Development of Radical Cascade via Gold(I) Photocatalysis and Application towards One-Pot Bromination/Carbocyclization

by

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A thesis submitted to the Faculty of Graduate Studies and Postdoctoral Studies in partial fulfillment for the degree of Master of Science (M.Sc.) in chemistry

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Abstract

Radical chemistry is a crucial tool to organic chemists. Recent trends in the field have been directed towards the development of photocatalysts capable of generating a radical through a renewable source like sunlight using a single electron transfer mechanism. The use of $Au_2dppm_2Cl_2$, having a stronger reducing potential, allows an expansion of the reactivity to those achieved by iridium and ruthenium catalysts.[1] The focus of this thesis is axed on the development of $Au_2dppm_2Cl_2$ as an efficient photoredox catalyst for a tandem one-pot catalysis and its application in a dual catalytic system.

The use of $Au_2dppm_2Cl_2$ in a dual catalysis for the synthesis of β-amino acids was undertaken. The problems encountered over the course of the investigation showed an insufficient oxidation potential of the photoredox catalyst in addition to the facile homolytic cleavage of the C-halogen bond under UV light. However, this shows great promise for the achievement of beta amino acids using solely organocatalysis.

The development of a tandem one-pot radical cyclization for the synthesis of fused-carbocycles, which are frequently encountered scaffolds in diterpenoid natural products, is reported. The initial experiments were conducted on a model substrate, enabling the verification of the proposed hypothesis. The success of this methodology was then applied to various substrates affording the desired fused 5 membered rings in good yields. These reactions show tremendous potential in the field of total synthesis for the rapid access of complex molecular structures.

Acknowledgements

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9-BBN	9-borabicyclo[3.3.1]nonane
Ac	acetate
AIBN	2,2'-azobisisobutyronitrile
Ar	aryl
Bn	benzyl
Boc	tert-butyloxycarbonyl
bpy	2,2'bypyridine
Bu	butyl
Bz	benzoyl
CFL	compact fluorescent light
CBz	carboxybenzyl
COSY	correlation Spectroscopy
DABCO	1,4-diazobicyclo[2.2.2]octane
DCM	dichloromethane
DIPEA	N,N-diisopropylethylamine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dppm	bis(diphenylphosphanyl)methane
DTBP	di-tert-butyl peroxide
dtbbpy	di-tert-butyl bipyridine
EDA	electron donor-acceptor
EI	electron ionization
Et	ethyl
eq.	equivalents
EtOAc	ethyl acetate
EWG	electron withdrawing group
HMQC	heteronuclear Multiple BondCorrelation

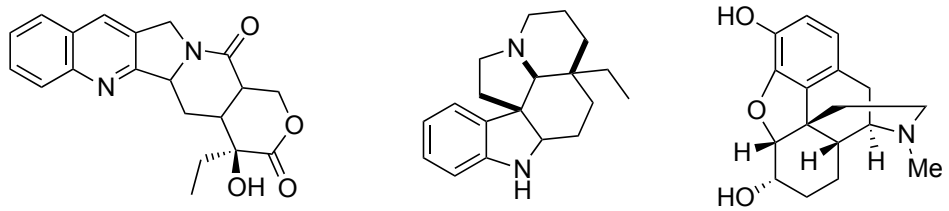
HOMO	highest occupied molecular orbital
HRMS	high-resolution mass spectrometry
iPr	isopropyl
IR	infra-red
ISC	inter-system crossing
LED	light emitting diodes
LG	leaving group
LUMO	lowest unoccupied molecular orbital
Me	methyl
Ms	methanesulfonyl (mesyl)
MTBE	methyl tert-butyl ether
MV	methyl viologen
NMR	nuclear magnetic resonnance
NOESY	nuclear overhauser effect spectroscopy
NOE	nuclear overhauser effect
O/N	overnight
OTf	triflate
Ph	phenyl
PMP	1,2,2,6,6-pentamethylpiperidine
ppm	parts per million
ppy	
quant.	quantitative yields
rt	room temperature
SCE	saturated calomel electrode
SET	single electron transfer
TBAF	tetra-n-butylammonium fluoride
TBS	tert-butyldimethylsilyl
tBu	tert-butyl
TEB	triethylborane
TEMPO	(2,2,6,6-tetramethyl-piperidin-1-yl)oxyl
Tf	triflyl

THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	n,n,n’,n’-tetramethylethylenediamine
TMS	trimethylsilyl
Ts	tosyl
UV	ultra-violet
V-50	2,2’-azobis(2-methylpropionamidine) dihydrochloride
V-70	2,2’-azobis(4-methoxy-2,4-dimethylpentanenitrile)

1. Introduction

1.1. Radical Chemistry

Radical chemistry has long been a valuable tool not only in polymer and physical chemistry but also in synthetic organic chemistry. Radical reactions are powerful tools for the formation of C-C bonds, but the selection of the appropriate reaction conditions is critical to be able to get an effective transformation. They have been important for the completion of the total synthesis of many natural products, including (−)-arctigenin[2], (+/−)-vindoline[3], martinelline, camptothecin[4], (±)-vincadifformine[5], (±)-morphine[6] and alliacolide[7] amongst many others.



1.0 camptothecin

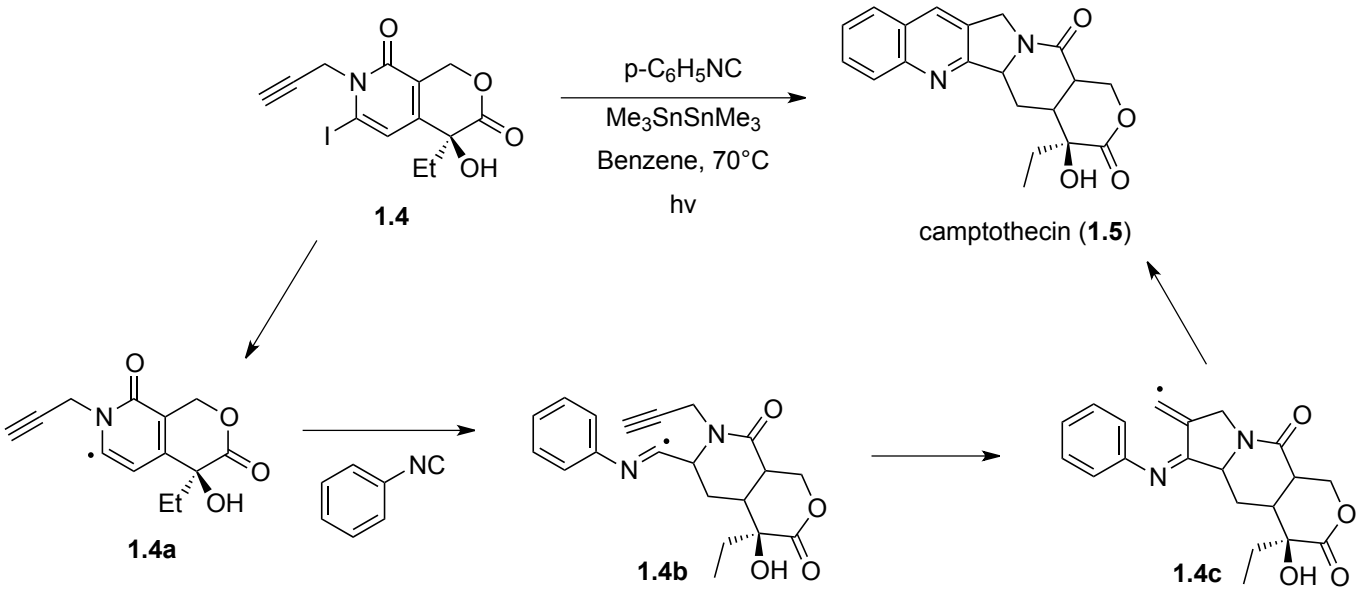
1.1 (±)-vincadifformine

1.2 morphine

Figure 1.1 Natural products synthesized by the means of radical reactions

The Curran group performed a selective radical cascade for the final step of their synthesis of camptothecin, thus demonstrating the power of radical reactions in synthesis (

Scheme 1.1).



Scheme 1.1 Radical key step in the synthesis of camptothecin

When designing a radical reaction it is important to keep in mind that radicals can undergo a variety of transformations including recombination, inter- and intramolecular reactions, which can lead to a mixture of products. With this in consideration, it is preferable to have a low concentration of radical species over the course of the reaction in order to diminish the possibilities for side reactions to occur. A higher concentration of radicals increases the odds for recombination, chain termination and decomposition reactions to occur, thus affecting the yield of the desired product. This suggests that radicals must be formed progressively instead of having a high concentration throughout the reaction. The most common method utilized that meets these requirements is the chain reaction process, which includes 3 important phases: initiation, propagation and termination.

Firstly, the initiation step involves the need for a catalytic amount of radical initiator to generate the first radical species. The most commonly used initiators in organic synthesis consist of azo compounds (AIBN, V-50 and V-70), peroxides (benzoyl peroxide, di-*tert*-butyl peroxide and acetyl peroxide), organometallic compounds (9-BBN or triethyl borane combined with oxygen) as well as inorganic compounds ($ZnCl_2$, SmI_2). In addition, these initiators usually demand an added source of energy such as heat, light or radiolysis to allow a homolytic cleavage of the covalent bond, thus producing a radical intermediate. Certainly these methods of initiation all have their advantages but their disadvantages are also quite prominent. Many are known to be toxic, explosive and unstable to air or they can require harsh reaction conditions. The structures of some initiators are presented in Figure 1.2.

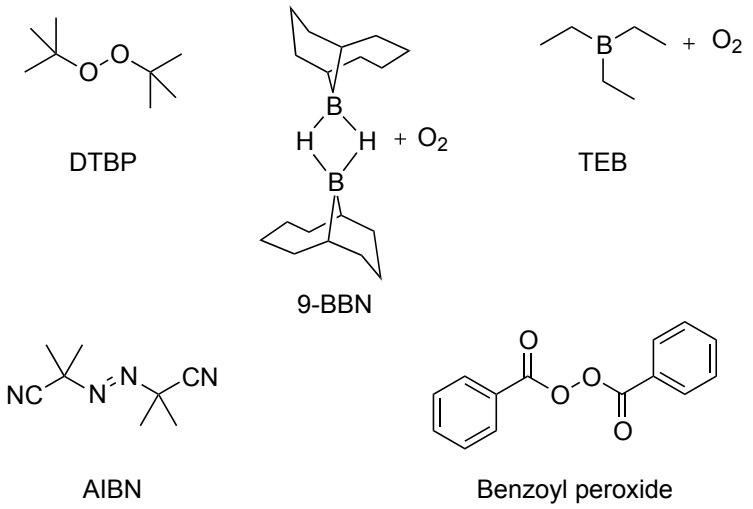
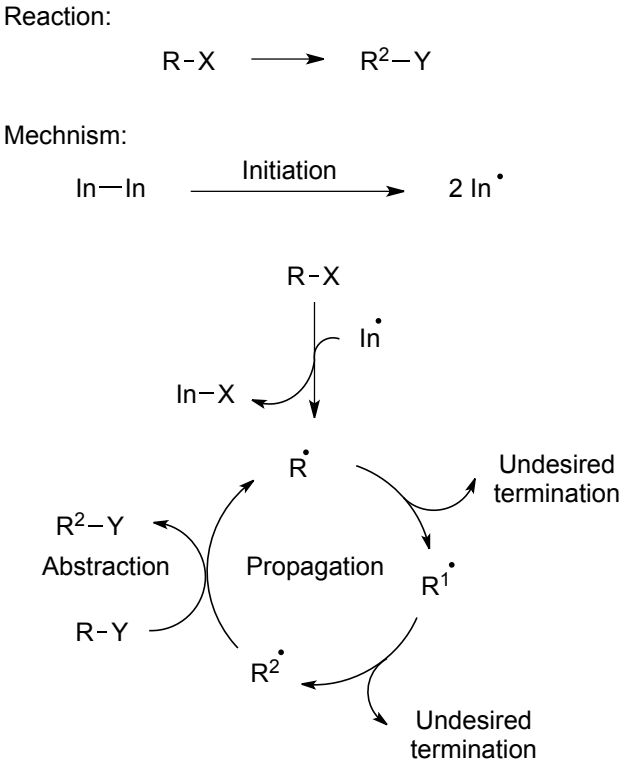


Figure 1.2 Structure of common radical initiators

The formation of the first free radical in the initiation stage leads to the propagation in order to have a productive chain reaction process. By definition, propagation is a succession of steps that produce a radical in one reaction and consumes it in the next. The initial radical ($R^{\bullet}$) can undergo a series of inter- or intramolecular reactions, thus forming a new radical ($R^{2\bullet}$). In Scheme 1.2 the $R^{\bullet}$ initially formed must undergo 2 consecutive

transformations before the termination step leading to the desired product R^2-X. This particular reaction gives room for 2 possible termination reactions to occur yielding the undesired products. It is important that the rate of these transformations be faster than the possible termination reactions some of which are disproportionation, hydrogen abstraction and recombination leading to undesired side products. The lifetime of the intermediate radical is also an important aspect to consider, it needs to be long enough to undergo the desired transformations but should not be too long to cause degradation and premature termination leading to undesired products. The careful consideration of these rates allows the formation of multiple carbon-carbon bonds in a single step.

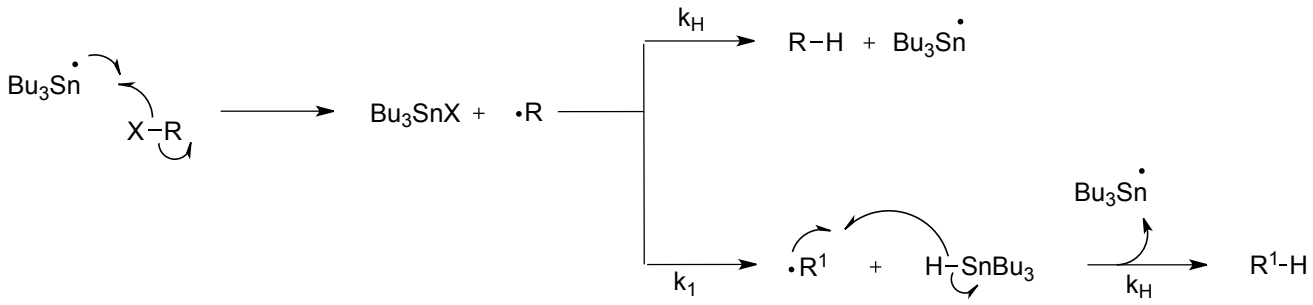


Scheme 1.2 Chain Reaction Mechanism including the initiation and propagation phases

Finally the termination phase consists of the formation of the final non-radical product. Termination can happen by disproportionation, abstraction, recombination, and oxidation or reduction reactions. Ideally this step takes place during the rate-determining step of propagation in order to achieve the desired product.

In summary, to have an efficient radical reaction special attention should be paid to the gradual generation of radical species over the course of the reaction, the site-selective radical generation in addition to the lifetime of the intermediate radical.

A method that meets most of these requirements and that has been very successful in organic synthesis is the organotin hydride method; because of it's controlled chain reaction process when appropriate conditions are used. It is important to note that there are two possible pathways the radical can follow during this process (Scheme 1.3). The first reaction consists of a simple hydrogen abstraction and the other is either an intra- or intermolecular reaction followed by a hydrogen abstraction. It is possible to obtain reaction selectivity for these different pathways by the relative rate of reactions. If the rate constant for the hydrogen abstraction (k_H) is faster than the rate constant for the inter- or intramolecular reaction (k_1), the hydrogen abstraction product will be more prominent than the transformed product and vice-versa. Since many of the reaction rate constants are known in the literature it is possible to carefully plan a successful reaction based on these data sets.

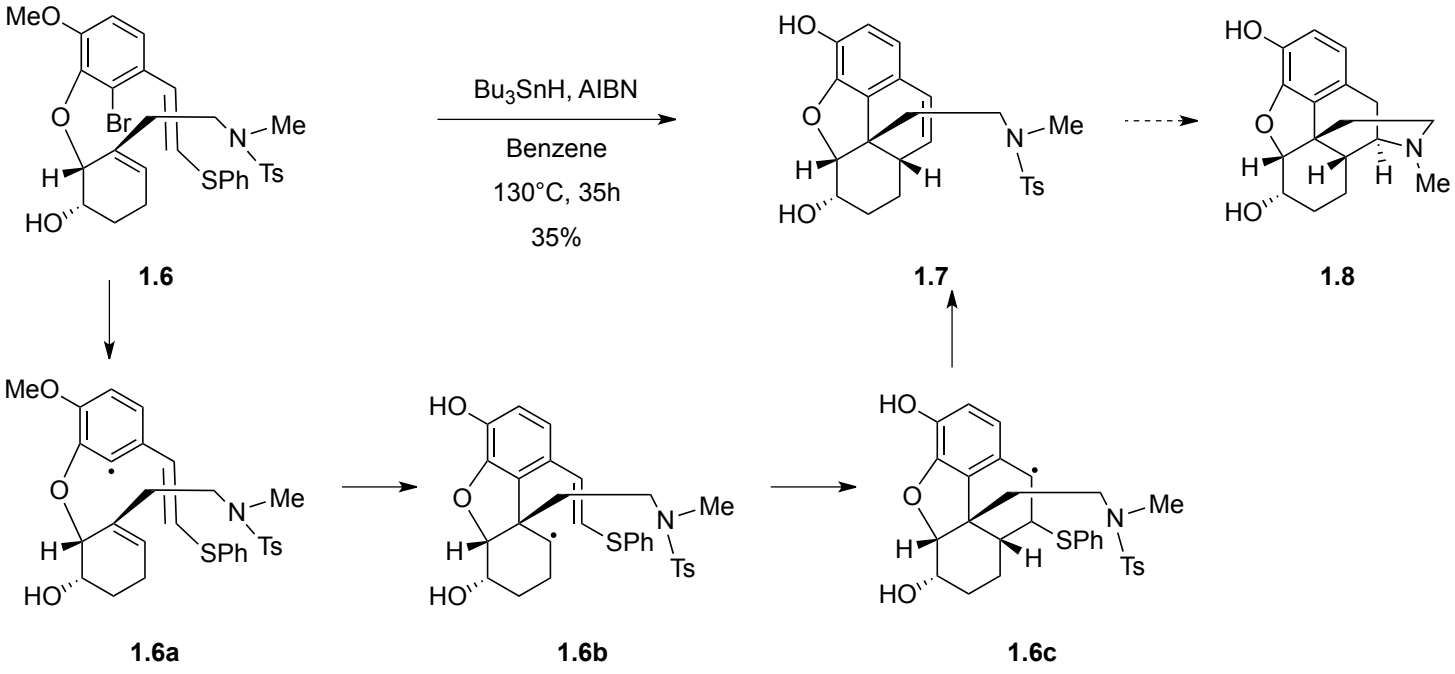


Scheme 1.3 Tin hydride competing reactions

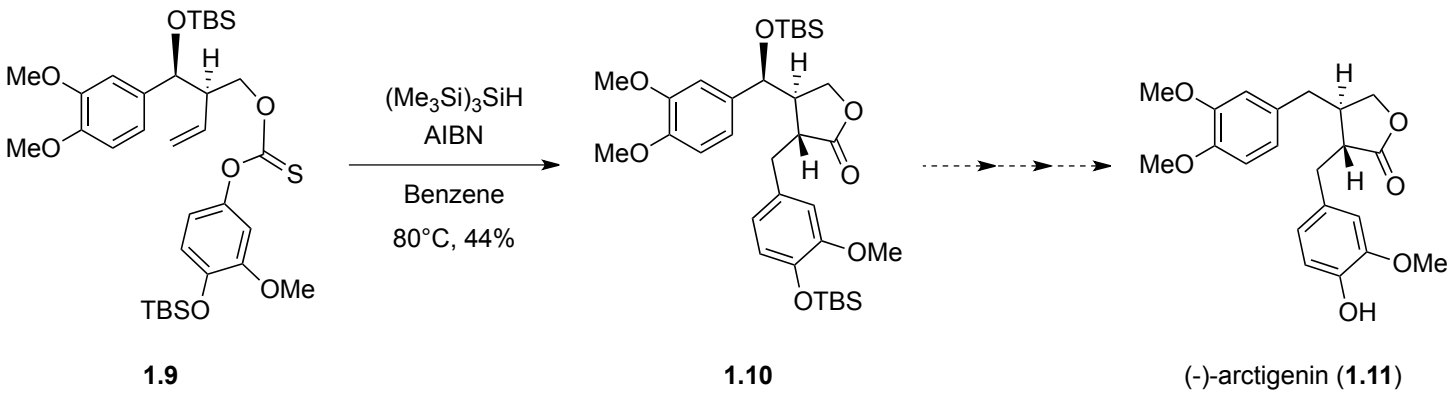
The organotin hydride method usually requires a stoichiometric amount of tin, which is undesirable because of its high toxicity.[8] Additionally, this method poses certain problems in view of attaining the desired product. The concentration of Bu_3SnH used for the reaction is clearly influential on the distribution of the products. The modification of the concentration of the tin hydride species in solution will allow the maximum product to be formed. When the concentration is low the desired product will predominate while

when the concentration is higher, the reduced product will be more prominent. Although this is an effective method, the window for the variation of concentration does have some constraints. It is important that the concentration of tin hydride be sufficient for effective chain propagation. With this in mind, slower reactions can be optimized by special procedures such as addition by syringe pump or by the modification of the tin hydride source.

This method has shown many successful applications in total synthesis by the appropriate design of reactions.[9] To name a few, the Parker group has carried out the formal synthesis of (±)-morphine (**1.8**) with the help of an ortho allyloxy aryl radical initiated cyclization.[6] Sherburn and coworkers have also showed significant applications of radical chemistry towards the total synthesis of (−)-arctigenin (**1.11**).[2]



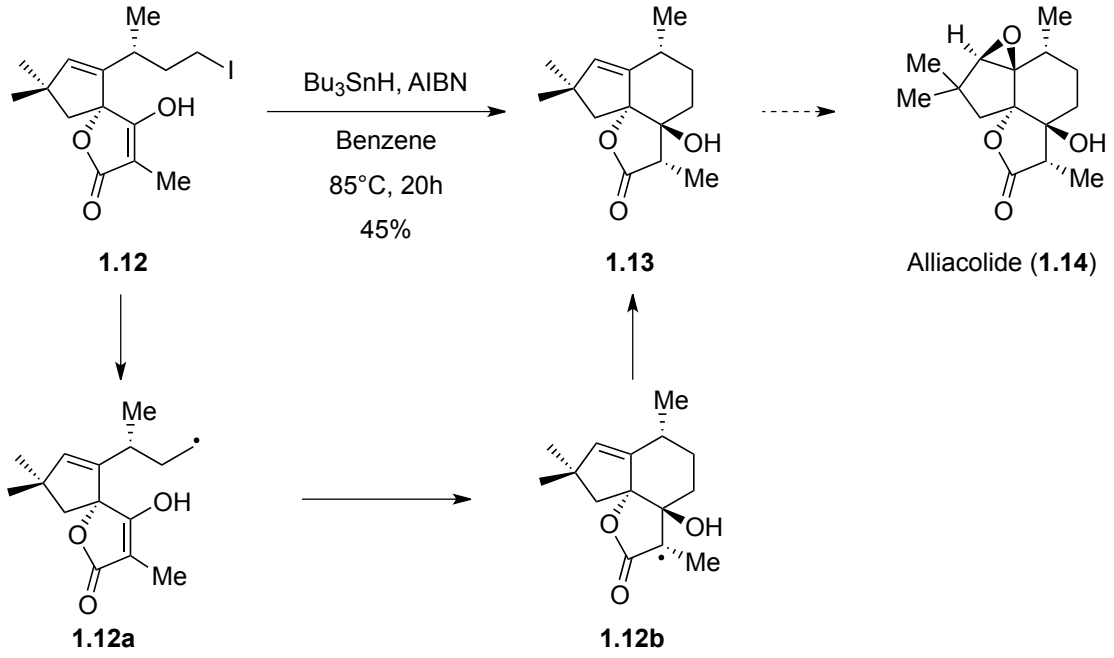
Scheme 1.4 Radical cyclization step in the formal synthesis of morphine from the Parker group



1.9 **1.10** (-)-arctigenin (**1.11**)

Scheme 1.5 Radical ring closing in the total synthesis of (−)-arctigenin (1.11)

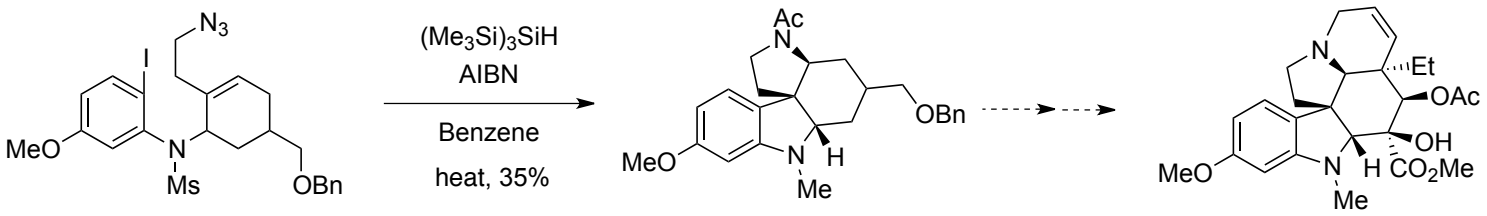
Natural product alliacolide (**1.14**) was synthesized by the group of Pattenden using Bu_3SnH and AIBN for the stereoselective intramolecular radical cyclisation to form the tricycle.[7] Murphy et al. have completed the formal synthesis of (±)-vindoline (**1.17**) in 2002 using a iodoaryl azide as a precursor for a tandem cyclization of radicals.[3]



1.12 **1.13** Alliacolide (**1.14**)

1.12a **1.12b**

Scheme 1.6 Final cyclization towards alliacolide (1.14) by a radical reaction



1.15 **1.16** (±)-vindoline (**1.17**)

Scheme 1.7 Tandem radical cyclization in the synthesis of (±)-vindoline

Although theses reactions display the successful application of radical chemistry in synthesis, the limitations of the method mentioned previously can still be problematic for their application towards efficient and high yielding product formation.

The stride towards cleaner and more atom economical reactions has been of substantial interest for many decades, thus pushing chemists to carefully design reactions with this ideal in mind. Catalysis has been a popular field in chemistry for centuries and the use of catalysis for the formation of radicals through redox reactions has been more recently revisited introducing softer reactions conditions for the generation of free radicals.

1.2. Photocatalysis

Chemists have been inspired by the plant's abilities to harvest sunlight as a source of clean renewable energy to create new molecules via photosynthesis. The development of methodologies that take advantage of an efficient conversion of solar energy into significant chemical potential has been a field of interest for organic synthesis.[10] The main problem resulting from the use of sunlight as an energy source in synthetic organic chemistry resides in the inability of most organic molecules to absorb visible light. Although the photochemistry of these organic molecules can pose problems, the development of transition metal complexes that have the ability to harvest sunlight is a promising alternative. Some catalysts have been exhaustively studied for their application in the conversion of solar energy into electricity and chemical fuels during the last century. These transition metal complexes have more recently played a significant role in the development of efficient photoredox reactions.

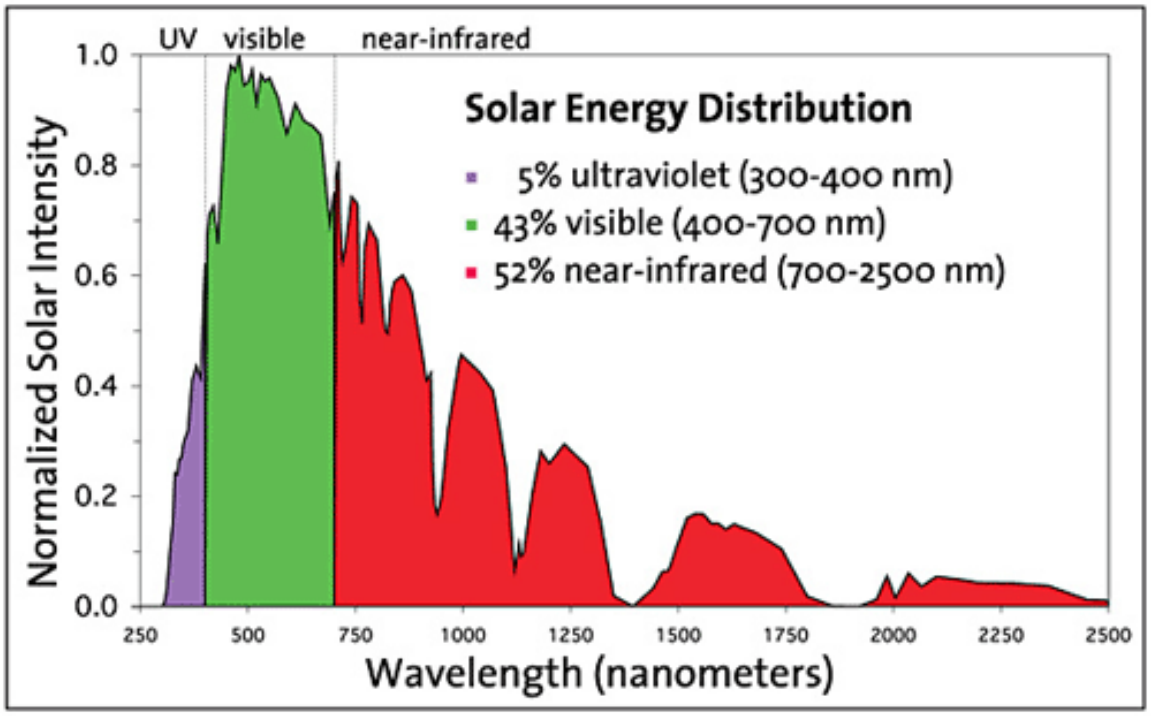


Figure 1.3 Solar emission spectrum[11]

Before moving forward, it is essential to note that the emission spectrum of the sun ranges from the infrared (IR) region to the ultraviolet (UV) wavelengths including visible white light as shown in Figure 1.3. Keeping this in mind, it is important to include but should not be limited to visible white light for the activation of transition metal complexes or organic dyes. The UV and IR wavelengths should also be considered for the excitation of these complex. On the other hand, it is important to remember that UV irradiation of absorbing molecules can possibly lead to unproductive degradation and undesired side reactions when determining the appropriate photocatalyst.

In order to have an efficient photocatalyst, the complex needs to exhibit specific properties. The first step towards the photochemical and photophysical processes is the absorption of a photon, thus forming an excited state. The three most important states present in a photochemical process include the ground state singlet (S_0), the excited singlet (S_1) and the excited state triplet (T_1) as shown in the simplified Jablonski diagram (Figure 1.4). Most commonly, the ground state is a singlet state while the excited state resides as the lowest energy triplet state. It is important to note that the excited triplet state cannot be attained by direct excitation because a transition from the ground state to an excited state with a different spin value is forbidden. Therefore, the ground state is first transitioned to a high energy and unstable excited singlet, which subsequently undergoes an intersystem crossing (ISC) leading to the more stable excited triplet state. This excited complex needs to be sufficiently long-lived to allow a chemical reaction to occur.

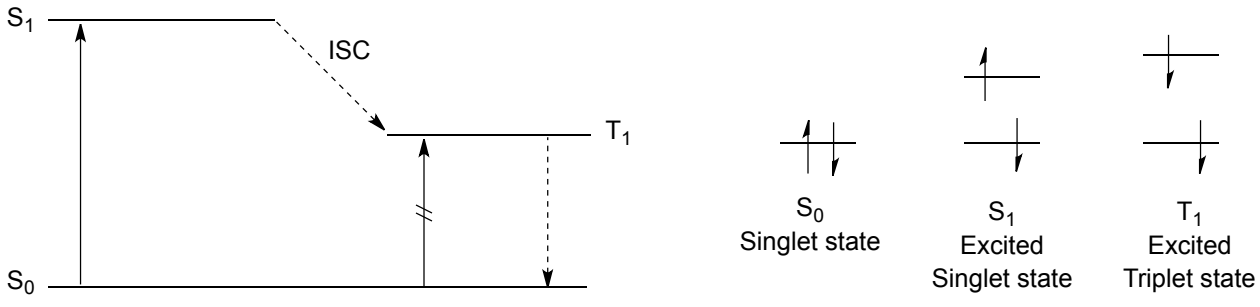
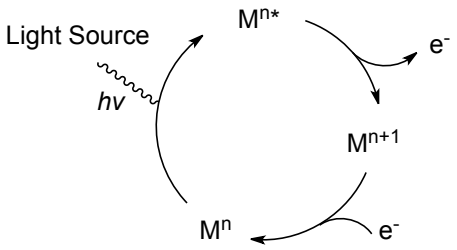


Figure 1.4 Simplified Jablonski diagram

These electron transfers can occur by one of two electron transfer mechanisms, inner sphere or outer sphere. The inner sphere mechanism is defined by a significant interaction between the donor and the acceptor during the single electron transfer. Since the electron transfer occurs within a complex that consists of both interacting molecules, a metal center needs an empty coordination orbital to proceed through this mechanism. On the other hand, the outer sphere mechanism does not require strong coordination between both reactants during the single electron transfer, where the electronic properties are reorganized.



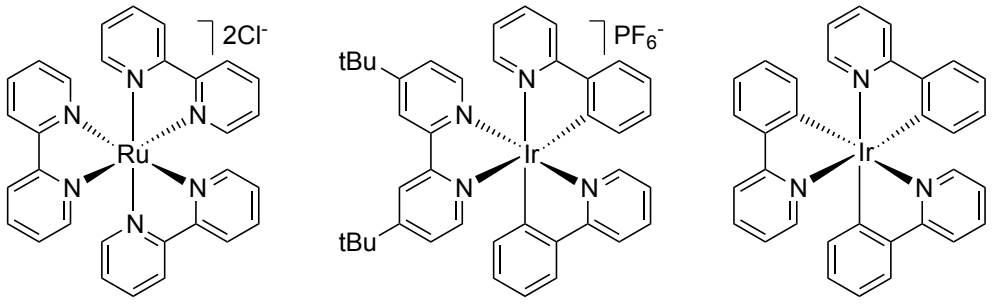
Scheme 1.8 General Photoredox catalytic cycle

Photoinduced electron transfers via an excited state catalyst will produce a reactive radical species by oxidation or reduction. In order to have a closed catalytic cycle it is important to have two electron transfers. The first will quench the excited state catalyst (M^n*) giving the oxidized catalyst (M^{n+1}) and a radical species while the second regenerates the ground state catalyst (M^n) and re-oxidizes an electron donor as seen in Scheme 1.8. In order to have a productive electron transfer the reducing potential of the excited state catalyst needs to be higher than the bond dissociation energy of the substrate, thus creating the radical intermediate. Importantly the reduction and oxidation potentials of a catalyst are usually different in the ground state and in the excited state. Most frequently, the excited state potentials are higher than in the ground state because of their higher energy levels. The relative rates of these electron transfers greatly influence the rate of radical formation. Slow radical generations are favorable for the formation of the desired products with minimal side products that result from recombination and cross-reactions of the radical species. Thus, the adjustment of the rate of the rate-determining step in the photocatalytic cycle is a crucial tool for the design of appropriate reaction

conditions. These types of reactions are difficult to scale up because they require full penetration of light through the reaction mixture, which becomes more difficult in larger volumes; thus reaction times are longer and yields suffer. On the other hand, it has been shown to be applicable to flow systems. The Stephenson group has used photoredox chemistry in flow systems for the α-functionalization of amines,[12] the deiodination reactions[13] and the fragmentation reactions towards a total synthesis.[14]

1.3. Ruthenium and Iridium complexes

Some catalysts have been exhaustively studied for their application in the conversion of solar energy into electricity and chemical fuels during the last century.[15] Over the past decade, there has been a resurgence of interest in metal complexes that possess the ability to convert the energy from natural sunlight into a renewable source of chemical potential. The most exhaustively used catalysts for applications in organic synthesis are surely $Ru(bpy)_3Cl_2$ (**1.18**), $Ir(ppy)_2(dtbbpy)PF_6$ (**1.19**) and *fac*-$Ir(ppy)_3$ (**1.20**) complexes (Figure 1.5).



1.18
$Ru(bpy)_3Cl_2$
-1.31V vs. SCE

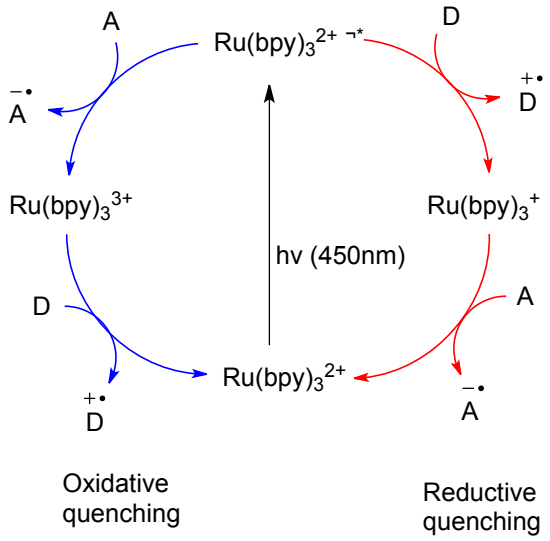
1.19
$Ir(ppy)_2(dtbbpy)PF_6$
-1.51V vs. SCE

1.20
fac-$Ir(ppy)_3$
-1.73V vs. SCE

Figure 1.5 Ruthenium and Iridium visible light photocatalysts

Although there has been a remarkable acceleration in the development of methods using a $Ru(bpy)_3^{2+}$ **1.21** catalyst in the past decade, the complex was first isolated by the Burstall group in 1936.[16] Ruthenium has been thoroughly studied in the field of

photocatalysis and is an important transition metal in the development of photoredox catalysis.[17] These complexes have shown excellent chemical stability, resistance to high temperatures and tolerance for strong acidic and basic conditions making it an excellent choice for catalysis. It exhibits a strong metal-to-ligand charge transfer at ~450nm which is within the visible light region.[18] The excitation of $Ru(bpy)_3^{2+}$ **1.21** leads to a long-lived excited state which is indispensible for single electron transfer processes. Scheme 1.9 shows the mechanism by which this Ruthenium catalyst performs photoredox catalysis.[19] The absorption of a photon promotes an electron from the metal center to the π* of the ligand by a metal to ligand charge transfer yielding the excited state catalyst $[Ru(bpy)_3^{2+}]$*. This initial excitation forms a highly reactive singlet state that consequently undergoes intersystem crossing to give its more stable luminescent triplet state $[Ru(bpy)_3^{2+}]$* **1.22**.



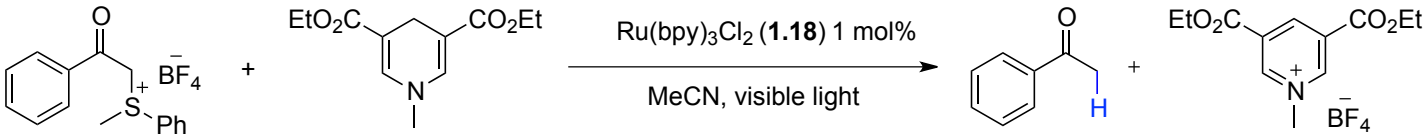
Scheme 1.9 Oxidative and reductive quenching mechanisms of Ruthenium catalyst

Once the long-lived triplet state is formed it can act as either an oxidant or a reductant depending on the nature of the substrates in solution. In the oxidative quenching reaction, the excited state donates an electron to the acceptor (A) producing a strong oxidant $[Ru(bpy)_3^{3+}]$ **1.23** (+1.29V vs. SCE in MeCN). One the other hand, in the reductive quenching reaction, the excited state accepts an electron from the donor (D) yielding a strong reductant $[Ru(bpy)_3^{+}]$ **1.24** (-1.33V vs. SCE in MeCN).[20] The nature of the

quencher used for the reaction will determine the type of photoreaction (oxidative or reductive quenching) that will occur. The correct design of a reaction will influence the pathway taken by the catalyst.

The first application of this ruthenium complex for photoredox reactions dates back to the 1970's when the Kellogg group noticed the acceleration of their reduction of phenacylsulphonium salts **1.25** in presence of $Ru(bpy)_3Cl_2$ (Figure 1.6).

Kellog et al. 1978 and 1979

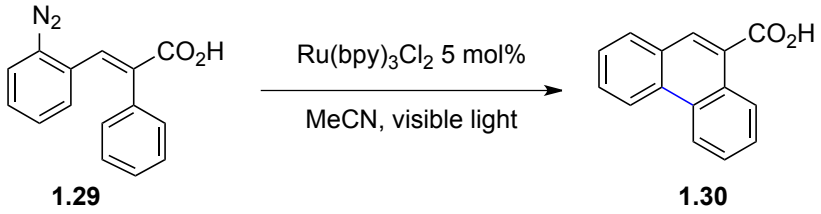


1.25 **1.26** **1.27** **1.28**

Figure 1.6 Reduction of phenacylsulphonium salts by the Kellogg group

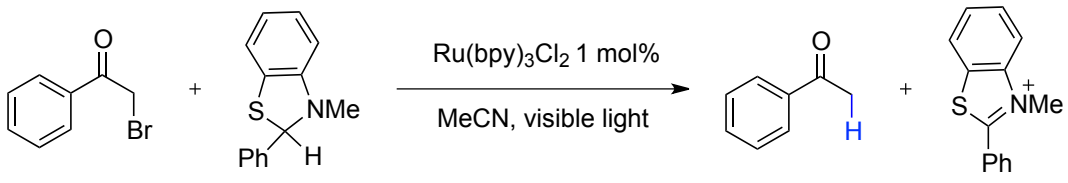
In 1984 Cano-Yelo and Deronzier demonstrated the formation of phenantrene **1.30** from diazo coumpound **1.29** via visible light activated $Ru(bpy)_3Cl_2$ for a photocatalytic Pschorr reaction in 1984 (Figure 1.7).[21] Other examples of these applications shown in Figure 1.7 include the dehalogenation reaction using the same catalyst by the Kellogg group in 1985.[22] Fukuzumi and coworkers also performed a dehalogenation of phenacyl halide **1.31** to yield acetophenone **1.33.**[23]

Cano-Yelo and Deronzier 1984



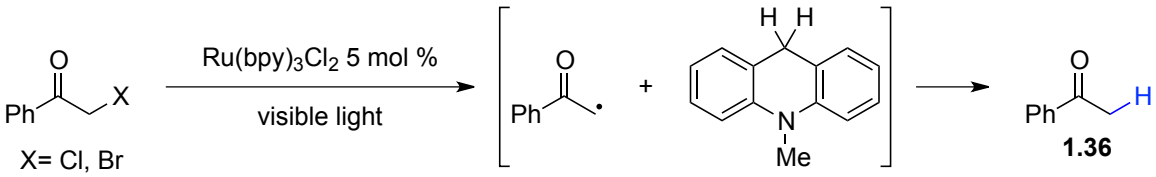
1.29 **1.30**

Kellog et al. 1985



1.31 **1.32** **1.33** **1.34**

Fukuzumi and co-workers 1990

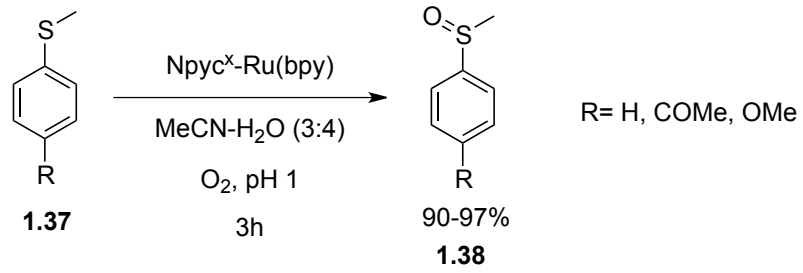


1.35 **1.36**

Figure 1.7 Previously developed methods using $Ru(bpy)_3Cl_2$

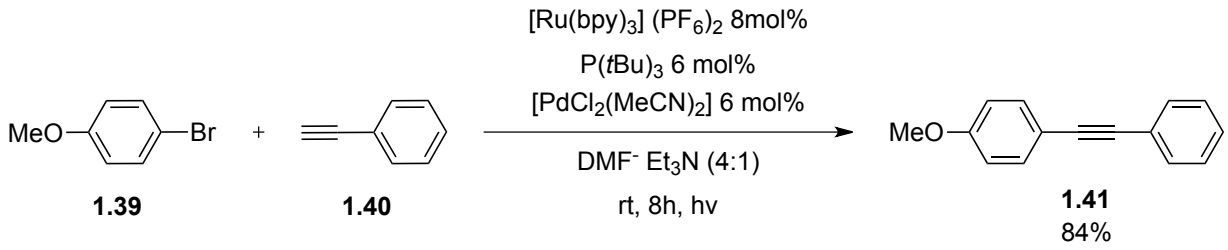
In 2008, a significant increase in publications in the field of photoredox chemistry started to overwhelm the chemical society. Many applications of this concept have proved its potential in various organic transformations. The pivotal work done by the MacMillan, Stephenson, Yoon, Gagné, Zeithler and Rueping groups, amongst others, have been pushing the field to its many recent successes.

In 2003, the Zen group reported the oxidation of sulfides **1.37** with a ruthenium photocatalyst ($NPyc^x$-Ru(bpy)) in excellent yields (Scheme 1.10).[24]

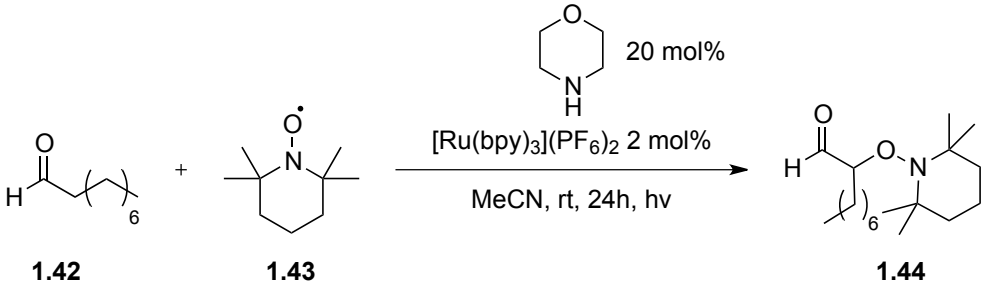


Scheme 1.10 Oxidation of sulfides using photoredox chemistry

Photoredox chemistry has also shown potential in cross-coupling reactions. In Scheme 1.11 aryl bromides and alkynes are coupled through visible light promoted photocatalysis.[25] Koike and Akita have developed a α-oxyamination of aldehydes using a ruthenium photocatalyst and (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl (TEMPO) as shown in Scheme 1.12.[26]



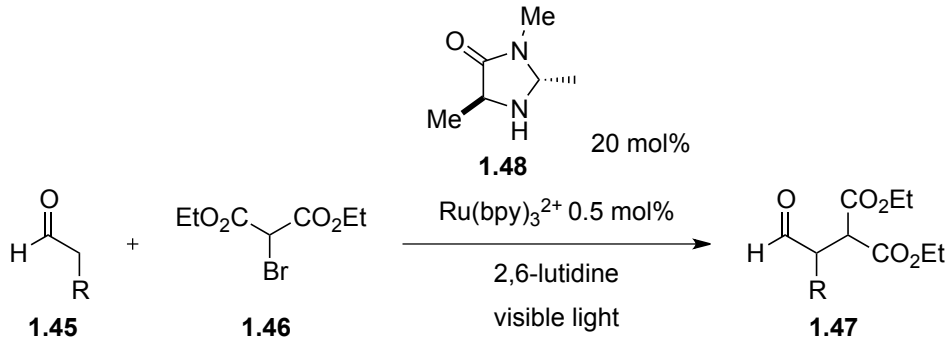
Scheme 1.11 Coupling of aryl bromides using light



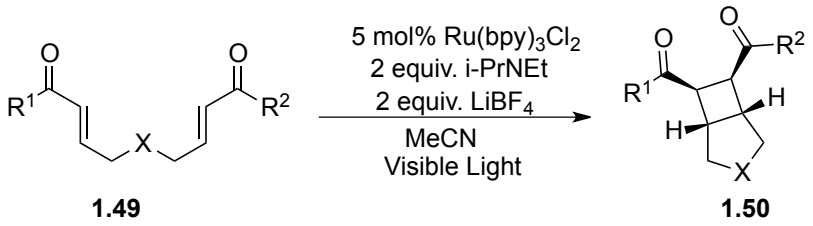
Scheme 1.12 α-oxyamination of aldehydes

The group of David W. C. MacMillan has successfully merged organocatalysis with photoredox chemistry with an interwoven catalytic cycle (Scheme 1.13). They were able to couple aldehydes **1.45** with α-bromoketones **1.46** with high enantioselectivity via a

chiral amine catalyst **1.48** and a catalytic amount of $Ru(bpy)_3Cl_2$.[27] The use of a photocatalyst for catalysis of the [2+2] cycloaddition of a bis-(enone) **1.49** substrate through a single electron transfer reduction of the enone (Scheme 1.14) was achieved by the Yoon group.[28]

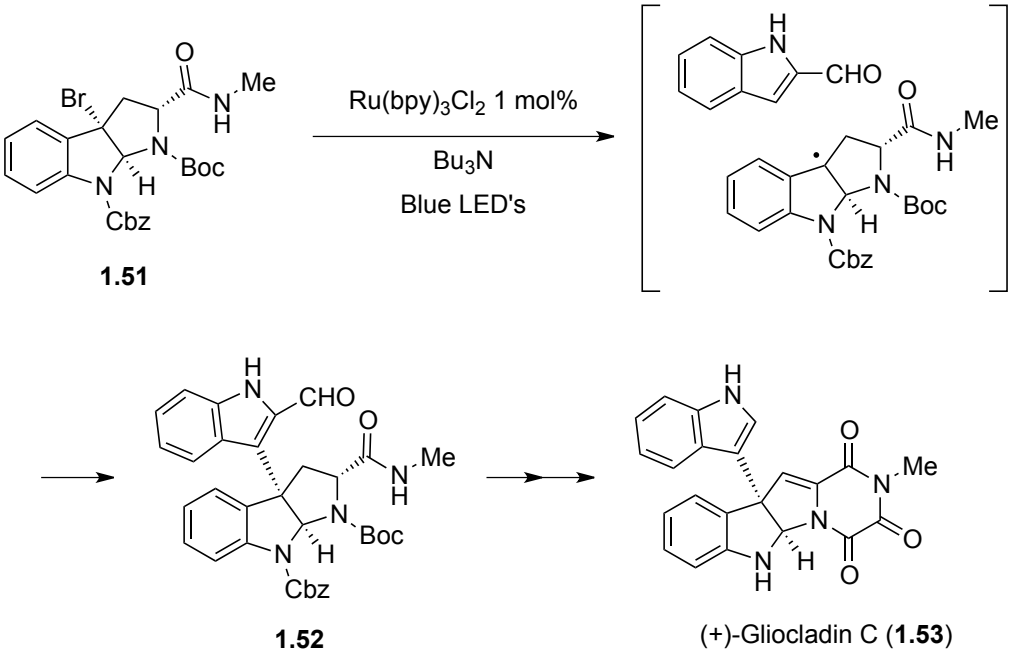


Scheme 1.13 Formation of enantioenriched α-alkylated aldehyde via organocatalysis merged with photoredox catalysis



Scheme 1.14 Yoon's [2+2] cycloaddition catalyzed by photocatalyst $Ru(bpy)_3Cl_2$

In 2009, the Stephenson group demonstrated the reductive dehalogenation of activated alkyl and aryl halides using photoredox conditions. Thereafter, the formation of alkyl and aryl radicals via photoredox has been a constant theme in their research. In addition, they took advantage of the mild conditions and the photochemical properties of $Ru(bpy)_3Cl_2$ for its application in total synthesis. The synthesis of the alkaloid (+)-gliocladin C was achieved with a photoredox step, where bromopyrroloindoline **1.51** was the radical precursor to give the desired coupling product **1.52** in an 82% yield (Scheme 1.15).[29] They have also more recently applied this method towards the total synthesis of (-)-pseudotabersonine, (-)-pseudovincadifformine and (+)-coronaridine.[14]



Scheme 1.15 Total synthesis of gliocladin C via radical cascade cyclization

The iridium species are also often utilized for their abilities to catalyze photoredox reactions. The $Ir(bpy)_3^{3+}$ catalyst was first isolated in 1958 by Martin et al.[30] These iridium complexes are good oxidizing agents but contrary to the ruthenium species, they are weak reducing agents. The λ_{max} for $Ir(bpy)_3(PF_6)_3$ is at 355 nm while for the neutral *fac*-$Ir(ppy)_3$ **1.20** species the absorption maxima is also found in the visible light region, more specifically at 375 nm. Therefore the use of regular sunlight or a regular light bulb is sufficient for the excitation of this iridium species.

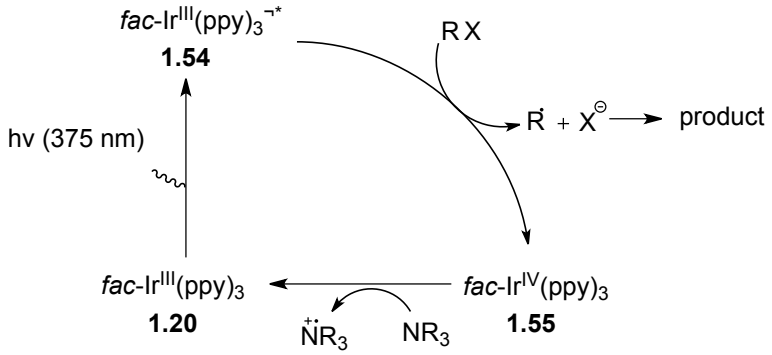
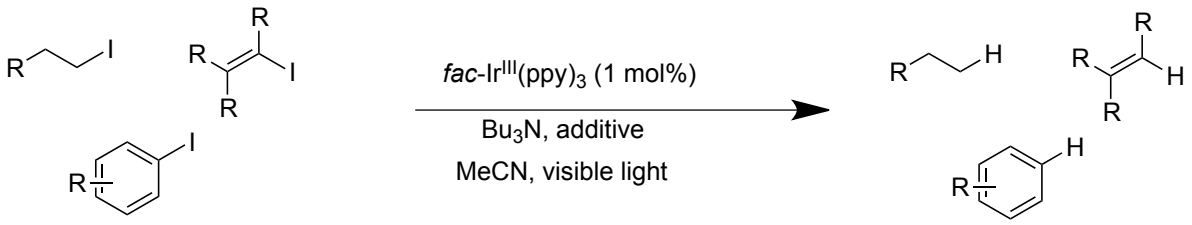


Figure 1.8 Iridium photoredox cycle

The first step for photocatalysis with *fac*-$Ir^{(III)}(ppy)_3$ **1.20** is the absorption of a photon giving the excited state singlet. This subsequently goes through intersystem crossing to give the more stable excited triplet state *fac*-$Ir^{(III)}(ppy)_3$* **1.54** (-1.71V vs. SCE). A single electron transfer (SET) from the excited triplet state gives the oxidized catalyst *fac*-$Ir^{(IV)}(ppy)_3$ **1.55** and the desired carbon centered radical. The oxidized catalyst then needs to be reduced. An electron transfer from a sacrificial electron donor such as an amine, thus regenerating the ground state catalyst, generally achieves this.



Scheme 1.16 Reductive dehalogenation of alkyl, alkenyl and aryl iodides by the Stephenson group.

The more negative reducing potential exhibited by the *fac*-$Ir^{(III)}(ppy)_3$ complex allowed the reduction of stronger bonds. Efforts by the Stephenson group resulted in the development of an efficient protocol for the reductive dehalogenation of alkyl, alkenyl and aryl iodides. In addition, this method displays a wide tolerance for various functional groups (Scheme 1.16). The use of iridium has also been successful for the α-alkylation of tertiary amines as well as the β-alkylation of ketones and aldehydes. [31-34]

1.4. Dinuclear gold complex

Previous studies by Che and coworkers have reported the photophysical properties of dimeric gold complexes that show possible photochemical behavior.[35] Their studies suggest that these potential photocatalysts have the ability to absorb light in the UV region, thus producing a high energy excited state catalyst. More precisely, the cationic complex $[Au_2dppm_2]^{2+}$ **1.56** (dppm= bis(diphenylphosphanyl)methane) shown in Figure 1.9 exhibits a absorption maxima at 295 nm which is found in the UVB range. Additionally, the excited state catalyst that is generated has a sufficient lifetime for a single electron transfer to occur for efficient generation of carbon centered radical intermediates.

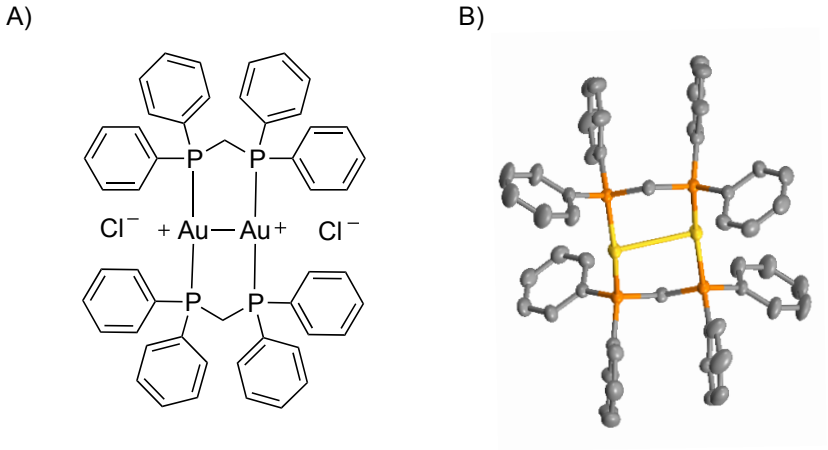


Figure 1.9 A) Molecular structure of $Au_2dppm_2Cl_2$ B) Crystal structure of Au_2dppm_2

They have conducted NMR studies in presence of LiCl and LiBr, which revealed a shift in the P^{31} spectrum in presence of these salts. This finding suggests that the catalyst possesses substrate-binding capabilities. The shift in the absorption and emission of the catalyst in presence of LiCl gives further evidence that there is significant binding of the catalyst and the quencher during the electron transfer. These results suggest that the electron transfer mechanism would go through an inner-sphere mechanism rather that an outer-sphere mechanism similarly to the ruthenium and iridium complexes.[35]

The Che group conducted quenching experiments revealing that organic halides have the ability to quench the phosphorescence of the catalyst in acetonitrile. This gave further evidence that these dinuclear gold species have significant potential for efficient photoredox chemistry applications.[36]

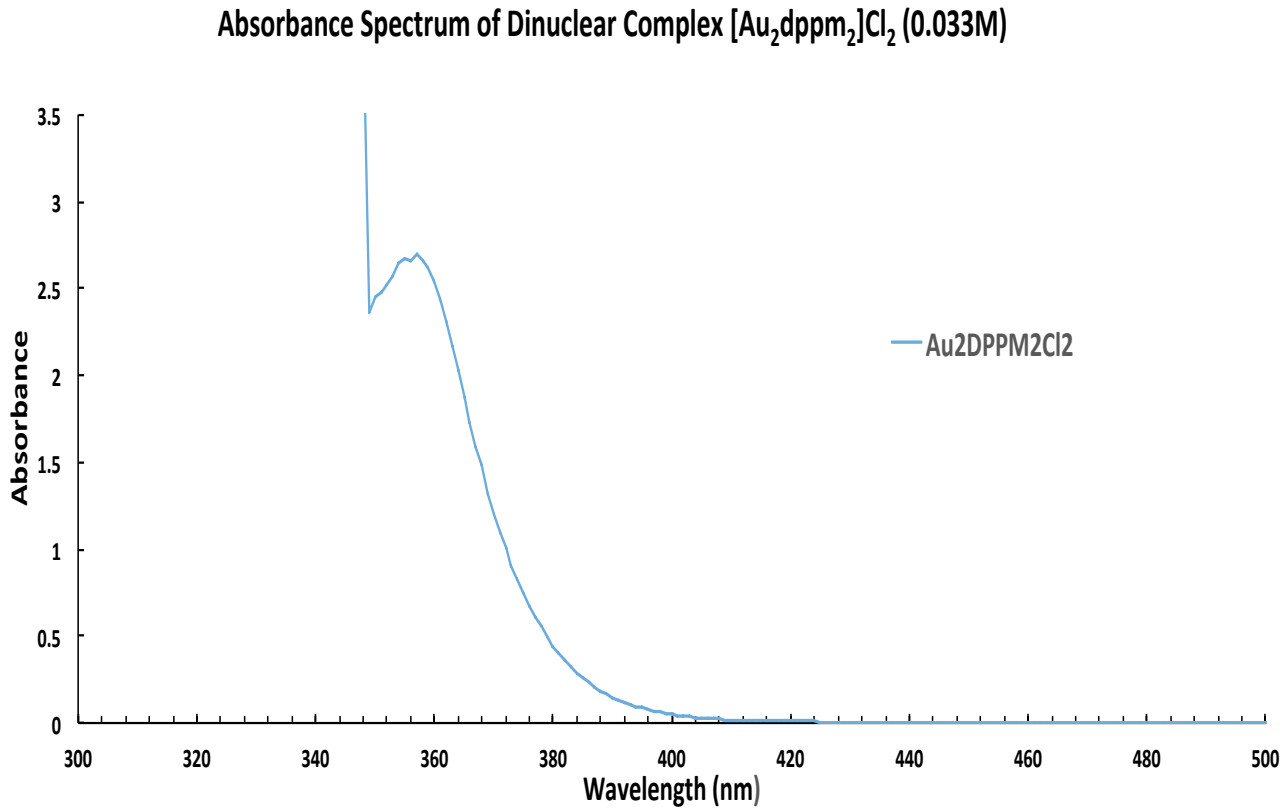


Figure 1.10 Absorption diagram of $Au_2dppm_2Cl_2$

Recent studies from our group have shown that even though the maximum absorption is at 295 nm, one can also observe an absorption peak around 365 nm (Figure 1.10), which is attributed to a spin allowed $d_{\sigma^*}-p_{\sigma}$ transition. This peak appearing at a higher wavelength is situated in the ultraviolet region and could allow us to attain the excited state catalyst with a UV light source. Since UVA is abundant in the sun's emission spectrum, it is possible to excite this catalyst using simple sunlight. Alternatively, the use

of a simple setup with 365 nm light emitting diodes (LED's) as shown in Figure 1.11 is also a good irradiation source.

A) B)

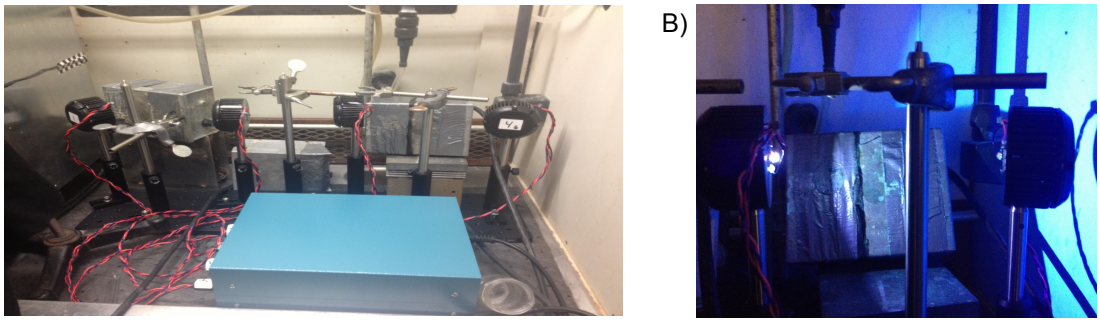


Figure 1.11 A) UV LED setup B) Reaction exposure to 365 nm light

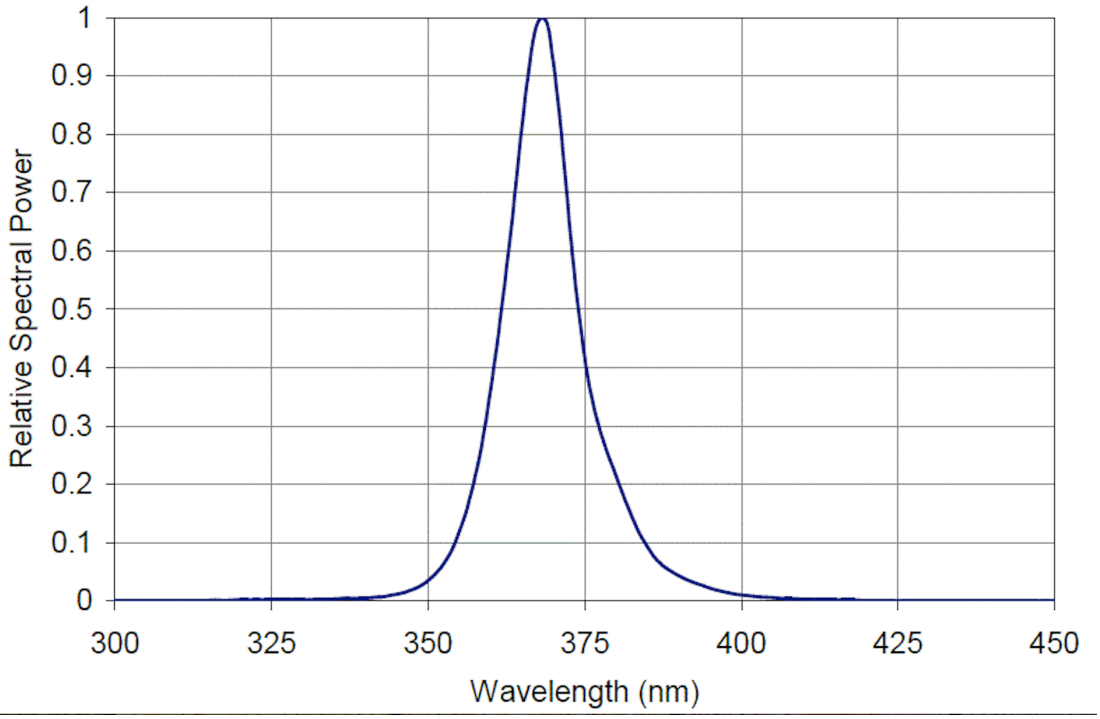
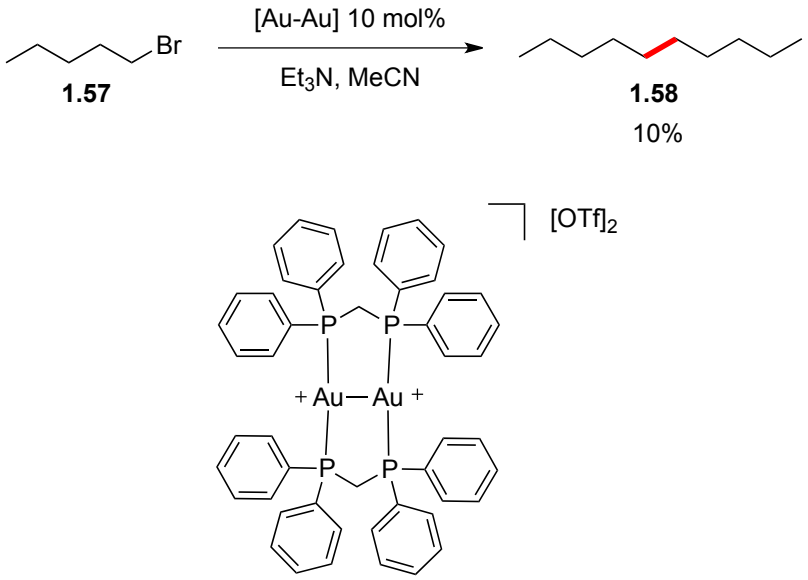


Figure 1.12 Relative emission spectrum of 365 nm light emitting diodes

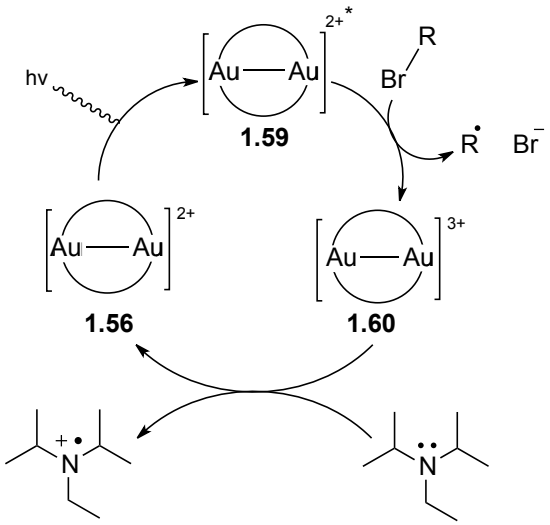
In 1992, Che et al. investigated the photocatalytic reactivity of the phosphine gold dimer catalyst. They successfully observed the formation of decane (**1.58**) from 1-bromopentane (**1.57**) in the presence of $[Au_2dppm_2][OTf]_2$ and triethylamine in

acetonitrile (Scheme 1.17). A 10% yield of the dimerization product was formed upon excitation with a λ greater than 300 nm.[36]



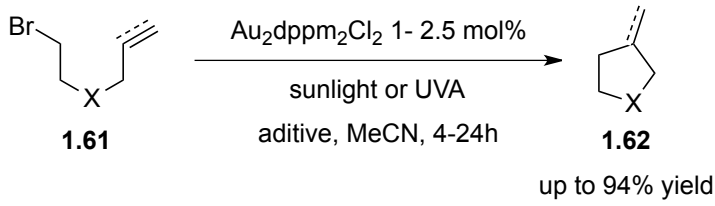
Scheme 1.17 Dimerization reaction catalyzed by dinuclear gold photocatalyst by the Che group

Our proposed mechanism for this dimeric phosphine-gold catalyst begins with the absorption of a photon by the catalyst upon irradiation, thus promoting an electron from the HOMO of the ground state to the LUMO forming the excited state singlet. This complex then undergoes intersystem crossing to yield the more stable and long-lived excited triplet state, $[Au_2dppm_2]^{2+}$* **1.59**. A single electron transfer then occurs to produce a carbon centered radical in addition to the oxidized catalyst, $[Au_2dppm_2]^{3+}$ **1.60**. The oxidized catalyst then needs to be reduced by a second single electron transfer with a sacrificial electron donor to regenerate the ground state catalyst $[Au_2dppm_2]^{2+}$ **1.56**. The sacrificial electron donor used in Scheme 1.18 is the amine base.



Scheme 1.18 Proposed mechanism for gold photoredox

These previous studies by Che and coworkers have inspired our group to further develop the applicability of this catalyst for photoredox reactions. A recent paper from our group describes a method that uses the basis of this research to initiate the radical cyclization of bromoalkene **1.61** (Scheme 1.19).[1] This demonstrated the ability of the dinuclear gold catalyst to effectively reduce unactivated alkyl and aryl bromide bonds, which require a stronger reducing potential than those attainable with ruthenium and iridium catalysts (Figure 1.13).



Scheme 1.19 Radical cyclization method for the formation of cyclized products from a linear bromo alkyl by the Barriault group.

The examples presented thus far have surely shown the importance of photoredox catalysis in the formation of C-C, C-N, C-O bonds as well as oxidation and reduction. It also illustrates the immense potential for further development of new catalysts and reactivity in this field of research.

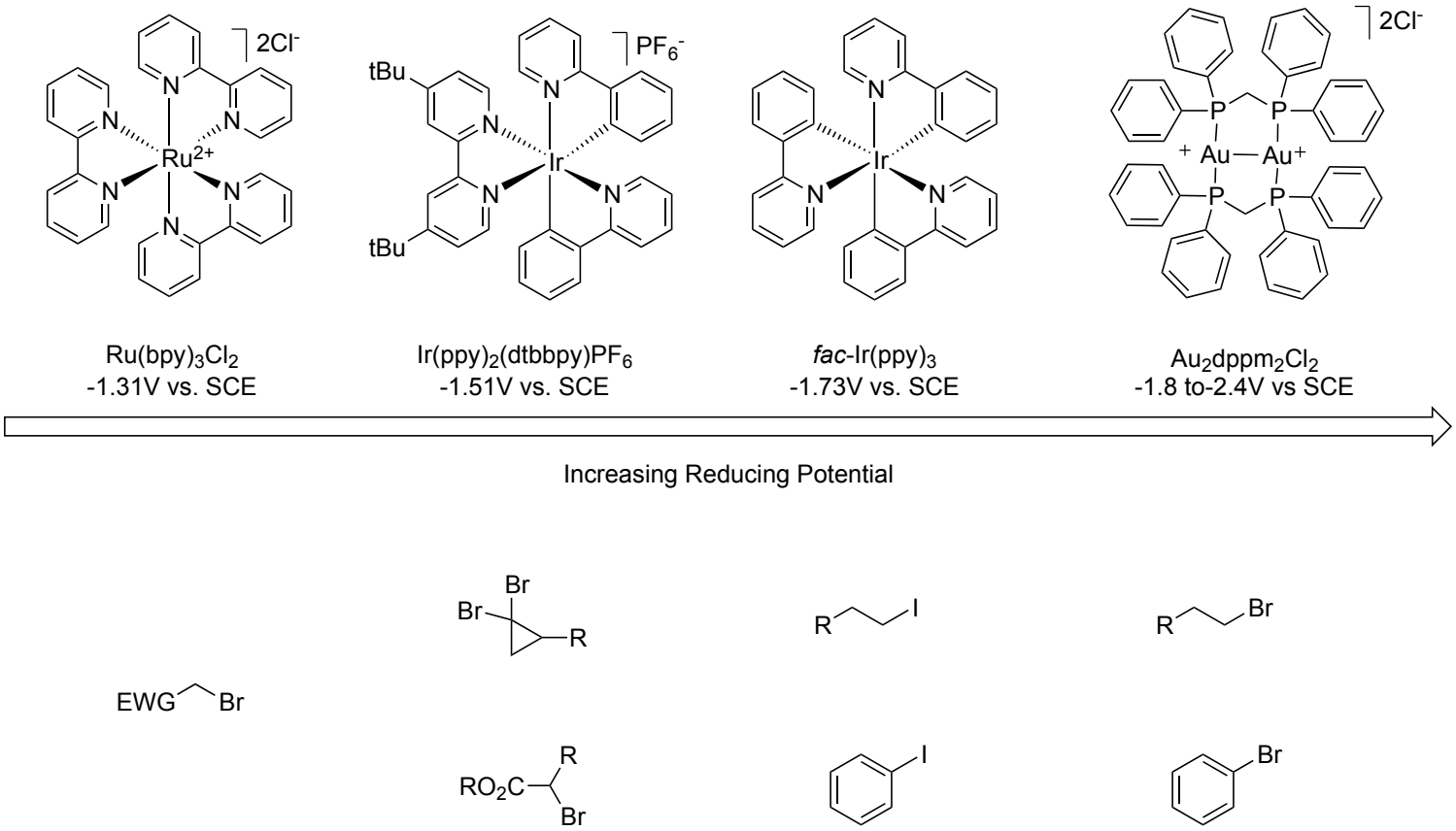


Figure 1.13 Photoredox catalysts and their corresponding reduction potentials

1.5. Research Goals and Thesis Overview

We have envisioned the development of two different methodologies that take advantage of the many benefits of photoredox catalysis. Recent interest in our group has focused on the use of $Au_2dppm_2Cl_2$ as a powerful photoredox catalyst. The aim of the research presented in this thesis was to investigate a methodology that will later be applicable in total synthesis. The second chapter begins with an introduction to organocatalysis and its combination with photoredox catalysis in dual catalysis. Precedents in this field will also be covered. Afterwards, the exploration of the possibility of [$Au_2dppm_2Cl_2$] to participate in a dual catalytic system with an organocatalyst for the formation of β-amino acids will be described. Chapter 3 covers radical cascade cyclizations and some of the precedent literature in this field. The development of a radical cascade reaction initiated by a dimeric gold catalyst will be presented. Finally the last chapter will show future directions for these methodologies and general conclusions.

2. Efforts in the formation of β-Amino Acids by means of Dual Catalysis

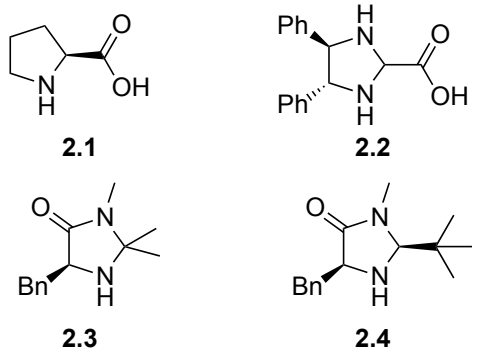
2.1. Organocatalysis in chemistry

Catalysis is one of the central fields in chemistry. The acceleration of reactions with a substoichiometric amount of catalyst presents a large number of advantages, including atom economy, mild reactions conditions and faster and more efficient reactions. Organocatalysis, the catalysis of a reaction by an organic compound that does not contain any metal centers, has become a concept of high interest in the past few decades. There are 4 essential types of organocatalysts: Lewis acids, Lewis bases, Brønsted acids and Brønsted bases.[37] The use of organocatalysts for the formation of C-C, C-O, C-N and C-halogen bonds has proven its vital importance in organic synthesis and recent developments in this field have demonstrated immense potential for enantioselective transformations.[38]

For example, biological systems are made up of enantiomeric building blocks; thus it is imperative to consider that enantiomers can have significantly different biological activities. Hence, the enantioselectivity becomes an important focal point in organic synthesis. In the field of pharmaceuticals, the chirality of drugs is essential.[39] For example, two different enantiomers may be metabolized by different pathways and therefore have different pharmacokinetic properties. One isomer can have the desired therapeutic effects while the other can be inactive or even produce harmful effects. Consequently, there is a constant demand for the development of novel enantioselective reactions in organic synthesis.

Chiral secondary amines have proven to be successful catalysts in asymmetric organocatalysis. They have shown the ability to form iminium ions with aldehydes and ketones leading to the formation of nucleophilic enamines. This allows the addition of an electrophile in inter or intra-molecular fashion. One of the most successful catalysts for

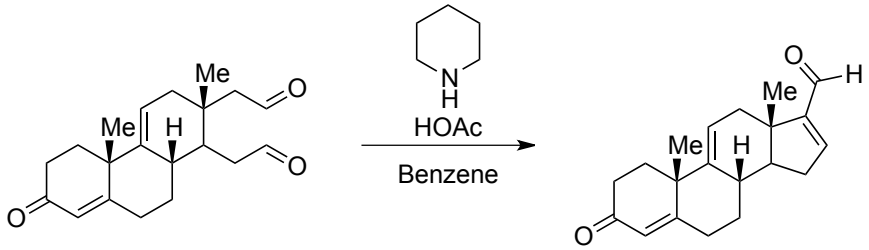
these types of reactions has been L-proline **2.1**, but many other analogs have also proven to be useful (Figure 2.1).[38]



2.1 **2.2** **2.3** **2.4**

Figure 2.1 Secondary amine organocatalysts

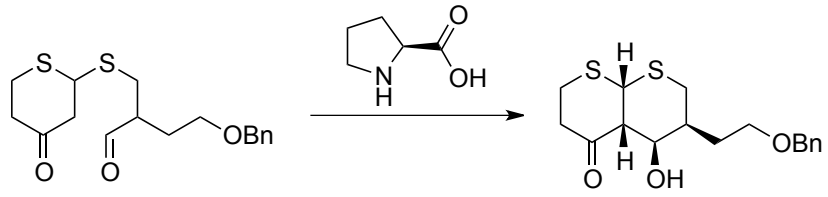
In 1952, Woodward reported the formation of a steroid core using piperidine as shown in Scheme 2.1.[40]



2.5 **2.6**

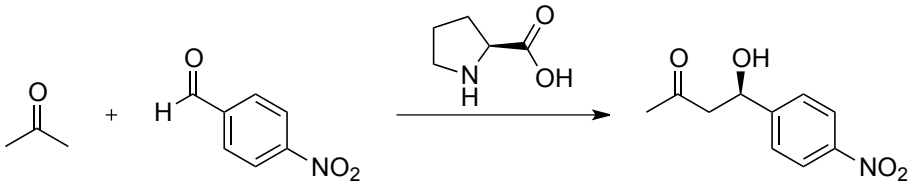
Scheme 2.1 Amine organocatalysis for steroid cores

Enamine organocatalysis was also utilized in the synthesis of the antibiotic erythromycin. Woodward et al. took advantage of the catalytic properties of L-proline for the aldolization of **2.7** to form **2.8**, which is an intermediate in the preparation of the well-known antibiotic (Scheme 2.3).[41] List and coworkers have clearly demonstrated the utility of L-proline for the asymmetric aldol reaction between acetone (**2.9**) and aldehydes (**2.10**) (Scheme 2.3).[42] Another interesting application of L-proline was developed by the same group in 2002 for the direct α-amination of aldehydes as shown in Scheme 2.4.[43]



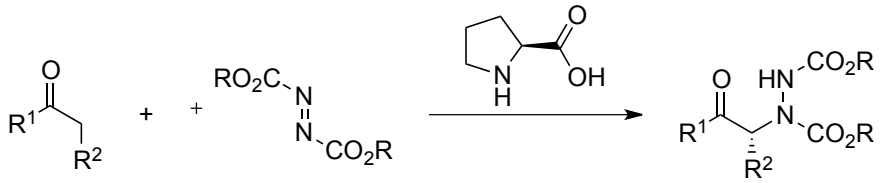
2.7 **2.8**

Scheme 2.2 Organocatalysis a step in the synthesis of erythromycin



2.9 **2.10** **2.11**

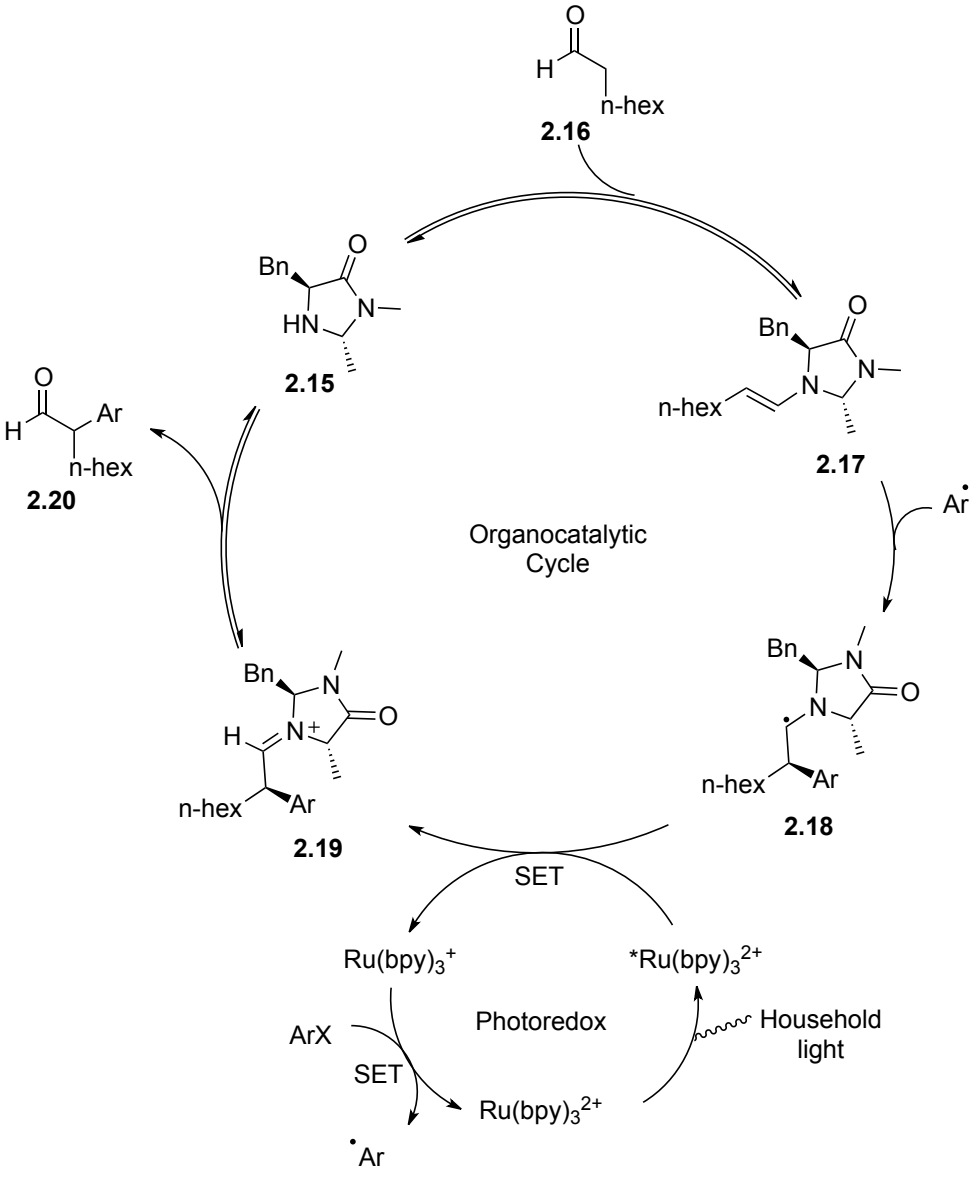
Scheme 2.3 Direct asymmetric aldol reaction catalyzed by L-proline



2.12 **2.13** **2.14**

Scheme 2.4 Access to α-amino acids through L-proline

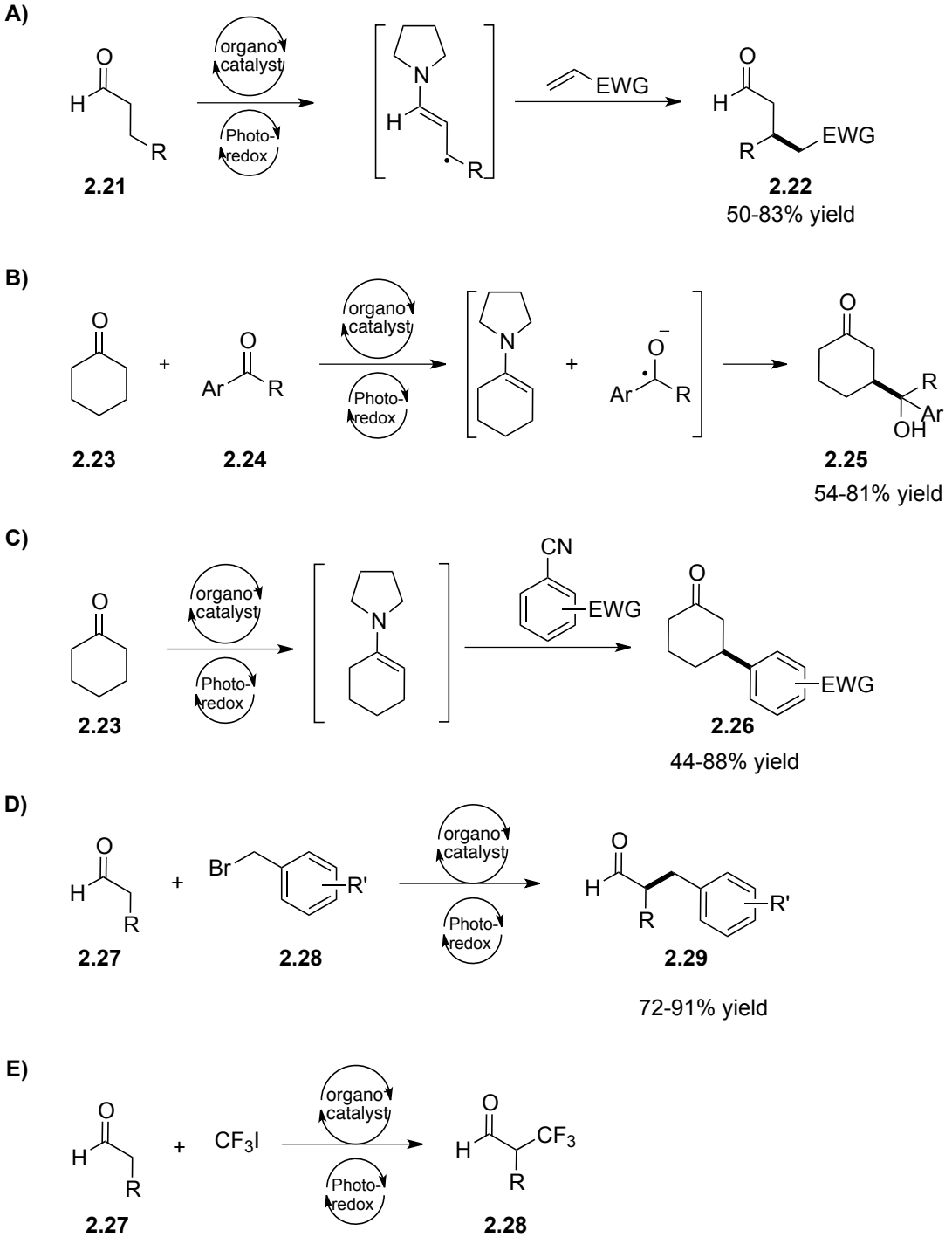
The innovative developments by the MacMillan group have significantly contributed to the advances in the field of enantioselective synthesis in recent years. They have successfully achieved the marriage between organocatalysis and photocatalysis in a dual catalytic system.



Scheme 2.5 Proposed mechanism for dual catalysis with imidazolidinone and photocatalyst

The proposed mechanism for these transformations shown in Scheme 2.5 begins with the simultaneous generation of both an electron rich enamine **2.18** resulting from the condensation of an aldehyde **2.16** with the amine catalyst **2.15** and the electron deficient radical •Ar by photoredox catalysis. The key alkylation step takes place by an addition of the radical to the π-rich olefin, forming the α-amino radical **2.18**. The convergence of both cycles then permits the oxidation of **2.18** to **2.19** through a single electron transfer,

thus generating the reduced ruthenium catalyst [$Ru(bpy)_3^+$]. The final step is the hydrolysis of the iminum **2.19,** thus liberating the desired enantioenriched α-alkylated aldehyde product **2.20**. This step also liberates the active organocatalyst (**2.15**). This method was also adapted for a photoredox process using an iridium catalyst and was successful in many transformations including: asymmetric alkylation[27], α-trifluoromehtylation[44], α-benzylation[45], β-alkylation[32] and β-arylation of aldehydes[31] as well as β-arylation[31] and β-functionalization of cyclic ketones[34] (Scheme 2.6).

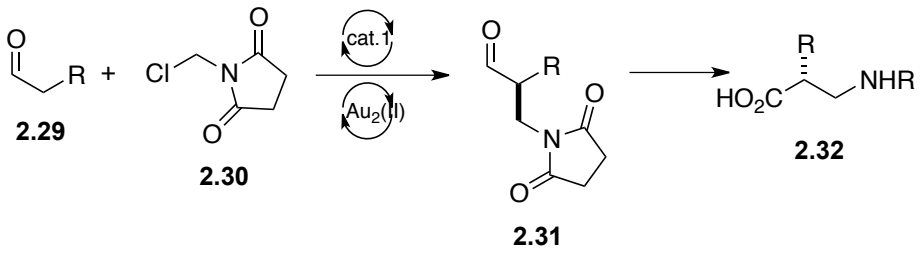


Scheme 2.6 A) β-alkylation of aldehydes B) β-functionalization of cyclic ketones C) β-arylation of ketones D) α-benzylation of aldehydes E) α-trifluoromethylation of aldehydes

2.2. Initial goal of research

Drawing inspiration from previous research conducted by the MacMillan group on dual catalysis, we imagined the use of phosphine gold dimers in a similar system. The replacement of ruthenium and iridium catalysts by $[Au_2dppm_2Cl_2]$, which has a stronger reducing potential, would allow us to further expand the substrate scope for intermolecular this dual catalysis methodology. We imagined that this strategy for catalytic synergy would be applicable towards the formation of β-amino acids, essential building blocks in bioorganic and protein chemistry. With the successful application of this methodology, these biochemical synthons would be readily available through a series of very few simple steps.

We first envisioned the α-alkylation of an aldehyde **2.29** with a *N*-(chloromethyl)-phtalidimide **2.30** to give a β-amino acid precursor (**2.31**). Thereafter, the oxidation of the aldehyde to the carboxylic acid followed by deprotection of the amine would give the desired product **2.32** (Scheme 2.7).

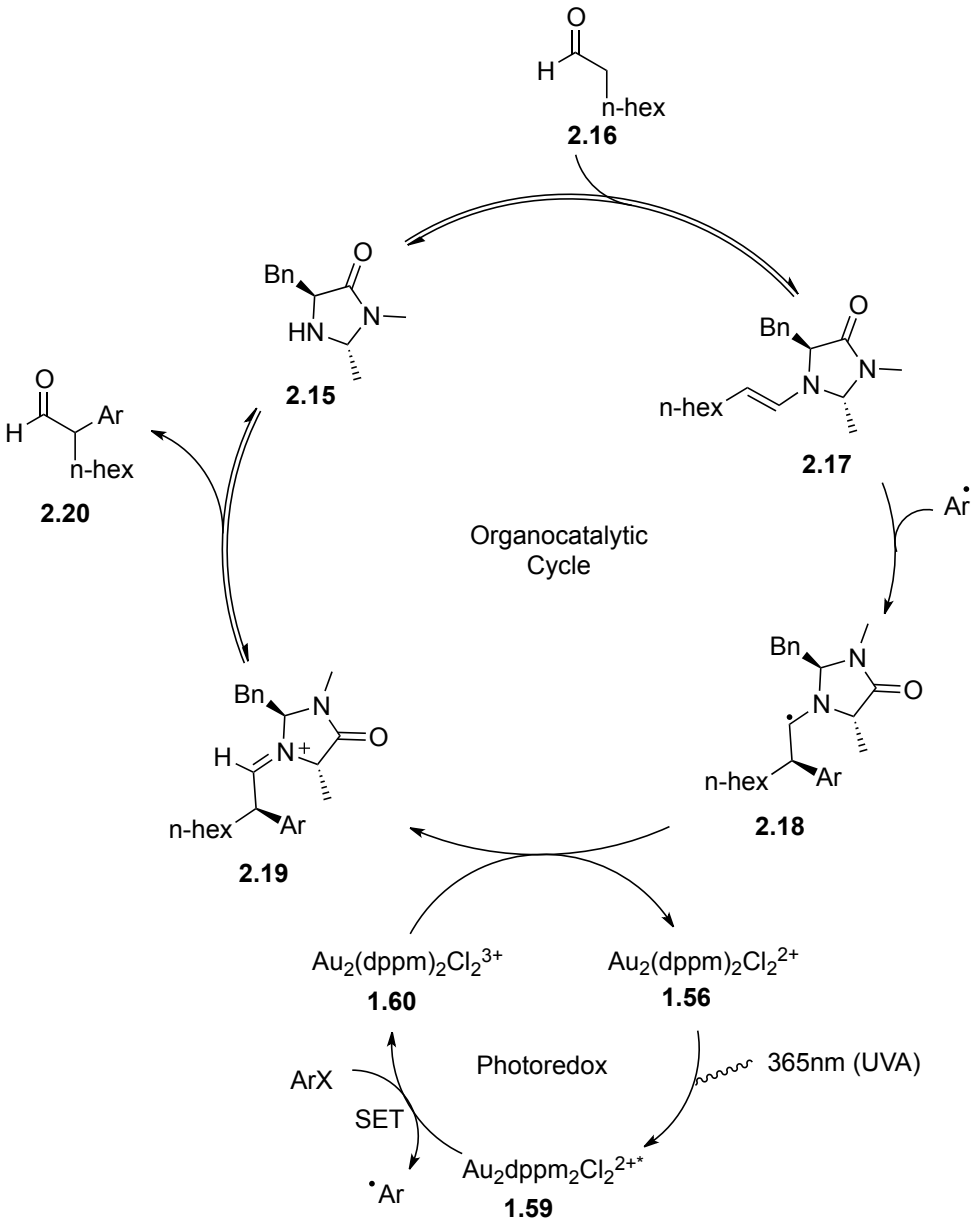


Scheme 2.7 Synthesis of β-amino-acids by few simple steps

The mechanism we proposed for this transformation (Scheme 2.8) is similar to that presented by the MacMillan group in 2010 using the *fac*-*$Ir^{(III)}(ppy)_3$ catalyst.[45] Hence, the first step requires the condensation of the aldehyde **2.16** with the imidazolidinone catalyst **2.15** for the formation of a π-nucleophilic enamine **2.17**. Simultaneously the formation of an electrophilic radical •Ar is formed in the photoredox cycle by a single electron from the excited state gold catalyst **1.59**. The combination of the enamine and

the electrophilic radical leads to the α-amino radical **2.18** which is subsequently rapidly oxidized by the redox cycle, thus reducing the catalyst to its ground state **1.56** and giving the correspondent iminium **2.19**. The resulting iminium cation is hydrolyzed, releasing the aldehyde adduct **2.20** and the organocatalyst.

This method was first tested with substrates that have shown success in these previously developed reactions.

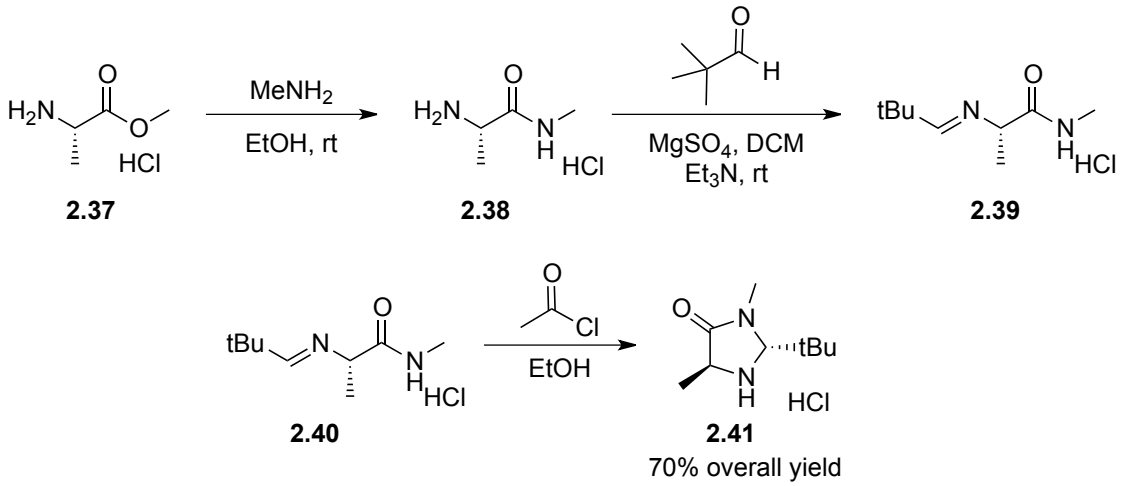


Scheme 2.8 Our proposed mechanism for organo-photoredox with dinuclear gold complex

2.3. Efforts towards β-alkylation of aldehydes for the formation of β-amino acids

Based on previous studies in this field, we identified initial reaction conditions for the development of unexplored reactivity. The substrates we determined to start our investigation were based on a previously working model, in order to initially test the compatibility of $[Au_2dppm_2Cl_2]$ for dual catalysis.

The organocatalyst was synthesized in three simple steps according to literature precedents (Scheme 2.9).[46] The first step consisted of the formation of the amide with L-alanine hydrochloride and methylamine. The amide is then subjected to the reductive amination conditions with pivaldehyde to afford **2.39**. Lastly, the imine is submitted to a reaction with acetyl chloride in ethanol to yield the final amine catalyst **2.41**. The synthesis only required purification after the final step for an overall yield of 70%.



Scheme 2.9 Synthesis of the imidazolidinone organocatalyst

We began our studies with similar conditions used by the MacMillan group for the α-benzylation of aldehydes (Figure 2.2).[45] The reaction conditions consisted in the dissolution of starting materials, the imidazolidinone catalyst **2.41** (20 mol%) and the $[Au_2dppm_2Cl_2]$ (2.5 mol%) in dimethylformamide (DMF) followed by the addition of

2,6-lutidine. The mixture was then degassed by argon sparging before being submitted to UV irradiation. Importantly, these reactions were performed using pyrex sealed tubes and placed in front of UVA bulb panels for irradiation, thus requiring no special or sophisticated equipment.

We first subjected octanal (**2.45**) and 2,4-dinitrobenzyl chloride (**2.43**) to these conditions (Scheme 2.10) and the initial trial (entry 1, Table 2.1) showed a promising 33% conversion to the desired addition product **2.46**. Unfortunately, the starting material was still present in the crude NMR indicating an incomplete reaction but the results presented in Table 2.1 revealed promising formation of **2.46**.

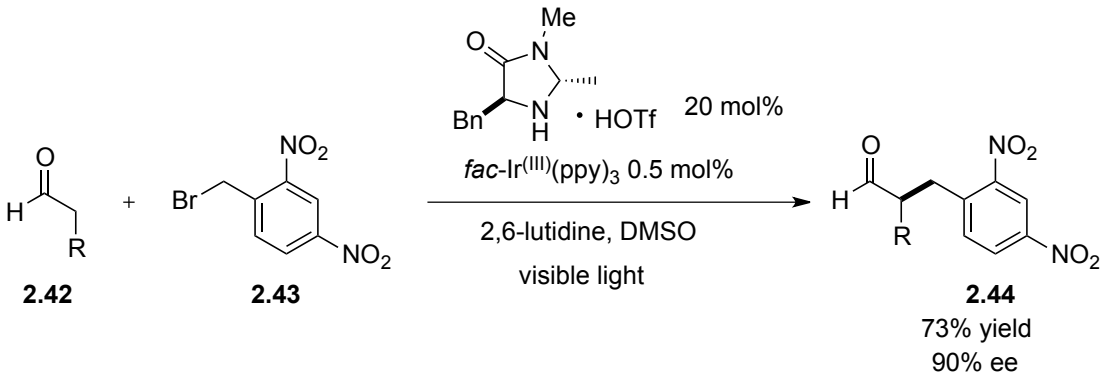
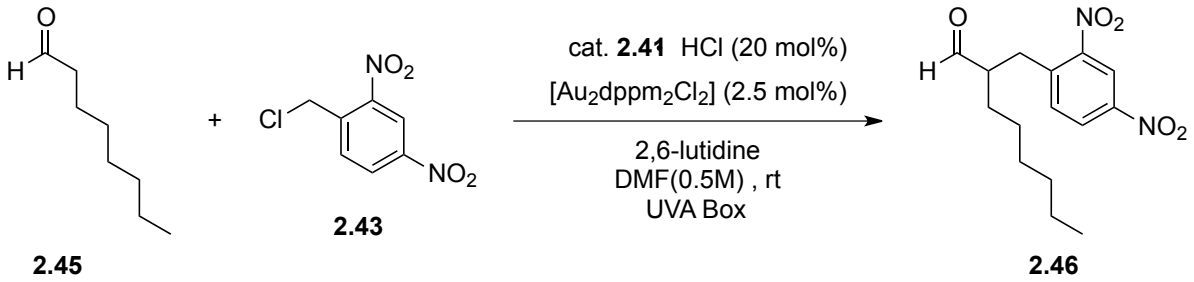


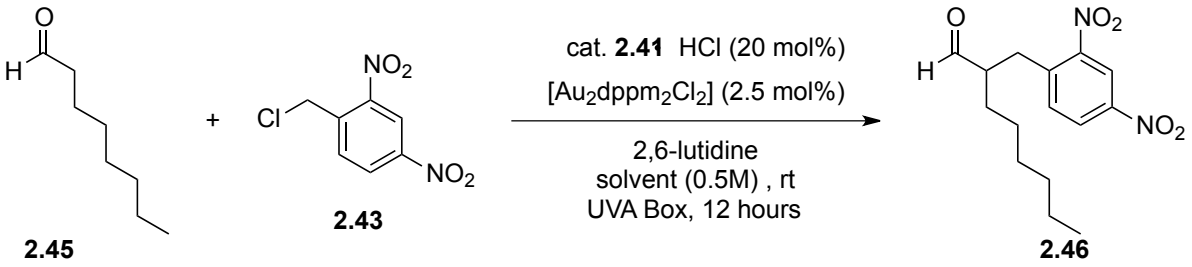
Figure 2.2 Model reaction for the development of dual catalysis[45]



Scheme 2.10 Model substrates used for the development of a photoredox organocatalysis methodology

We varied the reaction solvents (DMF+H_2O, MeCN and DMSO) to improve the conversion. The use of acetonitrile provided the desired product, however, in a slightly lower conversion (entry 2, Table 2.1). The experiment conducted in DMSO only showed starting material in the crude NMR (entry 3, Table 2.1). The combination of DMF and H_2O was tested in view of improving the hydrolysis process, releasing the desired aldehyde adduct **2.46**. As shown in entry 4, this solvent combination gave a similar conversion to the first trial, yielding a 30% conversion. With these results in hand, we decided to continue our investigation with DMF as the solvent of choice.

Table 2.1 Initial investigation of solvents

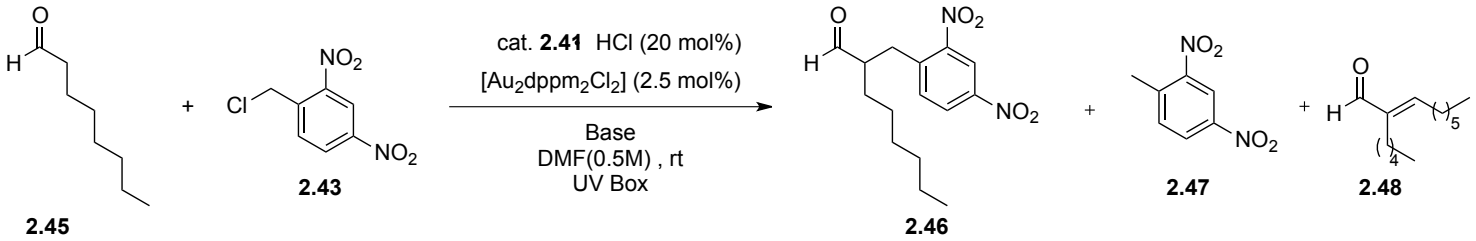


Entry	Solvent	% Conversion (by NMR)
1	DMF	33
2	MeCN	23
3	DMSO	-
4	DMF + H_2O	30

Next, various bases were examined. We initially proposed that the base is not required since intermediate **2.18** would act as the reducing agent for our gold photoredox cycle. Upon trial of these conditions (entry 1, Table 2.2) we quickly noticed the formation of the auto aldolisation product **2.48**. In the absence of a base, the slightly acidic medium makes the aldol condensation reaction favorable. Therefore, a basic medium is required for the elimination of this side reaction. The use of *N,N*-diisopropylethylamine (*i*Pr_2EtN) yielded

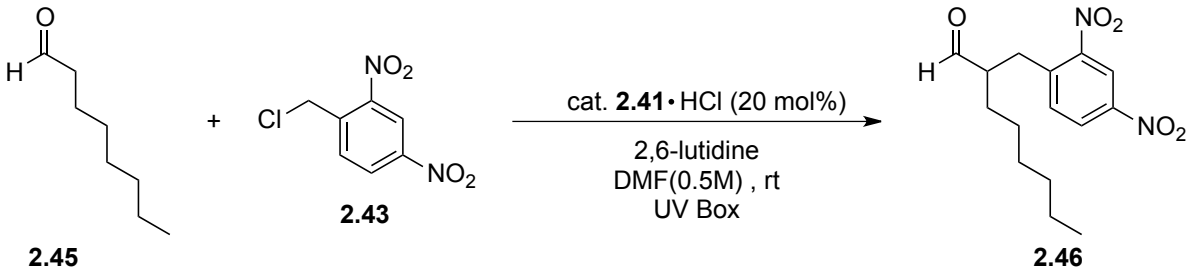
2,6-dinitrotoluene (**2.47**) as the major product. One might propose that the hydrogen abstraction from DIPEA competes with the radical addition to the enamine (*cf.* **2.18** to **2.19**). The best results to date were observed with the combination of 2,6-lutidine and DMF.

Table 2.2 Initial base screen



Entry	Base	% Conversion	% Auto-aldol product	% Reduced
1	None	-	66	-
2	DIPEA	-	-	50
3	2,6-lutidine	33	-	10

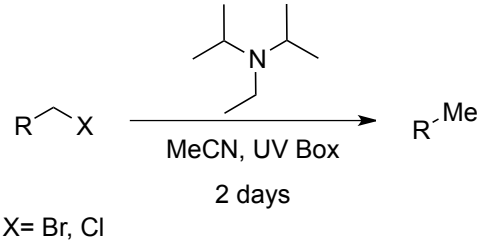
At this point, the conduction of control experiments was performed. First, the reaction was carried out in the absence of the gold photocatalyst. To our surprise, the crude NMR showed the presence of **2.46** (Scheme 2.11). These results indicated that the C-Cl could be reduced directly via a SET in the presence of an amine or enamine **2.17**. In order to demonstrate the reaction mechanism, various activated compounds containing an activated C-X bond were irradiated in the presence of DIPEA without the dimeric gold complex. As expected, the corresponding reduced products were obtained in quantitative yields (Table 2.3). The control experiment for this reaction was conducted in the absence of UV light and, in this case, halogen reduction products were not observed, thus indicating that irradiation is required for this reduction to occur.



2.45 **2.43** **2.46**

Scheme 2.11 Control experiment conditions

Table 2.3 Reduction of carbon halogen bonds using UV light



Entry	Substrate	Product	Conversion
1	**2.49**	**2.52**	Quant.
2	**2.50**	**2.47**	Quant.
3	**2.51**	**2.53**	Quant.

These results strongly suggested that the problem resided in the catalyst turnover. Our first thought was that the imidazolidinone catalyst was interacting with the gold complex and consequently quenching its photoredox properties. To test this hypothesis, we performed a known photoredox cyclization reaction in presence of the organocatalyst (Figure 2.3). The results from this study showed that the radical cyclisation of bromo alkyne **2.49** readily occurs even when organocatalyst (**2.41**) is present in the mixture. We observed the formation of the cyclized product in a 66% conversion after 12 hours irradiation. Nevertheless, this experiment did not afford a proof for the absence of interaction between the two catalysts. On the other hand, it allowed us to confirm that the gold photoredox system is in fact functional in the presence of the amine catalyst.

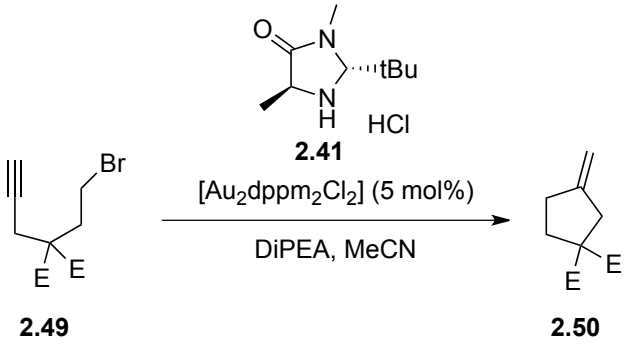
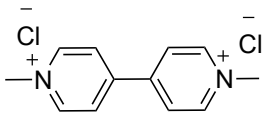


Figure 2.3 Reaction conducted for the analysis of the

Moving forward, one might imagine that the oxidation potential of $[Au_2dppm_2Cl_2]$ is not strong enough to turn over the amine catalyst, thereby limiting the yield of the reaction. Replacing the gold catalyst by another oxidant would allow the efficient turnover of the organocatalytic cycle, consequently increasing the yield. In this case, we investigated the addition of external oxidants.

Firstly, we left our reactions open to air, hoping that oxygen would act as the oxidant. Unfortunately, we did not observe any improvement in the reaction development. Then, oxygen was bubbled directly into the mixture during the reaction to raise its concentration and increase the probability of oxidation, but again no improvements were

observed under these conditions. Finally, we turned towards methyl viologen (Figure 2.4) and were disappointed to see that the results were not favoring the formation of the aldehyde adduct.

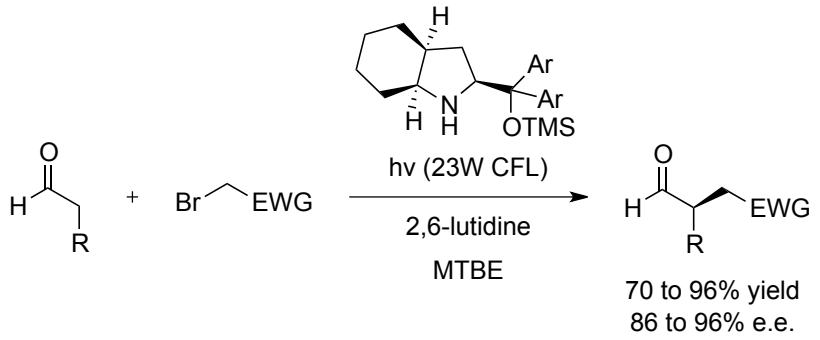


2.51

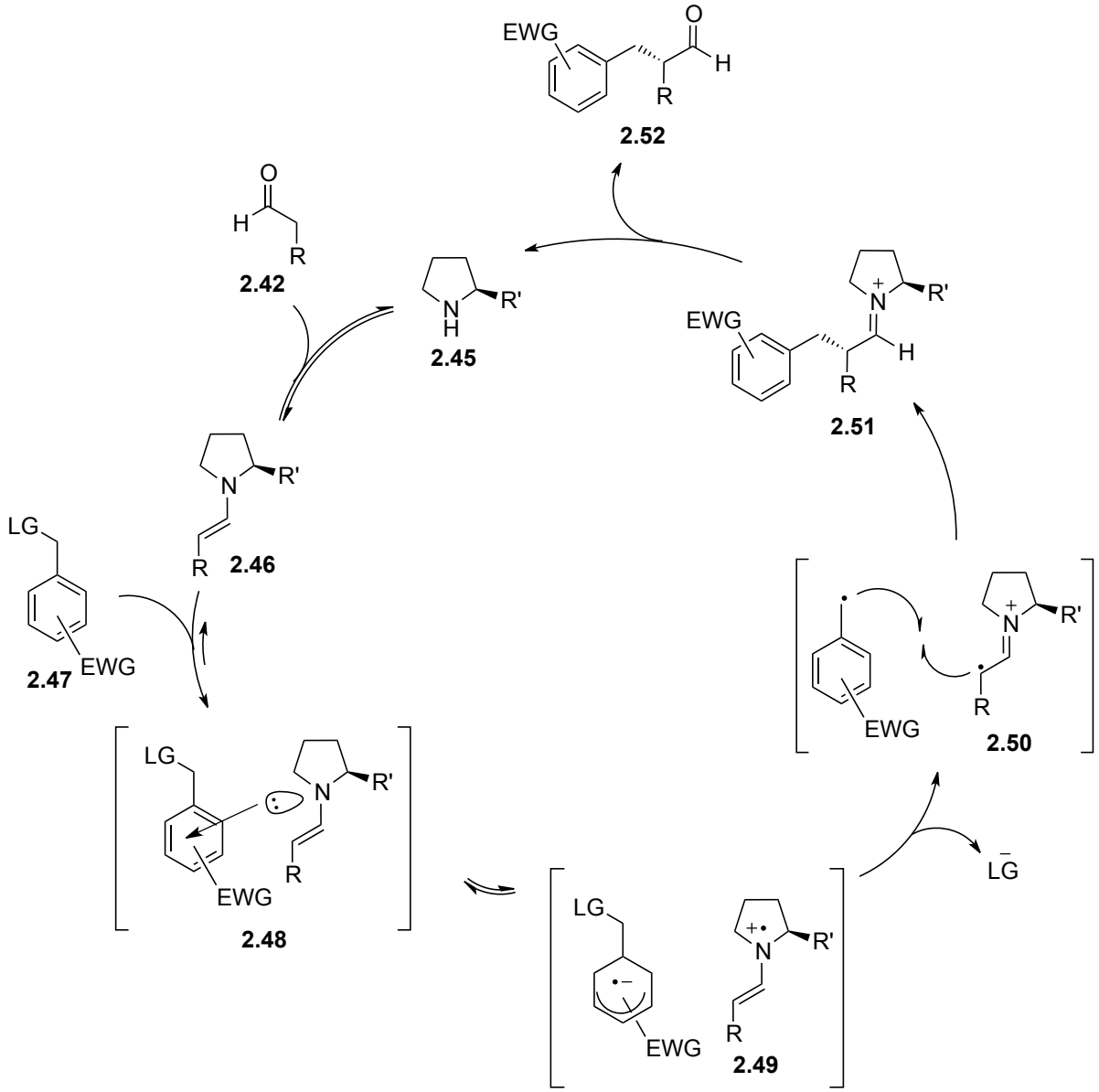
Figure 2.4 Methyl Viologen

Although there were still some options left to explore for the oxidation step, and the change of organocatalyst could be investigated, we decided at this point to focus our energy in a different project.

Later, the Melchiore group reported a novel approach for the coupling of organocatalysis with photochemical processes. Instead of utilizing the popular photoredox catalysts, they turned towards electron donor-acceptor (EDA) complexes, which are capable of undergoing electron transfer steps. The use of a chiral amine organocatalyst was used to induce selectivity in the final product. What they suggested as the mechanism is shown in Scheme 2.13, where a lone pair enamine **2.48** is formed from a condensation of the chiral amine catalyst **2.45** and the aldehyde **2.42** could allow the formation of the EDA complex. Afterwards, this newly formed complex undergoes a photochemical transformation and a photoinduced electron transfer reaction yields the radical ion pair **2.49**. Subsequently, fragmentation of the leaving group gives radical species **2.50** and a recombination step can occur to yield the final aldehyde adduct **2.52**.They were able to apply this methodology to the photochemical alkylation of aldehydes affording the aldehyde adduct in good to excellent yields and stereocontrol (Scheme 2.12).



Scheme 2.12 The α-alkylation of aldehydes through an electron donor-acceptor complex



Scheme 2.13 Proposed mechanism α-alkylation of aldehydes by the Melchiore group

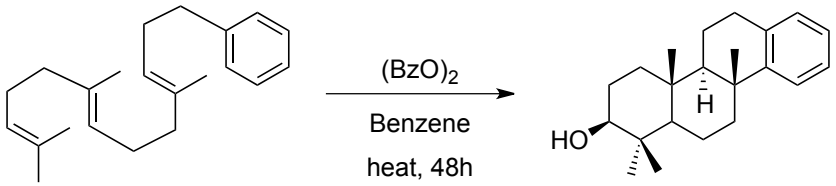
2.4. Conclusion of the project

In summary, we were able to observe the formation of the desired aldehyde adduct **2.46**. Unfortunately, the conversion did not exceed 33% and the control reactions demonstrated that the carbon halogen bond reduction is possible by direct single electron transfer under UV irradiation conditions. We also showed that the reactivity of the photoredox catalyst is not quenched by the presence of the imidazolidinone catalyst. Lastly, the addition of external oxidants such as oxygen and methyl viologen did not improve the catalyst turnover or the yield of the reaction.

3. Development of a Radical Cascade Reaction towards Fused Carbocyclic Cores

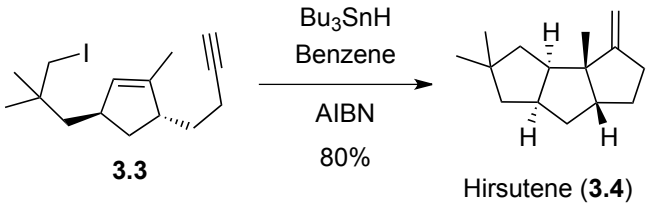
3.1. Radical cascade reactions

Radical cascade reactions are a very useful tool in a synthetic organic chemist's toolbox. These types of reactions are often used for the formation of multiple C-C bonds in a single step, all while adding molecular complexity. Selectivity becomes a very important concept to consider when designing radical cascades. It is important to carefully construct a radical precursor for the desired reaction to occur. When designing a radical cyclization reaction it is crucial to keep in mind the Baldwin rules. [47,48] These rules allow the prediction of the favored cyclization mode according to geometry and orbital overlap. The Baldwin rules are a vital tool that have allowed scientists to access complex molecules through selective radical cascade cyclization. A great example of this was presented by Julia and coworkers in 1973, where they accomplished three sequential 6-endo trig cyclizations for the formation of steroid like cores (Scheme 3.1).[49]



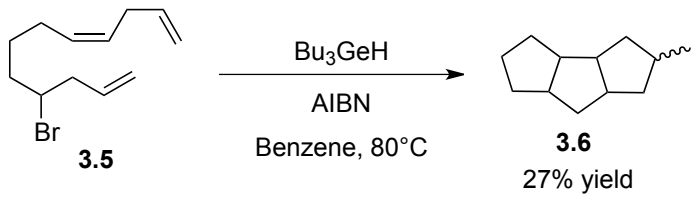
Scheme 3.1 Sequential radical 6-endo trig cyclization

The use of cascade reactions has also been an important strategy for the total synthesis of (±)-hirsutene by the Curran group. As shown in Scheme 3.2 a radical cyclization reaction for the formation of the fused carbocylic core was the final step in their synthesis. In this case, **3.3** was treated with tributyltin hydride and AIBN in benzene to obtain the final product **3.4** in an 80% yield.[50]



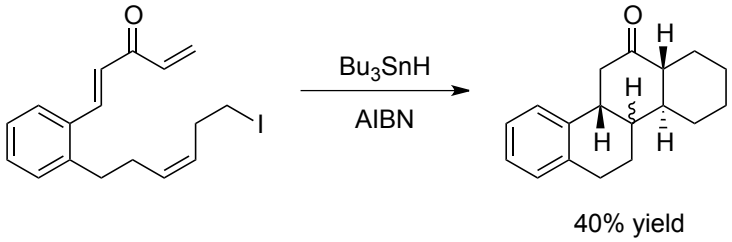
Scheme 3.2 Final step in the total synthesis of (+/-)-hirsutene

Beckwith et al. have demonstrated the access of linear triquinane cores in one simple step. They were able to synthesize **3.6** in a 27% yield starting from a brominated linear substrate **3.5**.[51]



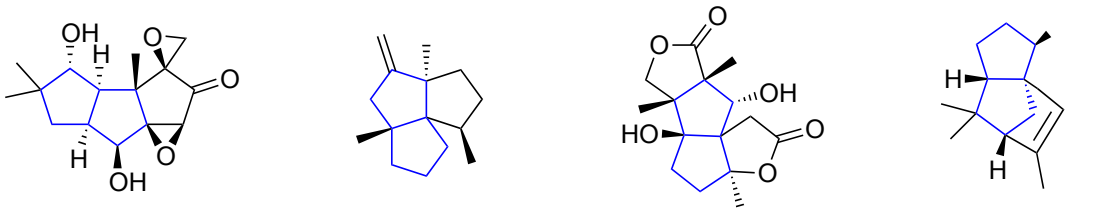
Scheme 3.3 Radical cascade for the formation of linear triquinane

The Pattenden group has also seen many successes in the field of radical cascades, including the macrocyclization-transannulation approach for the formation of oestrogen steroids (Scheme 3.4). [52,53] This clearly demonstrated the selectivity that is achievable when following the Baldwin rules.



Scheme 3.4 Method for the formation of oestrogen steroids

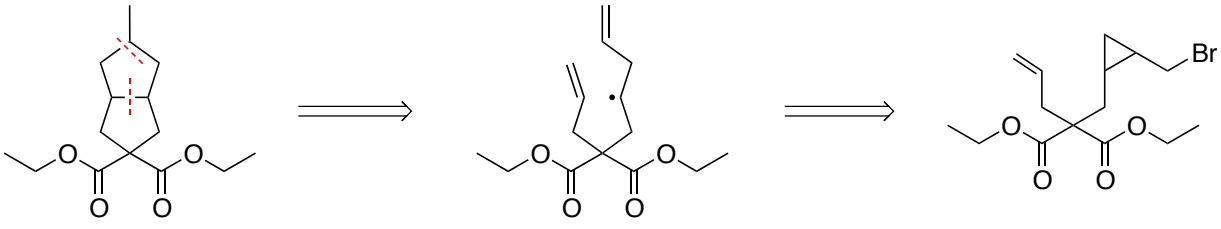
3.2. Research goal



coriolin (**3.9**) beta-isocomene (**3.10**) anislactone A (**3.11**) (-)-cedrene (**3.12**)

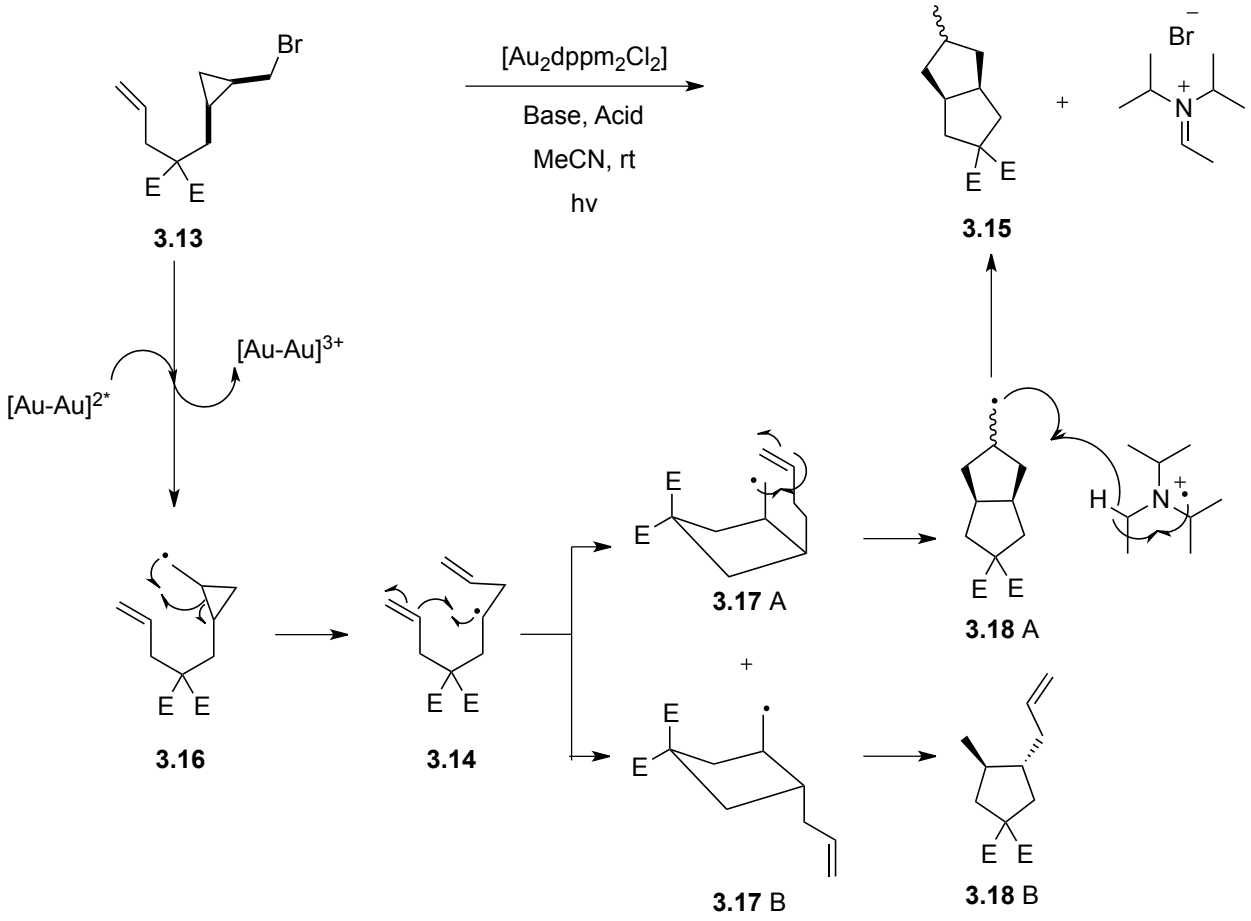
Figure 3.1 Natural products containing [6.3.0.0] undecane carbon skeleton

Fused carbocycles are frequently encountered scaffolds in natural products and are attractive structures for synthetic organic chemists. Previous studies from our group have shown opportunity for the development of a radical cascade reaction leading to these types of scaffolds. We envisioned the formation of two fused 5-membered rings by the means of gold photoredox catalysis (Figure 3.2). The feasibility of this proposed approach will firstly be tested on model substrate **3.13**, which was designed for selective and consecutive 5-exo cyclizations according to the Baldwin rules. The proposed mechanism for this transformation is presented in Scheme 3.5. The cascade sequence is triggered by irradiation of **3.13** using UVA and the gold photocatalyst to generate the radical intermediate **3.16,** which rapidly undergoes a cyclopropane ring opening to afford **3.14**. The latter is poised to undertake two consecutive 5-exo cyclisations to give the final radical species **3.18**, which will abstract a hydrogen from the amine base (radical ammonium) leading to the desired fused carbocyclic compound **3.15**.



3.15 **3.14** **3.13**

Figure 3.2 Retrosynthetic analysis towards fused carbocycles



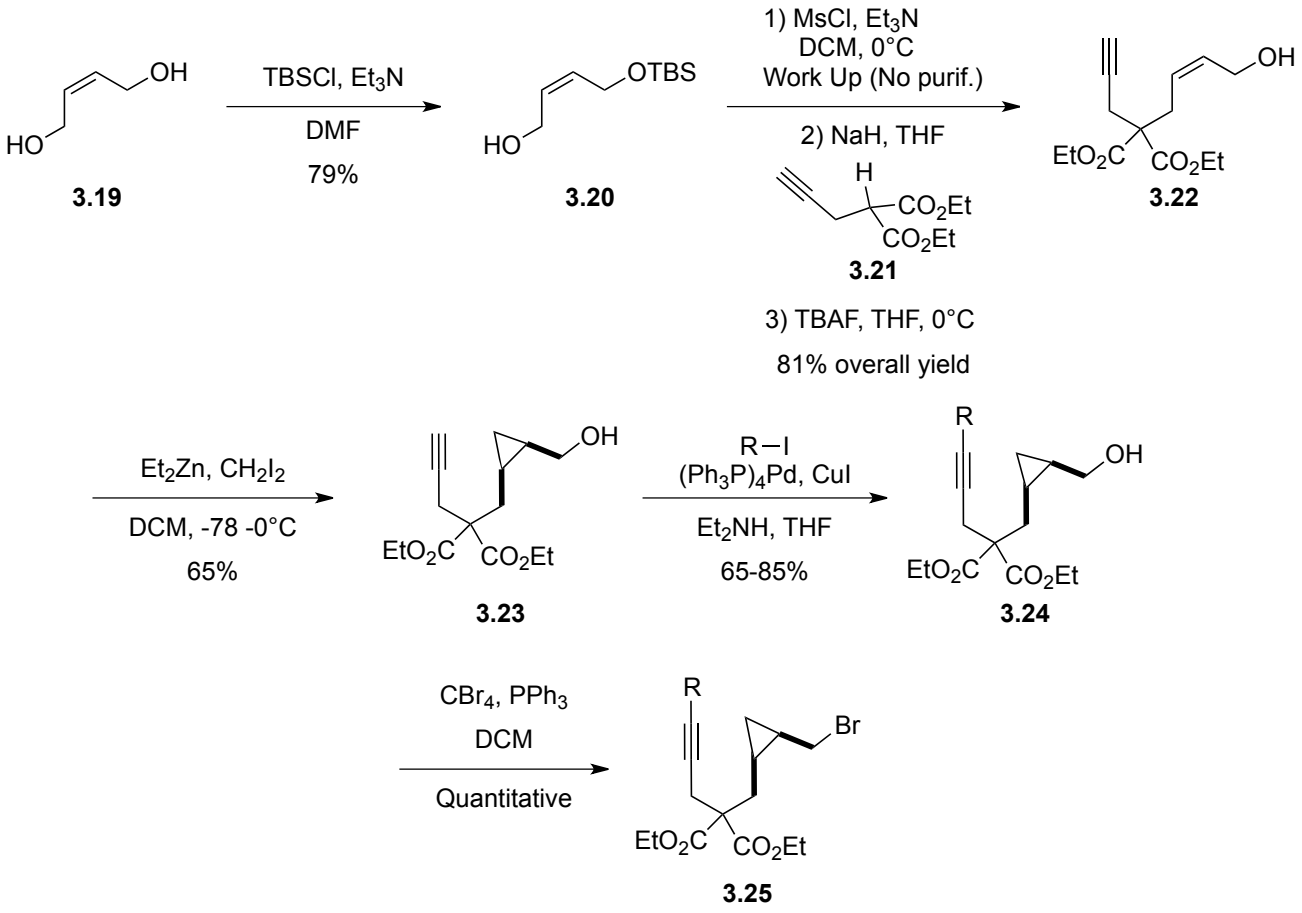
Scheme 3.5 Proposed mechanism for the cascade cyclization

The formation of the fused carbocyclic system is foreseen to form a favored 5,5-*cis* fused rings (**3.18 A**), thus leaving the possibility to observe two diastereomers. The formation of a *trans* ring junction (**3.18 B**) would require the formation of a bond between two oppositely oriented chains, which is much higher in energy and therefore unfavorable.

3.3. Substrate synthesis

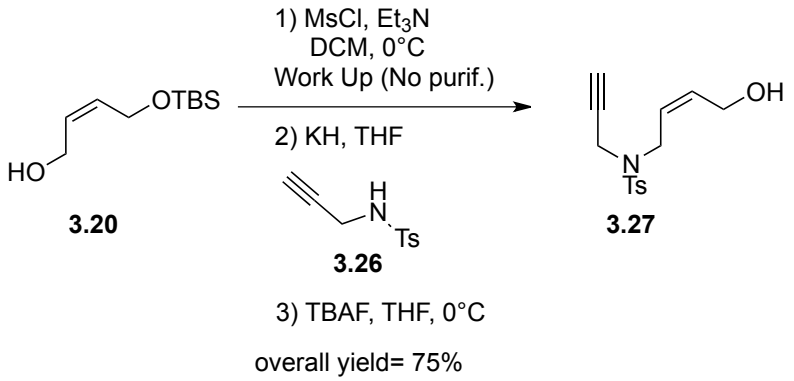
The construction of the substrates for the radical reaction necessitates simple synthetic steps starting from commercially available materials. The synthesis begun with protection of *cis*-2-butene-1,4-diol with a *tert*-butyldimethylsilyl group (TBS) to provide

the mono-protected diol **3.20** in 79% yield. Conversion of **3.20** to the corresponding mesylate followed by the addition of the malonate chain **3.21** and treatment with TBAF gave product **3.22** in 81% yield. The liberated alcohol can then participate as the directing group in the Simmons-Smith cyclopropanation of the alkene forming **3.23** in a 65% yield. At this point, a Sonogashira reaction was performed to add various substituents (R) to the terminal alkyne **3.24**. Finally, the bromination of the alcohol was done through an Appel reaction yielding the desired alkyl bromide **3.25** in quantitative yields.



Scheme 3.6 Synthetic sequence for the formation of starting materials to the gold cyclization reaction

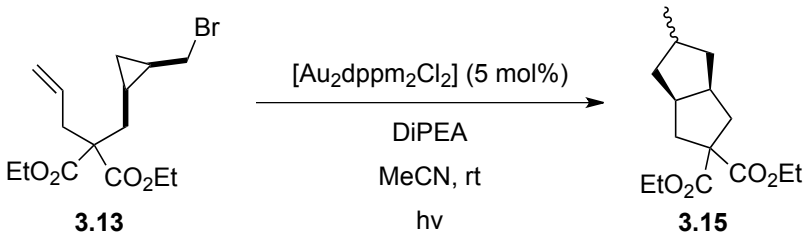
The synthesis of compounds having a sulfonamide tether were prepared following the synthetic route described above (Scheme 3.7). The synthesis of the tosylamine chain is synthesized by the alkylation of tosylamine with either allyl or propargyl bromide, similarly to the diethyl malonate chain. The tosylamine chains can be purified by simple flash chromatography on silica gel.



Scheme 3.7 Alkylation with tosylamine chain

3.4. Development of radical cascade cyclizations initiated by photoredox catalysis

Our model reaction for the development of methodology is shown in Scheme 3.8. We determined initial reaction conditions based on previous results from our group.[1] The first experiment conducted consisted in the dissolution of substrate **3.13** and 5 mol% of $[Au_2dppm_2Cl_2]$ catalyst in acetonitrile (MeCN) before the addition of *N,N*-diisopropylethylamine (DIPEA). We then degassed the mixture by argon sparging and the reaction was submitted to UVA irradiation in a photochemical reactor as seen in Figure 3.3. As anticipated, we observed the desired cyclized product **3.15** in a 50% conversion based on ^{1}H NMR analysis of the crude mixture (Table 3.1, entry 1).

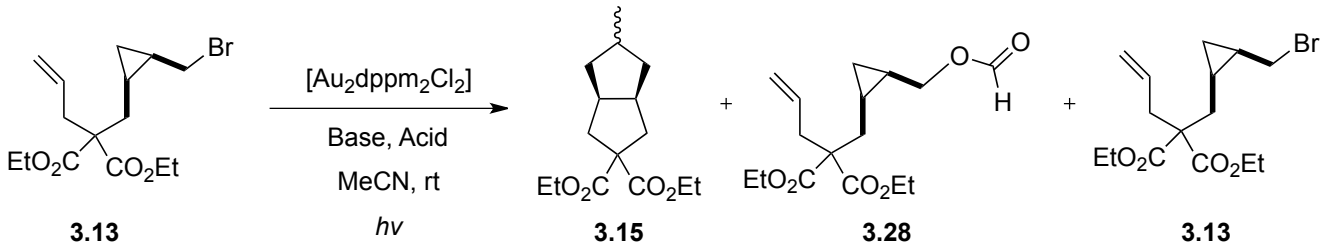


Scheme 3.8 Model reaction for development of methodology

Figure 3.3 Initial UVA photoreactor

At this point, it is important to note that the addition of formic acid has been shown to greatly accelerate the rate of the reaction, but its exact role in the mechanism remains unclear.[1,54] Studies are currently ongoing to determine the explanation behind this significant acceleration. Further investigation was done regarding the content of formic acid and DIPEA in the reaction (Table 3.1). The results of entries 2 and 3 have shown that a higher concentration of formic acid versus DIPEA slightly increases the rate of the reaction. In consequence, the conversion of **3.13** to **3.15** is higher in presence of 5 equivalents of acid and 2 equivalents of base.

Table 3.1 Initial results using UVA photoreactor



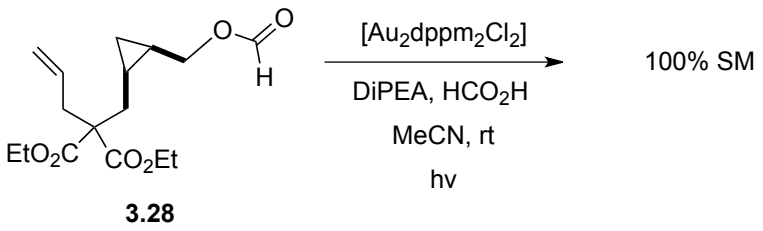
3.13 **3.15** **3.28** **3.13**

Entry	Catalyst	Time (hrs)	Base (eq.)	Acid (eq.)	% Conv. By NMR
1	5 mol%	24	DiPEA (2 eq)	-	~50% **3.15** + 50% **3.13**
2	5 mol%	24	DiPEA (5 eq)	HCO_2H (2 eq)	~66% **3.15** + 33% **3.13**
3	5 mol%	24	DiPEA (2 eq)	HCO_2H (5 eq)	~88% **3.15** + 20% **3.13**
4	-	24	DiPEA (2 eq)	HCO_2H (5 eq)	**3.28**
5	5 mol%	48	DiPEA (5 eq)	HCO_2H (2 eq)	~90% **3.15** + 10% **3.13**
6[a]	5 mol%	48	DiPEA (5 eq)	HCO_2H (2 eq)	~80% **3.15** + 20% (**3.28** + **3.13**)

[a] Scale of the reaction was 120 mg (0.4 mmol) rather than 60 mg (0.2 mmol)

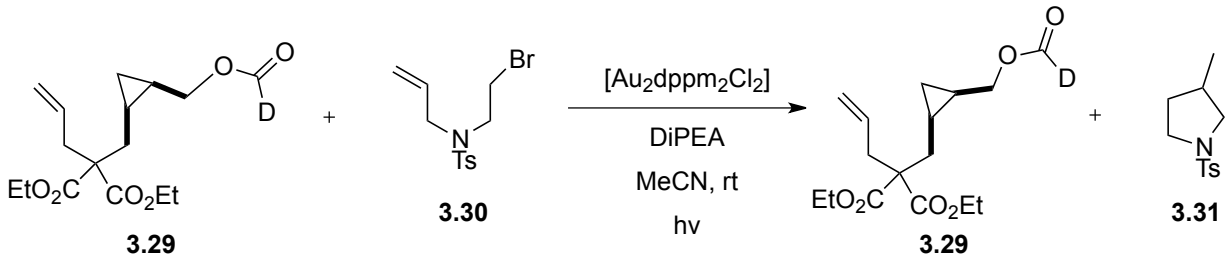
The control reactions were performed and revealed that in absence of the dinuclear gold catalyst (Table 3.1, entry 4) there is formation of **3.28**. This side product is the result of an S_N2 displacement of the bromine by the formic acid. In order to prevent the appearance of the undesired formate product in future reactions, we carried on our investigations with 5 equivalents of base and 2 equivalents of acid.

With the instances shown so far, one might consider that **3.28** is an intermediate in the reaction. Thus, we directly submitted **3.28** to the photoredox conditions shown in Scheme 3.9. Following irradiation, we observed exclusively the starting material. This result allowed us to rule out the possibility that this product could directly produce a radical species under photoredox conditions.



Scheme 3.9 Formate substrate investigation

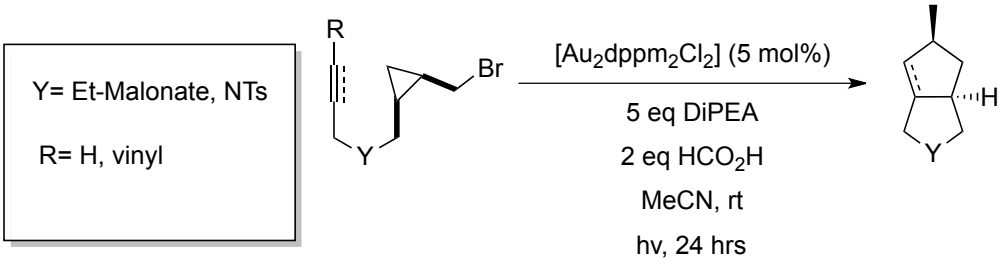
Furthermore, we investigated the possibility that the hydrogen from the formate product could be the source of hydrogen for the reduction of the final radical. If this were the case, you could have abstraction of the hydrogen followed by the liberation of CO_2 and **3.16**, consequently leading to **3.15**. In order to verify this hypothesis, we synthesized the deuterated formate product (**3.29**) and added to a known reaction.[1] The results didn't show any incorporation of deuterium in product **3.31**. Hence, this experiment allowed us to rule out the possibility that **3.29** is an intermediate in our cascade reaction.

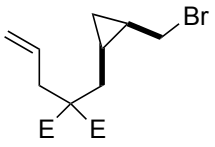
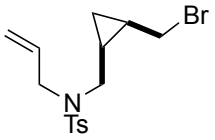
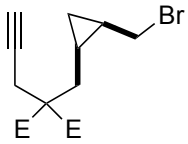
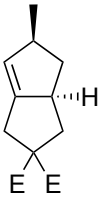


Scheme 3.10 Investigation of the formate product as a reaction intermediate

Thereafter, we subjected the newly developed method to different substrates (Table 3.2). The process proved to be efficient given the conversion of **3.13** to **3.15** was achieved in 90% (Table 3.2, entry 1). Similar conversion was observed using tosylamine (**3.32**) to give the cyclized product (**3.34**) (Table 3.2, entry 2). We noticed a significant decrease in conversion, falling from 90% to 50% when the alkene functionality was replaced by an alkyne (**3.33**) (Table 3.2, entry 3).

Table 3.2 Initial results for photoredox catalysis



Entry	Substrate	Product	Conversion [a]
1	 **3.13**	 **3.15**	90%
2	 **3.32**	 **3.34**	90%
3	 **3.33**	 **3.35**	50%

[a] Determined by ^{1}H NMR of the crude reaction mixture

At this point, we began to encounter difficulties with the light source. We observed inconsistencies in irradiation and the reactions became irreproducible. Soon thereafter, we came across the availability of newly developed light emitting diodes (LED) that emit light specifically at 365 nm. This system, shown in Figure 3.4, emits concentrated UVA rays, which can be directed towards the reaction vessel.

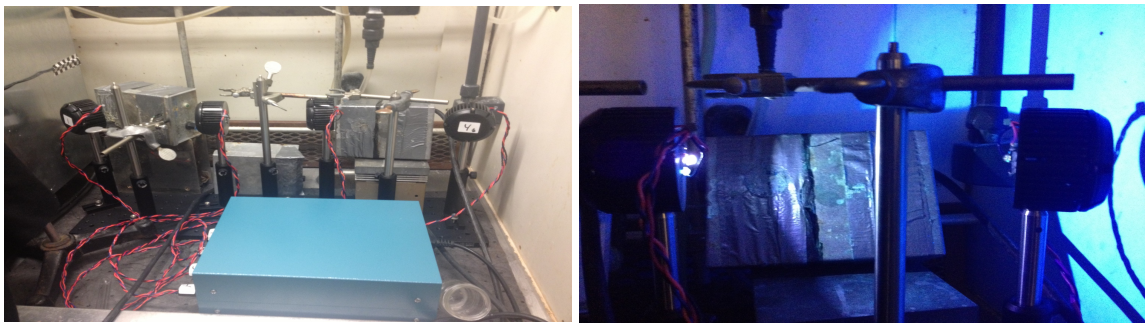


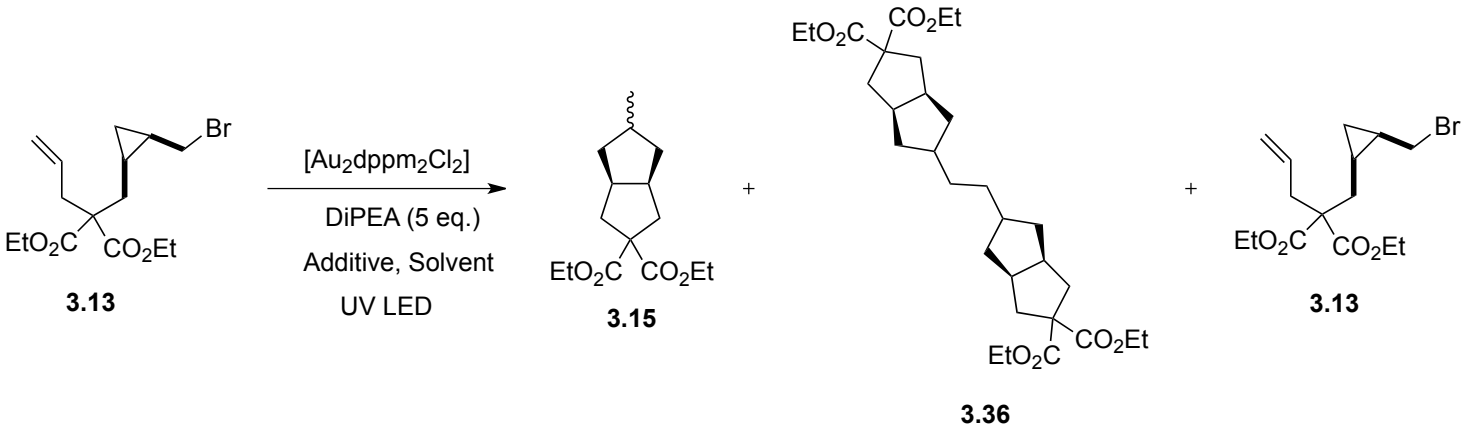
Figure 3.4 UV LED setup

Having an improved light source in our hands, our initial optimization needed to be revisited. Therefore, we revised our previous optimal conditions, 5 mol% of [$Au_2dppm_2Cl_2$] with 5 equivalents of DiPEA and 2 equivalents of formic acid in acetonitrile (Table 3.3, entry 1). This experiment afforded **3.15** in 32% isolated yield. To our surprise, we observed the formation of the dimer (**3.36**) (as a mixture of diastereomer) resulting from the recombination of the final radical species **3.18** in 56% yield. Keeping these results in mind, we noticed that the change in the source of UV light significantly increased the rate of our reactions. The rapid turnover of the catalyst induced a fast accumulation of radical species in solution, thus increasing the odds for radical recombination to occur. Owing to the fast reaction rates, the addition of formic acid was no longer necessary. Entry 2 of Table 3.3 shows the reaction in absence of formic acid was completed after 10 minutes of irradiation, however the formation of **3.36** was still observed in 23% yield.

Following these results, a variety of solvents were investigated (Table 3.3, entries 2-4). The use of isopropanol (iPrOH) gave 12% of dimerized product, but increased the yield from 32% to 45% of **3.15**. On the other hand, the dimer was less prominent (3% yield) when the reaction was conducted in DMF. The progression of the reaction was slightly slower in DMF, thus increasing the isolated yield of **3.15** to 50%. Subsequently, we turned our attention to the catalyst loading of our reaction. We proposed that lowering the catalyst loading would slow down the formation of radicals, consequently reducing the concentration of radicals in solution. One could imagine that this would favor reduction of the radical over dimerization. The use of 2.5 mol% instead of 5 mol% did not show

much deviation for the yield of the reaction, but the reaction needed 20 minutes for complete conversion (Table 3.3, entry 5). Lowering the loading to 1 mol% indicated an important increase in the reaction time; starting material was still present after 40 minutes (Table 3.3, entry 6). Therefore, catalyst loading of 2.5 mol% was used for further reactions. The optimal conditions determined for the radical cascade reaction afforded an isolated yield of 76% (Table 3.3, entry 5). The control reactions demonstrated full recovery of the starting material in absence of $Au_2dppm_2Cl_2$ (Table 3.3, entry 7).

Table 3.3 Cascade cyclization optimization

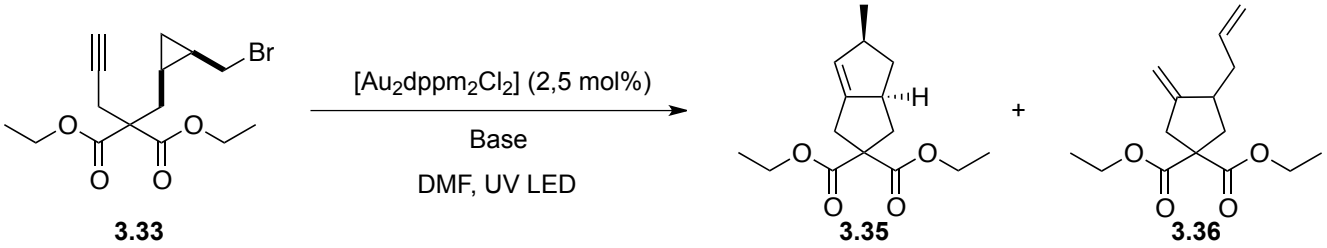


Entry	Loading	Time (min)	Additive	Solvent	% Yield
1	5 mol%	30	HCO_2H	MeCN	32% **3.15** + 56% **3.36**
2	5 mol%	10	-	MeCN	32% **3.15** + 23% **3.36**
3	5 mol%	10	-	iPrOH	45% **3.15** + 12% **3.36**
4	5 mol%	10	-	DMF	50% **3.15** + 3% **3.36**
5	2.5 mol%	20	-	DMF	76% **3.15**
6	1 mol%	40	-	DMF	Mixture **3.15**, **3.36**, **3.13**
7	-	20	-	DMF	Quant. **3.13**

Once the optimization was complete, as part of our methodology studies, we evaluated the substrate scope. Unexpectedly, when we altered the terminal alkene for an alkyne (**3.33**), we encountered a new side product, **3.36 (**Table 3.4**)**. This is the result of an abstraction of a hydrogen atom following the first 5-exo cyclization, but before the

second cyclization. As shown in entry 1 of Table 3.4, the use of DIPEA afforded a ratio of 5:1 favoring **3.35**. In response, one could envision that using a slower hydrogen donor would slow down the reduction and improve the ratio between these two products. The use of 1,4-diazobicyclo[2.2.2]octane (DABCO) did not show improvement (Table 3.4, entry 2). However, the use of 1,2,2,6,6-pentamethylpiperidine (PMP) showed the best selectivity favoring the desired product with a ratio of 7:1 (Table 3.4, entry 3). Stereochemistry of the final product was determined by NOE correlations observed in the NOESY NMR spectrum.

Table 3.4 Base screen for Ratio improvement



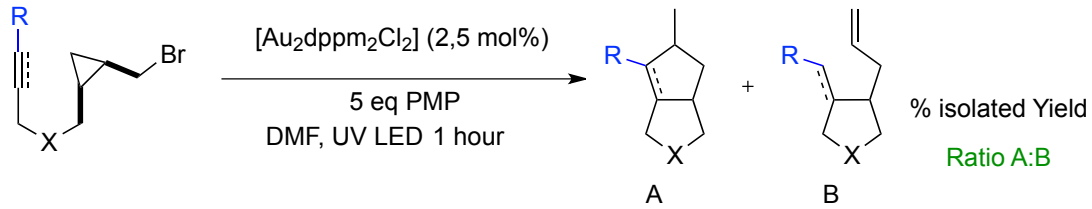
3.33 **3.35** **3.36**

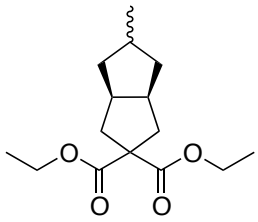
Entry	Base	Ratio (**3.35** : **3.36**) [a]
1	DiPEA	5:1
2	DABCO	4:1
3	PMP	7:1

[a] Determined by ^{1}H NMR of the product mixture

These results encouraged us to further use PMP as the sacrificial electron donor in the further photoredox reactions. In consequence to this change, the reaction times increased from 20 minutes to 1 hour to reach completion. Then, we submitted different substrates to irradiation under the improved reaction conditions and obtained satisfying yields between 26% and 76% depending on the nature of the substrate as shown in Table 3.5.

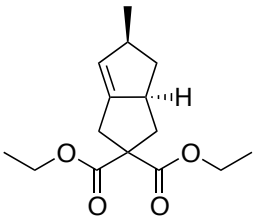
Table 3.5 Radical Cascade reaction





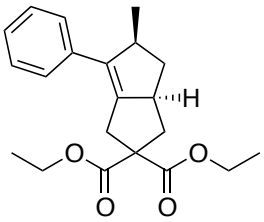
3.15

76%



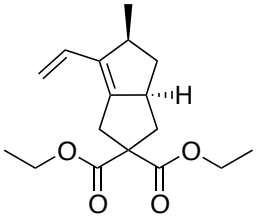
3.35

54% 7 : 1



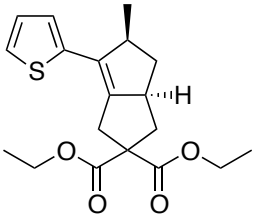
3.38

32% 7.5 : 1



3.39

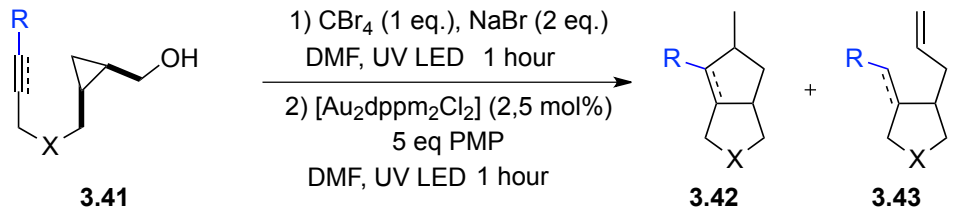
26%



3.40

36% 10.5 : 1

The success of this methodology inspired us to take it one step further. Most recent studies from our group (work of T. McCallum and M. Morin) have been successful in the bromination of primary alcohols with CBr_4 and NaBr in DMF under UV irradiation. Optimal conditions for this transformation are shown in the first step of Scheme 3.11. Hence, we envisioned the development of a one-pot process combining bromination and radical cascade cyclizations (Scheme 3.11) allowing us to start with a more readily available substrate (alcohol) as well as the elimination of a purification step.

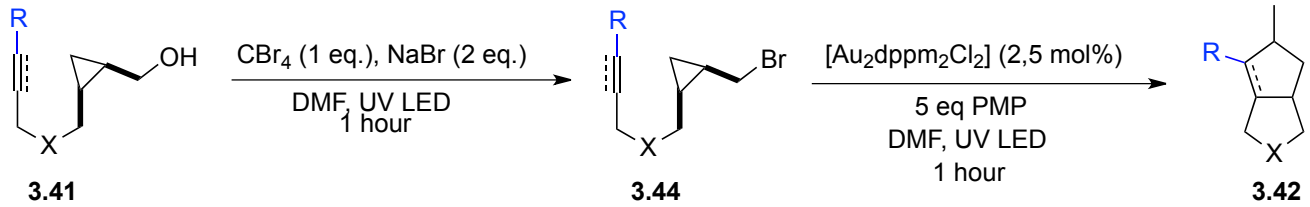


3.41 **3.42** **3.43**

Scheme 3.11 Vision for a one-pot process

3.5. Application to a one-pot reaction

The idea behind this one-pot process was to submit our starting alcohol **3.41** to previously determined bromination conditions. After completion of this reaction, the gold catalyst and the base would be added and the mixture would be resubmitted to UVA irradiation (Scheme 3.12).

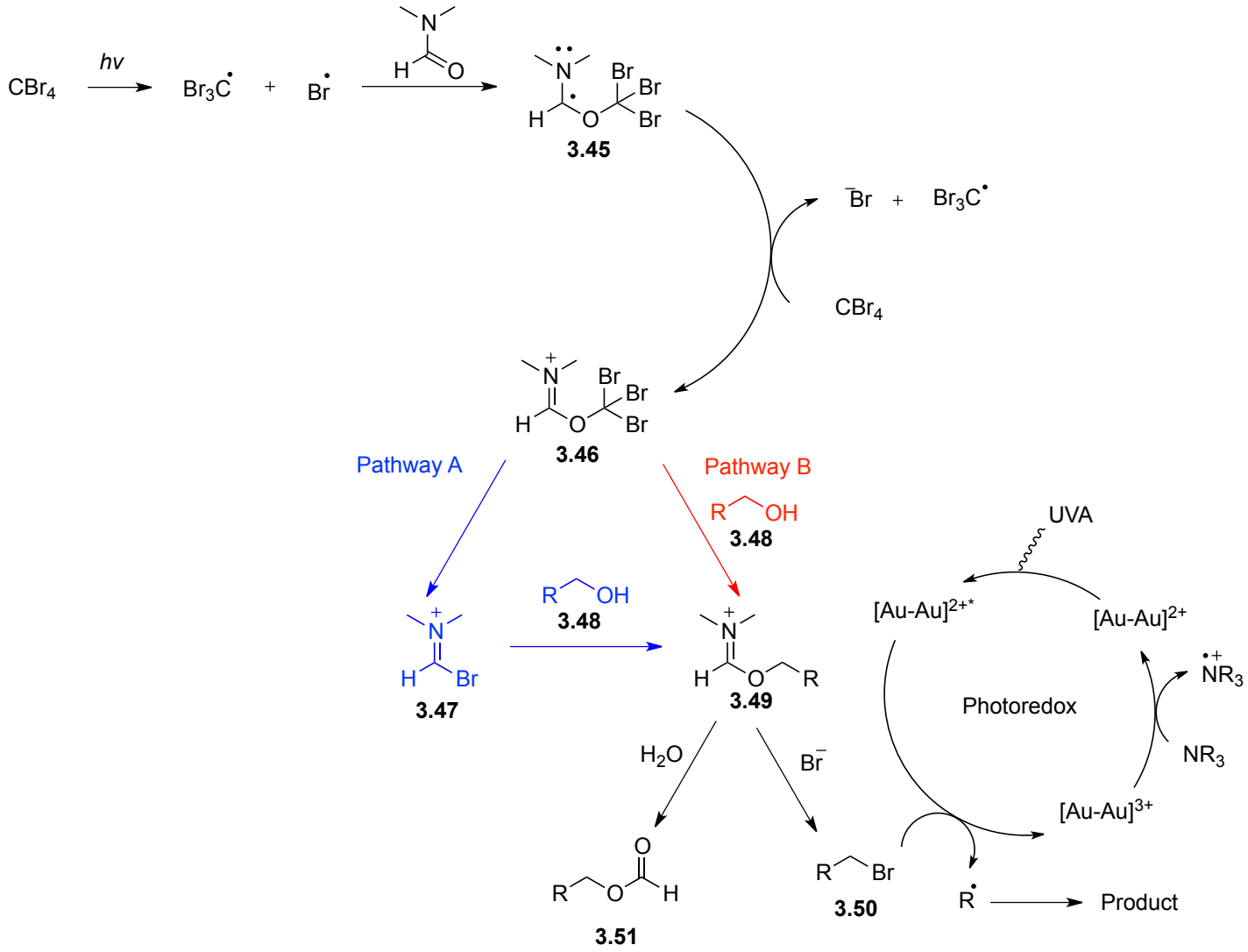


3.41 **3.44** **3.42**

Scheme 3.12 One-pot bromination and cyclization process

The proposed mechanism for the bromination under UV light was inspired by the work of the Stephenson group and is shown in Scheme 3.13. The first step is the generation of •CBr_3 by UV irradiation. The trapping of this radical species by DMF gives the stabilized radical **3.45**, which is subsequently oxidized to the iminium (**3.46**) by another molecule of CBr_4.[55] From here, two pathways are possible. Pathway A relies on the addition of the bromide ion to **3.46**, thus forming the Vilsmeier-Haack reagent **3.47**. This intermediate reacts with alcohol **3.48** to give **3.49**. On the other hand, pathway B has direct addition of the alcohol to **3.46** affording **3.49**. Both pathways converge for the final step of the mechanism, where **3.49** undergoes a S_N2 displacement by the bromide ion yielding the

final product **3.50**. The brominated product can then take part in the photoredox cycle for the initiation of the cascade cyclization.

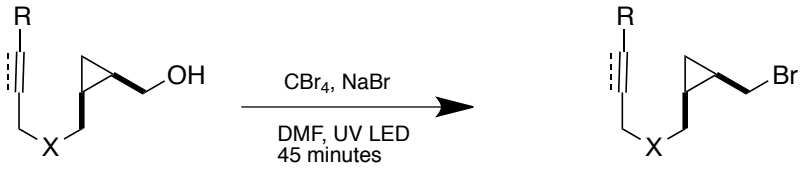


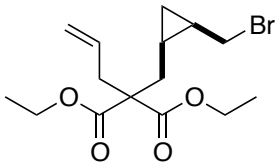
Scheme 3.13 Proposed mechanism for the one-pot methodology

Before proceeding with the one-pot process, we tested the bromination of our substrates. We submitted a variety of our substrates to the optimal conditions for the bromination method. The setup of this reaction is simple and consists of adding CBr_4, NaBr and the alcohol in DMF and stirring in presence of the UVA light for 45 minutes. Fortunately, the

bromination of all substrates afforded good to excellent yields, between 58% and 89% as shown in Table 3.6.

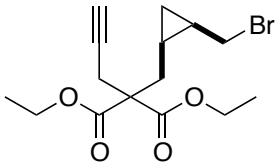
Table 3.6 Bromination of alcohols





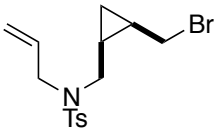
3.13

89%



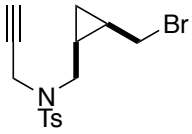
3.33

80%



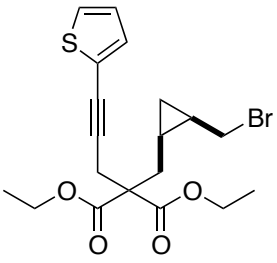
3.32

81%



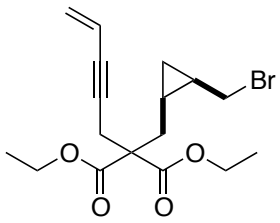
3.52

77%



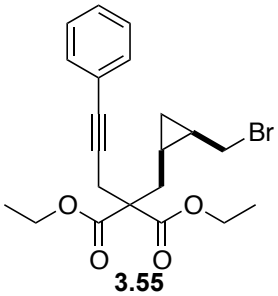
3.53

87%



3.54

58%



3.55

74%

The efficient bromination encouraged us to begin evaluating the one-pot process. The transition between the two reactions was done in the stepwise process as illustrated in Figure 3.5. After the bromination judged complete by thin layer chromatography (TLC) 10 equivalents of water are added to ensure the hydrolysis of any remaining Vilsmeier-Haack reagent (**3.57**). The base and the gold catalyst are then respectively added to the mixture. The final step before the second irradiation is the flushing of air by argon sparging. Irradiation of the mixture for an additional hour provided the final product.

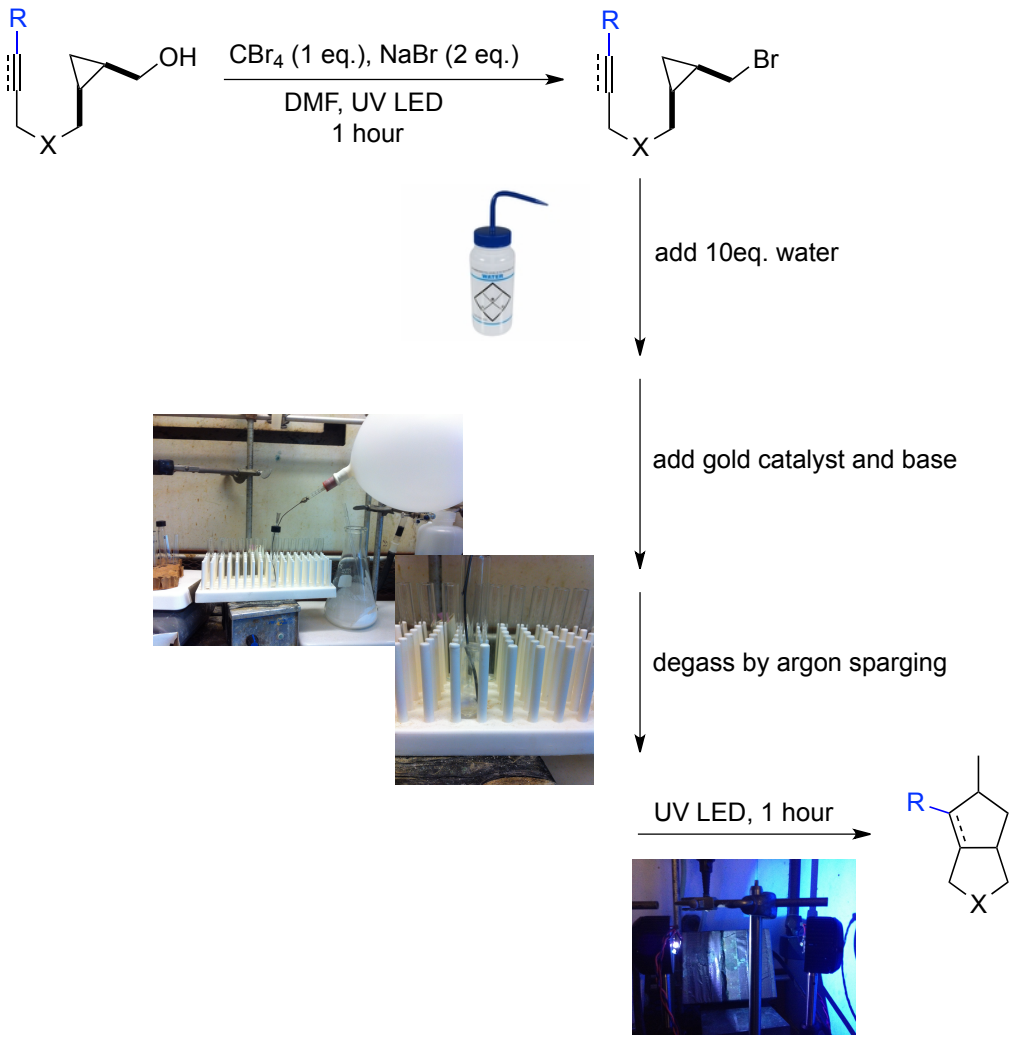
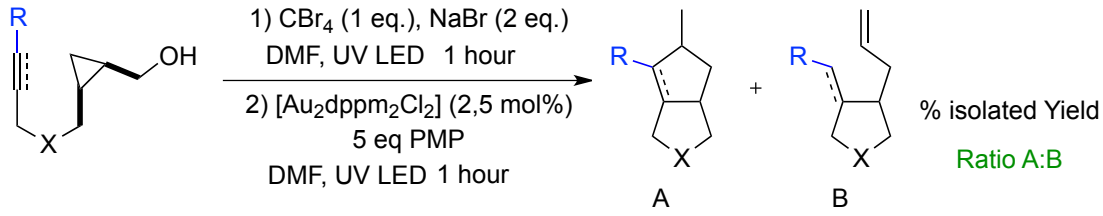


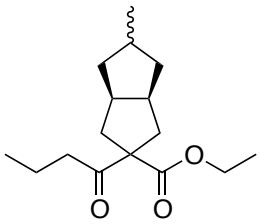
Figure 3.5 Methodology for the one-pot process

This technique was successfully used in the formation of fused carbocycles (Table 3.7). **3.15** and **3.34** were obtained in a 45% and 36% yield respectively in a 1:1 diastereomeric mixture of the fully cyclized product. In those cases, no monocyclized products were isolated. However, substrates bearing a terminal alkyne gave a single diastereomer and a mixture of bicyclized and monocyclized product. Product **3.35** was obtained in a 52% yield with a 5:1 mixture of A and B favoring A. The substrate with a tosylamine tether gave an isolated yield of 45% and a mixture of 4:1 with **3.59** as the major product. Product **3.39** showed a low yield of 12%. Substrates with an aromatic substituent on the

alkyne gave relatively good yields, but products **3.57** and **3.58** were not isolated with this method because of incomplete reactions.

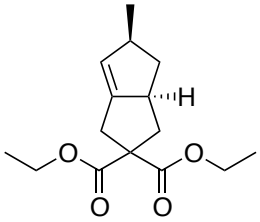
Table 3.7 Results of the one-pot synthesis using PMP





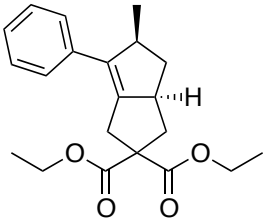
3.15

45%



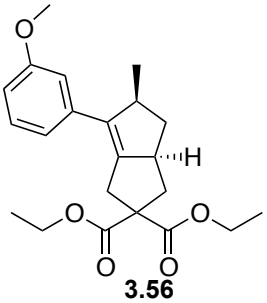
3.35

52% 5:1



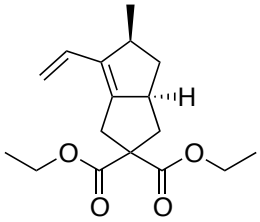
3.38

50% 12:1



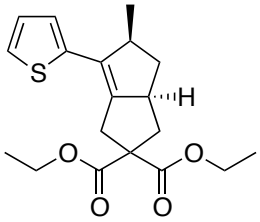
3.56

34% 10:1



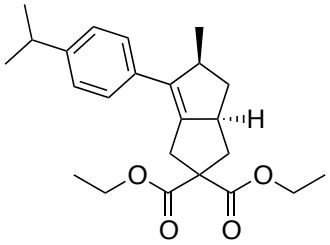
3.39

12%



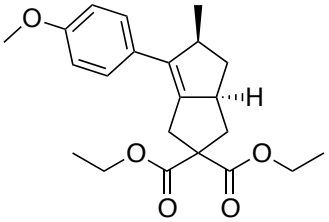
3.40

43% 11:1



3.57

N/A

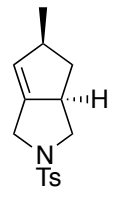


3.58

N/A

3.34

36%



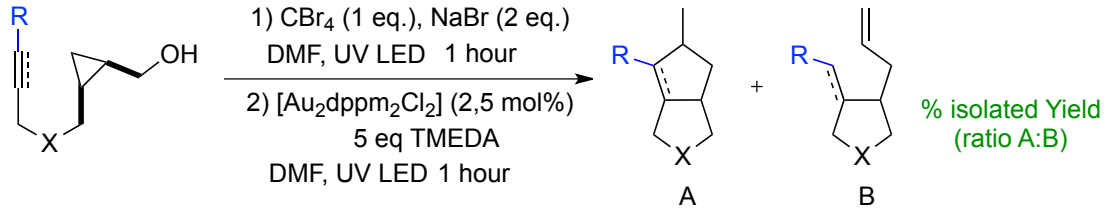
3.59

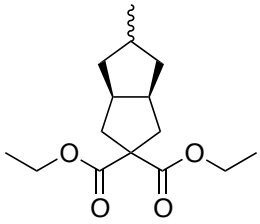
45% 4:1

Turning to the literature, conditions from the Yoon group for a [3+2] cycloaddition inspired us to try a diamine base.[56] The use of *N,N,N',N'*-tretramethylethylenediamine

(TMEDA) for the reaction again gave us yields comparable to those obtained with the previously used base, but we noticed an improvement in the ratio of products. The reactions conducted under these new conditions (Table 3.8) gave exclusively product **A** as the major product with the exception of **3.35** and **3.34**.

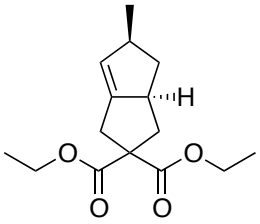
Table 3.8 Results of the one-pot cyclization using TMEDA





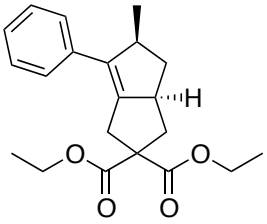
3.15

48%



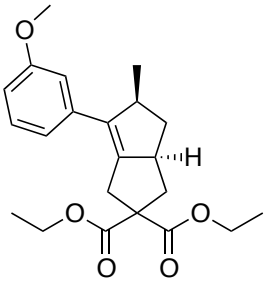
3.35

53% (7:1)



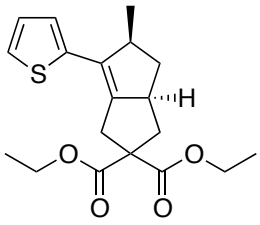
3.38

55%



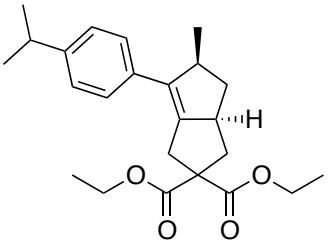
3.56

46%



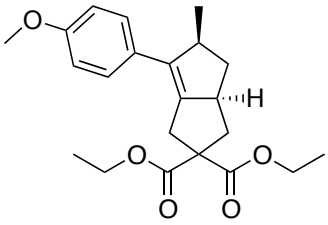
3.40

49%



3.57

49%



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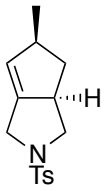

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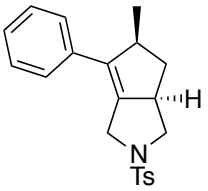

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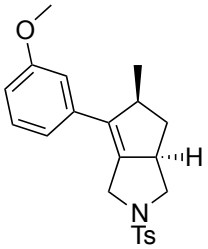


3.61

50%

Finally, we determined of the stereochemistry of the major products. Figure 3.6 shows the interactions observed by NOESY NMR. We observed an interaction between the methyl group and H^1. A second interaction was prominent between H^1 and H^2 suggesting that they were in the *cis* conformation. The absence of interaction between the methyl group and H^2 showed further proof that this was the correct diastereomer.

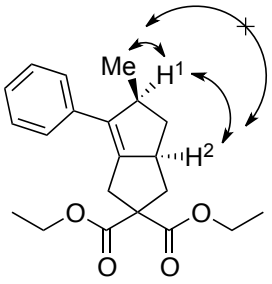


Figure 3.6 NOE interactions for 3.38

3.6. Conclusion

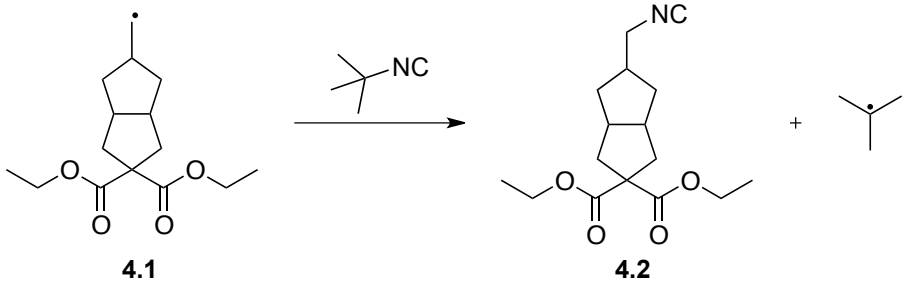
We have successfully developed a simple method for radical cascade cyclizations using $Au_2dppm_2Cl_2$. This one step process allows the formation of two fused rings by a radical cyclization cascade, thus forming fused carbocycles originating from a simple bromine substrate in relatively good yields. This method allows for a variety of aryl substituents to be introduced at the alkyne position allowing for further reactivity at a later step. Additionally, we've successfully applied this optimized methodology to a one-pot bromination/carbocyclization process granting us the possibility to start with a more readily available alcohol substrate, thus shortening the synthesis of the starting material by one step. Aside from these recent successes, we are still looking to diversify the substrate scope by adding other functionalities to our scaffolds. Furthermore, we are looking into similar reactivity in an intermolecular system as well as the application of this methodology towards natural product synthesis.

4. Future Directions and General Conclusions

4.1. Opportunities for diversification

Although our methodology has proven to be successful, it is important to consider the addition of other functionalities to the substrates. The insertion of more functionality would allow for further manipulation of the final product and could serve as molecular handles for the application of this method in total synthesis.

We have also considered the regioselective trapping of the final radical by a trapping agent.[57] An attractive reagent for these types of transformations is *tert*-butyl isocyanide, where you would have the transfer of a cyano group to the final cyclized product. This versatile cyano group would then allow for further reactivity of the substrate.



4.1 **4.2**

Scheme 4.1 Radical trapping by *tert*-butyl isocanide

This methodology also showed immense potential for the quick access of fused-carbocyclic cores, which are often found in diterpenoid and triquinane natural products (Figure 4.1). The application of this method in synthesis remains to be explored.

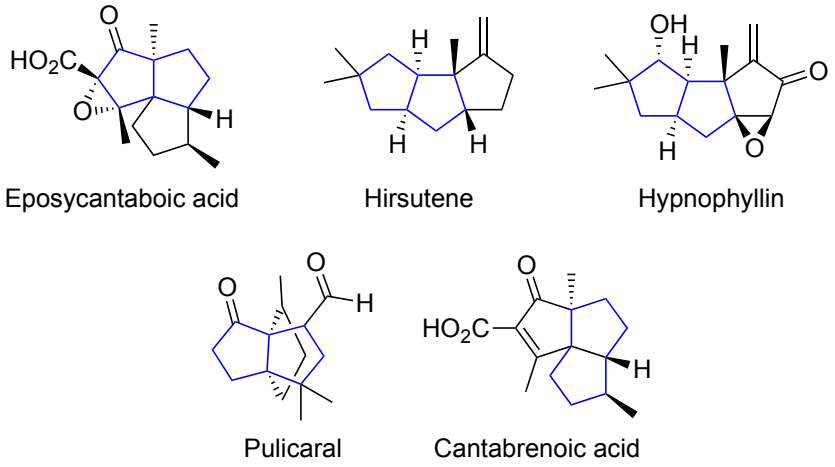
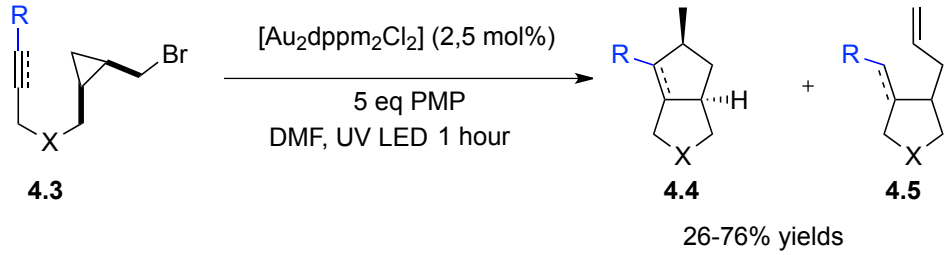


Figure 4.1 Triquinane natural products

4.2. General Conclusions

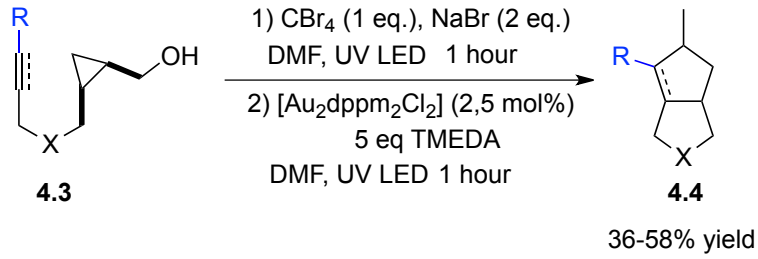
In summary, the investigations into a dual catalytic system merging organocatalysis and gold(I) photoredox catalysis has lead us to believe that the oxidation potential of the gold catalyst is insufficient for the turnover of the organocatalyst. Additionally, the addition product has not shown an increase in yield even in the presence of external oxidants. The control reactions revealed that the activated C-X bond can be reduced directly via a SET in the presence of an amine or enamine and yield the addition product in a 30% conversion without the photoredox catalyst.



Scheme 4.2 Gold(I) photocatalyzed radical cascade

On the other hand, we have successfully developed a cascade cyclization catalyzed by a dinuclear gold photocatalyst. The use of brominated substrates containing a cyclopropyl

ring (**4.3**) afforded cyclized products (**4.4**) in yields ranging from 26% to 76%. The application of this methodology in a one-pot tandem reaction allowed bromination of the alcohol substrate followed by photoredox cyclization to afford **4.4**. The one-pot reactions yielded the cyclized products in range from 36-58% yields.



Scheme 4.3 One-pot Tandem bromination/ carbocyclization

4.3. Claims to Original Research

- Investigation of organocatalysis and gold photoredox catalysis synergy for the formation of β-amino acid precursors.
- Development and optimization of a radical cascade cyclization via gold (I) photocatalysis.
- Investigations of the reaction scope a variety of substrates.
- Application of the radical cascade cyclization in a tandem one-pot process, achieving bromination followed by carbocyclization.
- Exploration of the one-pot reaction on various substrates.

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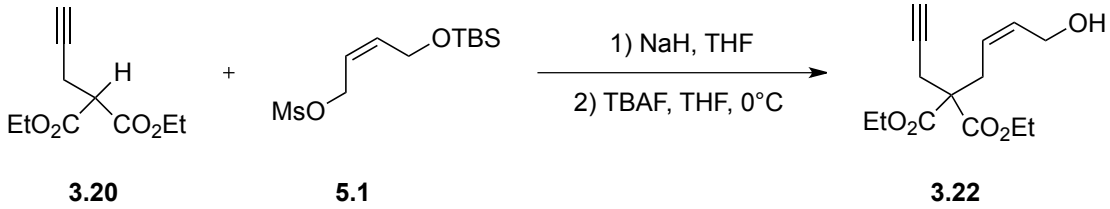
5. Experimental Information

5.1. General Information

All reactions were performed under nitrogen or argon atmosphere in flame-dried glassware equipped with a magnetic stir bar and a rubber septum, unless otherwise indicated. All solvents were freshly distilled prior to use; diethyl ether and THF over sodium and benzophenone; toluene, triethylamine, and DCM over calcium hydride. All other commercial reagents were used without purification, unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC) analysis of aliquots using glass sheets pre-coated (0.2 mm layer thickness) with silica gel 60 F_{254} (E. Merck). Thin layer chromatography plates were viewed under UV light and stained with phosphomolybdic acid, *p*-anisaldehyde staining solution or potassium permanganate solution. Column chromatographies were carried out with silica gel 60 (230-400 mesh, Merck). ^{1}H and ^{13}C NMR spectra were recorded in deuterated solvents, on Bruker AMX 300 MHz, Bruker AMX 500 MHz and Bruker AMX 400 MHz spectrometers. IR spectra were recorded with a Bomem Michaelson 100 FTIR spectrometer. HRMS were obtained on a Kratos Analytical Concept instrument (University of Ottawa Mass Spectrum Centre).

5.1. General Procedures

5.1.1. General procedure 1

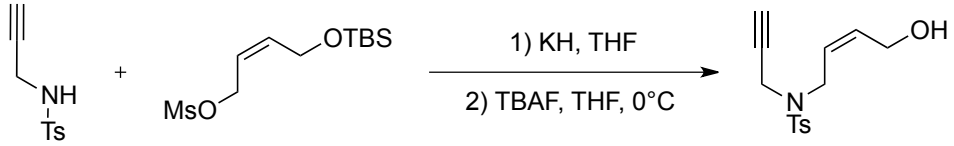


3.20 **5.1** **3.22**

Alkylation of malonate substrates:

To a flame dried flask loaded with a magnetic stirrer NaH (1.05 g, 26.2 mmol) was added and dissolved in THF (50.0 mL). The mixture was cooled to 0°C before adding the malonate chain (17.4 mmol) dropwise in THF. The reaction was stirred for 30 minutes before slowly adding freshly prepared **5.1** (20.9 mmol) and stirred for 2 hours. The reaction was quenched with NH_4Cl and extracted with ether. Organics were dried with $MgSO_4$, filtered and solvent was evaporated. The crude mixture was dissolved in THF (90.0 mL) and cooled to 0°C. 1 M TBAF in THF (19.2 mL, 19.2 mmol) was then added dropwise to the mixture and stirred overnight. The reaction was quenched with water and extracted with diethyl ether. Organics were dried with $MgSO_4$, filtered and solvent was evaporated. Product was purified by flash chromatography (30% EtOAc in Hexanes) to yield 75% of yellow oil over 2 steps.

5.1.2. General procedure 2



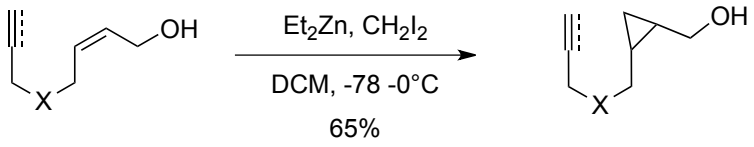
3.26 **5.1** **3.27**

Alkylation of amine substrates:

To a flame dried flask loaded with a magnetic stirrer KH (1.90 g, 14.3 mmol) was added and dissolved in THF (25.0 mL). The mixture was cooled to 0°C before adding tosylated

amine (9.56 mmol) dropwise in THF. The reaction was stirred for 30 minutes before slowly adding freshly prepared **5.1** (11.4 mmol) and stirred for 2 hours. The reaction was quenched with NH_4Cl and extracted with ether. Organics were dried with $MgSO_4$, filtered and solvent was evaporated. The crude mixture was dissolved in THF (50.0 mL) and cooled to 0°C. 1M TBAF in THF (10.5 mL, 10.5 mmol) was then added dropwise to the mixture and stirred overnight. The reaction was quenched with water and extracted with diethyl ether. Organics were dried with $MgSO_4$, filtered and solvent was evaporated. Product was purified by flash chromatography (30% EtOAc in Hexanes) to yield 75% of yellow oil over 2 steps.

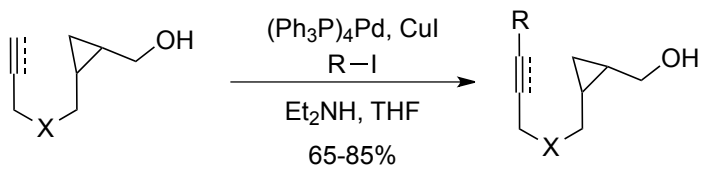
5.1.3. General procedure 3



Cyclopropanation:

To a flame dried flask loaded with a magnetic stirrer, Diiodomethane (2.10 mL, 26.0 mmol) was added to dichloromethane (26.0 mL). The mixture was cooled to 0°C before a 1M solution of diethylzinc (26.1 mL, 26.1 mmol) was added dropwise. This was stirred for 45 minutes before the mixture was cooled to -78°C. The alcohol substrate in dichloromethane was then added dropwise, stirred for 30 minutes at -78°C and then warmed to -20°C. Addition of another amount of diiodomethane (2.10 mL, 26.0 mmol) at this point pushed the reaction to completion. The reaction was quenched by slowly adding ammonium chloride and subsequently stirred for 30 minutes. Extract with dichloromethane, combined organics were dried with $MgSO_4$ and concentrated. Purification by flash chromatography (20% EtOAc: Hexanes) yielded product.

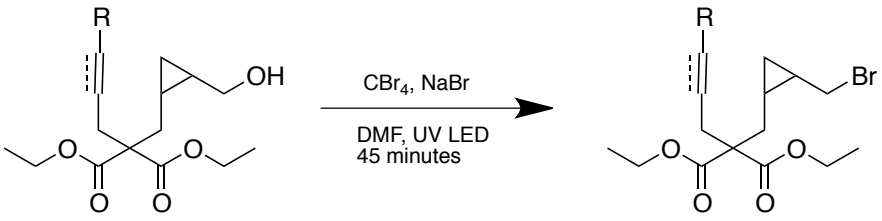
5.1.4. General procedure 4



Sonogashira:

To a flame dried flask loaded with a magnetic stirrer, copper iodide (0.011 g, 0.060 mmol) and $Pd(PPh_3)_4$ (0.035 g, 0.030 mmol) were added and dissolved in THF (4.0 mL). Alcohol substrate (1.0 mmol), R-I (1.6 mmol) and diisopropylethylamine (0.60 mL, 4.3 mmol) were added subsequently to the mixture. The reaction was then heated at 50°C for 2 hours. Dry pack with silica and purify by flash chromatography (30% EtOAc: Hexanes) to yield the desired product.

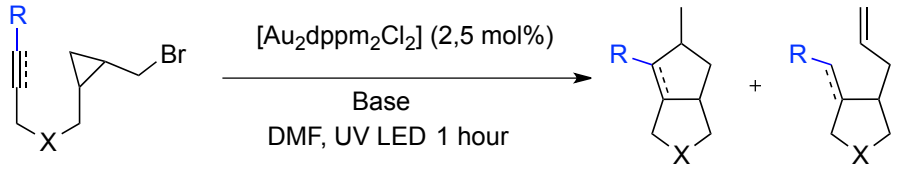
5.1.5. General procedure 5



Bromination:

To an oven dried pyrex screw cap tube loaded with a magnetic stirrer the alcohol substrate (0.20 mmol), CBr_4 (0.066 g, 0.20 mmol) and NaBr (0.041 g, 0.40 mmol) were added and dissolved in dry DMF. The mixture was exposed to 325 nm UV LED for 45 minutes. EtOAc was added and the organics were washed with water. Combined organics were dried with $MgSO_4$, filtered and concentrated. Purification was done by flash chromatography (5% EtOAc: Hexanes) to yield brominated product.

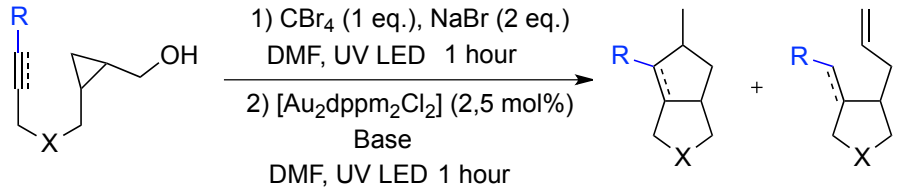
5.1.6. General procedure 6



Gold radical cyclization:

To an oven dried Pyrex screw cap tube loaded with a magnetic stirrer add the brominated substrate (0.20 mmol) and gold catalyst (0.025 mmol). Dissolve in 3.0 mL DMF and degas the mixture by argon sparging for 15 minutes before adding the amine base (1.0 mmol). The reaction vessel is placed in front of UV LED and is stirred for 45 to 90 minutes. Once the reaction is complete add ethyl acetate and wash with water. Dry organics with MgSO4, filter and evaporate solvent. Purify by chromatography (1-5% EtOAc: Hexanes) yielding the desired mixture of products.

5.1.7. General procedure 7

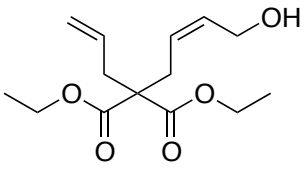


One-pot reactions:

To an oven dried pyrex screw cap tube loaded with a magnetic stirrer alcohol substrate (0.20 mmol), CBr_4 (0.066 g, 0.20 mmol) and NaBr (0.041 g, 0.40 mmol) were added and dissolved in dry DMF. The mixture was stirred in front of UV LED for 45 minutes. Water (36 uL, 2.0 mmol) was then added to the mixture and stirred for 10 minutes before adding the amine base (1.0 mmol) and stirred for an additional 10 minutes. The gold catalyst (6.0 mg, 0.025 mmol) was added and the reaction was degased by argon sparging. This was exposed to UV LED and stirred for 45 to 90 minutes. Once the

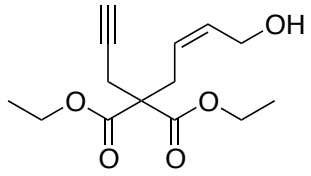
reaction is completed, ethyl acetate was added and the organics were washed with water, dried with $MgSO_4$, filtered and concentrated. Purification was done by chromatography (1-5% EtOAc: Hexanes) to yield the desired mixture of products.

5.2. Substrate and Product Characterization



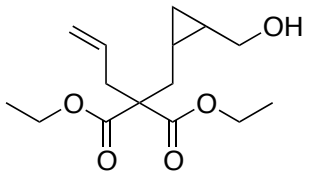
(*Z*)-diethyl 2-allyl-2-(4-hydroxybut-2-en-1-yl)malonate (3.62)

To a flame dried flask loaded with a magnetic stirrer NaH (0.22 g, 5.3 mmol) was added and dissolved in THF (20 mL). The mixture was cooled to 0°C before adding allyl malonate (0.84 g, 3.5 mmol) dropwise in THF. The reaction was stirred for 30 minutes before slowly adding freshly prepared **5.1** (1.3 g, 5.3 mmol) and stirred for 2 hours. The reaction was quenched with NH_4Cl and extracted with ether. Organics were dried with $MgSO_4$, filtered and solvent was evaporated. The crude mixture was dissolved in THF (50 mL) and cooled to 0°C. 1 M TBAF in THF (9.4 mL, 9.4 mmol) was then added dropwise to the mixture and stirred overnight. The reaction was quenched with water and extracted with diethylether. Organics were dried with $MgSO_4$, filtered and solvent was evaporated. Product was purified by flash chromatography (30% EtOAc in Hexanes) to yield 85% of **3.62** (1.9 g) as a yellow oil over 2 steps. **IR (thin film):** 1718, 1190, 1008 cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 5.76 (dtt, *J* = 11.0, 6.9, 1.5 Hz, 1H), 5.71-5.60 (m, 1H), 5.43 (dtt, *J* = 11.0, 7.9, 1.4 Hz, 1H), 5.15-5.12 (m, 1H), 5.10 (t, *J* = 1.1 Hz, 1H), 4.25-4.13 (m, 6H), 2.68-2.64 (m, 4H), 1.25 (t, *J* = 7.1 Hz, 6H). **13-C NMR (101 MHz; $CDCl_3$):** δ 170.7(2x C), 132.1(CH), 132.0(CH), 125.8(CH), 119.2(CH_2), 61.3(2x CH_2), 58.2(CH_2), 57.3(C), 37.1(CH_2), 30.3(CH_2), 14.0(2x CH_3). **HRMS (EI**) m/z calcd for $C_{14}H_{22}O_5$ 270.1467, found 270.1466.



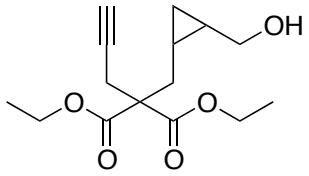
(*Z*)-diethyl 2-(4-hydroxybut-2-en-1-yl)-2-(prop-2-yn-1-yl)malonate (3.22)

To a flame dried flask loaded with a magnetic stirrer NaH (0.80 g, 20 mmol) was added and dissolved in THF (30 mL). The mixture was cooled to 0°C before adding the malonate chain (13.5 mmol) dropwise in THF. The reaction was stirred for 30 minutes before slowly adding freshly prepared **5.1** (5.50 g, 16.2 mmol) and stirred for 2 hours. The reaction was quenched with NH_4Cl and extracted with ether. Organics were dried with $MgSO_4$, filtered and solvent was evaporated. The crude mixture was dissolved in THF (70 mL) and cooled to 0°C. 1 M TBAF in THF (15 mL, 15 mmol) was then added dropwise to the mixture and stirred overnight. The reaction was quenched with water and extracted with diethyl ether. Organics were dried with $MgSO_4$, filtered and solvent was evaporated. Product was purified by flash chromatography (30% EtOAc in Hexanes) to yield 77% of **3.22** (2.8 g) as a yellow oil over 2 steps. **IR (thin film):** 3282, 1718, 1186, 1016 cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 5.76 (dtt, *J* = 11.0, 6.9, 1.5 Hz, 1H), 5.71-5.60 (m, 1H), 5.43 (dtt, *J* = 11.0, 7.9, 1.4 Hz, 1H), 5.15-5.10 (m, 2H), 4.25-4.13 (m, 6H), 2.68-2.64 (m, 4H), 1.25 (t, *J* = 7.1 Hz, 6H). **13-C NMR (101 MHz; $CDCl_3$):** δ 169.8(2x C), 133.4(CH), 125.4(CH), 79.1(C), 71.7(CH), 62.0(2x CH_2), 58.4(CH_2), 56.7(C), 30.1(CH_2), 22.8(CH_2), 14.2(2x CH_3). **HRMS (EI**) m/z calcd for $C_{14}H_{20}O_5$ [$(M-C_3H_5O_2)^+$] 195.1021, found 195.1029.



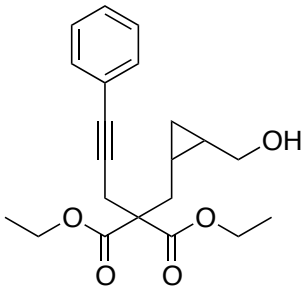
Diethyl 2-allyl-2-((2-(hydroxymethyl)cyclopropyl)methyl)malonate (3.63)

To a flame dried flask loaded with a magnetic stirrer, Diiodomethane (2.1 mL, 26 mmol) was added to dichloromethane (30 mL). The mixture was cooled to 0°C before a 1M solution of diethylzinc (26 mL, 26 mmol) was added dropwise. This was stirred for 45 minutes before being cooled to -78°C. The alcohol **3.62** in dichloromethane was added dropwise, stirred for 30 minutes at -78°C and then warmed to -20°C. Addition of more diiodomethane (2.1 mL, 26 mmol) at this point pushed the reaction to completion. The reaction was quenched by the slow addition of ammonium chloride and stirred for 30 minutes. Extracted with dichloromethane, the combined organics were dried with $MgSO_4$ and concentrated. Purification by flash chromatography (20% EtOAc: Hexanes) yielded 63% of **3.63** (1.3 g) as a colorless oil. **IR (thin film):** 1718, 1020 cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 5.66 (ddt, *J* = 17.1, 10.0, 7.2 Hz, 1H), 5.15-5.07 (m, 2H), 4.25-4.12 (m, 4H), 3.69 (dd, *J* = 11.5, 6.5 Hz, 1H), 3.52 (dd, *J* = 11.5, 8.3 Hz, 1H), 2.76 (dd, *J* = 7.4, 1.1 Hz, 2H), 2.23 (dd, *J* = 14.4, 4.5 Hz, 1H), 1.70 (dd, *J* = 14.4, 9.1 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 6H), 1.17-1.07 (m, 1H), 0.87-0.78 (m, 1H), 0.73 (dt, *J* = 8.3, 4.7 Hz, 1H), -0.01 (q, *J* = 5.2 Hz, 1H). **13-C NMR (101 MHz; $CDCl_3$):** δ 171.4(C), 171.3(C), 132.5(CH), 119.1(CH_2), 62.9(CH_2), 61.3(CH_2), 61.2(CH_2), 57.8(C), 37.3(CH_2), 30.9(CH_2), 17.6(CH), 14.1(2x CH_3), 10.9(CH), 9.5(CH_2). **HRMS (EI)** m/z calcd for $C_{15}H_{24}O_5$ [$(M\text{-}OH)^+$] 267.1596, found 267.1602.



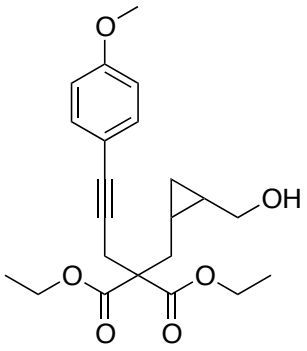
Diethyl 2-((2-(hydroxymethyl)cyclopropyl)methyl)-2-(prop-2-yn-1-yl)malonate (3.23)

To a flame dried flask loaded with a magnetic stirrer, Diiodomethane (5.75 mL, 71.4 mmol) was added to dichloromethane (70 mL). The mixture was cooled to 0°C before a 1M solution of diethylzinc (71.4 mL, 71.4 mmol) was added dropwise. This was stirred for 45 minutes before the mixture was cooled to -78°C. The alcohol **3.22** in dichloromethane was added dropwise. Stirred for 30 minutes at -78°C and then warmed to -20°C. Addition of more diiodomethane (2.1 mL, 26 mmol) at this point pushed the reaction to completion. The reaction was quenched by slowly adding ammonium chloride and stirred for 30 minutes. Extracted with dichloromethane, the combined organics were dried with $MgSO_4$ and concentrated. Purification by flash chromatography (20% EtOAc: Hexanes) yielded 66% of **3.23** (2.7 g) as a yellow oil. **IR (thin film):** 3290, 1733, 1018 cm^{-1}.**1H-NMR (400 MHz; $CDCl_3$):** δ 4.28-4.15 (m, 4H), 3.72 (dd, *J* = 11.5, 6.6 Hz, 1H), 3.57 (dd, *J* = 11.6, 8.3 Hz, 1H), 3.01-2.90 (m, 2H), 2.42 (dt, *J* = 14.0, 2.5 Hz, 1H), 2.02 (t, *J* = 2.7 Hz, 1H), 1.93-1.87 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 6H), 1.20-1.10 (m, 1H), 0.78-0.72 (m, 2H), 0.10 (q, *J* = 7.8 Hz, 1H). **13-C NMR (101 MHz; $CDCl_3$):** δ 170.4(C), 170.3(C), 79.4(C), 71.7(CH), 63.0(CH_2), 61.8(CH_2), 61.8(CH_2)), 57.4(C), 30.4(CH_2), 23.0(CH_2), 17.6(CH), 14.2(2x CH_3), 11.1(CH), 9.4(CH_2). **HRMS (EI)** m/z calcd for $C_{15}H_{22}O_5$ [(M-$C_3H_5O_2$)$^+$] 209.1178, found 209.1192.



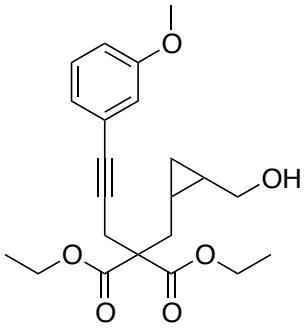
Diethyl 2-((2-(hydroxymethyl)cyclopropyl)methyl)-2-(3-phenylprop-2-yn-1-yl)malonate (3.64)

To a flame dried flask loaded with a magnetic stirrer, copper iodide (11 mg, 0.060 mmol) and $Pd(PPh_3)_4$ (35 mg, 0.030 mmol) were added and dissolved in THF (4.0 mL). Alcohol **3.23** (0.30 g, 1.1 mmol), iodobenzene (0,18 mL, 1.6 mmol) and diisopropylamine (0.60 mL, 4.2 mmol) were added subsequently to the mixture. The reaction was then heated at 50°C for 2 hours. Dry pack with silica and purify by flash chromatography (30% EtOAc: Hexanes) to yield 75% of **3.64** (0.34 g) as a colorless oil. **IR (thin film):** 1730, 1211, 755, 692 cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 7.33 (dd, *J* = 6.7, 3.1 Hz, 2H), 7.27-7.23 (m, 3H), 4.29-4.14 (m, 4H), 3.70 (dd, *J* = 11.5, 6.5 Hz, 1H), 3.57 (dd, *J* = 11.5, 8.3 Hz, 1H), 3.14 (q, *J* = 15.0 Hz, 2H), 2.47-2.42 (m, 1H), 1.94 (dd, *J* = 14.5, 8.8 Hz, 1H), 1.25 (dt, *J* = 7.1, 0.7 Hz, 6H), 1.19-1.10 (m, 2H), 0.83-0.72 (m, 2H), 0.11 (q, *J* = 4.8 Hz, 1H). **13-C NMR (101 MHz; $CDCl_3$):** δ 170.4(C), 170.3(C), 131.5(CH), 128.2(CH), 128.0(CH), 123.1(C), 84.5(C), 83.6(C), 62.8(CH_2), 61.6(CH_2), 61.6(CH_2), 57.6(C), 30.4(CH_2), 23.7(CH_2), 17.5(CH), 14.0(2x CH_3), 11.0(CH), 9.2(CH_2). **HRMS (EI)** m/z calcd for $C_{21}H_{26}O_5$ [$(M-C_3H_5O_2)^+$] 285.1491, found 285.1491.



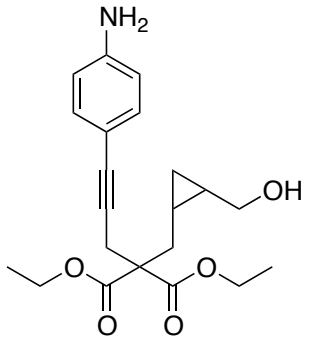
Diethyl 2-((2-(hydroxymethyl)cyclopropyl)methyl)-2-(3-(4-methoxyphenyl)prop-2-yn-1-yl)malonate (3.65)

To a flame dried flask loaded with a magnetic stirrer, copper iodide (16 mg, 0.085 mmol) and $Pd(PPh_3)_4$ (50 mg, 0.043 mmol) were added and dissolved in THF (5.0 mL). Alcohol **3.23** (0.40 g, 1.40 mmol), 4-iodoanisole (0.50 g, 2.1 mmol) and diisopropylamine (0.80 mL, 5.7 mmol) were added subsequently to the mixture. The reaction was then heated at 50°C for 2 hours. Dry pack with silica and purify by flash chromatography (30% EtOAc: Hexanes) to yield 89% of **3.65** (0.48 g) of colorless oil. **IR (thin film):** 1730, 1031, 831 cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 7.30-7.26 (dt, *J* = 9.25, 2.41 Hz, 2H), 6.81-6.78 (dt, *J* = 9.25, 2.41 Hz, 2H), 4.30-4.15 (m, 4H), 3.79 (s, 3H), 3.72 (dd, *J* = 11.6, 6.5 Hz, 1H), 3.58 (dd, *J* = 11.6, 8.4 Hz, 1H), 3.14 (q, *J* = 14.8 Hz, 2H), 2.47-2.42 (m, 1H), 1.96 (dd, *J* = 14.5, 8.7 Hz, 1H), 1.27 (dt, *J* = 7.1, 0.7 Hz, 6H), 1.21-1.11 (m, 1H), 0.85-0.76 (m, 2H), 0.12 (q, *J* = 4.7 Hz, 1H). **13-C NMR (101 MHz; $CDCl_3$):** δ 170.6(C), 170.5(C), 159.5(C), 133.1(2x CH), 115.4(C), 114.0(2x CH), 83.6(C), 83.1(C), 63.0(CH_2), 61.8(CH_2), 61.7(CH_2), 57.9(C), 55.4(CH_3), 30.6(CH_2), 24.0(CH_2), 17.8(CH), 14.2(2x CH_3), 11.2(CH), 9.4(CH_2). **HRMS (EI**) m/z calcd for $C_{22}H_{28}O_6$ 388.1886, found 388.1856.



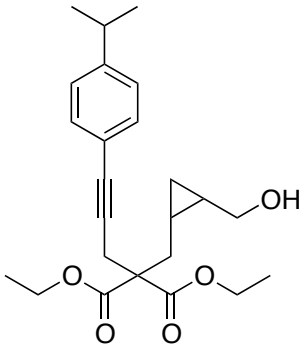
Diethyl 2-((2-(hydroxymethyl)cyclopropyl)methyl)-2-(3-(3-methoxyphenyl)prop-2-yn-1-yl)malonate (3.66)

To a flame dried flask loaded with a magnetic stirrer, copper iodide (16 mg, 0.085 mmol) and $Pd(PPh_3)_4$ (50 mg, 0.043 mmol) were added and dissolved in THF (5.0 mL). Alcohol **3.23** (0.40 g, 1.4 mmol), 3-iodoanisole (0.25 mL, 2.1 mmol) and diisopropylamine (0.80 mL, 5.7 mmol) were added subsequently to the mixture. The reaction was then heated at 50°C for 2 hours. Dry pack with silica and purified by flash chromatography (30% EtOAc: Hexanes) to yield 90% of **3.66** (0.49 g) as a colorless oil. **IR (thin film):** 1733, 784 cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 7.18 (t, *J* = 7.9 Hz, 1H), 6.95 (dt, *J* = 7.6, 1.1 Hz, 1H), 6.88 (t, *J* = 1.9 Hz, 1H), 6.84 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 4.31-4.16 (m, 4H), 3.78 (s, 3H), 3.73 (dd, *J* = 11.5, 6.5 Hz, 1H), 3.58 (dd, *J* = 11.6, 8.3 Hz, 1H), 3.16 (q, *J* = 14.8 Hz, 2H), 2.48-2.44 (m, 1H), 1.99-1.93 (m, 1H), 1.27 (dt, *J* = 7.1, 0.8 Hz, 6H), 1.21-1.12 (m, 1H), 0.85-0.74 (m, 2H), 0.12 (q, *J* = 4.8 Hz, 1H). **13-C NMR (101 MHz; $CDCl_3$):** δ 170.5(C), 170.4(C), 159.4(C), 129.4(CH), 124.3(C), 124.2(CH), 116.7(CH), 114.6(CH), 84.6(C), 83.7(C), 63.0(CH_2), 61.8(CH_2), 61.7(CH_2), 57.8(C), 55.4(CH_3), 30.7(CH_2), 24.0(CH_2), 17.7(CH), 14.2(2x CH_3), 11.2(CH), 9.4(CH_2). **HRMS (EI)** m/z calcd for $C_{22}H_{28}O_6$ 388.1886, found 388.1875.



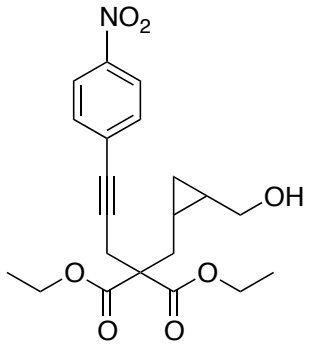
Diethyl 2-(3-(4-aminophenyl)prop-2-yn-1-yl)-2-((2-(hydroxymethyl)cyclopropyl) methyl)malonate (3.67)

To a flame dried flask loaded with a magnetic stirrer, copper iodide (11 mg, 0.060 mmol) and $Pd(PPh_3)_4$ (35 mg, 0.030 mmol) were added and dissolved in THF (4.00 mL). Alcohol **3.23** (0.30 g, 1.1 mmol), 4-iodoaniline (0.35 g, 1.6 mmol) and diisopropylamine (0.60 mL, 4.3 mmol) were added subsequently to the mixture. The reaction was then heated at 50°C for 2 hours. Dry pack with silica and purified by flash chromatography (40-50% EtOAc: Hexanes) to yield 54% of **3.67** (0.21 g) as a colorless oil. **IR (thin film):** 2983, 1720, 1240, 1041, 829 cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 7.17 (t, *J* = 2.3 Hz, 1H), 7.14 (t, *J* = 2.1 Hz, 1H), 6.60 (t, *J* = 2.3 Hz, 1H), 6.57 (t, *J* = 2.1 Hz, 1H), 4.30-4.15 (m, 4H), 3.72 (dd, *J* = 11.6, 6.5 Hz, 1H), 3.57 (dd, *J* = 11.6, 8.3 Hz, 1H), 3.13 (q, *J* = 14.8 Hz, 2H), 2.46-2.41 (m, 1H), 1.96 (dd, *J* = 14.5, 8.6 Hz, 1H), 1.28-1.24 (m, 6H), 1.20-1.10 (m, 1H), 0.84-0.73 (m, 2H), 0.11 (q, *J* = 4.8 Hz, 1H). **13-C NMR (101 MHz; $CDCl_3$):** δ 170.7(C), 170.6(C), 146.5(C), 133.0(2x CH), 114.8(2x CH), 112.7(C), 84.2(C), 82.1(C), 63.0(CH_2), 61.7(CH_2), 61.7(CH_2), 57.9(C), 30.5(CH_2), 24.0(CH_2), 17.8(CH), 14.2(2x CH_3), 11.2(CH), 9.3(CH_2). **HRMS (EI)** m/z calcd for $C_{21}H_{27}NO_5$ 373.1889, found 373.1936.



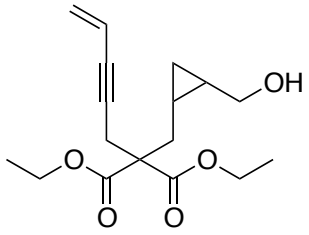
Diethyl 2-((2-(hydroxymethyl)cyclopropyl)methyl)-2-(3-(4-isopropylphenyl)prop-2-yn-1-yl)malonate (3.68)

To a flame dried flask loaded with a magnetic stirrer, copper iodide (11 mg, 0.060 mmol) and $Pd(PPh_3)_4$ (35 mg, 0.030 mmol) were added and dissolved in THF (4.0 mL). Alcohol **3.23** (0.30 g, 1.1 mmol), 4-isopropyl-iodobenzene (0.26 mL, 1.6 mmol) and diisopropylamine (0.60 mL, 4.3 mmol) were added subsequently to the mixture. The reaction was then heated at 50°C for 2 hours. Dry pack with silica and purified by flash chromatography (20-30% EtOAc: Hexanes) to yield 70% of **3.68** (0.30 g) as a colorless oil. **IR (thin film):** 1733, 1020, 748 cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 7.29-7.27 (m, 2H), 7.13 (d, *J* = 8.1 Hz, 2H), 4.30-4.15 (m, 4H), 3.72 (dd, *J* = 11.6, 6.5 Hz, 1H), 3.58 (dd, *J* = 11.6, 8.3 Hz, 1H), 3.15 (q, *J* = 15.0 Hz, 2H), 2.87 (7, *J* = 6.9 Hz, 1H), 2.47-2.42 (m, 1H), 1.96 (dd, *J* = 14.5, 8.7 Hz, 1H), 1.27 (dt, *J* = 7.1, 0.8 Hz, 6H), 1.22 (d, *J* = 6.9 Hz, 6H), 1.16 (ddt, *J* = 8.3, 6.1, 2.2 Hz, 1H), 0.77 (dd, *J* = 8.5, 4.4 Hz, 2H), 0.12 (q, *J* = 4.8 Hz, 1H). **13-C NMR (101 MHz; $CDCl_3$):** δ 170.6(C), 170.5(C), 149.1(C), 131.7(2x CH), 126.5(2x CH), 120.6(C), 83.9(C), 83.8(C), 63.0(CH_2), 61.8(CH_2), 61.7(CH_2), 57.9(C), 34.2(CH), 30.6(CH_2), 23.9(CH_2), 23.9(2x CH_3), 17.8(CH), 14.2(2x CH_3), 11.2(CH), 9.4(CH_2). **HRMS (EI**) m/z calcd for $C_{24}H_{32}O_5$ 400.2250, found 400.2235.



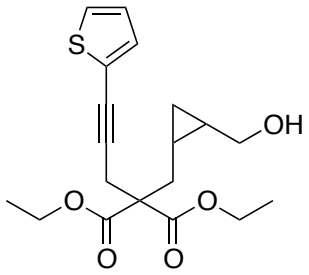
Diethyl 2-((2-(hydroxymethyl)cyclopropyl)methyl)-2-(3-(4-nitrophenyl)prop-2-yn-1-yl)malonate (3.69)

To a flame dried flask loaded with a magnetic stirrer, copper iodide (11 mg, 0.060 mmol) and $Pd(PPh_3)_4$ (35 mg, 0.030 mmol) were added and dissolved in THF (4.00 mL). Alcohol **3.23** (0.30 g, 1.1 mmol), para-nitro-iodobenzene (0.40 g, 1.6 mmol) and diisopropylamine (0.60 mL, 4.3 mmol) were added subsequently to the mixture. The reaction was then heated at 50°C for 2 hours. Dry pack with silica and purified by flash chromatography (20-30% EtOAc: Hexanes) to yield 88% of **3.69** (0.38 g) as a yellow oil. **IR (thin film):** 1733, 1233, 1043, 650cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 8.17-8.13 (m, 2H), 7.51-7.47 (m, 2H), 4.31-4.17 (m, 4H), 3.75 (dd, *J* = 11.3, 6.1 Hz, 1H), 3.60 (t, *J* = 9.1 Hz, 1H), 3.21 (q, *J* = 14.2 Hz, 2H), 2.47 (dd, *J* = 14.6, 4.4 Hz, 1H), 1.93 (dd, *J* = 14.6, 9.0 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 6H), 1.23-1.11 (m, 1H), 0.84-0.76 (m, 2H), 0.11 (q, *J* = 4.6 Hz, 1H). **13-C NMR (101 MHz; $CDCl_3$):** δ 170.3(C), 170.2(C), 147.1(C), 132.5(2x CH), 130.2(C), 123.7(2x CH), 90.9(C), 82.2(C), 63.0(CH_2), 62.0(CH_2), 61.9(CH_2), 57.7(C), 30.8(CH_2), 24.1(CH_2), 17.7(CH), 14.2(2x CH_3), 11.1(CH), 9.6(CH_2). **HRMS (EI**) m/z calcd for $C_{21}H_{25}O_7N$ 403.1631, found 403.1612.



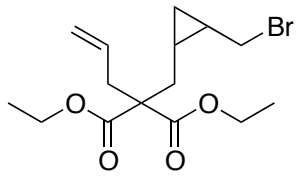
Diethyl 2-((2-(hydroxymethyl)cyclopropyl)methyl)-2-(pent-4-en-2-yn-1-yl)malonate (3.70)

To a flame dried flask loaded with a magnetic stirrer, copper iodide (8.0 mg, 0.043 mmol) and $Pd(PPh_3)_4$ (25 mg, 0.021 mmol) were added and dissolved in THF (5.0 mL). Alcohol **3.23** (0.33 g, 1.1 mmol), vinyl bromide (1.06 mL, 1.06 mmol, 1M) and diisopropylamine (0.40 mL, 2.8 mmol) were added subsequently to the mixture. The reaction was then heated at 50°C for 2 hours. Dry pack with silica and purified by flash chromatography (10-50% EtOAc: Hexanes) to yield 70% of **3.70** (0.18 g) as a yellow oil. **IR (thin film):** 1733, 1018 cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 5.71 (ddt, *J* = 17.5, 11.0, 1.9 Hz, 1H), 5.54 (ddd, *J* = 17.5, 2.2, 0.4 Hz, 1H), 5.40 (ddd, *J* = 11.0, 2.3, 0.3 Hz, 1H), 4.28-4.14 (m, 4H), 3.71 (dd, *J* = 11.6, 6.6 Hz, 1H), 3.56 (dd, *J* = 11.5, 8.3 Hz, 1H), 3.12-3.00 (m, 2H), 2.42-2.37 (m, 1H), 1.92-1.84 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 6H), 1.19-1.10 (m, 1H), 0.79-0.71 (m, 2H), 0.11-0.05 (m, 1H). **13-C NMR (101 MHz; $CDCl_3$):** δ 170.4(C), 170.3(C), 126.7(CH_2), 116.9(CH), 85.1(C), 82.3(C), 62.8(CH_2), 61.6(CH_2), 61.6(CH_2), 57.5(C), 30.4(CH_2), 23.4(CH_2), 17.5(CH), 14.0(2x CH_3), 11.0(CH), 9.2(CH_2). **HRMS (EI)** m/z calcd for $C_{17}H_{24}O_5$ 308.1624, found 308.1648.



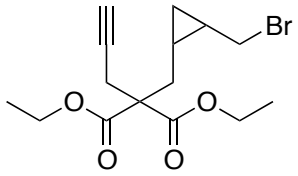
Diethyl 2-((2-(hydroxymethyl)cyclopropyl)methyl)-2-(3-(thiophen-2-yl)prop-2-yn-1-yl)malonate (3.71)

To a flame dried flask loaded with a magnetic stirrer, copper iodide (11 mg, 0.060 mmol) and $Pd(PPh_3)_4$ (35 mg, 0.030 mmol) were added and dissolved in THF (5.0 mL). Alcohol **3.23** (0.30 g, 1.1 mmol), iodothiophene (0.18 mL, 1.6 mmol) and diisopropylamine (0.6 mL, 4.2 mmol) were added subsequently to the mixture. The reaction was then heated at 50°C for 2 hours. Dry pack with silica and purified by flash chromatography (% EtOAc: Hexanes) to yield 75% of **3.71** (0.34 g) as a yellow oil. **IR (thin film):** 1730, 1216, 698 cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 7.19 (dd, *J* = 5.2, 1.1 Hz, 1H), 7.11 (dd, *J* = 3.6, 1.1 Hz, 1H), 6.93 (dd, *J* = 5.2, 3.6 Hz, 1H), 4.31-4.16 (m, 4H), 3.73 (dd, *J* = 11.5, 6.6 Hz, 1H), 3.59 (dd, *J* = 11.5, 8.2 Hz, 1H), 3.19 (q, *J* = 15.3 Hz, 2H), 2.47-2.42 (m, 1H), 1.96-1.91 (m, 1H), 1.27 (td, *J* = 7.1, 0.7 Hz, 6H), 1.20-1.12 (m, 2H), 0.94-0.75 (m, 3H), 0.13 (q, *J* = 4.9 Hz, 1H). **13-C NMR (101 MHz; $CDCl_3$):** δ 170.4(C), 170.4(C), 131.8(CH), 127.0(CH), 126.7(CH), 88.9(C), 77.3(C), 63.1(C), 61.93(CH_2), 61.84(CH_2), 57.8(C), 30.7(CH_2), 30.7(CH_2), 24.3(CH_2), 17.7(CH), 14.2(2 x CH_3), 11.2(CH), 9.5(CH_2). **HRMS (EI**) m/z calcd for $C_{19}H_{24}O_5S$ 364.1344, found 364.1366.



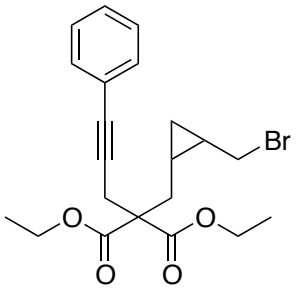
diethyl 2-allyl-2-((2-(bromomethyl)cyclopropyl)methyl)malonate (3.13)

To an oven dried pyrex screw cap tube loaded with a magnetic stirrer the Alcohol **3.63** (57 mg, 0.20 mmol), CBr_4 (0.066 g, 0.20 mmol) and NaBr (0.041 g, 0.40 mmol) were added and dissolved in dry DMF. The mixture was exposed to 365 nm UV LED for 45 minutes. EtOAc was added and the organics were washed with water. Combined organics were dried with $MgSO_4$, filtered and concentrated. Purification was done by flash chromatography (5% EtOAc: Hexanes) to yield 89% of **3.13** (0.062 g) as colorless oil. **IR (thin film):** 1735, 661 cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 5.65 (ddt, *J* = 17.1, 10.0, 7.2 Hz, 1H), 5.15-5.08 (m, 2H), 4.25-4.11 (m, 4H), 3.49 (dd, *J* = 10.4, 7.8 Hz, 1H), 3.37 (dd, *J* = 10.4, 8.5 Hz, 1H), 2.80-2.69 (m, 2H), 2.41 (dd, *J* = 14.3, 3.3 Hz, 1H), 1.57 (dd, *J* = 14.3, 10.4 Hz, 1H), 1.34 (quintetd, *J* = 8.3, 5.4 Hz, 1H), 1.25 (dt, *J* = 7.1, 1.9 Hz, 6H), 1.01-0.94 (m, 1H), 0.90 (tt, *J* = 8.3, 4.2 Hz, 1H), 0.10 (q, *J* = 5.4 Hz, 1H). **13-C NMR (101 MHz; $CDCl_3$):** δ 171.3(C), 171.1(C), 132.5(CH), 119.3(CH_2), 61.4(CH_2), 61.3(CH_2), 57.7(C), 37.1(CH_2), 35.2(CH_2), 30.5(CH_2), 18.1(CH), 14.6(CH), 14.4(CH_2), 14.2(2 x CH_3). **HRMS (EI**) m/z calcd for $C_{14}H_{23}O_4Br$ [$(M-C_3H_5O_2)^+$] 273.0490, found 273.0552.



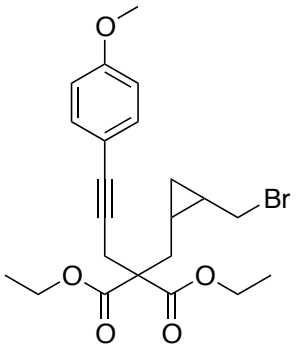
diethyl 2-((2-(bromomethyl)cyclopropyl)methyl)-2-(prop-2-yn-1-yl)malonate (3.33)

To an oven dried pyrex screw cap tube loaded with a magnetic stirrer the Alcohol **3.23** (0.10 mmol), CBr_4 (33 mg, 0.10 mmol) and NaBr (20 mg, 0.20 mmol) were added and dissolved in dry DMF. The mixture was exposed to 365 nm UV LED for 45 minutes. EtOAc was added and the organics were washed with water. Combined organics were dried with $MgSO_4$, filtered and concentrated. Purification was done by flash chromatography (5% EtOAc: Hexanes) to yield 80% of **3.33** (28 mg) of a white solid. **IR (thin film):** 1733, 628 cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 4.26-4.14 (m, 4H), 3.50 (dd, *J* = 10.4, 7.9 Hz, 1H), 3.41 (dd, *J* = 10.2, 8.5 Hz, 1H), 2.92 (qd, *J* = 16.7, 2.6 Hz, 2H), 2.57 (dd, *J* = 13.8, 2.7 Hz, 1H), 2.01 (t, *J* = 2.6 Hz, 1H), 1.76 (dd, *J* = 14.5, 10.3 Hz, 1H), 1.35 (ddt, *J* = 16.7, 8.4, 5.6 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 6H), 0.91-0.83 (m, 4H), 0.21 (q, *J* = 4.8 Hz, 1H). **13-C NMR (101 MHz; $CDCl_3$):** δ 170.24(C), 170.10(C), 79.2(C), 71.9(CH), 61.91(CH_2), 61.81(CH_2), 57.2(C), 35.1(CH_2), 29.9(CH_2), 22.8(CH_2), 18.1(CH), 14.7(CH), 14.1(2 x CH_3), 14.0(CH_2). **HRMS (EI**) m/z calcd for $C_{15}H_{21}O_4Br$ [$(M-C_3H_5O_2)^+$] 271.0334, found 271.0336.



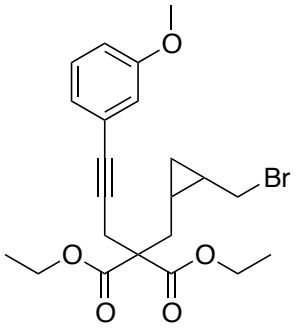
diethyl 2-((2-(bromomethyl)cyclopropyl)methyl)-2-(3-phenylprop-2-yn-1-yl) malonate (3.55)

To an oven dried pyrex screw cap tube loaded with a magnetic stirrer the Alcohol **3.64** (51 mg, 0.20 mmol), CBr_4 (66 mg, 0.20 mmol) and NaBr (0.041 g, 0.40 mmol) were added and dissolved in dry DMF. The mixture was exposed to 365 nm UV LED for 45 minutes. EtOAc was added and the organics were washed with water. Combined organics were dried with $MgSO_4$, filtered and concentrated. Purification was done by flash chromatography (5% EtOAc: Hexanes) to yield 74% of **3.55** (0.043 g) of white solid. **IR (thin film):** 1733, 660cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 7.35-7.31 (m, 2H), 7.25 (dd, *J* = 6.4, 2.4 Hz, 3H), 4.28-4.14 (m, 4H), 3.50 (dd, *J* = 10.3, 8.0 Hz, 1H), 3.42 (dd, *J* = 10.3, 8.4 Hz, 1H), 3.13 (q, *J* = 16.5 Hz, 2H), 2.61 (dd, *J* = 14.4, 2.5 Hz, 1H), 1.83 (ddd, *J* = 8.7, 8.4, 6.1 Hz, 1H), 1.36 (dtd, *J* = 12.4, 8.2, 4.2 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 6H), 0.97-0.89 (m, 2H), 0.27-0.21 (m, 1H). **13-C NMR (101 MHz; $CDCl_3$):** δ 170.2(C), 170.1(C), 131.6(2 x CH), 128.3(2 x CH), 128.0(CH), 123.1(C), 84.5(C), 83.8(C), 61.7(CH_2), 61.6(CH_2), 57.4(C), 35.0(CH_2), 30.1(CH_2), 23.7(CH_2), 18.0(CH), 14.7(CH), 14.1(2 x CH_3), 14.0(CH_2). **HRMS (EI)** m/z calcd for $C_{21}H_{25}O_4Br$ 420.0936, found 420.0938.



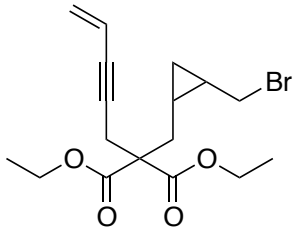
diethyl 2-((2-(bromomethyl)cyclopropyl)methyl)-2-(3-(4-methoxyphenyl)prop-2-yn-1-yl)malonate (3.72)

To an oven dried pyrex screw cap tube loaded with a magnetic stirrer the Alcohol **3.65** (78 mg, 0.20 mmol), CBr_4 (66 mg, 0.20 mmol) and NaBr (41 mg, 0.40 mmol) were added and dissolved in dry DMF. The mixture was exposed to 365 nm UV LED for 45 minutes. EtOAc was added and the organics were washed with water. Combined organics were dried with $MgSO_4$, filtered and concentrated. Purification was done by flash chromatography (5% EtOAc: Hexanes) to yield 50% of **3.72** (42 mg) colorless oil. **IR (thin film):** 1730, 1031,628 cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 7.29 (t, *J* = 2.4 Hz, 1H), 7.27 (t, *J* = 2.4 Hz, 1H), 6.81 (t, *J* = 2.4 Hz, 1H), 6.78 (t, *J* = 2.4 Hz, 1H), 4.29-4.15 (m, 4H), 3.78 (s, 3H), 3.53-3.42 (m, 2H), 3.16 (d, *J* = 17.2 Hz, 1H), 3.09 (d, *J* = 17.2 Hz, 1H), 2.62 (dd, *J* = 14.1, 2.9 Hz, 1H), 1.88-1.79 (m, 1H), 1.37 (quintetd, *J* = 8.3, 5.5 Hz, 1H), 1.26 (dt, *J* = 7.1, 1.1 Hz, 7H), 1.00-0.90 (m, 2H), 0.29-0.22 (m, 1H). **13-C NMR (101 MHz; $CDCl_3$):** δ 170.41(C), 170.29(C), 159.5(C), 133.1(2 x CH), 115.4(C), 114.0(2 x CH), 83.7(C), 83.0(C), 61.7(CH_2), 61.6(CH_2), 57.5(C), 55.4(CH_3), 35.2(CH_2), 30.1(CH_2), 23.8(CH_2), 18.1(CH), 14.8(CH), 14.21(2 x CH_3), 14.14(CH_2). **HRMS (EI)** m/z calcd for $C_{22}H_{27}O_5Br$ 450.1042, found 450.1050.



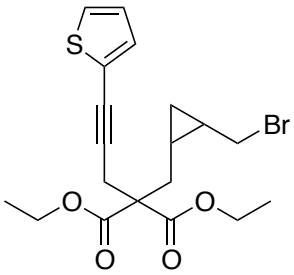
diethyl 2-((2-(bromomethyl)cyclopropyl)methyl)-2-(3-(3-methoxyphenyl)prop-2-yn-1-yl)malonate (3.73)

To an oven dried pyrex screw cap tube loaded with a magnetic stirrer the Alcohol **3.66** (0.20 mmol), CBr_4 (66 mg, 0.20 mmol) and NaBr (41 mg, 0.40 mmol) were added and dissolved in dry DMF. The mixture was exposed to 365 nm UV LED for 45 minutes. EtOAc was added and the organics were washed with water. Combined organics were dried with $MgSO_4$, filtered and concentrated. Purification was done by flash chromatography (5% EtOAc: Hexanes) to yield 83% of **3.73** (74 mg) as a colorless oil. **IR (thin film):** 1733, 1041, 686 cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 7.18 (t, *J* = 7.9 Hz, 1H), 6.95 (dt, *J* = 7.6, 1.2 Hz, 1H), 6.88 (t, *J* = 1.8 Hz, 1H), 6.84 (ddd, *J* = 8.3, 2.6, 0.7 Hz, 1H), 4.30-4.16 (m, 4H), 3.78 (s, 3H), 3.52 (dd, *J* = 10.4, 8.0 Hz, 1H), 3.45 (dd, *J* = 10.4, 8.3 Hz, 1H), 3.18 (d, *J* = 17.3 Hz, 1H), 3.11 (d, *J* = 17.3 Hz, 1H), 2.65-2.61 (m, 1H), 1.88-1.80 (m, 1H), 1.38 (quintetd, *J* = 8.3, 5.5 Hz, 1H), 1.27 (td, *J* = 7.1, 1.0 Hz, 6H), 1.01-0.91 (m, 2H), 0.29-0.23 (m, 1H). **13-C NMR (101 MHz; $CDCl_3$):** δ 170.3(C), 170.2(C), 159.4(C), 129.4(CH), 124.3(CH), 124.2(C), 116.7(CH), 114.7(CH), 84.5(C), 83.8(C), 61.8(CH_2), 61.7(CH_2), 57.5(C), 55.4(CH_3), 35.2(CH_2), 30.2(CH_2), 23.8(CH_2), 18.2(CH), 14.8(CH), 14.2(2 x CH_3), 14.1(CH_2). **HRMS (EI**) m/z calcd for $C_{22}H_{27}O_5Br$ 450.1042, found 450.1002.



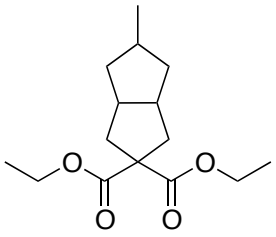
diethyl 2-((2-(bromomethyl)cyclopropyl)methyl)-2-(pent-4-en-2-yn-1-yl)malonate (3.54)

To an oven dried pyrex screw cap tube loaded with a magnetic stirrer the Alcohol **3.70** (74 mg, 0.20 mmol), CBr_4 (66 mg, 0.20 mmol) and NaBr (41 mg, 0.40 mmol) were added and dissolved in dry DMF. The mixture was exposed to 365 nm UV LED for 45 minutes. EtOAc was added and the organics were washed with water. Combined organics were dried with $MgSO_4$, filtered and concentrated. Purification was done by flash chromatography (5% EtOAc: Hexanes) to yield 49% of **3.54** (22 mg) as a yellow oil. **IR (thin film):** 1733, 748 cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 5.71 (ddt, *J* = 17.5, 11.0, 2.0 Hz, 1H), 5.53 (dd, *J* = 17.5, 2.2 Hz, 1H), 5.39 (dd, *J* = 11.0, 2.2 Hz, 1H), 4.26-4.12 (m, 5H), 3.49 (dd, *J* = 10.4, 8.0 Hz, 1H), 3.41 (dd, *J* = 10.3, 8.2 Hz, 1H), 3.09-2.96 (m, 2H), 2.57-2.52 (m, 1H), 1.75 (ddt, *J* = 12.6, 6.0, 3.1 Hz, 1H), 1.35 (dt, *J* = 8.3, 5.6 Hz, 1H), 1.24 (td, *J* = 7.1, 0.8 Hz, 8H), 0.92-0.84 (m, 4H), 0.20 (dt, *J* = 5.8, 3.2 Hz, 1H). **13-C NMR (101 MHz; $CDCl_3$):** δ 170.36(C), 170.24(C), 126.9(CH_2), 117.1(CH), 85.2(C), 82.6(C), 61.8(CH_2), 61.7(CH_2), 57.4(C), 35.2(CH_2), 30.1(CH_2), 23.7(CH), 18.1(CH), 14.8(2 x CH_3), 14.2(CH_2). **HRMS (EI**) m/z calcd for $C_{17}H_{23}BrO_4$ [$(M-Br)^+$] 291.1596, found 291.1676.



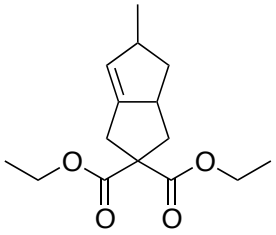
diethyl 2-((2-(bromomethyl)cyclopropyl)methyl)-2-(3-(thiophen-2-yl)prop-2-yn-1-yl)malonate (3.53)

To an oven dried pyrex screw cap tube loaded with a magnetic stirrer the Alcohol **3.71** (68 mg, 0.20 mmol), CBr_4 (66 mg, 0.20 mmol) and NaBr (41 mg, 0.40 mmol) were added and dissolved in dry DMF. The mixture was exposed to 365 nm UV LED for 45 minutes. EtOAc was added and the organics were washed with water. Combined organics were dried with $MgSO_4$, filtered and concentrated. Purification was done by flash chromatography (5% EtOAc: Hexanes) to yield 87% of **3.53** (68 mg) as a yellow oil. **IR (thin film):** 1733, 1184, 698 cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 7.18 (dd, *J* = 5.2, 1.0 Hz, 1H), 7.10 (d, *J* = 3.5 Hz, 1H), 6.92 (dd, *J* = 5.1, 3.6 Hz, 1H), 4.29-4.15 (m, 4H), 3.51 (dd, *J* = 10.4, 8.0 Hz, 1H), 3.43 (dd, *J* = 10.3, 8.4 Hz, 1H), 3.16 (q, *J* = 16.8 Hz, 2H), 2.60 (dd, *J* = 15.8, 2.4 Hz, 1H), 1.86-1.77 (m, 1H), 1.38 (ddt, *J* = 12.5, 8.3, 4.2 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 6H), 0.97-0.91 (m, 2H), 0.28-0.21 (m, 1H). **13-C NMR (101 MHz; $CDCl_3$):** δ 170.2(C), 170.1(C), 131.7(CH), 126.9(CH), 126.7(CH), 123.2(C), 88.7(C), 77.0(C), 61.8(CH_2), 61.7(CH_2), 57.4(C), 35.1(CH_2), 30.2(CH_2), 24.1(CH_2), 18.1(CH), 14.8(CH), 14.20(2 x CH_3), 14.17(CH_2). **HRMS (ESI**) m/z calcd for $C_{19}H_{23}O_4Br$ 426.0500, found 426.0501.



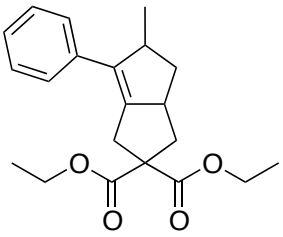
diethyl 5-methylhexahydropentalene-2,2(1*H*)-dicarboxylate (3.15)

To an oven dried pyrex screw cap tube loaded with a magnetic stirrer alcohol **3.63** (57 mg, 0.20 mmol), CBr_4 (66 mg, 0.20 mmol) and NaBr (41 mg, 0.40 mmol) were added and dissolved in dry DMF. The mixture was stirred in front of UV LED for 45 minutes. Water (36 uL, 2.0 mmol) was then added to the mixture and stirred for 10 minutes before adding TMEDA (0.15 mL, 1.0 mmol) and stirred for an additional 10 minutes. The gold catalyst (6 mg, 0.005 mmol) was added and the reaction was degased by argon sparging. This was exposed to UV LED and stirred for 45 to 90 minutes. Once the reaction is completed, ethyl acetate was added and the organics were washed with water, dried with MgSO4, filtered and concentrated. Purification was done by chromatography (1-5% EtOAc: Hexanes) to yield 48% of **3.15** (26 mg) as a colorless oil. **IR (thin film):** 1728, 1240 cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 4.20-4.12 (m, 4H), 2.60-2.44 (m, 4H), 2.09-1.91 (m, 2H), 1.88-1.82 (m, 1H), 1.65-1.58 (m, 1H), 1.50 (dd, *J* = 12.8, 5.8 Hz, 1H), 1.23 (m, 6H), 1.18-1.13 (m, 1H), 0.97 (dd, *J* = 6.1, 1.8 Hz, 3H), 0.90 (m, 1H). **13-C NMR (101 MHz; $CDCl_3$):** δ 172.5(C), 172.2(C), 64.5(C), 61.3(2 x CH_2), 44.0(CH), 42.8(CH_2), 42.2(CH), 41.9(CH_2), 41.4(CH_2), 41.0(CH_2), 39.5(CH), 19.7(CH_3), 18.9(CH_3), 14.2(CH_3). **HRMS (EI**) m/z calcd for $C_{15}H_{24}O_4$ [$(M-C_3H_5O_2)^+$] 195.1385, found 195.1331.

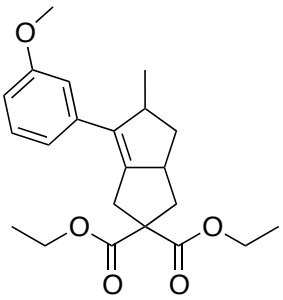


diethyl 5-methyl-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (3.35)

To an oven dried pyrex screw cap tube loaded with a magnetic stirrer alcohol **3.23** (34 mg, 0.20 mmol), CBr_4 (66 mg, 0.20 mmol) and NaBr (41 mg, 0.40 mmol) were added and dissolved in dry DMF. The mixture was stirred in front of UV LED for 45 minutes. Water (36uL, 2.0 mmol) was then added to the mixture and stirred for 10 minutes before adding TMEDA (0.15 mL, 1.0 mmol) and stirred for an additional 10 minutes. The gold catalyst (6 mg, 0.005 mmol) was added and the reaction was degased by argon sparging. This was exposed to UV LED and stirred for 45 to 90 minutes. Once the reaction is completed, ethyl acetate was added and the organics were washed with water, dried with MgSO4, filtered and concentrated. Purification was done by chromatography (1-5% EtOAc: Hexanes) to yield the desired mixture of products in 53% of **3.35** (28 mg) as a colorless oil. **IR (thin film):** 2952, 1730 cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 5.17 (bs, 1H), 4.18 (qd, *J* = 7.1, 5.7 Hz, 4H), 3.05-2.98 (m, 2H), 2.84 (m, *J* = 2H), 2.48 (dd, *J* = 12.8, 7.6 Hz, 1H), 2.26 (dt, *J* = 12.0, 6.6 Hz, 1H), 1.68 (dd, *J* = 12.6, 10.9 Hz, 1H), 1.24 (dt, *J* = 7.1, 3.4 Hz, 6H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.97 (dt, *J* = 12.0, 9.4 Hz, 2H). **13-C NMR (101 MHz; $CDCl_3$):** δ 172.6(C), 172.1(C), 149.0(C), 126.1(CH), 63.6(C), 61.6(CH_2), 61.5(CH_2), 51.0(CH), 46.0(CH), 41.8(CH_2), 40.4(CH_2), 33.0(CH_2), 21.4(CH_3), 14.2(2 x CH_3). **HRMS (EI**) m/z calcd for $C_{15}H_{22}O_4$ 266.1518, found 266.1518.

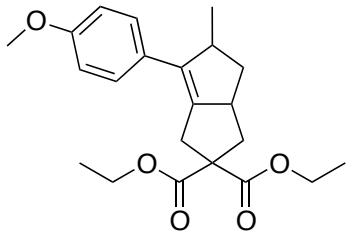


diethyl 5-methyl-6-phenyl-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (3.38) To an oven dried pyrex screw cap tube loaded with a magnetic stirrer alcohol **3.64** (84 mg, 0.20 mmol), CBr_4 (66 mg, 0.20 mmol) and NaBr (41 mg, 0.40 mmol) were added and dissolved in dry DMF. The mixture was stirred in front of UV LED for 45 minutes. Water (36uL, 2.0 mmol) was then added to the mixture and stirred for 10 minutes before adding TMEDA (0.15 mL, 1.0 mmol) and stirred for an additional 10 minutes. The gold catalyst (6 mg, 0.005 mmol) was added and the reaction was degased by argon sparging. This was exposed to UV LED and stirred for 45 to 90 minutes. Once the reaction is completed, ethyl acetate was added and the organics were washed with water, dried with MgSO4, filtered and concentrated. Purification was done by chromatography (1-5% EtOAc: Hexanes) to yield the desired product in 55% of **3.38**(38 mg) as a colorless oil. **IR (thin film):** 1728, 1654, 1558 cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 7.32-7.23 (m, 4H), 7.17 (tt, *J* = 7.1, 1.7 Hz, 1H), 4.22-4.13 (m, 4H), 3.49-3.41 (m, 1H), 3.18 (dt, *J* = 17.7, 2.2 Hz, 1H), 3.10-3.00 (m, 1H), 2.85 (ddd, *J* = 17.7, 3.7, 2.0 Hz, 1H), 2.59 (dd, *J* = 12.5, 7.3 Hz, 1H), 2.36 (dt, *J* = 11.9, 6.6 Hz, 1H), 1.75 (dd, *J* = 12.5, 11.4 Hz, 1H), 1.23 (dd, *J* = 14.2, 10.9 Hz, 6H), 1.13 (dt, *J* = 11.9, 9.9 Hz, 1H), 1.02 (d, *J* = 6.8 Hz, 3H). **13-C NMR (101 MHz; $CDCl_3$):** δ 172.3(C), 172.1(C), 145.7(C), 137.6(C), 135.6(C), 128.3(2 x CH), 127.4(2 x CH), 126.2(CH), 63.9(C), 61.6(2 x CH_2), 50.1(CH), 47.5(CH), 40.5(CH_2), 40.1(CH_2), 33.1(CH_2), 20.7(CH_3), 14.2(CH_3), 14.1(CH_3). **HRMS (EI)** m/z calcd for $C_{21}H_{26}O_4$ 342.1831, found 342.1843.



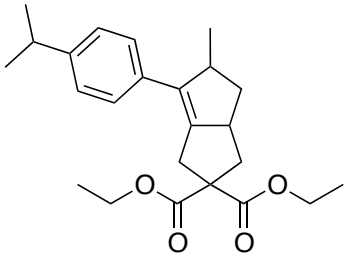
Diethyl 6-(3-methoxyphenyl)-5-methyl-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (3.56)

To an oven dried pyrex screw cap tube loaded with a magnetic stirrer alcohol **3.66** (78 mg, 0.20 mmol), CBr_4 (66 mg, 0.20 mmol) and NaBr (41 mg, 0.40 mmol) were added and dissolved in dry DMF. The mixture was stirred in front of UV LED for 45 minutes. Water (36uL, 2.0 mmol) was then added to the mixture and stirred for 10 minutes before adding TMEDA (0.15 mL, 1.0 mmol) and stirred for an additional 10 minutes. The gold catalyst (6 mg, 0.005 mmol) was added and the reaction was degased by argon sparging. This was exposed to UV LED and stirred for 45 to 90 minutes. Once the reaction is completed, ethyl acetate was added and the organics were washed with water, dried with MgSO4, filtered and concentrated. Purification was done by chromatography (1-5% EtOAc: Hexanes) to yield the product in 46% of **3.56** (35 mg) as a colorless oil. **IR (thin film):** 1733, 1558 cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 7.24 (t, *J* = 7.9 Hz, 1H), 6.86 (dt, *J* = 7.7, 1.5 Hz, 1H), 6.81 (t, *J* = 2.0 Hz, 1H), 6.75 (ddd, *J* = 8.3, 2.6, 0.8 Hz, 1H), 4.24-4.15 (m, 4H), 3.81 (s, 3H), 3.49-3.41 (m, 1H), 3.19 (dt, *J* = 17.8, 2.2 Hz, 1H), 3.10-3.01 (m, 1H), 2.87 (ddd, *J* = 17.7, 3.6, 2.0 Hz, 1H), 2.60 (dd, *J* = 12.6, 7.3 Hz, 1H), 2.37 (dt, *J* = 11.9, 6.5 Hz, 1H), 1.77 (dd, *J* = 12.5, 11.4 Hz, 1H), 1.25 (dt, *J* = 10.0, 7.1 Hz, 6H), 1.13 (dt, *J* = 11.9, 9.8 Hz, 1H), 1.04 (d, *J* = 6.8 Hz, 3H). **13-C NMR (101 MHz; $CDCl_3$):** δ 172.3(C), 172.1(C), 159.6(C), 145.9(C), 139.0(C), 135.5(C), 129.2(CH), 120.0(CH), 113.2(CH), 111.6(CH), 63.9(C), 61.7(2x CH_2), 55.3(CH_3), 50.1(CH), 47.5(CH), 40.5(CH_2), 40.0(CH_2), 33.2(CH_2), 20.7(CH_3), 14.2(CH_3), 14.1(CH_3). **HRMS (EI**) m/z calcd for $C_{22}H_{28}O_5$ 372.4547, found 372.4540.



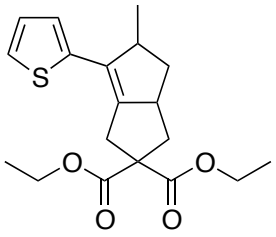
diethyl 6-(4-methoxyphenyl)-5-methyl-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (3.58)

To an oven dried pyrex screw cap tube loaded with a magnetic stirrer alcohol **3.65** (78 mg, 0.20 mmol), CBr_4 (66 mg, 0.20 mmol) and NaBr (41 mg, 0.40 mmol) were added and dissolved in dry DMF. The mixture was stirred in front of UV LED for 45 minutes. Water (36uL, 2.0 mmol) was then added to the mixture and stirred for 10 minutes before adding TMEDA (0.15 mL, 1.0 mmol) and stirred for an additional 10 minutes. The gold catalyst (6 mg, 0.005 mmol) was added and the reaction was degased by argon sparging. This was exposed to UV LED and stirred for 45 to 90 minutes. Once the reaction is completed, ethyl acetate was added and the organics were washed with water, dried with MgSO4, filtered and concentrated. Purification was done by chromatography (1-5% EtOAc: Hexanes) to yield the desired product in 58% of **3.58** (43 mg) as a colorless oil. **IR (thin film):** 1735, 1534 cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 7.22-7.19 (m, 2H), 6.88-6.85 (m, 2H), 4.23-4.15 (m, 4H), 3.80 (s, 3H), 3.46-3.39 (m, 1H), 3.16 (dt, *J* = 17.7, 2.3 Hz, 1H), 3.08-3.00 (m, 1H), 2.86 (ddd, *J* = 17.7, 3.9, 1.9 Hz, 1H), 2.59 (dd, *J* = 12.5, 7.3 Hz, 1H), 2.36 (dt, *J* = 12.0, 6.6 Hz, 1H), 1.75 (dd, *J* = 12.4, 11.3 Hz, 1H), 1.25 (dt, *J* = 9.2, 7.1 Hz, 7H), 1.14 (m, *J* = 2.9 Hz, 2H), 1.03 (d, *J* = 6.8 Hz, 2H), 0.90-0.83 (m, 2H). **13-C NMR (101 MHz; $CDCl_3$):** δ 172.4(C), 172.2(C), 158.0(C), 144.4(C), 135.1(C), 130.0(C), 128.5(2 x CH), 113.7(2 x CH), 64.0(C), 61.6(2 x CH_2), 55.4(CH_3), 50.0(CH), 47.5(CH), 40.6(CH_2), 40.2(CH_2), 33.2(CH_2), 20.9(CH_3), 14.24(CH_3), 14.20(CH_3). **HRMS (EI**) m/z calcd for $C_{22}H_{28}O_5$ 372.1937, found 372.1933.



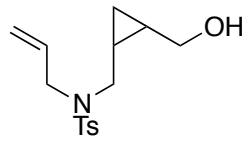
diethyl 6-(4-isopropylphenyl)-5-methyl-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (3.57)

To an oven dried pyrex screw cap tube loaded with a magnetic stirrer alcohol **3.68** (80 mg, 0.20 mmol), CBr_4 (66 mg, 0.20 mmol) and NaBr (41 mg, 0.40 mmol) were added and dissolved in dry DMF. The mixture was stirred in front of UV LED for 45 minutes. Water (36uL, 2.0 mmol) was then added to the mixture and stirred for 10 minutes before adding TMEDA (0.15 mL, 1.0 mmol) and stirred for an additional 10 minutes. The gold catalyst (6 mg, 0.005 mmol) was added and the reaction was degased by argon sparging. This was exposed to UV LED and stirred for 45 to 90 minutes. Once the reaction is completed, ethyl acetate was added and the organics were washed with water, dried with MgSO4, filtered and concentrated. Purification was done by chromatography (1-5% EtOAc: Hexanes) to yield the desired product in 49% of **3.57** (38 mg) as a colorless oil. **IR (thin film):** 2918, 1733, 748cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 7.21-7.16 (m, 4H), 4.25-4.15 (m, 4H), 3.49-3.41 (m, 1H), 3.20 (dt, *J* = 17.8, 2.3 Hz, 1H), 3.09-3.00 (m, 1H), 2.92-2.83 (m, 2H), 2.59 (dd, *J* = 12.5, 7.3 Hz, 1H), 2.36 (dt, *J* = 11.9, 6.6 Hz, 1H), 1.79-1.72 (m, 1H), 1.28-1.21 (m, 13H), 1.19-1.09 (m, 2H), 1.05 (d, *J* = 6.8 Hz, 3H). **13-C NMR (101 MHz; $CDCl_3$):** δ 172.4(C), 172.1(C), 146.8(C), 145.1(C), 135.5(C), 134.9(C), 127.3(2 x CH), 126.3(2 x CH), 64.0(C), 61.6(2 x CH_2), 50.1(CH), 47.5(CH), 40.5(CH_2), 40.1(CH_2), 33.9(CH), 33.3(CH_2), 24.1(2 x CH_3), 20.9(CH_3), 14.2(CH_3), 14.1(CH_3).



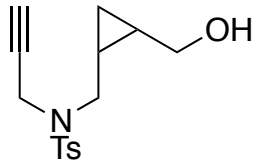
diethyl 5-methyl-6-(thiophen-2-yl)-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (3.40)

To an oven dried pyrex screw cap tube loaded with a magnetic stirrer alcohol **3.71** (85 mg, 0.20 mmol), CBr_4 (66 mg, 0.20 mmol) and NaBr (41 mg, 0.40 mmol) were added and dissolved in dry DMF. The mixture was stirred in front of UV LED for 45 minutes. Water (36uL, 2.0 mmol) was then added to the mixture and stirred for 10 minutes before adding TMEDA (0.15 mL, 1.0 mmol) and stirred for an additional 10 minutes. The gold catalyst (6 mg, 0.005 mmol) was added and the reaction was degased by argon sparging. This was exposed to UV LED and stirred for 45 to 90 minutes. Once the reaction is completed, ethyl acetate was added and the organics were washed with water, dried with MgSO4, filtered and concentrated. Purification was done by chromatography (1-5% EtOAc: Hexanes) to yield the desired mixture of products in 49% of **3.40** (35 mg) as a yellow oil. **IR (thin film):** 3689, 1730, 690 cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 7.22 (dd, *J* = 5.1, 1.0 Hz, 1H), 7.02 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.94 (dd, *J* = 3.6, 0.3 Hz, 1H), 4.25-4.01 (m, 5H), 3.71 (m, *J* = 4.3, 2.2 Hz, 1H), 2.81-2.70 (m, 3H), 2.50 (ddd, *J* = 13.0, 7.7, 1.5 Hz, 1H), 2.33 (m, 1H), 1.98 (dd, *J* = 13.2, 6.6 Hz, 2H), 1.91 (d, *J* = 1.5 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 6H), 1.17 (t, *J* = 7.1 Hz, 3H), 0.90-0.83 (m, 1H). **13-C NMR (101 MHz; $CDCl_3$):** δ 172.3(C), 171.6(C), 140.2(C), 134.3(C), 131.3(C), 126.8(CH), 125.0(CH), 124.0(CH), 62.1(C), 61.4(CH_2), 61.3(CH_2), 54.0(CH), 46.1(CH_2), 42.0(CH_2), 40.1(CH_2), 38.5(CH), 16.2(CH_3), 14.22(CH_3), 14.12(CH_3). **HRMS (EI**) m/z calcd for $C_{19}H_{24}O_4$ 348.1395, found 348.1429.



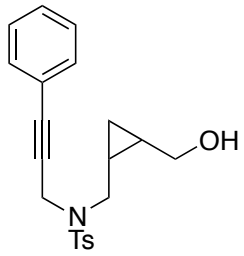
***N*-allyl-*N*-((2-(hydroxymethyl)cyclopropyl)methyl)-4-methylbenzene sulfonamide (3.74)**

To a flame dried flask loaded with a magnetic stirrer, Diiodomethane (0.79 mL, 9.8 mmol) was added to dichloromethane (15 mL). The mixture was cooled to 0°C before a 1M solution of diethylzinc (9.8 mL, 9.8 mmol) was added dropwise. This was stirred for 45 minutes before the mixture was cooled to -78°C. The alcohol **3.27** in dichloromethane was added dropwise. Stirred for 30 minutes at -78°C and then warmed to -20°C. Addition of more diiodomethane (0.79 mL, 9.8 mmol) at this point pushed the reaction to completion. The reaction was quenched by slowly adding ammonium chloride and stirred for 30 minutes. Extracted with dichloromethane, the combined organics were dried with $MgSO_4$ and concentrated. Purification by flash chromatography (20% EtOAc: Hexanes) yielded 59% of **3.74** (0.339 g) as a colorless oil. **IR (thin film):** 1683, 1018, 657 cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 5.65 (ddt, *J* = 17.1, 10.4, 6.5 Hz, 1H), 5.24-5.13 (m, 2H), 3.97-3.84 (m, 3H), 3.46 (dd, *J* = 12.1, 9.3 Hz, 1H), 3.36 (dd, *J* = 14.3, 7.8 Hz, 1H), 3.07 (dd, *J* = 14.6, 6.2 Hz, 1H), 2.43 (s, 3H), 1.31-1.21 (m, 1H), 1.13 (dd, *J* = 14.1, 8.2 Hz, 1H), 0.78 (dt, *J* = 8.6, 5.0 Hz, 1H), 0.14 (q, *J* = 5.5 Hz, 1H). **13-C NMR (101 MHz; $CDCl_3$):** δ 143.5(C), 136.8(C), 133.2(CH), 129.9(2 x CH), 127.4(2 x CH), 119.0(CH_2), 62.3(CH_2), 50.7(CH_2), 46.9(CH_2), 21.7(CH_3), 19.1(CH), 14.9(CH), 8.7(CH_2). **HRMS (EI**) m/z calcd for $C_{15}H_{21}NO_3S$ 295.1242, found 294.1178.



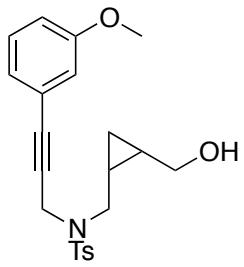
***N*-((2-(hydroxymethyl)cyclopropyl)methyl)-4-methyl-*N*-(prop-2-yn-1-yl) benzenesulfonamide (3.75)**

To a flame dried flask loaded with a magnetic stirrer, Diiodomethane (0.69 mL, 8.6 mmol) was added to dichloromethane (15 mL). The mixture was cooled to 0°C before a 1M solution of diethylzinc (8.6 mL, 8.6 mmol) was added dropwise. This was stirred for 45 minutes before the mixture was cooled to -78°C. The alcohol **3.27** in dichloromethane was added dropwise. Stirred for 30 minutes at -78°C and then warmed to -20°C. Addition of more diiodomethane (0.69 mL, 8.6 mmol) at this point pushed the reaction to completion. The reaction was quenched by slowly adding ammonium chloride and stirred for 30 minutes. Extracted with dichloromethane, the combined organics were dried with $MgSO_4$ and concentrated. Purification by flash chromatography (20% EtOAc: Hexanes) yielded 52% of **3.75** (0.262 g) as a colorless oil. **IR (thin film):** 3272, 2956, 1338 cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 7.72 (dt, *J* = 1.88, 8.4 Hz, 2H), 7.29 (m, 2H), 4.39 (ddd, *J* = 18.5, 2.5, 0.9 Hz, 1H), 4.20 (dd, *J* = 18.5, 2.4 Hz, 1H), 3.88 (dd, *J* = 12.0, 5.5 Hz, 1H), 3.49 (dd, *J* = 12.1, 9.2 Hz, 1H), 3.34 (ddd, *J* = 13.9, 8.5, 0.4 Hz, 1H), 3.23 (dd, *J* = 13.8, 6.2 Hz, 1H), 2.42 (s, 3H), 2.01 (t, *J* = 2.5 Hz, 1H), 1.34-1.25 (m, 2H), 1.21-1.12 (m, 2H), 0.83 (dt, *J* = 8.5, 5.0 Hz, 2H), 0.24 (q, *J* = 5.4 Hz, 1H). **13-C NMR (101 MHz; $CDCl_3$):** δ 143.9(C), 135.5(C), 129.7(2 x CH), 128.0 (2 x CH), 76.5(C), 74.2(CH), 62.3(CH_2), 45.9(CH_2), 36.3(CH_2), 21.7(CH_3), 18.8(CH), 14.0(CH), 8.4(CH_2). **HRMS (EI**) m/z calcd for $C_{15}H_{19}NO_3S$ [$(M\text{-}OH)^+$] 276.1058, found 276.1063.



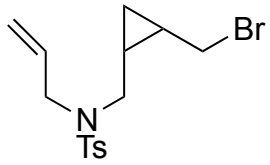
N-((2-(hydroxymethyl)cyclopropyl)methyl)-4-methyl-N-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (3.76)

To a flame dried flask loaded with a magnetic stirrer, copper iodide (11 mg, 0.060 mmol) and $Pd(PPh_3)_4$ (35 mg, 0.030 mmol) were added and dissolved in THF (4.0 mL). Alcohol **3.75** (0.30 g, 1.01 mmol), iodobenzene (0.18 mL, 1.6 mmol) and diisopropylethylamine (0.60 mL, 4.3 mmol) were added subsequently to the mixture. The reaction was then heated at 50°C for 2 hours. Dry pack with silica and purified by flash chromatography (% EtOAc: Hexanes) to yield 90% of **3.76** (0.35 g) as a colorless oil. **IR (thin film):** 3325, 1683, 657 cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 7.78-7.75 (m, 2H), 7.31-7.21 (m, 7H), 7.05-7.03 (m, 2H), 4.61 (dd, *J* = 18.7, 0.6 Hz, 1H), 4.40 (d, *J* = 18.7 Hz, 1H), 3.92 (dd, *J* = 12.1, 5.4 Hz, 1H), 3.53 (dd, *J* = 12.1, 9.2 Hz, 1H), 3.34 (qd, *J* = 13.9, 7.6 Hz, 2H), 2.33 (s, 3H), 1.37-1.28 (m, 1H), 1.22 (qt, *J* = 8.3, 5.9 Hz, 1H), 0.86 (td, *J* = 8.5, 5.0 Hz, 1H), 0.27 (q, *J* = 5.4 Hz, 1H). **13-C NMR (101 MHz; $CDCl_3$):** δ 143.8(C), 135.4(C), 131.6(2 x CH), 129.7(2 x CH), 128.6(CH), 128.3(2 x CH), 128.1(2 x CH), 122.2(C), 86.1(C), 81.6(C), 62.4(CH_2), 46.1(CH_2), 37.2(CH_2), 21.6(CH_3), 18.8(CH), 14.0(CH), 8.5(CH_3). **HRMS (ESI**) m/z calcd for $C_{21}H_{23}NO_3S$ 369.1399, found 369.1399.



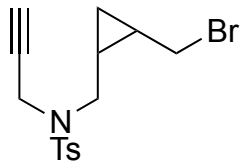
***N*-((2-(hydroxymethyl)cyclopropyl)methyl)-*N*-(3-(3-methoxyphenyl)prop-2-yn-1-yl)-4-methylbenzenesulfonamide (3.77)**

To a flame dried flask loaded with a magnetic stirrer, copper iodide (11 mg, 0.060 mmol) and $Pd(PPh_3)_4$ (35 mg, 0.030 mmol) were added and dissolved in THF (4.0 mL). Alcohol **3.75** (0.30 g, 1.1 mmol), 3-iodoanisole (0.20 mL, 1.6 mmol) and diisopropylethylamine (0.60 mL, 4.3 mmol) were added subsequently to the mixture. The reaction was then heated at 50°C for 2 hours. Dry pack with silica and purified by flash chromatography (% EtOAc: Hexanes) to yield 80% of **3.77** (0.147 g) as a colorless oil. **IR (thin film):** 3629, 1157, 659 cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 7.78-7.75 (m, 2H), 7.27-7.25 (m, 4H), 7.14 (t, *J* = 8.0 Hz, 1H), 6.83 (ddd, *J* = 8.4, 2.6, 0.8 Hz, 1H), 6.63 (dt, *J* = 7.6, 1.1 Hz, 1H), 6.58 (dd, *J* = 2.5, 1.4 Hz, 1H), 4.60 (d, *J* = 18.9 Hz, 1H), 4.40 (d, *J* = 18.7 Hz, 1H), 3.91 (dd, *J* = 12.1, 5.4 Hz, 1H), 3.77 (s, 3H), 3.52 (dd, *J* = 12.1, 9.1 Hz, 1H), 3.34 (qd, *J* = 14.1, 7.2 Hz, 2H), 2.35 (s, 3H), 1.37-1.28 (m, 1H), 1.27-1.17 (m, 1H), 0.86 (dt, *J* = 8.5, 5.0 Hz, 1H), 0.27 (q, *J* = 5.4 Hz, 1H). **13-C NMR (101 MHz; $CDCl_3$):** δ 159.3(C), 143.9(C), 135.4(C), 129.7(2 x CH), 129.4(CH), 128.1(2 x CH), 124.1(CH), 123.2(C), 117.2(CH), 114.6(CH), 86.0(C), 81.4(C), 62.4(CH_2), 55.4(CH_3), 46.1(CH_2), 37.2(CH_2), 21.6(CH_3), 18.8(CH), 14.0(CH), 8.5(CH_2). **HRMS (EI**) m/z calcd for $C_{15}H_{18}O_2N$ [(M-$C_7H_7O_2S)^+$] 244.1338, found 244.1344.



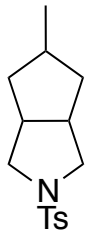
***N*-allyl-*N*-((2-(bromomethyl)cyclopropyl)methyl)-4-methylbenzenesulfonamide (3.32)**

To an oven dried pyrex screw cap tube loaded with a magnetic stirrer the Alcohol **3.74** (59 mg, 0.20 mmol), CBr_4 (66 mg, 0.20 mmol) and NaBr (41 mg, 0.40 mmol) were added and dissolved in dry DMF. The mixture was exposed to 365 nm UV LED for 45 minutes. EtOAc was added and the organics were washed with water. Combined organics were dried with $MgSO_4$, filtered and concentrated. Purification was done by flash chromatography (5% EtOAc: Hexanes) to yield 81% of **3.32** (59 mg) as a white solid. **IR(thin film):** 1153, 646 cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 7.73-7.68 (m, 2H), 7.33-7.29 (m, 2H), 5.69-5.58 (m, 1H), 5.21-5.13 (m, 2H), 3.90 (d, *J* = 6.2 Hz, 2H), 3.59-3.49 (m, 2H), 3.41-3.30 (m, 1H), 3.02 (ddd, *J* = 14.5, 8.8, 2.3 Hz, 1H), 2.43 (s, 3H), 1.50-1.40 (m, 1H), 1.30-1.21 (m, 2H), 1.00-0.94 (m, 1H), 0.90-0.84 (m, 1H), 0.39-0.35 (m, 1H). **13-C NMR (101 MHz; $CDCl_3$):** δ 13-C NMR (101 MHz; CDCl3): δ 143.4(C), 137.3(C), 133.4(CH), 129.9(2 x CH), 127.3(2 x CH), 118.9(CH_2), 50.4(CH_2), 46.2(CH_2), 34.8(CH_2), 21.7(CH_3), 19.7(CH), 18.0(CH), 14.2(CH_2). **HRMS (EI**) m/z calcd for $C_{15}H_{20}BrNO_2S$ [$(M\text{-}Br)^+$] 278.1215, found 278.1263.



***N*-((2-(bromomethyl)cyclopropyl)methyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzene sulfonamide (3.78)**

To an oven dried pyrex screw cap tube loaded with a magnetic stirrer the Alcohol **3.75** (56 mg, 0.20 mmol), CBr_4 (66 mg, 0.20 mmol) and NaBr (41 mg, 0.40 mmol) were added and dissolved in dry DMF. The mixture was exposed to 365 nm UV LED for 45 minutes. EtOAc was added and the organics were washed with water. Combined organics were dried with $MgSO_4$, filtered and concentrated. Purification was done by flash chromatography (5% EtOAc: Hexanes) to yield 77% of **3.78** (55 mg) as a white solid. **IR (thin film):** 1155, 892, 659 cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 7.73-7.69 (m, 2H), 7.29 (dd, *J* = 8.5, 0.6 Hz, 2H), 4.28 (ddd, *J* = 18.5, 2.5, 0.6 Hz, 1H), 4.22 (ddd, *J* = 18.5, 2.5, 0.4 Hz, 1H), 3.58 (dd, *J* = 8.7, 2.0 Hz, 1H), 3.55 (t, *J* = 3.2 Hz, 1H), 3.40 (dd, *J* = 10.7, 8.7 Hz, 1H), 3.07 (dd, *J* = 13.9, 8.4 Hz, 1H), 2.42 (s, 3H), 2.02 (t, *J* = 2.5 Hz, 1H), 1.49 (quintetd, *J* = 8.2, 5.7 Hz, 1H), 1.30 (qt, *J* = 8.4, 6.2 Hz, 1H), 1.02 (dt, *J* = 8.3, 5.3 Hz, 1H), 0.44 (q, *J* = 5.6 Hz, 1H). **13-C NMR (101 MHz; $CDCl_3$):** δ 143.7(C), 135.8(C), 129.6(2 x CH), 127.8(2 x CH), 76.6(C), 74.2(3), 45.2(CH_2), 36.1(CH_2), 34.5(CH_2), 21.7(CH_3), 19.4(CH), 17.2(CH), 13.7(CH_2). **HRMS (EI)** m/z calcd for $C_{15}H_{18}BrNO_2S$ $[(M-Br)^+]$ 276.1058, found 276.1056.

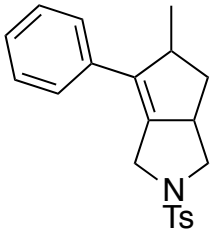


5-methyl-2-tosyloctahydrocyclopenta[*c*]pyrrole (3.34)

To an oven dried pyrex screw cap tube loaded with a magnetic stirrer alcohol **3.74** (59 mg, 0.20 mmol), CBr_4 (66 mg, 0.20 mmol) and NaBr (41 mg, 0.40 mmol) were added and dissolved in dry DMF. The mixture was stirred in front of UV LED for 45 minutes. Water (36uL, 2.0 mmol) was then added to the mixture and stirred for 10 minutes before adding TMEDA (0.15 mL, 1.0 mmol) and stirred for an additional 10 minutes. The gold catalyst (6 mg, 0.005 mmol) was added and the reaction was degased by argon sparging. This was exposed to UV LED and stirred for 45 to 90 minutes. Once the reaction is completed, ethyl acetate was added and the organics were washed with water, dried with MgSO4, filtered and concentrated. Purification was done by chromatography (1-5% EtOAc: Hexanes) to yield the desired mixture of products in 49% of **3.34** (20 mg) as a colorless oil. **IR (thin film):** 1340, 663 cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 7.68 (m, 2H), 7.32 (m, 2H), 3.13 (dd, *J* = 9.4, 1.3 Hz, 2H), 2.78 (dd, *J* = 9.5, 7.2 Hz, 2H), 2.51-2.46 (m, 2H), 2.43 (s, 3H), 1.98 (ddd, *J* = 13.0, 7.3, 6.0 Hz, 2H), 1.78 (qd, *J* = 12.0, 6.1 Hz, 1H), 0.97 (d, *J* = 6.5 Hz, 5H). **13-C NMR (101 MHz; $CDCl_3$):** δ 129.6(2 x CH), 128.2(2 x CH), 54.3(2 x CH_2), 42.9(2 x CH), 42.0(2 x CH_2), 37.0(CH), 21.7(CH_3), 19.0(CH_3). **HRMS (EI**) m/z calcd for $C_{15}H_{21}NO_2S$ 279.1293, found 279.1276.

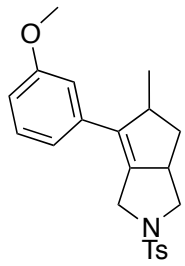
5-methyl-2-tosyl-1,2,3,3a,4,5-hexahydrocyclopenta[*c*]pyrrole (3.59)

To an oven dried pyrex screw cap tube loaded with a magnetic stirrer alcohol **3.75** (56 mg, 0.20 mmol), CBr_4 (66 mg, 0.20 mmol) and NaBr (41 mg, 0.40 mmol) were added and dissolved in dry DMF. The mixture was stirred in front of UV LED for 45 minutes. Water (36uL, 2.0 mmol) was then added to the mixture and stirred for 10 minutes before adding TMEDA (0.15 mL, 1.0 mmol) and stirred for an additional 10 minutes. The gold catalyst (6 mg, 0.005 mmol) was added and the reaction was degased by argon sparging. This was exposed to UV LED and stirred for 45 to 90 minutes. Once the reaction is completed, ethyl acetate was added and the organics were washed with water, dried with MgSO4, filtered and concentrated. Purification was done by chromatography (1-5% EtOAc: Hexanes) to yield the desired mixture of products in 49% of **3.59** (27 mg) as a colorless oil. **IR(thin film):** 1683, 1552, 666 cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 7.72-7.69 (m, 2H), 7.32 (m, 2H), 5.27 (s, 1H), 3.87-3.82 (m, 1H), 3.77-3.73 (m, 2H), 3.06-3.00 (m, 2H), 2.56 (t, *J* = 9.5 Hz, 1H), 2.43 (s, 3H), 2.20 (dt, *J* = 12.2, 6.5 Hz, 1H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.90 (dt, *J* = 12.2, 9.5 Hz, 1H). **13-C NMR (101 MHz; $CDCl_3$):** δ 144.3(C), 143.4(C), 134.6(C), 129.8(2 x CH), 127.6(CH), 127.6(2 x CH), 54.0(CH_2), 50.1(CH), 46.5(CH_2), 45.9(CH), 39.5(CH_2), 21.7(CH_3), 20.8(CH_3). **HRMS (EI**) m/z calcd for $C_{15}H_{19}NO_2S$ 277.1136, found 277.1126.



5-methyl-6-phenyl-2-tosyl-1,2,3,3a,4,5-hexahydrocyclopenta[*c*]pyrrole (3.60)

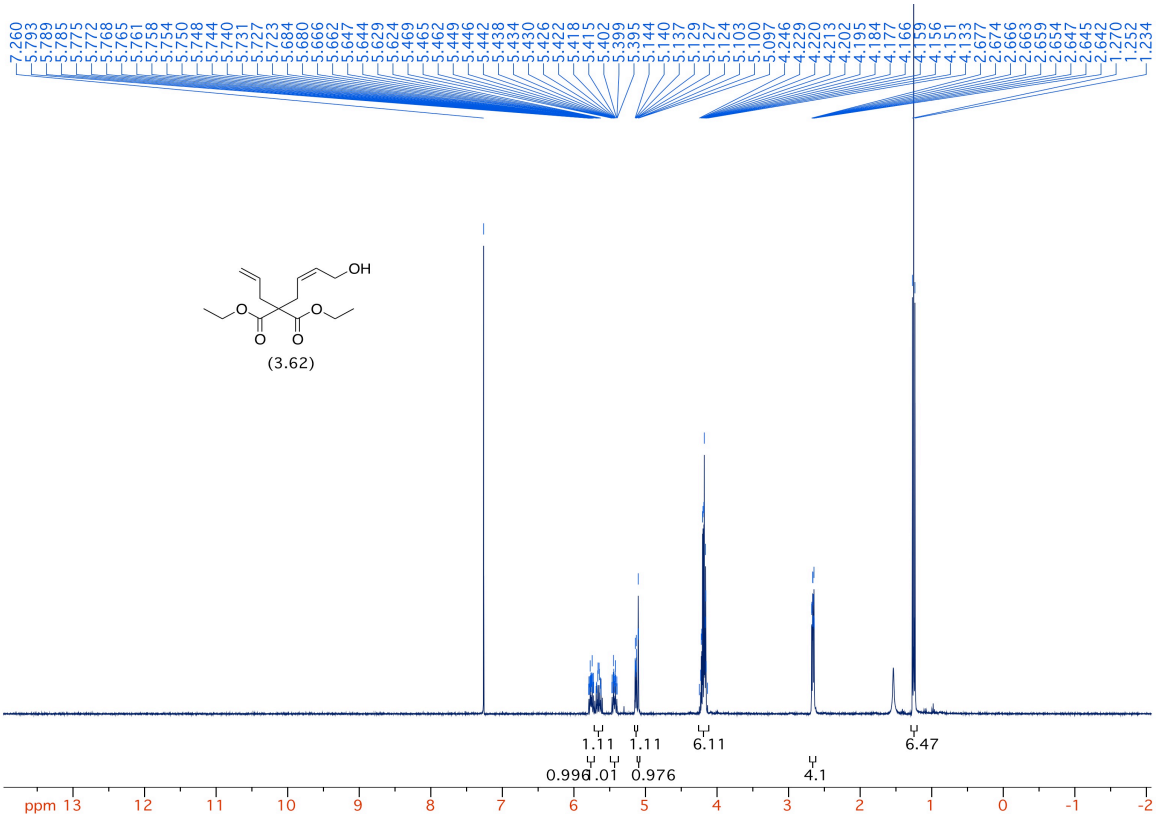
To an oven dried pyrex screw cap tube loaded with a magnetic stirrer alcohol **3.76** (74 mg, 0.20 mmol), CBr_4 (66 mg, 0.20 mmol) and NaBr (41 mg, 0.40 mmol) were added and dissolved in dry DMF. The mixture was stirred in front of UV LED for 45 minutes. Water (36uL, 2.0 mmol) was then added to the mixture and stirred for 10 minutes before adding TMEDA (0.15 mL, 1.0 mmol) and stirred for an additional 10 minutes. The gold catalyst (6 mg, 0.005 mmol) was added and the reaction was degased by argon sparging. This was exposed to UV LED and stirred for 45 to 90 minutes. Once the reaction is completed, ethyl acetate was added and the organics were washed with water, dried with MgSO4, filtered and concentrated. Purification was done by chromatography (1-5% EtOAc: Hexanes) to yield the desired product in 49% of **3.60** (33 mg) as a colorless oil. **IR (thin film):** 1091, 815, 661 cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 7.75-7.72 (m, 2H), 7.34-7.29 (m, 4H), 7.26-7.20 (m, 2H), 7.13-7.11 (m, 2H), 4.04 (dt, *J* = 14.5, 2.1 Hz, 1H), 3.88 (ddd, *J* = 14.5, 3.9, 2.1 Hz, 1H), 3.82 (dd, *J* = 9.0, 7.9 Hz, 1H), 3.44 (dtt, *J* = 9.8, 6.5, 3.3 Hz, 1H), 3.09 (ddt, *J* = 9.9, 7.4, 2.4 Hz, 1H), 2.70 (t, *J* = 9.7 Hz, 1H), 2.44 (s, 3H), 2.32 (dt, *J* = 12.2, 6.6 Hz, 1H), 1.12 (dt, *J* = 12.1, 9.8 Hz, 1H), 1.02 (d, *J* = 6.9 Hz, 3H). **13-C NMR (101 MHz; $CDCl_3$):** δ 143.6(C), 140.6(C), 137.7(C), 136.3(C), 134.5(C), 129.9(2 x CH), 128.5(2 x CH), 127.6(2 x CH), 127.3(2 x CH), 127.1(CH), 53.7(CH_2), 49.0(CH), 47.7(CH), 46.5(CH_2), 38.6(CH_2), 21.7(CH_3), 20.4(CH_3). **HRMS (EI)** m/z calcd for $C_{21}H_{23}NO_2S$ 353.1449, found 353.1477.



6-(3-methoxyphenyl)-5-methyl-2-tosyl-1,2,3,3a,4,5-hexahydrocyclopenta[*c*]pyrrole (3.61)

To an oven dried pyrex screw cap tube loaded with a magnetic stirrer alcohol **3.77** (80 mg, 0.20 mmol), CBr_4 (66 mg, 0.20 mmol) and NaBr (41 mg, 0.40 mmol) were added and dissolved in dry DMF. The mixture was stirred in front of UV LED for 45 minutes. Water (36uL, 2.0 mmol) was then added to the mixture and stirred for 10 minutes before adding TMEDA (0.15 mL, 1.0 mmol) and stirred for an additional 10 minutes. The gold catalyst (6 mg, 0.005 mmol) was added and the reaction was degased by argon sparging. This was exposed to UV LED and stirred for 45 to 90 minutes. Once the reaction is completed, ethyl acetate was added and the organics were washed with water, dried with MgSO4, filtered and concentrated. Purification was done by chromatography (1-5% EtOAc: Hexanes) to yield 49% of **3.61** (38 mg) as a colorless oil**. IR (thin film):** 1041, 661cm^{-1}. **1H-NMR (400 MHz; $CDCl_3$):** δ 7.74-7.71 (m, 2H), 7.33 (m, 2H), 7.23 (t, *J* = 7.9 Hz, 1H), 6.77 (ddd, *J* = 8.3, 2.6, 0.8 Hz, 1H), 6.70 (dt, *J* = 7.6, 1.1 Hz, 1H), 6.65 (dd, *J* = 2.4, 1.6 Hz, 1H), 4.04 (dt, *J* = 14.5, 2.1 Hz, 1H), 3.88 (ddd, *J* = 14.5, 3.9, 2.1 Hz, 1H), 3.84-3.81 (m, 1H), 3.80 (s, 3H), 3.45-3.39 (m, 1H), 3.11-3.06 (m, 1H), 2.69 (dd, *J* = 10.1, 9.3 Hz, 1H), 2.44 (s, 3H), 2.35-2.28 (m, 1H), 1.11 (dt, *J* = 12.1, 9.8 Hz, 1H), 1.02 (d, *J* = 6.9 Hz, 3H). **13-C NMR (101 MHz; $CDCl_3$):** δ 159.7(C), 143.6(C), 140.8(C), 137.6(C), 137.6(C), 134.5(C), 129.9(2 x CH), 129.5(CH), 127.6(2 x CH), 119.9(CH), 113.3(CH), 112.2(CH), 55.3(CH_3), 53.7(CH_2), 49.0(CH), 47.7(CH), 46.5(CH_2), 38.5(CH_2), 21.7(CH_3), 20.3(CH_3). **HRMS (EI**) m/z calcd for $C_{22}H_{25}NO_3S$ 383.1555, found 383.1570.

6. Supplemental Information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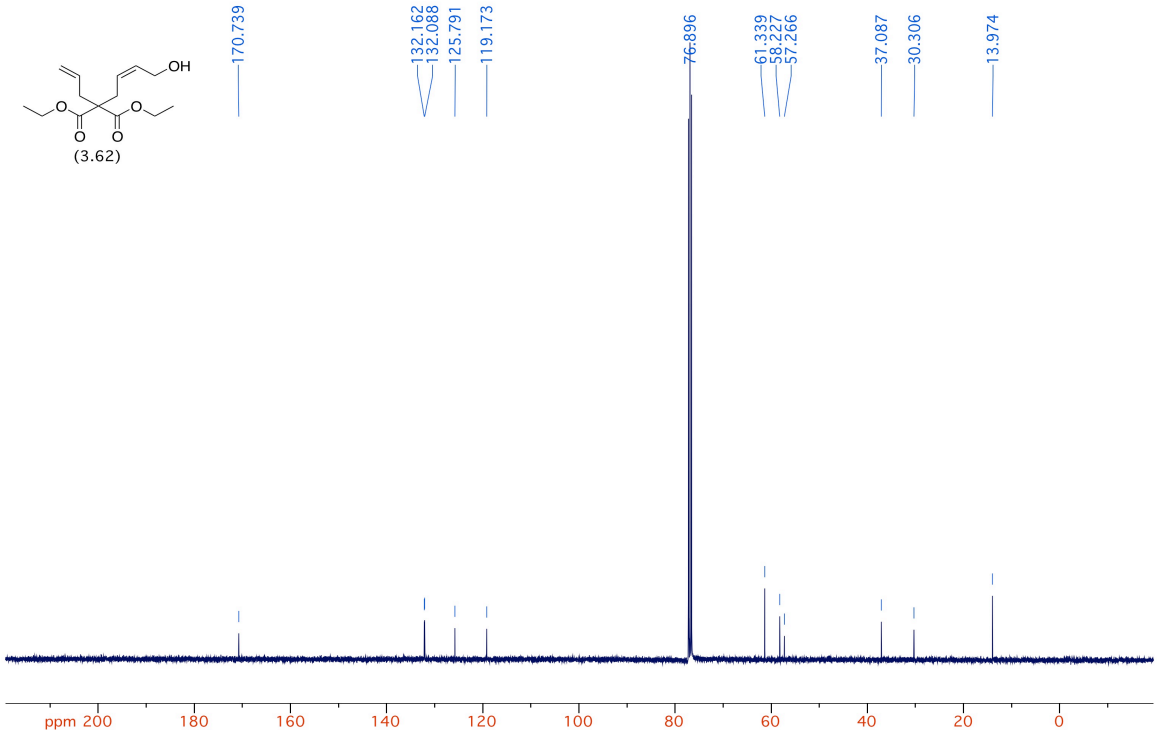
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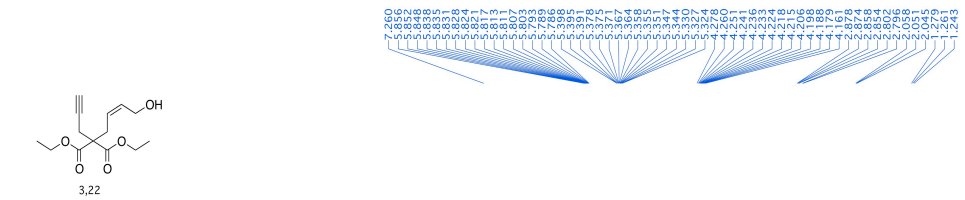
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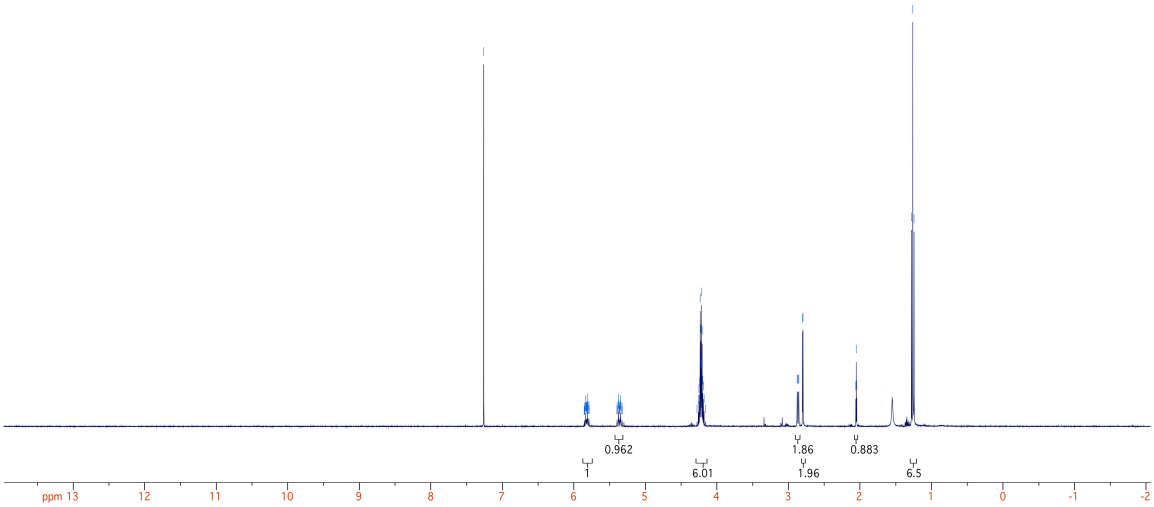
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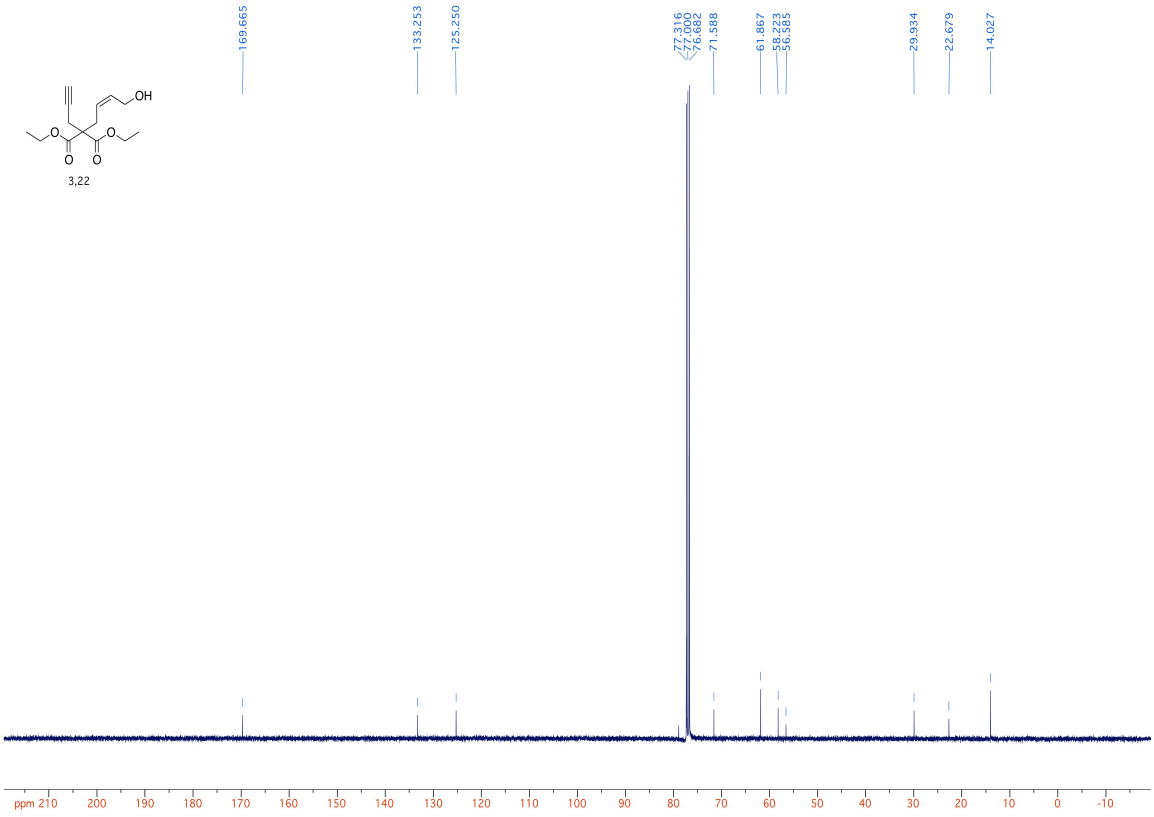
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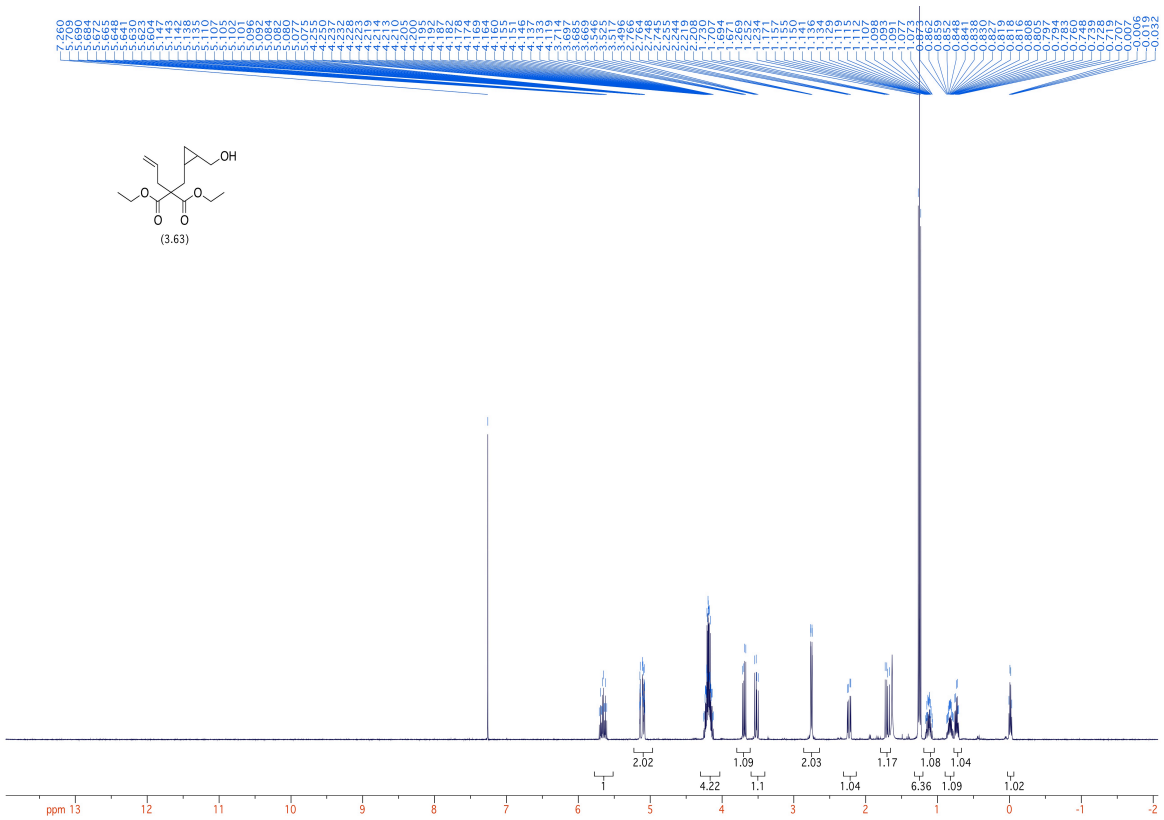
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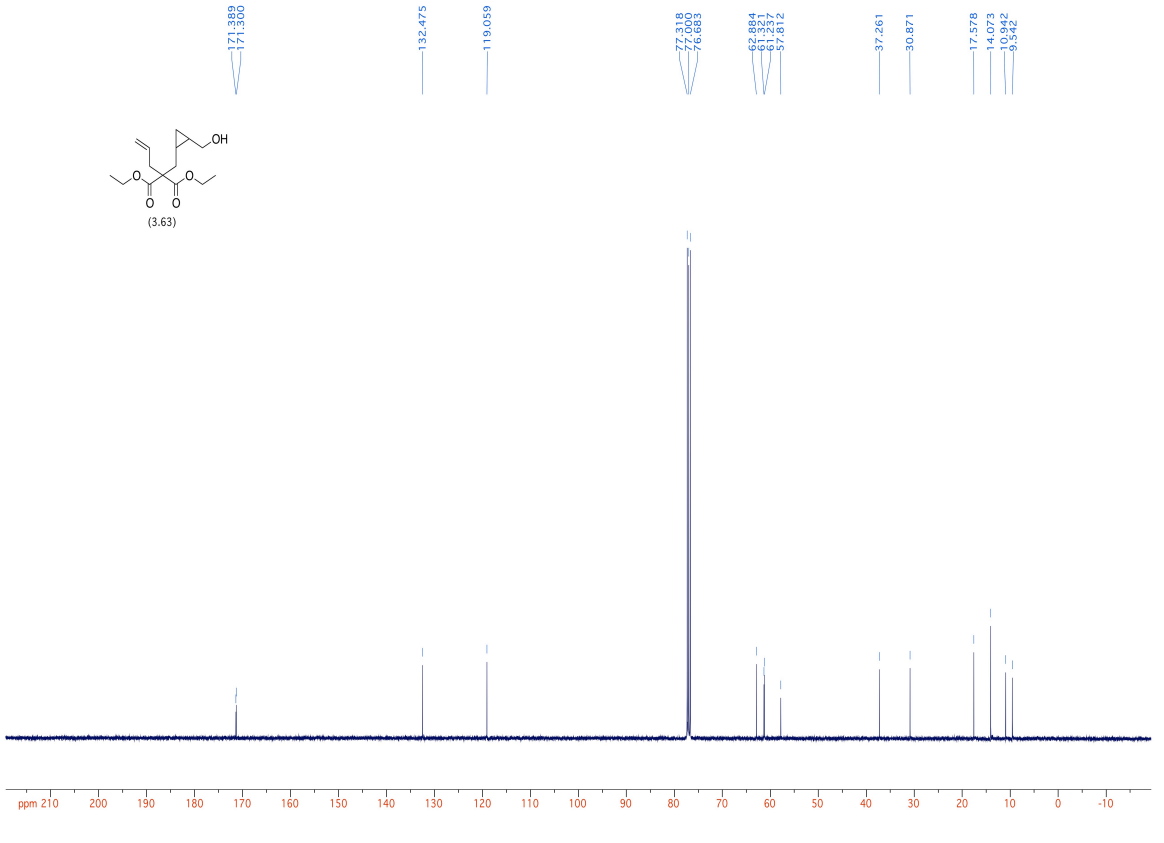
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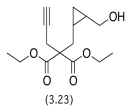
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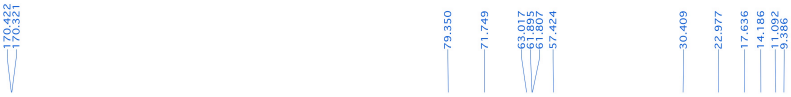
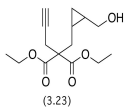
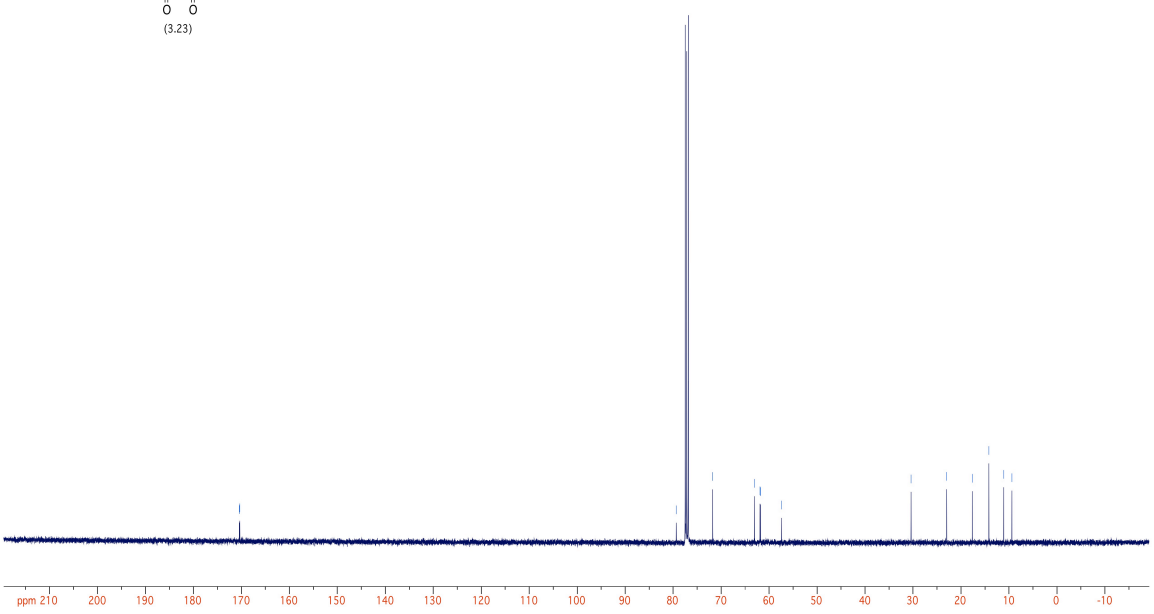
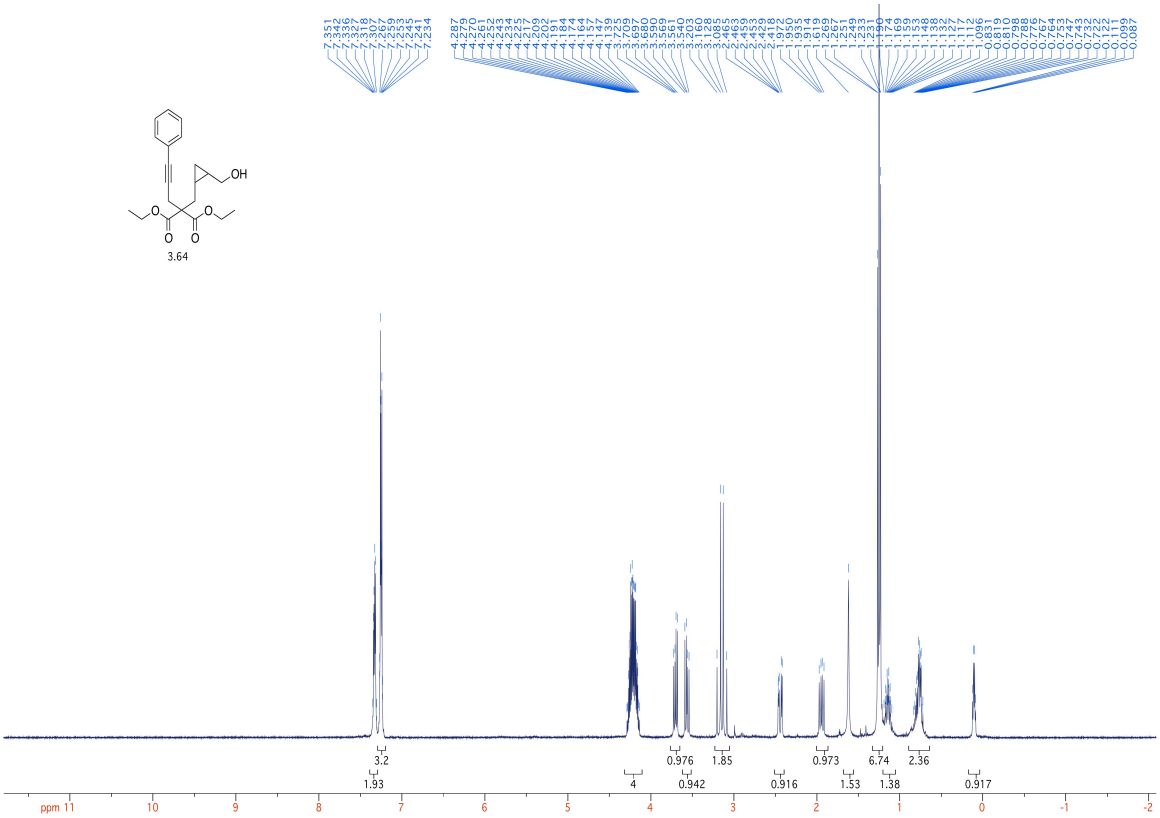
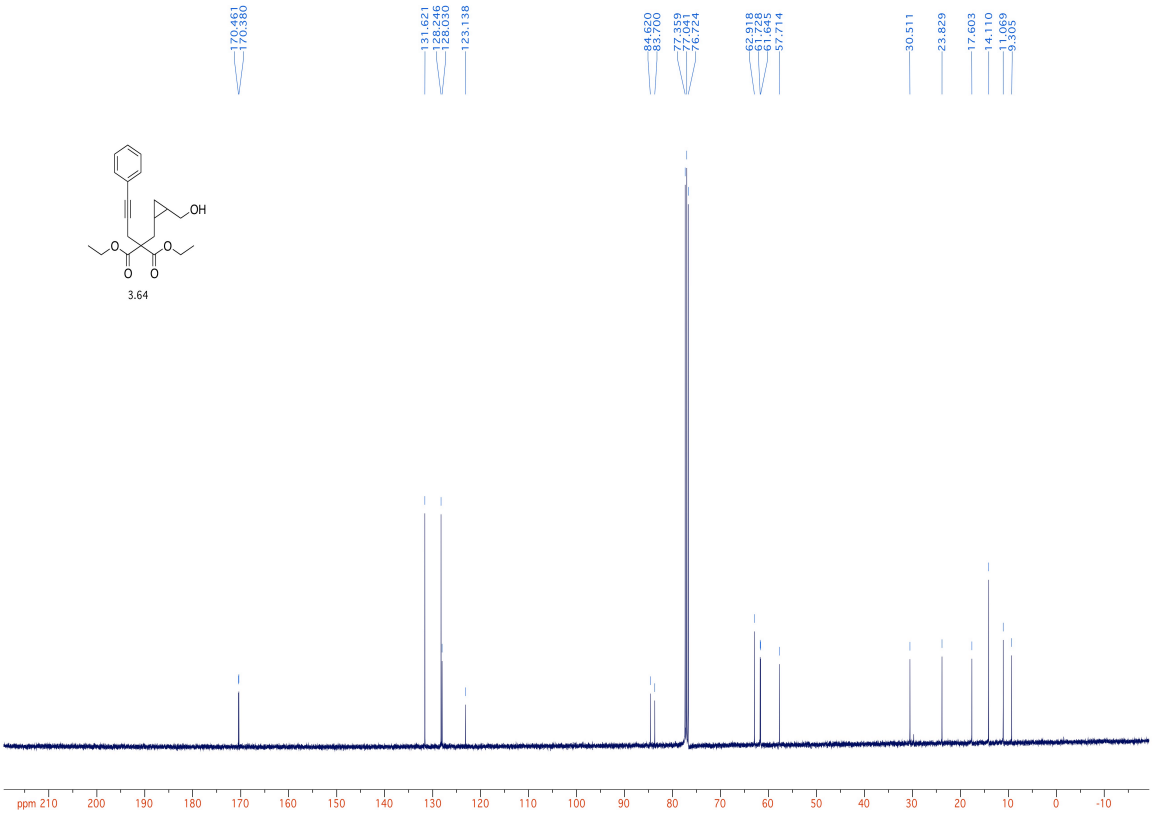
1.99
0.938
6.12
2.02
4.18
0.993
0.998
0.99
1.25
1.12
ppm 13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2

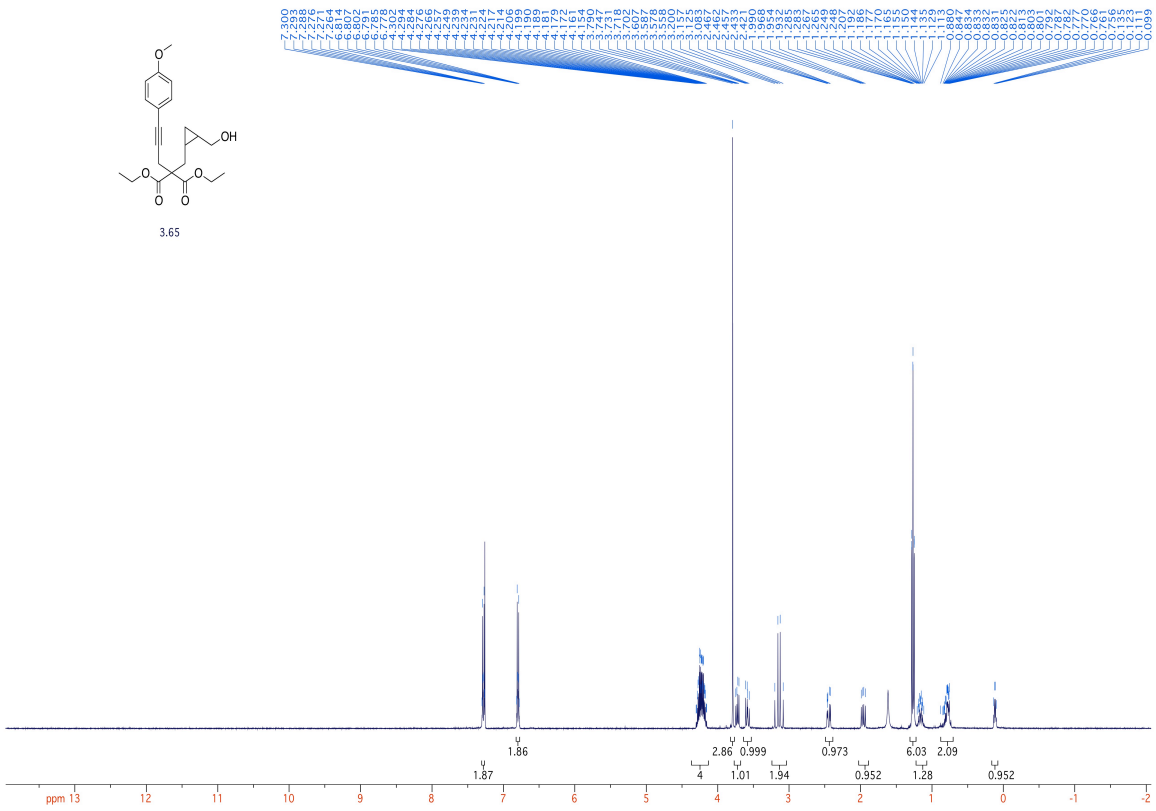


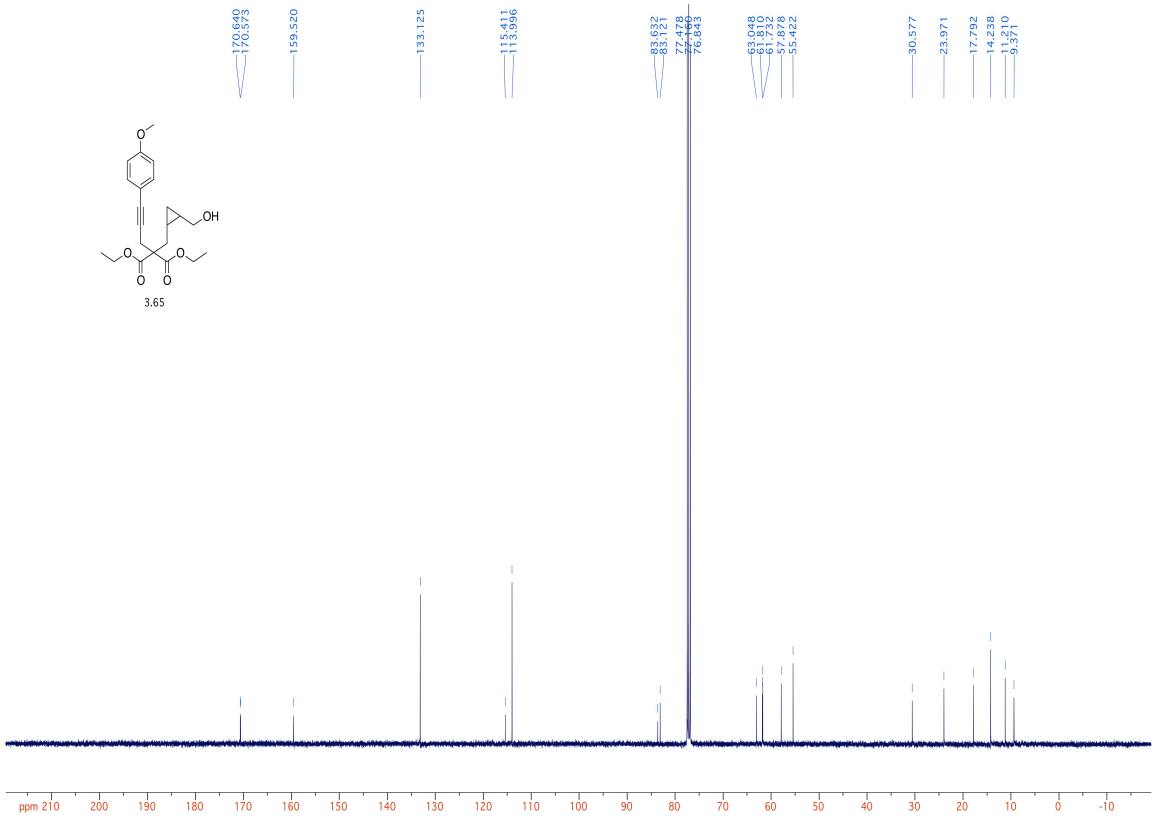

OH
O
O
O
O
(3.23)

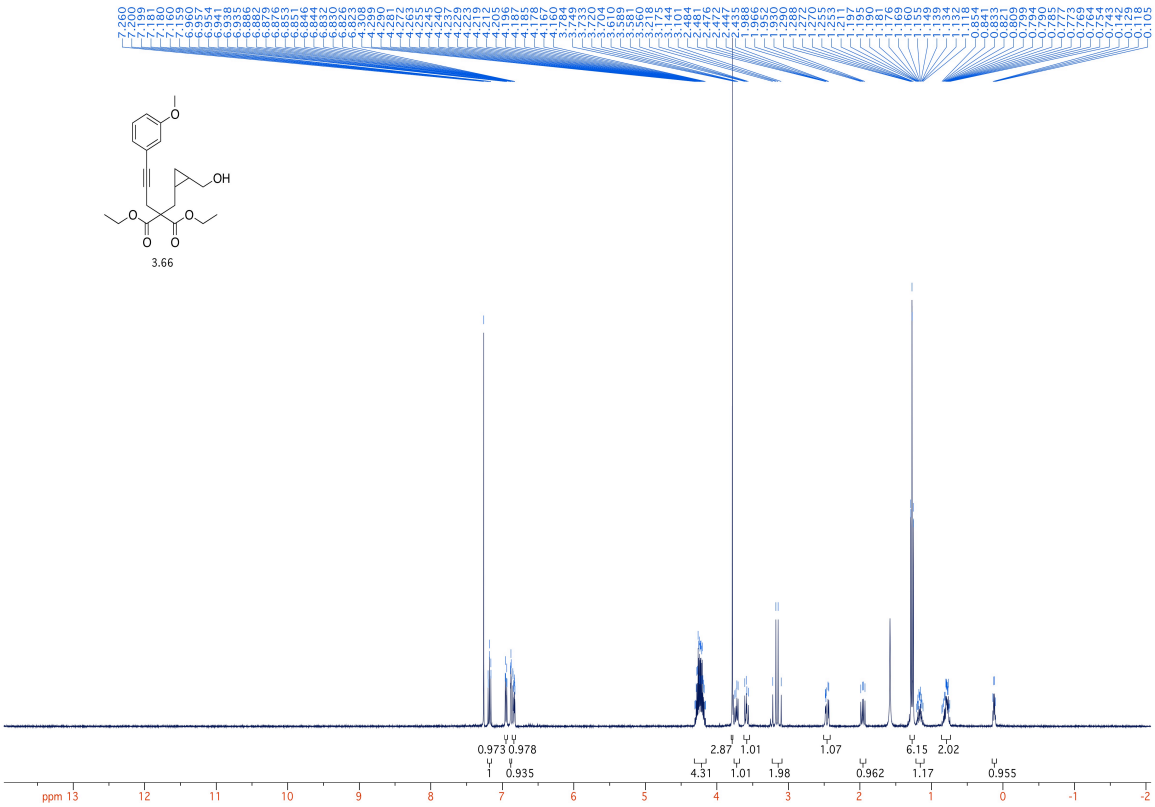

ppm 210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

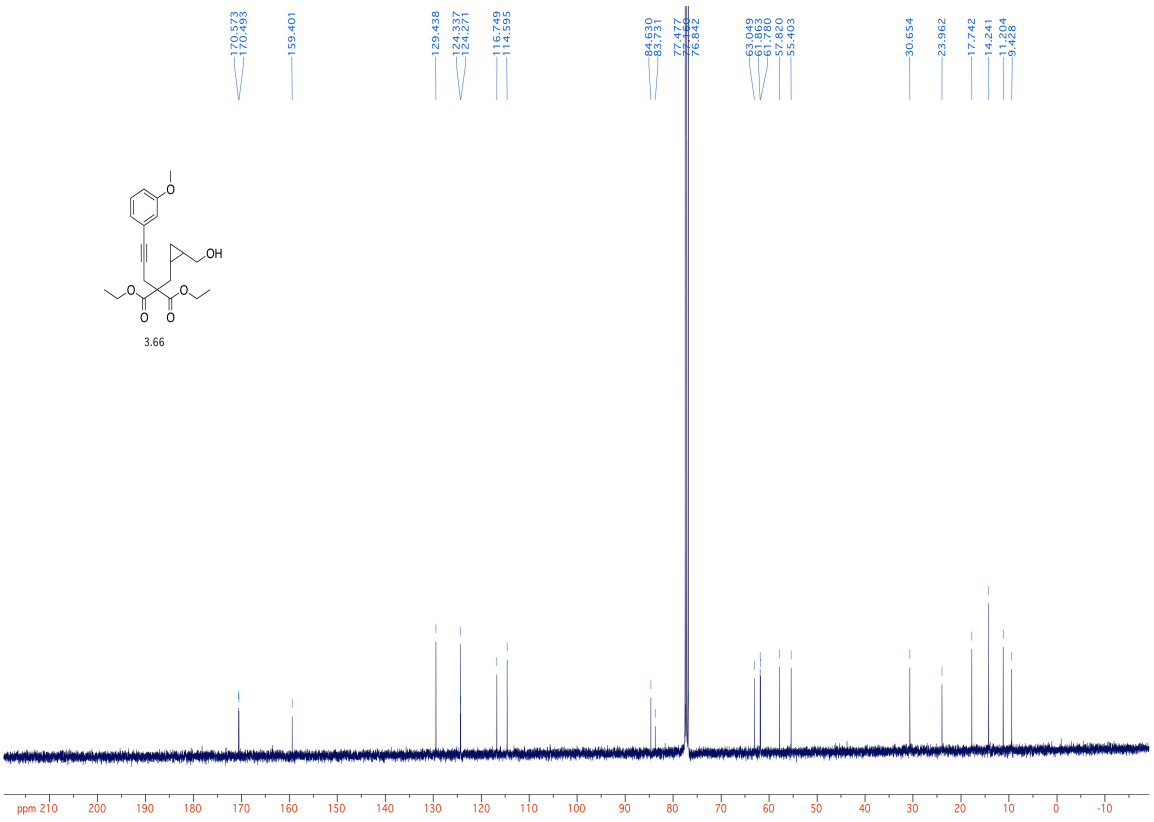

OH
O
O
O
O
3.64
3.2
1.93
0.976
1.85
4
0.942
0.916
0.973
1.53
6.74
1.38
2.36
0.917
ppm 11
10
9
8
7
6
5
4
3
2
1
0
-1
-2

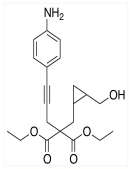

OH
O
O
O
O
3.64
ppm 210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


3.65
1.86
2.86
0.999
0.973
6.03
2.09
1.87
4
1.01
1.94
0.952
1.28
0.952
ppm 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2

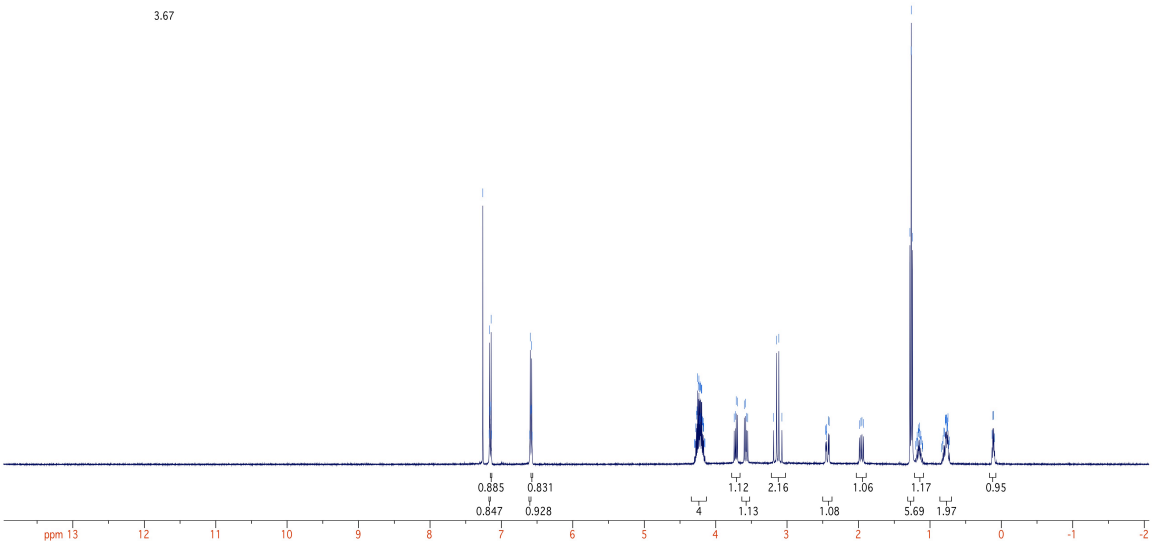

3.65
170.640
170.573
159.520
133.125
115.411
113.996
83.632
83.121
77.478
77.163
76.843
63.048
61.810
61.732
57.878
55.422
30.577
23.971
17.792
14.238
11.210
9.371
ppm 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

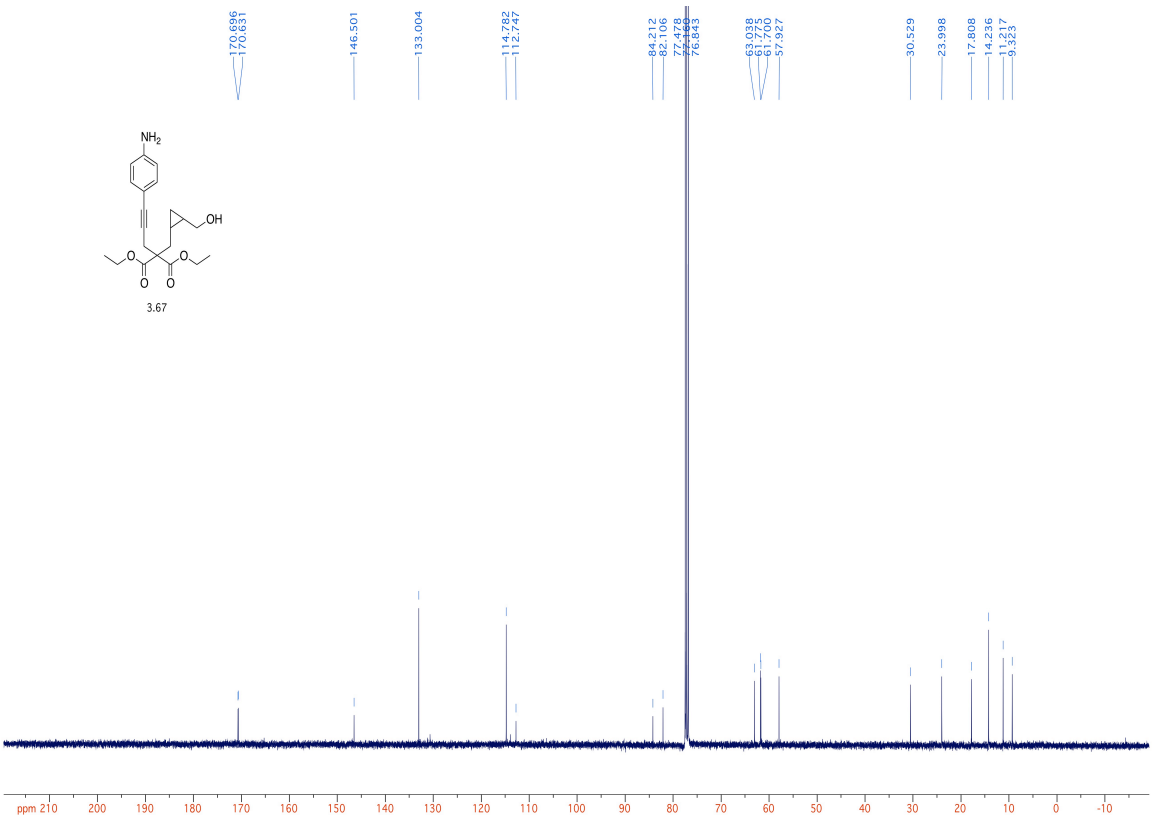

3.66
0.973
0.978
2.87
1.01
1.07
6.15
2.02
1
0.935
4.31
1.01
1.98
0.962
1.17
0.955
ppm 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2


3.66
ppm 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

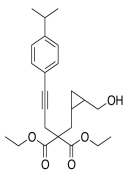

NH2
OH
O
O
O
O

3.67

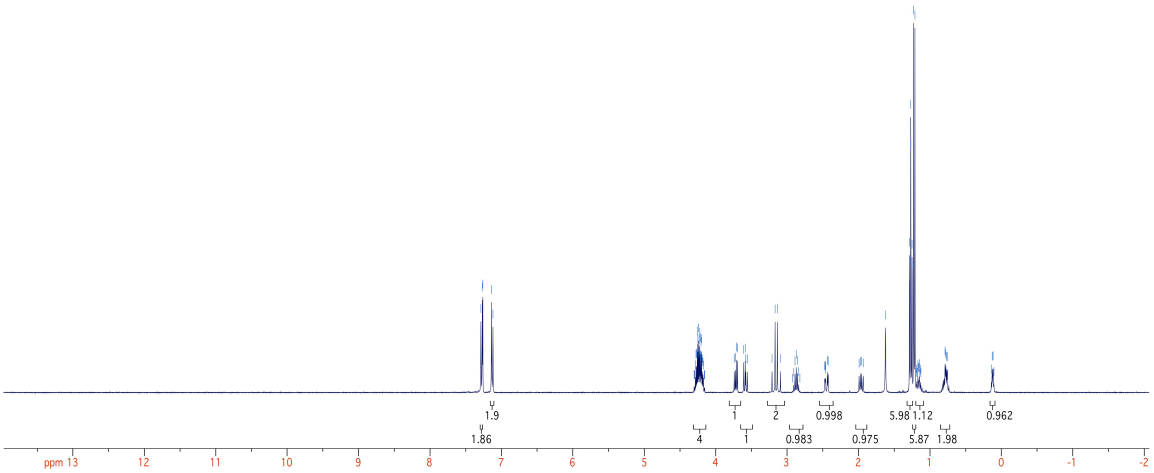

0.885
0.847
0.831
0.928
1.12
1.13
2.16
4
1.08
1.06
5.69
1.17
1.97
0.95
ppm 13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2

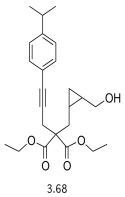

NH2
OH
O
O
O
O
ppm 210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

3.67

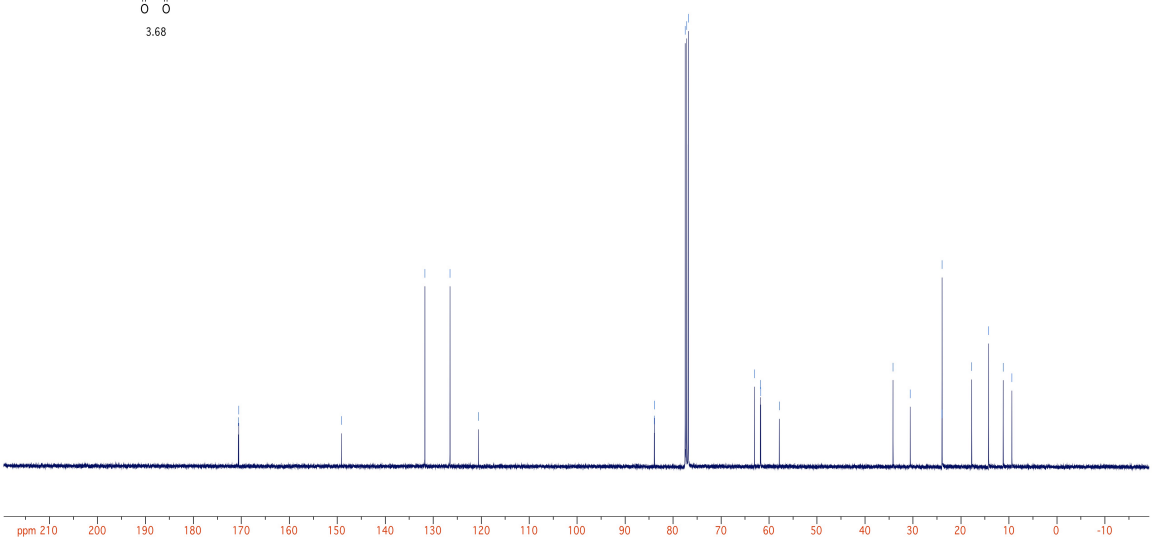

OH
O
O
O
O

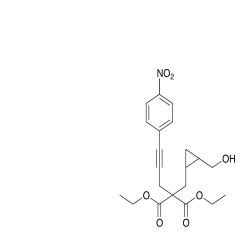
3.68


1.9
1.86
1
4
1
2
0.983
0.998
0.975
5.98
1.12
5.87
0.962
1.98
ppm 13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2

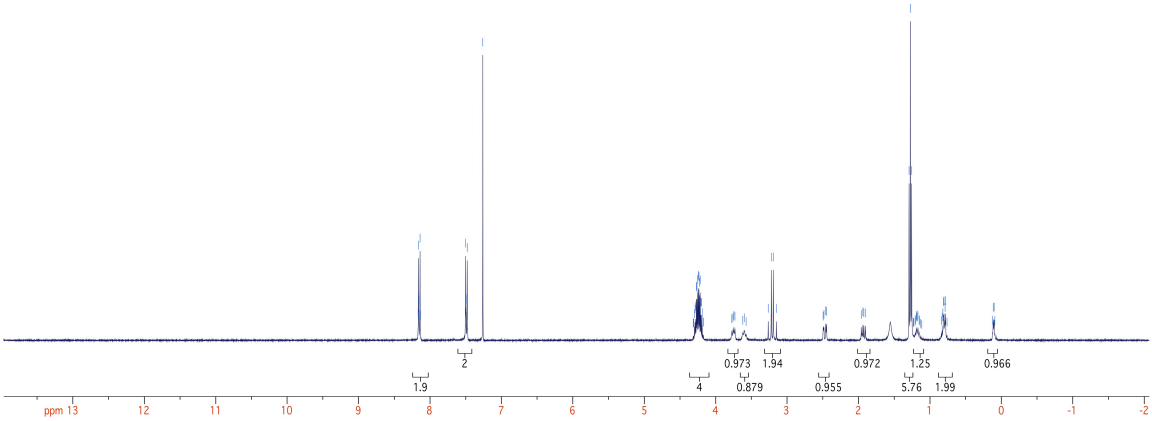

OH
O
O
O
O

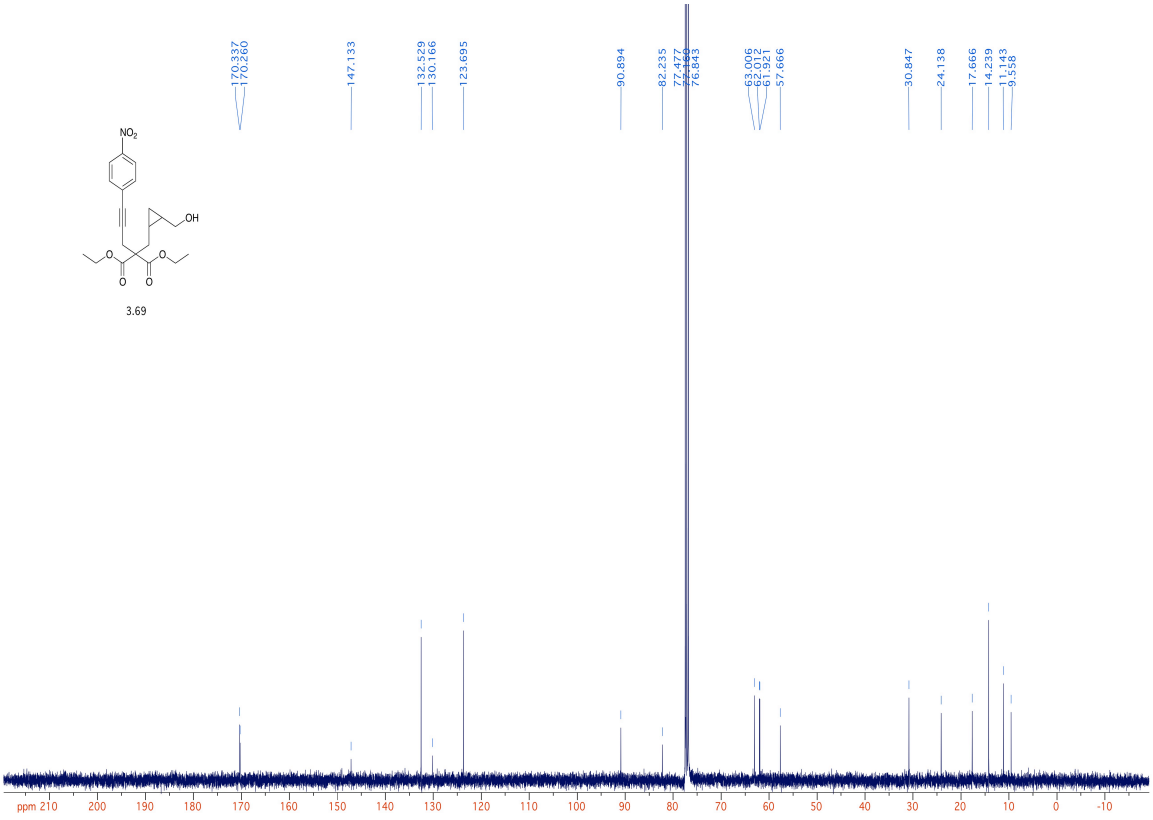
3.68


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


NO2
OH
O
O
O
O

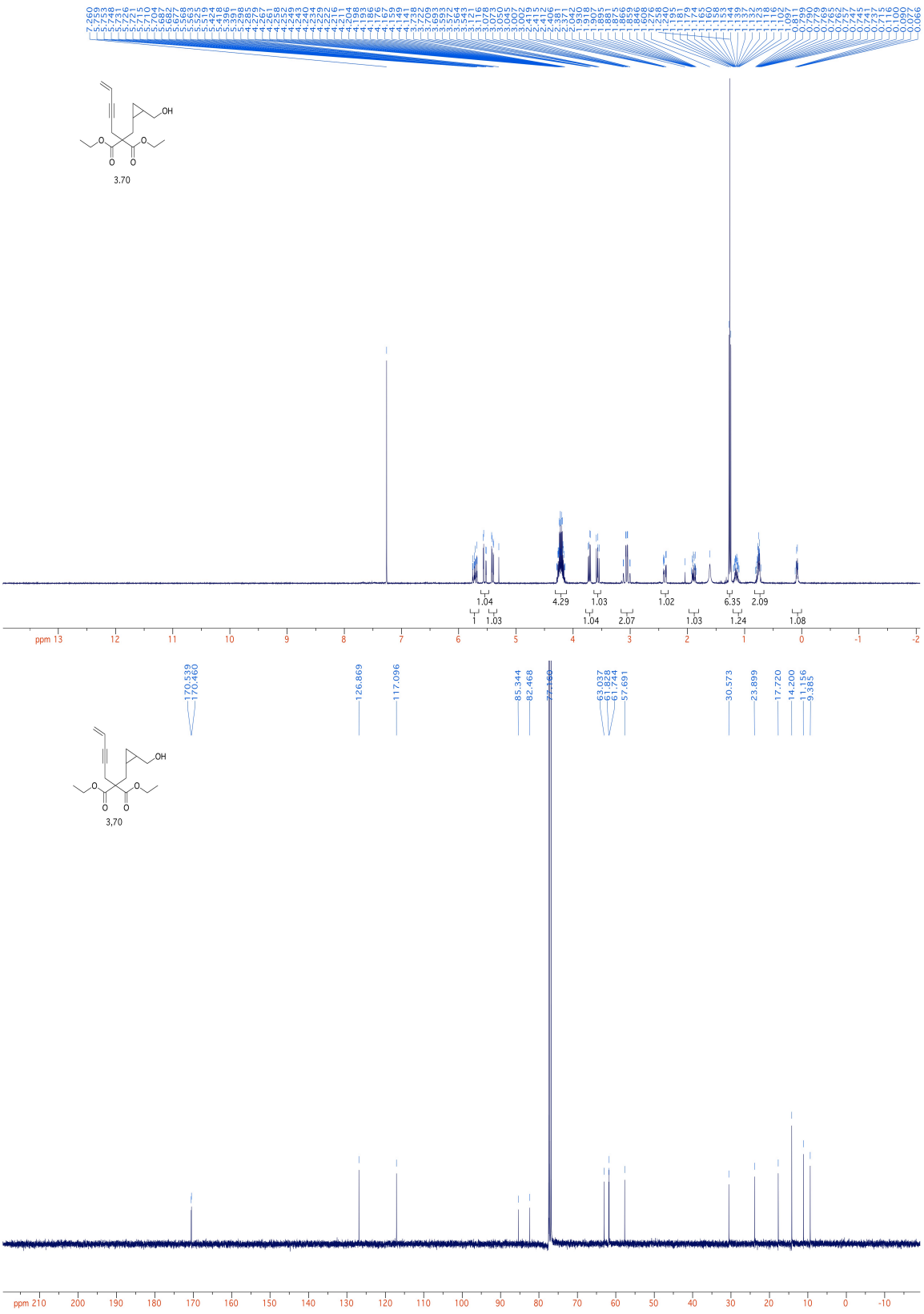
3.69

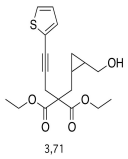

1.9
2
0.973
1.94
4
0.879
0.955
0.972
5.76
1.25
1.99
0.966
ppm 13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2


170.337
170.260
147.133
132.529
130.166
123.695
90.894
82.235
77.477
77.160
76.843
63.006
61.921
61.737
57.666
30.847
24.138
17.666
14.239
11.143
9.558
ppm 210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

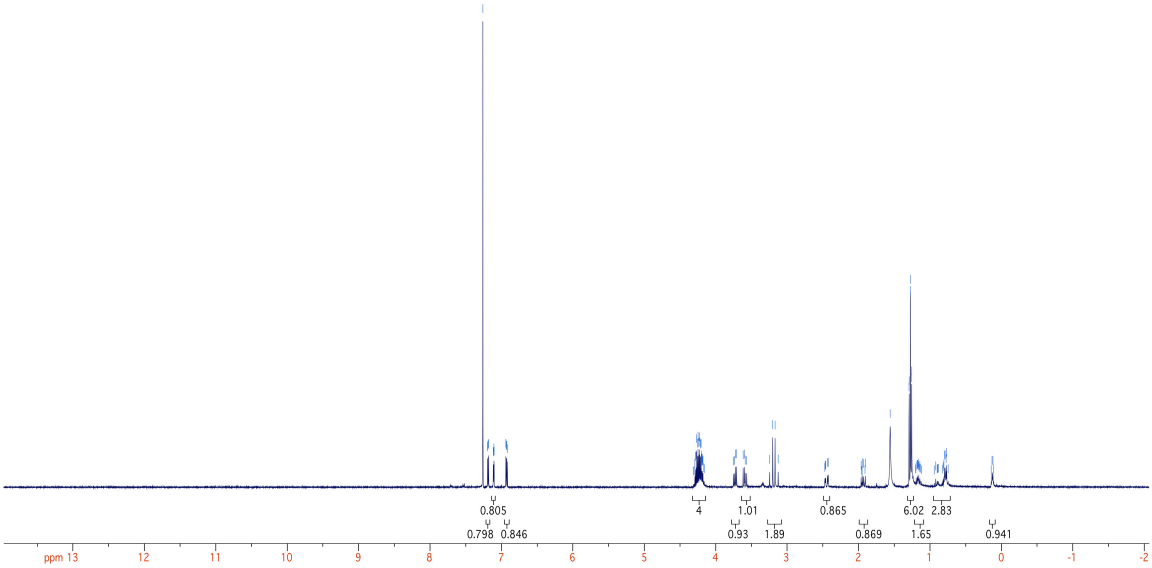
NO2
OH
O
O
O
O

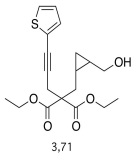
3.69


OH
O
O
O
O
3.70
1.04
4.29
1.03
1.02
6.35
2.09
1
1.03
1.04
2.07
1.03
1.24
1.08
ppm 13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
170.539
170.460
126.869
117.096
85.344
82.468
77.160
63.037
61.928
61.744
57.691
30.573
23.899
17.720
14.200
11.156
9.385
OH
O
O
O
O
3,70
ppm 210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


S
OH
O
O
O
O

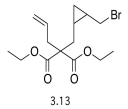
3,71


0.805
0.798
0.846
4
1.01
0.93
1.89
0.865
0.869
6.02
1.65
2.83
0.941
ppm 13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2

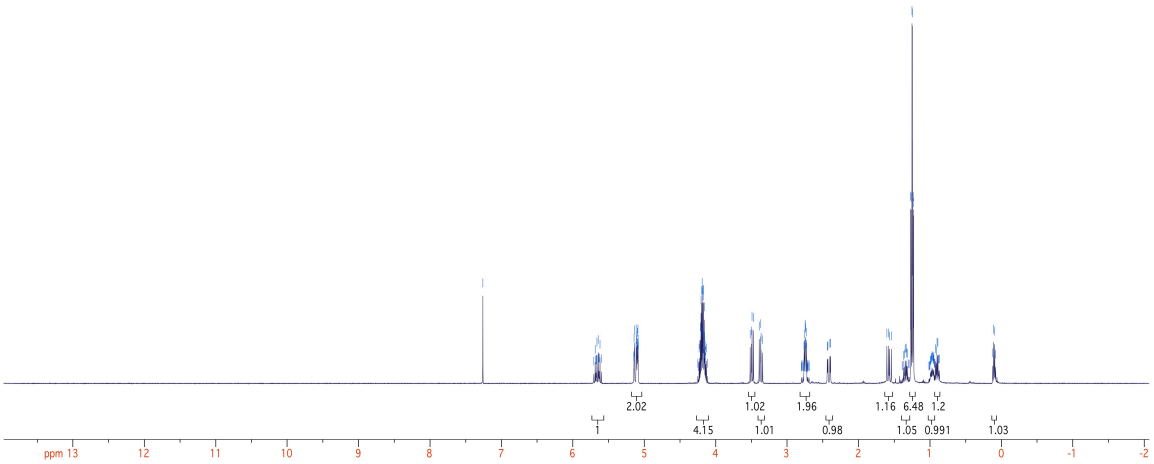

S
OH
O
O
O
O

3,71

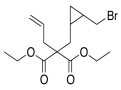
170.487
170.407
131.762
126.958
126.680
88.876
77.359
77.160
63.074
61.927
61.840
57.759
30.725
30.713
24.265
17.695
14.244
14.194
9.478
ppm 210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


Br
O
O
O
O

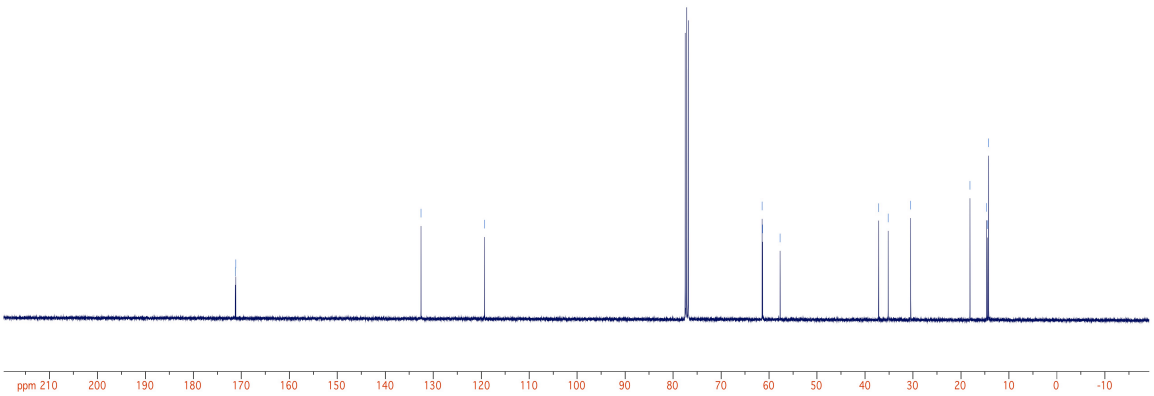
3.13

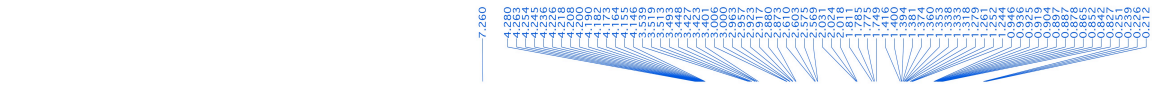

2.02
1.02
1.96
1.16
6.48
1.2
1
4.15
1.01
0.98
1.05
0.991
1.03
ppm 13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2

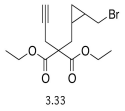

171.265
171.142
132.542
119.276
61.450
61.351
57.704
37.148
35.171
30.465
18.123
16.139
14.452
14.241


Br
O
O
O
O

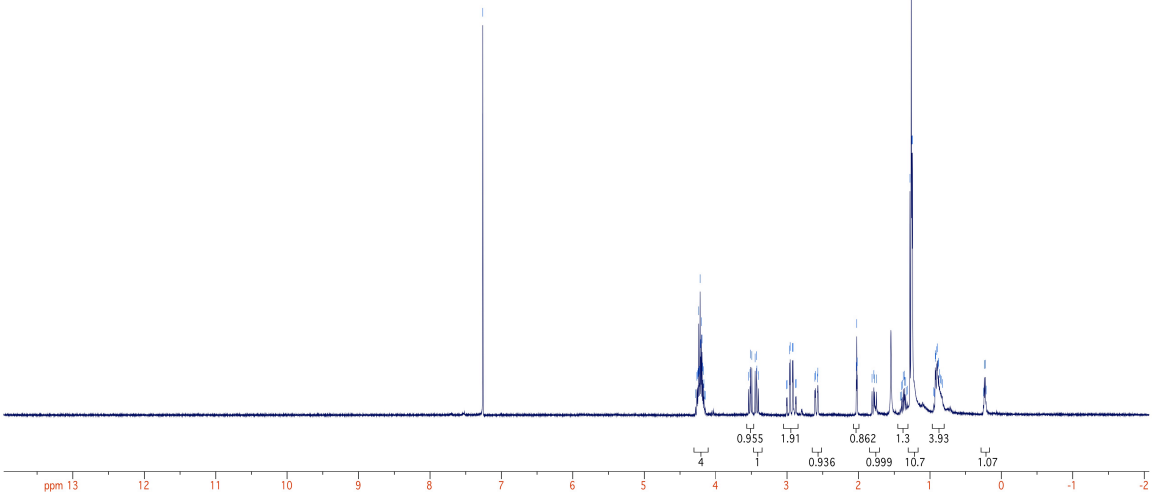
3.13

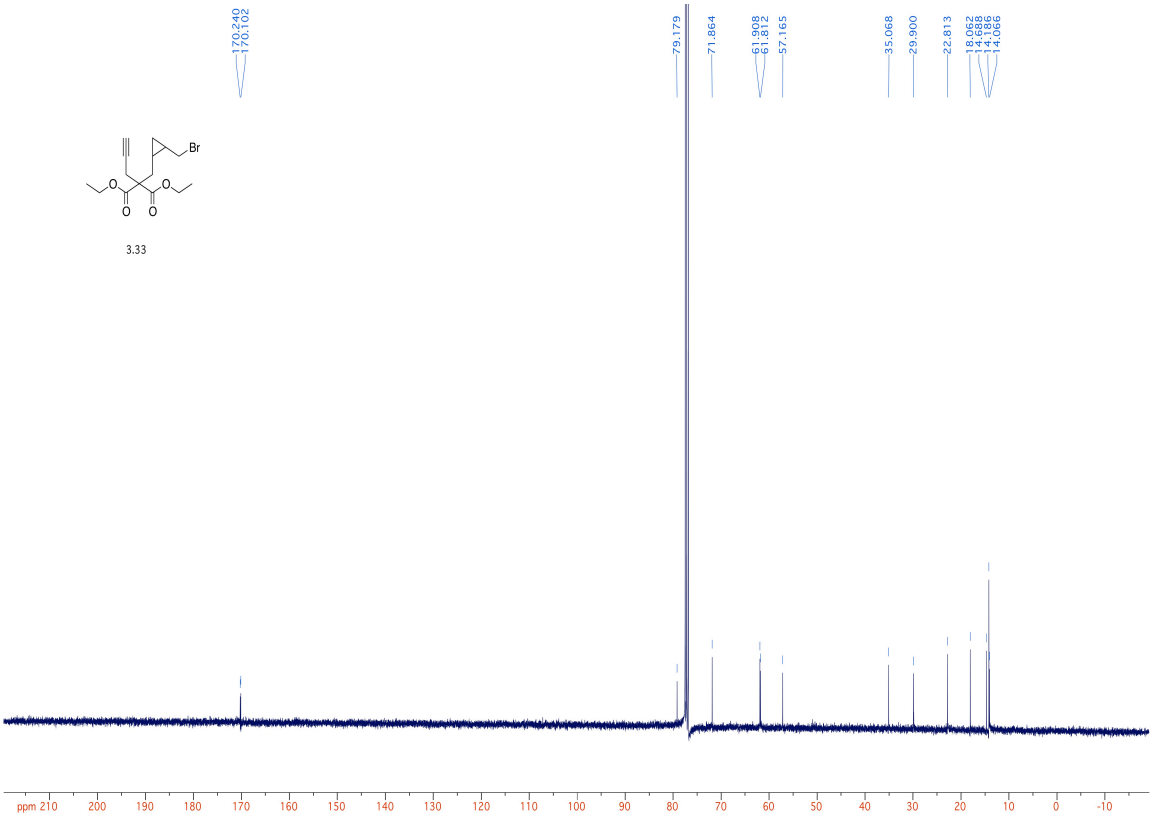

ppm 210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10



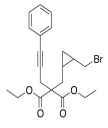


3.33

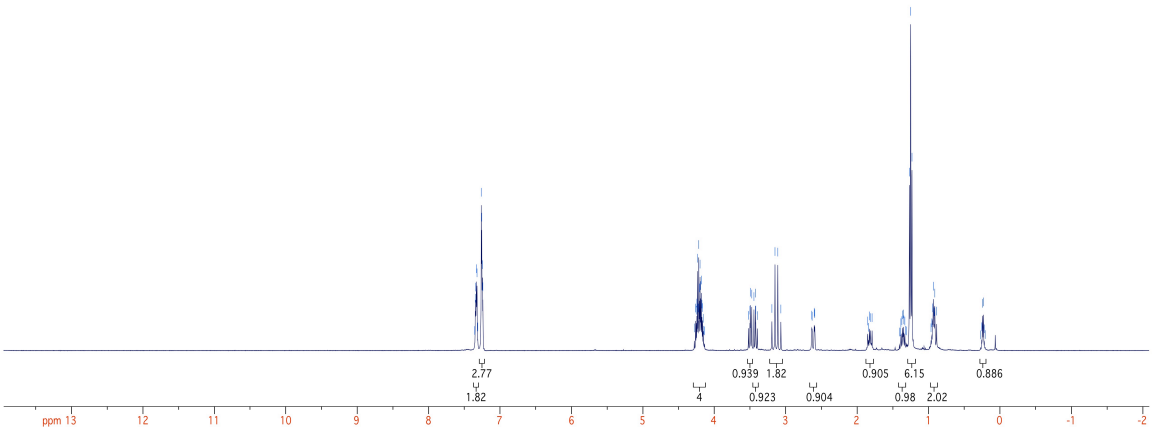


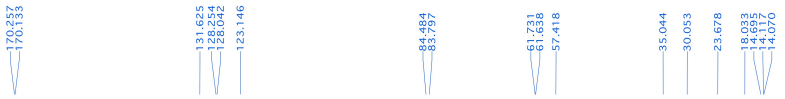


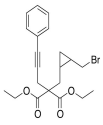
3.33



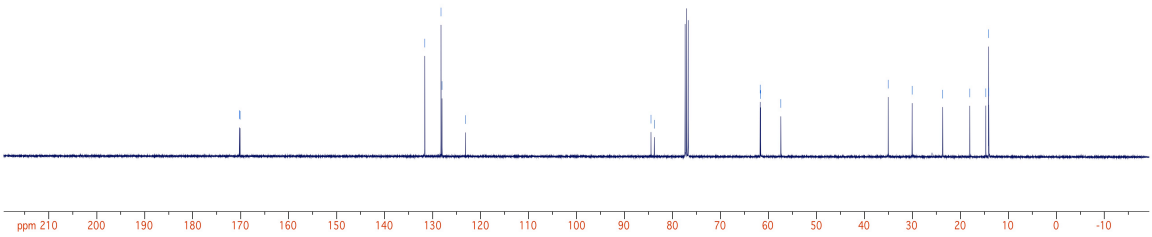
3.55

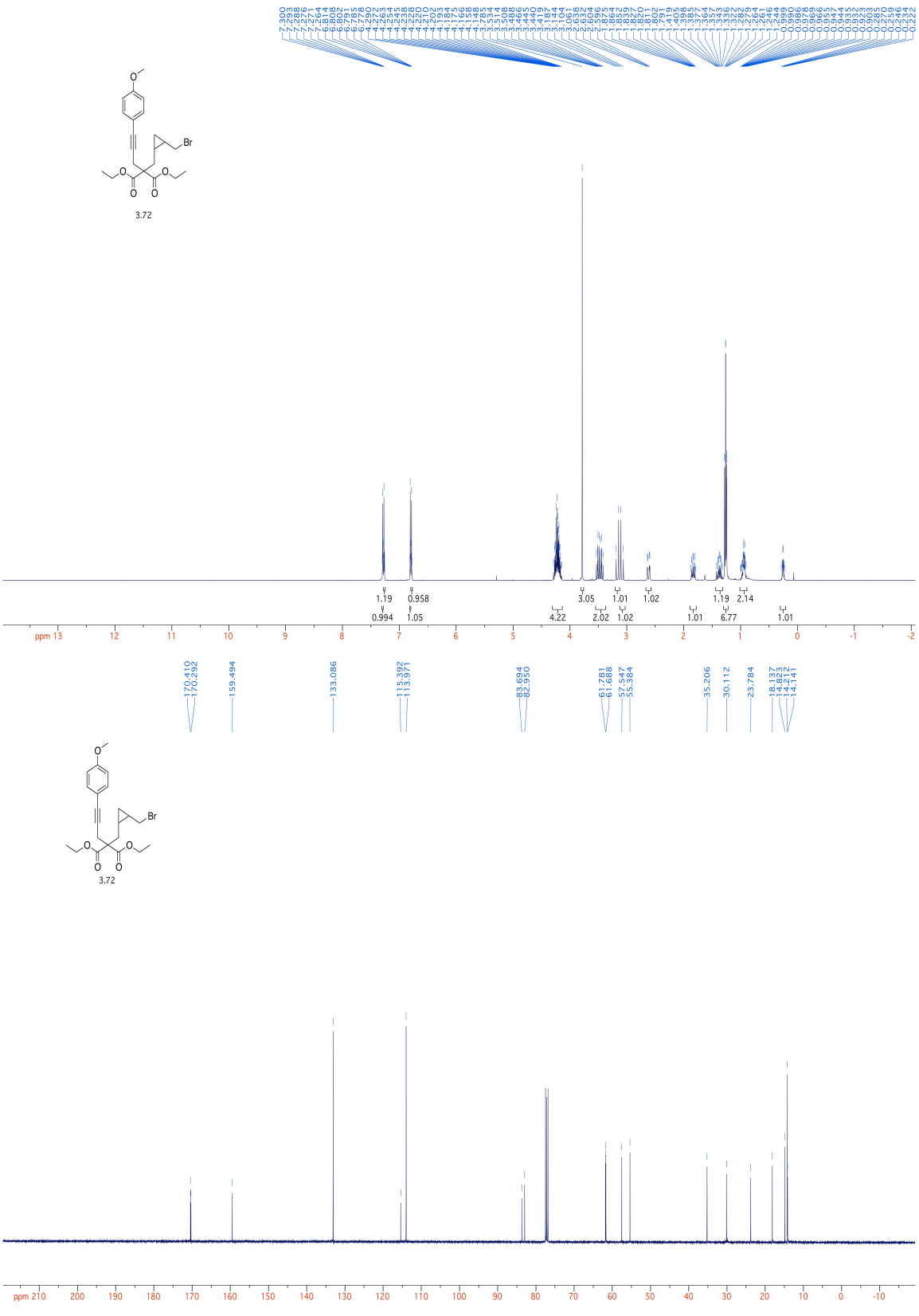

2.77
1.82
0.939
1.82
4
0.923
0.904
0.905
6.15
0.98
2.02
0.886
ppm 13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2

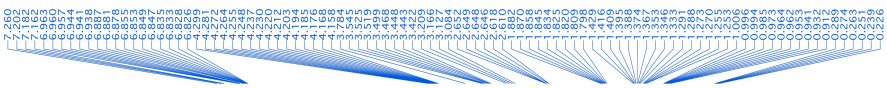


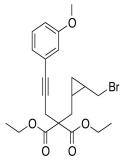


3.55

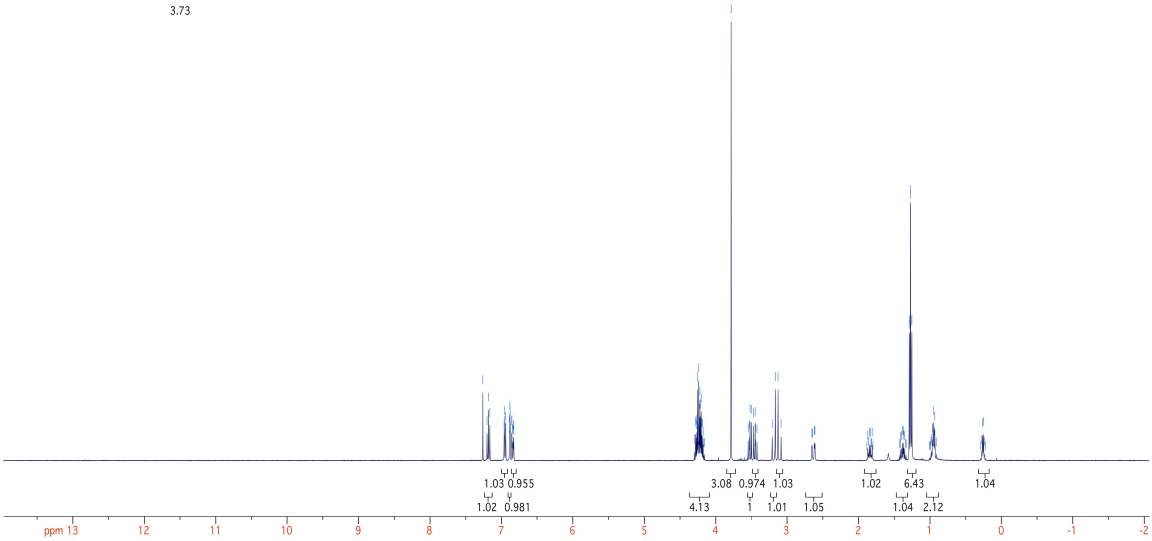

ppm 210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

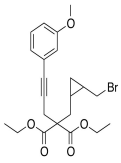

Br
3.72
1.19
0.958
3.05
1.01
1.02
1.19
2.14
0.994
1.05
4.22
2.02
1.02
1.01
6.77
1.01
ppm 13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
Br
3.72
ppm 210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10





3.73





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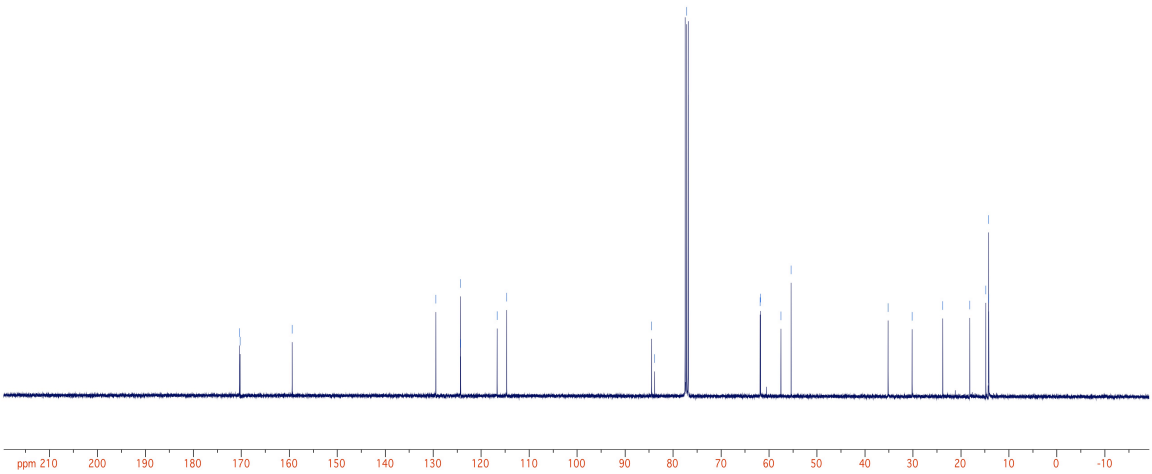

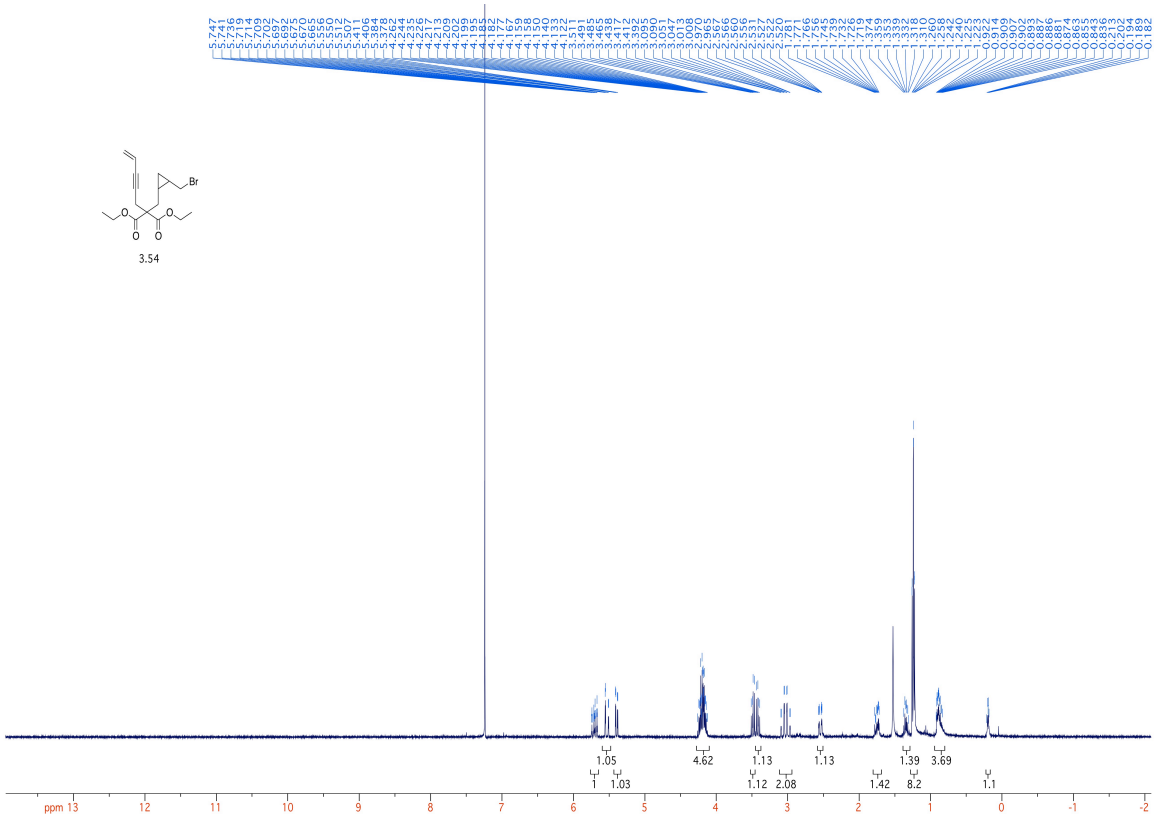
Br
O
O
O
O
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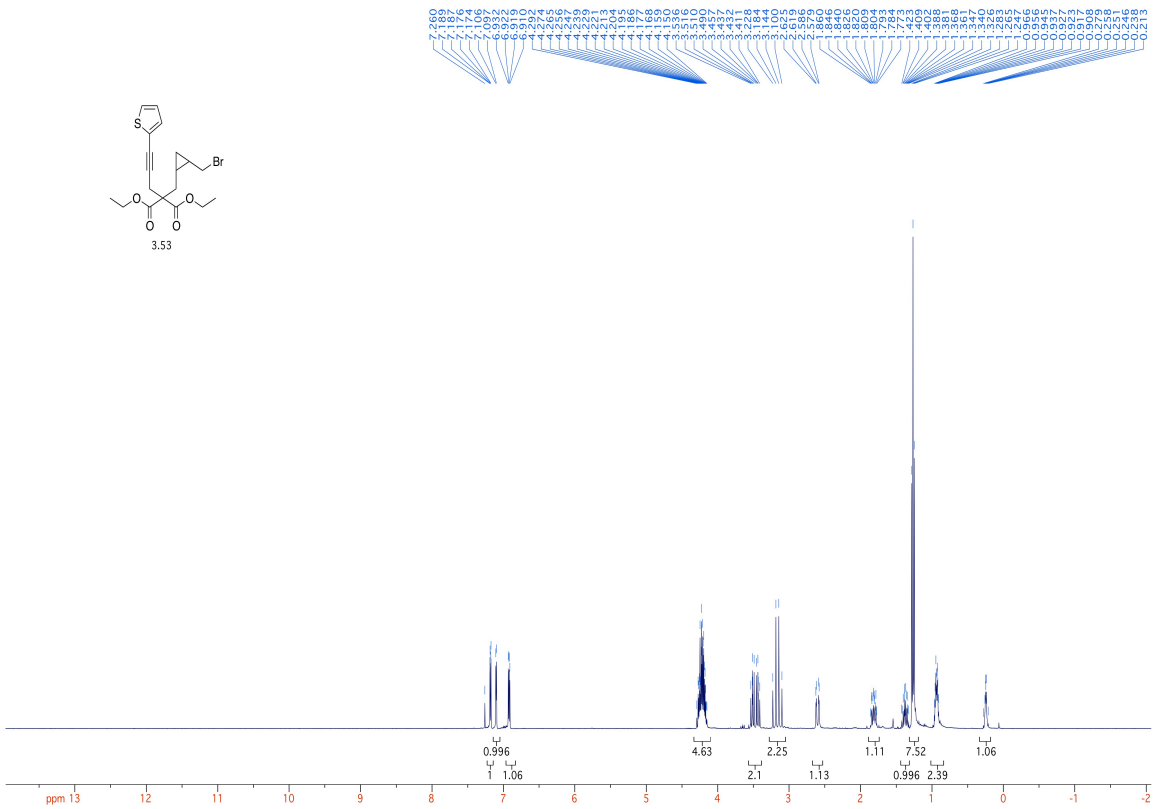
4.62
1.13
1.13
1.39
3.69
1
1.03
1.12
2.08
1.42
8.2
1.1
ppm 13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2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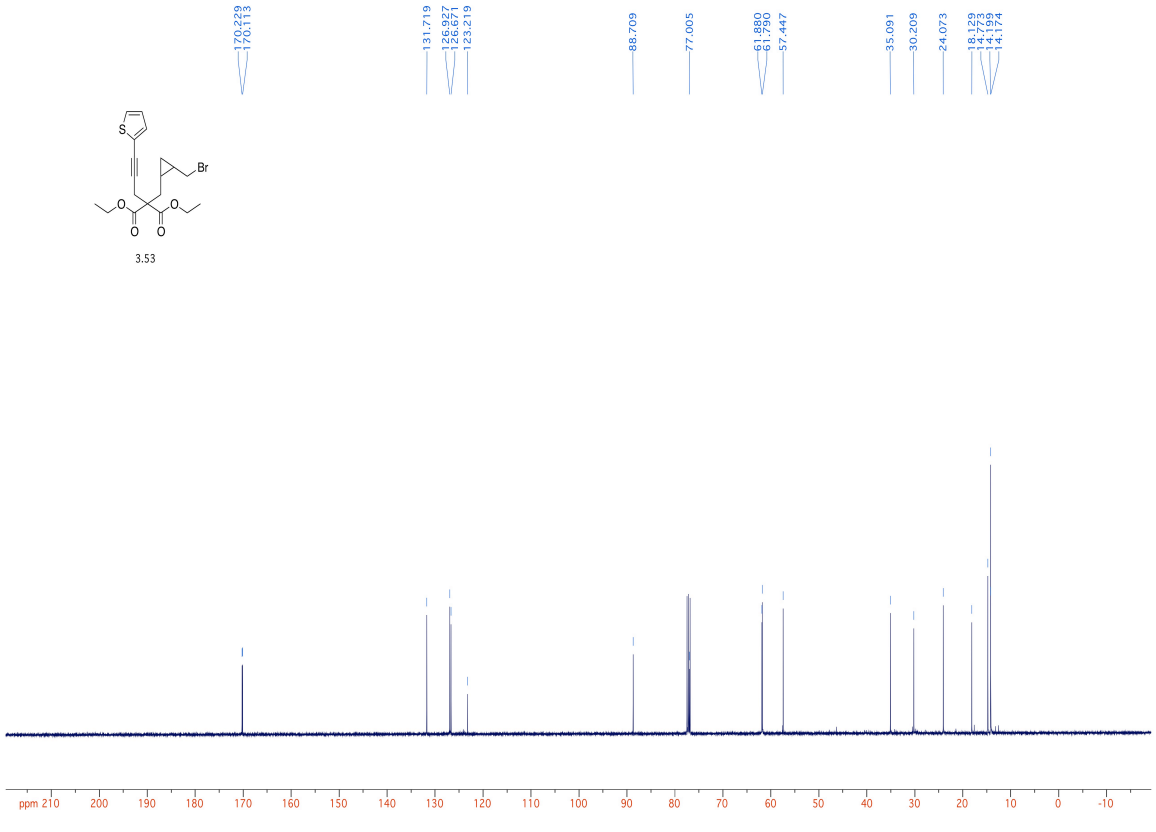
7.189
7.187
7.176
7.174
7.107
7.097
6.932
6.930
6.919
6.910
4.274
4.266
4.259
4.247
4.229
4.221
4.213
4.204
4.195
4.186
4.177
4.168
4.159
4.150
3.516
3.510
3.497
3.437
3.428
3.411
3.228
3.184
3.144
3.100
3.005
2.619
2.596
2.583
1.860
1.846
1.826
1.820
1.809
1.804
1.793
1.784
1.773
1.423
1.409
1.388
1.381
1.368
1.347
1.340
1.326
1.283
1.265
1.247
0.956
0.956
0.845
0.937
0.927
0.923
0.911
0.908
0.279
0.258
0.251
0.246
0.213
S
Br
O
O
O
O
3.53
0.996
1
1.06
4.63
2.1
2.25
1.13
1.11
0.996
7.52
2.39
1.06
ppm 13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2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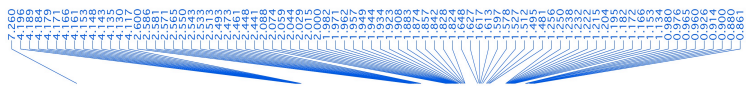
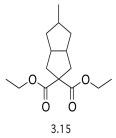
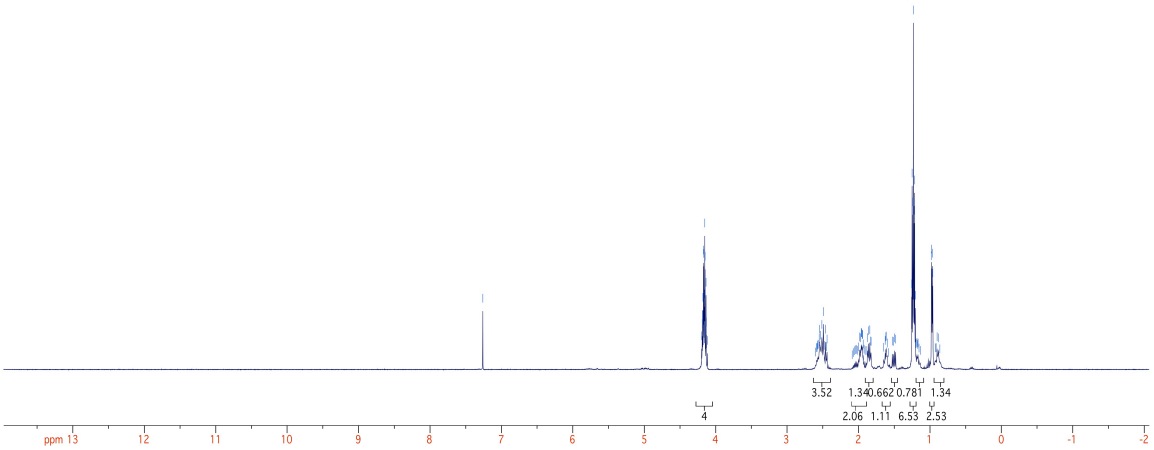
170.113
131.719
126.927
126.671
123.219
88.709
77.005
61.880
61.790
57.447
35.091
30.209
24.073
18.129
14.172
14.199
14.174
S
Br
O
O
O
O
3.53
ppm 210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10




3.15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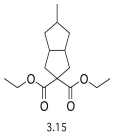
1.34
0.66
2.06
1.11
0.78
6.53
1.34
2.53
4
ppm 13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2


172.460
172.198
77.160
64.455
61.324
43.861
43.023
42.197
41.856
41.676
41.036
39.535
19.722
18.907
14.198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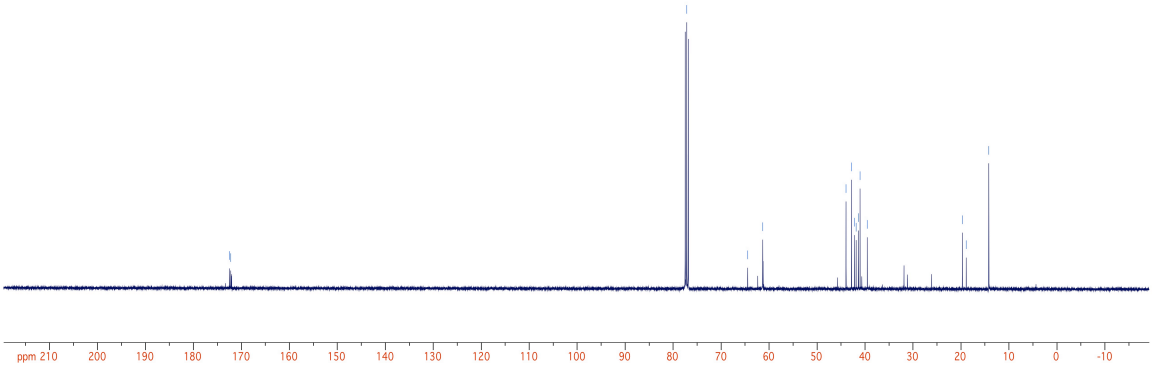
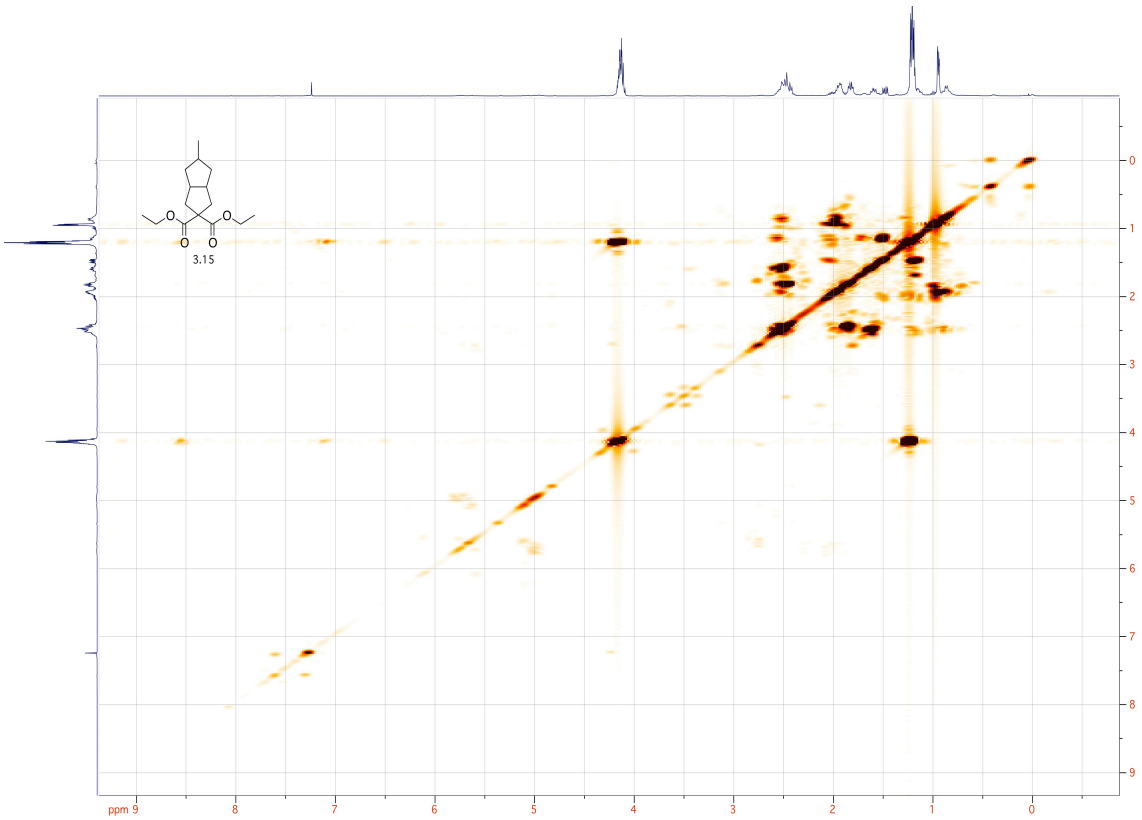
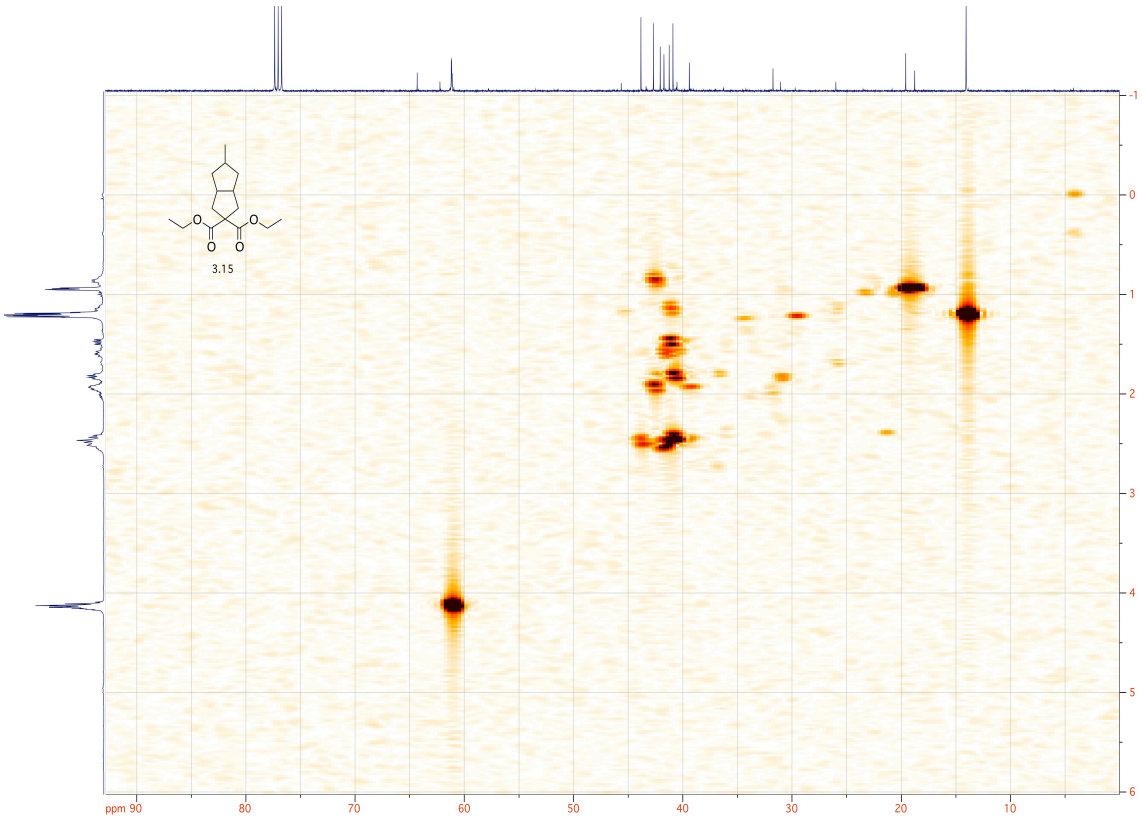
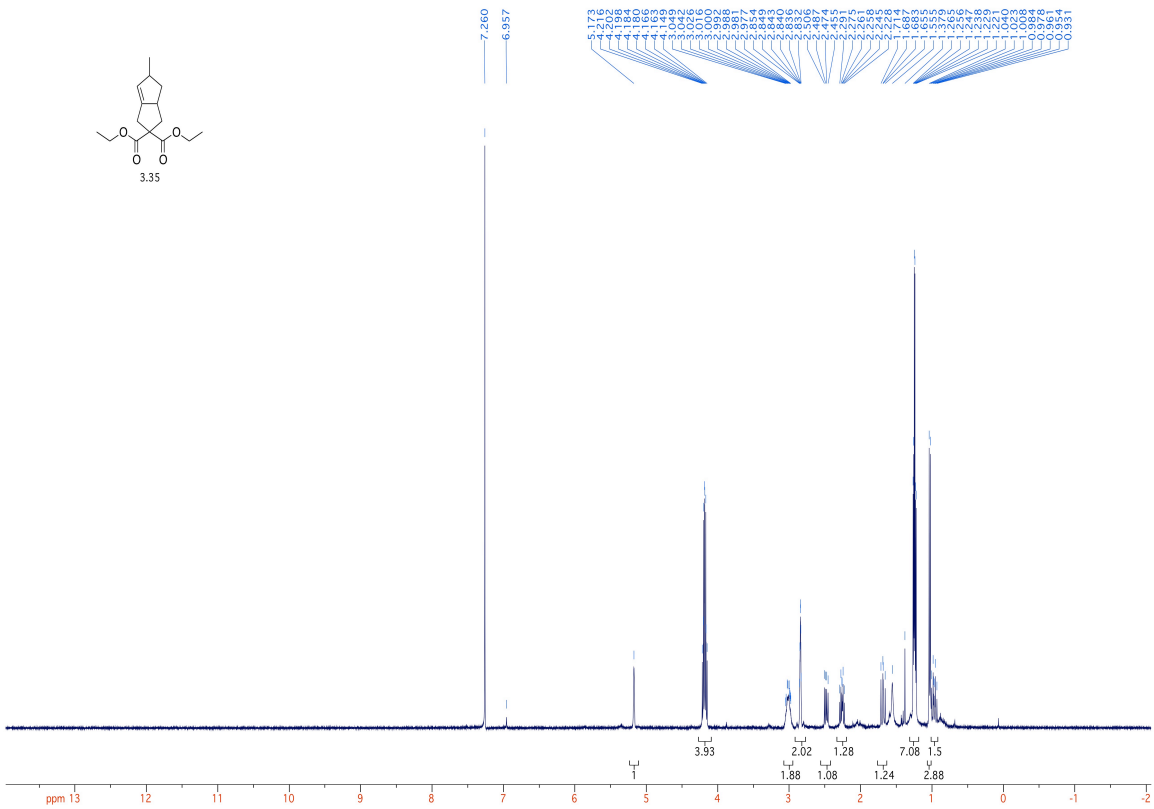
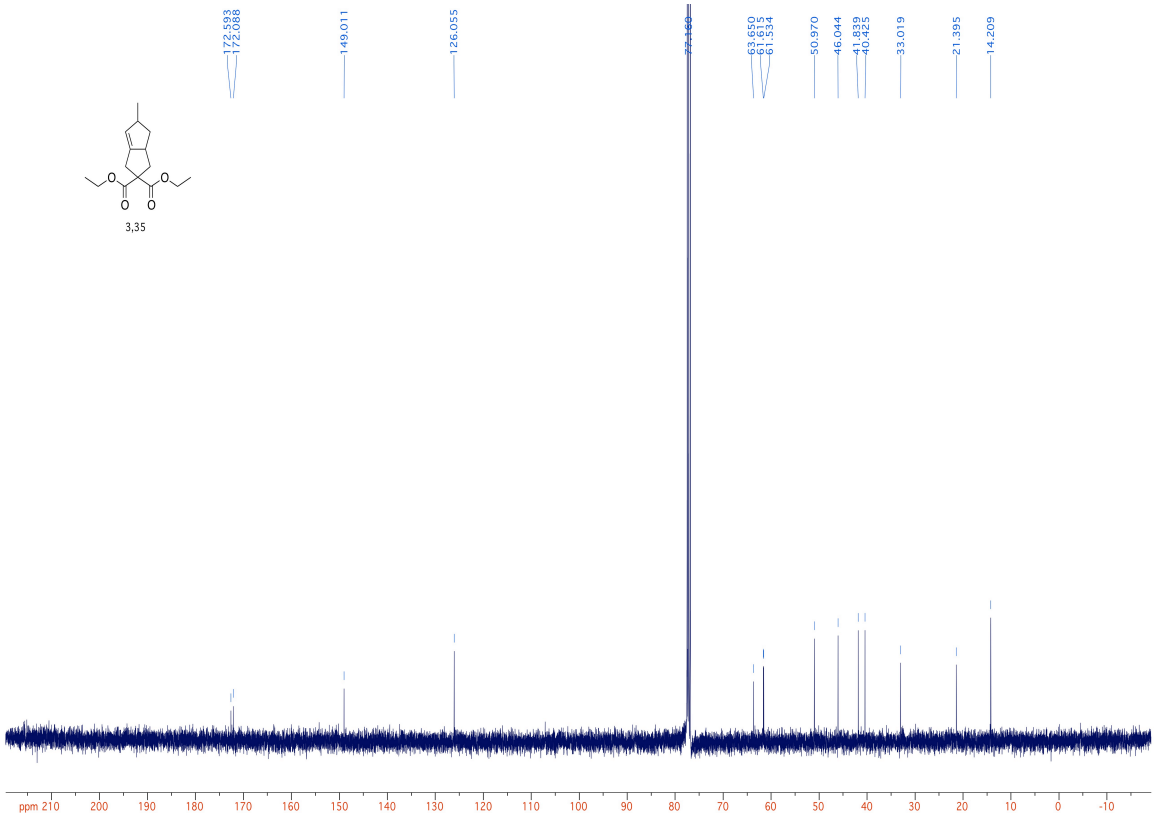

ppm 210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


3.15
ppm 9
8
7
6
5
4
3
2
1
0


3.15
ppm 90
80
70
60
50
40
30
20
10


3.35
7.260
6.957
3.93
2.02
1.28
7.08
1.5
1
1.88
1.08
1.24
2.88
ppm 13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2


3,35
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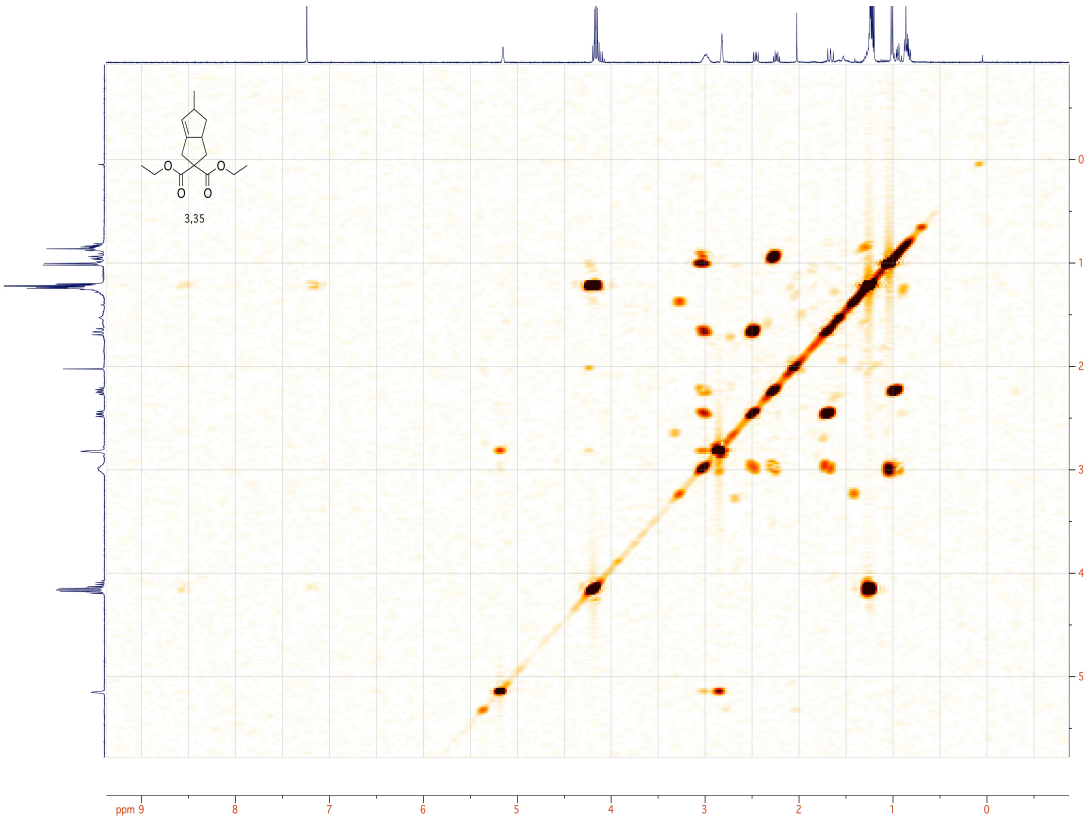
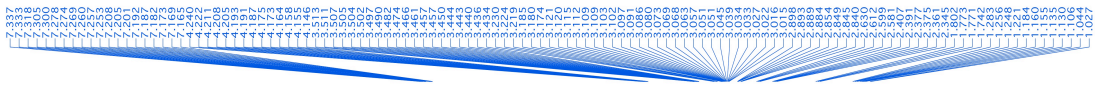
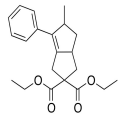
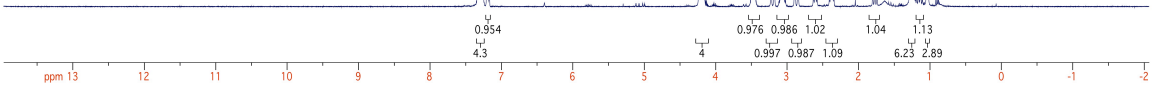
172.088
149.011
126.055
77.160
63.650
61.655
61.534
50.970
46.044
41.839
40.425
33.019
21.395
14.209
ppm 210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


3,35
ppm 9
8
7
6
5
4
3
2
1
0





3.38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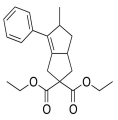
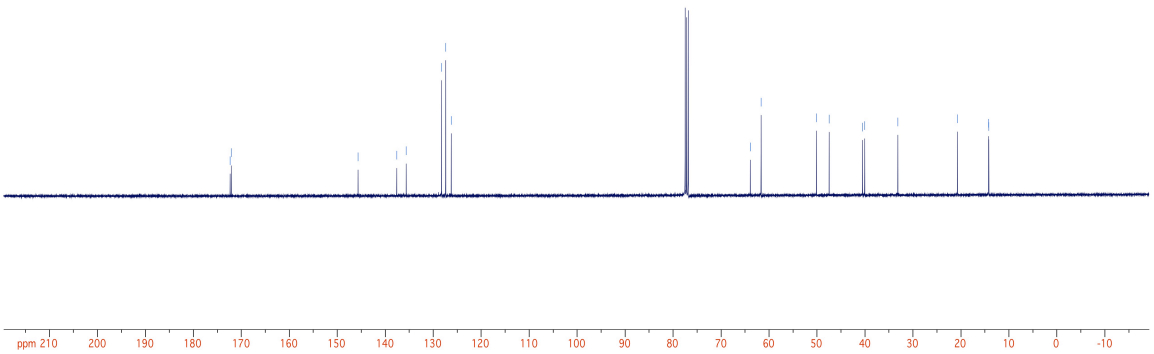
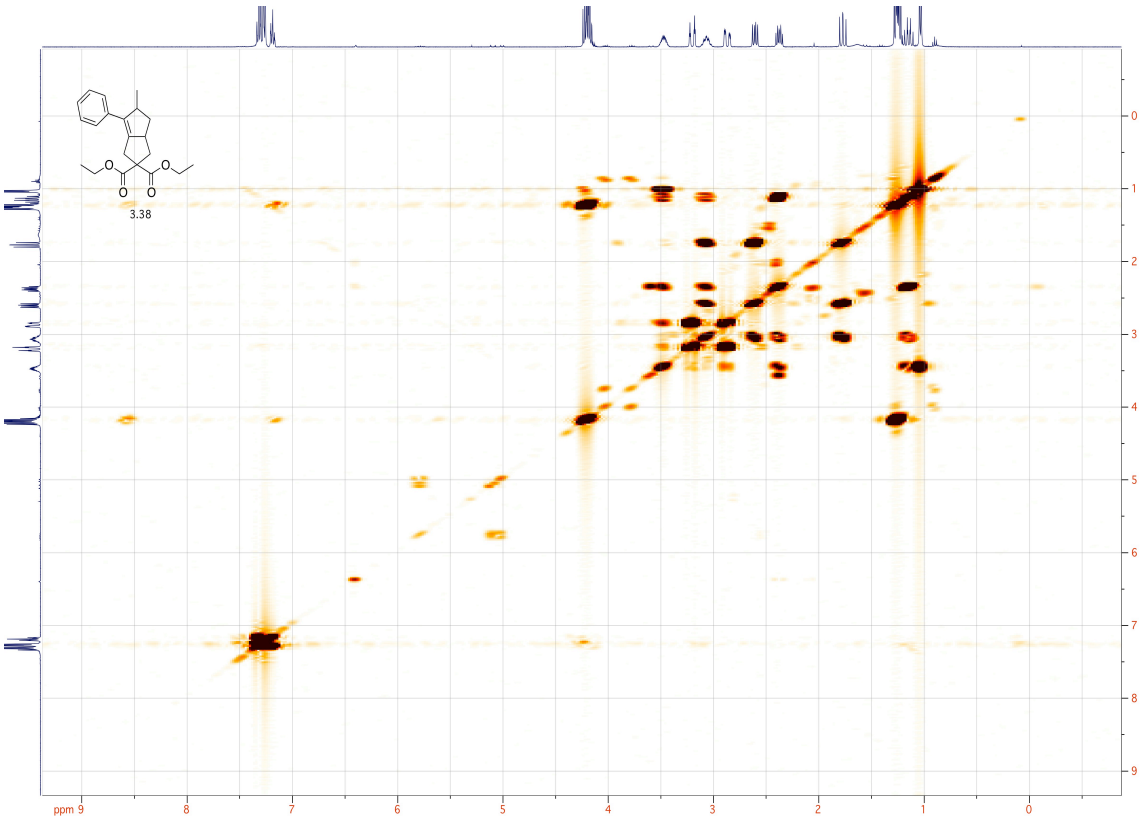
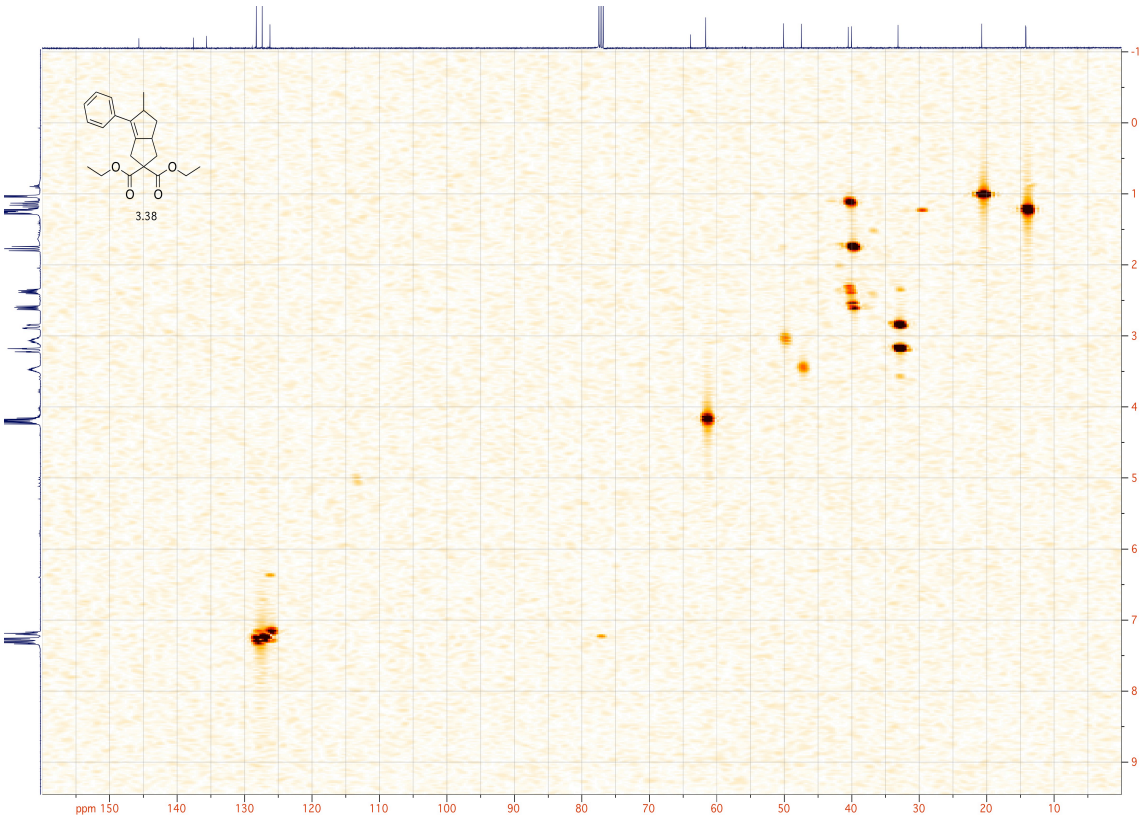
4.3
4
0.976
0.986
1.02
1.04
1.13
0.997
0.987
1.09
6.23
2.89
ppm 13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2

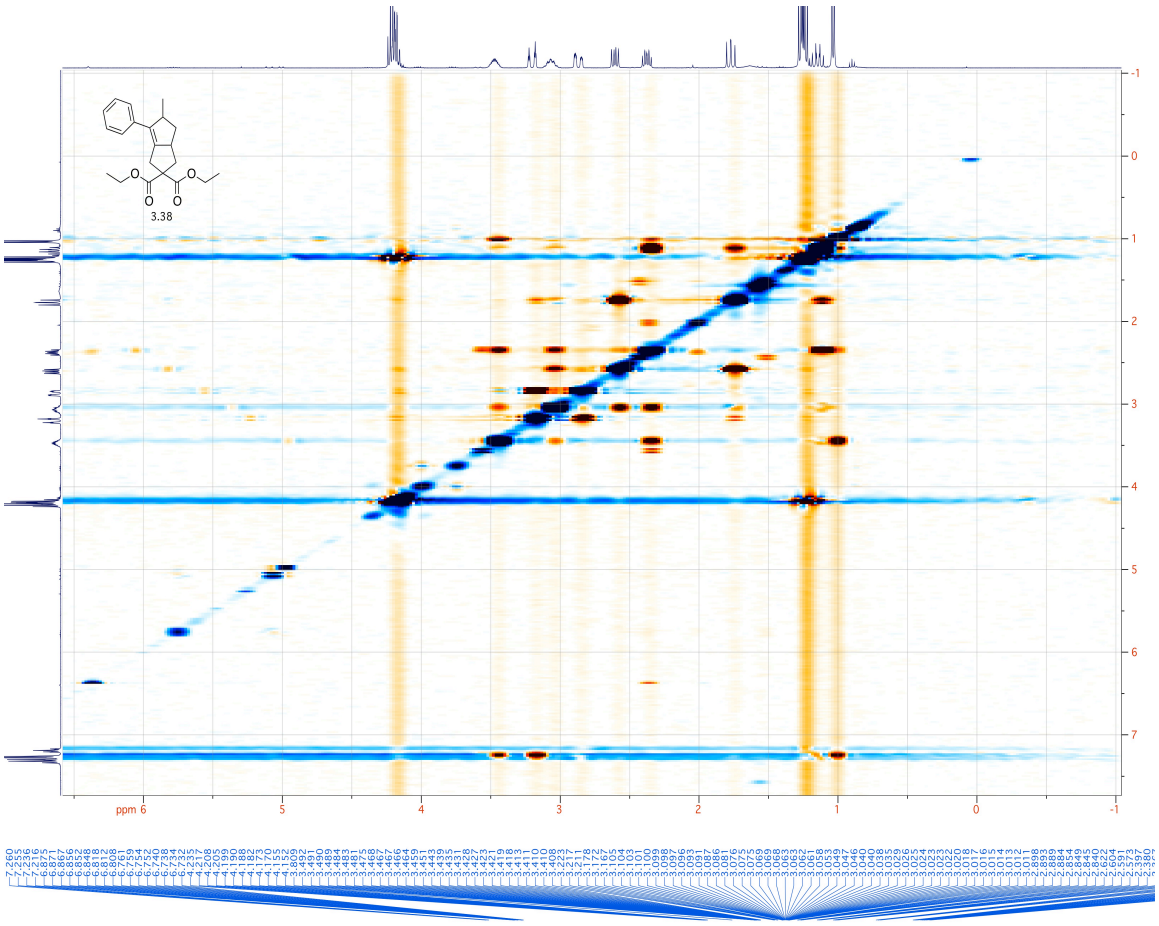


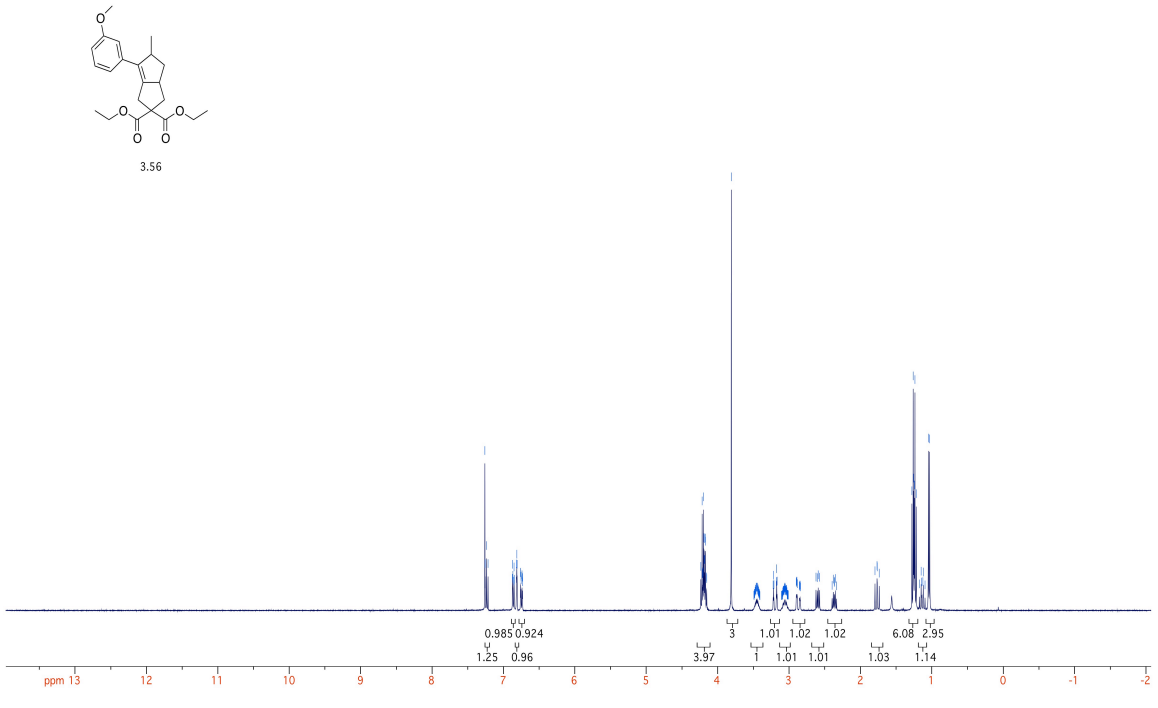
3.38


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


3.38
ppm 9
8
7
6
5
4
3
2
1
0


3,38
ppm 150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


3.38
ppm 6
5
4
3
2
1
0
-1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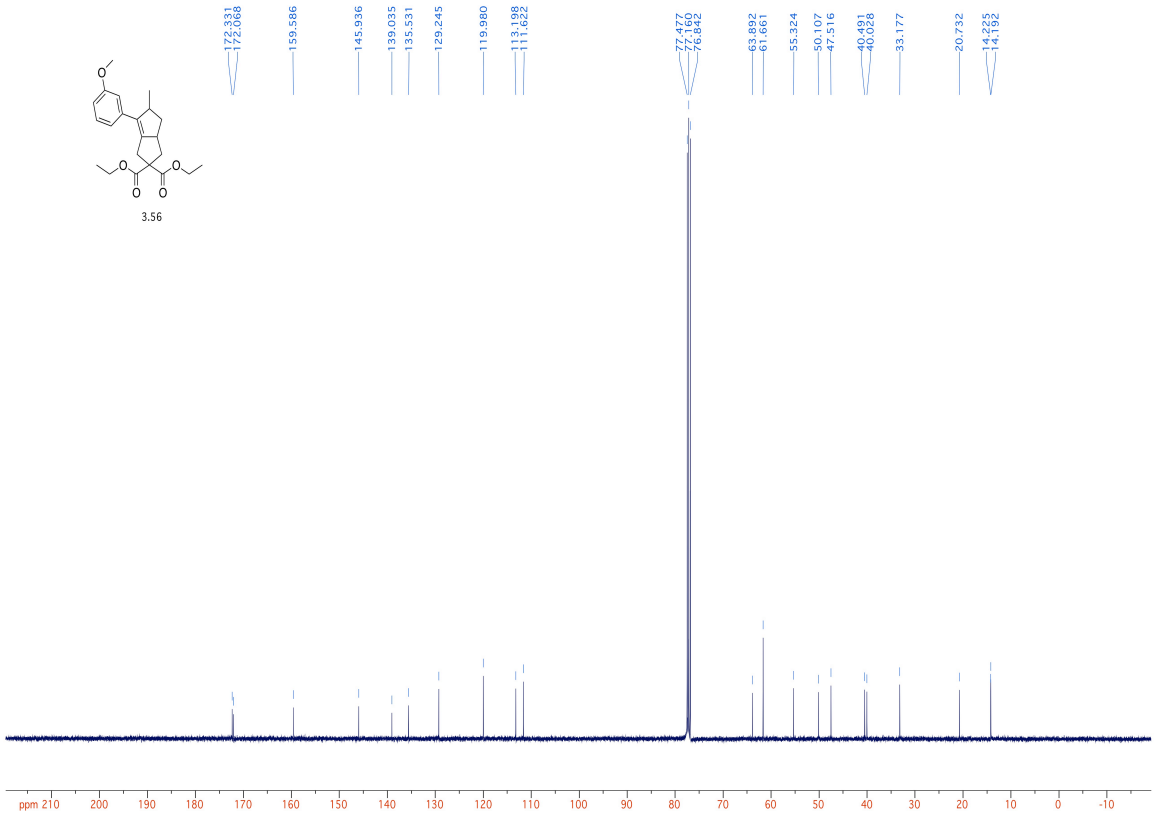
0.985
0.924
1.25
0.96
3.97
3
1
1.01
1.01
1.02
1.01
1.02
1.03
6.08
1.14
2.95
ppm 13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2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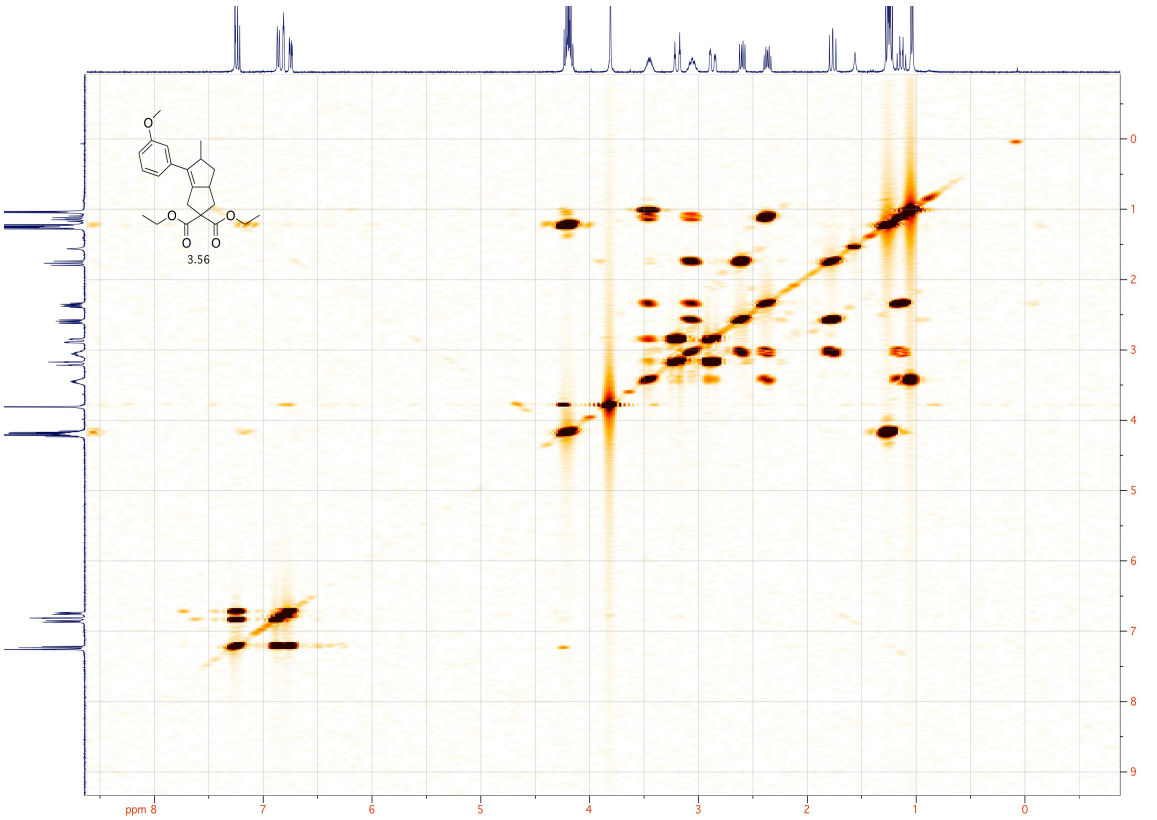
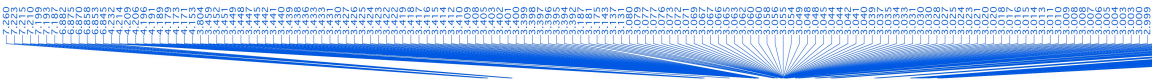
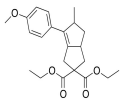
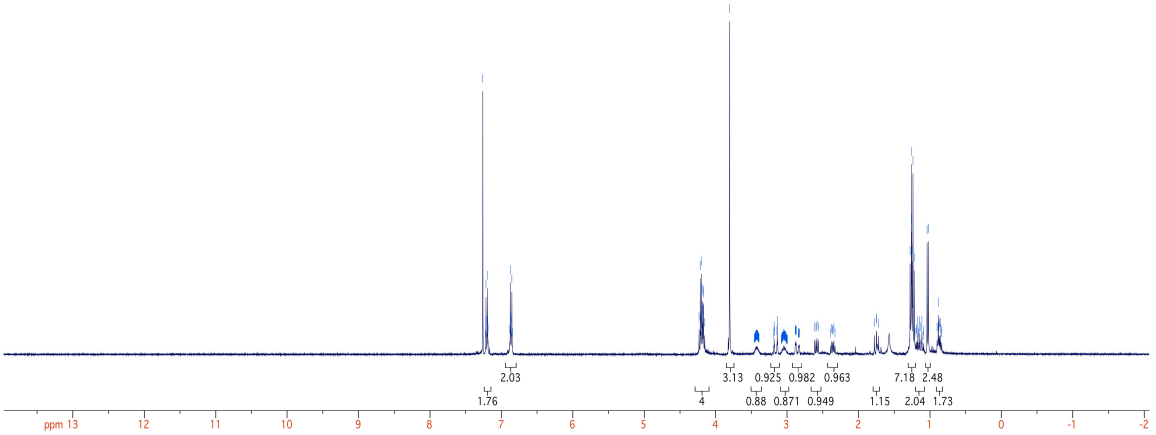
172.088
159.586
145.936
139.035
135.531
129.245
119.980
113.198
111.622
77.477
77.160
76.842
63.892
61.661
55.324
50.107
47.516
40.491
40.028
33.177
20.732
14.225
14.192
3.56
ppm 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

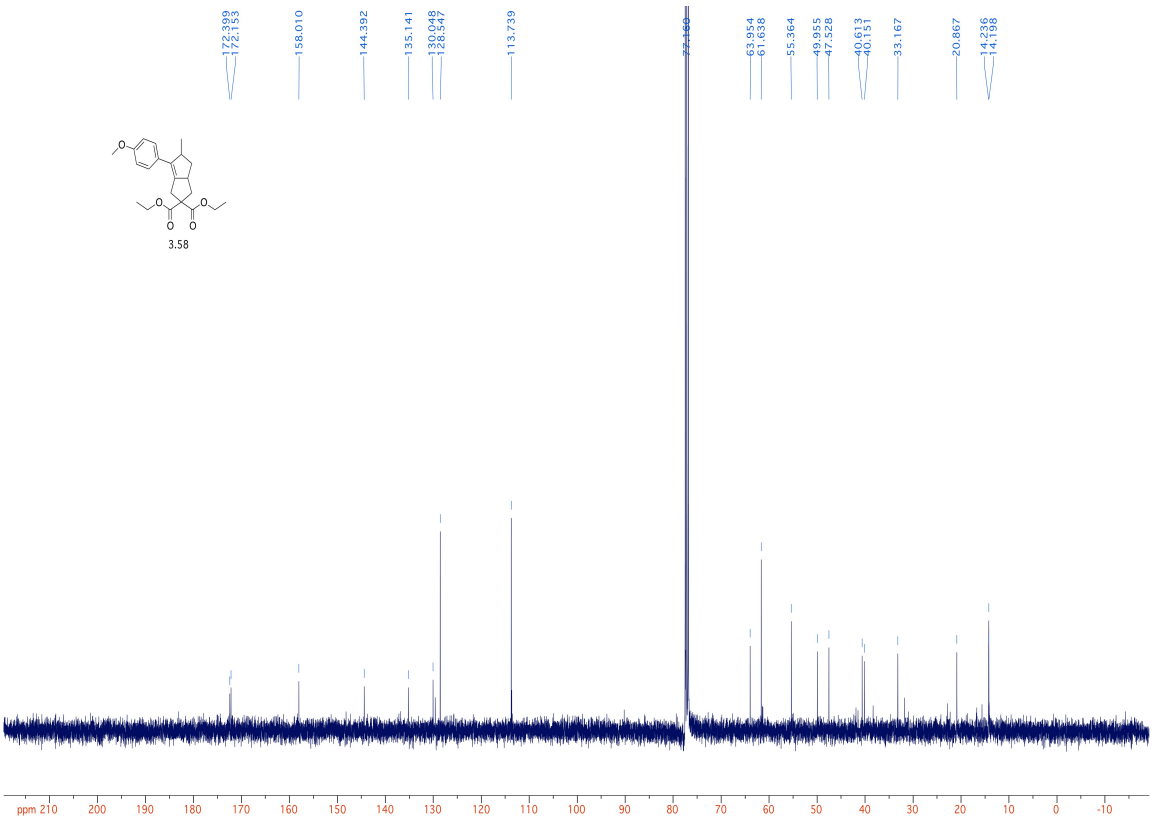

3.56
ppm 8 7 6 5 4 3 2 1 0





3.58


2.03
3.13
0.925
0.982
0.963
7.18
2.48
1.76
4
0.88
0.871
0.949
1.15
2.04
1.73
ppm 13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2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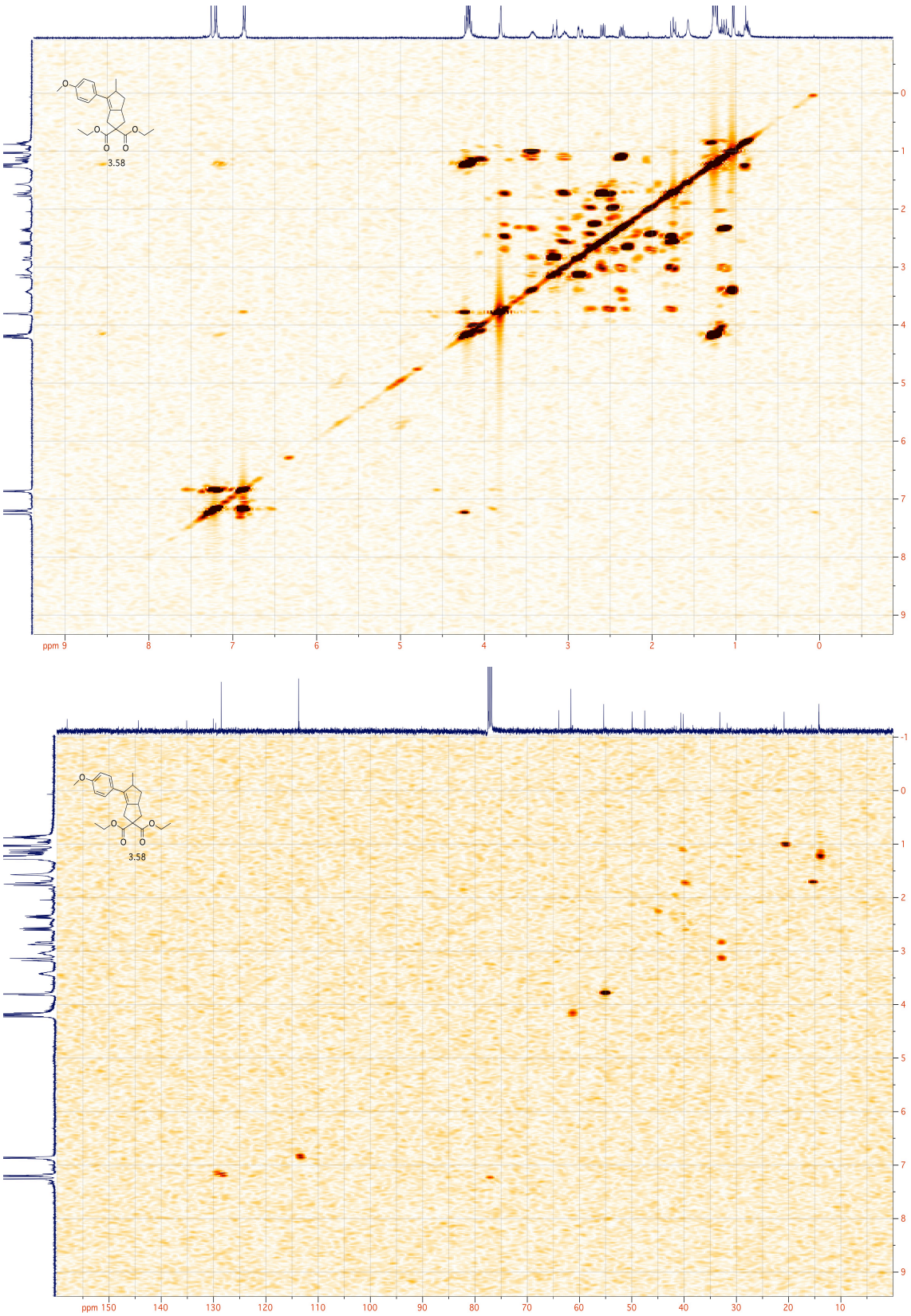
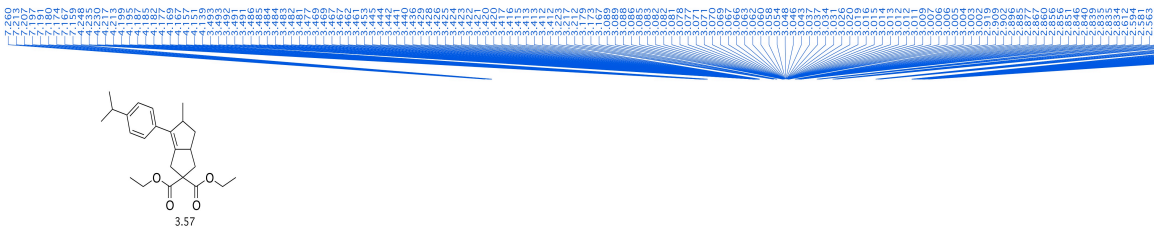
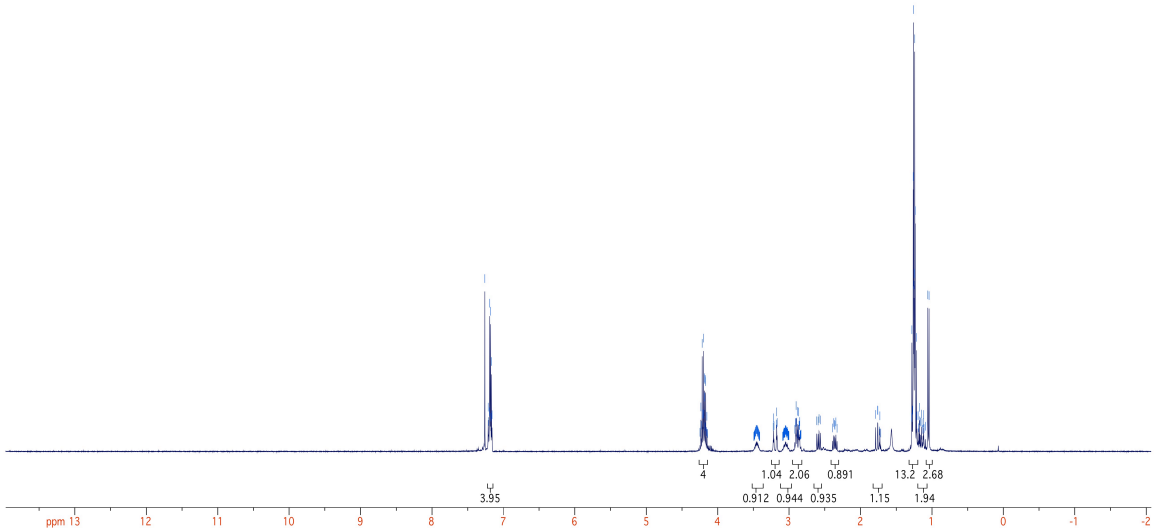
172.193
158.010
144.392
135.141
130.048
128.547
113.739
77.160
63.954
61.638
55.364
49.955
47.528
40.613
40.151
33.167
20.867
14.236
14.198
ppm 210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

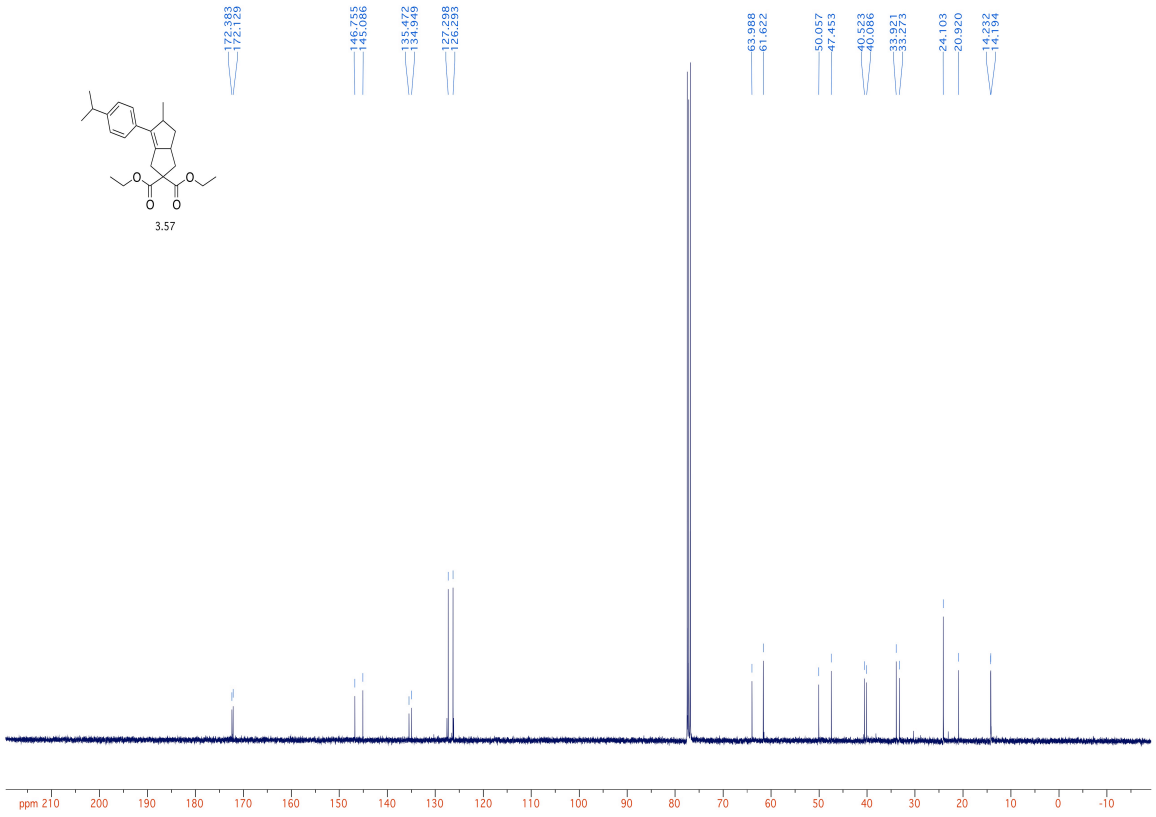
3.58


3.58
ppm 9
8
7
6
5
4
3
2
1
0
3.58
ppm 150
140
130
120
110
100
90
80
70
60
50
40
30
20
10



3.57


4
1.04
2.06
0.891
13.2
2.68
3.95
0.912
0.944
0.935
1.15
1.94
ppm 13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2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172.129
146.755
145.086
135.472
134.949
127.298
126.293
63.988
61.622
50.057
47.453
40.523
40.086
33.921
33.273
24.103
20.920
14.232
14.194
ppm 210
200
190
180
170
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150
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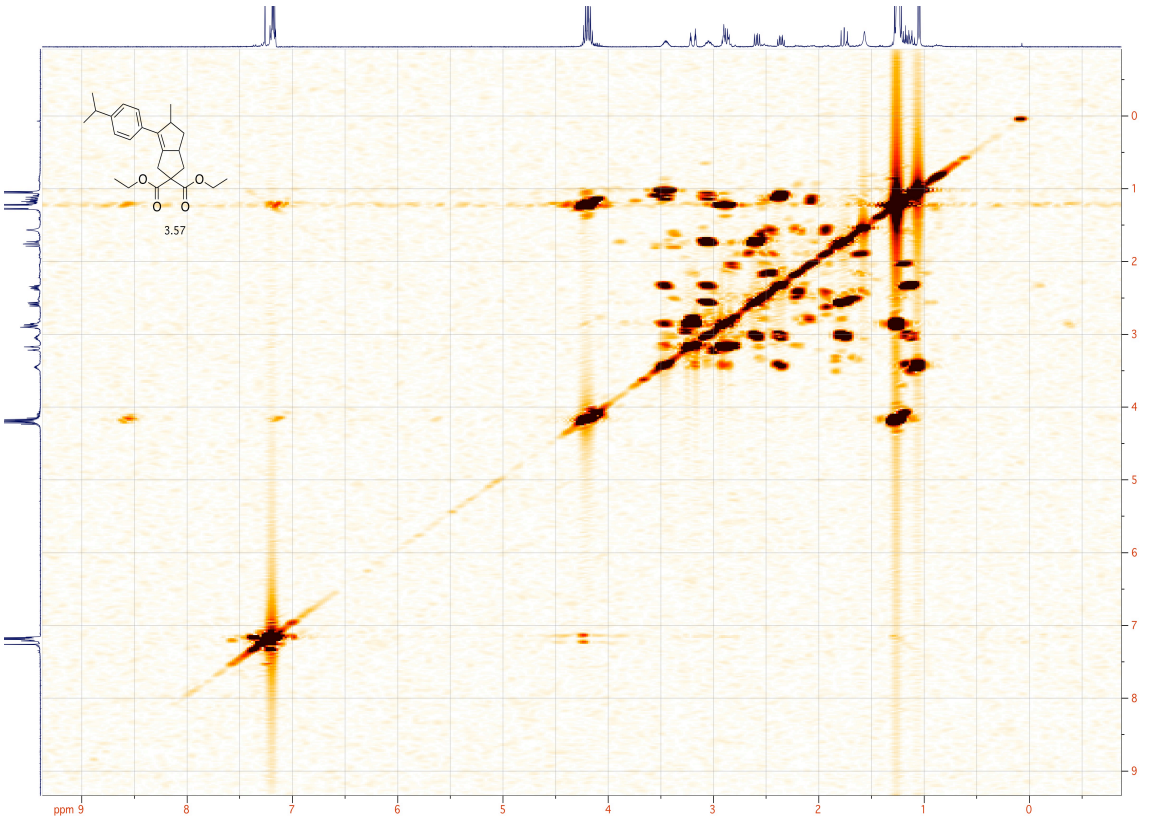
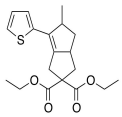
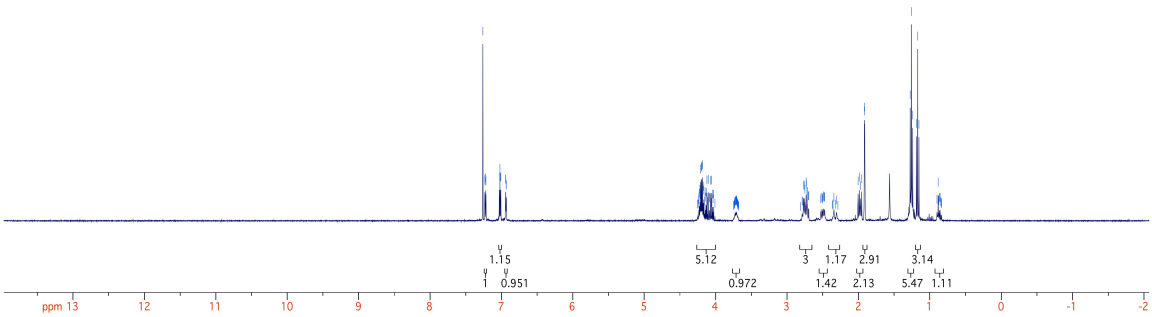
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

3.57


3.57
ppm 9
8
7
6
5
4
3
2
1
0


3.40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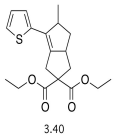
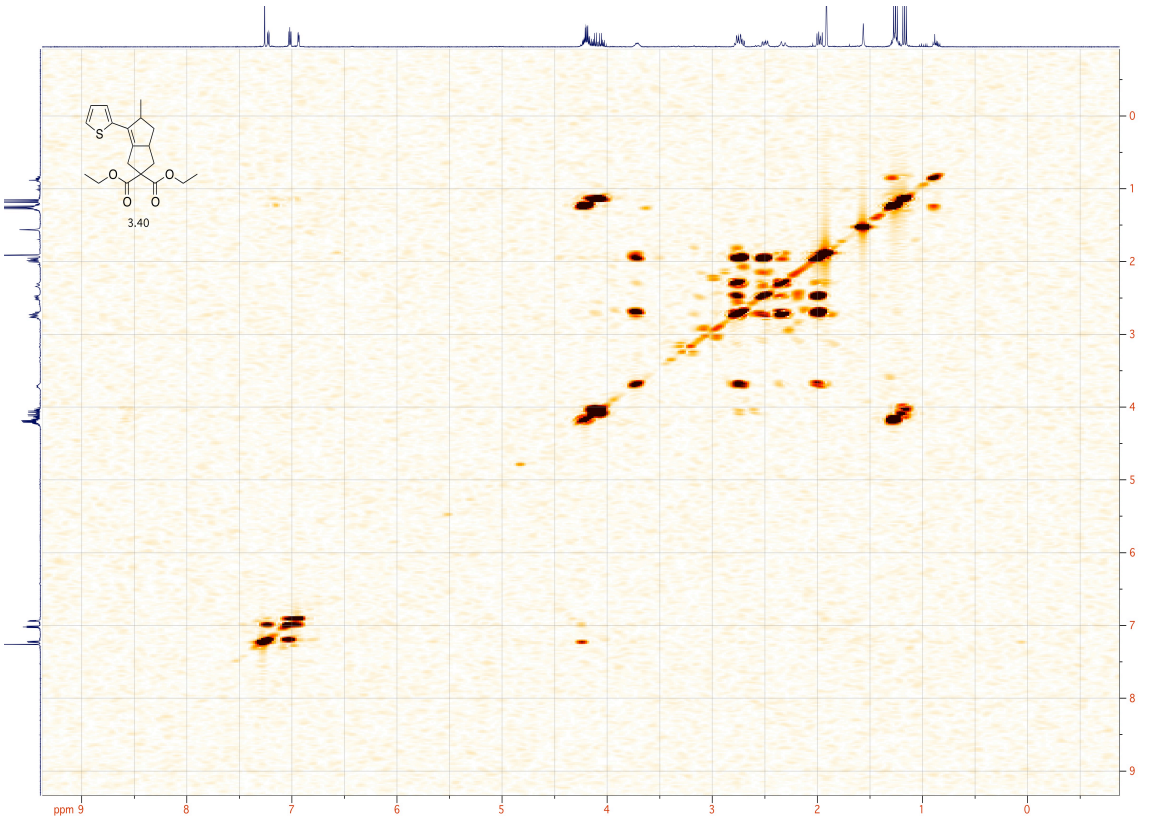
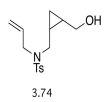
5.12
0.972
3
1.17
1.42
2.91
2.13
3.14
5.47
1.11
ppm 13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2

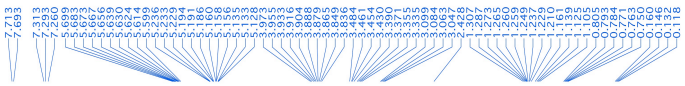

3.40

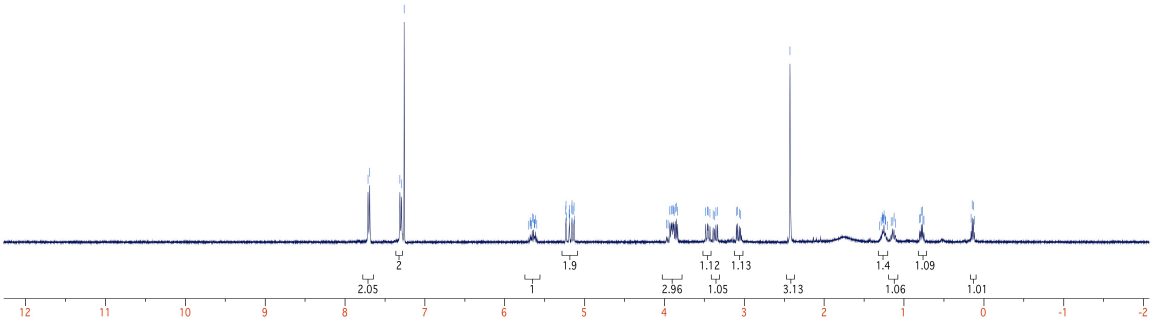
172.274
171.639
140.242
134.304
131.264
126.787
124.953
123.962
77.160
62.116
61.490
61.387
53.984
46.142
41.975
41.055
38.456
16.217
14.218
14.119
ppm 210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

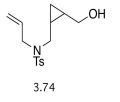

S
O
O
O
O
3.40
ppm 9
8
7
6
5
4
3
2
1
0


OH
N
Ts

3.74

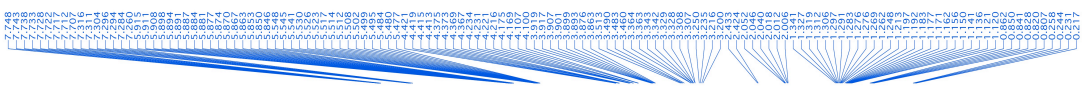



2
1.9
1.12
1.13
1.4
1.09
2.05
1
2.96
1.05
3.13
1.06
1.01


OH
N
Ts

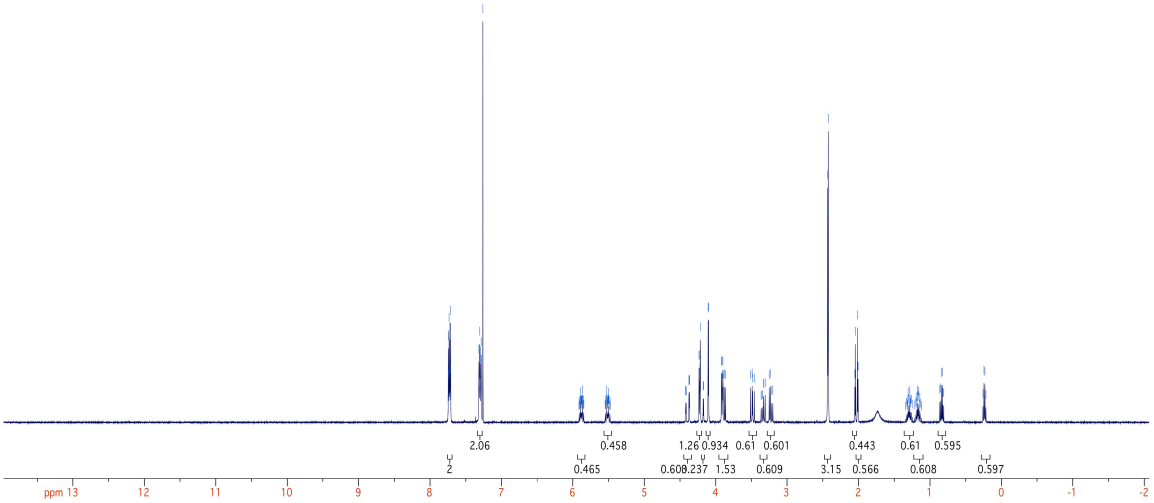
3.74

143.564
133.222
129.886
127.401
118.970
62.327
50.712
46.938
21.679
19.066
14.889
8.645




OH
N
Ts

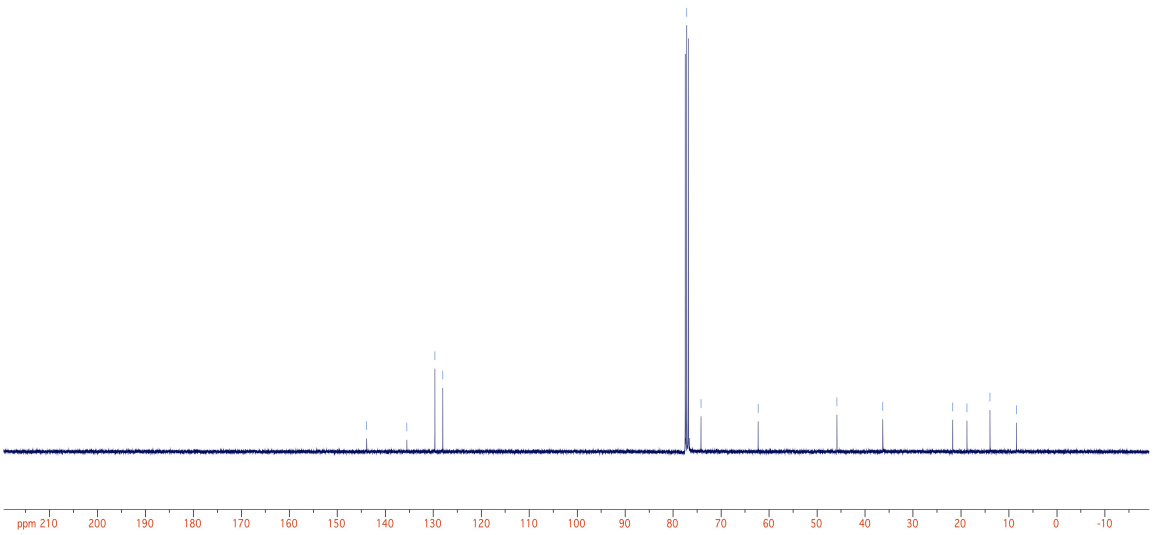
3,75

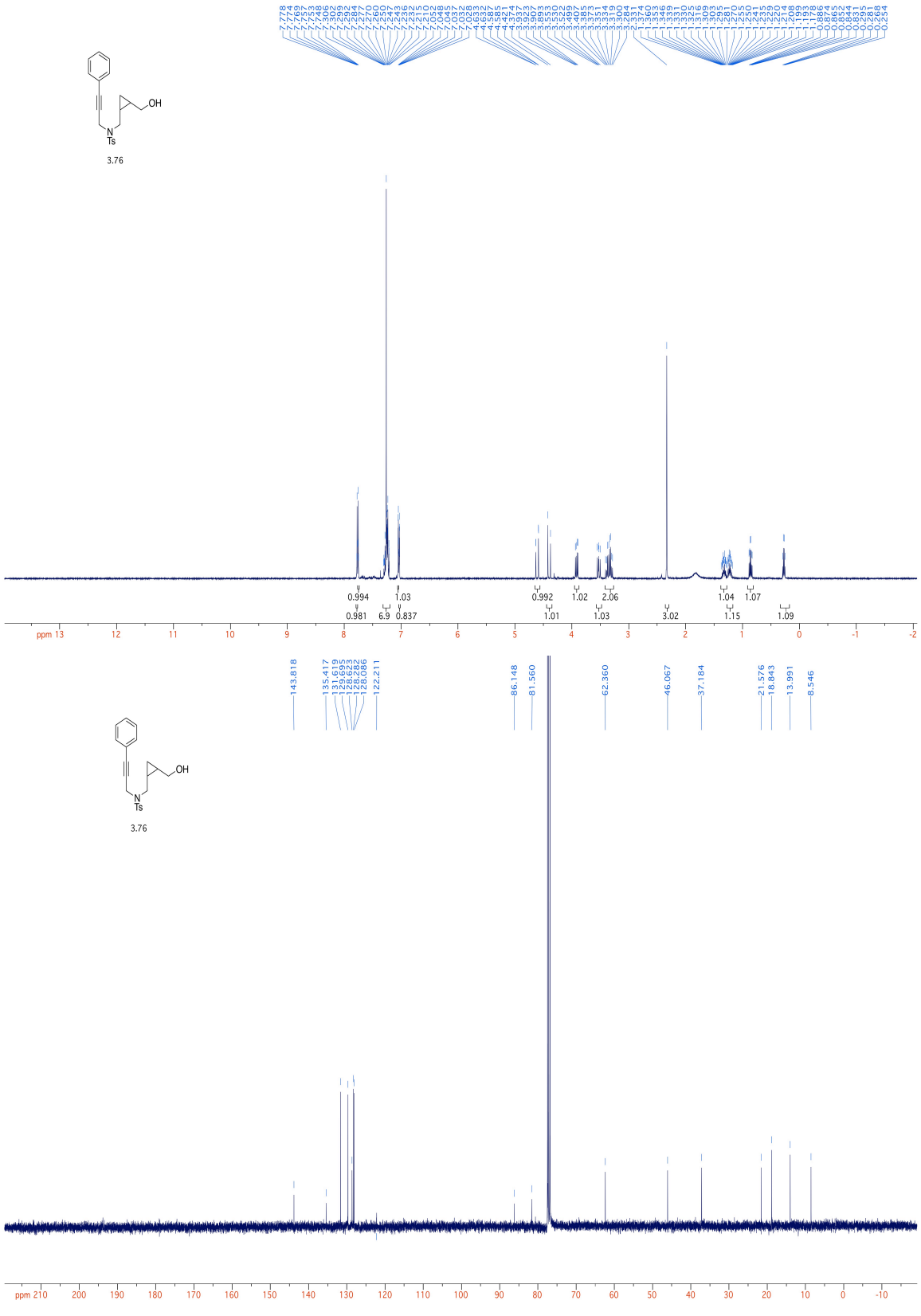

2.06
0.458
1.26
0.934
0.61
0.601
0.443
0.61
0.595
2
0.465
0.608
0.237
1.53
0.609
3.15
0.566
0.608
0.597
ppm 13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2

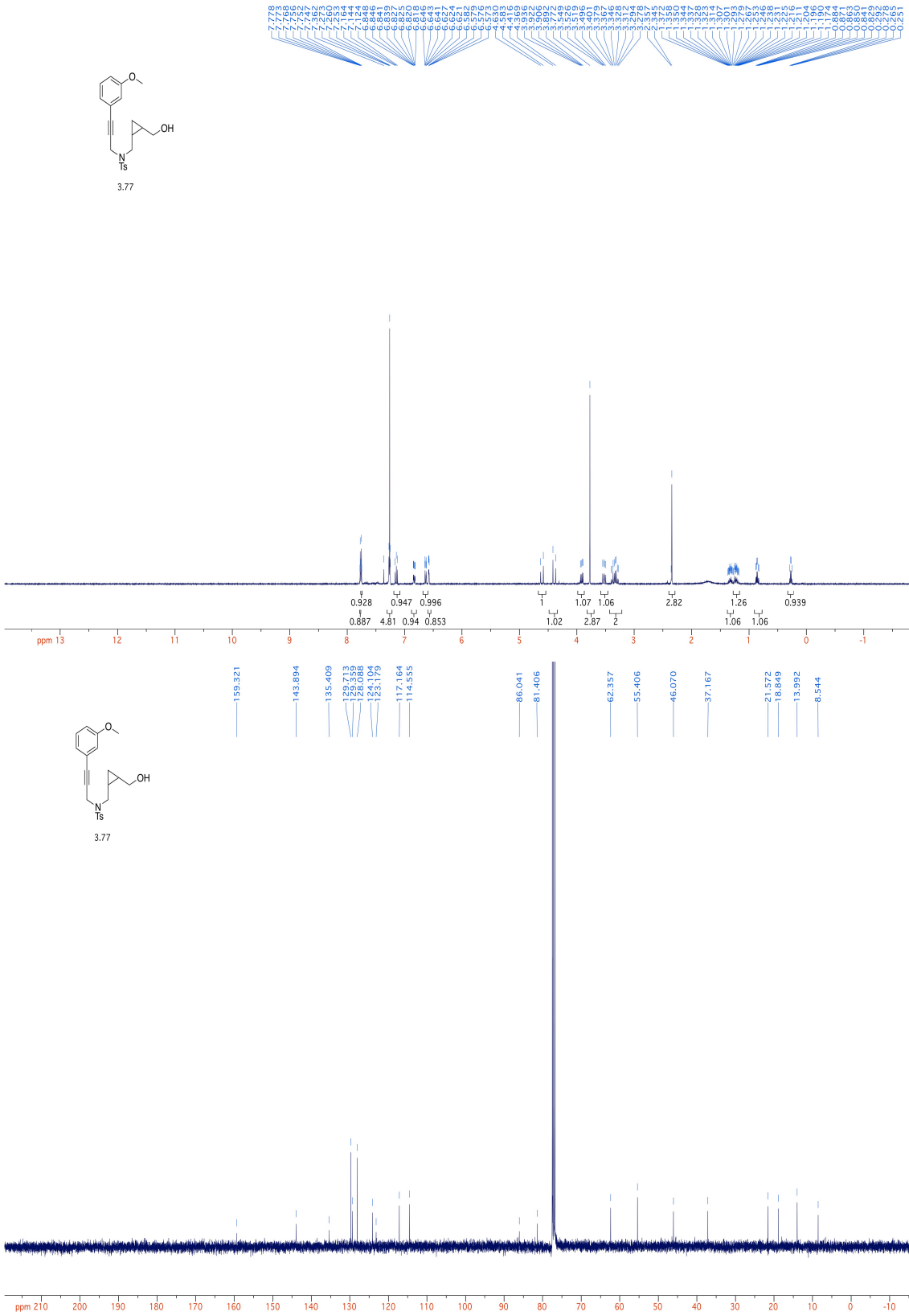

143.862
135.493
129.650
128.002
77.160
74.187
62.286
45.855
36.301
21.706
18.753
13.960
8.445

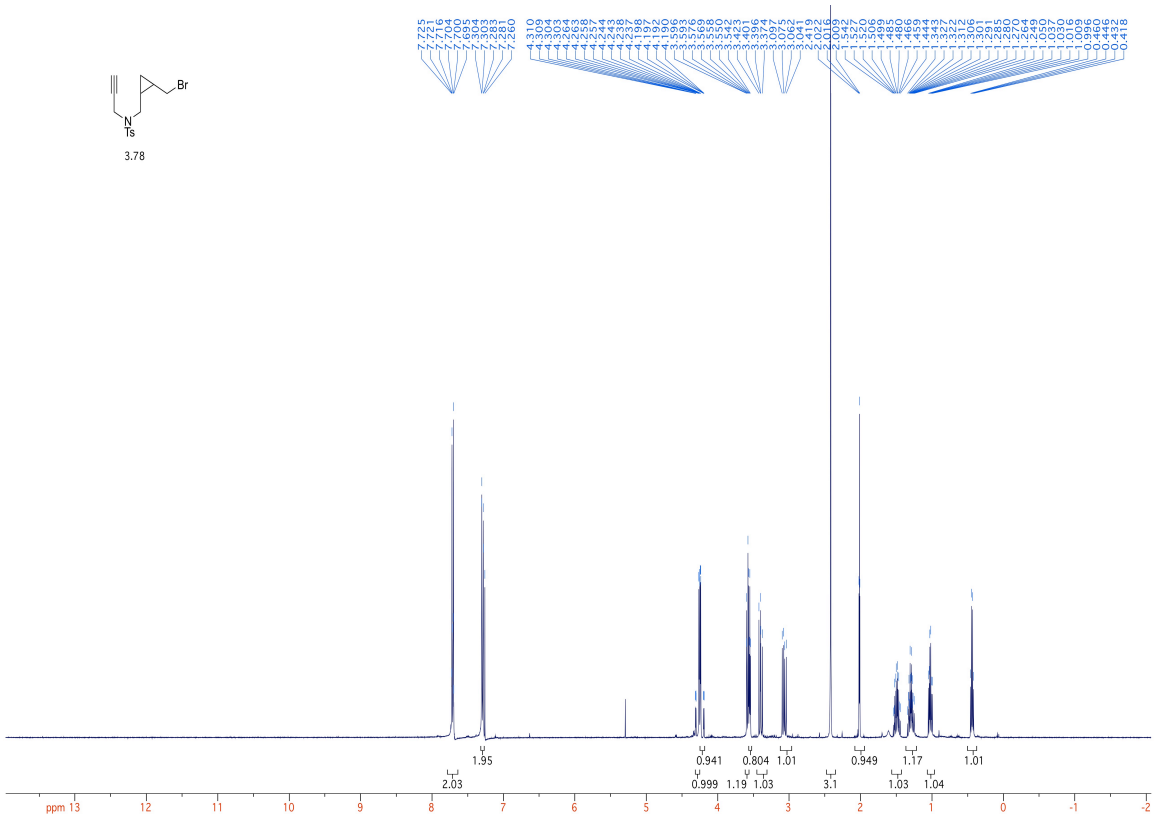

OH
N
Ts

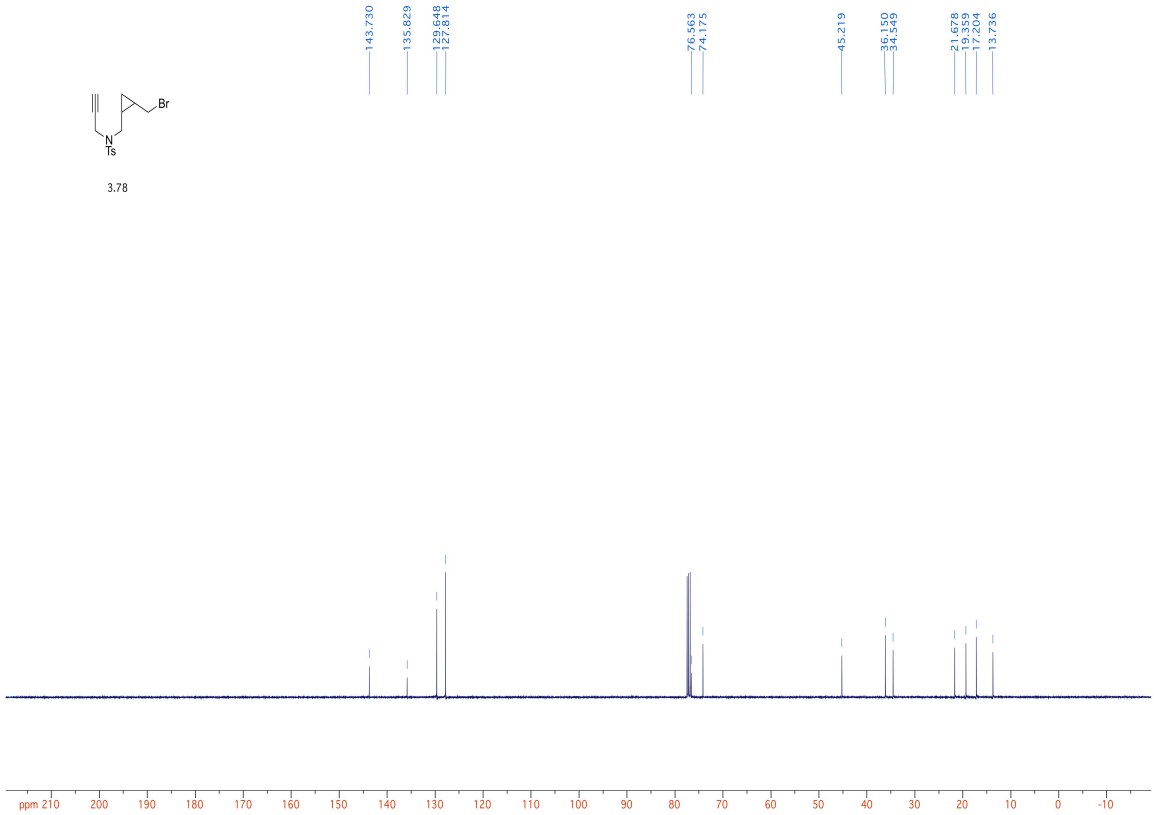
3,75

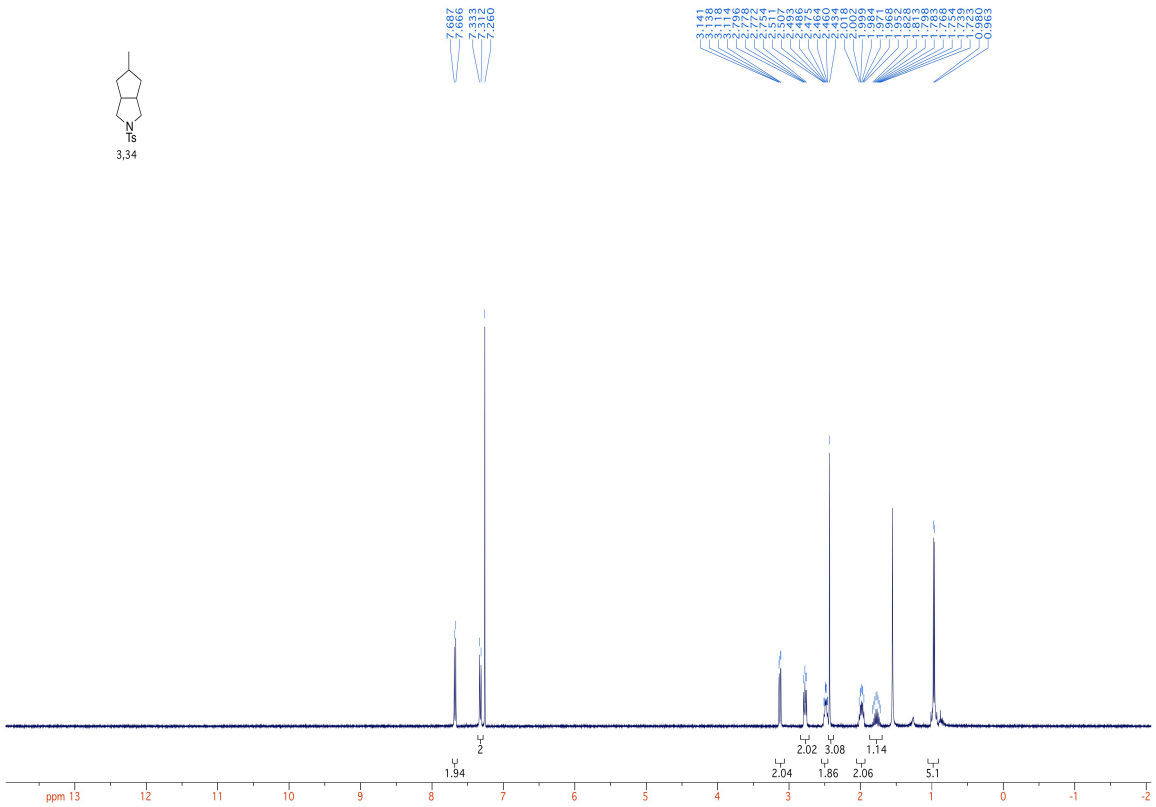

ppm 210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

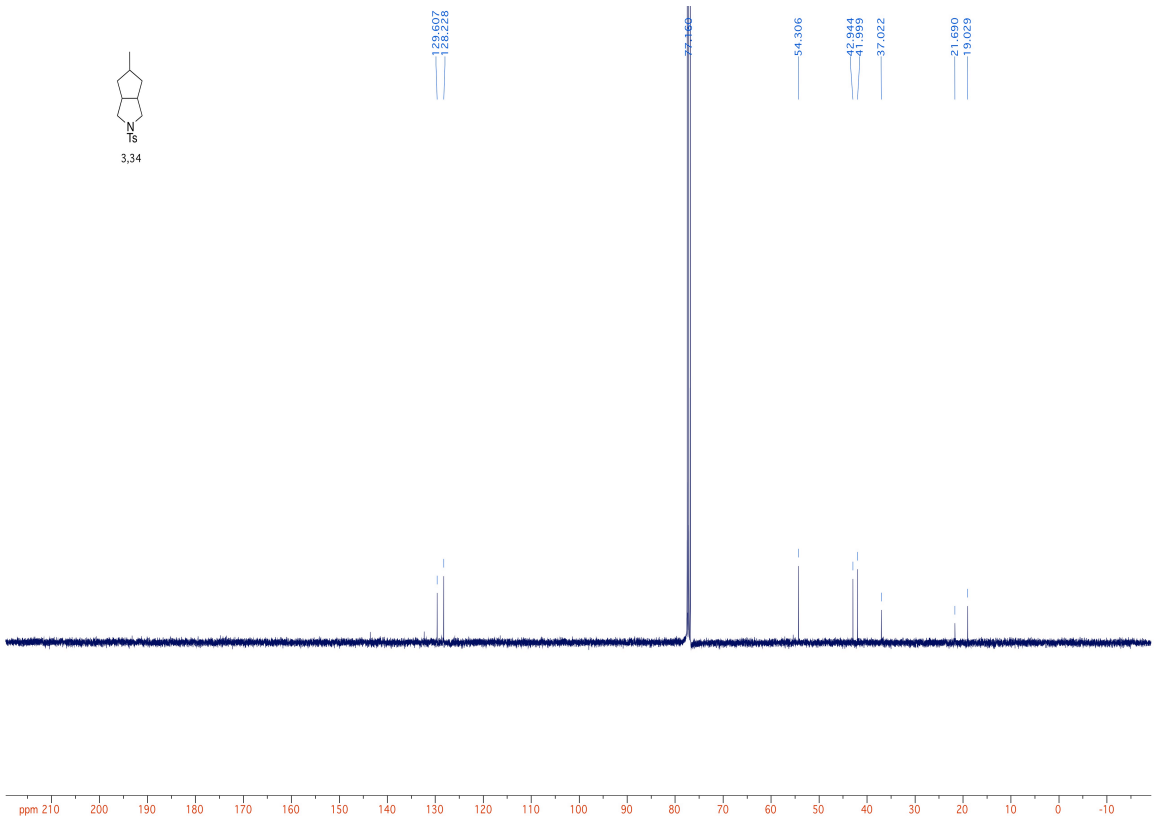

OH
N
Ts
3.76
7.778 7.774 7.769 7.753 7.748 7.306 7.299 7.292 7.284 7.277 7.270 7.260 7.247 7.236 7.215 7.210 7.048 7.045 7.037 7.032 7.028 4.633 4.627 4.585 4.421 4.374 3.837 3.907 3.893 3.530 3.522 3.449 3.407 3.395 3.351 3.334 3.319 3.300 3.284 2.381 1.374 1.360 1.353 1.346 1.339 1.331 1.330 1.316 1.309 1.295 1.291 1.255 1.250 1.241 1.235 1.220 1.214 1.206 1.199 1.193 1.178 0.886 0.874 0.865 0.852 0.844 0.831 0.295 0.291 0.268 0.254
0.994 1.03 0.992 1.02 2.06 1.04 1.07
0.981 6.9 0.837 1.01 1.03 3.02 1.15 1.09
ppm 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
143.818 135.417 131.619 129.695 128.623 128.242 128.086 122.211 86.148 81.560 62.360 46.067 37.184 21.576 18.843 13.991 8.546
ppm 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

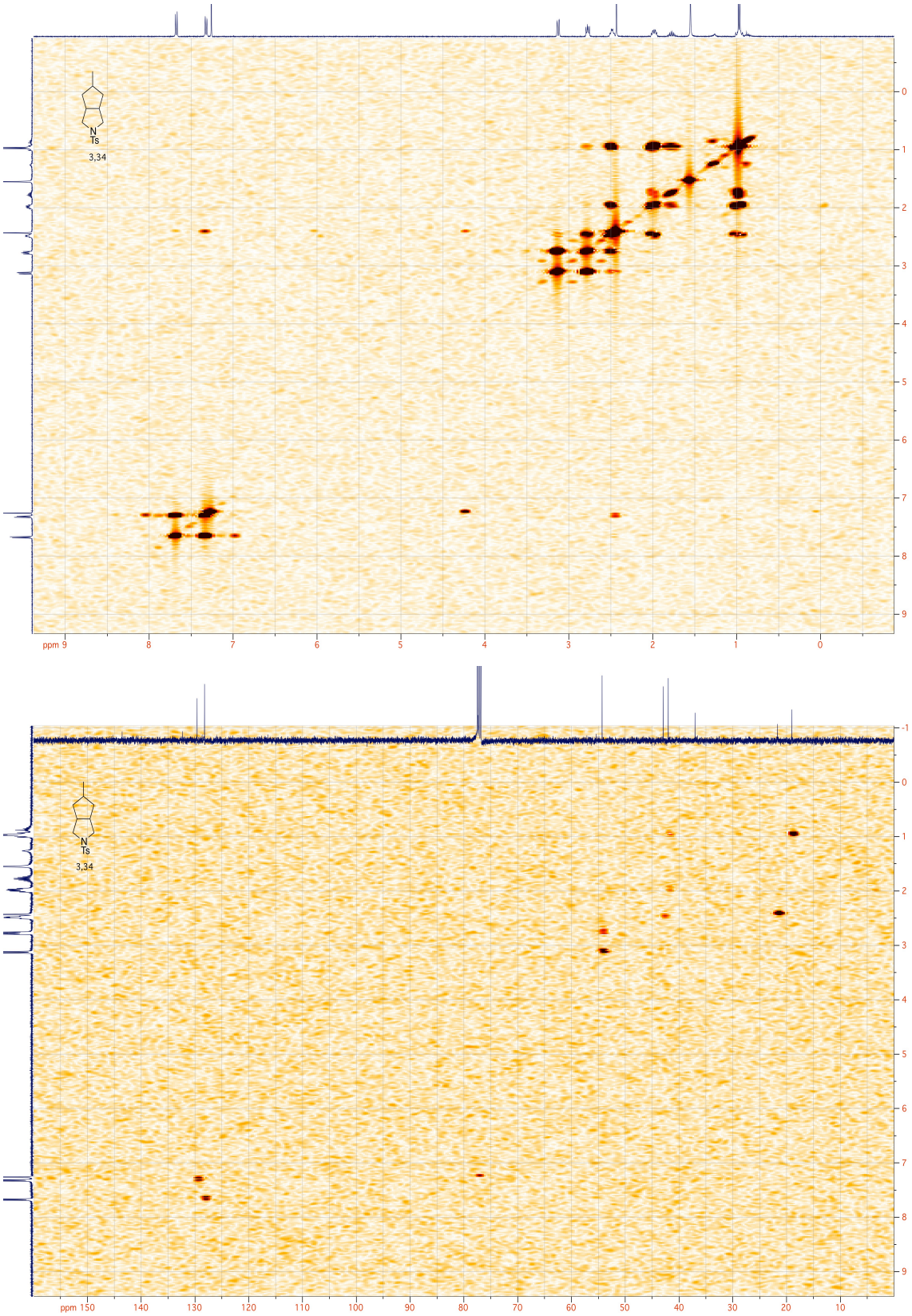

7.778
7.773
7.768
7.756
7.752
7.747
7.742
7.273
7.260
7.164
7.124
6.848
6.846
6.841
6.839
6.837
6.825
6.820
6.818
6.646
6.643
6.641
6.627
6.624
6.621
6.582
6.579
6.576
6.573
4.583
4.581
4.415
4.413
3.936
3.906
3.902
3.897
3.546
3.526
3.518
3.496
3.491
3.479
3.367
3.346
3.332
3.312
3.294
3.284
2.357
2.345
2.337
1.558
1.350
1.344
1.337
1.323
1.314
1.307
1.301
1.293
1.267
1.256
1.246
1.238
1.231
1.225
1.211
1.204
1.196
1.190
1.174
0.894
0.891
0.863
0.850
0.841
0.829
0.278
0.265
0.251
OH
N
Ts
3.77
0.928
0.887
0.947
4.81
0.996
0.94
0.853
1
1.02
1.07
2.87
1.06
2
2.82
1.26
1.06
1.06
0.939
ppm 13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
159.321
143.894
135.409
129.713
129.358
129.088
124.104
123.179
117.164
114.555
86.041
81.406
62.357
55.406
46.070
37.167
21.572
18.849
13.992
8.544
OH
N
Ts
3.77
ppm 210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

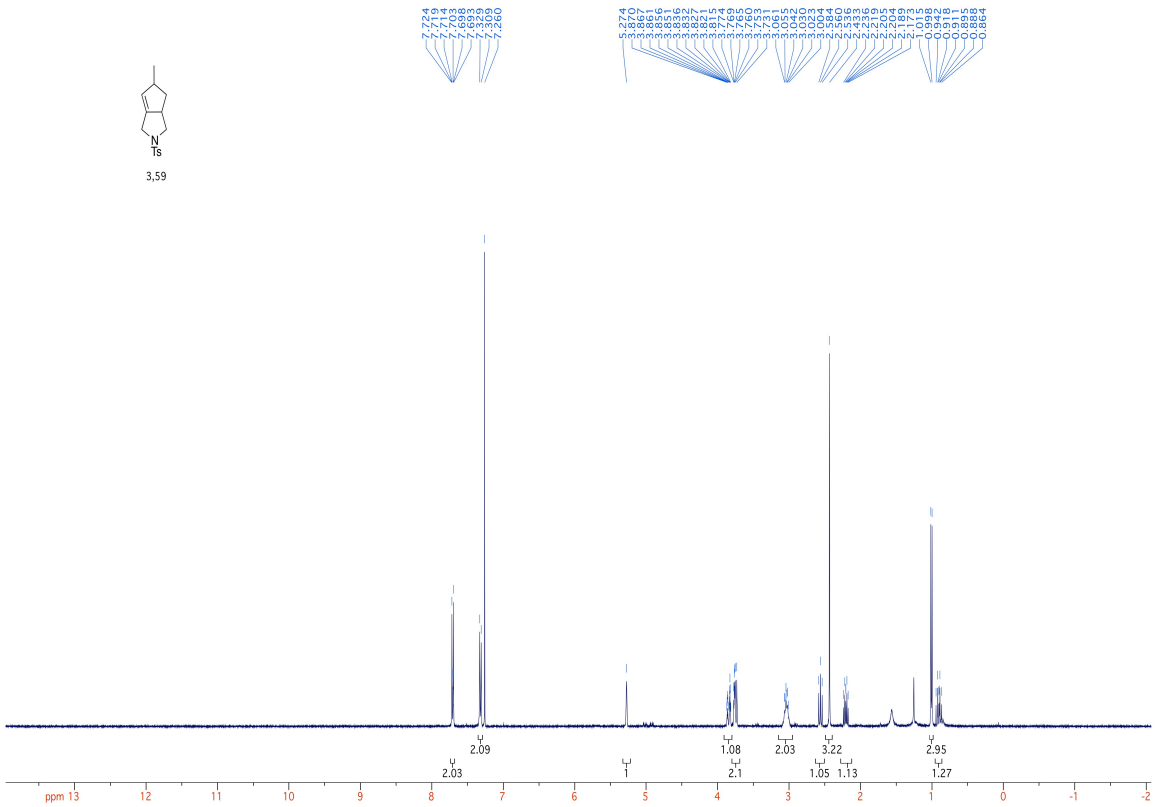

Br
N
Ts
3.78
7.725 7.721 7.716 7.714 7.700 7.695 7.694 7.303 7.283 7.260
4.310 4.309 4.304 4.303 4.264 4.263 4.258 4.257 4.244 4.243 4.238 4.237 4.198 4.197 4.192 4.190 3.596 3.593 3.576 3.569 3.558 3.550 3.543 3.491 3.376 3.374 3.077 3.075 3.062 3.041 2.419 2.021 2.009 1.542 1.527 1.520 1.496 1.485 1.460 1.459 1.454 1.343 1.327 1.322 1.312 1.306 1.301 1.291 1.285 1.270 1.244 1.050 1.030 1.016 1.009 0.996 0.460 0.446 0.432 0.418
1.95 2.03 0.941 0.999 0.804 1.19 1.01 1.03 3.1 0.949 1.03 1.17 1.04 1.01
ppm 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2

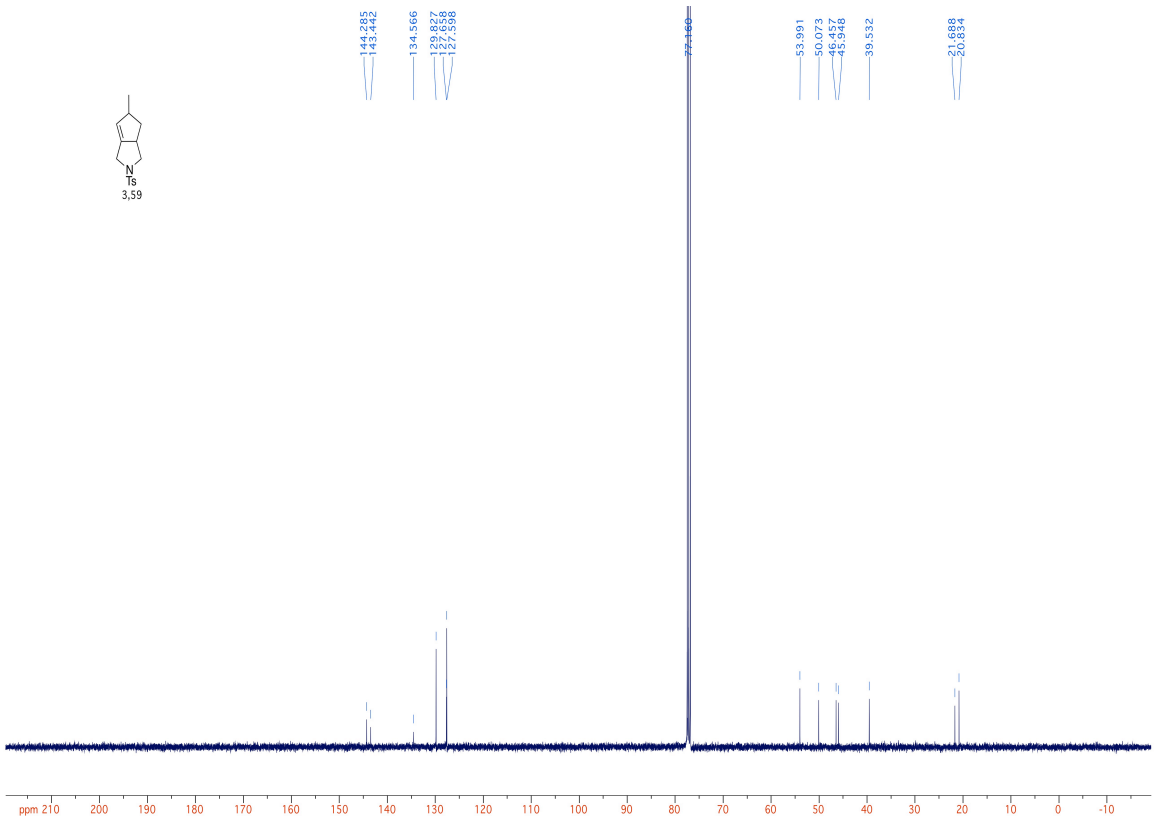

143.730
135.829
129.648
127.814
76.563
74.175
45.219
36.150
34.549
21.678
19.359
17.204
13.736
Br
N
Ts
3.78
ppm 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

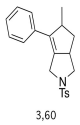

7.687
7.666
7.333
7.312
7.260
3.141
3.138
3.118
3.114
2.796
2.775
2.754
2.751
2.507
2.493
2.486
2.475
2.464
2.460
2.434
2.018
2.007
1.999
1.994
1.991
1.968
1.852
1.828
1.813
1.798
1.783
1.768
1.754
1.739
1.363
0.960
0.963
N
Ts
3,34
1.94
2
2.04
2.02
1.86
3.08
2.06
1.14
5.1
ppm 13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2


129.607
128.228
77.160
54.306
42.944
41.999
37.022
21.690
19.029
N
Ts
3,34
ppm 210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


N
Ts
3,34
ppm 9
8
7
6
5
4
3
2
1
0
N
Ts
3,34
ppm 150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

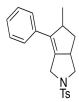

7.724
7.719
7.714
7.703
7.698
7.693
7.369
7.368
7.260
5.274
5.270
3.867
3.861
3.856
3.851
3.833
3.827
3.821
3.815
3.774
3.765
3.760
3.731
3.061
3.055
3.042
3.030
3.020
3.004
2.864
2.850
2.536
2.236
2.219
2.205
2.204
2.189
1.177
1.015
0.998
0.994
0.992
0.918
0.891
0.895
0.888
0.864
N
Ts
3,59
2.09
2.03
1
1.08
2.1
2.03
3.22
1.05
1.13
2.95
1.27
ppm 13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2


144.285
143.442
134.566
129.827
127.658
127.598
77.160
53.991
50.073
46.457
45.948
39.532
21.688
20.834
N
Ts
3,59
ppm 210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


N
Ts

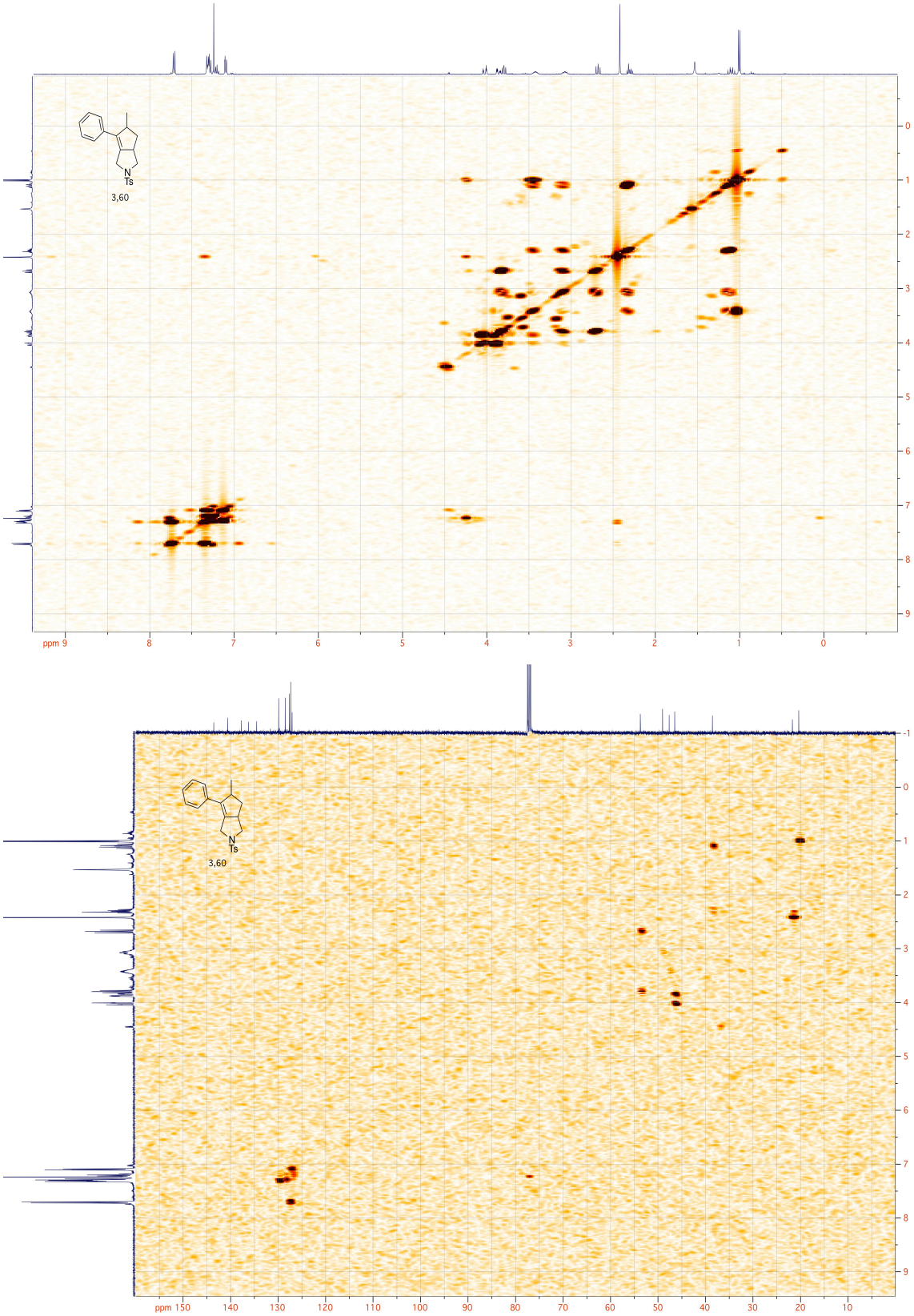
3,60

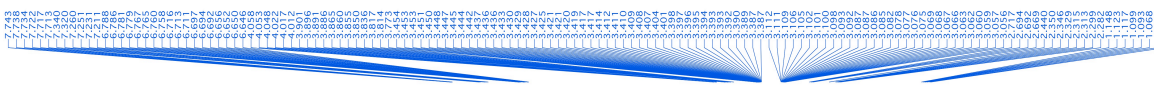
4.08
1.92
1.96
1.01
1.01
1.07
1.08
0.987
1.29
3.02
3.01
1.08
ppm 13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2

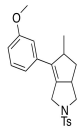

N
Ts

3,60

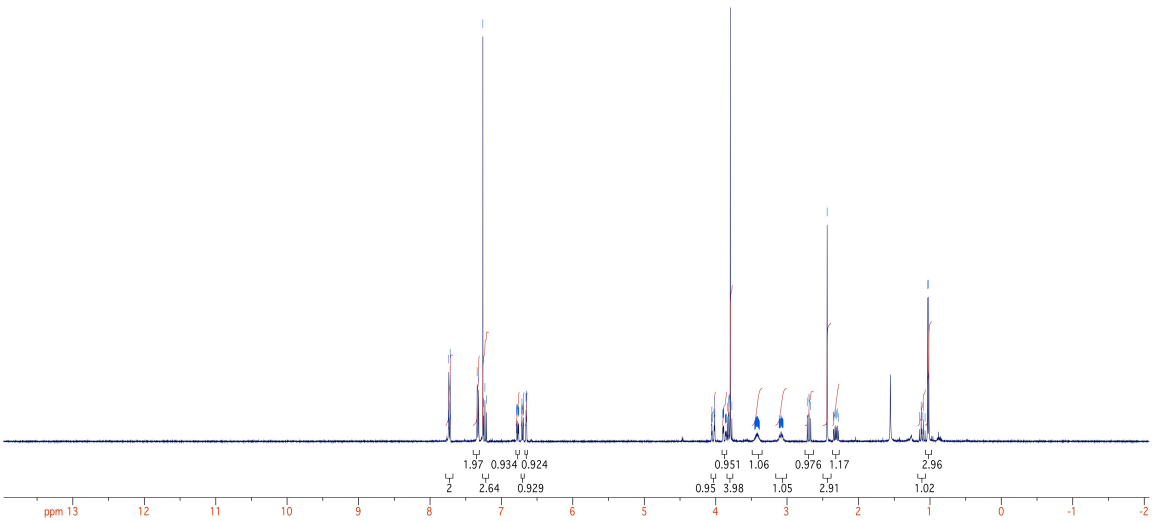
143.552
140.621
137.243
136.745
134.515
129.883
128.133
127.649
127.344
127.034
53.735
49.044
47.657
46.933
38.551
21.708
20.376
ppm 210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

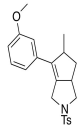

N
Ts
3,60
ppm 9
8
7
6
5
4
3
2
1
0
N
Ts
3,60
ppm 150
140
130
120
110
100
90
80
70
60
50
40
30
20
10





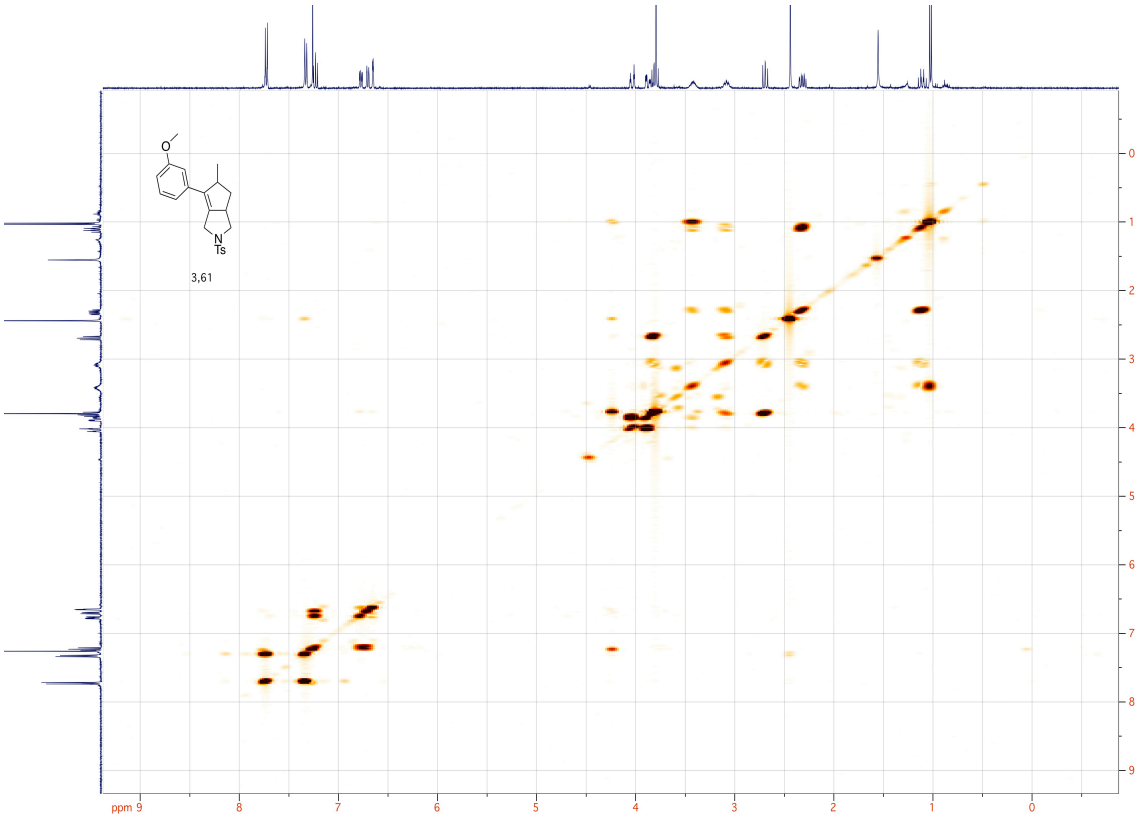
3,61

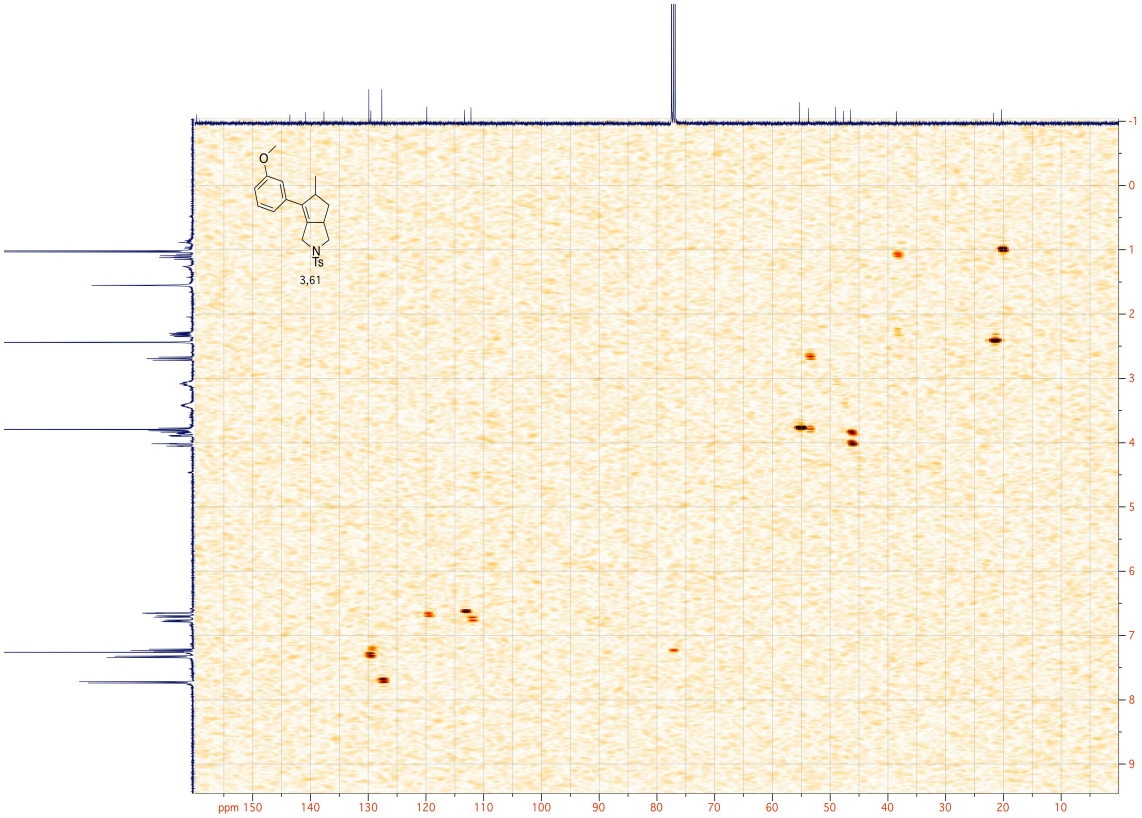

1.97
0.934
0.924
2
2.64
0.929
0.951
1.06
0.976
1.17
2.96
0.95
3.98
1.05
2.91
1.02
ppm 13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2



3,61

159.684
143.558
140.826
137.660
134.491
129.888
129.533
127.642
119.853
113.341
112.201
77.160
55.348
53.729
49.037
47.476
46.475
38.520
21.705
20.346
ppm 210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


O
N
Ts
3,61
ppm 9
8
7
6
5
4
3
2
1
0


O
N
Ts
3,61
ppm 150
140
130
120
110
100
90
80
70
60
50
40
30
20
10