DEVELOPMENT OF CROSS COUPLING REACTIONS WITH EARTH ABUNDANT METALS

By

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DEVELOPMENT OF CROSS COUPLING
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To my family

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Abstract:

The ability to prepare complex molecules has been advanced and enabled by cross-coupling reactions as exemplified by the 2010 Nobel Prize being awarded to the progenitors of palladium catalyzed cross-coupling technology. This is a powerful approach to bond formation that has been utilized in fine chemical synthesis, the agro and pharmaceutical industries, material/polymer preparation, and natural product synthesis. The problem our society is facing is that a majority of the transition and main group metals that are used in cross-coupling reactions are being depleted. The 40 year development of cross-coupling reactions has centered on precious metals (Pd, Pt, Rh, Ru, Ir, Os, & Au), in part due to their high functional group compatibility. Unfortunately, cross-couplings with precious metals is not sustainable. There is an ever growing need to develop new sustainable methods that employ earth abundant metals. The focus of this dissertation is my progress in the development of cross-coupling reactions with earth abundant 1st row transition metals. Two approaches are being pursued: 1) tandem/iterative cross couplings of titanacycles as a means to modularly form two bonds in a single reaction vessel, and 2) dual catalysis for the nickel catalyzed cross-coupling of *in situ* generated carbon radicals. It is shown that the titanacyclopropene has been coupled with Weinreb amides to synthesize various enones regioselectively. The work is extended to couple second electrophile (Lewus acid activated benzaldehyde) to modularly synthesize tetrasubstituted furan in moderate to good yields. At last the dual catalytic approach has been successfully utilized to couple aryl/alkyl halide with aryl/alkyl nitriles to synthesize ketones in good yields by using nickel and titanium catalyst. These synthesized enones, furans and ketones are complex building blocks valued in medicinal chemistry, library preparation, and natural product.

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LIST OF ABBREVIATIONS

CNT	Carbon NanoTube
cp	cyclopentadienyl
cy	Cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DMA	N, N-Dimethylacetamide
DMF	N,N-Dimethylformamide
DME	Dimethoxyethane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(*1H*)-pyrimidinone
dtbbp	3,3'-Di*tert*butylbipyridine
EWG	Electron Withdrawing Group
EDG	Electron Donating Group
GC	Gas Chromatography
GCMS	Gas Chromatography Mass Spectometer
G-H II	Grubbs Hoveyda second generation catalysts
h	hour
IBX	o-iodoxybenzoic acid
^{i}Pr	isopropyl
iPrMgCl	isopropyl magnesium chloride
IR	Infrared Spectroscopy
L.A.	Lewis Acid
MIDA	methyliminodiacetic acid
mmol	Millimole

MW	Microwave
nBuLi	normal butyllithium
NHPI	N-hydroxyphthalimide
NMP	N-methylpyrrolidinone
NMR	Nuclear Magnetic Resonance Spectroscopy
Piv	Pivaloyl
PMHS	Polymethylhydrosiloxane
ppy	phenyl pyridine
r.t.	room temperature
Red.	Reductant
SET	Single Electron Transfer
TBAB	tetrabutylammonium bromide
^{t}Bu	*tertiary*butyl
TBS	*tertiary* butyl dimethyl silyl
TEA·HCl	Triethylamine·Hydrogen Chloride
TFA	Trifluoroacetic acid
Temp.	Temperature
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
TMSCl	Trimethylsilyl Chloride
°C	degree celsius

CHAPTER I

INTRODUCTION

The declining productivity of the pharmaceutical research and development[1-2] has raised a debatable question as to which tactic[3] has to be utilized for developing new therapeutic probes that have high efficacy, minimal side effects, and can expand the druggable genome.[4] The development of new therapeutics can be accelerated by enhancing the current screening collections. Up until the 1990s, the trend of drug discovery heavily emphasized the incorporation of natural products in biological screenings. Natural products have played a prominent role in drug discovery. In fact, about 26% of FDA approved drugs from 1981-2014 were natural products or modified natural products. If one includes small molecules that have been designed to mimic the binding of the pharmacophore fragment of a natural product the number of FDA approved drugs increases to 51%.[5] Natural products have demonstrated broad spectrum activity against various diseases, having a large impact on anti-cancer (76% of approved drugs) and anti-bacterial (91% of approved drugs) treatments. Natural products have played an important role in drug discovery, being a source of inspiration[6] with a proven track record.[7-10] Despite this strong foundation, the use of natural products as new drug candidates suffered a backlash[11] due to the difficulty in identifying new natural products[12-13] and the development/implementation of synthetic methods for the rapid synthesis of large libraries of compounds for submission to high-throughput screenings. The steady decline[2] of FDA approved drugs have been highlighted by the absence of natural products and natural product mimics[14] in current high-throughput screening

collections. Thus, natural products, natural product analogs, and libraries of complex natural product-mimic[12-13] compounds need to be re-included in screening collections for identification of new lead hits and expansion of the druggable genome.[4] The inherent problem that inhibits inclusion of natural products in screening collections is the steady decline in natural product isolation, there naturally scarce supply, and increased difficulty in identifying new natural products.[12-13]

There has been growing interests in the total synthesis of macrocylic, terpene, and alkaloid natural products.[15] Any natural product can be made with current synthetic methods, but our ability to prepare these natural products on a multi-gram scale, or prepare hundreds to thousands of analogs is not easily achieved. Resultantly, inhibiting our ability to find new pharmacological tools to study disease biology and discover new lead hits. The importance of fulfilling this gap is exemplified by the recent scalable synthesis of various natural products such as Halaven®,[16] (+)-discodermolide, spongistatin 1,[17] actinophyllic acid,[18] tetracycline,[19-20] kapakahine F,[21] ingenol,[22] and erythromycin analogs.[23, 24]. While there has been advances in this area it still takes a long time (Kyprolis® took 13 years, Halaven® took 24-30 years)[53] and requires an enormous effort which may be the reason why pharmaceutical and biotechnology companies have been reluctant to pursue natural products. Additionally, several creative strategies have been forwarded to rapidly generate natural product-like complex molecules,[14] Diversity-oriented synthesis (DOS),[25-27] function-oriented synthesis (FOS),[28] diverted-total synthesis (DTS),[29] biology-oriented synthesis,[30] peptoid synthesis,[31-33] natural product scaffold diversification,[34-35] skeletal diversifications,[36-38] and natural product ring-distortion[39-41] are the strategies that have been helpful in generating hits in various divergent screens.[42-46] Despite these important advances, methodology for scalable natural product synthesis or rapid generation of libraries of complex molecules with characteristic natural product features is still scarce.[47-52] The other issue is that the methods and strategies used in scalable and library synthesis are divergent. Scalable natural product synthesis focuses on developing the most efficient route to a single target, whereas library design is directed towards modular methods to easily

prepare analogs. The ultimate goal is the development of methods and strategies that could be used in both. The ability to prepare a complex natural product mimic library, identify a lead hit, and then scale the synthesis of the hit with minimal medication.

Natural products have characteristic features that are absent in small molecule drugs such as being structurally diverse and rigid, large macromolecule, more fuse, bridged, and spirocyclic ring system, higher percentage of sp^3-to sp^2- carbons, greater number of stereo-centers, and higher C-O bond count in combination with a lower C-N bond count[47-52] (Fig. 1.1). These features are either missing or under-represented in drug molecules and library compounds. Thus, there is a strong need for synthetic techniques that can incorporate these characteristic features into drug discovery design strategies for library and probe development. One way is by focusing on C-C bond forming reactions. Cross couplings, C-H functionalization, and cross metathesis reactions are conventional C-C bond forming reactions (Scheme 1.1). These are great methods for C-C bond formation as evidenced by the Nobel Prize being awarded to this field twice. Once to Grubbs and Schrock in 2005 and in 2010 to Suzuki, Negishi and Heck for their discoveries. A common drawback suffered by all of these conventional reactions are the use of stoichiometric organometallic species, which can be difficult to synthesize and limit functional group tolerance. Also, they employ 2^{nd} and 3^{rd} row precious transition metals like Pd, Ir, and Ru in the transformation.

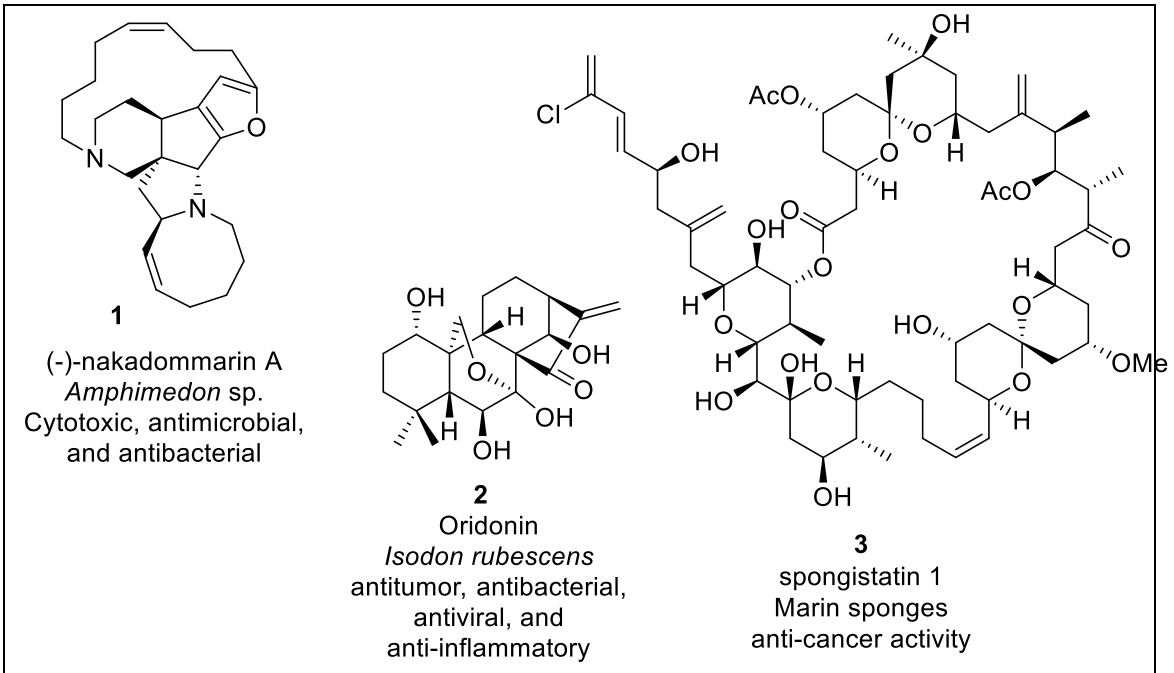
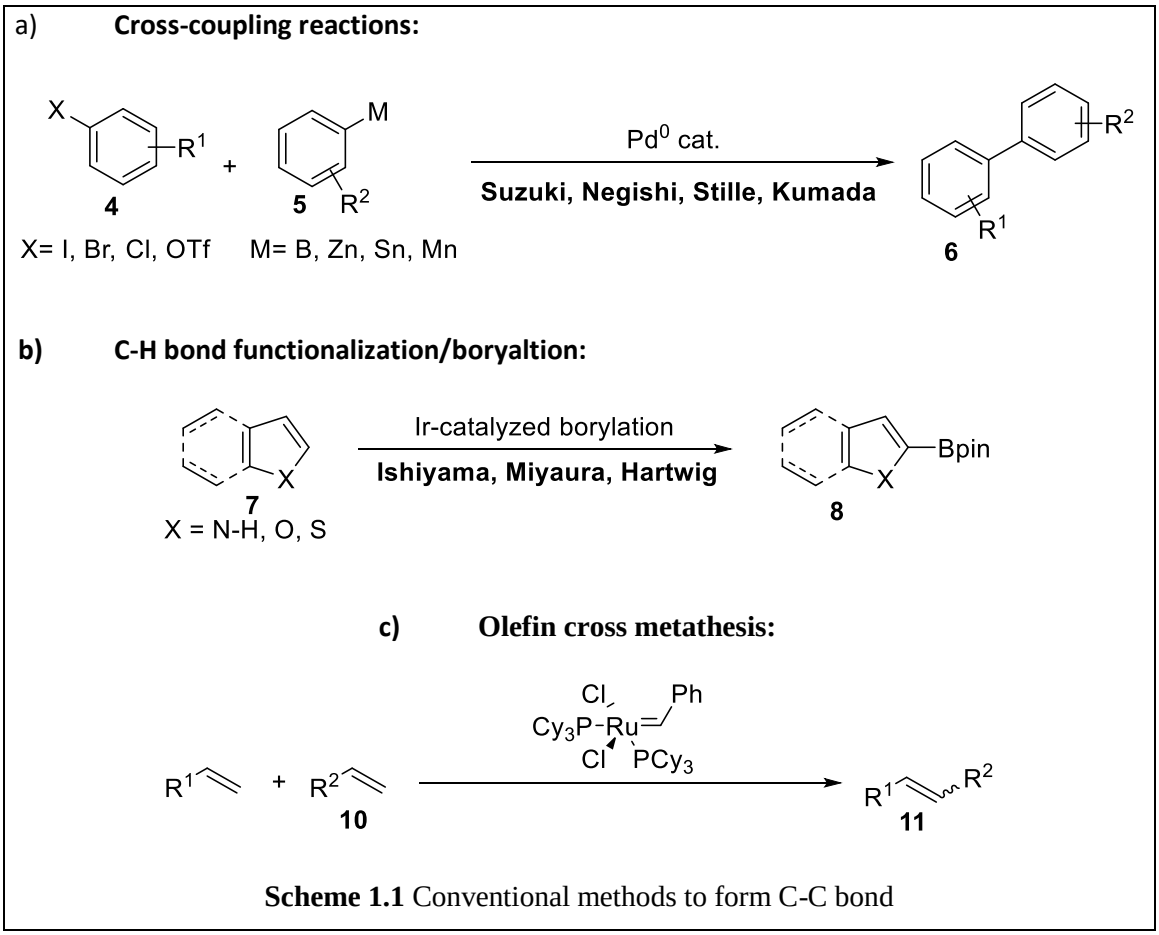


Fig. 1.1 Biologically active natural products as source of inspiration

The 2nd and 3rd row late transition metals like Ru, Rh, Pd, Ir, Pt and Au have been exploited to do the various kinds of transformations. The natural abundance of these transition metals in the earth's crust are summarized in Fig. 1.2.[54] The 2nd and 3rd row transition metals which have been over exploited are present in rare amounts and are in the verge of depletion. Although some earth abundant metals such as titanium have been used for catalytic transformations (e.g. Sharpless asymmetric epoxidation) and industrial polymerization processes; relative to the less abundant metals, there are a limited number of reactions that employ metals that are plentiful. And this lack is not due to that they cannot perform but due to the need for the further development of the processes. The growing use of these metals has been encouraged also due to the low cost, ready availability, low toxicity, and greater sustainability.



Scheme 1.1 Conventional methods to form C-C bond

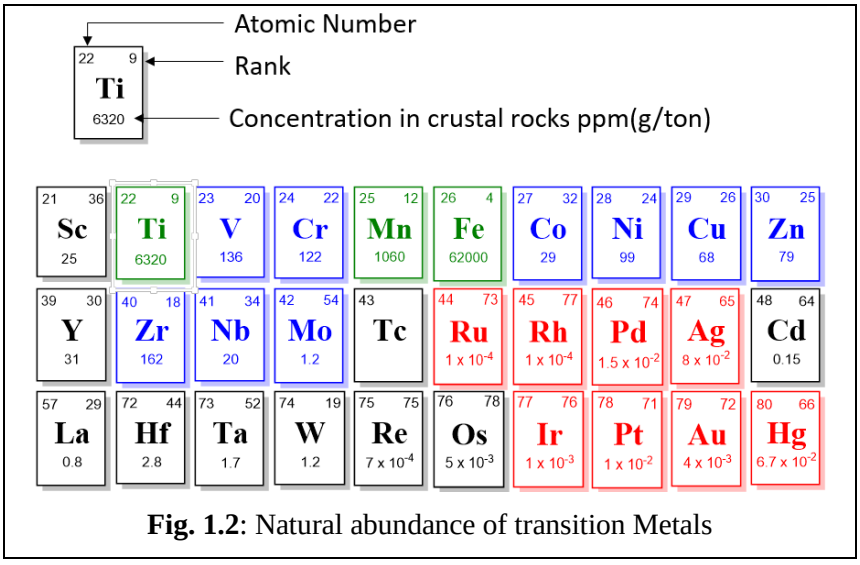
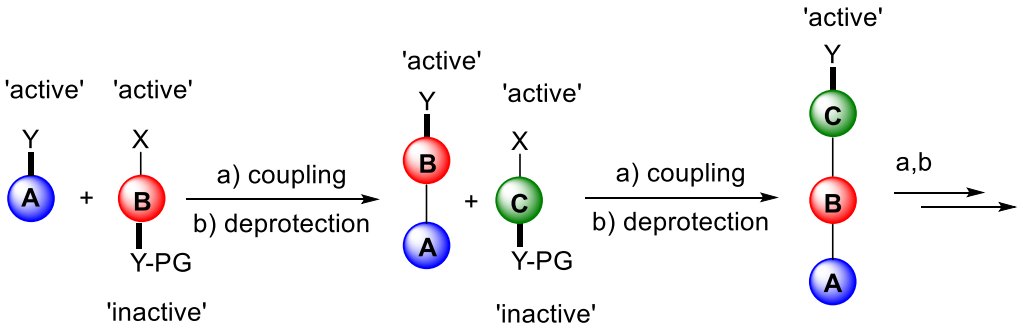


Fig. 1.2: Natural abundance of transition Metals

The focus of this dissertation is the development of new bond forming reactions using earth abundant metals that can be utilized in preparing natural product libraries. This will be accomplished through two approaches: 1) tandem/iterative cross coupling reactions, and 2) dual catalysis. Both of these approaches will focus on using earth abundant titanium and nickel.

1.1. Tandem/iterative cross coupling reaction

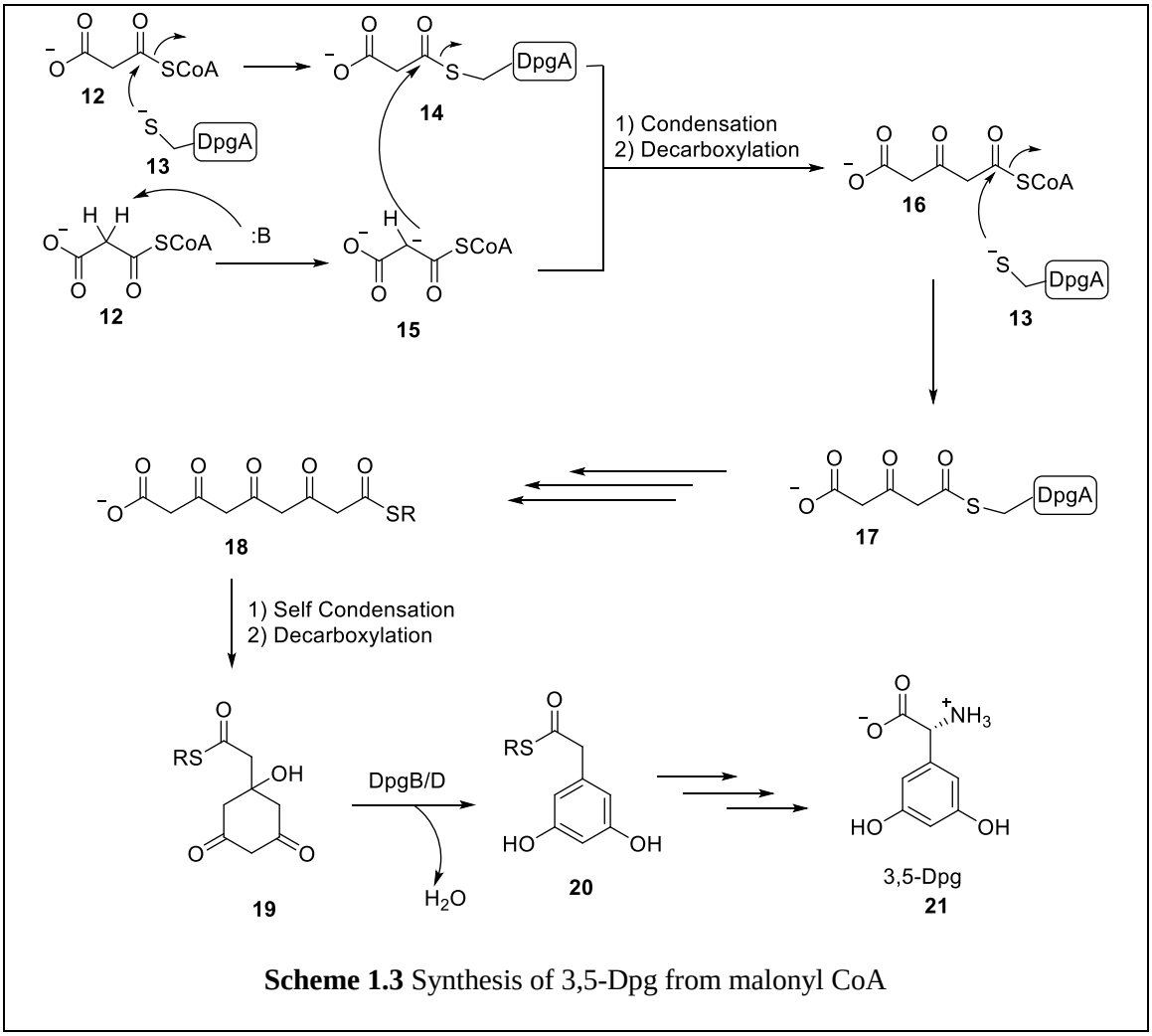
Tandem/iterative cross couplings take advantage of bifunctional starting materials. One of the functional groups is initially active while the other one is inactive. The active site of the bifunctional molecule couples with another substrate. After the reaction is completed, the inactive site is then activated by deprotection or functional group conversion. The newly activated site is then coupled with the active site of another bifunctional substrate and the reaction sequence is repeated until the desired product is obtained (Scheme 1.2).[55]



Scheme 1.2 Schematic representation of iterative cross-coupling reaction

Nature frequently utilizes this technique. One simple example is shown in Scheme 1.3 where mother nature utilizes four molecules of Malonyl CoA to produce 3,5 Dihydroxyphenylglycine.[56] First Malonyl CoA **12** is activated by the enzyme **13** by nucleophilic addition to the carbonyl followed by loss of the leaving group. Deprotonation of another molecule of Malonyl CoA **12** is done by a basic site of enzymes and then condensation followed by decarboxylation would result into the adduct **16**. Enzyme **13** again activates adduct **16** followed by

condensation with Malonyl CoA. In this way Nature incorporates as many carbons as needed and finally intramolecular condensation and decarboxylation to form the ringed precursor which is later converted to the desired product.



Scheme 1.3 Synthesis of 3,5-Dpg from malonyl CoA

Inspired by Mother Nature, people have been trying to mimic this type of technology in their reaction vessel by finding bifunctional compounds that can undergo iterative cross coupling reactions. However, most of these bifunctional compounds take two to three steps to be synthesized.[57] Some, even require the use of precious metals and/or toxic metals, like tin, to be synthesized.[58] Our lab is looking to address this issue be developing tandem coupling reactions

with easily synthesized bifunctional reagents prepared and coupled with earth abundant metals.[59-60] Chapter 2-4 of this dissertation will elaborate our effort in the utilization of titanacyclopropene's in tandem/iterative cross-coupling reactions.

1.2. Dual catalytic cross coupling reaction

Catalysis is one of the most efficient and powerful tools in chemical synthesis. Scientists have been able to create new C-C bonds and perform different functional group manipulations with the help of catalysis. Catalysts have been used to increase the rate of a reaction, polarize bonds, and form reactive intermediates. Mono-catalysis, the activation of a single substrate by a unique catalyst, as well as dual catalysis, two catalytic systems work side by side to activate two substrates have been equally used by different researchers for the formation of new bonds.

A number of multi-catalysis mechanisms have evolved in recent years (Fig 1.3). Bifunctional catalysis is one where both the substrate, nucleophile, and electrophile are activated separately by two different active sites present in the same catalyst.[61] The use of two catalysts to activate a single component has been termed double activation catalysis.[62] If one catalyst reacts with a substrate to form a stable intermediate which is then activated by a second catalyst and subsequently reacts with a second substrate has been called cascade catalysis.[63-64] Whereas, if the two catalysts present will simultaneously activate the nucleophile and the electrophile then this has been coined dual/synergistic catalysis.[63]

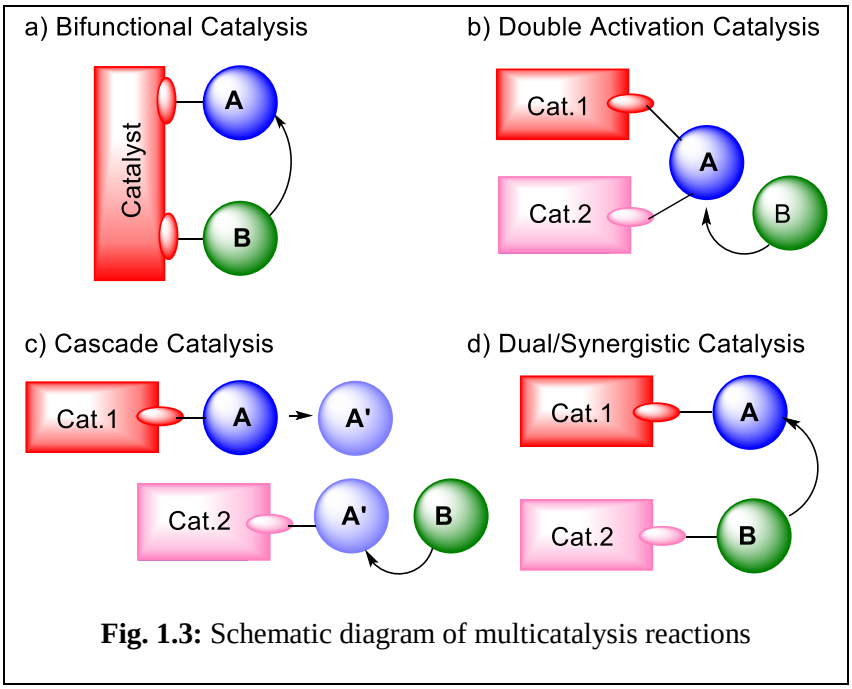
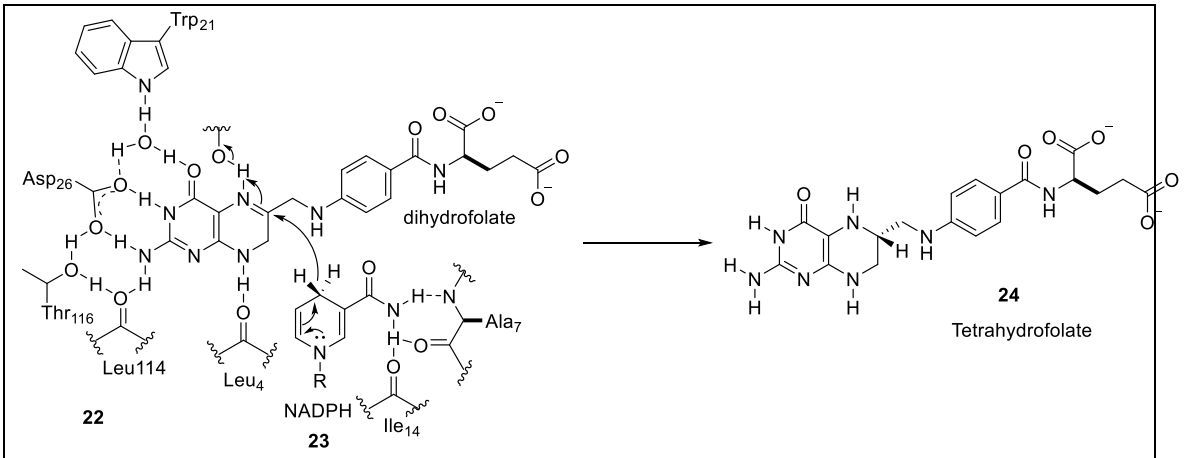


Fig. 1.3: Schematic diagram of multicatalysis reactions

Nature has been utilizing these multicatalysis techniques in generating complex compounds. One such example is depicted during the formation of tetrahydrofolate. During its formation, coenzyme $NADP^+$ catalytically activates hydride by generating NADPH and on the other hand enzyme dihydrofolate reductase binds dihydrofolate through protonation of an imine and activates it for hydride addition. NADPH cofactor binds to the enzyme and the hydride is delivered to produce tetrahydrofolate by regeneration of $NADP^+$ (Scheme 1.4).[63]



Scheme 1.4 Synthesis of tetrahydrofolate in nature

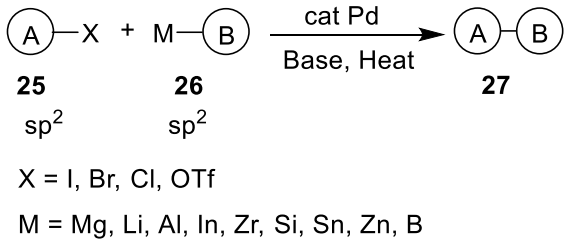
The precious metal, palladium, has been widely utilized to develop the majority of cross-coupling reactions to date because of its high functional group compatibility and specially directed towards C(sp^2)-C(Sp^2) coupling (Scheme 1.5). Even though C(sp^2)-C(sp^3) and C(sp^3)-C(sp^3) bond formation is crucial, methods to construct those linkage are far less advanced. The pioneer work in this field demonstrated nickel catalysts to be competent at facilitating the coupling of sp^3-hybridized alkyl halide electrophiles or organometallic nucleophiles.[65] These ground breaking studies have recently been expanded and studied in further details, resulting in more reliable and robust methods, such as Fu's stereoconvergent cross-couplings, that indicate the formation of radical intermediates in the catalytic cycle.[66-68] However, the use of pre-functionalized organometallic reagents[69-82] are required in those methods. This is a drawback because they require additional step to prepare the reagent, stoichiometric metal waste is generated, limited functional group compatibility depending on the metal, toxicity issues, non-atom economical, sensitivity to air and/or moisture, and a limited shelf life. To address these issues, Weix demonstrated the cross-electrophile coupling of aryl halides with aliphatic halides using nickel catalyst, and provided strong evidence of a single-electron-transfer (SET) process occurring in the catalytic cycle.[83] The

current need is more focused on the strategies that can replace or as alternatives to the organometallic reagents.

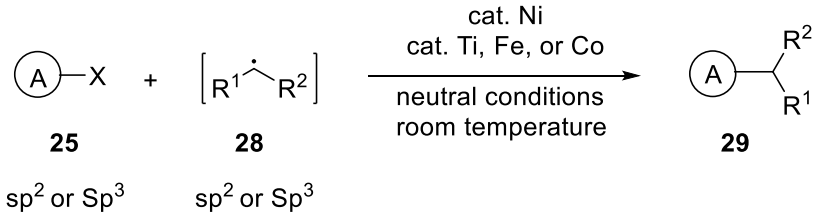
Due to evidence that nickel catalyzed cross-couplings occur through radical intermediates, and the ease with which nickel can adjust its oxidation state between Ni^0, Ni^I, Ni^{II}, and Ni^{III} a viable alternative coupling partner would be carbon radicals.[84] For this approach to be successful the radicals would need to be generated in catalytic amount to minimize radical propagation and termination events. Fortunately, advancements in catalytic radical generation has been made recently using titanium, cobalt, and iron, in addition to photoinduced electron transfer.[85] Thus, a radical generating catalyst along with the dual catalysis approach can enable new bond forming processes. The feasibility of this dual catalytic approach was initially demonstrated by Sanford by merging palladium-catalyzed C-H arylation and photoredoxcatalysis.[86-87] Building on this seminal study the Molander, MacMillan, and Doyle groups merged nickel and photocatalysis. Molander generated carbon radicals from alkyl organometallic reagents, potassium trifluoroborates,[88-90] and ammonium silicates.[91] MacMillan used carboxylic acids[92-94] for radical generation, while Doyle has employed α-amino radicals.[95] The common ground for these groups has been radical generation through photoinduced electron transfer, which has benefits of milder reaction conditions, and enabling new bond formations, which has attracted additional groups to this area.[96-97]

The other way to generate the carbon radical catalytically is through transition metals, such as titanium, cobalt, and iron. Yet, dual catalytic reactiond using Ni/Ti, Ni/Co, or Ni/Fe has remained nearly unexplored (Scheme 1.6). The exploration of which would complement the existing dual photo-catalytic methods, and more importantly it would enhance the radical coupling partner by expanding upon the available starting materials. The scaling of these dual radical cross-couplings can be easily achieved whereas the photo-catalytic methods need specialized flow reactors that are not readily available. Despite the important advances to nickel catalyze cross-couplings with sp^3-hybridized coupling partners, there exists a clear need for new methods that use readily available, inexpensive, and non-organometallic coupling partners.

In the Rahaim group we have tried developing dual catalytic methods for cross-coupling two abundant functional groups which otherwise could not be coupled through existing technologies. Overall fewer steps to prepare compounds under milder conditions with expanded substrate scope and chemoselectivity would be a clear advantage of dual catalytic radical cross-couplings over classical palladium catalyzed cross-couplings. This is significant as imines, ketones, and quaternary carbons can efficiently and selective prepared. These classes of compounds are routinely used in medicinal chemistry synthesis strategies to prepare drug targets that display activity over a vast range of therapeutic targets. The development of this new technology would expand the medicinal chemist tool box to new bond forming strategies, namely $C(sp^2)$-Csp^3) and $C(sp^3)$-$C(sp^3)$ bond connections.



Scheme 1.5 Classical Pd-cross-couplings



Scheme 1.6 Dual catalytic radical cross-coupling

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CHAPTER II

CROSS-COUPLING OF TITANACYCLES TO PREPARE TRI- AND TETRASUBSTITUTED OLEFINS, CATALYZED BY EARTH ABUNDANT METALS

2.1. INTRODUCTION

Metal-catalyzed cross couplings have been widely used to synthesize fine chemicals, agro chemicals, materials, therapeutics, and natural products. This mode of C-C bond forming reaction has been well developed as an invaluable tool for synthetic chemists, yet, the need for new environment friendly reactions with improved chemical efficiency is in high demand. This has urged the development of new methods where multiple C-C bonds can be selectively formed from readily available starting materials. Organoboron reagents have dominated the field of transition metal cross-couplings due to their functional group compatibility, established methods of preparation, and stability. However, boron is the 41st most abundant elements that is mined, in combination with the growing use of this element, it has been predicted to deplete within the next century. Titanium, on the other hand, is the 9th most abundant element in the earth crust and 5th most abundant metal that is mined; and is not currently in danger of being depleted. In addition to that, the use of organotitanium reagents would produce TiO_2 as the byproduct, which is environmentally benign and non-toxic. Unlike organoboron reagents, organotitanium reagents can form titanacycles which are 1,2-dicarbanions. These titanacycles have been well established to be

useful in reductive couplings of π–unsaturated substrates and have proven to be a powerful method in natural product syntheses. [1-2] However, the use of these reagents in transition metal catalyzed cross-couplings is nearly undeveloped. This study aims to develop a general approach for cross-coupling titanacycles to generate C-C and C-heteroatom bonds from readily available π–unsaturated substrates (alkynes) and organohalides.

Tri- and tetrasubstituted olefins are an important scaffold that can be found in small molecule drugs,[3] materials, and natural products (fig. 2.1).[4-6] They are also extremely useful building blocks for the generation of stereogenic centers through asymmetric transformations such as epoxidation,[7] dihydroxylation,[8-9] hydrogenation,[10-11] and metal catalyzed coupling reactions.[12] Olefins have also been established as versatile building blocks in radical reactions, ionic and radical polymerization reactions,[13] and materials research.[14] The challenge is to synthesize the substituted alkenes stereoselectively. While progress has been made in the stereocontrolled synthesis of substituted olefins there is still a need for modular methods that use earth abundant metals.[15] In our approach titanacyle dicarbanions have been used in the mono- and di-functionalization of alkynes. Available methods focus on transition metal catalyzed three component couplings of terminal alkynes, alkyl iodides, and organometallic reagents under palladium[16-18] or nickel catalysis[19-21] to prepare substituted olefins from alkynes (Scheme 2.1). This is an efficient and rapid approach to prepare substituted alkenes, but does have some restrictions that our approach can address. Namely, these methods are limited to alkyl iodides or activated alkyl bromides which need to be used in excess (2 equiv.), as does the organometallic reagent. Additionally, the organometallic reagent requires separate resources, energy, and time to be prepared prior to use. While a vast assortment of organoboron reagents are commercially available it should be kept in mind that resources and energy are being expended in their preparation.

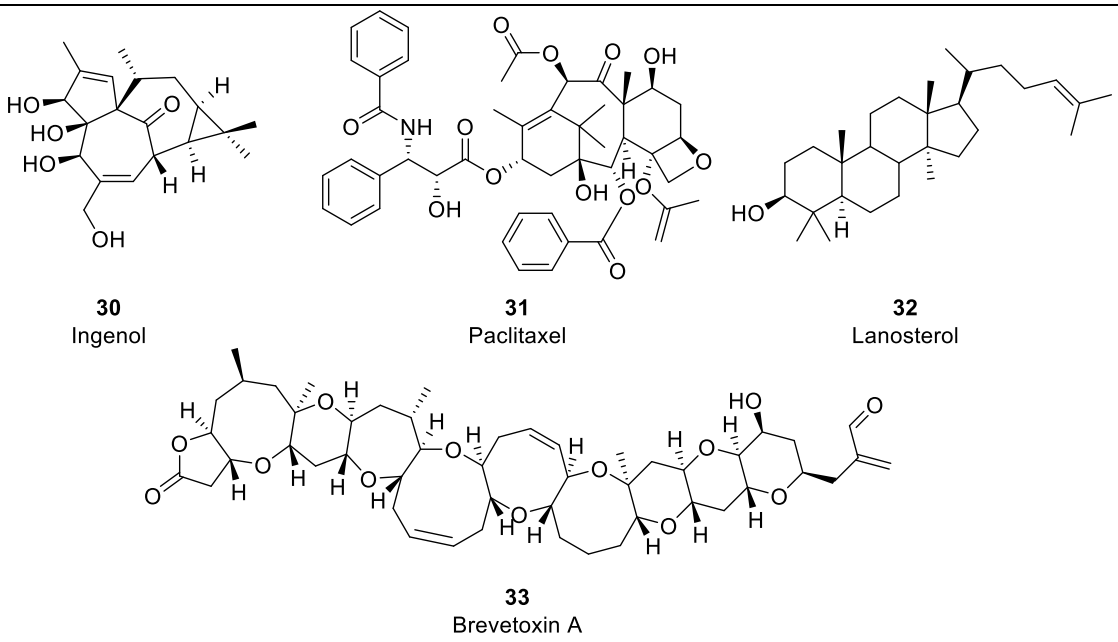
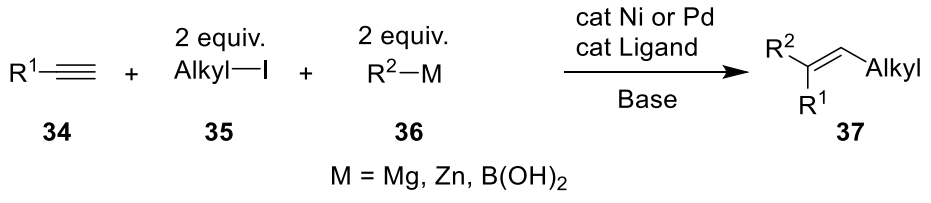
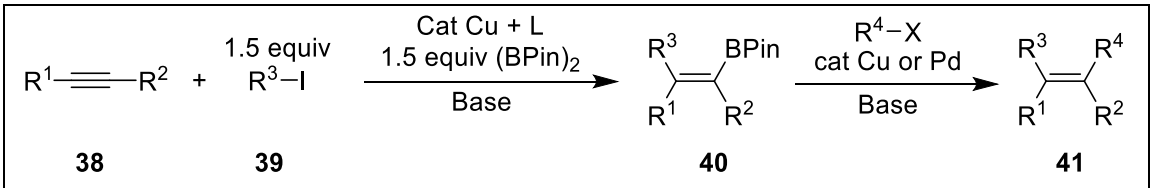


Fig 2.1 Alkene containing natural products

Another approach has been the copper catalyzed carboboration of alkynes, which is also restricted to alkyl- and aryl iodides, and also requires the vinyl boronate product to be used in excess in a separate cross-coupling reaction (Scheme 2.2).[22-23] Our approach will expand the halide coupling partners, use the titanacycle as the limiting reagent, and run the reaction in one pot so less resources, energy, and time are expended, and less waste is generated.



Scheme 2.1 Three component coupling

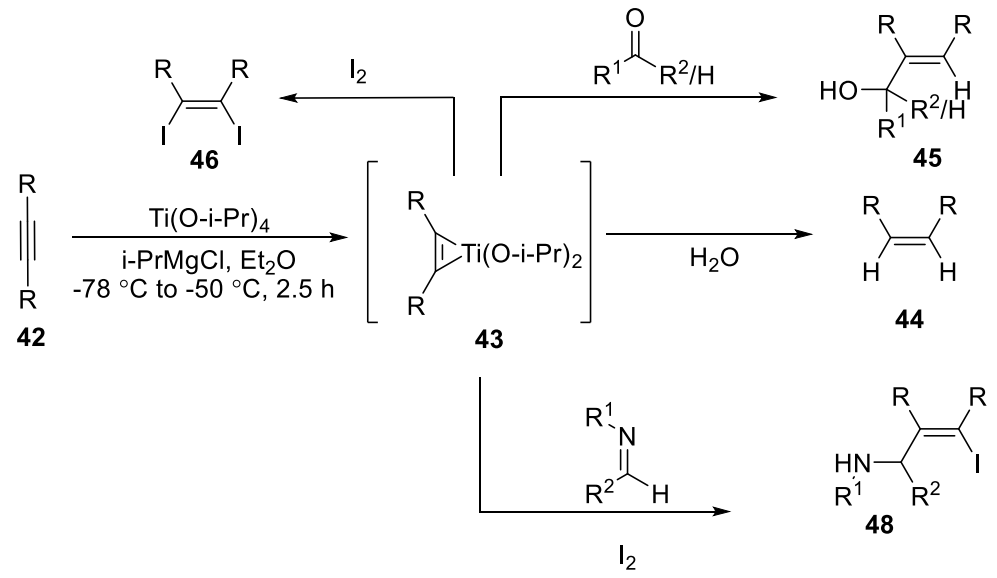


38 **39** **40** **41**

Scheme 2.2 Copper catalyzed carboboration

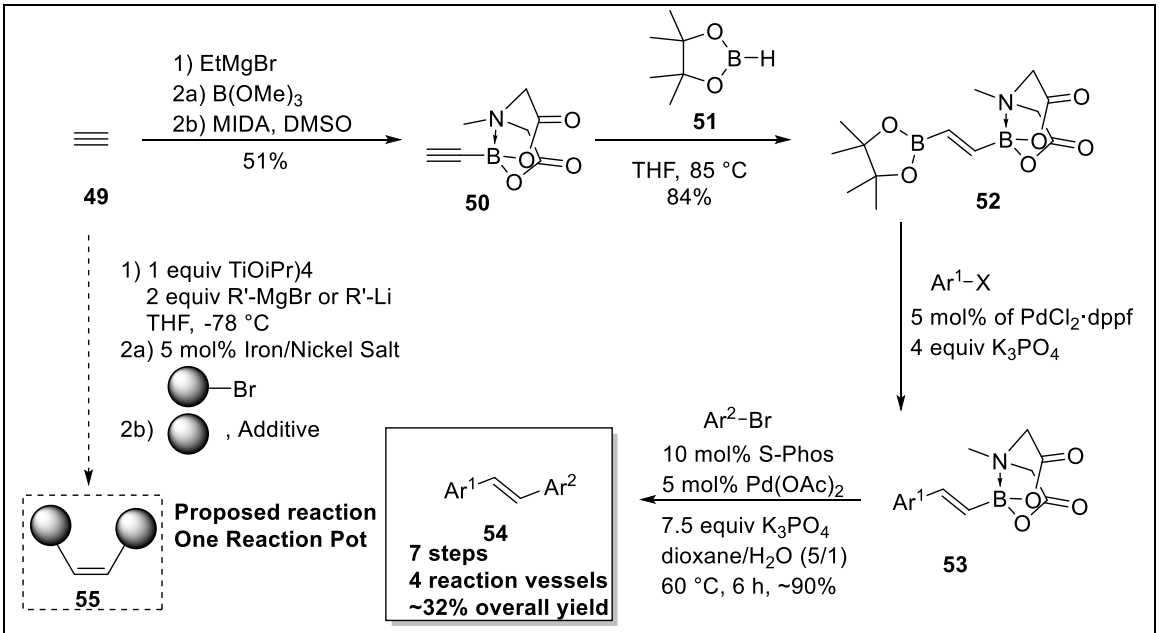
Titanacycles have an established track record to perform intra- and intermolecular reactions with readily available ubiquitous π-unsaturated substrates.[24-26] Low valent titanium has been used to react with and/or reductively couple alkynes, alkenes, allenes, aldehydes, ketones, imines, and nitriles in the synthesis of a myriad of structures (Scheme 2.3). The robustness and utility of these reactions is exemplified by Micalizio's and Phillip's applications in the total synthesis of pectenotoxin 2,[27] lehualide B,[28] macbecin I,[29] spirastrellolide B,[30] spirolaxine methyl ether,[31] and dictyostatin.[1] This powerful synthetic technology has also been used in the preparation of natural product analogs[32-35] and for a divergent synthesis of carbocycles.[36] Surprisingly, application of these reagents in transition metal catalyzed cross-couplings is nearly undeveloped. Cross-coupling of zirconacycles and titanacycles has only been accomplished with stoichiometric (≥ 1 equiv.) amounts of copper salts, and a limited range of electrophiles, including aryl iodides, alkynyl iodides, alkynyl bromides, and allyl halides. Additional pitfalls are that these dicarbanion reagents have only been cross-coupled with a single electrophile twice and only symmetrical alkenes and alkynes were utilized. A powerful modular approach to prepare complex molecules would be the development of tandem catalytic cross-couplings of titanacycles, generated from unsymmetrical alkynes, and with two different electrophiles. This would be an economical approach. Iterative reactions are a powerful strategy to construct complex molecules from simple starting materials, exemplified by nature's biosynthesis of polyketides.[37] The utilization of bimetallic or bifunctional reagents in iterative cross-couplings has been established,[38-39] and is still an active area of research[40]

with elegant contributions surfacing from the research groups of Morken,[41-42] Molander,[43] and Burke.[44]



Scheme 2.3 Electrophile couplings with titanacyclopropene

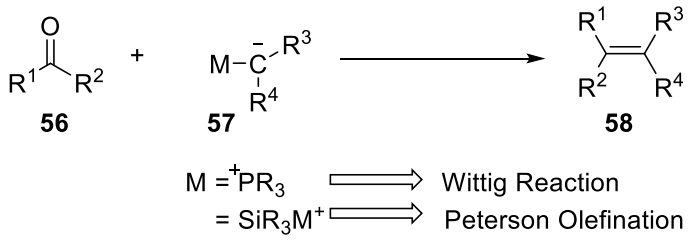
While these approaches are extremely powerful strategies that can prepare complex molecules in a modular, convergent, and regioselective manner, there still exist areas for improvement. Iterative cross-coupling with a bimetallic methyliminodiacetic acid (MIDA) boronate is a multi-step (reaction vessel) process that requires the boron coupling partners to be used in excess (1.5–2 equivalents) in both couplings (Scheme 2.4), meaning 33 to 75% of the bimetallic reagent is wasted. Thus, an approach that could prepare a bimetallic reagent with differential reactivity and couple it in a single reaction vessel would increase the efficiency of iterative cross-couplings, and require less time, resources, and energy.



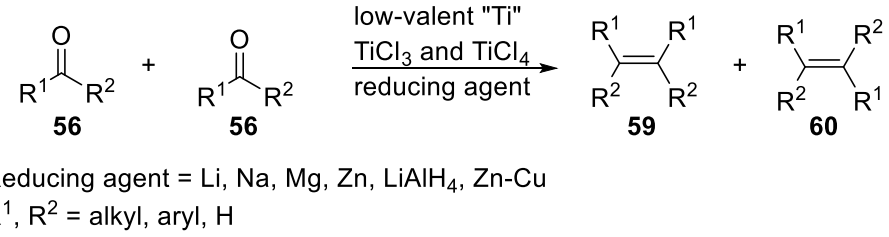
Scheme 2.4 Tandem titanacycle cross-coupling compared to current bimetallic strategies

2.2. Approaches to synthesize tetrasubstituted olefins

Various methods have been utilized to access tri- and tetrasubstituted olefins. The Wittig[45] and McMurry[46] reactions are the most common classical approaches. In the Wittig reaction, various phosphorous ylides are reacted with with aldehydes and ketones to obtain tri- and tetrasubstituted olefins.[45, 47] In 1968, D. J. Peterson showed the silicon-variant of the Wittig-type reactions where α-silyl carbanions are reacted with carbonyl compounds to obtain olefins.[48] This reaction is commonly known as Peterson olefination (Scheme 2.5). In the McMurry coupling reaction, the reductive homo coupling of carbonyl compounds is performed with low valent titanium complexes to form the corresponding substituted olefins (Scheme 2.6).[46] Though, these are the most commonly employed methods to generate tri- and tetrasubstituted olefins, they suffer from major drawbacks such as limited functional group tolerance and poor stereoselectivity.



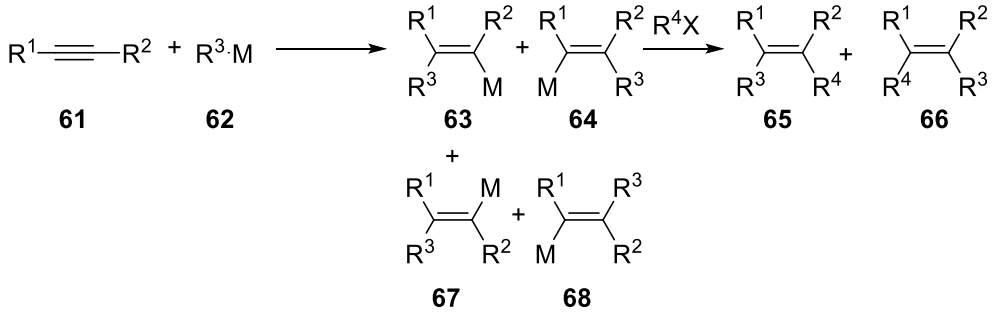
Scheme 2.5 Alkene synthesis from ylide reagents



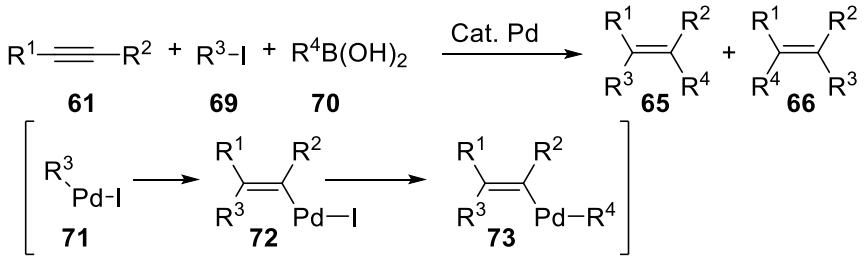
Scheme 2.6 McMurry Coupling

Modern technologies involve carbometalation of alkynes using organometallic reagents such asGrignard reagents, organocuprates, and organozinc reagents. The resultant alkenyl-metal bond is trapped by various processes such as addition of electrophiles, cross-coupling, and oxidative coupling. These techniques have been widely used because readily accessible reactants such as alkynes and alkyl halides are used to build up a huge variety of complex olefins. The use of pyrophoric organometallic reagents, poor functional group tolerance, difficult to control regio- and stereoselectivity are the major drawbacks suffered by these techniques (Scheme 2.7). Thus, a reaction technique is required that can have better function group tolerance, and better regio- and stereocontrol. One of the most recent method for synthesizing tetrasubstituted olefins is direct functionalization of alkynes in a three component domino reaction. Internal alkynes, aryl iodides and arylboronic acids are catalyzed by various Pd[49-52] and Ni[53] salts to synthesize tetrasubstituted olefins regio- and steroselectively.[49] The proposed mechanism involves oxidative addition of aryl iodide to the Pd(0) and then aryl palladation of an internal alkyne to form an alkenyl palladium

species. This key intermediate then reacts with the arylboronic acid to give the tetrasubstituted olefin after reductive elimination (Scheme 2.8).



Scheme 2.7. Possible regio- and stereo-isomer



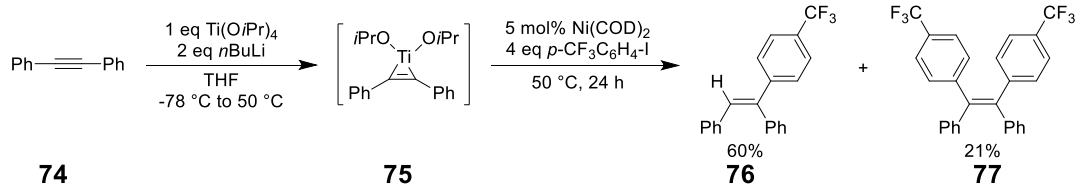
Scheme 2.8 Pd-catalyzed direct functionalization of alkynes

However, these are the efficient methods to synthesize the tetrasubstituted olefins, the use of stoichiometric amount of organoboron reagent is the major set back of this reaction.

2.3. RESULT AND DISCUSSION

The cross-coupling of aryl titanium(IV) reagents [ArTi(O*i*Pr)$_3$] has been successfully completed under palladium[54] and nickel[55] catalysis. These reagents are electronically very different than the titanacyclopropenes but it demonstrates the feasibility of cross-coupling titanacycles under nickel catalysis. A seminal paper by Tsuji demonstrated that bis(1,5-cyclooctadiene)nickel(0) can catalyze the cross coupling of symmetrical titanacyclopropenes with aromatic iodides (Scheme 2.9).[56] This work established the feasibility and laid the foundation for iterative cross-couplings of

titanacycles. The potential reason why this paper has been overlooked is that it indicates that an iterative cross-coupling is possible but not highly selective or efficient. While Tsuji designed the system with the intent of performing a double cross-coupling, as seen by using four equivalents of the aryl iodide and prolonged reaction times, it is our supposition based on his data that modification of the system can result in a selective and efficient iterative cross-coupling. Based on the theory that the reactivity difference between the titanacycle and the resultant organotitanium(IV) intermediate is vast, a selective mono-cross-coupling of the titanacycle should occur with just one equivalent of aryl halide. This theory is also validated by the reactivity difference of these two titanium reagents with aldehydes. Titanacyclopropenes readily undergo reductive coupling with aldehydes, whereas organotitanium(IV) reagents require Lewis acid activation.[57] Therefore, by controlling the concentration of the first electrophile, and adding an additive to activate the titanium(IV) intermediate through formation of an ate-complex, a second selective cross-coupling with a second different electrophile is anticipated to occur.



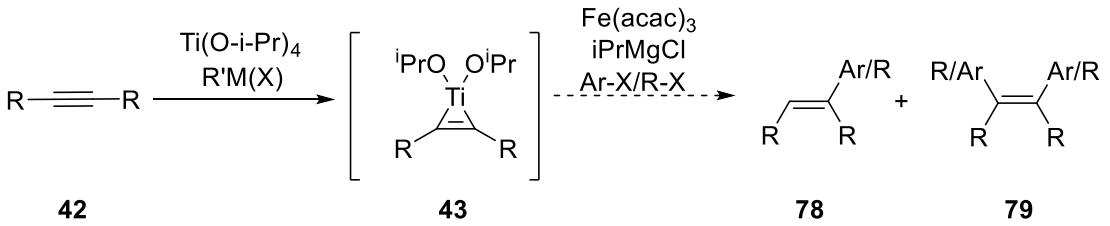
Scheme 2.9 Tsuji's nickel catalyzed iterative cross-coupling of symmetrical titanacyclopropenes

As a first step to achieve this one-pot iterative cross-coupling with two different organohalides, we will cross-couple the titanacyclopropene with an earth abundant catalyst, then react the vinyl titanium(IV) intermediate with a variety of electrophiles to gain insight into its reactivity profile, assisting efforts in achieving a second cross-coupling. Tsuji's original protocol

used $Ni(COD)_2$ as the catalyst. Due to the high reactivity, instability, and requirement of a glovebox to use $Ni(COD)_2$ we opted to screen bench stable iron, nickel, and copper salts.

2.3.1. Attempts on an Iron Catalyzed Cross-Coupling Between a Titanacyclopropene and an Aryl Halide.

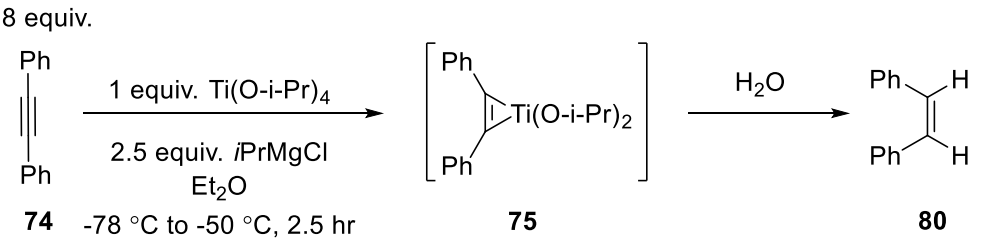
As the starting point to develop the iterative cross-coupling of titanacyclopropenewe chose to begin with iron catalysts. This was chosen in part due to iron being the greenest choice. Iron is the 3rd most abundant metal that is mined. It is currently not in danger of being depleted, is not toxic, and environmentally benign.[58] Additionally, iron has been established as a competent catalyst in cross-coupling Grignard reagents. The first iron catalyzed homo-coupling of aryl Grignard reagents was described in 1941 by Kharasch and Fields.[59] Cross-coupling reactions catalyzed by iron started in the early 1970s when Kochi was able to show the coupling of alkenyl halides with Grignard reagents.[60] Through the 1990s, some publications appeared in this area, but not until the 2000s the growth and development of iron-catalyzed cross-coupling reactions has occurred and now it is a major focus of many scientists around the globe.[58] Since Fürstner and Leitner published optimized conditions for highly selective iron-catalyzed cross couplings of alkyl halides with alkyl magnesium halides in the presence of NMP as co-solvent,[61] the iron-catalyzed cross coupling reactions have matured to an effective C-C and C-X bond forming reaction with broad scope. Organomagnesium species have been the most successful nucleophiles in iron catalyzed cross coupling reactions. Organotitanium compounds have shown a very similar reaction profile to organomagnesium compounds.[25] Thus, we started looking at whether iron catalysts could be used to cross-couplie titanacycles. The reaction was envisioned to be carried out as shown in Scheme 2.10.



Scheme 2.10. Proposed iron catalyzed cross-coupling reaction

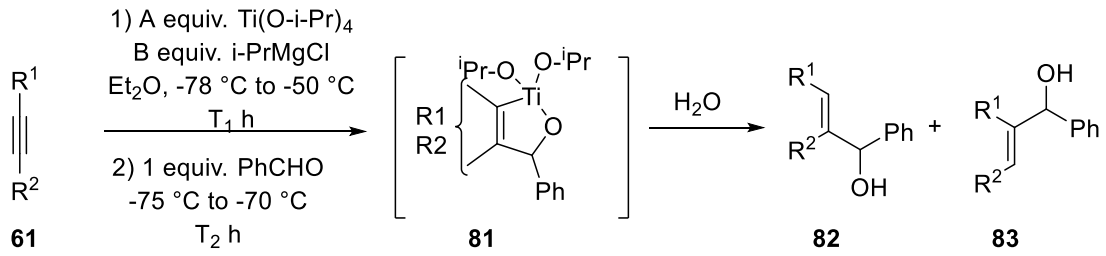
2.3.2. Test reactions to establish titanacylce formation and iron cross coupling are reproducible

η^3-Allyltitanium(III) complexes were synthesized in 1967 by Martin and Jellinek by reacting Cp_2TiCl_2 with 2 equivalents of alkyl Grignard reagents and conjugated dienes,[62] which were later demonstrated to be allylating reagent by Sato and Tauben independently.[25] Similarly, the synthesis of η^2-alkene-, η^2-alkyne titanium complexes have also been reported by Bercaw, *et al*. using alkene/alkyne with Cp'_2TiCl_2 and sodium amalgam[63-64] which have been shown to react with aldehydes and ketones.[25] Sato *et al*. has generated (η^2-propene)Ti (O-i-Pr)$_2$ *in situ* from Ti(O-i-Pr)$_4$ and i-PrMgCl which was then treated with acetylenes to form acetylene-titanium alkoxide complexes.[65] These alkyne-titanium alkoxide complexes function as vicinal dianionic species and couple with reactive electrophiles like aldehydes and ketones,[25, 65] imines, carbonmonoxide[66] and carbon dioxide.[67] Tsuji showed that thermally stable titanium(II)-alkyne complexes could be formed *in situ* by reacting Ti(O-i-Pr)$_4$ and n-BuLi at -78 ^{o}C, followed by ligand exchange with an alkyne under thermal heating.[56] The titanacyclopropenes formed by Sato and Tsuji are similar, the only difference being the reducing agent. As isopropylmagnesium chloride was less pyrophoric than n-BuLi, and the titanacyclopropene thus formed can react under cryogenic conditions (from -78 °C to -50 °C), and also the cross coupling of aryl halides with Grignard reagents using an iron catalyst was performed in the cold condition, Sato's methods was chosen as the starting point.



Scheme 2.11. Practicing and ensuring titanacycle formation occurs in our hands

The main aim was to cross couple the reactive titanacyclopropene. Initially they have been quenched with the strong electrophiles. Now, they have to be carried over to the next step. So, to figure out whether these reaction is reproducible and can be carried out further to cross couple, I tried to reproduce the formation of three and five membered titanacycle and quench it with water. For this the well described method by Sato[65] was utilized (Scheme 2.11 and 2.12). Cis-stilbene(**80**) was isolated in 81% yield which showed reaction worked well in our hands. The main purpose of forming the titanacyclopropene was to use it *in situ* for an iron catalyzed cross coupling reaction. The cross coupling reaction of titanacyclopropene to couple it with benzaldehyde to form five-membered titanacycles is a well established method. Various experiments were performed with different stoichiometries and various times to see the maximum conversion of reactant to titanacycles (Scheme 2.12). The experiments performed and the outcomes are stated in Table 2.1. Here, the focus was only on the formation of titanacycles(**81**) so the regioisomeric ratios of products **82** and **83** was not determined. With increasing reaction time and equivalents of $Ti(O\text{-}i\text{-}Pr)_4$/i-PrMgCl, the yield of product was increased which meant that titanacycles at lower temperatures takes a longer time to be formed (entry 3, table 2.1).



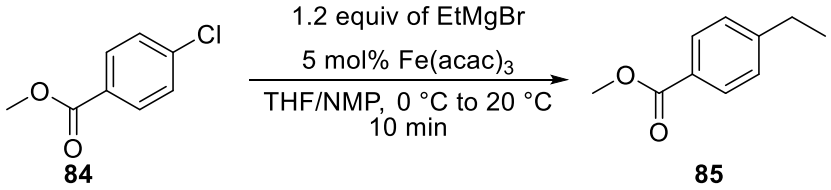
Scheme 2.12 Reaction of titanacyclopropene with carbonyl compunds

Table 2.1 Test reproducibility and optimization of titanacycle formation

No.	R_1	R_2	A eq.	B eq.	T_1 (hr)	T_2 (hr)	Yield (pdt)
1.	Ph	Ph	1	2.5	2.5	1	59%
2.	Ph	Me	1	2.5	2.5	1	37%
3.	Ph	Me	1	2.5	3	2	81%
4.	Ph	Me	1.2	2.8	2.5	1	63%

Having established that the titanacycle could be reproducibly made the second step was to test the feasibility of performing an iron cross-coupling, before attempting the iron catalyzed cross-coupling of the in situ prepared titanacycle. As the starting point for this the cross-coupling of ethyl magnesium bromide with an aryl chloride using Fürstner's conditions was attempted (Scheme 2.13).[61] The cross-coupled product was isolated in >95% demonstrating that an iron catalyzed cross-coupling could be performed in our hands. Since this cross-coupling was accomplished under a dual solvent system (THF/NMP), we sought to examine if the high boiling point polar solvent NMP was truly necessary, for it was perceived to be incompatible with the titanacycle. Titanacyles are prototypically formed in ether solvents, as such, the cross-coupling was rerun in just THF. Under these conditions the product was formed but with a slightly deceased yield (69%). When the solvent was changed to diethyl ether only 10% of the product was formed. Demonstrating that the cross-coupling can be performed in the absence of highly polar coordination solvents, and that

THF would be the optimal solvent to start with in attempting the iron catalyzed cross-coupling of titanacycles.



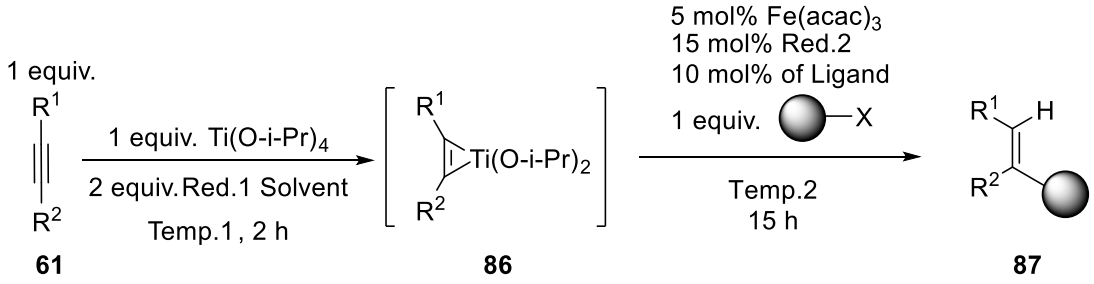
Scheme 2.13 Iron catalyzed cross-coupling reaction

2.3.3. Conditions screened for an iron catalyzed cross-coupling of a titanacyclopropene and aryl halide

Titanacyclopropene was prepared by both Sato's method[65] and Tsuji's method.[56] Both methods have their own advantages. The titanacyclopropene made via Sato's method would be stable up to -30 °C while that of Tsuji's method would be stable up to 50 °C. So, the reactivity could be monitored over a wide range of temperatures by using these two techniques. Additionally, Sato's method forms the titanacycle from a Grignard reagent typically in Et_2O, whereas Tsuji's method forms the titanacycle from *n*-BuLi in THF. Both methods were screened for the choice of reducing agent and solvent could also affect the cross-coupling. Terminal as well as internal (both symmetrical as well as unsymmetrical) alkynes were screened. Both aryl as well as alkyl halides were tested. The reactions of titanacycle and the iron catalyzed reactions were established as solvent dependent. Both polar and non-polar solvents as well as mixed solvents were used in the reaction. Reducing agent to reduce both titanium and iron were varied. The reactions were monitored at regular time points: 1, 2, 6, and 15 hours. The reagents were added simultaneously as well as stepwise. The progress of the reaction was monitored by GC with a calibration curve. The conditions that were varied are described in Scheme 2.14. The formation of desired coupled product

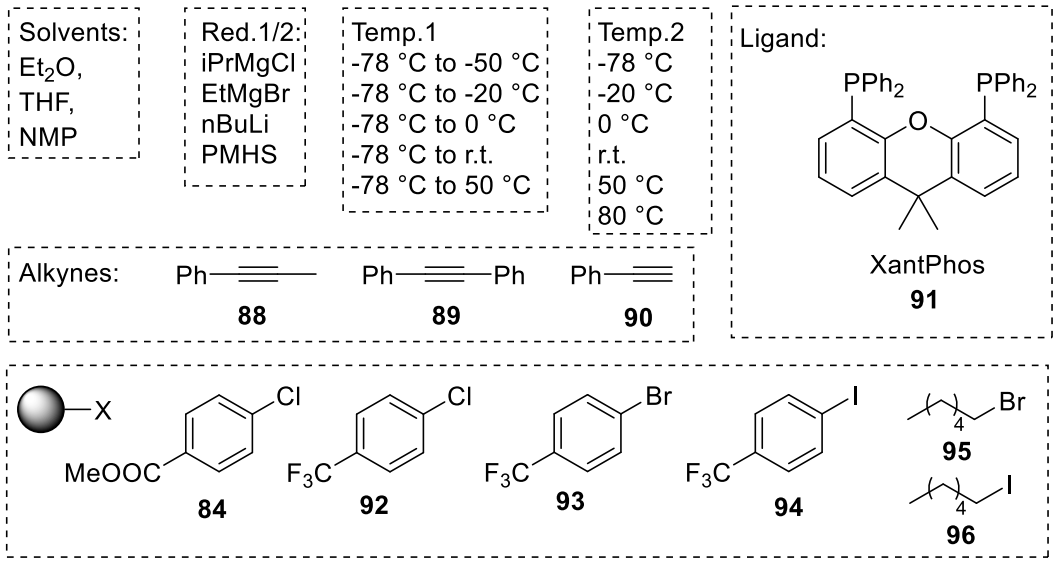
was not observed. Instead only recovered alkyne starting material and reduced alkene product were observed in all the cases.

In 2012, Nakamura and his group published a paper where he showed the iron catalyzed alkyl-alkyl Suzuki-Miyaura coupling reaction facilated by a bisphosphine with a large bite angle, XantPhos (9,9-dimethyl-4,5-bis (diphenylphosphino)xanthene).[68] Based on this report, we attempted activating the iron catalyst by adding 10 mol% of XantPhos instead of using 15 mol% of Grignard reagent. Every reaction sequence was redone using this new facilitator, but the desired product was not observed. Addition of the XantPhos ligand did not help facilitate the cross coupling reaction. Pre-activating the iron catalyst with the reductant and ligands was also tried with no improvement of the obtained results. Titanacyclopropenes are presumed to exist as an equilibrium mixture of two resonance forms, the coordinated titanium alkyne π-complex and as the titanacycle. Most experimental evidence indicates the titanacycle is favored. Even our examination of reaction mixtures prior to cross-coupling indicated that the titanacycle was formed by evidence of the cis-alkene being formed by GC and GC/MS analysis of a quenched aliquot. Yet, what was seen when the cross-coupling was attempted in the presence of an iron catalyst was that the equilibrium was shifted back towards the π-complex. As evident of the large amounts of alkyne seen by GC, GC/MS, and isolation after quenching the reaction. It appears that the iron catalysts prefer to reverse the titanacycle formation, making cross-coupling not feasible.



Scheme 2.14 Iron catalyzed cross-coupling of titanacyclopropene and aryl halide

Conditions Screened:



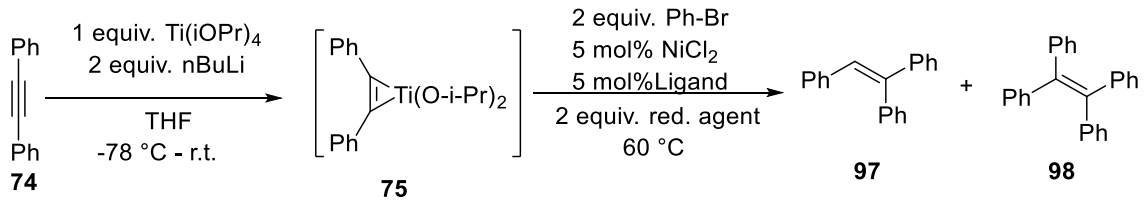
2.3.4. Nickel catalyzed cross coupling reaction of titanacycles with aryl halide

As a result of the inability of iron to catalyze the cross-coupling, we changed gears and focused on catalyzing the reaction with nickel. While Tsuji had already established that nickel cross-coupling of titanacylopropenes was feasible, the intent was to improve the original method and expand its utility. To make the reaction more user friendly, we opted to start screening simple bench stable nickel salts. Based off of the information gathered from the iron attempts and literature, we chose to run the initial catalysis screening in THF using *n*-BuLi as the reductant. $NiCl_2$ was found to work better at 60 °C than all other Ni-salts as the Ni-catalyst giving 48% of the

trisubstituted alkene without any tetrasubstituted alkene. With the good starting point and knowing that ligands can play vital role in nickel catalyzed reaction through steric and electronic effects, several ligands were screened to increase the yield of the alkene. Various carbene ligands have been tested in nickel catalyzed cross-coupling reactions.[69] Thus, N-heterocyclic carbene ligands were among the first ones tested with various Ni-salts, and the product formation was monitored by GC with a calibration curve using tri- and tetrasubstituded alkenes from commercial sources. The results, Table 2.2 (Entries **99-101**), showed that addition of carbene ligands did not help product formation. Also, various phosphines (entries **106-111**), mono and bidentate nitrogen containing ligands (entries **102-105**) were screened because of their proven track record in facilitating nickel catalyzed cross-coupling reactions.[70] The result showed no further improvement in the yield of the product.

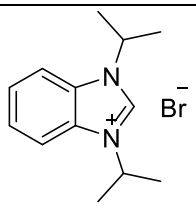
It is known in Stille couplings that the addition of copper salts enhances the efficiency of the reaction by increasing the rate of reaction by $>10^3$ fold.[71-72] The enhancement is speculated to be from the copper salt undergoing a metathesis reaction with the organostannane resulting in formation of a more reactive organocuprate. This organocuprate in turn undergoes transmetalation with the palladium complex faster. We speculated that copper salts could also undergo a metathesis process with the titanacycle reagent to afford an organocuprate, that would more efficiency participate in the nickel catalyzed cross-coupling. Also, organocopper reagents have a proven track record of reacting with Grignard reagents,[73] and the titanacycles have comparable reactivity. Thus, 5 mol% of copper salts such as $CuCl_2$, $CuBr_2$, $Cu(OTf)_2$, CuI, Cu(OAc), $CuBr.SMe_2$, $Cu(O^tBu)$ were screened as the additives. Among them, CuI gave 25% of the product with the remaining affording poorer results.

The addition of ligands to Ni(II) catalyst would facilitate to form Ni(0) active catalyst. In the same way we tried to reduce the catalyst precursor to Ni(0) by using 2 equivalent of reducing metals like magnesium, manganese and zinc.[70] When manganese was used as reducing agent 36 % of product



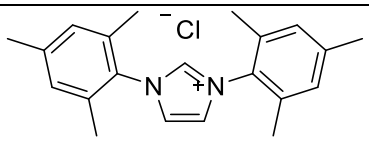
Scheme 2.15 Screening various ligands with various Ni-salts

Table 2.2: Screening various ligands

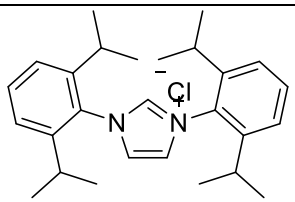


99

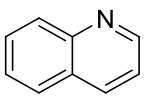
97= 22%
98= 4%



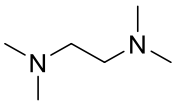
100
IMesCl
97= 11%
98= 3%



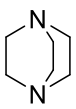
101
DIPPCl
97= 13%
98= 3%



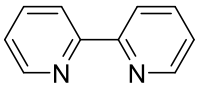
102
Quinoline
97= 31%
98= 6%



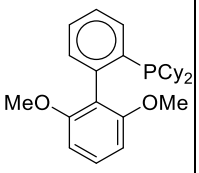
103
TMEDA
97= 17%
98= 11%



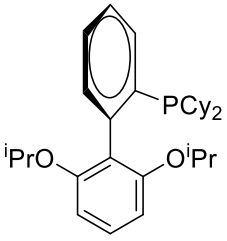
104
DABCO
97= 21%
98= 5%



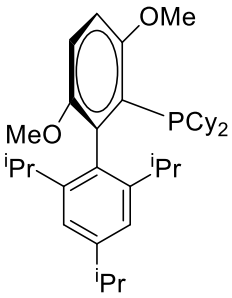
105
Bipyridine
97= 20%
98= 4%



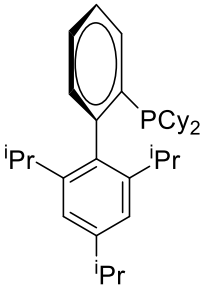
106
SPhos
97= 22%
98= 4%



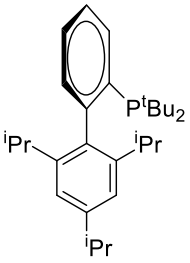
107
RuPhos
97= 22%
98= 5%



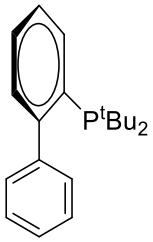
108
BrettPhos
97= 27%
98= 4%



109
XPhos
97= 24%
98= 5%



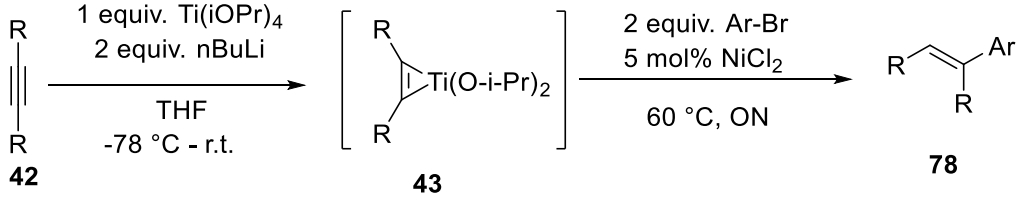
110
tbutyl-Xphos
97= 27%
98= 4%



111
2(Ditbutylphosphino)biphyenyl
97= 20% **98**= 5%

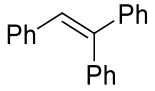
97 was isolated. Other reducing agent like n-BuLi and i-PrMgCl produced less than 5% of the desired product.

With the optimized condition as in scheme 2.16, various substrates were screened and the results are shown in Table 2.3.

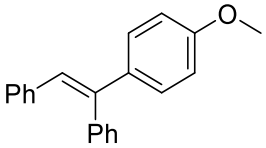


Scheme 2.16 Optimized reaction conditions

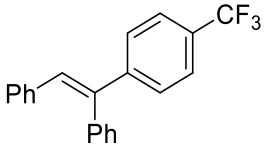
Table 2.3 Initial Substrate Screening



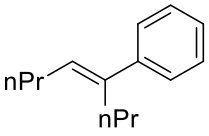
97
48%



112
48%



113
36%



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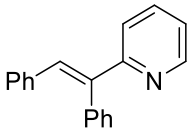

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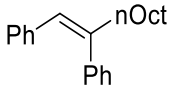

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2.4. CONCLUSIONS

After screening various sets of reaction conditions, it has been observed that the iron catalyzed cross coupling reaction of titanacycle, in cold conditions yields partial reduction of alkyne with untouched aryl and/or alkyl halides and in the hot conditions the titanacyclopropene would open up to give alkynes back. Nickel proved to be better catalyst over iron and $NiCl_2$ has been found as the better catalyst to perform cross coupling reactions with titanocyclopropene. Unlike in Tsuji's method which used glovebox conditions with aryl iodide,[56] aryl bromides were

capable of selectively giving trisubstituted olefins with bench stable Ni-salts. The maximum temperature the reaction could tolerate was 60 °C; the titanacycle started decomposing above this temperature. Nitrogen containing bidentate ligands were better than carbene or phosphine ligands, but they had the effect of slowing the reaction. Aryl bromides were better substrates than aryl iodides which gave a greater amount of di-arylated product, while aryl chlorides were the least reactive and alkyl bromides could not be coupled at all. Electron-rich aryl bromides reacted better than electron-poor aryl bromides. In the alkyne, di-aliphatic substituted alkynes reacted similar to the di-aromatic substituted alkynes.

Various tri-substituted olefins can be obtained via nickel catalyzed cross-coupling reaction of titanocyclopropene with aryl bromides in moderate yields. The bench stable $NiCl_2$ salt can be used as a catalyst for the transformation. The exclusive tri-substituted product showed that there is a further possibility of adding second electrophile to obtain tetra-substituted olefins as well. However, further modification is needed to improve the reaction itself to get better yields.

2.5. FUTURE DIRECTIONS

As various substituents in the bi- and tri-dentate nitrogen containing ligands play vital role in the Ni-catalyzed cross coupling reactions,[70, 74] one of the strategies to improve the reaction yields may be screening substituted bipyridines and terpyridines that are known to promote Ni-catalyzed transformations. Another strategy may involve making a more thermally stable titanocyclopropene by using other titanium reagents. This might be fruitful as various iron and nickel catalyzed reactions proceed at higher temperatures. Recently, there has been a growing interest in hypervalent iodonium compounds[75] as an electrophile in various cross couplings. In particular, copper catalyzed cross couplings of hypervalent iodonium compounds have been shown.[76-77]So, one of the probable directions would be using copper to catalyze the reaction with diaryliodonium reagents or Togni reagent.[78] In fact, the initial results showed a promising outcome. When titanacyclopropene was

reacted with diphenyliodonium iodide in thepresence of copper bromide at 60 °C, a 45% conversion to the product **97** was realized.[79] Further developments will be reported.

2.6. SUPPORTING INFORMATION

2.6.1. Methods

All of the reactions were carried out in oven-dried or flame-dried glassware under an atmosphere of argon with magnetic stirring. Reactions were monitored either by thin-layer chromatography with 0.25 mm precoated silica gel plates or by gas chromatography. Visualization of all TLCs was performed with UV light and/or staining with phosphomolybdic acid, $KMnO_4$, or Seebach's stain. Purifications were performed by flash chromatography with silica gel (60 Å, 230–400 mesh) packed in glass columns and elution with hexanes/EtOAc, unless otherwise noted.

2.6.2. Materials

Diethyl ether, dichloromethane, chloroform, and tetrahydrofuran were purified and dried using a solvent purification system that contained activated alumina. 1,2-Dichloroethane and pyridine were freshly distilled from calcium hydride under argon. $Ti(O\text{-}iPr)_4$ was distilled once a month.

2.6.3. Instrumentation

^1H NMR and ^{13}C NMR spectra were obtained on a 400 MHz NMR spectrometer (400 MHz for ^1H and 101 MHz for ^{13}C), and chemical shifts (δ, ppm) are reported relative to residual chloroform solvent peaks (δ = 7.26 ppm for ^1H and δ = 77.0 ppm for ^{13}C). Data for ^1H NMR are reported as follows: chemical shift (multiplicity, coupling constant(s) in Hz, integration). Multiplicities are indicated as follows: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sex = sextet, sept = septet, m = multiplet or unresolved. Low-resolution mass spectra were obtained by GC–MS

2.6.4. General procedure A: formation of three membered titanacyclopropene (Scheme 2.11)

In flame dried, argon treated 25mL round bottomed. flask was treated diphenylacetylene (0.8 mmol, 0.1086 g) and $Ti(i\text{-}O\text{-}Pr)_4$ (1 mmol, 0.22 mL) was added, then added the solvent diethethyl ether (8mL). It was cooled to -78°C. iPrMgCl (2.0 M in Et_2O, 2.5 mmol, 0.93 mL) was added slowly to the reaction mixture until it is homogeneous. The solution was warmed up to -50°C over half an hour. Stirred the mixture at same temperature for 2hr. The reaction was quenched with water, dried and purified through hexane in silica gel. Cis-stillbene was obtained as white solid in about 81%.

2.6.5. General procedure B: formation of five membered titanacyclopropene (Scheme 2.12)

A 25mL round bottomed flask was flame dried and argon treated. Diphenyl acetylene (0.8 mmol, 0.1086 g) was added with $Ti(i\text{-}O\text{-}Pr)_4$ (1 mmol, 0.22 mL) in ether (8mL). It was cooled to -78°C. iPrMgCl (2.0 M in Et_2O, 2.5 mmol, 0.93 mL) was added slowly to the reaction mixture until it is homogeneous. The solution was warmed up to -50 °C over 30 min. The mixture was stirred at same temperature for 2hr. Benzaldehyde(1 mmol, 0.10mL) was added at -78°C and the reaction mixture was continued to stir at -75 °C to -70 °C. The reaction was quenched with water (0.8 mL), dried by $MgSO_4$ and purified through hexane:EtOAc 95:5 in silica gel to obtain respective alcohol in about 60% yield.

2.6.6. General procedure C: iron catalyzed cross coupling of aryl chloride with Grignard reagent (Scheme 2.13)

A flame dried 25 mL round bottomed flask was charged under Argon. 4-chlorobenzoic acid methyl ester (1 mmol, 0.1704g) was added with $Fe(acac)_3$ (5 mol%, 0.0170g) in THF (6 mL) and NMP (0.56 mL). A solution of ethyl magnesium bromide (3.0 M in Et_2O, 1.2 mmol, 0.40 mL) was added via syringe slowly resulting red solution to change to dark brown and finally to violet colored solution. The resulting mixture was stirred for 10min and is diluted with diethylether and

carefully quenched with aqueous HCl. The mixture was dried with $MgSO_4$ and purified under silica gel to get 98% coupled product.

2.6.7. General procedure D: iron catalyzed cross coupling of titanacycles with aryl halides (Scheme 2.14)

A round bottomed flask 25 mL was set up and flame dried charged under Argon flow. It was charged with acetylene(1 mmol) and $Ti(i\text{-}O\text{-}Pr)_4$ (1.5 mmol, 0.33 mL) in 2.5 mL of THF and was cooled to -78 ^oC and iPrMgCl (2.0 M in Et_2O, 2.5 mmol, 0.93 mL) was added slowly until the mixture is homogeneous. The solution was warmed upto -50 ^oC in 0.5 hr and stirred it to same temperature for about 3 hr. Bromobenzene(1 mmol, 0. 11 mL) , $Fe(acac)_3$ (5 mol%, 0.0170 g), reductant (15 mol%) and 2.5 mL THF was mixed together in another flame dried, argon treated 25 mL round bottomed flask. And the titanacycle was slowly transferred the second round bottom flask. And the reaction is stirred at given temperatures. The reaction is monitored by GC in 1hr, 2hr, 6hr, 15h and 24h.

Modification 1: After the formation of titanacyle, bromobenzene, $Fe(acac)_3$ and reductant was sequentially added to titanacycle

Modification 2: Ligands and additives or reducing agents were added along with the iron catalyst and aryl bromide before adding the organotitanium reagents.

2.6.8. General procedure E: nickel catalyzed cross coupling of titanacycles with aryl halides

In 25 mL round bottomed flask (flame dried argon treated) diphenyl acetylene (1 mmol, 0.18 g), $Ti(i\text{-}O\text{-}Pr)_4$ (1.5 mmol, 0.33 mL) in 5 mL of THF was cooled to -78 ^oC. n-BuLi (1.6 M in hexane, 2 mmol, 1.25 mL) was added drop by drop to the solution mixture. The reaction mixture was warmed to r.t. after stirring 3 h, the solution was added to the round bottomed flask (flame dried argon treated) containing $NiCl_2$ (0.05 mmol, 0.0064 g). Then bromobenzene (2 mmol, 0.211

mL) was added last. The solution was taken to 60 °C bath and stirred overnight to quench with water 1 mL and allowed to cool down to r.t. dried over $MgSO_4$, filtered and concentrated in rotovap. It was purified under flash chromatography by eluting with Hexane:EtOAc 98:2.

Note 1: The ligands were added along with the $NiCl_2$ in the dried argon treated Round bottomed flask prior to the addition of titanacycles

Note 2: The alequate was taken and run through the GC and compared with the calibration curve to find out the percent yields of the particular reaction**.**

2.6.9. Spectral data for the products

Cis-stillbene (80): Following general procedure A, a product (81%, 0.0894 g) was isolated as while solid after the column chromatography with 100% hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.19 (m, 10H), δ 7.65 (s, 1H). ^{13}C NMR (101 MHz, $cdcl_3$) δ 137.2, 130.2, 128.9, 128.2, 127.1. The physical and spectral data were consistent with those reported in the literature.[80]

(*E*)-1,2,3-Triphenylprop-2-en-1-ol (82): Following the general procedure B, a product (59%, 0.1368g) was isolated after the column chromatography with hexane/EtOAc (90:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.18 (m, 9H), 7.07 (m, 3H), 7.69 (m, 4H), 5.54 (s, 1H), 2.03 (s, 1H). The physical and spectral data were consistent with those reported in the literature.[81]

4-Ethylbenzoic acid methyl ester (85): Following the general procedure C, a product (95%, 0.1560g) was isolated after the column chromatography with hexane/EtOAc (98:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (d, J = 8.4Hz, 2H), 7.22 (d, J = 8.4Hz, 2H), 3.857 (s, 3H), 2.65 (q, J = 7.6H, 2H), 1.21 (t, J = 7.6H, 3H). The physical and spectral data were consistent with those reported in the literature.[82]

1,1,2-Triphenylethene (97): Subjection to the general procedure E, the diphenylacetylene (1 mmol, 0.1870 g), with bromobenzene (2 mmol, 0.211mL), gave 48% of the product **97** (0.122 g)

as colorless solid after column chromatography Haxanes:Ethylacetate (98:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 8H), 7.27 (m, 2H), 7.18 (m, 3H), 7.09 (m, 2H), 7.02 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.4, 142.6, 140.3, 137.4, 130.4, 129.5, 128.6, 128.2, 128.1, 127.9, 127.6, 127.5, 127.4, 126.7. The physical and spectral data were consistent with those reported in the literature.[83]

(*E*)-1-(4-Methoxyphenyl)-1,2-diphenylethene (112): Subjection to the general procedure E, the diphenylacetylene (0.5 mmol, 0.0891 g), with 4-bromoanisole (1 mmol, 0.105 mL), gave 48 % the product **112** (0.0687 g) as oily liquid after column chromatography with Haxanes:Ethylacetate (98:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-6.79 (m, 14 H), 3.81 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 142.1, 140.5, 137.6, 136.0, 130.3, 129.4, 128.7, 128.6, 127.9, 127.3, 126.6, 126.4, 113.6, 55.4. The physical and spectral data were consistent with those reported in the literature.[84]

(*E*)-1-(4-Trifluoromethylphenyl)-1,2-diphenylethene (113): Subjection to the general procedure E, the diphenylacetylene (0.5 mmol, 0.0891 g), with 4-trifluoromethylbromobenzene (1 mmol, 0.140 mL), gave 36% of the product **113** (0.0585 g) after column chromatography with Hexane:Ethylacetate (98:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (m, 2H), 7.39 (m, 5H), 7.19 (m, 4H), 7.07 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.3, 139.6, 136.8, 130.9, 130.3, 130.0, 129.7, 128.9, 128.2, 128.1, 127.8, 127.3, 125.6, 125.2, 77.4, 77.0, 76.7. The physical and spectral data were consistent with those reported in the literature.[84]

(*E*)-4-Phenyl-4-octene (114): Subjection to the general procedure E, the 4-octyne (1 mmol, 0.146mL), with bromobenzene (2 mmol, 0.211mL), gave the product **114** as yellow oil in 43% (0.0816 g) yield after column chromatography with 100% hexane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.20 (m, 5H), 5.69 (t, J = 7.2 Hz, 1H), 2.51 (t, J = 7.6 Hz, 2H), 2.21 (q, J = 7.2 Hz, 2H), 1.50 (q, J = 7.2 Hz, 2 H), 1.39 (q, J = 7.6 Hz, 2H), 0.99 (t, J = 7.6 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5, 140.0, 129.2, 128.1, 126.9, 126.4, 31.7, 30.7, 23.1, 21.8, 14.0, 14.0. The physical and spectral data were consistent with those reported in the literature.[85]

(*E*)-2-(1,2-diphenylvinyl)pyridine (115): Subjection to the general procedure E, the diphenylacetylene (0.5 mmol, 0.0891 g), with 2-bromopyridine (1 mmol, 0.095 mL) gave the product **115** as yellow oil in 11% (0.0137 g) after the column chromatography with Hexane:Ethylacetate (98:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, *J* = 4.4 Hz, 1H), 7.90 (s, 1H), 7.55 (m, 1H), 7.40 (m, 3H), 7.27 (m, 5H), 7.13 (m, 3H), 6.99 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7, 149.0, 140.3, 139.0, 136.6, 136.3, 130.7, 130.1, 129.9, 128.9, 127.8, 127.5, 127.1, 122.3, 121.8. The physical and spectral data were consistent with those reported in the literature.[86]

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CHAPTER III

SELECTIVE SYNTHESIS OF ENONES VIA A TITANIUM PROMOTED COUPLIING OF UNSYMMETRICAL ALKYNES WITH WEINREB AMIDES

3.1. INTRODUCTION

α,β-Unsaturated carbonyl compounds are an important class of building blocks for natural product synthesis and small molecule library development. Within this realm α-β unsaturated ketones, also known as enones have been versatile building blocks in complex molecule synthesis. Enones are present in natural products[1-3] as well pharmaceutical drugs having divergent biological activities (Fig 3.1). Enones contain two functionalizable handles, and as such, a diverse array of structures can be accessed from this motif. They have been selectively[4-6] and enantioselectively reduced,[7-8] subjected to 1,2- and 1,4-additions,[9-12] Robinson annulations,[13] Diels-Alder reactions,[14] radical addition reactions,[15-16] and used as building blocks in heterocycle synthesis (see Scheme 3.1).[17-19] As a result of their synthetic utility, numerous methods have been developed for the preparation of enones. While all of these methods complement each other, they have narrowly focused on mono- and di-substituted enones (acryloyl groups). Few of these methods are amenable to applications in library preparation, and there is still a need for a method that can be used to prepare tri- and tetrasubstituted enones in a modular manner from readily available and easily modifiable substrates. A diverse array of three- and five-member ring titanacycles can be prepared from alkynes, alkenes, allenes, carbonyls, imines, and nitriles through intra- and intermolecular

reductive coupling. These titanium promoted couplings have proven to be a powerful strategy for bond construction. The Rahaim group is interested in leveraging the dicarbanion nature of titanacycles to rapidly and efficiently prepare complex molecules/building blocks/scaffolds, in a modular and economical (atom, step, redox) manner. To address this gap in enone synthesis we sought to adopt our sequential one pot reactions of titanacycles to this issue.

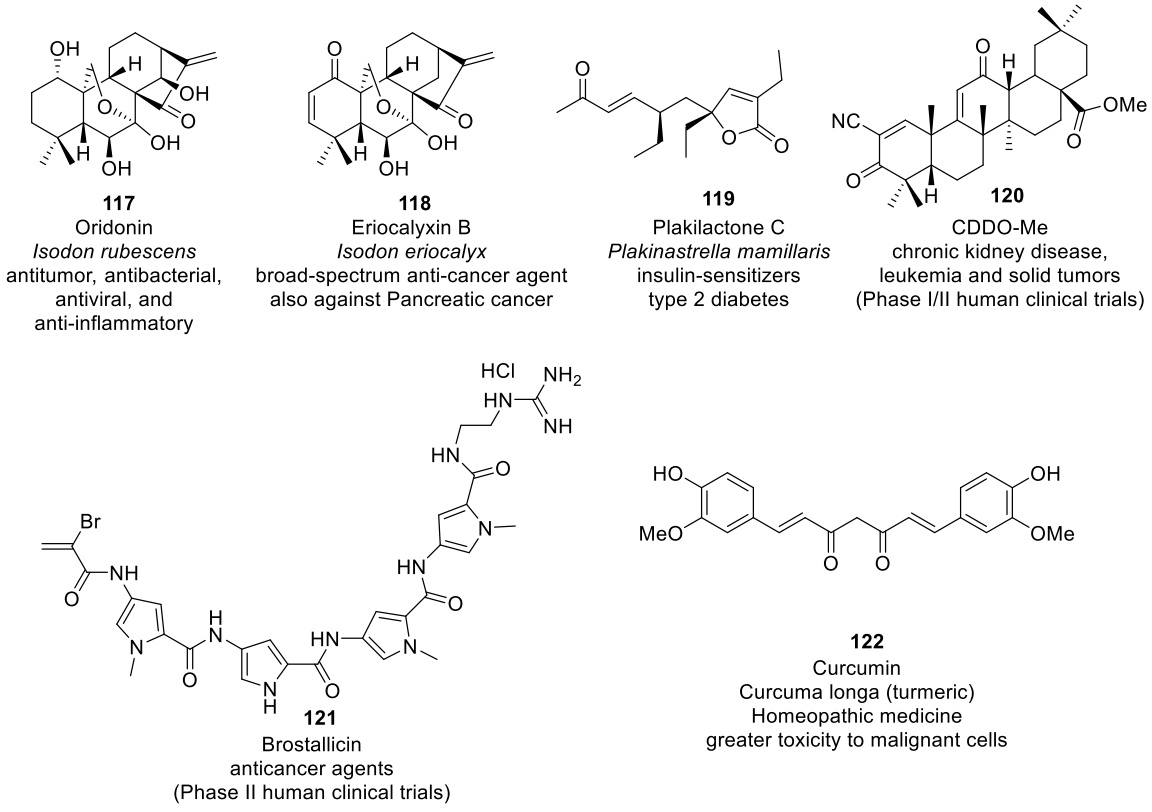
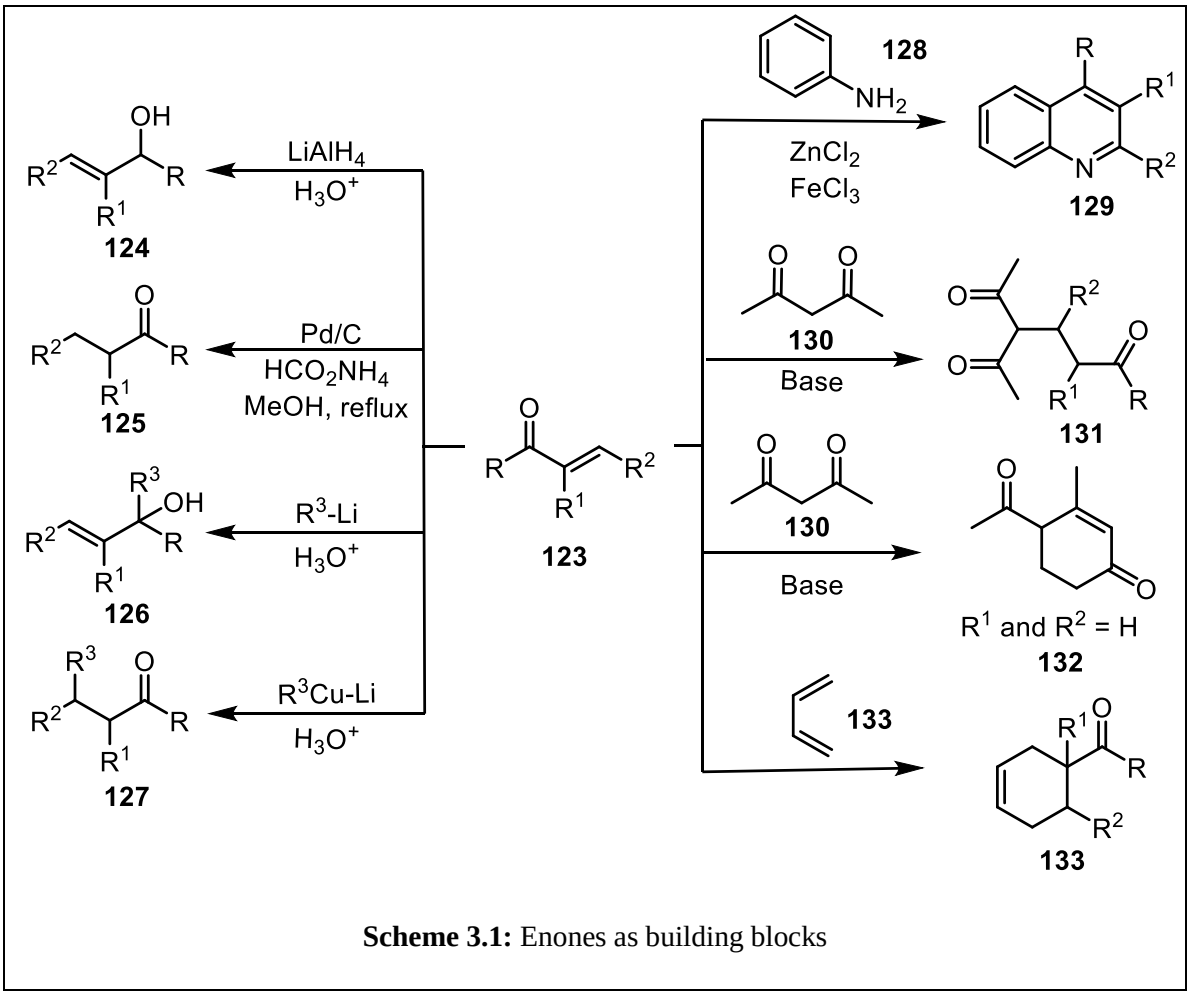


Fig. 3.1 Enones in natural products and pharmaceuticals



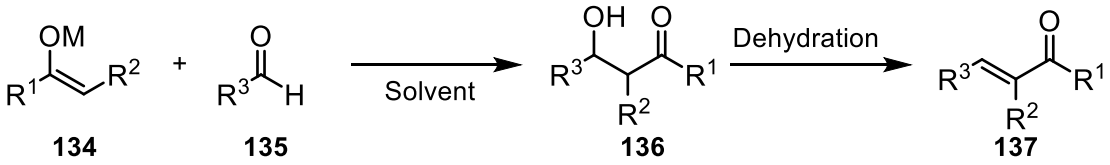
Scheme 3.1: Enones as building blocks

3.2. BACKGROUND: ENONE SYNTHESIS

A divergent array of methods has been developed for the preparation of enones[20-22] such as, dehydrative aldols,[23-24] oxidations,[25-29] olefination reactions with α-ketophosphonates,[30-31] palladium dehydrogenation,[32] transition metal catalyzed isomerization of propargylic alcohols,[33-37] hydroacylation of alkynes,[38-40] and acylation of organometallic reagents. These strategies for the synthesis of enones complement each other; however, each possess individual drawbacks. Let us discuss them in brief:

3.2.1. Synthesis of enones from enols and enolates

The classical method for preparing enones is an aldol condensation, a reaction between an enol or enolate nucleophile and an aldehyde or ketone followed by thermal dehydration. [23, 41] Aldol condensations can be catalyzed with Brønsted acids or bases, Lewis acids, or run with preformed metal enolates. The catalyzed versions typically have undesired competing pathways, such as self-condensation and poly-condensation resulting in diminished yields and mixtures of products that can be difficult to separate. Additionally, the catalyzed methods are not selective and produce mixtures of stereoisomers. The use of preformed enolates circumvents the self- and poly-condensation issues, but this approach requires an additional step to prepare the metal enolate, which has been accomplished with main group[24, 42] and transition metals. [43-44] The most commonly utilized metal enolates are lithium,[24, 45] titanium,[43, 46-48] boron,[42, 49-51] and silicon.[52-55] While some specific substrates in the enolate approach to enones selectively afford a single diastereomer, in general this approach also suffers from being non-selective affording mixtures of stereo-isomers. As a result this strategy is typically employed only for the synthesis of mono- and disubstituted enones.



134 **135** **136** **137**

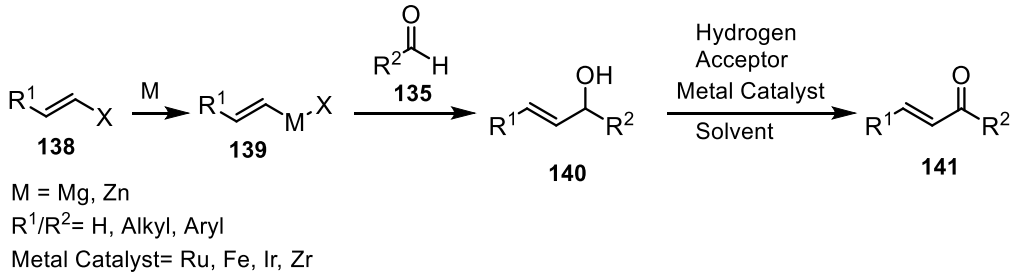
M= Li, B, Na, Si, Al, Ti, Fe, Co, Zn, Zr, Mo, Rh, Ce, W, Re,
R^1= Alkyl, Aryl, -NR_2, -OR,-SR
R^2= Alkyl, Aryl, -OR
R^3= H, Alkyl, Aryl

Scheme 3.2 Aldol condensation reaction.

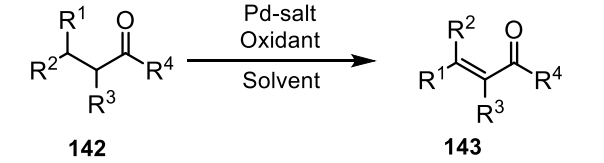
3.2.2. Enone synthesis via oxidative reactions:

A second classical approach to enones is oxidation of secondary allylic alcohols, which can be accomplished with stoichiometric oxidizing reagents,[56-62] or with more modern metal

catalyzed methods.[25-27, 63-65] The limitation of this approach lies in the available methods to prepare the allylic alcohols. This is typically accomplished by the addition of a vinyl metal nucleophile to an aldehyde. The problems are that (1) this requires an additional step to prepare the vinylic nucleophile, making this approach at minimum three steps, (2) the vinylic nucleophile may have functional group compatibility issues limiting the scope of the substrates, and (3) methods to prepare polysubstituted vinylic metals are limited. Of the methods that exist, the preparation of tri- and tetrasubstituted metal-alkenes is not trivial and is accompanied by poor regio- and stereoselectivity, which diminishes the overall yield of the enone and affords mixtures of stereoisomers that may be difficult to separate (Scheme 3.3). A relatively recent advance in this area was developed by Nicolaou and coworkers, where they demonstrated that the hypervalent iodine reagent IBX in combination with a stoichiometric oxidant could perform a tandem oxidation dehydration to form enones from alcohols. While this method has increased process efficiency it still also produces mixtures of stereoisomers for tri-substituted enones, and is unable to prepare tetrasubstituted cases.[29, 66] Palladium promoted dehydration of ketones to form enones has been known since the 1970s.[32] Recent endeavors in this area have focused on developing catalytic versions through the addition of stoichiometric oxidants.[32, 67] These reactions have demonstrated good functional group compatibility affording the enone in moderate to high yields (Scheme 3.4). Yet, this approach also produces mixtures of diastereomers for acyclic trisubstituted enones and is problematic for tetrasubstituted targets only working for specialized substrates. Furthermore, these palladium catalyzed dehydrations can have a competing reduction pathway affording the allylic alcohol, sometimes as the major product.[32, 67]



Scheme 3.3 Oxidation of allylic alcohols



Scheme 3.4 Dehydrogenation using a Pd-salt

3.2.3. Synthesis of enones by hydroacylation of alkynes and acylation of organometallic reagents

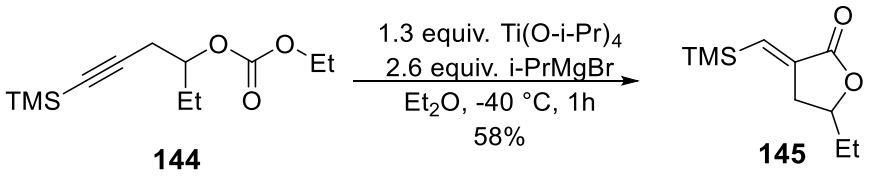
Hydroacylation[38] involves the addition of an acyl group and a hydrogen atom across a carbon-carbon π bond, which is accomplished by C-H activation of an aldehyde with a transition metal. This is an atom economical approach to preparing enones. The inter- and intramolecular hydroacylation of alkynes has been accomplished under rhodium,[40, 68-70] ruthenium,[71] and nickel catalysis.[72] This reaction has typically been done intramolecularly to form 5- and 6-membered cyclic enones. Intermolecular hydroacylation has been less developed due to regioselectivity issues when using unsymmetrical alkynes. Some progress has been made but these methods are restricted to using terminal alkynes and a directing group on the aldehyde, which limits the substrate scope of the reaction and only affords disubstituted enones.

Palladium catalyzed cross-couplings of organolithiums[73], organomagnesiums[74], organosilanes[75], organostannanes[76] and organoboranes[77] have been utilized to synthsize enones. Two approaches have been developed, the first being the cross-coupling of vinylstannanes with acid chlorides, which has the drawback of using a toxic organometallic reagent and is limited to only preparing disubstituted enones selectively. The second approach is palladium catalyzed carbonylation which is typically performed with vinylboronic acids / esters. The drawbacks of carbonylation are the use of carbon monoxide, a toxic flammable gas, and the restriction of only being able to readily prepare mono- and disubstituted enones. Polysubstituted enones can be prepared through these cross-couplings but this then requires an arduous multistep process to prepare the vinyl coupling partner, either as the vinyl halide or as the vinyl metal nucleophile. These two approaches also have a narrowed substrate scope do to the limitation of performing palladium cross-couplings with only sp^2-hybridized organohalides.

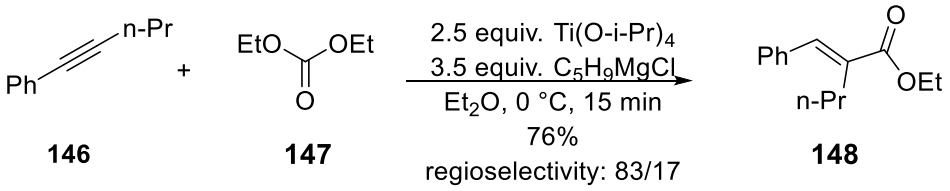
3.3. RESULTS AND DISCUSSION

We speculated that a titanium-promoted coupling[78] of alkynes and acyl electrophiles could afford enones in a modular manner with high selectivity. Stemming from the seminal work of Kulinkovich on the cyclopropanation of esters,[79] Sato demonstrated that diisopropoxytitanacyclopropenes undergo intramolecular nucleophilic acyl substitution with carbonates (Scheme 3.5).[80-81] Six expanded this work to include the formation of α,β-unsaturated carboxylic acids and esters *via* an intermolecular titanium-mediated reductive coupling of alkynes with carbon dioxide[82] and carbonates (Scheme 3.6).[78] Complementarily, zirconocene-mediated couplings of alkynes with chloroformates[83] and carbon dioxide[84] have also been reported. Surprisingly, the use of group IV metallacycles to form enones from alkynes has not been reported. For applications in library preparation, a vast pool of readily available acyl electrophiles are needed to facilitate diversification of the library. On the basis of this requirement, we chose to investigate Weinreb amides, which are bench-stable reactive acyl electrophiles that can easily and efficiently

be prepared from ubiquitous carboxylic acids.[85-86] Weinreb amides have been utilized in enone synthesis with vinyllithium[87] and Grignard[88] reagents but not with titana- or zircona-cyclopropenes.

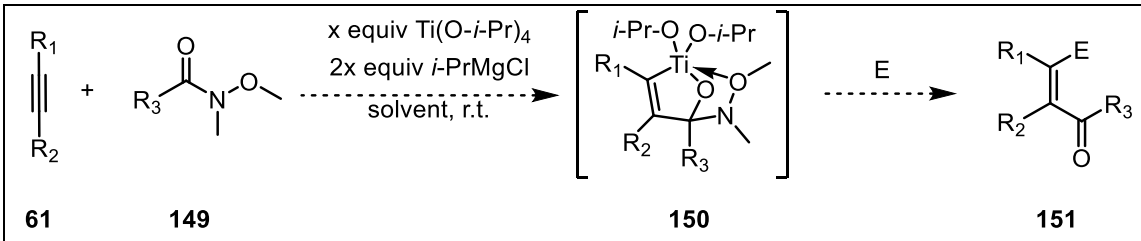


Scheme 3.5 Sato's intramolecular nucleophilic acyl substitution



Scheme 3.6 Six's alkyne-carbonate coupling

Evaluation of the titanacycle literature indicated that the optimal starting point would be generation of the titanacyclopropene via Sato's method, which involves reduction of Ti(O-*i*-Pr)$_4$ with *i*-PrMgCl followed by ligand exchange with an alkyne.[89-90] A limitation of this method for applications in small-molecule library synthesis is that diisopropoxytitanacyclopropenes are thermally unstable and typically cannot be warmed above −30 °C. It was speculated that the rate of reaction of the titanacyclopropene with a Weinreb amide would be faster than the decomposition pathways and side reactions at room temperature. Additionally, the coupling would generate a stabilized intermediate that would be thermally stable through coordination of the methoxy group to the titanium (**150**).

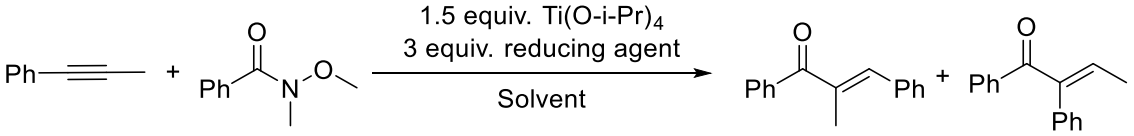


61 149 150 151

Scheme: 3.7 Proposed reaction of titanocyclopropene with Weinreb amides

3.3.1. Optimization of the titanium-promoted coupling reaction

While the ultimate goal was the development of a simple mix-and-stir procedure that would operate at room temperature, the reaction was first investigated under cryogenic reaction conditions. A room-temperature procedure would require the titanacyclopropene to be generated in the presence of the Weinreb amide, and it was not clear whether the Grignard reagent would preferentially react with $Ti(OiPr)_4$ over the Weinreb amide. Thus, for the initial optimization reactions, the titanacyclopropene of 1-phenyl-1-propyne (**88**) was generated under prototypical cryogenic conditions (−78 to −40 °C for 3 h), after which the Weinreb amide (**152**) was added at −78 °C and the reaction mixture was warmed to room temperature. Under these conditions the desired enone was formed (Table 3.1, entry 1), establishing that a titanacyclopropene can undergo coupling with a Weinreb amide with high regioselectivity, favoring enone **153**. Increasing the amount of Weinreb amide **152** to 2 equiv increased the yield of the enone (entry 2), but further increases had no effect (entry 3). Attempts to further increase the yield through adjustment of the solvent (entries 4−6) established Et_2O as the optimal choice. The choice of reducing agent was critical, as a negative effect was seen with EtMgBr (entry 7) and cyclopentylmagnesium chloride (entry 8). It has been demonstrated that the use of *n*-BuLi produces thermally stable titanacycles.[91-93] Surprisingly, under this reaction manifold the use of n-BuLi to generate the titanacyclopropene afforded the enone in moderate yield but with a complete reversal in regioselectivity, favoring enone **154** (entry 9). Simplification of the procedure by generating the titanacyclopropene in the



88 **152** **153** **154**

Scheme 3.8: Reaction of Titanacyclopropene with Weinreb amide

Table 3.1: Optimization of the Titanium-Promoted Coupling Conditions:

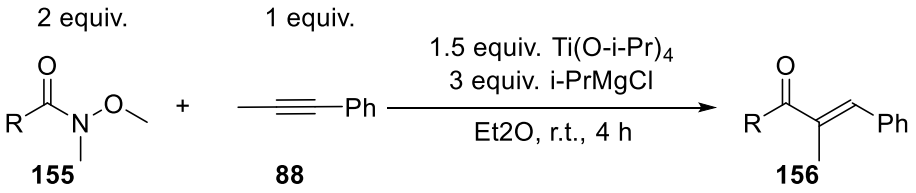
Entry	**Solvent**	**equiv. of 152**	**Reducing agent**	**%yield (153:154)**	**Conditions**
1.	Et_2O	1	*i*-PrMgCl	32%(>99:1)	-78 to -40 °C for 3 h 44 added at -78 °C and warmed to r.t.
2.	Et_2O	2	*i*-PrMgCl	59%(97:3)	Condition same as entry 1
3.	Et_2O	5	*i*-PrMgCl	52%(97:3)	Condition same as entry 1
4.	THF	2	*i*-PrMgCl	34%	Condition same as entry 1
5.	MTBE	2	*i*-PrMgCl	0%	Condition same as entry 1
6.	Toluene	2	*i*-PrMgCl	0%	Condition same as entry 1
7.	Et_2O	2	EtMgBr	0%	Condition same as entry 1
8.	Et_2O	1	*C*-C_5H_9MgCl	20%	Condition same as entry 1
9.	THF	2	*n*-BuLi	37%(13:87)	**152** added after warming to r.t.
10.	THF	2	*n*-BuLi	0%	*n*-BuLi added last at r.t.
11.	Et_2O	2	*i*-PrMgCl	58%(97:3)	*i*-PrMgCl added at -78 °C and warmed to r.t.
12.	**Et_2O**	**2**	***i*-PrMgCl**	**67%(97:3)**	***i*-PrMgCl added last at r.t**

presence of the Weinreb amide was explored next. It was found that addition of n-BuLi to the reaction mixture last did not result in titanacycle formation; instead, the n-BuLi selectively reacted with only the Weinreb amide to afford 1-phenylpentanone (entry 10). Conversely, addition of i-PrMgCl to the reaction mixture last at −78 °C followed by warming to room temperature (entry 11) afforded the desired enone in the same yield and regioselectivity as the stepwise process (entry 2). The yield was increased further to 67% by running this sequential addition of reagents at room temperature (entry 12).

3.3.2. Substrate scope of titanium-promoted alkyne Weinreb amide coupling

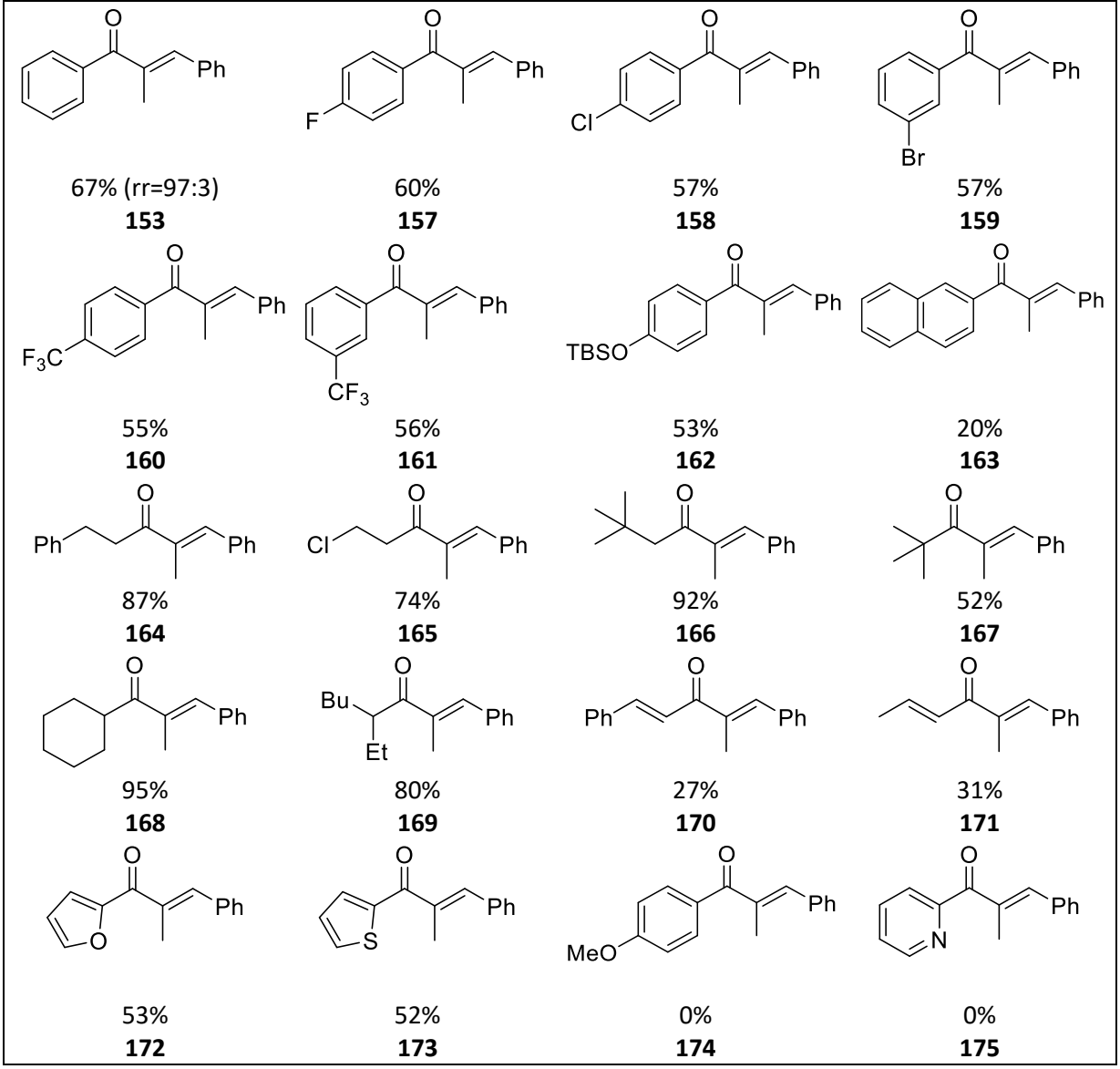
Having established the optimal conditions to be the operationally simple procedure of combining all of the reagents and then adding the i-PrMgCl last at room temperature followed by stirring for 4 h, substrate screening was initiated to determine the scope of this coupling reaction (Table 3.2).

Initial efforts focused on varying the Weinreb amide while keeping the alkyne static, using the unsymmetrical alkyne **88**. In all of the cases examined (Table 3.2), the regioselectivity of the coupling reaction was greater than 97/3. Formation of the carbon−carbon bond favored the alkyne carbon that contained the sterically smaller substituent, regardless of the Weinreb amide employed. Aliphatic Weinreb amides (entries **164-169**) were higher-yielding than aromatic Weinreb amides (entries **153**, **157-163**), except for the sterically large N-methoxy-N-methylpivalamide (entry **167**), which afforded the enone in a moderate yield comparable to those for aromatic counterparts. The system tolerated aromatic and aliphatic halogens (entries **157-161, 165**), although it is noteworthy that an aromatic bromide did not undergo magnesium halogen exchange with the Grignard reagent.[94] The system tolerated meta- and para-substituted aromatic Weinreb amides, whereas ortho-substituted[95] aromatics (I, OMe, Me) would not react with the *in-situ* formed titanacycle, with the exception of a naphthalene (entry **163**). Methoxy groups inhibited the coupling (entry **174**), presumably because of coordination with the titanium complex. To establish that coordination was the issue and not deactivation of the Weinreb amide carbonyl by electron donation, a Weinreb amide with a TBS-protected phenol was prepared and reacted without incident (entry **162**). Additional functional groups on the aromatic Weinreb amide that were found to be incompatible with the system were $-NO_2$, −CN, −OAc, and $-C(O)CH_3$. Furan (entry **172**) and thiophene (entry **173**) heteroaromatics were tolerated, but a pyridine (entry **175**) inhibited coupling.[96] Conjugated Weinreb amides underwent the coupling to produce the corresponding 1,4-dien-3-ones in modest yields (entry **170** and **171**). These products have the potential to undergo a Nazarov cyclization,[97] but under these reaction conditions less than 3% yield of the Nazarov product was observed.



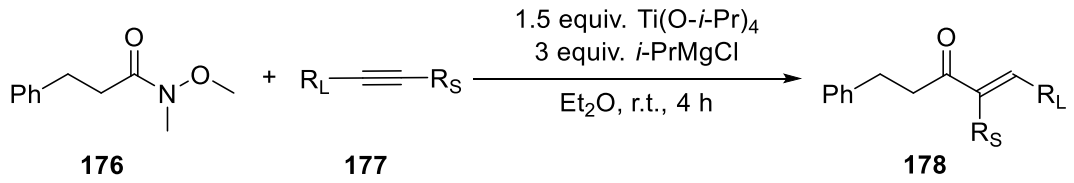
Scheme 3.9 Optimized reaction of titanacyclopropene with various Weinreb amides

Table 3.2: Weinreb amides scope in the titanium-mediated coupling reactions:



A nearly quantitative yield was obtained with 4-octyne (Table 3.3, entry **179**), whereas sterically more congested diphenylacetylene (entry **180**) afforded the enone in moderate yield. As already demonstrated with 1-phenyl-1-propyne, an alkyne with a clear steric difference between the groups

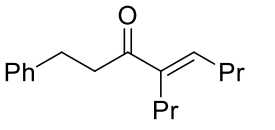
attached to the alkyne undergoes the coupling with high regioselectivity. To test the limits of the regioselectivity, unsymmetrical alkynes of varying steric bulk were examined. The coupling reaction afforded a near 1:1 mixture of regioisomers when the steric differentiating group was distal to the alkyne (entry **181**) or when the two groups were similarly sized (entry **182**). A single isomer was obtained with 3-benzyloxy-1-propynylbenzene (entry **188**), albeit in low yield, presumably as a result of the formation of a dimeric titanacycle that inhibited the reaction with the Weinreb amide. High regioselectivity was seen with silylprotected terminal alkynes (entries **184**-**186**). Sterically congested phenyl(tert-butyl)acetylene participated in the coupling, affording the



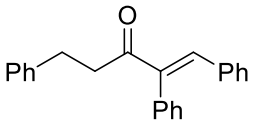
176 **177** **178**

Scheme 3.10 Optimized Reaction of various titanacyclopropene with Weinreb amide

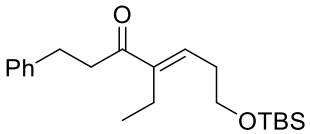
Table 3.3: Alkyne substrate scope of the coupling reaction



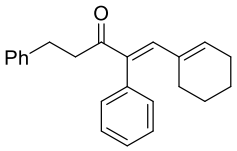
95%
179



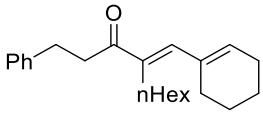
48%
180



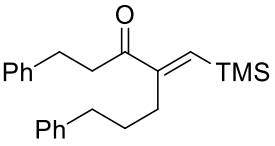
75% (53:47)
181



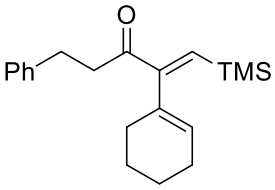
60% (50:50)
182



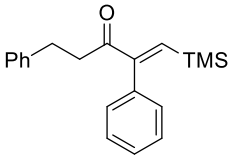
64% (77:23)
183



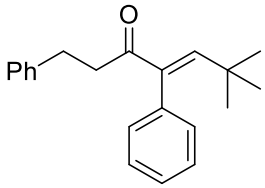
51% (91:9)
184



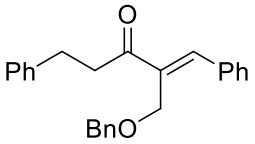
46% (86:14)
185



53% (86:14)
186



35%
187



13%
188

enone in moderate yield but with high selectivity (entry **187**). Increasing the sterics further with tert-butyl- (trimethylsilyl)acetylene completely inhibited the reaction as depicted by complete recovery of alkyne.

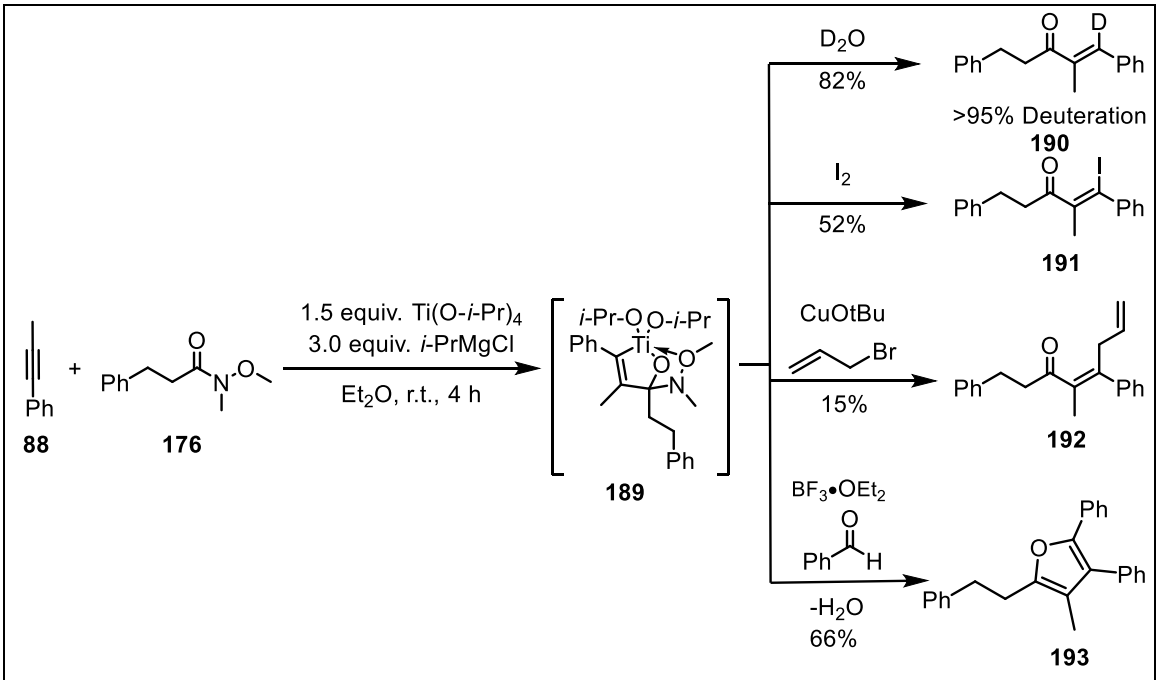
3.3.3. Control experiments to probe the change in regioselectivity when changing the reductant to *n*-BuLi

Our earlier findings demonstrated that when n-BuLi was used as the reducing agent (Table 3.1, entry 9), the enone was formed favoring the opposite regioisomer. On the basis of this result, we became interested in the possibility of selectively accessing either regioisomer simply by changing the reducing agent. Unfortunately, when *n*-BuLi was employed in the coupling reaction the yields were considerably lower, and with a number of the substrates screened there was no reaction. Control reactions were run to help determine which element was the cause of the reversal in regioselectivity. First, we explored the possibility of a solvent effect. Since the solution of *i*-PrMgCl used was in ether and the *n*-BuLi was in hexanes, we ran the coupling reaction with the Grignard reagent in the presence of added hexanes. This resulted only in a lower yield of enone with no erosion in the selectivity, consistent with the solvent screening data, where the reaction did not take place in toluene (Table 3.1, entry 6). Next we examined the role of the metal cation. To examine whether the lithium cation interacted with the titanium complex and thereby affected the regiocontrol, 10 equiv. of LiCl was added to the reaction with *i*-PrMgCl and was found to have no effect. In theory, reduction of the $Ti(O\textit{i}Pr)_4$ with the reducing agent produces 2 equiv. of a metal alkoxide, which could affect the aggregate structure of the titanacycle and/or coordinate to the titanium to form an ate complex. Thus, we ran the coupling reaction using *i*-PrMgCl with 2 equiv. of lithium tert-butoxide added, which lowered the yield of the enone from 92% to 66% and slightly eroded the regiocontrol to 96:4. The root cause of the regioselectivity difference with n-BuLi and *i*-PrMgCl remains unclear. It is well established that Grignard and organo-lithium reagents do not exist as monomeric species, but as oligomers. The aggregate structure of these complexes can be modified through variation of the conditions: solvent, temperature, concentration, rate of addition,

etc. Organotitanium reagents most likely also exist as oligomers, so at this point, it is conjectured that the change in reducing agent from *i*-PrMgCl to *n*-BuLi is changing the aggregate structure of the reactive titanacyclopropene. Leading to the change in regioselectivity. To determine this detailed NMR studies of the titanacyclopropene's formed from each reducing agent would need to be done. At this point these structural mechanistic NMR studies are beyond what is need for this project, and as such were not done.

3.3.4. Addition of second electrophile to access tetra-substituted enones

Titanacycles are carbanion reagents, so we examined subsequent reactions of the stabilized titanacycle intermediate. As shown in Scheme 3.11, the *in-situ* formed titanacycle **189** could be quenched with deuterium oxide to afford the deuterated enone in 82% yield with greater than 95% deuterium incorporation, and titanium halogen exchange of **189** with iodine afforded the conjugated vinyl iodide in moderate yield. Attempts to transmetalate the chelated and stabilized titanium−carbon bond in titanacycle **189** with copper(I) salts were successful only with CuO*t*Bu, albeit in low yield, but this could be used to couple with allyl bromide to form the skipped dienone **192**. The reaction of titanacycle **189** with benzaldehyde did not occur because of the decreased reactivity of the stabilized titanacycle, but precomplexation of the aldehyde with $BF_3{\cdot}OEt_2$ facilitated the addition and subsequent cyclization to yield tetrasubstituted furan **193** in 66% yield.[98-99] A more detailed examination of this approach to furan and heterocycle synthesis is reported in chapter 4.



Scheme 3.11 Subsequent Reactions of Stabilized Intermediate Titanacyle

3.4. CONCLUSIONS

In summary, this report has described a titanium-mediated coupling of internal alkynes with Weinreb amides to yield *E*-trisubstituted enones in moderate to good yields. The regioselectivity of the reaction is due to the steric difference between the groups attached to the alkyne, with levels as high >99/1 being obtained. Additionally, this is the first demonstration that organotitanium reagents react with Weinreb amides, thereby expanding the arsenal of nucleophiles that can react with this important acyl electrophile.

3.5. FUTURE DIRECTIONS

Weix in his investigation of Ni catalyzed cross electrophile coupling has shown another bench stable electrophile (2-pyridyl)-thioesters have the same reactivity profile as acid chlorides under his reaction conditions.[100] These thioesters can also prepared from the wide pool of carboxylic acids using di(2-pyridyl)disulfide and triphenylphosphine in single step.[101] This substrate also has the chelating pyridine moiety which would form six-membered chelates making

it stabler that the intermediate **189**. This might be a good starting point to increase the yields and chemoselectivity of the reaction. Furthermore, copper catalyzed coupling of diaryl iodonium iodide can also be tested to react to this chelated five-membered titanacycle. Copper might be able to transmetallate with the titanium of chelated intermediate then to react with the hypervalent iodonium compound to get tetrasubstituted enones. Also, the tetrasubstituted furan as formed in **79** should be further studied.[102]

3.6. SUPPORTING INFORMATIONS

3.6.1. Methods

All of the reactions were carried out in oven-dried or flame-dried glassware under an atmosphere of argon with magnetic stirring. Reactions were monitored either by thin-layer chromatography with 0.25 mm precoated silica gel plates or by gas chromatography. Visualization of all TLCs was performed with UV light and/or staining with phosphomolybdic acid, $KMnO_4$, or Seebach's stain. Purifications were performed by flash chromatography with silica gel (60 Å, 230–400 mesh) packed in glass columns and elution with hexanes/EtOAc, unless otherwise noted.

3.6.2. Materials

Diethyl ether, dichloromethane, chloroform, and tetrahydrofuran were purified and dried using a solvent purification system that contained activated alumina. 1,2-Dichloroethane and pyridine were freshly distilled from calcium hydride under argon. All of the Weinreb amides were prepared following literature procedures[103] from purchased carboxylic acids.

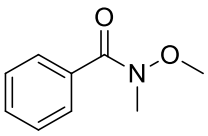
3.6.3. Instrumentation

^{1}H NMR and ^{13}C NMR spectra were obtained on a 400 MHz NMR spectrometer (400 MHz for ^{1}H and 101 MHz for ^{13}C), and chemical shifts (δ, ppm) are reported relative to residual chloroform solvent peaks (δ = 7.26 ppm for ^{1}H and δ = 77.0 ppm for ^{13}C). Data for ^{1}H NMR are reported as follows: chemical shift (multiplicity, coupling constant(s) in Hz, integration). Multiplicities are

indicated as follows: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sex = sextet, sept = septet, m = multiplet or unresolved. The reported melting points are uncorrected. Low-resolution mass spectra were obtained by GC–MS, and high-resolution mass spectrometry (HRMS) was performed using an Orbitrap operated in FT mode to provide a nominal resolution of 100 000.

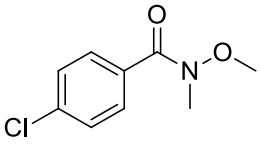
3.6.4. Spectral data of Weinreb amides:

***N*-methoxy-*N*-methylbenzamide (152):**



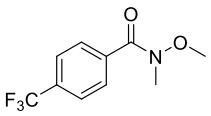
Subjection of benzoic acid (10 mmol, 1.22 g) to the standard literature procedure afforded 1.44 g (87%) of *N*-methoxy-*N*-methylbenzamide (**152**) as a colorless oil after flash chromatography (Hex/EtOAc: 75:25); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (m, 2H), 7.32 – 7.14 (m, 3H), 3.34 (s, 3H), 3.14 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 134.3, 130.6, 128.1, 128.1, 61.0, 33.8. Physical and spectral data were consistent with the literature.[95, 103]

4-chloro-*N*-methoxy-*N*-methylbenzamide (194)



Subjection of 4-chloro-benzoic acid (10 mmol, 1.56 g) to the standard literature procedure afforded 1.82 g (91%) of 4-chloro-*N*-methoxy-*N*-methylbenzamide (**194**) as a colorless oil after flash chromatography (Hex/EtOAc: 75:25); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.49 (m, 2H), 7.39 – 7.20 (m, 2H), 3.41 (s, 3H), 3.24 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.71, 136.79, 132.51, 130.00, 128.38, 61.23, 33.70. Physical and spectral data were consistent with the literature.[104]

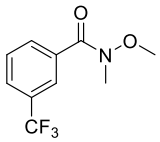
***N*-methoxy-*N*-methyl-4-(trifluoromethyl)benzamide (195)**



Subjection of 4-triflouromethyl-bonzoic acid (10 mmol, 1.90 g) to the standard literature procedure afforded 2.16 g (92%) of *N*-methoxy-*N*-methyl-4-(trifluoromethyl)benzamide (**195**) as a colorless oil after flash chromatography (Hex/EtOAc: 75:25); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 8.1, 3.2 Hz, 2H), 7.55 (dd, *J* = 8.3, 3.6 Hz, 2H),

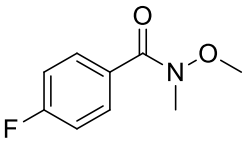
3.44 (s, 3H), 3.25 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 132.3, 132.0, 131.7, 131.4, 128.3, 127.6, 124.9, 124.7, 119.5, 60.8, 33.0. Physical and spectral data were consistent with the literature.

***N*-methoxy-*N*-methyl-3-(trifluoromethyl)benzamide (196)**



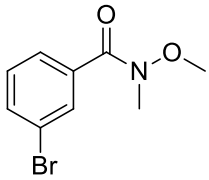
Subjection of 3-triflouromethyl-bonzoic acid (10 mmol, 1.90 g) to the standard literature procedure afforded 2.17 g (93%) of *N*-methoxy-*N*-methyl-3-(trifluoromethyl)benzamide (**196**) as a colorless oil after flash chromatography (Hex/EtOAc: 75:25); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 2.0 Hz, 1H), 7.82 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.67 – 7.61 (m, 1H), 7.47 (t, *J* = 7.9 Hz, 1H), 3.46 (s, 3H), 3.30 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 134.7, 131.4, 130.7, 130.4, 130.1, 129.7, 128.4, 127.7, 127.0, 127.0, 127.0, 126.9, 125.1, 125.1, 125.0, 125.0, 124.9, 122.3, 119.6, 60.9, 33.1. Physical and spectral data were consistent with the literature.[105]

4-fluoro-*N*-methoxy-*N*-methylbenzamide (197)



Subjection of 4-fluoro-benzoic acid (10 mmol, 1.40 g) to the standard literature procedure afforded 1.69 g (92%) of 4-fluoro-*N*-methoxy-*N*-methylbenzamide (**194**) as a colorless oil after flash chromatography (Hex/EtOAc: 75:25); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.54 (m, 2H), 7.12 – 6.89 (m, 2H), 3.42 (s, 3H), 3.25 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 164.9, 162.4, 130.5, 130.4, 129.7, 129.7, 114.8, 114.6, 60.6, 33.2.

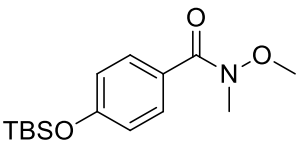
3-bromo-*N*-methoxy-*N*-methylbenzamide (198)



Subjection of 3-bromo-benzoic acid (10 mmol, 2.01 g) to the standard literature procedure afforded 2.37 g (97%) of 3-bromo-*N*-methoxy-*N*-methylbenzamide (**198**) as a colorless oil after flash chromatography (Hex/EtOAc: 75:25); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (t, *J* = 1.8 Hz, 1H), 7.60 – 7.47 (m, 2H), 7.23 (t, *J* = 7.9 Hz, 1H), 3.49 (s, 3H), 3.30 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 135.8,

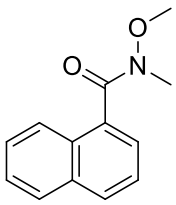
133.4, 131.1, 129.5, 126.7, 121.9, 61.1, 33.4. Physical and spectral data were consistent with the literature.[95]

4-((tert-butyldimethylsilyl)oxy)-*N*-methoxy-*N*-methylbenzamide (199)



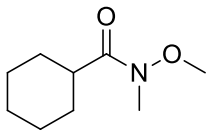
Subjection of TBS protected 4-hydroxy-bonzoic acid[106] (10 mmol, 2.52 g) to the standard literature procedure afforded 2.72 g (92%) of 4-((tert-butyldimethylsilyl)oxy)-*N*-methoxy-*N*-methylbenzamide (**199**) as a colorless oil after flash chromatography (Hex/EtOAc: 75:25); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.55 (m, 1H), 6.92 – 6.70 (m, 1H), 3.51 (s, 2H), 3.30 (s, 2H), 0.95 (s, 5H), 0.18 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 157.9, 130.3, 126.7, 119.4, 60.8, 33.9, 25.6, 18.2, -4.4.

***N*-methoxy-*N*-methyl-1-naphthamide (200)**



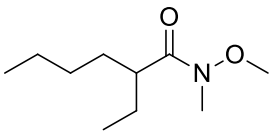
Subjection of 1-naphthoic acid (10 mmol, 1.73 g) to the standard literature procedure afforded 2.05 g (95%) of *N*-methoxy-*N*-methyl-1-naphthamide (**200**) as white solid after flash chromatography (Hex/EtOAc:75:25); ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 2.81(s, 3 H), 3.78 (s, 3 H) 7.44 - 7.57 (m, 4 H) 7.82 -7.95 (m, 3 H) 13C NMR ($CDCl_3$, 101 MHz) δ ppm 33.1, 61.1, 124.1, 124.6, 124.7, 126.1, 126.7, 128.2, 129.4, 129.5, 133.0, 133.1, 169.7. Physical and spectral data were consistent with the literature.[95]

***N*-methoxy-*N*-methylcyclohexanecarboxamide (201)**



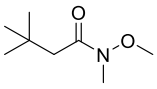
Subjection of cyclohexanoic acid (10 mmol, 1.28 g) to the standard literature procedure afforded 1.46 g (85%) of *N*-methoxy-*N*-methylcyclohexanecarboxamide (**201**) as colorless liquid after flash chromatography (Hex/EtOAc:75:25); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55 (s, 3H), 3.02 (s, 3H), 2.70 – 2.44 (m, 1H), 1.82 – 1.47 (m, 5H), 1.47 – 1.24 (m, 2H), 1.26 – 1.01 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4, 61.5, 42.9, 40.0, 32.3, 29.1, 25.8. Physical and spectral data were consistent with the literature.[104]

2-Ethyl-*N*-methoxy-*N*-methylhexanamide (202)



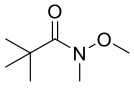
Subjection of 2-ethyl hexanoyl chloride (10 mmol, 1.7 mL) to the standard literature procedure afforded 0.86 g (46%) of 2-Ethyl-*N*-methoxy-*N*-methylhexanamide (**202**) as colorless liquid after flash chromatography (Hex/EtOAc:75:25); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (s, 3H), 3.16 (s, 3H), 2.78 – 2.65 (m, 1H), 1.66 – 1.51 (m, 2H), 1.50 – 1.33 (m, 2H), 1.32 – 1.13 (m, 4H), 0.88 – 0.79 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.9, 61.4, 42.4, 32.3, 29.9, 25.8, 22.9, 14.0, 12.2. Physical and spectral data were consistent with the literature.[95]

***N*-methoxy-*N*,3,3-trimethylbutanamide (203)**



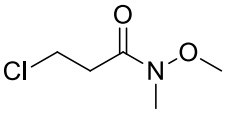
Subjection of 3,3-dimethyl butanoic acid (10 mmol, 1.3 mL) to the standard literature procedure afforded 0.61 g (38%) of *N*-methoxy-*N*,3,3-trimethylbutanamide (**203**) as colorless liquid after flash chromatography (Hex/EtOAc:75:25); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (s, 3H), 3.12 (s, 3H), 2.27 (s, 2H), 1.00 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 60.9, 43.7, 31.9, 31.3, 30.0.

***N*-methoxy-*N*-methylpivalamide (204)**



Subjection of 3,3-dimethyl propanoyl chloride (10 mmol, 1.2 mL) to the standard literature procedure afforded 0.63 g (43%) of *N*-methoxy-*N*-methylpivalamide (**204**) as colorless liquid after flash chromatography (Hex/EtOAc:75:25); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 (s, 3H), 3.10 (s, 3H), 1.17 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.1, 60.5, 39.3, 33.6, 27.0. Physical and spectral data were consistent with the literature.[104]

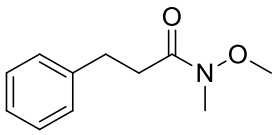
3-chloro-*N*-methoxy-*N*-methylpropanamide (205)



Subjection of 3-chloro- propanoic acid (10 mmol, 1.08 g) to the standard literature procedure afforded 0.79 g (52%) of 3-chloro-*N*-methoxy-*N*-methylpropanamide (**205**) as colorless liquid after flash chromatography (Hex/EtOAc:75:25); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (dtd, *J* = 6.8, 4.2, 2.0 Hz, 2H), 3.64 (s, 3H), 3.13 (s, 3H), 2.84 (dd,

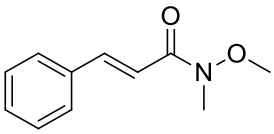
J = 8.1, 5.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 61.3, 39.2, 34.9, 31.9. Physical and spectral data were consistent with the literature.[104]

***N*-methoxy-*N*-methyl-3-phenylpropanamide (176)**



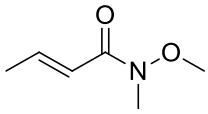
Subjection of 3-phenyl- propanoic acid (30 mmol, 4.505 g) to the standard literature procedure afforded 4.80 g (83%) of *N*-methoxy-*N*-methyl-3-phenylpropanamide (**176**) as colorless liquid after flash chromatography (Hex/EtOAc:75:25); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (ddd, *J* = 8.5, 5.0, 1.8 Hz, 2H), 7.22 – 7.13 (m, 3H), 3.55 (d, *J* = 1.4 Hz, 3H), 3.14 (d, *J* = 1.7 Hz, 3H), 2.94 (td, *J* = 7.9, 2.2 Hz, 2H), 2.71 (t, *J* = 8.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 141.5, 128.7, 128.6, 126.3, 61.4, 34.0, 32.4, 30.9. Physical and spectral data were consistent with the literature.[95]

***N*-methoxy-*N*-methylcinnamamide (206)**



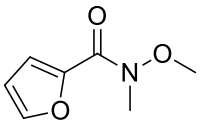
Subjection of cinnamic acid (15 mmol, 2.22 g) to the standard literature procedure afforded 2.80 g (97%) of *N*-methoxy-*N*-methylcinnamamide (**206)** as colorless liquid after flash chromatography (Hex/EtOAc:75:25); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 15.8 Hz, 1H), 7.56 (dq, *J* = 7.1, 1.8 Hz, 2H), 7.41 – 7.34 (m, 3H), 7.03 (dd, *J* = 15.8, 1.2 Hz, 1H), 3.75 (d, *J* = 1.9 Hz, 3H), 3.30 (d, *J* = 1.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 143.5, 135.2, 129.9, 128.9, 128.1, 115.9, 61.9, 32.6. Physical and spectral data were consistent with the literature.[95]

(*E*)-*N*-methoxy-*N*-methylbut-2-enamide (207)



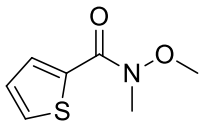
Subjection of crotonic acid (20 mmol, 1.74 g) to the standard literature procedure afforded 1.28 g (49%) of (*E*)-*N*-methoxy-*N*-methylbut-2-enamide (**207**) as colorless liquid after flash chromatography (Hex/EtOAc:75:25); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 – 6.55 (m, 1H), 6.24 – 6.05 (m, 1H), 3.50 – 3.30 (m, 3H), 3.00 – 2.85 (m, 3H), 1.70 – 1.53 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 141.9, 119.8, 61.0, 31.6, 17.5. Physical and spectral data were consistent with the literature.[107]

***N*-methoxy-*N*-methylfuran-2-carboxamide (208)**



Subjection of 2-furoic acid (10 mmol, 1.12 g) to the standard literature procedure afforded 1.52 g (97%) of *N*-methoxy-*N*-methylfuran-2-carboxamide (**208**) as colorless liquid after flash chromatography (Hex/EtOAc:75:25); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.44 (m, 1H), 7.13 – 6.98 (m, 1H), 6.41 (td, *J* = 3.5, 1.7 Hz, 1H), 3.66 (s, 3H), 3.24 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 145.5, 145.1, 117.3, 111.5, 61.2, 33.0. Physical and spectral data were consistent with the literature.[107]

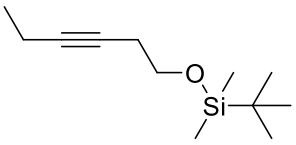
***N*-methoxy-*N*-methylthiophene-2-carboxamide (209)**



Subjection of thiophene-2-carboxylic acid (10 mmol, 1.28 g) to the standard literature procedure afforded 1.63 g (95%) of *N*-methoxy-*N*-methylthiophene-2-carboxamide (**209**) as colorless liquid after flash chromatography (Hex/EtOAc:75:25); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 3.8, 1.4 Hz, 1H), 7.47 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.04 – 6.99 (m, 1H), 3.68 (s, 3H), 3.28 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3, 134.5, 133.4, 132.5, 127.0, 61.7, 33.2. Physical and spectral data were consistent with the literature.[107]

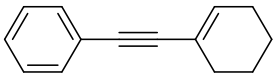
3.6.6. Synthesis and characterization of alkynes

***tert*-butyl(hex-3-yn-1-yloxy)dimethylsilane (210)**



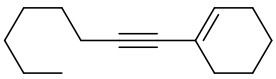
Subjection of *tert*-butyldimethyl silyl chloride (18 mmol, 2.71 g), hex-3-yn-1-ol (15 mmol, 1.6 mL) and imidazole (37.5 mmol, 2.55 g) to the standard literature procedure[108] afforded 2.85 g (89%) of *tert*-butyl(hex-3-yn-1-yloxy)dimethylsilane (**210**) as a colorless oil after flash chromatography (Hex/EtOAc: 98:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (t, *J* = 7.3, 2H), 2.34 (t, *J* = 7.2, 2H), 2.13 (q, *J* = 7.5, 2H), 1.09 (t, *J* = 7.5, 3H), 0.88 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 82.8, 76.2, 62.4, 25.9, 23.1, 18.3, 14.2, 12.4, -5.3. The physical and spectral data were consistent with those reported in the literature.[78]

(cyclohex-1-en-1-ylethynyl)benzene (211)



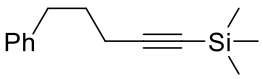
Subjection of iodobenzene (5 mmol, 0.60 mL) and 1-ethynyl-1-cyclohexene (5 mmol, 0.60 mL) to the standard literature procedure[109] afforded 0.67 g (74%) of (cyclohex-1-en-1-ylethynyl)benzene (**211**) as a yellow colored liquid after flash chromatography in Hexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.38 (m, 2H), 7.29 (m, 3H), 6.22 (m, 1H), 2.25 (m, 2H), 2.15 (m, 2H), 1.74 – 1.57 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.2, 131.4, 128.2, 127.7, 123.8, 120.7, 91.3, 86.8, 29.3, 25.8, 22.4, 21.6. The physical and spectral data were consistent with those reported in the literature.[110]

1-(oct-1-yn-1-yl)cyclohex-1-ene (212)



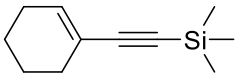
Subjection of 1-ethynyl-1-cyclohexene (5 mmol, 0.60 mL), *n*-BuLi (1.6 M in hexane, 6 mmol, 3.75 mL), and hexyliodide (5 mmol, 0.74 mL) to the standard literature procedure[111] afforded 0.24 g (25%) of 1-(oct-1-yn-1-yl)cyclohex-1-ene (**212**) as yellow oil after flash chromatography in Hexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (t, *J* = 3.5, 1H), 2.26 (t, *J* = 7.1 Hz, 2H), 2.06 (m, 4H), 1.67 – 1.45 (m, 6H), 1.43 – 1.20 (m, 6H), 0.87 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.1, 121.0, 87.4, 82.3, 31.4, 29.6, 28.9, 28.6, 25.5, 22.6, 22.4, 21.6, 19.3, 14.0.

trimethyl(5-phenylpent-1-yn-1-yl)silane (213)



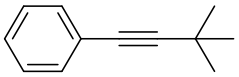
Subjection of 5-phenyl-1-pentyne (15 mmol, 2.16 g), *n*-BuLi (15.3 mmol, 9.56 mL), and trimethylchlorosilane (15.3 mmol, 1.94 mL) to the standard literature procedure[112] afforded 2.47 g (76%) of trimethyl(5-phenylpent-1-yn-1-yl)silane (**213**) as a colorless oil after flash chromatography (Hex:EtOAc: 98:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 2H), 7.22 (m, , 3H), 2.81 – 2.71 (m, 2H), 2.30 – 2.18 (m, 2H), 2.04 (s, 0H), 1.93 – 1.81 (m, 2H), 0.21 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.6, 141.4, 128.5, 128.3, 128.3, 125.9, 125.8, 107.1, 85.0, 84.1, 77.3, 77.0, 76.7, 68.7, 34.7, 34.6, 30.2, 30.0, 19.3, 19.1, 17.8, 0.4, 0.2, -0.1.

(cyclohex-1-en-1-ylethynyl)trimethylsilane (214)



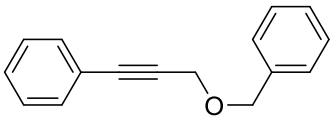
Subjection of 1-ethynyl-1-cyclohexene (10 mmol, 1.2 mL), TMSCl (10.2 mmol, 1.3 mL), and *n*-BuLi (1.6 M in hexane, 10.2 mmol, 6.4 mL) to the standard literature procedure[112] afforded 1.18 g (66%) of (cyclohex-1-en-1-ylethynyl)trimethylsilane (**214**) as colorless oil after flash chromatography(Hex:EtOAc: 98:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16 (t, *J* = 3.9 Hz, 1H), 2.16 – 2.01 (m, 4H), 1.65 – 1.49 (m, 4H), 0.16 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.2, 120.7, 107.3, 90.8, 29.0, 25.6, 22.2, 21.4, 0.1.

(3,3-dimethylbut-1-yn-1-yl)benzene (215)



Subjection of iodobenzene (10 mmol, 1.1 mL), 3,3-dimethyl-1-butyne (30 mmol, 3.7 mL), bis(triphenylphosphine)palladium dichloride (0.5 mmol, 0.34 g), cuprous iodide (1 mmol, 0.190 g) and triethylamine (25 mmol, 3.5 mL) to the standard literature procedure[113] afforded 1.45 g (92%) of (3,3-dimethylbut-1-yn-1-yl)benzene (**215**) as colorless oil after flash chromatography (Hex/EtOAc: 99:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (m, 2H), 7.33 – 7.27 (m, 3H), 1.37 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.5, 128.1, 127.4, 124.1, 98.5, 79.0, 31.0, 27.9.

(3-(benzyloxy)prop-1-yn-1-yl)benzene (216)



Subjection of iodobenzene (15 mmol, 1.7 mL), alkyne (15 mmol, 2.2 mL), bis(triphenylphosphine)palladium dichloride (0.075 mmol, 52 mg), cuprous iodide (0.15 mmol, 28 mg), and diethylamine 90 mL to the standard literature procedure[109] afforded 1.90 g (57%) of (3-(benzyloxy)prop-1-yn-1-yl)benzene (**216**) as colorless oil after flash chromatography (Hex/EtOAc: 98:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.45 (m, 2H), 7.43 – 7.29 (m, 8H), 4.69 (s, 2H), 4.41 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.4, 131.7, 128.4, 128.2, 128.1, 127.8, 122.6, 86.4, 85.0, 71.6, 57.8. The physical and spectral data were consistent with those reported in the literature.[110]

3.6.7. General procedure F: Synthesis of enones

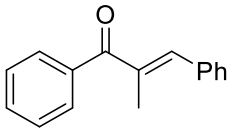
A round-bottom flask was sealed with a septum, and the system was placed under an atmosphere of argon by performing a vacuum-purge cycle three times and then attaching a balloon of argon. The round-bottom flask was charged with the alkyne (1 mmol), Weinreb amide (2 mmol), dry diethyl ether (10 mL), and titanium isopropoxide (1.5 mmol, 0.44 mL). To this stirring mixture was injected a solution of isopropylmagnesium chloride (2 M in ether, 3 mmol, 1.5 mL) dropwise over 5 min. The reaction mixture was stirred at room temperature for 4 h, after which the system was opened to the air and the mixture was quenched with 1 mL of water. The mixture was dried over magnesium sulfate, filtered, and concentrated. The crude material was subjected to flash chromatography, eluting with hexanes/EtOAc (98/2), unless otherwise noted.

Note 1: any solid reagents were added to the flask prior to the vacuum-purge cycle.

Note 2: a small aliquot of the quenched reaction mixture was used to determine the regioisomer ratio by GC–MS.

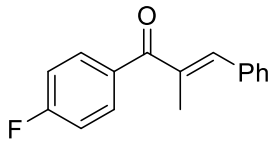
3.6.8. Spectral Data of enones

(*E*)-2-Methyl-1,3-diphenylprop-2-en-1-one (Table 3.2, entry **153**):



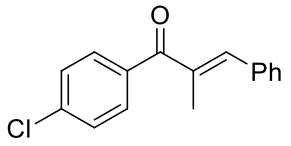
Subjection of 1-phenyl-1-propyne (1 mmol, 0.125 mL) and *N*-methoxy-*N*-methylbenzamide (2.0 mmol, 0.304 mL) to the general procedure **F** afforded 0.149 g (67% yield) of the enone as a yellow oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.75 (m, 3H), 7.59–7.52 (m, 1H), 7.51–7.32 (m, 7H), 7.21 (q, *J* = 1.2 Hz, 1H), 2.30 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.3, 142.1, 138.4, 136.7, 135.6, 131.5, 129.6, 129.4, 128.5, 128.4, 128.1, 14.3. The physical and spectral data were consistent with those reported in the literature.[104]

(*E*)-2-Methyl-3-phenyl-1-(4-fluorophenyl)prop-2-en-1-one (Table 3.2, entry **157**):



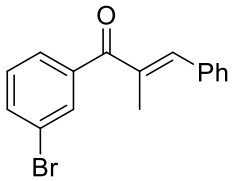
Subjection of 1-phenyl-1-propyne (1.0 mmol, 0.125 mL) and 4-fluoro-*N*-methoxy-*N*-methylbenzamide (2.0 mmol, 0.311 mL) to the general procedure **F** afforded 0.145 g (60% yield) of the enone as a yellowish liquid after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 8.6, 5.5 Hz, 2H), 7.42 (m, 5H), 7.14 (m, 3H), 2.27 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.9, 164.9, 163.6, 141.7, 136.6, 135.5, 134.4, 132.0, 131.9, 129.6, 128.6, 128.4, 115.4, 115.3, 14.5; IR (neat) 3055, 2923, 1644, 1594, 1258, 1225, 1154, 1010, 691, 637 cm^{-1}; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{13}FO$ 241.1024, found 241.1020.

(*E*)-1-(4-Chlorophenyl)-2-methyl-3-phenylprop-2-en-1-one (Table 3.2, entry **158**):



Subjection of 1-phenyl-1-propyne (1.0 mmol, 0.125 mL) and 4-chloro-*N*-methoxy-*N*-methylbenzamide (2.0 mmol, 0.326 mL) to the general procedure **F** afforded 0.145 g (57% yield) of the enone as a yellow oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (m, 2H), 7.42 (m, 7H), 7.14 (m, 1H), 2.26 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.0, 142.2, 137.9, 136.7, 136.5, 135.4, 130.8, 129.6, 128.7, 128.4, 128.4, 14.4. The physical and spectral data were consistent with those reported in the literature.[114]

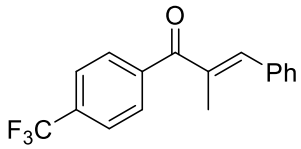
(*E*)-1-(3-Bromophenyl)-2-methyl-3-phenylprop-2-en-1-one (Table 3.2, entry **159**):



Subjection of 1-phenyl-1-propyne (1.0 mmol, 0.125 mL) and 3-bromo-*N*-methoxy-*N*-methylbenzamide (2.0 mmol, 0.334 mL) to the general procedure **F** afforded 0.171 g (57% yield) of the enone as a brownish liquid after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (m, 1H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.45–7.30 (m, 6H), 7.18 (s, 1H), 2.27 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.6, 142.9, 140.4, 136.4, 135.3, 134.4, 132.1, 129.7, 128.8, 128.4, 128.2, 127.8, 122.4, 14.2; IR (neat) 3058, 2923,

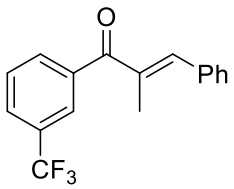
1645, 1562, 1248, 1018, 728, 695 cm^{-1}; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{16}H_{13}BrO$ 301.0223, found 301.0221.

(*E*)-2-Methyl-3-phenyl-1-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (Table 3.2, entry **160**):



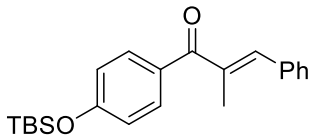
Subjection of 1-phenyl-1-propyne (1.0 mmol, 0.125 mL) and 4-trifluoromethyl-*N*-methoxy-*N*-methylbenzamide (2.0 mmol, 0.369 mL) to the general procedure **F** afforded 0.159 g (55% yield) of the enone as a yellow liquid after flash chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.42 (m, 5H), 7.17 (s, 1H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.1, 143.7, 141.9, 136.5, 135.3, 133.1, 132.7, 129.8, 129.5, 128.9, 128.5, 125.2, 125.2, 125.2, 125.1, 14.0; IR (neat) 3055, 2962, 1649, 1616, 1321, 1107, 1064, 1022, 693 cm^{-1}; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{17}H_{13}F_3O$ 291.0992, found 291.0992.

(*E*)-2-Methyl-3-phenyl-1-(3-trifluoromethyl)phenyl)prop-2-en-1-one (Table 3.2, entry **161**):



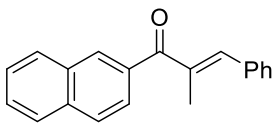
Subjection of 1-phenyl-1-propyne (1.0 mmol, 0.125 mL) and 3-trifluoromethyl-*N*-methoxy-*N*-methylbenzamide (2.0 mmol, 0.369 mL) to the general procedure **F** afforded 0.161 g (56% yield) of the enone as a yellow oil after flash chromatography. ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.43 (m, 5H), 7.17 (s, 1H), 2.30 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.8, 143.2, 139.2, 136.5, 135.3, 132.5, 130.9, 130.6, 129.7, 128.9, 128.8, 128.5, 128.07, 128.03, 128.00, 127.9, 126.17, 126.13, 126.09, 126.05, 14.2; IR (neat) 2926, 1647, 1611, 1575, 1331, 1244, 1093, 1071, 695 cm^{-1}; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{17}H_{13}F_3O$ 291.0992, found 291.0994.

(*E*)-1-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)-2-methyl-3-phenylprop-2-en-1-one (Table 3.2, entry **162**):



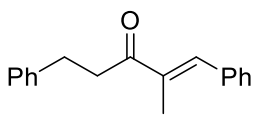
Subjection of 1-phenyl-1-propyne (1.0 mmol, 0.125 mL) and TBS-protected 4-hydroxy-*N*-methoxy-*N*-methylbenzamide (2.0 mmol, 0.529 mL) to the general procedure **F** afforded 0.189 g (53% yield) of the enone as a yellowish oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.8 Hz, 2H), 7.42 (m, 5H), 7.14 (s, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 2.27 (s, 3H), 1.02 (s, 9H), 0.27 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.2, 159.3, 140.0, 136.8, 135.8, 131.8, 131.2, 129.5, 128.2, 119.5, 29.8, 25.5, 18.1, 14.8, −4.4; IR (neat) 2955, 2928, 2857, 1643, 1595, 1505, 1253, 906, 837, 805, 736, 691 cm^{-1}; HRMS (ESI) *m*/*z* [M + H]$^{+}$ calcd for $C_{22}H_{28}O_2Si$ 353.1932, found 353.1936.

(*E*)-2-Methyl-1-(naphthalen-1-yl)-3-phenylprop-2-en-1-one (Table 3.2, entry **163**):



Subjection of 1-phenyl-1-propyne (1.0 mmol, 0.125 mL) and *N*-methoxy-*N*-methyl-1-naphthamide (2.0 mmol, 0.430 g) to the general procedure **F** afforded 0.055 g (20% yield) of the enone as a yellow oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.0 Hz, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.93 m, 1H), 7.53 (m, 4H), 7.40–7.29 (m, 5H), 7.22 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.8, 144.9, 138.5, 137.4, 135.6, 133.6, 131.0, 130.2, 129.8, 128.8, 128.4, 128.3, 126.9, 126.4, 126.3, 125.6, 124.4, 13.4; IR (neat) 3054, 2922, 1643, 1574, 1245, 1197, 777, 692 cm^{-1}; HRMS (ESI) *m*/*z* [M + H]$^{+}$ calcd for $C_{20}H_{16}O$ 273.1274, found 273.1270.

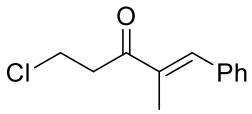
(*E*)-2-Methyl-1,5-diphenylpent-1-en-3-one (Table 3.2, entry **164**):



Subjection of 1-phenyl-1-propyne (1.0 mmol, 0.125 mL) and *N*-methoxy-*N*-methyl-3-phenylpropanamide (2.0 mmol, 0.365 mL) to the general procedure **F** afforded 0.217 g (87% yield) of the enone as a yellow oil after flash chromatography.

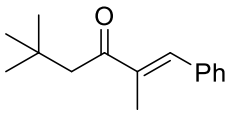
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.44–7.19 (m, 10H), 3.15 (t, *J* = 8.0 Hz, 2H), 3.02 (t, *J* = 8.0 Hz, 2H), 2.08 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.3, 141.5, 138.7, 137.2, 135.8, 129.7, 128.47, 128.42, 128.40, 126.1, 39.6, 30.8, 13.2. The physical and spectral data were consistent with those reported in the literature.[115]

(*E*)-5-Chloro-2-methyl-1-phenylpent-1-en-3-one (Table 3.2, entry **165**):



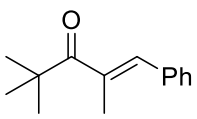
Subjection of 1-phenyl-1-propyne (1.0 mmol, 0.125 mL) and 3-chloro-*N*-methoxy-*N*-methylpropanamide (2.0 mmol, 0.266 mL) to the general procedure **F** afforded 0.153 g (74% yield) of the enone as a yellow oil after flash chromatography (r.r. = 97/3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.43 (m, 5H), 3.87 (t, *J* = 6.4 Hz, 2H), 3.31 (t, *J* = 6.9 Hz, 2H), 2.08 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.4, 139.4, 136.9, 135.4, 129.6, 128.7, 128.4, 40.2, 39.2, 12.9; IR (neat) 2962, 2919, 1661, 1575, 1195, 1065, 727, 694, 657 cm^{-1}; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{12}H_{13}ClO$ 209.0728, found 209.0729.

(*E*)-2,5,5-Trimethyl-1-phenylhex-1-en-3-one (Table 3.2, entry **166**):



Subjection of 1-phenyl-1-propyne (1.0 mmol, 0.125 mL) and *N*-methoxy-*N*,3,3-trimethylbutanamide (2.0 mmol, 0.340 mL) to the general procedure **F** afforded 0.198 g (92% yield) of the enone as a yellow liquid after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.37 (m, 5H), 2.71 (s, 2H), 2.04 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.6, 139.0, 138.6, 136.1, 129.57, 128.4, 128.3, 49.2, 31.4, 30.1, 13.2; IR (neat) 2953, 2866, 1655, 1362, 764, 698 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{20}O$ $[M + H]^+$ 217.1587, found 217.1585.

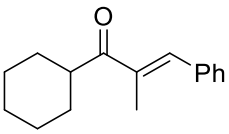
(*E*)-2,4,4-Trimethyl-1-phenylpent-1-en-3-one (Table 3.2, entry **167**):



Subjection of 1-phenyl-1-propyne (1.0 mmol, 0.125 mL) and *N*-methoxy-*N*-methylpivalamide (2.0 mmol, 0.310 mL) to the general procedure **F** afforded

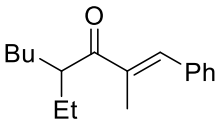
0.106 g (52% yield) of the enone as a yellowish liquid after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 5H), 6.93 (s, 1H), 2.09 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.9, 137.6, 135.9, 131.8, 129.1, 128.2, 127.5, 44.1, 27.9, 16.0; IR (neat) 2966, 2869, 1683, 1659, 1477, 1047, 765, 694 cm^{-1}; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{18}O$ 203.1431, found 203.1429.

(*E*)-1-Cyclohexyl-2-methyl-3-phenylprop-2-en-1-one (Table 3.2, entry **168**):



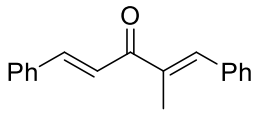
Subjection of 1-phenyl-1-propyne (1.0 mmol, 0.125 mL) and *N*-methoxy-*N*-methyl-1-cyclohexanamide (2.0 mmol, 0.335 mL) to the general procedure **F** afforded 0.217 g (95% yield) of the enone as a yellow liquid after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.40 (m, 5H), 3.16 (t, *J* = 11.7 Hz, 1H), 2.04 (s, 3H), 1.82 (d, *J* = 10.8 Hz, 4H), 1.53–1.19 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.8, 137.6, 136.4, 136.0, 129.5, 128.2, 128.2, 44.5, 29.8, 25.83, 25.80, 13.4; IR (neat) 2927, 2852, 1658, 1448, 1590, 1005, 753, 696 cm^{-1}; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{20}O$ 229.1587, found 229.1587.

(*E*)-4-Ethyl-2-methyl-1-phenyloct-1-en-3-one (Table 3.2, entry **169**):



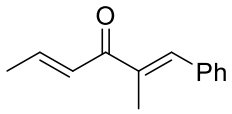
Subjection of 1-phenyl-1-propyne (1.0 mmol, 0.125 mL) and 2-ethyl-*N*-methoxy-*N*-methylhexanamide (2.0 mmol, 0.410 mL) to the general procedure **F** afforded 0.196 g (80% yield) of the enone as a yellow liquid after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.43 (m, 4H), 7.33 (m, 1H), 3.26 (quin, *J* = 6.8 Hz, 1H), 2.08 (s, 3H), 1.70 (m, 2H), 1.58–1.41 (m, 2H), 1.35–1.18 (m, 4H), 0.88 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.9, 138.5, 137.9, 136.1, 129.6, 128.3, 128.3, 46.5, 32.4, 29.8, 26.0, 22.9, 13.9, 13.4, 12.0; IR (neat) 2958, 2928, 2858, 1658, 1047, 694 cm^{-1}; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{24}O$ 245.1900, found 245.1900.

(*E*,*E*)-2-Methyl-1,5-diphenylpenta-1,4-dien-3-one (Table 3.2, entry **170**):



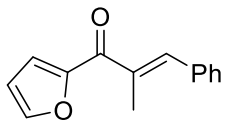
Subjection of 1-phenyl-1-propyne (1.0 mmol, 0.125 mL) and *N*-methoxy-*N*-methylcinnamamide (2.0 mmol, 0.382 g) to the general procedure **F** afforded 0.066 g (27% yield) of the enone as a yellow oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 15.6 Hz, 1H), 7.62 (m, 3H), 7.50–7.33 (m, 9H), 2.20 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.6, 143.4, 138.6, 138.5, 135.9, 135.1, 130.1, 129.7, 128.8, 128.5, 128.4, 128.2, 121.9, 13.8; IR (neat) 3025, 2920, 1650, 1593, 1494, 1448, 1328, 1200, 1061, 762, 698 cm^{-1}; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{16}O$ 249.1274, found 249.1272.

(*E*,*E*)-2-Methyl-1-phenylhexa-1,4-dien-3-one (Table 3.2, entry **171**):



Subjection of 1-phenyl-1-propyne (1.0 mmol, 0.125 mL) and (*E*)-*N*-methoxy-*N*-methylbut-2-enamide (2.0 mmol, 0.264 mL) to the general procedure **F** afforded 0.056 mg (31% yield) of the enone as a yellowish liquid after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (m, 1H), 7.44–7.30 (m, 5H), 6.95 (dq, *J* = 15.2, 6.8 Hz, 1H), 6.79 (dq, *J* = 15.2, 1.49 Hz, 1H), 2.11 (s, 3H), 1.95 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.8, 143.0, 138.4, 137.9, 135.9, 129.6, 128.3, 128.2, 126.9, 18.3, 13.5; IR (neat) 3024, 2913, 1659, 1612, 1575, 1491, 1441, 1287, 1206, 1063, 964, 915, 753, 694 cm^{-1}; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{14}O$ 187.1118, found 187.1116.

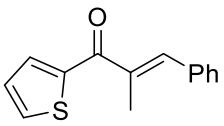
(*E*)-1-(Furan-2-yl)-2-methyl-3-phenylprop-2-en-1-one (Table 3.2, entry **172**):



Subjection of 1-phenyl-1-propyne (1.0 mmol, 0.125 mL) and *N*-methoxy-*N*-methylfuran-2-carboxamide (2.0 mmol, 0.268 mL) to the general procedure **F** afforded 0.111 g (53% yield) of the enone as a yellow oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.50 (s, 1H), 7.46–7.30 (m, 5H), 7.17 (d, *J* = 3.2 Hz, 1H), 6.55 (d, *J* = 3.6 Hz, 1H), 2.23 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.1, 151.8, 146.7, 139.3, 136.3, 135.7, 129.6, 128.4, 128.3, 119.5, 111.7, 14.5; IR (neat) 2916, 2848, 1630, 1575, 1558, 1463, 1389,

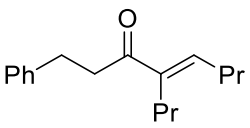
1273, 1024, 1011, 889, 761, 706, 692 cm^{-1}; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{12}O_2$ 213.0911, found 213.0910.

(*E*)-2-Methyl-3-phenyl-1-(thiophen-2-yl)prop-2-en-1-one (Table 3.2, entry **173**):



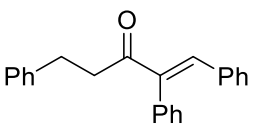
Subjection of 1-phenyl-1-propyne (1.0 mmol, 0.125 mL) and *N*-methoxy-*N*-methylthiophene-2-carboxamide (2.0 mmol, 0.281 mL) to the general procedure **F** afforded 0.117 g (52% yield) of the enone as a yellow oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 3.6 Hz, 1H), 7.67 (d, *J* = 4.8 Hz, 1H), 7.48–7.32 (m, 6H), 7.14 (t, *J* = 4.4 Hz, 1H), 2.26 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.5, 143.4, 139.0, 136.9, 135.6, 133.5, 133.4, 129.5, 128.4, 128.3, 127.6, 14.8; IR (neat) 2917, 1618, 1512, 1411, 1263, 1002, 847, 723, 693 cm^{-1}; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{12}OS$ 229.0682, found 229.0679.

(*E*)-1-Phenyl-4-propyloct-4-en-3-one (Table 3.3, entry **179**):



Subjection of 4-octyne (1.0 mmol, 0.147 mL) and *N*-methoxy-*N*-methyl-3-phenylpropanamide (2.0 mmol, 0.365 mL) to the general procedure **F** afforded 0.232 g (95% yield) of the enone as a yellow oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 2H), 7.21 (m, 3H), 6.57 (t, *J* = 7.3 Hz, 1H), 2.97 (m, 4H), 2.27 (m, 2H), 2.21 (q, *J* = 7.4 Hz, 2H), 1.47 (sex, *J* = 7.2 Hz, 2H), 1.33 (sex, *J* = 7.2 Hz, 2H), 0.95 (t, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.7, 142.8, 141.8, 141.6, 128.39, 128.38, 125.9, 39.2, 30.9, 30.8, 27.7, 22.5, 22.2, 14.2, 13.9. The physical and spectral data were consistent with those reported in the literature.[116]

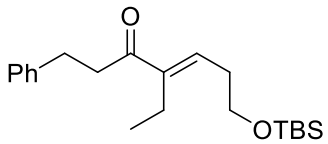
(*E*)-1,2,5-Triphenylpent-1-en-3-one (Table 3.3, entry **180**):



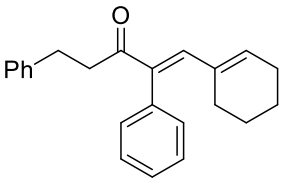
Subjection of diphenylacetylene (1.0 mmol, 0.178 g) and *N*-methoxy-*N*-methyl-3-phenylpropanamide (2.0 mmol, 0.365 mL) to the general

procedure **F** afforded 0.149 g (48% yield) of the enone as a colorless solid after flash chromatography. Mp = 88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.44 (m, 3H), 7.36–7.13 (m, 10H), 7.06 (m, 2H), 3.00 (t, *J* = 7.2 Hz, 2H), 2.93 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.4, 141.3, 140.4, 138.2, 136.8, 134.6, 130.8, 129.5, 129.1, 129.0, 128.39, 128.38, 128.2, 127.9, 125.9, 41.8, 30.4; IR (neat) 3027, 2922, 1676, 1568, 1353, 1281, 1190, 738, 696 cm^{-1}; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{20}O$ 313.1587, found 313.1584.

(*E*)-7-((*tert*-Butyldimethylsilyl)oxy)-4-ethyl-1-phenylhept-4-en-3-one (major isomer) and **(*E*)-4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1-phenylhept-4-en-3-one** (minor isomer) (Table 3.3, entry **181**): Subjection of *tert*-butyl(hex-3-yn-1-yloxy)dimethylsilane (1.0 mmol, 0.252 mL) and *N*-methoxy-*N*-methyl-3-phenylpropanamide (2.0 mmol, 0.365 mL) to the general procedure **F** afforded 0.259 g (75% yield) of an inseparable mixture of these regioisomeric enones (r.r. = 53/47) as a colorless liquid after flash chromatography. Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (m, 2H), 7.13 (m, 3H), 6.59 (t, *J* = 7.2 Hz, 1H, measured 0.43H), 3.51 (t, *J* = 6.8 Hz, 2H, measured 0.89H), 2.89 (m, 4H), 2.49 (t, *J* = 6.8 Hz, 2H, measured 0.87H), 2.27 (m, 2H), 0.99 (t, *J* = 7.6 Hz, 3H, measured 1.37H), 0.82 (s, 9H, measured 3.64H), −0.03 (s, 6H, measured 2.40H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.4, 146.4, 141.54, 137.6, 128.38, 128.33, 125.94, 62.2, 39.13, 32.3, 30.6, 29.4, 25.9, 18.3, 13.4, −5.4. Minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (m, 2H), 7.13 (m, 3H), 6.54 (t, *J* = 7.2 Hz, 1H, measured 0.49H), 3.65 (t, *J* = 6.4 Hz, 2H, measured 1.04H), 2.89 (m, 4H), 2.40 (q, *J* = 6.8 Hz, 2H, measured 1.09H), 2.24 (m, 2H), 0.88 (t, *J* = 7.6 Hz, 3H, measured 1.96H), 0.83 (s, 9H, measured 5.04H), 0.00 (s, 6H, measured 3.29H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.3, 144.4, 141.49, 138.7, 128.35, 128.32, 125.91, 61.8, 39.10, 30.7, 25.8, 22.4, 19.0, 18.2, 13.8, −5.4. IR (neat) 2955, 2928, 2856, 1668, 1496, 1471, 1251, 1094, 833, 774, 697 cm^{-1}; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{34}O_2Si$ 347.2401, found 347.2391.

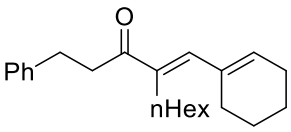


(*E*)-2-(Cyclohex-1-en-1-yl)-1,5-diphenylpent-1-en-3-one (isomer 1) and **(*E*)-1-(cyclohex-1-en-1-yl)-2,5-diphenylpent-1-en-3-one** (isomer 2) (Table 3.3, entry **182**):



Subjection of (cyclohex-1-en-1-ylethynyl)benzene (1.0 mmol, 0.189 mL) and *N*-methoxy-*N*-methyl-3-phenylpropanamide (2.0 mmol, 0.365 mL) to the general procedure **F** afforded 0.191 g (60% yield) of an inseparable mixture of these regioisomeric enones (r.r. = 50/50) as a yellow oil after flash chromatography. Isomer 1: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (m, 2H), 7.42–7.15 (m, 9H), 5.66 (m, 1H), 3.05 (m, 4H), 2.19 (m, 2H), 1.75 (m, 4H), 1.51 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.10, 142.40, 141.48, 137.6, 136.3, 135.7, 135.2, 130.2, 128.6, 128.3, 128.2, 127.8, 125.9, 40.6, 30.6, 28.3, 25.4, 22.3, 21.7. Isomer 2: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.15 (m, 11H), 6.22 (m, 1H), 2.92 (m, 2H), 2.84 (m, 2H), 2.11 (m, 4H), 1.65 (q, *J* = 7.6 Hz, 2H), 1.41 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.6, 142.8, 141.5, 140.8, 136.6, 134.1, 130.1, 129.0, 128.5, 128.4, 128.3, 127.4, 125.8, 41.6, 30.5, 27.2, 26.8, 22.5, 21.5. IR 3025, 2929, 1668, 1571, 1494, 1446, 1179, 1071, 908, 729 cm^{-1}; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{24}O$ 317.1900, found 317.1890.

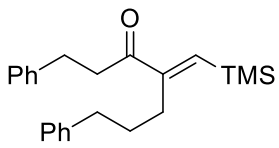
(*E*)-4-(Cyclohex-1-en-1-ylmethylene)-1-phenyldecan-3-one (major isomer) and **(*E*)-4-(cyclohex-1-en-1-yl)-1-phenylundec-4-en-3-one** (minor isomer) (Table 3.3, entry **183**):



Subjection of 1-(oct-1-yn-1-yl)cyclohex-1-ene (1.0 mmol, 0.219 mL) and *N*-methoxy-*N*-methyl-3-phenylpropanamide (2.0 mmol, 0.365 mL) to the general procedure **F** afforded 0.208 g (64% yield) of an inseparable mixture of these regioisomeric enones (r.r. = 77/23) as a yellowish liquid after flash chromatography. Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.05 (m, 5H), 6.75 (s, 1H, measured 0.58H), 5.85 (m, 1H, measured 0.56H), 2.89 (m, 4H), 2.35 (t, *J* = 7.2 Hz, 2H, measured 1.74H), 2.10 (m, 4H, measured 3.69H), 1.57 (m, 4H), 1.21 (m, 8H), 0.81 (t, *J* = 6.8 Hz, 3H). Minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.05 (m, 5H), 6.57 (t, *J* = 7.6 Hz, 1H, measured 0.19H), 6.53 (s, 1H, measured

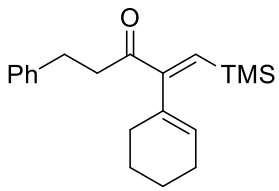
0.22H), 2.83 (m, 2H), 2.69 (m, 2H, measured 0.41H), 2.35 (m, 2H, measured 1.74H), 1.86 (m, 4H, measured 0.75H), 1.57 (m, 4H), 1.21 (m, 8H), 0.81 (t, J = 6.8 Hz, 3H). Combined isomers: ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.5, 141.9, 141.6, 139.3, 135.0, 133.6, 128.3, 127.1, 125.9, 39.5, 31.5, 30.9, 30.2, 29.5, 28.2, 26.6, 26.1, 22.6, 22.5, 21.7, 14.0. IR (neat) 3026, 2924, 2855, 1663, 1495, 1452, 1105, 921, 747, 697 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{23}H_{32}O$ 325.2526, found 325.2517.

(*E*)-1,7-Diphenyl-4-((trimethylsilyl)methylene)heptan-3-one (Table 3.3, entry **184**):



Subjection of trimethyl(5-phenylpent-1-yn-1-yl)silane (1.0 mmol, 0.240 mL) and *N*-methoxy-*N*-methyl-3-phenylpropanamide (2.0 mmol, 0.365 mL) to the general procedure **F** afforded 0.180 g (51% yield) of the enone as a yellowish liquid after flash chromatography (r.r. = 91/9; only a single isomer was isolated). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (m, 4H), 7.07 (m, 6H), 6.42 (s, 1H), 2.88 (t, J = 8.0 Hz, 2H), 2.80 (t, J = 7.6 Hz, 2H), 2.52 (t, J = 7.6 Hz, 2H), 2.28 (t, J = 8.0 Hz, 2H), 1.52 (quin, J = 7.6 Hz, 2H), 0.00 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.3, 156.1, 142.0, 141.4, 139.9, 128.4, 128.39, 128.37, 128.2, 126.0, 125.7, 39.4, 36.3, 31.9, 31.0, 30.6, −0.4; IR (neat) 3025, 2951, 1672, 1602, 1495, 1452, 1248, 836, 745, 696 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{23}H_{30}OSi$ 351.2139, found 351.2137.

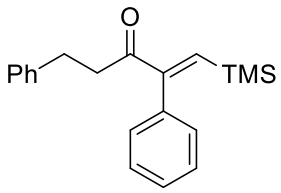
(*E*)-2-(Cyclohex-1-en-1-yl)-5-phenyl-1-(trimethylsilyl)pent-1-en-3-one (Table 3.3, entry **185**):



Subjection of (cyclohex-1-en-1-ylethynyl)trimethylsilane (1.0 mmol, 0.207 mL) and *N*-methoxy-*N*-methyl-3-phenylpropanamide (2.0 mmol, 0.365 mL) to the general procedure **F** afforded 0.143 g (46% yield) of the enone as a yellow oil after flash chromatography that was an inseparable mixture of regioisomers (r.r. = 86/14). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 2H), 7.24 (m, 3H), 6.57 (bs, 1H, measured 0.02H), 6.52 (bs, 1H, measured 0.75H), 5.62 (m, 1H, measured 0.18H), 5.53 (tt, J =

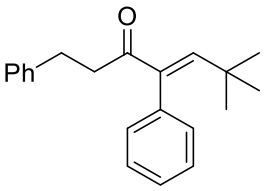
3.6, 1.7 Hz, 1H, measured 0.77H), 2.97 (m, 4H), 2.15 (m, 2H), 2.03 (m, 2H), 1.69 (m, 4H), 0.12 (s, 9H, measured 7.69H), −0.04 (s, 9H, measured 1.29H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.4, 158.8, 141.5, 139.5, 137.4, 128.4, 127.4, 126.0, 40.4, 30.5, 29.0, 25.1, 22.4, 21.7, −0.2; IR (neat) 3027, 2928, 1674, 1496, 1245, 836, 748, 697 cm^{-1}; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{28}OSi$ 313.1983, found 313.1978.

(*E*)-2,5-Diphenyl-1-(trimethylsilyl)pent-1-en-3-one (Table 3.3, entry **186**):



Subjection of 1-phenyl-2-trimethylsilylacetylene (1.0 mmol, 0.197 mL) and *N*-methoxy-*N*-methyl-3-phenylpropanamide (2.0 mmol, 0.365 mL) to the general procedure **F** afforded 0.149 g (53% yield) of the enone as a yellow liquid after flash chromatography that was an inseparable mixture of regioisomers (r.r. = 86/14). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.15 (m, 10H), 7.11 (m, 1H, measured 0.92H), 3.04 (m, 4H, measured 3.18H), 3.00–2.75 (m, 4H, measured 0.89H), 0.00 (bs, 9H, measured 6.96H), −0.37 (bs, 9H, measured 1.37H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 155.4, 142.3, 141.3, 138.7, 129.3, 128.4, 128.4, 127.9, 127.7, 125.9, 41.1, 30.4, −0.7; IR (neat) 3027, 2952, 1679, 1578, 1247, 1099, 856, 834, 747, 697 cm^{-1}; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{24}OSi$ 309.1670, found 309.1667.

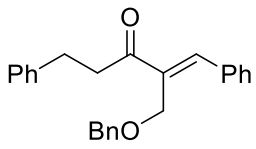
(*E*)-6,6-Dimethyl-1,4-diphenylhept-4-en-3-one (Table 3.3, entry **187**):



Subjection of (3,3-dimethylbut-1-yn-1-yl)benzene (1.0 mmol, 0.180 mL) and *N*-methoxy-*N*-methyl-3-phenylpropanamide (2.0 mmol, 0.365 mL) to the general procedure **F** afforded 0.104 g (35% yield) of the enone as a colorless liquid after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 3H), 7.30–7.18 (m, 4H), 7.13 (m, 3H), 6.89 (s, 1H), 2.89 (t, *J* = 8.0 Hz, 2H), 2.75 (t, *J* = 8.0 Hz, 2H), 0.94 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.8, 151.1, 141.4, 139.5, 137.0, 130.0, 128.3, 128.2, 127.8, 127.3,

125.8, 44.8, 41.5, 34.1, 30.4; IR (neat) 3026, 2959, 1688, 1593, 1495, 1475, 1359, 1215, 1111, 1072, 1030, 747 cm^{-1}; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{24}O$ 293.1900, found 293.1890.

(*E*)-2-((Benzyloxy)methyl)-1,5-diphenylpent-1-en-3-one (Table 3.3, entry **188**):



Subjection of (3-(benzyloxy)prop-1-yn-1-yl)benzene (1.0 mmol, 0.206 mL) and *N*-methoxy-*N*-methyl-3-phenylpropanamide (2.0 mmol, 0.365 mL) to the general procedure **F** afforded 0.045 g (13% yield) of the enone as a yellow oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.48 (m, 2H), 7.39–7.19 (m, 13H), 4.59 (s, 2H), 4.35 (s, 2H), 3.12 (t, *J* = 8.0 Hz, 2H), 3.01 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.2, 143.4, 141.4, 137.9, 136.8, 134.7, 129.8, 129.4, 128.5, 128.48, 128.43, 128.3, 128.2, 127.7, 126.1, 73.1, 63.6, 40.0, 30.4; IR (neat) 3026, 2924, 1668, 1494, 1452, 1069, 1027, 733 cm^{-1}; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{24}O_2$ 357.1850, found 357.1837.

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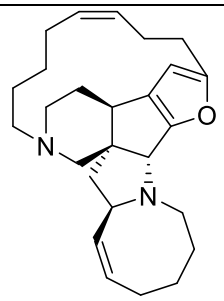
CHAPTER IV

MODULAR SYNTHESIS OF TETRA-SUBSTITUTED FURANS FROM ALKYNES, WEINREB AMIDES, AND ALDEHYDES E

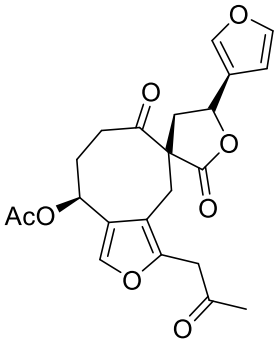
4.1. INTRODUCTION

There has been a long standing interest in the development of simple methods to synthesize substituted heterocycles,[1-2] as they are an important constitutents of natural products[3-4], drug molecules, agrochemicals, fine chemicals,[5-6] and materials.[7-8] In particular, oxygen-containing heterocycles such as furans are an important structural motif in many biologically active molecules. Selaginoidine,[9] nakadomarin A,[10] pukalide,[11] teubrevin G,[12] furodysin,[13] and pinguisone[14] are examples of complex natural products that contain furan rings (Fig 4.1)[15] and exhibit biological activity. Ranitidine (Zantac), **223**, is an FDA approved drug which is used to treat ulcers in the stomach and intestines was introduced in 1981 and became the highest selling drug in 1987. Furans not only have applications in pharmaceuticals but also in the flavoring and fragrance industries.[16] In addition to their wide spread presence in natural products, they are also used as important building blocks in synthetic chemistry to prepare heterocyclic and acyclic organic compounds.[17] The Diels-Alder reaction, oxidation to lactones, reduction to tetrahydrofurans, acting as 1,4-dicarbonyl surrogates, and reacting in re-cyclization processes are some of their important transformations (Scheme 4.1). A number of approaches have been utilized to synthesize various

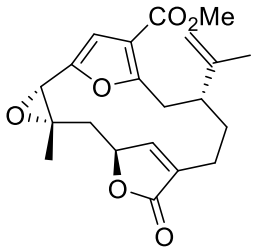
substituted furans.[18] Highly substituted furans can be prepared *via* current strategies, however, these methods utilize starting materials that have to be synthesized in 2-4 steps which is tedious and not atom economical. Additionally, they lack the ability to place a specific functional group at desired positions on the ring, thus limiting their utility in small molecule library development, performing SAR studies, and lead optimization of initial hits. What is needed is a method that can prepare polysubstituted furans in a single reaction vessel from readily available starting materials, and can also readily interchange functional groups around the ring selectively



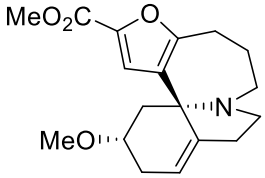
217
(-)-nakadommarin A
Amphimedon sp.
Cytotoxic, antimicrobial, and antibacterial



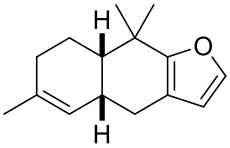
218
(-)-teubrevin G
Teucrium brevifolium



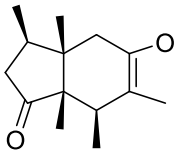
219
pukalide
Sinularia abrupta



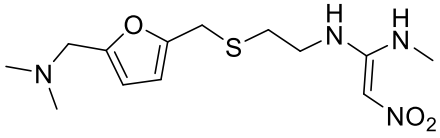
220
selaginoidine
Athrotaxis selaginoides



221
(±)-furodysin
Dysidea sp.
Antibiotic activity

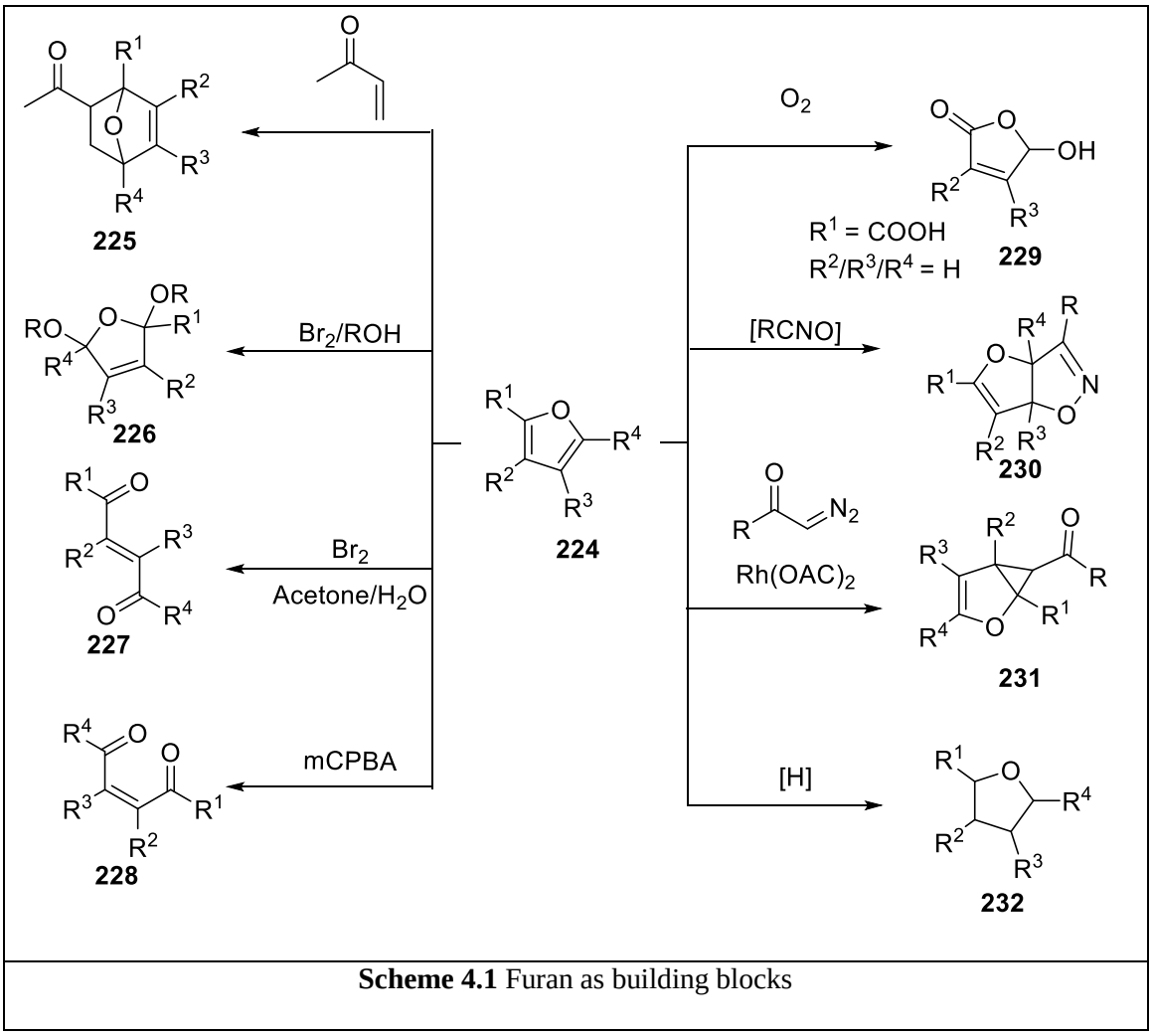


222
pinguisone
Aneura pinguis



223
ranitidine (Zantac)
ulcers in the stomach and intestine

Fig. 4.1 Biologically active furan containing natural products and drugs



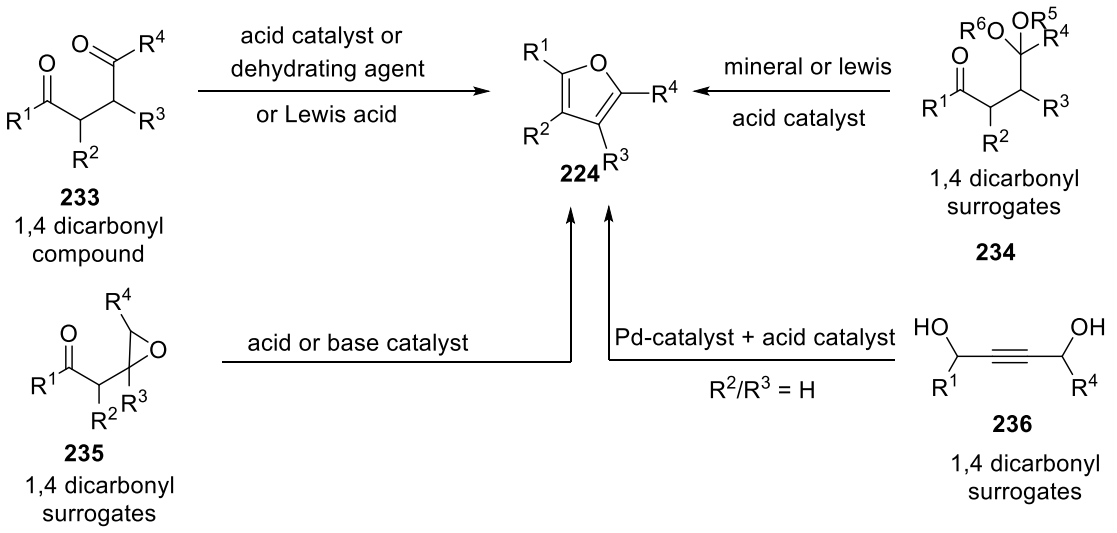
Scheme 4.1 Furan as building blocks

4.2. APPROACHES TO SYNTHESIZE FURANS

Polysubstituted furans comprise an important class of five membered heterocycles having broad utility. Therefore, these types of structural motifs have been synthesized by number of synthetic methods.[18-19] The classical approach to synthesize furan rings involves cyclocondensation of γ-diketones (Paal-Knorr furan synthesis)[20] and the Feist-Benary synthesis.[21] Modern approaches encompass olefin cross methathesis,[22] transition metal catalyzed cycloaddition,[23-26] metalloradical cyclization,[27] and metal-catalyzed cycloisomerization reactions.

4.2.1. Paal-Knorr furan synthesis

Intramolecular condensation of 1,4-dicarbonyl compounds, **233**, as well as their surrogates, **234-236**, results in formation of furan rings (Scheme 4.2).[20, 28-30] This method is known as the Paal-Knorr furan synthesis as C. Paal and L. Knorr simultaneously reported the transformation in 1884. Because the dehydration is facilitated by the presence of a mineral acid, functional groups that are sensitive to acidic conditions cannot tolerate the reaction conditions. Additionally, the necessary 1,4-diketones are relatively difficult to obtain.

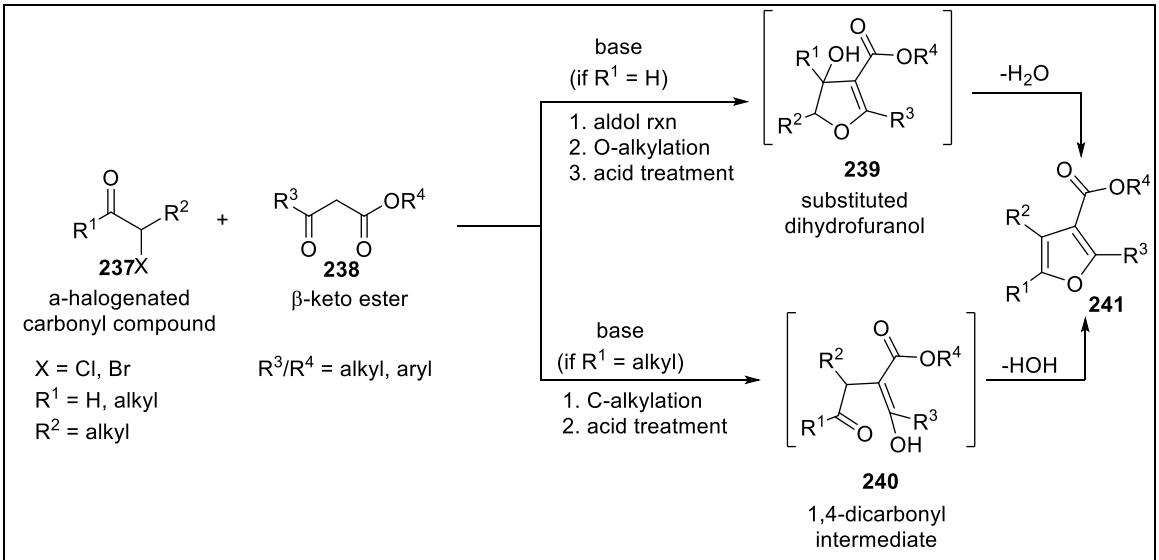


Scheme 4.2 Paal-Knorr furan synthesis

4.2.2. Feist-Benary furan synthesis

The reaction between β-keto esters, **238**, and α-halogenated carbonyl compounds, **237**, under basic conditions results in the formation of furans.[21, 31] This reaction is called the Feist-Benary reaction. The regiochemistry depends on the reactivity of the α-halogenated compound. If it is an aldehyde, then the reaction sequence involves an aldol condensation followed by O-alkylation to give the substituted dihydrofuranol intermediate **239.** However, if a ketone is employed, C-alkylation gives rise to a 1,4-dicarbonyl intermediate **240**.[21, 32] Both intermediates, upon acid treatment, result in substituted furans after dehydration (Scheme 4.3). The requirement of an

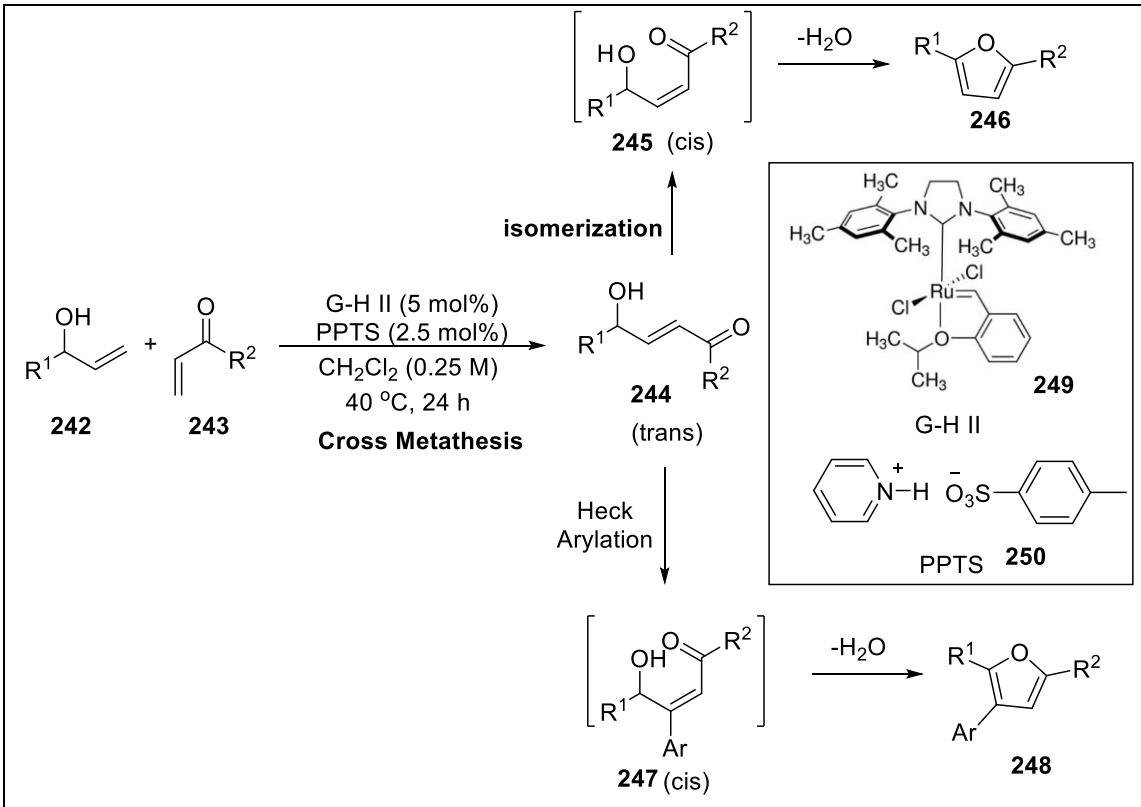
electron withdrawing group at the β-position of the carbonyl compound to promote deprotonation and the requirement of a strong base for the reaction to occur, limits functional group compatibility.



Scheme 4.3 Feist-Benary furan synthesis

4.2.3. Olefin cross metathesis

A powerful and widely used reaction to synthesize substituted alkenes is olefin cross metathesis. Recently, Donohoe and Bower were able to show the utility of this technique to synthesize 2,5-di- and 2,3,5-trisubstituted furans (Scheme 4.4).[22] The utilization of an expensive ruthenium catalyst (second generation Grubbs-Hoveyda catalyst), **249**, results in moderate to good yield of the substituted furans. This method is, however, limited to di- and trisubstituted furans.

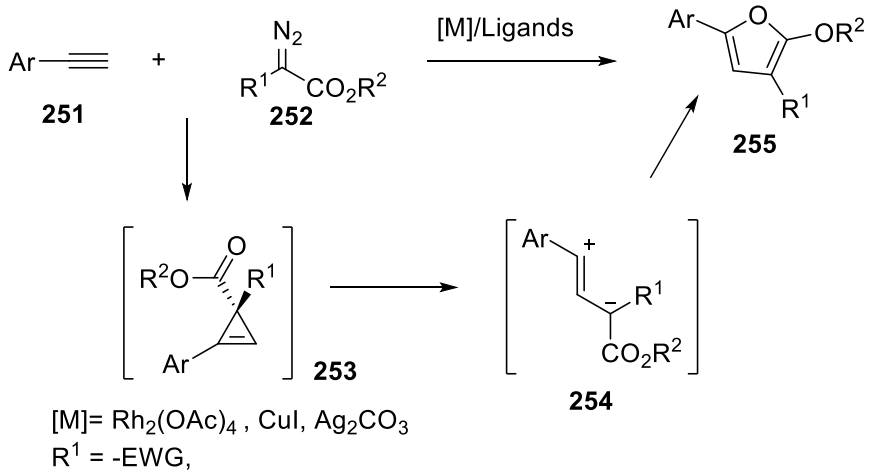


Scheme 4.4 Cross metathesis approach to synthesize di- and trisubstituted furans

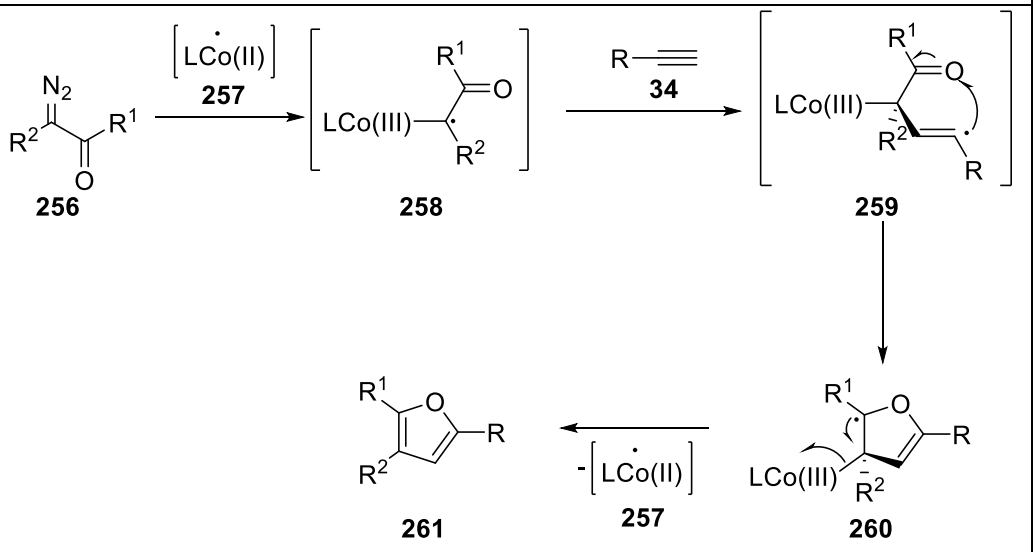
4.2.4. [3+2] Cycloaddition reaction:

The most direct approach to synthesize polysubstituted furans is the [3+2] cycloaddition reaction of arylacetylenes with α-diazocarbonyl compounds. This reaction can be catalyzed by Rh,[25-26, 33-34] Cu,[23] or Ag.[23] Electron rich arylacetylenes have been most effective in the reaction with diazocompounds containing electron withdrawing groups. These reactions are intrinsically ionic where the arylacetylene and electron withdrawing group stabilizes the zwitterion as shown in intermediate **254** (Scheme 4.5). Thus, aliphatic and electron deficient alkynes perform poorly and furans with sensitive functionalities also remain challenging. Recently, Zhang *et. al*. developed a similar transformation using a Co(II)-porphyrin catalyst which generates Co(III)-carbene radical **258** from α-diazocarbonyl compounds which undergo radical addition with alkynes to form furans (Scheme 4.6).[27] By using this metalloradical cycloaddition reaction approach, a wide range of

functional groups were well tolerated and both aliphatic and electron deficient alkynes produced moderate to good yields of furans. However, it is difficult to synthesize the electron-deficient diazo-compounds necessary to obtain trisubstituted furans.



Scheme 4.5 [3+2] cycloadditon reaction to synthesize trisubstituted furans

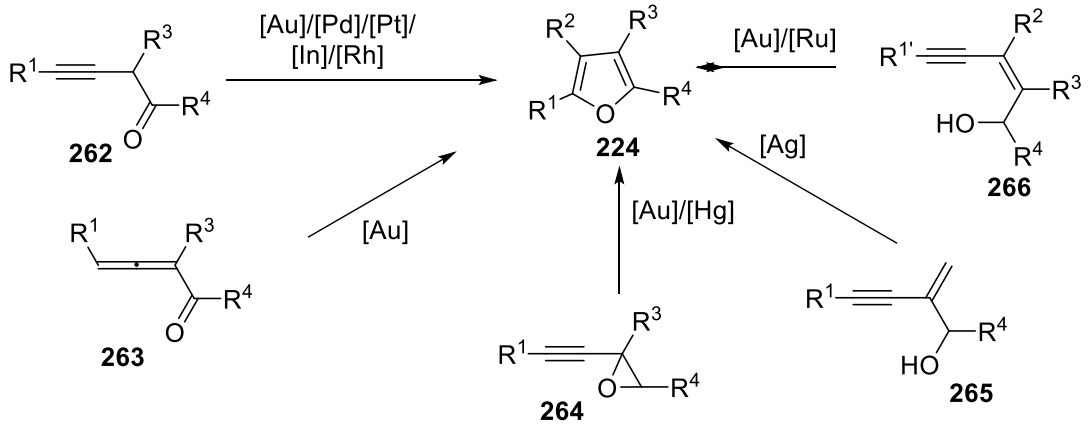


Scheme 4.6 Carbene radicals to synthesize trisubstituted furans

4.2.5. Metal-catalyzed cycloisomerization reaction

The cycloisomerization of alkyne **262** and allene-containing compound **263** serves as an alternative approach to synthesize substituted furans (Scheme 4.7). Typically, allene substrates[35-37]

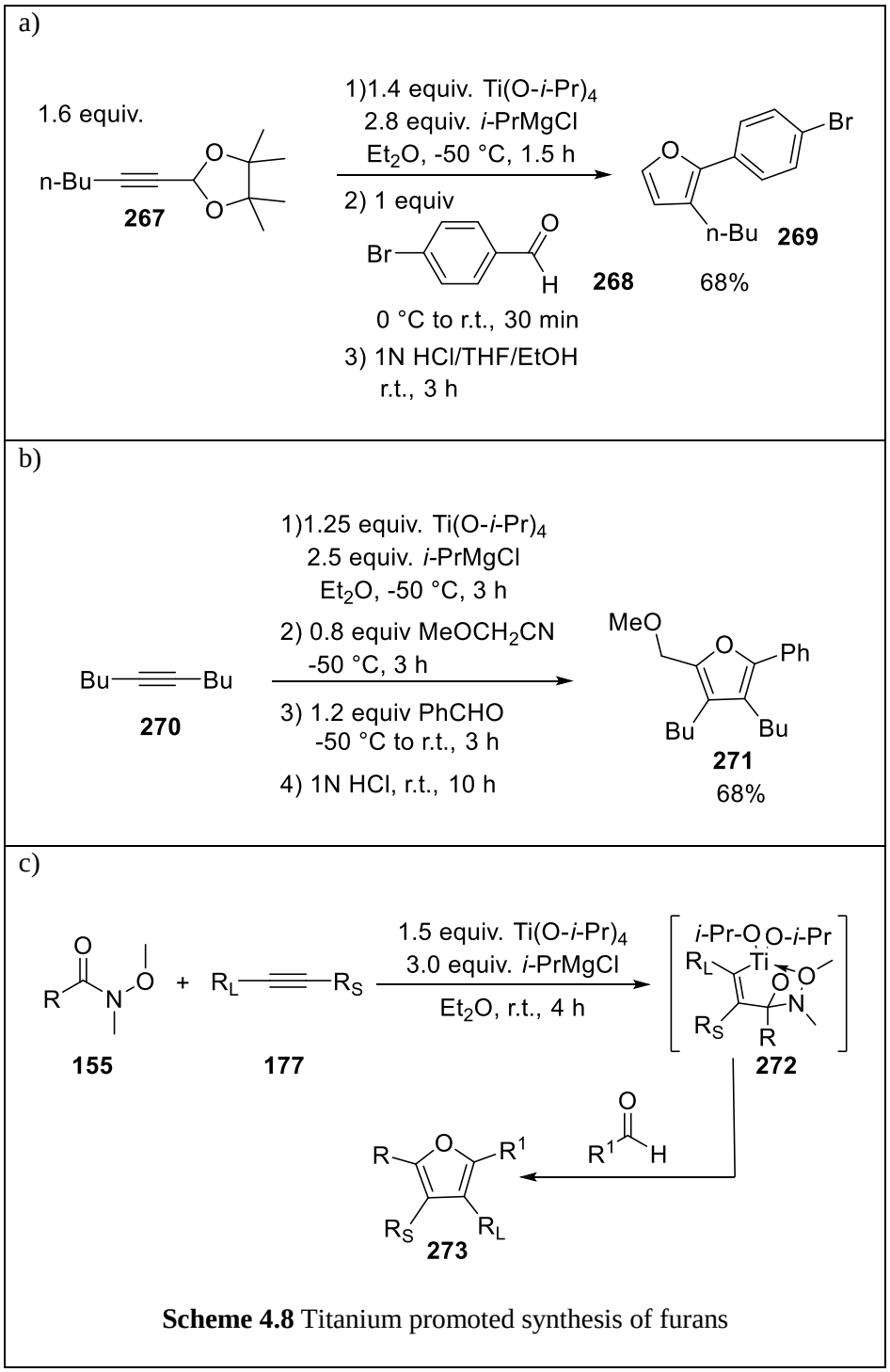
are less preferred over alkynyl substrates due to difficulties in their synthesis and issues with stability. Also, the furans obtained from reactions with the allenes cannot yield substitution at the 3 and 4 position of the furan generated. Various alkynyl substrates such as acetylenic ketones,[38-39] alkynyl epoxides,[40] and alkynyl allyl alcohols[41] have been used to generate substituted furans using transition metals such as Pt,[42] Pd,[39] Au,[37-38, 40] Ag,[41] In,[43] Hg,[44] Ru,[45] and Rh[46] catalysts. Use of these expensive metal catalysts and the starting materials which require several steps to synthesize are two limitations of this method.



Scheme 4.7 Cycloisomerization methods to synthesize substituted furans

4.2.6. Titanium promoted synthesis of substituted furans

Titanium promoted methods for the synthesis of 2,3-disubstituted furans[47] and polysubstituted furans[48] have been developed by Sato. While these methods can afford the furan in moderate yield they do require the use of specific substrates, 2-alkynal tetramethylethylene acetals



Scheme 4.8 Titanium promoted synthesis of furans

and α-methoxyacetonitrile, which creates limitations on the diversity of furans that can be prepared (Scheme 4.8). Additionally, the alkynyl acetal substrate requires a two-step synthesis. To increase the diversity of the prepared furans, a modular approach is necessary where the functional group

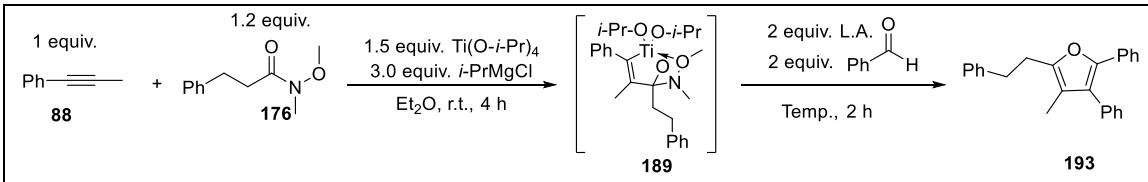
present at each specific position of the furan ring can be easily interchanged. As discussed in chapter 3, a method to prepare tri- and tetra-substituted enones via a titanium promoted reductive coupling of alkynes with Weinreb amides was developed. As part of that investigation we explored subsequent reactions of the in situ formed five-membered ring titanacycle and found that addition of a Lewis acid activated aldehyde reacted to form a tetrasubstituted furan in moderate yield. Based on this result we became interested in establishing the generality of this reaction to prepare tetrasubstituted furans modularly through the simple addition of unsymmetrical alkynes, Weinreb amides, and aldehydes. The potential power of this titanium promoted three component coupling is to selectively prepare tetrasubstituted furans, placing specific functional groups at desired positions by simply choosing the starting materials, that can also be easily interchanged allowing selective placement of functional groups.

4.3. RESULTS AND DISCUSSION

4.3.1. Optimization of furan synthesis

Having already established the optimized conditions to generate intermediate **189**[49] a screening of Lewis acids with benzaldehyde was performed to determine the optimal Lewis acid for furan formation (Table 4.1). The titanacyclopentene intermediate **189** was generated to which a Lewis acid and benzaldehyde were added. In the absence of a Lewis acid, 2 equiv. of benzaldehyde did not react with the titanacycle intermediate **189** only affording the enone and unreacted aldehyde upon workup (Table 4.1, entry 1). Of the Lewis acids screened $BF_3{\cdot}OEt_2$ (entry 2) afforded the highest yield of furan **193**. The addition of molecular sieves had no effect on the efficiency of the reaction. While lowering the equivalence of benzaldehyde and $BF_3{\cdot}OEt_2$ to 1.2 equiv. lowered the yield (entry 6), and increasing beyond 2 equiv. had no effect. The temperature of the reaction mixture upon addition of the Lewis acid and benzaldehyde had a direct effect on the yield (entries 7 and 8), with the highest yield being obtained when the reaction mixture was cooled to -78 °C before addition of the Lewis acid and aldehyde followed by warming to room temperature.

Additionally, it was found that the addition of a pre-complexed mixture of benzaldehyde and $BF_3{\cdot}OEt_2$ in diethyl ether produced the best result versus the sequential injection of each reagent in either order (entries 9 and 10). Attempts to change the order of addition of substrates by reductively coupling the alkyne and aldehyde together first followed by addition of a Weinreb amide only



Scheme 4.9 Titanium promoted modular synthesis of furan

Table 4.1 Optimization of the second step in furan synthesis

Entry	Lewis Acid	Temp.	%yield of 193	Additional conditions
1.	None	-78 °C to r.t.	0	
2.	**$BF_3{\cdot}OEt_2$**	**-78 °C to r.t.**	**66**	
3.	$Ti(O\text{-}i\text{-}Pr)_4$	-78 °C to r.t.	17	
4.	$Zn(OTf)_2$	-78 °C to r.t.	0	
5	$CuCl_2$	-78 °C to r.t.	0	
6.	$BF_3{\cdot}OEt_2$	-78 °C to r.t.	36	1.2 equiv of benzaldehyde
7.	$BF_3{\cdot}OEt_2$	0 °C to r.t.	56	
8.	$BF_3{\cdot}OEt_2$	r.t.	49	
9.	$BF_3{\cdot}OEt_2$	-78 °C to r.t.	56	$BF_3{\cdot}OEt_2$ and then aldehyde
10.	$BF_3{\cdot}OEt_2$	-78 °C to r.t.	41	aldehyde and then $BF_3{\cdot}OEt_2$

afforded the allylic alcohol. Stirring for longer than 2 h after addition of the $BF_3{\cdot}OEt_2$ and aldehyde did not improve the yield, with prolonged stirring (14–24 h) decreasing the yield of the furan by 10–15%.

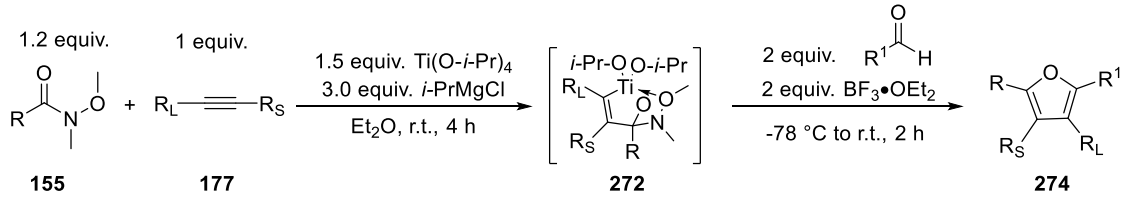
4.3.2. Screening of the substrates

With the optimized conditions for the two step one-pot reaction established, substrate screening was initiated (Table 4.2). In accordance with our initial findings in the preparation on enones,[49] aliphatic Weinreb amides (**275-279**, **287-290**) afforded the furan in higher yield than aromatic Weinreb amides (**280-286**). The drop in yields with aromatic Weinreb amides is attributed to sterics in the five-membered- ring titanacycle intermediate inhibiting reaction with the aldehyde. This is corroborated by the decreased yield for furan **278** where use of the sterically congested *N*-methoxy-*N*,3,3- trimethylbutanamide, which couples with an alkyne in near quantitative yield,[49] inhibits reaction of the aldehyde with the titanacyclopentene. Aromatic (**275-279**), heteroaromatic

(**289, 290**), and α,β-unsaturated aldehydes (**287, 288**) afforded the best results, whereas aliphatic aldehydes (**280-282**) afforded the furan in low yield due to competing aldol reactions. The system tolerated halogen substituted aromatic aldehydes (Br, Cl, and F) regardless of position (**275-278**). A para-substituted benzaldehyde with a nitrile or a methoxy group inhibited furan formation presumably due to coordination with the titanium complex and/or $BF_3{\cdot}OEt_2$. Whereas, a benzaldehyde with a TBS-protected phenol (**279**) participated in furan formation, indicating that coordination, not electronic deactivation, is the problem with the methoxy substituent. It had been established in our previous study that *N*-methoxy-*N*-methylpicolinamide inhibited coupling however the pyridine functional group was tolerated in the aldehyde, with nicotinaldehyde producing the 3(furan-2-yl) pyridine (**289**) in good yield. While aromatic Weinreb amides and aliphatic aldehydes afforded the furan in lower yield, it was established that the two could be combined to form the furan, albeit in low yield (**281, 282**).

As expected, unsymmetrical alkynes with a steric difference between the substituents attached to the alkyne afford the furan in high regioselectivity, with only one regioisomer being isolated. The use of an unsymmetrical alkyne with the steric differentiating group distal to the alkyne afforded a 60:40 mixture of regioisomers (**295**). The sterically more congested diphenylacetylene inhibited the efficiency of the reaction lowering the yield of the furan (**296**) product. A TMS protected alkyne was a viable substrate but the sterics of the silyl group also affected the yield of furan **297**. In our previous enone method it was established that a conjugated enyne could be reductively coupled with a Weinreb amide in good yield.[49] Whereas in this three component coupling the conjugated furan **298** formed from the enyne was obtained in low yield. It is suspected that furan **298** is being formed in high yield, but under the reaction conditions this conjugated furan is undergoing undesired reaction pathways leading to decomposition.

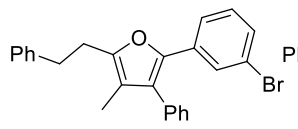
Weinreb amides containing aromatic halogens (**284-286**) and a primary alkyl chloride (**292**) were tolerated. An amide containing a TBS protected primary alcohol at the alpha carbon



155 **177** **272** **274**

Scheme 4.10 Optimized condition of titanium promoted modular furan synthesis

Table 4.2 Substrate scope of the reaction



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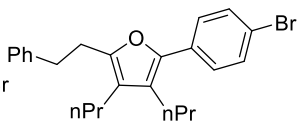

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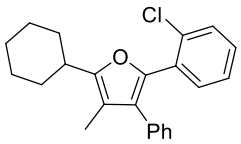

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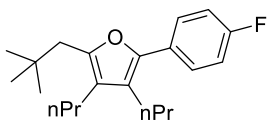

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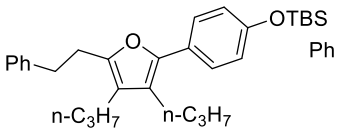

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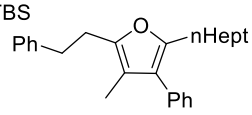

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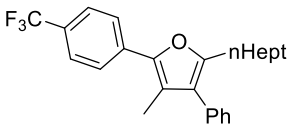

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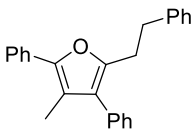

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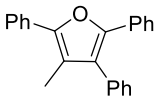

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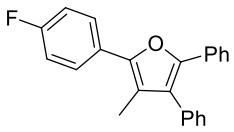

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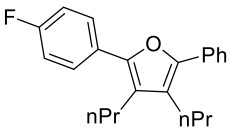

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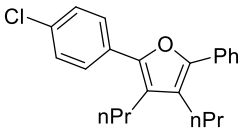

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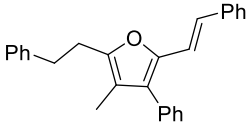

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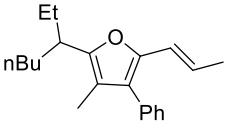

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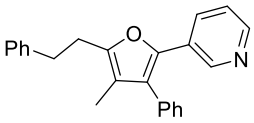

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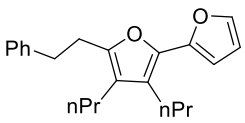

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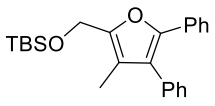

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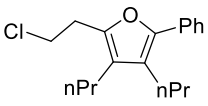

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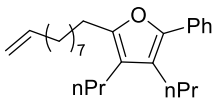

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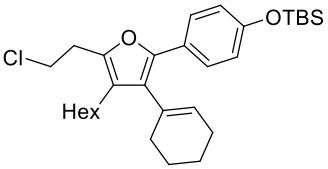

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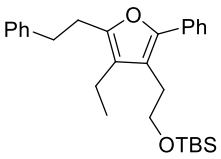

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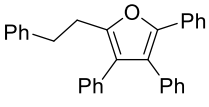

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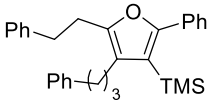

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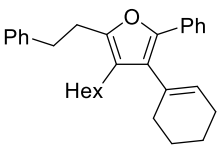

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afforded furan **291** in moderate yield. Again, the decrease in product formation with this amide is attributed to the sterics of the TBS group inhibiting reaction with the aldehyde. The system also tolerated a terminal olefin (**293**). The incorporation of trifluoromethyl groups into aromatic and heteroaromatic compounds has become an important issue due to the beneficial features of this functional group to positively affect lipophilicity, bioavailability, and metabolism in agro chemicals and drug candidates.[50-51] As such, we attempted to use 2,2,2-trifluoro-*N*-methoxy-*N*-methylacetamide to prepare a trifluoromethylfuran, unfortunately the desired product was formed in low yield. Attempts to prepare a furan substituted with an ester by employing either ethyl pent-2-ynoate, or ethyl *N*-(methoxy)-*N*-(methyl)carbamate failed to produce the furan. The Weinreb amide *N*-methoxy-*N*-methylacetamide for unclear reasons also did not form the desired furan.

4.4. CONCLUSIONS

In summary, it has been demonstrated that $BF_3{\cdot}OEt_2$ activated aldehydes react with titanacyclopentenes, prepared in situ via a titanium mediated reductive coupling of an alkyne and Weinreb amide, to afford tetrasubstituted furans modularly. Unsymmetrically alkynes with a steric difference between the substituents attached to the alkyne afford a single furan regioisomer. The system tolerated aromatic and aliphatic halogens, silyl ethers, olefins, furan, and pyridine substituents. This multicomponent coupling provides concise access to polysubstituted furans modularly. Efforts in modifying the method to improve yields and expand the substrate scope are underway and will be reported shortly.

4.5. SUPPORTING INFORMATIONS

4.5.1. Methods

All of the reactions were carried out in an oven-dried or a flame-dried glassware under an atmosphere of argon with magnetic stirring. Reactions were monitored either by thin-layer chromatography with 0.25 mm pre-coated silica gel plates or by gas chromatography. Visualization of all TLCs was performed with UV light and/or staining with phosphomolybdic acid, $KMnO_4$, or

Seebach's stain. Purifications were performed by flash chromatography with silica gel (60 Å, 230−400 mesh) packed in glass columns and elute with hexanes/DCM, unless otherwise noted.

4.5.2. Materials

Diethyl ether, dichloromethane, and chloroform were dried using a solvent purification system that contained activated alumina. 1,2-Dichloroethane and pyridine were freshly distilled from calcium hydride under argon. All of the Weinreb amides were prepared following known literature procedures[52] from purchased carboxylic acids.

4.5.3. Instrumentation

^{1}H NMR and ^{13}C NMR spectra were obtained on a 400 MHz NMR spectrometer (400 MHz for ^{1}H and 101 MHz for ^{13}C), and chemical shifts (δ, ppm) are reported relative to residual chloroform solvent peaks (δ = 7.26 ppm for ^{1}H and δ = 77.0 ppm for ^{13}C). Data for ^{1}H NMR are reported as follows: chemical shift (multiplicity, coupling constant(s) in Hz, integration). Multiplicities are indicated as follows: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sex = sextet, sept = septet, m = multiplet or unresolved. The reported melting points are uncorrected. Low-resolution mass spectra were obtained by GC−MS.

4.5.4. General procedure G

A dry round-bottom flask under an atmosphere of argon was charged with alkyne (1 mmol), Weinreb amide (1.2 mmol), Ti(O*i*Pr)$_4$ (1.5 mmol, 0.44 mL), and anhydrous Et_2O (10 mL). To this stirring mixture was injected *i*-PrMgCl (2M in Et_2O, 3 mmol, 1.5 mL) dropwise over 5 minutes, the reaction was stirred for 4 hours at room temperature. The round-bottom flask was then placed in a dry-ice acetone bath and equilibrated to -78 °C. In a separate dry pear-shaped flask under an atmosphere of argon BF_3•OEt_2 (2 mmol, 0.247 mL) was injected into a solution of aldehyde (2 mmol) in Et_2O (2 mL) precooled with a dry-ice acetone bath. The BF_3•OEt_2-aldehyde mixture was stirred for 30 seconds then pulled up into a syringe. The solution of complexed aldehyde was then injected into the cooled reaction mixture containing the titanacycle. The cooling bath was removed and the reaction was allowed to warm to room temperature over 2 hours. At which point the reaction

was quenched with 1 mL H_2O, dried over magnesium sulfate, filtered, and concentrated. The crude material was subjected to flash chromatography (hexanes/CH_2Cl_2: 90/10).

Note 1: any solid reagents were added to the flask prior to the vacuum-purge cycle.

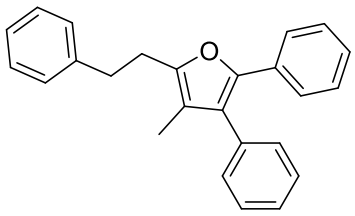
Note 2: a small aliquot of the quenched reaction mixture was used to measure the ratio of regioisomers of the product by NMR and GC.

4.5.5. General procedure H

A dry round-bottom flask under an atmosphere of argon was charged with alkyne (1 mmol), Weinreb amide (1.2 mmol), Ti(O*i*Pr)$_4$ (1.5 mmol, 0.44 mL), and anhydrous Et_2O (10 mL). To this stirring mixture was injected *i*-PrMgCl (2M in Et_2O, 3 mmol, 1.5 mL) dropwise over 5 minutes, the reaction was stirred for 4 hours at room temperature. The round-bottom flask was then placed in a dry-ice acetone bath and equilibrated to -78 °C, at which point BF_3•OEt_2 (2 mmol, 0.247 mL) and aldehyde (2 mmol) were sequentially injected. The cooling bath was removed and the reaction was allowed to warm to room temperature over 2 hours. At which point the reaction was quenched with 1 mL water, dried over magnesium sulfate, filtered, and concentrated. The crude material was subjected to flash chromatography (hexanes/CH_2Cl_2: 90/10).

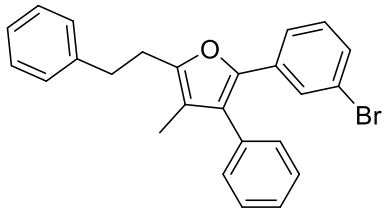
4.5.6. Spectral data of furans

3-methyl-2-phenethyl-4,5-diphenylfuran (193):



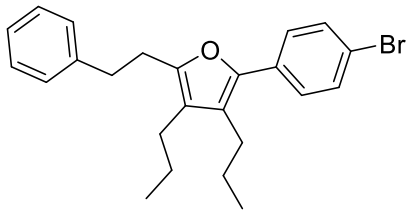
Subjection of 1-phenyl-1-propyne (1.0 mmol, 0.125 mL), *N*-methoxy-*N*-methyl-3-phenylpropanamide (1.2 mmol, 0.219 mL), and benzaldehyde (2 mmol, 0.204 mL) to general procedure **G** afforded 0.223 g (66%) of furan **193** as a yellow oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.15 (m, 15H), 3.05 (m, 4H), 1.74 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.5, 146.3, 141.4, 134.4, 131.5, 129.9, 128.6, 128.5, 128.3, 128.2, 127.0, 126.5, 126.0, 125.2, 124.0, 117.1, 34.9, 28.5, 8.5; IR (neat) 3026, 2922, 1759, 1601, 1496, 1445, 1070, 948, 908, 765, 731, 691 cm^{-1}; GCMS [M^+] 338.

2-(3-bromophenyl)-4-methyl-5-phenethyl-3-phenylfuran (275):



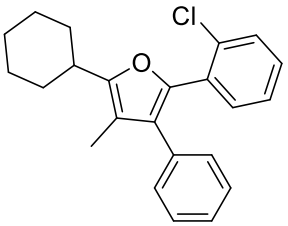
Subjection of 1-phenyl-1-propyne (1.0 mmol, 0.125 mL), *N*-methoxy-*N*-methyl-3-phenylpropanamide (1.2 mmol, 0.219 mL), and *m*-bromobenzaldehyde (2 mmol, 0.233 mL) to general procedure **G** afforded 0.265g (64%) of furan **275** as a yellow oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (m, 1H), 7.49-7.20 (m, 12H), 7.04 (m, 1H), 3.03 (m, 4H), 1.70 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.2, 144.6, 141.2, 133.9, 133.3, 129.7, 129.6, 129.2, 128.7, 128.5, 128.3, 127.8, 127.4, 126.1, 125.3, 123.4, 122.4, 117.4, 34.9, 28.5, 8.4; IR (neat) 3026, 2922, 1592, 1551, 1495, 1472, 1453, 1264, 1068, 993, 953, 907, 782, 698 cm^{-1}; GCMS [M^{+}] 416.

2-(4-bromophenyl)-5-phenethyl-3,4-dipropylfuran (276):



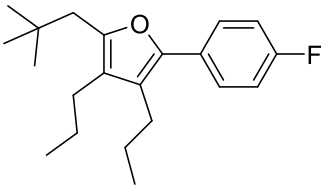
Subjection of 4-octyne (1.0 mmol, 0.147 mL), *N*-methoxy-*N*-methyl-3-phenylpropanamide (1.2 mmol, 0.219 mL), and 4-bromobenzaldehyde (2 mmol, 0.370 g) to general procedure **G** afforded 0.261 g (64%) of furan **276** as a yellow oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 4H), 7.31 (m, 2H), 7.26-7.17 (m, 3H), 3.01 (t, *J* = 7.2 Hz, 2H), 2.92 (t, *J* = 7.6 Hz, 2H), 2.54 (t, *J* = 8.0 Hz, 2H), 2.23 (t, *J* = 7.6 Hz, 2H), 1.60 (quin, *J* = 7.6 Hz, 2H), 1.42 (quin, *J* = 7.6 Hz, 2H), 1.02 (t, *J* = 7.2 Hz, 3H), 0.96 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.8, 145.2, 141.4, 131.5, 131.2, 128.4, 128.3, 126.3, 126.0, 122.9, 121.9, 119.7, 35.0, 28.6, 26.5, 25.4, 24.0, 23.3, 14.3, 14.1; IR (neat) 3026, 2955, 2928, 2869, 1590, 1571, 1551, 1482, 1466, 1453, 1392, 1139, 1101, 1074, 1005, 825, 733, 696 cm^{-1}; GCMS [M^{+}] 410.

2-(2-chlorophenyl)-5-cyclohexyl-4-methyl-3-phenylfuran (277):



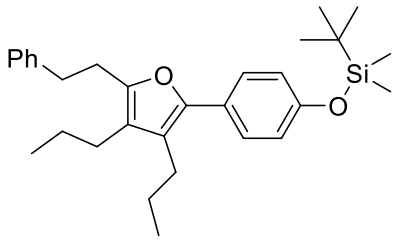
Subjection of 1-phenyl-1-propyne (1.0 mmol, 0.125 mL), *N*-methoxy-*N*-methylcyclohexane carboxamide (1.2 mmol, 0.201 mL), and 2-chlorbenzaldehyde (2 mmol, 0.225 g) to general procedure **G** afforded 0.180 g (51%) of furan **277** as a yellow oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (m, 1H), 7.32-7.16 (m, 7H), 7.12 (m, 1H), 2.76 (t, *J* = 11.6 Hz. 1H), 2.02 (s, 3H), 1.89 (t, *J* = 14 Hz, 4H), 1.72 (m, 3H), 1.36 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7, 144.3, 133.9, 133.6, 131.9, 130.8, 130.2, 129.4, 128.8, 128.2, 126.5, 126.2, 125.7, 113.1, 36.3, 31.6, 26.5, 26.0, 9.0; IR (neat) 3057, 2926, 2852, 1604, 1571, 1497, 1463, 1444, 1190, 1049, 1005, 906, 730, 697 cm^{-1}; GCMS [M^+] 350.

2-(4-fluorophenyl)-5-neopentyl-3,4-dipropylfuran (278):



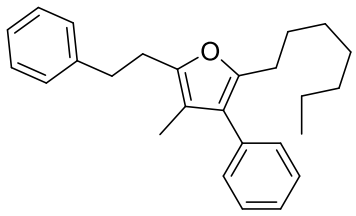
Subjection of 4-octyne (1.0 mmol, 0.147 mL), *N*-methoxy-*N*-3,3-trimethylbutanamide (1.2 mmol, 0.204 mL), and 4-fluorobenzaldehyde (2 mmol, 0.214 mL) to general procedure **G** afforded 0.080 g (25%) of furan **278** as a yellow oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 2H), 7.07 (m, 2H), 2.53 (m, 2H), 2.48 (s, 2H), 2.33 (m, 2H), 1.59 (sex, *J* = 8.0 Hz, 2H), 1.52 (sex, *J* = 8.0 Hz, 2H), 1.01 (m, 15H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4, 160.0, 149.2, 145.4, 128.8, 126.5, 126.4, 122.9, 121.6, 115.5, 115.2, 40.0, 32.3, 29.8, 26.6, 26.0, 24.0, 23.4, 14.3; IR (neat) 2955, 2931, 2870, 1593, 1559, 1503, 1464, 1393, 1377, 1364, 1231, 1157, 1140, 1093, 1012, 994, 832, 800 cm^{-1}; GCMS [M^+] 316.

tert-butyldimethyl(4-(5-phenethyl-3,4-dipropylfuran-2-yl)phenoxy)silane (279):



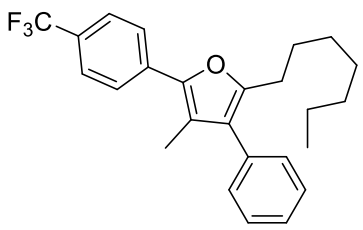
Subjection of 4-octyne (1.0 mmol, 0.147 mL) and *N*-methoxy-*N*-methyl-3-phenylpropanamide (1.2 mmol, 0.220 mL) and 4-((tert-butyldimethylsilyl)oxy)benzaldehyde (2 mmol, 0.487mL) to the general procedure **G** afforded 0.234 g (51%) of the furan **279** as a yellowish oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.4 Hz, 2H), 7.31 (m, 2H), 7.23 (m, 3H), 7.69 (d, *J* = 8.4 Hz, 2H), 3.01 (t, *J* = 8.0Hz, 2H), 2.93 (t, *J* = 8.0 Hz, 2H), 2.52 (m, 2H), 2.23 (t, *J* = 8.0Hz, 2H), 1.61 (sex, *J* = 8.0Hz, 2H), 1.41 (sex, *J* = 7.6Hz, 2H), 1.04 (s, 9H), 1.02 (t, *J* = 7.2Hz, 3H), 0.93 (t, *J* = 7.6Hz, 3H), 0.26 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.2, 148.7, 146.3, 141.7, 128.5, 128.3, 126.3, 125.9, 125.9, 121.4, 120.7, 120.1, 35.1, 28.7, 26.5, 25.7, 25.5, 24.0, 23.6, 18.2, 14.4, 14.1, -4.4. IR (neat): 2955, 2929, 2858, 1606, 1560, 1502, 1455, 1253, 1169, 907, 836, 779, 732, 697 cm^{-1}. GCMS [M^+] 462.

2-heptyl-4-methyl-5-phenethyl-3-phenylfuran (280):



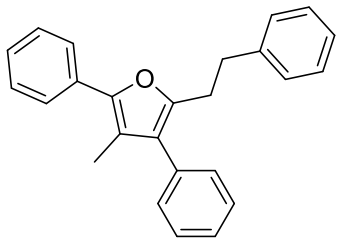
Subjection of 1-phenyl-1-propyne (1.0 mmol, 0.125 mL), *N*-methoxy-*N*-methyl-3-phenylpropanamide (1.2 mmol, 0.219 mL), and octanal (2 mmol, 0.312 mL) to general procedure **G** afforded 0.047g (13%) of furan **280** as a yellow oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (m, 2H), 7.36 – 7.20 (m, 8H), 2.99 (t, *J* = 8.0 Hz, 2H), 2.92 (t, *J* = 8.0 Hz, 2H), 2.64 (t, *J* = 7.6 Hz, 2H), 1.78 (s, 3H), 1.67 (quin, *J* = 7.2 Hz, 2H), 1.31 (m, 8H), 0.92 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.0, 147.9, 141.6, 134.4, 129.4, 128.5, 128.2, 128.2, 126.2, 125.9, 122.4, 114.3, 35.0, 31.8, 29.2, 28.9, 26.4, 22.6, 14.1, 8.8; IR (neat) 3027, 2923, 2855, 1605, 1584, 1495, 1453, 1069, 1005, 993, 748, 696 cm^{-1}; GCMS [M^+] 360.

2-heptyl-4-methyl-3-phenyl-5-(4-(trifluoromethyl)phenyl)furan (281):



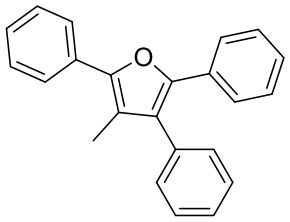
Subjection of 1-phenyl-1-propyne (1.0 mmol, 0.125 mL), 4-trifluoromethyl-*N*-methoxy-*N*-methyl-benzamide (2 mmol, 0.369 mL), and octanal (2 mmol, 0.312 mL) to general procedure **G** afforded 0.072g (18%) of furan **281** as a yellow oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (m, 2H), 7.67 (m, 2H), 7.46 (m, 2H), 7.37 (m, 1H), 7.31 (m, 2H), 2.70 (t, *J = 7.6 Hz*, 2H), 2.23 (s, 3H), 1.72 (quin, *J = 7.2 Hz*, 2H), 1.27 (m, 8H), 0.89 (t, *J = 7.2 Hz*, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.5, 145.4, 135.3, 133.2, 129.8, 128.4, 127.9, 126.9, 125.49, 125.45, 125.42, 125.38, 125.2, 124.8, 123.0, 118.7, 31.8, 29.2, 29.0, 28.6, 26.5, 22.6, 14.1, 10.9. IR (neat) 2927, 2856, 1617, 1444, 1322, 1165, 1123, 1068, 1012, 842, 769 cm^{-1}. GCMS [M^+] 400.

3-methyl-5-phenethyl-2,4-diphenylfuran (282):



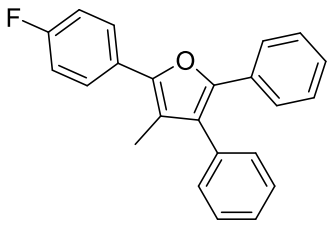
Subjection of 1-phenyl-1-propyne (1.0 mmol, 0.125 mL), *N*-methoxy-*N*-methyl-benzamide (2 mmol, 0.304 mL), and 3-phenyl propanaldehyde (2 mmol, 0.263 mL) to general procedure **G** afforded 0.028g (8%) of furan **282** as a yellow oil after flash chromatography. ^{1}H NMR (400 Hz, $CDCl_3$) δ 7.69 (m, 2 H), 7.51-7.24 (m, 10H), 7.13 (m, 3H), 3.01 (m, 4H), 2.18 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.9, 147.0, 141.3, 133.3, 132.0, 129.7, 128.5, 128.5, 128.32, 128.27, 126.7, 126.4, 126.0, 125.4, 125.3, 116.4, 34.9, 28.7, 10.7; IR (neat) 3025, 2922, 1598, 1494, 1442, 1072, 1004, 762 cm^{-1}. GCMS [M^+] 338.

3-methyl-2,4,5-triphenylfuran (283):



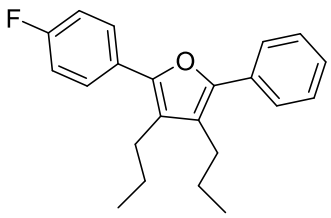
Subjection of 1-phenyl-1-propyne (1.0 mmol, 0.125 mL), *N*-methoxy-*N*-methyl-benzamide (2 mmol, 0.304 mL), and benzaldehyde (2 mmol, 0.204 mL) to general procedure **G** afforded 0.076g (24%) of furan **283** as a white solid after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (m, 2H), 7.52-7.15 (m, 13H), 2.15 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7, 147.1, 133.9, 131.7, 131.0, 130.2, 128.8, 128.6, 128.3, 127.4, 127.0, 126.9, 126.0, 125.5, 125.4, 118.8, 10.4. The physical and spectral data were consistent with those reported in the literature.[53]

2-(4-fluorophenyl)-3-methyl-4,5-diphenylfuran (284):



Subjection of 1-phenyl-1-propyne (1.0 mmol, 0.125 mL), 4-fluoro-*N*-methoxy-*N*-methyl-benzamide (2 mmol, 0.311 mL), and benzaldehyde (2 mmol, 0.204 mL) to general procedure **G** afforded 0.109g (33%) of furan **284** as a white solid (m.p. = 106 °C) after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (m, 2H), 7.61 – 7.41 (m, 7H), 7.36 – 7.19 (m, 5H), 2.19 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9, 160.5, 147.1, 146.9, 133.7, 130.9, 130.1, 128.8, 128.3, 127.9, 127.9, 127.4, 127.2, 127.1, 127.0, 125.9, 125.4, 118.4, 115.7, 115.5, 10.3; IR (neat) 3053, 2921, 1599, 1501, 1444, 1222, 1154, 1004, 943, 916, 832, 777, 765, 699 cm^{-1}; GCMS [M^{+}] 328.

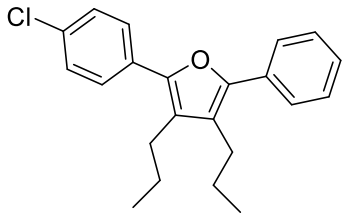
2-(4-fluorophenyl)-5-phenyl-3,4-dipropylfuran (285):



Subjection of 4-octyne (1.0 mmol, 0.147 mL), 4-fluoro-*N*-methoxy-*N*-methyl-benzamide (2 mmol, 0.311 mL), and benzaldehyde (2 mmol, 0.204 mL) to general procedure **G** afforded 0.052g (16%) of furan **285** as a white solid (m.p. = 38 °C) after flash chromatography.

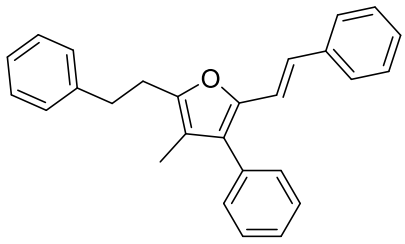
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 4H), 7.44 (m, 2H), 7.29 (m, 1H), 7.13 (m, 2H), 2.62 (m, 4H), 1.67 (m, 4H), 1.06 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9, 160.4, 147.2, 146.5, 131.8, 128.5, 128.3, 128.2, 127.1, 127.0, 126.7, 125.3, 123.9, 123.5, 115.6, 115.4, 26.3, 23.6, 14.4; IR (neat) 3051, 2956, 2930, 2869, 1601, 1500, 1489, 1468, 1453, 1228, 1155, 1096, 830, 719 cm^{-1}; GCMS [M^+] 322.

2-(4-chlorophenyl)-5-phenyl-3,4-dipropylfuran (286):



Subjection of 4-octyne (1.0 mmol, 0.147 mL), 4-chloro-*N*-methoxy-*N*-methyl-benzamide (2 mmol, 0.326 mL), and benzaldehyde (2 mmol, 0.204 mL) to general procedure **G** afforded 0.038g (11%) of furan **286** as a yellow oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 2H), 7.63 (m, 2H), 7.46-7.36 (m, 4H), 7.28 (m, 1H), 2.67-2.57 (m, 4H), 1.71-1.59 (m, 4H), 1.05 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.5, 146.2, 132.2, 131.7, 130.4, 128.7, 128.6, 126.8, 126.4, 125.4, 124.5, 124.1, 26.3, 26.3, 23.6, 23.5, 14.42, 14.41; IR (neat) 3053, 2956, 2929, 2870, 1601, 1491, 1485, 1467, 1395, 1377, 1093, 1010, 906, 827, 762, 715 cm^{-1}; GCMS [M^+] 338.

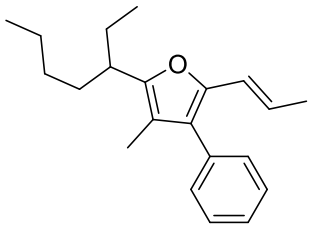
(E)-3-methyl-2-phenethyl-4-phenyl-5-styrylfuran (287):



Subjection of 1-phenyl-1-propyne (1.0 mmol, 0.125 mL), *N*-methoxy-*N*-methyl-3-phenylpropanamide (1.2 mmol, 0.219 mL), and *trans*-cinnamaldehyde (2 mmol, 0.252 mL) to general procedure **H** afforded 0.243 g (67%) of furan **287** as a yellow oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (m, 4H), 7.32 (m, 7H), 7.25(m, 4H), 7.06 (d, *J* = 16.4 Hz, 1H), 6.88 (d, *J* = 16.4 Hz, 1H), 3.05 (t, *J* = 6.8 Hz, 2H), 2.98 (t, *J* = 7.6 Hz, 2H), 1.79 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.4, 147.0, 141.3, 137.6, 133.4,

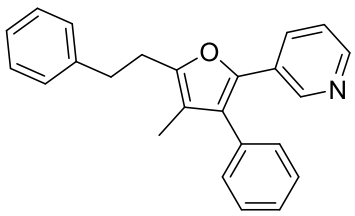
129.7, 128.6, 128.5, 128.4, 128.3, 127.1, 126.9, 126.5, 126.2, 126.0, 125.9, 116.2, 115.5, 34.9, 28.6, 8.6; IR (neat) 3025, 2922, 1600, 1494, 1447, 1264, 1071, 1006, 954, 768 cm^{-1}; GCMS [M^+] 364.

(E)-2-(heptan-3-yl)-3-methyl-4-phenyl-5-(prop-1-en-1-yl)furan (288):



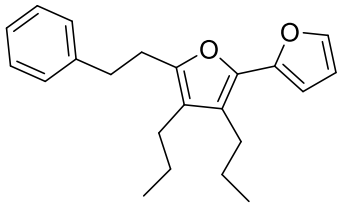
Subjection of 1-phenyl-1-propyne (1.0 mmol, 0.125 mL), 2-ethyl-*N*-methoxy-*N*-methylhexanamide (1.2 mmol, 0.246 mL), and crotonaldehyde (2 mmol, 0.166 mL) to general procedure **H** afforded 0.075 g (25%) of furan **288** as a yellow oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (m, 2H), 7.31 (m, 3H), 6.19 (m, 2H), 2.59 (sept, *J* = 5.2 Hz, 1H), 1.90 (s, 3H), 1.82 (d, *J* = 6 Hz, 3H), 1.68 (m, 4H), 1.30 (quin, *J* = 6.8 Hz, 2H), 1.23 (sex, *J* = 7.2 Hz, 2H), 0.88 (t, *J* = 6.8 Hz, 3H), 0.85 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.3, 146.5, 133.9, 129.7, 128.2, 126.4, 123.2, 123.1, 118.9, 115.4, 39.2, 33.9, 30.0, 27.5, 22.7, 18.4, 14.1, 12.3, 8.9; IR (neat) 2958, 2929, 2871, 1771, 1667, 1605, 1545, 1492, 1445, 1378, 1270, 1072, 1005, 991, 910, 731, 699 cm^{-1}; GCMS [M^+] 296.

3-(4-methyl-5-phenethyl-3-phenylfuran-2-yl)pyridine (289):



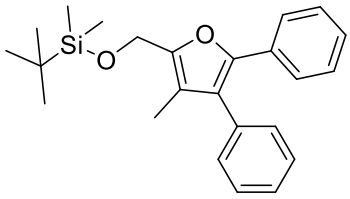
Subjection of 1-phenyl-1-propyne (1.0 mmol, 0.125 mL), *N*-methoxy-*N*-methyl-3-phenylpropanamide (1.2 mmol, 0.219 mL), and 3-pyridinecarboxaldehyde (2 mmol, 0.188 mL) to general procedure **H** afforded 0.234 g (69%) of furan **289** as a yellow oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (m, 1H), 8.38 (m, 1H), 7.64 (m, 1H), 7.48-7.20 (m, 10H), 7.14 (m, 1H), 3.04 (t, *J* = 6 Hz, 2H), 3.02 (t, *J* = 6 Hz, 2H), 1.72 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.6, 147.1, 146.3, 143.4, 141.1, 133.5, 131.8, 129.6, 128.8, 128.4, 128.4, 128.3, 127.5, 126.1, 125.8, 123.0, 117.4, 34.8, 28.4, 8.3; IR (neat) 3027, 2923, 1679, 1603, 1495, 1453, 1422, 1265, 1070, 1022, 1006, 908, 729, 698 cm^{-1}; GCMS [M^+] 339.

5-phenethyl-3,4-dipropyl-2,2'-bifuran (290):



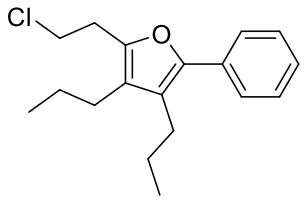
Subjection of 4-octyne (1.0 mmol, 0.147 mL), *N*-methoxy-*N*-methyl-3-phenylpropanamide (1.2 mmol, 0.219 mL), and furan-2-carbaldehyde (2 mmol, 0.166 mL) to general procedure **H** afforded 0.112 g (35%) of furan **290** as a yellow oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (m, 1H), 7.34-7.17 (m, 5H), 6.47 (m, 2H), 3.00 (t, *J* = 7.6 Hz, 2H), 2.90 (t, *J* = 7.2 Hz, 2H), 2.57 (t, *J* = 7.6 Hz, 2H), 2.20 (t, *J* = 7.6 Hz, 2H), 1.59 (sex, *J* = 8.0 Hz, 2H), 1.40 (sex, *J* = 7.6 Hz, 2H), 1.00 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.7, 147.6, 141.5, 140.9, 139.9, 128.4, 128.3, 125.9, 122.4, 121.3, 111.0, 104.2, 35.0, 28.7, 25.8, 25.3, 23.8, 23.6, 14.1, 14.0; IR (neat) 3026, 2957, 2929, 2869, 1652, 1603, 1533, 1498, 1477, 1453, 1377, 1211, 1164, 1070, 1029, 1004, 919, 885, 794, 725, 697 cm^{-1}; GCMS [M^{+}] 322.

***tert*-butyldimethyl((3-methyl-4,5-diphenylfuran-2-yl)methoxy)silane (291):**



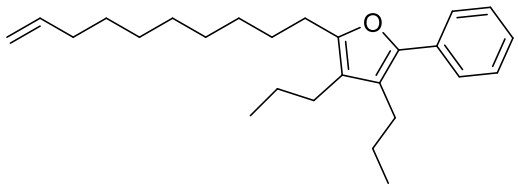
Subjection of 1-phenyl-1-propyne (1.0 mmol, 0.125 mL), 2-((tert-butyldimethylsilyl)oxy)-*N*-methoxy-*N*-methylacetamide (1.2 mmol, 0.296 mL), and benzaldehyde (2 mmol, 0.204 mL) to general procedure **G** afforded a mixture of regioisomers (85/15) yielding 0.101 g (27%) of the major furan isomer **291** as a yellow oil after flash chromatography. Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (m, 5H), 7.30 (m, 2H), 7.24-7.14 (m, 3H), 4.74 (s, 2H), 1.93 (s, 3H), 0.96 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.3, 147.4, 134.1, 131.2, 130.0, 128.7, 128.2, 127.2, 126.9, 125.5, 124.1, 119.6, 56.5, 26.0, 18.6, 8.8, -5.1; IR (neat) 2953, 2927, 2856, 1678, 1601, 1540, 1471, 1463, 1447, 1386, 1315, 1252, 1175, 1069, 1025, 1005, 910, 834, 772, 698 cm^{-1}; GCMS [M^{+}] 364.

2-(2-chloroethyl)-5-phenyl-3,4-dipropylfuran (292):



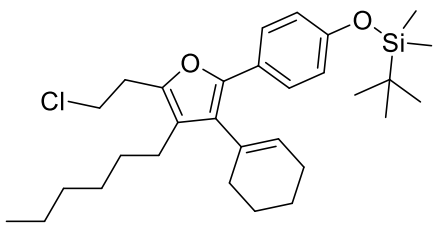
Subjection of 4-octyne (1.0 mmol, 0.147 mL) and *3*-chloro-*N*-methoxy-*N*-methylpropanamide (1.2 mmol, 0.160 mL) and benzaldehyde (2 mmol, 0.204 mL) to the general procedure **G** afforded 0.116 g (40%) of the furan **292** as a greenish oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (m, 2H), 7.41 (m, 2H), 7.26 (m, 1H), 3.79 (t, *J* = 8 Hz, 2H), 3.12 (t, *J = 7.6 Hz,* 2H), 3.58 (m, 2H), 2.37 (m, 2H), 2.61 (m, 4H), 1.03 (t, *J = 7.6Hz*, 3H), 1.01 (t, *J = 7.6Hz*, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) 147.1, 146.0, 132.0, 128.5, 126.5, 125.1, 123.4, 122.2, 42.3, 30.3, 26.5, 25.5, 24.2, 23.5, 14.4, 14.2. IR (neat): 2957, 2930, 2869, 1602, 1491, 1465, 1377, 1253, 1138, 1072, 762, 667 cm^{-1}. GCMS [M^{+}] 290.

2-(dec-9-en-1-yl)-5-phenyl-3,4-dipropylfuran (293):



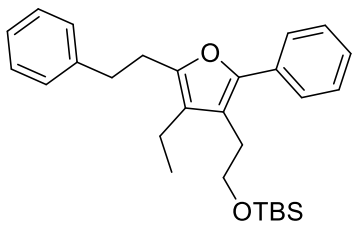
Subjection of 4-octyne (1.0 mmol, 0.147 mL) and N-methoxy-N-methylundec-10-enamide (1.2 mmol, 0.299 mL) and benzaldehyde (2 mmol, 0.204 mL) to the general procedure **G** afforded 0.185 g (51%) of the furan **293** as a yellowish oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J = 8.0 Hz,* 2H), 7.40 (t, *J = 8.0 Hz*, 2H), 7.23 (t, *J = 7.6 Hz*, 1H), 5.84 (m, 1H), 4.99 (dd, *J = 22.0 Hz , 10.0 Hz,* 2H), 2.59 (m, 4H), 2.34 (t, *J = 8.0 Hz,* 2H), 2.07 (q, *J = 7.2 Hz*, 2H), 1.66 (m, 4H), 1.54 (m, 2H), 1.34 (m, 10H), 1.04 (t, *J = 7.2 Hz*, 3H), 0.99 (t, *J = 7.6 Hz*, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.8, 145.9, 139.2, 132.5, 128.4, 125.9, 124.8, 122.2, 121.0, 114.1, 33.8, 29.4, 29.38, 29.36, 29.1, 28.9, 28.7, 26.6, 26.4, 25.6, 24.3, 23.5, 14.4, 14.2. IR (neat): 2955, 2925, 2854, 1639, 1602, 1558, 1491, 1464, 1138, 990, 761, 691 cm^{-1}. GCMS [M^{+}] 366.

***tert*-butyl(4-(5-(2-chloroethyl)-3-(cyclohex-1-en-1-yl)-4-hexylfuran-2-yl)phenoxy) dimethylsilane (294):**



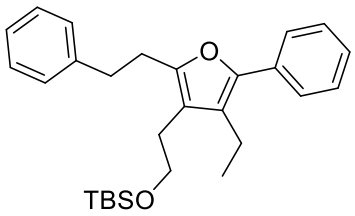
Subjection of 1-(oct-1-yn-1-yl)cyclohex-1-ene (1.0 mmol, 0.219 mL), 3-chloro-*N*-methoxy-*N*-methylpropanamide (1.2 mmol, 0.160 mL), and 4-((tert-butyldimethylsilyl)oxy) benzaldehyde (2 mmol, 0.487 mL) to general procedure **G** afforded 0.056 g (11%) of furan **294** as a yellow oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (m, 2H), 7.86 (m, 2H), 5.62 (s, 1H), 3.73 (t, *J* = 7.6 Hz, 2H), 3.06 (t, *J* = 7.6 Hz, 2H), 2.50 (m, 2H), 2.15 (m, 4H), 1.72 (m, 4H), 1.52 (quin, *J* = 7.6 Hz, 2H), 1.28 (m, 6H), 1.00 (s, 9H), 0.88 (t, *J* = 6.8 Hz, 3H), 0.22 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.5, 147.1, 144.8, 130.2, 128.2, 128.0, 126.8, 125.4, 120.5, 120.1, 77.3, 77.0, 76.7, 42.4, 31.5, 30.4, 30.4, 29.8, 29.4, 25.7, 25.6, 24.6, 23.1, 22.6, 22.2, 18.2, 14.1, -4.4; IR (neat) 2927, 2856, 1605, 1559, 1501, 1471, 1463, 1253, 1169, 1136, 1100, 1005, 908, 837, 804, 779, 733 cm^{-1}. GCMS [M^+] 500.

***tert*-butyl(2-(4-ethyl-5-phenethyl-2-phenylfuran-3-yl)ethoxy)dimethylsilane (295) (major isomer) and tert-butyl(2-(4-ethyl-2-phenethyl-5-phenylfuran-3-yl)ethoxy)dimethylsilane (minor isomer):**



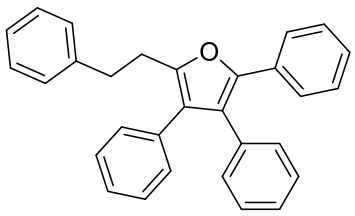
Subjection of *tert*-butyl(hex-3-yn-1-yloxy)dimethylsilane (1.0 mmol, 0.252 mL), *N*-methoxy-*N*-methyl-3-phenylpropanamide (1.2 mmol, 0.219 mL), and benzaldehyde (2 mmol, 0.204 mL) to general procedure **G** afforded 0.225 g (52%) of an inseparable mixture of these regioisomeric furans (r.r. = 60/40) as a yellow oil after flash chromatography. **Major isomer**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 2H, measured 1.26H), 7.41 (m, 2H), 7.33-7.15 (m, 6H), 3.79 (t, *J* = 6.8 Hz, 2H, measured 1.29H), 2.97 (m, 4H), 2.87 (t, *J* = 7.2 Hz, 2H, measured 1.35H), 2.30 (q, *J* = 7.6 Hz, 2H, measured 1.3H), 1.02 (t, *J* = 7.6 Hz, 3H, measured

1.94H), 0.91 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.2, 147.3, 141.5, 132.0, 128.47, 128.45, 128.32, 126.4, 125.97, 125.2, 123.62, 117.8, 63.1, 35.1, 28.6, 28.2, 25.98, 18.4, 16.5, 15.6, -5.29;



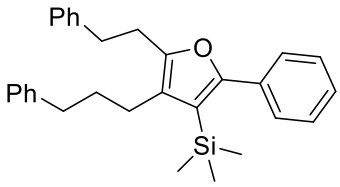
Minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (m, 2H, measured 0.68H), 7.41 (m, 2H), 7.33-7.15 (m, 6H), 3.52 (t, *J* = 7.2 Hz, 2H, measured 0.68H), 2.97 (m, 4H), 2.64 (q, *J* = 7.6 Hz, 2H, measured 0.70H), 2.51 (t, *J* = 7.2 Hz, 2H, measured 0.69H), 1.23 (t, *J* = 7.2 Hz, 3H, measured 1.09H), 0.91 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.4, 146.2, 141.4, 132.1, 128.47, 128.45, 128.3, 126.3, 126.0, 125.0, 123.65, 117.9, 63.7, 35.0, 28.7, 27.2, 25.99, 18.42, 17.5, 14.9, -5.25; IR (mixture of isomers, neat) 3027, 2953, 2927, 2856, 1602, 1559, 1493, 1471, 1463, 1386, 1252, 1087, 1025, 1005, 908, 833, 812, 774, 733, 694 cm^{-1}; GCMS [M^+] 434.

2-phenethyl-3,4,5-triphenylfuran (296):



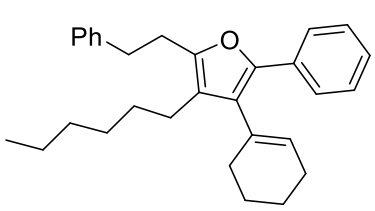
Subjection of diphenyl acetylene (1.0 mmol, 0.178 g), *N*-methoxy-*N*-methyl-3-phenylpropanamide (1.2 mmol, 0.219 mL), and benzaldehyde (2 mmol, 0.204 mL) to general procedure **G** afforded 0.135 g (34%) of furan **296** as a yellow solid (m.p. = 112 °C) after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 2H), 7.28 (m, 16H), 6.97 (m, 2H), 3.15 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.5, 146.9, 141.2, 133.6, 132.7, 131.2, 130.3, 130.2, 129.7, 128.5, 128.3, 128.2, 128.1, 127.9, 126.9, 126.4, 126.1, 125.6, 124.4, 122.9, 34.8, 28.7; IR (neat) 3025, 1600, 1495, 1440, 1068, 1025, 977, 955, 764, 698 cm^{-1}; GCMS [M^+] 400.

trimethyl(5-phenethyl-2-phenyl-4-(3-phenylpropyl)furan-3-yl)silane (297):



Subjection of trimethyl(5-phenylpent-1-yn-1-yl)silane (1.0 mmol, 0.240 mL) and *N*-methoxy-*N*-methyl-3-phenylpropanamide (1.2 mmol, 0.220 mL) and benzaldehyde (2 mmol, 0.204 mL) to the general procedure **G** afforded 0.135 g (31%) of the furan **297** as a colorless oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 2H), 7.25 (m, 3H), 7.16 (m, 4H), 7.05 (m, 6H), 2.81 (t, *J* = 7.6 Hz, 2H), 2.72 (t, *J* = 7.6 Hz, 2H), 2.50 (t, *J* = 7.6 Hz, 2H), 2.24 (m, 2H), 1.60 (pent, *J* = 8 Hz, 2H), 0.00 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7, 150.4, 142.2, 141.6, 133.6, 129.1, 128.4, 128.4, 128.3, 128.3, 128.0, 127.8, 126.0, 125.7, 125.2, 114.6, 35.9, 35.1, 33.5, 28.3, 25.1, 1.0. IR (neat): 3026, 2945, 2858, 1602, 1539, 1495, 1477, 1453, 1249, 1094, 1069, 1027, 908, 835, 732 cm^{-1}. GCMS [M^+] 438.

3-(cyclohex-1-en-1-yl)-4-hexyl-5-phenethyl-2-phenylfuran (298):



Subjection of 1-(oct-1-yn-1-yl)cyclohex-1-ene (1.0 mmol, 0.218 mL) and *N*-methoxy-*N*-methyl-3-phenylpropanamide (1.2 mmol, 0.220 mL) and benzaldehyde (2 mmol, 0.204 mL) to the general procedure **G** afforded 0.039 g (10%) of the furan **298** as a yellowish oil after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.4 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.28 (m, 4H), 7.18 (t, *J* = 7.6 Hz, 2H), 5.42 (m, 1H), 3.00 (t, *J* = 7.2 Hz, 2H), 2.93 (t, *J* = 7.6 Hz, 2H), 2.55 (m, 2H), 2.13 (m, 2H), 2.01 (m, 2H), 1.67 (m, 4H), 1.56 (m, 2H), 1.31 (m, 6H), 0.90 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.9, 146.1, 141.6, 132.3, 130.4, 128.5, 128.4, 128.3, 127.7, 127.0, 126.2, 125.9, 125.2, 122.0, 35.2, 31.5, 30.2, 29.8, 29.4, 28.8, 25.6, 24.7, 23.1, 22.6, 22.2, 14.1. IR (neat): 3026, 2924, 2854, 1727, 1601, 1558, 1491, 1454, 1377, 1134, 1071, 1023, 918, 763, 693 cm^{-1}. GCMS [M^+] 412.

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CHAPTER V

CROSS-COUPLING OF AROMATIC/ALIPHATIC NITRILES WITH ORGANOHALIDES: A DUAL CATALYTIC APPROACH

5.1. INTRODUCTION

Ketones are important functional groups that are present in a wide range of agro-chemicals, pharmaceuticals,[1] biologically active complex natural products,[2-4] and electronic[5] as well as polymeric materials.[6] Natural products as simple as vanillin, *R*-carvone, *Z*-jasmone, camphor, and *R*-muscone which have been widely used in the fragrance industries and as complex as progesterone, a female sex hormone, spongistatin 1,[4] isolated from a marine sponge, which has potential anti-cancer activity all contain a ketone functional group in their structure. Not only natural products, but also a large number of marketed drugs such as Tasmar used to treat Parkinson's disease, oxycodone a semi-synthetic opioid used as an analgesic, rimexolone used for inflammation of the eyes, and raloxifene for the prevention of osteoporosis and reduction of breast cancer,[7] contain ketones and there are many more (Fig 5.1). Besides being ubiquitous, ketones are also used as versatile building blocks that can be converted to many different functional groups as well as being utilized to form new C-C bonds.[8-9] Ketones can be reduced to alcohols and simple alkanes, converted to hemiketals and ketals, and can form new C-C bonds when reacted with the organometallic reagents and other carbon nucleophiles. They can also be converted to imines, enamines, and oximes by reacting with suitable amines (Scheme 5.1).[8]

Due to the widespread use of this functional group, many approaches to form ketones have been well established. Yet, there is still room for improvement. New methodologies that couple readily available substrates utilizing earth abundant metals catalytically instead of using pre-formed organometallic species would be a great improvement.

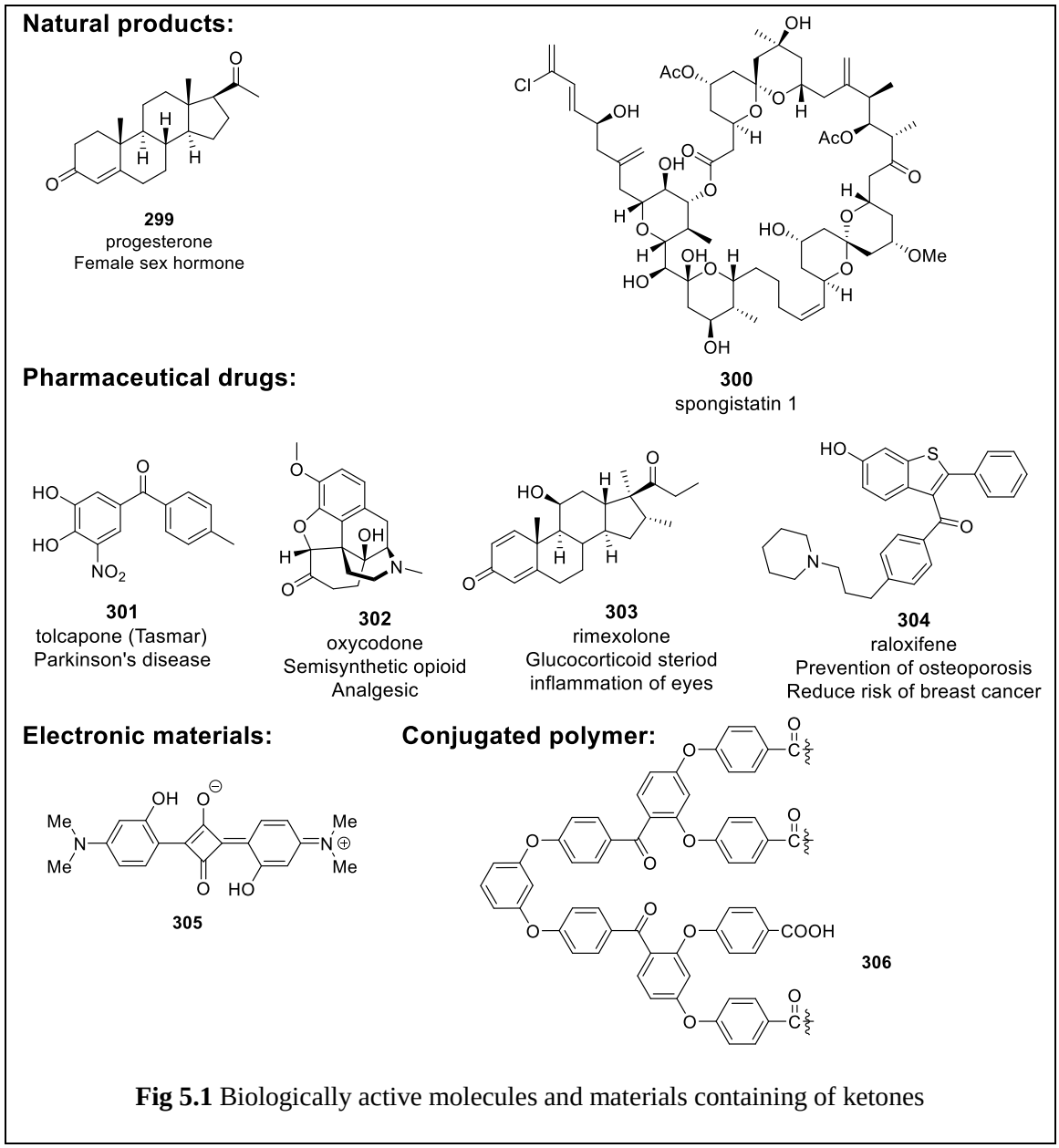
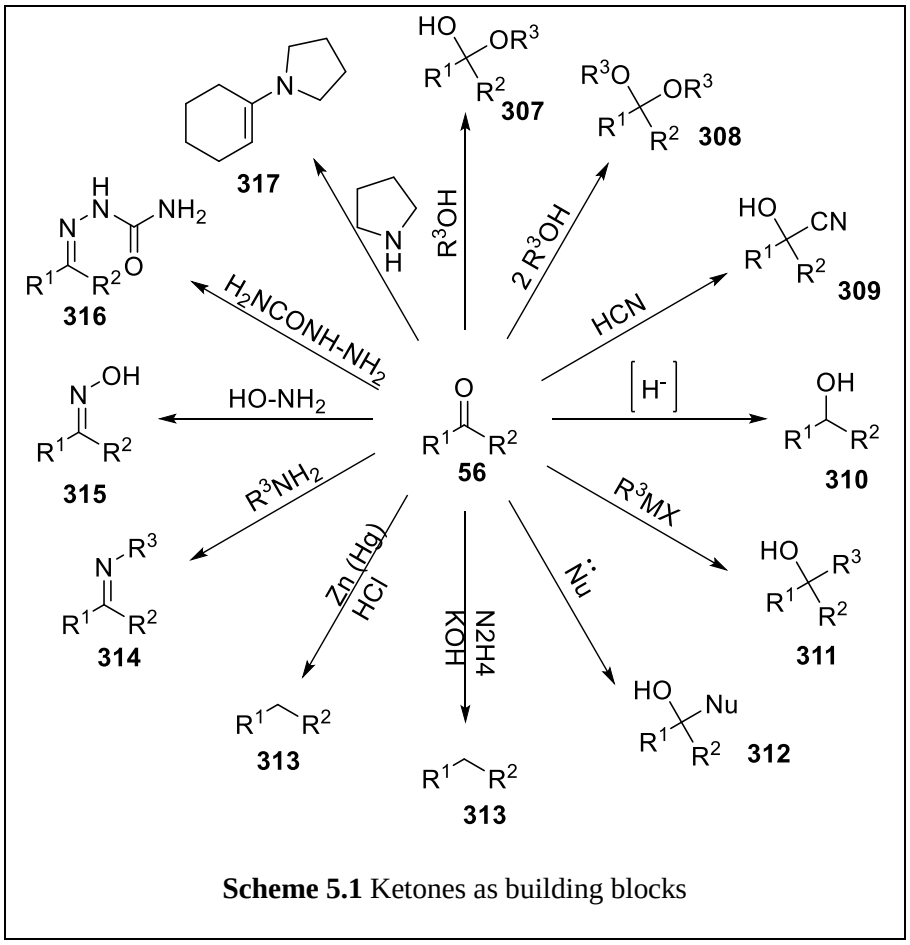


Fig 5.1 Biologically active molecules and materials containing of ketones

5.2. APPROACHES TO KETONES SYNTHESIS

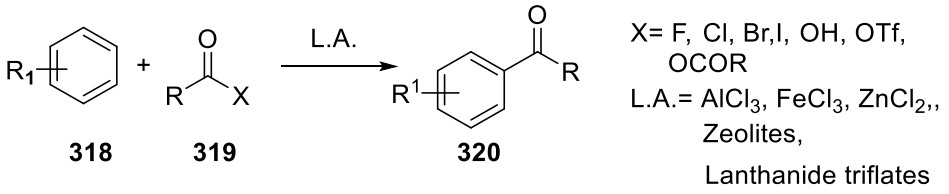
Ketones are one of the most useful functional groups in organic chemistry. For a synthetic chemist it is a very important group as it can be manipulated into various other functional groups readily (Scheme 5.1). Therefore, many conventional techniques to synthesize ketones exist such as Friedel-Crafts acylations;[10] organometallic species reacting with the carbonyl precursors such as nitriles, Weinreb amides and acid chlorides; the oxidation of alcohols, alkanes, and alkenes;[11] the hydration of alkynes;[12] the carbonylation of aryl halides with organometallic reagent,[13] and the hydroacylation of olefins[14] The most recent developments have been nickel catalyzed cross-electrophile-coupling,[15] and dual catalytic radical cross couplings. All of these methods complement each other and have some strengths and limitations.



Scheme 5.1 Ketones as building blocks

5.2.1. Friedel-Crafts acylation reaction

Electron rich aromatic compounds can be treated with acyl halides/pseudohalides or anhydrides in the presence of a Lewis acid catalyst to form ketones (Scheme 5.2). This reaction is known as the Friedel-Crafts acylation reaction and it is commonly used to prepare aryl ketones.[10, 16] However, the presence of strong electron withdrawing groups (e.g., $-NO_2$, $-CF_3$) on the aromatic or heteroaromatic ring (e.g., quinoline, pyridine) shuts down the reaction and acylation does not occur. Mixtures of regioisomers are routinely observed and the reaction requires a slight excess of the Lewis acid catalyst due to the coordination with the acylated final product.

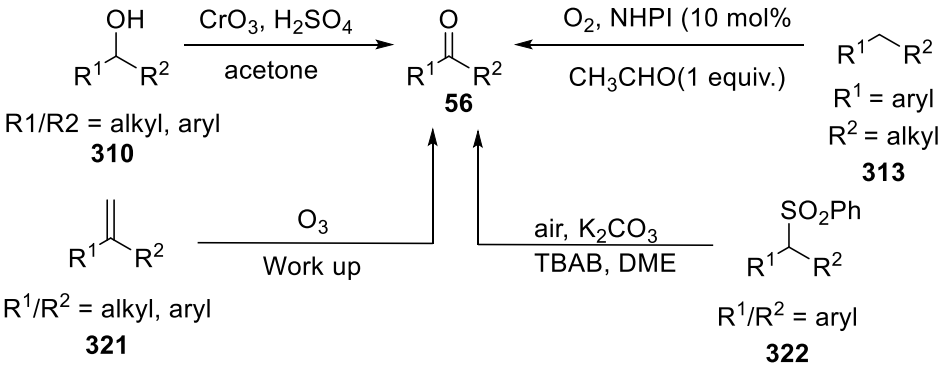


318 **319** **320**

Scheme 5.2 Friedel-Crafts acylation

5.2.2. Oxidation reaction

Ketones can also be accessed from the oxidation of various substrates such as 2° alcohols, alkanes, and alkenes.[11] Oxidation of 2° alcohols to ketones by utilizing the Jones reagent is the most commonly used synthetic method. Other oxidizing agents used recently are $Fe(NO_3)_3$ using clayfen as solid support,[17] silica supported activated manganese dioxide,[18] [bis(acetoxy)iodo]benzene on alumina under microwave irradiation,[19] catalytic use of [*N*-(arylseleno)-4-chlorobenzenesulfonamide],[20] carbon nanotube (CNT) supported iron(II) catalyst,[21] and oxidovanadium complexes with tridentate aroylhydrazones[22] to name a few. Earlier methods used toxic chromium metals while more recent developments have been more environmentally friendly.



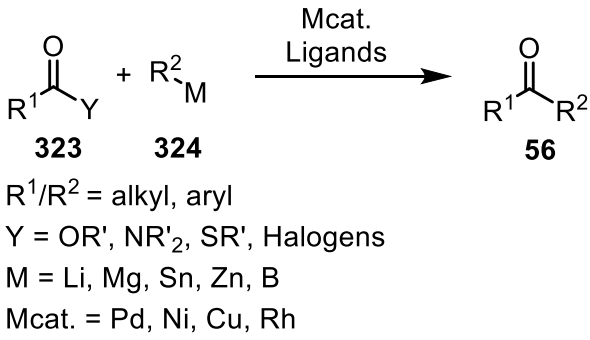
Scheme 5.3 Synthesis of ketone through oxidation

While limited to the oxidation of benzylic alkanes, the corresponding ketones can be observed by using a catalytic amount of *N*-hydroxyphthalimide (NHPI), molecular oxygen, and acetaldehyde.[23] Alkenes can undergo oxidative cleavage via ozonolysis to give the corresponding carbonyl compounds albeit with the waste of formaldehyde, at minimum, and potentially much more functionalized carbons. Benzylic sulfones can be converted to ketones through an auto-oxidation process in the presence of K_2CO_3 and tetrabutylammonium bromide (TBAB), however, this process is limited to nitrobenzosulfones (Scheme 5.3).[24]

5.2.3. Conversion of carboxylic acid derivatives to ketones with organometallic reagents

Carboxylic acid derivatives such as esters, Weinreb amides, thioesters, acid halides, and nitriles can be converted to the corresponding ketones by treating them with the organometallic reagents (Scheme 5.4). Organometallic reagents like Grignards and organolithiums can react directly without the use of transition metal catalysts, however, overreaction to form the corresponding alcohols can limit their utility. The less reactive organometallic nucleophiles such as organotin,[25-27] organozinc,[28-29] and organoboron[30-31] reagents use transition metal catalysts to perform these reactions. Limiting the 3° alcohol formation when strong nucleophiles are reacted has been achieved, to some extent, by using chelating ligands.[32-33] Not only more reactive acid derivatives, but also less reactive electrophiles such as benzaldehyde have also been converted to

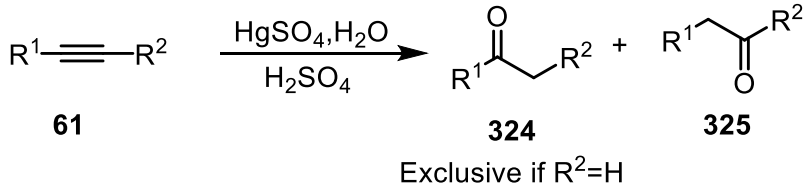
the respective ketones recently with the help of rhodium catalyzed organoboron reagents.[34] Limited functional group tolerance, cryogenic reaction conditions, prefunctionalization of the organometallic reagents are some of the shortcomings of these transformations.



Scheme 5.4 Synthesis of ketone via organometallic reagents

5.2.4. Hydration of triple bonds

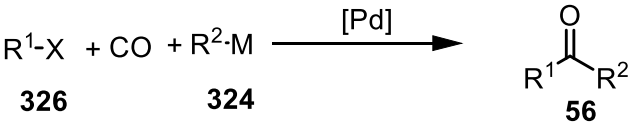
Both terminal and internal alkynes can be hydrated to obtain ketones. The classical approaches are the oxymercuration-demercuration of alkynes[12] and the hydroboration-oxidation of internal alkynes. More modern approaches utilize precious metals like Au,[35-37] Rh,[38-39] Ru,[40] and Ir[41-42] to catalyzed such transformations. While the reaction of terminal alkynes is regioselective, the reaction of non-symmetrical internal alkynes results in the formation of two regioisomers **324** and **325** in an almost 1:1 ratio.



Scheme 5.5 Hydration of alkynes

5.2.5. Carbonylative cross-coupling

One of the more useful methods to prepare symmetrical as well as unsymmetrical ketones is to use palladium catalyzed multicomponent cross-coupling reactions where organic electrophiles such as organic halides and pseudohalides are treated with carbon monoxide in the presence of organometallic reagents (Scheme 5.6).[13] Carbonylative Stille couplings employ organotin reagents and aryl bromides, iodides, or sulfonyl chlorides to afford diaryl ketones in moderate to good yields.[43-44] Carbonylative Suzuki couplings of aryliodides with arylboronic acids in the presence of one bar of carbon monoxide was initially shown by Suzuki in 1993.[45] Since then, the use of this methodology has gained more interest over the organotin reagents due to toxicity issues. Several improvements have been made but limitations include side products such as biaryl formation, required employment of additives, and limited substrates.[46-53] Triorganoindium compounds were used for the first time in 2003 to perform such a transformation.[54-55] They were good at selectivity and reactivity with simple operation procedure and low toxicity but the yields were moderate. Other organometallic reagents used earlier were organoaluminum,[56] organosilane,[57] organoantimony,[58-60] and organozinc[61] for such transformations. The famous Sonogashira coupling reaction has also performed well in carbonylative three-component reactions involving aryl halides, terminal alkynes and carbon monoxide in presence of amines as base to produce alkynyl ketones.[62-65]



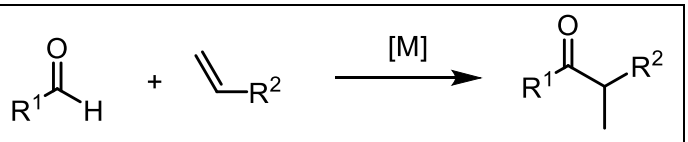
326 **324** **56**

R^1 = alkyl, aryl R^2 = Aryl
X = I, Br, OSO_2R, SO_2Cl, N_2^+
M = B, Al, Si, Sb,Zn, Sn, In

Scheme 5.6 Carbonylative cross-coupling

5.2.6. Hydroacylation of alkenes

The addition of the C-H bond of an aldehyde to an unsaturated C=C by using a transition metal catalyst, commonly rhodium, is a powerful tool to synthesize ketones.[14] Inter- as well as intramolecular hydroacylation has been established with the recent development in new catalytic systems. In 1972, Sakai and co-workers, initially identified rhodium as a catalyst for this transformation[66] and it still remains the frontrunner in this area.[14] Besides using various Rh-species as catalysts for specific substrates, other transition metals such as Co,[67-70] Ru,[71-73] Ir,[74] and Ni[75-77] have also been explored for similar transformations.



327 **328** **329**

R^1/R^2 = Alkyl, aryl

[M] = Rh, Co, Ru, Ir, Ni

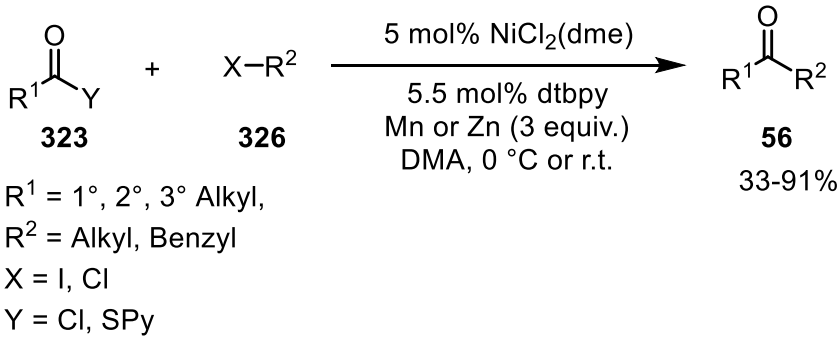
Scheme 5.7 Hydroacylation of alkenes and alkynes

Despite the advancements in this methodology, some challenging aspects still remain to be overcome: limited substrate scope in the intermolecular reaction, the high cost of rhodium bisphosphine complexes, the limited activity and the failure of the intramolecular reaction to form medium and large rings in the absence of functional groups that can stabilize the catalytic intermediates.

5.2.7. Cross electrophile coupling

During the development of cross-electrophile coupling of vinyl or aryl halides with alkyl electrophiles, Weix found that unsymmetrical dialkyl ketones can be prepared from the reductive coupling of acid chlorides with alkyl iodides or benzylic chlorides under nickel catalysis.[15, 78] Pre-formed carbon nucleophiles, which would generate the functional group intolerance, could be avoided when the coupling took place between two electrophiles. By using an acid chloride as the

acylating agent a moderate to good yield was obtained. While searching for more stable acylating agents, 2-pyridyl thioesters were found to produce similar results.[15]

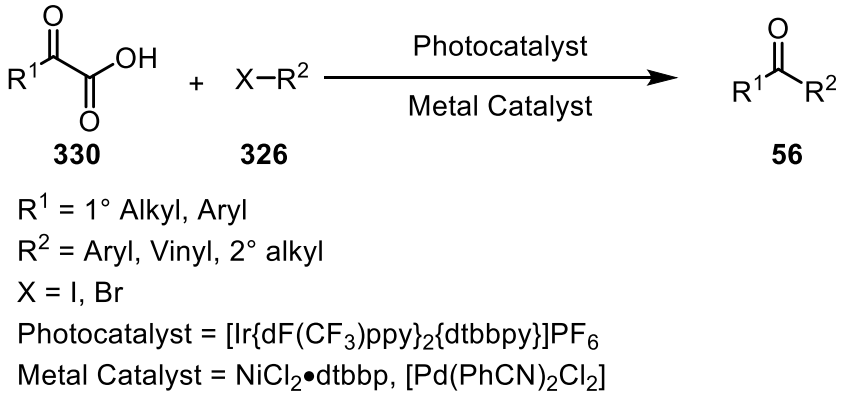


Scheme 5.8 Cross Electrophile coupling

5.2.8. Dual catalytic cross coupling

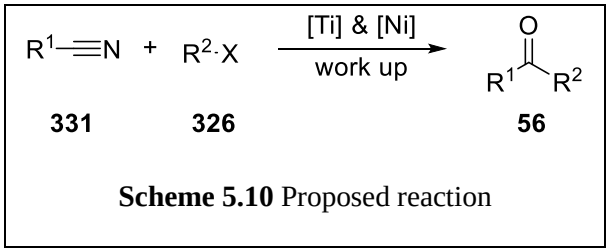
MacMillan, recently, put forth that photoredox catalysts can be used to generate the acyl radicals from the decarboxylation of α-keto acids. Nickel catalyst after oxidative addition of aryl iodides would trap those acyl radical. The desired ketone would be formed after reductive elimination.[79] Following the same pattern, the reaction process was further extended to aryl bromides, vinyl bromides, and secondary alkyl bromides with good yields.[79] A similar transformation was observed by Fu *et. al*. by combining a photoredox catalyst with palladium catalysis;[80] however, this reaction was limited to aryl iodides and bromides being able to generate diaryl ketones.

Utilization of the expensive iridium photoredox catalyst, shown in Scheme 5.9, and the limited availability of α-keto acids are only two of the drawbacks of this reaction. The reaction also takes nearly 3 days to complete in very dilute (0.02 M) solution and requires a high boiling point polar solvent (DMF). Therefore, there is room for improvement. Employing a more earth abundant



Scheme 5.9 Dual catalytic approach to ketone synthesis

metal would decrease the cost of the reaction dramatically, being able to employ starting materials that are more readily available than α-keto acids, and shortening reaction times would increase the utility of the reaction tremendously. Thinking along this line, our group identified that an imidoyl radical could be generated from the wide pool of easily available nitriles by using a titanium(III) catalyst.[81-83] Also, Weix has demonstrated that radicals generated from the opening of epoxides with catalytic titanium could be coupled with aryl halides under nickel catalysis.[84] Taking inspiration from these established methods, we sought to develop nitrile cross coupling with aryl/alkyl halides utilizing a dual catalytic cycle of earth abundant metals titanium and nickel. The initially formed imine would be hydrolyzed to afford ketones. Our dual catalytic cross-coupling meets the challenges posed by the existing methods discussed earlier and represents a mechanistically unique method for ketone synthesis.



Scheme 5.10 Proposed reaction

5.3. RESULTS AND DISCUSSION

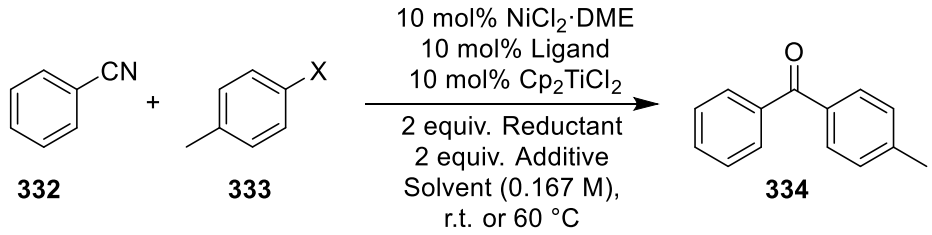
The objective of this study is to develop a reliable, robust, and widely applicable approach to dual catalytic radical cross-couplings. It is speculated that an organonickel(II) complex would trap a catalytically generated carbon radical to catalyze the cross-coupling of organohalides. Titanium catalysts would help generate radicals from nitriles. Nickel is known to catalyze the cross coupling of generated radical intermediates under dual catalysis. Weix has effectively coupled aryl halides with benzylic mesylates using a Ni/Co system.[85] He also has utilized the well-known chemistry of radical generation from epoxides with titanium(III) catalysts[82] in his Ni/Ti dual catalytic system to cross-couple aryl halides with epoxides. It appears as Weix is more interested with the radical generated from the epoxides,[84, 86] however, proper exploration is needed to figure out other possible carbon radicals that can be used in dual catalysis. This study tries to expand the scope of the radical coupling partner to a readily available functional group, nitriles. In literature, super stoichiometric amounts of SmI_2 (6 equivalents) have been used to generate imidoyl radicals in the reduction of nitriles to amines.[87] The other example showed titanium(III) catalysts used to generate imidoyl radicals from nitriles in cross-coupling reactions with ketones.[81-83] The success of Ni/Ti dual catalytic cross coupling of epoxides enabled our group to develop the nitrile cross-coupling with titanium.[88-89] Our proposed approach will generate an imine, an important building block that can be used to prepare amines and heterocycles. For this study, the imine products will be hydrolyzed in the workup to isolate ketone.

The proposed Ti/Ni dual catalytic reaction had the multiple components that needed to be screened. Weix has already shown that bidentate ligands can be used to coordinate with Ni-catalyst to improve the outcome of the cross electrophile coupling reactions.[78] Also, in various titanium catalyzed reactions, Gansäuer had shown that the choice of hydrogen chloride source to turn over the titanium catalytic cycle is also specific for different specific reactions.[90-91] Streuff has generated imidoyl radicals in a moderately polar aprotic solvent like THF[82] whereas Weix has used highly polar solvents like DMPU, DMF, and DMA for cross-electrophile coupling reactions.[78] Reductant

metals, either Zn or Mn, have been used by Weix in the ketone forming cross-electrophile coupling reaction, one acting better than other depending on the acyl radical precursor.[78] Imidoyl radicals have been generated at room temperature while most of the cross-electrophile coupling reaction examples occurred at 60 °C.[78, 82] Therefore, the proposed reaction had multiple parameters that needed to be reconciled.

5.3.1. Reaction optimization

As a starting point, benzonitrile **332** was treated with iodotoluene **335** and 10 mol% of each of the catalysts, bipyridine as the ligand, 2 equivalents of reductant, and TMSCl as an additive (chloride source) in THF (0.167 M concentration) at room temperature. To our delight, 10% product was seen by GC, utilizing a calibration curve (Table 5.1, Entry 1). Upon using trimethylamine·HCl as an additive, the reaction produced only 2% of the product (Entry 2) and this result was consistent when this additive was screened with various solvents and Mn as the reductant (results not shown). Different polar and non-polar solvents were screened (Entry 3-10), with 1,4-dioxane as the solvent producing a 47% yield (Entry 10). Powdered manganese metal as the reductant was screened for each solvent system without formation of product as shown in Entry 11. The ratio of Zn to substrate was incrementally varied from 1:1 to 5:1 with the maximum yield obtained with 2 equivalents of Zn (Entry 10 and others not shown). Subsequently, various commercially available ligands were tested (entry 12-15) with 4,4′-di-*tert*-butyl-2,2’-bipyridine affording the highest yield. Now, different ratios of the reactants and a variety of concentrations for the reaction were investigated. The optimal conditions were found to be 1 equivalent of benzonitrile, 2 equivalents of iodotoluene at a 0.5 M concentration (Entry 16). Various Ni-salts such as $NiCl_2$, $NiBr_2$, $Ni(acac)_2$ were also screened with minimal or no product formation. Similarly, no product formation was found in the absence of either of the catalysts or TMSCl. Similar optimizations were explored with chlorotoluene, **337,** without success. The optimization of the reaction conditions with bromotoluene, **336,** was performed with similar results (Table 3, X = Br).[92]



Scheme 5.11 Optimization of the proposed cross-coupling reaction

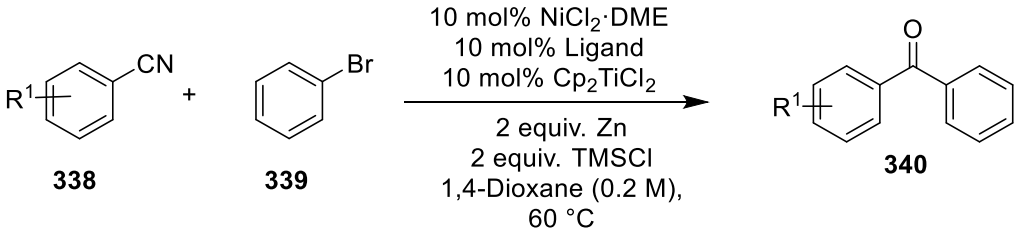
Table 5.1: Optimization of dual catalytic reaction

Entry	**Ligand**	**Reduc-tant**	**Additive**	**Solvent**	**% Yield**		
					X = I **335**	X = Br **336**[92]	X=Cl **337**
1.	Bipyridine	Zn	TMSCl	THF	10%	21%	0%
2.	Bipyridine	Zn	TEA·HCl	THF	2%	1%	0%
3.	Bipyridine	Zn	TMSCl	Et_2O	0%	NA	NA
4.	Bipyridine	Zn	TMSCl	DCM	19%	NA	NA
5.	Bipyridine	Zn	TMSCl	1,2-DCE	14%	12%	0%
6.	Bipyridine	Zn	TMSCl	Chloroform	0%	0%	NA
7.	Bipyridine	Zn	TMSCl	DMF	0%	8%	NA
8.	Bipyridine	Zn	TMSCl	NMP	5%	NA	NA
9.	Bipyridine	Zn	TMSCl	DMPU	2%	NA	NA
10.	Bipyridine	Zn	TMSCl	1,4-Dioxane	47%	44%	0%
11.	Bipyridine	Mn	TMSCl	1,4-Dioxane	0%	0%	NA
12.	4,4′-Di-*tert*-butyl bipyridine	Zn	TMSCl	1,4-Dioxane	50%	61%	NA
13.	4,4′-Di-methyl bipyridine	Zn	TMSCl	1,4-Dioxane	34%	43%	NA
14.	4,4′-Di-methoxy bipyridine	Zn	TMSCl	1,4-Dioxane	20%	NA	NA
15.	Phenanthroline	Zn	TMSCl	1,4-Dioxane	0%	22%	NA
16.	**4,4′-Di-*tert*-butyl bipyridine**	**Zn**	**TMSCl**	**1,4-Dioxane**	**77%**	**69%** (0.5M)	NA

5.3.2. Substrate scope of the nickel catalyzed radical coupling reaction

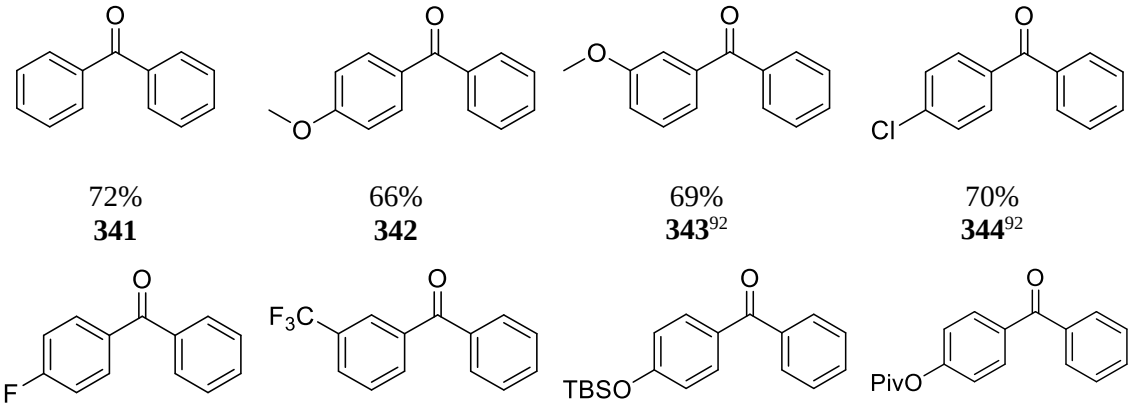
Having identified the optimized reaction conditions, the scope and chemoselectivity of the benzonitrile coupling partner was examined and this has been summarized in Table 5.2. Both electron donating and electron withdrawing groups were tolerated in the reaction. Meta and para substituted benzonitriles produced good yields while ortho substituted benzonitriles resulted in

little to no reaction, presumably due to the steric hindrance around the reaction center. Positioning the electron donating group meta rather than para to the nitrile resulted in slightly higher yield



Scheme 5.12 Optimized reaction condition of dual catalytic reaction

Table 5.2 Benzonitrile scope

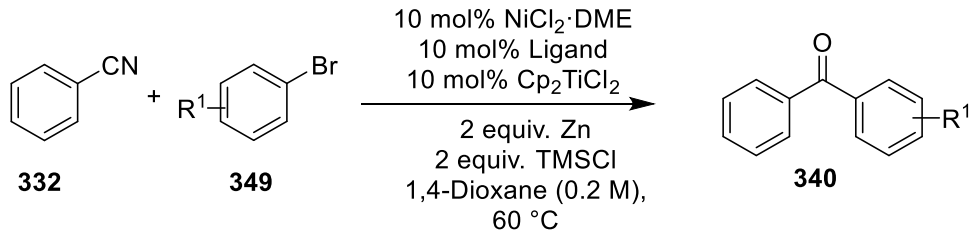


72% **341**	66% **342**	69% **343**[92]	70% **344**[92]
68% **345**	55% **346**	74% **347**	91% **348**

(Entries **342** and **343**). Halogens like chlorine and fluorine were not effected under the reaction conditions, therefore leaving the halogen as further functionalizable handle. Employing a medicinally important trifluoromethyl group meta to the nitrile, **346,** produced a good yield. The presence of a free phenolic group failed to produce results, however, simple silyl protection allowed for a high yield of the TBS-protected phenol, **347**. The very hindered Piv-ester, **348,** also worked well under our reaction conditions resulting in the highest yield in the reaction with benzonitrile. Adding tifluoroacetic acid (TFA) in catalytic amounts has been shown to improve the results in cross-electrophile coupling reactions.[93] Following the same analogy, the slightly lower yielding reactions to form **341**, **345,** and **348** were increased by adding 5 mol% TFA. Benzonitriles that had

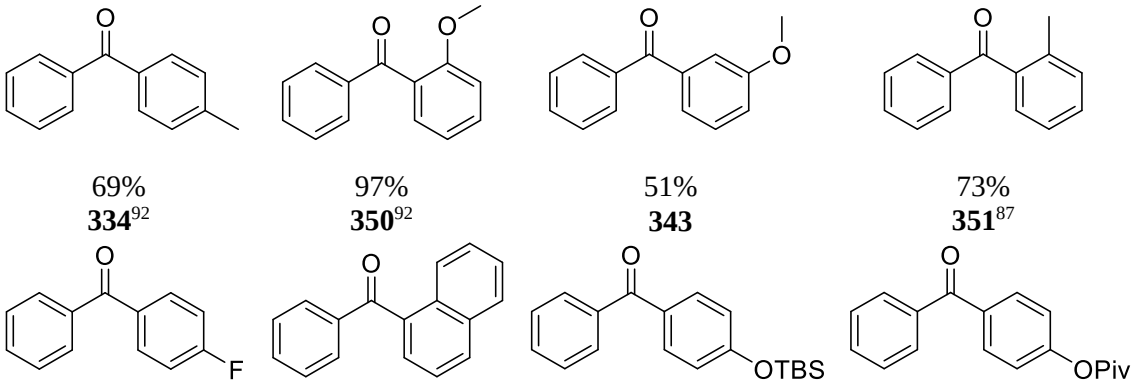
substituents that consist more basic oxygen atom than the nitrogen atom in nitrile such as keto-, amino-, amido, heteroaromatics and nitro- groups failed to give product.

After screening the nitrile coupling partner, the scope of the aryl halide was also examined. Aryl bromides are readily available and cheaper reagents than the aryl iodides and most importantly give similar results to aryl iodides at elevated temperature (60 °C) (Table 5.1, Entry 12 and 16). Unlike with the benzonitrile, ortho substitution not only worked but also gave excellent yields (Table 5.3, Entry **350** and **351**). Increasing the sterics further to naphthalene also resulted in excellent yield (Table 5.3, Entry **352**) but if the sterics were further increased by employing 2-



Scheme 5.13 Screening arylbromide scope of the reaction

Table 5.3 Arylbromide Scope



69% **334**[92]	97% **350**[92]	51% **343**	73% **351**[87]
41% **345**	84% **352**[92]	56% **347**	76% **348**

bromo-1,3-dimethylbenzene the reaction was inhibited. The aryl bromides screened with electron donating substituents all worked well. Less reactive halogens, Cl or F, on the aryl bromide, survived as substituents on the benzonitrile, (Table 5.3, Entry **345**) gave only moderate yields here. Free phenols, amines, amides, ketones, and heteroaromatics all shut down the reaction whereas the TBS

protected phenol again gave moderate yields (Table 5.3, Entry **347**). Methyl esters on the arylbromide did not result in product whereas a pivaloyl ester resulted in good yield (Table 5.3, compound **348**). Free aldehyde groups either on the benzonitrile or arylbromide were not tolerated, however the corresponding acetal showed promise resulting in are approximate 10% yield of the aldehyde product due to cleavage of the protecting group during the reaction.

5.3.3. Efforts to produce mixed ketones

In an effort to extend the methodology beyond aryl ketones, a variety of nitriles and halides were employed under the optimized reaction conditions, the results of which are shown in Table 5.4. To our delight, not only aromatic nitriles and bromides, but also aliphatic nitriles and bromides worked with our reaction conditions. Aliphatic nitriles gave low to moderate yields with aryl iodides and bromides (Table 5.4, Entry 1-4). The 2° aliphatic bromide, cyclohexyl bromide, worked well producing a similar result as itsaromatic counterparts (Entry 5). The moderate yield produced from the employment of 4-chloroiodobenzene was increased by 10% at 40 °C (Entry 6). Re examining whether an aryl bromide would remain intact, the reaction of meta-bromobenzonitrile with iodotoluene was run at r.t. rather than 60 °C. The reaction occurred, and after the first coupling, the second benzonitrile ended up coupling with the product giving **363** (Table 5.3, Entry 7) as the sole product in 48% which is a quantitative yield. The work is still ongoing on to synthesize various mixed ketones and to screen other functional groups.

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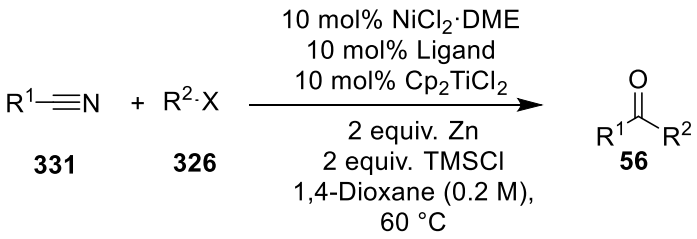
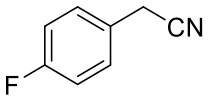
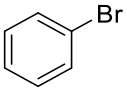
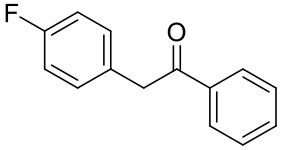
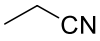
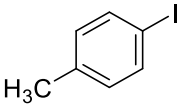
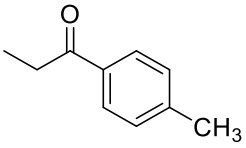
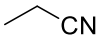
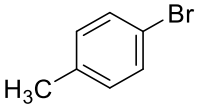
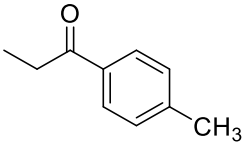
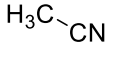
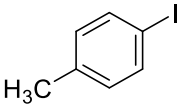
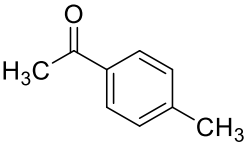
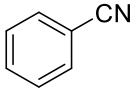
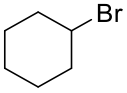
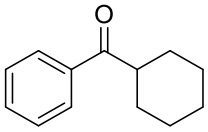
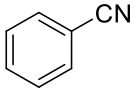
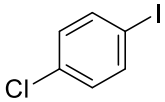
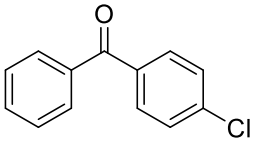
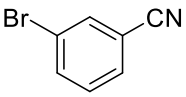
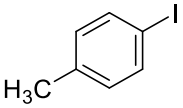
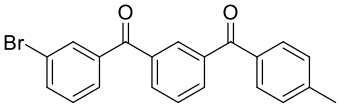


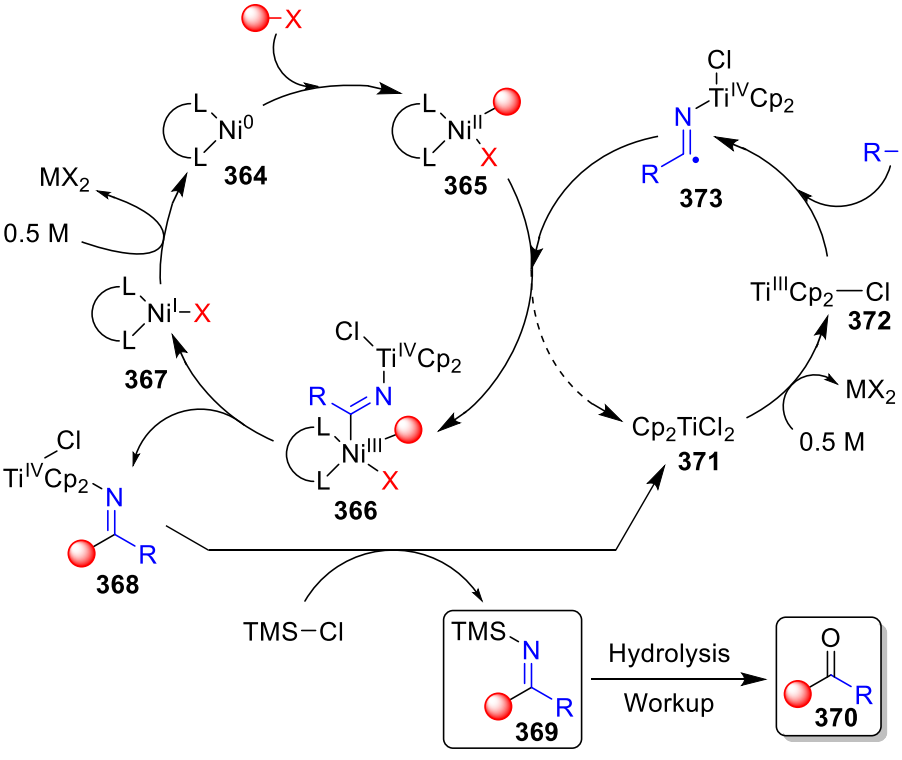
Scheme 5.14 Synthesis of some mixed ketones

Table 5.4 Synthesis of various mixed ketones

Entry	R^1CN	R^2X	Product	% yield	Extra condition
1.	 **353**	 **339**	 **354**	41%	5 mol% TFA
2.	 **355**	 **335**	 **356**	42%	r.t.
3.	 **355**	 **336**	 **356**	32%	
4.	 **357**	 **335**	 **358**	21%	r.t.
5.[92]	 **332**	 **359**	 **360**	69%	
6.	 **332**	 **361**	 **344**	54%	40 °C
7.[92]	 **362**	 **335**	 **363**	48%	r.t.

5.3.4 Proposed mechanism:

A full mechanistic study has not yet been performed, but from the results observed a proposed mechanism is outlined in Scheme 5.15. The catalytic cycle would start after the oxidative addition of the aryl halide to a Ni(0) species, **364**, to form Ni(II) adduct **365**. This adduct is known to trap *in situ* generated imidoyl radicals, such as **373**, to form di-organo Ni(III) intermediate **366**. The generation of the imidoyl radical takes place in the titanium catalytic cycle where titanocene dichloride, **371**, is reduced to a Ti(III) species, **372**, and coordination of the nitrile followed by single electron transfer would create the imidoyl radical, **373**. The diorgano Ni(III) species, **366**, would undergo reductive elimination to get imine, **368**, and the Ni(I) species, **367** which is turned over after reduction by the metal reductant. To turn over the Ti-catalytic cycle, the TMSCl would transmetalate with the cross coupled imine **368** to produce silylated imine **369** and regenerate the Ti(IV) species **371**. The imine **369** is hydrolyzed during work up to afford ketone **370**.



Scheme 5.15 Proposed mechanism for dual catalytic cycle

5.4. CONCLUSIONS

The first coupling of aryl and alkyl halides with an *in situ* generated arylimidoyl radical has been developed. Although to a lesser extent, aliphatic nitriles could also be employed to generate imidoyl radicals. Aliphatic halides couple equally well as aromatic halides under our reaction conditions. Electron donating and withdrawing groups can both be tolerated as substituents of the benzonitrile, while electron donating groups on the aryl bromide facilitate the coupling process. The reaction procedure is equally capable of producing aliphatic, aromatic, and mixed ketones from readily available starting materials using catalytic earth abundant metals.

5.5. FUTURE DIRECTIONS

Imines are precursors to a wide range of other functional groups such as amines, enamines, and heterocycles. The *in situ* generated imine intermediate **369** can be treated with other nucleophiles to generate additional sets of functionally important compounds in single pot tandem reaction.

5.6. SUPPORTING INFORMATIONS

5.6.1. Methods

All of the solid reagents were added to an oven-dried MW tube inside the glove box and the capped tube is taken out to add the remaining liquid reagents and solvents. The reaction mixture was degassed for five minutes before warming. Reactions were monitored either by thin-layer chromatography with 0.25 mm precoated silica gel plates or by gas chromatography. Visualization of all TLCs was performed with UV light and/or staining with phosphomolybdic acid, $KMnO_4$, or Seebach's stain. Purifications were performed by flash chromatography with silica gel (60 Å, 230−400 mesh) packed in glass columns and elute with hexanes/EtOAc, unless otherwise noted.

5.6.2. Materials

Diethyl ether, dichloromethane, and chloroform were dried using a solvent purification system that contained activated alumina. 1,2-Dichloroethane and TMSCl were freshly distilled from calcium hydride under argon. 1,4-Dioxane was freshly distilled from benzophenone and sodium under argon. The nitriles and aryl bromides were purchased and used as is. The following compounds were prepared from literature procedures: 4-((tert-butyldimethylsilyl)oxy)benzonitrile,[94] 4-cyanophenyl pivalate,[95] (4-bromophenoxy)(tert-butyl)dimethylsilane,[94] and 4-bromophenyl pivalate.[95]

5.6.3. Instrumentation

^{1}H NMR and ^{13}C NMR spectra were obtained on a 400 MHz NMR spectrometer (400 MHz for ^{1}H and 101 MHz for ^{13}C), and chemical shifts (δ, ppm) are reported relative to residual chloroform solvent peaks (δ = 7.26 ppm for ^{1}H and δ = 77.0 ppm for ^{13}C). Data for ^{1}H NMR are reported as follows: chemical shift (multiplicity, coupling constant(s) in Hz, integration). Multiplicities are indicated as follows: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sex = sextet, sept = septet, m = multiplet or unresolved. The reported melting points are uncorrected. Low-resolution mass spectra were obtained by GC−MS.

5.6.4. General Procedure I

An oven dried MW vial with a stir bar was taken into an argon filled glovebox and charged with titanocene dichloride (0.1 mmol, 0.0249 g), zinc powder (-325 mesh, 2 mmol, 0.1308 g), $NiCl_2$·DME (0.1 mmol, 0.0219 g), and ditertbutylbipyridine (0.1 mmol, 0.0156 g). An aluminum sealed septa was then crimped to the vial, which was then removed from the glovebox. The vial was then sequentially injected with benzonitrile (1 mmol), bromoarene (2 mmol), TMSCl (1 mmol, 0.13 mL), and dioxane (2 mL). The vial was then connected to a bubbler and an argon inlet to degas the reaction mixture under a positive flow of argon for five minutes. The vial was then disconnected from the inlets and placed in a preheated oil bath at 60 °C. The reaction was monitored every 12 h by GC, and typically the starting materials were fully consumed by 36 hours. The vial was removed

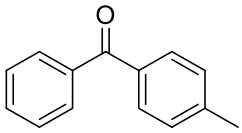
from the oil bath and cooled to room temperature. The reaction was opened to the air and quenched with 2 mL of 1 M HCl and stirring the mixture for 3 hours. The crude reaction mixture was then filtered through a plug of silica gel, which was rinsed with Et_2O. The filtrate was then dried over magnesium sulfate, filtered, and concentrated. The crude material was then loaded onto a 50g silica gel cartridge and purified by MPLC on a Biotage Isolera system using a hexanes/EtOAc gradient.

Note 1: If any of the reagents were solids, they were weighed into the MW vial inside a glove box before capping.

Note 2: 5 mol% of TFA was added after adding solvent for those reactions where the yield was low.

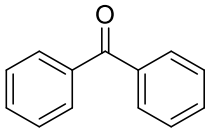
5.6.5 Spectral data of ketones

phenyl(p-tolyl)methanone (334):



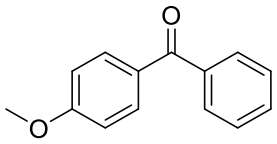
Subjection of benzonitrile (1.0 mmol, 0.103 mL) and 4-iodotoluene (2 mmol, 0.4360 g) to general procedure **I** at room temperature afforded 0.1511 g (77%) of ketone **321** as a colorless liquid after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.2 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.4, 143.1, 137.9, 134.8, 132.1, 130.2, 129.8, 128.9, 128.1, 21.6. Physical and spectral data were consistent with those reported in the literature.[55]

Benzophenone (341):



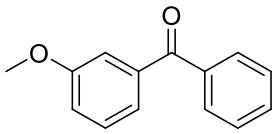
Subjection of benzonitrile (1.0 mmol, 0.103 mL) and bromobenzene (2 mmol, 0.211 mL) to general procedure **I** at 60 °C afforded 0.1312 g (72%) of ketone **328** as colorless liquid after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.2 Hz, 4H), 7.58 (t, *J* = 7.2 Hz, 2H), 7.47 (t, *J* = 7.6 Hz, 4H), ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.6, 137.5, 132.3, 130.0, 128.2. Physical and spectral data were consistent with those reported in the literature.[96]

(4-methoxyphenyl)(phenyl)methanone (342):



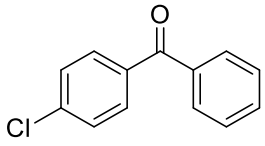
Subjection of 4-methoxybenzonitrile (1.0 mmol, 0.1331 g) and bromobenzene (2 mmol, 0.211 mL) to general procedure **I** at 60 °C afforded 0.1397 g (66%) of ketone **329** as colorless liquid after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (m, 2H), 7.74 (m, 1 H), 7.55 (m, 2H), 7.46 (m, 2H), 6.94 (m, 2H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.4, 163.1, 138.2, 132.5, 131.8, 130.0, 129.6, 128.1, 113.5, 55.5. Physical and spectral data were consistent with those reported in the literature.[96]

(3-methoxyphenyl)(phenyl)methanone (343[92]):



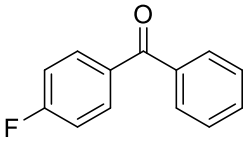
Subjection of benzonitrile (1.0 mmol, 0.103 mL), 3-methoxybromobenzene (2 mmol, 0.253 g), to general procedure **I** at 60 °C 0.1084 g (51%) of ketone **330** as colorless liquid after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.80 (m, 2H), 7.64-7.57 (m, 1 H), 7.53-7.47 (m, 2H), 7.43-7.34 (m, 3H), 7.18-7.13 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.4, 159.5, 138.8, 137.5, 132.4, 130.0, 129.1, 128.2, 122.8, 118.8, 114.3, 55.4. Physical and spectral data were consistent with the literature.[96]

(4-chlorophenyl)(phenyl)methanone (344[92]):



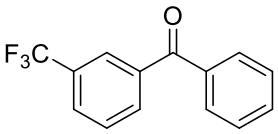
Subjection of 4 Chlorobenzonitrile (1.0 mmol, 0.1376 g), Bromobenzene (2 mmol, 0.211 mL), to general procedure **I** at 60 °C afforded 0.1511 g (70%) of ketone **331** as colorless liquid after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.71 (m, 3H), 7.50-7.40 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.3, 138.7, 137.1, 135.7, 132.5, 131.3, 129.0, 128.5, 128.3. Physical and spectral data were consistent with the literature.[96]

(4-fluorophenyl)(phenyl)methanone (345)



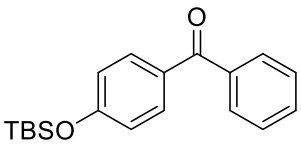
Subjection of 4 Fluorobenzonitrile (1.0 mmol, 0.1211 g), Bromobenzene (2 mmol, 0.211 mL), to general procedure **I** afforded 0.1362 g (68%) of ketone **332** as colorless liquid after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.79 (m. 2H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 2H), 7.14 (t, *J* = 9.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.2, 166.6, 164.1, 137.4, 133.8, 133.7, 132.7, 132.6, 132.4, 129.8, 128.3, 115.5, 115.3. Physical and spectral data were consistent with the literature.[97]

phenyl(3-(trifluoromethyl)phenyl)methanone (346)



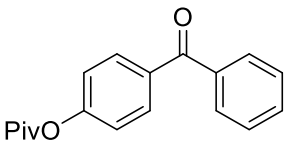
Subjection of 3-(trifluoromethyl)benzonitrile (1.0 mmol, 0.134 mL), Bromobenzene (2 mmol, 0.211 mL), to general procedure **I** at 60 °C afforded 0.1363 g (55%) of ketone **333** as white solid after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.97 (d, *J* = 7.6 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.81-7.76 (m, 2H), 7.62 (t, *J* = 7.2 Hz, 2H), 7.50 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.2, 138.3, 136.7, 133.1, 133.0, 131.5, 131.2, 130.8, 130.5, 130.0, 129.0, 128.9, 128.9, 128.8, 128.8, 128.6, 127.8, 126.8, 126.7, 126.7, 126.6, 125.0, 122.3, 119.6. Physical and spectral data were consistent with the literature.[98]

(4-((tert-butyldimethylsilyl)oxy)phenyl)(phenyl)methanone (347)



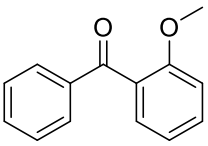
Subjection of 4-((tert-butyldimethylsilyl)oxy)benzonitrile (1.0 mmol, 0.2334 g), Bromobenzene (2 mmol, 0.211 mL), to general procedure **I** at 60 °C afforded 0.2312 g (74%) of ketone **334** as yellowish solid after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.71 (m, 4H), 7.53 (m, 1H), 7.45 (m, 2H), 6.89 (m, 2H), 0.99 (s, 9H), 0.24 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.6, 159.9, 138.2, 132.4, 131.8, 130.6, 129.7, 128.1, 119.6, 77.3, 77.0, 76.7, 25.5, 18.2, -4.4. Physical and spectral data were consistent with the literature.[99]

4-benzoylphenyl pivalate (348)



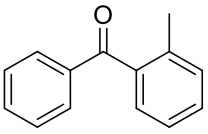
Subjection of 4-cyanophenyl pivalate (1.0 mmol, 0.186 mL), Bromobenzene (2 mmol, 0.211 mL) to general procedure **I** at 60 °C afforded 0.2569 g (91%) of ketone **335** as white solid after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.8 Hz, 2 H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.18 (d, *J* = 8.8 Hz, 2H), 1.37 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.4, 176.4, 154.3, 137.4, 134.7, 132.3, 131.5, 129.8, 128.2, 121.4, 77.3, 77.0, 76.7, 39.1, 27.0. Physical and spectral data were consistent with the literature.[100]

(2-methoxyphenyl)(phenyl)methanone (350)



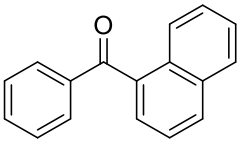
Subjection of benzonitrile (1.0 mmol, 0.101 mL), o-bromoanisole (2 mmol, 0.249 mL), to general procedure **I** at 60 °C afforded 0.206 g (97%) of ketone **337** as colorless liquid after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.79 (m, 2H), 7.58 – 7.51 (m, 1H), 7.51 – 7.40 (m, 3H), 7.38 (dt, *J* = 7.6, 1.9 Hz, 1H), 7.10 – 6.95 (m, 2H), 3.73 – 3.66 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.2, 157.1, 137.6, 132.8, 131.7, 129.6, 129.3, 128.7, 128.1, 120.3, 111.3, 55.4.

phenyl(o-tolyl)methanone (351)



Subjection of benzonitrile (1.0 mmol, 0.101 mL), o-bromotoluene (2 mmol, 0.240 mL), to general procedure **I** at 60 °C afforded 0.1432 g (73%) of ketone **338** as colorless liquid after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.66 (m, 2H), 7.47 – 7.41 (m, 1H), 7.36 – 7.29 (m, 2H), 7.26 (td, *J* = 7.5, 1.6 Hz, 1H), 7.21 – 7.08 (m, 3H), 2.22 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.4, 138.5, 137.6, 136.6, 133.0, 130.9, 130.1, 130.0, 128.4, 128.3, 125.1, 19.9.

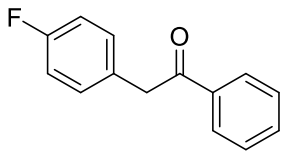
naphthalen-1-yl(phenyl)methanone (352)



Subjection of benzonitrile (1.0 mmol, 0.101 mL), 1-bromonaphthalene (2 mmol, 0.280 mL), to general procedure **I** at 60 °C afforded 0.1951 g (84%)

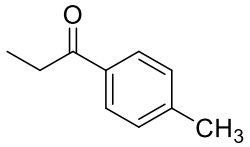
of ketone **338** as white solid after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 8.08 (m, 1H), 8.01 (m, 1H), 7.95 – 7.91 (m, 1H), 7.90 – 7.85 (m, 2H), 7.59 (m, 2H), 7.55 – 7.50 (m, 3H), 7.50 – 7.44 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.0, 138.3, 136.3, 133.7, 133.2, 131.2, 130.9, 130.4, 128.4, 128.4, 127.7, 127.2, 126.4, 125.6, 124.3.

2-(4-fluorophenyl)-1-phenylethan-1-one (354)



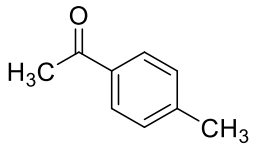
Subjection of (4-fluorophenyl)acetonitrile (1.0 mmol, 0.120 mL), 1-bromobenzene (2 mmol, 0.211 mL), to general procedure **I** at 60 °C afforded 0.0879 g (41%) of ketone **340** as colorless liquid after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 7.6 Hz, 2H, 7.45 (t, J = 7.2 Hz, 1H), 7.34 (t, J = 7.6 Hz, 2H), 7.10 (m, 2H), 6.89 (t, J = 8.4 Hz. 2H), 4.14 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.3, 163.0, 160.6, 136.4, 133.2, 131.0, 130.9, 130.1, 130.1, 128.6, 128.4, 115.5, 115.3, 44.4.

1-(p-tolyl)propan-1-one (356)



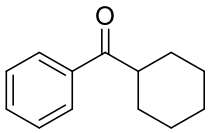
Subjection of propanenitrile (1.0 mmol, 0.066 mL), 4-bromotoluene (2 mmol, 0.246 mL), to general procedure **I** at 60 °C afforded 0.0472 g (32%) of ketone **342** as colorless liquid after flash chromatography.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.75 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 2.89 (q, *J* = 7.3 Hz, 2H), 2.32 (s, 3H), 1.13 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.4, 143.5, 134.4, 129.2, 128.0, 77.3, 77.0, 76.7, 31.6, 21.5, 8.3.

1-(p-tolyl)ethan-1-one (358)



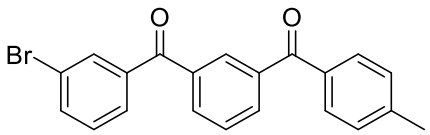
Subjection of acetonitrile (1.0 mmol, 0.052 mL), 4-iodotoluene (2 mmol, 0.436 g), to general procedure **I** at room temperature afforded 0.0277 g (21%) of ketone **344** as colorless liquid after flash chromatography.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (m, 2H), 7.16 (m, 2H), 2.50 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.8, 143.8, 134.7, 129.2, 128.4, 26.5, 21.6.

cyclohexyl(phenyl)methanone (360)



Subjection of benzonitrile (1.0 mmol, 0.101 mL), cyclohexylbromide (2 mmol, 0.246 mL), to general procedure **I** at 60 °C afforded 0.1299 g (69%) of ketone **346** as colorless liquid after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.82 (m, 2H), 7.45 (t, *J* = 7.3 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 2H), 3.18 (tt, *J* = 11.5, 3.3 Hz, 1H), 1.86 – 1.71 (m, 4H), 1.71 – 1.57 (m, 1H), 1.48 – 1.25 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.8, 136.3, 132.6, 128.5, 128.2, 45.6, 29.4, 25.9, 25.8.

(3-(3-bromobenzoyl)phenyl)(p-tolyl)methanone (363)



Subjection of 3-bromobenzonitrile (1.0 mmol, 0.1820 g), iodotoluene (2 mmol, 0.4360 g), to general procedure **I** at room temperature afforded 0.1821 g (48%) of ketone **348** as white solid after flash chromatography.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (t, *J* = 1.8 Hz, 1H), 7.80 (t, *J* = 1.7 Hz, 1H), 7.74 (m, 1H), 7.72 – 7.66 (m, 4H), 7.60 (m, 1H), 7.36 (m, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.8, 143.8, 139.8, 136.1, 135.0, 134.7, 134.2, 132.7, 130.7, 130.6, 130.2, 129.8, 129.1, 128.4, 122.9, 122.5, 117.3, 114.2, 21.7.

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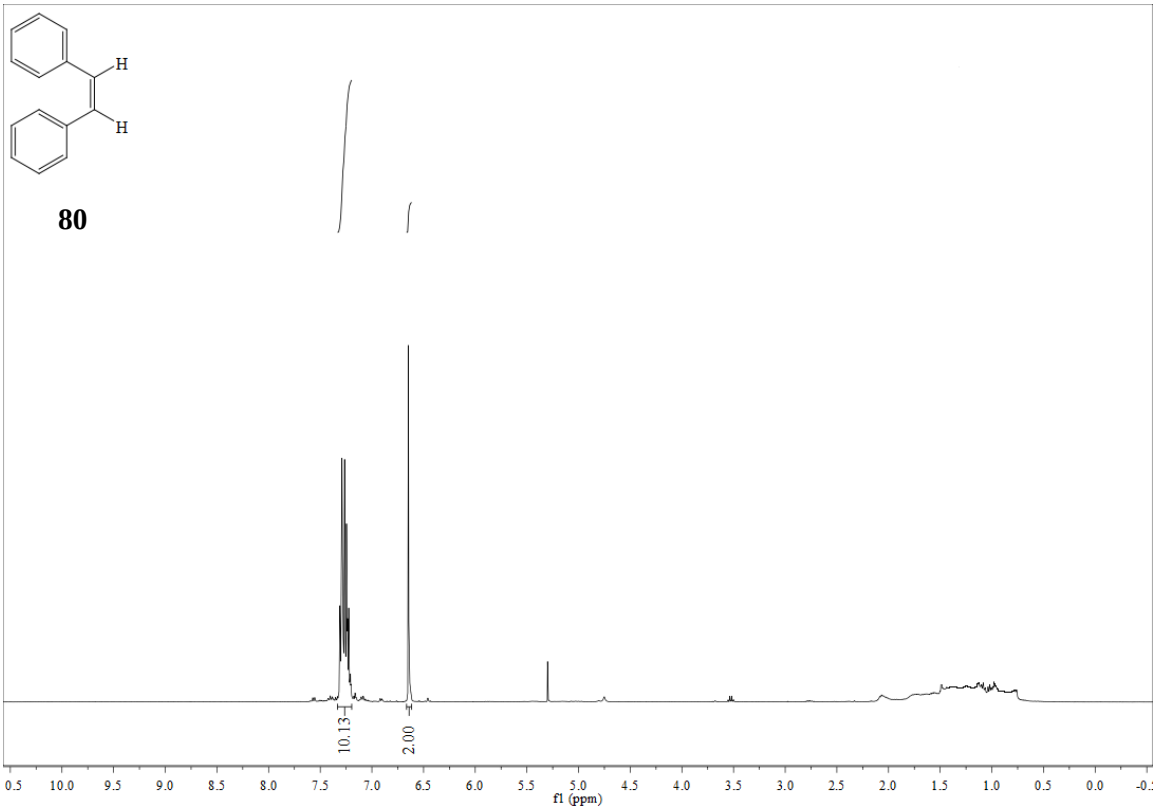
APPENDICES

List of Appendices



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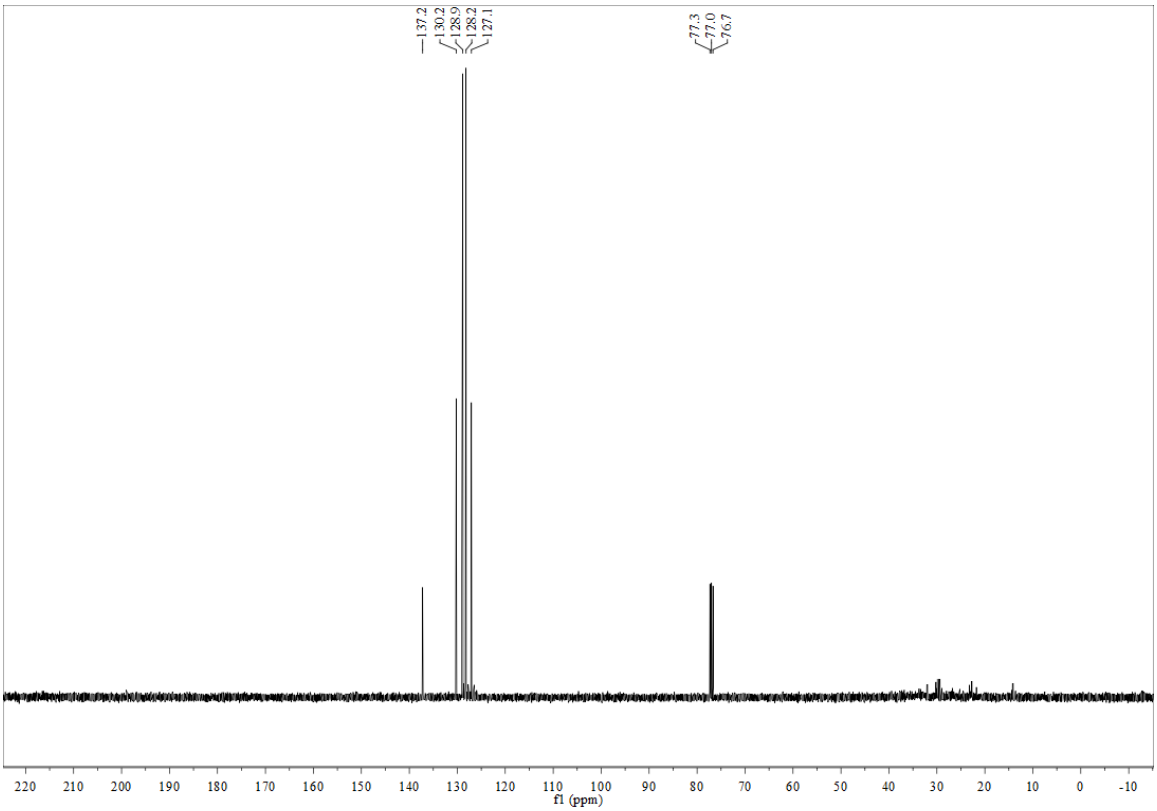

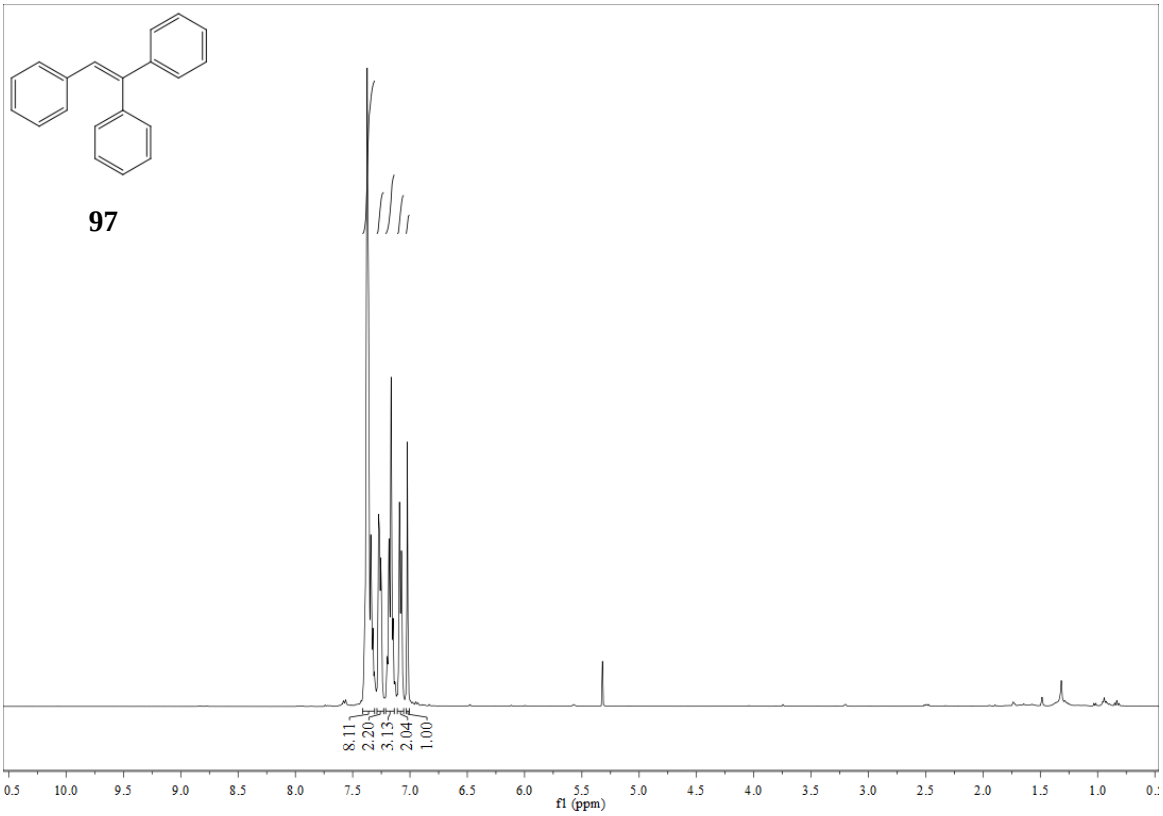
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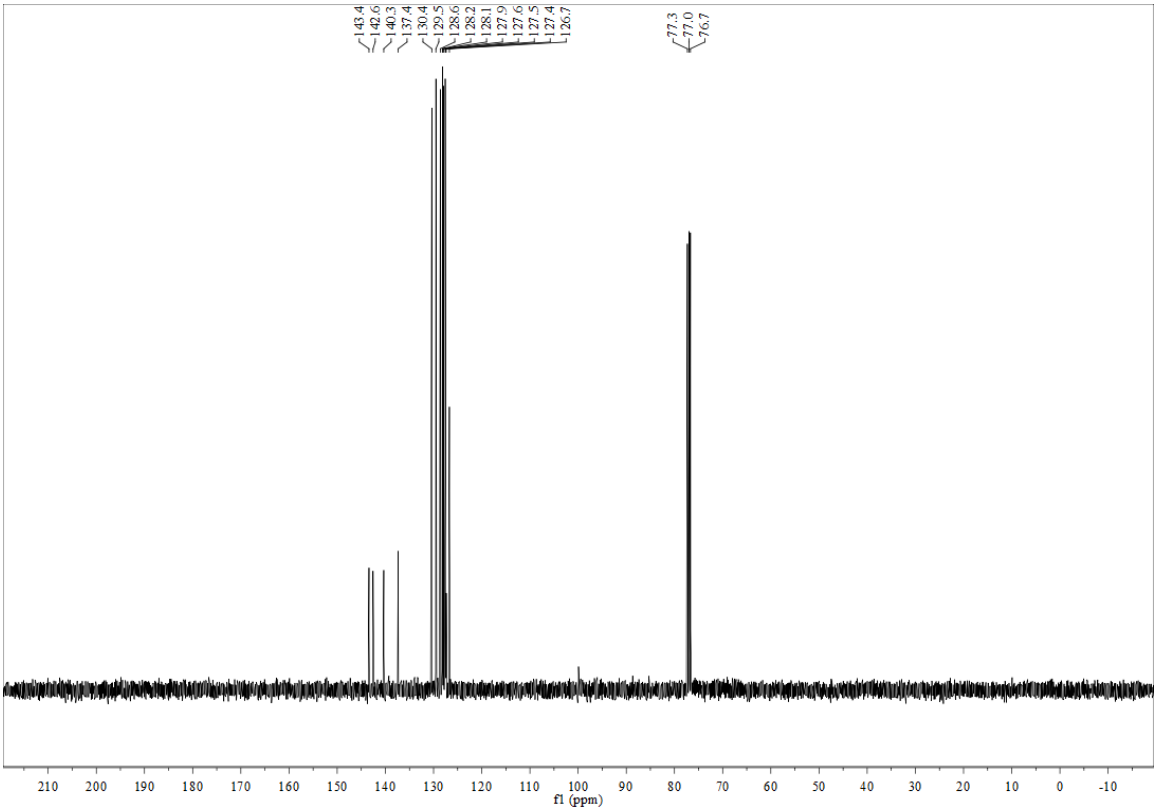
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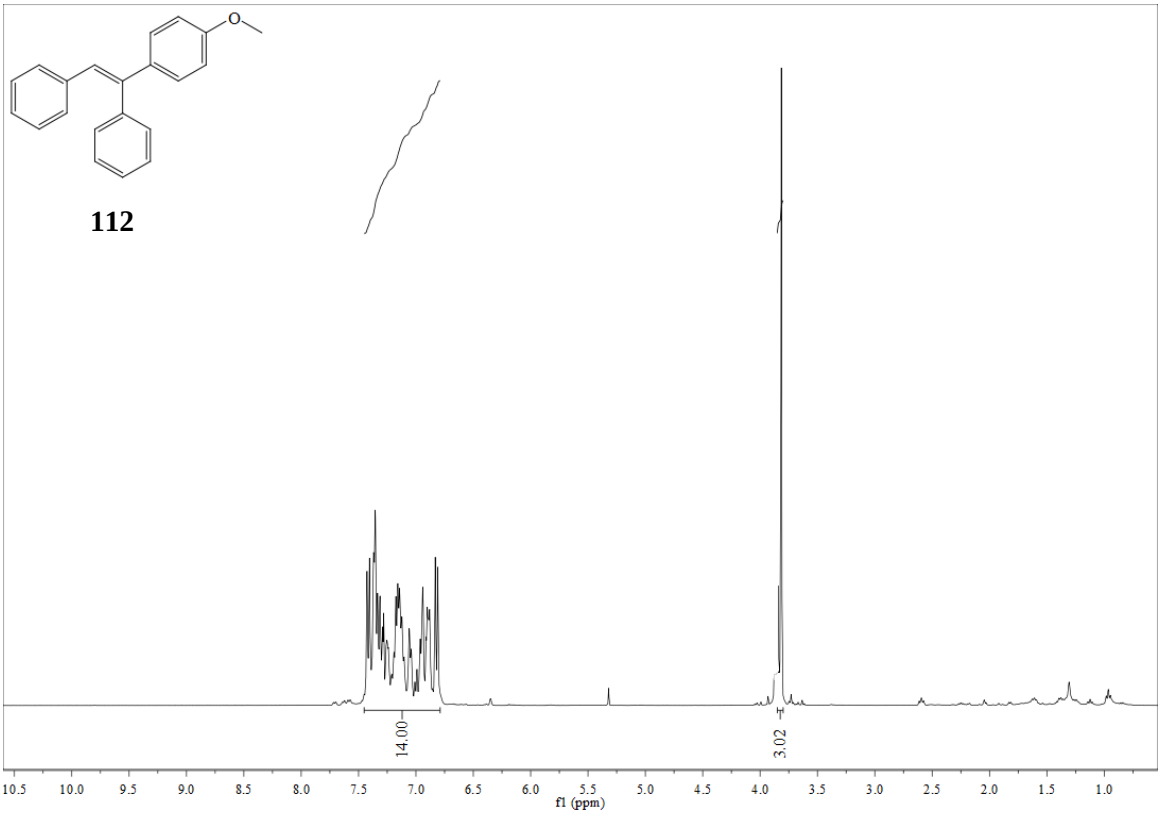
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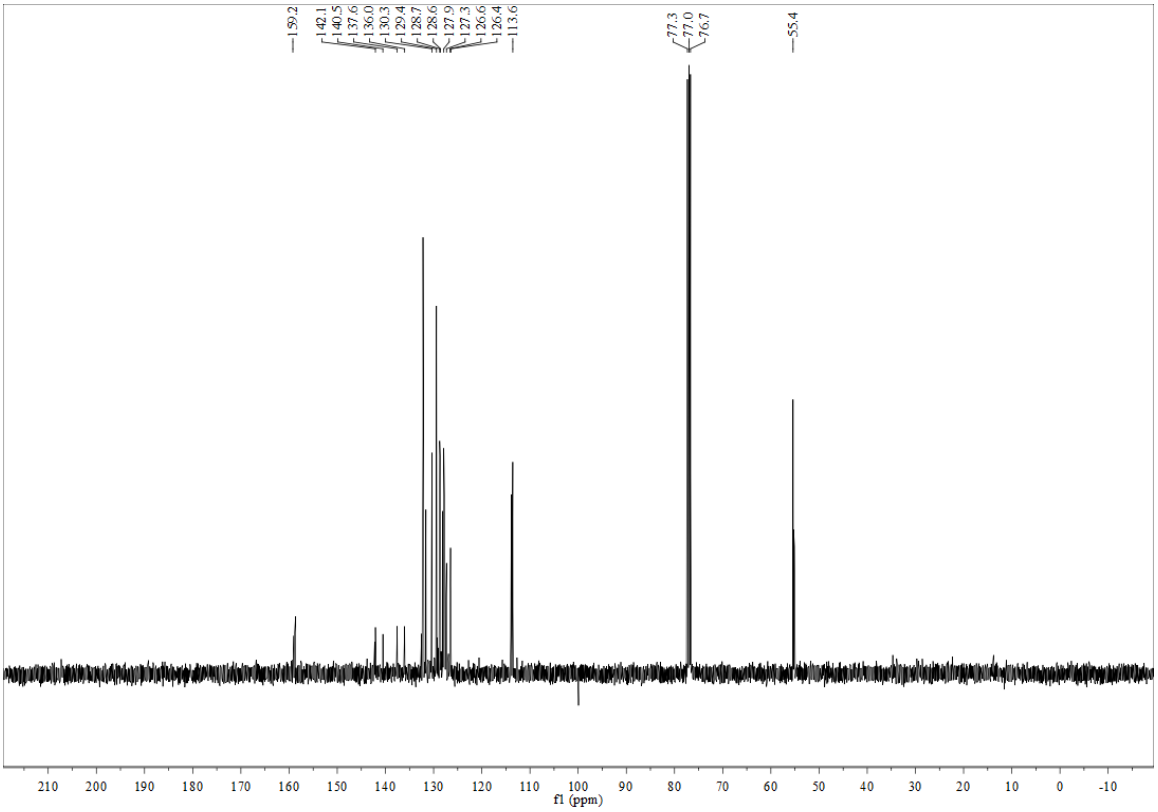
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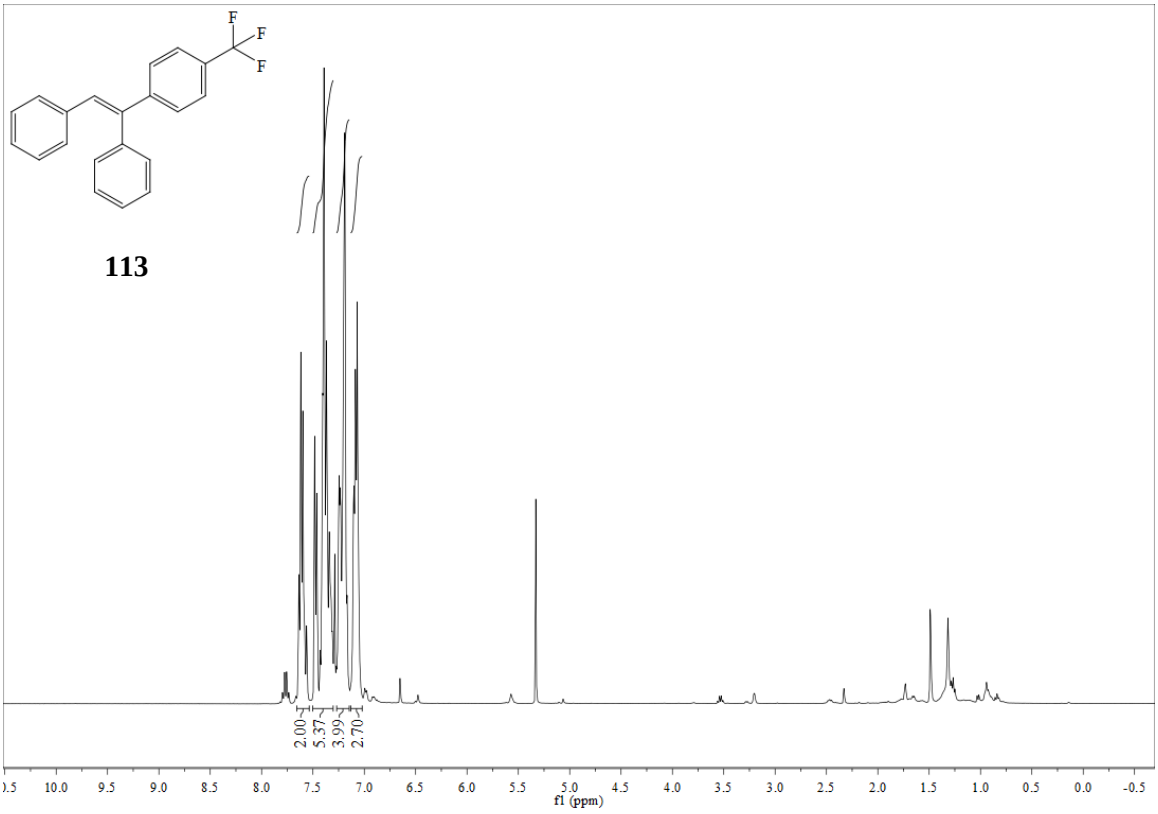
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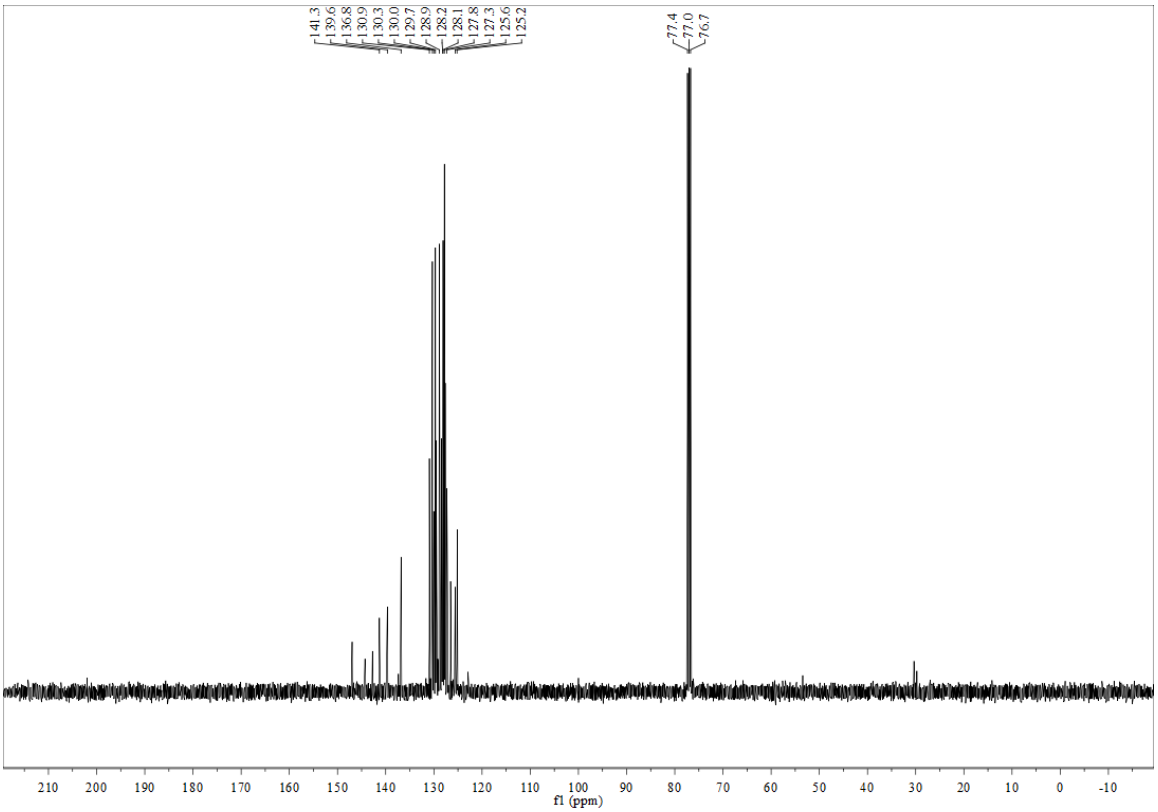
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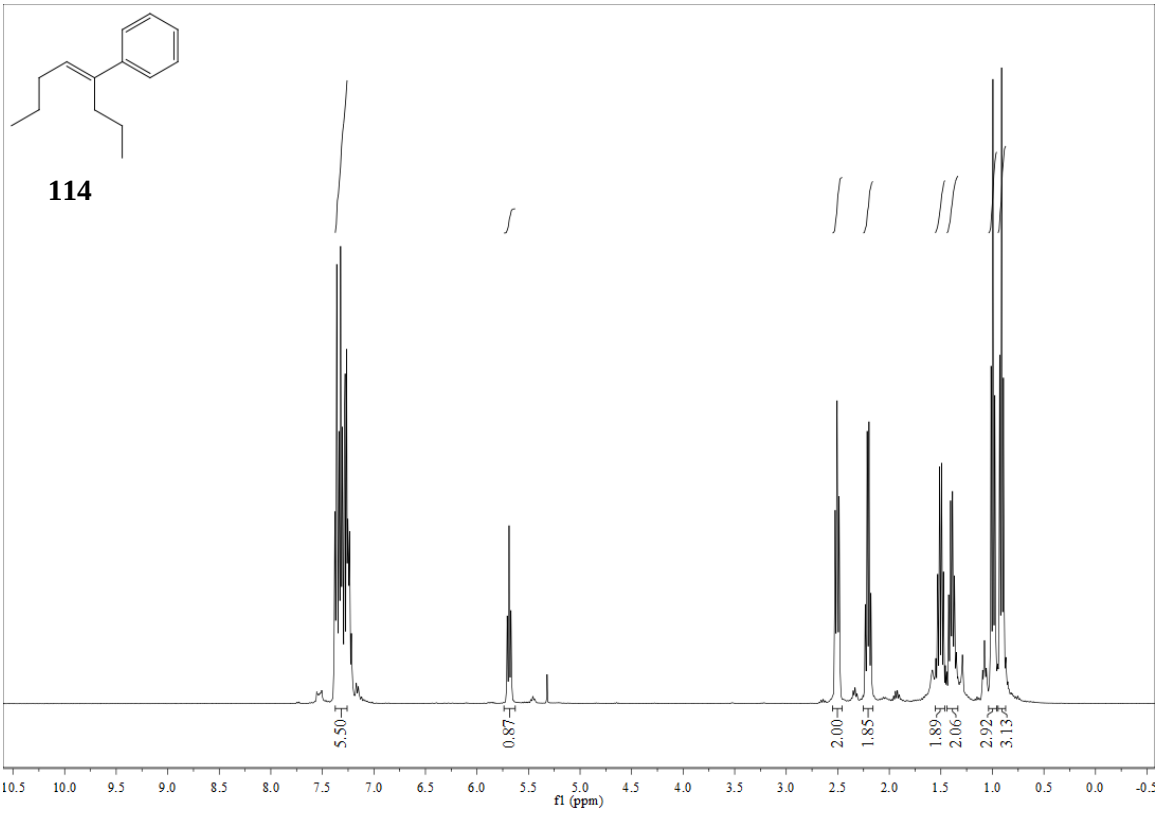
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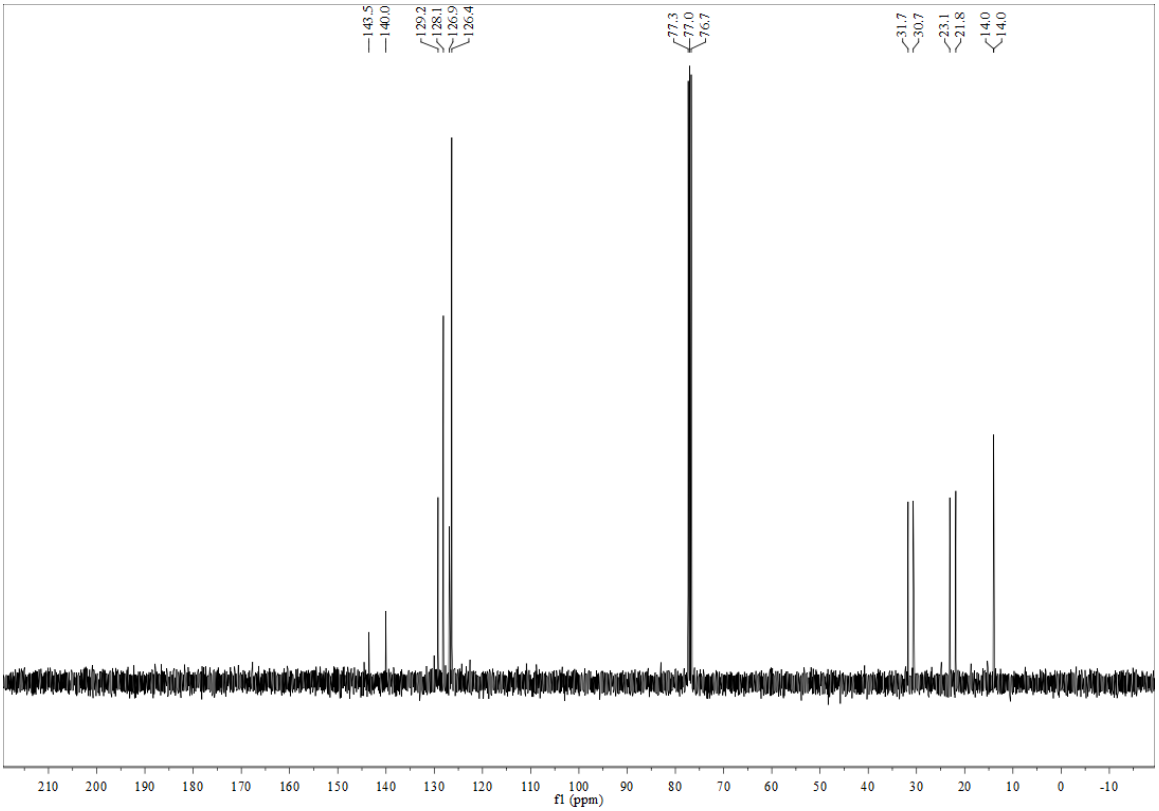
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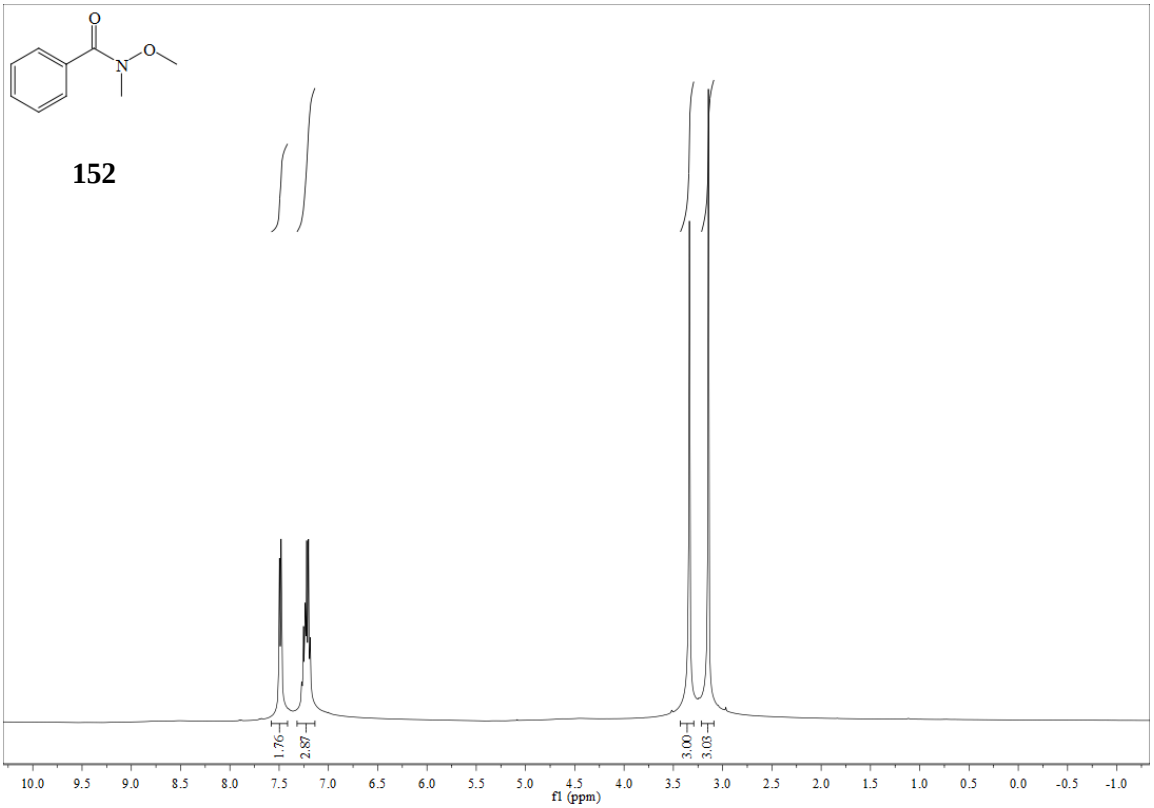
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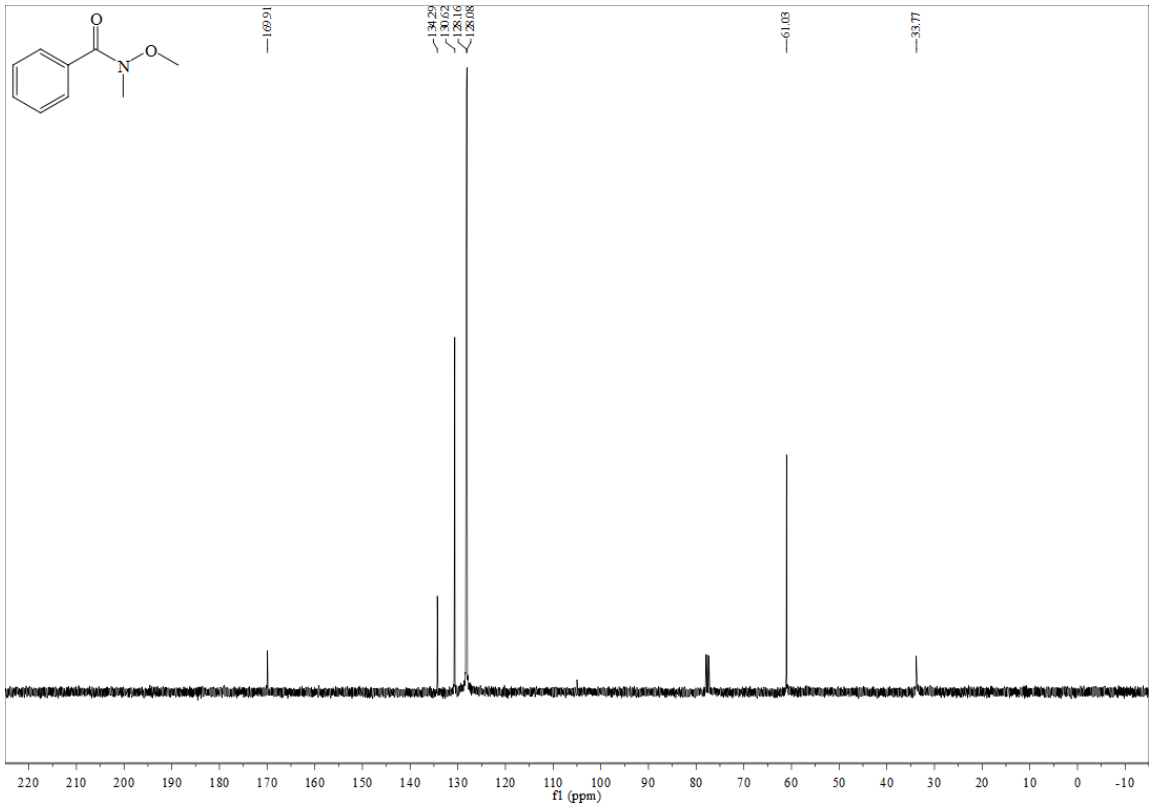
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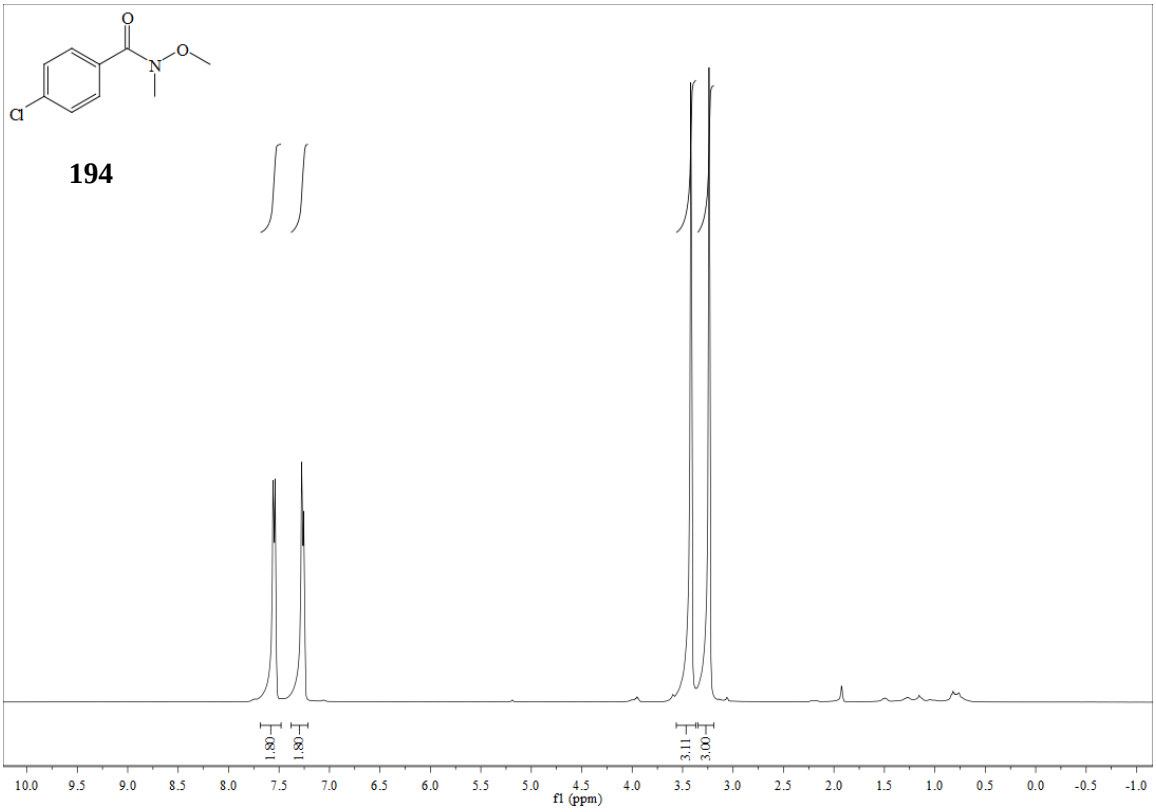
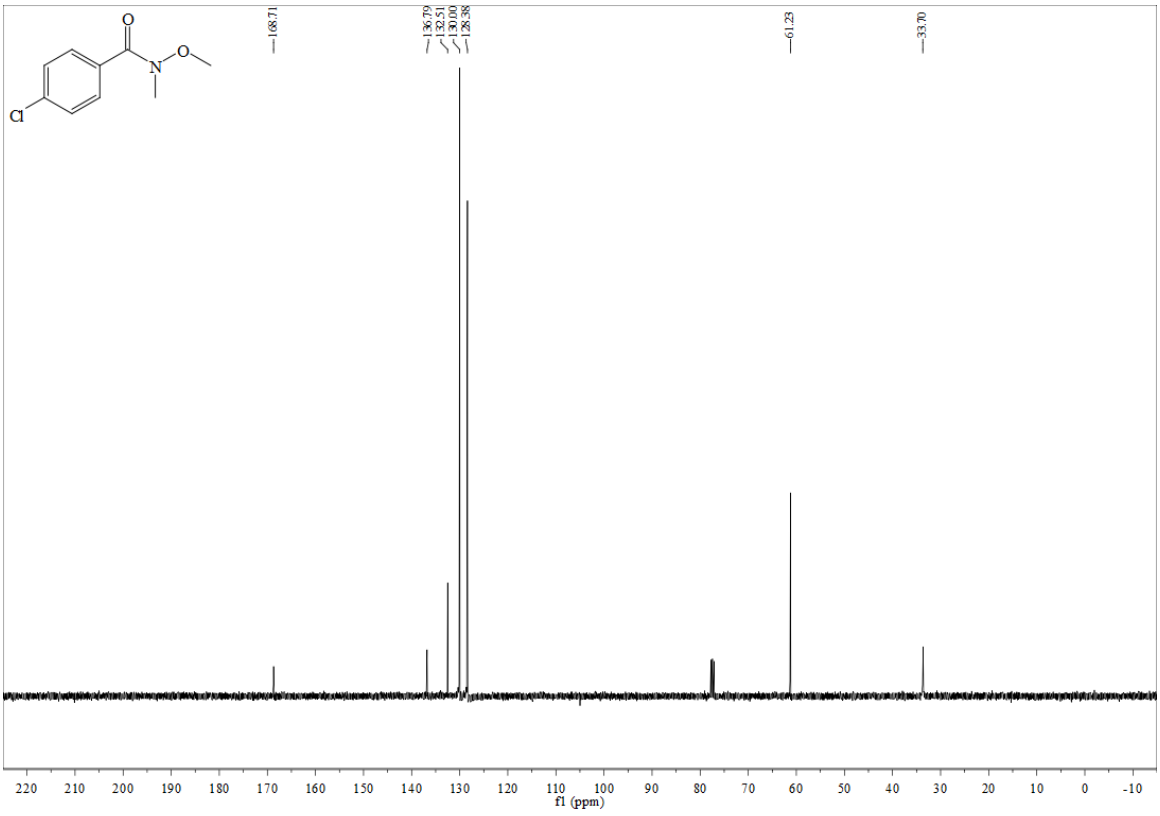
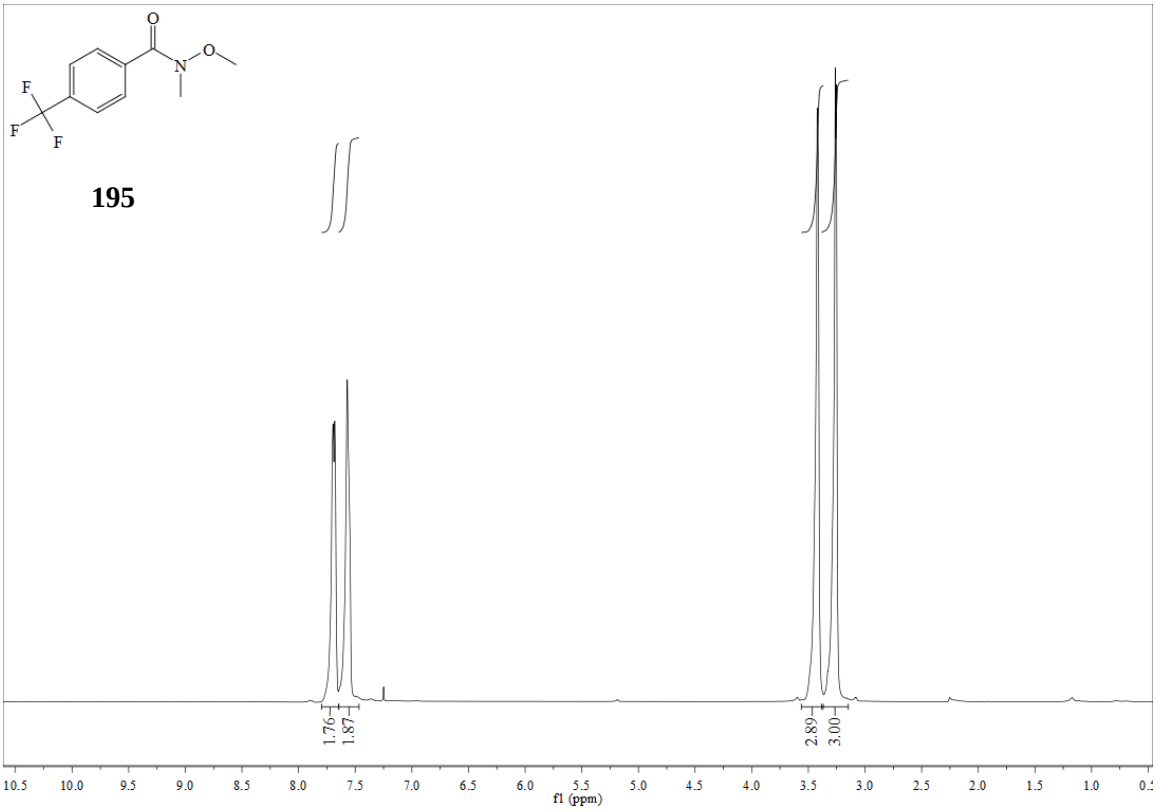
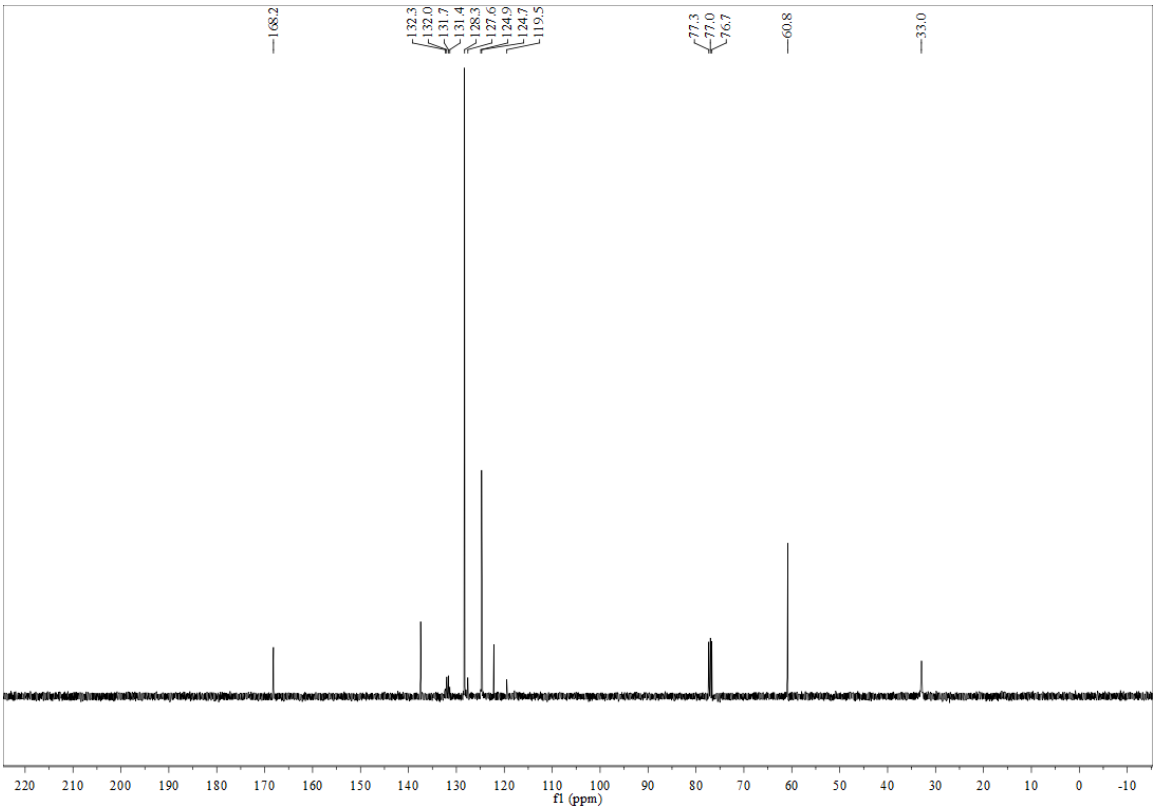
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

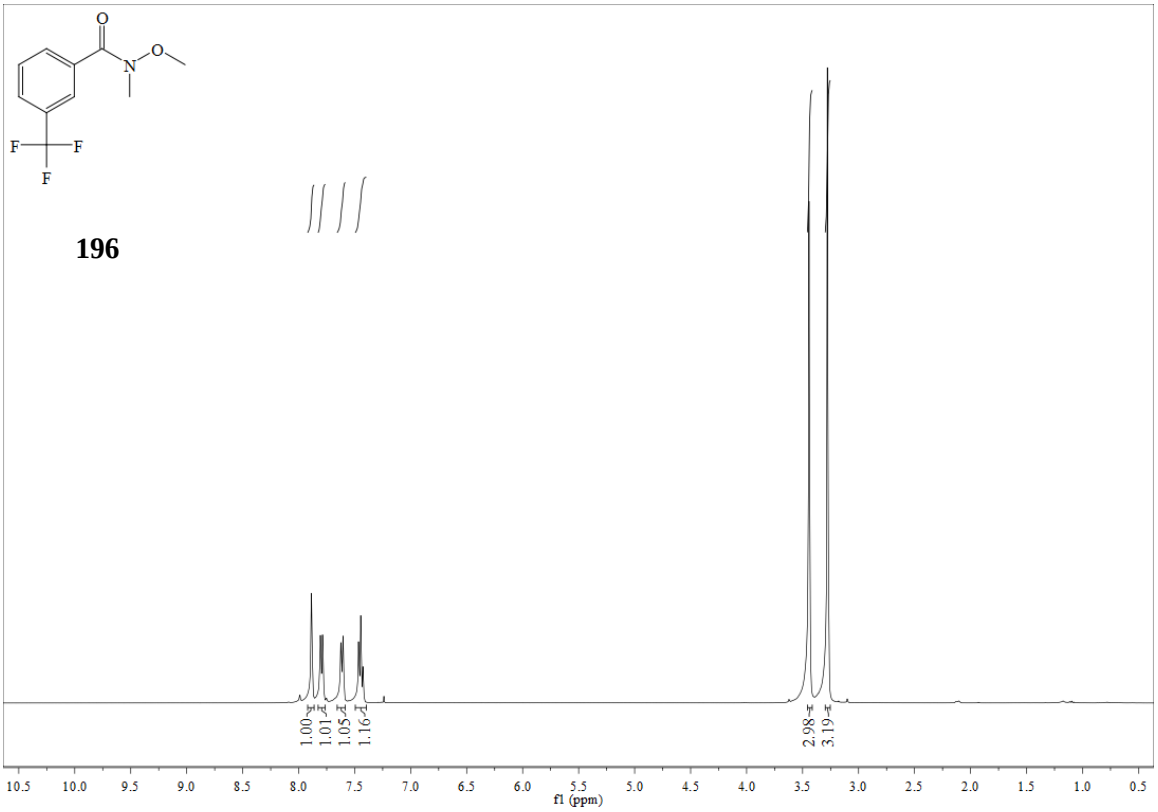

O
N
O
Cl
194
1.80
1.80
3.11
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

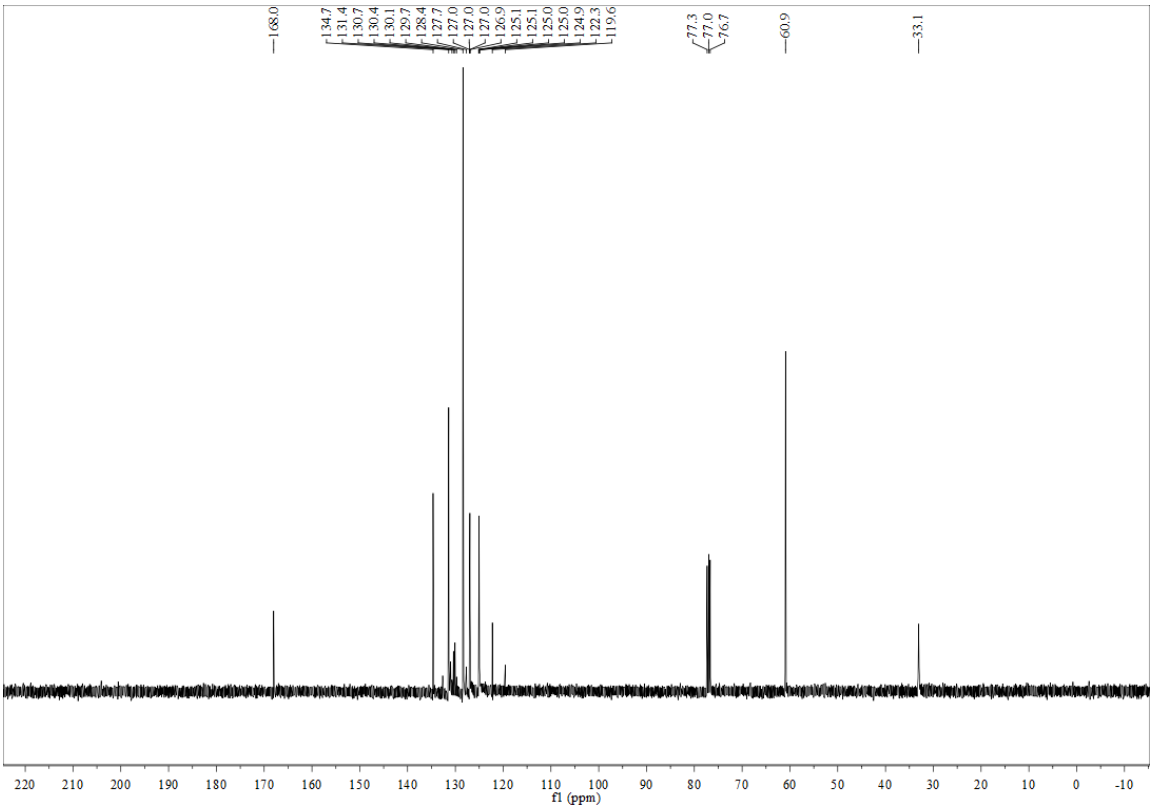

O
N
O
Cl
168.71
136.79
132.51
130.00
128.38
61.23
33.70
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

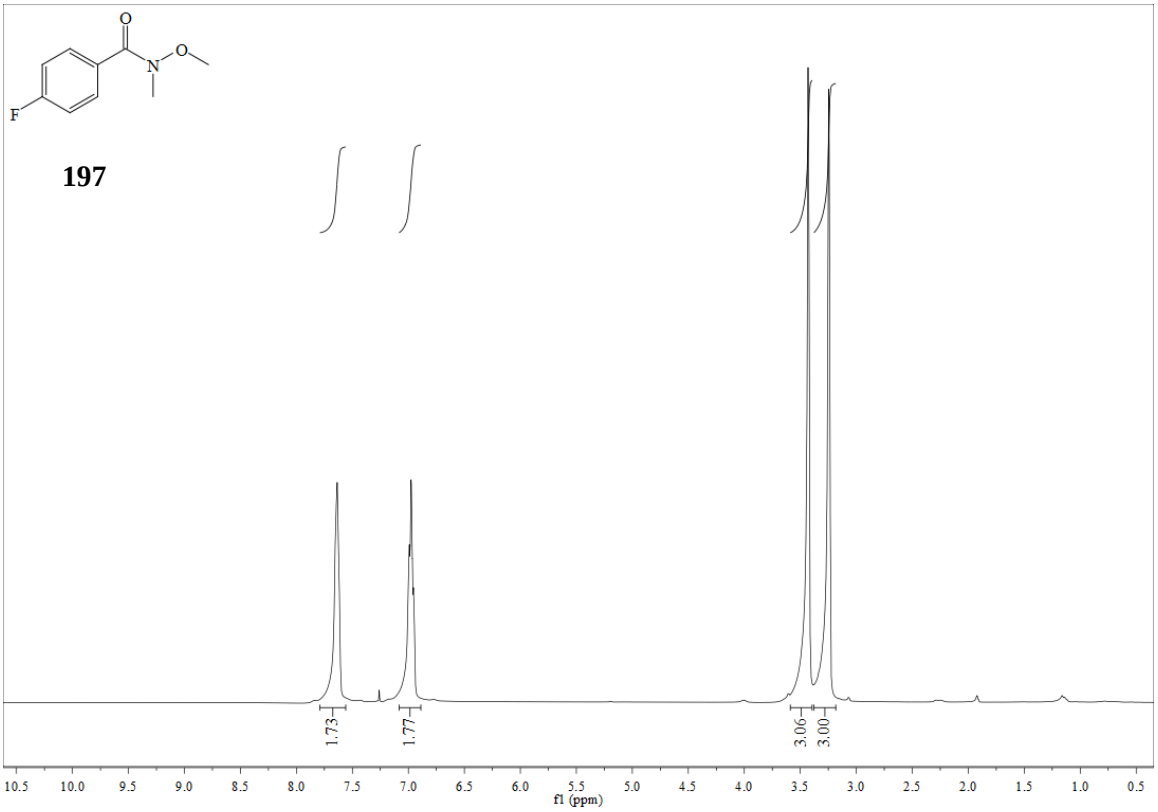

O
N
O
F
F
F
1.76
1.87
2.89
3.00
f1 (ppm)

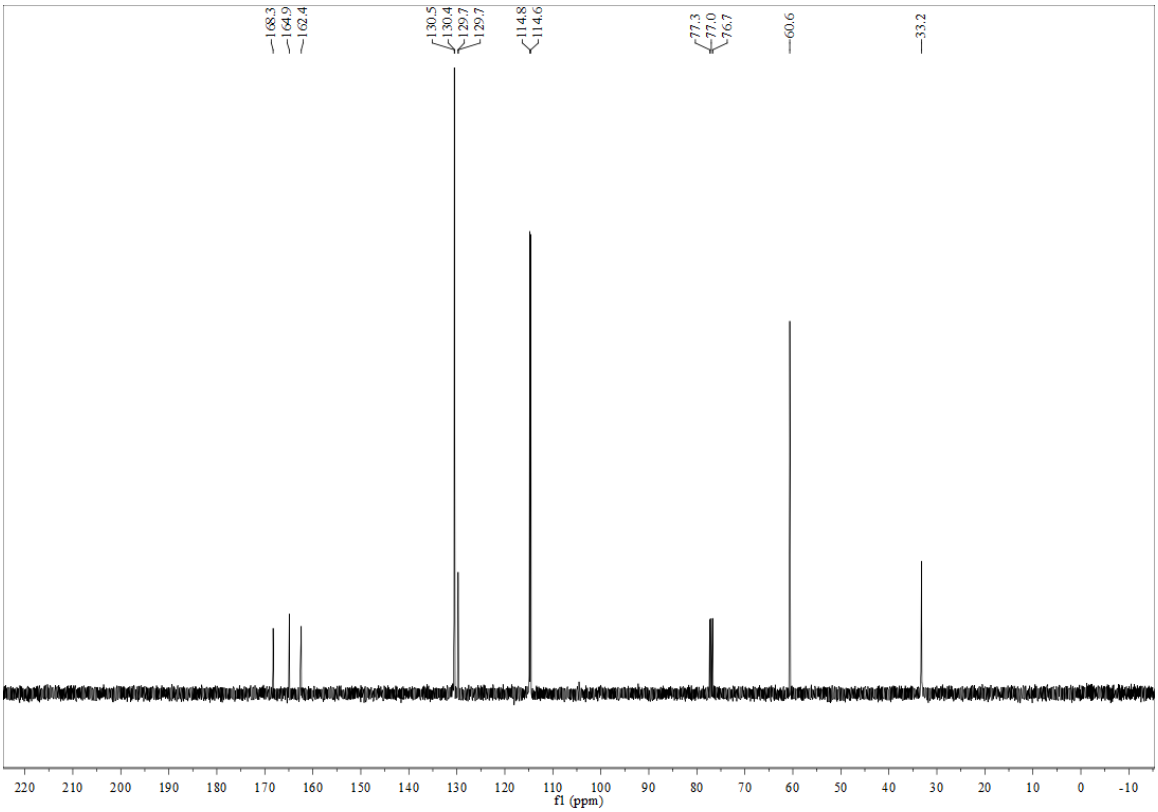
195

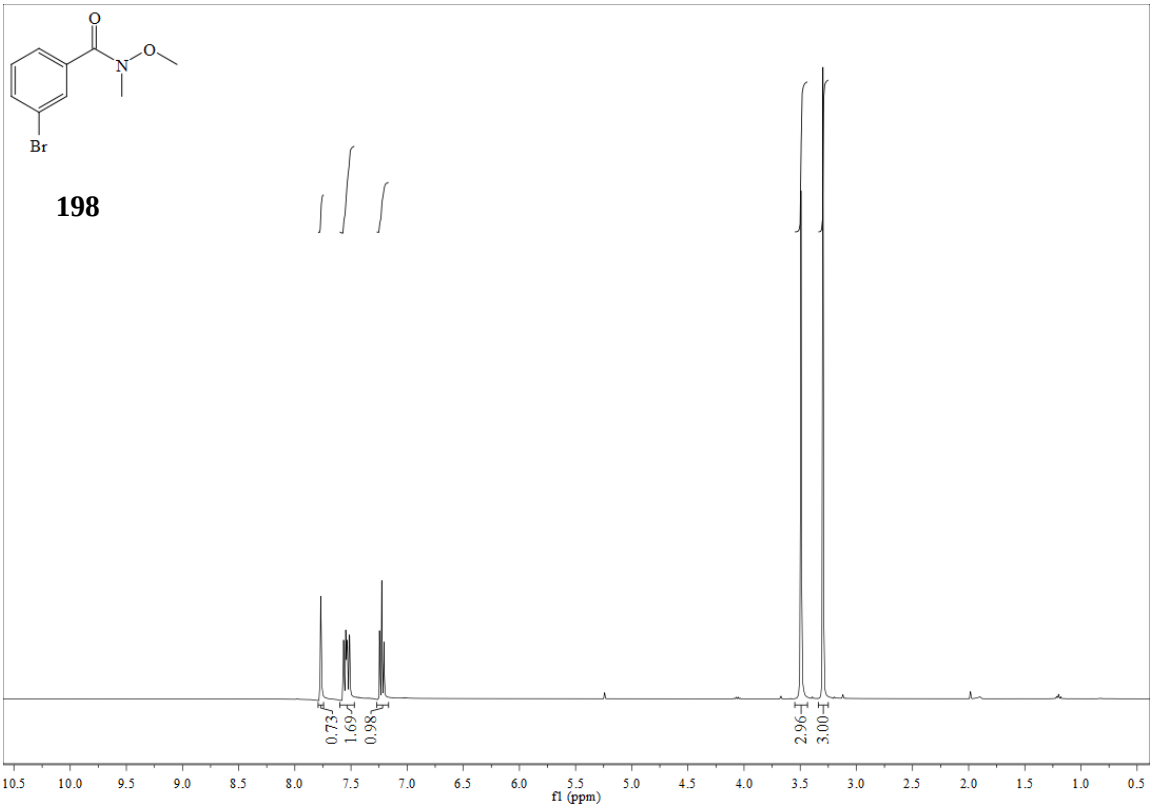

168.2
132.3
132.0
131.7
131.4
128.3
127.6
124.9
124.7
119.5
77.3
77.0
76.7
60.8
33.0
f1 (ppm)

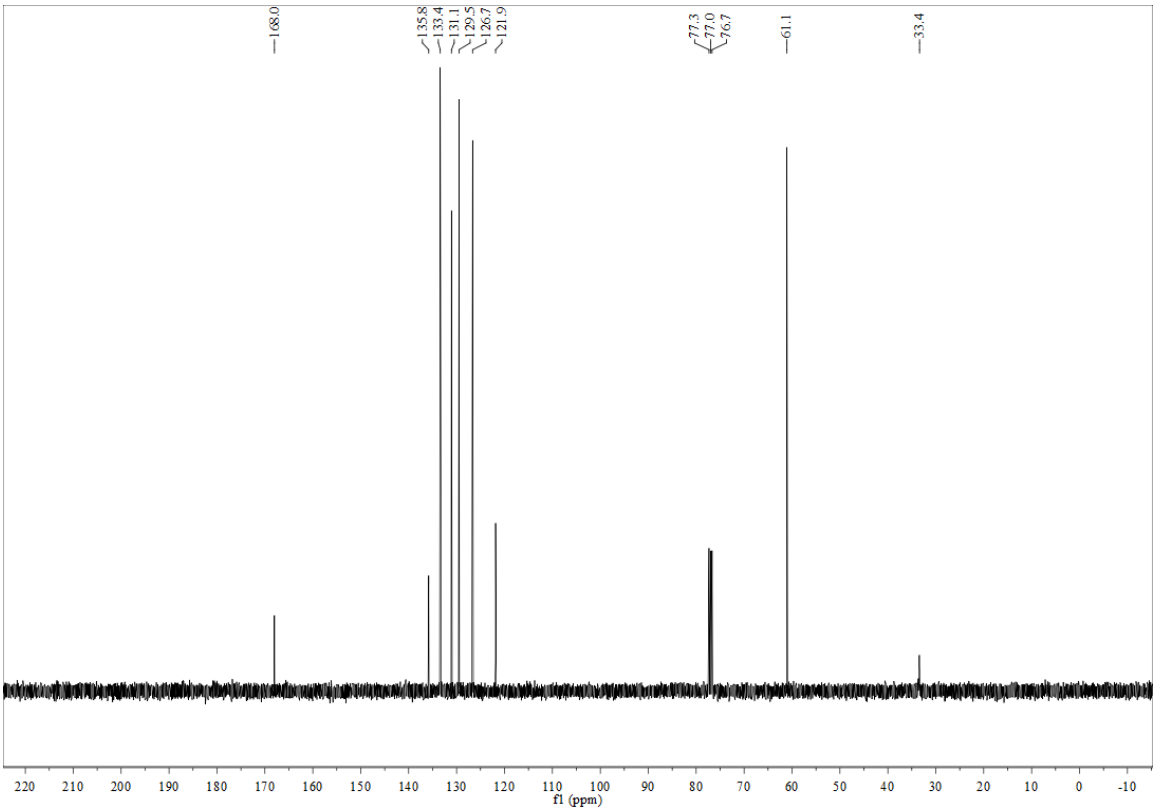

O
N
O
F
F
F
196
1.00
1.01
1.05
1.16
2.98
3.19
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

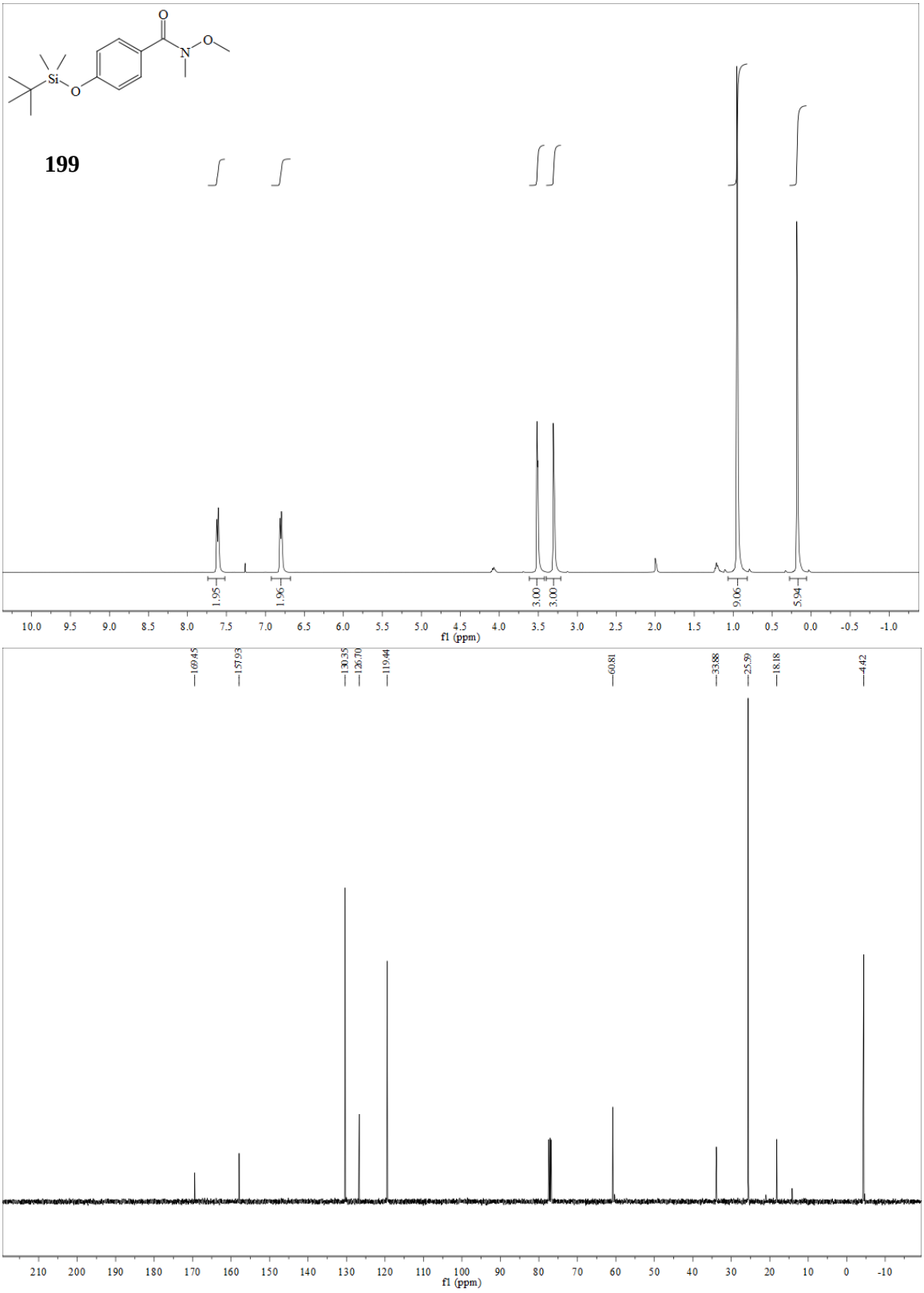

168.0
134.7
131.4
130.7
130.4
130.1
129.7
128.4
127.7
127.0
127.0
127.0
126.9
125.1
125.1
125.0
125.0
124.9
122.3
119.6
77.3
77.0
76.7
60.9
33.1
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

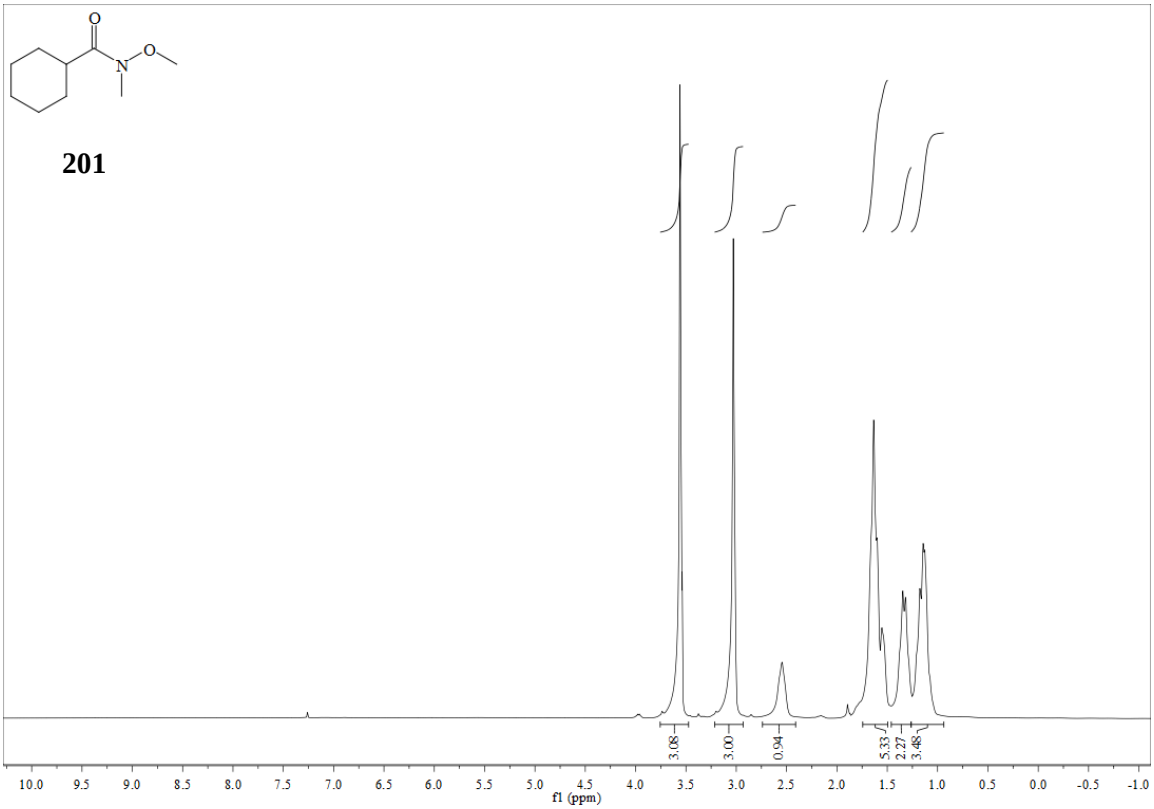

O
N
O
F
197
1.73
1.77
3.06
3.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

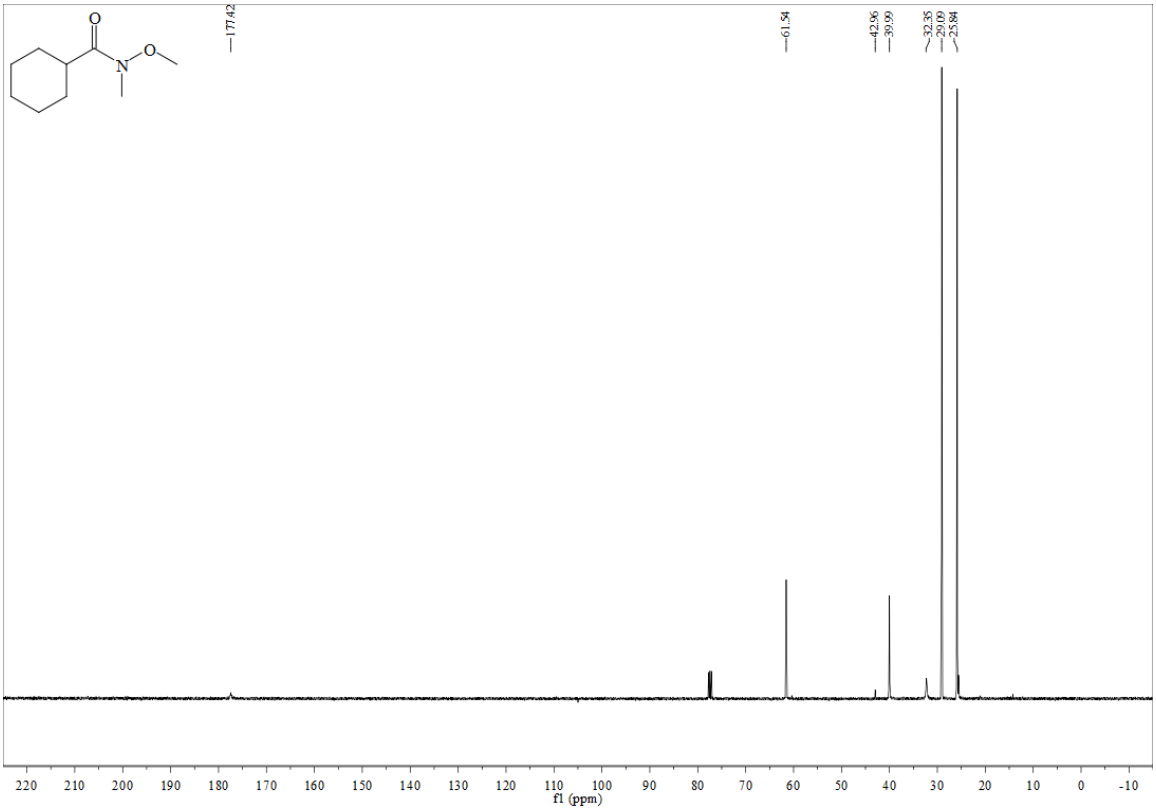

168.3
164.9
162.4
130.5
130.4
129.7
129.7
114.8
114.6
77.3
77.0
76.7
60.6
33.2
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

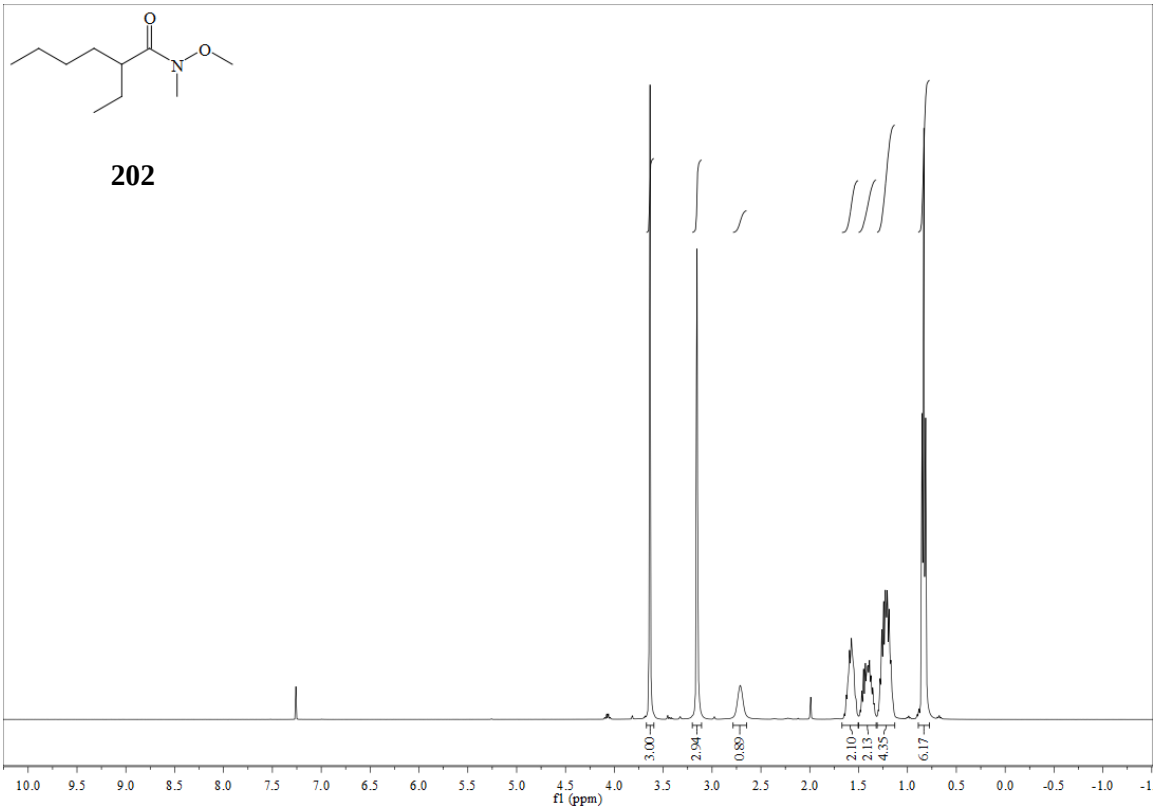

O
N
O
Br
198
0.73
1.69
0.98
2.96
3.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


168.0
135.8
133.4
131.1
129.5
126.7
121.9
77.3
77.0
76.7
61.1
33.4
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

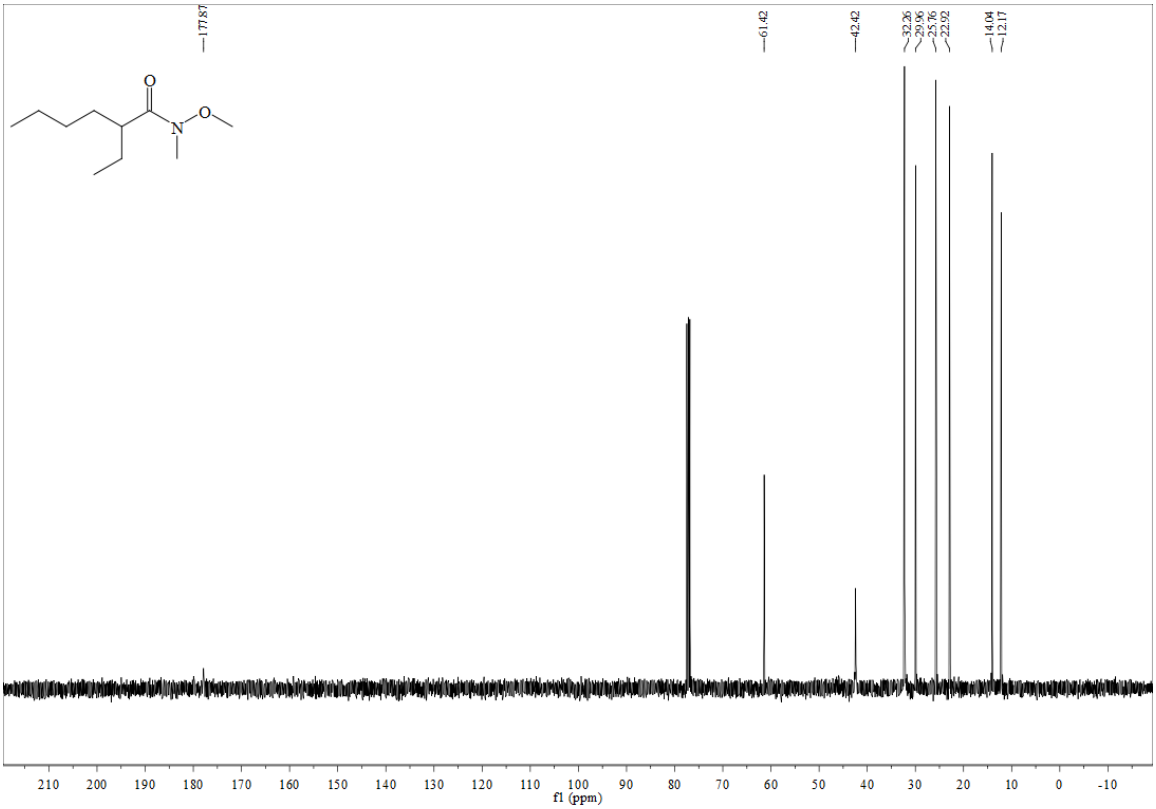

199
1.95
1.96
3.00
3.00
9.06
5.94
f1 (ppm)
169.45
157.93
130.35
126.70
119.44
60.81
33.88
25.59
18.18
-4.42
f1 (ppm)

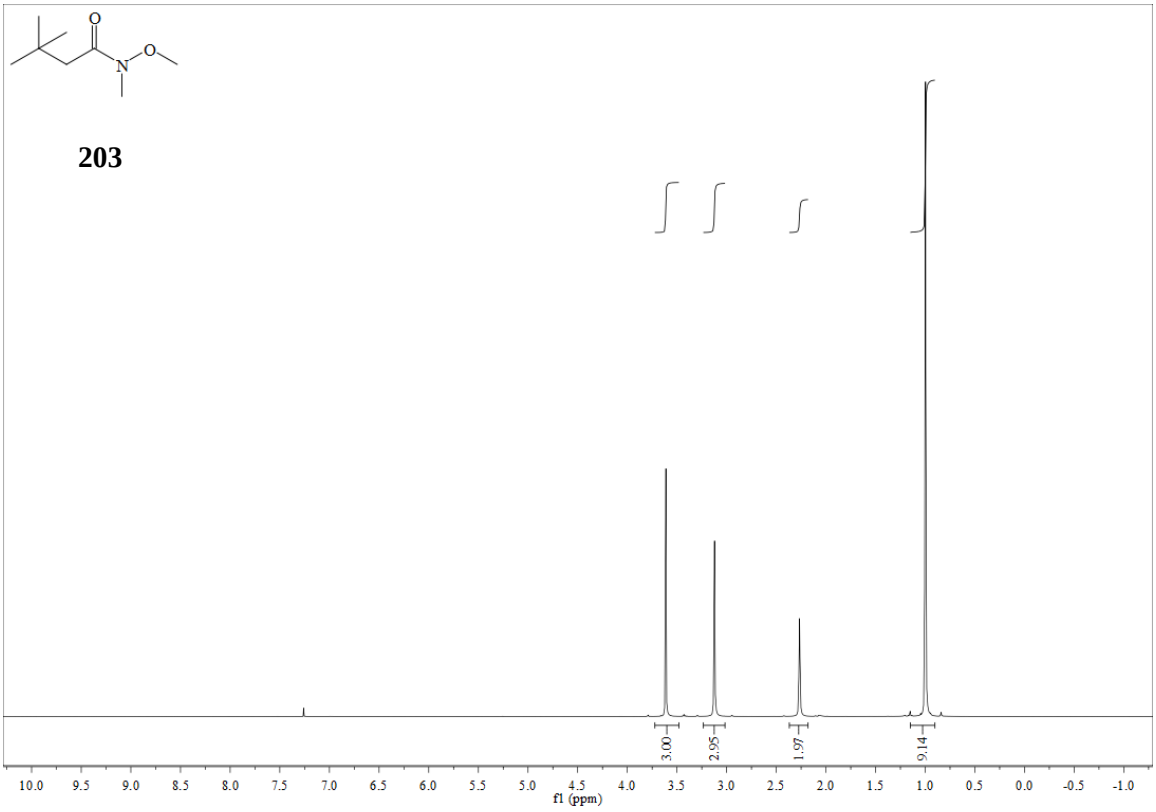

O
N
O
201
3.08
3.00
0.94
5.33
2.27
3.48
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

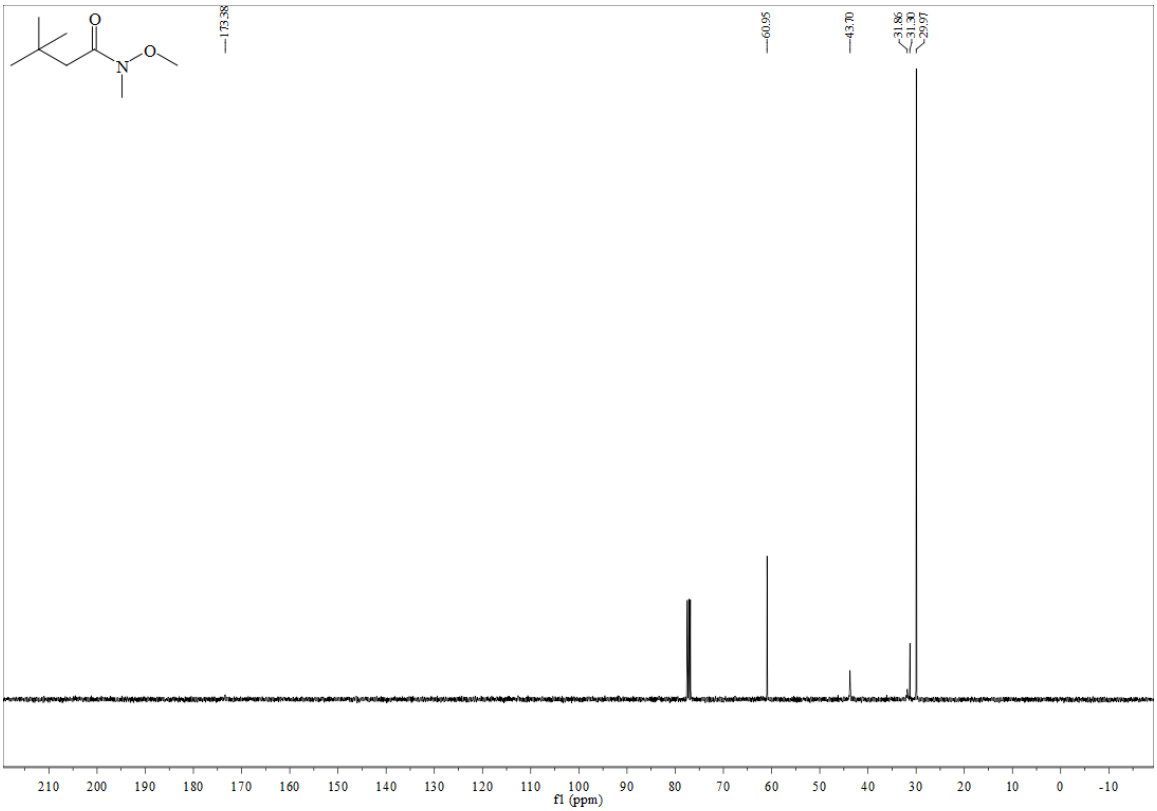

O
N
O
177.42
61.54
42.96
30.99
32.35
29.09
25.84
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

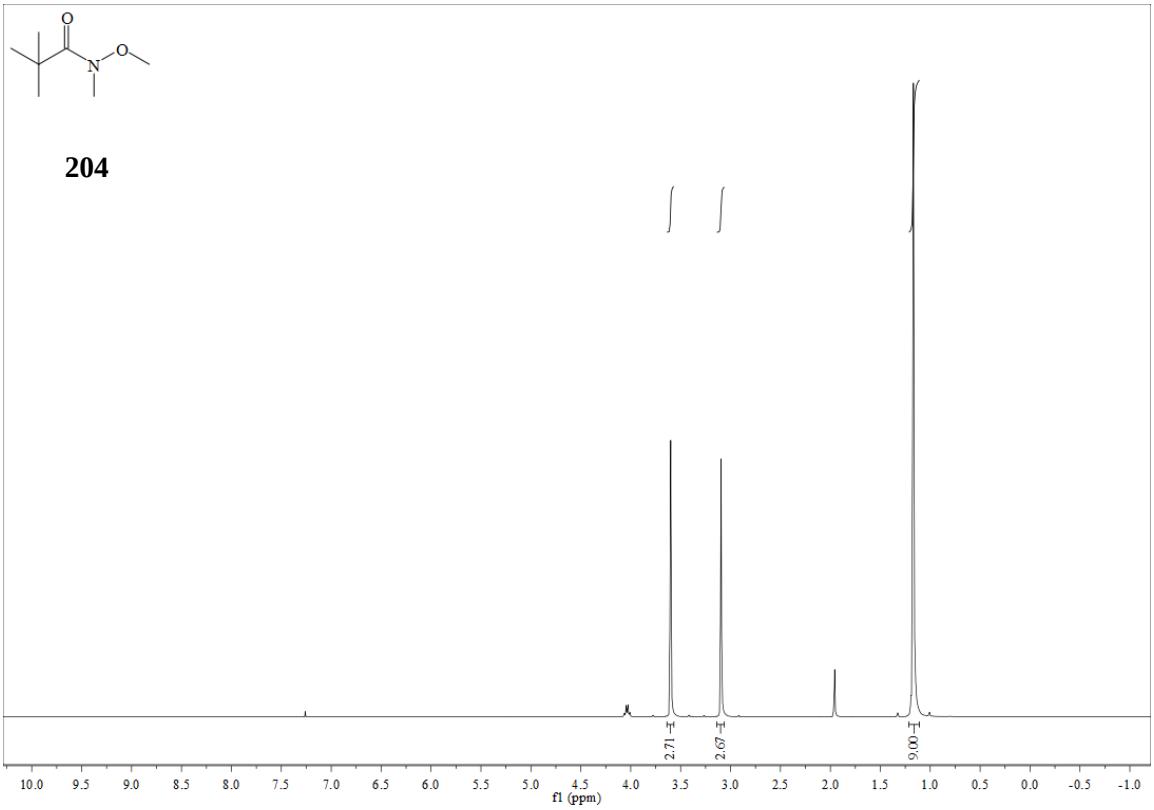

O
N
O
3.00
2.94
0.89
2.10
2.13
4.35
6.17
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1
f1 (ppm)

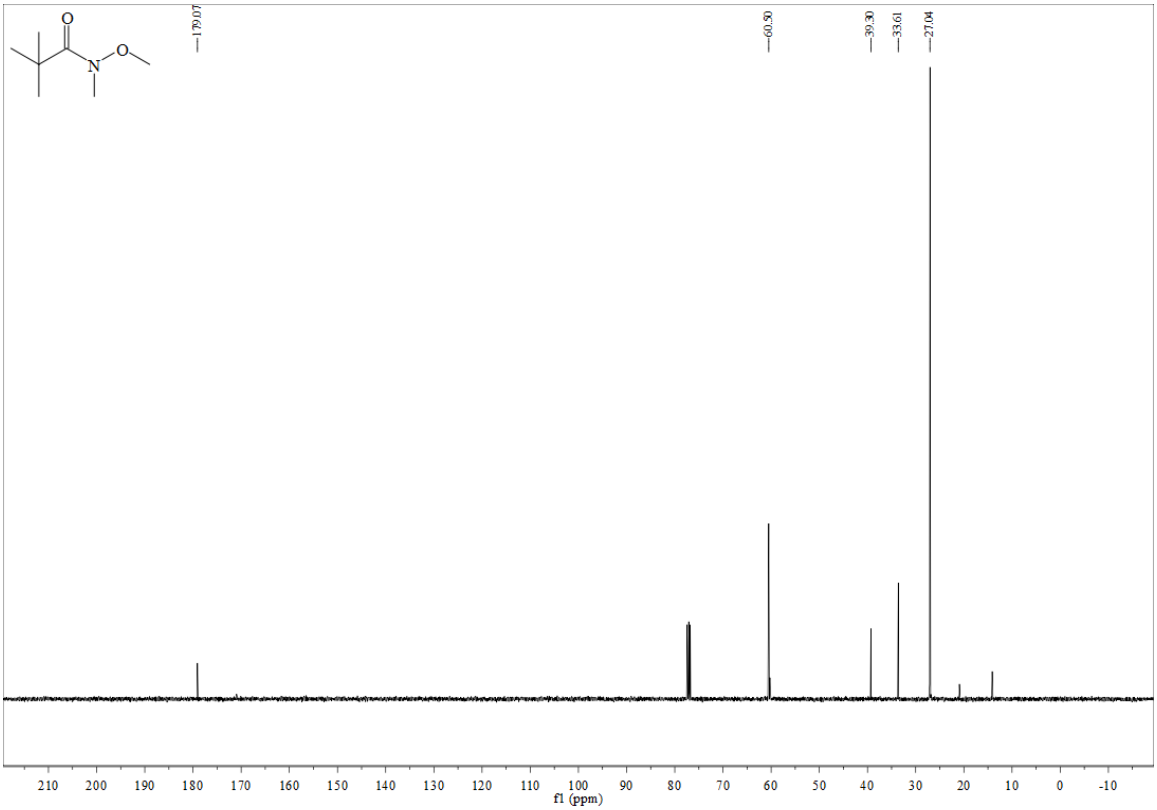
202

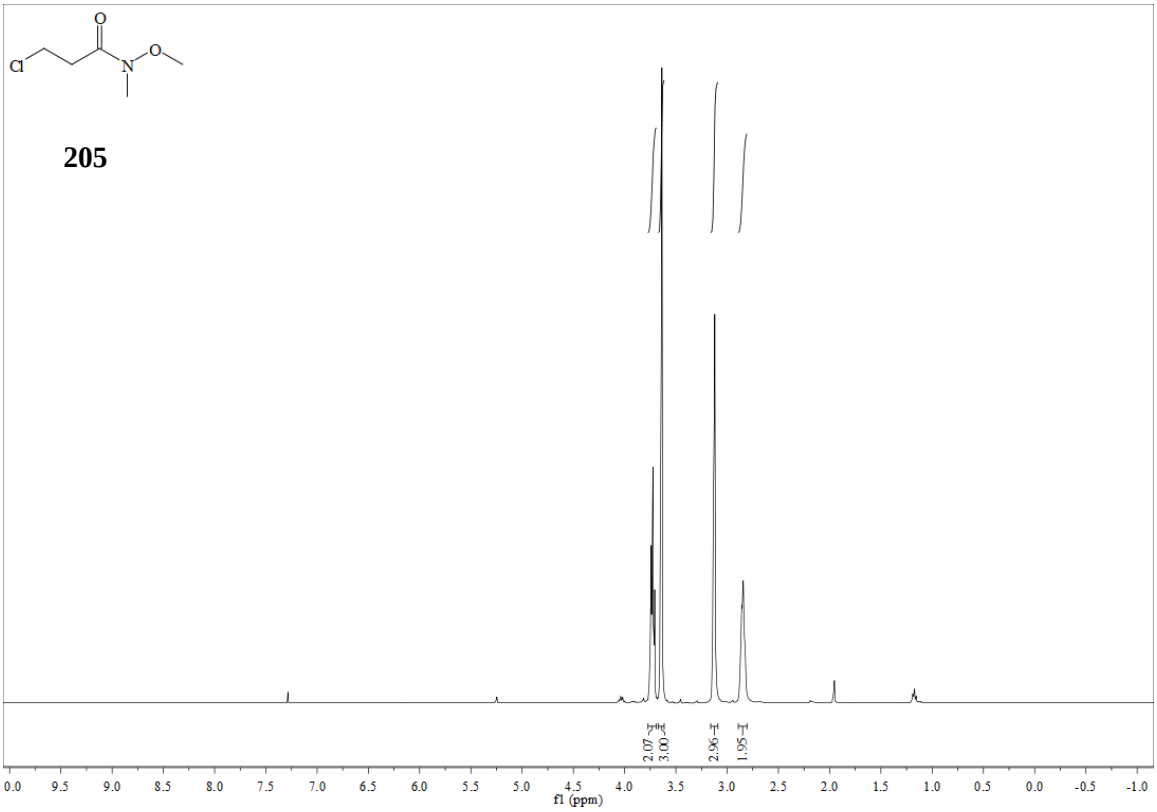

177.87
61.42
42.42
32.26
29.96
25.76
22.92
14.04
12.17
O
N
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

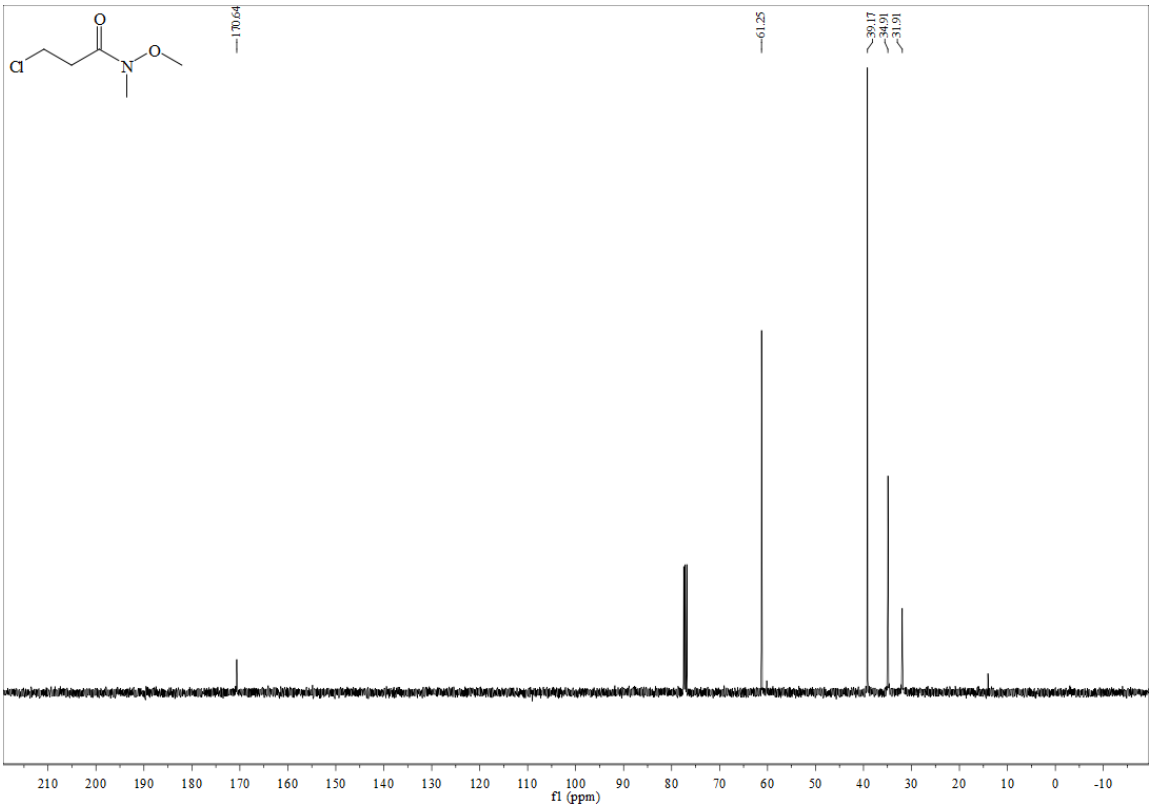

O
N
O
203
3.00
2.95
1.97
9.14
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

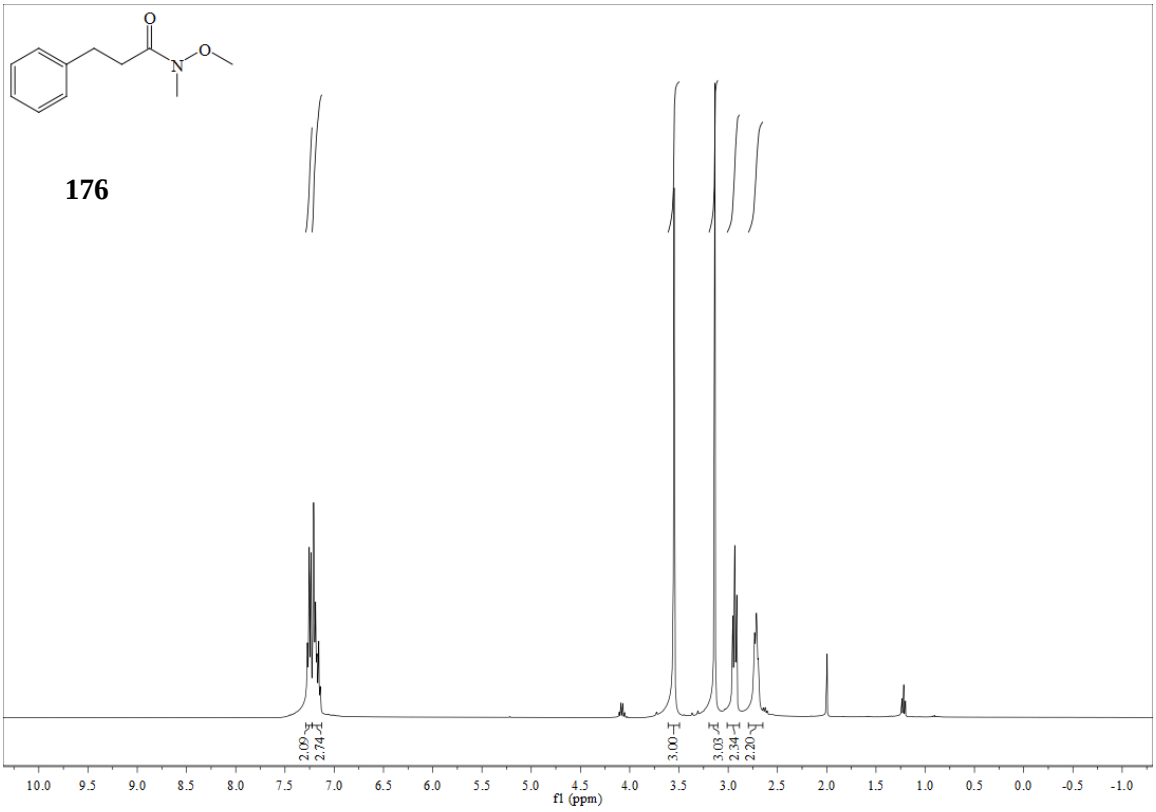

O
N
O
173.38
60.95
43.70
31.86
31.30
29.97
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

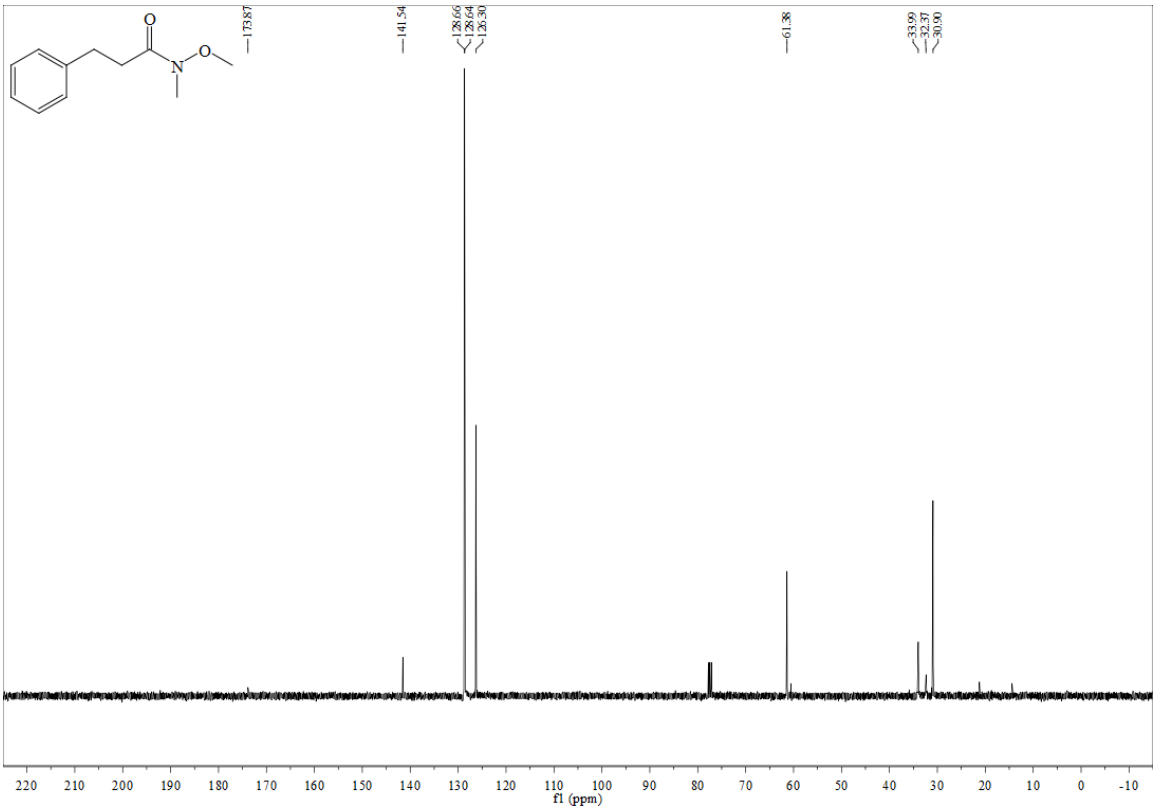

O
N
O
204
2.71
2.67
9.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

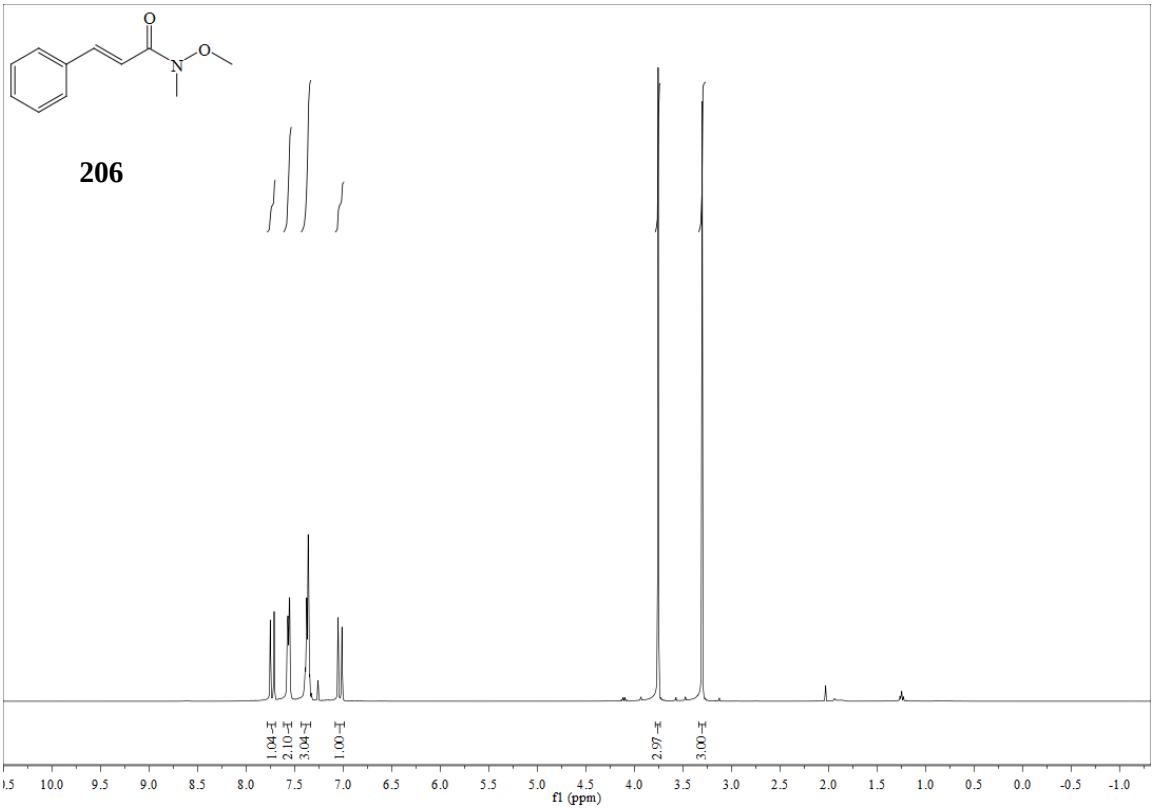

O
N
O
179.07
60.50
39.30
33.61
27.04
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

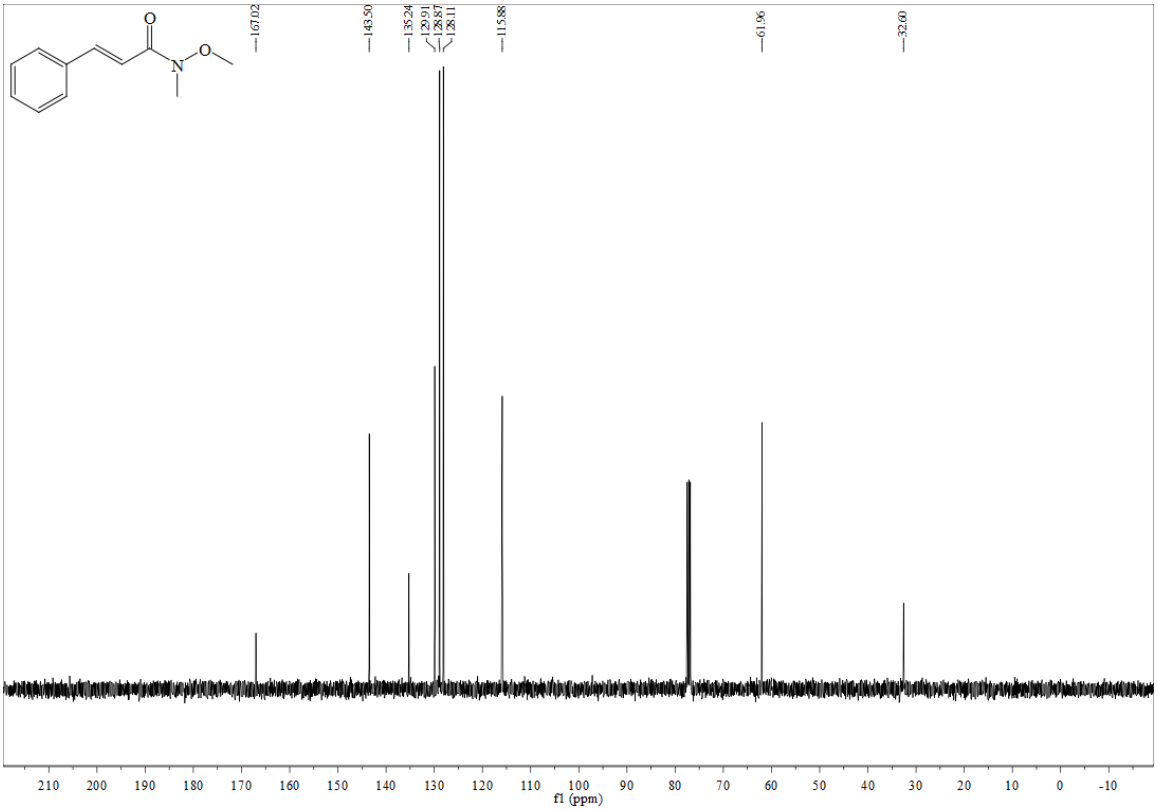

Cl
O
N
O
205
2.07
3.00
2.96
1.95
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

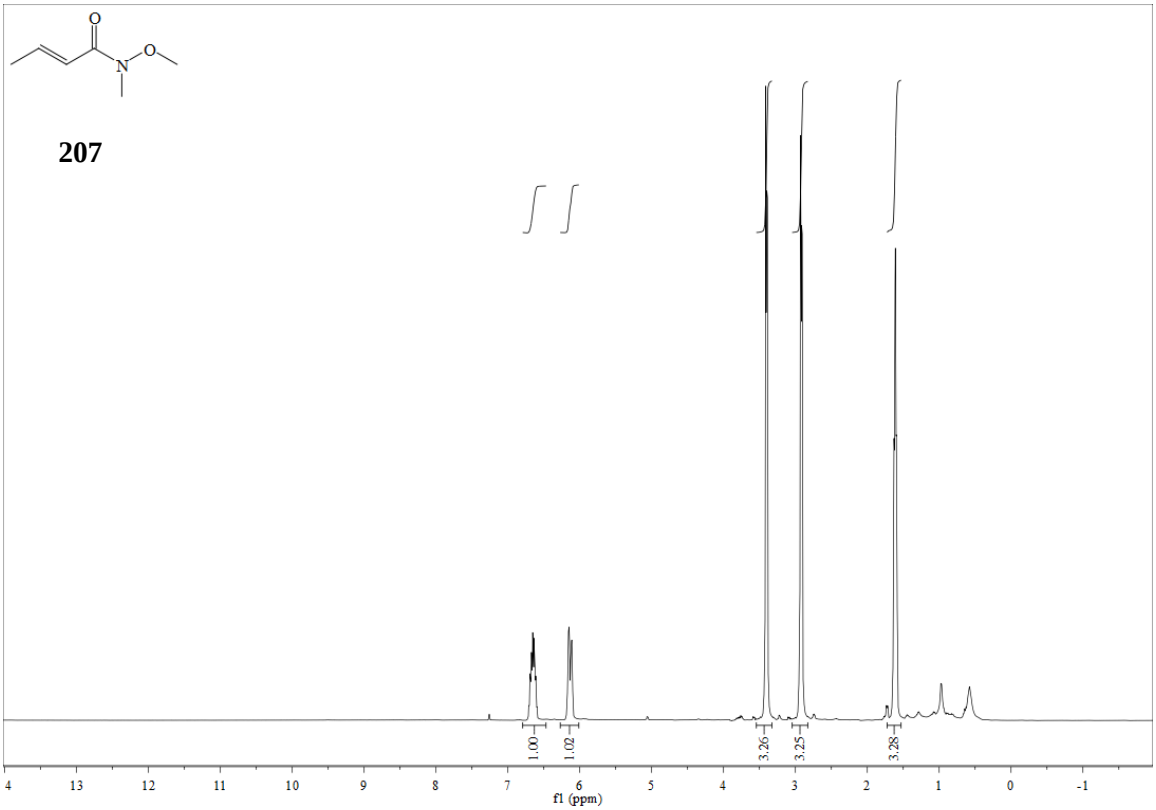

Cl
O
N
O
170.64
61.25
39.17
34.91
31.91
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

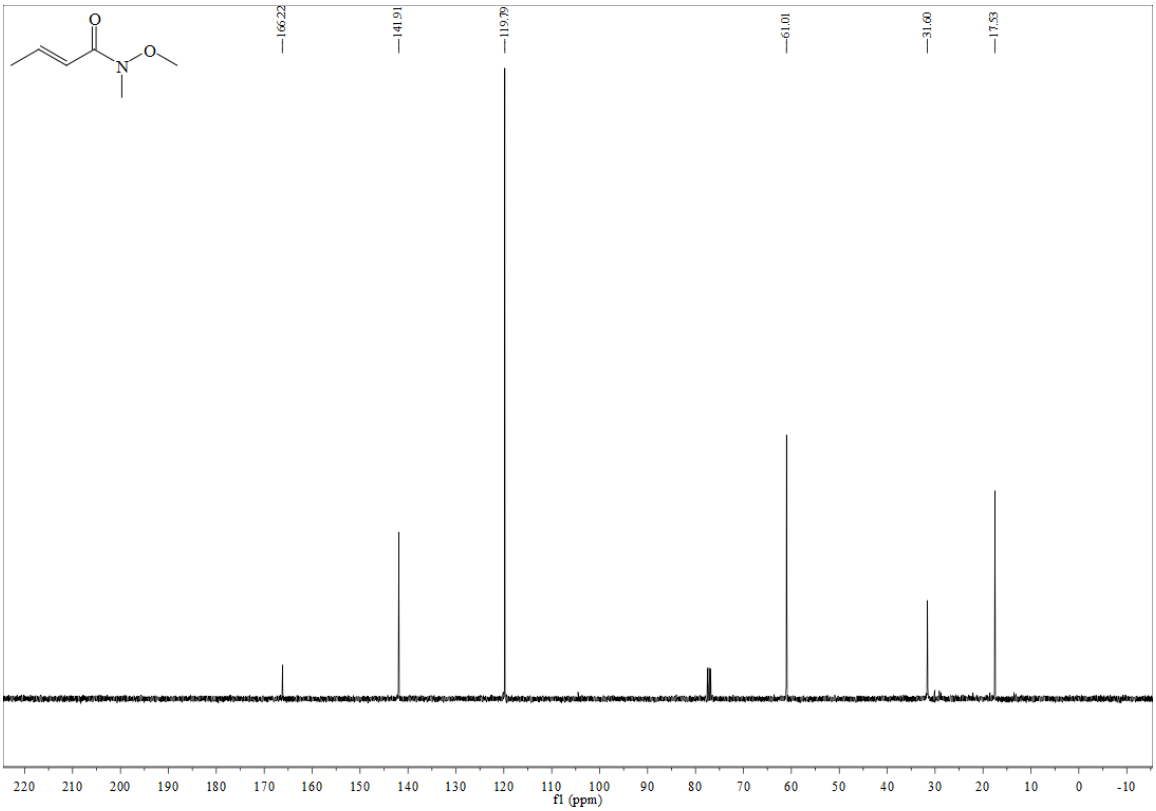

O
N
O
176
2.09
2.74
3.00
3.03
2.34
2.20
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

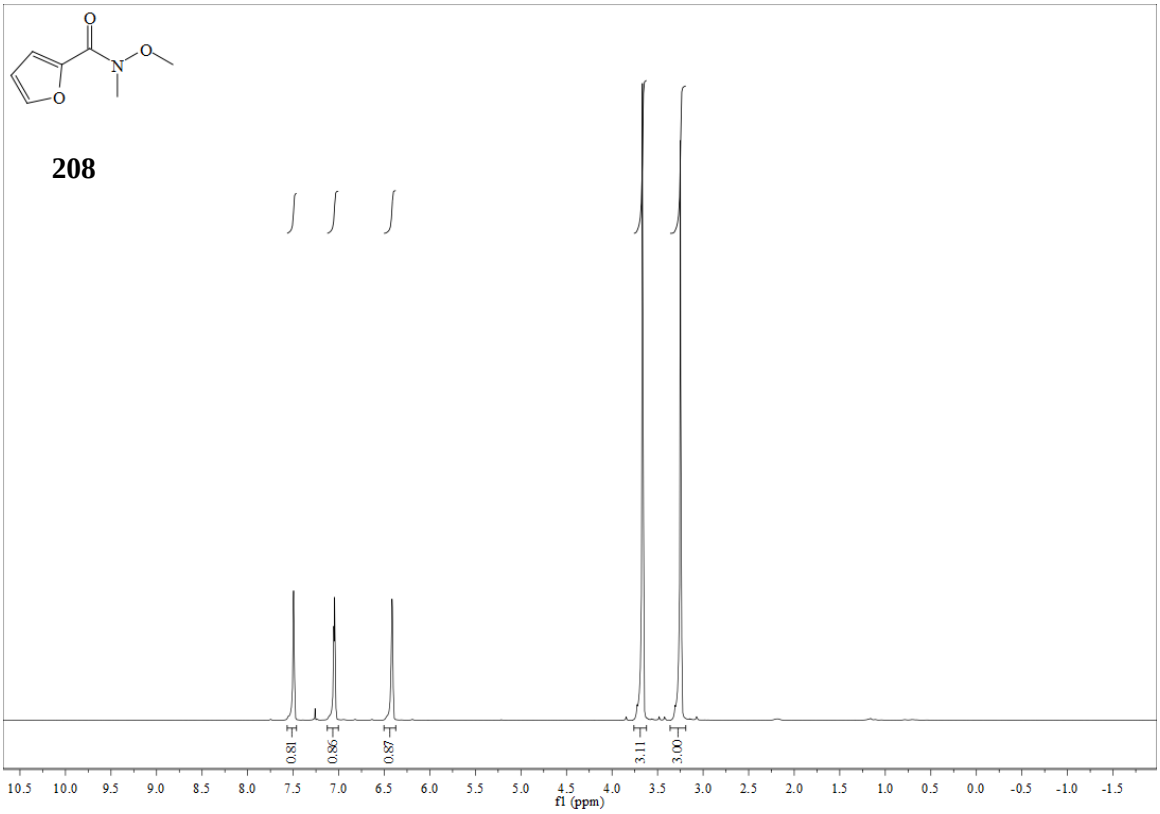

O
N
O
173.87
141.54
129.66
128.64
126.30
61.38
33.99
32.37
30.90
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

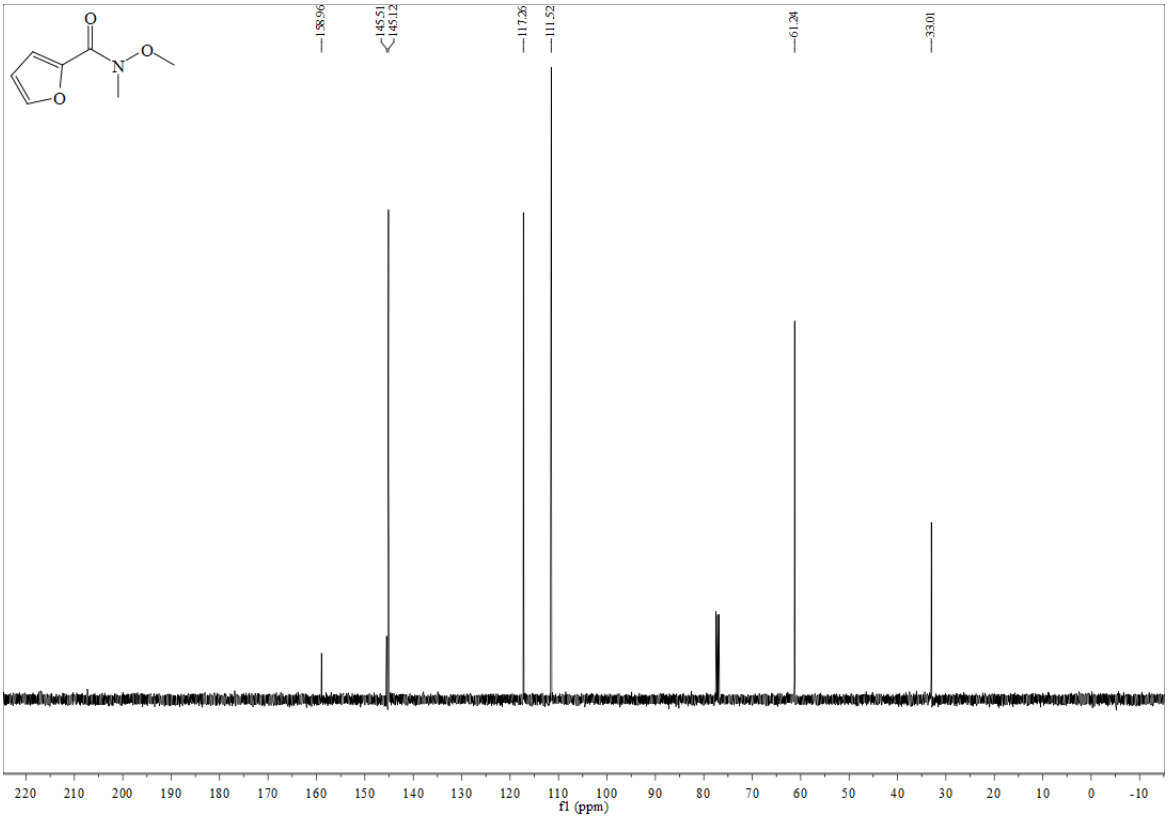

O
N
O
206
1.04
2.10
3.04
1.00
2.97
3.00
f1 (ppm)

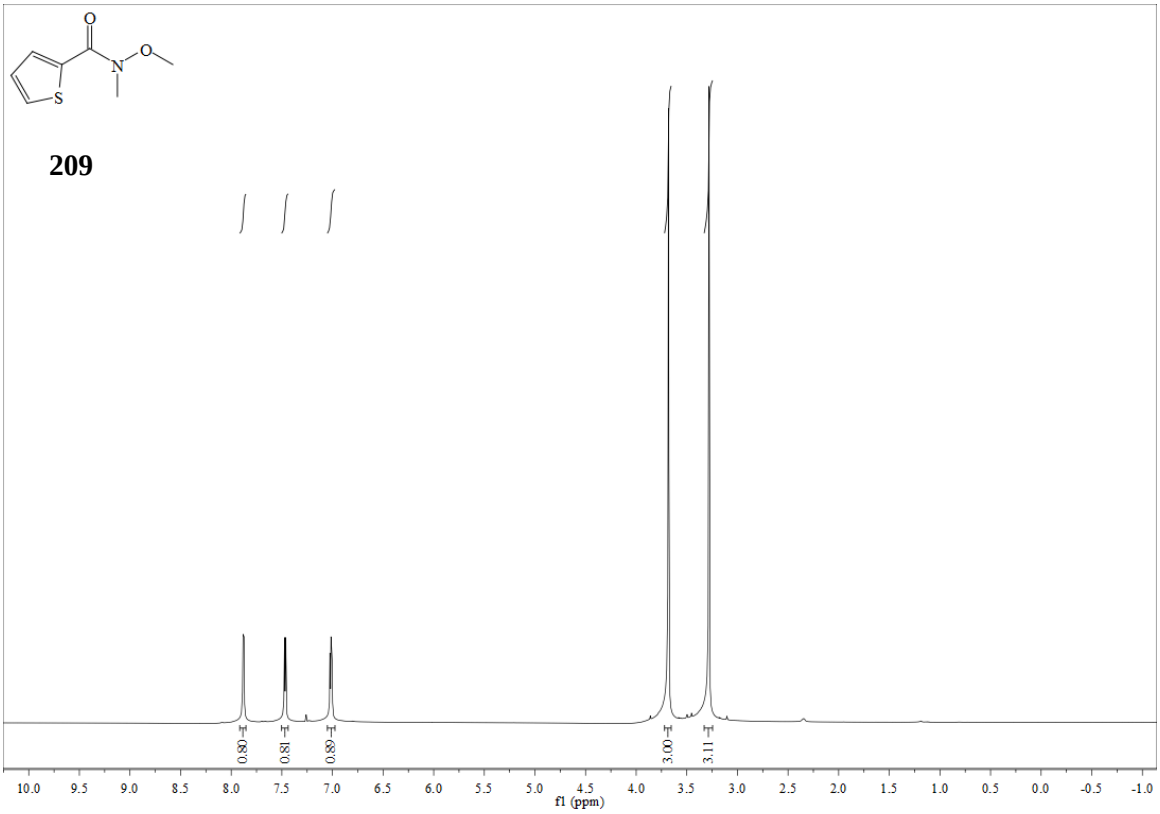

O
N
O
167.02
143.50
135.24
129.91
128.87
128.11
115.88
61.96
32.60
f1 (ppm)

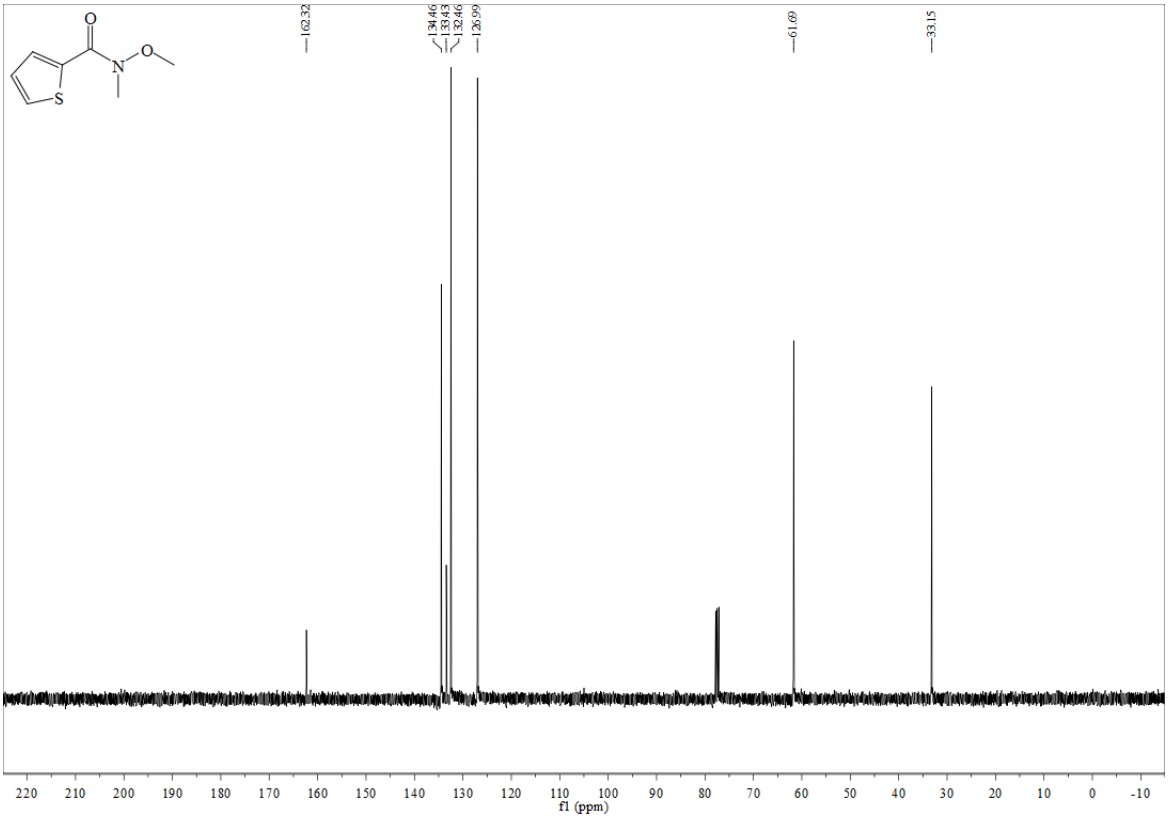

O
N
O
207
1.00
1.02
3.26
3.25
3.28
4
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

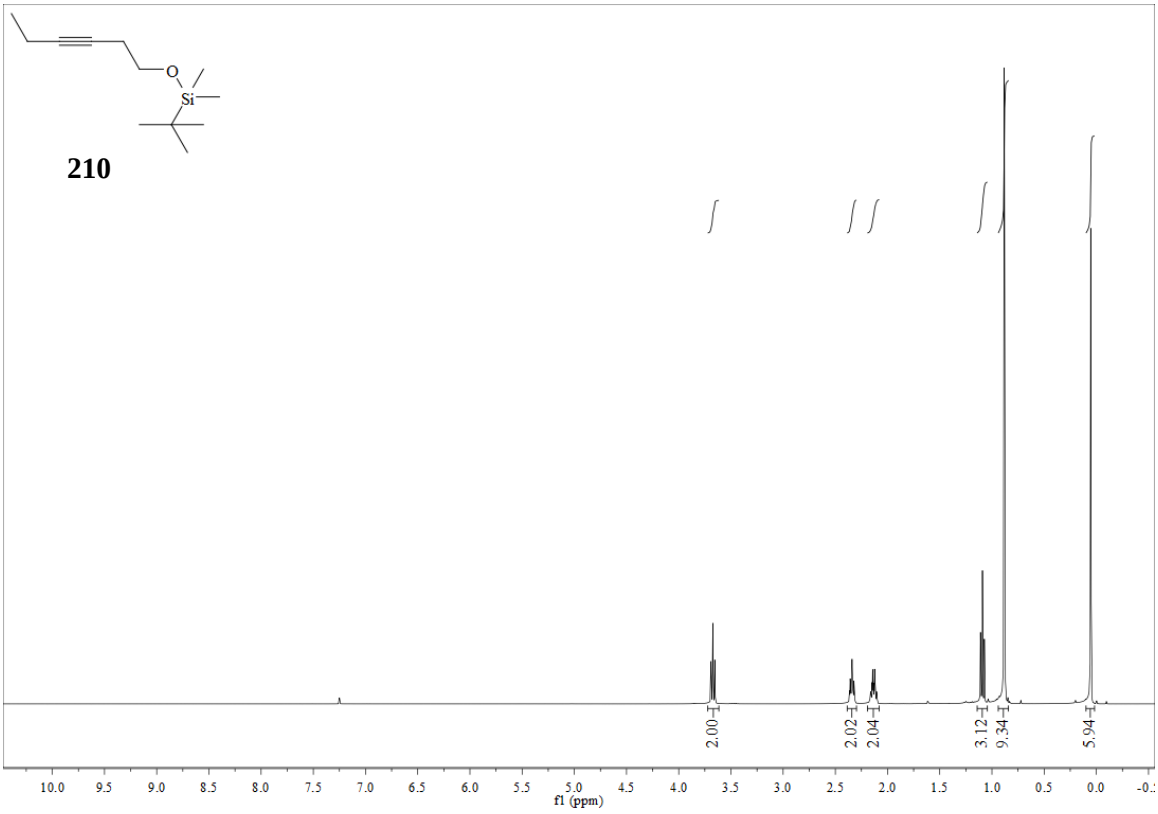

O
N
O
166.22
141.91
119.79
61.01
31.60
17.53
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
N
O
O
208
0.81
0.86
0.87
3.11
3.00
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 -1.0 -1.5
f1 (ppm)

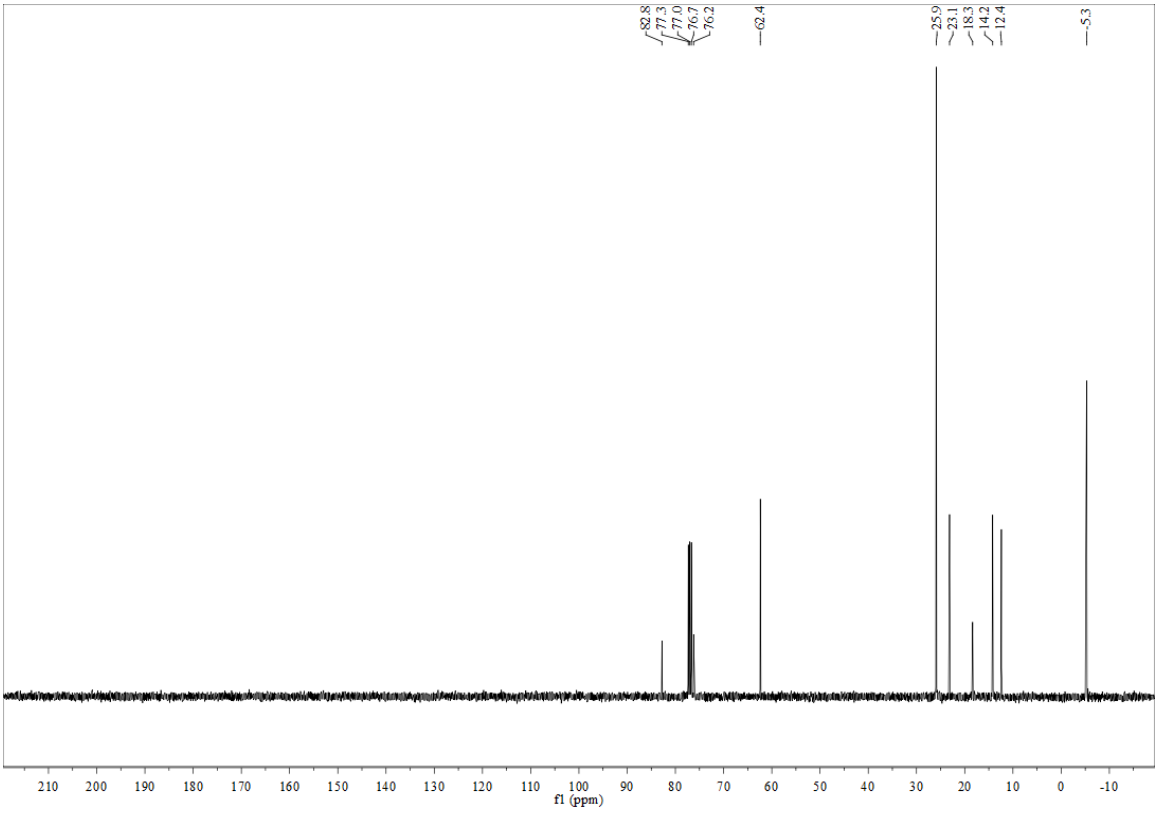

O
N
O
O
158.96
145.51
145.12
117.26
111.52
61.24
33.01
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

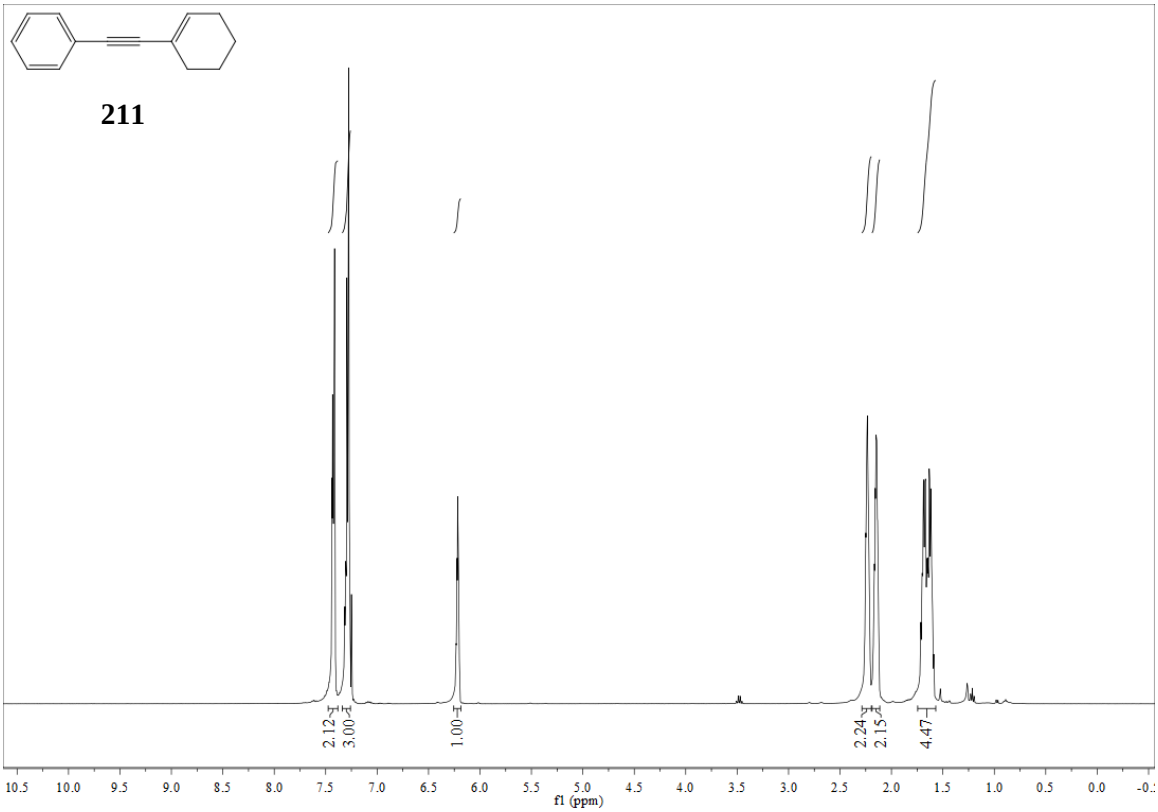

O
N
O
S
209
0.80
0.81
0.89
3.00
3.11
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

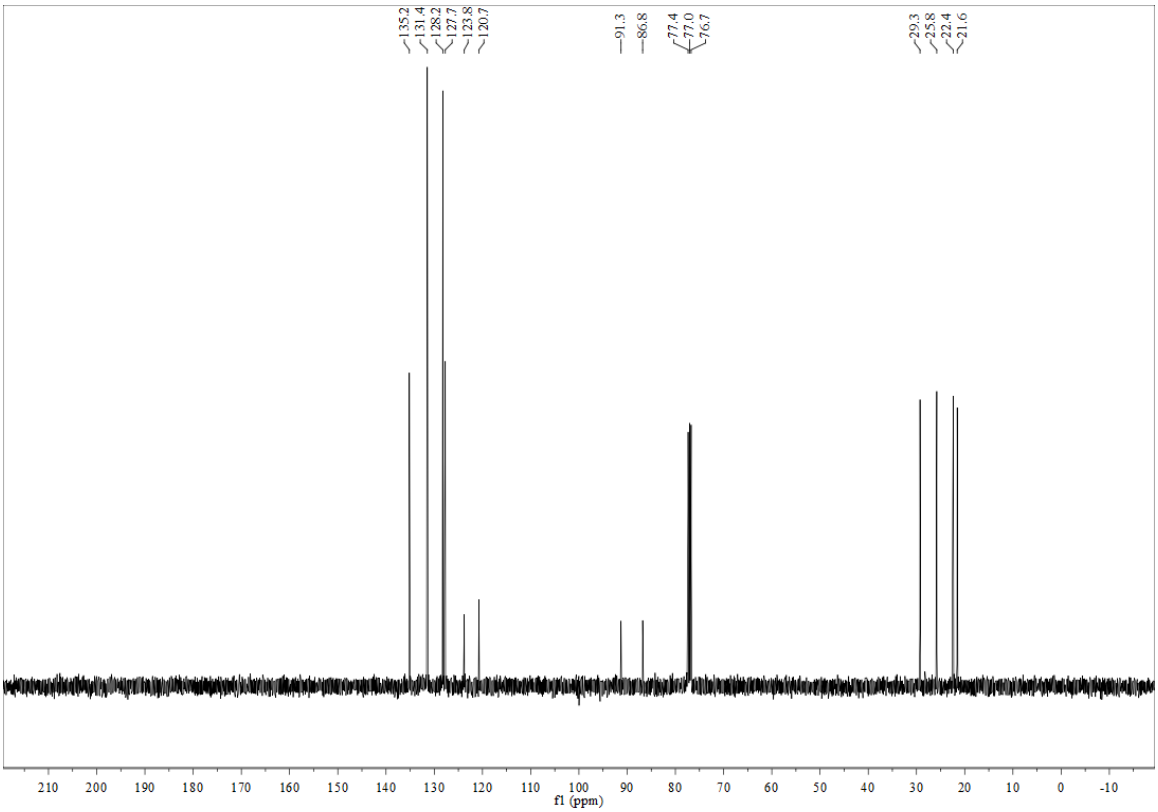

O
N
O
S
162.32
134.46
133.43
132.46
126.99
61.69
33.15
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

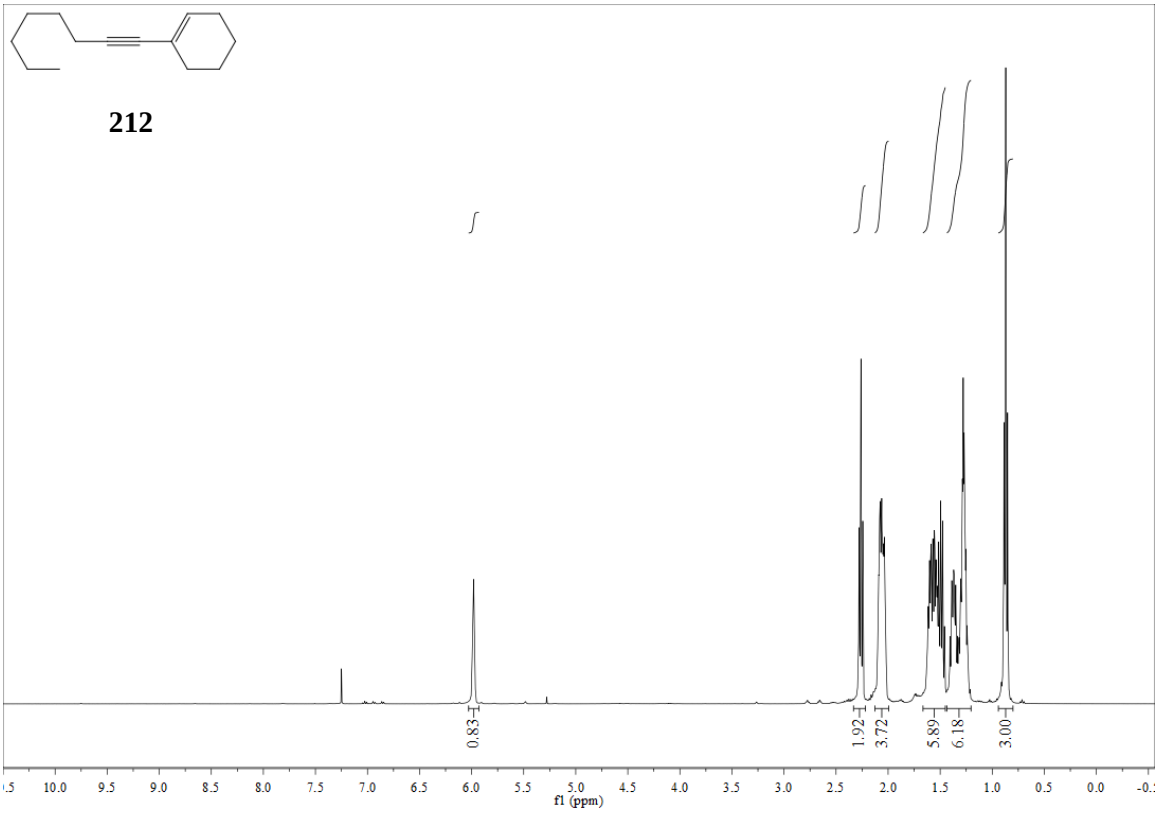

O
Si
2.00
2.02
2.04
3.12
9.34
5.94
f1 (ppm)

210


82.8
77.3
77.0
76.7
76.2
62.4
25.9
23.1
18.3
14.2
12.4
-5.3
f1 (ppm)

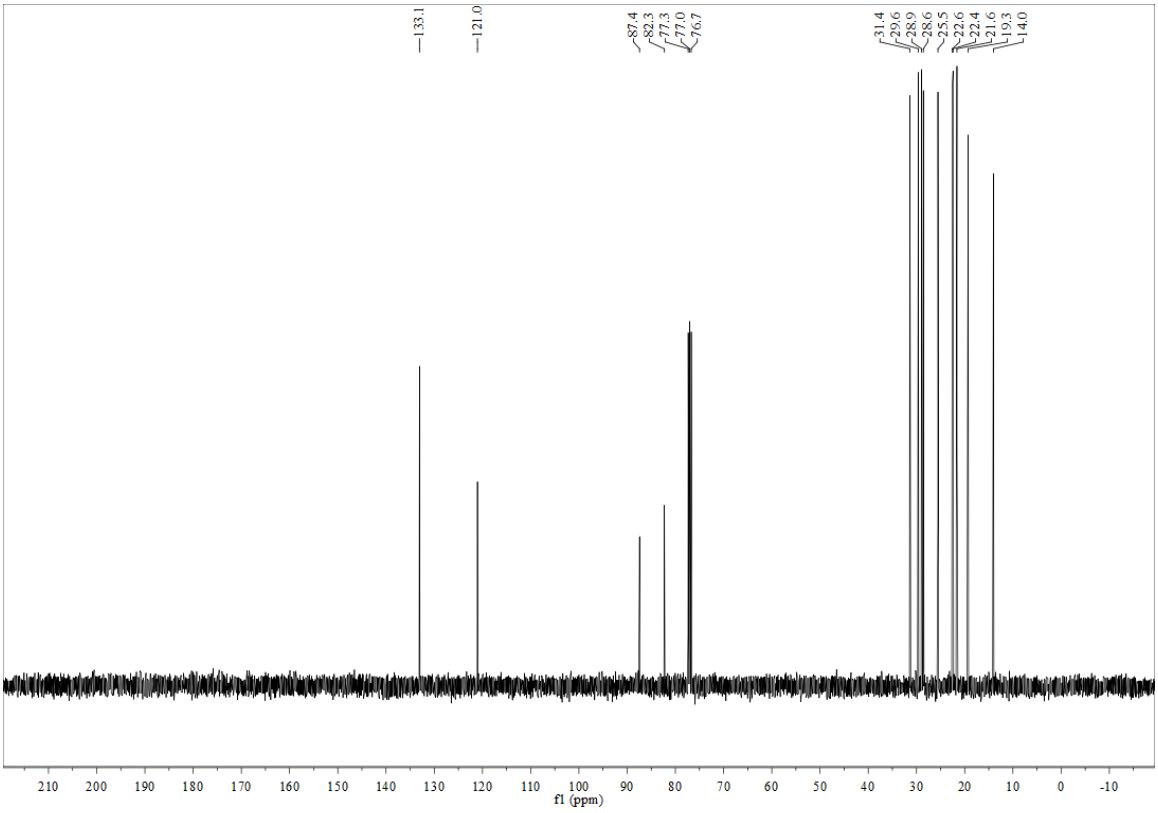

211
2.12
3.00
1.00
2.24
2.15
4.47
f1 (ppm)


135.2
131.4
128.2
127.7
123.8
120.7
91.3
86.8
77.4
77.0
76.7
29.3
25.8
22.4
21.6
f1 (ppm)

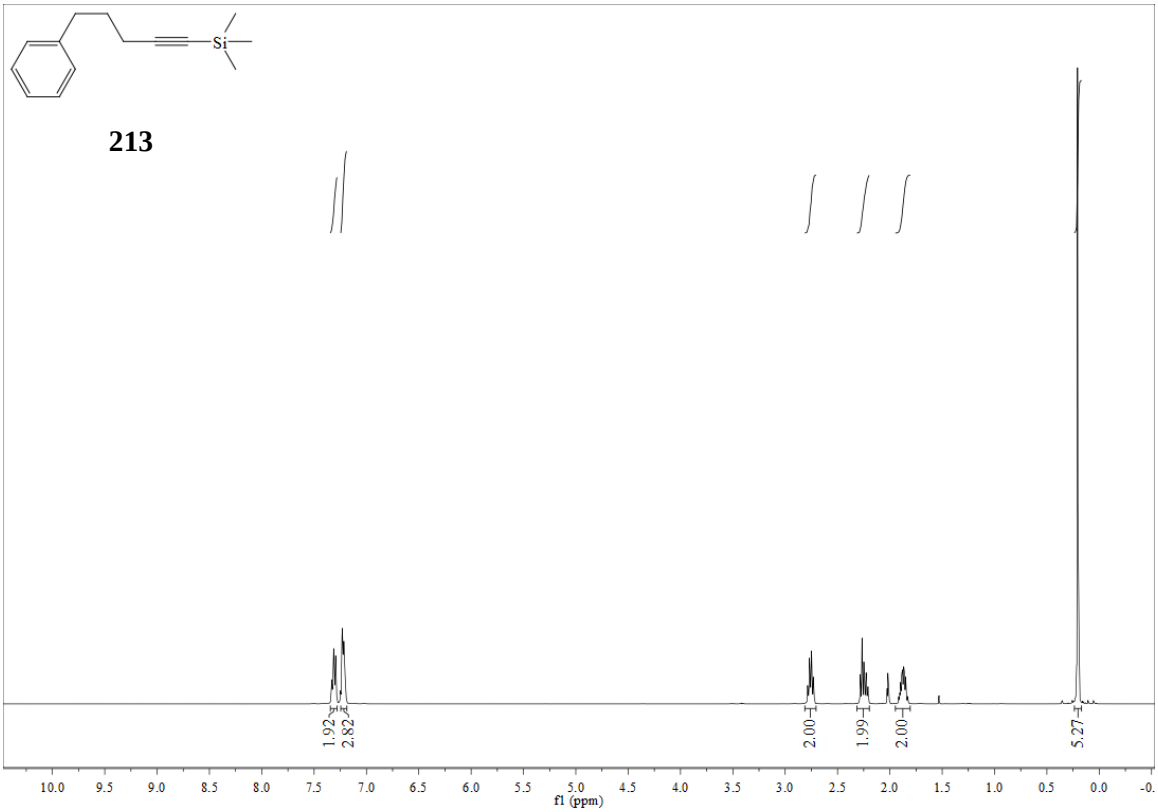


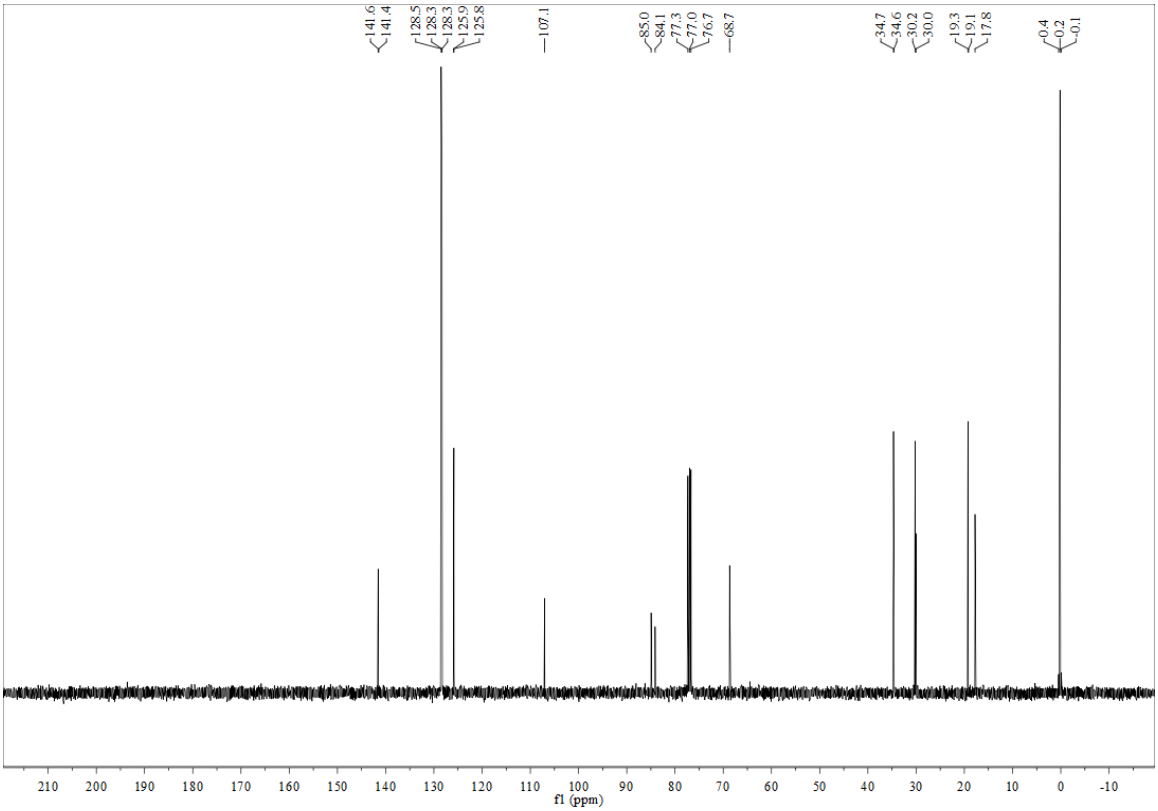
212

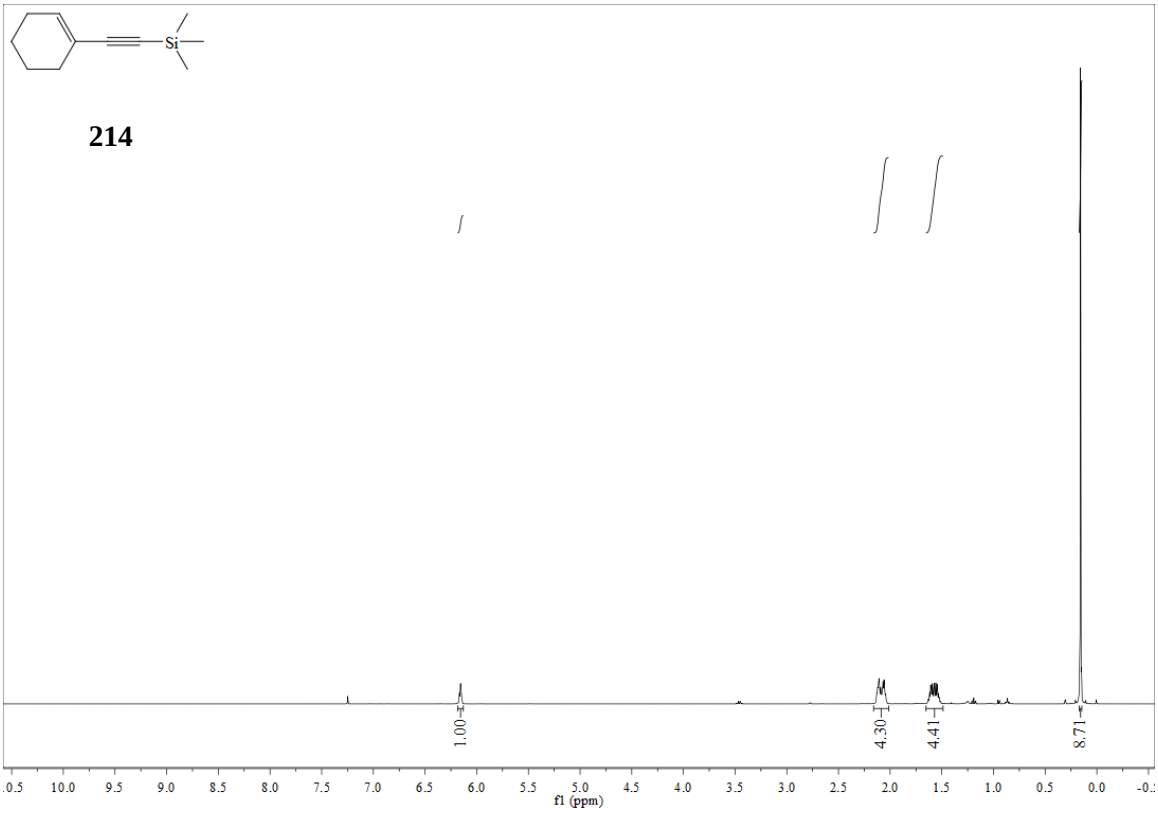
0.83
1.92
3.72
5.89
6.18
3.00
f1 (ppm)



133.1
121.0
87.4
82.3
77.3
77.0
76.7
31.4
29.6
28.9
28.6
25.5
22.6
22.4
21.6
19.3
14.0
f1 (ppm)

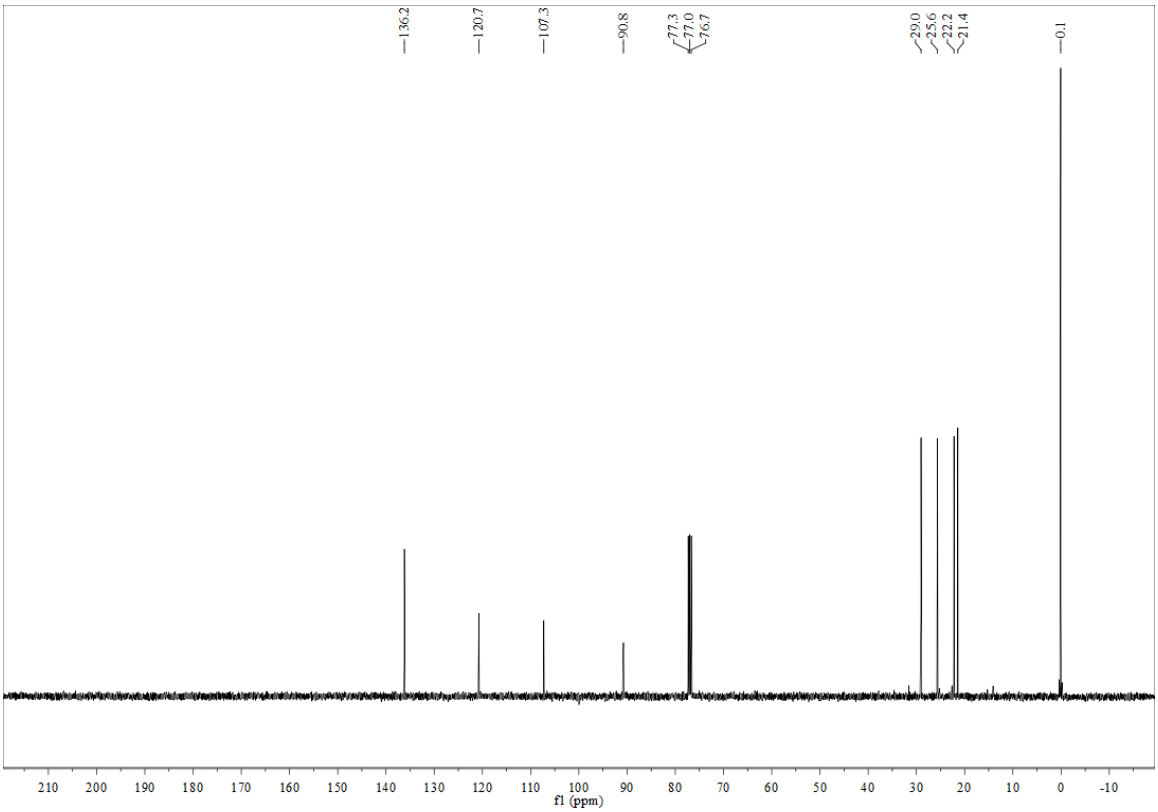

Si
213
1.92
2.82
2.00
1.99
2.00
5.27
f1 (ppm)

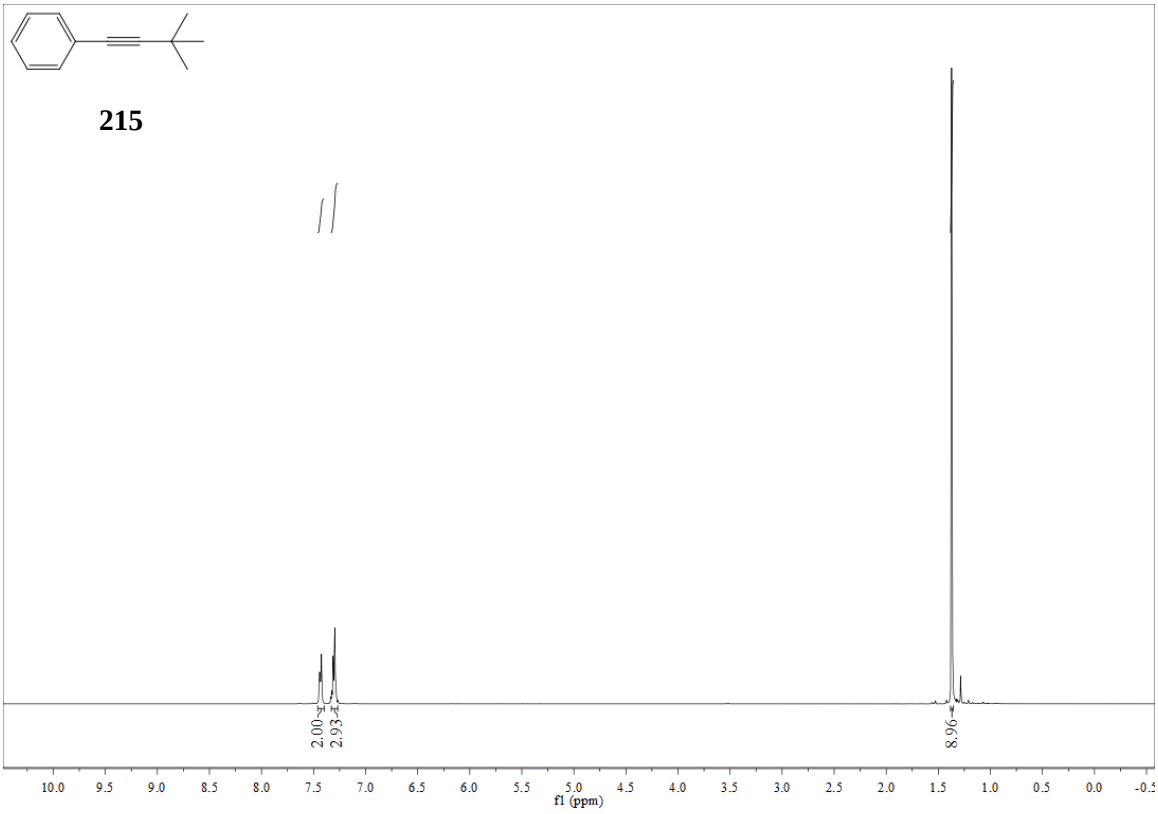

141.6
141.4
128.5
128.3
128.3
125.9
125.8
107.1
85.0
84.1
77.3
77.0
76.7
68.7
34.7
34.6
30.2
30.0
19.3
19.1
17.8
0.4
0.2
-0.1
f1 (ppm)


Si

214

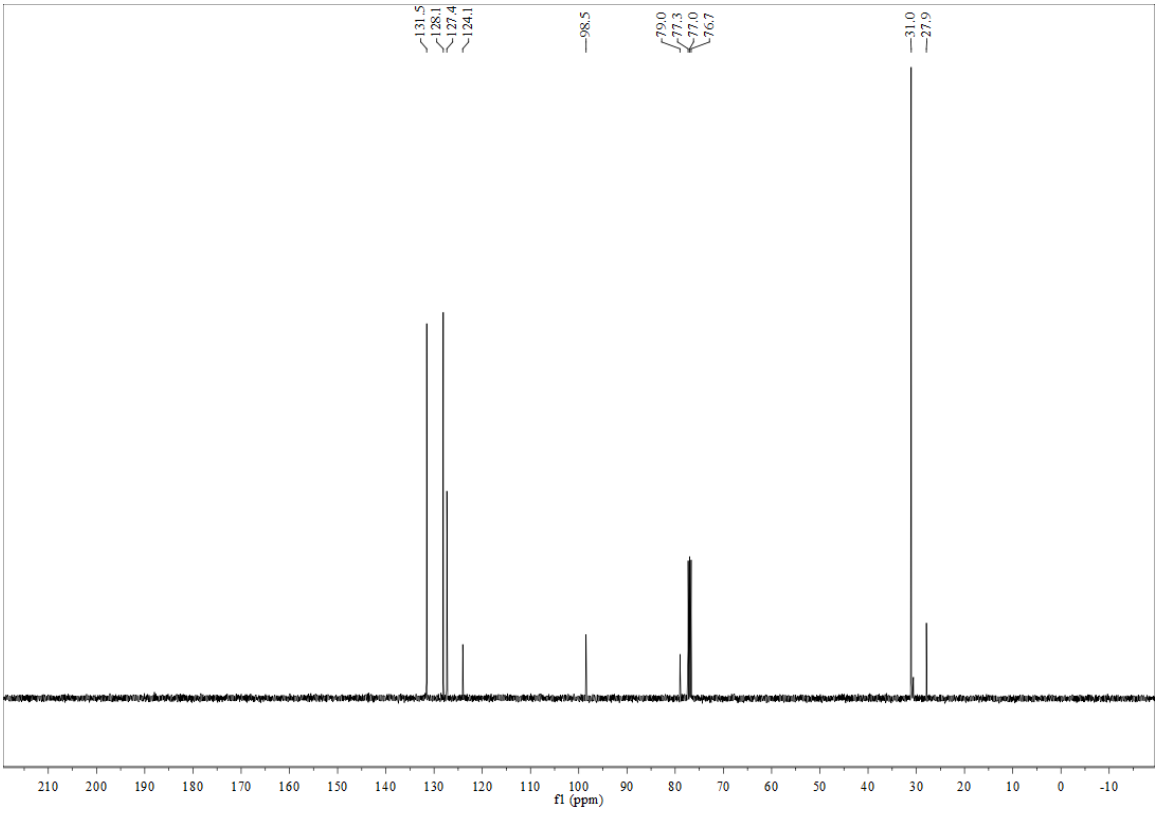
1.00
4.30
4.41
8.71
f1 (ppm)


136.2
120.7
107.3
90.8
77.3
77.0
76.7
29.0
25.6
22.2
21.4
0.1
f1 (ppm)

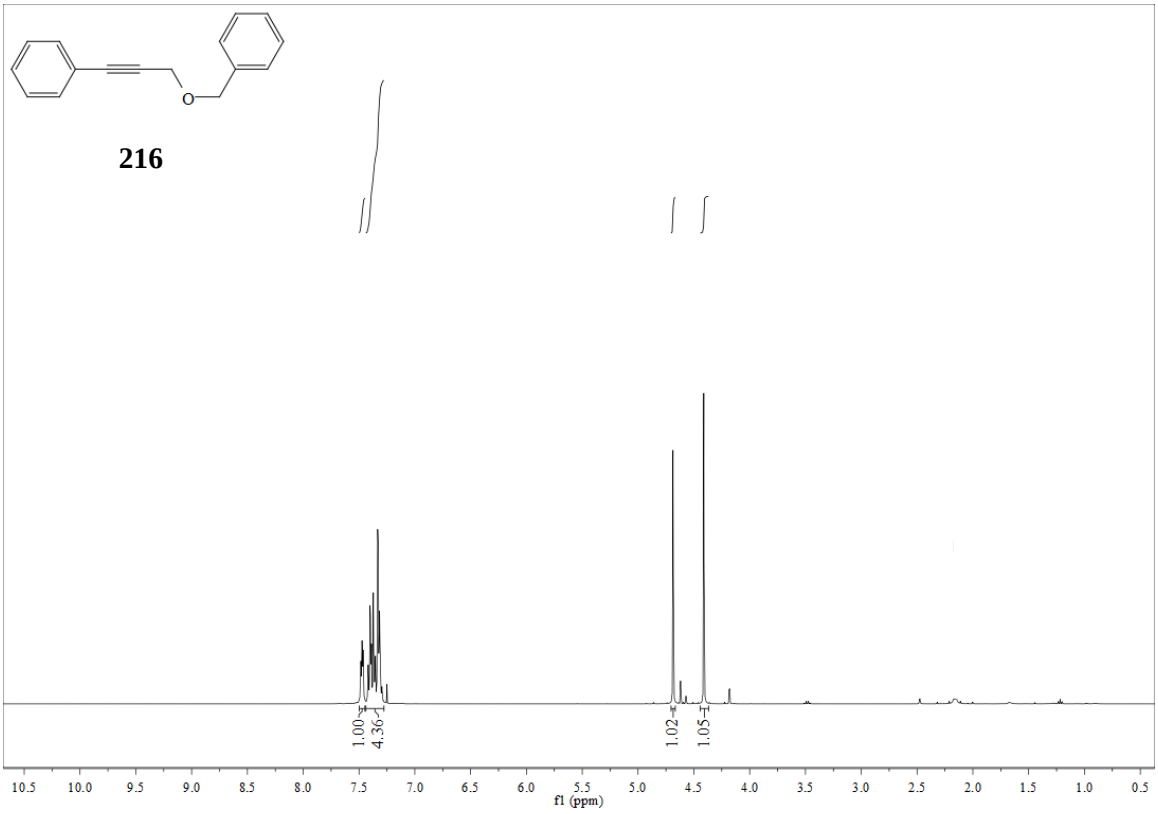


215

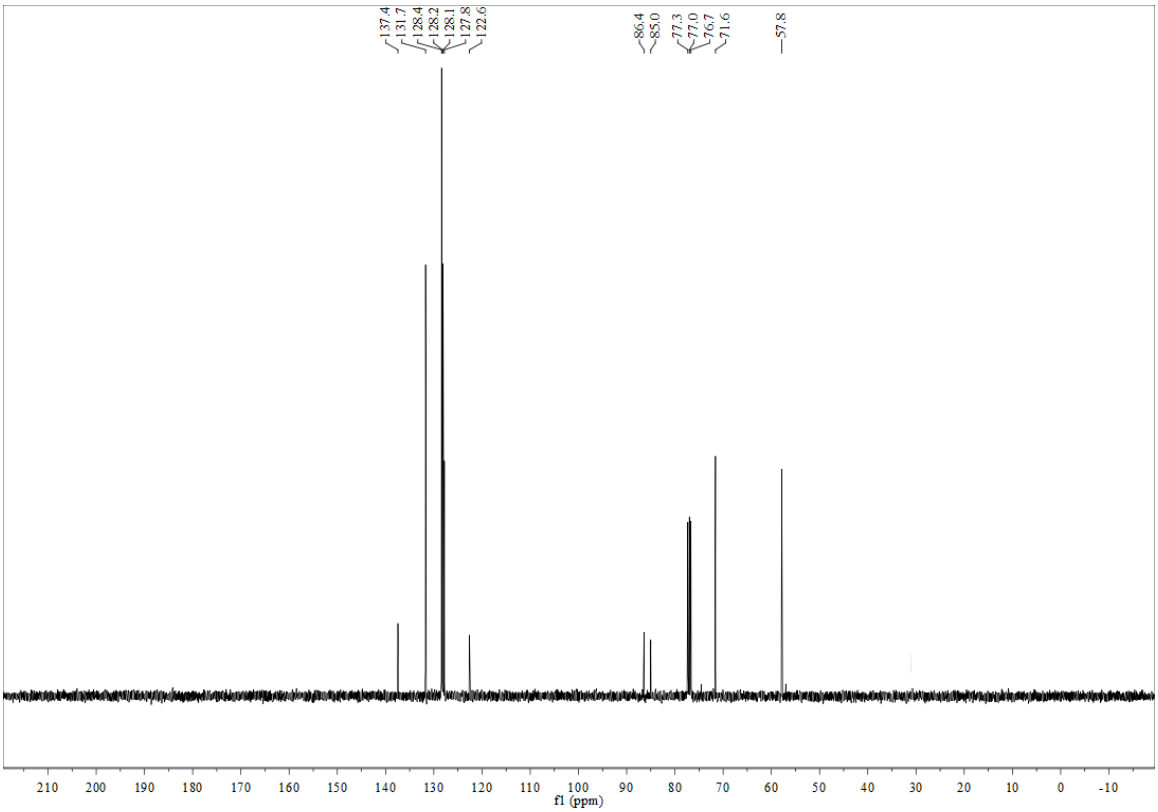
2.00
2.93
8.96
f1 (ppm)

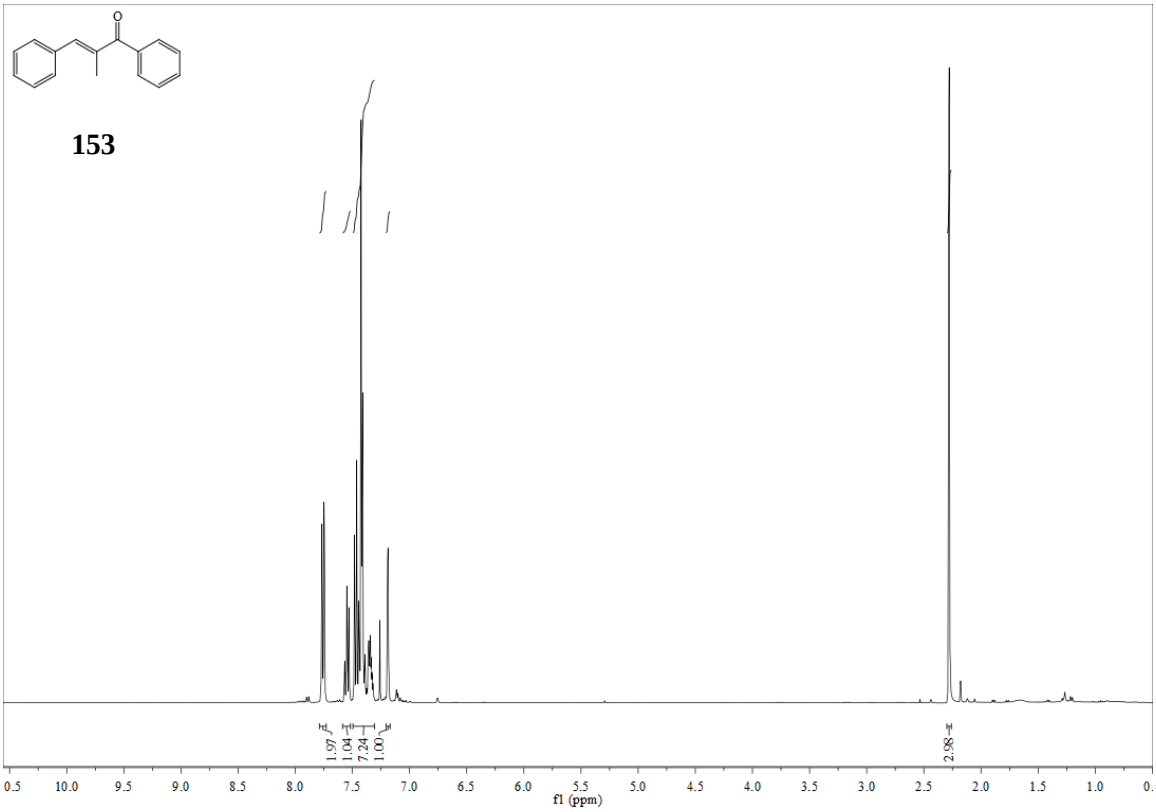


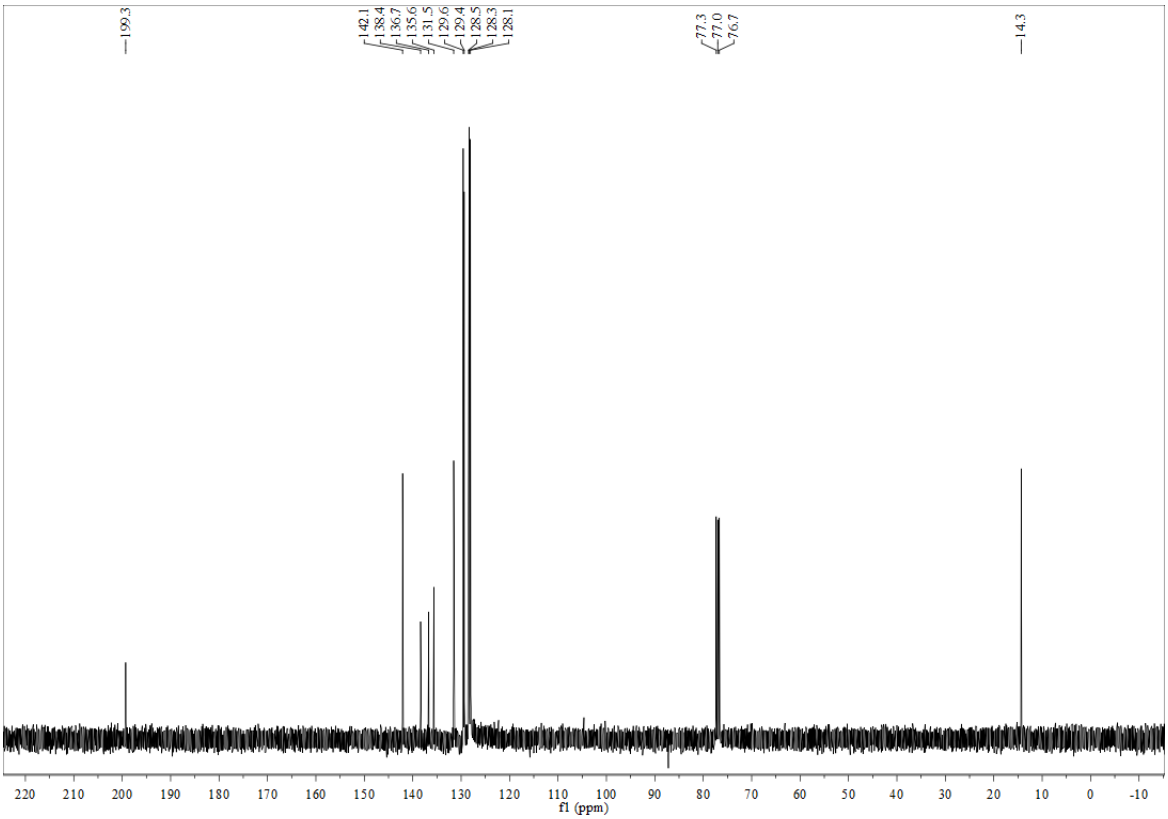
131.5
128.1
127.4
124.1
98.5
79.0
77.3
77.0
76.7
31.0
27.9
f1 (ppm)

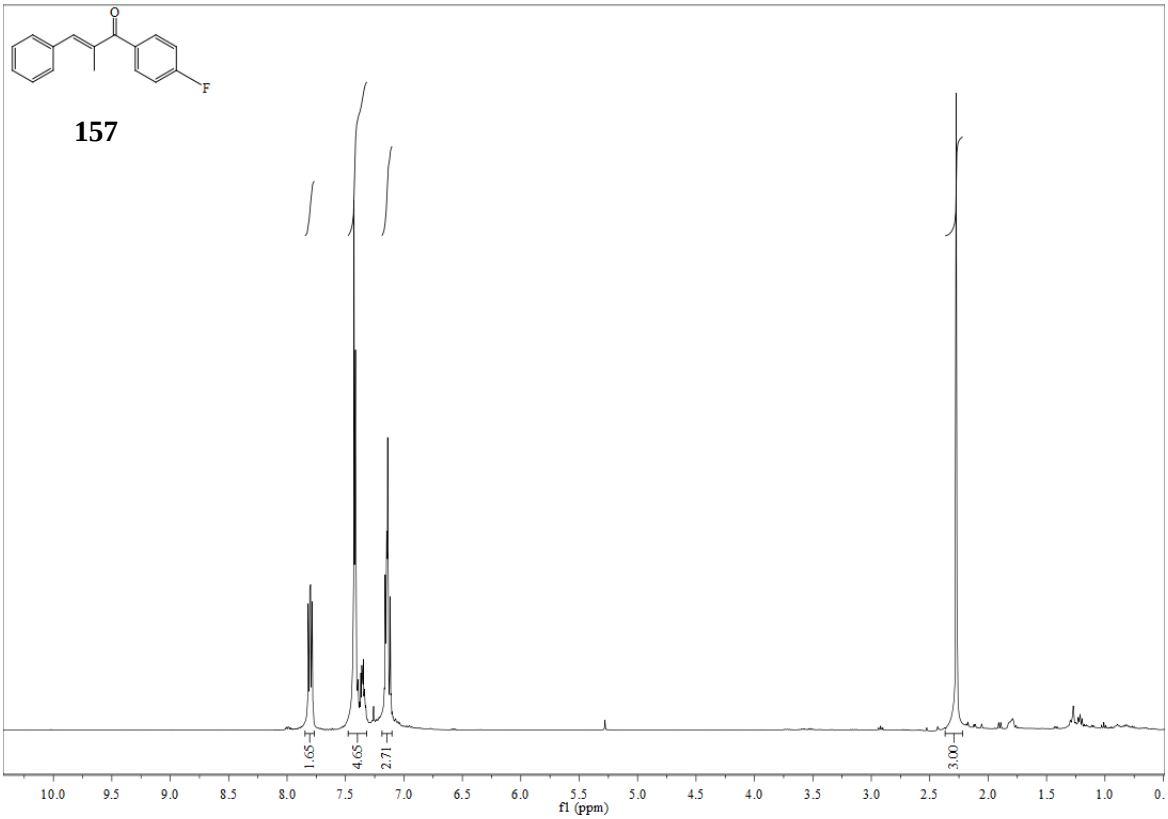

O
1.00
4.36
1.02
1.05
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

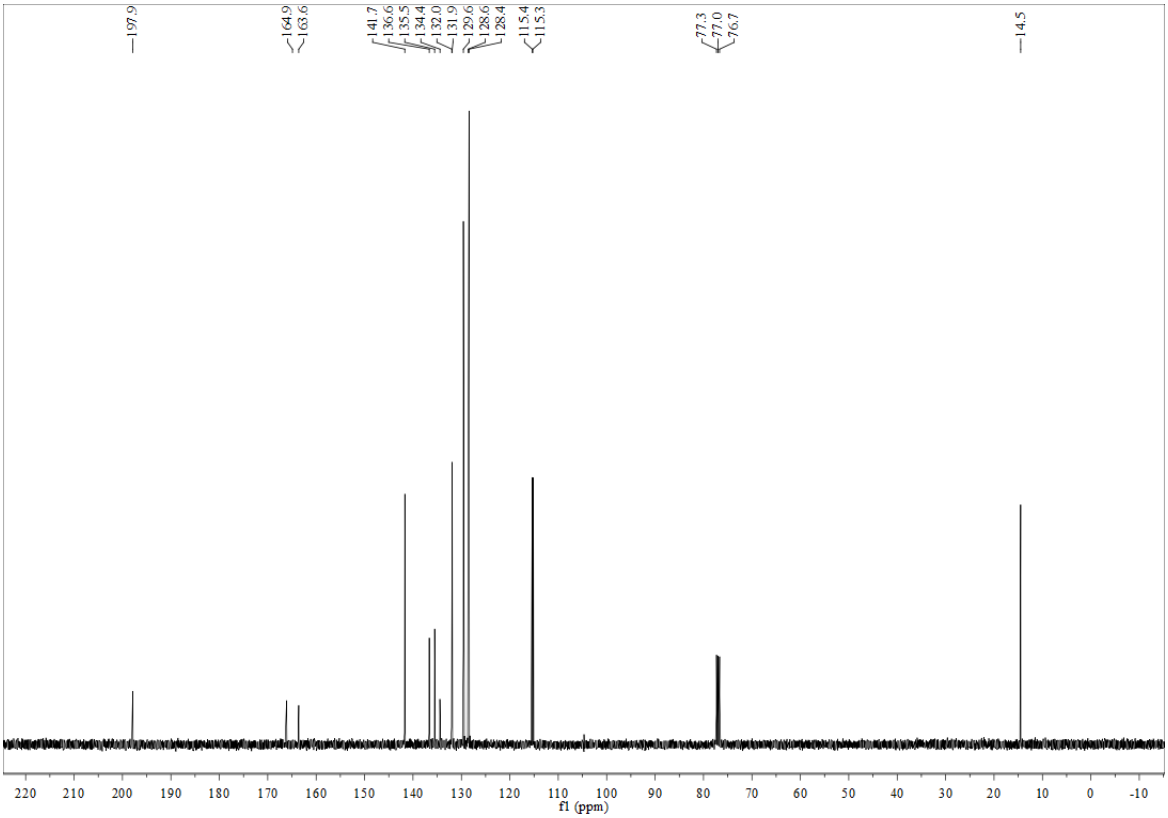
216

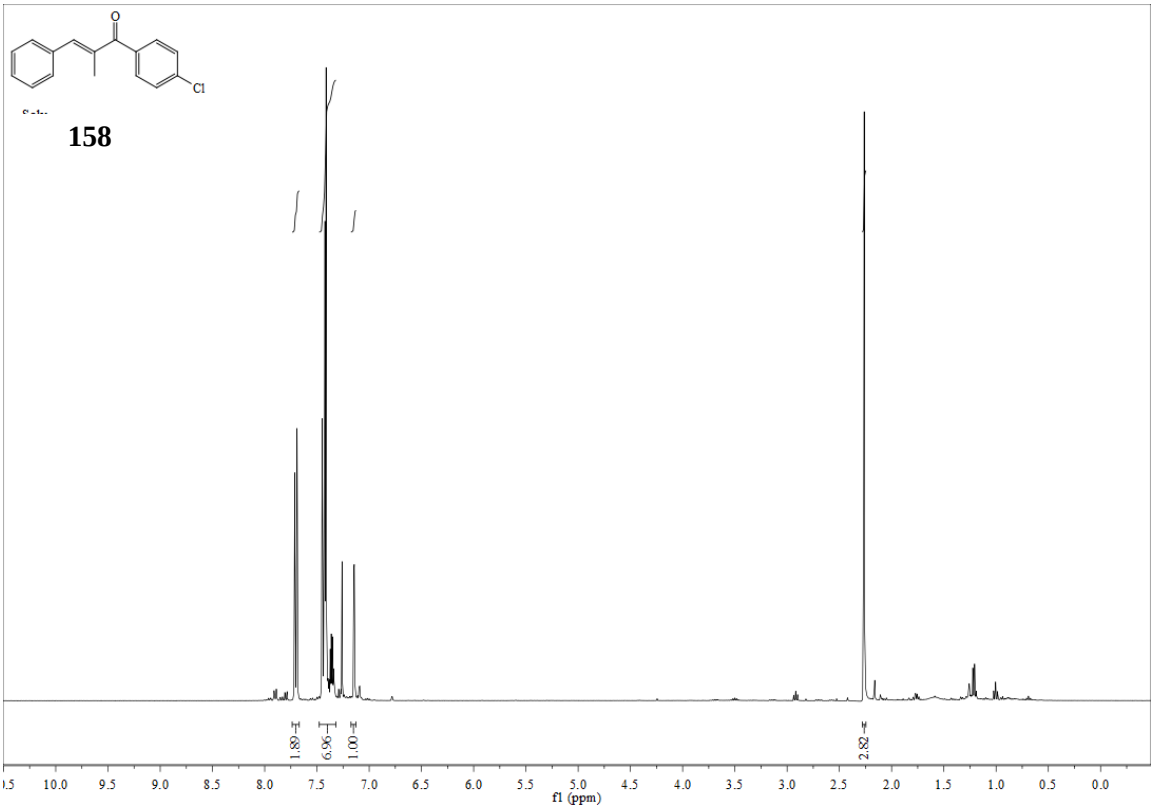

137.4
131.7
128.4
128.2
128.1
127.8
122.6
86.4
85.0
77.3
77.0
76.7
71.6
57.8
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

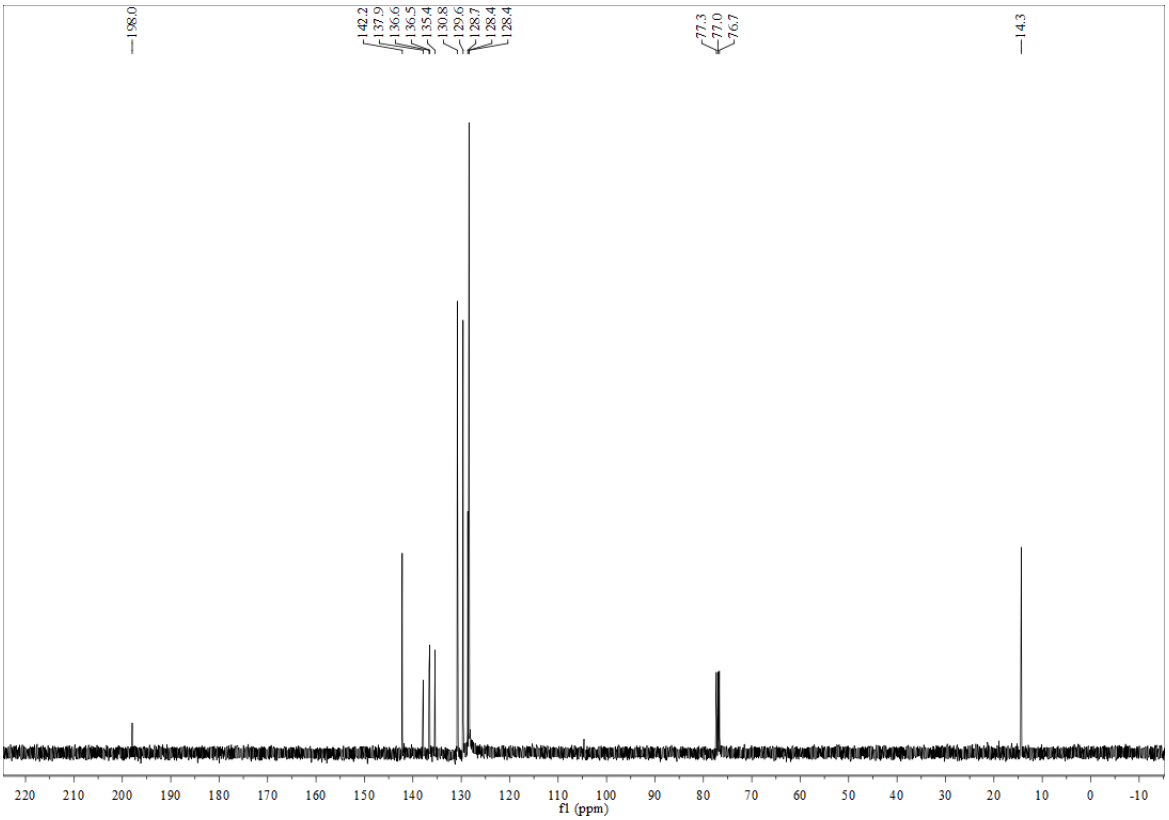

O
153
1.97
1.04
7.24
1.00
2.98
f1 (ppm)

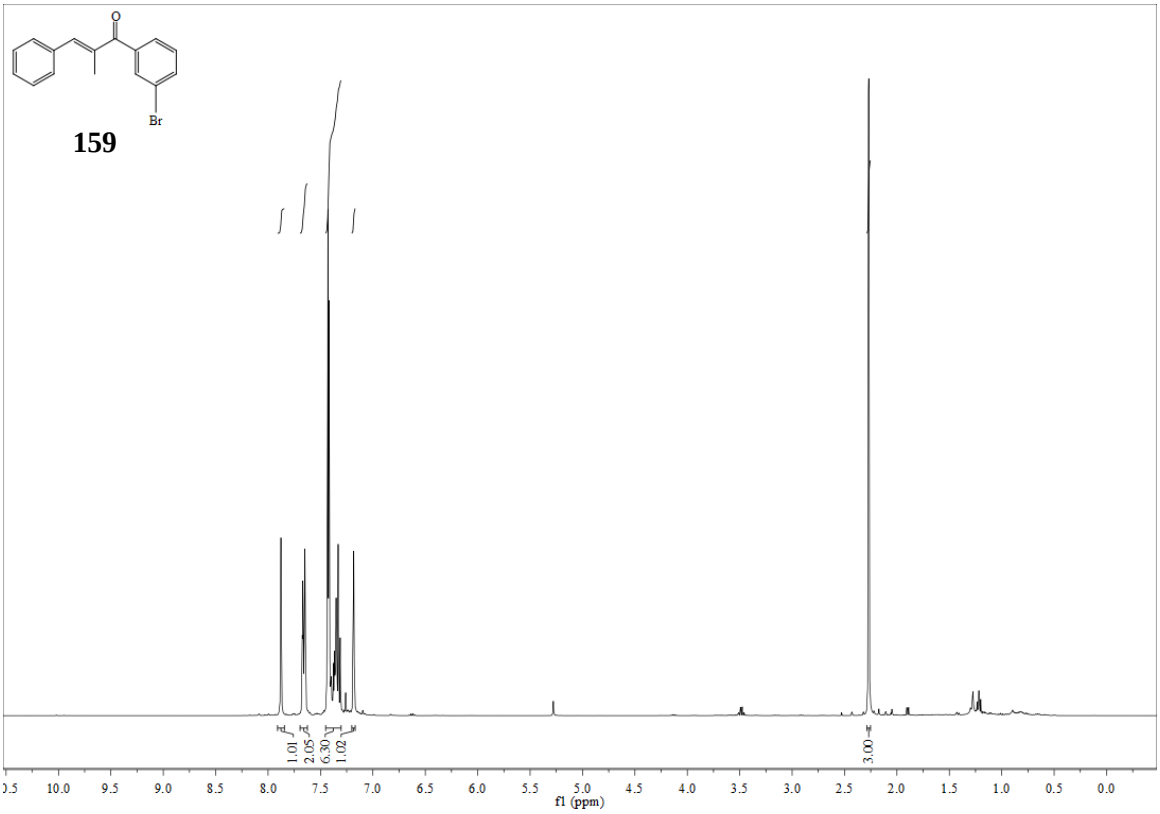

199.3
142.1
138.4
136.7
135.6
131.5
129.6
129.4
128.5
128.3
128.1
77.3
77.0
76.7
14.3
f1 (ppm)

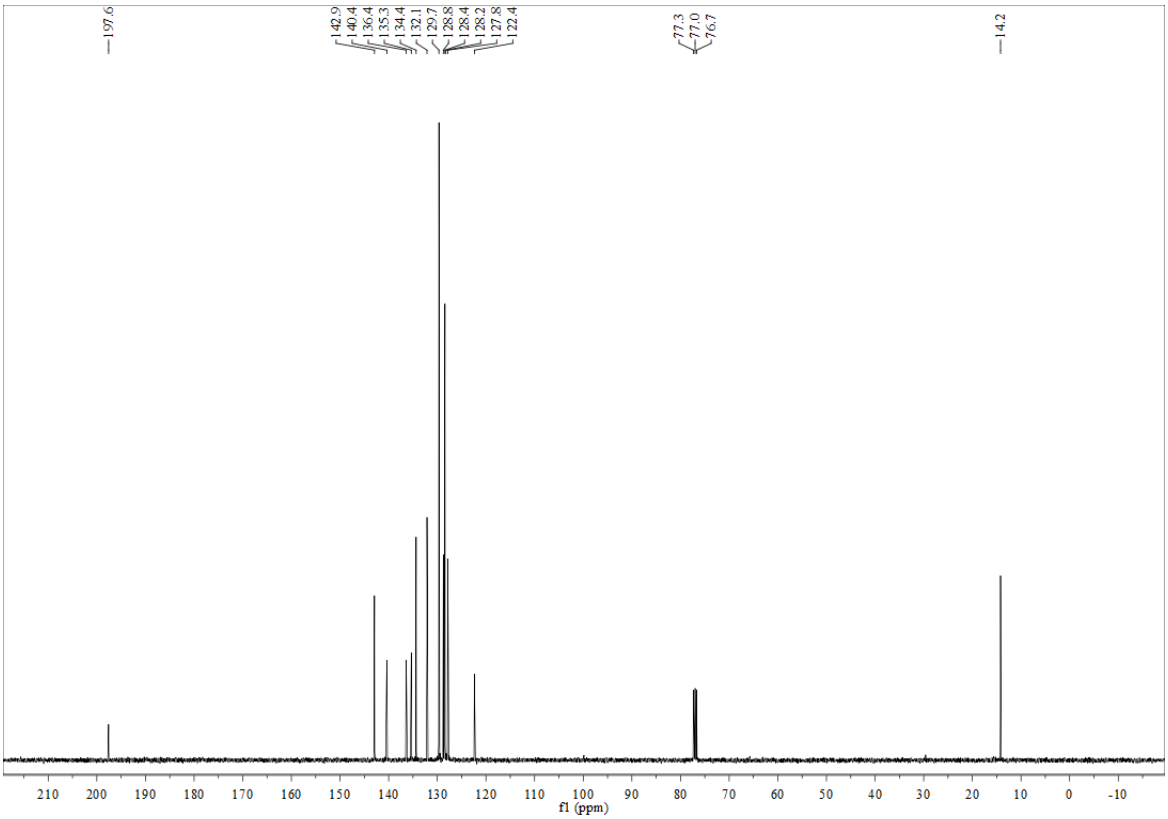

O
F
157
1.65
4.65
2.71
3.00
f1 (ppm)

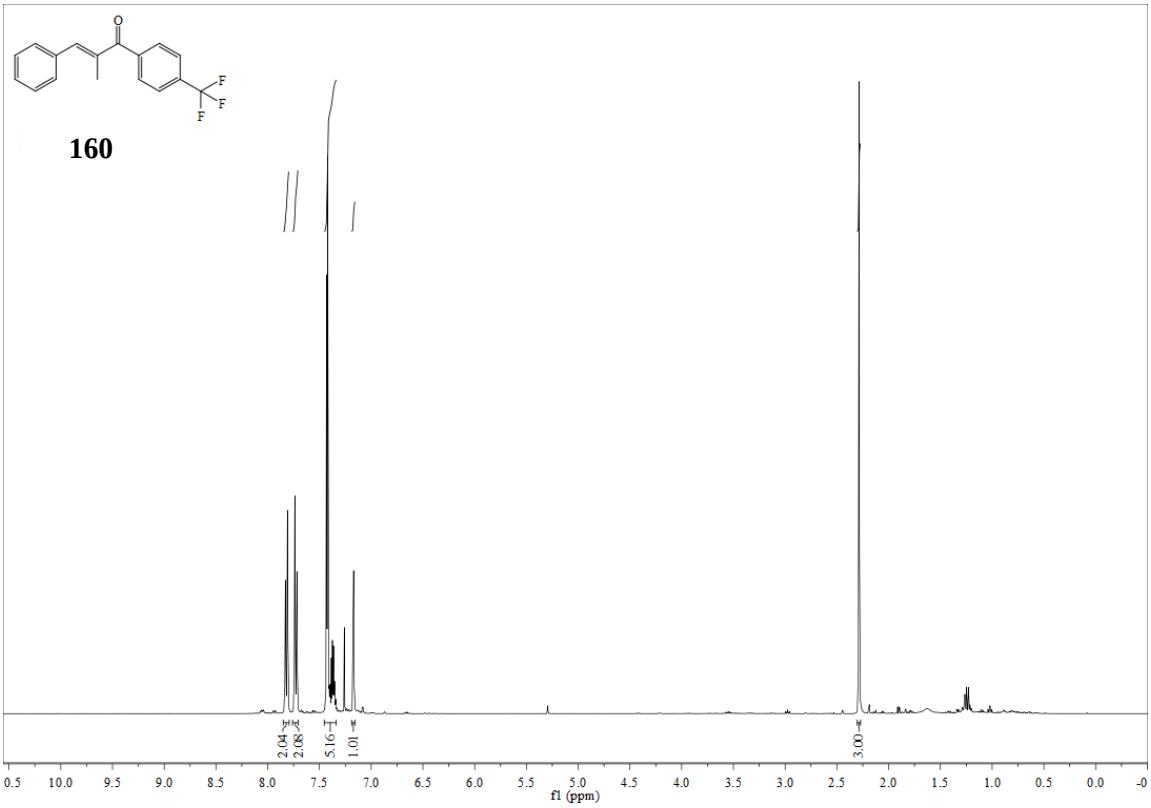

197.9
164.9
163.6
141.7
136.6
135.5
134.4
132.0
131.9
129.6
128.6
128.4
115.4
115.3
77.3
77.0
76.7
14.5
f1 (ppm)

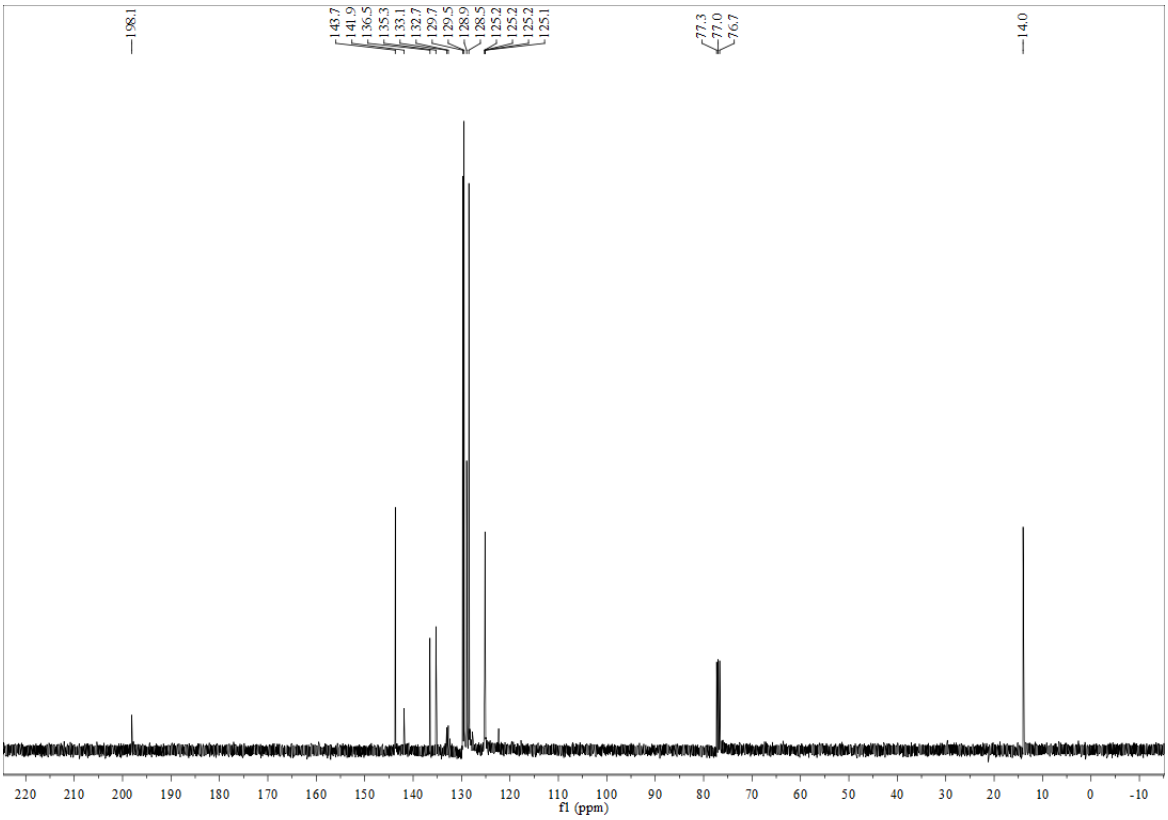

O
Cl
158
1.89
6.96
1.00
2.82
f1 (ppm)

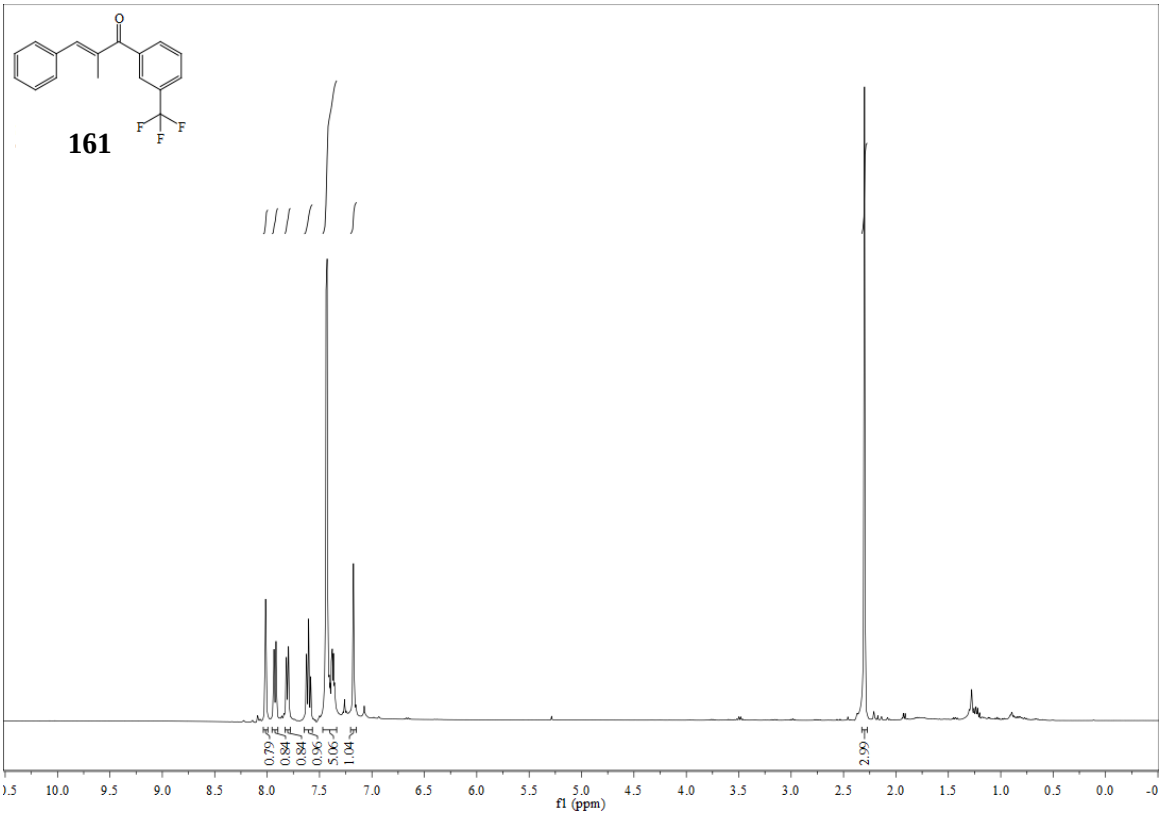

198.0
142.2
137.9
136.6
136.5
135.4
130.8
129.6
128.7
128.4
128.4
77.3
77.0
76.7
14.3
f1 (ppm)

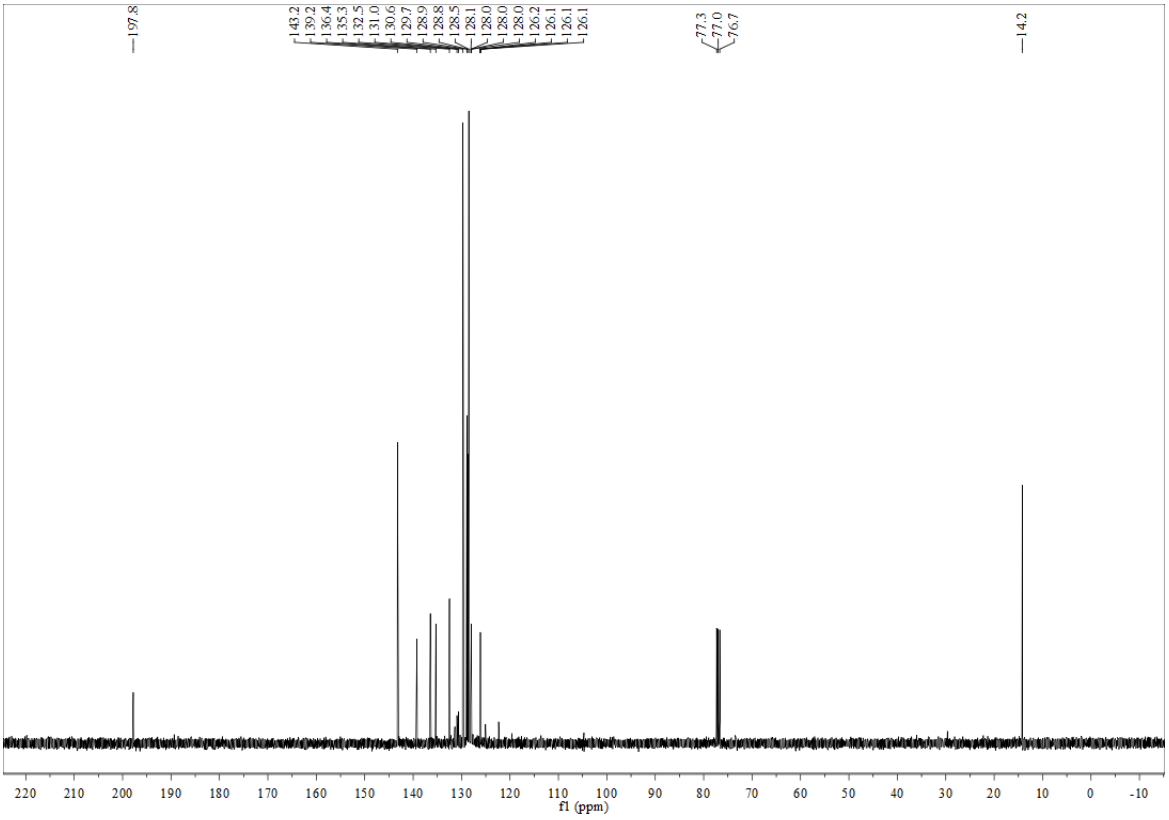

O
Br
159
1.01
2.05
6.30
1.02
3.00
f1 (ppm)

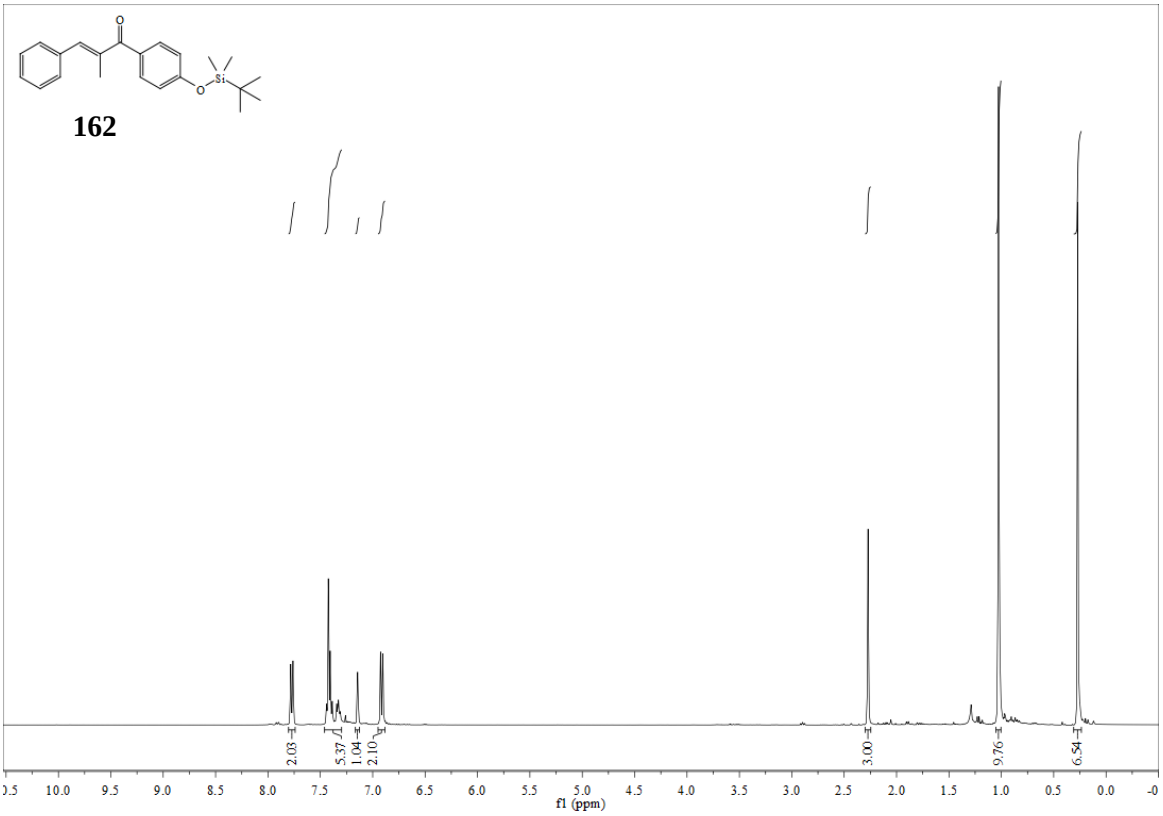

197.6
142.9
140.4
136.4
135.3
134.4
132.1
129.7
128.8
128.4
128.2
127.8
122.4
77.3
77.0
76.7
14.2
f1 (ppm)

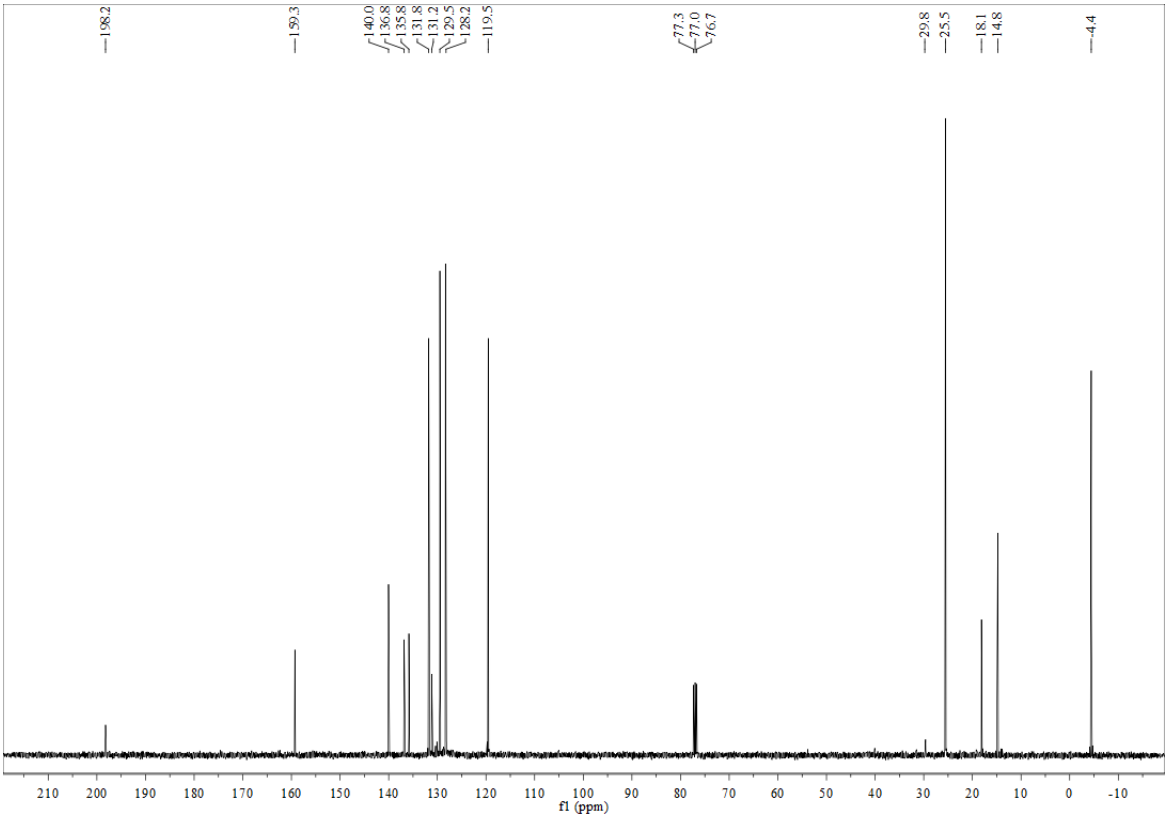

O
F
F
F
160
2.04
2.08
5.16
1.01
3.00
0.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

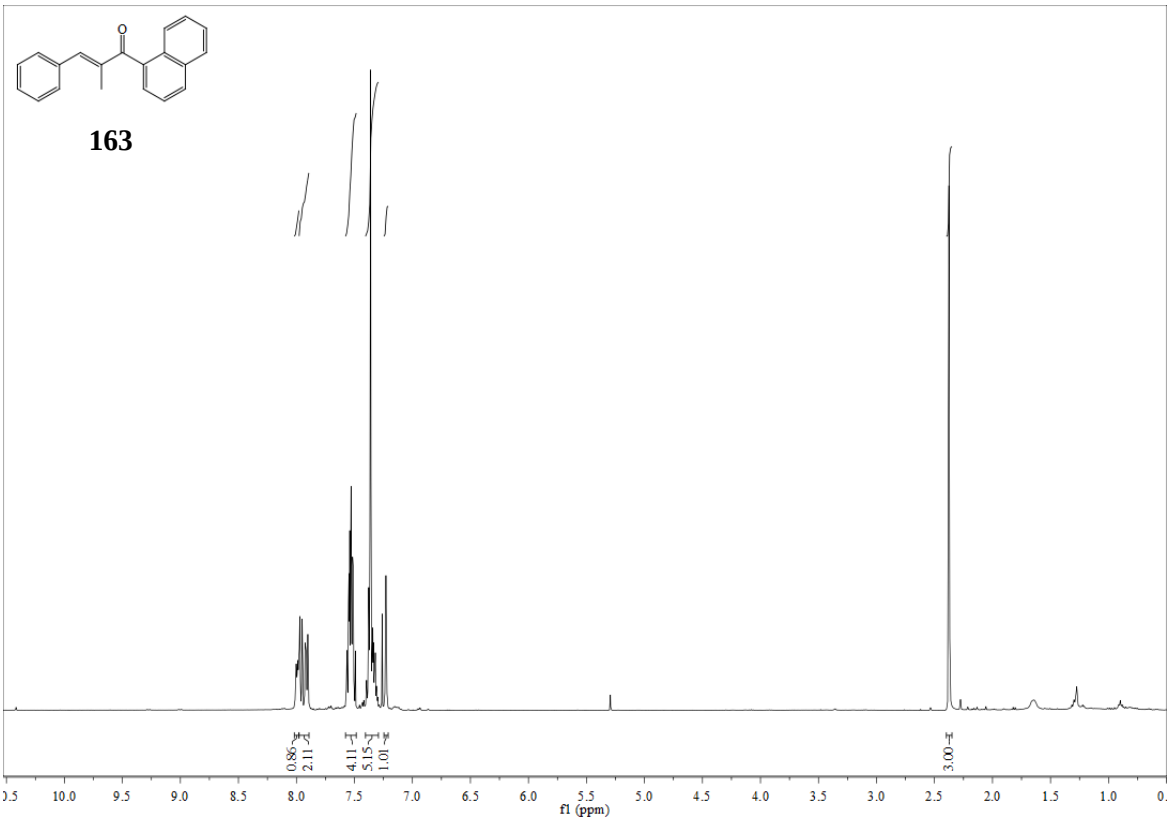

198.1
143.7
141.9
136.5
135.3
133.1
132.7
129.7
129.5
128.9
128.5
125.2
125.2
125.2
125.1
77.3
77.0
76.7
14.0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
F
F
F
161
0.79
0.84
0.84
0.96
5.06
1.04
2.99
f1 (ppm)

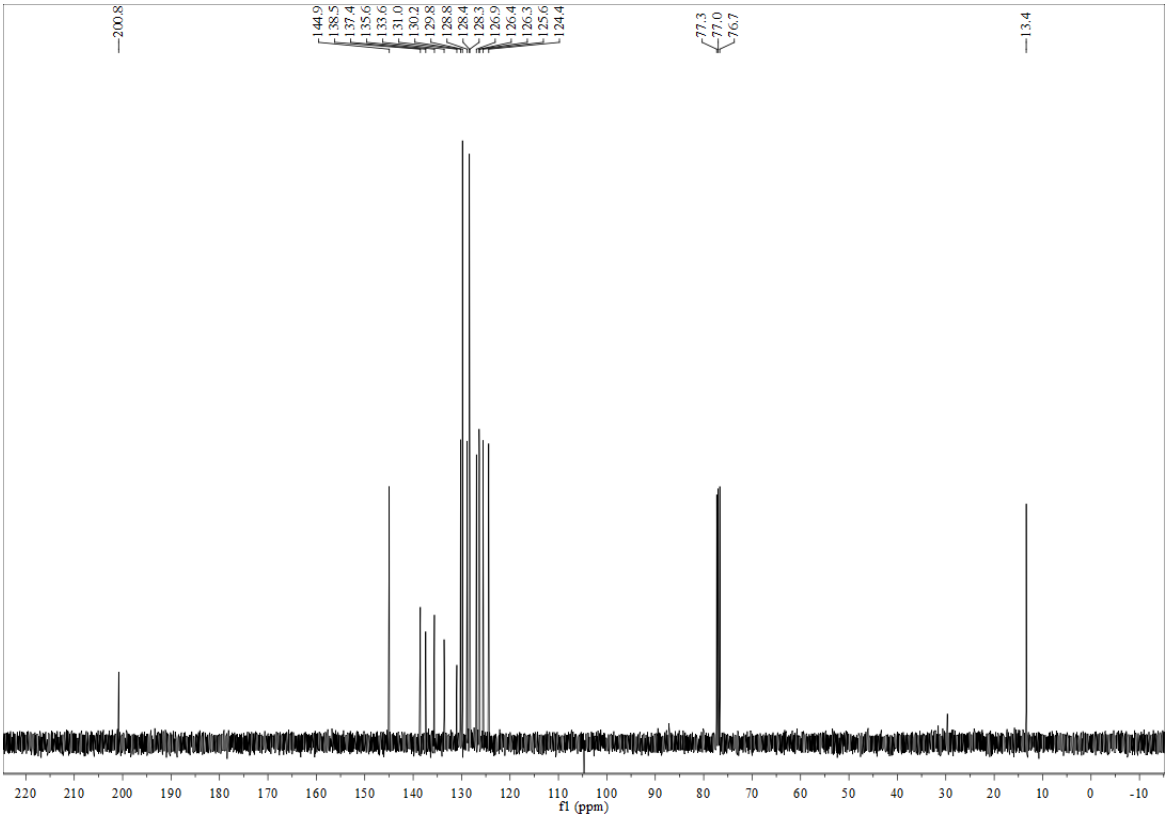

197.8
143.2
139.2
136.4
135.3
132.5
131.0
130.6
129.7
128.9
128.8
128.5
128.1
128.0
128.0
128.0
126.2
126.1
126.1
126.1
77.3
77.0
76.7
14.2
f1 (ppm)

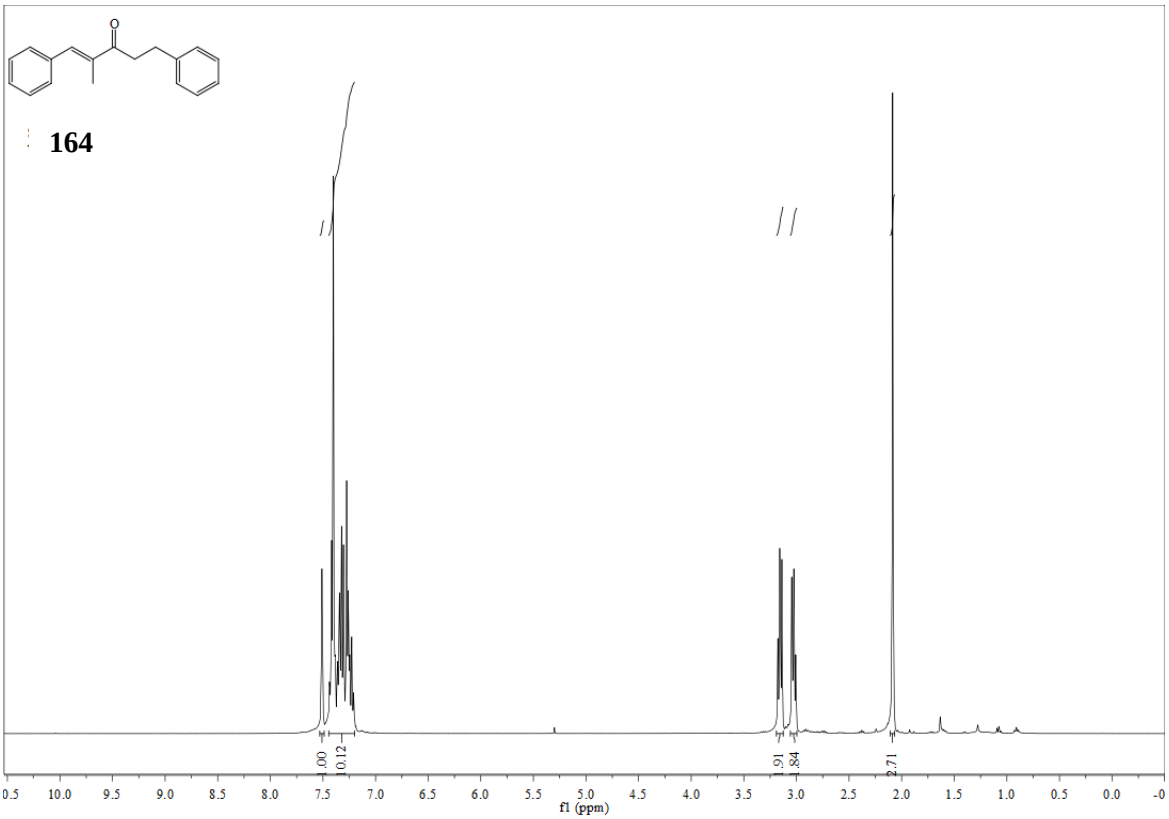

O
Si
O
162
2.03
5.37
1.04
2.10
3.00
9.76
6.54
f1 (ppm)

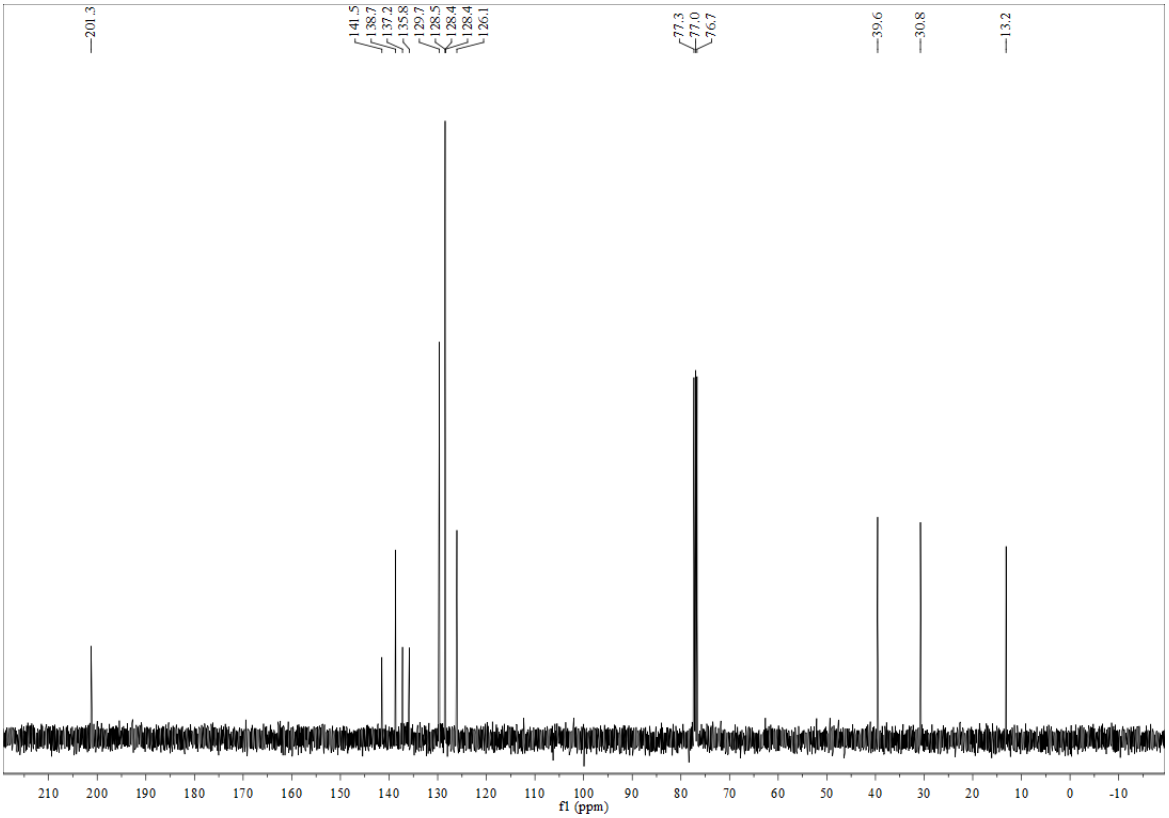

198.2
159.3
140.0
136.8
135.8
131.8
131.2
129.5
128.2
119.5
77.3
77.0
76.7
29.8
25.5
18.1
14.8
-4.4
f1 (ppm)

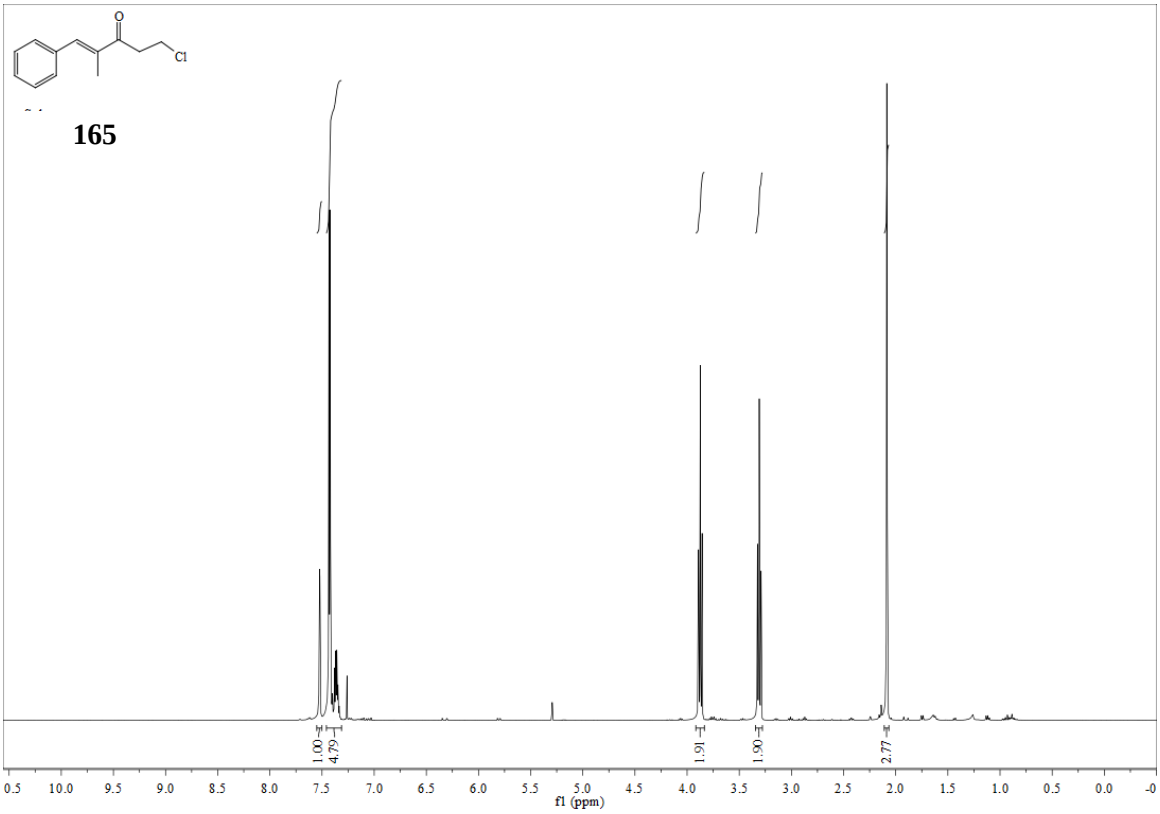

O
0.86
2.11
4.11
5.15
1.01
3.00
f1 (ppm)

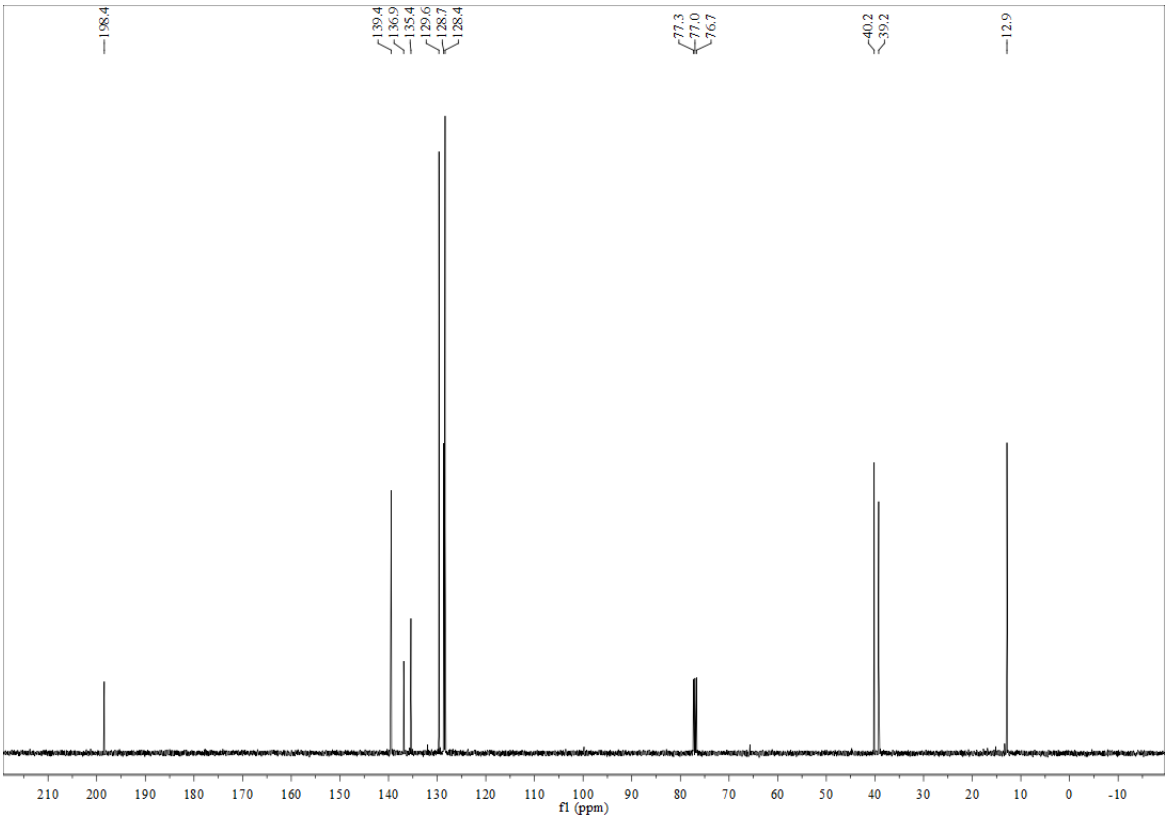
163

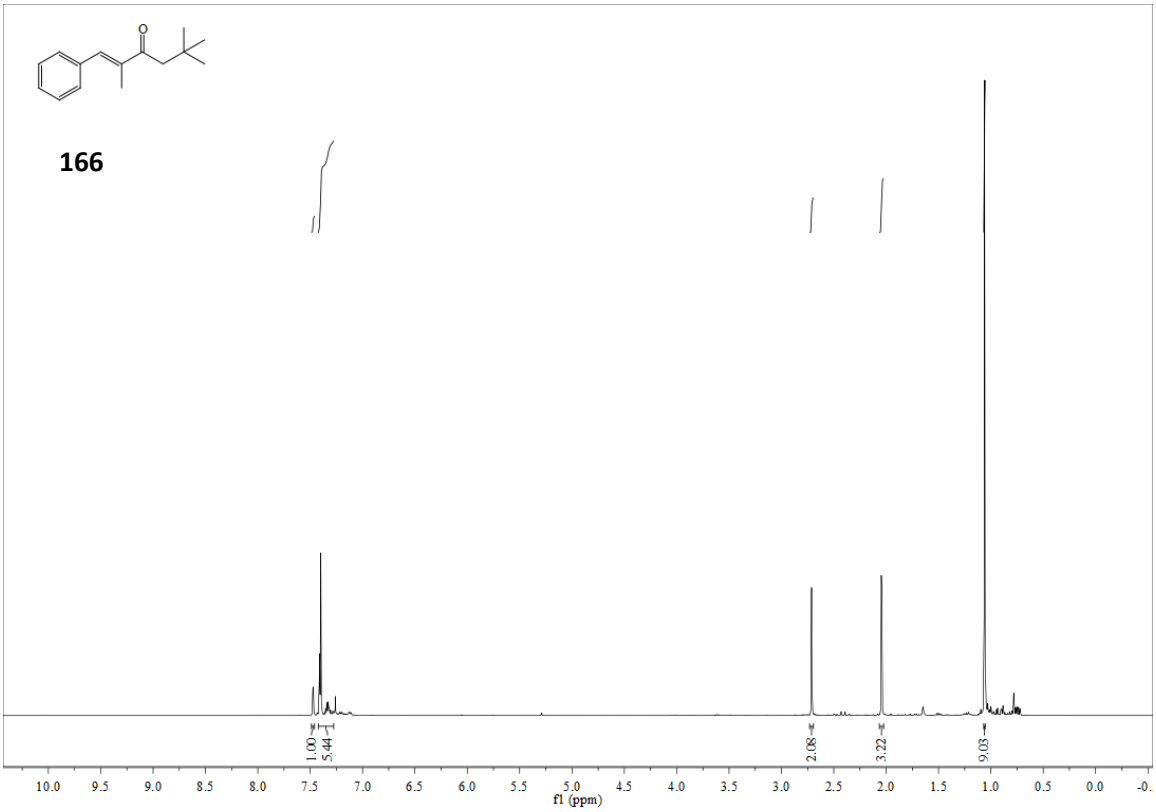

200.8
144.9
138.5
137.4
135.6
133.6
131.0
130.2
129.8
128.8
128.4
128.3
126.9
126.4
126.3
125.6
124.4
77.3
77.0
76.7
13.4
f1 (ppm)

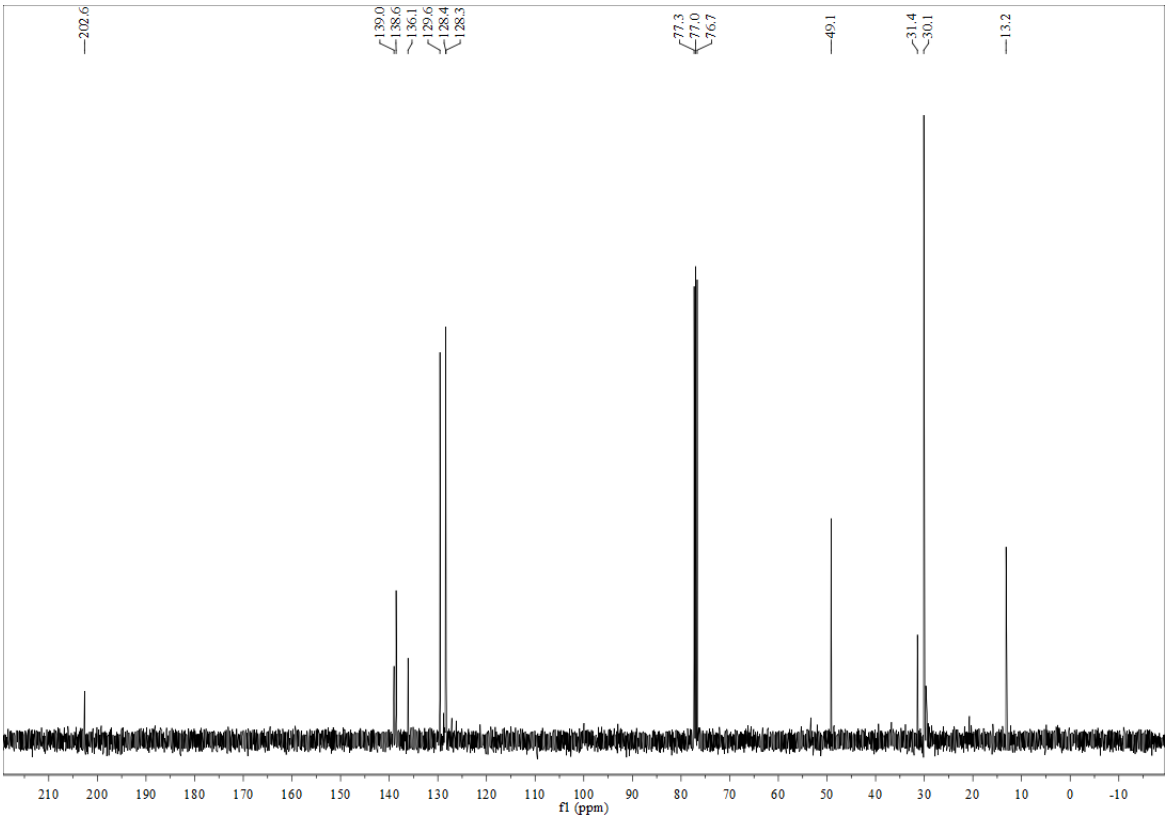

O
164
1.00
0.12
1.91
1.84
2.71
f1 (ppm)

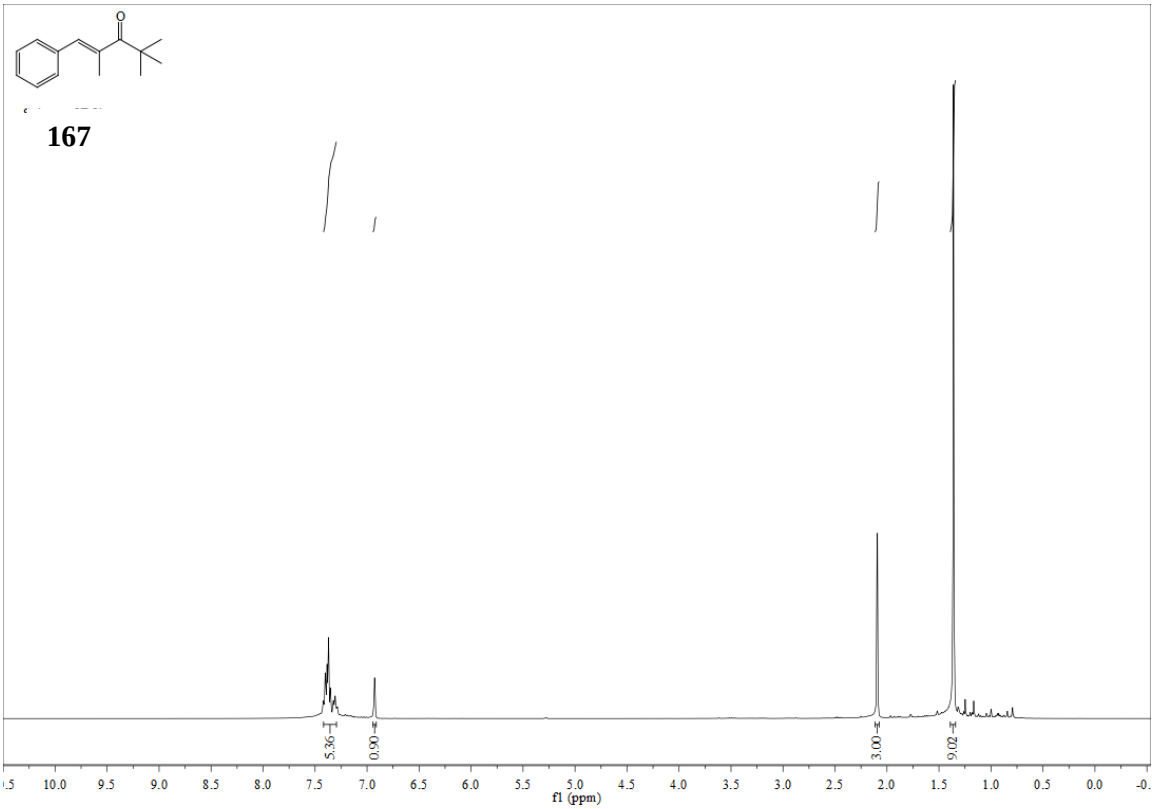

201.3
141.5
138.7
137.2
135.8
129.7
128.5
128.4
128.4
126.1
77.3
77.0
76.7
39.6
30.8
13.2
f1 (ppm)


O
Cl
165
1.00
4.79
1.91
1.90
2.77
f1 (ppm)

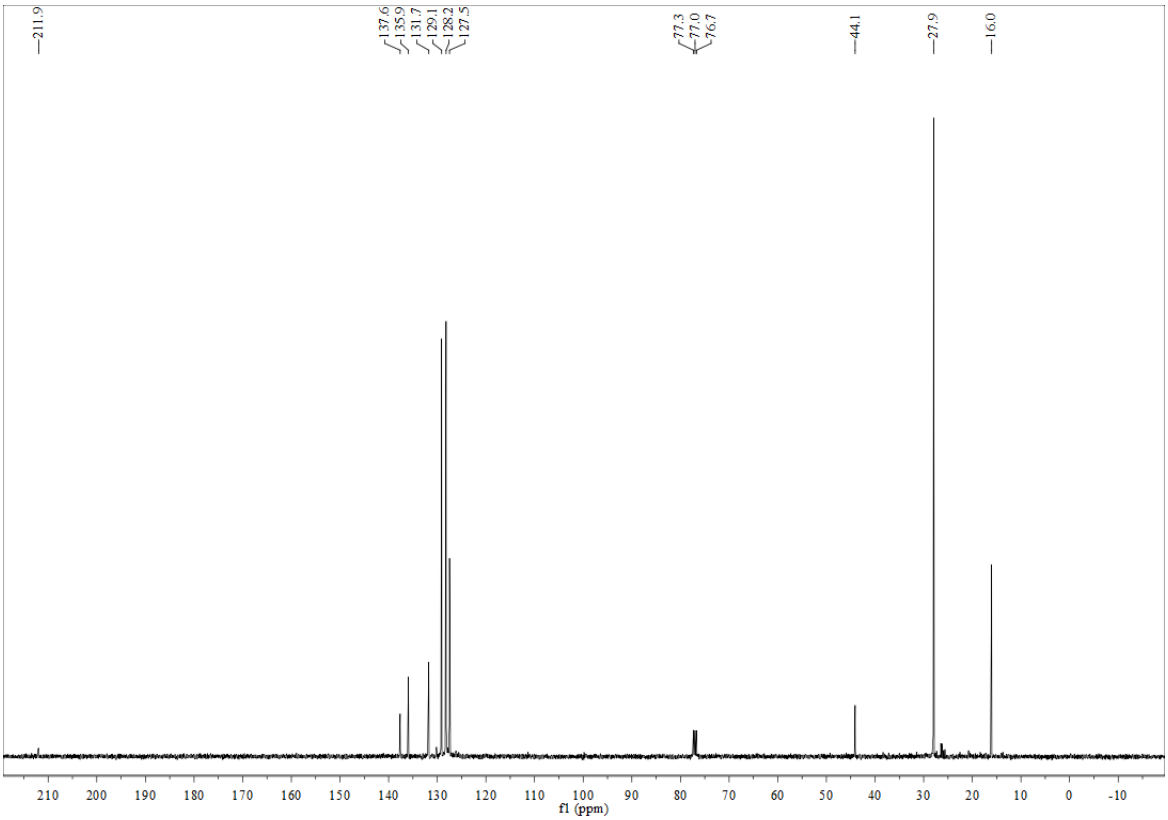

198.4
139.4
136.9
135.4
129.6
128.7
128.4
77.3
77.0
76.7
40.2
39.2
12.9
f1 (ppm)

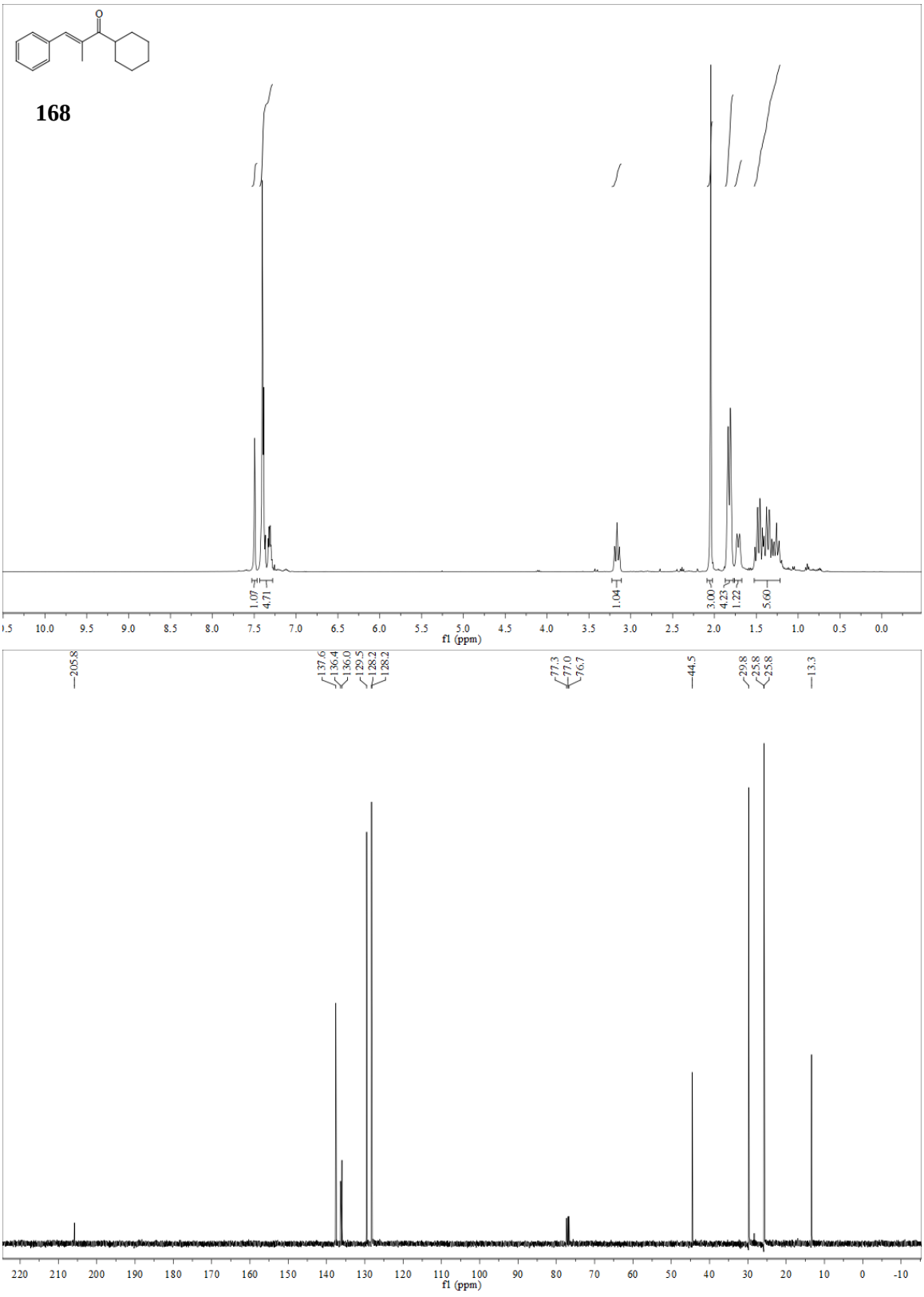

166
1.00
5.44
2.08
3.22
9.03
f1 (ppm)

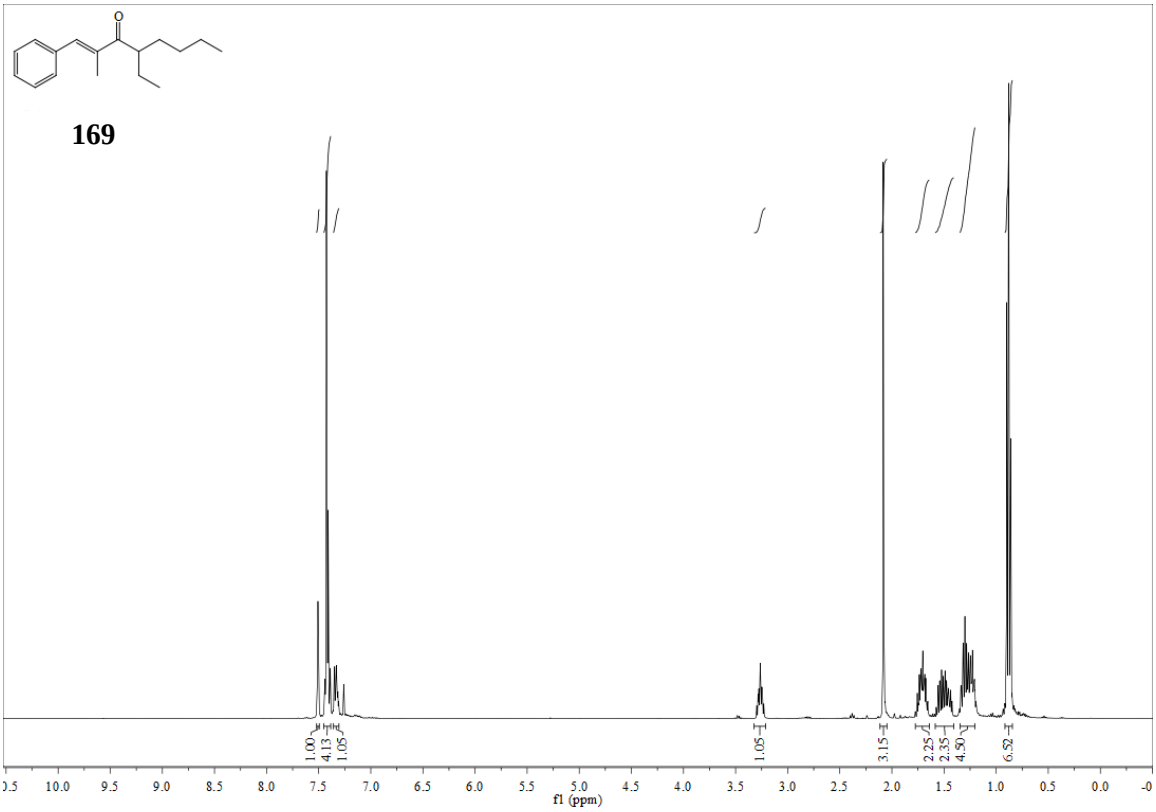

202.6
139.0
138.6
136.1
129.6
128.4
128.3
77.3
77.0
76.7
49.1
31.4
30.1
13.2
f1 (ppm)

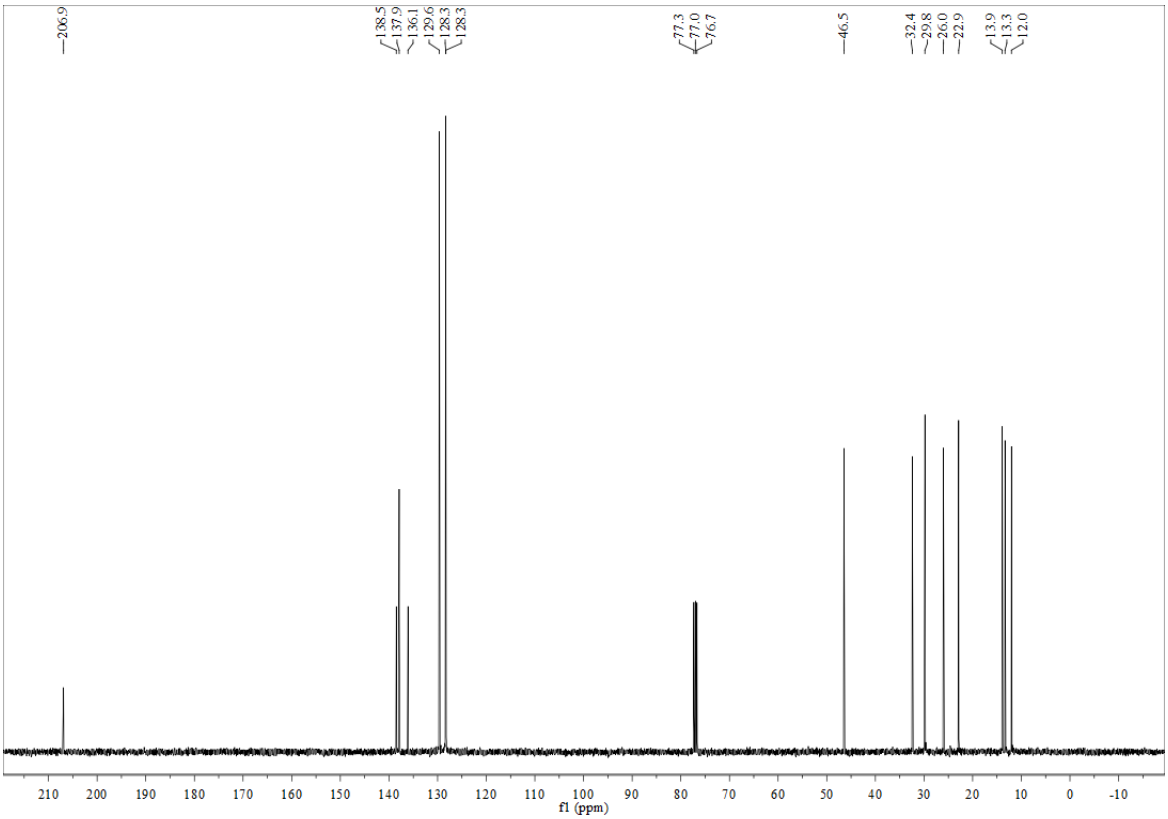

O
5.36
0.90
3.00
9.02
f1 (ppm)

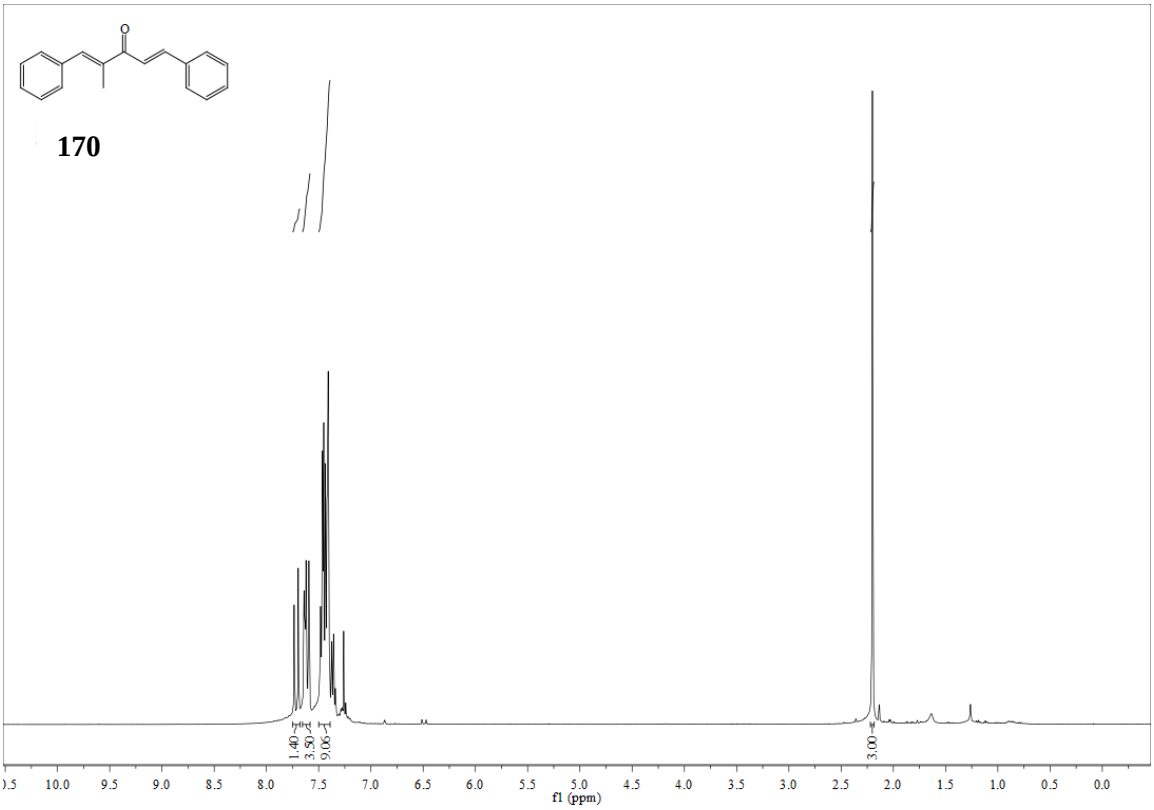
167

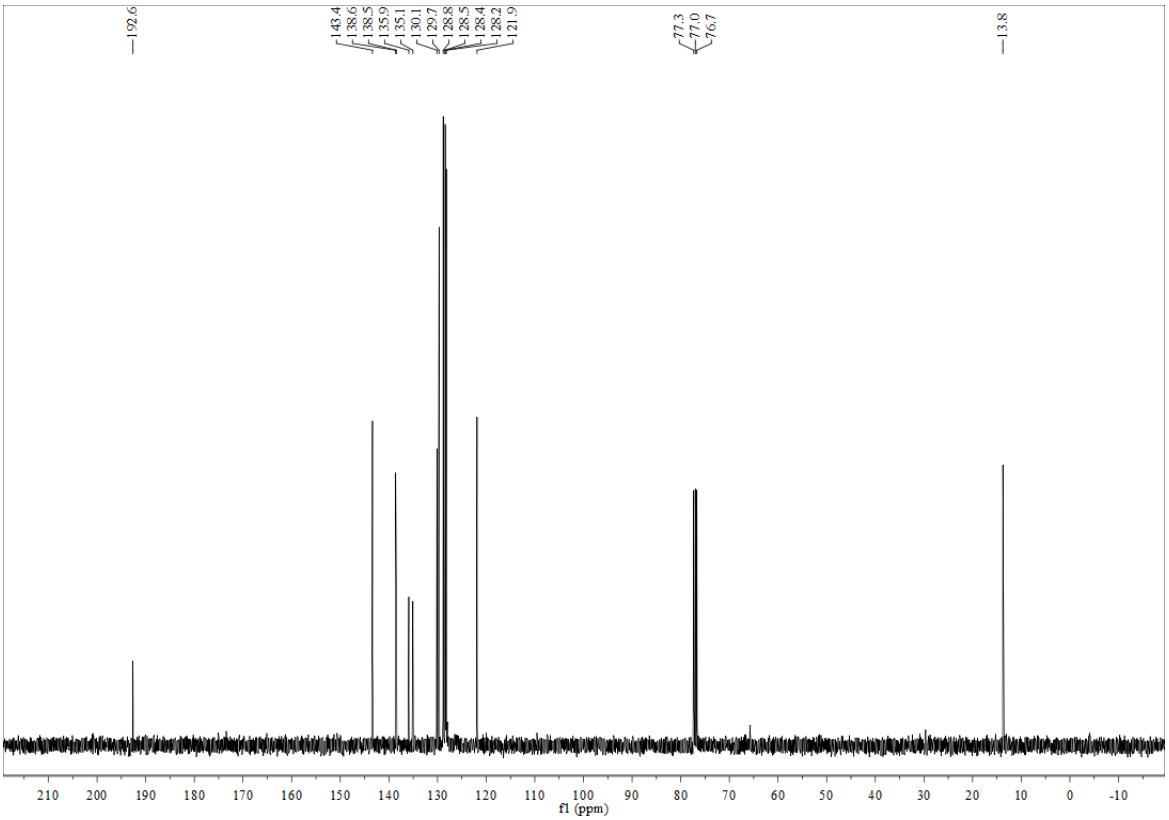

211.9
137.6
135.9
131.7
129.1
128.2
127.5
77.3
77.0
76.7
44.1
27.9
16.0
f1 (ppm)

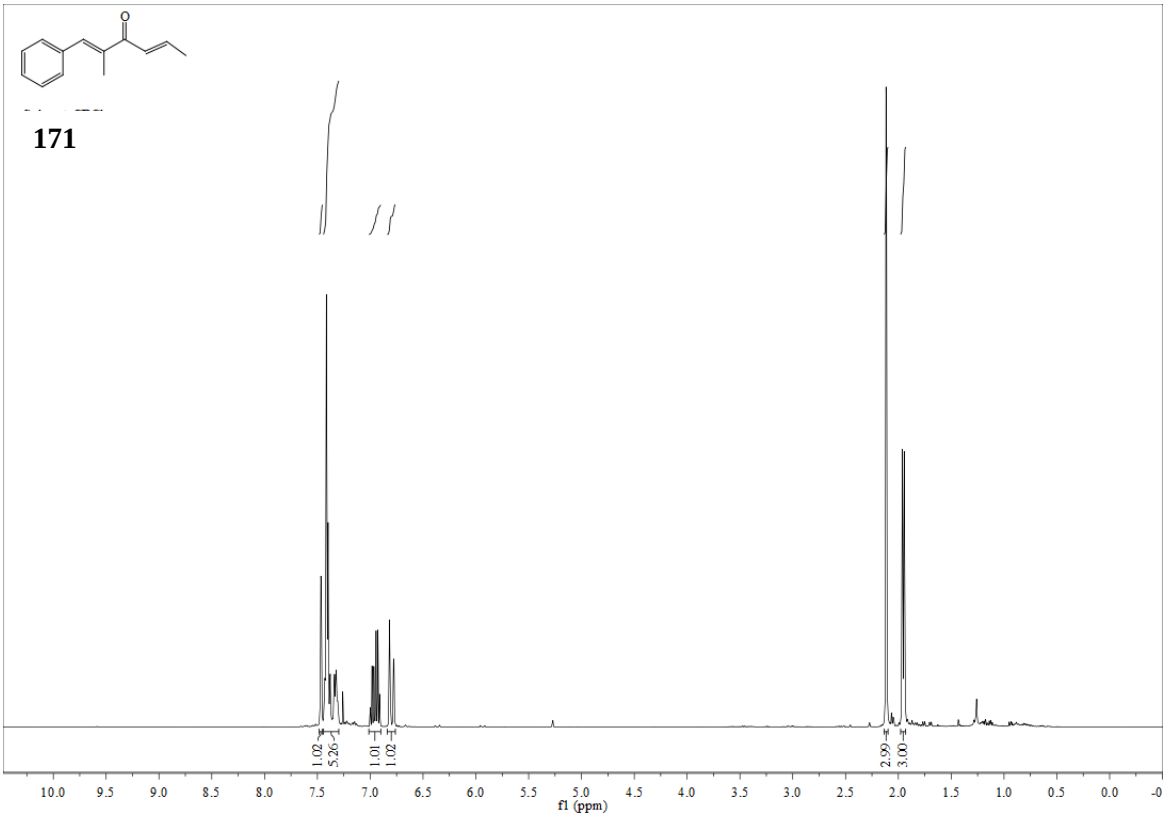

O
168
1.07
4.71
1.04
3.00
4.23
1.22
5.60
f1 (ppm)
205.8
137.6
136.4
136.0
129.5
128.2
128.2
77.3
77.0
76.7
44.5
29.8
25.8
25.8
13.3
f1 (ppm)

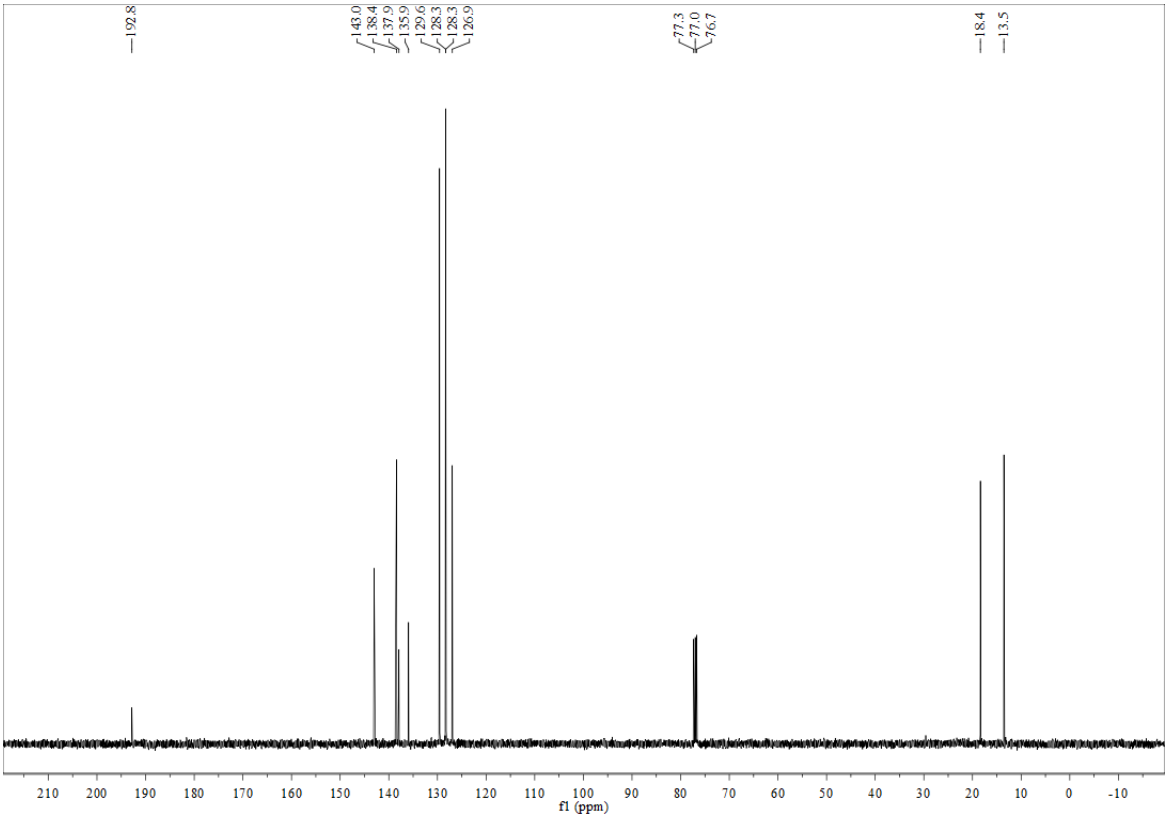

O
169
1.00
4.13
1.05
1.05
3.15
2.25
2.35
4.30
6.52
f1 (ppm)

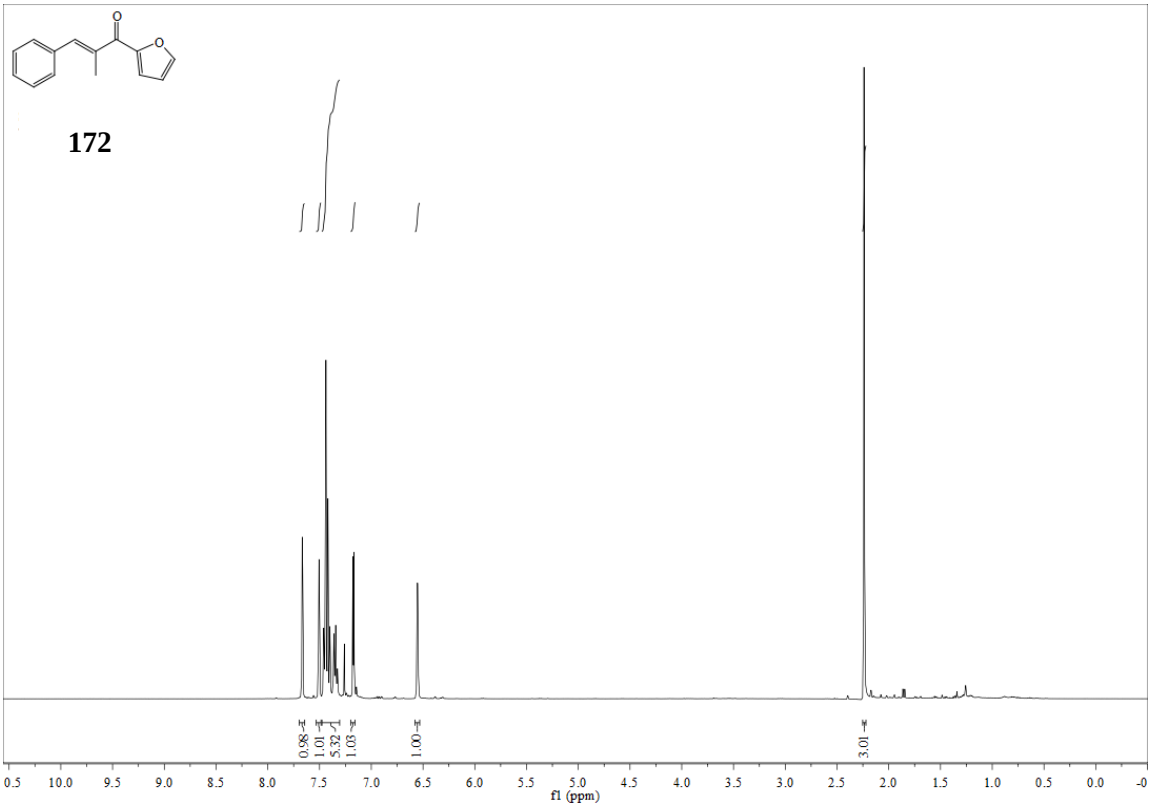

206.9
138.5
137.9
136.1
129.6
128.3
128.3
77.3
77.0
76.7
46.5
32.4
29.8
26.0
22.9
13.9
13.3
12.0
f1 (ppm)

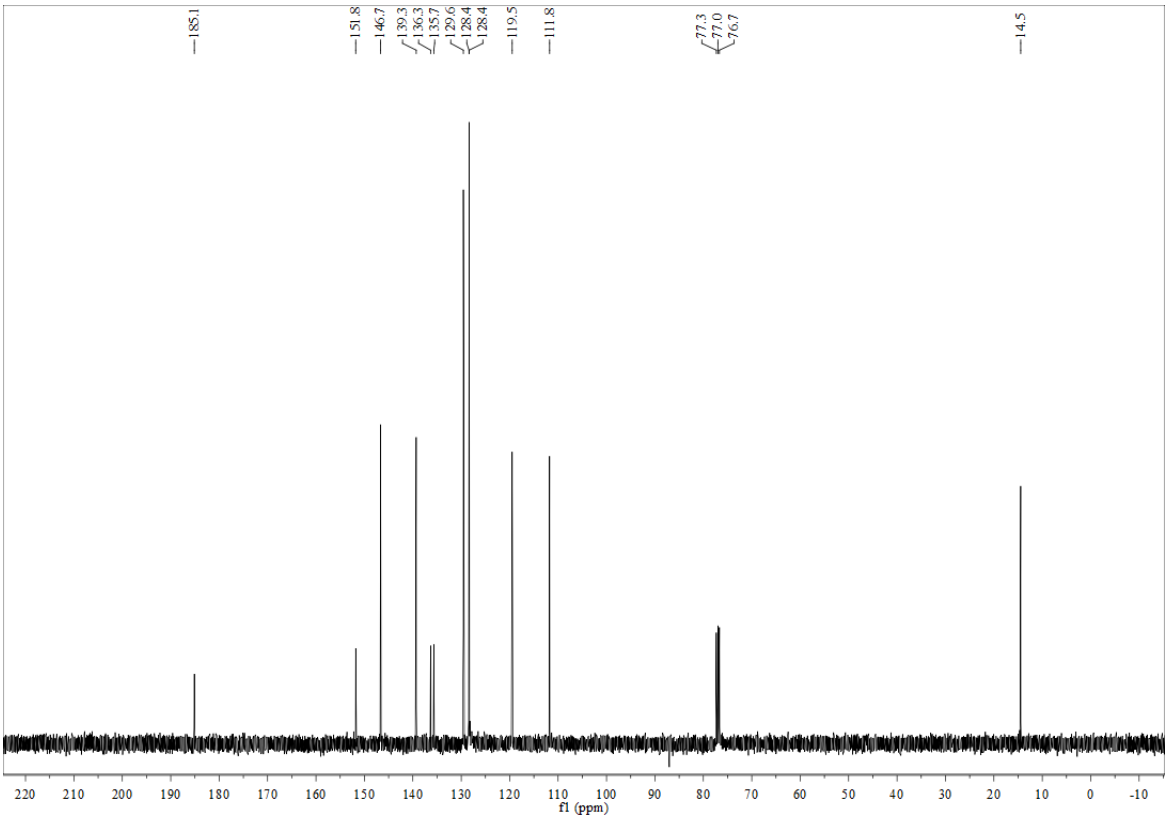

O
170
1.40
3.50
9.06
3.00
f1 (ppm)

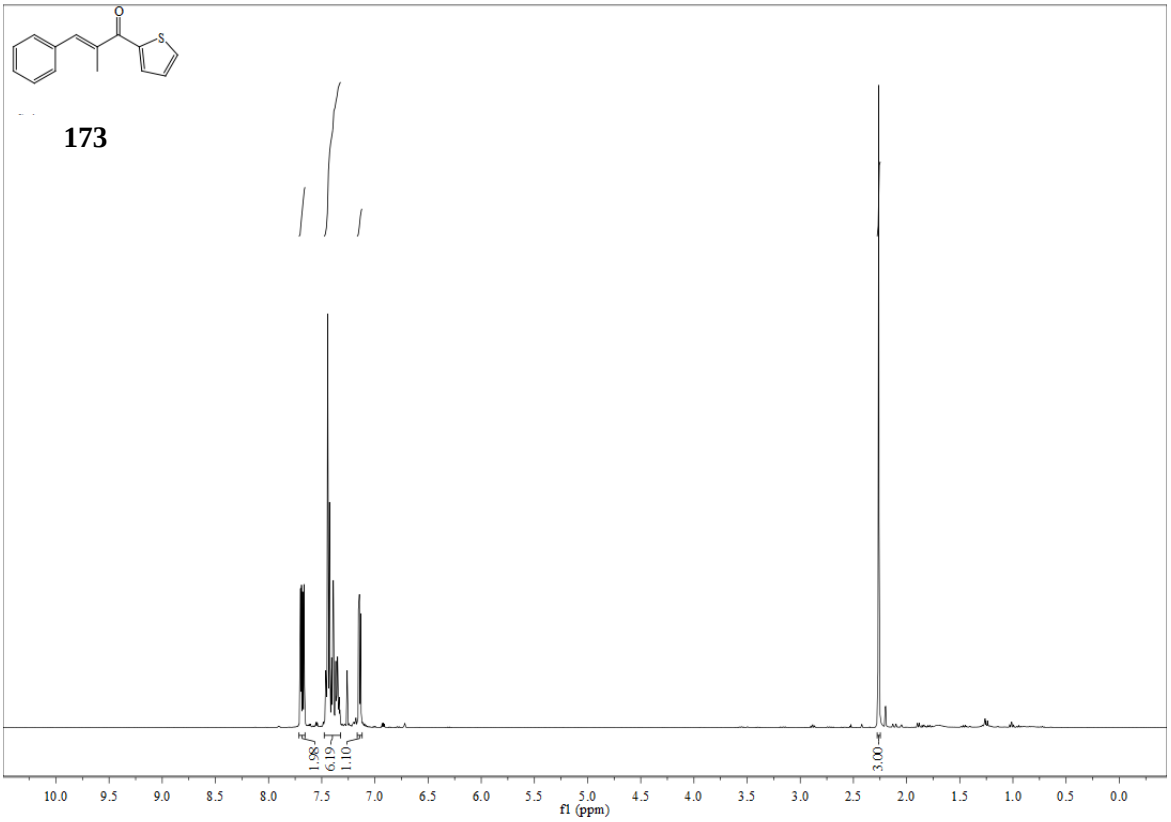

192.6
143.4
138.6
138.5
135.9
135.1
130.1
129.7
128.8
128.5
128.4
128.2
121.9
77.3
77.0
76.7
13.8
f1 (ppm)

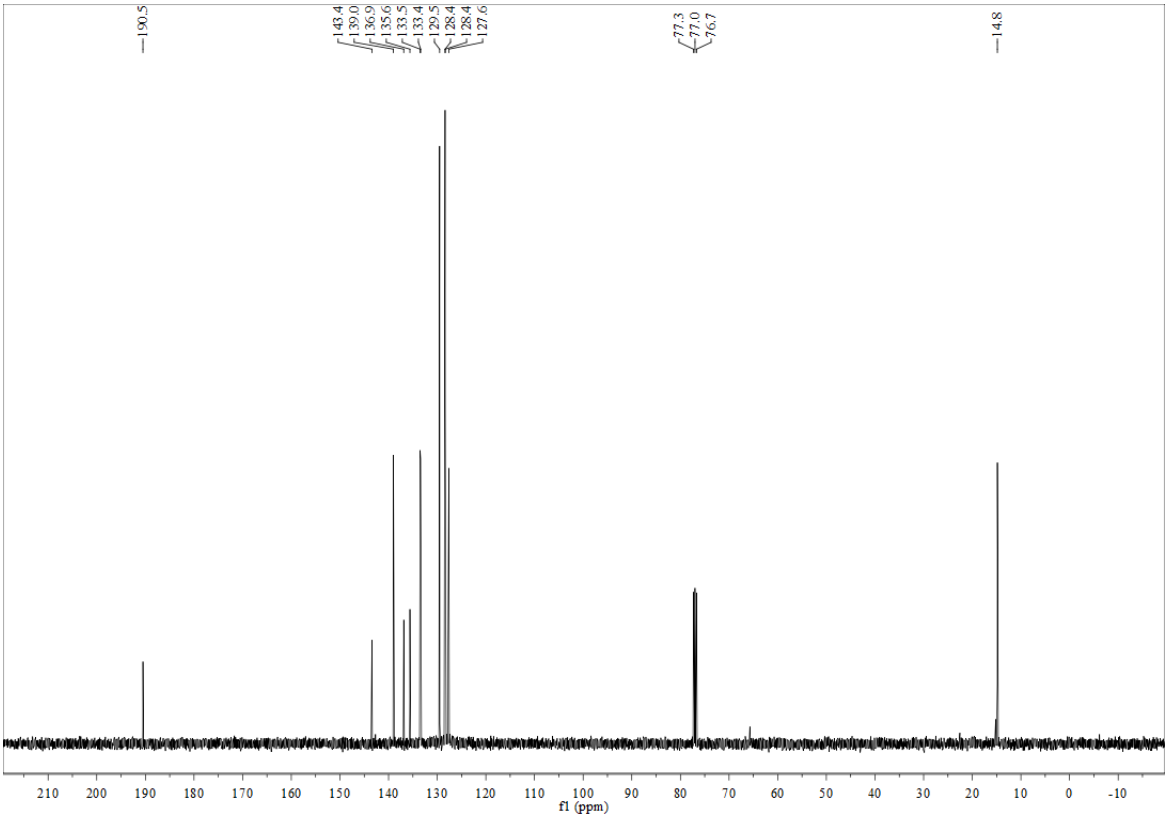

O
171
1.02
5.26
1.01
1.02
2.99
3.00
f1 (ppm)

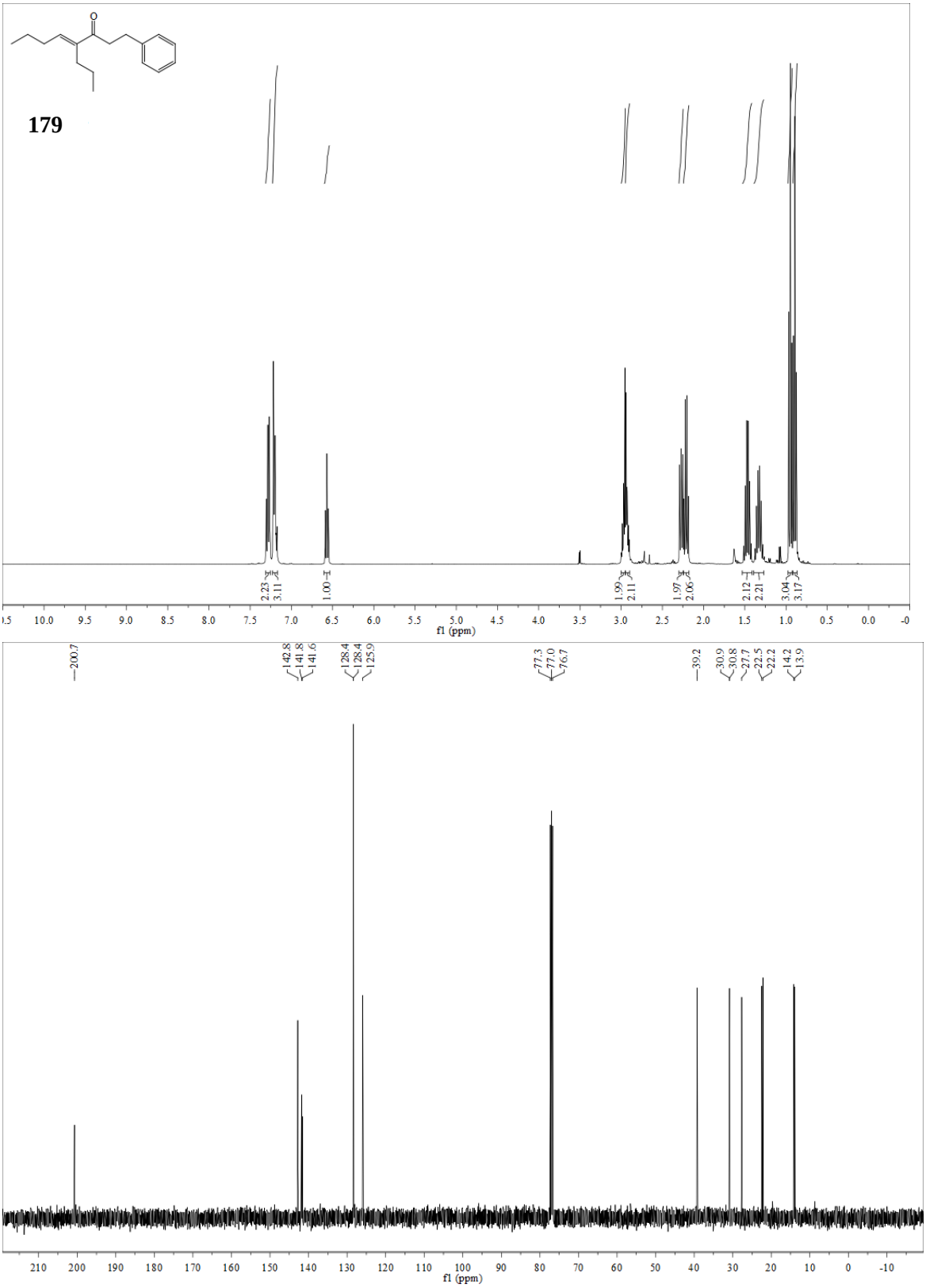

192.8
143.0
138.4
137.9
135.9
129.6
128.3
128.3
126.9
77.3
77.0
76.7
18.4
13.5
f1 (ppm)

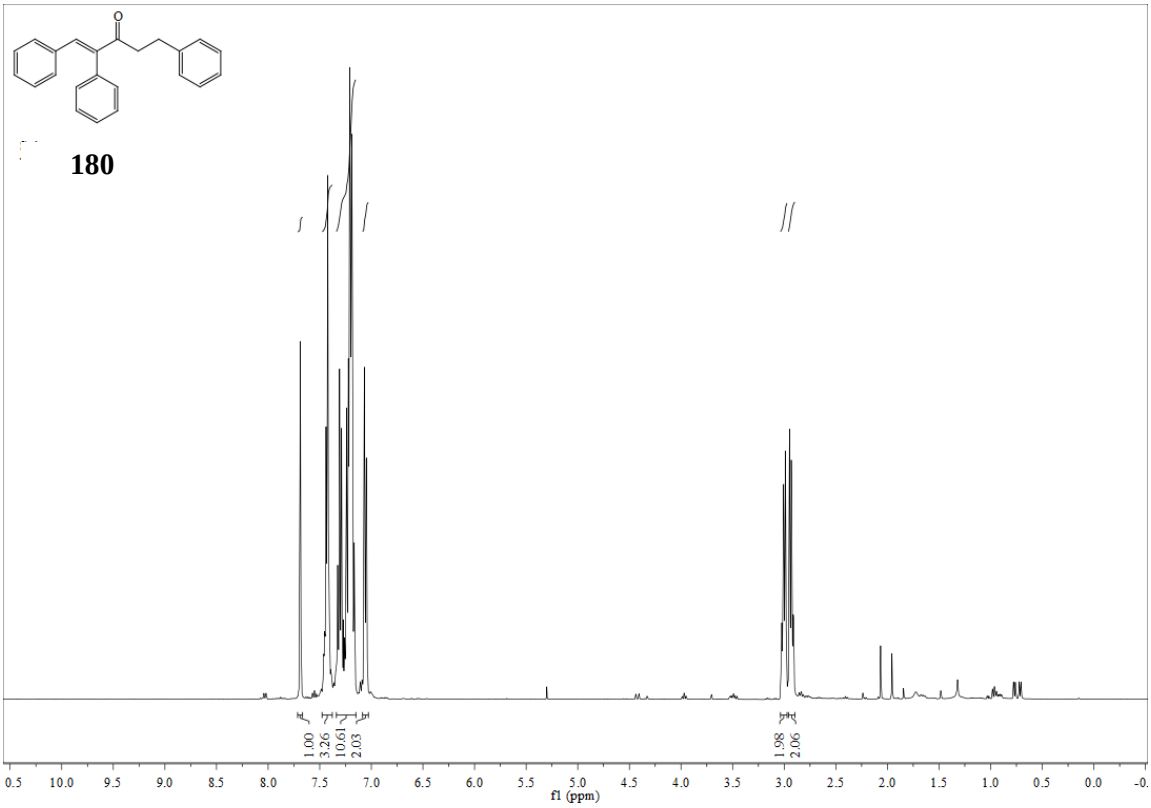

O
O
172
0.98
1.01
5.32
1.03
1.00
3.01
f1 (ppm)

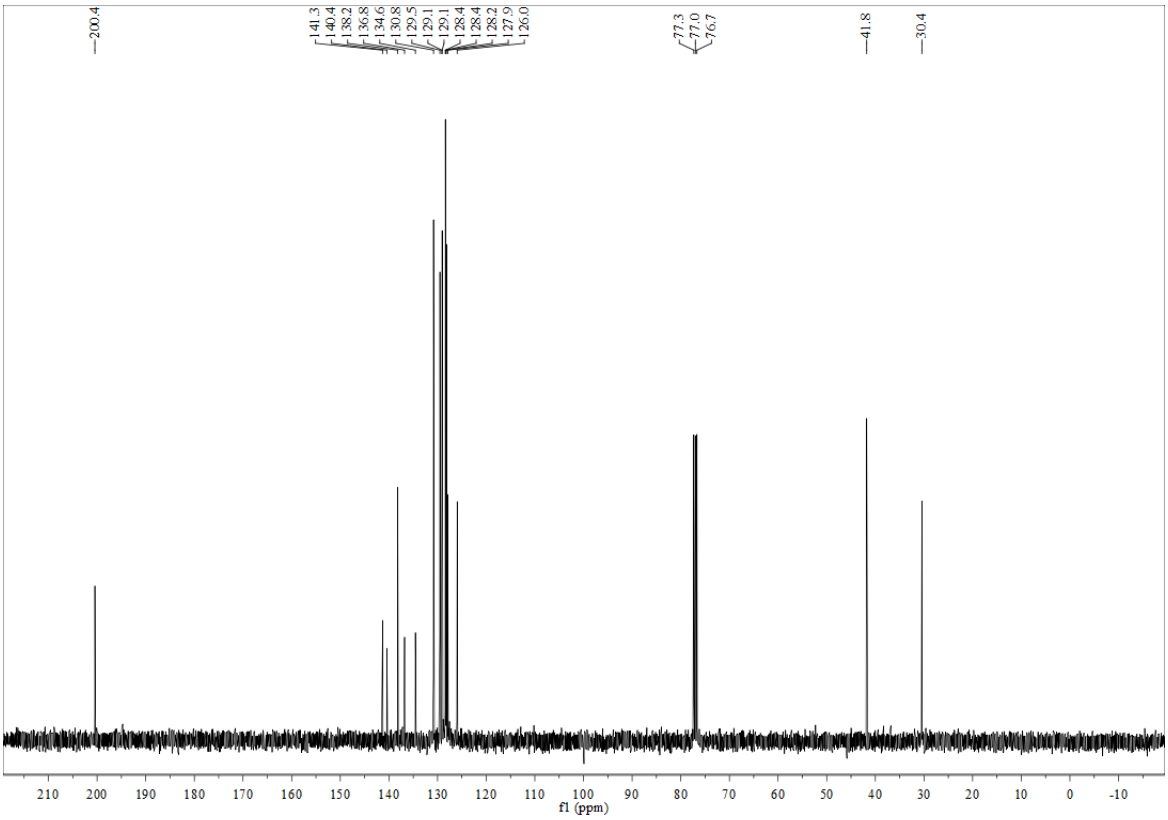

185.1
151.8
146.7
139.3
136.3
135.7
129.6
128.4
128.4
119.5
111.8
77.3
77.0
76.7
14.5
f1 (ppm)

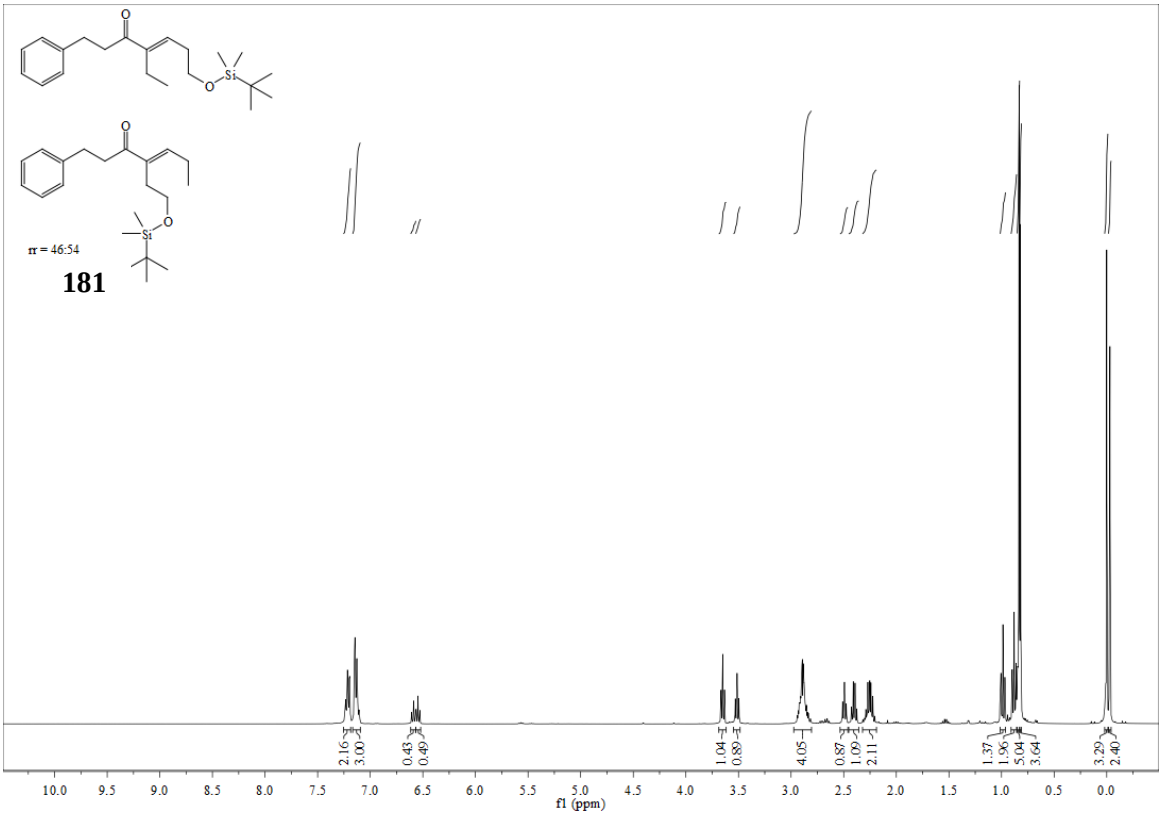

O
S
173
1.98
6.19
1.10
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

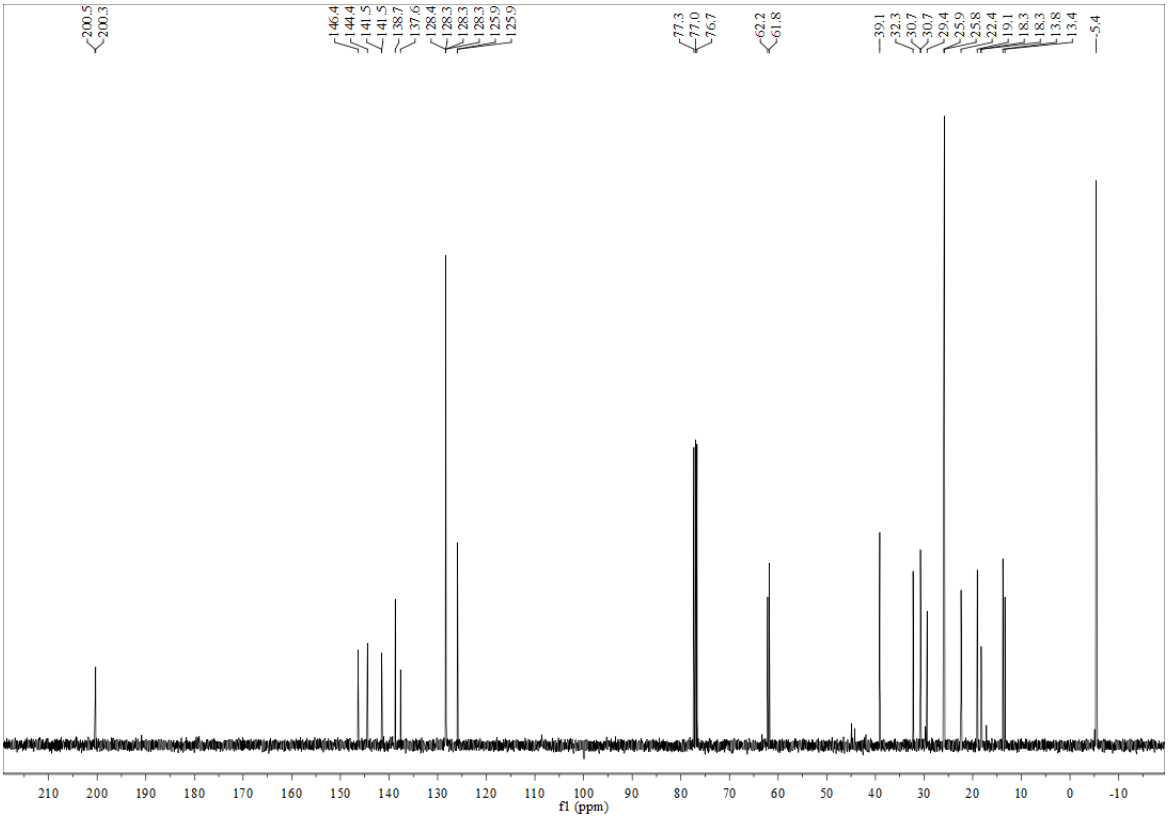

190.5
143.4
139.0
136.9
135.6
133.5
133.4
129.5
128.4
128.4
127.6
77.3
77.0
76.7
14.8
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

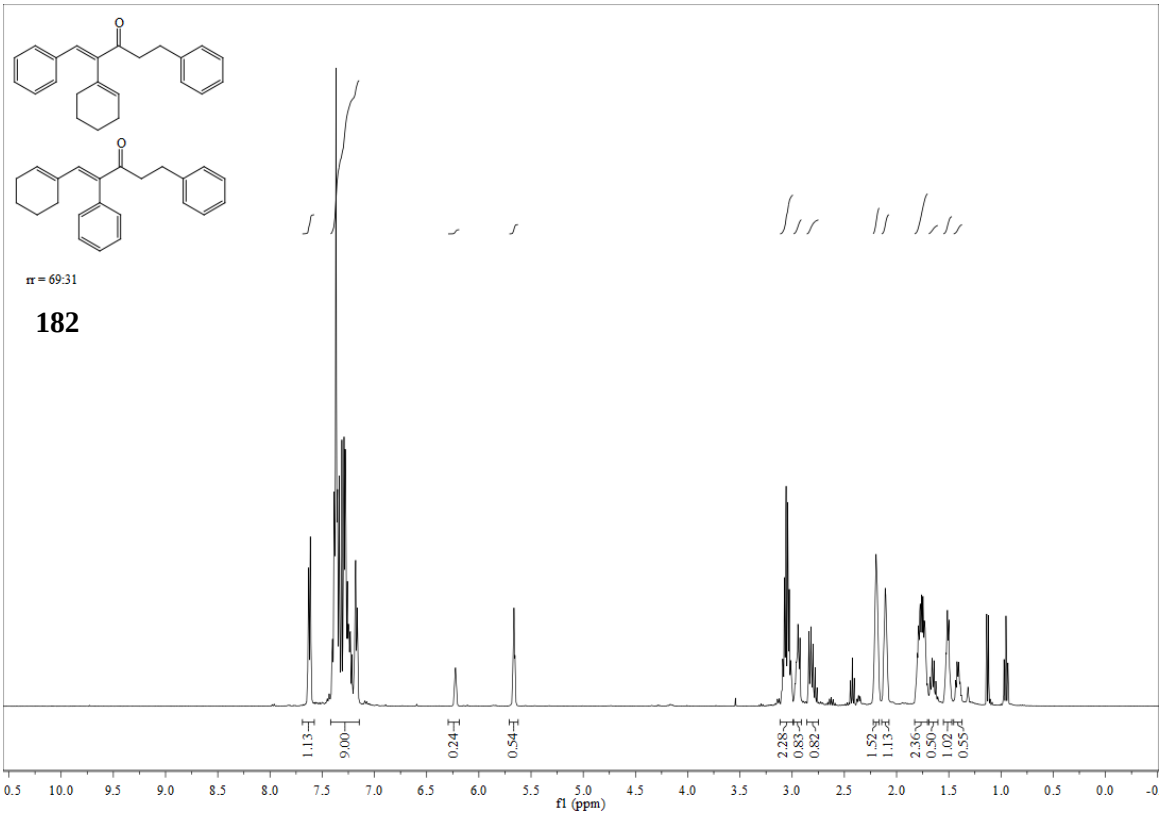

179
2.23
3.11
1.00
1.99
2.11
1.97
2.06
2.12
2.21
3.04
3.17
f1 (ppm)
200.7
142.8
141.8
141.6
128.4
128.4
125.9
77.3
77.0
76.7
39.2
30.9
30.8
27.7
22.5
22.2
14.2
13.9
f1 (ppm)

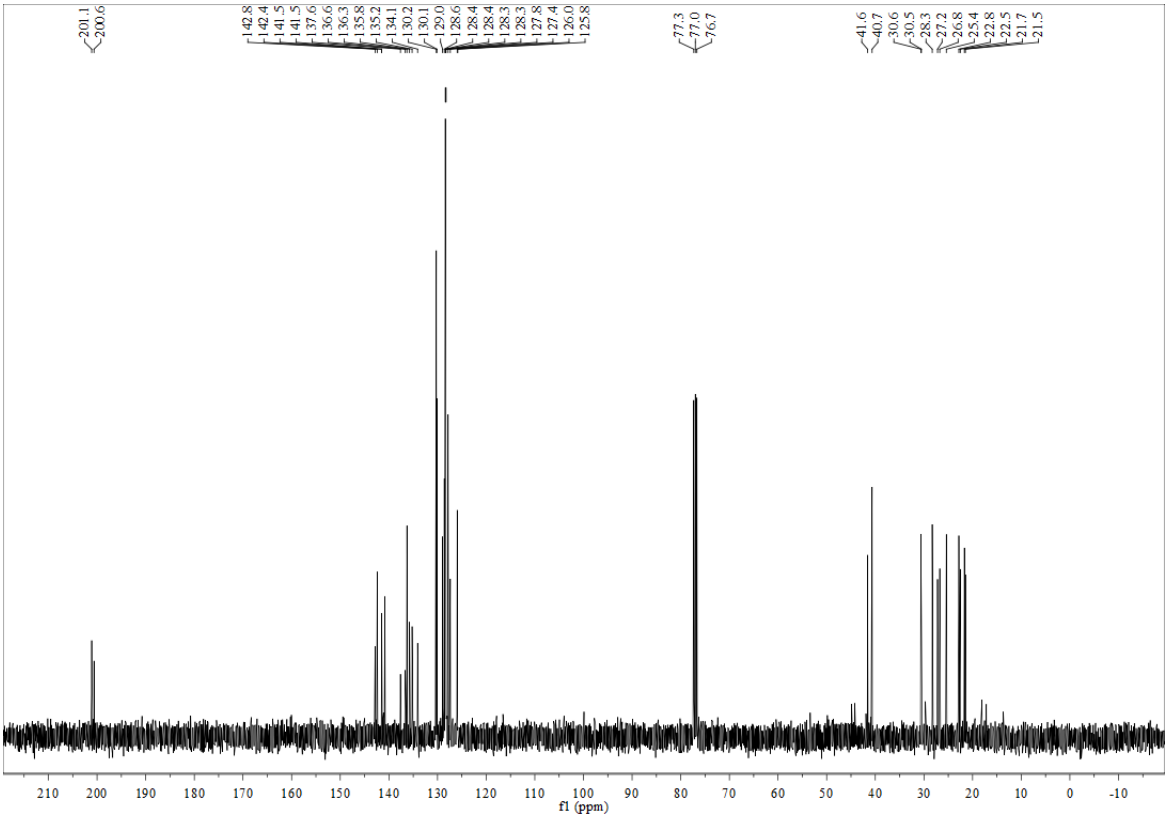

O
180
1.00
3.26
10.61
2.03
1.98
2.06
f1 (ppm)

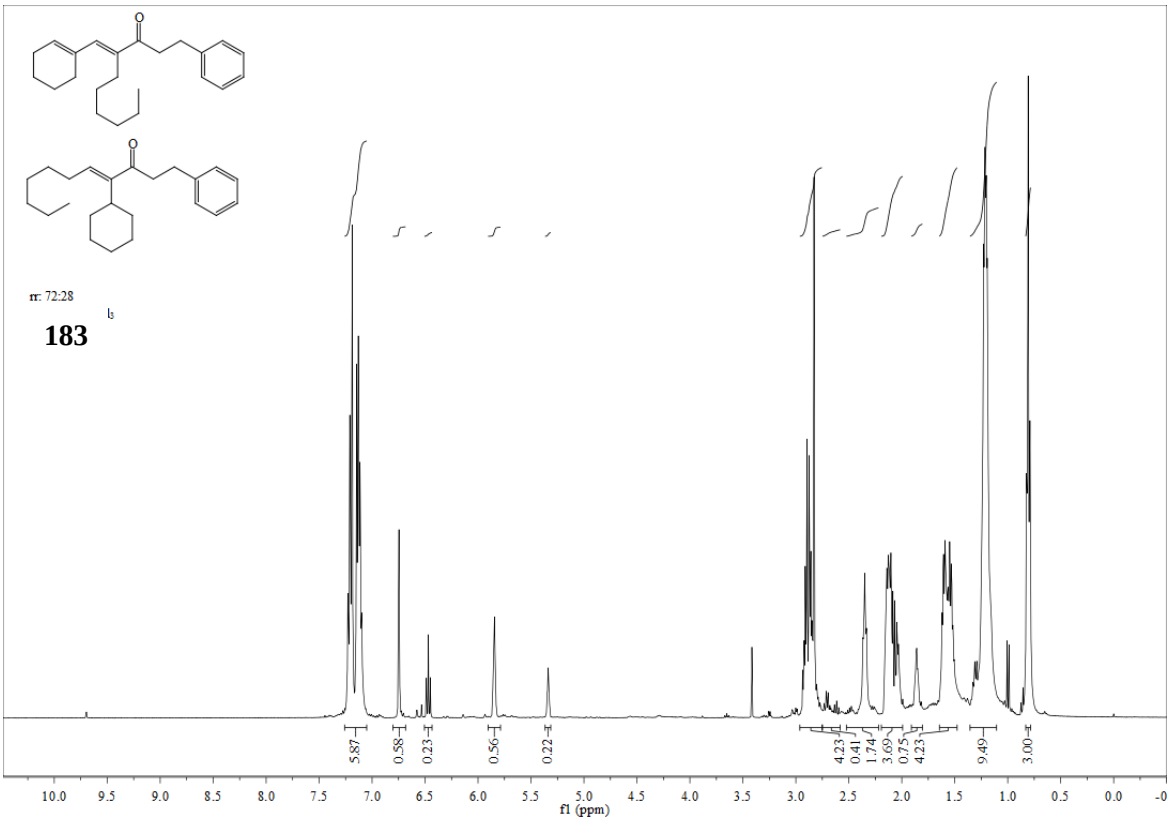

200.4
141.3
140.4
138.2
136.8
134.6
130.8
129.5
129.1
129.1
128.4
128.4
128.2
127.9
126.0
77.3
77.0
76.7
41.8
30.4
f1 (ppm)

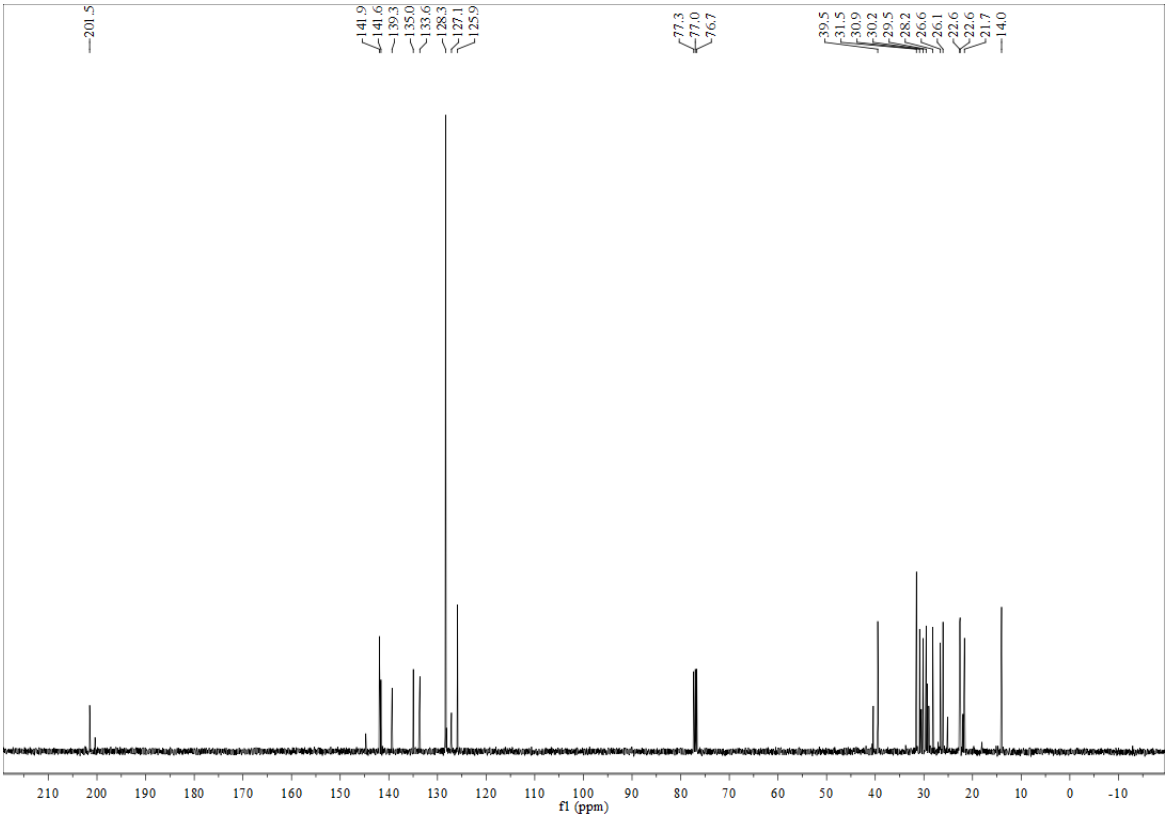

rr = 46:54
181
2.16
3.00
0.43
0.49
1.04
0.89
4.05
0.87
1.09
2.11
1.37
1.96
5.04
3.64
3.29
2.40
f1 (ppm)

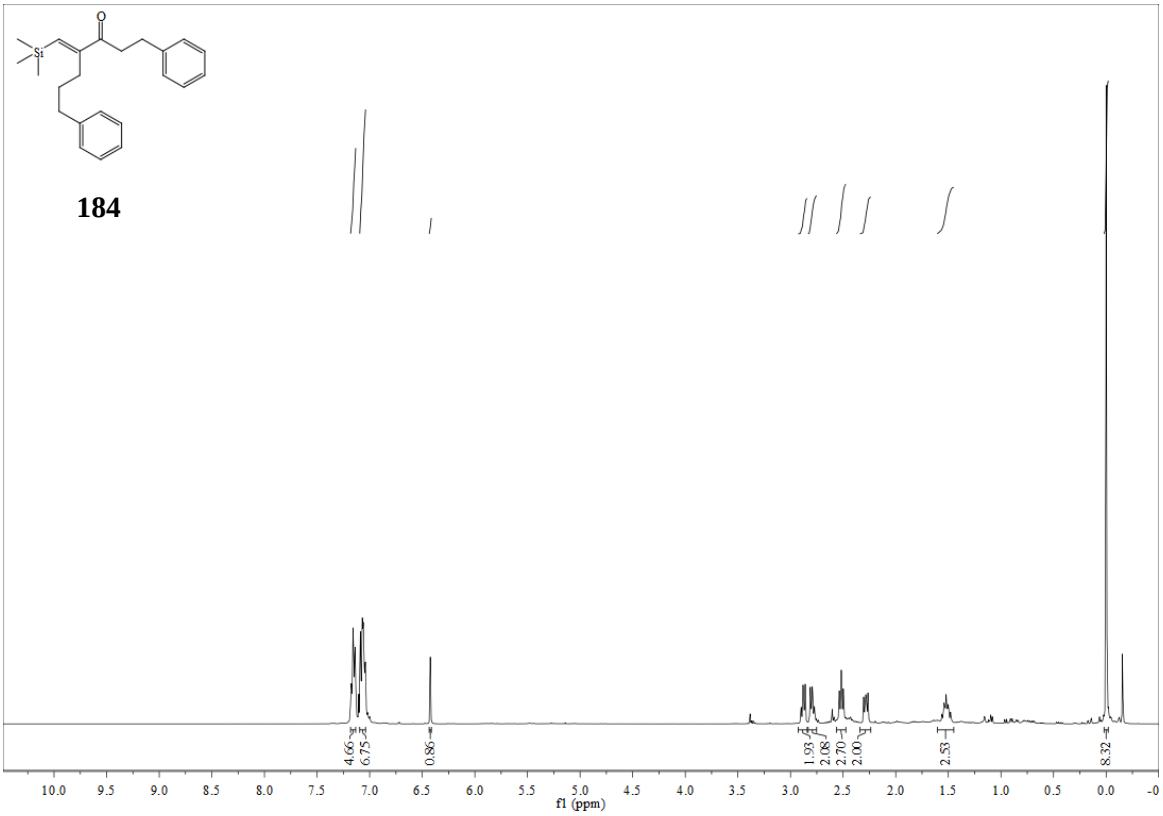

200.5
200.3
146.4
144.4
141.5
141.5
138.7
137.6
128.4
128.3
128.3
125.9
125.9
77.3
77.0
76.7
62.2
61.8
39.1
32.3
30.7
30.7
29.4
25.9
25.8
22.4
19.1
18.3
18.3
13.8
13.4
-5.4
f1 (ppm)


rr = 69:31
182
1.13
9.00
0.24
0.54
2.28
0.83
0.82
1.52
1.13
2.36
0.50
1.02
0.55
f1 (ppm)

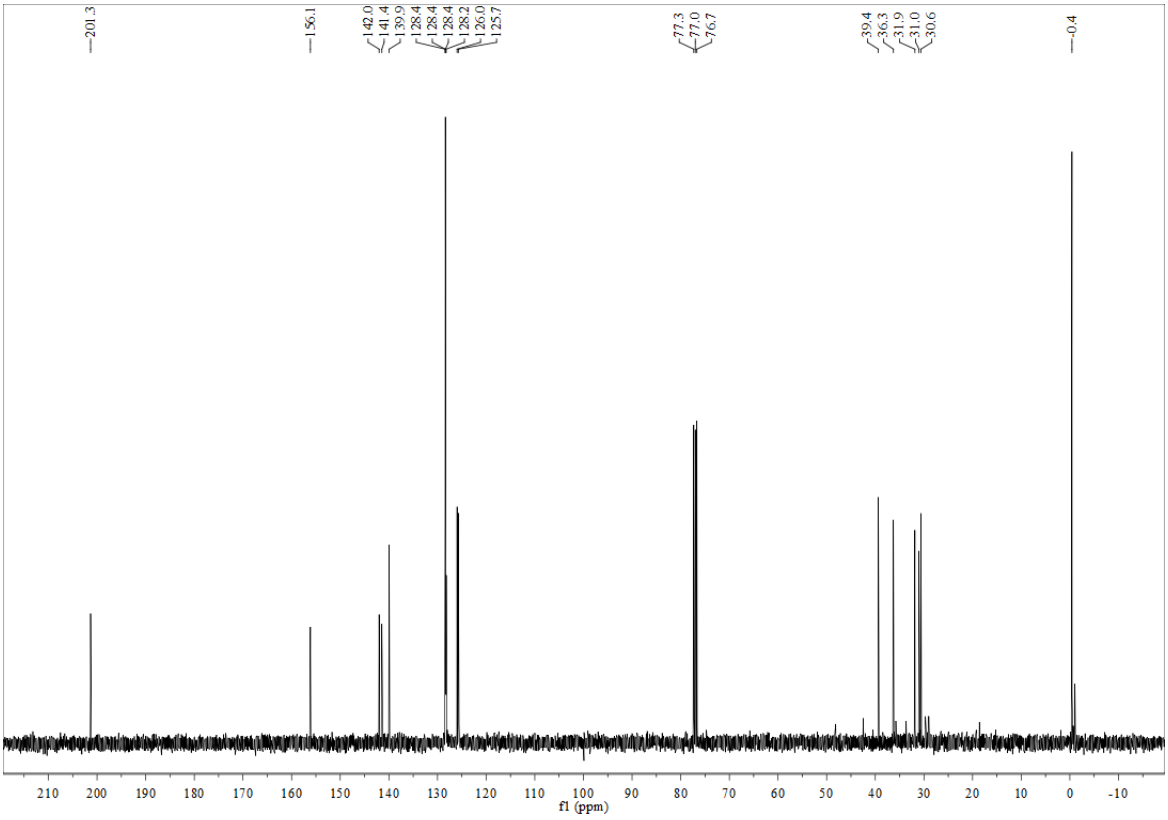

201.1
200.6
142.8
142.4
141.5
141.5
137.6
136.6
136.3
135.8
135.2
134.1
130.2
130.1
129.0
128.6
128.4
128.4
128.3
128.3
127.8
127.4
126.0
125.8
77.3
77.0
76.7
41.6
40.7
30.6
30.5
28.3
27.2
26.8
25.4
22.8
22.5
21.7
21.5
f1 (ppm)

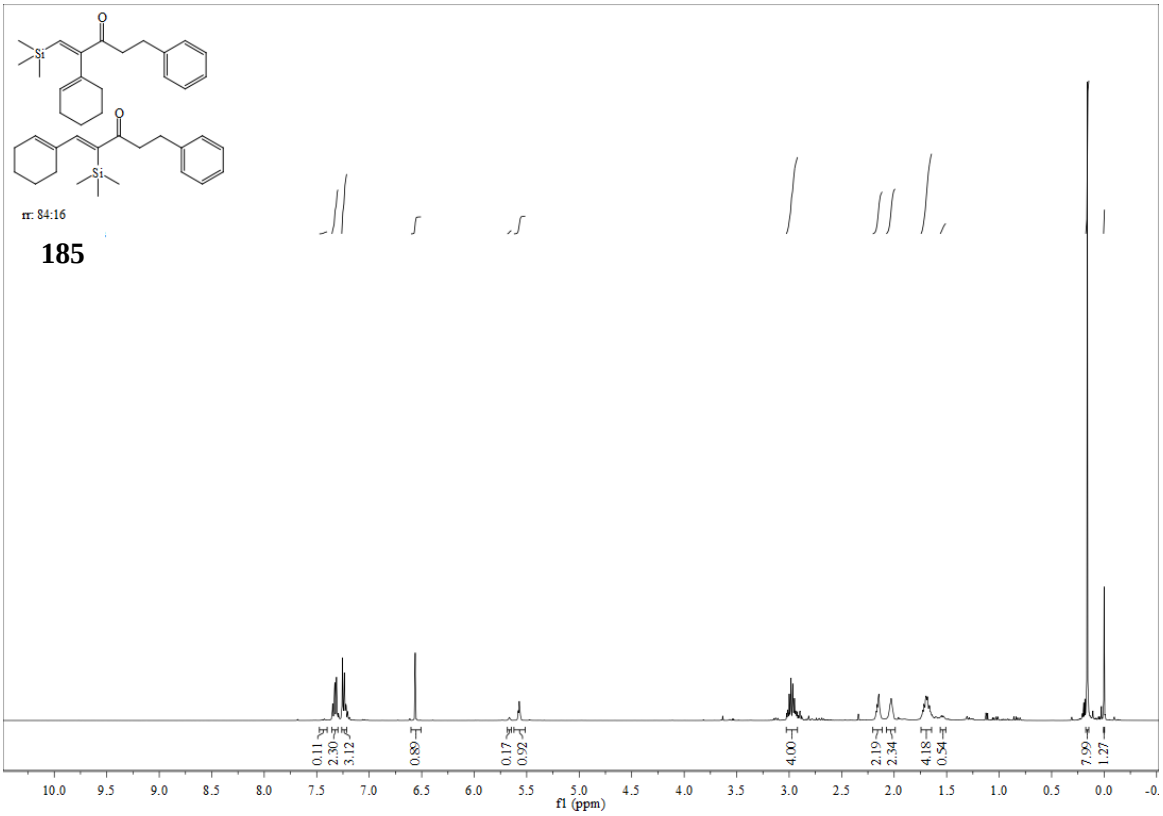

rr: 72:28
183
5.87
0.58
0.23
0.56
0.22
4.23
0.41
1.74
3.69
0.75
4.23
9.49
3.00
f1 (ppm)

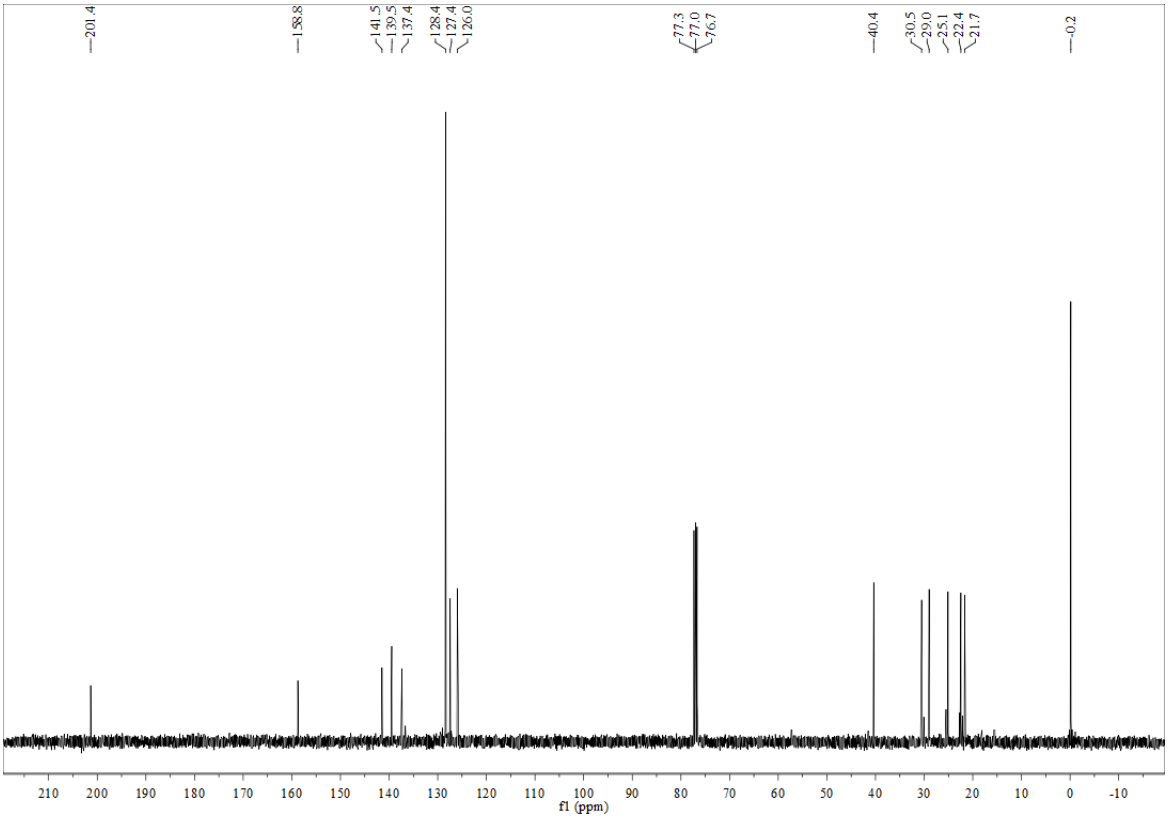

201.5
141.9
141.6
139.3
135.0
133.6
128.3
127.1
125.9
77.3
77.0
76.7
39.5
31.5
30.9
30.2
29.5
28.2
26.6
26.1
22.6
22.6
21.7
14.0
f1 (ppm)

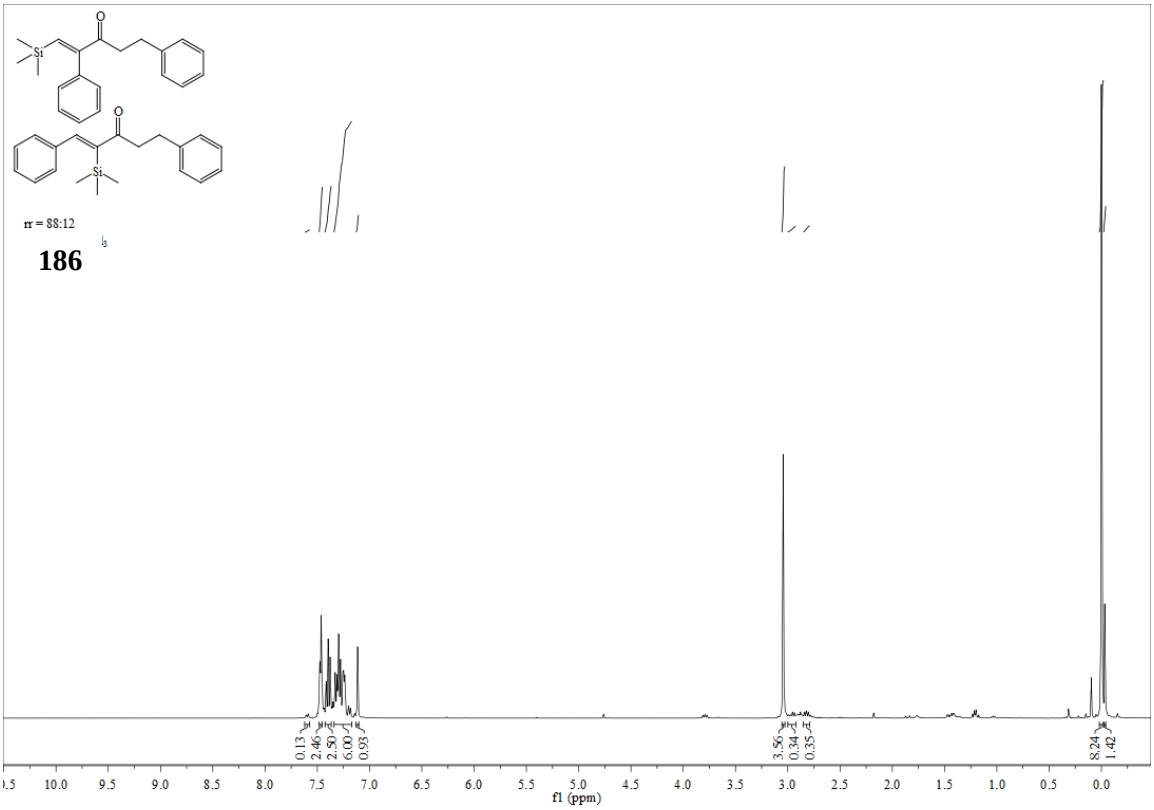

Si
O
4.66
6.75
0.86
1.93
2.08
2.70
2.00
2.53
8.32
f1 (ppm)

184

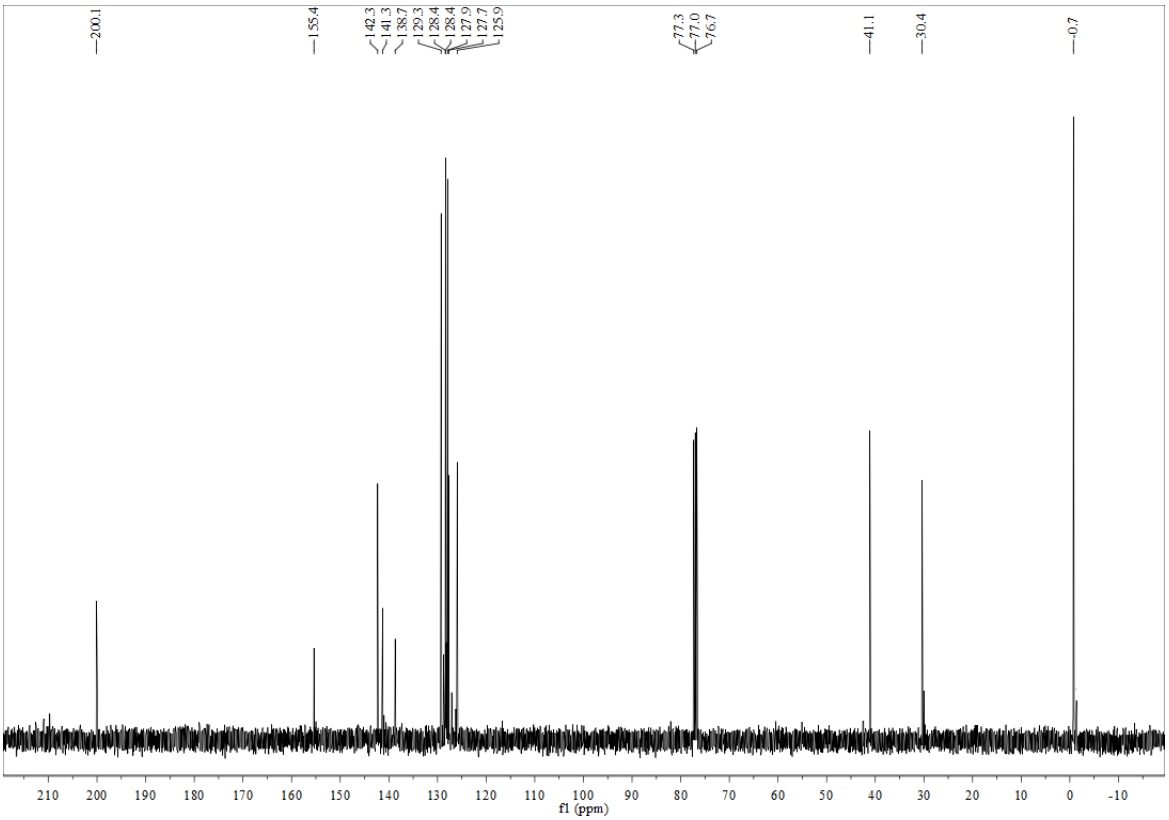

201.3
156.1
142.0
141.4
139.9
128.4
128.4
128.4
128.2
126.0
125.7
77.3
77.0
76.7
39.4
36.3
31.9
31.0
30.6
-0.4
f1 (ppm)

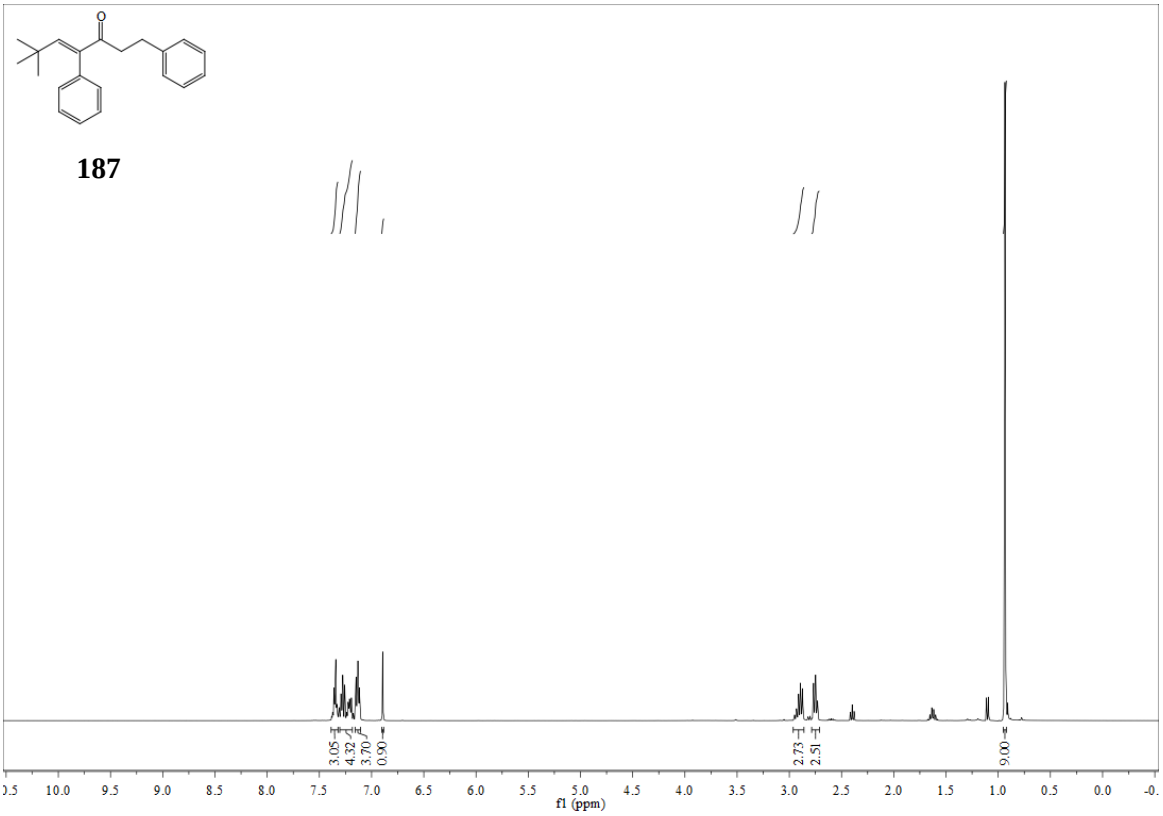

rr: 84:16
185
0.11
2.30
3.12
0.89
0.17
0.92
4.00
2.19
2.34
4.18
0.54
7.99
1.27
f1 (ppm)


201.4
158.8
141.5
139.5
137.4
128.4
127.4
126.0
77.3
77.0
76.7
40.4
30.5
29.0
25.1
22.4
21.7
-0.2
f1 (ppm)

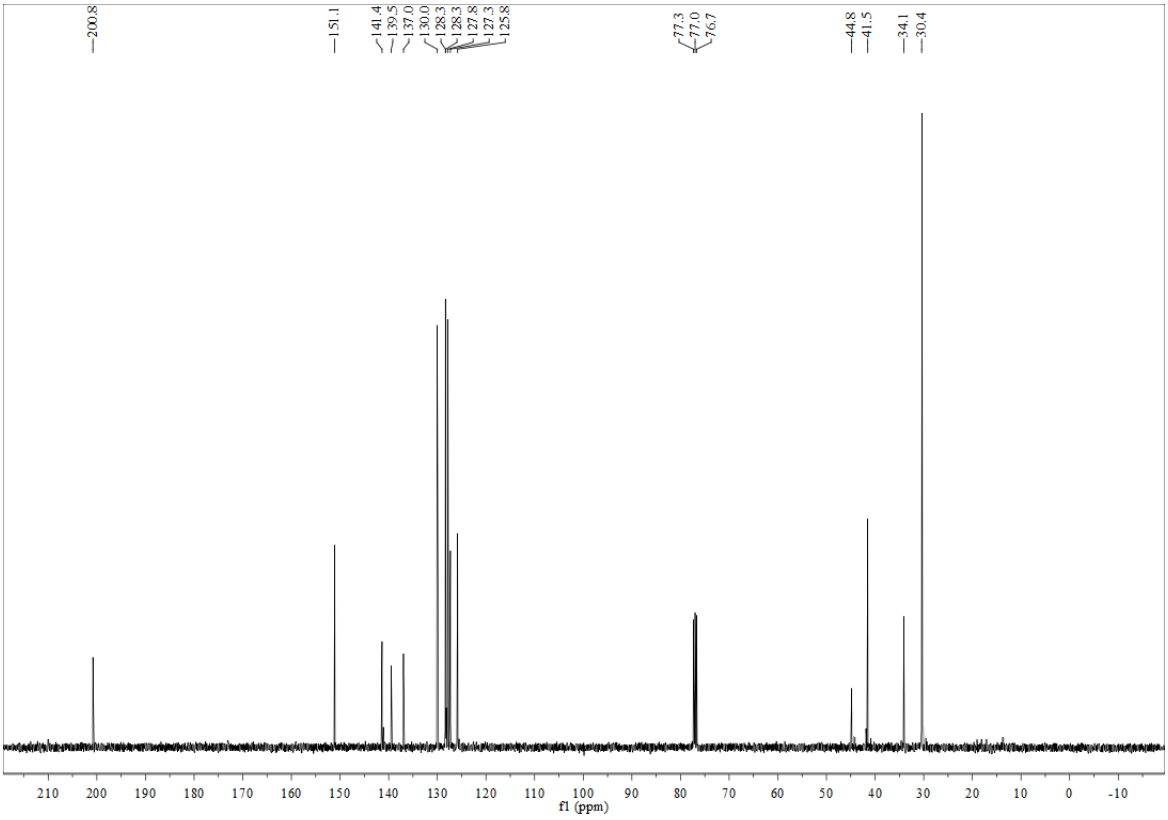

rr = 88:12
0.13
2.46
2.50
6.00
0.93
3.56
0.34
0.35
8.24
1.42
f1 (ppm)

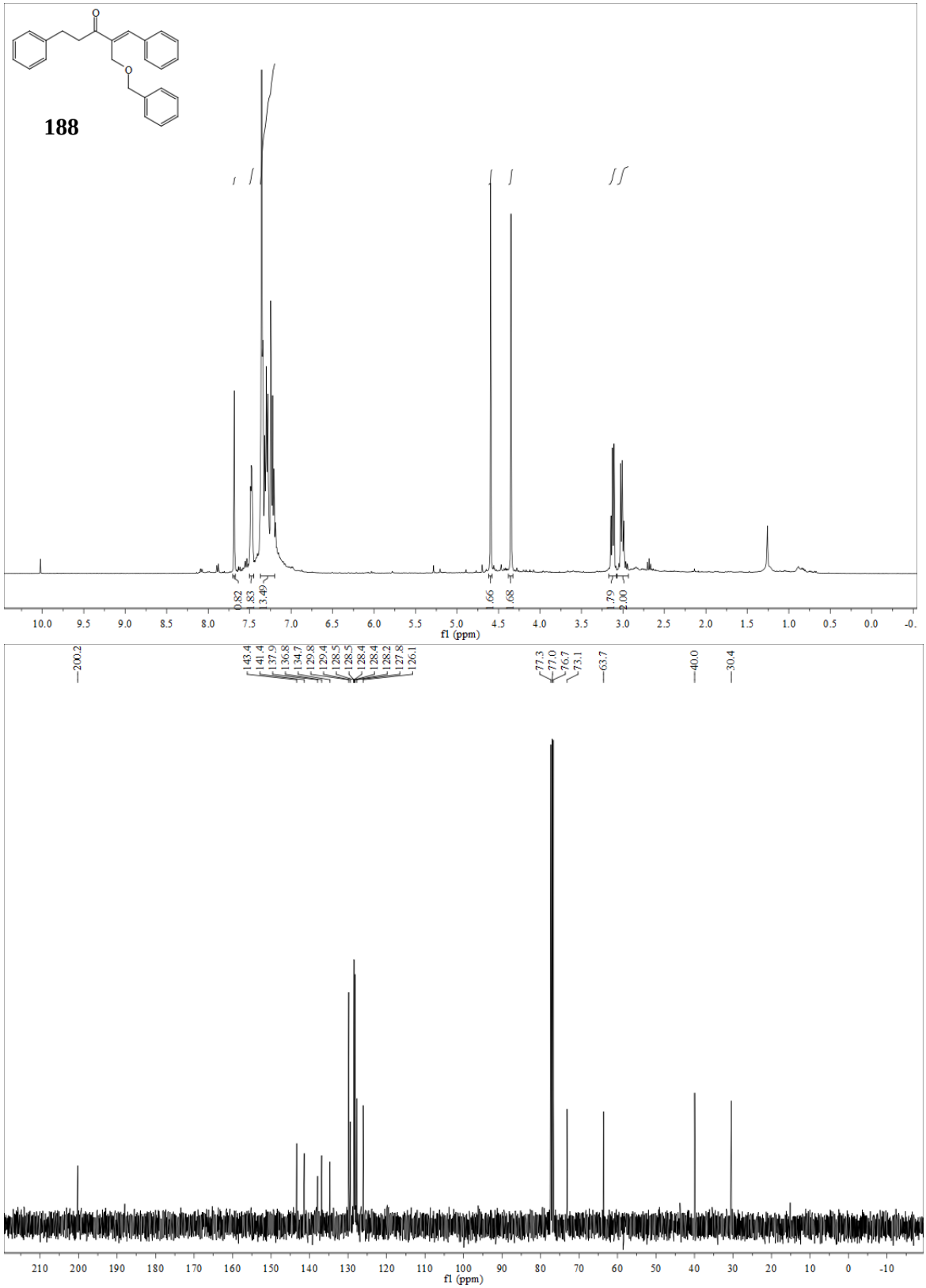
186

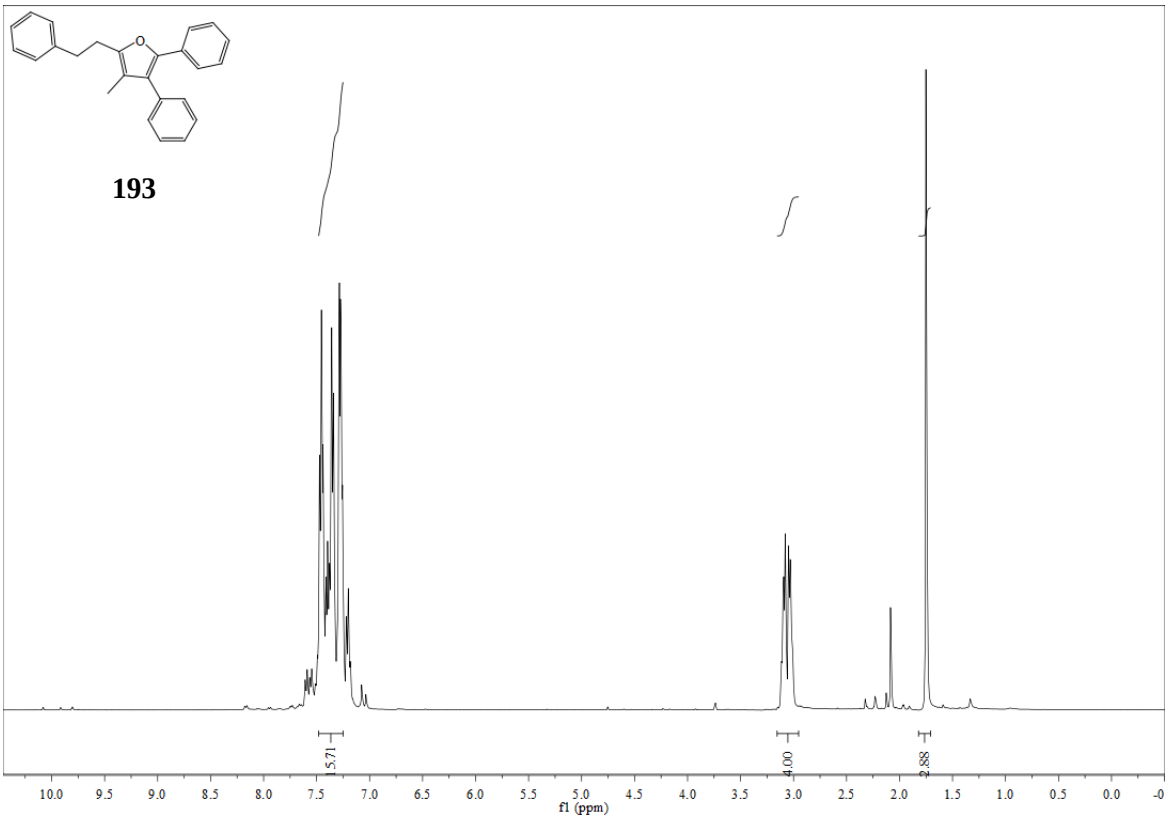

200.1
155.4
142.3
141.3
138.7
129.3
128.4
128.4
127.9
127.7
125.9
77.3
77.0
76.7
41.1
30.4
0.7
f1 (ppm)

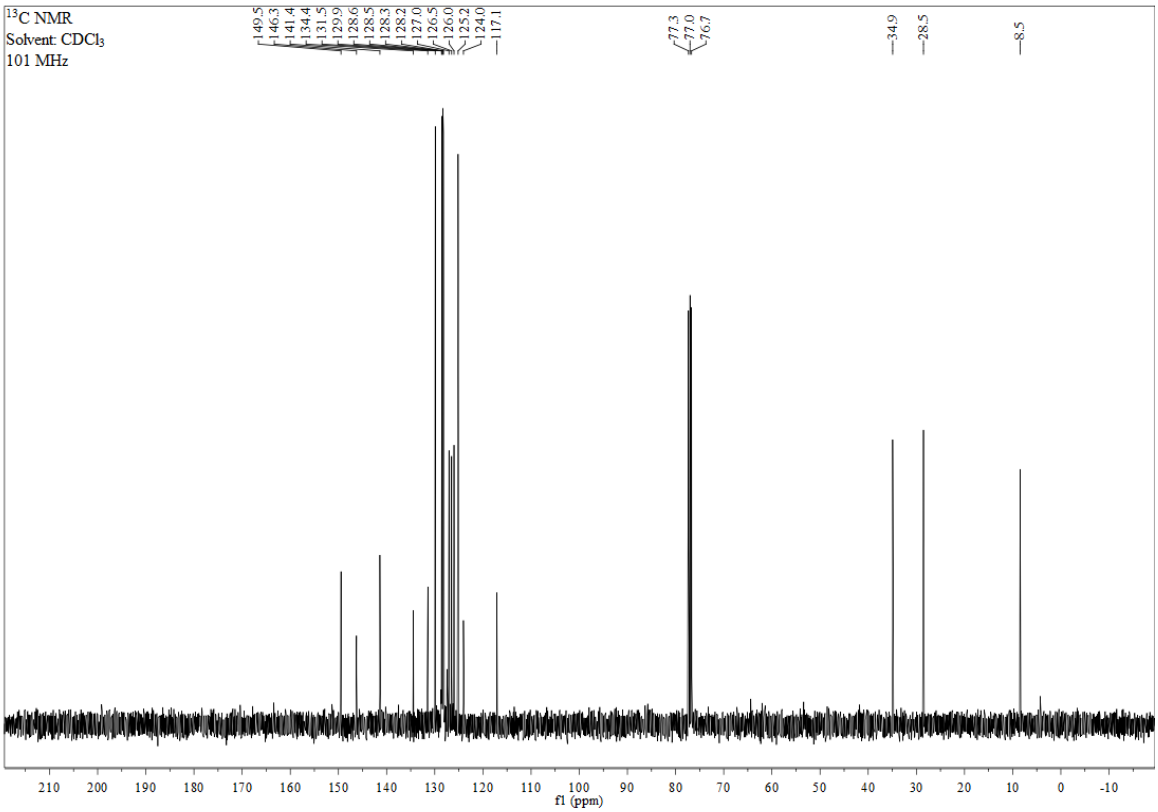

O
3.05
4.32
3.70
0.90
2.73
2.51
9.00
f1 (ppm)

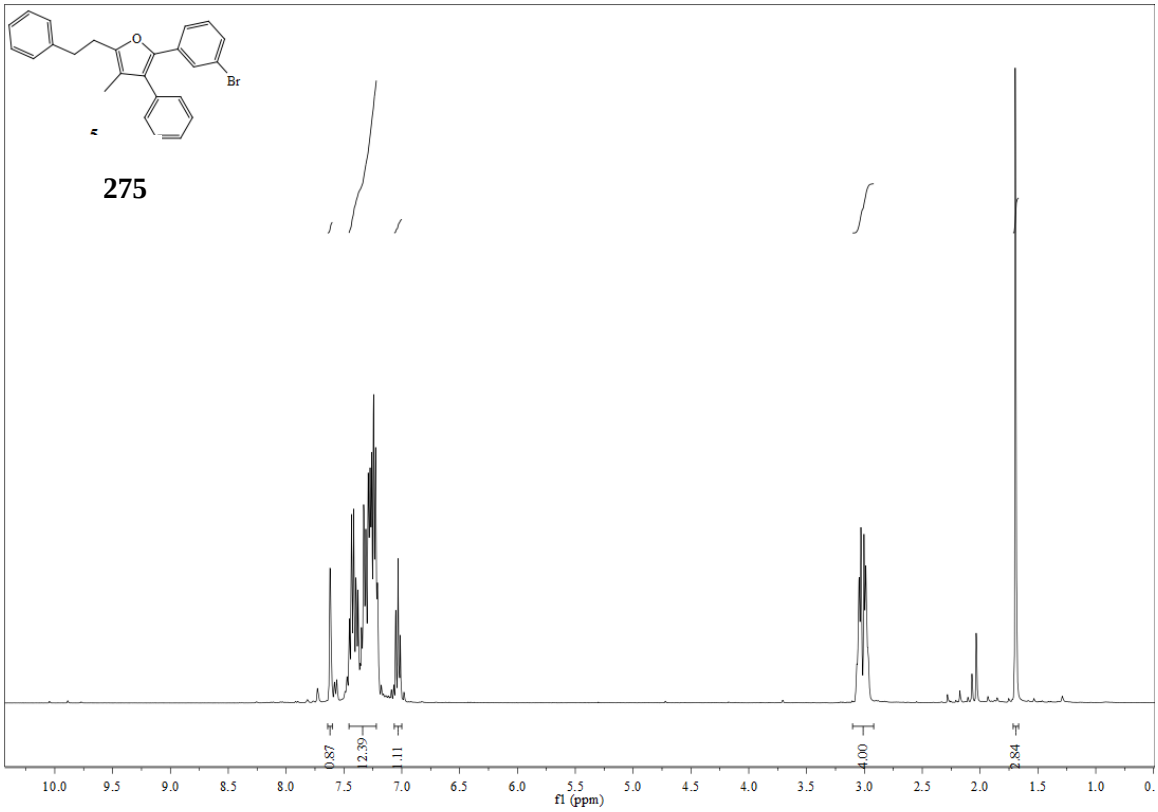
187

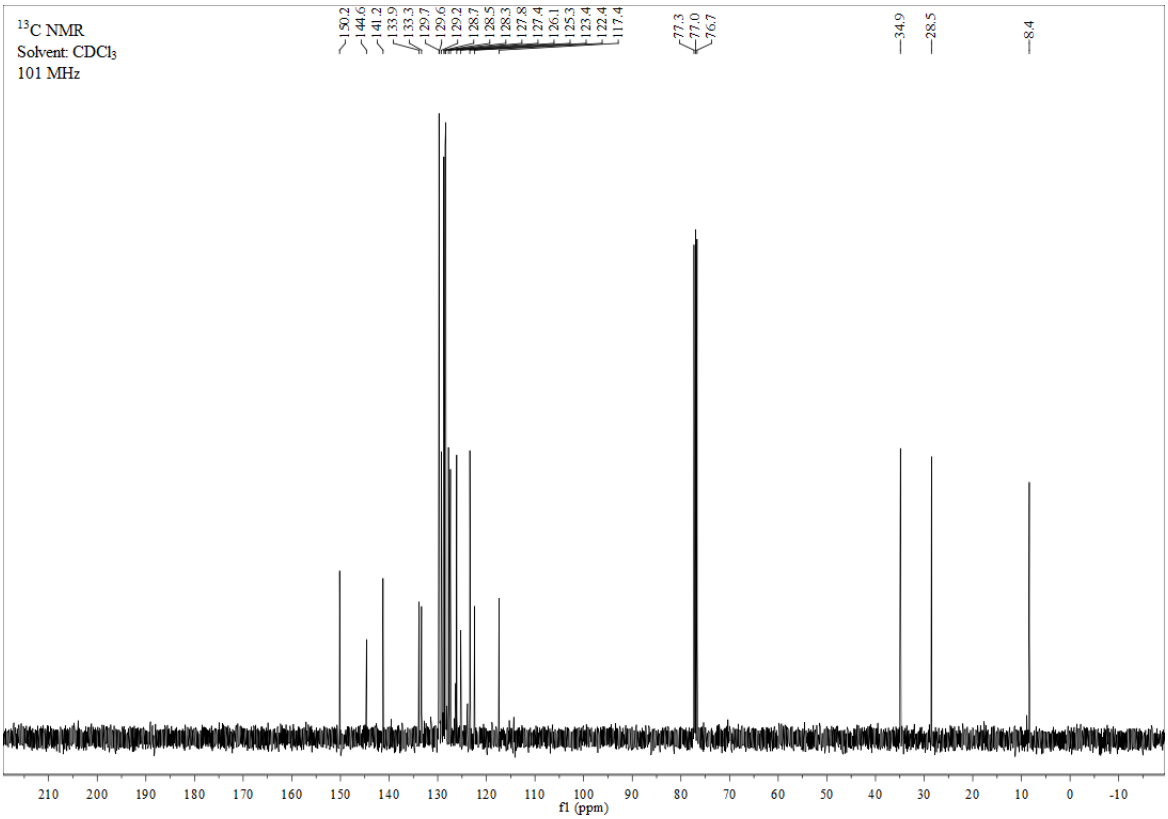

200.8
151.1
141.4
139.5
137.0
130.0
128.3
128.3
127.8
127.3
125.8
77.3
77.0
76.7
44.8
41.5
34.1
30.4
f1 (ppm)

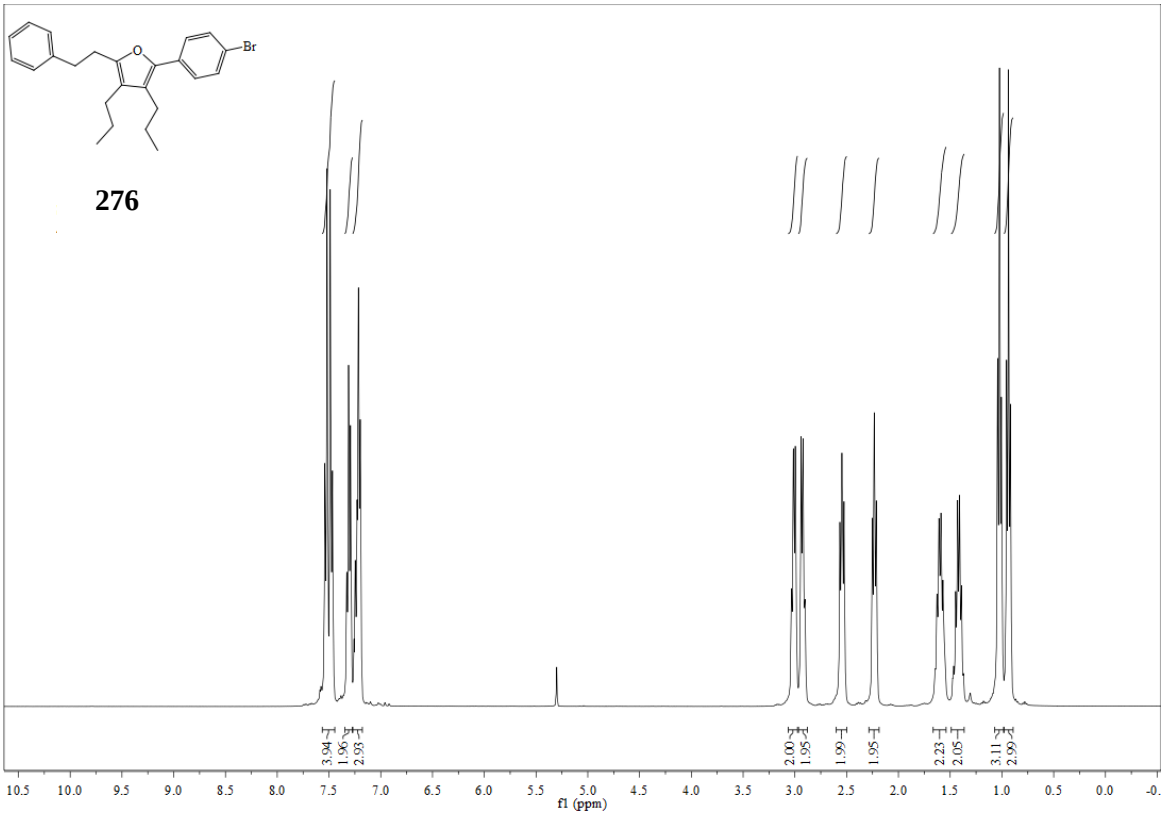

188
0.82
1.83
3.49
1.66
1.68
1.79
2.00
f1 (ppm)
200.2
143.4
141.4
137.9
136.8
134.7
129.8
129.4
128.5
128.5
128.4
128.4
128.2
127.8
126.1
77.3
77.0
76.7
73.1
63.7
40.0
30.4
f1 (ppm)

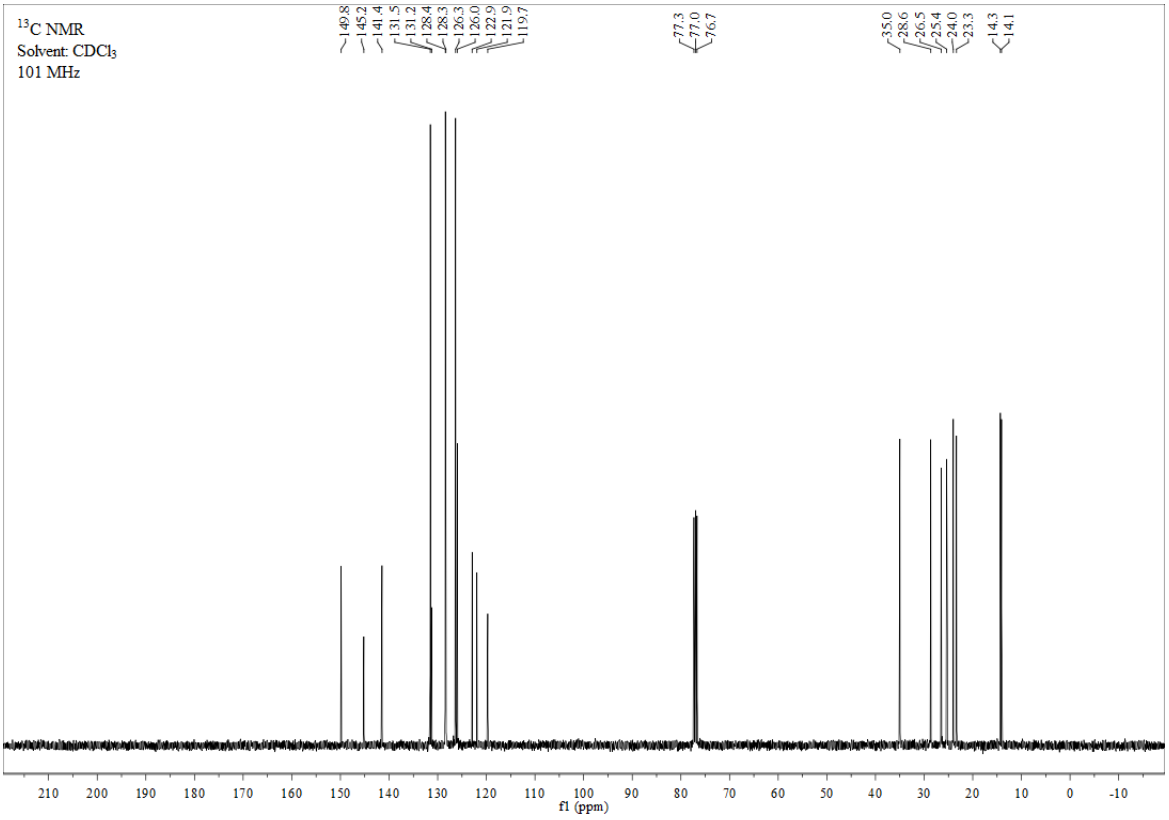

193
5.71
4.00
2.88
f1 (ppm)

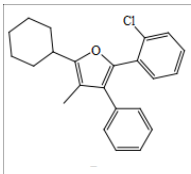

13C NMR
Solvent: CDCl3
101 MHz
149.5
146.3
141.4
134.4
131.5
129.9
128.6
128.5
128.3
128.2
127.0
126.5
126.0
125.2
124.0
117.1
77.3
77.0
76.7
34.9
28.5
8.5
f1 (ppm)


Br
275
0.87
2.39
1.11
4.00
2.84
f1 (ppm)


^{13}C NMR
Solvent: $CDCl_3$
101 MHz
150.2
144.6
141.2
133.9
133.3
129.7
129.6
129.2
128.7
128.5
128.3
127.8
127.4
126.1
125.3
123.4
122.4
117.4
77.3
77.0
76.7
34.9
28.5
8.4
f1 (ppm)

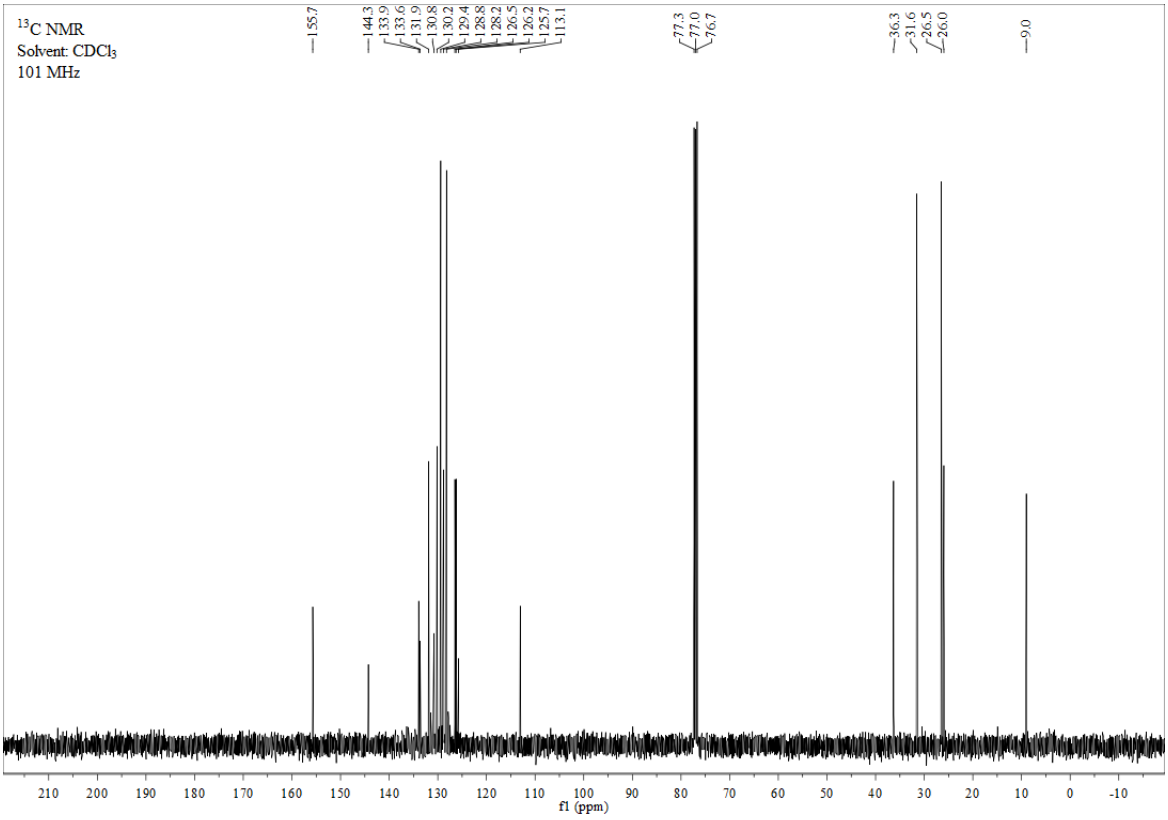

Br
O
276
3.94
1.96
2.93
2.00
1.95
1.99
1.95
2.23
2.05
3.11
2.99
f1 (ppm)

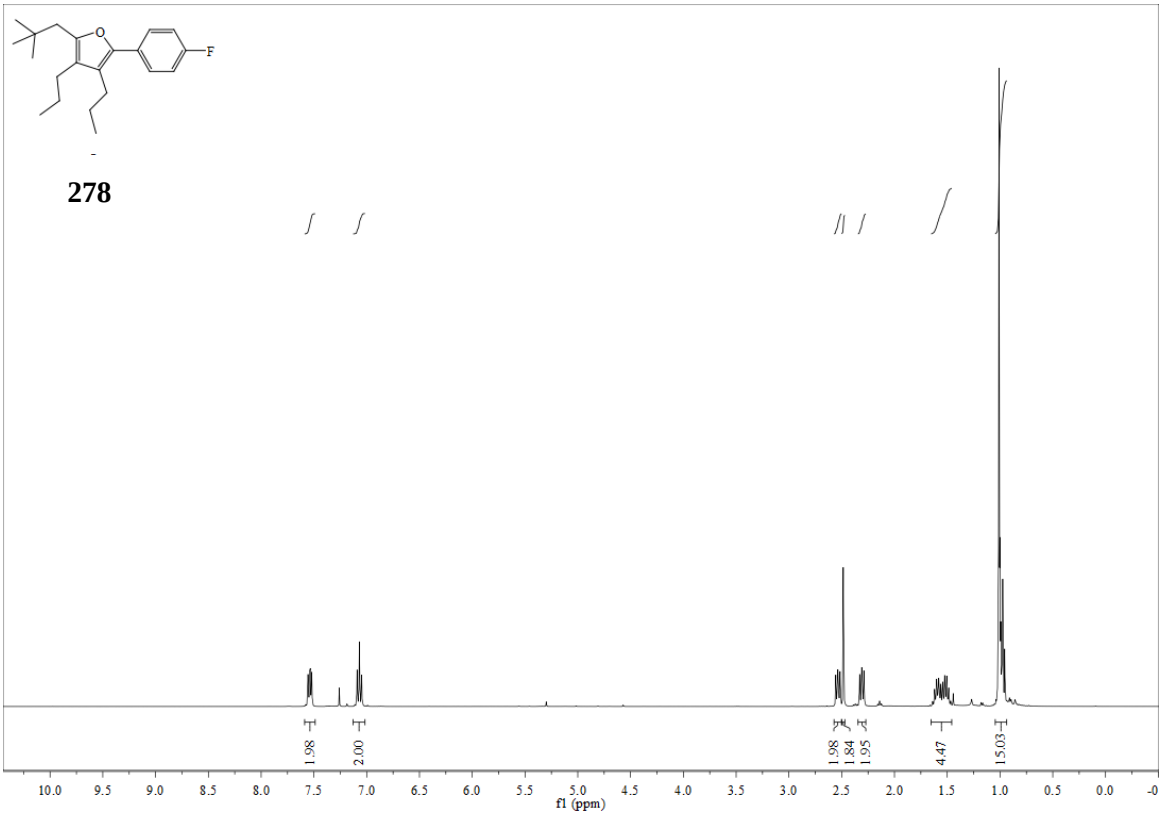

^{13}C NMR
Solvent: $CDCl_3$
101 MHz
149.8
145.2
141.4
131.5
131.2
128.4
128.3
126.3
126.0
122.9
121.9
119.7
77.3
77.0
76.7
35.0
28.6
26.5
25.4
24.0
23.3
14.3
14.1
f1 (ppm)

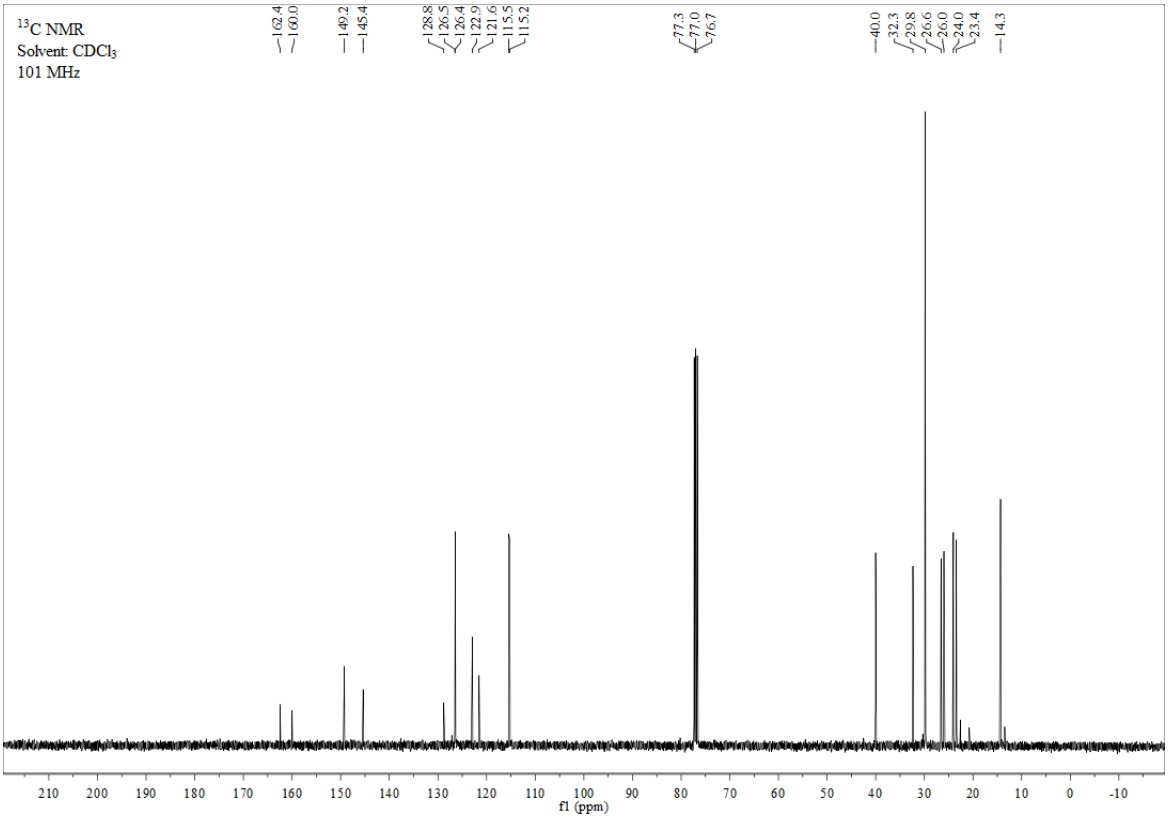

Cl
O

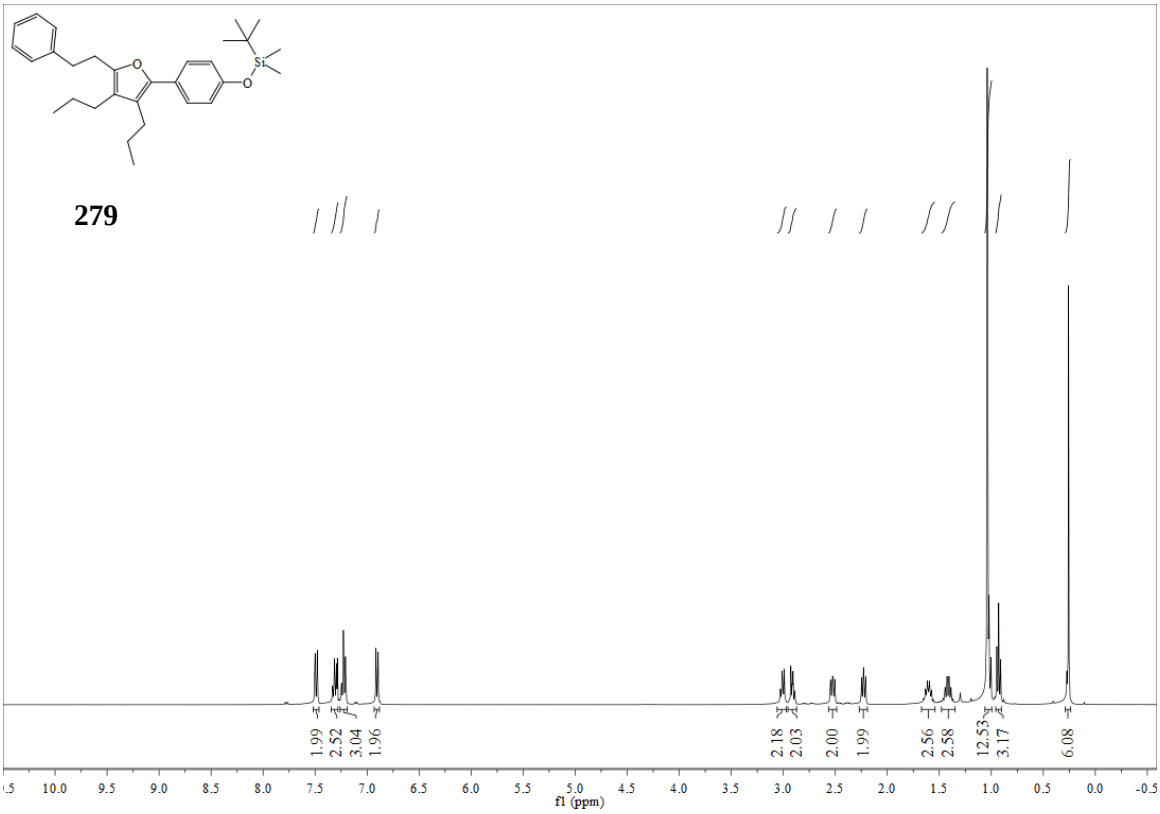
277

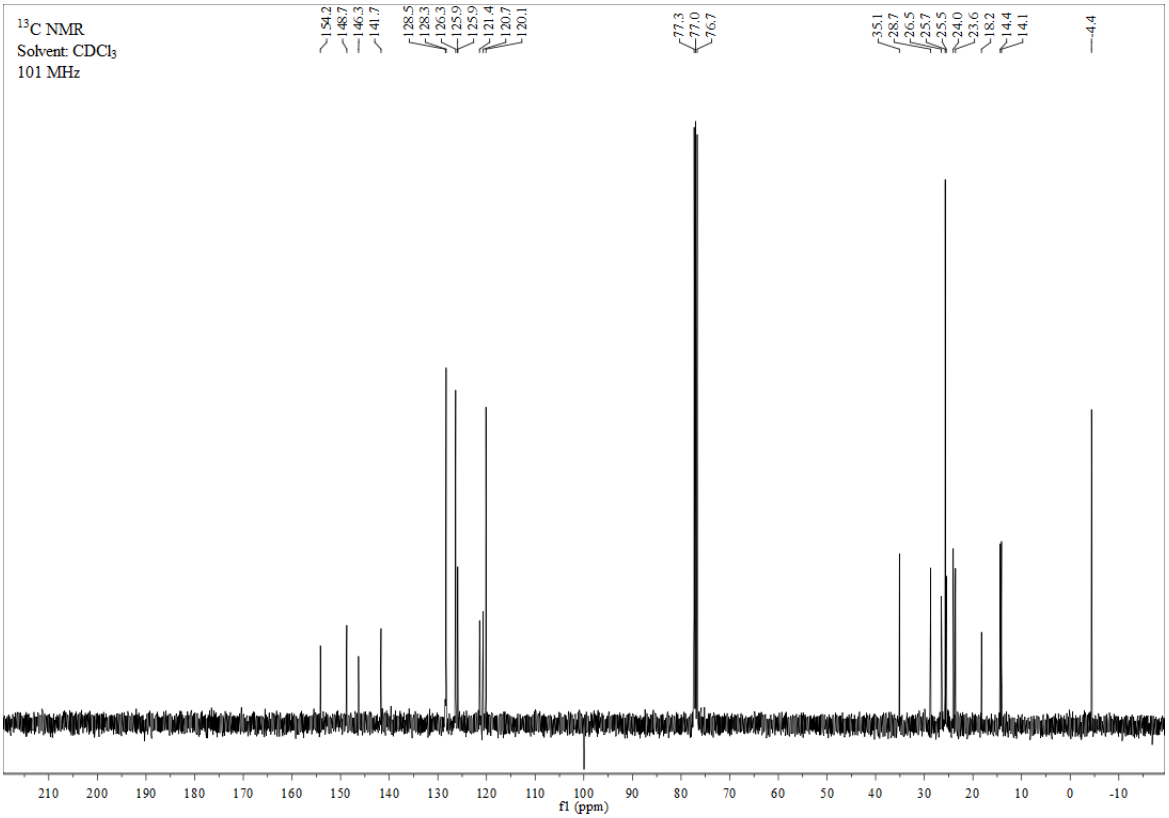
1.09
7.37
1.06
1.00
2.99
4.33
3.40
3.56
f1 (ppm)

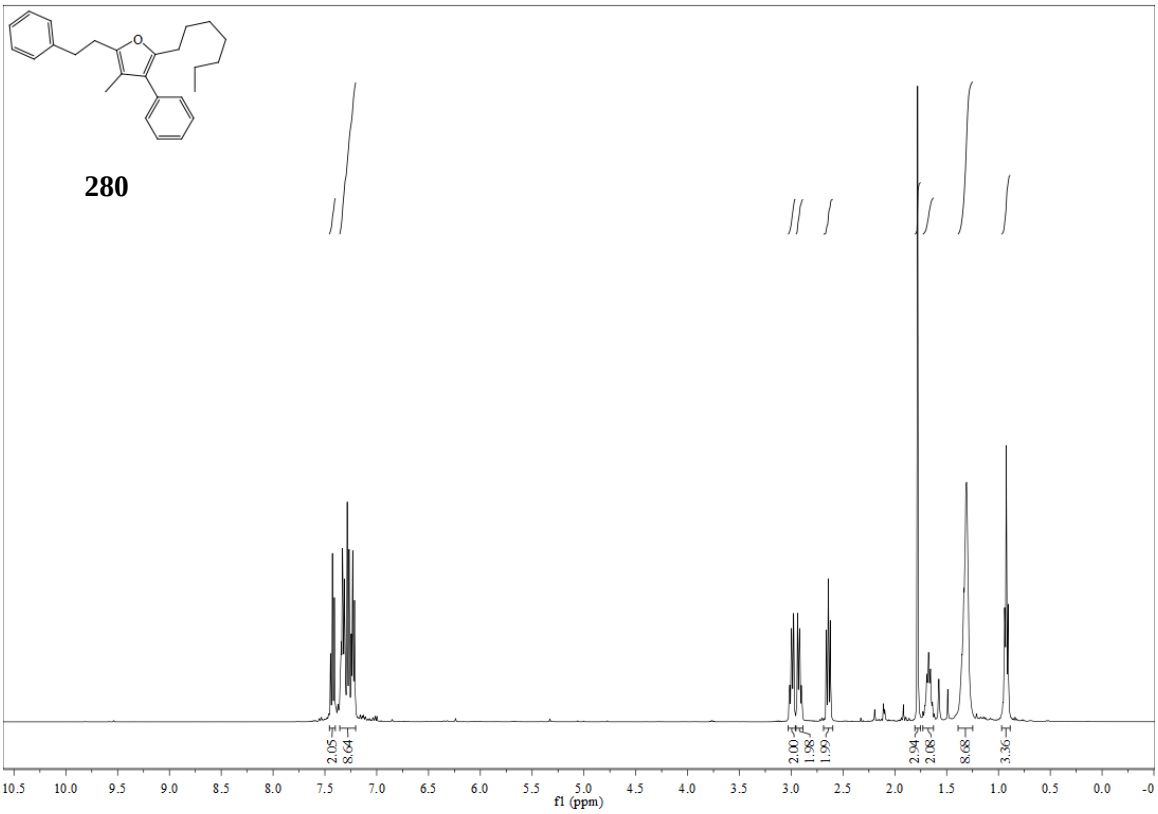

^{13}C NMR
Solvent: $CDCl_3$
101 MHz
155.7
144.3
133.9
133.6
131.9
130.8
130.2
129.4
128.8
128.2
126.5
126.2
125.7
113.1
77.3
77.0
76.7
36.3
31.6
26.5
26.0
9.0
f1 (ppm)

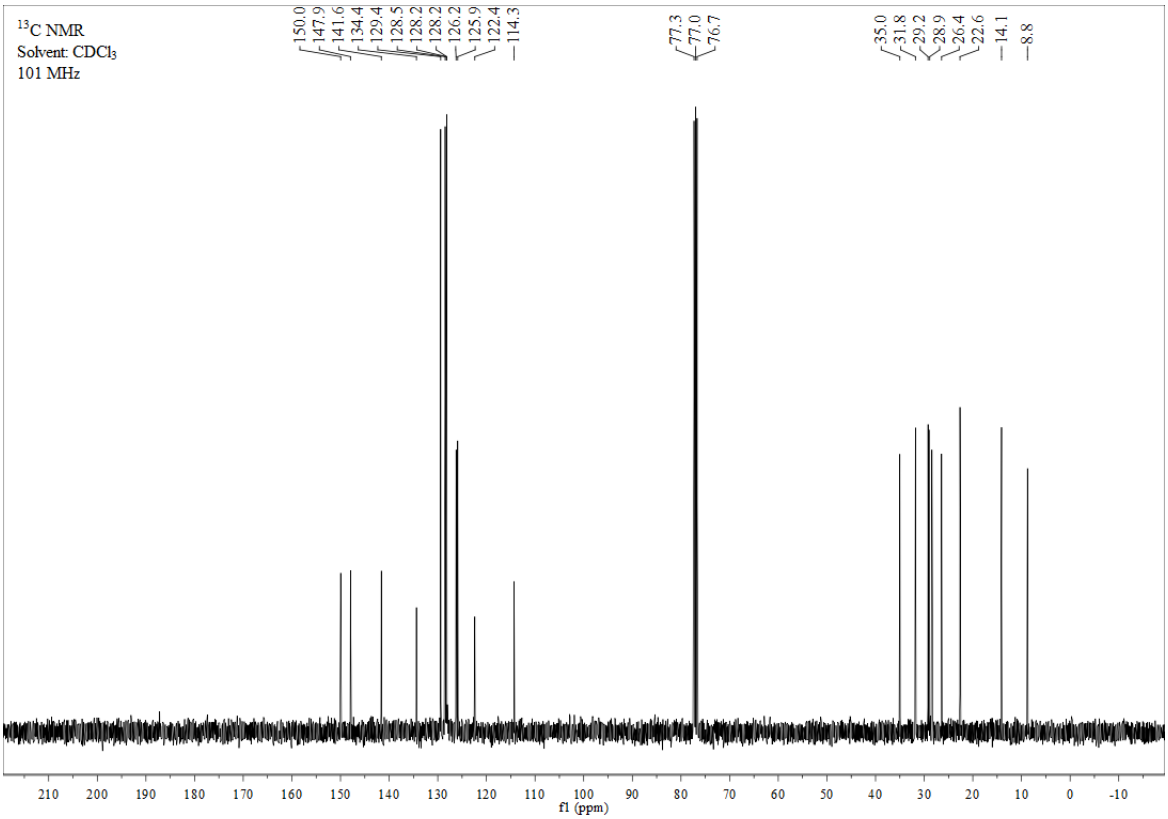

O
F
278
1.98
2.00
1.98
1.84
1.95
4.47
15.03
f1 (ppm)

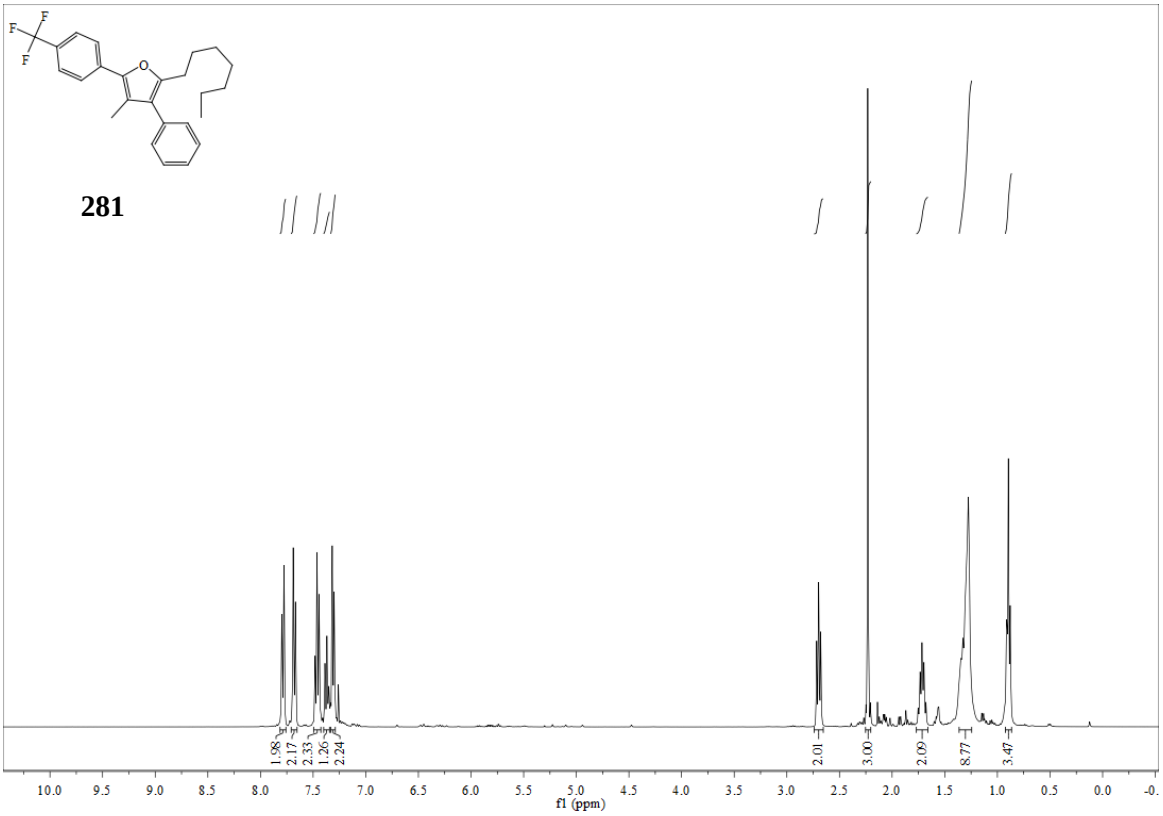

13C NMR
Solvent: CDCl3
101 MHz
162.4
160.0
149.2
145.4
128.8
126.5
126.4
122.9
121.6
115.5
115.2
77.3
77.0
76.7
40.0
32.3
29.8
26.6
26.0
24.0
23.4
14.3
f1 (ppm)


279
1.99
2.52
3.04
1.96
2.18
2.03
2.00
1.99
2.56
2.58
12.53
3.17
6.08
f1 (ppm)

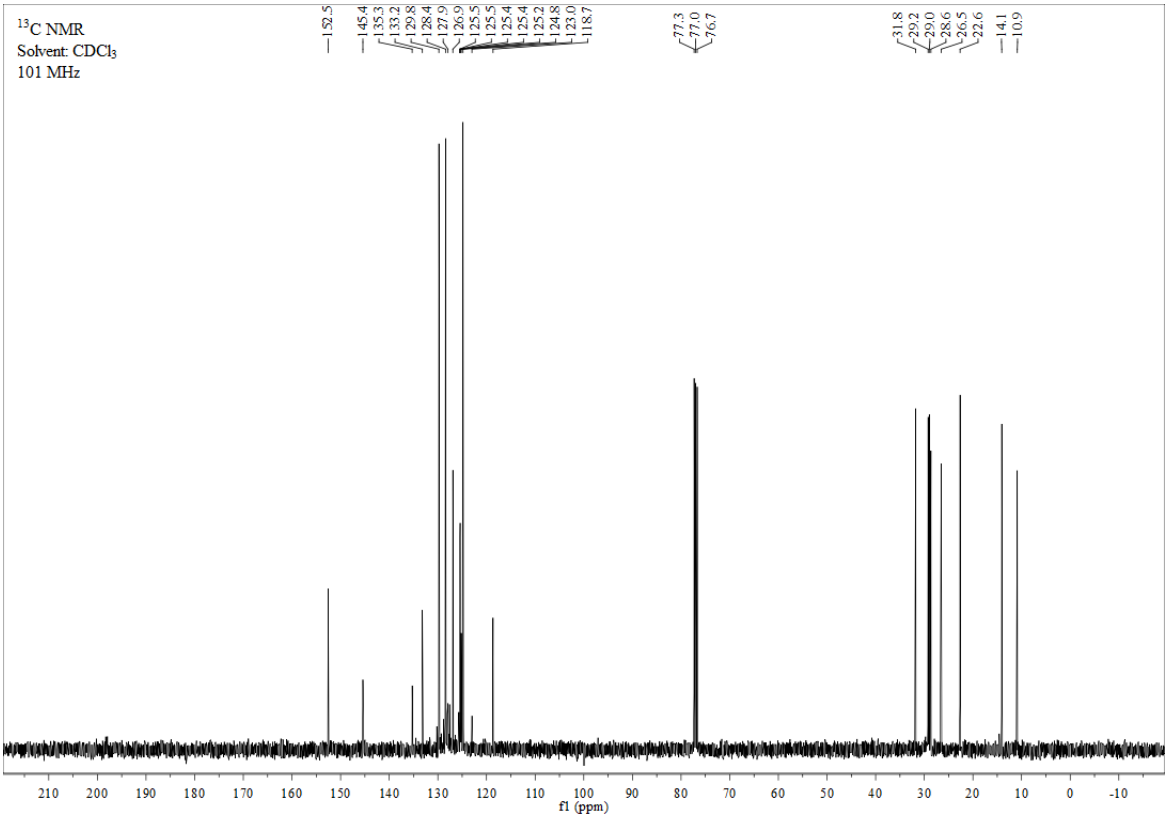

13C NMR
Solvent: CDCl3
101 MHz
154.2
148.7
146.3
141.7
128.5
128.3
126.3
125.9
125.9
121.4
120.7
120.1
77.3
77.0
76.7
35.1
28.7
26.5
25.7
25.5
24.0
23.6
18.2
14.4
14.1
-4.4
f1 (ppm)

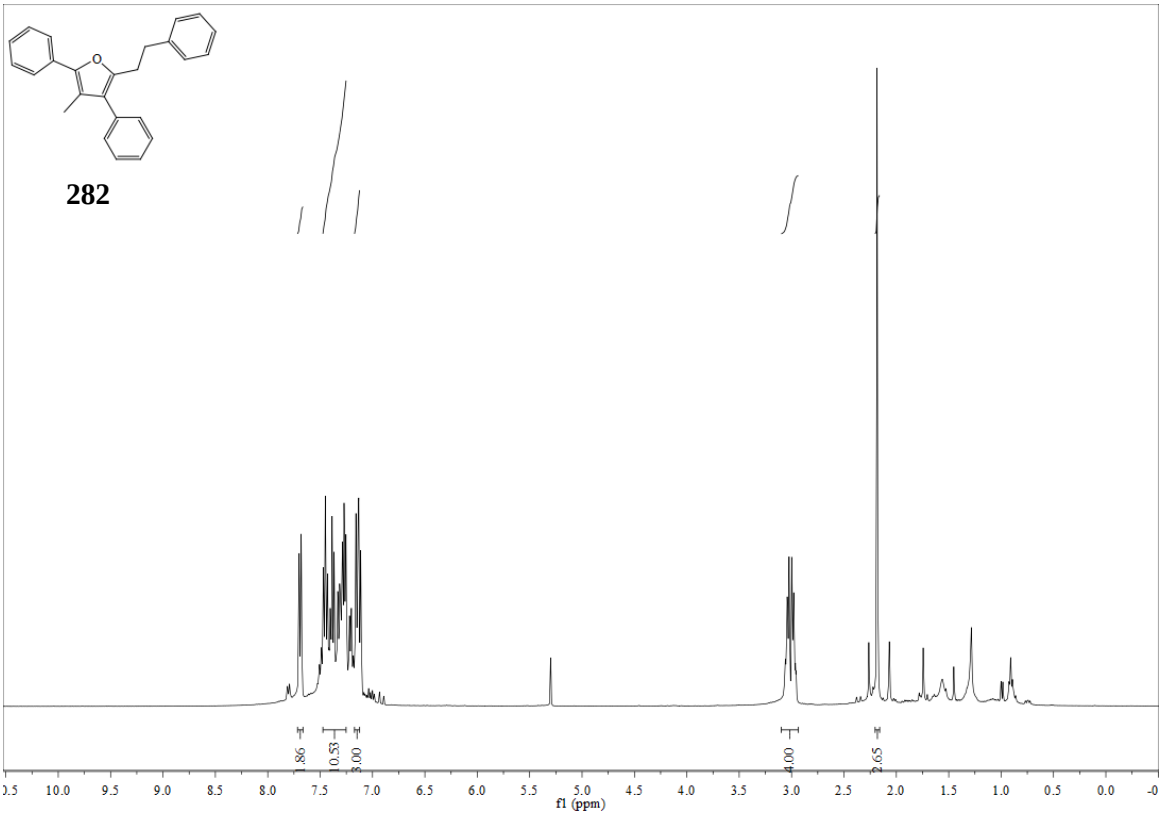

280
2.05
8.64
2.00
1.98
1.99
2.94
2.08
8.68
3.36
f1 (ppm)

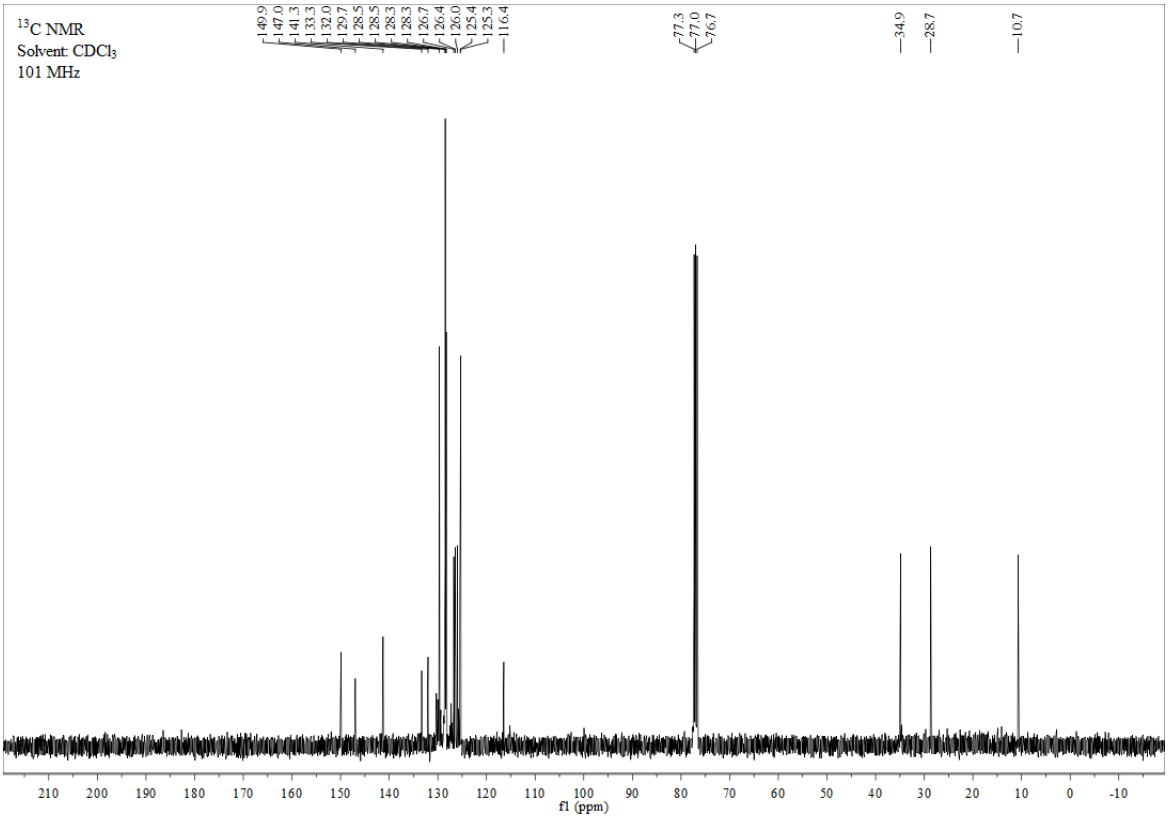

^{13}C NMR
Solvent: $CDCl_3$
101 MHz
150.0
147.9
141.6
134.4
129.4
128.5
128.2
128.2
126.2
125.9
122.4
114.3
77.3
77.0
76.7
35.0
31.8
29.2
28.9
26.4
22.6
14.1
8.8
f1 (ppm)

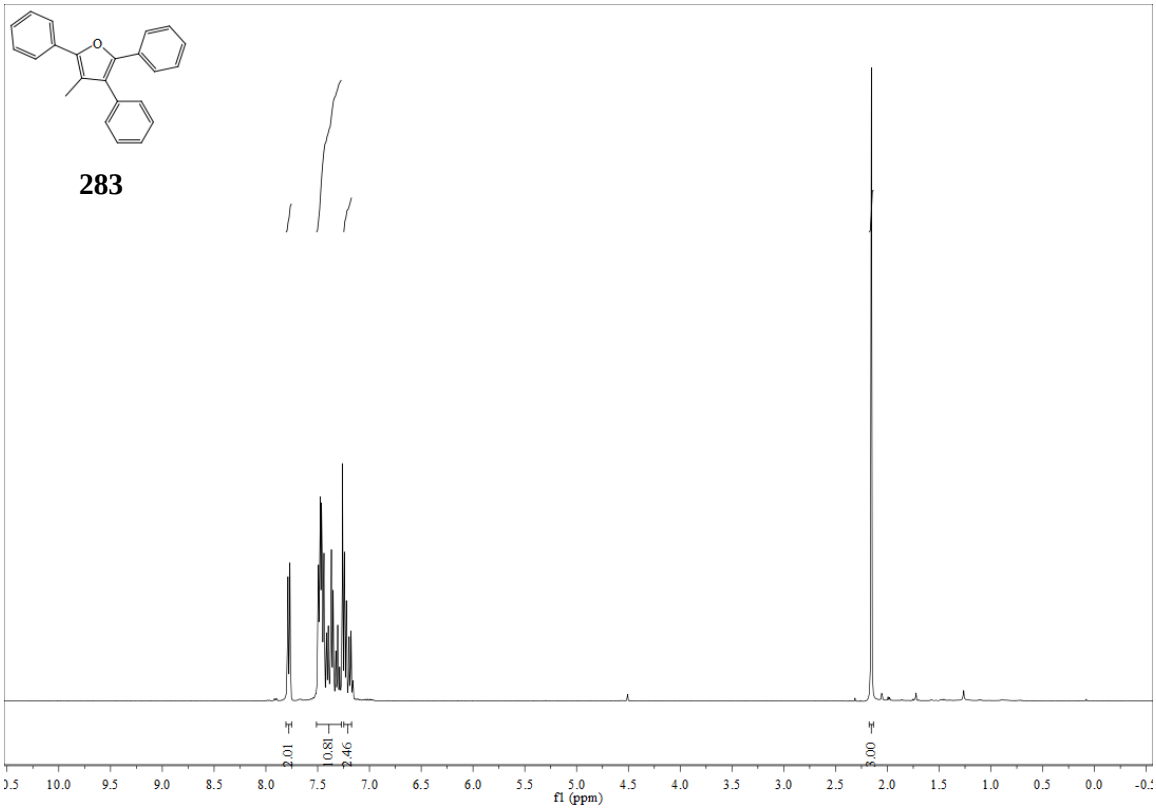

F
F
F
O
1.98
2.17
2.33
1.26
2.24
2.01
3.00
2.09
8.77
3.47
f1 (ppm)

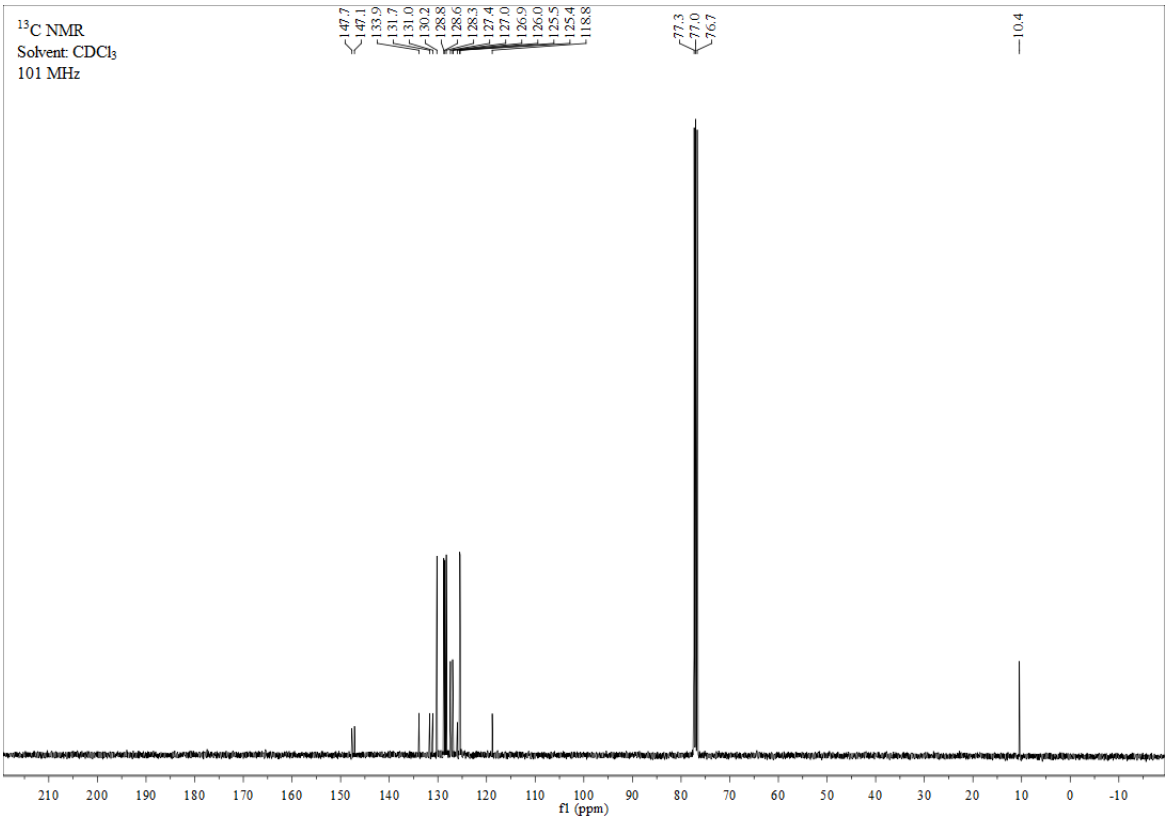
281


^{13}C NMR
Solvent: $CDCl_3$
101 MHz
152.5
145.4
135.3
133.2
129.8
128.4
127.9
126.9
125.5
125.5
125.4
125.4
125.2
124.8
123.0
118.7
77.3
77.0
76.7
31.8
29.2
29.0
28.6
26.5
22.6
14.1
10.9
f1 (ppm)


282
1.86
10.53
3.00
4.00
2.65
f1 (ppm)


^{13}C NMR
Solvent: CDCl$_3$
101 MHz
149.9
147.0
141.3
133.3
132.0
129.7
128.5
128.5
128.3
128.3
126.7
126.4
126.0
125.4
125.3
116.4
77.3
77.0
76.7
34.9
28.7
10.7
f1 (ppm)


283
2.01
0.81
2.46
3.00
f1 (ppm)


13C NMR
Solvent: CDCl3
101 MHz
147.7
147.1
133.9
131.7
131.0
130.2
128.8
128.6
128.3
127.4
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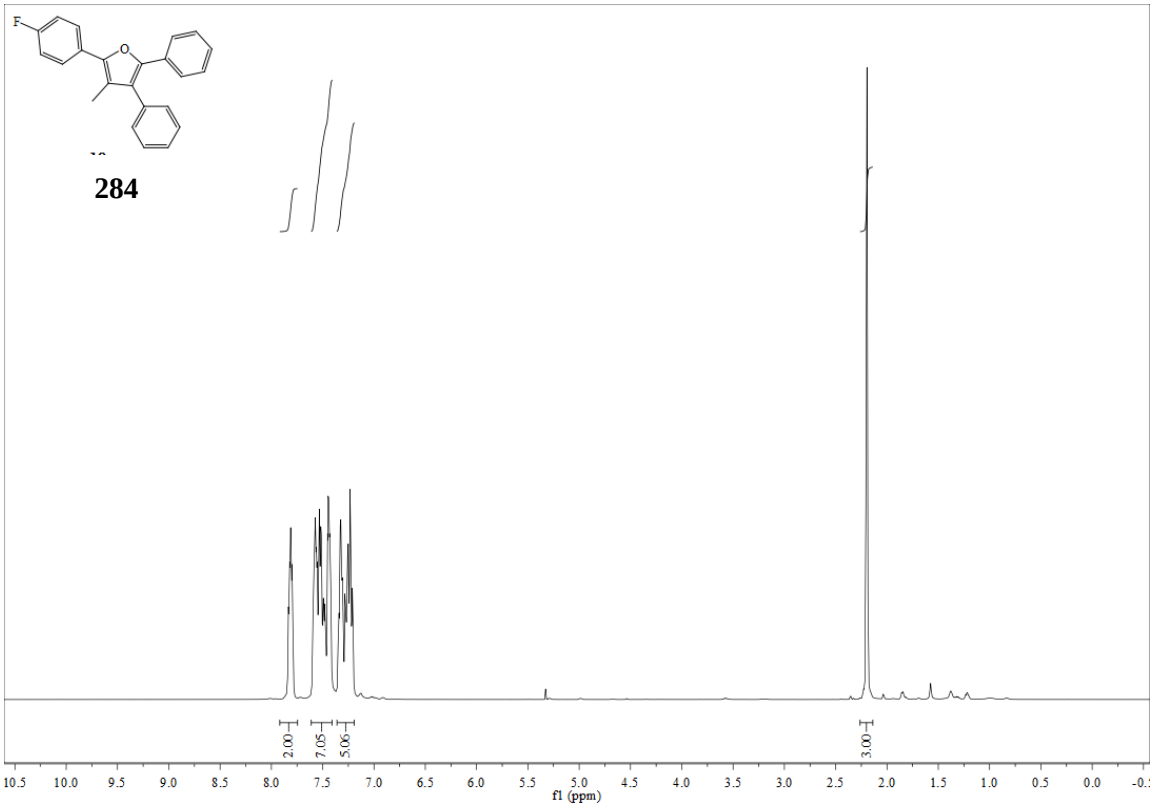
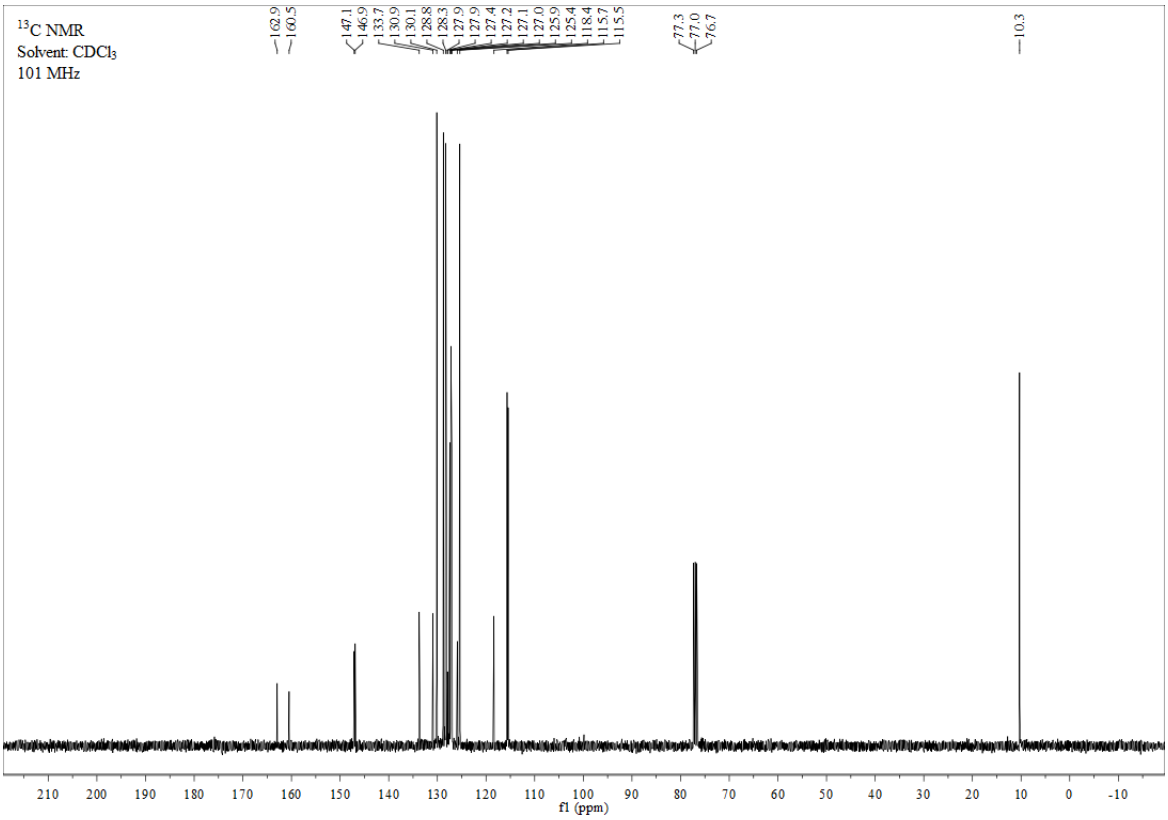
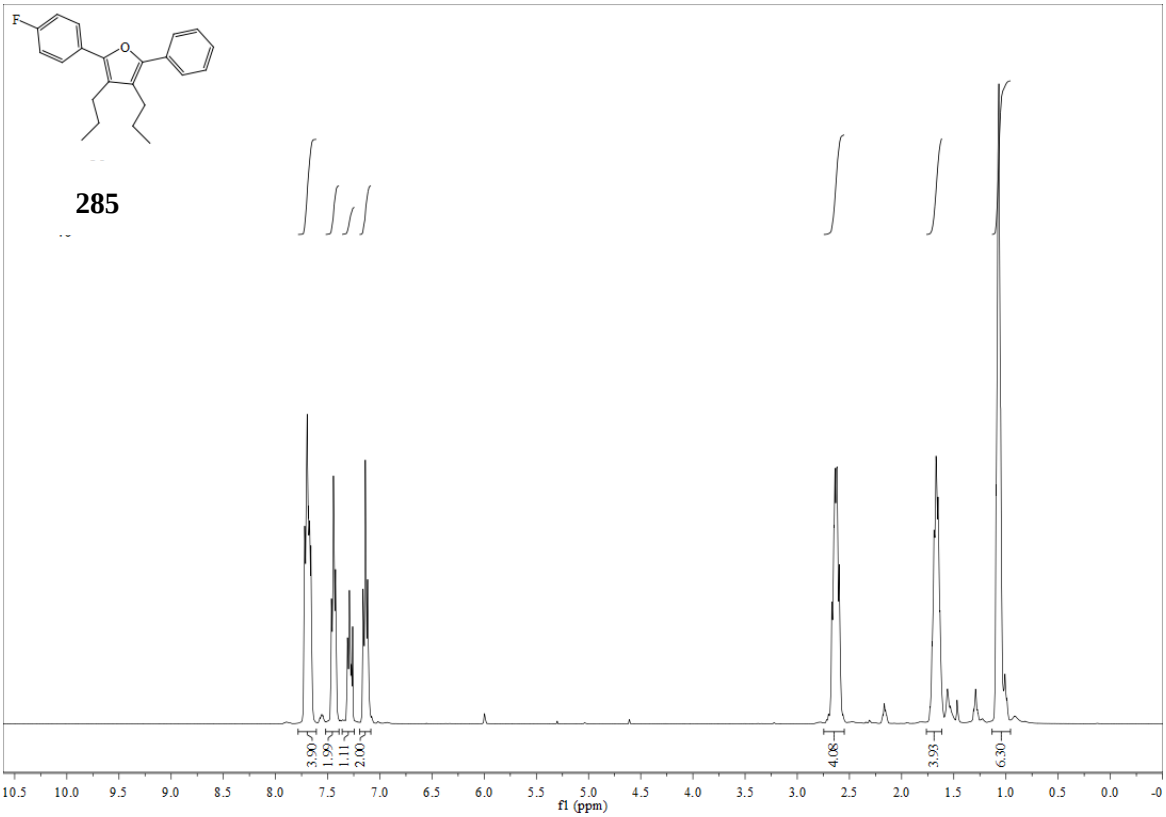
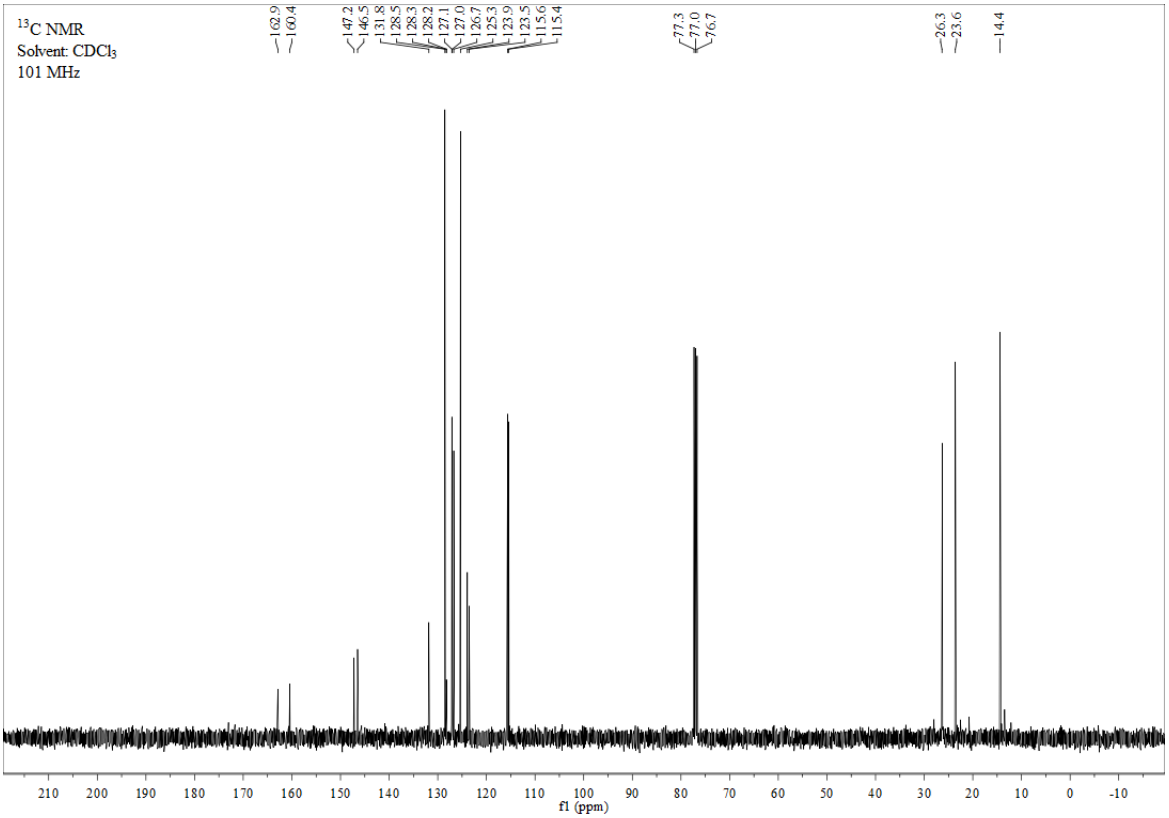
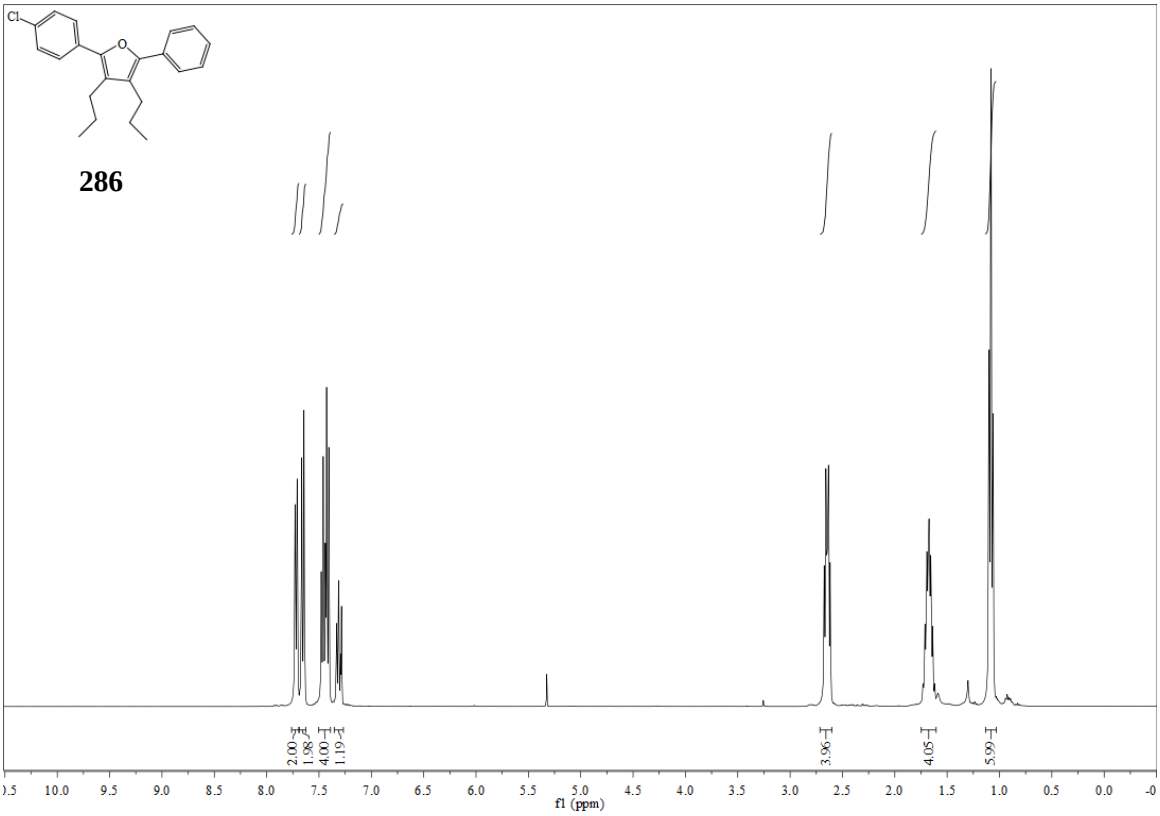
126.0
125.5
125.4
118.8
77.3
77.0
76.7
10.4
f1 (ppm)

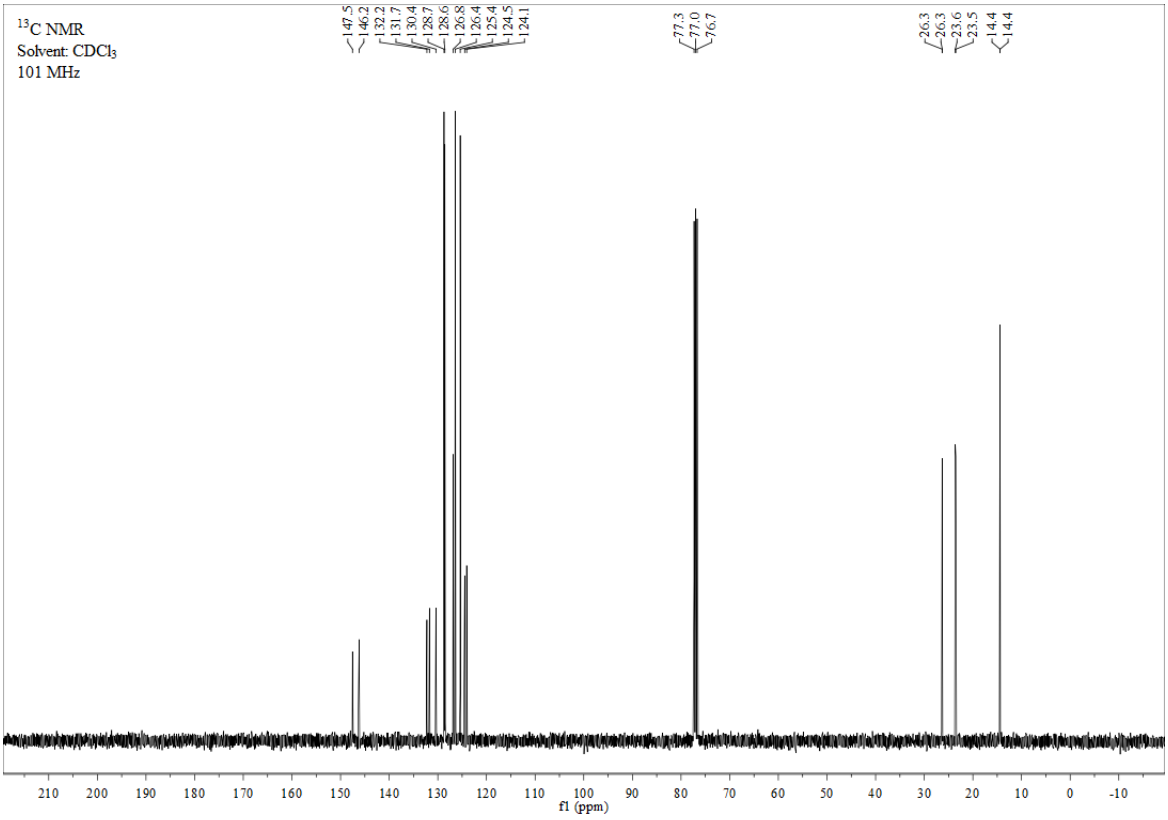

F
O
284
2.00
7.05
5.06
3.00
f1 (ppm)

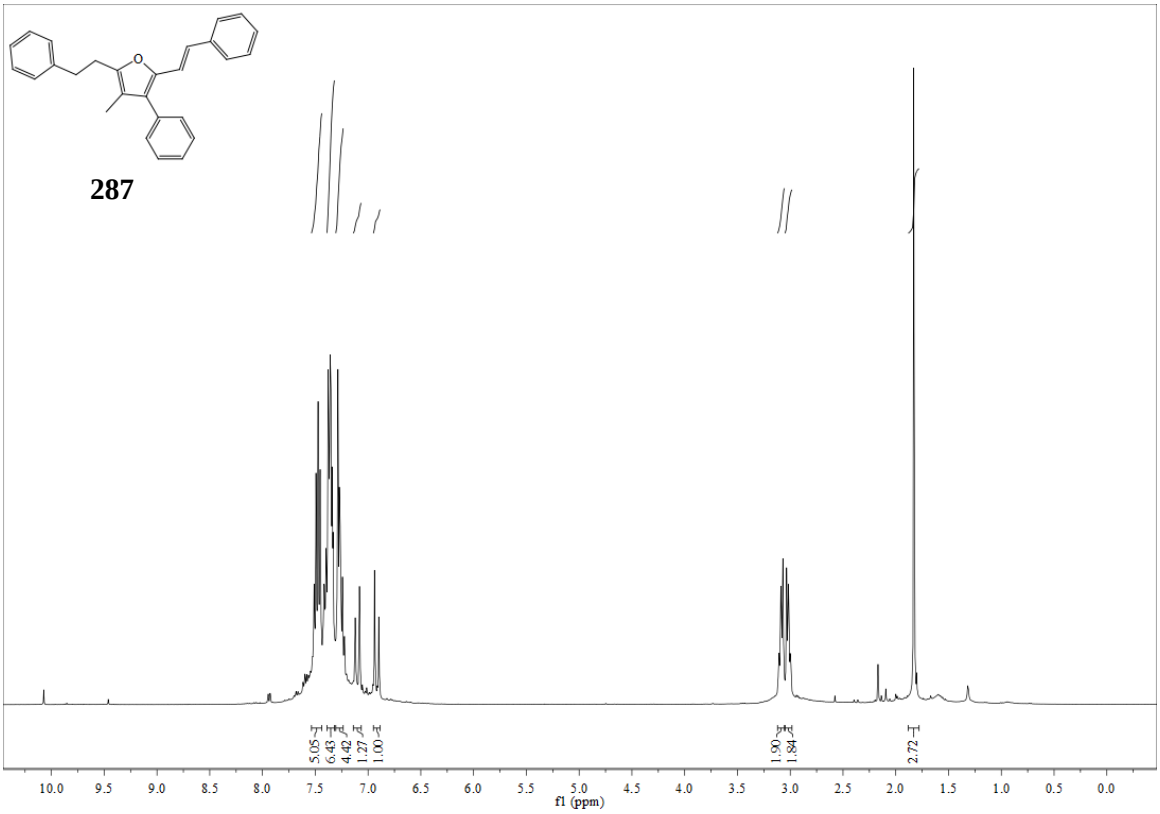

13C NMR
Solvent: CDCl3
101 MHz
162.9
160.5
147.1
146.9
133.7
130.9
130.1
128.8
128.3
127.9
127.9
127.4
127.2
127.1
127.0
125.9
125.4
118.4
115.7
115.5
77.3
77.0
76.7
10.3
f1 (ppm)


F
O
285
3.90
1.99
1.11
2.00
4.08
3.93
6.30
f1 (ppm)

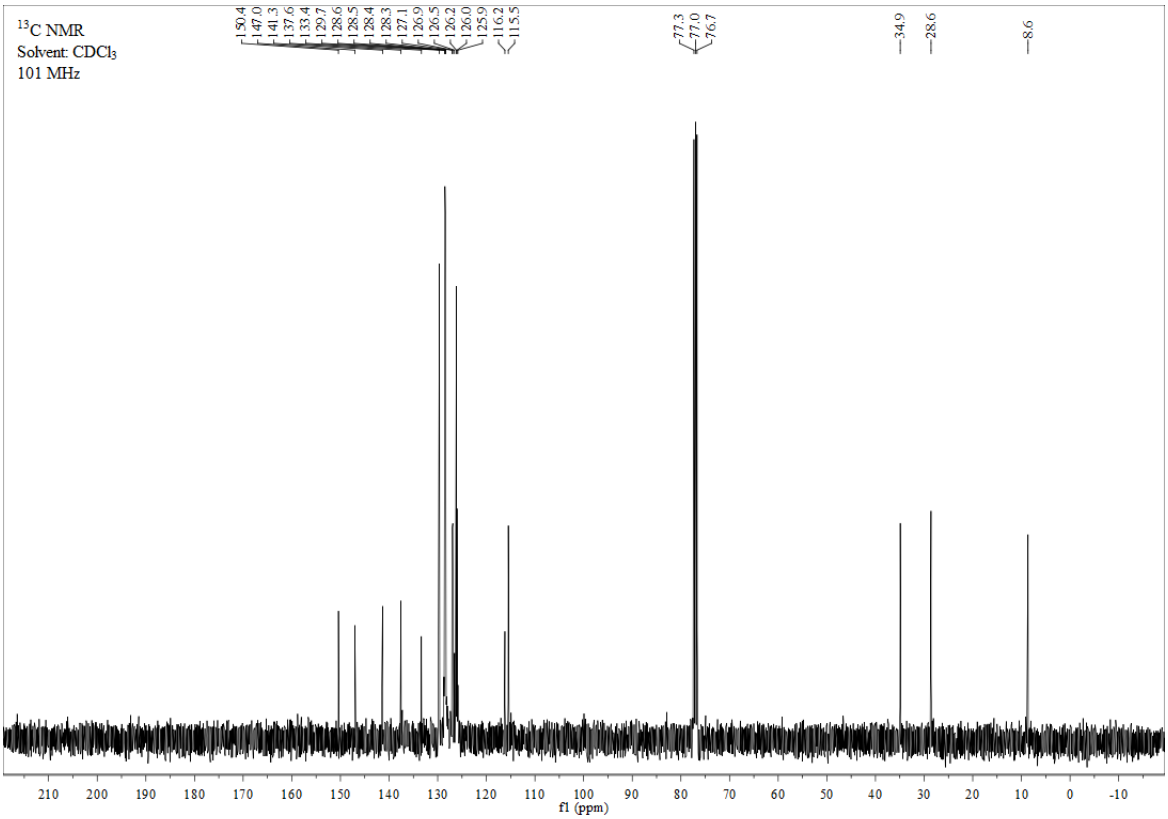

^{13}C NMR
Solvent: $CDCl_3$
101 MHz
162.9
160.4
147.2
146.5
131.8
128.5
128.3
128.2
127.1
127.0
126.7
125.3
123.9
123.5
115.6
115.4
77.3
77.0
76.7
26.3
23.6
14.4
f1 (ppm)

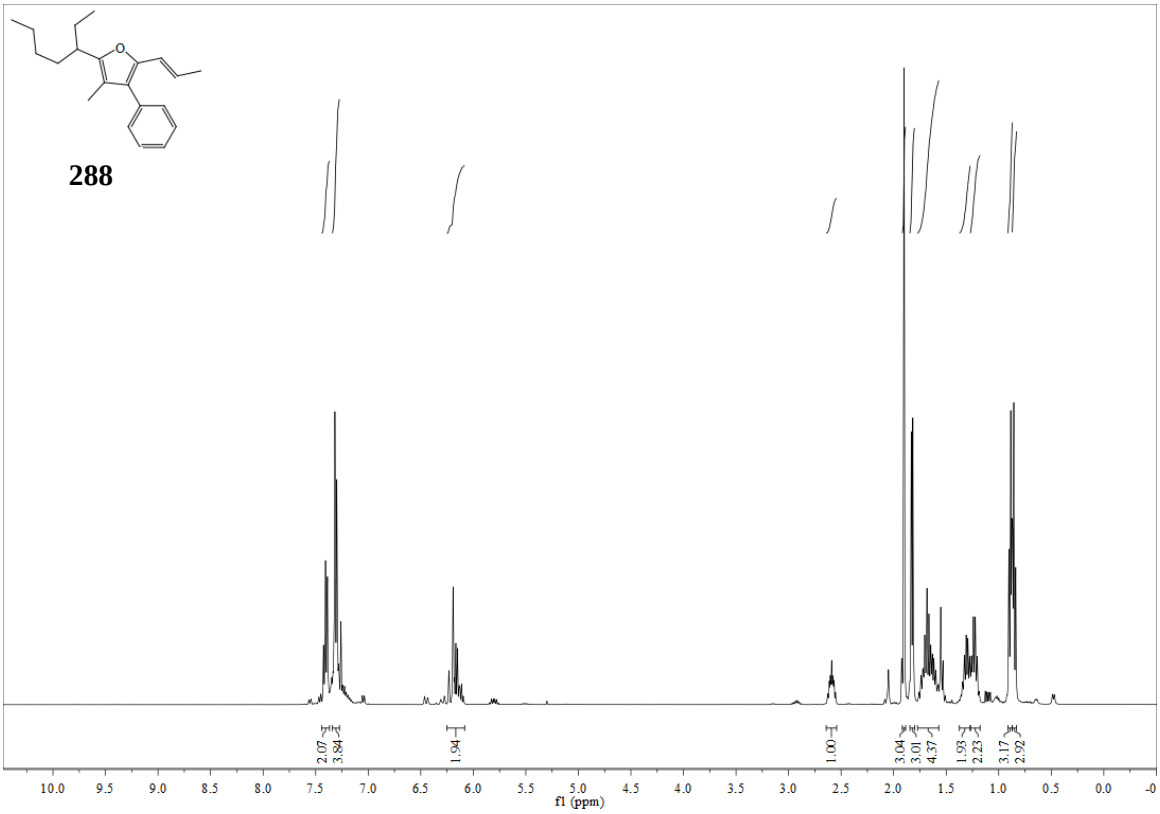

Cl
O
286
2.00
1.58
4.00
1.19
3.96
4.05
5.99
f1 (ppm)

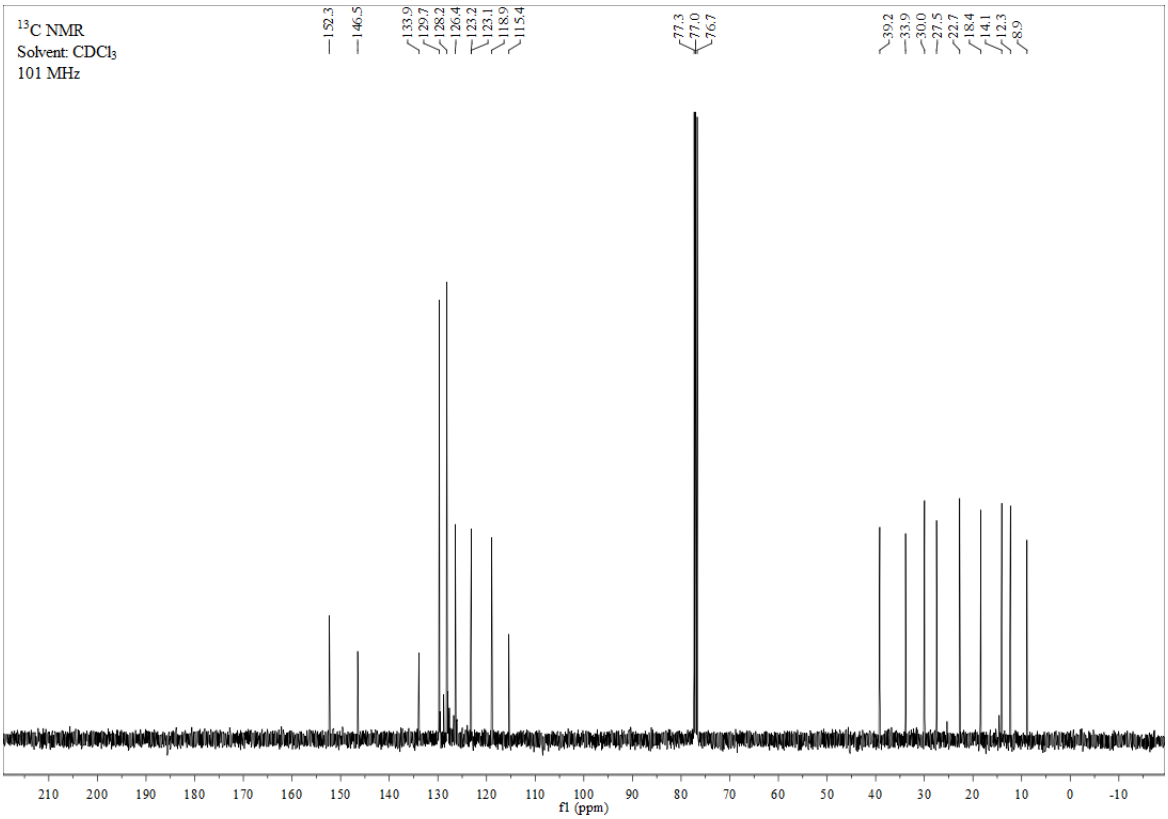

^{13}C NMR
Solvent: $CDCl_3$
101 MHz
147.5
146.2
132.2
131.7
130.4
128.7
128.6
126.8
126.4
125.4
124.5
124.1
77.3
77.0
76.7
26.3
26.3
23.6
23.5
14.4
14.4
f1 (ppm)

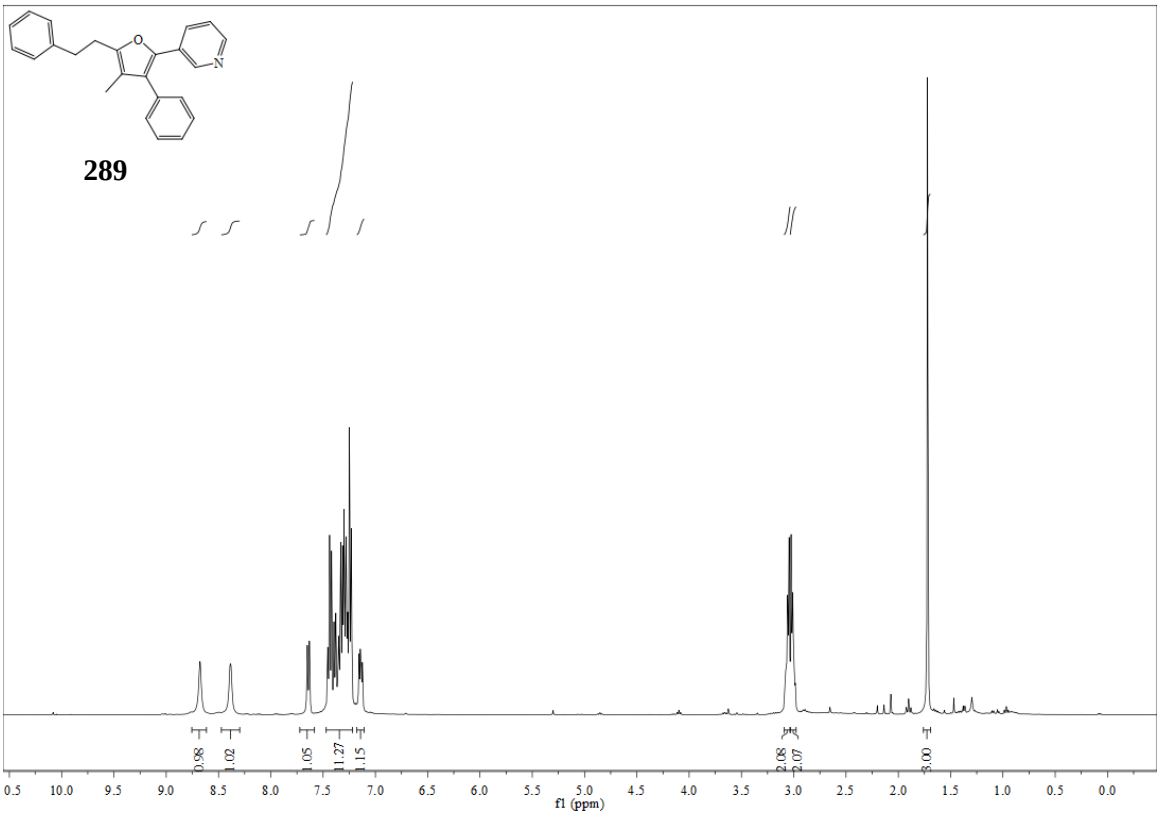

O
5.05
6.43
4.42
1.27
1.00
1.90
1.84
2.72
f1 (ppm)

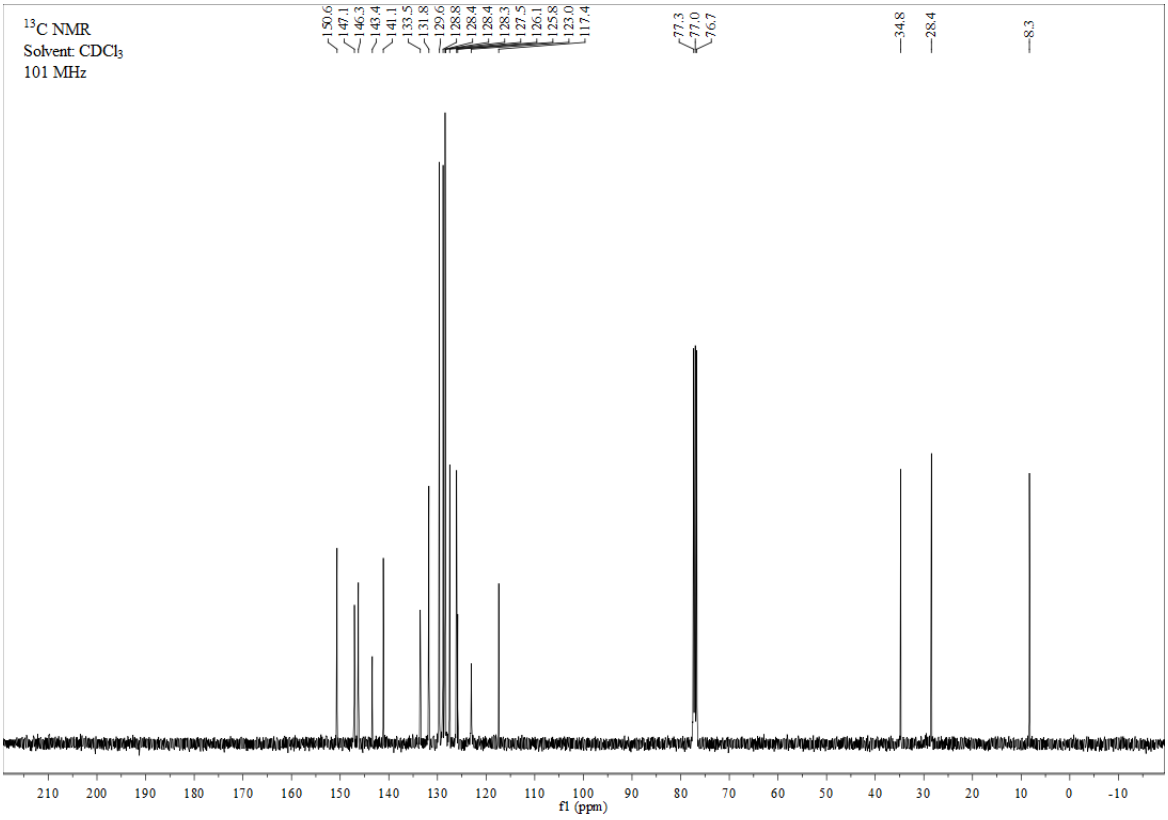
287

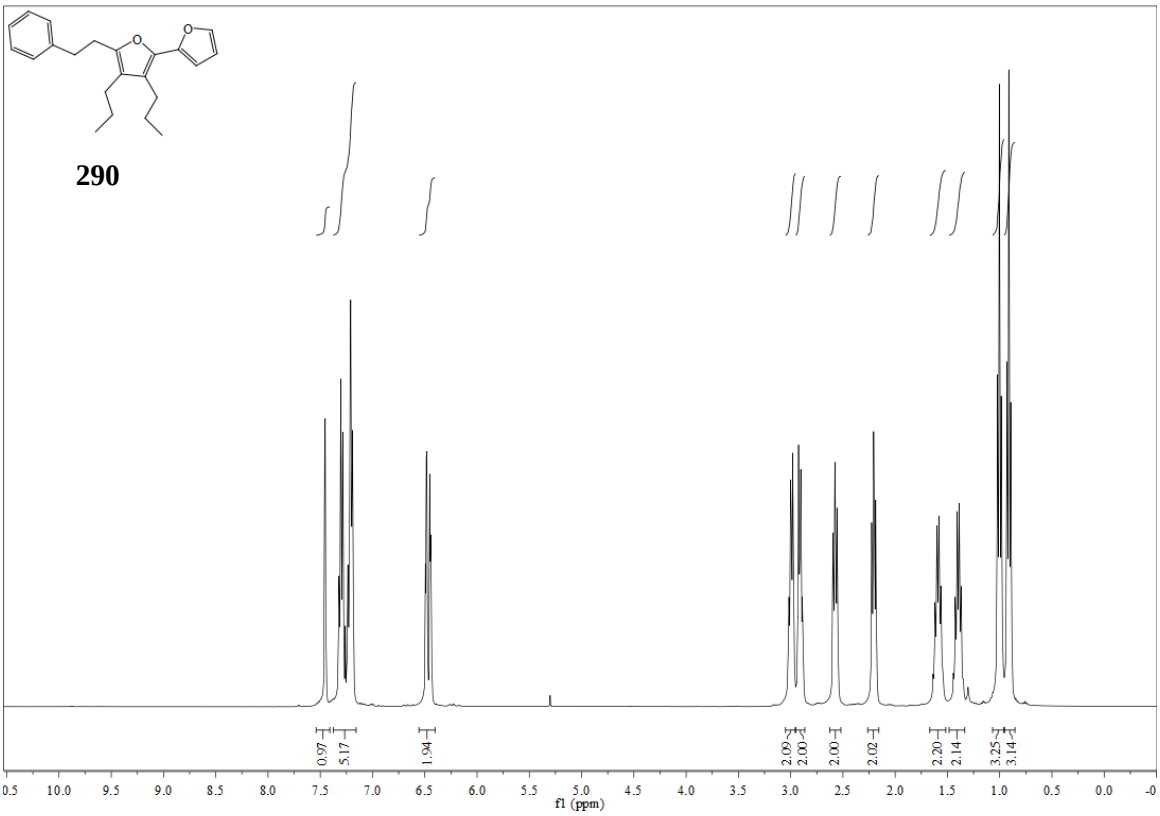

^{13}C NMR
Solvent: $CDCl_3$
101 MHz
150.4
147.0
141.3
137.6
133.4
129.7
128.6
128.5
128.4
128.3
127.1
126.9
126.5
126.2
126.0
125.9
116.2
115.5
77.3
77.0
76.7
34.9
28.6
8.6
f1 (ppm)

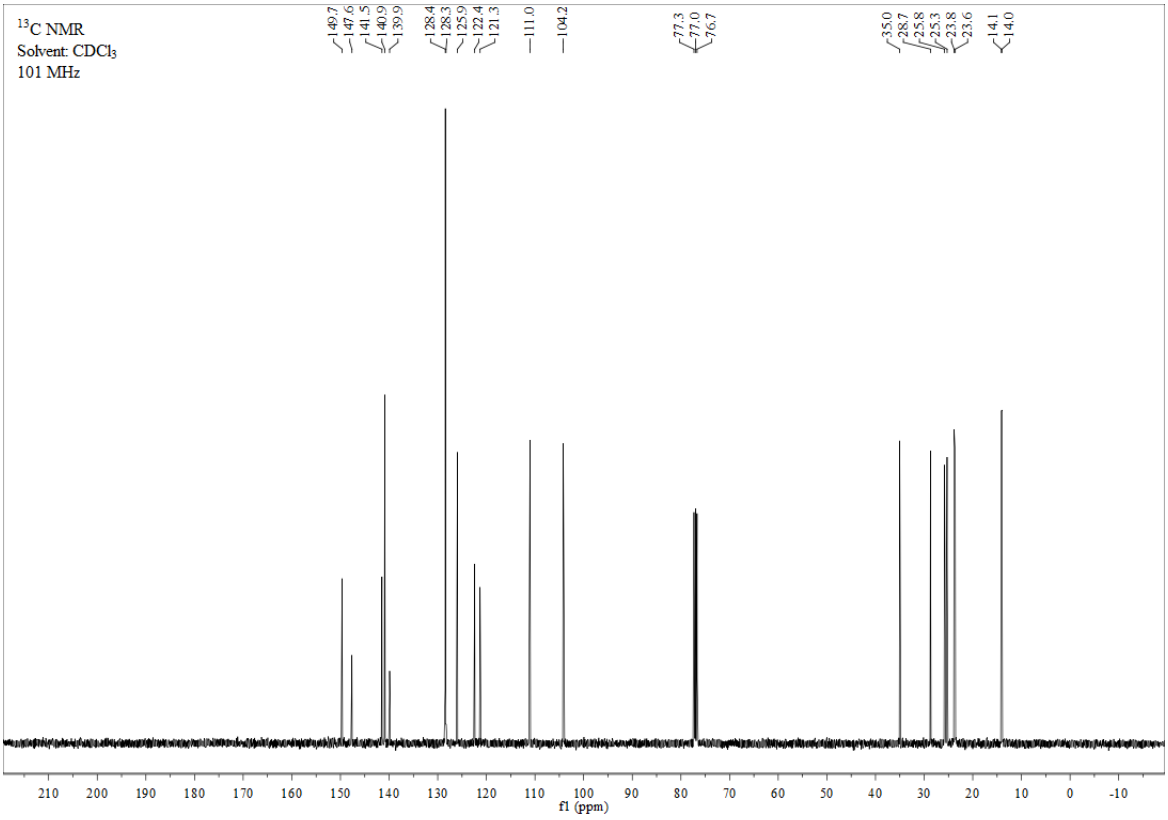

288
2.07
3.84
1.94
1.00
3.04
3.01
4.37
1.93
2.23
3.17
2.92
f1 (ppm)

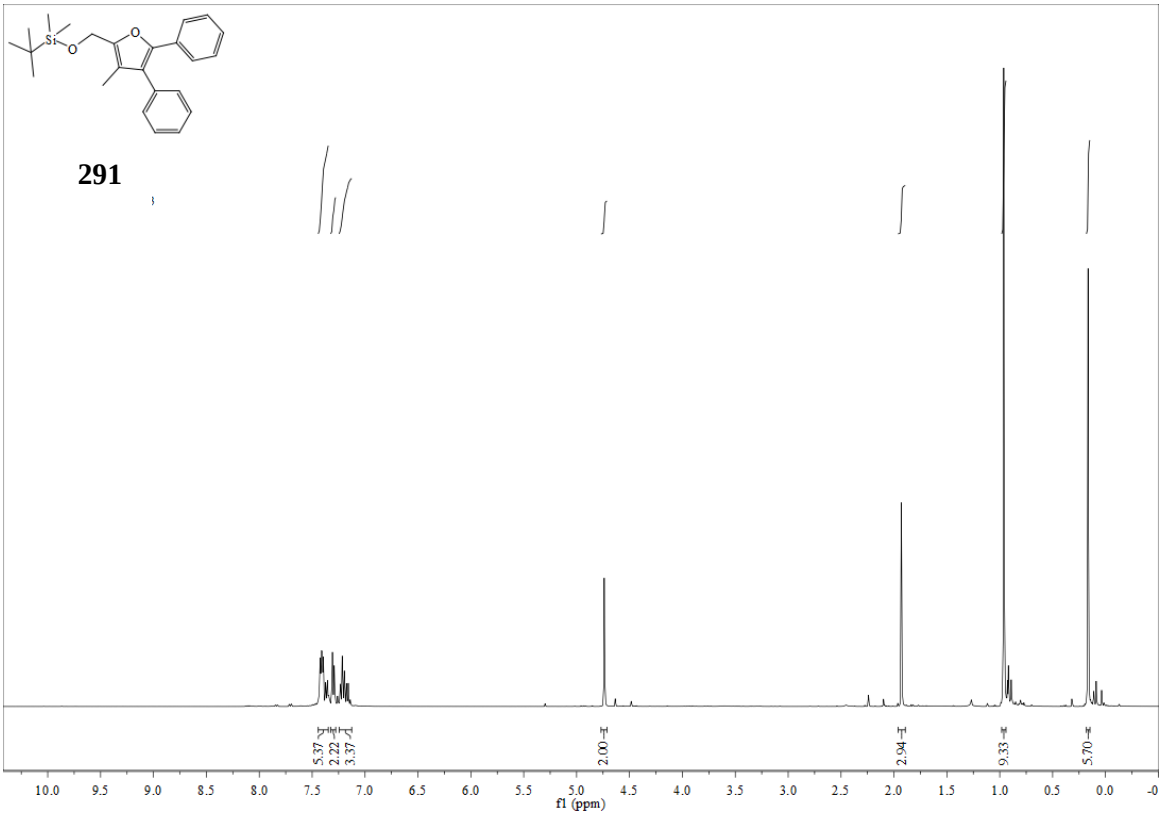

13C NMR
Solvent: CDCl3
101 MHz
152.3
146.5
133.9
129.7
128.2
126.4
123.2
123.1
118.9
115.4
77.3
77.0
76.7
39.2
33.9
30.0
27.5
22.7
18.4
14.1
12.3
8.9
f1 (ppm)


O
N
289
0.98
1.02
1.05
11.27
1.15
2.08
2.07
3.00
f1 (ppm)

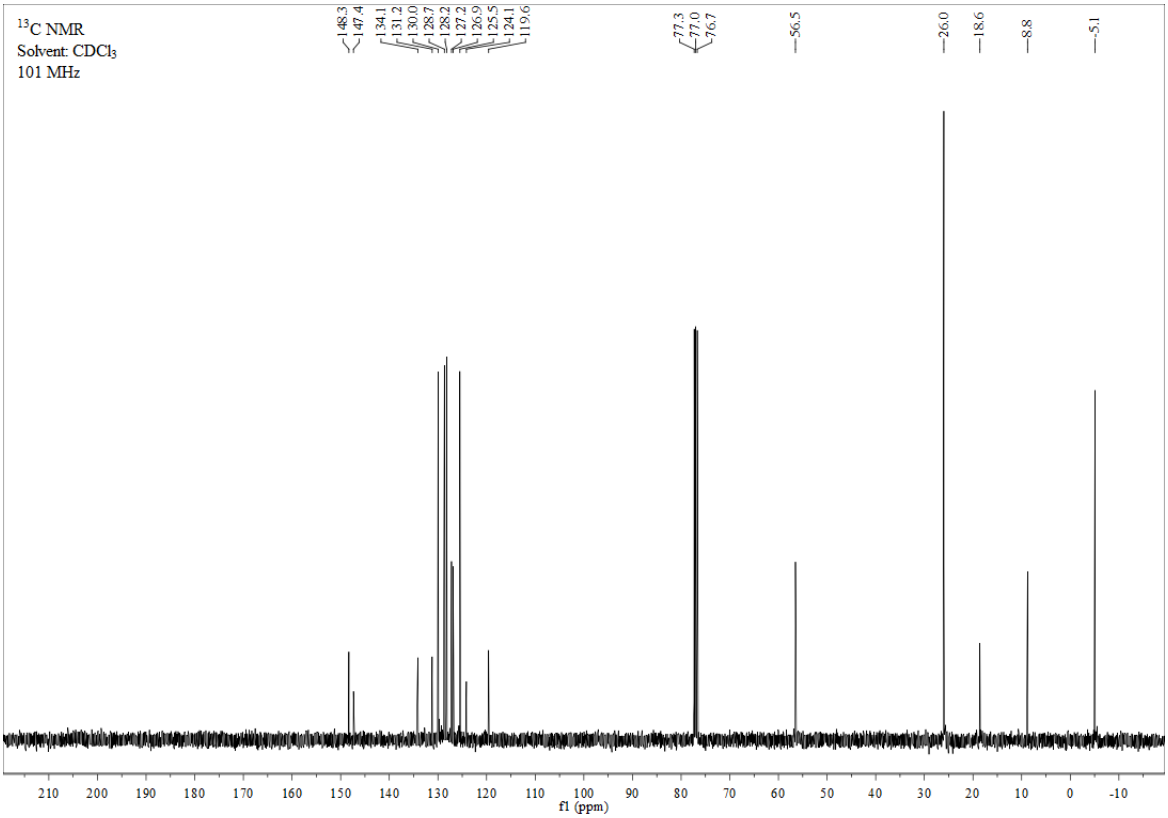

^{13}C NMR
Solvent: $CDCl_3$
101 MHz
150.6
147.1
146.3
143.4
141.1
133.5
131.8
129.6
128.8
128.4
128.4
128.3
127.5
126.1
125.8
123.0
117.4
77.3
77.0
76.7
34.8
28.4
8.3
f1 (ppm)

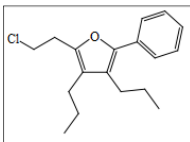

290
0.97
5.17
1.94
2.09
2.00
2.00
2.02
2.20
2.14
3.25
3.14
f1 (ppm)


^{13}C NMR
Solvent: $CDCl_3$
101 MHz
149.7
147.6
141.5
140.9
139.9
128.4
128.3
125.9
122.4
121.3
111.0
104.2
77.3
77.0
76.7
35.0
28.7
25.8
25.3
23.8
23.6
14.1
14.0
f1 (ppm)


5.37
2.22
3.37
2.00
2.94
9.33
5.70
f1 (ppm)

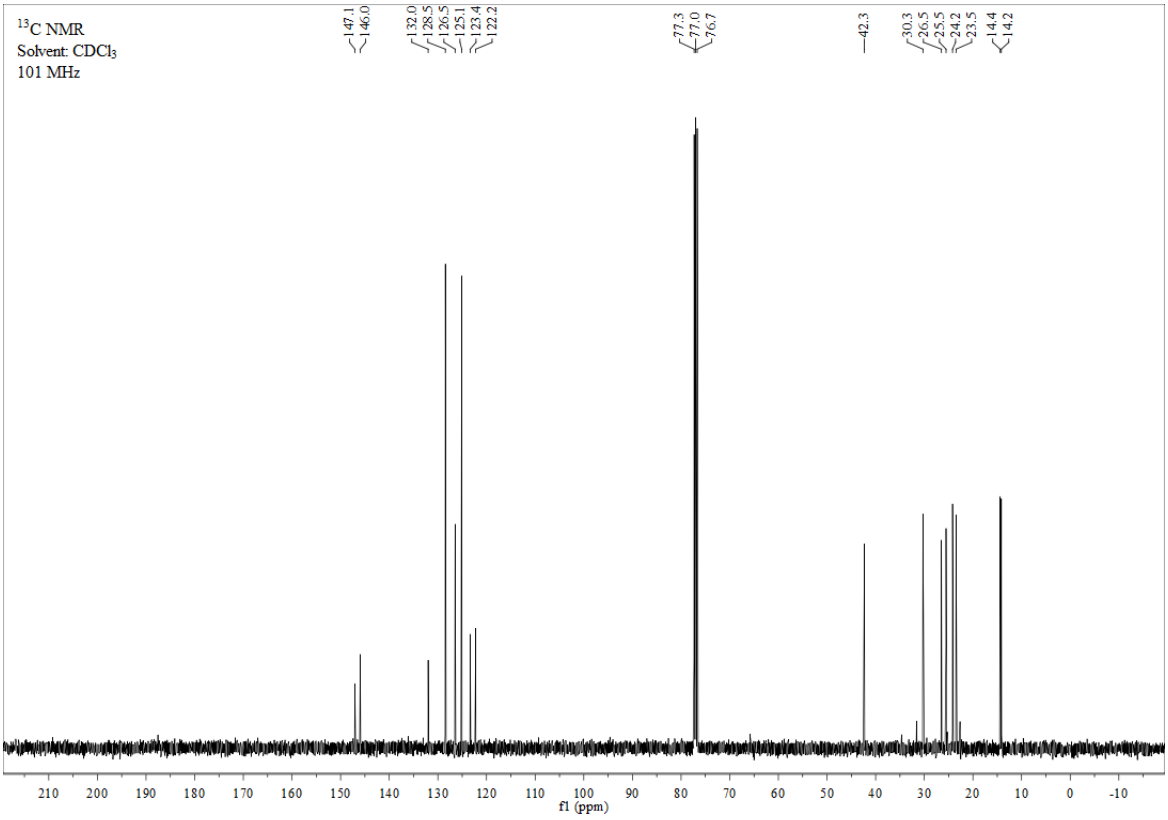
291

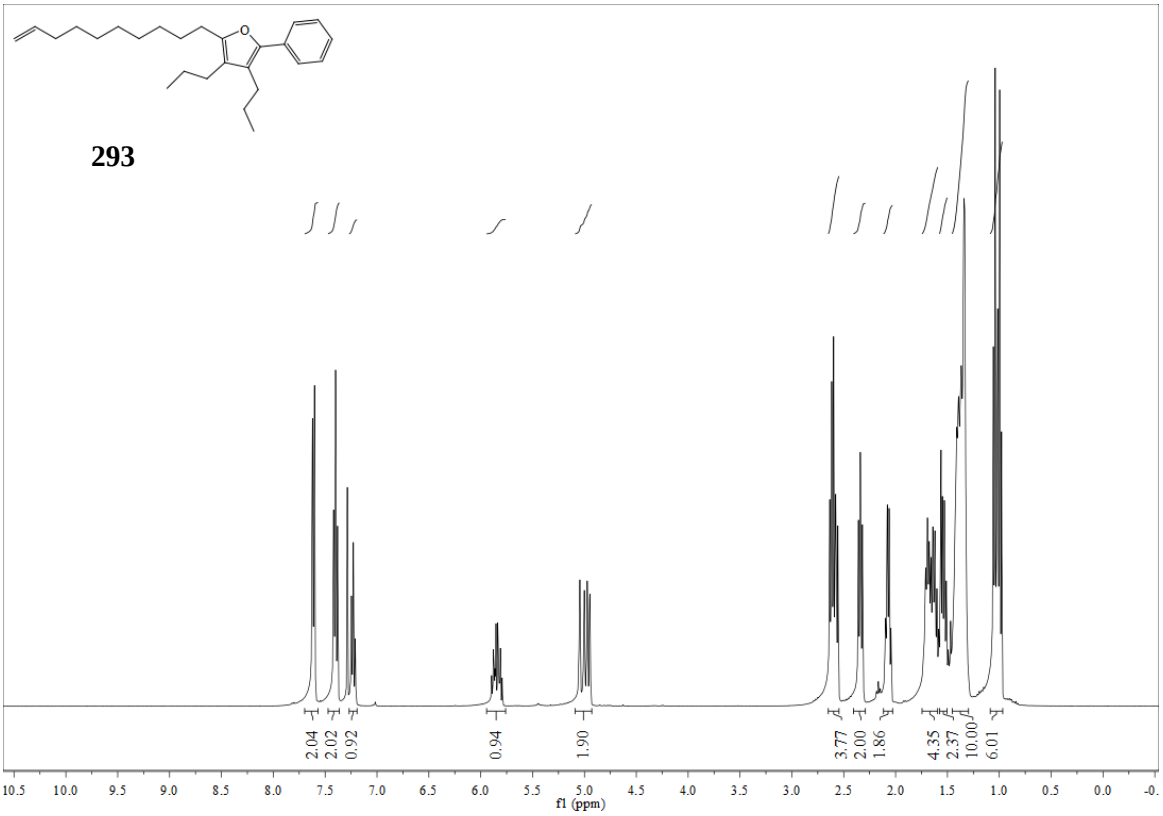

^{13}C NMR
Solvent: $CDCl_3$
101 MHz
148.3
147.4
134.1
131.2
130.0
128.7
128.2
127.2
126.9
125.5
124.1
119.6
77.3
77.0
76.7
56.5
26.0
18.6
8.8
-5.1
f1 (ppm)

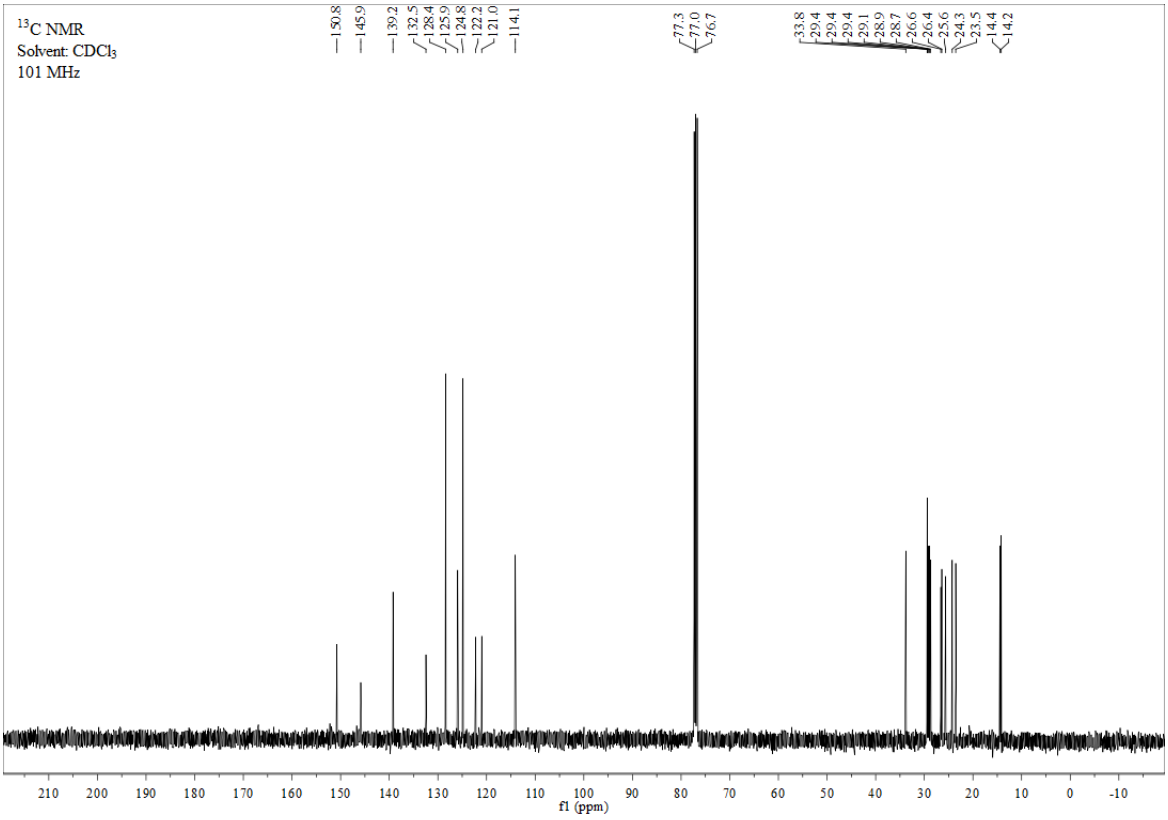

Cl
O

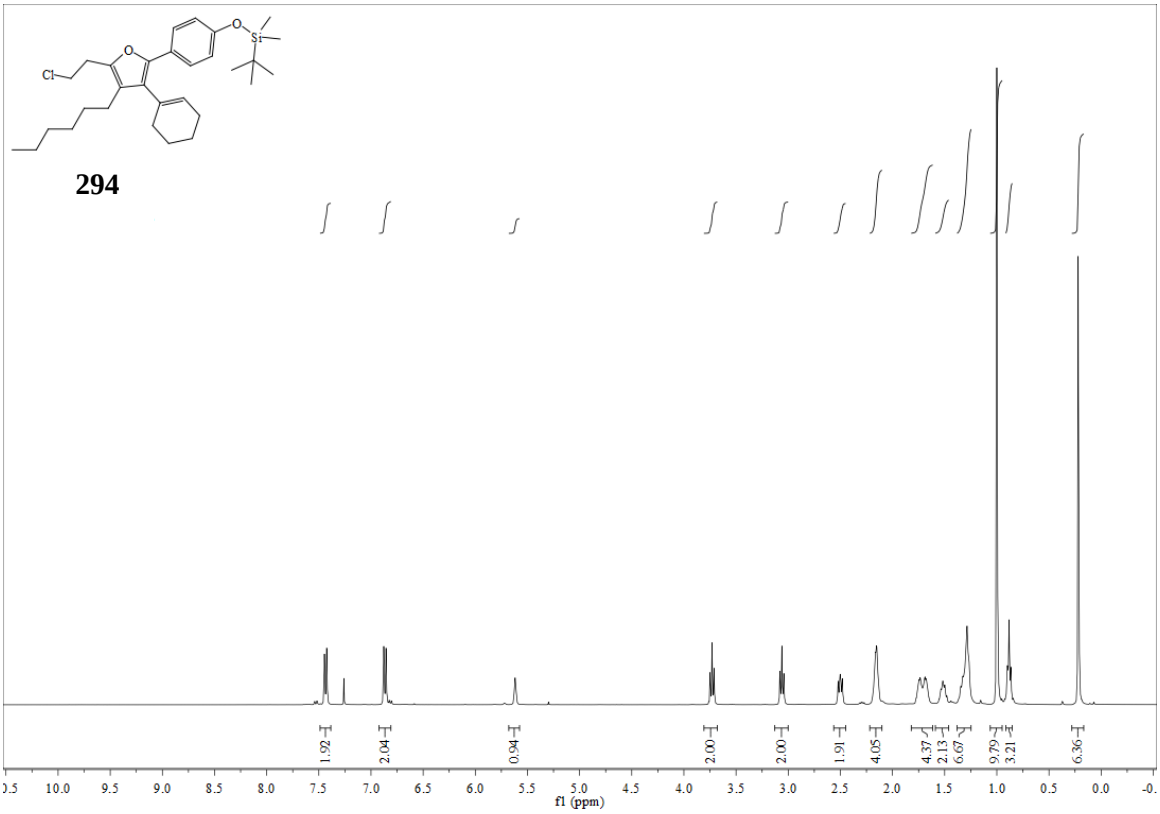
292

2.00
2.04
1.28
2.00
2.00
2.02
2.03
4.50
6.25
f1 (ppm)

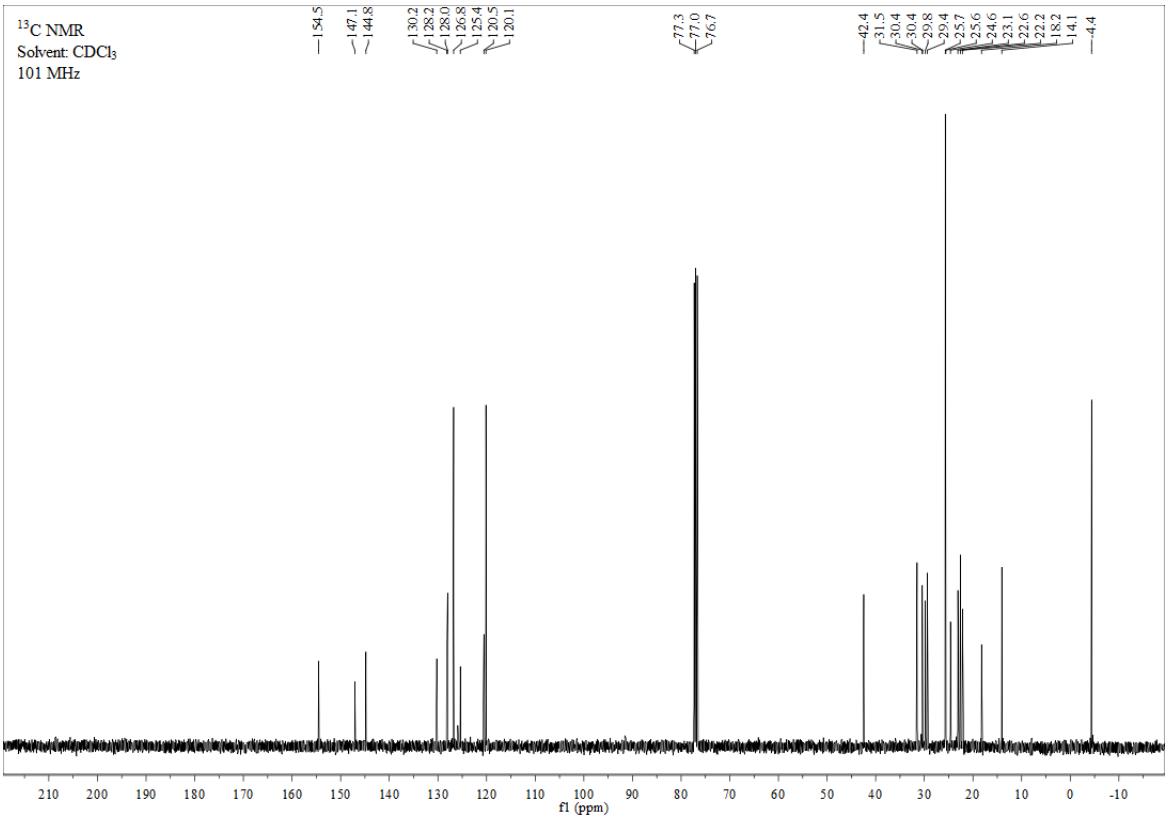

^{13}C NMR
Solvent: CDCl$_3$
101 MHz
147.1
146.0
132.0
128.5
126.5
125.1
123.4
122.2
77.3
77.0
76.7
42.3
30.3
26.5
25.5
24.2
23.5
14.4
14.2
f1 (ppm)

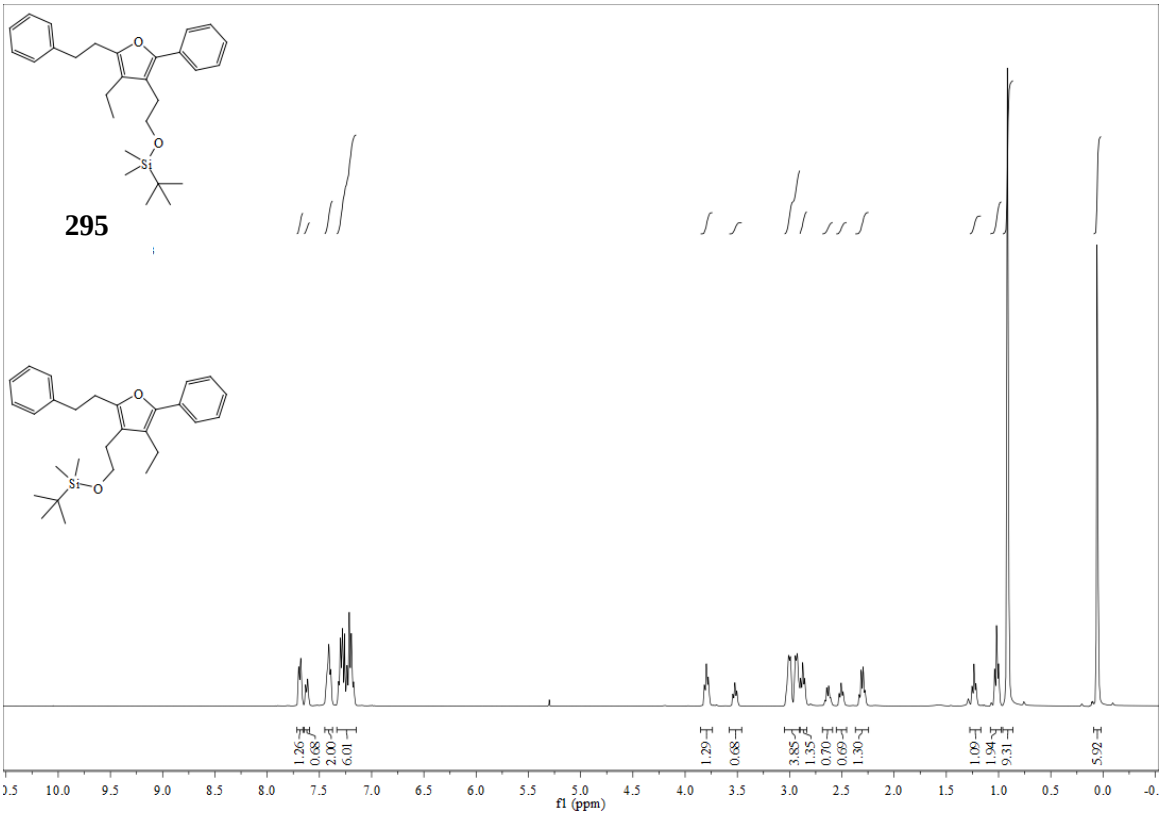

293
2.04
2.02
0.92
0.94
1.90
3.77
2.00
1.86
4.35
2.37
10.00
6.01
f1 (ppm)

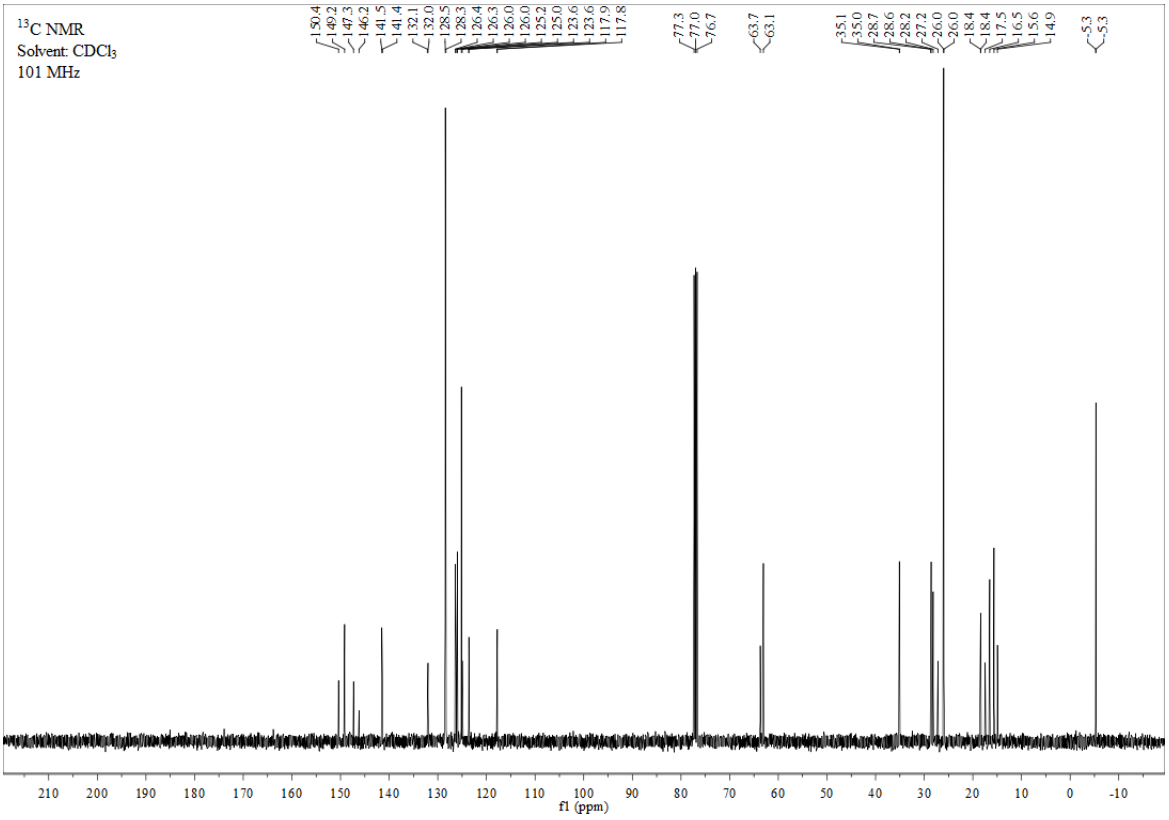

13C NMR
Solvent: CDCl3
101 MHz
150.8
145.9
139.2
132.5
128.4
125.9
124.8
122.2
121.0
114.1
77.3
77.0
76.7
33.8
29.4
29.4
29.4
29.1
28.9
28.7
26.6
26.4
25.6
24.3
23.5
14.4
14.2
f1 (ppm)

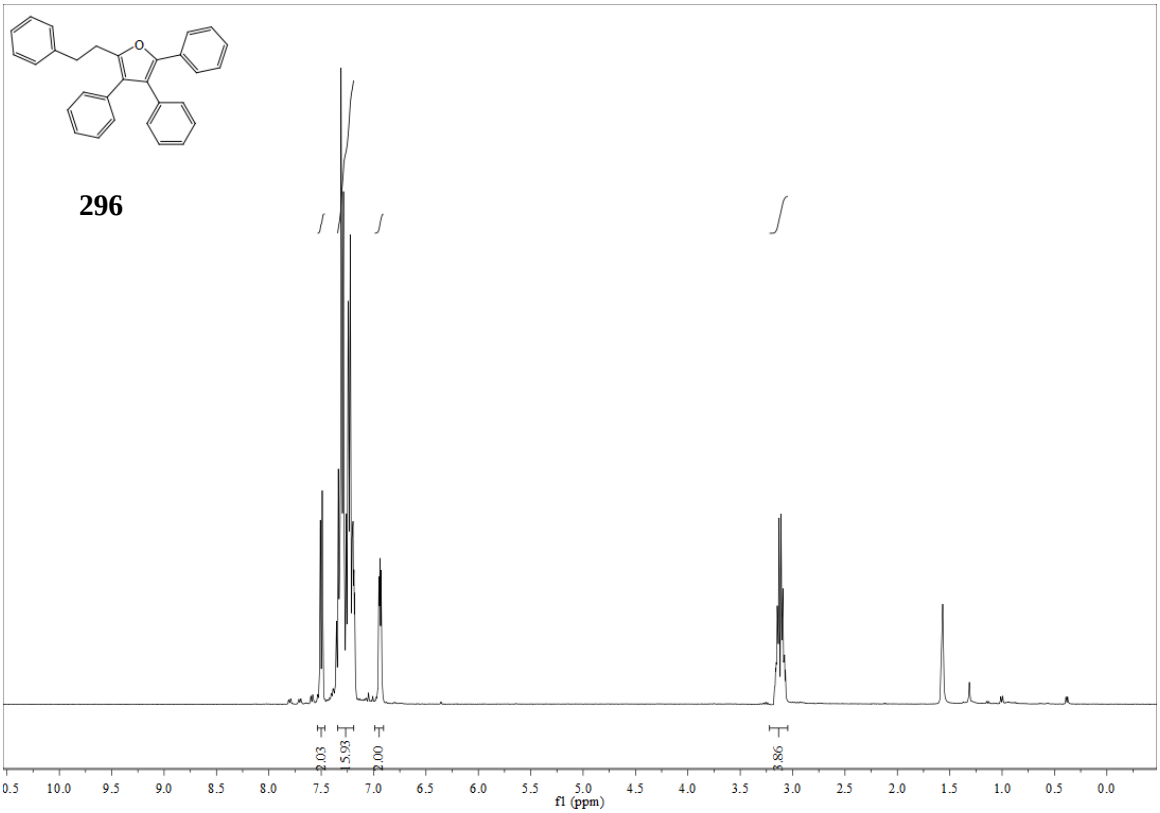

Cl
O
O
Si
1.92
2.04
0.94
2.00
2.00
1.91
4.05
4.37
2.13
6.67
9.79
3.21
6.36
f1 (ppm)

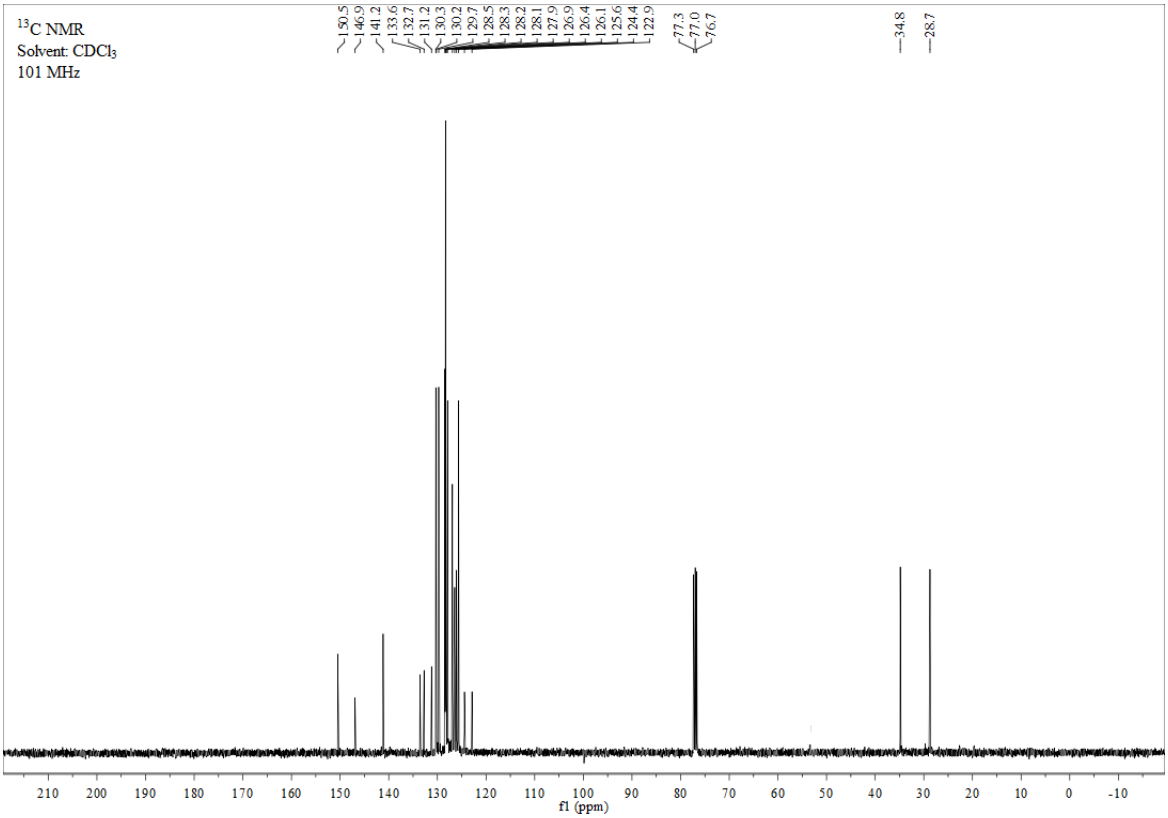
294

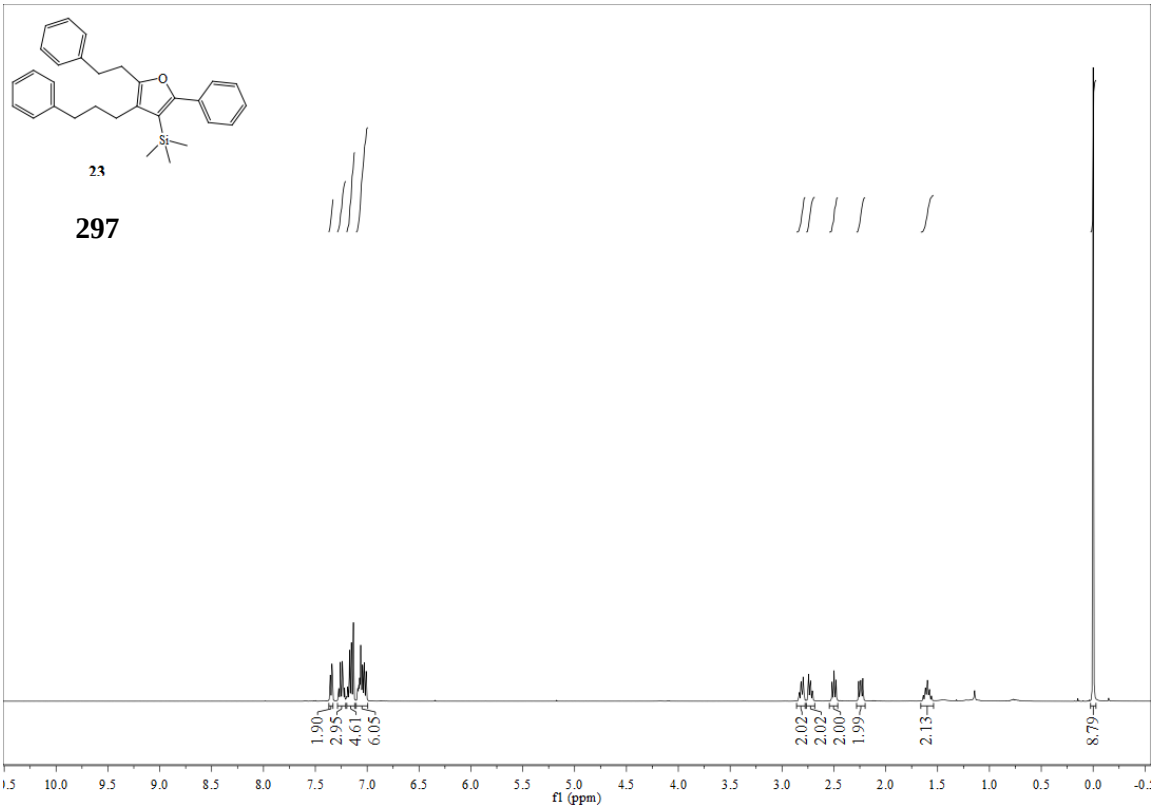

13C NMR
Solvent: CDCl3
101 MHz
154.5
147.1
144.8
130.2
128.2
128.0
126.8
125.4
120.5
120.1
77.3
77.0
76.7
42.4
31.5
30.4
30.4
29.8
29.4
25.7
25.6
24.6
23.1
22.6
22.2
18.2
14.1
-4.4
f1 (ppm)

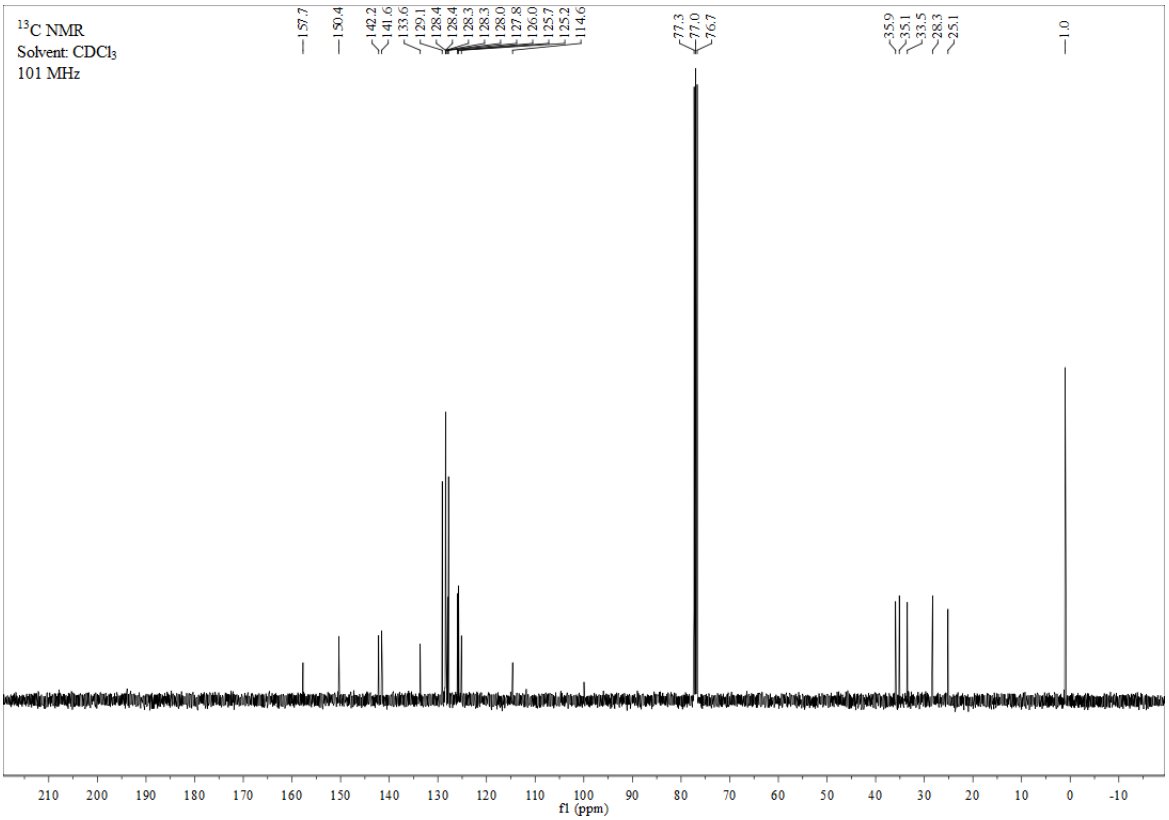

295
1.26
0.68
2.00
6.01
1.29
0.68
3.85
1.35
0.70
0.69
1.30
1.09
1.94
9.31
5.92
f1 (ppm)

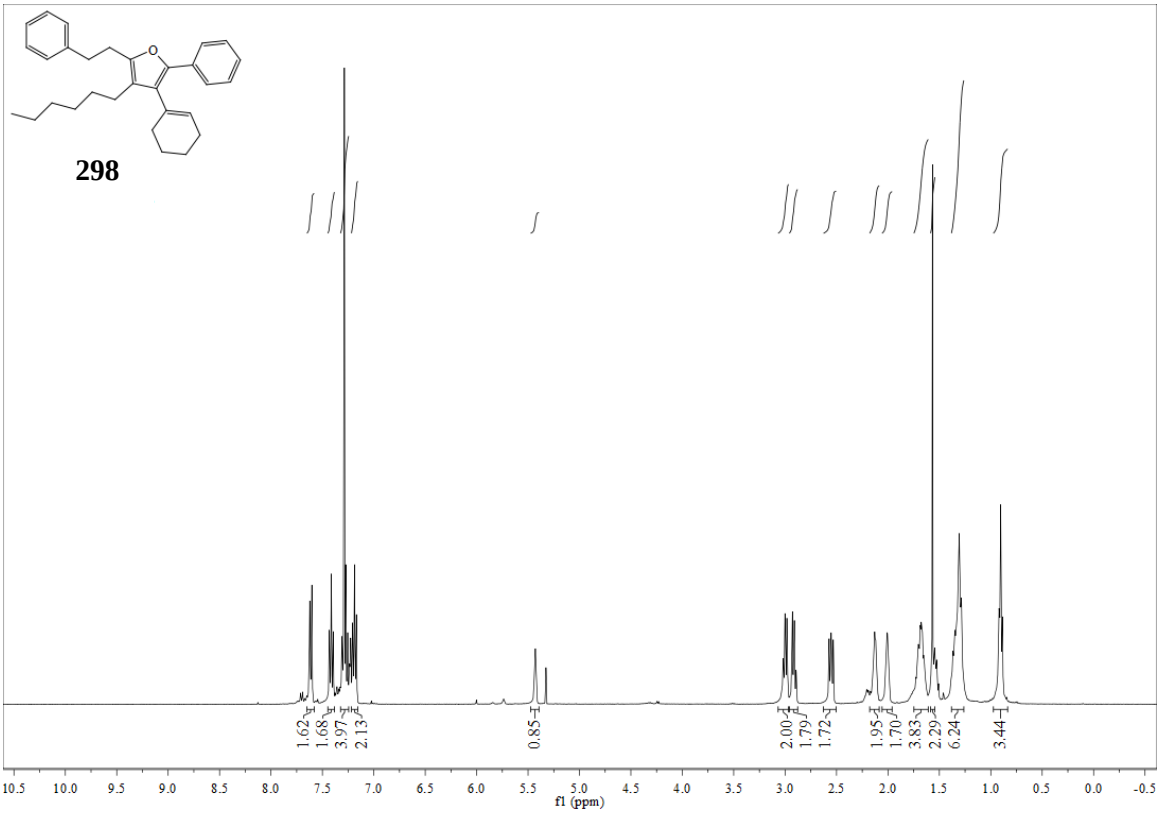

13C NMR
Solvent: CDCl3
101 MHz
150.4
149.2
147.3
146.2
141.5
141.4
132.1
132.0
128.5
128.3
126.4
126.3
126.0
126.0
125.2
125.0
123.6
123.6
117.9
117.8
77.3
77.0
76.7
63.7
63.1
35.1
35.0
28.7
28.6
28.2
27.2
26.0
26.0
18.4
18.4
17.5
16.5
15.6
14.9
-5.3
-5.3
f1 (ppm)

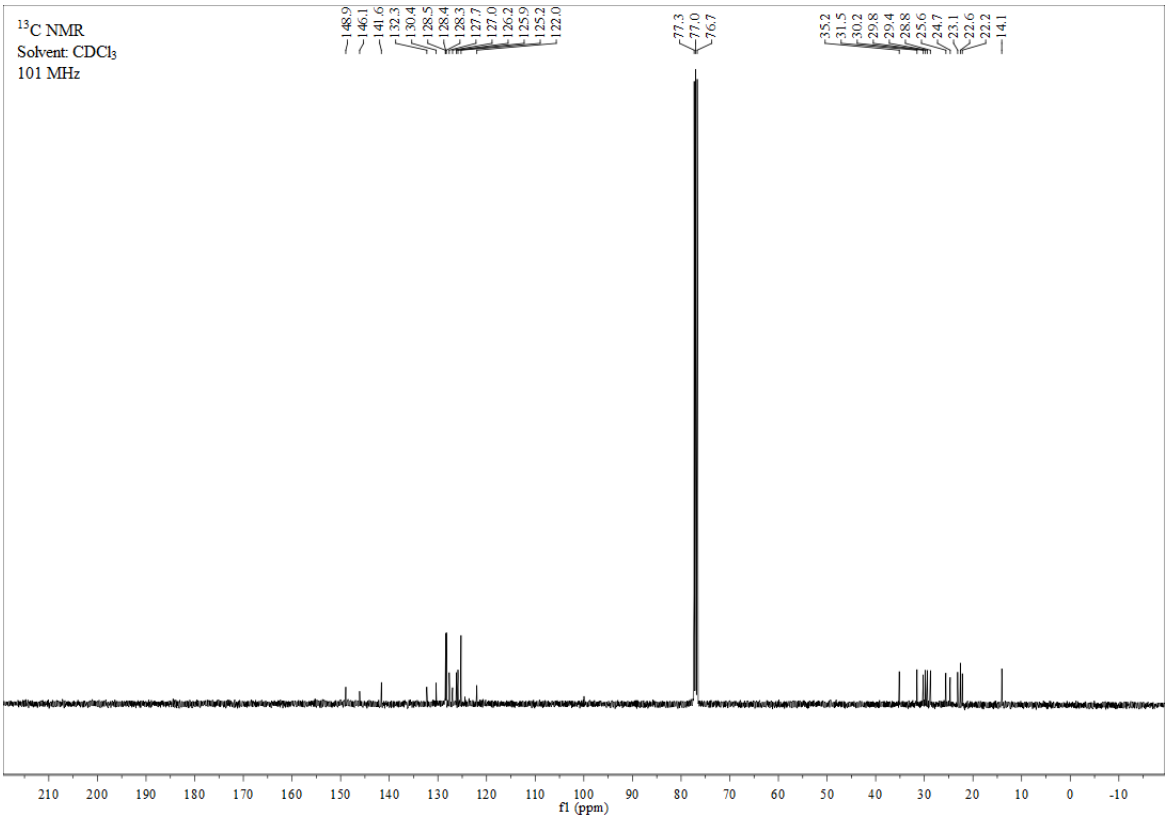

296
2.03
5.93
2.00
3.86
f1 (ppm)


13C NMR
Solvent: CDCl3
101 MHz
150.5
146.9
141.2
133.6
132.7
131.2
130.3
130.2
129.7
128.5
128.3
128.2
128.1
127.9
126.9
126.4
126.1
125.6
124.4
122.9
77.3
77.0
76.7
34.8
28.7
f1 (ppm)


23
297
1.90
2.95
4.61
6.05
2.02
2.02
2.00
1.99
2.13
8.79
f1 (ppm)


13C NMR
Solvent: CDCl3
101 MHz
157.7
150.4
142.2
141.6
133.6
129.1
128.4
128.4
128.3
128.3
128.0
127.8
126.0
125.7
125.2
114.6
77.3
77.0
76.7
35.9
35.1
33.5
28.3
25.1
1.0
f1 (ppm)


298
1.62
1.68
3.97
2.13
0.85
2.00
1.79
1.72
1.95
1.70
3.83
2.29
6.24
3.44
f1 (ppm)


13C NMR
Solvent: CDCl3
101 MHz
148.9
146.1
141.6
132.3
130.4
128.5
128.4
128.3
127.7
127.0
126.2
125.9
125.2
122.0
77.3
77.0
76.7
35.2
31.5
30.2
29.8
29.4
28.8
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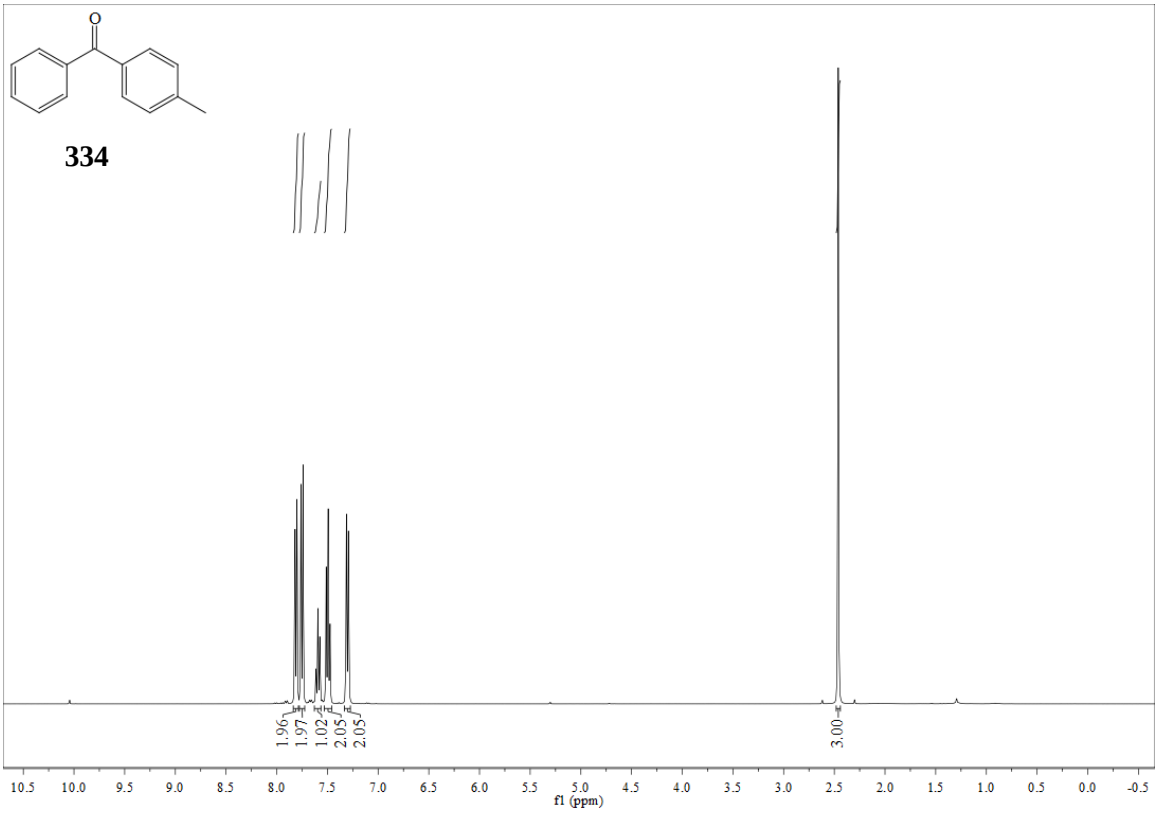
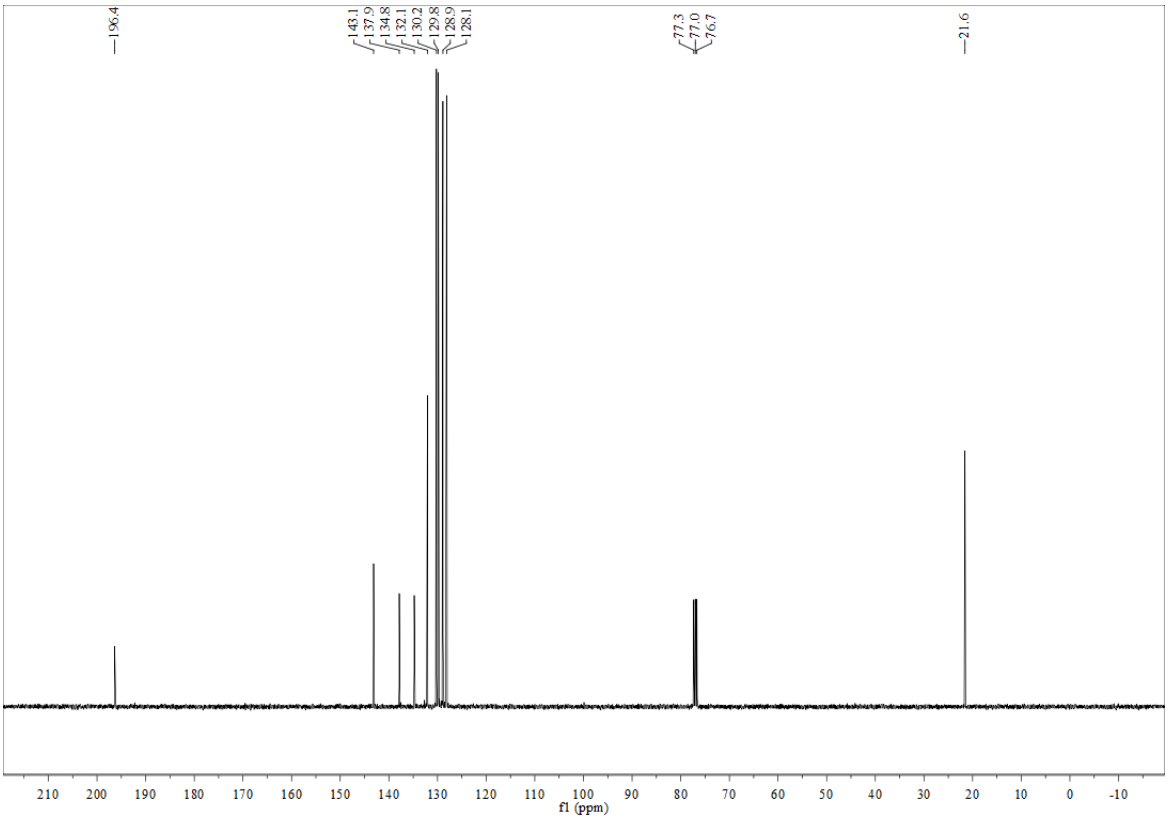
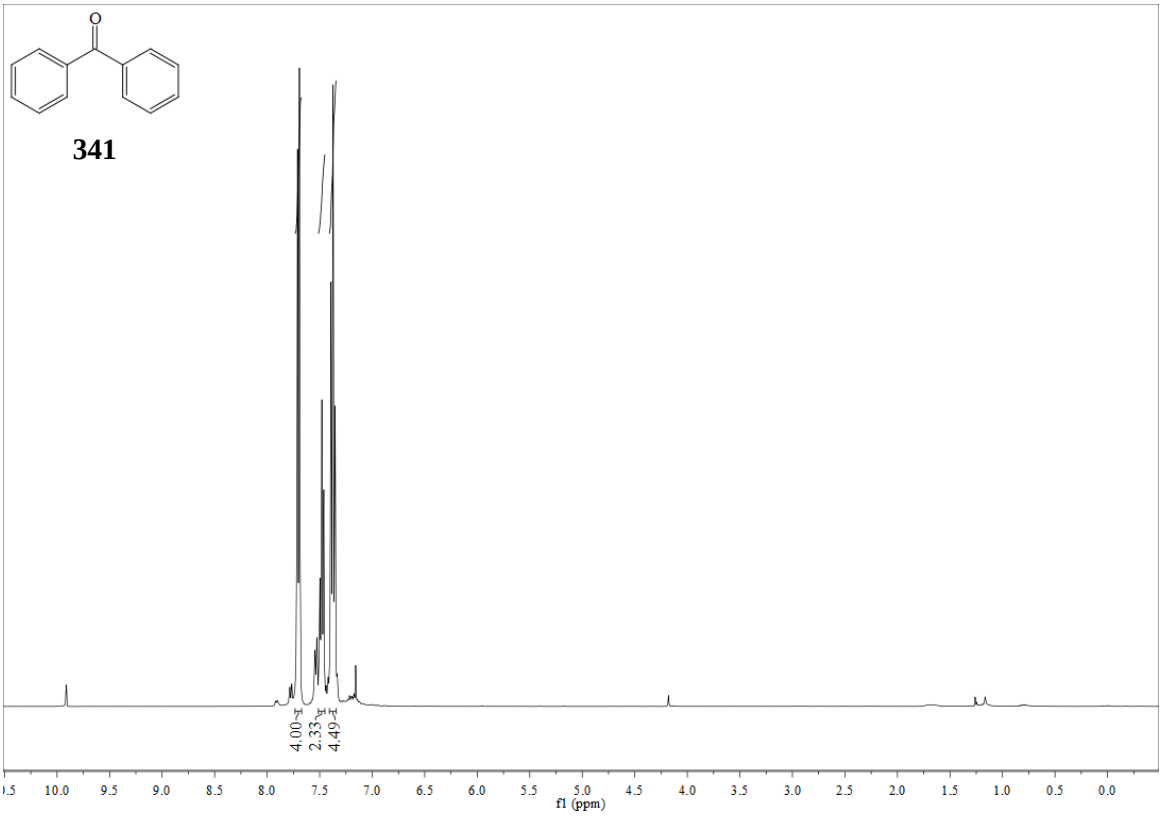
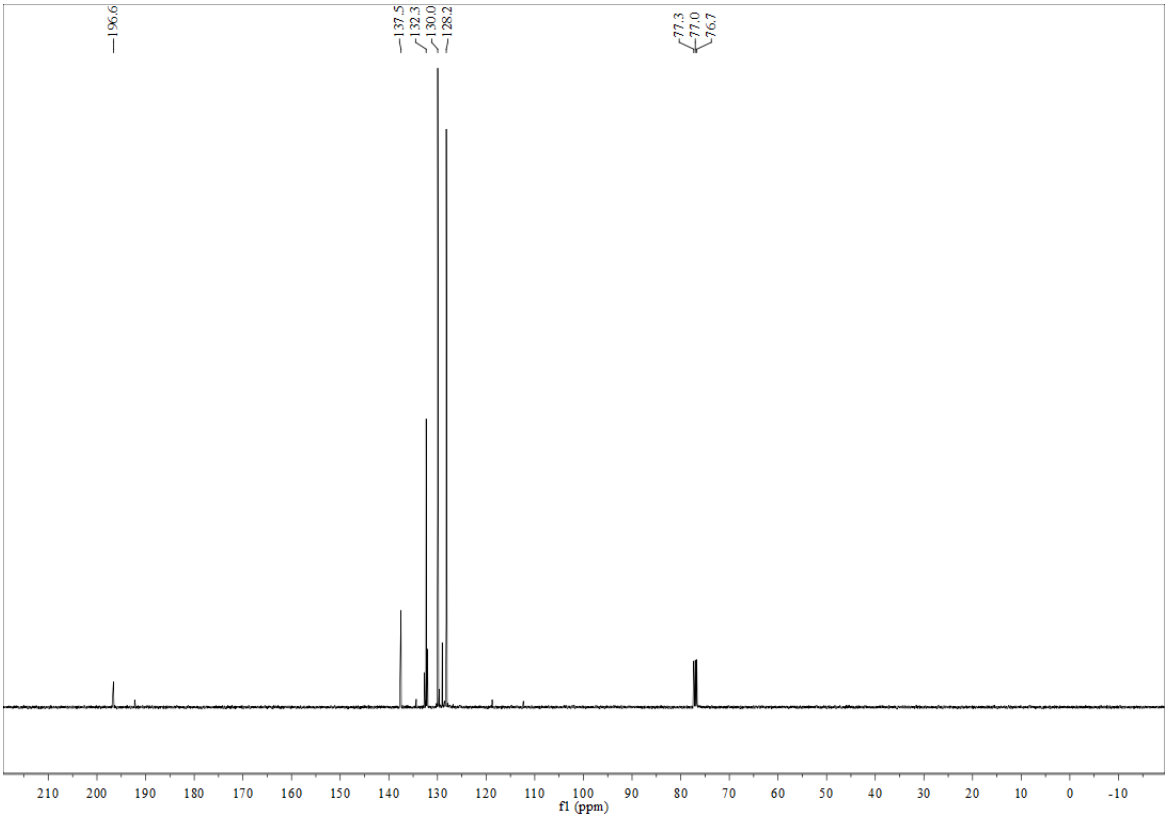
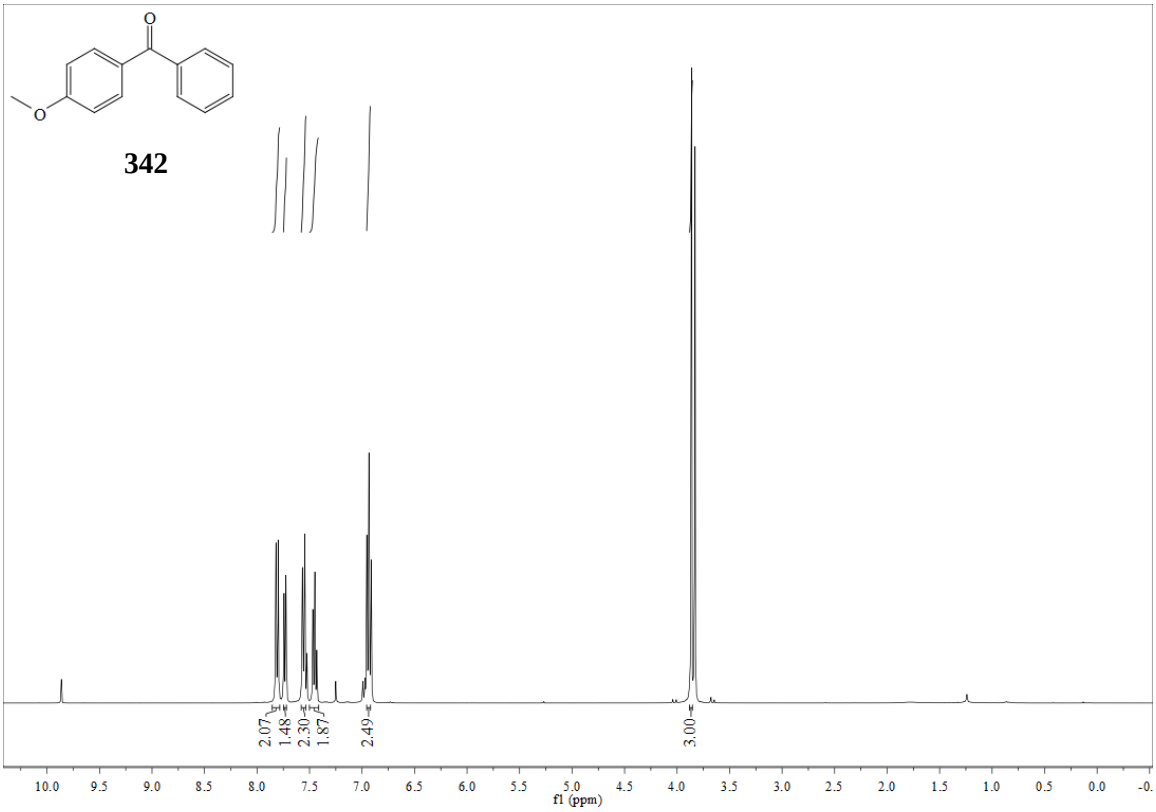
24.7
23.1
22.6
22.2
14.1
f1 (ppm)

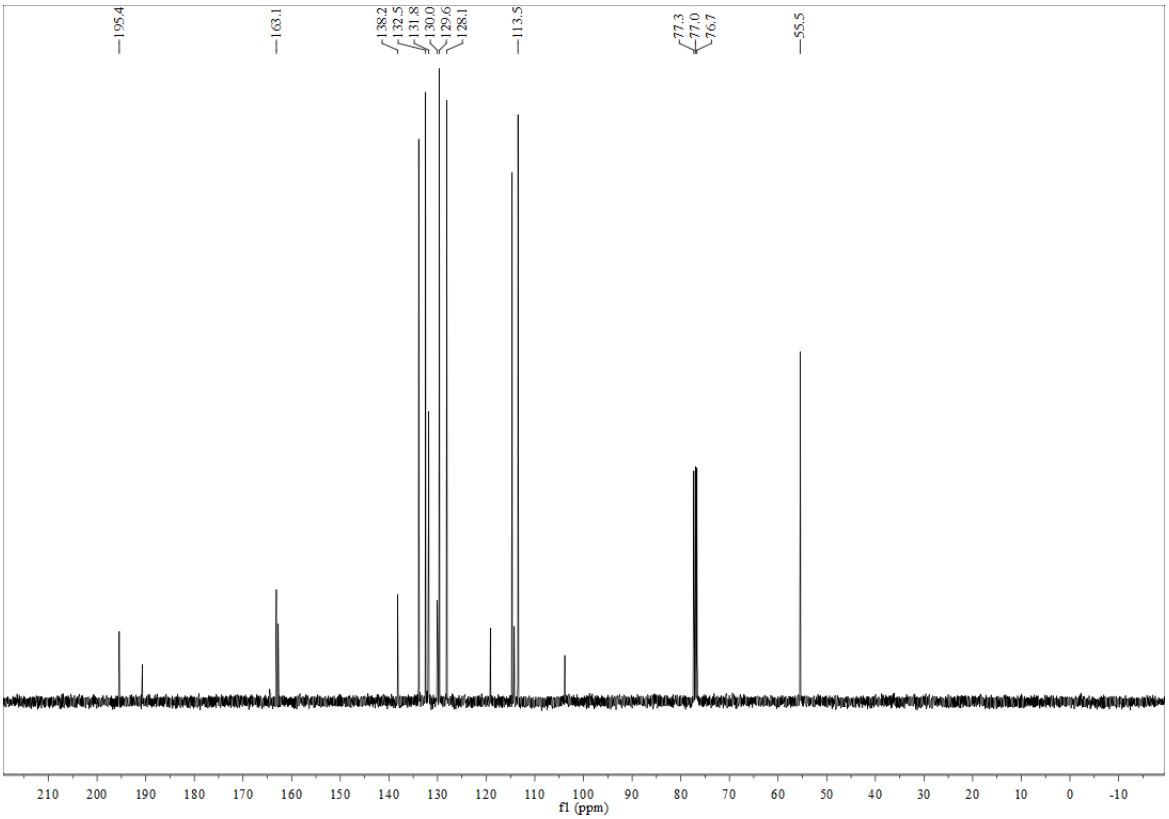

O
334
1.96
1.97
1.02
2.05
2.05
3.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

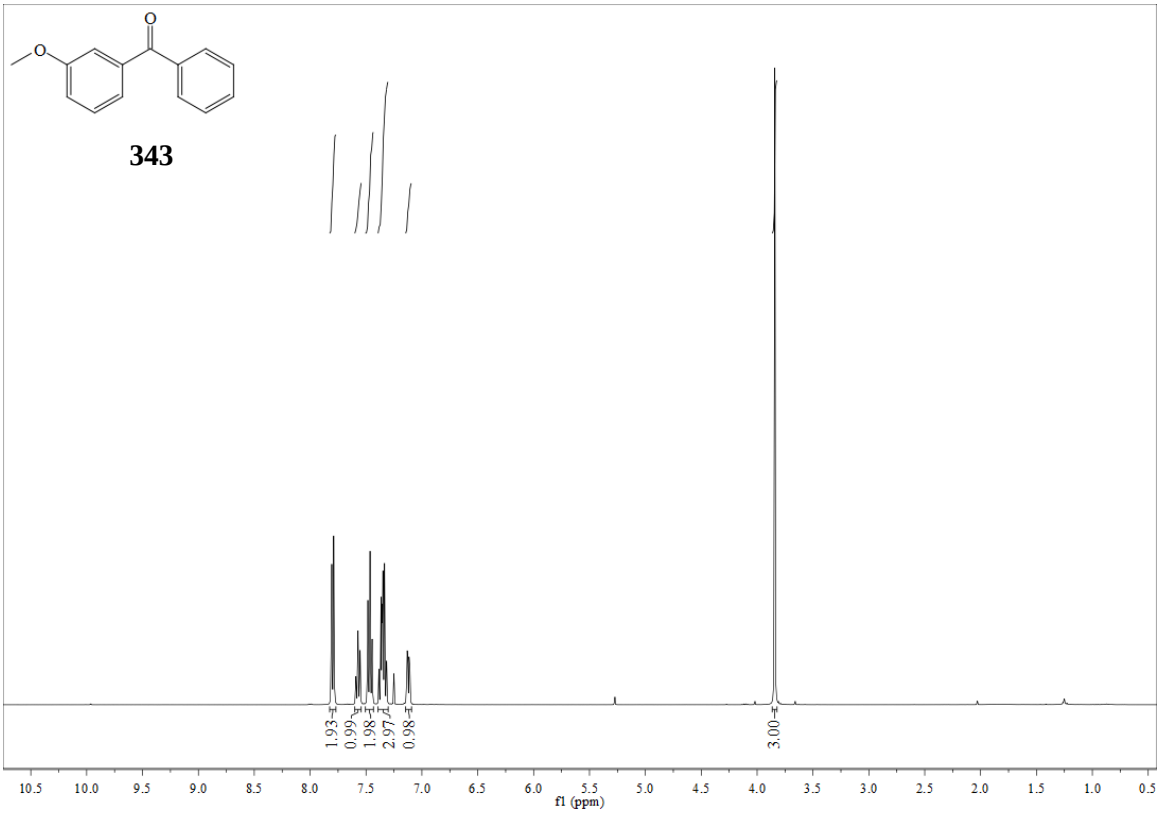

196.4
143.1
137.9
134.8
132.1
130.2
129.8
128.9
128.1
77.3
77.0
76.7
21.6
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

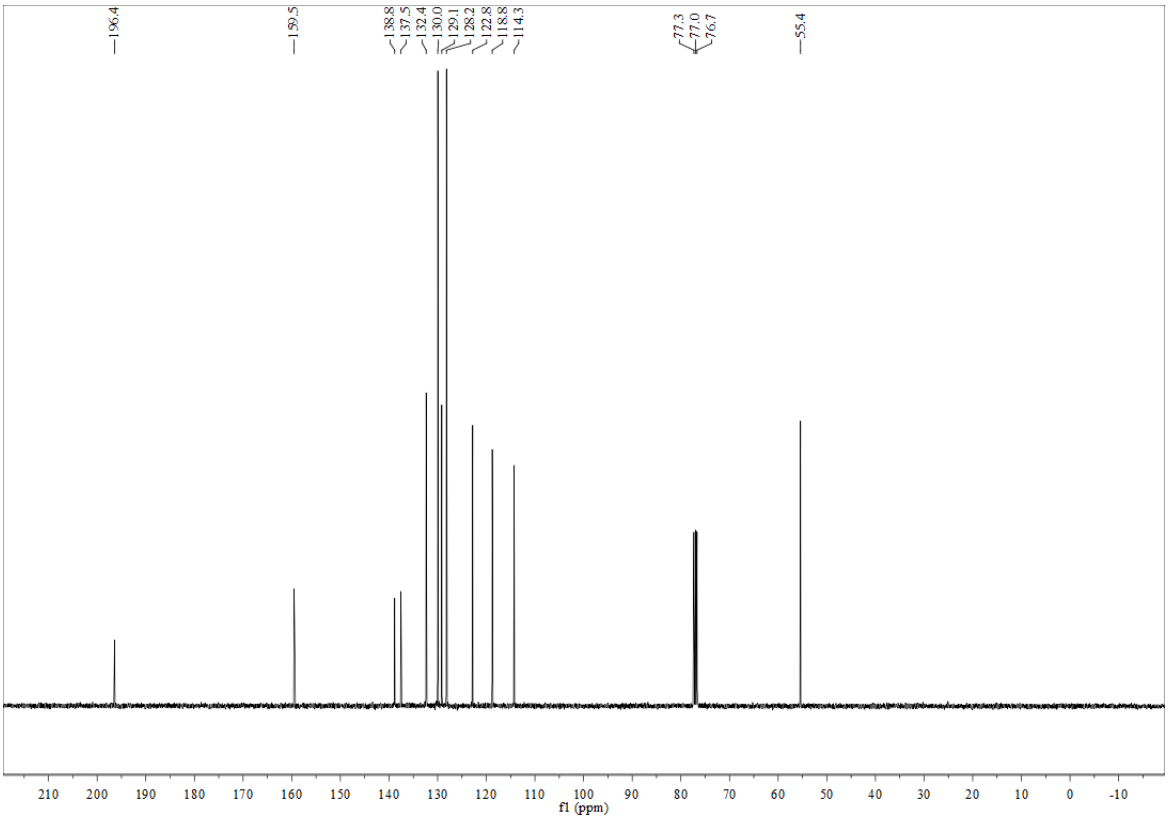

O
341
4.00
2.33
4.49
f1 (ppm)

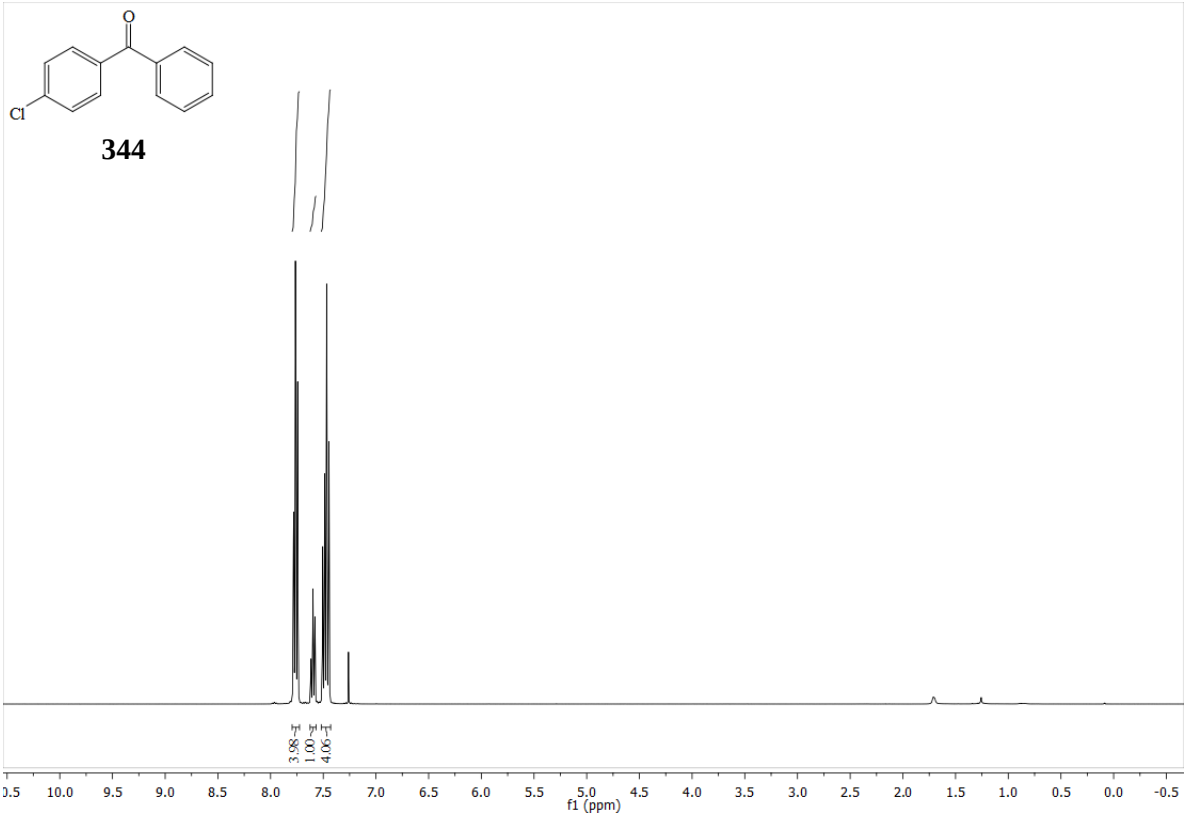

196.6
137.5
132.3
130.0
128.2
77.3
77.0
76.7
f1 (ppm)

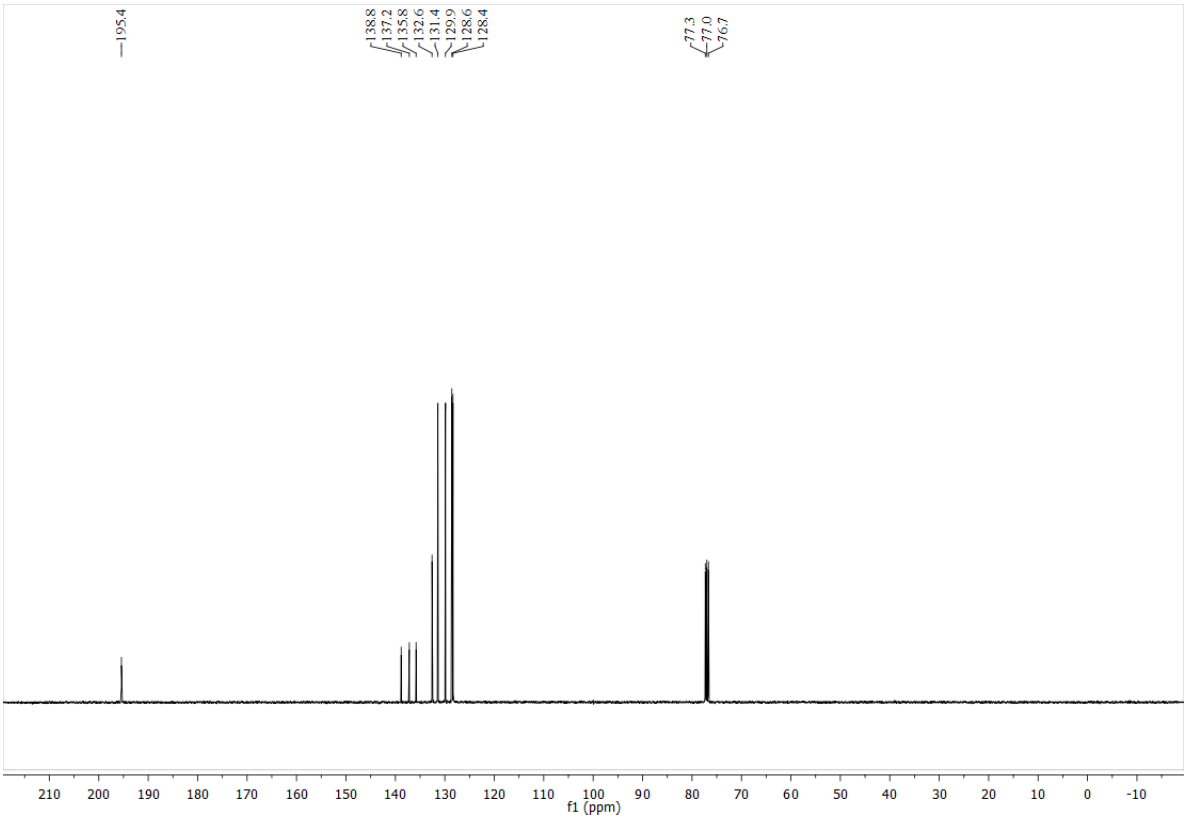

O
O
342
2.07
1.48
2.30
1.87
2.49
3.00
f1 (ppm)

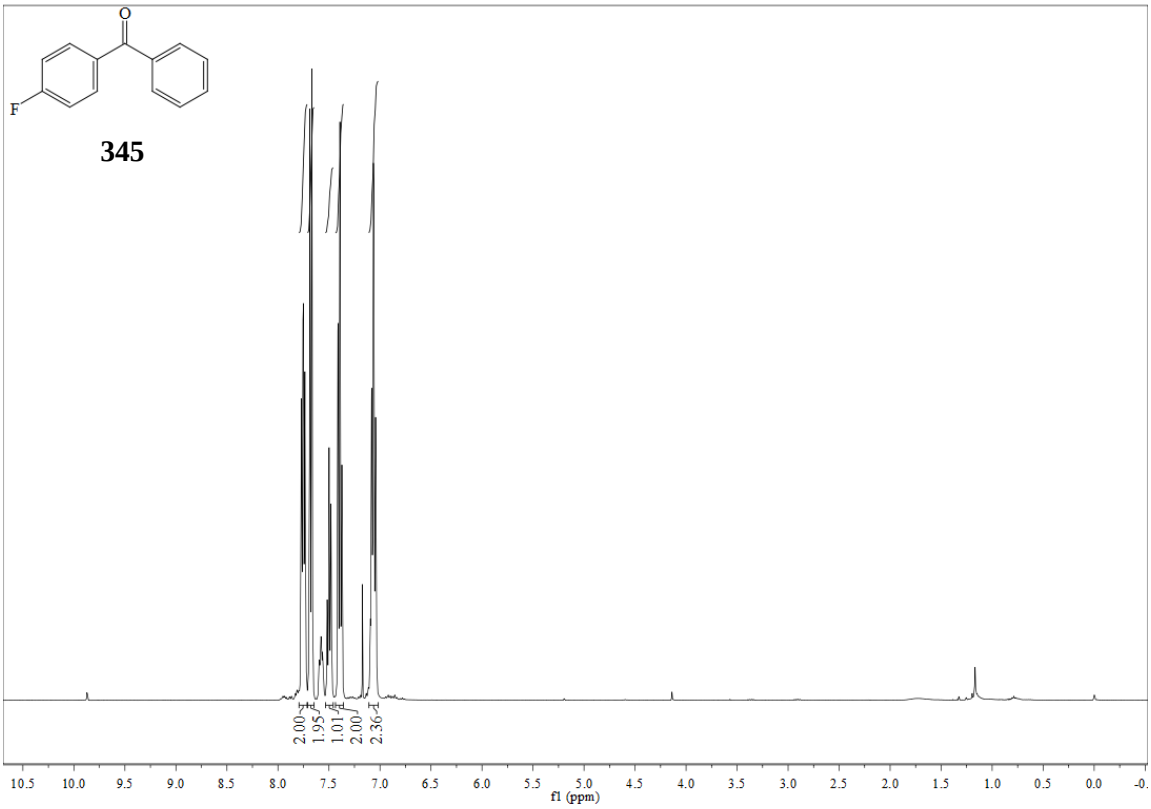

195.4
163.1
138.2
132.5
131.8
130.0
129.6
128.1
113.5
77.3
77.0
76.7
55.5
f1 (ppm)

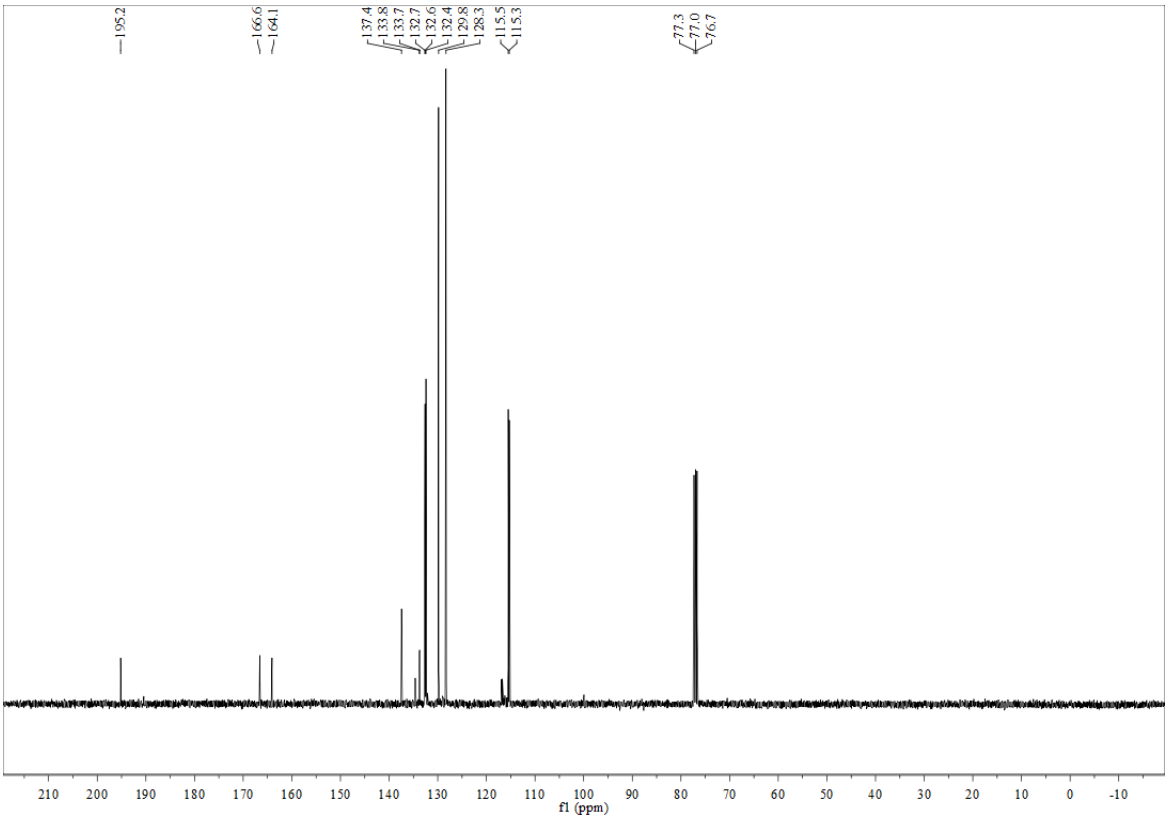

O
O
343
1.93
0.99
1.98
2.97
0.98
3.00
f1 (ppm)

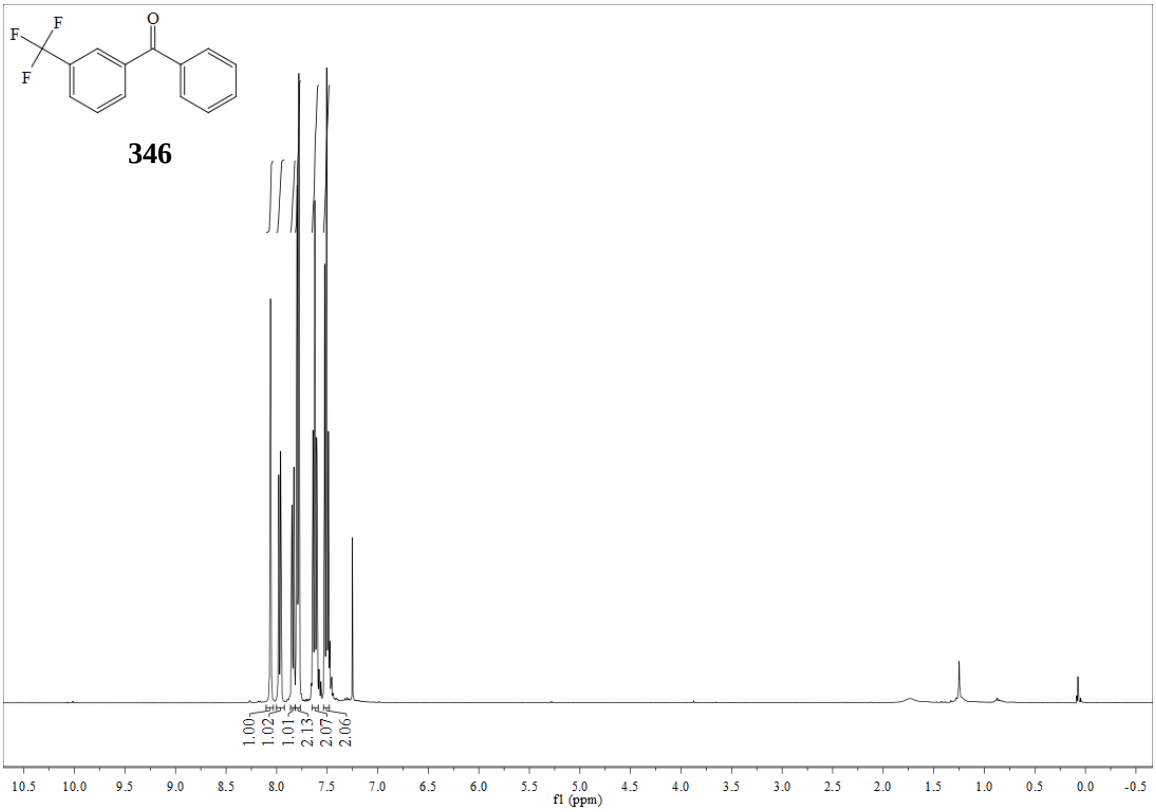

196.4
159.5
138.8
137.5
132.4
130.0
129.1
128.2
122.8
118.8
114.3
77.3
77.0
76.7
55.4
f1 (ppm)

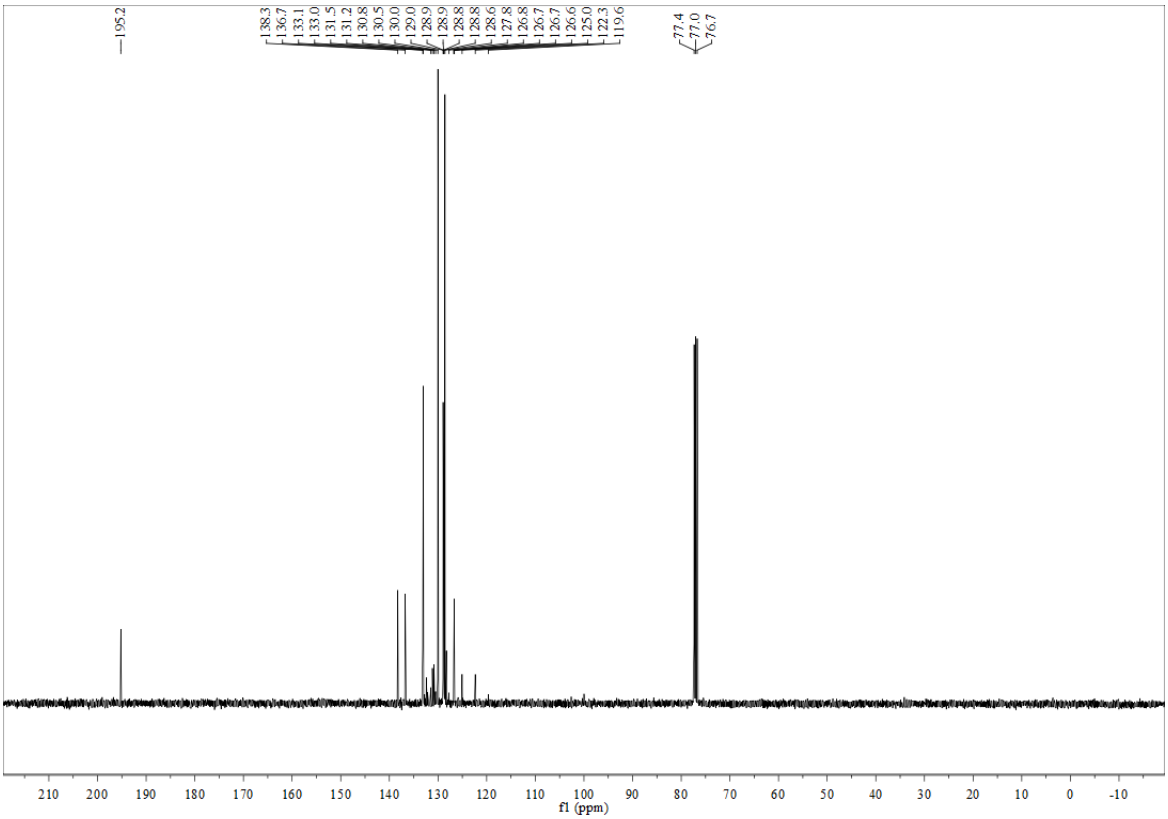

O
Cl
344
3.98
1.00
4.06
f1 (ppm)

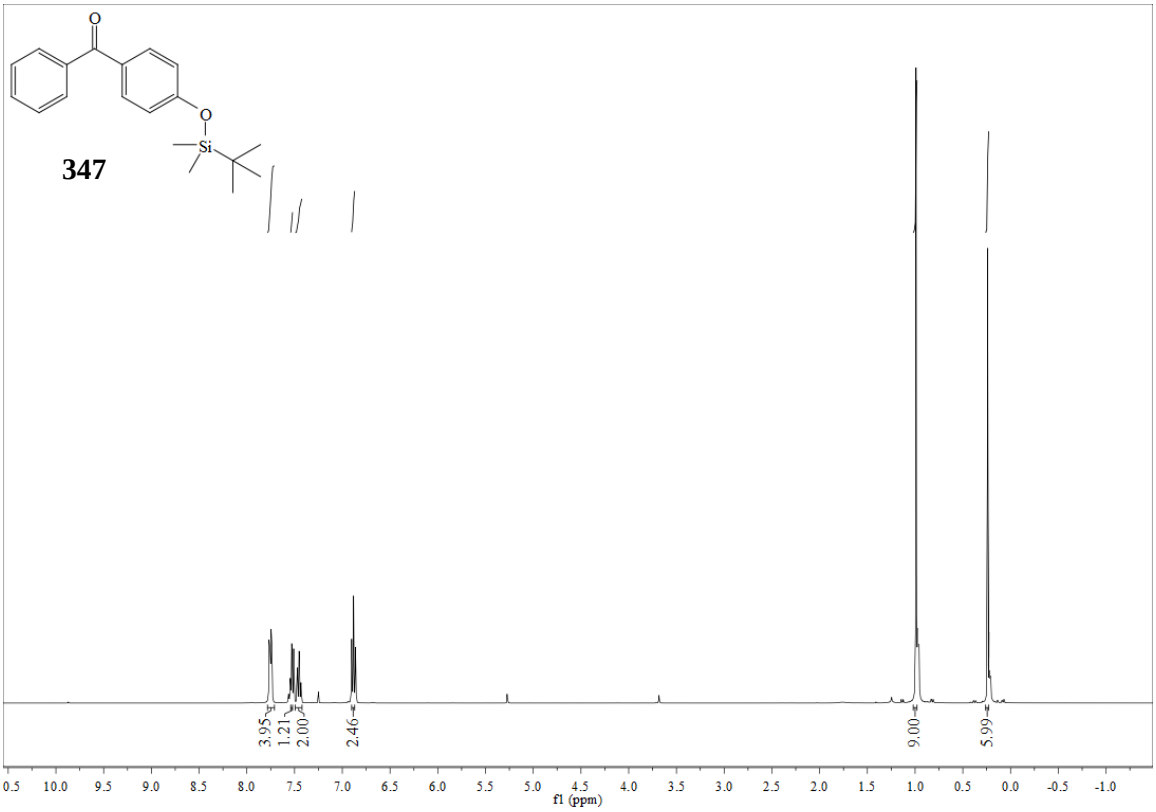

195.4
138.8
137.2
135.8
132.6
131.4
129.9
128.6
128.4
77.3
77.0
76.7
f1 (ppm)

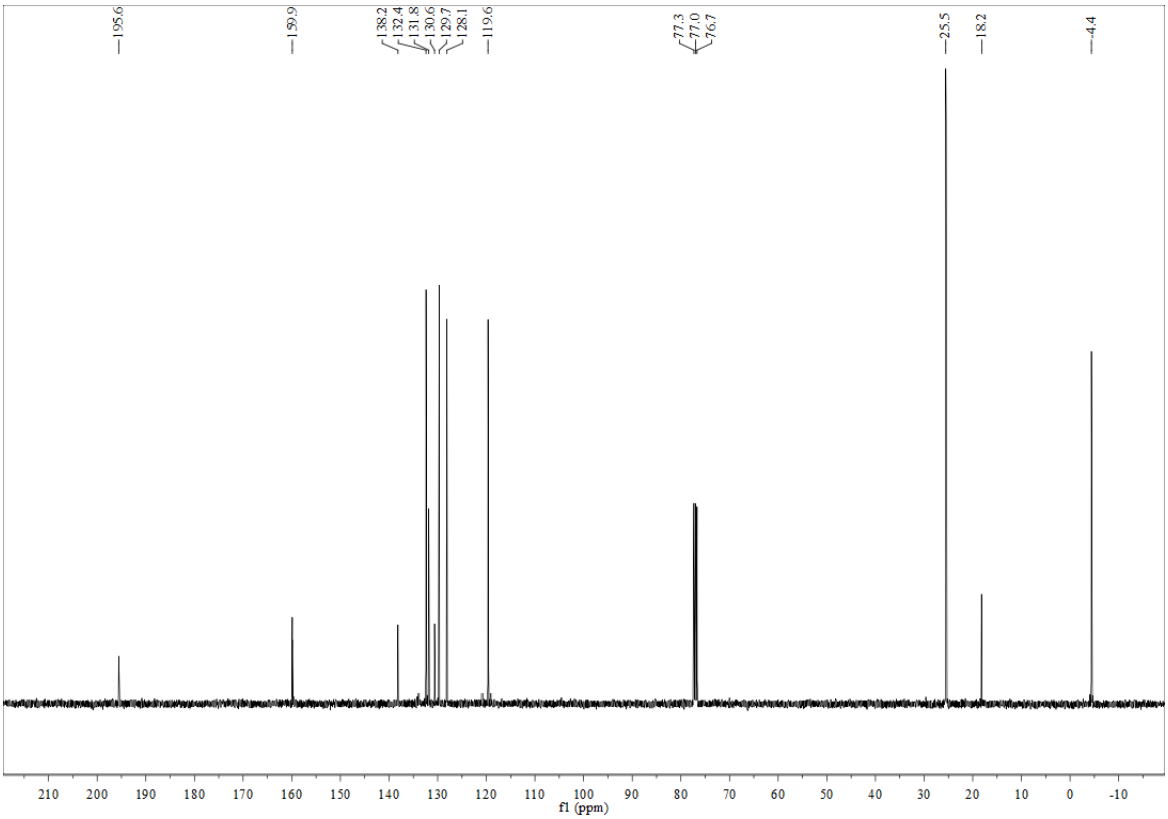

O
F
345
2.00
1.95
1.01
2.00
2.36
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

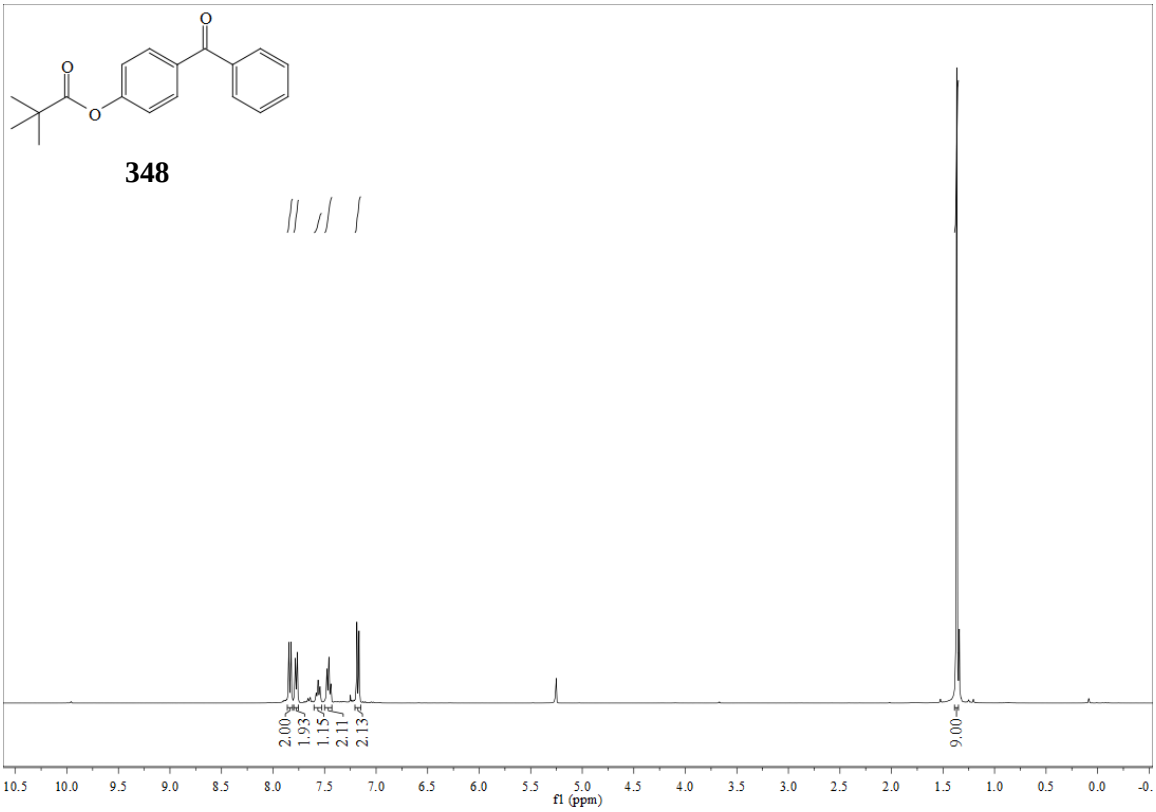

195.2
166.6
164.1
137.4
133.8
133.7
132.7
132.6
132.4
129.8
128.3
115.5
115.3
77.3
77.0
76.7
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

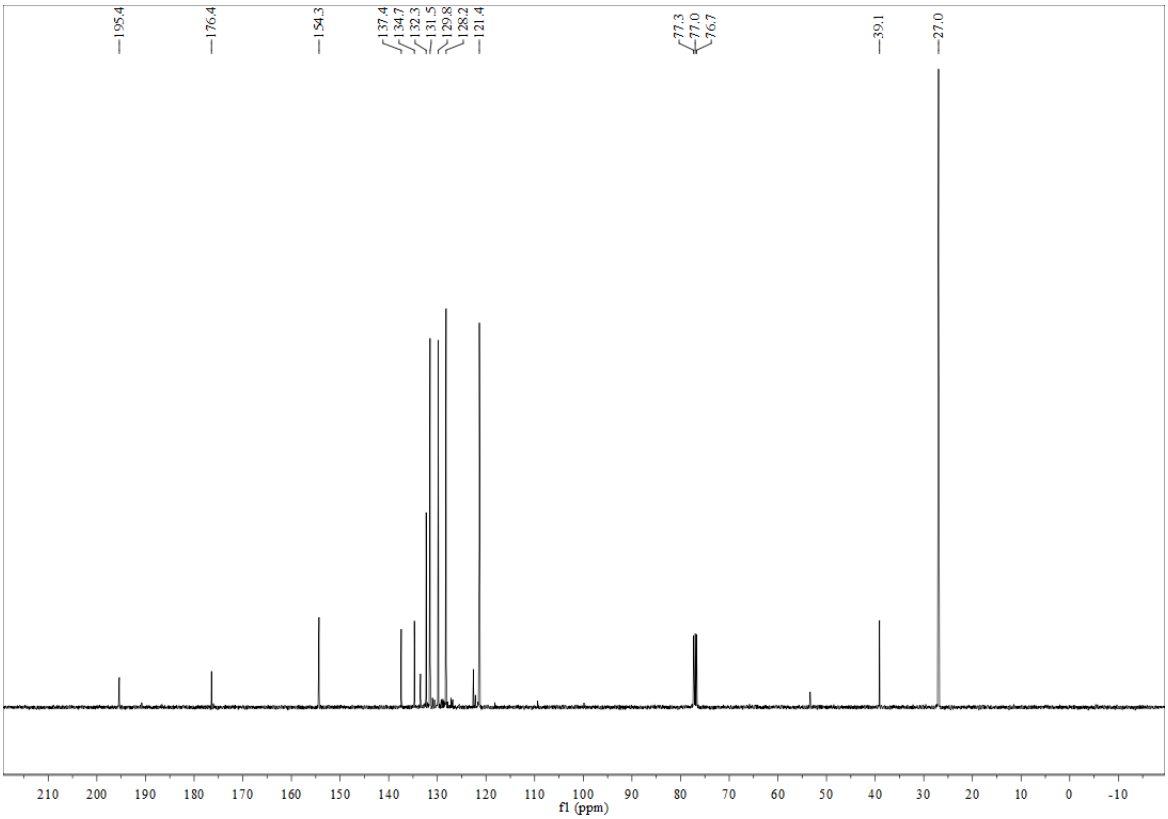

F
F
F
O
346
1.00
1.02
1.01
2.13
2.07
2.06
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

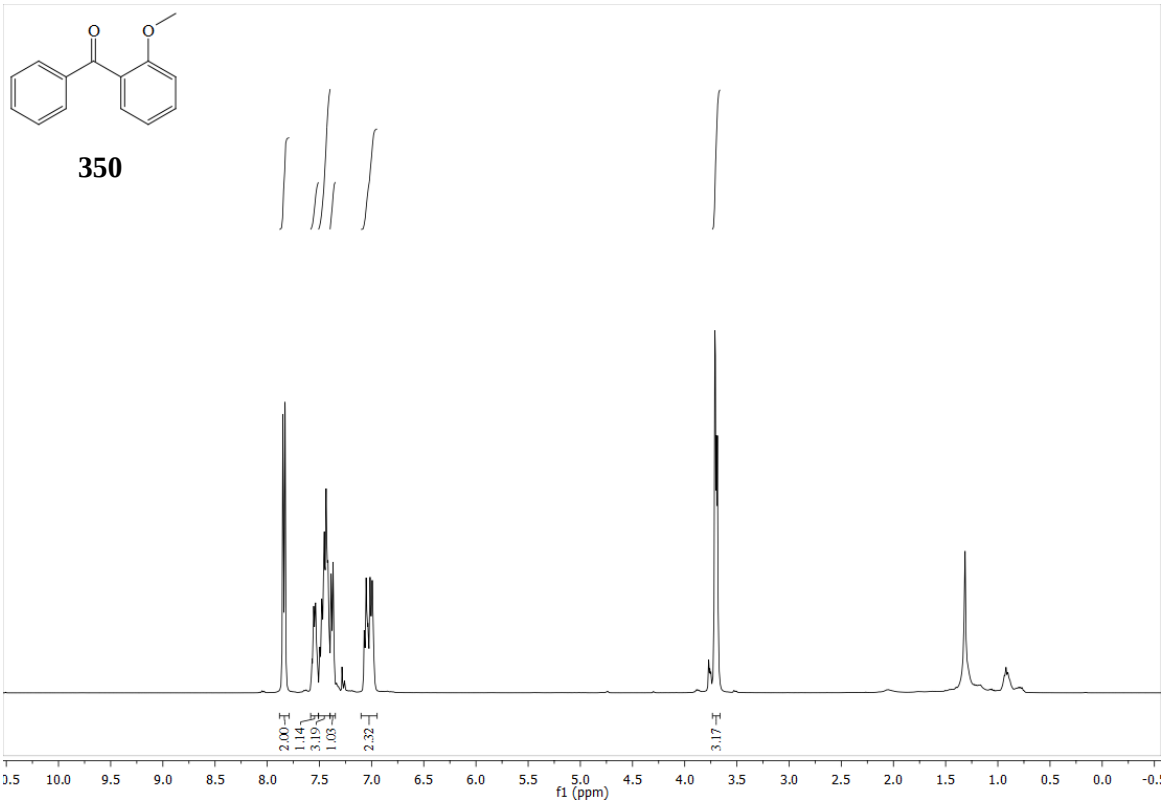

195.2
138.3
136.7
133.1
133.0
131.5
131.2
130.8
130.5
130.0
129.0
128.9
128.9
128.8
128.8
128.6
127.8
126.8
126.7
126.7
126.6
125.0
122.3
119.6
77.4
77.0
76.7
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
O
Si
347
3.95
1.21
2.00
2.46
9.00
5.99
f1 (ppm)

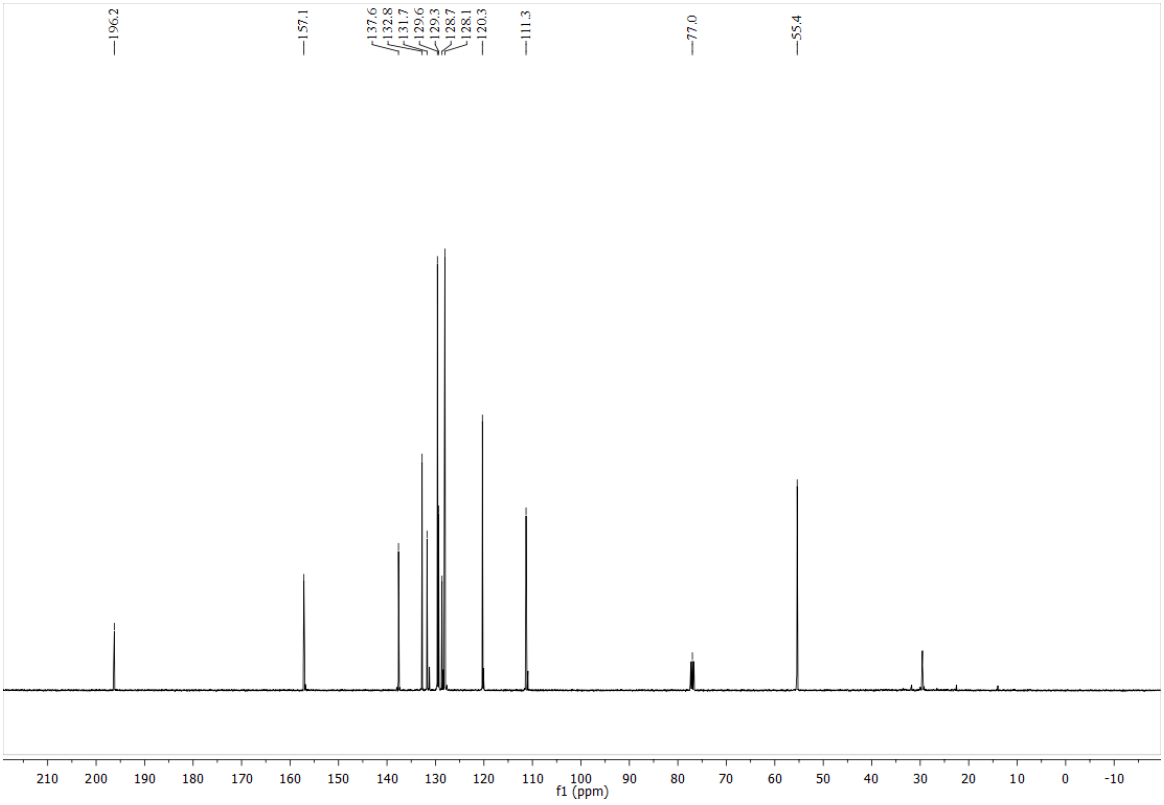

195.6
159.9
138.2
132.4
131.8
130.6
129.7
128.1
119.6
77.3
77.0
76.7
25.5
18.2
-4.4
f1 (ppm)

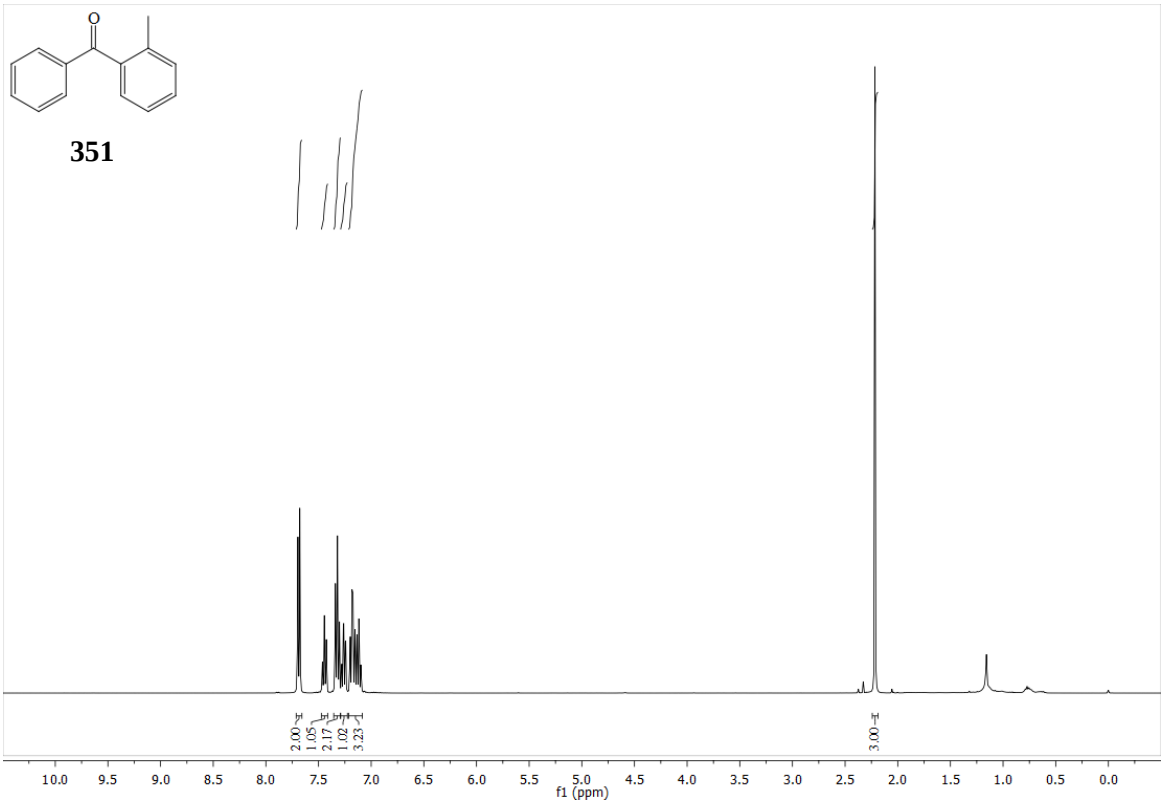

348
2.00
1.93
1.15
2.11
2.13
9.00
f1 (ppm)

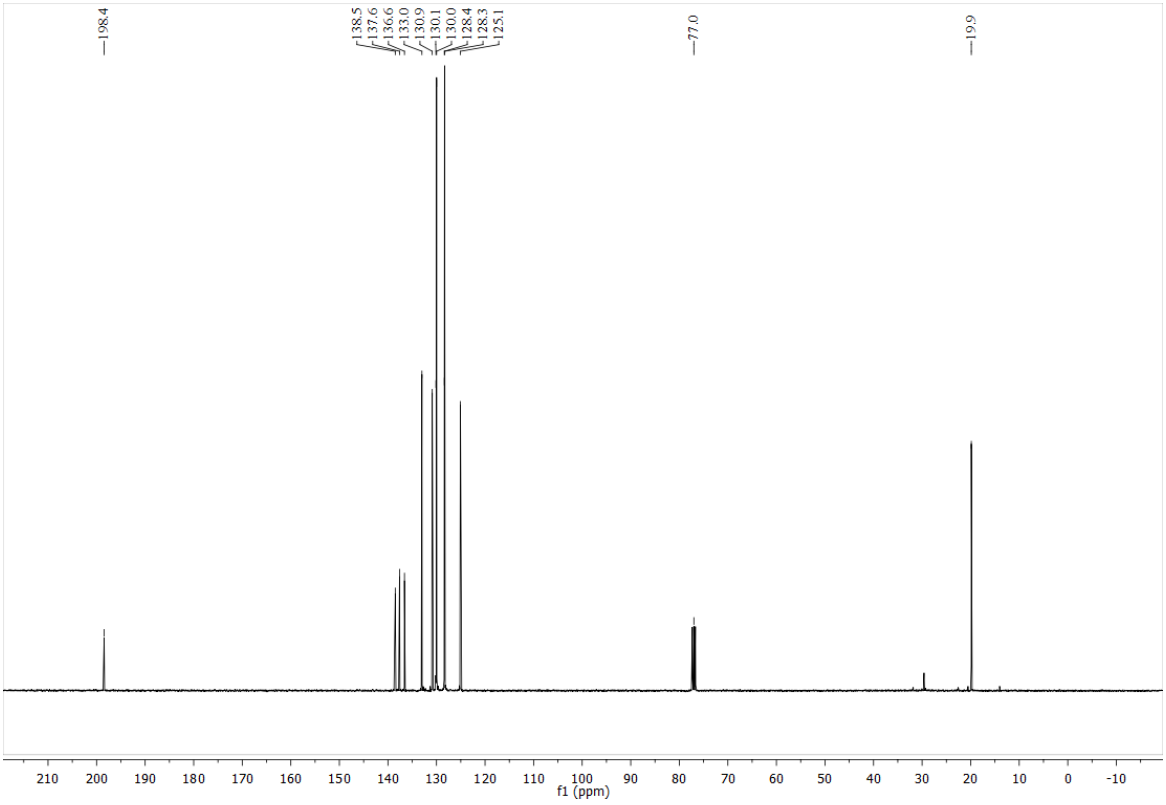

195.4
176.4
154.3
137.4
134.7
132.3
131.5
129.8
128.2
121.4
77.3
77.0
76.7
39.1
27.0
f1 (ppm)

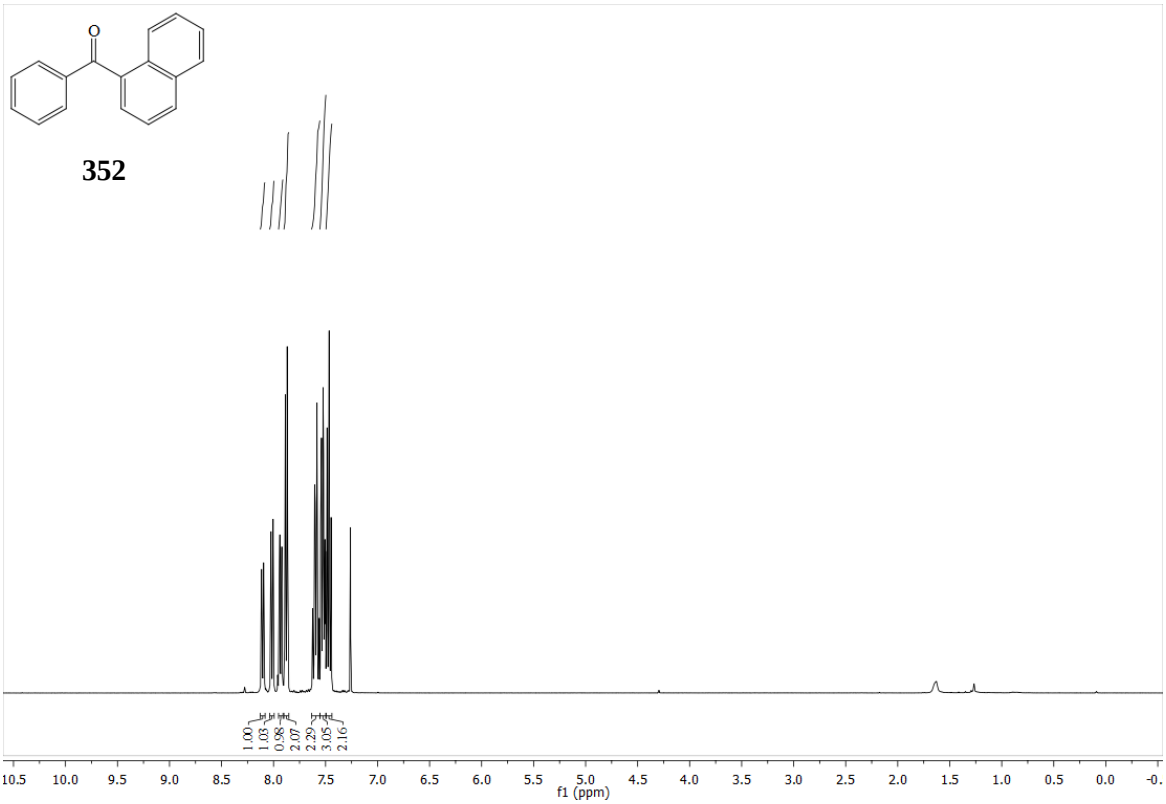

O
O
2.00
1.14
3.19
1.03
2.32
3.17
f1 (ppm)

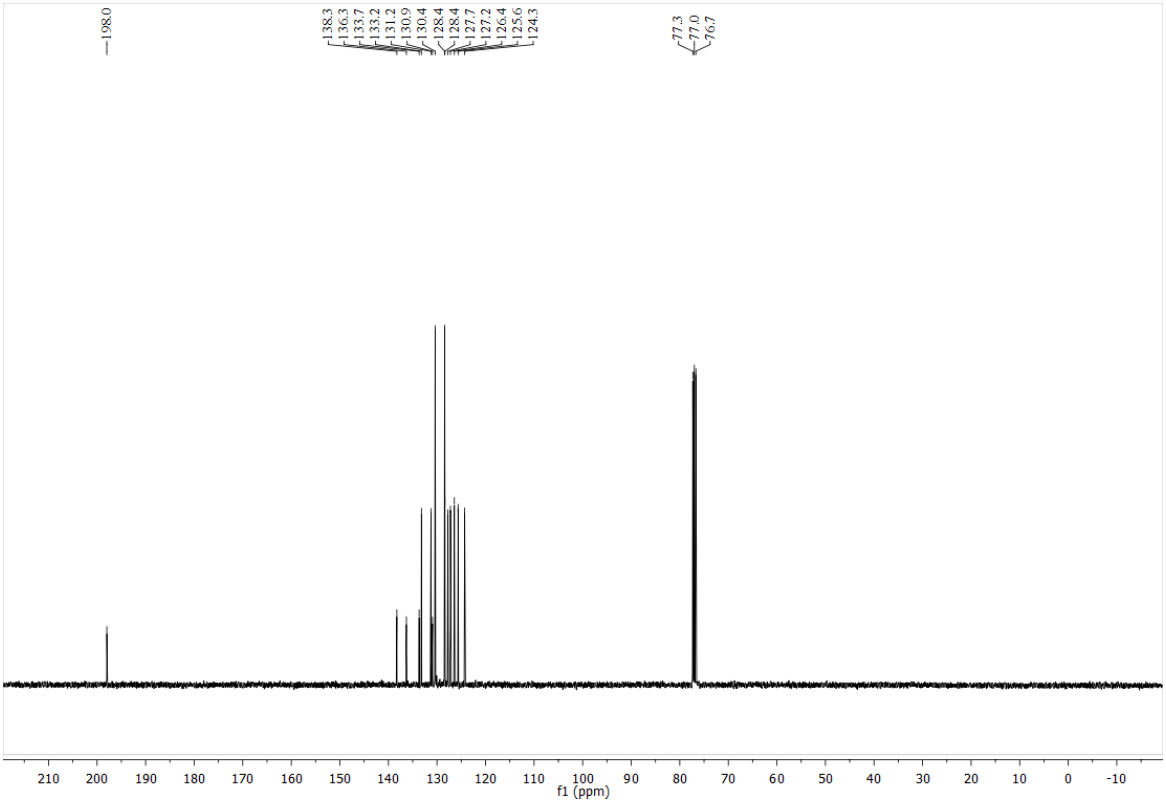
350


196.2
157.1
137.6
132.8
131.7
129.6
129.3
128.7
128.1
120.3
111.3
77.0
55.4
f1 (ppm)


O
351
2.00
1.05
2.17
1.02
3.23
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 0.0
f1 (ppm)


198.4
138.5
137.6
136.6
133.0
130.9
130.1
130.0
128.4
128.3
125.1
77.0
19.9
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)


O
352
1.00
1.03
0.98
2.07
2.29
3.05
2.16
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.
f1 (ppm)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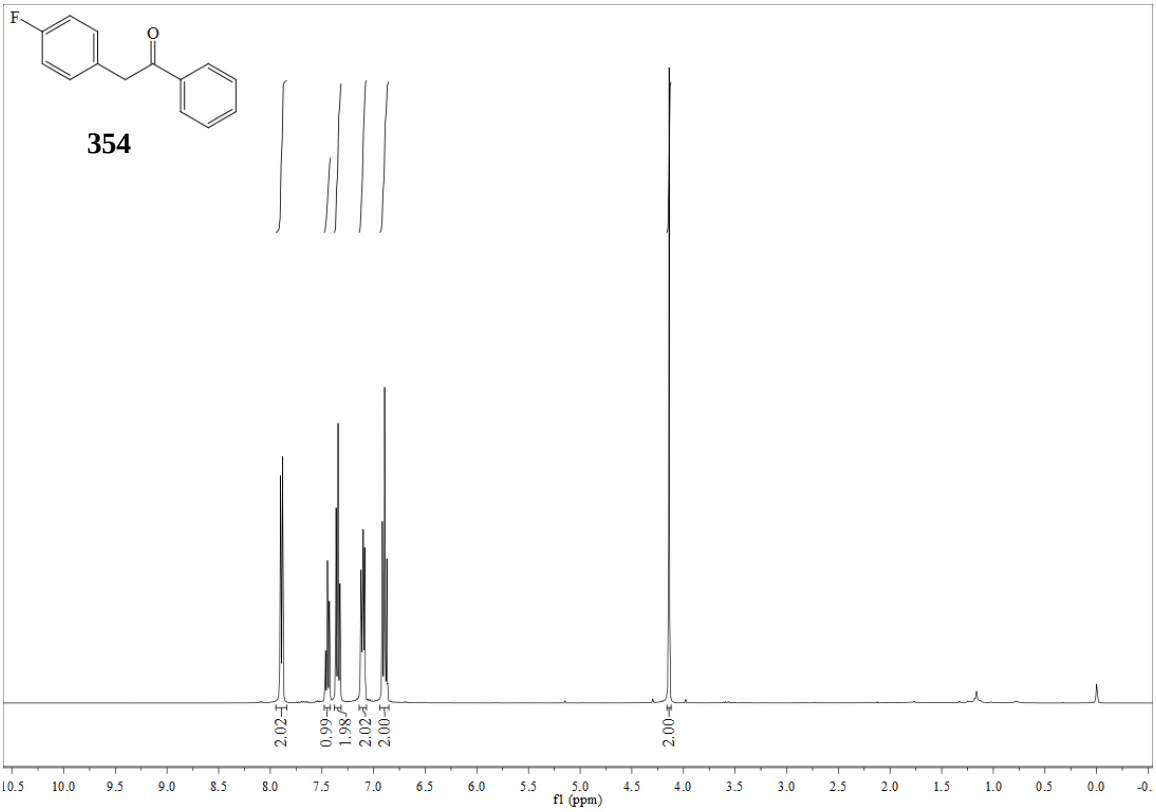
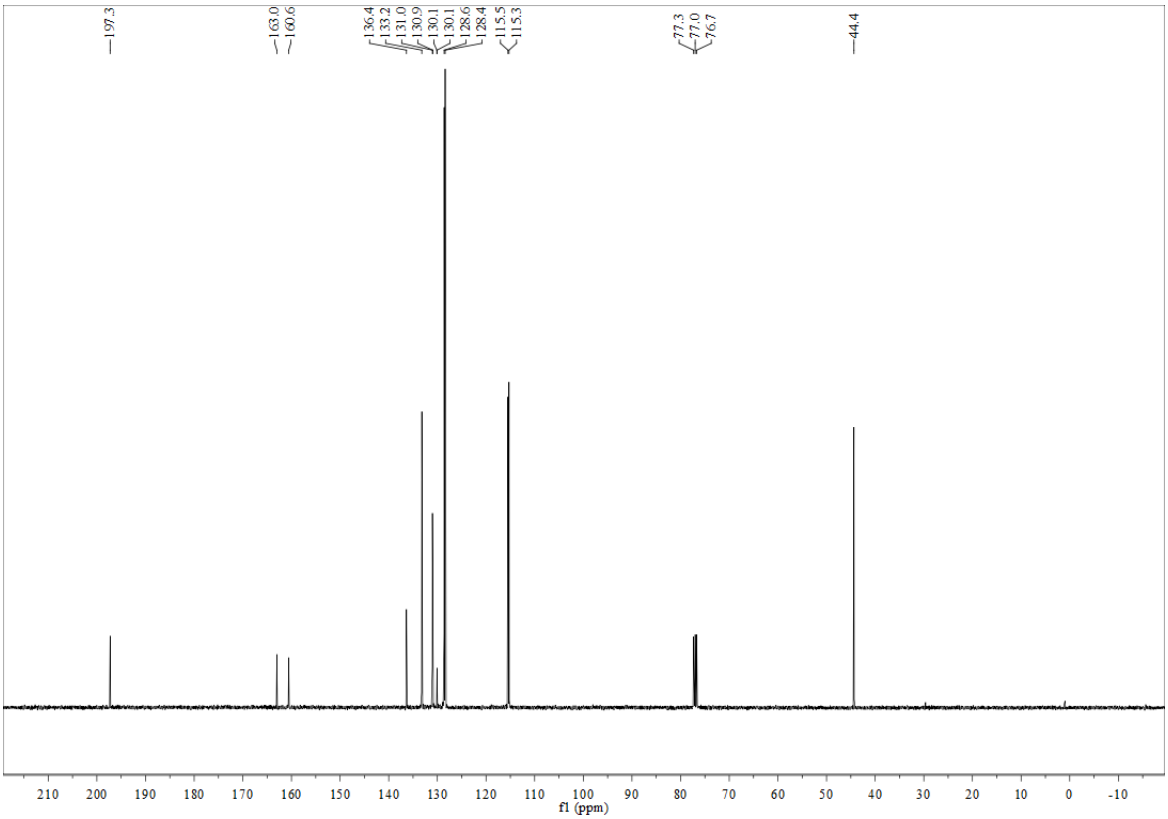
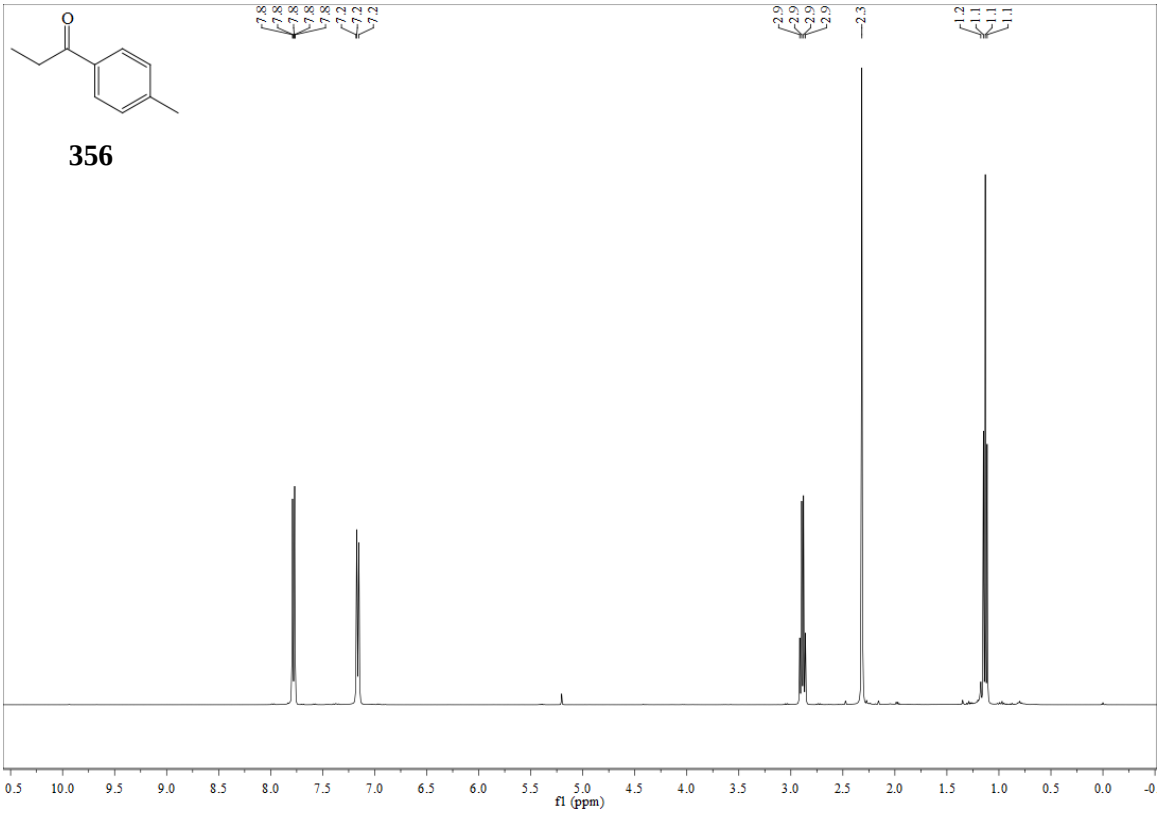
138.3
136.3
133.7
133.2
131.2
130.9
130.4
128.4
128.4
127.7
127.2
126.4
125.6
124.3
77.3
77.0
76.7
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


F
O
354
2.02
0.99
1.98
2.02
2.00
2.00
f1 (ppm)


197.3
163.0
160.6
136.4
133.2
131.0
130.9
130.1
130.1
128.6
128.4
115.5
115.3
77.3
77.0
76.7
44.4
f1 (ppm)


O
356
7.8
7.8
7.8
7.8
7.8
7.2
7.2
7.2
2.9
2.9
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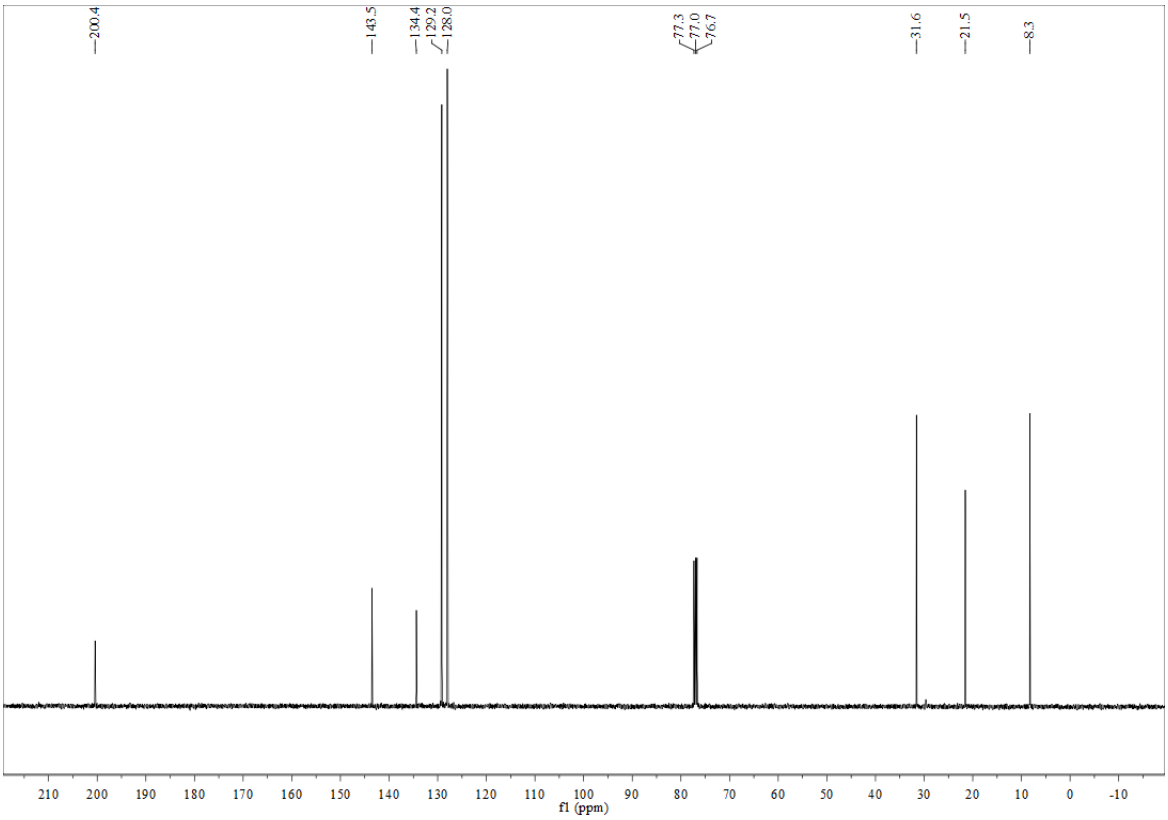
2.9
2.3
1.2
1.1
1.1
1.1
f1 (ppm)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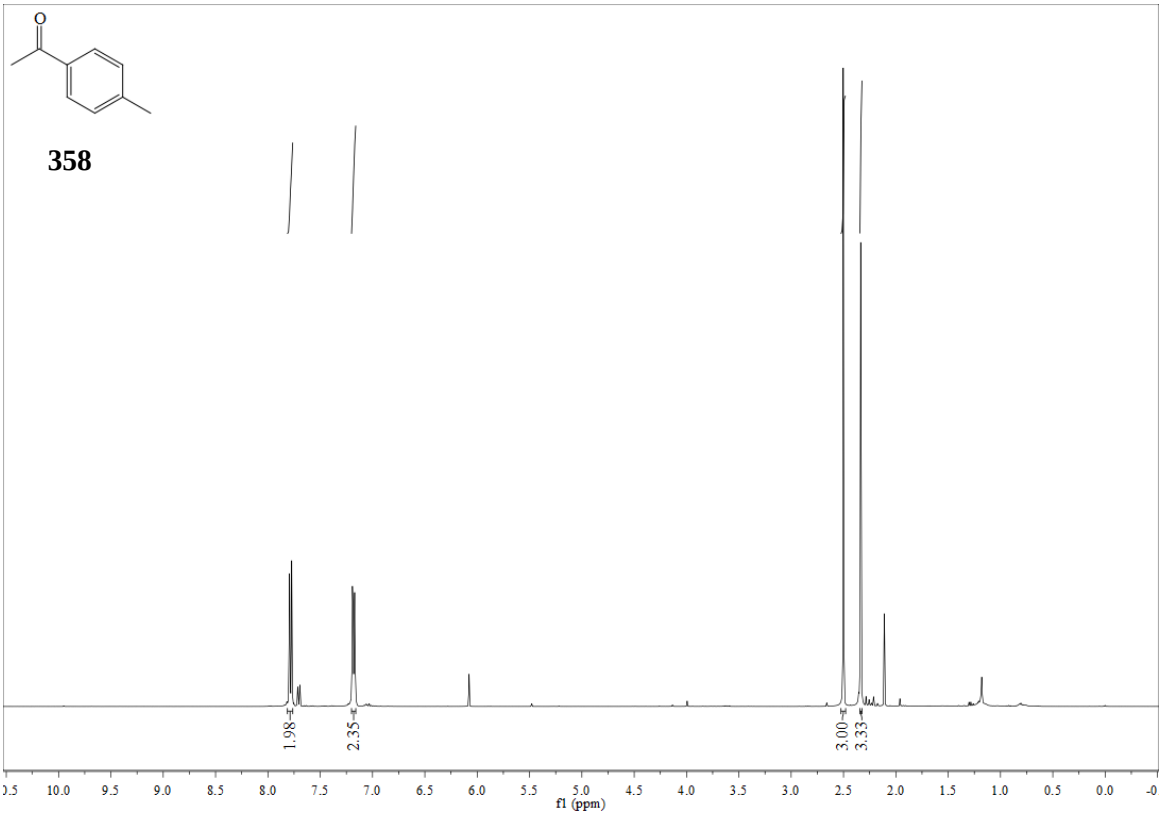
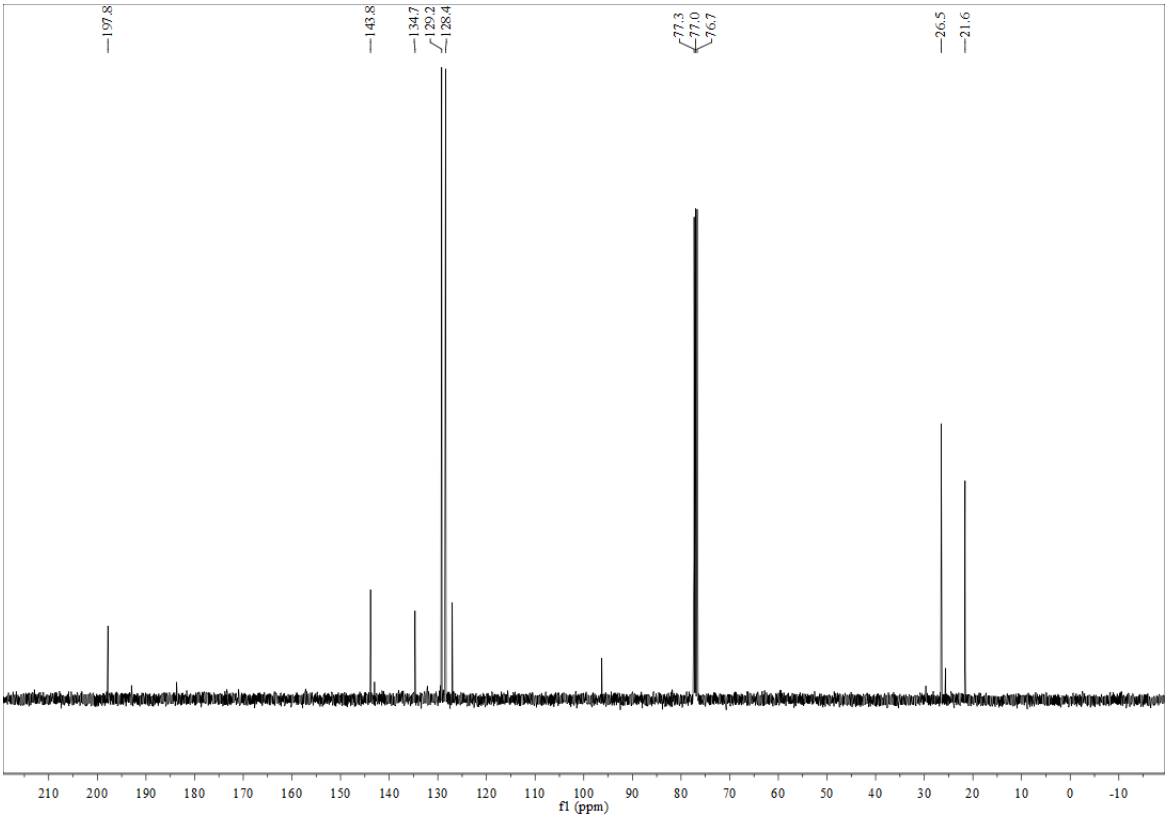
134.4
129.2
128.0
77.3
77.0
76.7
31.6
21.5
8.3
f1 (ppm)


O
358
1.98
2.35
3.00
3.33
f1 (ppm)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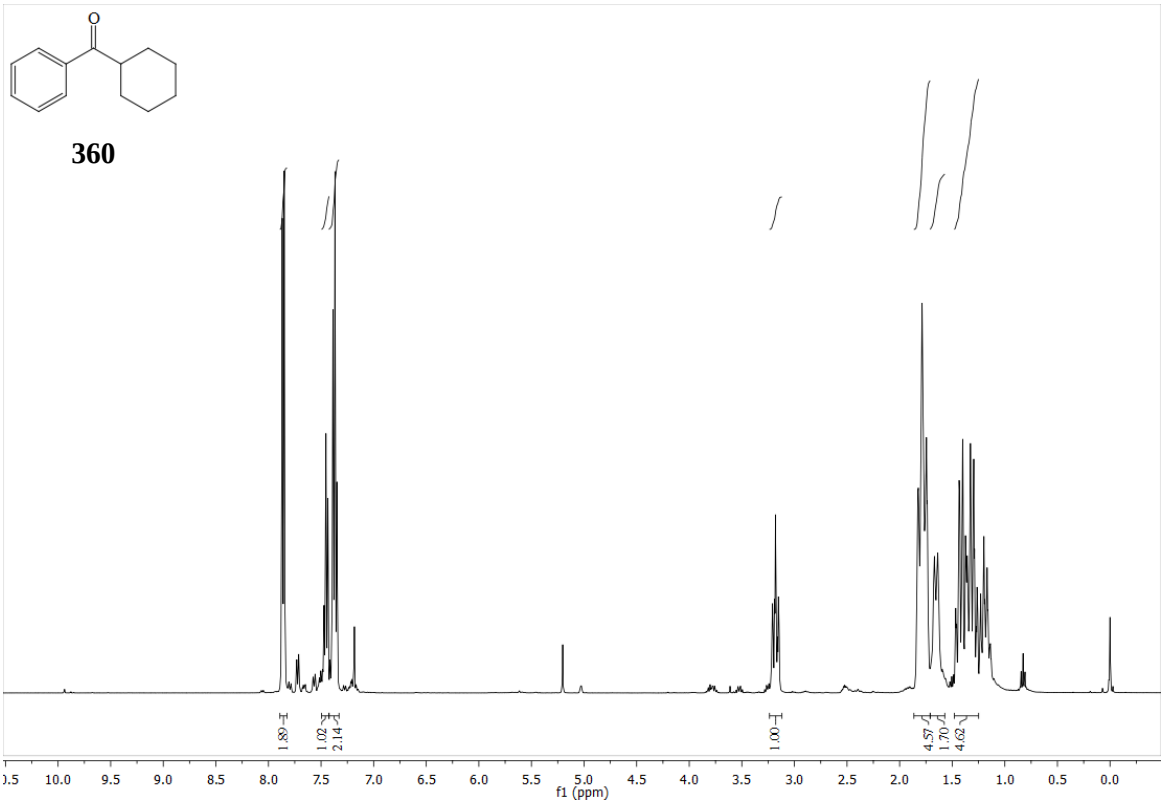
143.8
134.7
129.2
128.4
77.3
77.0
76.7
26.5
21.6
f1 (ppm)


O
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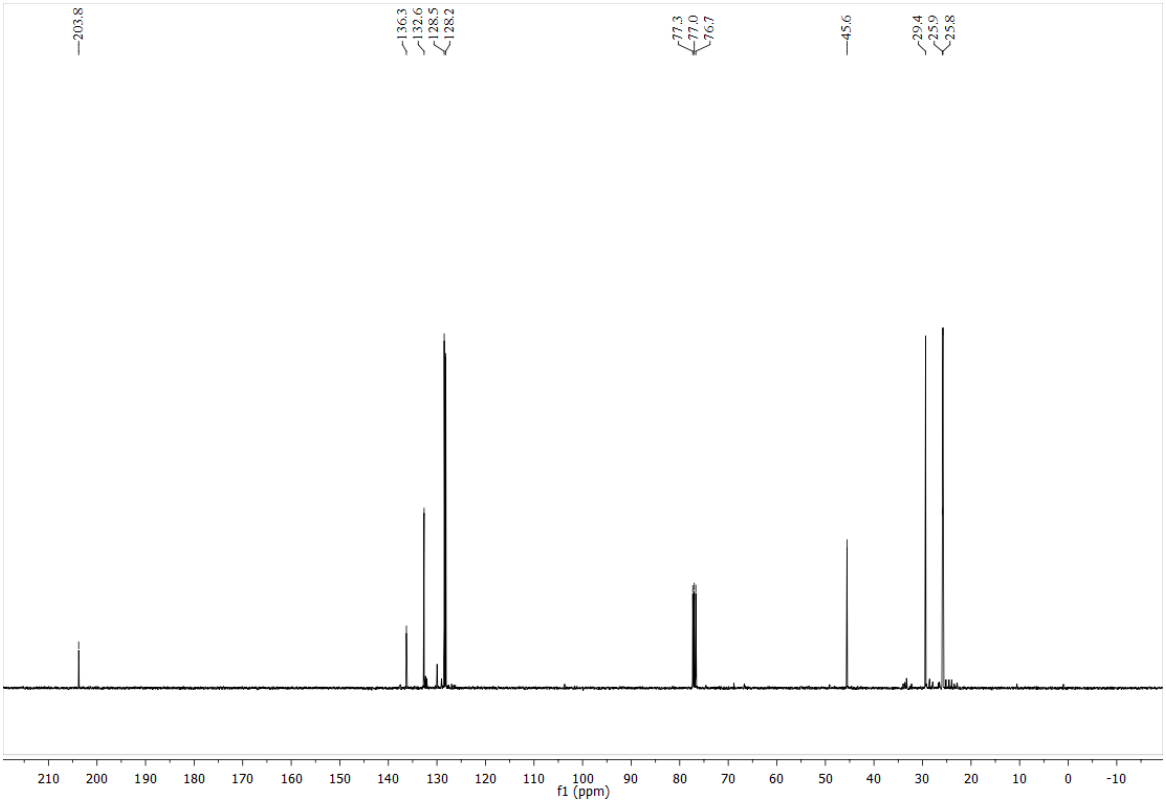
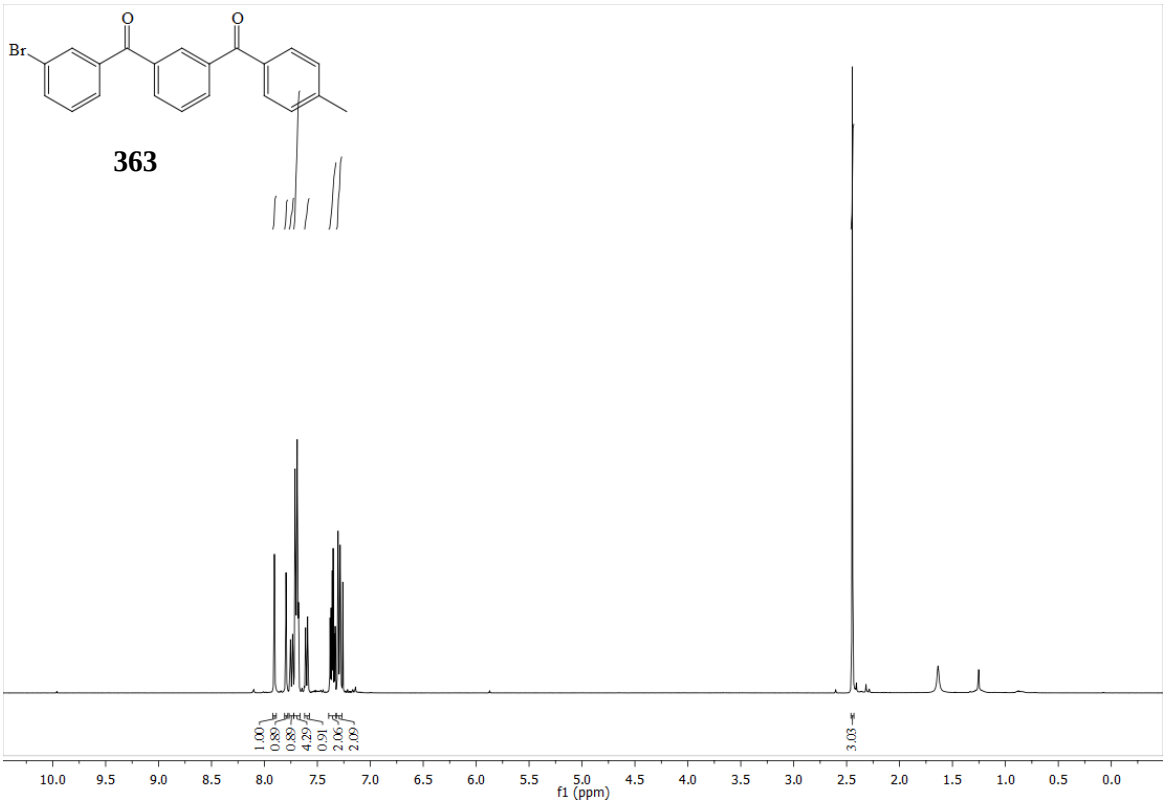
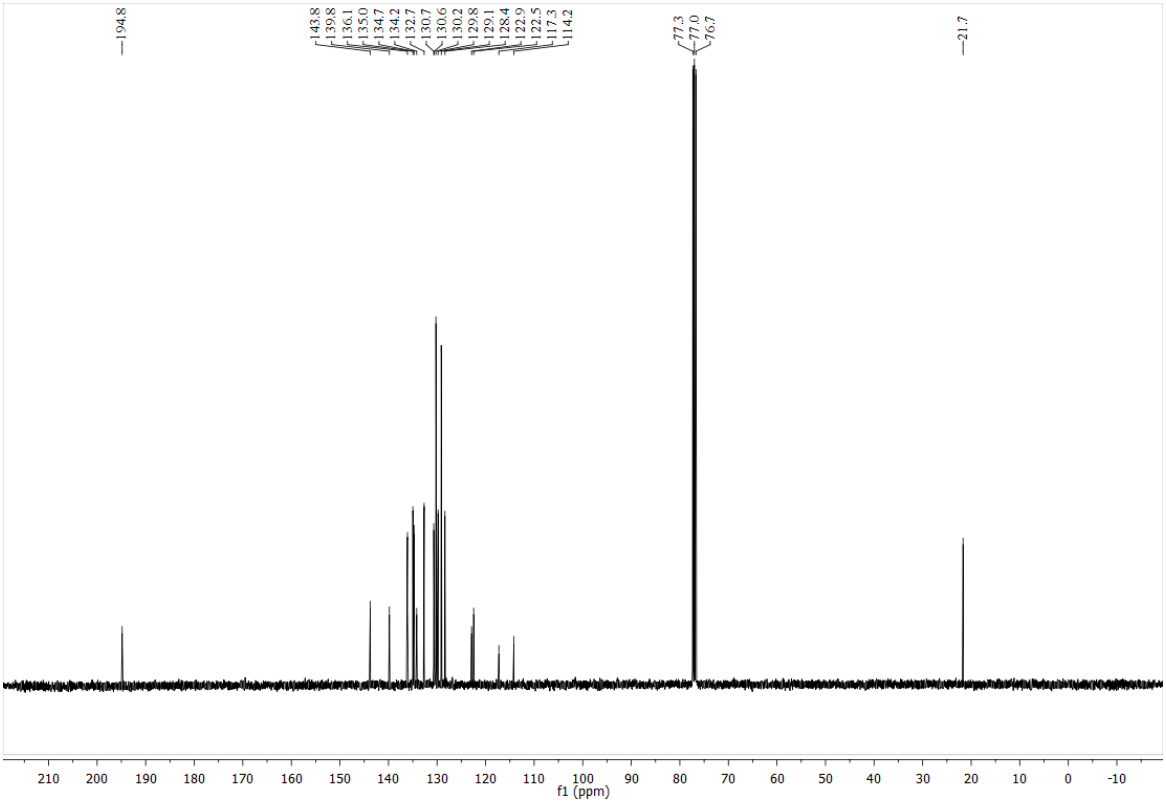
1.02
2.14
1.00
4.57
1.70
4.62
f1 (ppm)

360


203.8
136.3
132.6
128.5
128.2
77.3
77.0
76.7
45.6
29.4
25.9
25.8
f1 (ppm)


Br
O
O
363
1.00
0.89
0.89
4.29
0.91
2.06
2.09
3.03
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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143.8
139.8
136.1
135.0
134.7
134.2
132.7
130.7
130.6
130.2
129.8
129.1
128.4
122.9
122.5
117.3
114.2
77.3
77.0
76.7
21.7
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)

VITA

Sajan Silwal

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Doctor of Philosophy

Thesis: DEVELOPMENT OF CROSS COUPLING REACTIONS WITH EARTH ABUNDANT METALS

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Graduate Research Assistant at OSU

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Phi Kappa Phi

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