CROSS-COUPLINGS OF UNCONVENTIONAL ELECTROPHILES WITH EARTH-ABUNDANT METALS

By

VINOTH KUMAR CHENNIAPPAN

Bachelor of Science in Chemistry
Bharathiar University
Coimbatore, Tamilnadu
2007

Master of Science in Chemistry
Bharathiar University
Coimbatore, Tamilnadu
2009

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Dissertation Approved:

Dr. Ronald J. Rahaim

Dissertation Adviser

Dr. Jimmie D. Weaver

Dr. Toby L. Nelson

Dr. Allen W. Apblett

Dr. Jeffery L. White

To My Parents, Wife and Son

Acknowledgements reflect the views of the author and are not endorsed by committee members or Oklahoma State University.

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Abstract:

Transition metal catalyzed cross-coupling reactions are a reliable and robust approach for performing bond formation with high selectivity, predictable connectivity patterns, and versatility to form C–C and C–heteroatom bonds in numerous variations. As a result of this cross-coupling reactions have become an invaluable tool in the synthesis of complex molecules and have found wide spread use in the synthesis of drug candidates, materials, and natural products. While this approach is formidable in forming Csp^2–Csp^2 bonds, current systems have limitations in forming Csp^2–alkyl and alkyl–alkyl bonds. In addition, most of these methods utilize precious metals and preformed organometallic reagents which is not sustainable. As a means to expand the scope of cross-coupling partners and meet society's ever growing need for sustainability, our group has been developing cross-coupling methods utilizing earth abundant metals. This dissertation will cover our progress in developing cross-couplings with *in situ* generated organo-titanium reagents, titanacycles, our dual catalytic Ni/Ti method for cross-coupling nitriles, Ni-catalyzed cross-coupling of alcohols, and our endeavors in photocatalysis.

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LIST OF ABBREVIATIONS

Ac	Acetyl
ACN	Acetonitrile
BDE	Bond Dissociation Energy
bpy	bipyridyl
Cp	Cyclopentadienyl
Cy	Cyclohexyl
Cyp	Cyclopentyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	Dichloromethane
DMA	*N*,*N*-Dimethylacetamide
DMF	*N*,*N*-Dimethylformamide
DME	Dimethoxyethane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
dtbbpy	4,4'-Ditertiarybutylbipyridine
EDG	Electron Donating Group
EWG	Electron Withdrawing Group
GC	Gas Chromatography
GC-MS	Gas Chromatography-Mass Spectometer
h	hour
HAT	Hydrogen Atom Transfer
iPr	Isopropyl

iPrMgCl	Isopropyl magnesium chloride
IR	Infrared Spectroscopy
L.A.	Lewis Acid
mmol	Millimole
nBuLi	normal butyllithium
NHPI	N-hydroxyphthalimide
NMP	N-methylpyrrolidinone
NMR	Nuclear Magnetic Resonance Spectroscopy
NP	Natural Product
PC	Photocatalyst
Piv	Pivaloyl
PMB	para-Methoxybenzyl
ppy	Phenyl pyridine
RT	Room temperature
Red.	Reductant
SET	Single Electron Transfer
^{t}Bu	tertiarybutyl
TBS	tertiary butyl dimethyl silyl
TEA•HCl	Triethylamine•Hydrogen Chloride
Tf	Triflate
THP	2-tetrahydropyranyl
Ts	Tosyl
PC	Photocatalyst
Ph	Phenyl
Py•HCl	Pyridine•Hydrogen Chloride
TBS	tert-butyldimethylsilyl

TFA	Trifluoroacetic acid
Temp.	Temperature
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
TMSCl	Trimethylsilyl Chloride
°C	degree celsius

CHAPTER I

INTRODUCTION

Cross-coupling reactions have emerged as a powerful tool in the arena of synthetic organic chemistry over the past 20 years both in academia and industries.[1] Transition metal catalyzed cross-coupling reactions are a reliable and robust approach for performing bond formation with high selectivity, predictable connectivity patterns, and versatility to form C–C and C–heteroatom bonds in numerous variations.[2] The advent of these cross-couplings have actually changed the way chemists design and construct molecules.[3, 4] Owing to its invaluable utility, it is widely used in various synthesis of pharmaceuticals,[5, 6] organic materials,[7] agrochemicals[8] and complex natural products.[9, 10] These reactions enabled a flexible synthetic strategy making the traditional synthetic routes short, cost-effective and less time-consuming. The impact of these cross coupling methods was greatly recognized by the award of 2010 Nobel Prize in chemistry to the pioneers of Pd-catalyzed cross-coupling.[11]

Precious metals like rhodium, ruthenium, palladium and platinum have indeed played a vital role in catalysis in the process of transforming organic starting materials into valuable pharmaceuticals and agrochemicals. There are also some disadvantages in using them: high cost, low abundance and toxicity. Conversely, earth-abundant metals are much more sustainable and they exhibit appealing properties to address the disadvantages of precious metals.

Pharmaceutical industries carry out catalysis at various different scales, yet at all scales there are advantages to find ways to replace precious metals with earth-abundant metals. Moreover, earth-abundant metals are available in large quantities globally and utilizing them in the manufacture of pharmaceuticals will result in savings of a large amount of money.[12]

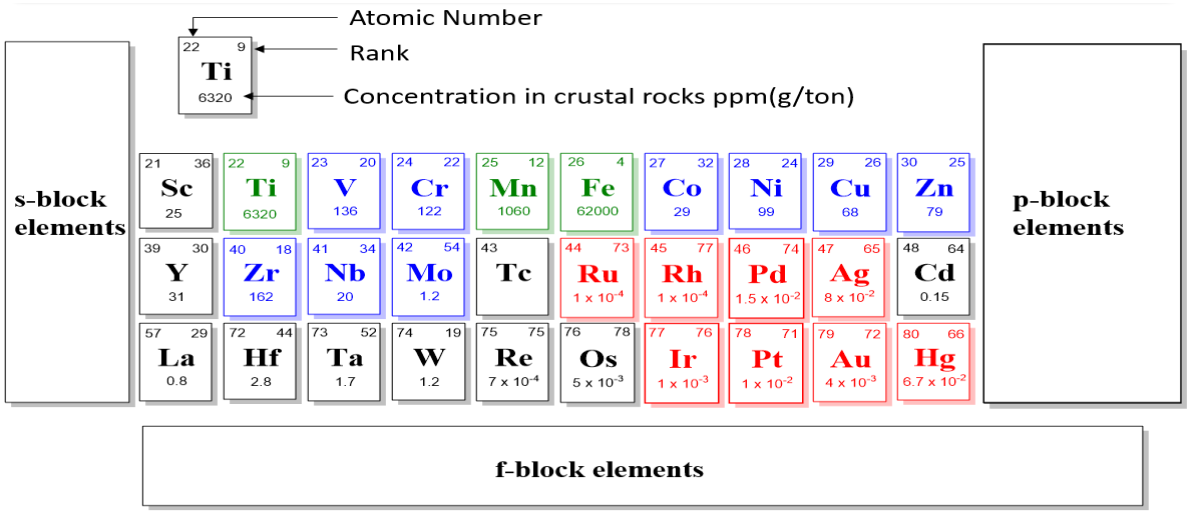


Fig. 1.1 Natural abundance of transition metals.

The natural abundance of the transition metals is illustrated in fig.1.1. The development of environmentally benign and sustainable synthetic protocols continue to be the central attention in the realm of cross-coupling. Most of the traditional cross-couplings use the precious metals like Pd, Rh, Ir, etc. These 2nd and 3rd row transition metals are not only expensive but also exiguous in the earth's crust, thereby making sustainability questionable. But generally, the 1st row transition metals like titanium, iron, cobalt, nickel, and copper are some of the most abundant metals in the earth's crust.[13-15] They are globally available and nearly unlimited supply of these 3d metals would allow us to run reactions on large scale.[5] These earth-abundant metals often tend to be benign, have less health and environmental issues as compared to the precious metals. The advantages of employing the earth-abundant metals in cross-coupling reactions are summarized as follows 1) Inexpensive metals 2) continuous supply of the metal catalysts 3) relatively less toxic than the precious metals and 4)

applicable for large-scale reactions. Considering these facts, it is clear that the motivation to focus on earth-abundant metal catalysis is compelling.

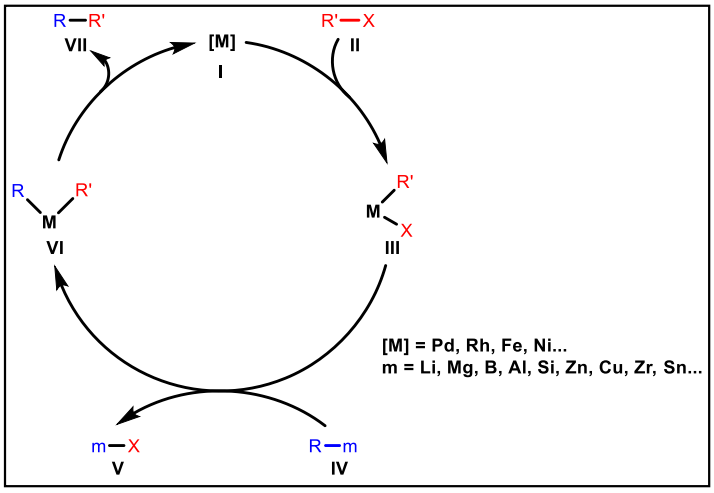
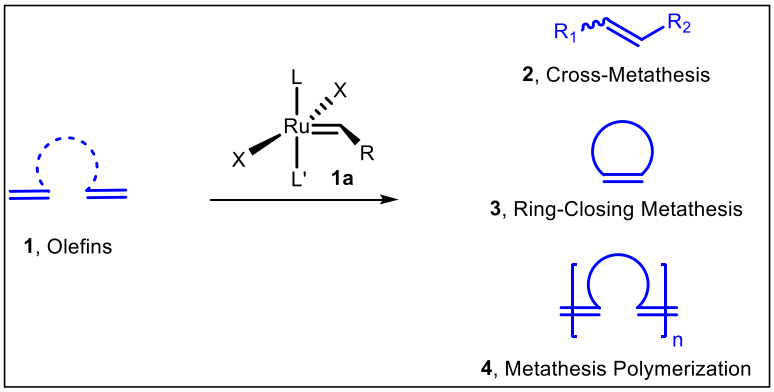


Fig. 1.2 General catalytic cycle for cross-coupling reactions.

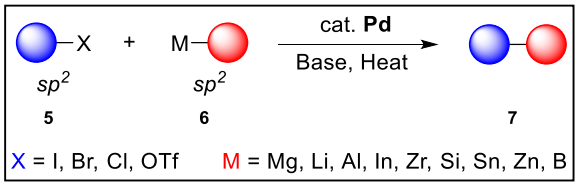
A significant advancement has been achieved to make carbon–carbon bonds in the past decades as evidenced by the Nobel Prizes for Olefin metathesis in 2005[16] and Pd-catalyzed cross-couplings in 2010.



Scheme 1.1 Metathesis reactions.

Whilst these current cross-coupling techniques are formidable, they are mostly limited to C_{sp2}–C_{sp2} bond formation reactions. There has been a little progress made to address the challenges involved in C_{sp3}–C_{sp3} couplings. Most of the early studies on cross-coupling was focused primarily on

palladium. In general, the cross-coupling reactions occur by a sequence of oxidative addition-transmetallation-reductive elimination process. The palladium catalyzed cross-couplings were restricted to aryl–aryl couplings because of the facile β-hydride elimination of the Pd–alkyl complexes, making the employment of aliphatic coupling partners unfeasible.



Scheme 1.2 Traditional cross coupling reactions with palladium.

C_{sp3}–C_{sp3} types of bonds are prevalent in natural products (NPs) which have historically been inspirational for drug discovery. The crucial role of NPs is exemplified by the fact that out of 1073 drugs approved by FDA from 1981 to 2010, 540 were either natural products or their pharmacophores derived from a natural product.[17-19] Clearly this indicates a strong correlation between natural products and the drug discovery process, especially in realm of hit identification. NPs are often considered as privileged structures since they are pre-optimized for various ligand-target bindings, making them fall into biologically relevant chemical space.[18, 19] NPs tend to have more C_{sp3}–C_{sp3} bonds, stereogenic centers (Avg. number = 6.2 vs 2.3 in drugs), fewer aromatic atoms (5.1 vs 12.4 for drugs) fewer rotatable bonds (5.2 vs 6.7 for drugs), more oxygen atoms (5.9 vs 3.4 for drugs), fewer nitrogen (0.7 vs 3.0 for drugs), sulfur, and halogen atoms, more fused, bridged, and spiro rings.[20, 21] In contrast to the NPs, combinatorial drugs developed by the pharma industries often have more C_{sp2}–C_{sp2} bonds, and more nitrogen atoms, while containing fewer oxygen atoms and fewer stereocenters. Another facet of current cross-coupling techniques is that they are mostly limited to C_{sp2}–C_{sp2} bond formation, and arguably this is due to limitations in terms of scope. Inspite of these great biological properties shown by the natural products, pharma industries still neglect NPs. The structural complexity and the scarcity of the NPs pushes the pharma industries to opt for the small molecules as

they are easy to synthesis with the current cross coupling methods in hand. Evidently, there is a lack of efficient cross coupling techniques to access those complex structures in an efficient manner.[22] Thus, effort aimed at expanding the scope of cross-coupling techniques that enable C_{sp2}–C_{sp3} and C_{sp3}–C_{sp3} cross-couplings under mild conditions, might be truly enabling. Moreover moving to new metals presents new opportunities which might enable us to circumvent these limitations to traditional ways.

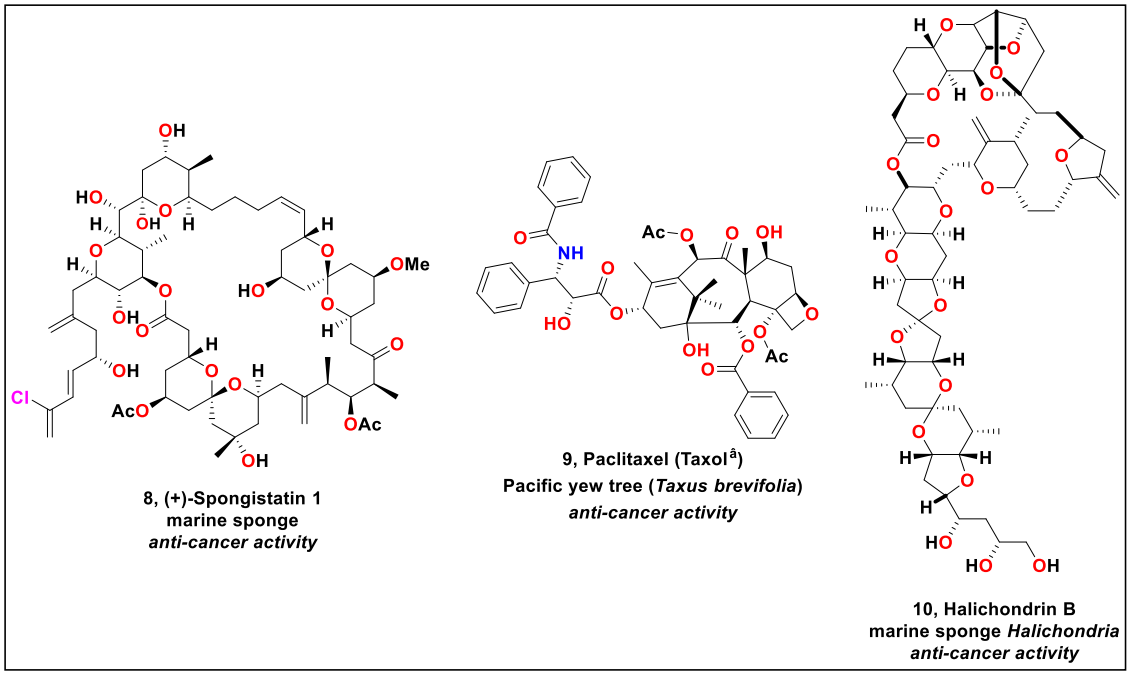


Fig. 1.3 Natural products–Biological activity, structure and complexity.

There have certainly several advancements been made in the area of organic synthesis to make natural product-like molecules over these years. Having realized the importance of natural products in the process of drug discovery, there have several strategies like diversity-oriented synthesis (DOS),[23, 24] function-oriented synthesis (FOS),[25, 26] biology-oriented synthesis,[27] natural product scaffold diversification,[28, 29] skeletal diversifications,[30-32] and natural product ring-distortion,[33-35] been developed to make complex and diverse compounds. These strategies are directed towards the synthesis of molecules that mimic natural products and rapid identification of hit

molecules against more complex targets. Despite these advancements, methodologies to access or to generate library of complex molecules, especially on large scale, with all elements of natural products are still lacking.[36-42]

A typical cross-coupling reaction employs a transition metal like palladium or nickel to couple an organic (pseudo)halide with an organometallic precursor to make either C–C bonds or C–Heteroatom bonds. As mentioned before, the traditional cross-coupling reactions occur by a sequence of oxidative addition-transmetallation-reductive elimination process The transmetallation step necessitates the use of a preformed organometallic precursor like magnesiates (Kumada coupling),[43] boronic acids (Suzuki coupling),[44, 45] organozinc (Negishi coupling),[46, 47] organostannanes (Stille coupling),[48] and organosilanes (Hiyama coupling).[49] Generally speaking, these organometallic reagents such as boronic acids have limited commercial availability, therefore, they generally are made in the lab adding to the overall steps, cost, and time to obtain the desired product.[50] Furthermore, many of these preformed organometallic reagents like organozinc reagents require special care as they tend to have poor shelf-life, air and moisture sensitivity. Additionally, some of the organometallic reagents require more additives in the reactions, like fluoride in the case of the Hiyama coupling in order to activate the organometallic reagent towards transmetallation. This prevents substrates from having other functional groups such as TBS-protected alcohols and phenols, where a fluoride ion can cleave the TBS and deprotonate respectively. Moreover these reactions are not atom-economical requiring stoichiometric organometallic reagents which eventually produce stoichiometric amounts of metal by-products. These metal residues including those from the catalyst are often considered toxic in the synthesis of target drug molecules, and great effort and care must be taken to remove these from pharmaceuticals.[51] Thus, replacing the transmetallation step in a classical catalytic cycle with a single electron transfer (SET) transmetallation has the potential to completely eliminate or avoid a series of problems associated with the use of pre-formed reagents. In a SET transmetallation, M^{II} species is intercepted with an *in situ* generated radical to form M^{III}, whereas in

traditional transmetallation process, M^{II} swaps groups with the pre-formed organometallic reagent and remains as M^{II}. In traditional cross-coupling like Suzuki coupling, the chemoselectivity is determined by the reactivity of nucleophiles (boronic acids), which undergoes transmetallation with the metal catalyst and the electrophiles (aryl halides) undergo oxidative addition with the catalyst. However, in addition to the aforementioned short comings of preformed organometallics, there are also shortcomings that pertain to their selectivity. One potential way to circumvent these issues that I will actually discuss is to completely avoid the use of preformed organometallics by replacing it with radical intermediates in the catalytic cycle. Here, the radicals are generated *in situ* and intercepted with M^{II} formed after the oxidative addition process (eg. $ArNi^{II}X$), thus avoiding the necessity to use any pre-formed organometallic reagents. Furthermore, these organometallic reagents like boronic acids, organozincs and magnesiates are mostly made from electrophiles such as aryl/alkyl halides, the opportunity for the direct employment of those electrophiles in the cross electrophile-coupling reactions can potentially avoid the use of any pre-formed organometallic reagents. This would also help to accelerate the synthetic process of the target product since readily available starting materials are used. Considering these advantages, we hoped to develop methodologies in which two electrophiles can be cross-coupled via the help of a metal catalyst. This has a distinct advantage in terms of the larger number commercially available electrophiles that are available. Our effort in cross-coupling two electrophiles, nitriles and organobromides, and unconventional electrophiles like alcohols is described in Chapter 3 and 4 respectively.

As a means to expand the scope of cross-coupling partners and meet society's ever growing need for sustainability our group has been developing cross-coupling methods utilizing earth abundant metals, titanium and nickel. Owing to their unique properties of these metals, they can be used for both radical and non-radical chemical transformations. The striking difference between the nickel and its group members is the ease of accessibility of multiple (Ni^0, Ni^I, Ni^{II}, Ni^{III} & Ni^{IV}) oxidation states whereas, palladium and platinum complexes are more restricted to M^0, M^{II} & M^{IV}

oxidation states.[52] This property makes nickel a viable catalyst for the cross-coupling involving single electron transfer process (SET). Since nickel is relatively cheaper than its group members, it is a viable metal for large industrial scale reactions.[53] Titanium is the second-abundant transition metal after iron, hence it is cheap and appropriate even for stoichiometric chemical reactions. Its unique property to exist in several oxidation states makes it a viable metal to employ in redox catalysis. By using appropriate titanium source and reductant, oxidation states such as Ti^{II}, Ti^{III} and Ti^{IV} can be achieved.[54] The most appealing characteristic of titanium is its reactivity with π–bonds to form Ti–ligand multiple bonds (eg. formation of titanacyclopropane with an alkene), which is not common with other first row transition metals.[55] The oxophilicity of titanium and the formation of a strong Ti–O bond (BDE = 158 kcal/mol) is often times the driving force of titanium-mediated reactions.[56] Even though titanium has been used in reactions like Sharpless asymmetric epoxidation and large-scale olefin polymerization processes, still there is plentiful opportunities and necessity to utilize this earth-abundant metal in redox catalysis. Moreover, the by-product TiO_2 formed from titanium-mediated reactions is nontoxic and has a wide application in the field of photocatalysis.[57, 58]

1.1. Tandem/Iterative Cross-Coupling Reaction

One of the areas of interest of our group is the development of iterative cross couplings with earth-abundant metals. Iterative synthesis can also be found in nature.[59] Typically di or multifunctional compounds are used in the iterative cross couplings where only one of the functional groups is active at a time and the others remain inactive.[60, 61] After the coupling of the first active functional group, then one of the other inactive functional groups is activated (eg. deprotection) and the process is continued until the target structure is achieved. The problem associated with those couplings is it requires several steps to make the multifunctional compounds.

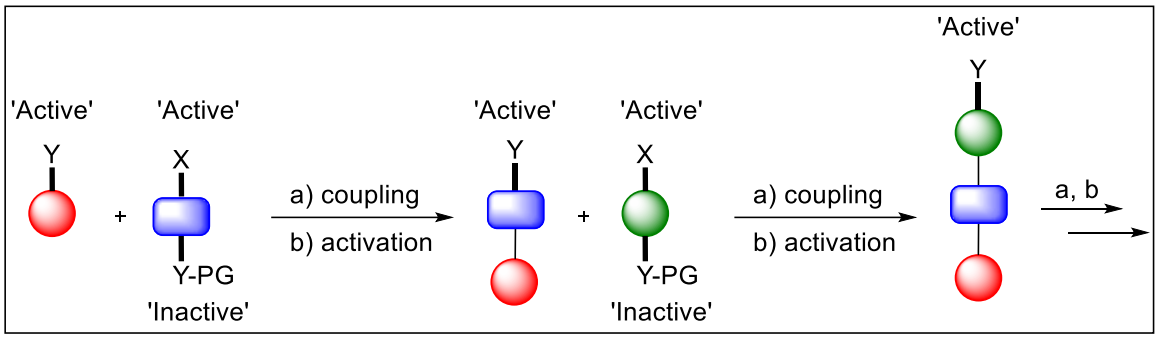


Fig. 1.4 Iterative cross-coupling reactions.

Titanium is an appropriate metal for the development of tandem/iterative cross coupling. The dicarbanionic nature of the titanacyclopropene generated from an alkyne allows us to make two cabon–carbon or carbon–heteroatom bonds using a one-pot procedure by a sequential addition of two electrophiles. Our progress towards the generation and utilization of titanacyclopropene as a bifunctional reagent in iterative cross coupling is elaborated in Chapter 2.[62]

1.2. Dual Catalysis

Catalysis is indeed a powerful tool in forming bonds and modifying functional groups.[63, 64] Since monocatalysis is limited to the activation of a single substrate, several types of multicatalysis have been developed over these years as illustrated in fig 1.5. Bifunctional catalysis involves the activation of both electrophile and nucleophile by the same catalyst but at different sites.[65] In double activation catalysis two different catalysts work together to activate one substrate.[66] Two different catalysts are employed in cascade catalysis and one catalyst activates the substrate, which is activated again by the second catalyst before it reacts with another substrate.[67] But in dual or synergistic catalysis, there are two different catalysts which activate two different substrates simultaneously.[68] Dual transition metals catalysis, where two different transition metal catalysts are employed to activate two different substarates concurrently, has gained more attention in current cross-coupling arena due to its diversity in coupling partners.[69] It can enable the cross-coupling

between electrophiles also as demonstrated by Weix,[70] while the traditional cross-coupling reactions are limited to bond formation between an electrophile and a nucleophile.

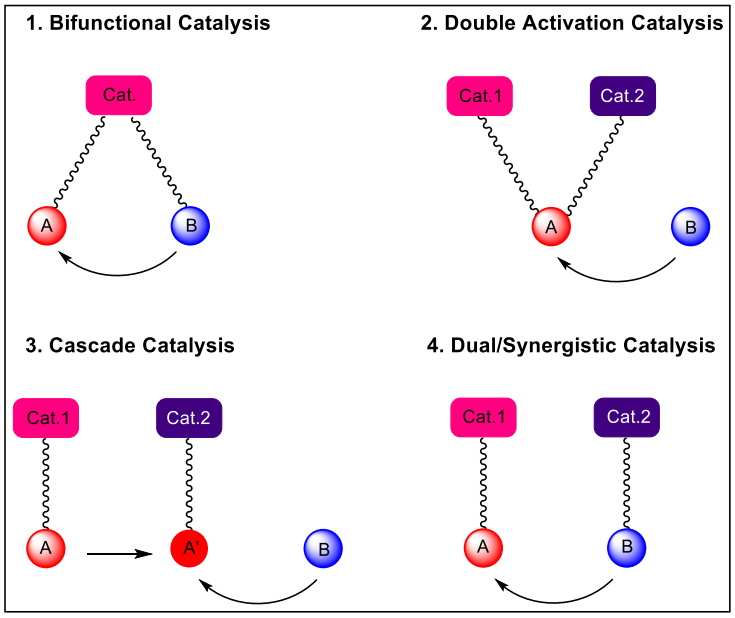


Fig. 1.5 Schematic representation of multicatalysis.

In a typical dual catalytic system, two catalysts work in a synergistic way to form a C–C or C–Heteroatom bond. Here, the first catalyst generates a reactive intermediate which is intercepted by another organometallic species formed by the second catalyst. Although the concept of dual catalysis dates back to Sonogashira coupling, dual transition metals catalysis where a radical intermediate is involved is of our interest. Sanford demonstrated the feasibility of merging palladium catalyzed C–H arylation using aryldiazonium salts and photoredoxcatalysis.[71, 72] Later on, this approach has been expanded to merge nickel catalysis with photocatalysis by many groups like Macmillan,[73-75] Molander[76-78] and Doyle,[79] where the radicals were generated from carboxylic acids, trifluoroborates, silicates, dihydropyridines and alpha amino acids respectively. Our effort to generate radicals from amino acids with an organophotocatalyst and attempt to synthesize cis-allyl amines is described in Chapter 5.

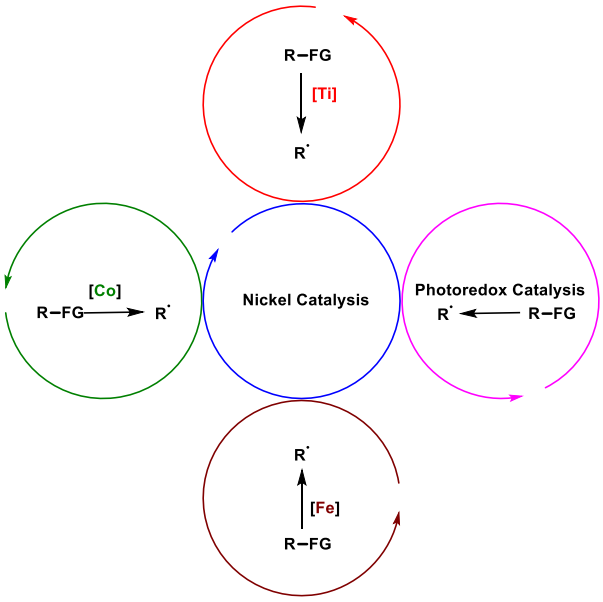


Fig 1.6. Dual catalytic cross-coupling of radicals.

The dual catalysis is not just limited to photocatalysis in terms of radical generation but two different metal catalysis can be merged together.[80, 81] The radical intermediate can also be generated by a metal catalyst like titanium,[82-84] cobalt[85] or iron[86] and intercept with nickel (II) species under non-photocatalytic conditions which have been less explored (Fig 1.6). Our recent Ni/Ti dual catalytic approach to cross-couple nitriles with organohalides is elaborated in Chapter 3.[82] These type of cross-couplings replace the traditional transmetallation process with single electron transmetallation where the employment of pre-formed organometallic reagents is not needed. The mild conditions of these current cross-coupling reactions help to tolerate the functional groups that were not suitable under the classical cross-coupling conditions. These cross-coupling reactions also enable the bond formation between electrophiles, which are more abundant than the nucleophiles in the chemical space.

This dissertation will cover our progress in developing cross-couplings with *in situ* generated organo-titanium reagents, titanacycles (Chapter 2), dual catalytic Ni/Ti method for cross-coupling nitriles (Chapter 3), nickel catalyzed cross coupling of benzyl and allyl alcohols (Chapter 4) and our endeavors in photocatalytic radical addition to alkynes to access cis-allyl amines (Chapter 5). The

work presented here is primarily focused on the development of methodologies to access various building blocks with earth-abundant metals, titanium and nickel. The building blocks namely conjugated amides, ketones, diarylmethanes and allylarenes, made through our cross-coupling protocols are of high synthetic utility which can be employed to access complex natural products or library synthesis for high throughput screening in medicinal chemistry. The development of these new technologies with earth-abundant metals would expand the medicinal chemists' tool box to synthesize drug candidates and natural product-like molecules in a cheap and efficient manner.

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CHAPTER II

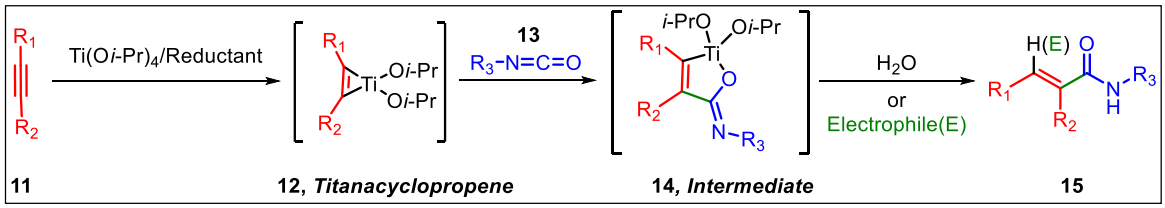
TITANIUM-PROMOTED CROSS-COUPLING FOR THE SELECTIVE SYNTHESIS OF POLYSUBSTITUTED, CONJUGATED AMIDES

2.1. INTRODUCTION

Amides are a common structural motif in drugs, and currently amide bond formation is one of the most common reactions performed in the pharmaceutical industry.[1] Despite the importance of amides in drug discovery, this functional group is typically only formed through the dehydrative condensation of a carboxylic acid and amine utilizing a coupling reagent. While this process is robust, there is a need for new methods that are more environmentally friendly[2, 3] and can readily generate complex, hindered, and/or electron-deficient amides.[4] As such, there have been investigations to address some of these issues, a notable example being the use of arylboronic acids as catalysts.[5, 6] This has also spurred the development of new amide-forming reactions[7] through new mechanistic approaches, such as Danishefsky's use of isonitriles,[8] Rovis' carbene-catalyzed relay coupling between amines and α-reducible aldehydes,[9] and Bode's ketoacid-hydroxylamine ligation.[10] Examples that caught our attention were the rhodium-catalyzed additions of arylboronic acids[11] and -stannanes[12] to isocyanates and the addition of sterically hindered Grignard reagents to sterically hindered isocyanates by Bode.[13]

Based on these precedents, it was conjectured that isocyanates can undergo a titanium promoted coupling with alkynes, alkenes, allenes, or imines to form complex amides directly.

Scheme 2.1. Cross-coupling of titanacyclopropene with isocyanates to access conjugated amides



2.2. CONJUGATED AMIDES IN NATURAL PRODUCTS

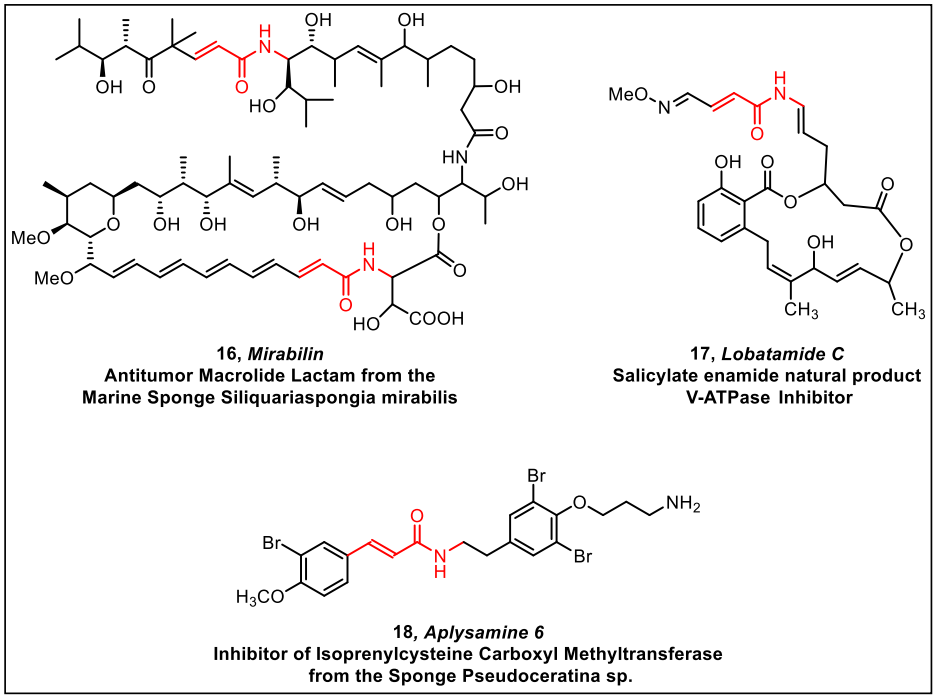
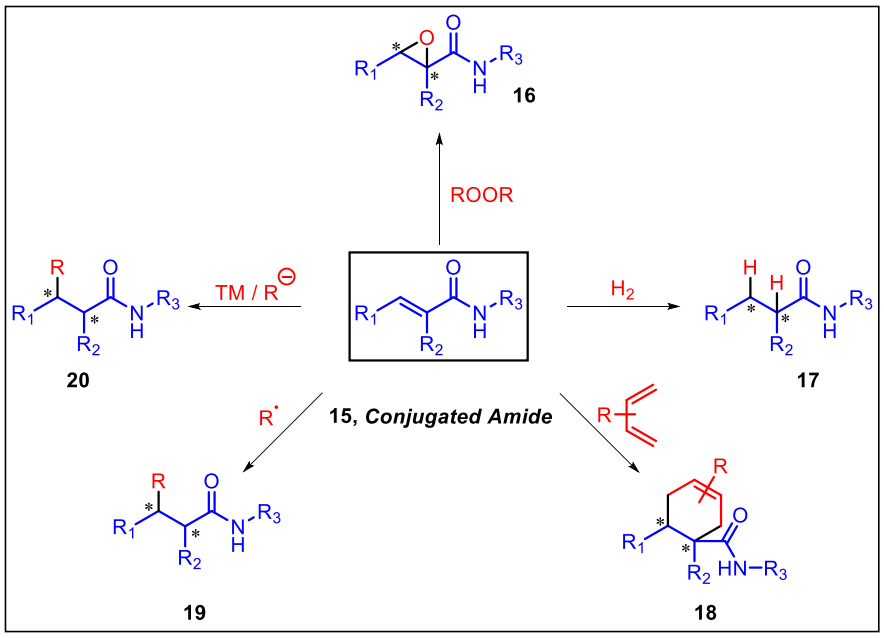


Fig. 2.1. Conjugated amides in natural products.

Conjugated amides are found in biologically active natural products such as lobatamide C,[14] muironolide A,[15] aplysamine 6,[16] and mirabilin.[17] They are also key building blocks used in the preparation of polymers and biologically active compounds. α,β-Unsaturated amides are

versatile building blocks that have been utilized in radical additions,[18-20] pericyclic reactions,[21, 22] asymmetric hydrogenation,[23, 24] asymmetric conjugate additions,[25-31] asymmetric epoxidation,[32, 33] and transition-metal-mediated reactions.[31, 34-40]

Scheme 2.2. Synthetic transformations of conjugated amides

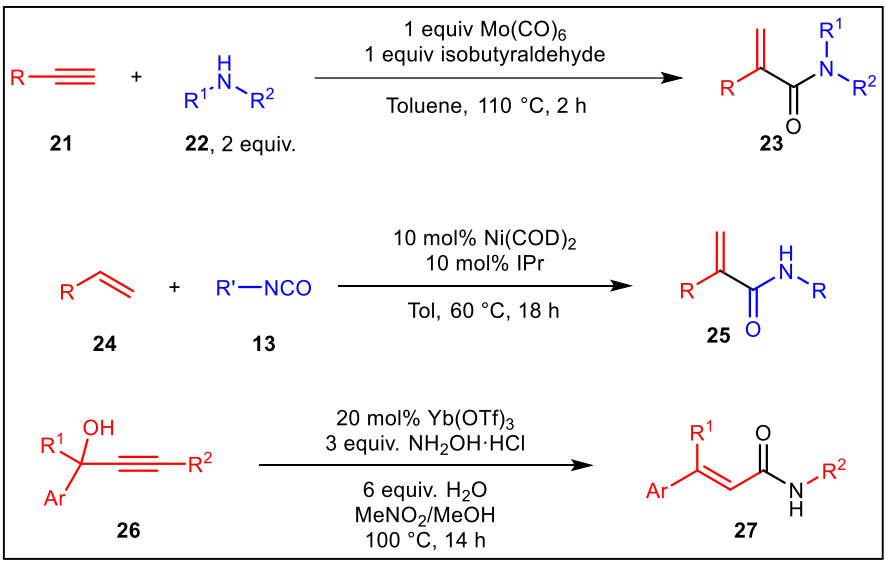


Despite the importance and utility of α,β-unsaturated amides, methods to prepare this functional group directly are limited. Of the few methods to prepare conjugated amides, most have focused on disubstituted α,β-unsaturated amides using traditional Wittig, Horner−Wadsworth−Emmons,[41] and Peterson[42] olefination reactions with a more recent advance being crossmetathesis.[43] A majority of the methods to prepare disubstituted α,β-unsaturated amides have been directed toward α-branched acrylamides[44-46] and α,β,γ,δ-unsaturated amides.[47-49]

Methods to prepare tri- and tetrasubstituted α,β-unsaturated amides directly and selectively are severely lacking.[50-52] Approaches to this class of conjugated amides that have been developed are aminocarbonylation[53] and hydrocarbamoylation[54, 55] of alkynes and rearrangements

of propargyl alcohols.[56, 57] While these new approaches have enabled the synthesis of trisubstituted α,β- unsaturated amides, issues still exist such as obtaining high regioselectivity with unsymmetrical internal alkynes and/or the ease with which the substituents can be interchanged.

Scheme 2.3. Current approaches to access conjugated amides



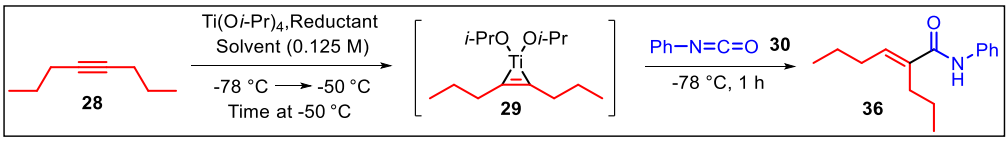
2.3. RESULTS AND DISCUSSION

2.3.1. Optimization of Reaction Conditions

We sought to address this gap by expanding upon our recent titanium-promoted coupling of alkynes and Weinreb amides to prepare (E)-trisubstituted enones selectively.[58] Using this as a starting point, we began optimization of the alkyne-isocyanate coupling (Table 2.1) by reduction of Ti(O-*i*-Pr)$_4$ in the presence of 4-octyne to generate a titanacyclopropene followed by addition of phenyl isocyanate. It was determined that higher yields were obtained when a slight excess of Ti(O-*i*-Pr)$_4$ was reduced with isopropylmagnesium chloride in a 1:2 ratio (entry 7). The temperature of the reaction mixture upon addition of the isocyanate had a dramatic effect on the efficiency of the reaction. Little to no desired enamide was obtained if phenyl isocyanate was

added at -50 °C or above. At these temperatures, the magnesium isopropoxide byproduct preferentially reacted with the isocyanate to form a carbamate. Selective reaction of the isocyanate with the in situ generated titanacyclopropene could be accomplished when the reaction mixture was cooled to -78 °C. Decreasing the concentration of the isocyanate to 0.8 equiv had no effect, whereas increasing its concentration to 1.2 equiv lowered the yield (entries 8 and 9). The standard solvents employed in titanium reductive couplings were screened (Et_2O, THF, 1,4-dioxane, and toluene) with Et_2O producing the highest yield.

Table 2.1. Optimization of reaction conditions for the synthesis of conjugated amides



Entry	28 (equiv.)	30 (equiv.)	$Ti(OiPr)_4$ (equiv.)	Reductant (equiv.)	Solvent	Time at -50 °C (h)	% Conv. to 29	% Yield[b]
1	1.0	1.0	1.1	*i*PrMgCl 1.8	Et_2O	0.5	59	27
2	1.0	1.0	1.1	*i*PrMgCl 2.2	Et_2O	0.5	78	38
3	1.0	1.0	1.1	*i*PrMgCl 2.4	Et_2O	0.5	88	34
4	1.0	1.0	1.5	*i*PrMgCl 2.5	Et_2O	0.5	73	45
5	1.0	0.6	1.5	*i*PrMgCl 3.0	Et_2O	0.5	95	50
6	1.0	0.8	1.5	*i*PrMgCl 3.0	Et_2O	0.5	97	63
7	**1.0**	**1.0**	**1.5**	***i*PrMgCl 3.0**	**Et_2O**	**0.5**	**97**	**57(62)[c]**
8	1.0	1.2	1.5	*i*PrMgCl 3.0	Et_2O	0.5	96	53
9	1.0	1.5	1.5	*i*PrMgCl 3.0	Et_2O	0.5	90	37
10	1.0	2.0	1.5	*i*PrMgCl 3.0	Et_2O	0.5	96	43

11	1.0	1.0	1.5	*i*PrMgCl 3.3	Et_2O	0.5	96	50
12	1.0	1.0	2.0	*i*PrMgCl 4.0	Et_2O	0.5	96	40
13	1.0	1.0	3.0	*i*PrMgCl 6.0	Et_2O	0.5	98	48
14	1.0	0.8	1.5	*i*PrMgCl 3.0	Toluene	0.5	97	49
15	1.0	0.8	1.5	*i*PrMgCl 3.0	THF	0.5	16	6
16	1.0	0.8	1.5	*i*PrMgCl 3.0	THF	3.0	6	2
17	1.0	0.8	1.5	nBuLi 3.0	THF	0.5	4	2
18	1.0	0.8	1.5	nBuLi 3.0	THF	3.0	17	7
19	1.0	0.8	1.5	CypMgBr 3.0	Et_2O	0.5	94	46

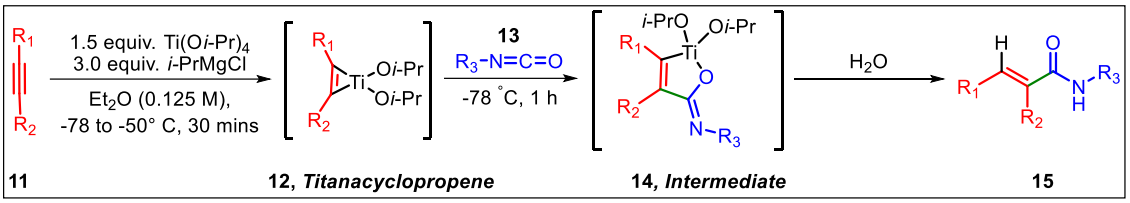
[a] Conditions: 0.5 mmol alkyne (1a), 0.5 mmol isocyanate (2a); [b] Determined by GC using biphenyl as an internal standard; [c] Isolated by flash chromatography.

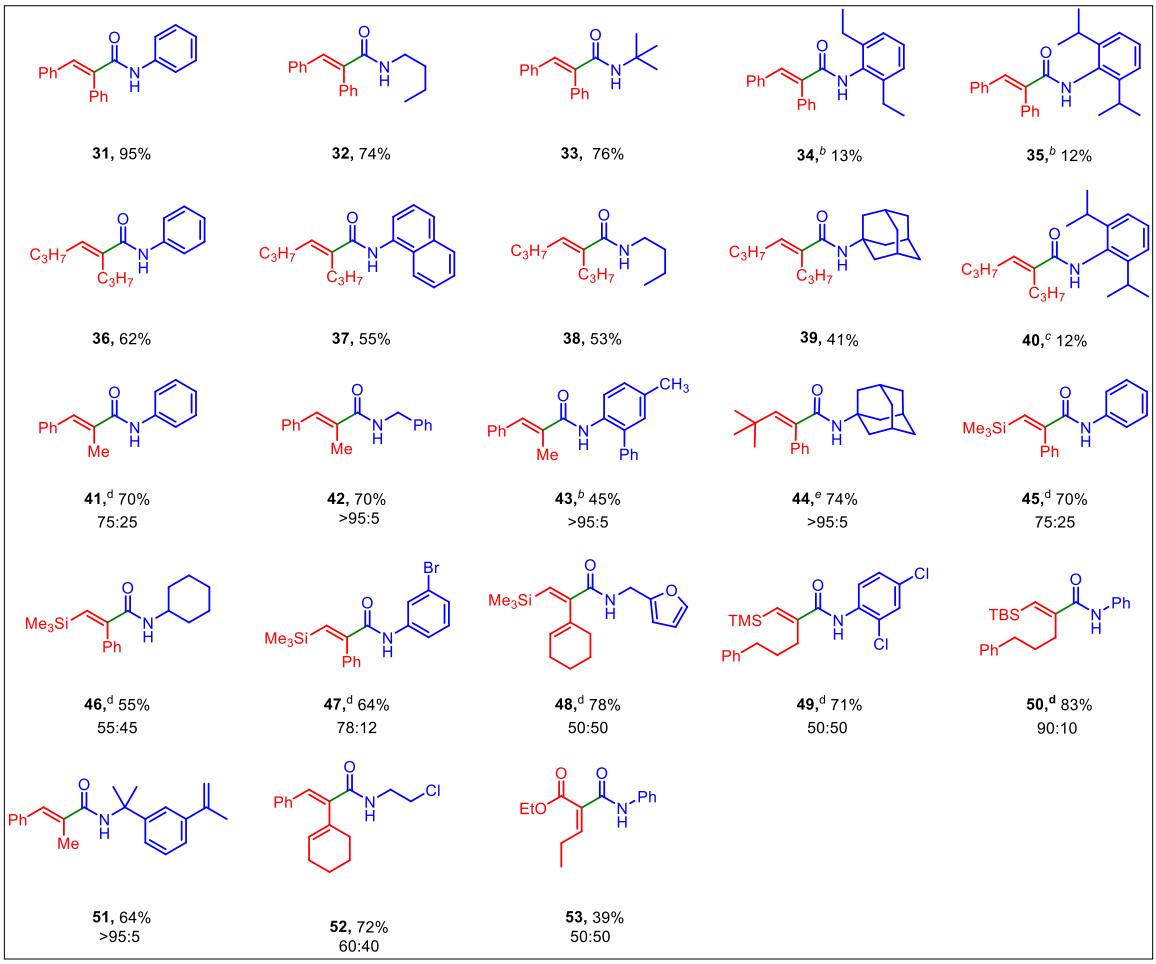
2.3.2. Substrate screening of titanium promoted cross-couling of alkynes with isocyanates

Substrate screening was initiated to determine the scope of this coupling reaction under the optimized conditions. First, we examined what effect the sterics of the isocyanate had on the coupling with symmetrical alkynes, diphenylacetylene, and 4-octyne. Higher yields were typically obtained with diphenylacetylene versus 4-octyne, where undesired reductive couplings and decomposition of the titanacycle occurred. Simple phenyl isocyanate (Table 2.2, **31** and **36**) and sterically larger 1-naphthyl isocyanate (**37**) reacted well, whereas 2,6-disubstituted phenyl isocyanates inhibited the coupling, affording the conjugated amide in low yields (34, 35, and 40). Sterically congested aliphatic isocyanates produced the amides in good yields (**33** and **39**), but the steric bulk of the adamantyl isocyanate did inhibit the rate of the reaction requiring prolonged reaction times for complete conversion to the product. In the case of substrate **39**, the increased reaction time led to decreased yield due to decomposition of the titanacyclopropene, which is

corroborated by amide **44** being afforded in higher yield. From here, the regioselectivity of the reaction was examined with unsymmetrical alkynes. In our prior enone synthesis method, it was

Table 2.2. Substrate scope of α,β-unsaturated amides



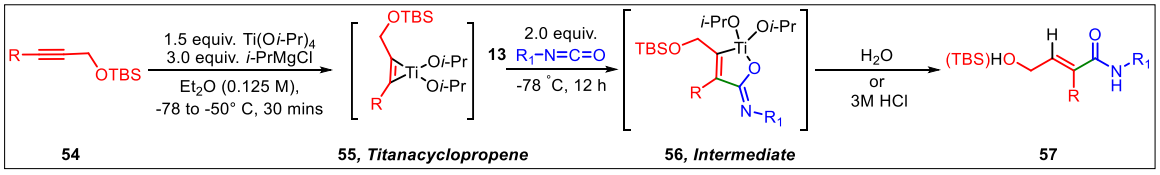


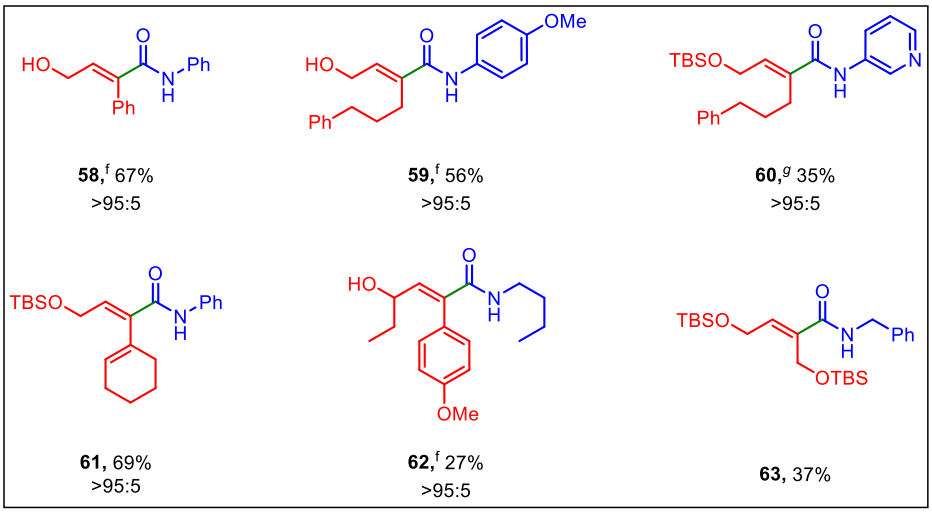
[a]Conditions: alkyne (0.5 mmol), Ti(O-i-Pr)$_4$ (0.75 mmol), *i*-PrMgCl (2.0 M in Et_2O, 1.5 mmol), Et_2O (4 mL), -78 to -50 °C, 0.5 h, isocyanate (0.5 mmol) at -78 °C for 1 h, addition of H_2O. [b]Isolated yields after flash chromatography. [c]Regioisomeric ratios determined by ^{1}H NMR of the crude reaction mixture. [d]Combined isolated yield of regioisomers. [e]Stirred at -78 °C for 12 h after isocyanate addition.

determined that regioselectivity was based on the steric difference between the substituents on the unsymmetrical alkyne regardless of Weinreb amide employed. That was found not to be the case for the titanium-promoted coupling of unsymmetrical alkynes with isocyanates. In this system, the regioselectivity was based on a synergistic steric interaction between the larger alkyne substituent and the isocyanate. It was determined that for high regioselectivity the steric element of the isocyanate needed to be distal. Coupling of phenyl isocyanate with 1-phenyl-1-propyne afforded amide **41** with a 75:25 regioselectivity, favoring bond formation on the side of the alkyne with the smaller substituent. Simply changing to benzyl isocyanate, pushing the phenyl group away by one carbon, afforded conjugated amide **42** as a single regioisomer. To probe this further, 2-isocyanato-5-methyl-1,1′- biphenyl was prepared, and as speculated, the addition of a substituent ortho to the isocyanate induced a steric interaction yielding **43** as a single regioisomer. Moving the substituent to the meta position only had a minor positive effect (**45** vs **47** and **65** vs **66**).

The system demonstrated complete regioselectivity with 1-phenyl-2-tert-butylacetylene (14) favoring bond formation α to the phenyl group opposite to 1-phenyl-1-propyne, demonstrating that selectivity is biased toward steric hindrance rather than electronic effects. Trimethylsilylalkynes showed moderate selectivity, presumably due to the longer silicon−carbon bonds, decreasing the steric hindrance in the formation of the titanacyclopropene. To compensate, the TMS was changed to the sterically larger TBS, which increased the regioselectivity (**49** vs **50**).

Scheme 2.4. Synthesis of conjugated amides from TBS-protected propargyl alcohols

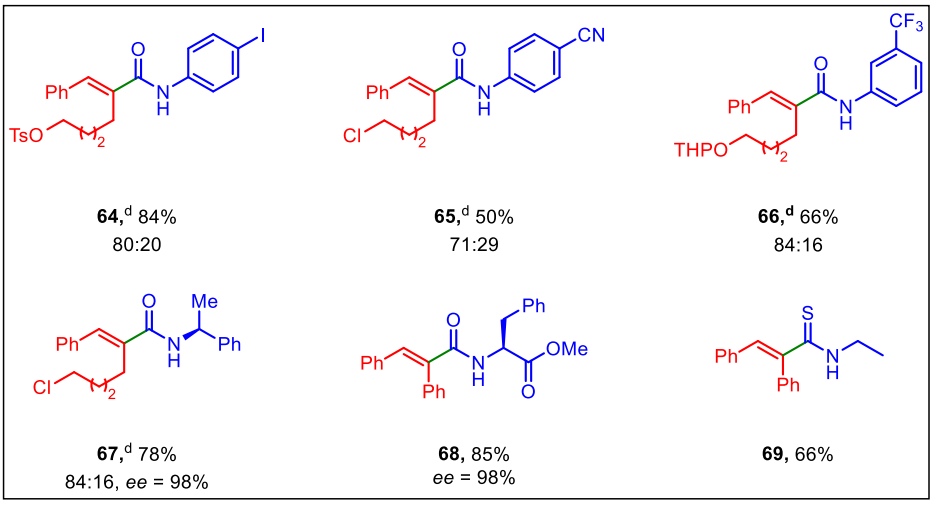




[f]Quenched with 3 M HCl. [g]Et2O/THF (1/1) used.

On the basis of this result, a variety of TBS-protected propargyl alcohols were screened (**58**–**63**). By placing the steric element farther away from the alkyne, a single regioisomer was formed regardless of the other alkyne substituent or the isocyanate employed, even with a small aliphatic chain isocyanate (**61**). The yields for amides **62** and **63** were low due to incomplete conversion of the alkyne to the titanacyclopropene.

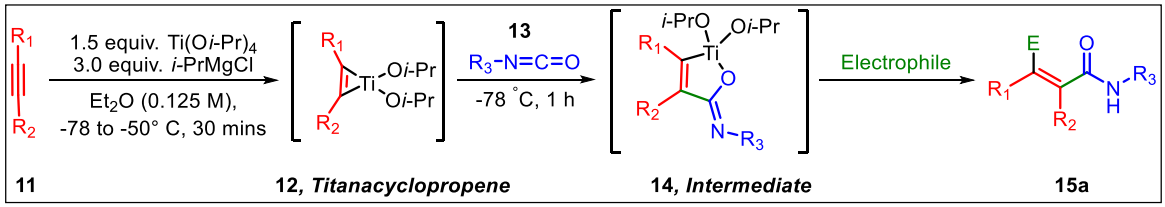
Table 2.3. Substrate scope of α,β-unsaturated amides-continued

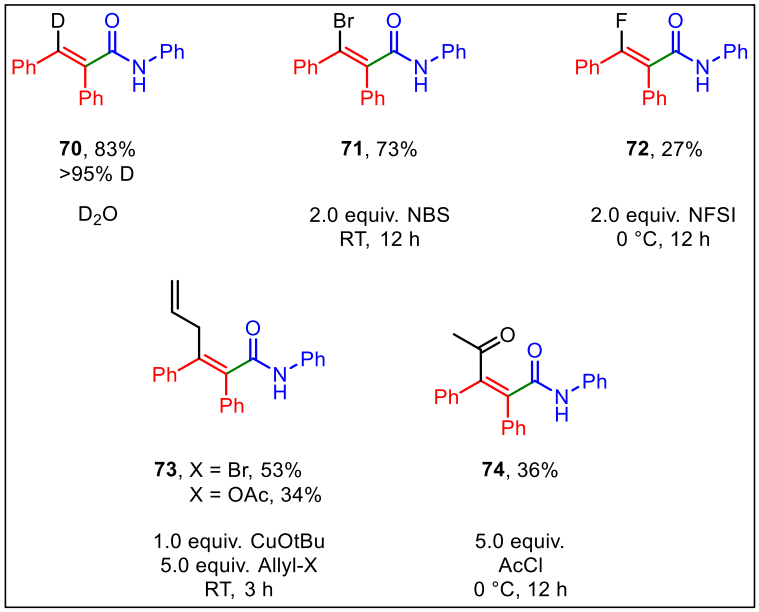


[d]Combined isolated yield of regioisomers.

The stereoselectivity of the reaction was excellent, with every α,β-unsaturated amide prepared having an E-configuration. The system had high functional group compatibility, tolerating aromatic and primary aliphatic halides (I, Br, Cl), primary tosylate, silyl ethers, ethers, esters, nitriles, alkenes, a furan, and a pyridine. Due to the poor solubility of 3-isocyanatopyridine in ether, this coupling was performed in a dual solvent system (Et_2O/THF). While the THF cosolvent solubilized the 3-isocyanatopyridine, it also contributed to the lower yield of **60**. Chiral, nonracemic amides **67** and **68** were efficiently prepared from chiral isocyanates with no loss of enantiomeric purity. Of note is that an isothiocyanate could also be employed with no modification to the system, efficiently affording the conjugated thioamide (**69**).

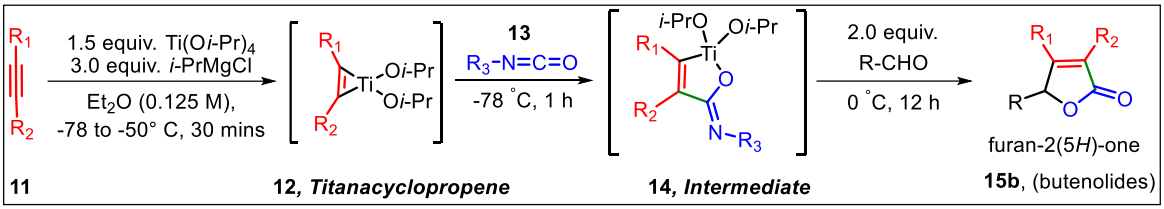
Scheme 2.5. Reaction with the second electrophile to access tetra-substituted conjugated amides

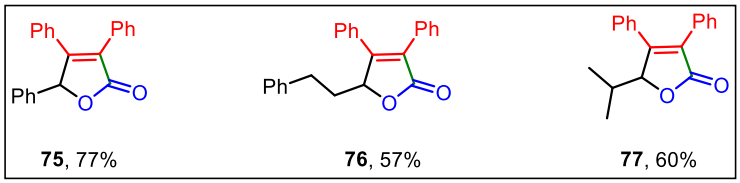




To access tetrasubstituted α,β-unsaturated amides, the addition of a second electrophile was examined. The 5-membered ring titanacycle was quenched with D_2O to afford the β-deuterated conjugated amide (**70**) in 83% yield with greater than 95% deuterium incorporation. The titanacycle could be brominated to afford the vinylic bromide (**71**), a useful handle for further diversification. Additionally, the remaining titanium−carbon bond could be fluorinated, enabling access to β-fluorinated conjugated amide building blocks (72). The addition of allyl bromide produced a mixture of C– and N–alkylation products, but the use of a stoichiometric amount of CuO-t-Bu in combination with the allyl bromide solely afforded the skipped diene (**73**).

Scheme 2.6. Aldehyde as the second electrophile





An aldehyde did not give rise to an allylic alcohol but rather formed a butenolide (**75**–**77**).[59]

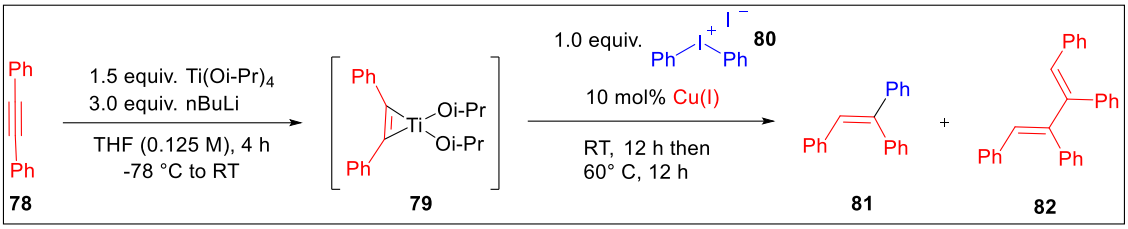
2.4. CONCLUSION

In summary, titanium-promoted coupling of alkynes and isocyanates enables modular access to tri- and tetrasubstitued enamides. The α,β-unsaturated amides are afforded as a single stereoisomer with high regioselectivity (>95/5) for unsymmetrical internal alkynes when a distal steric element is present on either the isocyanate or alkyne. Application of these amides in dual

catalytic radical cross-couplings and in the preparation of natural product mimic libraries is underway.

2.5. FUTURE DIRECTIONS

Scheme 2.7. Synthesis of tri- and tetra-substituted alkenes with iodonium salts

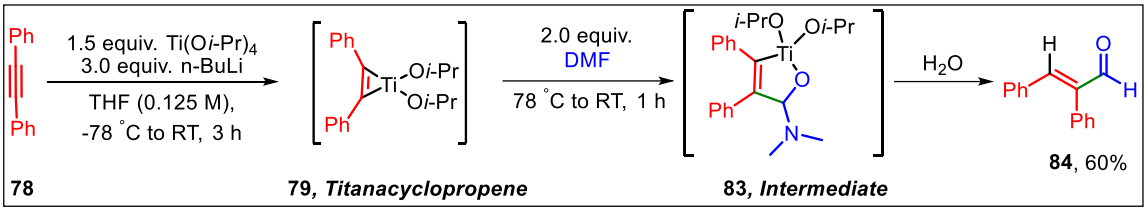


Alkenes are important class of compounds in organic synthesis. Synthesis of sterodefined tri and tetra-substituted alkenes still remain challenging.[60, 61] Traditional methods like Wittig and Horner-Wasdworth-Emmons reaction are not very general and have stereoselectivity issues. Here, we attempted to develop a method to access tri- and tetra-substituted alkenes with stereo control. We found that the dicarbanionic titanacyclopropene undergoes copper catalyzed cross coupling with hypervalent iodonium salts and up to 45% conversion to ethene-1,1,2-triyltribenzene from diphenylacetylene was observed.[62] This cross coupling should be further studied.

Table 2.4. Attempt to optimize the cross-coupling of titanacyclopropene with iodonium salts.

Entry	[Cu]	% Conv. to 81		% Conv. to 82	
		RT	60 °C	RT	60 °C
1	CuBr	-	45	-	12
2	CuOAc	6	25	0	8
3	CuCl	9	29	0	4
4	CuI	2	40	0	6
5	No Cu	-	0 (12 h) 3 (24 h)	-	17 (24 h)

Scheme 2.8. Synthesis of conjugated aldehydes with DMF as the formylating agent



α,β-Unsaturated aldehydes are important class of compounds that are widely used in the synthesis of various heterocycles.[63, 64] Problems like unavailability of many functionalized substrates, and stoichiometric formation of phosphorous byproduct make the conventional methods like Wittig, Horner-Wasdworth-Emmons, and Peterson olefination reactions less attractive.[65] The current technique to make these versatile building blocks primarily rely on hydroformylation reactions catalyzed by precious metals like rhodium.[66] We attempted to develop a protocol to access conjugated aldehydes from cross coupling alkyne with dimethylformamide (DMF) using titanium. As expected, the titanacyclopropene coupled with DMF to give the product in 60% isolated yield. This cross coupling needs further optimization and detailed studies.

2.6. SUPPORTING INFORMATION

2.6.1. Methods

Unless stated otherwise, all 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 0.25mm precoated silica gel plates, or Gas Chromatography. Visualization of all TLCs was performed by UV and/or staining with phosphomolybdic acid, KMnO4, or Seebach's stain. Purifications were performed by silica gel flash chromatography with silica gel (Silicycle, 60 Å, 230-400 mesh) packed in glass columns and eluting with hexanes/EtOAc, unless otherwise noted.

2.6.2. Materials

Diethyl ether, dichloromethane, chloroform, and tetrahydrofuran were dried using a solvent purification system that contained activated alumina. Chlorotrimethylsilane was distilled from calcium hydride under an argon atmosphere. All other reagents and solvents were reagent grade and used without further purification unless otherwise stated. 1-iodo-4-isocyanatobenzene,[67] methyl (S)-2-isocyanato-3-phenylpropanoate,[68] 2-isocyanato-5-methyl-1,1'-biphenyl,[69] 3-phenylprop-2-yn-1-ol,[70] tert-butyldimethyl((3-phenylprop-2-yn-1-yl)oxy)silane,[71] 2,2,3,3,10,10,11,11-octamethyl-4,9-dioxa-3,10-disiladodec-6-yne[72] were prepared using standard literature procedures. The remaining substrates were purchased and used as received.

2.6.3. Instrumentation

^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker Avance 400 MHz NMR Spectrometer (400 MHz for ^{1}H and 101 MHz for ^{13}C) with chemical shifts reported relative to either residual chloroform solvent peaks (δ = 7.26 ppm for ^{1}H and δ = 77.0 ppm for ^{13}C) or residual dimethylsulfoxide solvent peaks (δ = 2.50 ppm for ^{1}H and δ = 39.52 ppm for ^{13}C). Data for ^{1}H NMR were recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sex = sextet, sept = septet, m = multiplet, or unresolved), coupling constant(s) in Hz, integration. The reported melting points are uncorrected. IR spectra were obtained on a NICOLET iS50 FT-IR spectrometer. Low resolution mass spectra were obtained on a Shimidazu QP2010S GC/MS with a SHR5XlB column (30 m, 0.25 mm ID, 0.25 µm df, injection temp. = 260 °C) using a standard ramp of 40 °C to 280 °C at 10 °C/min, holding at 280 °C for 10 minutes. High Resolution Mass Spectra (HRMS) were determined using a Thermo LTQ-OrbitrapXL mass spectrometer operated in FT mode to provide a nominal resolution of 100,000. Enantiomeric excess (%ee) was determined by chiral HPLC

using Lux 3µm Cellulose-1, LC Column 250 x 4.6 mm ID, Eluent: 4%IPA+ 0.1 %TFA in Hexanes for 60 mins, flowrate = 0.5 mL/min. λ = 254 nm.

2.6.4. General procedure A, for the synthesis of α,β-unsaturated amides

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 (0.5 mmol), Ti(O*i*Pr)$_4$ (0.75 mmol, 0.22 mL), and anhydrous Et_2O (4 mL). The round-bottom flask was placed in a dry-ice acetone bath and equilibrated to -78 °C. A solution of isopropylmagnesium chloride (2M in Et_2O, 1.5 mmol, 0.75 mL) was injected dropwise over 5 minutes into the cooled reaction mixture which turned yellow upon complete addition. After stirring at -78 °C for 5 minutes the round-bottom flask was transferred to a -50 °C bath cooled by a chiller and the reaction was stirred for 30 minutes at this temperature. During this time the reaction mixture turned black. The chiller was turned down and the bath was cooled to -78 °C. Once the reaction mixture equilibrated the isocyanate (0.5 mmol) was injected dropwise. The reaction was stirred at -78 °C until complete as judged by TLC or GC, typically 1 hour. The reaction mixture was then opened to the atmosphere, quenched with 2 mL of water, then warmed to room temperature. The crude mixture was passed through a pad of celite in a coarse frit filter funnel, which was then rinsed with Et_2O. The filtrate was transferred to a separatory funnel and the water layer was separated. The organic layer was dried over magnesium sulfate, filtered, and concentrated down. The crude material was purified by flash chromatography using hexanes/EtOAc as the eluting solvent.

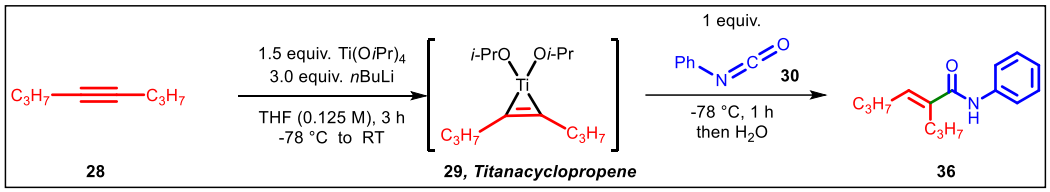
Note 1: Any solid alkynes were added to the flask prior to the vacuum-purge cycle.

Note 2: A small aliquot of the crude material was analyzed by ^{1}H NMR to determine the regioisomer ratio.

2.6.5. Synthesis of α,β-unsaturated amides using *n*-BuLi as a reductant

It has been demonstrated in the literature by Tsuji[73] that thermally stable titanacyclopropenes can be formed when using *n*-BuLi as the reductant. In our initial optimization study *n*-BuLi was screened in an Et_2O solvent system. It has been established that titanacycle formation when using *n*-BuLi only occurs in THF. This discrepancy was determined near the end of this study. When we reexamined the titanium promoted coupling reaction using *n*-BuLi as the reductant in a THF solvent system it was determined coupling occurred producing amide **6** in the same yield as the *i*-PrMgCl/Et_2O system. The advantage of using *n*-BuLi as the reductant is that the procedure becomes slightly more operationally simple, in that the chiller can be omitted. The reaction can be cycled from -78 °C to room temperature back to -78 °C just by using a single dry-ice acetone bath. While not tested we do not for see any change in the chemoselectivity of the coupling if *n*-BuLi is used. We do suspect that the regioselectivity of the reaction may be affected, but to what extent is not clear. In our titanium promoted coupling of alkynes with Weinreb amides to form (E)-trisubstituted enones it was found that the regioselectivity of the reaction was flipped when changing the reducing agent from *i*-PrMgCl to *n*-BuLi.[58]

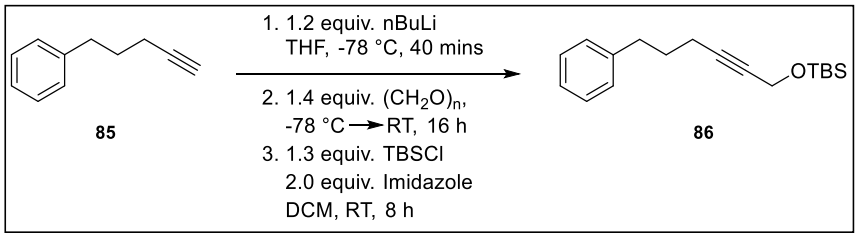
Scheme 2.9. Synthesis of α,β-unsaturated amides using *n*-BuLi as a reductant



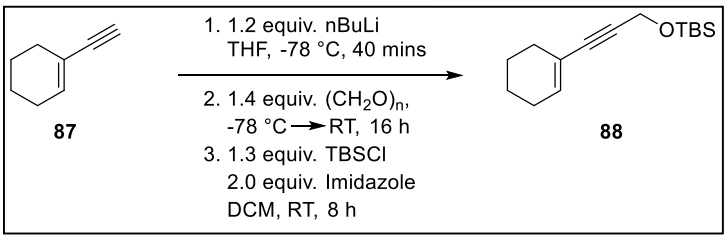
2.6.6. Procedure for the synthesis of (*E*)-*N*-phenyl-2-propylhex-2-enamide (6) using *n*BuLi as the reductant

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 4-octyne (0.5 mmol, 0.073 mL), $Ti(OiPr)_4$ (0.75 mmol, 0.22 mL), and anhydrous THF (4 mL). The round-bottom flask was placed in a dry-ice acetone bath and equilibrated to -78 °C. A solution of *n*-BuLi (1.6 M in hexanes, 1.5 mmol, 0.94 mL) was injected dropwise over 5 minutes into the cooled reaction mixture which turned yellow upon complete addition. After stirring at -78 °C for 5 minutes the round-bottom flask was removed from the bath and gradually warmed to room temperature. During this time the reaction mixture turned black. After stirring at room temperature for 3 hours the round-bottom flask was placed in the -78 °C bath. Once the reaction mixture equilibrated phenylisocyanate (0.5 mmol, 0.055 mL) was injected dropwise. The reaction was stirred at -78 °C for 1 hour. The reaction mixture was then opened to the atmosphere, quenched with 2 mL of water, then warmed to room temperature. The crude mixture was passed through a pad of celite in a coarse frit filter funnel, which was then rinsed with Et_2O. The filtrate was transferred to a separatory funnel and the water layer was separated. The organic layer was dried over magnesium sulfate, filtered, and concentrated down. The crude material was purified by flash chromatography (Hex/EtOAc: 95/5) which afforded 71 mg (62%) of amide **6** as a white solid.

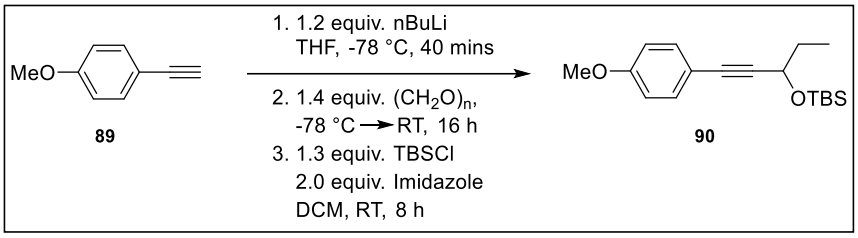
2.6.7. Experimental details of alkyne starting materials



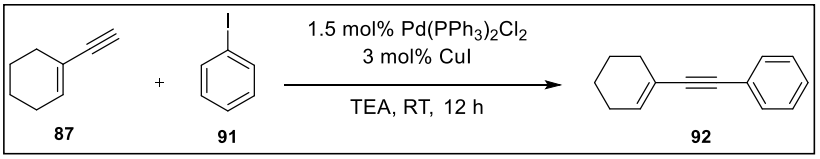
Preparation of tert-butyldimethyl((6-phenylhex-2-yn-1-yl)oxy)silane (86): Following the literature procedure by Wolfe,[74] 5-phenyl-1-pentyne (5.0 mmol, 0.76 mL) was reacted with paraformaldehyde (7.0 mmol, 0.21 g) to afford 6-phenylhex-2-yn-1-ol, the crude product was subjected to TBS protection using a standard literature procedure[71] affording 1.37 g (95%) of tert-butyldimethyl((6-phenylhex-2-yn-1-yl)oxy)silane as a colorless oil after flash chromatography (Hex/EtOAc: 95/5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17-7.12 (m, 2H), 7.07 (m, 3H), 4.19 (t, *J* = 2 Hz, 2H), 2.59 (t, *J* = 7.6 Hz, 2H), 2.09 (tt, *J* = 2.0, 7.2 Hz, 2H), 1.69 (quin, *J* = 7.2 Hz, 2H), 0.79 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.6, 128.5, 128.3, 125.8, 84.9, 79.2, 52.0, 34.8, 30.2, 25.9, 18.3, 18.2, -5.1; IR (neat) 2928, 2856, 1252, 1074, 833, 775, 697 cm^{-1}; GCMS [M-*t*Bu]$^{+}$ 201.



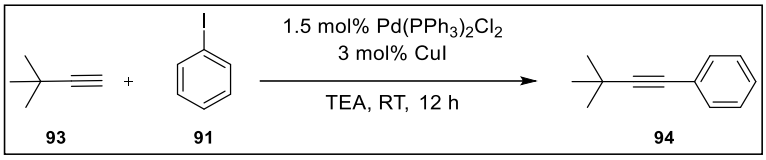
Preparation of tert-butyl((3-(cyclohex-1-en-1-yl)prop-2-yn-1-yl)oxy)dimethylsilane (88): Following the literature procedure by Wolfe,[74] 1-ethynylcyclohex-1-ene (10.0 mmol, 1.18 mL) was reacted with paraformaldehyde (14.0 mmol, 0.42 g) to afford 3-(cyclohex-1-en-1-yl)prop-2-yn-1-ol, the crude product was subjected to TBS protection using a standard literature procedure[71] affording 2.46 g (98%) of tert-butyl((3-(cyclohex-1-en-1-yl)prop-2-yn-1-yl)oxy)dimethylsilane as a colorless oil after flash chromatography (hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (quin, 1H), 4.42 (s, 2H), 2.08 (m, 4H), 1.66-1.54 (m, 4H), 0.9 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.7, 120.4, 86.6, 85.1, 52.2, 29.0, 25.9, 25.6, 22.3, 21.5, 18.3, -5.0; IR (neat) 2928, 1253, 1080, 832, 775 cm^{-1}; GCMS [M-*t*Bu]$^{+}$ 193.



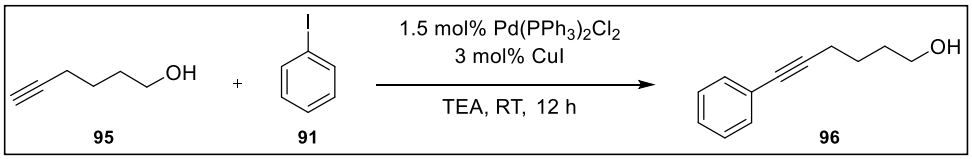
Preparation of tert-butyl((1-(4-methoxyphenyl)pent-1-yn-3-yl)oxy)dimethylsilane (90): Following the literature procedure by Wolfe,[74] 1-ethynyl-4-methoxybenzene (5.0 mmol, 0.65 mL) was reacted with propionaldehyde (7.0 mmol, 0.5 mL) to afford 1-(4-methoxyphenyl)pent-1-yn-3-ol, the crude product was subjected to TBS protection using a standard literature procedure[71] affording 1.2 g (92%) of tert-butyl((3-(cyclohex-1-en-1-yl)prop-2-yn-1-yl)oxy)dimethylsilane as a yellow oil after flash chromatography (Hex/EtOAc: 99/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 4.49 (t, *J* = 6.4 Hz, 1H), 3.80 (s, 3H), 1.77 (quin, *J* = 7.2 Hz, 2H), 1.02 (t, *J* = 7.2 Hz, 3H), 0.94 (s, 9H), 0.17 (d, *J* = 8.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4, 132.9, 115.4, 113.8, 89.6, 83.9, 64.8, 55.3, 31.9, 25.9, 18.3, 9.8, -4.4, -4.9; IR (neat) 2956, 1508, 1246, 829, 775 cm^{-1}; GCMS $[M\text{-}tBu]^+$ 247.



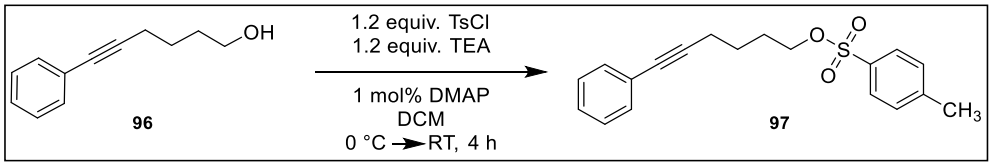
Preparation of (cyclohex-1-en-1-ylethynyl)benzene (92): Following the literature procedure by Liang[70] 1-ethynylcyclohex-1-ene (10.0 mmol, 1.18 mL) was reacted with iodobenzene (9.0 mmol, 1 mL) to afford 1.64 g (99%) of (cyclohex-1-en-1-ylethynyl)benzene as a yellow oil after flash chromatography (Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (m,2H),7.32-7.27 (m, 3H), 6.22 (sept, *J* = 2 Hz, 1H), 2.23 (m, 2H), 2.18-2.12 (m, 2H), 1.72-1.59 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.1, 131.4, 128.2, 127.7, 123.7, 120.7, 91.2, 86.7, 29.2, 25.8, 22.3, 21.5; IR (neat) 2926, 1487, 916, 752 cm^{-1}; GCMS $[M]^+$ 182.



Preparation of (3,3-dimethylbut-1-yn-1-yl)benzene (94): Following the literature procedure by Liang[70] 3,3-dimethyl-1-butyne (10.0 mmol, 1.23 mL) was reacted with iodobenzene (9.0 mmol, 1 mL) to afford 1.43 g (99%) of (3,3-dimethylbut-1-yn-1-yl)benzene as a yellow oil after flash chromatography (Hex/EtOAc: 99/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, 2H), 7.30 (m, 3H), 1.36 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.5, 128.1, 127.4, 124.0, 98.5, 79.0, 31.0, 27.9; IR (neat) 2968, 1488, 1288, 732, 689 cm^{-1}; GCMS $[M]^+$ 158.

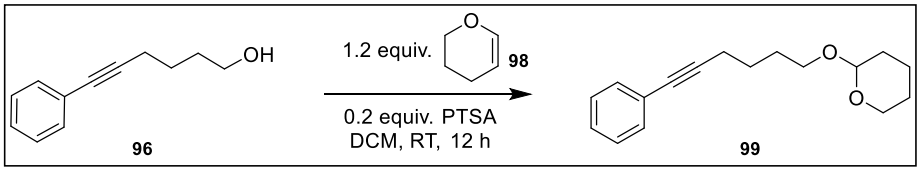


Preparation of 6-phenylhex-5-yn-1-ol (96): Following the literature procedure by Liang[70] 5-hexyn-1-ol (20.0 mmol, 2.2 mL) was reacted with iodobenzene (18.0 mmol, 2 mL) to afford 3.13 g (99%) of 6-phenylhex-5-yn-1-ol as a pale brown oil after flash chromatography (Hex/EtOAc: 90/10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, 2H), 7.31 (m, 3H), 3.73 (t, J = 6 Hz, 2H), 2.48 (t, J = 6.8 Hz, 2H), 1.82-1.68 (m, 4H), 1.49 (bs, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.5, 128.2, 127.5, 123.8, 89.8, 80.9, 62.4, 31.9, 25.0, 19.2; IR (neat) 3321, 2937, 2864, 1489, 1061, 754, 690 cm^{-1}; GCMS $[M\text{-}H_2O]^+$ 155.



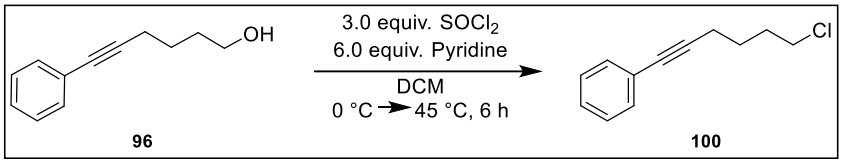
Preparation of 6-phenylhex-5-yn-1-yl 4-methylbenzenesulfonate (97): To a stirred solution of 6-phenylhex-5-yn-1-ol (5 mmol, 0.87 g) in DCM (30 mL) were sequentially added DMAP (0.05

mmol, 0.061 g), tosyl chloride (6 mmol, 1.14 g) and triethylamine (6 mmol, 0.83 mL) at 0 °C. The reaction mixture was then stirred at room temperature for 4 hours, followed by the addition of water (50 mL) and extracting the mixture with Et_2O (3x30 mL). The combined organic layers were washed with water then brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography (hexanes) affording 1.35 g (82%) of 6-phenylhex-5-yn-1-yl 4-methylbenzenesulfonate as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8 Hz, 2H), 7.38 (m, 3H), 7.35 (s, 1H), 7.30 (m, 3H), 4.12 (t, *J* = 6.4 Hz, 2H), 2.46 (s, 3H), 2.42 (t, *J* = 7.2 Hz, 2H), 1.87 (quin, *J* = 6.8 Hz, 2H), 1.66 (quin, *J* = 6.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7, 133.1, 131.5, 129.8, 128.2, 127.8, 127.6, 123.6, 88.9, 81.3, 70.0, 27.9, 24.5, 21.6, 18.7; IR (neat) 2952, 1489, 1355, 1172, 930, 755, 661 cm^{-1}; GCMS $[M\text{-}Ts]^+$ 173.

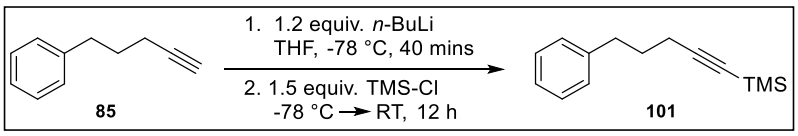


Preparation of 2-((6-phenylhex-5-yn-1-yl)oxy)tetrahydro-2H-pyran (99): To a stirred solution of 6-phenylhex-5-yn-1-ol (3.8 mmol, 0.67 g) in DCM (20 mL), were sequentially added 3,4-dihydro-2H-pyran (4.6 mmol, 0.42 mL) and *para*-toluenesulfonic acid (0.77 mmol, 0.146 g) at room temperature. The reaction mixture was stirred overnight, then concentrated down. The crude slurry was taken up with Et_2O, washed with water then brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography (Hex/EtOAc: 97/3, 85/15, then 80/20) affording 0.56 g (56%) of 2-((6-phenylhex-5-yn-1-yl)oxy)tetrahydro-2H-pyran as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, 2H), 7.30 (m, 3H), 4.62 (t, *J* = 3.6 Hz, 1H), 3.99-3.88 (m, 1H), 3.85-3.80 (m, 1H), 3.55-3.45 (m, 2H), 2.48 (t, *J* = 7.2 Hz, 2H), 1.90-1.69 (m, 6H), 1.63-1.53 (m, 4H); ^{13}C NMR (101

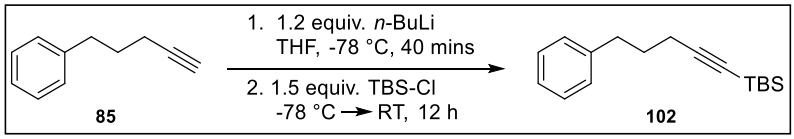
MHz, $CDCl_3$) δ 131.5, 128.1, 127.5, 124.0, 98.8, 90.0, 80.8, 67.0, 30.7, 29.0, 25.6, 25.5, 19.6, 19.3; IR (neat) 2939, 2866, 1489, 1032, 754, 690 cm^{-1}; GCMS $[M\text{-}THP]^+$ 174.



Preparation of (6-chlorohex-1-yn-1-yl)benzene (100): a round bottom flask was connected to a reflux condenser, sealed with a septum, and placed under an atmosphere of argon. A balloon of argon was then attached to the system through the septum. 6-Phenylhex-5-yn-1-ol (7.9 mmol, 1.38 g), pyridine (47.5 mmol, 3.83 mL), and DCM (20 mL) were sequentially injected down the condenser. The round bottom was then placed in an ice-bath. Once the mixture equilibrated thionyl chloride (23.8 mmol, 1.73 mL) was injected down the condenser dropwise. The round bottom flask was then transfer to an oil bath and the reaction mixture was heated to reflux for 6 hours. The cooled reaction mixture was transferred into a separator funnel containing Et_2O, to which a saturated $NaHCO_3$ (aq) solutions was carefully and slowly added. The aqueous layer was extracted with Et_2O two times. The combined organic layers were washed with water then brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography (hexanes) affording 0.53 g (35%) of (6-chlorohex-1-yn-1-yl)benzene as a colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 2H), 7.19-7.13 (m, 3H), 3.48 (t, J = 6.8 Hz, 2H), 2.35 (t, J = 6.8 Hz, 2H), 1.85 (quin, J = 6.8 Hz, 2H), 1.64 (quin, J = 7.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.5, 128.2, 127.6, 123.7, 89.2, 81.2, 44.5, 31.6, 25.9, 18.7; IR (neat) 2907, 1489, 754, 690, 649 cm^{-1}; GCMS $[M]^+$ 192.

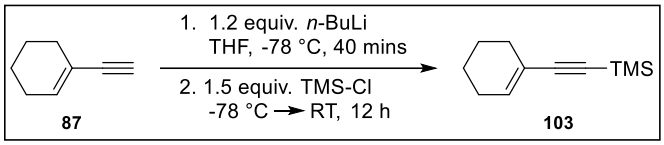


Preparation of trimethyl(5-phenylpent-1-yn-1-yl)silane (101): Following a modified procedure by Chen[75] a solution of 5-phenyl-1-pentyne (5.0 mmol, 0.76 mL) in THF (10 mL) was cooled with a dry-ice acetone bath, to which *n*-BuLi (1.6 M in hexanes, 6.0 mmol, 3.75 mL) was slowly injected. The mixture was stirred for 40 mins then chlorotrimethylsilane (7.5 mmol, 0.95 mL) was injected dropwise. After complete addition the reaction mixture was gradually warmed to room temperature over 12 hours. The reaction was quenched with 4 mL of saturated NH_4Cl(aq) and extracted with Et_2O (3x30 mL). The combined organic layers were washed with water then brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography (hexanes) affording 1.024 g (95%) of trimethyl(5-phenylpent-1-yn-1-yl)silane as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (q, *J* = 7.2 Hz, 2H), 7.02 (m, 3H), 2.55 (t, *J* = 6.8 Hz, 2H), 2.07 (t, *J* = 7.2 Hz, 2H), 1.67 (quin, *J* = 7.2 Hz, 2H), 0.00 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.6, 128.5, 128.3, 125.9, 107.1, 85.0, 34.7, 30.2, 19.3, 0.2; IR (neat) 3027, 2956, 2173, 1248, 836, 697 cm^{-1}; GCMS $[M\text{-}CH_3]^+$ 201.

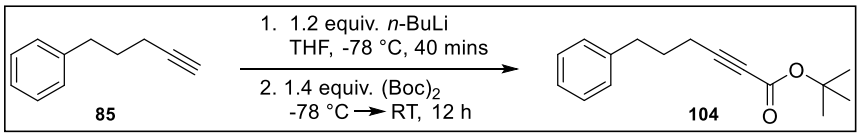


Preparation of tert-butyldimethyl(5-phenylpent-1-yn-1-yl)silane (102): Following a modified procedure by Chen[75] a solution of 5-phenyl-1-pentyne (5.0 mmol, 0.76 mL) in THF (10 mL) was cooled with a dry-ice acetone bath, to which *n*-BuLi (1.6 M in hexanes, 6.0 mmol, 3.75 mL) was slowly injected. The mixture was stirred for 40 mins then *tert*-butyldimethylchlorosilane (7.5 mmol, 1.13 g) was added in one portion. After complete addition the reaction mixture was gradually warmed to room temperature over 12 hours. The reaction was quenched with 4 mL of saturated NH_4Cl(aq) and extracted with Et_2O (3x30 mL). The combined organic layers were washed with water then brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography (hexanes) affording 1.26

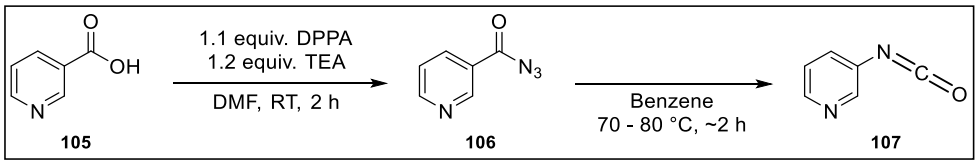
g (97%) of tert-butyldimethyl(5-phenylpent-1-yn-1-yl)silane as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19-7.13 (m, 2H), 7.08 (m, 3H), 2.63 (t, *J* = 7.2 Hz, 2H), 2.14 (t, *J* = 7.2 Hz, 2H), 1.73 (quin, *J* = 7.2 Hz, 2H), 0.85 (s, 9H), 0.0 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.7, 128.5, 128.3, 125.9, 107.6, 83.1, 34.7, 30.4, 26.1,19.3, 16.5, -4.4; IR (neat) 3027, 2928, 2856, 2172, 1470, 773, 697 cm^{-1}; GCMS $[M\text{-}t\text{Bu}]^+$ 201.



Preparation of (cyclohex-1-en-1-ylethynyl)trimethylsilane (103): Following a modified procedure by Chen[75] a solution of 1-ethynylcyclohex-1-ene (10 mmol, 1.18 mL) in THF (20 mL) was cooled with a dry-ice acetone bath, to which *n*-BuLi (1.6 M in hexanes, 12 mmol, 7.5 mL) was slowly injected. The mixture was stirred for 40 mins then chlorotrimethylsilane (15 mmol, 1.9 mL) was injected dropwise. After complete addition the reaction mixture was gradually warmed to room temperature over 12 hours. The reaction was quenched with 10 mL of saturated NH_4Cl(aq) and extracted with Et_2O (3x30 mL). The combined organic layers were washed with water then brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography (hexanes) affording 1.7 g (95%) of (cyclohex-1-en-1-ylethynyl)trimethylsilane as a colorless oil; ^{1}H NMR (400 MHz, CDCl3) δ 6.18 (quin, *J* = 1.6 Hz, 1H), 2.14-2.06 (m, 4H), 1.65-1.53 (m, 4H), 0.17 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.2, 120.7, 107.3, 29.0, 25.6, 22.2, 21.4, 0.1; IR (neat) 2932, 2146, 1248, 836, 757 cm^{-1} ; GCMS $[M\text{-}CH_3]^+$ 163.



Preparation of tert-butyl 6-phenylhex-2-ynoate (104): Following a modified procedure by Ferreira[76] a solution of 5-phenyl-1-pentyne (5.0 mmol, 0.76 mL) in THF (10 mL) was cooled with a dry-ice acetone bath, to which *n*-BuLi (1.6 M in hexanes, 6.0 mmol, 3.75 mL) was slowly injected. The mixture was stirred for 40 mins then di-*tert*-butyl dicarbonate (7.0 mmol, 1.61 mL) was injected dropwise. After complete addition the reaction mixture was gradually warmed to room temperature over 12 hours. The reaction was quenched with 4 mL of saturated NH_4Cl(aq) and extracted with Et_2O (3x30 mL). The combined organic layers were washed with water then brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography (Hex/EtOAc: 100/0, 98/2, then 96/4) affording 1.06 g (87%) of *tert*-butyl 6-phenylhex-2-ynoate as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 2H), 7.22 (m, 3H), 2.76 (t, *J* = 7.6 Hz, 2H), 2.33 (t, *J* = 7.2 Hz, 2H), 1.92 (quin, *J* = 7.2 Hz, 2H), 1.53 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.9, 140.9, 128.5, 128.4, 126.0, 86.3, 83.0, 74.9, 34.7, 29.1, 28.0, 18.0; IR (neat) 2979, 2934, 2234, 1701, 1256, 1156, 751 cm^{-1}; GCMS $[M+H\text{-}tBu]^+$ 188.

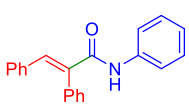


Preparation of 3-isocyanatopyridine (107): Nicotinic acid (20 mmol, 2.46 g) was suspended in dry DMF (15 mL) and was dissolved upon addition of triethylamine (22 mmol, 2.8 mL) at room temperature. Diphenylphosphoryl azide (22 mmol, 4.7 mL) was added and the solution warmed slightly. After stirring at room temperature for 2 hours, the solution had become slightly yellow and was poured into cold water (50 mL) and extracted with diethyl ether. The organic layers were combined and washed with water, brine, dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure to yield 2.96 g (71%) of nicotinoyl azide as a colourless solid after trituration with pentane. Nicotinoyl azide[77] (12.15 mmol, 1.8 g) in benzene (10 mL)

was heated to 75-80 °C until the effervescence ceases (~2 h). The solvent was removed and the product was obtained by distillation under high vacuum to afford 0.95 g (65%) of 3-isocyanatopyridine as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 2H), 7.42 (m, 1H), 7.29 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.6, 146.1, 136.7, 131.4, 131.0, 123.9; IR (neat) 3107, 1706, 1543, 1471, 1313, 887, 658 cm^{-1}.

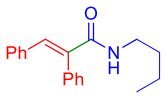
2.6.8. Synthesis of α,β-unsaturated amides

(*E*)-*N*,2,3-triphenylacrylamide (31):



Subjection of diphenylacetylene (0.5 mmol, 0.089 g) and phenyl isocyanate (0.5 mmol, 0.055 mL) to general procedure A afforded 0.150 g (95%) of **31** as a white solid after flash chromatography (Hex/EtOAc: 100/0, then 96/4); m.p. = 136-138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.54-7.49 (m, 3H), 7.47-7.42 (m, 2H), 7.36 (m, 2H), 7.32-7.27 (m, 2H), 7.23-7.14 (m, 4H), 7.09 (m, 1H), 7.04 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.0, 138.3, 137.8, 135.8, 134.8, 134.5, 130.5, 130.0, 129.9, 128.94, 128.91, 128.8, 128.2, 124.4, 119.9; IR (neat) 3406, 3047, 2923, 1669, 1436, 681, 540 cm^{-1}. Physical and spectral data were consistent with those reported in literature.[78]

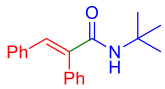
(*E*)-*N*-butyl-2,3-diphenylacrylamide (32):



Subjection of diphenylacetylene (0.5 mmol, 0.089 g) and butyl isocyanate (0.5 mmol, 0.060 mL) to general procedure A afforded 0.104 g (74%) of **32** as a white solid after flash chromatography (Hex/EtOAc: 95/5, then 90/10); m.p. = 36-38 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.49-7.42 (m, 3H), 7.27 (m, 2H), 7.20-7.12 (m, 3H), 7.0 (m, 2H), 5.51 (bs, 1 H), 3.35-3.30 (q, *J* = 6 Hz, 2H), 1.45 (quin, *J* = 7.2 Hz, 2H), 1.28 (sex, *J* = 7.6 Hz, 2H), 0.90 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 137.0, 136.3, 135.0, 134.4, 130.3, 129.8, 129.5, 128.5, 128.4, 128.1, 39.9, 31.5, 20.0, 13.7; IR (neat) 3336, 3025,

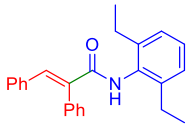
2919, 1654, 1613, 1503, 1364, 1267, 779, 689 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{19}H_{22}NO$ [M + H]$^+$: 280.1696, Found: 280.1685. Physical and spectral data were consistent with those reported in literature.[79]

(*E*)-*N*-(*tert*-butyl)-2,3-diphenylacrylamide (33):



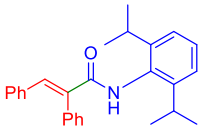
Subjection of diphenylacetylene (0.5 mmol, 0.089 g) and tertiarybutyl isocyanate (0.5 mmol, 0.057 mL) to general procedure A afforded 0.107 g (76%) of **33** as a white solid after flash chromatography (Hex/EtOAc: 95/5, 92/8); m.p. = 105-107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.48-7.40 (m, 3H), 7.27 (m, 2H), 7.19-7.11 (m, 3H), 6.99 (m, 2H), 5.37 (bs, 1 H), 1.34 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 136.5, 135.6, 135.1, 130.2, 129.8, 129.5, 128.4, 128.3, 128.0, 51.4, 28.6; IR (neat) 3410, 3048, 2973, 1666, 1614, 1502, 1214, 781, 706 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{19}H_{22}NO$ [M + H]$^+$: 280.1696, Found: 280.1688. Physical and spectral data were consistent with those reported in literature.[80]

(*E*)-*N*-(2,6-diethylphenyl)-2,3-diphenylacrylamide (34):



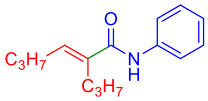
Subjection of diphenylacetylene (0.5 mmol, 0.089 g) and 2,6-diethylphenyl isocyanate (0.5 mmol, 0.086 mL) to general procedure A afforded 0.023 g (13%) of **34** as a white solid after flash chromatography (Hex/EtOAc: 97/3, 95/5, 93/7); m.p. = 78-80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.52 (m, 2H), 7.49−7.42 (m, 3H), 7.24-7.15 (m, 4H), 7.11-7.06 (m, 4H), 6.71 (bs,1H), 2.55 (q, *J* = 7.6 Hz, 4H), 1.13 (t, *J* = 7.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 141.2, 137.7, 136.7, 134.8, 134.1, 132.9, 130.5, 129.9, 129.6, 128.8, 128.7, 128.2, 127.9, 126.3, 25.0, 14.4; IR (neat) 3386, 2960, 2924, 1669, 1471, 1445, 694 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{25}H_{26}NO$ [M + H]$^+$: 356.2009, Found: 356.2003.

(*E*)-*N*-(2,6-diisopropylphenyl)-2,3-diphenylacrylamide (35):



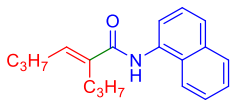
Subjection of diphenylacetylene (0.5 mmol, 0.089 g) and 2,6-diisopropylphenyl isocyanate (0.5 mmol, 0.107 mL) to general procedure A afforded 0.023 g (12%) of **35** as a white solid after flash chromatography (Hex/EtOAc: 97/3, 96/4, 94/6); m.p. = 103-105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.47-7.41 (m, 2H), 7.37 (m, 2H), 7.21-7.17 (m, 2H), 7.13-7.05 (m, 5H), 7.03-6.99 (m, 2H), 6.55 (s,1H), 2.93 (sept, *J* = 6.8 Hz, 2H), 1.09 (d, *J* = 6.8 Hz, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 145.8, 137.7, 136.7, 134.8, 134.1, 131.7, 130.5, 129.9, 129.6, 128.8, 128.7, 128.2, 128.2, 123.4, 28.9, 23.5; IR (neat) 3255, 2958, 1634, 1503, 1269, 688 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{27}H_{30}NO$ $[M + H]^+$: 384.2322, Found: 384.2313.

(*E*)-*N*-phenyl-2-propylhex-2-enamide (36):



Subjection of 4-octyne (0.5 mmol, 0.073 mL) and phenyl isocyanate (0.5 mmol, 0.055 mL) to general procedure A afforded 0.071 g (62%) of **36** as a white solid after flash chromatography (Hex/EtOAc: 98/2, 96/4, 95/5); m.p. = 74-76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.6 Hz, 2H), 7.47 (bs, 1H), 7.32 (t, *J* = 8.4 Hz, 2H), 7.10 (t, *J* = 8.4 Hz, 2H), 6.28 (t, *J* = 7.2 Hz, 1H), 2.38 (t, *J* = 8 Hz, 2H), 2.18 (q, *J* = 7.6 Hz, 2H), 1.48 (sex, *J* = 7.6 Hz, 4H), 0.96 (q, *J* = 7.2 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 138.2, 137.9, 135.4, 128.9, 124.0, 119.8, 30.3, 29.3, 22.33, 22.26, 14.0, 13.9; IR (neat) 3224, 3054, 2956, 1594, 1537, 1462, 1323, 1239, 753, 694 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{15}H_{22}NO[M + H]^+$: 232.1696, Found: 232.1688.

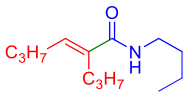
(*E*)-*N*-(naphthalen-1-yl)-2-propylhex-2-enamide (37):



Subjection of 4-octyne (0.5 mmol, 0.073 mL) and 1-Naphthyl isocyanate (0.5 mmol, 72 mL) to general procedure A afforded 0.077 g (55%) of **37**

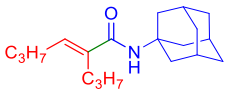
as a white solid after flash chromatography (Hex/EtOAc: 97/3, 95/5, 93/7); m.p. = 60-62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01(d, *J* = 7.6 Hz, 1H),7.89-7.80 (m, 3H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.56-7.47 (m, 3H), 6.46 (t, *J* = 7.2 Hz, 1H), 2.47 (t, *J* = 8 Hz, 2H), 2.24 (q, *J* = 7.2 Hz, 2H), 1.63-1.49 (m, 4H), 1.01 (td, *J* =7.6, 2.4 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 137.7, 135.9, 134.1, 132.6, 128.8, 127.1, 126.3, 125.9, 125.8, 125.5, 120.6, 120.4, 30.4, 29.5, 22.4, 22.39, 14.1, 14.0; IR (neat) 3212, 2956, 2869, 1651, 1622, 1496, 794, 771 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{19}H_{24}NO[M + H]^{+}$: 282.1852, Found: 282.1842.

(*E*)-*N*-butyl-2-propylhex-2-enamide (38):



Subjection of 4-octyne (0.5 mmol, 0.073 mL) and butyl isocyanate (0.5 mmol, 0.056 mL) to general procedure A afforded 0.056 g (53%) of **38** as a colorless sticky liquid after flash chromatography (Hex/EtOAc: 92/8, 90/10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12 (t, *J* = 7.2 Hz, 1H), 5.69 (bs, 1H), 3.29 (q, *J* = 6 Hz, 2H), 2.27 (t, *J* = 8 Hz, 2H), 2.10 (q, *J* = 7.6 Hz, 2H), 1.55-1.31 (m, 9H), 0.95-0.91 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 137.1, 134.4, 39.4, 31.8, 30.1, 29.2, 22.4, 22.2, 20.1, 14.0, 13.9, 13.8; IR (neat) 3303, 2957, 2929, 2871, 1615, 1531, 1462, 1308, 906, 653 cm^{-1}. Physical and spectral data were consistent with those reported in literature.[80]

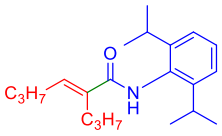
(*E*)-*N*-(adamantan-1-yl)-2-propylhex-2-enamide (39):



Subjection of 4-octyne (0.5 mmol, 0.073 mL) and 1-Adamantyl isocyanate (0.5 mmol, 0.089 g) to general procedure A afforded 0.058 g (41%) of **39** as a white solid after flash chromatography (Hex/EtOAc: 97/3, 96/4, 95/5); m.p. = 110-112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03 (t, *J* = 7.2 Hz, 1H), 5.38 (bs, 1H), 2.23 (t, *J* = 7.6 Hz, 2H), 2.08-2.03 (m, 11H), 1.68 (s, 6H), 1.41 (sept, *J* = 7.2 Hz, 4H), 0.92 (q, *J* = 7.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 138.3, 133.4, 51.7, 41.6, 36.4, 30.1, 29.5, 29.3, 22.4, 22.3,

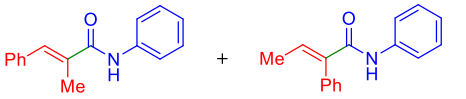
14.1, 14.0; IR (neat) 3309, 3037, 2906, 2849, 1593, 1536, 1442, 1345, 688 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{19}H_{32}NO$ $[M + H]^+$: 290.2478, Found: 290.2466.

(*E*)-*N*-(2,6-diisopropylphenyl)-2-propylhex-2-enamide (40):



Subjection of 4-octyne (0.5 mmol, 0.073 mL) and 2,6-diisopropylphenyl isocyanate (0.5 mmol, 0.107 mL) to general procedure A afforded 0.019 g (12%) of **40** as a white solid after flash chromatography (Hex/EtOAc: 95/5, 93/7). The reaction mixture was stirred at -78 °C for 3 hours; m.p. = 162-164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.27 (m, 1H), 7.18 (d, *J* = 8 Hz, 2H), 6.88 (bs, 1H), 6.35 (t, *J* = 7.6 Hz, 1H), 2.99 (sept, *J* = 6.8 Hz, 2H), 2.35 (t, *J* = 7.6 Hz, 2H), 2.13 (q, *J* = 7.6 Hz, 2H), 1.44 (sex, *J* = 7.2 Hz, 4H), 1.14 (d, *J* = 6.8 Hz, 12H), 0.91 (td, *J* = 7.6, 3.2 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 146.3, 137.6, 134.9, 131.4, 128.2, 123.4, 30.3, 29.7,29.4, 28.8, 23.6, 22.4, 22.1, 14.0; IR (neat) 3273, 2959, 2868, 1624, 1507, 1254, 739 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{21}H_{34}NO$ $[M + H]^+$: 316.2635, Found: 316.2629.

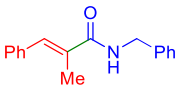
(*E*)-2-methyl-*N*,3-diphenylacrylamide (41):



Subjection of 1-phenyl-1-propyne (0.5 mmol, 0.063 mL) and phenyl isocyanate (0.5 mmol, 0.055 mL) to general procedure A produced a mixture of regioisomers (75/25, crude), affording 0.060 g (63%) of (E)-2-methyl-*N*,3-diphenylacrylamide (**41**) as a pale brown solid, and 0.008 g (7%) of (E)-*N*,2-diphenylbut-2-enamide (**41a**) as a pale brown solid after flash chromatography (Hex/EtOAc: 94/6, 93/7, then 92/8); (E)-2-methyl-*N*,3-diphenylacrylamide (**41**): m.p. = 85-87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (bs, 1H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.42-7.38 (m, 3H), 7.36-7.30 (m, 5H), 7.13 (t, *J* = 7.2 Hz, 1H), 2.18 (d, *J* = 1.2 Hz, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 138.0, 135.8, 134.2, 132.8, 129.3, 128.9, 128.3, 128.0, 124.3, 120.2, 14.4; IR (neat) 3263, 3056, 2922, 1642, 1504, 691 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{16}H_{16}NO$ $[M + H]^+$: 238.1226,

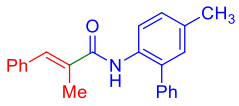
Found: 238.1220. Physical and spectral data were consistent with those reported in literature;[81] (E)-*N*,2-diphenylbut-2-enamide (**41a**): m.p. = 78-80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (m, 2H), 7.44-7.39 (m, 3H), 7.28-7.21 (m, 5H), 7.06 (m, 2H), 1.70 (d, *J* = 7.2 Hz, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 137.8, 137.6, 137.0, 135.1, 129.9, 129.2, 128.8, 128.4, 124.3, 119.9, 15.3; IR (neat) 3303, 3053, 2920, 1649, 1595, 1437, 1317, 751 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{16}H_{16}NO$ $[M + H]^+$: 238.1226, Found: 238.1220.

(*E*)-*N*-benzyl-2-methyl-3-phenylacrylamide (42):



Subjection of 1-phenyl-1-propyne (0.5 mmol, 0.063 mL) and benzyl isocyanate (0.5 mmol, 0.062 mL) to general procedure A afforded 0.088 g (70%) of **42** as a white solid after flash chromatography (Hex/EtOAc: 90/10), 85/15, 82/18, 80/20); m.p. = 73-75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.34 (m, 9H), 7.30 (m, 2H), 6.26 (bs, 1H), 4.58 (d, *J* = 5.6 Hz, 2H), 2.11 (d, *J* = 0.8 Hz, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 138.3, 136.0, 134.1, 131.8, 129.3, 128.7, 128.3, 127.9, 127.8, 127.5, 44.1, 14.3; IR (neat) 3321, 3028, 2921, 1655, 1615, 1531, 1283, 1011, 699 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{17}H_{18}NO$ $[M + H]^+$: 252.1383, Found: 252.1372.

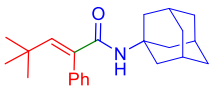
(*E*)-2-methyl-*N*-(5-methyl-[1,1'-biphenyl]-2-yl)-3-phenylacrylamide (43):



Subjection of 1-phenyl-1-propyne (0.5 mmol, 0.063 mL) and 2-isocyanato-5-methyl-1,1'-biphenyl (1.5 mmol, 0.163 g (crude)), which was prepared using the literature procedure[69] and used crude, to general procedure A afforded 0.074 g (45%) of **43** as a pale brown solid after flash chromatography (Hex/EtOAc: 95/5, 93/7); The reaction mixture was stirred at -78 °C for 12 hours; m.p. = 80-82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.4 Hz, 1H), 7.69 (bs, 1H), 7.52 (m, 2H), 7.44 (m, 3H), 7.39 (m, 2H), 7.31(m, 3H), 7.25 (m, 1H), 7.12 (d, *J* = 1.2 Hz, 1H), 2.40 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 138.3, 135.9, 134.6, 133.8, 132.43, 132.41, 132.2, 130.4, 129.31, 129.30,

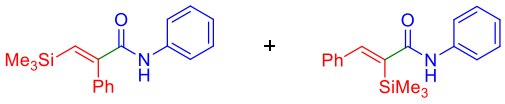
129.04, 128.3, 127.9, 121.2, 20.9, 14.0 ; IR (neat) 3427, 3023, 2919, 1669, 1513, 1294, 757, 699 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{23}H_{22}NO$ $[M + H]^+$: 328.1696, Found:328.1692. Physical and spectral data were consistent with those reported in literature.[69]

(*E*)-*N*-(adamantan-1-yl)-4,4-dimethyl-2-phenylpent-2-enamide (44):



Subjection of (3,3-dimethylbut-1-yn-1-yl)benzene (0.5 mmol, 0.079 g) and 1-Adamantyl isocyanate (0.5 mmol, 0.089 g) to general procedure A afforded 0.120 g (74%) of **44** as a white solid after flash chromatography (Hex/EtOAc: 97/3, 95/5); The reaction mixture was stirred at -78 °C for 12 hours; m.p. = 100-102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.32 (m, 3H), 7.18 (m, 2H), 7.00 (s, 1H), 4.93(s, 1H), 2.00 (s, 3H), 1.85 (d, *J* = 2.8 Hz, 6H), 1.61(s, 6H), 0.88 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.48, 148.49, 136.90, 133.51, 130.34, 128.28, 127.79, 51.74, 41.35, 36.32, 33.66, 30.49, 29.36; IR (neat) 3405, 3327, 2900, 2850, 1621, 1513, 709 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{23}H_{32}NO$ $[M + H]^+$: 338.2478, Found: 338.2472.

(*E*)-*N*,2-diphenyl-3-(trimethylsilyl)acrylamide (45):

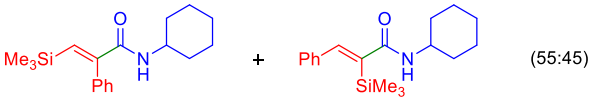


(75:25)

Subjection of 1-phenyl-2-trimethylsilylacetylene (0.5 mmol, 0.098 mL) and phenyl isocyanate (0.5 mmol, 0.055 mL) to general procedure A produced a mixture of regioisomers (75/25, crude), affording 0.078 g (53%) of (E)-*N*,2-diphenyl-3-(trimethylsilyl)acrylamide (**45**) as a white solid, and 0.025 g (17%) of (Z)-*N*,3-diphenyl-2-(trimethylsilyl)acrylamide (**45a**) as a white solid after flash chromatography (Hex/EtOAc: 97/3, 96/4, 95/5, 94/6); (E)-*N*,2-diphenyl-3-(trimethylsilyl)acrylamide (**45**): m.p. = 150-152 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (s, 1H), 7.69 (d, *J* = 8 Hz, 2H), 7.56 (s, 1H), 7.43 (m, 2H), 7.37-7.29 (m, 5H), 7.05 (t, *J* = 7.2 Hz, 1H), 0.05 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.5, 144.3, 142.6, 139.5, 137.7, 128.6, 128.2, 128.1, 123.1, 119.6, 0.1; IR (neat) 3305, 2950,

1633, 1592, 1433, 1245, 840, 690 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{18}H_{22}NOSi$ $[M + H]^+$: 296.1465, Found: 296.1459; (Z)-*N*,3-diphenyl-2-(trimethylsilyl)acrylamide (**45a**): m.p. = 133-135 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 7.64 (d, *J* = 7.6 Hz, 2H), 7.42-7.35 (m, 3H), 7.32-7.27 (m, 4H), 7.06 (t, *J* = 7.2 Hz, 1H), 6.56 (s, 1H), -0.09 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.2, 152.7, 139.0, 138.4, 135.7, 128.9, 128.5, 127.9, 127.8, 123.5, 120.1, -0.3; IR (neat) 3250, 3053, 2953, 1652, 1596, 1439, 1246, 858, 691 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{18}H_{22}NOSi$ $[M + H]^+$: 296.1465, Found: 296.1459.

(*E*)-*N*-cyclohexyl-2-phenyl-3-(trimethylsilyl)acrylamide (46):

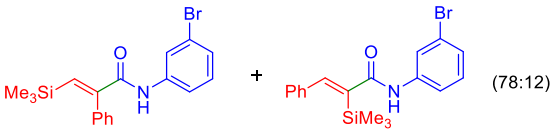


(55:45)

Subjection of 1-phenyl-2-trimethylsilylacetylene (0.5 mmol, 0.098 mL) and cyclohexylisocyanate (0.5 mmol, 0.064 mL) to general procedure A produced a mixture of regioisomers (55/45, crude), affording 0.048 g (32%) of (E)-*N*-cyclohexyl-2-phenyl-3-(trimethylsilyl)acrylamide (**46**) as a white solid, and 0.034 g (23%, 80% purity) of (Z)-*N*-cyclohexyl-3-phenyl-2-(trimethylsilyl)acrylamide (**46a**) as a white solid after flash chromatography (Hex/EtOAc: 96/4, 94/6, 92/8); (E)-*N*-cyclohexyl-2-phenyl-3-(trimethylsilyl)acrylamide (**46**): m.p. = 145-147 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.30-7.23 (m, 3H), 7.19 (m, 2H), 5.41 (d, *J* = 7.6 Hz, 1H), 3.82-3.73 (m, 1H), 1.94 (m, 2H), 1.71-1.66 (m, 2H), 1.61-1.56 (m, 1H), 1.40-1.29 (m, 2H), 1.19-1.09 (m, 3H), 0.0 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 144.3, 144.1, 138.0, 128.3, 128.0, 127.9, 48.3, 33.3, 25.6, 24.9. 0.1; IR (neat) 3265, 2929, 2853, 1605, 1533, 1348, 1241, 836, 751, 694 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{18}H_{28}NOSi$ $[M + H]^+$: 302.1935, Found: 302.1930; (Z)-*N*-cyclohexyl-3-phenyl-2-(trimethylsilyl)acrylamide (**46a**): ^1H NMR (400 MHz, DMSO-d_6) δ 7.54-7.41 (m, 4H), 7.37-7.25 (m, 2H), 6.61 (s, 1H), 3.73 (m, 1H), 1.87-1.78 (m, 4H), 1.41-1.13 (m, 6H), 0.00 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.7, 152.6, 138.8, 134.8, 128.9, 127.8, 127.7, 48.0, 32.2, 25.2, 24.7, -

0.4.; IR (neat) 3279, 2928, 2853, 1537, 1244, 836, 701 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{18}H_{28}NOSi$ $[M + H]^+$: 302.1935, Found: 302.1929.

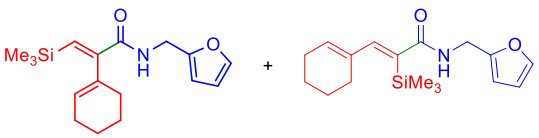
(*E*)-*N*-(3-bromophenyl)-2-phenyl-3-(trimethylsilyl)acrylamide (47):



(78:12)

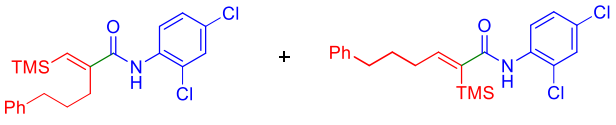
Subjection of 1-phenyl-2-trimethylsilylacetylene (0.5 mmol, 0.098 mL) and 3-bromophenyl isocyanate (0.5 mmol, 0.062 mL) to general procedure A produced a mixture of regioisomers (78/12, crude), affording 0.102 g (55%) of (E)-*N*-(3-bromophenyl)-2-phenyl-3-(trimethylsilyl)acrylamide (**47**) as a white solid, and 0.018 g (10%) of (Z)-*N*-(3-bromophenyl)-3-phenyl-2-(trimethylsilyl)acrylamide (**47a**) as a white solid after flash chromatography (Hex/EtOAc: 97/3, 95/5, 92/8); (E)-*N*-(3-bromophenyl)-2-phenyl-3-(trimethylsilyl)acrylamide (**47**): m.p. = 152-153 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (bs, 1H), 7.67 (s, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.39-7.33 (m, 4H), 7.30 (m, 2H), 7.25-7.19 (m, 2H), 0.11 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 145.6, 144.0, 139.3, 137.3, 130.3, 128.3, 128.1, 127.2, 122.6, 118.4, 118.3, 0.1; IR (neat) 3289, 2950, 1638, 1581, 1475, 1246, 837, 697 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{18}H_{21}BrNOSi$ $[M + H]^+$: 374.0570, Found: 374.0565; (Z)-*N*-(3-bromophenyl)-3-phenyl-2-(trimethylsilyl)acrylamide (**47a**): m.p. = 150-152 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.59 (m, 3H), 7.50 (m, 2H), 7.42 (m, 2H), 7.38 (s, 1H), 7.33 (d, *J* = 8 Hz, 1H), 7.26 (m, 2H), 0.0 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 149.0, 143.4, 139.0, 137.5, 130.2, 129.6, 128.9, 128.9, 127.4, 122.7, 122.5, 118.3, -0.8; IR (neat) 3222, 2954, 1643, 1586, 1527, 1419, 837, 697 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{18}H_{21}BrNOSi$ $[M + H]^+$: 374.0570, Found: 374.0569.

(*E*)-2-(cyclohex-1-en-1-yl)-*N*-(furan-2-ylmethyl)-3-(trimethylsilyl)acrylamide (48) + (*Z*)-3-(cyclohex-1-en-1-yl)-*N*-(furan-2-ylmethyl)-2-(trimethylsilyl)acrylamide (48a):



Subjection of (cyclohex-1-en-1-ylethynyl)trimethylsilane (0.5 mmol, 0.089 mg) and furfuryl isocyanate (0.5 mmol, 0.054 mL) to general procedure A afforded a partially separable mixture of regioisomers (50/50, crude), 0.046 g (31%) of **48** and 0.072 g (47%) of **48** + **48a** (56/44) as a colorless sticky solid after flash chromatography (Hex/EtOAc: 95/5, 90/10); (*E*)-2-(cyclohex-1-en-1-yl)-*N*-(furan-2-ylmethyl)-3-(trimethylsilyl) acrylamide (**48**): ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (s, 1H), 6.70 (s, 1H), 6.31 (s, 1H), 6.27 (bs, 1H), 6.21 (m, 1H), 5.68 (m, 1H), 4.47 (d, *J* = 5.6 Hz, 2H), 2.12 (m, 2H), 2.02 (m, 2H), 1.64 (m, 4H), 0.09 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 152.3, 151.4, 142.1, 137.4, 136.7, 129.2, 110.4, 107.1, 37.0, 28.9, 25.1, 22.5, 21.6, -0.2; IR (neat) 3330, 2929, 1649, 1507, 1245, 836, 757 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{17}H_{26}NO_2Si$ $[M + H]^+$: 304.1727, Found: 304.1724; (*Z*)-3-(cyclohex-1-en-1-yl)-*N*-(furan-2-ylmethyl)-2-(trimethylsilyl)acrylamide (**48a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (s, 1H), 6.77 (s, 1H), 6.31 (s, 1H), 6.24 (m, 1H), 5.80 (m, 1H), 5.65 (s, 1H), 4.44 (d, *J* = 5.2 Hz, 2H), 2.07 (m, 2H), 1.96 (m, 2H), 1.64-1.56 (m, 4H), 0.16 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 151.6, 147.9, 142.0, 139.8, 136.2, 126.9, 110.4, 107.3, 36.5, 28.0, 25.3, 22.3, 21.8, 0.4.

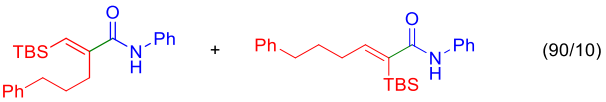
(*E*)-*N*-(2,4-dichlorophenyl)-5-phenyl-2((trimethylsilyl)methylene)pentanamide (49):



Subjection of trimethyl(5-phenylpent-1-yn-1-yl)silane (0.5 mmol, 0.108 g) and 2,4-dichlorophenylisocyanate (0.5 mmol, 0.094 g) to general procedure A produced a mixture of regioisomers (50/50, crude), affording 0.0725 g (35.5%) of (E)-*N*-(2,4-dichlorophenyl)-5-phenyl-2((trimethylsilyl)methylene)pentanamide (**49**) as a white solid, and 0.0725 (35.5%) of (Z)-*N*-(2,4-

dichlorophenyl)-6-phenyl-2-(trimethylsilyl)hex-2-enamide (**49a**) as a clear oil after flash chromatography (Hex/EtOAc: 97/3, then 95/5); (E)-*N*-(2,4-dichlorophenyl)-5-phenyl-2((trimethylsilyl)methylene)pentanamide (**49**): m.p. = 55-57 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 9.2 Hz, 1H), 7.87 (bs, 1H), 7.24 (d, *J* = 2.4 Hz, 1H), 7.14–7.09 (m, 3H), 7.03 (m, 3H), 6.19 (s, 1H), 2.53 (t, *J* = 7.6 Hz, 2H), 2.38 (m, 2H), 1.69-1.61 (m, 2H), 0.0 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 152.8, 141.6, 135.0, 133.5, 128.9, 128.6, 128.5, 128.4, 127.9, 125.9, 123.3, 122.0, 36.1, 32.1, 31.4, -0.3; IR (neat) 3293, 3083, 2953, 1654, 1575, 1496, 1310, 832, 698 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{21}H_{26}Cl_2NOSi$ $[M + H]^+$: 406.1155, Found: 406.1150; (Z)-*N*-(2,4-dichlorophenyl)-6-phenyl-2-(trimethylsilyl)hex-2-enamide (**49a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 9.2 Hz, 1H), 7.34 (bs, 1H), 7.16 (d, *J* = 2.4 Hz, 1H), 7.08 (t, *J* = 7.2 Hz, 2H), 7.02 (m, 2H), 6.99 (m, 3H), 6.45 (t, *J* = 7.6 Hz, 1H), 2.46 (t, *J* = 7.6 Hz, 2H), 2.07 (q, *J* = 7.6 Hz, 2H), 1.57 (quin, *J* = 7.6 Hz, 2H), 0.0 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 148.7, 141.6, 141.5, 133.7, 128.7, 128.7, 128.6, 128.4, 127.9, 126.0, 123.1, 122.0, 35.5, 31.3, 30.9, 0.1; IR (neat) 3423, 3026, 2925, 1672, 1494, 1293, 839, 697 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{21}H_{26}Cl_2NOSi$ $[M + H]^+$: 406.1155, Found: 406.1150.

(*E*)-2-((tert-butyldimethylsilyl)methylene)-*N*,5-diphenylpentanamide (50) + (*Z*)-2-(*tert*-butyldimethylsilyl)-N,6-diphenylhex-2-enamide (50a):

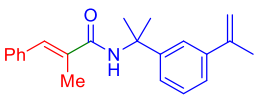


(90/10)

Subjection of tert-butyldimethyl(5-phenylpent-1-yn-1-yl)silane (0.5 mmol, 0.129 g) and phenylisocyanate (0.5 mmol, 0.055 mL) to general procedure A produced a mixture of regioisomers (90/10, crude), affording 0.143 g (75%) of (E)-2-((tert-butyldimethylsilyl)methylene)-*N*,5-diphenylpentanamide (20) as a white solid, and 0.015 g (8%) of (*Z*)-2-(*tert*-butyldimethylsilyl)-N,6-diphenylhex-2-enamide (**50a**) as a white solid after flash chromatography (Hex/EtOAc: 96/4, 92/8); (E)-2-((tert-butyldimethylsilyl)methylene)-*N*,5-diphenylpentanamide (**50**): m.p. = 68-70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (m, 2H,), 7.29

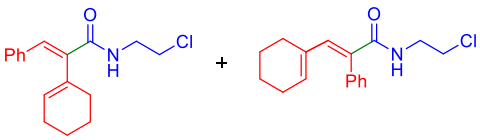
(bs, 1H), 7.18 (m, 2H,), 7.09 (m, 2H,), 6.11 (s, 1H), 2.58 (t, *J* = 15.2 Hz, 2H,), 2.43 (m, 2H), 1.73-1.65 (m, 2H,), 0.82 (s, 9H), 0.0 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 154.9, 141.8, 137.9, 130.3, 129.0, 128.5, 128.4, 125.9, 119.9, 36.1, 32.3, 31.3, 26.4, 17.0, -4.5; IR (neat) 3323, 2952, 2926, 2853, 1645, 1591, 1530, 1245, 783, 695 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{24}H_{34}NOSi$ $[M + H]^+$: 380.2404, Found: 380.2395; (*Z*)-2-(*tert*-butyldimethylsilyl)-N,6-diphenylhex-2-enamide (**50a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.33-7.28 (m, 5H), 7.22-7.15 (m, 4H), 6.63 (t, *J* = 7.2 Hz, 1H), 2.68 (t, *J* = 7.6 Hz, 2H), 2.27 (q, *J* = 7.6 Hz, 2H), 1.78 (quin, *J* = 7.6 Hz, 2H), 0.96 (s, 9H), 0.15 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 148.9, 141.7, 138.2, 129.0, 128.9, 128.5, 128.4, 126.0, 124.0, 119.8, 35.7, 32.4, 30.9, 27.1, 18.1, -3.7.

(*E*)-2-methyl-3-phenyl-*N*-(2-(3-(prop-1-en-2-yl)phenyl)propan-2-yl)acrylamide (51):



Subjection of 1-phenyl-1-propyne (0.5 mmol, 0.063 mL) and α,α-dimethylbenzyl isocyanate (0.5 mmol, 0.099 mL) to general procedure A afforded 0.103 g (64%) of **51** as a white solid after flash chromatography (Hex/EtOAc: 90/10, 88/12); The reaction mixture was stirred at -78 °C for 12 hours; m.p. = 88-90 °C; ^{1}H NMR (400 MHz, CDCl3) δ 7.53 (bs, 1H), 7.40-7.30 (m, 9H), 6.16 (s, 1H), 5.36 (s, 1H), 5.09 (s, 1H), 2.17 (s, 3H), 2.10 (s, 3H), 1.81 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) 168.7, 146.8, 143.5, 141.4, 136.2, 133.2, 133.1, 129.3, 128.3, 128.3, 127.7, 124.0, 123.9, 121.9, 112.5, 56.1, 29.1, 21.9, 14.4; IR (neat) 3320, 2975, 1615, 1520, 1283, 883, 691 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{22}H_{26}NO$ $[M + H]^+$: 320.2009, Found: 320.2009.

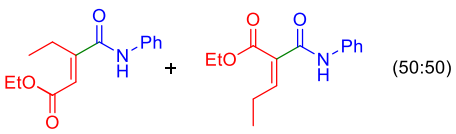
(*E*)-*N*-(2-chloroethyl)-2-(cyclohex-1-en-1-yl)-3-phenylacrylamide (52) + (*E*)-*N*-(2-chloroethyl)-3-(cyclohex-1-en-1-yl)-2-phenylacrylamide (52a):



Subjection of (cyclohex-1-en-1-ylethynyl)benzene (0.5 mmol, 0.091 g) and 2-

chloroethyl isocyanate (0.5 mmol, 0.043 mL) to general procedure A afforded an inseparable mixture of regioisomers (50/50, crude), 0.105 g (72%) of **52** + **52a** as a brown solid after flash chromatography (Hex/EtOAc: 90/10, 85/15, 80/20); m.p. = 70-72 °C; (*E*)-*N*-(2-chloroethyl)-2-(cyclohex-1-en-1-yl)-3-phenylacrylamide (**52**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (m, 3H), 7.42 (m, 2H), 7.29 (m, 1H), 6.80 (bs, 1H), 5.89 (quin, *J* = 1.6 Hz, 1H), 3.75-3.70 (m, 2H), 3.59 (m, 2H,), 2.25 (m, 2H), 2.15-2.10 (m, 2H), 1.81-1.71 (m, 2H), 1.50-1.45 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7,141.5,139.0, 136.0, 135.0, 130.5, 130.4, 129.9, 128.3, 44.4, 41.4, 28.1, 25.5, 22.9, 21.7; *E*)-*N*-(2-chloroethyl)-3-(cyclohex-1-en-1-yl)-2-phenylacrylamide (**52a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.31 (m, 3H), 7.28 (m, 3H), 6.15 (t, *J* = 3.2 Hz, 1H), 5.73 (bs, 1H), 3.75-3.70 (m, 2H), 3.59 (m, 2H), 2.15-2.10 (m, 2H), 1.81-1.71 (m, 2H), 1.50-1.45 (m, 2H), 1.41-1.37 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 136.7, 135.2, 135.3, 134.7, 129.6, 128.6, 128.5, 128.2, 43.8, 41.7, 27.1, 26.5, 22.6, 21.6; IR (neat) 3313, 2928, 2858, 1644, 1503, 1262, 709 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{17}H_{21}ClNO$ $[M + H]^+$: 290.1306, Found: 290.1298.

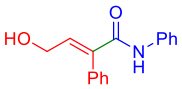
Ethyl (*E*)-3-(phenylcarbamoyl)pent-2-enoate (53) + ethyl (*Z*)-2-(phenylcarbamoyl)pent-2-enoate (53a):



Subjection of ethyl-2-pentynoate (0.5 mmol, 0.066 mL) and phenylisocyanate (0.5 mmol, 0.055 mL) to general procedure A afforded an inseparable mixture of regioisomers (50/50, crude), 0.048 g (39%, 50% purity, contaminated with grease and some unknown aliphatic impurities) of **53** + **53a** as a pale yellow sticky solid after flash chromatography (Hex/EtOAc: 97/3, 95/5, 93/7); The reaction mixture was stirred at -78 °C for 12 hours; Ethyl (*E*)-3-(phenylcarbamoyl)pent-2-enoate (**53**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (s. 1H), 7.57 (d, *J* = 8 Hz, 2H), 7.34 (q, *J* = 7.6 Hz, 2H), 7.15 (t, *J* = 7.6 Hz, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 2.93 (q, *J* = 7.2 Hz, 2H), 1.42-1.30 (m, 3H), 1.18-1.13 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 159.1, 155.8, 137.32, 129.1, 129.0, 120.6, 120.1, 60.7, 22.1, 14.2, 13.1; Ethyl

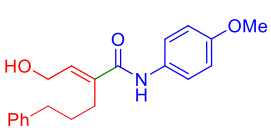
(*Z*)-2-(phenylcarbamoyl)pent-2-enoate (**53a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11 (s. 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.34 (q, *J* = 7.6 Hz, 2H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 7.2 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 2.78 (quin, *J* = 7.6 Hz, 2H), 1.42-1.30 (m, 3H), 1.18-1.13 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 158.7, 155.8, 137.34, 124.9, 124.3, 120.3, 120.2, 61.7, 23.8, 14.1, 13.2; IR (neat) 3271, 2973, 2931, 1714, 1658, 1598, 1459, 1189, 752, 691 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{14}H_{18}NO_3$ $[M + H]^+$: 248.1281, Found: 248.1278.

(*E*)-4-hydroxy-*N*,2-diphenylbut-2-enamide (58):



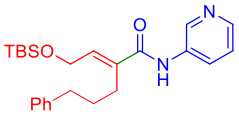
tert-Butyldimethyl((3-phenylprop-2-yn-1-yl)oxy)silane (0.5 mmol, 0.123 g) and phenyl isocyanate (1.0 mmol, 0.109 mL) was subjected to general procedure A with the following modification. After addition of the isocyanate the reaction mixture was stirred for 12 h at -78 °C, followed by opening the system to the air an adding 3 mL of 3M HCl then stirring at RT for 1 hour. The reaction mixture was extracted with Et_2O three times. The combined organic layers were washed with water then brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude material was purified by flash chromatography (Hex/EtOAc: 90/10, 85/15, 82/18) affording 0.084 g (67%) of **58** as a white solid; m.p. = 151-152 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.02 (s 1H), 7.73 (d, *J* = 7.6 Hz, 2H), 7.56 (d, *J* = 7.6 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.41-7.32 (m, 4H), 7.08 (t, *J* = 7.2 Hz, 1H), 5.31 (t, *J* = 5.2 Hz, 1H), 4.39 (d, *J* = 4.8 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.2, 139.3, 136.8, 135.5, 135.1, 129.4, 128.6, 128.4, 123.3, 119.8, 99.5, 56.1; IR (neat) 3171, 3055, 2920, 1638, 1544, 1440, 1021, 771, 687 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{16}H_{16}NO_2$[M + H]$^+$: 254.1176, Found: 254.1171.

(*E*)-2-(2-hydroxyethylidene)-*N*-(4-methoxyphenyl)-5-phenylpentanamide (59):



tert-Butyldimethyl((6-phenylhex-2-yn-1-yl)oxy)silane (0.5 mmol, 0.144 g) and 4-methoxyphenyl isocyanate (1.0 mmol, 0.130 mL) was subjected to general procedure A with the following modification. After addition of the isocyanate the reaction mixture was stirred for 12 h at -78 °C, followed by opening the system to the air an adding 3 mL of 3M HCl then stirring at RT for 1 hour. The reaction mixture was extracted with Et_2O three times. The combined organic layers were washed with water then brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude material was purified by flash chromatography (Hex/EtOAc: 85/15, 80/20, 75/25, 70/30, 67/33) affording 0.086 g (56%) of **59** as a white solid; m.p. = 47-49 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (bs, 1H), 7.48 (d, *J* = 9.2 Hz, 2H), 7.34-7.29 (m, 2H), 7.26-7.19 (m, 3H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.70 (t, *J* = 7.6 Hz, 1H), 4.42 (d, *J* = 5.2 Hz, 2H), 3.82 (s, 3H), 2.69 (t, *J* = 14.8 Hz, 2H), 2.29 (q, *J* = 7.6 Hz, 2H), 1.84 (quin, *J* = 7.6 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 156.3, 141.5, 140.4, 133.6, 131.1, 128.4, 128.4, 126.0, 121.9, 114.1, 57.9, 55.5, 35.3, 30.2, 27.3; IR (neat) 3264, 3061, 2934,1618, 1507, 1243, 1024, 838, 697 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{20}H_{24}NO_3$ $[M + H]^+$: 326.1751, Found: 326.1748.

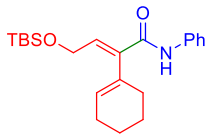
(*E*)-2-(2-((*tert*-butyldimethylsilyl)oxy)ethylidene)-5-phenyl-*N*-(pyridin-3-yl)pentanamide (60):



Subjection of *tert*-butyldimethyl((6-phenylhex-2-yn-1-yl)oxy)silane (0.5 mmol, 0.144 g) and 3-isocyanatopyridine (1.0 mmol, 0.120 g) to general procedure A afforded 0.035 mg (35%) of **60** as a colorless liquid after flash chromatography (Hex/EtOAc: 95/5, 90/10, 85/15, 80/20, 75/25, 70/30, 65/35); the reaction mixture was stirred at -78 °C for 12 hours; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.47 (bs, 1H), 8.28-8.14 (m, 2H), 7.20-7.14 (m, 4H), 7.09-7.04 (m, 4H), 4.32 (s, 2H), 2.55 (t, *J* = 7.6 Hz, 2H), 2.18 (q, *J* = 7.6 Hz,

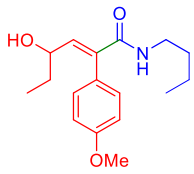
2H), 1.70 (q, *J* = 7.6 Hz, 2H), 0.82 (s, 9H), 0.0 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 144.3, 142.3, 141.4, 140.7, 131.7, 128.40, 128.38, 127.5, 126.0, 123.9, 58.2, 35.3, 30.3, 27.4, 25.8, 18.1, -5.3; IR (neat) 3305, 2928, 2855, 1676, 1533, 1252, 1062, 834, 698 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{24}H_{35}N_2O_2Si$ $[M + H]^+$: 411.2462, Found: 411.2443.

(*E*)-4-((*tert*-butyldimethylsilyl)oxy)-2-(cyclohex-1-en-1-yl)-*N*-phenylbut-2-enamide (61):



Subjection of *tert*-butyl((3-(cyclohex-1-en-1-yl)prop-2-yn-1-yl)oxy)dimethylsilane (0.5 mmol, 0.125 g) and phenyl isocyanate (1.0 mmol, 0.109 mL) to general procedure A afforded 0.128 mg (69%) of **61** as a white solid after flash chromatography (Hex/EtOAc: 97/3, 96/4); the reaction mixture was stirred at -78 °C for 12 hours; m.p. = 58-60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, 1H), 7.58 (d, *J* = 8 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.19 (bs,, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 5.73 (bs, 1H), 4.64 (s, 1H), 2.15 (d, *J* = 19.6 Hz, 4H), 1.72-1.60 (m, 4H), 0.96 (s, 9H), 0.14 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 142.3, 138.6, 133.9, 131.5, 130.3, 128.9, 123.7, 119.9, 59.0, 28.5, 25.8, 25.7, 22.5, 21.8, 18.2, -5.2; IR (neat) 3372, 2928, 2855, 1672, 1497, 1308, 1032, 834, 749 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{22}H_{34}NO_2Si$ $[M + H]^+$: 372.2353, Found: 372.2348.

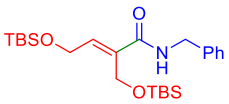
(*E*)-*N*-butyl-4-hydroxy-2-(4-methoxyphenyl)hex-2-enamide (62):



tert-butyl((1-(4-methoxyphenyl)pent-1-yn-3-yl)oxy)dimethylsilane (0.5 mmol, 0.152 g) and butyl isocyanate (1.0 mmol, 0.113 mL) was subjected to general procedure A with the following modification. After addition of the isocyanate the reaction mixture was stirred for 12 h at -78 °C, followed by opening the system to the air an adding 3 mL of 3M HCl then stirring at RT for 1 hour. The reaction mixture was extracted with Et_2O three times. The combined organic layers were washed with water then brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude material was purified by flash chromatography (Hex/EtOAc: 85/15, 80/20, 75/25, 70/30) affording 0.039 g (27%) of **62** as a

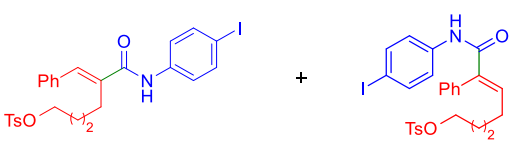
pale yellow sticky liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, *J* = 7.6 Hz, 2H), 6.82 (d, *J* = 8 Hz, 2H), 4.69 (bs, 1 H), 3.76 (s,3H), 3.35-3.23 (m, 2H), 1.84-1.75 (m, 1H), 1.65-1.58 (m,2H), 1.49 (m,2H), 1.35-1.30 (m,3H), 1.21 (s, 1H), 0.88 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 159.4, 136.1, 135.0, 130.5, 127.5, 113.8, 70.3, 55.2, 39.2, 31.5, 29.1, 20.2,13.7, 10.5; IR (neat) 3295, 2959, 2931, 2872, 1604, 1509, 1248, 1032, 752 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{17}H_{26}NO_3$ $[M + H]^+$: 292.1907, Found: 292.1901.

(*E*)-*N*-benzyl-4-((tert-butyldimethylsilyl)oxy)-2-(((*tert*-butyldimethylsilyl)oxy) methyl)but-2-enamide (63):



Subjection of 2,2,3,3,10,10,11,11-octamethyl-4,9-dioxa-3,10-disiladodec-6-yne (0.5 mmol, 0.157 g) and benzyl isocyanate (1.0 mmol, 0.124 mL) to general procedure A afforded 0.084 g (37%, 50% purity, contaminated with isopropyl benzylcarbamate) of **63** as a colorless sticky oil after flash chromatography (Hex/EtOAc: 92/8, 90/10); the reaction mixture was stirred at -78 °C for 12 hours; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (bs, 1H), 7.27-7.15 (m, 5H), 6.69 (t, *J* = 6 Hz, 1H), 4.43 (d, *J* = 5.6 Hz, 2H), 4.33 (s, 2H), 4.28 (s, 2H), 0.82 (s, 9H), 0.70 (s, 9H), 0.0 (s, 6H), -0.05 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 139.0, 138.2, 132.2, 128.6, 127.9, 127.3, 59.6, 58.4, 43.7, 25.8, 25.6, 18.2, 17.9, -5.3, -5.5; IR (neat) 3330, 2928, 2856, 1695, 1532, 1252, 833, 775, 697 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{24}H_{44}NO_3Si_2$ $[M + H]^+$: 450.2854, Found: 450.2835.

(*E*)-5-((4-iodophenyl)carbamoyl)-6-phenylhex-5-en-1-yl 4-methylbenzenesulfonate (64) + (*E*)-7-((4-iodophenyl)amino)-7-oxo-6-phenylhept-5-en-1-yl 4-methylbenzenesulfonate (64a):

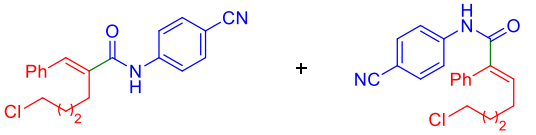


(80:20)

Subjection of 6-phenylhex-5-yn-1-yl 4-methylbenzenesulfonate (0.5 mmol, 0.164 g) and 1-iodo-4-isocyanatobenzene (0.5 mmol, 0.123 g) to general procedure A afforded a partially separable mixture of regioisomers

(80/20, crude), 0.129 g (45%) of **30** as a colorless oil, and 0.113 g (39%) of **64** + **64a** (79/21) as a colorless stick oil after flash chromatography (Hex/EtOAc: 95/5, 90/10, 85/15, 80/20); (E)-5-((4-iodophenyl)carbamoyl)-6-phenylhex-5-en-1-yl 4-methylbenzenesulfonate (**64**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.4 Hz, 3H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.43 (m, 4H), 7.32 (d, *J* = 7.6 Hz, 4H), 7.29 (s, 1H), 7.25 (s, 1 H), 4.03 (t, *J* = 6.4 Hz, 2H), 2.61 (t, *J* = 7.6 Hz, 2H), 2.45 (s, 3H), 1.73 (quin, *J* = 6.8 Hz, 2 H), 1.62 (quin, *J* = 7.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 144.8, 138.6, 137.9, 137.8, 135.3, 133.7, 132.9, 129.8, 128.8, 128.6, 128.3, 127.8, 121.9, 87.6, 70.0, 28.7, 27.2, 24.6, 21.6; IR (neat) 3281, 2922, 1649, 1501, 1391, 1173, 933, 577 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{26}H_{27}INO_4S$ $[M + H]^+$: 576.0700, Found: 576.0690; (*E*)-7-((4-iodophenyl)amino)-7-oxo-6-phenylhept-5-en-1-yl 4-methylbenzenesulfonate (**64a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (bs, 1H), 7.76 (t, *J* = 7.6 Hz, 3H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.52-7.47 (m, 3H), 7.22 (m, 4H), 7.07 (t, *J* = 8 Hz, 1H), 3.96 (t, *J* = 6 Hz, 2H), 2.47 (s, 3H), 2.0 (q, *J* = 7.2 Hz, 2H), 1.66-1.58 (m, 2H), 1.47 (quin, *J* = 7.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 144.7, 141.9, 137.81, 137.5, 136.5, 134.7, 132.9, 129.7, 129.3, 128.7, 127.8, 121.6, 87.5, 70.0, 29.7, 28.6, 28.3, 24.6, 21.6.

(E)-2-benzylidene-6-chloro-*N*-(4-cyanophenyl)hexanamide (65) + (*E*)-7-chloro-*N*-(4-cyanophenyl)-2-phenylhept-2-enamide (65a):

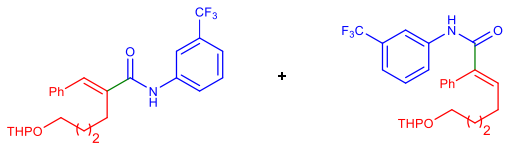


(71:29)

Subjection of (6-chlorohex-1-yn-1-yl)benzene (0.5 mmol, 0.096 g) and 4-cyanophenyl isocyanate (0.5 mmol, 0.072 g) to general procedure A afforded a partially separable mixture of regioisomers (71/29, crude), 0.036 g (22%) of **31** as a pale yellow viscous oil, and 0.048 g (28%) of **65** + **65a** (71/29) as a pale yellow viscous oil after flash chromatography (Hex/EtOAc: 94/6, 92/8, 90/10, 88/12, 86/14); (E)-2-benzylidene-6-chloro-*N*-(4-cyanophenyl)hexanamide (**65**) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.69 (d, *J* = 8.8 Hz,

2H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.35 (m, 2H), 7.30-7.25 (m, 3H), 7.20 (m, 1H), 3.48 (t, *J* = 6.4 Hz, 2H), 2.56 (t, *J* = 8 Hz, 2H), 1.78 (quin, *J* = 6.8 Hz, 2H), 1.69-1.62 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 142.1, 138.2, 135.0, 134.4, 133.3, 128.8, 128.7, 128.6, 119.8, 118.8, 107.1, 44.5, 32.1, 27.0, 25.9; IR (neat) 3298, 3109, 2923, 2223, 1640, 1513, 1320, 843, 688 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{20}H_{20}ClN_2O$ $[M + H]^+$: 339.1259, Found: 339.1256; (*E*)-7-chloro-*N*-(4-cyanophenyl)-2-phenylhept-2-enamide **(65a):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (bs, 1H), 7.46-7.40 (m, 8H), 7.13-7.08 (m, 2H), 3.38 (t, *J* = 6.8 Hz, 2H), 1.99 (q, *J* = 6.8 Hz, 2H), 1.66 (quin, *J* = 6.4 Hz, 2H), 1.52 (quin, *J* = 7.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5, 143.3, 141.7, 138.3, 136.1, 135.1, 133.1, 129.7, 129.5, 128.9, 119.6, 107.1, 44.4, 31.9, 28.7, 25.9.

(*E*)-2-benzylidene-6-((tetrahydro-2*H*-pyran-2-yl)oxy)-*N*-(3-(trifluoromethyl)phenyl)hexanamide (66):

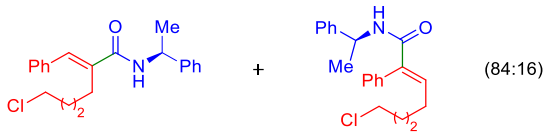


(84:16)

Subjection of 2-((6-phenylhex-5-yn-1-yl)oxy)tetrahydro-2H-pyran (0.5 mmol, 0.129 g) and 3-trifluoromethylphenyl isocyanate (0.5 mmol, 0.069 mL) to general procedure A afforded a partially separable mixture of regioisomers (84/16, crude), 0.091 g (41%) of **66** as a clear oil, and 0.056 g (25%) of **66 + 66a** (74/26) as a clear oil after flash chromatography (Hex/EtOAc: 95/5, 90/10, 88/12); (*E*)-2-benzylidene-6-((tetrahydro-2*H*-pyran-2-yl)oxy)-*N*-(3-(trifluoromethyl)phenyl)hexanamide **(66):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.94 (s, 1H), 7.87 (d, *J* = 8 Hz, 1H), 7.52-7.46 (m, 1H), 7.42 (m, 3H), 7.34 (m, 4H), 4.56 (m, 1H), 3.89-3.84 (m, 1H), 3.82-3.78 (m, 1H), 3.48 (m, 2H), 2.69 (m, 2H), 1.71 (m, 5H), 1.52 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 143.5, 138.6, 138.49, 138.5, 134.0, 129.8, 129.5, 128.9, 128.5, 128.2, 123.35, 123.34, 120.9, 120.88, 120.84, 117.0, 116.9, 99.3, 67.0, 62.9, 30.8, 29.4, 27.5, 25.6, 25.3, 19.9; IR (neat) 3295, 2940, 2867, 1653, 1538, 1440, 1330, 1121, 795, 696 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{25}H_{29}F_3NO_3$ $[M + H]^+$: 448.2094, Found: 448.2093; (*E*)-2-phenyl-7-((tetrahydro-2*H*-pyran-2-yl)oxy)-*N*-(3-

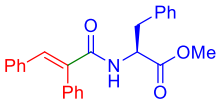
(trifluoromethyl)phenyl)hept-2-enamide (**66a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.62 (s, 1H), 7.55 (d, *J* = 8 Hz, 1H), 7.45-7.38 (m, 2H), 7.33-7.24 (m, 2H), 7.19 (m, 2H), 7.12 (t, *J* = 8 Hz, 1H), 7.06 (bs, 1H), 4.46 (m, 1H), 3.79-3.69 (m, 2H), 3.65-3.56 (m, 1H), 3.40 (m, 2H), 3.27-3.22 (m, 1H), 2.0 (q, *J* = 6.8 Hz, 2H), 1.61 (m, 3H), 1.48 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8, 143.4, 138.3, 135.7, 135.5, 134.8, 134.0, 131.5, 131.4, 131.1, 129.4, 129.3, 128.6, 128.5, 123.4, 122.9, 120.72, 120.73, 120.77, 120.8, 120.7, 120.7, 117.0, 117.0, 116.9, 116.63, 116.59, 116.55, 116.51, 98.8, 67.0, 62.2, 30.7, 29.7, 29.3, 25.5, 25.4, 19.5.

(*S*,*E*)-2-benzylidene-6-chloro-*N*-(1-phenylethyl)hexanamide (67) + (*S*,*E*)-6-chloro-2-phenyl-*N*-(1-phenylethyl)hex-2-enamide (67a):



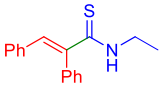
Subjection of (6-chlorohex-1-yn-1-yl)benzene (0.5 mmol, 0.096 g) and (*S*)-(-)-α-methylbenzyl isocyanate (0.5 mmol, 0.070 mL) to general procedure A afforded an inseparable mixture of regioisomers (84/16, crude), 0.133 g (78%) of **67** as a white solid after flash chromatography (Hex/EtOAc: 93/7, 90/10, 88/12, 85/15); m.p. = 58-60 °C; (*S*,*E*)-2-benzylidene-6-chloro-*N*-(1-phenylethyl)hexanamide (**67**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.38 (m, 5H), 7.34-7.29 (m, 5H),7.14 (s, 1H), 6.16 (d, *J* = 7.2 Hz, 1H), 5.27 (quin, *J* = 6.8 Hz, 1H), 3.53 (t, *J* = 6.4 Hz, 2H), 2.57 (t, *J* = 8 Hz, 2H), 1.81 (quin, *J* = 7.2 Hz, 2H), 1.72-1.65 (m, 2H), 1.61 (d, *J* = 1.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 143.2, 138.5, 135.8, 132.5, 128.74, 128.73, 128.47, 127.9, 127.4, 126.2, 49.1, 44.6, 32.1, 27.0, 25.9, 21.7; IR (neat) 3293, 2928, 1637, 1519, 758, 696 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{21}H_{25}ClNO$ $[M + H]^+$: 342.1619, Found: 342.1617; (*S*,*E*)-6-chloro-2-phenyl-*N*-(1-phenylethyl)hex-2-enamide (**67a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.38 (m, 5H), 7.34-7.29 (m, 3H),7.21 (m, 2H), 7.04 (t, *J* = 7.6 Hz, 1H), 5.59 (d, *J* = 7.6 Hz, 1H), 5.21 (quin, *J* = 7.2 Hz, 1H), 3.45 (t, *J* = 6.4 Hz, 2H), 2.03 (q, *J* = 7.2 Hz, 2H), 1.81 (quin, *J* = 7.2 Hz, 2H), 1.72-1.65 (m, 2H), 1.40 (d, *J* = 6.8 Hz, 3H).

methyl (*E*)-(2,3-diphenylacryloyl)-L-phenylalaninate (68):



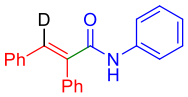
Subjection of diphenylacetylene (0.5 mmol, 0.089 g) and methyl (S)-2-isocyanato-3-phenylpropanoate (0.5 mmol, 0.091 mL) to general procedure A afforded 0.164 g (85%) of **68** as a colorless paste after flash chromatography (Hex/EtOAc: 90/10, 85/15, 80/20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.41-7.36 (m, 3H), 7.20 (m, 3H), 7.17-7.10 (m, 5H), 6.99 (m, 2H), 6.92 (m, 2H), 5.87 (d, *J* = 7.6 Hz, 1H), 4.93 (q, *J* = 7.6 Hz, 1H), 3.70 (s, 1H), 3.07 (dq, *J* = 26.4, 6.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 166.5, 137.5, 135.6, 134.7, 133.8, 130.4, 129.7, 129.5, 129.0, 128.6, 128.52, 128.49, 128.1, 127.0, 53.5, 52.3, 37.5; IR (neat) 3410, 3026, 2950, 1741, 1664, 1615, 1497, 1201, 752, 692 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{25}H_{24}NO_3$ $[M + H]^+$: 386.1751, Found: 386.1742.

(*E*)-*N*-ethyl-2,3-diphenylprop-2-enethioamide (69):



Subjection of diphenylacetylene (0.5 mmol, 0.089 g) and ethylisothiocyanate (1.0 mmol, 0.088 mL) to general procedure A afforded 0.088 g (66%) of **69** as a yellow solid after flash chromatography (Hex/EtOAc: 98/2, 96/4, 94/6); the reaction mixture was stirred at -78 °C for 12 hours; m.p. = 72-74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.55-7.42 (m, 3H), 7.38-7.31 (m, 1H), 7.22 (m, 2H), 7.18-7.09 (m, 3H), 7.0-6.95 (m, 2H), 3.80-3.73 (m, 2H), 1.16 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.9, 141.0, 139.6, 135.8, 135.2, 130.5, 130.2, 129.8, 128.8, 128.0, 41.6, 13.1; IR (neat) 3162, 2923, 2852, 1520, 1444, 1386, 752, 716 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{17}H_{18}NS$ $[M + H]^+$: 268.1154, Found: 268.1146.

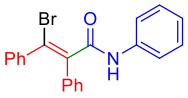
(*E*)-*N*,2,3-triphenylacrylamide-3-*d* (70):



diphenylacetylene (0.5 mmol, 0.089 g) and phenylisocyanate (0.5 mmol, 0.055 mL) was subjected to general procedure A with the following modification, the reaction mixture was quenched with D_2O (1.35 mL), affording 0.125 g (83%) of **70** as a white

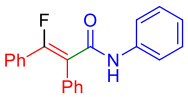
solid after flash chromatography (Hex/EtOAc: 99/1, 98/2, 97/3, 96/4); m.p. = 132-134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 0.04H, >95% D incorporation), 7.51 (m, 3H), 7.44 (m, 2H), 7.37 (m, 2H), 7.30 (t, *J* = 8 Hz, 2H), 7.16 (m, 4H), 7.09 (t, *J* = 7.2 Hz, 1H), 7.05 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 137.8, 135.8, 134.7, 134.4, 130.4, 130.0, 129.9, 128.9, 128.9, 128.8, 128.2, 124.4, 119.8; IR (neat) 3280, 3057, 1640, 1531, 1439, 787, 687 cm^{-1}; HRMS (ESI) *m/z* $[M + H]^+$ Calcd for $C_{21}H_{17}DNO$ 301.1446, Found: 301.1435.

(*Z*)-3-bromo-*N*,2,3-triphenylacrylamide (71):



diphenylacetylene (0.5 mmol, 0.089 g) and phenylisocyanate (0.5 mmol, 0.055 mL) were subjected to general procedure A with the following modification, after consumption of the starting material (~1 h) NBS (1.0 mmol, 0.178 g) was added and the reaction mixture was slowly warmed up to RT over 12 hours, affording 0.137 g (73%) of **71** as a white solid after flash chromatography (Hex/EtOAc: 99/1, 98/2, 97/3, 96/4, 95/5); m.p. = 220-222 °C; ^{1}H NMR (400 MHz, CDCl3) δ 7.60 (d, *J* = 7.6 Hz, 2H), 7.36 (m, 3H), 7.28 (m, 2H), 7.23-7.14 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 139.7, 138.6, 137.4, 135.2, 129.8, 129.1, 128.9, 128.9, 128.5, 128.2, 128.2, 124.8, 123.6, 120.1; IR (neat) 3230, 1647, 1537, 1442, 1324, 752, 691 cm^{-1}; HRMS (ESI) *m/z* $[M + H]^+$ Calcd for $C_{21}H_{17}BrNO$ 378.0488, Found: 378.0479, 380.0456.

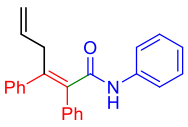
(*Z*)-3-fluoro-*N*,2,3-triphenylacrylamide (72):



diphenylacetylene (0.5 mmol, 0.089 g) and phenylisocyanate (0.5 mmol, 0.055 mL) were subjected to general procedure A with the following modification, after consumption of the starting material (~1 h) *N*-fluorosulfonimide (1.0 mmol, 0.315 g) was added and the reaction mixture was warmed up to 45 °C and stirred for 12 hours, affording 0.034 g (27%) of **72** as a white solid after flash chromatography (Hex/EtOAc: 95/5, 93/7); m.p. = 175-177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (bs, 1H), 7.59-7.43 (m, 2H), 7.38-7.13 (m, 11H),

7.07-6.94 (m, 2H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 137.8, 130.4, 130.3, 130.1, 129.0, 128.9, 128.8, 128.7, 128.4, 128.1, 124.5, 119.9, 100.0; ^{19} F NMR (400 MHz, $CDCl_3$) δ -94.16 (d, *J* = 5.2 Hz, 1F); IR (neat) 3282, 3056, 2922, 1644, 1598, 1441, 1333, 755, 688 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{21}H_{17}FNO$ $[M + H]^+$: 318.1289, Found: 318.1289.

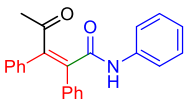
(*E*)-*N*,2,3-triphenylhexa-2,5-dienamide (73):



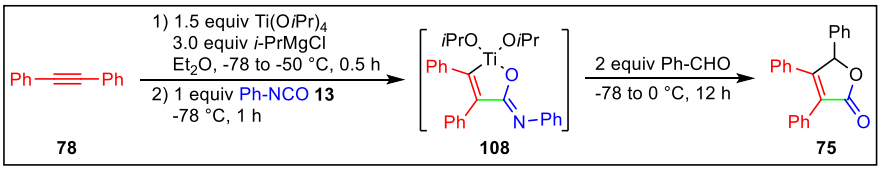
diphenylacetylene (0.5 mmol, 0.089 g) and phenylisocyanate (0.5 mmol, 0.055 mL) were subjected to general procedure A with the following modification, after consumption of the starting material the round bottom flask was placed in an ice-bath and the reaction mixture was allowed to equilibrate to 0 °C. A freshly prepared solution of CuO*t*Bu (0.5 mmol, 0.25 M in THF, 2 mL) was injected and the mixture was stirred for 10 minutes, followed by the addition of allyl bromide (25 mmol, 0.218 mL). The reaction mixture was then stirred at RT for 3 hours and worked up per procedure A affording 0.067 g (53%) of **73** as a white solid after flash chromatography (Hex/EtOAc: 97/3, 96/4, 95/5); m.p. = 155-157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (m, 2H), 7.37-7.29 (m, 2H), 7.17-7.07 (m, 12H), 5.95-5.85 (m, 1H), 5.08 (m, 2H), 3.58 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 144.0, 140.4, 137.8, 137.1, 136.0, 135.3, 130.5, 130.0,129.1, 129.0, 128.3, 128.0, 127.4, 127.2, 124.4, 116.6, 40.7; IR (neat) 3267, 2923, 1647, 1437, 905, 757 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{24}H_{22}NO[M + H]^+$: 340.1696, Found: 340.1700.

Preparation of CuOtBu: an oven dried 2-5 mL microwave vial was charged with CuI (0.5 mmol, 0.096 g) sealed and placed under an atmosphere of argon. Dry THF (1 mL) was injected and the vial was place in an ice-bath. A solution of NaOtBu (0.525 mmol, 0.051 g) dissolved in THF (1 mL) was then injected dropwise and the mixture was stirred for 30 minutes. At which point the mixture was taken up into a 5 mL syringe with a 4 inch 22G needle for transfer into the above reaction flask.

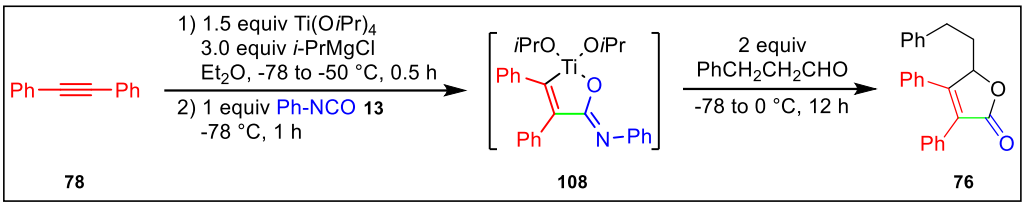
(*Z*)-4-oxo-*N*,2,3-triphenylpent-2-enamide (74):



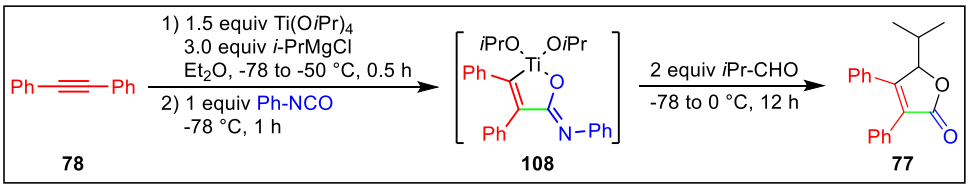
diphenylacetylene (0.5 mmol, 0.089 g) and phenylisocyanate (0.5 mmol, 0.055 mL) were subjected to general procedure A with the following modification, after consumption of the starting material (~1 h) acetyl chloride (2.5 mmol, 0.178 mL) was added dropwise and the reaction mixture was slowly warmed to 0 °C over 12 hours, affording 0.062 g (36%) of **74** as a pale yellow paste after flash chromatography (Hex/EtOAc: 95/5, 93/7, 90/10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 1H), 7.24-7.10 (m, 9H), 7.00 (d, *J* = 8 Hz, 2H), 6.85-6.80 (m, 4H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 173.3, 138.6, 137.8, 137.7, 134.9, 134.6, 130.1, 129.3, 128.5, 128.4, 128.1,127.8, 127.8, 25.6; IR (neat) 3236, 3059, 2980, 1697, 1257, 1091, 756, 690 cm^{-1}; HRMS (ESI) *m/z* Calcd for $C_{23}H_{20}NO_2$ $[M + H]^+$: 342.1489, Found: 342.1489.



3,4,5-triphenylfuran-2(5*H*)-one (75): diphenylacetylene (0.5 mmol, 0.089 g) and phenylisocyanate (0.5 mmol, 0.055 mL) were subjected to general procedure A with the following modification, after consumption of the starting material (~1 h) benzaldehyde (1.0 mmol, 0.102 mL) was added dropwise and the reaction mixture was slowly warmed to 0 °C over 12 hours, affording 0.156 g (77%) of **75** as a pale yellow paste after flash chromatography (Hex/EtOAc: 97/3, 95/5, 92/8); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (m, 3H), 7.29-7.18 (m, 11H), 7.15-7.08 (m, 3H), 7.03 (d, *J* = 7.2 Hz, 3H), 6.19 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 159.3, 134.8, 131.1, 129.9, 129.8, 129.4, 129.4, 128.9, 128.8, 128.7, 128.5, 128.3, 127.6, 126.9, 83.7; IR (neat) 3470, 3376, 3062, 2922, 1747, 1156, 745, 694 cm^{-1}; HRMS (ESI) *m/z* $[M + H]^+$ Calcd for $C_{22}H_{17}O_2$ 313.1223, Found: 313.1222.



5-phenethyl-3,4-diphenylfuran-2(5*H*)-one (76): diphenylacetylene (0.5 mmol, 0.089 g) and phenylisocyanate (0.5 mmol, 0.055 mL) were subjected to general procedure A with the following modification, after consumption of the starting material (~1 h) 3-phenylpropionaldehyde (1.0 mmol, 0.132 mL) was added dropwise and the reaction mixture was slowly warmed to 0 °C over 12 hours, affording 0.096 g (57%) of **76** as a pale brown solid after flash chromatography (Hex/EtOAc: 97/3, 95/5, 92/8); m.p. = 93-95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 3H), 7.25 (m, 5H), 7.19 (m, 2H), 7.11 (m, 1H), 7.06 (m, 4H), 5.35 (dd, *J* = 5.6, 2,8 Hz, 1H), 2.78-2.69 (m, 2H), 2.10-2.02 (m, 1H), 1.78-1.69 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) 172.4, 160.4, 140.5, 131.1, 130.1, 129.8, 129.3, 129.0, 128.6, 128.5, 128.5, 128.5, 128.0, 126.6, 126.2, 80.6, 34.8, 31.0; IR (neat) 2920, 1730, 1259, 1018, 796, 715 cm^{-1}; HRMS (ESI) *m/z* $[M + H]^+$ Calcd for $C_{24}H_{21}O_2$ 341.1536, Found: 341.1529.



5-isopropyl-3,4-diphenylfuran-2(5*H*)-one (77): diphenylacetylene (0.5 mmol, 0.089 g) and phenylisocyanate (0.5 mmol, 0.055 mL) were subjected to general procedure A with the following modification, after consumption of the starting material (~1 h) isobutyraldehyde (1.0 mmol, 0.091 mL) was added dropwise and the reaction mixture was slowly warmed to 0 °C over 12 hours, affording 0.084 g (60%) of **77** as a yellow solid after flash chromatography (Hex/EtOAc: 97/3, 96/4, 95/5, 93/7, 90/10, 87/13); m.p. = 84-86 °C; ^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.30 (m, 5H), 7.23 (m, 3H), 7.16 (m, 2H), 5.31 (d, *J* = 2 Hz, 1H), 1.92 (dsept, *J* = 6.8, 2.0 Hz, 1H), 1.13 (d, *J* = 6.8 Hz, 3H), 0.61 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 159.8, 131.4, 129.9, 129.8, 129.2, 129.0, 128.5, 128.4, 128.0, 127.2, 85.6, 30.1, 20.0, 13.4; IR (neat) 2963, 1726, 1442, 1222, 750, 693 cm^{-1}; HRMS (ESI) *m/z* $[M + H]^+$ Calcd for $C_{19}H_{19}O_2$ 279.1380, Found: 279.1369.

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CHAPTER III

Ni/Ti DUAL CATALYTIC CROSS-COUPLING OF NITRILES AND ORGANOBROMIDES TO ACCESS KETONES

3.1. INTRODUCTION

Transition-metal-catalyzed cross-coupling reactions have become an invaluable tool in the synthesis of complex molecules. This process to bond formation has found widespread use in the synthesis of drug candidates,[1] materials, and natural products in part due to its high selectivity, predictable connectivity patterns, and versatility to form C–C and C–heteroatom bonds in numerous variations. Society's ever-growing need for sustainability has directed the expansion of cross-coupling reactions to meet this challenge. This can be accomplished through the use of earth-abundant metals; in addition, the use of in situ generated carbon radicals as coupling partners has emerged as an alternative to preformed organometallic reagents. Owing to the fact that nickel can readily adjust its oxidation state between Ni^0, Ni^I, Ni^{II}, and Ni^{III}, and evidence that nickel catalyzed cross-couplings occur through radical intermediates, nickel is an ideal metal for cross-coupling carbon radicals.[2] For this approach to be successful, the radicals would need to be generated catalytically to minimize undesired radical pathways. Major advancements in catalytic radical formation has occurred with titanium,[3-5] cobalt,[6,7] copper,[8,9] and iron,[10,11] in addition to photoinduced electron transfer.[12-16] Thus, the development of

dual catalysis approaches with a nickel catalyst and a radical generating catalyst can enable new bond-forming processes.

In the past three years, the merger of nickel and photoredox catalysis has seen rapid progress.[17-20] Catalytic radical generation can also be accomplished with transition metals, yet the development of Ni/Ti, Ni/Co or Ni/Fe dual catalysis has remained nearly unexplored.[21, 22] Exploration into these dual radical cross-couplings would greatly enhance the pool of viable coupling partners and enable bond formations between functional groups that would otherwise not be possible. Titanium has been demonstrated to generate carbon-centered radicals from epoxides,[23, 24] oxetanes, ozonides, aldehydes,[25] ketones, aziridines,[26] imines, allylic-, propargylic-, and alkyl-halides.[3,23-26] Building off this work, Cuerva has shown that titanium and nickel catalysis can be combined for an Oppolzer type cyclization with allylic carbonates, allylations, and the conjugate addition of aryl and alkenyl halides to α,β- unsaturated carbonyls.[27-29] A dual Ni/Ti cross-coupling of aryl halides and epoxides has also been accomplished.[30, 31] Radical additions to polar π-bonds, such as a nitrile, is typically an unfavorable process; however, activation of the nitrile with titanium can overcome this barrier. Titanium(III) catalysts have been shown to catalyze the coupling of nitriles to epoxides[32-35] and ketones through a radical pathway.[36-38] The activation of a nitrile for reaction with organohalides has yet to be accomplished. The ability to cross-couple an organohalide with a nitrile would give direct access to imines or ketones after hydrolysis.

3.2. IMPORTANCE AND APPROACHES TO ACCESS KETONES

As ketones are a ubiquitous functional group that can be found in fine and agro chemicals, pharmaceuticals, materials/polymers, natural products, and are versatile building blocks, we sought to develop a dual Ni/Ti cross-coupling of nitriles. Due to their importance, a number of approaches have been developed for ketone synthesis. Modern cross-coupling approaches have

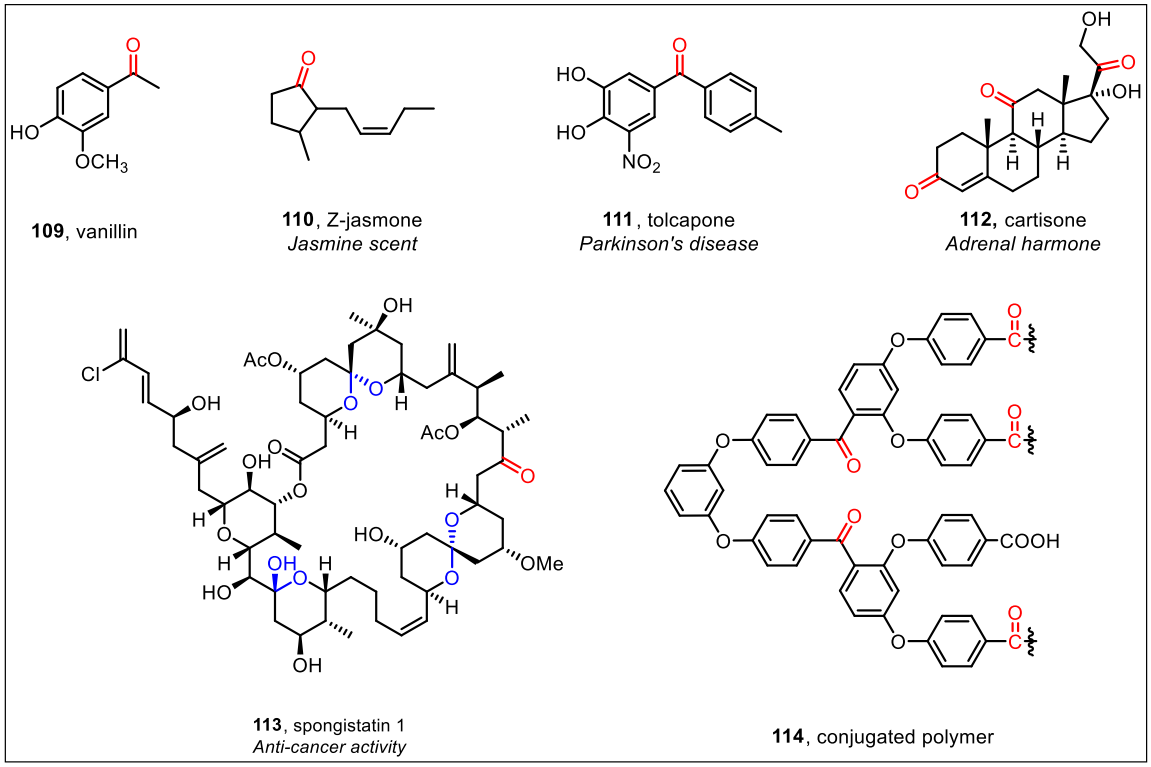
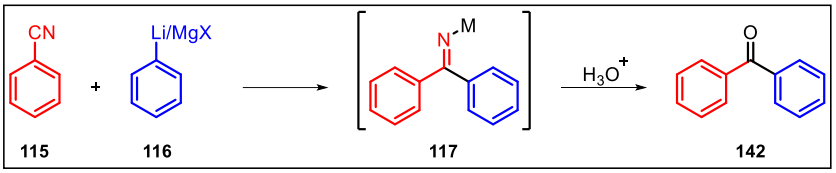


Fig. 3.1. Prevalence of ketones in natural products and materials.

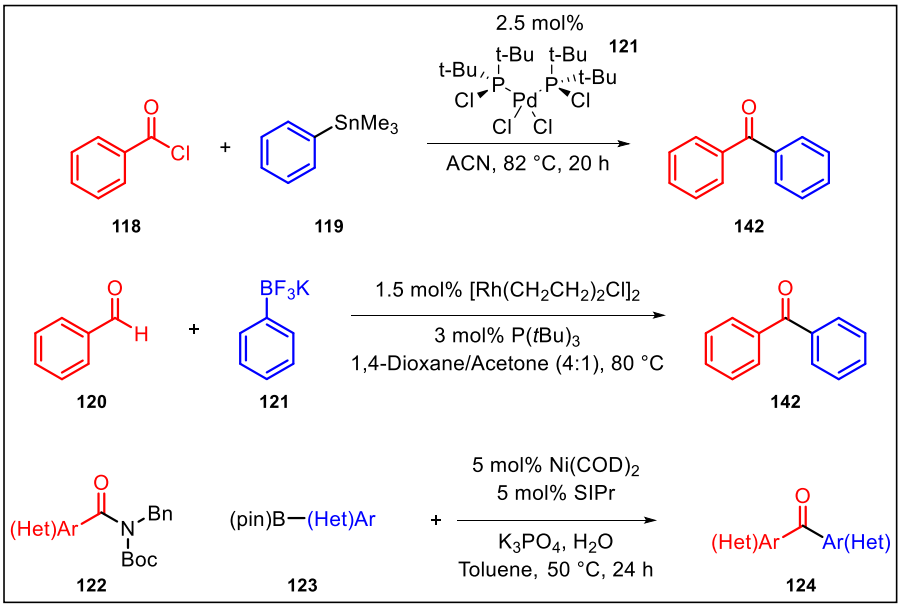
been Stille couplings with acyl chlorides,[39] carbonylation of aryl halides with an organometallic reagent,[40] transition metal catalyzed coupling of nitriles with organoboron reagents,[41-45] metallaphotoredox couplings,[46-48] decarboxylative couplings,[49] and a cross-electrophile coupling with acyl chlorides.[50, 51] Although these methods complement each other, they do have features that may detract from their use, such as the use of highly reactive acid chloride coupling partners, toxic reagents (tin reagents or carbon monoxide), preformed organometallic reagents, limited selection of coupling partners, and/or starting materials that need to be prepared. Direct access to ketones from nitriles has been accomplished with harsh organometallic reagents (Scheme 3.1).

Scheme 3.1. Synthesis of ketones from nitriles with Grignard/lithium reagents

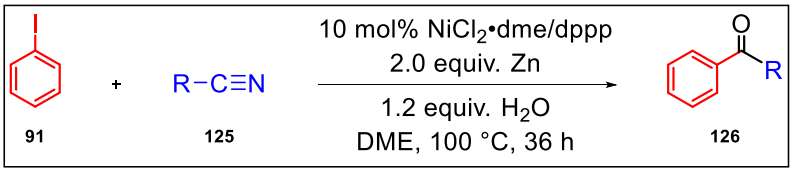


Hsieh has also shown that nickel can catalyze the insertion of aryl iodides to nitriles, but this method is limited to aryl iodides, requires elevated temperatures, and prolonged reaction times (Scheme 3.3).[52]

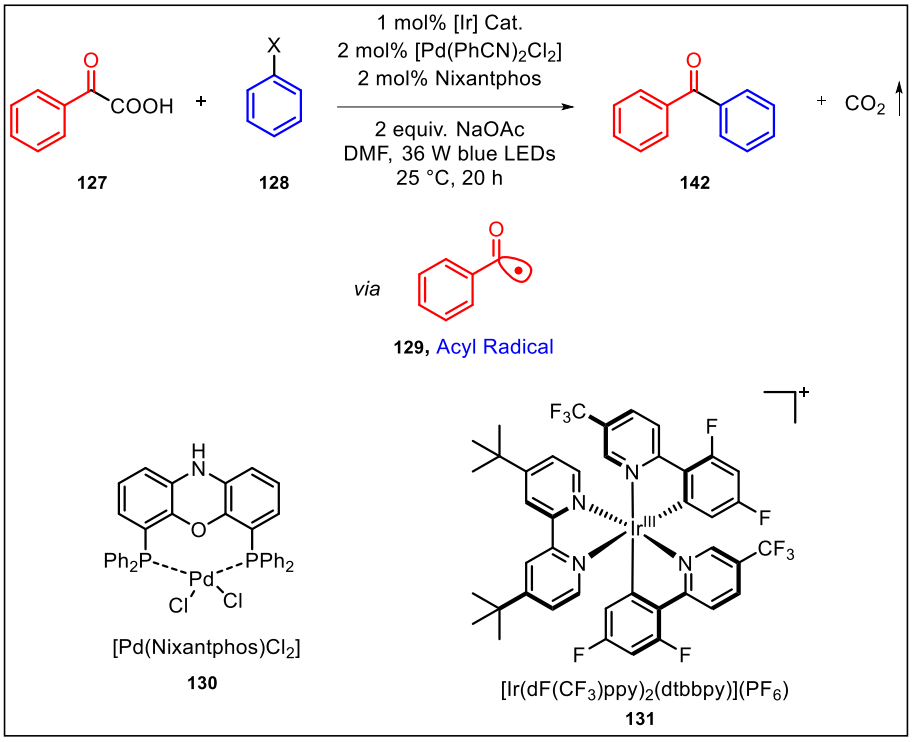
Scheme 3.2. Cross-coupling methods to access ketones



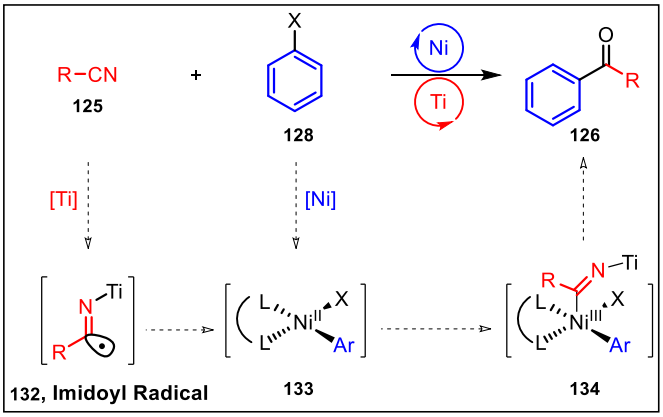
Scheme 3.3. Nickel catalyzed insertion of nitriles with aryl iodides



Scheme 3.4. Dual catalytic approach using ketoacids

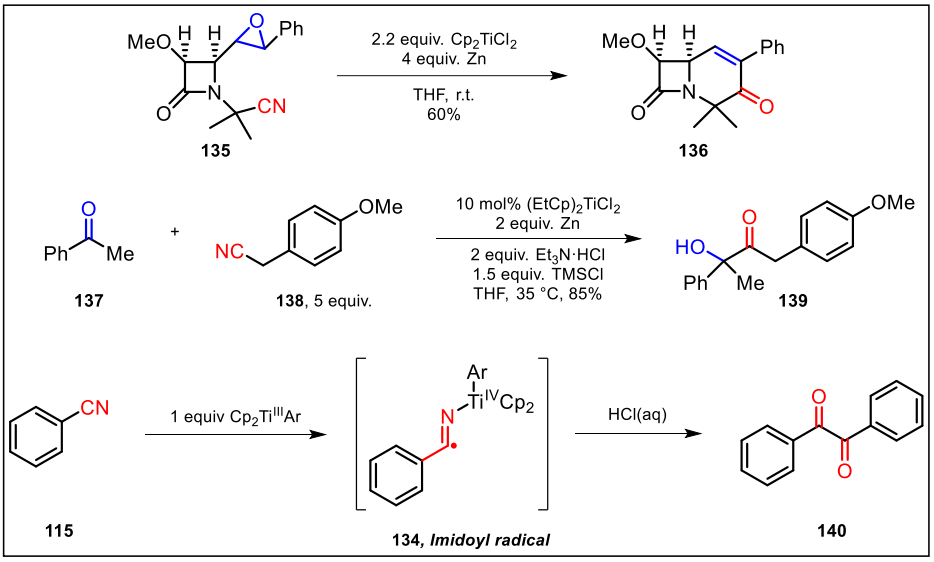


Scheme 3.5. Our dual catalytic approach using organobromides



In light of these limitations and the power to directly couple an organohalide with a nitrile to access imines or ketones, we questioned if activation of the nitrile with a titanium(III) catalyst would enable a nickel catalyzed crosscoupling with organobromides. It was reasoned that

Scheme 3.6. Activation of nitriles with titanium



the titanium(III) catalyst could coordinate to the nitrile and either activate the nitrile for reaction with a nickel intermediate or generate an imidoyl radical that would be trapped by a nickel(II) intermediate, thereby facilitating a cross-coupling (Scheme 3.5).

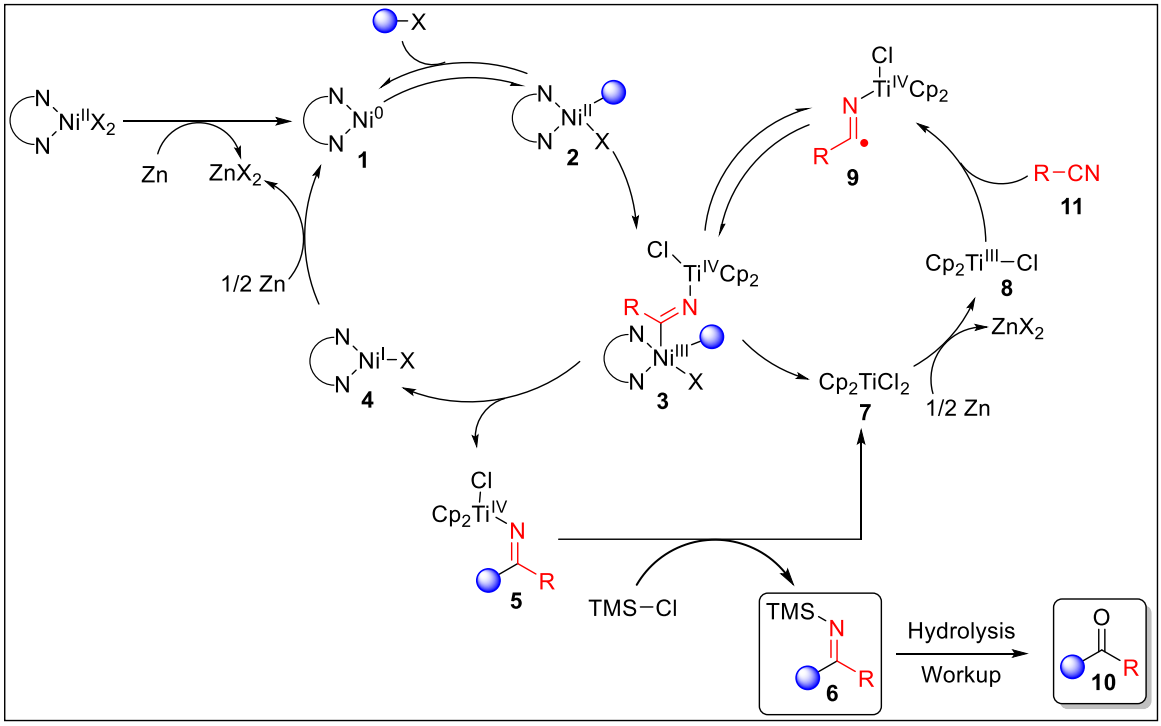
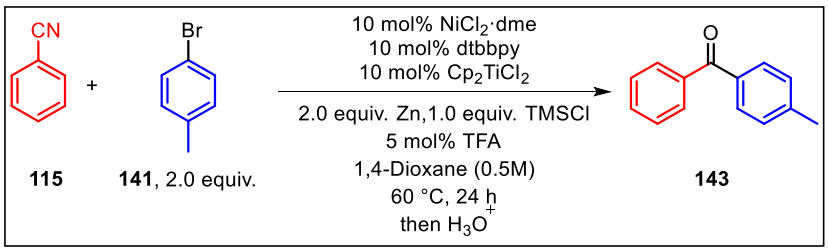


Fig 3.2. Proposed mechanism for the dual catalytic cross-coupling of nitriles with organobromides

3.3. RESULTS AND DISCUSSION

3.3.1. Optimization of reaction conditions

Table 3.1. Optimization of reaction conditions for the cross-coupling of nitriles with organobromides



Entry	Deviation from Conditions Above	Yield (%)
1	none	69
2	1 equiv. ArBr instead of 2 equiv.	61
3	Mn instead of Zn	<1%
4	no Zn metal	0
5	no TFA	60
6	Et_3N•HCl instead of TMS-Cl	<1%
7	no TMS-Cl	0
8	no Cp_2TiCl_2	0
9	no $NiCl_2$•DME	0
10	no Cp_2TiCl_2 & $NiCl_2$•DME	0

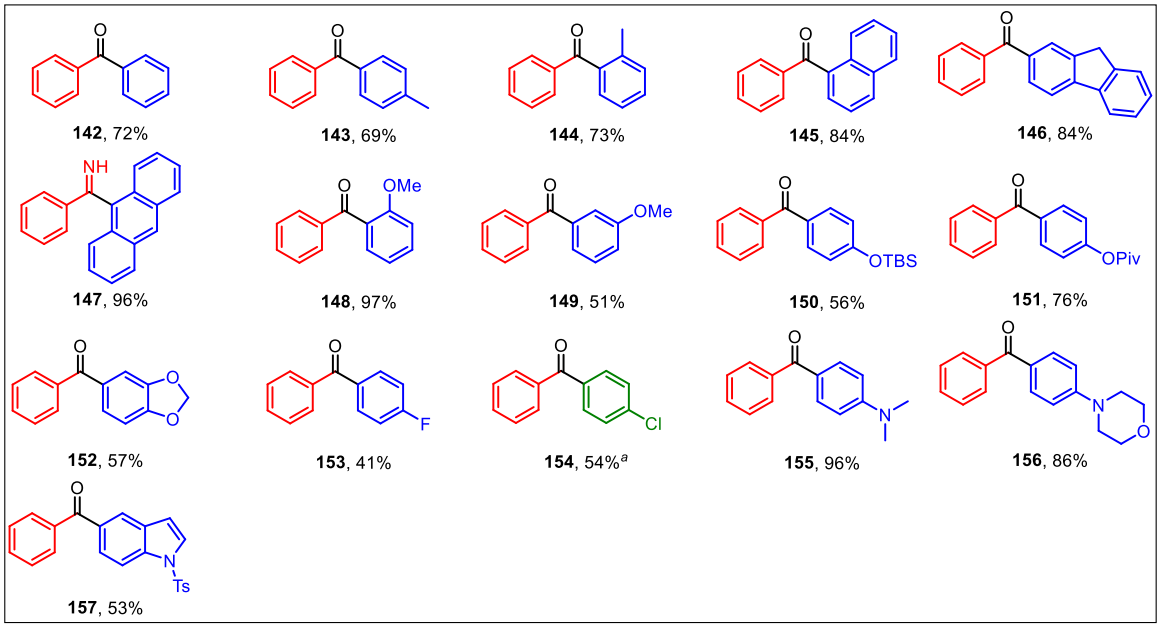
To test the feasibility of coupling an aryl bromide with a nitrile under Ni/Ti dual catalysis, we explored the coupling of 4-bromotoluene and benzonitrile (Table 3.1). As expected, our hypothesis was proven correct, and the benzophenone derivative was obtained after hydrolysis of the reaction mixture. In the process of optimizing the reaction, it was determined that for optimal yields 2 equiv of the aryl bromide were needed to compensate for undesired homocoupling (entry 2). Manganese metal was found to be an insufficient reductant (entry 3) and in the absence of a reductant no reaction occurred (entry 4). It has been found in reactions using a metal reductant that the addition of a catalytic amount of acid can improve the yields, which is theorized to be a result of the acid cleaning the surface of the metal.[53] We found that addition of a catalytic amount of trifluoroacetic acid (TFA) improved the yield of the coupled product (entry 5). Mechanistically, we conjectured that in the process of the coupling reaction, a titanium(IV)

coordinated imine would be generated. In order to be able to turn over the titanium catalyst, an amine salt or trimethylchlorosilane would need to be used as an additive. Under these conditions, only TMS–Cl was found to be competent in turning over the titanium catalyst (entry 6), and in its complete absence, none of the ketone was formed (entry 7). Control reactions were run to establish that the reaction was occurring through a dual catalytic pathway and not via a nickel catalyzed insertion. In the absence of either the titanium (entry 8) or nickel catalyst (entry 9), no reaction took place. Formation of an arylzinc intermediate from the metal reductant was discounted because no product was formed in absence of the nickel and/or titanium catalyst (entries 8−10).

3.3.2. Substrate screening

With these results in hand, substrate screening was conducted, thus demonstrating that the system can cross couple a broad scope of aryl- and aliphatic-bromides with aryl and aliphatic-nitriles (Tables 3.2, 3.3, 3.4, 3.5). The system tolerated electron-donating groups on the aryl bromide component regardless of position; however, moderate electron-withdrawing groups on the aryl bromide resulted in slightly lower yields (Table 3.2, **153** and **154**).

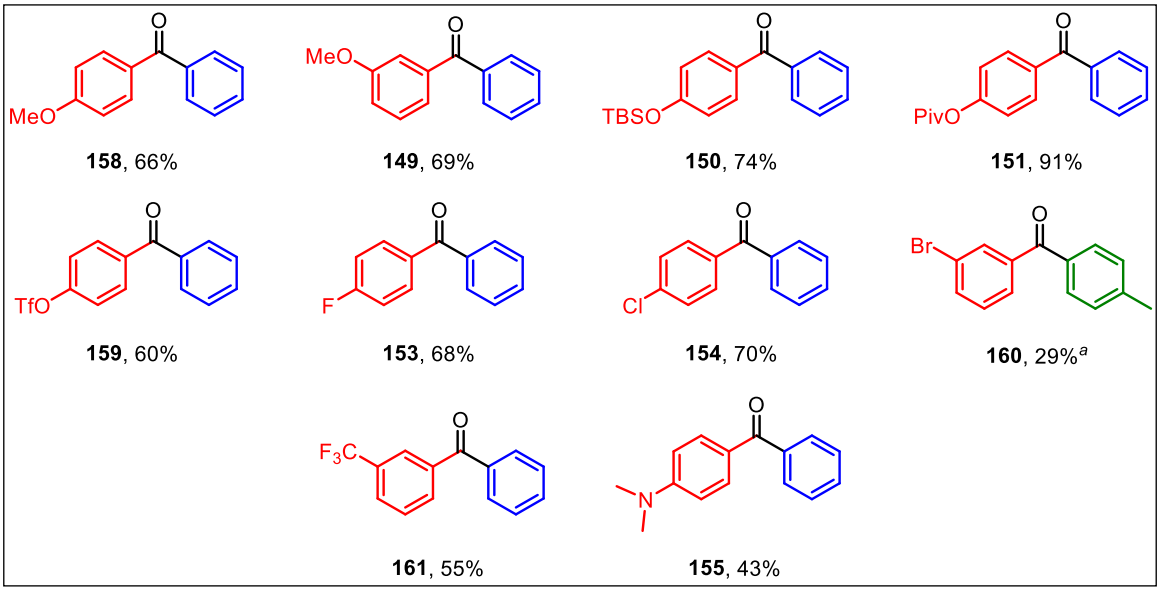
Table 3.2. Substrate scope of aryl bromides



[a] 1-chloro-4-iodobenzene was used.

Strong electron-withdrawing groups, such as $-CF_3$, inhibited the coupling, whereas the benzonitrile component was not affected by the electronic nature of the substituent on the aryl ring.

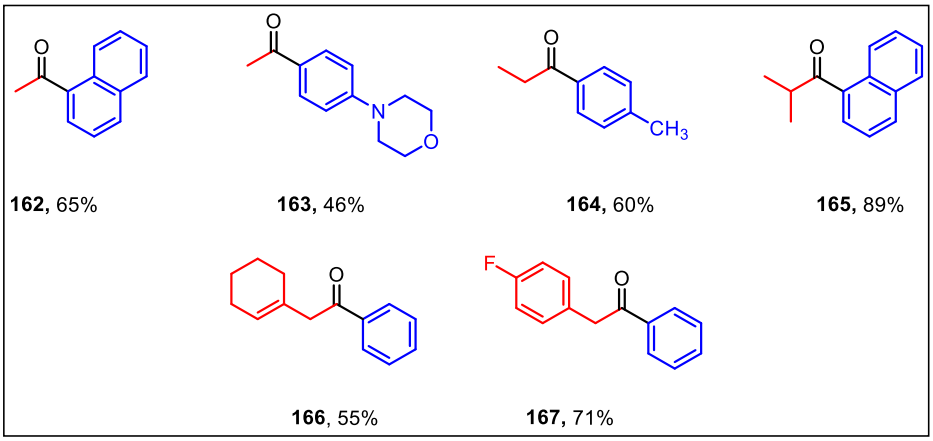
Table 3.3. Substarate scope of benzonitriles



[a] 4-Iodotoluene was used.

However, ortho-substituents inhibited the coupling, presumably from either steric shielding inhibiting complexation of the nitrile with the titanium(III) or reaction of the resultant titanium-nitrile complex/imidoyl radical.

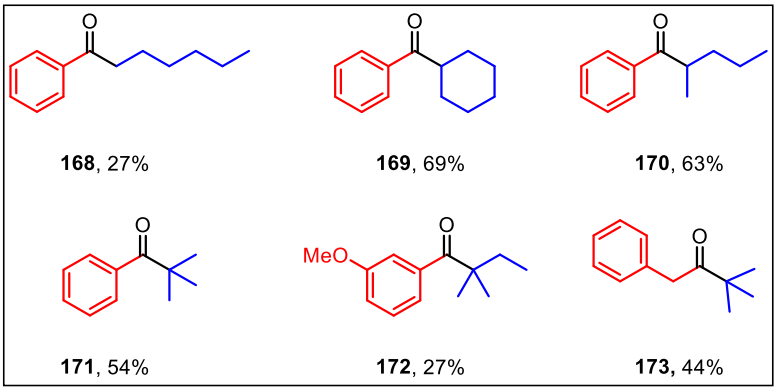
Table 3.4. Substrate scope of aliphatic nitriles



It was found that alkyl nitriles were slightly less reactive but simply raising the loading of the titanium catalyst to 20 mol % increased the yield of the ketone products. The system was

capable of coupling acetonitrile to access methyl ketones (Table 3.4, **162** and **163**), along with primary and secondary alkyl–, allylic–, and benzylic–nitriles (**164**–**167**).

Table 3.5. Substrate scope of aliphatic bromides



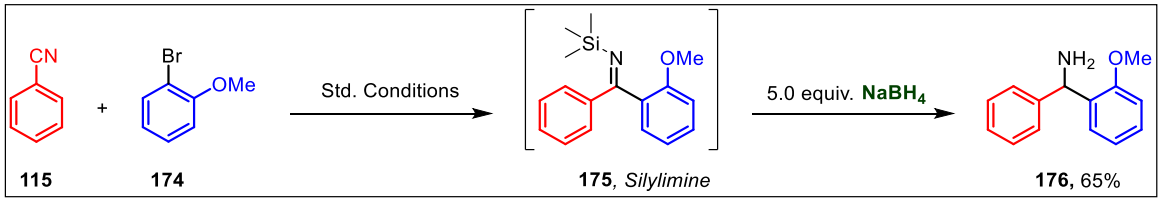
One of the positive attributes of nickel-catalyzed cross-couplings is the potential ability to use alkyl halides as coupling partners. Gratifyingly, it was demonstrated that our system was also capable of cross-coupling alkyl bromides, where secondary aliphatic bromides resulted in highest yields (**168**–**172**). The method was also capable of cross-coupling an alkyl nitrile with a tertiary alkyl bromide (**173**). It is known that activated alkyl bromides can undergo a Blaise reaction with nitriles in the presence of zinc metal.[54] To establish that an alkyl zinc regent was not formed and added to the nitrile, we coupled bromocyclohexane with benzonitrile in the absence of the nickel catalyst, titanium catalyst, and both catalysts. In all cases, no reaction took place, and the nitrile was recovered in near quantitative yield.

The system demonstrated good chemoselectivity, tolerating a variety of functional groups. What is notable was the ability of the system to selectively cross-couple an iodide or bromide in the presence of other functionalizable handles. By lowering the temperature of the reaction, 4-iodotoluene could be selectively coupled with 3-bromobenzonitrile, generating a benzophenone containing a bromine handle (**160**). A bromine could be selectively coupled in the presence of a chloride (**154**) or a pivolate (**151**) on either coupling partner. A bromine was even

selectively coupled in the presence of a reactive triflate (**159**). These examples showcase the potential of this approach to be sequentially combined with other cross coupling methods to rapidly and selectively generate complex molecules.

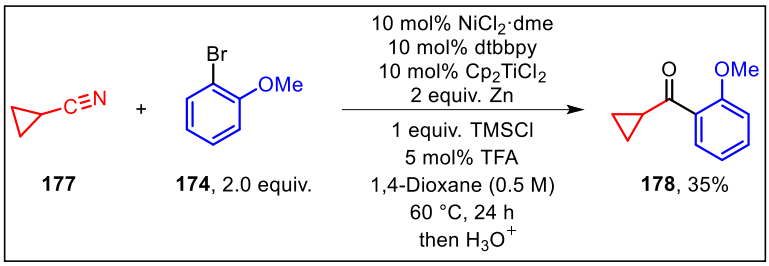
3.3.3. Mechanistic studies

Scheme 3.7. Reduction to confirm formation of silyl-imine



Additional experiments were performed to probe the mechanism of this reaction. It was envisioned that the coupling would produce a titanium imine complex that would be turned over by the TMS–Cl regenerating the titanocene and a TMS silyl imine. Replacing the aqueous quench with $NaBH_4$ resulted in the isolation of α-disubstituted methyl amine (Scheme 3.7), thus corroborating the generation of a TMS–silyl imine.[38]

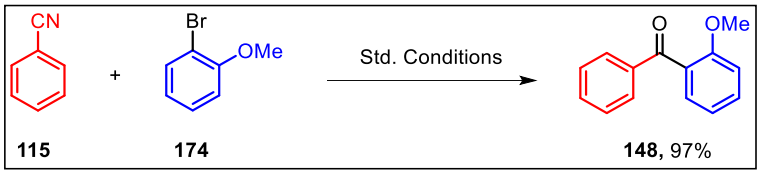
Scheme 3.8. Radical clock experiment

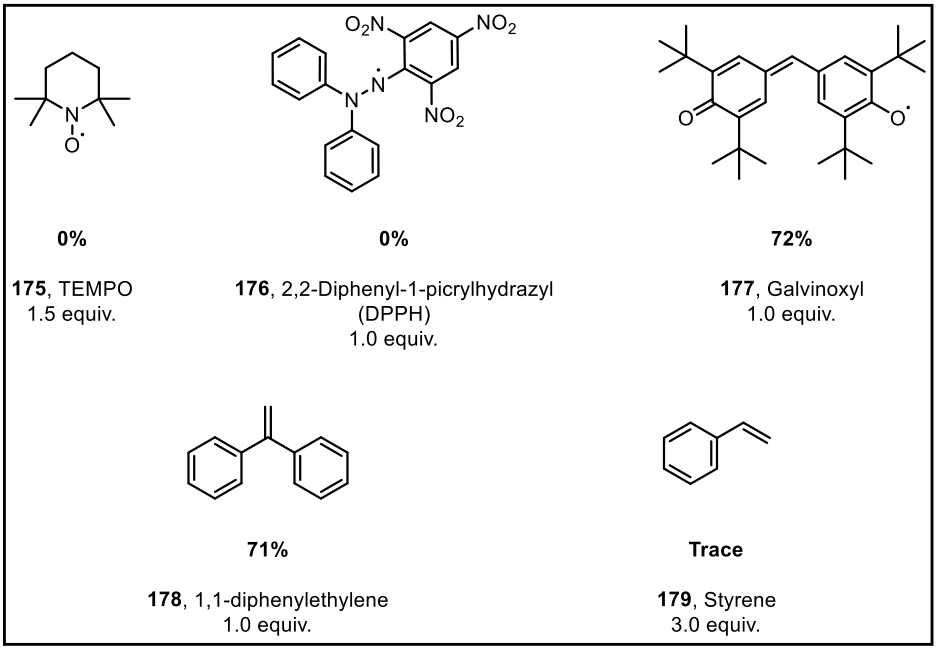


To probe the possibility of an imidoyl radical being generated, the coupling was attempted with cyclopropanecarbonitrile, but only the cross-coupled product with no ring opening, and unreacted nitrile was isolated (Scheme 3.8). Similar results have been seen in the

titanium catalyzed reductive coupling of ketones to nitriles,[37] and the stoichiometric SmI_2 reduction of nitriles.[55] Evidence that did support the possibility of an imidoyl radical being formed was the formation of a small amount (<10%) of aldehyde when an electron-rich benzonitrile (**158**) was utilized. This could occur via hydrogen atom transfer from the solvent to an imidoyl radical. Additionally, titanium(III) has been shown to dimerize nitriles through an imidoyl radical.[56] In the coupling to prepare **172**, 19% of 1,2-bis(3-methoxyphenyl)- ethan-1-one was also isolated, which would be formed through a dimerization of the nitrile followed by a reduction which could be promoted by the zinc metal and/or titanium.

Scheme 3.9. Radical trapping experiments

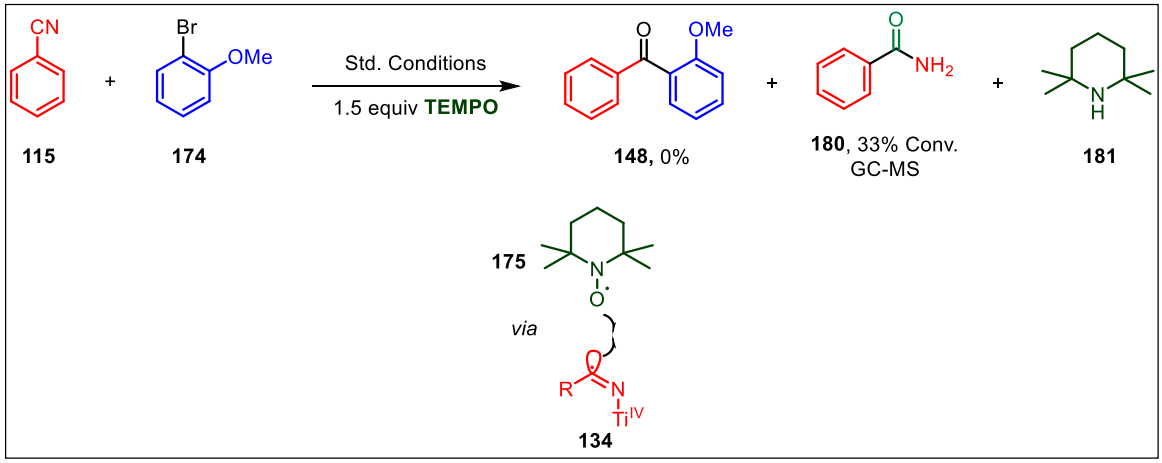




Other potential pathways for this coupling could be the titanium activating the nitrile to enable the nickel to insert the organobromides, or the nickel catalyst could be generating a carbon

radical which does addition to the activated nitrile. To probe this, the coupling was attempted in the presence of additives (Scheme 3.9).

Scheme 3.10. Radical trapping experiment with TEMPO



Addition of TEMPO completely inhibited the reaction. Examination of this reaction mixture by GCMS showed the presence benzamide which formed from the TEMPO–acetimidate, indicating either radical coupling between TEMPO and imidoyl radical or radical addition to the activated nitrile. The radical trapping agent DPPH inhibited the reaction giving only starting material, whereas galvinoxyl decreased the yield but no products from reaction with it could be detected. Additionally, we screened the addition of styrene and 1,1-diphenylethylene to try and trap and identify any radicals. Styrene inhibited the coupling only affording product from styrene coupling with itself, and 1,1-diphenylethylene slightly decreased the yield but no radical addition products could be detected. Further studies are needed to determine the mechanism of this coupling.

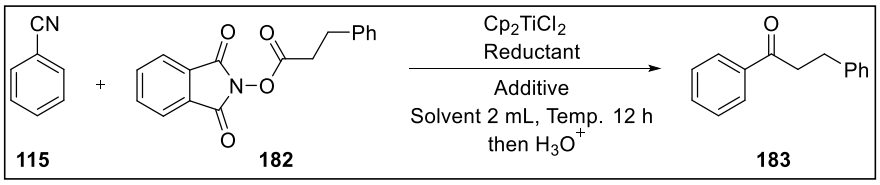
3.4. CONCLUSION

In summary, we have developed a dual catalytic approach for the cross-coupling of nitriles with organobromides under mild conditions. By utilizing a titanium catalyst to activate the

nitrile, the coupling of aryl and alkyl–bromides could be accomplished with a nickel catalyst. A broad assortment of unsymmetrical ketones could be accessed. Notably, the cross-coupling of bromides could be selectively accomplished in the presence of other functionalizable handles. Further studies on applying this Ti/Ni dual catalytic approach to cross-couplings with alternative coupling partners is underway.

3.5. FUTURE DIRECTIONS

Scheme 3.11. Titanium-mediated radical addition to nitriles with 1° NHPI esters



N–Hydroxy pthalimide (NHPI) esters are known to be redox active as they can accept an electron in the single electron transfer (SET) process and have been widely used as radical precursors in many cross coupling reactions.[57-61] They can be easily prepared by the condensation of N–hydroxy pthalimide with the corresponding carboxylic acids using carbodiimide coupling reagents or via acid chloride. It has been found that radicals can be generated when NHPI esters are treated with Zn metal via a SET process.[62] Since Zn is known to act as a reducing agent in Ti^{III} catalyzed reactions, [37, 38, 63] we envisioned that Ti/Zn mediated radical addition to nitriles could be possible with NHPI esters as a radical precursor. We attempted to optimize the reaction conditions with 1°, 2° and 2° benzylic NHPI esters but the reaction did not furnish yields greater than 29% overall. It seems that the by-product pthalimide coordinates with the titanium much strongly preventing the nitrile to coordinate with titanium. Hence more studies with different titanium catalysts and further optimization needs to be accomplished.

Table 3.6. Attempt to optimize the conditions for the radical addition to nitriles with 1° NHPI ester

S.No.	Solvent 2 mL	PhCN (equiv.)	NHP (equiv.)	Cp_2TiCl_2 (mol%)	Reductant (equiv.)	Additive (equiv.)	Temp. ° C	% GC Yield[a]
1	THF	1.0	1.0	10	Zn (2.0)	TMSCl (1.0)	RT	0
2	THF	1.0	1.0	10	Mn (2.0)	TMSCl (1.0)	RT	0
3	THF	1.0	1.0	10	Zn (2.0)	TMSCl (1.0)	60	**12**
4	THF	1.0	1.0	10	Zn (2.0)	TMSCl (2.0)	60	0
5	THF	1.0	1.0	10	Zn (2.0)	TMSCl (3.0)	60	0
6	THF	1.0	2.0	10	Zn (2.0)	TMSCl (2.0)	RT	0
7	THF	1.0	1.0	10	Zn (2.0)	TMSCl (4.0)	60	0
8	THF	1.0	1.0	10	Zn (2.0)	TEA•HCl (1.0)	60	0
9	THF	1.0	1.0	10	Zn (2.0)	TEA•HCl (1.0) + TMSCl(1.0)	60	0
10	THF	1.0	1.0	10	Mn (2.0)	TMSCl (1.0)	60	0
11	Dioxane	1.0	1.0	10	Zn (2.0)	TMSCl (1.0)	RT	0
12	Dioxane	1.0	1.0	10	Mn (2.0)	TMSCl (1.0)	RT	0
13	Dioxane	1.0	1.0	10	Zn (2.0)	TMSCl (1.0)	60	0
14	Dioxane	1.0	1.0	10	Mn (2.0)	TMSCl (1.0)	60	0
15	DMA	1.0	1.0	10	Zn (2.0)	TEA•HCl (1.0)	60	0
16	DMA	1.0	2.0	10	Zn (2.0)	TMSCl (2.0)	60	0
17	DMA	1.0	1.0	10	Mn (2.0)	TEA•HCl (1.0)	60	0
18	DMA	1.0	2.0	10	Mn (2.0)	TMSCl (2.0)	60	0
19	DMF	1.0	1.0	10	Zn (2.0)	TEA•HCl (1.0)	60	0
20	DMF	1.0	1.0	10	Mn (2.0)	TEA•HCl (1.0)	60	0
21	DME	1.0	2.0	10	Zn (2.0)	TMSCl (2.0)	60	0
22	DME	1.0	2.0	10	Mn (2.0)	TMSCl (2.0)	60	0
23	Toluene	1.0	1.0	10	Zn (2.0)	TMSCl	60	0

						(1.0)		
24	Toluene	1.0	1.0	10	Mn (2.0)	TMSCl (1.0)	60	0
25	DCE	1.0	1.0	10	Zn (2.0)	TMSCl (1.0)	60	**15**
26	DCE	1.0	1.0	10	Zn (2.0)	TMSCl (1.0)	RT	**10**
27	DCE	1.0	1.0	10	Zn (2.0)	TEA•HCl (1.0)	RT	0
28	DCE	1.0	1.0	10	Mn (2.0)	TMSCl (1.0)	60	0
29	DCM	1.0	1.0	10	Zn (2.0)	TMSCl (1.0)	RT	10
30	DCM	1.0	1.0	10	Zn (2.0)	TEA•HCl (1.0)	RT	0

[a] Yields were determined using an internal standard against a calibration curve.

Scheme 3.12. Titanium-mediated radical addition to nitriles with 2° NHPI esters

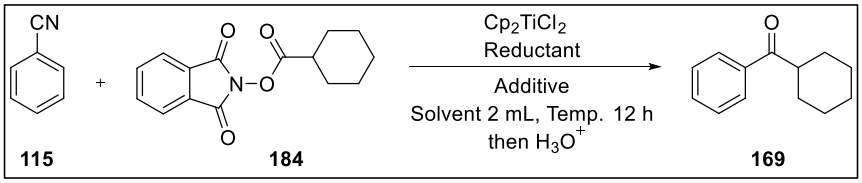


Table 3.7. Attempt to optimize the conditions for the radical addition to nitriles with 2° NHP ester

S.No.	Solvent 2 mL	PhCN (equiv.)	NHP (equiv.)	Cp_2TiCl_2 (mol%)	Reductant (equiv.)	Additive (equiv.)	Time (h)	Temp. ° C	% Conv.[a]
1	THF	1.0	1.0	10	Zn (2.0)	TMSCl (1.0)	12	60	3
2	THF	1.0	1.0	10	Zn (2.0)	TMSCl (1.0)	12	RT	8
3	DCE	1.0	1.0	10	Zn (2.0)	TMSCl (1.0)	12	RT	8
4	DCE	1.0	1.0	10	Zn (2.0)	TEA•HCl (1.0)	12	RT	0
5	DCM	1.0	1.0	10	Zn (2.0)	TMSCl (1.0)	12	RT	27
6	DCM	1.0	1.0	10	Zn (2.0)	TMSCl (1.0)	24	RT	29
7	DCM	1.0	1.0	10	Zn (2.0)	TMSCl (1.0)	24	60	4
8	DCM	1.0	1.0	10	Zn (2.0)	TMSCl (**2.0**)	24	RT	25
9	DCM	1.0	1.0	10	Zn (2.0)	TMSCl	24	RT	17

						(1.0) + Collidine (1.0)			
10	DCM	1.0	1.0	10	Zn (2.0)	-	24	RT	8
11	THF	1.0	1.0	10	Zn (2.0)	TMSCl (1.0) + NiCl2.dme + dtbbpy (10mol%)	24	RT	10
12	DCM	1.0	1.0	10	Zn (2.0)	TMSCl (1.0) + NiCl2.dme + dtbbpy (10mol%)	24	RT	25
13	DCM	1.0	1.0	10	Zn (2.0)	TEA•HCl (1.0)	12	RT	0
14	$CHCl_3$	1.0	1.0	10	Zn (2.0)	TMSCl (1.0)	24	RT	0
15	MeOH	1.0	1.0	10	Zn (2.0)	-	24	RT	0
16	MeOH	1.0	1.0	10	Zn (2.0)	TEA•HCl (1.0)	24	RT	0

[a] Determined using GC.

Scheme 3.13. Titanium-mediated radical addition to nitriles with 2° benzylic NHPI esters

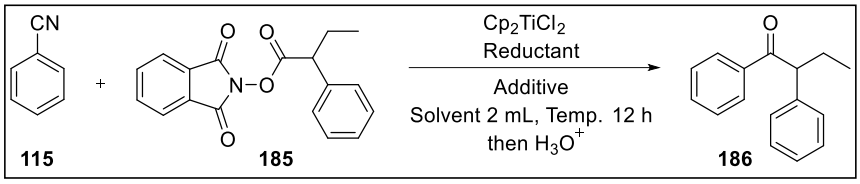


Table 3.8. Attempt to optimize the conditions for the radical addition to nitriles with 2° benzylic NHPI ester

S.No.	Solvent 2 mL	PhCN (equiv.)	NHP (equiv.)	Cp_2TiCl_2 (mol%)	Reductant (equiv.)	Additive (equiv.)	Time (h)	Temp. ° C	% Conv.[a]
1	DCM	1.0	1.0	10	Zn (2.0)	TMSCl (1.0)	24	RT	17

[a] Determined using GC

3.6. SUPPORTING INFORMATION

3.6.1. Methods

Unless stated otherwise, all reactions were carried out in an oven dried 10 mL microwave vial under an atmosphere of argon, with magnetic stirring (800 rpm). Reactions were monitored either by thin-layer chromatography with 0.25 mm precoated silica gel plates, or gas chromatography. Visualization of all TLCs was performed by UV and/or staining with phosphomolybdic acid, $KMnO_4$, or Seebach's stain. Purifications were performed by MPLC on a Biotage Isolera system with 50 g cartridges packed with silica gel (Silicycle, 60 Å, 230-400 mesh) eluted using a hexanes/EtOAc gradient, unless otherwise noted.

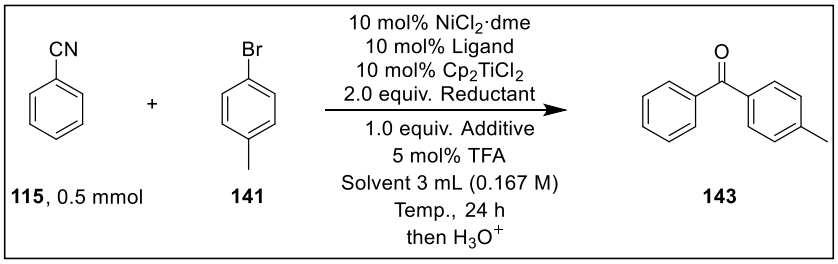
3.6.2. Materials

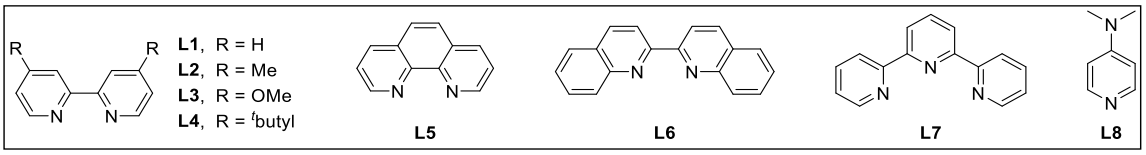
Diethyl ether, dichloromethane, chloroform, *N*,*N*-dimethylformamide and tetrahydrofuran were dried using a solvent purification system that contained activated alumina. 1,2-dichloroethane and chlorotrimethylsilane were freshly distilled from calcium hydride under an argon atmosphere. 1,4-dioxane was freshly distilled from sodium benzophenone ketyl under argon atmosphere. All other reagents and solvents were reagent grade and used without further purification unless otherwise stated. (4-bromophenoxy)(tert-butyl)dimethylsilane,[64] 4-((tert-butyldimethylsilyl)oxy)benzonitrile,[65] 4-cyanophenyl pivalate,[66] 4-bromophenyl pivalate,[67] 4-(4-bromophenyl)morpholine,[68] 5-bromo-1-tosyl-1*H*-indole,[69] 4-cyanophenyl trifluoromethanesulfonate,[70] and 4-(dimethylamino)benzonitrile[71] were prepared using standard literature procedures. The remaining substrates were purchased and used as received. $NiCl_2$.glyme, 4,4′-di-*tert*-butyl-2,2′-dipyridyl and zinc powder were purchased from Strem chemicals, Sigma Aldrich, and Alfa Aesar respectively.

3.6.3. Instrumentation

^{1}H NMR, ^{13}C NMR and ^{19}F spectra (no decoupling) were obtained on a Bruker Avance 400 MHz NMR Spectrometer (400 MHz for ^{1}H and 101 MHz for ^{13}C) with chemical shifts reported relative to either residual chloroform solvent peaks (δ = 7.26 ppm for ^{1}H and δ = 77.0 ppm for ^{13}C) or residual dimethylsulfoxide solvent peaks (δ = 2.50 ppm for ^{1}H and δ = 39.52 ppm for ^{13}C). Data for ^{1}H NMR were recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sex = sextet, sept = septet, m = multiplet, or unresolved), coupling constant(s) in Hz, integration. The reported melting points are uncorrected. IR spectra were obtained on a NICOLET iS50 FT-IR spectrometer. Low resolution mass spectra were obtained on a Shimadzu QP2010S GC/MS with a SHR5XlB column (30 m, 0.25 mm ID, 0.25 µm df, injection temp. = 260 °C) using a standard ramp of 40 °C to 280 °C at 10 °C/min, holding at 280 °C for 10 minutes. High Resolution Mass Spectra (HRMS) were determined using a Thermo LTQ-OrbitrapXL mass spectrometer operated in FT mode to provide a nominal resolution of 100,000.

Table 3.9. Complete optimization table for cross-coupling nitriles and organobromides





Entry	PhCN (equiv.)	ArBr (equiv.)	Solvent	Temp. (°C)	Ligand (10 mol%)	Reductant (2.0 equiv.)	Additive (1.0 equiv.)	Yield[a] (%)
1	1.0	1.0	DMPU	60	L1	Mn	TMSCl	0
2	1.0	1.0	DMPU	60	L1	Zn	TMSCl	9
3	1.0	1.0	DMPU	60	L1	Mn	TEA·HCl	24
4	1.0	1.0	DMPU	60	L1	Zn	TEA·HCl	0
5	1.0	1.0	DMF	60	L1	Zn	TMSCl	8
6	1.0	1.0	DMF	60	L1	Zn	TEA·HCl	3
7	1.0	1.0	NMP	60	L1	Mn	TMSCl	12
8	1.0	1.0	NMP	60	L1	Zn	TMSCl	10
9	1.0	1.0	DCM	40	L1	Mn	TMSCl	0
10	1.0	1.0	DCM	40	L1	Zn	TMSCl	10
11	1.0	1.0	DCE	60	L1	Mn	TMSCl	0
12	1.0	1.0	DCE	60	L1	Zn	TMSCl	12
13	1.0	1.0	Et_2O	40	L1	Zn	TMSCl	0
14	1.0	1.0	MTBE	60	L1	Mn	TMSCl	0
15	1.0	1.0	MTBE	60	L1	Zn	TMSCl	0
16	1.0	1.0	DME	60	L1	Mn	TMSCl	29
17	1.0	1.0	DME	60	L1	Zn	TMSCl	4
18	1.0	1.0	THF	60	L1	Mn	TMSCl	23
19	1.0	1.0	THF	60	L1	Zn	TMSCl	37
20	1.0	1.0	THF	60	L1	Mn	TEA·HCl	3
21	1.0	1.0	THF	60	L1	Zn	TEA·HCl	1
22	1.0	1.0	THF	60	L2	Mn	TMSCl	39
23	1.0	1.0	THF	60	L2	Zn	TMSCl	18
24	1.0	1.0	THF	60	L3	Mn	TMSCl	16
25	1.0	1.0	THF	60	L3	Zn	TMSCl	26
26	1.0	1.0	THF	60	L4	Mn	TMSCl	26
27	1.0	1.0	THF	60	L4	Zn	TMSCl	26
Entry	**PhCN (equiv.)**	**ArBr (equiv.)**	**Solvent**	**Temp. (°C)**	**Ligand (10 mol%)**	**Reductant (2.0 equiv.)**	**Additive (1.0 equiv.)**	**Yield[a] (%)**
28	1.0	1.0	THF	60	L8 (20 mol%)	Mn	TMSCl	30
29	3 mL (58 equiv.)	1.0	-	60	L1	Mn	TMSCl	20
30	3 mL (58 equiv.)	1.0	-	60	L1	Zn	TMSCl	1
31	3 mL (58 equiv.)	1.0	-	60	L1	Mn	TEA·HCl	3
32	3 mL (58 equiv.)	1.0	-	60	L1	Zn	TEA·HCl	18
33	1.0	1.0	Dioxane	60	L1	Mn	TMSCl	1

34	1.0	1.0	Dioxane	60	L1	Zn	TMSCl	44
35	1.0	1.0	Dioxane	60	L1	Mn	TEA·HCl	1
36	1.0	1.0	Dioxane	60	L1	Zn	TEA·HCl	1
37	1.0	1.0	Dioxane	RT	L1	Mn	TMSCl	1
38	1.0	1.0	Dioxane	RT	L1	Zn	TMSCl	6
39	1.0	1.0	Dioxane	60	L2	Zn	TMSCl	43
40[c]	1.0	2.0	Dioxane	60	L3	Zn	TMSCl	53[b]
41	1.0	1.0	Dioxane	60	L4	Zn	TMSCl	61
42	1.0	1.0	Dioxane	RT	L4	Zn	TMSCl	12
43	1.0	1.0	Dioxane	45	L4	Zn	TMSCl	33
44	1.0	2.0	Dioxane	60	L4	Zn	TMSCl	63[d]
45	1.0	2.0	Dioxane (0.167M)	60	L4	Zn	TMSCl	64[b]
46[c]	1.0	2.0	Dioxane (0.5 M)	60	L4	Zn	TMSCl	**69**[b]
47[c]	1.0	2.0	Dioxane (1.0 M)	60	L4	Zn	TMSCl	61[b]
48	1.0	2.0	Dioxane (0.5 M)	60	L4	Zn	TMSCl (2.0 equiv.)	46[b]
49[c]	1.0	2.0	Dioxane (0.5 M)	60	L4	Zn (1.0 equiv.)	TMSCl	46[b]
50[c,e]	1.0	2.0	Dioxane (0.5 M)	60	L4	Zn	TMSCl	53[b]
51	1.0	1.0	Dioxane	60	L5	Zn	TMSCl	22
52	1.0	2.0	Dioxane (0.5 M)	60	L6	Zn	TMSCl	20
53	1.0	2.0	Dioxane (0.5 M)	60	L7	Zn	TMSCl	17[b]

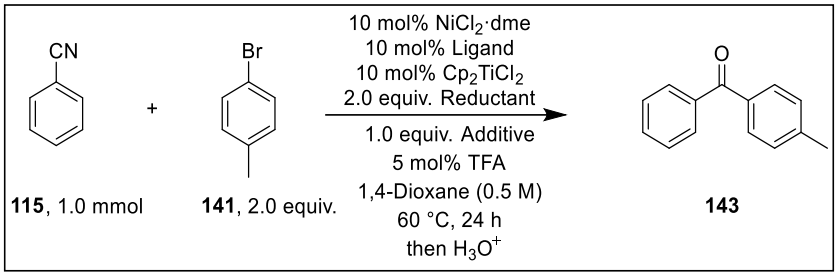
[a] Yields were determined via GC using a standard calibration curve after hydrolysis. [b] Isolated yield using flash chromatography. [c] Reaction ran on 1.0 mmol scale in 0.5 M concentration. [d] 10 mol% $NiBr_2$•dme was used. [e] Reaction ran in presence of oxygen (The rubber septum was pierced with a needle attached to a dry tube (Drierite) and left on for 24 h).

Table 3.9. Discussion

As to why Zn is the optimal reductant in this cross-coupling is not clear. In nickel catalyzed cross-electrophile couplings where a reductant is used, it has been seen in some cases Zn is the optimal reductant where as in other reactions Mn is the optimal reductant. There is no clear answer to why this is occurring and to which one will be the best reductant for a coupling reaction.

Nickel and titanium catalyst are potentially sensitive to oxygen which could have deleterious effects on the cross-coupling reaction. To test this the coupling was setup in a vial that was exposed to the air through a drying tube (Table S1, entry 50). It was found that exposure of the reaction to oxygen in the air did not inhibit the reaction but did lower the yield slightly.

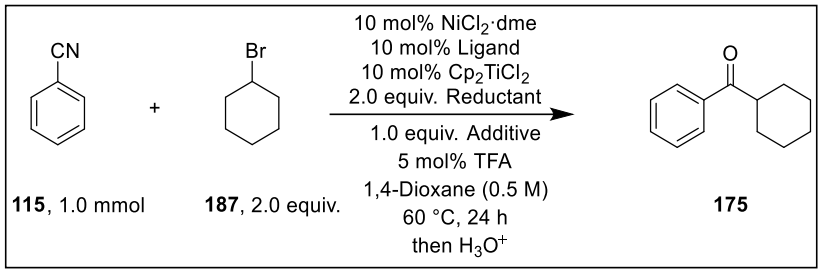
Table 3.10. Control experiments with aryl bromide



Entry	$NiCl_2$·dme	Cp_2TiCl_2	Ligand (10 mol%)	Reductant (2.0 equiv.)	Additive (1.0 equiv.)	Yield (%)
1	10 mol%	10 mol%	L4	Zn	TMSCl	69[a]
2	×	10 mol%	L4	Zn	TMSCl	0
3	10 mol%	×	L4	Zn	TMSCl	0
4	×	×	L4	Zn	TMSCl	0
5	10 mol%	10 mol%	L4	Zn	×	0

[a] Isolated yield after flash chromatography.

Table 3.11. Control experiments with alkyl bromide

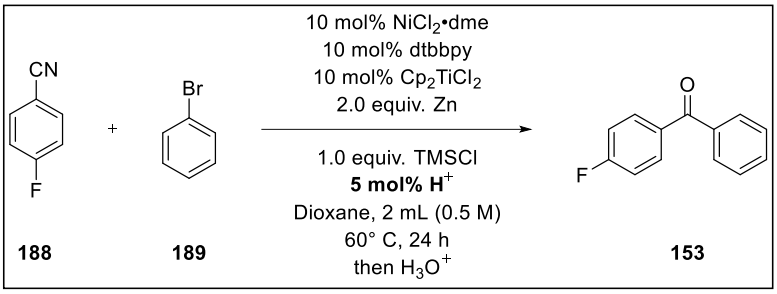


Entry	$NiCl_2$·dme	Cp_2TiCl_2	Ligand (10 mol%)	Reductant (2.0 equiv.)	Additive (1.0 equiv.)	Yield (%)
1	10 mol%	10 mol%	L4	Zn	TMSCl	69[a]
2	×	10 mol%	L4	Zn	TMSCl	< 5[a]

3	10 mol%	×	L4	Zn	TMSCl	< 3[a,b]
4	×	×	L4	Zn	TMSCl	0

[a] Isolated yield after flash chromatography. [b] Cyclohexyl bromide was fully consumed and converted to 1,1'-bi(cyclohexane).

Table 3.12. Screening of various acids



S.No.	H^+ (5 mol%)	Isolated Yield (%)
1	TFA	68
2	AcOH	61
3	$PhCO_2H$	69
4	PhOH	54
5	PTSA	53
6	TfOH	48

3.6.4. General procedure A for the cross-coupling of aryl nitriles and aryl/alkyl bromides

An oven dried 10 mL microwave vial with a magnetic stir bar was taken into an argon filled glovebox and charged with titanocene dichloride (0.1 mmol, 0.025 g), zinc powder (-325 mesh, 2 mmol, 0.131 g), $NiCl_2$.glyme (0.1 mmol, 0.022 g), and 4,4′-di-*tert*-butyl-2,2′-dipyridyl ligand (0.1 mmol, 0.027 g). An aluminum sealed septa was then crimped onto the vial, which was then taken out of the glovebox. The vial was then sequentially injected with aryl nitrile (1 mmol), aryl/alkyl bromide (2 mmol), TMSCl (1 mmol, 0.13 mL), TFA (5 mol%, 0.004 mL) and 1,4-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, the septa was wrapped with parafilm and placed in a preheated oil bath at 60 °C, during this time the reaction mixture turned brownish black. The reaction was monitored every 12 hours by GC, and typically the starting materials were fully consumed by 24 hours. The vial was removed from the oil bath and cooled to room temperature. The reaction was opened to the air, quenched with 2 mL of 1 M HCl, and stirred for 3 hours. The crude reaction mixture was then filtered through a celite bed, which was rinsed with dichloromethane. 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, unless otherwise stated.

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

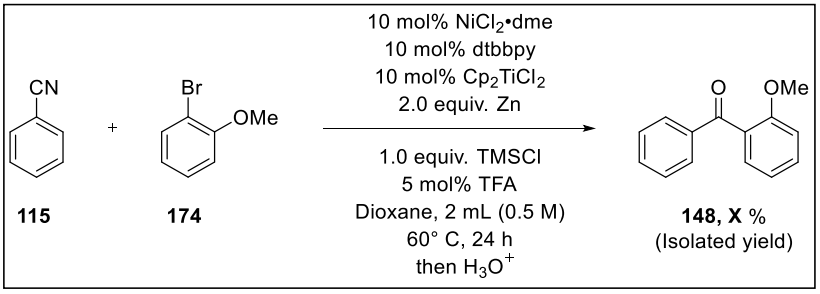
3.6.5. General procedure B for the cross-coupling of alkyl nitriles and aryl/alkyl bromides

An oven dried 10 mL microwave vial with a magnetic stir bar was taken into an argon filled glovebox and charged with titanocene dichloride (0.2 mmol, 0.050 g), zinc powder (-325 mesh, 2 mmol, 0.131 g), $NiCl_2$•glyme (0.1 mmol, 0.022 g), and 4,4′-di-*tert*-butyl-2,2′-dipyridyl ligand (0.1 mmol, 0.027 g). An aluminum sealed septa was then crimped onto the vial, which was then taken out of the glovebox. The vial was then sequentially injected with aryl nitrile (1 mmol), aryl/alkyl bromide (2 mmol), TMSCl (1 mmol, 0.13 mL), TFA (5 mol%, 0.004 mL) and 1,4-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, the septa was wrapped with parafilm and placed in a preheated oil bath at 60 °C, during this time the reaction mixture turned brownish black. The reaction was monitored every 12 hours by GC, and typically the starting materials were fully consumed by 24 hours. The vial was removed from the oil bath and cooled to room temperature. The reaction was opened to the air,

quenched with 2 mL of 1 M HCl, and stirred for 3 hours. The crude reaction mixture was then filtered through a celite bed, which was rinsed with dichloromethane. 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, unless otherwise stated.

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

Scheme 3.14. Bench-top reaction



X = 97%, Reaction was set up in glovebox under Ar atmosphere.

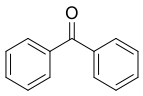
X = 23%, Reaction was set up on bench-top and degassed after the addition of TMSCl & TFA.

X = 18%, Reaction was set up on bench-top and degassed before the addition of TMSCl & TFA.

As we determined in the optimization studies that exposure of small amounts of oxygen to the reaction only slightly diminished the yield. We attempted to take the setup of the reaction out of the glovebox, and perform the setup on the bench top followed by placing the reaction under an inert atmosphere using stander techniques. It was found that weighing the reagents out on the bench top had a deleterious effect, dramatically lowering the yield of the product. This could be occurring because the $NiCl_2$•glyme salt is hydroscopic, and/or because the surface of the zinc metal is being oxidized by the air.

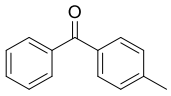
3.6.6. Synthesis and Characterization of Ketones

Benzophenone (142):



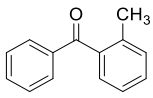
Subjection of benzonitrile (1.0 mmol, 0.102 mL) and bromobenzene (2 mmol, 0.211 mL) to general procedure A at 60 °C for 24 h afforded 0.131 g (72%) of **142** as a white solid after flash chromatography (Hex/EtOAc); m.p. = 47-49 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.2 Hz, 4H), 7.58 (t, *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; IR (neat) 3059, 1702, 1655, 1597, 1446, 1316, 1274, 940, 761, 694 cm^{-1}; Physical and spectral data were consistent with those reported in the literature.[72]

phenyl(*p*-tolyl)methanone (143):



Subjection of benzonitrile (1.0 mmol, 0.102 mL) and 4-bromotoluene (2 mmol, 0.246 mL) to general procedure A at 60 °C for 24 h afforded 0.136 g (69%) of **143** as a yellow oil after flash chromatography (Hex/EtOAc); ^{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; IR (neat) 3027, 2919, 1653, 1604, 1274, 728 cm^{-1}; Physical and spectral data were consistent with those reported in the literature.[72]

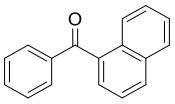
phenyl(*o*-tolyl)methanone (144):



Subjection of benzonitrile (1.0 mmol, 0.102 mL) and 2-bromotoluene (2 mmol, 0.240 mL) to general procedure A at 60 °C for 24 h afforded 0.144 g (73%) of **144** as a pale yellow oil after flash chromatography (Hex/EtOAc); ^{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,

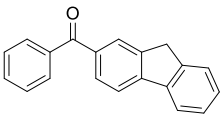
130.9, 130.1, 130.0, 128.4, 128.3, 125.1, 19.9; IR (neat) 3060, 2925, 1661, 1447, 1264, 923, 697 cm^{-1}; Physical and spectral data were consistent with those reported in the literature.[72]

naphthalen-1-yl(phenyl)methanone (145):



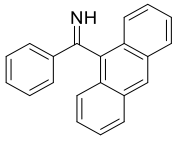
Subjection of benzonitrile (1.0 mmol, 0.102 mL) and 1-bromonaphthalene (2 mmol, 0.280 mL) to general procedure A at 60 °C for 48 h afforded 0.195 g (84%) of **145** as a white solid after flash chromatography (Hex/EtOAc); m.p. = 63-65 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 8.08 (m, 1H), 8.01 (m, 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; IR (neat) 3064, 1655, 1247, 788, 691 cm^{-1}; Physical and spectral data were consistent with those reported in the literature.[72]

(9*H*-fluoren-2-yl)(phenyl)methanone (146):



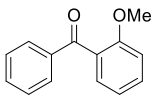
Subjection of benzonitrile (1.0 mmol, 0.102 mL) and 2-bromo-9H-fluorene (2 mmol, 0.490 g) to general procedure A at 60 °C for 24 h afforded 0.231 g (84%) of **146** as a yellow solid after flash chromatography (Hex/EtOAc); m.p. = 89-91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 8.05 – 7.96 (m, 5H), 7.79 – 7.72 (m, 2H), 7.66 (t, J = 7.7 Hz, 2H), 7.56 (m, 2H), 4.09 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.6, 145.8, 144.3, 143.0, 140.4, 138.1, 135.7, 132.0, 129.8, 129.5, 128.1, 127.9, 126.9, 126.7, 125.1, 120.7, 119.3, 36.8; IR (neat) 3053, 1643, 1609, 1591, 1467, 1442, 1420, 1400, 1301, 1271, 1000, 997 cm^{-1}; HRMS (ESI) *m/z* Calculated for $C_{20}H_{15}O^{+}$ $[M + H]^{+}$: 271.1117, Found: 271.1116.

anthracen-9-yl(phenyl)methanimine (147):



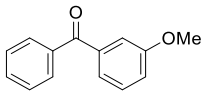
Subjection of benzonitrile (1.0 mmol, 0.102 mL) and 9-bromoanthracene (2 mmol, 0.514 g) to general procedure A at 60 °C for 24 h afforded 0.270 g (96%) of **147** as yellow solid after flash chromatography (Hex/EtOAc); m.p. = 146-148 °C; The ketimine (**147**) is not readily hydrolyzed to ketone, even with 3M HCl heated at 150 °C in a sealed tube for 12 h. It just forms the ketimine hydrochloride (orange crystalline solid, m.p. = > 250 °C) with 3M HCl; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (bs, 1H), 8.53 (s, 1H), 8.06 (d, *J* = 8.4 Hz, 2H), 7.90 – 7.83 (m, 2H), 7.82 – 7.73 (m, 2H), 7.51 – 7.31 (m, 7H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.3, 138.5, 134.9, 131.2, 131.1, 128.5, 128.5, 128.2, 128.1, 127.6, 126.3, 125.6, 125.4; IR (neat) 3042, 1595, 1568, 1445, 1323, 1184, 1041, 8881, 765 cm^{-1}; Physical and spectral data were consistent with those reported in the literature.[73] This imine has been shown in the literature to be reluctant to undergo hydrolysis.[73]

(2-methoxyphenyl)(phenyl)methanone (148):



Subjection of benzonitrile (1.0 mmol, 0.102 mL) and 2-bromoanisole (2 mmol, 0.249 mL) to general procedure A at 60 °C for 24 h afforded 0.206 g (97%) of **148** as a pale yellow oil after flash chromatography (Hex/EtOAc); ^{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; IR (neat) 2927, 1660, 1597, 1241, 923, 750 cm^{-1}; Physical and spectral data were consistent with those reported in the literature.[74]

(3-methoxyphenyl)(phenyl)methanone (149):

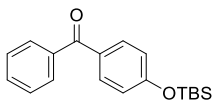


Subjection of benzonitrile (1.0 mmol, 0.102 mL) and 3-methoxybromobenzene (2 mmol, 0.253 g) to general procedure A at 60 °C

for 36 h afforded 0.108 g (51%) of **149** as a colorless oil after flash chromatography (Hex/EtOAc).

Subjection of 3-methoxybenzonitrile (1.0 mmol, 0.122 mL) and bromobenzene (2 mmol, 0.211 mL) to general procedure A at 60 °C for 24 h afforded 0.147 g (69%) of **149** as a colorless oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.78 (m, 2H), 7.61 – 7.55 (m, 1H), 7.48 (tt, *J* = 6.8, 1.3 Hz, 2H), 7.41 – 7.31 (m, 3H), 7.13 (ddd, *J* = 8.1, 2.5, 1.4 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.4, 192.1, 159.5, 138.8, 137.6, 132.4, 130.0, 129.2, 128.2, 122.8, 118.8, 114.3, 55.4; IR (neat) 3060, 2835, 1655, 1275, 1039, 720 cm^{-1}; Physical and spectral data were consistent with those reported in the literature.[75]

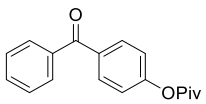
(4-((*tert*-butyldimethylsilyl)oxy)phenyl)(phenyl)methanone (150):



Subjection of benzonitrile (1.0 mmol, 0.103 mL) and (4-(tert-butyldimethylsilyl)oxy)bromobenzene (2 mmol, 0.489 mL) to general procedure A at 60 °C for 36 h afforded 0.0982 g (56%) of **150** as a colorless oil after flash chromatography (Hex/EtOAc).

Subjection of 4-((*tert*-butyldimethylsilyl)oxy)benzonitrile (1.0 mmol, 0.233 g) and bromobenzene (2 mmol, 0.211 mL) to general procedure A at 60 °C for 24 h afforded 0.231 g (74%) of **150** as a colorless oil after flash chromatography (Hex/EtOAc); ^{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; IR (neat) 2954, 2929, 2857, 1654, 1595, 1505, 1264, 1166, 1148, 904, 937, 805 cm^{-1}; HRMS (ESI) *m/z* Calculated for $C_{19}H_{25}SiO_2^+$ $[M + H]^+$: 313.1618, Found: 313.1618.

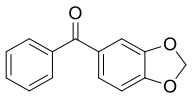
4-benzoylphenyl pivalate (151):



Subjection of benzonitrile (1.0 mmol, 0.102 mL) and 4-bromophenyl pivalate benzene (2 mmol, 0.385 mL) to general procedure A at 60 °C for 24 h afforded 0.214 g (76%) of **151** as a white solid after flash chromatography (Hex/EtOAc).

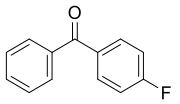
Subjection of 4-cyanophenyl pivalate (1.0 mmol, 0.186 mL) and bromobenzene (2 mmol, 0.211 mL) to general procedure A at 60 °C for 24 h afforded 0.257 g (91%) of **151** as a white solid after flash chromatography (Hex/EtOAc); m.p. = 82-84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.8 Hz, 2 H), 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; IR (neat) 2969, 1741, 1645, 1595, 1277, 1196, 1159, 1102, 939 cm^{-1}; HRMS (ESI) *m/z* Calculated for $C_{18}H_{19}O_3^+$ [M + H]$^+$: 283.1329, Found: 283.1328.

benzo[1,3]dioxol-5-yl(phenyl)methanone (152):



Subjection of benzonitrile (1.0 mmol, 0.102 mL) and 4-bromo-1,2-(methylenedioxy)benzene (2 mmol, 0.241 mL) to general procedure A at 60 °C for 24 h afforded 0.129 g (57%) of **152** as an orange oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.71 (m, 2H), 7.59 – 7.53 (m, 1H), 7.50 – 7.43 (m, 2H), 7.37 (d, *J* = 7.5 Hz, 2H), 6.88 – 6.82 (m, 1H), 6.05 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.0, 151.5, 147.9, 138.1, 131.9, 129.6, 128.1, 126.8, 109.8, 107.6, 101.8; IR (neat) 2901, 1648, 1439, 1277, 1033, 703 cm^{-1}; Physical and spectral data were consistent with those reported in the literature.[72]

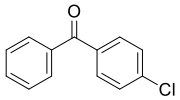
(4-fluorophenyl)(phenyl)methanone (153):



Subjection of benzonitrile (1.0 mmol, 0.103 mL) and 4-Fluorobromobenzene (2 mmol, 0.219 mL) to general procedure A at 60 °C for 48 h afforded 0.0831 g (41%) of **153** as a colorless liquid after flash chromatography (Hex/EtOAc).

Subjection of 4-Fluorobenzonitrile (1.0 mmol, 0.121 g) and bromobenzene (2 mmol, 0.211 mL) to general procedure A at 60 °C for 24 h afforded 0.136 g (68%) of **153** as a colorless liquid after flash chromatography (Hex/EtOAc); ^{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; ^{19}F NMR (376 MHz, $CDCl_3$) δ -105.93, -105.94, -105.95, -105.96, -105.97, -105.98, -105.98, -105.99, -106.00; IR (neat) 3068, 1658, 1596, 1503, 1445, 1298, 1275, 1149, 992, 848, 734, 698, 677 cm^{-1}; Physical and spectral data were consistent with those reported in the literature.[72]

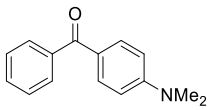
(4-chlorophenyl)(phenyl)methanone (154):



Subjection of benzonitrile (1.0 mmol, 0.102 mL) and 1-chloro-4-iodobenzene (2 mmol, 0.478 g) to general procedure A at 40 °C for 48 h afforded 0.117 g (54%) of **154** as a white solid after flash chromatography (Hex/EtOAc).

Subjection of 4-chlorobenzonitrile (1.0 mmol, 0.138 g) and bromobenzene (2 mmol, 0.211 mL) to general procedure A at 60 °C for 24 h afforded 0.151 g (70%) of **154** as a white solid after flash chromatography (Hex/EtOAc); m.p. = 65-67 °C; ^{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; IR (neat) 3089, 1648, 1278, 1087, 843, 693 cm^{-1}; Physical and spectral data were consistent with those reported in the literature.[72]

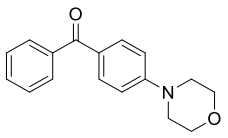
(4-(dimethylamino)phenyl)(phenyl)methanone (155):



Subjection of benzonitrile (1.0 mmol, 0.102 mL) and 4-bromo-*N*,*N*-dimethylaniline (2 mmol, 0.40 g) to general procedure A at 60 °C for 24 h afforded 0.215 g (96%) of **155** as a pale green solid after flash chromatography (100% DCM).

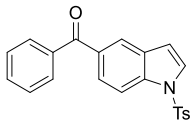
Subjection of 4-(dimethylamino)benzonitrile (1.0 mmol, 0.146 g) and bromobenzene (2 mmol, 0.211 mL) to general procedure A at 60 °C for 48 h afforded 0.096 g (43%) of **155** as a pale green solid after flash chromatography (100% DCM); m.p. = 58-60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.77 (m, 2H), 7.75 – 7.69 (m, 2H), 7.55 – 7.41 (m, 3H), 6.70 – 6.64 (m, 2H), 3.07 (d, *J* = 1.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.1, 153.2, 139.3, 132.7, 131.0, 129.4, 127.9, 124.7, 110.5, 40.0; IR (neat) 3060, 2955, 1594, 1283, 825, 701 cm^{-1}; Physical and spectral data were consistent with those reported in the literature.[76]

(4-morpholinophenyl)(phenyl)methanone (156):



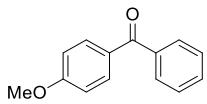
Subjection of benzonitrile (1.0 mmol, 0.102 mL) and 4-(4-bromophenyl)morpholine (2 mmol, 0.484 g) to general procedure A at 60 °C for 24 h afforded 0.229 g (86%) of **156** as a tan solid after flash chromatography (DCM/MeOH); m.p. = 134-136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 8.8, 1.4 Hz, 2H), 7.76 – 7.71 (m, 2H), 7.58 – 7.51 (m, 1H), 7.46 (m, 2H), 6.90 (dd, *J* = 9.0, 2.0 Hz, 2H), 3.87 (td, *J* = 4.9, 1.8 Hz, 4H), 3.36 – 3.29 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.2, 153.9, 138.6, 132.4, 131.5, 129.5, 128.1, 127.8, 113.2, 66.5, 47.6; IR (neat) 3054, 2991, 1635, 1595, 1216, 1115, 922, 632 cm^{-1}; HRMS (ESI) *m/z* Calculated for $C_{17}H_{18}NO_2^+$ $[M + H]^+$: 268.1332, Found: 268.1329.

phenyl(1-tosyl-1*H*-indol-5-yl)methanone (157):



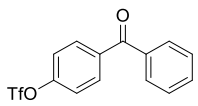
Subjection of benzonitrile (1.0 mmol, 0.102 mL) and 5-bromo-1-tosyl-1*H*-indole (2 mmol, 0.70 g) to general procedure A at 60 °C for 48 h afforded 0.199 g (53%) of **157** as a tan solid after flash chromatography (100% DCM); m.p. = 130-132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 8.7, 0.8 Hz, 1H), 7.88 – 7.85 (m, 1H), 7.70 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.69 – 7.63 (m, 4H), 7.53 (d, *J* = 3.7 Hz, 1H), 7.49 – 7.43 (m, 1H), 7.40 – 7.32 (m, 2H), 7.16 – 7.10 (m, 2H), 6.60 (dd, *J* = 3.8, 0.8 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.4, 145.4, 138.0, 137.0, 135.0, 132.9, 132.2, 130.2, 130.0, 129.9, 128.2, 127.7, 126.9, 126.5, 124.4, 113.3, 109.4, 21.6; IR (neat) 3112, 2922, 1651, 1596, 1286, 1189, 726 cm^{-1}; HRMS (ESI) *m/z* Calculated for $C_{22}H_{18}NO_3S^+$ $[M + H]^+$: 376.1002, Found: 376.0999.

(4-methoxyphenyl)(phenyl)methanone (158):



Subjection of 4-methoxybenzonitrile (1.0 mmol, 0.133 g) and bromobenzene (2 mmol, 0.211 mL) to general procedure A at 60 °C for 24 h afforded 0.1397 g (66%) of **158** as a colorless oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.79 (m, 2H), 7.78 – 7.73 (m, 2H), 7.59 – 7.53 (m, 1H), 7.47 (dd, *J* = 8.3, 6.9 Hz, 2H), 7.00 – 6.93 (m, 2H), 3.89 (d, *J* = 0.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.5, 163.2, 138.3, 132.5, 131.8, 130.1, 129.7, 128.1, 113.5, 55.5; IR (neat) 2935, 2804, 1683, 1650, 1598, 1507, 1303, 1280, 1253, 1170, 1147, 1024, 834 cm^{-1}; Physical and spectral data were consistent with those reported in the literature.[72]

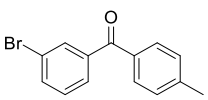
4-benzoylphenyl trifluoromethanesulfonate (159):



Subjection of 4-cyanophenyl trifluoromethanesulfonate (1.0 mmol, 0.251 g) and bromobenzene (2 mmol, 0.211 mL) to general procedure A at 60 °C for 48 h afforded 0.199 g (60%) of **159** as a pale yellow oil after flash chromatography (Hex/EtOAc); ^{1}H

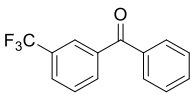
NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.88 (m, 2H), 7.82 – 7.76 (m, 2H), 7.65 – 7.60 (m, 1H), 7.54 – 7.48 (m, 2H), 7.43 – 7.37 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.7, 151.9, 137.5, 136.7, 134.5, 133.0, 132.1, 130.0, 128.5, 121.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -72.73, -72.74, -72.76; IR (neat) 3067, 1662, 1424, 1135, 880, 605 cm^{-1}; HRMS (ESI) *m/z* Calculated for $C_{14}H_{10}F_3O_4S^+$ $[M + H]^+$: 331.0246, Found: 331.0247.

(3-bromophenyl)(*p*-tolyl)methanone (160):



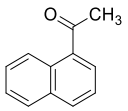
Subjection of 3-bromobenzonitrile (1.0 mmol, 0.182 g) and 4-iodotoluene (2 mmol, 0.436 g) to general procedure A at 45 °C for 24 h afforded 0.079 g (29%) of **160** as a white solid after flash chromatography (Hex/EtOAc); m.p. = 63-65 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (t, *J* = 1.8 Hz, 1H), 7.73 – 7.67 (m, 4H), 7.39 – 7.27 (m, 3H), 2.45 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.8, 143.8, 139.8, 135.0, 134.2, 132.7, 130.2, 129.8, 129.1, 128.4, 122.5, 21.7; IR (neat) 3092, 2916, 1706, 1558, 1408, 704 cm^{-1}. Physical and spectral data were consistent with those reported in the literature.[77]

phenyl(3-(trifluoromethyl)phenyl)methanone (161):



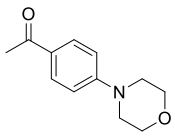
Subjection of 3-(trifluoromethyl)benzonitrile (1.0 mmol, 0.134 mL) and bromobenzene (2 mmol, 0.211 mL) to general procedure A at 60 °C for 36 h afforded 0.1363 g (55%) of **161** as a white solid after flash chromatography (Hex/EtOAc); m.p. = 39-41 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.97 (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; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.75; IR (neat) 3066, 1654, 1607, 1597, 1318, 1306, 1266, 1166, 1095, 1071, 712, 689, 657 cm^{-1}; Physical and spectral data were consistent with those reported in the literature.[78]

1-(naphthalen-1-yl)ethan-1-one (162):



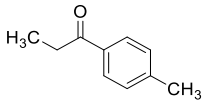
Subjection of acetonitrile (1.0 mmol, 0.052 mL) and 1-bromonaphthalene (2 mmol, 0.280 mL) to general procedure B at 60 °C for 48 h afforded 0.111 g (65%) of **162** as a pale yellow oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (dt, *J* = 8.7, 1.0 Hz, 1H), 7.93 – 7.75 (m, 3H), 7.51 (m, 1H), 7.47 – 7.37 (m, 2H), 2.65 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.8, 135.4, 133.9, 133.0, 130.1, 128.6, 128.4, 128.0, 126.4, 125.9, 124.3, 29.9; IR (neat) 3048, 1672, 1239, 772, 588 cm^{-1}; HRMS (ESI) *m/z* Calculated for $C_{12}H_{11}O^+$ $[M + H]^+$: 171.0804, Found: 171.0803.

1-(4-morpholinophenyl)ethan-1-one (163):



Subjection of acetonitrile (1.0 mmol, 0.052 mL) and 4-(4-bromophenyl)morpholine (2 mmol, 0.484 g) to general procedure B at 60 °C for 24 h afforded 0.094 g (46%) of **163** as a pale yellow solid after flash chromatography (Hex/EtOAc); m.p. = 84-86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.84 (m, 2H), 6.88 – 6.81 (m, 2H), 3.87 – 3.81 (m, 4H), 3.32 – 3.26 (m, 4H), 2.51 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.4, 154.1, 130.2, 128.0, 113.2, 66.5, 47.4, 26.1; IR (neat) 2968, 2841, 1658, 1592, 1116, 817, 589 cm^{-1}; Physical and spectral data were consistent with those reported in the literature.[79]

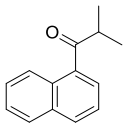
1-(*p*-tolyl)propan-1-one (164):



Subjection of propionitrile (1.0 mmol, 0.066 mL) and 4-bromotoluene (2 mmol, 0.246 mL) to general procedure B at 60 °C for 48 h afforded 0.089 g (60%) of **164** as a colorless liquid after flash chromatography (Hex/EtOAc); ^{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,

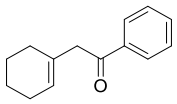
128.0, 31.6, 21.5, 8.3; IR (neat) 2977, 2937, 1682, 1607, 1458, 1407, 1376, 1224, 1208. 1180, 950, 787 cm^{-1}; Physical and spectral data were consistent with those reported in the literature.[80]

2-methyl-1-(naphthalen-1-yl)propan-1-one (165):



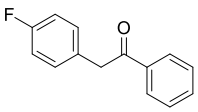
Subjection of isobutyronitrile (1.0 mmol, 0.090 mL) and 1-bromonaphthalene (2 mmol, 0.280 mL) to general procedure B at 60 °C for 24 h afforded 0.177 g (89%) of **165** as a pale yellow oil after flash chromatography (Hex/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 – 8.28 (m, 1H), 7.96 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.90 – 7.85 (m, 1H), 7.74 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.60 – 7.46 (m, 3H), 3.52 (sept, *J* = 6.9 Hz, 1H), 1.26 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.0, 136.9, 133.8, 131.6, 130.4, 128.3, 127.5, 126.3, 125.8, 125.6, 124.3, 39.5, 18.7; IR (neat) 3048, 2969, 1679, 943, 776 cm^{-1}; Physical and spectral data were consistent with those reported in the literature.[81]

2-(cyclohex-1-en-1-yl)-1-phenylethan-1-one (166):



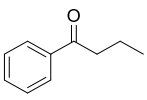
Subjection of 2-(cyclohex-1-en-1-yl)acetonitrile (1.0 mmol, 0.130 mL) and bromobenzene (2 mmol, 0.211 mL) to general procedure B at 60 °C for 24 h afforded 0.109 g (55%) of **166** as a pale yellow oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.95 (m, 2H), 7.58 – 7.51 (m, 1H), 7.45 (dd, *J* = 8.4, 6.9 Hz, 2H), 5.57 (tq, *J* = 3.1, 1.5 Hz, 1H), 3.59 (d, *J* = 1.6 Hz, 2H), 2.07 – 1.96 (m, 4H), 1.69 – 1.52 (m, 4H); ^{13}C NMR (101 MHz, CDCl3) δ 198.7, 137.0, 132.9, 132.2, 128.5, 128.4, 126.0, 47.8, 28.8, 25.4, 22.8, 22.0; IR (neat) 2930, 2859, 2837, 1679, 1597,1447, 1437, 1413, 1000, 920, 755 cm^{-1}; Physical and spectral data were consistent with those reported in the literature.[82]

2-(4-fluorophenyl)-1-phenylethan-1-one (167):



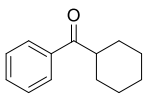
Subjection of (4-fluorophenyl)acetonitrile (1.0 mmol, 0.120 mL) and bromobenzene (2 mmol, 0.211 mL) to general procedure B at 60 °C for 24 h afforded 0.151 g (71%) of **167** as a white solid after flash chromatography (Hex/EtOAc); m.p. = 82-84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.98 (m, 2H), 7.60 – 7.54 (m, 1H), 7.50 – 7.44 (m, 2H), 7.25 – 7.19 (m, 2H), 7.06 – 6.98 (m, 2H), 4.27 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.3, 163.1, 160.6, 136.4, 133.3, 131.0, 130.97, 130.12, 130.09, 128.7, 128.5, 115.6, 115.4, 44.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.00, -116.01, -116.02, -116.04, -116.05, -116.06, -116.07; IR (neat) 3071, 2920, 1681, 1594, 1508, 1447, 1419, 1332, 1218, 1195, 1155, 1016, 993, 846, 824, 795, 752, 689 cm^{-1}; Physical and spectral data were consistent with those reported in the literature.[83]

1-phenylbutan-1-one (168):



Subjection of benzonitrile (1.0 mmol, 0.102 mL) and 1-bromopropane (2 mmol, 0.182 mL) to general procedure A at 60 °C for 24 h afforded 0.042 g (28%) of **168** as a colorless oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.93 (m, 2H), 7.58 – 7.52 (m, 1H), 7.49 – 7.42 (m, 2H), 2.95 (t, *J* = 7.3 Hz, 2H), 1.78 (sex, *J* = 7.4 Hz, 2H), 1.01 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.4, 137.1, 132.8, 128.5, 128.0, 40.5, 17.8, 13.9; IR (neat) 2962, 2874, 1682, 1447, 1211, 688 cm^{-1}; Physical and spectral data were consistent with those reported in the literature.[84]

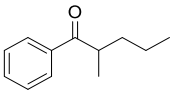
cyclohexyl(phenyl)methanone (169):



Subjection of benzonitrile (1.0 mmol, 0.102 mL) and cyclohexylbromide (2 mmol, 0.246 mL) to general procedure A at 60 °C for 24 h afforded 0.129 g (69%) of **169** as a colorless oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 –

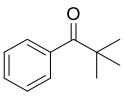
7.90 (m, 2H), 7.54 (m, 1H), 7.49 – 7.41 (m, 2H), 3.31 – 3.21 (m, 1H), 1.94 – 1.80 (m, 4H), 1.74 (m, 1H), 1.57 – 1.33 (m, 4H), 1.27 (m, , 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.8, 136.3, 132.7, 128.5, 128.2, 45.6, 29.4, 26.0, 25.8; IR (neat) 2928, 2852, 1678, 1446, 972, 695 cm^{-1}; Physical and spectral data were consistent with those reported in the literature.[85]

2-methyl-1-phenylpentan-1-one (170):



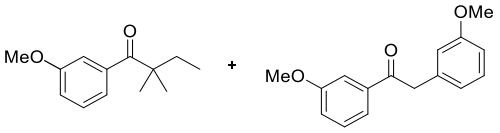
Subjection of benzonitrile (1.0 mmol, 0.102 mL) and (±)-2-bromopentane (2 mmol, 0.247 mL) to general procedure A at 60 °C for 24 h afforded 0.111 g (63%) of **170** as a colorless oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.91 (m, 2H), 7.58 – 7.51 (m, 1H), 7.45 (m, 2H), 3.48 (sex, *J* = 6.8 Hz, 1H), 1.82 – 1.74 (m, 1H), 1.47 – 1.24 (m, 3H), 1.19 (d, *J* = 6.8 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.5, 136.7, 132.7, 128.5, 128.2, 40.3, 35.9, 20.5, 17.1, 14.1; IR (neat) 3063, 2959, 1680, 1447, 1209, 971, 700 cm^{-1}; Physical and spectral data were consistent with those reported in the literature.[86]

2,2-dimethyl-1-phenylpropan-1-one (171):



Subjection of benzonitrile (1.0 mmol, 0.102 mL) and 2-bromo-2-methylpropane (2 mmol, 0.225 mL) to general procedure A at 60 °C for 24 h afforded 0.087 g (54%) of **171** as a colorless liquid after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.56 (m, 2H), 7.39 – 7.33 (m, 1H), 7.30 (m, 2H), 1.26 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.1, 138.5, 130.7, 127.9, 127.7, 44.1, 27.9; IR (neat) 3061, 2968, 1673, 1174, 958, 696 cm^{-1}; Physical and spectral data were consistent with those reported in the literature.[85]

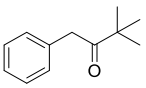
1-(3-methoxyphenyl)-2,2-dimethylbutan-1-one (172):



Subjection of 3-methoxybenzonitrile (1.0 mmol, 0.122 mL) and 2-bromo-2-methylbutane (2 mmol, 0.256 mL) to general procedure B at 60 °C for 24 h afforded 0.055 g (27%) of **172** as a colorless liquid and 0.024 g (19%) of 1,2-bis(3-methoxyphenyl)ethan-1-one as a colorless oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.15 (m, 2H), 7.09 (dd, *J* = 2.6, 1.5 Hz, 1H), 6.92 (ddd, *J* = 8.1, 2.6, 1.2 Hz, 1H), 3.76 (s, 3H), 1.72 (q, *J* = 7.5 Hz, 2H), 1.22 (s, 6H), 0.78 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.2, 159.2, 140.5, 129.0, 119.7, 116.4, 113.0, 55.3, 48.2, 33.5, 25.6, 9.2; IR (neat) 2966, 2877, 1672, 1578, 1256, 1152, 978, 748 cm^{-1}; HRMS (ESI) *m/z* Calculated for $C_{13}H_{19}O_2^+$ $[M + H]^+$: 207.1380, Found: 207.1379.

1,2-bis(3-methoxyphenyl)ethan-1-one (172a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.44 (dd, *J* = 2.7, 1.5 Hz, 1H), 7.27 (d, *J* = 16.0 Hz, 1H), 7.19 – 7.12 (m, 1H), 7.04 – 6.98 (m, 1H), 6.80 – 6.68 (m, 3H), 4.15 (s, 2H), 3.75 (s, 3H), 3.69 (d, *J* = 1.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.3, 159.8, 137.9, 136.0, 129.6, 129.6, 121.7, 121.3, 119.6, 115.0, 112.8, 112.4, 55.4, 55.1, 45.6; IR (neat) 3003, 2938, 1678, 1582, 1487, 1256, 1037, 690 cm^{-1}. GC-MS $[M^+]$ = 256.

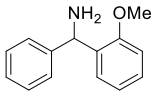
3,3-dimethyl-1-phenylbutan-2-one (173):



Subjection of phenylacetonitrile (1.0 mmol, 0.115 mL) and 2-bromo-2-methylpropane (2 mmol, 0.225 mL) to general procedure B at 60 °C for 24 h afforded 0.078 g (44%) of **173** as a pale yellow oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.18 (m, 2H), 7.17 – 7.11 (m, 1H), 7.11 – 7.06 (m, 2H), 3.71 (s, 2H), 1.11 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.7, 134.9, 129.5, 128.3, 126.5, 44.6, 43.2,

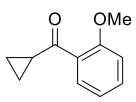
26.3; IR (neat) 3030, 2968, 1709, 1477, 1059, 722, 695 cm^{-1}; Physical and spectral data were consistent with those reported in the literature.[87]

(2-methoxyphenyl)(phenyl)methanamine (176):



After the subjection of benzonitrile (1.0 mmol, 0.102 mL) and 2-bromoanisole (2 mmol, 0.249 mL) to general procedure A at 60 °C for 24 h, the reaction mixture was cooled down to 0 °C and $NaBH_4$ (5 mmol, 0.189 g) followed by methanol (2 mL) was added. The reaction mixture was allowed to warm up to RT, stirred for 6 h and filtered through a celite bed using DCM and concentrated. The crude material was diluted with ether (50 mL) and washed with 3M HCl (2x50 mL). Then the aqueous layer was basified with 1M NaOH, extracted with ether (2x50 mL), washed with brine solution, dried over $MgSO_4$, filtered, concentrated and purified using flash chromatography (DCM/MeOH) to afford 0.139 g (65%) of the product as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.6 Hz, 2H), 7.39 – 7.29 (m, 3H), 7.25 (t, *J* = 7.3 Hz, 2H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.90 (d, *J* = 8.1 Hz, 1H), 5.57 (s, 1H), 3.83 (s, 3H), 1.90 (bs, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.67, 145.04, 134.04, 128.05, 127.88, 127.44, 126.96, 126.47, 120.56, 110.57, 55.26, 53.72; IR (neat) 3375, 3303, 3057, 2939, 2834, 1597, 1487, 1238, 1026, 906 cm^{-1}; GC-MS [M^+] = 213.

cyclopropyl(2-methoxyphenyl)methanone (178):



Subjection of cyclopropane carbonitrile (1.0 mmol, 0.074 mL) and 2-bromoanisole (2 mmol, 0.250 mL) to general procedure B at 60 °C for 48 h afforded 0.061 g (35%) of **178** as a pale yellow oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.46 – 7.38 (m, 1H), 7.01 – 6.92 (m, 2H), 3.88 (s, 3H), 2.72 (tt, *J* = 8.0, 4.6 Hz, 1H), 1.20 (quin, *J* = 3.7 Hz, 2H), 0.97 (dq, *J* = 7.3, 3.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.2, 158.2, 132.8, 129.7, 129.5, 120.4, 111.5, 55.5, 21.4, 11.9; IR

(neat) 3006, 2839, 1660, 1595, 1380, 1244, 989, 752 cm^{-1}; HRMS (ESI) *m/z* Calculated for $C_{11}H_{13}O_2^+$ $[M + H]^+$: 177.0910, Found: 177.0910.

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CHAPTER IV

NICKEL-CATALYZED CROSS-COUPLING OF ARYL BROMIDES WITH BENZYL AND ALLYL ALCOHOLS

4.1. INTRODUCTION

Cross coupling of electrophiles to form carbon-carbon has been gaining more attention.[1, 2] But the high reactivity of alkyl halides makes it less viable in selective cross-coupling reactions.[1] Coupling partners that are less reactive to achieve selectivity and readily available are particularly demanding. Alcohols are abundant, relatively more stable and nontoxic. The use of alcohols as coupling partners is less explored due to the inert nature of C–O bond and high activation energy.[3] The employment of alcohols in cross coupling to form C–C bond is extremely difficult.[4] The inherent challenges in using unprotected alcohols are 1) O–H bond is acidic and typically not a very good leaving group[5] 2) Alcohols tend to form metal-alkoxide complex and 3) the basicity of the alcohols. Most of reported cross couplings require either precious metals or a preformed organometallic reagent like boronic acids. The development of protocols to cross couple alcohols to form C–C bond without any preformed organometallic reagent is highly needed.[6]

4.2. CROSS-COUPLING OF BENZYL ALCOHOLS WITH ARYL BROMIDES

Diarylmethanes are important structural motifs that are prevalent in drug molecules.[7-9] Current methods either use benzyl halides[10-13] or palladium catalyzed Suzuki couplings with activated groups derived from benzyl alcohol[14-16] with a preformed organometallic reagent like boronic acid.[17, 18] The tedious synthesis of starting materials and the employment of precious metal palladium make these methods inviable. We sought to address this by developing a strategy to cross couple cheap and readily available starting materials. We speculated that aryl bromides and benzyl alcohols can be cross coupled to access diarylmethanes with earth-abundant metals, nickel and titanium.

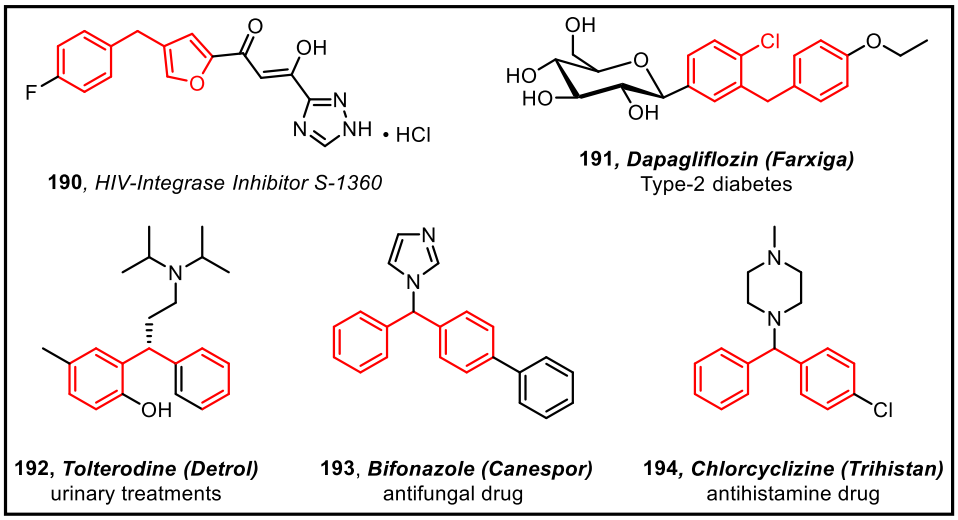
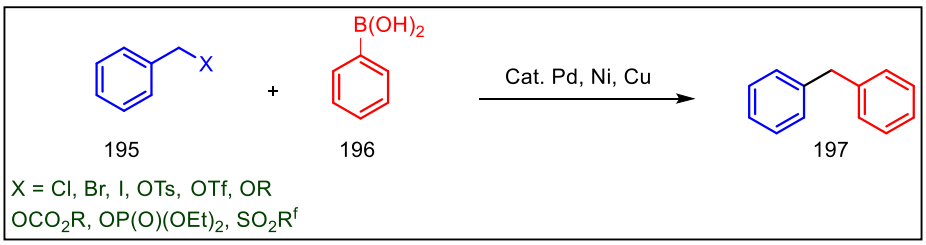
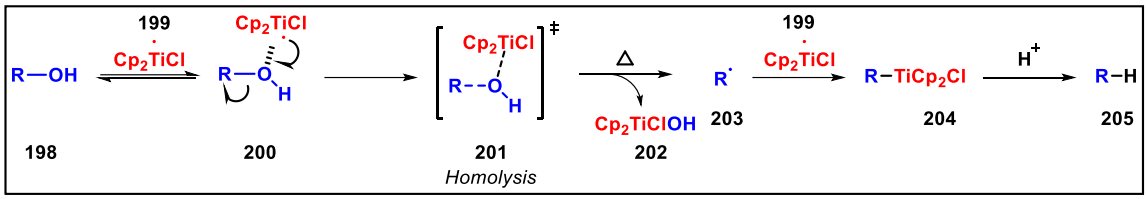


Fig 4.1. Diarylmethanes in drug molecules.

Scheme 4.1. Suzuki couplings for the synthesis of diarylmethanes[19]



Barrero et al first reported the feasibility of generating radicals from alcohols with Ti (III) (scheme 1).[20] The radical generated by a Ti(III) is trapped by another Ti(III) which forms alkane on protonation of the R–Ti bond.



Scheme 4.2. Mechanism for Ti(III)-Promoted C–O bond homolysis.

But we envisioned that these radicals (**203**) could be cross-coupled with the aryl halides with nickel under dual catalysis and it is illustrated in fig 4.2.

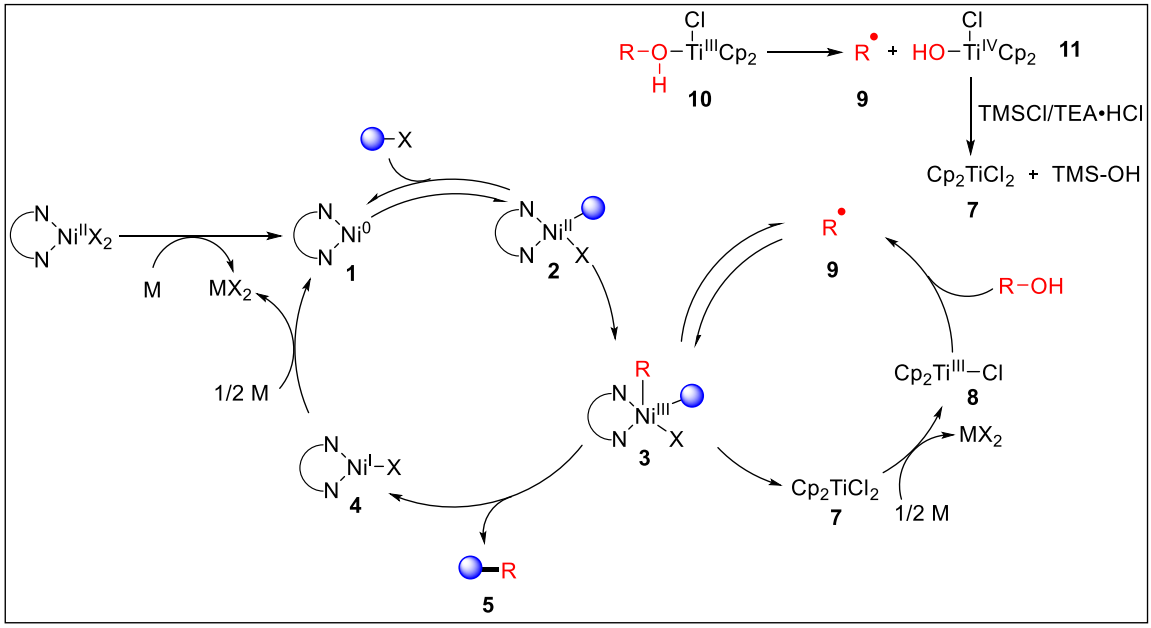
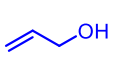
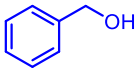
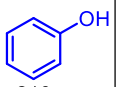


Fig 4.2. Dual catalytic cross-coupling of alcohols and aryl halides with nickel and titanium.

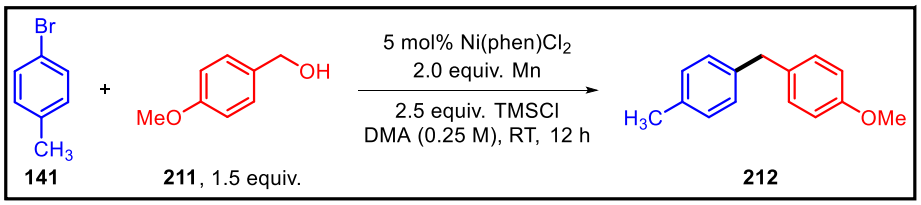
Table 4.1. BDE of alcohols[21]

Alcohol					
	206	207	208	209	210
C-O BDE (*kcal/mol*)	80	83	92	96	112

4.3. RESULTS AND DISCUSSION FOR THE CROSS-COUPLING OF BENZYL ALCOHOLS AND ARYL BROMIDES

4.3.1. Optimization of reaction conditions with 4-bromotoluene and PMB–OH

Table 4.2. Optimization table for the cross-coupling of aryl bromides and *p*-methoxybenzyl alcohol



Entry	Deviations from above	% Conv.[a]
1	None	(96)
2	10 mol% $NiCl_2$•glyme/10 mol% phen	(99)
3	$NiI_2.H_2O$	98
4	10 mol% Ni(phen)Cl_2	(87)
5	1.0 equiv. Mn	42
6	3.0 equiv. TMSCl	(94)
7	10 mol% $NiCl_2$•glyme/10 mol% phen/1.5 equiv. TMSCl	(82)
8	PMB-OH as limiting/1.5 equiv. ArBr	(42)

9	$NiCl_2$	26
10	DMF/10 mol% $NiCl_2$•glyme/10 mol% di-OMe bpy	(95)
11	Phosphine/Carbene Ligands	<15/0

[a] Determined using GC. Yields in the parenthesis are isolated yields after flash chromatography.

We began optimizing the reaction conditions by taking p-methoxy alcohol (PMB–OH) and 4-bromotoluene with titanium and nickel. While carrying out the control experiments, we observed the product formation even in the absence of titanium. Being encouraged by this result, we continued optimizing the reaction conditions with TMSCl and nickel.

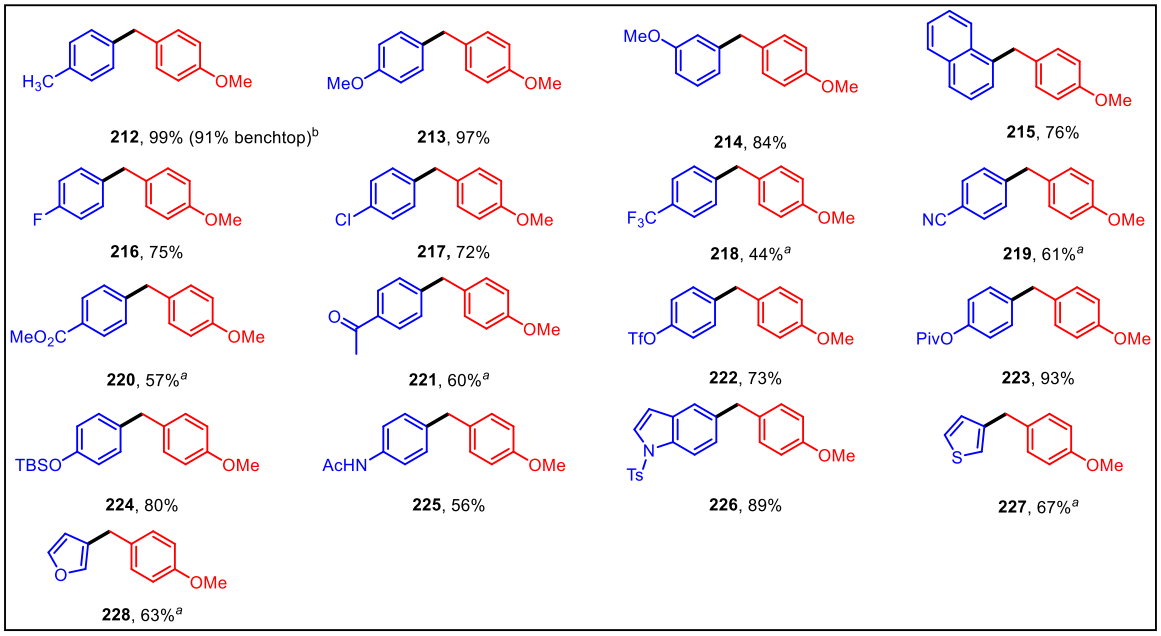
The reaction worked the best in DMA as the solvent and phenanthroline (phen) ligand outperformed all other ligands (99%, entry 1). The reaction worked equally well in DMF but with dimethoxy bipyridyl ligand (95%, entry 10). Even though NiCl2•glyme and phen gave similar results we used a precomplex, Ni(phen)Cl_2 for consistency (entry 2). Phosphine and carbene ligands furnished a little to no product (entry 11). Control reaction revealed the necessity of nickel, ligand and TMSCl.

4.3.2. Substrate screening with various aryl bromides

Substrate screening was initiated to determine the scope of this coupling reaction under the optimized conditions. First, we examined the scope of aryl bromides by varying different substituents on the aryl bromide. Electron-donating groups like methyl and methoxy were tolerated at both meta and para positions (**212-214**). However, ortho-substituents inhibited the coupling due to the steric hindrance with the nickel. The system also tolerated bulky substituent like naphthyl and halogens, fluoro and chloro (**216**, **217**). The system did not produce good yields with the electron-deficient aryl bromides under the reaction conditions due to the rapid homocoupling reaction. Switching the limiting reagent from aryl bromide to benzyl alcohol gave

good yields (**218-221**). Heterocycles such as *N*–Tosylated indole, thiophene and furan were well tolerated under the reaction conditions (**226-228**). Other functionlizable handles like triflate and pivalate (**222**, **223**) were tolerated well under the optimized conditions.

Table 4.3. Substrate scope of aryl bromides



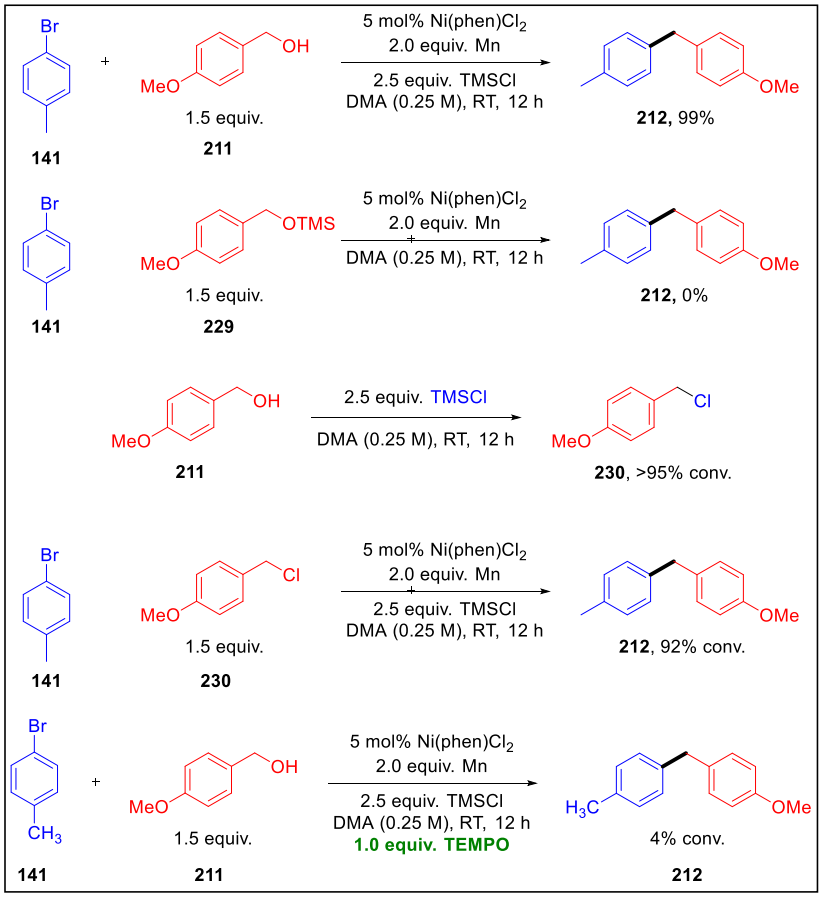
[a] 2.0 equiv. of ArBr was used. [b] Yield was determined using GC.

We then started examining different substituents on the benzyl alcohol, unfortunately only a little to no product was obtained with simple benzyl alcohol and other benzyl alcohol with electron withdrawing group on it. The system appeared to be limited for electron-rich benzyl alcohols.

In order to gain more mechanistic insights and determine why the system was limited to PMB–OH, several control reactions were carried out (scheme 4.3). While the TMS-protected PMB–OH did not form any product, PMB–Cl gave 92% conversion to product. It was also found that the PMB–OH was fully converted to PMB–Cl when reacted with TMSCl in DMA. This suggests that the PMB–OH is converted into PMB–Cl, which undergoes cross-coupling reaction

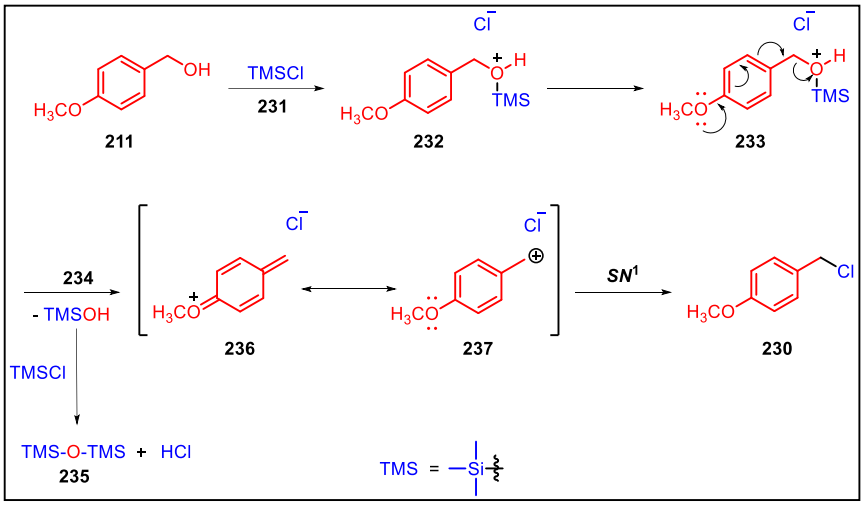
with aryl bromide to form diarylmethanes.[22] The addition of 1.0 equiv. of TEMPO completely shut down the reaction. The mechanism of formation of PMB–Cl is illustrated in scheme 4.4.

Scheme 4.3. Control experiments

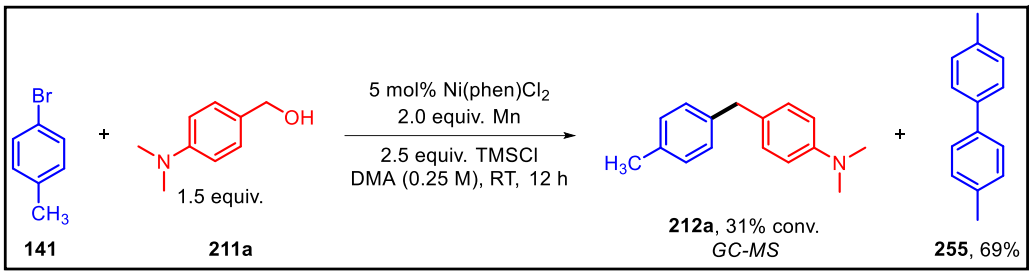


These control reactions clearly signify the role of methoxy group on the benzyl alcohol is crucial for the formation of benzyl chloride (Scheme 4.4). The inability to form the benzyl chloride by other substituents on the benzyl alcohol resulted in no product formation. Also, substituting $–NMe_2$ at para position on the benzyl alcohol instead of –OMe resulted in lower yield (31% conversion by GC-MS) presumably due to the formation of quaternary ammonium species on reaction with TMSCl (Scheme 4.5).

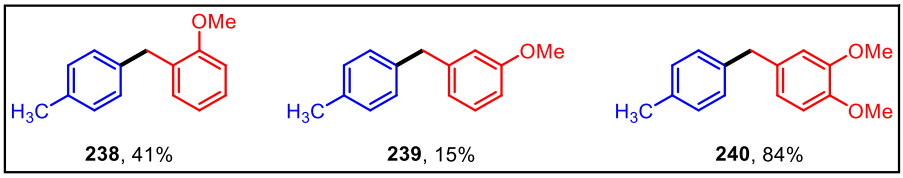
Scheme 4.4. Possible mechanism for the formation of PMB–Cl



Scheme 4.5. Reaction with 4-NMe_2 benzyl alcohol



4.3.3 Reactions with –OMe substituents at different positions



We then examined the position effect of –OMe group on benzyl alcohol. Methoxy at ortho position gave lower yield (41% vs 99%), presumably due to the steric hindrance. Subjecting meta-methoxy benzyl alcohol to the reaction conditions only yielded 15% of the product. But having –OMe group at both meta and para positions formed the product in good yield (84%).

This clearly suggests that the ability to form quinone methide intermediate by –OMe is crucial for this cross-coupling. This also explains why a lower yield (15% vs 99%) was obtained with –OMe at meta position, where the quinone methide (**236**, Scheme 4.4) formation is not feasible.

Since the reaction proceeds through a benzyl chloride intermediate (PMB–Cl), we speculated that the benzyl chlorides would cross-couple with aryl bromides under the optimized conditions. Gratifyingly, benzyl chlorides cross-coupled with aryl bromides with no addition of TMSCl (Scheme 4.6). But electron deficient substituents like –F or $–CF_3$ on the benzyl chloride did not yield the desired products. This might be due to deficiency in nucleophilicity of the metal center to undergo oxidative addition with ArBr, when a benzyl with an electron withdrawing group is attached (**3**, fig. 4.3).

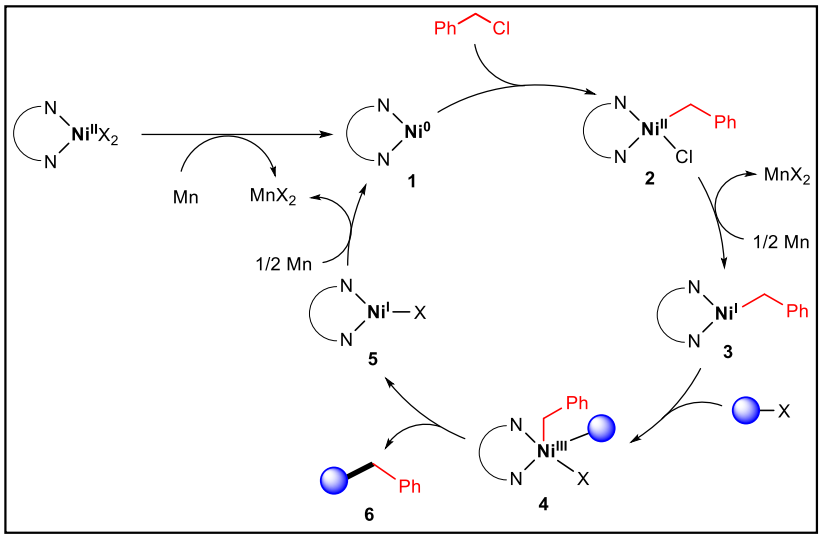
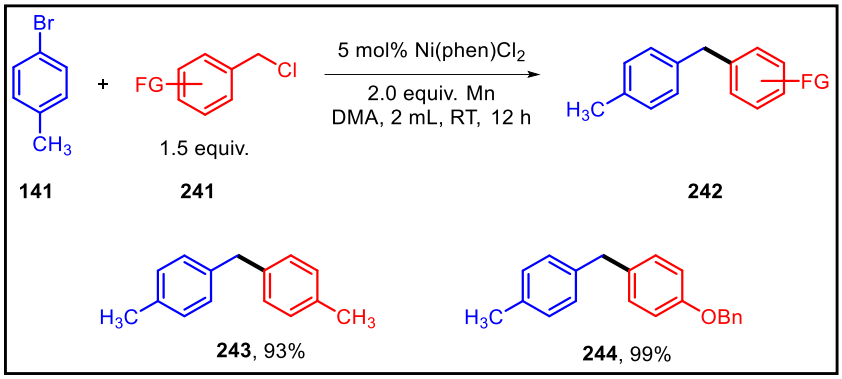


Fig. 4.3. Plausible mechanism for the cross-coupling of benzyl chlorides with aryl bromides.

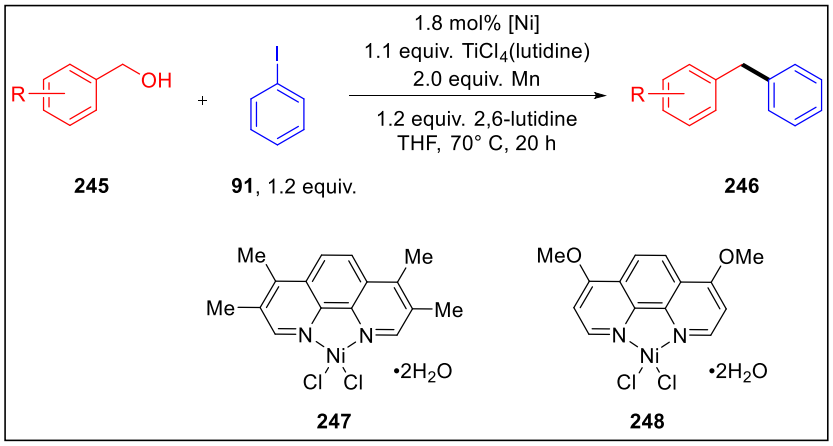
Scheme 4.6. Cross-coupling of benzyl chlorides with aryl bromides



4.4. CONCLUSION FOR THE CROSS-COUPLING OF PMB–OH WITH ARYL BROMIDES

In conclusion, we have developed a cross-coupling method to access diarylmethanes via *in situ* generation of *para*-methoxybenzyl chloride. This method enables the cross coupling of a variety of aryl bromides with PMB–OH at room temperature. Although this method is limited to PMB–OH, this strategy of converting the alcohols into a reactive species *in situ* which can undergo cross-coupling can be applied for other alcohols also.

Scheme 4.7. Cross-coupling of benzyl alcohols with aryl iodides with nickel and titanium



Much similar to our strategy, Ukaji recently reported a nickel-catalyzed cross-coupling of benzyl alcohols with aryl iodides (Scheme 4.7). They used stoichiometric amounts of $TiCl_4$(lutidine) as the co-reductant to generate radicals from benzyl alcohols.[23] Evidently, the chemistry of titanium and nickel is gaining much attention in the area of cross-couplings.

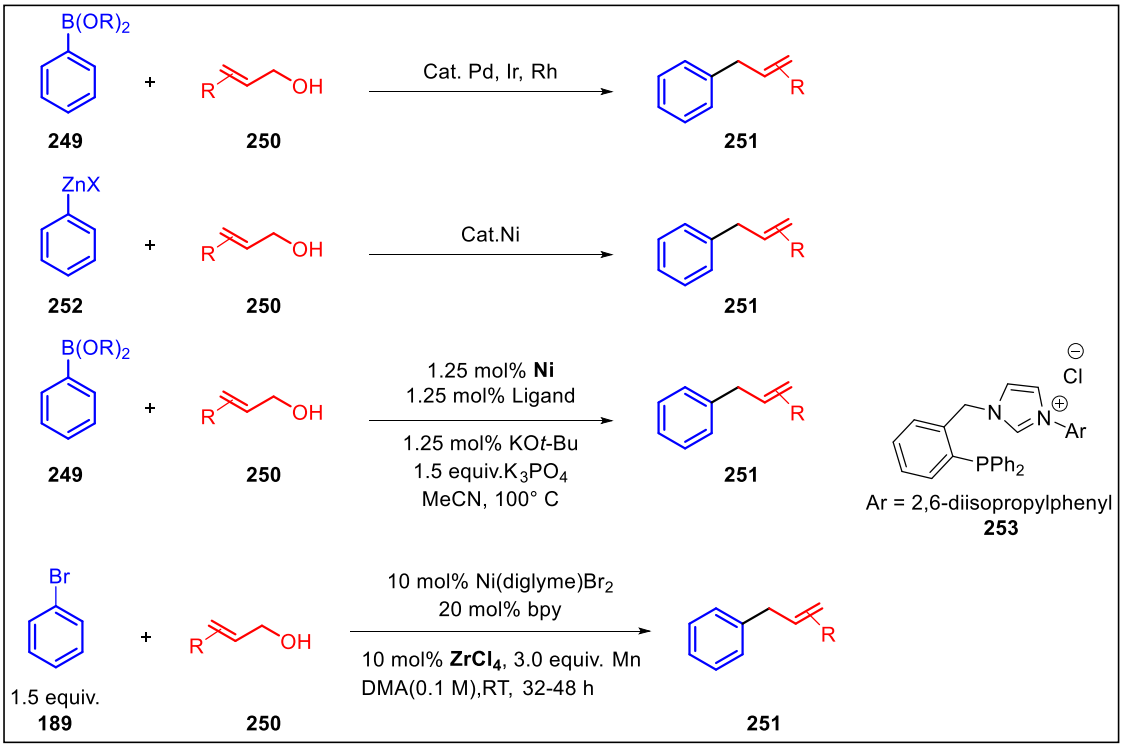
4.5. CROSS-COUPLING OF ALLYL ALCOHOLS WITH ARYL BROMIDES

4.5.1 INTRODUCTION

Allyl arenes are synthetically useful building blocks, which can undergo a variety of chemical transformations.[24-26] Most of the current cross-coupling techniques either use a functionalized allyl alcohol[27-29] or a precious metal (Iridium ,[30-33] Ruthenium,[34] Rhodium,[35-37] Palladium,[5, 38-42]) with a preformed organometallic regents like boronic ester or organozinc.[43, 44] There is a recent report which involves a rather expensive zirconium as the lewis acid to activate the allyl alcohols in cross-coupling aryl bromides.[45] Hence there is a definite demand for the employment of earth-abundant metals to cross couple unactivaed allyl alcohols with readily available aryl halides.

Our strategy to address this issue was to generate radical from allyl alcohols using titanium and intercept those radical with an in situ generated Ni(II) species made from aryl bromide.We initiated our optimization by taking cinnamyl alcohol and 4-bromotoluene as the test substrates.

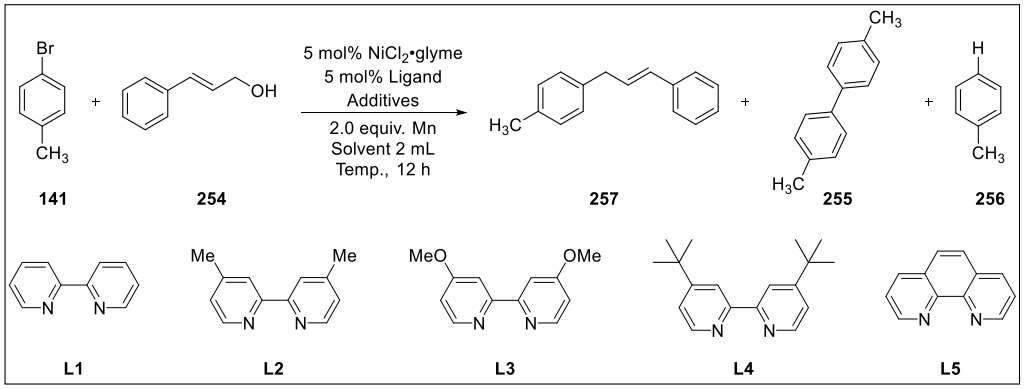
Scheme 4.8. Current strategies to cross-couple unprotected allyl alcohols[4, 45]



4.6. RESULTS AND DISCUSSION FOR THE CROSS-COUPLING OF ALLYL ALCOHOLS AND ARYL BROMIDES

4.6.1 Optimization of reaction conditions with nickel and titanium

Table 4.4. Optimization table for the cross-coupling of allyl alcohol and aryl bromide with nickel and titanium



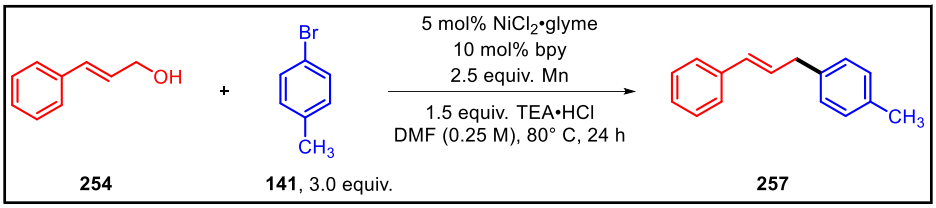
S.No	Solvent (mL)	Ar-Br (equiv.)	Allyl-OH (equiv.)	Ni (5 mol%)	Ligand (5 mol%)	[M] (2.0 equiv.)	Additives (equiv.)	Temp °C	% Conversion			
									ArBr	257	255	256
1	DMA	1.0	1.5	Ni(di-OMe-bpy)Cl_2	-	Mn	Cp_2TiCl_2 (5 mol%)	60	0	16	75	9
2	DMA	1.0	1.5	Ni(di-OMe-bpy)Cl_2	-	Mn	Cp_2TiCl_2 (5 mol%) TEA•HCl (1.0 eq.)	RT	85	9	1	5
3	DMA	1.0	1.5	Ni(di-OMe-bpy)Cl_2	-	Mn	Cp_2TiCl_2 (5 mol%) TEA•HCl (1.0 eq.)	60	0	51	27	22
4	DMA	1.0	1.5	$NiCl_2$·dme	L1	Mn	Cp_2TiCl_2 (5 mol%) TEA•HCl (1.0 eq.)	60	0	41	42	17
5	DMA	1.0	1.5	$NiCl_2$·dme	L2	Mn	Cp_2TiCl_2 (5 mol%) TEA•HCl (1.0 eq.)	60	0	59	16	25
6	DMA	1.0	1.5	$NiCl_2$·dme	L3	Mn	Cp_2TiCl_2 (5 mol%) TEA•HCl (1.0 eq.)	60	0	57	14	29
7	DMA	1.0	1.5	$NiCl_2$·dme	L4	Mn	Cp_2TiCl_2 (5 mol%) TEA•HCl (1.0 eq.)	60	0	58	22	20
8	DMA	1.0	1.5	$NiCl_2$·dme	L5	Mn	Cp_2TiCl_2 (5 mol%) TEA•HCl (1.0 eq.)	60	50	12	2	36
9	DMA	1.0	1.5	$NiCl_2$·dme	DMAP (10 mol%)	Mn	Cp_2TiCl_2 (5 mol%) TEA•HCl (1.0 eq.)	60	100	-	-	-
10	DMA	1.0	1.5	$NiCl_2$·dme	L1	Mn	Cp_2TiCl_2 (10 mol%) TEA•HCl (1.0 eq.)	60	37	26	5	32
11	DMA	1.0	1.5	$NiCl_2$·dme	L2	Mn	Cp_2TiCl_2 (10 mol%) TEA•HCl (1.0 eq.)	60	0	53	26	21
12	DMA	1.0	1.5	$NiCl_2$·dme	L3	Mn	Cp_2TiCl_2 (10 mol%) TEA•HCl (1.0 eq.)	60	21	38	6	35
13	DMA	1.0	1.5	$NiCl_2$·dme	L4	Mn	Cp_2TiCl_2 (10 mol%) TEA•HCl (1.0 eq.)	60	0	67	12	21
14	DMF	1.0	1.5	$NiCl_2$·dme	L1	Mn	Cp_2TiCl_2 (5 mol%) TEA•HCl (1.0 eq.)	60	0	**72**	5	23
15	DMF	1.0	1.5	$NiCl_2$·dme	L2	Mn	Cp_2TiCl_2 (5 mol%) TEA•HCl (1.0 eq.)	60	0	**75**	8	18
16	DMF	1.0	1.5	$NiCl_2$·dme	L3	Mn	Cp_2TiCl_2 (5 mol%) TEA•HCl (1.0 eq.)	60	2	**75**	3	20
17	DMF	1.0	1.5	$NiCl_2$·dme	L4	Mn	Cp_2TiCl_2 (5 mol%) TEA•HCl (1.0 eq.)	60	0	**67**	14	18

18	DMF	1.0	1.5	$NiCl_2$·dme	L5	Mn	Cp_2TiCl_2 (5 mol%) TEA•HCl (1.0 eq.)	60	33	23	2	41
19	THF	1.0	1.5	$NiCl_2$·dme	L1	Mn	Cp_2TiCl_2 (5 mol%) TEA•HCl (1.0 eq.)	60	87	7	0	6
20	THF	1.0	1.5	$NiCl_2$·dme	L5	Mn	Cp_2TiCl_2 (5 mol%) TEA•HCl (1.0 eq.)	60	76	10	2	12
21	THF	1.0	1.5	$NiCl_2$·dme	L2	Mn	Cp_2TiCl_2 (5 mol%) TEA•HCl (1.0 eq.)	60	82	2	7	9
22	THF	1.0	1.5	$NiCl_2$·dme	L4	Mn	Cp_2TiCl_2 (5 mol%) TEA•HCl (1.0 eq.)	60	65	10	10	15
23	THF	1.0	1.5	$NiCl_2$·dme	L3	Mn	Cp_2TiCl_2 (5 mol%) TEA•HCl (1.0 eq.)	60	78	9	2	11
24	DMPU	1.0	1.5	$NiCl_2$·dme	L1	Mn	Cp_2TiCl_2 (5 mol%) TEA•HCl (1.0 eq.)	60	19	51	11	19
25	DMPU	1.0	1.5	$NiCl_2$·dme	L5	Mn	Cp_2TiCl_2 (5 mol%) TEA•HCl (1.0 eq.)	60	0	24	32	44
26	DMPU	1.0	1.5	$NiCl_2$·dme	L2	Mn	Cp_2TiCl_2 (5 mol%) TEA•HCl (1.0 eq.)	60	20	32	16	32
27	DMPU	1.0	1.5	$NiCl_2$·dme	L4	Mn	Cp_2TiCl_2 (5 mol%) TEA•HCl (1.0 eq.)	60	41	36	8	15
28	DMPU	1.0	1.5	$NiCl_2$·dme	L3	Mn	Cp_2TiCl_2 (5 mol%) TEA•HCl (1.0 eq.)	60	60	17	6	17

dme = dimethoxyethane; Cp_2TiCl_2 = Titanacene dichloride; TEA•HCl = Triethylamine hydrochloride.

The reaction was found to be optimal in DMF and gave up to 75% yield with ligands L1, L2 and L3. When we were optimizing the reaction conditions with nickel and titanium (Cp_2TiCl_2), we found that there was product formation even in the absence of titanium. Being encouraged by these results, we then continued optimizing the reaction conditions with nickel and TEA•HCl.

Table 4.5. Optimization table for the cross-coupling of allyl alcohols and aryl bromides with nickel and TEA•HCl



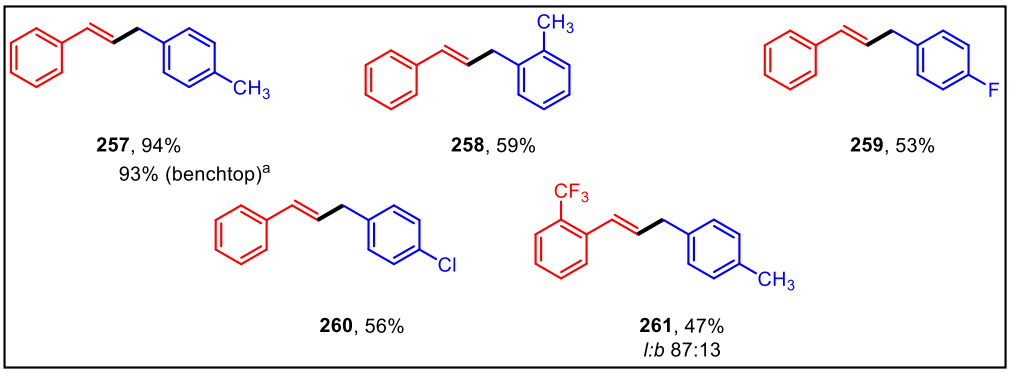
Entry	Deviations from above	Isolated yield
1	None	94
2	2.0 equiv. of ArBr	80
3	2.0 equiv. of ArBr/2.0 equiv. of TEA•HCl	78
4	3.0 equiv. of Mn	45
5	12 h	65
6	2.0 equiv. of ArBr/60 °C	60
7	2.0 equiv. of ArBr/10 mol% Ni/20 mol% bpy	71
8	NMP/2.0 equiv. of ArBr/10 mol% Ni/20 mol% bpy	64
9	DMA/2.0 equiv. of ArBr/10 mol% Ni/20 mol% bpy	56
10	Phosphine Ligands	0

TEA•HCl = Triethylamine hydrochloride, TMG•HCl = Tetramethylguanidine hydrochloride, Py•HCl = Pyridine hydrochloride, TFA = Trifluoroacetic acid. Yields in the parenthesis are isolated yields.

DMF was found to be the optimal solvent after an extensive solvent screening (Table 4.5). The reaction yielded 60% of the desired product at 60 °C with 2.0 equivalence of 4-bromotoluene (entry 6).The yield was further increased to 80% by rising the temperature to 80 °C (entry 2). We observed about 10-15% of reduced product presumably through the formation of

Ni–H. This was resolved by increasing the amount of aryl bromide from two to three equivalence which not only eliminated the formation of the reduced product but also increased the product to 94% (entry 1). Lowering the amount of TEA•HCl and the addition of water as an additive was found to be detrimental. The reaction took 24 h with 5 mol% nickel versus 12 h with 10 mol% nickel to afford similar yields (entry 5).

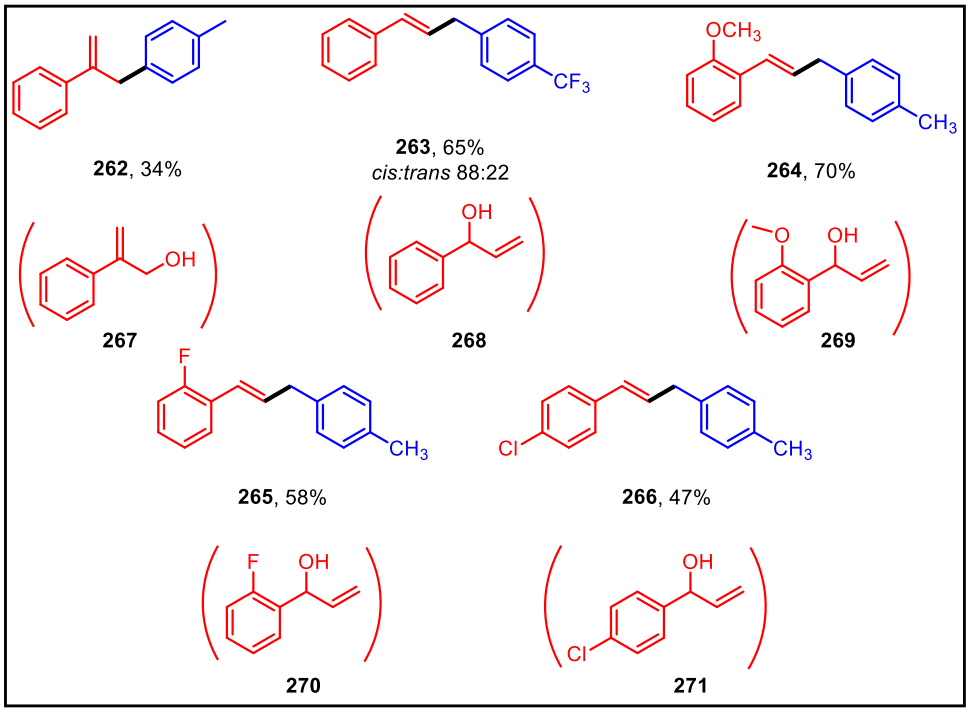
Table 4.6. Substrate scope cinnamyl alcohols



[a] Yield was determined using GC.

With the optimized conditions in hand, substrate screening was pursued. Cinnamyl alcohols were found to work well under the optimized conditions. Functional groups like methyl, chloro and fluoro were tolerated on aryl bromide part. The system also tolerated ortho substituents on both aryl bromide and cinnamyl alcohol (**258** and **261**).

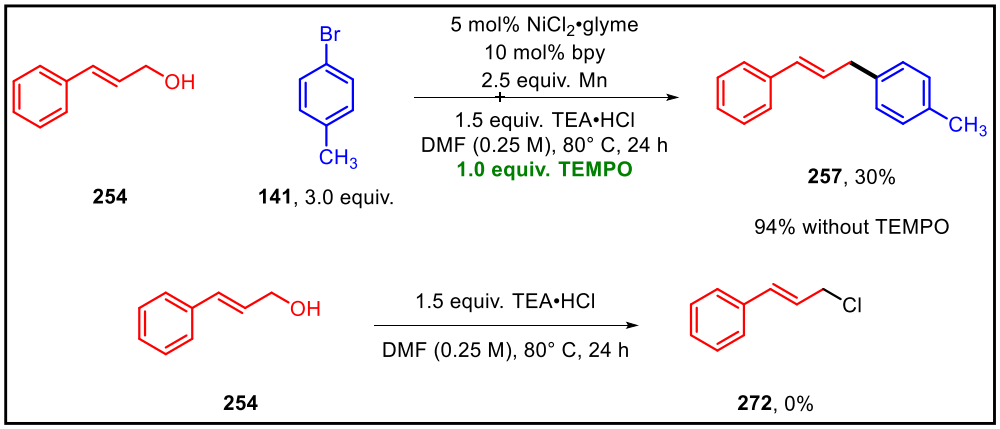
Table 4.7. Substrate scope of alpha- and beta-substituted allyl alcohols



We were delighted to find the reaction can be further extended to both alpha (**262**) and beta-substituted allyl alcohols. The beta-substituted allyl alcohols furnished the linear products majorly. The system tolerated ortho substituted alcohol (**264**) and also halides like chloro and fluoro groups were well tolerated on the alcohol part (**265** and **266**).

To probe the mechanism of this cross-coupling, 1.0 equiv. of TEMPO was added to the reaction mixture. The yield of the product was lowered to 30% versus 94% when no TEMPO added (Scheme 4.9). We did not find any evidence for radical formation under the reaction conditions. Also, reacting the cinnamyl alcohol alone with 1.5 equiv. of TEA•HCl at 80 °C did not form any cinnamyl chloride.

Scheme 4.9. Control and radical trapping experiments



Although the exact mechanism for the activation of allyl alcohols is not clear, it appears that the MnX_2 salt formed during the progress of the reaction could acts act as a lewis acid.[44, 45] The role of TEA•HCl appears to protonate any Ni–O–Allyl bond that is formed and regenerate the allyl alcohol. This also explains why we observed trace amounts of reduced products during the optimization, as nickel also forms Ni–H when it activates the –OH bond of the alcohol.

4.7. CONCLUSION FOR THE CROSS-COUPLING OF ALLYL ALCOHOLS WITH ARYL BROMIDES

In conclusion, we have developed a less expensive method for cross-coupling of activated allyl alcohols with aryl bromides. It is also noteworthy to mention that this protocol does not require any external activator for the allyl alcohol. We hypothesize that the manganese salt (MnX_2) formed *in situ* acts as the lewis acid for the activation of the allyl alcohol. Cinnamyl, α- and β-substituted allyl alcohols can be cross coupled with the aryl bromides employing this methodology.

4.8. SUPPORTING INFORMATION

4.8.1. Methods

Unless stated otherwise, all reactions were carried out in an oven dried 10 mL microwave vial under an atmosphere of argon, with magnetic stirring (800 rpm). Reactions were monitored either by thin-layer chromatography with 0.25 mm precoated silica gel plates, or gas chromatography. Visualization of all TLCs was performed by UV and/or staining with phosphomolybdic acid, $KMnO_4$, or Seebach's stain. Purifications were performed by MPLC on a Biotage Isolera system with 50 g cartridges packed with silica gel (Silicycle, 60 Å, 230-400 mesh) eluted using a hexanes/EtOAc gradient, unless otherwise noted.

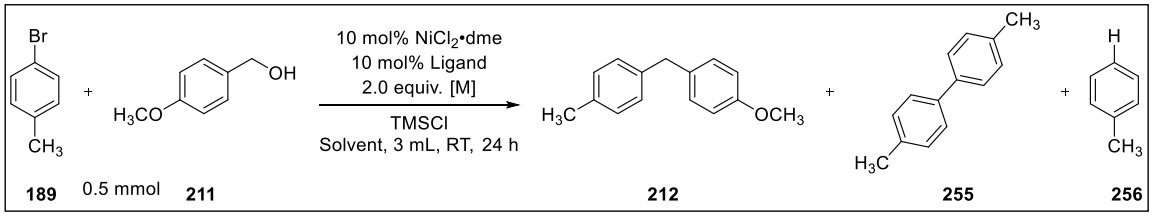
4.8.2. Materials

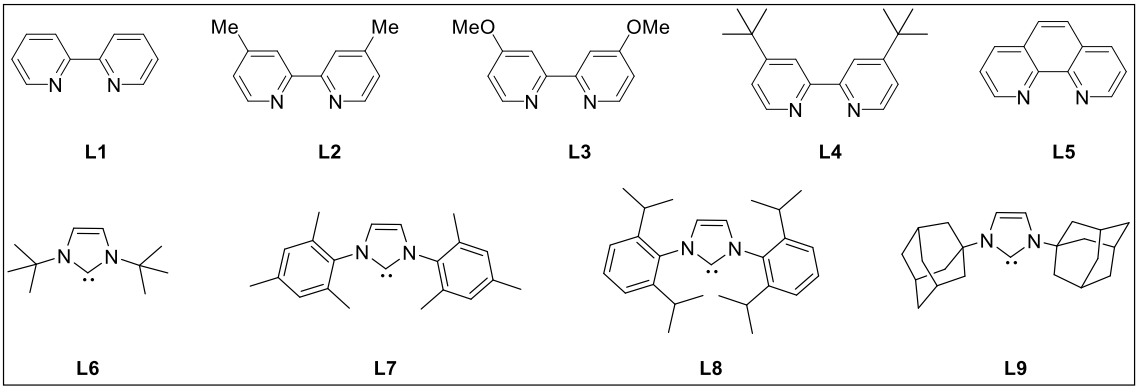
Diethyl ether, dichloromethane, chloroform, *N*,*N*-dimethylformamide and tetrahydrofuran were dried using a solvent purification system that contained activated alumina. 1,2-dichloroethane and chlorotrimethylsilane were freshly distilled from calcium hydride under an argon atmosphere. 1,4-dioxane was freshly distilled from sodium benzophenone ketyl under argon atmosphere. All other reagents and solvents were reagent grade and used without further purification unless otherwise stated. All the solvents were degassed for 30 minutes before use. Ni(phen)Cl_2 and Ni(di-OMe-bpy)Cl_2 were prepared according to the known literature procedure.[47] $NiCl_2$.glyme was purchased from Strem Chemicals and all other ligands were purchased from different commercial sources. Mn powder (-325 mesh) and zinc powder (-100 mesh) were purchased from Alfa Aesar. (4-bromophenoxy)(tert-butyl)dimethylsilane,[48] 4-bromophenyl pivalate,[49] 5-bromo-1-tosyl-1*H*-indole,[50] *N*-(4-bromophenyl)acetamide,[51] and 4-bromophenyl trifluoromethanesulfonate[52] and the allyl alcohols used were prepared using standard literature procedures.[53, 54] The remaining substrates were purchased and used as received.

4.8.3. Instrumentation

^{1}H NMR, ^{13}C NMR and ^{19}F spectra (pulse decoupling) were obtained on a Bruker Avance 400 MHz NMR Spectrometer (400 MHz for ^{1}H and 101 MHz for ^{13}C) with chemical shifts reported relative to either residual chloroform solvent peaks (δ = 7.26 ppm for ^{1}H and δ = 77.0 ppm for ^{13}C) or residual dimethylsulfoxide solvent peaks (δ = 2.50 ppm for ^{1}H and δ = 39.52 ppm for ^{13}C). Data for ^{1}H NMR were recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sex = sextet, sept = septet, m = multiplet, or unresolved), coupling constant(s) in Hz, integration. The reported melting points are uncorrected. IR spectra were obtained on a NICOLET iS50 FT-IR spectrometer. Low resolution mass spectra were obtained on a Shimadzu QP2010S GC/MS with a SHR5XlB column (30 m, 0.25 mm ID, 0.25 µm df, injection temp. = 260 °C) using a standard ramp of 40 °C to 280 °C at 10 °C/min, holding at 280 °C for 10 minutes. High Resolution Mass Spectra (HRMS) were determined using a Thermo LTQ-OrbitrapXL mass spectrometer operated in FT mode to provide a nominal resolution of 100,000.

Table 4.8. Complete optimization table for the cross-coupling of *para*-methoxybenzyl alcohol and aryl bromides





S.No.	Solvent (mL)	Ar-Br (equiv.)	$ArCH_2OH$ (equiv.)	$NiCl_2$·dme (mol%)	Ligand (10 mol%)	[M] (equiv.)	TMSCl (equiv.)	Temp °C	% Conversion[a]			
									ArBr	212	255	256
1	THF	1.0	1.5	10	L4	Mn	3.0	60	0	26	65	9
2	THF	1.0	1.5	10	L4	Zn	3.0	60	64	15	9	11
3	THF	1.0	1.5	10	L4	Mn	3.0	RT	0	52	33	15
4	THF	1.0	1.5	10	L4	Zn	3.0	RT	49	11	27	13
5	DMSO	1.0	1.5	10	L4	Mn	3.0	60	50	42	1	7
6	DMSO	1.0	1.5	10	L4	Zn	3.0	60	92	0	0	8
7	DMSO	1.0	1.5	10	L4	Mn	3.0	RT	87	13	0	0
8	DMSO	1.0	1.5	10	L4	Zn	3.0	RT	98	0	0	2
9	ACN	1.0	1.5	10	L4	Mn	3.0	60	91	8	0	1
10	ACN	1.0	1.5	10	L4	Zn	3.0	60	91	1	0	8
11	Dioxane	1.0	1.5	10	L4	Mn	3.0	60	100	0	0	0
12	Dioxane	1.0	1.5	10	L4	Zn	3.0	60	94	0	0	6
13	NMP	1.0	1.5	10	L4	Mn	3.0	60	88	10	0	2
14	NMP	1.0	1.5	10	L4	Zn	3.0	60	83	0	0	17
15	NMP	1.0	1.5	10	L4	Mn	3.0	RT	97	2	0.5	0.5
16	NMP	1.0	1.5	10	L4	Zn	3.0	RT	100	0	0	0
17	DCE	1.0	1.5	10	L4	Mn	3.0	60	100	0	0	0
18	DCE	1.0	1.5	10	L4	Zn	3.0	60	100	0	0	0
DMF												
19	DMF	1.0	1.5	10	L4	Mn	3.0	60	0	87(**70**)	6	7
20	DMF	1.0	1.5	10	L4	Zn	3.0	60	76	1	0	23
21	DMF	1.0	1.5	10	L4	Mn	3.0	RT	0	86	6	8
22	DMF	1.0	1.5	10	L4	Zn	3.0	RT	98	2	0	0
23	DMF	1.0	1.5	10	L1	Mn	3.0	RT	5	14	55	26
24	DMF	1.0	1.5	10	L2	Mn	3.0	RT	0	89	4	7
25	DMF	1.0	1.5	10	L3	Mn	3.0	RT	0	92(**89**)	3	5
26	DMF	1.0	1.5	10	L3	Mn	3.5	RT	0	(**78**)	3	5
S.No.	**Solvent (mL)**	**Ar-Br (equiv.)**	**$ArCH_2OH$ (equiv.)**	**$NiCl_2$·dme (mol%)**	**Ligand (10 mol%)**	**[M] (equiv.)**	**TMSCl (equiv.)**	**Temp °C**	**% Conversion**			
									ArBr	**A**	**B**	**C**
27	DMF (2 mL)	1.0	1.5	10	L3	Mn	3.0	RT	0	(**95**)	3	5
28	DMF (2 mL)	1.0	1.5	Ni(**L3**)Cl_2 5 mol%	-	Mn	2.5	RT	0	(**75**)	3	5
29	DMF	1.0	1.5	10	L5	Mn	3.0	RT	0	44	49	7
30	DMF	1.0	1.5	10	L6	Mn	3.0	RT	100	0	-	-
31	DMF	1.0	1.5	10	L7	Mn	3.0	RT	100	0	-	-
32	DMF	1.0	1.5	10	L8	Mn	3.0	RT	100	0	-	-
33	DMF	1.0	1.5	10	L9	Mn	3.0	RT	100	0	-	-
DMA												
34	DMA	1.0	1.5	10	L4	Mn	3.0	60	0	91(**6**	3	6

										0)		
35	DMA	1.0	1.5	10	L4	Zn	3.0	60	0	43	30	27
36	DMA	1.0	1.5	10	L4	Mn	3.0	RT	0	89	6	5
37	DMA	1.0	1.5	10	L4	Zn	3.0	60	58	33	2	7
38	DMA	1.0	1.5	10	L1	Mn	3.0	RT	0	89(**6 2**)	2	9
39	DMA	1.0	1.5	10	L2	Mn	3.0	RT	33	62	1	3
40	DMA	1.0	1.5	10	L3	Mn	3.0	RT	0	65	4	31
41	DMA	1.0	1.5	10	L5	Mn	3.0	RT	3	96(**8 1**)	0.5	0.5
42	DMA	1.0	1.5	10	L5	Mn	3.5	RT	-	(**65**)	-	-
43	DMA (2 mL)	1.0	1.5	10	L5	Mn	3.0	RT	-	(**96**)	-	-
44	DMA (2 mL)	1.0	1.5	10	L5	Mn	1.5	RT	0	93(**8 2**)	2	5
45	DMA (2 mL)	1.0	1.5	10	L5	Mn	2.0	RT	0	60(**3 8**)	30	9
46	DMA (2 mL)	1.0	1.5	10	L5	Mn	4.0	RT	3	91	3	3
47	DMA (2 mL)	1.0	1.5	10	L5	Mn	5.0	RT	17	79	1	3
48	DMA (2 mL)	1.0	1.5	10	L5	Mn	20 mol%	RT	0	27	67	6
49	DMA (2 mL)	1.0	1.25	10	L5	Mn	2.5	RT	-	(**61**)	-	-
50	DMA (2 mL)	1.0	1.5	10	L5	Mn	2.5	RT	-	(**99**)	-	-
51	DMA (2 mL)	1.0	1.5	5	L5 5 mol%	Mn	2.5	RT	-	(**86**)	-	-
52	DMA (2 mL)	1.0	1.5	$Ni(phen)Cl_2$ 10 mol%	-	Mn	3.0	RT	-	(**87**)	-	-
53	DMA (2 mL)	1.0	1.5	$Ni(phen)Cl_2$ 5 mol%	-	Mn	3.0	RT	-	(**94**)	-	-
54	DMA (2 mL)	1.0	1.5	$Ni(phen)Cl_2$ 5 mol%	-	Mn	2.5	RT	-	(**96**)	-	-
55	DMA (2 mL)	1.0	1.5	$Ni(phen)Cl_2$ 5 mol%	-	Mn (1.0 eq.)	2.5	RT	50	42	3	5
56	DMA (2 mL)	1.0	1.5	Ni(phen)Cl2 5 mol%	L5	Mn	2.0 SiO_2	RT	100	0	0	0
57	DMA (2 mL)	1.5	1.0	10	L5	Mn	2.0	RT	-	(**42**)	-	-

Screening of various Nickel Salts

S.No.	Solvent (mL)	Ar-Br (equiv.)	$ArCH_2OH$ (equiv.)	Ni Salt 5 mol%	Ligand (5 mol%)	[M] (equiv.)	TMSCl (equiv.)	Temp °C	% Conversion			
									ArBr	A	B	C
58	DMA (2 mL)	1.0	1.5	$NiCl_2$	L5	Mn	2.5	RT	68	26	4	2
59	DMA (2 mL)	1.0	1.5	$NiBr_2$	L5	Mn	2.5	RT	31	49	9	10
60	DMA (2 mL)	1.0	1.5	$NiBr_2$·dme	L5	Mn	2.5	RT	0	85	10	5
61	DMA (2 mL)	1.0	1.5	$NiI_2·H_2O$	L5	Mn	2.5	RT	0	98	1	1
62	DMA (2 mL)	1.0	1.5	$Ni(acac)_2$	L5	Mn	2.5	RT	0	88	8	4
Screening of Phosphine Ligands												
63	DMA (2 mL)	1.0	1.5	$Ni(PPh_3)_2Cl_2$	-	Mn	2.5	RT	97	2	0	1
64	DMA (2 mL)	1.0	1.5	$Ni(PCy_3)_2Cl_2$	-	Mn	2.5	RT	100	-	-	-
65	DMA (2 mL)	1.0	1.5	$Ni(PMe_3)_2Cl_2$	-	Mn	2.5	RT	100	-	-	-

66	DMA (2 mL)	1.0	1.5	$Ni(dppe)Cl_2$	-	Mn	2.5	RT	100	-	-	-
67	DMA (2 mL)	1.0	1.5	$Ni(dppp)Cl_2$	-	Mn	2.5	RT	100	-	-	-
68	DMA (2 mL)	1.0	1.5	$Ni(dppf)Cl_2$	-	Mn	2.5	RT	77	13	2	8

[a]Yields were determined using GC. The yields in the parenthesis are isolated yields after flash chromatography.

4.8.4. General procedure A for the cross-coupling of *para*-methoxy benzyl alcohol and aryl bromides

An oven dried 10 mL microwave vial with a magnetic stir bar was taken into an argon filled glovebox and charged with $Ni(phen)Cl_2$ (0.025 mmol, 0.008 g) and Manganese powder (-325 mesh, 1 mmol, 0.055 g). An aluminum sealed septa was then crimped onto the vial, which was then taken out of the glovebox. The vial was then sequentially injected with aryl bromide (0.5 mmol), *para*-methoxy benzyl alcohol (PMB–OH) (0.75 mmol), TMSCl (1.25 mmol, 0.159 mL) and stirred for 5 minutes at RT. Then degassed DMA (2 mL) was added and the septum was wrapped with parafilm. The reaction mixture was stirred for 12 hours at room temperature and poured into water (50 mL). The aqueous layer was extracted with EtOAc (2x 50 mL) and the combined organic layer was washed with 1 M HCl to remove the metal residue and then with water (50 mL) followed by brine solution (50 mL). The EtOAc layer was separated, 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, unless otherwise stated.

Notes:

1. If any of the reagents were solids, they were weighed into the microwave vial inside glove box before capping.

2. Adding TMSCl last i.e. after the addition of the solvent (DMA), yielded only TMS-protected PMB–OH.

3. **Purificaton**: Some of the products were isolated as an inseparable mixture with 1,2-bis(4-methoxyphenyl)ethane and the yields of those products were calculated using the ratio of the benzylic protons of the desired product and by-product in ^{1}H NMR.

4.8.5. General procedure B for the cross-coupling of *para*-methoxy benzyl alcohol and electron deficient aryl bromides

An oven dried 10 mL microwave vial with a magnetic stir bar was taken into an argon filled glovebox and charged with Ni(phen)Cl_2 (0.025 mmol, 0.008 g) and Manganese powder (-325 mesh, 1 mmol, 0.055 g). An aluminum sealed septa was then crimped onto the vial, which was then taken out of the glovebox. The vial was then sequentially injected with aryl bromide (1.0 mmol), *para*-methoxy benzyl alcohol (PMB–OH) (0.5 mmol), TMSCl (1.25 mmol, 0.159 mL) and stirred for 5 minutes at RT. Then degassed DMA (2 mL) was added and the septum was wrapped with parafilm. The reaction mixture was stirred for 12 hours at room temperature and poured into water (50 mL). The aqueous layer was extracted with EtOAc (2x 50 mL) and the combined organic layer was washed with 1 M HCl to remove the metal residue and then with water (50 mL) followed by brine solution (50 mL). The EtOAc layer was separated, 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, unless otherwise stated.

Notes:

1. If any of the reagents were solids, they were weighed into the microwave vial inside glove box before capping.

2. Adding TMSCl last i.e. after the addition of the solvent, DMA yielded only TMS-protected PMB–OH.

3. **Purificaton**: Some of the products were isolated as an inseparable mixture with 1,2-bis(4-methoxyphenyl)ethane and the yields of those products were calculated using the ratio of the benzylic protons of the desired and by-product in ^{1}H NMR.

4.8.6. General procedure C for the cross-coupling of benzyl chlorides and aryl bromides

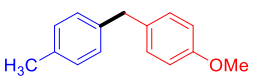
An oven dried 10 mL microwave vial with a magnetic stir bar was taken into an argon filled glovebox and charged with Ni(phen)Cl_2 (0.025 mmol, 0.008 g) and Manganese powder (-325 mesh, 1 mmol, 0.055 g). An aluminum sealed septa was then crimped onto the vial, which was then taken out of the glovebox. The vial was then sequentially injected with aryl bromide (0.5 mmol) and benzyl chloride (0.75 mmol). Then degassed DMA (2 mL) was added and the septum was wrapped with parafilm. The reaction mixture was stirred for 12 hours at room temperature and poured into water (50 mL). The aqueous layer was extracted with EtOAc (2x 50 mL) and the combined organic layer was washed with 1 M HCl to remove the metal residue and then with water (50 mL) followed by brine solution (50 mL). The EtOAc layer was separated, 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, unless otherwise stated.

Notes:

1. If any of the reagents were solids, they were weighed into the microwave vial inside glove box before capping.

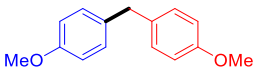
4.8.7. Synthesis and characterization of diarylmethanes

1-methoxy-4-(4-methylbenzyl)benzene (212):



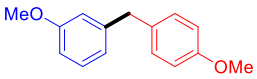
Subjection of 4-bromotoluene (0.5 mmol, 0.062 mL) and 4-methoxybenzyl alcohol (0.75 mmol, 0.093 mL) to general procedure A at RT for 12 h afforded 0.105 g (99%) of **212** as a colorless oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 – 7.06 (m, 6H), 6.90 – 6.80 (m, 2H), 3.93 – 3.88 (m, 2H), 3.83 – 3.77 (m, 3H), 2.36 – 2.30 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.9, 138.5, 135.4, 133.5, 129.8, 129.1, 128.7, 113.8, 55.2, 40.6, 21.0; IR (neat) 3013, 2965, 2912, 2841, 1606, 1506, 1273, 1026, 804 cm^{-1}. Physical and spectral data were consistent with those reported in the literature.[55]

bis(4-methoxyphenyl)methane (213):



Subjection of 4-bromoanisole (0.5 mmol, 0.063 mL) and 4-methoxybenzyl alcohol (0.75 mmol, 0.093 mL) to general procedure A at RT for 12 h afforded an inseparable mixture of **213,** 0.110 g (97%) and 1,2-bis(4-methoxyphenyl)ethane as a white solid after flash chromatography (Hex/EtOAc); m.p. = 38-40 °C ^{1}H NMR (400 MHz,) δ 7.12 – 7.05 (m, 4H, measured 4.69H), 6.86 – 6.78 (m, 4H, measured 4.71H), 3.87 (s, 2H), 3.79 (s 6H, measured 6.92H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.9, 133.7, 129.7, 113.8, 55.3, 40.1; IR (neat) 3032, 3006, 2916, 2836, 1609, 1508, 1239, 1175, 1026, 807 cm^{-1}. Physical and spectral data were consistent with those reported in the literature.[56]

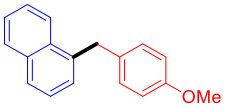
1-methoxy-3-(4-methoxybenzyl)benzene (214):



Subjection of 3-bromoanisole (0.5 mmol, 0.063 mL) and 4-methoxybenzyl alcohol (0.75 mmol, 0.093 mL) to general procedure A at RT for 12 h afforded an inseparable mixture of **214,** 0.096 g (84%) and 1,2-bis(4-

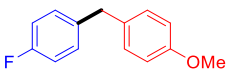
methoxyphenyl)ethane as a colorless oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.17 (m, 1H), 7.15 – 7.06 (m, 2H, measured 3.43H), 6.84 (m, 2H, measured 3.29H), 6.81 – 6.71 (m, 3H), 3.91 (s, 2H), 3.79 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 158.0, 157.8, 143.2, 133.9, 133.0, 129.8, 129.3, 121.2, 119.7, 114.6, 113.8, 113.7, 111.2, 55.1, 41.0, 37.3; IR (neat) 2999, 2931, 2834, 1599, 1509, 1242, 1175, 1031, 830 cm^{-1}. Physical and spectral data were consistent with those reported in the literature.[55]

1-(4-methoxybenzyl)naphthalene (215):



Subjection of 1-bromonaphthalene (0.5 mmol, 0.070 mL) and 4-methoxybenzyl alcohol (0.75 mmol, 0.093 mL) to general procedure A at RT for 12 h afforded 0.094 g (76%) of **215** as a colorless oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dddd, *J* = 7.3, 4.6, 2.6, 1.2 Hz, 1H), 7.70 – 7.64 (m, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.31 – 7.20 (m, 3H), 7.12 – 7.06 (m, 1H), 6.97 – 6.89 (m, 2H), 6.66 – 6.60 (m, 2H), 4.20 (s, 2H), 3.57 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.9, 137.0, 133.9, 132.6, 132.1, 129.6, 128.6, 127.1, 127.0, 125.9, 125.5, 125.5, 124.2, 113.8, 55.2, 38.1; IR (neat) 3038, 2929, 2833, 1508, 1243, 1174, 1033, 778 cm^{-1}. Physical and spectral data were consistent with those reported in the literature.[55]

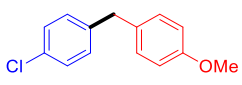
1-fluoro-4-(4-methoxybenzyl)benzene (216):



Subjection of 1-bromo-4-fluorobenzene (0.5 mmol, 0.055 mL) and 4-methoxybenzyl alcohol (0.75 mmol, 0.093 mL) to general procedure A at RT for 12 h afforded 0.081 g (75%) of **216** as a colorless oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.07 (m, 4H), 7.04 – 6.95 (m, 2H), 6.87 (dd, *J* = 8.9, 2.3 Hz, 2H), 3.92 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 160.1, 158.0, 137.2, 133.0, 130.1, 130.1, 129.7, 115.2, 115.0, 113.9, 55.2, 40.1; ^{19}F NMR (376 MHz,

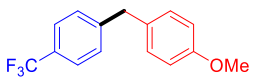
$CDCl_3$) δ -117.49; IR (neat) 3002, 2907, 2835, 1607, 1504, 1243, 1219, 1034, 811, 765 cm^{-1}. Physical and spectral data were consistent with those reported in the literature.[55]

1-chloro-4-(4-methoxybenzyl)benzene (217):



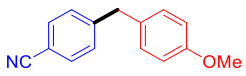
Subjection of 1-bromo-4-chlorobenzene (0.5 mmol, 0.096 g) and 4-methoxybenzyl alcohol (0.75 mmol, 0.093 mL) to general procedure A at RT for 12 h afforded 0.084 g (63%) of **217** as a colorless oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 2H), 7.14 – 7.06 (m, 4H), 6.85 (d, *J* = 8.6 Hz, 2H), 3.90 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1, 140.0, 132.6, 131.7, 130.1, 129.8, 128.5, 113.9, 55.2, 40.3; IR (neat) 2999, 2906, 2833, 1610, 1509, 1243, 1174, 1034, 840 cm^{-1}. Physical and spectral data were consistent with those reported in the literature.[55]

1-methoxy-4-(4-(trifluoromethyl)benzyl)benzene (218):



Subjection of 4-bromobenzotrifluoride (1.0 mmol, 0.140 mL) and 4-methoxybenzyl alcohol (0.5 mmol, 0.062 mL) to general procedure B at RT for 12 h afforded 0.059 g (44%) of **218** as a colorless oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.15 – 7.07 (m, 2H), 6.86 (dd, *J* = 8.7, 2.3 Hz, 2H), 3.98 (s, 2H), 3.80 (d, *J* = 1.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 145.7, 132.1, 129.9, 129.0, 125.4, 125.4, 125.3, 125.3, 114.0, 113.7, 55.2, 40.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.35; IR (neat) 2909, 2837, 1612, 1510, 1301, 1245, 1159, 1107, 807 cm^{-1}. Physical and spectral data were consistent with those reported in the literature.[57]

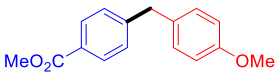
4-(4-methoxybenzyl)benzonitrile (219):



Subjection of 4-bromobenzonitrile (1.0 mmol, 0.182 g) and 4-

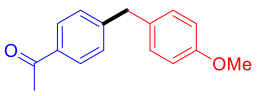
methoxybenzyl alcohol (0.5 mmol, 0.062 mL) to general procedure B at RT for 12 h afforded 0.068 g (61%) of **219** as a colorless oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.02 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 3.88 (s, 2H), 3.70 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3, 147.2, 132.2, 131.3, 129.9, 129.4, 119.0, 114.1, 109.8, 55.2, 41.0; IR (neat) 2924, 2835, 2225, 1608, 1510, 1243, 1175, 1031, 808 cm^{-1}. Physical and spectral data were consistent with those reported in the literature.[55]

methyl 4-(4-methoxybenzyl)benzoate (220):



Subjection of methyl-4-bromobenzoate (1.0 mmol, 0.215 g) and 4-methoxybenzyl alcohol (0.5 mmol, 0.062 mL) to general procedure B at RT for 12 h afforded 0.073 g (57%) of **220** as a colorless oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.83 (m, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 7.00 (d, *J* = 8.6 Hz, 2H), 6.78 – 6.71 (m, 2H), 3.88 (s, 2H), 3.80 (s, 3H), 3.69 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 158.1, 147.0, 132.2, 129.9, 129.7, 128.8, 127.9, 114.0, 55.2, 51.9, 41.0; IR (neat) 2998, 2950, 2835, 1716, 1610, 1510, 1275, 1243, 1175, 1106, 1033, 740 cm^{-1}. Physical and spectral data were consistent with those reported in the literature.[58]

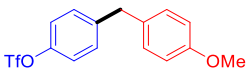
1-(4-(4-methoxybenzyl)phenyl)ethan-1-one (221):



Subjection of methyl-4-bromoacetophenone (1.0 mmol, 0.199 g) and 4-methoxybenzyl alcohol (0.5 mmol, 0.062 mL) to general procedure B at RT for 12 h afforded 0.073 g (60%) of **221** as a colorless oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.88 (m, 2H), 7.32 – 7.27 (m, 2H), 7.15 – 7.09 (m, 2H), 6.90 – 6.85 (m, 2H), 4.00 (s, 2H), 3.81 (s, 3H), 2.60 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.7, 158.1, 147.2, 135.1, 132.1, 129.8, 128.9, 128.6, 114.0, 55.18, 41.0, 26.5; IR

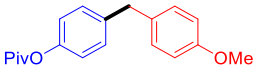
(neat) 3000, 2919, 2835, 1678, 1605, 1509, 1264, 1243, 1175, 1032, 957, 801 cm^{-1}. Physical and spectral data were consistent with those reported in the literature.[59]

4-(4-methoxybenzyl)phenyl trifluoromethanesulfonate (222):



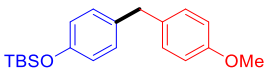
Subjection of 4-bromophenyl trifluoromethanesulfonate (0.5 mmol, 0.153 g) and 4-methoxybenzyl alcohol (0.75 mmol, 0.093 mL) to general procedure A at RT for 12 h afforded 0.126 g (73%) of **222** as a colorless oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.7 Hz, 2H), 7.21 – 7.15 (m, 2H), 7.12 – 7.07 (m, 2H), 6.86 (dd, *J* = 8.4, 1.6 Hz, 2H), 3.95 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3, 147.9, 142.2, 131.9, 130.4, 129.9, 129.0, 121.2, 114.1, 55.2, 40.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -72.90; IR (neat) 2911, 2837, 1511, 1416, 1177, 1133, 1035, 881, 805 cm^{-1}; HRMS (ESI) *m/z* Calculated for $C_{15}H_{12}F_3O_4S^+$ $[M - H]^+$: 345.0409, Found: 345.0400.

4-(4-methoxybenzyl)phenyl pivalate (223):



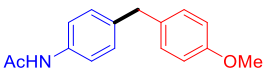
Subjection of 4-bromophenyl pivalate (0.5 mmol, 0.129 g) and 4-methoxybenzyl alcohol (0.75 mmol, 0.093 mL) to general procedure A at RT for 12 h afforded 0.138 g (93%) of **223** as a white solid after flash chromatography (Hex/EtOAc); m.p. = 44-46 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.1 Hz, 2H), 7.12 – 7.06 (m, 2H), 6.99 – 6.93 (m, 2H), 6.86 – 6.80 (m, 2H), 3.92 (s, 2H), 3.79 (s, 3H), 1.35 (d, *J* = 1.3 Hz, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.2, 158.0, 149.3, 138.8, 133.0, 129.8, 129.6, 121.3, 113.9, 55.3, 40.4, 39.0, 27.1; IR (neat) 2959, 2927, 2832, 1744, 1502, 1190, 1110, 895, 816 cm^{-1}; HRMS (ESI) *m/z* Calculated for $C_{19}H_{23}O_3^+$ $[M + H]^+$: 299.1642, Found: 299.1638.

***tert*-butyl(4-(4-methoxybenzyl)phenoxy)dimethylsilane (224):**



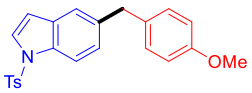
Subjection of (4-bromophenoxy)(*tert*-butyl)dimethylsilane (0.5 mmol, 0.144 g) and 4-methoxybenzyl alcohol (0.75 mmol, 0.093 mL) to general procedure A at RT for 12 h afforded 0.131 g (80%) of **224** as a colorless oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 – 7.07 (d, *J* = 8.24 Hz, 2H), 7.06 – 6.99 (d, *J* = 8.04 Hz, 2H), 6.87 – 6.81 (d, *J* = 8.16 Hz, 2H), 6.79 – 6.73 (d, *J* = 7.52 Hz, 2H), 3.87 (s, 2H), 3.79 (s, 3H), 1.02 – 0.97 (s, 9H), 0.22 – 0.16 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.9, 153.8, 134.2, 133.7, 129.7, 129.7, 119.9, 113.8, 55.2, 40.2, 25.7, 18.2, -4.4; IR (neat) 2954, 2929, 2856, 1608, 1505, 1243, 909, 821, 778 cm^{-1}; HRMS (ESI) *m/z* Calculated for $C_{20}H_{29}O_2Si^+$ $[M + H]^+$: 329.1931, Found: 329.1927.

***N*-(4-(4-methoxybenzyl)phenyl)acetamide (225):**



Subjection of *N*-(4-bromophenyl)acetamide (0.5 mmol, 0.107 g) and 4-methoxybenzyl alcohol (0.75 mmol, 0.093 mL) to general procedure A at RT for 12 h afforded 0.072 g (56%) of **225** as a white solid after flash chromatography (Hex/EtOAc); m.p. = 79-81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.36 (d, *J* = 8.4 Hz, 2H), 7.27 (bs, 1H), 7.15 – 7.04 (m, 4H), 6.85 – 6.79 (d, *J* = 8.6 Hz, 2H), 3.88 (s, 2H), 3.78 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 157.9, 137.7, 135.8, 133.2, 129.8, 129.3, 120.1, 113.8, 55.2, 40.4, 24.5; IR (neat) 3299, 2956, 2913, 2835, 1659, 1601, 1239, 1030, 815 cm^{-1}. Physical and spectral data were consistent with those reported in the literature.[60]

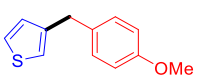
5-(4-methoxybenzyl)-1-tosyl-1*H*-indole (226):



Subjection of 5-bromo-1-tosyl-1*H*-indole (0.5 mmol, 0.175 g) and 4-methoxybenzyl alcohol (0.75 mmol, 0.093 mL) to general procedure A at RT for 12 h afforded 0.175 g (89%) of **226** as a white solid after flash chromatography (Hex/EtOAc); m.p. = 117-119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 8.5, 0.8 Hz, 1H),

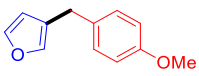
7.78 – 7.72 (m, 2H), 7.52 (d, *J* = 3.7 Hz, 1H), 7.31 – 7.28 (m, 1H), 7.23 – 7.18 (m, 2H), 7.14 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.12 – 7.07 (m, 2H), 6.85 – 6.79 (m, 2H), 6.57 (dd, *J* = 3.7, 0.8 Hz, 1H), 3.97 (s, 2H), 3.78 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.9, 144.8, 136.7, 135.3, 133.3, 131.0, 129.8, 126.8, 126.4, 125.7, 121.1, 113.8, 113.4, 108.9, 55.2, 40.8, 21.5; IR (neat) 2911, 2834, 1508, 1360, 1277, 1090, 834, 802 cm^{-1}; HRMS (ESI) *m/z* Calculated for $C_{23}H_{22}NO_3S^+$ $[M + H]^+$: 392.1315, Found: 392.1301.

3-(4-methoxybenzyl)thiophene (227):



Subjection of 3-bromothiophene (1.0 mmol, 0.094 mL) and 4-methoxybenzyl alcohol (0.5 mmol, 0.062 mL) to general procedure B at RT for 12 h afforded 0.068 g (67%) of **227** as a colorless oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 – 7.13 (m, 1H), 7.06 – 7.00 (d, *J* = 8.12 Hz, 2H), 6.83 – 6.79 (d, *J* = 3.76 Hz , 2H), 6.75 (dd, *J* = 8.4, 1.5 Hz, 2H), 3.83 (s, 2H), 3.70 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0, 142.0, 132.7, 129.7, 128.4, 125.5, 121.0, 113.8, 55.2, 35.6; IR (neat) 2904, 2833, 1508, 12402, 1174, 1032, 810 cm^{-1}. Physical and spectral data were consistent with those reported in the literature.[61]

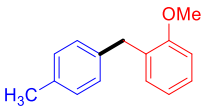
3-(4-methoxybenzyl)furan (228):



Subjection of 3-bromofuran (1.0 mmol, 0.090 mL) and 4-methoxybenzyl alcohol (0.5 mmol, 0.062 mL) to general procedure B at RT for 12 h afforded an inseparable mixture of **228**, 0.059 g (63%) and 1,2-bis(4-methoxyphenyl)ethane as a pale yellow oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (t, *J* = 1.6 Hz, 1H), 7.21 (d, *J* = 1.6 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 2H), 6.89 – 6.84 (m, 2H), 6.27 – 6.23 (m, 1H), 3.81 (s, 3H, measured 3.92H), 3.73 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0, 143.0, 139.4, 132.4, 129.5, 124.7, 113.8, 111.2, 55.2, 30.2; IR (neat) 2998, 2907, 2835, 1610, 1510,

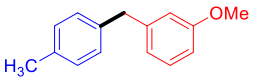
1243, 1174, 1034, 872, 781 cm^{-1}. Physical and spectral data were consistent with those reported in the literature.[62]

1-methoxy-2-(4-methylbenzyl)benzene (238):



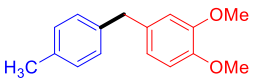
Subjection of 4-bromotoluene (0.5 mmol, 0.062 mL) and 2-methoxybenzyl alcohol (0.75 mmol, 0.100 mL) to general procedure A at RT for 12 h afforded an inseparable mixture of **219**, 0.043 g (41%) and some unknown impurities as a colorless oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (td, *J* = 7.92, 1.8 Hz, 1H), 7.13 – 7.00 (m, 3H, measured 5.40H), 7.00 – 6.95 (m, 1H), 6.91 – 6.81 (m, 2H), 6.77 (d, *J* = 8.2 Hz, 1H), 3.90 (s, 2H), 3.78 (s, 3H, measured 4.94H), 2.32 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2, 155.6, 138.1, 135.0, 132.7, 131.2, 130.2, 130.1, 129.5, 128.9, 128.8, 127.5, 127.1, 120.4, 110.3, 55.4, 35.4, 35.0, 21.0; IR (neat) 3000, 2918, 2833, 1491, 1240, 1104, 1030, 806, 749 cm^{-1}. Physical and spectral data were consistent with those reported in the literature.[63]

1-methoxy-3-(4-methylbenzyl)benzene (239):



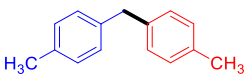
Subjection of 4-bromotoluene (0.5 mmol, 0.062 mL) and 3-methoxybenzyl alcohol (0.75 mmol, 0.094 mL) to general procedure A at RT for 12 h afforded 0.016 g (15%) of **220** as a colorless oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz,) δ 7.23 – 7.17 (m, 1H), 7.09 (s, 4H), 6.82 – 6.70 (m, 3H), 3.92 (s, 2H), 3.77 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 143.0, 137.8, 135.5, 129.4, 129.1, 128.8, 121.3, 114.7, 111.2, 55.1, 41.5, 21.0; IR (neat) 3000, 2919, 2834, 1598, 1255, 1147, 1041, 739, 691 cm^{-1}. Physical and spectral data were consistent with those reported in the literature.[64]

1,2-dimethoxy-4-(4-methylbenzyl)benzene (240):



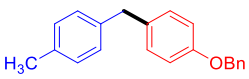
Subjection of 4-bromotoluene (0.5 mmol, 0.062 mL) and 3,4-dimethoxybenzyl alcohol (0.75 mmol, 0.109 mL) to general procedure A at RT for 12 h afforded 0.101 g (83%) of **19** as a colorless oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 – 7.06 (m, 4H), 6.80 (d, *J* = 7.9 Hz, 1H), 6.73 (d, *J* = 8.6 Hz, 2H), 3.90 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.9, 147.3, 138.3, 135.4, 133.9, 129.1, 128.6, 120.8, 112.1, 111.1, 55.7, 41.0, 21.0; IR (neat) 2999, 2933, 2832, 1590, 1510, 1462, 1233, 1137, 1027, 798 cm^{-1}. Physical and spectral data were consistent with those reported in the literature.[59]

di-*p*-tolylmethane (243):



Subjection of 4-bromotoluene (0.5 mmol, 0.062 mL) and 4-methylbenzyl chloride (0.75 mmol, 0.099 mL) to general procedure C at RT for 12 h afforded a partially separable mixture of **21**, 0.091 g (93%) and 1,2-di-*p*-tolylethane as a colorless oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz,) δ 7.11 (m, 8H, measured 8.65H), 3.93 (s, 2H), 2.34 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.3, 135.4, 129.1, 128.7, 41.1, 21.0; IR (neat) 3019, 2919, 2857, 1512, 1436, 799, 747 cm^{-1}. Physical and spectral data were consistent with those reported in the literature.[64]

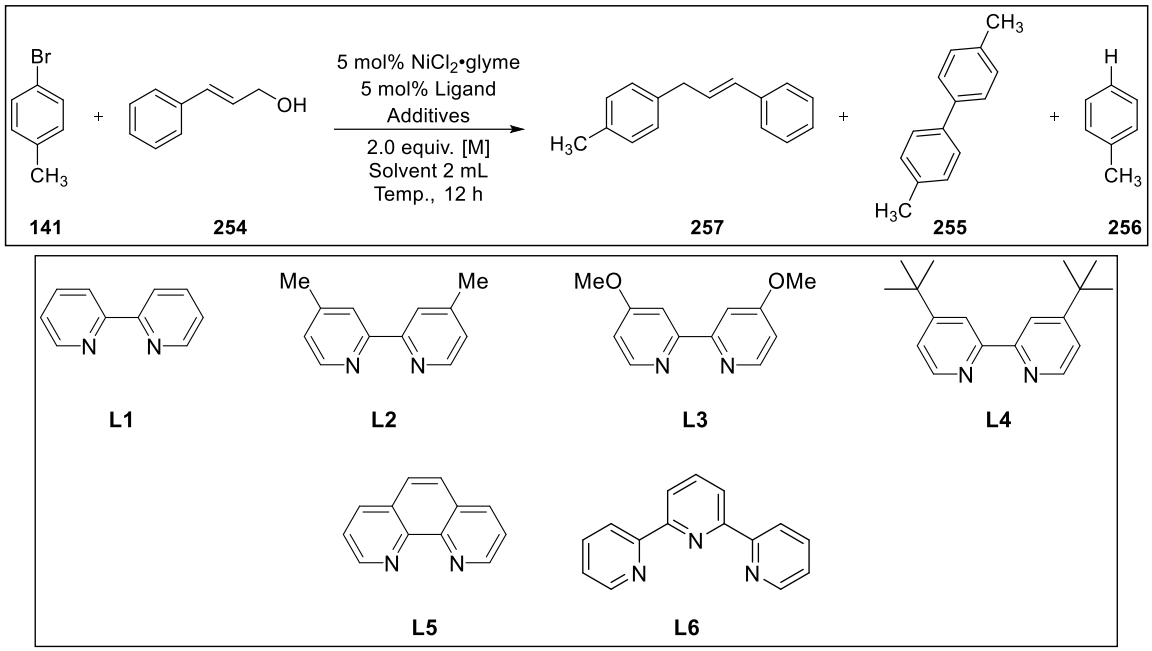
1-(benzyloxy)-4-(4-methylbenzyl)benzene (244):



Subjection of 4-bromotoluene (0.5 mmol, 0.062 mL) and 1-(benzyloxy)-4-(chloromethyl)benzene (0.75 mmol, 0.175 g) to general procedure C at RT for 12 h afforded 0.143 g (99%) of **22** as a white solid after flash chromatography (Hex/EtOAc); m.p. = 72-74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.35 (m, 4H), 7.35 – 7.29 (m, 1H), 7.15 – 7.03 (m, 6H), 6.93 – 6.87 (d, *J* = 8.6 Hz, 2H), 5.04 (s, 2H), 3.89 (s, 2H), 2.32 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.1, 138.4, 137.2, 135.4, 133.8, 129.8, 129.1, 128.7, 128.5,

127.9, 127.4, 114.8, 70.0, 40.6, 21.0; IR (neat) 3032, 2917, 1511, 1235, 1015, 854, 740, 694 cm^{-1}; HRMS (ESI) *m/z* Calculated for $C_{21}H_{21}O^+$ $[M + H]^+$: 289.1587, Found: 289.1579.

Table 4.9. Complete optimization table for the cross-coupling of allyl alcohols and aryl bromides



S.No	Solvent (mL)	Ar-Br (equiv.)	Allyl-OH (equiv.)	Ni (5 mol%)	Ligand (5 mol%)	[M] (2.0 equiv.)	Additives (equiv.)	Temp °C	% Conversion			
									ArBr	257	255	256
1	DMF	1.0	1.5	$NiCl_2$·dme	L1	Mn	TEA•HCl (0.5 eq.)	60	0	45	26	29
2	DMF	1.0	1.5	$NiCl_2$·dme	L1	Mn	TEA•HCl (1.0 eq.)	60	0	34	36	30
3	DMF	1.0	1.5	$NiCl_2$·dme	L1 (5 mol%)	Mn	TEA•HCl (1.5 eq.)	60	0	38	18	44
4	DMF	1.0	1.5	$NiCl_2$·dme	L1 (10 mol%)	Mn	TEA•HCl (1.5 eq.)	60	0	55	7	38
5	DMF	1.0	1.5	$NiCl_2$·dme	L1 (10 mol%)	Mn	TEA•HCl (1.5 eq.)	45	42	27	1	30
6	DMF	1.0	1.5	$NiCl_2$·dme	L1 (10 mol%)	Mn	TEA•HCl (1.5 eq.)	RT	84	7	1	8
7	DMF	1.0	1.5	$NiCl_2$·dme	L1 (15 mol%)	Mn	TEA•HCl (1.5 eq.)	60	0	51	2	47
8	DMF	1.0	1.5	$NiCl_2$·dme	L1 (20 mol%)	Mn	TEA•HCl (1.5 eq.)	60	0	54	2	44
9	DMF	1.0	1.5	$NiCl_2$·dme	L1	Mn	TEA•HCl (2.0 eq.)	60	0	51	7	42
10	DMF	1.0	1.5	$NiCl_2$·dme	L1	Mn	TEA•HCl (2.5 eq.)	60	0	41	12	47
11	DMF	1.0	1.5	$NiCl_2$·dme	L1	Zn	TEA•HCl	60	4	19	10	67

							(1.0 eq.)					
12	DMF	1.0	1.5	$NiCl_2$·dme	L1	Mn	TEA•HCl (1.0 eq.)	RT	41	20	7	32
13	DMF	1.0	1.5	$NiCl_2$·dme	L1	Zn	TEA•HCl (1.0 eq.)	RT	83	3	0	14
14	DMF	1.0	1.5	$NiCl_2$·dme	L1 (10 mol%)	Mn	TEA•HCl (1.5 eq.) + 2.0 eq. H_2O	60	33	17	1	49
15	DMF	1.0	1.5	$NiCl_2$·dme	L1 (10 mol%)	Mn	TEA•HCl (1.5 eq.) + 5.0 eq. H_2O	60	33	18	1	47
16	DMF	1.0	1.5	$NiCl_2$·dme	L1 (10 mol%)	Mn	TEA•HCl (1.5 eq.) + 8.0 eq. H_2O	60	18	23	2	57
S.No	**Solvent (mL)**	**Ar-Br (equiv.)**	**Allyl-OH (equiv.)**	**Ni (5 mol%)**	**Ligand (5 mol%)**	**[M] (2.0 equiv.)**	**Additives (equiv.)**	**Temp °C**	**% Conversion**			
									ArBr	**A**	**B**	**C**
17	DMF	1.0	1.5	$NiCl_2$·dme	L1 (10 mol%)	Mn	TEA•HCl (1.5 eq.) + 10.0 eq. H_2O	60	41	13	0	46
18	DMF	1.0	1.5	$NiCl_2$·dme	L2 (10 mol%)	Mn	TEA•HCl (1.5 eq.)	60	0	60	5	35
19	DMF	1.0	1.5	$NiCl_2$·dme	L2 (10 mol%)	Mn	TEA•HCl (1.5 eq.)	45	65	10	8	17
20	DMF	1.0	1.5	$NiCl_2$·dme	L2 (10 mol%)	Mn	TEA•HCl (1.5 eq.)	RT	93	3	0	4
21	DMF	1.0	1.5	$NiCl_2$·dme	L3 (10 mol%)	Mn	TEA•HCl (1.5 eq.)	60	0	**66**	9	25
22	DMF	2.0	1.0	$NiCl_2$·dme	L1 (10 mol%)	Mn	TEA•HCl (1.5 eq.)	60	-	**(60)**	-	-
23	DMF	2.0	1.0	$NiCl_2$·dme (10 mol%)	L1 (20 mol%)	Mn	TEA•HCl (1.5 eq.)	60	-	**(60)**	-	-
24	DMF	2.0	1.0	$NiCl_2$·dme	L1 (10 mol%)	Mn	TEA•HCl (1.0 eq.)	60	-	**(53)**	-	-
25	DMF	2.0	1.0	$NiCl_2$·dme (10 mol%)	L1 (20 mol%)	Mn	TEA•HCl (1.5 eq.)	80	-	**(80) 12 h**	-	-
26	DMF	2.0	1.0	$NiCl_2$·dme (5 mol%)	L1 (10 mol%)	Mn	TEA•HCl (1.5 eq.)	80	-	**(80) 24 h**	-	-
27	DMF	3.0	1.0	$NiCl_2$·dme (5 mol%)	L1 (10 mol%)	Mn (2.5 eq.)	TEA•HCl (1.5 eq.)	80	-	**(94) 24 h**	-	-
28	DMF	2.0	1.0	$NiCl_2$·dme (5 mol%)	L1 (10 mol%)	Mn	TEA•HCl (1.5 eq.)	80	-	**(65) 12 h**	-	-
29	DMF	2.0	1.0	$NiCl_2$·dme (5 mol%)	L1 (10 mol%)	Mn (3.0 eq)	TEA•HCl (1.5 eq.)	80	-	**(45) 24 h**	-	-
30	DMF	2.0	1.0	$NiCl_2$·dme (5 mol%)	L1 (10 mol%)	Mn	TEA•HCl (2.0 eq.)	80	-	**(78) 24 h**	-	-
31	DMF	2.0	1.0	$NiCl_2$·dme (10 mol%)	L1 (20 mol%)	Mn	TEA•HCl (1.5 eq.)	80	-	**(71) 24 h**	-	-
32	DMF	2.0	1.0	$NiCl_2$·dme (10 mol%)	L1 (20 mol%)	Mn (3.0 eq)	TEA•HCl (1.5 eq.)	80	-	**(57) 24 h**	-	-
33	DMF	2.0	1.0	$NiCl_2$·dme	L3 (10 mol%)	Mn	TEA•HCl (1.5 eq.)	60	-	**(34)**	-	-
34	DMF	2.0	1.0	$NiCl_2$·dme	L3 (10 mol%)	Mn	TEA•HCl (1.0 eq.)	60	-	**(57)**	-	-
35	DMF	1.5	1.0	$NiCl_2$·dme	L3 (10 mol%)	Mn	TEA•HCl (1.5 eq.)	60	-	**(33)**	-	-
36	DMF	2.0	1.0	$NiCl_2$·dme (10 mol%)	L3 (20 mol%)	Mn	TEA•HCl (1.5 eq.)	60	-	**(33)**	-	-
37	DMF	1.0	1.5	$NiCl_2$·dme	L3 (10 mol%)	Mn	TEA•HCl (1.5 eq.)	45	81	6	1	12
38	DMF	1.0	1.5	$NiCl_2$·dme	L3 (10 mol%)	Mn	TEA•HCl (1.5 eq.)	RT	95	2	0	3

39	DMF	1.0	1.5	$NiCl_2$·dme	L3 (10 mol%)	Mn	DABCO•HCl (1.5 eq.)	60	1	21	28	50
40	DMF	1.0	1.5	$NiCl_2$·dme	L3 (10 mol%)	Mn	Py•HCl (1.5 eq.)	60	42	20	7	31
41	DMF	1.0	1.5	$NiCl_2$·dme	L3 (10 mol%)	Mn	TMG•HCl (1.5 eq.)	60	68	9	1	22
42	DMF	1.0	1.5	$NiCl_2$·dme	L3 (10 mol%)	Mn	TFA (1.5 eq.)	60	37	16	9	38
43	DMF	1.0	1.5	$NiCl_2$·dme	L4 (10 mol%)	Mn	TEA•HCl (1.5 eq.)	60	0	56	13	31
44	DMF	1.0	1.5	$NiCl_2$·dme	L4 (10 mol%)	Mn	TEA•HCl (1.5 eq.)	45	80	8	1	11
45	DMF	1.0	1.5	$NiCl_2$·dme	L4 (10 mol%)	Mn	TEA•HCl (1.5 eq.)	RT	91	5	0	4
46	DMF	1.0	1.5	$NiCl_2$·dme	L5 (10 mol%)	Mn	TEA•HCl (1.5 eq.)	60	0	45	4	51
47	DMF	1.0	1.5	$NiCl_2$·dme	L6 (10 mol%)	Mn	TEA•HCl (1.5 eq.)	60	51	2	2	45
S.No	**Solvent (mL)**	**Ar-Br (equiv.)**	**Allyl-OH (equiv.)**	**Ni (5 mol%)**	**Ligand (5 mol%)**	**[M] (2.0 equiv.)**	**Additives (equiv.)**	**Temp °C**	**% Conversion**			
									ArBr	**A**	**B**	**C**
48	DMF	1.0	1.5	$Ni(dppe)Cl_2$ (5 mol%)	-	Mn	TEA•HCl (1.5 eq.)	80	91	0	0	9
49	DMF	1.0	1.5	$Ni(dppp)Cl_2$ (5 mol%)	-	Mn	TEA•HCl (1.5 eq.)	80	89	0	0	11
50	DMF	1.0	1.5	$Ni(dppf)Cl_2$ (5 mol%)	-	Mn	TEA•HCl (1.5 eq.)	80	65	3	0	32
51	NMP	1.0	1.5	$NiCl_2$·dme	L1	Mn	TEA•HCl (0.5 eq.)	60	7	17	42	34
52	NMP	1.0	1.5	$NiCl_2$·dme	L1	Mn	TEA•HCl (1.0 eq.)	60	6	49	16	29
53	NMP	1.0	1.5	$NiCl_2$·dme	L1	Zn	TEA•HCl (1.0 eq.)	60	7	22	14	57
54	NMP	1.0	1.5	$NiCl_2$·dme	L1	Mn	TEA•HCl (1.5 eq.)	60	7	29	17	47
55	NMP	1.0	1.5	$NiCl_2$·dme	L1	Mn	TEA•HCl (2.0 eq.)	60	5	40	7	48
56	NMP	2.0	1.0	$NiCl_2$·dme (10 mol%)	L1 (20 mol%)	Mn	TEA•HCl (1.5 eq.)	60	**(64)**	-	-	-
57	DMA	1.0	1.5	$NiCl_2$·dme	L1	Mn	TEA•HCl (1.0 eq.)	60	0	33	32	35
58	DMA	1.0	1.5	$NiCl_2$·dme	L1	Zn	TEA•HCl (1.0 eq.)	60	0	24	29	47
59	DMA	2.0	1.0	$NiCl_2$·dme (10 mol%)	L1 (20 mol%)	Mn	TEA•HCl (1.5 eq.)	60	**(56)**	-	-	-
60	THF	1.0	1.5	$NiCl_2$·dme	L1	Mn	TEA•HCl (1.0 eq.)	60	95	2	0	3
61	THF	1.0	1.5	$NiCl_2$·dme	L1	Zn	TEA•HCl (1.0 eq.)	60	89	3	0	8
62	DMSO	1.0	1.5	$NiCl_2$·dme	L1	Mn	TEA•HCl (1.0 eq.)	60	59	20	2	19
63	DMSO	1.0	1.5	$NiCl_2$·dme	L1	Zn	TEA•HCl (1.0 eq.)	60	45	20	6	29
64	DMPU	1.0	1.5	$NiCl_2$·dme	L1	Mn	TEA•HCl (1.0 eq.)	60	74	5	0	21
65	DMPU	1.0	1.5	$NiCl_2$·dme	L1	Zn	TEA•HCl (1.0 eq.)	60	27	20	2	51
66	ACN	1.0	1.5	$NiCl_2$·dme	L1	Mn	TEA•HCl (1.0 eq.)	60	80	9	3	8
67	ACN	1.0	1.5	$NiCl_2$·dme	L1	Zn	TEA•HCl (1.0 eq.)	60	63	5	2	30

TEA•HCl = Triethylamine hydrochloride, TMG•HCl = Tetramethylguanidine hydrochloride, Py•HCl = Pyridine hydrochloride, TFA = Trifluoroacetic acid. Yields in the parenthesis are isolated yields.

4.8.8. General procedure D for the cross-coupling of allyl alcohols and aryl bromides

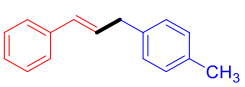
An oven dried 10 mL microwave vial with a magnetic stir bar was taken into an argon filled glovebox and charged with $NiCl_2$•glyme (0.025 mmol, 0.005 g), bipyridine (0.05 mmol, 0.008 g), Manganese powder (-325 mesh, 1.25 mmol, 0.069 g) and TEA•HCl (0.75 mmol, 0.103 g). An aluminum sealed septa was then crimped onto the vial, which was then taken out of the glovebox. The vial was then sequentially injected with allyl alcohol (0.5 mmol), aryl bromide (1.5 mmol), then degassed DMF (2 mL) was added and the septum was wrapped with parafilm. The reaction mixture was stirred for 24 hours at 80 °C and poured into water (50 mL). The aqueous layer was extracted with EtOAc (2x 50 mL) and the combined organic layer was washed with 1 M HCl to remove the metal residue and then with water (50 mL) followed by brine solution (50 mL). The EtOAc layer was separated, 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, unless otherwise stated.

Notes:

1. If any of the reagents were solids, they were weighed into the microwave vial inside glove box before capping.
2. **Purificaton**: Some of the products were isolated as an inseparable mixture with 4,4'-dimethyl-1,1'-biphenyl and the yields of those products were calculated using the ratio of the methyl protons of the desired and by-product in ^{1}H NMR.

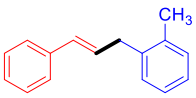
4.8.9. Synthesis and Characterization of Allylarenes

1-cinnamyl-4-methylbenzene (257):



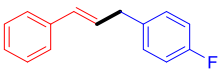
Subjection of cinnamyl alcohol (0.5 mmol, 0.064 mL) and 4-bromotoluene (1.5 mmol, 0.185 mL) to general procedure D at 80 °C for 24 h afforded 0.098 g (94%) of **257** as a colorless oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (dt, *J* = 8.1, 1.7 Hz, 2H), 7.23 – 7.16 (m, 2H), 7.15 – 7.08 (m, 1H), 7.04 (d, *J* = 1.6 Hz, 4H), 6.40 – 6.19 (m, 2H), 3.42 (d, *J* = 6.6 Hz, 2H), 2.24 (d, *J* = 1.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.5, 137.0, 135.6, 130.8, 129.5, 129.2, 128.5, 128.5, 127.0, 126.1, 38.91, 21.0; IR (neat) 3023, 2919, 1513, 1495, 962, 807, 753, 726, 690 cm^{-1}. Physical and spectral data were consistent with those reported in the literature.[53]

1-cinnamyl-2-methylbenzene (258):



Subjection of cinnamyl alcohol (0.5 mmol, 0.064 mL) and 2-bromotoluene (1.5 mmol, 0.180 mL) to general procedure D at 80 °C for 24 h afforded 0.061 g (59%) of **258** as a colorless oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.27 (m, 4H), 7.25 – 7.13 (m, 5H), 6.44 – 6.31 (m, 2H), 3.56 (d, *J* = 4.5 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2, 137.5, 136.4, 130.9, 130.2, 129.2, 128.5, 128.5, 127.0, 126.4, 126.1, 126.1, 36.9, 19.4; IR (neat) 3023, 2923, 1493, 963, 763, 690 cm^{-1}. Physical and spectral data were consistent with those reported in the literature.[53]

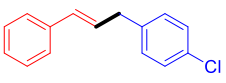
1-cinnamyl-4-fluorobenzene (259):



Subjection of cinnamyl alcohol (0.5 mmol, 0.064 mL) and 1-bromo-4-fluorobenzene (1.5 mmol, 0.165 mL) to general procedure D at 80 °C for 24 h afforded 0.056 g (53%) of **259** as a colorless oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.35 (m, 2H), 7.32 (td, *J* = 7.5, 1.5 Hz, 2H), 7.26 – 7.18 (m,

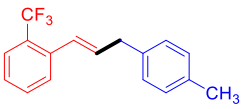
3H), 7.02 (td, *J* = 8.6, 1.4 Hz, 2H), 6.46 (dd, *J* = 15.8, 1.4 Hz, 1H), 6.34 (dtd, *J* = 15.6, 6.7, 1.2 Hz, 1H), 3.54 (d, *J* = 6.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.3, 135.7, 131.2, 130.0, 129.96, 129.0, 128.5, 127.2, 126.1, 115.3, 115.1, 38.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -117.22; IR (neat) 3025, 2899, 1599, 1507, 1219, 1155, 964, 827, 727, 690 cm^{-1}. Physical and spectral data were consistent with those reported in the literature.[53]

1-chloro-4-cinnamylbenzene (260):



Subjection of cinnamyl alcohol (0.5 mmol, 0.064 mL) and 1-bromo-4-chlorobenzene (1.5 mmol, 0.287 g) to general procedure D at 80 °C for 24 h afforded 0.064 g (56%) of **260** as a colorless oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dt, *J* = 8.2, 1.8 Hz, 2H), 7.38 – 7.30 (m, 4H), 7.29 – 7.25 (m, 1H), 7.24 – 7.19 (m, 2H), 6.49 (dd, *J* = 15.8, 1.5 Hz, 1H), 6.36 (ddd, *J* = 15.8, 7.5, 6.1 Hz, 1H), 3.56 (d, *J* = 6.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.6, 137.2, 131.9, 131.5, 130.0, 128.5, 128.5, 127.2, 126.1, 38.6; IR (neat) 3025, 2898, 1490, 1090, 1014, 963, 822, 742, 690 cm^{-1}. Physical and spectral data were consistent with those reported in the literature.[53]

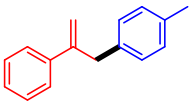
(*E*)-1-(3-(*p*-tolyl)prop-1-en-1-yl)-2-(trifluoromethyl)benzene (261):



Subjection of (*E*)-3-(2-(trifluoromethyl)phenyl)prop-2-en-1-ol (0.5 mmol, 0.101 g) and 4-bromotoluene (1.5 mmol, 0.185 mL) to general procedure D at 80 °C for 24 h afforded an inseparable mixture of **261** (*l*:*b* = 87:13) 0.064 g (47%) and 4,4'-dimethyl-1,1'-biphenyl as a colorless oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (td, *J* = 13.4, 11.9, 7.9 Hz, 2H), 7.61 – 7.55 (m, 1H, measured 2.55H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.41 – 7.30 (m, 2H, measured 3.98H), 7.23 (m, 2H, measured 4.24H), 6.96 (dq, *J* = 15.5, 2.1 Hz, 1H), 6.39 (dt, *J* = 15.5, 7.0 Hz, 1H), 3.64 (d, *J* = 7.0 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.3, 136.7, 136.7, 136.7, 136.5, 135.8, 133.8, 131.8, 131.7,131.6, 131.2, 129.4, 129.2, 128.5, 127.3, 126.9, 126.9, 126.8, 126.7, 126.2, 126.1, 125.7,

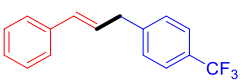
125.7, 125.6, 125.5, 123.1, 39.2, 21.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -59.49, -59.64; IR (neat) 2921, 1513, 1312, 1105, 965, 762 cm^{-1}; HRMS (ESI) *m/z* Calculated for $C_{17}H_{16}F_3^+$ $[M + H]^+$: 277.1199, Found: 277.1213.

1-methyl-4-(2-phenylallyl)benzene (262):



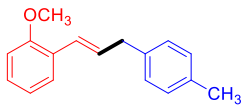
Subjection of 2-phenylprop-2-en-1-ol (0.5 mmol, 0.067 g) and 4-bromotoluene (1.5 mmol, 0.185 mL) to general procedure D at 80 °C for 24 h afforded an inseparable mixture of **262,** 0.035 g (34%) and 4,4'-dimethyl-1,1'-biphenyl as a colorless oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 7.0, 1.7 Hz, 2H), 7.21 – 7.15 (m, 2H), 7.15 – 7.11 (m, 4H), 7.05 – 6.95 (m, 1H, measured 3.92H), 5.38 (d, *J* = 1.3 Hz, 1H), 4.92 (q, *J* = 1.4 Hz, 1H), 3.69 (s, 2H), 2.20 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.1, 140.8, 136.4, 135.5, 129.0, 128.8, 128.2, 127.4, 126.1, 114.4, 41.2, 21.1; IR (neat) 3021, 2919, 1513, 1494, 1443, 896, 777, 700 cm^{-1}; HRMS (ESI) *m/z* Calculated for $C_{16}H_{17}^+$ $[M + H]^+$: 209.1325, Found: 209.1318.

1-cinnamyl-4-(trifluoromethyl)benzene (263):



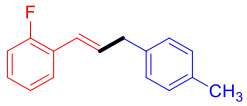
Subjection of 1-phenylprop-2-en-1-ol (0.5 mmol, 0.067 g) and 4-bromobenzotrifluoride (1.5 mmol, 0.210 mL) to general procedure D at 80 °C for 24 h afforded 0.085 g (65%) (*cis:trans* = 22:88) of **263** as a colorless oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 9.7 Hz, 2H), 7.41 – 7.29 (m, 6H, measured 6.56H), 7.25 (m, 1H, measured 1.98H), 6.53 – 6.45 (m, 1H), 6.34 (dtd, *J* = 15.6, 6.8, 1.6 Hz, 1H), 3.62 (d, *J* = 6.9 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.3, 139.5, 137.1, 132.1, 131.9, 129.8, 129.0, 128.7, 128.6, 128.6, 127.9, 127.4, 126.4, 126.2, 126.15, 125.5, 125.1, 125.4, 125.3, 39.3, 39.1;^{19}F NMR (376 MHz, $CDCl_3$) δ -62.31; IR (neat) 3027, 1617, 1321, 1118, 1107, 1065, 1017, 964, 831, 692 cm^{-1}. Physical and spectral data were consistent with those reported in the literature.[53]

(*E*)-1-methoxy-2-(3-(*p*-tolyl)prop-1-en-1-yl)benzene (264):



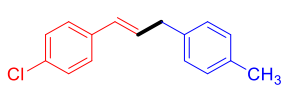
Subjection of 1-(2-methoxyphenyl)prop-2-en-1-ol (0.5 mmol, 0.082 g) and 4-bromotoluene (1.5 mmol, 0.185 mL) to general procedure D at 80 °C for 24 h afforded 0.083 g (70%) of **264** as a colorless oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dddd, *J* = 11.6, 9.7, 3.8, 1.9 Hz, 1H), 7.24 – 7.06 (m, 5H), 6.97 – 6.80 (m, 3H), 6.36 (dtdd, *J* = 15.8, 6.9, 4.2, 1.9 Hz, 1H), 3.90 – 3.83 (m, 3H), 3.56 (dd, *J* = 7.6, 3.8 Hz, 2H), 2.40 – 2.30 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4, 137.4, 135.5, 130.1, 129.1, 128.5, 128.0, 126.6, 125.5, 120.6, 110.8, 55.4, 39.4, 21.0; IR (neat) 3001, 2919, 2834, 1596, 1487, 1240, 1028, 970, 747 cm^{-1}; HRMS (ESI) *m/z* Calculated for $C_{17}H_{19}O^+$ $[M + H]^+$: 239.1430, Found: 239.1421.

(*E*)-1-fluoro-2-(3-(*p*-tolyl)prop-1-en-1-yl)benzene (265):



Subjection of 1-(2-fluorophenyl)prop-2-en-1-ol (0.5 mmol, 0.076 g) and 4-bromotoluene (1.5 mmol, 0.185 mL) to general procedure D at 80 °C for 24 h afforded a partially separable mixture of **265,** 0.066 g (58%) and 4,4'-dimethyl-1,1'-biphenyl as a colorless oil after flash chromatography (Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (td, *J* = 7.7, 1.8 Hz, 1H), 7.39 (m, 1H), 7.35 – 7.27 (m, 4H), 7.23 – 7.11 (m, 2H), 6.82 – 6.72 (m, 1H), 6.57 (m, 1H), 3.69 (d, *J* = 7.0 Hz, 2H), 2.48 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.2, 158.8, 138.3, 136.8, 135.7, 132.2, 132.1, 129.4, 129.2, 128.5, 128.25, 128.17, 127.14, 127.10, 126.8, 125.3, 125.2, 124.0, 123.9, 123.2, 123.1, 115.7, 115.5, 39.3, 21.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -118.51;IR (neat) 3021, 2918, 1485, 1228, 965, 801, 751 cm^{-1}; HRMS (ESI) *m/z* Calculated for $C_{16}H_{16}F^+$ $[M + H]^+$: 227.1231, Found: 227.1267.

(*E*)-1-chloro-4-(3-(*p*-tolyl)prop-1-en-1-yl)benzene (266):



Subjection of 1-(4-chlorophenyl)prop-2-en-1-ol (0.5 mmol, 0.084 g)

and 4-bromotoluene (1.5 mmol, 0.185 mL) to general procedure D at 80 °C for 24 h afforded a partially separable mixture of **266,** 0.057 g (47%) and 4,4'-dimethyl-1,1'-biphenyl as a white solid after flash chromatography (Hex/EtOAc); m.p. = 39-41°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.14 (m, 4H), 7.04 (s, 4H), 6.36 – 6.19 (m, 2H), 3.42 (d, J = 6.1 Hz, 2H), 2.25 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.7, 136.0, 135.8, 132.6, 130.3, 129.6, 129.2, 128.6, 128.5, 127.3, 38.9, 21.0; IR (neat) 3020, 2917, 2887, 1486, 1091, 972, 801 cm^{-1}. Physical and spectral data were consistent with those reported in the literature.[65]

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CHAPTER V

VISIBLE LIGHT-MEDIATED SYNTHESIS OF CIS-ALLYL AMINES VIA DECARBOXYLATIVE RADICAL ADDITION TO PHENYL ACETYLENES

5.1. INTRODUCTION

Allyl amines are important class of biologically active motifs that are widely found in pharmaceuticals and natural products.[1-4] Due to the bifunctional characteristic of the allyl amines they serve as versatile building blocks for the synthesis of chiral bioactive molecules.[5-9]

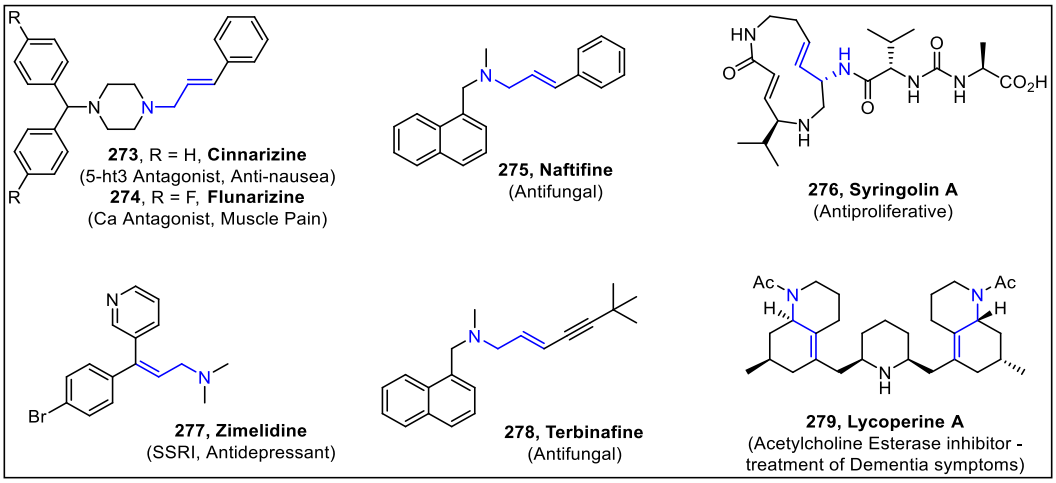
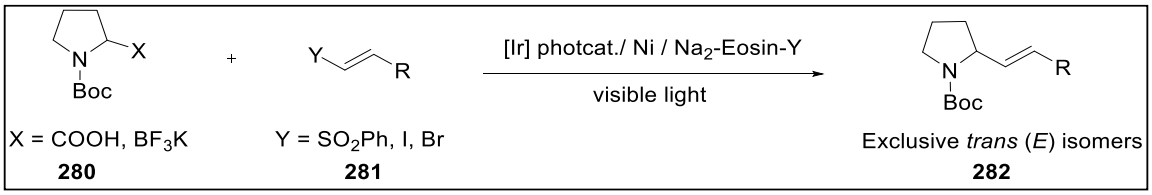


Fig 5.1. Occurrence of allyl amines in in pharmaceuticals and natural products.

Several efforts have been made to access allyl amines under photocatalytic conditions, which are relatively mild and provides good functional group tolerance. But the current methods

employ either an expensive Iridium photocatalyst[10, 11] or a preformed trifluoroborates[12] which are limited to access the *trans*-allyl amines exclusively. Although the trans isomer can be isomerized to cis isomer photocatalytically,[13] a one pot procedure for accessing allyl amines from readily available starting materials is much demanding.



Scheme 5.1. Current Photocatalytic Methods to Access Allylic Amines.

A general photocatalytic cycle is illustrated in fig 5.2. It is well established that alpha amino radicals can be generated from readily available amino acids.[10, 11, 14, 15] We envisioned that the addition of the alpha amino radical should generate a vinyl radical which can abstract a hydrogen atom either from the solvent or an appropriate HAT source to furnish cis/trans allyl amine.[16, 17]

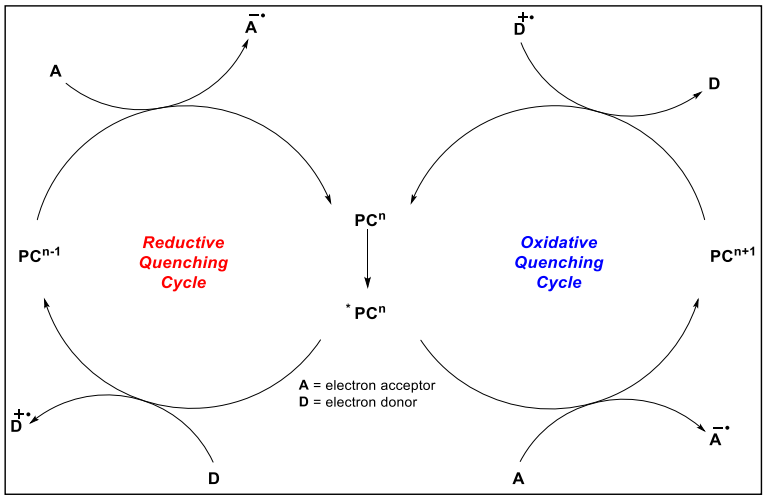
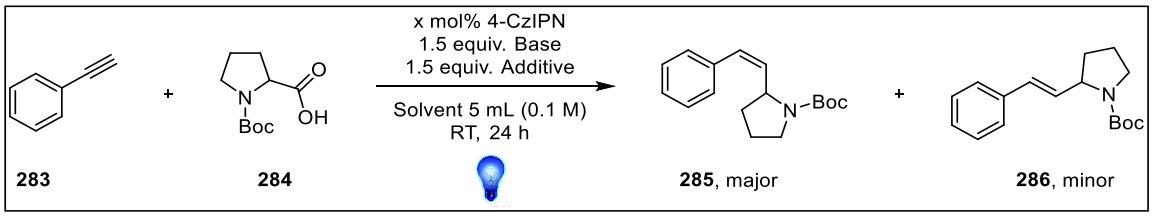


Fig 5.2. General photocatalytic cycle.

5.2. RESULTS AND DISCUSSION

Table 5.1. Attempt to optimize the reaction conditions for the decarboxylative radical addition to phenyl acetylenes



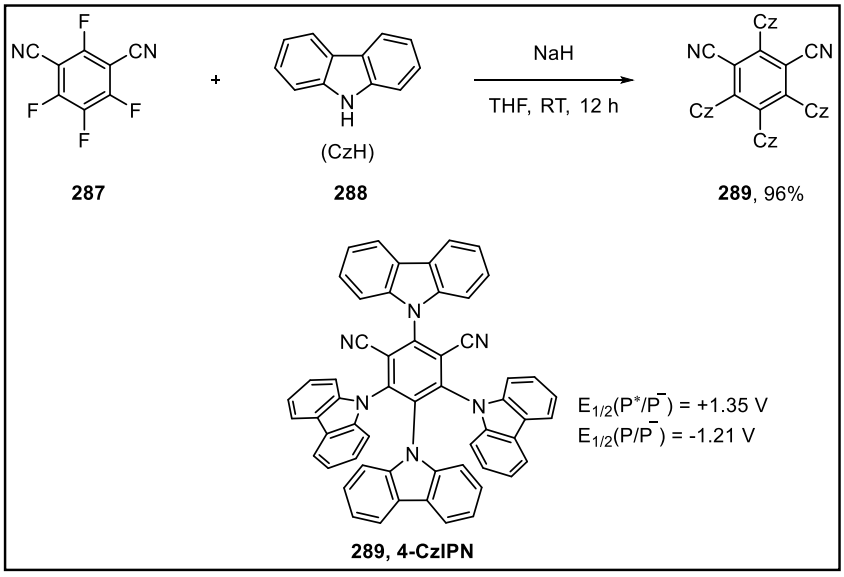
Entry	Solvent (0.1 M)	283 (equiv.)	284 (equiv.)	Base (1.5 equiv.)	4-CzIPN (x mol%)	H-atom Source/ Additive (equiv.)	*Z:E* Ratio	Ratio[a] Prod : I.S.	Isolated Yield (%)
1.	DMF	1.0	1.5	Cs_2CO_3	5.0	None	-	-	39
2.	DMF	1.0	1.5	Cs_2CO_3	2.5	None	73 : 27	1 : 10.5	26
3.	DMF	1.0	1.5	Cs_2CO_3	2.5	None	72 : 28	1 : 12.0	-
4.	DMF	1.0	3.0	Cs_2CO_3	2.5	None	78 : 22	1 : 2.27	31
5.	DMF	3.0	1.0	Cs_2CO_3	2.5	None	72 : 28	1 : 4.0	-
6.	DMF	1.0	1.5	Cs_2CO_3	5.0	H_2O (10 equiv.)	72 : 28	-	48
7.	DMF (4 mL)	1.0	1.5	Cs_2CO_3	5.0	H_2O (1 mL)	72 : 28	-	15
8.	DMF	1.0	1.5	Cs_2CO_3	5.0	H_2O (10 equiv.)	-	-	46 (48 h)
9.	DMF	1.0	1.5	Cs_2CO_3	5.0	H_2O (10 equiv.)	75:25	-	37 (12 h)
10.	DMF	1.0	2.0	Cs_2CO_3	5.0	H_2O (10 equiv.)	74:26	-	39
11.	DMF (0.05 M)	1.0	1.5	Cs_2CO_3	5.0	H_2O (10 equiv.)	-	-	47
12.	DMF (0.05 M)	1.0	2.5	Cs_2CO_3 (2.5 equiv.)	5.0	H_2O (10 equiv.)	-	-	45
13.	DMF (0.05 M)	1.0	3.0	Cs_2CO_3 (3.0 equiv.)	5.0	H_2O (10 equiv.)	-	-	47
14.	DMF	1.0	1.5	Cs_2CO_3 (2.0 equiv.)	5.0	H_2O (10 equiv.)	75:25	-	26
15.	DMF	1.0	1.5	Cs_2CO_3 (2.5 equiv.)	5.0	H_2O (10 equiv.)	75:25	-	23
16.	**DMF**	**1.0**	**1.5**	**Cs_2CO_3**	**5.0**	**H_2O (5 equiv.)**	**75:25**	**-**	**48**
17.	DMF	1.0	1.5	Cs_2CO_3	5.0	H_2O (20 equiv.)	85:15	-	44
18.	DMF	1.0	1.5	Cs_2CO_3	5.0	H_2O (30 equiv.)	81:19	-	33
19.	DMF	1.0	1.5	Cs_2CO_3	2.5	H_2O (5 equiv.)	-	-	30
20.	DMF	1.0	1.5	Cs_2CO_3	5.0	H_2O (5 equiv.)	-	-	35 (60 °C)
21.	DMF	1.0	1.5	Cs_2CO_3	5.0	H_2O (5 equiv.)	-	-	26 (45 °C)
22.	DMF	1.0	1.5	Cs_2CO_3	5.0	D_2O (10 equiv.)	-	-	42 (20% D)
23.	DMF	1.0	1.5	Cs_2CO_3	10.0	H_2O (5 equiv.)	75:25	-	34
24.	DMF (0.025 M)	1.0	1.5	Cs_2CO_3	5.0	H_2O (5 equiv.)	60:40	-	43

25.	DMF (0.02 M)	1.0	1.5	Cs_2CO_3	5.0	H_2O (5 equiv.)	58:42	-	52
26.	DMF (0.25 M)	1.0	1.5	Cs_2CO_3	5.0	H_2O (5 equiv.)	-	-	26
27.	DMF (0.167 M)	1.0	1.5	Cs_2CO_3	5.0	H_2O (5 equiv.)	-	-	19
28.	DMF	1.0	1.5	Cs_2CO_3	[Ir][c] 1 mol%	H_2O (5 equiv.)	70:30	-	37 (48 h)
29.	DMF	1.0	1.5	Cs_2CO_3	5.0	H_2O (5 equiv.)	70:30	-	32 (45 °C)
30.	DMF	1.5	1.0	Cs_2CO_3	5.0	H_2O (5 equiv.)	-	-	37
31.	DMF	2.0	1.0	Cs_2CO_3	5.0	H_2O (5 equiv.)	-	-	28
32.	DMF	2.0	1.0	Cs_2CO_3	5.0	H_2O (10 equiv.)	62:38	-	23
33.	DMF	3.0	1.0	Cs_2CO_3	5.0	H_2O (10 equiv.)	52:48	-	17
34.	DMF (4 mL)	3.0	1.0	Cs_2CO_3	5.0	THF (1 mL)	80:20	-	25
35.	DMF (4 mL)	3.0	1.0	Cs_2CO_3	5.0	Toluene (1 mL)	78:22	-	44
36.	DMF (4 mL)	3.0	1.0	Cs_2CO_3	5.0	Ethylbenzene (1 mL)	77:23	-	45
37.	DMF (4 mL)	3.0	1.0	Cs_2CO_3	5.0	Mesitylene (1 mL)	79:21	-	34
38.	DMF	1.0	1.5	Cs_2CO_3	5.0	H_2O (20 equiv.) + Fluorene (0.5 equiv.)	80:20	-	14
39.	DMF	1.0	1.5	Cs_2CO_3	2.5	1.5 equiv. Fluorene	69 : 31	1 : 1.8	56[b]
40.	DMF	1.0	1.5	Cs_2CO_3	1.0	1.5 equiv. Fluorene	-	0	-
41.	DMF	1.0	1.5	Cs_2CO_3	10.0	1.5 equiv. Fluorene	76 : 14	1 : 1.92	-
42.	DMF	1.0	1.5	Cs_2CO_3	5.0	H_2O (10 equiv.) + Thiophenol (1.0 equiv.)	-	-	0
43.	DMF	1.0	1.5	Cs_2CO_3	2.5	1 equiv. Thiophenol	-	0	-
44.	DMF	1.0	1.5	Cs_2CO_3	2.5	None	74 : 26	1 : 2.8	33 (48 h)
45.	DMSO	1.0	1.5	Cs_2CO_3	5.0	H_2O (5 equiv.)	-	-	7
46.	DMSO	1.0	1.5	Cs_2CO_3	2.5	None	87 : 13	1 : 8.3	-
47.	DMPU	1.0	1.5	Cs_2CO_3	5.0	H_2O (5 equiv.)	78:22	-	17
48.	DMA	1.0	1.5	Cs_2CO_3	5.0	H_2O (10 equiv.)	75:25	-	29
49.	NMP	1.0	1.5	Cs_2CO_3	5.0	H_2O (10 equiv.)	70:30	-	13
50.	NMP	1.0	1.5	Cs_2CO_3	2.5	None	86 : 14	1 : 3.6	-
51.	THF	1.0	1.5	Cs_2CO_3	5.0	H_2O (10 equiv.)	80:20	-	17
52.	THF	1.0	1.5	Cs_2CO_3	2.5	None	77 : 23	1 : 6.8	-
53.	Dioxane	1.0	1.5	Cs_2CO_3	2.5	None	77 : 23	1 : 10.9	-
54.	ACN	1.0	1.5	K_2CO_3 (2.0 equiv.)	5.0	H_2O (20 equiv.)	-	-	0
55.	ACN	1.0	1.5	Cs_2CO_3	[Ir] [c] 1 mol%	H_2O (20 equiv.)	80:20	-	15
56.	Toluene	1.0	1.5	Cs_2CO_3	5.0	H_2O (10 equiv.)	-	-	0
57.	DCE	1.0	1.5	Cs_2CO_3	2.5	None	83 : 17	1 : 13.4	-
58.	CHCl3	1.0	1.5	Cs_2CO_3	2.5	None	83 : 17	1 : 7.14	-
59.	DCM	1.0	1.5	Cs_2CO_3	2.5	None	87 : 13	1 : 6.1	8
60.	DCM	1.0	1.5	Cs_2CO_3	2.5	2 equiv. Indene	91 : 9	1 : 9.1	-

61.	DCM	1.0	1.5	Cs_2CO_3	2.5	2 equiv. PMHS	83 : 17	1 : 5.26	-
62.	DCM	1.0	1.5	Cs_2CO_3	2.5	2 equiv. DABCO	93 : 7	1 : 9.1	-
63.	DCM	1.0	1.5	Cs_2CO_3	2.5	2 equiv. Fluorene	82 : 18	1 : 3.7	-
64.	DCM	1.0	1.5	Cs_2CO_3	2.5	2 equiv. 4-Fluorophenyl Acetonitrile	-	1 : 5.0	-
65.	DCM	1.0	1.5	Cs_2CO_3	2.5	2 equiv. Hantzsch Ester	-	0	-
66.	DCM	1.0	1.5	Cs_2CO_3	2.5	2 equiv. N-Hydroxyphthalimide	71 : 29	1 : 357	-
67.	DCM	1.0	1.5	Cs_2CO_3	2.5	2 equiv. 1,4 cyclohexadiene	73 : 17	1 : 2.9	-
68.	DCM	1.0	1.5	Li_2CO_3	2.5	None		0	-
69.	DCM	1.0	1.5	K_2CO_3	2.5	None	85 : 15	1 : 9.3	-
70.	DCM	1.0	1.5	Collidine	2.5	None	-	0	-
71.	DCM	1.0	1.5	DIPEA	2.5	None	-	0	-
72.	DCM	1.0	1.5	DBU	2.5	None	78 : 22	1 : 9.8	-
73.	DCM	1.0	3.0	Cs_2CO_3	2.5	None	87 : 13	1 : 5.0	-
74.	DCM	3.0	1.0	Cs_2CO_3	2.5	None	85 : 15	1 : 9.1	-
75.	DCM	1.0	1.5	Cs_2CO_3	2.5	None	56 : 44	1 : 4.8	32 (48 h)
76.	DCM	1.0	1.5	Cs_2CO_3	5.0	H_2O (5 equiv.)	-	-	16
77.	Acetone	1.0	1.5	Cs_2CO_3	5.0	H_2O (20 equiv.)	-	-	12
78.	IPA	1.0	1.5	Cs_2CO_3	5.0	H_2O (10 equiv.)	-	-	0
79.	H_2O (5 mL)	1.0	1.5	Cs_2CO_3	5.0	-	-	-	0

[a] Ratio determined by GC, area of product to area of internal standard mesitylene. [b] 23 W CFL bulb instead of Blue LED. [c] [Ir] = $(Ir[dF(CF_3)ppy)]_2(dtbpy))PF_6$.

We started optimizing the reaction conditions using phenylacetylene and N-Boc proline as the test substrates. Our initial effort of solvent screening revealed that DMF is the optimal solvent which afforded the desired product in 39% yield with 5 mol% of the organophotocalyst, 4-CzIPN. A comparable yield was obtained when iridium photocatalyst was used which yielded the product in 37% yield after 48 h (entry 28). 4-CzIPN was used a standard catalyst for further screening and it is noteworthy to mention that this organophotocatalyst is less expensive than the iridium catalysts and easy to make from cheap starting materials.[18]



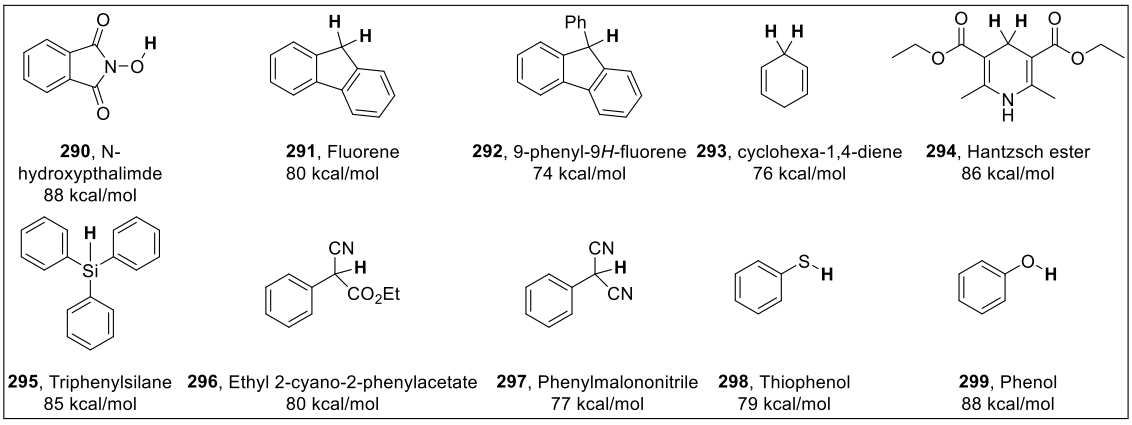
Scheme 5.2. Synthesis and reduction potential of 4-CzIPN.

Cesium carbonate was found to be the optimal base and other bases like DBU, DIPEA yielded only trace product. We were delighted to find that the reaction furnished the cis-allyl amine as the major product probably by the energy transfer from the photocatalyst isomerizing the trans isomer to cis product.

It was found that the addition of 5-10 equiv. of water increased the yield by about 10%. Even though the addition of 30 equiv. of water decreased the yield slightly, the cis:trans ratio improved from 75:25 to 85:15 (entry 17). Concentration studies revealed that the formation of the trans isomer increased with the dilution of the reaction mixture (entry 23-25).

Further several HAT sources with various BDE were screened in DMF and other solvents to improve the yield and the ratio of cis:trans product was determined using GC with mesitylene as the internal standard. The proposed mechanism for synthesis of cis-allyl amine with an HAT source is illustrated in fig 3. None of the HAT source provided a higher yield and were rather detrimental.

5.3. Bond dissociation energy (BDE) of some HAT sources[19-23]



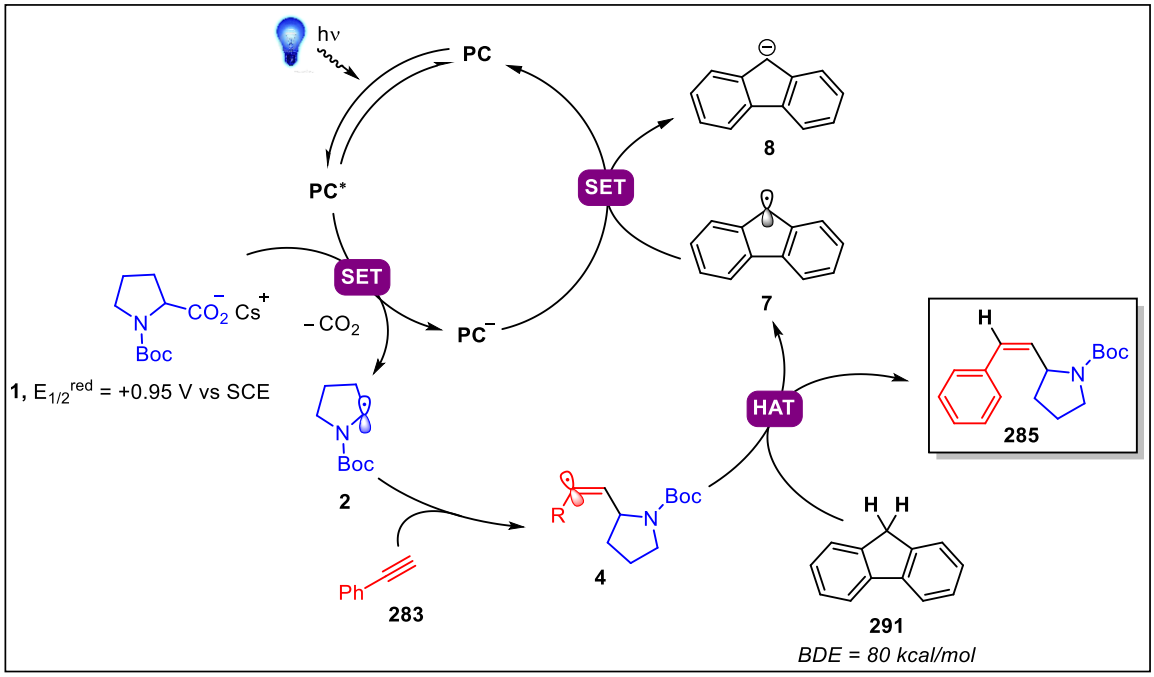


Fig 5.3. Proposed mechanism for the synthesis of *cis*-allyl amines with Fluorene as a HAT source.

Exclusive thiol radical addition to alkyne was observed when thiophenol was used as HAT source. Aliphatic terminal alkynes yielded no product under the conditions mentioned in entry 6. The yield improved slightly from 48% to 56% (entry 39) when 23 W CFL bulb was used as the light source. Replacing the water with D_2O as an additive resulted in about 20% deuterium incorporation in the vinyl position of the product (entry 22). This suggests that there could be a

formation of vinyl anion intermediate and H_2O/D_2O would protonate the vinylic carbon to afford the allyl amine product. Raising the temperature to 45 or 65 °C resulted in lower yields (entry20-21).

5.4. CONCLUSION

Any further attempt to optimize the reaction conditions and improving the yield resulted in vain. It appears that the reaction requires an extensive screening of photocatalysts in the presence or absence of HAT sources. While we were optimizing the conditions for this reaction, Macmillan reported a similar strategy "Ni/Photoredox-Mediated Decarboxylative Hydroalkylation of Alkynes" to access allyl amines.[24] A similar strategy has been reported to access cis-allyl amines with NHPI esters as the radical precursors.[25]

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APPENDICES

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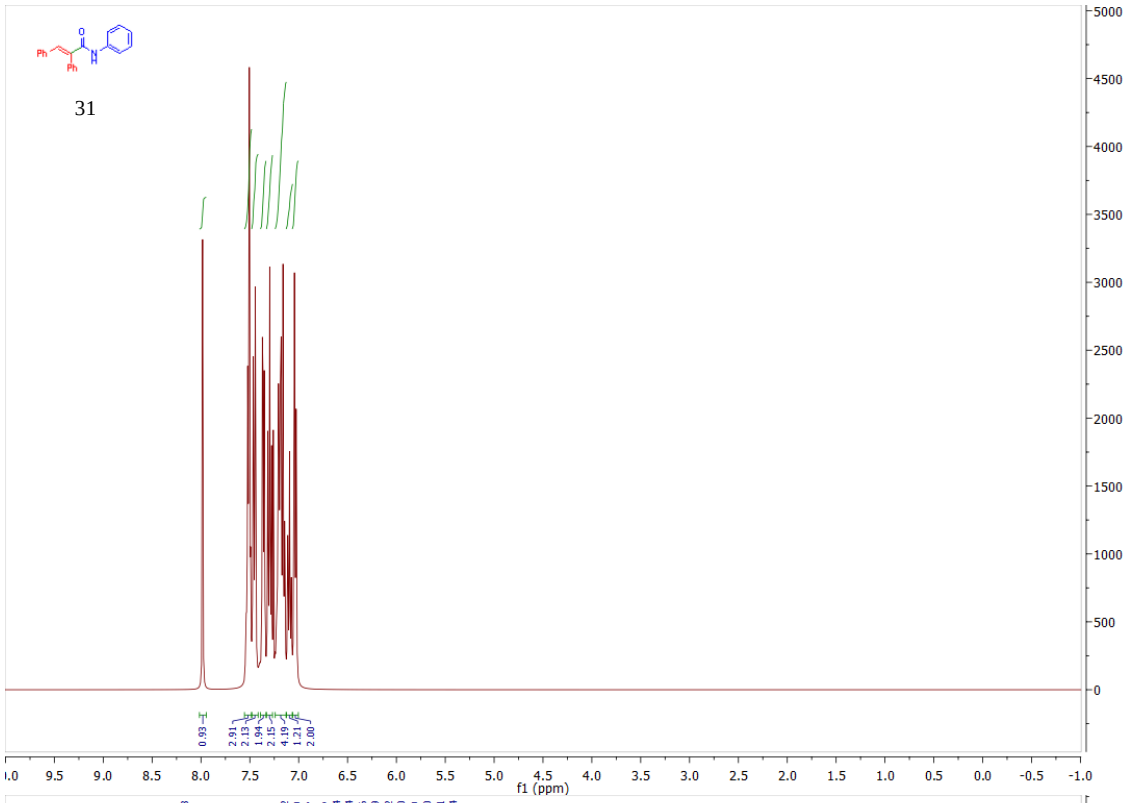
Chapter II

NMR spectra of conjugated amides

Chapter IV

NMR spectra of diarylmethanes and allylarenes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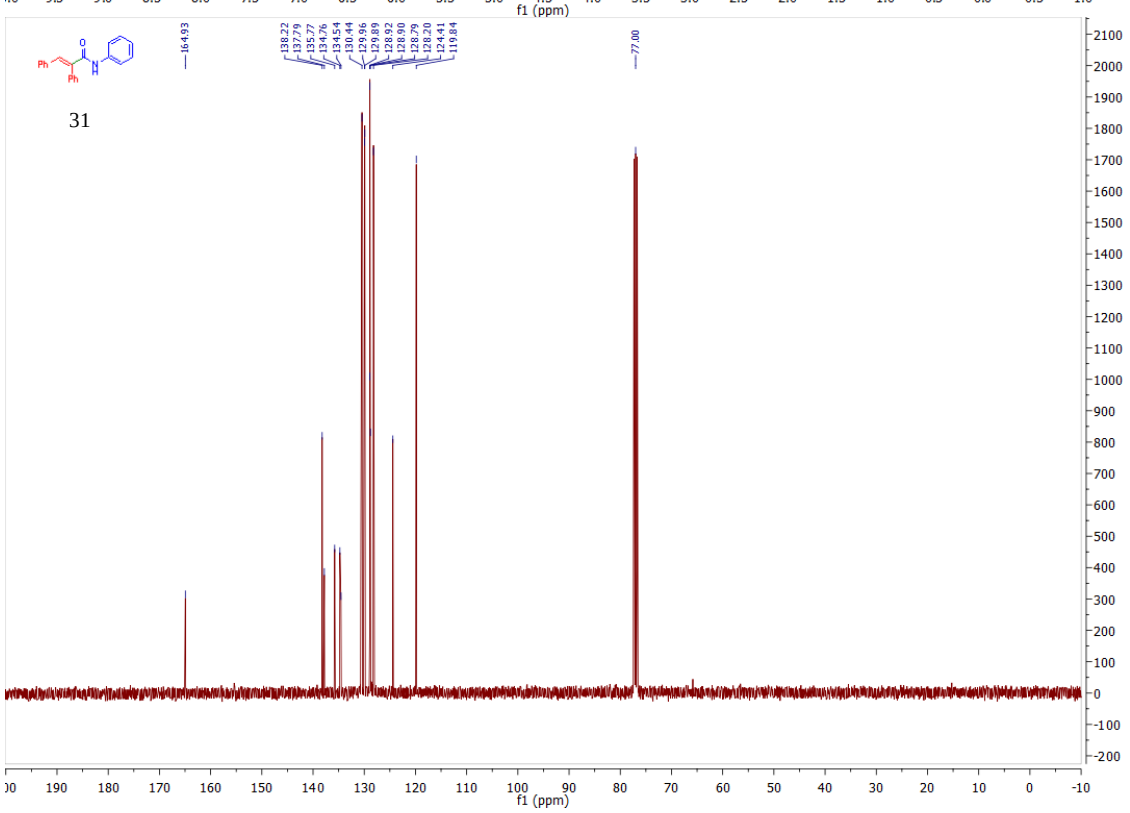
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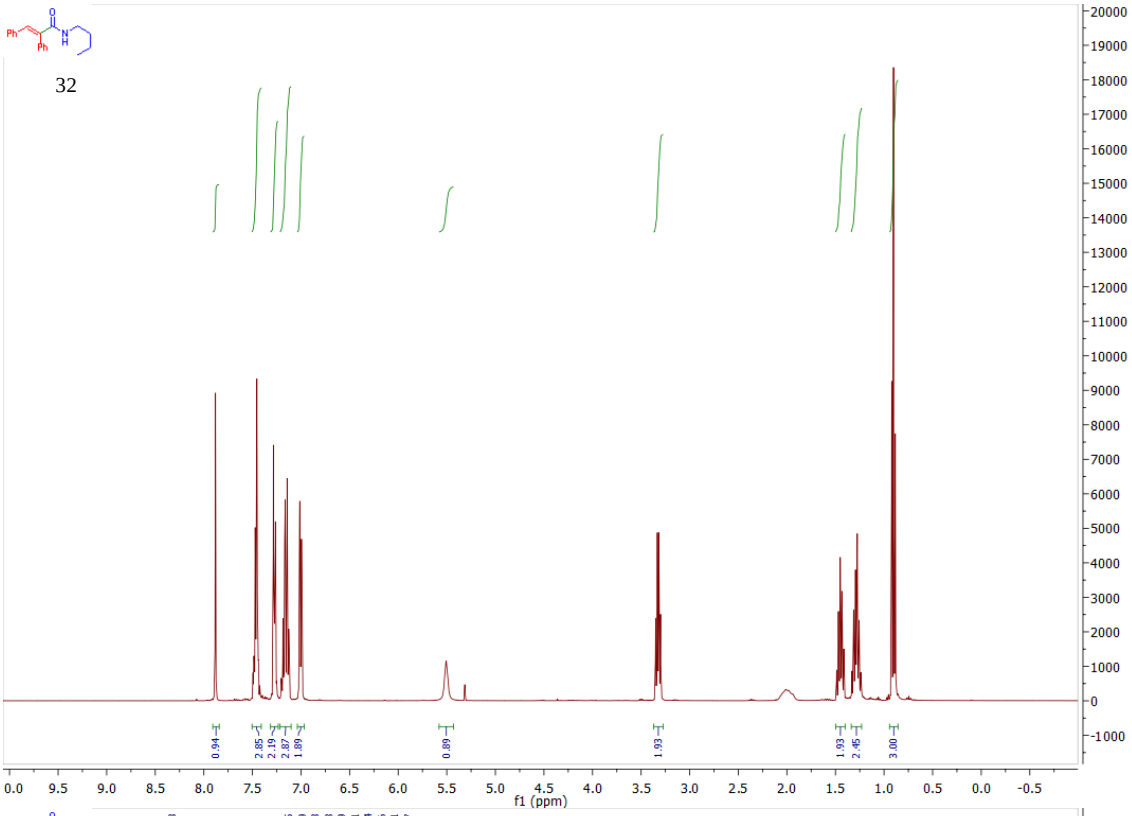
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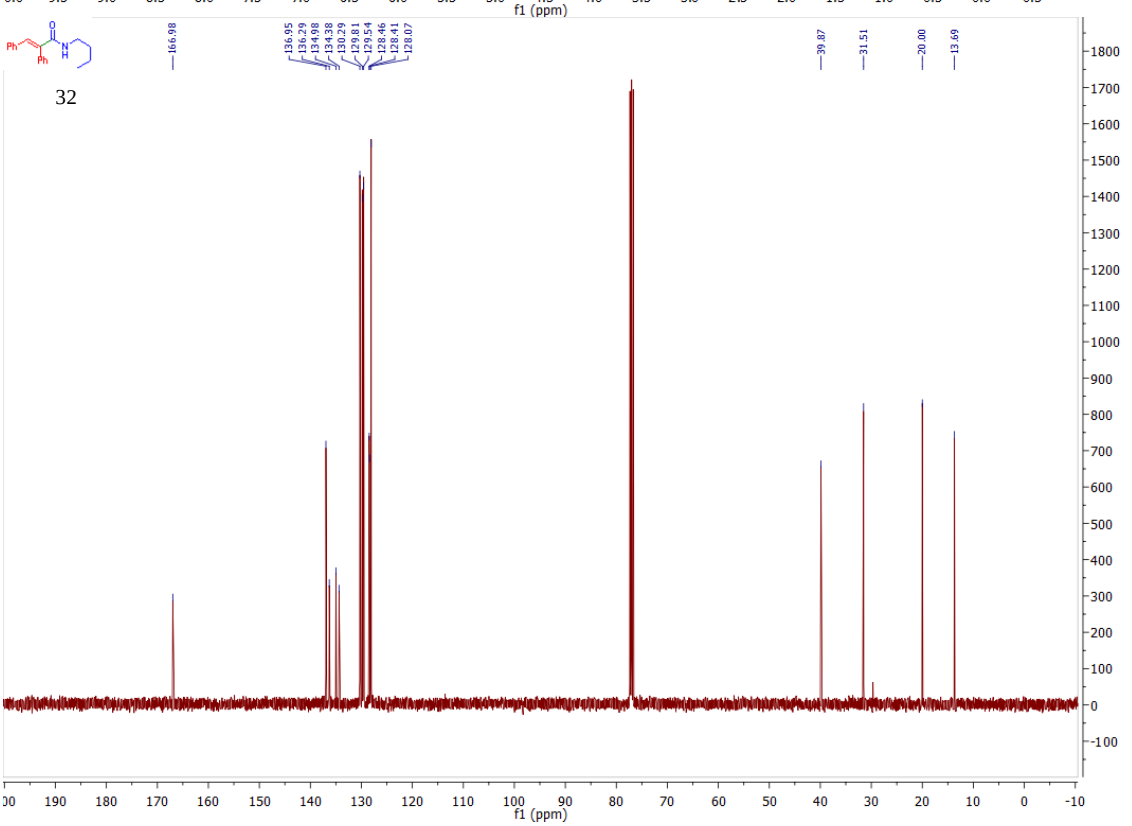
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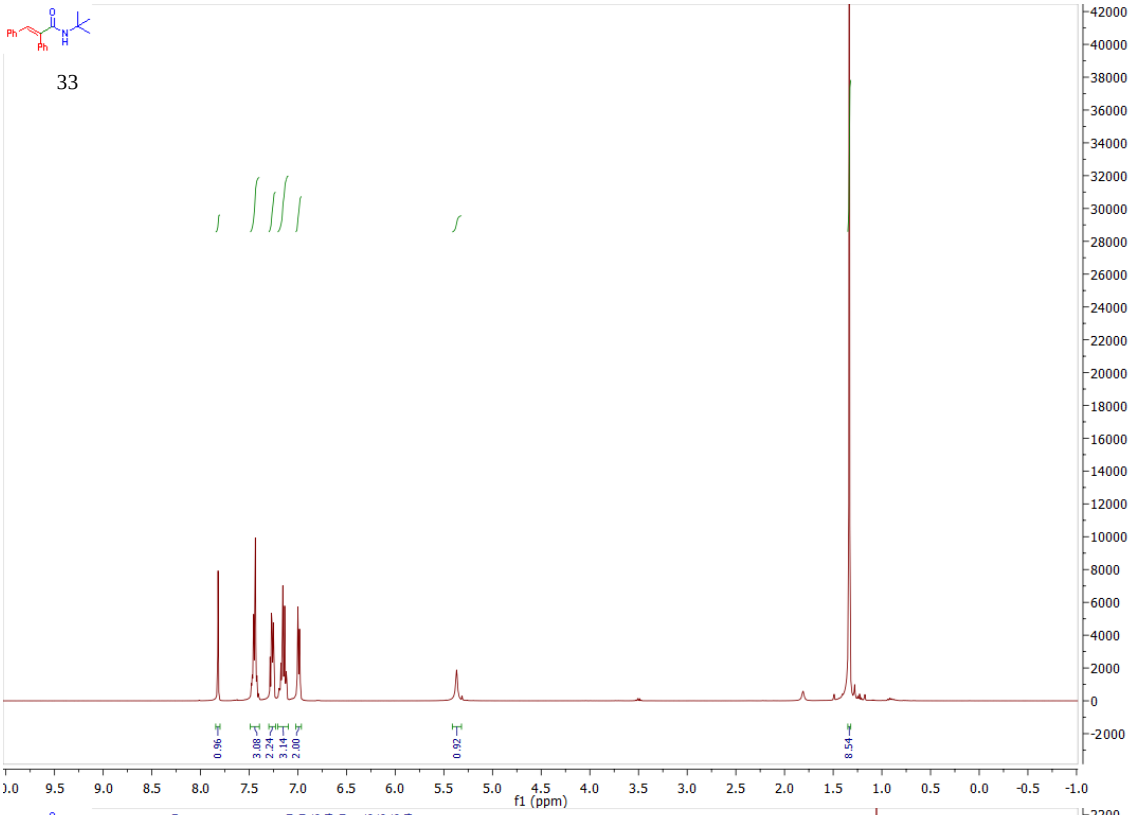
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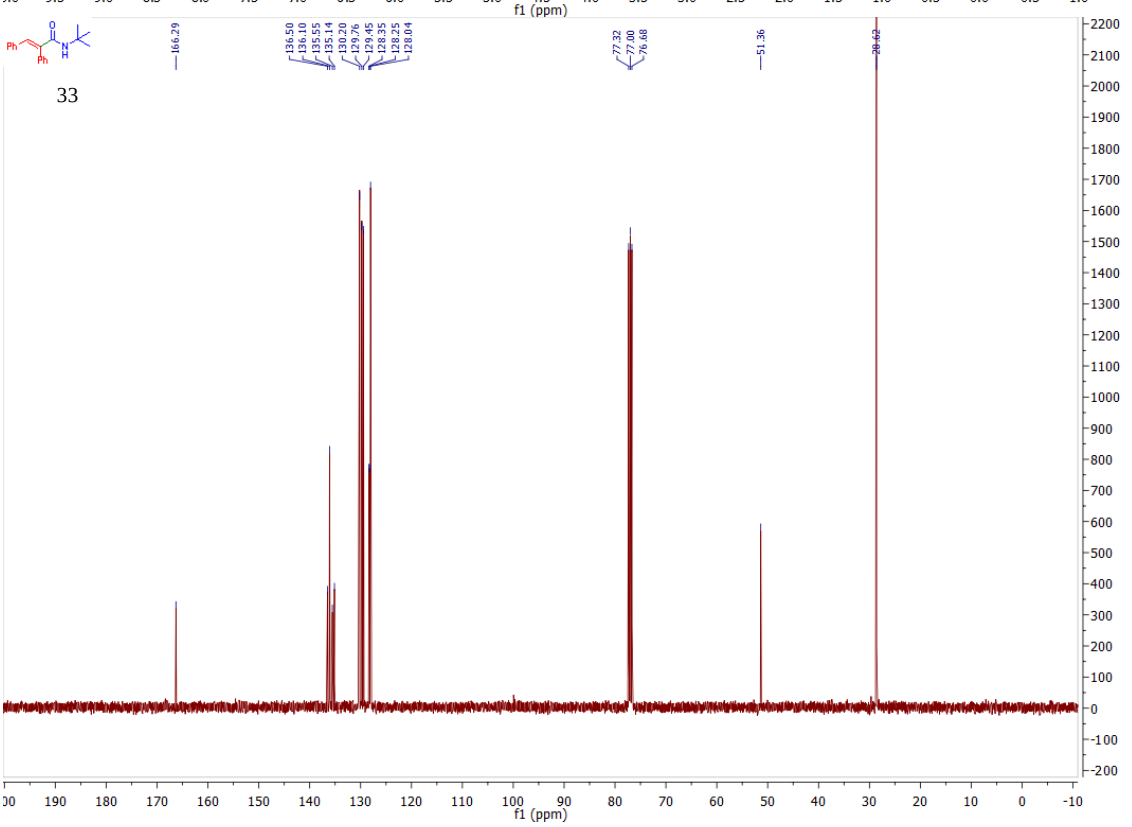
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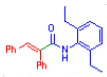

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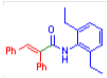

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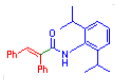

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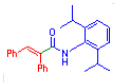

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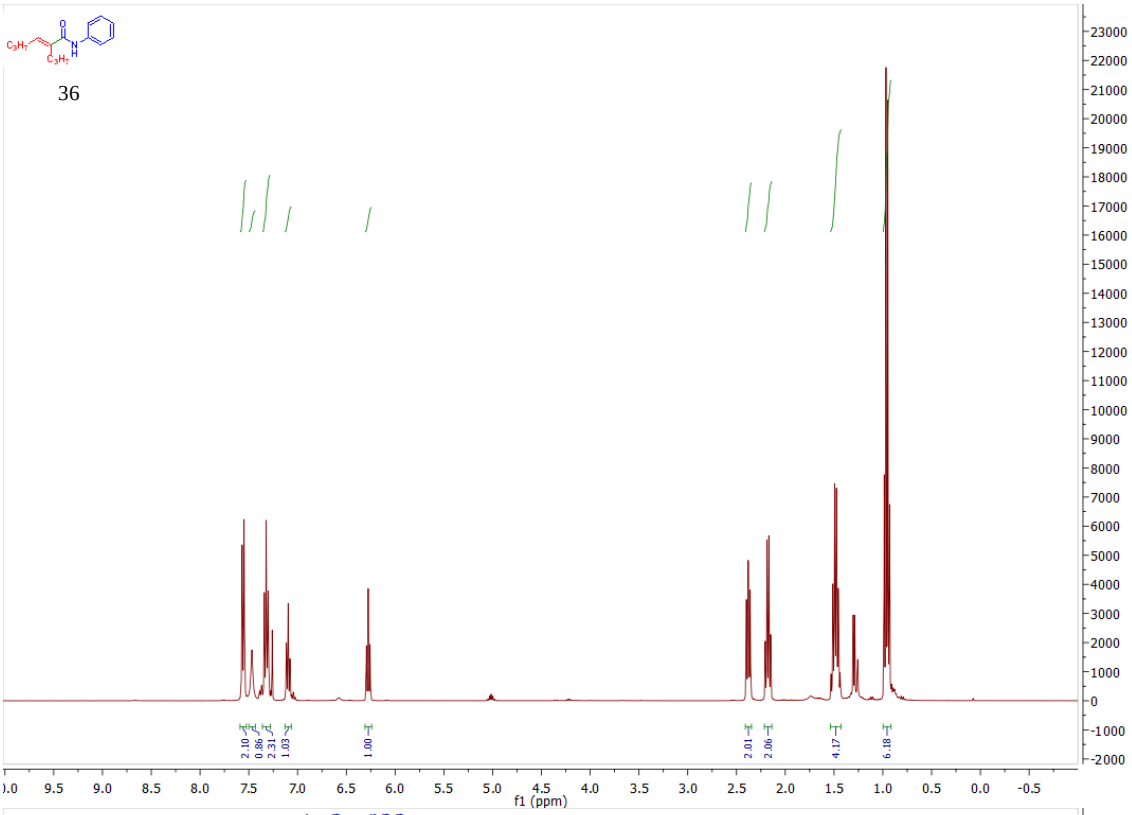
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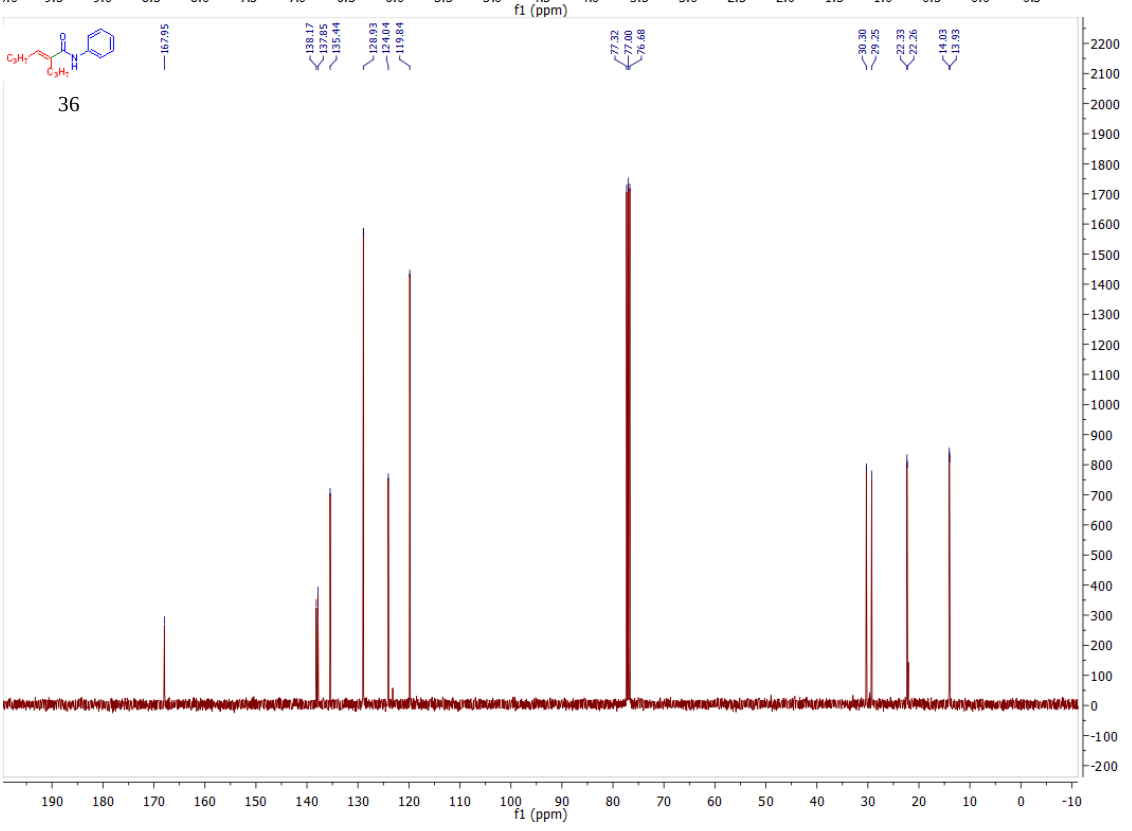
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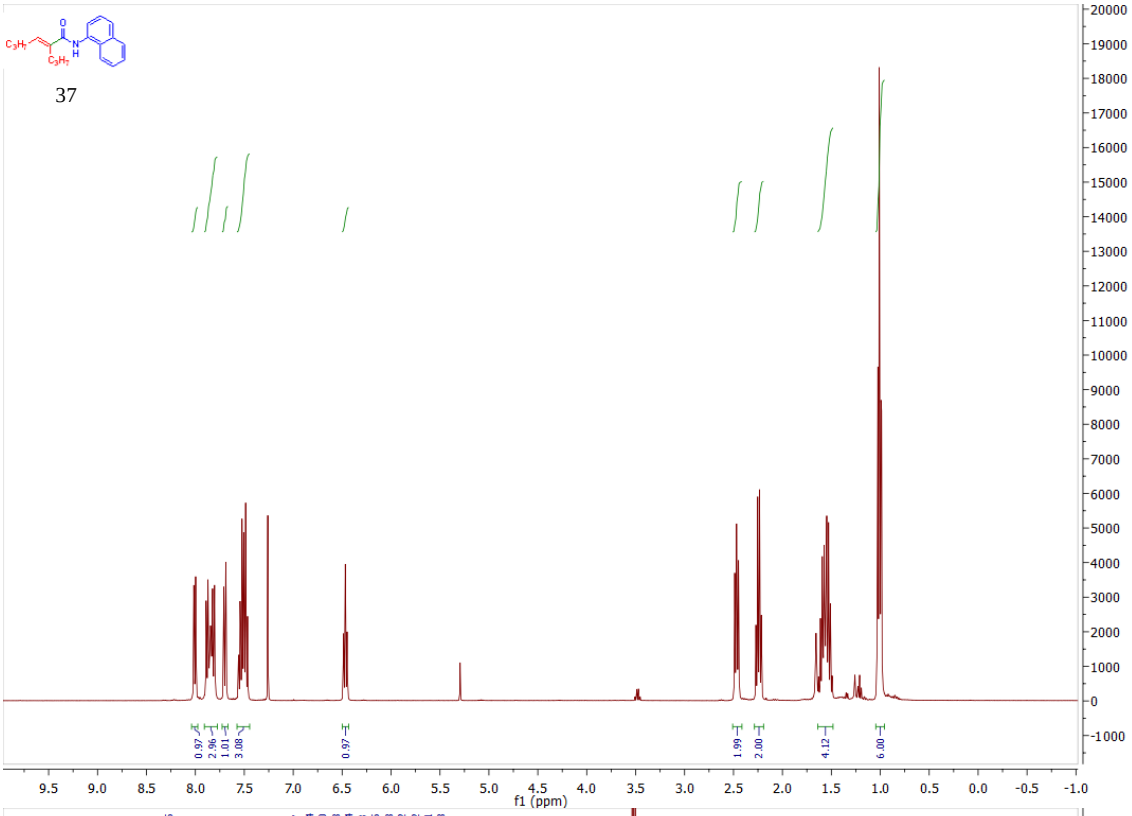
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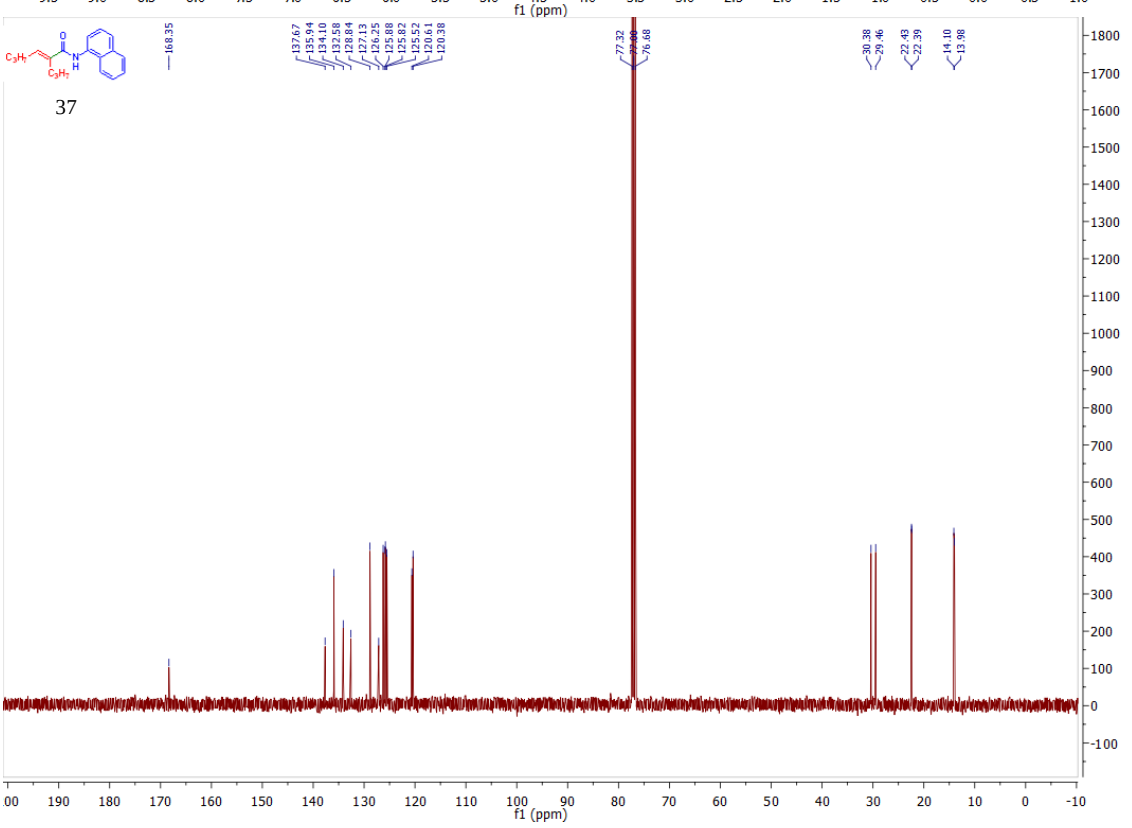
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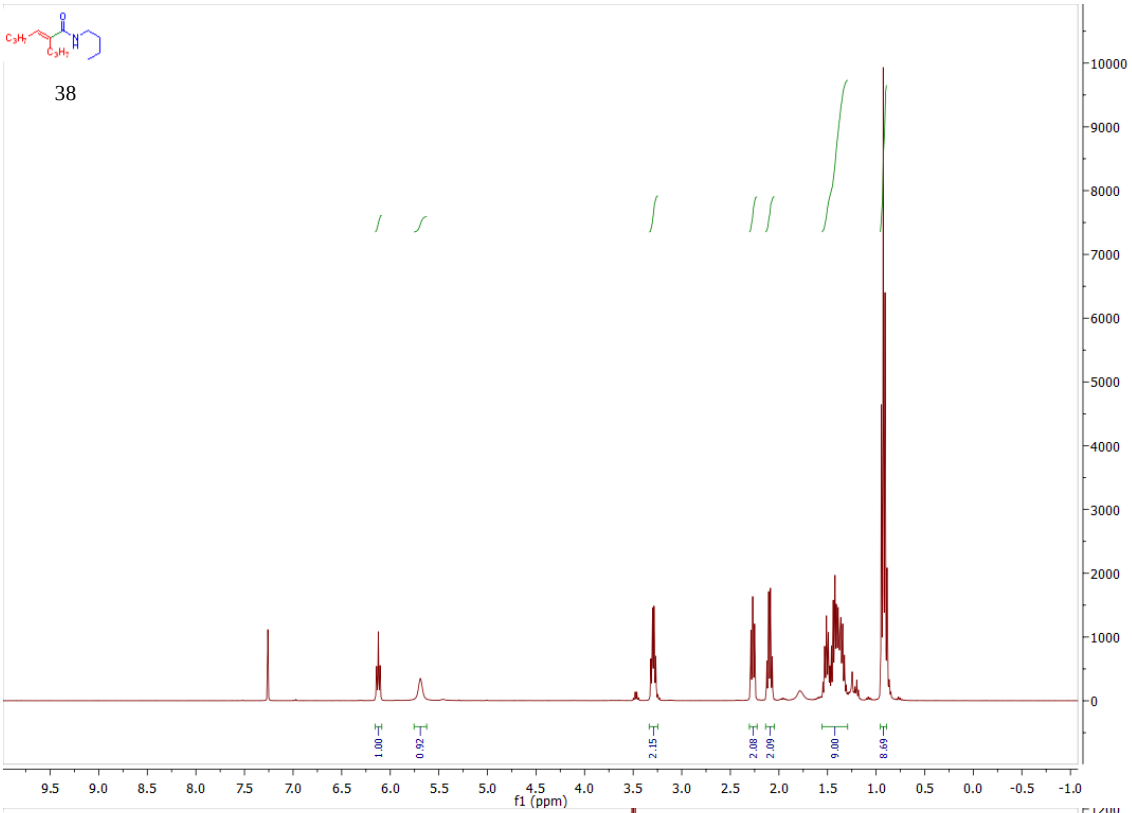
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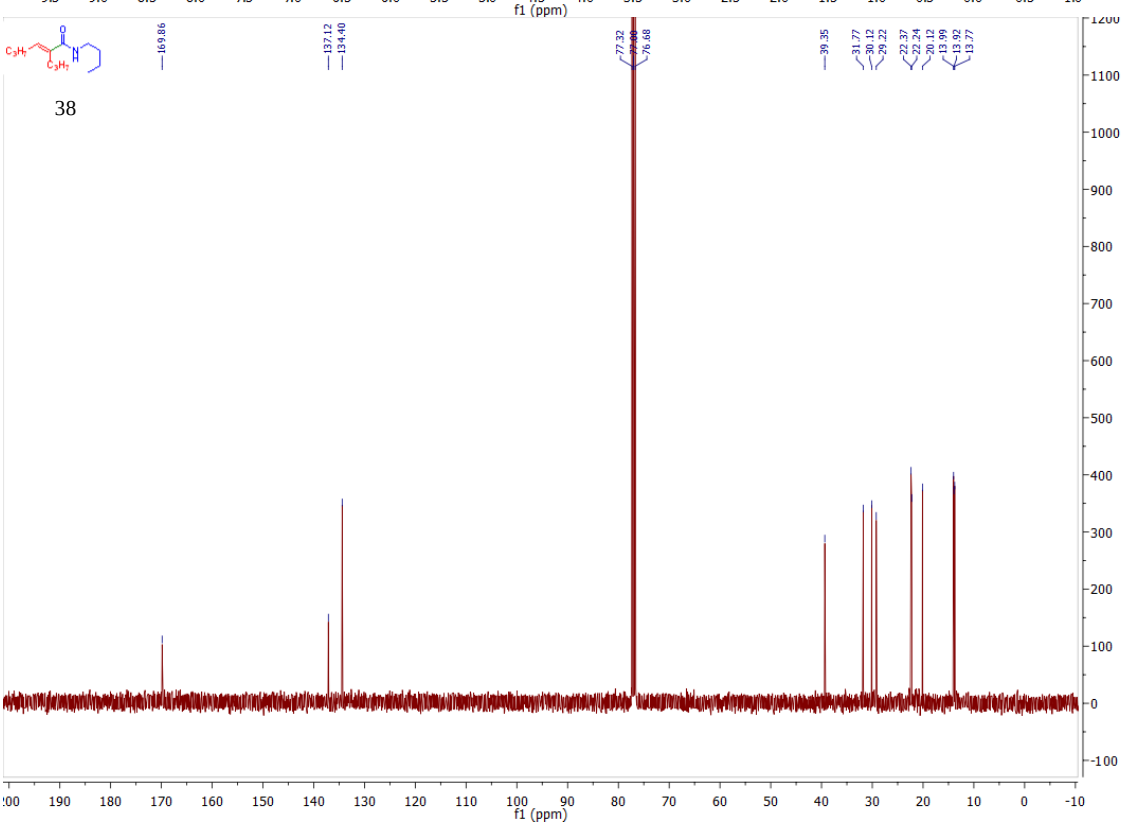
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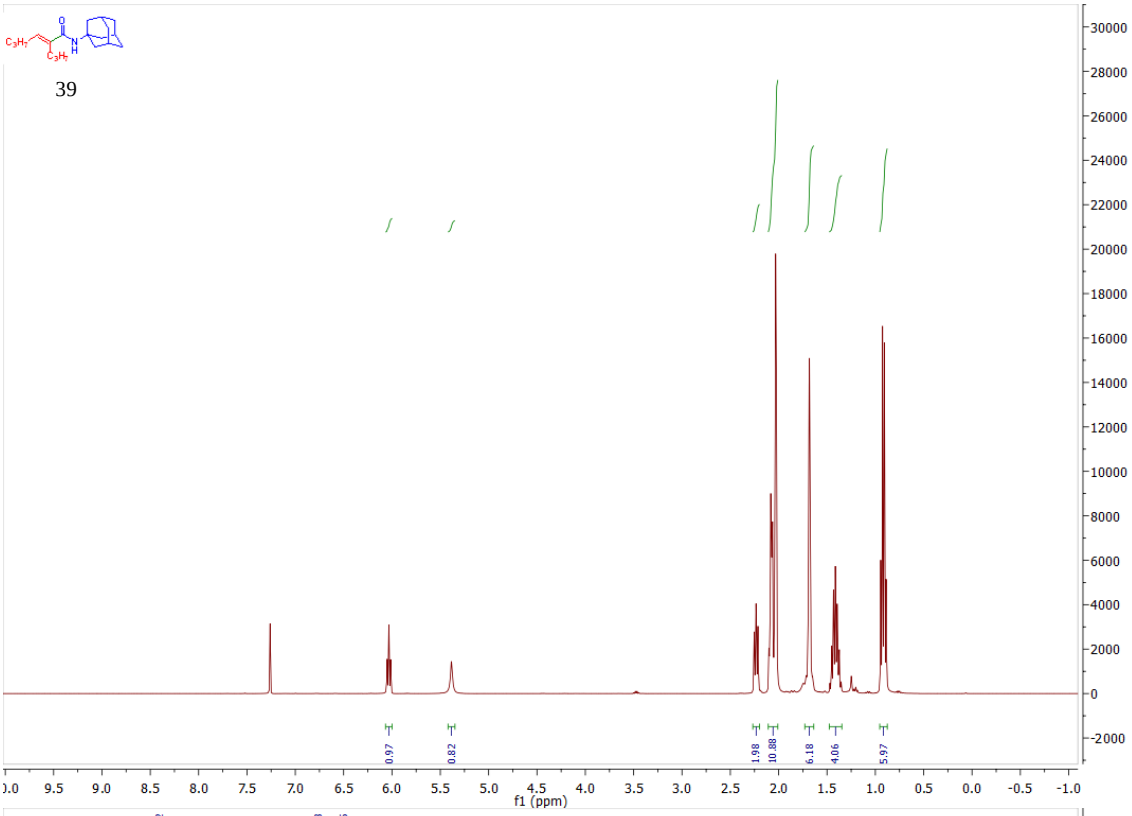
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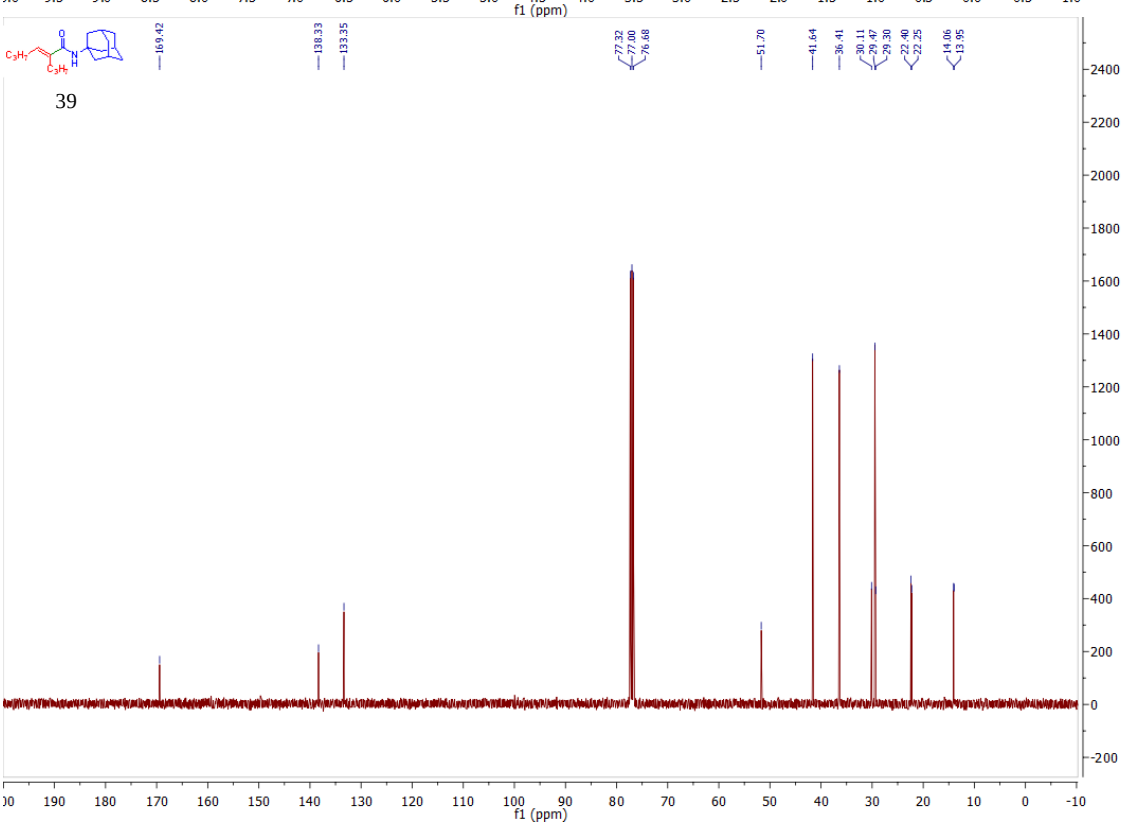
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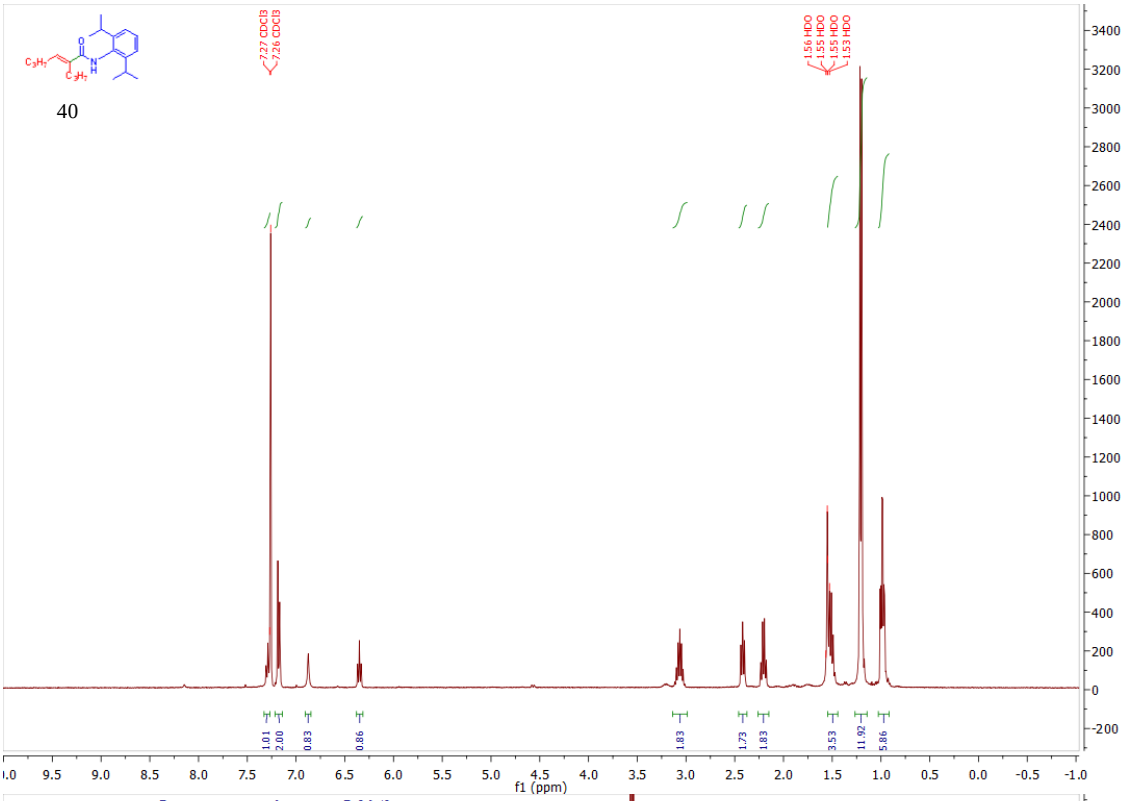
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1.83
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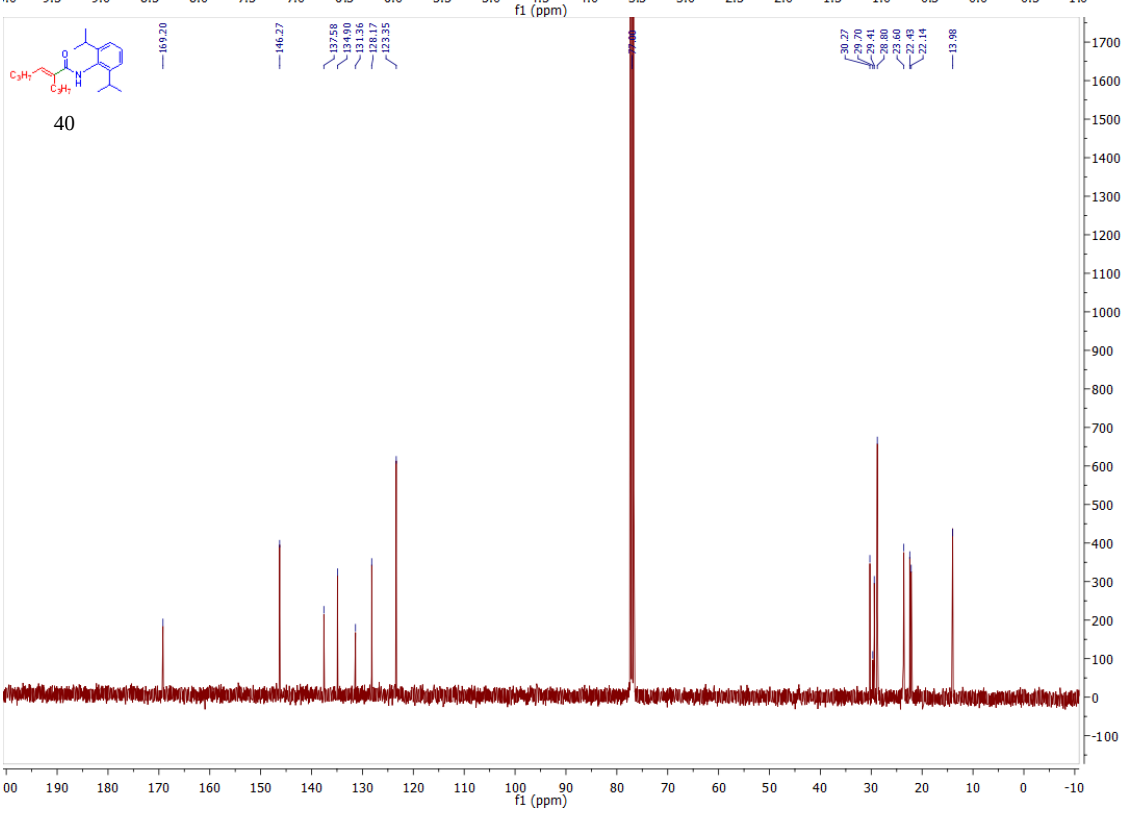
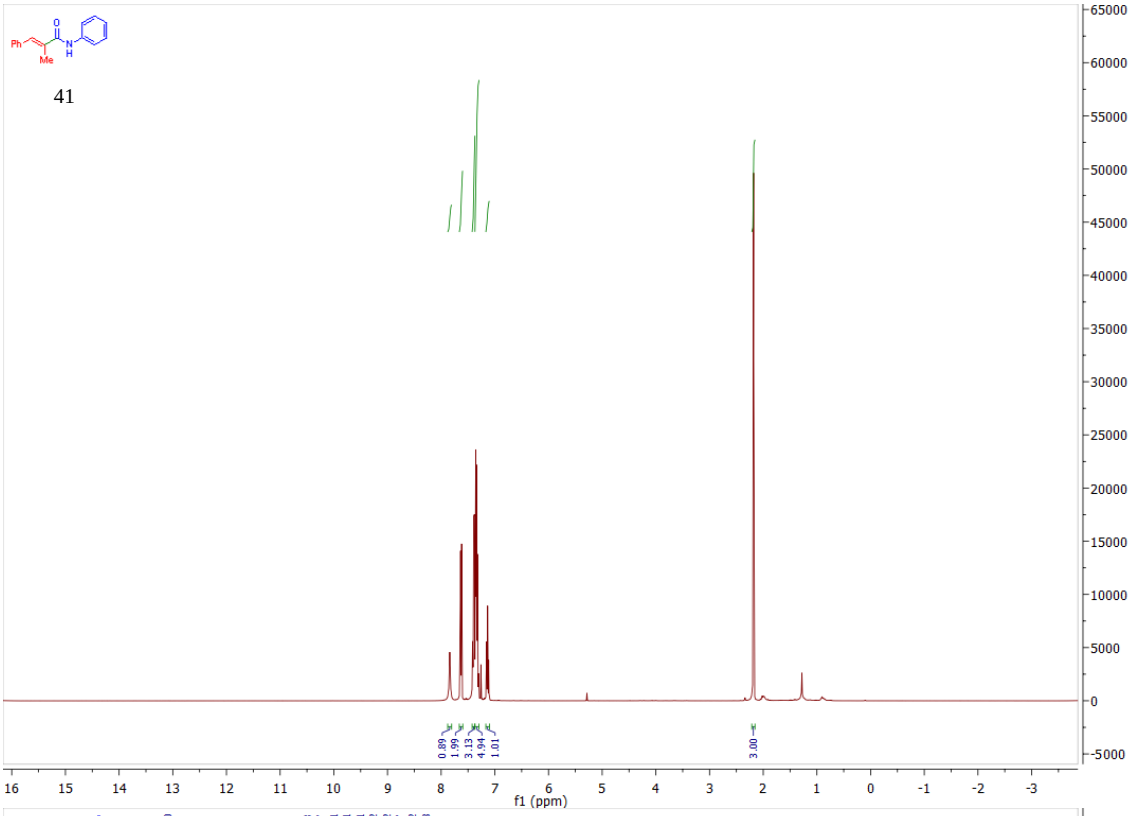
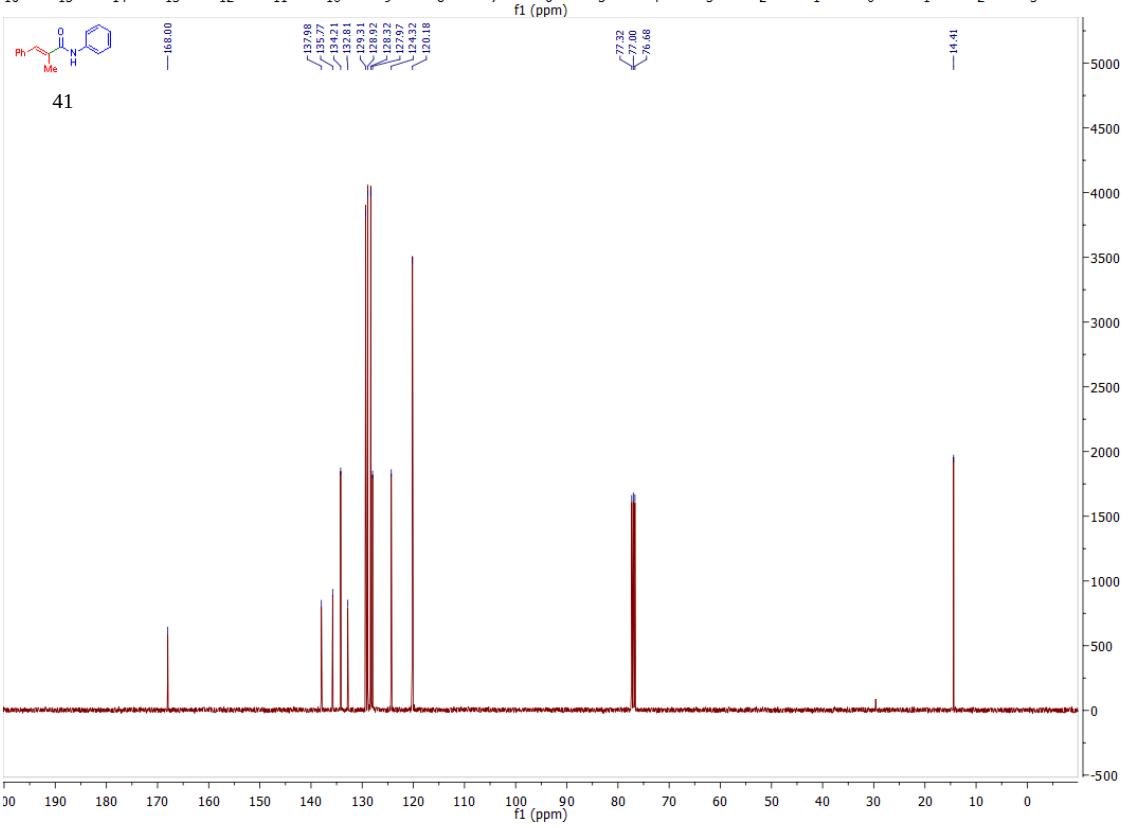
1.83
3.53
11.92
5.86
f1 (ppm)

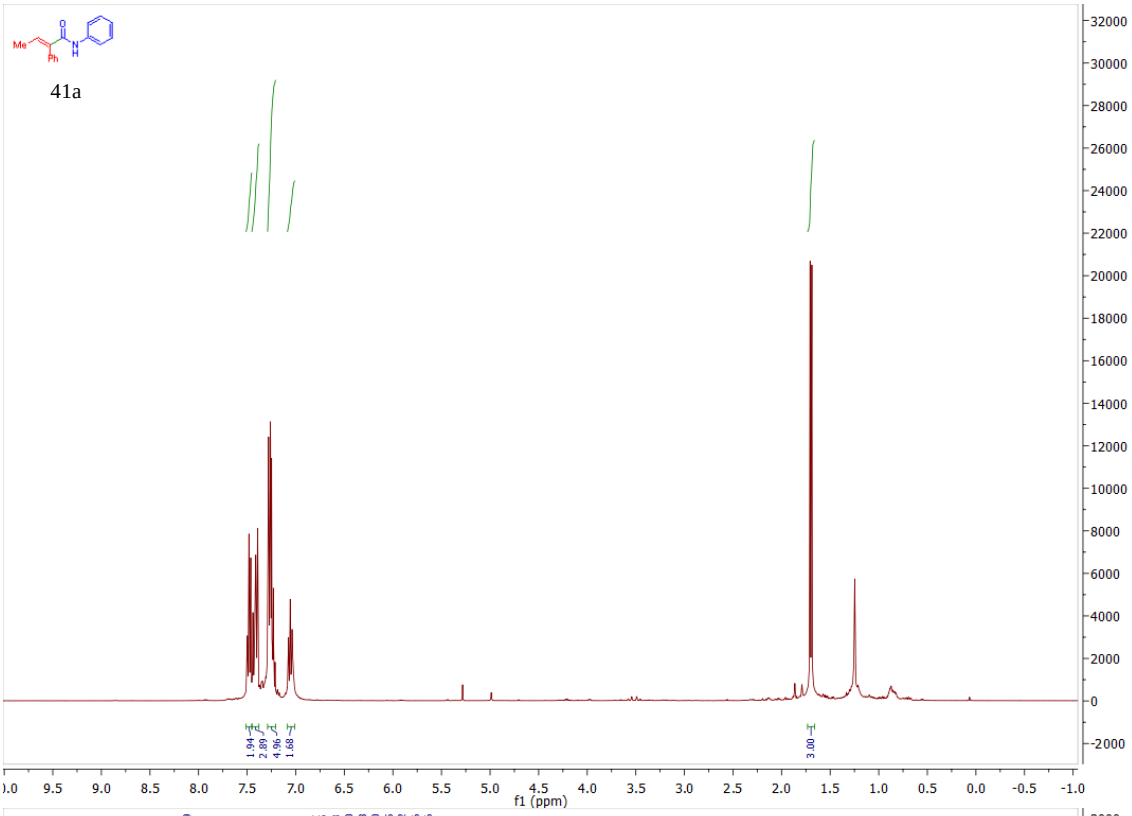
40

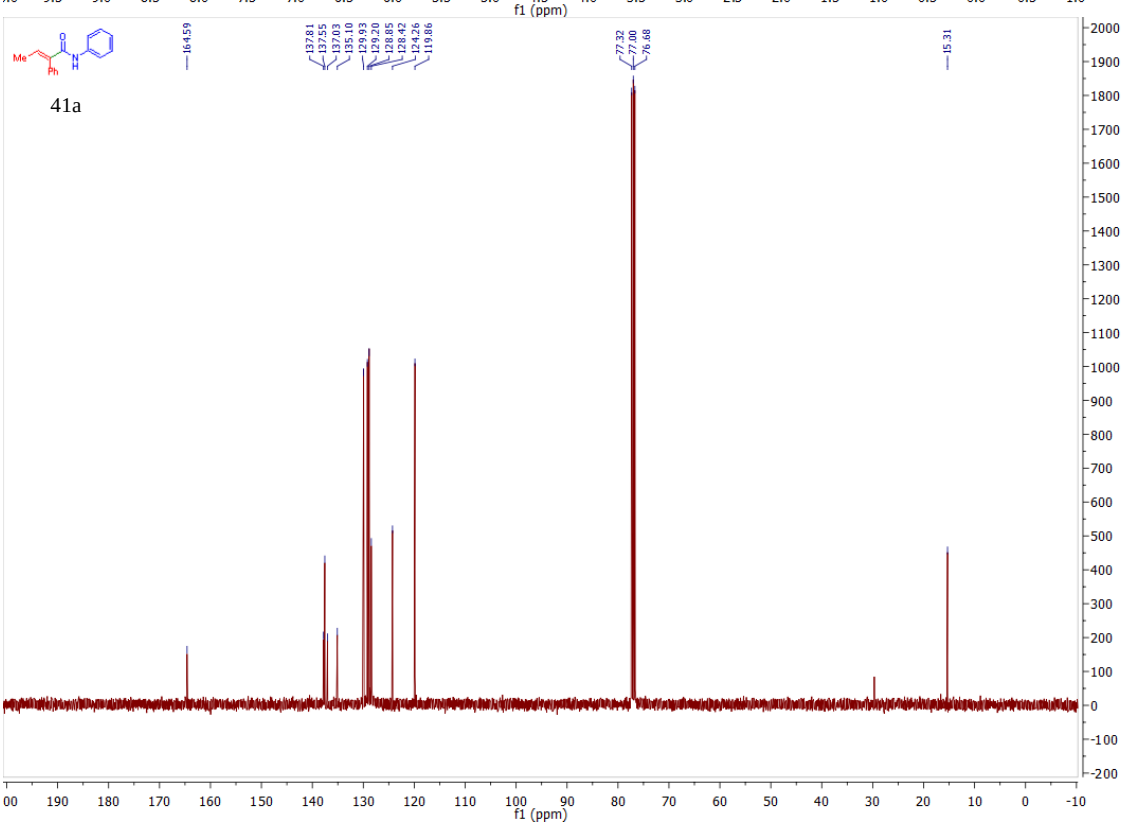

169.20
146.27
137.58
134.90
131.36
128.37
123.35
77.00
30.27
29.70
29.41
28.80
23.60
22.43
22.14
13.98
f1 (ppm)

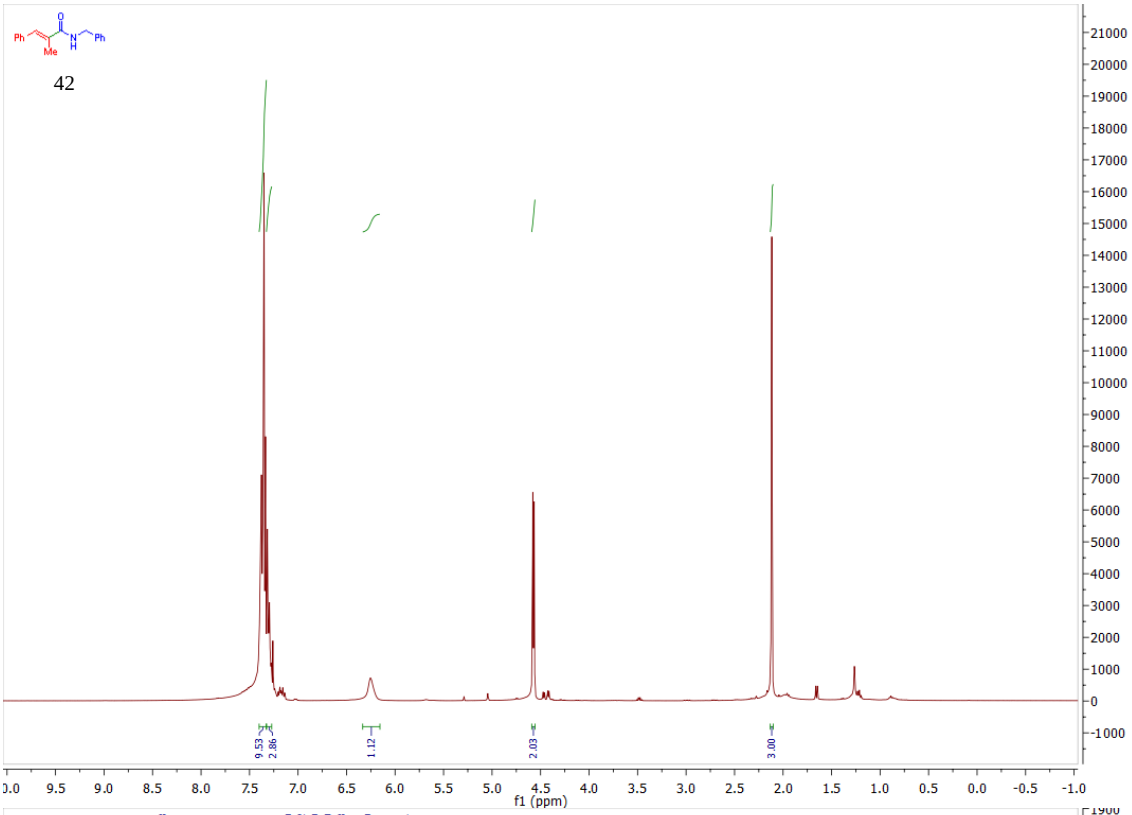
40

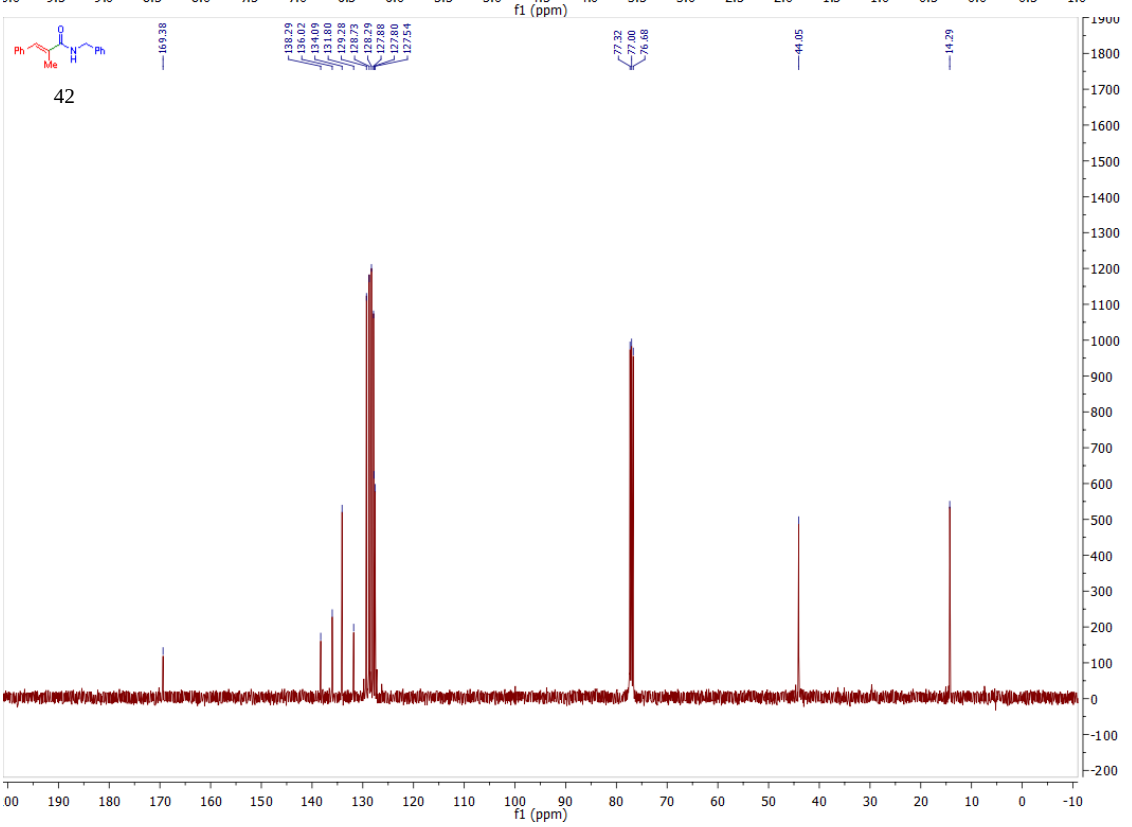

41
f1 (ppm)

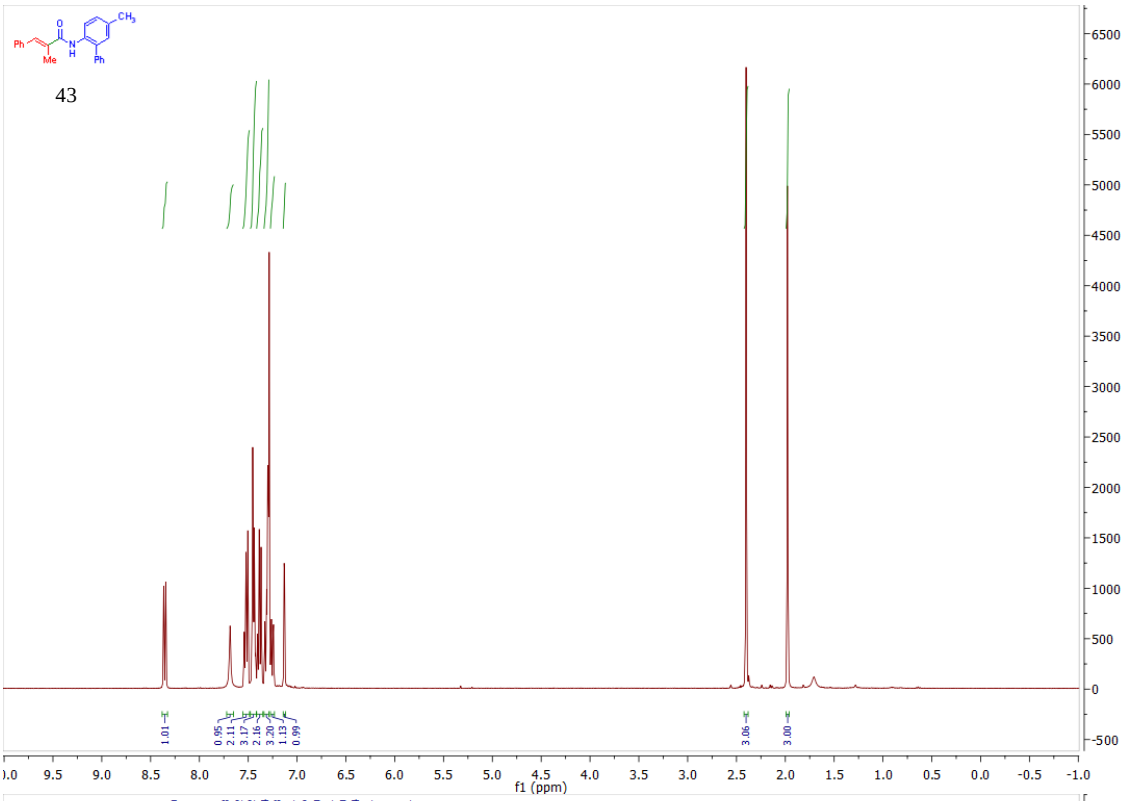

41
168.00
137.98
135.77
134.21
132.81
129.31
128.92
128.32
127.97
124.32
120.18
77.32
77.00
76.68
14.41
f1 (ppm)

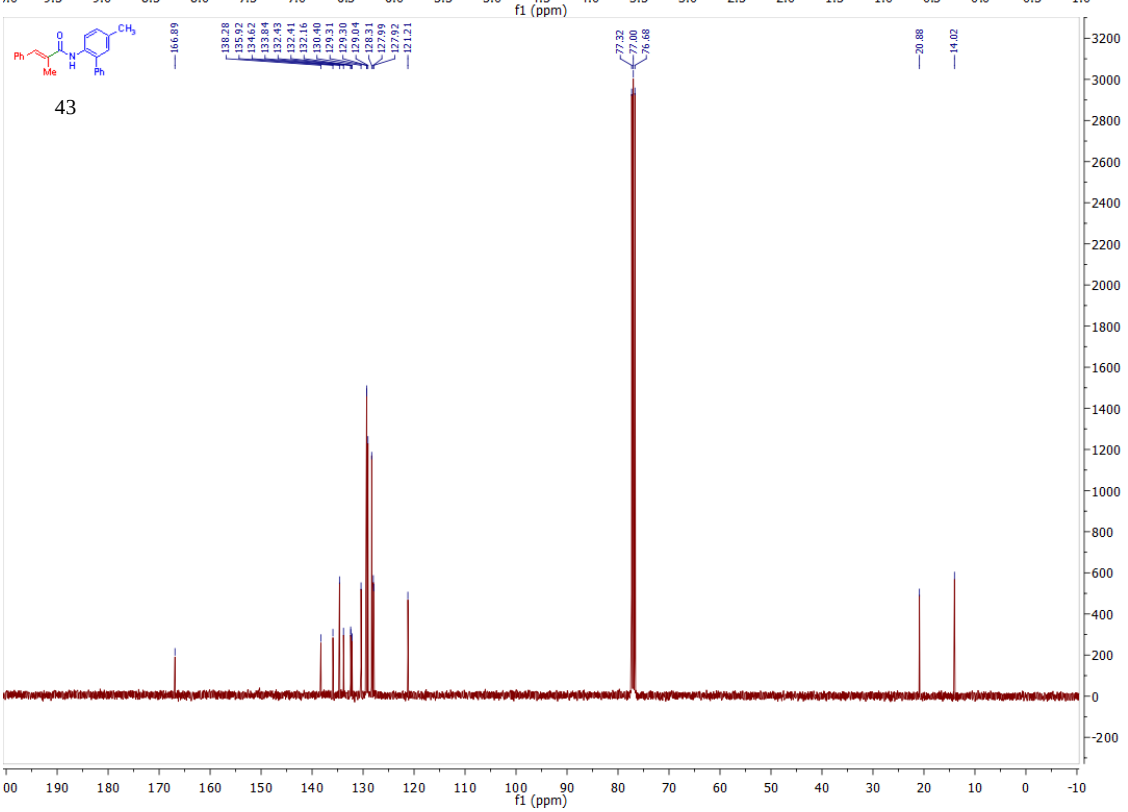

41a
1.94
2.89
4.96
1.68
3.00
f1 (ppm)

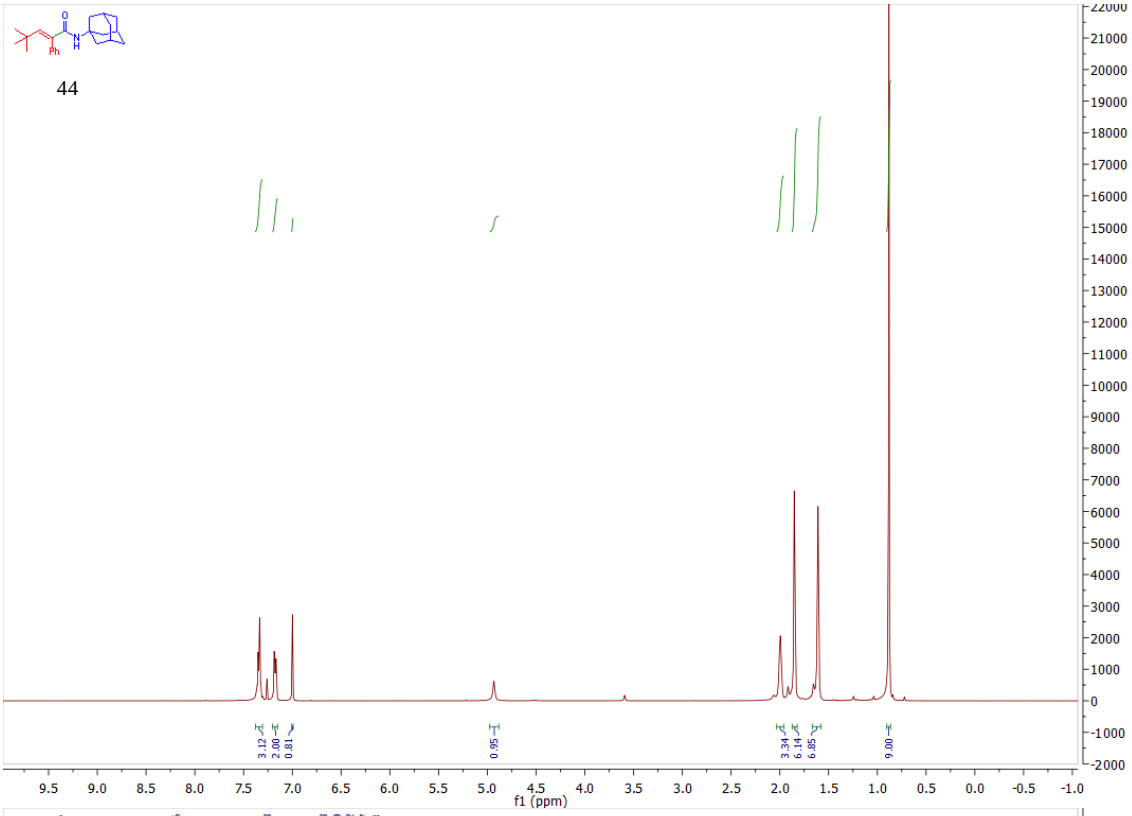

41a
164.59
137.81
137.55
137.03
135.10
129.93
129.20
128.85
128.42
124.26
119.86
77.32
77.00
76.68
15.31
f1 (ppm)

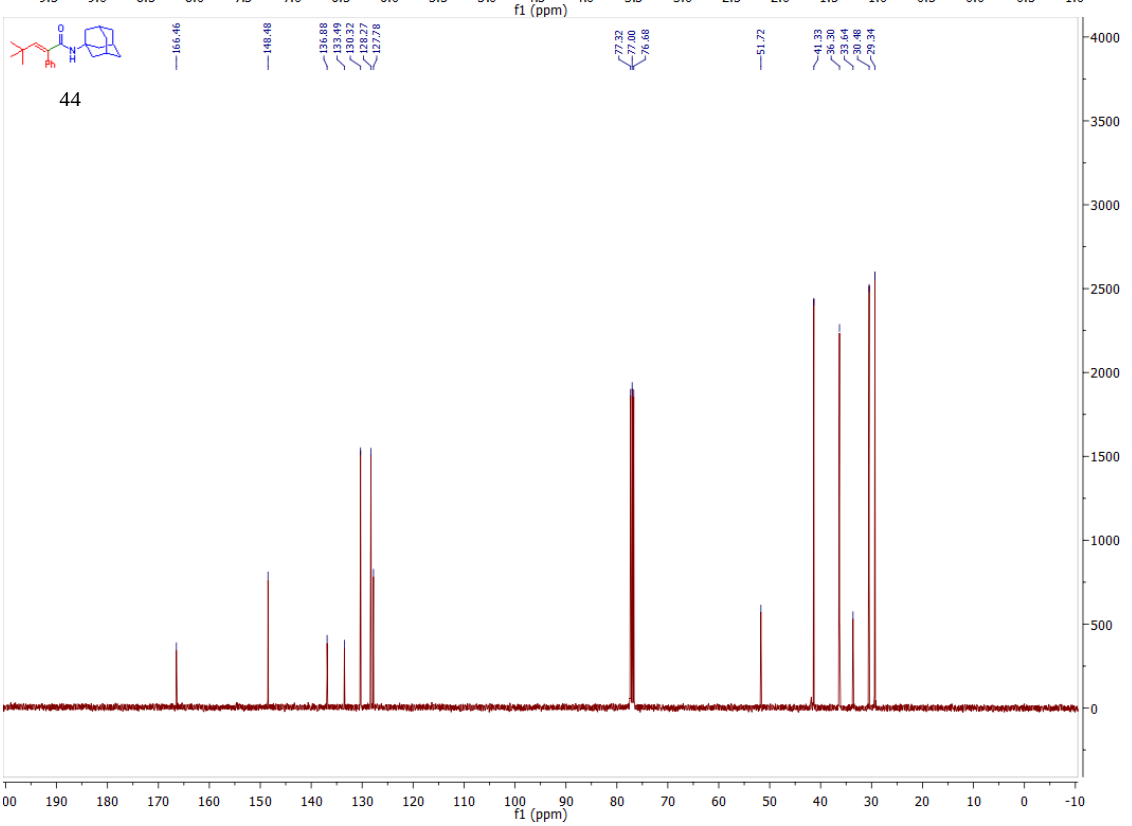

42
9.53
2.86
1.12
2.03
3.00
f1 (ppm)

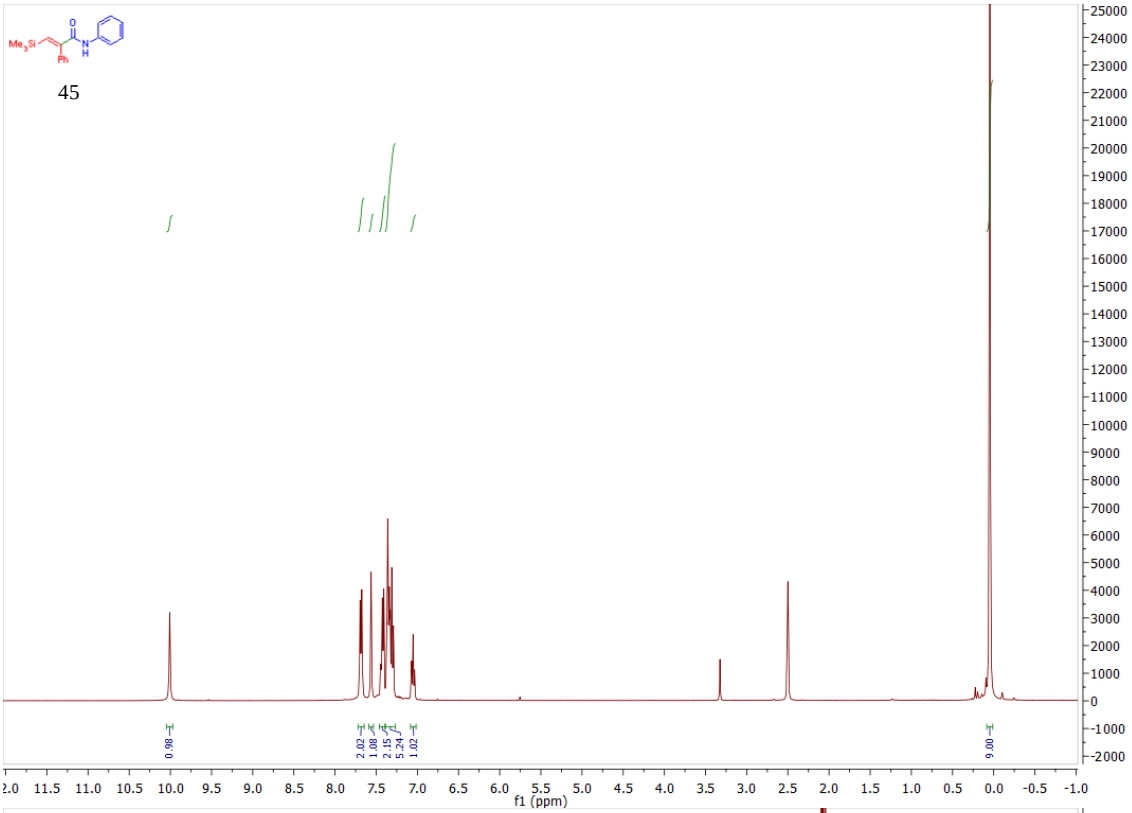

42
169.38
138.29
136.02
134.09
131.80
129.28
128.73
128.29
127.88
127.80
127.54
77.32
77.00
76.68
44.05
14.29
f1 (ppm)

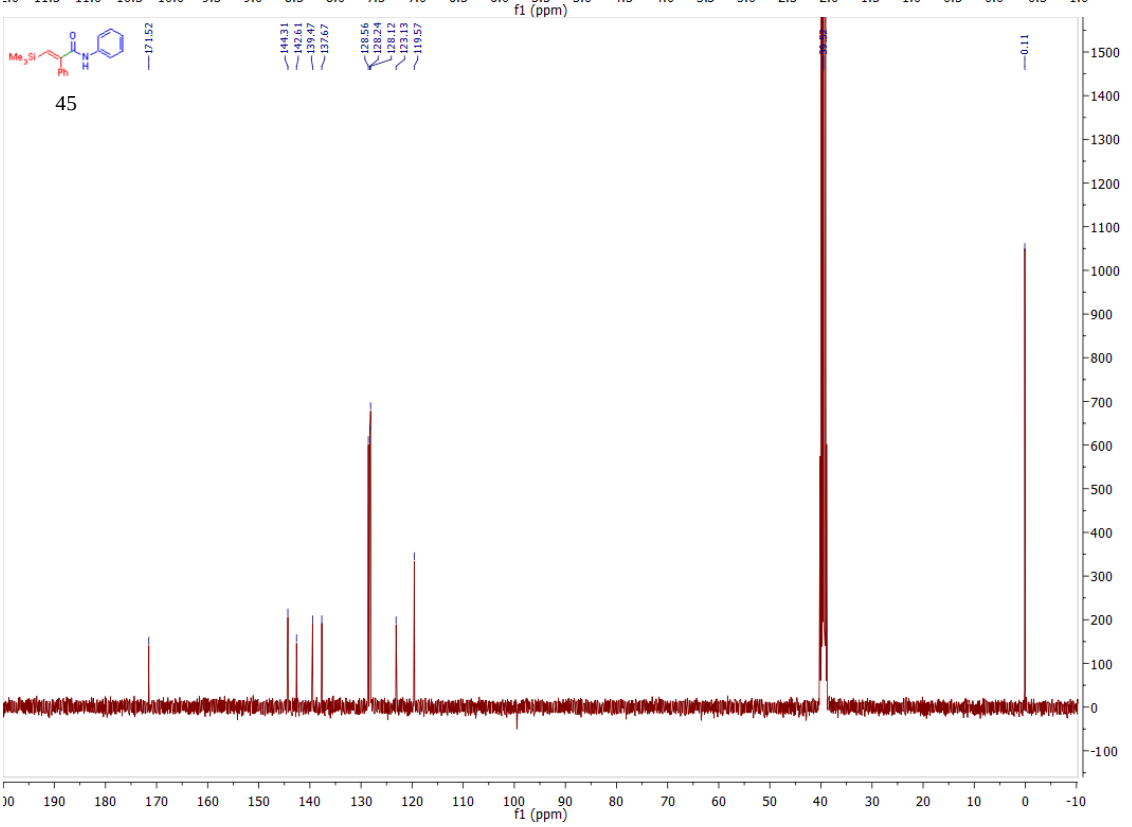

43
1.01
0.95
2.11
3.17
2.16
3.20
1.13
0.99
3.06
3.00
f1 (ppm)

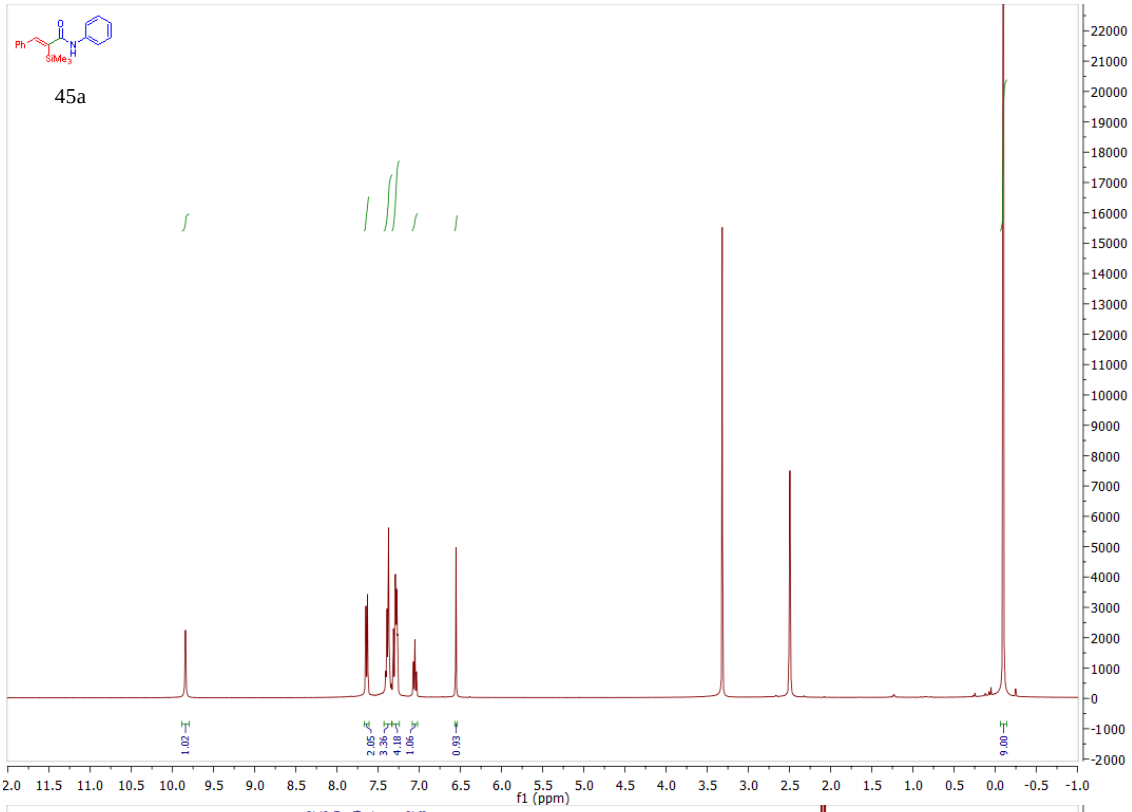

43
166.89
138.28
135.92
134.62
133.84
132.43
132.41
132.16
130.40
129.31
129.30
129.04
128.31
127.99
127.92
121.21
77.32
77.00
76.68
20.88
14.02
f1 (ppm)

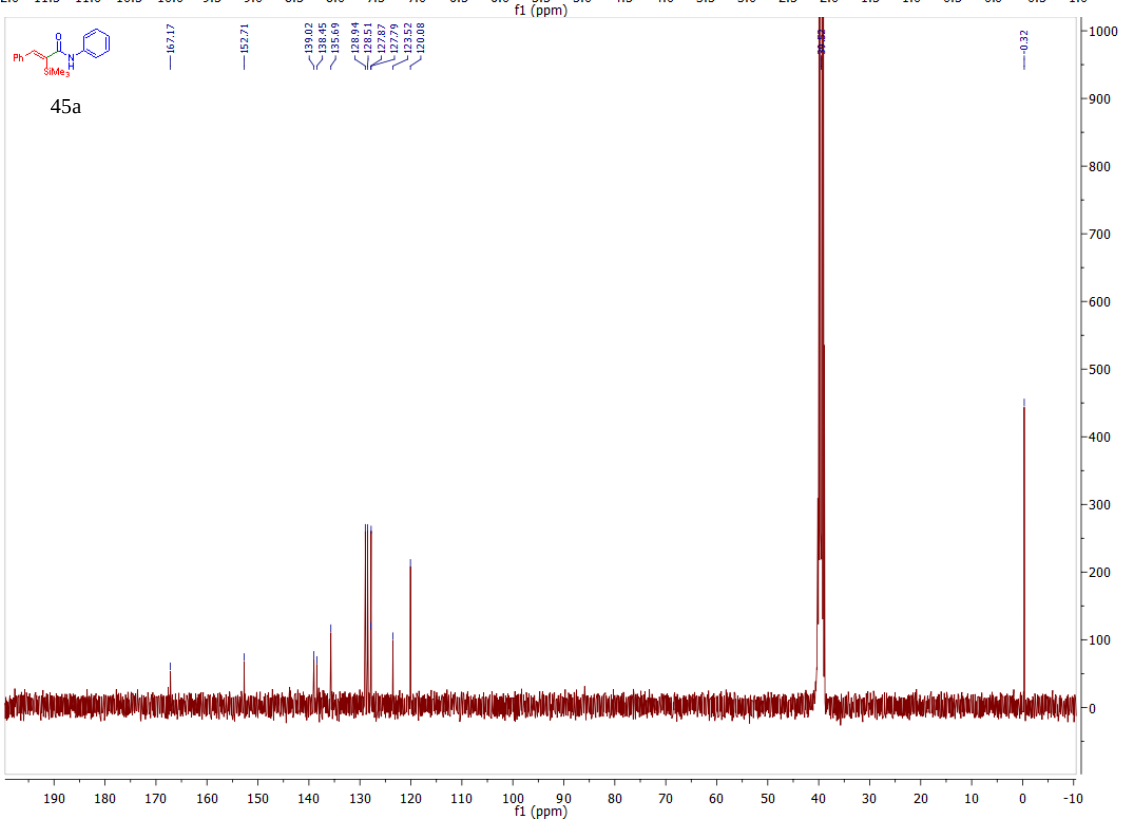

44
3.12
2.00
0.81
0.95
3.34
6.14
6.85
9.00
f1 (ppm)

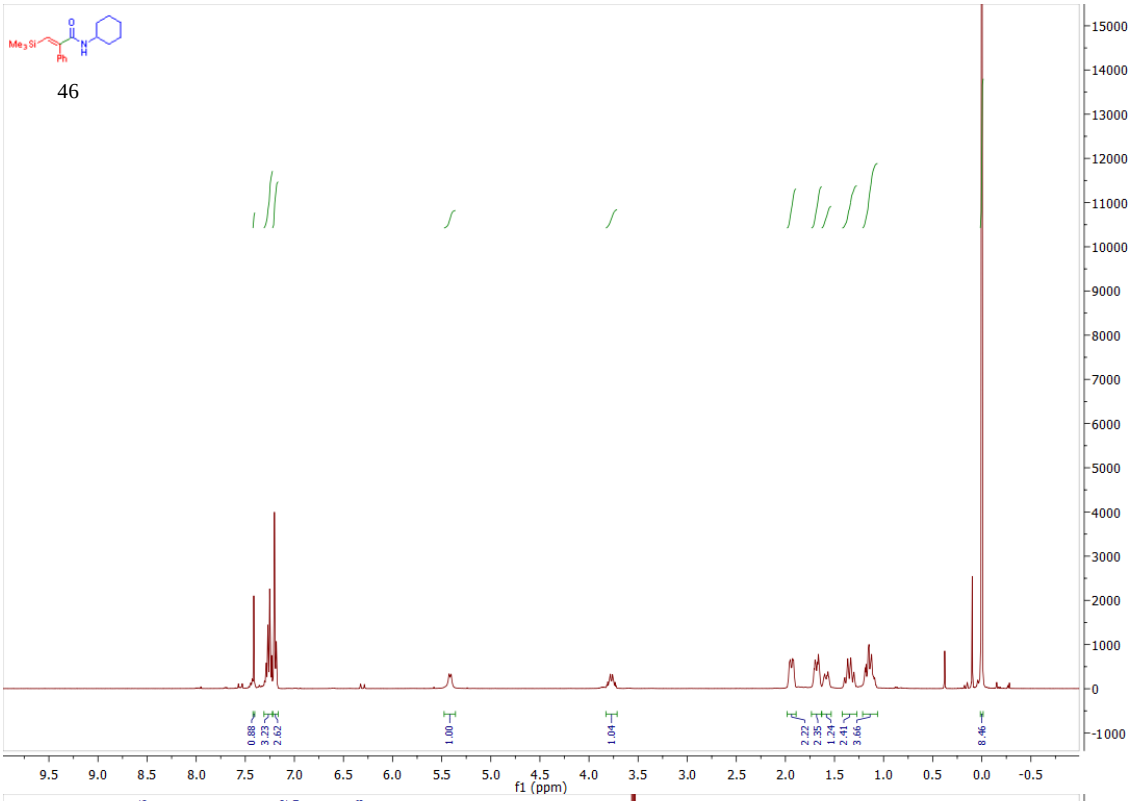

44
166.46
148.48
136.88
133.49
130.32
128.27
127.78
77.32
77.00
76.68
51.72
41.33
36.30
33.64
30.48
29.34
f1 (ppm)

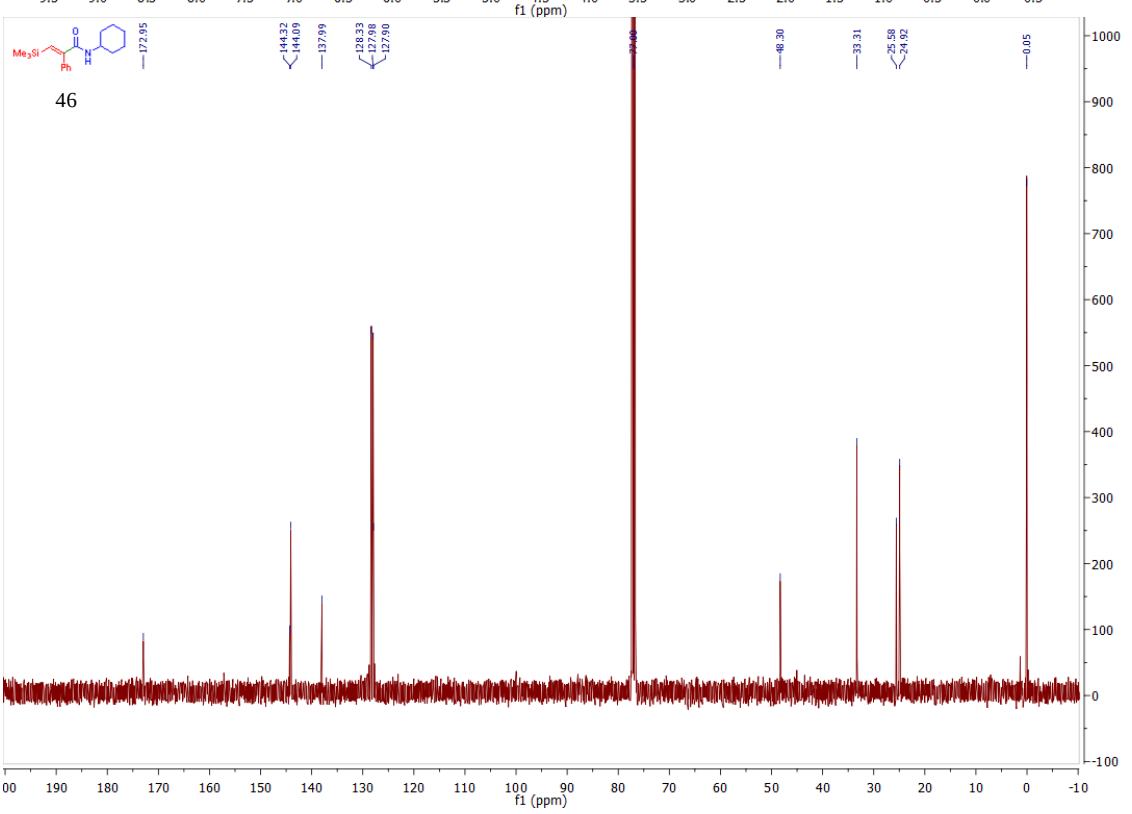

45
0.98
2.02
1.08
1.15
2.24
1.02
9.00
f1 (ppm)

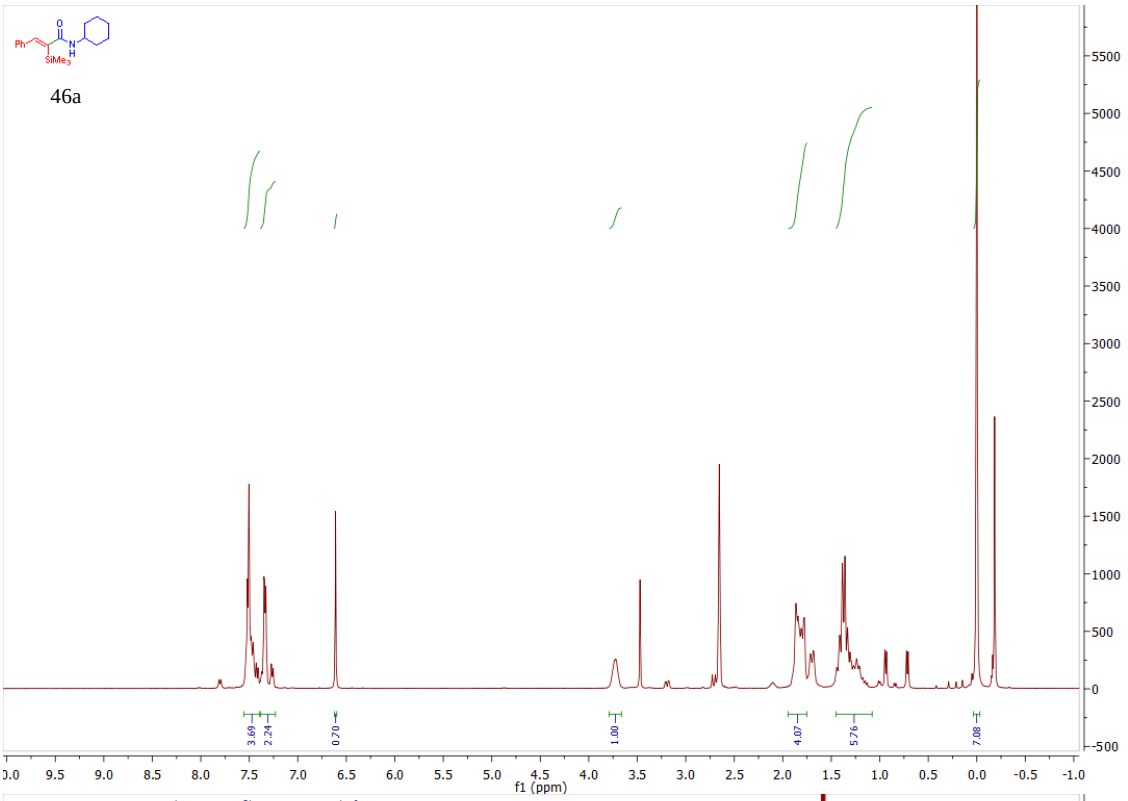

45
171.52
144.31
142.61
139.47
137.67
128.56
128.24
128.12
123.13
119.57
39.52
0.11
f1 (ppm)


45a
1.02
2.05
3.36
4.18
1.06
0.93
9.00
f1 (ppm)


45a
167.17
152.71
139.02
138.45
135.69
128.94
128.51
127.87
127.79
123.52
120.08
39.82
0.32
f1 (ppm)


46
f1 (ppm)


46
172.95
144.32
144.09
137.99
128.33
127.98
127.90
77.00
40.30
33.31
25.58
24.92
0.05
f1 (ppm)


46a
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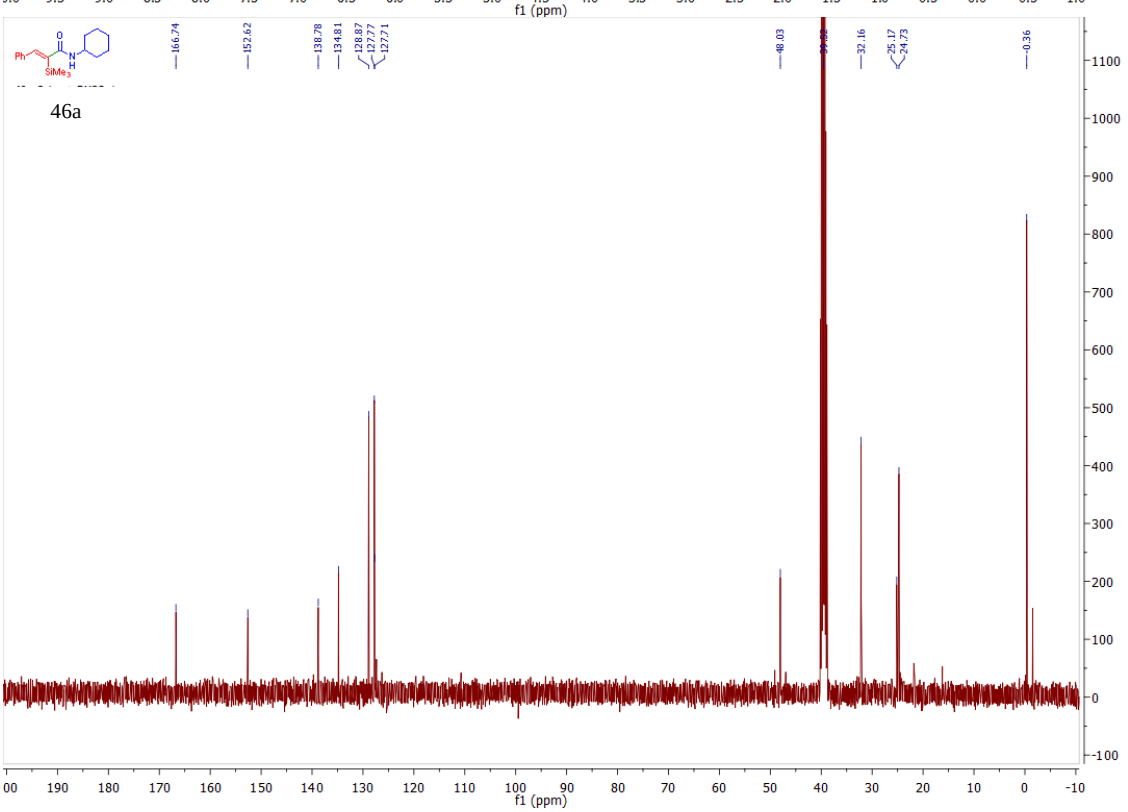
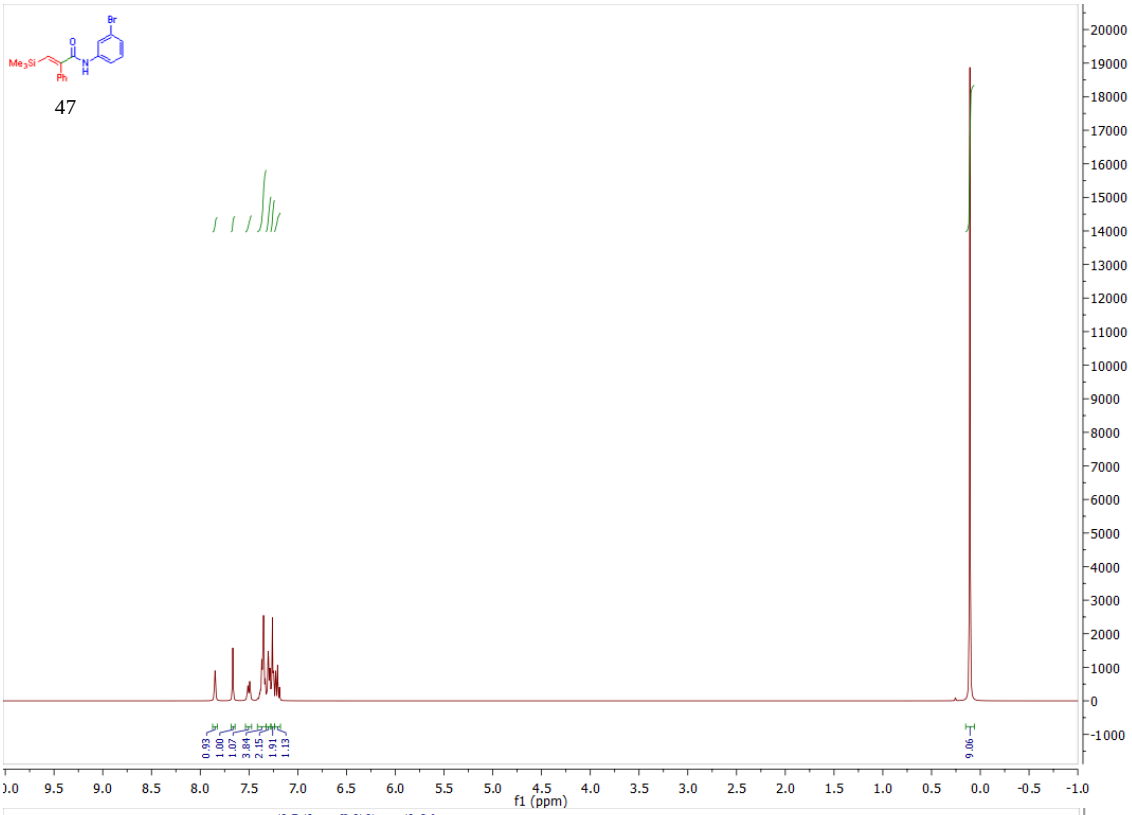
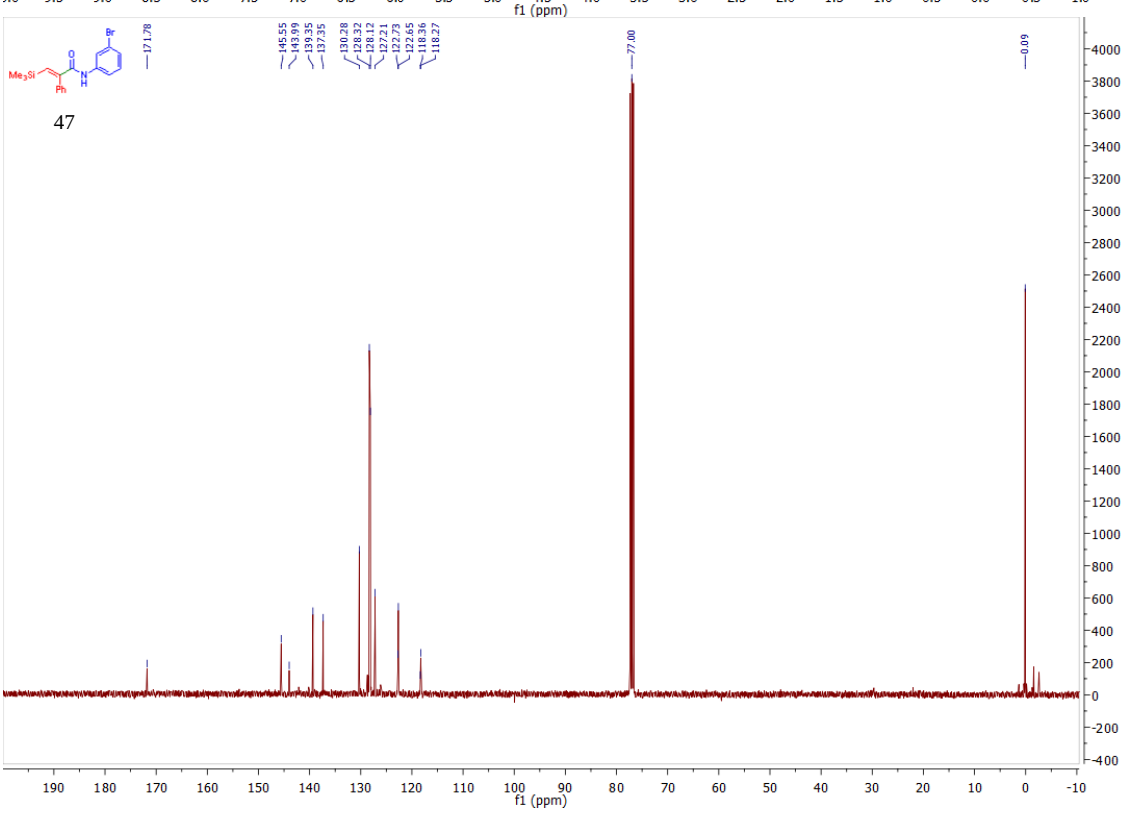
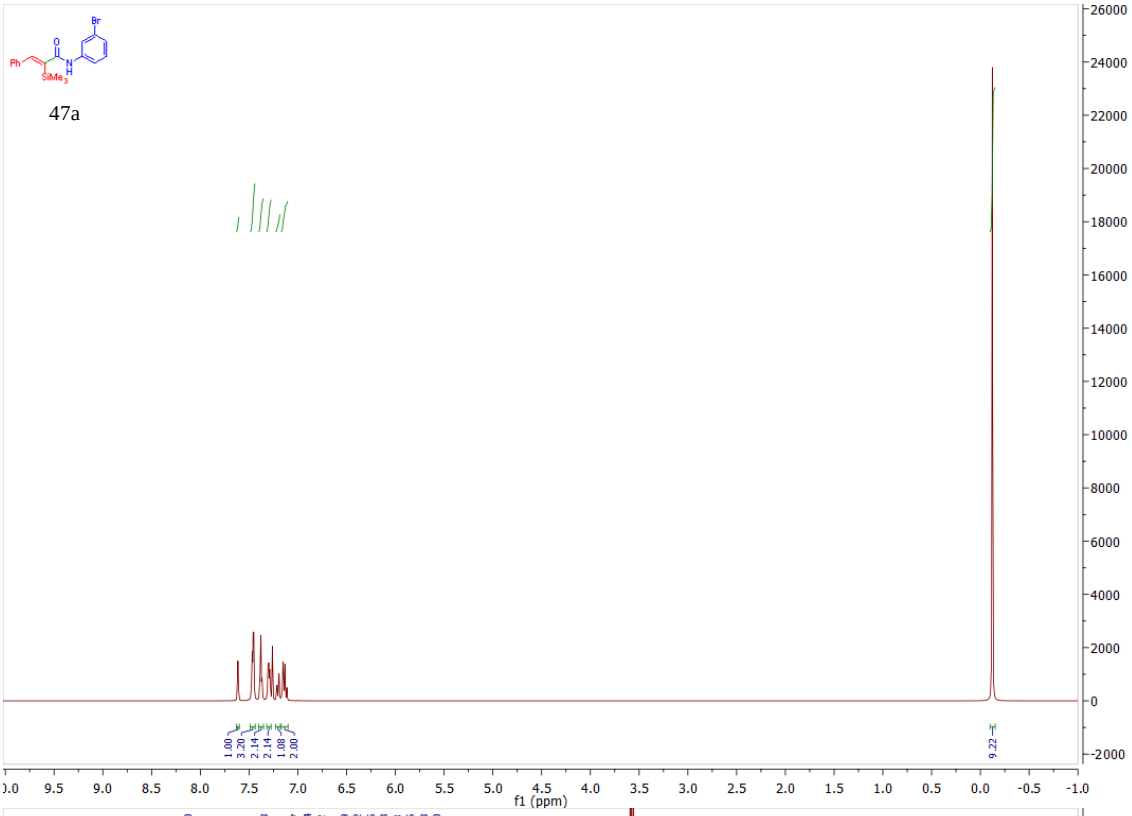
2.24
0.70
1.00
4.07
5.76
7.08
f1 (ppm)


46a
166.74
152.62
138.78
134.81
128.87
127.77
127.71
48.03
32.16
25.17
24.73
0.36
f1 (ppm)


47
0.93
1.00
1.07
3.84
2.15
1.91
1.13
9.06
f1 (ppm)


47
171.78
145.55
143.99
139.35
137.35
130.28
128.32
128.12
127.21
122.73
122.65
118.36
118.27
77.00
0.09
f1 (ppm)


47a
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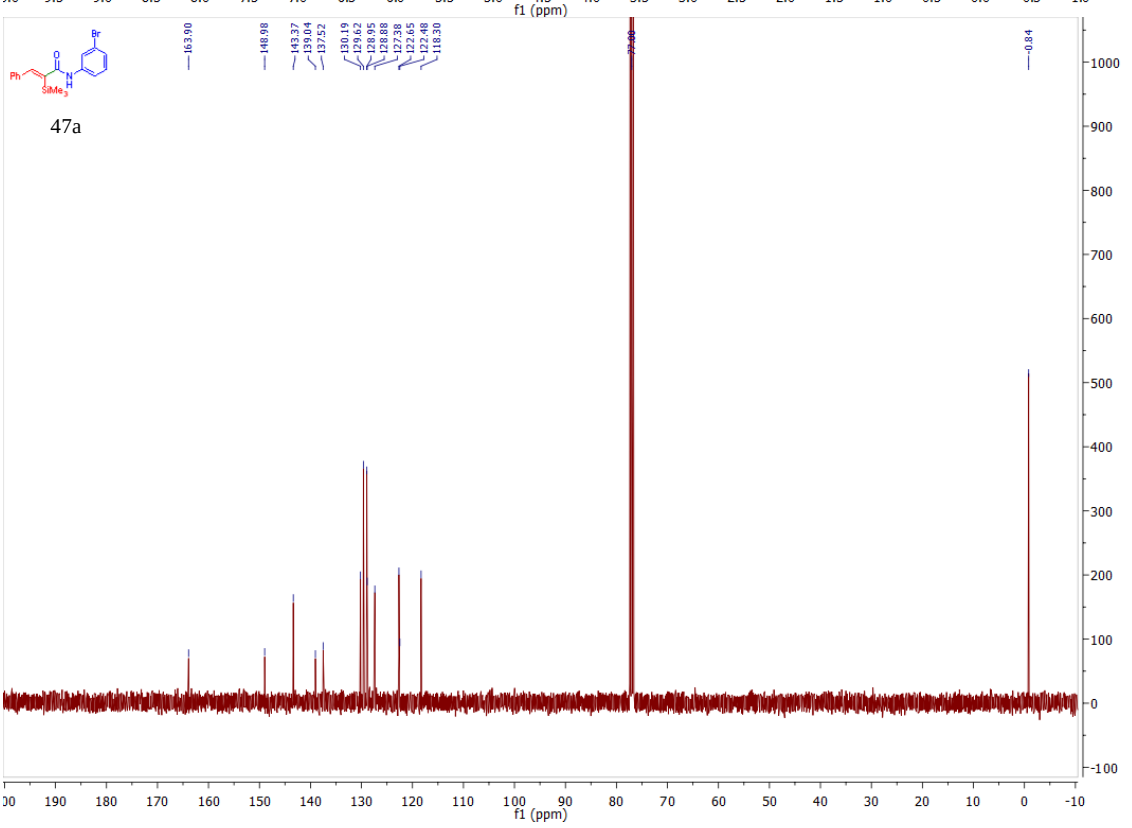
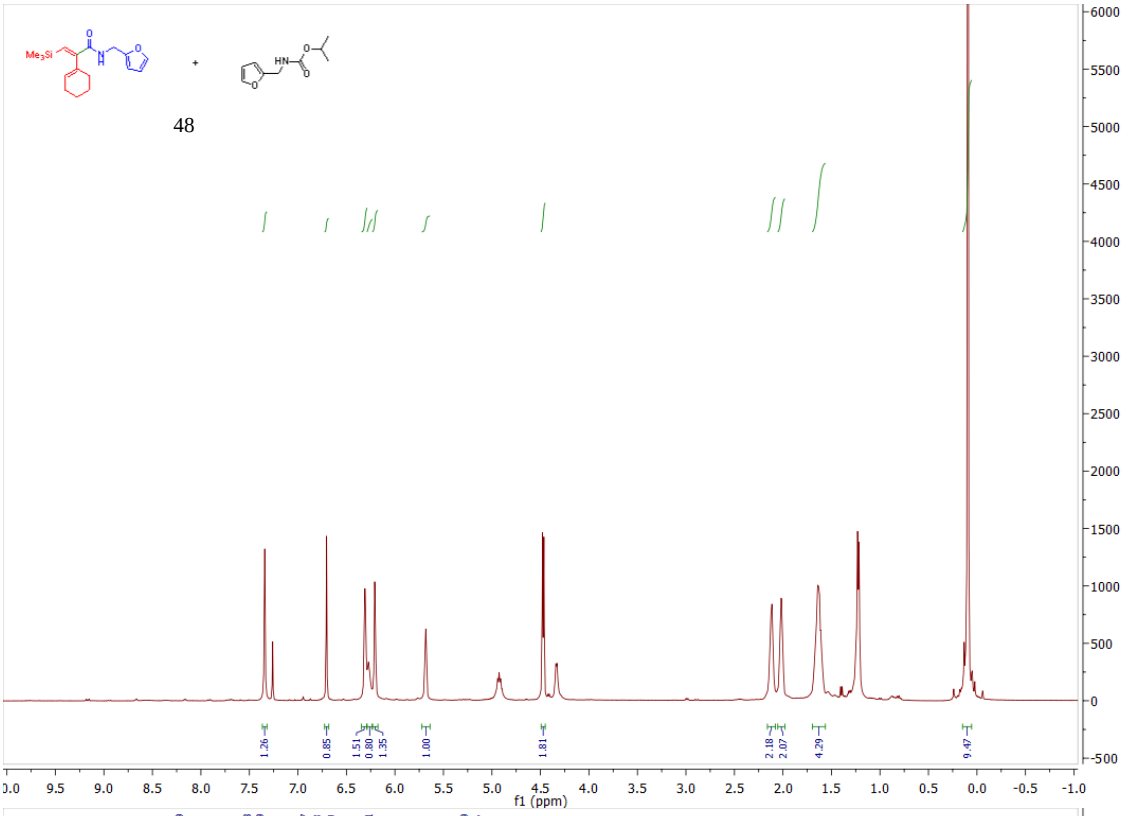
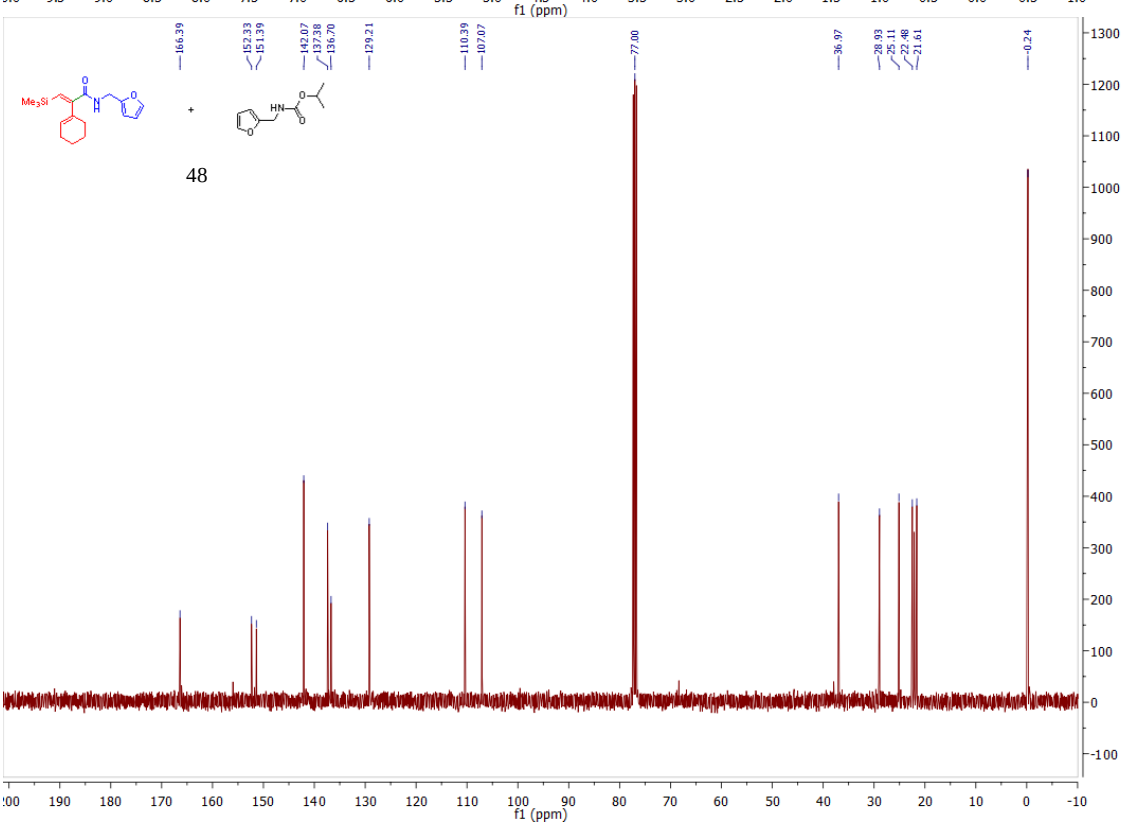
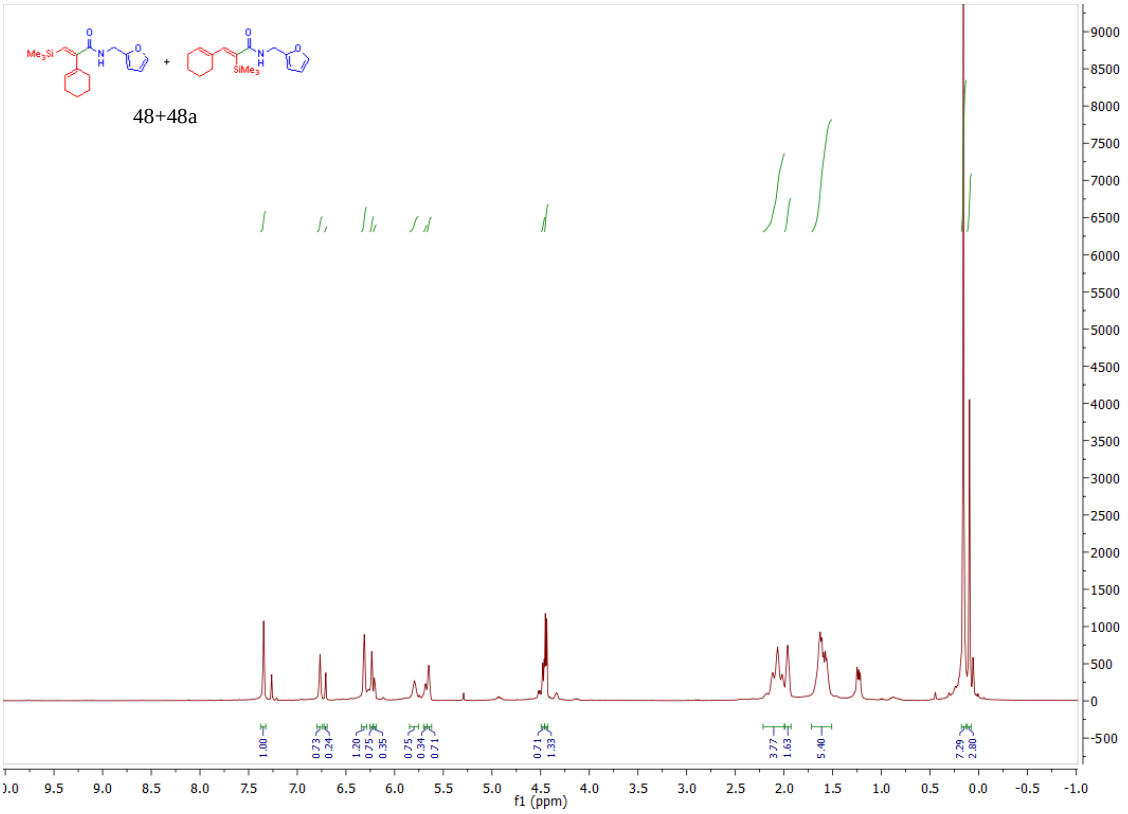
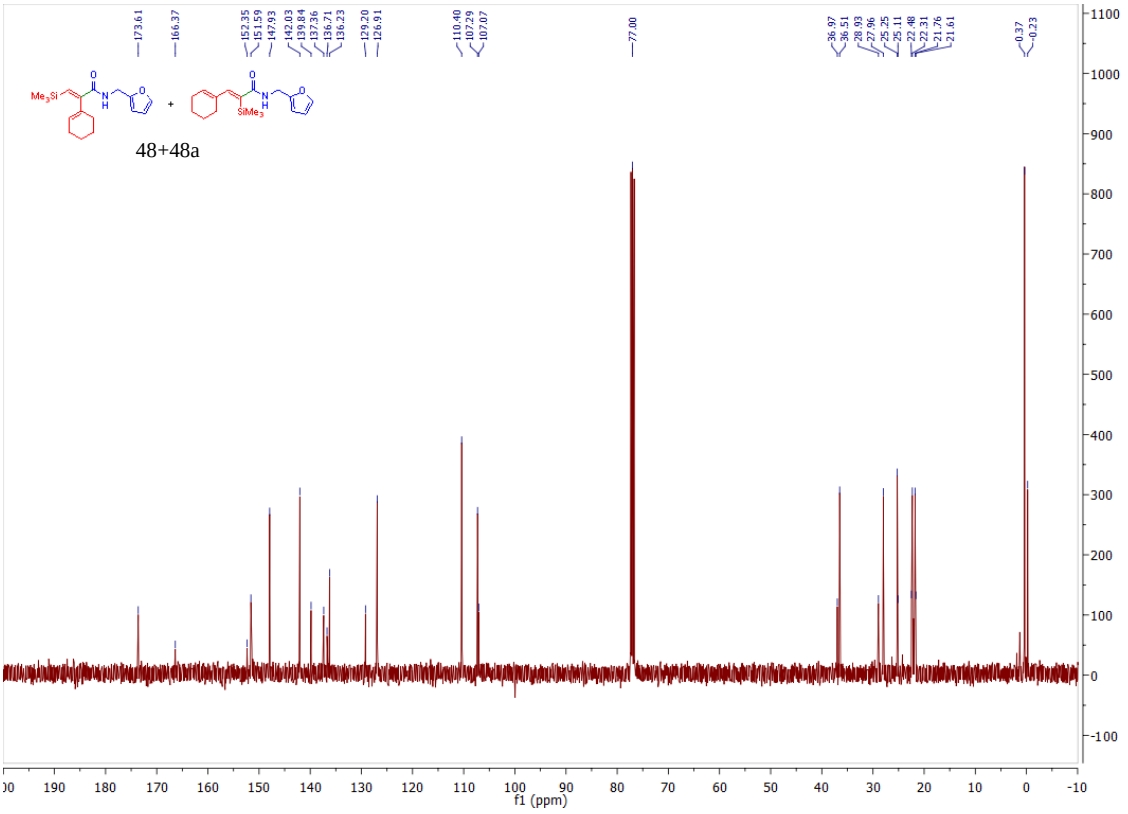
3.20
2.14
2.14
1.08
2.00
9.22
f1 (ppm)

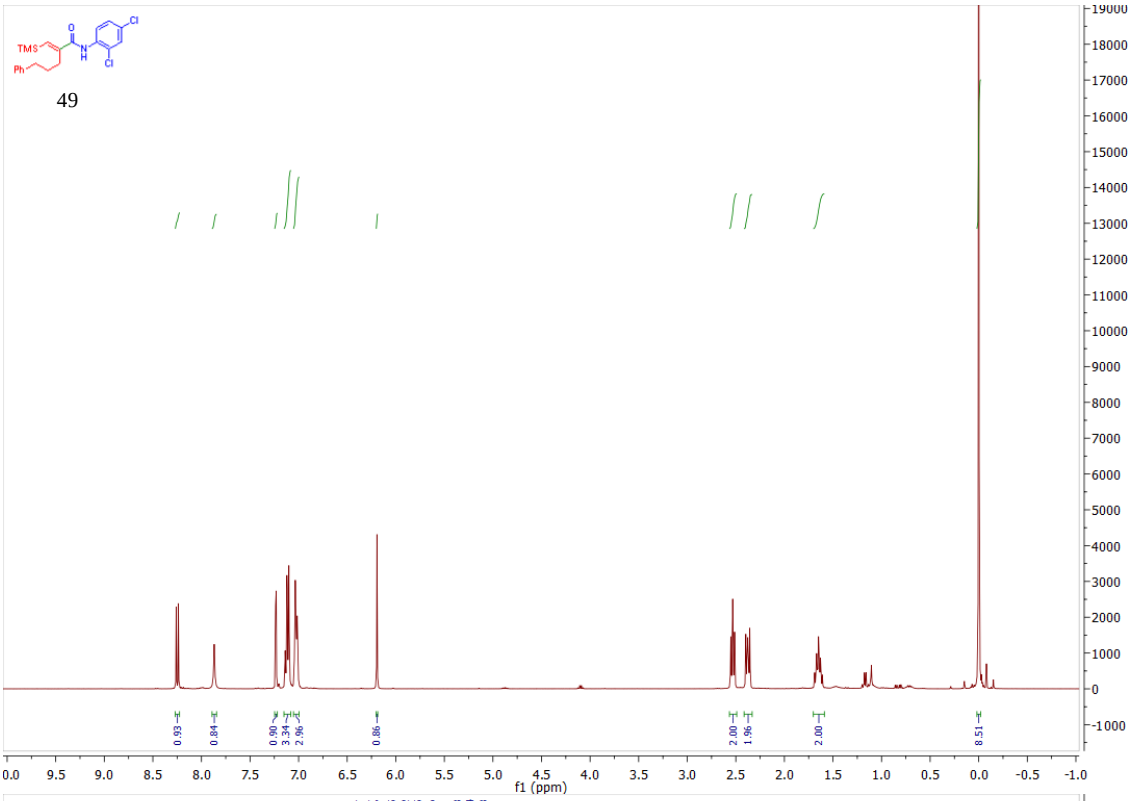

47a
163.90
148.98
143.37
139.04
137.52
130.19
129.62
128.95
128.88
127.38
122.65
122.48
118.30
77.48
0.84
f1 (ppm)

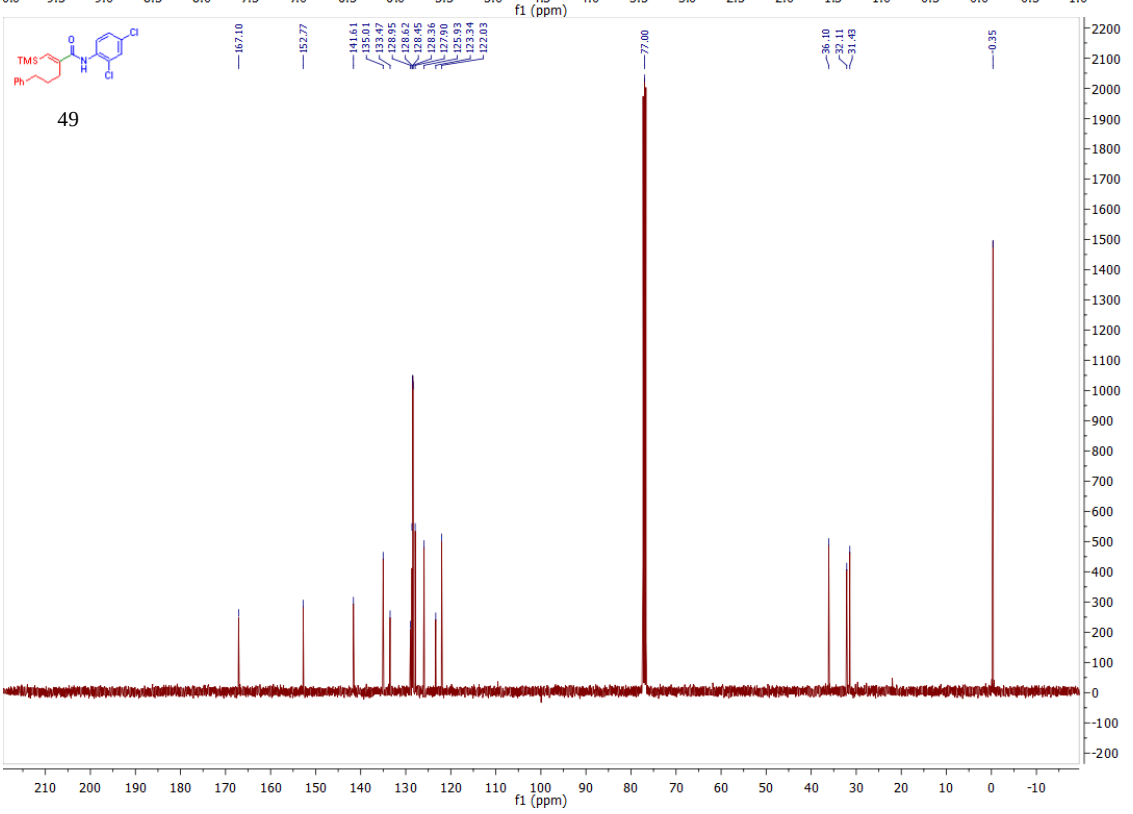

48
1.26
0.85
1.51
0.80
1.35
1.00
1.81
2.18
2.07
4.29
9.47
f1 (ppm)

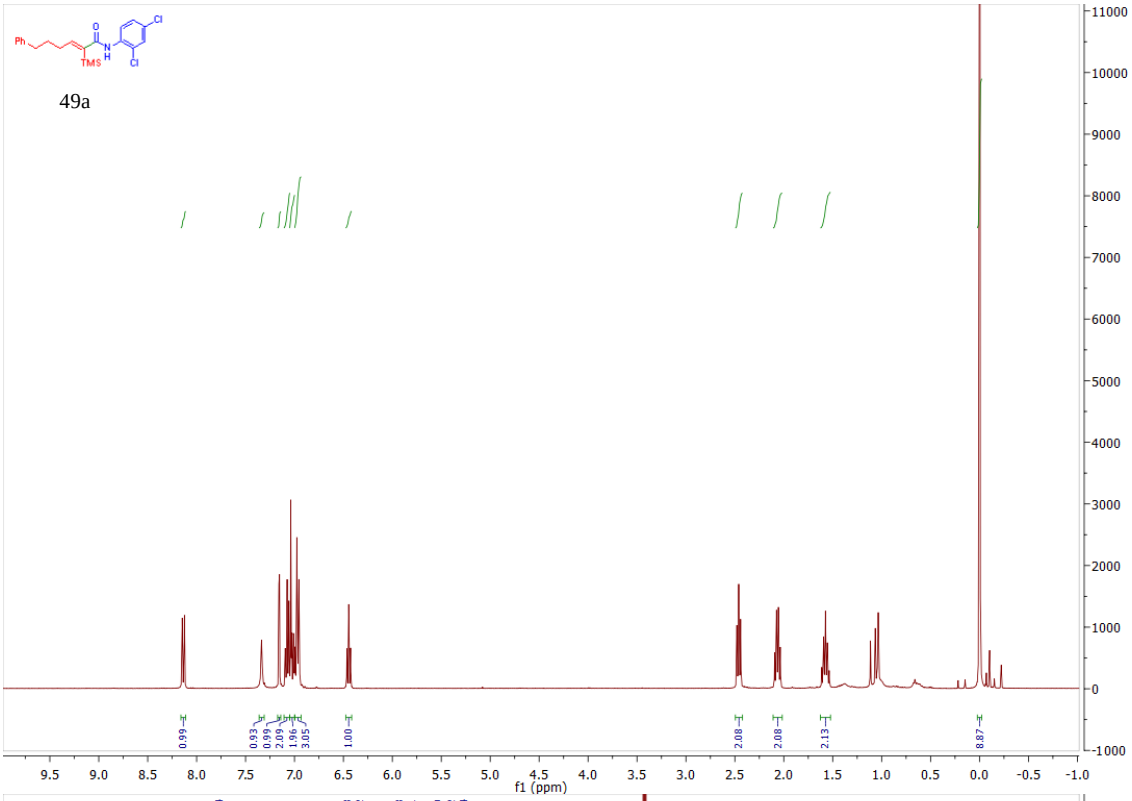

48
166.39
153.33
151.39
143.07
137.38
136.70
129.21
110.39
107.07
77.00
36.97
28.93
25.11
23.48
21.61
-0.24
f1 (ppm)

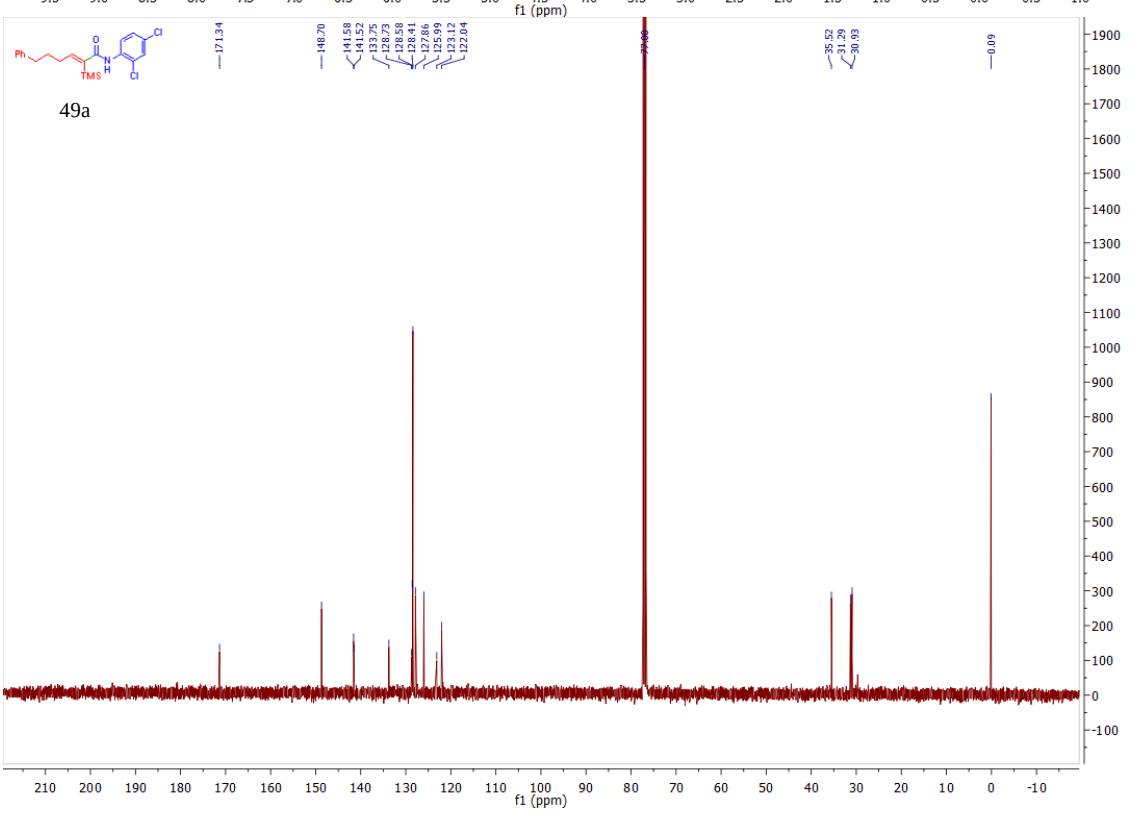

48+48a
f1 (ppm)

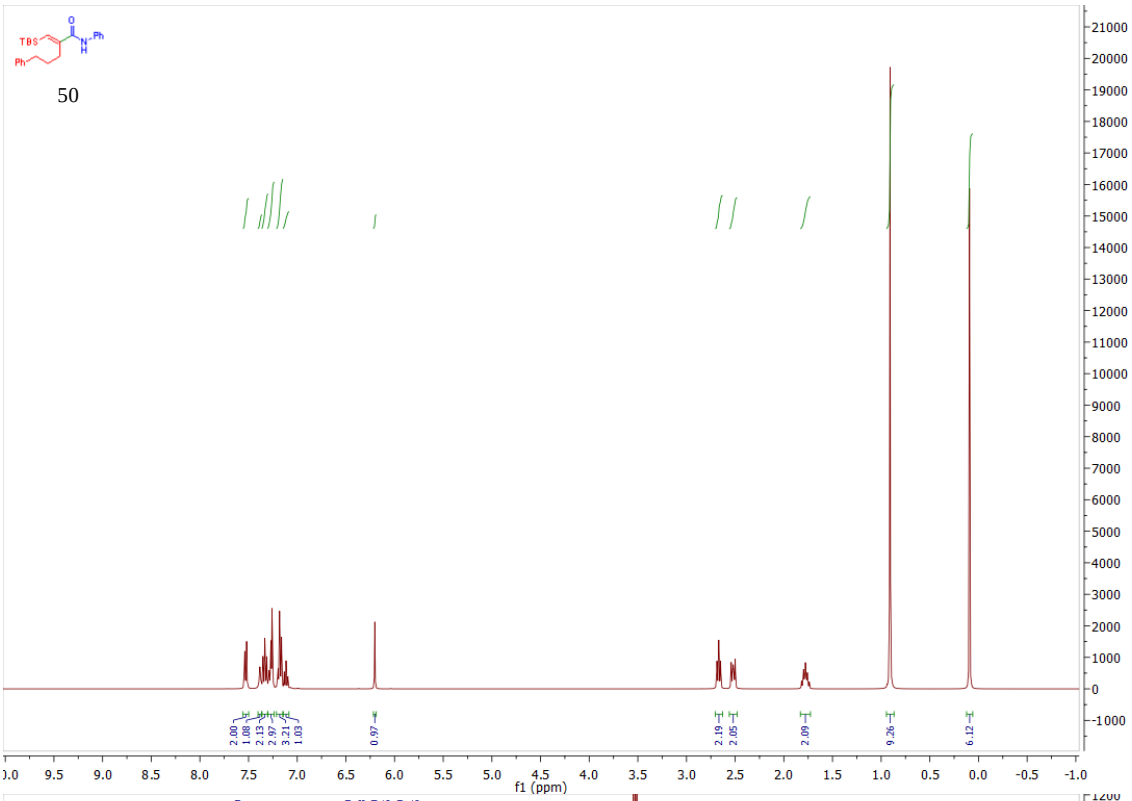

48+48a
f1 (ppm)

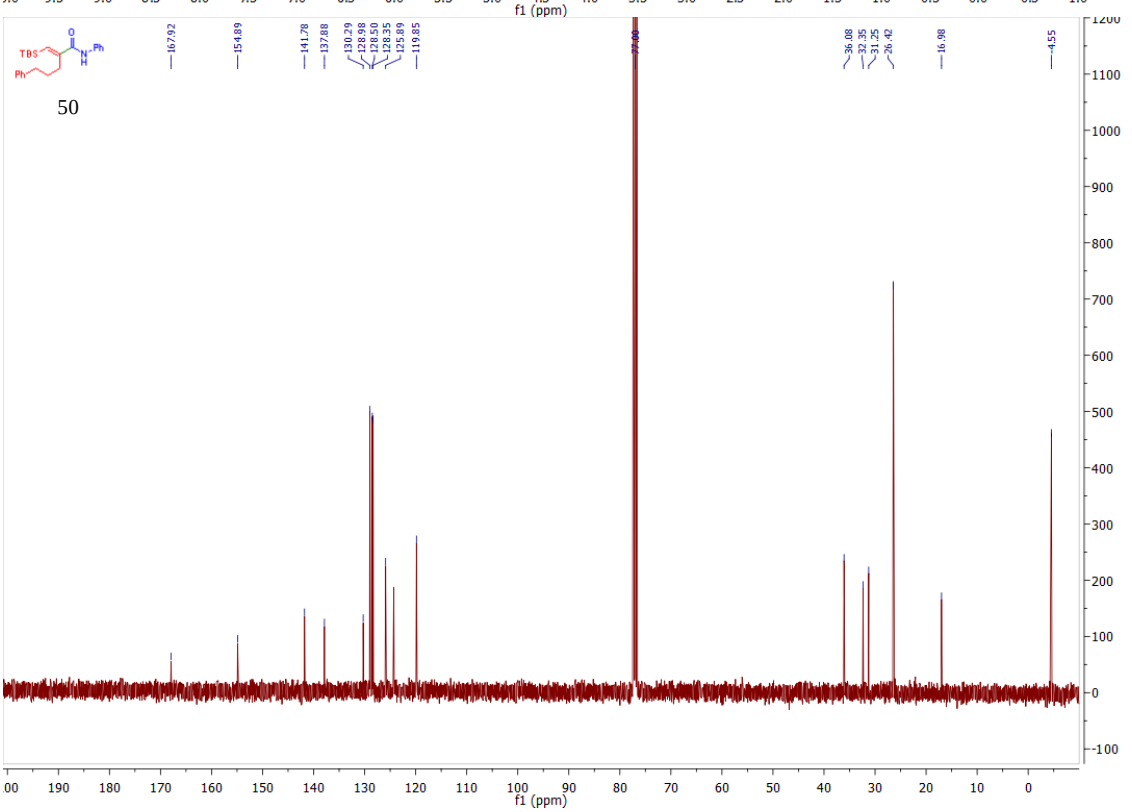

TMS
Ph
Cl
Cl
O
N
H
49
0.93
0.84
0.90
3.34
2.96
0.86
2.00
1.96
2.00
8.51
f1 (ppm)

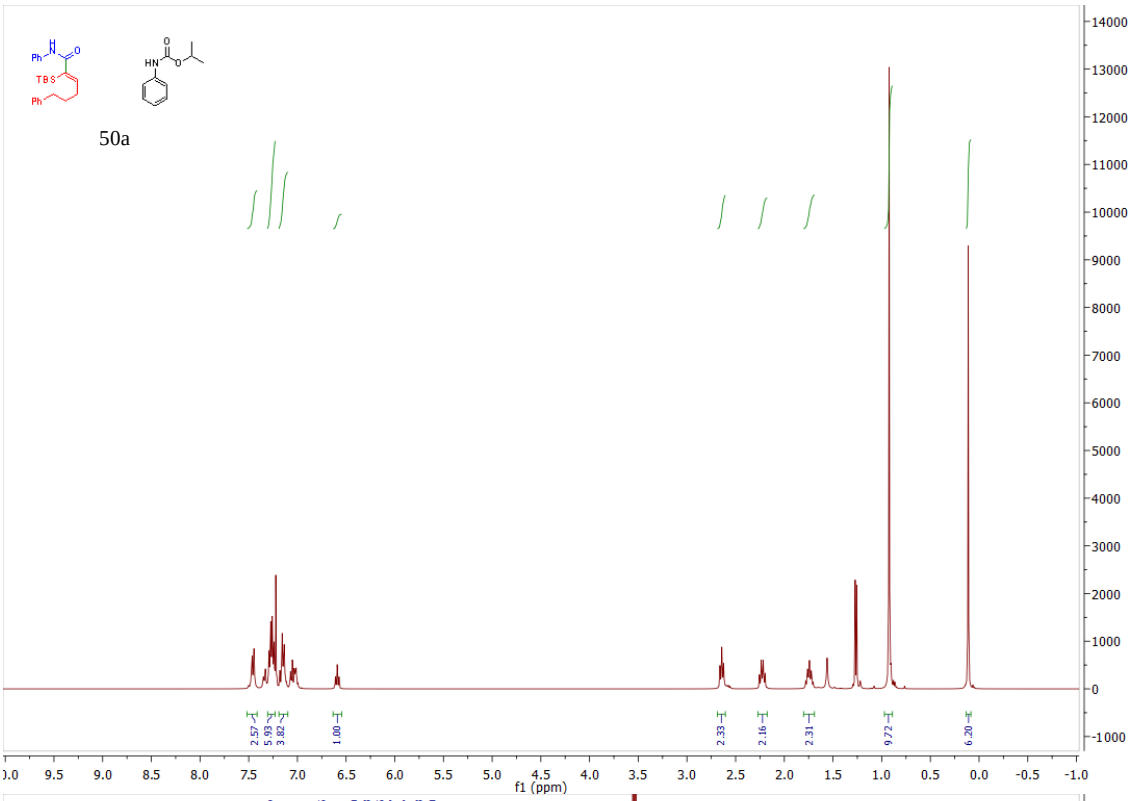

TMS
Ph
Cl
Cl
O
N
H
49
167.10
152.77
141.61
135.01
133.47
128.95
128.62
128.45
128.36
127.90
125.93
123.34
122.03
77.00
36.10
32.11
31.43
0.35
f1 (ppm)

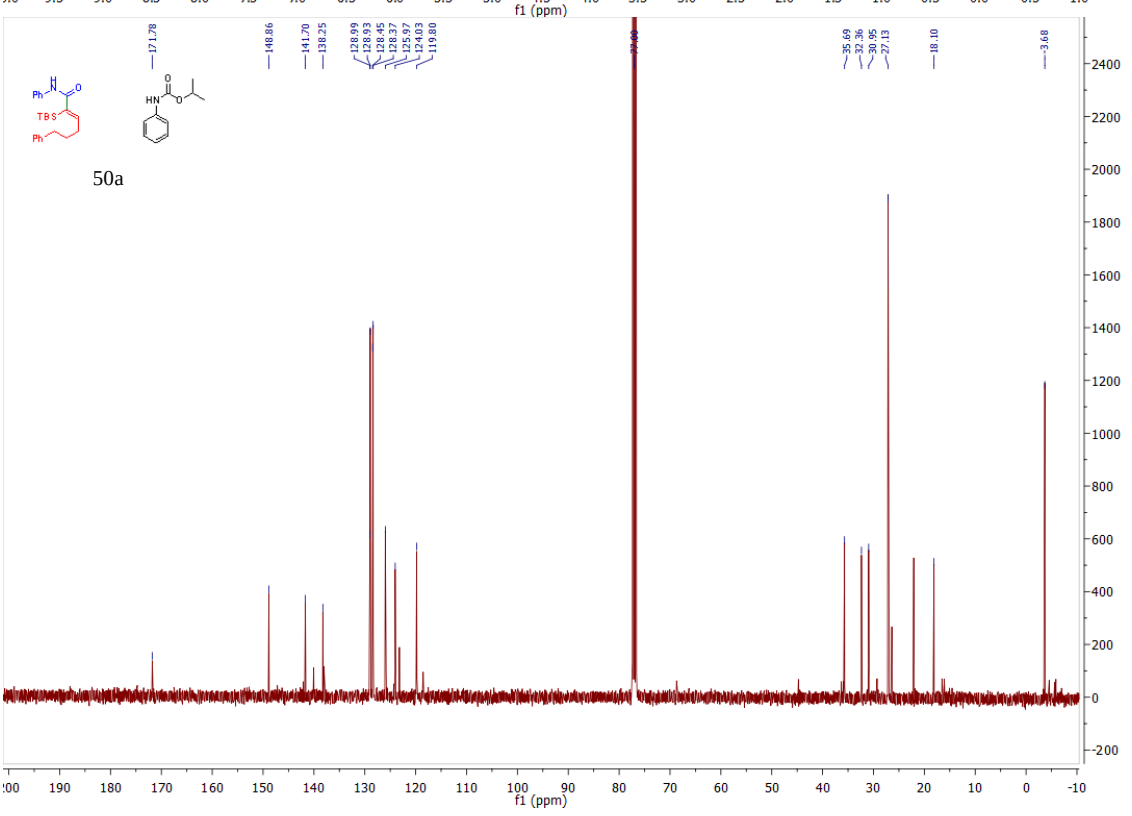

49a
f1 (ppm)

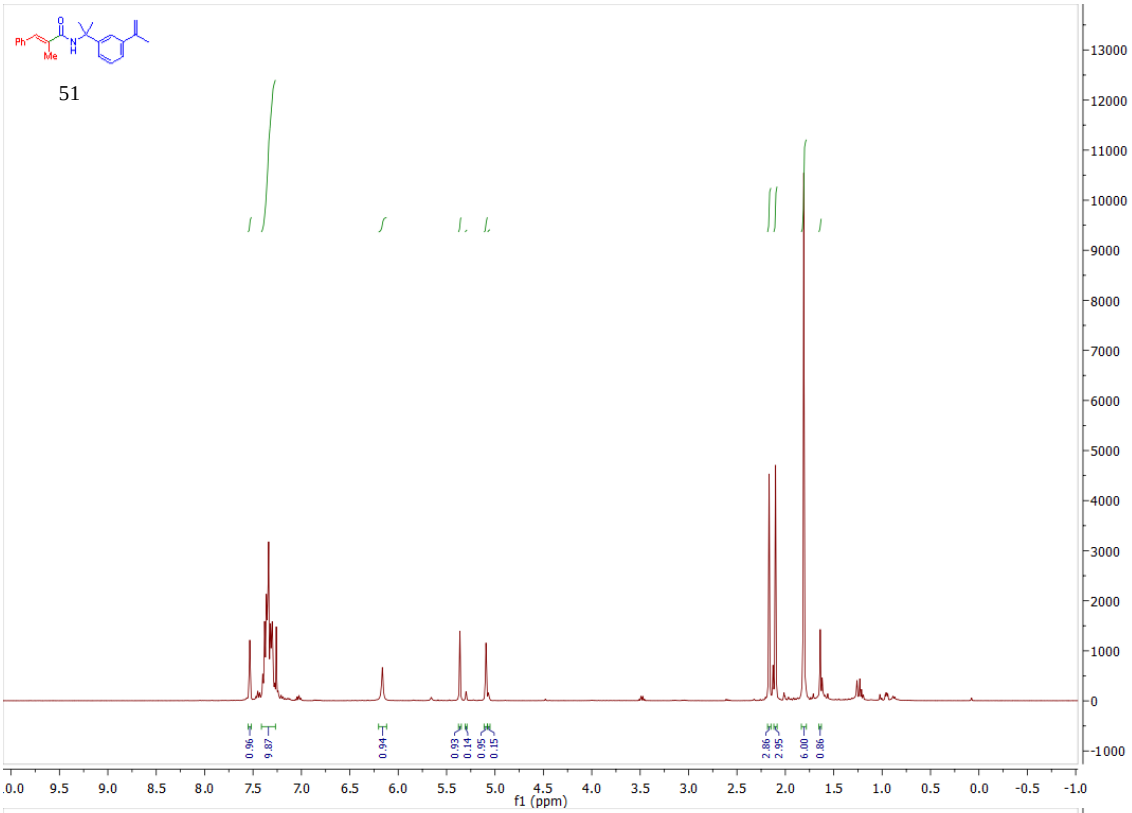

49a
171.34
148.70
141.58
141.52
138.75
138.23
128.58
128.41
127.86
125.99
123.12
122.04
77.48
35.52
31.29
30.93
0.09
f1 (ppm)

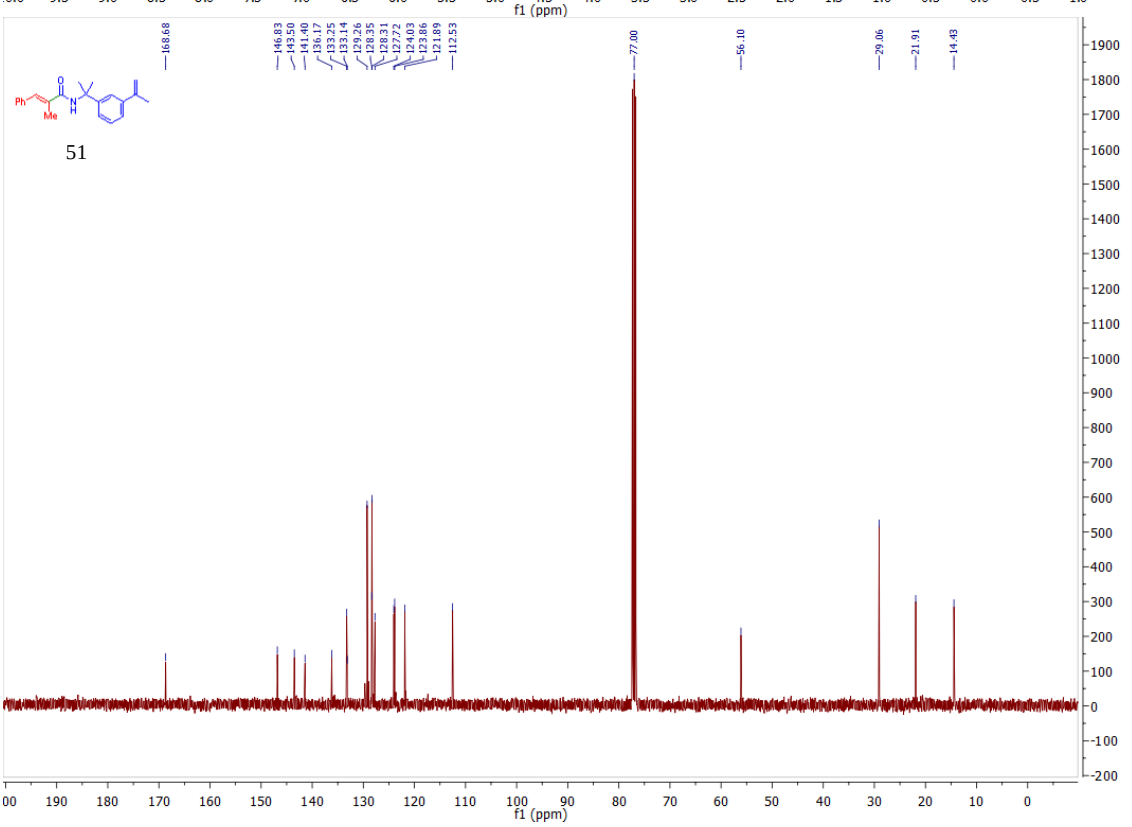

50
f1 (ppm)

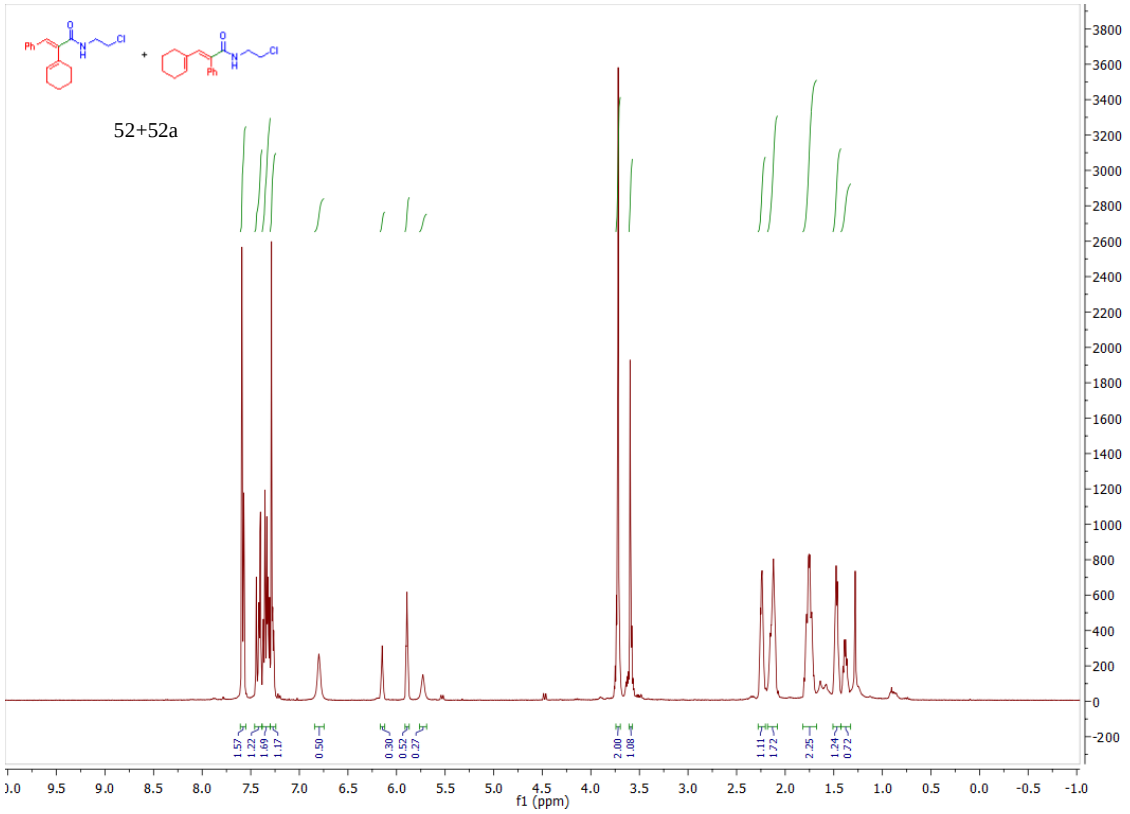

50
f1 (ppm)

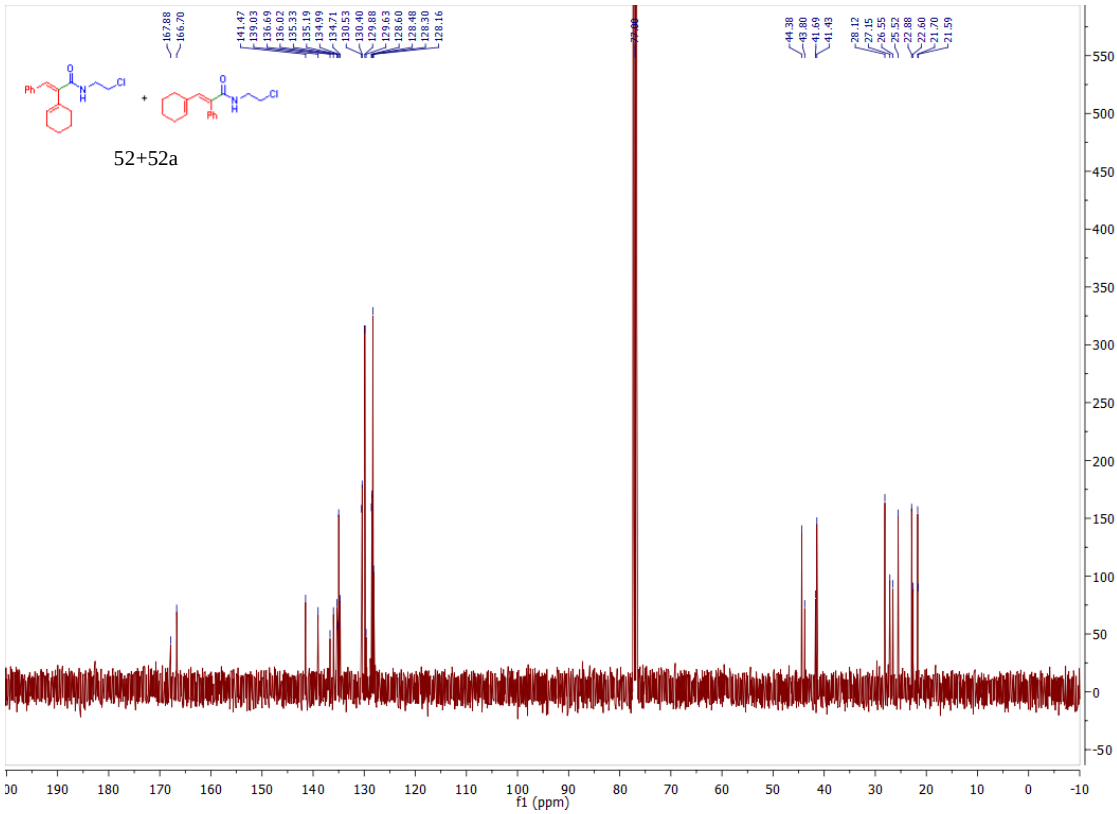

50a
2.57
5.93
3.82
1.00
2.33
2.16
2.31
9.72
6.20
f1 (ppm)

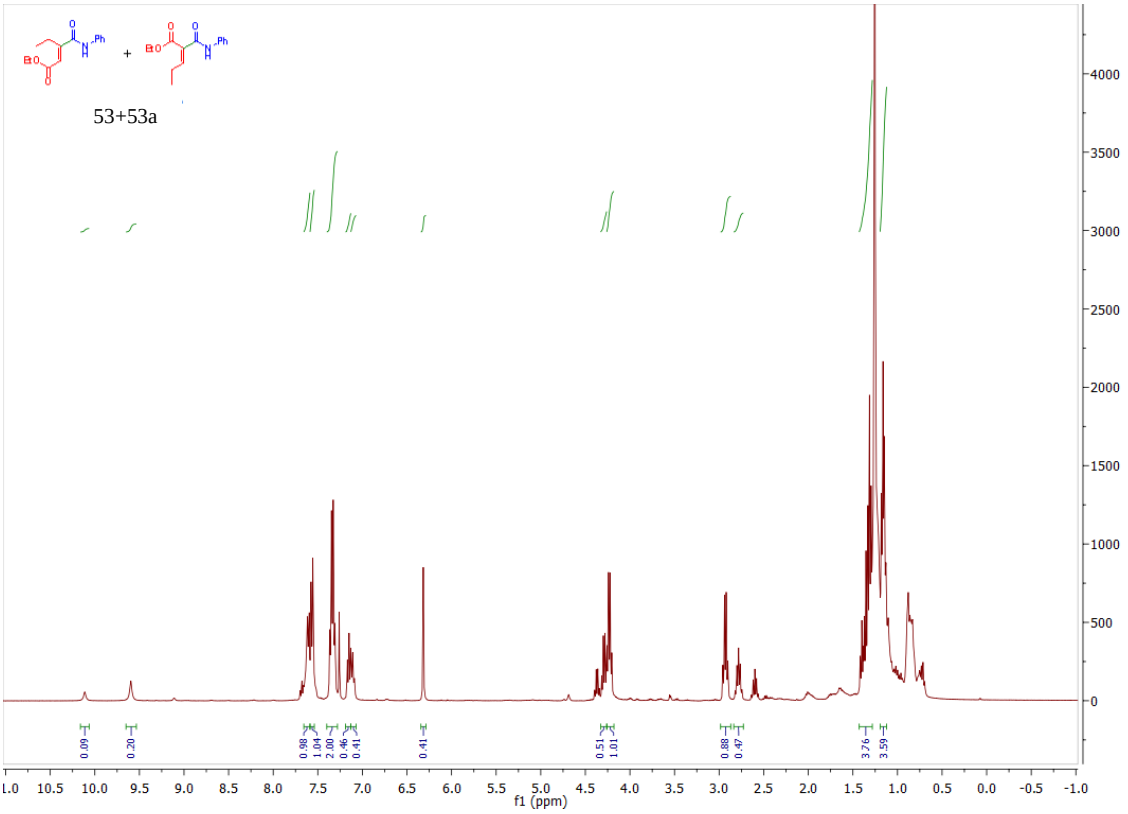

50a
171.78
148.86
141.70
138.25
128.99
128.93
128.45
128.37
125.97
124.03
119.80
77.00
35.69
32.36
30.95
27.13
18.10
-3.68
f1 (ppm)

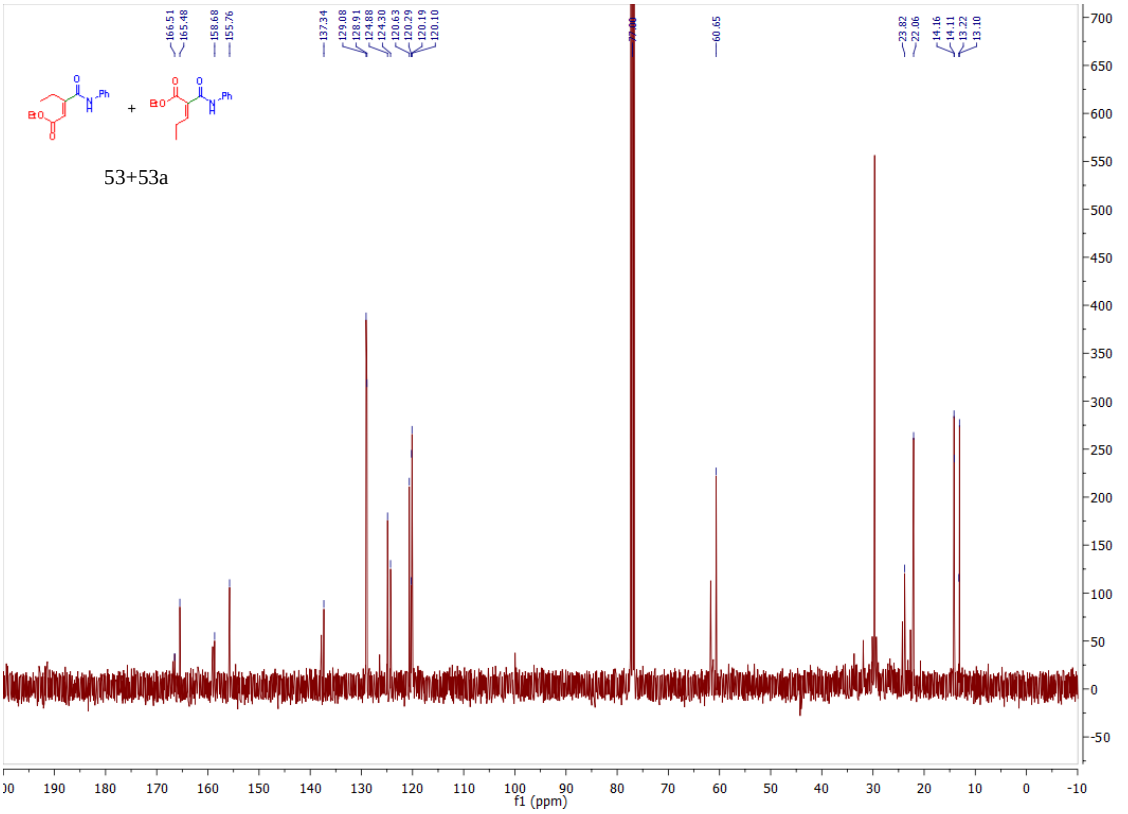

51
0.96
9.87
0.94
0.93
0.14
0.95
0.15
2.86
2.95
6.00
0.86
f1 (ppm)

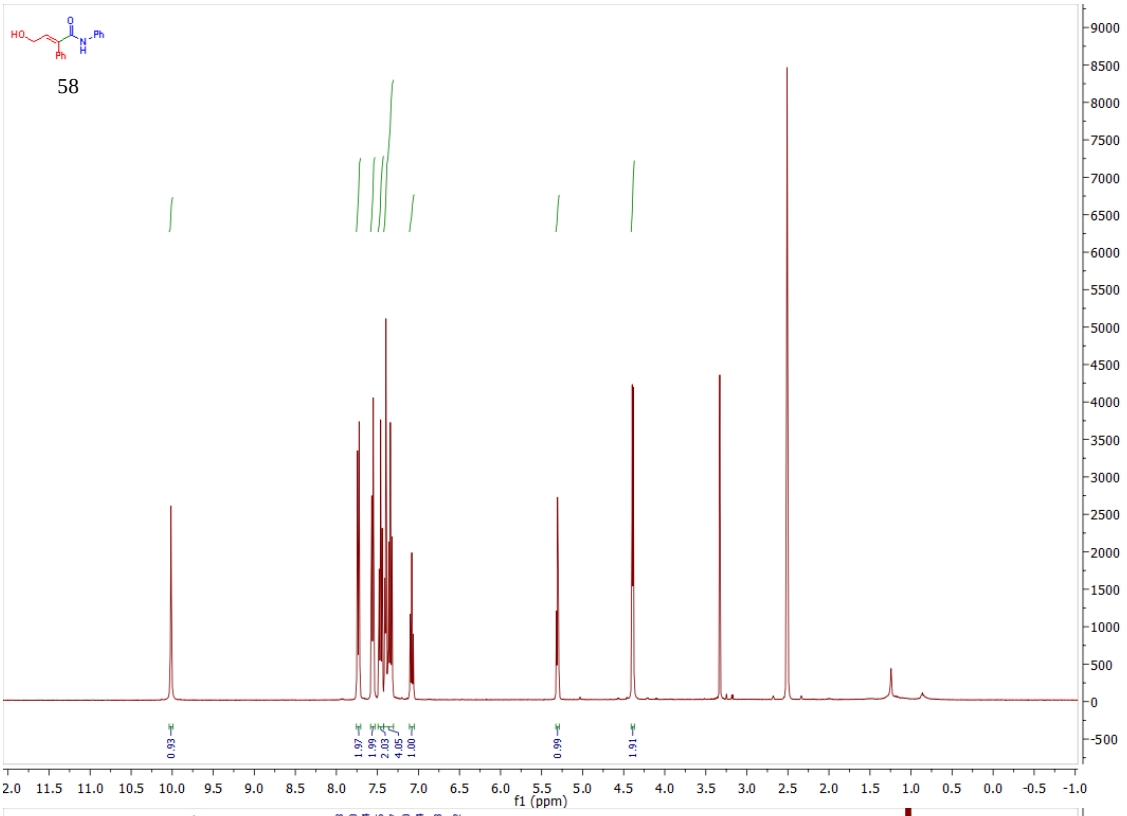

51
168.68
146.83
143.50
141.40
136.17
133.35
133.14
129.26
128.35
128.31
127.72
124.03
123.86
121.89
112.53
77.00
56.10
29.06
21.91
14.43
f1 (ppm)

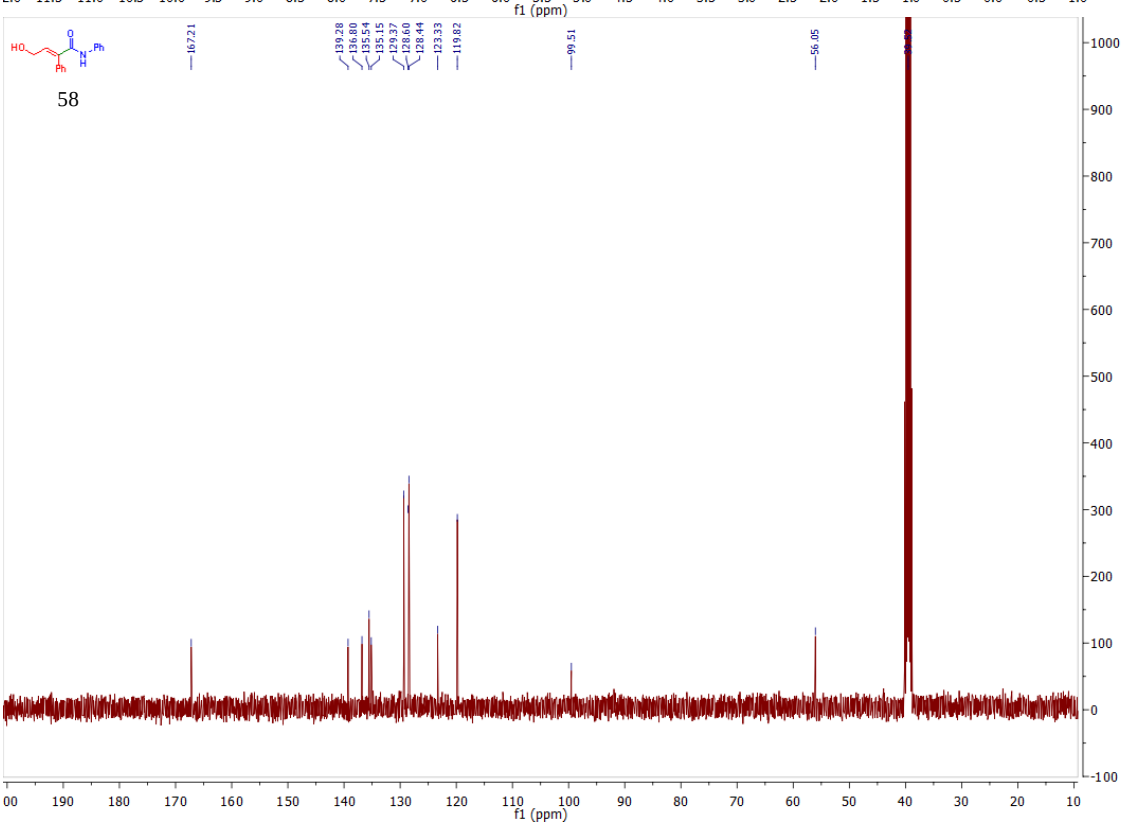

52+52a
f1 (ppm)

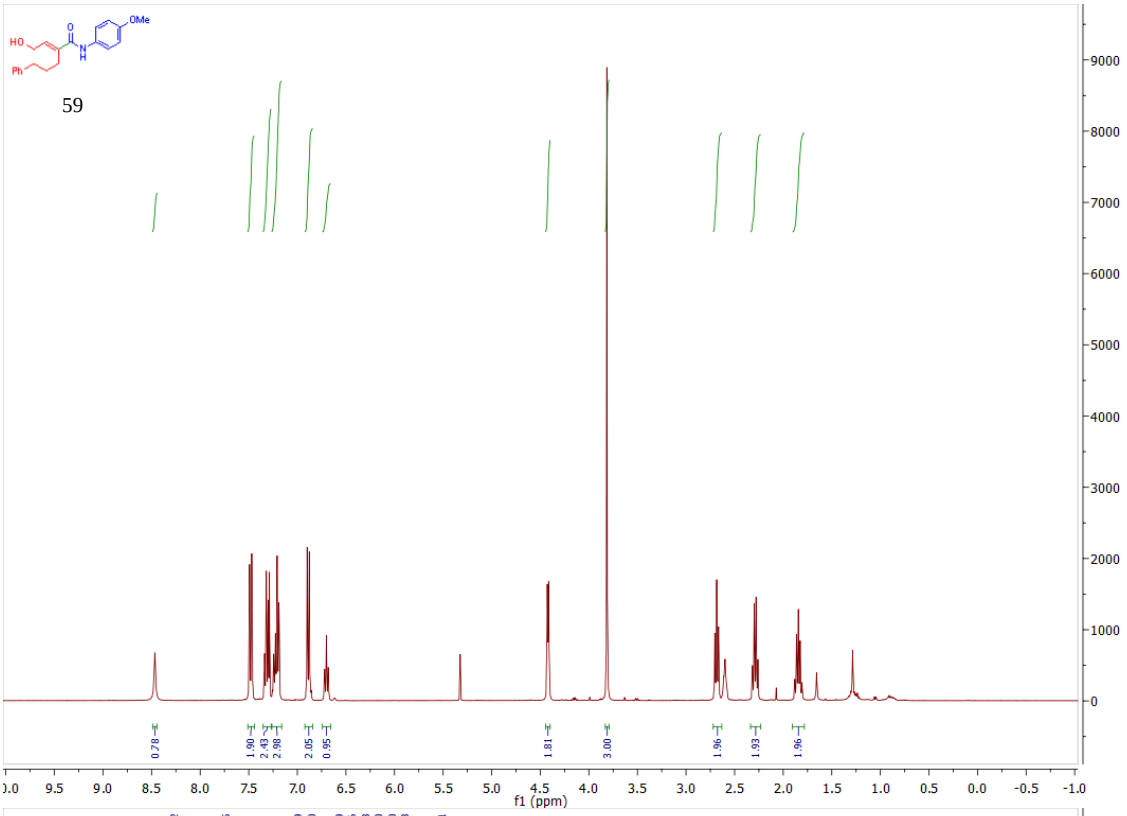

52+52a
f1 (ppm)

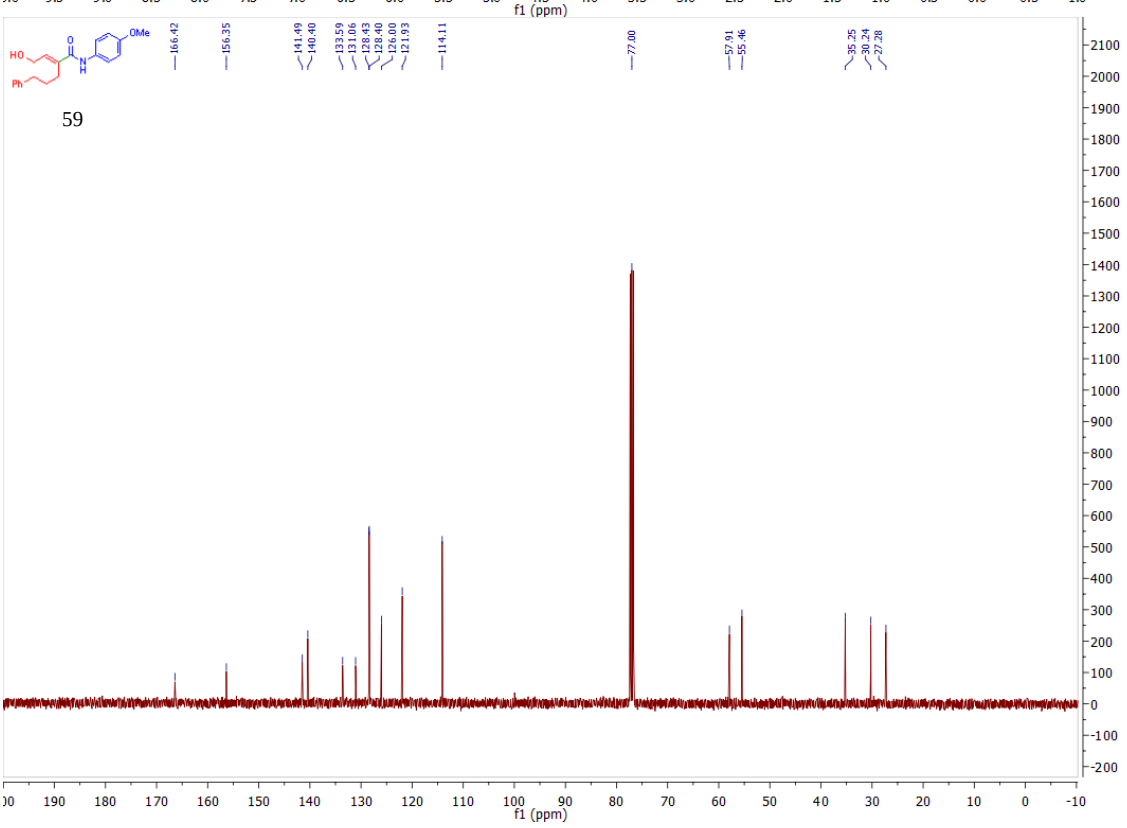

53+53a
f1 (ppm)

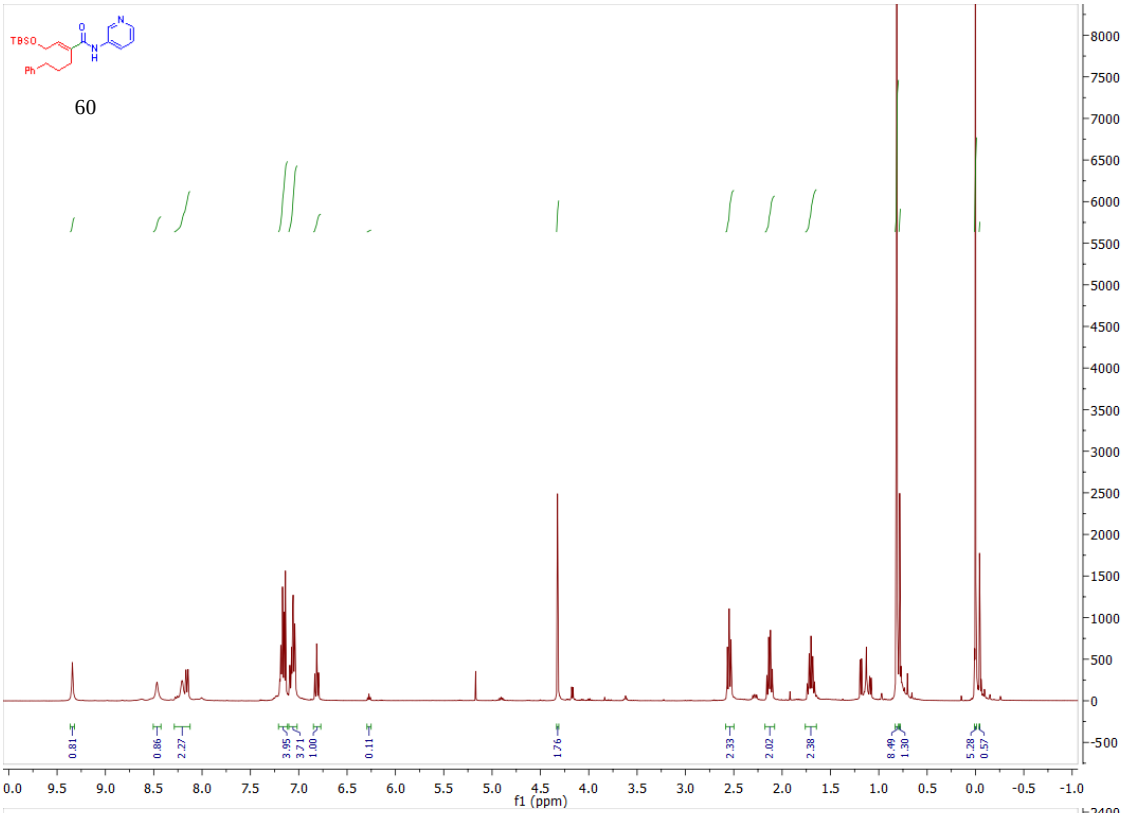

53+53a
f1 (ppm)

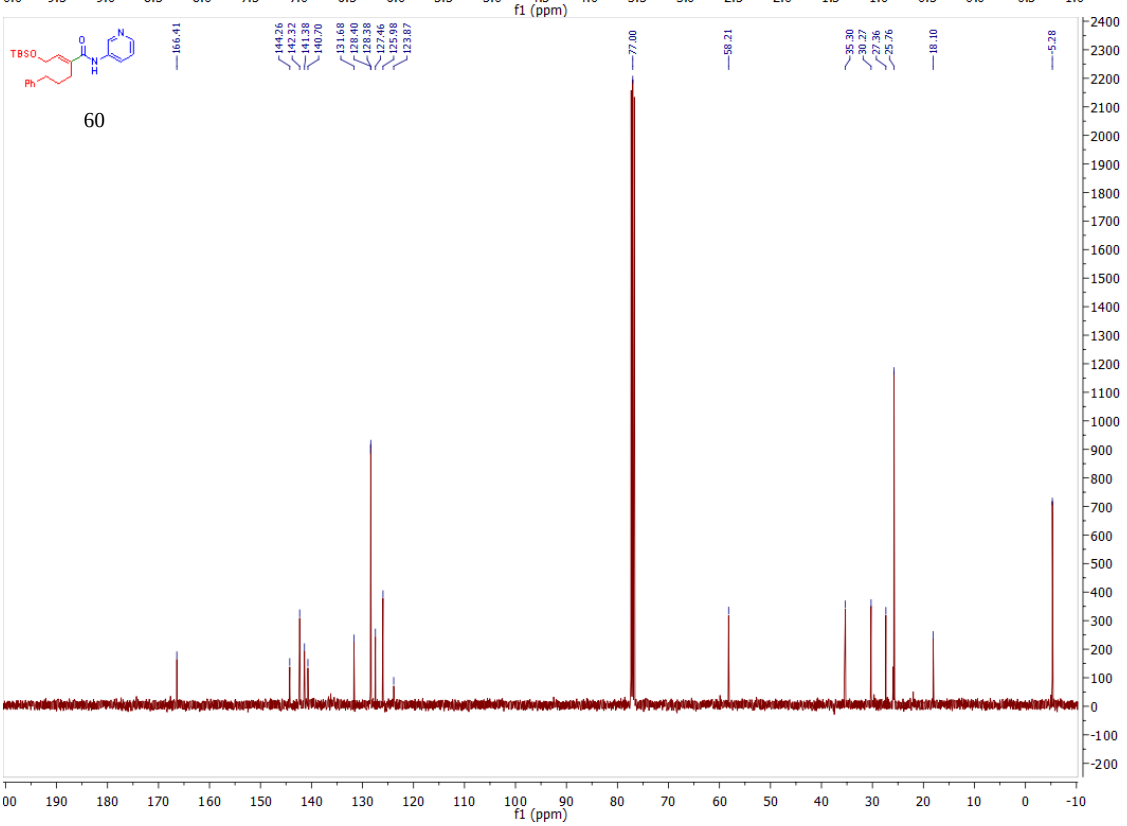

58
0.93
1.97
1.99
2.03
4.05
1.00
0.99
1.91
f1 (ppm)

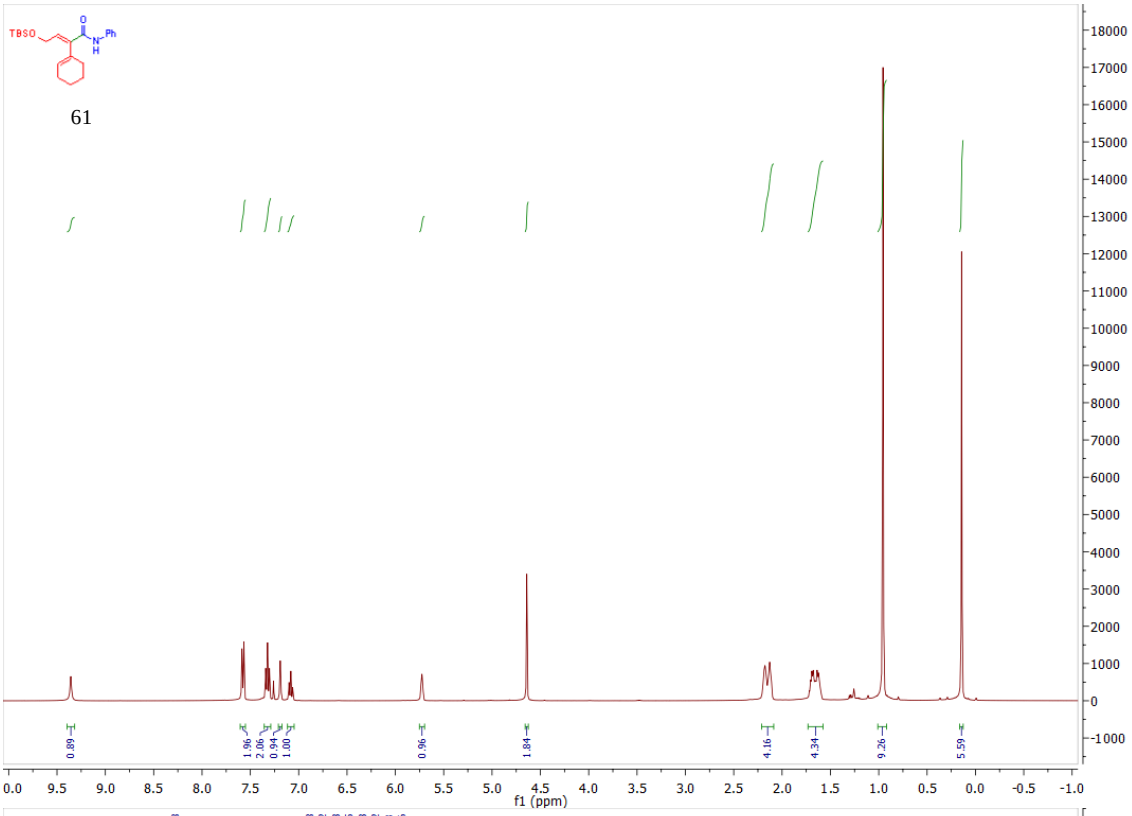

58
16.72.1
139.28
136.80
135.54
135.15
129.37
128.60
128.44
123.33
119.82
99.51
56.05
f1 (ppm)

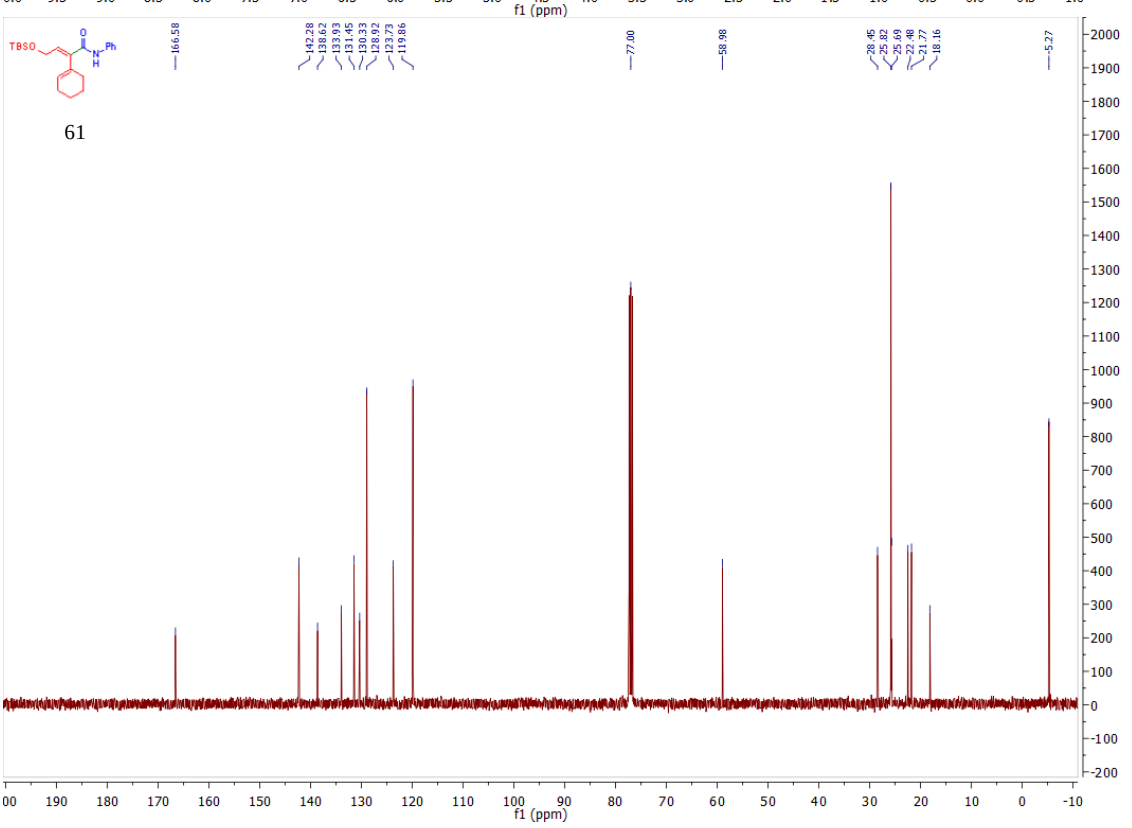

HO
Ph
O
N
H
OMe
59
0.78
1.90
2.49
2.98
2.05
0.95
1.81
3.00
1.96
1.93
1.96
f1 (ppm)

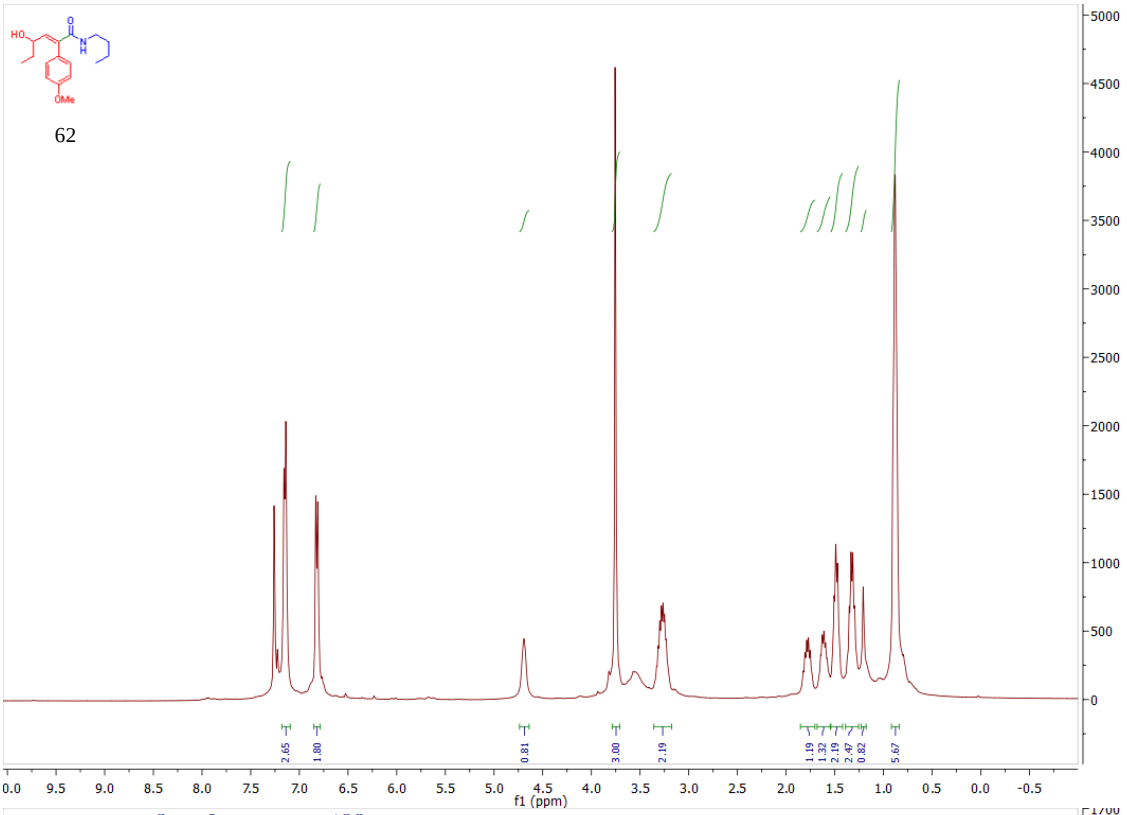

HO
Ph
O
N
H
OMe
59
166.42
156.35
141.49
140.40
133.59
131.06
128.43
128.40
126.00
121.93
114.11
77.00
57.91
55.46
35.25
30.24
27.28
f1 (ppm)

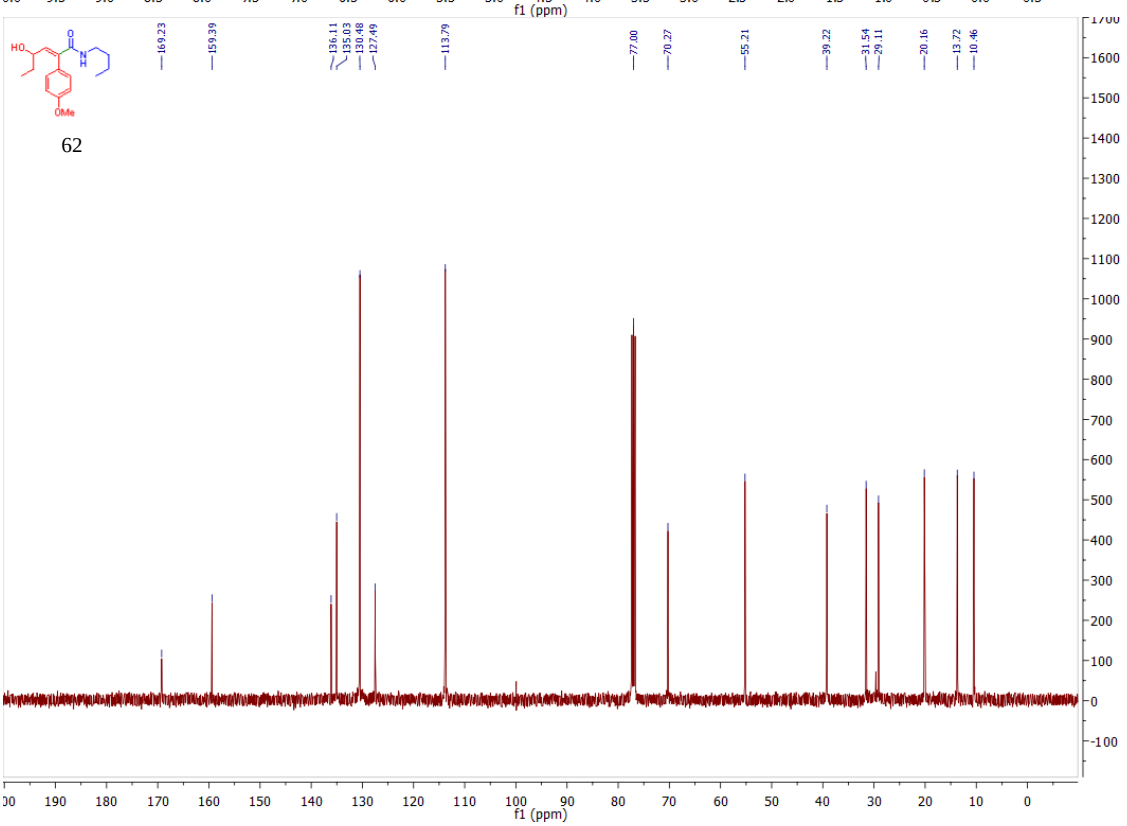

TBSO
Ph
O
N
H
N
60
0.81
0.86
2.27
3.95
3.71
1.00
0.11
1.76
2.33
2.02
2.38
8.49
1.30
5.28
0.57
f1 (ppm)

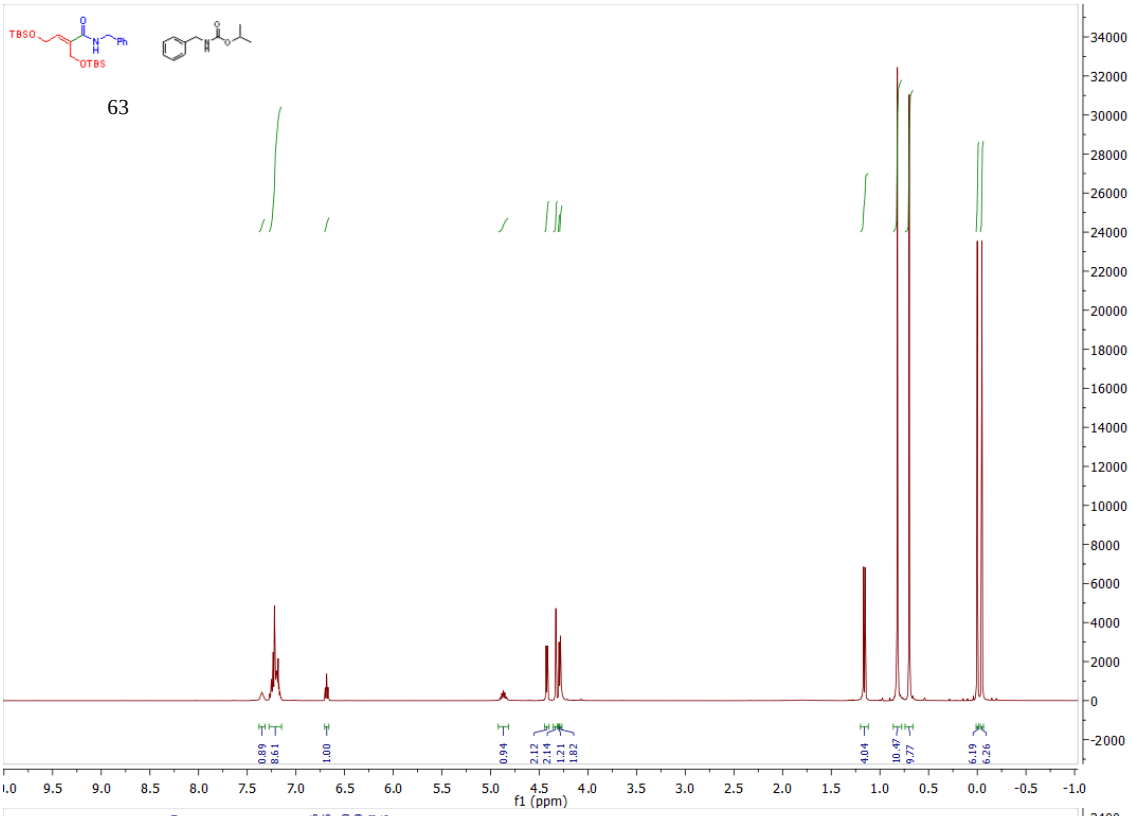

TBSO
Ph
O
N
H
N
60
166.41
144.26
142.32
141.38
140.70
131.68
128.40
128.38
127.46
125.98
123.87
77.00
58.21
35.30
30.27
29.36
25.76
18.10
-5.28
f1 (ppm)

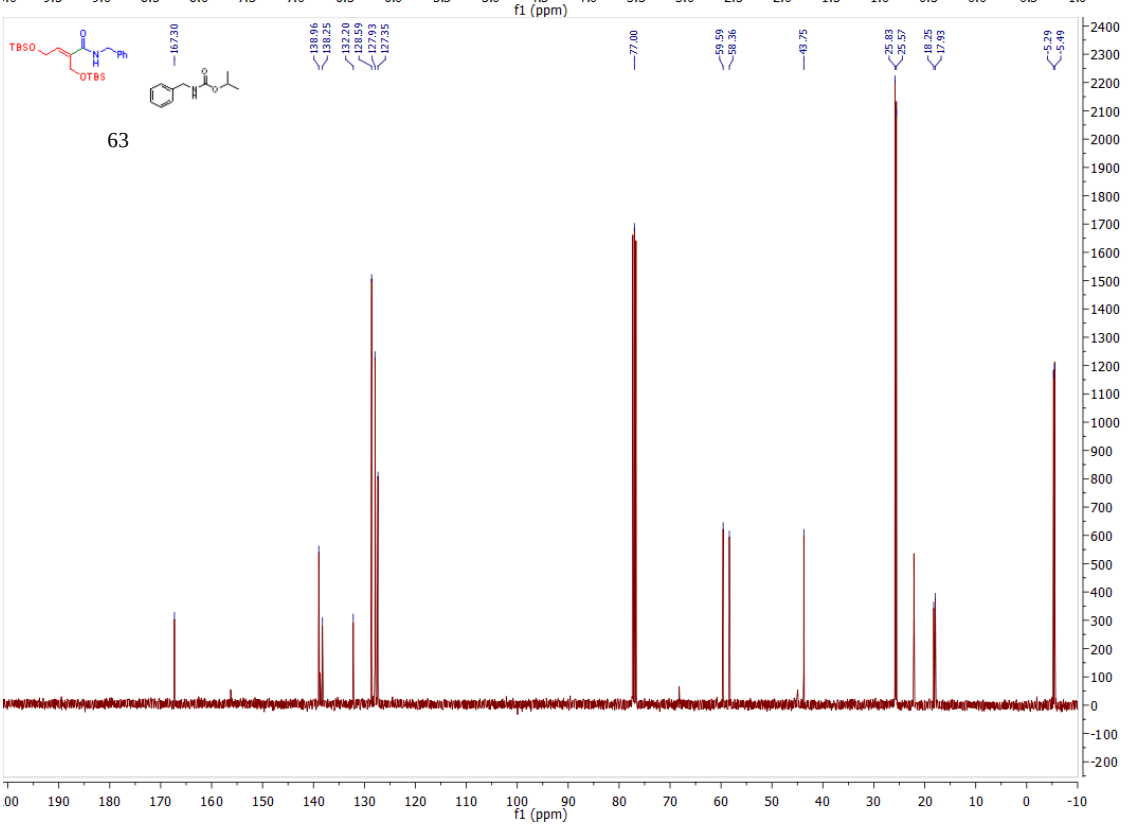

TBSO
O
N
H
Ph
61
0.89
1.96
2.06
0.94
1.00
0.96
1.84
4.16
4.34
9.26
5.59
f1 (ppm)

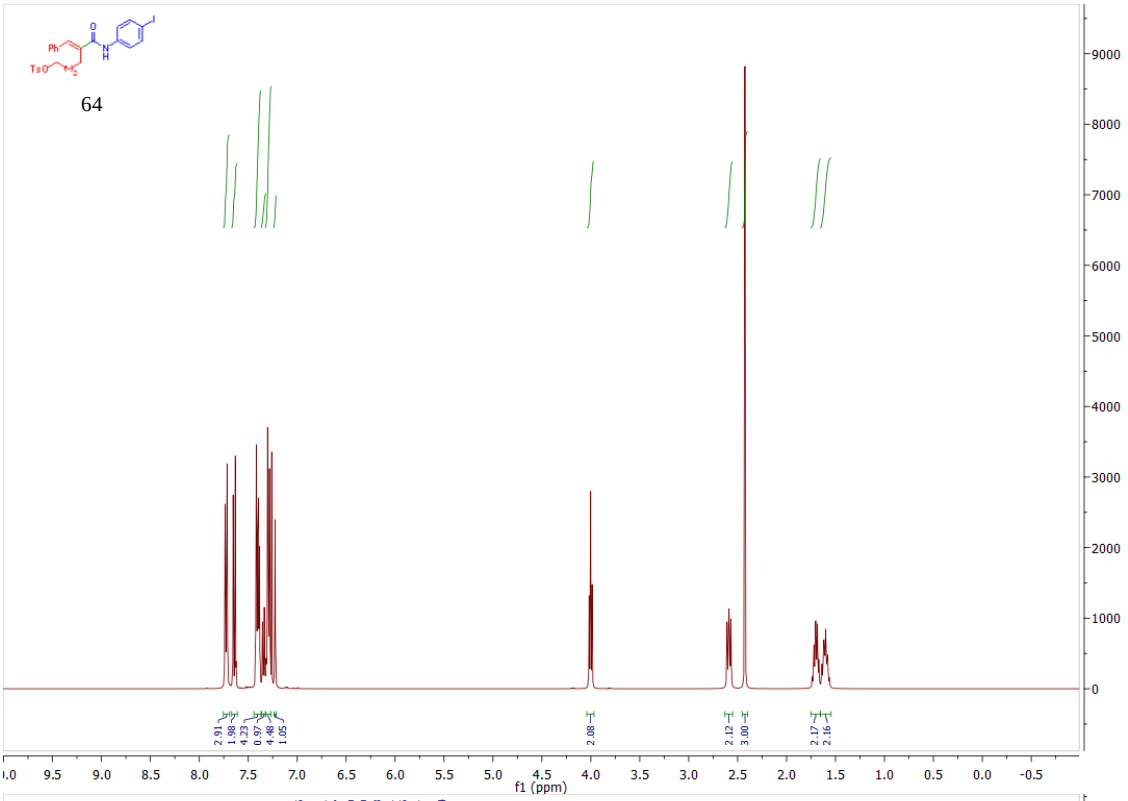

TBSO
O
N
H
Ph
61
166.58
142.28
138.62
133.93
131.45
130.33
128.92
123.73
119.86
77.00
58.98
28.45
25.82
25.69
22.48
21.77
18.16
-5.27
f1 (ppm)

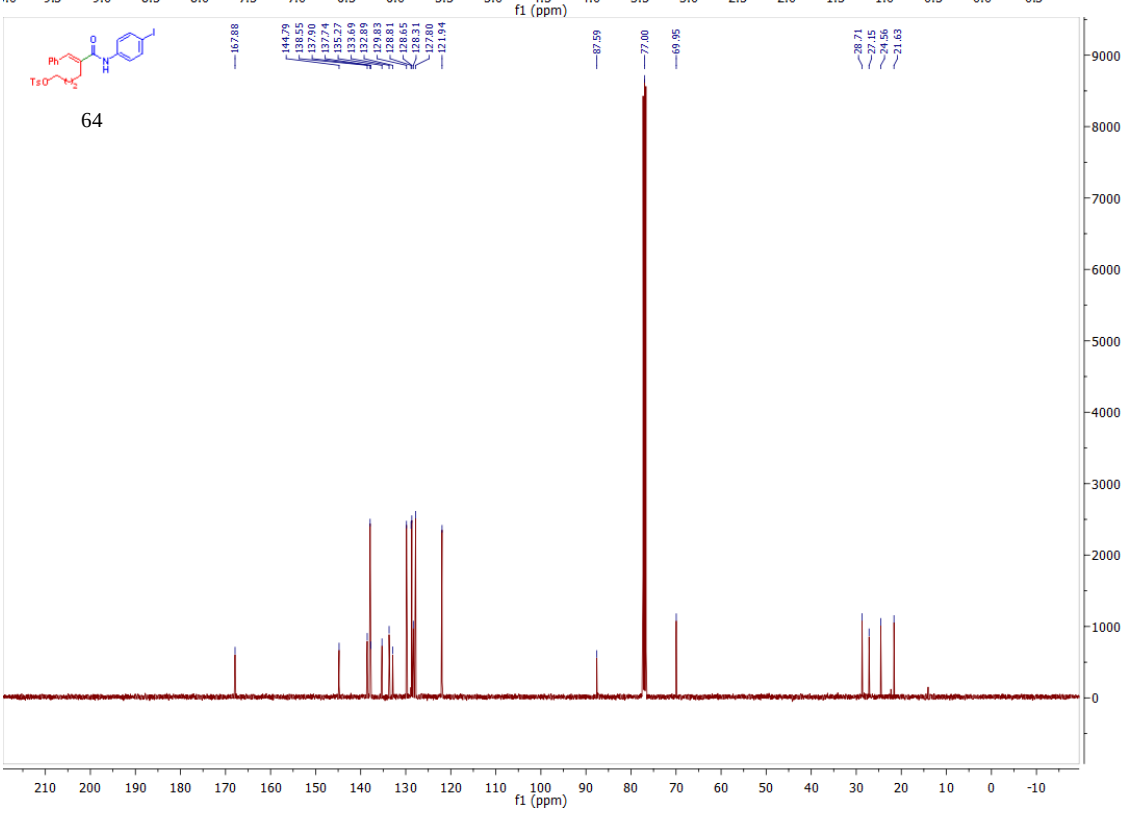

HO
O
N
OMe
62
2.65
1.80
0.81
3.00
2.19
1.19
1.32
2.19
2.47
0.82
5.67
f1 (ppm)

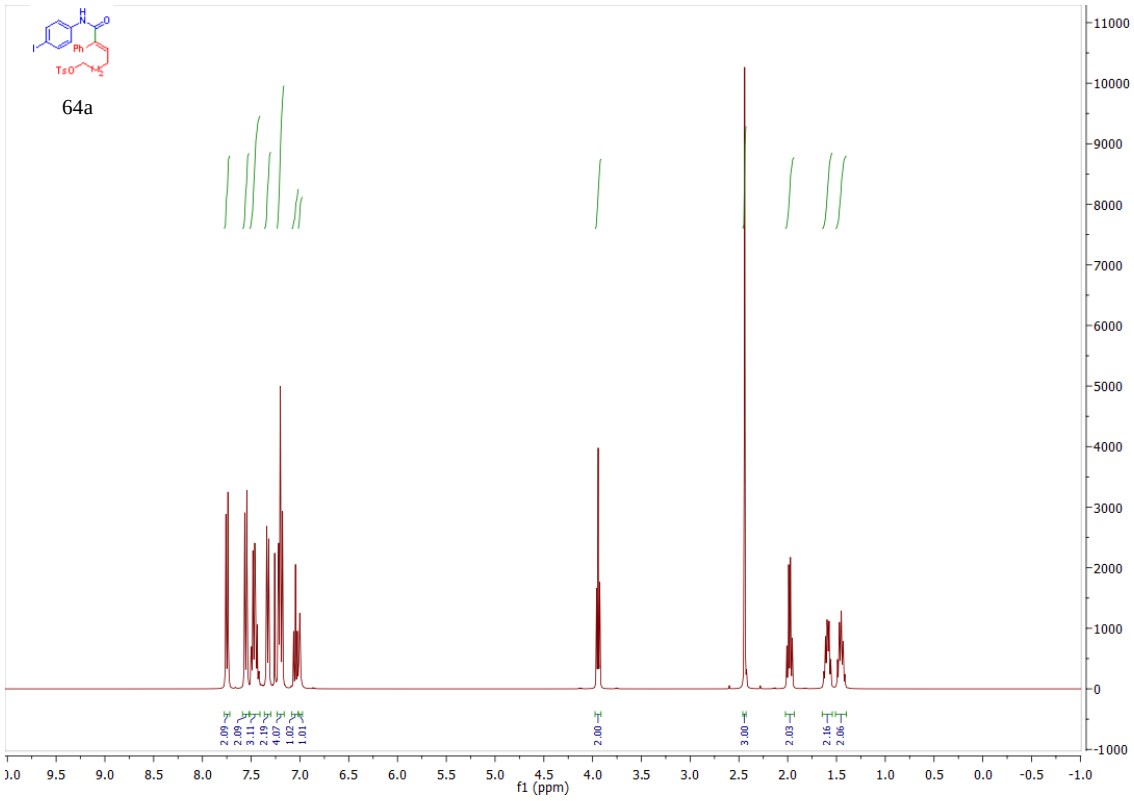

HO
O
N
OMe
62
169.23
159.39
136.11
135.03
130.48
127.49
113.79
77.00
70.27
55.21
39.22
31.54
29.11
20.16
13.72
10.46
f1 (ppm)

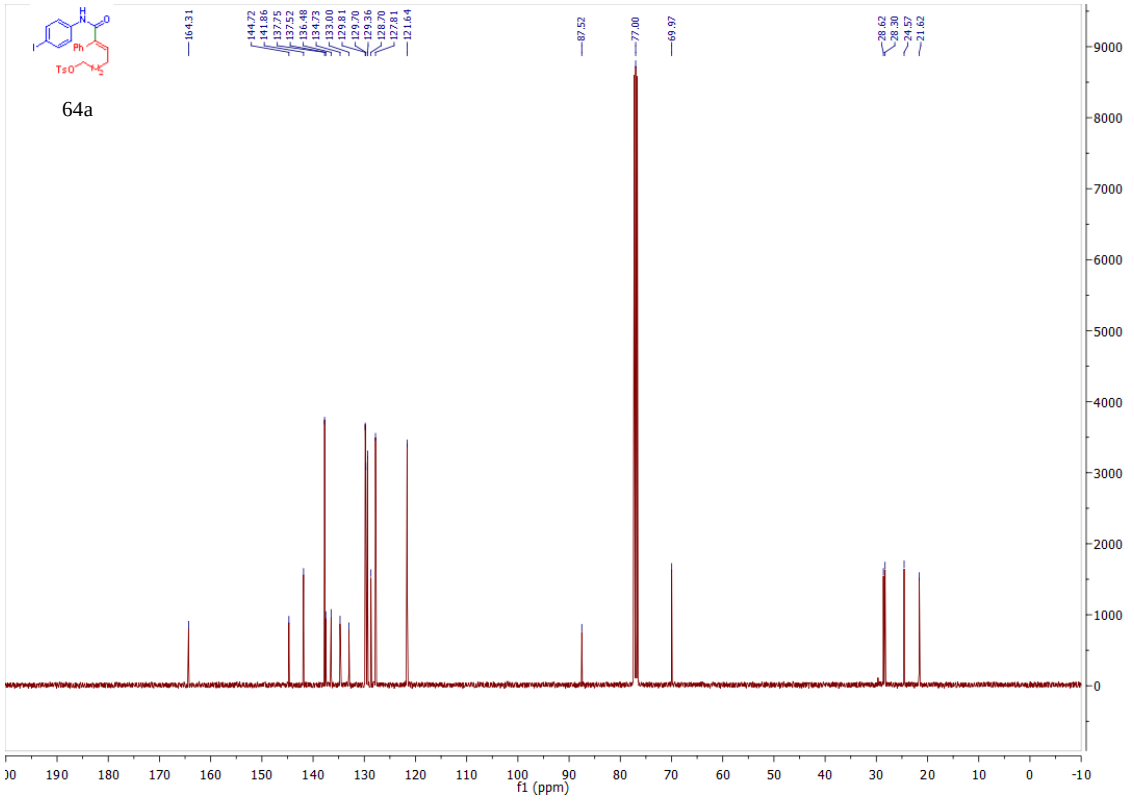

TBSO
OTBS
Ph
63
0.89
8.61
1.00
0.94
2.12
2.14
1.21
1.82
4.04
10.47
9.77
6.19
6.26
f1 (ppm)

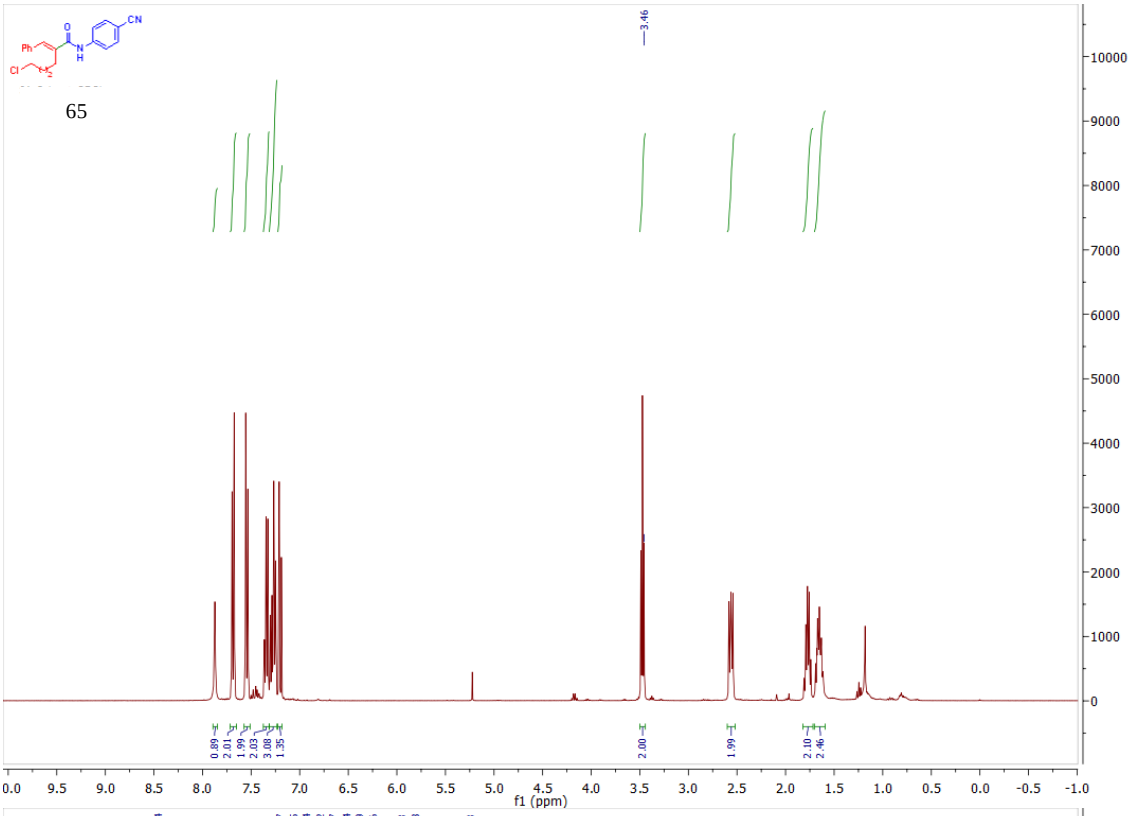

TBSO
OTBS
63
167.30
138.96
138.25
133.20
129.59
127.93
127.35
77.00
59.59
58.36
43.75
25.83
25.57
18.25
17.93
-5.29
-5.49
f1 (ppm)

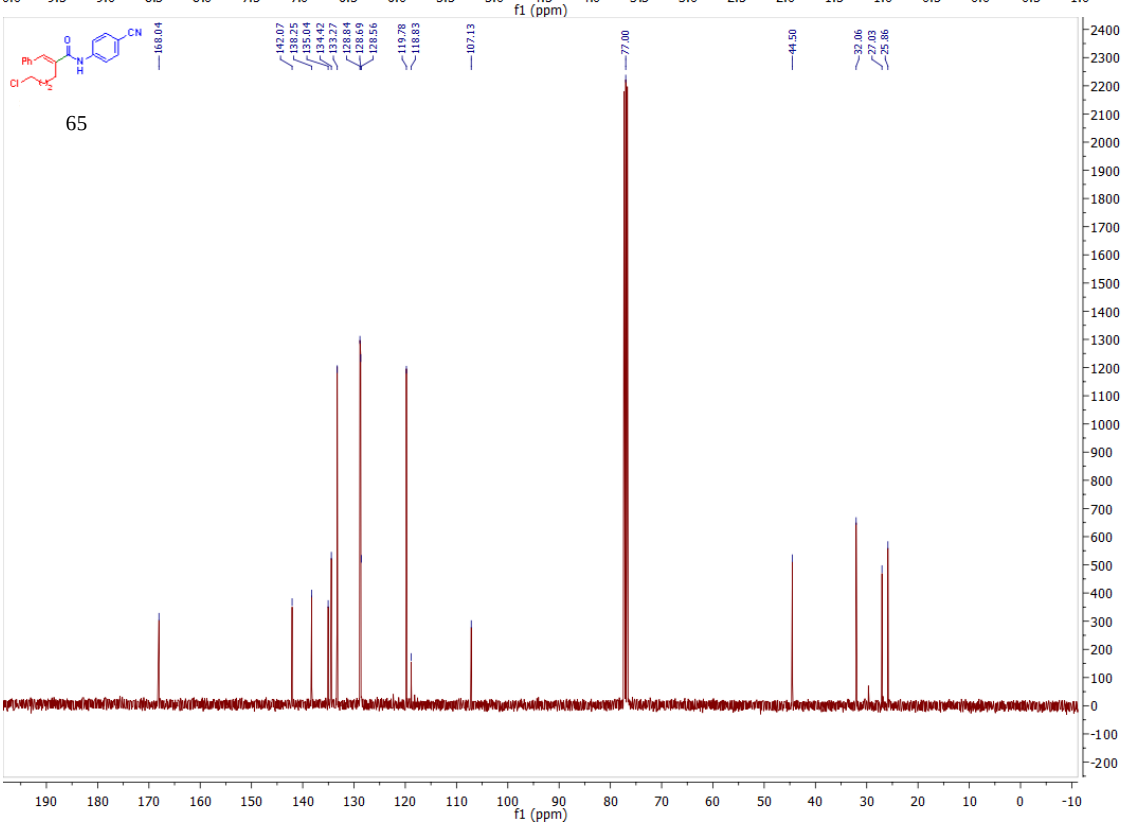

64
2.91
1.98
4.23
0.97
4.48
1.05
2.08
2.12
3.00
2.17
2.16
f1 (ppm)

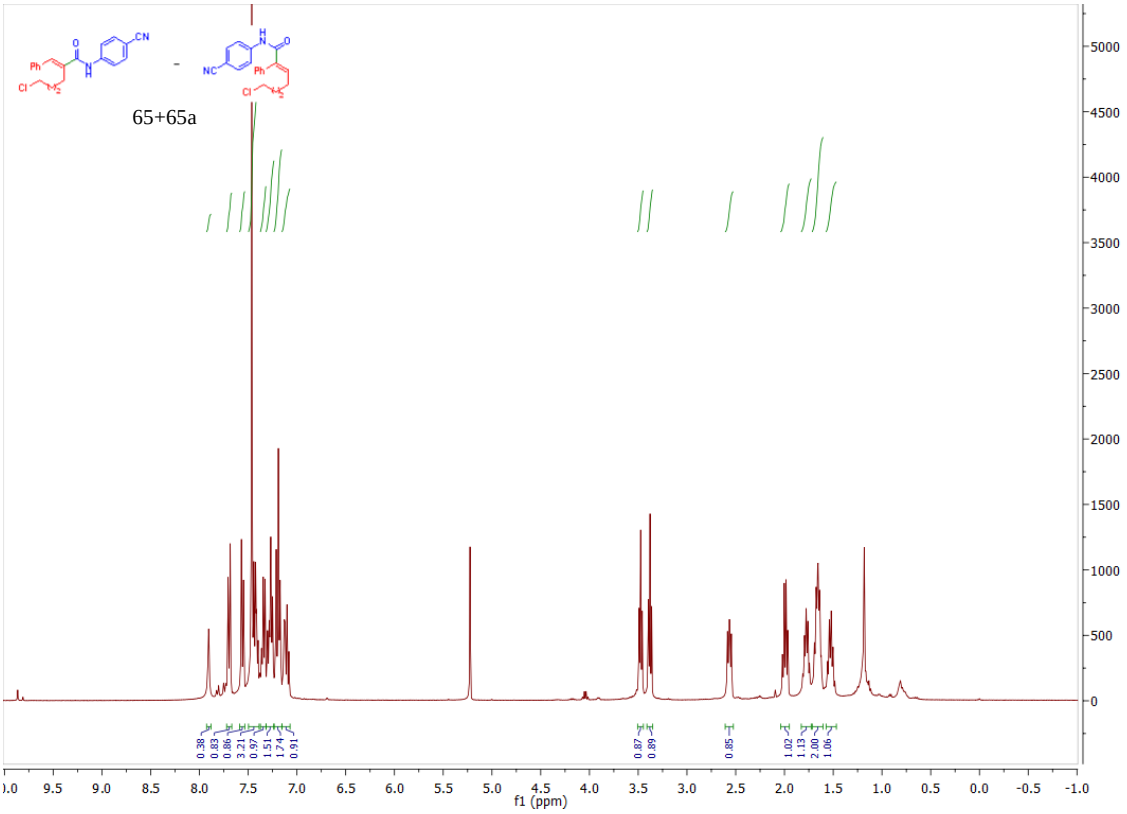

64
16.88
144.79
138.55
137.90
137.74
135.27
133.69
132.89
129.83
128.81
128.65
128.31
127.80
121.94
87.59
77.00
69.95
28.71
27.15
24.56
21.63
f1 (ppm)

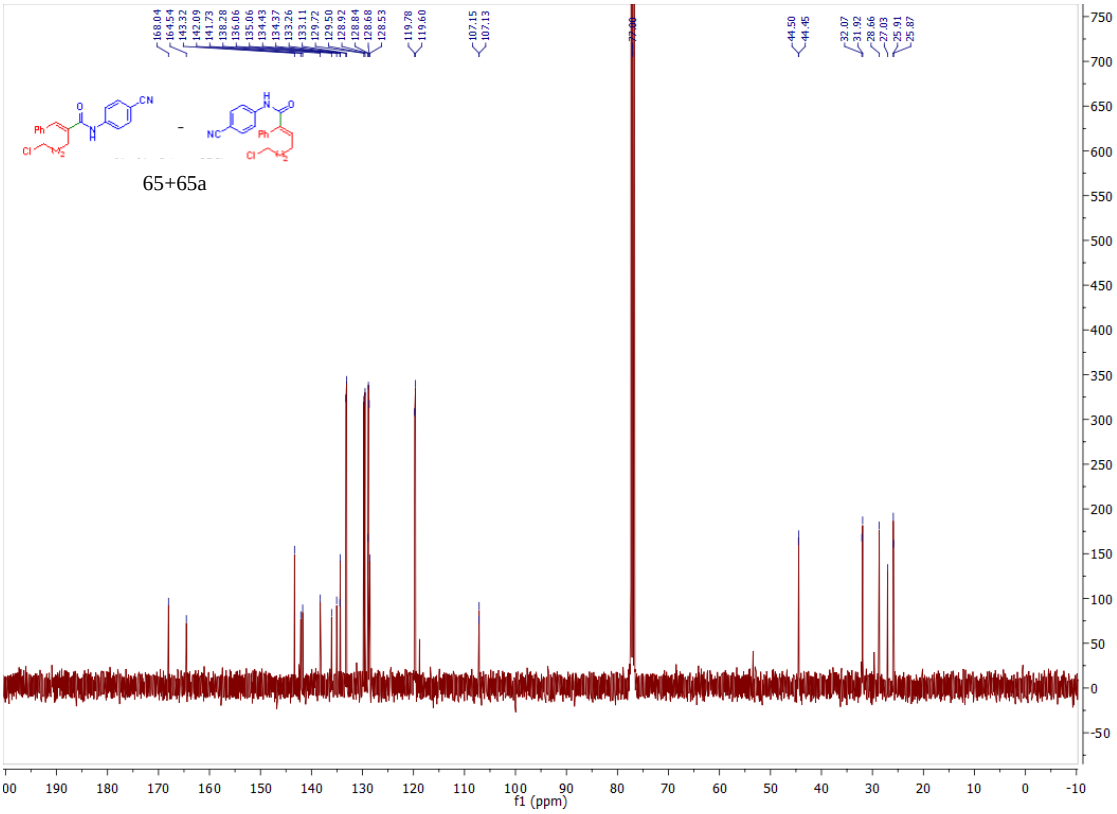

64a
2.09
2.09
3.11
2.19
4.00
1.02
1.01
2.00
3.00
2.03
2.16
2.06
f1 (ppm)

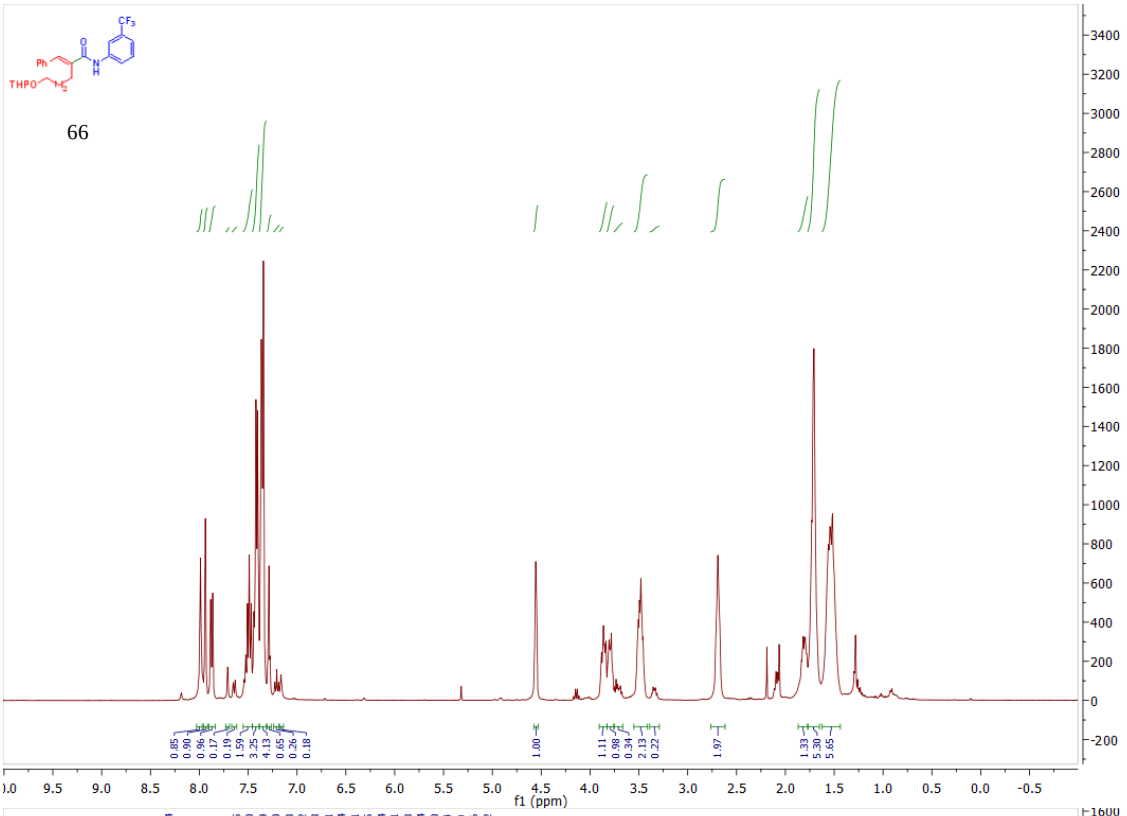

64a
164.31
144.72
141.86
137.75
137.52
136.48
134.73
133.00
129.81
129.70
129.36
128.70
127.81
121.64
87.52
77.00
69.97
28.62
28.30
24.57
21.62
f1 (ppm)

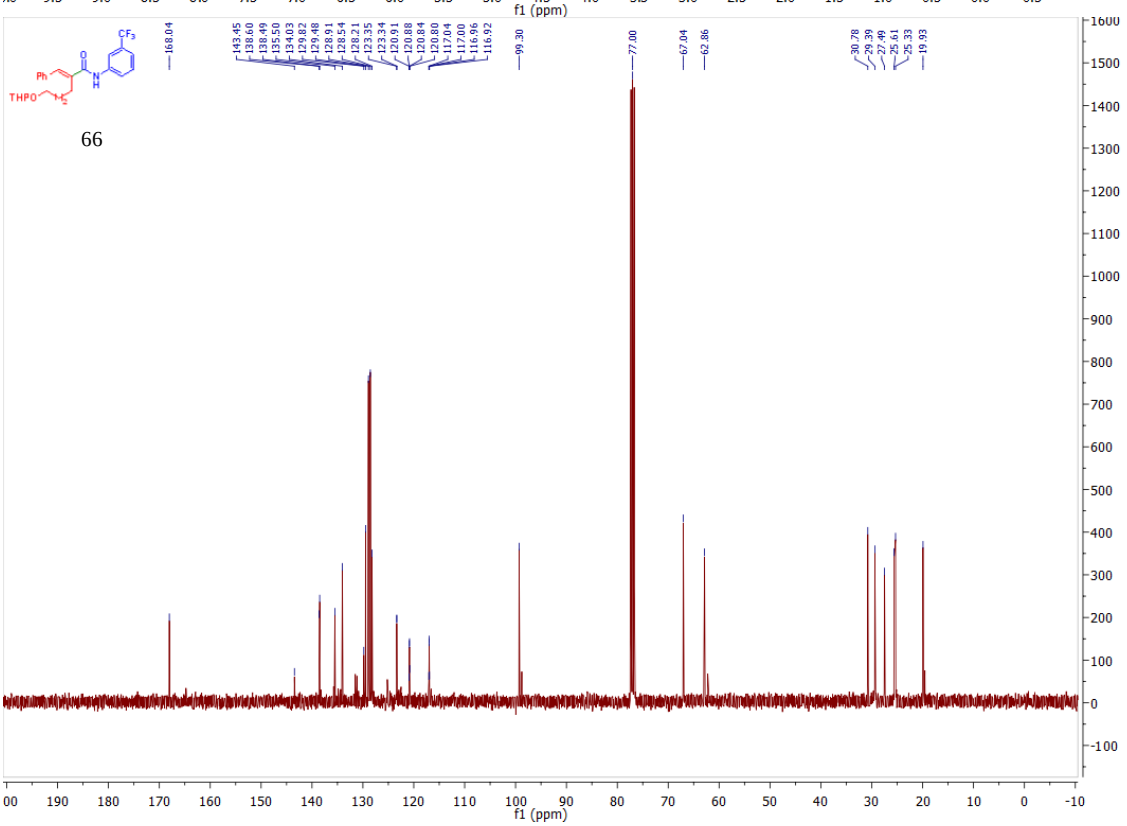

65
3.46
0.89
2.01
1.99
2.03
3.08
1.35
2.00
1.99
2.10
2.46
f1 (ppm)


65
168.04
142.07
138.25
135.04
134.42
133.27
128.84
128.69
125.56
119.78
118.83
107.13
77.00
44.50
32.06
27.03
25.86
f1 (ppm)


65+65a
f1 (ppm)


65+65a
f1 (ppm)


66
f1 (ppm)


66
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143.45
138.60
138.49
135.50
134.03
131.82
129.48
128.91
128.54
128.21
123.35
123.34
120.91
120.88
120.84
120.80
117.04
117.00
116.96
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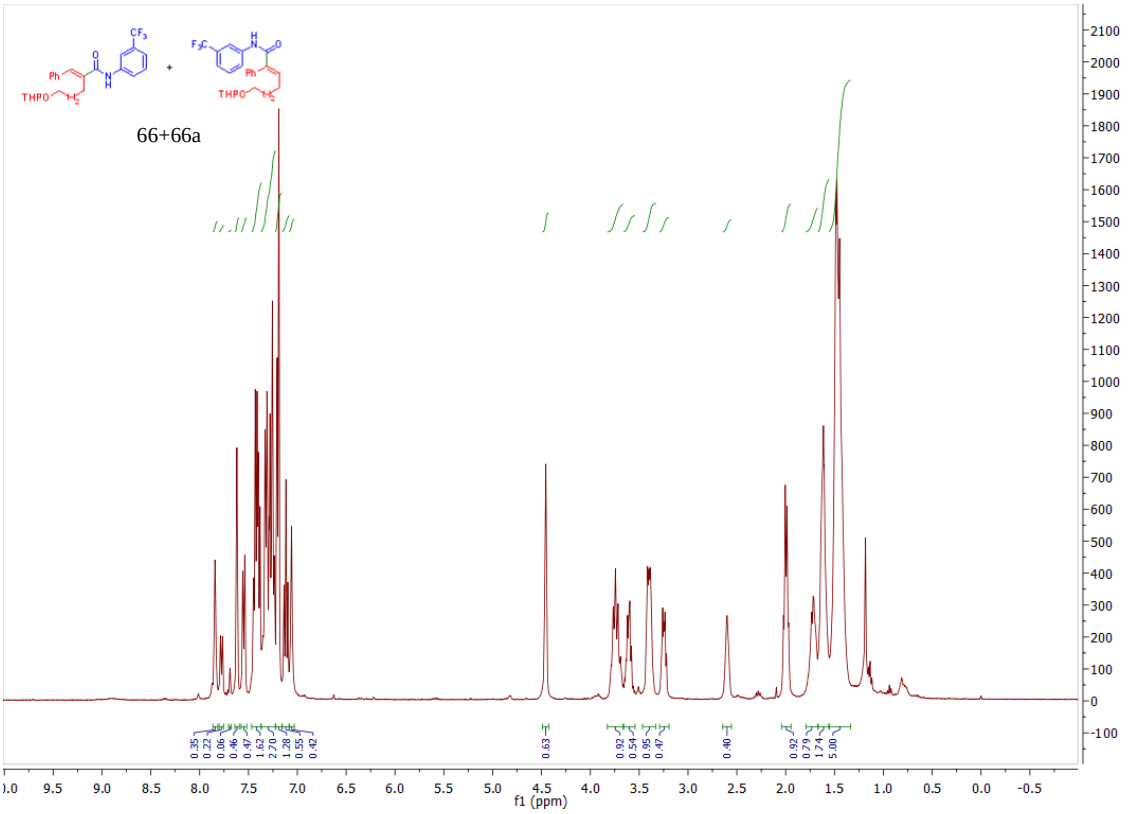
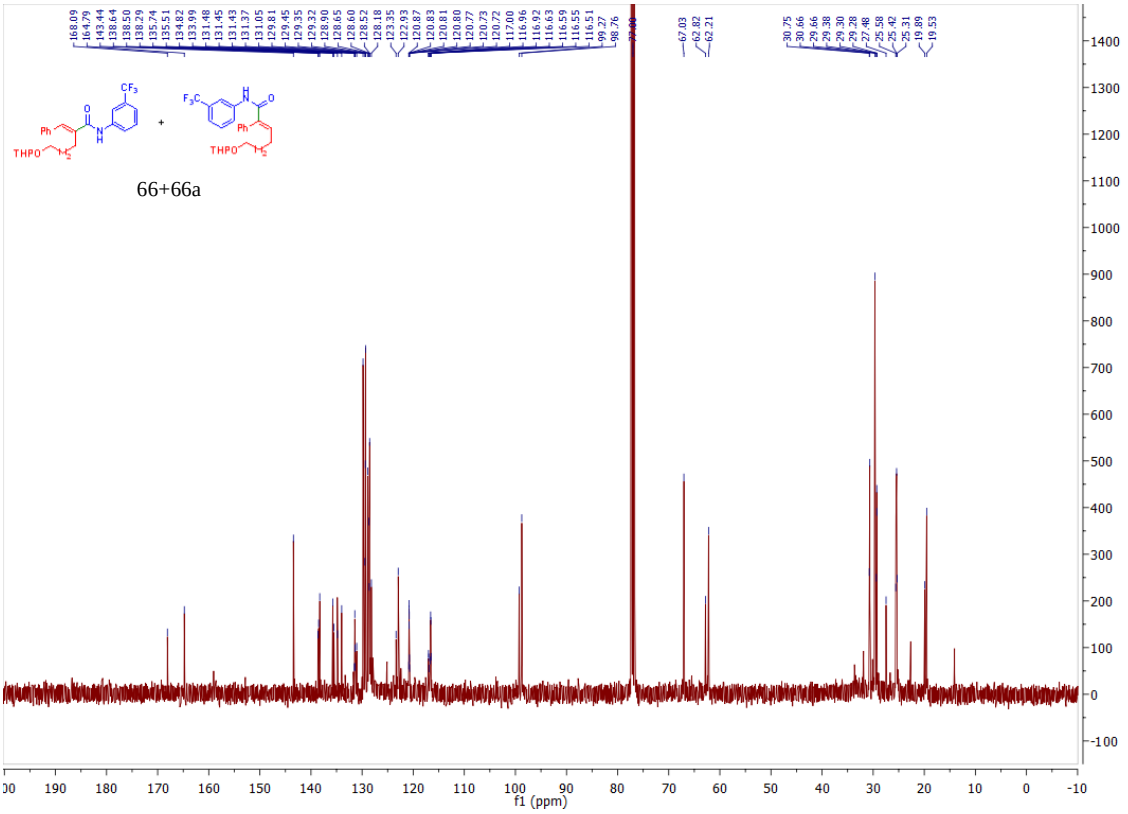
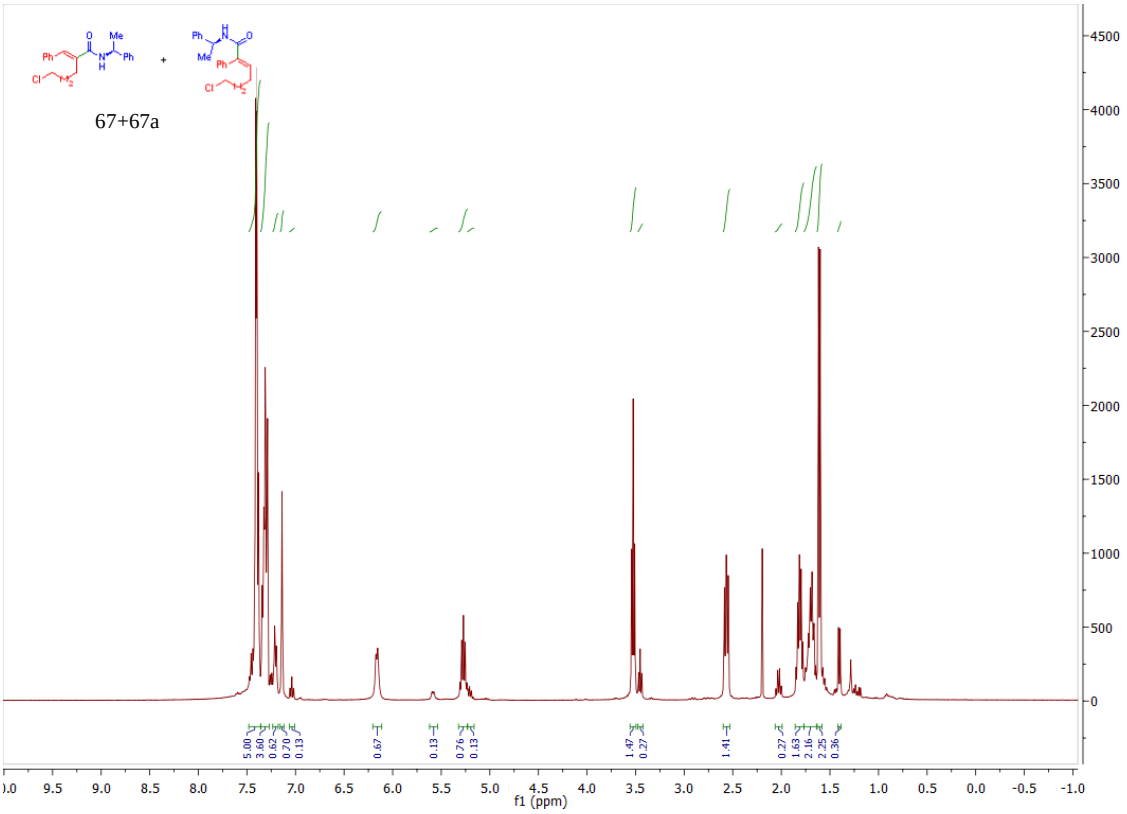
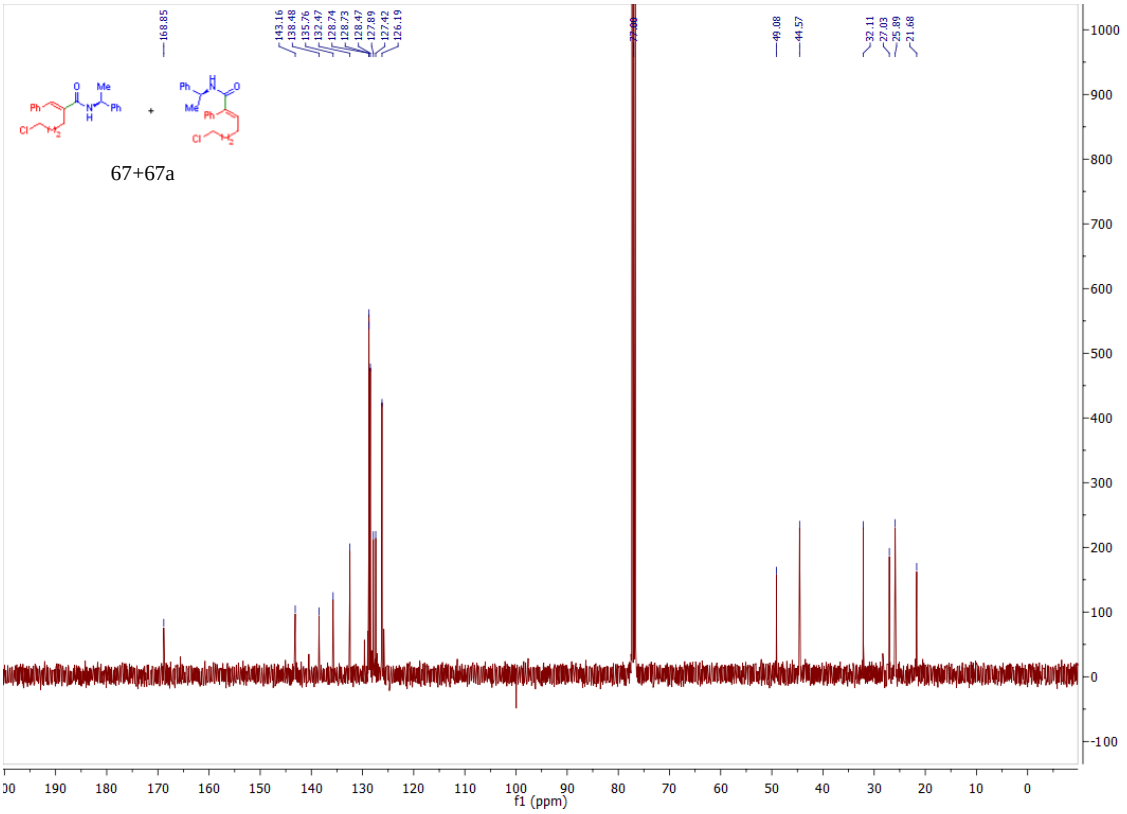
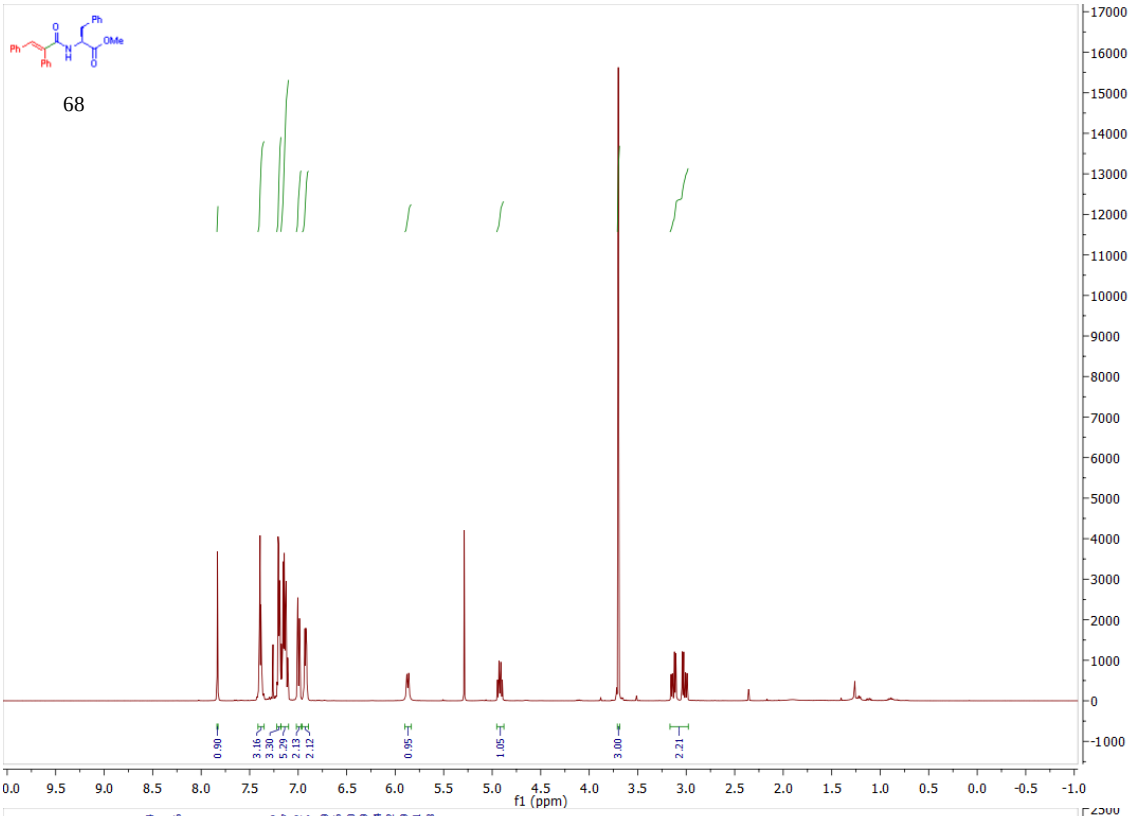
27.49
25.61
25.33
19.93
f1 (ppm)

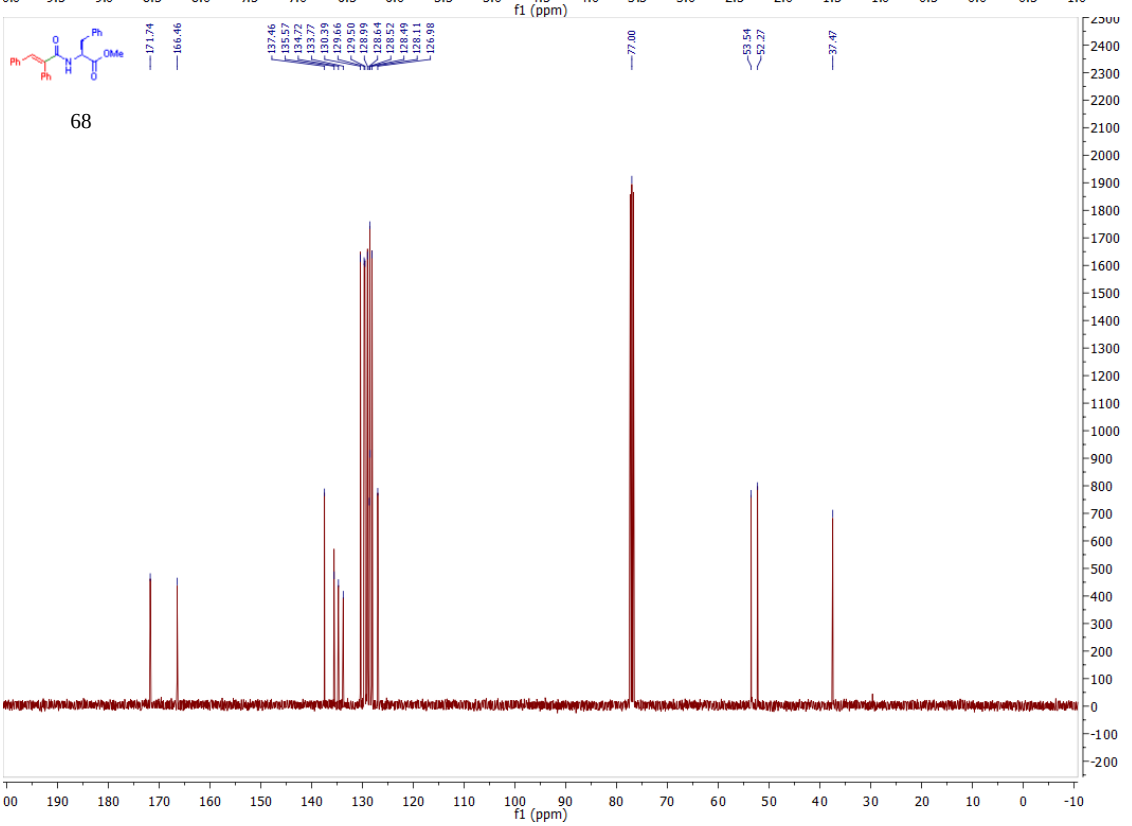

66+66a
f1 (ppm)


66+66a
f1 (ppm)


67+67a
f1 (ppm)


168.85
143.16
138.48
135.76
132.47
128.74
128.23
128.43
127.89
127.42
126.19
77.00
49.08
44.57
32.11
27.03
25.89
21.68
67+67a
f1 (ppm)


68
0.90
3.16
3.30
5.29
2.13
2.12
0.95
1.05
3.00
2.21
f1 (ppm)


68
171.74
166.46
137.46
135.57
134.72
133.77
130.39
129.66
129.50
128.99
128.64
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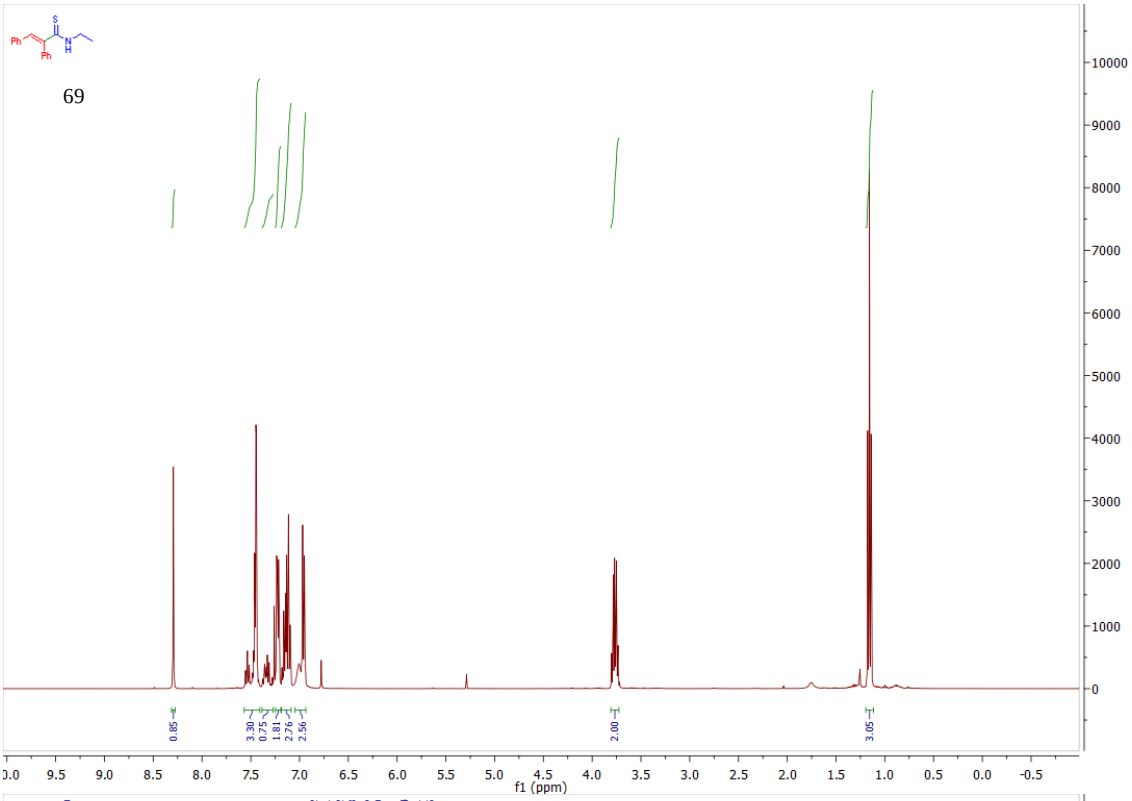
77.00
53.54
52.27
37.47
f1 (ppm)


69
0.85
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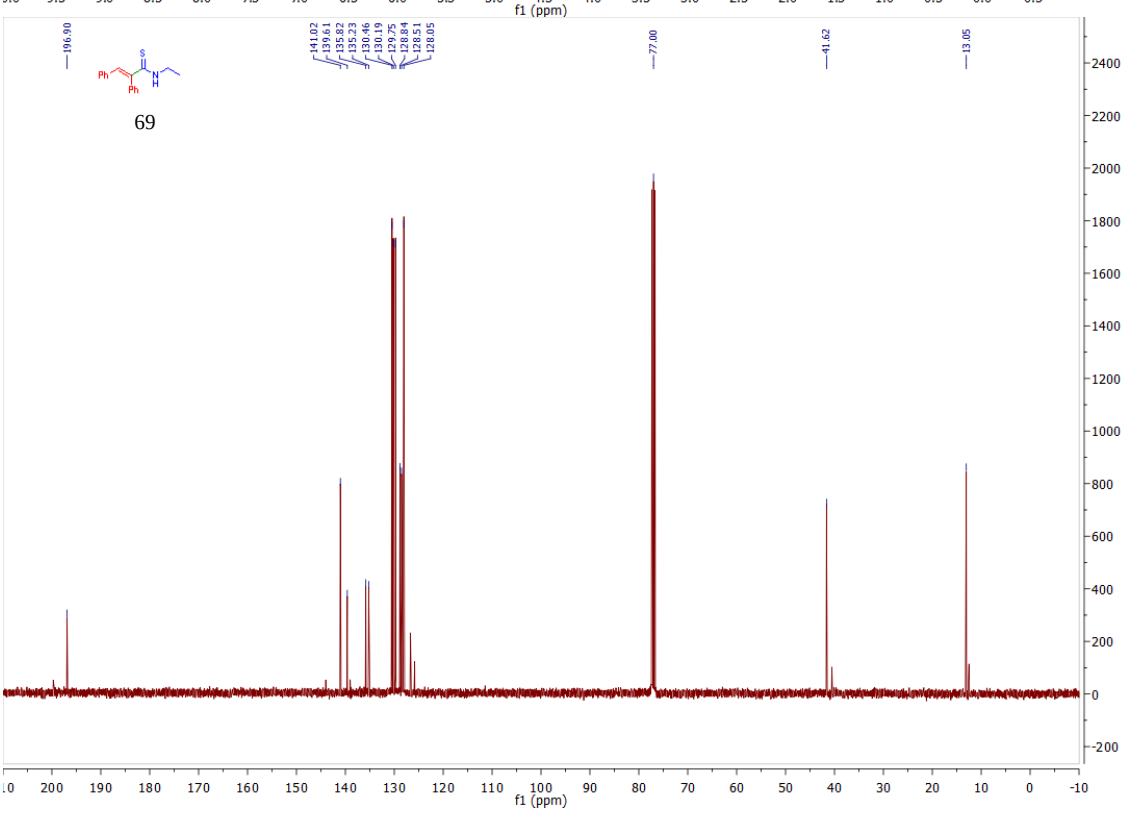
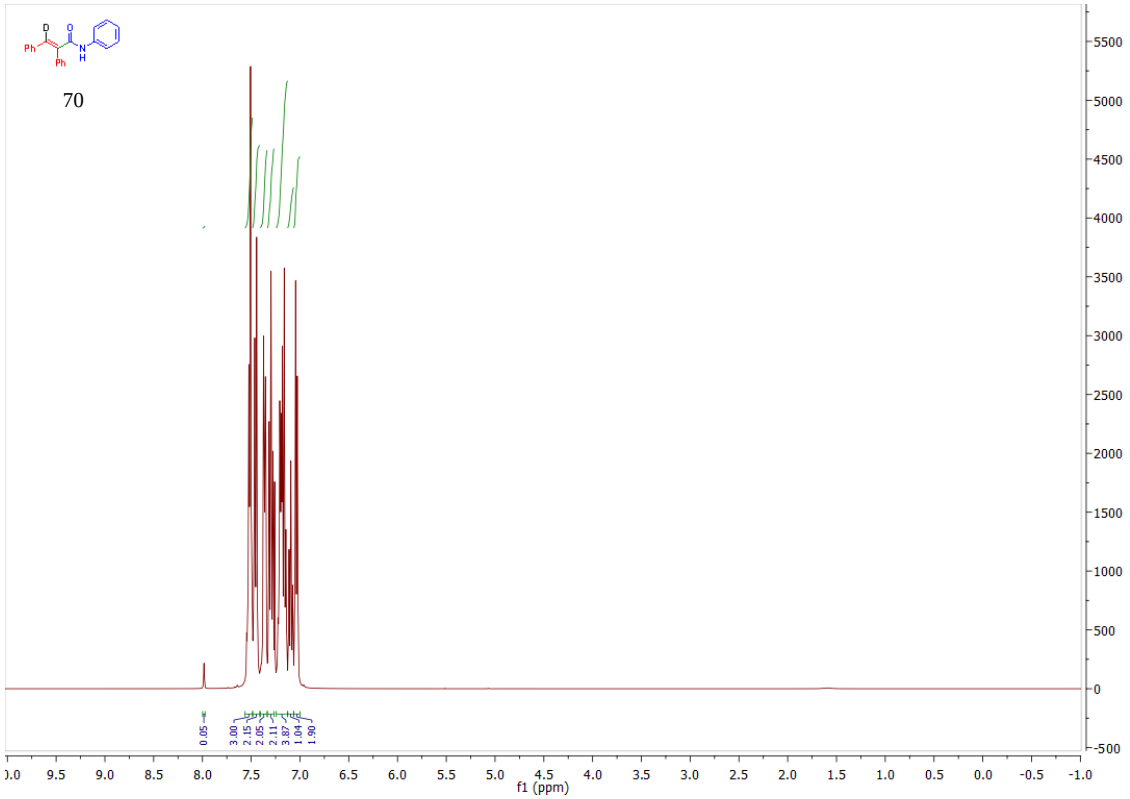
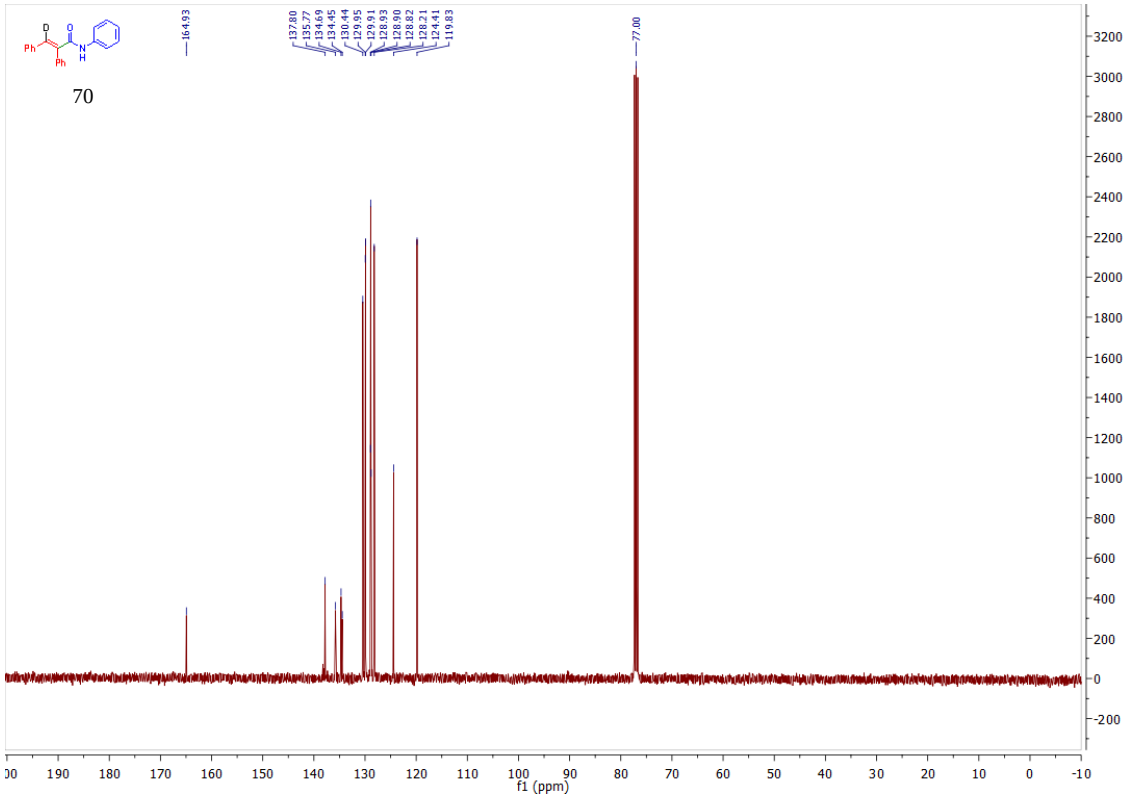
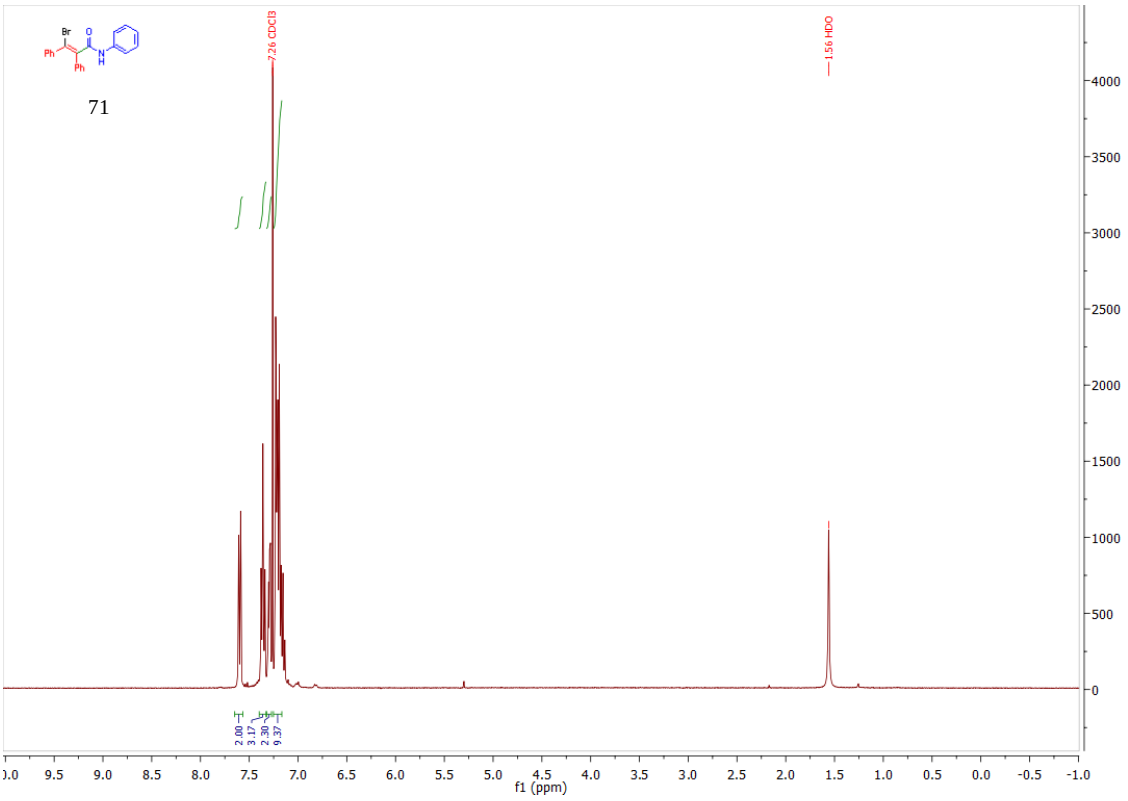
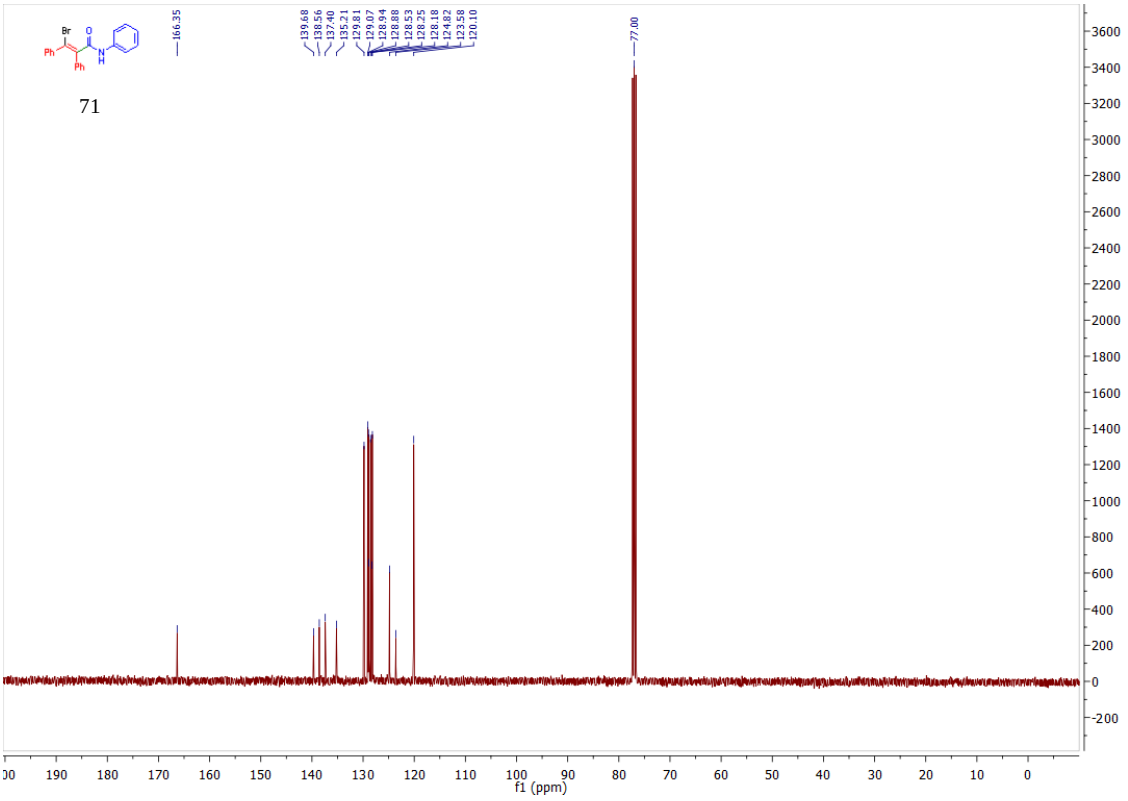
0.75
1.81
2.76
2.56
2.00
3.05
f1 (ppm)

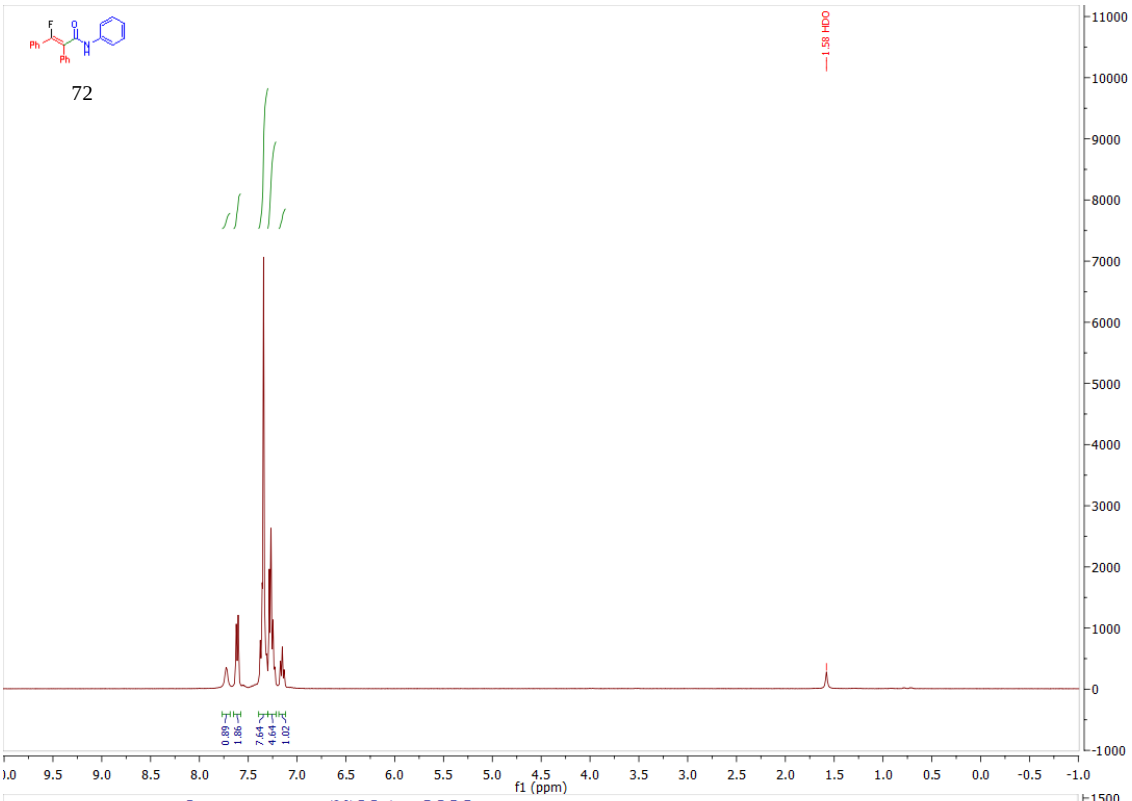

196.90
141.02
139.61
135.82
135.23
130.46
130.19
129.75
128.84
128.51
128.05
77.00
41.62
13.05
69
f1 (ppm)

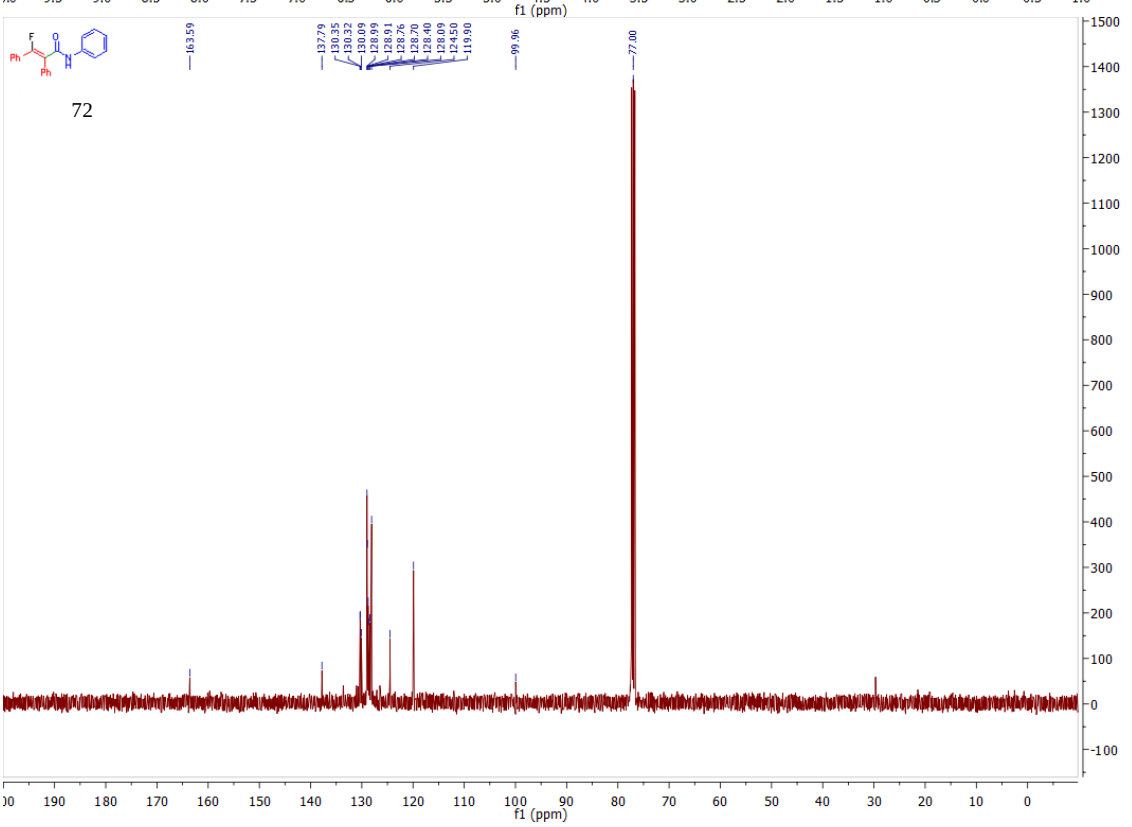

70
0.05
3.00
2.15
2.05
2.11
3.87
1.04
1.90
f1 (ppm)

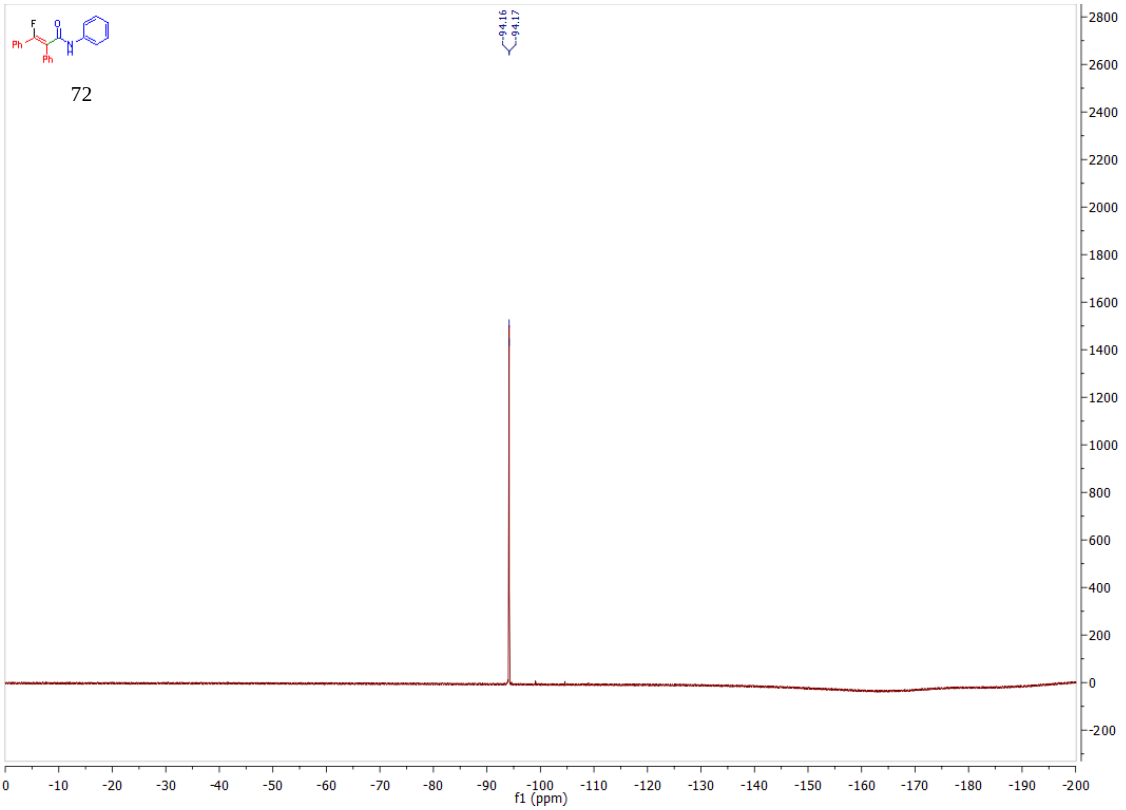

70
164.93
137.80
135.77
134.46
134.45
130.44
129.95
129.91
128.93
128.90
128.82
128.21
124.41
119.83
77.00
f1 (ppm)

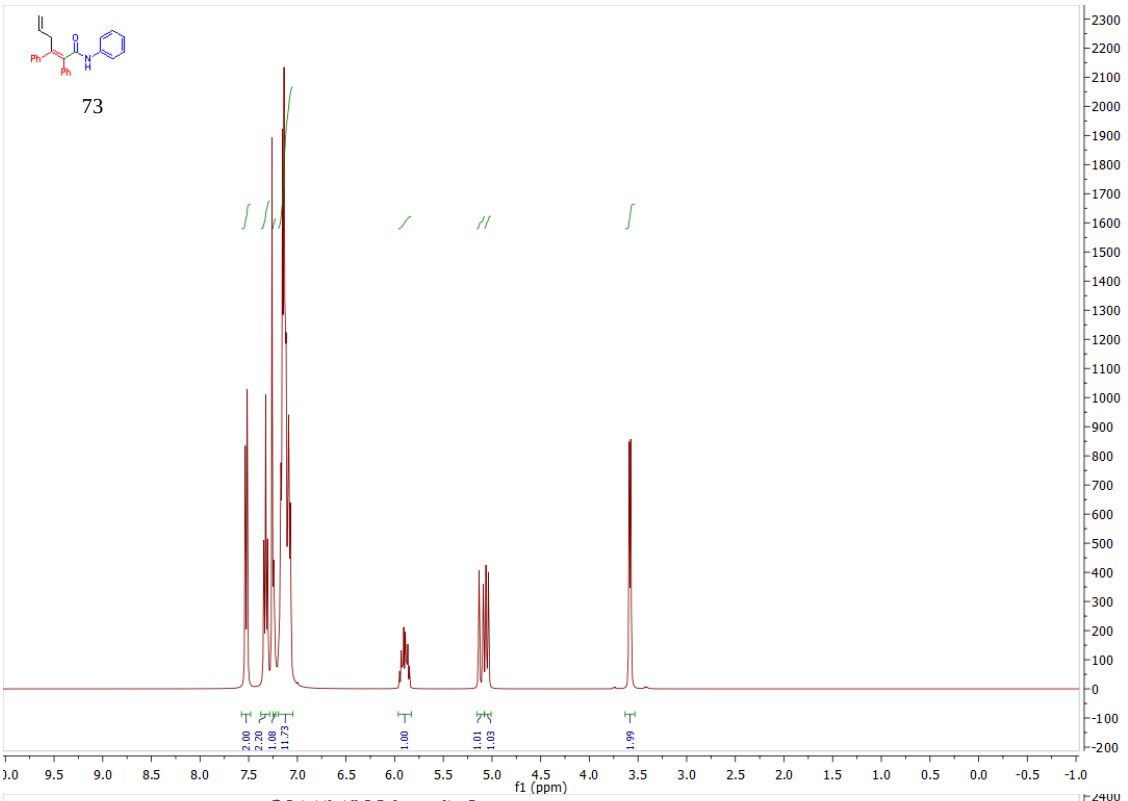

71
7.26 CDCl3
1.56 HDO
2.00
3.17
2.30
9.37
f1 (ppm)

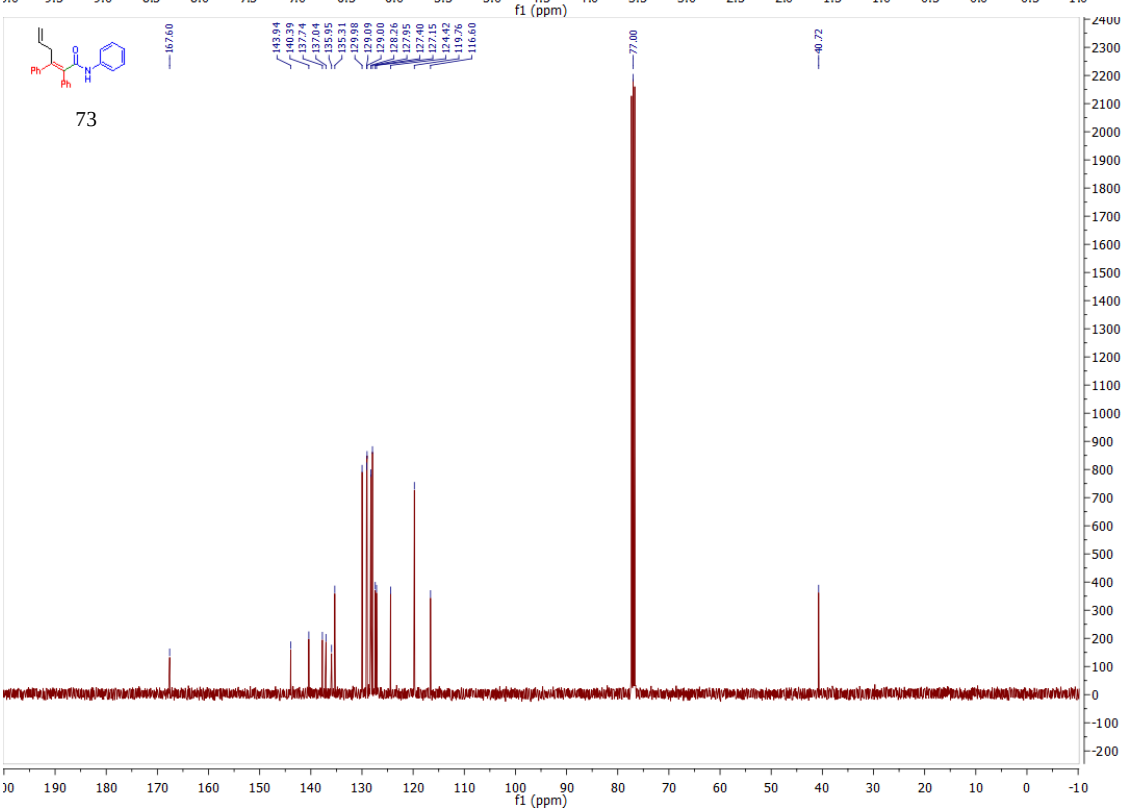

71
166.35
139.68
135.56
132.40
129.81
129.07
128.94
128.88
128.53
128.25
128.18
124.82
123.58
120.10
77.00
f1 (ppm)

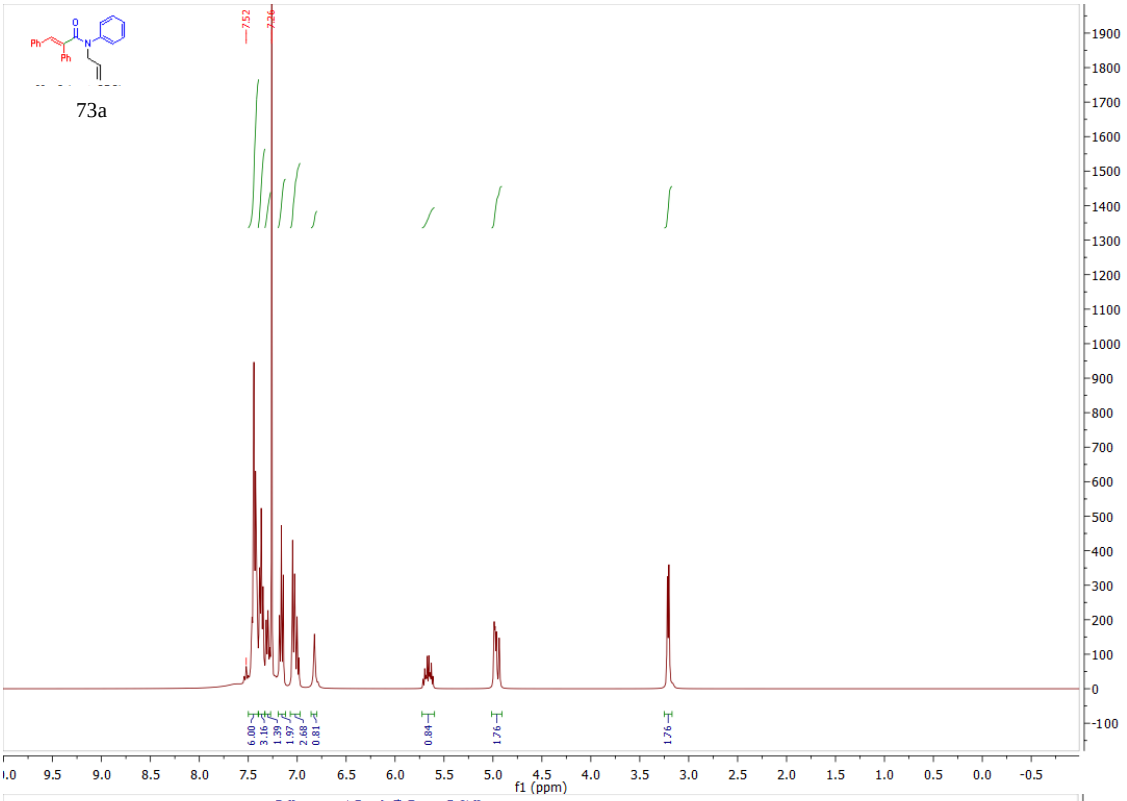

72
1.58 HDO
0.89
1.86
7.64
4.64
1.02
f1 (ppm)

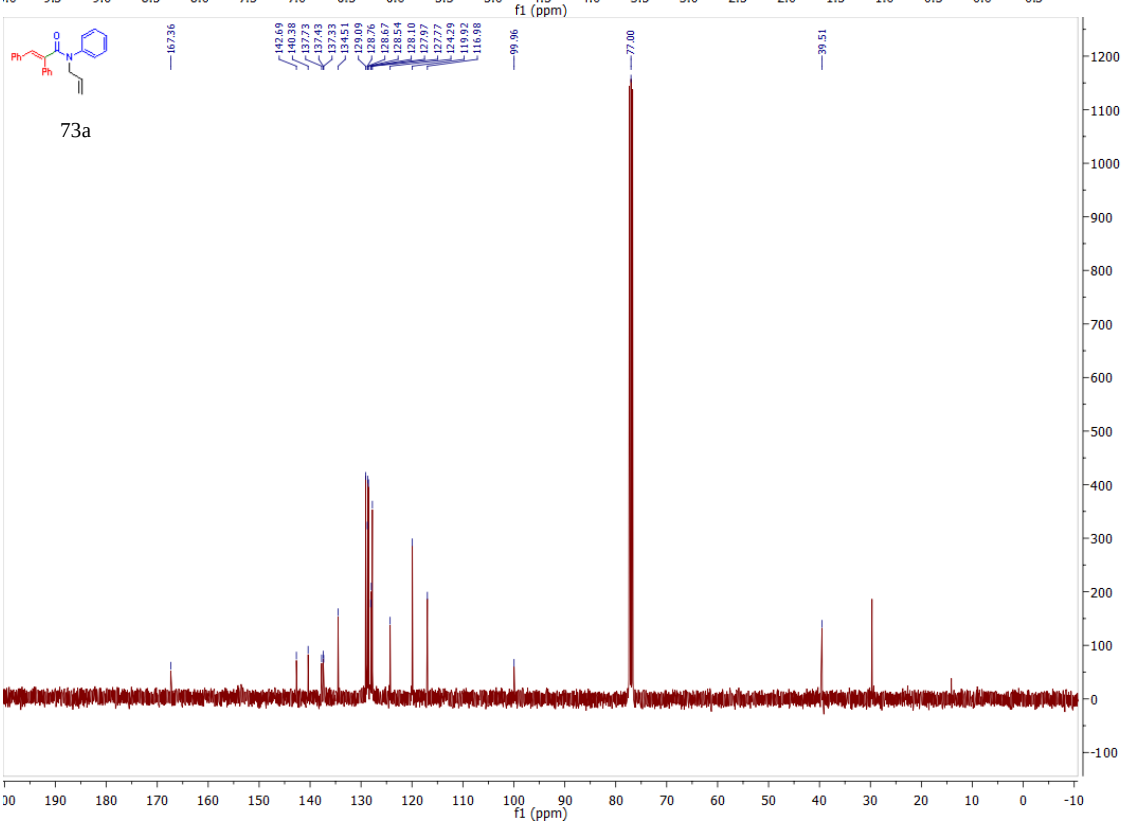

72
163.59
137.79
130.35
130.32
130.09
128.99
128.91
128.76
128.70
128.40
128.09
124.50
119.90
99.96
77.00
f1 (ppm)

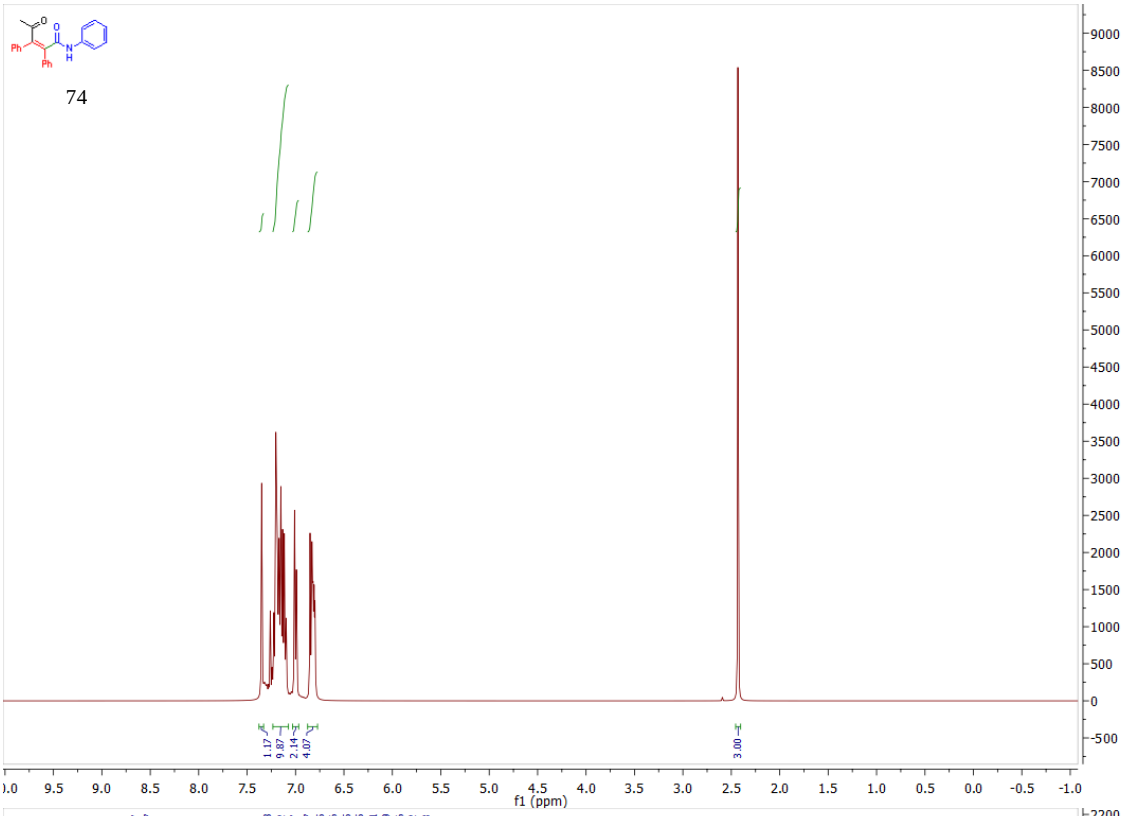

F
O
N
Ph
Ph
72
-94.16
-94.17
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

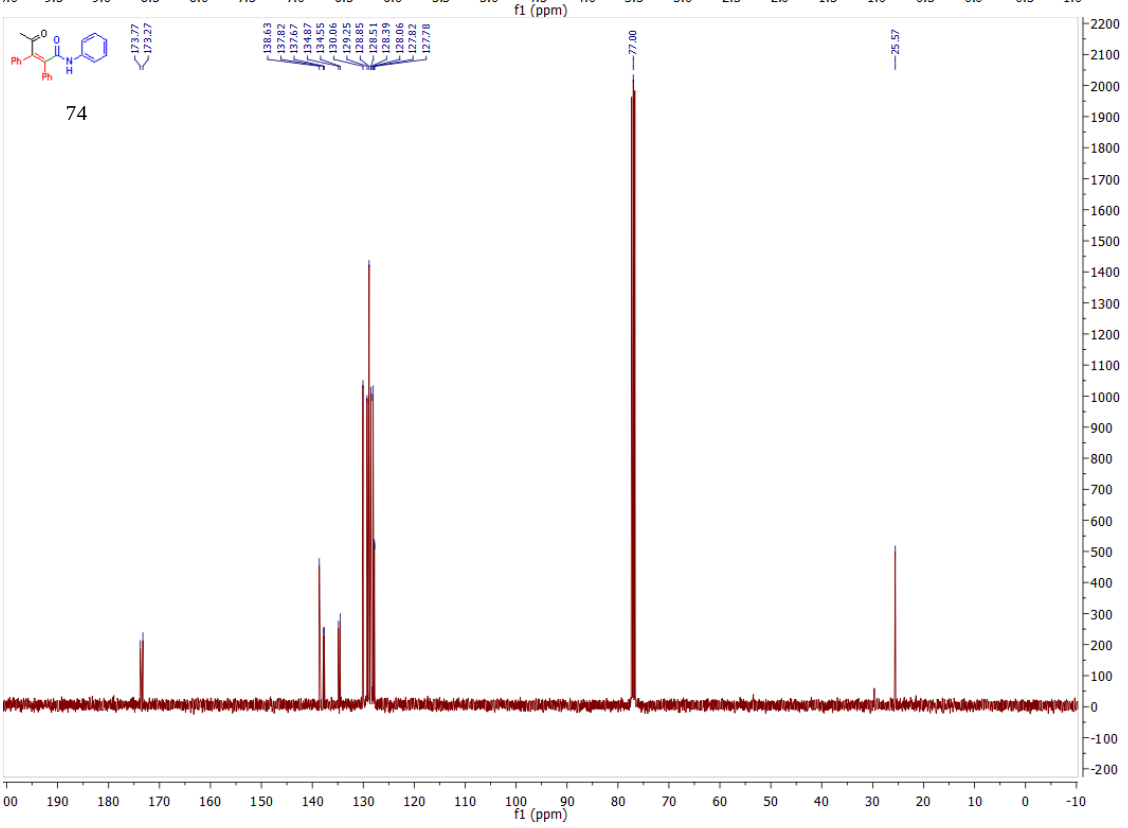

73
2.00
2.20
1.08
11.73
1.00
1.01
1.03
1.99
f1 (ppm)

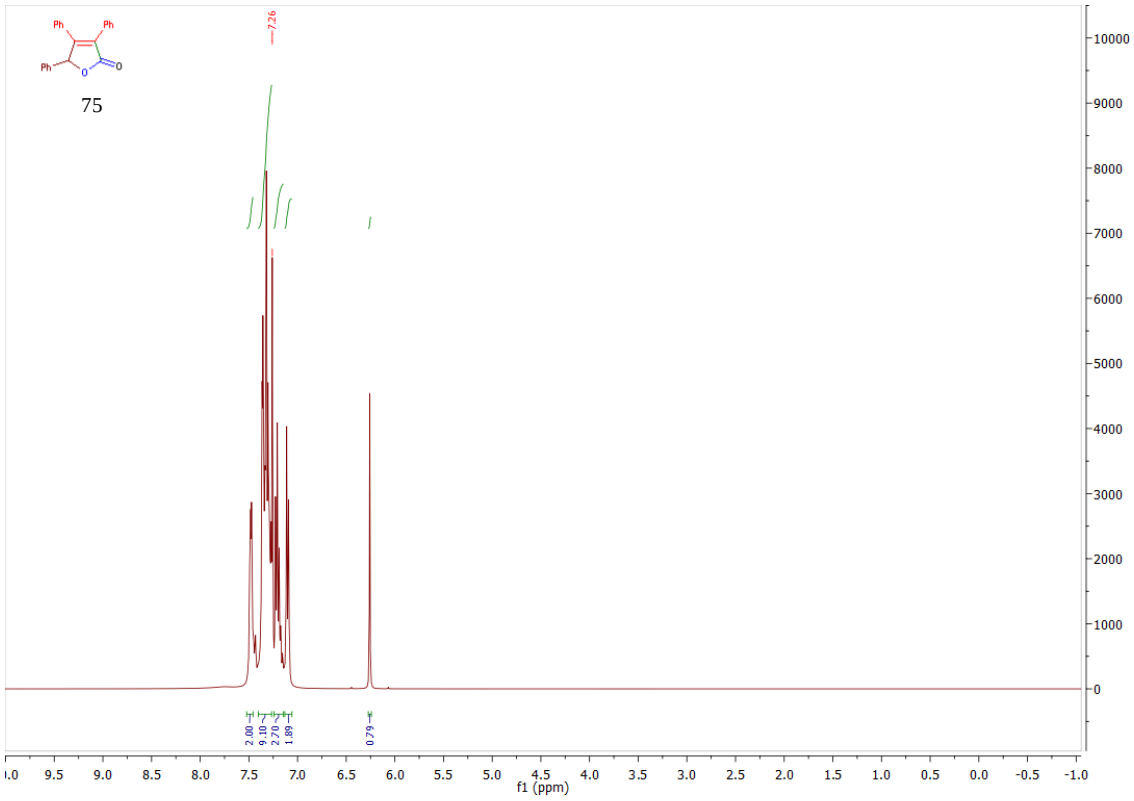

73
167.60
143.94
140.39
137.74
137.04
135.95
135.31
129.98
129.09
129.00
128.26
127.95
127.40
127.15
124.42
119.76
116.60
77.00
40.72
f1 (ppm)

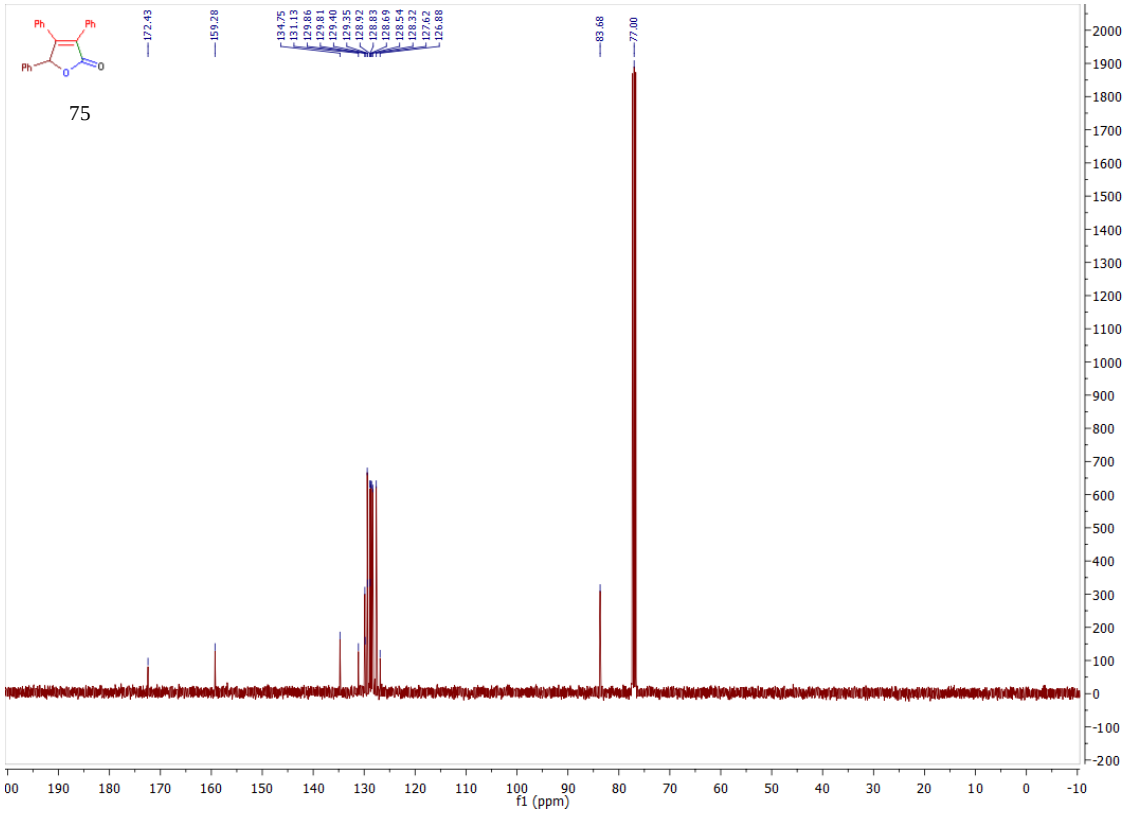

73a
7.52
7.26
6.00
3.16
1.39
1.97
2.68
0.81
0.84
1.76
1.76
f1 (ppm)

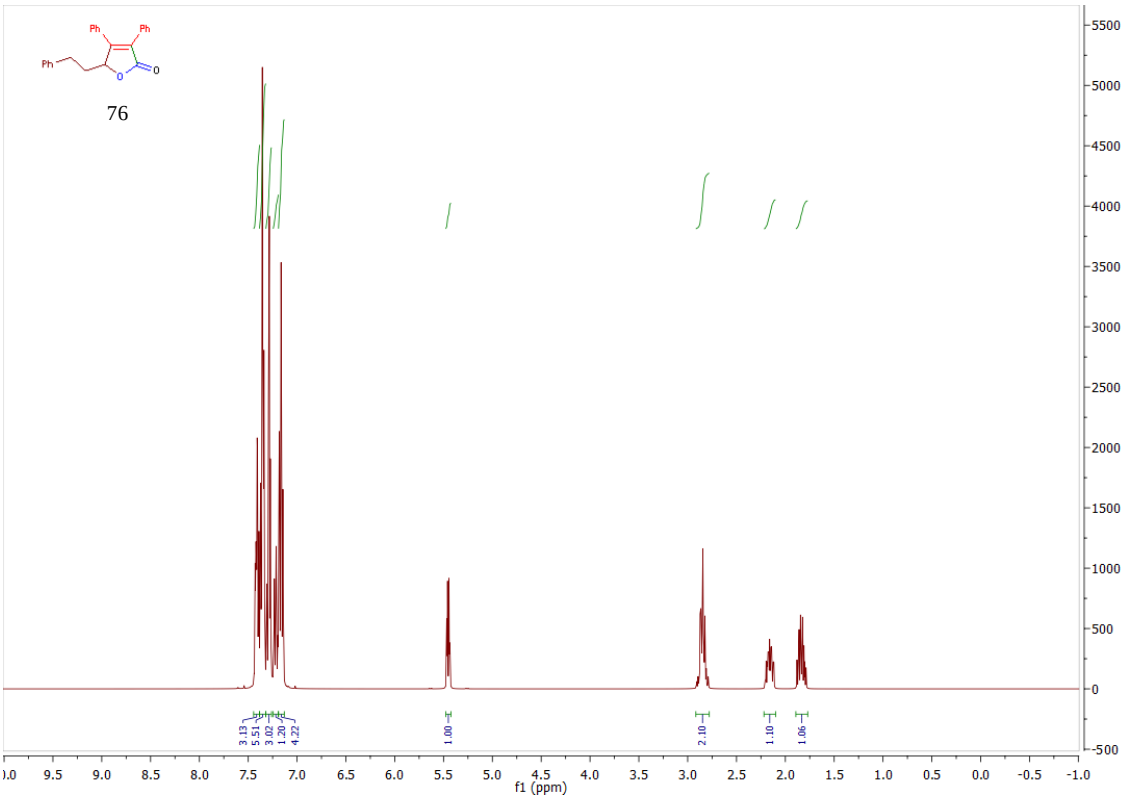

73a
167.36
142.69
140.38
137.73
137.43
137.33
134.51
129.10
128.76
128.67
128.54
128.10
127.97
127.77
124.29
119.92
116.98
99.96
77.00
39.51
f1 (ppm)

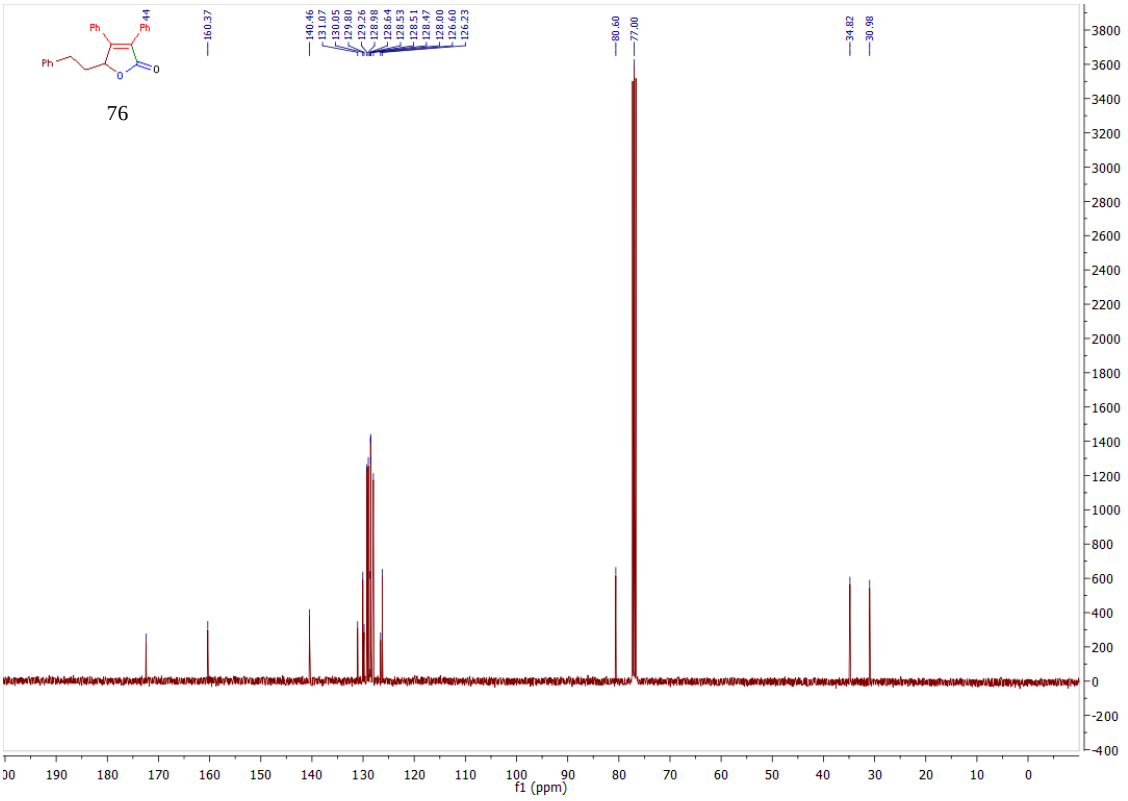

74
1.17
9.87
2.14
4.07
3.00
f1 (ppm)

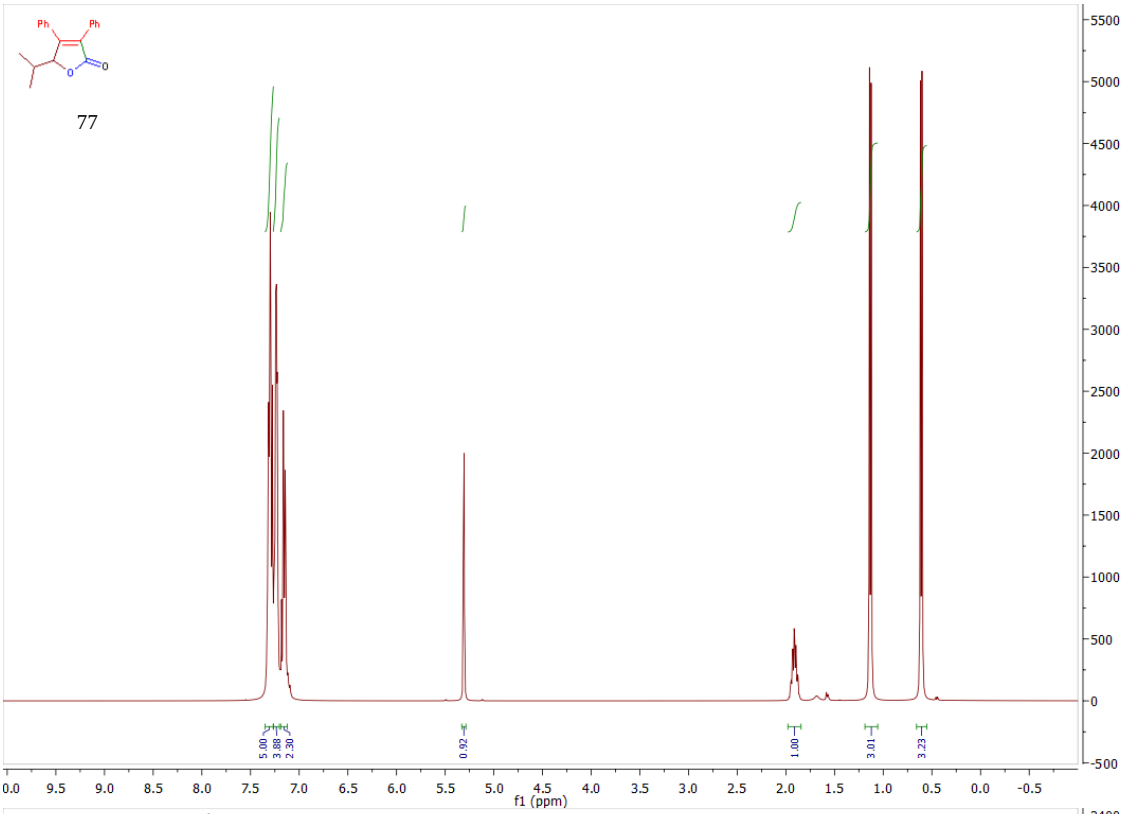

74
173.77
173.27
138.63
137.82
137.67
134.87
134.55
130.06
129.25
128.85
128.51
128.39
128.06
127.82
127.78
77.00
25.57
f1 (ppm)

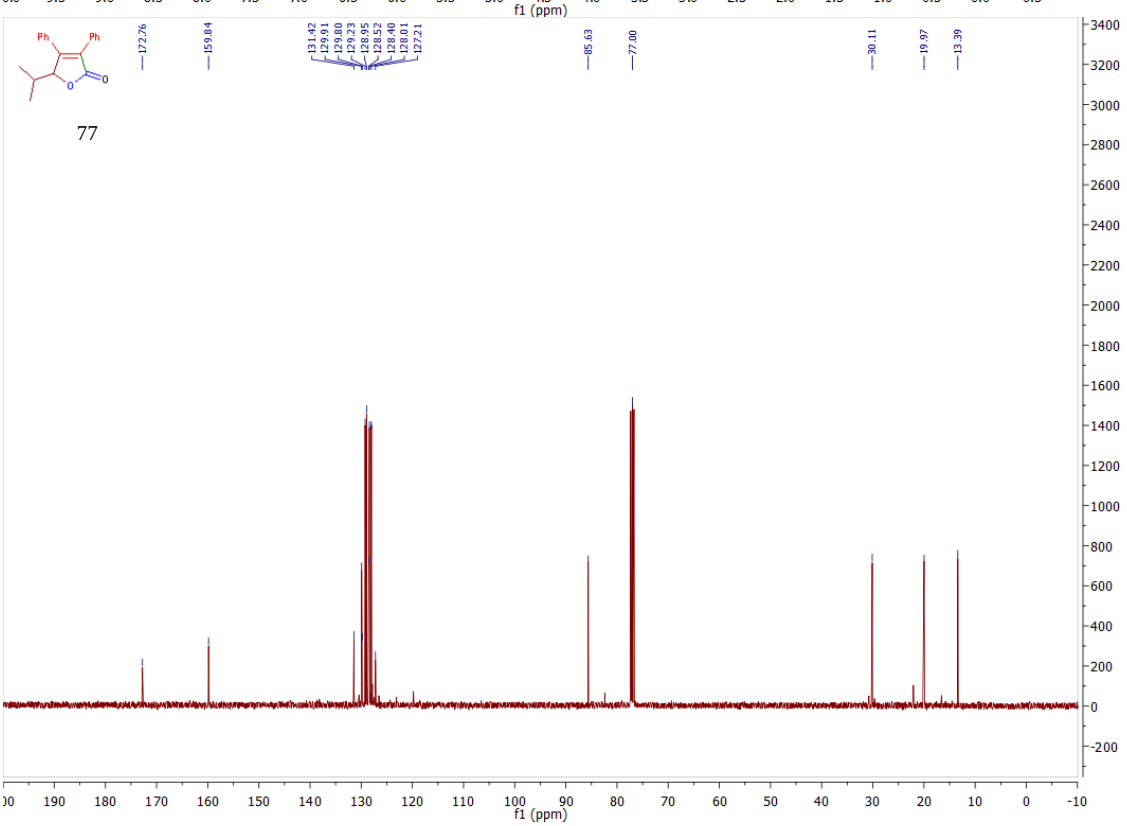

Ph
Ph
Ph
O
O
75
7.26
2.00
9.10
2.70
1.89
0.79
f1 (ppm)


Ph
Ph
Ph
O
O
75
172.43
159.28
134.75
131.13
129.86
129.81
129.40
129.35
128.92
128.83
128.69
128.54
128.32
127.62
126.88
83.68
77.00
f1 (ppm)


Ph
Ph
Ph
O
O
76
3.13
5.51
3.02
1.20
4.22
1.00
2.10
1.10
1.06
f1 (ppm)


Ph
Ph
Ph
O
O
76
160.37
140.46
131.07
130.05
129.80
129.26
128.98
128.64
128.53
128.51
128.47
128.00
126.60
126.23
80.60
77.00
34.82
30.98
f1 (ppm)


77
5.00
3.88
2.30
0.92
1.00
3.01
3.23
f1 (ppm)


77
172.76
159.84
131.42
129.91
129.80
129.23
128.95
128.52
128.40
128.01
127.21
85.63
77.00
30.11
19.97
13.39
f1 (ppm)

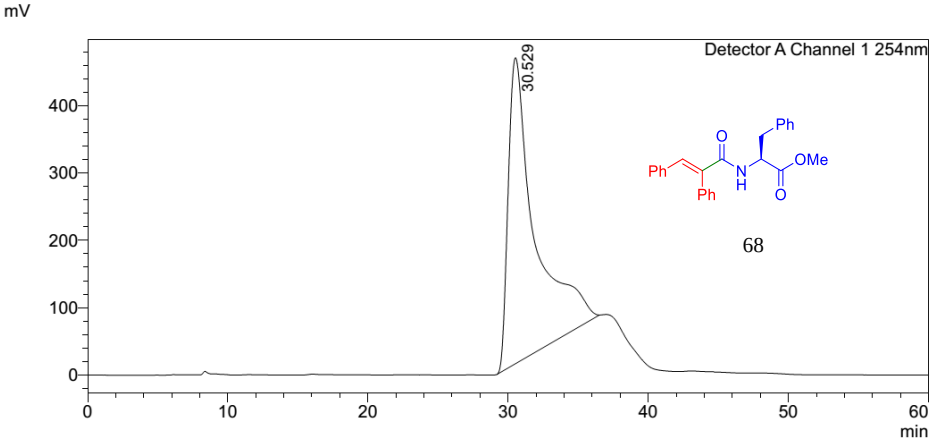
SHIMADZU LabSolutions

Analysis Report

<Sample Information>

Sample Name	:		
Sample ID	:		
Data Filename	: I-cvk-256-Lux-4%IPA+ 0.1%TFA in Hexanes-60 mins-D2-0.5 mLmin.lcd		
Method Filename	: Lux-4%IPA+ 0.1%TFA in Hexanes-60 mins-D2-0.5 mLmin.lcm		
Batch Filename	: 8-3-15.lcb		
Vial #	: 1-2	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 8/3/2015 7:54:01 PM	Acquired by	: System Administrator
Date Processed	: 6/25/2016 12:42:29 PM	Processed by	: System Administrator

<Chromatogram>



Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	30.529	60515670	454104	100.000			
Total		60515670	454104				

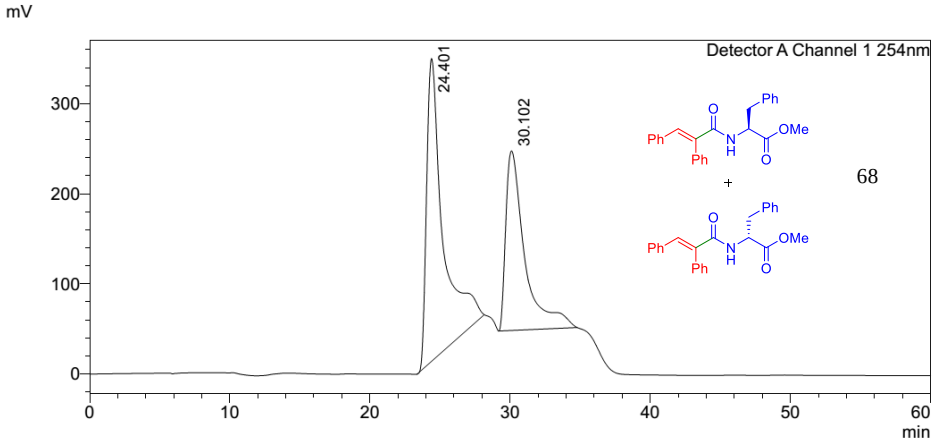
SHIMADZU LabSolutions

Analysis Report

<Sample Information>

Sample Name	:		
Sample ID	:		
Data Filename	: Lux-4%IPA+ 0.1%TFA in Hexanes-60 mins-D2-0.5 mLmin.lcd		
Method Filename	: Lux-4%IPA+ 0.1%TFA in Hexanes-60 mins-D2-0.5 mLmin.lcm		
Batch Filename	: 7-24-15.lcb		
Vial #	: 1-1	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 7/27/2015 7:58:54 PM	Acquired by	: System Administrator
Date Processed	: 7/27/2015 8:58:54 PM	Processed by	: System Administrator

<Chromatogram>



Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	24.401	27423337	336103	59.319		M	
2	30.102	18806605	199483	40.681		M	
Total		46229941	535586				

SHIMADZU LabSolutions

Analysis Report

<Sample Information>

Sample Name	:		
Sample ID	:		
Data Filename	: I-cvk-220- Iso Pure.lcd		
Method Filename	: Lux-4%IPA+ 0.1%TFA in Hexanes-60 mins-D2-0.5 mLmin.lcm		
Batch Filename	: 8-3-15.lcb		
Vial #	: 1-3	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 8/6/2015 7:33:50 PM	Acquired by	: System Administrator
Date Processed	: 6/25/2016 12:12:24 PM	Processed by	: System Administrator

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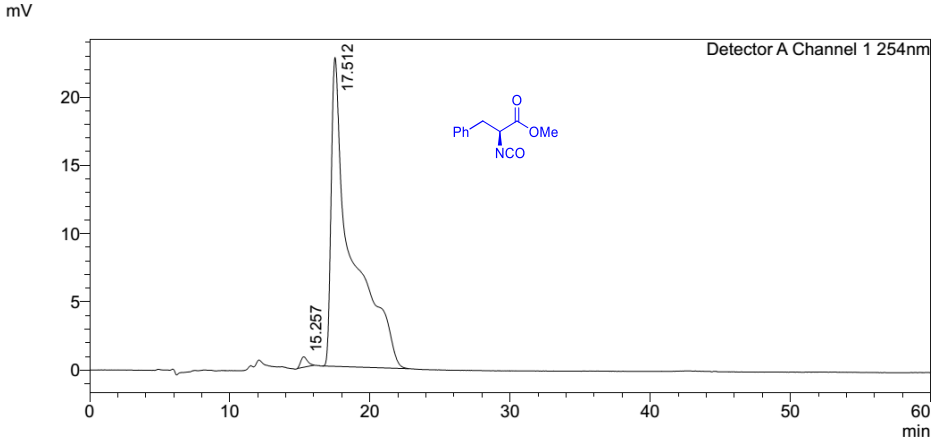


Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	15.257	25451	761	1.102		M	
2	17.512	2283589	22628	98.898			
Total		2309040	23389				

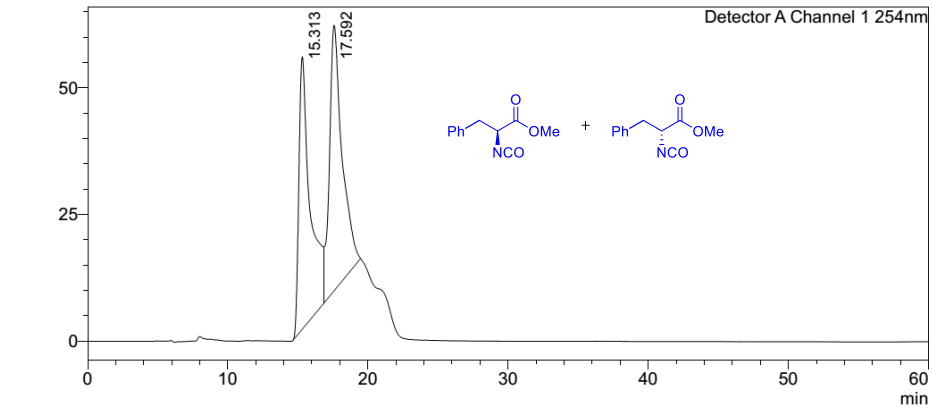
SHIMADZU LabSolutions

Analysis Report

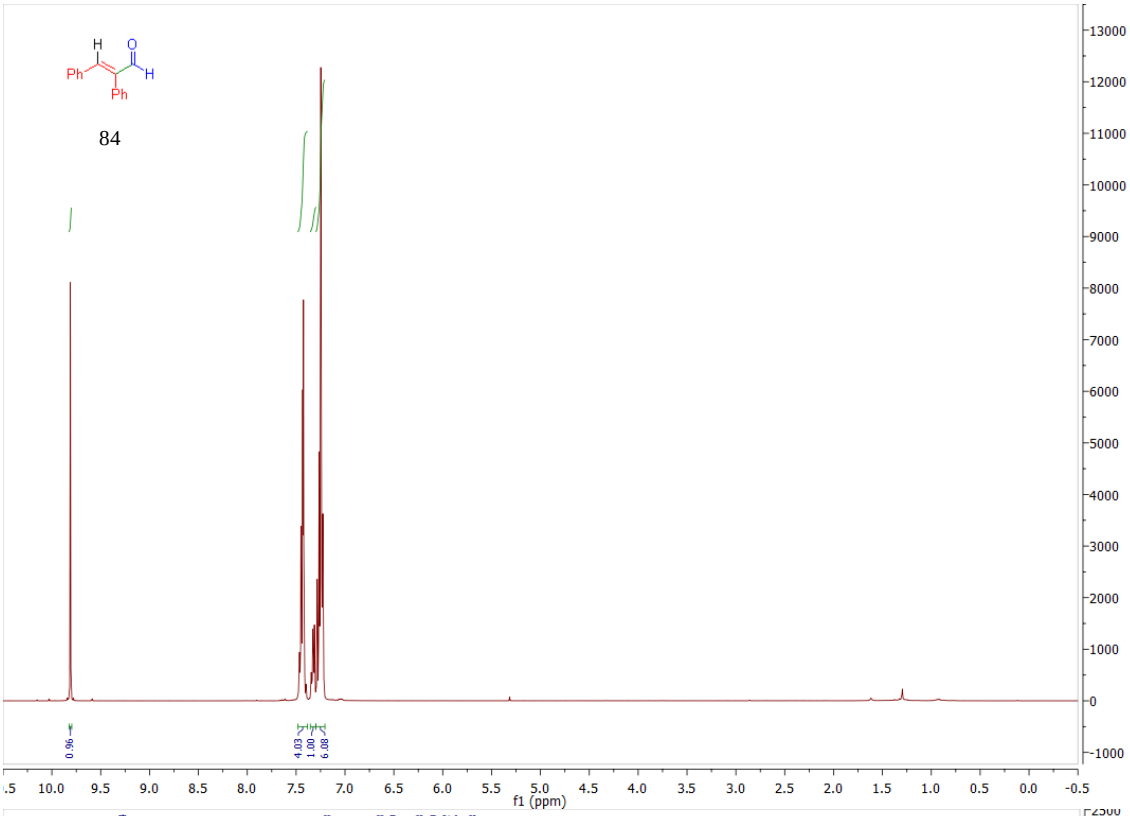
<Sample Information>

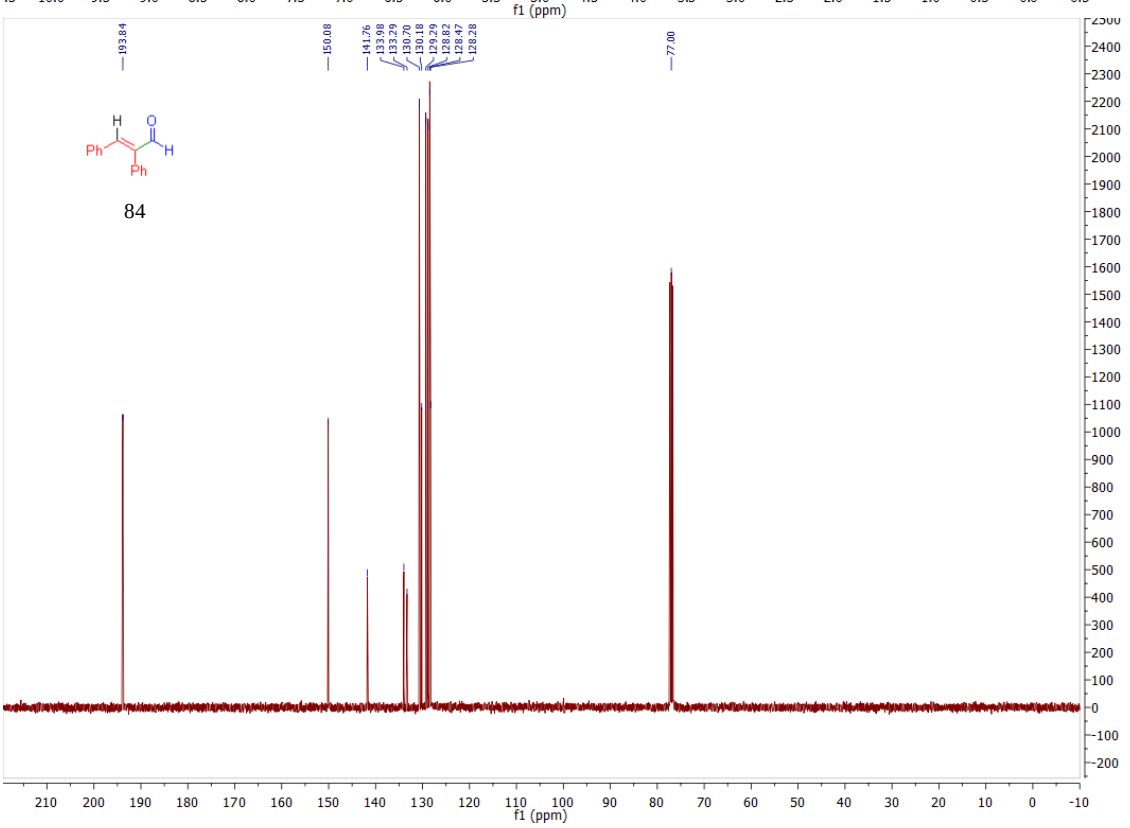
Sample Name	:		
Sample ID	:		
Data Filename	: I-cvk-270-Iso mix.lcd		
Method Filename	: Lux-4%IPA+ 0.1%TFA in Hexanes-60 mins-D2-0.5 mLmin.lcm		
Batch Filename	: 8-3-15.lcb		
Vial #	: 1-4	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 8/6/2015 9:35:16 PM	Acquired by	: System Administrator
Date Processed	: 6/25/2016 12:13:34 PM	Processed by	: System Administrator

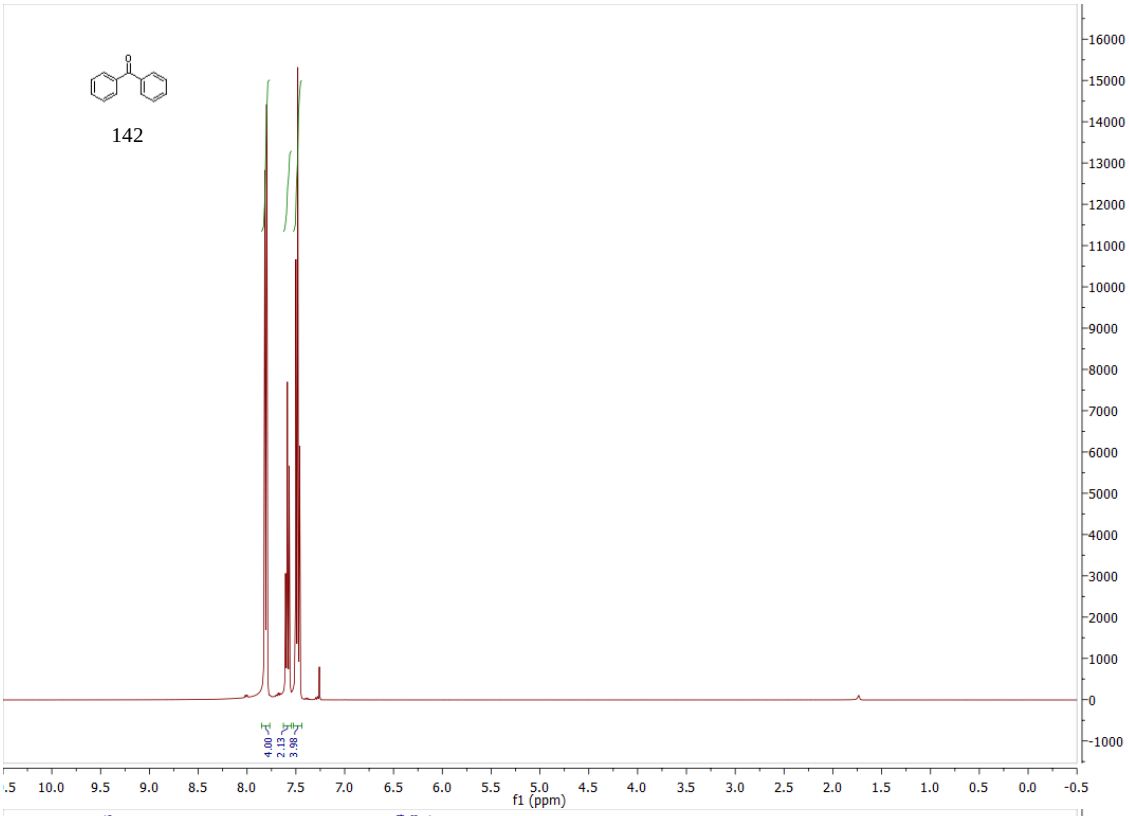
<Chromatogram>

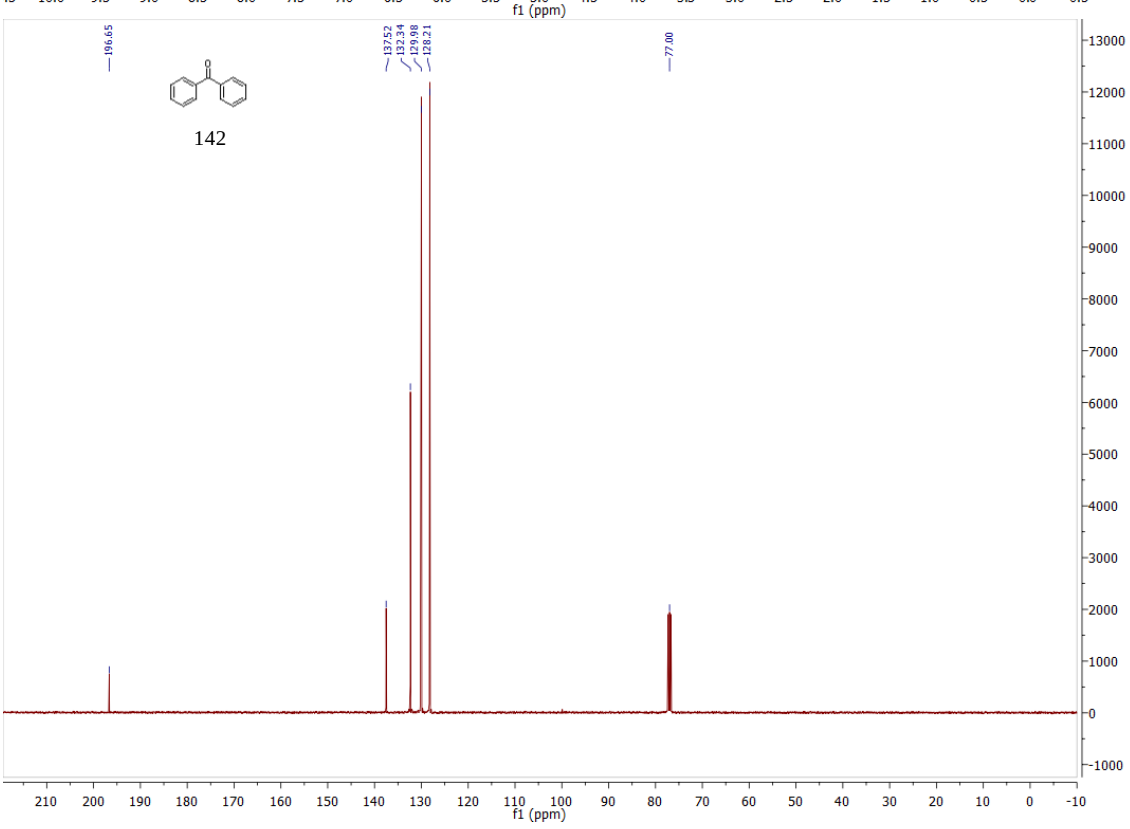


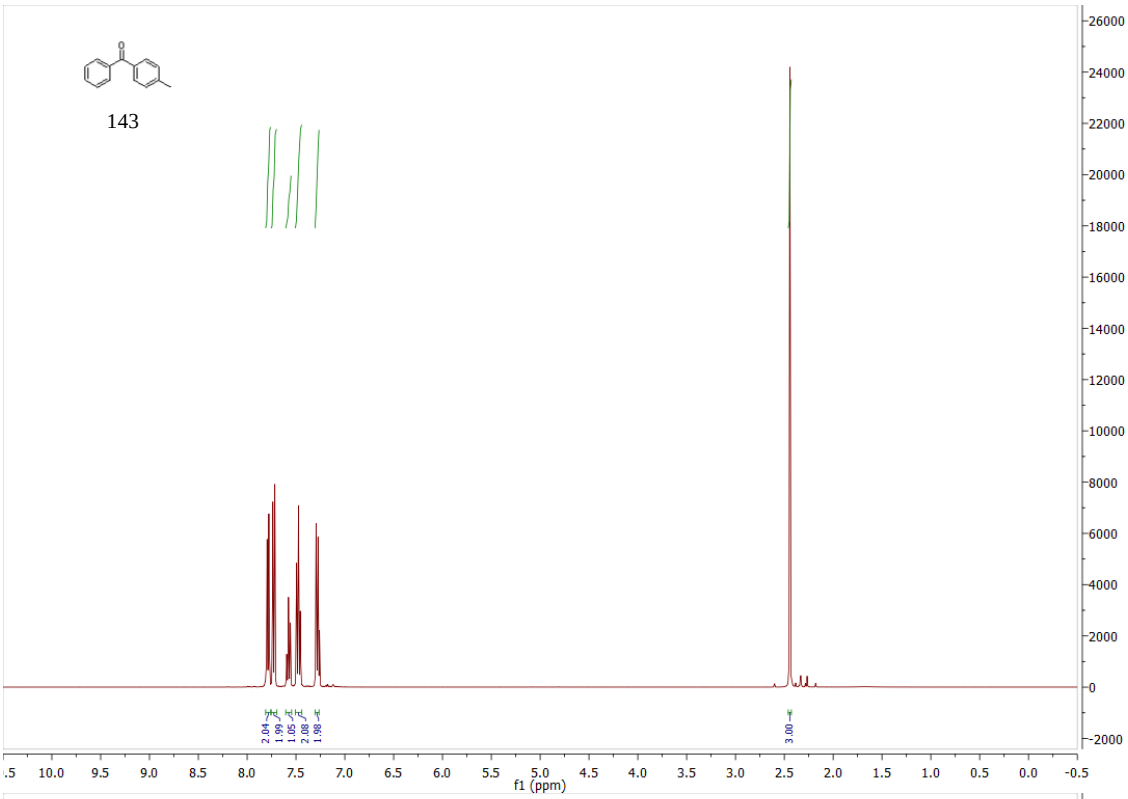
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	15.313	2991263	53762	47.577			
2	17.592	3295970	52355	52.423		V	
Total		6287232	106117				

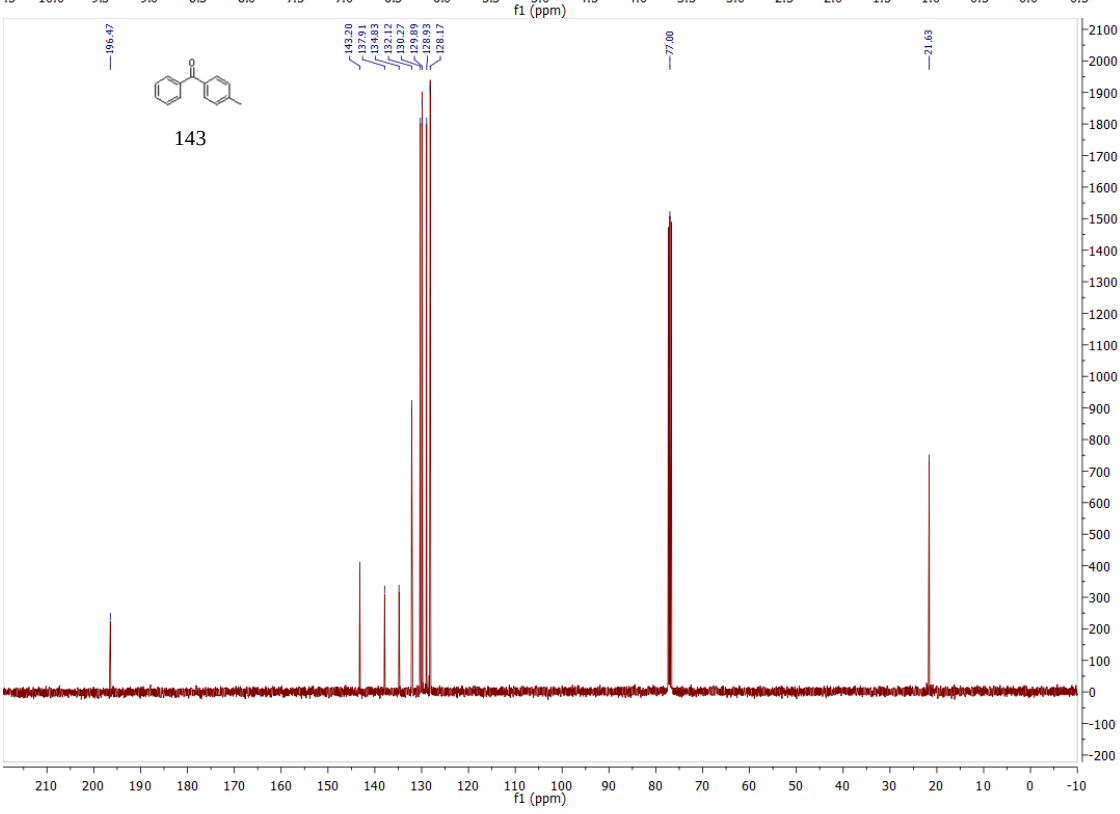

84
0.96
4.03
1.00
6.08
f1 (ppm)

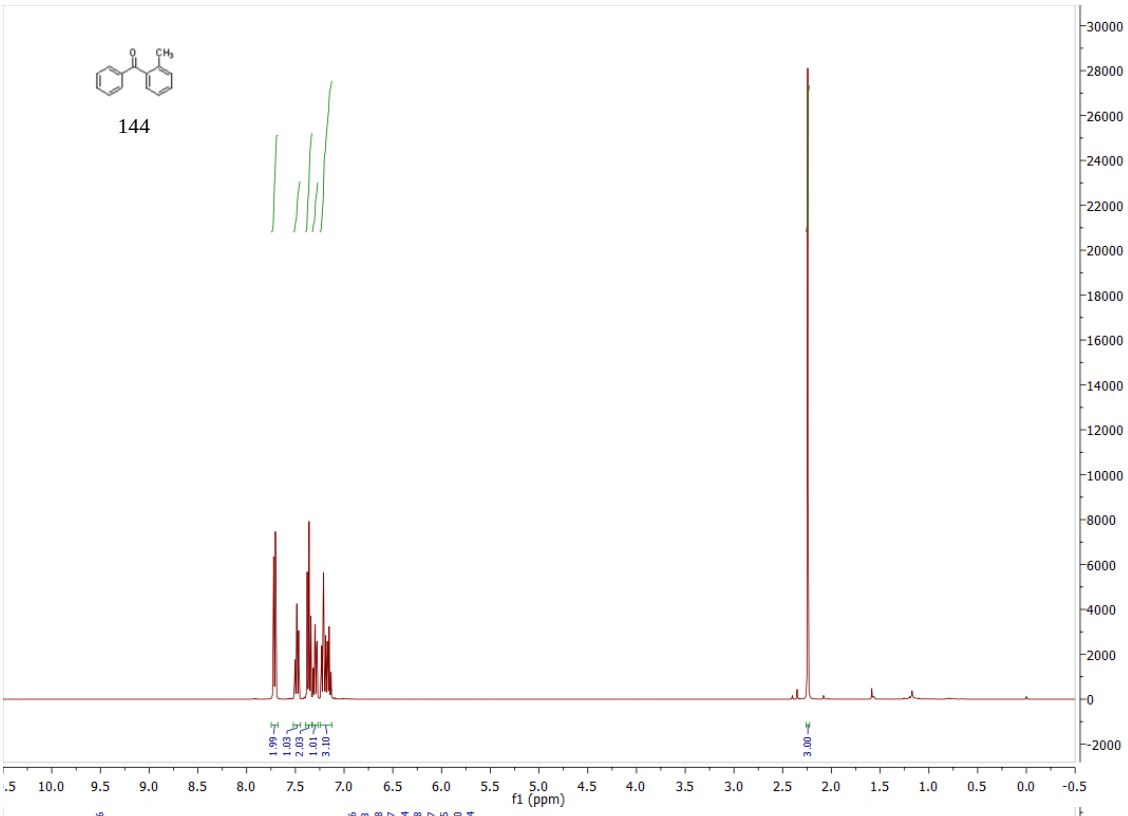

193.84
150.08
141.76
133.98
133.29
130.70
130.18
129.29
128.82
128.47
128.28
77.00
84
f1 (ppm)

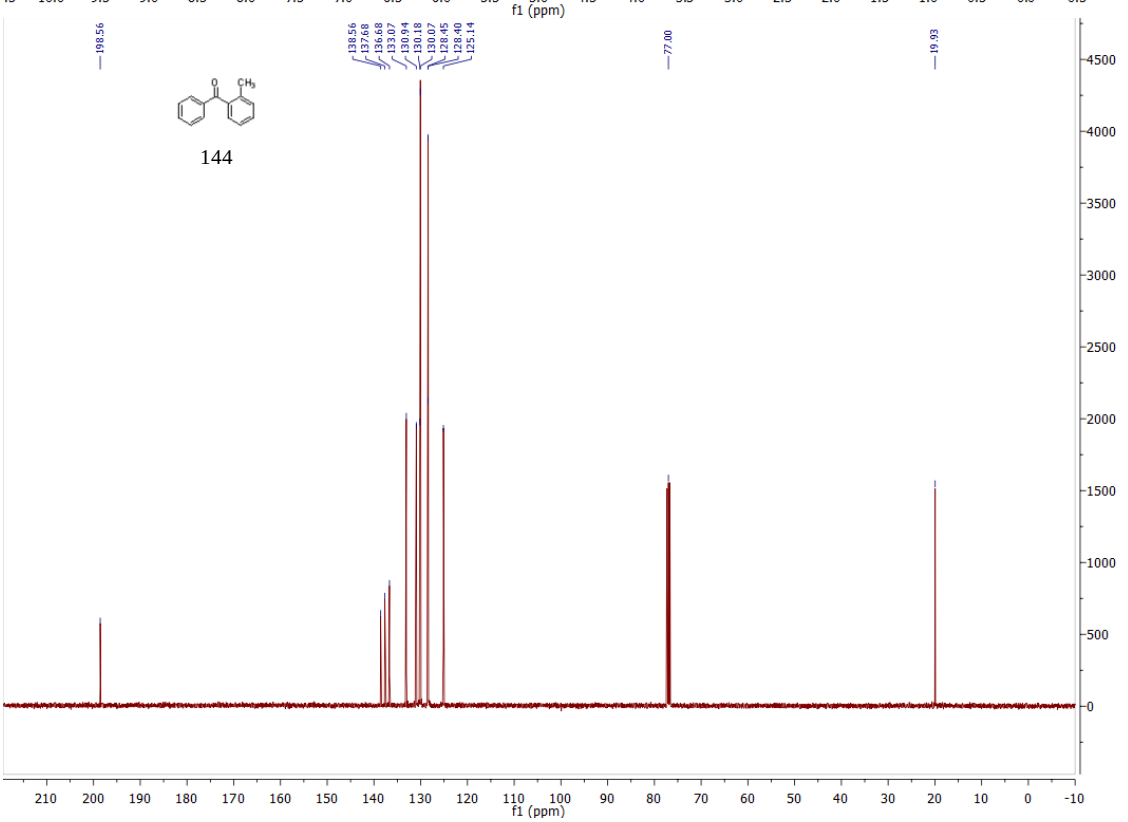

142
4.00
2.13
3.98
f1 (ppm)

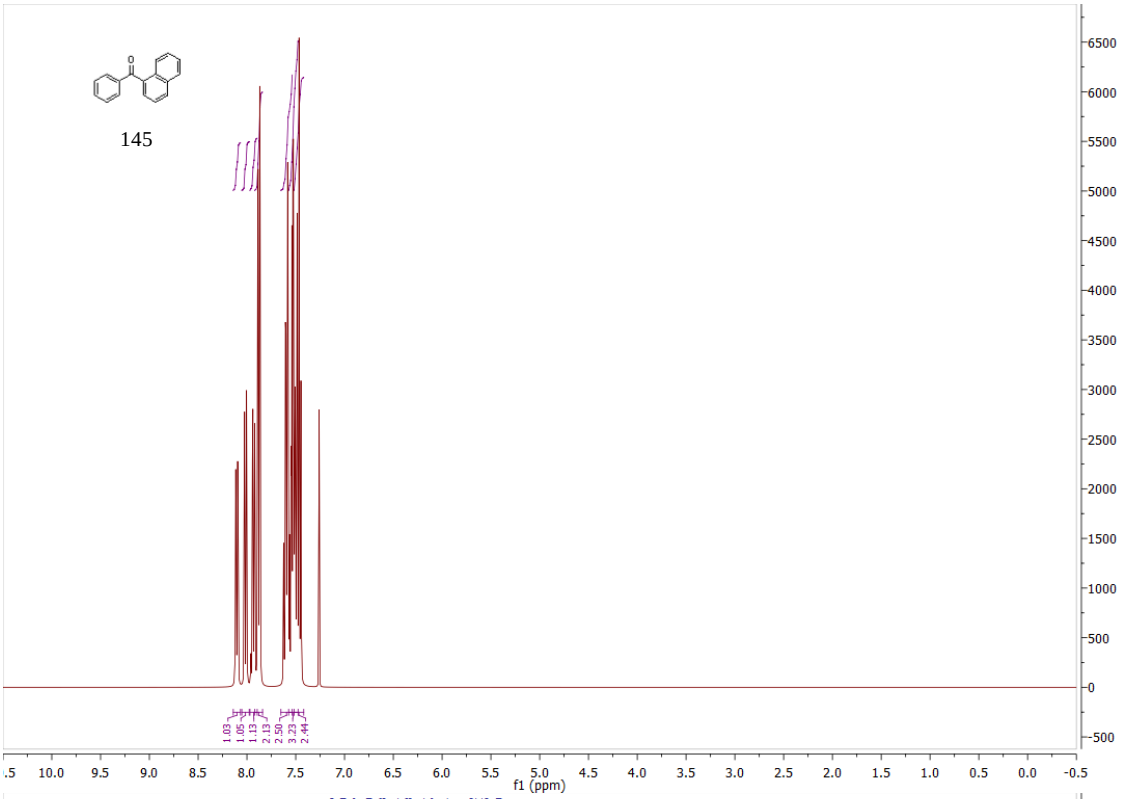

196.65
137.52
132.34
129.98
128.21
77.00
142
f1 (ppm)

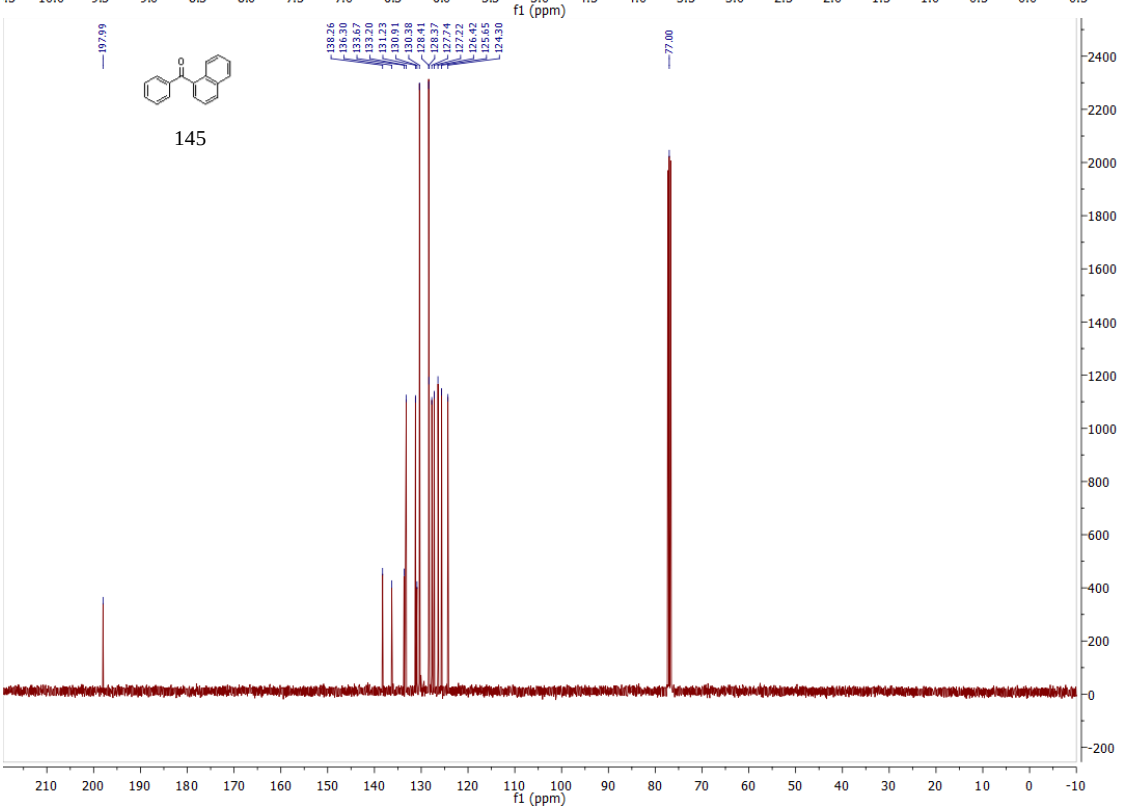

143
2.04
1.99
1.05
2.08
1.98
3.00
f1 (ppm)

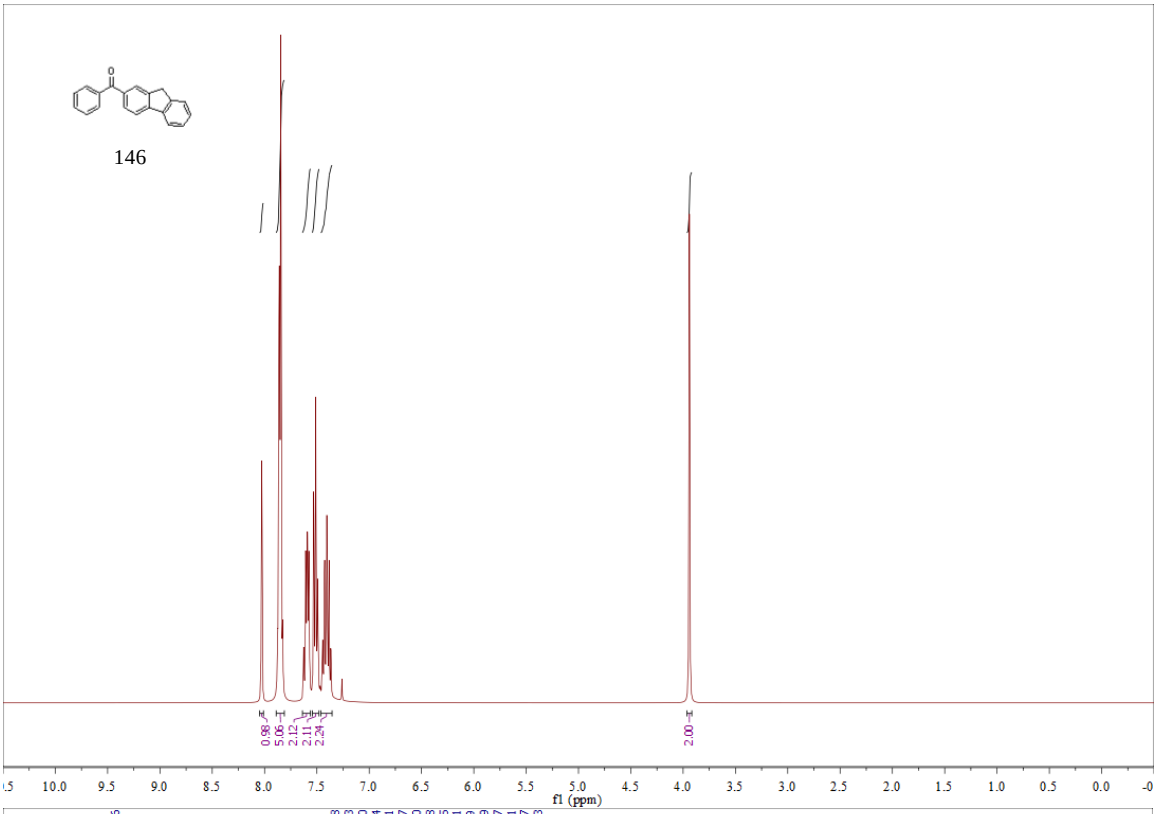

196.47
143.20
137.91
134.83
132.12
130.27
129.89
128.93
128.17
77.00
21.63
143
f1 (ppm)

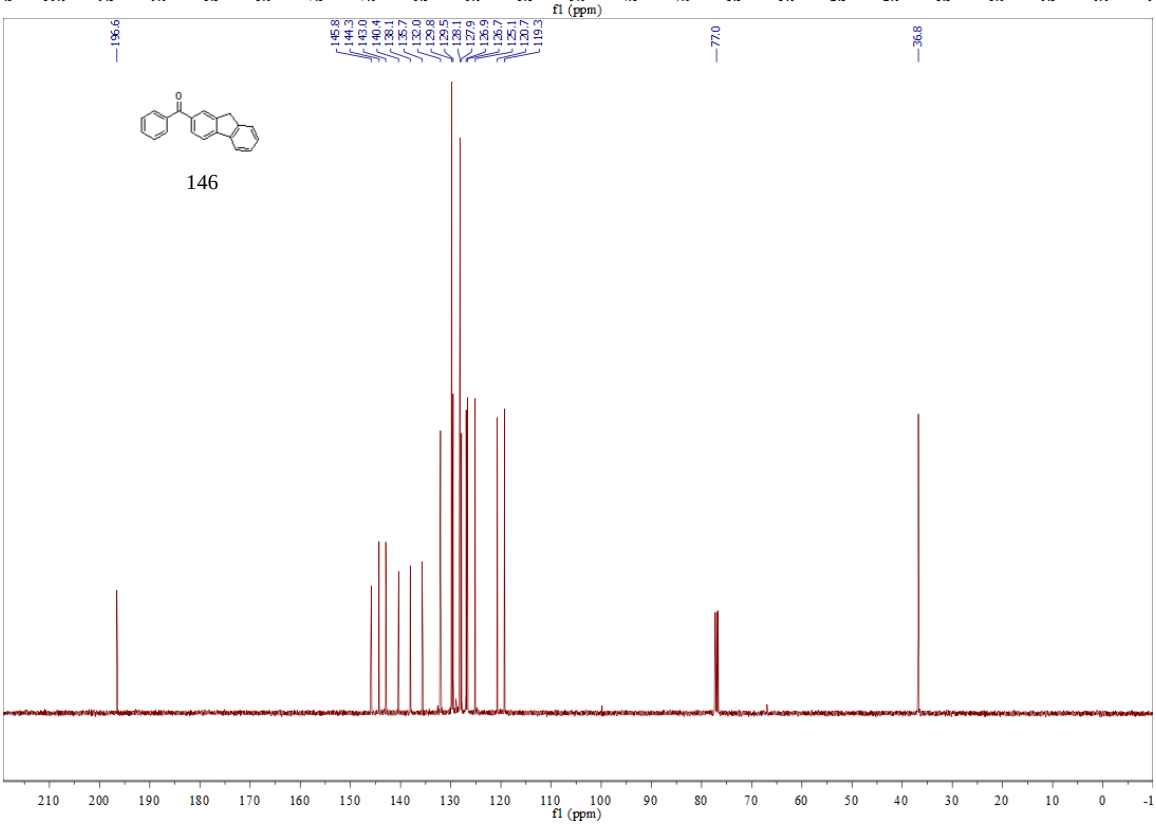

144
1.99
1.03
2.03
1.01
3.10
3.00
f1 (ppm)

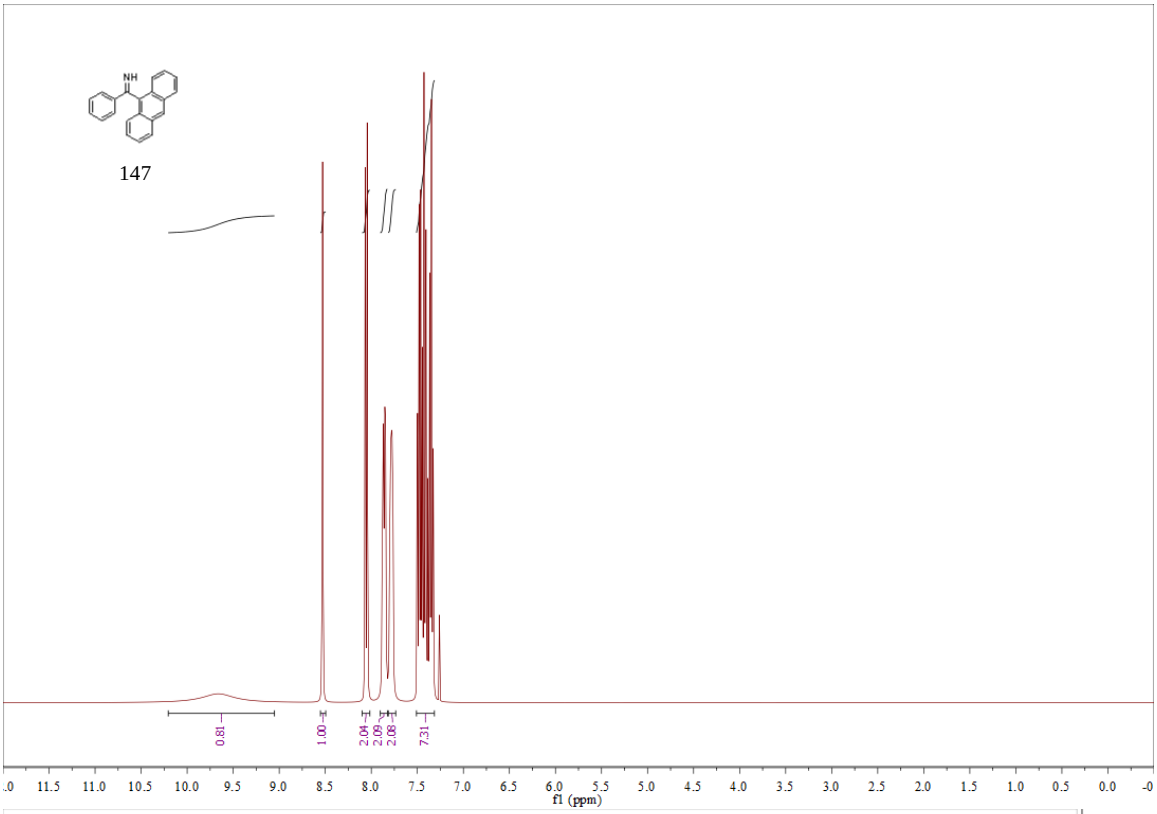

198.56
138.56
137.68
136.68
133.07
130.94
130.18
130.07
128.45
128.40
125.14
77.00
19.93
144
f1 (ppm)

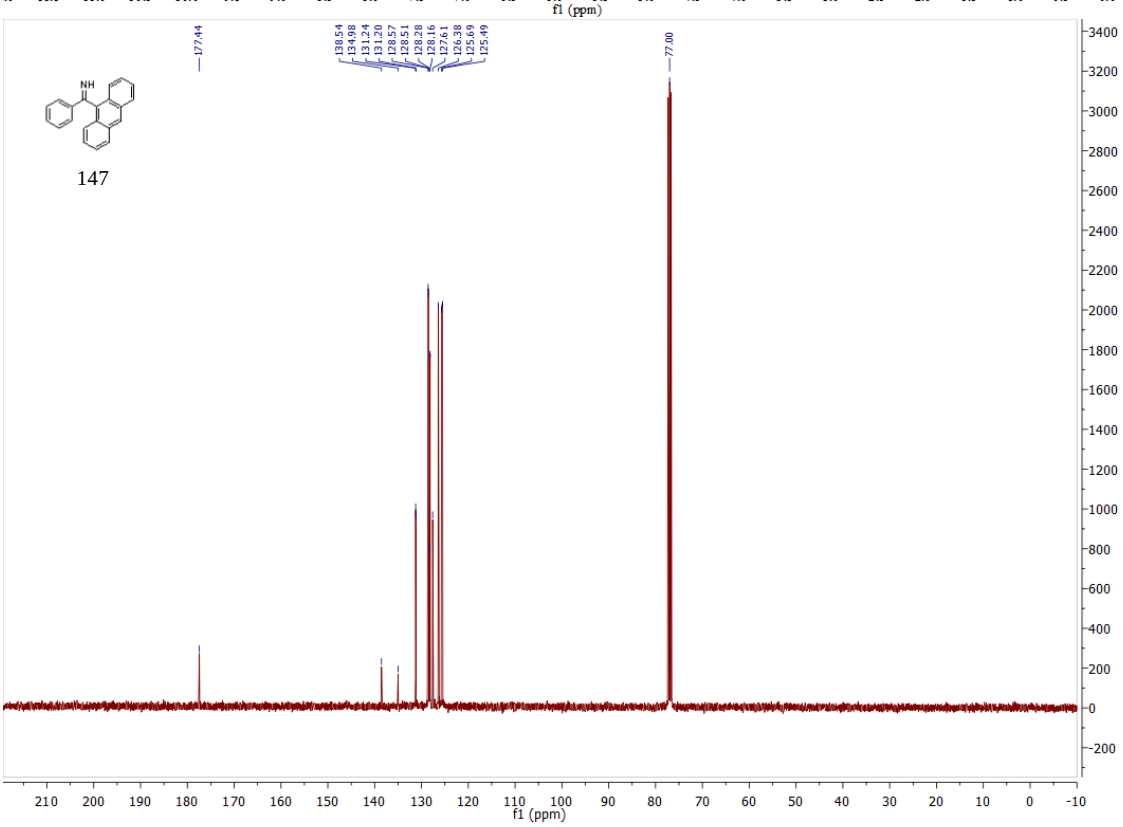

145
1.03
1.05
1.13
2.13
2.50
3.23
2.44
f1 (ppm)

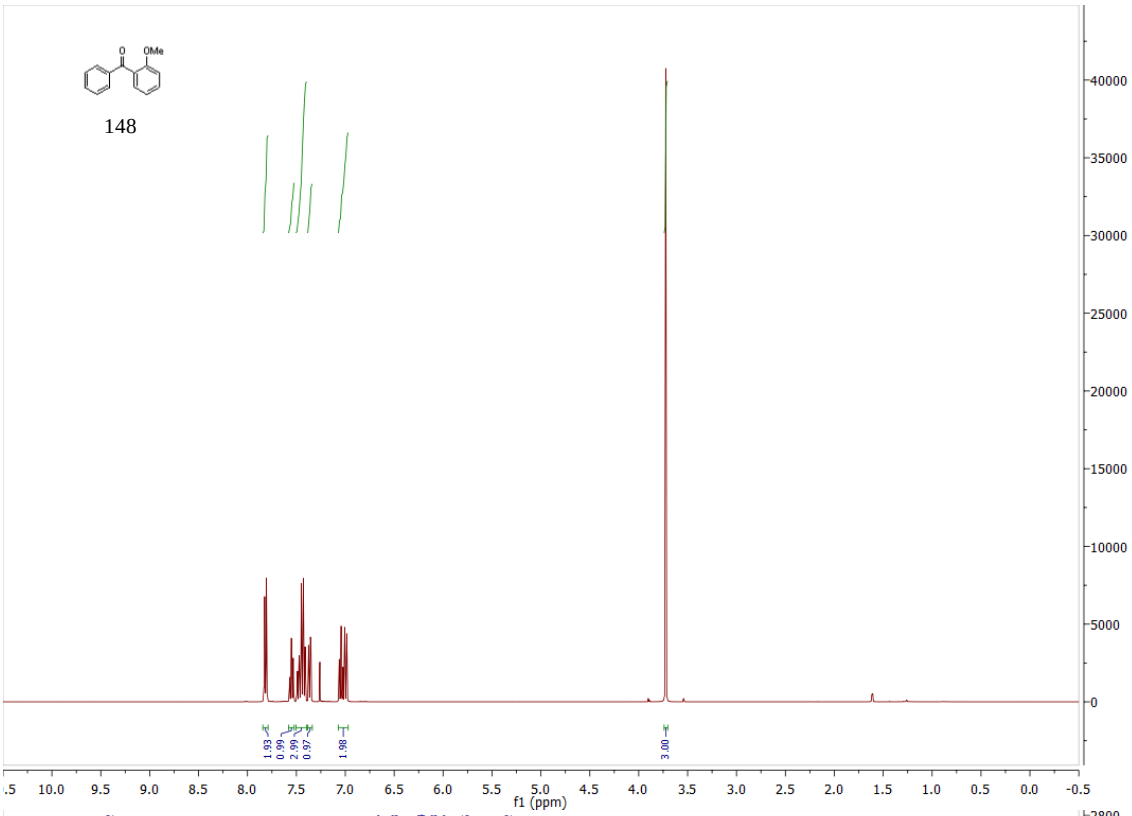

197.99
138.26
136.30
133.67
133.20
131.23
130.91
130.38
128.41
128.37
127.74
127.22
126.42
125.65
124.30
77.00
145
f1 (ppm)

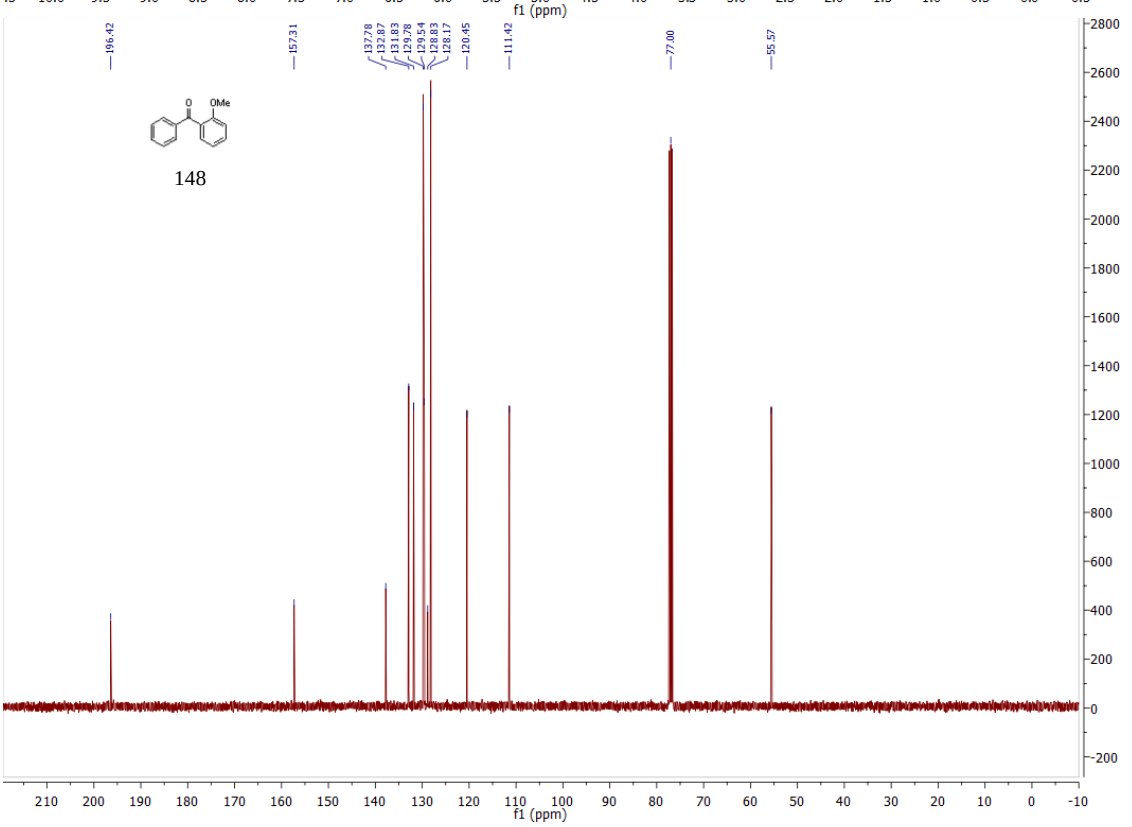

146
0.98
5.06
2.12
2.11
2.24
2.00
f1 (ppm)

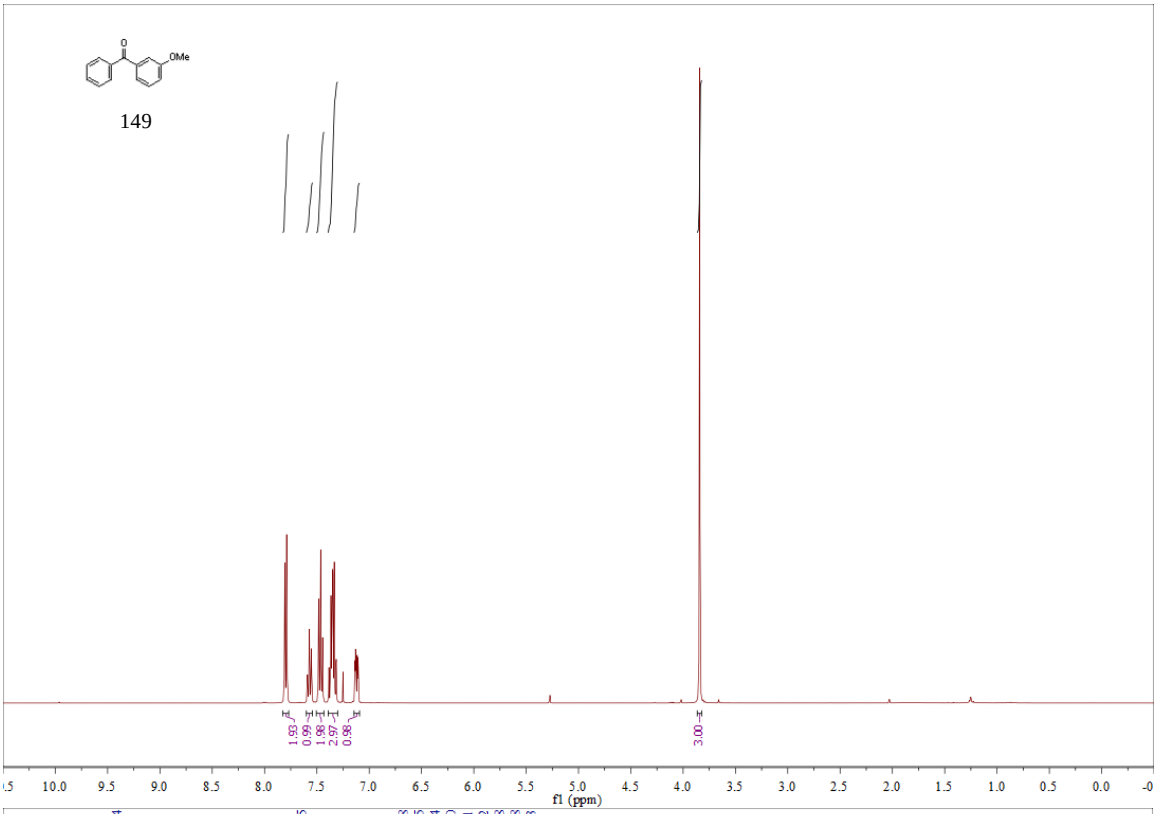

196.6
145.8
144.3
143.0
140.4
138.1
135.7
132.0
129.8
129.5
128.1
127.9
126.9
126.7
125.1
120.7
119.3
77.0
36.8
146
f1 (ppm)

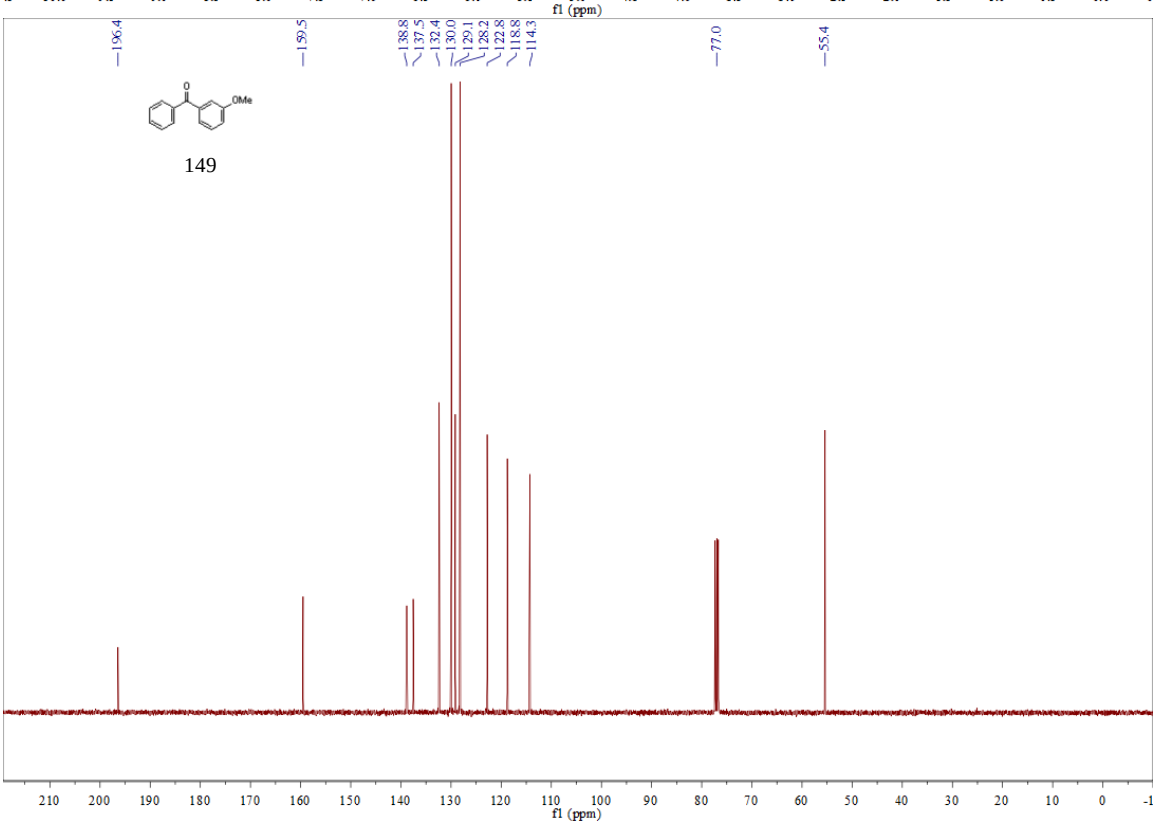

NH
147
0.81
1.00
2.04
2.09
2.08
7.31
f1 (ppm)

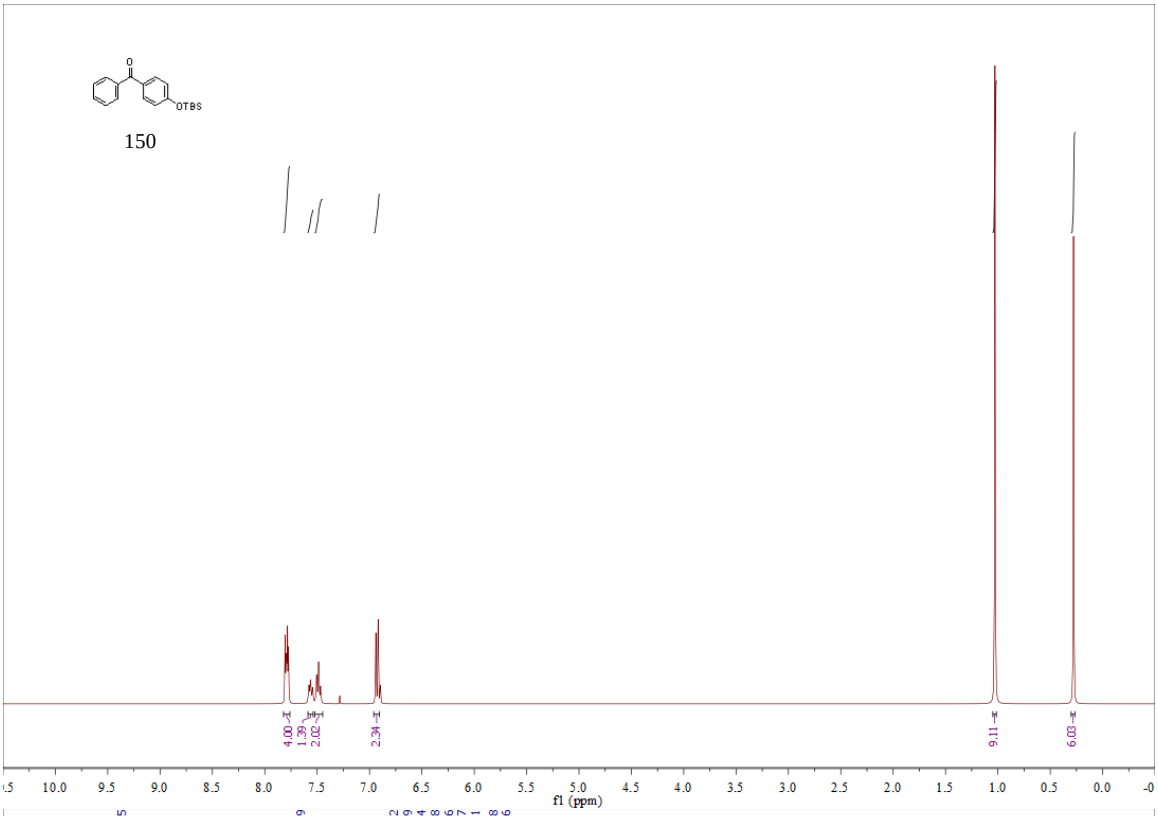

NH
147
177.44
138.54
134.98
131.24
131.20
128.57
128.51
128.28
128.16
127.61
126.38
125.60
125.49
77.00
f1 (ppm)

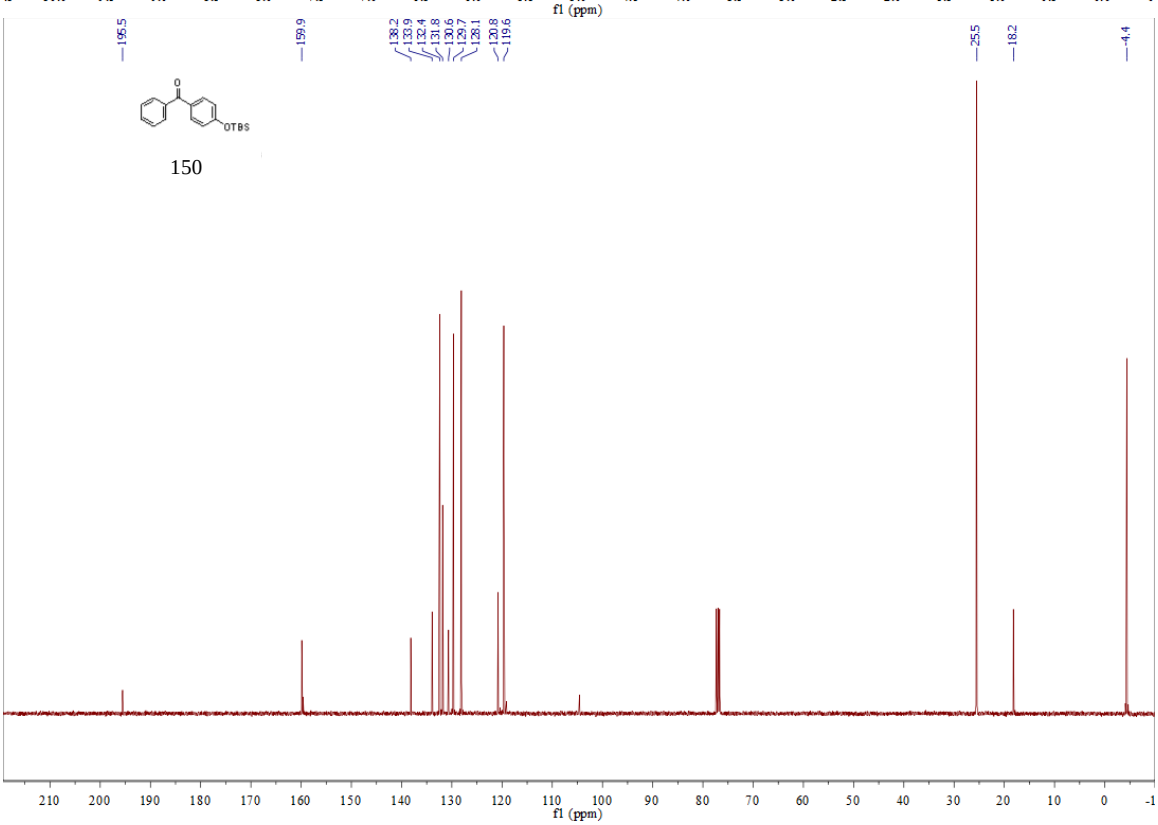

148
1.93
0.99
2.99
0.97
1.98
3.00
f1 (ppm)

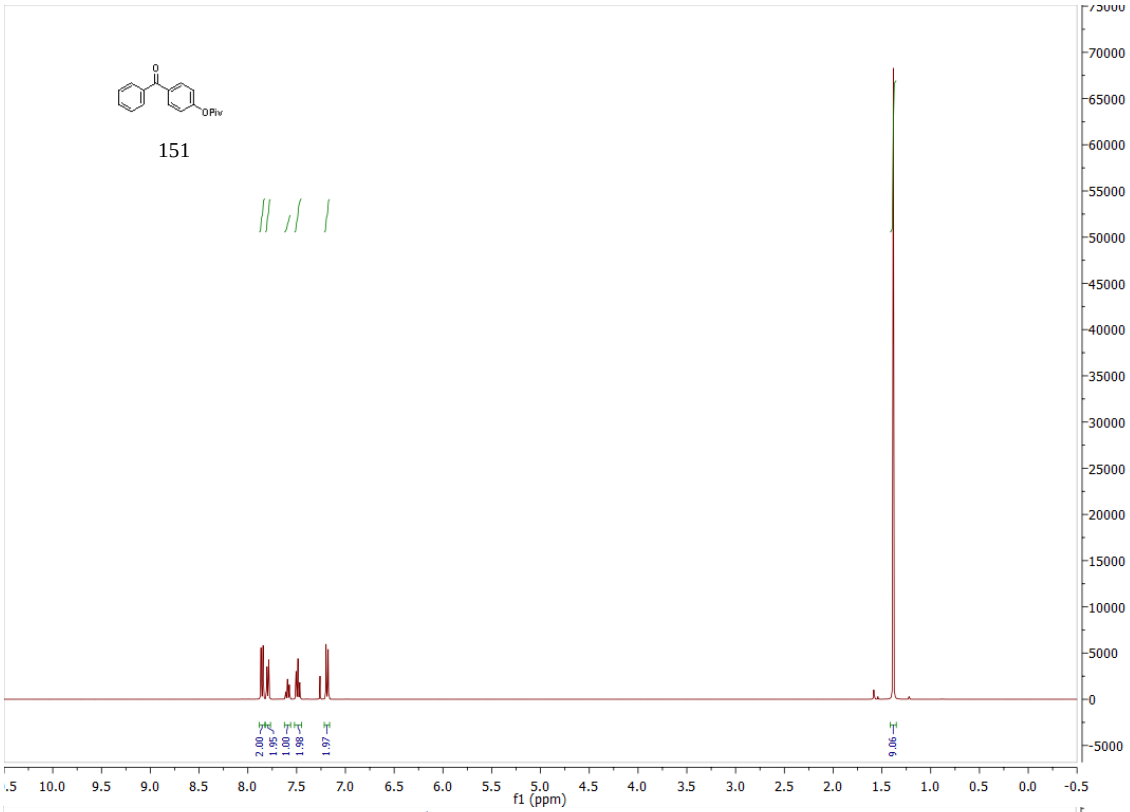

196.42
157.31
137.78
132.87
131.83
129.78
129.54
128.83
128.17
120.45
111.42
77.00
55.57
148
f1 (ppm)


OMe
149
1.93
0.99
1.98
2.97
0.98
3.00
f1 (ppm)

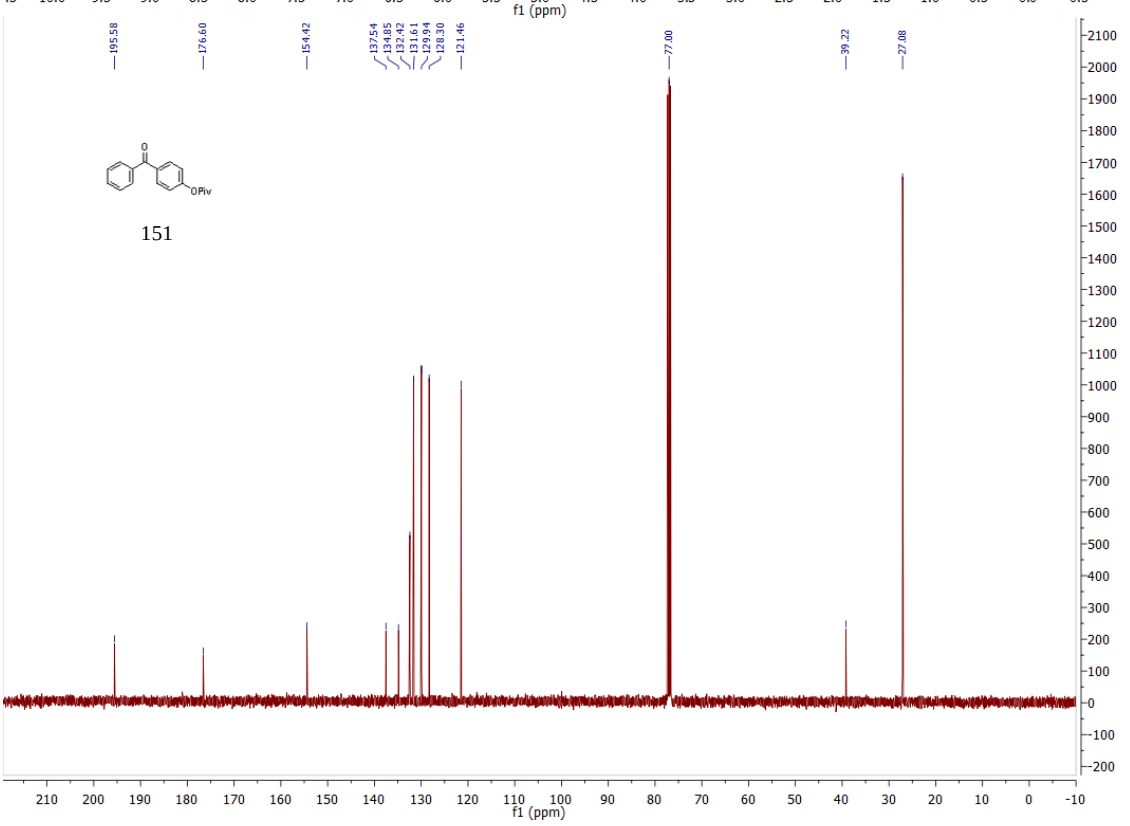

196.4
159.5
138.8
137.5
132.4
130.0
129.1
128.2
122.8
118.8
114.3
77.0
55.4
OMe
149
f1 (ppm)


OTBS
150
4.00
1.39
2.02
2.34
9.11
6.03
f1 (ppm)

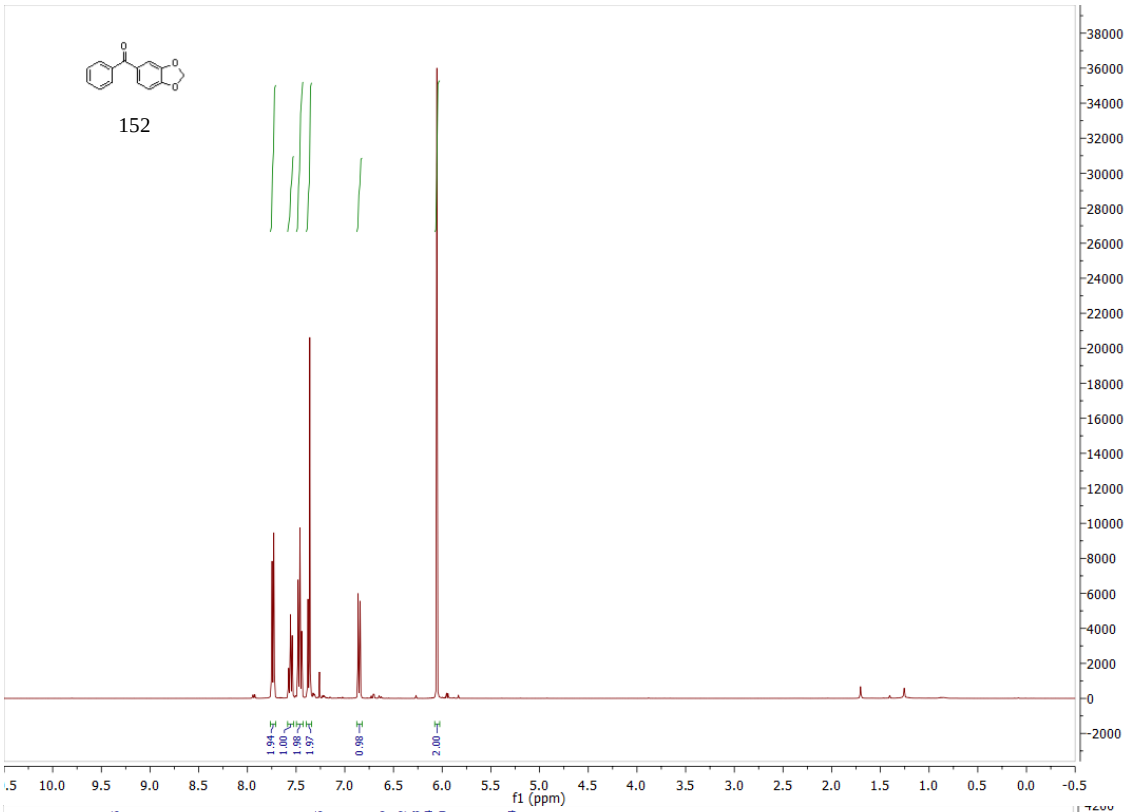

195.5
159.9
138.2
133.9
132.4
131.8
130.6
129.7
128.1
120.8
119.6
25.5
18.2
-4.4
OTBS
150
f1 (ppm)

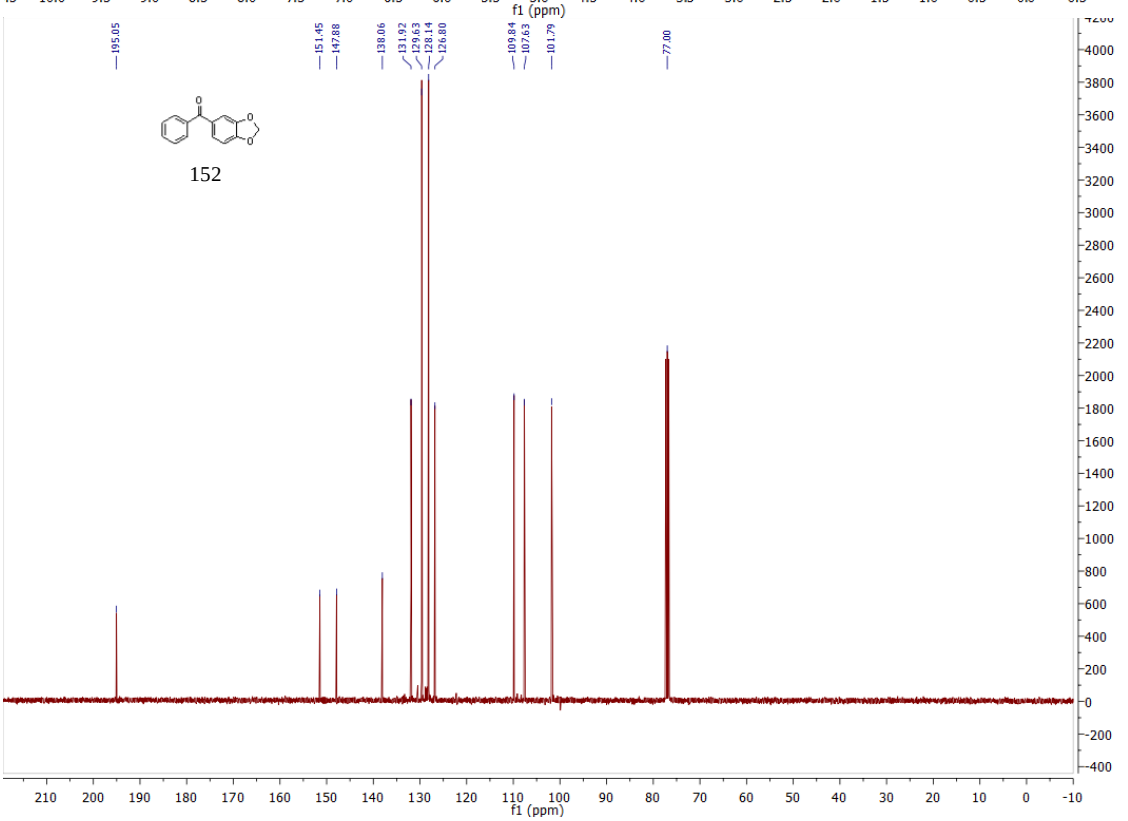

OPiv
2.00
1.95
1.00
1.98
1.97
9.06
f1 (ppm)

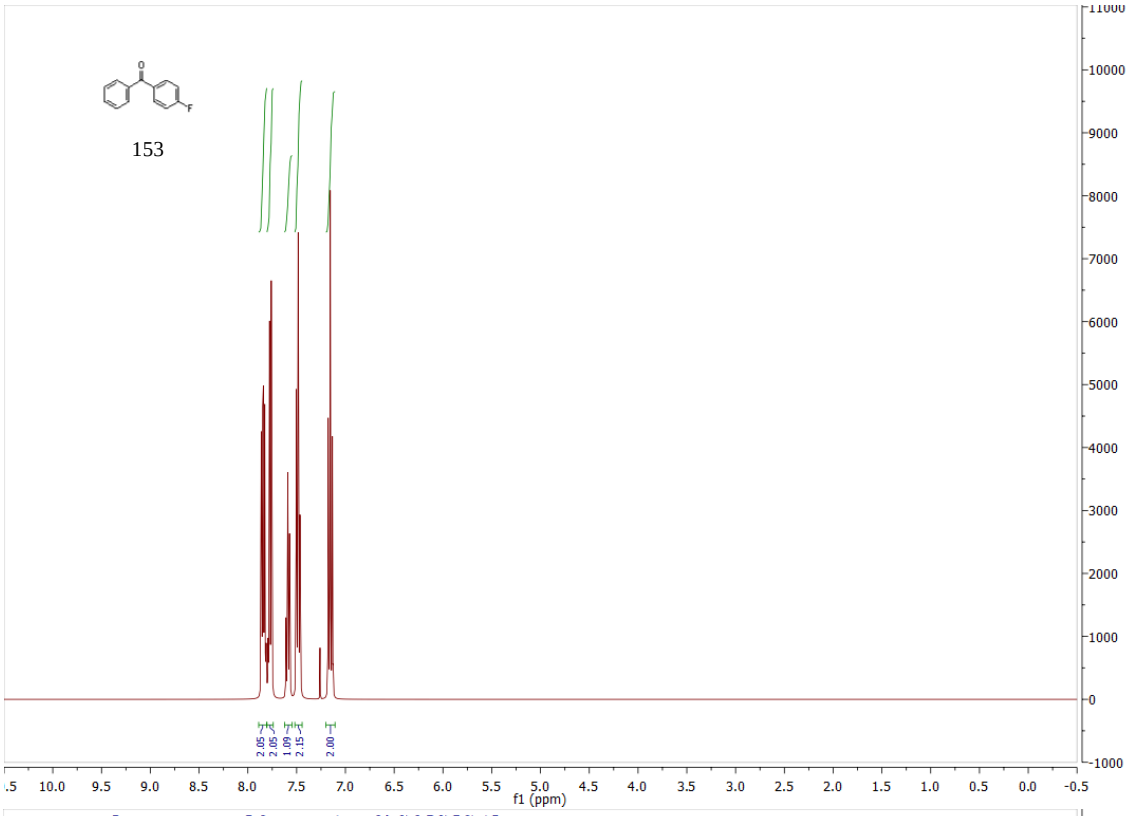
151

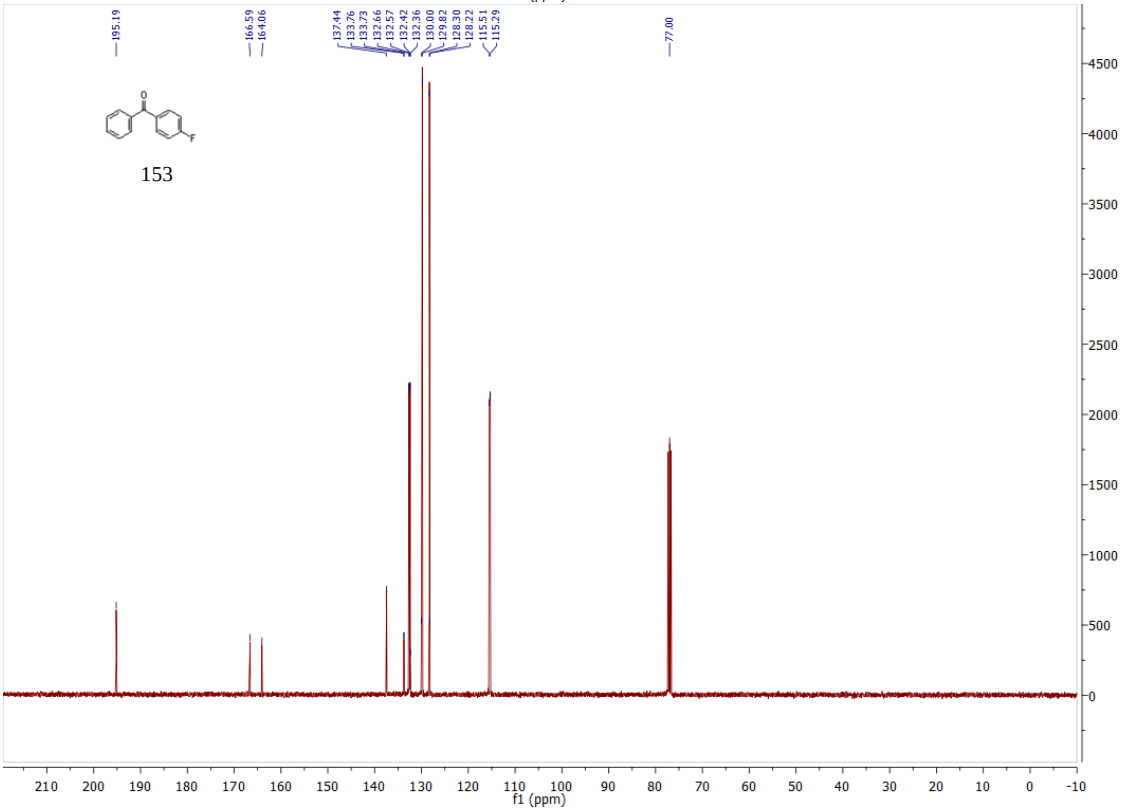

195.58
176.60
154.42
137.54
134.65
132.22
131.61
129.94
128.30
121.46
77.00
39.22
27.08
OPiv
f1 (ppm)

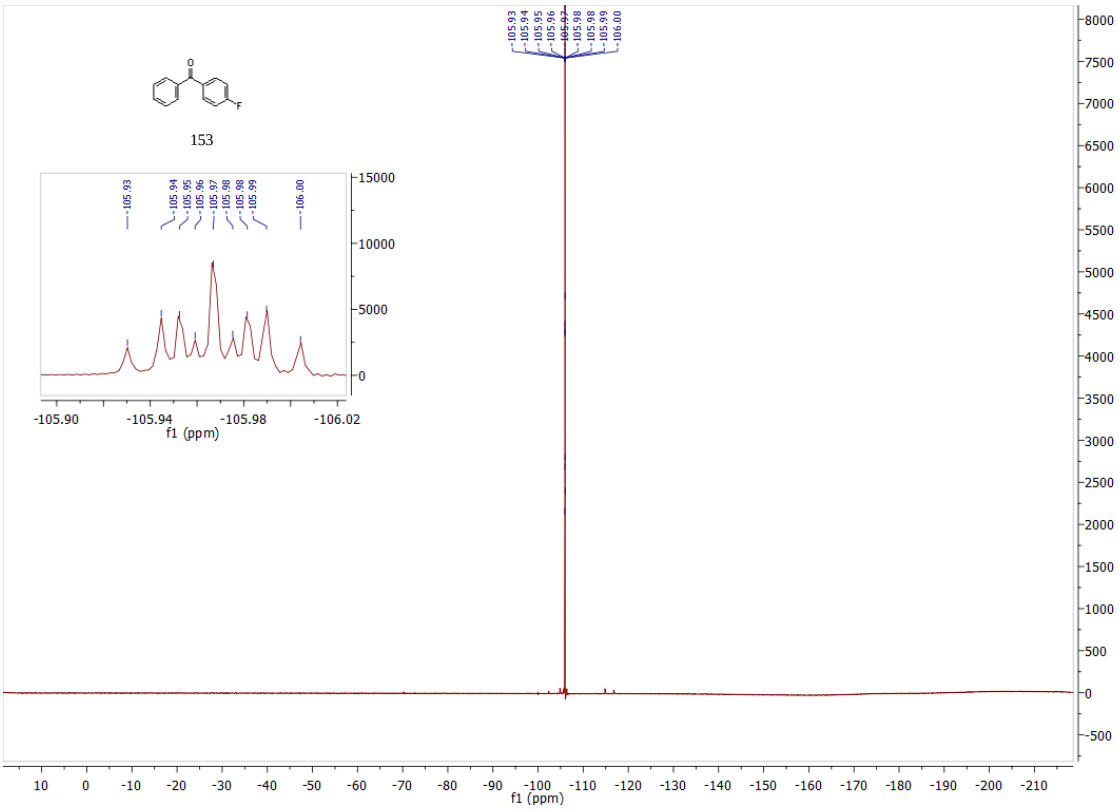
151

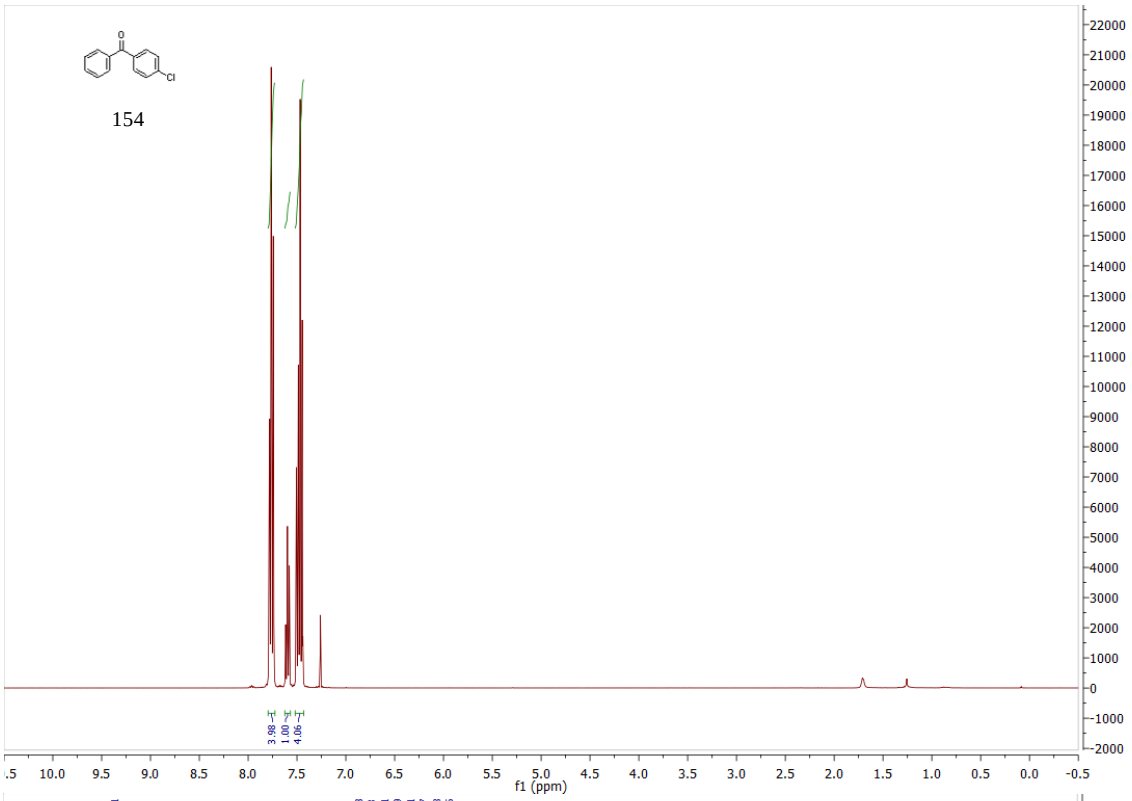

152
1.94
1.00
1.98
1.97
0.98
2.00
f1 (ppm)

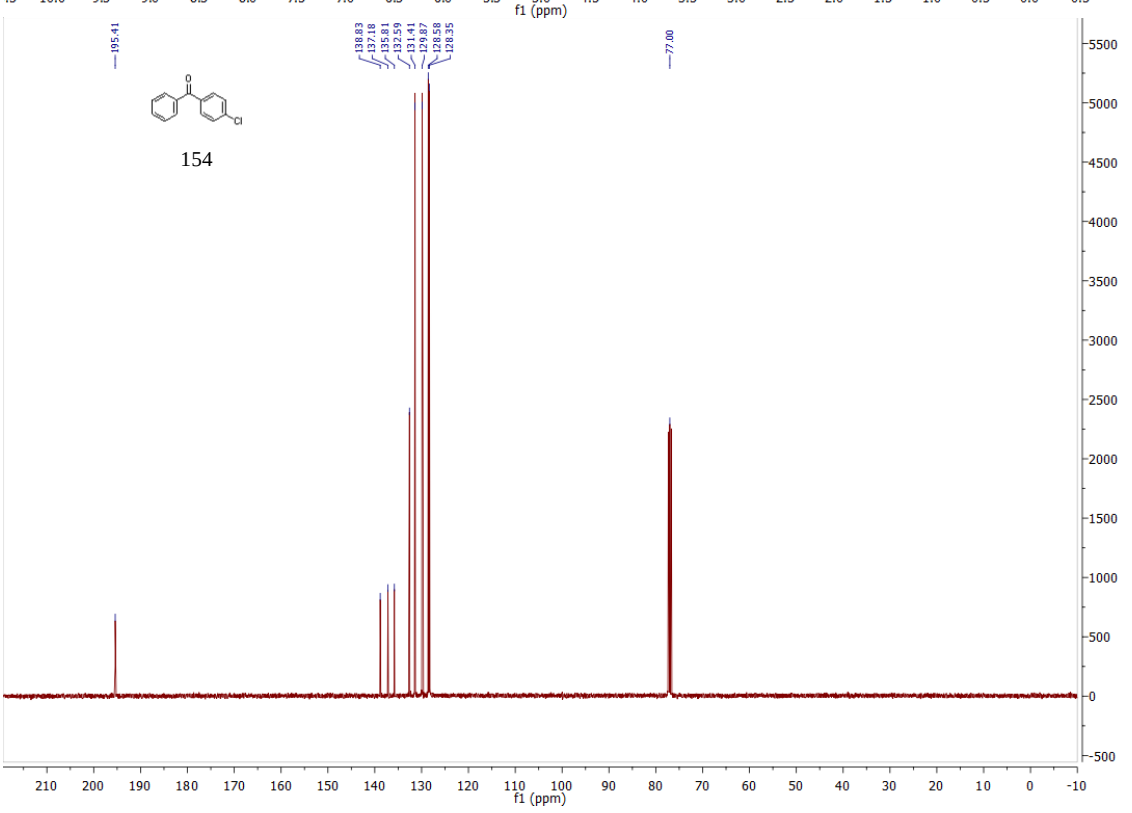

195.05
151.45
147.88
138.06
131.92
129.63
128.14
126.80
109.84
107.63
101.79
77.00
152
f1 (ppm)

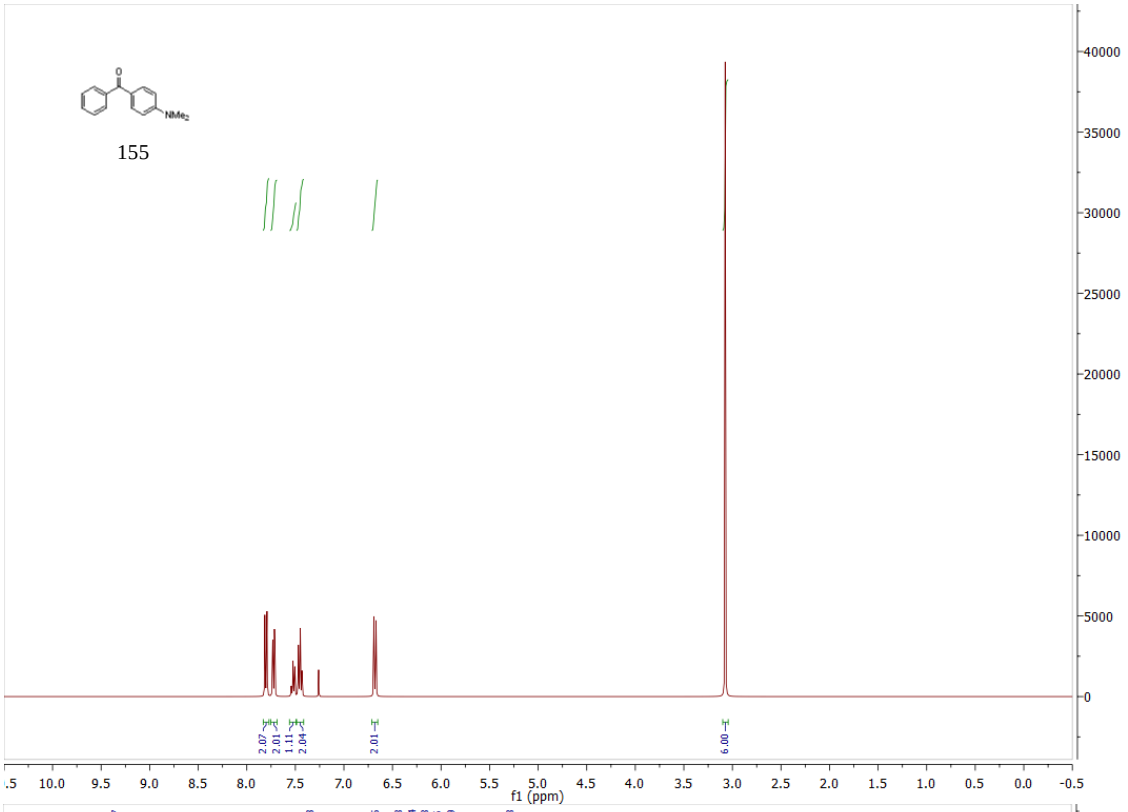

153
2.05
2.05
1.09
2.15
2.00
f1 (ppm)

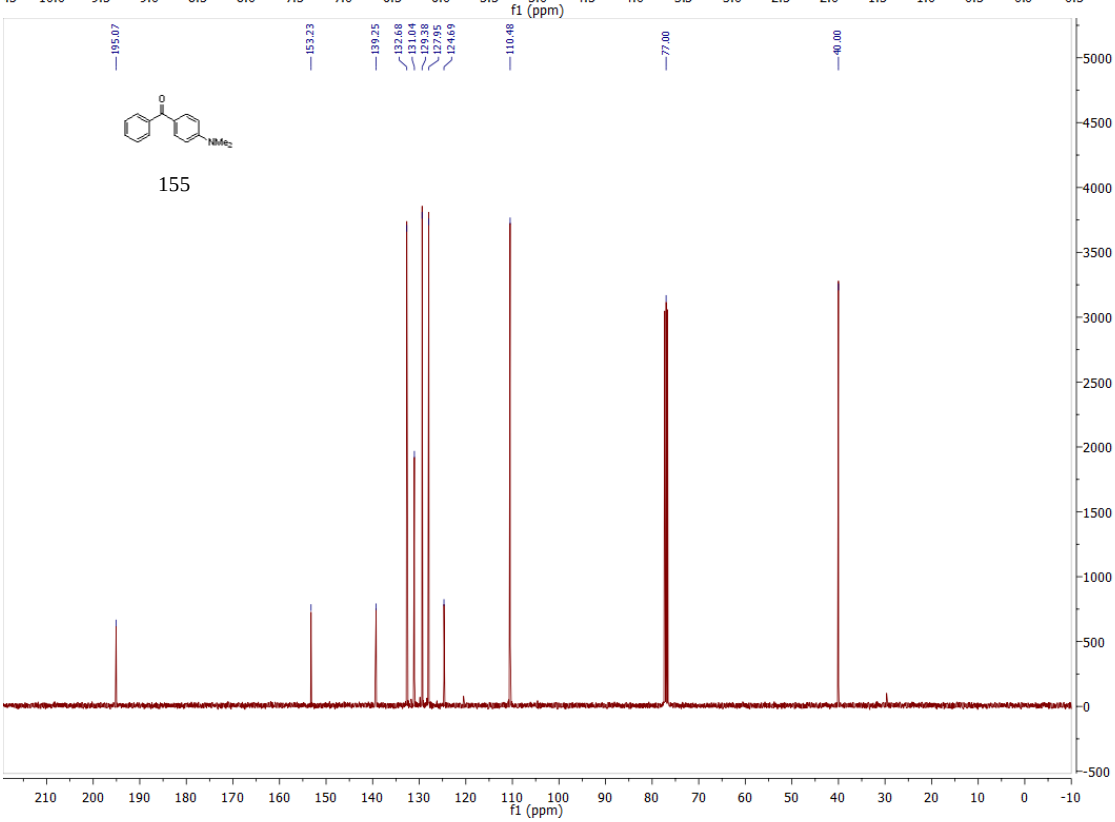

195.19
166.59
164.06
137.44
133.76
133.73
132.66
132.57
132.42
132.36
130.00
129.92
128.83
128.22
115.51
115.29
77.00
153
f1 (ppm)

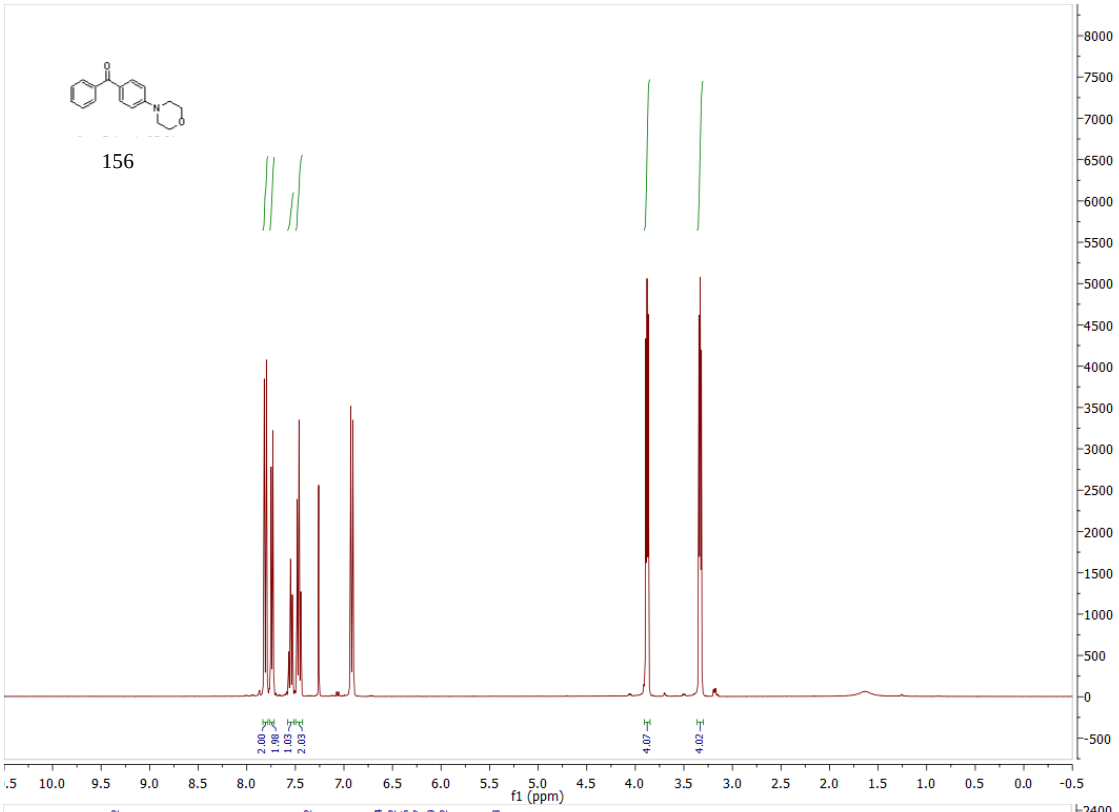

153
-105.93
-105.94
-105.95
-105.96
-105.97
-105.98
-105.98
-105.99
-106.00
f1 (ppm)
f1 (ppm)

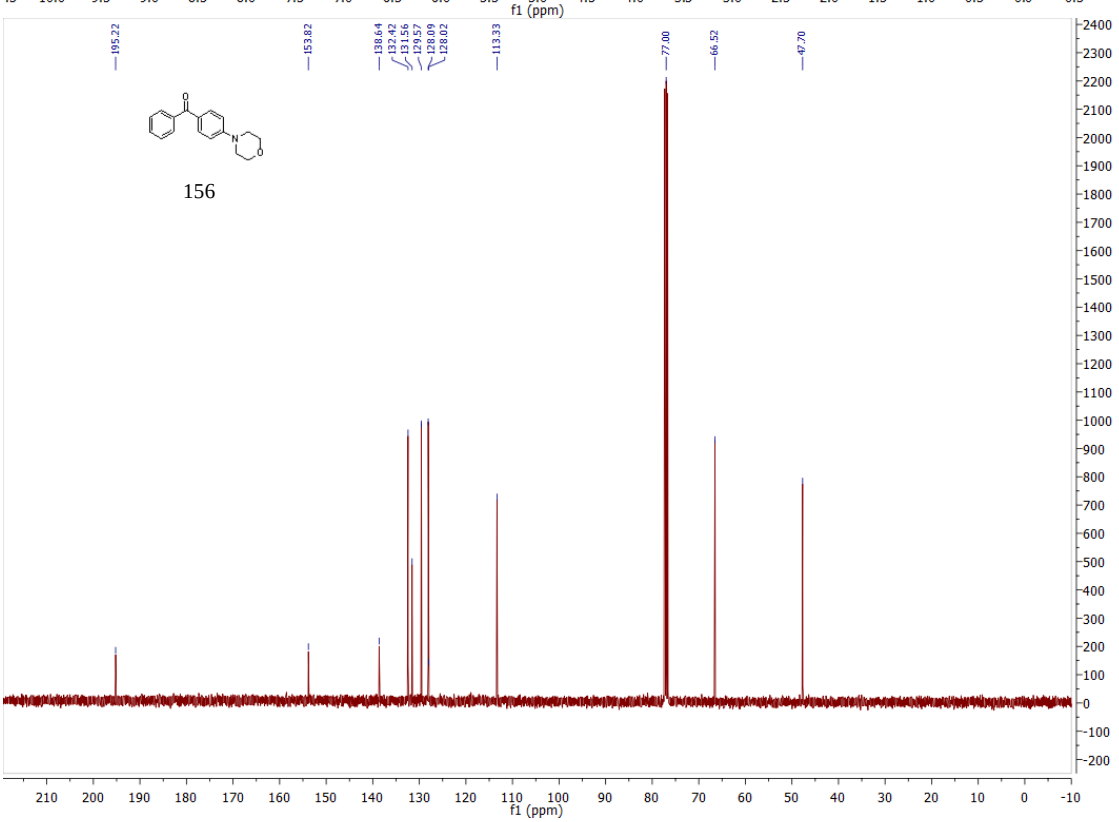

154
3.98
1.00
4.06
f1 (ppm)

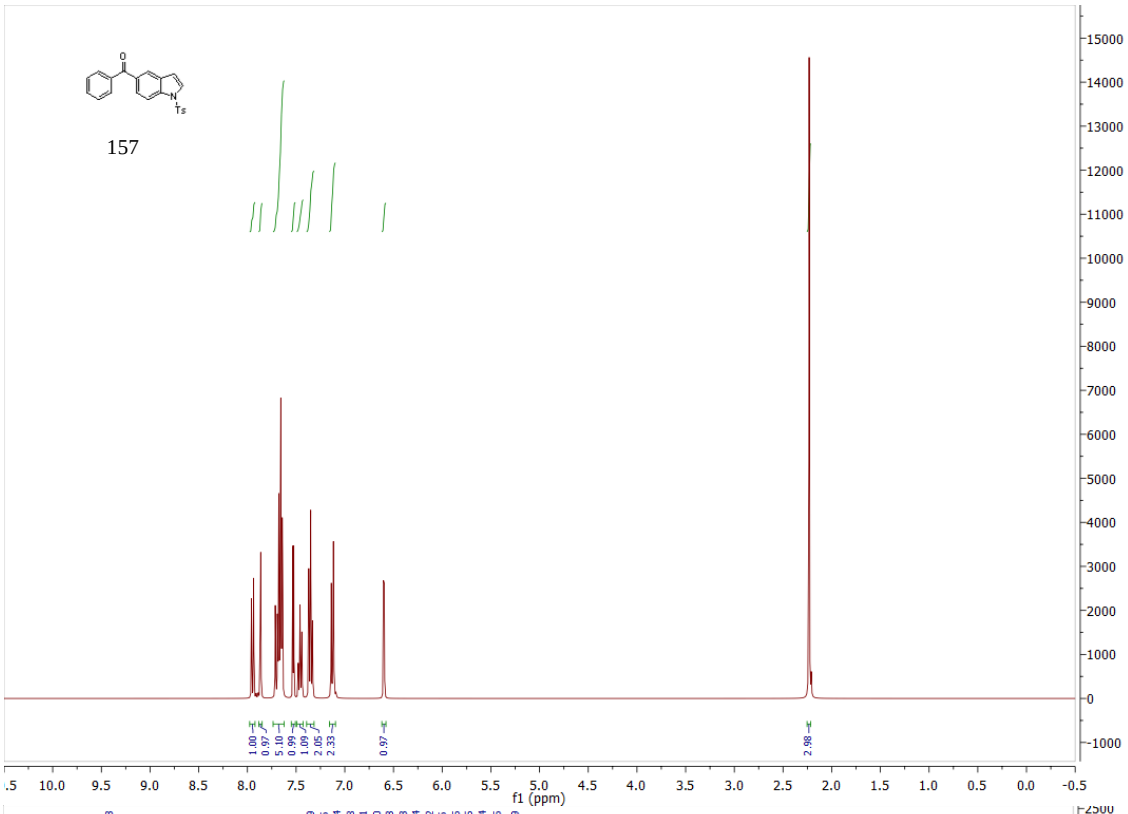

195.41
138.83
137.18
135.81
132.59
131.41
129.87
128.58
128.35
77.00
154
f1 (ppm)

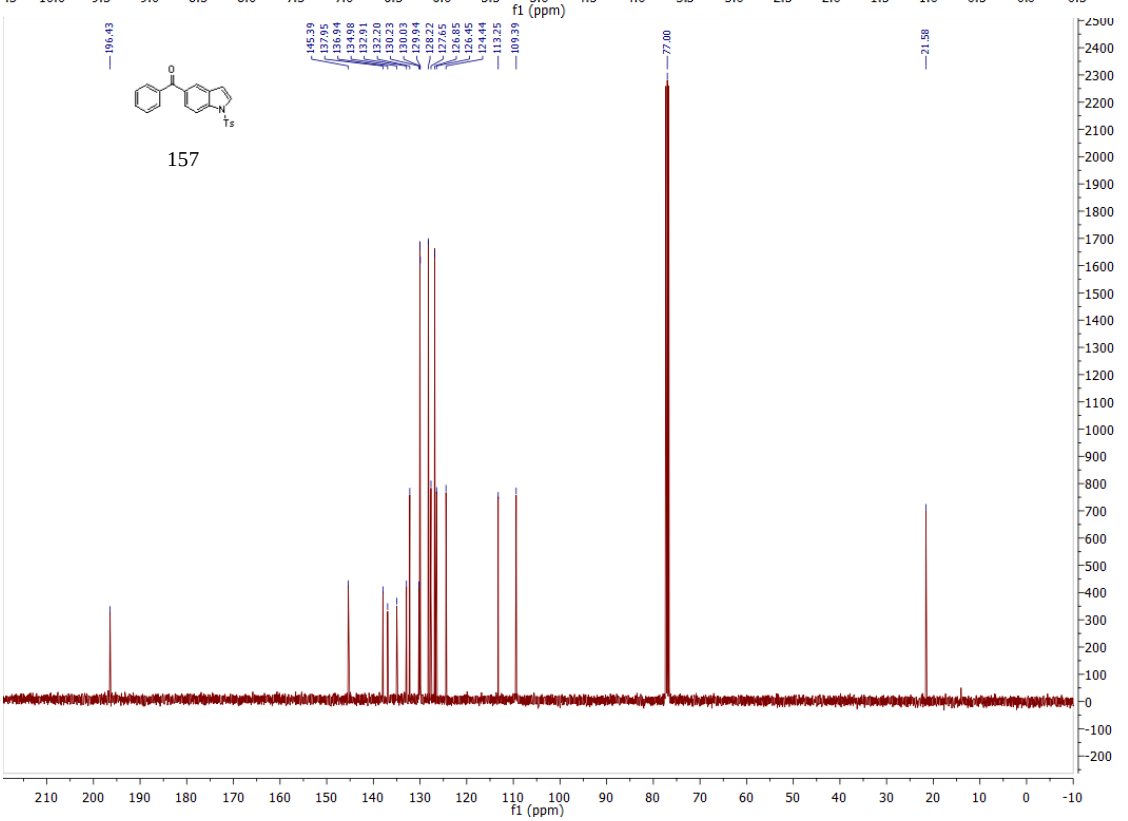

155
2.07
2.01
1.11
2.04
2.01
6.00
f1 (ppm)

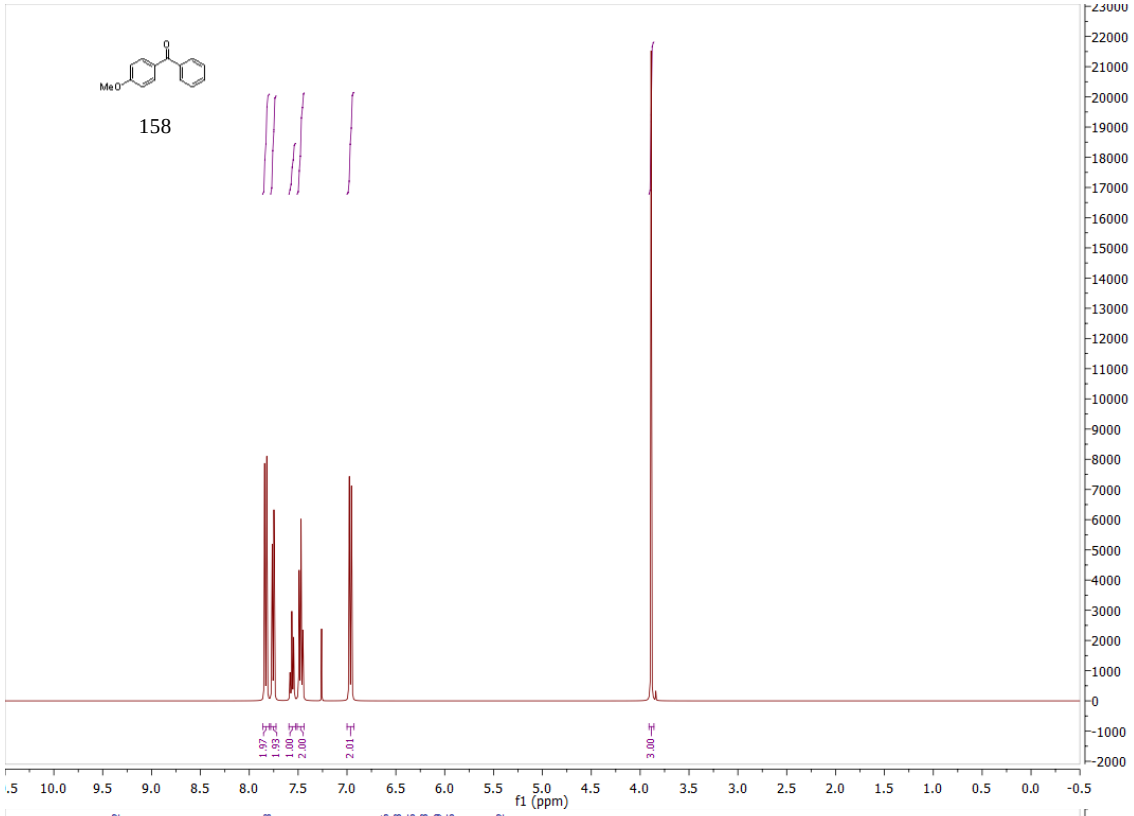

195.07
153.23
139.25
132.68
131.04
129.38
127.95
124.69
110.48
77.00
40.00
155
f1 (ppm)

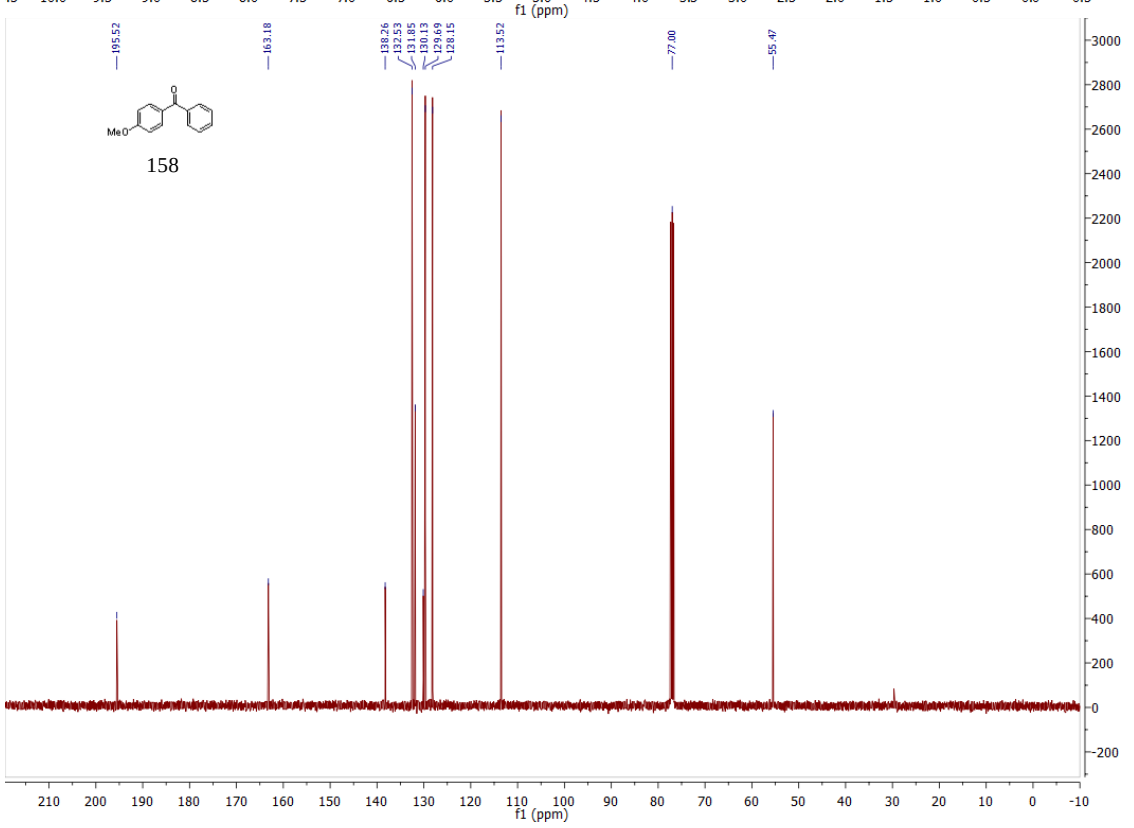

156
2.00
1.98
1.03
2.03
4.07
4.02
f1 (ppm)

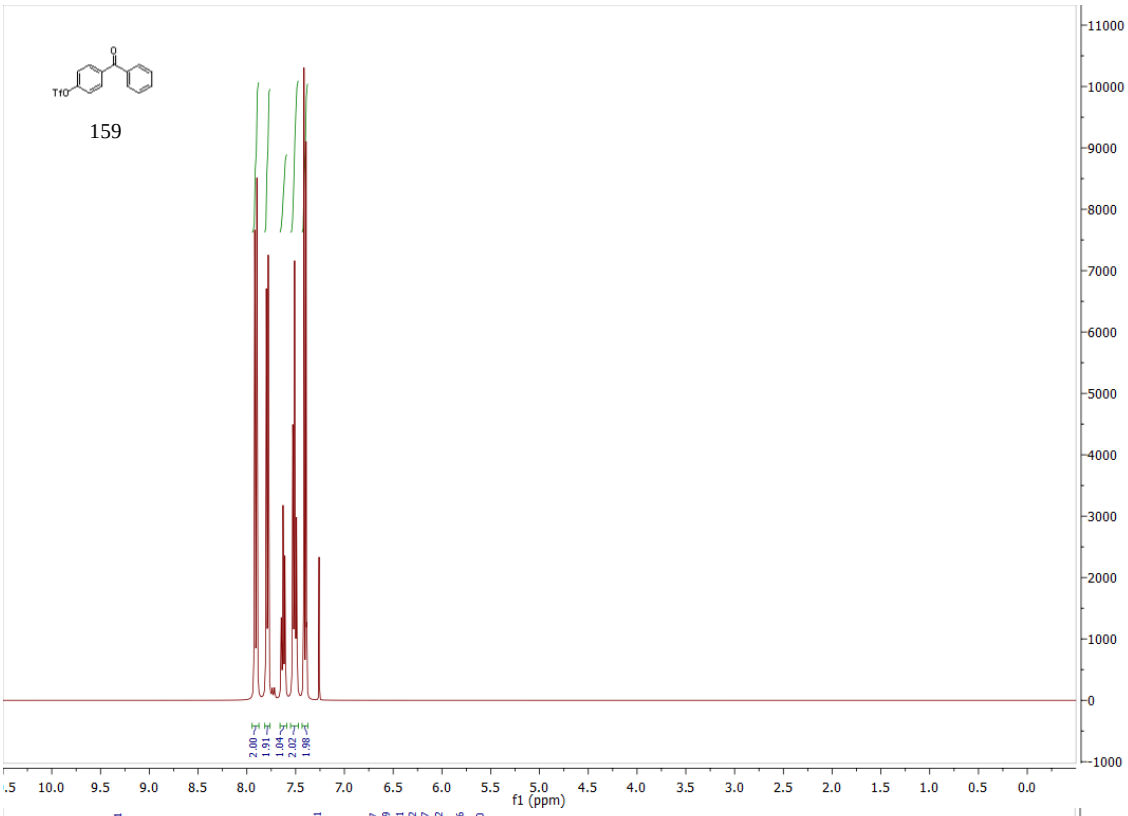

195.22
153.82
138.64
132.42
131.56
129.57
128.09
128.02
113.33
77.00
66.52
47.70
156
f1 (ppm)

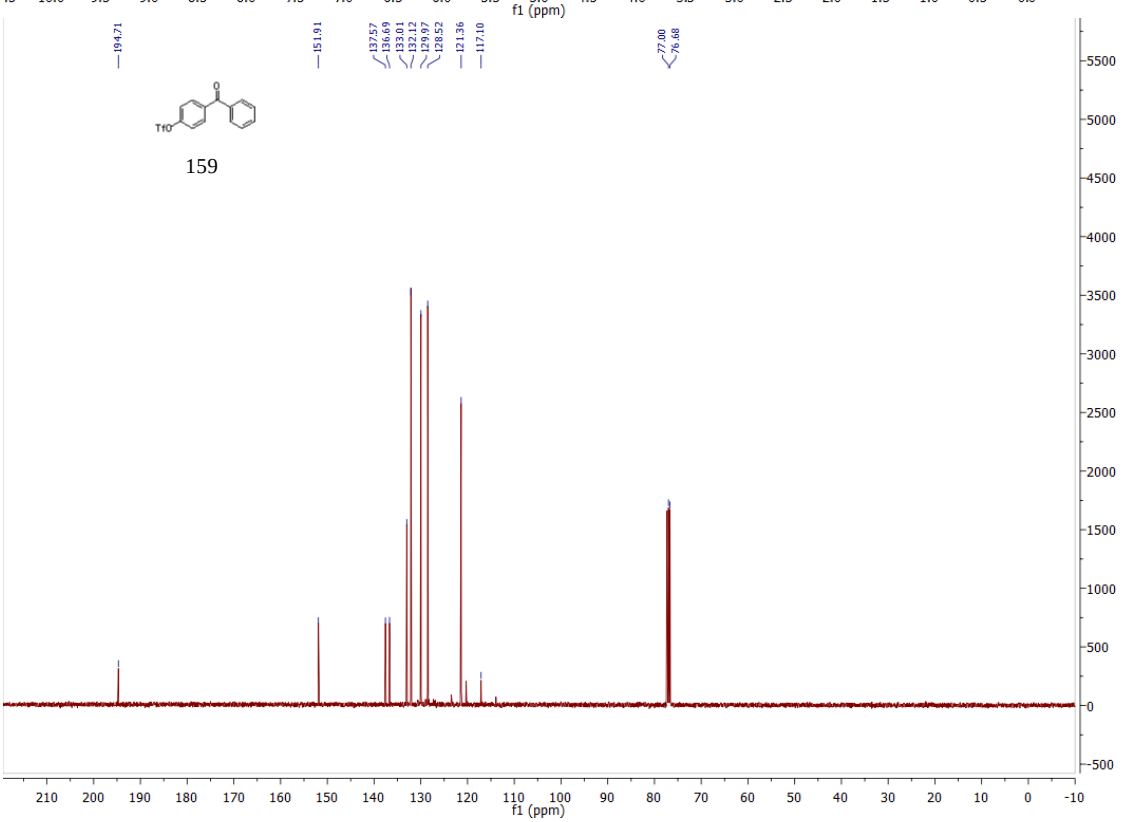

157
1.00
0.97
5.10
0.99
1.09
2.05
2.33
0.97
2.98
f1 (ppm)

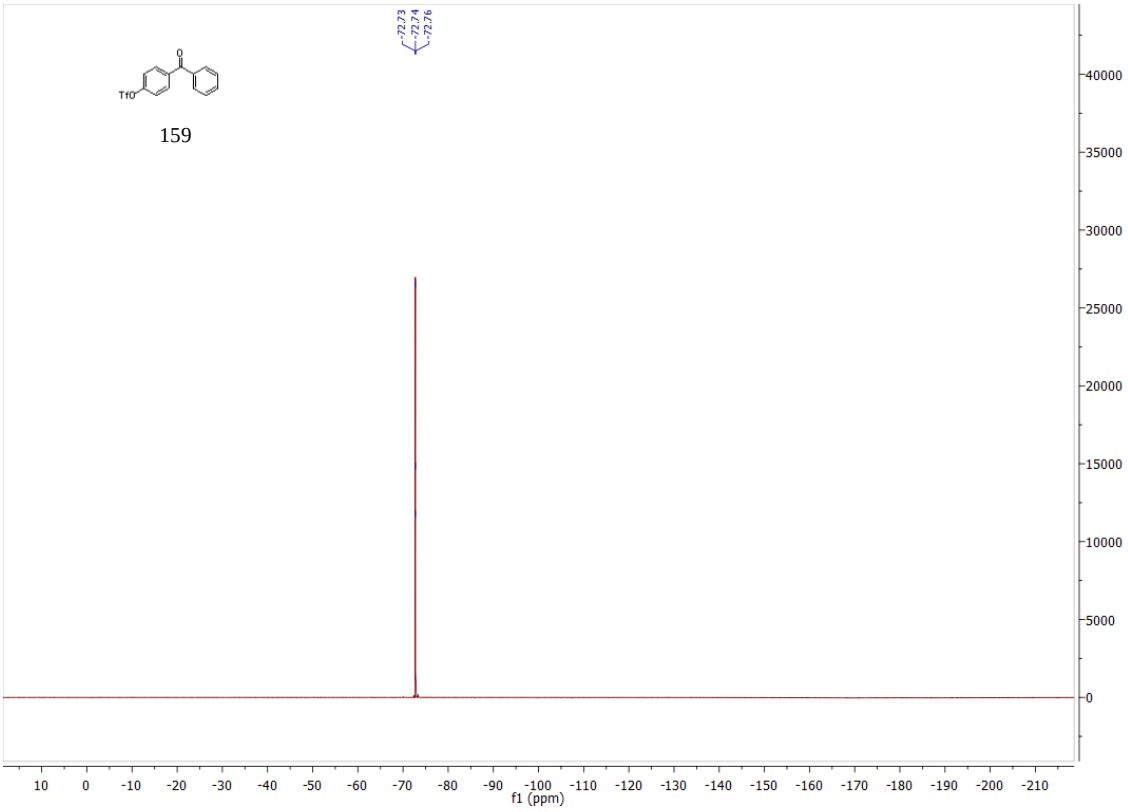

196.43
145.39
137.95
136.94
134.98
132.91
132.20
130.23
130.03
129.94
128.22
127.65
126.85
126.45
124.44
113.25
109.39
77.00
21.58
157
f1 (ppm)


MeO
158
1.97
1.93
1.00
2.00
2.01
3.00
f1 (ppm)

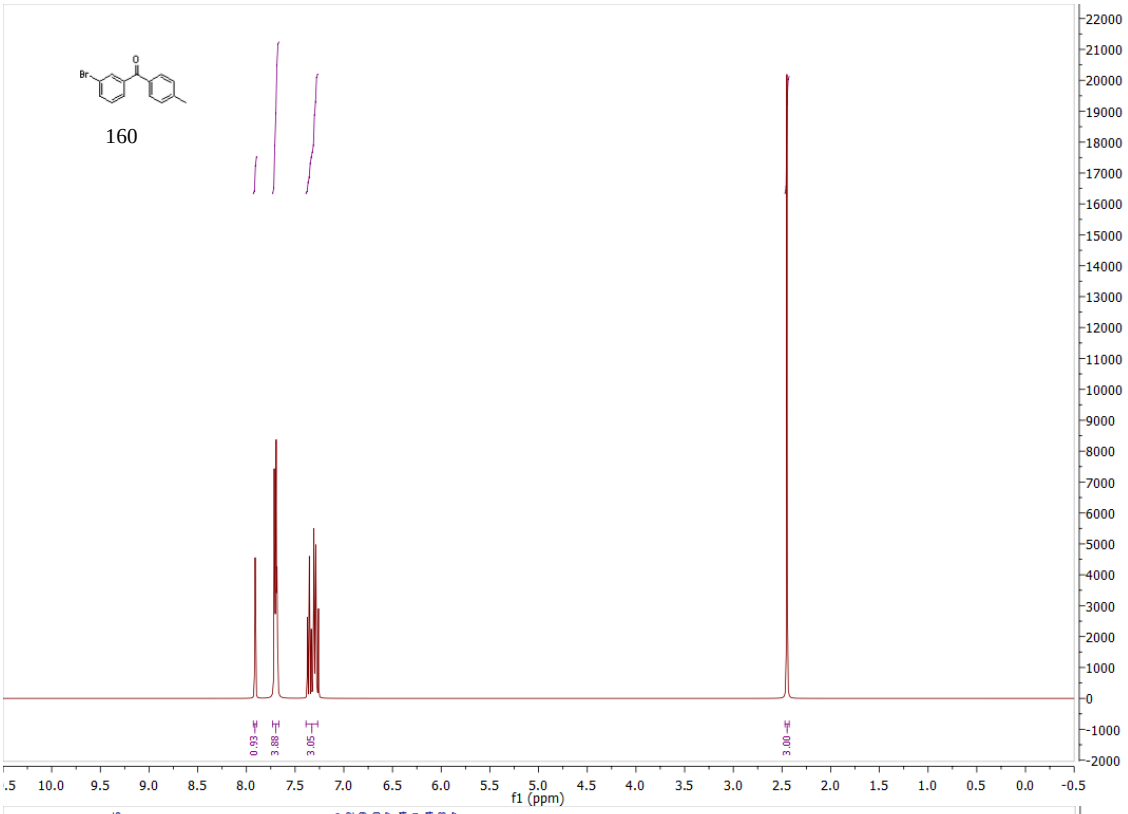

195.52
163.18
138.26
132.53
131.85
130.13
129.69
128.15
113.52
77.00
55.47
MeO
158
f1 (ppm)

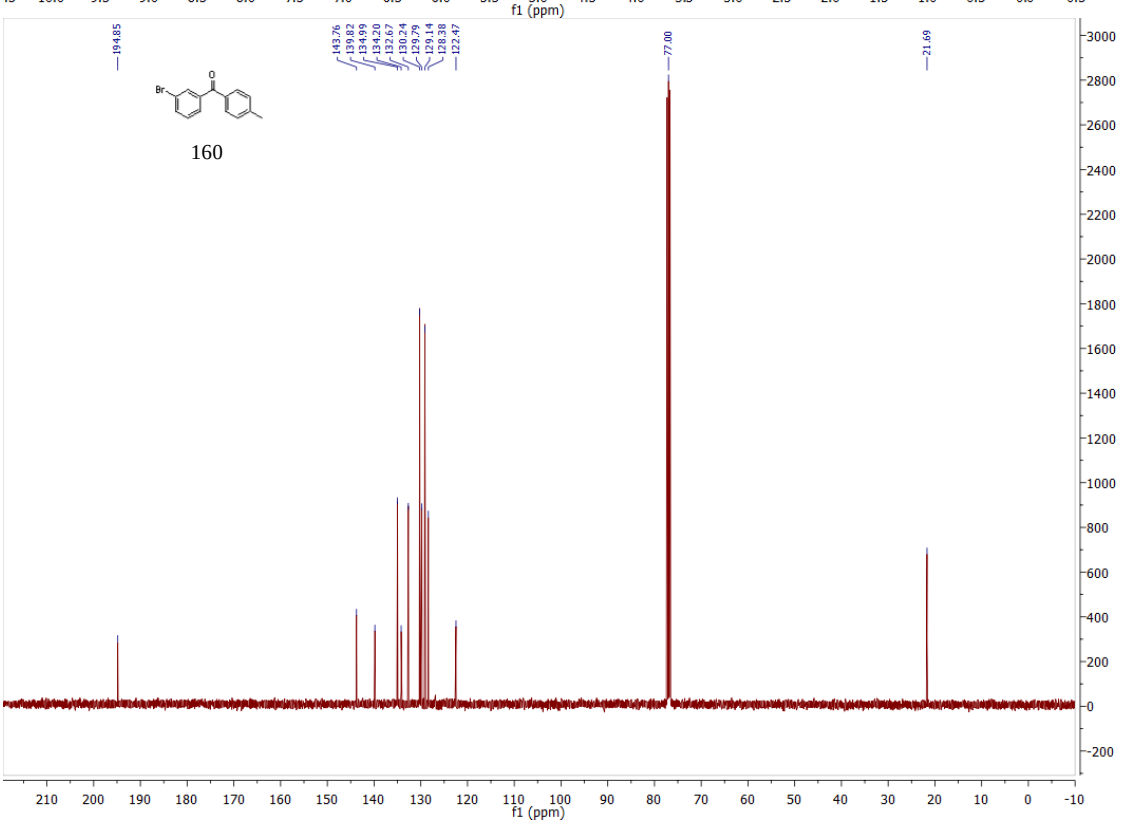

159
2.00
1.91
1.04
2.02
1.98
f1 (ppm)

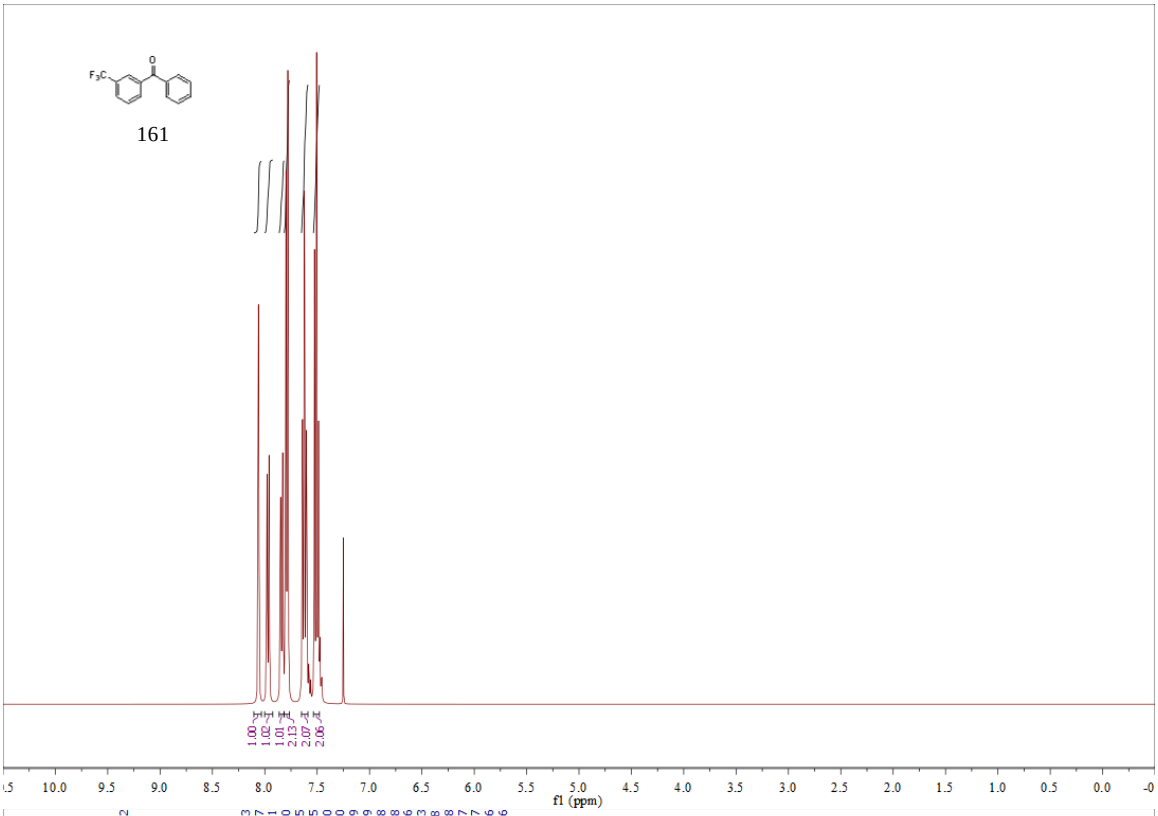

194.71
151.91
137.57
136.69
133.01
132.12
129.97
128.52
121.36
117.10
77.00
76.68
159
f1 (ppm)

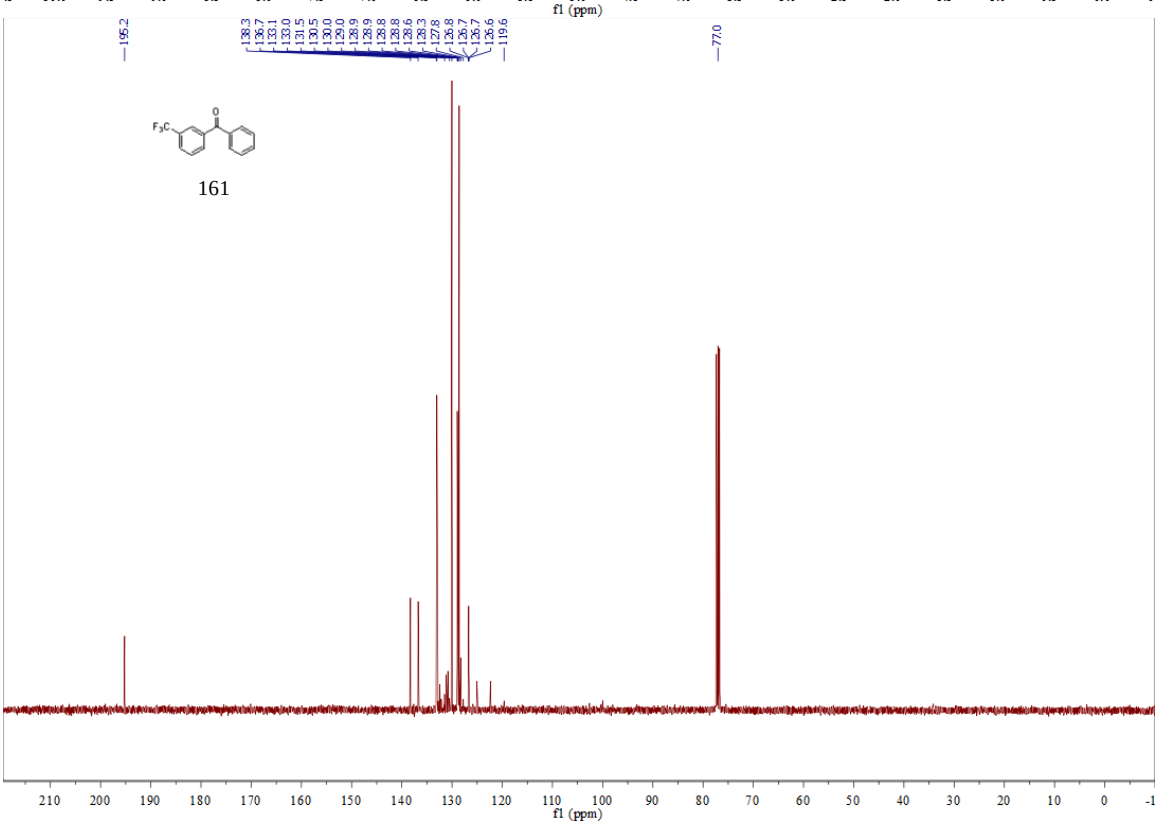

-72.73
-72.74
-72.76
40000
35000
30000
25000
20000
15000
10000
5000
0
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

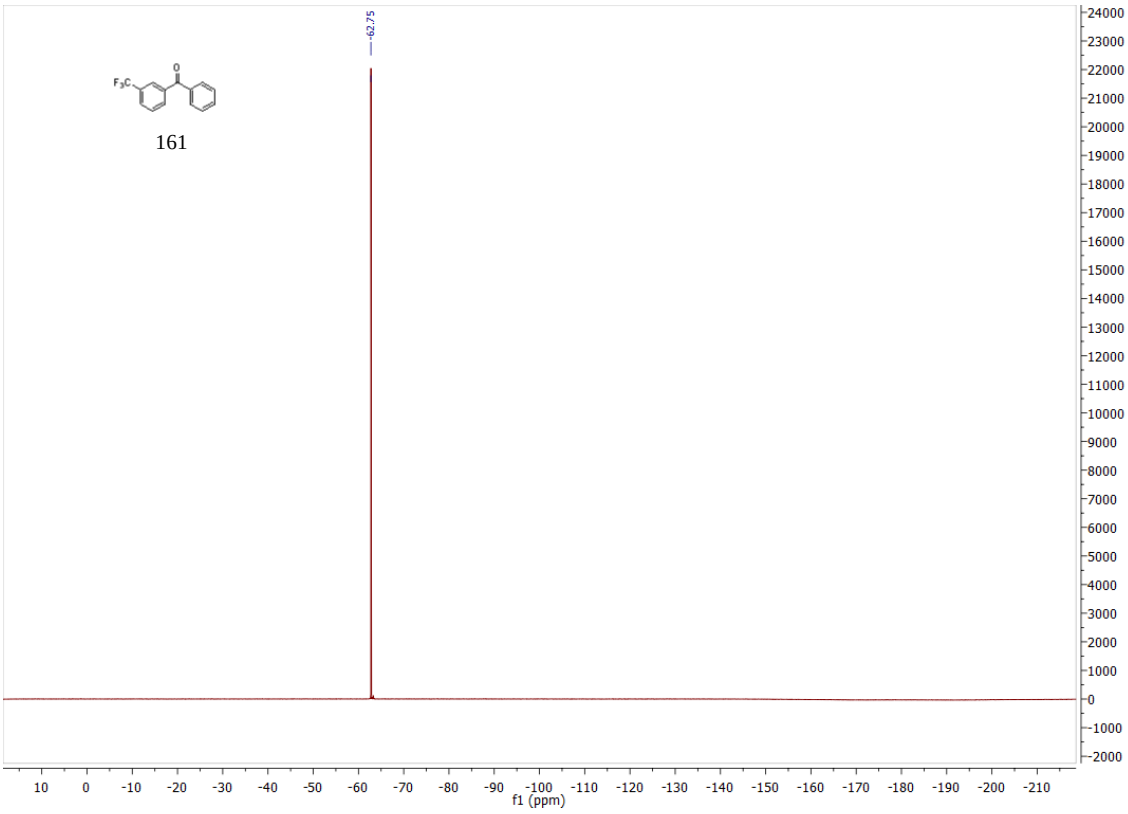
159


160
0.93
3.88
3.05
3.00
f1 (ppm)

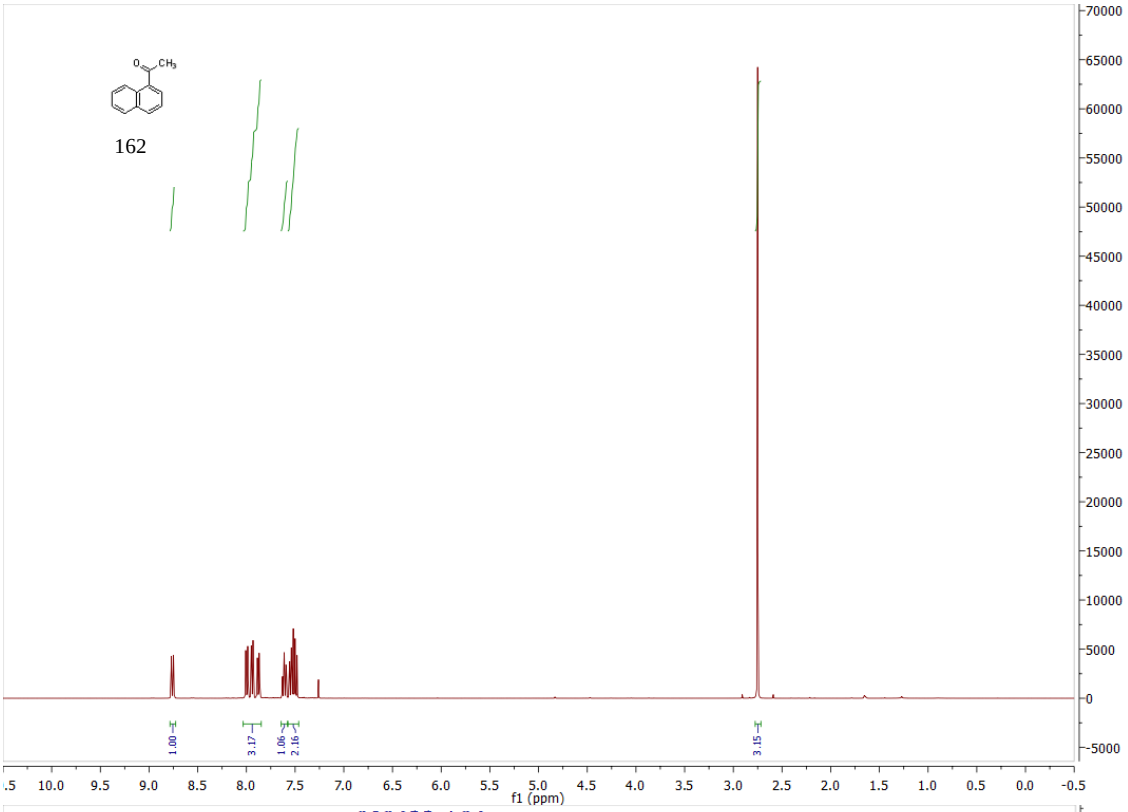

194.85
143.76
139.82
134.99
134.20
132.67
130.24
129.79
129.14
128.38
122.47
77.00
21.69
160
f1 (ppm)

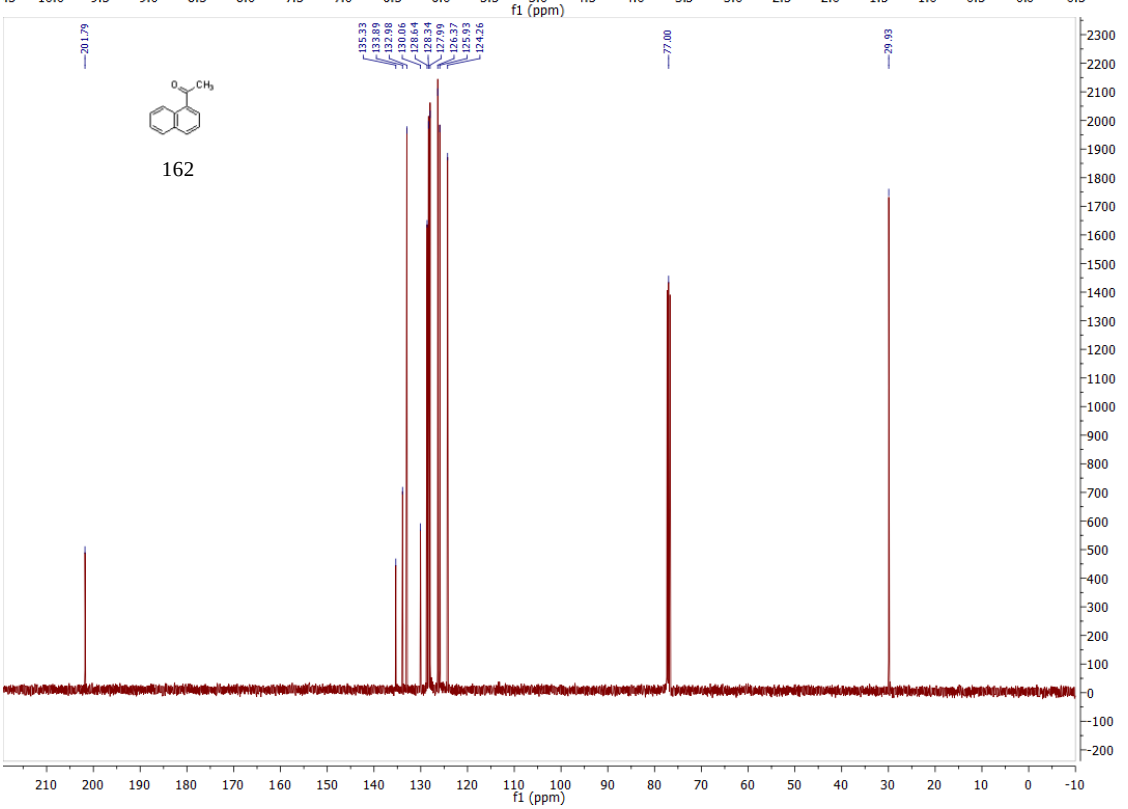

161
1.00
1.02
1.01
2.13
2.07
2.06
f1 (ppm)

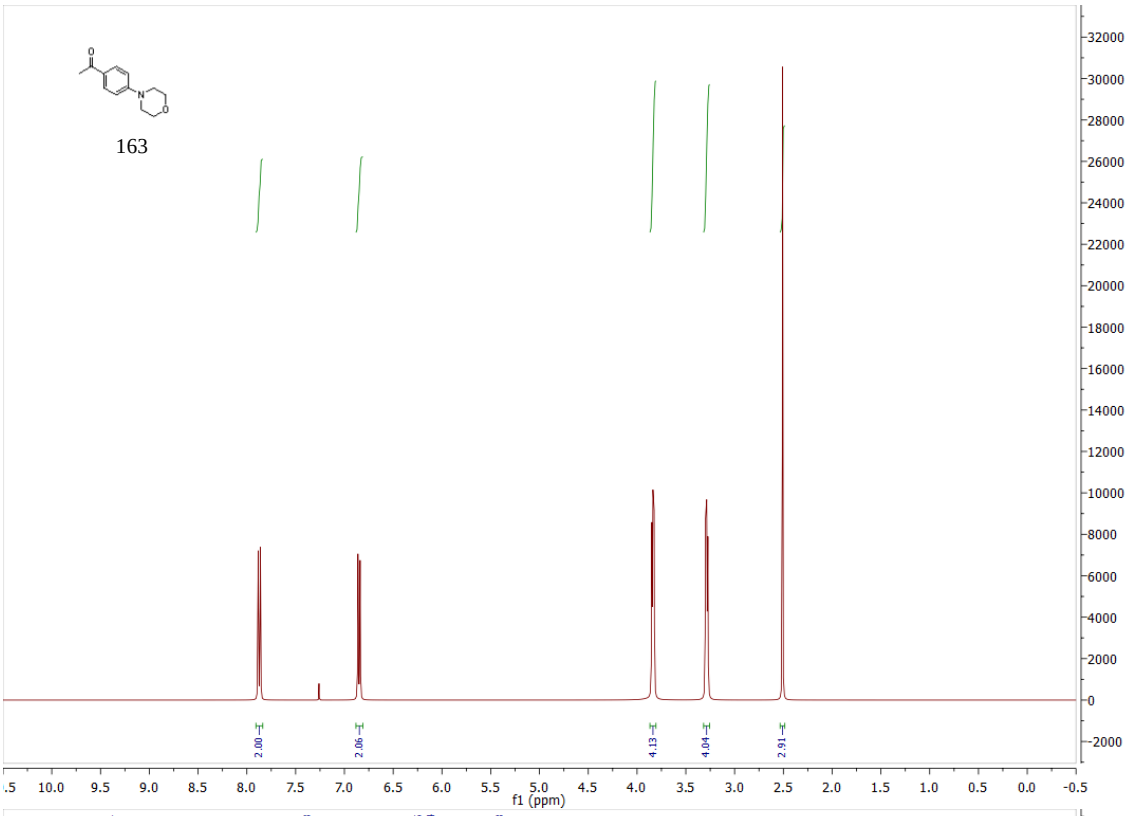

195.2
138.3
136.7
133.1
133.0
131.5
130.5
130.0
129.0
128.9
128.9
128.8
128.8
128.6
128.3
127.8
126.8
126.7
126.7
126.6
119.6
77.0
161
f1 (ppm)

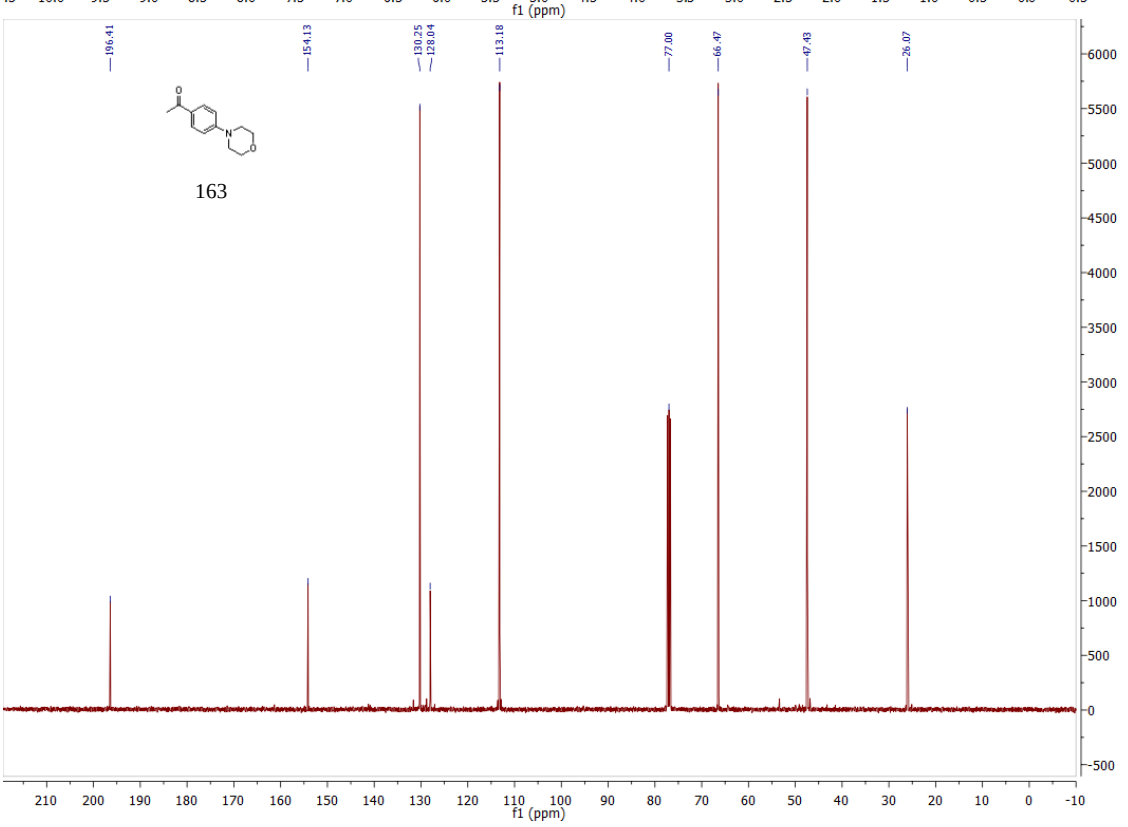

-62.75
24000
23000
22000
21000
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-2000
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

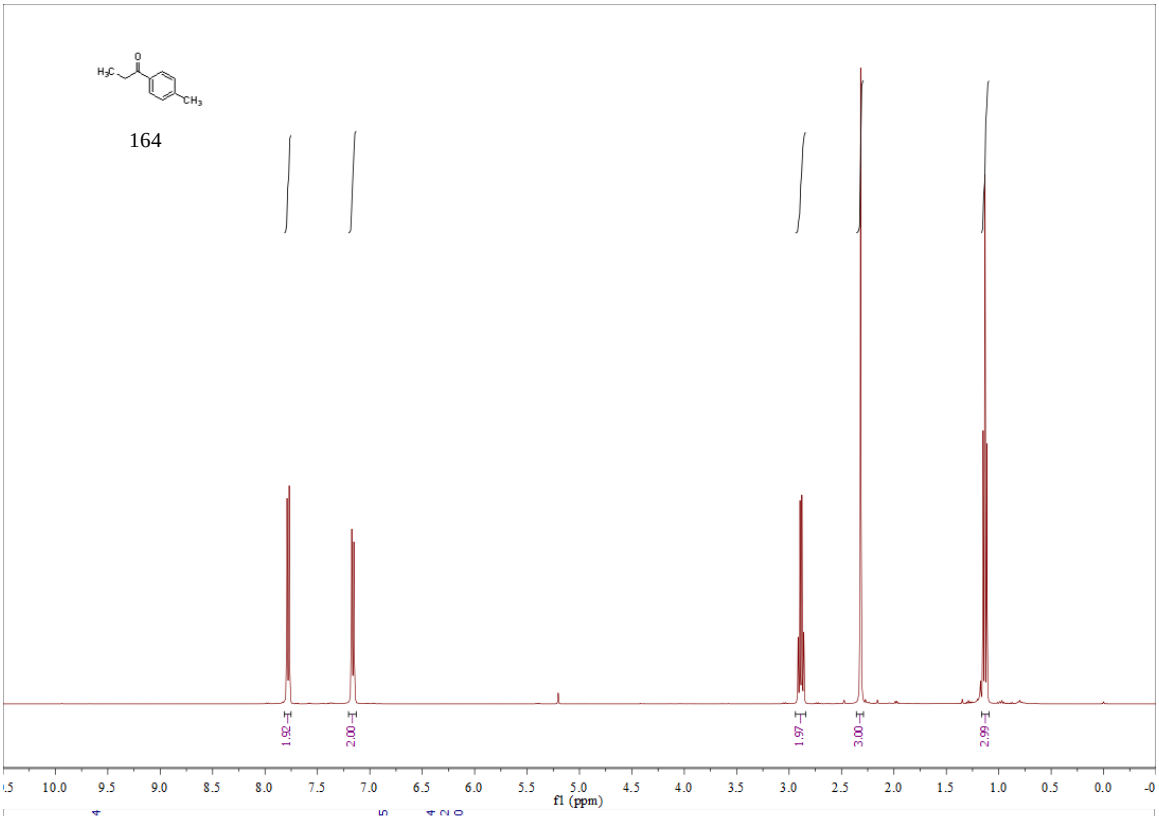
161

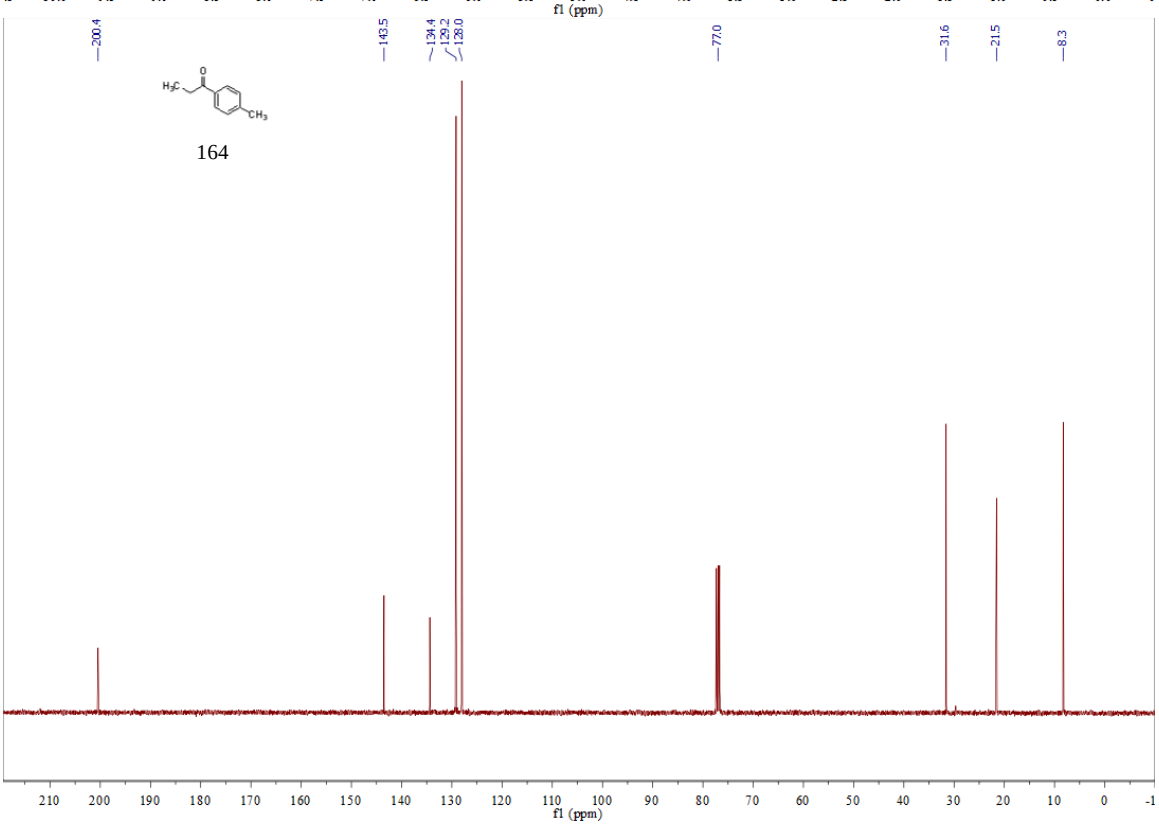

162
1.00
3.17
1.06
2.16
3.15
f1 (ppm)

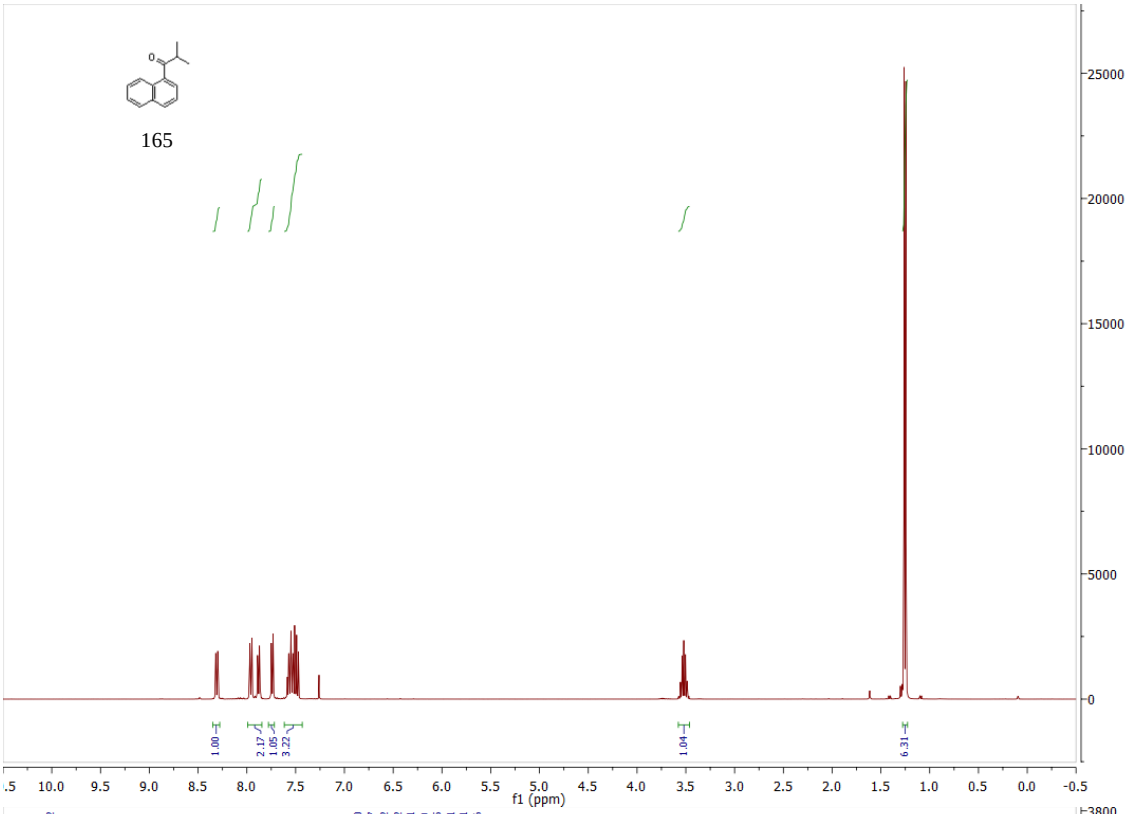

201.79
135.33
133.89
132.98
130.06
129.64
128.34
127.99
126.37
125.93
124.26
77.00
29.93
162
f1 (ppm)

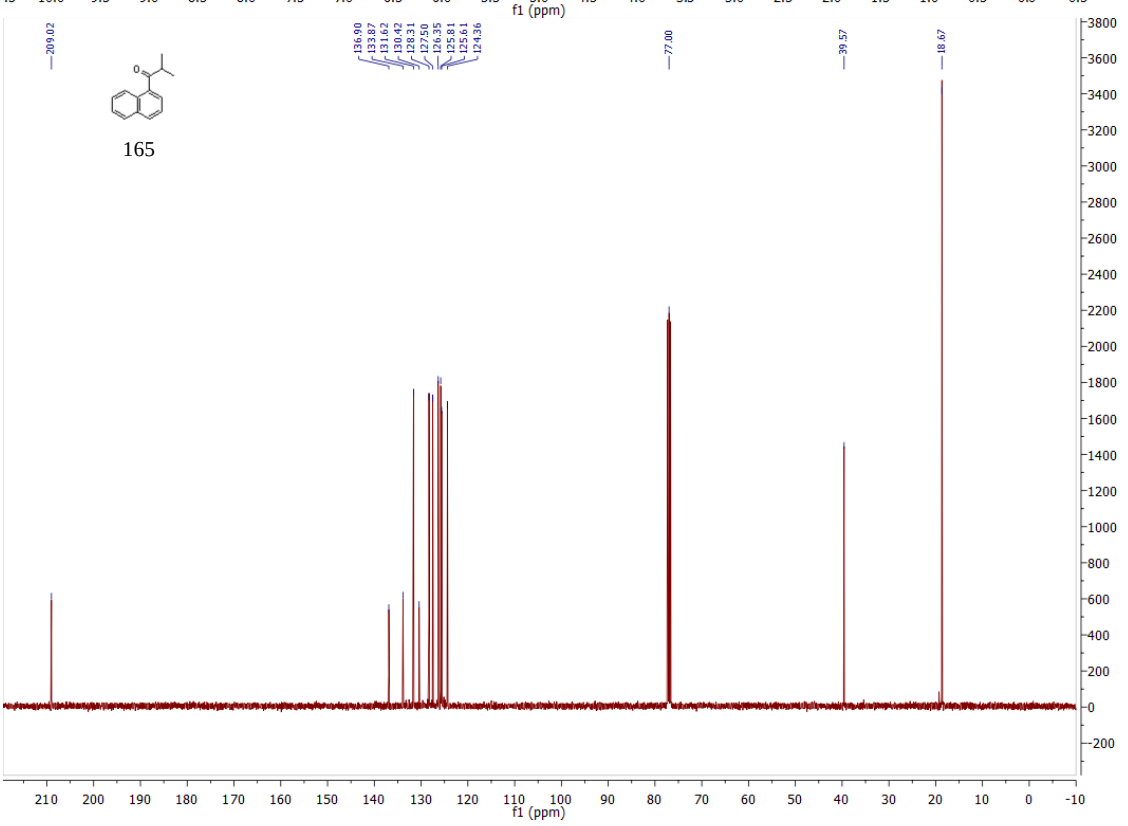

163
2.00
2.06
4.13
4.04
2.91
f1 (ppm)

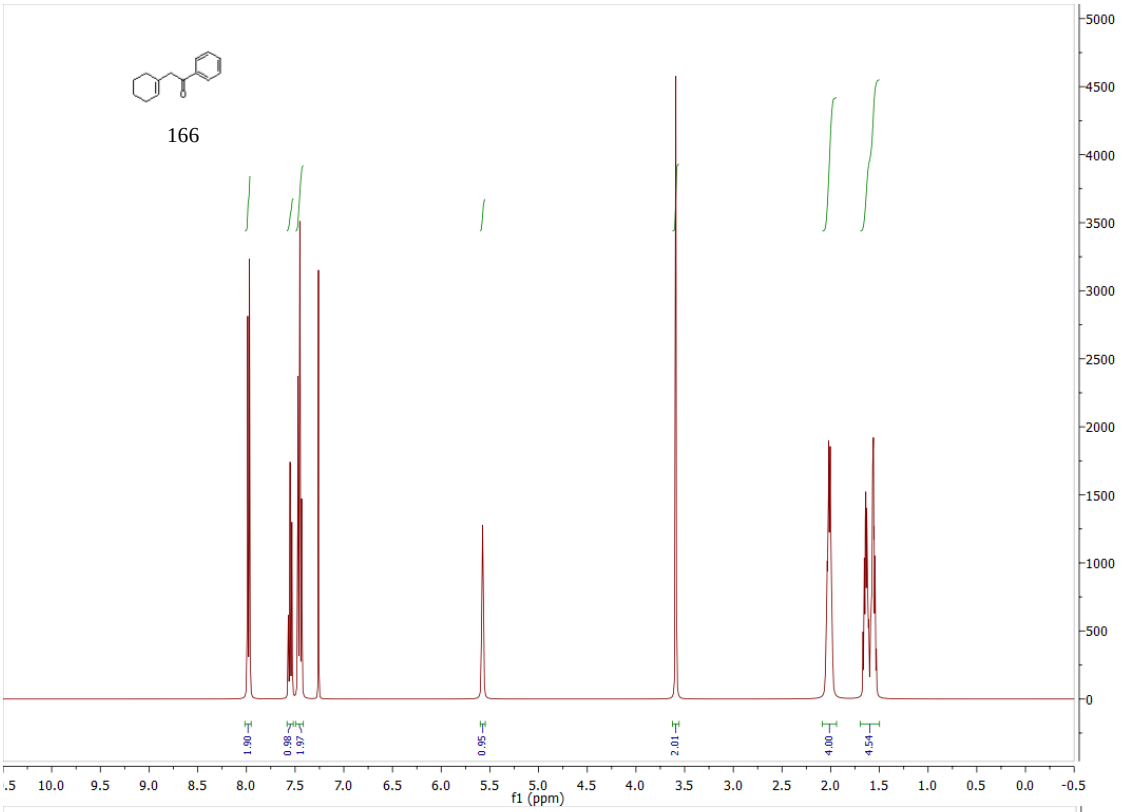

196.41
154.13
130.25
128.04
113.18
77.00
66.47
47.43
26.07
163
f1 (ppm)

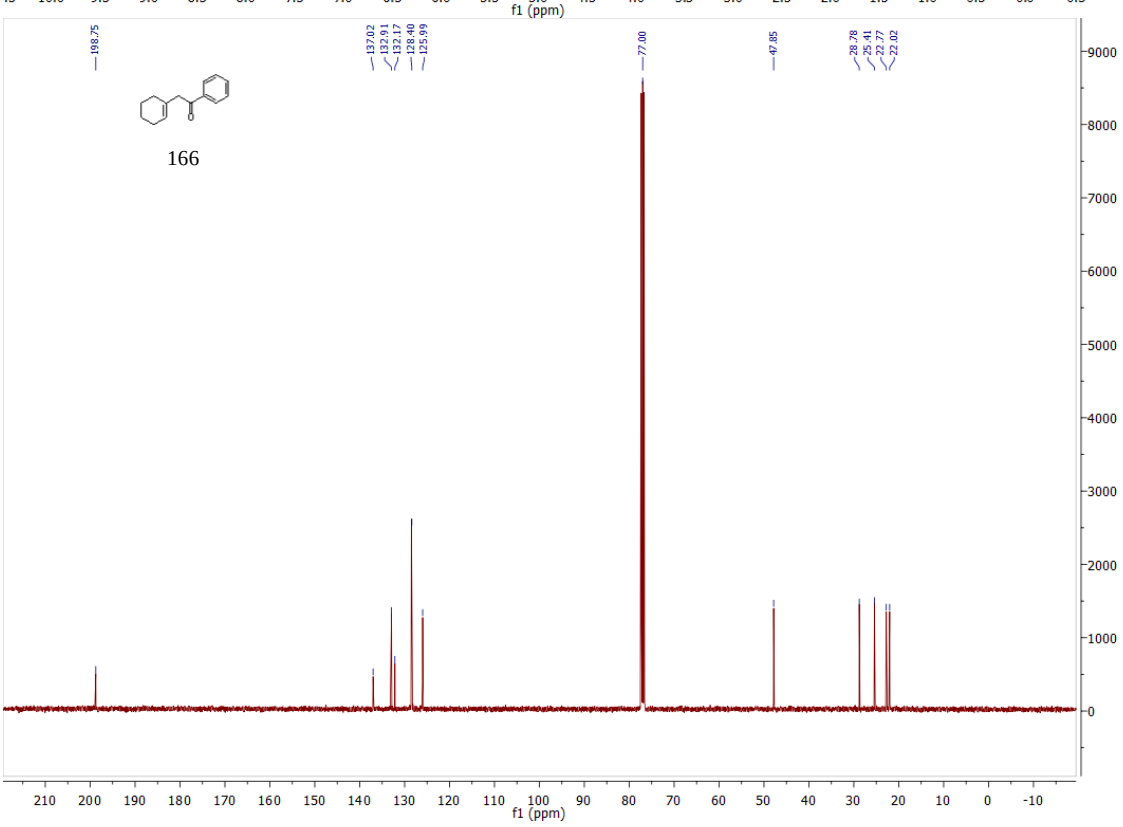

164
1.92
2.00
1.97
3.00
2.99
f1 (ppm)

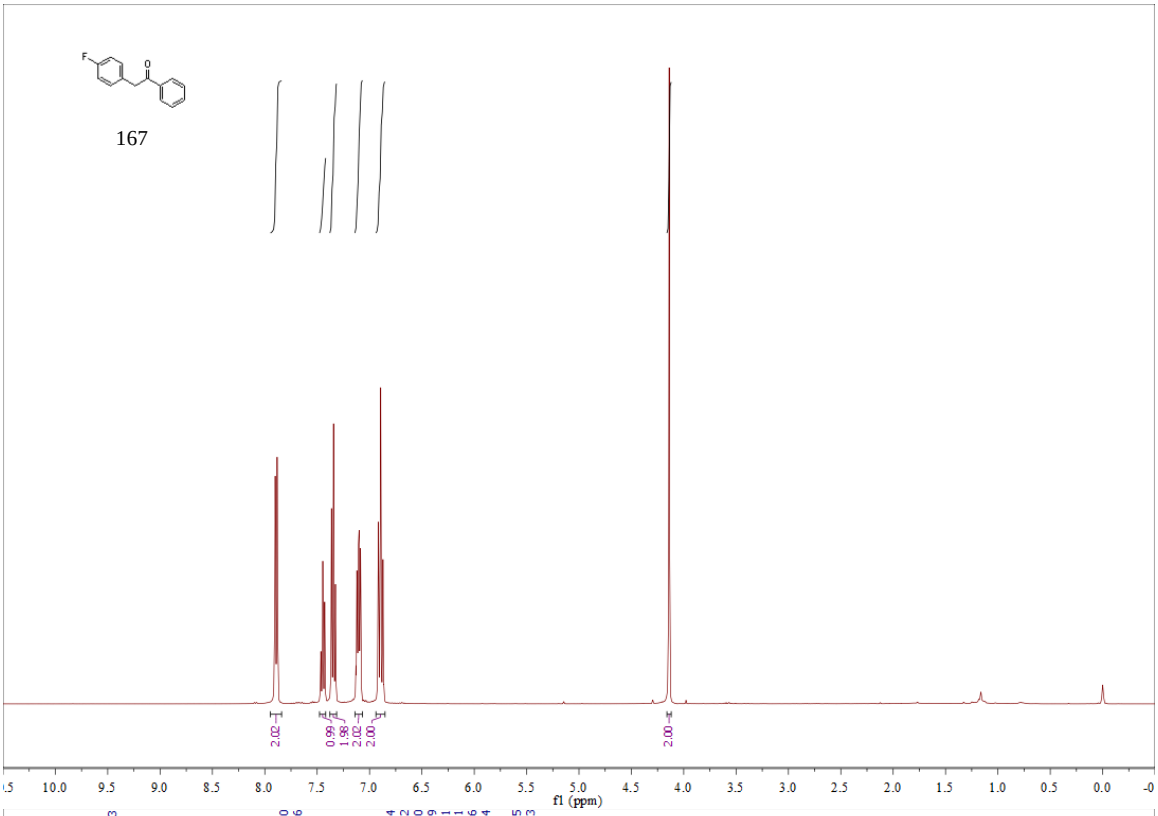

200.4
143.5
134.4
129.2
128.0
77.0
31.6
21.5
8.3
164
f1 (ppm)

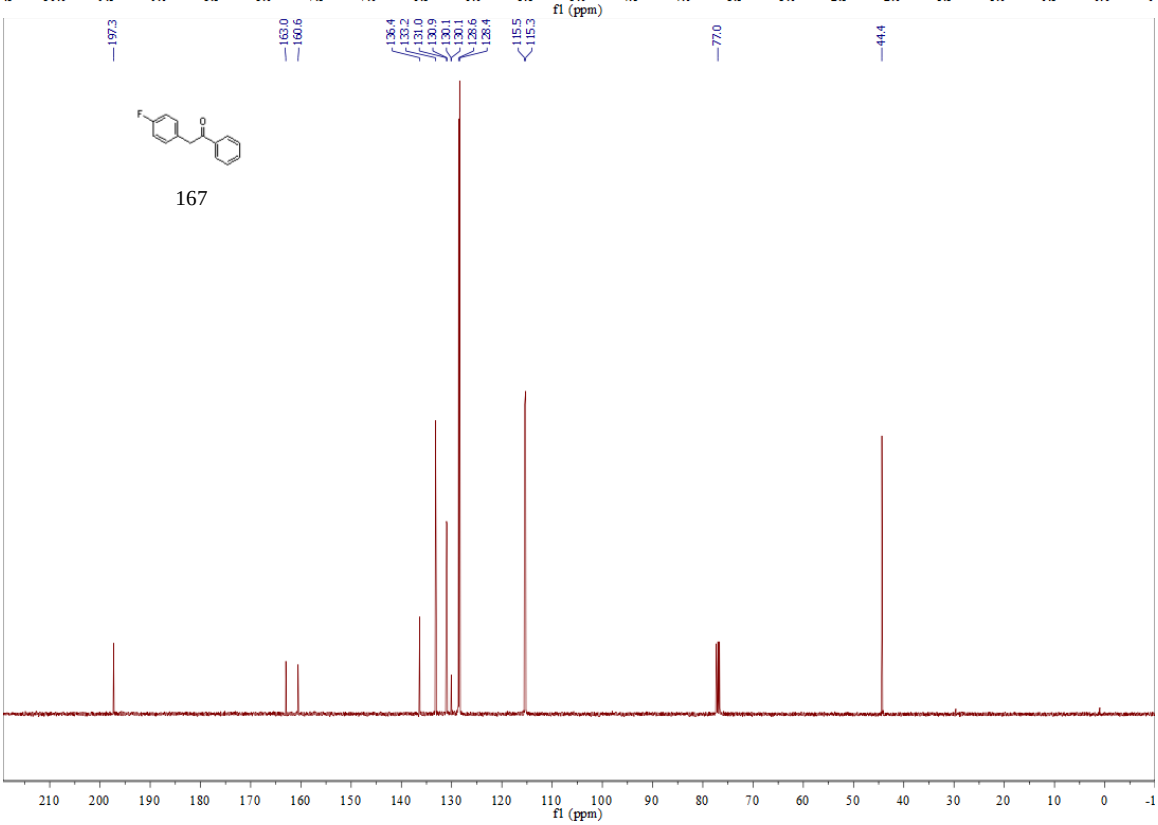

165
1.00
2.17
1.05
3.22
1.04
6.31
f1 (ppm)

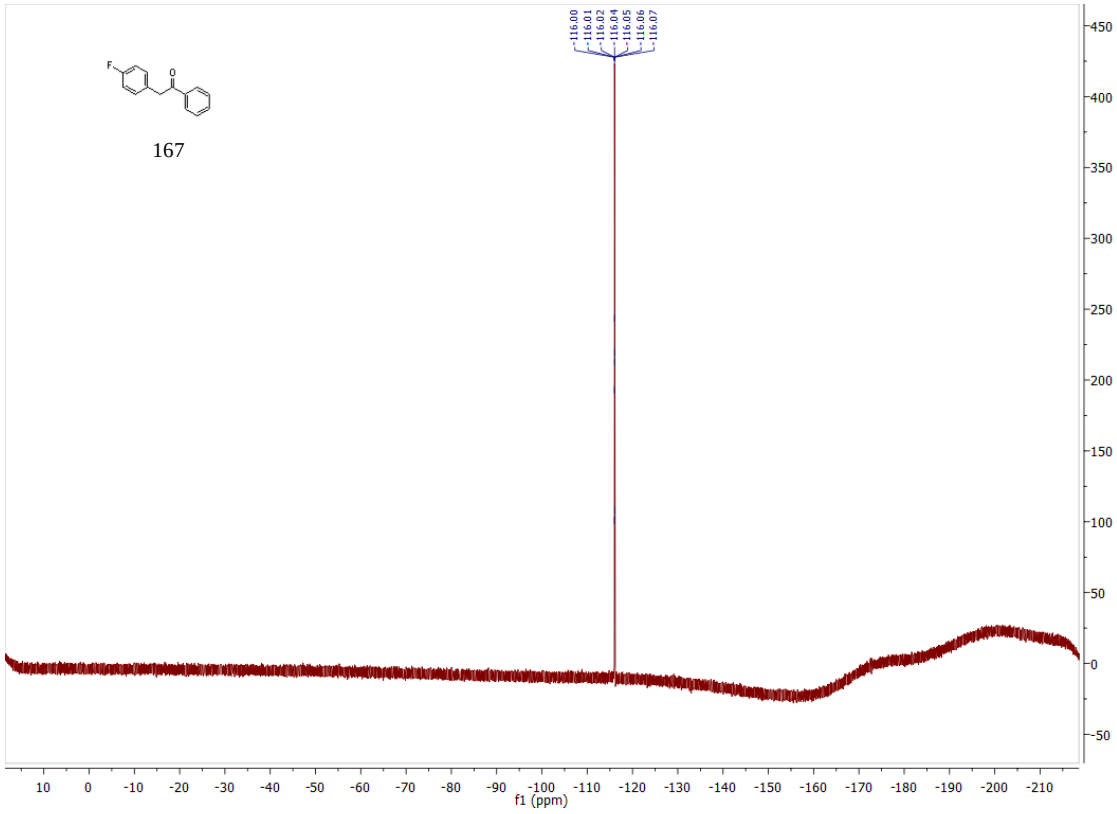

209.02
136.90
133.87
131.62
130.42
128.31
127.50
126.35
125.81
125.61
124.36
77.00
39.57
18.67
165
f1 (ppm)


166
1.90
0.98
1.97
0.95
2.01
4.00
4.54
f1 (ppm)

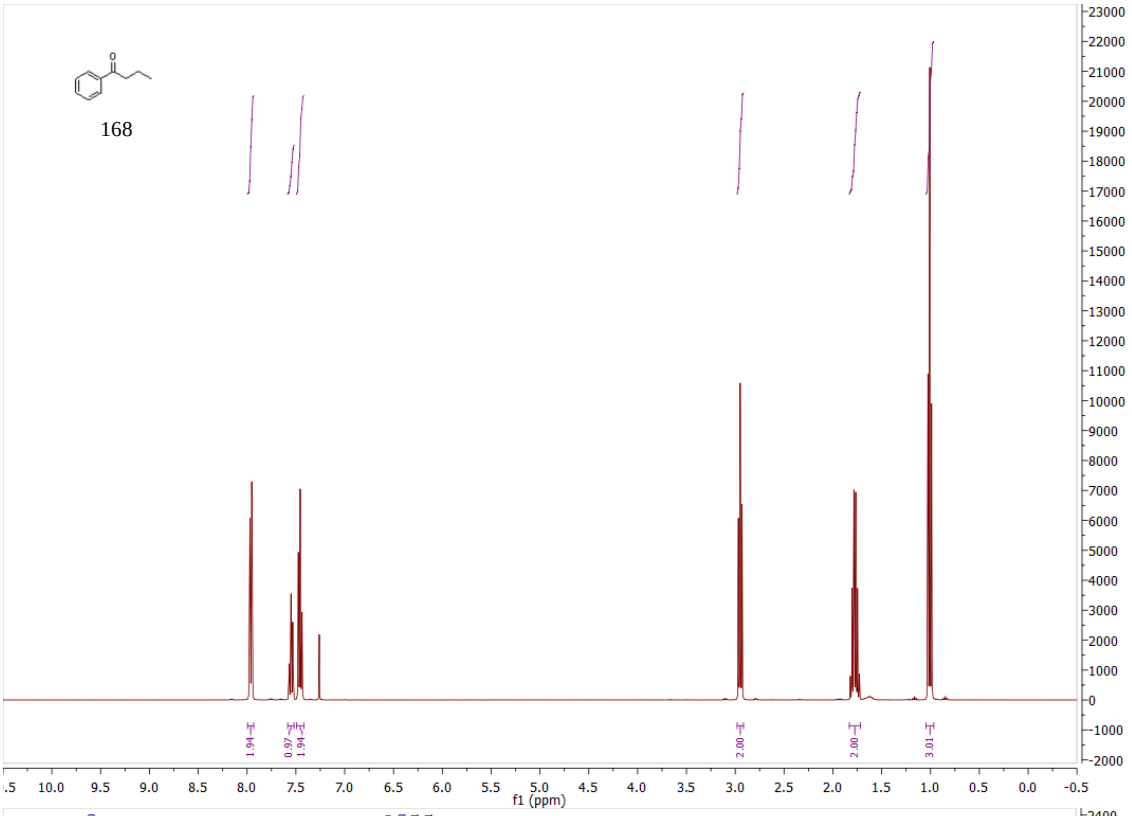

198.75
137.02
132.91
132.17
128.40
125.99
77.00
47.85
28.78
25.41
22.77
22.02
166
f1 (ppm)

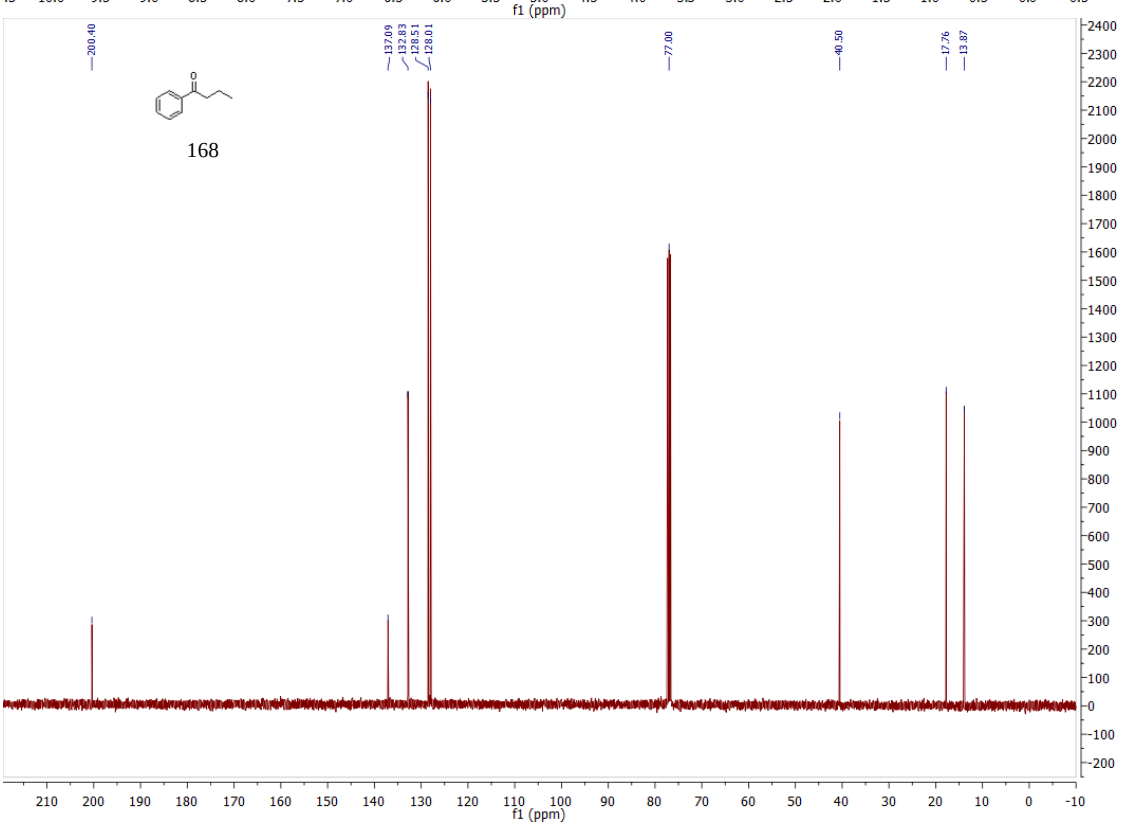

F
O
167
2.02
0.99
1.98
2.02
2.00
2.00
f1 (ppm)

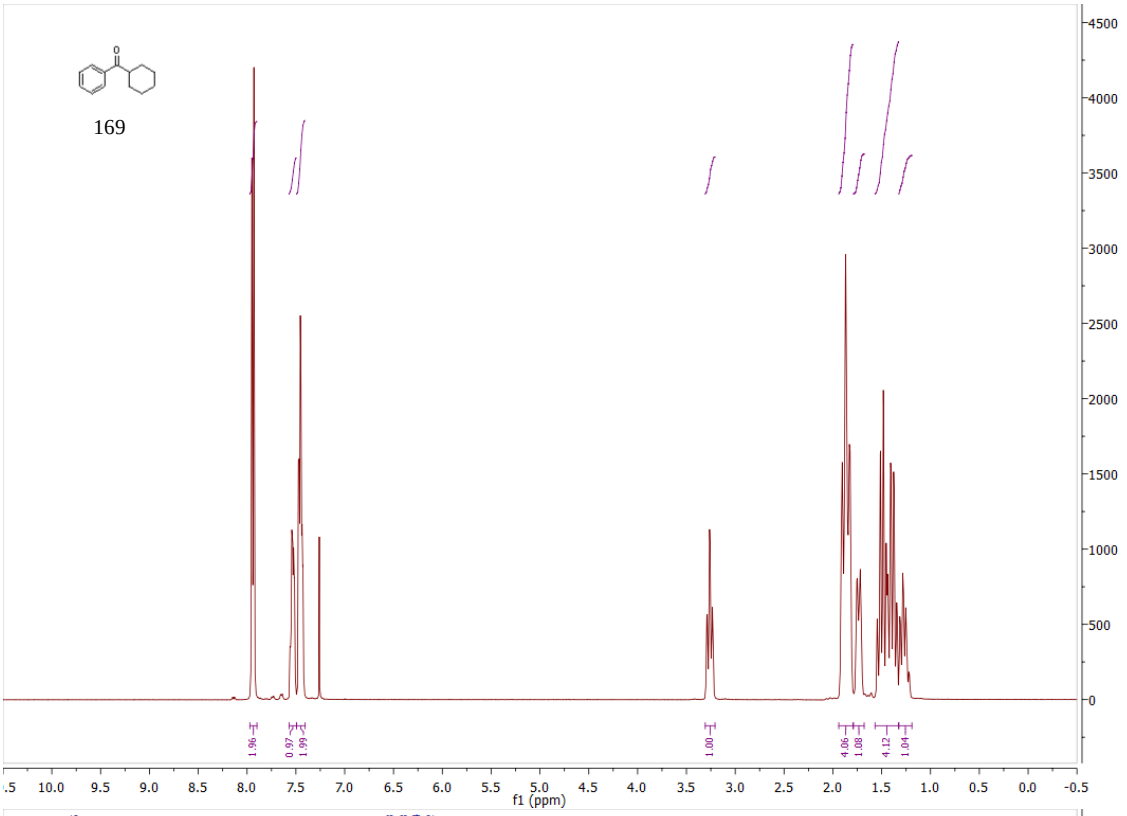

197.3
163.0
160.6
136.4
133.2
131.0
130.9
130.1
128.6
128.4
115.5
115.3
77.0
44.4
F
O
167
f1 (ppm)

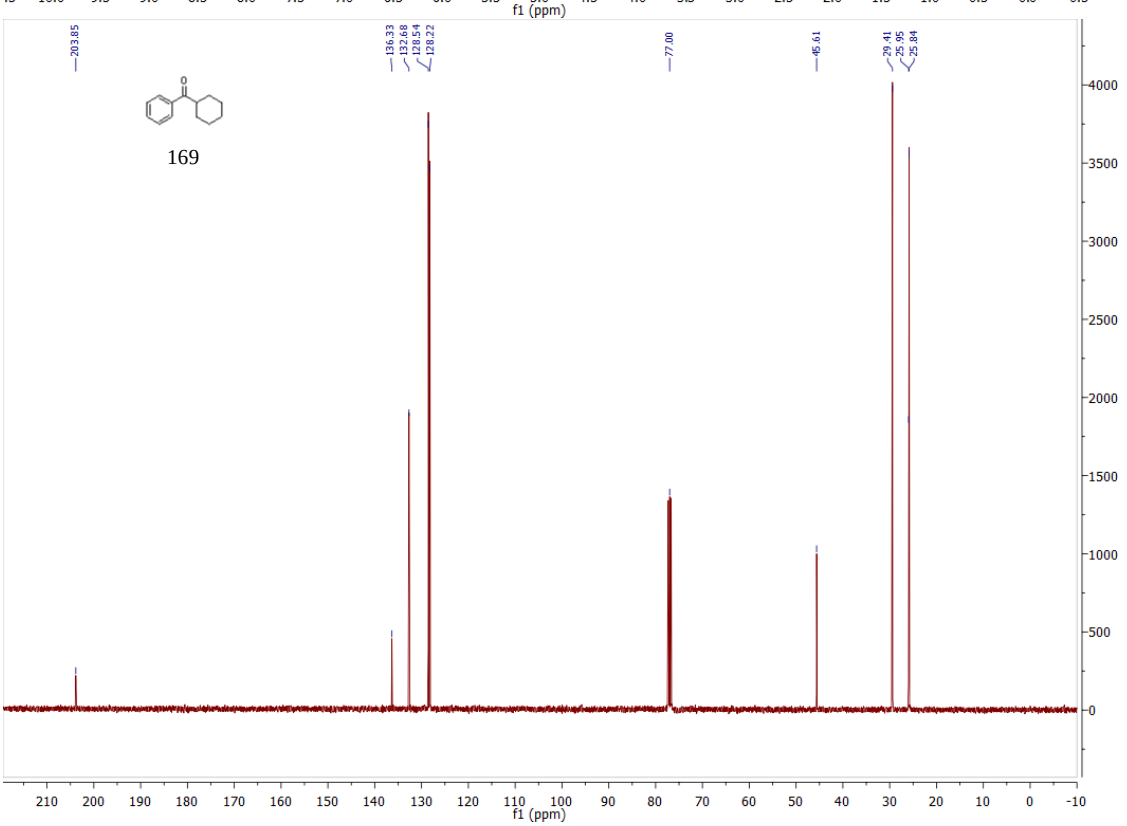

F
O
-116.00
-116.01
-116.02
-116.04
-116.05
-116.06
-116.07
450
400
350
300
250
200
150
100
50
0
-50
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

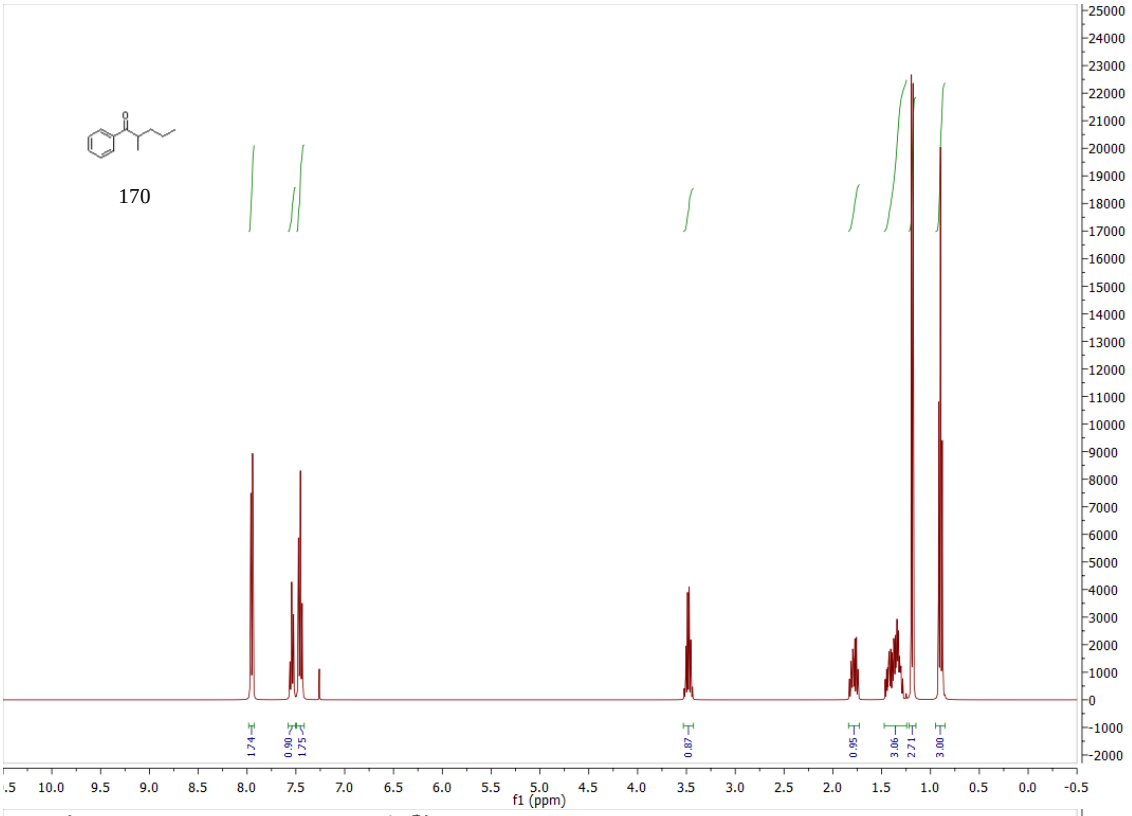
167

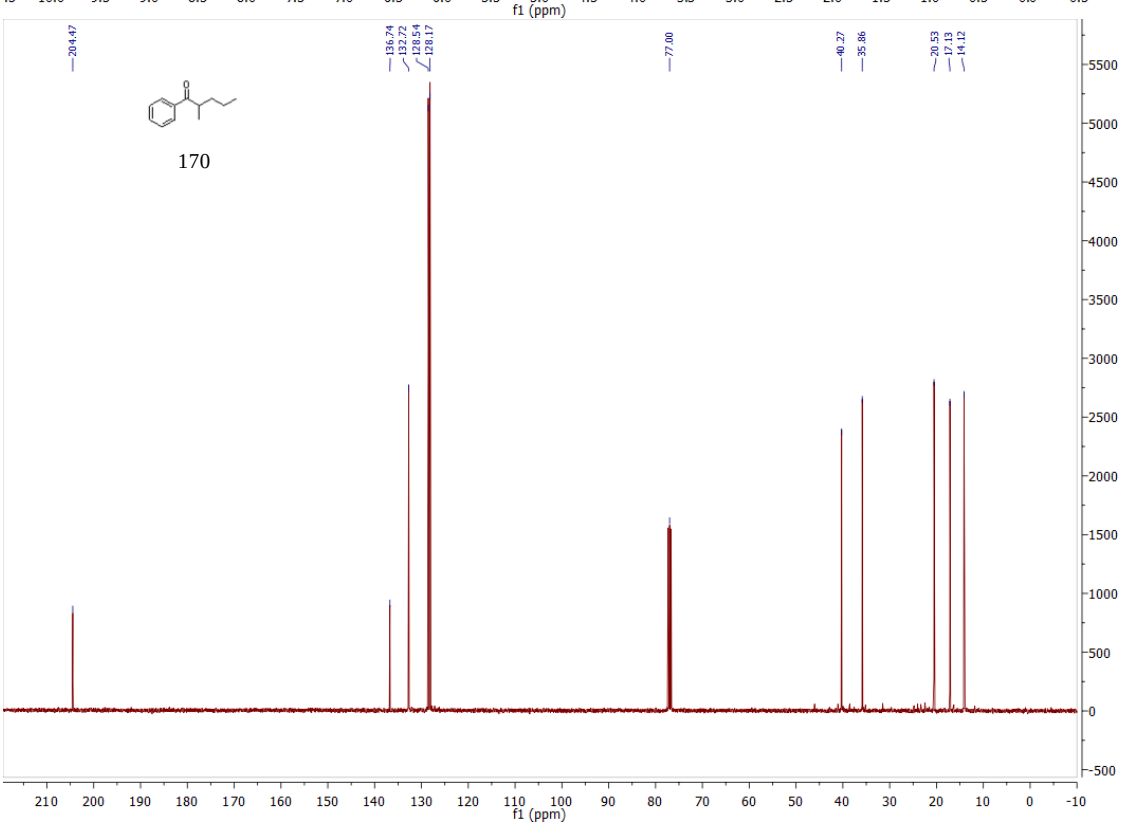

168
1.94
0.97
1.94
2.00
2.00
3.01
f1 (ppm)

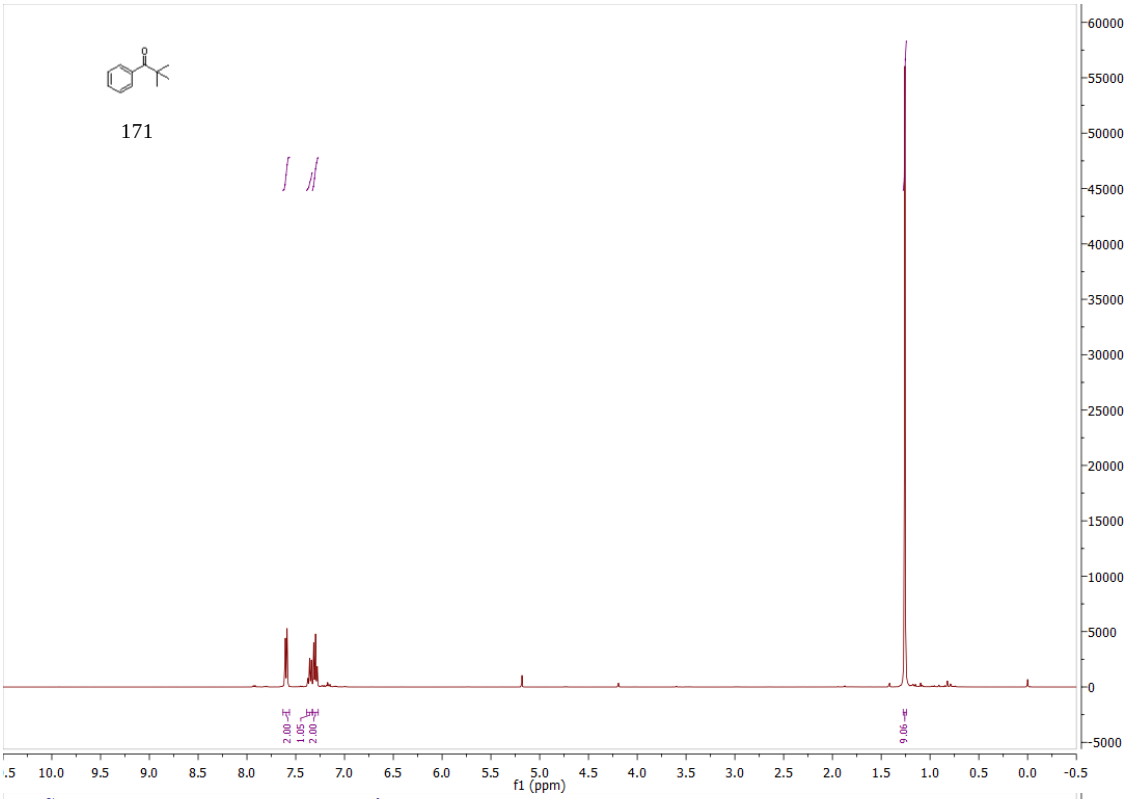

200.40
137.09
133.83
128.51
128.01
77.00
40.50
17.76
13.87
168
f1 (ppm)

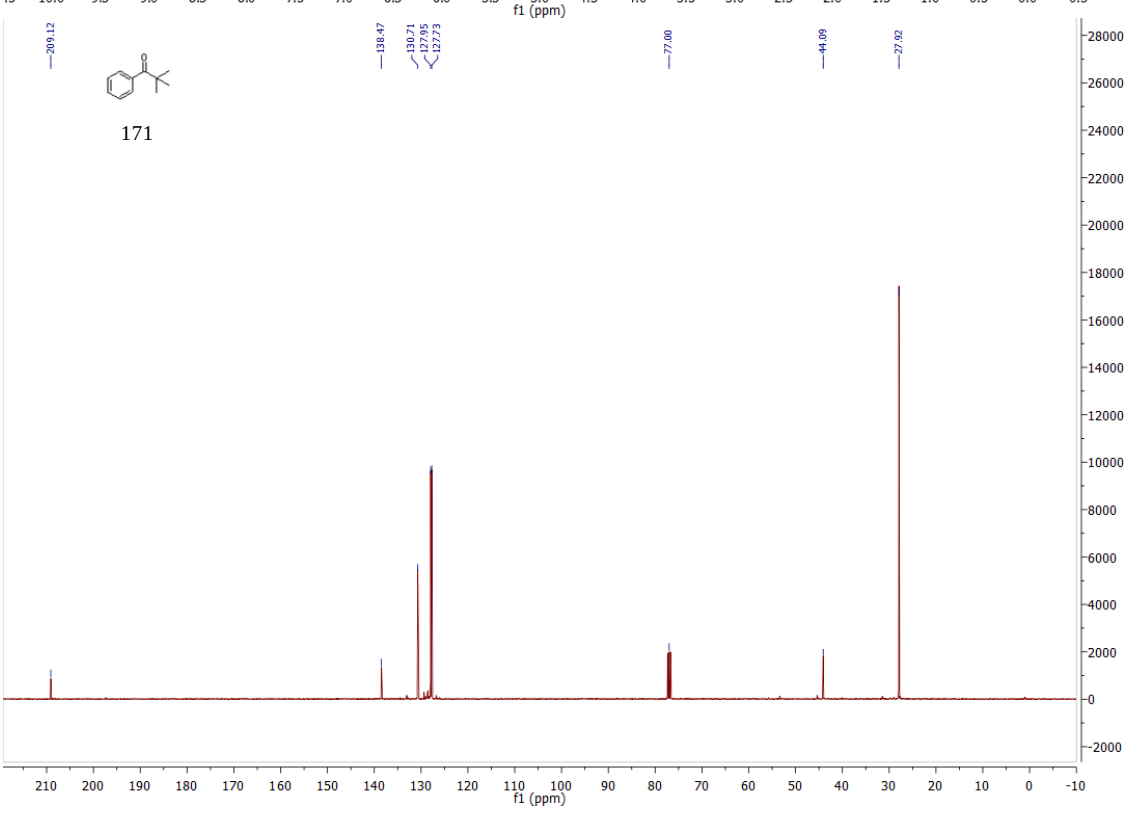

169
1.96
0.97
1.99
1.00
4.06
1.08
4.12
1.04
f1 (ppm)

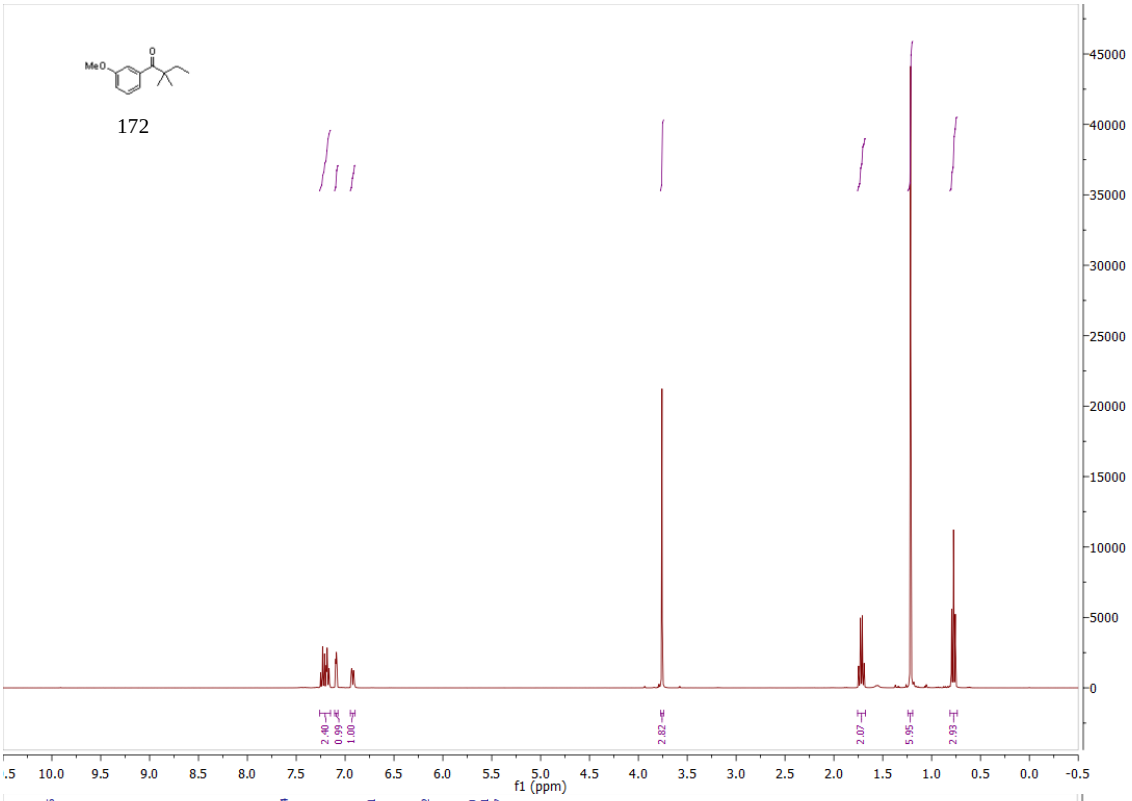

203.85
136.33
132.68
128.54
128.22
77.00
45.61
29.41
25.95
25.84
169
f1 (ppm)

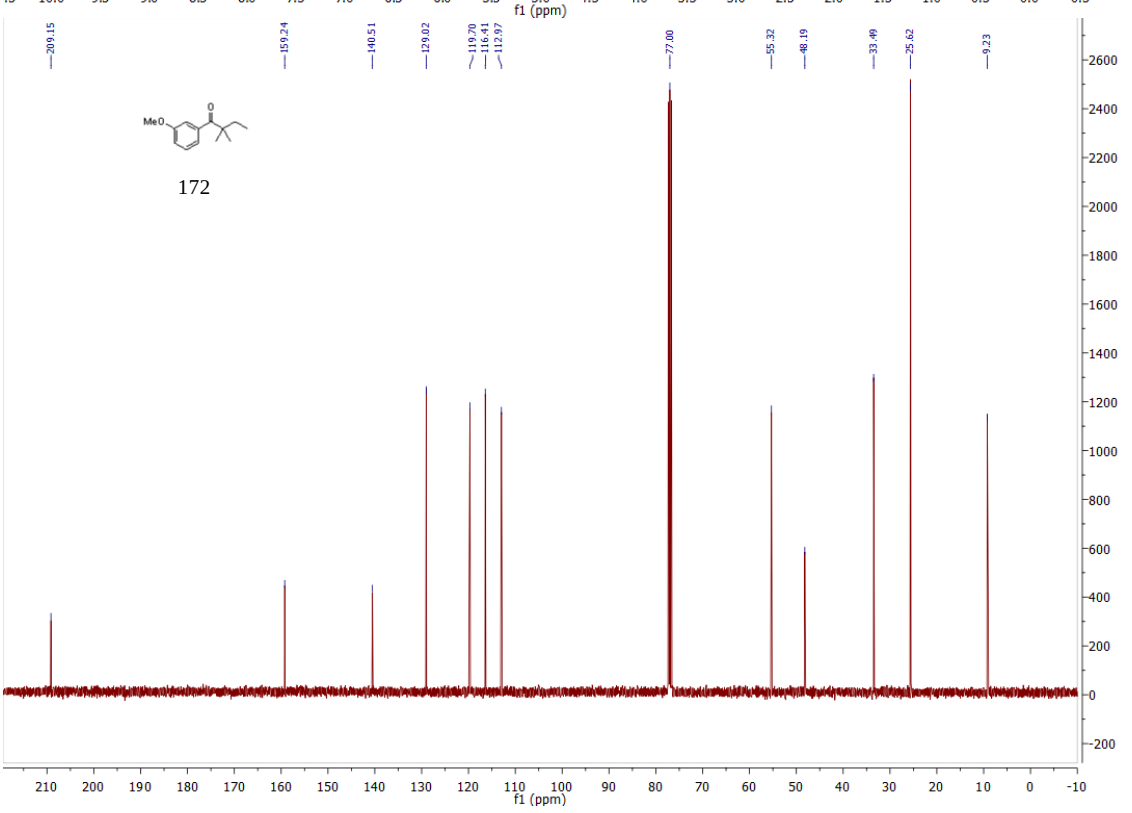

170
1.74
0.90
1.75
0.87
0.95
3.06
2.71
3.00
f1 (ppm)

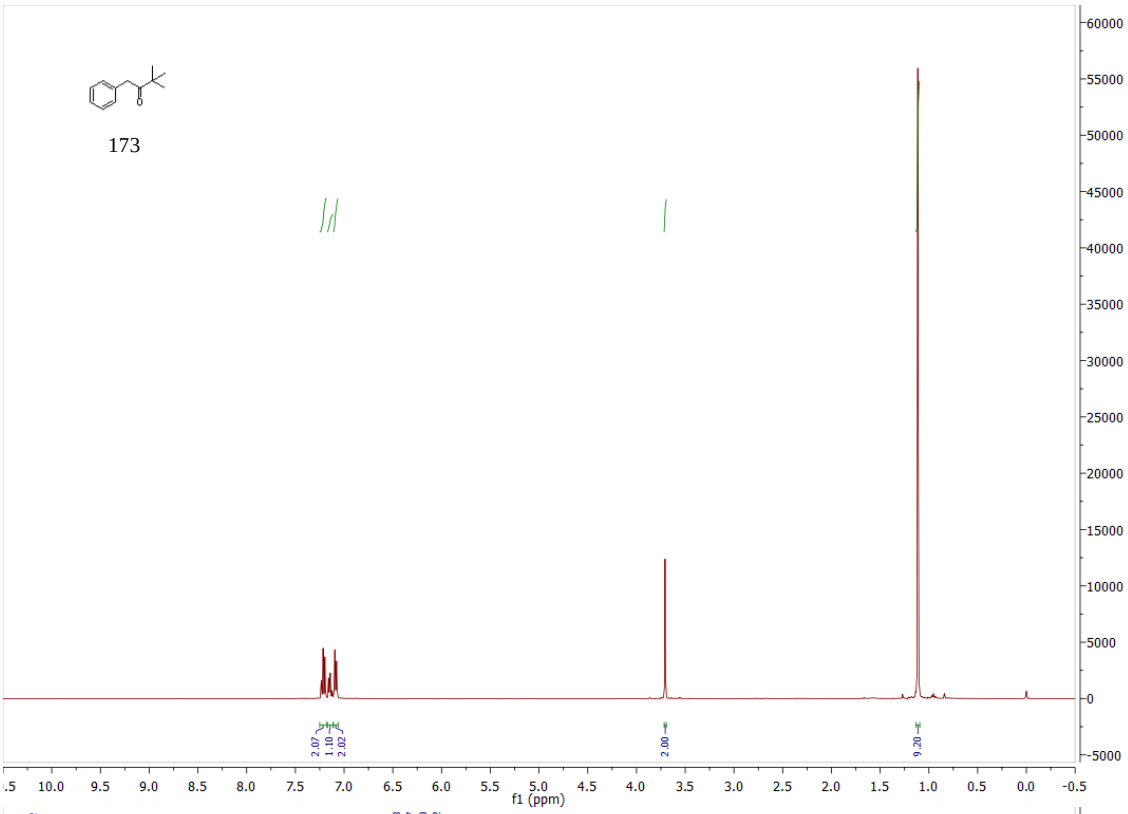

204.47
136.74
132.72
128.54
128.17
77.00
40.27
35.86
20.53
17.13
14.12
170
f1 (ppm)

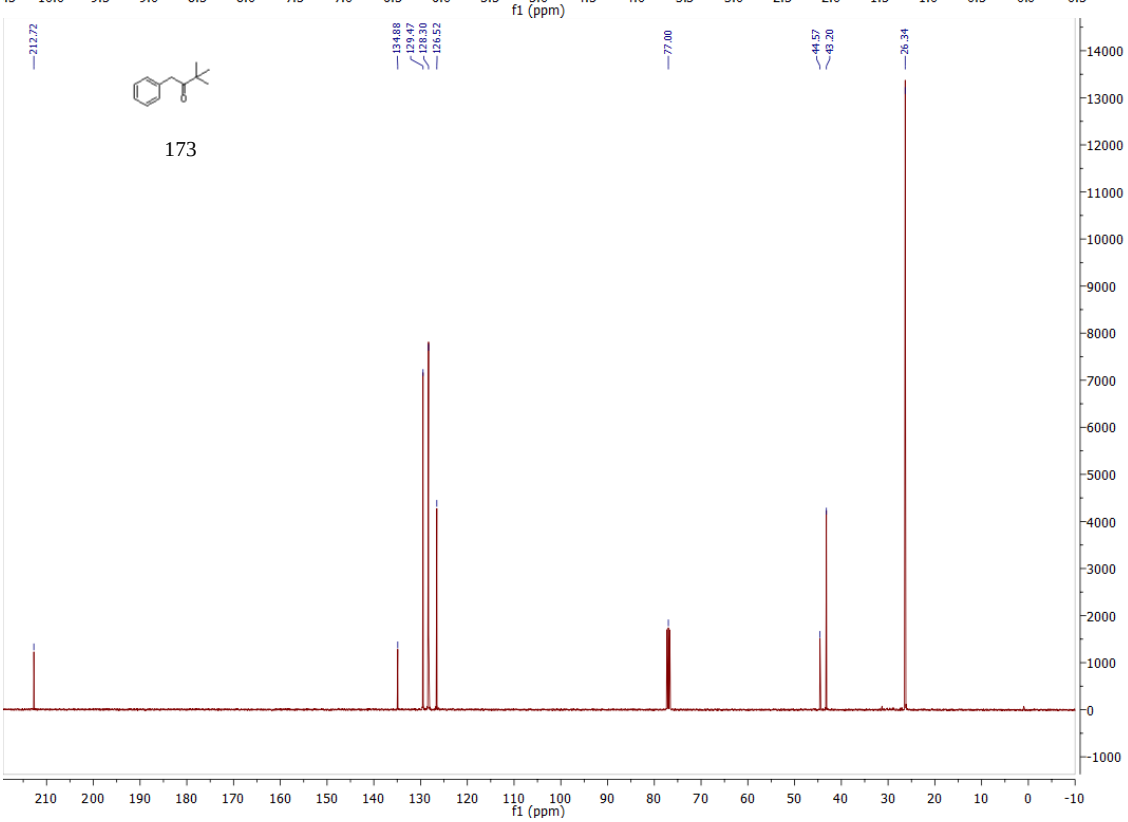

171
2.00
1.05
2.00
9.06
f1 (ppm)

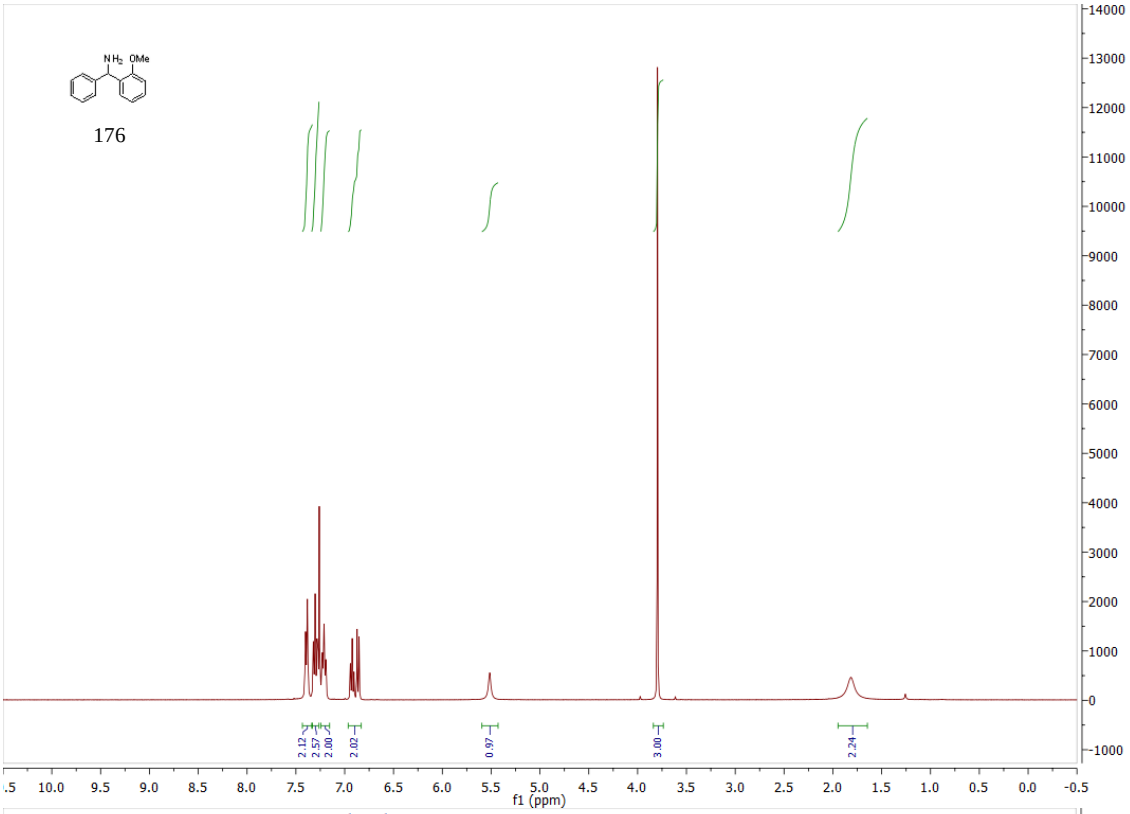

209.12
138.47
130.71
127.95
127.73
77.00
44.09
27.92
171
f1 (ppm)

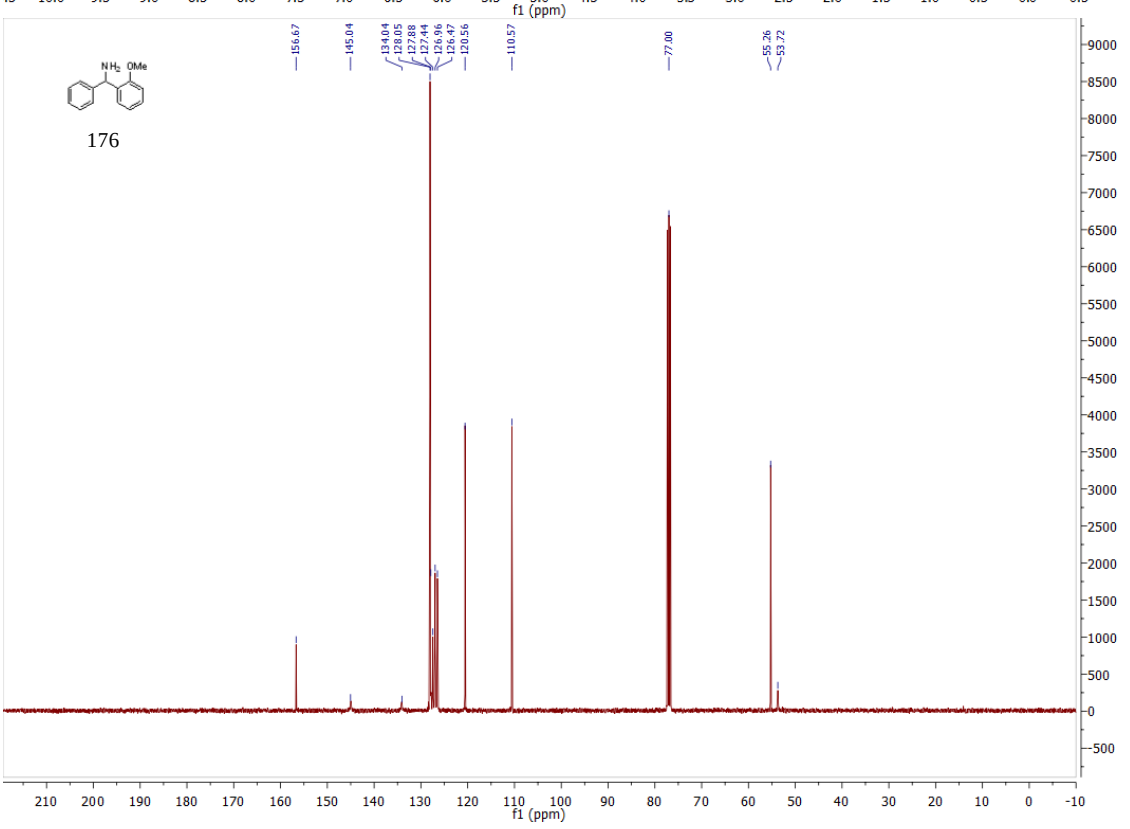

MeO
O
172
2.40
0.99
1.00
2.82
2.07
5.95
2.93
f1 (ppm)

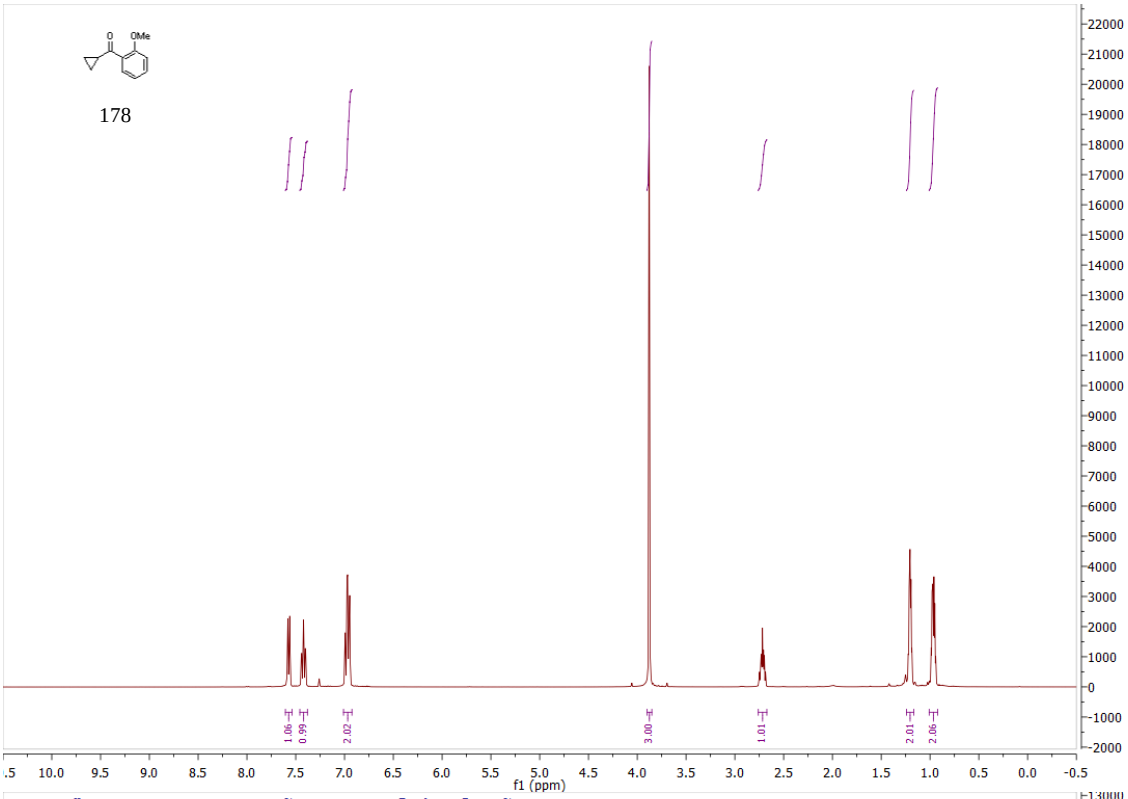

209.15
159.24
140.51
129.02
119.70
115.41
112.97
77.00
55.32
48.19
33.49
25.62
9.23
MeO
O
172
f1 (ppm)

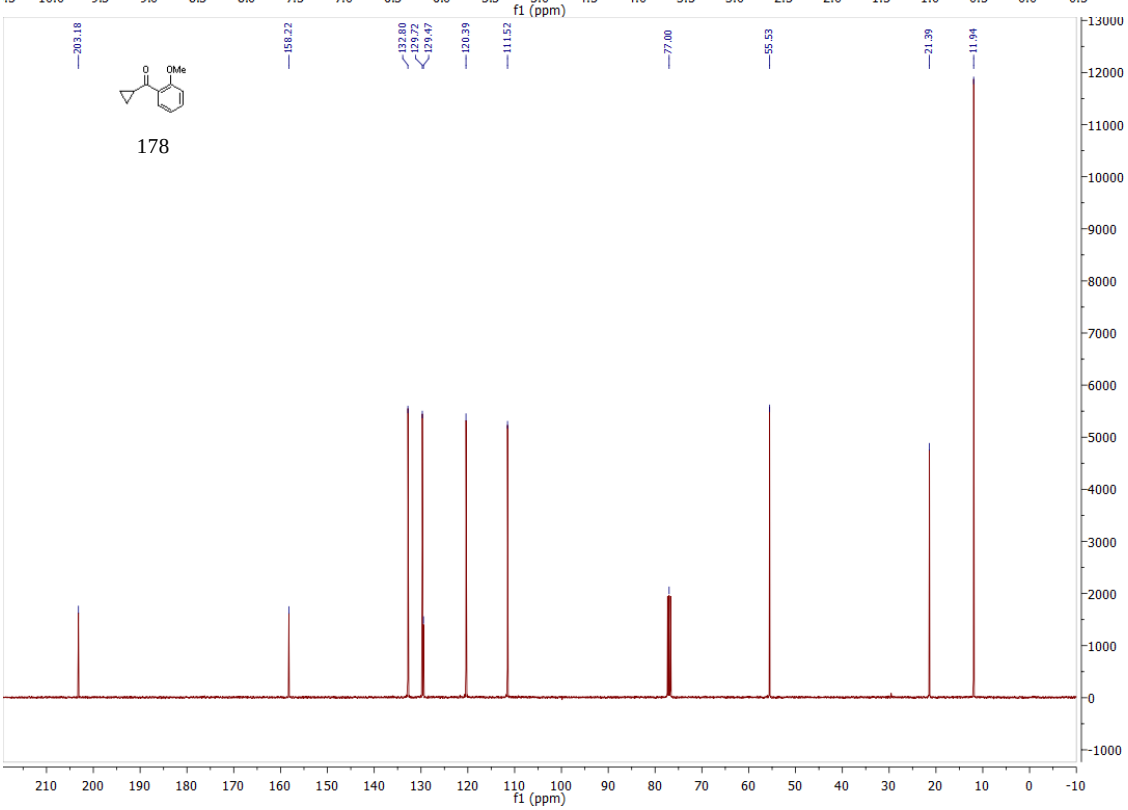

173
2.07
1.10
2.02
2.00
9.20
f1 (ppm)


212.72
134.88
129.47
128.30
126.52
77.00
44.57
43.20
26.34
173
f1 (ppm)

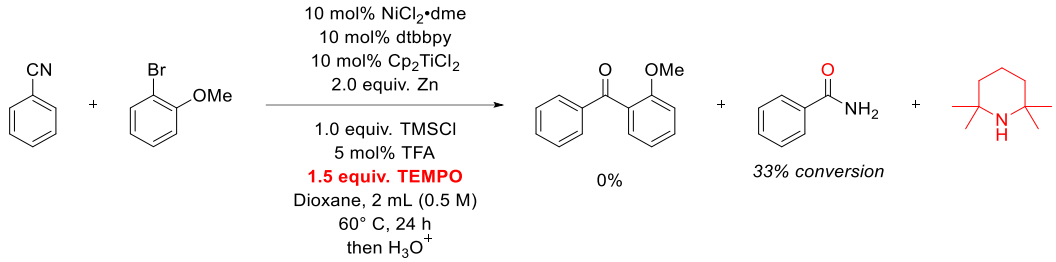

NH2 OMe
176
2.12
2.57
2.00
2.02
0.97
3.00
2.24
f1 (ppm)


NH2 OMe
176
156.67
145.04
134.04
128.05
127.88
127.44
126.96
126.47
120.56
110.57
77.00
55.26
53.72
f1 (ppm)


O
OMe
178
1.06
0.99
2.02
3.00
1.01
2.01
2.06
f1 (ppm)


203.18
158.22
132.80
130.72
129.47
120.39
111.52
77.00
55.53
21.39
11.94
O
OMe
178
f1 (ppm)

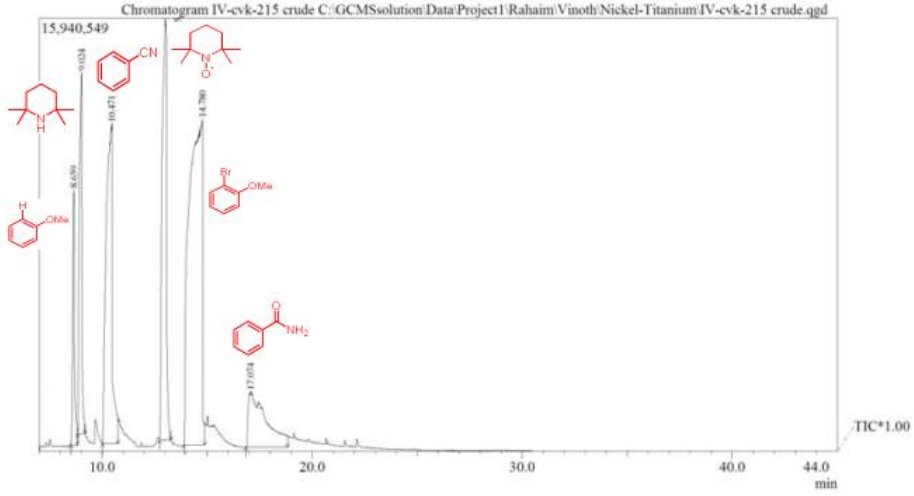
Scheme 2. Radical Trap Experiment with TEMPO.



Sample Information

Analyzed by	: Weaver, Jimmie
Analyzed	: 1/12/2018 1:43:14 PM
Sample Type	: Unknown
Level #	: 1
Sample Name	: IV-cvk-215 crude
Sample ID	:
IS Amount	: [1]=1.000
Sample Amount	: 1.000
Dilution Factor	: 1.000
Vial #	: 20
Injection Volume	: 1.000
Data File	: C:\GCMSsolution\Data\Project1\Rahaim\Vinoth\Nickel-Titanium\IV-cvk-215 crude.qgd
Org Data File	: C:\GCMSsolution\Data\Project1\Rahaim\Vinoth\Nickel-Titanium\IV-cvk-215 crude.qgd
Method File	: C:\GCMSsolution\Data\Project1\Rahaim\Vinoth\Titanium-45 mins-280 degree-1.qgm
Org Method File	: C:\GCMSsolution\Data\Project1\Rahaim\Vinoth\Titanium-45 mins-280 degree-1.qgm
Report File	:
Tuning File	: C:\GCMSsolution\System\Tune1\QP2010S.qgt
Modified by	: Weaver, Jimmie
Modified	: 1/12/2018 3:16:50 PM

Chromatogram IV-cvk-215 crude C:\GCMSsolution\Data\Project1\Rahaim\Vinoth\Nickel-Titanium\IV-cvk-215 crude.qgd

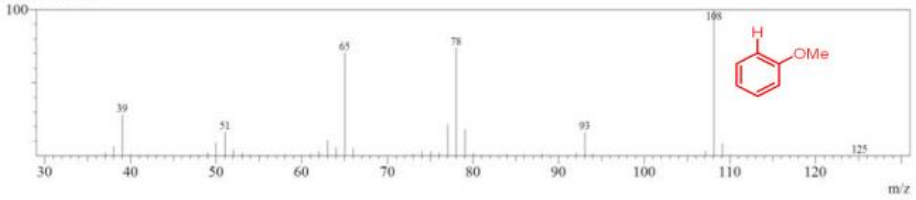


Peak Report TIC

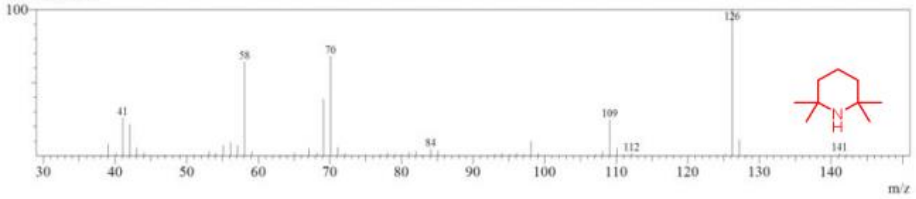
Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	8.659	8.525	8.817	59309452	4.64	9433783	14.71	6.28	MI	
2	9.024	8.850	9.192	109418904	8.56	13305774	20.75	8.22	MI	
3	10.471	10.025	10.767	245724524	19.22	11783894	18.37	20.85	MI	
4	13.025	12.742	13.283	223363565	17.47	15531550	24.22	14.38	MI	
5	14.780	13.883	14.883	520626102	40.73	12021312	18.74	43.30	MI	
6	17.074	16.833	18.842	119856178	9.38	2055653	3.21	58.30	MI	
				1278298725	100.00	64131966	100.00			

Spectrum

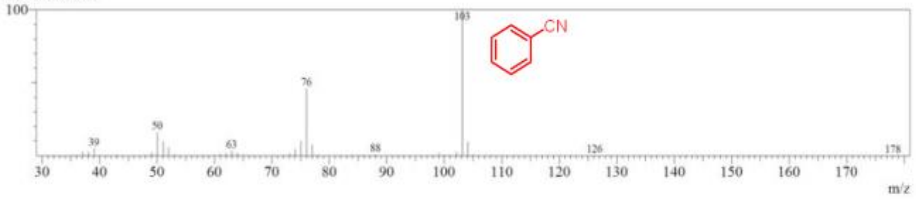
Line#:1 R.Time:8.6(Scan#:197)
MassPeaks:67
RawMode:Single 8.6(197) BasePeak:108(1936114)
BG Mode:None



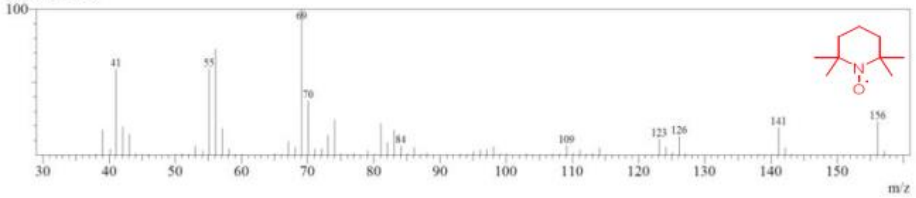
Line#:2 R.Time:9.0(Scan#:237)
MassPeaks:83
RawMode:Single 9.0(237) BasePeak:126(2504361)
BG Mode:None



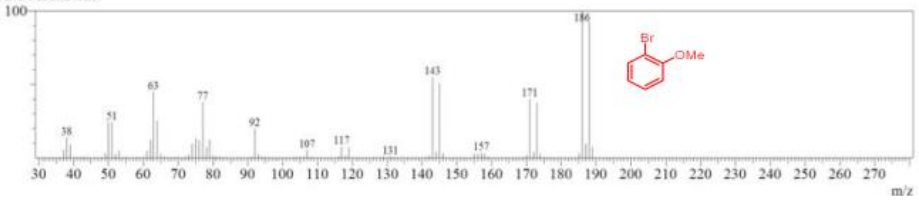
Line#:3 R.Time:10.4(Scan#:403)
MassPeaks:61
RawMode:Single 10.4(403) BasePeak:103(4562905)
BG Mode:None



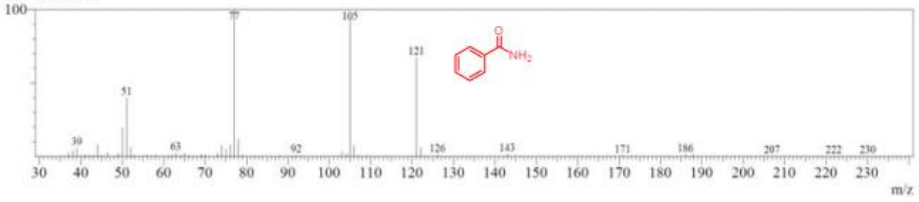
Line#:4 R.Time:13.0(Scan#:721)
MassPeaks:98
RawMode:Single 13.0(721) BasePeak:69(2256092)
BG Mode:None

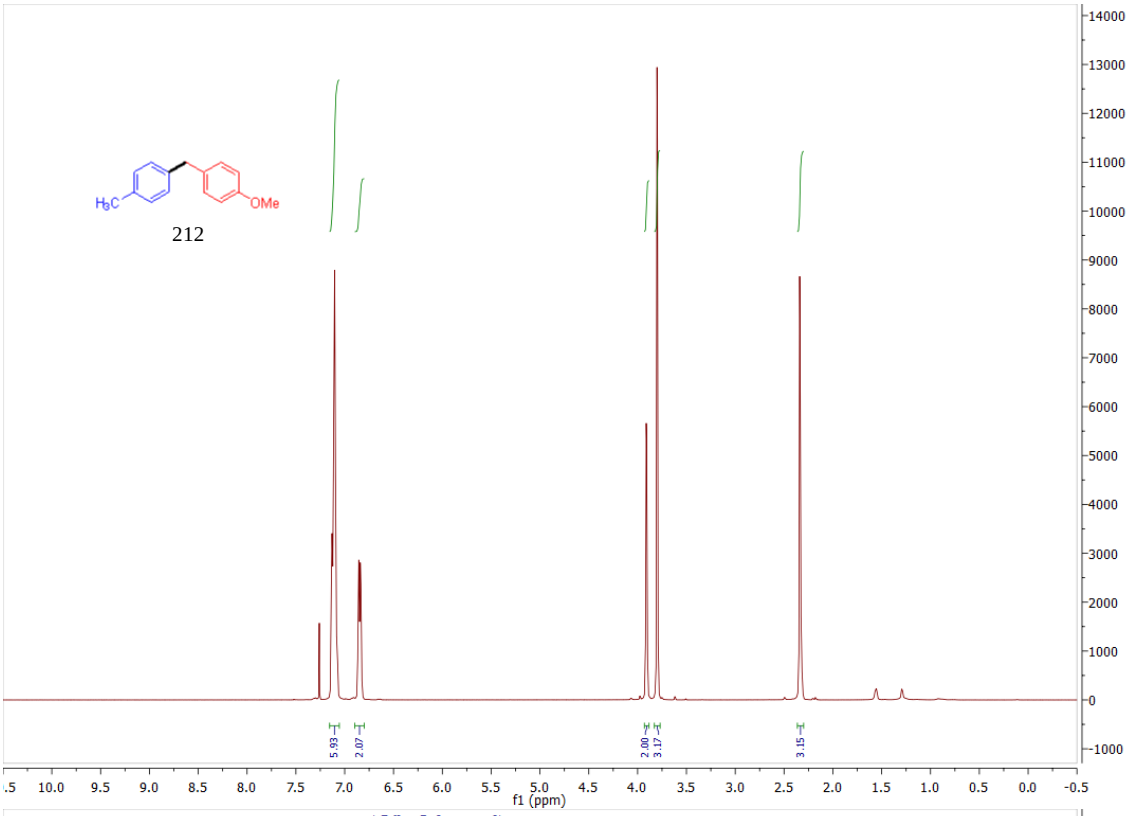


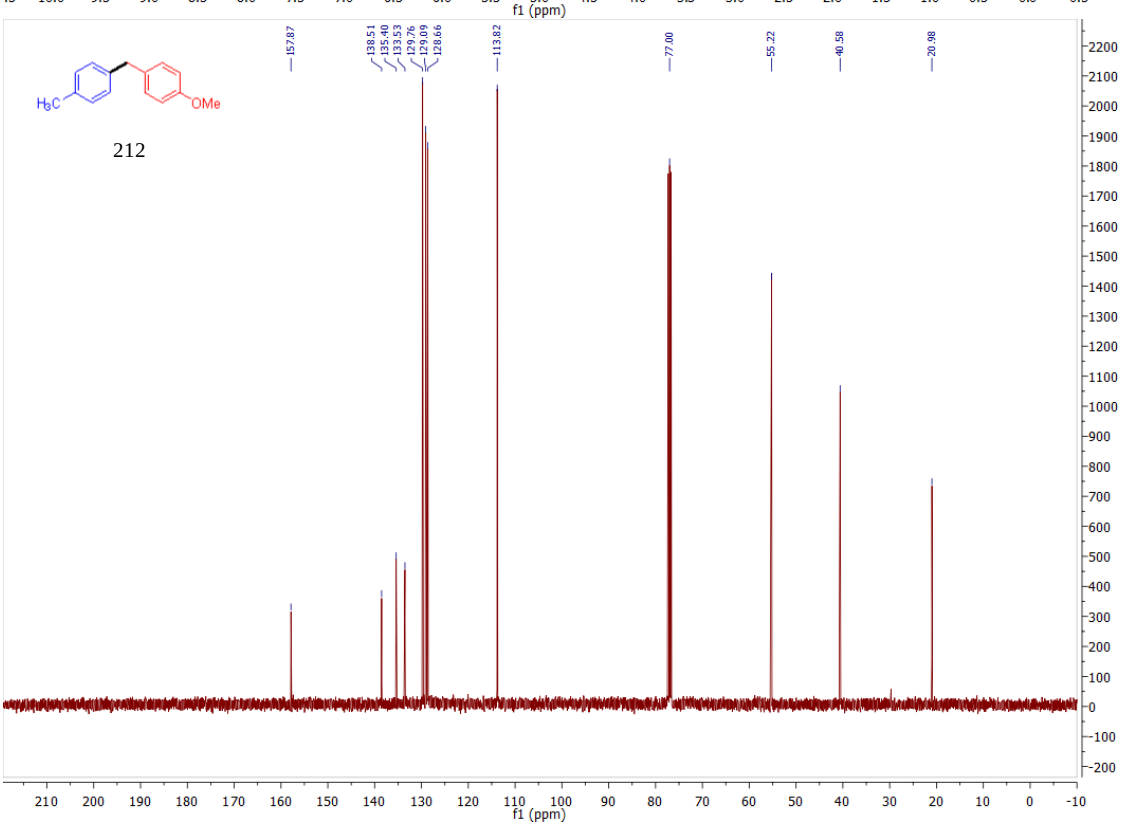
Line#:5 R.Time:14.5(Scan#:905)
MassPeaks:101
RawMode:Single 14.5(905) BasePeak:186(1496014)
BG Mode:None

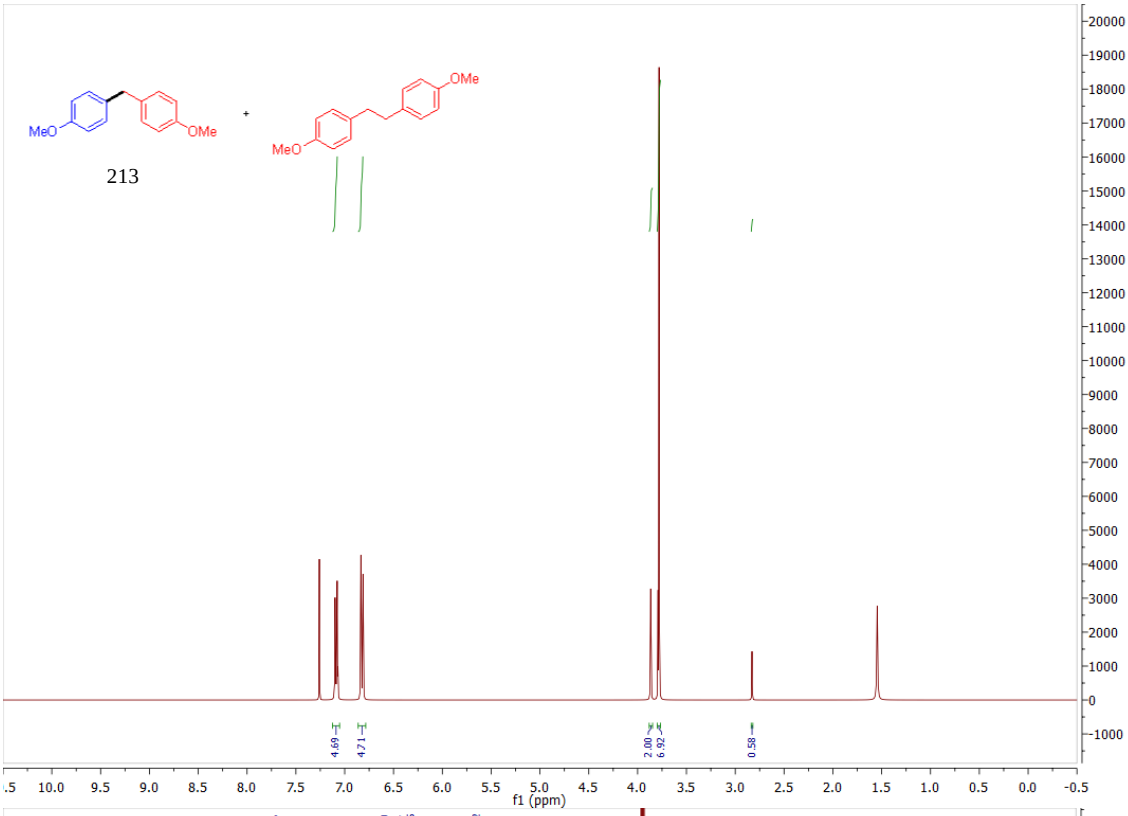


Line#:6 R.Time:17.3(Scan#:1232)
MassPeaks:67
RawMode:Single 17.3(1232) BasePeak:77(392707)
BG Mode:None

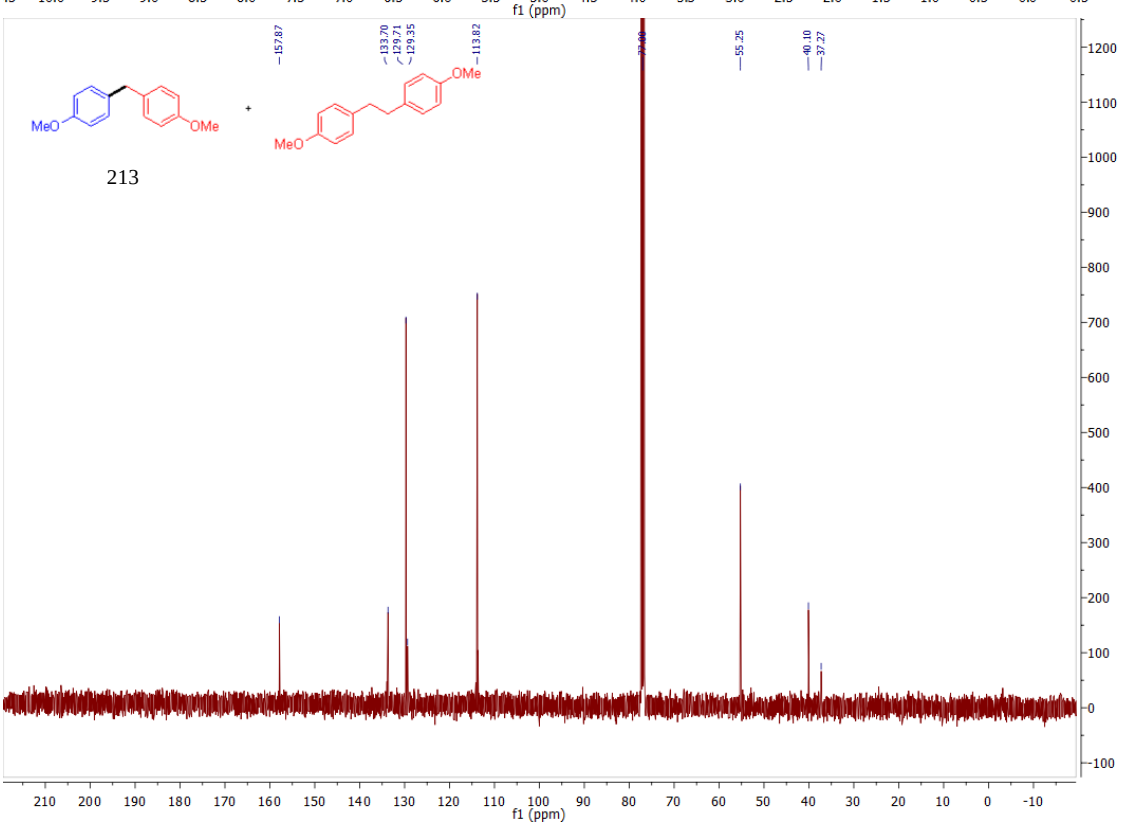



H3C
OMe
212
5.93
2.07
2.00
3.17
3.15
f1 (ppm)

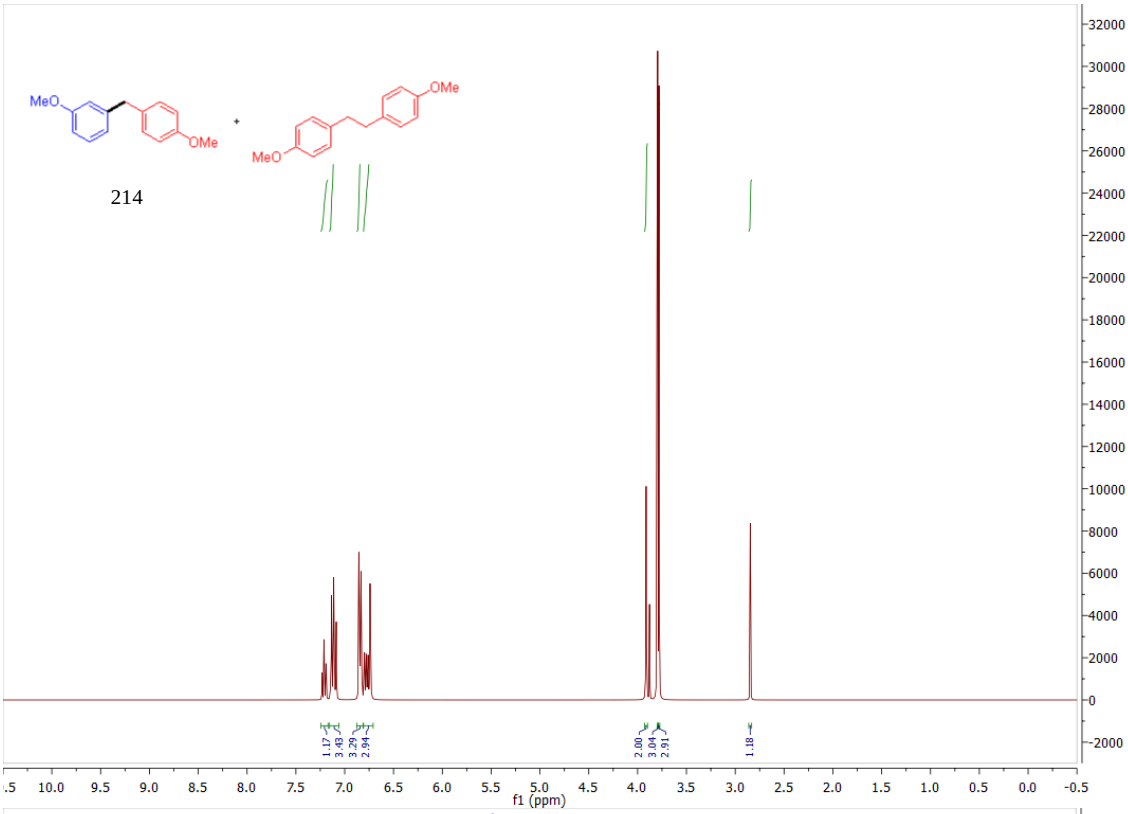

H3C
OMe
212
157.87
138.51
135.40
133.53
129.76
129.09
128.66
113.82
77.00
55.22
40.58
20.98
f1 (ppm)

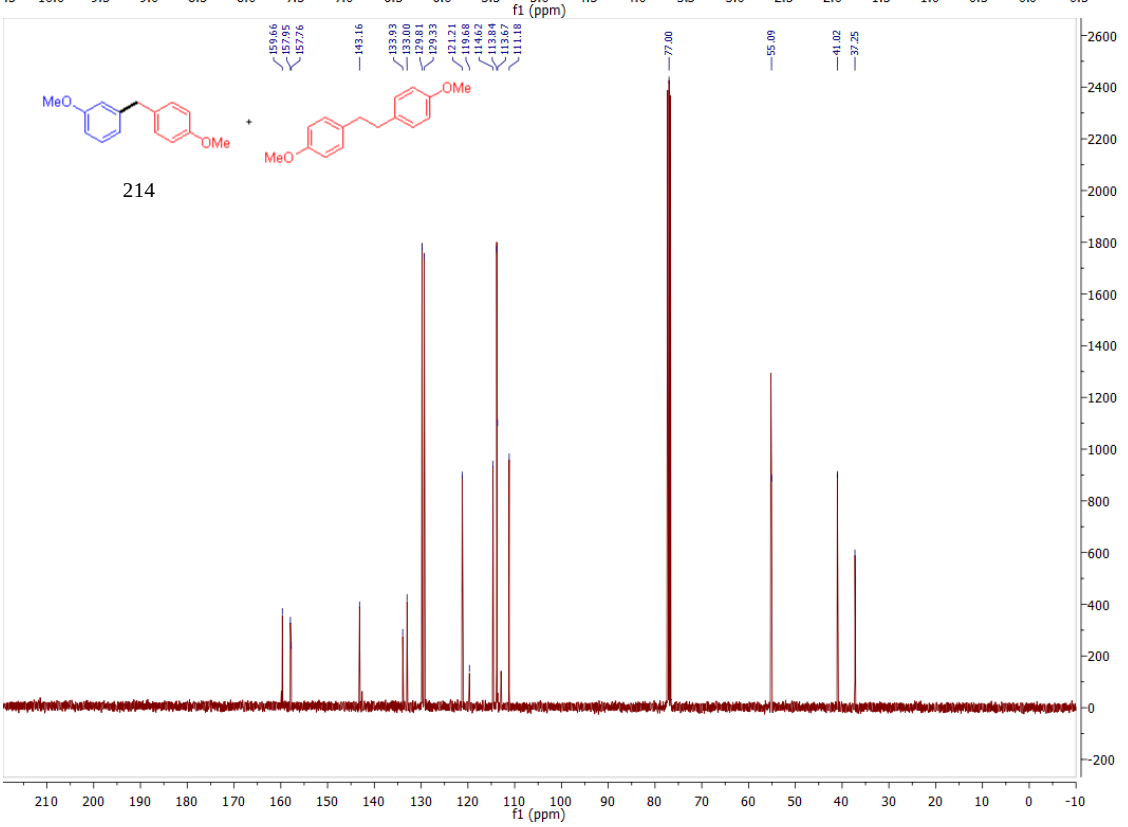

MeO
OMe
MeO
OMe
4.69
4.71
2.00
6.92
0.58
f1 (ppm)

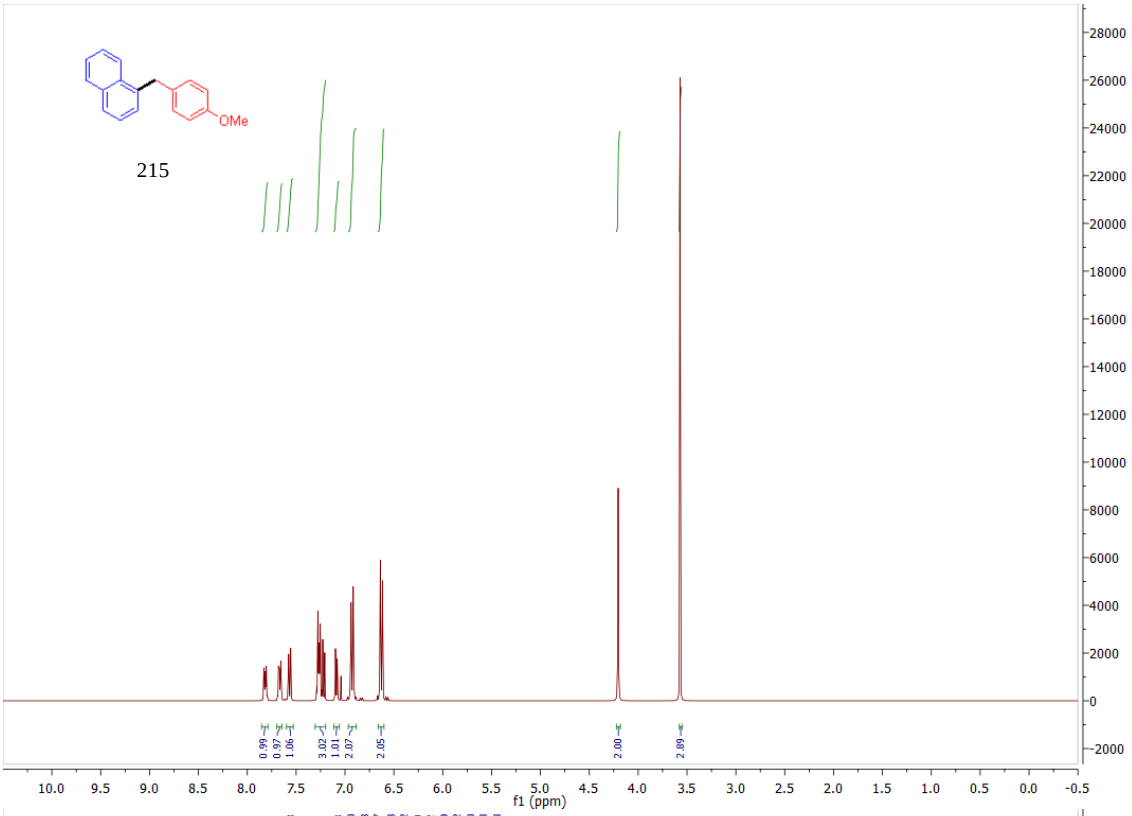
213

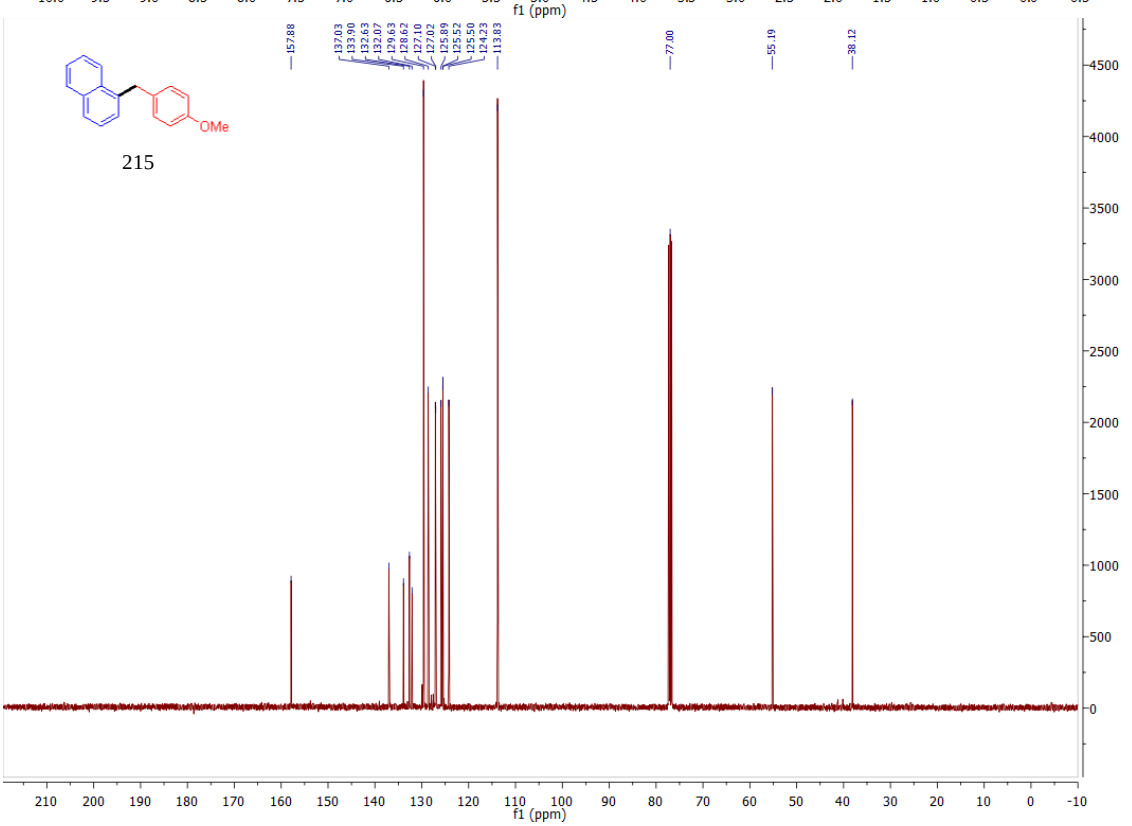

157.87
133.70
129.71
129.35
113.82
77.48
55.25
40.10
37.27
MeO
OMe
MeO
OMe
f1 (ppm)

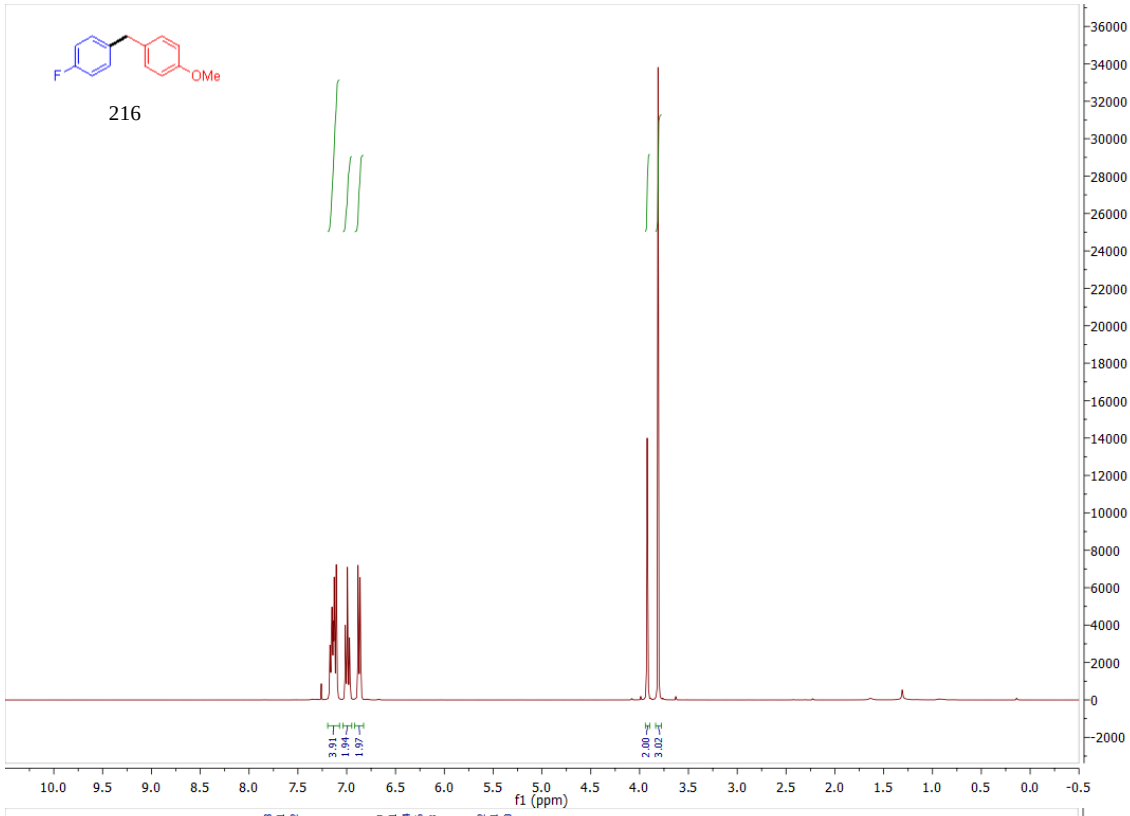
213


MeO
OMe
MeO
OMe
214
1.17
3.43
3.29
2.94
2.00
3.04
2.91
1.18
f1 (ppm)

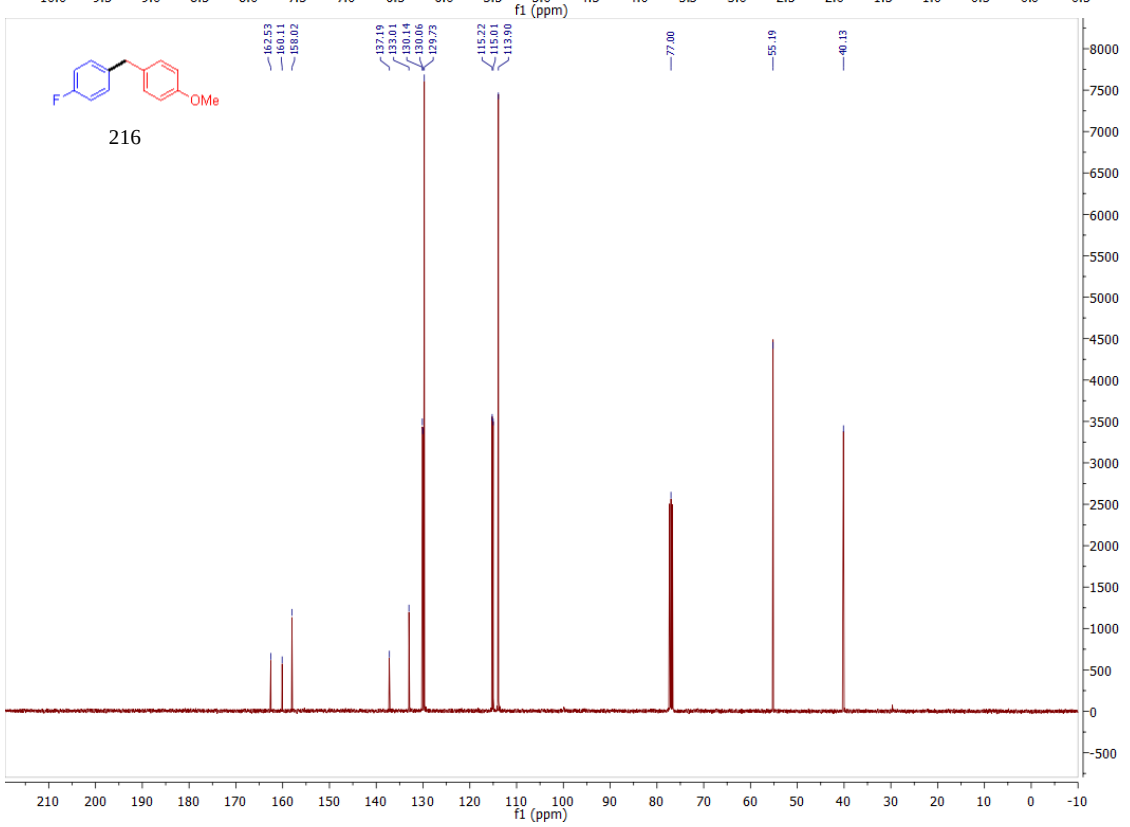

159.66
157.95
157.76
143.16
133.93
133.00
129.81
129.33
121.21
119.68
114.62
113.84
113.67
111.18
77.00
55.09
41.02
37.25
MeO
OMe
MeO
OMe
214
f1 (ppm)


OMe
215
0.99
0.97
1.06
3.02
1.01
2.07
2.05
2.00
2.89
f1 (ppm)

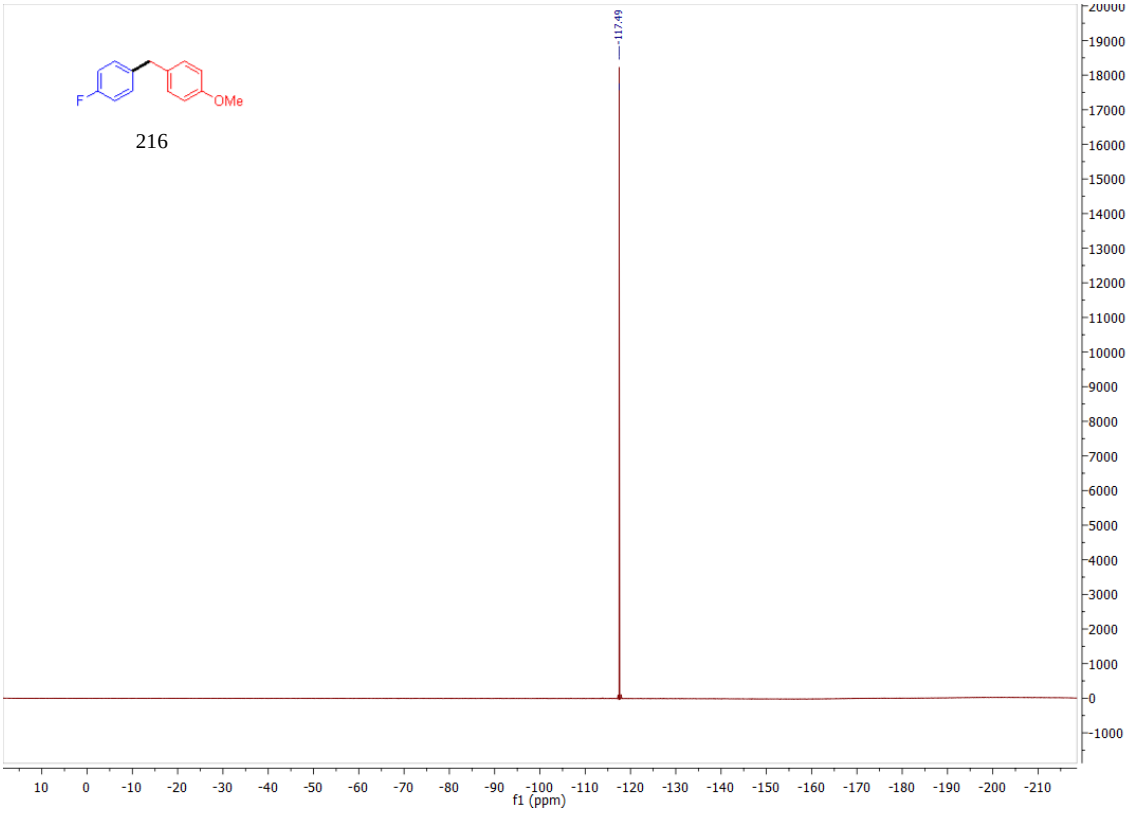

OMe
215
157.88
137.03
133.90
132.63
132.07
129.63
128.62
127.10
127.02
125.89
125.52
125.50
124.23
113.83
77.00
55.19
38.12
f1 (ppm)

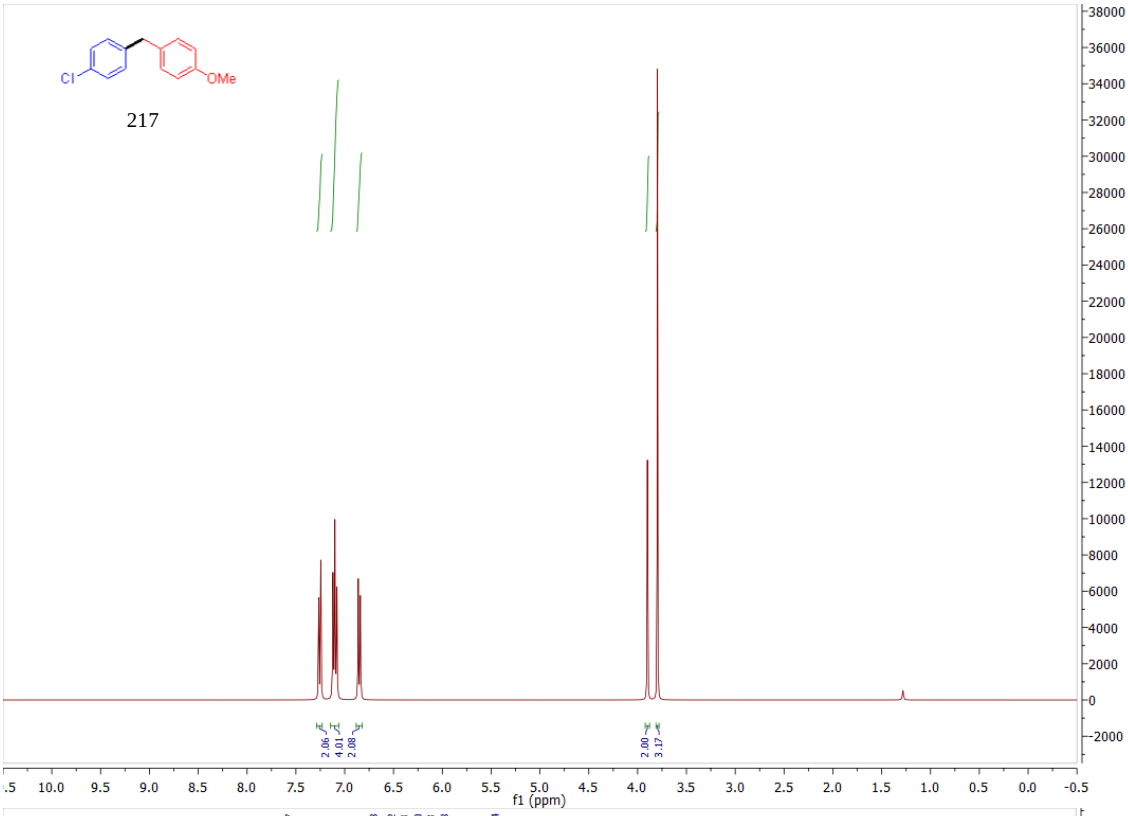

F
OMe
3.91
1.94
1.97
2.00
3.02
f1 (ppm)

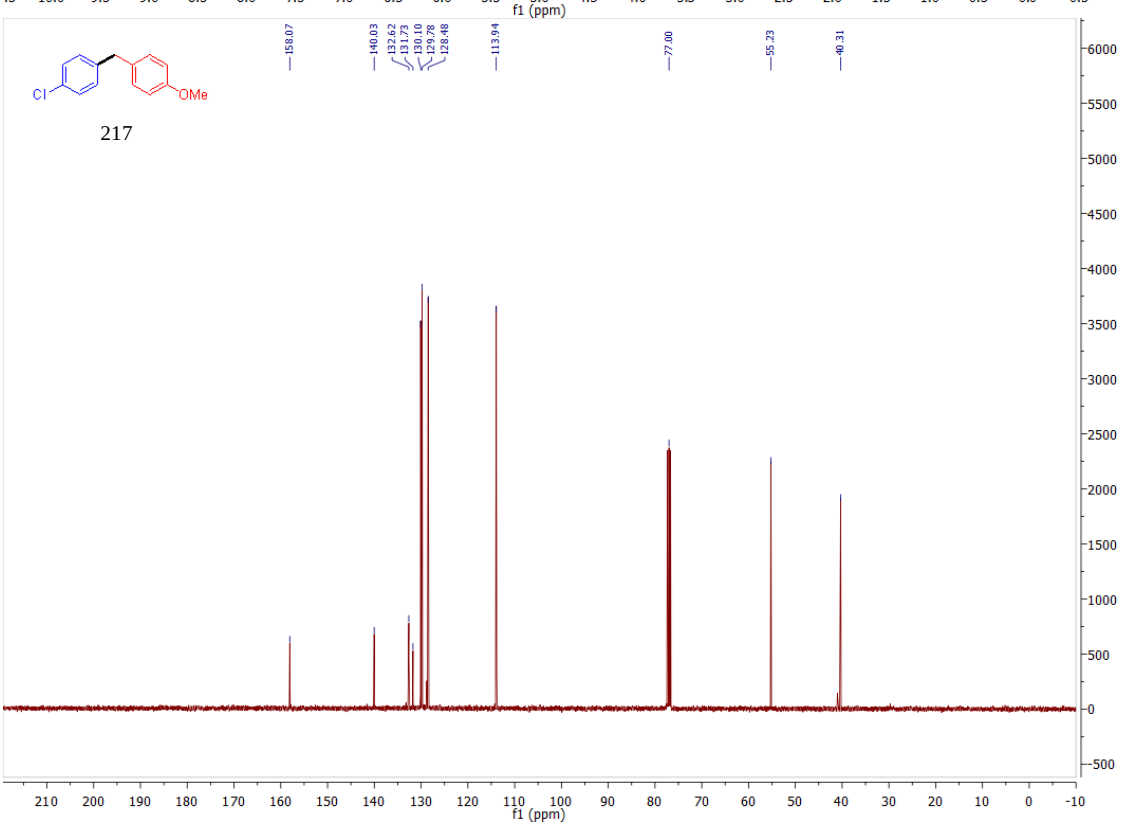
216

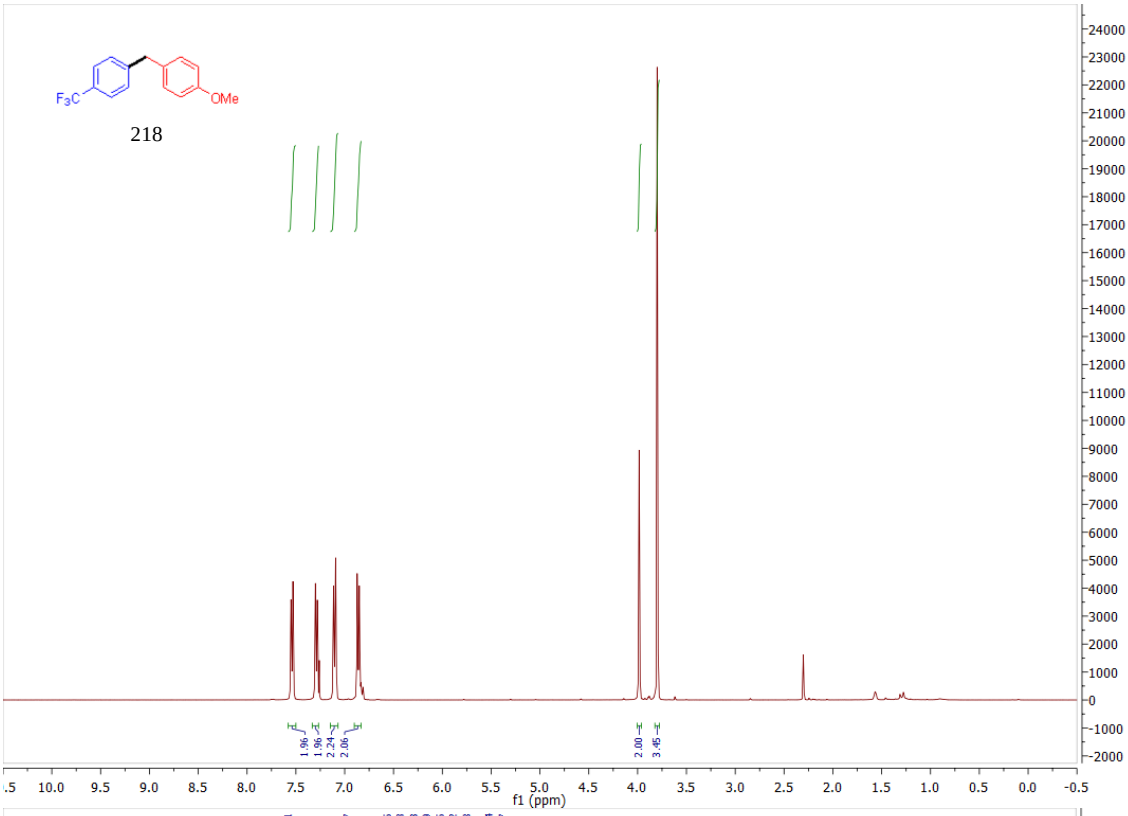

F
OMe
162.53
160.11
158.02
137.19
133.01
130.14
130.06
129.73
115.22
115.01
113.90
77.00
55.19
40.13
f1 (ppm)

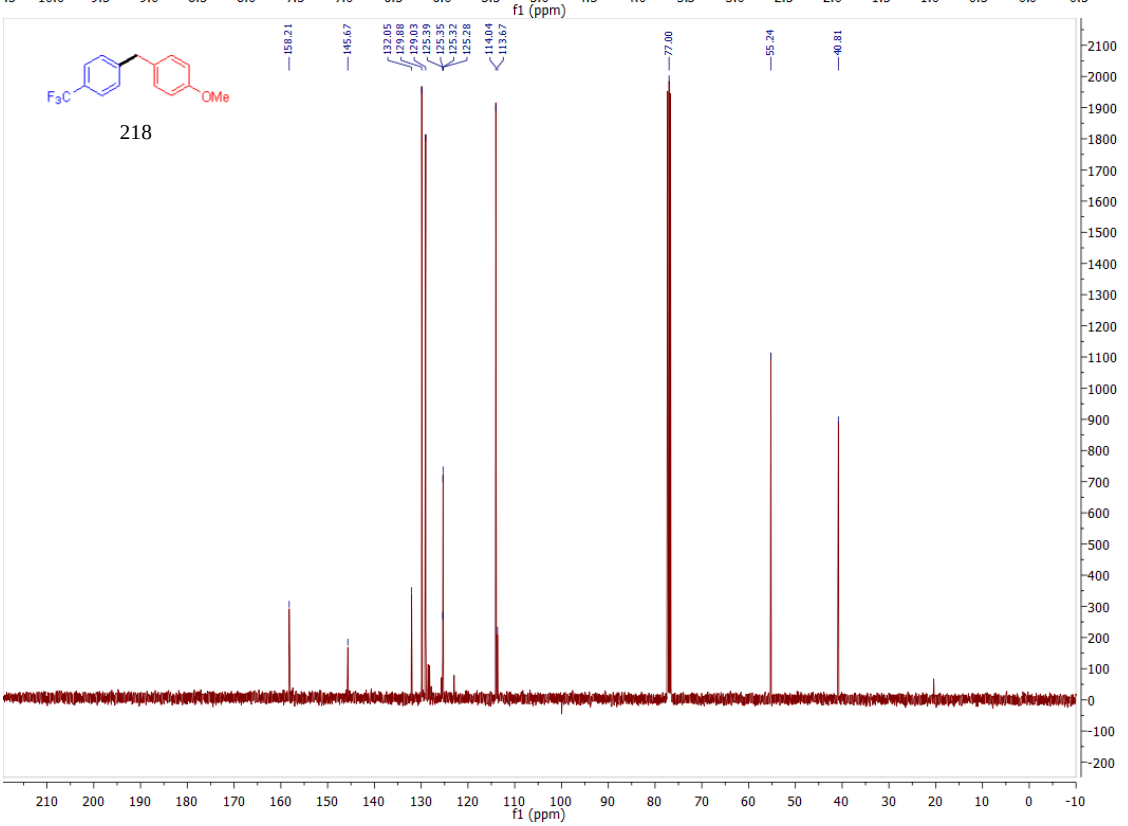
216

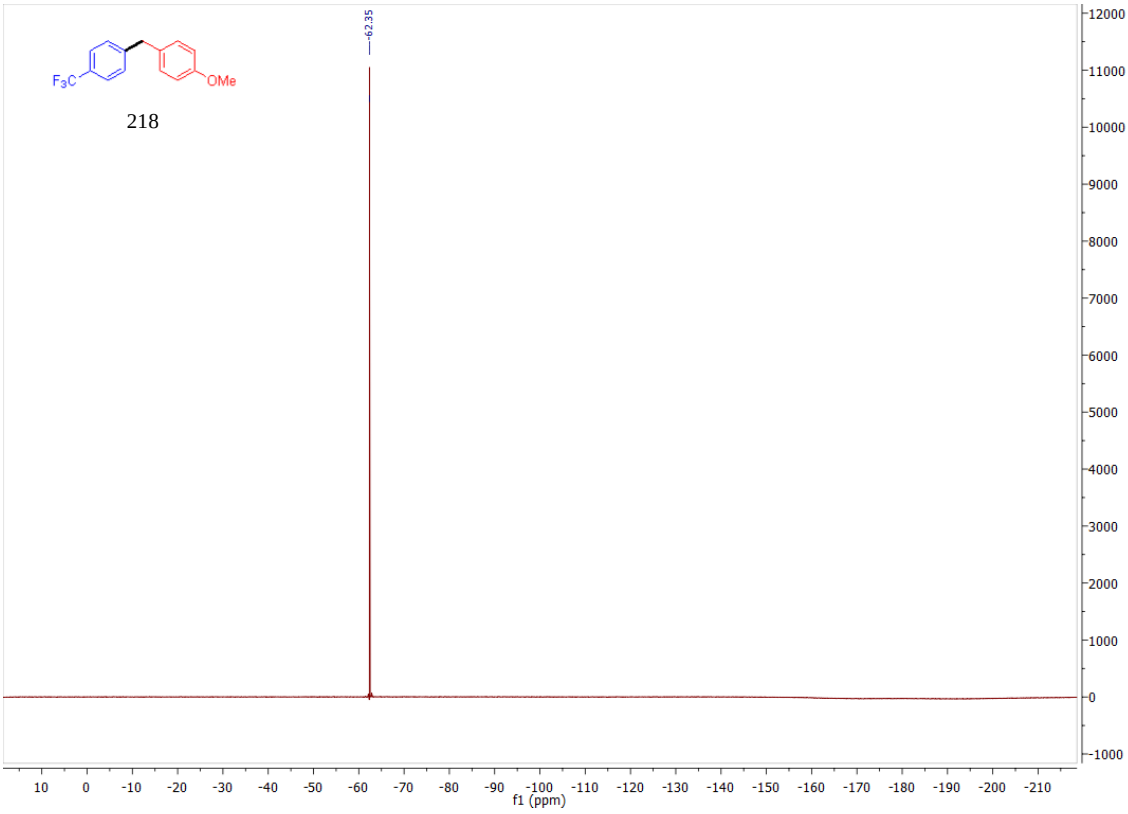

F
OMe
216
-117.49
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)


Cl
OMe
217
2.06
4.01
2.08
2.00
3.17
f1 (ppm)

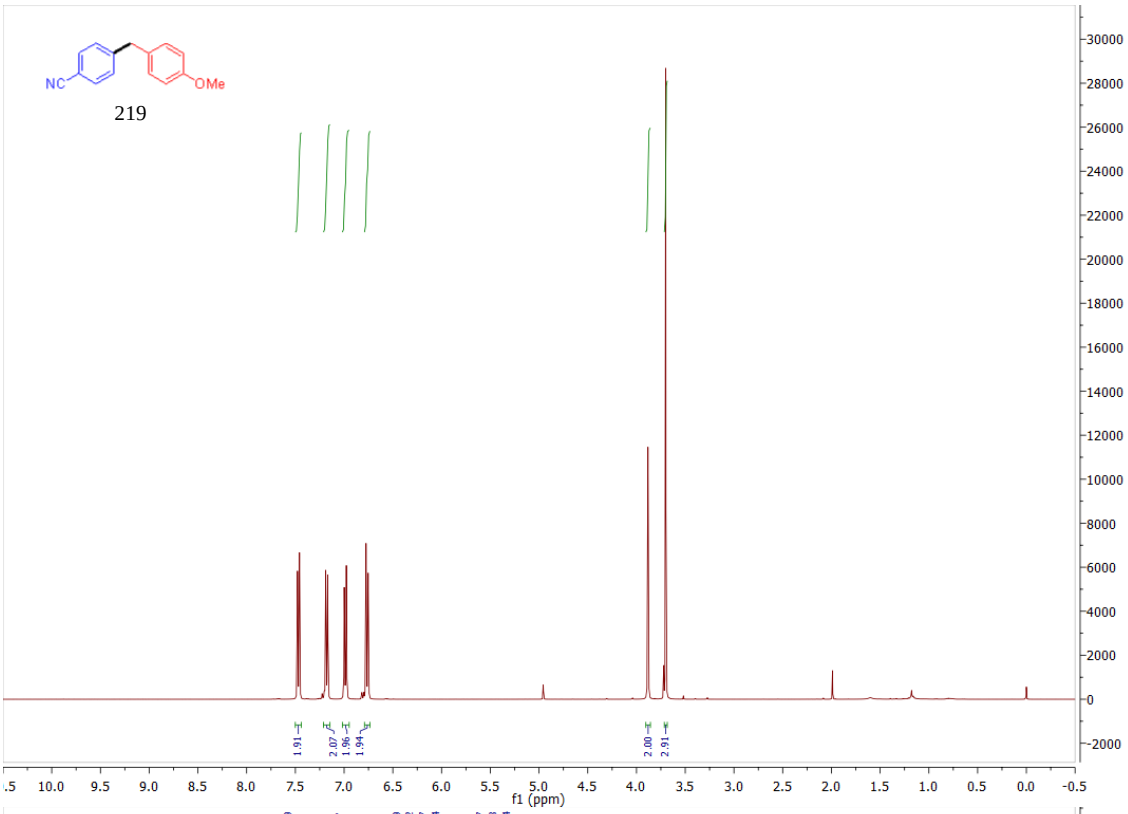

Cl
OMe
217
158.07
140.03
132.62
131.73
130.10
129.78
128.48
113.94
77.00
55.23
40.31
f1 (ppm)

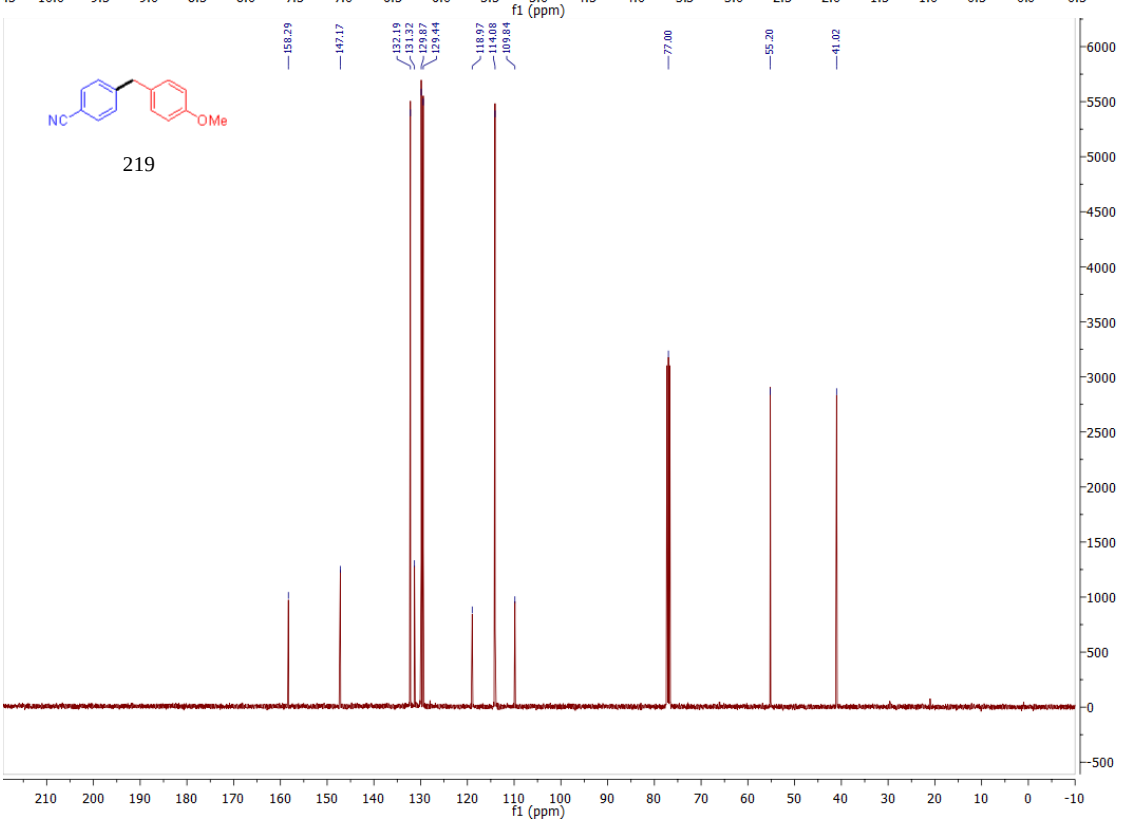

F3C
OMe
218
1.96
1.96
2.24
2.06
2.00
3.45
f1 (ppm)

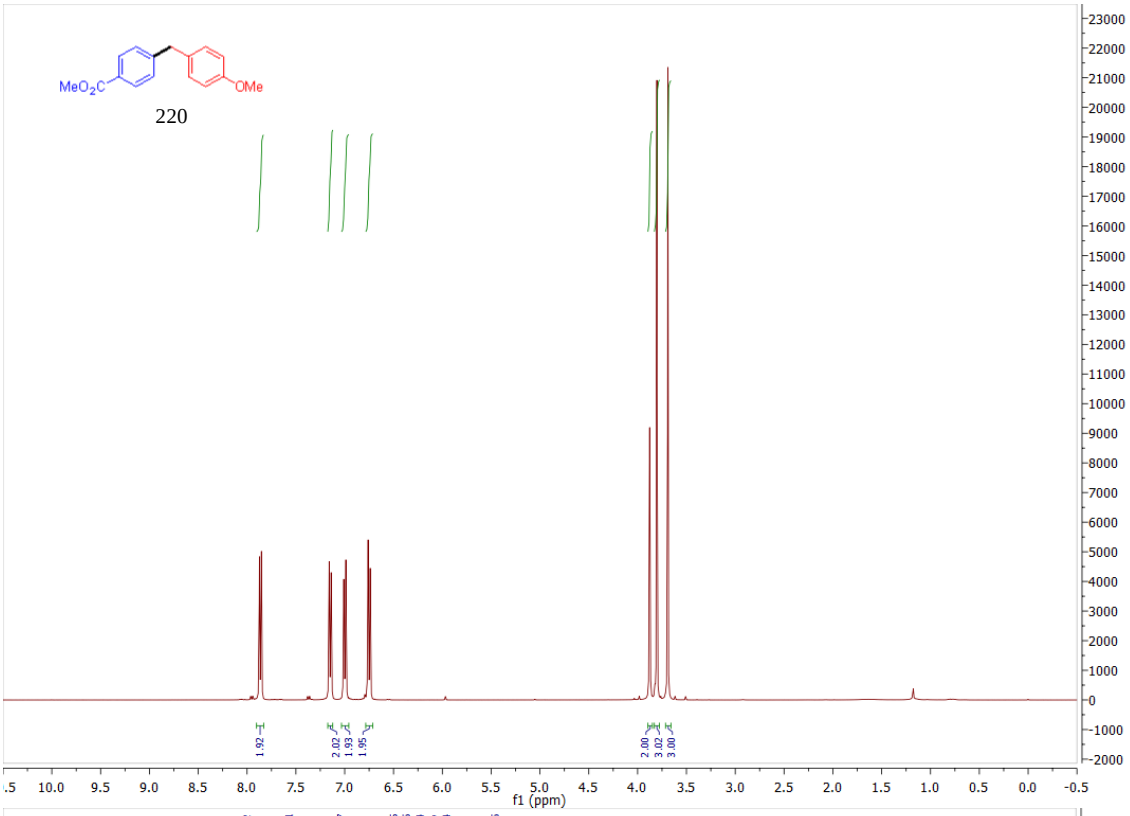

F3C
OMe
218
158.21
145.67
132.05
129.88
129.03
125.39
125.35
125.32
125.28
114.04
113.67
77.00
55.24
40.81
f1 (ppm)

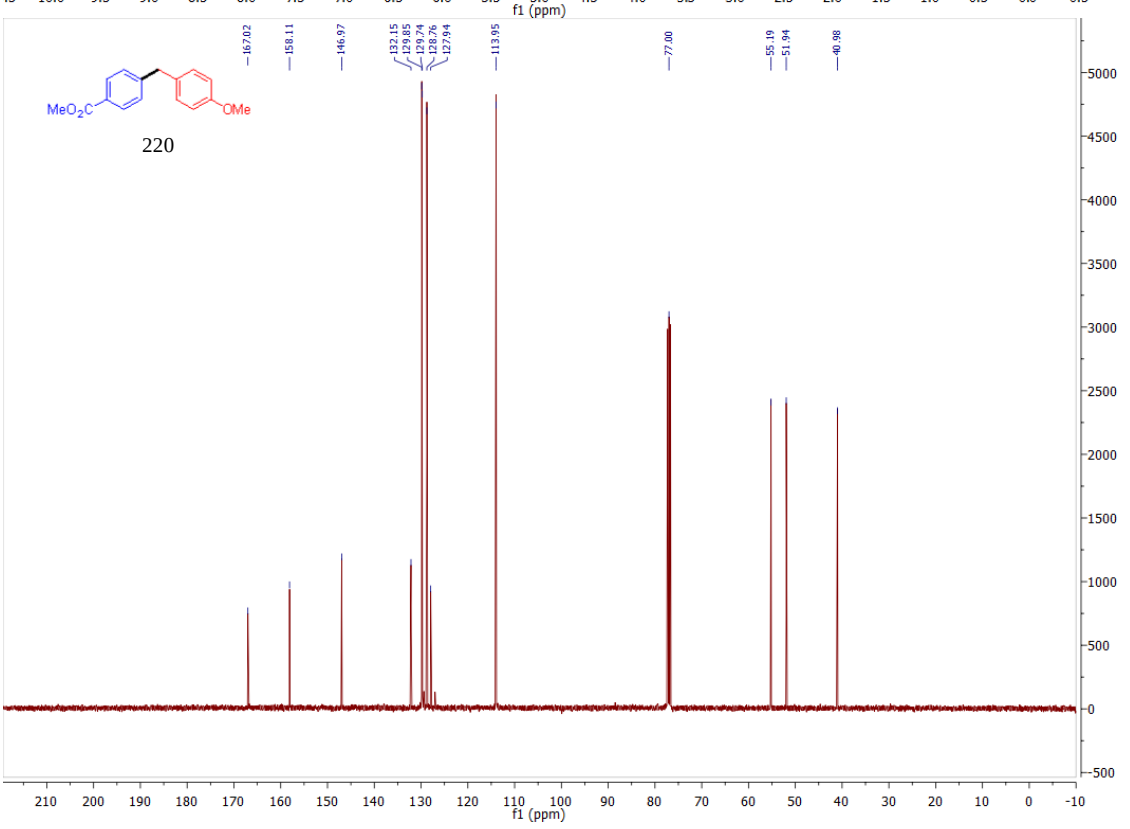

F3C
OMe
-62.35
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

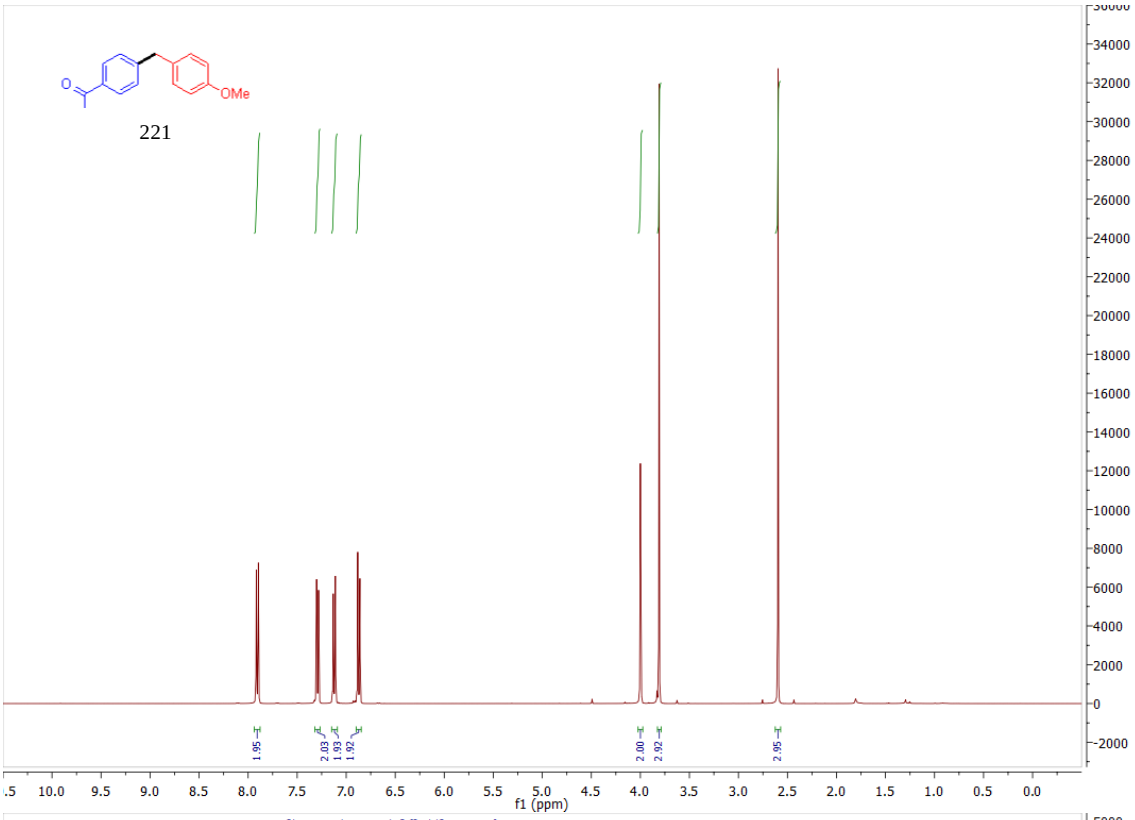
218


NC
OMe
219
1.91
2.07
1.96
1.94
2.00
2.91
f1 (ppm)

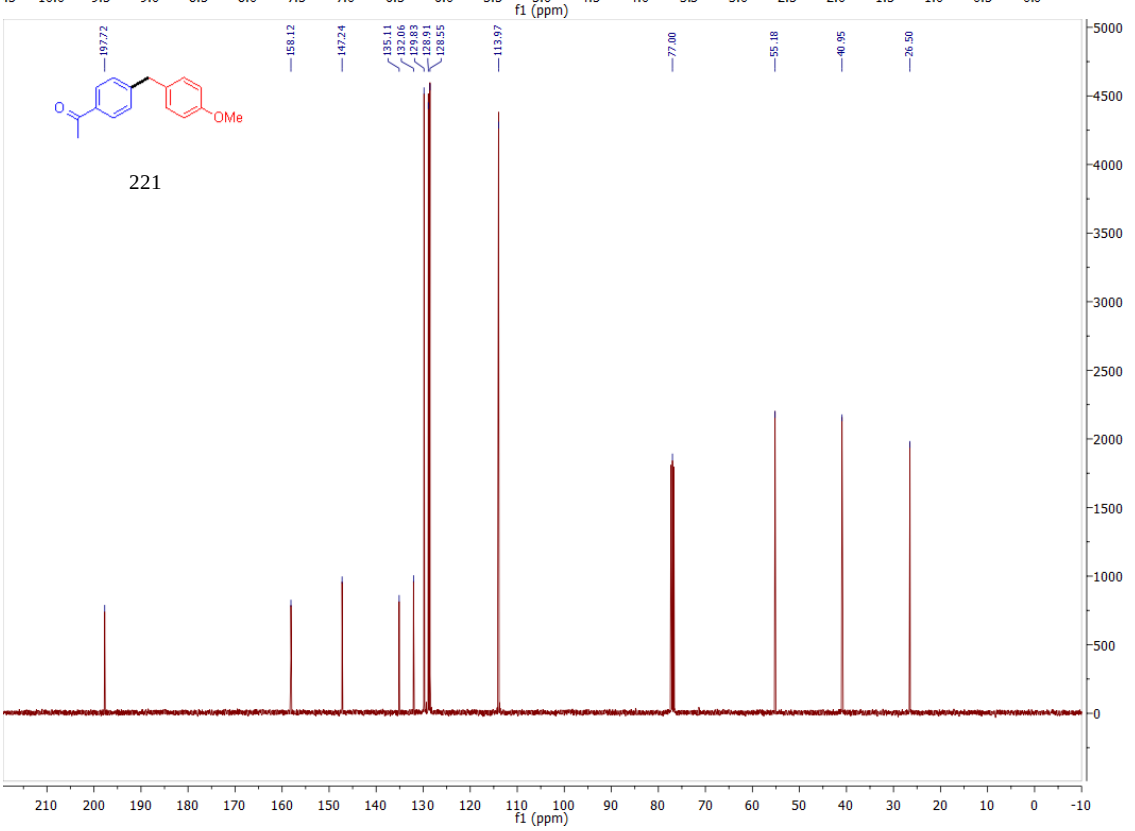

NC
OMe
219
158.29
147.17
132.19
131.32
129.87
129.44
118.97
114.08
109.84
77.00
55.20
41.02
f1 (ppm)


MeO2C
OMe
220
f1 (ppm)

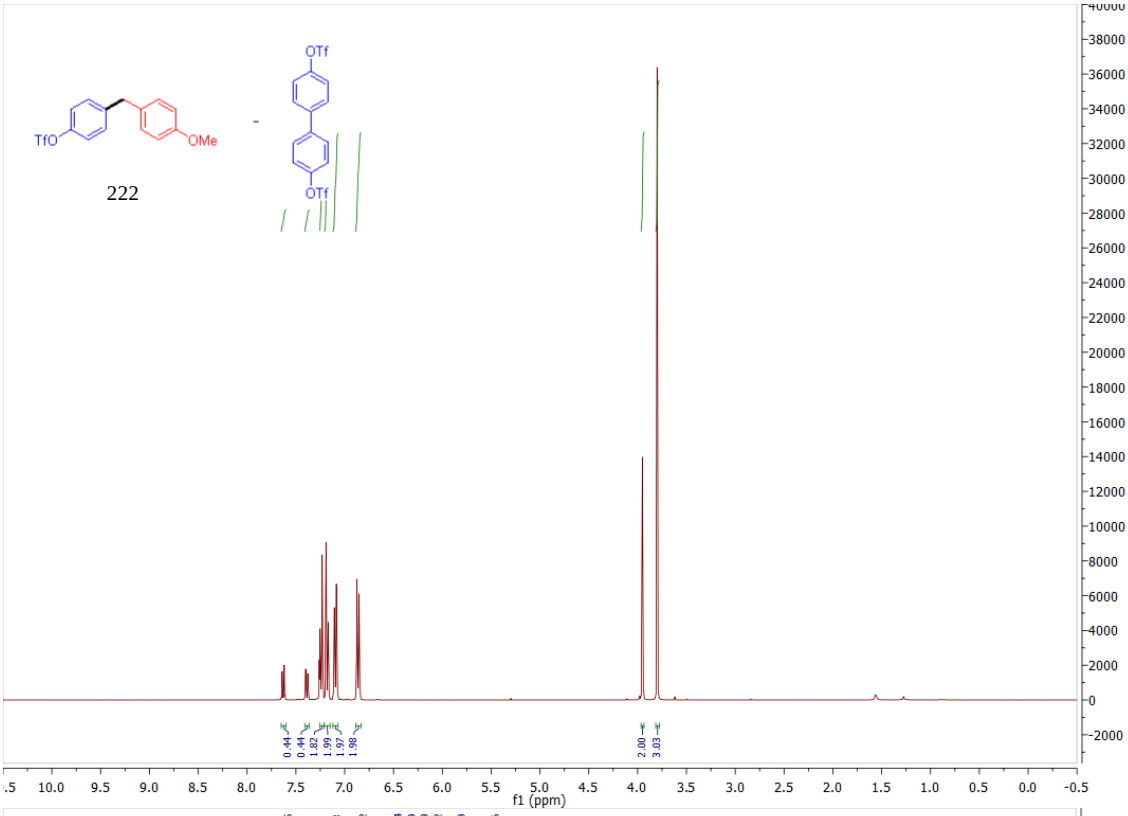

167.02
158.11
146.97
132.15
129.85
129.74
128.76
127.94
113.95
77.00
55.19
51.94
40.98
MeO2C
OMe
220
f1 (ppm)

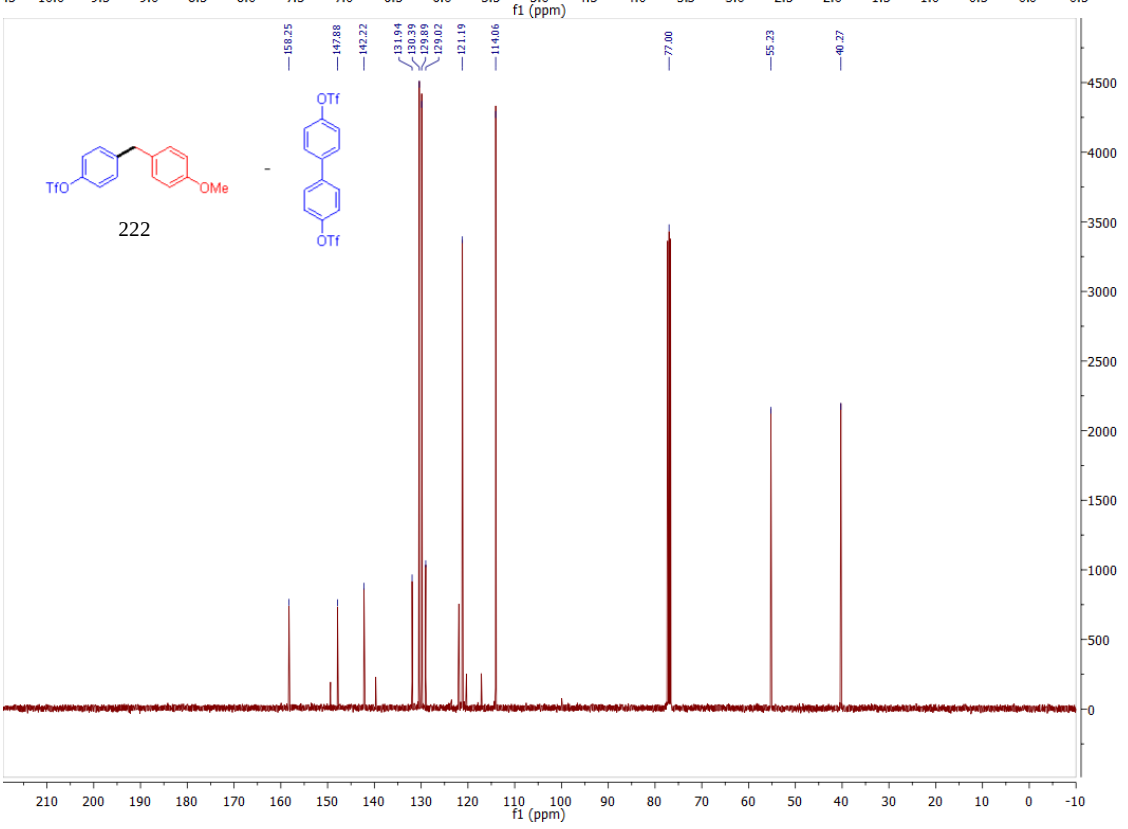

OMe
1.95
2.03
1.93
1.92
2.00
2.92
2.95
f1 (ppm)

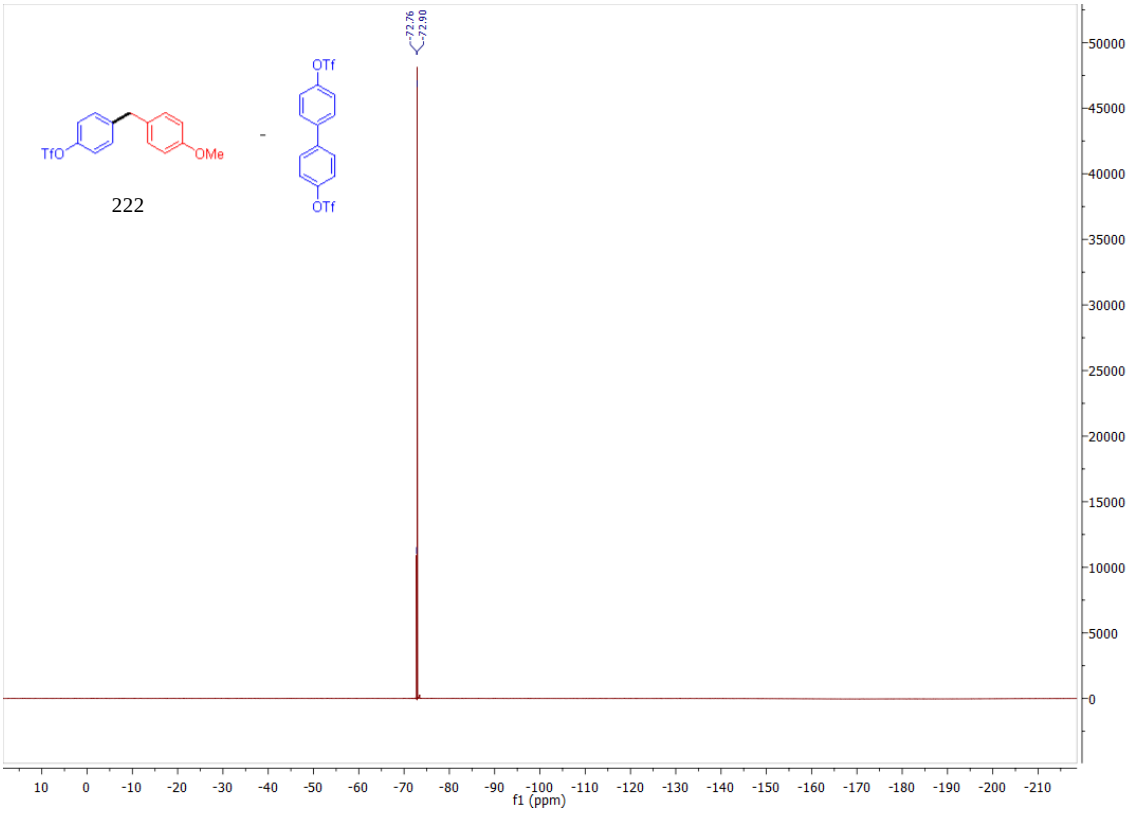
221


197.72
158.12
147.24
135.11
132.06
129.83
128.91
128.55
113.97
77.00
55.18
40.95
26.50
OMe
f1 (ppm)

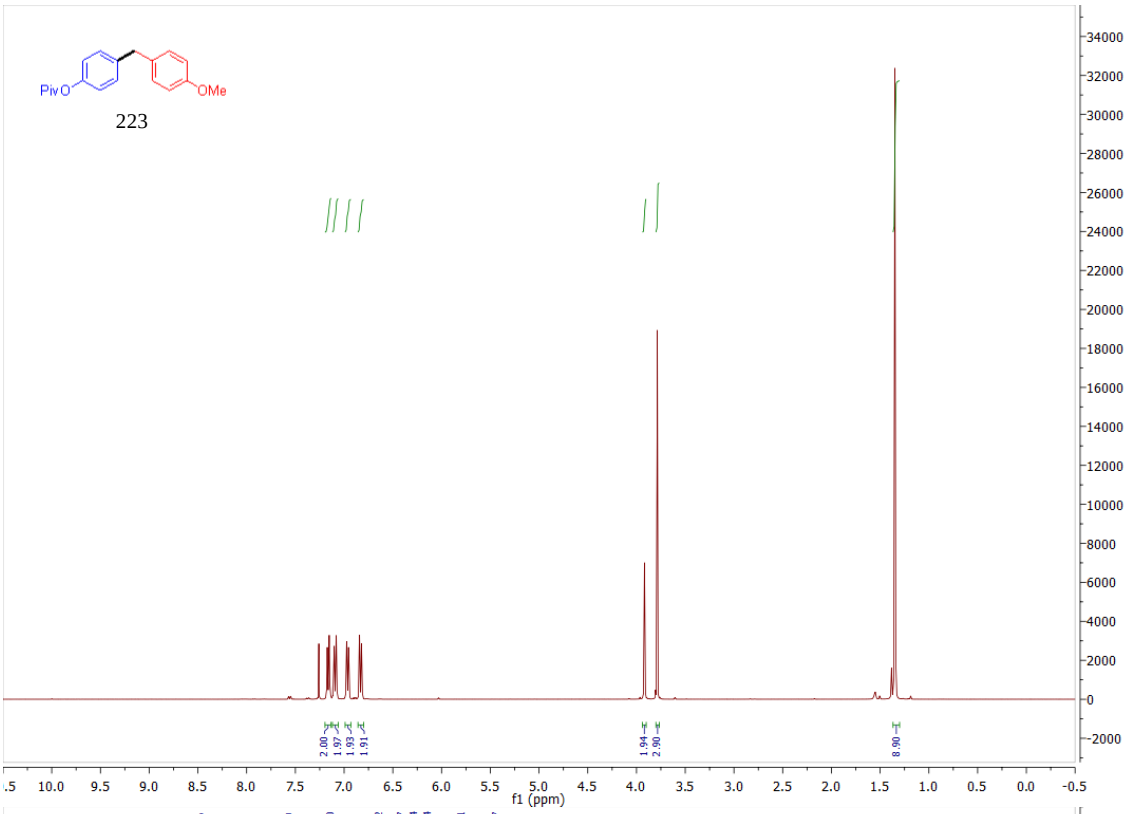
221

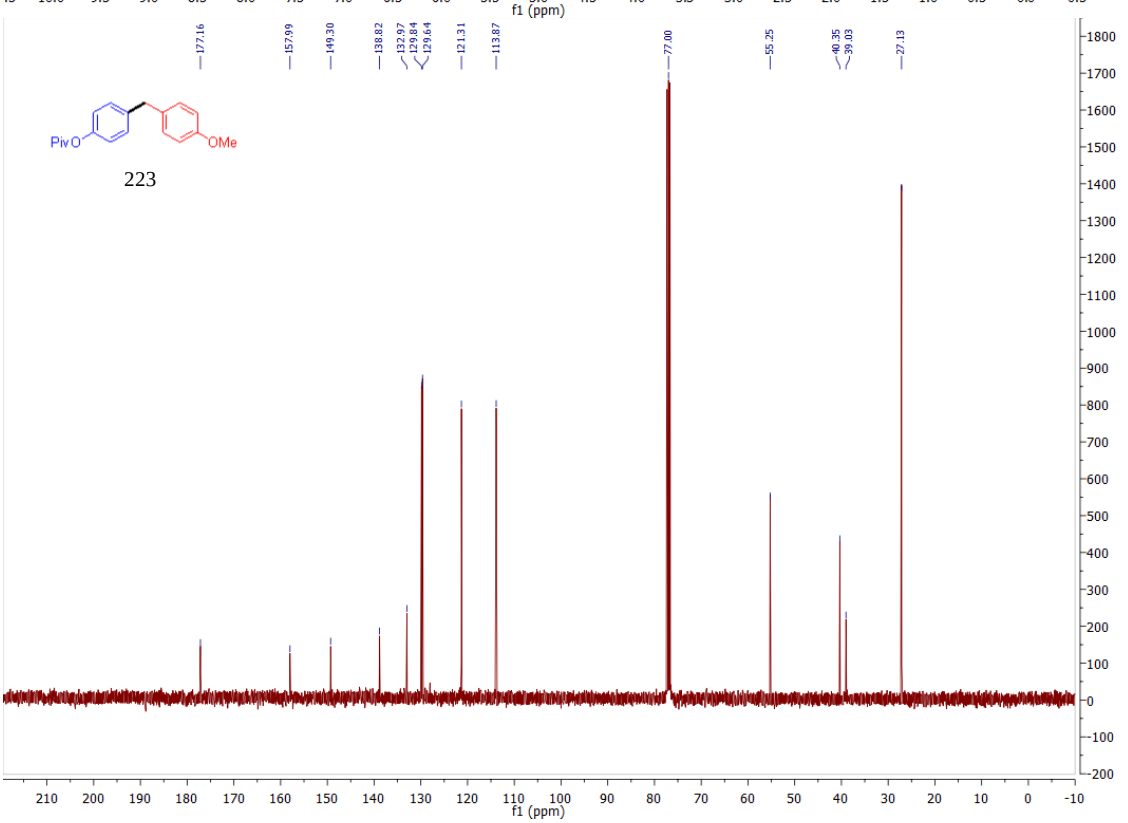

TfO
OMe
222
OTf
OTf
0.44
0.44
1.82
1.99
1.97
1.98
2.00
3.03
f1 (ppm)

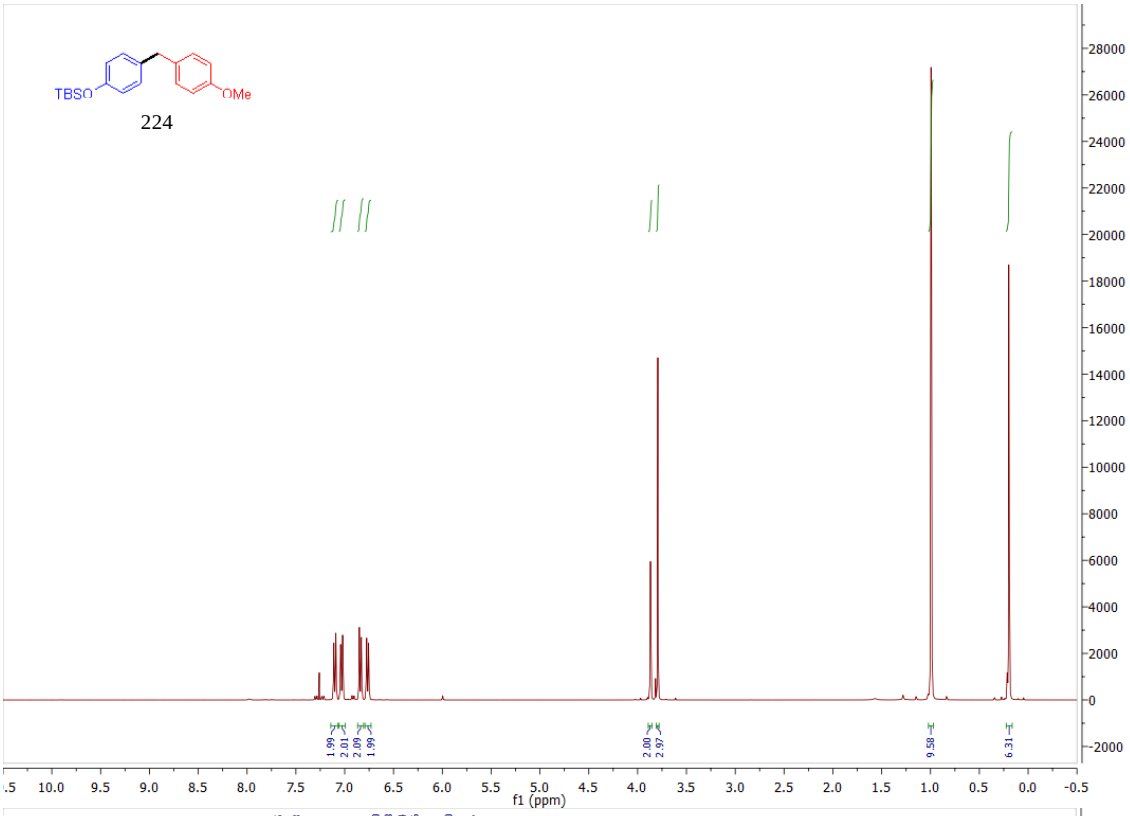

158.25
147.88
142.22
131.94
130.39
129.89
129.02
121.19
114.06
77.00
55.23
40.27
TfO
OMe
222
OTf
OTf
f1 (ppm)

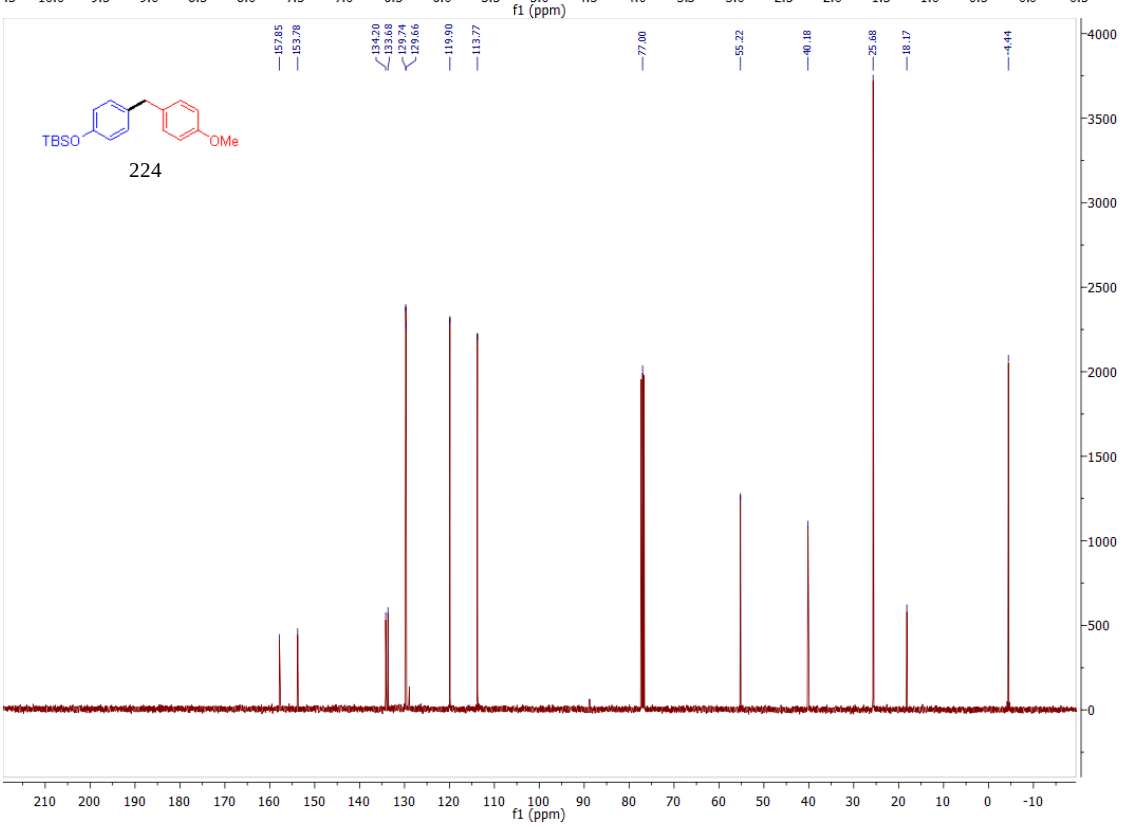

TfO
OMe
OTf
OTf
-72.76
-72.90
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

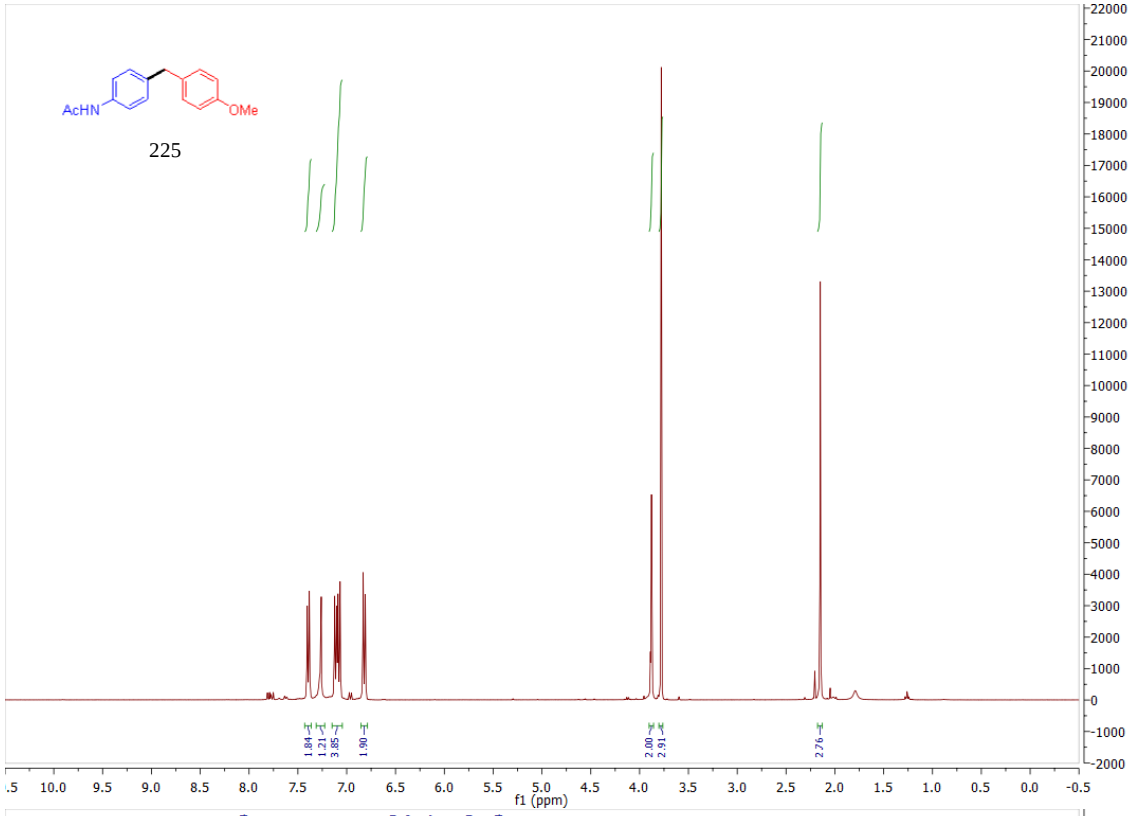
222

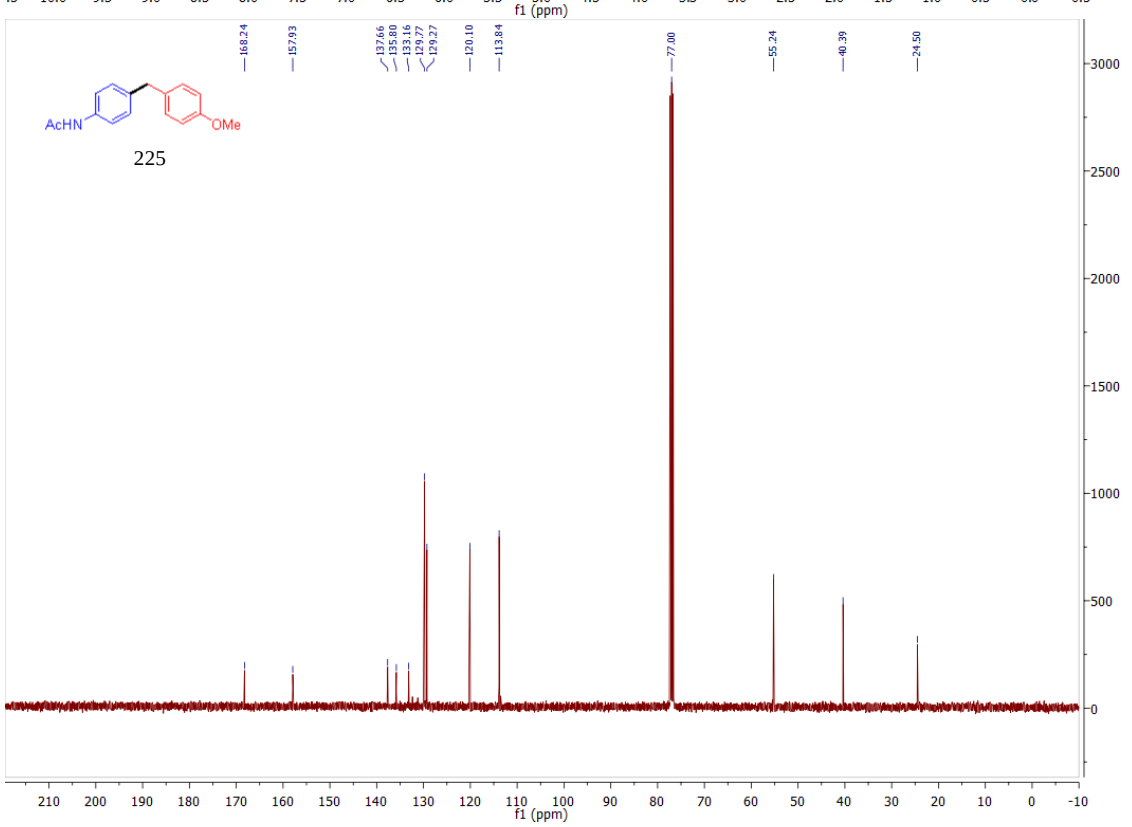

PivO
OMe
223
2.00
1.97
1.93
1.91
1.94
2.90
8.90
f1 (ppm)

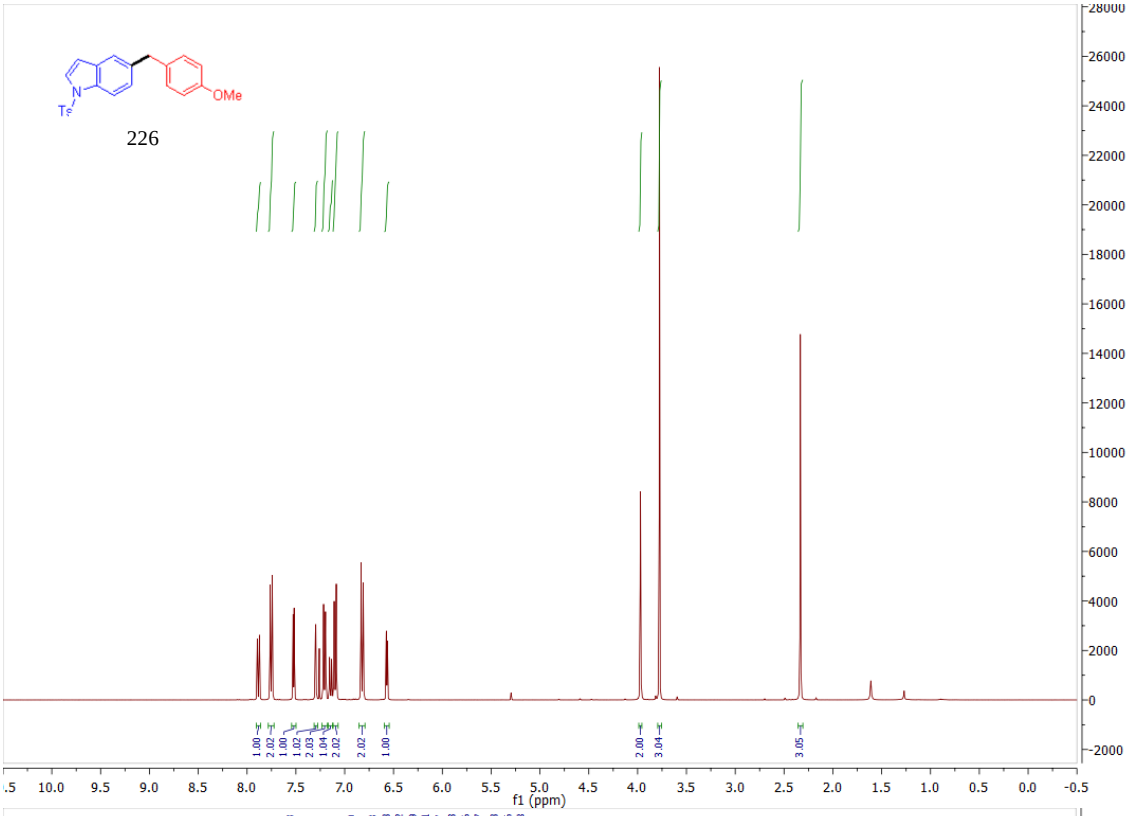

177.16
157.99
149.30
138.82
132.97
129.84
129.64
121.31
113.87
77.00
55.25
40.35
39.03
27.13
PivO
OMe
223
f1 (ppm)

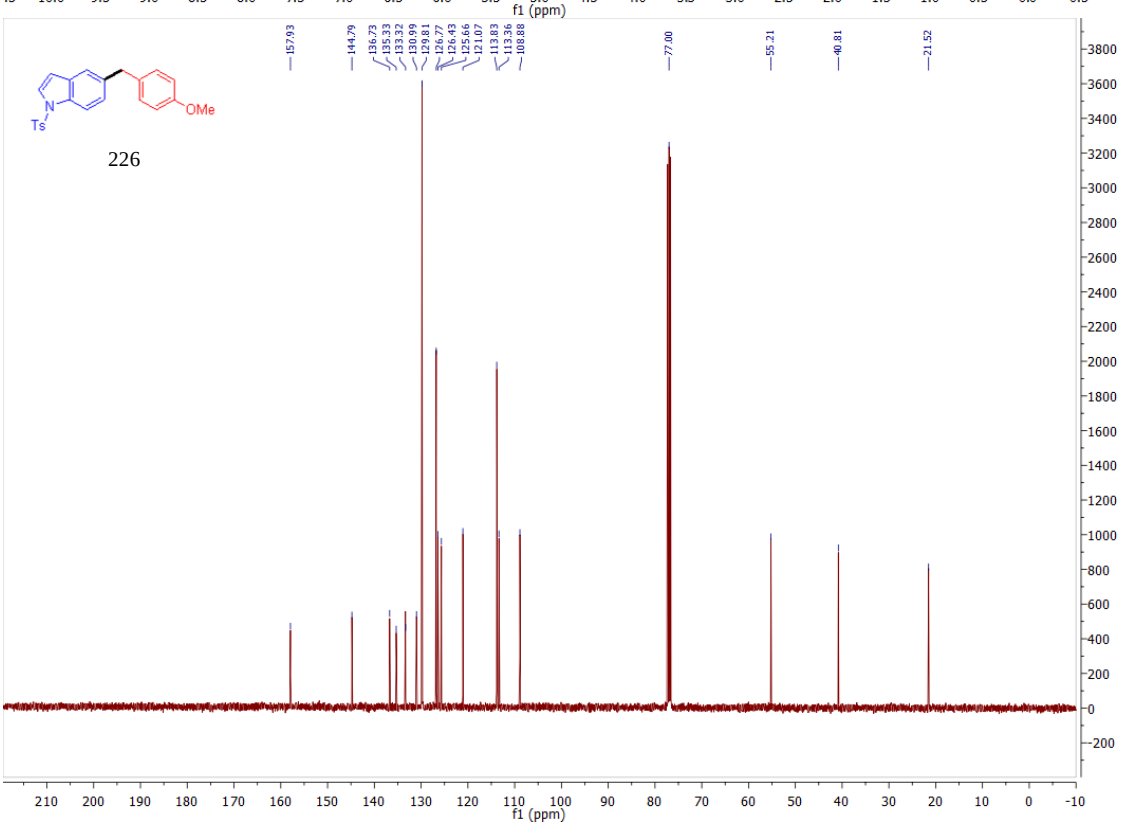

TBSO
OMe
224
1.99
2.01
2.09
1.99
2.00
2.97
9.58
6.31
f1 (ppm)

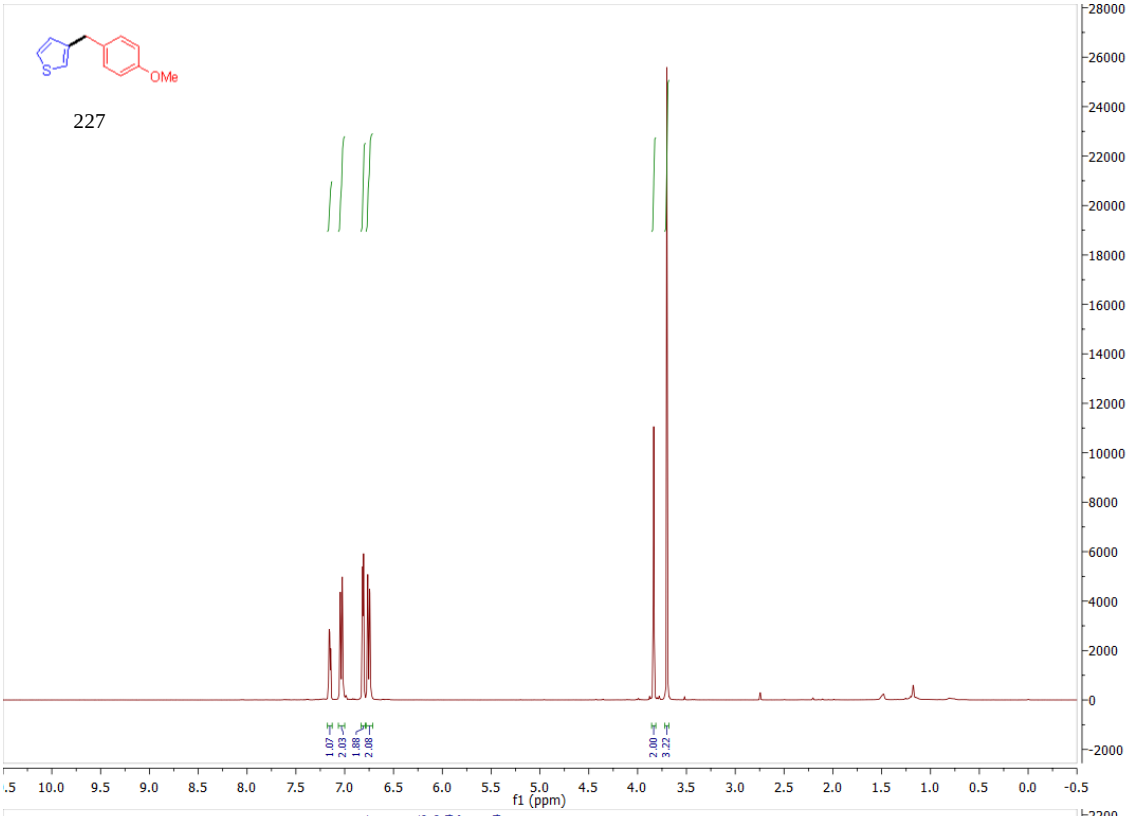

157.85
153.78
134.20
133.68
129.74
129.66
119.90
113.77
77.00
55.22
40.18
25.68
18.17
-4.44
TBSO
OMe
224
f1 (ppm)

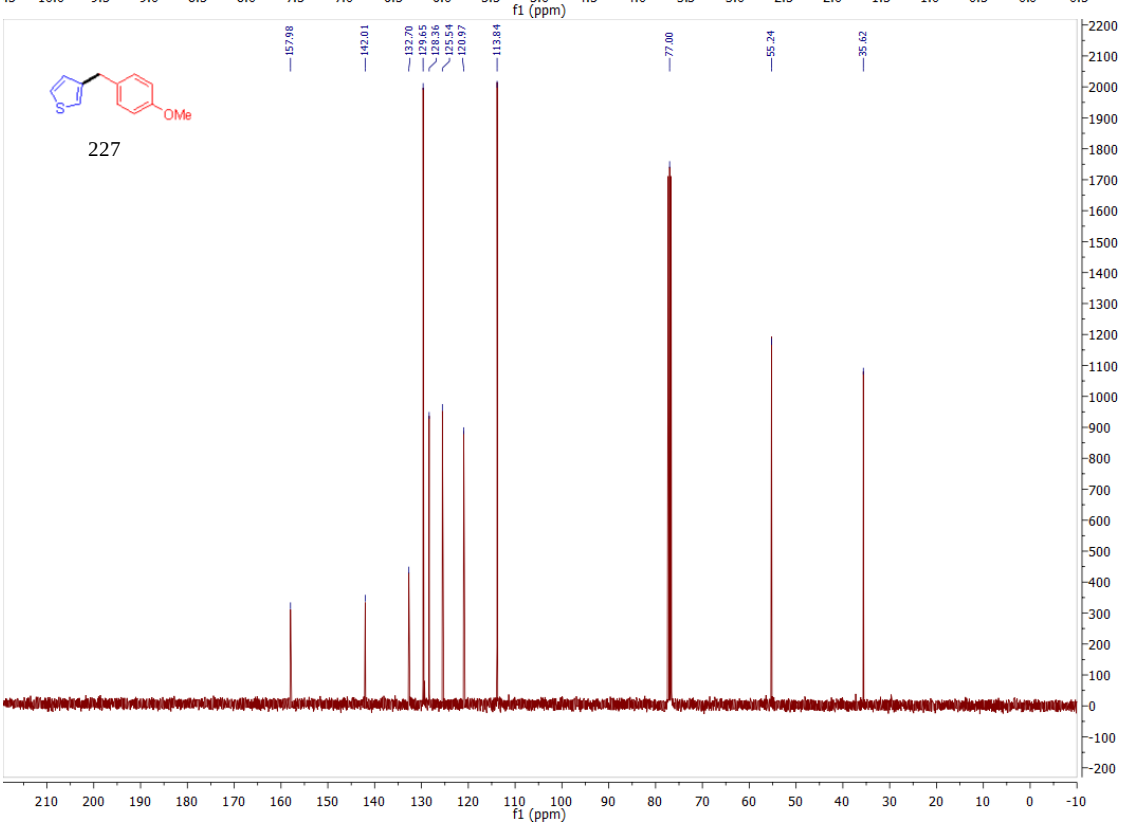

AcHN
OMe
225
1.84
1.21
3.85
1.90
2.00
2.91
2.76
f1 (ppm)

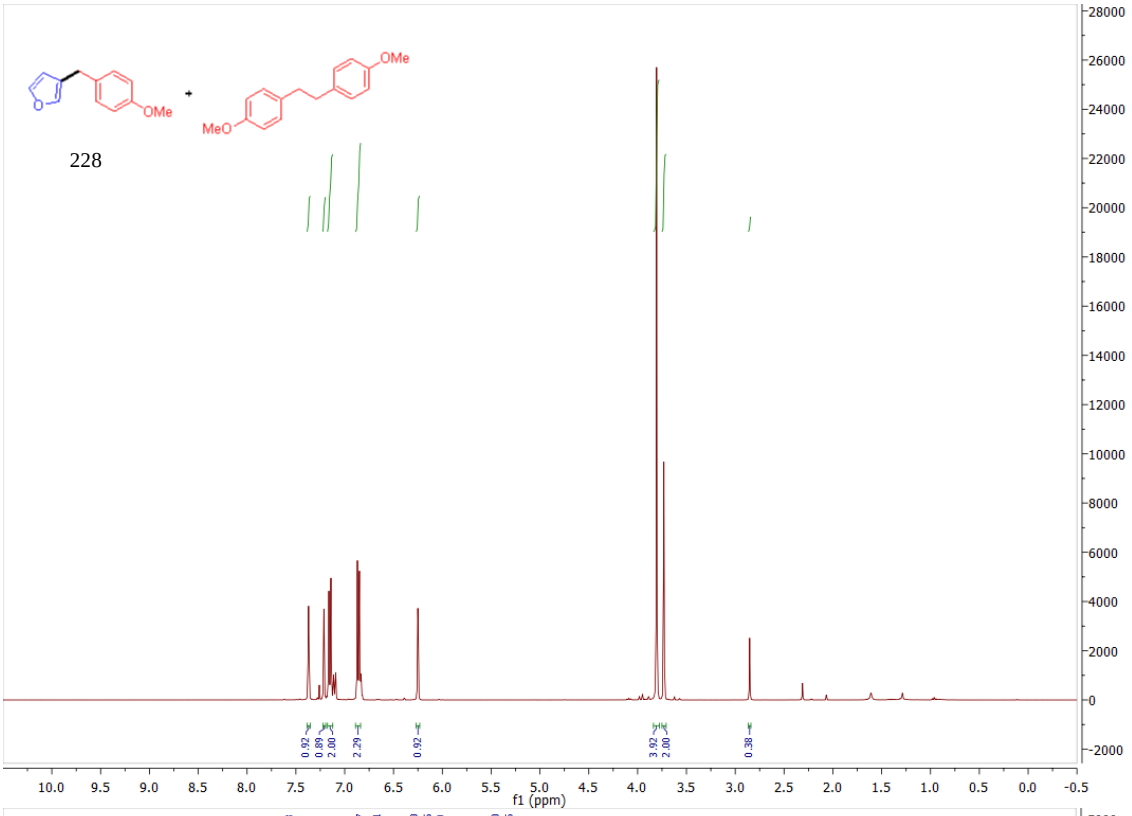

AcHN
OMe
225
168.24
157.93
137.66
135.80
133.16
129.77
129.27
120.10
113.84
77.00
55.24
40.39
24.50
f1 (ppm)

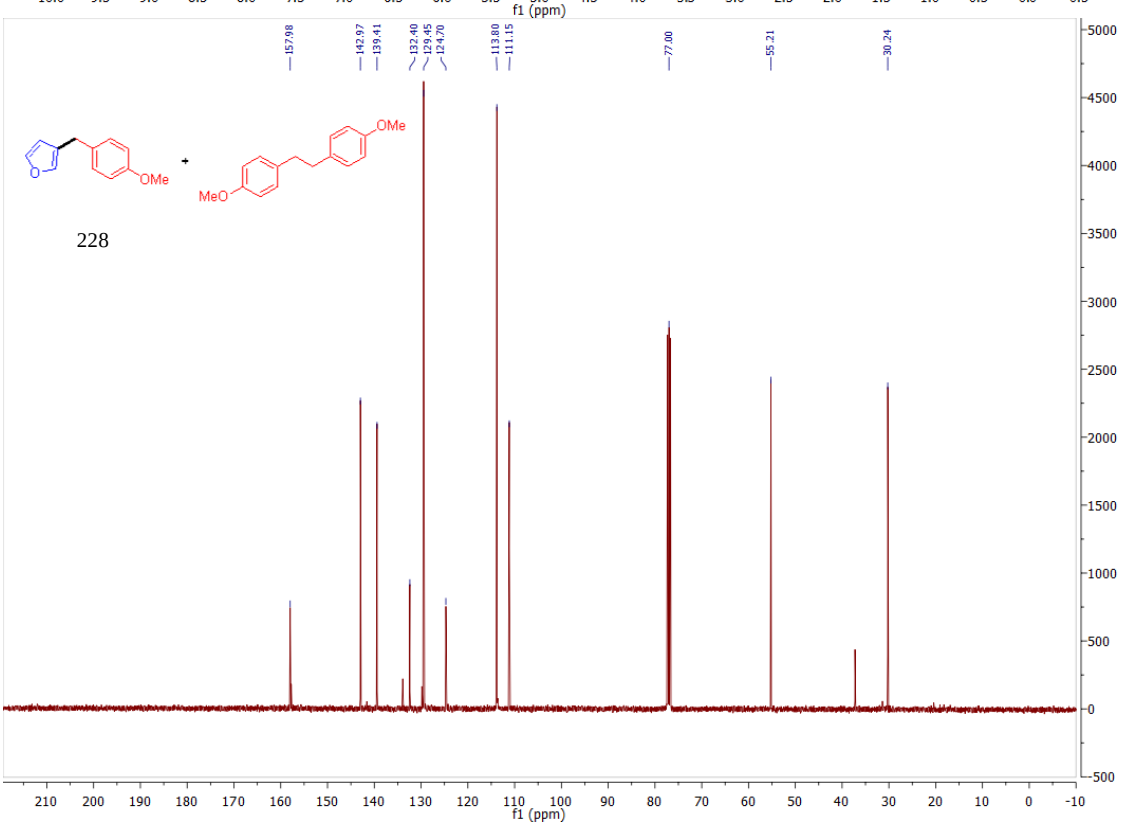

OMe
Ts
226
1.00
2.02
1.00
1.02
2.03
1.04
2.02
2.02
1.00
2.00
3.04
3.05
f1 (ppm)

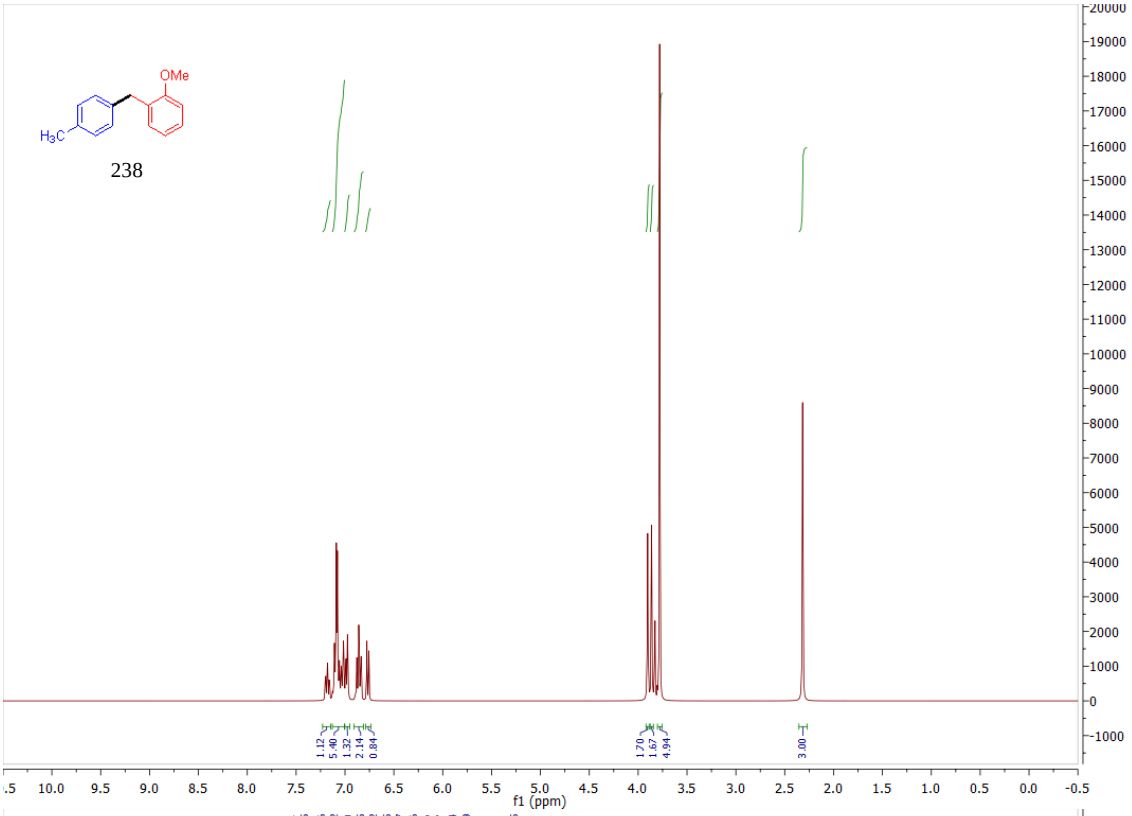

OMe
Ts
226
157.93
144.79
136.73
135.23
133.32
130.99
129.81
126.77
126.43
125.66
121.07
113.83
113.36
108.88
77.00
55.21
40.81
21.52
f1 (ppm)

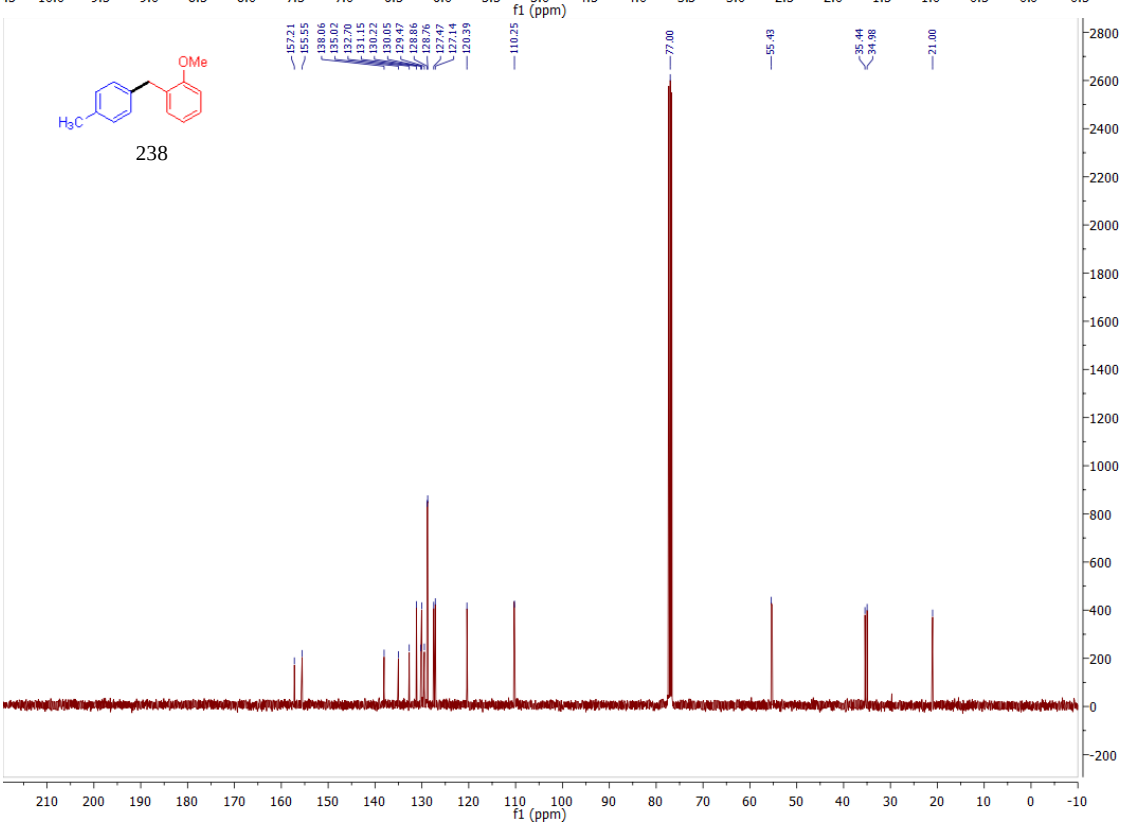

OMe
227
1.07
2.03
1.88
2.08
2.00
3.22
f1 (ppm)

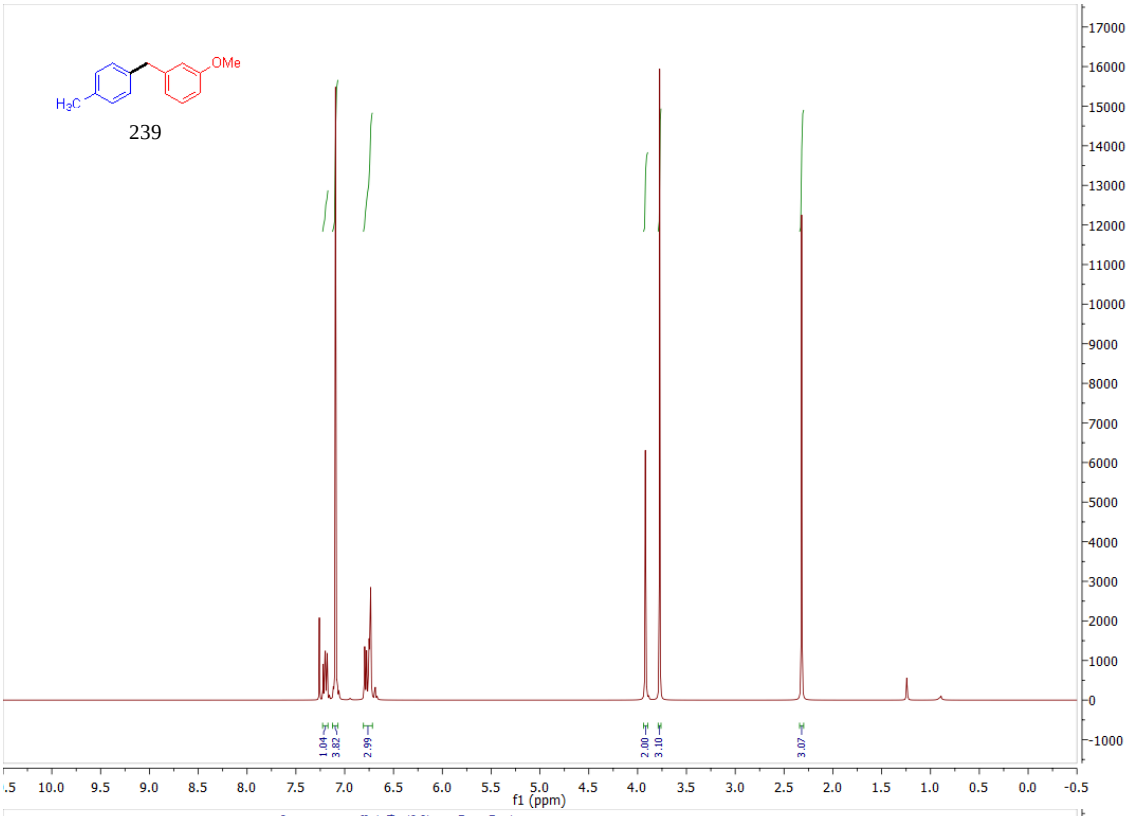

OMe
227
157.98
142.01
132.70
129.65
128.36
125.54
120.97
113.84
77.00
55.24
35.62
f1 (ppm)

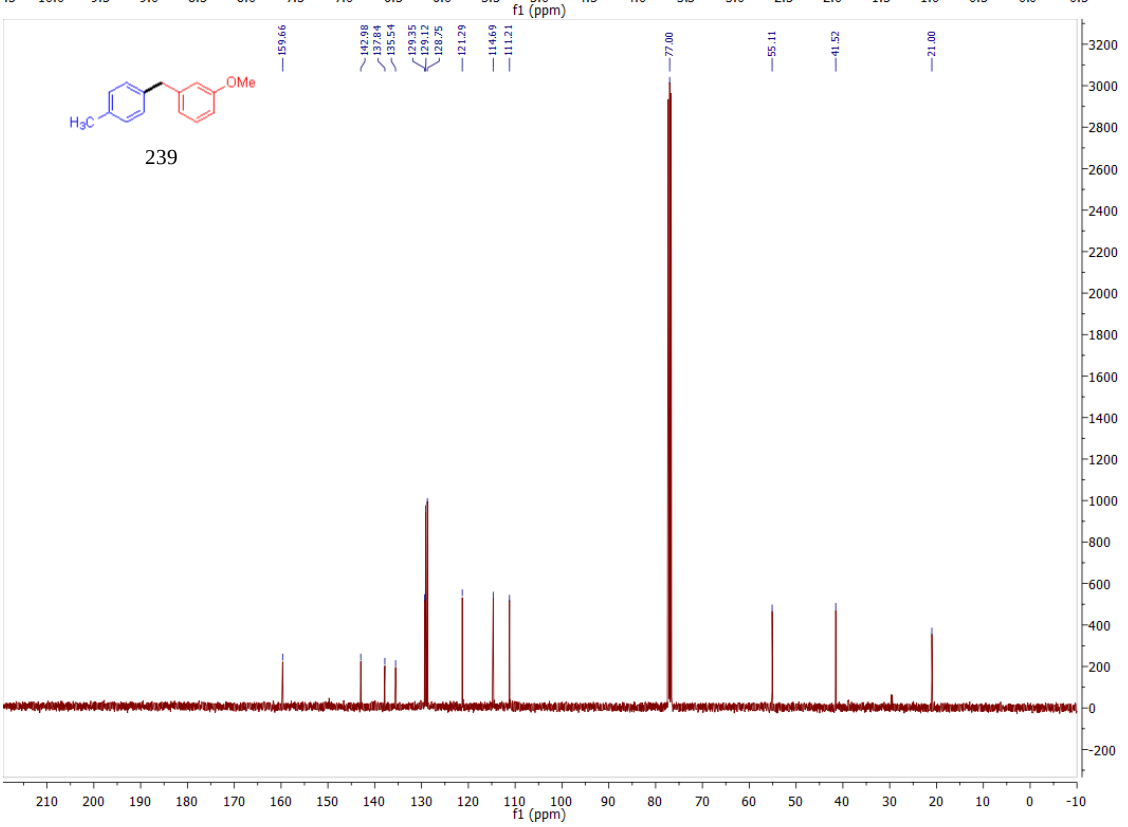

OMe
MeO
228
0.92
0.89
2.00
2.29
0.92
3.92
2.00
0.38
f1 (ppm)

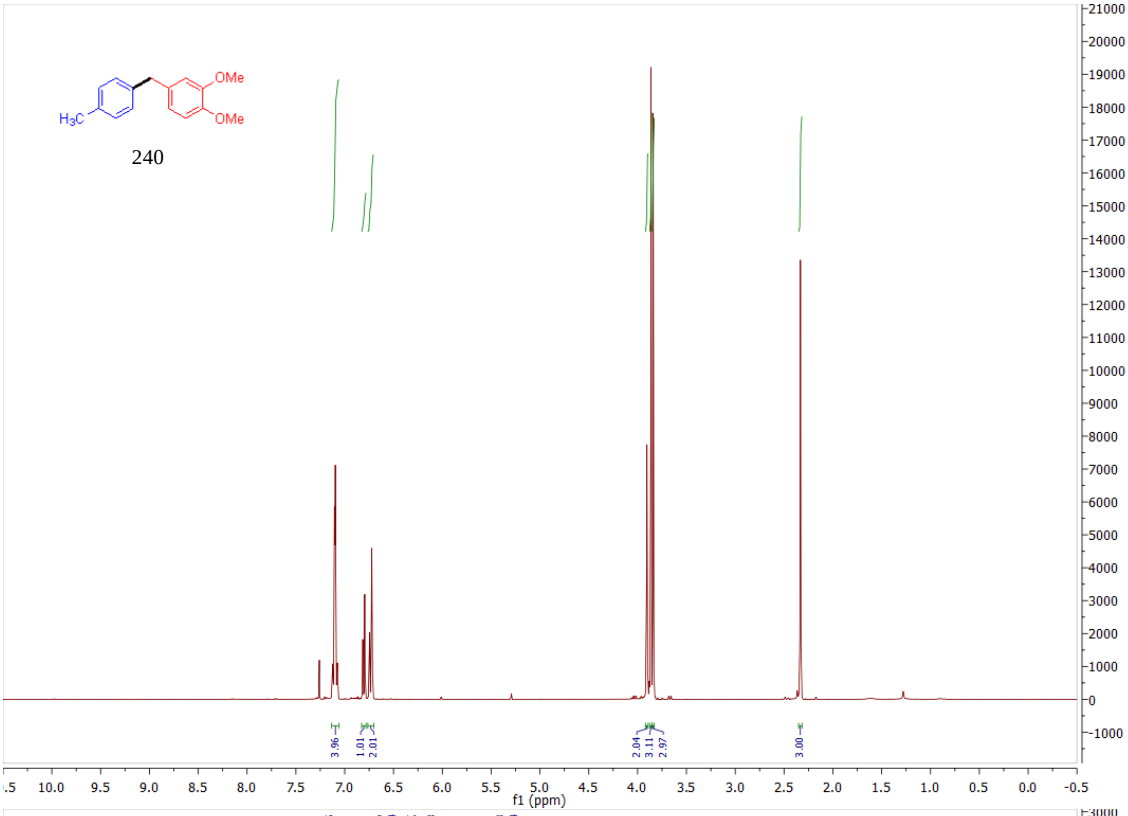

157.98
142.97
139.41
132.40
129.45
124.70
113.80
111.15
77.00
55.21
30.24
OMe
MeO
228
f1 (ppm)


OMe
H3C
238
1.12
5.40
1.32
2.14
0.84
1.70
1.67
4.94
3.00
f1 (ppm)

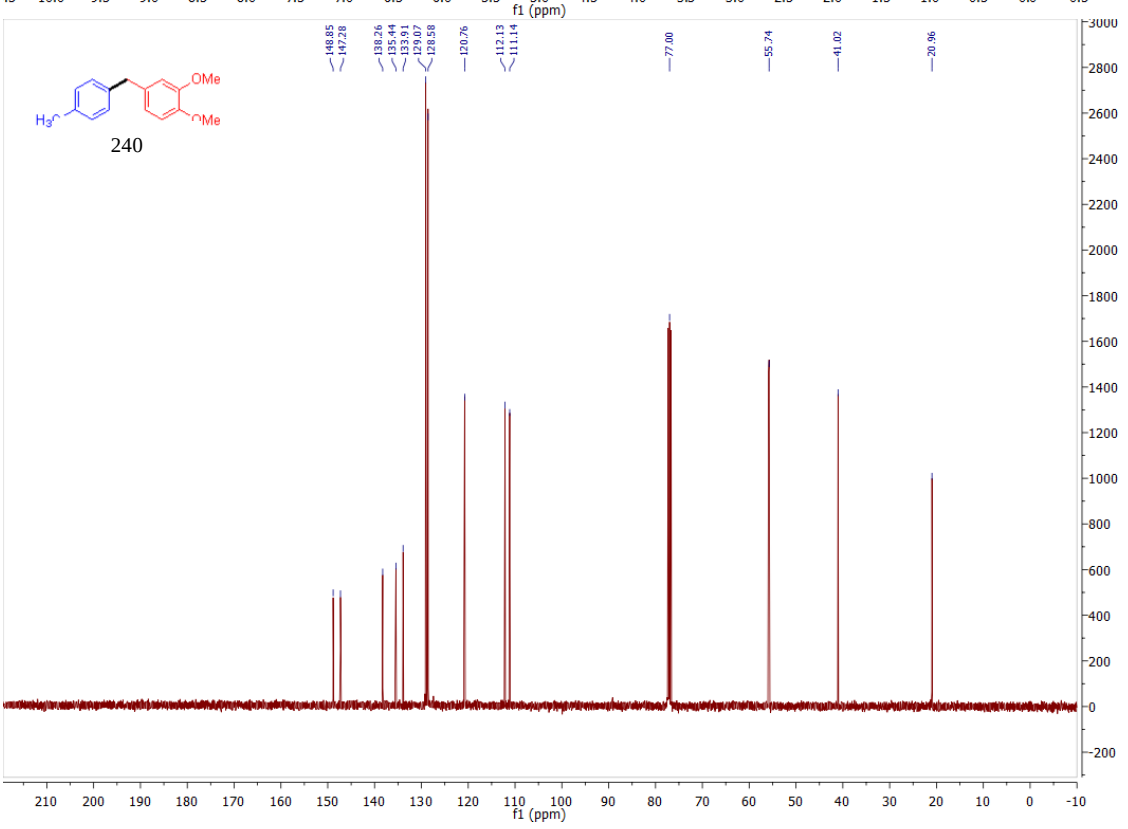

OMe
H3C
238
157.21
155.55
138.06
135.02
132.70
131.15
130.22
130.05
129.47
128.86
128.76
127.47
127.14
120.39
110.25
77.00
55.43
35.44
34.98
21.00
f1 (ppm)


OMe
H3C
239
1.04
3.82
2.99
2.00
3.10
3.07
f1 (ppm)

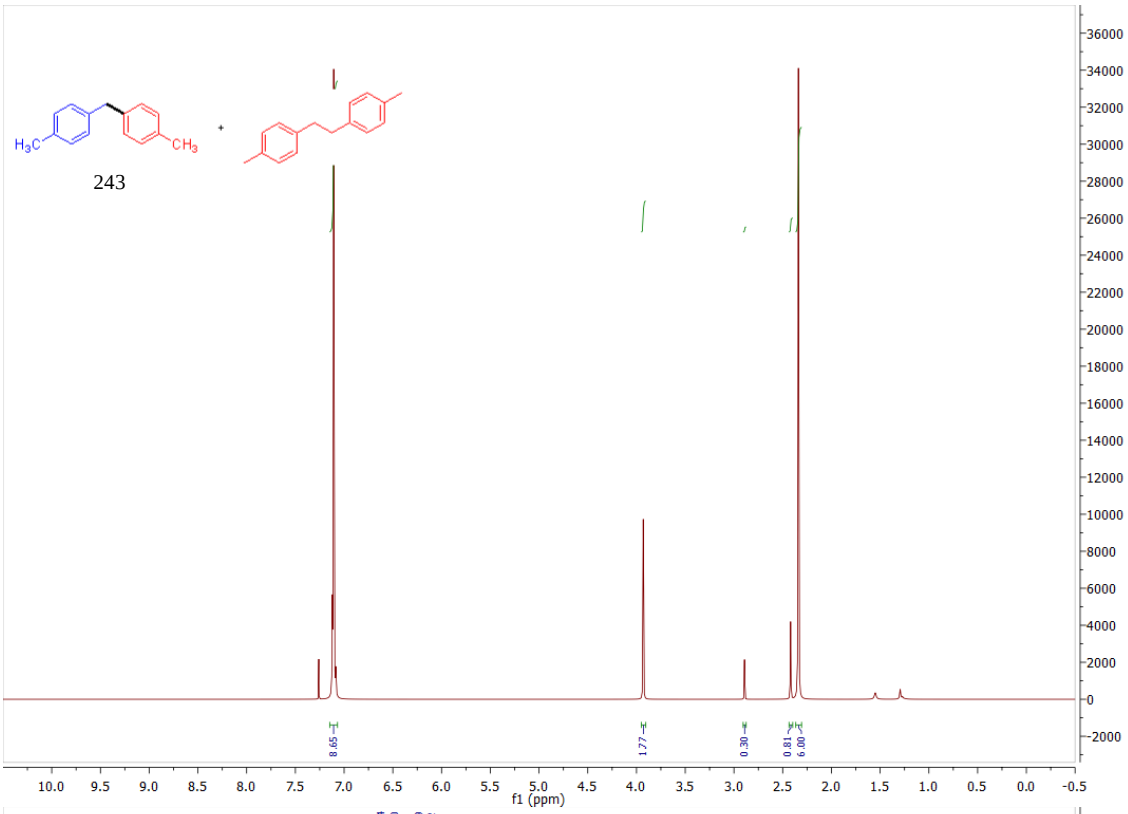

OMe
H3C
239
159.66
142.98
137.84
135.54
129.35
129.12
128.75
121.29
114.69
111.21
77.00
55.11
41.52
21.00
f1 (ppm)

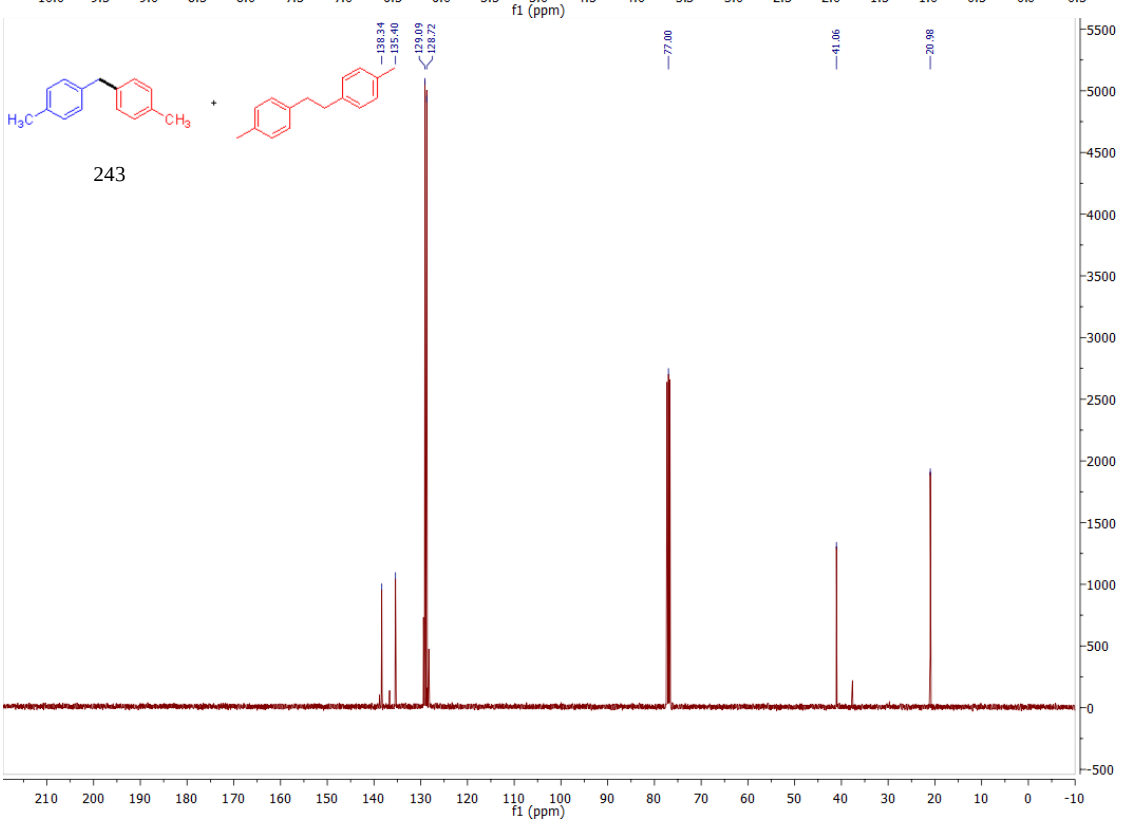

OMe
OMe
H3C
3.96
1.01
2.01
2.04
3.11
2.97
3.00
f1 (ppm)

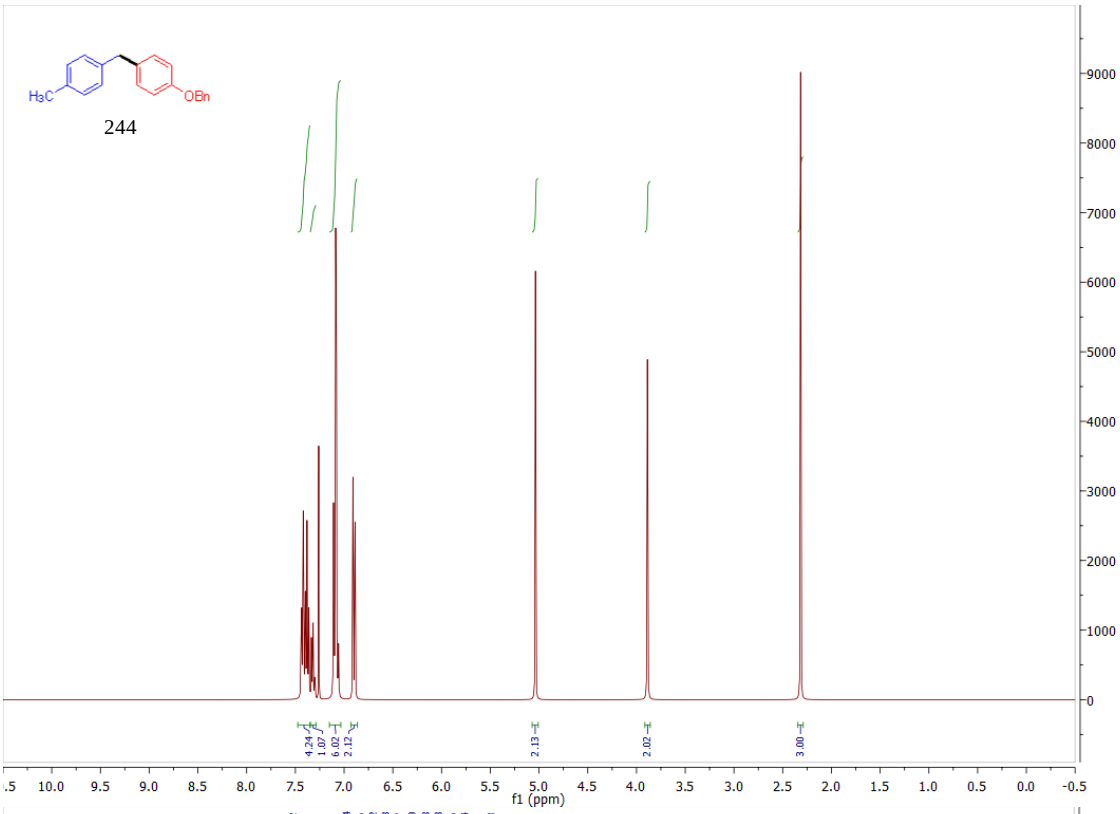
240

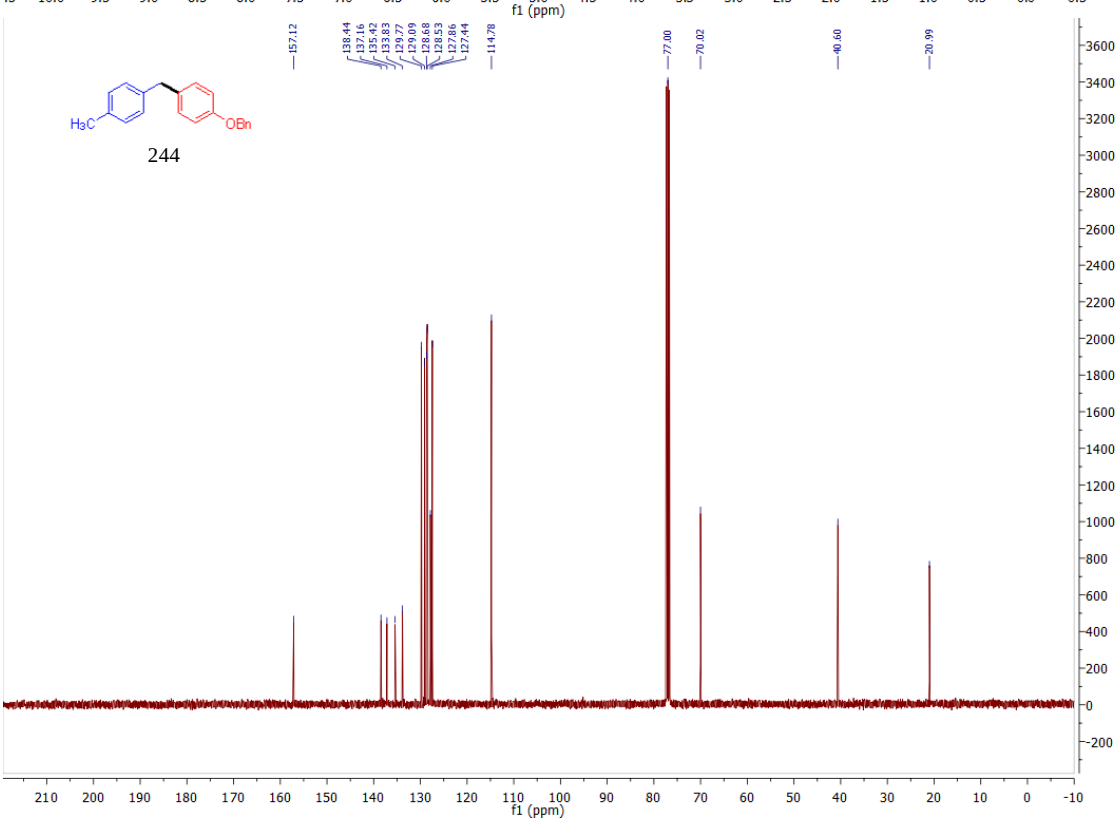

OMe
OMe
H3C
148.85
147.28
138.26
135.44
133.91
129.07
128.58
120.76
112.13
111.14
77.00
55.74
41.02
20.96
f1 (ppm)

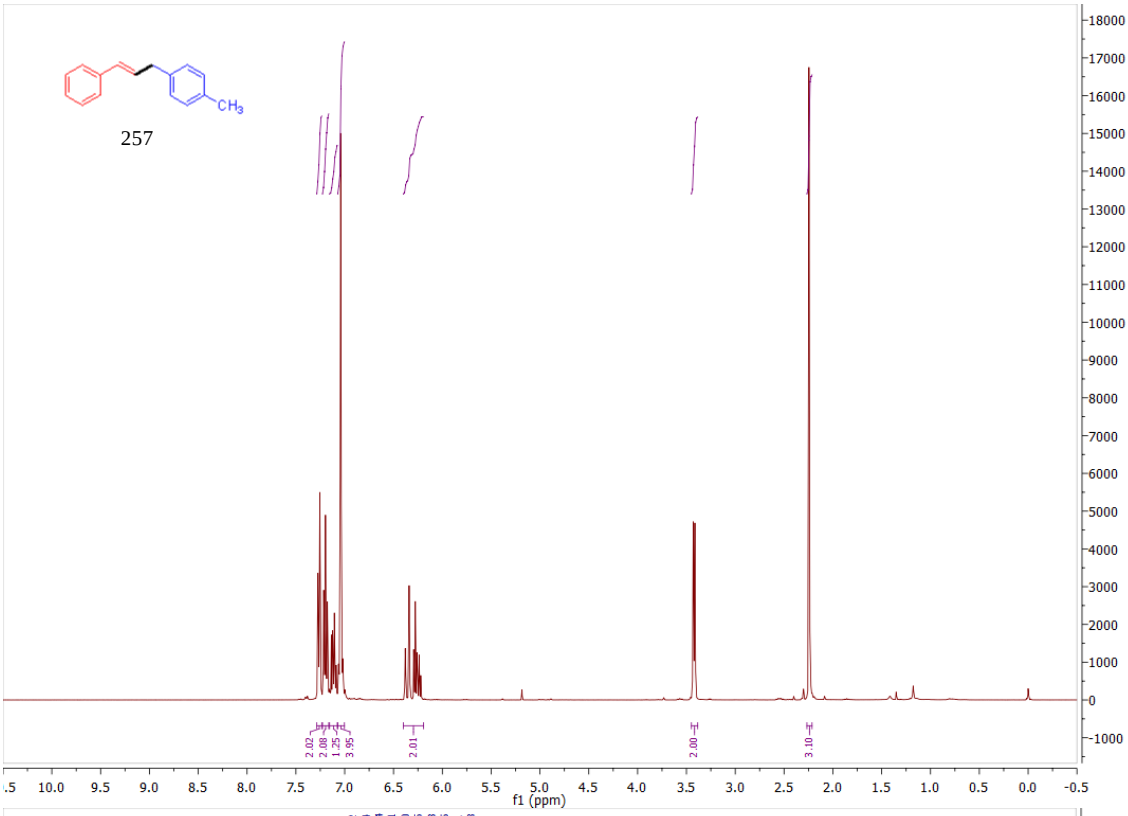
240

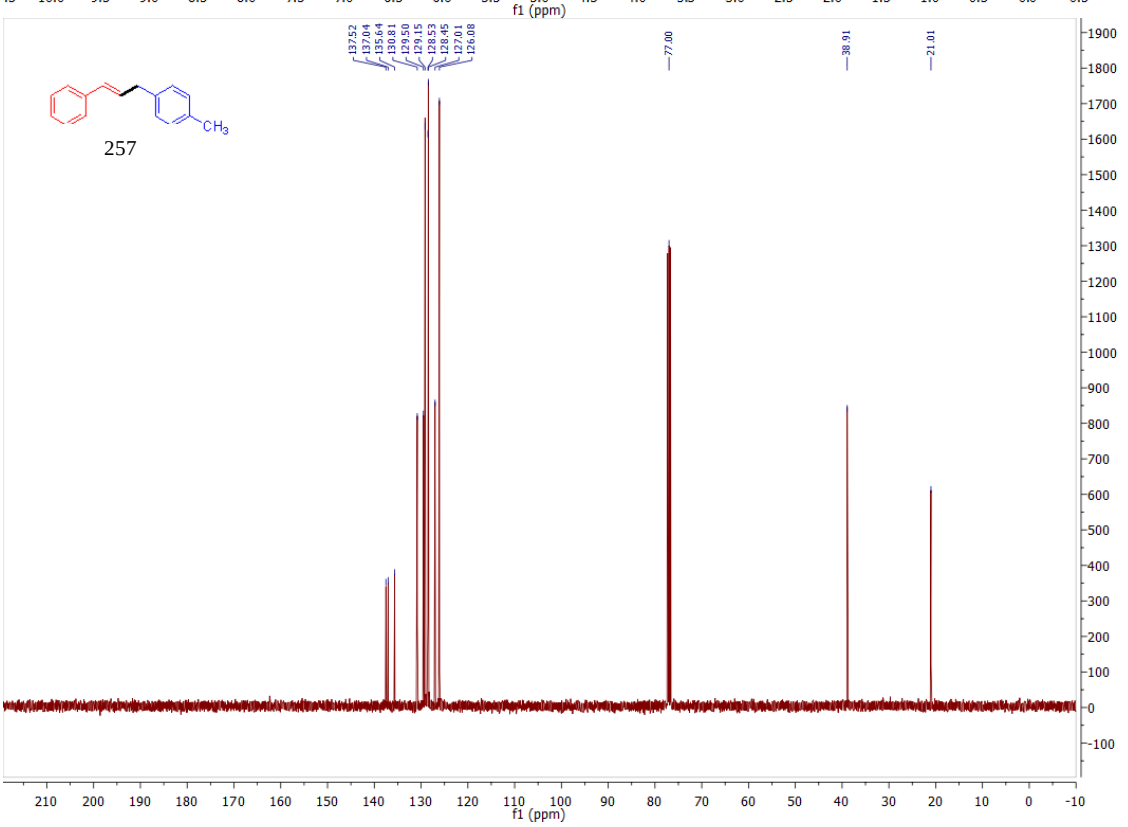

243
8.65
1.77
0.30
0.81
6.00
f1 (ppm)

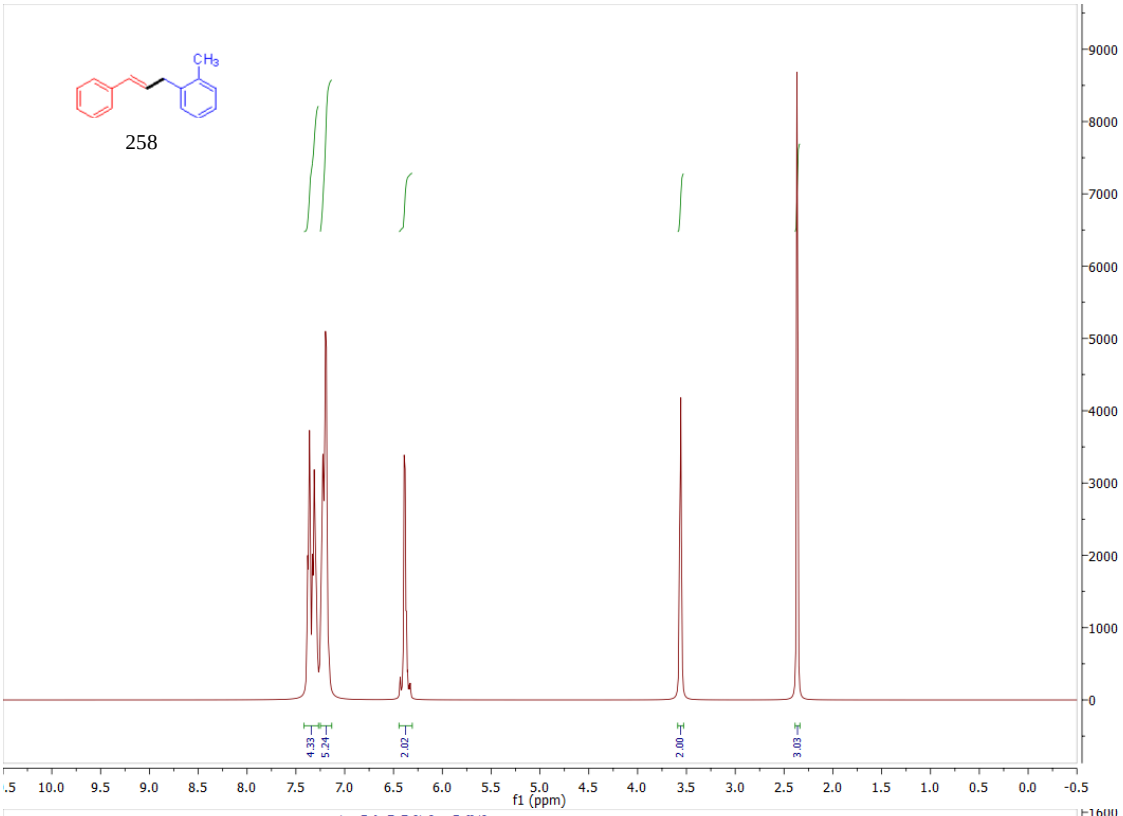

243
138.34
135.40
129.09
128.72
77.00
41.06
20.98
f1 (ppm)

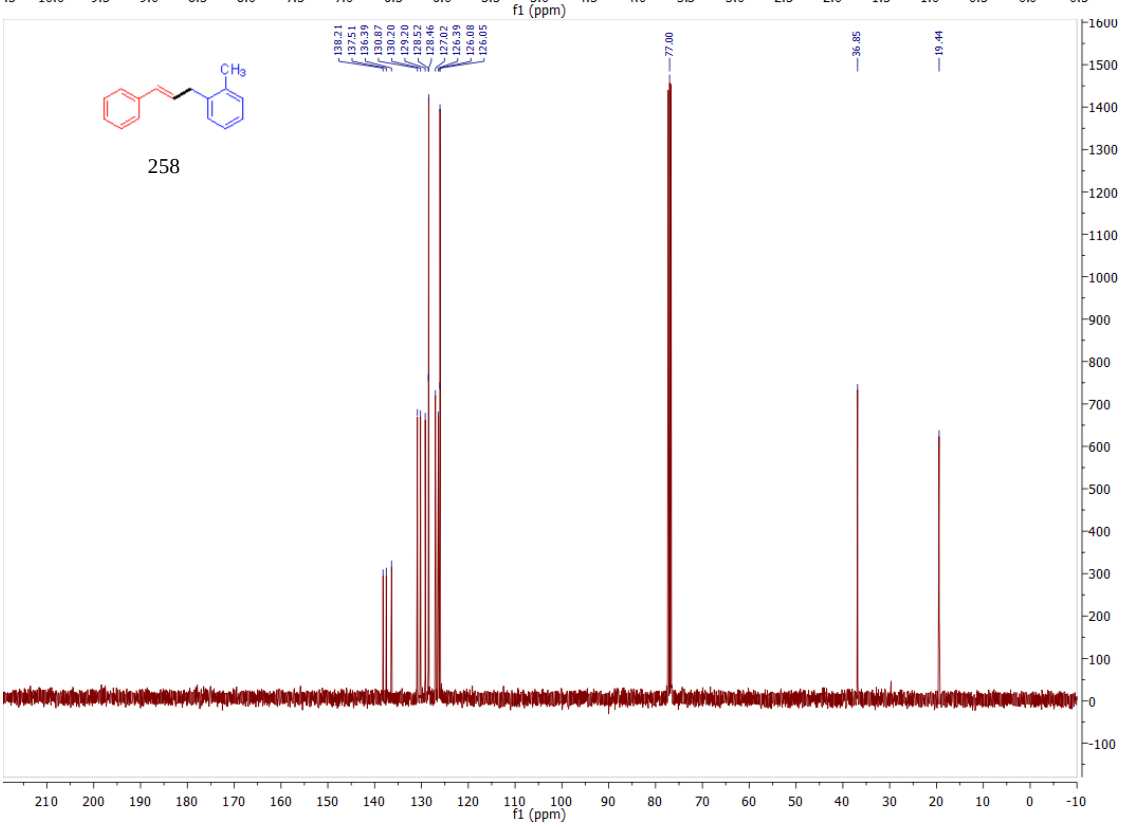

H3C
OBn
244
4.24
1.07
6.02
2.12
2.13
2.02
3.00
f1 (ppm)

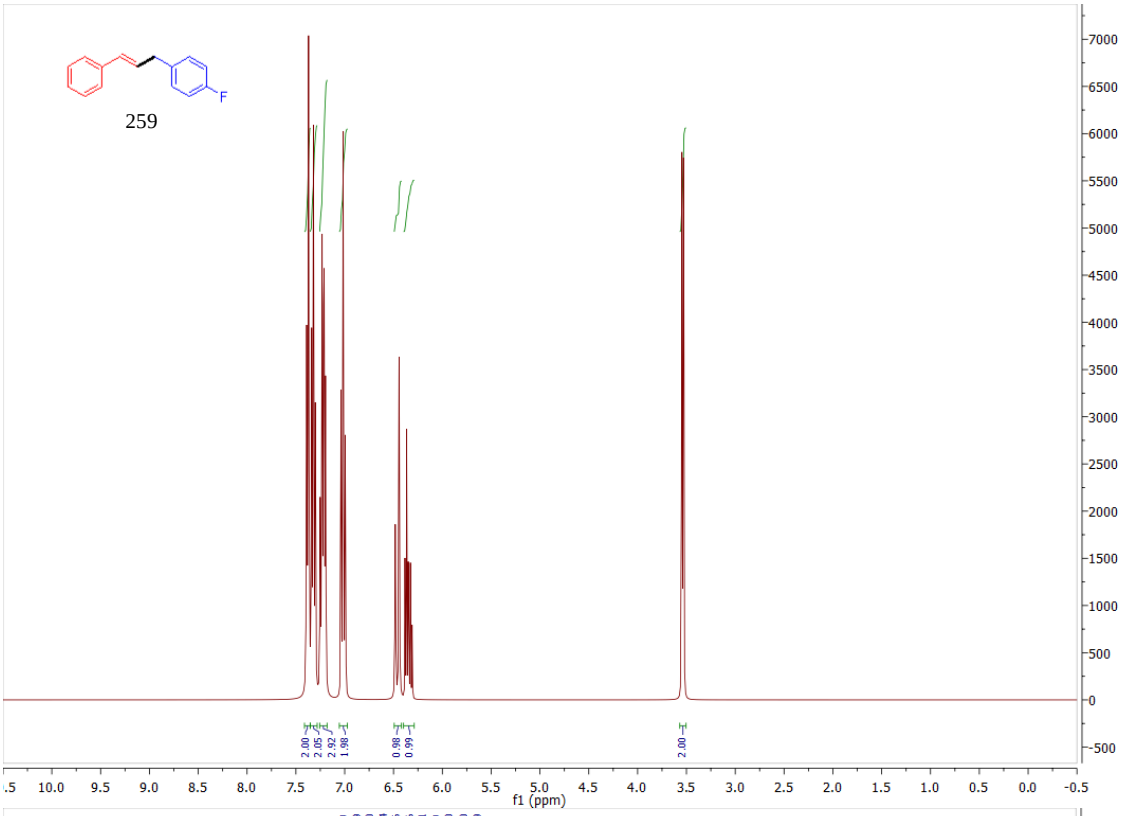

H3C
OBn
244
157.12
138.44
137.16
135.82
133.83
129.77
129.09
128.68
128.53
127.86
127.44
114.78
77.00
70.02
40.60
20.99
f1 (ppm)

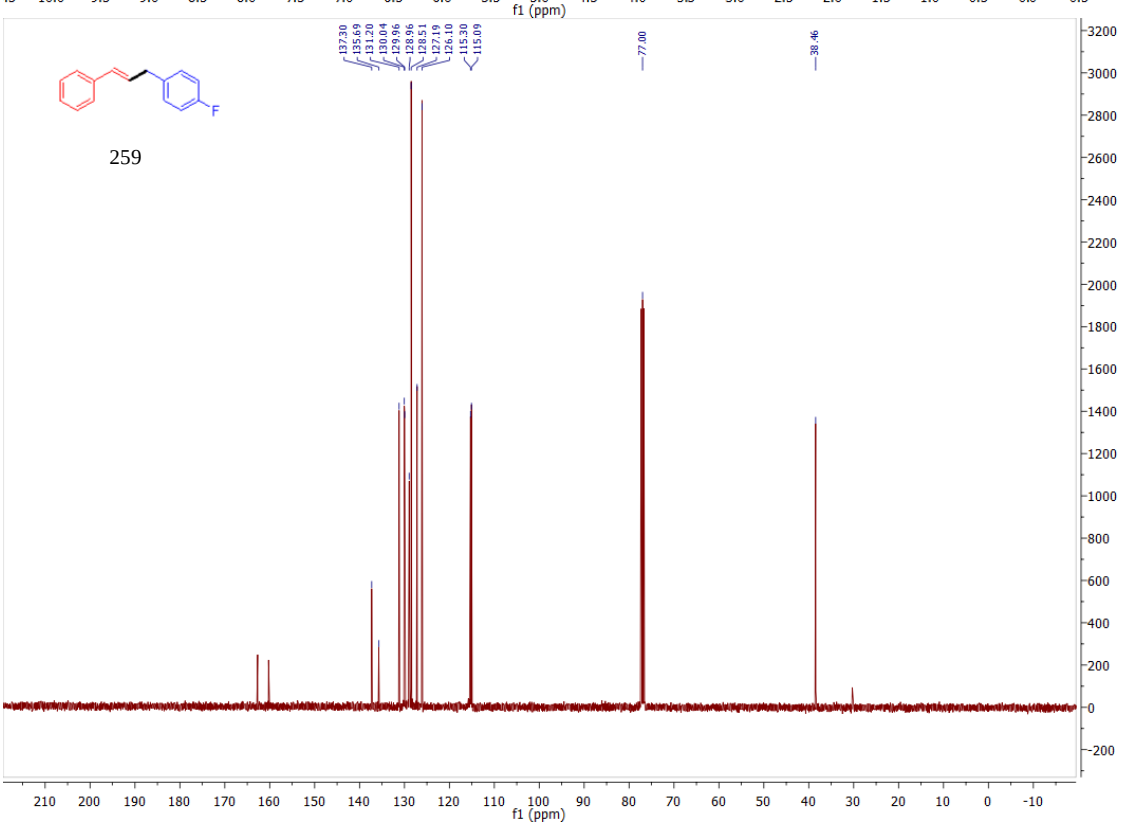

257
2.02
2.08
1.25
3.95
2.01
2.00
3.10
f1 (ppm)

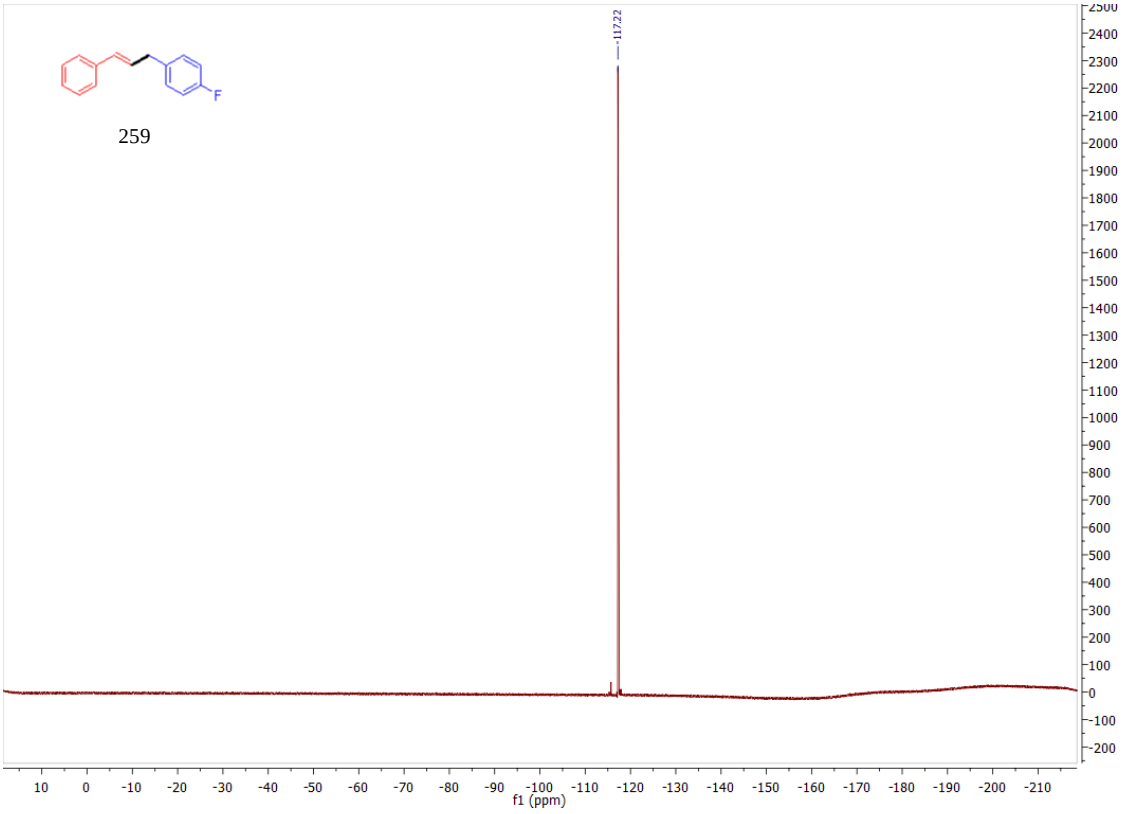

257
137.52
137.04
135.64
130.81
129.50
129.15
128.53
128.45
127.01
126.08
77.00
38.91
21.01
f1 (ppm)

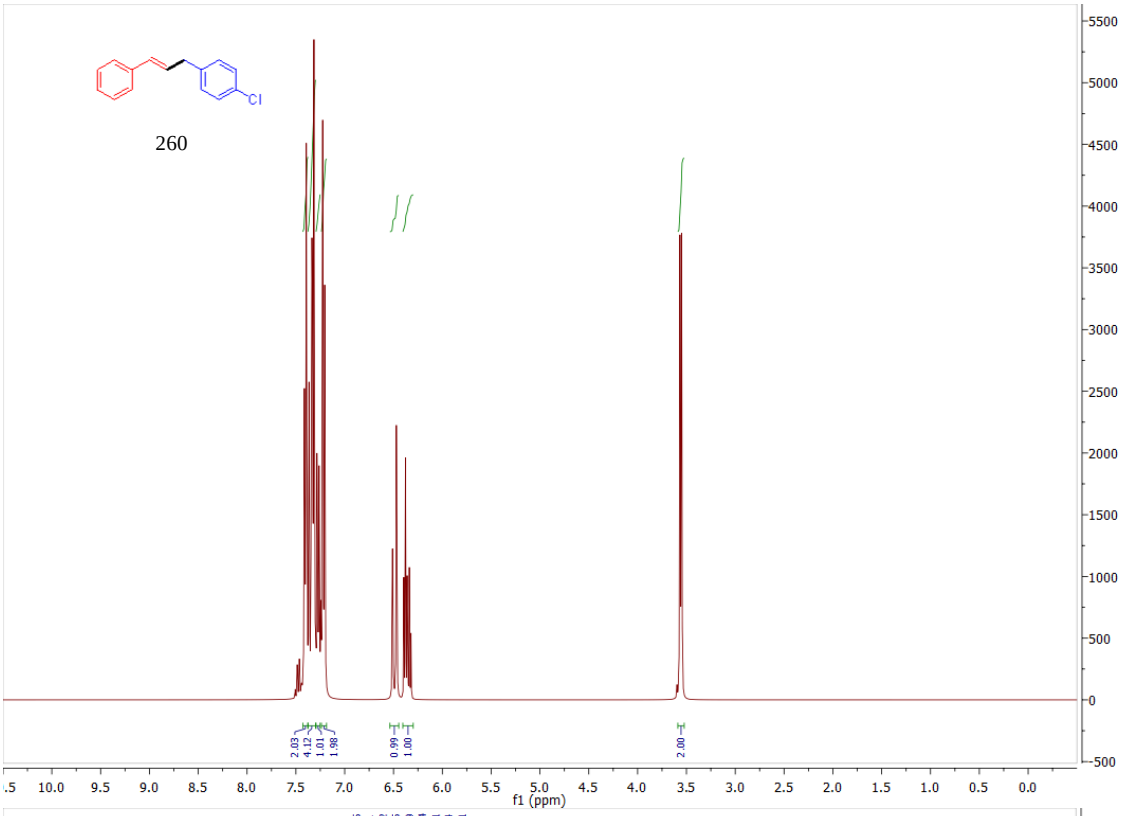

CH3
258
4.33
5.24
2.02
2.00
3.03
f1 (ppm)

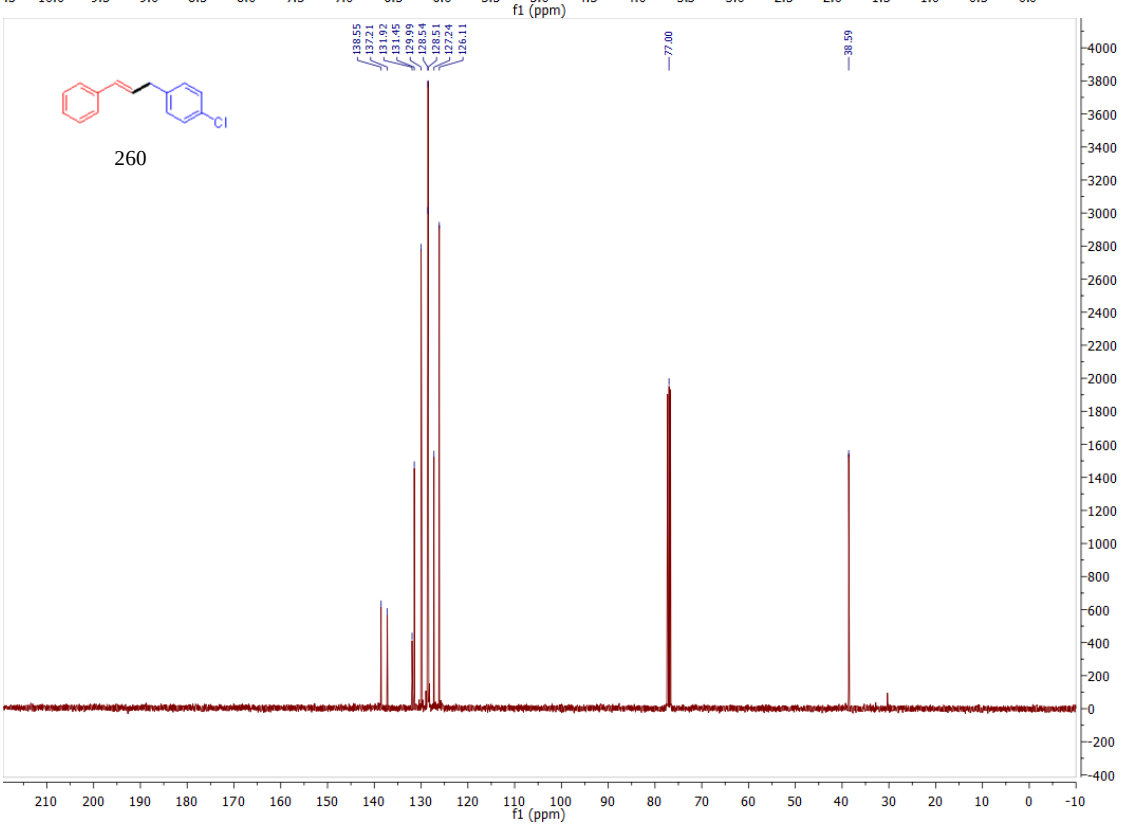

CH3
258
138.21
137.51
136.39
130.87
130.20
129.20
128.52
128.46
127.02
126.39
126.08
126.05
77.00
36.85
19.44
f1 (ppm)

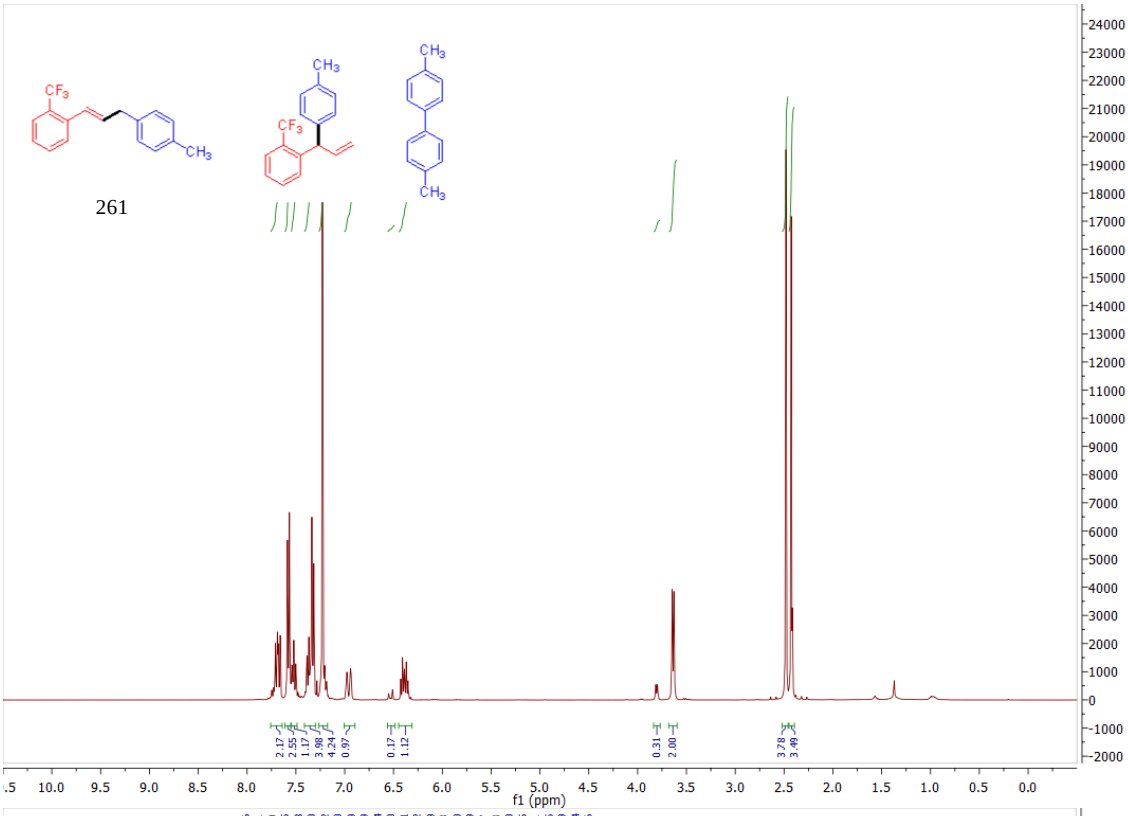

259
F
2.00
2.05
2.92
1.98
0.98
0.99
2.00
f1 (ppm)

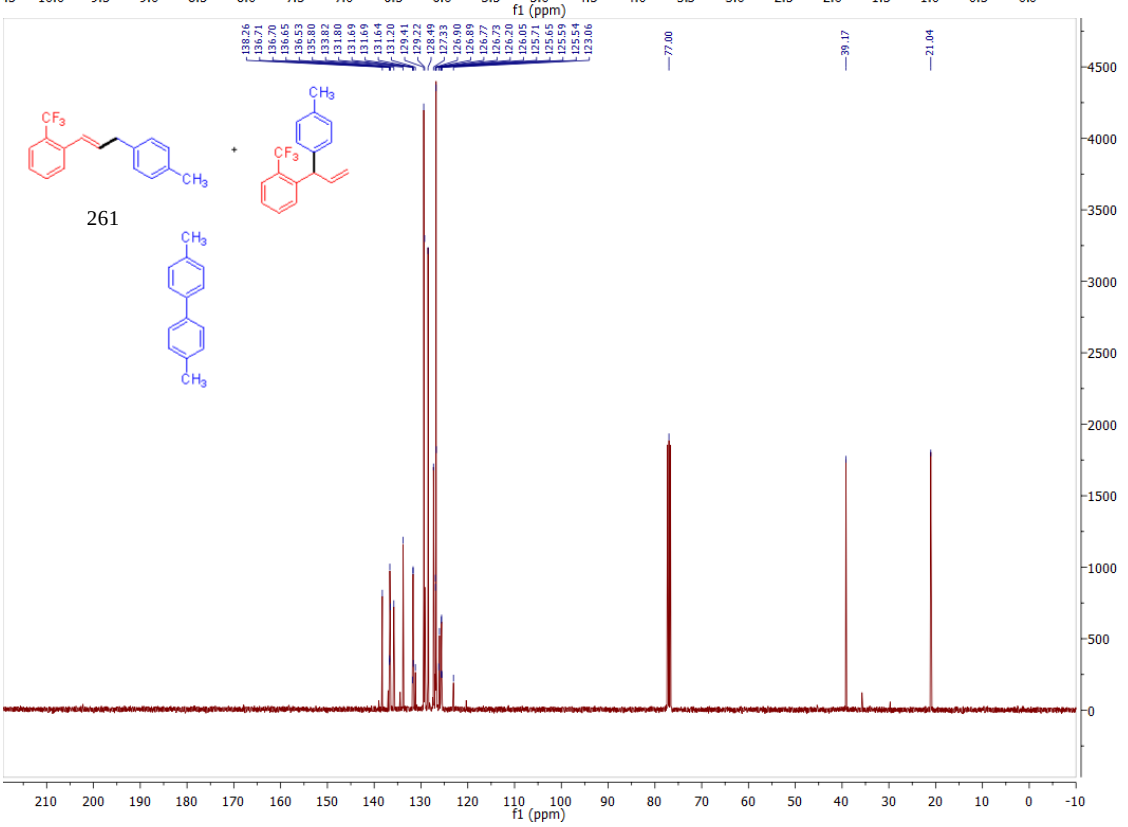

259
F
137.30
135.69
131.20
130.04
129.96
128.96
128.51
127.19
126.10
115.30
115.09
77.00
38.46
f1 (ppm)

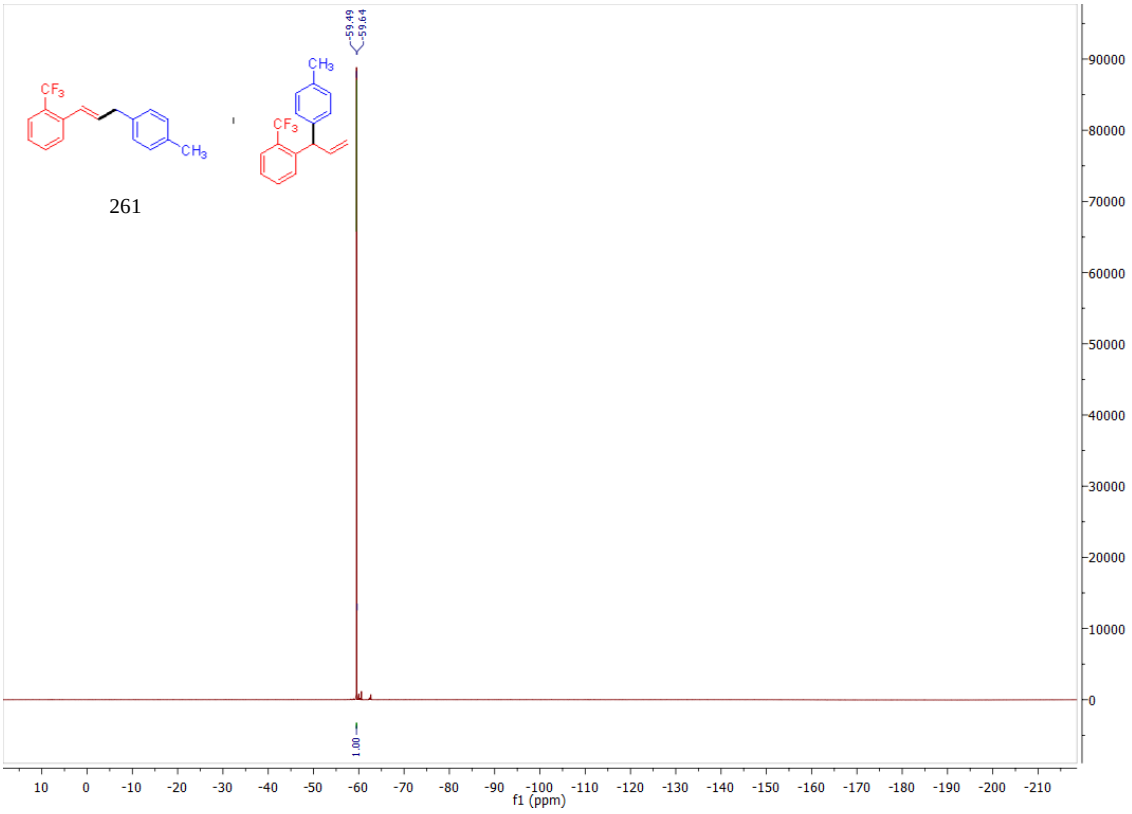

F
259
-117.22
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

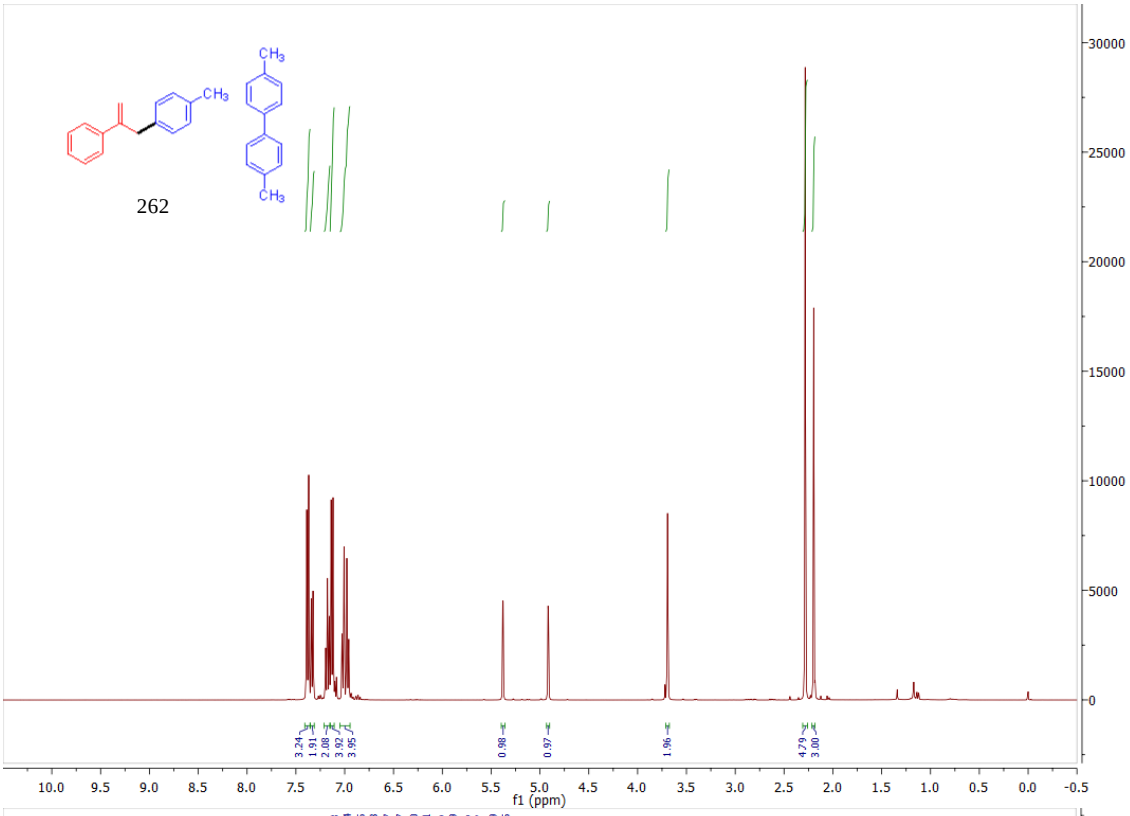

Cl
260
2.03
4.12
1.01
1.98
0.99
1.00
2.00
f1 (ppm)

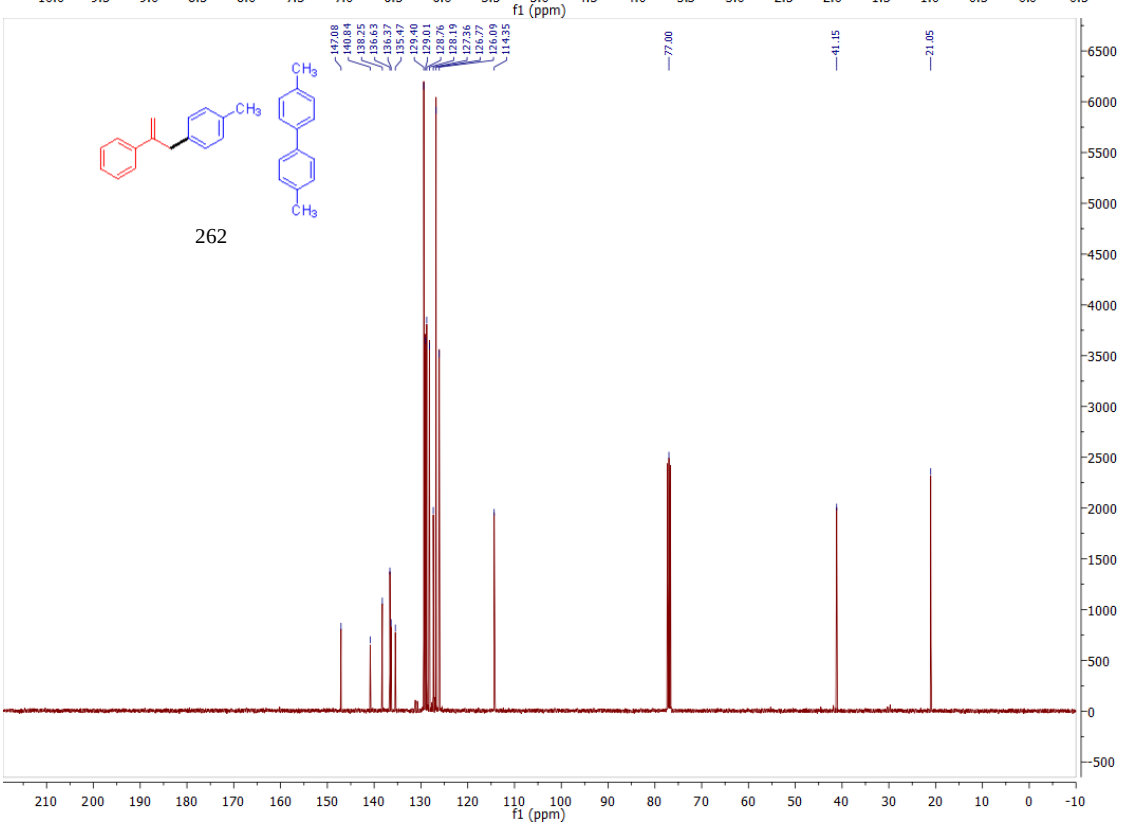

Cl
260
138.55
137.21
131.92
131.45
129.99
128.54
128.51
127.24
126.11
77.00
38.59
f1 (ppm)

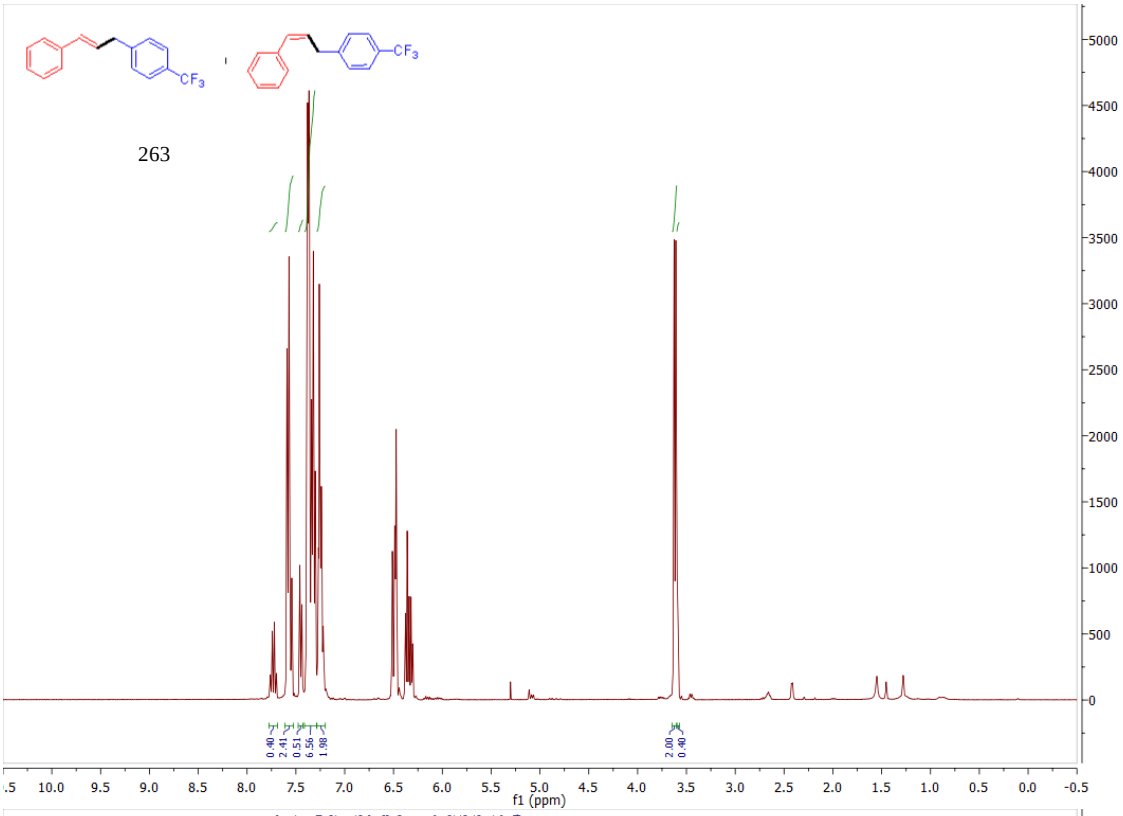

261
f1 (ppm)

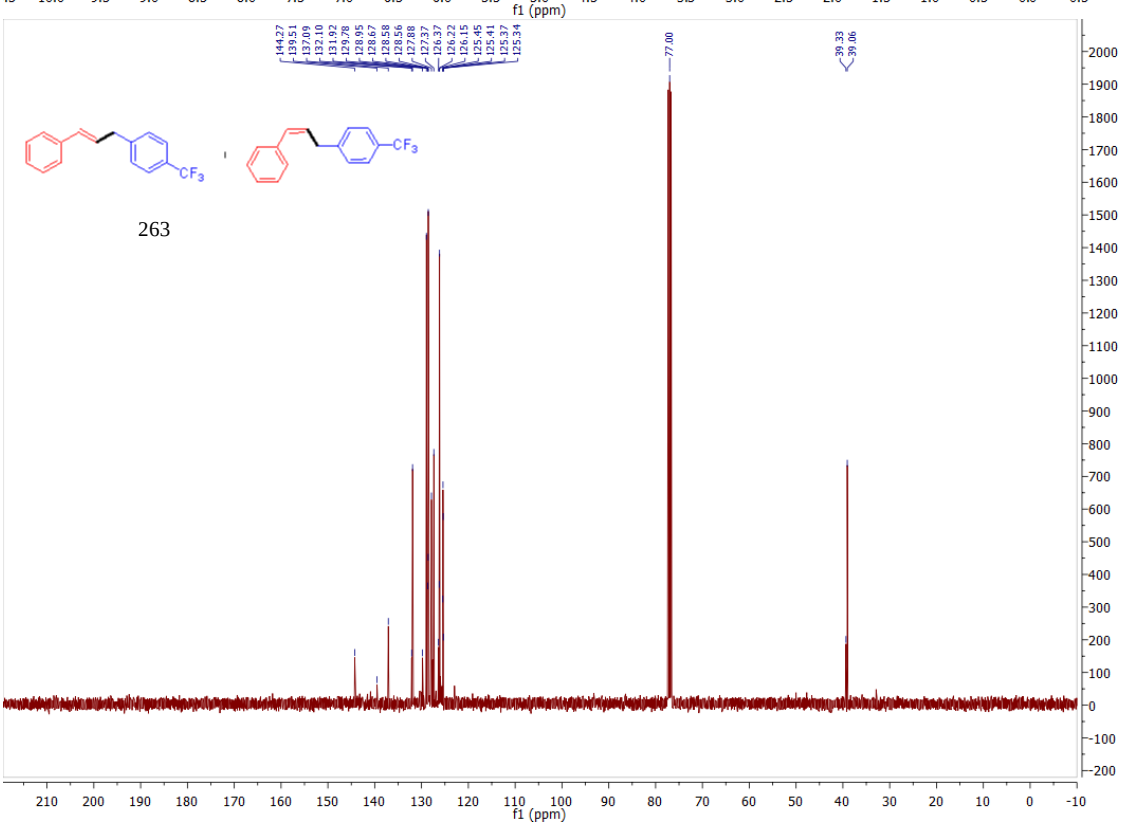

261
f1 (ppm)

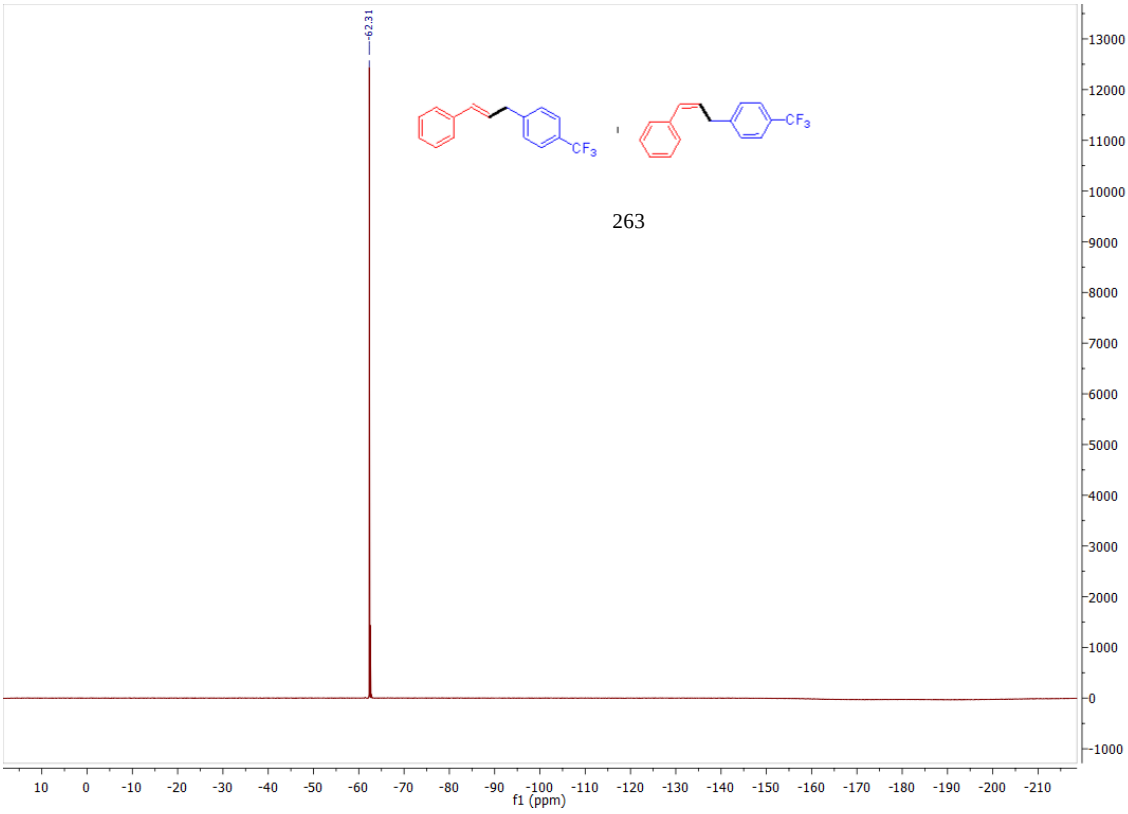

CF3
CH3
CH3
CF3
261
-59.49
-59.64
1.00
f1 (ppm)


262
3.24
1.91
2.08
3.92
3.95
0.98
0.97
1.96
4.79
3.00
f1 (ppm)

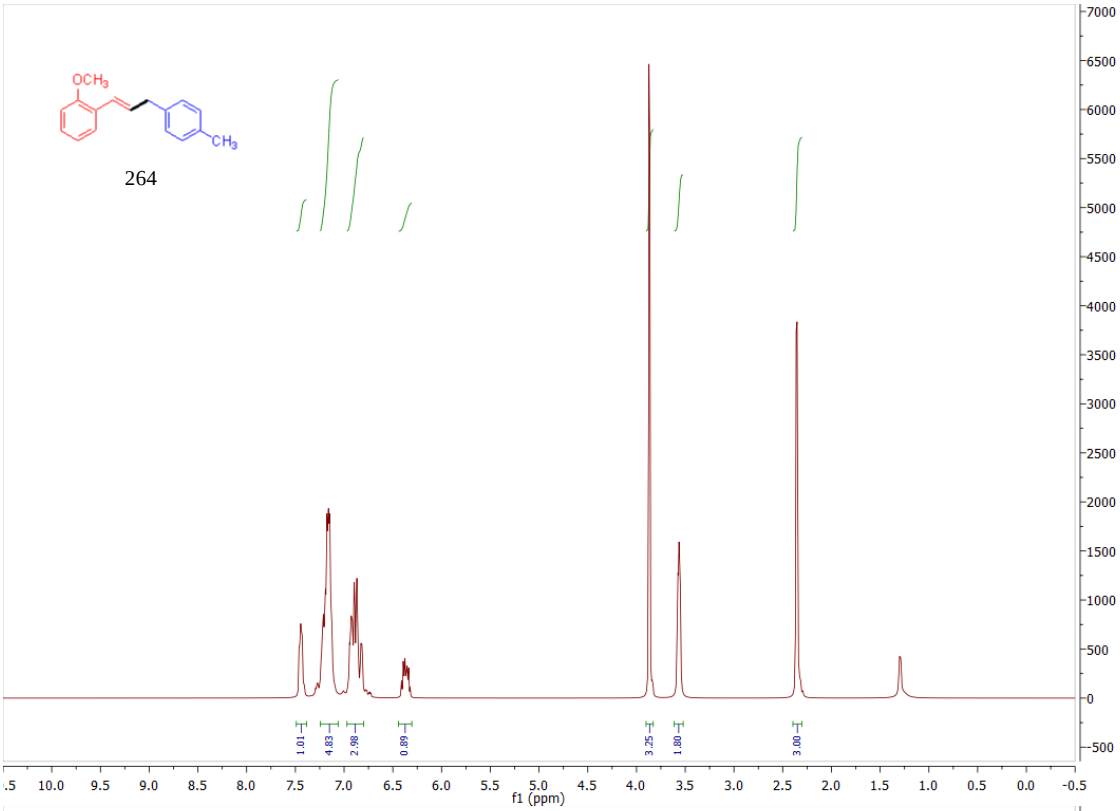

262
147.08
140.84
138.25
136.63
136.37
135.47
129.40
129.01
128.76
128.19
127.36
126.77
126.09
114.35
77.00
41.15
21.05
f1 (ppm)


263
f1 (ppm)

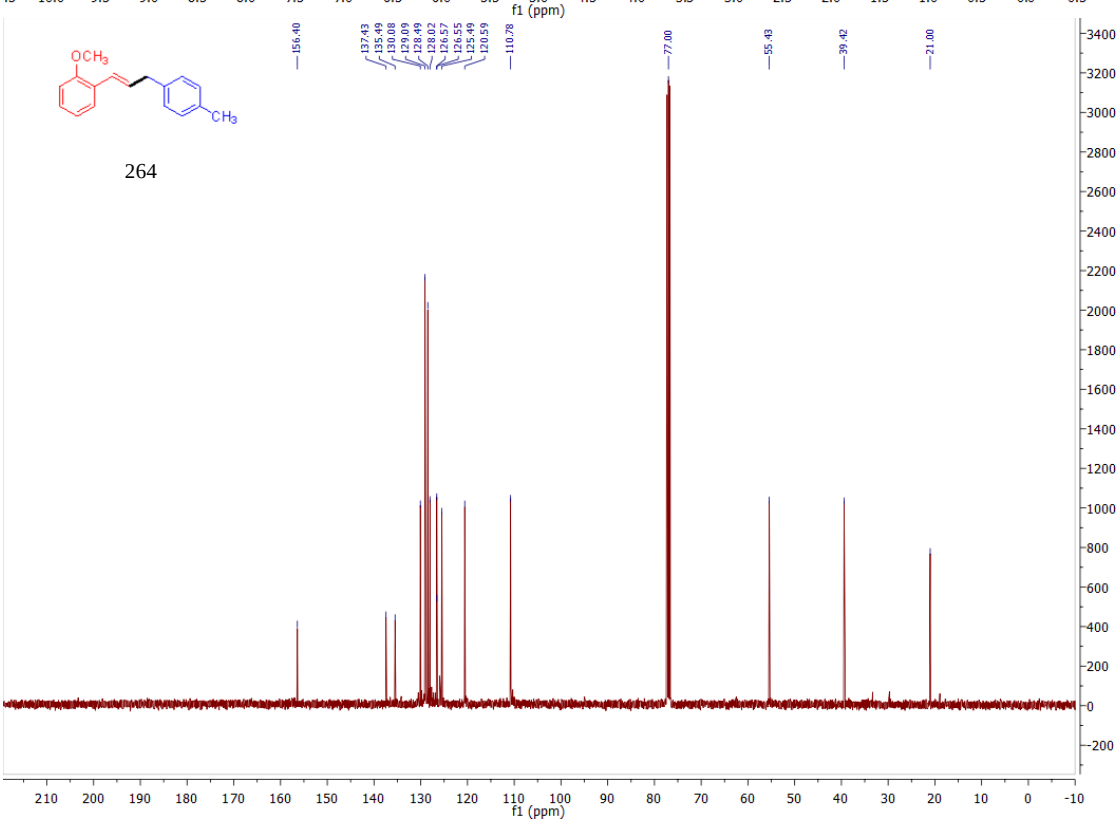

263
f1 (ppm)


-62.31
CF3
CF3
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

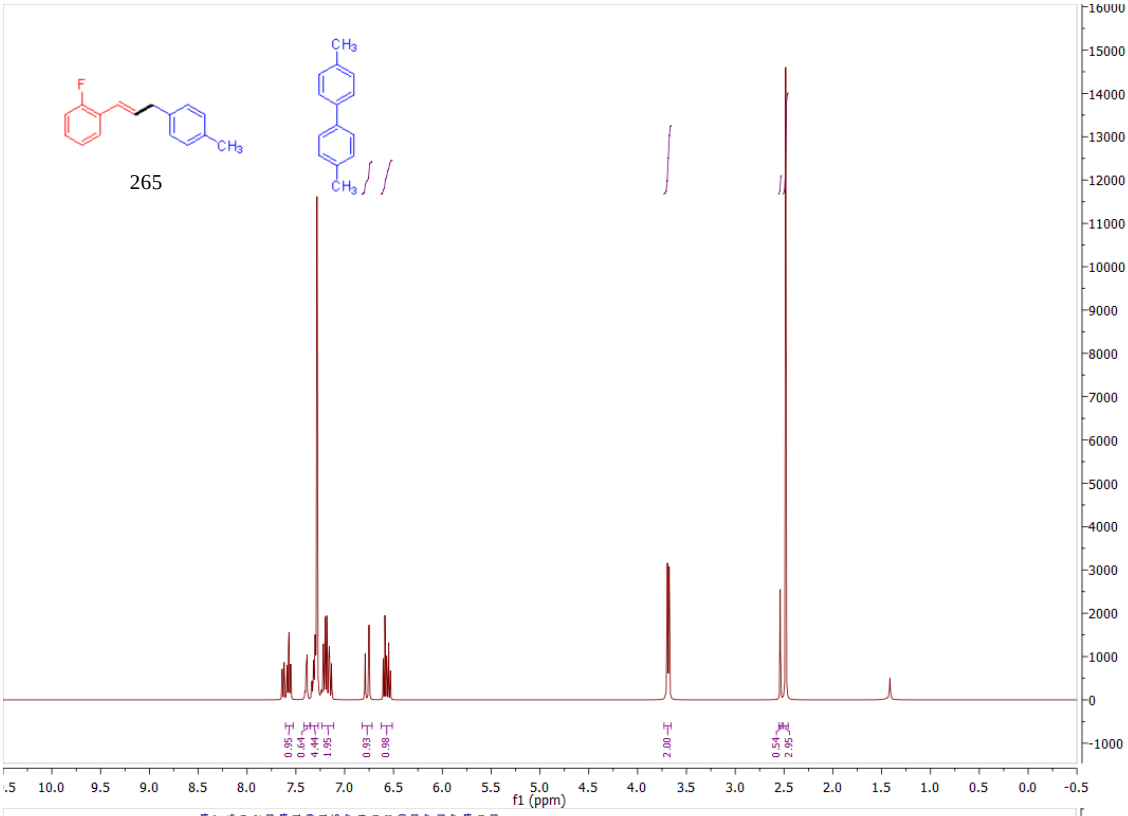
263

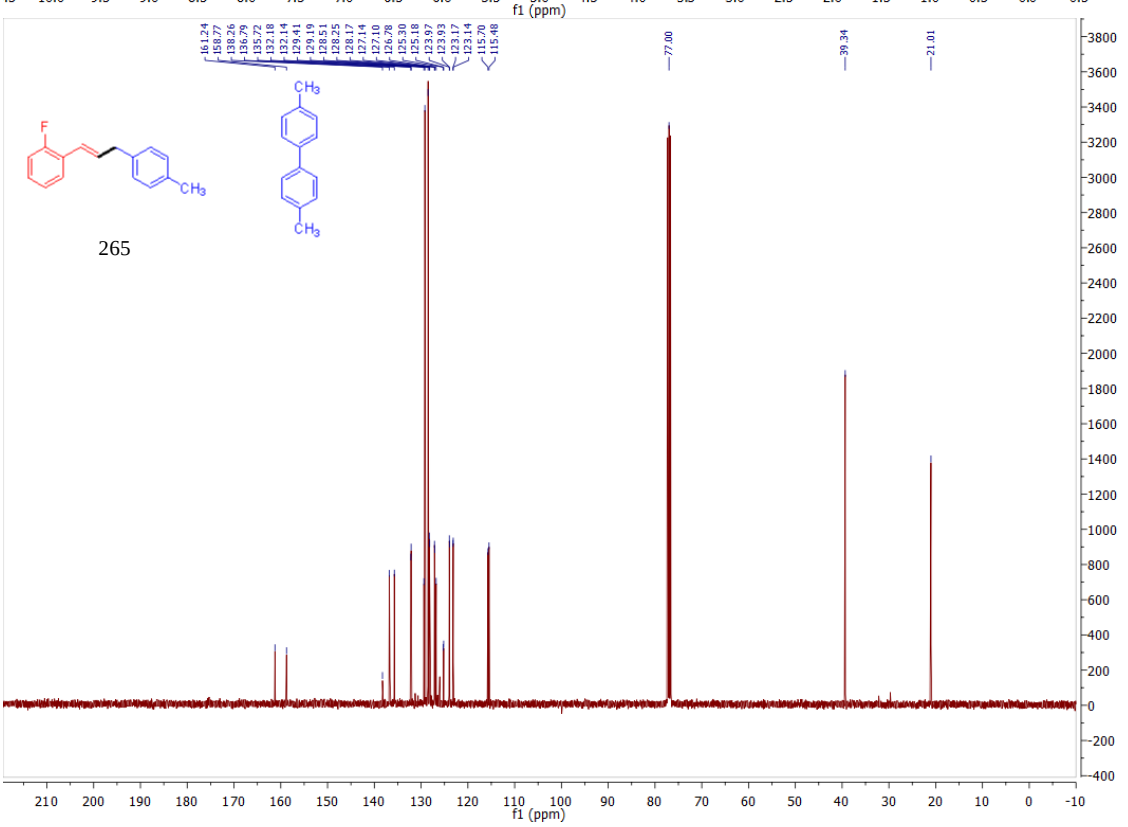

OCH3
CH3
1.01
4.83
2.98
0.89
3.25
1.80
3.00
f1 (ppm)

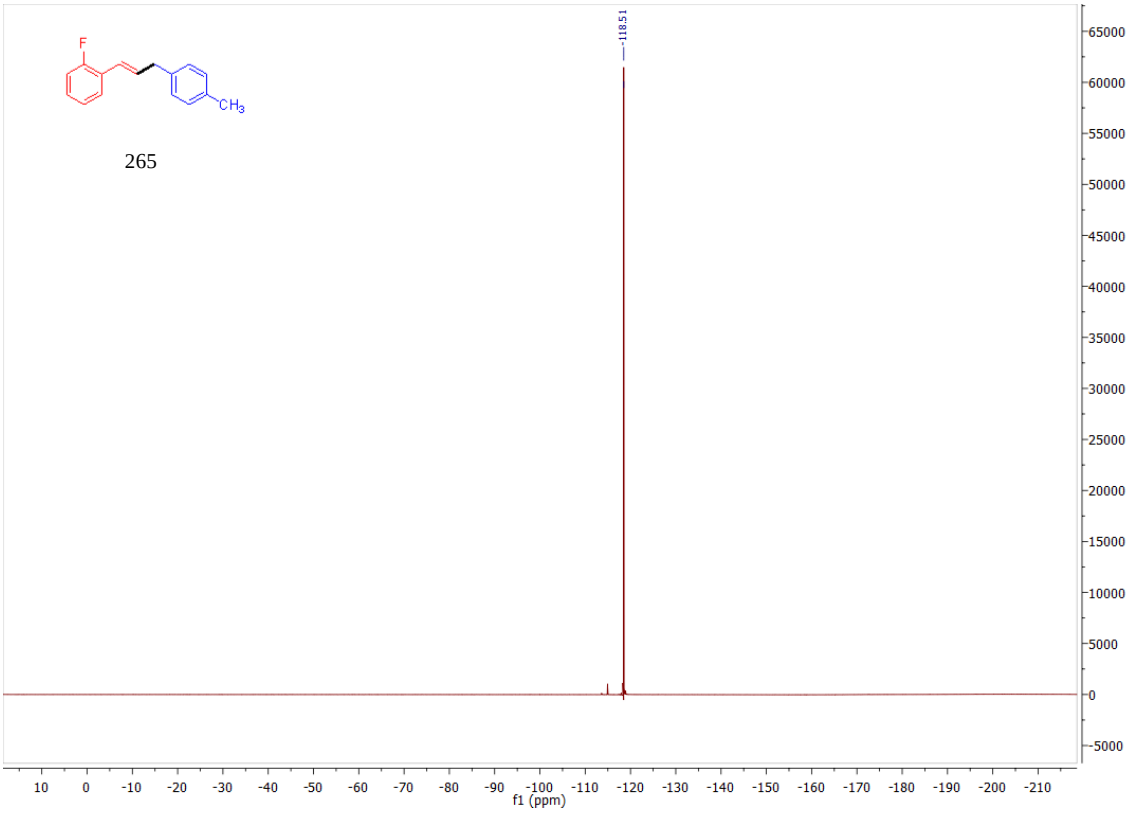
264


OCH3
CH3
156.40
137.43
135.49
130.08
129.09
128.49
128.02
126.57
126.55
125.49
120.59
110.78
77.00
55.43
39.42
21.00
f1 (ppm)

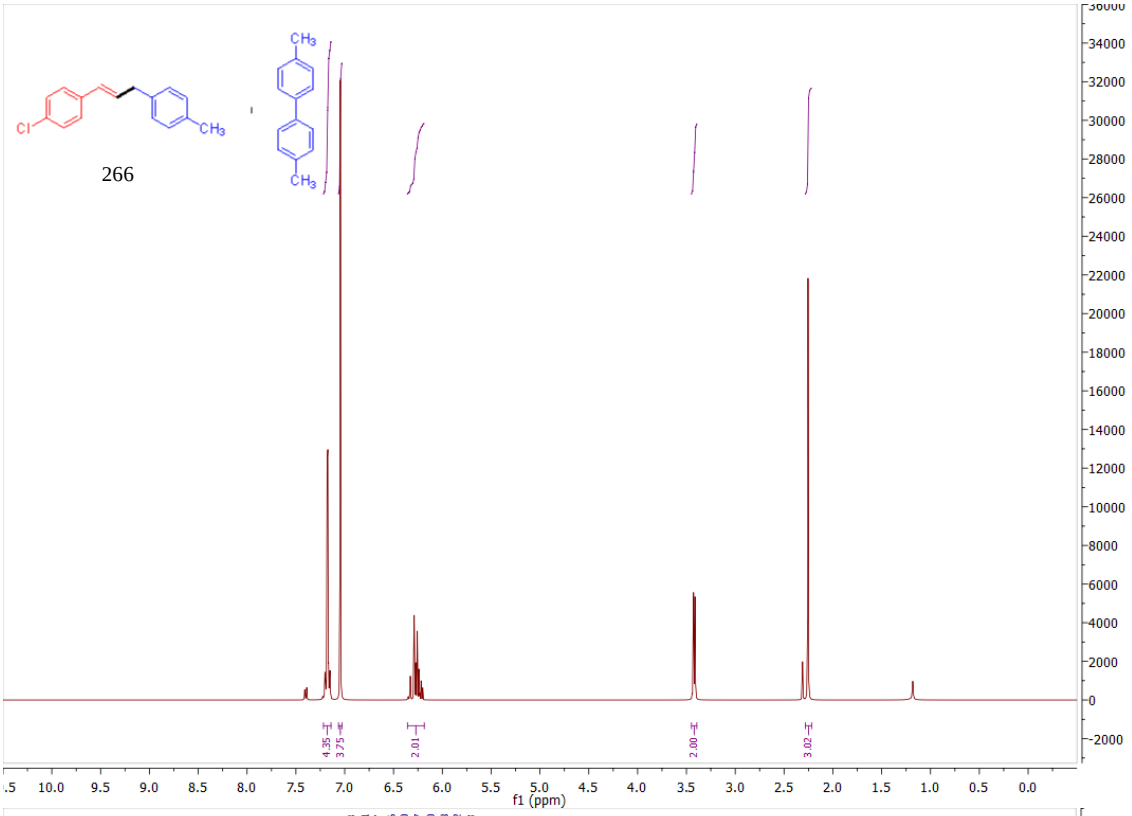
264

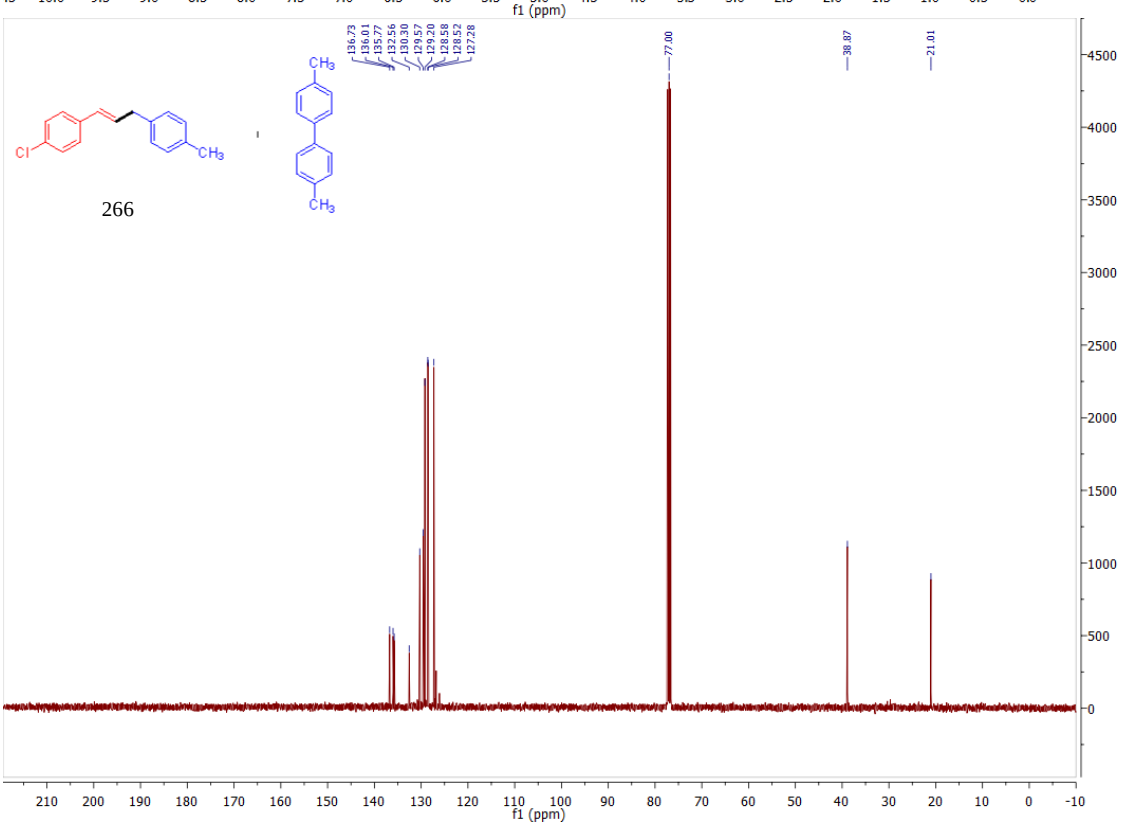

F
CH3
CH3
CH3
265
0.95
0.64
4.44
1.95
0.93
0.98
2.00
0.54
2.95
f1 (ppm)

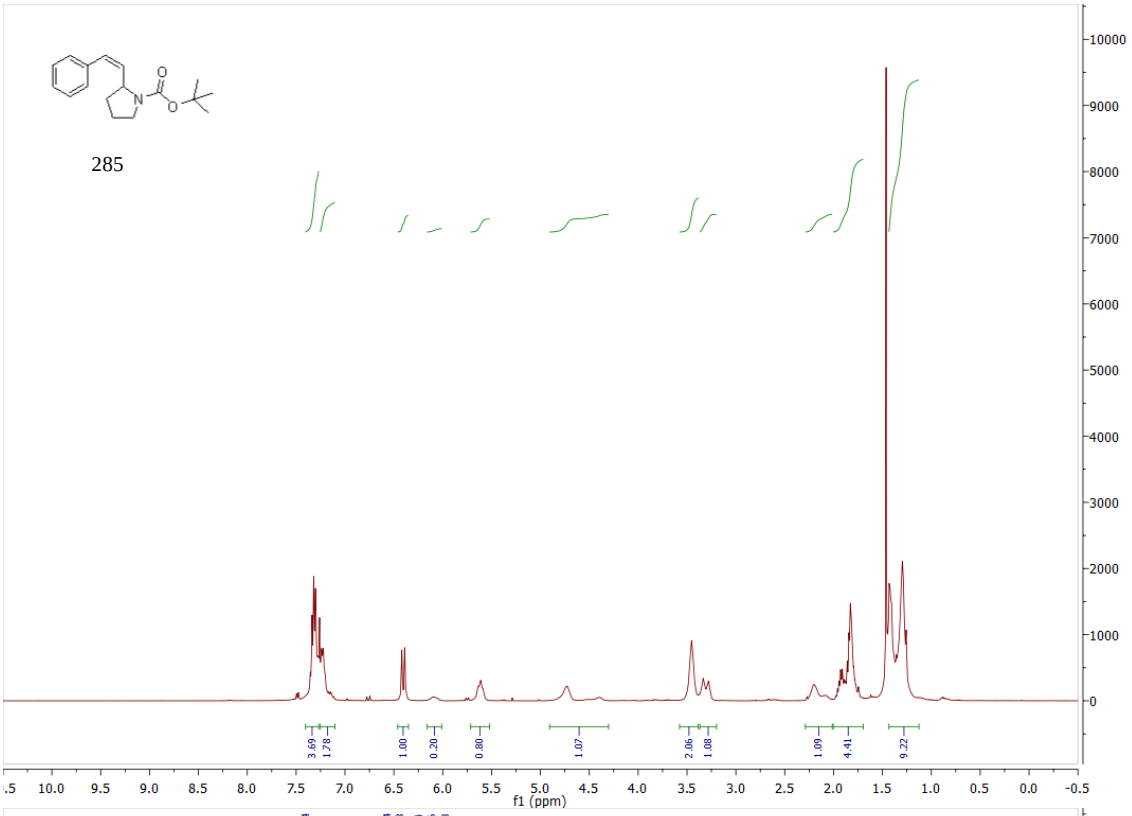

161.24
159.77
138.26
136.79
135.72
132.18
132.14
129.41
129.19
128.51
128.25
128.17
127.14
127.10
126.78
125.30
125.18
125.14
123.97
123.93
123.17
123.14
115.70
115.48
77.00
39.34
21.01
F
CH3
CH3
CH3
265
f1 (ppm)


F
CH3
-118.51
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

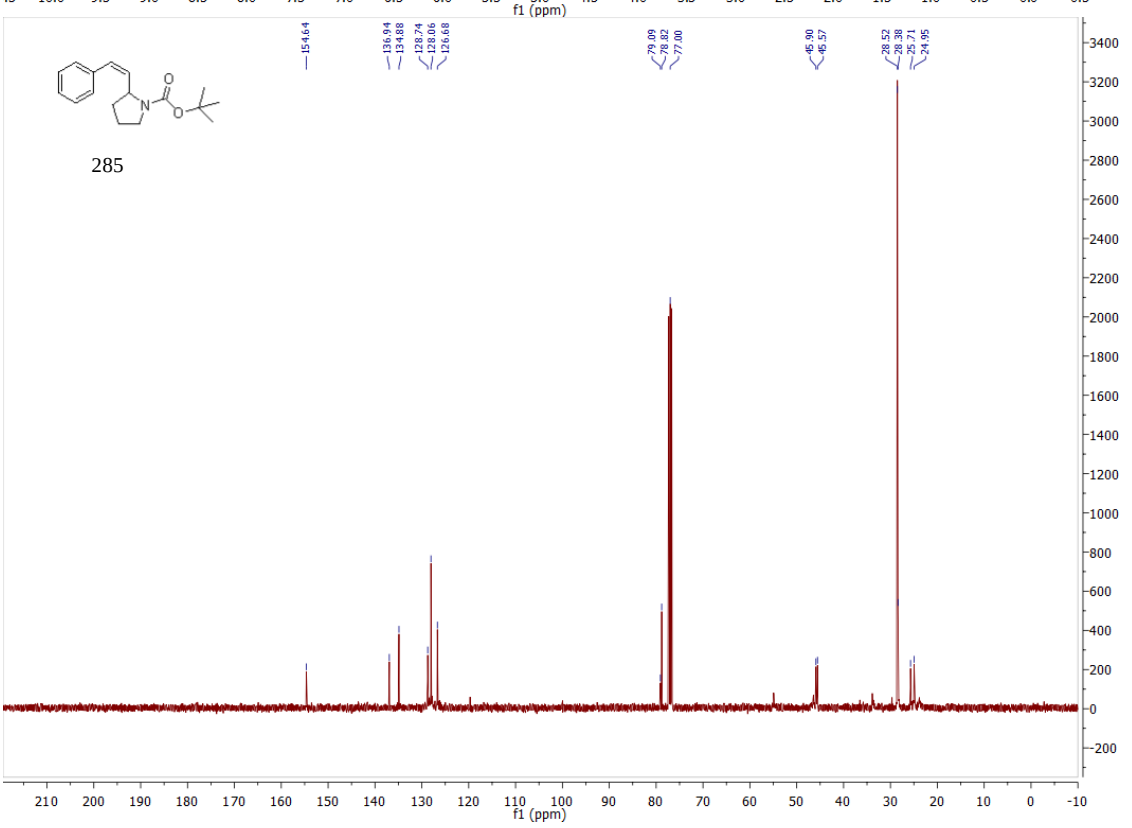
265


Cl
CH3
CH3
CH3
266
4.35
3.75
2.01
2.00
3.02
f1 (ppm)


Cl
CH3
CH3
CH3
266
136.73
136.01
135.77
132.56
130.30
129.57
129.20
128.58
128.52
127.28
77.00
38.87
21.01
f1 (ppm)



285



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VITA

Vinoth Kumar Chenniappan

Candidate for the Degree of

Doctor of Philosophy

Dissertation: CROSS-COUPLINGS OF UNCONVENTIONAL ELECTROPHILES WITH EARTH-ABUNDANT METALS

Major Field: Chemistry

Biographical:

Education:

Doctor of Philosophy, Organic Chemistry — May 2019
Oklahoma State University, Stillwater, OK

Master of Science, Chemistry — April 2009
Bharathiar University,
Coimbatore, Tamilnadu, India

Bachelor of Science, Chemistry, — April 2007
Bharathiar University,
Erode, Tamilnadu, India

Experience:

Graduate Teaching Assistant — August 2013 - May 2019
Oklahoma State University, OK, USA

Research Executive — September 2009 - May 2013
Medicinal Chemistry- New Drug Discovery
Orchid Chemicals & Pharmaceuticals Ltd.
Chennai, Tamilnadu, India

Professional Memberships:

American Chemical Society (ACS)

Awards:

Sigma-Aldrich Fellowship - 2017, Dept. of Chem., OSU
Johnston Chemistry Fellowship - 2018, Dept. of Chem., OSU
Niblack Scholarship - 2018, Oklahoma State University