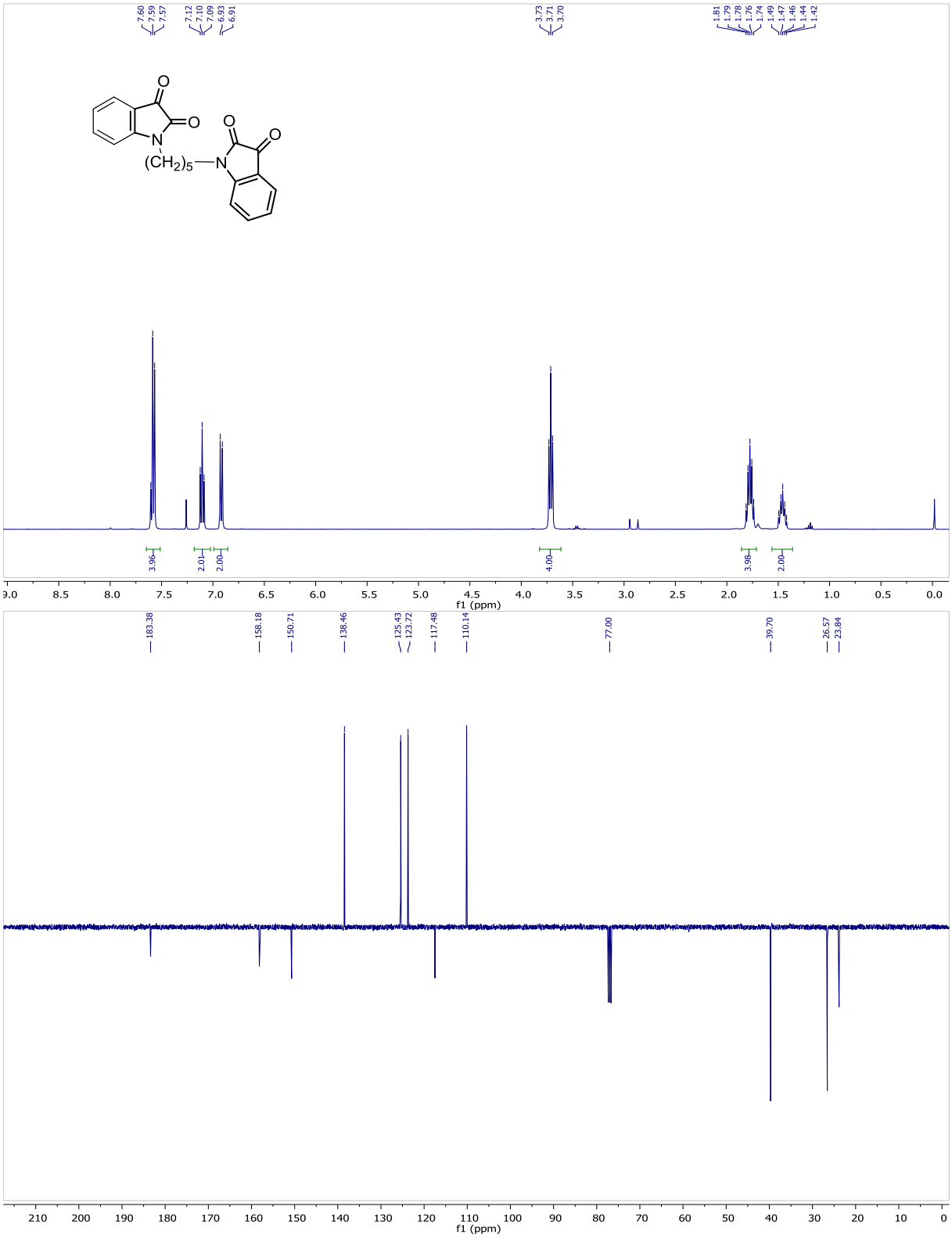

182.75
166.47
158.41
150.92
138.30
125.30
123.83
117.58
110.50
77.31
76.99
76.67
61.68
40.85
32.41
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

2.127j

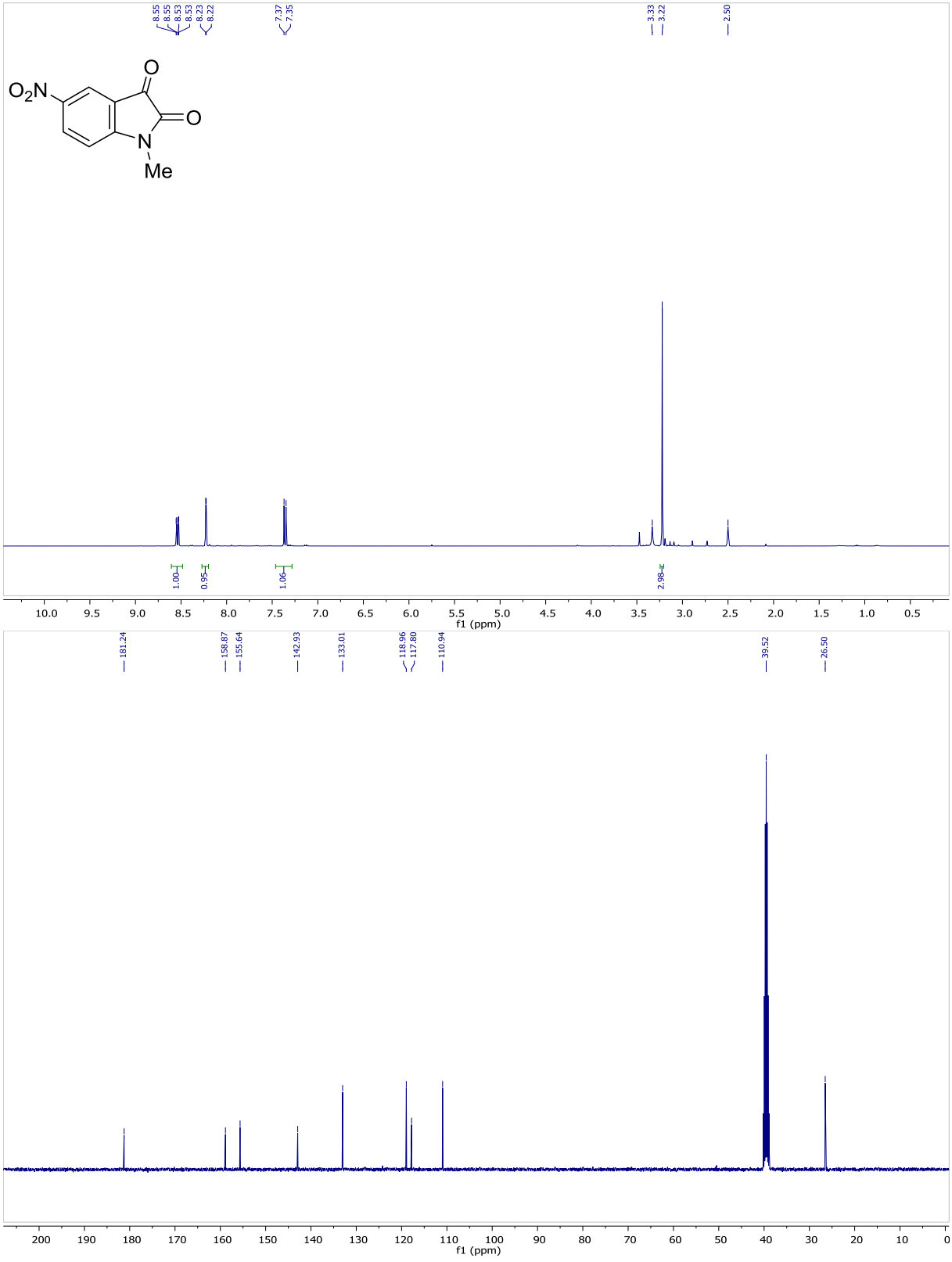

7.72
7.70
7.58
7.27
7.24
3.33
3.16
2.51
O
F3CO
O
N
Me
1.00
0.95
1.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


182.32
158.27
150.12
143.80
130.62
121.38
118.83
118.40
117.49
111.91
39.52
26.17
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

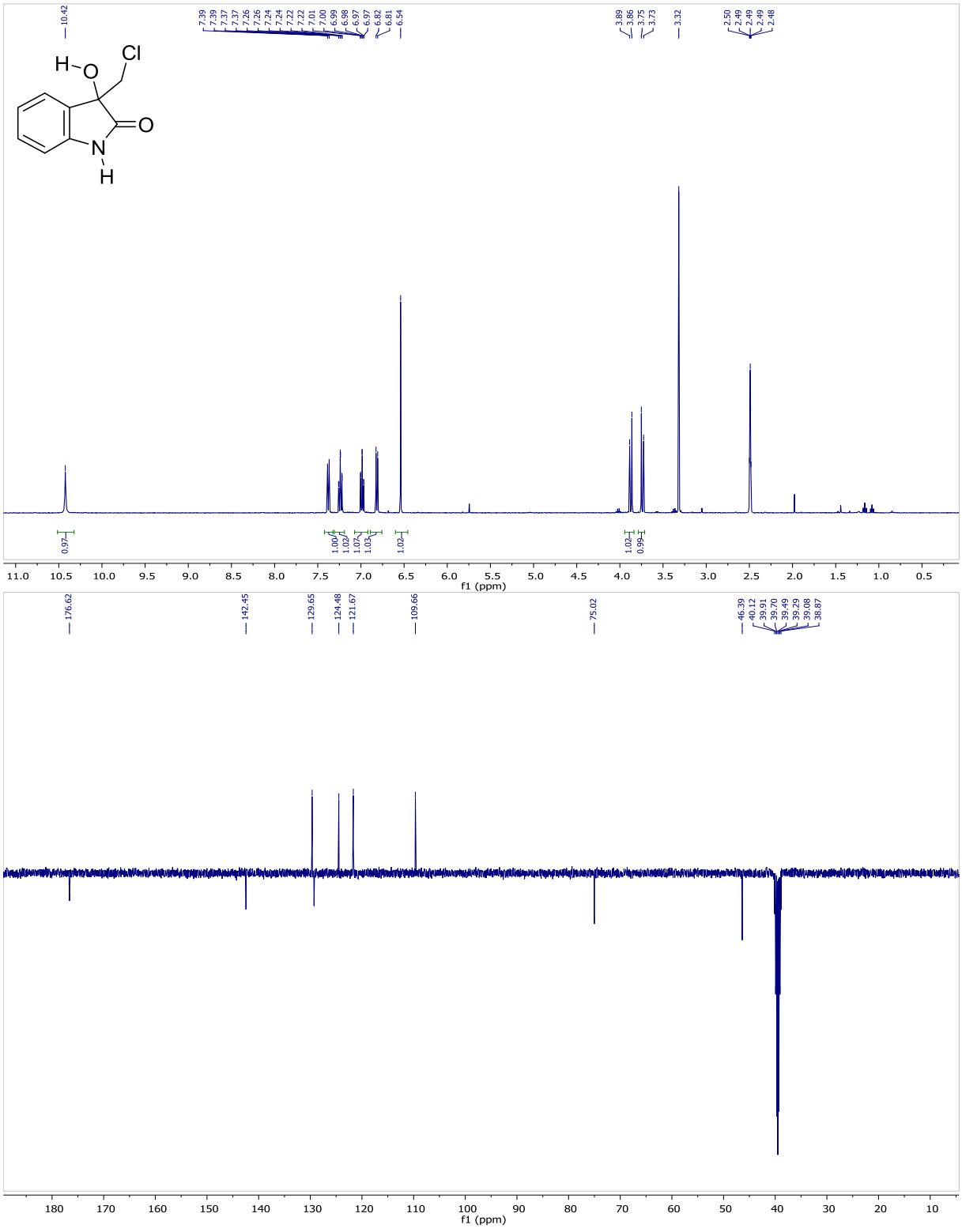
2.127k


7.60
7.59
7.57
7.12
7.10
7.09
6.93
6.91
3.73
3.71
3.70
1.81
1.79
1.78
1.76
1.74
1.49
1.47
1.46
1.44
1.42
O
O
N
(CH2)5
N
O
O
3.96
2.01
2.00
4.00
3.98
2.00
f1 (ppm)
183.38
158.18
150.71
138.46
125.43
123.72
117.48
110.14
77.00
39.70
26.57
23.84
f1 (ppm)

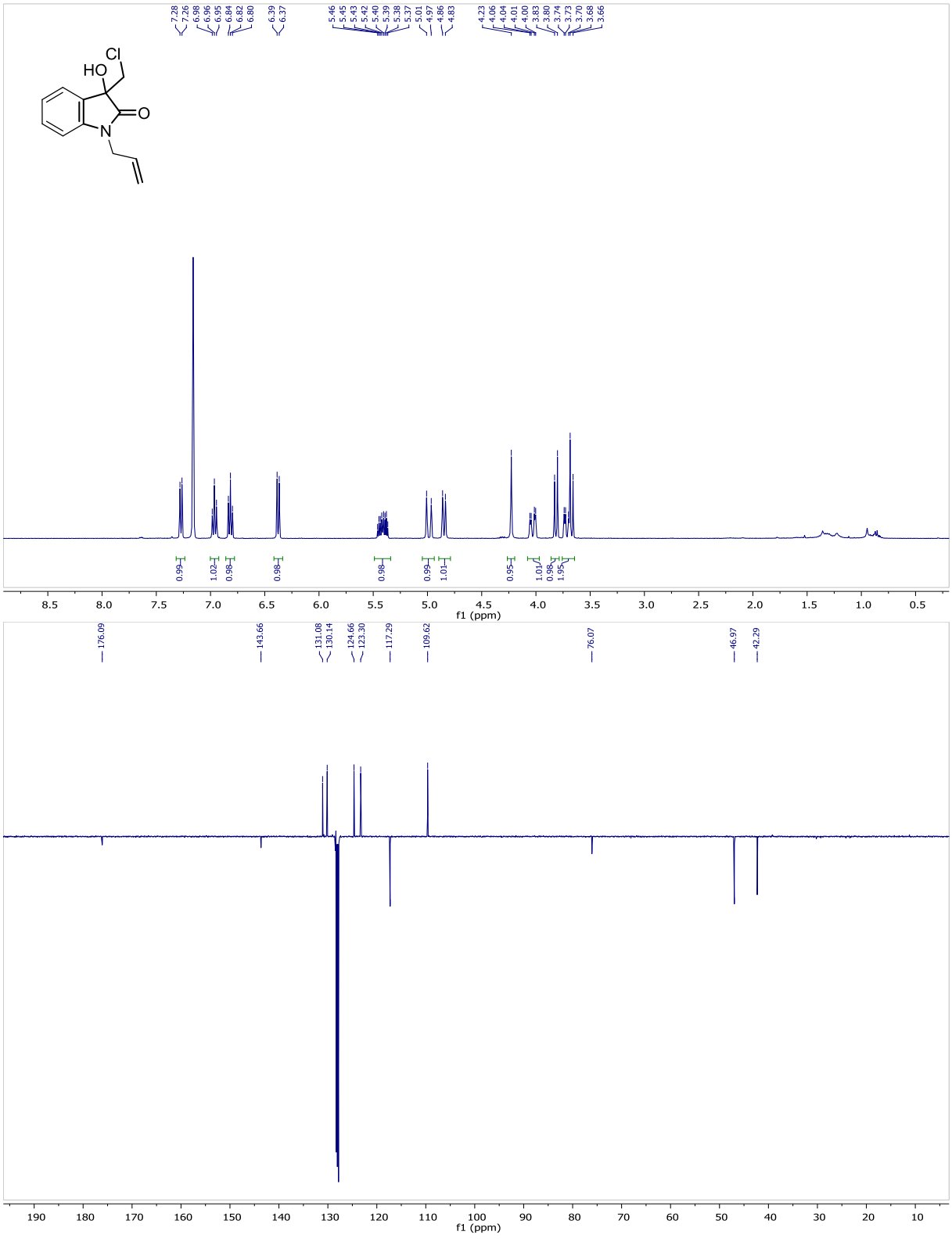
2.127i


8.55
8.55
8.53
8.53
8.23
8.22
7.37
7.35
3.33
3.22
2.50
O
O2N
O
N
Me
1.00
0.95
1.06
2.98
f1 (ppm)
181.24
158.87
155.64
142.93
133.01
118.96
117.80
110.94
39.52
26.50
f1 (ppm)

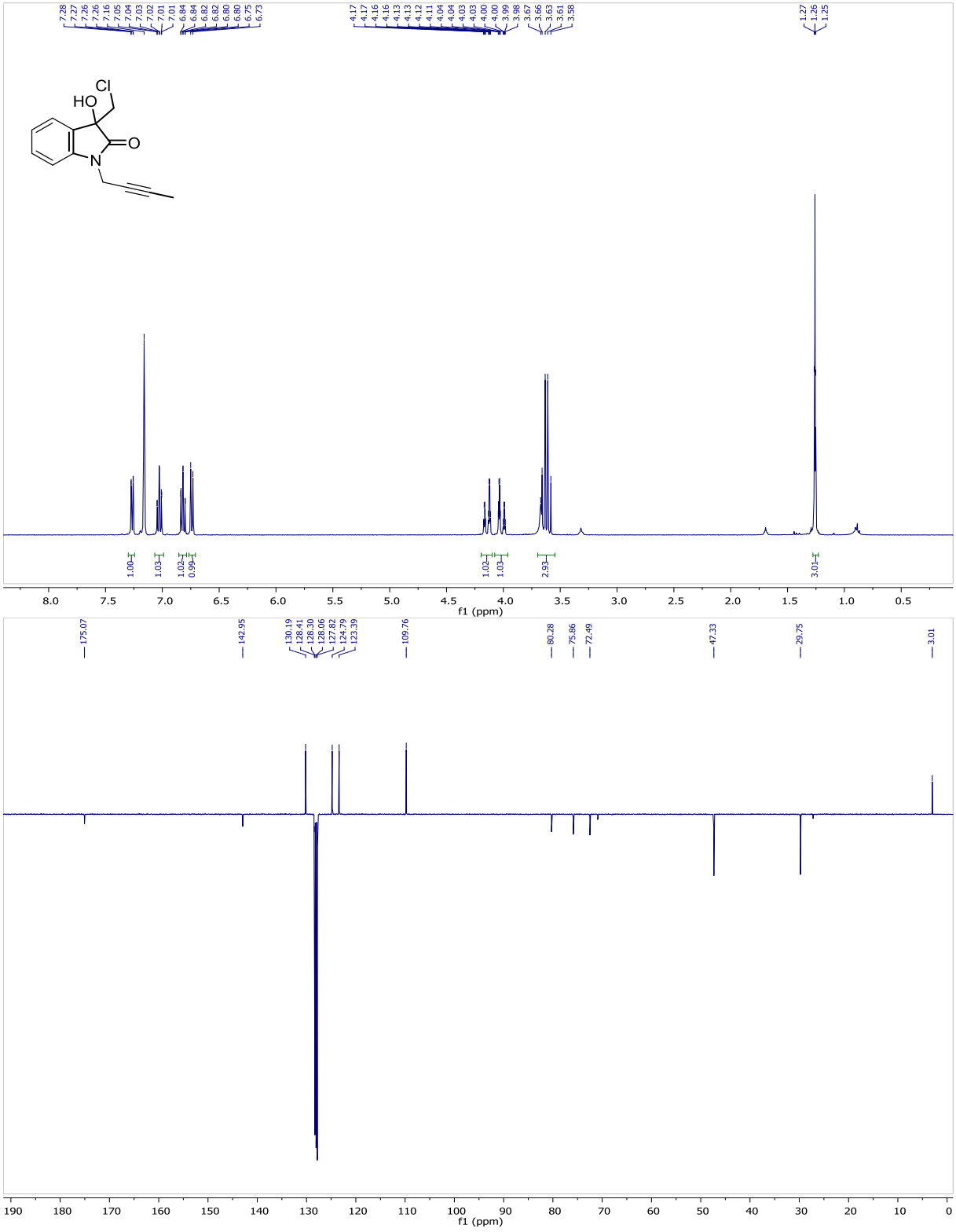
2.126b


10.42
7.39
7.39
7.37
7.37
7.26
7.26
7.24
7.24
7.22
7.22
7.01
7.00
6.99
6.98
6.97
6.97
6.82
6.81
6.54
3.89
3.86
3.75
3.73
3.32
2.50
2.49
2.49
2.49
2.48
Cl
H
O
O
N
H
0.97
1.00
1.02
1.07
1.03
1.02
1.02
0.99
f1 (ppm)
176.62
142.45
129.65
124.48
121.67
109.66
75.02
46.39
40.12
39.91
39.70
39.49
39.29
39.08
38.87
f1 (ppm)

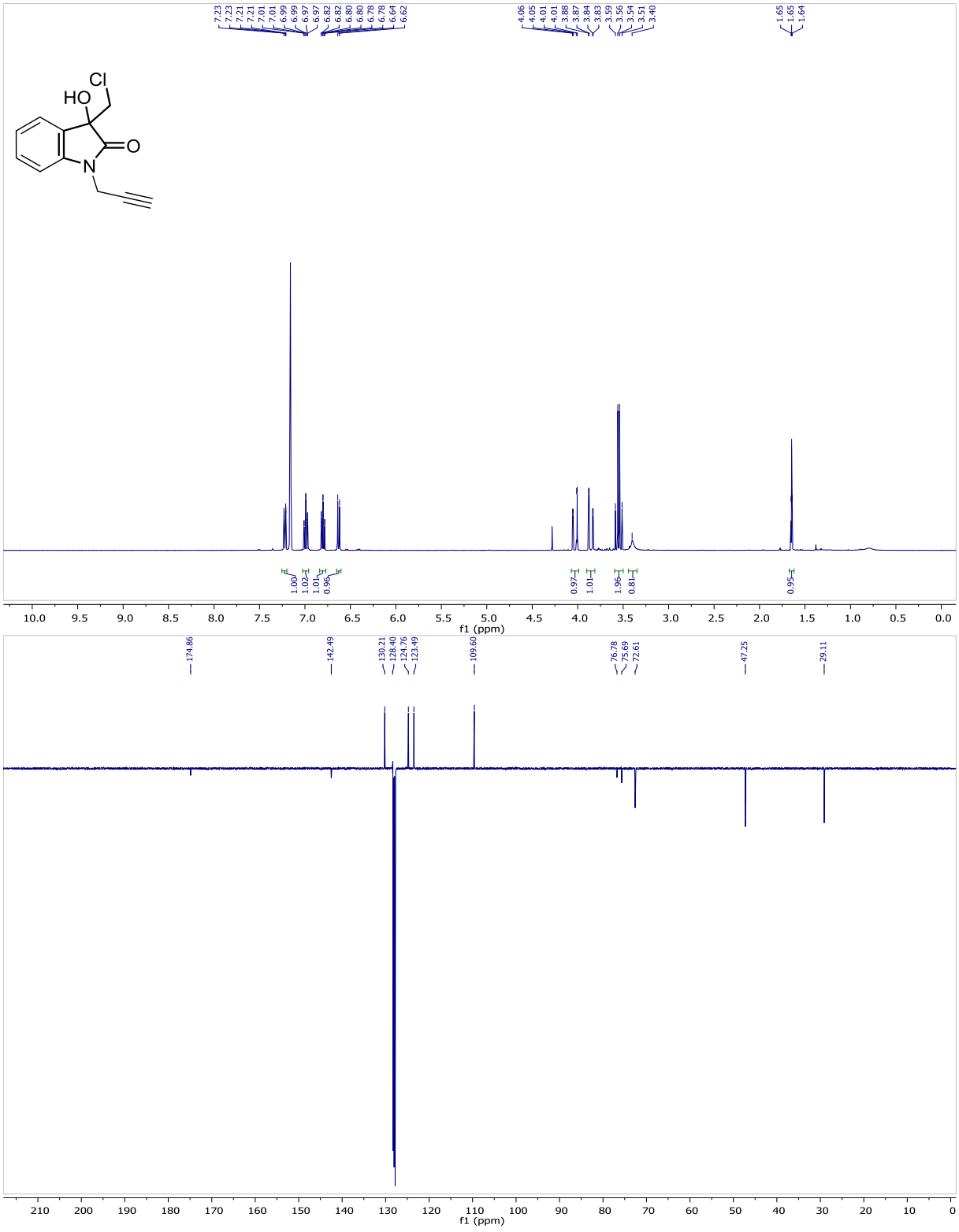
2.130


Cl
HO
O
N
7.28
7.26
6.98
6.96
6.95
6.84
6.82
6.80
6.39
6.37
5.46
5.45
5.43
5.42
5.40
5.39
5.38
5.37
5.01
4.97
4.86
4.83
4.23
4.06
4.04
4.01
4.00
3.83
3.80
3.74
3.73
3.70
3.68
3.66
0.99
1.02
0.98
0.98
0.98
0.99
1.01
0.95
1.01
0.98
1.95
f1 (ppm)
176.09
143.66
131.08
130.14
124.66
123.30
117.29
109.62
76.07
46.97
42.29
f1 (ppm)

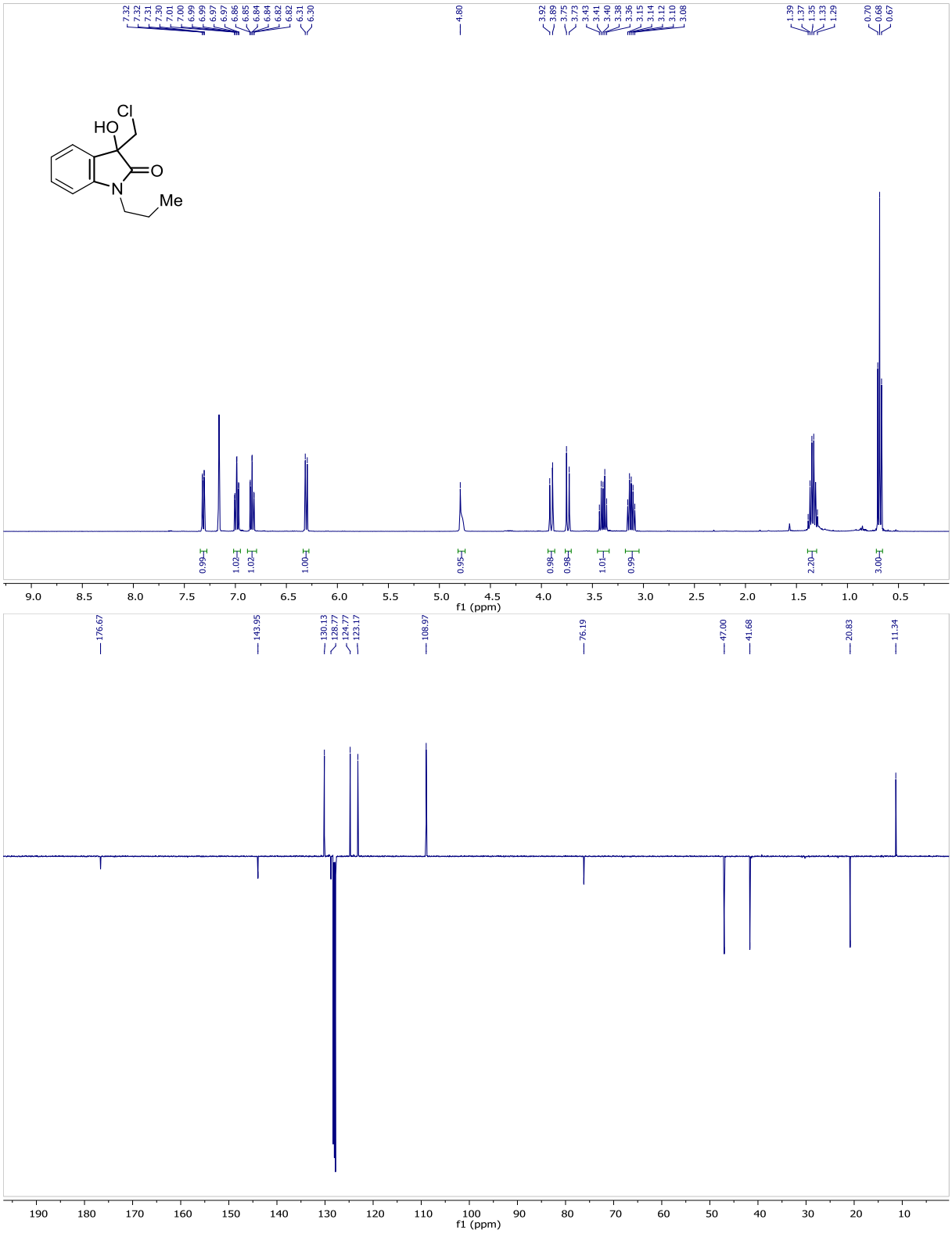
2.131


Cl
HO
O
N
7.28 7.27 7.26 7.26 7.16 7.05 7.04 7.03 7.02 7.01 7.01 6.84 6.84 6.82 6.82 6.80 6.80 6.75 6.73
4.17 4.17 4.16 4.16 4.13 4.13 4.12 4.11 4.04 4.04 4.03 4.00 4.00 3.99 3.98 3.67 3.66 3.63 3.61 3.58
1.27 1.26 1.25
1.00 1.03 1.02 0.99 1.02 1.03 2.93 3.01
f1 (ppm)
175.07 142.95 130.19 128.41 128.30 128.06 127.82 124.79 123.39 109.76 80.28 75.86 72.49 47.33 29.75 3.01
f1 (ppm)

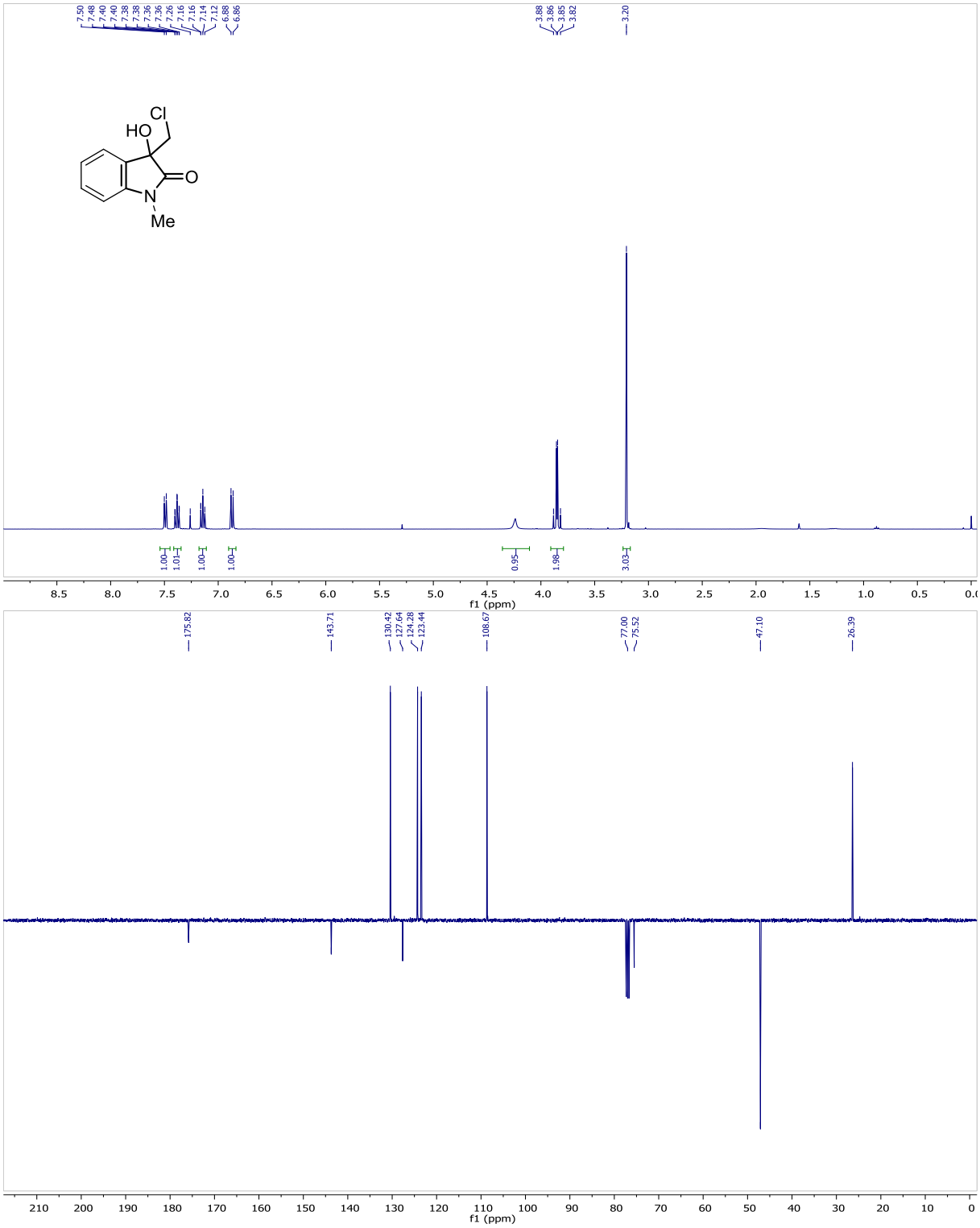
2.132


Cl
HO
O
N
7.23
7.23
7.21
7.21
7.01
7.01
6.99
6.99
6.97
6.97
6.82
6.82
6.80
6.80
6.78
6.78
6.64
6.62
4.06
4.05
4.01
4.01
3.88
3.87
3.84
3.83
3.59
3.56
3.54
3.51
3.40
1.65
1.65
1.64
1.00
1.02
1.01
0.96
0.97
1.01
1.96
0.81
0.95
f1 (ppm)
174.86
142.49
130.21
128.40
124.76
123.49
109.60
76.78
75.69
72.61
47.25
29.11
f1 (ppm)

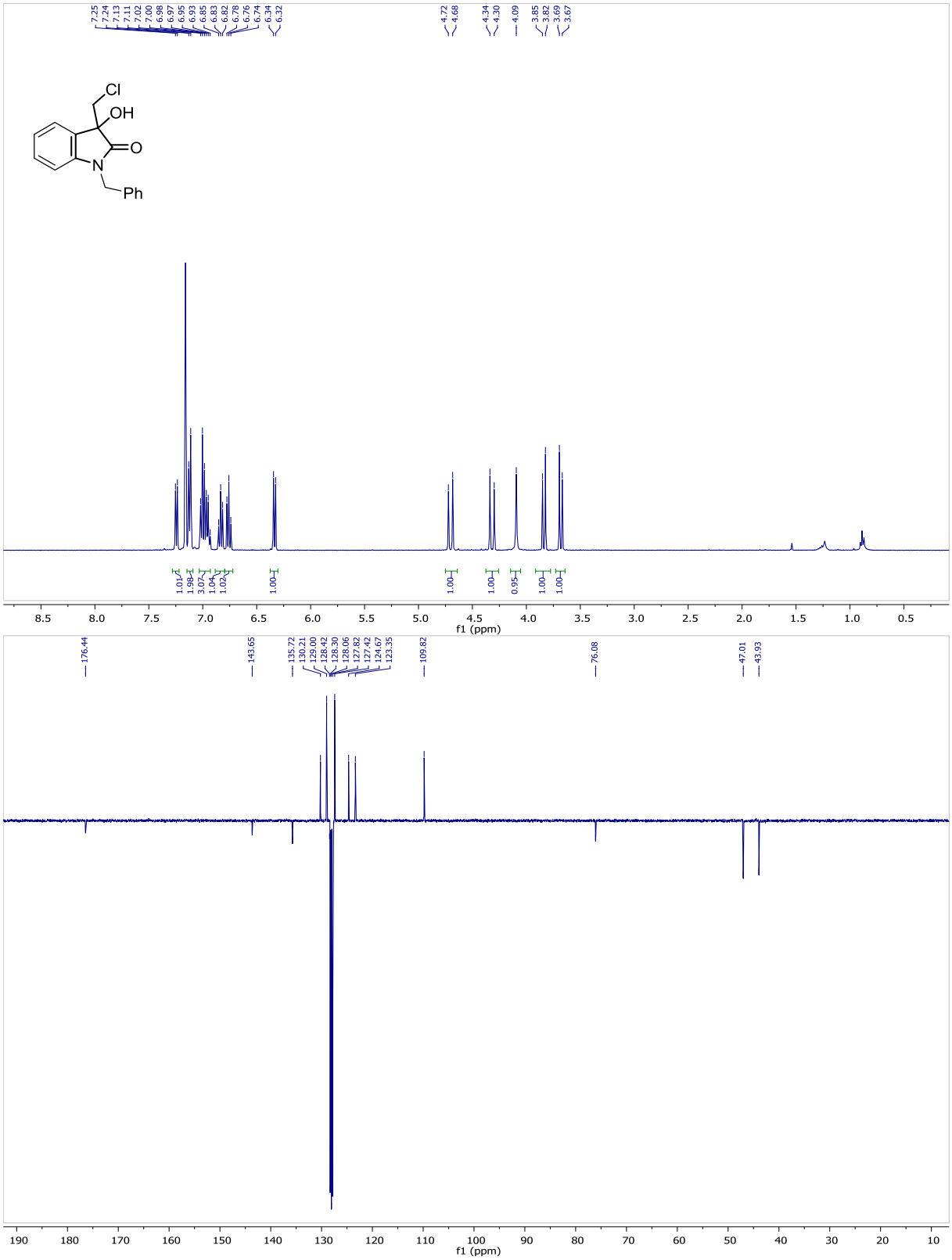
2.133



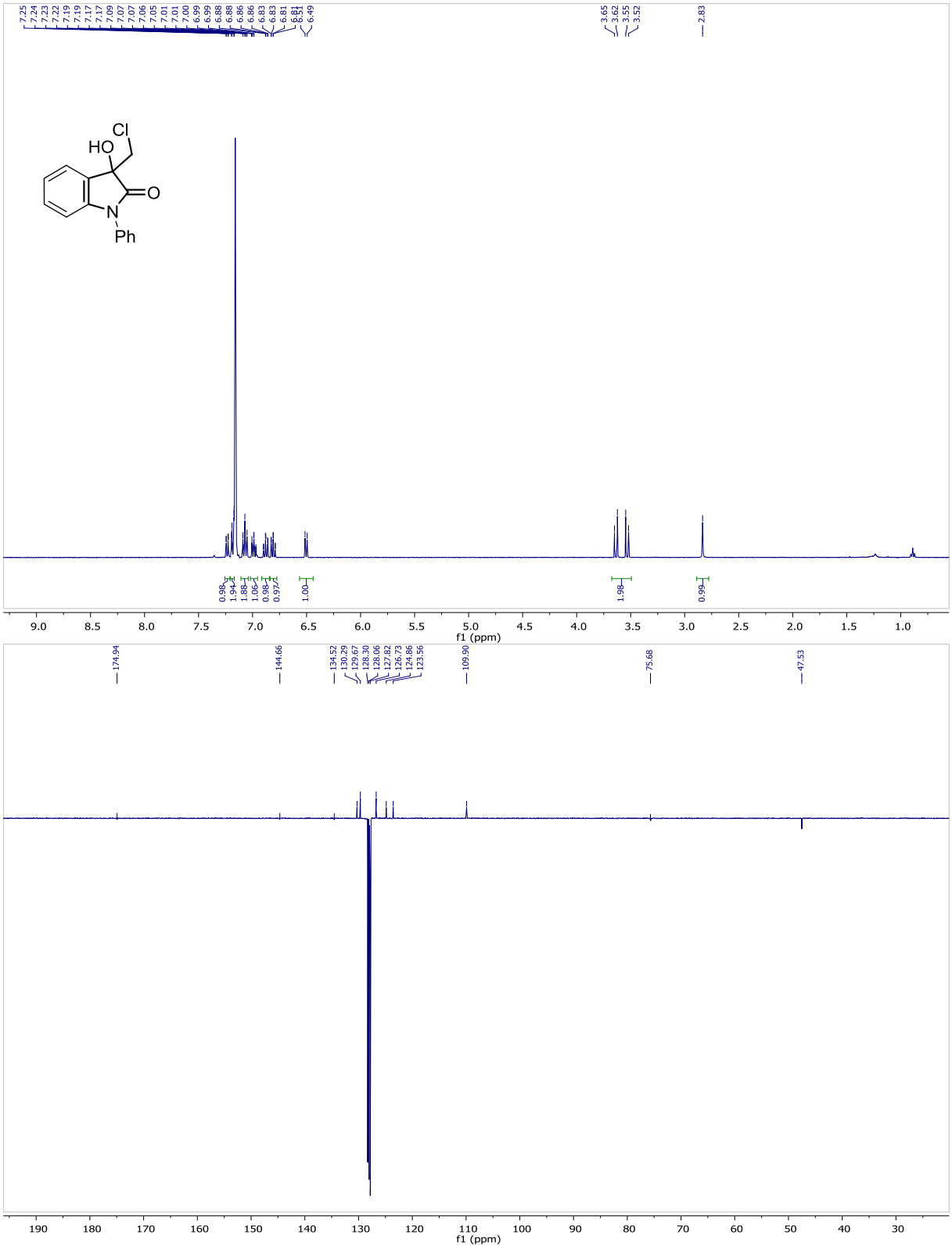
2.134


7.50
7.48
7.40
7.40
7.38
7.38
7.36
7.36
7.26
7.16
7.16
7.14
7.12
6.88
6.86
3.88
3.86
3.85
3.82
3.20
Cl
HO
O
N
Me
1.00
1.01
1.00
1.00
0.95
1.98
3.03
f1 (ppm)
175.82
143.71
130.42
127.64
124.28
123.44
108.67
77.00
75.52
47.10
26.39
f1 (ppm)

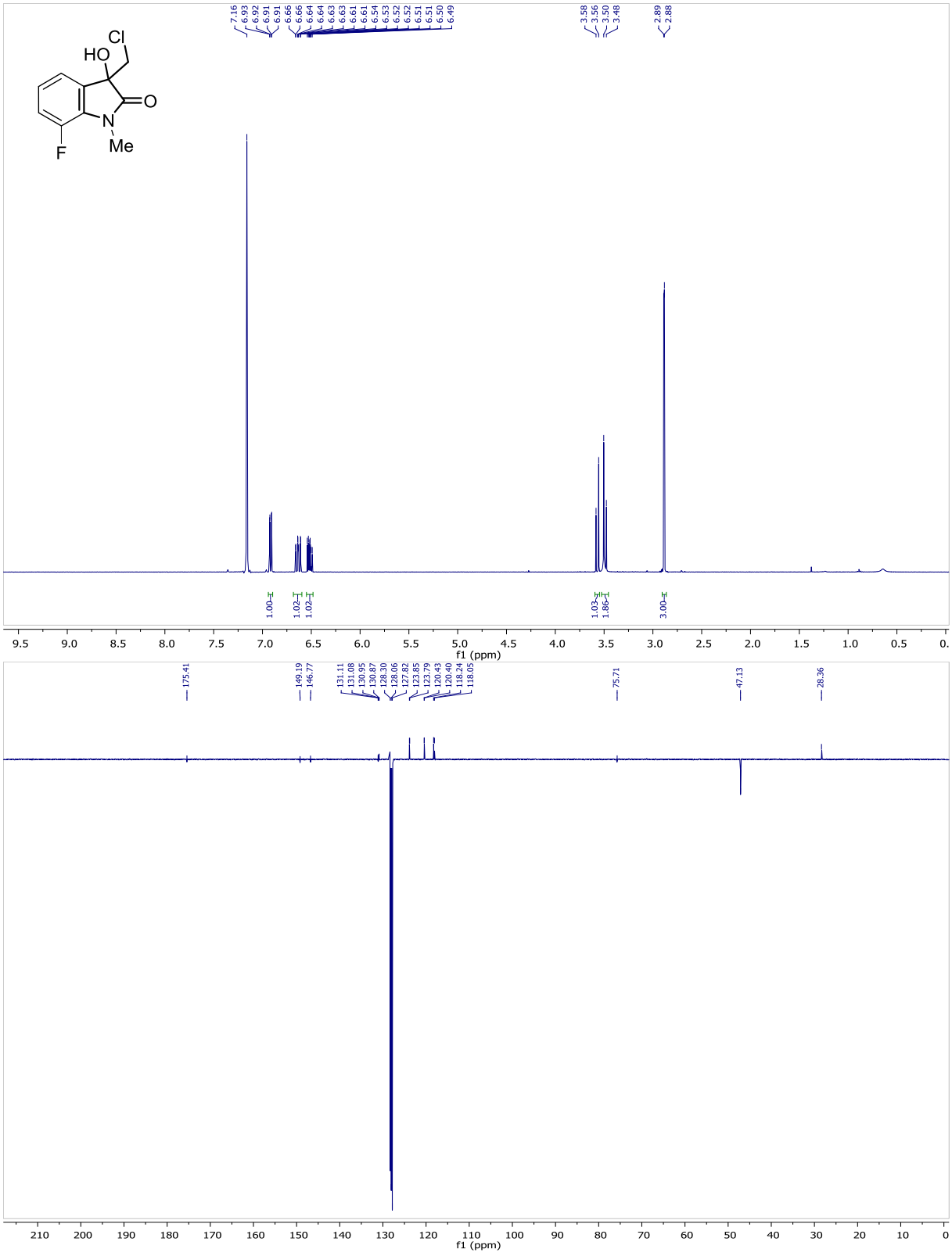
2.135


7.25
7.24
7.13
7.11
7.02
7.00
6.98
6.97
6.95
6.93
6.85
6.83
6.82
6.78
6.76
6.74
6.34
6.32
4.72
4.68
4.34
4.30
4.09
3.85
3.82
3.69
3.67
Cl
OH
O
N
Ph
1.01
1.98
3.07
1.04
1.02
1.00
1.00
1.00
0.95
1.00
1.00
f1 (ppm)
176.44
143.65
135.72
130.21
129.00
128.42
128.30
128.06
127.82
127.42
124.67
123.35
109.82
76.08
47.01
43.93
f1 (ppm)

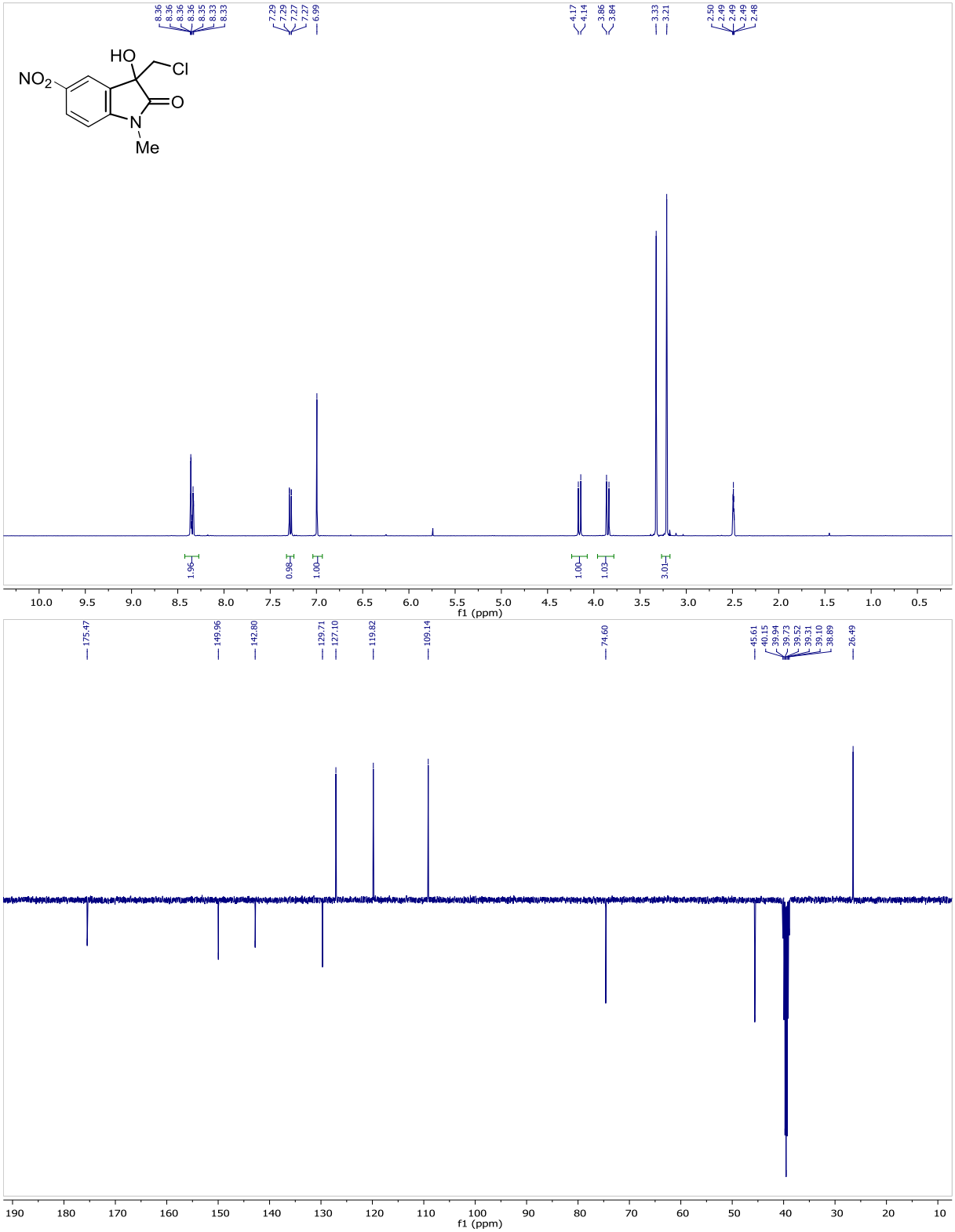
2.136


7.25 7.24 7.23 7.22 7.19 7.19 7.17 7.17 7.09 7.07 7.07 7.06 7.05 7.01 7.01 7.00 6.99 6.99 6.88 6.88 6.86 6.86 6.83 6.83 6.81 6.81 6.49
3.65 3.62 3.55 3.52
2.83
Cl
HO
O
N
Ph
0.98 1.94 1.88 1.06 0.98 0.97 1.00 1.98 0.99
f1 (ppm)
174.94 144.66 134.52 130.29 129.67 128.30 128.06 127.82 126.73 124.86 123.56 109.90 75.68 47.53
f1 (ppm)

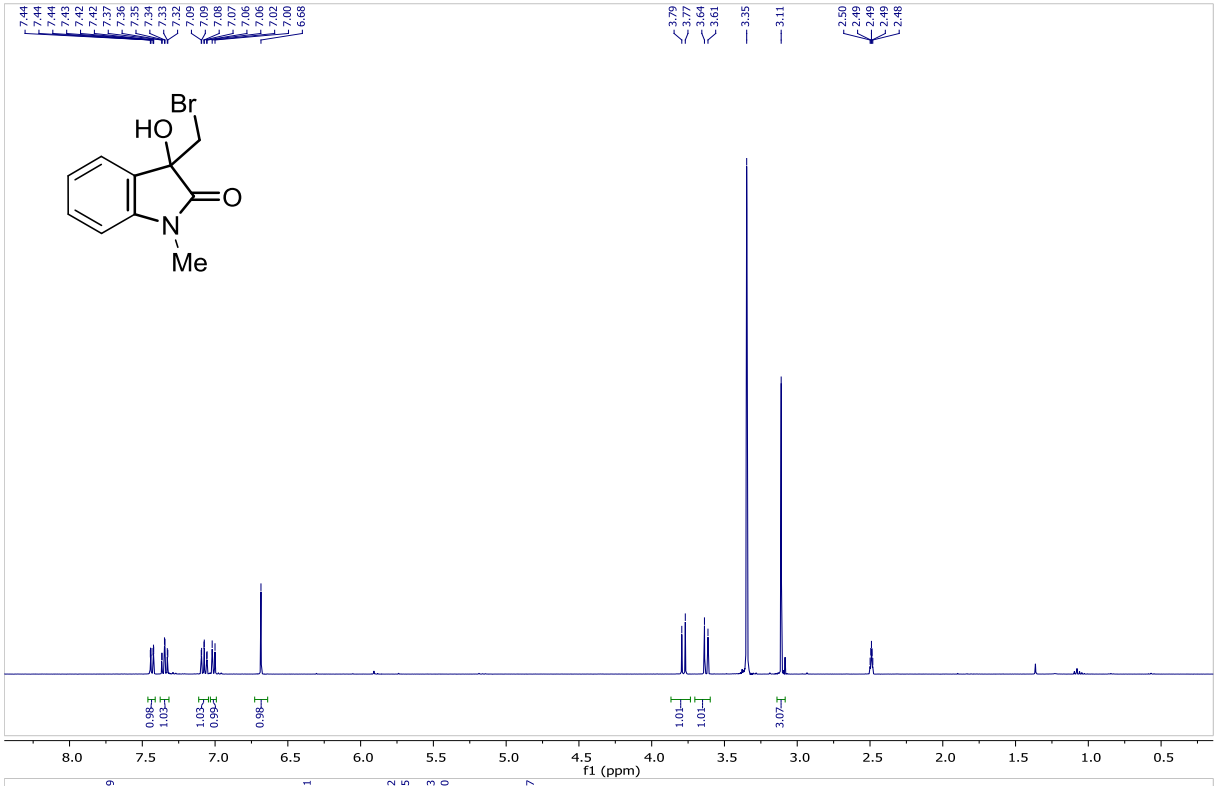
2.137

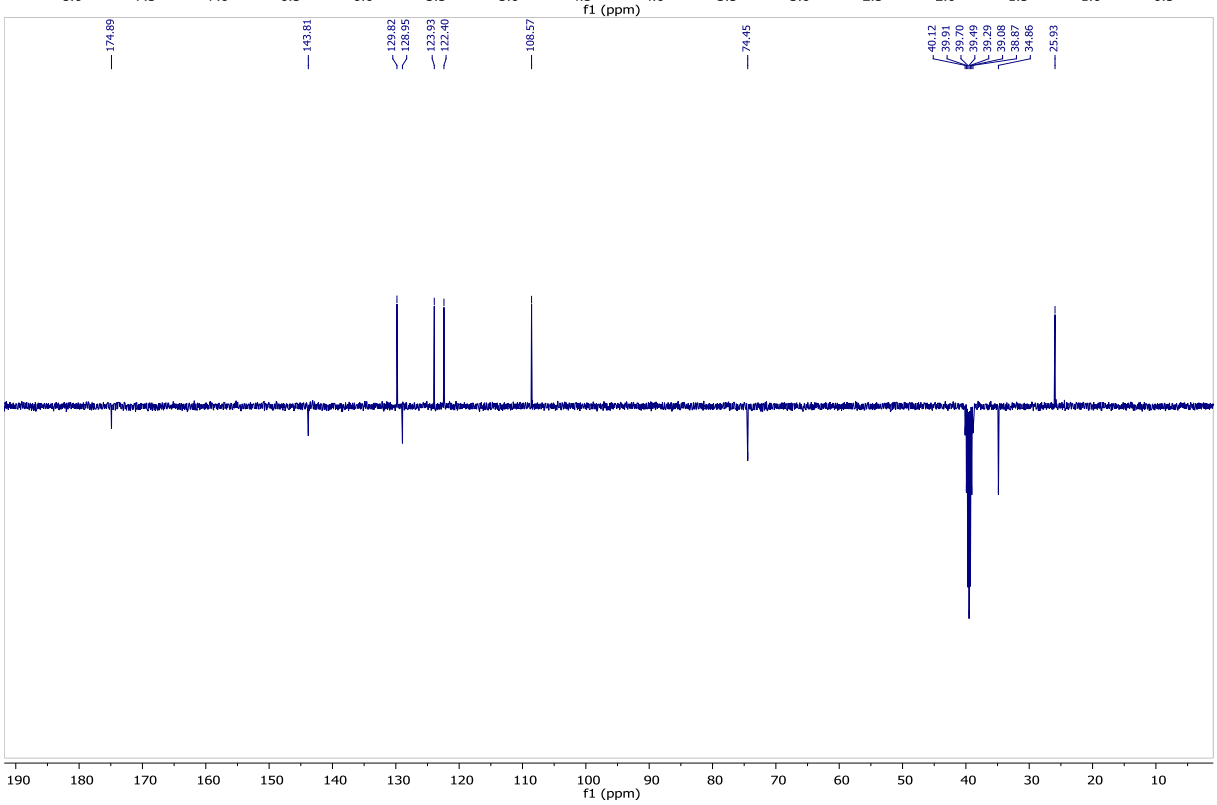

Cl
HO
O
N
Me
F
7.16
6.93
6.92
6.91
6.91
6.66
6.66
6.64
6.64
6.63
6.63
6.61
6.61
6.54
6.53
6.52
6.52
6.51
6.51
6.50
6.49
3.58
3.56
3.50
3.48
2.89
2.88
1.00
1.02
1.02
1.03
1.86
3.00
f1 (ppm)
175.41
149.19
146.77
131.11
131.08
130.95
130.87
128.30
128.06
127.82
123.85
123.79
120.43
120.40
118.24
118.05
75.71
47.13
28.36
f1 (ppm)

2.138

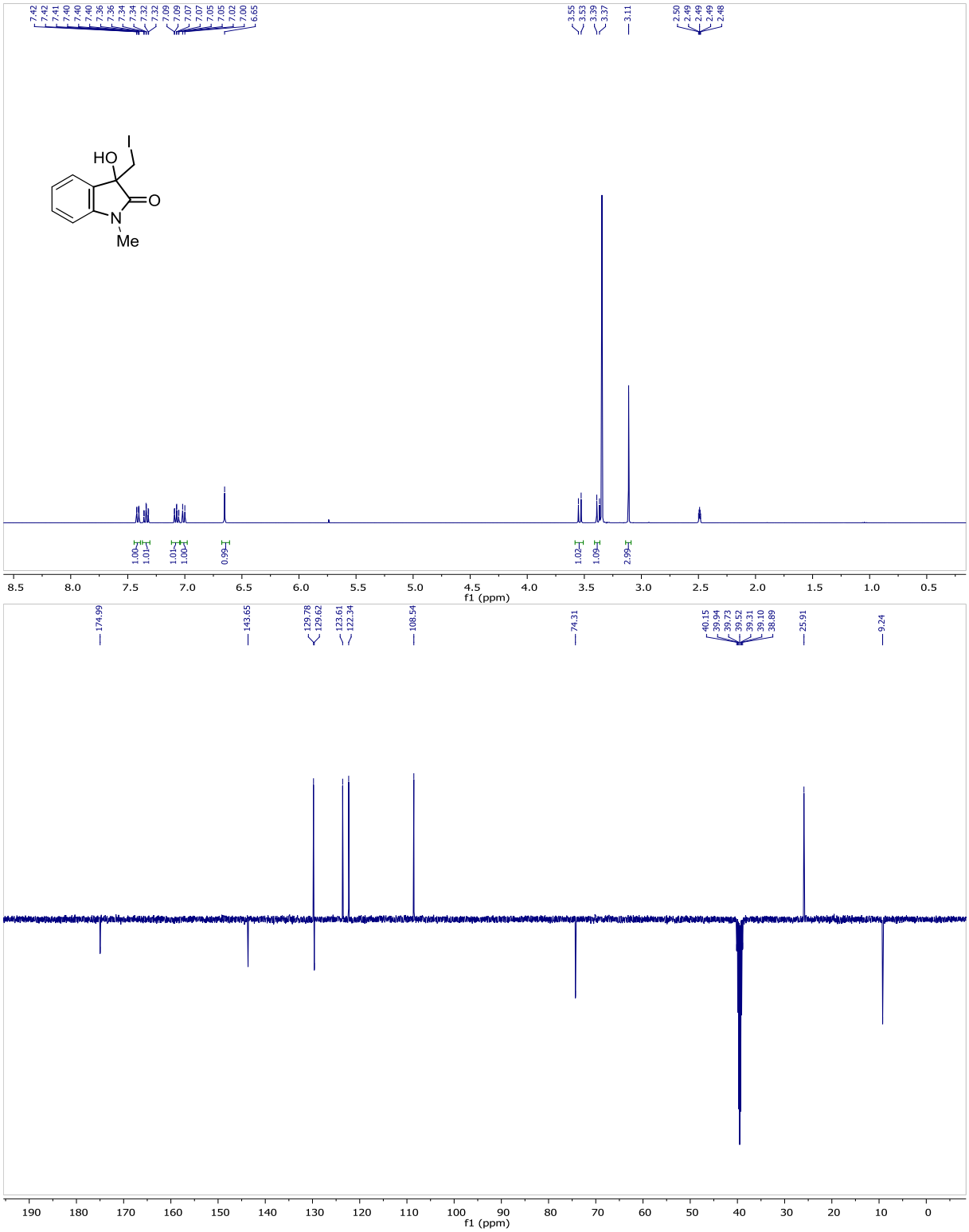

HO
Cl
NO2
O
N
Me
8.36
8.36
8.36
8.36
8.35
8.33
8.33
7.29
7.29
7.27
7.27
6.99
4.17
4.14
3.86
3.84
3.33
3.21
2.50
2.49
2.49
2.49
2.48
1.96
0.98
1.00
1.00
1.03
3.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)
175.47
149.96
142.80
129.71
127.10
119.82
109.14
74.60
45.61
40.15
39.94
39.73
39.52
39.31
39.10
38.89
26.49
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

2.139

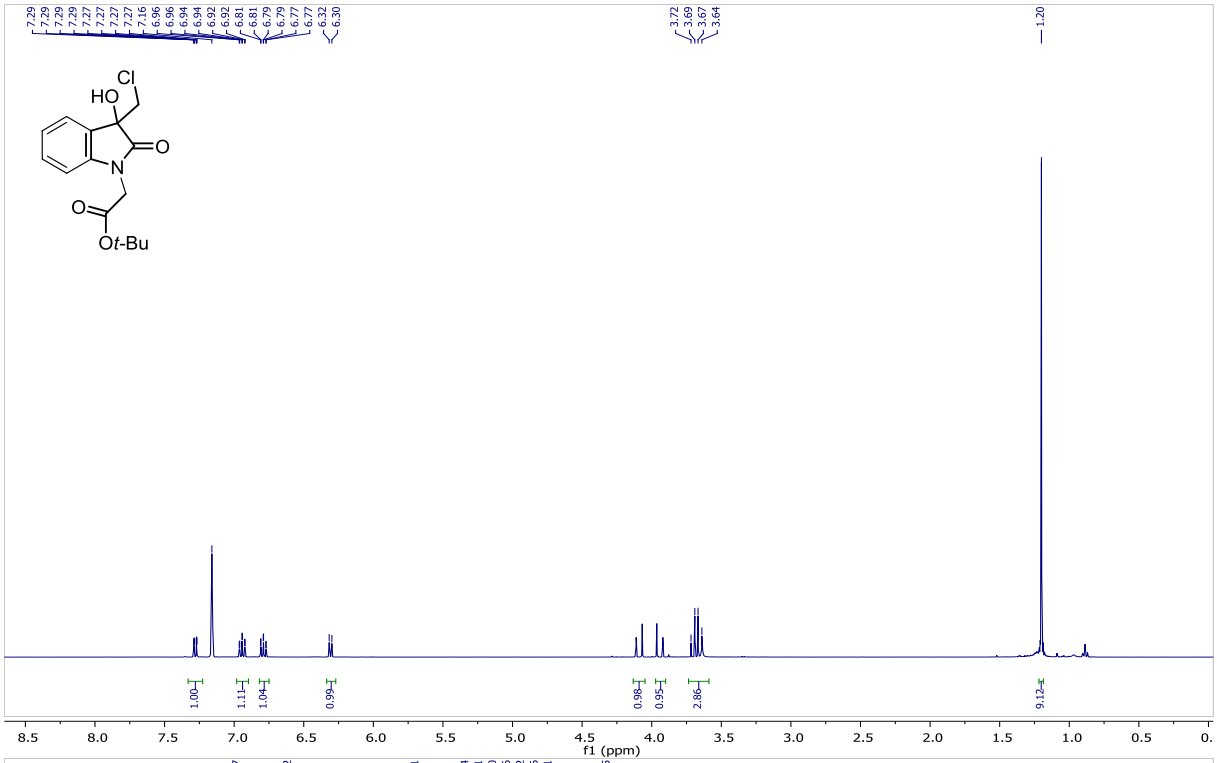


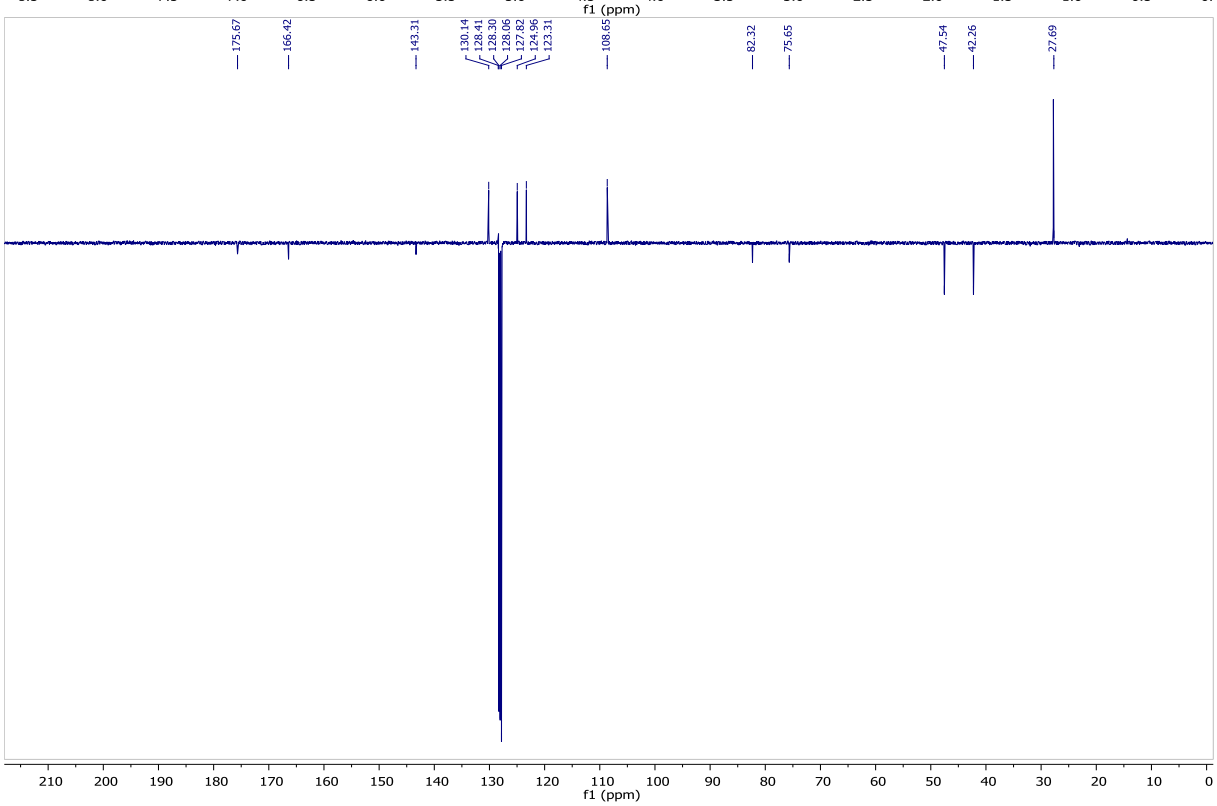


2.140

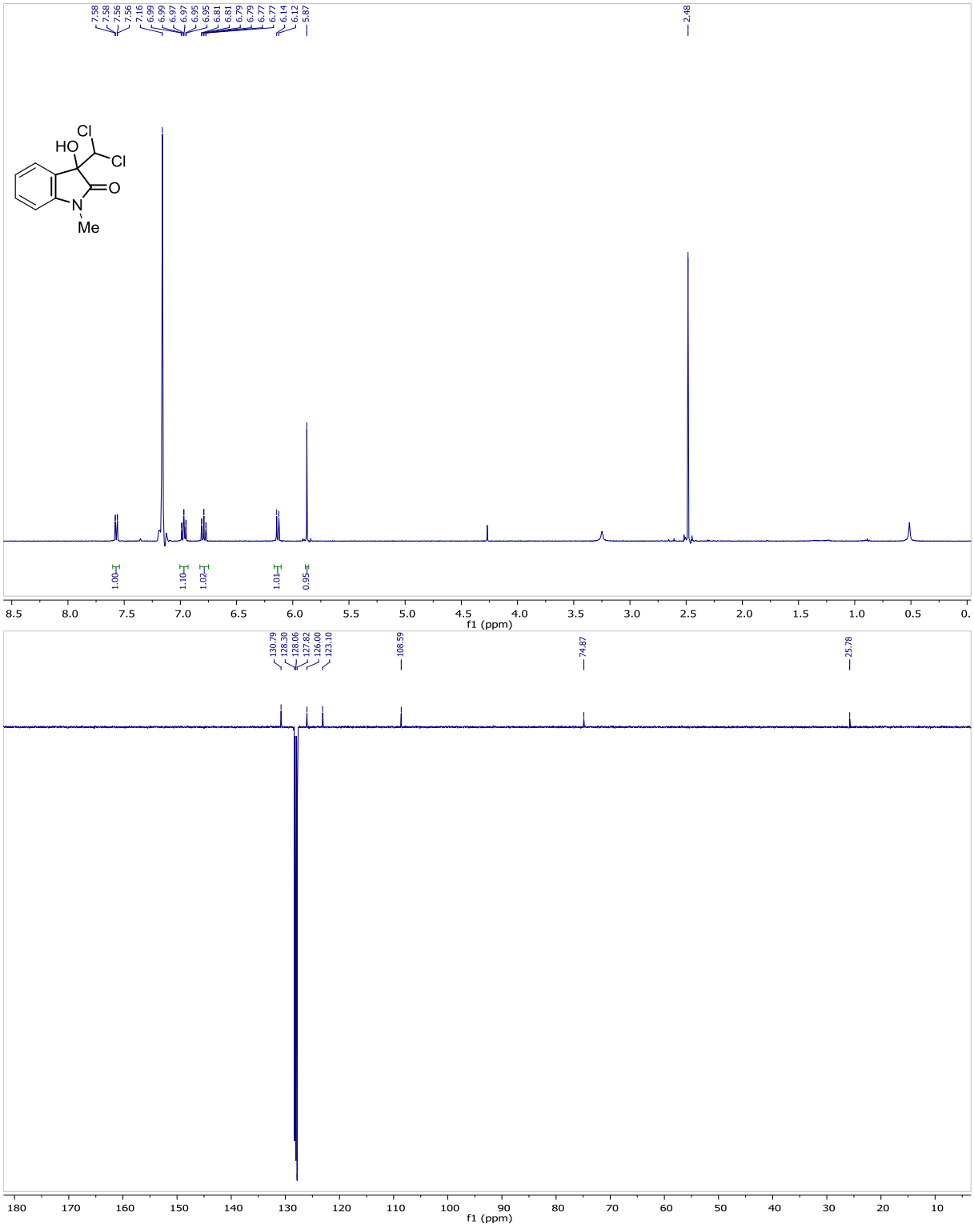


2.141

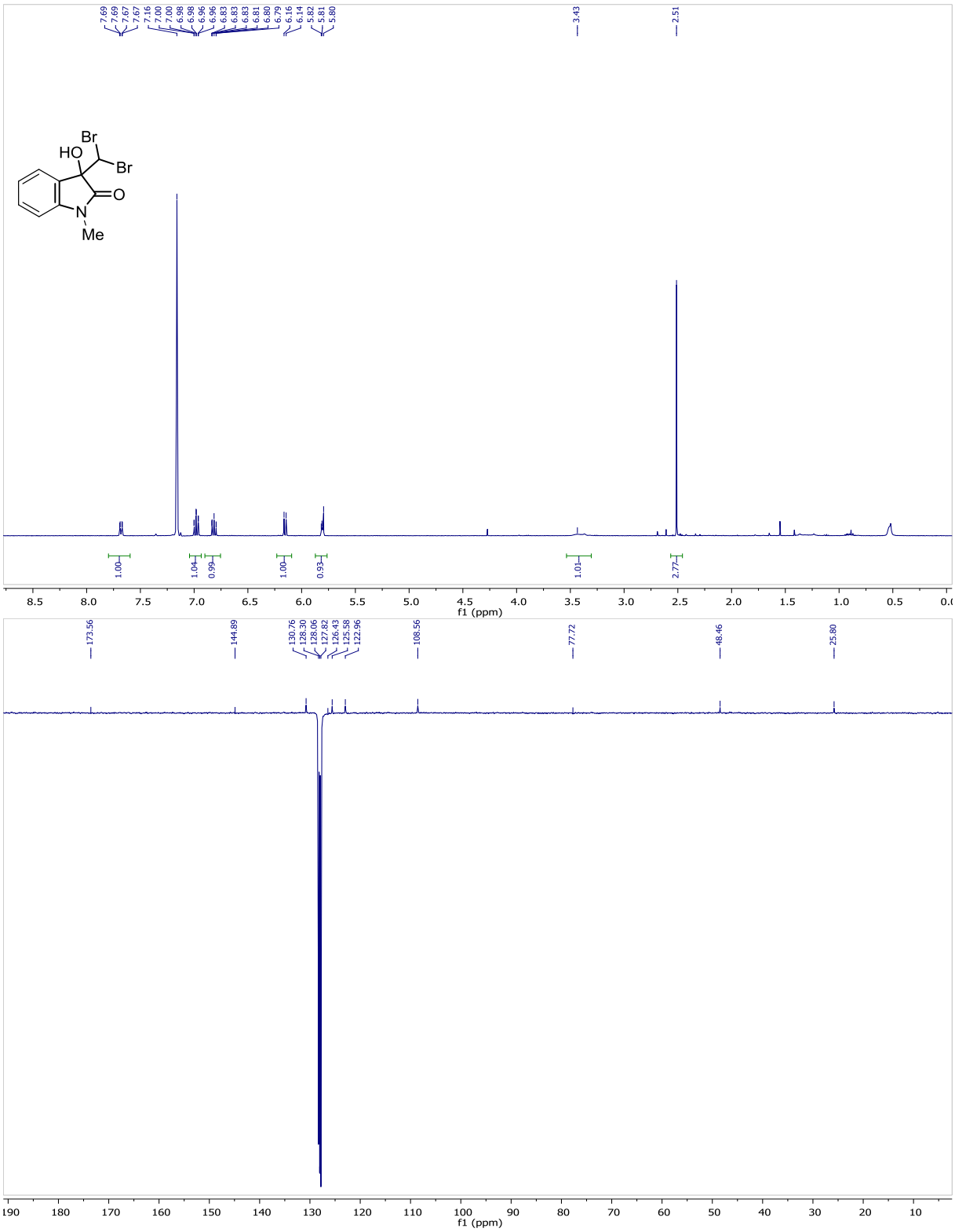

Cl
HO
O
N
O
Ot-Bu
7.29
7.29
7.29
7.29
7.27
7.27
7.27
7.27
7.16
6.96
6.96
6.94
6.94
6.92
6.92
6.81
6.81
6.79
6.79
6.77
6.77
6.32
6.30
3.72
3.69
3.67
3.64
1.20
1.00
1.11
1.04
0.99
0.98
0.95
2.86
9.12
f1 (ppm)


175.67
166.42
143.31
130.14
128.41
128.30
128.06
127.82
124.96
123.31
108.65
82.32
75.65
47.54
42.26
27.69
f1 (ppm)

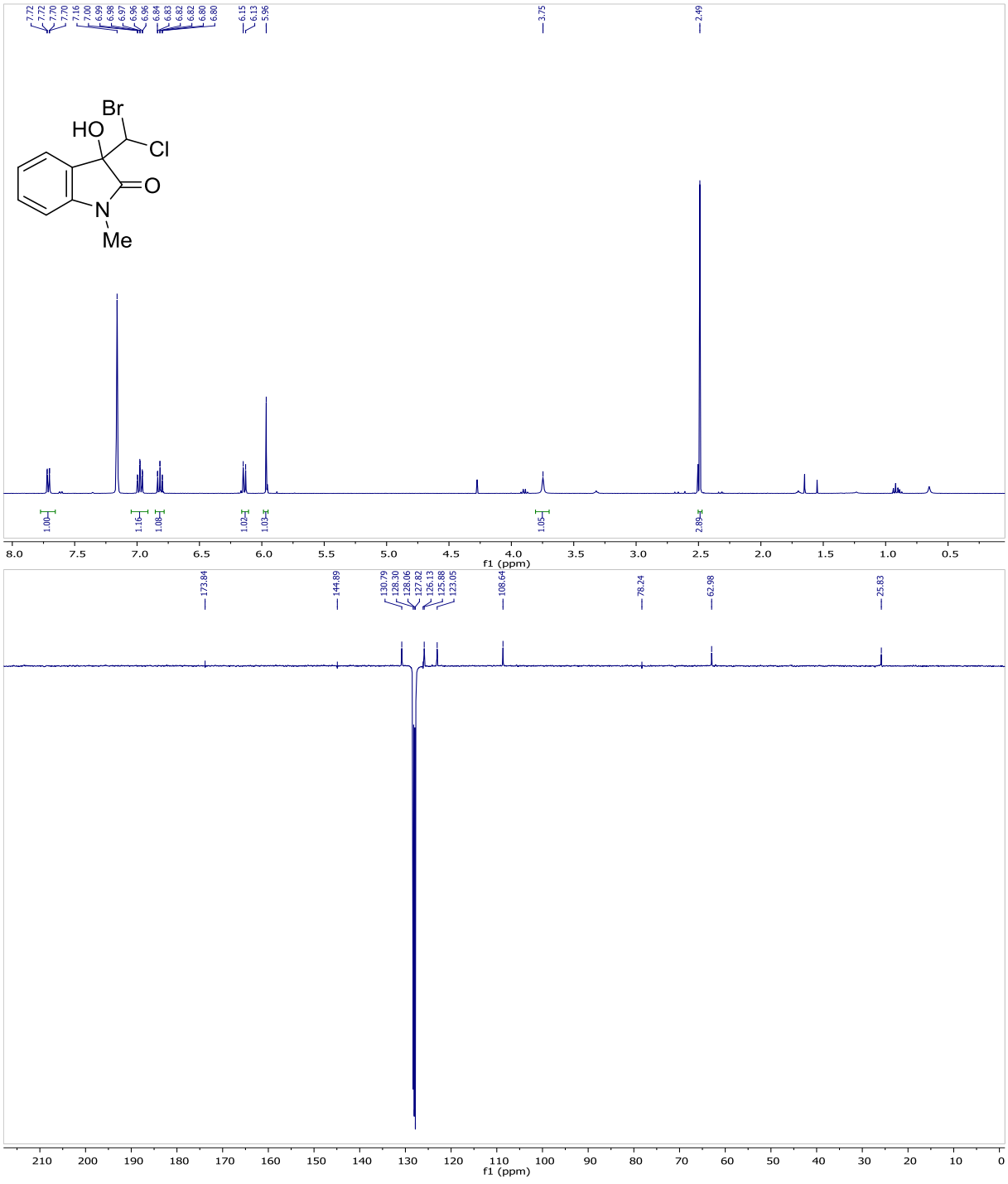
2.144a


7.58
7.58
7.56
7.56
7.16
6.99
6.99
6.97
6.97
6.95
6.95
6.81
6.81
6.79
6.79
6.77
6.77
6.14
6.12
5.87
2.48
Cl
HO
Cl
O
N
Me
1.00
1.10
1.02
1.01
0.95
f1 (ppm)
130.79
128.30
128.06
127.82
126.00
123.10
108.59
74.87
25.78
f1 (ppm)

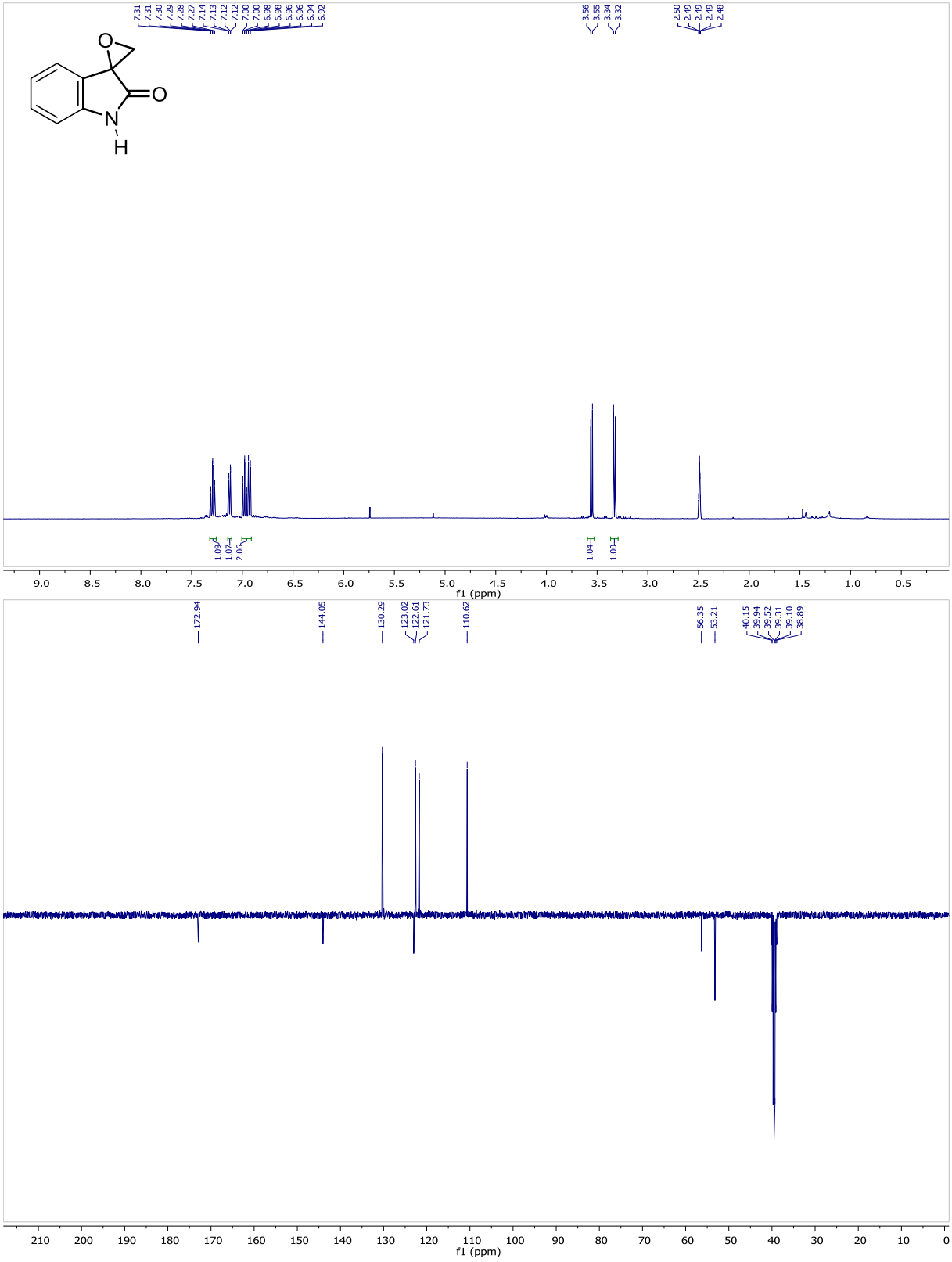
2.144b



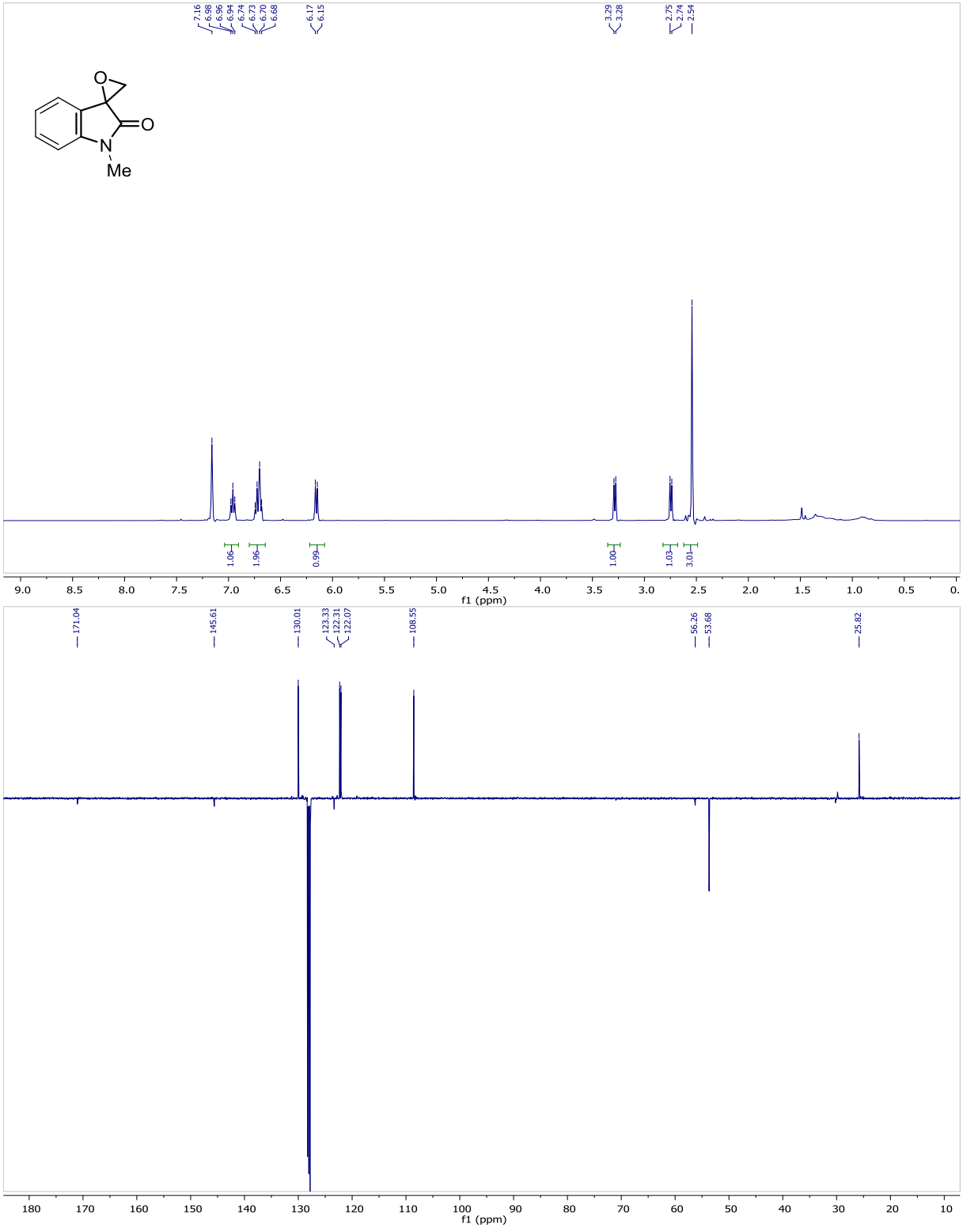
2.144c



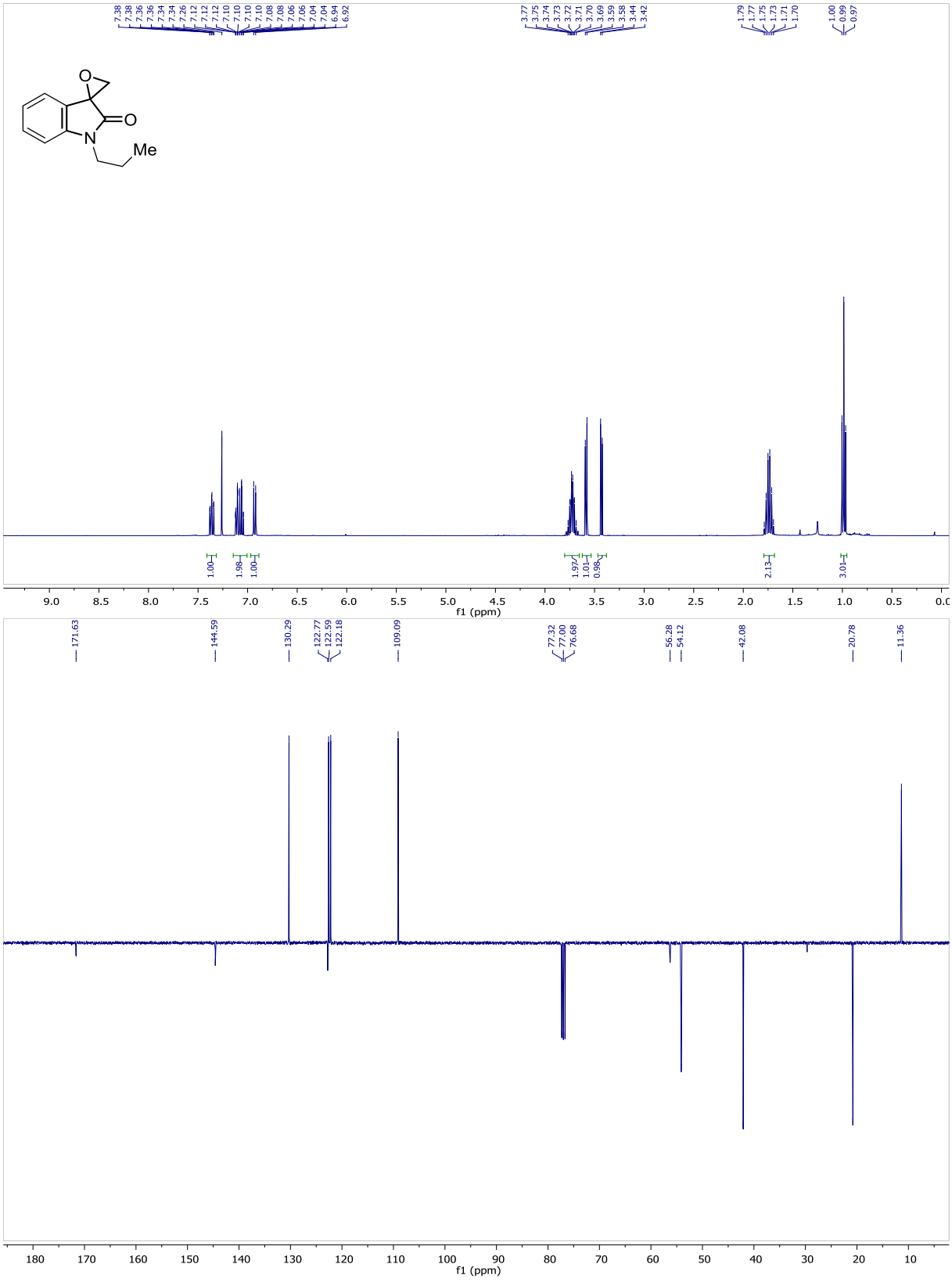
2.145


7.31
7.31
7.30
7.29
7.28
7.27
7.14
7.13
7.12
7.10
7.00
7.00
6.98
6.98
6.96
6.96
6.94
6.92
3.56
3.55
3.34
3.32
2.50
2.49
2.49
2.49
2.48
O
O
N
H
1.09
1.07
2.06
1.04
1.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
172.94
144.05
130.29
123.02
122.61
121.73
110.62
56.35
53.21
40.15
39.94
39.52
39.31
39.10
38.89
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

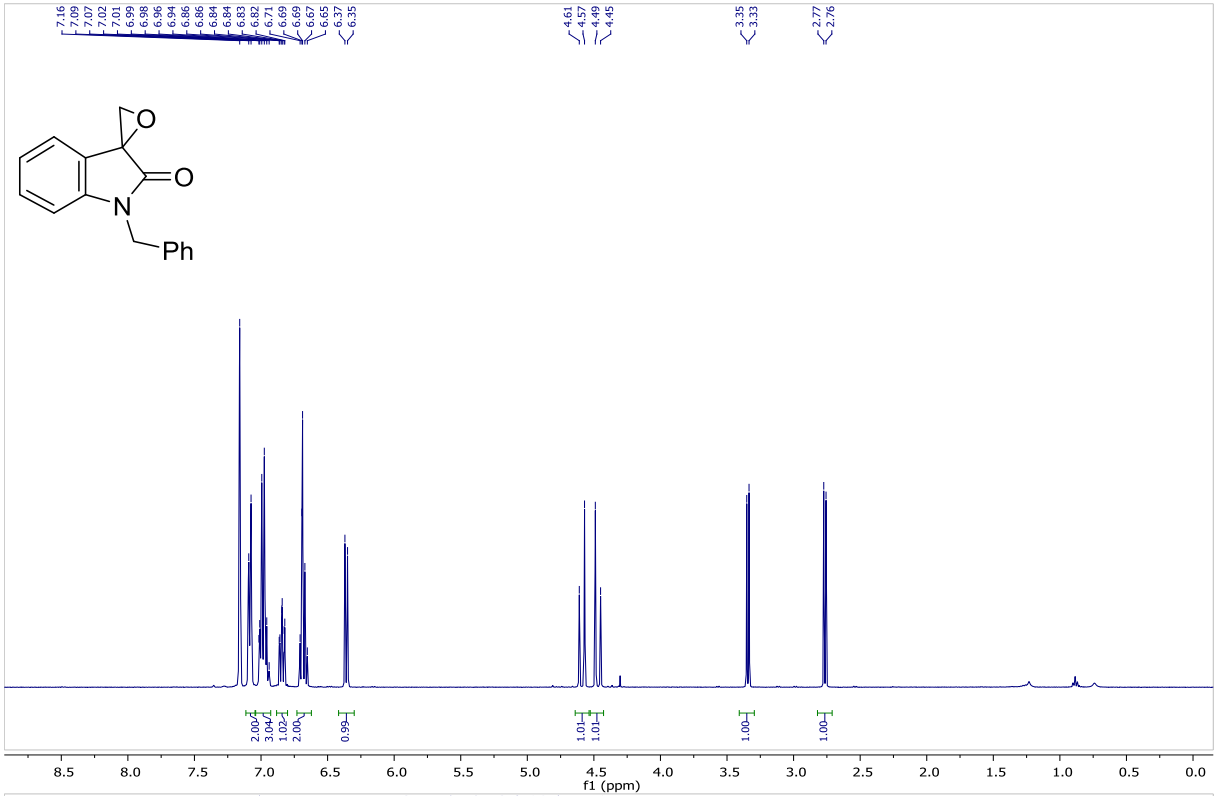
2.146

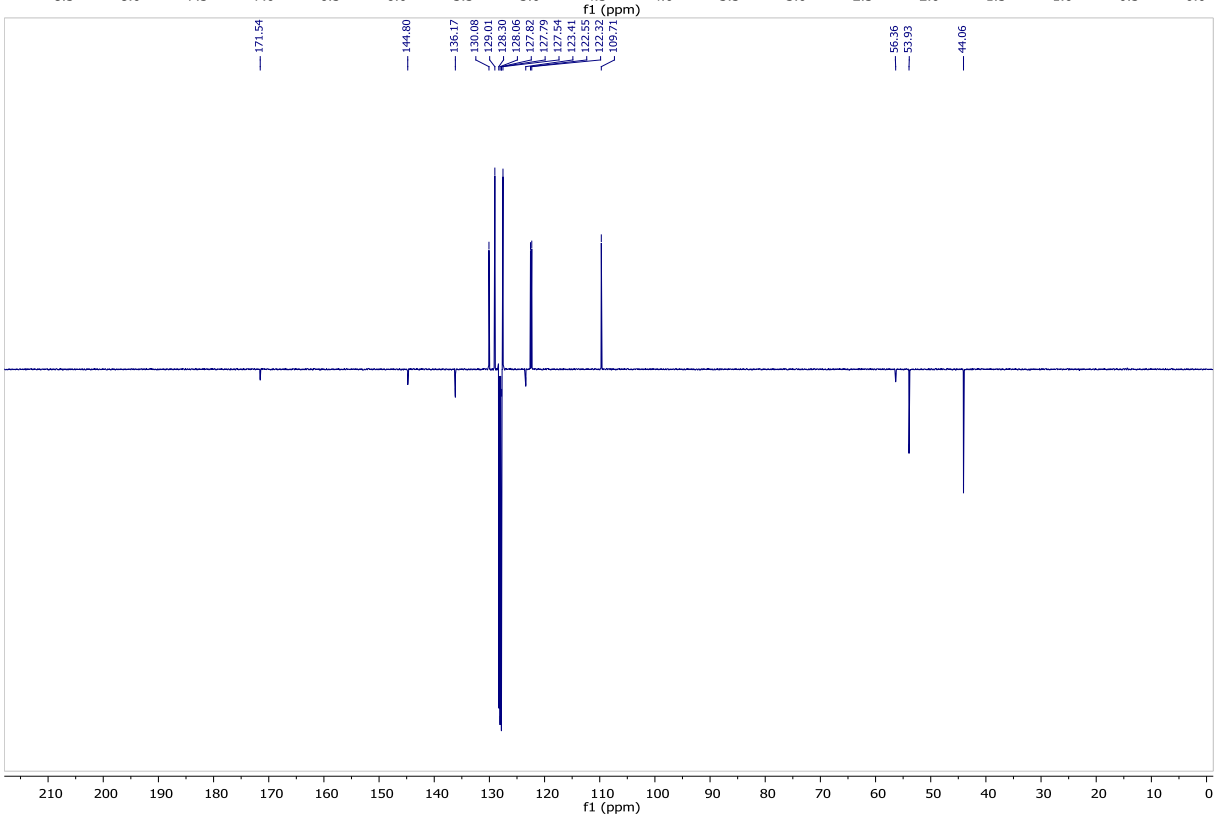

7.16
6.98
6.96
6.94
6.74
6.73
6.70
6.68
6.17
6.15
3.29
3.28
2.75
2.74
2.54
O
O
N
Me
1.06
1.96
0.99
1.00
1.03
3.01
f1 (ppm)
171.04
145.61
130.01
123.33
122.31
122.07
108.55
56.26
53.68
25.82
f1 (ppm)

2.147

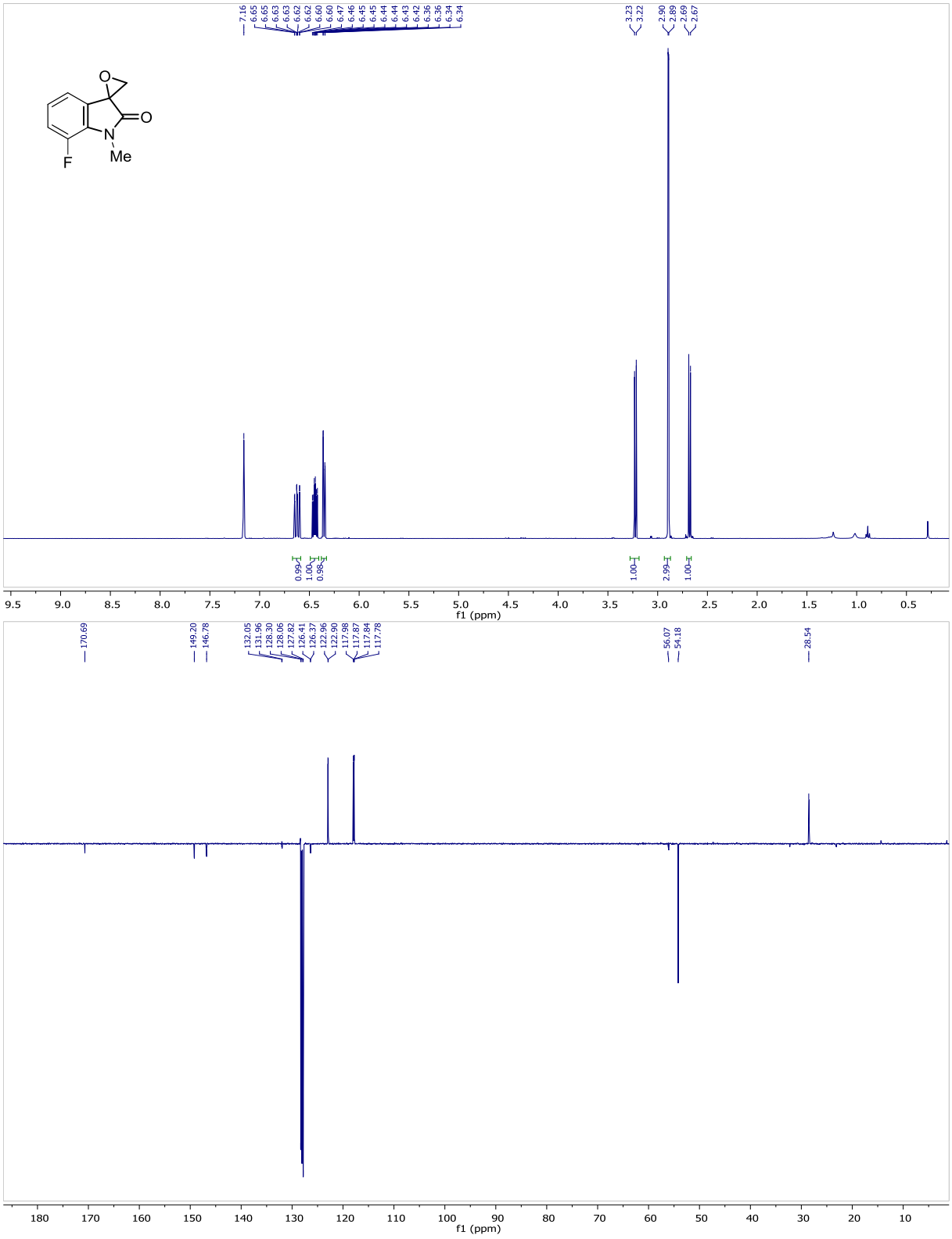

7.38
7.38
7.36
7.36
7.34
7.34
7.26
7.12
7.12
7.10
7.10
7.10
7.08
7.08
7.06
7.06
7.04
7.04
6.94
6.92
3.77
3.75
3.74
3.73
3.72
3.71
3.70
3.69
3.59
3.58
3.44
3.42
1.79
1.77
1.75
1.73
1.71
1.70
1.00
0.99
0.97
O
O
N
Me
1.00
1.98
1.00
1.97
1.01
0.98
2.13
3.01
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
171.63
144.59
130.29
122.77
122.59
122.18
109.09
77.32
77.00
76.68
56.28
54.12
42.08
20.78
11.36
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

2.148

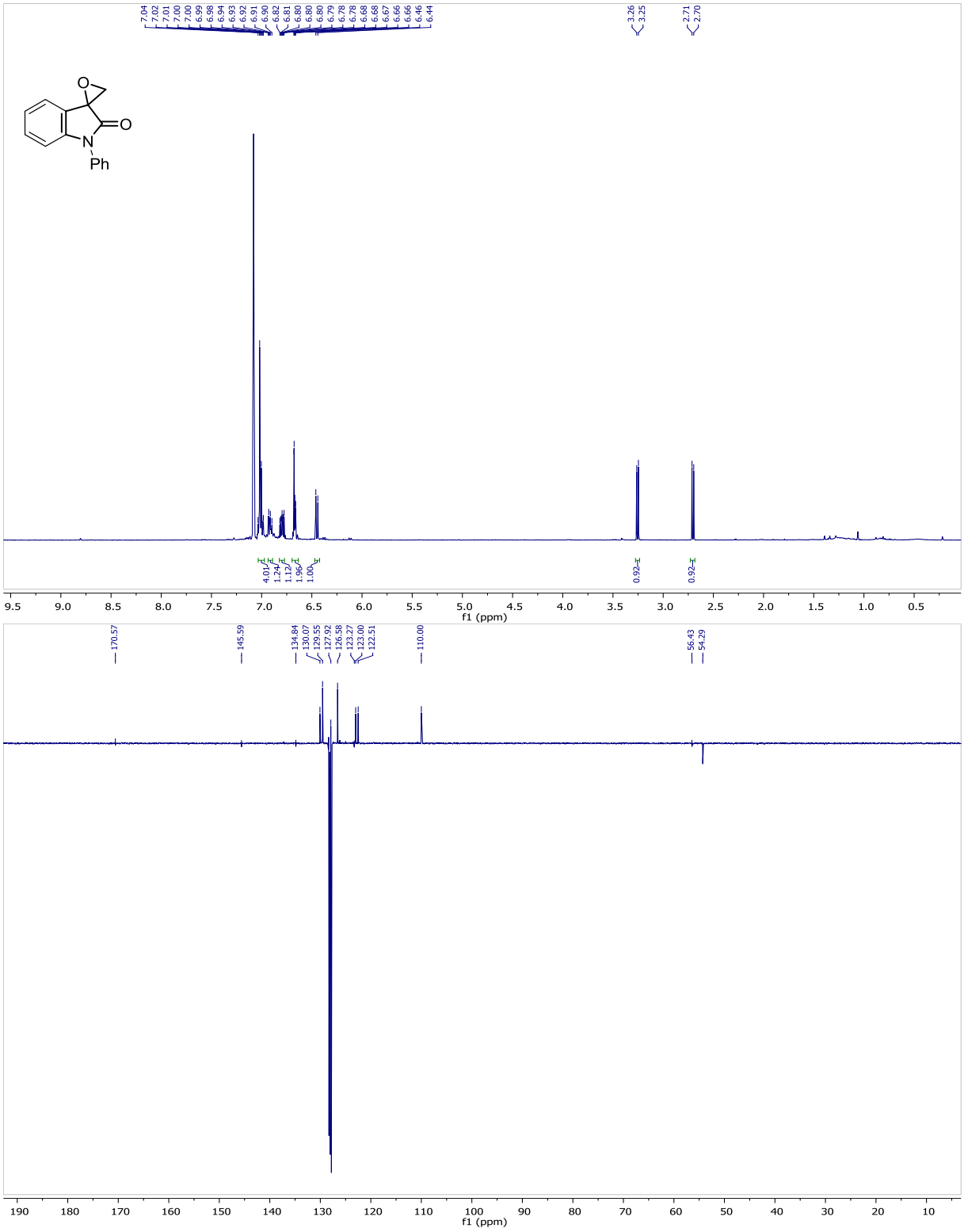

7.16
7.09
7.07
7.02
7.01
6.99
6.98
6.96
6.94
6.86
6.86
6.84
6.84
6.83
6.82
6.71
6.69
6.69
6.67
6.65
6.37
6.35
4.61
4.57
4.49
4.45
3.35
3.33
2.77
2.76
O
O
N
Ph
2.00
3.04
1.02
2.00
0.99
1.01
1.01
1.00
1.00
f1 (ppm)


171.54
144.80
136.17
130.08
129.01
128.30
128.06
127.82
127.79
127.54
123.41
122.55
122.32
109.71
56.36
53.93
44.06
f1 (ppm)

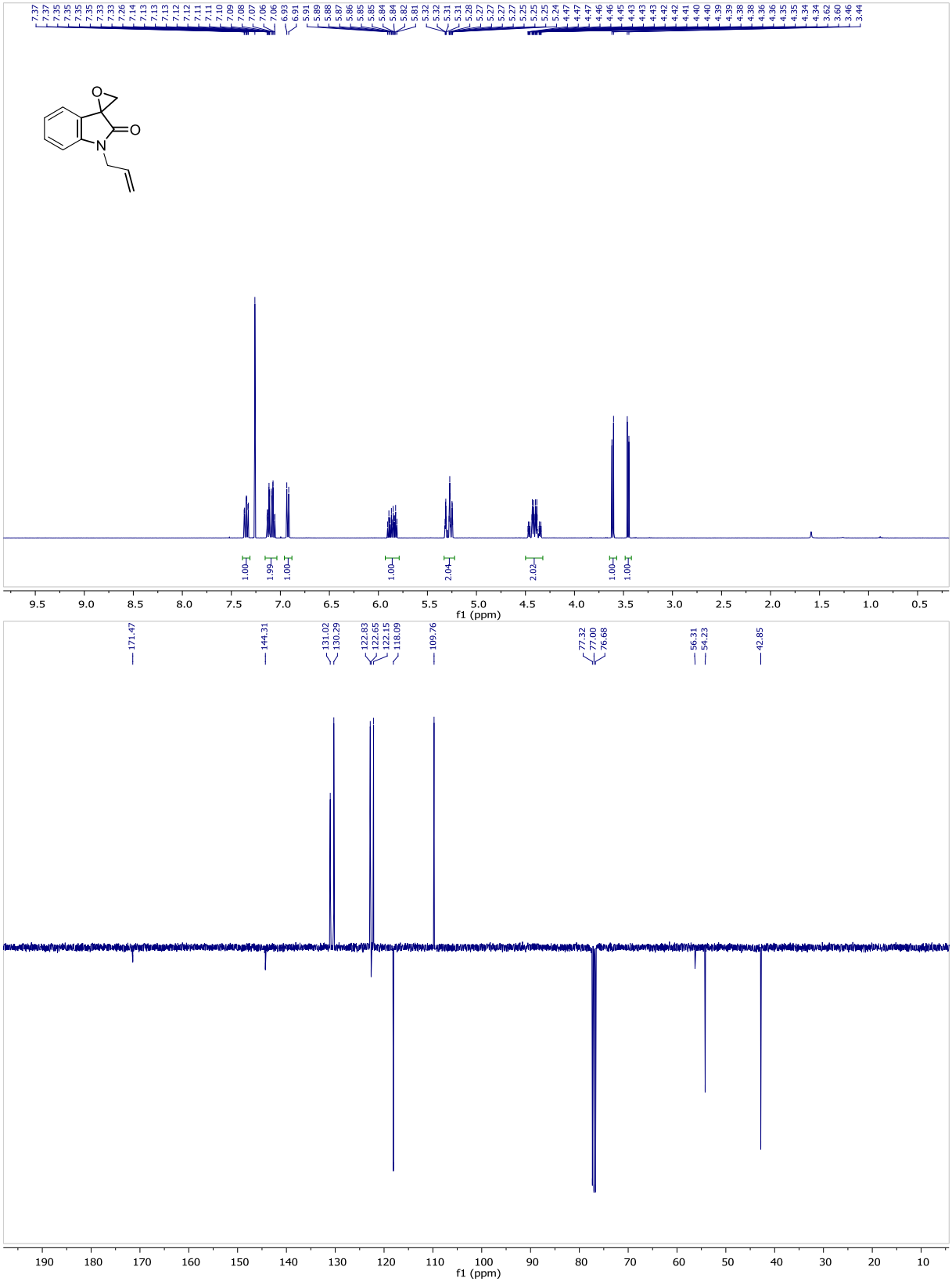
2.149


7.16
6.65
6.65
6.63
6.63
6.62
6.62
6.60
6.60
6.47
6.46
6.45
6.45
6.44
6.44
6.43
6.42
6.36
6.36
6.34
6.34
6.34
3.23
3.22
2.90
2.89
2.69
2.67
O
O
N
Me
F
0.99
1.00
0.98
1.00
2.99
1.00
f1 (ppm)
170.69
149.20
146.78
132.05
131.96
128.30
128.06
127.82
126.41
126.37
122.96
122.90
117.98
117.87
117.84
117.78
56.07
54.18
28.54
f1 (ppm)

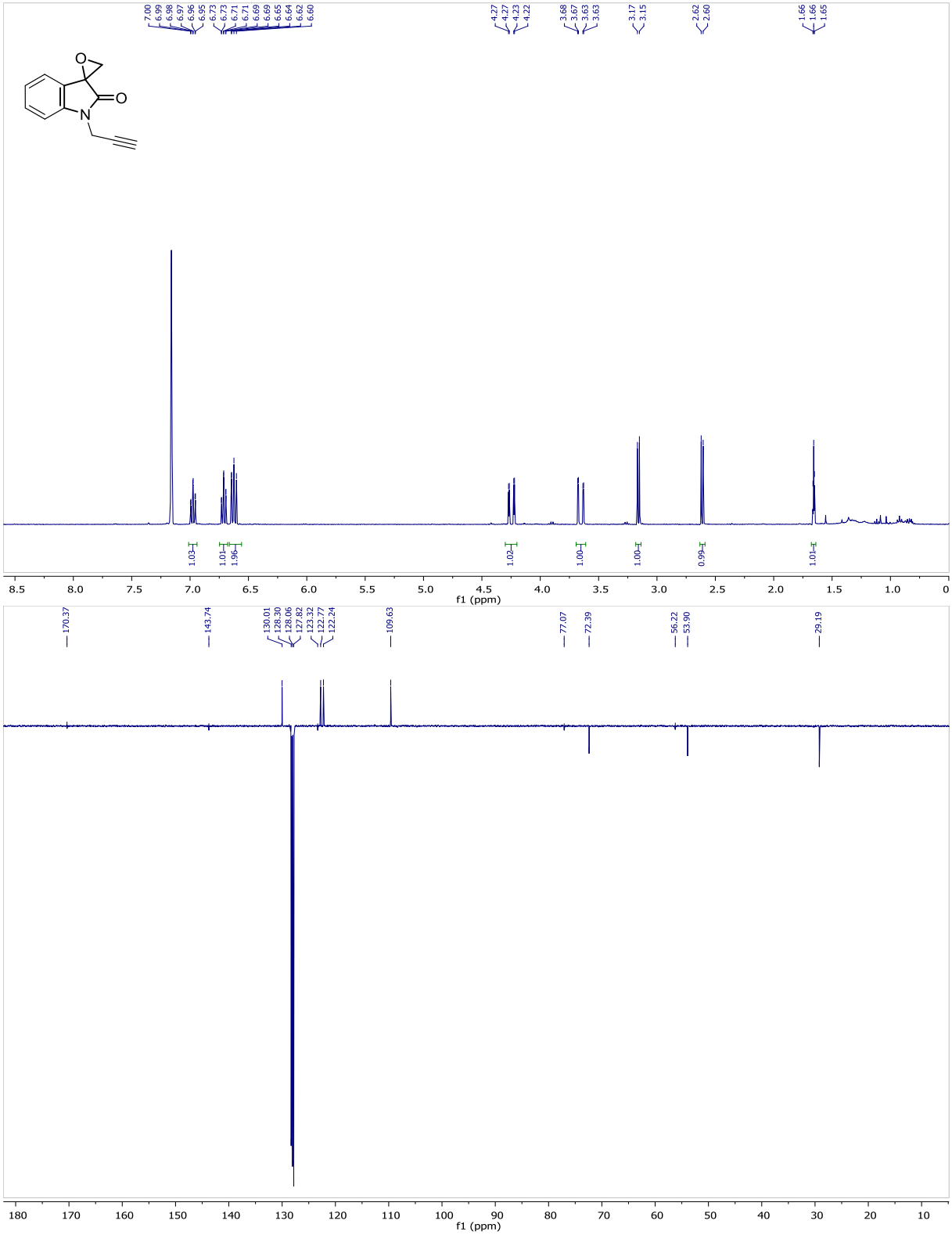
2.150


7.04
7.02
7.01
7.00
7.00
6.99
6.98
6.94
6.93
6.92
6.91
6.90
6.82
6.81
6.80
6.80
6.80
6.79
6.78
6.78
6.68
6.68
6.67
6.66
6.66
6.46
6.44
3.26
3.25
2.71
2.70
O
O
N
Ph
4.01
1.24
1.12
1.96
1.00
0.92
0.92
f1 (ppm)
170.57
145.59
134.84
130.07
129.55
127.92
126.58
123.27
123.00
122.51
110.00
56.43
54.29
f1 (ppm)

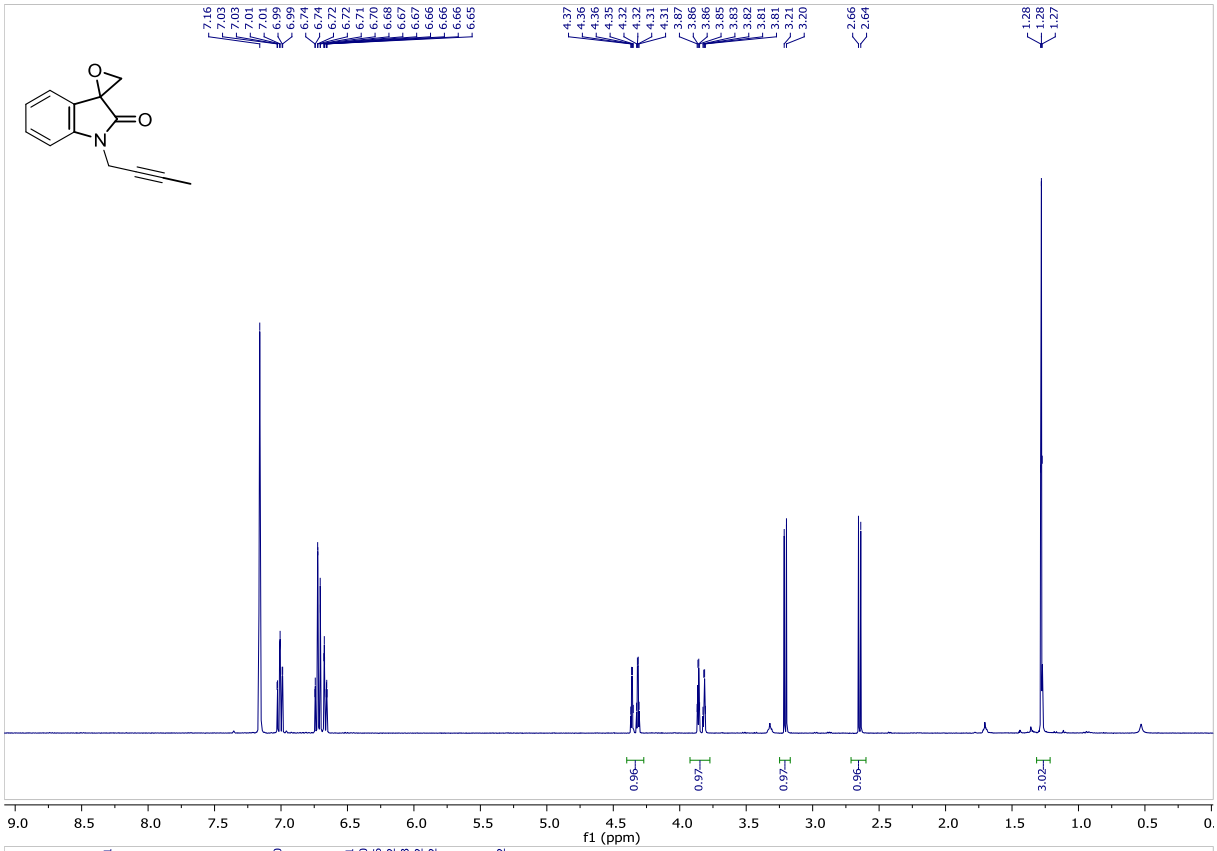
2.151


7.37 7.37 7.35 7.35 7.35 7.35 7.33 7.33 7.26 7.14 7.13 7.13 7.13 7.12 7.12 7.11 7.11 7.10 7.09 7.08 7.07 7.06 7.06 6.93 6.91 5.91 5.89 5.88 5.87 5.86 5.85 5.85 5.84 5.84 5.82 5.81 5.32 5.32 5.31 5.31 5.28 5.27 5.27 5.27 5.27 5.25 5.25 5.25 5.24 4.47 4.47 4.46 4.46 4.45 4.43 4.43 4.42 4.42 4.41 4.40 4.40 4.39 4.39 4.38 4.38 4.36 4.36 4.35 4.35 4.34 3.44 3.02 3.00 3.46 3.44
O
O
N
1.00 1.99 1.00 1.00 2.04 2.02 1.00 1.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)
171.47 144.31 131.02 130.29 122.83 122.65 122.15 118.09 109.76 77.32 77.00 76.68 56.31 54.23 42.85
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

2.152


7.00
6.99
6.98
6.97
6.96
6.95
6.73
6.73
6.71
6.71
6.69
6.69
6.65
6.64
6.62
6.60
4.27
4.27
4.23
4.22
3.68
3.67
3.63
3.63
3.17
3.15
2.62
2.60
1.66
1.66
1.65
O
O
N
1.03
1.01
1.96
1.02
1.00
1.00
0.99
1.01
f1 (ppm)
170.37
143.74
130.01
128.30
128.06
127.82
123.32
122.77
122.24
109.63
77.07
72.39
56.22
53.90
29.19
f1 (ppm)

2.153


7.16
7.03
7.03
7.01
7.01
6.99
6.99
6.74
6.74
6.72
6.72
6.71
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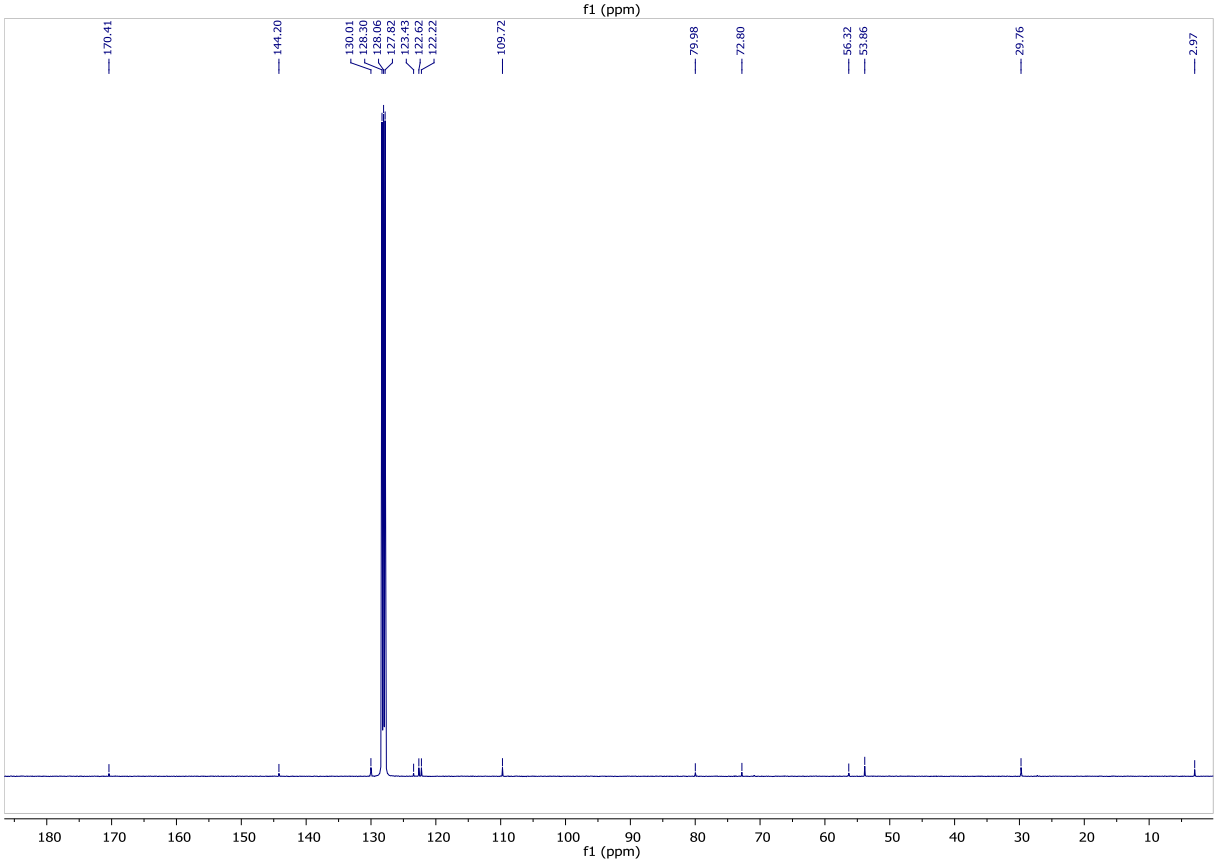
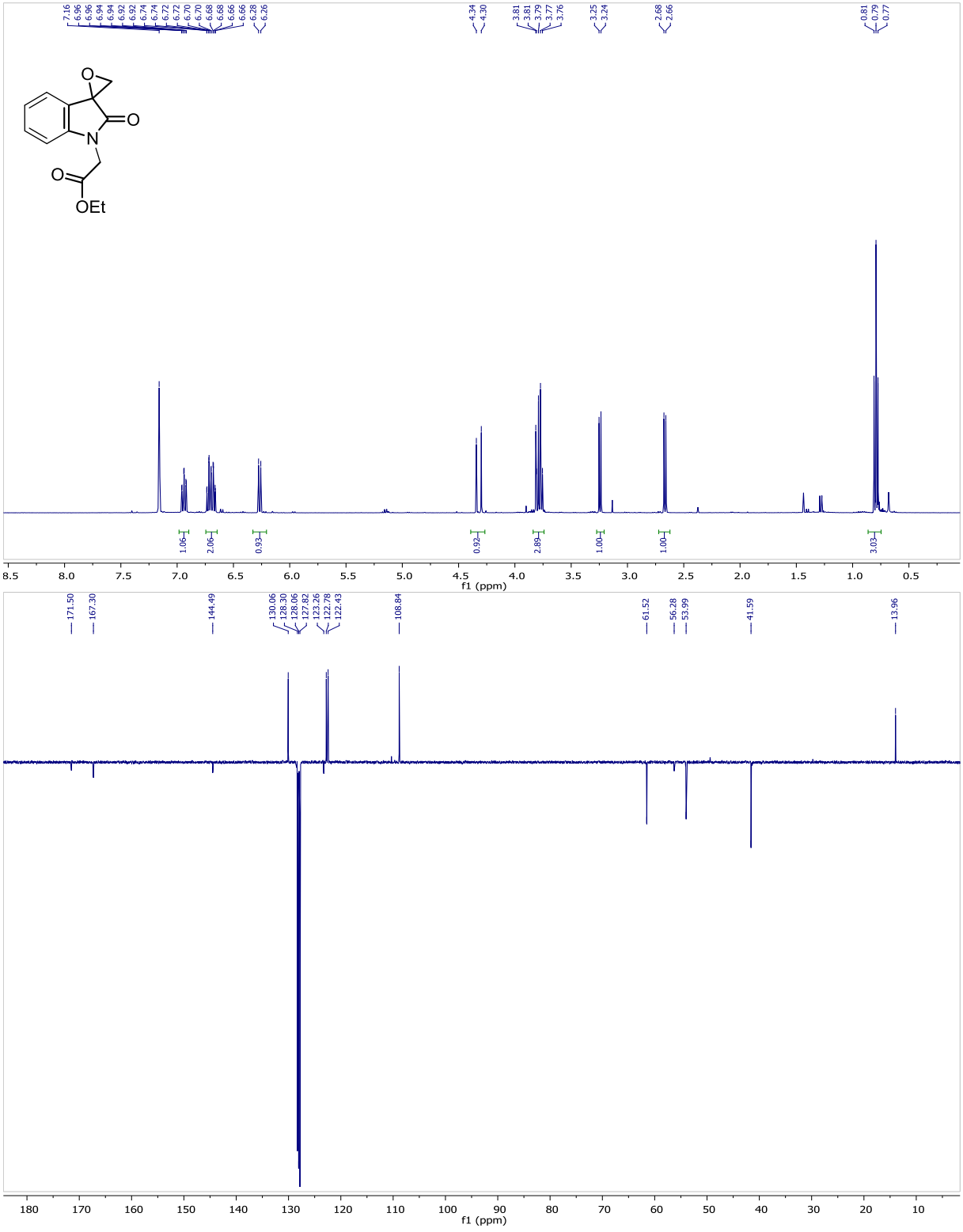
6.68
6.67
6.67
6.66
6.66
6.66
6.66
6.65
4.37
4.36
4.36
4.35
4.32
4.32
4.31
4.31
3.87
3.86
3.86
3.85
3.83
3.82
3.81
3.81
3.21
3.20
2.66
2.64
1.28
1.28
1.27
O
O
N
0.96
0.97
0.97
0.96
3.02
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


170.41
144.20
130.01
128.30
128.06
127.82
123.43
122.62
122.22
109.72
79.98
72.80
56.32
53.86
29.76
2.97
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

2.154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6.96
6.96
6.94
6.94
6.92
6.92
6.74
6.74
6.72
6.72
6.70
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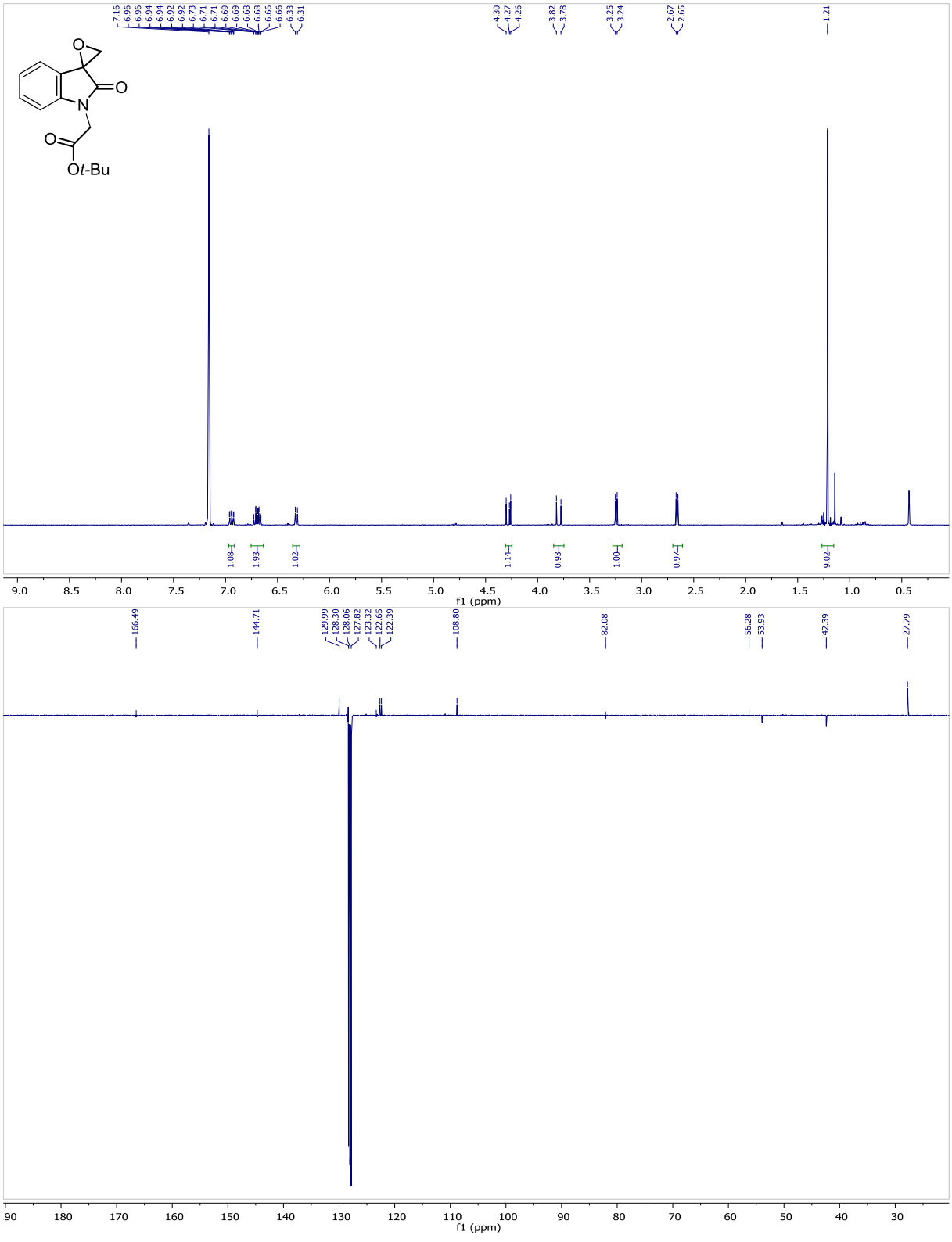
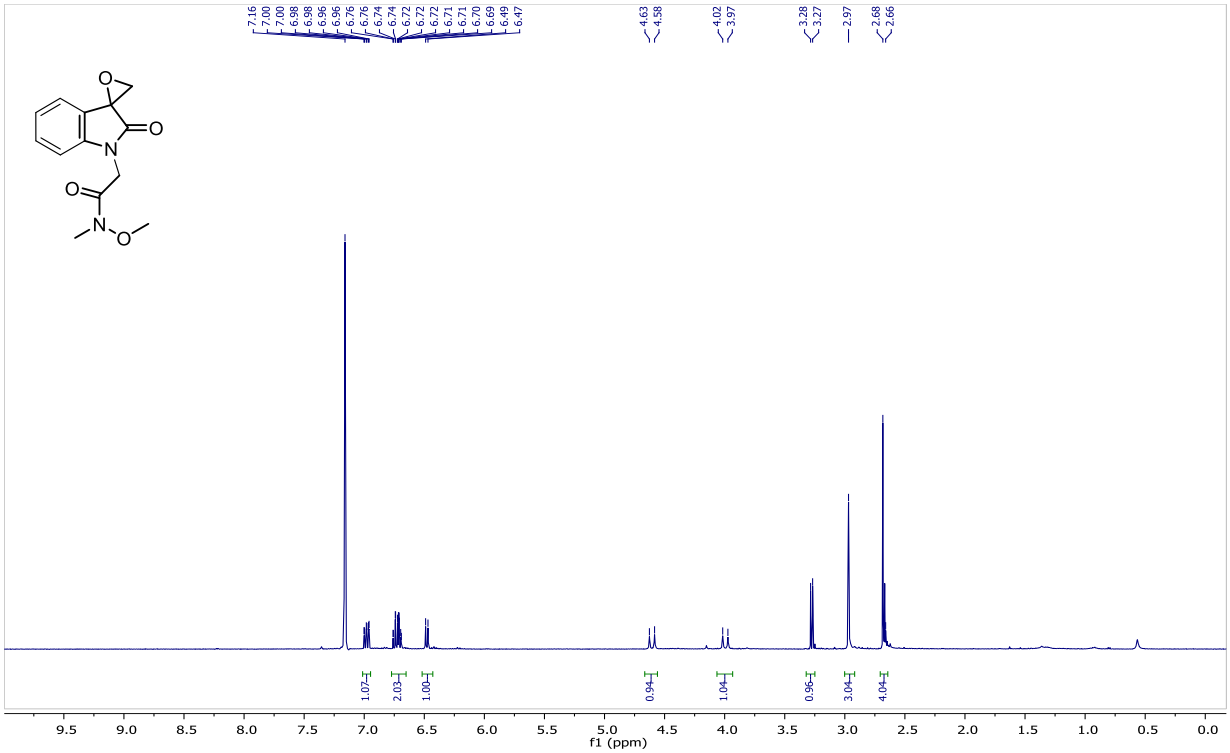
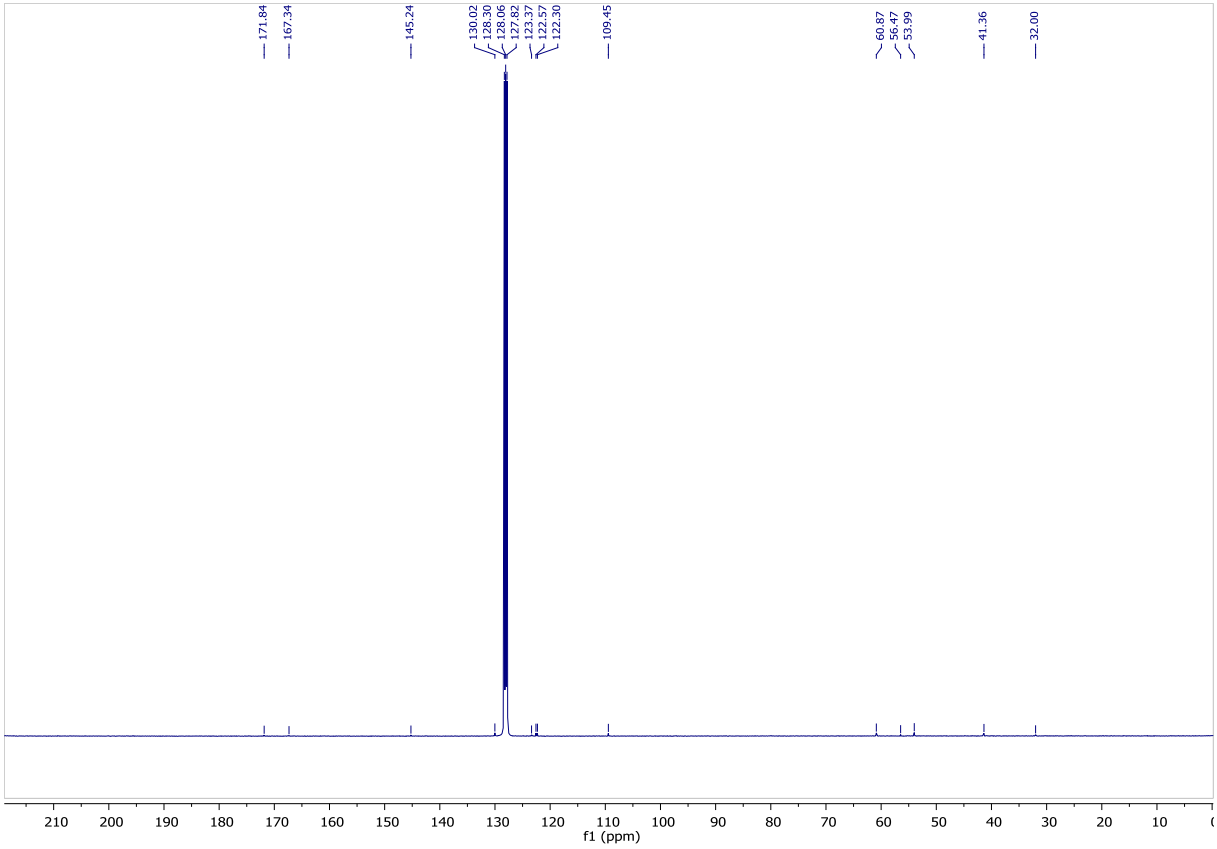
6.68
6.68
6.66
6.66
6.28
6.26
4.34
4.30
3.81
3.81
3.79
3.77
3.76
3.25
3.24
2.68
2.66
0.81
0.79
0.77
O
O
N
O
OEt
1.06
2.06
0.93
0.92
2.89
1.00
1.00
3.03
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
171.50
167.30
144.49
130.06
128.30
128.06
127.82
123.26
122.78
122.43
108.84
61.52
56.28
53.99
41.59
13.96
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

2.155

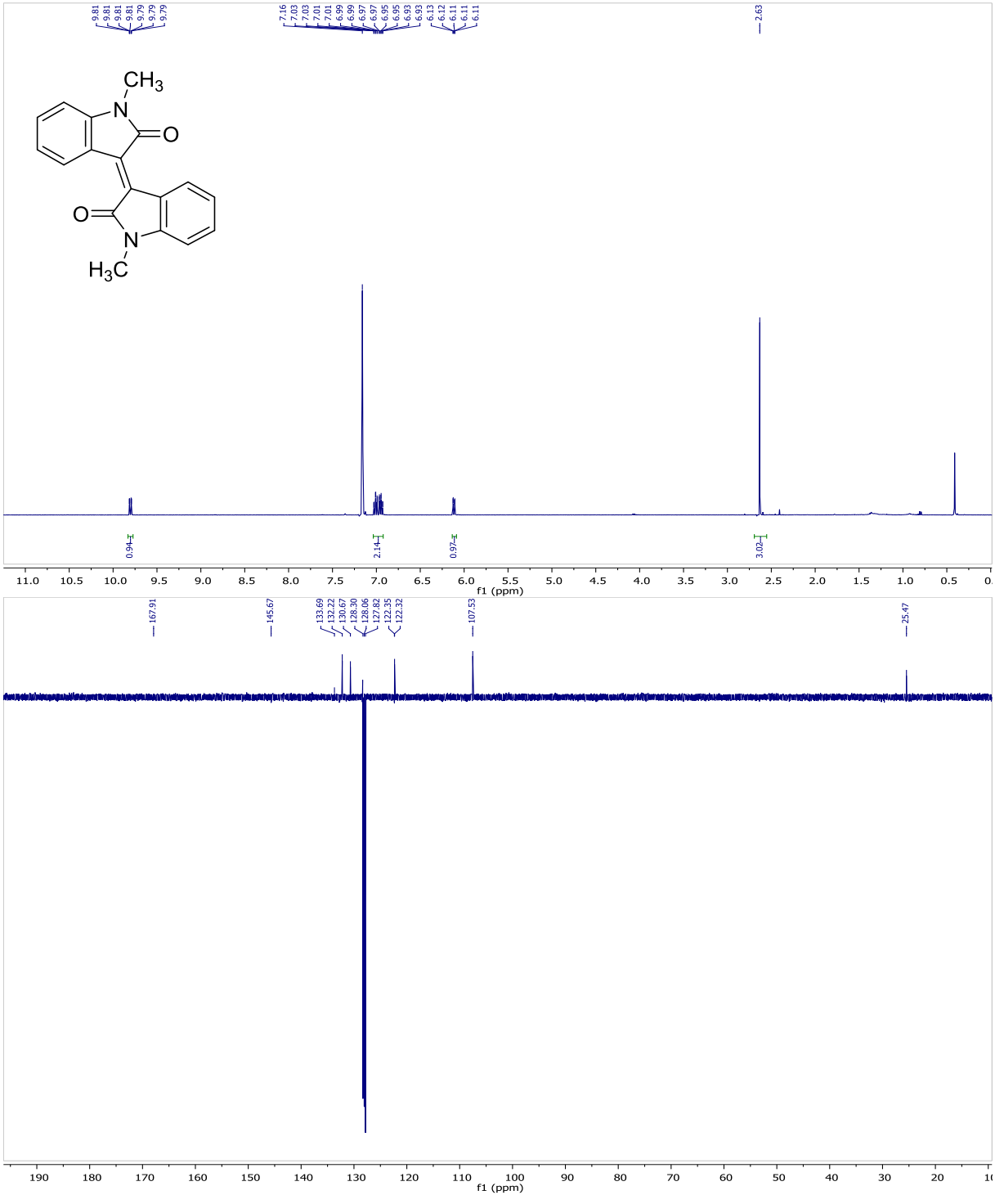

7.16
6.96
6.96
6.94
6.94
6.92
6.92
6.73
6.71
6.71
6.69
6.69
6.68
6.68
6.66
6.66
6.33
6.31
4.30
4.27
4.26
3.82
3.78
3.25
3.24
2.67
2.65
1.21
O
O
N
O
Ot-Bu
1.08
1.93
1.02
1.14
0.93
1.00
0.97
9.02
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)
166.49
144.71
129.99
128.30
128.06
127.82
123.32
122.65
122.39
108.80
82.08
56.28
53.93
42.39
27.79
90 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30
f1 (ppm)

2.156


7.16
7.00
7.00
6.98
6.98
6.96
6.96
6.76
6.76
6.74
6.74
6.72
6.72
6.72
6.72
6.71
6.71
6.70
6.69
6.49
6.47
4.63
4.58
4.02
3.97
3.28
3.27
2.97
2.68
2.66
1.07
2.03
1.00
0.94
1.04
0.96
3.04
4.04
f1 (ppm)

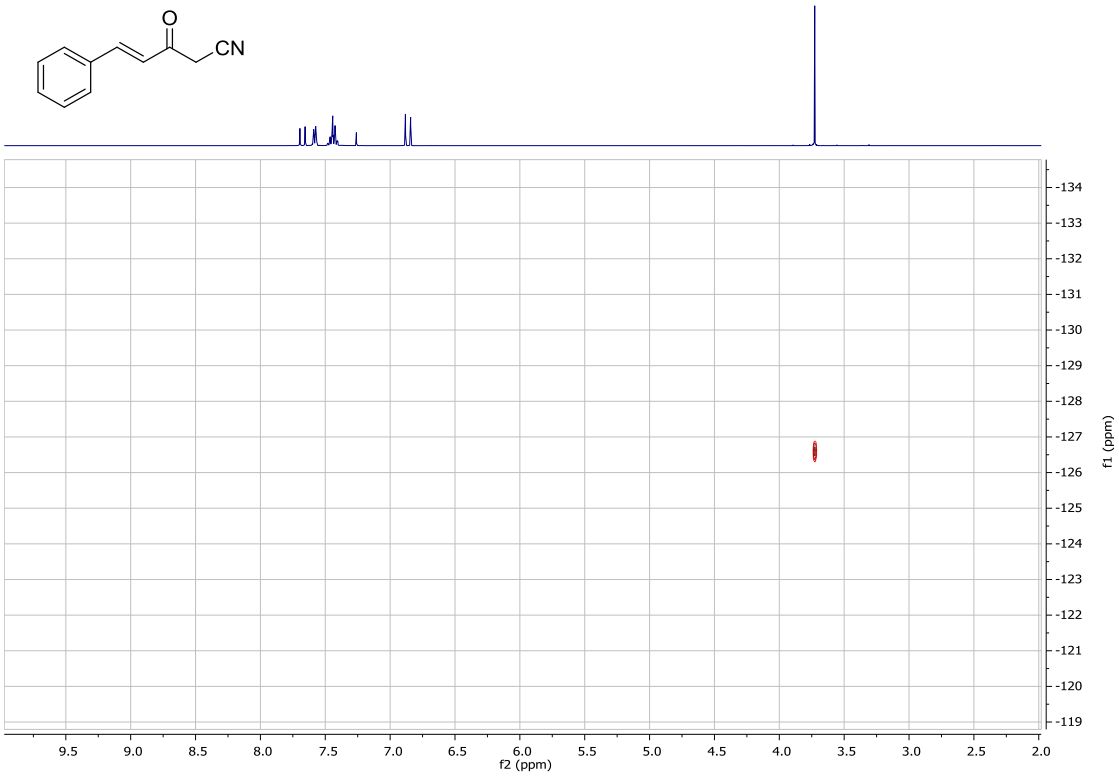

171.84
167.34
145.24
130.02
128.30
128.06
127.82
123.37
122.57
122.30
109.45
60.87
56.47
53.99
41.36
32.00
f1 (ppm)

2.157

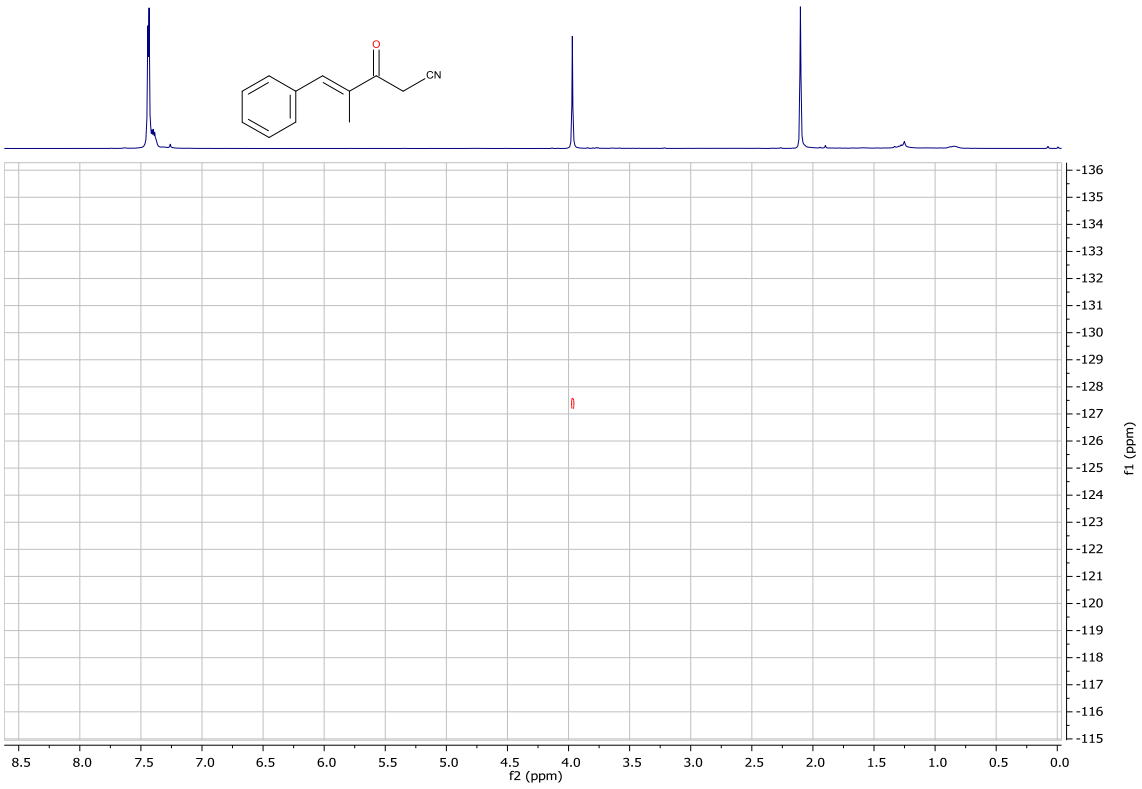

9.81
9.81
9.81
9.81
9.79
9.79
9.79
7.16
7.03
7.03
7.01
7.01
6.99
6.99
6.97
6.97
6.95
6.95
6.93
6.93
6.13
6.12
6.11
6.11
6.11
2.63
CH3
N
O
O
N
H3C
0.94
2.14
0.97
3.02
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
167.91
145.67
133.69
132.22
130.67
128.30
128.06
127.82
122.35
122.32
107.53
25.47
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

S.2.4 Copies of ^{15}N NMR Spectras for Selected compounds

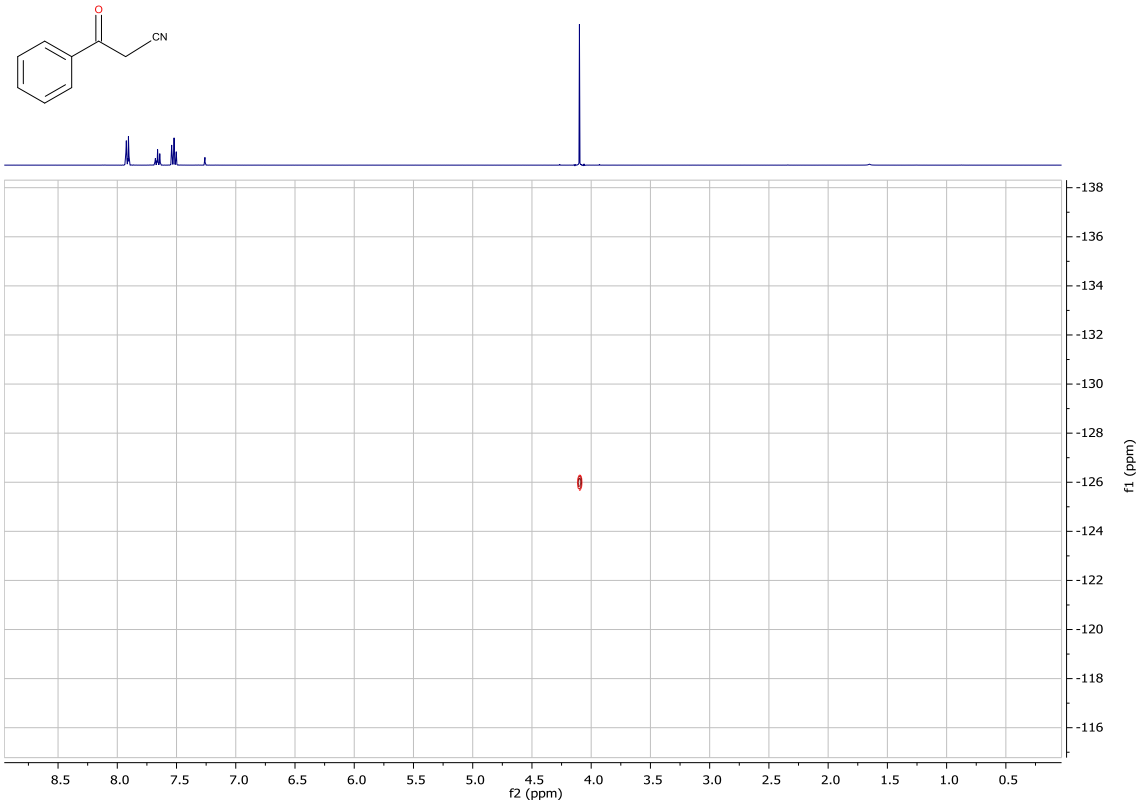
2.112 (^{1}H,^{15}N - HMBC)



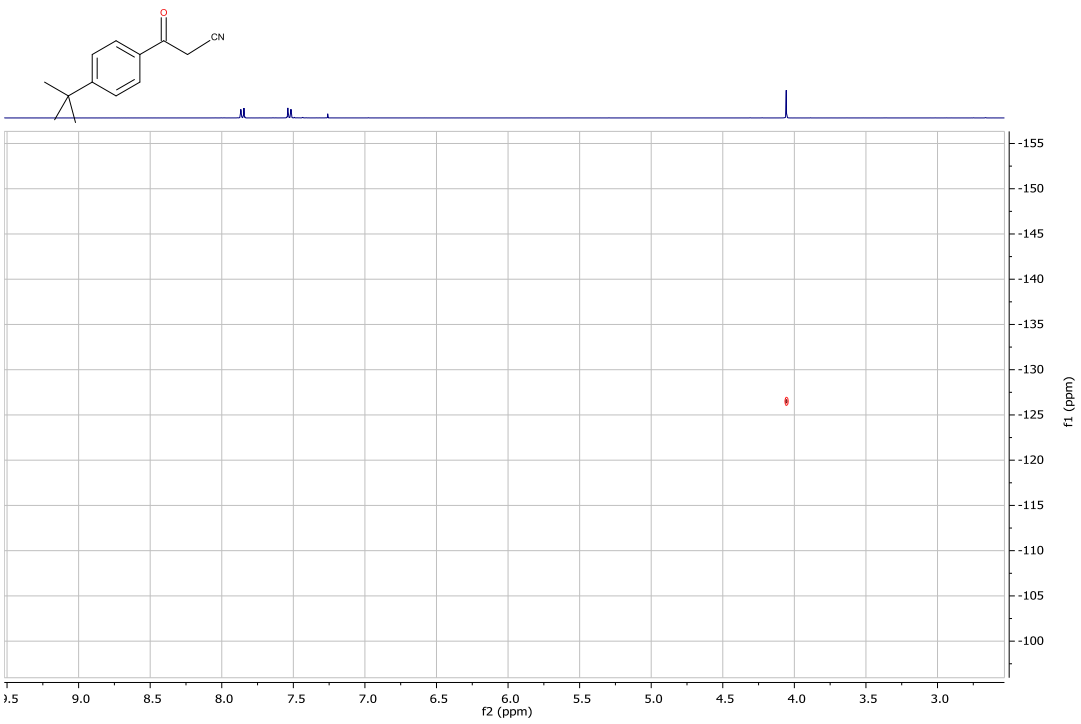
2.114a (^{1}H,^{15}N - HMBC)



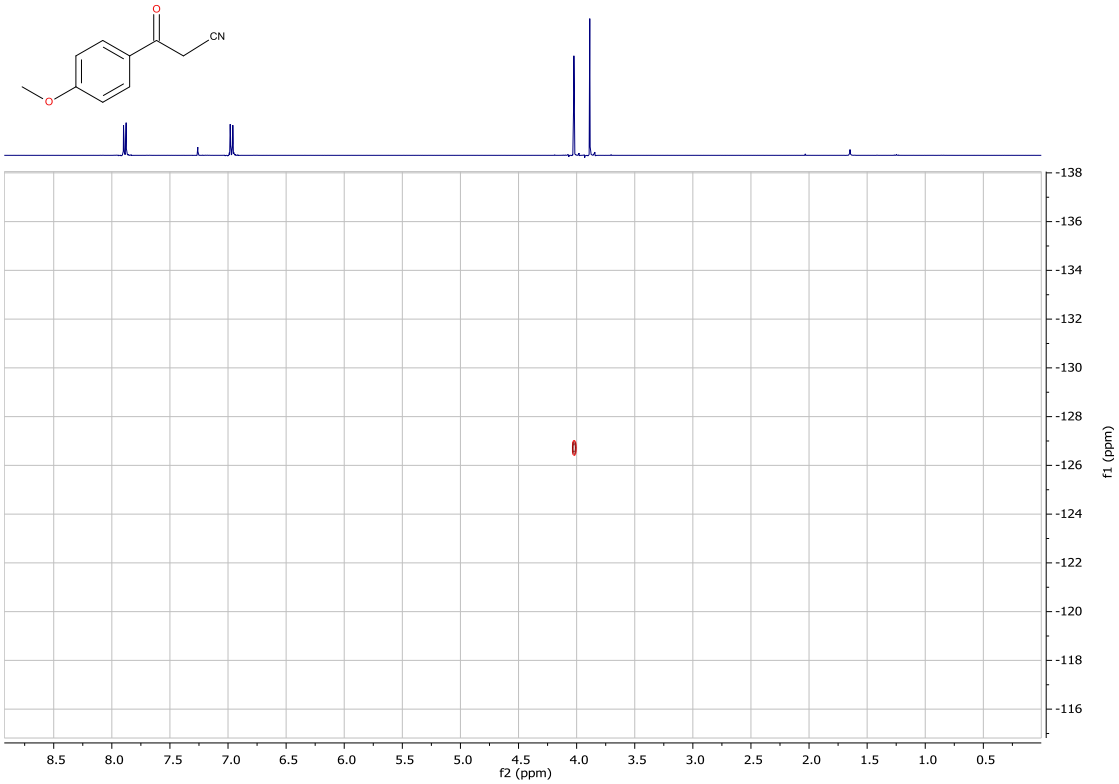
2.114d (^{1}H,^{15}N - HMBC)



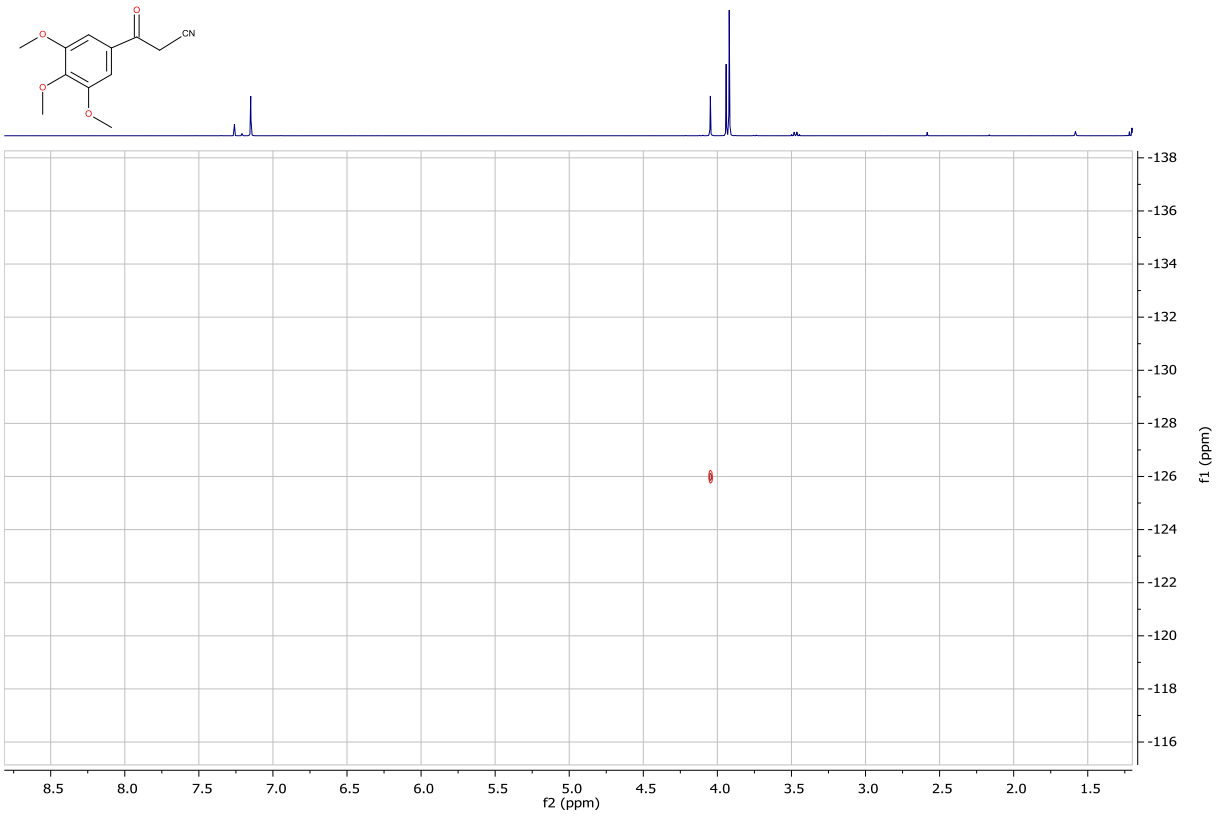
2.114e (^{1}H,^{15}N - HMBC)



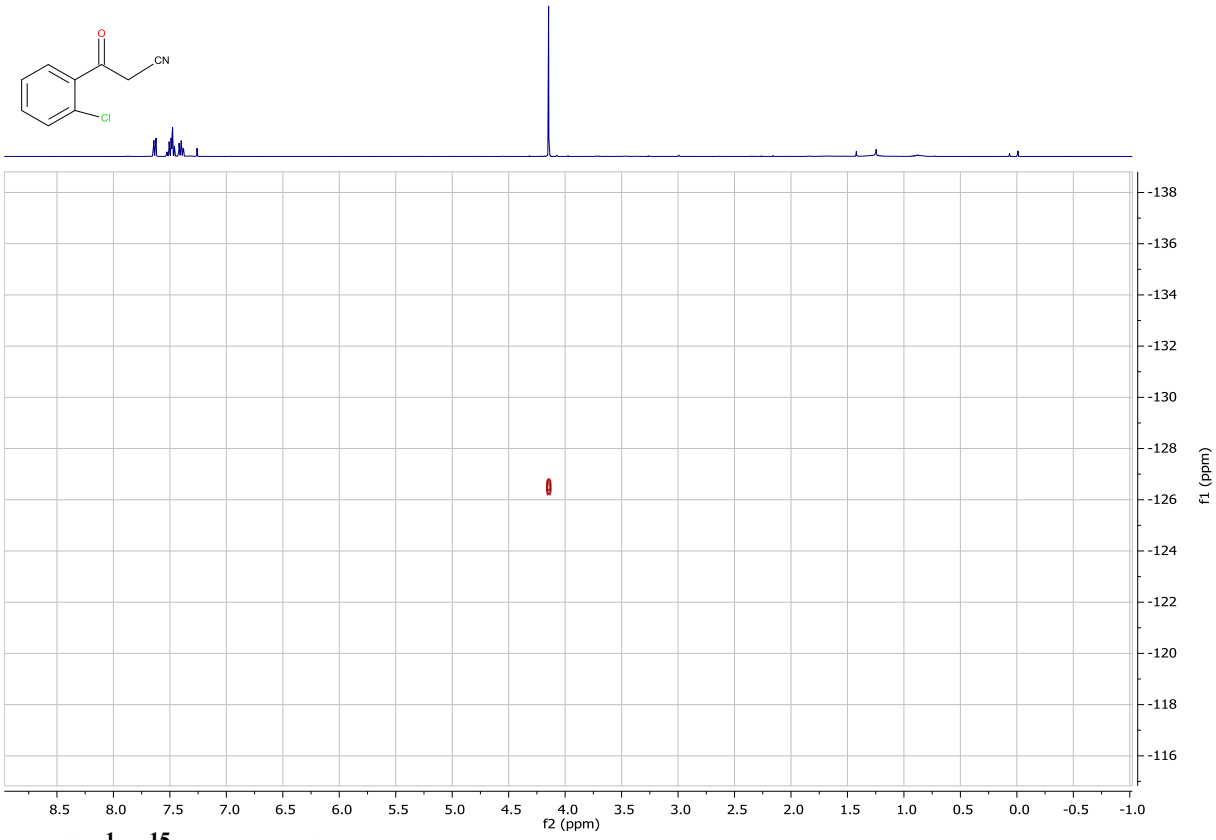
2.114f (^{1}H,^{15}N - HMBC)



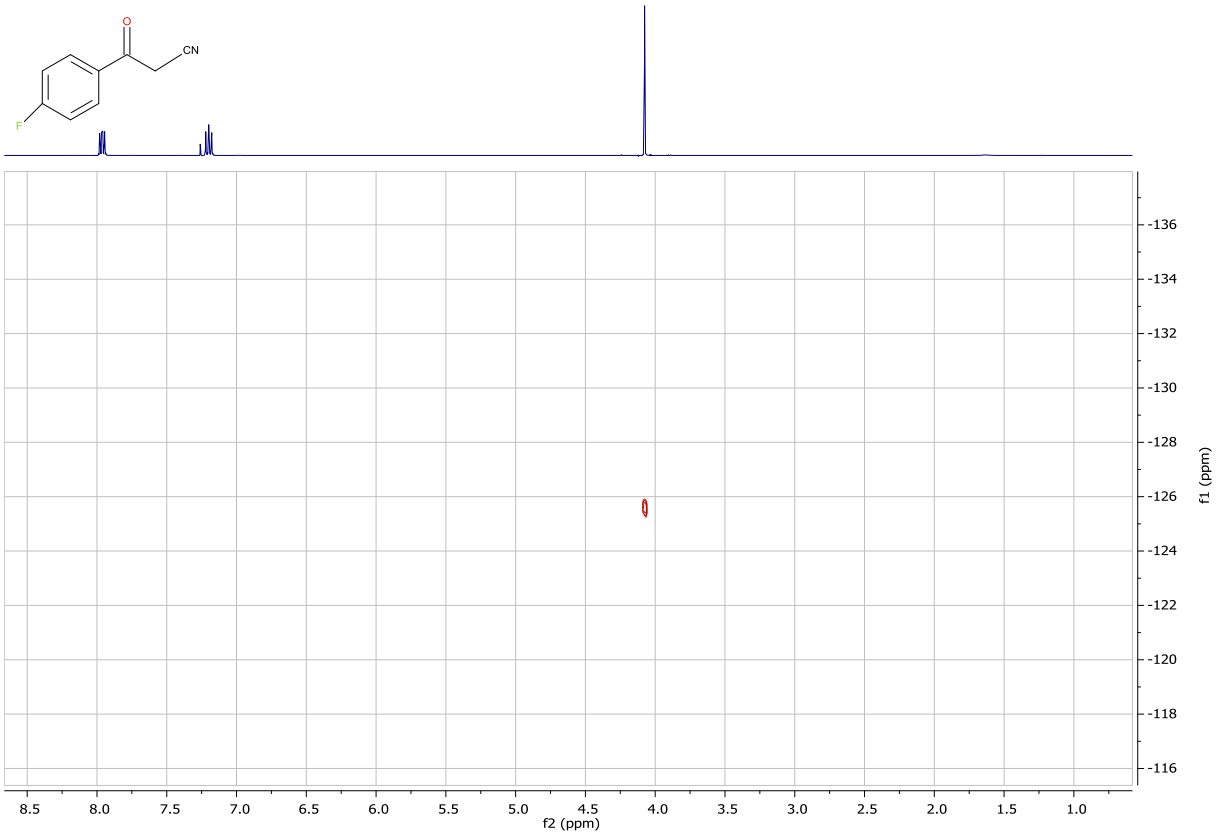
2.114g (^{1}H,^{15}N - HMBC)



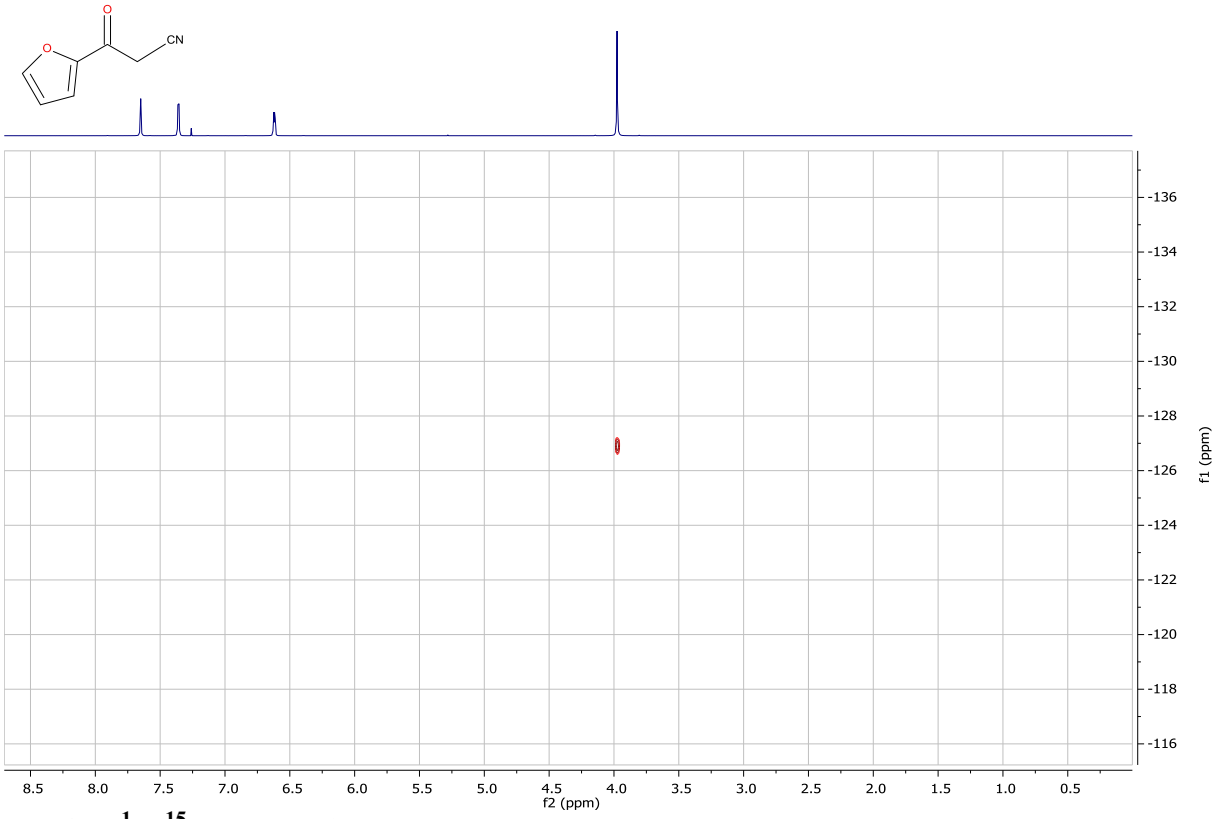
2.114h (^{1}H,^{15}N - HMBC)



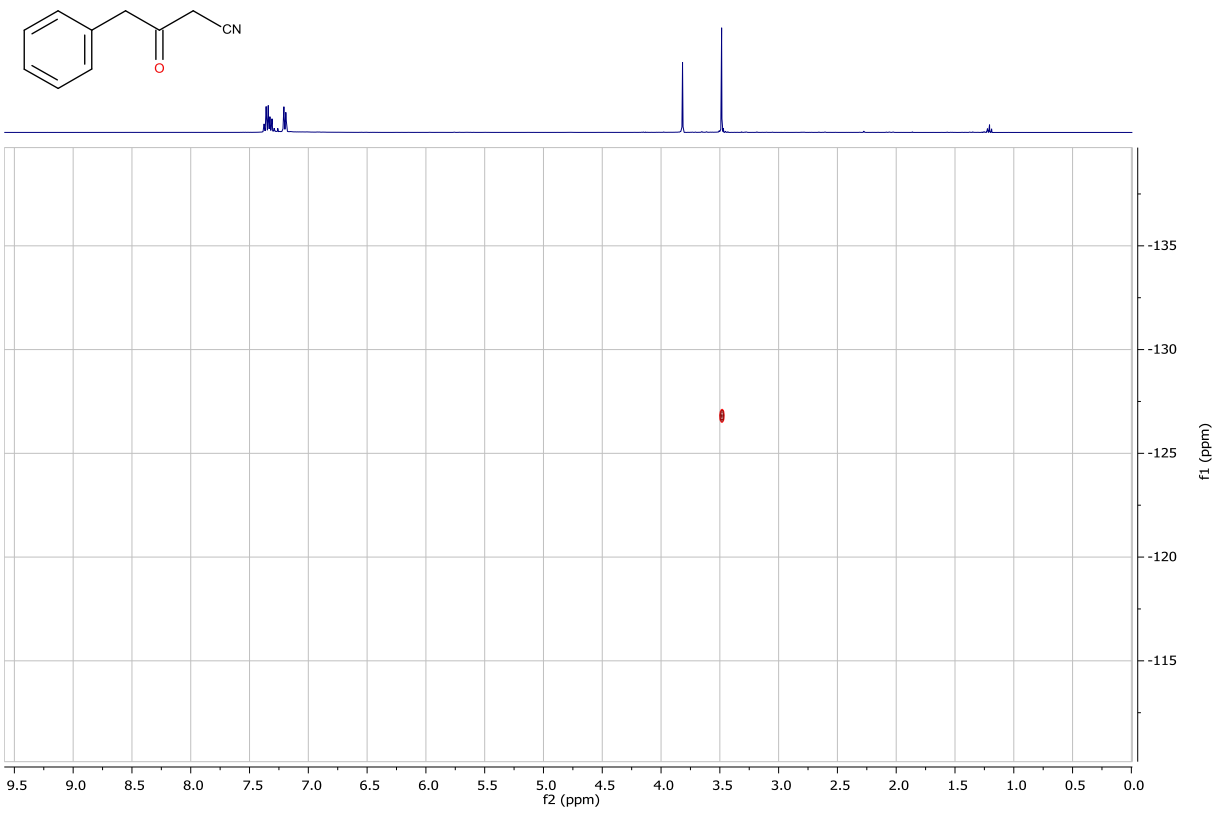
2.114j (^{1}H,^{15}N - HMBC)



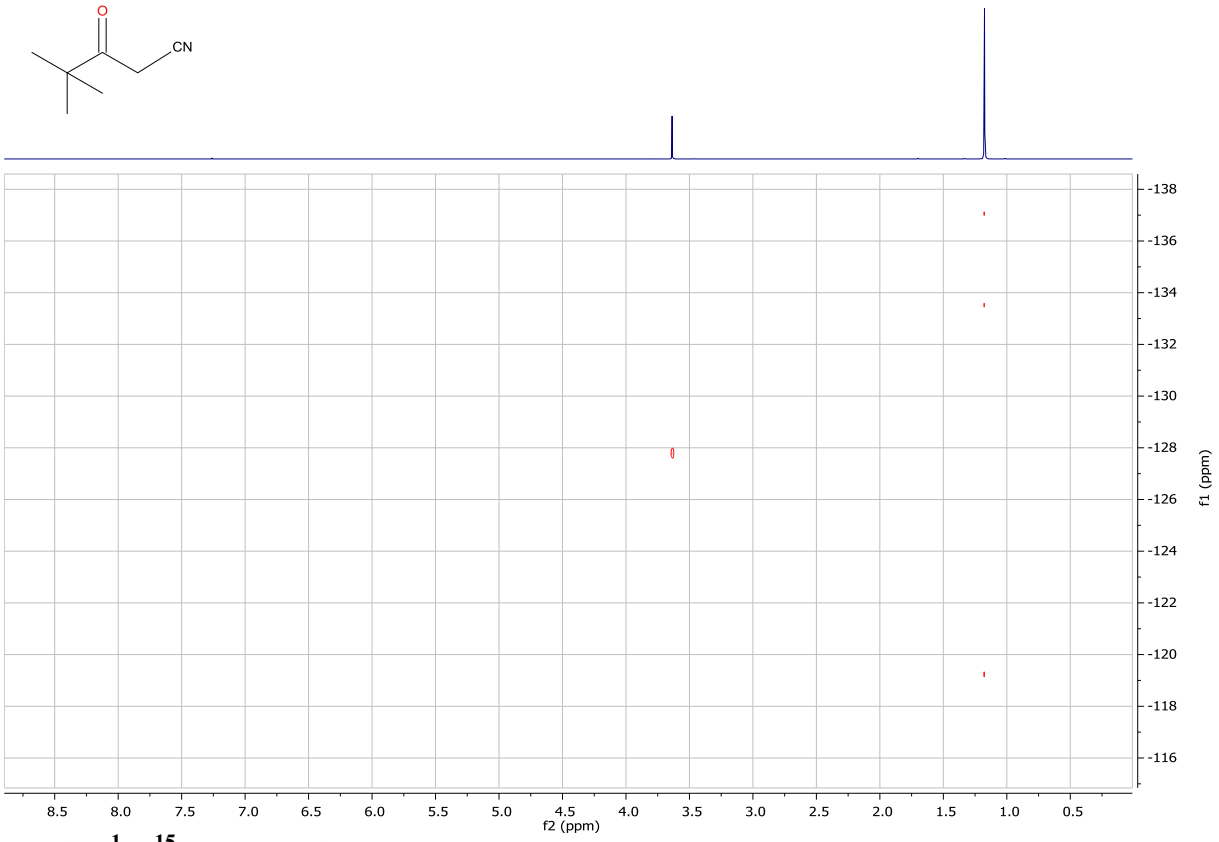
2.114k (^{1}H,^{15}N - HMBC)



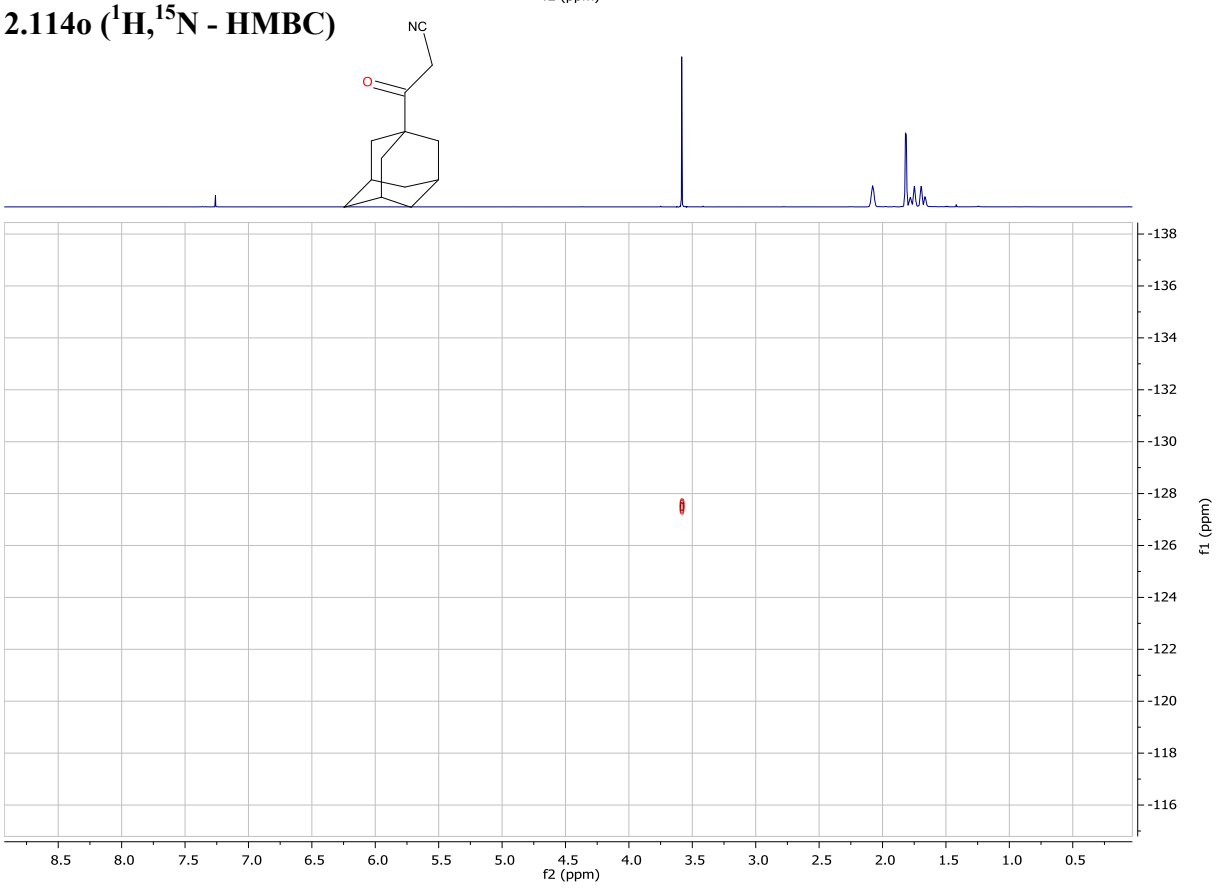
2.114m (^{1}H,^{15}N - HMBC)



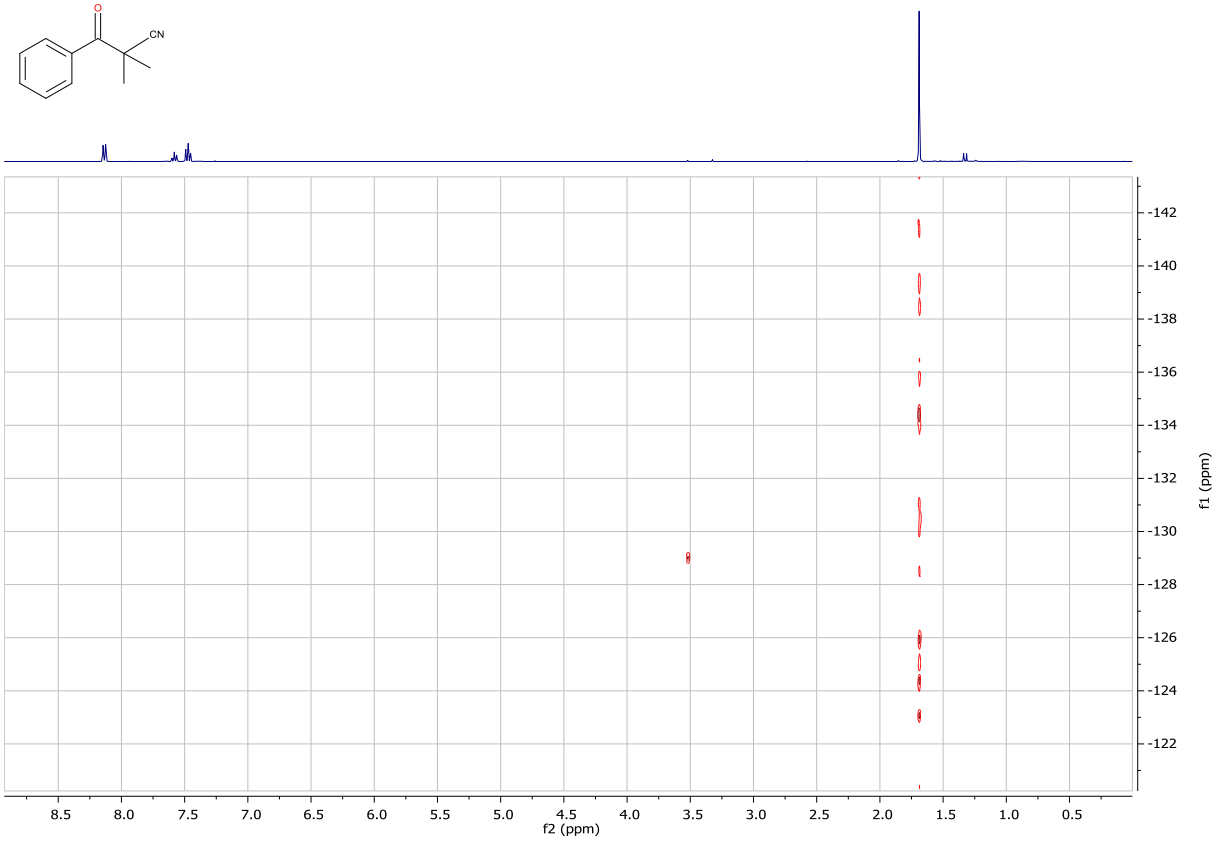
2.114n (^{1}H,^{15}N - HMBC)



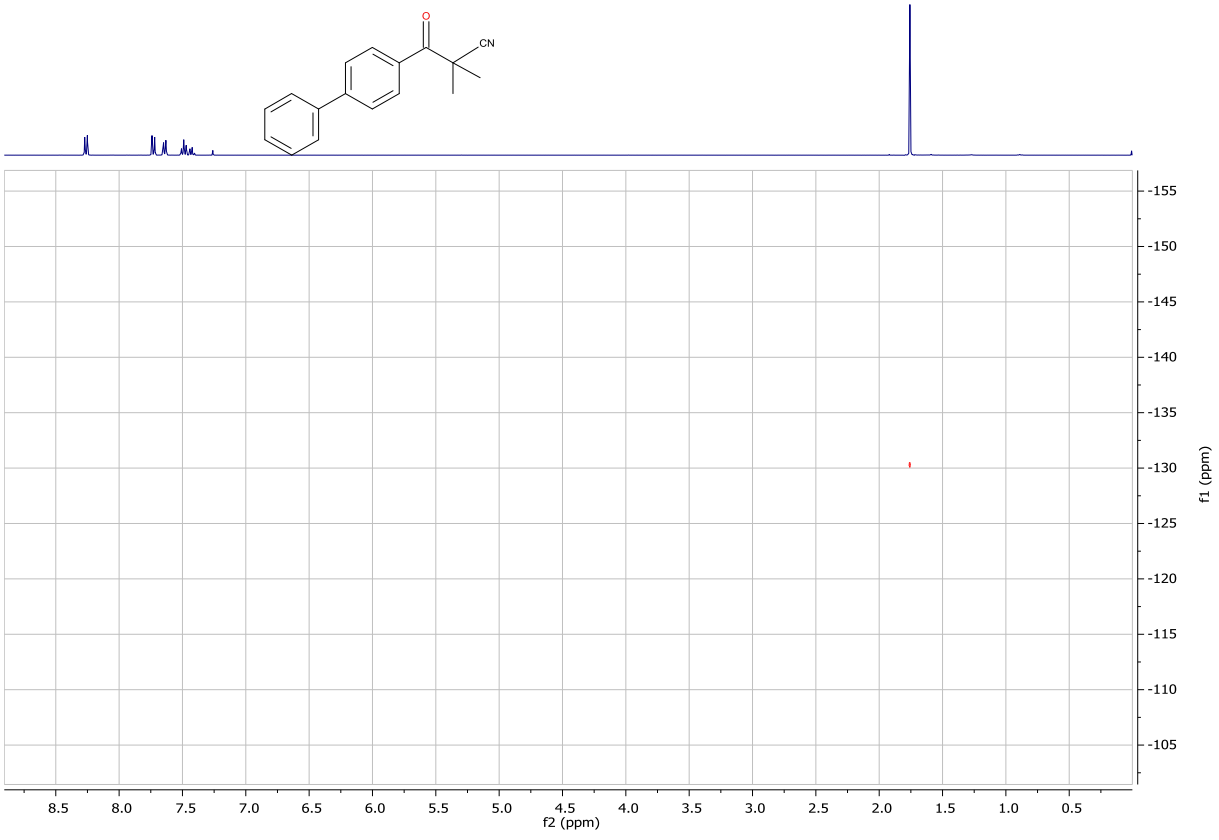
2.114o (^{1}H,^{15}N - HMBC)



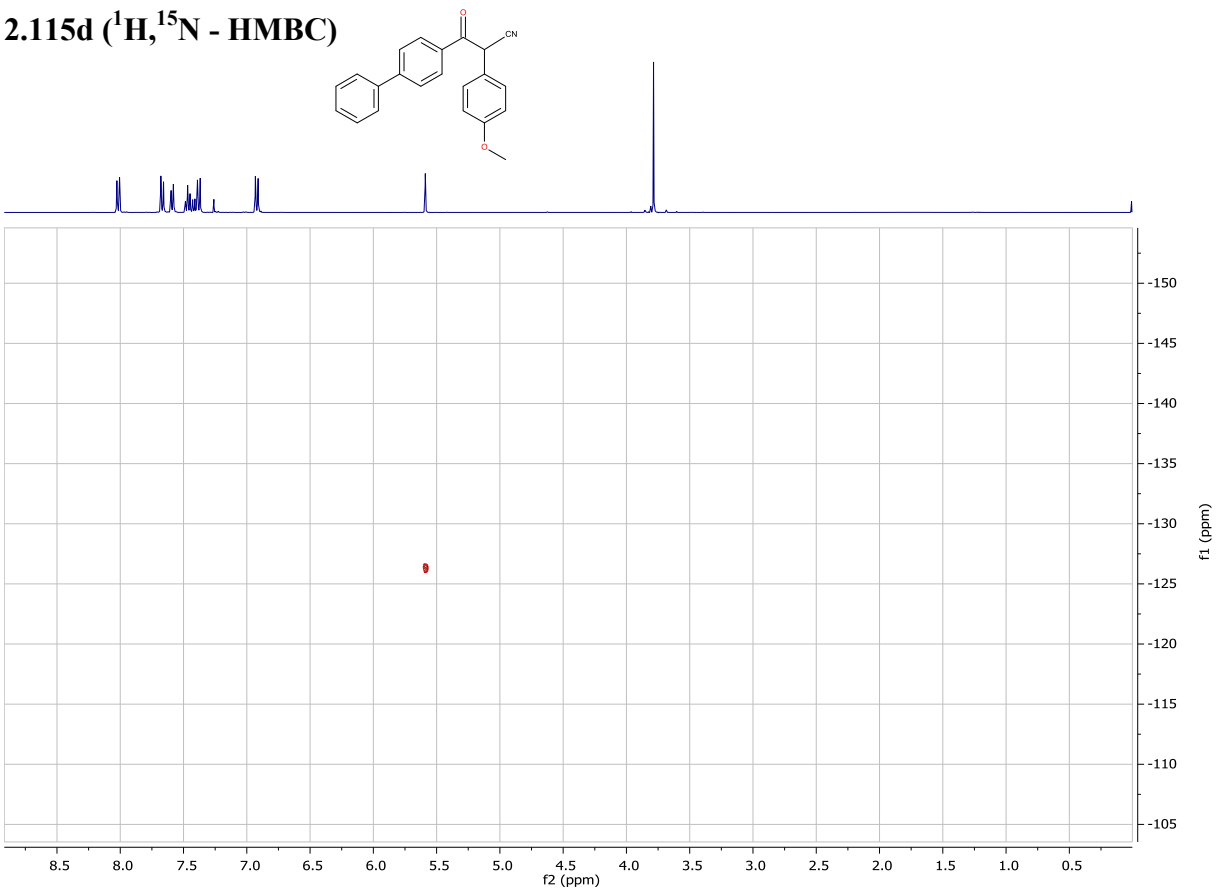
2.115b (^{1}H,^{15}N - HMBC)



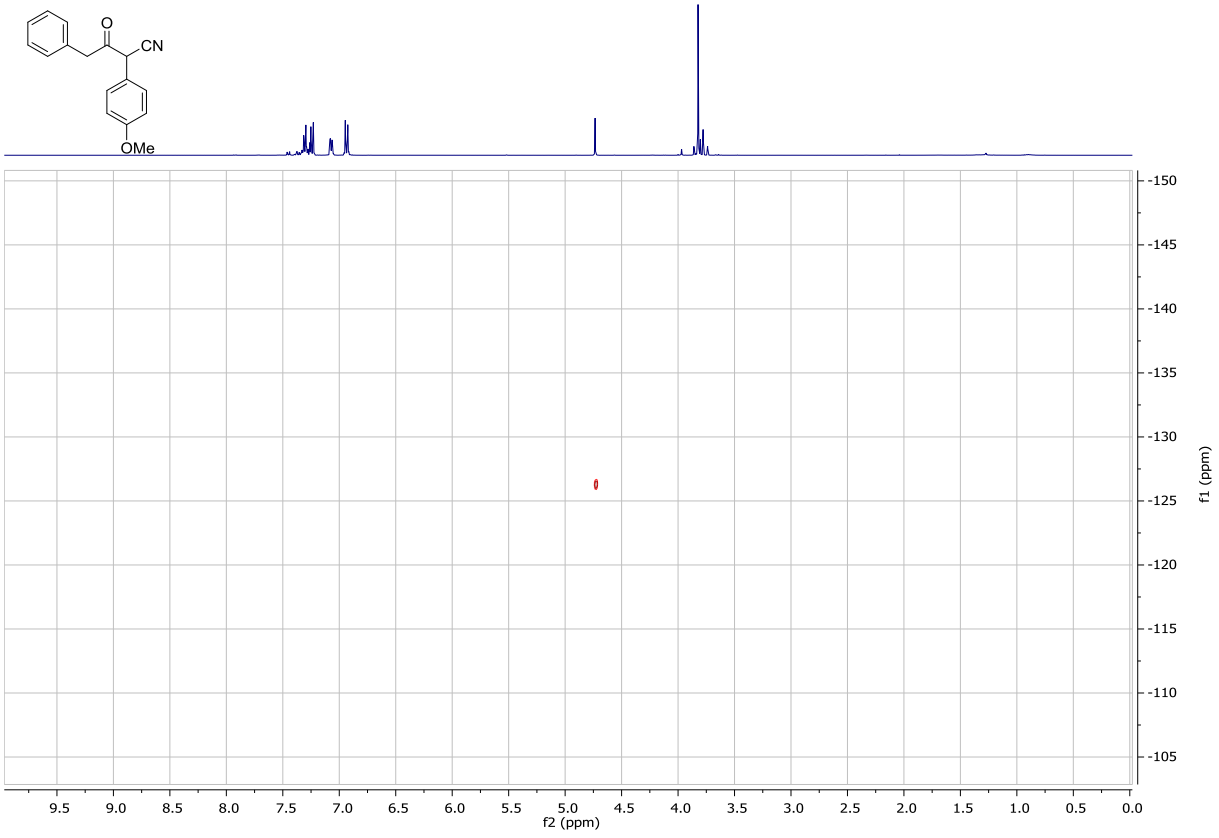
2.115c (^{1}H,^{15}N - HMBC)



2.115d (^{1}H,^{15}N - HMBC)

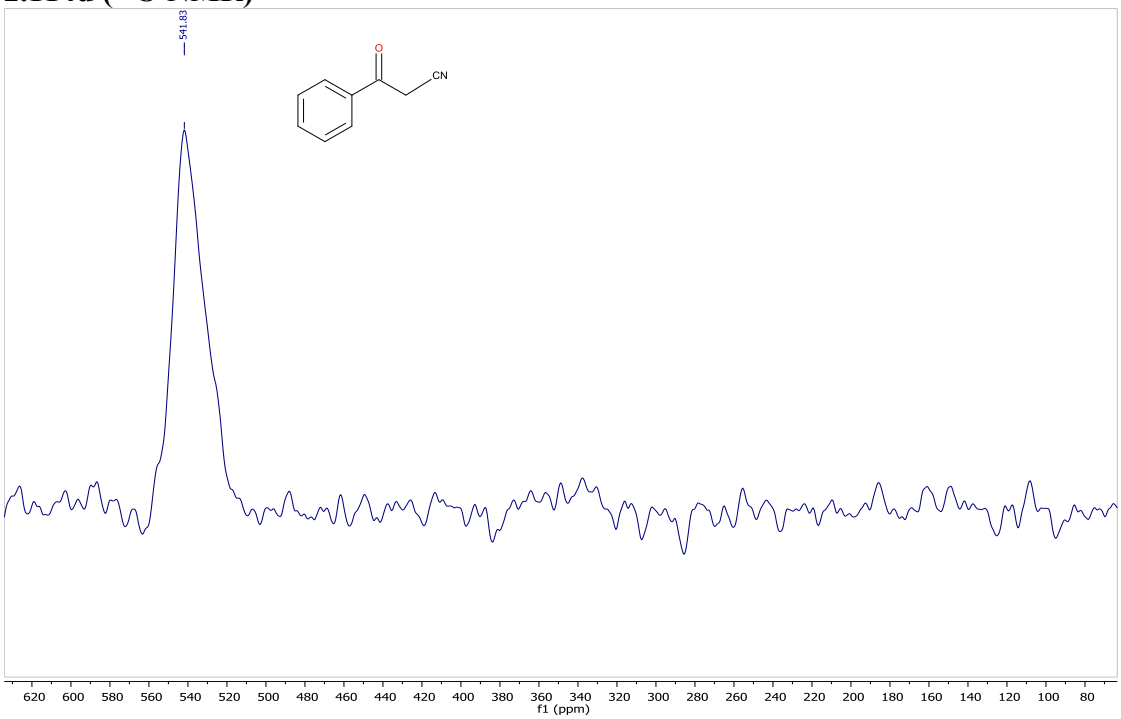


2.115e (^{1}H,^{15}N - HMBC)

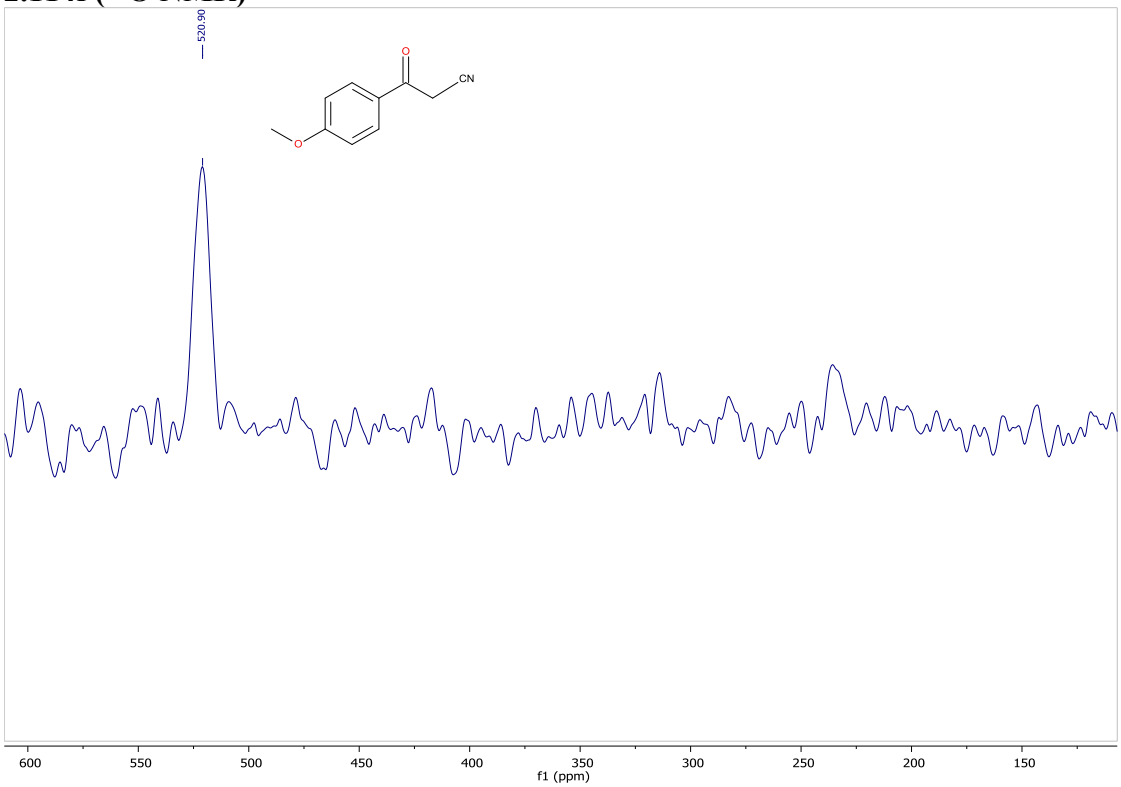


S.2.5 Copies of ^{17}O NMR Spectras for Selected compounds

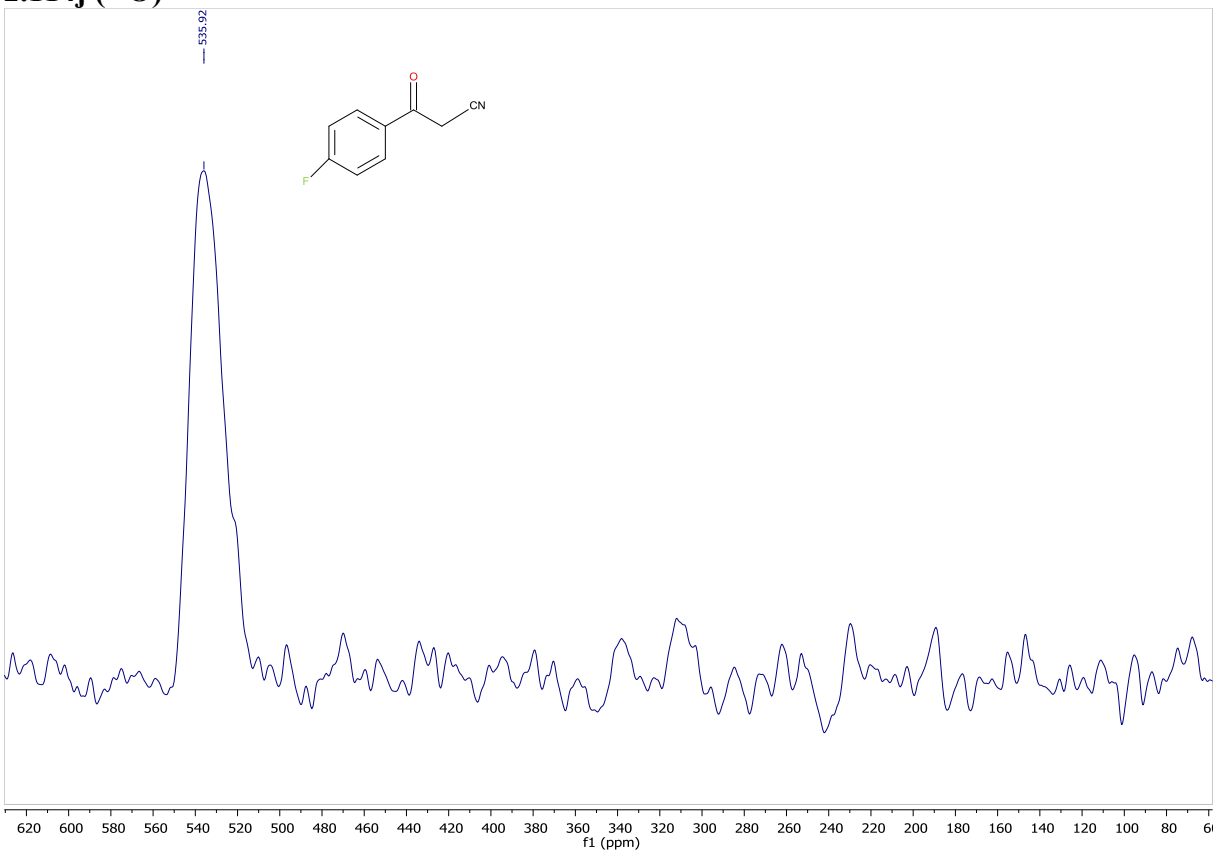
2.114d (^{17}O NMR)



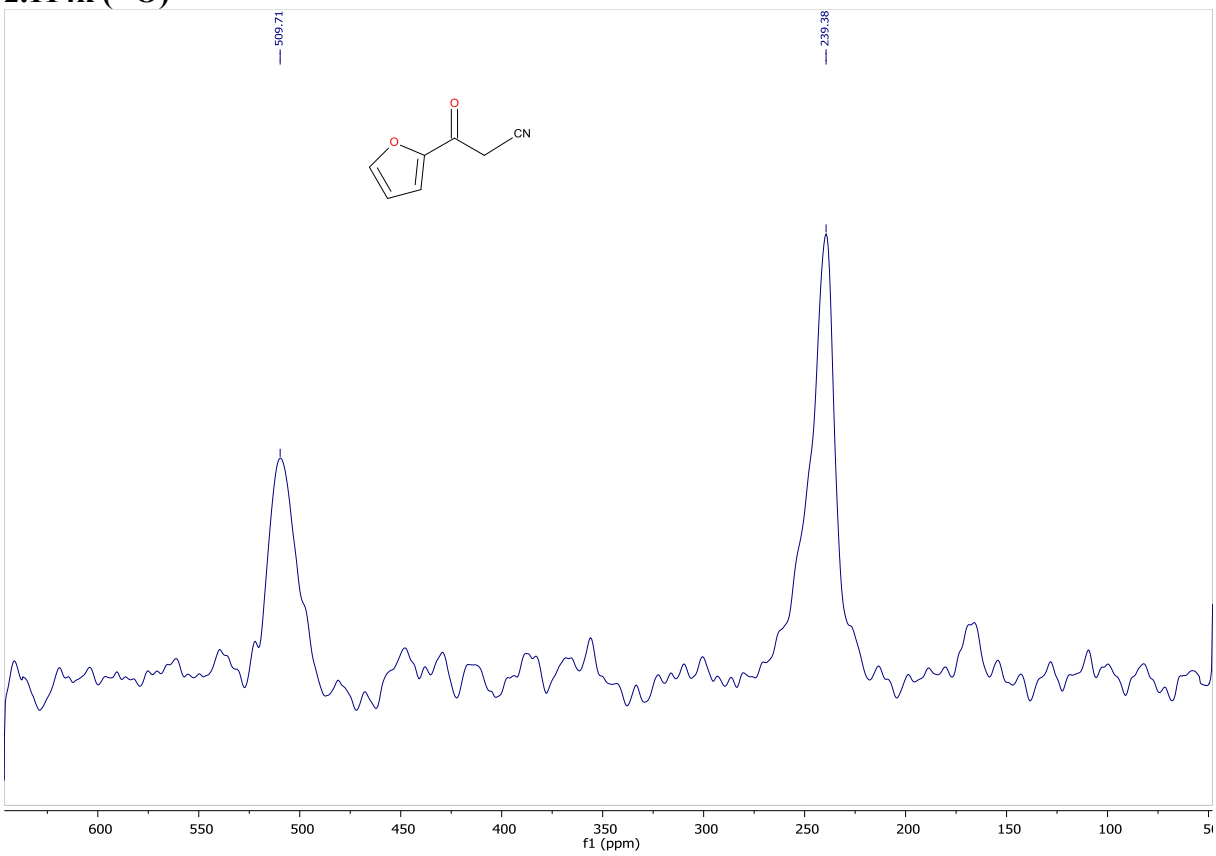
2.114f (^{17}O NMR)



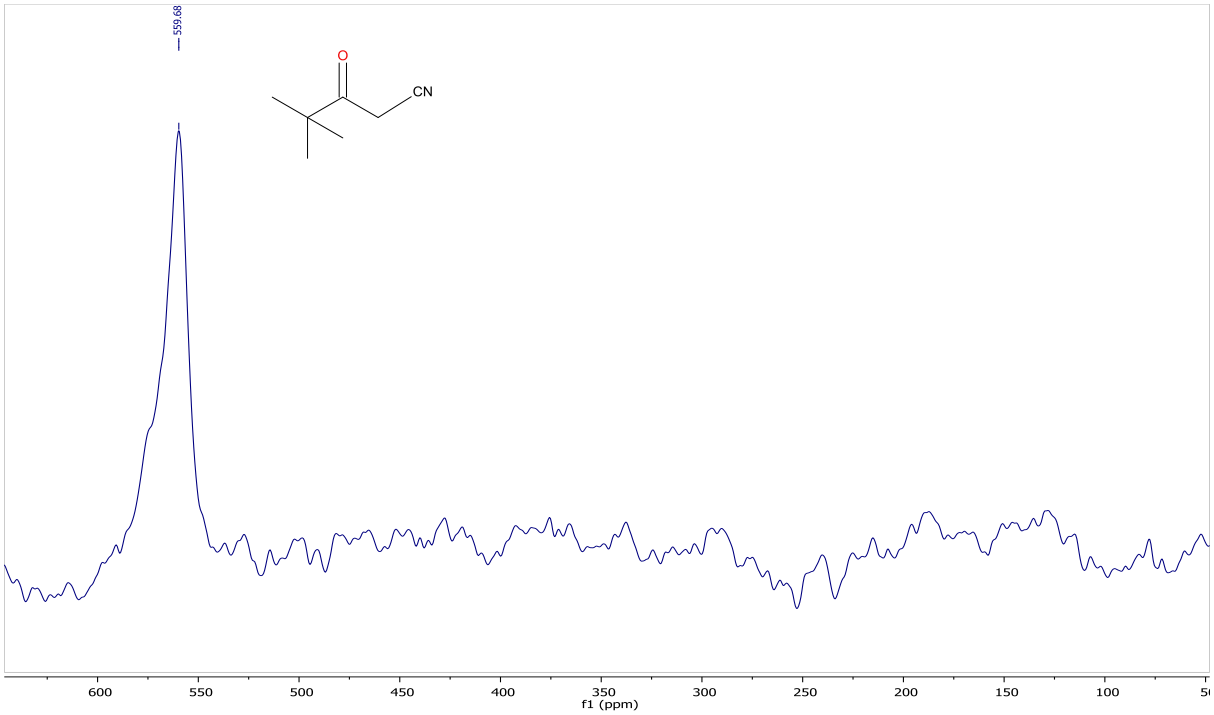
2.114j (^{17}O)



2.114k (^{17}O)



2.114n (^{17}O)



2.114o (^{17}O)