Here Comes the Sun: Applications of Photoredox Catalysis in Organic Synthetic Chemistry

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Abstract

Photoredox catalysis has been a flourishing field in synthetic organic chemistry. Organic chemists have been inspired by Nature and the conversion of photons into potential energy by light-harvesting biomolecules. Recent developments in photoredox catalysis have led to a rapid increase in development of new methodologies in synthetic organic chemistry. The use of transition metal photocatalysts and organic dyes in photo-mediated processes has been proven to be an effective alternative to the harsh and toxic reaction conditions that area needed in classical radical formation. Photoredox catalysis eliminates the need of initiators, stoichiometric additives, and strong oxidants, and allows for the highly efficient formation of new C-C bonds under mild conditions. Photochemistry and radical chemistry work in unison in their ability to undergo photoinduced single electron transfers (SET) or photoinduced electron transfers (PET) and enable one electron reaction pathways.

A plethora of photocatalysts have been developed, mainly using Ir- and Ru-based polypyridyl complexes. Polynuclear gold complexes have come to light in the last decade as another class of photocatalysts. This bench stable complex is marked by its unique photophysical and electrochemical properties, most notable the relatively long-lived excited state. This triplet excited state can be used as a powerful reductant or oxidant when irradiated with UVA light. A class of organic substrates that can be used when working with this gold photocatalyst, is nonactivated bromoalkanes, which could not be used if working with other photocatalysts.

First, the alkylative semi-pinacol using gold photoredox chemistry and nonactivated bromoalkanes was described. A new mode of reactivity of the gold binuclear photocatalyst was found where it was shown to work as a photocatalyst and a Lewis acid. Next, a follow-up to that

report was the halogen atom transfer radical addition (ATRA) using gold photoredox catalysis. A mild ATRA reaction was presented where the dual reactivity of the gold photocatalyst was exploited. Mild bromine and iodine transfer reactions, without the use of strong oxidants or toxic additives, are largely unknown, and a metal-based mechanistic pathway was proposed to explain this transformation.

Minisci-type alkylation is of high-interest in the field of medicinal chemistry and drug discovery. With this is mind, a photoredox catalysed Minisci reaction was presented, where the alkylation of an activated heteroarenes was achieved by HAT *via* chlorine atom generation. Knowing this, the alkylation using primary alcohols was presented, were a the α-alkoxy radical is formed after a HAT by chlorine atom. When secondary alcohols were used, a reduction of the heteroarene occurred and was described.

Finally, a photo-mediated [3 + 2] cycloaddition using *N*-aryl cyclopropylamines and α, β-unsaturated carbonyl systems was described. This simple method that was presented does not require the use of photocatalysts or added additives, as it is self-catalyzed. The reaction is proceeding through a single electron transfer (SET) and offers a wide scope for the synthesis of *N*-arylaminocycloalkyl compounds.

Overall, the collection of work described in this thesis represents the growth of photoredox catalysis in organic synthetic chemistry and the ability to form highly reactive radical without the need of harsh conditions, toxic reagents, or strong oxidants. The use of binuclear gold(I) complexes as a photocatalyst with unique photophysical and electrochemical properties was shown. Compared to Ir- and Ru-based polypyridyl complexes, which cannot react with nonactivated bromoalkanes, the binuclear gold(I) complexes offer broader redox potentials and

a newfound dual mode of reactivity. Furthermore, photo-mediated synthetical useful reactions were shown. The application of photoredox catalysis in synthetic chemistry will continue to flourish, and this work is sample of all the possibilities that a simple photon can bring.

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I would like to dedicate this thesis to Saeed Kashani, who passed away after the tragic January 2020 Tehran plane crash. He was taken from us too early and could not complete his Ph.D.

Contribution Statement

The work in this thesis is my own, unless specified. All of the projects described in this thesis were conducted under the guidance and supervision of Prof. Louis Barriault. The projects presented in thesis were published in various journals, all the figures, tables and data have been reproduced with the permission of the publishers.

All starting material synthesis, product formation, purification and isolation, and characterization described in the individual experimental sections pertain to my work, unless otherwise noted. Compounds that appear in each chapter but do not appear in the experimental section were synthetized by students under my guidance or working in the same project and will appear in their undergraduate thesis/report. Most notably, in Chapter 2, certain starting materials and desired products were synthetized by Léa Thai-Savard, Weldon Blastorah and Patrick Ferrari.

In Chapter 2, the use of $Au_2(dppm)_2Cl_2$ to perform an alkylative semi-pinacol rearrangement using nonactivated bromoalkanes was conceived by Dr. Terry M^{c}Callum, Dr. Mathieu Morin. Experimental design was developed by all authors affiliated with this publication. My contributions entailed to optimization and scope formation, including synthesis of starting materials, product isolation and characterization. Mechanistic studies and quenching experiments were performed by Dr. Terry M^{c}Callum. Discovery of the alkylative tetrahydrofuran-ring formation using gold photoredox and Lewis acid catalysis was done while the scope of alkylative semi-pinacol rearrangement was being finished. Further work in the alkylative ring formation was carried out by Weldon Blastorah and Patrick Ferrari under my guidance during his undergraduate studies.

In Chapter 3, the use of $Au_2(dppm)_2Cl_2$ to photo-mediate the formal halogen atom transfer radical addition was discovered by Dr. Terry M^{c}Callum, Dr. Mathieu Morin, and Prof. Louis Barriault. Early studies and optimization were explored by Rowan Swann under my supervision during her undergraduate studies. My contributions included finishing the optimization of the reaction and developing the scope of the reaction, along with product isolation and subsequent characterization.

In Chapter 4, the alkylation and reduction of heteroarenes using photoredox catalysis and chlorine atom generation was proposed by Dr. Terry M^{c}Callum and Prof. Louis Barriault. My role consisted in the development of the reaction conditions, isolation of the products and characterization. Reaction optimization was performed with Avery O. Morris, under my guidance during his honours project. Designing corresponding mechanistic studies was done by Dr. Terry M^{c}Callum. Characterization of deuterated products was done alongside Dr. Terry M^{c}Callum.

In Chapter 5, the application of photoredox catalysis to perform [3 + 2] of *N*-aryl cyclopropylamines was proposed by Prof. Louis Barriault. My role consisted of the development of the reaction's conditions, synthesis of the starting materials, isolation of the products, subsequent characterization, and design of mechanistic studies. Furthermore, my role extended into the discovery and development of photo-mediated [4 + 2] *N*-aryl cyclobutylamines.

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But, with a little bit of luck, with a little bit of luck

I could have spread my wings and done a thousand things

- Alan Jay Lerner, My Fair Lady, 1956

Dios Mediante

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Glossary of Abbreviations

Ac	acetate
Ad	adamantyl
AIBN	2,2’-azobisisobutyronitrile
ATRA	atom transfer radical addition
Ar	aryl
BDE	bond dissociation enthalpy
Bn	benzyl
bpy	2,2’-bipyridine
brsm	based on recovered starting material
$CDCl_3$	d-chloroform
CFL	Compact fluorescent light bulb
DABCO	1,4- diazobicyclo[2.2.2]octane
DCE	dichloroethane
DCM	dichloromethane
DIPEA	*N,N*-diisopropylethylamine
DMA	*N,N*-dimethylacetamide
DMF	*N,N*-dimethylformamide
DMS	dimethylsulfide
dppm	bis(diphenylphosphino)methane
dtbbpy	4,4’-di-tertbutyl-2,2’dipyridyl
EDG	electron donating group

EDW	electron withdrawing group
equiv	equivalents
Et	ethyl
EtOAc	ethyl acetate
h	hours
HRMS	high-resolution mass spectrometry
IC	internal conversion
*i*Pr	isopropyl
IR	infrared
ISC	intersystem crossing
KIE	kinetic isotope effect
LED	light-emitting diodes
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MLCT	metal-to-ligand charge transfer
NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million
ppy	2-phenylpyridine
rt	room temperature
SCE	saturated calomel electrode

SET	single electron transfer
*t*BuOH	*tert*-butanol
TEA	triethylamine
Tf	trifyl, trifluorosulfonyl
THF	tetrahydrofuran
TLC	thin Layer chromatography
TMS	trimethylsilane
Ts	tosyl, toluenesulfonyl
UV	Ultraviolet
UVA	Ultraviolet A
vs	*versus*

Chapter 1 - INTRODUCTION

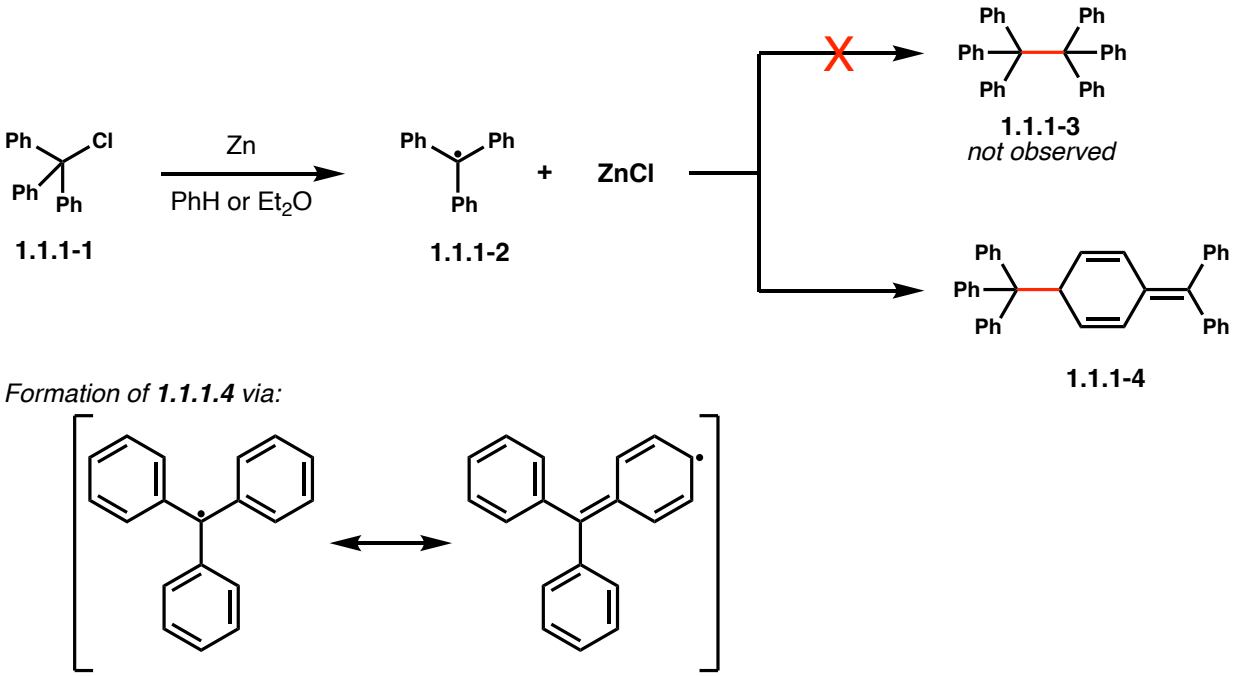
1.1. Radical Chemistry and Photocatalysis in Organic Synthetic Chemistry

1.1.1. Radical Chemistry and its Beginnings

The study of organic chemistry started upon the need of chemists to distinguish compounds coming from living organisms and inorganic compounds. In the 18th century, the concept of vitalism made scientists believe that compounds coming from living organisms were equipped with a *vital force*.[1] Many believed that only living organisms could synthesize new compounds utilizing this vital force. However, it was shown that one could produce new chemical compounds *in vitro*, having no need for living organisms. This was demonstrated in the early 19th century when Michel Chevreul studied the formation of soaps that were made from various extracted fatty acids and alkaline bases.[2] In 1828, It was Freidrich Wöhler, also disproved the theory of vitalism when he synthesized urea from potassium cyanate and ammonium sulfate, now commonly referred as the Wöhler synthesis.[3] This was the first time an organic compound was formed *in vitro* and without any materials provided from biological sources.

Up to this point, mechanism elucidation was not common, and only two electron reactions were studied. Radicals were not really studied as their lifetime was too short to isolate or detect. It was not until 1900, that Moses Gomberg was able to report the formation of triphenylmethyl radical (**Scheme 1.1**).[4] The reaction of triphenylmethyl chloride **1.1.1-1** with metallic Zn formed tertiary radical **1.1.1-2** and a zinc chloride precipitate. Gomberg proposed that **1.1.1-2** would then dimerize to form triphenyl methyl dimer, hexaphenylethane (**1.1.1-3**), which was his intended target. This is what we would now call a *head-to-head* dimerization. Nearly half a century later, it was shown that **1.1.1-3** was never formed, and it was, in fact,

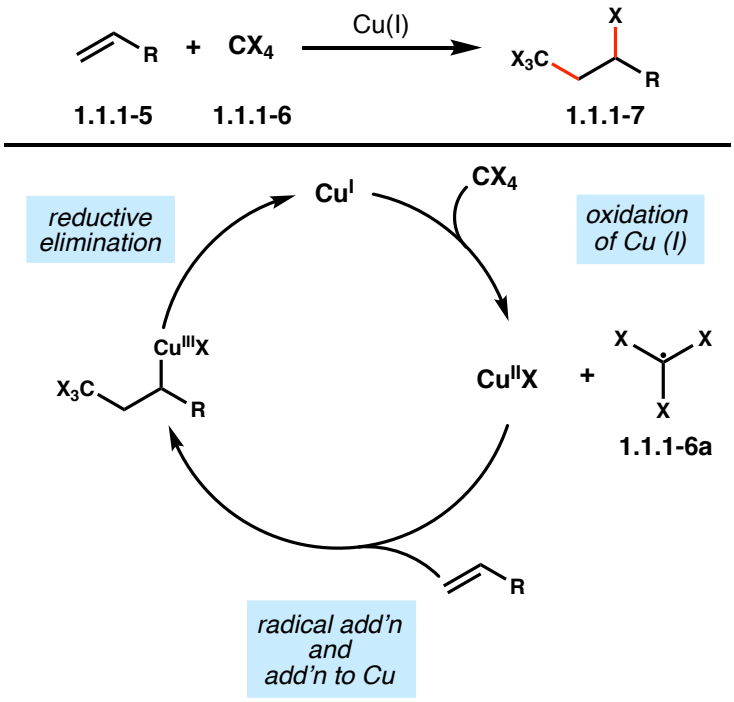
quinoid **1.1.1-4**. The formation of this quinoid derivative comes from the radical attacking from the *para-* position of one the phenyl substituents; a *head-to-tail* dimerization occurs.[4e]



Scheme 1.1- M. Gomberg's discovery of the triphenylmethyl radical, the predicted dimerization product, and the observed dimerization product.

Flashforward to 1945, Kharasch and coworkers reported the first atom transfer radical addition (ATRA) in the difunctionalization of alkenes (**Scheme 1.2**).[5] They proposed that Cu(I) catalyst could be oxidized by carbon tetrahalogen, **1.1.1-6.** A single electron transfer (SET) would occur between Cu(I) and **1.1.1-6**, and form the Cu(II) species and carbon centered radical, **1.1.1-6a**. A radical addition unto olefin **1.1.1-5**, followed by radical oxidative addition unto Cu(II) to formed an organocopper species. This Cu(III) species would perform a rapid reductive elimination to return the catalyst to Cu(I) and the desired product **1.1.1-7**. The same reaction could be performed using Ru(II) catalysts or acetic anhydrides to form the initial radical species. Furthermore, the reaction scope was later expanded to include several electrophilic radical precursors, such as haloforms and ethyl bromo acetates.[6] The ATRA reaction was later also used

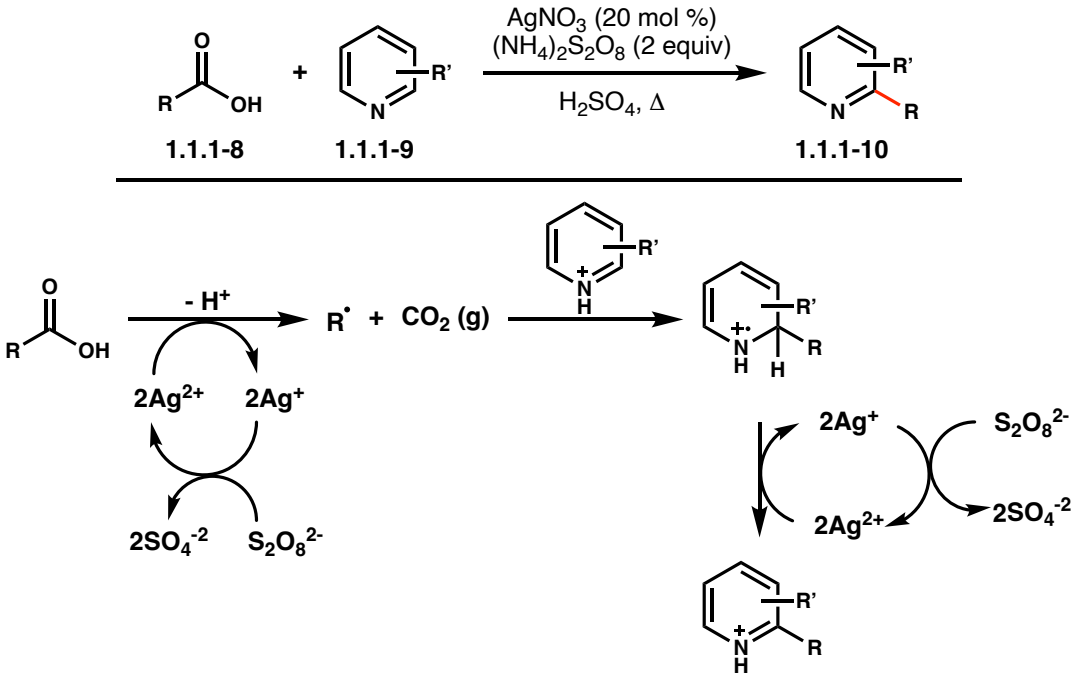
to perform atom transfer radical cyclizations to form highly functionalized ring systems. Light initiated radical formation was also performed. This type of radical formation will be discussed later in this chapter.



Scheme 1.2- Kharasch's first atom transfer radical addition (ATRA) reaction, and Cu(I)/Cu(III) mechanism of the reaction.

Radical reactions continued to increase in popularity by the end of the 20th century. In 1971, F. Minisci published his report on the addition of a nucleophilic radical to electron deficient heteroaryl compounds.[7] This reaction, now called the Minisci reaction, in its honour, is an important transformation in radical chemistry and has been recreated numerous times. The highly cited pioneering work has reached critical acclaim as demonstrated by the multitudes of research it has inspired. The first published report has been cited close to 400 times. The alkyl radical is generated from carboxylic acids (**1.1.1-8**) using $AgNO_3$ and persulfates (**Scheme 1.3**). The carboxylic acid forms a carboxylate ion, which gets oxidized by Ag^{2+}. Carbon dioxide is expelled and thus the alkyl radical is formed. A nucleophilic radical addition then occurs unto the

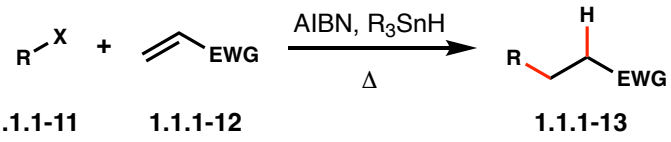
protonated heteroarene **1.1.1-9**, and the desired product **1.1.1-10** is formed after subsequent oxidation. A protonated heteroarene is needed to increase the electrophilicity of the radical acceptor, and to better align the electronic characteristics of the nucleophilic radical, for addition to occur. Multiple different variations of this benchmark reaction have been developed to circumvent the harsh conditions and oxidants that are needed to obtain good yields and minimize the possibility of side products.[8]



Scheme 1.3- Seminal work by F. Minisci using carboxylic acids as alkylating agents of protonated heteroarenes.

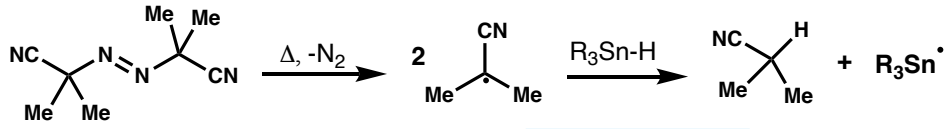
As time went on, radical reactivity started gaining popularity and was becoming a better understood field. However, the radical formation was only performed under harsh conditions, needing strong oxidants, and toxic or explosive initiators.[9] A perfect example of these hazardous conditions is "the tin-method": Using radical inhibitors such and AIBN and organostannanes.[10] Although this method provided good results, it involves stoichiometric amounts of toxic tin, and presented hazardous conditions. Organostannanes were greatly used in the context of the Giese

reaction. The reaction worked very well and is thermodynamically driven; the mechanism can be categorized into three separate steps: *initiation*, *propagation,* and *termination*. These steps are commonly used to describe any radical reaction. In broader terms, the Giese reaction is the 1,4-addition unto an α,β-unsaturated system, analogous to the traditional two-electron process known as the Michael reaction.[11] In this case, the nucleophilic radical species will be formed using alkyl halides. The philicity of radicals was stablished by Giese and coworkers, and it all depends on the nature of the substituents. One can perform polarity reversal reactions to change the polarity of a radical, most notably taking an electrophilic radical and performing an addition reaction unto olefins to form a consequent nucleophilic radical. The initiation step of the reaction consists of heating a catalytic amount of azo-initiator, AIBN, to form nitrogen gas and two equivalents of cyanopropyl radicals (**Scheme 1.4**). These tertiary radicals abstract a hydrogen from the organostannane (k_H ~ 2 X 10^6 $M^{-1}s^{-1}$) to form a tin-centered radical. The tin-centered radical will then abstract a halide from alkyl halide **1.1.1-11**. This process is thermodynamically favoured, as the bond between Sn-X is stronger than the C-X bond that is broken. (i.e. X= Br, BDE: C-Br ~70 kcal/mol, Bu_3Sn-Br ~132 kcal/mol).[12]



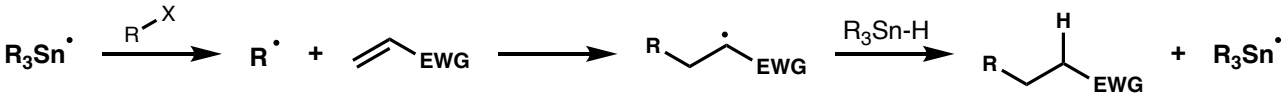
1.1.1-11 1.1.1-12 1.1.1-13

initiation:



$k_H \sim 2 \times 10^6\ M^{-1}s^{-1}$

propagation:



X = I, $k_p > 10^9\ M^{-1}s^{-1}$
X = Br, $k_p \sim 10^6\ M^{-1}s^{-1}$
X = Cl, $k_p < 10^5\ M^{-1}s^{-1}$

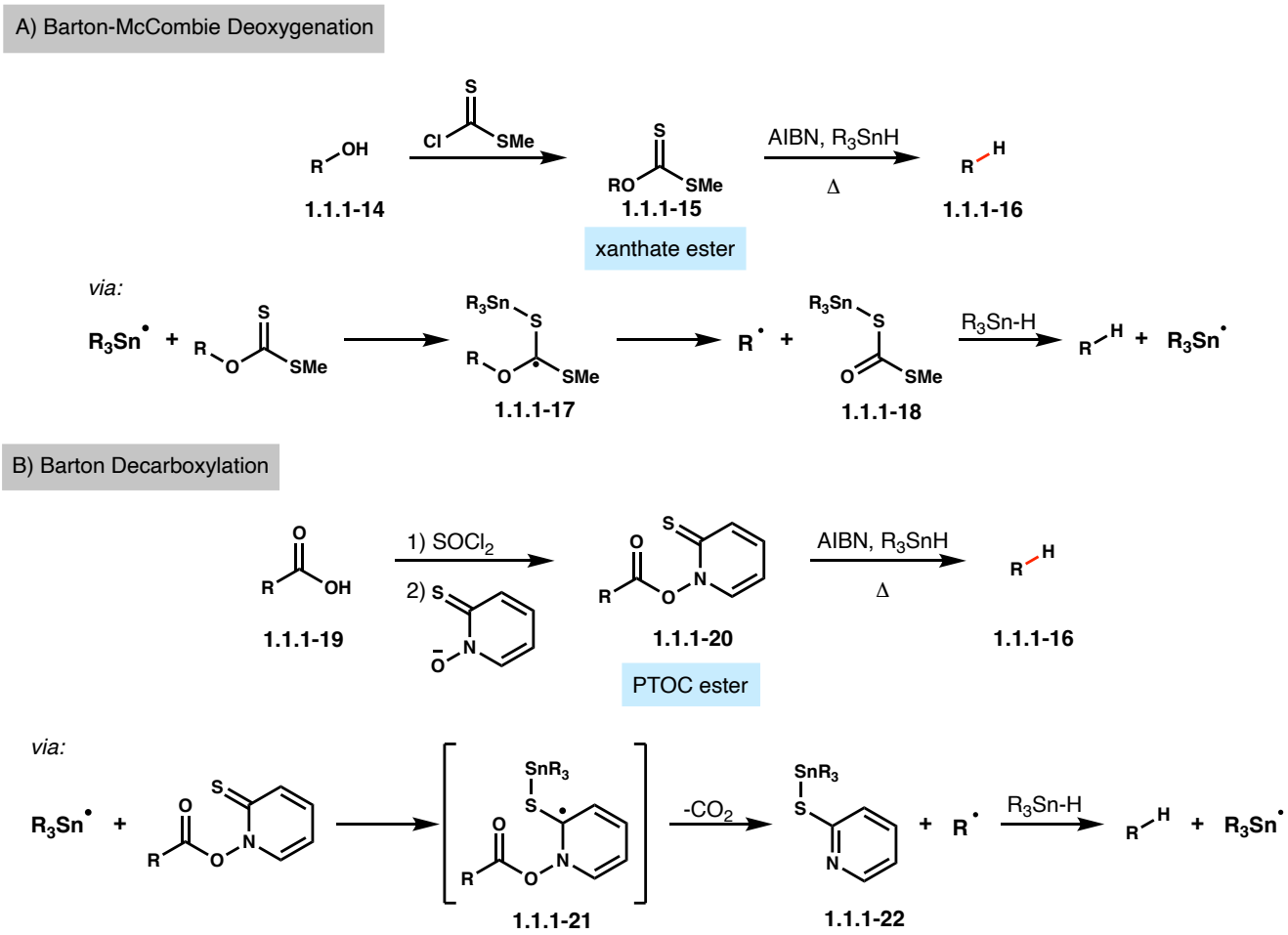
chain is continued

termination: $R^{\bullet} + R^{\bullet} \longrightarrow R{-}R$

Scheme 1.4- Thermodynamically-driven Giese reaction using organostannanes and AIBN as radical initiator.

The resulting alkyl radical will then add unto the Michael acceptor **1.1.1-12**, and then abstract a hydrogen atom from the tin hydride. This sequence forms the desired product **1.1.1-13** and another tin-centered radical, which propagates the chain reactions, thus and continuing with the same process detailed above. The termination step of the reaction comes from the radical-radical recombination of the remaining radical species. Of course, one can see where this reaction could have some pitfalls. First, if the concentration of the Michael acceptor is lower that the concentration of a hydrogen atom donor, the radical formed could perform a HAT and not add unto the olefin system. Furthermore, one must carefully gauge the concentration of Michael acceptor to also avoid polymerization to occur. Overall, the Giese reaction system requires large excess of the Michael acceptor relative to the alkyl halide and the slow addition of the tin hydride to avoid formation of side products and polymerization.

The use of tin method to perform radical reactions is not limited to alkyl halides. The same reactivity can be applied to xanthates.[13] Sir Derek Barton and Stuart W. McCombie developed a deoxygenation reaction which takes an alkyl alcohol and transforms it into a xanthate to perform a radical reduction known as the Barton-McCombie deoxygenation (**Scheme 1.5A**).[14] Alkyl alcohol **1.1.1-14** forms xanthate ester **1.1.1-15**, and tin hydride and AIBN is added to start the reaction. After the traditional radical initiation using AIBN, the tin-centered radical adds on the xanthate to form radical intermediate **1.1.1-17**, which then quickly collapses, thus forming the alkyl radical and by-product trialkyl tin xanthate, **1.1.1-18**.[15] The alkyl radical that is formed, abstracts a hydrogen from tin hydride, to form desired product **1.1.1-16** and continuing the radical chain. This reaction works well but produces stoichiometric amounts of tin by-products. Similarly, Barton continued his work in radical precursors, this time exploring decarboxylation of alkyl carboxylic acids. Instead of using xanthates to perform the radical reaction, he converted carboxylic acids to thiohydroximate esters (referred to Barton PTOC esters) (**Scheme 1.5B**).[16] Once the carboxylic acid **1.1.1-19** is transformed into PTOC ester **1.1.1-20**, it is submitted to the same radical initiating conditions. The tin-centered radical adds unto the PTOC ester to form intermediate **1.1.1-21**. Then, after the expulsion of carbon dioxide and tin-derivative **1.1.1-22**, the alkyl radical abstracts a hydrogen, thus creating the chain propagating species all over again.



Scheme 1.5- Formation of a new brand of suitable radical precursors. A) Barton-McCombie Deoxygenation reaction using xanthate esters as radical precursors. B) Barton Decarboxylation reaction using PTOC esters as radical precursors.

Barton's PTOC ester **1.1.1-20** became a great radical precursor, not only performing a radical decarboxylation, but also opening the door to multiple different substitutions. The PTOC ester could be transformed into alkyl halides, alkyl nitriles, thiols, etc. (**Figure 1.1**).[17] Although PTOC esters are great radical precursors, the use of toxic and hazardous tin, and the stoichiometric by-products this a non-atom economical approach to the formation of radicals. Inspired by Nature, chemists looked at light to avoid harsh conditions, strong oxidants, and toxic materials. The need for milder conditions initiated the boom of photocatalysis.

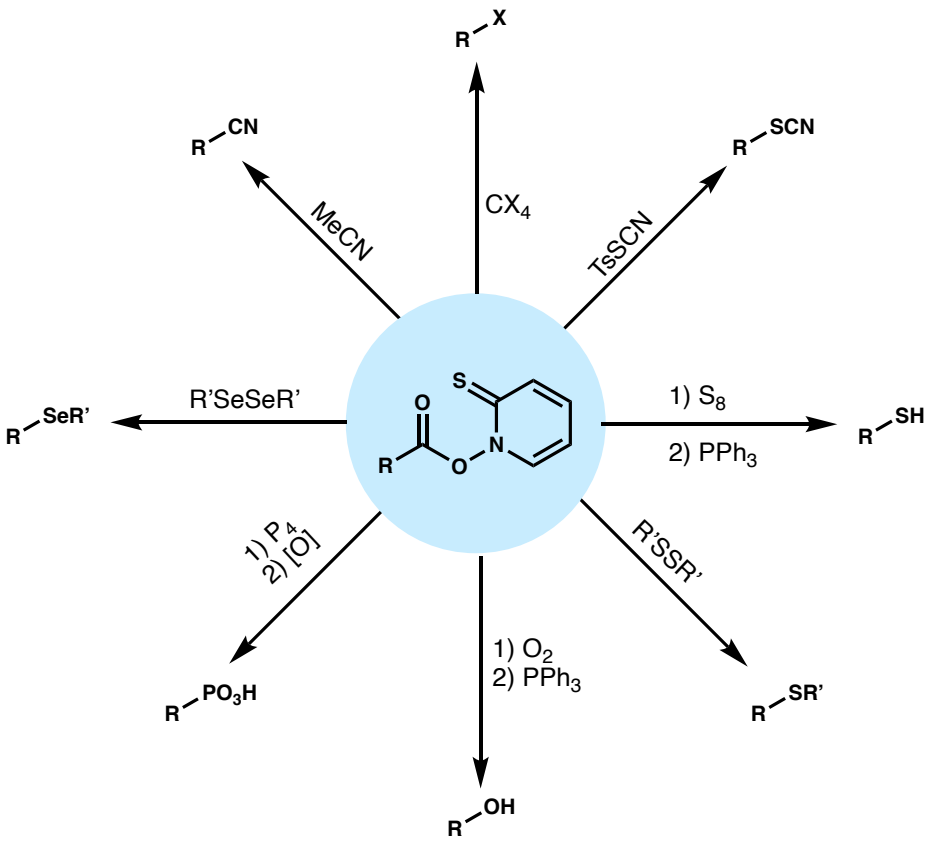


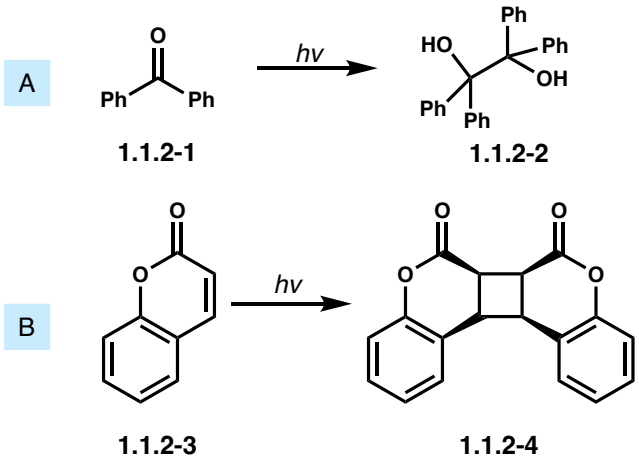
Figure 1.1- Modern uses of Barton PTOC esters

1.1.2. Introduction to Photoredox Catalysis

Photochemistry was chemist's way of imitating Nature and plants. Needing milder conditions to initiate radical reactions, mostly to avoid toxic and hazardous materials, harsh oxidants, and unwanted side products, chemists looked to harvest the power of the sun.[18] However, photochemistry was already being popularized thanks to Giacomo Ciamician, who was working as an experimental organic photochemist in the late 19th century.[19] He delivered an address at the 8th International Congress of Applied Chemistry in 1912 in New York to press the need to look at solar energy, in a time where coal and fossil fuels dominated the energy sector, to restore the economy and close the gap between economic social classes.[20]

"On the arid lands there will spring up industrial colonies without smoke and without smokestacks; forests of glass tubes will extend over the plains and glass buildings will rise everywhere; inside of these will take place the photochemical processes that hitherto have been the guarded secret of the plants, but that will have been mastered by human industry which will know how to make them bear even more abundant fruit than nature, for nature is not in a hurry and mankind is. […] The photochemistry of the future should not however be postponed to such distant times; I believe that industry will do well in using from this very day all the energies that nature puts at its disposal. So far, human civilization has made use almost exclusively of fossil solar energy. Would it not be advantageous to make better use of radiant energy?"[20c]

Early work in organic photochemistry involved the photoactivation of benzophenone. Ciamician and Silber proposed that light could excite benzophenone **1.1.2-1**, which then dimerizes to afford diol **1.1.2-2** (**Scheme 1.6A**).[20a] Following this, Ciamician was then involved in the photodimerization ([2 + 2] cycloaddition) of coumarin **1.1.2-3** to afford product **1.1.2-4**. (**Scheme 1.6B**).[20b]



Scheme 1.6- Initial studies in organic synthetic photochemistry led by Ciamician. A) Photodimerization of benzophenone **1.1.2-1**. B) Photodimerization of coumarin **1.1.2-3**.

Inspired by the work of Ciamicin, there was a need to harvest light to promote complexes to their excited states and trigger single electron transfers (SET) processes to initiate radical propagations. *It is the start of the field of photoredox catalysis*. To understand how these processes could happen, one needs to understand the two governing laws of photochemistry: (1) The Grotthus-Draper Law states that light must be absorbed for a photochemical reaction to take place; (2) The Stark-Einstein Law states that each photon of light that is absorbed by the system, no more than one molecule is activated to perform a subsequent reaction.[21] A Jablonski Diagram is a great tool to describe the fundamentals of photochemistry (**Figure 1.2**). Following the first law of photochemistry, molecule **A** must absorb a photon to become excited molecule **A***. Upon excitation of its ground state ($\mathbf{S_0}$), an electron may be promoted from its highest occupied molecular orbital (HOMO) to a higher vibrational level in the singlet state ($\mathbf{S_n}$) of the lowest unoccupied molecular orbital (LUMO). The two orbitals occupying the spin-paired electrons now are the singly occupied molecular orbitals (SOMO). Following Kasha's Rule, the electrons will fall to the most stable vibrational level $\mathbf{S_1}$, which is known as vibrational relaxation.[21c, g] Once in the singlet-state $\mathbf{^1S_1}$, the electron can lose energy in two different ways: radiative or non-radiative pathways. A radiative pathway will be emitting a photon, while a non-radiative process will be a movement to other vibrational modes. An electron in $\mathbf{^1S_1}$ can lose energy in the radiative process of fluorescence (F), thus bringing the electron back to its ground state, $\mathbf{S_0}$. Alternatively, the electron in $\mathbf{^1S_1}$ could go through a non-radiative process of internal conversion (IC), bringing the electron back to its ground state, $\mathbf{S_0}$. Alternatively, intersystem crossing (ISC) can occur where the electron goes from the singlet-state, $\mathbf{^1S_1}$, to its triplet-state, $\mathbf{^3T_1}$. From there, we can have another IC process that can occur, or a photon can be emitted through phosphorescence (P). It is believed

that phosphorescence is a longer-lived process as it requires a (forbidden) spin flip process of the electron to return to its ground state, S_0. These electron rearrangements occur following the Franck-Condon principle and the Born-Oppenheimer approximation. The Franck-Condon principle states that electron rearrangements occur so rapidly that the nuclei are considered stationary until the rearrangement is complete. The Born-Oppenheimer approximation states that it is assumed that electronic and nuclear movement is separated.[21c, g]

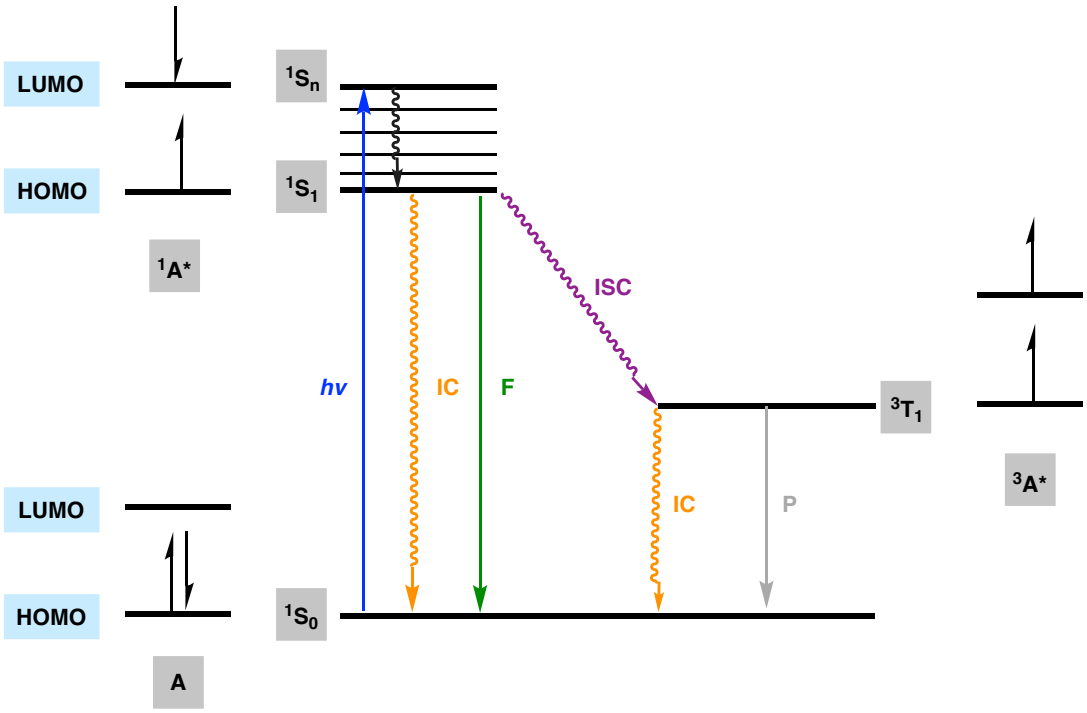
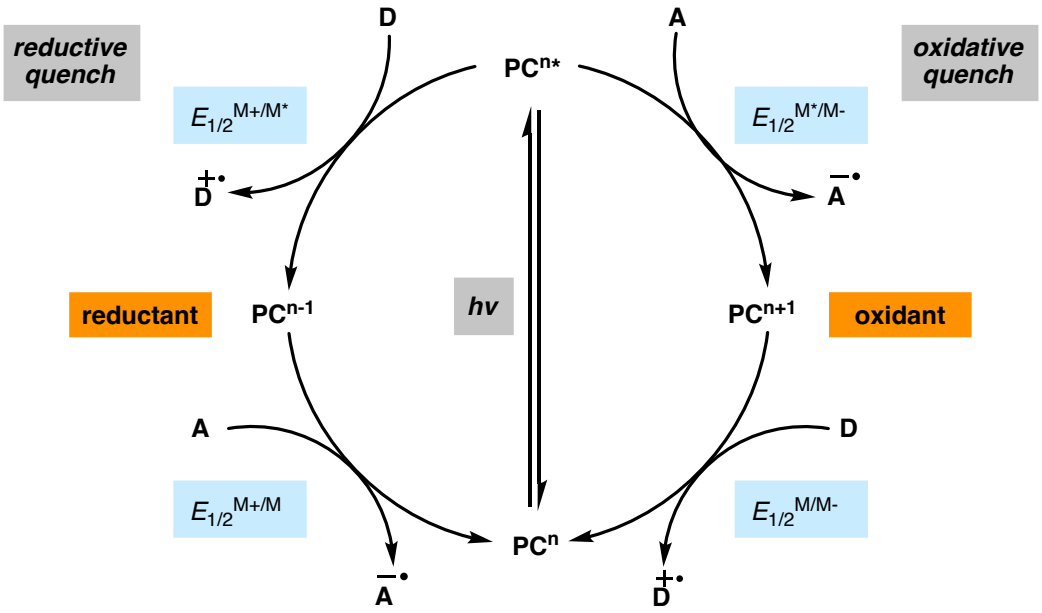


Figure 1.2- Jablonski diagram describing all paths that an excited electron can undertake.

The excited states can promote SET chemistry to occur as well as other photochemical process can occur such as oxygen quenching, Forster resonance energy transfer (FRET), Dexter energy transfer, or triplet-triplet sensitization (annihilation).[21] Generally, a good photocatalyst, requires longer excited-state lifetimes so SET events can occur.[21e-f] Upon excitation of a complex, SET can occur through an oxidative or reductive quench of the excited complex. Excited states have been shown to be better redox agents (either reductants or oxidants) than their ground

state complex. This is because the ionisation potential is lower than its ground state. With this knowledge at hand, a photocatalyst, **PC,** can be designed to promote a SET process or energy transfer. A general photoredox catalyst can be selected depending on its properties and ability to go through a reductive or oxidative quench (**Scheme 1.7**). Using light, we can excite $\mathbf{PC^n}$ to its excited state, $\mathbf{PC^{n*}}$. In the reductive quench cycle, $\mathbf{PC^{n*}}$ acts as an oxidant towards donor substrate (**D**) to form $\mathbf{PC^{n-1}}$ and a radical cation of **D**. $\mathbf{PC^{n-1}}$, now a reductant, can donate an electron to an acceptor molecule (**A**) to return to its ground state. If going through an oxidative quench, $\mathbf{PC^{n*}}$ can act as a reductant towards a molecule **A**, to form $\mathbf{PC^{n+1}}$ and a radical anion of **A**. $\mathbf{PC^{n+1}}$, now an oxidant, which can receive an electron from **D** to return to its ground state.[21-22]



Scheme 1.7- Fates of a photocatalyst: Oxidative and reductive quenching pathways.

Depending on the reaction needs, the choice of photocatalyst comes down to 1) light needed for the reaction, 2) the quenching pathway that will be used, 3) the triplet-state lifetime or the singlet-state lifetime of the excited state ($[\mathbf{^3PC^{n*}}]$ or $[\mathbf{^1PC^{n*}}]$) and 4) the redox potentials needed for the reaction. *There is a plethora of photocatalysts out there.* Most notably, transition

metal based photocatalysts such as Ru- and Ir-base polypyridyl complexes, or organic dyes are widely used.[22] Some common photocatalysts are shown below (**Figure 1.3**), they range from organometallics to charged organic species to organic neutral aromatic molecules.

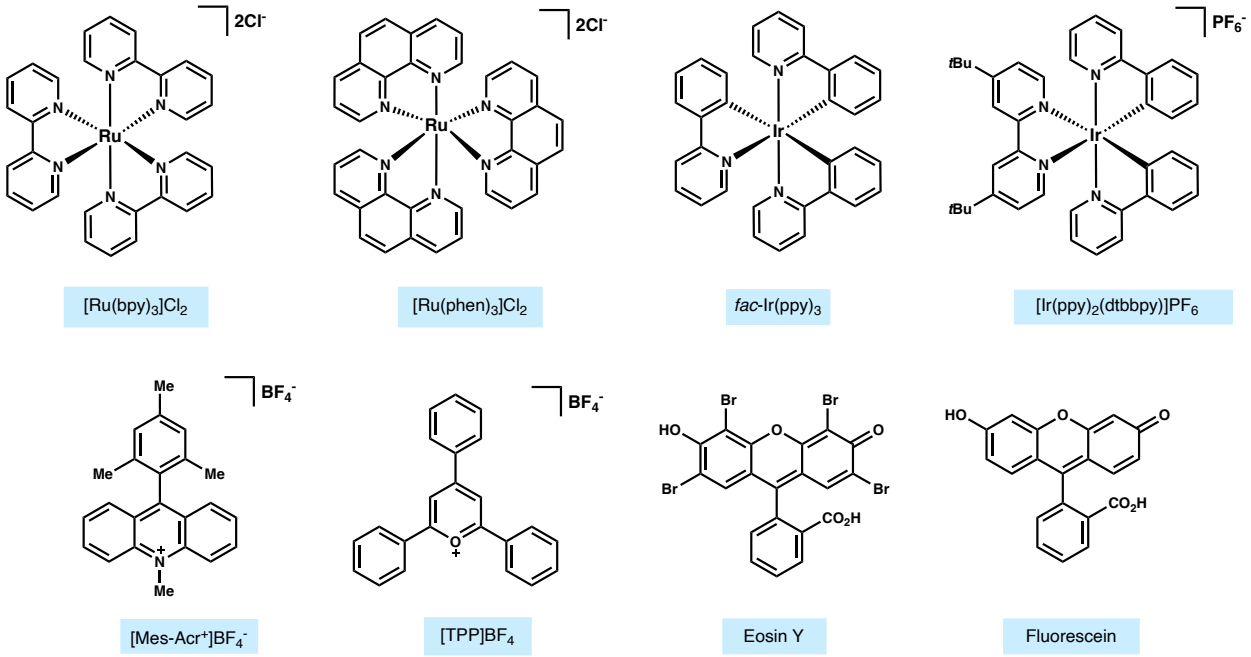


Figure 1.3- Common photocatalysts in mordern photoredox chemistry.

In modern photoredox times, Ru- and Ir-based polypyridyl complexes are the most popular due to the way they can undergo SET processes, and ease of ligand modification to tune electronic and luminescent properties.[22a] They typically undergo excited-state SET proceses through an outer sphere metal-to-ligand charge transfer (MLCT) mechanism. This can be seen as an electron being transferred from the metal center to the polypyridyl ligand. The redox potentials of these complexes can be finely tuned when changing the ligands. Overall, Ir-based polypyridyl complexes are more reducing than their Ru counterparts, however, this can be changed with ligand design and counter-anion variation. Furthermore, it is typical that these photocatalysts react from their triplet excited state as it is longer lived than their singlet excited

stat as spin orbit coupling from the large atom allows for a more stable triplet excited state. Organic dyes do not benefit from this process, which is why they typically react from the singlet excited state. Another alternative to transition metal base complexes are organic dyes, which can be used as photocatalysts.[22c] Some of these organic dyes have long lived singlet excited-states and thus can react from either excited-state. Photophysical and electrochemical properties of the catalyst will affect the choice of reaction conditions as one must fine-tune the reaction conditions to match the redox potentials requisite of electron transfer for a given substrate. A summary of photophysical and electrochemical properties is found below (**Table 1.1**).[22] Photocatalysts are often described by different parameters: 1) the max absorption wavelength (λ^{max}_{abs}), 2) the lifetime of the excited state (τ_0), 3) the redox potentials of the excited state and their reduced/oxidized counterpart. We can categorize the redox potentials in two categories: oxidative and reductive. If we look at the redox potentials in an oxidative quench, we have the $E_{1/2}^{(M^*/M^-)}$ which is the oxidation potential of the excited state and $E_{1/2}^{(M/M^-)}$; the reduction potential to go back to the ground state $\mathbf{PC^n}$ from $\mathbf{PC^{n+1}}$. In the reductive quench, we have $E_{1/2}^{(M^+/M^*)}$, which is the reduction potential to quench the excited state and $E_{1/2}^{(M^+/M)}$; the oxidation potential to go back to the ground state **PC** from $\mathbf{PC^{n-1}}$.

Table 1.1- Photophysical and electrochemical properties of common photocatalysts.[22a,c]

Entry	Complex	λ^{max}_{abs} (nm)	τ_0 (ns)	Oxidative		Reductive	
				$E_{1/2}$ $(M^+/M^*)^a$	$E_{1/2}$ $(M^+/M)^a$	$E_{1/2}$ $(M^*/M^-)^a$	$E_{1/2}$ $(M/M^-)^a$
1	$^3[Ru(bpy)_3]Cl_2$	452	1100	-0.81	+1.29	+0.77	-1.31
2	$^3[Ru(phen)_3]Cl_2$	422	500	-0.87	+1.26	+0.82	-1.36
3	^{3}*fac*-$Ir(ppy)_3$	375	1900	-1.73	+0.77	+0.31	-2.19
4	$^3[Ir(ppy)_2(dtbbpy)]PF_6$	410	557	-0.96	+1.21	+0.66	-1.51
5	$^1[MesAcr]BF_4$	425	6	-	-	+2.18	-0.49
6	$^1[TPP]BF_4$	415	4	-	-	+2.55	-0.32
7	^{3}Eosin Y	539	24	-	-	+0.79	-1.06
8	Fluorescein	528	4.2	-	-	+0.78	-1.27

[a] Potentials in V vs SCE measured in MeCN at room temperature (298 K).

The selection of a photocatalyst all depends on the organic substrate which is used in the reaction. Substrates that are most likely compatible with the reductive quenching cycle of a photocatalyst mean that they would most likely get oxidized by the excited state, **PC***. In most cases, that means that the oxidation potential of this substrates must be smaller than the $E_{1/2}^{(M^*/M^-)}$. If undergoing the oxidative quench, that would mean substrates would be getting reduced by the excited state of the photocatalyst, **PC***. Generally, that would entail that the reduction potential of the substrate would be smaller than $E_{1/2}^{(M^+/M^*)}$. The comparison of redox potentials allows a chemist to assess the thermodynamic feasibility of a potential reaction. A redox diagram can show the redox potentials of different organic substrates (**Figure 1.4**).[23] It is important to see that some of these substrates cannot be oxidized with the common photocatalysts mentioned prior. This opens the field to catalyst design and finding better ways to access these substrates.

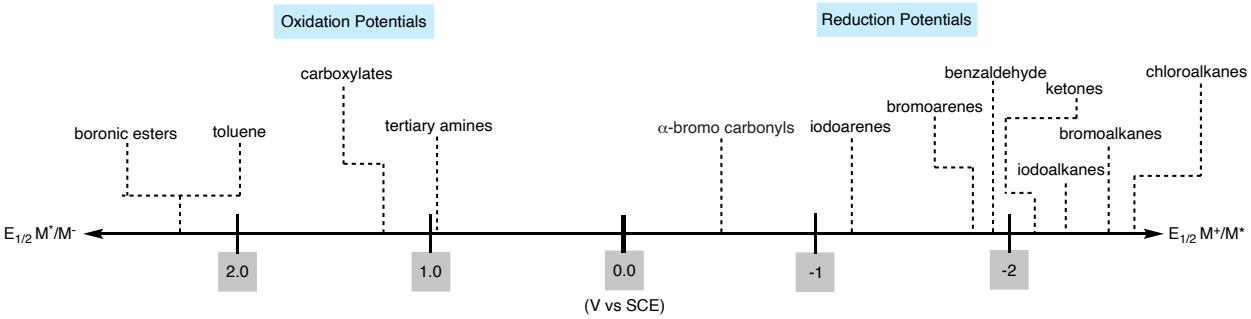
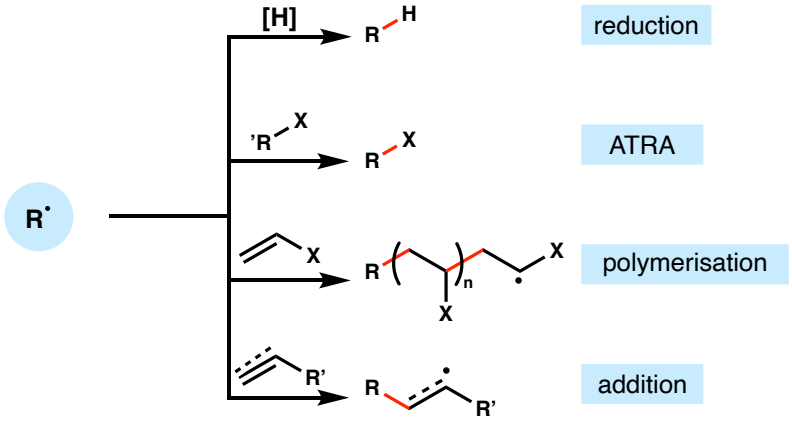


Figure 1.4- Redox potentials of common organic substrates.

1.1.3. Formation of C-C Bonds using Photoredox Catalysis

Initial formation of radicals is just the beginning in the world of radical reactions. Once the radical is formed, the fates of the intermediates need to be regarded. Most common

organic radical reactions are reductions, ATRA reactsions, additions, and polymerisation chemistry (**Scheme 1.8**). It is important to note, that when designing a photoredox reaction one must consider all the reactions that the radical intermediates can do with other substrates or even the photocatalyst itself. Chemists often look to make a net redox-neutral system, meaning that a radical intermediate would have to react with an intermediate of the photocatalyst, thus closing the cycle. This not only minimizes the components of a reaction but also minimizes the addition of stoichiometric oxidants or reductants, and means that the photocatalyst could in fact, act as catalyst.



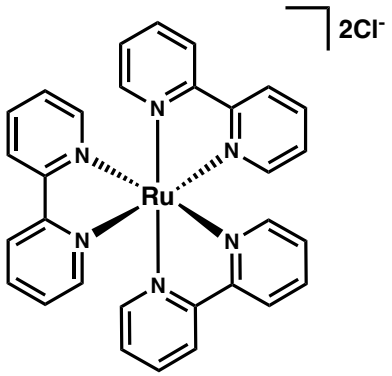
Scheme 1.8- Fate of radical intermediates and formation of C-C bonds using radical reactions.

1.2. Redox-Neutral Transformations using Transition Metal Complexes as Photocatalysts

1.2.1. Early Work: Boom of Ruthenium Polypyridyl-based Photocatalysts

Recently, a plethora of ruthenium polypyridyl complexes have been synthesized to cover immense ground. However, it all started with the most commonly employed tris(2,2'-bipyridine) ruthenium (II) complex, $Ru(bpy)_3^{2+}$ (**Figure 1.5**). Its photophysical and electrochemical properties (**Table 1.1, Entry 1**) make this catalyst very suitable for visible light photocatalysis, and it has

gained immense popularity not only in organic chemistry, but also inorganic and materials chemistry.[22a]



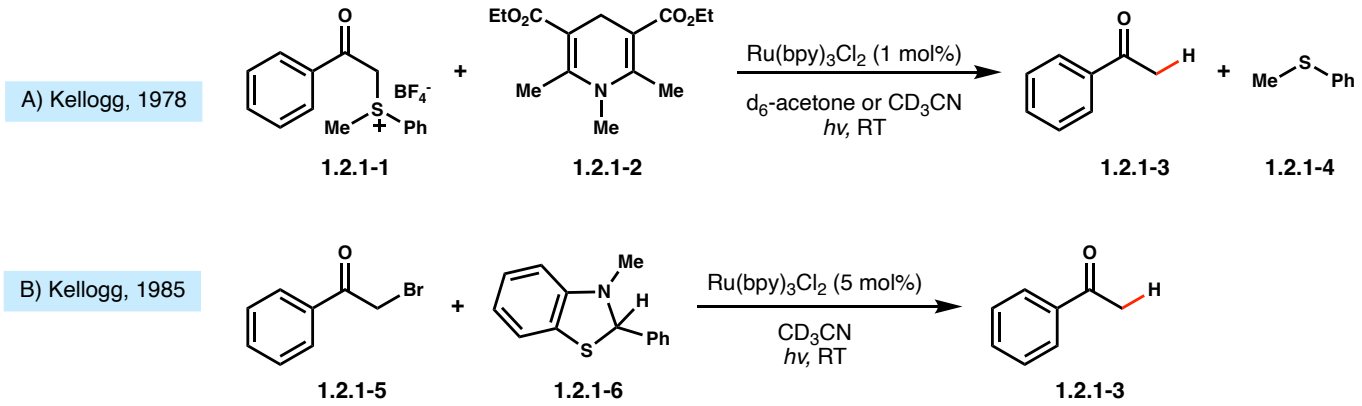
$[Ru(bpy)_3]Cl_2$

Figure 1.5- tri(2,2'-bipyridine) ruthenium (II) chloride complex, $Ru(bpy)_3Cl_2$.

The discovery of $[Ru(bpy)_3]^{2+}$ salts was performed by Burstall in 1936, when he isolated salts of this compound.[24] It was found that the compound was not only chemically robust but also possessed different configurationally stable species. Upon absorption of a photon (λ_{max}= 452nm) an electron from the metal center is excited to the ligand-centered π* orbital and gives the excited photocatalyst, $*[Ru(bpy)_3]^{2+}$. After excitation, $*[Ru(bpy)_3]^{2+}$ can then act as a reductant or oxidant, depending on the reaction conditions.[22a]

One of the earliest works of organic transformations using the photoredox catalysis of $Ru(bpy)_3^{2+}$ was done by Kellogg and co-workers, in 1978 (**Scheme 1.9**).[25a] This published work identified the use of $Ru(bpy)_3^{2+}$ as an effective photocatalyst in the reduction of phenacyl sulfonium salts **1.2.1-1** (**Scheme 1.9A**). It was found that there was a need of 1,4-dihydropyrines **1.2.1-2** to achieve an overall net reductive reaction and act as H-atom donor. The reaction gave the desired product **1.2.1-3** in quantitative yields. Although, the reaction needs stoichiometric amounts of **1.2.1-2** it was found through Stern-Volmer quenching studies, that neither **1.2.1-2**

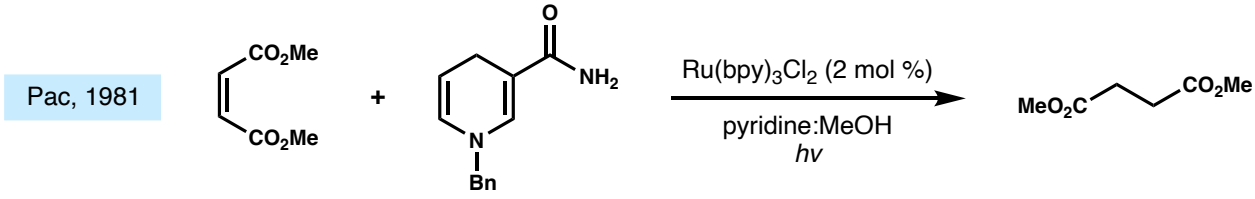
nor **1.2.1-1** quench *$[Ru(bpy)_3]^{2+}$. In fact, the authors propose that Hantzsh ester **1.2.1-2** becomes photoexcited, absorbing light at the visible region, and gives an electron to the sulfonium salts **1.2.1-1**. This is the initiation step of the reaction. The same reaction condition would also work with ammonium salts, phosphonium salts, and 4-nitrobenzyl halides.[25b] In 1985, Kellogg and co-workers published the reduction of α-bromo acetophenone **1.2.1-5**, using $Ru(bpy)_3Cl_2$ as photocatalyst and **1.2.1-6** as H-atom donor to obtain **1.2.1-3** in good yields (**Scheme 1.9B**).[26] In this case, the $Ru(bpy)_3^{2+}$ gets excited to *$[Ru(bpy)_3]^{2+}$ and **1.2.1-5** quenches the photocatalyst through an oxidative quench. The α-carbonyl radical formed abstracts a H-atom from **1.2.1-6**. The radical intermediate formed of **1.2.1-6** then gives back an electron to $Ru(bpy)_3^{3+}$ so it can return to its ground state of $Ru(bpy)_3^{2+}$ and go through another round of the catalytic cycle.



Scheme 1.9-Kellogg's seminal work on the use of $Ru(bpy)_3Cl_2$ as a photocatalyst in synthetic organic chemistry. A) Reduction of sulfonium salts 1.2.1-1, using $Ru(bpy)_3Cl_2$ as photocatalyst and Hantzsch ester **1.2.1-1** as H-atom donor and oxidant. B) Reduction of α-bromo acetophenone using $Ru(bpy)_3Cl_2$ as photocatalyst and **1.2.1-6** as H-atom donor and reductant

Also among some of the earliest reports is Pac and co-workers, with their 1981 contribution of the reduction of electron-poor olefins using $Ru(bpy)_3Cl_2$ (**Scheme 1.10**).[27] Upon excitation of the photocatalyst, olefin **1.2.1-7** will go through an SET to form a radical anion. The anion will get quenched by the protons in the reaction mixture, and the radical with abstract a H-atom from

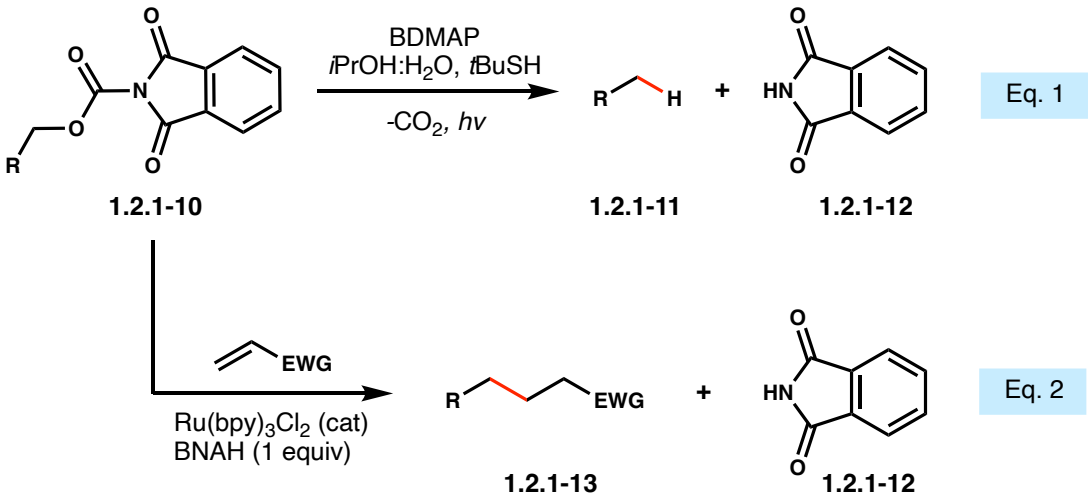
1.2.1-8 to form desired product **1.2.1-9**. The resulting radical intermediate from **1.2.1-8** will then give an electron back to the photocatalyst to restart the catalytic cycle. Similarly, to the seminal work by Kellogg and co-workers, a stoichiometric reductant is needed to return the photocatalyst to the ground-state.



1.2.1-7 **1.2.1-8** **1.2.1-9**

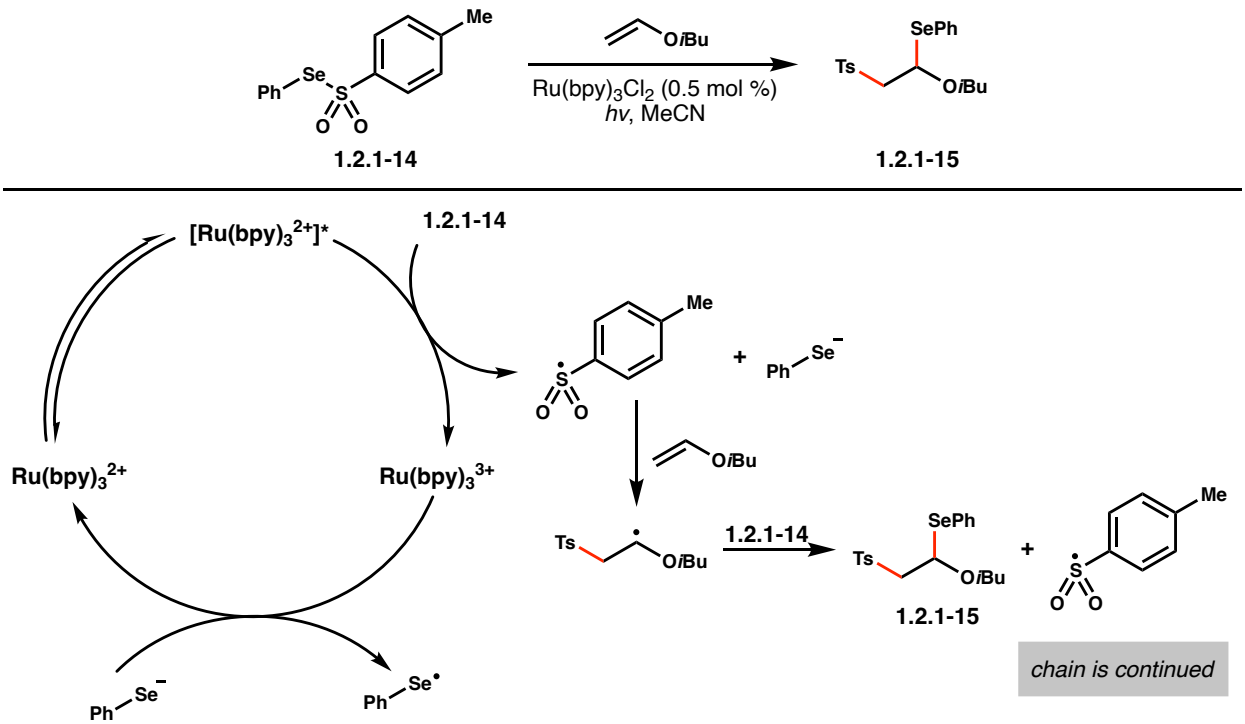
Scheme 1.10- Reduction of electron-poor olefins using $Ru(bpy)_3cl_2$ and **1.2.1-8** as H-atom donor and reductant.

Inspired by PTOC esters, in 1988, Okada and co-workers started using *N*-hydroxyphthalimide esters as radical precursors (**Scheme 1.11**, **Eq. 1**).[28a] *N*-hydroxyphthalimide esters **1.2.1-10** goes through a net-reduction after losing carbon dioxide and phthalimide **1.2.1-12**. The photocatalyst in this case is BDMAP (1,6-bis(di- methylamino)pyrene), it absorbs visible light and proceeds to give an electron to **1.2.1-10**. The reduced **1.2.1-10** will quickly decompose and form an alkyl radical, carbon dioxide, and phthalimide **1.2.1-12**. The alkyl radical will then abstract an H-atom from the thiol to form desired product **1.2.1-11**. Just a couple of years later, in 1991, Okada and co-workers used the same radical precursor **1.2.1-10**, but this time in a net-reductive Giese Reaction using $Ru(bpy)_3Cl_2$ as photocatalyst, Michael acceptor and BNAH (1-benzyl-1,4-dihxwxydronicotinamide) as the stoichiometric reductant (**Scheme 1.11, Eq. 2**).[28b] Desired product **1.2.1-13** and phthalimide **1.2.1-12** is formed. The use of this type of radical precursor avoids the use of tin and allows for less toxic conditions. However, a stoichiometric reductant is needed, making the need for redox neutral catalytic cycle greater.



Scheme 1.11- Okada's radical precursor inspired by Barton PTOC esters.

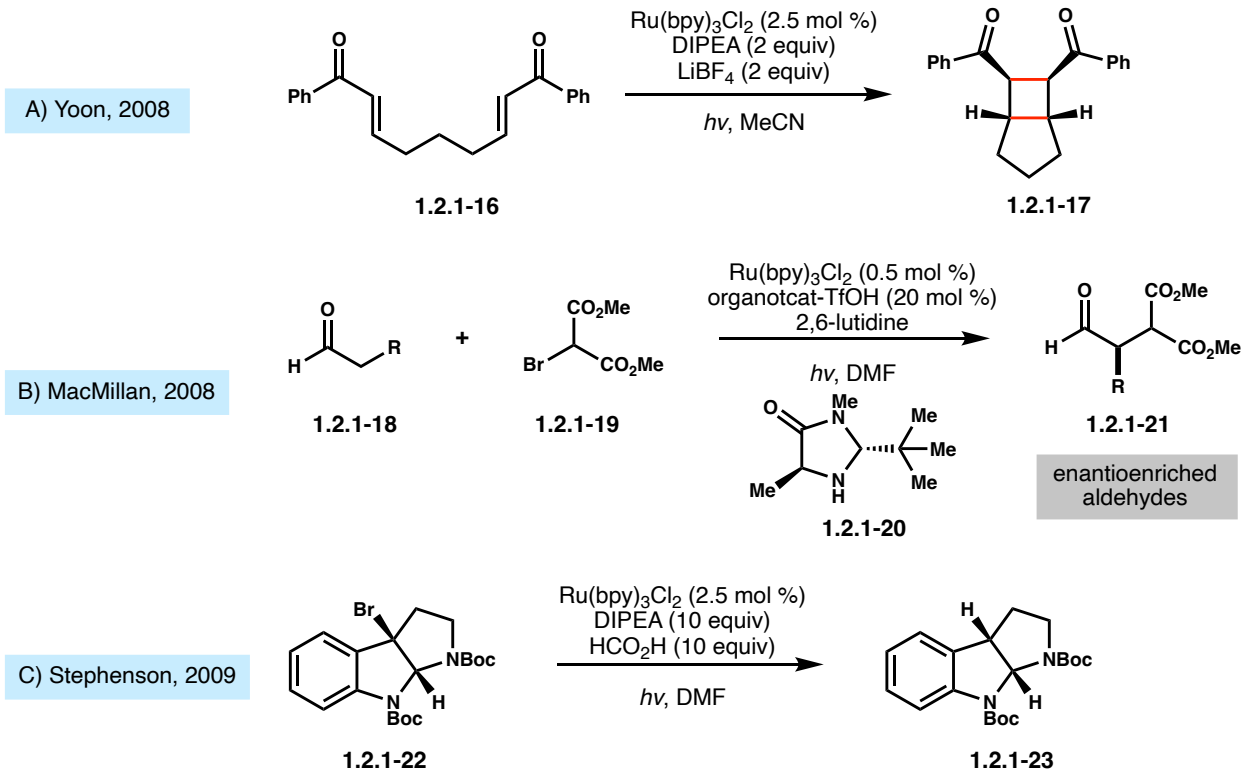
An early contribution to redox-neutral photocatalysis is the work in 1994 done by Barton and co-workers.[29] They envisioned a redox-neutral ATRA reaction of p-tolyl benzeneselenosulfonate **1.2.1-14** unto olefins, to form the desired product **1.2.1-15** (**Scheme 1.12**). They hypothesized that after the absoption of visible light by $Ru(bpy)_3^{2+}$, $[Ru(bpy)_3^{2+}]^*$ would be able to perform a SET and reduce **1.2.1-14**. The resulting tosyl radical would add unto the olefin, which in turn would react with another equivalent of **1.2.1-14** to perform the ATRA reaction and transfer over the benzeneselenol group. The desired product **1.2.1-15** would be formed along with another equivalent of the tosyl radical. This intermediate would be the chain propagating radical. Once formed it can react with another olefin to form the desired product without the need of the photocatalyst. To make the whole cycle redox-neutral, the benzeneselenol anion would give back an electron to $Ru(bpy)_3^{3+}$ to bring back the photocatalyst back to its ground state and restart the photocatalytic cycle. Both the photocatalyst and the chain propagation will produce desired product **1.2.1-15**.



Scheme 1.12- Redox-neutral ATRA reaction of tosyl and benzeneselenol group reported by Barton and coworkers.

Since the first publications in the late 20th century, there has been sporadic use of these complexes as photocatalysts. There has been a resurgence in photoredox catalysis, mostly attributed to work performed by Yoon, MacMillan, and Stephenson, that has brought photocatalysis into the limelight.[22] In 2008, Yoon and co-workers were inspired by Ciamician [2 + 2] photodimerization (**Scheme 1.6**) to develop visible light enabled [2 + 2] photocycloaddition of enones **1.2.1-16** (**Scheme 1.13A**).[30] The use of $[Ru(bpy)_3Cl_2]^*$ as a photoreductant to promote the cycloaddition with high diastereoselectivity and formed bicycles **1.2.1-17**. In the same year, MacMillan and coworkers published the functionalization of enantioenriched aldehydes **1.2.1-21** by combining their organocatalyzed formation of enamines with photoredox catalysis (**Scheme 1.13B**).[31] They envisioned an SET of **1.2.1-19** with $[Ru(bpy)_3Cl_2]^*$, to form an alkyl radical. Aldehyde **1.2.1-18** would then condense the organocatalyst **1.2.1-20** to form an enamine, which

would act as a radical acceptor, thus forming an α-amino radical after the radical addition. The photocatalyst then returns to the ground state after another SET with the α-amino radical to form an iminum. Desired product **1.2.1-21** is formed after an acid work-up. In 2009, Stephenson and co-workers developed a tin-free dehalogenation of bromo-pyrroloindolines **1.2.1-22** (**Scheme 1.13C**).[32] This reaction allowed for the reduction of C-Br bonds in great yields, all while avoiding toxic and hazardous tin conditions, and forming reduced product **1.2.1-23**.

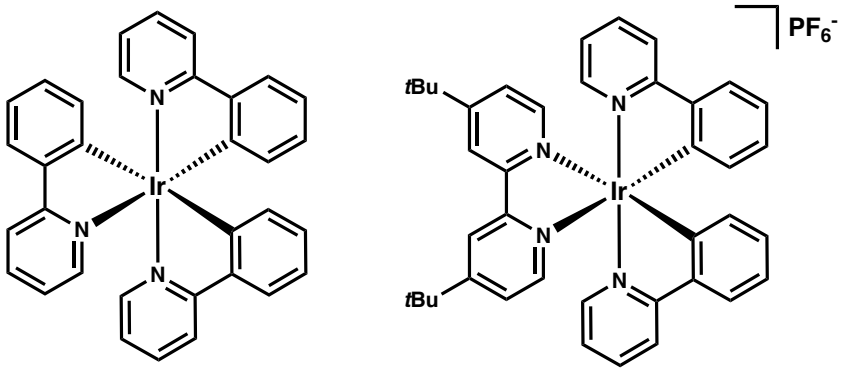


Scheme 1.13- Resurgence of photoredox chemistry performed by Yoon, Macmillan, and Stephenson in the late-2000s.

1.2.2. Iridium Polypyridyl Complexes as Photocatalyst

Shortly after the boom of Ru-based polypyridyl complexes as photocatalysts, the tide turned to Ir-based polypyridyl complexes (**Figure 1.6**). Their photophysical properties are very similar to their Ru polypyridyl counterparts as they both function in photoredox chemistry *via*

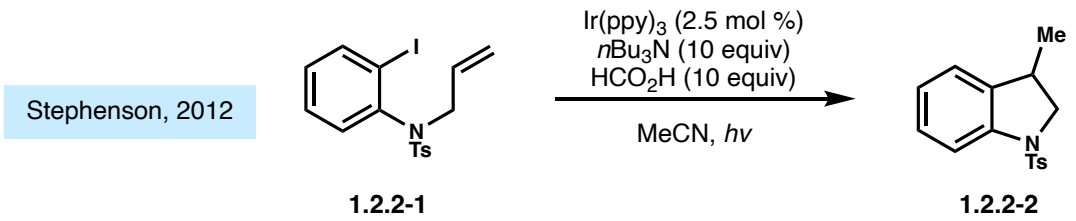
MLCT.[22] Overall, iridium photocatalyst have been found to be more reducing than the ruthenium photocatalysts. However, redox potentials can be easily tuned with ligand modification. Some useful physicochemical parameters are available *vide supra* (**Table 1.1**)[22a]



fac-Ir(ppy)$_3$ [Ir(ppy)$_2$(dtbbpy)]PF$_6$

Figure 1.6- Popular iridium-base polypyridyl complexes in photoredox catalysis.

One of the first reports using Ir-based polypyridyl photocatalyst was done by Stephenson and coworkers in 2012 (**Scheme 1.14**).[33a] The reductive radical cyclization of **1.2.2-1** was performed, starting with the reductive quenching of the [Ir(ppy$_3$)]* is performed by the tributylamine to generate Ir(ppy)$_3^{2+}$ which then reduces the iodoarene to perform a dehalogenation and bring the photocatalyst back to its ground-state. A rapid 5-*exo-trig* cyclization then occurs, followed by an H-atom abstraction from formic acid to give the desired product **1.2.2-2**. Not only does this reaction work well performing 5-*exo-trig* cyclization but can also perform 5-*exo-dig* cyclization in moderate to excellent yields. By changing the ligand coordinating on the iridium metal center, highly activated bromoalkanes can also work in the cyclization reaction.[33b]



1.2.2-1 **1.2.2-2**

Scheme 1.14- Stephenson's early report using tris(2-phenylpyridine) iridum (III) in the cyclization and reduction of C-I bonds.

Although the use of iridium based polypyridyl photocatalyst has expanded the redox potentials that can be worked with, there are still some organic compounds, such as bromoalkanes, that cannot be reduced, unless they contain highly activating functional groups such as polyhaloalkanes, bromoacetates, bromonitriles, etc. There is a necessity for a photocatalyst with more powerful reducing potentials that could react with nonactivated, bench stable substrates.

1.2.3. Polynuclear Gold Photoredox Catalysis

Although known Ru- and Ir-based polypyridyl photocatalysts can react with different organic compounds, they must be highly activated, thus not always bench-stable. Nonactivated bromoalkanes are not only bench-stable, but also great radical precursors to access alkyl radicals. They are difficult to reduce by SET processes (> 2.0 V *vs* SCE), thus the currently known Ru- and Ir- based polypyridyl catalysts and organic dyes are not capable of performing an oxidative quenching with nonactivated bromoalkanes. In 1989, binuclear Au(I) biphosphine complexes (such as, $Au_2dppm_2Cl_2$) were found to have photophysical and photoredox properties, coming from the Au-Au interaction.[34a-c]In 2015, Che and workers reported that the aurophilic interaction in binuclear Au(I) bisphosphine complexes is greatly increased when these complexes are taken to their excited-state, compared to their ground-state.[34d] Upon excitation of [Au_2] complexes an

electron is promoted from the anti-bonding orbital $5d_z^2$ into $6p_z$ bonding orbital, thus forming an Au-Au bond (^{1}5dσ*6pσ) and rapidly undergoing ISC to ^{3}5dσ*6pσ (~0.15ps) (**Figure 1.7**).[34]

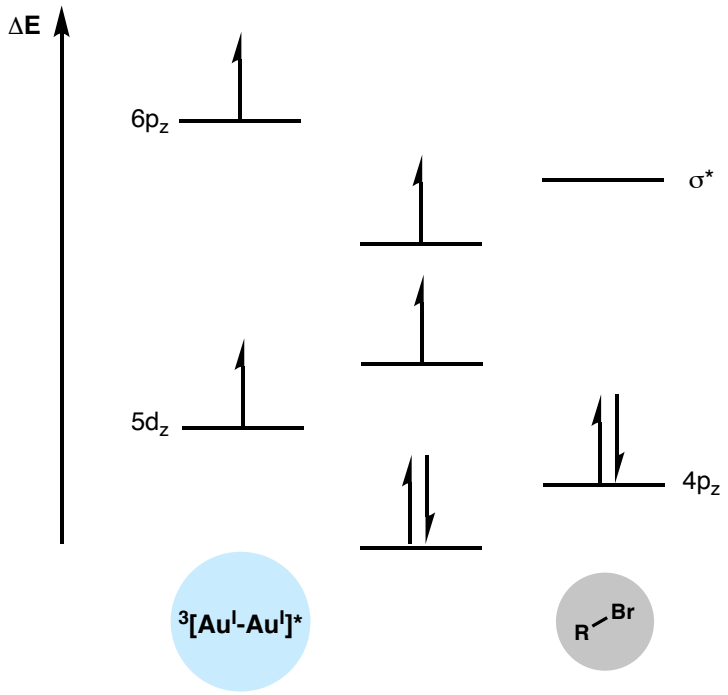


Figure 1.7- Molecular orbital diagram of excited $Au_2dppm_2Cl_2$ and bromoalkane.

The excited triplet-state complex (^{3}5dσ*6pσ) lifetimes were found to live for ~510ps (in DCM) and 850ns (in MeCN) and increased their coordination site number at the Au(I) center through an inner-sphere exciplex formation to perform an oxidative quench of the excited triplet-state with a C-X bond and forming a [ClAu^I-Au^{II}ClX] complex (**Figure 1.8**).[34,35] This process allows the excited-state complex to form alkyl radicals with nonactivated radical precursors even though the redox potential of the excited-state *[Au_2] complex is not capable of nonactivated bromoalkane reduction through outer-sphere processes upon inspection of the thermodynamic requirements.

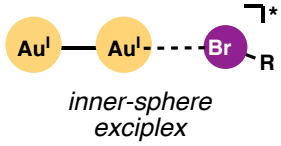
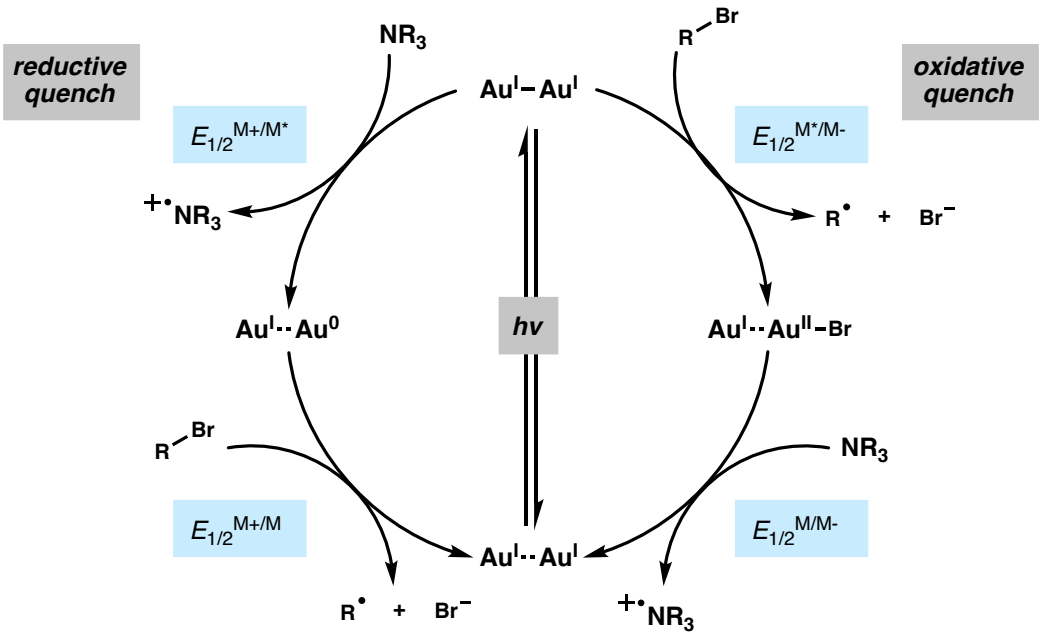


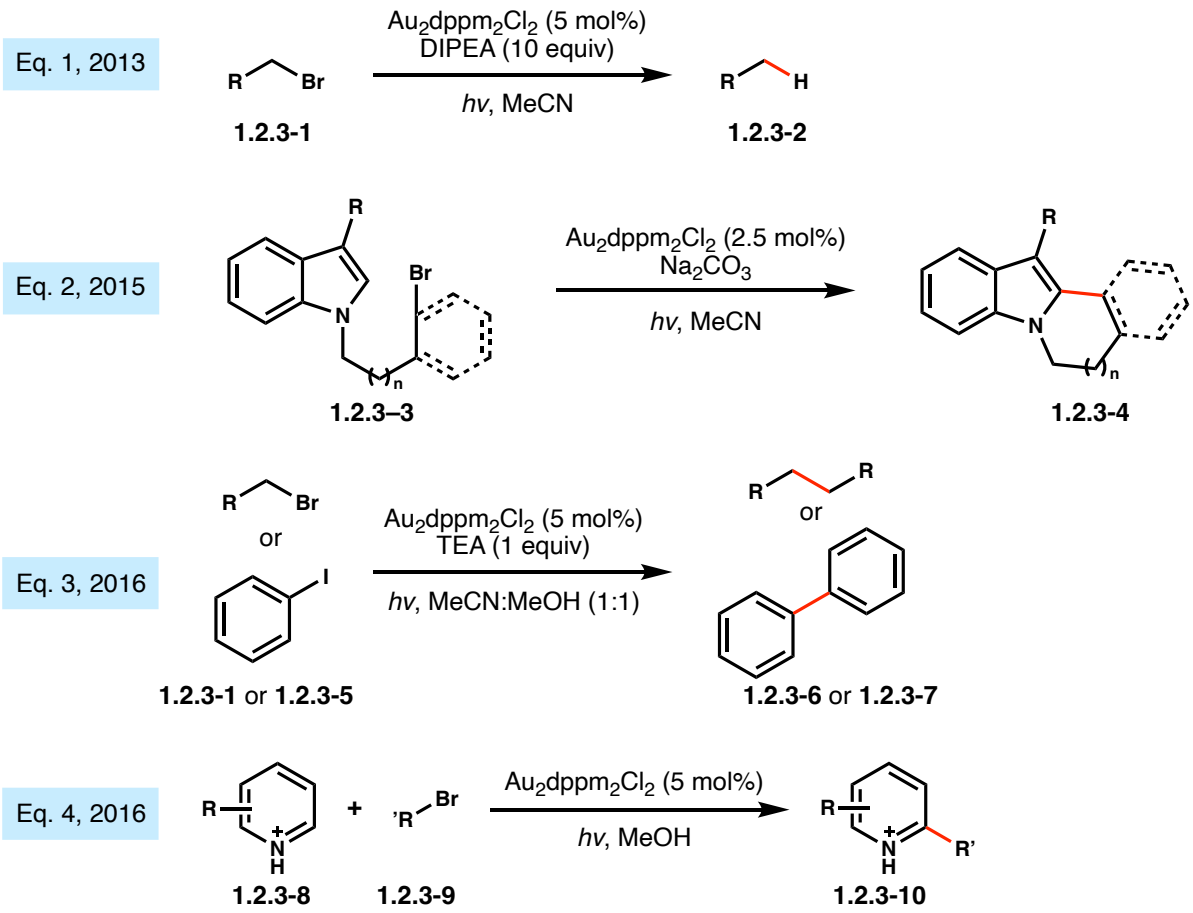
Figure 1.8- Inner-sphere exciplex complex: Mode of activation of binuclear Au(I) excited photocatalyst.

In 2016, Barriault and Scaiano elucidated the different quenching pathways that these polynuclear Au(I) biphosphines can undergo.[35] Upon excitation, Au_2* can undergo an oxidative or reductive quenching process (**Scheme 1.15**). When undergoing a reductive quench, the Au_2* complex will oxidize trialkylamines to form a nitrogen centered radical cation and a presumptive Au^1-Au^0 complex. This complex can now act as a reductant to break a C-X bond, returning the Au_2 complex to the ground state, and generating an alkyl radical. If the Au_2* complex undergoes an oxidative quench, it will reduce a C-X bond to form an alkyl radical and Au^I-Au^{II} complex. The binuclear Au complex will then act as an oxidant and react with a tertiary amine, or a carbon-centered radical to return to its Au_2 ground-state complex and thus form an amine radical cation or a carbocation. For example, the quenching rate for the bromoalkane is roughly ten times slower than the rate of trialkylamines for binuclear $Au_2(dppm)_2Cl_2$ complex. Therefore, concentration of each species significantly affects the reaction.



Scheme 1.15- Quenching pathways of $[Au_2]$*.

The different mode of activation of the polynuclear Au complexes and their use in photoredox catalysis opens another realm of radical precursors that can be used in radical reactions. The Barriault group has published several publications over the last decade using the $Au_2dppm_2Cl_2$ catalyst (**Scheme 1.16**).[36] In 2013, Barriault and Gagosz demonstrated the reduction of bromoalkanes **1.2.3-1** using $Au_2dppm_2Cl_2$ and DIPEA as H-atom donor.[36a] This transformation was performed undergoing a reductive quenching pathway, where DIPEA was not only the H-atom donor, but also the initial quencher. In 2015, the functionalization of indoles **1.2.3-3** was reported by Barriault, where it was demonstrated that Csp^2-Br bonds would also be reduced with this photocatalyst.[36b] Performing an oxidative quench, the C-Br bond of **1.2.3-3** is reduced, and the resulting radical performs an *exo-trig* cyclization unto an indole. Oxidation at the carbon-centered radical brings the photocatalyst back to the ground state and forms a carbocation. A proton elimination occurs to form the desired functionalized indole **1.2.3-4**. In 2016, the homocoupling of R-Br and Ar-I species (**1.2.3-1** and **1.2.3-5**, respectively) was reported.[36c] The homocoupled alkane product **1.2.3.-6** was formed in excellent yields, and a wide scope of iodoarenes was also converted to the homocoupled products **1.2.3-7** in excellent yields. Following this publication, the Barriault group reported the gold photoredox catalyzed alkylation of heteroarenes **1.2.3-8** using nonactivated bromoalkanes **1.2.3-9**. Barriault's work on the Minisci alkylation, provides an efficient way to form functionalized heteroarenes **1.2.3-10** without the use of harsh conditions or stoichiometric oxidants.[36d] Along with the Barriault group, Hashmi and coworkers have also contributed several reports using this photocatalyst in synthetic organic chemistry.[34e-f, 36j-n]



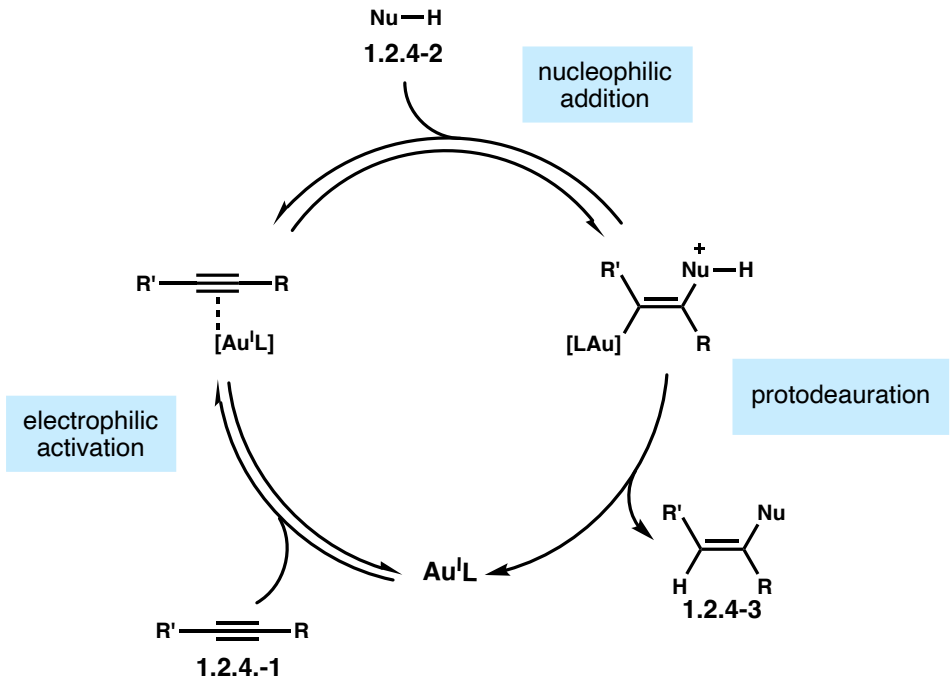
Scheme 1.16- Important work published by Barriault and coworkers involving $Au_2dppm_2Cl_2$ as photocatalyst.

Circling back to the 2016 homocoupling of nonactivated bromoalkanes, the Barriault group studied the possibility of a Lewis acid-type intermediate occurring.[36c] Giving the low concentration of radical intermediates, a second mechanistic hypothesis was developed. The high concentration of bromoalkane compared to the trialkylamine base means that the binuclear Au photocatalyst can undergo an oxidative or reductive quenching pathway. If undergoing the reductive quenching pathway, $[Au_2]^*$ is quenched by triethylamine, forming presumably a Au^I-Au^0 intermediate. This reductant will then perform a SET to form the alkyl radical and the ground-state photocatalyst. The resulting alkyl radicals will then do a radical-radical recombination to afford the desired product. However, due to the high excess of bromoalkane compared to

triethylamine, there is a higher chance that $[Au_2]^*$ will undergo an oxidative quenching pathway. This pathway will form Au^{I}-Au^{II} intermediate, and due to the high concentration of carbon-centered radicals, the Au^{II} center is prone to accept a radical to reach a more stable Au^{I}-Au^{III} intermediate. The desired product is formed through a reductive elimination, which in part also brings back the photocatalyst to the photoactive Au(I)-Au(I) state. The formation of the Au(III) intermediate means that the binuclear Au photocatalyst also has some Lewis acid character. This can open another realm of reactions performed with the $Au_2dppm_2X_2$ photocatalyst. Binuclear $Au_2dppm_2X_2$ has a double identity, not only acting as a photocatalyst, but also acting as a Lewis acid. This mode of reactivity will be explored in more detail *vide infra*.

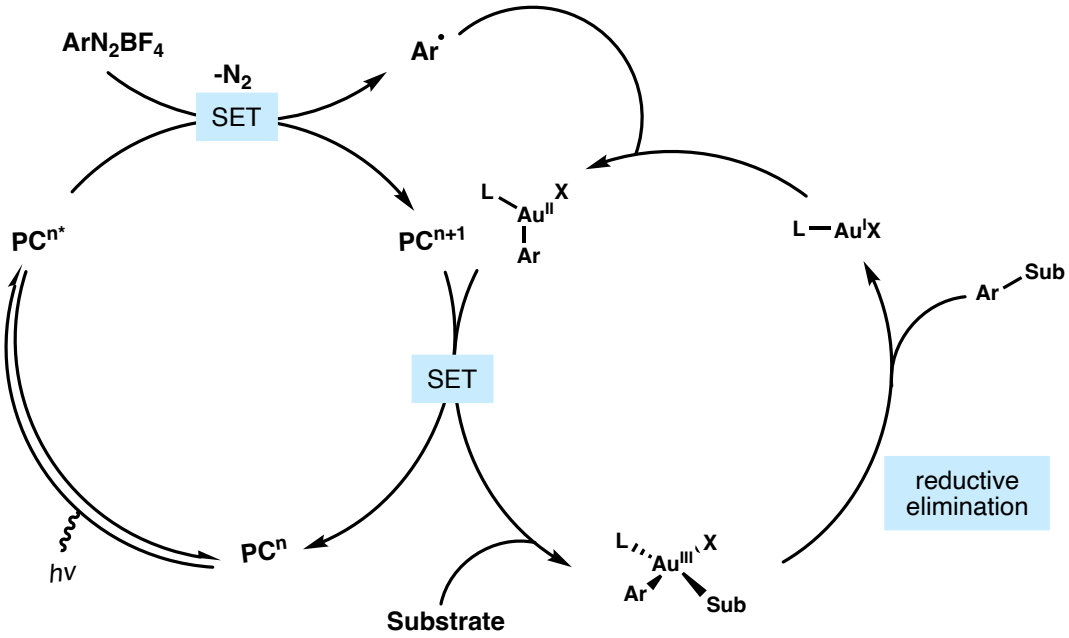
1.2.4. Dual Gold Photoredox Catalysis

Lewis acid catalysis using Au(I) and Au(III) complexes has been well established in literature in their use to activate alkynes/akenes/allenes.[37,38] Traditionally, an electron rich π bond, **1.2.4-1**, will perform a reversible electrophilic activation with an Au(I) species. Then, a nucleophile **1.2.4-2** will add unto the π bond, which will attack the Au(I) species to form a vinyl gold species containing a C-Au bond. To turn over the catalyst a protodeauration step occurs to give desired product **1.2.4-3** (**Scheme 1.17**).[39] When Au(I)/Au(III) redox neutral cycles are used, strong stoichiometric oxidants are needed to turn over the catalyst.



Scheme 1.17- General catalytic cycle of Au(I) as a Lewis acid.

Glorius and coworkers published seminal work, which replaces the use of strong oxidants with a photocatalyst that turns over the catalyst (**Scheme 1.18**).[40] The use of aryldiazoniums salts to replace the nucleophile was demonstrated. Once an aryl radical was formed from an SET with the excited photocatalyst, it adds unto the Au(I) catalyst to form Ar-Au^{II}X. This complex will then perform a SET with the oxidized photocatalyst to form an Au(III) species. Typical Au(III) reactivity is seen, and another nucleophilic substrate attacks the Au-center to form an additional C-Au bond. Reductive elimination turns over the catalyst and form the desired product.



Scheme 1.18- Dual gold photoredox catalysis.

The formation of highly reactive Au(II) species sparks the question if polynuclear gold catalysts could not only act as photocatalysts, but also as a Lewis acids. Further studies in this field will be discussed in later chapters of this thesis.

1.3. Outlook

In summary, the field of photoredox chemistry has grown immensely since the Ciamician address in 1912.[20c] Ciamician had an idea to replace the coal and gas fueled energy sector, by a cleaner energy source that was available to everyone: rays from the sun. This idea was not only to help with the pollution attributed with coal- and fossil-fuelled energy sector, but to also to diminish the economic gap in social classes. The need for more environmentally friendly, milder conditions and non-stoichiometric alternatives was high in radical chemistry, and photochemistry was the ideal solution. Inspired by the early work performed in the 80's, MacMillan, Yoon and Stephenson have taken the field of photoredox catalysis to great new heights. They have developed redox-neutral photocatalytic methodologies using mild conditions, that are more

environmentally friendly and waste-limiting, unlike the early radical precursors used in the past. Furthermore, contributions from fellow chemists have found more photocatalysts that are able react with bench-stable organic compounds as radical precursors.

Although this introductory chapter could not contain all the literature examples in photoredox catalysis that are out there, a small portion of the seminal works is shown. More examples of photocatalyzed transformations in synthetic organic chemistry are shown in the references all throughout the text. This chapter is written in the hopes to provide the reader with an overview of the field and how its evolution brought the need for bench-stable and nonactivated radical precursors and gave context to the direction of the research shown in this thesis.

1.4. References

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Chapter 2 – ALKYLATIVE SEMI-PINACOL REARRANGEMENT USING BINUCLEAR GOLD PHOTOREDOX CATALYSIS

Zidan, M.; McCallum, T.; Thai-Savard, L.; Barriault, L., Photoredox meets gold Lewis acid catalysis in the alkylative semipinacol rearrangement: A photocatalyst with a dark side, *Org. Chem. Front.* **2017**, *4*, 2092-2096.

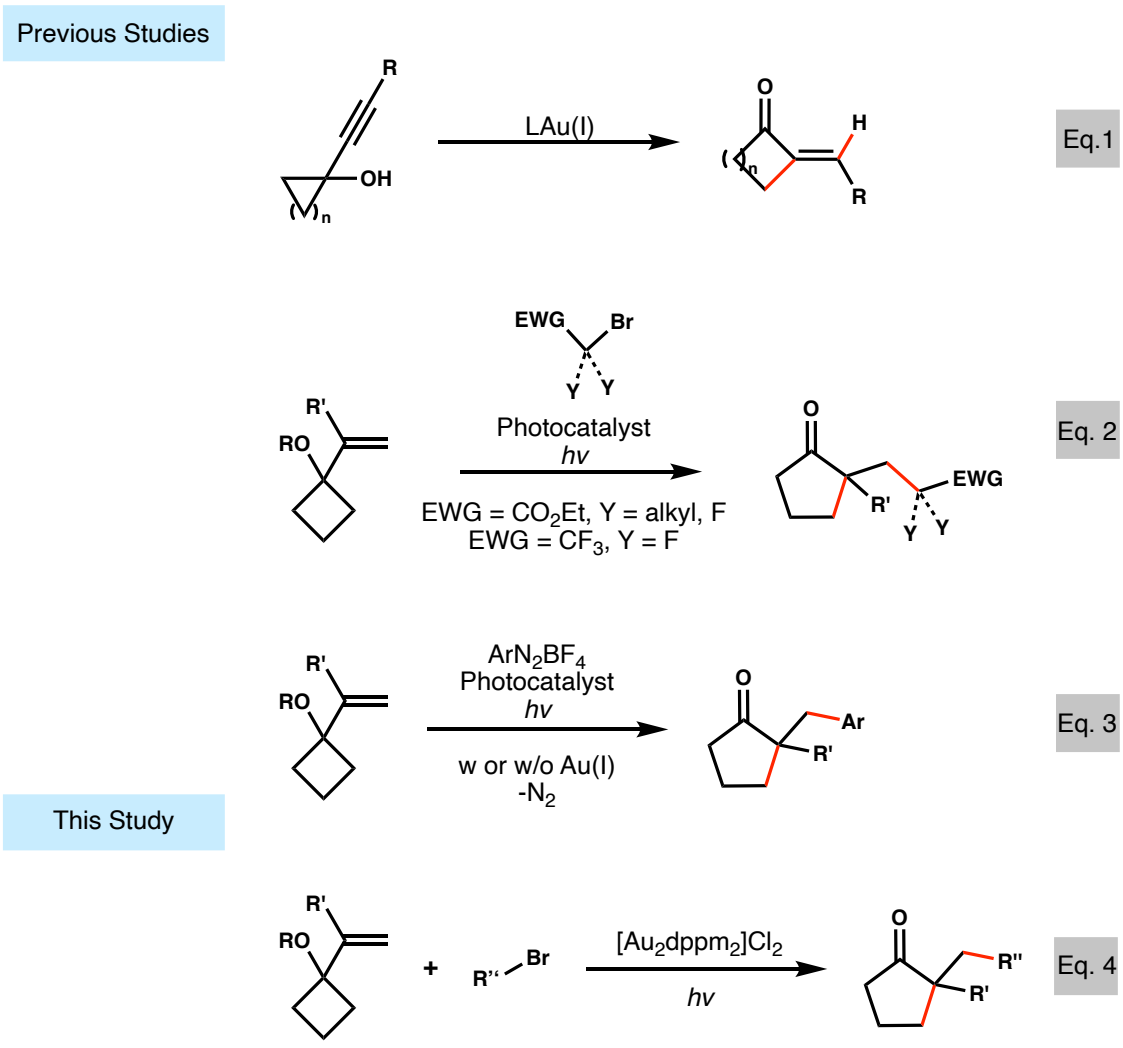
2.1- Abstract

The alkylative semi-pinacol rearrangement of a variety of TMS protected α-styrenyl substituted cyclic alcohols with nonactivated bromoalkanes that merge photoredox and Au(I)/Au(III) catalysis has been achieved. This redox neutral rearrangement is marked by a dimeric Au(I) photocatalyst that plays two roles; photoredox activation of bromoalkanes and Au(III)-mediated semi-pinacol rearrangement coupled with $C(sp^3)$–$C(sp^3)$ reductive elimination; a reaction mode rarely accessed. This operationally simple methodology contains readily available starting materials that undergo reaction with $[Au_2(dppm)_2]Cl_2$ upon irradiation with UVA LEDs, furnishing diversified ketone products. Primary, secondary, and tertiary bromoalkanes and a range of TMS protected α-styrenyl substituted alcohols were investigated in this transformation.

2.2- Introduction

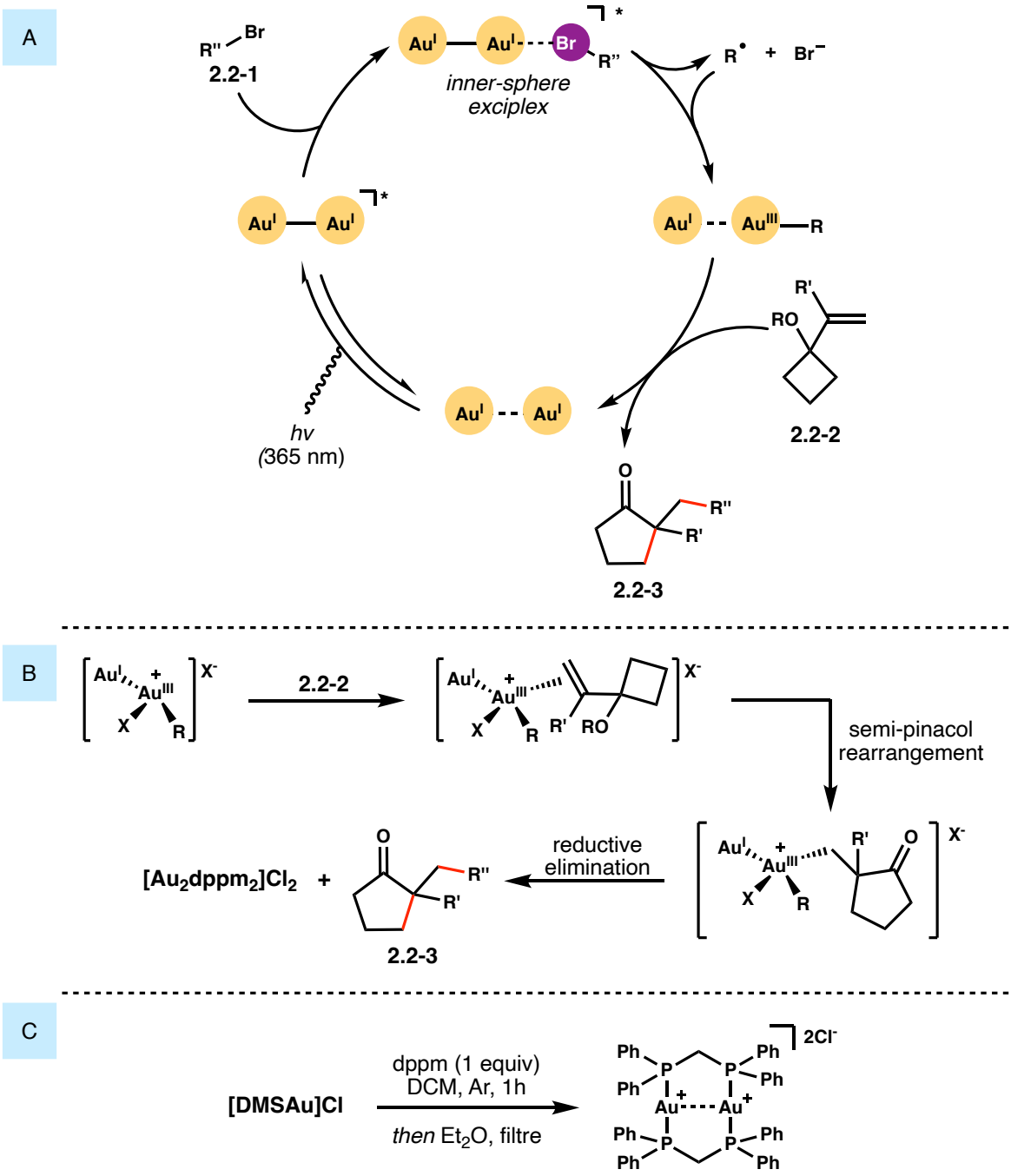
Photochemistry is a mainstay technique of chemical activation in synthetic organic chemistry. The blueprints of light-harvesting biomolecules found in Nature have given chemists the ability to use transition metal complexes and organic dyes to transform photons into chemical energy.[1] Photochemistry and radical chemistry are united in their ability to undergo photo-induced (single) electron transfers (PET or SET) and one electron reaction modes.[2] A combination

of these unique fields, photoredox catalysis has emerged as a mild and efficient alternative to classical methodology for radical generation. Based on transition metal complexes and organic dyes, photoredox catalysts and sensitizers have provided organic chemists with a large collection of methodologies for the assembly of new C–C bonds.[3] The semi-pinacol rearrangement is a unique approach to prepare functionalized ketones starting from vinyl substituted cyclic and acyclic alcohols. This transformation has been utilized in several syntheses of complex natural products and is usually achieved through alkene activation with acids, halogens and transition metals (especially with Au).[4] Au complexes are known to have an affinity to alkynes where ring expansions have been demonstrated (**Scheme 2.1, eq. 1**).[4b–d,f,6h] Recently, the semi-pinacol transformation has been accessed via photoredox catalyzed pathways.[5] In this context, a free radical generated by some initiation process could add to an Au(I) based catalyst to generate an Au(III) intermediate in situ (**Scheme 2.2B**).[1] This intermediate could activate a vinyl substituted alcohol, where upon rearrangement and reductive elimination, a functionalized ketone could be obtained along with regeneration of the photocatalyst. To this effect, the methodologies developed with photoredox catalysis have been restricted to Ru and Ir-based polypyridyl complexes which limit substrate engagement to activated C–X bonds (**Scheme 2.1, eq. 2 and 3**). Herein, we report the alkylative semi-pinacol rearrangement using nonactivated bromoalkanes using a binuclear Au(I) photoredox catalyst, $[Au_2(dppm)_2]Cl_2$ (**Scheme 2.1, eq. 4**). Based on previous methodologies developed in our laboratory, we hypothesized that a redox neutral reaction pathway could be achieved by an oxidative quenching cycle.[7]



Scheme 2.1- Previous and present work in photoredox mediated alkylative semi-pinacol rearrangements.

Recently it has been shown that the genesis of alkyl radicals hailing from readily available nonactivated bromoalkanes **2.2-1** (~ 2.5 V vs. SCE)[8] can be accomplished via inner-sphere exciplex formation and oxidative quenching with excited state binuclear Au(I) complex, *$[Au_2(dppm)_2]Cl_2$ (1.63 V vs. SCE, **Scheme 2.2A**).[9] This is an important distinction as this interaction allows for the activation of bromoalkanes **2.2-1** with much higher redox potentials. Ru and Ir-based polypyridyl and many other complexes undergo SET via an outer sphere metal-to-ligand charge transfer (MLCT) pathway, limiting substrate activation to redox potentials inherent to each complex.



Scheme 2.2- Proposed mechanism. A) Gold photoredox catalytic cycle. B) Binuclear gold catalyst as a Lewis acid and the alkylative semi-pinacol rearrangement. C)

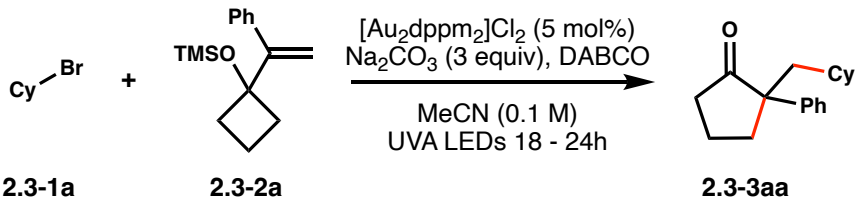
We envisioned that the incumbent alkyl radical could then undergo addition to the [Au^{I}–Au^{II}]$^{3+}$ intermediate, resulting in an alkylated [Au^{I}–Au^{III}–R] intermediate that may participate in Lewis acid type activation of the α-styrenyl substituted alcohol **2.2-2** (**Scheme 2.2B**). The resulting

intermediate could then undergo semi-pinacol rearrangement and reductive elimination, regenerating the ground state photocatalyst and substituted ketone product **2.2-3**.[10] This transformation would provide a direct access to functionalized cyclic ketone products under mild and non-acidic conditions.

2.3- Results and Discussion

Initial screening of a variety of bases and solvents found that bromocyclohexane **2.3-1a** and Na_2CO_3 (3 equiv) in MeCN gave full conversion of the TMS protected α-styrenyl cyclobutanol **2.3-2a** but gave cyclic ketone **2.3-3aa** in 15% under UVA LED irradiation with 5 mol% $[Au_2(dppm)_2]Cl_2$ (**Table 2.1, Entry 1**). The use of sub-stoichiometric amount of DABCO as an additive proved to be beneficial for the reaction, up to 82% yield (**Table 2.1, Entries 2 and 3**). Use of stoichiometric DABCO resulted in a slightly lower yield (**Table 2.1, Entry 4**). Using 4 equivalents of **2.3-1a** increased the yield to 83% (82% isolated). Finally, control experiments showed that both light and photocatalyst were essential for the reaction to progress (**Table 2.1, Entries 7 and 8**).

Table 2.1- Optimization of reaction conditions



2.3-1a **2.3-2a** **2.3-3aa**

Entry	2.3-1a [equiv]	DABCO [equiv]	Yield[a] [%]
1	3	0	15
2	3	0.2	69
3	3	0.4	82
4	3	1.0	80

5	4	0.4	83 (82)
6	5	0.4	80
7	10	0.4	81
8	4	0.4	0
9	4	0.4	0
10	4	0.4	0

[a] ^{1}H NMR yield using mesitylene as internal standard (isolated yield). [b] In absence of UVA LED irradiation. [c] In absence of $[Au_2(dppm)_2]Cl_2$. [d] Heating to 80°C with $[Au_2(dppm)_2]Cl_2$.

After establishing the optimal reaction conditions for the transformation, the reaction scope was then evaluated using TMS protected cyclobutanols (**2.3-2a–f**) and bromoalkanes (**2.3-1a-j**) varying from 1°, 2° and 3° alkyl chains. Au(I)-catalyzed photoredox transformation between TMS-cyclobutanol (**2.3-2a**) and bromoalkanes (**2.31a–j**) produced the desired α-alkylated ketone products (**2.3-3aa-ja**) from the corresponding semi-pinacol rearrangement in 32–88% yields (**Figure 2.1**). Notably, this reaction tolerated 1°, 2° and 3° bromoalkanes as coupling precursors as well as an acetylated glucose derivate. Similarly, the photoredox reaction of **2.3-2b–f** with cyclohexyl bromide (**2.3-1a**) and ethyl bromoacetate (**2.3-1c**) provided the semi-pinacol rearrangement products in 27–67% yields (**Figure 2.2**). Substrate **2.3-2f** was used without silyl protection as degradation occurred in presence of the TMS group. When unprotected version **2.3-2f** was used, the desired products **2.3-3af** and **2.3-3cf** were obtained in a diastereomeric ratios of 2:1 in 57% and 53% yields, respectively. One can hypothesize that the TMS group was bulky enough to impede the addition of the alkyl moieties.

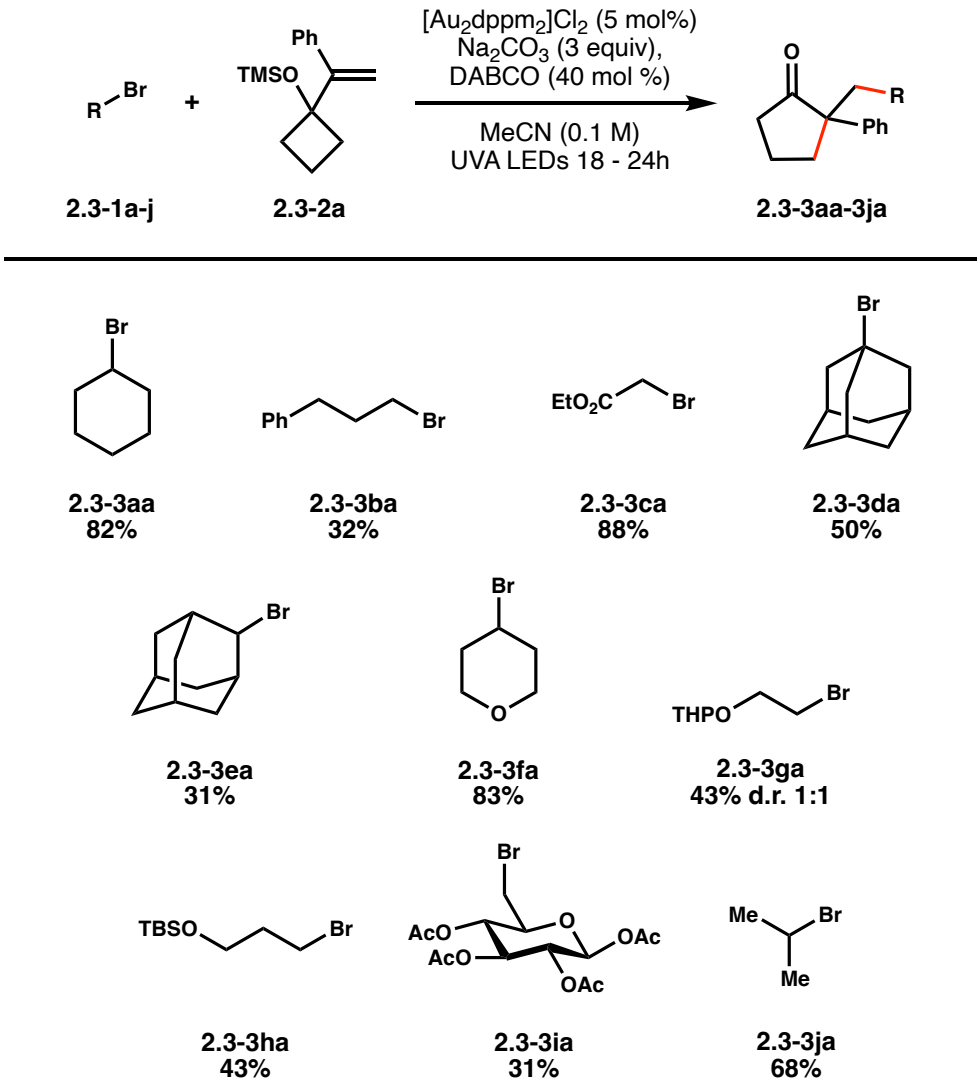


Figure 2.1- Reaction of **2.3-2a** with various alkyl bromides **2.3-1**.

Extending the described conditions to alkyl functionalized alkenes as well as acyclic α-styrenyl substituted TMS-protected alcohols (to attempt alkyl and aryl migrations) were incompatible with this methodology. Furthermore, the use of unprotected α-styrenyl alcohols resulted in by-product formation.

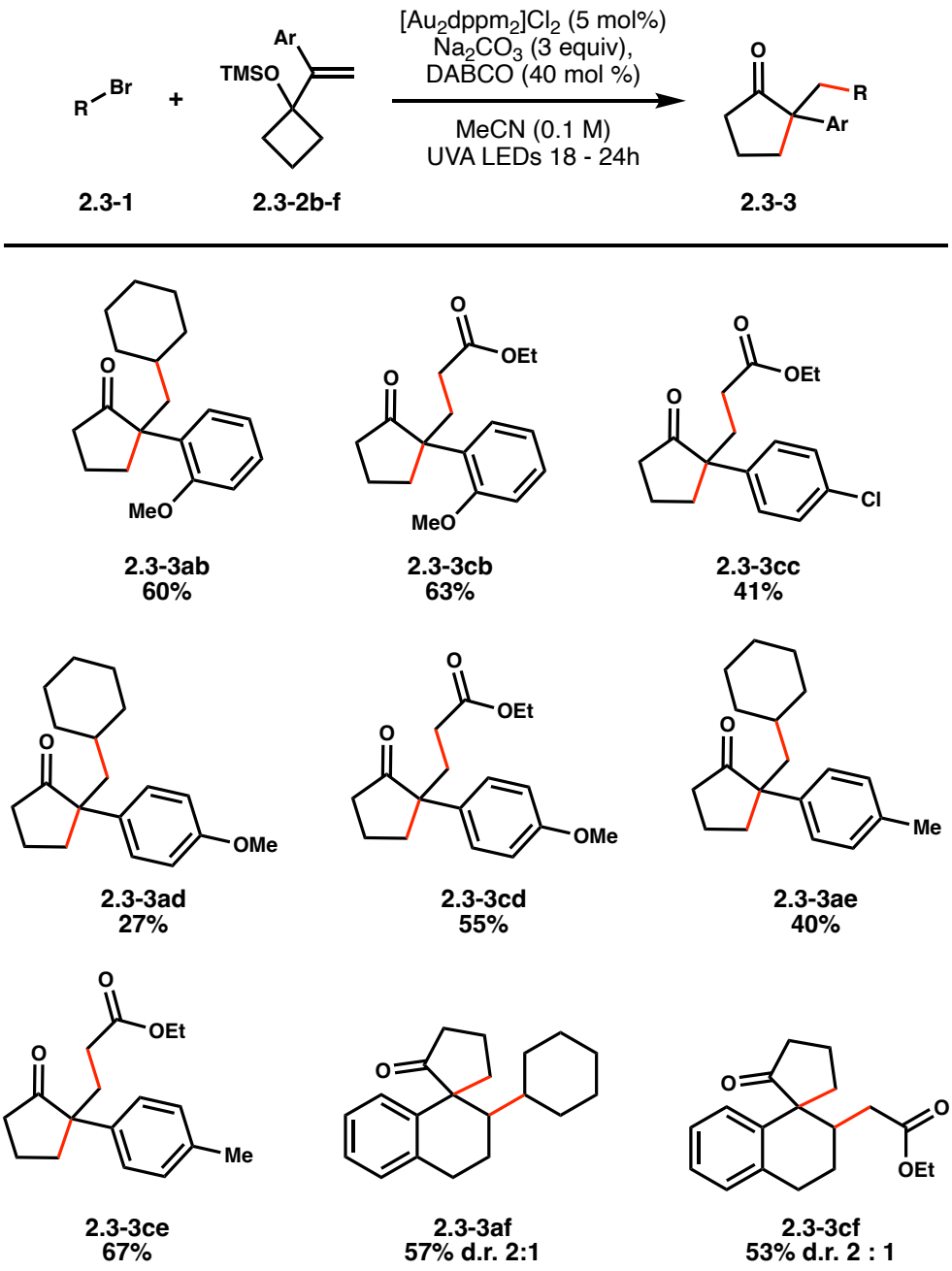
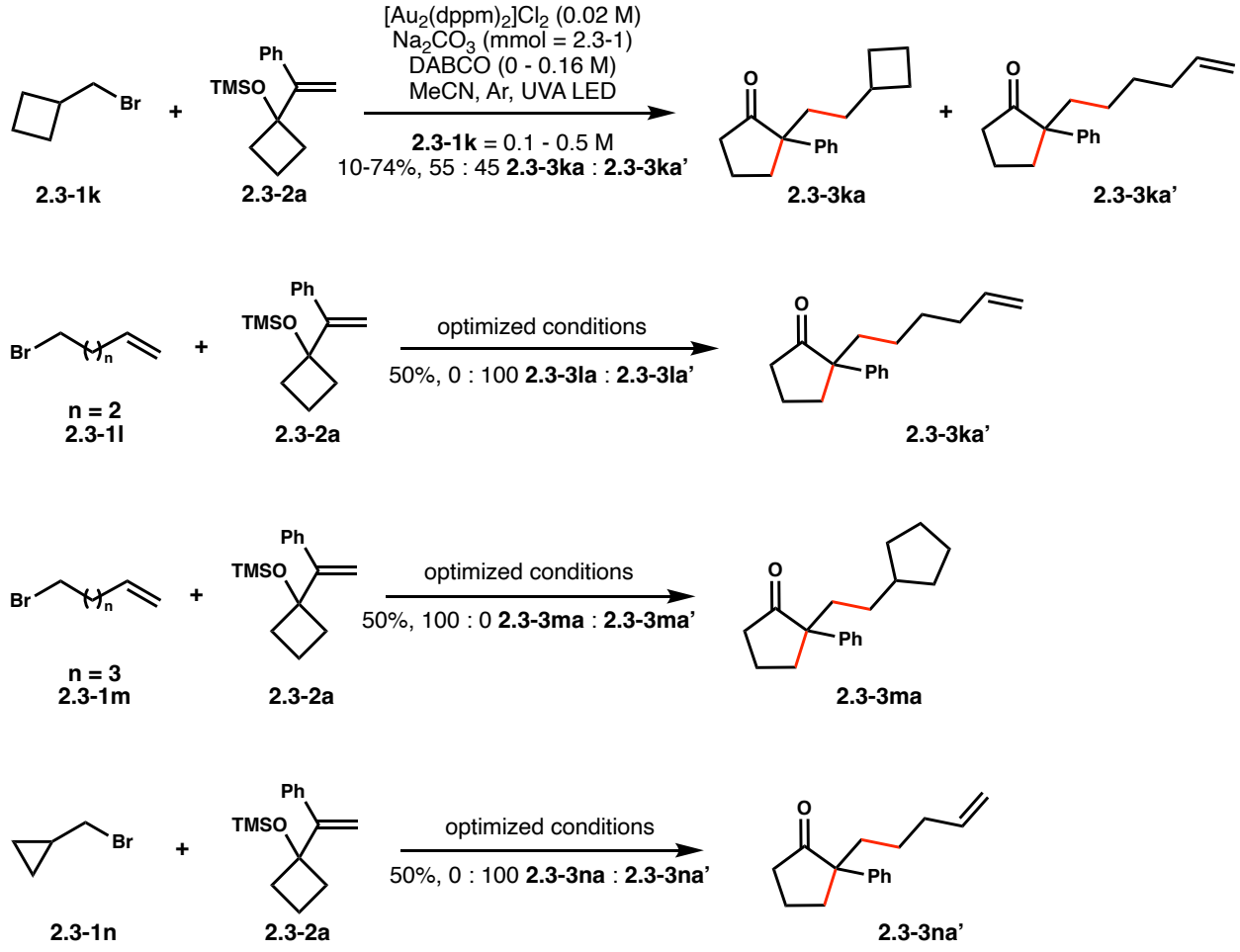


Figure 2.2- Expansion of scope using various functionalized starting materials.

The mechanism of this transformation was further investigated with examination of the product distribution obtained when (bromomethyl)cyclobutane (a known radical clock) **2.3-1k** with TMS protected alcohol **2.3-2a** were coupled (**Scheme 2.3**). A kinetic study was conducted by increasing the molarity of **2.3-2a** from 0.1 M to 0.5 M in presence and absence of DABCO to

determine the absolute rate of alkyl radical addition.[7d,11] One would expect as the concentration of acceptor is increased, the ratio of unopened to opened cyclobutane rearrangement (k = 3.0 × 10^2 s^{-1}) in the products (**2.3-3ka**:**2.3-3ka'**) would increase if the transformation proceeded via a free radical addition followed by oxidation (polar radical crossover) and semi-pinacol rearrangement.[11] Interestingly, increasing the acceptor concentration resulted in the same ratio of products (55 : 45 **2.3-3ka**:**2.3-3ka'**) in all cases. It is possible that DABCO may be operating through a reductive quench with the excited state catalyst, leading to a different mechanism of product formation. It was found that DABCO does undergo quenching with the excited state catalyst (k_q^{DABCO} = 1.97 ± 0.54 × 10^8 $M^{-1}s^{-1}$, see **Section 2.5- Further Information**) at a rate faster than nonactivated bromoalkanes ($k_q^{n\text{-BuBr}}$ = 2.9 × 10^6 $M^{-1}s^{-1}$).[9b] Given the equivalents of each, the bromoalkane will undergo quenching more frequently. Furthermore, DABCO may facilitate reduction of Au-intermediates that may undergo degradation, where DABCO acts as a resuscitation agent.[9k] To completely suppress the possibility of a reductive quenching cycle, DABCO was removed, and repetition of the experiment also resulted in obtaining the same ratios of **2.3-3ka**:**2.3-3ka'** over increasing concentrations of acceptor **2.3-2a**. Furthermore, repetition of the experiment at 0.25 M of 2a and increasing the catalytic loading from 5% to 25% and 50% also resulted in the same ratios of **2.3-3ka**:**2.3-3ka'**. Bromoalkane **2.3-1l** coupled to **2.3-2a** exclusively as the open form **2.3-3ka'** (excluding alternative non-radical pathways that may lead to **2.3-3ka**:**2.3-3ka'** reversibly). Bromoalkanes **2.3-1m** (5-*exo*-*trig*, k = 1.8 × 10^5 s^{-1}) and **2.3-1n** (methylcyclopropane opening, k = 7.8 × 10^7 s^{-1}) were also coupled to **2.3-2a**, where the exclusive 5-*exo*-*trig* cyclization (**2.3-3ma**) and ring opening (**2.3-3na'**) products were isolated, indicative that an intermediate free radical was formed.[11] Considering this data, it seems that the alkylative

addition of **2.3-2a** does not proceed directly via a free radical mechanism but possibly through radical addition to an Au(I) intermediate followed by Au(III)-mediated Lewis acid type reactivity (**Scheme 2.2A-B**). It is unclear whether the Au(III) intermediate is formed via an Au(II)–Au(II) adduct that may disproportionate versus direct addition of a radical to the Au(II) center. It has been demonstrated that the absolute rate of alkyl radical addition to phenyl substituted alkenes ($k = 2.6 \times 10^5$ $M^{-1}s^{-1}$ for methyl radical addition to styrene) is faster than alkyl substituted alkenes ($k = 1.4 \times 10^4$ $M^{-1}s^{-1}$ for methyl radical addition to alkenes).



Scheme 2.3- Mechanistic studies: Radical clock experiments with **2.3-3a**.

Interestingly, electrophilic alkyl radicals (i.e., α-ester) undergo the same radical additions at slower rates than alkyl radicals ($k = 1.9 \times 10^3$ $M^{-1}s^{-1}$ for styrenes and $k = 5.4 \times 10^1$ $M^{-1}s^{-1}$ for

alkenes).[12] If a radical addition to an Au intermediate is at play, it is expected that it would have a relatively slow rate. If this process was reversible, one would expect the **2.3-3ka**:**2.3-3ka'** ratios to vary with concentration of acceptor or Au-catalyst loadings. If the process was fast, it would be expected that no cyclobutane rearrangement of **2.3-1k** would be observed. One can suggest that these results support a mechanism involving the formation of an Au(III) intermediate which triggers the semi-pinacol rearrangement followed by a reductive elimination.[13]

2.4- Conclusions

In summary, the regioselective synthesis of diversified ketone products from TMS protected α-styrenyl substituted cyclic alcohols and bromoalkanes was mediated by photoredox gold cata- lysis. This process displayed a Au(III)-mediated coupling of the starting materials rather than a polar radical crossover triggered semi-pinacol rearrangement pathway. It was shown that sterics hindered the transformation and relatively electron withdrawing alkyl radicals (ethyl bromoacetate) were also compatible towards coupling to the α-styrenyl functionalized substrates. Further methodological studies evaluating the suitability of dual role dimeric Au(I) complexes for the photo- chemical generation of Au(III)–R, coupling and reductive elimination towards natural product synthesis are currently underway.

2.5- Further Information

2.5.1- Kinetic Quenching Data of $^3[Au_2(dppm)_2]Cl_2$ by DABCO

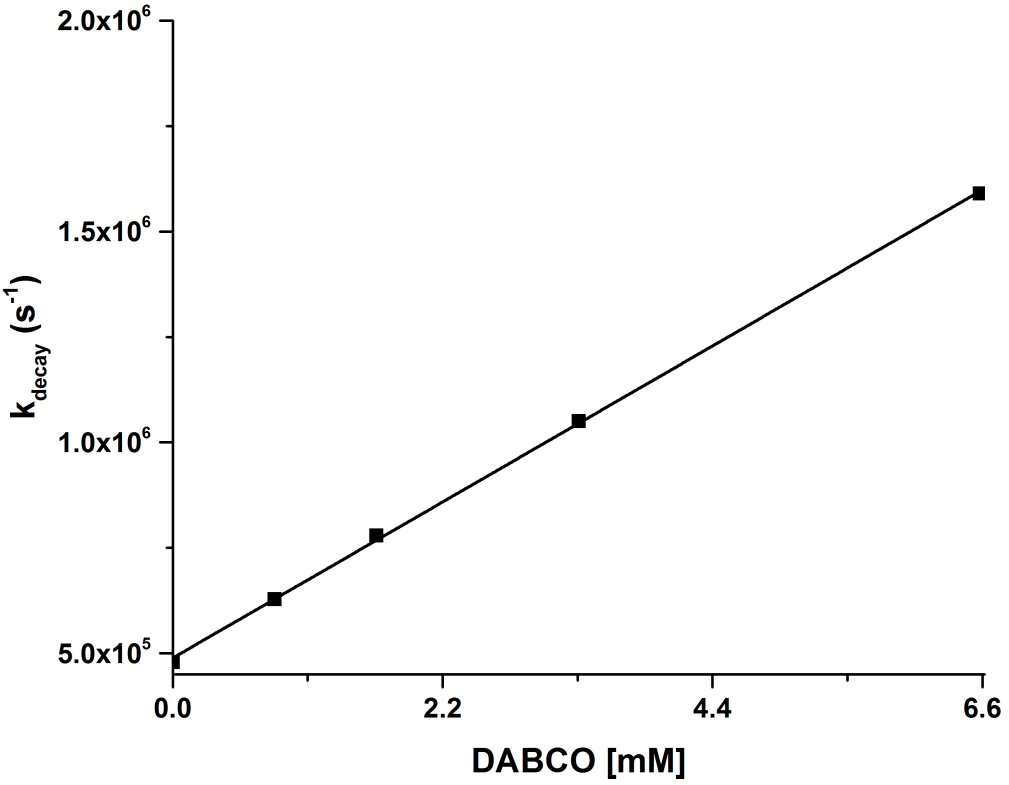
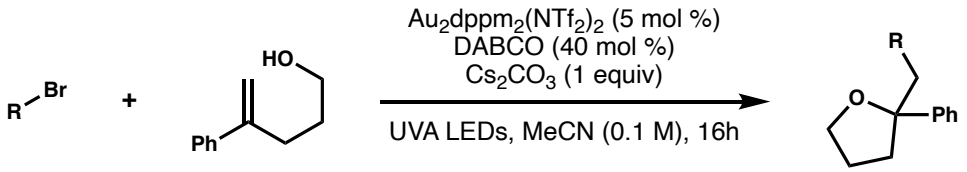


Figure 2.3- Kinetic quenching plot showing the quenching of $^3[Au_2(dppm)_2]Cl_2$ by DABCO. The slope of this plot corresponds to the bimolecular rate constant. See ref. 9b for transient emission spectrum obtained upon laser pulse excitation (355 nm, 10 mJ) and decay trace (at 560 nm) of $^3[Au_2(dppm)_2]_2Cl_2$ from $[Au_2(dppm)_2]Cl_2$ sampled purged of oxygen.

2.5.2- Finding the Au(III) intermediate: Alkylative Tetrahydrofuran-Ring Formation using Gold Photoredox Catalysis

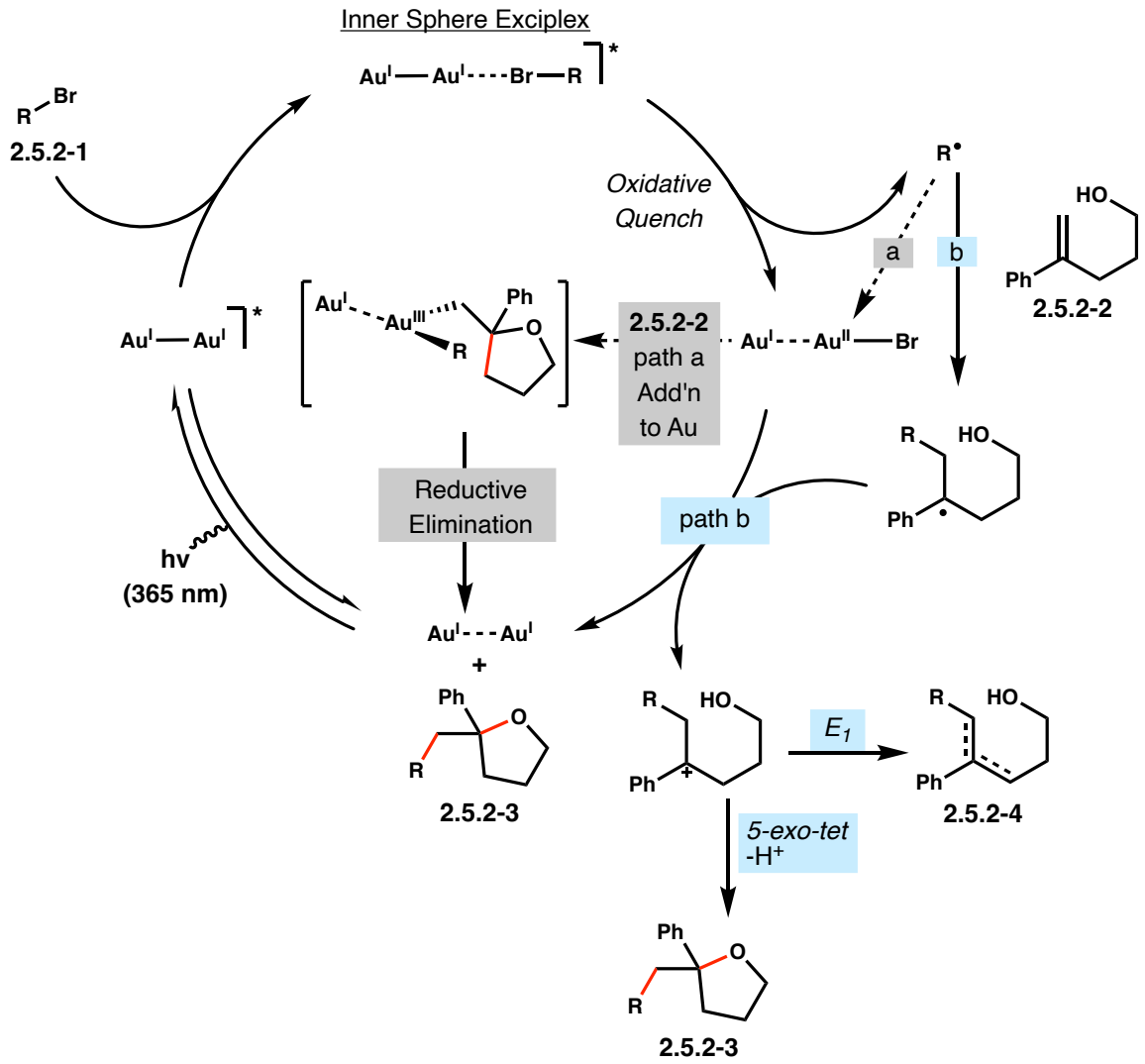
The breadth of success of this methodology, led us to imagine different ways to intercept the much wanted Au(III) intermediate of the binuclear $[Au]_2$ photocatalyst. We developed an alkylative tetrahydrofuran-ring formation using a combination of gold photoredox catalysis and gold Lewis acid catalysis (**Scheme 2.4**)



2.5.2-1 **2.5.2-2a** **2.5.2-3**

Scheme 2.4- Alkylative tetrahydrofuran-ring formation using gold photoredox and Lewis acid catalysis.

It was envisioned that upon excitation of binuclear $[Au_2(dppm)_2]X_2$ catalyst to $^3[Au_2]^*$, it would perform an oxidative quenching pathway *via* an inner sphere exciplex complex formation with an bromoalkane **2.5.2-1** (**Scheme 2.5**). The alkyl radical that is formed could then undergo two different paths: Path A would see the alkyl radical adding unto Au^{II}-metal center, thus forming a Au^{III} intermediate, which can act as a Lewis acid. This newly formed Lewis acid will interact with olefin **2.5.2-2** and promote a nucleophilic attack of the alcohol through a *5-exo-trig* cyclization, and add unto the gold center, forming a C-Au bond. This binuclear gold intermediate will perform a rapid reductive elimination to form desired product **2.5.2-3** and regenerate the binuclear gold photocatalyst. However, alkyl radical could also undergo Path B: alkyl radical would add unto the olefin **2.5.2-2**, forming a carbon-centered benzylic radical. This radical intermediate would then undergo an SET process with the Au^I-Au^{II} to form a benzylic carbocation and regenerate the ground-state photocatalyst. The benzylic carbocation will then undergo two different reactions: the desired reaction is the nucleophilic attack of the alcohol moiety to form the desired tetrahydrofuran ring **2.5.2-3** after the loss of a proton. However, it could also perform an undesired E_1 elimination and form undesired products **2.5.2-4**. Olefins **2.5.2-4** could be a mixture of 4 different isomers, as there is no inherent selectivity and there is the possibility of elimination 4 different protons.

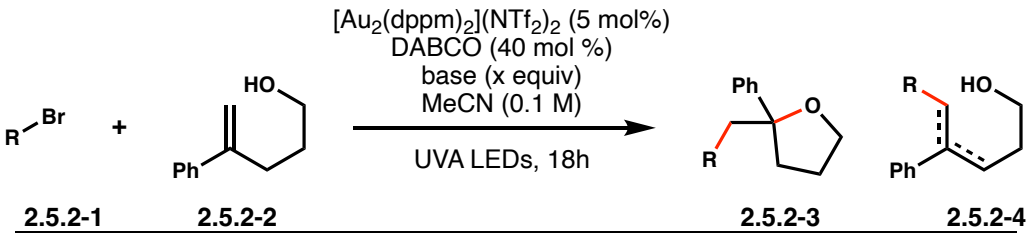


Scheme 2.5- Proposed mechanism of the alkylative tetrahydrofuran-ring formation using gold photoredox catalysis.

Initial experiments showed that using NTf_2 as a the photocatalyst's counter anion proved to be very efficient. Furthermore, we discovered that the desired product **2.5.2-3** was acid and base sensitive and overtime it would degrade and form **2.5.2-4**. Furthermore, over time the desired product slowly degrades to become **2.5.2-4**. This proved optimization difficult, as it would degrade upon any sort of work-up. We turned to GC-FIC to optimize the reaction without fear of degradation. External standard calibration curves were created to calculate yield of **2.5.2-3** and conversion percentage of **2.5.2-2**. We attempted to isolate the four different regioisomers of

2.5.2-4 to also include them in the calibration curves, however, the regioisomers were not separable using chromatography techniques such as column liquid chromatography or High-Performance Column Chromatography. Furthermore, we did not know if the formation of **2.5.2-4** was only happening through the reaction or if it was attributed to degradation of the desired product **2.5.2-3**. We opted in simply optimization formation of **2.5.2-3** and explore formation **2.5.2-4** at a later point. Using pentafluorobenzene as internal standard, we submitted all our reaction mixtures to the GC-FID. A small magnesium silicate plug was needed to remove inorganic and non-volatile impurities. We first optimized the base and base equivalents in the reaction using bromo cyclohexane as **2.5.2.-1** (**Table 2.2**). Initial studies were done with 1.5 equivalents of Na_2CO_3 as inorganic base, and desired product **2.5.2-3** was formed in 59% (**Table 2.2, Entry 1**). It was found that 1.5 equivalents of inorganic Cs_2CO_3 base provided the best results for the reaction, providing desired product 2.5.2-3 in 65% yield (**Table 2.2, Entry** 3). Lowering the equivalents to one, increased the yield of the reaction to 72% (**Table 2.2, Entry 8**).

Table 2.2- Reaction optimization: Base and base equivalents.

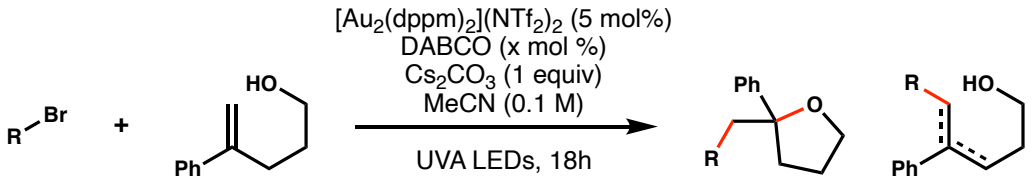


2.5.2-1 **2.5.2-2** **2.5.2-3** **2.5.2-4**

Entry	Base	Base (equiv)	Conversion **2.5.2-2** (%)	Yield **2.5.2-3** (%)
1	Na_2CO_3	1.5	100	59
2	K_2CO_3	1.5	100	45
3	Cs_2CO_3	1.5	100	65
4	KH_2PO_4	1.5	100	50
5	K_2HPO_4	1.5	100	48
6	K_3PO_4	1.5	100	51
7	Cs_2CO_3	3	100	68
8	Cs_2CO_3	1	100	72
9	Cs_2CO_3	0.05	100	45

Our attention was turned to the use of DABCO in the reaction. Much like reaction conditions of the alkylative semi-pinacol rearrangement discussed earlier in this chapter (see **2.3-Results and Discussion**) we found that using a catalytic amount of DABCO increased the yield of **2.5.2-3** (**Table 2.3**). This reaction mainly reacts through the oxidative quenching of triplet excited state of binuclear gold catalyst, however, DABCO can react with the photocatalyst through a reductive quenching cycle. Because of statistical analysis, we believe that there is a higher chance the quenching of $^3[Au_2]^*$ will be performed by the bromoalkane and not DABCO. Thus, we believe in this case DABCO acts a catalyst resuscitator and solely acts as an additive in the reaction. It was found that adding stoichiometric amounts of DABCO decreased the yield of **2.5.2-3** to 48% (**Table 2.3, Entry 2**). Using 40 mol % of quinuclidine instead of DABCO showed a lower yield of **2.5.2-3** (42%, **Table 2.3, Entry 7**).

Table 2.3- Reaction optimization: DABCO loading.



2.5.2-1 **2.5.2-2** **2.5.2-3** **2.5.2-4**

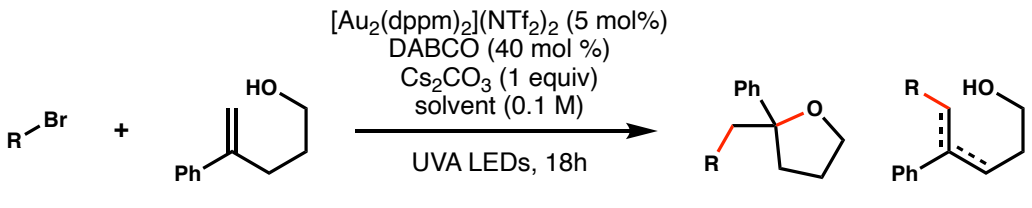
Entry	DABCO (x mol %)	Conversion **2.5.2-2** (%)	Yield **2.5.2-3** (%)
1	40	100	72
2	100	100	48
3	80	100	71
4	60	100	66
5	20	100	64
6	0	100	62
7	40[a]	100	42

[a] Using quinuclidine instead of DABCO

Solvent optimization showed MeCN to be the best solvent for our methodology (**Table 2.4, Entry 1**). Other UVA-light compatible solvents were tried, but lower yields of **2.5.2-3** were found (**Table**

2.4, Entries 2-4). We hypothesized that the use of MeOH would help us determine the mechanism of the reaction. If a carbocation was formed, it could react intramolecularly or intermolecularly fashion with MeOH and some by-products would be formed. However, no by-products were found that alluded to a MeOH nucleophilic attack unto the benzylic position, only lower yields of **2.5.2-3**.

Table 2.4- Reaction optimization: Solvent optimization.

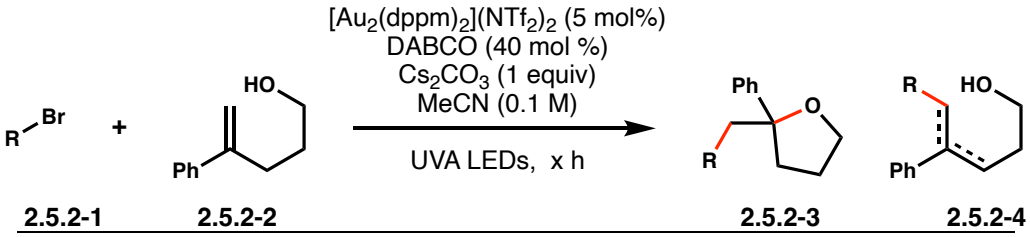


2.5.2-1 **2.5.2-2** **2.5.2-3** **2.5.2-4**

Entry	Solvent	Conversion **2.5.2-2** (%)	Yield **2.5.2-3** (%)
1	MeCN	100	72
2	Acetone	100	45
3	MeOH	100	40
4	MeOH : MeCN (1:1)	100	33
5	Benzene	93	61

Concerned with possible degradation of the product from **2.5.2-3** to **2.5.2-4** in the reaction mixture and solution, we optimized the time of the reaction (**Table 2.5**). It was found that full conversion of the starting material **2.5.2-2** was achieved after 16h, yielding 80 % of **2.5.2-3** (**Table 2.5, Entry 7**). If the reaction was left for 24h, we found that the yield dropped to 74% (**Table 2.5, Entry 8**). This result led us to believe that the desired product **2.5.2-3** was unstable and would quickly degrade if left in solution.

Table 2.5- Reaction optimization: Time optimization.



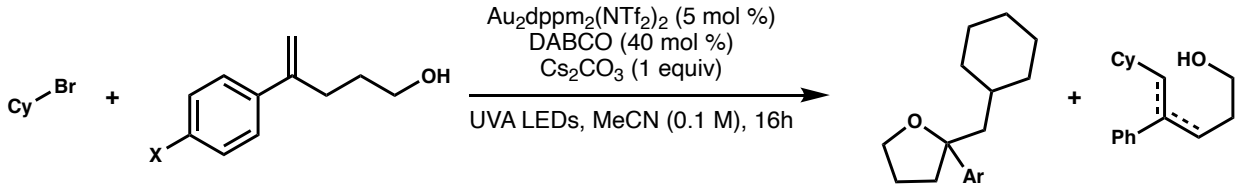
2.5.2-1 **2.5.2-2** **2.5.2-3** **2.5.2-4**

Entry	Time (h)	Conversion **2.5.2-2** (%)	Yield **2.5.2-3** (%)
1	18	100	72
2	1	66	47
3	2	73	55
4	4	83	55
5	6	82	54
6	8	84	60
7	16	100	80
8	24	100	74

Wanting to further study the reaction mechanism, we studied the effect of varying functionalization on the aromatic group of **2.5.2-2**. Functionalizing the *para*-position of the phenyl group, we hypothesized that if both mechanisms displayed in **Scheme 2.5** were synchronous, and varying X-substitution would vary the amount of **2.5.2-3** and **2.5.2-4** formed due to a more electron donating substrate that will want to bind to the Au metal center (**Scheme 2.5, Path A**). Having EWG should create the opposite effect and it would push the reaction mechanism towards the formation of a carbocation (**Scheme 2.5, Path B**). It was found that having EWG- CF_3 as substituent increased the yield of the four regioisomers of **2.5.2-4ab** to a combined 38% combined, and 19% yield of desired product **2.5.2.3ab** (**Table 2.6, Entry 1**). As we increased the electron donation of the substituents, we saw a decrease of **2.5.2-4** formation and an increase in yield of **2.5.2-3** (**Table 2.6, Entries 2-5**). When electron-rich substituent -OMe was used we only saw trace amount of **2.5.2-4** regioisomers and 59% of **2.5.2-3ag** (**Table 2.6, Entry 6**). This result led us to believe that having electrodonating substituents pushed the mechanism

of the reaction to only go through path A, or that the additional electron donation stabilizes the carbocation and changes the rate of reaction between the *5-exo-trig* and possible E_1 eliminations.

Table 2.6- Comparison of **2.5.2-3** and **2.5.2-4** yields when varying X substitution on aromatic group.



2.5.2-1a **2.5.2-2b-g**, X = CF_3, Cl, F, Ph, Me, OMe **2.5.2-3** **2.5.2-4**

Entry	**2.5.2-2**	σ_{para}	Yield **2.5.2-3** (%)	Yield **2.5.2-4** (%)
1	**2.5.2-2b**, X = CF_3	0.54	19	38
2	**2.5.2-2c**, X= Cl	0.227	34	32
3	**2.5.2-2d**, X= F	0.062	47	25
4	**2.5.2-2e**, X = Ph	-0.01	58	22
5	**2.5.2-2f**, X = Me	-0.17	52	18
6	**2.5.2-2g**, X = OMe	-0.268	59	<5

We hypothesized that both mechanistic pathways were at play, and one pathway will be favoured when different substituent were used. A Hammett Plot could be utilized to determine the ratio between the products if they are undergoing different mechanisms. Submitting non-substituted starting material **2.5.2-2a** to the reaction conditions in a 1:1 mixture with **2.5.2-2b-g** could provide us with evidence of two different mechanisms. Once the ratio of product is obtained, we plot the ratio as a logarithmic function to determine if there is a correlation. We attempted to create a Hammett Plot to see if we had a linear or nonlinear correlation to the value of σ_{para}, depicting the change in the mechanism. Our hypothesis was that we would see a rate acceleration of the addition of **2.5.2-2** to the Au^{III} intermediate due to the EDG on the phenyl substituent. We developed the Hammett plot experiments and saw a rate acceleration due to EDG substituents when using substituents -OMe, Me, and, Ph (**Figure 2.4**, Orange Plot). Using more electron neutral substituent -F, changed the slope of the curve, showing that there could a

change in the rate determining step mechanism. However, when EWG substitution was used such as -Cl and -CF_3 was used, there was no longer an observable trend. Our Hammett Plot experiment did not give us more answers regarding the possible mechanisms of the reaction.

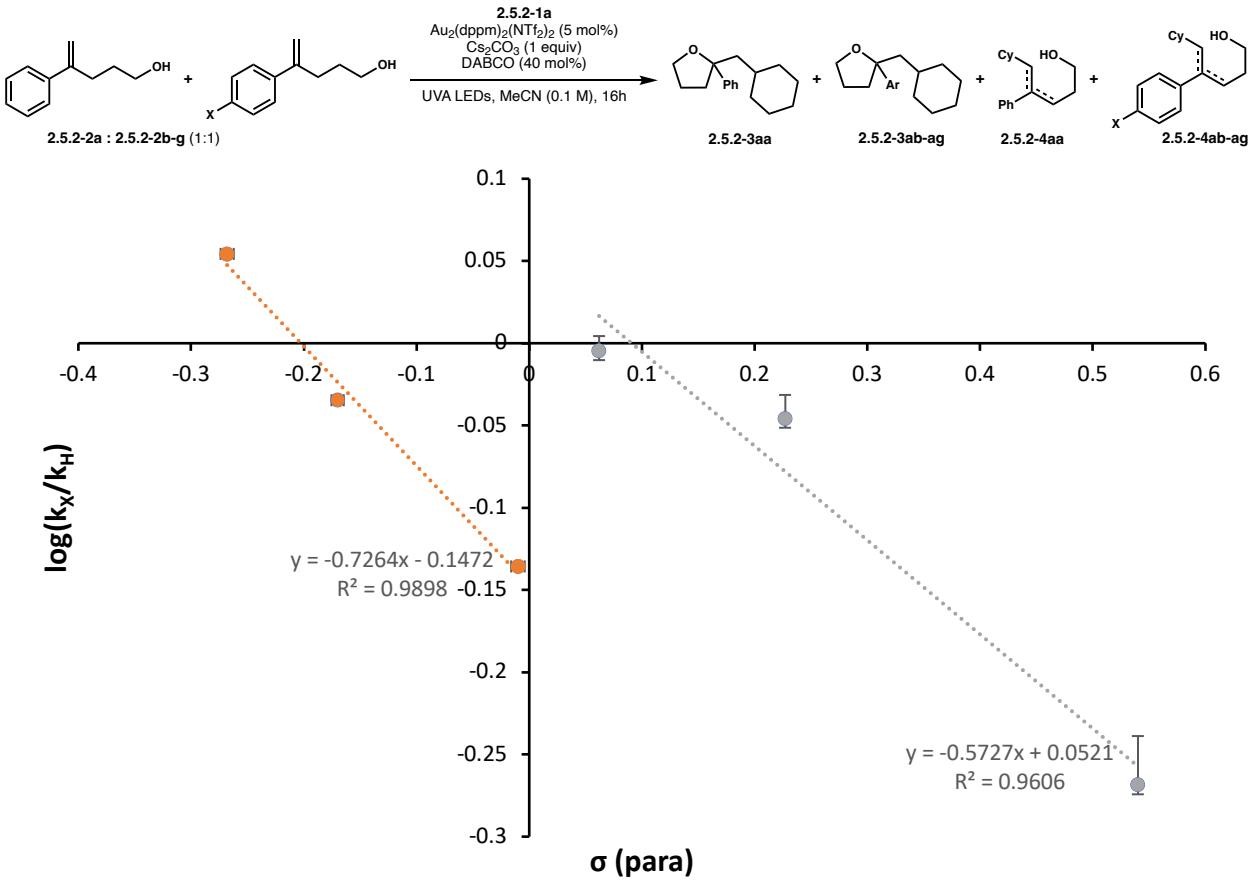


Figure 2.4- Attempted Hammett plot of alkylative tetrahydrofuran-ring formation using gold photoredox catalysis.

We then attempted to perform a kinetic study of the absolute rate of primary radical addition of **2.5.2-1f** to **2.5.2-2g**. In pseudo-first order conditions, we can find the rate of addition of a radical unto the radical acceptor. If the reaction is purely going through a radical process (**Scheme 2.5, Path B**), we would see a positive linear correlation, where the slope would equal to the rate of addition of the radical. We performed this experiment using **2.5.2-2g** and **2.5.2-1f** in great excess to create pseudo first-order conditions. The resulting radical formed from **2.5.2-1f** will either add

unto the olefin in its closed form or will rapidly open (k ~ 5 x 10^3 $M^{-1}s^{-1}$) and then add unto the olefin. Plotting the ratios of both products (**2.5.2-2fg** being the closed product and **2.5.2-2fg'** being the opened product) *versus* an increasing [**2.5.2-2g**] (M), would give the rate of the radical addition. When performing the experiment, we found no significant statistical correlation. Although the 'slope' of the best fit linear curve does give a rate of addition of 0 $M^{-1}s^{-1}$, the coefficient of determination was negligeable, thus we could not rely on the data provided. No conclusions can be made at this time.

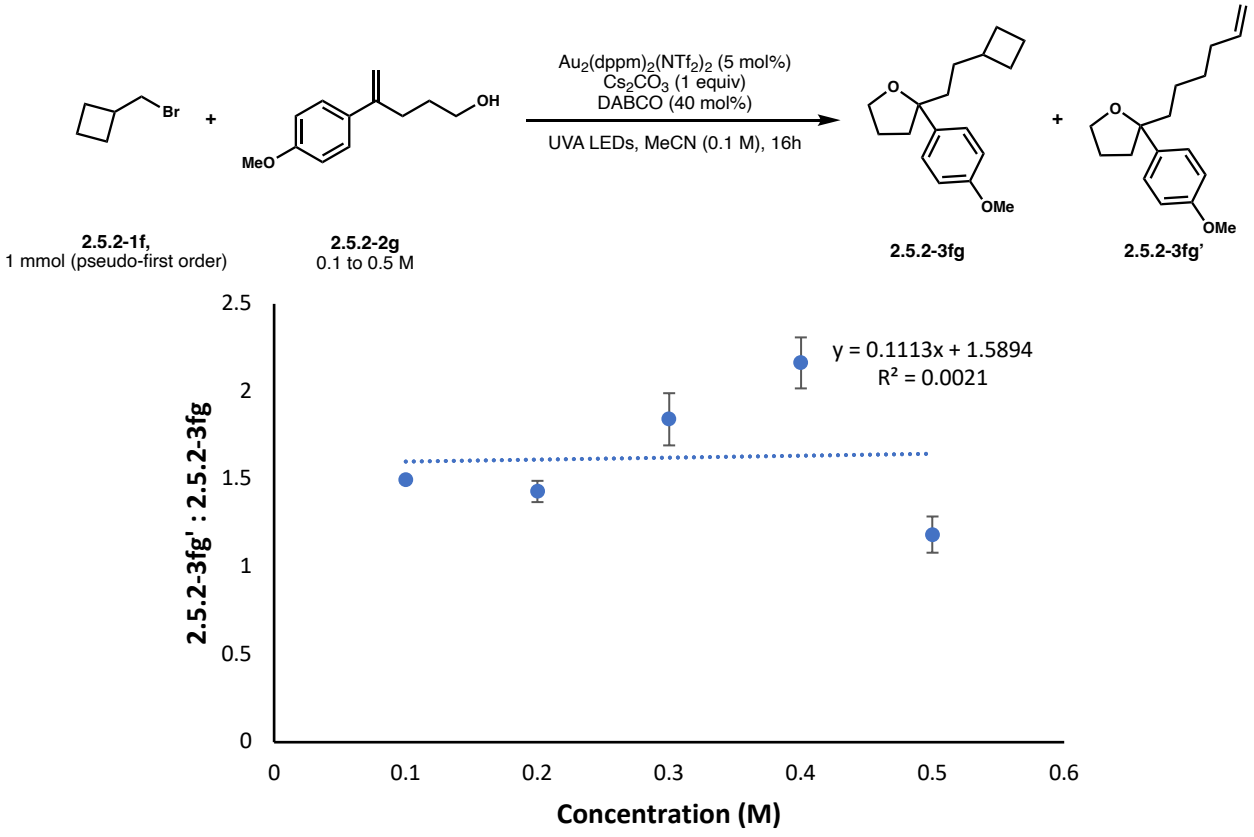


Figure 2.5- Kinetic study of the absolute rate of primary radical addition to **2.5.2-2g**, ratio of products 2.5.2-3fg' / 2.5.2-3fg vs. [**2.5.2-2g**] (M).

2.6- Experimental Data and Procedures

2.6.1-General Information

All reactions were performed under argon atmosphere in Pyrex glassware equipped with a magnetic stir bar, capped with a septum, unless otherwise indicated. All commercial reagents were used without further purification, unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC) analysis. TLC plates were viewed under UV light and stained with potassium permanganate or *p*-anisaldehyde staining solution. Yields refer to products isolated after purification, unless otherwise stated. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AMX 400 MHz. NMR samples were dissolved in deuterated chloroform (unless specified otherwise) and chemical shifts are reported in ppm referenced to residual undeuterated solvent. Data are reported as follows: chemical shift, multiplicity, coupling, integration. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on the same Bruker instruments as in proton NMR at 101 MHz. IR spectra were recorded with an Agilent Technologies Cary 630 FTIR Spectrometer equipped with a diamond ATR module. HRMS were obtained on a Kratos Analytical Concept instrument (University of Ottawa Mass Spectrum Centre).

Vinyl substituted cyclic alcohols were synthesized according to previously described methodology.[5a] The corresponding TMS protected analogs were synthesized according to Wang's procedure where the products were purified by partitioning in hexane and water in a separatory funnel and washing 3 times with water (**2.3-2a**, **2.3-2c**, **2.3-2e**) or by flash column chromatography (**2.3-2b**, **2.3-2d**).[14] Relevant fractions were combined, concentrated and characterized by proton and carbon NMR (400 and 101 MHz, respectively), HR-MS, and IR.

2.6.2- General Procedures

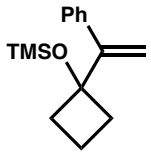
General Procedure 1 (GP1): Preparation of TMS-protected cyclobutanols. To a solution of Mg (3 equiv) in THF (0.6 M) was added a crystal of iodine under N_2 atmosphere. A solution of 1,2-dibromoethane (0.4 equiv) in THF (0.8 M) was added. The solution was stirred when small bubble was observed. A solution of α-bromostyrene (1 equiv) in THF (1.3 M) was then added. When the mixed solution was stirred at 60^{o}C for 1 h, a solution of cyclobutanone (1.4 equiv) in THF (1.87 M) was added. After stirring at the same temperature for 5 h, the reaction mixture was quenched with aqueous ammonium chloride solution (NH_4Cl (aq)) and extracted with ethyl acetate (2×40 mL). The combined organic layers were washed with H_2O, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (0-50% EtOAc:Hexanes) to obtain the desired cyclobutanol as an oil. To a solution of purified cyclobutanol (1 equiv) in DCM (0.15 M) was added imidazole (2.4 equiv). The solution was cooled down to 0^{o}C and trimethylsilyl chloride (1.2 equiv) was added. The solution was warmed to room temperature and stirred for 1h. The reaction mixture was quenched with a solution of $NaHCO_3$ (aq) and extracted with DCM (3 X 10 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo.* The residue was purified by flash column chromatography (0-10% EtOAc:Hexanes) to obtain the desired TMS-protected cyclobutanol as a yellow clear oil.

General Procedure 2 (GP2): Preparation of α,α-disubstituted ketones. To an oven dried 8 mL Pyrex screw-top reaction vessel was added the TMS-protected vinyl substituted cyclic alcohol **2.3-2** (0.25 mmol, 1.0 equiv), bromoalkane **2.3-1** (1.00 mmol, 4.0 equiv), $[Au_2(dppm)_2]Cl_2$ (0.0125 mmol, 0.05 equiv), Na_2CO_3 (0.75 mmol, 3.0 equiv), 1,4-diazabicyclo[2.2.2]octane (DABCO, 0.10 mmol, 0.4 equiv), and MeCN (2.5 mL, 0.10 M). The reaction vessel was capped, degassed with

argon by sparging for 5 minutes (volatile bromoalkanes were added after sparging), then irradiated with a UVA (365 nm) LED at an approximate distance of 5 mm for 16-24 hours, tracking by TLC until full conversion of **2.3-2** was achieved. The resulting mixture was filtered through a cotton plug with DCM and concentrated *in vacuo*. The crude mixture was further purified by flash chromatography (0-100% EtOAc:Hexanes), where relevant fractions were combined, concentrated and characterized by proton and carbon NMR (400 and 101 MHz, respectively), and HR-MS, and IR when needed.

2.7- Characterization Data

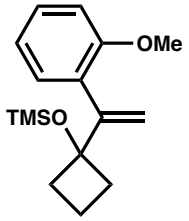
2.7.1- Starting Materials 2.3-2 Characterization



trimethyl(1-(1-phenylvinyl)cyclobutoxy)silane (2.3-2a)

Synthesized according to GP1. Crude mixture was purified by flash chromatography (0-5% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a yellow oil.

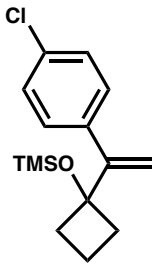
IR (neat, cm^{-1}): 2986 (m), 2953 (m), 1495 (m), 1249 (s), 1122 (s), 989 (s), 836 (vs), 776 (s), 752 (s), 703 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.55 – 7.52 (m, 2H) 7.32 – 7.26 (m, 3H), 5.45 (d, *J* = 0.7 Hz, 1H), 5.39 (d, *J* = 0.6 Hz, 1H), 2.48 – 2.41 (m, 2H), 2.38 – 2.29 (m, 2H), 1.83 (dtt, *J* = 10.9, 9.3, 3.8 Hz, 1H), 1.60 – 1.49 (m, 1H), 0.00 (s, 9H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 151.8 (C), 139.6 (C), 128.0 (2 X CH), 127.7 (2 X CH), 127.1 (CH), 112.2 (CH_2), 78.9 (C), 37.1 (2 X CH_2), 13.5 (CH_2), 1.6 (3 X CH_3) ppm; **HRMS** (EI) m/z calc'd for $C_{15}H_{22}OSi$ [M^+] 246.1440, found 246.1443.



(1-(1-(2-methoxyphenyl)vinyl)cyclobutoxy)trimethylsilane (2.3-2b)

Synthesized according to GP1. Crude mixture was purified by flash chromatography (0-10% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a yellow oil (substrate begins to degrade over prolonged duration in $CDCl_3$).

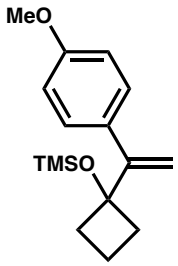
IR (neat, cm^{-1}): 2985 (m), 2950 (m), 1598 (m), 1491 (s), 1241 (vs), 1121 (m), 992 (s), 839 (vs), 750 (vs); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.27 – 7.16 (m, 2H), 6.95 – 6.88 (m, 2H), 5.52 (d, *J* = 1.7 Hz, 1H), 5.07 (d, *J* = 1.7 Hz, 1H), 3.80 (s, 3H), 2.51 – 2.42 (m, 2H), 2.30 – 2.22 (m, 2H), 1.83 – 1.72 (m, 1H), 1.47 – 1.37 (m, 1H), 0.09 (s, 9H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 157.0 (C), 150.7 (C), 131.2 (CH), 130.4 (C), 128.1 (CH), 119.8 (CH), 113.4 (CH_2), 110.6 (CH), 79.5 (C), 55.3 (CH_3), 36.7 (2 X CH_2), 13.6 (CH_2), 1.8 (3 X CH_3) ppm; **HRMS** (EI) m/z calc'd for $C_{16}H_{24}O_2Si$ [M^+] 276.1546, found 276.1537.



(1-(1-(4-chlorophenyl)vinyl)cyclobutoxy)trimethylsilane (2.3-2c)

Synthesized according to GP1. Crude mixture was purified by flash chromatography (0-5% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a yellow oil.

IR (neat, cm^{-1}): 2956 (m), 2925 (m), 2857 (m), 1491 (m), 1252 (m), 837 (m), 669 (vs); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.50 – 7.46 (m, 2H), 7.28 (s, 1H), 7.26 (d, *J* = 2.0 Hz, 1H), 5.46 (d, *J* = 0.6 Hz, 1H), 5.40 (s, 1H), 2.43 – 2.29 (m, 4H), 1.90 – 1.78 (m, 2H), 0.00 (s, 9H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 150.6 (C), 137.8 (C), 133.0 (C), 129.2 (2 X CH), 127.8 (2 X CH), 112.5 (CH_2), 78.7 (C), 37.0 (2 X CH_2), 13.5 (CH_2), 1.6 (3 X CH_3) ppm; **HRMS** (EI) m/z calc'd for $C_{15}H_{21}OClSi$ [M^+] 280.1050, found 280.1099.

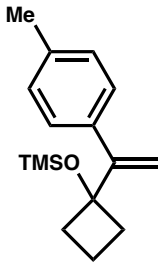


(1-(1-(4-methoxyphenyl)vinyl)cyclobutoxy)trimethylsilane (2.3-2d)

Synthesized according to GP1. Crude mixture was purified by flash chromatography (0-10% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a yellow oil.

IR (neat, cm^{-1}): 2986 (m), 2952 (m), 2901 (m), 2835 (m), 1608 (m), 1509 (s), 1246 (vs), 1119 (m), 988 (s), 832 (vs), 752 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ =7.52 – 7.47 (m, 2H), 6.87 – 6.81 (m, 2H), 5.41 (d, *J* = 0.8 Hz, 1H), 5.31 (d, *J* = 0.9 Hz, 1H), 3.82 (s, 3H), 2.48 – 2.39 (m, 2H), 2.37 – 2.27 (m, 2H), 1.82 (dtt, *J* = 10.9, 9.4, 3.8 Hz, 1H), 1.59 – 1.48 (m, 1H), 0.00 (s, 9H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 158.8 (C), 150.9 (C), 131.8 (C), 129.0 (2 X CH), 113.0 (2 X CH), 110.8 (CH_2), 79.0 (C), 55.2

(CH_3), 37.1 (2 X CH_2), 13.6 (CH_2), 1.6 (3 X CH_3) ppm; **HRMS** (EI): m/z calc'd for $C_{16}H_{24}O_2Si$ [M^+] 276.1546, found 276.1545.

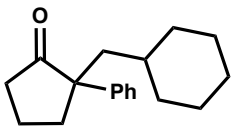


trimethyl(1-(1-(p-tolyl)vinyl)cyclobutoxy)silane (2.3-2e)

Synthesized according to GP1. Crude mixture was purified by flash chromatography (0-5% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a yellow oil.

IR (neat, cm^{-1}): 2985 (m), 2953 (m), 2871 (m), 1513 (m), 1250 (s), 1160 (m), 1122 (m), 991 (m), 838 (vs), 753 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.47 – 7.41 (m, 2H), 7.13 – 7.09 (m, 2H), 5.44 (d, *J* = 0.9 Hz, 1H), 5.35 (d, *J* = 0.8 Hz, 1H), 2.47 – 2.39 (m, 2H), 2.35 (d, *J* = 2.6 Hz, 3H), 2.34 – 2.27 (m, 2H), 1.82 (dtt, *J* = 10.9, 9.4, 3.9 Hz, 1H), 1.55 – 1.49 (m, 1H), 0.00 (s, 9H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 151.4 (C), 136.7 (C), 136.5 (C), 128.2 (2 X CH), 127.8 (2 X CH), 111.55 (CH_2), 79.0 (C), 37.1 (2 X CH_2), 21.1 (CH_3), 13.6 (CH_2), 1.6 (3 X CH_3) ppm; **HRMS** (EI) m/z calc'd for $C_{16}H_{24}OSi$ [M^+] 260.1596, found 260.1593.

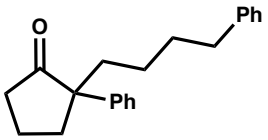
2.7.2- Product 2.3-3 Characterization



2-(cyclohexylmethyl)-2-phenylcyclopentan-1-one (2.3-3aa)

Synthesized according to GP2. Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a yellow oil. (42 mg, 82%)

IR (neat, cm^{-1}): 2923 (s), 2852 (m), 1736 (vs), 1447 (m), 701 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.44 – 7.28 (m, 4H), 7.25 – 7.20 (m, 1H), 2.80 – 2.68 (m, 1H), 2.37 – 2.16 (m, 2H), 2.09 – 1.75 (m, 5H), 1.61 – 1.46 (m, 4H), 1.32 – 1.22 (m, 1H), 1.19 – 0.98 (m, 4H), 0.95 – 0.83 (m, 1H), 0.83 – 0.70 (m, 1H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 219.7 (C), 139.5 (C), 128.4 (2 X CH), 126.9 (2 X CH), 126.6 (CH), 56.7 (C), 46.3 (CH_2), 36.9 (CH_2), 34.7 (CH_2), 34.5 (CH), 34.4 (CH_2) 33.8 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 26.2 (CH_2), 18.6 (CH_2) ppm; HRMS (EI): m/z calc'd for $C_{18}H_{24}O$ [M^+ -C_7H_{12}] 160.0883, found 160.0931 (McLafferty rearrangement).

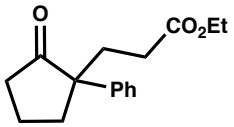


2-phenyl-2-(4-phenylbutyl)cyclopentan-1-one (2.3-3ba)

Synthesized according to GP2. Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a yellow oil. (19 mg, 32%)

IR (neat, cm^{-1}): 2937 (m), 2858 (m), 1735 (vs), 1497 (m), 1454 (m), 751 (m), 700 (vs); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.42 – 7.40 (m, 2H), 7.36 – 7.32 (m, 2H), 7.27 – 7.23 (m, 3H), 7.18 – 7.14 (m, 1H), 7.11 – 7.09 (m, 2H), 2.65 – 2.58 (m, 1H), 2.57 – 2.47 (m, 2H), 2.37 – 2.18 (m, 2H), 2.05 – 1.88 (m, 3H), 1.88 – 1.78 (m, 1H), 1.66 (ddd, *J* = 13.6, 11.9, 5.0 Hz, 1H), 1.56 – 1.47 (m, 2H), 1.23 – 1.05 (m, 2H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 219.8 (C), 142.5 (C), 139.6 (C), 128.5 (2 X CH), 128.3 (2 X CH), 128.2 (2 X CH), 126.8 (2 X CH), 126.7 (CH), 125.6 (CH), 56.8 (C), 38.7 (CH_2), 37.5 (CH_2), 35.6

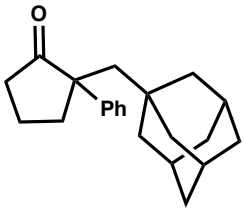
(CH_2), 33.8 (CH_2), 31.8 (CH_2), 24.3 (CH_2), 18.7 (CH_2) ppm; **HRMS** (EI): m/z calc'd for $C_{21}H_{24}O$ [M^+-$C_{10}H_{12}$] 160.0888, found 160.0861 (McLafferty rearrangement).



ethyl 3-(2-oxo-1-phenylcyclopentyl)propanoate (2.3-3ca)

Synthesized according to GP2. Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a yellow oil. (46 mg, 88%)

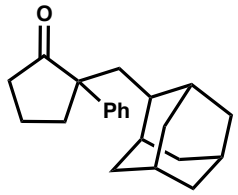
IR (neat, cm^{-1}): 2970 (m), 1735 (vs), 1497 (m), 1447 (m), 702 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.41 – 7.31 (m, 4H), 7.28 – 7.23 (m, 1H), 4.04 (q, *J* = 7.1 Hz, 2H), 2.65 – 2.56 (m, 1H), 2.39 – 2.22 (m, 3H), 2.21 – 2.02 (m, 2H), 2.02 – 1.92 (m, 3H), 1.89 – 1.75 (m, 1H), 1.20 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 219.0 (C), 173.3 (C), 138.5 (C), 128.7 (2 X CH), 127.0 (CH), 126.9 (2 X CH), 60.3 (CH_2), 55.9 (C), 37.5 (CH_2), 34.5 (CH_2), 33.5 (CH_2), 29.9 (CH_2), 18.6 (CH_2), 14.1 (CH_3) ppm; **HRMS** (ESI): m/z calc'd for $C_{16}H_{20}O_3$ [M^+] 260.1412, found 260.1423.



2-(1-adamantanylmethyl)-2-phenylcyclopentan-1-one (2.3-3da)

Synthesized according to GP2. Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a yellow oil. (31 mg, 50%)

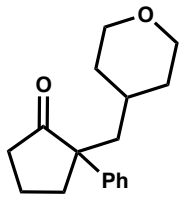
IR (neat, cm^{-1}): 2903 (s), 2849 (m), 1736 (vs), 1453 (m), 1152 (m), 702 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.49 – 7.45 (m, 2 H), 7.33 – 7.28 (m, 2 H), 7.24 – 7.19 (m, 1 H), 3.05 – 2.98 (m, 1 H), 2.27 – 2.07 (m, 3 H), 2.07 – 1.92 (m, 2 H), 1.90 – 1.73 (m, 5 H), 1.60 – 1.58 (m, 1 H), 1.53 – 1.44 (m, 4 H), 1.35 – 1.30 (m, 4 H), 1.27 – 1.20 (m, 3 H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 219.3 (C), 138.1 (C), 128.3 (2 X CH), 127.6 (2 X CH), 126.7 (CH), 56.2 (C), 53.2 (CH_2), 43.7 (3 X CH_2), 36.8 (3 X CH_2), 35.7 (CH_2), 34.8 (CH_2), 34.3 (C), 28.7 (3 X CH), 18.6 (CH_2) ppm; **HRMS** (EI): m/z calc'd for $C_{22}H_{28}O$ [M^+] 308.2140, found 308.2104.



2-(2-adamantanylmethyl)-2-phenylcyclopentan-1-one (2.3-3ea)

Synthesized according to GP2. Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a yellow oil. (20 mg, 31%)

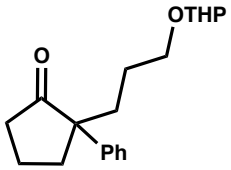
IR (neat, cm^{-1}): 2903 (s), 2849 (m), 1736 (vs), 1453 (m), 1152 (m), 702 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.46 – 7.41 (m, 2H), 7.35 – 7.28 (m, 2H), 7.25 – 7.19 (m, 1H), 2.68 (dddd, *J* = 13.0, 6.0, 3.3, 1.4 Hz, 1H), 2.38 – 2.24 (m, 2H), 2.08 – 1.90 (m, 3H), 1.89 – 1.71 (m, 8H), 1.68 – 1.59 (m, 4H), 1.56 – 1.44 (m, 3H), 1.40 – 1.32 (m, 1H), 1.13 – 1.07 (m, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 219.7 (C), 139.5 (C), 128.3 (2 X CH), 126.9 (2 X CH), 126.6 (CH), 57.3 (C), 42.2 (CH_2), 40.8 (CH), 39.2 (CH_2), 39.0 (CH_2), 38.1 (CH_2), 37.3 (CH_2), 33.4 (CH_2), 33.3 (CH), 33.3 (CH), 31.8 (CH_2), 31.7 (CH_2), 27.7 (CH), 27.6 (CH), 18.6 (CH_2) ppm; **HRMS** (EI): m/z calc'd for $C_{22}H_{28}O$ [M+-$C_{11}H_{16}$] 160.0888, found 160.0892 (McLafferty rearrangement).



2-phenyl-2-((tetrahydro-2H-pyran-4-yl)methyl)cyclopentan-1-one (2.3-3fa)

Synthesized according to GP2 (showing rotamers in ^{13}C NMR). Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a yellow oil. (43 mg, 84%)

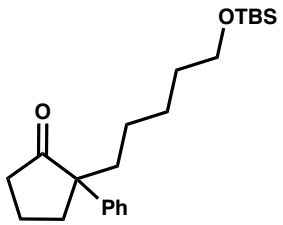
IR (neat, cm^{-1}): 2952 (m), 2930 (m), 2841 (m), 1735 (vs), 1446 (m), 1154 (m), 1132 (m), 1098 (m), 704 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.43 – 7.29 (m, 4H), 7.26 – 7.21 (m, 1H), 3.86 – 3.79 (m, 1H), 3.78 – 3.71 (m, 1H), 3.26 – 3.14 (m, 1H), 2.84 – 2.68 (m, 1H), 2.41 – 2.16 (m, 3H), 2.08 – 1.92 (m, 3H), 1.90 – 1.75 (m, 2H), 1.56 – 1.42 (m, 2H), 1.39 – 1.19 (m, 2H), 1.17 – 1.08 (m, 1H) ppm; **Major rotamer ^{13}C NMR** (101 MHz, CDCl3) δ = 219.2 (C), 138.8 (C), 128.5 (2 X CH), 126.8 (2 X CH), 126.8 (CH), 67.8 (CH_2), 67.7 (CH_2), 56.4 (C), 45.9 (CH_2), 36.7 (CH_2), 34.3 (CH_2), 34.2 (CH_2), 34.1 (CH_2), 31.8 (CH), 18.6 (CH_2) ppm; HRMS (EI): m/z calc'd for $C_{17}H_{22}O_2$ [M^+- C_5H_9O] 173.0966, found 173.0956.



2-phenyl-2-(3-((tetrahydro-2H-pyran-2-yl)oxy)propyl)cyclopentan-1-one (2.3-3ga)

Synthesized according to GP2 (isolated as a 1:1 mixture of diastereomers). Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a yellow oil. (26 mg, 43%)

IR (neat, cm^{-1}): 2943 (s), 2870 (m), 1736 (vs), 1497 (m), 1446 (m), 1136 (m), 1121 (m), 1033 (vs), 702 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.44 – 7.39 (m, 2H), 7.30 (dd, *J* = 8.5, 6.9 Hz, 2H), 7.26 – 7.20 (m, 1H), 4.46 (dd, *J* = 4.5, 2.9 Hz, 0.5H, **minor diastereoisomer**), 4.44 (dd, *J* = 4.5, 2.9 Hz, 0.5H, **minor diastereoisomer**), 3.81 – 3.73 (m, 1H), 3.61 (t, *J* = 6.5 Hz, 0.5H, **minor diastereoisomer**), 3.58 (t, *J* = 6.5 Hz, 0.5H, **minor diastereoisomer**), 3.52 – 3.40 (m, 1H), 3.25 (t, *J* = 6.6 Hz, 0.5H, **minor diastereomer**), 3.22 (t, *J* = 6.6 Hz, 0.5H, **minor diastereoisomer**), 2.73 – 2.59 (m, 1H), 2.38 – 2.20 (m, 2H), 2.07 – 1.90 (m, 3H), 1.90 – 1.74 (m, 2H), 1.74 – 1.61 (m, 3H), 1.56 – 1.46 (m, 3H), 1.44 – 1.29 (m, 2H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 219.6 (C), 139.3 (C), 139.3 (C, **minor diastereoisomer**), 128.5 (2 X CH), 126.9 (2 X CH), 126.7 (CH), 98.8 (CH, **minor diastereoisome**r) 98.7 (CH), 67.5 (CH_2), 62.4 (CH_2, **minor diastereoisomer**), 62.3 (CH_2), 56.5 (C), 37.5 (CH_2), 35.4 (CH_2), 33.9 (CH_2, **minor diastereoisomer**) and 33.8 (CH_2), 30.7 (CH_2), 25.4 (CH_2), 25.1 (CH_2), 25.0 (CH2, **minor diastereoisomer**), 19.7 (CH_2), 19.6 (CH_2, **minor diastereoisomer**), 18.6 (CH_2) ppm; HRMS (EI): m/z calc'd for $C_{19}H_{26}O_3$ [M^+] 302.1882, found 302.1833.

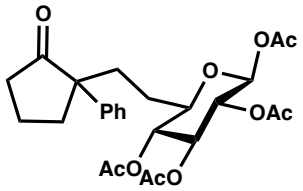


2-(4-((tert-butyldimethylsilyl)oxy)butyl)-2-phenylcyclopentan-1-one (2.3-3ha)

Synthesized according to GP2. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a yellow oil. (31 mg, 43%)

IR (neat, cm^{-1}): 2951 (m), 2929 (m), 2857 (m), 1736 (vs), 1462 (m), 1253 (m), 1099 (s), 835 (vs), 775 (vs), 701 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.43 – 7.38 (m, 2H), 7.35 – 7.30 (m, 2H), 7.25 –

7.20 (m, 1H), 2.67 – 2.59 (m, 1H), 2.37 – 2.20 (m, 2H), 2.15 – 1.75 (m, 5H), 1.69 – 1.53 (m, 2H), 1.50 – 1.33 (m, 2H), 1.22 – 0.99 (m, 2H), 0.85 (s, 9H), -0.01 (m, 6H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 219.8 (C), 139.5 (C), 128.5 (2 X CH), 126.8 (2 X CH), 126.6 (CH), 62.8 (CH_2), 56.8 (C), 38.7 (CH_2), 37.5 (CH_2), 33.8 (CH_2), 33.1 (CH_2), 25.9 (3 X CH_3), 21.0 (CH_2), 18.7 (CH_2), 18.3 (C), -5.3 (2 X CH_3) ppm; **HRMS** (EI): m/z calc'd for $C_{21}H_{34}O_2Si$ [M^+-C4H9] 289.1624, found 289.1585.

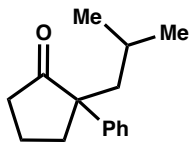


(2R,3S,4R,5S,6S)-6-(2-(2-oxo-1-phenylcyclopentyl)ethyl)tetrahydro-2H-pyran-2,3,4,5- tetrayl tetraacetate (2.3-3ia)

Synthesized according to GP2 (showing rotamers in 1H and 13C NMR). Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a yellow oil. (31 mg, 31%)

IR (neat, cm-1): 2925 (m), 1753 (vs), 1369 (m), 1246 (m), 1219 (vs), 1073 (m), 1037 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.37 – 7.29 (m, 4H), 7.25 – 7.20 (m, 1H), 5.60 (d, *J* = 3.1 Hz, 0.5H, rotamer), 5.59 (d, *J* = 3.1 Hz, 0.5H, rotamer), 5.16 – 5.00 (m, 2H), 4.86 – 4.76 (m, 1H), 3.50 – 3.34 (m, 1H), 2.62 – 2.51 (m, 1H), 2.33 – 2.23 (m, 2H), 2.10 (s, 3H), 2.10 – 2.02 (m, 4H), 2.02 – 2.00 (m, 3H, rotamers), 1.99 – 1.97 (m, 3H, rotamers), 1.90 – 1.86 (m, 3H, rotamers), 1.84 – 1.77 (m, 1H), 1.72 – 1.63 (m, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 219.1 and 219.1 (C, rotamers) 170.1 and 170.1 (C, rotamers), 169.5 and 169.4 (C, rotamers), 169.3 and 169.2 (C, rotamers), 169.0 and 168.9 (C, rotamers), 139.1 and 138.7 (C, rotamers), 128.6 and 128.6 (2 X CH, rotamers), 126.9 and 126.8 (2 X CH, rotamers), 126.8 and 126.8 (CH, rotamers), 91.8 and 91.8 (CH, rotamers), 74.7 and 74.1

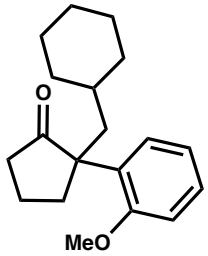
(CH, rotamers), 73.0 and 72.8 (CH, rotamers), 71.1 and 70.7 (CH, rotamers), 70.5 and 70.5 (CH, rotamers), 56.1 and 56.0 (C, rotamers), 37.5 and 37.4 (CH_2, rotamers), 34.6 and 34.2 (CH_2, rotamers), 33.8 and 32.9 (CH_2, rotamers), 26.0 and 25.8 (CH_2, rotamers), 20.8 and 20.8 (CH_3, rotamers), 20.6 and 20.5 (2 X CH_3, rotamers), 20.5 and 20.4 (CH_3, rotamers), 18.6 (CH_2) ppm; **HRMS** (EI): m/z calc'd for $C_{26}H_{32}O_{10}$ [M^+-$C_{15}H_{20}O_9$] 160.0888, found 160.0952 (McLafferty rearrangement).



2-isobutyl-2-phenylcyclopentanone (2.3-3ja)

Synthesized according to GP2. Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a yellow oil. (29 mg, 68%)

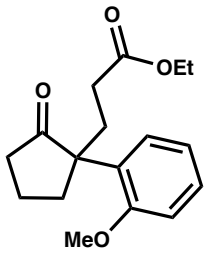
IR (neat, cm^{-1}): 2955 (s), 2932 (m), 2871 (m), 1736 (vs), 1467 (m), 1151 (m), 750 (m), 702 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.46 – 7.41 (m, 2H), 7.36 – 7.30 (m, 2H), 7.25 – 7.15 (m, 1H), 2.84 – 2.73 (m, 1H), 2.34 – 2.17 (m, 2H), 2.08 – 1.91 (m, 3H), 1.91 – 1.75 (m, 1H), 1.53 – 1.37 (m, 2H), 0.82 (d, *J* = 6.3 Hz, 3H), 0.66 (d, *J* = 6.4 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 219.6 (C), 139.1 (C), 128.4 (2 X CH), 127.0 (2 X CH), 126.6 (CH), 56.8 (C), 47.7 (CH_2), 36.8 (CH_2), 33.9 (CH_2), 25.0 (CH_3), 24.4 (CH), 23.7 (CH_3), 18.6 (CH_2) ppm; **HRMS** (EI): m/z calc'd for $C_{16}H_{20}O$ [M^+-C4H8] 160.0888, found 160.0896 (McLafferty rearrangement).



2-(cyclohexylmethyl)-2-(2-methoxyphenyl)cyclopentan-1-one (2.3-3ab)

Synthesized according to GP2. Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a yellow oil. (34 mg, 60%)

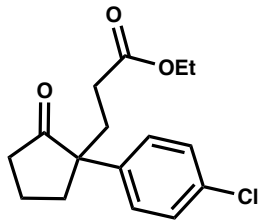
IR (neat, cm^{-1}): 2923 (vs), 2850 (m), 1736 (vs), 1490 (s), 1464 (m), 1450 (m), 1244 (vs), 1029 (m), 753 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.25 – 7.20 (m, 2H), 6.96 – 6.91 (m, 1H), 6.90 – 6.86 (m, 1H), 3.76 (s, 3H), 2.58 – 2.37 (m, 3H), 1.99 – 1.90 (m, 3H), 1.85 – 1.69 (m, 5H), 1.68 – 1.60 (m, 3H), 1.29 – 1.10 (m, 5H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 221.2 (C), 156.8 (C), 132.8 (C), 127.9 (CH), 127.8 (CH), 120.6 (CH), 112.1 (CH), 55.2 (C), 55.0 (CH_3), 41.2 (CH_2) 37.5 (CH_2), 36.7 (CH_2), 35.5 (CH_2), 35.4 (CH_2), 33.9 (CH), 26.5 (CH_2), 26.4 (CH_2), 26.3 (CH_2), 19.2 (CH_2) ppm; **HRMS** (EI): m/z calc'd for $C_{19}H_{26}O_2$ [M^+-C_7H_{12}] 190.0994, found 190.1012 (McLafferty rearrangement).



ethyl 3-(1-(2-methoxyphenyl)-2-oxocyclopentyl)propanoate (2.3-3cb)

Synthesized according to GP2. Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a yellow oil. (37 mg, 63%)

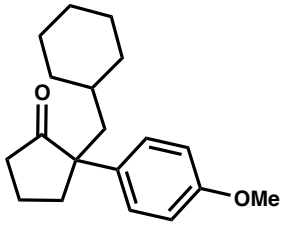
IR (neat, cm^{-1}): 2966 (m), 2941 (m), 1732 (vs), 1492 (m), 1459 (m), 1246 (m), 1180 (m), 1026 (m), 756 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.27 – 7.17 (m, 2H), 6.98 – 6.87 (m, 2H), 4.12 (qd, *J* = 7.2, 2.6 Hz, 2H), 3.75 (s, 3H), 2.61 – 2.29 (m, 6H), 2.18 (ddd, *J* = 14.5, 10.3, 6.1 Hz, 1H), 2.07 – 1.87 (m, 3H), 1.24 (t, *J* = 7.2 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 220.2 (C), 173.8 (C), 156.7 (C), 131.0 (C), 128.1 (CH), 127.7 (CH), 120.9 (CH), 112.3 (CH), 60.4 (CH_2), 55.1 (CH_2), 53.4 (C), 38.4 (CH_2), 37.5 (CH_2), 29.4 (CH_2), 27.8 (CH_2), 19.4 (CH_2) 14.2 (CH_2) ppm; **HRMS** (ESI): m/z calc'd for $C_{17}H_{22}O_4Na$ [M^+ + Na] 313.1416, found 313.1416.



ethyl 3-(1-(4-chlorophenyl)-2-oxocyclopentyl)propanoate (2.3-3cc)

Synthesized according to GP2. Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a yellow oil. (24 mg, 41%)

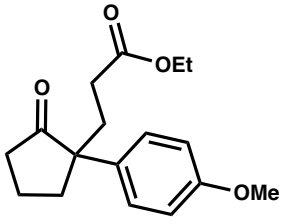
IR (neat, cm^{-1}): 2977 (m), 2961 (m), 1735 (vs), 1493 (m), 1180 (m), 1096 (m), 1014 (m), 837 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36 – 7.29 (m, 4H), 4.05 (q, *J* = 7.1 Hz, 2H), 2.58 – 2.49 (m, 1H), 2.36 – 2.29 (m, 2H), 2.27 – 2.15 (m, 1H), 2.14 – 1.90 (m, 5H), 1.87 – 1.77 (m, 1H), 1.21 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 219.5 (C), 173.1 (C), 137.2 (C), 133.1 (C), 128.8 (2 X CH), 128.3 (2 X CH), 60.5 (CH_2), 55.4 (C), 37.5 (CH_2), 34.5 (CH_2), 33.4 (CH_2), 29.8 (CH_2), 18.6 (CH_2), 14.1 (CH_3) ppm; **HRMS** (ESI): m/z calc'd for $C_{16}H_{19}ClO_3Na$ [M^+ + Na] 317.0920, found 317.0922.



2-(cyclohexylmethyl)-2-(4-methoxyphenyl)cyclopentan-1-one (2.3-3ad)

Synthesized according to GP2. Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a yellow oil. (16 mg, 27%)

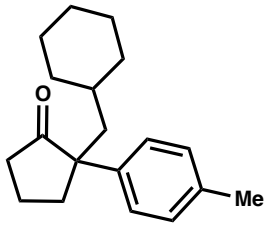
IR (neat, cm^{-1}): 2921 (s), 2849 (m), 1733 (vs), 1511 (vs), 1251 (vs), 1185 (m), 1037 (m), 831 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.36 – 7.30 (m, 2H), 6.89 – 6.83 (m, 2H), 3.80 (s, 3H), 2.69 (dddd, *J* = 10.8, 6.5, 4.7, 2.5 Hz, 1H), 2.32 – 2.14 (m, 2H), 2.05 – 1.75 (m, 4H), 1.65 – 1.43 (m, 5H), 1.31 – 1.22 (m, 1H), 1.16 – 1.00 (m, 4H), 0.94 – 0.83 (m, 1H), 0.82 – 0.69 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 219.8 (C), 158.2 (C), 131.2 (C), 128.0 (2 X CH), 113.8 (2 X CH), 56.0 (C), 55.2 (CH_3), 46.3 (CH_2), 36.7 (CH_2), 34.7 (CH_2), 34.4 (CH), 34.4 (CH_2), 33.9 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 26.2 (CH_2), 18.6 (CH_2) ppm; HRMS (EI) m/z calc'd for $C_{19}H_{26}O_2$ [M^+] 286.1933, found 286.1916.



ethyl 3-(1-(4-methoxyphenyl)-2-oxocyclopentyl)propanoate (2.3-3cd)

Synthesized according to GP2. Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a yellow oil. (32 mg, 55%)

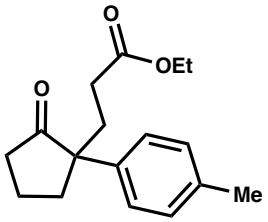
IR (neat, cm^{-1}): 2959 (m), 1735 (vs), 1512 (s), 1253 (s), 1186 (m), 1034 (m), 836 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.29 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 4.04 (q, *J* = 7.3 Hz, 2H), 3.79 (s, 3H), 2.58 – 2.54 (m, 1H), 2.33 – 2.19 (m, 3H), 2.15 – 2.03 (m, 2H), 1.98 – 1.78 (m, 4H), 1.19 (t, *J* = 7.2 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 219.0 (C), 173.3 (C), 158.6 (C), 130.1 (C), 128.0 (2 X CH), 114.0 (2 X CH), 60.3 (CH_2), 55.2 (C), 55.2 (CH_3), 37.3 (CH_2), 34.4 (CH_2), 33.5 (CH_2), 29.9 (CH_2), 18.5 (CH_2), 14.1 (CH_3) ppm; **HRMS** (EI) m/z calc'd for $C_{17}H_{22}O_4$ [M^+] 290.1518, found 290.1532.



2-(cyclohexylmethyl)-2-(p-tolyl)cyclopentan-1-one (2.3-3ae)

Synthesized according to GP2. Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a yellow oil. (22 mg, 40%)

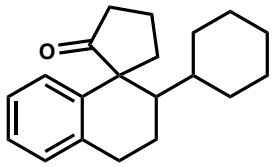
IR (neat, cm-1): 2921 (vs), 2851 (m), 1736 (vs), 1512 (m), 1449 (m), 842 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.32 – 7.28 (m, 2H), 7.15 – 7.10 (m, 2H), 2.72 (ddq, *J* = 12.8, 6.0, 2.1 Hz, 1H), 2.39 – 2.30 (m, 4H), 2.28 – 2.15 (m, 2H), 2.04 – 1.75 (m, 5H), 1.55 – 1.46 (m, 3H), 1.34 – 1.24 (m, 2H), 1.18 – 1.01 (m, 5H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 219.8 (C), 136.3 (C), 136.2 (C), 129.2 (2 X CH), 126.8 (2 X CH), 56.4 (C), 46.3 (CH_2), 36.8 (CH_2), 34.8 (CH_2), 34.5 (CH), 34.4 (CH_2), 33.8 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 26.2 (CH_2), 20.93 (CH_3), 18.63 (CH_2) ppm; **HRMS** (EI) m/z calc'd for $C_{19}H_{26}O$ [M^+] 270.1984, found 270.1978.



ethyl 3-(2-oxo-1-(p-tolyl)cyclopentyl)propanoate (2.3-3ce)

Synthesized according to GP2. Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a yellow oil. (37 mg, 67%)

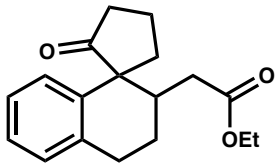
IR (neat, cm^{-1}): 2966 (m), 2935 (m), 2889 (m), 1735 (vs), 1183 (m), 1160 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.26 (d, *J* = 7.8 Hz, 2H), 7.18 – 7.11 (m, 2H), 4.04 (q, *J* = 7.1 Hz, 2H), 2.59 (ddt, *J* = 9.8, 6.2, 2.1 Hz, 1H), 2.33 (s, 3H), 2.31 – 2.23 (m, 3H), 2.11 (ddd, *J* = 17.4, 10.7, 5.0 Hz, 2H), 2.00 – 1.89 (m, 3H), 1.86 – 1.75 (m, 1H), 1.20 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 219.1 (C), 173.3 (C), 136.7 (C), 135.3 (C), 129.4 (2 X CH), 126.8 (2 X CH), 60.3 (CH_2), 55.6 (C), 37.4 (CH_2), 34.4 (CH_2), 33.5 (CH_2), 30.0 (CH_2), 20.9 (CH_3), 18.6 (CH_2), 14.2 (CH_3) ppm; **HRMS** (ESI) m/z calc'd for $C_{17}H_{22}O_3$ [M^+-C_2H_5] 245.1178, found 245.1134.



2'-cyclohexyl-3',4'-dihydro-2'H-spiro[cyclopentane-1,1'-naphthalen]-2-one (2.3-3af)

Synthesized according to GP2 (isolated as a 2:1 mixture of diastereomers). Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a yellow oil. (32 mg, 57%)

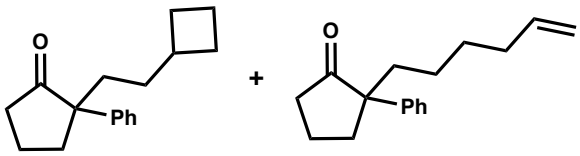
IR (neat, cm^{-1}): 2960 (m), 2933 (m), 1729 (vs), 1185 (m), 1160 (m), 754 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.18 – 6.96 (m, 4H), 2.93 (dt, *J* = 16.8, 4.7 Hz, 1H, 2:1 diastereomers), 2.77 (ddd, J = 16.5, 10.5, 5.7 Hz, 1H), 2.49 (d, *J* = 3.2 Hz, 4H), 2.23-2.08 (m, 3H), 1.81 – 1.62 (m, 7H), 1.55 – 1.42 (m, 2H), 1.39 – 1.25 (m, 4H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 222.4 (C), 141.9 (C), 137.5 (C), 129.2 (CH), 127.4 (CH), 126.1 (CH), 126.0(CH), 55.2 (C), 50.3 (CH), 40.3 (CH_2), 40.2 (CH_2), 38.3 (CH), 34.6 (CH_2), 30.1 (CH_2), 28.5 (CH_2), 27.2 (CH_2), 27.0 (CH_2), 26.5 (CH_2), 20.3 (CH_2), 20.2 (CH_2) ppm; **HRMS** (EI) m/z calc'd for $C_{20}H_{26}O$ [M^+] 282.1984, found 282.2015.



ethyl 2-(2-oxo-3',4'-dihydro-2'H-spiro[cyclopentane-1,1'-naphthalen]-2'-yl)acetate (2.3-3cf)

Synthesized according to GP2 (isolated as a 2:1 mixture of diastereomers). Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a yellow oil. (30 mg, 53%)

IR (neat, cm^{-1}): 2960 (m), 2935 (m), 1730 (vs), 1186 (m), 1162 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.17 – 7.10 (m, 2H), 7.10 – 7.04 (m, 1H), 6.83 – 6.77 (m, 1H), 4.11 (qq, *J* = 10.8, 7.1 Hz, 2H), 2.86 (ddd, *J* = 17.6, 11.8, 5.9 Hz, 1H), 2.73 (ddd, *J* = 17.4, 6.0, 2.9 Hz, 1H), 2.66 – 2.55 (m, 3H), 2.49 – 2.32 (m, 2H), 2.27 – 2.13 (m, 3H), 2.13 – 2.01 (m, 2H), 1.85 (dddd, *J* = 13.5, 6.0, 4.1, 2.9 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 222.8 (C), 173.3 (C), 138.9 (C), 136.1 (C), 129.2 (CH), 128.8 (CH), 126.5 (CH), 126.3 (CH), 60.4 (CH_2), 56.5 (C), 42.5 (CH_2), 39.9 (CH_2), 34.3 (CH), 33.7 (CH_2), 24.9 (CH_2), 24.5 (CH_2), 19.0 (CH_2), 14.2 (CH_3) ppm; **HRMS** (EI) m/z calc'd for $C_{18}H_{22}O_3$ [M^+] 286.1569 found 286.1572.



2-(2-cyclobutylethyl)-2-phenylcyclopentan-1-one (2.3-3ka)/2-(hex-5-enyl)-2-phenylcyclopentan- 1-one (2.3-3ka') (55:45)

Synthesized according to GP2 (NMR determined by deduction from experiment using 2.3-1l arising in only 2.3-3ka'). Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a yellow oil. (36 mg, 74%)

IR (neat, cm^{-1}): 2965 (m), 2931 (m), 2858 (m), 1735 (vs), 1446 (m), 1156 (m), 701 (s);

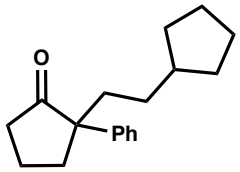
2.3-3ka

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.44 – 7.38 (m, 2H), 7.38 – 7.30 (m, 2H), 7.27 – 7.21 (m, 1H), 2.67 – 2.57 (m, 1H), 2.32 – 2.22 (m, 1H), 2.16 – 2.07 (m, 1H), 2.07 – 1.67 (m, 8H), 1.52 – 1.40 (m, 4H), 1.21 – 1.01 (m, 2H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 219.7 (C), 139.6 (C), 128.5 (2 X CH), 126.8 (2 X CH), 126.6 (CH), 56.4 (C), 37.5 (CH_2), 36.3 (CH_2), 36.1 (CH) 34.0 (CH_2), 31.8 (CH_2), 28.0 (CH_2), 27.9 (CH_2), 18.7 (CH_2), 18.2 (CH_2) ppm.

2.3-3ka'

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.44 – 7.38 (m, 2H), 7.38 – 7.30 (m, 2H), 7.27 – 7.21 (m, 1H), 5.72 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 4.98 – 4.85 (m, 2H), 2.67 – 2.57 (m, 1H), 2.37 – 2.19 (m, 2H), 2.07 – 1.91 (m, 4H), 1.91 – 1.78 (m, 1H), 1.67 – 1.59 (m,1H), 1.66 – 1.58 (m, 1H) 1.36 – 1.28 (m, 2H), 1.19 – 0.99 (m, 2H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 219.9 (C), 139.5 (C), 138.8 (CH), 128.5 (2 X CH), 126.8 (2 X CH), 126.7 (CH), 114.3 (CH_2), 56.8 (C), 38.7 (CH_2), 37.5 (CH_2), 33.8 (CH_2), 33.5

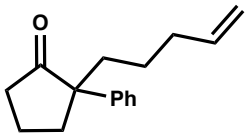
(CH_2), 29.2 (CH_2), 24.1 (CH_2), 18.7 (CH_2)ppm; **HRMS** (EI): m/z calc'd for $C_{17}H_{22}O$ [M^+-C_6H_{10}] 160.0888, found 160.0904 (McLafferty rearrangement).



2-(2-cyclopentylethyl)-2-phenylcyclopentan-1-one (2.3-3ma)

Synthesized according to GP2. Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a yellow oil. (26 mg, 50%)

IR (neat, cm^{-1}): 2946 (s), 2863 (m), 1737 (vs), 1450 (m), 1154 (m), 701 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.44 – 7.37 (m, 2H), 7.37 – 7.29 (m, 2H), 7.26 – 7.21 (m, 1H), 2.71 – 2.54 (m, 1H), 2.38 – 2.21 (m, 2H), 2.06 – 1.77 (m, 4H), 1.74 – 1.58 (m, 4H), 1.54 – 1.39 (m, 3H), 1.31 – 1.24 (m, 1H), 1.17 – 0.87 (m, 4H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 219.9 (C), 139.8 (C), 128.4 (2 X CH), 126.8 (2 X CH), 126.6 (CH), 56.8 (C), 40.3 (CH), 38.1 (CH_2), 37.6 (CH_2), 33.7 (CH_2), 32.6 (CH_2), 32.5 (CH_2), 31.0 (CH_2), 25.1 (CH_2), 18.7 (CH_2) ppm; **HRMS** (EI): m/z calc'd for $C_{18}H_{24}O$ [M^+-C_7H_{12}] 160.0888, found 160.0891 (McLafferty rearrangement).



2-(pent-4-enyl)-2-phenylcyclopentan-1-one (2.3-3na')

Synthesized according to GP2. Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a yellow oil. (23 mg, 50%)

IR (neat, cm^{-1}): 2938 (m), 2859 (m), 1736 (vs), 1154 (m), 912 (m), 701 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.43 – 7.38 (m, 2H), 7.37 – 7.29 (m 2H), 7.26 – 7.21 (m, 1H), 5.70 (ddt, *J* = 16.9, 10.2, 6.7, 1H), 4.96 – 4.87 (2H), 2.72 – 2.58 (m, 1H), 2.34 – 2.19 (m, 2H), 2.06 – 1.89 (m, 5H), 1.89 – 1.78 (m, 1H), 1.63 (ddd, *J* = 13.7, 11.7, 5.1 Hz, 1H), 1.25 – 1.08 (m, 2H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 219.7 (C), 139.5 (C), 138.4 (CH), 128.5 (2 X CH), 126.8 (2 X CH), 126.7 (CH), 114.6 (CH_2), 56.7 (C), 38.4 (CH_2), 37.5 (CH_2), 34.0 (CH_2), 33.9 (CH_2), 24.0 (CH_2), 18.7 (CH_2) ppm; **HRMS** (EI): m/z calc'd for $C_{16}H_{20}O$ [M^{+}-C_5H_8] 160.0888, found 160.0893 (McLafferty rearrangement).

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Chapter 3 - FORMAL HALOGEN ATOM TRANSFER RADICAL ADDITION USING GOLD PHOTOREDOX CATALYSIS

Zidan, M.; McCallum, T.; Swann, R.; Barriault, L., Formal Bromine Atom Transfer Radical Addition of Nonactivated Bromoalkanes Using Photoredox Gold Catalysis. *Org. Lett.,* **2020**, *22*, 8401-8406.

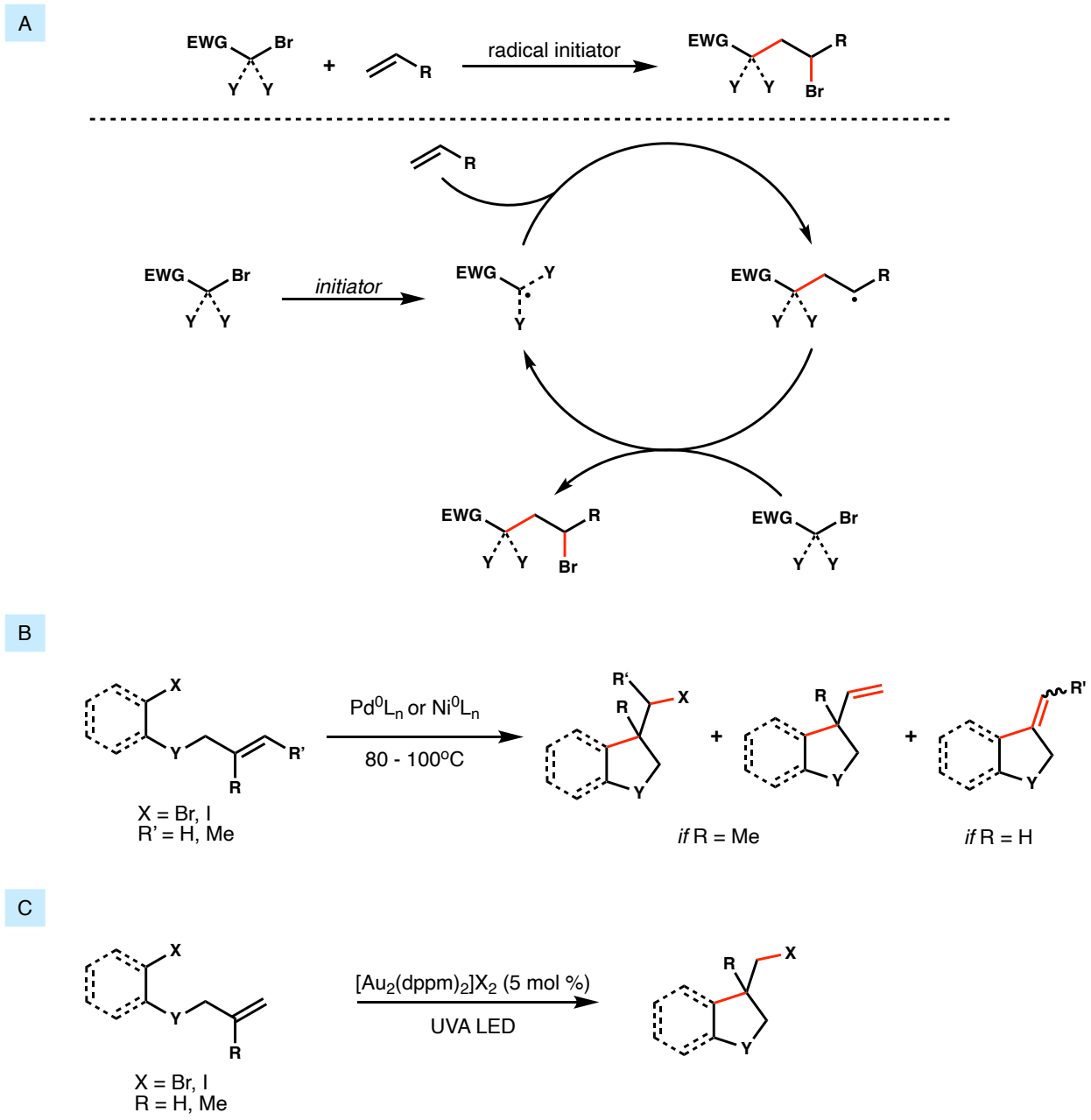
3.1- Abstract

Organic transformations mediated by photoredox catalysis have been at the forefront of reaction discovery. Recently, it has been demonstrated that binuclear Au(I) bisphosphine complexes, such as $[Au_2(dppm)_2]X_2$, are capable of mediating electron transfer to nonactivated bromoalkanes for the generation of a variety of alkyl radicals. The transfer reactions of bromine, derived from nonactivated bromoalkanes, are largely unknown. Therefore, we propose that unique metal-based mechanistic pathways are at play, as this binuclear gold catalyst has been known to produce Au(III) Lewis acid intermediates. The scope and proposed mechanistic overview for the formal bromine atom transfer reaction of nonactivated bromoalkanes mediated by photoredox Au(I) catalysis is presented. The methodology presented afforded good yields and a broad scope which include examples using bromoalkanes and iodoarenes.

3.2- Introduction

Photoredox catalysis has been a growing field in synthetic organic chemistry. Photochemistry combined with radical chemistry can perform photoinduced single-electron transfers (PET or SET) and follow one-electron reaction pathways.[1] The harnessing of both fields of chemistry synergistically makes for a great match for accessing new chemical reactions. While some traditional radical reactions require strong oxidants and harsh conditions, photoredox chemistry allows for the formation of new C–C bonds under mild conditions.[2] Organic chemists

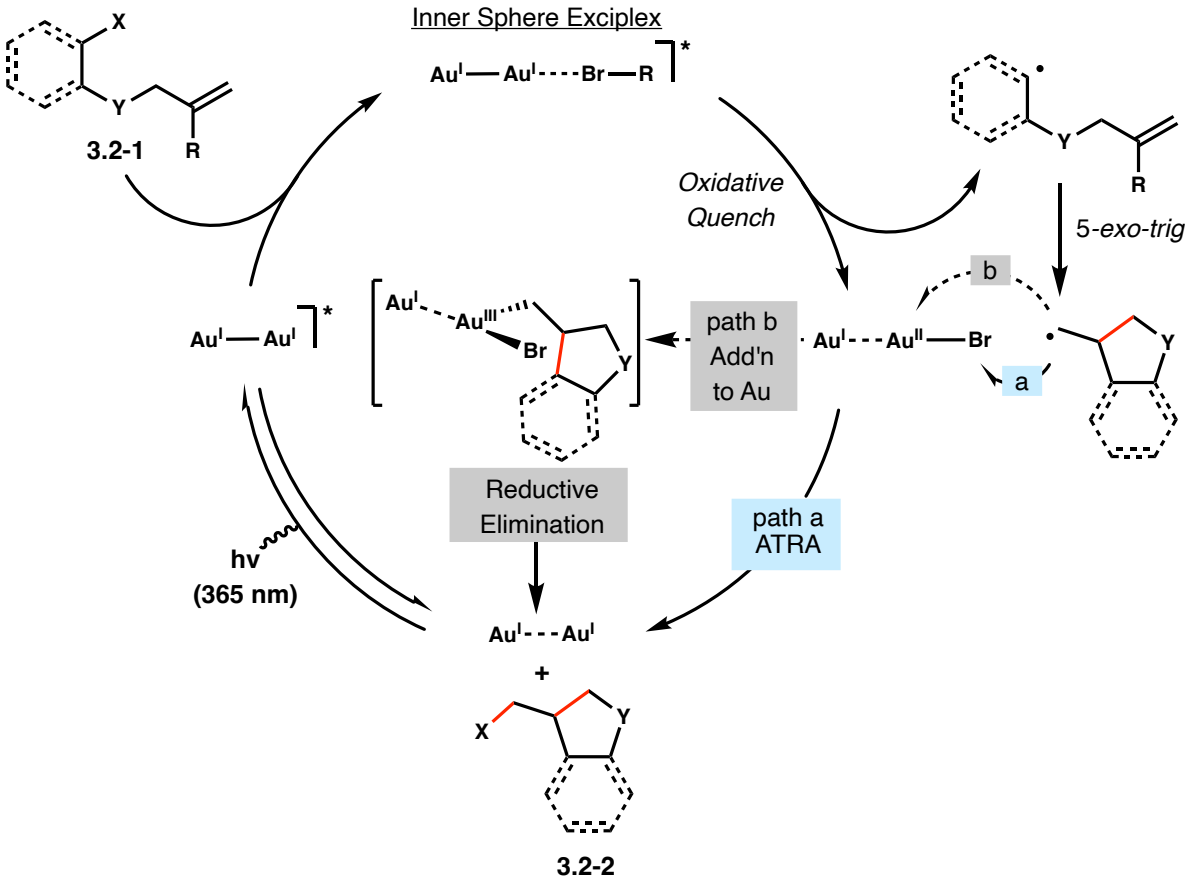
now have new methods of functionalization using transition metal or organic dye photosensitizers, imitating what biomolecules can do in Nature, where photons can be transformed into chemical energy.[3]



Scheme 3.1- Previous and present work in formal Br-ATRA reactions

In 1945, Kharasch and co-workers reported the first atom transfer radical addition (ATRA) reaction, utilizing it in the difunctionalization of alkenes.[4] ATRA reactions became a great method to functionalize unsaturated C−C bonds. The addition of electrophilic radicals derived from α-bromoesters to relatively nucleophilic alkenes became a great way to perform the conventional ATRA reaction.[5] To this end, these reactions require harsh conditions and the need for radical initiators (peroxides, or triethyl borane), and additives (organotin reagents) as the reaction follows a radical chain-type mechanism (**Scheme 3.1A**). Recently, intramolecular formal ATRA reactions have been accomplished using transition metals. The groups of Sanford and Lautens utilized Heck reaction intermediates to perform carbohalogenation reactions starting from iodoarenes and have expanded their method- ology by using Pd- and Ni-based catalysts (**Scheme 3.1B**).[6] In most cases, metal-catalyzed carbohalogenation reactions require the use of disubstituted geminal olefins (R = Me and R′ = H) to avoid β-hydride elimination products. Alexanian and co-workers have reported palladium-catalyzed carbocyclization of bromoalkanes.[7] Although this method generates mainly Heck type products, the formation of primary and secondary (when R = H) bromocycloalkanes via a formal bromine atom transfer radical addition (Br-ATRA) has been observed in a few cases. Bromine transfer reactions from nonactivated bromocycloalkanes remain largely undeveloped. In this context, we report a photoredox Br-ATRA reaction using dimeric gold complexes (**Scheme 3.1C**).[8] This strategy would also be waste limiting as a redox neutral reaction pathway could be achieved by an oxidative quenching cycle, combined with gold Lewis acid catalysis.[9] Recently, we reported the homocoupling of alkyl radicals generated from bromoalkanes through the reductive elimination of a putative Au(III) intermediate.[10] Furthermore, the unprecedented alkylative semi-pinacol rearrangement

demonstrated further evidence for the formation of Au(III) intermediates and subsequent reductive elimination processes.[11,12] Looking to probe the Au(III) intermediates further, we set out to investigate the elementary reaction more closely.



Scheme 3.2- Proposed mechanism of the gold photoredox catalyzed Br-ATRA reaction.

During this time, products deriving from the formal Br-ATRA were identified. Due to the unprecedented nature of the peculiar reaction, it demanded a closer look. Mechanistically, we hypothesized that this transformation was mediated by the excitation of $[Au_2(dppm)_2](NTf_2)_2$ ($^*[Au^I–Au^I]$) with UVA light followed by an oxidative quenching event with bromoalkene (**3.2-1**) through an inner-sphere exciplex (bromoalkanes: $E_{1/2}^{red}$ = ~−2.5 V vs SCE and $^*[Au_2(dppm)_2]Cl_2$: $E_{1/2}^{red}$ = −1.63 V vs SCE) as shown in **Scheme 3.2**.[13,15] The resulting free alkyl radical undergoes a 5- *exo-trig* cyclization to form a 5-membered ring exocyclic radical which can react further

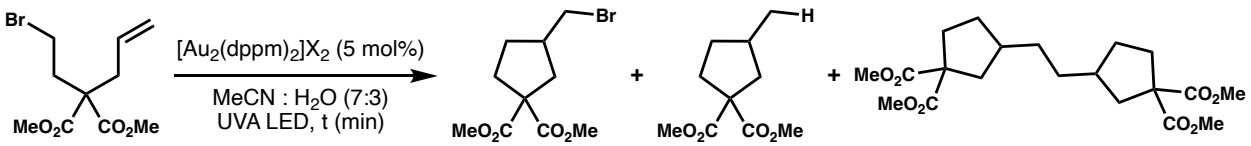
through path A or path B. Path A proposes an unprecedented atom transfer radical addition (Br-ATRA), where the alkyl radical abstracts a bromine atom from an Au−Br species, giving the new bromoalkene and regenerating the ground state of the gold catalyst. Path B proposes the addition of the radical to the Au^{II} center to form an [Au^{I}–Au^{III}–R] intermediate. This may also proceed via alkyl radical addition to the Au^{I} center, giving [R–Au^{II}–Au^{II}], followed by reorganization to the [Au^{I}–Au^{III}–R] intermediate.[14] Reductive elimination of the alkyl group and the bromide can form **3.2-2** and regenerate the ground state of the catalyst. Alternatively, a chain reaction mechanism could be considered, but this is unlikely since this process requires the use of activated haloalkanes.[15]

3.3- Results and Discussion

Initial experiments showed that irradiation of bromoalkane **3.3-1a** in the presence of $[Au_2(dppm)_2]Cl_2$ (5 mol %) in MeCN:H2O (7:3) gave a mixture of products **3.3-2a** (56%), **3.3-3a** (10%), and **3.3-4a** (14%) (**Table 3.1, Entry 1**). It is important to note that we previously reported the specific formation of compounds **3.3-3a** and **3.3-4a** using the photoexcited $[Au_2(dppm)_2]Cl_2$ under reductive quenching conditions.[9,13b,f] We found that the variation in counterions had an effect on the reaction performance; the reactions carried out with counterions such as OTf and NTf_2 provided better yields for the formation of **3.3-2a** than Cl, SbF_6, and BF_4 (**Table 3.1, Entries 1–5**). The best result was observed using $[Au_2(dppm)_2][NTf_2]_2$ (5 mol %), where **3.3-2a** was obtained in 61% yield along with trace amounts of **3.3-3a** and **3.3-4a** (**Table 3.1, Entry 5**). Lowering the catalyst loading did not improve the yield of the reaction as only 42% conversion of **3.3-1a** was observed (**Table 3.1, Entry 6**). Monitoring the reaction with NMR in deuterated solvent revealed that the reaction was fully converted in 10 min providing **3.3-2a** in 80% yield

with trace amounts of **3.3-3a** and **3.3-4a** (**Table 3.1, Entry 7**). The reaction run in only MeCN-d_3 led to poor conversion and yields (**Table 3.1, Entry 8**).

Table 3.1- Optimization of Reactions Conditions.



3.3-1a **3.3-2a** **3.3-3a** **3.3-4a**

Entry	X	[M]	Time (min)	**3.3-1a** (%)	Yield (%)[a] **3.3-2a**:**3.3-3a**:**3.3-4a**
1	Cl	0.067	180	0	56:10:14
2	OTf	0.067	180	0	53:2:0
3	SBF_6	0.067	180	5	49:5:7
4	BF_4	0.067	180	5	26:1:0
5	NTf_2	0.067	180	4	61:4:5
6[b]	NTf_2	0.067	180	58	22:5:0
7[c]	NTf_2	0.067	10	0	80:3:8
8[d]	NTf_2	0.067	10	29	43:11:6
9[c]	NTf_2	0.033	10	0	82:3:8
10	NTf_2	0.033	10	0	82:16:0
11[e]	NTf_2	0.033	10	100	0:0:0
12[f]	NTf_2	0.033	10	100	0:0:0
13[g]	NTf_2	0.033	10	100	0:0:0

[a] ^{1}H NMR yield using mesitylene as internal standard. [b] 2 mol% of $[Au_2dppm_2](NTf_2)_2$ used. [c] MeCN-d_3:D_2O (7:3) used. [d] Reaction run in MeCN-d_3. [e] In the absence of $[Au_2dppm_2](NTf_2)_2$. [f] In the absence of UVA LED light, in the presence of $[Au_2dppm_2](NTf_2)_2$. [g] Heating to 80°C with $[Au_2dppm_2](NTf_2)_2$ in the absence of UVA LED Irradiation.

Lowering the concentration to 0.033 M did not affect the yield of the reaction (**Table 3.1, Entry 9**). Using the same conditions but with nondeuterated solvents showed a similar yield of **3.3-2a** and a slight increase of **3.3-3a** (16%; likely due to hydrogen atom abstraction from the solvent), but no **3.3-4a** was observed (**Table 3.1, Entry 10**). Finally, control experiments showed that the photocatalyst and light were needed to perform the reaction (**Table 3.1, Entries 11–13**).

With optimized reaction conditions in hand, we explored the reaction scope using allyl-functionalized NTs− and malonate- tethered bromo alkanes as well as pyran- and furan-based compounds (**Figure 3.1**). The investigation showed that all of the compound patterns listed above are compatible with our methodology. Having monosubstituted olefins and disubstituted terminal olefins was also compatible with our methodology (**Figure 3.1**). The cyclization of malonate-based substrates **3.3-1a** and **3.3-1b** gave the desired compounds **3.3-2a** and **3.3-2b** in 82% and 55% yields, respectively. In both cases, small amounts of the reduced side products **3.3-3a** (16%) and **3.3-3b** (29%) were observed. Moving onto the NTs-based substrates, the use of monosubstituted alkenes **3.3-1c** provided the desired product **3.3-2c** in 82% yield with trace amounts of its reduced counterpart (>5%), while disubstituted olefins **3.3-1d** gave bromo cycloalkane **3.3-2d** in 50% yield along with **3.3-3c** (21%).

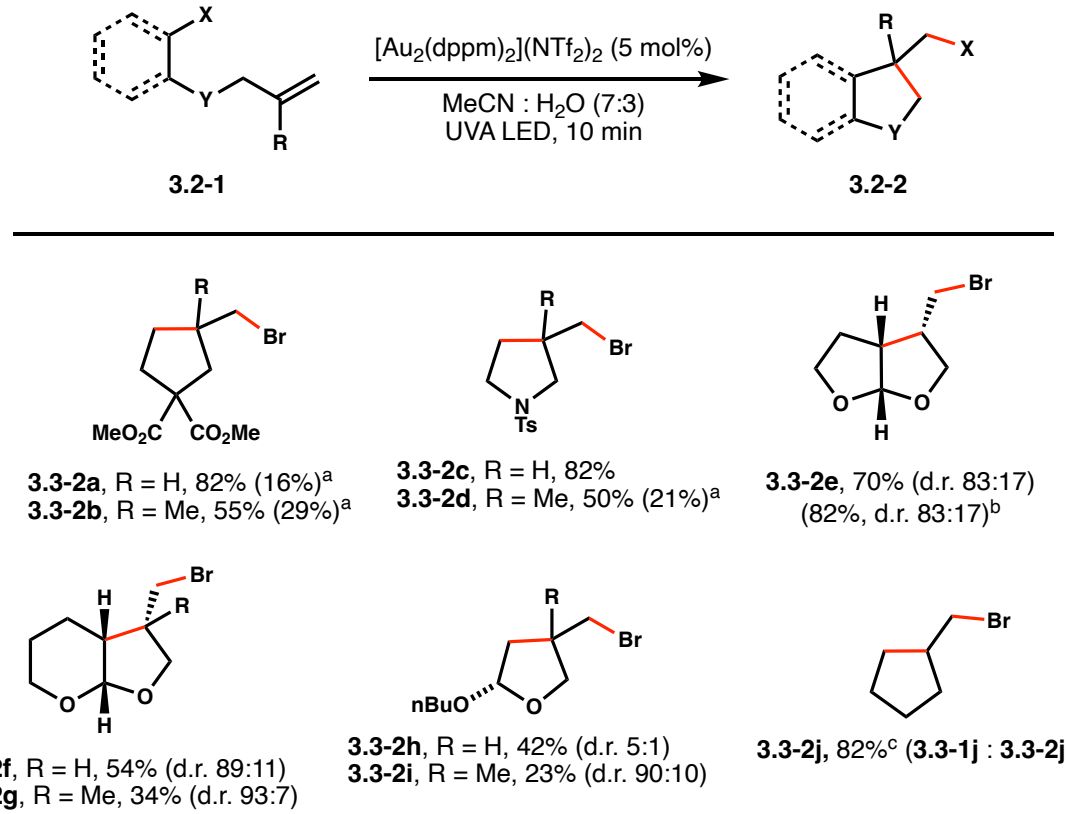
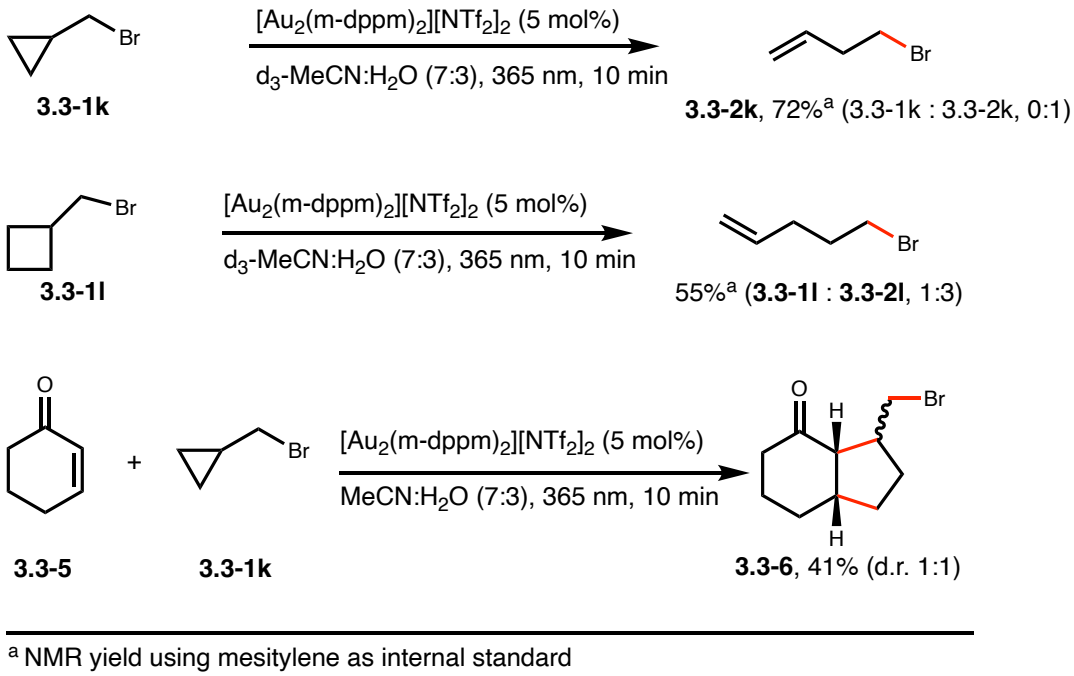


Figure 3.1- Intramolecular Formal Bromine Atom Transfer Radical Addition Reaction Scope.

These results suggest that paths A or B are affected by steric hindrance leading to the formation of competitive processes. Switching to allyl ethers **3.3-1e–i**, the corresponding 5- and 6-membered rings **3.3-2e–i** were obtained in moderate to good yields. Volatile bromoalkanes were also employed, and their results were recorded using NMR spectroscopy (**3.3-2j**–**3.3-2l**) (**Scheme 3.3**). Using starting material **3.3-1j** provided a mixture of **3.3-1j** and the desired product **3.3-2j** (82%, 1:4 **3.3-1j**:**3.3-2j**). Furthermore, the opening of **3.3-1k** and **3.3-1l** was also compatible with the methodology (**Scheme 3.3**). Linear alkyl bromides **3.3-2k** and **3.3-2l** were formed in good yields (72% and 55% respectively). These results provide support for the formation of free alkyl radicals in solution. Unfortunately, meaningful data was not obtained when varying the

concentrations of gold catalyst, bromoalkane, or solution to obtain absolute rates for the transformation using radical clocking methods. Given the formation of **3.3-2k** through a radical ring opening, we envisaged an intermolecular photoredox cascade reaction between **3.3-1k** and cyclohex-2-enone **3.3-5**. Under standard conditions, the desired bicyclic compound **3.3-6** was obtained in 41% as a mixture of diastereomer (1:1).

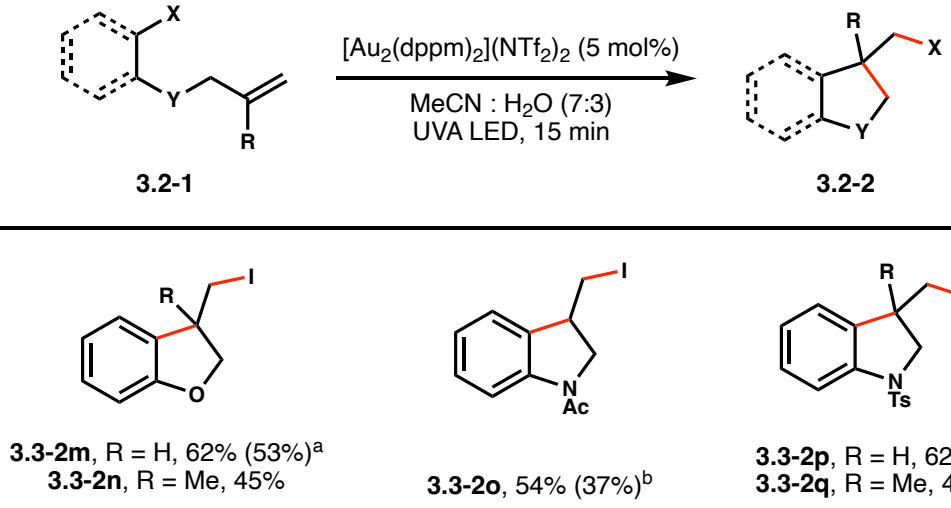


[a] NMR yield using mesitylene as internal standard

Scheme 3.3- Intra- and Intermolecular Formal Bromine- Atom Transfer Radical Addition using Volatile Bromoalkanes.

Next, we tested iodoarenes to see if similar reactivity to the bromoalkanes could be achieved (**Figure 3.2**). It should be noted that iodoalkanes are known to undergo chain reaction mechanisms and as such, were excluded from this study. In past methodologies, the use of iodoarenes resulted in products from β-hydride elimination when not using a blocking group; therefore, we were curious if our methodology was mild enough to isolate the corresponding iodoalkanes. Starting with O-tethered iodoarenes, the desired product was obtained in good yields. Having a monosubstituted olefin **3.3-1m** and disubstituted olefin **3.3-1n** gave the desired

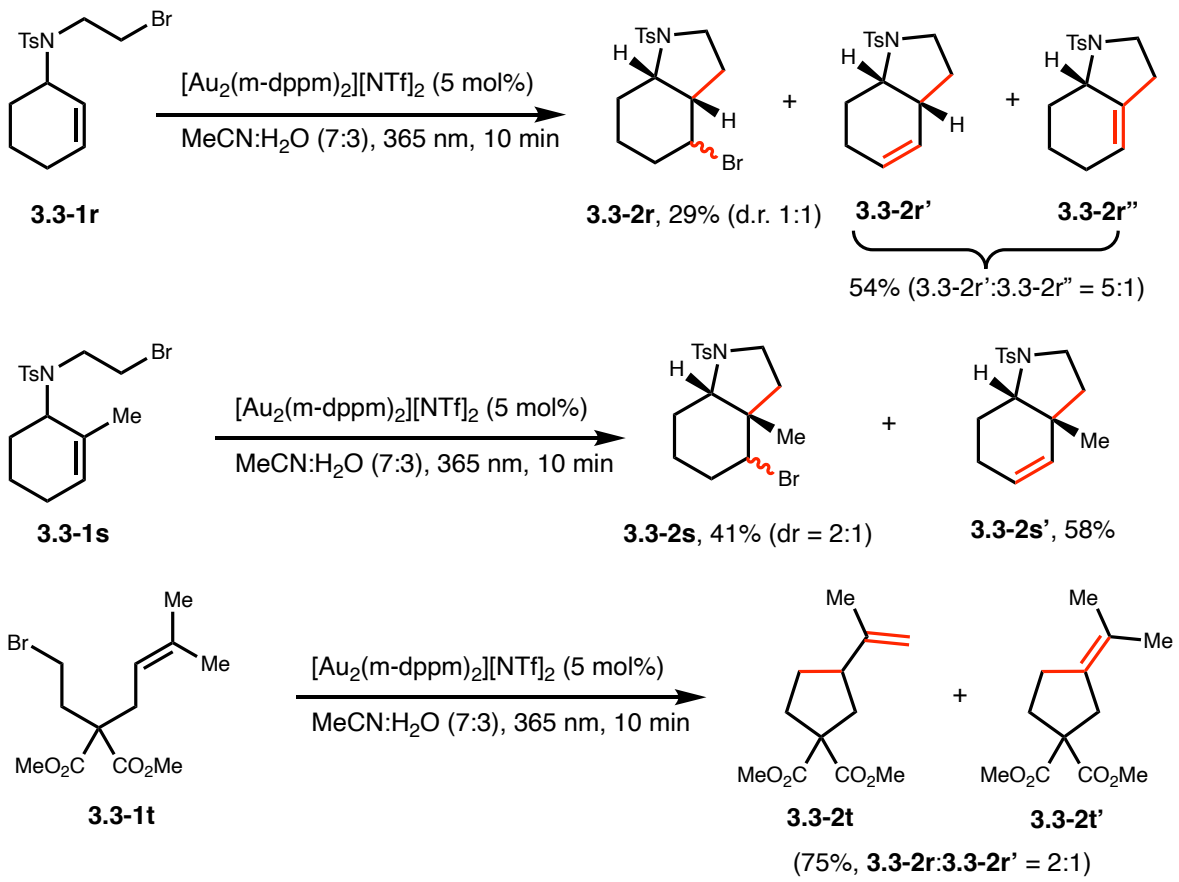
products **3.3-2m** and **3.3-2n** in 62% and 45% yields, respectively. Nitrogen-based substrates using Ac- and Ts- protecting groups were also compatible with the methodology, giving the desired product in good yields. Compared to other methods pertaining to this transformation, the described protocol showed no need of a blocking group to obtain the primary alkyl iodide.



[a] Isolated yield at 1 mmol scale. [b] Yields in parentheses correspond to the reduced product, X = H

Figure 3.2- Intramolecular Formal Iodine Atom Transfer Radical Addition.

The scope of the formal bromine transfer radical reaction was extended to substituted alkenes (**Scheme 3.4**). Interestingly, under the usual reaction conditions, the cyclization of alkene **3.3-1r** led to the formation of the desired bicyclic bromide **3.3-2r** in 29% (d.r. 1:1) along with the elimination products **3.3-2r'** and **3.3-2r''** in 54% yield (**3.3-2r'**:3.**3-2r''**, 5:1). Similarly, the conversion of trisubstituted **3.3-1s** gave the desired product **3.3-2s** in 41% yield (d.r. 2:1) along with the Heck-like compound **3.3-2s''** in 58% yield. However, the photoredox cyclization of nonterminal olefin such as **3.3-1t** led to the exclusive formation **3.3-2t** and **3.3-2t'** in 75% yield as a mixture (**3.3-2t**:**3.3-2t'**, 2:1). This could be attributed to a fast elimination of the tertiary bromine in the reaction medium.



Scheme 3.4- Intramolecular Formal Bromine Atom Transfer Radical Addition unto Substituted Alkenes.

3.4- Conclusion

In conclusion, we have developed a mild and operationally simple intramolecular bromine atom transfer radical addition (Br-ATRA) reaction taking advantage of the dual character of the $[Au_2(dppm)_2](NTf_2)_2$ as photoredox catalyst. The scope of this unprecedented formal Br- and I-ATRA reaction includes the use of 1° and 2° bromo alkanes and iodoarenes. New forays into cross-coupling reactions, mechanistic investigation, and subsequent application to synthesis are underway and will be reported in due course.

3.5- Further Information

3.5.1- NMR Time Study of the Reaction

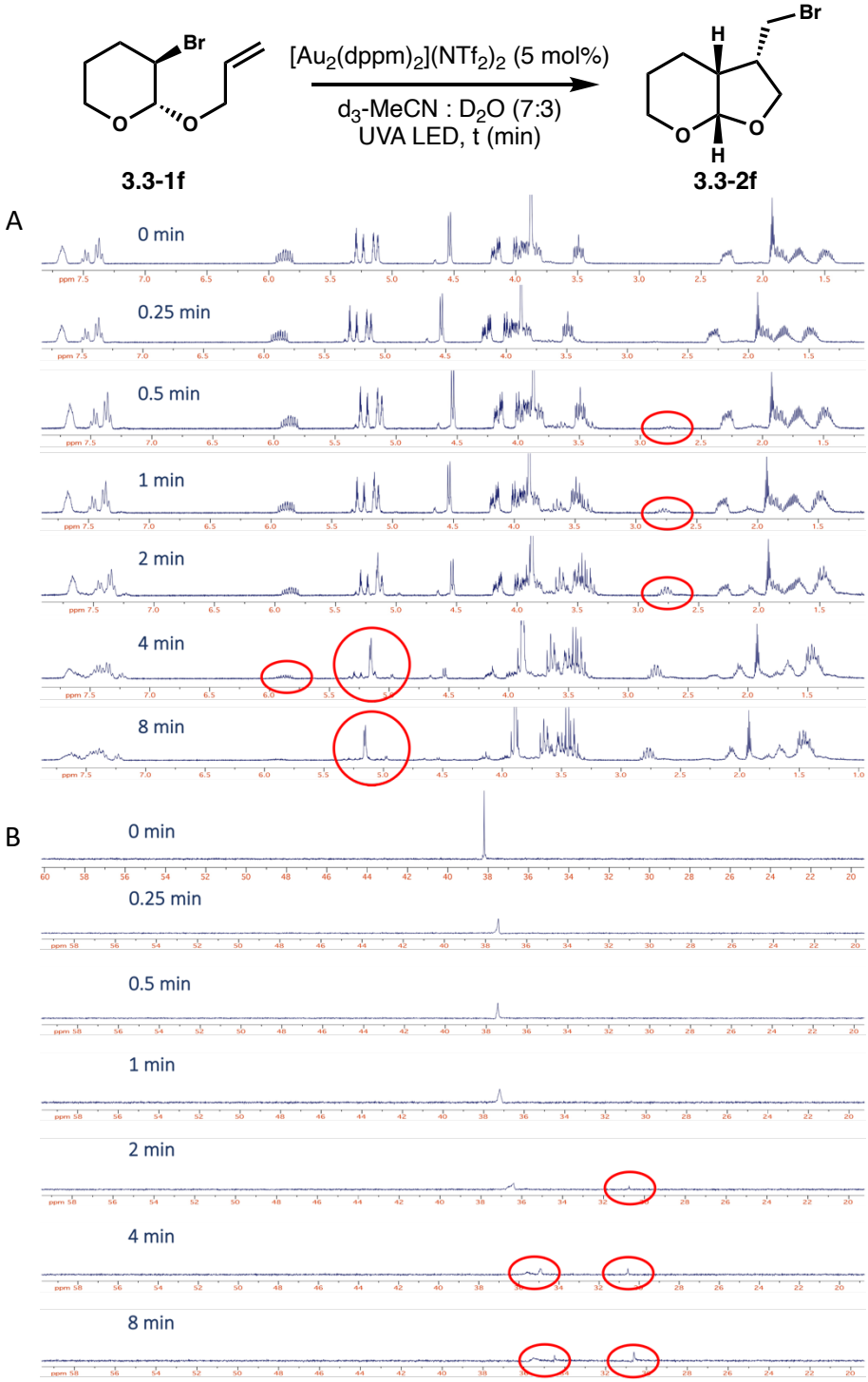
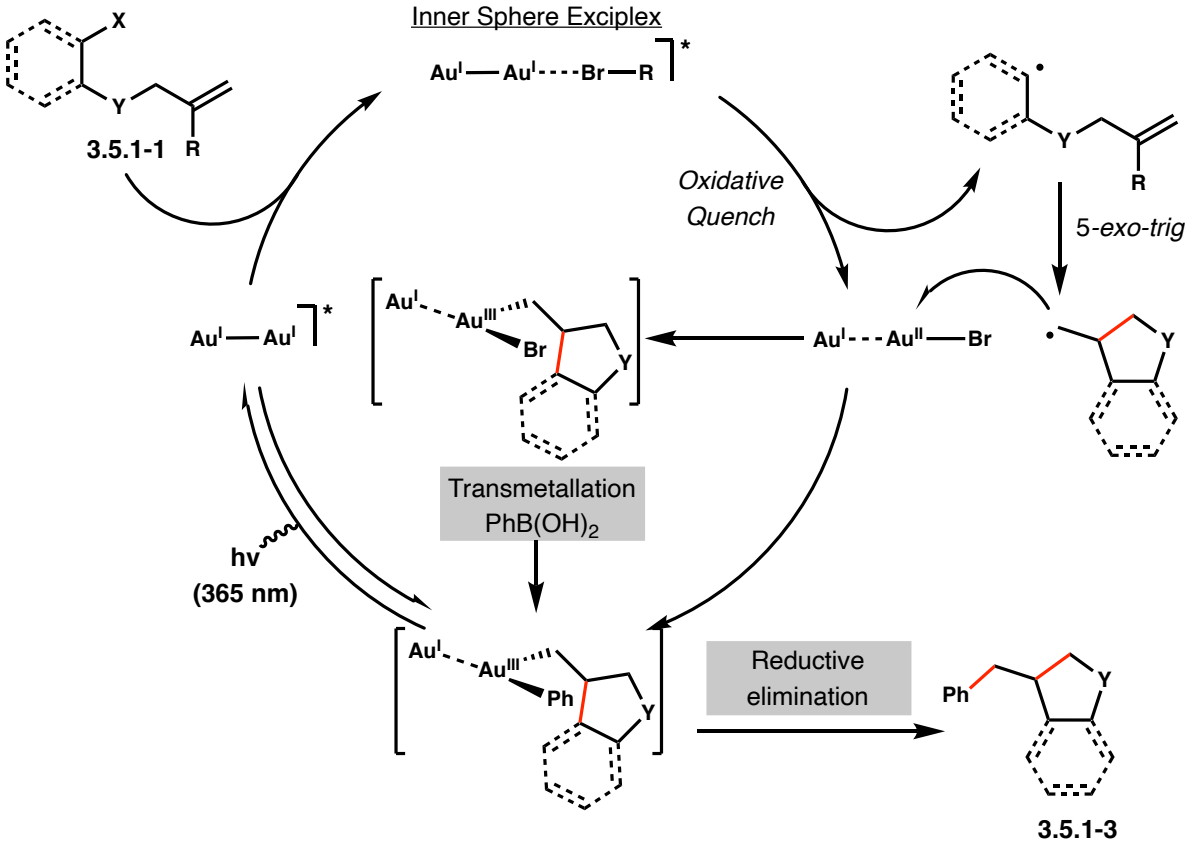


Figure 3.3- Tracking of reaction conditions *via* ^{1}H NMR and ^{31}P NMR. A) ^{1}H NMR tracking of the reaction upon irradiation with UVA LEDs. Full conversion was achieved after 8 minutes of irradiation. B) ^{31}P NMR tracking of the reaction upon irradiation with UVA LEDs. Catalyst degradation was found after 2 minutes of irradiation where dppm ligand peak (30.8 ppm) peak appear.

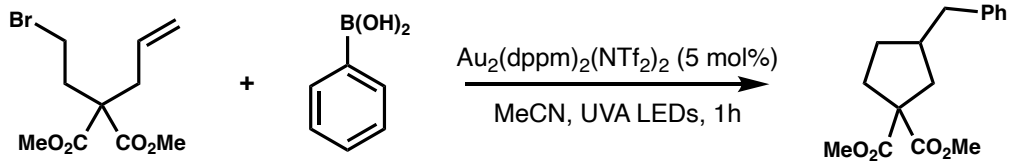
3.5.2- Dual Gold Photoredox and Lewis acid Catalysis: C(sp^3)-C(sp^3) coupling with boronic acids using Gold Photoredox Catalysis

We envisioned that our ATRA methodology using gold photoredox catalysis could be applied in a C(sp^2)-C(sp^3) coupling. We proposed using the same reaction conditions except instead of performing a reductive elimination to perform the formal Br-ATRA reaction, we would have a transmetallation between the catalyst and an added boronic acid (**Scheme 3.5**). We predicted this reaction working because of the suspected Lewis acid character that our binuclear gold photocatalyst was displaying. Our gold photocatalyst, $[Au_2(dppm)_2(NTf_2)_2]$, will absorb UVA light and form an inner sphere exciplex with **3.5.1-1**.



Scheme 3.5- Proposed mechanism of C(sp^3)-C(sp^2) coupling with boronic acids using gold photoredox catalysis.

An oxidative quenching pathway will then occur to homolyze the C-Br bond of **3.5.1-1**. The resulting carbon-centered radical will perform a 5-*exo-trig* cyclization and add unto the gold-center to form a C-Au bond and a Au^{III} species. A transmetallation with phenyl boronic acid **3.5.1-2** will then occur, followed by a reductive elimination that will regenerate the photocatalyst and give desired product **3.5.1-3**. We tested our theory by submitting **3.5.1-1a** and **3.5.1-2a** to our reaction conditions, and it was found that desired product **3.5.1-3a** was formed in 36% (**Scheme 3.6**). This product was confirmed by mass spectrometry (ESI) and by NMR comparison.[16] We excitedly started optimizing the reaction conditions to increase the yield of **3.5.1-3a.** However, when optimization reactions were conducted, the desired product **3.5.1-3a** was never found again. We re-ran the same reaction as in **Scheme 3.6** in triplicate and did could not find the desired product **3.5.1-3aa**. The reaction conditions were not reproducible.



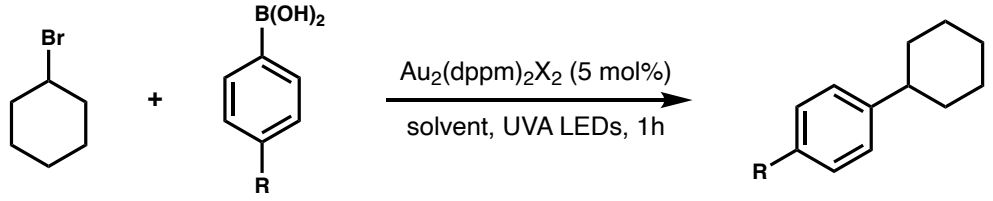
3.5.1-1a **3.5.1-2a** 36%, **3.5.1-3aa**

Scheme 3.6- C(sp^3)-C(sp^3) coupling with boronic acids using gold photoredox catalysis.

We still believe the gold binuclear photocatalyst has a dual photocatalyst and Lewis acid character that can be explored further. We set out to perform an easier C(sp^3)-C(sp^2) coupling, between bromocyclohexane **3.5.1-1b** and phenyl boronic acids **3.5.1-2** and see if it was in fact possible to perform the transmetallation between Au^{III} intermediate and **3.5.1-2** (**Table 3.2**). We started our investigation using $Au_2(dppm_2)(NTf_2)_2$ and 40 mol % of DABCO as a catalyst resuscitator, **3.5.1-2b** as boronic acid, and 60 equivalents of H_2O to help the transmetallation step (**Table 3.2, Entry 1**). Unfortunately, desired product **3.5.1-3ba** was not found. Bringing back simpler binuclear photocatalyst, $Au_2(dppm)_2Cl_2$, we screened a variety of inorganic bases and

equivalents of H_2O, in the hopes of speeding up transmetallation step (**Table 3.2**). Furthermore, adding additives such as DABCO, additional DPPM ligand or CsF did not provide the desired product. (**Table 3.2, Entries 3-4, 9, 11, 13**). Furthermore, using a more electron rich boronic acid (**3.5.1-2b**) did not yield positive results. Because of the volatile nature of **3.5.1-1b**, we were not able to determine if an H-atom abstraction was occurring after formation of the carbon-centered radical. We changed the **3.5.1-1** coupling partner, to see if a by-product could be isolated.

Table 3.2- Screening reaction conditions of $C(sp^3)$-$C(sp^3)$ coupling with boronic acids using gold photoredox catalysis.



3.5.1-1b

R = H, **3.5.1-2a**
R = OMe, **3.5.1-2b**

R = H, **3.5.1-3ba**
R = OMe, **3.5.1-3bb**

Entry	X	**3.5.1-2**, (x equiv)	Additive	Base, (x equiv)	Solvent [M]	H_2O, (x equiv)
1	NTf_2	3.5.1-2b, 1 equiv	DABCO (40 mol%)	-	MeCN (0.1M)	60
2	Cl	3.5.1-2b, 1 equiv	-	K_2CO_3 (1.5 equiv)	MeCN (0.1M)	60
3	Cl	3.5.1-2b, 1 equiv	DABCO (40 mol%)	K_2CO_3 (1.5 equiv)	MeCN (0.1M)	60
4	Cl	3.5.1-2b, 1 equiv	DABCO (40 mol%)	K_2CO_3 (1.5 equiv)	MeCN (0.1M)	-
5	Cl	3.5.1-2b, 1 equiv	-	K_2CO_3 (1.5 equiv)	MeCN (0.1M)[a]	-
6	Cl	3.5.1-2b, 1 equiv	-	K_2CO_3 (1.5 equiv)	MeCN (0.1M)[a]	30
7	Cl	3.5.1-2b, 1 equiv	-	K_2CO_3 (1.5 equiv)	MeCN (0.1M)[b]	-
8	Cl	3.5.1-2a, 1 equiv	-	K_2CO_3 (1.5 equiv)	MeCN (0.1M)	30
9	Cl	3.5.1-2a, 1 equiv	dppm (10 mol%)	K_2CO_3 (1.5 equiv)		30
10	Cl	3.5.1-2a, 1 equiv	-	K_2CO_3 (1.5 equiv)	MeCN (0.1M)	15
11	Cl	3.5.1-2b, 1 equiv	dppm (10 mol%)	K_2CO_3 (1.5 equiv)	MeCN (0.1M)	30

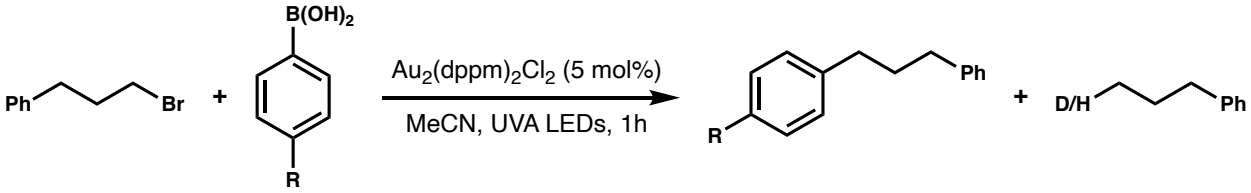
12	Cl	3.5.1-2a, 1 equiv	-	K_2CO_3 (1.5 equiv)	MeCN (0.1M)	30
13	Cl	3.5.1-2a, 1 equiv	CsF (1.5 equiv)	K_2CO_3 (1.5 equiv)	MeCN (0.1M)	30
14	Cl	3.5.1-2b, 1 equiv	-	Cs_2CO_3 (1.5 equiv)	MeCN (0.1M)	30
15	Cl	3.5.1-2b, 1 equiv	-	K_2CO_3 (1.5 equiv)	Et_2O (0.1 M)	30
16	Cl	3.5.1-2b, 1 equiv	-	K_2CO_3 (1.5 equiv)	DMF (0.1 M)	30
17	Cl	3.5.1-2b, 1 equiv	-	K_2CO_3 (1.5 equiv)	THF (0.1 M)	30
18	Cl	3.5.1-2b, 1 equiv	-	K_2CO_3 (1.5 equiv)	Et_2O (0.1 M)	30
19	F[c]	3.5.1-2b, 1 equiv	-	K_2CO_3 (1.5 equiv)	MeCN (0.1M)	30
20	Cl	3.5.1-2b, 1.1 equiv	CsF (1.1 equiv)	-	MeCN : H_2O (7:3)	-
21	NTf_2	3.5.1-2b, 1.2 equiv	-	*t*BuOK (1.5 equiv)	MeOH (0.1 M)	-
22	NTf_2	3.5.1-2b, 1 equiv	-	-	-	-

[a] anhydrous MeCN. [b] MeCN with traces of H_2O. [c] $Au_2dppm_2F_2$ was synthesized but only NMR could be performed.

We thought of using coupling partner **3.5.1-1c** in the reaction conditions to see if we could isolate by-product **3.5.1-4c** (**Table 3.3**). The formation of this by-product would be an indication of an H-atom abstraction which in turn could be hindering the reactivity of the boronic acid. If the boronic acid is acting as an H-atom donor it cannot also act as a transmetallation agent. We set up deuteration experiments to determine if H/D-atom abstraction was happening after the formation of the carbon-centered radical. When performing the reaction using d_3-MeCN and 60 equivalents of D_2O alongside boronic acid **3.5.1-2b** (**Table 3.3**, **Entry 1**) we found that there was incorporation of deuterium, and some by-product was formed. However, there was a complex mixture of products with deuterium added at different positions of the chain and they could not be individually isolated. Unfortunately, no desired product **3.5.1-3cb** was observed. We then

alternate the source of D-atom (**Table 3.3, Entries 2-3**), and we found similar results. Too much D-atom scrambling, and multiple by-products that would not be separated.

Table 3.3- Screening reaction conditions of $C(sp^3)$-$C(sp^3)$ coupling with boronic acids using gold photoredox catalysis.

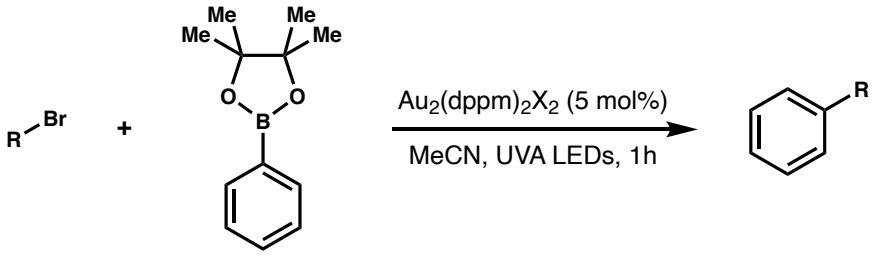


3.5.1-1c R = H, **3.5.1-2a**; R = OMe, **3.5.1-2b** → R = H, **3.5.1-3ca**; R = OMe, **3.5.1-3cb** + **3.5.1-4c**

Entry	**3.5.1-2**, (x equiv)	Additive	Base, (x equiv)	Solvent [M]	H_2O, (x equiv)
1	3.5.1-2b, 1.1 equiv	CsF (1.1 equiv)	-	d_3-MeCN	D_2O, 60 equiv
2	3.5.1-2b, 1.1 equiv	CsF (1.1 equiv)	-	d_3-MeCN	H_2O
3	3.5.1-2b, 1.1 equiv	CsF (1.1 equiv)	-	MeCN	D_2O

To avoid the formation of several by-products with deuterium scrambling we updated our reaction conditions and opted to use phenyl boronic ester **3.5.1-2c** as coupling partner. This blocks any opportunity of an H-atom abstraction from the boronic acid, but also gives a good coupling partner for the reaction. Using bromocyclohexane **3.5.1-1b** or ethyl bromoacetate **3.5.1-1d** and phenyl boronic pinacol ester **3.5.1-2c** with our reaction conditions saw no formation of desired product **3.5.1-3** (**Table 3.4**). We also saw no consumption of the boronic esters using our reaction conditions, therefore we do not believe that any transmetallation is happening. At this point, we believe that a simple $C(sp^3)$-$C(sp^2)$ coupling is not possible under these reaction conditions. The initial hit was most likely due to a contamination in the reaction conditions and the $C(sp^3)$-$C(sp^2)$ coupling was likely due to some metal contamination in the reaction vessel.

Table 3.4- Screening reaction conditions of C(sp^3)-C(sp^3) coupling with boronic pinacol esters using gold photoredox catalysis.



R = Cy, **3.5.1-1b**
R = CH_2CO_2Et, **3.5.1-1d**

3.5.1-2c

R = Cy**, 3.5.1-3ba**
R = CH_2CO_2Et**, 3.5.1-3da**

Entry	X	3.5.1-1	3.5.1-2c (x equiv)	Additive	Base (x equiv)	Solvent
1	NTf_2	3.5.1-1b	1.5	-	Na_2CO_3 (1.5 equiv)	MeCN : H_2O (7:3)
2	NTf_2	3.5.1-1b	1.5	-	Na_2CO_3 (1.5 equiv)	DMF (0.1M)
3	Cl	3.5.1-1b	1.5	-	*t*BuOK (3 equiv)	MeCN (0.1 M)
4	Cl	3.5.1-1b	1.5	-	K_3PO_4 (2 equiv)	MeCN (0.1 M)
5	Cl	3.5.1-1d	1.5	-	K_3PO_4 (2 equiv)	MeCN (0.1 M)
6	Cl	3.5.1-1d	1	DABCO (40 mol%)	Na_2CO_3 (1.5 equiv)	MeCN (0.1 M)

3.6- Experimental Procedures

3.6.1- General Information

All reactions were performed under argon atmosphere in Pyrex glassware equipped with a magnetic stir bar, capped with a septum, unless otherwise indicated. All commercial reagents were used without further purification, unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC) analysis. TLC plates were viewed under UV light and stained with potassium permanganate or *p*-anisaldehyde staining solution. Yields refer to products isolated after purification, unless otherwise stated. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AMX 400 MHz. NMR samples were dissolved in deuterated chloroform (unless specified otherwise) and chemical shifts are reported in ppm referenced to residual undeuterated solvent. Data are reported as follows: chemical shift, multiplicity, coupling,

integration. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on the same Bruker instruments as in proton NMR at 101 MHz. IR spectra were recorded with an Agilent Technologies Cary 630 FTIR Spectrometer equipped with a diamond ATR module. HRMS were obtained on a Kratos Analytical Concept- Magnetic Sector Electron Impact Mass Spectrometer instrument and Micromass Q-TOF I-TOF Electrospray Ionisation mass spectrometer (University of Ottawa Mass Spectrum Centre).

3.6.2- General Procedures

General Procedure 1- Synthesis of malonate derived bromoalkanes: To a flame-dried round bottom flash with a magnetic stir bar, K_2CO_3 (3 equiv) was added to a solution of dimethylmalonate (1 equiv) and allyl bromide in acetone (0.6 M). The reaction was left stirring for 72 h at room temperature. Once the reaction was deemed complete via TLC, it was put through a silica plug and concentrated *in vacuo*. Crude mixture was purified by distillation under pressure to afford the dimethyl 2-allyl malonate product. To a high-pressure tube, NaH (1.2 equiv) was added slowly to THF. The dimethyl 2-allyl malonate was slowly added and allowed all NaH to react. Once bubbling subsided, 1,2-dibromomethane was added and heated the reaction for 72 h. Using ether and water, the organic phase was extracted and concentrated *in vacuo*. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined, concentrated and characterized by proton and carbon NMR (400 and 101 MHz, respectively), HR-MS and IR.

General Procedure 2- Synthesis of *p*-toluenesulfonamide based bromoalkanes: To a flame-dried round bottom flash with a magnetic stir bar, K_2CO_3 (3 equiv) was added to a solution of p-toluenesulfomamide (1.5 equiv) and allyl bromide (1 equiv) in acetone (0.2 M). The reaction was

refluxed, using an oil bath as heat source, overnight. Once the reaction was deemed complete via TLC, it was put through a silica plug and concentrated *in vacuo*. Crude mixture was purified by distillation under pressure to afford the dimethyl *N*-allyl sulfonamide product. To a high-pressure tube, K_2CO_3 (3 equiv) was added slowly to a solution of allyamine in THF (0.25 M). 1,2-dibromomethane was added and the reaction was heated to reflux for 48 h. Using ether and water, the organic phase was extracted and concentrated *in vacuo*. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined, concentrated and characterized by proton and carbon NMR (400 and 101 MHz, respectively), HR-MS and IR.

General Procedure 3- Synthesis of acetal derived bromoalkanes: At 0°, *N*-Bromosuccinimide was added to a solution of the alcohol, enol ether and DCM. Warm to room temperature and stir for 16 h. The reaction was quench with H_2O and extracted with DCM three times. Combined organic layers were washed with $NaHCO_3$ (aq) and brine, and dried, filtered and concentrated *in vacuo*. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined, concentrated and characterized by proton and carbon NMR (400 and 101 MHz, respectively), HR-MS and IR.

General Procedure 4- Synthesis of aryl iodides: At 0°C add NaH (1.1 equiv) was added in one portion to a solution aryl iodide (1 equiv) in DMF (0.1 M). Once the reaction stops bubbling and producing H_2, add allyl bromide (1.2 equiv) and bring to room temperature. Resulting mixture was quenched with H_2O after 2 h and extracted with EtOAc. Combined organic layers were dried,

filtered, and concentrated *in vacuo*. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined, concentrated and characterized by proton and carbon NMR (400 and 101 MHz, respectively), HR-MS and IR.

General Procedure 5- Formal Bromine Atom Transfer using Gold Photoredox Catalysis: To an oven dried 8 mL Pyrex screw-top reaction vessel was added the alkyl bromide (0.2 mmol, 1.0 equiv), $[Au_2(dppm)_2](NTf_2)_2$ (0.01 mmol, 5 mol %), MeCN and H_2O (7:3, 6 mL, 0.033 M). The reaction Pyrex vessel was capped, degassed with argon by sparging for 5 minutes, then irradiated with a UVA (365 nm) LED (LuxiGen 365 nm UV LED Emitter, LZ4-04UV0R, 3.8-6 W) at an approximate distance of 5 mm for 10 minutes. The resulting mixture was extracted with DCM and H_2O, and the organic layers were combined, dried, filtered and concentrated *in vacuo*. The crude mixture was further purified by flash chromatography (0-100% EtOAc:Hexanes), where relevant fractions were combined, concentrated and characterized by proton and carbon NMR (400 and 101 MHz, respectively), HR-MS, and IR.

Synthetic example: To an oven dried Pyrex screw-top reaction vessel was added the alkyl bromide (1 mmol, 1.0 equiv), $[Au_2(dppm)_2](NTf_2)_2$ (0.05 mmol, 5 mol %), MeCN and H_2O (7:3, 15 mL, 0.067 M). The reaction Pyrex vessel was capped, degassed with argon by sparging for 5 minutes, then irradiated with a UVA (365 nm) LED (LuxiGen 365 nm UV LED Emitter, LZ4-04UV0R, 3.8-6 W) at an approximate distance of 5 mm for 15 minutes. The resulting mixture was extracted with DCM and H_2O, and the organic layers were combined, dried, filtered and concentrated *in vacuo*. The crude mixture was further purified by flash chromatography (0-100% EtOAc:Hexanes), where

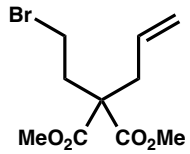
relevant fractions were combined, concentrated and characterized by proton and carbon NMR (400 and 101 MHz, respectively), HR-MS, and IR.

General Procedure 6- Formal Iodine Atom Transfer using Gold Photoredox Catalysis: To an oven dried 8 mL Pyrex screw-top reaction vessel was added the aryl iodide (0.2 mmol, 1.0 equiv), $Au_2(dppm)_2(NTf_2)_2$ (0.01 mmol, 5 mol %), MeCN and H2O (7:3, 6 mL, 0.033 M). The reaction Pyrex vessel was capped, degassed with argon by sparging for 5 minutes, then irradiated with a UVA (365 nm) LED (LuxiGen 365 nm UV LED Emitter, LZ4-04UV0R, 3.8-6 W) at an approximate distance of 5 mm for 15 minutes. The resulting mixture was extracted with DCM and H2O, and the organic layers were combined, dried, filtered and concentrated *in vacuo*. The crude mixture was further purified by flash chromatography (0-100% EtOAc:Hexanes), where relevant fractions were combined, concentrated and characterized by proton and carbon NMR (400 and 101 MHz, respectively), HR-MS, and IR.

Synthetic example: To an oven dried Pyrex screw-top reaction vessel was added the aryl iodide (1 mmol, 1.0 equiv), $[Au_2(dppm)_2](NTf_2)_2$ (0.05 mmol, 5 mol %), MeCN and H_2O (7:3, 15 mL, 0.067 M). The reaction Pyrex vessel was capped, degassed with argon by sparging for 5 minutes, then irradiated with a UVA (365 nm) LED (LuxiGen 365 nm UV LED Emitter, LZ4-04UV0R, 3.8-6 W) at an approximate distance of 5 mm for 20 minutes. The resulting mixture was extracted with DCM and H_2O, and the organic layers were combined, dried, filtered and concentrated *in vacuo*. The crude mixture was further purified by flash chromatography (0-100% EtOAc:Hexanes), where relevant fractions were combined, concentrated and characterized by proton and carbon NMR (400 and 101 MHz, respectively), HR-MS, and IR.

3.7- Characterization Data

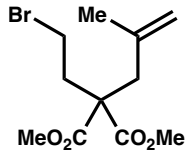
3.7.1- Characterization 3.3-1 Starting Materials



dimethyl-2-allyl-2-(2-bromoethyl)malonate (3.3-1a)

Synthesized according to GP1. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Synthesized as a yellow oil. Contains 10% of dimethyl 2,2-diallylmalonate. (27.9 g, 80%)

IR (neat, cm^{-1}): 2954 (m), 1731 (vs), 1435 (m), 1209 (s), 1164 (m), 925 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.70 – 5.57 (m, 1H), 5.17 – 5.07 (m, 2H), 3.74 (s, 6H), 3.39 – 3.31 (m, 2H), 2.70 – 2.61 (m, 2H), 2.49 – 2.39 (m, 2H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 170.7 (2 X C), 131.7 (CH), 119.8 (CH2), 57.6 (C), 52.7 (2 X CH_3), 37.9 (CH_2), 36.3 (CH_2), 26.9 (CH_2) ppm; **HRMS** (ESI) m/z: $[M^+ + Na^+]$ Calc'd for $C_{10}H_{15}BrO_4Na$ 301.0046; Found 301.0051.

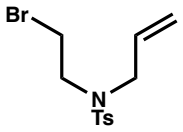


dimethyl-2-(2-bromoethyl)-2-(2-methylallyl)malonate (3.3-1b)

Synthesized according to GP1. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Synthesized as a yellow oil. (1.70 g, 68%)

IR (neat, cm^{-1}): 2956 (m), 1735 (vs), 1437 (m), 1263 (s), 1217 (s), 1203 (s), 1165 (m), 906 (m.); 1H **NMR** (400 MHz, $CDCl_3$) δ = 4.91 (p, *J* = 1.6 Hz, 1H), 4.76 (m, *J* = 1.8, 1.0 Hz, 1H), 3.75 (s, 6H), 3.38 – 3.28 (m, 2H), 2.74 (d, *J* = 1.0 Hz, 2H), 2.50 – 2.43 (m, 2H), 1.65 (dd, *J* = 1.5, 0.8 Hz, 3H) ppm; **^{13}C**

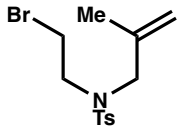
NMR (101 MHz, $CDCl_3$) δ = 171.0 (2 X C), 139.8 (C), 116.3 (CH_2), 57.1 (C), 52.7 (2 X CH_3), 41.2 (CH_2), 36.3 (CH_2), 27.2 (CH_2), 22.9 (CH_3) ppm; **HRMS** (ESI) m/z: [M^++Na^+] Calc'd for $C_{11}H_{17}BrO_4Na$ 315.0202; Found 315.0208.



***N*-allyl-*N*-(2-bromoethyl)-4-methylbenzenesulfonamide (3.3-1c)**

Synthesized according to GP2 and characterized according to NMR comparison.[13j] Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Synthesized as a clear oil. (1.62 g, 48%)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 – 7.67 (m, 2H), 7.37 – 7.29 (m, 2H), 5.68 (ddt, *J* = 16.2, 10.4, 6.5 Hz, 1H), 5.22 (dq, *J* = 6.6, 1.3 Hz, 1H), 5.19 (t, *J* = 1.3 Hz, 1H), 3.82 (dt, *J* = 6.5, 1.3 Hz, 2H), 3.50 – 3.38 (m, 4H), 2.44 (s, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 143.7 (C), 136.3 (C), 132.8 (CH), 129.8 (2 X CH), 127.2 (2 X CH), 119.7 (CH_2), 52.0 (CH_2), 48.9 (CH_2), 29.2 (CH_2), 21.5 (CH_3) ppm.

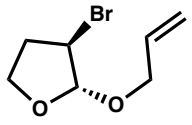


N-(2-bromoethyl)-4-methyl-N-(2-methylallyl)benzenesulfonamide (3.3-1d)

Synthesized according to GP2 and characterized according to NMR comparison.[7b] Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Synthesized as an amorphous solid. (2.49 g ,89%)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.73 – 7.67 (m, 2H), 7.36 – 7.29 (m, 2H), 4.94 (tt, *J* = 1.5, 0.7 Hz, 1H), 4.90 (p, *J* = 1.1 Hz, 1H), 3.70 (s, 2H), 3.46 – 3.34 (m, 4H), 2.44 (s, 3H), 1.73 (s, 3H) ppm; **^{13}C**

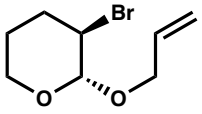
NMR (101 MHz, CDCl3) δ = 143.6 (C), 140.4 (C), 136.1 (C), 129.8 (2 X CH), 127.1 (2 X CH), 115.3 (CH_2), 55.8 (CH_2), 49.5 (CH_2), 28.9 (CH_2) , 21.5 (CH_3), 19.7 (CH_3) ppm.



(2S,3R)-2(allyloxy)-3-bromotetrahydrofuran (3.3-1e)

Synthesized according to GP3 and characterized according to NMR comparison.[17] Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Synthesized as a clear oil. (1.75 g, 35%)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.89 (dddd, *J* = 17.2, 10.4, 6.1, 5.3 Hz, 1H), 5.32 – 5.24 (m, 2H), 5.20 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.25 (dd, *J* = 6.0, 1.6 Hz, 1H), 4.22 – 4.14 (m, 2H), 4.08 (td, *J* = 8.5, 3.4 Hz, 1H), 3.99 (ddt, *J* = 12.8, 6.1, 1.4 Hz, 1H), 2.73 – 2.61 (m, 1H), 2.23 (dddd, *J* = 14.0, 7.0, 3.4, 1.7 Hz, 1H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 134.0 (CH), 117.4 (CH_2), 108.0 (CH), 68.1 (CH_2), 66.7 (CH_2), 50.0 (CH), 33.9 (CH_2) ppm.

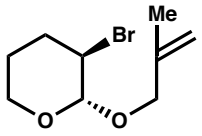


(2S,3R)-2(allyloxy)-3-bromotetrahydro-2H-pyr (3.3-1f)

Synthesized according to GP3 and characterized according to NMR comparison.[18] Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Synthesized as a clear oil. (3.19 g, 64%)

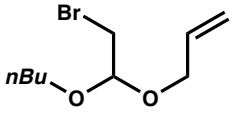
^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.94 (dddd, *J* = 16.9, 10.4, 6.1, 5.2 Hz, 1H), 5.33 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.21 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.66 (d, *J* = 4.4 Hz, 1H), 4.27 (ddt, *J* = 12.9, 5.2, 1.5 Hz, 1H), 4.06 (ddt, *J* = 12.9, 6.2, 1.4 Hz, 1H), 4.01 (dt, *J* = 6.7, 4.2 Hz, 1H), 3.93 (ddd, *J* = 11.2, 7.8, 3.2 Hz,

1H), 3.63 – 3.55 (m, 1H), 2.46 – 2.36 (m, 1H), 2.00 – 1.89 (m, 2H), 1.59 – 1.49 (m, 1H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 133.9 (CH), 117.5 (CH_2), 100.1 (CH), 68.7 (CH_2), 62.5 (CH_2), 49.3 (CH), 30.0 (CH_2), 23.2 (CH_2) ppm.



(2S,3R)-3-bromo-2-((2-methylallyl)oxy)tetrahydro-2H-pyr (3.3-1g)

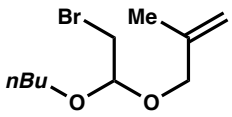
Synthesized according to GP3. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Synthesized as a clear oil. (3.30 g, 70%) **IR** (neat, cm^{-1}): 2948 (m), 2929 (m), 2854 (m), 1438 (m), 1204 (s), 1130 (vs), 1071 (vs), 1021 (vs), 948 (s), 900 (vs), 869 (vs), 729 (vs), 711 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.03 – 4.97 (m, 1H), 4.95 – 4.89 (m, 1H), 4.63 (d, *J* = 4.5 Hz, 1H), 4.19 – 4.11 (m, 1H), 4.04 – 3.88 (m, 3H), 3.58 (dddd, *J* = 11.2, 6.4, 3.6, 1.0 Hz, 1H), 2.46 – 2.35 (m, 1H), 1.93 (dddd, *J* = 15.8, 13.5, 7.8, 3.7 Hz, 2H), 1.77 (s, 3H), 1.55 (dddd, *J* = 13.7, 11.1, 6.8, 3.9 Hz, 1H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 141.4 (C), 112.8 (CH2), 100.1 (CH), 71.6 (CH_2), 62.6 (CH_2), 49.4 (CH), 30.2 (CH_2), 23.4 (CH_2), 19.6 (CH_3) ppm; **HRMS** (ESI) m/z: [M^++Na^+] Calc'd for $C_9H_{15}BrO_2Na$ 257.0148; Found 257.0153.



1-(1-(allyloxy)-2-bromoethoxy)butane (3.3-1h)

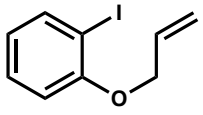
Synthesized according to GP3 and characterized according to NMR comparison.[19] Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Synthesized as a clear oil. (1.89 g, 67%)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.92 (dddd, *J* = 17.1, 10.3, 5.9, 5.4 Hz, 1H), 5.32 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.20 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.71 (t, *J* = 5.5 Hz, 1H), 4.16 (ddt, *J* = 12.7, 5.4, 1.5 Hz, 1H), 4.07 (ddt, *J* = 12.7, 5.9, 1.4 Hz, 1H), 3.63 (dt, *J* = 9.2, 6.5 Hz, 1H), 3.51 (dt, *J* = 9.2, 6.6 Hz, 1H), 3.38 (d, *J* = 5.5 Hz, 2H), 1.63 – 1.54 (m, 3H), 1.46 – 1.35 (m, 3H), 0.93 (t, *J* = 7.4 Hz, 4H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 134.1 (CH), 117.3 (CH_2), 101.0 (CH), 67.5 (CH_2), 66.6 (CH_2), 31.8 (CH_2), 31.6 (CH_2), 19.3 (CH_2), 13.8 (CH_3) ppm.



1-(2-bromo-1-((2-methylallyl)oxy)ethoxy)butane (3.3-1i)

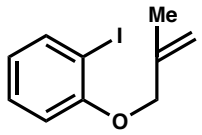
Synthesized according to GP3. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Synthesized as a clear oil. (2.34 g, 74%) **IR** (neat, cm^{-1}): 2959 (m), 2933 (m), 2871 (m), 1458 (m), 1424 (m), 1115 (s), 1066 (s), 1033 (vs), 900 (s), 683 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.03 – 4.98 (m, 1H), 4.91 (t, *J* = 1.8 Hz, 1H), 4.70 (t, *J* = 5.5 Hz, 1H), 4.01 (dd, *J* = 32.7, 12.4 Hz, 2H), 3.62 (dt, *J* = 9.1, 6.6 Hz, 1H), 3.52 (dt, *J* = 9.2, 6.5 Hz, 1H), 3.39 (d, *J* = 5.5 Hz, 2H), 1.77 (s, 3H), 1.63 – 1.54 (m, 2H), 1.46 – 1.35 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 141.6 (C), 112.7 (CH_2), 101.0 (CH), 70.5 (CH_2), 66.6 (CH_2), 31.8 (CH_2), 31.6 (CH_2), 19.6 (CH_3), 19.3 (CH_2), 13.8 (CH_3) ppm; **HRMS** (EI) m/z: [M^+ -C4H9O] Calc'd for $C_6H_{10}BrO$ 176.9915; Found 176.9894.



1-(allyloxy)-2-iodobenzene (3.3-1m)

Synthesized according to GP4 and characterized according to NMR comparison.[20] Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Synthesized as a yellow oil. (4.94 g, 97%)

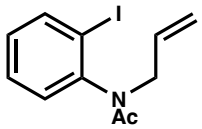
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.79 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.32 – 7.26 (m, 1H), 6.81 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.72 (td, *J* = 7.6, 1.4 Hz, 1H), 6.07 (ddt, *J* = 17.2, 10.6, 4.8 Hz, 1H), 5.53 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.32 (dq, *J* = 10.6, 1.5 Hz, 1H), 4.60 (dt, *J* = 4.9, 1.7 Hz, 2H) ppm; **^{13}C NMR** (101 MHz, CDCl3) δ = 157.1 (C), 139.5 (CH), 132.6 (CH), 129.4 (CH), 122.7 (CH), 117.6 (CH_2), 112.5 (CH), 86.7 (C), 69.6 (CH_2) ppm.



1-iodo-2-((2-methylallyl)oxy)benzene (3.3-1n)

Synthesized according to GP4 and characterized according to NMR comparison.[21] Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Synthesized as a yellow oil. (5.88 g, 96%)

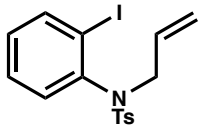
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.32 – 7.27 (m, 1H), 6.82 (dd, *J* = 8.3, 1.4 Hz, 1H), 6.72 (td, *J* = 7.6, 1.4 Hz, 1H), 5.22 (dd, *J* = 1.7, 0.9 Hz, 1H), 5.04 (hept, *J* = 1.5 Hz, 1H), 4.50 (s, 2H), 1.89 (d, *J* = 0.8 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.1 (C), 140.2 (C), 139.4 (CH), 129.3 (CH), 122.5 (CH), 112.9 (CH_2), 112.3 (CH), 86.5 (C), 72.5 (CH_2), 19.5 (CH_3) ppm.



***N*-allyl-*N*-(2-iodophenyl)acetamide (3.3-1o)**

Synthesized according to GP4 and characterized according to NMR comparison.[23] Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Synthesized as an amorphous solid. (1.40 g, 68%)

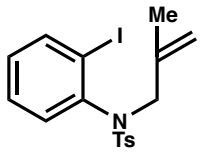
^{1}H NMR (400 MHz, $CDCl_3$) δ ¬= 7.95 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.39 (td, *J* = 7.6, 1.4 Hz, 1H), 7.18 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.08 (ddd, *J* = 7.9, 7.4, 1.6 Hz, 1H), 5.90 (dddd, *J* = 17.1, 10.1, 7.8, 5.5 Hz, 1H), 5.11 (dq, *J* = 10.1, 1.2 Hz, 1H), 5.05 (dq, *J* = 17.1, 1.5 Hz, 1H), 4.85 (ddt, *J* = 14.7, 5.5, 1.5 Hz, 1H), 3.59 (ddt, *J* = 14.6, 7.7, 1.0 Hz, 1H), 1.80 (s, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 169.8 (C), 144.7 (C), 140.2 (CH), 132.7 (CH), 130.5 (CH), 129.8 (CH), 129.4 (CH), 118.6 (CH_2), 100.5 (C), 51.0 (CH_2), 22.8 (CH_3) ppm.



***N*-allyl-*N*-(2-iodophenyl)-4-methylbenzenesulfonamide (3.3-1p)**

Synthesized according to GP4 and characterized according to NMR comparison.[22] Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Synthesized as an amorphous solid. (0.8324 g, 95%)

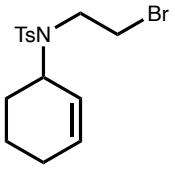
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.91 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.72 – 7.64 (m, 2H), 7.32 – 7.29 (m, 2H), 7.28 – 7.25 (m, 1H), 7.02 (ddd, *J* = 7.9, 7.4, 1.6 Hz, 1H), 6.94 (dd, *J* = 7.9, 1.6 Hz, 1H), 5.87 (ddt, *J* = 17.0, 10.1, 6.8 Hz, 1H), 5.04 (dq, *J* = 10.1, 1.1 Hz, 1H), 4.98 (dq, *J* = 17.0, 1.4 Hz, 1H), 4.24 – 4.07 (m, 2H), 2.45 (s, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 143.7 (C), 141.1 (C), 140.3 (C), 136.5 (CH), 132.3 (CH), 131.0 (CH), 129.9 (CH), 129.5 (2 X CH), 128.6 (CH), 128.2 (2 X CH), 119.6 (CH_2), 103.1 (C), 54.5 (CH_2), 21.59 (CH_3) ppm.



***N*-(2-iodophenyl)-4-methyl-*N*-(2-methylallyl)benzenesulfonamide (3.3-1q)**

Synthesized according to GP4. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Synthesized as an amorphous solid. (2.83 g, 78%)

IR (neat, cm^{-1}): 2960 (m), 2926 (m), 2862 (m), 1599 (s), 1476 (s), 1461 (s), 1356 (vs), 1166 (vs); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.92 – 7.83 (m, 1H), 7.65 – 7.56 (m, 2H), 7.31 – 7.26 (m, 3H), 7.04 – 6.94 (m, 2H), 4.76 (p, *J* = 1.5 Hz, 1H), 4.62 (dq, *J* = 1.8, 0.9 Hz, 1H), 4.20 (d, *J* = 14.1 Hz, 1H), 4.04 (d, *J* = 14.1 Hz, 1H), 2.45 (s, 3H), 1.91 – 1.81 (m, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 143.7 (C), 141.3 (C), 140.6 (CH), 139.8 (C), 136.3 (C), 131.1 (CH), 129.6 (CH), 129.4 (2 X CH), 128.5 (CH), 128.2 (2 X CH), 116.38 (CH_2), 101.7 (C), 57.8 (CH_2), 21.6 (CH_3), 21.0 (CH_3) ppm; **HRMS** (ESI) m/z: [M^++Na^+] calc'd for $C_{17}H_{18}INO_2SNa$ 450.0001; Found 449.9995.

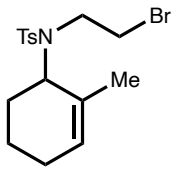


***N*-(2-bromoethyl)-*N*-(cyclohex-2-en-1-yl)-4-methylbenzenesulfonamide (3.3-1r)**

Synthesized according to GP2 and characterized according to NMR comparison.[7b] Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Synthesized as an amorphous solid. (1.25 g, 43%)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.78 – 7.68 (m, 2H), 7.36 – 7.28 (m, 2H), 5.88 – 5.74 (m, 1H), 4.96 (dp, *J* = 10.2, 2.0 Hz, 1H), 4.46 (dtd, *J* = 11.5, 5.5, 2.6 Hz, 1H), 3.70 – 3.62 (m, 1H), 3.51 – 3.37 (m,

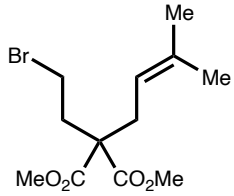
2H), 3.32 – 3.19 (m, 1H), 2.43 (s, 3H), 2.01 – 1.92 (m, 2H), 1.92 – 1.83 (m, 1H), 1.82 – 1.72 (m, 1H), 1.65 – 1.58 (m, 1H), 1.42 (tdd, *J* = 12.7, 10.1, 3.0 Hz, 1H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 143.6 (C), 137.2 (C), 133.3 (CH), 129.8 (2 X CH), 127.1 (CH), 126.8 (2 X CH), 55.4 (CH), 45.6 (CH_2), 31.1 (CH_2), 29.1 (CH_2), 24.4 (CH_2), 21.5 (CH_3), 21.5 (CH_2) ppm.



***N*-(2-bromoethyl)-4-methyl-*N*-(2-methylcyclohex-2-en-1-yl)benzenesulfonamide (3.3-1s)**

Synthesized according to GP2 and characterized according to NMR comparison.[7b] Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Synthesized as an amorphous solid. (1.02 g, 46%)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.72 (dt, *J* = 8.8, 2.1 Hz, 2H), 7.33 – 7.27 (m, 2H), 5.69 (ddq, *J* = 5.1, 3.5, 1.7 Hz, 1H), 4.29 – 4.18 (m, 1H), 3.74 – 3.63 (m, 1H), 3.59 – 3.38 (m, 2H), 3.26 – 3.15 (m, 1H), 2.42 (s, 3H), 2.06 – 1.85 (m, 2H), 1.85 – 1.74 (m, 1H), 1.63 – 1.50 (m, 3H), 1.25 (s, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 143.4 (C), 137.6 (C), 131.7 (C) 129.9 (CH), 129.7 (2 X CH), 127.1 (2 X CH), 57.7 (CH), 45.9 (CH_2), 30.5 (CH_2), 30.1 (CH_2), 25.0 (CH_2), 21.5 (CH_3), 20.9 (CH_2), 20.6 (CH_3) ppm.

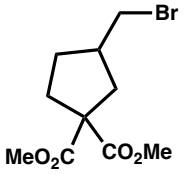


dimethyl-2-(2-bromoethyl)-2-(3-methylbut-2-en-1-yl)malonate (3.3-1t)

Synthesized according to GP1 and characterized according to NMR comparison.[16] Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Synthesized as a yellow oil. (1.3 g, 72%)

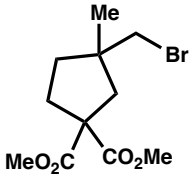
^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.00 – 4.87 (m, 1H), 3.74 (s, 6H), 3.39 – 3.26 (m, 2H), 2.63 (dq, *J* = 7.3, 0.9 Hz, 2H), 2.49 – 2.36 (m, 2H), 1.71 (d, *J* = 1.3 Hz, 3H), 1.63 (d, *J* = 1.2 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 171.0 (2 X C), 136.5 (C), 116.9 (CH), 57.8 (C), 52.6 (2 X CH_3), 36.3 (CH_2), 32.1 (CH_2), 27.3 (CH_2), 26.0 (CH_3), 17.9 (CH_3) ppm.

3.7.2- Characterization of 3.3-2 Products



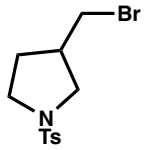
Dimethtl-3-(bromomethyl)cyclopentane-1,1-dicarboxylate (3.3-2a)

Synthesized according to GP5. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Isolated as 39 mg of a yellow oil (82 %). **IR** (neat, cm^{-1}) 2954 (m), 1731 (vs), 1435 (m), 1259 (s), 1197 (m), 1161 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.72 (s, 6H), 3.42 – 3.35 (m, 2H), 2.56 – 2.41 (m, 2H), 2.33 (ddd, *J* = 13.4, 8.5, 4.8 Hz, 1H), 2.26 – 2.16 (m, 1H), 2.01 – 1.90 (m, 2H), 1.54 – 1.41 (m, 1H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 172.5 (2 X C), 60.1 (C), 52.8 (2 X CH_3), 41.6 (CH), 39.3 (CH_2), 37.2 (CH_2), 33.8 (CH_2), 30.8 (CH_2) ppm; **HRMS** (EI) m/z: [M^+] calc'd for $C_{10}H_{15}BrO_4$ 278.0154; Found 278.0138.



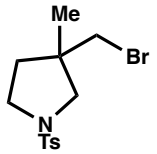
Dimethyl-3-(bromomethyl)-3-methylcyclopentane-1,1-dicarboxylate (3.3-2b)

Synthesized according to GP5. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Isolated as 32 mg of a yellow oil (55 %). **IR** (neat, cm^{-1}): 2358 (s), 2342 (s), 1735 (vs), 1261 (m), 1197 (m), 1181 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.73 (s, 7H), 3.38 (s, 2H), 2.39 – 2.30 (m, 3H), 2.17 (d, *J* = 14.4 Hz, 1H), 1.82 – 1.72 (m, 1H), 1.65 – 1.58 (m, 1H), 1.56 (s, 3H), 1.17 (s, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 172.8 (C), 172.6 (C), 60.3 (C), 52.9 (CH_3), 52.8 (CH_3), 45.1 (CH_2), 44.9 (CH_2), 44.2 (C), 37.5 (CH_2), 33.6 (CH_2), 26.0 (CH_3) ppm; **HRMS** (ESI) m/z: [M^+-CH3O] calc'd for $C_{10}H_{13}BrO_3$ 261.0126; Found 261.0086.



3-(bromomethyl)-1-tosylpyrrolidine (3.3-2c)

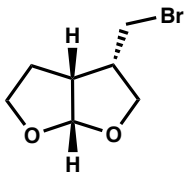
Synthesized according to GP5. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Isolated as 52 mg of white solid (82 %). **IR** (neat, cm^{-1}): 2973 (m), 2919 (m), 1598 (m), 1335 (vs), 1299 (s), 1235 (s). 1155 (vs), 1114 (s), 1091 (s), 1027 (s), 1013 (s), 821 (s), 811 (s), 776 (s), 707 (s), 667 (vs); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.71 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 3.43 (dd, *J* = 10.3, 7.4 Hz, 1H), 3.35 (ddd, *J* = 9.9, 8.2, 4.7 Hz, 1H), 3.28 – 3.15 (m, 3H), 3.04 (dd, *J* = 10.3, 6.8 Hz, 1H), 2.49 (p, *J* = 7.2 Hz, 1H), 2.43 (s, 3H), 2.06 – 1.95 (m, 1H), 1.61 (dq, *J* = 12.7, 7.8 Hz, 1H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 143.6 (C), 133.3 (C), 129.7 (2 X CH), 127.6 (2 X CH), 52.1 (CH_2), 47.3 (CH_2), 40.9 (CH), 34.1 (CH_2), 30.3 (CH_2), 21.5 (CH_3) ppm; HRMS (ESI) m/z: [M^++Na^+] calc'd for $C_{12}H_{16}BrNO_2SNa$ 339.9977; Found 339.9983.



3-(bromomethyl)-3-methyl-1-tosylpyrrolidine (3.3-2d)

Synthesized according to GP5. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Isolated as 33 mg of white powder (50 %).

IR (neat, cm^{-1}): 2961 (m), 2928 (m), 2874 (m), 1598 (m), 1454 (m), 1335 (s), 1153 (vs), 1093 (s), 1052 (s), 912 (m), 816 (s), 805 (s), 731 (s), 661 (vs); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.71 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 7.7 Hz, 2H), 3.35 – 3.30 (m, 2H), 3.24 (d, *J* = 10.1 Hz, 1H), 3.21 (s, 2H), 3.03 (d, *J* = 10.1 Hz, 1H), 2.43 (s, 3H), 1.84 (dt, *J* = 12.8, 7.2 Hz, 1H), 1.70 – 1.60 (m, 1H), 1.05 (s, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 143.6 (2 X C), 133.5 (2 X C), 129.7 (2 X CH_2), 127.5 (2 X CH_2), 57.5 (CH_2), 46.7 (CH_2), 43.4 (C), 41.5 (CH_2), 36.2 (CH_2), 23.2 (CH_3), 21.5 (CH_3) ppm; **HRMS** (ESI) m/z: [M^++Na^+] calc'd for $C_{13}H_{18}BrNO_2SNa$ 354.0134; Found 354.1102.

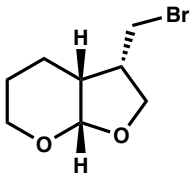


3-(bromomethyl)hexahydrofuro[2,3-b]furan (3.3-2e)

Synthesized according to GP5. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Isolated as 29 mg of clear oil (70%, 83:17 d.r.) and 0.1780 g (82%, 83:17 d,r.) when performed in a 1 mmol scale.

IR (neat, cm^{-1}): 2957 (m), 2872 (m), 2252 (m), 1712 (m), 1231 (m), 1108 (m), 1065 (m), 1016 (vs), 1000 (vs), 955 (m), 941 (m), 922 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.76 (d, *J* = 4.9 Hz, 1H), 5.73-

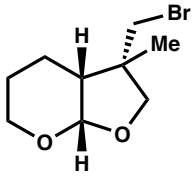
5.71 (m, 0.05 H, **minor diastereoisomer**), 4.04 (dd, *J* = 8.6, 7.2 Hz, 1H), 3.90 (dd, *J* = 7.6, 6.1 Hz, 2H), 3.51 (dd, *J* = 11.0, 8.6 Hz, 1H), 3.38 (dd, *J* = 8.0, 1.7 Hz, 2H), 2.99 – 2.89 (m, 1H), 2.89 – 2.77 (m, 1H), 1.97 – 1.90 (m, 1H), 1.89 – 1.82 (m, 1H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 109.8 (CH), 71.3 (CH_2), 69.1 (CH_2), 45.6 (CH), 44.8 (CH), 29.2 (CH_2), 24.7 (CH_2) ppm; **HRMS** (EI) m/z: [M^+-H^+] calc'd for $C_7H_{10}BrO_2$ 204.9864; Found 204.9832.



3-(bromomethyl)hexahydrofuro[2,3-b]pyran (3.3-2f)

Synthesized according to GP5. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Isolated as 24 mg of clear oil (54 %, 89:11 dr).

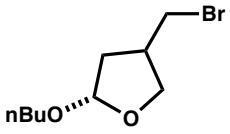
IR (neat, cm^{-1}): 2937 (m), 2872 (m), 2360 (s), 2341 (m), 1148 (m), 1048 (m), 1024 (vs); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.26 (d, *J* = 3.7 Hz, 1H), 5.05 (d, *J* = 3.7 Hz, 0.09 H, **minor diastereoisomer**) 4.04 (t, *J* = 8.3 Hz, 1H), 3.84 – 3.72 (m, 2H), 3.62 (dtd, *J* = 11.3, 3.9, 1.5 Hz, 1H), 3.48 – 3.36 (m, 2H), 2.83 (pd, *J* = 8.2, 6.4 Hz, 1H), 2.15 (dtd, *J* = 9.8, 6.4, 3.6 Hz, 1H), 1.84 – 1.73 (m, 1H), 1.62 – 1.55 (m, 2H), 1.54 – 1.46 (m, 1H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 101.7 (CH), 69.3 (CH_2), 61.4 (CH_2), 43.8 (CH), 37.6 (CH), 30.7 (CH_2), 22.8 (CH_2), 19.0 (CH_2) ppm; **HRMS** (EI) m/z: [M^+-HBr] calc'd for $C_8H_{12}O_2$ 140.0871; Found 140.0837.



3-(bromomethyl)-3-methylhexahydro-4H-furo[2,3-b]pyran (3.3-2g)

Synthesized according to GP5. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combine. Isolated as 16 mg of clear oil (34%, 93:7 dr).

IR (neat, cm^{-1}): 2932 (m), 2870 (m), 1383 (m), 1241 (m), 1142 (s), 1089 (s), 1044 (s), 1024 (vs), 971 (s), 929 (s), 891 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.37 (d, *J* = 3.8 Hz, 1H), 4.01 (d, *J* = 8.5 Hz, 1H), 3.81 – 3.73 (m, 1H), 3.61 – 3.54 (m, 3H), 3.42 (d, *J* = 10.0 Hz, 1H), 1.96 – 1.82 (m, 2H), 1.62 – 1.51 (m, 3H), 1.29 (s, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 101.8 (CH), 75.6 (CH_2), 61.6 (CH_2), 45.3 (C), 44.11 (CH), 39.6 (CH_2), 24.2 (CH_3), 22.8 (CH_2), 20.3 (CH_2) ppm; **HRMS** (ESI) m/z: [M^++Na^+] calc'd for $C_9H_{15}BrO_2Na$ 257.0148; Found 257.0153.



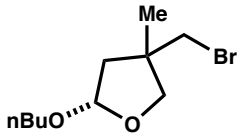
3-(bromomethyl)-2-butoxytetrahydrofuran (3.3-2h)

Synthesized according to GP5. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Isolated as 20 mg of a clear oil (42%, 5:1 d.r.).

IR (neat, cm^{-1}): 2956 (s), 2925 (vs), 2885 (s), 1464 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.14 (dd, *J* = 5.3, 1.6 Hz, 1H), 4.05 (ddd, *J* = 10.7, 8.8, 7.4 Hz, 1H), 3.75 – 3.61 (m, 2H), 3.56 – 3.43 (m, 2H), 3.40 – 3.31 (m, 2H), 2.90 – 2.83 (m, 0.2 H, **minor diastereoisomer**) 2.75 – 2.63 (m, 1H, **major diastereoisomer**), 2.21 (ddd, *J* = 13.5, 9.7, 5.3 Hz, 1H, **major diastereoisomer**), 2.09 (ddd, *J* = 13.5, 9.7, 5.3 Hz, 0.2 H, **minor diastereoisomer**) 1.78 (ddd, *J* = 13.6, 4.5, 1.5 Hz, 0.2H, **minor diastereoisomer**) 1.72 (ddd, *J* = 13.6, 4.5, 1.5 Hz, 1H, **major diastereoisomer**), 1.59 – 1.49 (m, 3H), 1.35 (dtd, *J* = 15.4, 7.7, 5.2 Hz, 3H), 0.91 (td, *J* = 7.4, 1.9 Hz, 4H) ppm;

Major diastereoisomer: **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 104.0 (CH), 71.2 (CH_2), 67.2 (CH_2), 40.8 (CH), 38.4 (CH_2), 35.8 (CH_2), 31.8 (CH_2), 19.4 (CH_2), 13.8 (CH_3) ppm; **Minor diastereoisomer**:**^{13}C NMR** (101 MHz, $CDCl_3$) δ = 104.0 (CH), 70.4 (CH_2), 67.1 (CH_2), 40.0 (CH), 38.5 (CH_2), 36.0 (CH_2), 31.8 (CH_2), 19.4 (CH_2), 13.8 (CH_3) ppm;

HRMS (ESI) m/z: [M^++Na] calc'd for $C_9H_{17}BrO_2Na$ 259.0304; Found 259.0310.

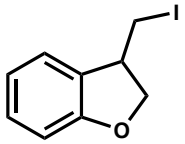


3-(bromomethyl)-2-butoxy3-methyltetrahydrofuran (3.3-2i)

Synthesized according to GP5. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Isolated as 12 mg of a clear oil (23%, 90:10 d.r.).

IR (neat, cm^{-1}): 2958 (m), 2931 (m), 2869 (m), 1458 (m), 1443 (m), 1380 (m), 1250 (m), 1098 (s), 1084 (s), 1030 (vs), 1016 (vs), 923 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.17 (dd, *J* = 5.3, 2.3 Hz, 1H, **major diastereoisomer**), 5.14 (dd, *J* = 5.3, 2.3 Hz, 0.2 H, **minor diastereoisomer**) 3.85 (d, *J* = 8.7 Hz, 1H, **major diastereoisomer**), 3.80 (d, *J* = 8.7 Hz, 0.2 H, **minor diastereoisomer**), 3.69 – 3.63 (m, 1H), 3.61 – 3.57 (m, 2H), 3.52 (d, *J* = 9.8 Hz, 1H), 3.39 – 3.32 (m, 1H), 1.98 (d, *J* = 5.3 Hz, 0.2 H, **minor diastereoisomer**), 1.95 (d, *J* = 5.3 Hz, 1H, **major diastereoisomer**), 1.92 (d, *J* = 2.3 Hz, 1H, **major diastereoisomer**), 1.88 (d, *J* = 2.3 Hz, 0.2 H, **minor diastereoisomer**), 1.55 – 1.51 (m, 2H), 1.41 – 1.31 (m, 3H), 1.29 (s, 0.6 H, **minor diastereoisomer**), 1.25 (s, 3H, **major diastereoisomer**), 0.92 (t, *J* = 7.4 Hz, 4H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 104.6 (CH, **major diastereoisomer**) 104.5 (CH, **minor diastereoisomer**), 76.4 (CH_2), 67.4 (CH_2), 45.2 (CH_2), 43.5 (C) 43.0 (CH_2), 31.8

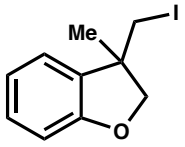
(CH_2), 24.8 (CH_3), 19.4 (CH_2), 13.8 (CH_3) ppm; **HRMS** (ESI) m/z: [M^+-C4H9O] calc'd for $C_6H_{10}BrO$ 176.9915; Found 176.9910.



3-(iodomethyl)-2,3-dihydrobenzofuran (3.3-2m)

Synthesized according to GP6. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Isolated as 32 mg of a yellow oil (62%) & 0.1367 g (53 %) when performed in a 1 mmol scale.

IR (neat, cm^{-1}): 2965 (m), 2887 (m), 1596 (m), 1479 (s), 1461 (s), 1229 (s), 1161 (m), 1100 (m), 965 (s), 842 (m), 746 (vs); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.21 (td, *J* = 7.6, 5.8 Hz, 2H), 6.93 – 6.86 (m, 1H), 6.81 (d, *J* = 7.9 Hz, 1H), 4.65 (t, *J* = 9.1 Hz, 1H), 4.34 (dd, *J* = 9.4, 5.5 Hz, 1H), 3.85 (tt, *J* = 9.5, 4.9 Hz, 1H), 3.46 (dd, *J* = 9.9, 4.3 Hz, 1H), 3.22 (t, *J* = 9.9 Hz, 1H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 160.1 (C), 129.3 (CH), 128.7 (C), 124.3 (CH), 120.6 (CH), 110.2 (CH), 77.6 (CH_2),44.8 (CH), 9.0 (CH_2) ppm; **HRMS** (EI) m/z: [M^+] calc'd for C_9H_9IO 259.9698; Found 259.9713.

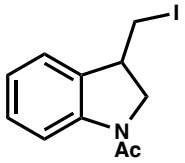


3-(iodomethyl)-3-methyl-2,3-dihydrobenzofuran (3.3-2n)

Synthesized according to GP6. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Isolated as 25 mg of a yellow oil (45%).

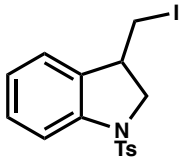
IR (neat, cm^{-1}):2962 (m), 2924 (m), 2879 (m), 1596 (s), 1478 (vs), 1459 (s), 1209 (vs), 1016 (s), 975 (vs), 838 (s), 747 (vs); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.19 (ddd, *J* = 8.0, 7.4, 1.4 Hz, 1H), 7.12 (ddd,

J = 7.4, 1.4, 0.6 Hz, 1H), 6.91 (td, *J* = 7.4, 1.0 Hz, 1H), 6.81 (dt, *J* = 8.0, 0.8 Hz, 1H), 4.49 (d, *J* = 9.1 Hz, 1H), 4.17 (dt, *J* = 9.1, 0.6 Hz, 1H), 3.39 (s, 2H), 1.52 (s, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 159.5 (C), 131.6 (C), 129.2 (CH), 122.7 (CH), 120.7 (CH), 110.3 (CH), 82.9 (CH_2), 45.8 (C), 25.3 (CH_3), 18.2 (CH_2) ppm; **HRMS** (EI) m/z: [M^+] calc'd for $C_{10}H_{11}IO$ 274.9855; Found 274.9889.



1-(3-(iodomethyl)indolin-1-yl)ethan-1-one (3.3-2o)

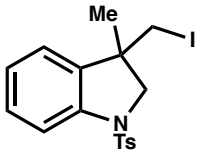
Synthesized according to GP6. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Isolated as 33 mg of a yellow oil (54%). **IR** (neat, cm^{-1}): 2959 (m), 2925 (m), 1662 (vs), 1596 (s), 1481 (vs), 1462 (m), 1402 (vs), 1344 (m), 1287 (m), 755 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.20 (d, *J* = 8.1 Hz, 1H), 7.31 – 7.27 (m, 1H), 7.19 (d, *J* = 7.4 Hz, 1H), 7.05 (td, *J* = 7.5, 1.1 Hz, 1H), 4.21 (dd, *J* = 10.7, 9.2 Hz, 1H), 3.84 (dd, *J* = 10.7, 5.2 Hz, 1H), 3.76 (tt, *J* = 9.2, 4.3 Hz, 1H), 3.52 (dd, *J* = 10.1, 3.7 Hz, 1H), 3.19 (t, *J* = 9.9 Hz, 1H), 2.26 (s, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 168.6 (C), 142.9 (C), 132.3 (C), 129.0 (CH), 123.8 (CH), 123.8 (CH), 117.4 (CH), 56.2 (CH_2), 42.8 (CH), 24.3 (CH_3), 9.9 (CH) ppm; **HRMS** (EI) m/z: [M^+] calc'd for $C_{11}H_{12}INO$ 300.9964; Found 300.9948.



3-(iodomethyl)-1-tosylindoline (3.3-2p)

Synthesized according to GP6. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Isolated as 51 mg of white solid (62%).

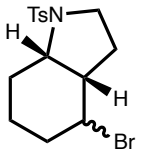
IR (neat, cm^{-1}): 2953 (m), 2923 (s), 2854 (m), 1599 (m), 1477 (m), 1461 (m), 1355 (s), 1167 (vs), 1108 (m), 1092 (m), 756 (m), 664 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.72 – 7.61 (m, 3H), 7.31 – 7.19 (m, 3H), 7.14 – 6.97 (m, 2H), 4.11 – 3.99 (m, 1H), 3.79 (ddd, *J* = 11.4, 5.0, 1.6 Hz, 1H), 3.53 – 3.37 (m, 1H), 3.25 – 3.16 (m, 1H), 2.65 (td, *J* = 10.1, 1.5 Hz, 1H), 2.37 (s, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 144.3 (C), 142.0 (C), 133.8 (C), 132.9 (C), 129.8 (2 X CH), 129.1 (CH), 127.3 (2 X CH), 124.5 (CH), 123.9 (CH), 115.5 (CH), 56.5 (CH_2), 43.0 (CH), 21.5 (CH_3), 8.7 (CH_2) ppm; **HRMS** (EI) m/z: [M^+] calc'd for $C_{16}H_{16}INO_2S$ 412.9946; Found 412.9923.



3-(iodomethyl)-3-methyl-1-tosylindoline (3.3-2q)

Synthesized according to GP6. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Isolated as 38 mg of white solid oil (45%).

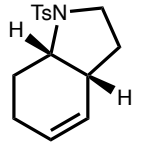
IR (neat, cm^{-1}): 2955 (m), 2920 (s), 2854 (m), 1601 (m), 1480 (m), 1455 (m), 1361 (s), 1176 (vs), 1111 (m), 1097 (m), 758 (m), 669 (s); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.75 – 7.64 (m, 3H), 7.29 – 7.24 (m, 3H), 7.04 – 7.00 (m, 2H), 3.97 (d, *J* = 11.1 Hz, 1H), 3.57 (dd, *J* = 11.1, 1.1 Hz, 1H), 3.14 (dd, *J* = 10.1, 1.1 Hz, 1H), 2.82 (d, *J* = 10.1 Hz, 1H), 2.37 (s, 3H), 1.32 (s, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 144.3 (C), 141.2 (C), 135.4 (C), 134.0 (C), 129.8 (2 X CH), 129.1 (CH) 127.3 (2 X CH) 123.9 (CH), 122.9 (CH), 115.2 (CH), 62.2 (CH_2), 44.2 (C), 26.0 (CH_3), 21.6 (CH_3), 18.2 (CH_2) ppm; **HRMS** (ESI) m/z: [M^++Na_+] Calc'd for $C_{17}H_{18}INO_2SNa$ 450.000; Found 449.9995.



(3aS,7aS)-4-bromo-1-tosyloctahydro-1H-indole (3.3-2r)

Synthesized according to GP5. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Isolated as 21 mg of a yellow oil as a 1:1 mixture of diastereoisomers (29%). Characterized according to NMR comparaison.[7b]

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.73 – 7.67 (m, 2H), 7.35 – 7.28 (m, 2H), 4.18 (dt, *J* = 12.5, 5.1 Hz, 1H), 3.72 (dt, *J* = 11.1, 6.3 Hz, 1H), 3.61 – 3.54 (m, 1H), 3.14 (td, *J* = 9.8, 8.4 Hz, 1H), 2.44 (s, 3H), 2.20 – 2.08 (m, 1H), 2.08 – 1.96 (m, 4H), 1.83 – 1.69 (m, 2H), 1.43 – 1.20 (m, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 143.4 (C), 135.3 (C), 129.8 (2 X CH), 127.2 (2 X CH), 59.8 (CH), 50.0 (CH), 46.0 (CH_2), 45.4 (CH), 31.8 (CH_2), 29.0 (CH_2), 25.8 (CH_2), 24.2 (CH_3), 21.5 (CH_2) ppm; **HRMS** (EI) m/z: [M^+] calc'd for $C_{15}H_{20}BrNO_2S$ 357.0398; Found 357.03911.

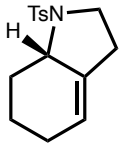


(3aR,7aS)-1-tosyl-2,3,3a,6,7,7a-hexahydro-1H-indole (3.3-2r')

Synthesized according to GP5. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Isolated as 21 mg of a yellow oil as a 1:1 mixture of 3.3-2r' and 3.3-2r'' (29%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.73 – 7.65 (m, 2H), 7.32 – 7.25 (m, 2H), 5.78 – 5.71 (m, 1H), 5.50 – 5.42 (m, 1H), 3.70 – 3.63 (m, 1H), 3.55 – 3.46 (m, 1H), 3.46 – 3.39 (m, 1H), 3.16 – 3.08 (m, 1H), 2.40 (s, 3H), 2.34 – 2.23 (m, 1H), 2.14 – 2.04 (m, 1H), 2.03 – 1.91 (m, 1H), 1.84 – 1.67 (m, 1H), 1.61

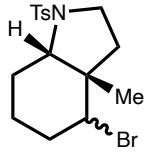
– 1.48 (m, 1H), 1.40 – 1.26 (m, 1H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 143.2 (C), 134.8 (C), 129.6 (2 X CH), 129.5 (CH), 127.4 (2 X CH), 127.3 (CH), 58.4 (CH), 47.9 (CH_2), 38.9 (CH), 30.7 (CH_2), 27.20 (CH_2), 22.6 (CH_2), 21.6 (CH_3) ppm; **HRMS** (EI) m/z: [M^+] calc'd for $C_{15}H_{19}NO_2S$ 277.1136; Found 277.1135.



1-tosyl-2,3,5,6,7,7a-hexahydro-1H-indole (3.3-2r'')

Synthesized according to GP5. Isolated as 21 mg of a yellow oil as a 1:1 mixture of 3.3-2r' and 3.3-2r'' (29%).

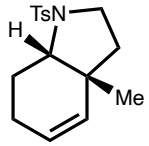
^{1}H NMR (400 MHz, $CDCl_3$) δ =7.73 – 7.65 (m, 2H), 7.32 – 7.25 (m, 2H), 5.50 – 5.42 (m, 1H), 3.70 – 3.63 (m, 1H), 3.55 – 3.46 (m, 1H), 3.46 – 3.39 (m, 1H), 3.16 – 3.08 (m, 1H), 2.40 (s, 3H), 2.34 – 2.23 (m, 1H), 2.14 – 2.04 (m, 1H), 2.03 – 1.91 (m, 2H), 1.84 – 1.67 (m, 1H), 1.61 – 1.48 (m, 1H), 1.40 – 1.26 (m, 1H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 143.3 (C), 143.0 (C), 134.5 (C), 128.6 (2 X CH), 126.7 (2 x CH), 122.1 (CH), 58. 7 (CH), 47.1 (CH_2), 29.9 (CH_2), 26.3 (CH_2), 24.3 (CH_2), 23.2 (CH_2), 21.6 (CH_3) ppm; **HRMS** (EI) m/z: [M^+] calc'd for $C_{15}H_{19}NO_2S$ 277.1136; Found 277.1135.



(3aS,7aS)-4-bromo-3a-methyl-1-tosyloctahydro-1H-indole (3.3-2s)

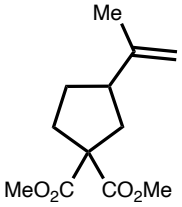
Synthesized according to GP5. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Isolated as 31 mg of a yellow oil as a 2:1 mixture of diastereoisomers (41%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.74 – 7.69 (m, 2H, **major diasteroisomer**), 7.69 – 7.65 (m, 1H, **minor diastereoisomer**), 7.35 – 7.32 (m, 1H, **minor diastereoisomer**), 7.32 – 7.27 (m, 2H, **major diastereoisomer**), 4.27 (dd, *J* = 11.9, 4.2 Hz, 0.5H, **minor diastereoisomer**), 3.94 (dd, *J* = 12.6, 4.8 Hz, 1H, **major diastereoisomer**), 3.59 – 3.53 (m, 0.5H, **minor diastereoisomer**), 3.53 – 3.45 (m, 1H, **major diastereoisomer**), 3.39 (dt, *J* = 10.6, 5.2 Hz, 1H, **major diastereoisomer**), 3.36 – 3.26 (m, 0.5H, **minor diastereoisomer**), 3.19 (td, *J* = 10.0, 7.7 Hz, 1H, **major diastereoisomer**), 2.99 (d, *J* = 3.4 Hz, 0.5H, **minor diastereoisomer**), 2.44 (s, 1.5H, **minor diastereoisomer**), 2.42 (s, 3H, **major diastereoisomer**), 2.19 – 2.08 (m, 2H, **major diastereoisomer**), 2.19 – 2.08 (m, 1H, **minor diastereoisomers**) 1.95 – 1.77 (m, 2H), 1.70 – 1.58 (m, 2H, **major diastereoisomer**), 1.70 – 1.58 (m, 1H, **major diastereoisomers**) 1.44 – 1.30 (m, 2H), 1.24 – 1.09 (m, 2H), 1.06 (s, 1.5H, **minor diastereoisomer**), 0.70 (s, 3H, **major diastereoisomer**) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 143.6 (C, **minor diastereoisomer**), 143.2 (C, **major diastereoisomer**), 135.9 (C, **major diastereoisomer**), 133.4 (C, **minor diastereoisomer**), 129.7 (2 X CH, **minor diastereoisomer**), 129.59 (2 X CH, **major diastereoisomer**), 127.6 (2 X CH, **minor diastereoisomer**), 66.2 (CH, **minor diastereoisomer**), 65.4 (CH, **major diastereoisomer**), 60.0 (CH, **major diastereoisomer**), 58.5 (CH, **minor diastereoisomer**), 47.0 (CH_2, **major diastereoisomer**), 46.8 (CH_2, **minor diastereoisomer**), 46.6 (CH_2, **minor diastereoisomer**), 44.0 (CH_2, **major diastereoisomer**), 35.0 (CH_2, **minor diastereoisomer**), 33.8 (CH_2, **major diastereoisomer**), 33.3 (CH_2, **minor diastereoisomer**), 31.6 (CH_2, **major diastereoisomer**), 31.1 (CH_2, **major diastereoisomer**), 25.46 (CH_3), 24.86 (CH_2, **minor diastereoisomer**), 24.2 (CH_2, **major diastereoisomer**), 21.6 (CH_3, **minor diastereoisomer**), 21.5 (CH_3, **major diastereoisomer**), 20.1 (C) ppm; **HRMS** (EI) m/z: [M^+] calc'd for $C_{16}H_{22}BrNO_2S$ 371.0555; Found 371.0565.



(3aR,7aS)-3a-methyl-1-tosyl-2,3,3a,6,7,7a-hexahydro-1H-indole (3.3-2s')

Synthesized according to GP5. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Isolated as 31 mg of a yellow oil (58%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.75 – 7.69 (m, 2H), 7.33 – 7.27 (m, 2H), 5.71 (dt, *J* = 10.0, 3.8 Hz, 1H), 5.31 – 5.24 (m, 1H), 3.35 – 3.26 (m, 3H), 2.42 (s, 3H), 2.21 – 2.11 (m, 1H), 2.02 – 1.79 (m, 4H), 1.59 (ddd, *J* = 12.0, 6.5, 5.3 Hz, 1H), 0.74 (s, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 143.1 (C), 134.9 (C), 132.4 (CH), 129.6 (2 X CH), 127.4 (2 X CH), 127.3 (CH), 64.5 (CH), 47.1 (CH_2), 37.5 (CH_2), 26.2 (CH_2), 25.4 (CH_3), 21.5 (CH_3), 21.3 (CH_2) ppm; **HRMS** (EI) m/z: [M^+] calc'd for $C_{16}H_{21}BrNOS$ 291.1293; Found 291.1300.

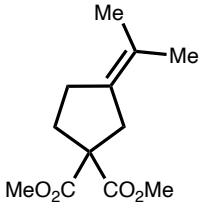


Dimethyl-3-(prop-1-en-2-yl)cyclopentane-1,1-dicarboxylate (3.3-2t)

Synthesized according to GP5. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Isolated as 34 mg of a yellow oil (75 %) in a 2:1 mixture of 3.3-2t and 3.3-2t'.

IR (neat, cm^{-1}): 2954 (m), 2873 (m), 1731 (vs), 1646 (m),1435 (s), 1247 (s), 1215 (s), 1195 (s), 1155 (s), 1099 (m), 1065 (m), 888 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.73 – 4.67 (m, 2H), 3.71 (s, 6H), 2.61 – 2.51 (m, 1H), 2.48 (ddd, *J* = 12.7, 7.2, 1.7 Hz, 1H), 2.40 – 2.28 (m, 2H), 2.21 – 2.13 (m, 1H), 1.97 (dd, *J* = 12.9, 10.9 Hz, 1H), 1.92 – 1.83 (m, 1H), 1.71 (s, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$)

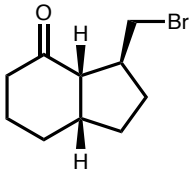
δ = 173.0 (C), 172.9 (C), 146.5 (C), 109.3 (CH_2), 59.6 (C), 52.6 (CH_3), 52.6 (CH_3), 46.4 (CH), 39.0 (CH_2), 33.7 (CH_2), 30.6 (CH_2), 21.0 (CH_3) ppm; **HRMS** (ESI) m/z: [M^++Na^+] calc'd for $C_{12}H_{18}O_4Na$ 249.1097; Found 249.1103.



Dimethyl-3-(propan-2-ylidene)cyclopentane-1,1-dicarboxylate (3.3-2t')

Synthesized according to GP5. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Isolated as 34 mg of a yellow oil (75 %) in a 2:1 mixture of 3.3-2t and 3.3-2t'.

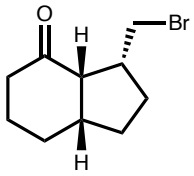
IR (neat, cm^{-1}): 2954 (m), 2873 (m), 1731 (vs), 1646 (m),1435 (s), 1247 (s), 1215 (s), 1195)s), 1155 (s), 1099 (m), 1065 (m), 888 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.72 (s, 6H), 2.86 – 2.80 (m, 2H), 2.25 – 2.22 (m, 2H), 1.62 – 1.57 (m, 6H), 1.56 – 1.50 (m, 2H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 172.4 (2 X C), 131.0 (C), 123.3 (C), 60.3 (C), 52.6 (2 X CH_3), 38.4 (CH_2), 34.0 (CH_2), 28.9 (CH_2), 21.0 (CH_3), 21.0 (CH_3) ppm; **HRMS** (ESI) m/z: [M^++Na^+] calc'd for $C_{12}H_{18}O_4Na$ 249.1097; Found 249.1103.



(3S, 3aS, 7aS)-3-(bromomethyl)octahydro-4H-inden-4-one (3.3-4)

Synthesized according to GP5. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combine. Isolated as a mixture of diastereoisomers. (41%, d.r. 1:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.47 – 3.29 (m, 2H), 2.77 – 2.66 (m, 2H), 2.66 – 2.57 (m, 1H), 2.51 – 2.38 (m, 1H), 2.38 – 2.26 (m, 1H), 2.19 – 1.97 (m, 3H), 1.97 – 1.84 (m, 3H), 1.80 – 1.67 (m, 1H), 1.67 – 1.60 (m, 1H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 213.2 (C), 50.4 (CH), 39.6 (CH_2), 39.4 (CH_2), 36.9 (CH), 31.9 (CH), 30.9 (CH_2), 30.7 (CH_2), 28.1 (CH_2), 21.9 (CH_2) ppm ; **HRMS** (ESI) m/z: [M^+] calc'd for $C_{10}H_{15}BrO$ 230.0306; Found 230.0280.



(3R, 3aS, 7aS)-3-(bromomethyl)octahydro-4H-inden-4-one (3.3-4')

Synthesized according to GP5. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined. Isolated as a mixture of diastereoisomers. (41%, d.r. 1:1)

^{1}H NMR (400 MHz, $CDCl_3$) 3.32 (t, *J* = 7.0 Hz, 2H), 2.77 (td, *J* = 9.3, 3.0 Hz, 1H), 2.71 – 2.62 (m, 1H), 2.49 – 2.33 (m, 2H), 2.33 – 2.19 (m, 2H), 2.05 – 1.88 (m, 4H), 1.86 – 1.77 (m, 1H), 1.77 – 1.68 (m, 1H), 1.65 – 1.58 (m, 2H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 215.1 (C), 43.0 (CH), 42.4 (CH), 41.0 (CH_2), 38.9 (CH_2), 36.4 (CH), 30.9 (CH_2), 29.3 (CH_2), 26.2 (CH_2), 22.3 (CH_2) ppm ; **HRMS** (ESI) m/z: [M^+] calc'd for $C_{10}H_{15}BrO$ 230.0306; Found 230.0280.

3.8- References

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Chapter 4 – ALKYLATION AND REDUCTION OF HETEROARENES WITH ALCOHOLS USING PHOTOREDOX CATALYZED HYDROGEN ATOM TRANSFER VIA CHLORINE RADICAL GENERATION

Zidan, M.; Morris, A. O.; McCallum, T.; Barriault, L., The Alkylation and Reductions of Heteroarenes with Alcohols using Photoredox Catalyzed Hydrogen Atom Transfer via Chlorine Atom Generation, *Eur. J. Org. Chem.* **2020**, *2020*, 1453-1458.

4.1- Abstract

Radical additions to heteroaromatic bases are frequently employed for the rapid synthesis of complex products using C–H functionalization strategies. The conditions that are commonly employed are typically harsh, routinely requiring stoichiometric oxidants and other additives. In search for milder reaction environments allowing late-stage functionalization, we present the alkylation of *N*-heteroarenes using primary alcohols and ethers as radical precursors, where the corresponding alkyl radical is formed via hydrogen atom transfer process with a photoredox catalyzed chlorine atom generation as HAT agent. Furthermore, we explore the reduction of the heteroarenes in moderate to high yields when using secondary alcohols.

4.2- Introduction

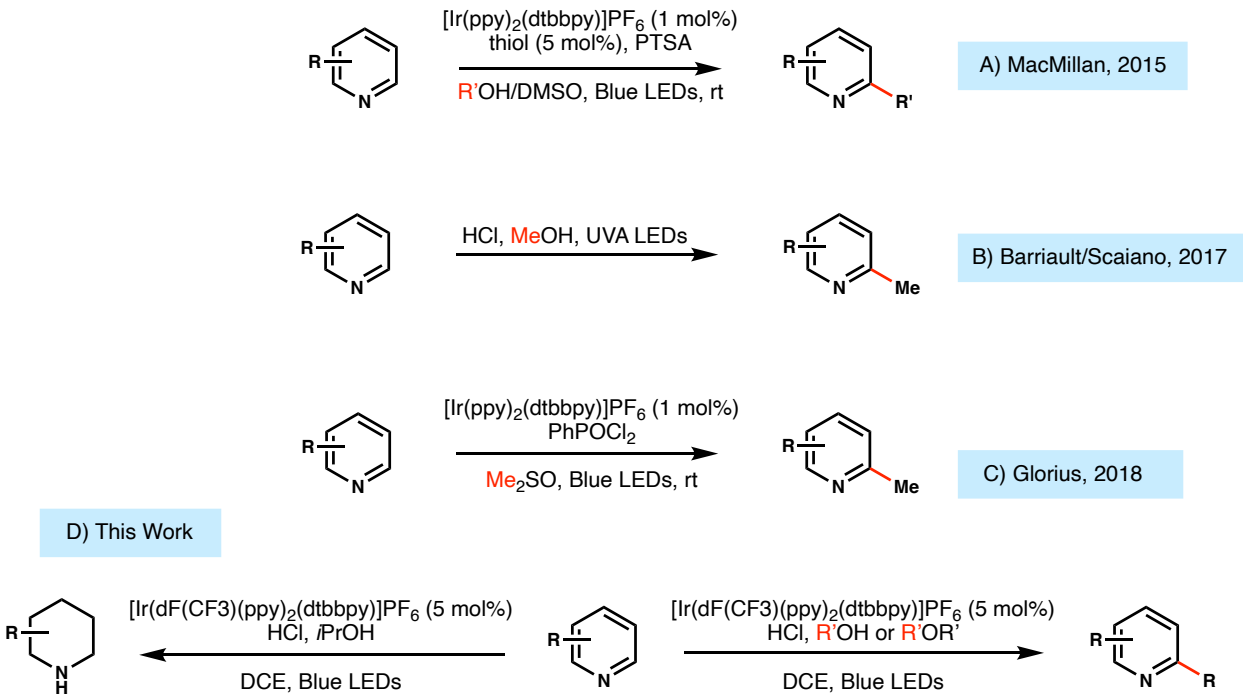
Recent advancements in photoredox catalysis have led to a rapid increase of method development in organic synthesis.[1] The use of transition metal catalysts and organic dyes in photoredox mediated processes has been proven to be an effective alternative to classical radical formation.[2] Eliminating the need for initiators, harsh reaction conditions, and stoichiometric additives has resulted in robust organic transformations that are mild and highly efficient. The conversion of photons into potential energy has captivated chemists in search of new activation models for synthesis, in by the light-harvesting biomolecules found in nature.[3]

Hydrogen atom transfer (HAT) reactions are widely used processes in synthesis and have been an emerging strategy for method development in photoredox catalysis.[4] These processes can be achieved via photocatalyst-mediated HAT with tetra-*n*-butylammonium decatungstate (TBADT)[4a-c]and Eosin Y[4d] as well as in dual photoredox catalysis processes using additives/catalysts such as thiols, amines, amides, and phosphates.[4e-s] The catalytic generation of atomic halogens (chlorine or bromine) for HAT processes in synthetic applications is largely unexplored. Recently, Molander and Doyle have made advances in Ir^{III}/Ni^{0} dual photoredox HAT catalysis that have allowed the cross-coupling of alkanes with haloarenes through the generation of atomic halogens.[5] Our group and others have explored the photoredox mediated catalytic generation of chlorine atoms for the functionalization of a variety of alkanes.[6] Herein, we describe the photoredox mediated activation of alcohols and ethers using an Ir-based polypyridyl complex for the alkylation and reduction of heteroarenes. The transformation is mediated by the generation of chlorine atoms, a highly reactive intermediate seldom utilized in organic synthesis that undergoes HAT processes.

The alkylation of electron-deficient heteroarenes has been developed by Minisci.[7] The initial protocol utilized silver-mediated decarboxylation processes to produce alkyl radicals. Per-sulfate additives were necessary to oxidize the silver catalyst as well as the corresponding radical cation subsequent to radical addition to the heteroarene.

Although great success has been achieved with this strategy, many cases suffer from lower yields and the formation of multiple by-products. To circumvent these restrictions and harsh conditions, photoredox mediated strategies have been employed to create broad methodologies for the alkylation of heteroarenes.[8]

The use of alcohols in the photo-mediated alkylation of heteroarenes was developed over half a century ago, however, these protocols were met with low yields and functionality tolerance due to the requirement of forcing conditions.[9] In 2015, MacMillan and co-workers used the concept of polarity reversal catalysis to alkylate heteroarenes using alcohols (**Scheme 4.1A**).[10a] In a collaborative effort with the Scaiano group, we detailed the photo-mediated (UVA) methylation of heteroarenes using MeOH as alkylating agent with no need for extraneous additives, where a report from the Li group also appeared during this time (**Scheme 4.1B**).[6a,10b] Most recently, Glorius and co-workers has developed a photoredox catalyzed methylation process using DMSO as the alkylating agent (**Scheme 4.1C**).[10c]

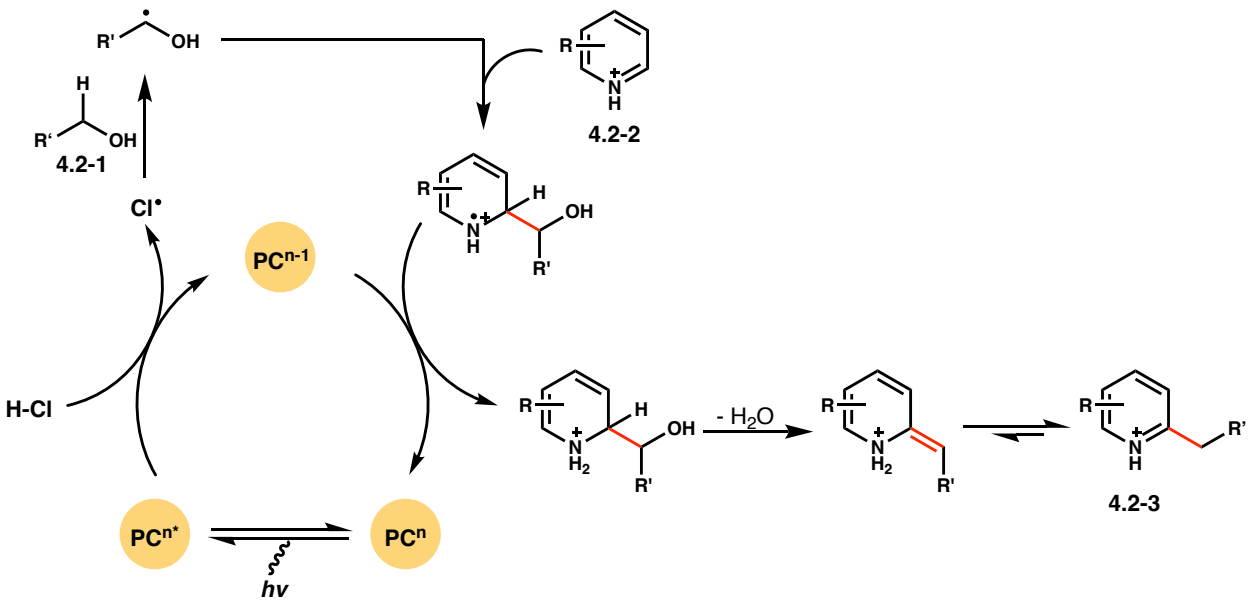


Scheme 4.1- Past and present work in photo-mediated catalytic alkylation of heteroarenes.

In order to overcome the challenges encountered in our previous methodology, we reported the development of a photoredox process that improves on several factors: 1) using visible light mediated activation to negate UV-mediated decomposition pathways, 2) having

alcohol as a reagent avoids its use as a solvent, and 3) increasing the scope of the transformation from methanol to longer chain alcohols.

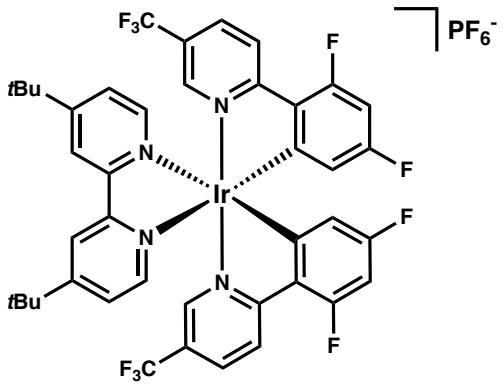
We envisioned alkylation of heteroarenes via a photocatalyzed HAT reaction using organic dyes or Ir-based polypyridyl complexes. Mechanistically, we hypothesized that a redox neutral alkylation strategy that merged photo-mediated single electron transfer (SET) and HAT processes would allow for the desired methodological improvements (**Scheme 4.2**). We propose that upon excitation of the photocatalyst PC^{n}* would go through a reductive quench to oxidize chloride into a chlorine atom. The latter would then abstract a hydrogen atom from the alkylating agent **4.2-1** at the most hydridic position. The resulting nucleophilic radical could then add to the heteroarene to generate nitrogen centered radical intermediate, where the radical cation that is produced would get reduced by the PC^{n-1} species, hydro-alkylated heteroarene. After the elimination of water, the corresponding enamine will tautomerize to give the desired product **4.2-3**.



Scheme 4.2- Proposed mechanism for the photo-mediated alkylation of heteroarenes.

4.3- Results and Discussion

After initial screening of different organic photocatalysts such as substituted diphenyl quinolines and acridinium salts, we found that the Ir-based polypyridyl complex, [Ir(dF(CF_3)ppy)$_2$(dtbbpy)]PF6 (**4.3-1**) (**Figure 4.1**), proved to be compatible in the methodology.



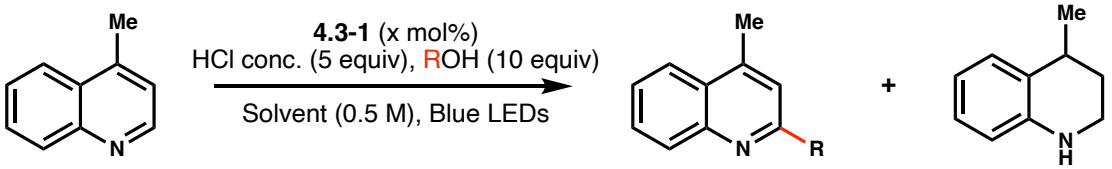
4.3-1
[Ir(dF(CF_3)ppy)$_2$(dtbbpy)]PF_6

Figure 4.1- Ir-based polypyridyl catalyst used in the photo-mediated alkylation of heteroarenes.

Using *i*BuOH (**4.3-3a**) as an alkylating agent, we began the optimization of this process by exploring the catalyst loading necessary to achieve the desired reactivity (**Table 4.1**). Using 5 mol% of **4.3-1** with lepidine (**4.3-2a**) in the presence of conc. HCl (5 equiv.) and **4.3-3a** (10 equiv.) in DCE gave a 50% yield of **4.3-4aa** and 28% of the reduced starting material **4.3-5a** (**Table 4.1, Entry 1**). Reduction of the catalyst loading to 2 mol% did not change the amount of by-product formed (**Table 4.1, Entry 2**). The reaction was performed in other solvents such as $CHCl_3$, MeCN and DCM, but lower yields were obtained (**Table 4.1, Entries 3–5**). Interestingly, using DMSO as solvent did not produce the desired alkylated product, but instead the methylated product **4.3-4ac** in 41 % (**Table 4.1, Entry 6**). It was hypothesized that DMSO acts as alkylating agent, and it could be reacting through a similar pathway as described by Glorious and co-workers.[10c] Trying to avoid product **4.3-5a** we changed the alkylating agent from a branched *i*BuOH **4.3-3a** to linear

*n*BuOH **4.3-3b**. It proved to be successful and **4.3-5a** was lowered to 7 % and **4.3-4ab** increased to 64 % yield (49 % isolated) (**Table 4.1, Entry 7**). Lowering the acid and alcohol equivalents did not favor the reaction and full conversion was achieved only when an excess of conc. HCl and alcohol **4.3-3** was employed. Finally, control experiments showed that light and photocatalyst and heat were essential for the reaction to progress (**Table 4.1, Entries 8 and 9**).

Table 4.1- Optimization of reaction conditions of the photo-mediated alkylation of heteroarenes.



4.3-2a **4.3-4** **4.4-5a**

Entry	**4.3-1** (x mol%)	Solvent	**4.3-3** ROH (10 equiv)	**4.3-4** (%)[a]	**4.3-5a** (%)
1	5	DCE	**4.3-3a** R = *i*-butyl	**4.3-4aa** 50	28
2	2	DCE	**4.3-3a**	**4.3-4aa** 41	30
3	5	$CHCl_3$	**4.3-3a**	**4.3-4aa** 38	21
4	5	MeCN	**4.3-3a**	**4.3-4aa** 27	10
5	5	DCM	**4.3-3a**	**4.3-4aa** 41	10
6	5	DMSO	**4.3-3a**	**4.3-4ac** 41	0
7	5	DCE	**4.3-3b** R = *n*-butyl	**4.3-4ab** 64 (49)	7
8	0	DCE	**4.3-3b**	0	0
9[b]	5	DCE	**4.3-3b**	0	0
10[c]	5	DCE	**4.3-3b**	0	0
11[d]	5	DCE	**4.3-3b**	0	0

[a] NMR yield using mesitylene as internal standard, in parenthesis is the isolated yield. [b] In absence of light and heat [c] In the absence of light, heating to 80°C. [d] At room temperature.

After establishing the reaction conditions, we investigated the reaction scope using different primary alcohols **4.3-3a-g** and ethers **4.3-3h–k** with lepidine **4.3-2a** to produce alkylated lepidines **4.3-4aa-al** (**Figure 4.2**). Since the reaction did not need the alkylating agent as solvent, longer chained alcohols were compatible with this methodology; only primary and secondary alcohols could be used in accordance with the proposed mechanism. Starting with primary alcohols, it was found that shorter chains **4.3-3c** and **4.3-3d** gave the corresponding alkylated lepidines **4.3-4ac** and **4.3-4ad** in 77 % yields whereas the longer chain alcohols **4.3-3b** and **4.3-3e** produced lepidines **4.3-4ab** and **4.3-4ae** in 49 % yields. Alkylation using branched primary alcohols such **4.3-3a** gave the desired product **4.4-4aa** in 41 % isolated yield along with a significant amount of 5a (see Table 4.1). Photoredox reactions with primary diols **4.3-3f** and **4.3-3g** provided heteroarene alkylated with alcohol chains **4.3-4af** [R = $(CH_2)_2CH_2OH$] and **4.3-4ag** [R = $(CH_2)_3CH_2OH$] in 66 % and 61 % yields, respectively. Cyclic ethers **4.3-3h** and **4.3-3i** gave **4.3-4ah** [R = $(CH_2)_3CH(OH)CH_2OH$] and **4.3-4ag** in 76 % and 71 % yields whereas acyclic **4.3-3k** ether led to the formation of **4.3-4ab** in 80 % yield. A lower yield was observed with pyran **4.3-3j**. Interestingly, the formation of **4.3-4ah** was selective as only one C-H position reacted. One can explain the exclusive regioselectivity by the subtle inductive effect of neighbouring oxygen atoms on C–H bond dissociation energy.

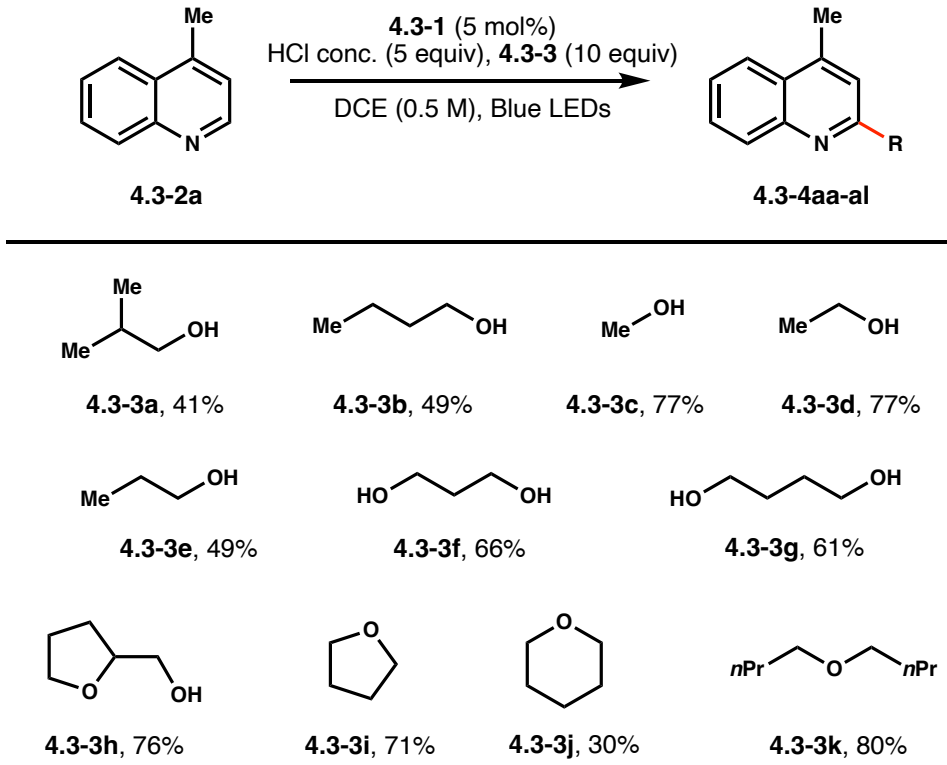


Figure 4.2- Scope of the photoredox-catalyzed alkylation of heteroarenes using alkyl alcohols and ethers.

While studying the heteroarene scope, we found that a variety of quinolines were compatible with the methodology (**Figure 4.3**). In general, the light-enabled addition of butyl to quinolines using dibutyl ether gave the desired compounds in yields ranging from 24 to 72 %. When 6-functionalized quinolines where used only degradation was observed. We found that lowering the equivalents of conc. HCl to 2 equivalents, and lowering the reaction time to 2h, the reaction successfully gave desired quinolines **4.3-4ek**–**4.3-4gk** in 24 %, 72 %, and 60 %, respectively.

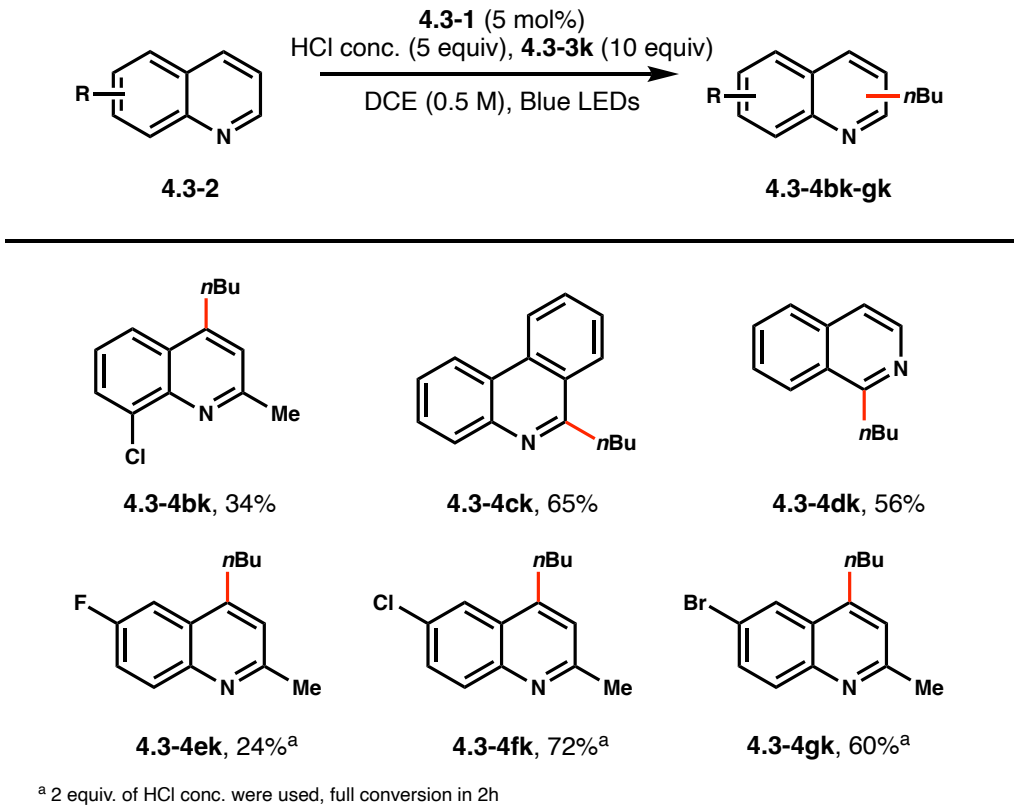


Figure 4.3- Photoredox-catalyzed alkylation of various heteroarenes.

When *i*PrOH was used as the alkylating agent, the major product was the reduced heteroarene **4.3-5**. This result led us to explore the reduction of heteroarenes using these conditions (**Figure 4.4**). It was observed that electron-poor and electron neutral quinolines gave the reduced product **4.3-5a–f** in good yields (Figure 4.4). In the case of the reduction of phenanthridine **4.3-5g**, only 15 % of **4.3-5g** was observed. This can be attributed to the highly aromatic nature of phenanthridine and its resistance to lose this aromaticity.

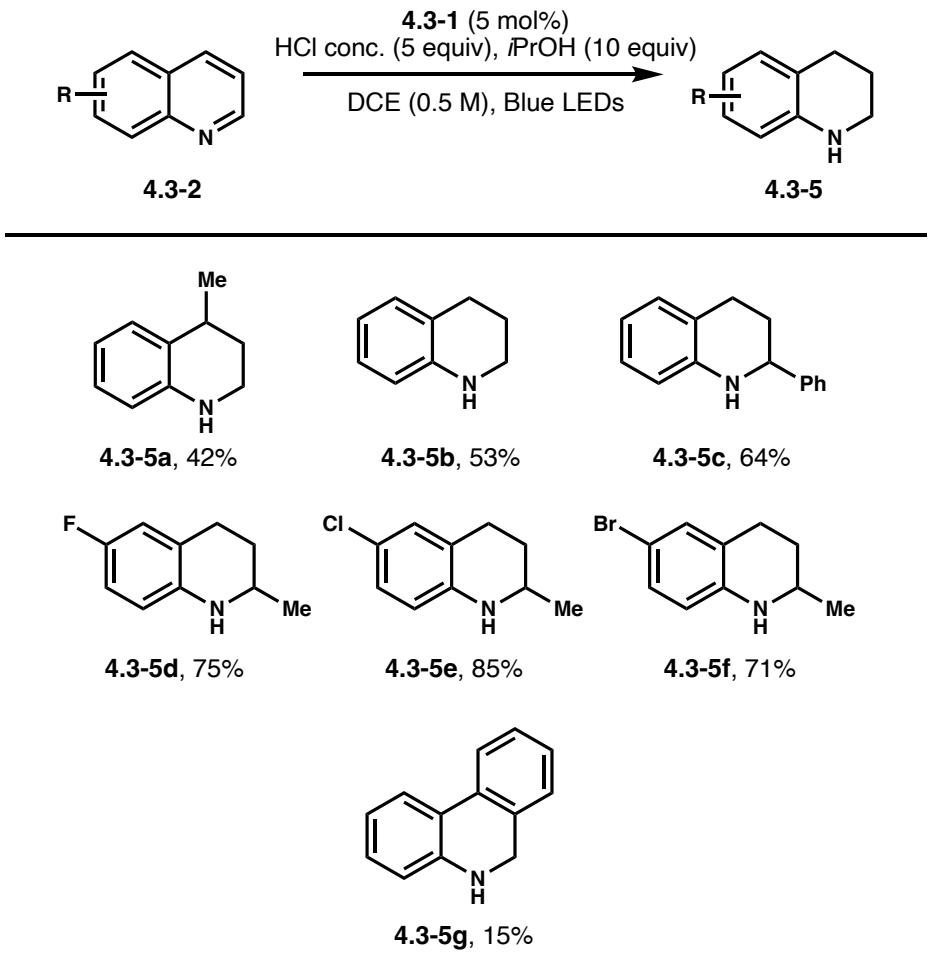
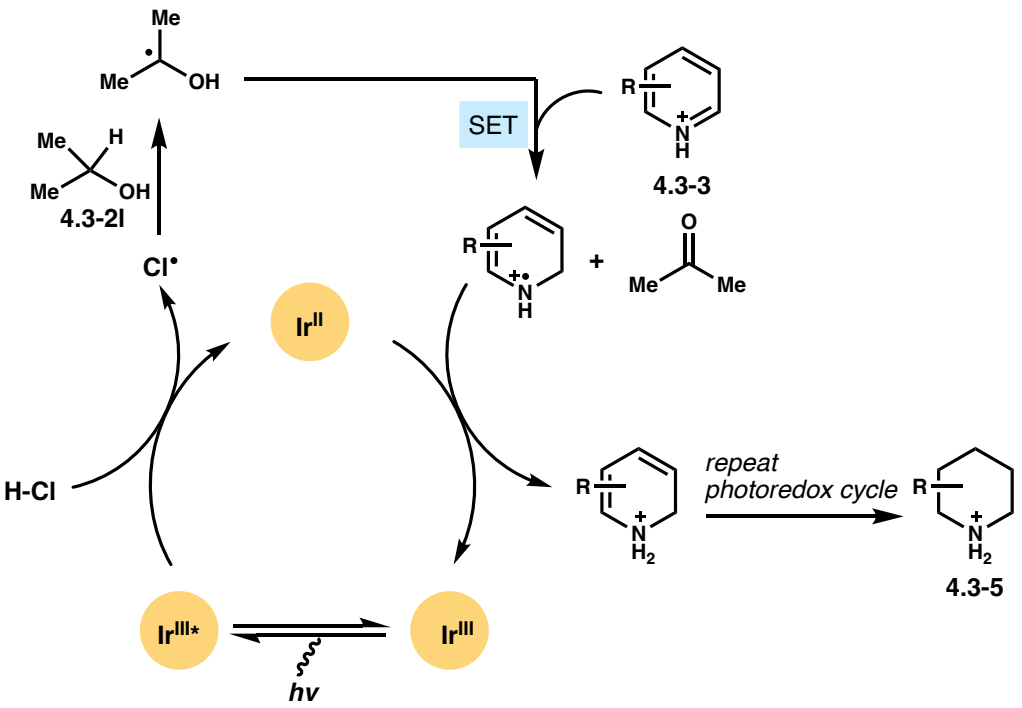


Figure 4.4- Photoredox mediated reduction of heteroarenes.

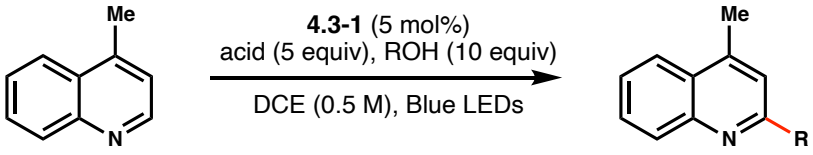
A similar mechanism to the alkylation of heteroarenes is proposed for this reaction (**Scheme 4.3**). We propose that upon excitation of the photocatalyst **4.3-1**, it would go through a reductive quench to oxidize chloride into a chlorine atom and form Ir^{II} intermediate. When the chlorine atom undergoes HAT with *i*PrOH **4.3-2l**, the corresponding ketyl radical gives an electron to the heteroarene to form nitrogen centered radical cation and acetone as the by-product. One can suggest that the reaction is driven by the strong reducing nature of the ketyl radical that is formed. Then, the Ir^{II} species will also give an electron to the heterocycle, giving a partially reduced heteroarene intermediate. In its resonance-stabilized form, the species will undergo the catalytic cycle once more to get fully reduced and form desired product **4.3-5**.



Scheme 4.3- Photoredox mediated reduction of heteroarenes mechanism.

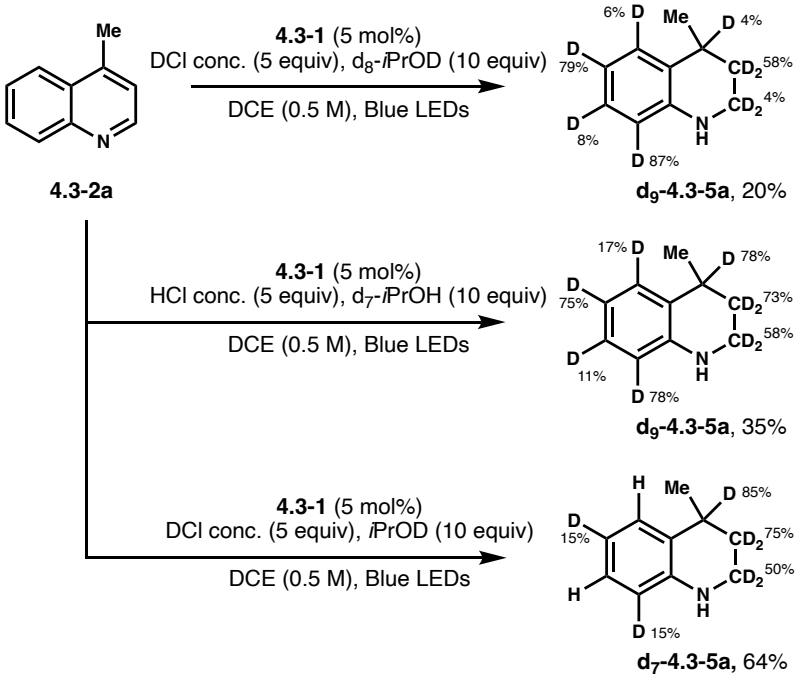
To obtain more information on the mechanism of the transformation, deuterated studies were performed (**Table 4.2**). As expected, when submitting fully deuterated conditions CD_3OD and DCl in D_2O we obtained **d_3-4.3-4ac** in 20 % yield. Using CD_3OH and HCl in H_2O the product found was **d_2-4.3-4ac** in 16 % yield. When CH_3OD with DCl in D_2O was used, **d-4.3-4ac** in 60 % yield was obtained (**Table 4.3, Entries 1–3**). These studies are in support with the proposed mechanism and the irreversible tautomerization of the enamine since no deuterium scrambling was observed. Furthermore, when a mixture of CD_3OH and CH_3OH (1:1) a ratio of products **4.3-4ac:d_2-4.3-4ac** was found (1.17:1) giving a kinetic isotope effect (KIE) of 1.17 (**Table 4.2, Entry 4**). Doing similar studies with THF gave analogous results, albeit in higher yields (**Table 4.2, Entries 5– 7**). Submitting a mixture of THF and d_8-THF (1:1) provided a mixture of **d-4.3-4ai** and **d_7-4.3-4ai** (1.19:1) in 88 % yield and provided a KIE of 1.19 (**Table 4.2, Entry 8**).

Table 4.2- Deuterium labelling experiments on the photo-mediated alkylation of heteroarenes.



4.3-2a **4.3-4**

Entry	Acid (5 equiv)	ROH (10 equiv)	**4.3-4**, yield (%)
1	DCl in D_2O	CD_3OD	**d_3-4.3-4ac**, 20
2	HCl in H_2O	CD_3OH	**d_2-4.3-4ac**, 16
3	DCl in D_2O	CH_3OD	**d-4.3-4ac**, 60
4	HCl in H_2O	CD_3OH : CH_3OH	**d_2-4.3-4ac : 4.3-4ac**, 45 KIE = 1.17
5	DCl in D_2O	d_8-THF	**d_8-4.3-4ai**, 76
6	HCl in H_2O	d_8-THF	**d_7-4.3-4ai**, 90
7	DCl in D_2O	THF	**d-4.3-4ai**, 77
8	HCl in H_2O	d_8-THF : THF	**d_7-4.3-4ai : 4.3-4ai**, 88 KIE = 1.19



Scheme 4.4- Deuterium labelling experiments in the photo-mediated reduction of heteroarenes.

Similar steps were taken to study the reaction with *i*PrOH (**Scheme 4.4**). Using fully deuterated conditions with d_8-*i*PrOD and DCl in D_2O gave product **d_9-4.3-5a** in 20 % yield. When using d_7-

*i*PrOH with HCl in H_2O, d_9-4.3-5a in 35 % yield was obtained. Finally, when *i*PrOD with DCl in D_2O was used, **d_8-4.3-5a** was observed in 64 % yield.

The amount of deuterium scrambling observed in these products could be indicative of the resonance structures possible *en route* to the fully reduced desired products. To gain insight on the nature of the photochemical transformation, Stern-Volmer quenching experiments were performed to probe the excited-state reactivity of the photocatalyst (**See 4.5- Further Information**). Evaluating the quenching rate determined by Doyle and coworkers for the Ir complex **4.3-1** (k_qTBACl = 5.3×10^4 $M^{-1}s^{-1}$), we were interested in comparing the quenching with the alcohol substrate.[6b] First, we explored the quenching of the **4.3-1-PF_6** counterion. Little quenching was observed and when plotting the corresponding Stern-Volmer data; a Stern-Volmer constant (K_{SV}) 0.038 was found. Using the excited-state lifetime ($\tau = 2.3 \times 10^{-6}$ s) of **4.3-1**, a rate of quenching $<10^5$ $M^{-1}s^{-1}$ was obtained.[1f] Since our conditions require a large excess of HCl, **4.3-1-Cl** was synthesized as well to see how it differed from its **4.3-1-PF_6** salt.[6c] In MeCN, the quenching experiment was done using MeOH and quenching of the catalyst was observed (K_{SV} = 0.29, k_qMeOH = 1.3×10^5 $M^{-1}s^{-1}$).[11] In our hands, k_qTBACl = 1.1×10^6 $M^{-1}s^{-1}$ in MeCN was found for complex **4.3-1-PF6**.[6a] This mechanistic data supports the proposed mechanism.

4.4- Conclusion

In conclusion, a redox neutral photoredox mediated protocol has been developed to alkylate functionalized quinolines from alcohols and ethers. Furthermore, a photocatalytic reduction using *i*PrOH has been described. Deuterium labelling studies helped to determine that the mechanism was indeed going through an enamine intermediate, with the formation of the CD_3, CD_2H and CDH_2 **4.3-4** adducts. The formation of the chlorine atom can be broadly applied to

other HAT substrates and its use in other catalytic systems are currently being explored in our laboratory and will be discussed in due course.

4.5- Further Information

4.5.1- Fluorescence Quenching Experiments

The fluorescence emission measurements required for the $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ and $[Ir(dF(CF_3)ppy)_2(dtbbpy)]Cl$ quenching experiments were carried out in a Photon Technology International (PTI) spectrofluorimeter at room temperature in Ar atmosphere using 1 × 1 cm^2 quartz cuvettes. Samples of $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ and $[Ir(dF(CF_3)ppy)_2(dtbbpy)]Cl$ were prepared with a final absorbance of 0.01 at 380 nm, the wavelength employed for excitation, in MeCN, degassed in Ar. The MeOH used in the quenching studies was also degassed prior to use with Ar. Addition of MeOH increased the polarity of the solution, thus changing the medium. Therefore, the $[Ir(dF(CF_3)ppy)_2(dtbbpy)]X$ catalyst was being quenched in a different polar medium and its absorbance is affected.

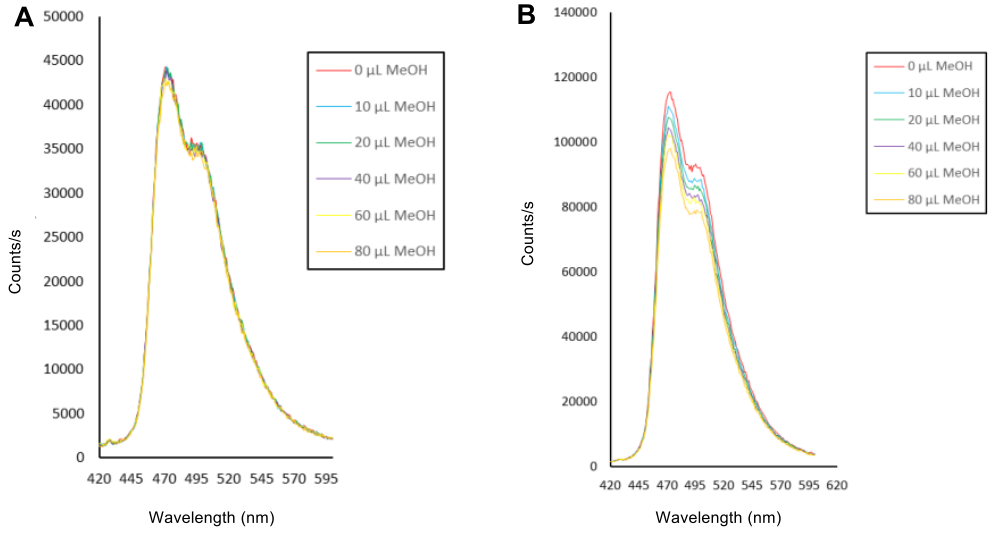


Figure 4.5- Data for the steady-state quenching experiments of $[Ir(dF(CF_3)ppy)_2(dtbbpy)]X$ (X = Cl or PF_6) by MeOH in MeCN. (A) Quenching of the emission of [Ir(dF(CF3)ppy)2(dtbbpy)]PF6 upon increasing concentrations of MeOH. (B) Quenching of the emission of $[Ir(dF(CF_3)ppy)_2(dtbbpy)]Cl$ upon increasing concentrations of MeOH.

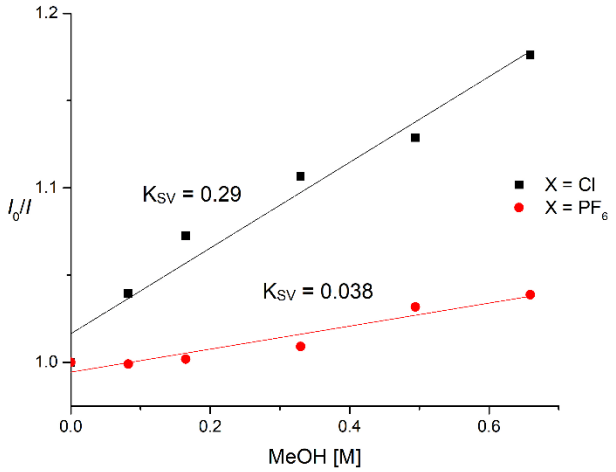


Figure 4.6- Corresponding Stern-Volmer plots for the steady-state quenching experiments of $[Ir(dF(CF_3)ppy)_2(dtbbpy)]X$ (X = Cl or PF_6) by MeOH in MeCN.

4.5.2- Unsuccessful Substrates

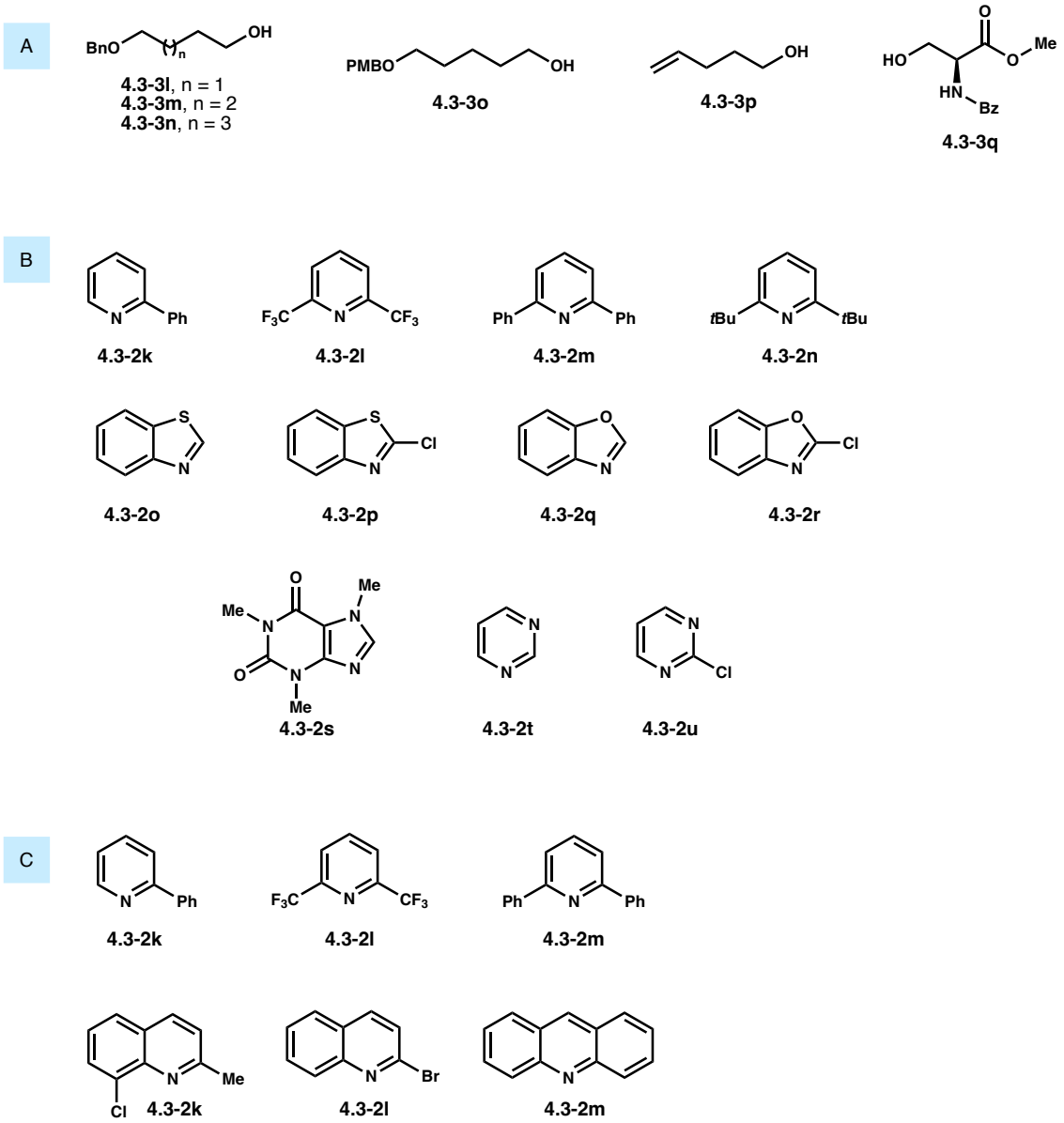


Figure 4.7- Unsuccessful substrates used in the reaction. A) Unsuccessful alcohols **4.3.-1l-q** in the photo-mediated alkylation of heteroarenes. B) Unsuccessful heteroarenes **4.3-2k-u** in the photo-mediated alkylation of heteroarenes. C) Unsuccessful heteroarenes **4.3-2k-u** in the photo-mediated reduction of heteroarenes.

4.6- Experimental Procedures

4.6.1- General Information

All reactions were performed under argon atmosphere in Pyrex glassware equipped with a magnetic stir bar, capped with a septum, unless otherwise indicated. All commercial reagents were used without further purification, unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC) analysis. TLC plates were viewed under UV light and stained with

potassium permanganate or *p*-anisaldehyde staining solution. Yields refer to products isolated after purification, unless otherwise stated. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AMX 400 MHz. NMR samples were dissolved in deuterated chloroform (unless specified otherwise) and chemical shifts are reported in ppm referenced to residual undeuterated solvent. Data are reported as follows: chemical shift, multiplicity, coupling, integration. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on the same Bruker instruments as in proton NMR at 101 MHz. IR spectra were recorded with an Agilent Technologies Cary 630 FTIR Spectrometer equipped with a diamond ATR module. HRMS were obtained on a Kratos Analytical Concept instrument (University of Ottawa Mass Spectrum Centre).

4.6.2- General Procedures

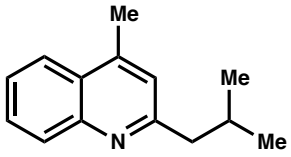
General Procedure 1 (GP1)- Preparation of alkylated heteroarenes: To an oven dried 8 mL Pyrex screw-top reaction vessel was added the heteroarene (0.2 mmol, 1.0 equiv), ROH (2 mmol, 10.0 equiv), concentrated HCl (1 mmol, 5 equiv), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (0.01 mmol, 0.05 equiv), DCE (0.4 mL, 0.5 M). The reaction vessel was capped, degassed with Ar by sparging for 5 minutes (volatile alkyl alcohols were added after sparging), then irradiated with a blue (465 nm) LED (2-2.4 W) at an approximate distance of 1-5 mm for 24 hours. The resulting mixture was poured into DCM and extracted with NaOH (1M) in a separatory funnel, dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was further purified by flash chromatography (0-100% EtOAc:Hexanes), where relevant fractions were combined, concentrated, and characterized by proton and carbon NMR (400 and 101 MHz, respectively), HR-MS, and IR.

General Procedure 2 (GP2)- Preparation of alkylated 6-halide-2-methyl quinolines: To an oven dried 8 mL Pyrex screw-top reaction vessel was added the heteroarene (0.2 mmol, 1.0 equiv), ROH (2 mmol, 10.0 equiv), concentrated HCl (0.4 mmol, 2 equiv), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (0.01 mmol, 0.05 equiv), DCE (0.4 mL, 0.5 M). The reaction vessel was capped, degassed with Ar by sparging for 5 minutes (volatile alkyl alcohols were added after sparging), then irradiated with a blue (465 nm) LED (2-2.4 W) at an approximate distance of 1-5 mm for 2 hours. The resulting mixture was poured into DCM and extracted with NaOH (1M) in a separatory funnel, dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was further purified by flash chromatography (0-100% EtOAc:Hexanes), where relevant fractions were combined, concentrated, and characterized by proton and carbon NMR (400 and 101 MHz, respectively), HR-MS, and IR.

General Procedure 3 (GP3)- Preparation of reduced heteroarenes: To an oven dried 8 mL Pyrex screw-top reaction vessel was added the heteroarene (0.2 mmol, 1.0 equiv), *i*PrOH (2 mmol, 10.0 equiv), concentrated HCl (1 mmol, 5 equiv), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (0.01 mmol, 0.05 equiv), DCE (0.4 mL, 0.5 M). The reaction vessel was capped, degassed with Ar by sparging for 5 minutes (volatile alkyl alcohols were added after sparging), then irradiated with a blue (465 nm) LED (2-2.4 W) at an approximate distance of 1-5 mm for 24 hours. The resulting mixture was poured into DCM and extracted with NaOH (1M) in a separatory funnel, dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was further purified by flash chromatography (0-100% EtOAc:Hexanes), where relevant fractions were combined, concentrated, and characterized by proton and carbon NMR (400 and 101 MHz, respectively), HR-MS, and IR.

4.7- Characterization Data

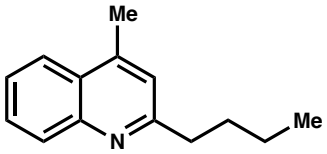
4.7.1- Product 4.3-4aa Characterization



2-isobutyl-4-methyl quinoline (4.3-4aa)

Synthesized according to GP1. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined characterized according to NMR comparison.[12] Isolated as a yellow oil (16 mg, 39%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.05 (dd, *J* = 8.6, 1.3 Hz, 1H), 7.95 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.67 (ddd, *J* = 8.4, 6.8, 1.5 Hz, 1H), 7.50 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.11 (d, *J* = 1.1 Hz, 1H), 2.80 (d, *J* = 7.4 Hz, 2H), 2.67 (s, 3H), 2.21 (dqt, *J* = 13.8, 6.9 Hz, 1H), 0.98 (d, *J* = 6.6 Hz, 6H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 161.9 (C), 147.7 (C), 143.8 (C), 129.4 (CH), 128.9 (CH), 126.7 (C), 125.3 (CH), 123.5 (CH), 122.7 (CH), 48.2 (CH_2), 29.4 (CH), 22.6 (2 X CH_3), 18.7 (CH_3) ppm.

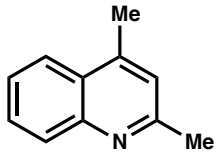


2-butyl-4-methylquinoline (4.3-4ab & 4.3-4ak)

Synthesized according to GP1. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined characterized according to NMR comparison.[12] Isolated as of a yellow oil (19 mg, 49%) using 4.3-3e and as a yellow oil (32 mg, 80%) using 4.3-3k.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.04 (ddd, *J* = 8.5, 1.3, 0.6 Hz, 1H), 7.94 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.66 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.49 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.13 (s, 1H), 2.96–2.88 (m, 2H),

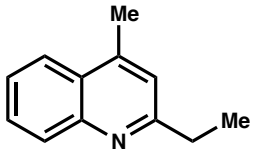
2.66 (d, *J* = 0.9 Hz, 3H), 1.85–1.72 (m, 2H), 1.44 (sxt, *J* = 7.4 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 162.7 (C), 147.7 (C), 144.1 (C), 129.3 (CH), 128.9 (CH), 126.7 (C), 125.3 (CH), 123.5 (CH), 122.0 (CH), 39.0 (CH_2), 32.2 (CH_2), 22.7 (CH_2), 18.6 (CH_3), 14.0 (CH_3) ppm.



2,4-dimethylquinoline (4.3-4ac)

Synthesized according to GP1. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[6a] Isolated as a yellow oil (24 mg, 77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.01 (dt, *J* = 8.5, 0.9 Hz, 1H), 7.97–7.90 (m, 1H), 7.67 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.50 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.14 (s, 1H), 2.69 (s, 3H), 2.66 (d, *J* = 1.0 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 158.7 (C), 147.7 (C), 144.1 (C), 129.1 (CH), 129.1 (CH), 126.5 (C), 125.4 (CH), 123.6 (CH), 122.7 (CH), 25.2 (CH_3), 18.6 (CH_3) ppm.

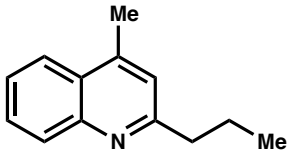


2-ethyl-4-methylquinoline (4.3-4ad)

Synthesized according to GP1. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[6a] Isolated as a yellow oil (26 mg, 77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.04 (ddd, *J* = 8.5, 1.3, 0.6 Hz, 1H), 7.97–7.91 (m, 1H), 7.67 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.49 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.15 (s, 1H), 2.95 (q, *J* = 7.6 Hz, 2H), 2.67

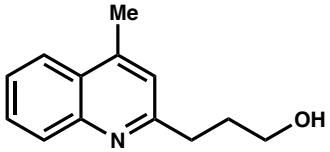
(d, *J* = 1.0 Hz, 3H), 1.38 (t, *J* = 7.6 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 163.7 (C), 147.7 (C), 144.2 (C), 129.3 (CH), 129.0 (CH), 126.7 (C), 125.4 (CH), 123.5 (CH), 121.5 (CH), 32.2 (CH_2), 18.7 (CH_3), 14.1 (CH_3) ppm.



2-propyl-4-methylquinoline (4.3-4ae)

Synthesized according to GP1. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[12] Isolated as a yellow oil (18 mg, 49%).

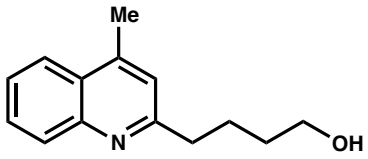
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.04 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.95 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.67 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.49 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.14 (s, 1H), 2.95–2.86 (m, 2H), 2.67 (s, 3H), 1.89–1.77 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 162.5 (C), 147.7 (C), 144.1 (C), 129.3 (CH), 129.0 (CH), 126.8 (C), 125.3 (CH), 123.5 (CH), 122.1 (CH), 41.2 (CH_2), 23.3 (CH_2), 18.7 (CH_3), 14.1 (CH_3) ppm.



3-(4-methylquinolin-2-yl)propan-1-ol (4.3-4af)

Synthesized according to GP1. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[13] Isolated as a yellow oil (23 mg, 66%).

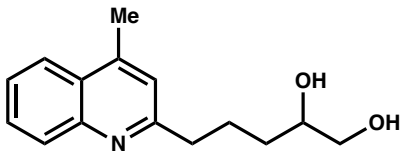
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.01 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.95 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.67 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.51 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.16 (s, 1H), 3.77 (t, *J* = 5.7 Hz, 2H), 3.13 (t, *J* = 6.8 Hz, 2H), 2.68 (s, 3H), 2.12–2.04 (m, 2H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 161.6 (C), 146.9 (C), 144.9 (C), 129.3 (CH), 128.8 (CH), 126.7 (C), 125.7 (CH), 123.6 (CH), 122.4 (CH), 62.6 (CH_2), 36.4 (CH_2), 31.0 (CH_2), 18.7 (CH_3) ppm.



4-(4-methylquinolin-2-yl)butan-1-ol (4.3-4ag & 4.3-4ai)

Synthesized according to GP1. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[6a] Isolated as a yellow oil (26 mg, 61%) using **4.3-3g** and as a yellow oil (31 mg, 71%) using **4.3-3i**.

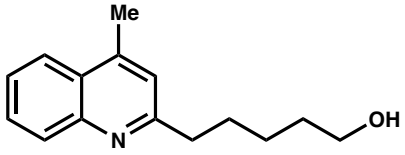
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.04–8.00 (m, 1H), 7.93 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.66 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.50 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.12 (d, *J* = 1.1 Hz, 1H), 3.69 (t, *J* = 6.3 Hz, 2H), 2.96 (t, *J* = 7.5 Hz, 2H), 2.65 (d, *J* = 1.0 Hz, 3H), 1.9-1.88 (m, 2H), 1.69 (dq, *J* = 8.6, 6.4 Hz, 2H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 162.2 (C), 147.4 (C), 144.5 (C), 129.1 (CH), 129.1 (CH), 126.8 (C), 125.5 (CH), 123.6 (CH), 122.2 (CH), 62.1 (CH_2), 38.1 (CH_2), 32.2 (CH_2), 25.4 (CH_2), 18.6 (CH_3) ppm.



5-(4-methylquinolin-2-yl)pentane-1,2-diol (4.3-4ah)

Synthesized according to GP1. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[6a] Isolated as a yellow oil (37 mg, 76%).

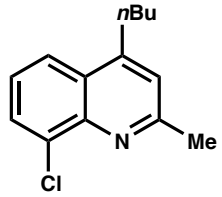
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02–8.00 (m, 1H), 7.93 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.65 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.48 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.11 (s, 1H), 4.01 (br. s, 2H), 3.78 (tdd, *J* = 7.6, 5.0, 3.4 Hz, 1H), 3.63 (dd, *J* = 11.1, 3.3 Hz, 1H), 3.48 (dd, *J* = 11.1, 7.3 Hz, 1H), 2.96 (td, *J* = 7.3, 3.4 Hz, 2H), 2.65 (d, *J* = 0.9 Hz, 3H), 1.99–1.92 (m, 2H), 1.58–1.50 (m, 2H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 161.9 (C), 147.1 (C), 144.8 (C), 129.2 (CH), 128.7 (CH), 126.7 (C), 125.6 (CH), 123.6 (CH), 122.2 (CH), 71.5 (CH), 66.7 (CH_2), 37.9 (CH_2), 32.5 (CH_2), 25.0 (CH_2), 18.6 (CH_3) ppm.



5-(4-methylquinolin-2-yl)pentan-1-ol (4.3-4aj)

Synthesized according to GP1. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[13] Isolated as a yellow oil (14 mg, 30%).

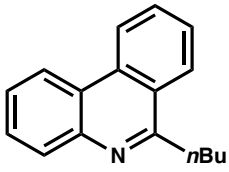
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.04 (dt, *J* = 8.4, 1.0 Hz, 1H), 7.94 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.67 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.50 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.13 (d, *J* = 1.1 Hz, 1H), 3.67 (t, *J* = 6.5 Hz, 2H), 2.98–2.90 (m, 2H), 2.67 (d, J = 1.0 Hz, 3H), 2.07–1.96 (m, 1H), 1.91–1.79 (m, 2H), 1.69–1.59 (m, 2H), 1.55–1.43 (m, 2H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 162.3 (C), 147.6 (C), 144.3 (C), 129.2 (CH), 129.1 (CH), 126.8 (C), 125.4 (CH), 123.6 (CH), 122.1 (CH), 62.7 (CH_2), 38.8 (CH_2), 32.5 (CH_2), 29.4 (CH_2), 25.4 (CH_2), 18.7 (CH_3) ppm.



4-butyl-8-chloro-2-methylquinoline (4.3-4bk)

Synthesized according to GP1. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined and characterized. Isolated as a yellow oil (16 mg, 34%).

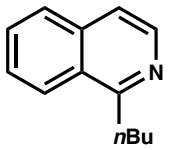
IR (neat, cm^{-1}): 2957 (s), 2929 (s), 2871 (s), 2360 (s), 2336 (m), 1603 (vs), 1503 (s), 1456 (m), 1413 (m), 757 (vs); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.92 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.78 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.39 (dd, *J* = 8.4, 7.5 Hz, 1H), 7.19 (s, 1H), 3.07–2.95 (m, 2H), 2.77 (s, 3H), 1.81–1.67 (m, 2H), 1.45 (dq, *J* = 14.7, 7.3 Hz, 2H), 0.98 (t, *J* = 7.4 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 159.7 (C), 149.0 (C), 144.4 (C), 133.4 (C), 129.1 (CH), 127.3 (C), 125.0 (CH), 122.5 (CH), 122.5 (CH), 32.2 (CH_2), 32.1 (CH_2), 25.7 (CH_3), 22.8 (CH_2), 13.9 (CH_3) ppm; **HRMS** (EI) m/z calc'd for $C_{14}H_{16}ClN$ [M^+] 233.0971, found 233.0989.



6-butylphenanthridine (4.3-4ck)

Synthesized according to GP1. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[14] Isolated as a white amorphous solid (31 mg, 65%).

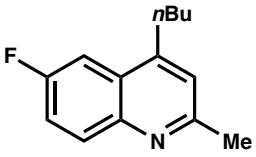
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.67–8.60 (m, 1H), 8.54 (dd, *J* = 8.2, 1.5 Hz, 1H), 8.28–8.22 (m, 1H), 8.16–8.10 (m, 1H), 7.82 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1H), 7.70 (dddd, *J* = 9.2, 8.3, 7.0, 1.3 Hz, 2H), 7.61 (ddd, *J* = 8.3, 7.0, 1.4 Hz, 1H), 3.43–3.29 (m, 2H), 2.00–1.86 (m, 2H), 1.57 (sxt, *J* = 7.4 Hz, 2H), 1.01 (t, *J* = 7.4 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, CDCl3) δ = 162.5 (C), 143.7 (C), 132.9 (C), 130.2 (CH), 129.5 (CH), 128.5 (CH), 127.2 (CH), 126.3 (CH), 126.2 (CH), 125.2 (C), 123.6 (C), 122.4 (CH), 121.9 (CH), 36.2 (CH_2), 31.7 (CH_2), 23.1 (CH_2), 14.0 (CH_3) ppm.



1-butylisoquinoline (4.3-4dk)

Synthesized according to GP1. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[15] Isolated as a yellow oil (21 mg, 56%).

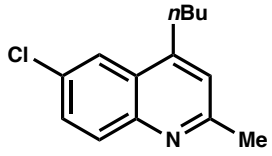
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.43 (d, *J* = 5.7 Hz, 1H), 8.16 (dq, *J* = 8.3, 1.0 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.65 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.58 (ddd, *J* = 8.3, 6.9, 1.4 Hz, 1H), 7.49 (dd, *J* = 5.8, 0.8 Hz, 1H), 3.33–3.26 (m, 2H), 1.89–1.80 (m, 2H), 1.50 (sxt, *J* = 7.4 Hz, 2H), 0.98 (t, *J* = 7.4 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 162.4 (C), 141.9 (CH), 136.2 (C), 129.7, (CH) 127.3 (CH), 126.9 (C), 126.9 (CH), 125.3 (CH), 119.1 (CH), 35.3 (CH_2), 31.9 (CH_2), 23.0 (CH_2), 14.0 (CH_3) ppm.



4-butyl-6-fluoro-2-methylquinoline (4ek)

Synthesized according to GP2. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined and characterized. Isolated as a yellow oil (11 mg, 24%).

IR (neat, cm^{-1}): 2957 (vs), 2927 (s), 2861 (s), 1624 (s), 1606 (s), 1473 (s), 1427 (s), 1377 (s), 1171 (s), 924 (m), 869 (vs), 854 (vs), 839 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.00 (dd, *J* = 9.2, 5.6 Hz, 1H), 7.57 (dd, *J* = 10.1, 2.8 Hz, 1H), 7.42 (ddd, *J* = 9.2, 8.1, 2.8 Hz, 1H), 7.14 (s, 1H), 2.99–2.90 (m, 2H), 2.69 (s, 3H), 1.78–1.69 (m, 2H), 1.46 (dq, *J* = 14.6, 7.4 Hz, 2H), 0.98 (t, *J* = 7.3 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 160.0 (d, *J* = 245.6 Hz, C), 157.9 (d, *J* = 2.7 Hz, C), 148.0 (d, *J* = 5.5 Hz, C), 145.1 (C), 131.6 (d, *J* = 9.0 Hz, CH), 126.5 (d, *J* = 9.0 Hz, C), 122.1 (CH), 118.8 (d, *J* = 25.5 Hz, CH), 107.0 (d, *J* = 22.3 Hz, CH), 31.9 (CH_2), 31.9 (CH_2), 25.1 (CH_3), 22.8 (CH_2), 13.9 (CH_3) ppm; **HRMS** (EI) m/z calc'd for $C_{14}H_{16}FN$ [M^+] 217.1267, found 217.1247.

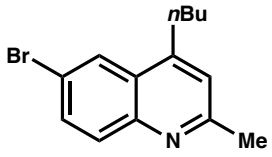


4-butyl-6-chloro-2-methylquinoline (4.3-4fk)

Synthesized according to GP2. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined and characterized. Isolated as a yellow oil (34 mg, 72%).

IR (neat, cm^{-1}): 2955 (s), 2928 (vs), 2871 (s), 1601 (vs), 1560 (m), 1492 (m), 1459 (m), 1379 (s), 1089 (m), 875 (s), 831 (vs), 811 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.96–7.88 (m, 2H), 7.58 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.13 (s, 1H), 2.98–2.93 (m, 2H), 2.68 (s, 3H), 1.71 (tt, *J* = 9.3, 6.9 Hz, 2H), 1.45 (dq, *J* = 14.7, 7.3 Hz, 2H), 0.98 (t, *J* = 7.3 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 158.9 (C),

147.8 (C), 146.4 (C), 131.1 (C), 130.9 (CH), 129.7 (CH), 126.6 (C), 122.5 (CH), 122.2 (CH), 32.0 (CH_2), 31.7 (CH_2), 25.2 (CH_3), 22.7 (CH_2), 13.9 (CH_3) ppm; **HRMS** (EI) m/z calc'd for $C_{14}H_{16}ClN$ [M^+] 233.0971, found 233.1001.

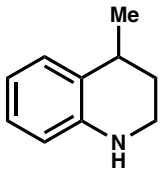


6-bromo-4-butyl-2-methylquinoline (4.3-4gk)

Synthesized according to GP2. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined and characterized. Isolated as a yellow oil (33 mg, 60%).

IR (neat, cm^{-1}): 2959 (s). 2927 (vs), 2868 (s), 1616 (vs), 1465 (s), 1351 (s), 1012 (s), 869 (vs), 860 (vs), 840 (m); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.09 (d, *J* = 2.1 Hz, 1H), 7.86 (d, *J* = 8.9 Hz, 1H), 7.70 (dd, *J* = 8.9, 2.1 Hz, 1H), 7.12 (s, 1H), 3.00–2.89 (m, 2H), 2.67 (s, 3H), 1.71 (qt, *J* = 7.6 Hz, 2H), 1.45 (sxt, *J* = 7.4 Hz, 2H), 0.98 (t, *J* = 7.3 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 159.1 (C), 147.7 (C), 146.6 (C), 132.3 (CH), 131.1 (CH), 127.2 (C), 125.8 (CH), 122.2 (CH), 119.3 (C), 32.0 (CH_2), 31.6 (CH_2), 25.3 (CH_3), 22.7 (CH_2), 13.9 (CH_3) ppm; **HRMS** (EI) m/z calc'd for $C_{14}H_{16}BrN$ [M^+] 277.0466, found 277.04426.

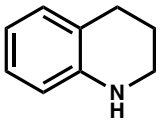
4.7.2- Product 4.3-5 Characterization



4-methyl- 1,2,3,4-tetrahydroquinoline (4.3-5a)

Synthesized according to GP3. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[6a] Isolated as a yellow oil (12 mg, 42%).

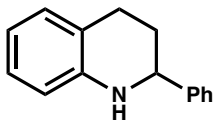
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.06 (dt, *J* = 7.6, 1.2 Hz, 1H), 6.97 (dddd, *J* = 7.9, 7.2, 1.6, 0.6 Hz, 1H), 6.64 (td, *J* = 7.4, 1.3 Hz, 1H), 6.48 (dd, *J* = 7.9, 1.2 Hz, 1H), 3.85 (s, 1H), 3.40–3.21 (m, 2H), 2.92 (sxt, *J* = 6.6 Hz, 1H), 2.06–1.94 (m, 1H), 1.69 (dddd, *J* = 13.0, 6.8, 6.1, 3.6 Hz, 1H), 1.30 (d, *J* = 7.0 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 144.2 (C), 128.4 (CH), 126.7 (CH), 126.6 (C), 116.9 (CH), 114.1 (CH), 39.0 (CH_2), 30.2 (CH), 29.9 (CH_2), 22.6 (CH_3) ppm.



1,2,3,4-tetrahydroquinoline (4.3-5b)

Synthesized according to GP3. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[6a] Isolated as mg of a yellow oil (14 mg, 53%).

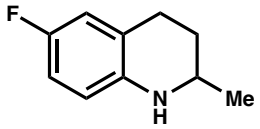
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.00–6.92 (m, 2H), 6.61 (td, *J* = 7.4, 1.2 Hz, 1H), 6.48 (dd, *J* = 7.9, 1.1 Hz, 1H), 3.81 (s, 1H), 3.36–3.22 (m, 2H), 2.77 (t, *J* = 6.4 Hz, 2H), 2.07–1.87 (m, 2H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 144.7 (C), 129.5 (CH), 126.7 (CH), 121.4 (C), 116.9 (CH), 114.1 (CH), 41.9 (CH_2), 26.9 (CH_2) 22.1 (CH_2) ppm.



2-phenyl- 1,2,3,4-tetrahydroquinoline (4.3-5c)

Synthesized according to GP3. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[16] Isolated (as an inseparable mixture with 4-isopropyl-2-phenyl- 1,2,3,4-tetrahydroquinoline) as a white amorphous solid (27 mg, 64%).

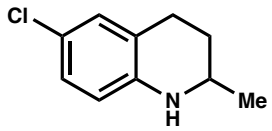
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.46 – 7.36 (m, 4H), 7.36 – 7.28 (m, 1H), 7.10 – 6.99 (m, 2H), 6.69 (td, *J* = 7.4, 1.2 Hz, 1H), 6.60 – 6.46 (m, 1H), 4.47 (dd, *J* = 9.3, 3.3 Hz, 1H), 4.05 (s, 1H), 3.04 – 2.88 (m, 1H), 2.77 (dt, *J* = 16.3, 4.7 Hz, 1H), 2.16 (dddd, *J* = 13.2, 5.4, 4.5, 3.3 Hz, 1H), 2.03 (dddd, *J* = 13.0, 10.7, 9.3, 5.1 Hz, 1H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 144.8 (C), 144.7 (C), 129.2 (CH), 128.5 (CH x 2), 127.4 (CH), 126.9 (CH), 126.5 (CH x 2), 120.8 (C), 117.1 (CH), 113.9 (CH), 56.2 (CH), 30.9 (CH_2), 26.3 (CH_2) ppm.



6-fluoro-2-methyl- 1,2,3,4-tetrahydroquinoline (4.3-5d)

Synthesized according to GP3. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[16] Isolated as a yellow oil (25 mg, 75%).

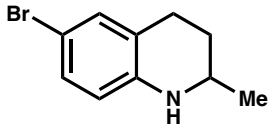
^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.68 (ddt, *J* = 7.7, 6.8, 1.9 Hz, 2H), 6.44–6.36 (m, 1H), 3.58 (s, 1H), 3.34 (dtd, *J* = 12.6, 6.3, 2.8 Hz, 1H), 2.89–2.77 (m, 1H), 2.70 (ddd, *J* = 16.7, 5.5, 3.3 Hz, 1H), 1.92 (ddt, *J* = 12.4, 5.9, 3.1 Hz, 1H), 1.56 (dddd, *J* = 12.9, 11.5, 10.0, 5.5 Hz, 1H), 1.21 (d, *J* = 6.2 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 155.5 (d, *J* = 234.5 Hz, C), 140.9 (d, *J* = 2.0 Hz, C), 122.4 (d, *J* = 6.7 Hz, C), 115.3 (d, *J* = 21.6 Hz, CH), 114.7 (d, *J* = 7.6 Hz, CH), 113.1 (d, *J* = 22.4 Hz, CH), 47.3 (CH), 29.9 (CH_2), 26.7 (CH_2), 22.5 (CH_3) ppm.



6-chloro-2-methyl- 1,2,3,4-tetrahydroquinoline (4.3-5e)

Synthesized according to GP3. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[6a] Isolated as a yellow oil (31 mg, 85%).

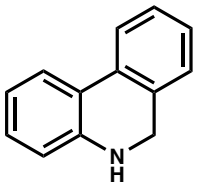
^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.95 – 6.87 (m, 2H), 6.38 (d, *J* = 8.4 Hz, 1H), 3.70 (bs, 1H), 3.37 (dtd, *J* = 12.6, 6.3, 2.9 Hz, 1H), 2.86 – 2.64 (m, 2H), 1.95 – 1.89 (m, 1H), 1.60 – 1.50 (m, 1H), 1.21 (d, *J* = 6.3 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 143.3 (C), 128.8 (CH), 126.4 (CH), 122.6 (C), 121.2 (C), 114.9 (CH), 47.1 (CH), 29.7 (CH_2), 26.4 (CH_2), 22.4 (CH_3) ppm.



6-bromo-2-methyl- 1,2,3,4-tetrahydroquinoline (4.3-5f)

Synthesized according to GP3. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[6a] Isolated as a yellow oil (32 mg, 71%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.09 – 6.99 (m, 2H), 6.34 (d, *J* = 8.4 Hz, 1H), 3.71 (s, 1H), 3.37 (dtd, *J* = 9.9, 6.3, 2.9 Hz, 1H), 2.80 (dddt, *J* = 17.1, 11.4, 5.7, 1.0 Hz, 1H), 2.74 – 2.64 (m, 1H), 1.91 (dddd, *J* = 13.0, 5.6, 3.6, 2.9 Hz, 1H), 1.61 – 1.48 (m, 1H), 1.20 (d, *J* = 6.3 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, CDCl3) δ = 143.7 (C), 131.6 (CH), 129.3 (CH), 123.1 (C), 115.3 (CH), 108.2 (C), 47.1 (CH), 29.6 (CH_2), 26.4 (CH_2), 22.4 (CH_3) ppm.

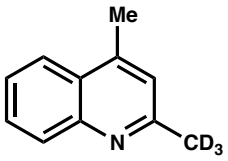


5,6-dihydrophenanthridine (4.3-5g)

Synthesized according to GP3. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[6a] Isolated a white amorphous solid (5 mg, 15%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.69 (ddd, *J* = 7.7, 4.5, 1.3 Hz, 2H), 7.31 (td, *J* = 7.7, 1.6 Hz, 1H), 7.21 (td, *J* = 7.4, 1.3 Hz, 1H), 7.14 – 7.06 (m, 2H), 6.84 (td, *J* = 7.6, 1.2 Hz, 1H), 6.67 (dd, *J* = 7.9, 1.2 Hz, 1H), 4.40 (s, 2H), 3.97 (s, 1H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 145.7 (C), 132.7 (C), 132.0 (C), 128.8 (CH), 127.6 (CH), 127.1 (CH), 126.0 (CH), 123.6 (CH), 122.4 (CH), 122.0 (C), 119.3 (CH), 115.1 (CH), 46.4 (CH_2) ppm.

4.7.3- Deuterium Labelling Experiments Characterization

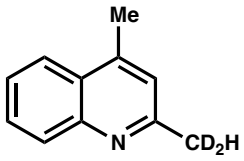


2-[$^{2}H_3$]-methyl-4-methyl-quinoline (d_3-4.3-4ac)

Synthesized according to GP1. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[6a] Isolated as a yellow oil (6 mg, 20%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.06 – 8.01 (m, 1H), 7.97 – 7.90 (m, 1H), 7.67 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.50 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.14 (t, *J* = 1.0 Hz, 1H), 2.67 (d, *J* = 1.0 Hz, 3H) ppm; **^{13}C**

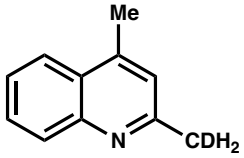
NMR (101 MHz, $CDCl_3$) δ = 158.6 (C), 147.6 (C), 144.3 (C), 129.1 (CH), 129.0 (CH), 126.3 (C), 125.4 (CH), 123.6 (CH), 122.7 (CH), 22.7 (CD_3), 18.6 (CH_3) ppm.



2-[$^2H_2$]-methyl-4-methyl-quinoline (d_2-4.3-4ac)

Synthesized according to GP1. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[6a] Isolated as a yellow oil (5 mg, 16%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02 (dt, *J* = 8.5, 0.9 Hz, 1H), 7.95 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.67 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.50 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.17 – 7.11 (m, 1H), 2.67 (d, *J* = 1.1 Hz, 4H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 158.6 (C), 147.7 (C), 143.3 (C), 129.1 (CH), 129.1 (CH), 126.6 (C), 125.4 (CH), 123.6 (CH), 122.7 (CH), 29.7 (CD_2H), 18.6 (CH_3) ppm.

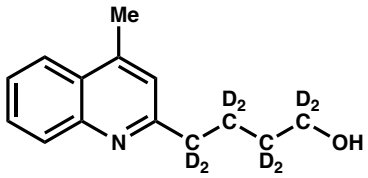


2-[^{2}H]-methyl-4-methyl-quinoline (d-4.3-4ac)

Synthesized according to GP3. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[6a] Isolated as a yellow oil (19 mg, 60%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.01 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.94 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.66 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.49 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.13 (s, 1H), 2.70 – 2.63 (m, 5H) ppm;

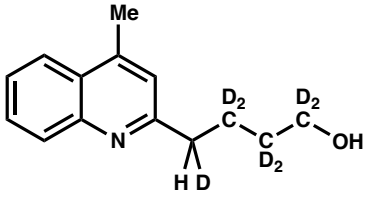
^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.6 (C), 147.7 (C), 144.1 (C), 129.1 (CH), 129.1 (CH), 126.5 (C), 125.4 (CH), 123.5 (CH), 122.7 (CH), 24.8 (CH_2, t, *J* = 19.9 Hz), 18.5 (CH_3) ppm.



4-(4-methylquinolin-2-yl)-[$^2H_8$]-butan-1-ol (d_8-4.3-4ai)

Synthesized according to GP1. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined and characterized. Isolated as a yellow oil (34 mg, 76%).

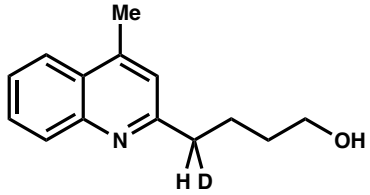
IR (neat, cm^{-1}): 3215 (br), 2209 (m), 2102 (m), 1603 (vs), 1560 (s), 973 (s), 760 (vs); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.03 (dd, *J* = 8.5, 1.2 Hz, 1H), 7.93 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.66 (ddd, *J* = 8.3, 5.8, 1.3 Hz, 1H), 7.50 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.13 (d, *J* = 1.1 Hz, 1H), 2.66 (d, *J* = 1.0 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 162.2 (C), 147.3 (C), 144.5 (C), 129.1 (CH), 128.9 (CH), 126.7 (C), 125.5 (CH), 125.4 (CH), 123.5 (CH), 122.1 (CH), 18.62 (CH_3) ppm; **HRMS** (EI) m/z calc'd for $C_{14}H_9D_8NO$ [M^+] 223.1812, found 223.1825.



4-(4-methylquinolin-2-yl)-[$^2H_7$]-butan-1-ol (d_7-4.3-4ai)

Synthesized according to GP3. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined and characterized. Isolated as a yellow oil (39 mg, 90%).

IR (neat, cm^{-1}): 3290 (br), 2361 (m), 2202 (m), 1603 (vs), 1560 (s), 1508 (s), 1448 (s), 973 (s), 761 (vs); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02 (ddd, *J* = 8.4, 1.3, 0.6 Hz, 1H), 7.93 (ddd, *J* = 8.3, 1.5, 0.6 Hz, 1H), 7.65 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.49 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.14 – 7.09 (m, 1H), 2.93 (s, 1H), 2.65 (d, *J* = 1.0 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.2 (C), 147.4 (C), 144.5 (C), 129.1 (CH), 129.0 (CH), 126.7 (C), 125.5 (CH), 123.5 (CH), 122.1 (CH), 61.16 (CH_2, t, *J* = 20.6 Hz), 37.48 (CH, t, *J* = 18.9 Hz), 31.00 (CH_2 t, *J* = 18.4 Hz), 24.43 (CH_2, t, *J* = 19.1 Hz), 18.63 (CH_3) ppm; **HRMS** (EI) m/z calc'd for $C_{14}H_{10}D_7NO$ [M+] 222.1750, found 222.1764.



4-(4-methylquinolin-2-yl)-[^{2}H]-butan-1-ol (**d-4.3-4ai**)

Synthesized according to GP3. Crude mixture was purified by flash chromatography (0-100% EtOAc:Hexane) where relevant fractions were combined and characterized. Isolated as a yellow oil (34 mg, 77%).

IR (neat, cm-1): 3360 (br), 2931 (s), 2863 (s), 1603 (vs), 1561 (s), 1508 (s), 1446 (s), 1063 (s), 761 (vs), 655 (vs); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.02 (ddd, *J* = 8.4, 1.3, 0.6 Hz, 1H), 7.93 (dt, *J* = 8.4, 1.0 Hz, 1H), 7.65 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.49 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 7.12 (d, *J* = 1.1 Hz, 1H), 3.69 (t, *J* = 6.3 Hz, 2H), 3.00 – 2.89 (m, 1H), 2.65 (d, *J* = 1.0 Hz, 3H), 1.91 (q, *J* = 7.4 Hz, 2H), 1.74 – 1.61 (m, 2H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 162.2 (C), 147.3 (C), 144.5 (C), 129.1 (CH), 129.0 (CH), 126.7 (C), 125.5 (CH), 123.5 (CH), 122.1 (CH), 62.0 (CH_2), 37.78 (CH, q, *J* = 19.7, Hz), 32.2 (CH_2), 25.45 (CH_2), 18.63 (CH_3) ppm; **HRMS** (EI) m/z calc'd for $C_{14}H_{16}DNO$ [M^{+}] 216.1373, found 216.1347.

4.8- References

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Chapter 5 – Photoactivated Cycloadditions of *N*-Aryl Cyclopropylamines

Zidan, M.; Barriault, L., Photoactivated Formal [3 + 2] Cycloaddition of *N*-Aryl Cyclopropylamines, *ChemRxiV., Cambridge: Cambridge Open Engage;* **2022***. This content is a preprint and has not been peer-reviewed.* (DOI: 10.26434/chemrxiv-2022-tq6zk)

5.1- Abstract

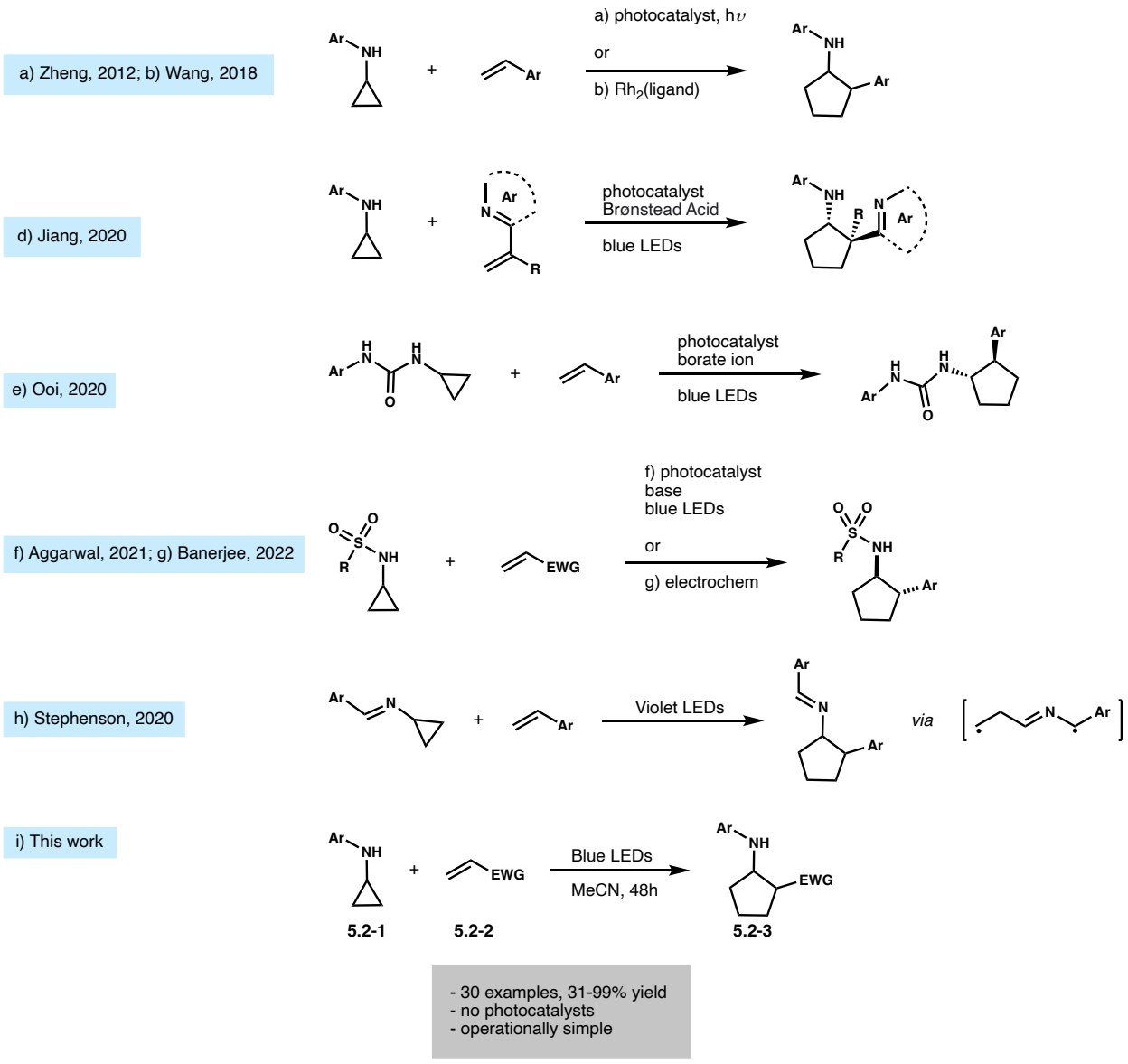
Organic transformations initiated by photochemical activation have been at the forefront of reaction discovery. We have seen the [2 + 2] photocycloaddition performed upon excitation of α,β-unsaturated carbonyl compounds, and more recently [3 + 2] cycloadditions of aryl cyclopropyl ketones have been reported. These methodologies required a photocatalyst and/or external activators, adding some limitations to the substrates used. Herein, we report a formal photochemical [3 + 2] cycloaddition using *N*-aryl cyclopropylamines and α,β-unsaturated carbonyl systems without the use of photocatalysts or additives. This simple method proceeding through a Single Electron Transfer (SET) offers a wide scope for the synthesis of *N*-arylaminocycloalkyl compounds in good to excellent yields.

5.2- Introduction

Cyclopropanes have special and unique reactivity that can be attributed to the torsional and angular strain of the ring.[1] Recently, the use of transition metals to cleave cyclopropanes to form cyclopentane rings has been demon-strated.[2] The addition of an activating handle such as an attached nitrogen-based functional group, which allows the exploitation of C-C bond cleavage opening the formation of key intermediates.[3] From a radical formation perspective, cyclopropylamines can be employed in the formation of cyclopentanes through the formation of the nitrogen center radical initiating the β-scission of the three-membered ring.[4-6] However,

most of these methods requires often the use of harsh conditions such as high energy light, or strong oxidants. Recently, modern visible-light photoredox catalysis has provided an attractive alternative method for the formation nitrogen and carbon centered radical.[7] In 2012, Zheng and coworkers reported a [3 + 2] photocatalytic cycloaddition of cyclopropyl anilines and styrenes for the synthesis of aminocyclopentanes (**Scheme 5.1A**).[8] Following these reports, other groups utilized organic dyes and Ir(III) based catalysts to perform diastereoselective and enantioselective [3 + 2] cycloadditions where the proceed through a stepwise process (**Scheme 5.1B-G**).[9] Recently, photoexcitation of cyclopropylimines to generate nitrogen-centered radicals has been shown to be an alternative strategy for the formation of amino-cyclopentanes (**Scheme 5.1H**).[10]

With this in mind, the process of photoinduced single electron transfers (SET) can be carried out using a diverse photoactivated molecules, leading to different free-radical reaction pathways and new methodologies in C-C bond formation. To broaden the scope of *N*-aryl cyclopropylamine **5.2-1** cycloaddition, we first examined the reaction with electron-poor olefins **5.2-2** and the use of other photoredox catalysts such as $Au_2dppm_2Cl_2$ (5 mol%). Initial results shown that the gold(I)-catalyzed photoredox cycloaddition of **5.2-1a** (Ar = Ph) and ethyl acrylate **5.2-2a** (Y = CO_2Et) using 365 nm LEDs gave **5.2-3aa** (Ar = Ph and Y = CO_2Et) in good yields as an inseparable mixture of diastereomers (dr = 3:2). However, a control experiment revealed that irradiation (365 nm) of **5.2-1a** and **5.2-2a** in the absence of a photocatalyst gave the desired cycloadduct product **5.2-3aa** in 72% yield (dr = 3:2) (**Scheme 5.1I**). This exciting result indicates that the initial SET could be triggered by photoexcitation of the cyclopropylaniline **5.2-1a**. This unexpected result prompted us to investigate the general applicability of this reaction. Herein, we report the synthesis of *N*-aryl aminocycloalkyl **5.2-3** harnessing a distinct activation mode.



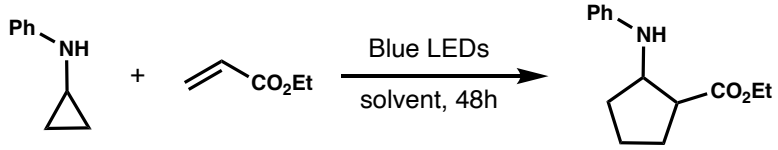
Scheme 5.1- Previous and present work in the formal [3 + 2] cycloadditions of aryl cyclopropylamines.

5.3- Results and Discussion

Initial optimization revealed that cycloaddition proceeded as well as with UVA and blue LEDs (365 and 465 nm, respectively). Although complete conversion was achieved in a shorter time with 365 nm (24h) irradiation compared to 465 nm (48 h), better yields were obtained using visible light thus avoiding product degradation. The equivalent number of **5.3-2a** was found to be an important factor in the yield of the reaction (**Table 5.1, Entries 1-4**). The desired

aminocyclopentane **5.3-3aa** was obtained in 95% yield using 10 equivalents of ethyl acrylate. (**Table 5.1**, **Entry 4**). Next, a screening of solvents was examined (**Table 5.1, Entries 4-8**). Reactions performed in acetonitrile provided the best yield (**Table 5.1, Entry 4**) while a lower yield was observed in a protic solvent such as ethanol (**Table 5.1, Entry 5**). Interestingly, a reversal of the diastereoselectivity of the reaction was observed when the reaction was performed in non-protic and less polar solvents (**Table 5.1, Entries 6-8**). By optimizing the reaction conditions, we found that the reaction in 0.2 M afforded **5.3-3aa** in 98% yield (88% isolated) (**Table 5.1, Entry 10**). Increasing the concentration above 0.2 M proved to be disadvantageous for the yield as the reaction mixture became too viscous (**Table 5.1, Entry 11**). Lower yields were observed when the photochemical cycloaddition was performed in an open flask (**Table 5.1, Entry 12**). Finally, control experiments showed that no trace of the desired product was observed when the solution was heated to 80°C in the absence of light, only the starting product **5.3-1a** was recovered (**Table 5.1, Entry 13**).

Table 5.1- Optimization of reaction conditions.



5.3-1a **5.3-2a** **5.2-3aa**

Entry	**5.3-2a** (equiv)	Solvent	[M]	**5.3-3aa** (%)[a]	dr[b]
1	1	MeCN	0.1	72	3:2
2	2	MeCN	0.1	56	3:2
3	5	MeCN	0.1	45	3:2
4	10	MeCN	0.1	95	3:2
5	10	EtOH	0.1	78	3:2
6	10	CyH	0.1	75	1:2
7	10	DCE	0.1	73	2:3
8	10	PhH	0.1	88	2:3
9	10	MeCN	0.05	79	3:2
10	10	MeCN	0.2	98 (88)	3:2
11	10	MeCN	0.2	85	3:2
12[c]	10	MeCN	0.2	70	1:1

13[d]	10	MeCN	0.2	0[e]	-

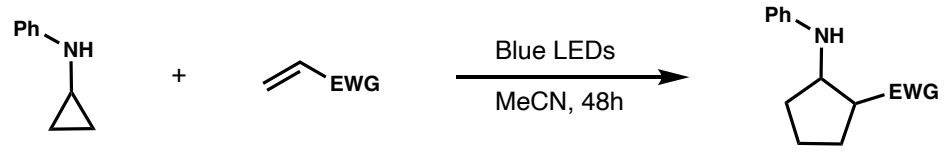
[a]NMR yield using phenyltrimethylsilane as internal standard. [b]Determined by crude ^{1}H NMR analysis. [c]Reaction run without degassing and in normal atmosphere. [d]Heating at 80°C in the absence of light. [e]71% of **5.3-2a**.

Having identified the optimal reaction conditions, we explored the reaction scope by examining different olefin substituents. Irradiation of **5.3-1a** in the presence of monosubstituted acrylates gave the desired compounds in good yields (**Scheme 5.2**, **5.3-3aa**-**5.3-3ac**). Cycloaddition with methyl methacrylate **5.3-2d** led to the formation of **5.3-3ad** in quantitative yield, albeit with modest diastereoselectivity, whereas a higher diastereoselectivity was achieved with the use of a trisubstituted olefin such as **5.3-2e**, giving the cycloaddition product **5.3-3ae** in 57% yield (dr = 9:1). Methyl vinyl ketone **5.3-2f** led to the formation of **5.3-3af** in 57% yield along with a side product **5.3-3af'** (16%) resulting of a Michael addition. To our delight, the reaction scope was expended to styrene (**5.3-2g**), vinyl phenyl sulfone (**5.3-2h**), and acrylonitrile (**5.3-2i**), also provided moderate to excellent yields of the desired products (**5.3-3ag**, 84%, dr = 3:2; **5.3-3ah**, 65%, dr = 6:1; **5.3-3ai**, 99%, dr = 2:1).

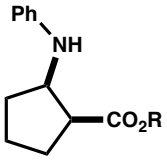
To gain more mechanistic insight, we then performed the reaction with dimethyl maleate (**5.3-2j**) and dimethyl fumarate (**5.3-2k**). The corresponding aminocyclopentanes **5.3-3aj** were isolated in 79% and 75% yields, respectively. Based on ^{1}H and ^{13}C NMR analyses, both reactions converged to the same mixture of diastereomers. These results demonstrate that the olefin geometry was not preserved in the final product supporting the premise that the reaction proceeds through a SET pathway. In addition, no conversion of methyl maleate **5.3-2j** to fumarate **5.3-2k** under these conditions was observed. Interestingly, reaction with cyclohexenone (**5.3-2m**) and *N*-phenylmaleimide (**5.3-2n**) proceeded smoothly with **5.3-1a** to

give the endo products **5.3-3am** and **5.3-3an** as the major diastereomer in 31% and 75% yields respectively.

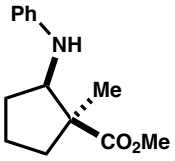
As shown in **Scheme 5.3**, we examined the scope of the reaction with different *N*-arylaminocyclopropanes **5.3-1**. Initially, the electronic properties of the aryl unit appear to have little impact on the desired reactivity. Reactions with para substituted electron-rich aryl units such as methoxy (**5.3-1b**) and methyl (**5.3-1c**) or bearing an electron-withdrawing group such as Cl (**5.3-1d**) and ester (**5.3-1e-f**) allowed the formation of the desired products (**5.3-3ba**-**5.3-3fa**) in good yields. However, we observed a significant decrease in yield using the *p*-trifluoromethyl substituent (**5.3-3ga**, R= CF_3, 29%, dr = 1:1). This indicates that the electron density of the aryl amine can influence the SET process. High yields were obtained with *o*- and *m*-methoxy substituted cyclopropylamines **5.3-1h** and **5.3-1i** as well as with **5.3-1j**. The steric hindrance of the cyclopropylamine substituent has no influence on the reaction outcome, as shown by the reaction of *o*-phenyl and 2-naphthalenes **5.3-1k** and **5.3-1l**. Both provided the desired aminocyclopentanes (**5.3-3ka** and **5.3-3la**) in 84% and 99% yields, respectively. It is worth mentioning that the pyridine group is well tolerated under the reaction conditions, which is in contrast to the Rh(II)-catalyzed version.[2] The compound **5.3-3ma** was isolated in 95% yield.



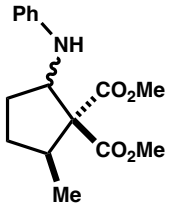
5.3-1a **5.3-2** **5.3-3aa-an**



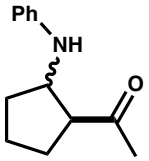
5.3-3aa, R= Et, 88%, 3:2 dr
5.3-3ab, R= Me, 78%, 3:2 dr
5.3-3ac, R= *t*Bu, 70%, 1:1 dr



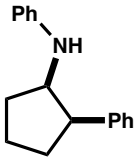
5.5-3ad, 99%, 4:3 dr



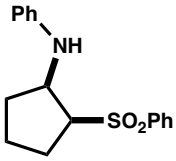
5.3-3ae, 57% 9:1 dr



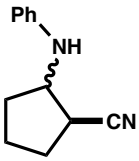
5.3-3af, 57%[a], 1:1 dr



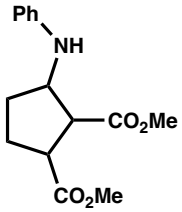
5.3-3ag, 84%, 3:2 dr



5.3-3ah, 65%, 6:1 dr

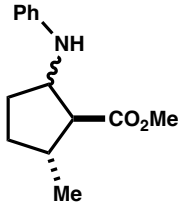


5.3-3ai, 99%, 1:2 dr

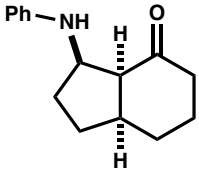


5.3-3aj

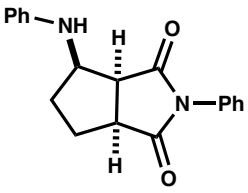
75%, 3:1 dr from **5.3-2j**
79%, 2:1 dr from **5.3-2k**



5.3-3al, 84%, 2:1 dr



5.3-3am, 31%, 6:1 dr



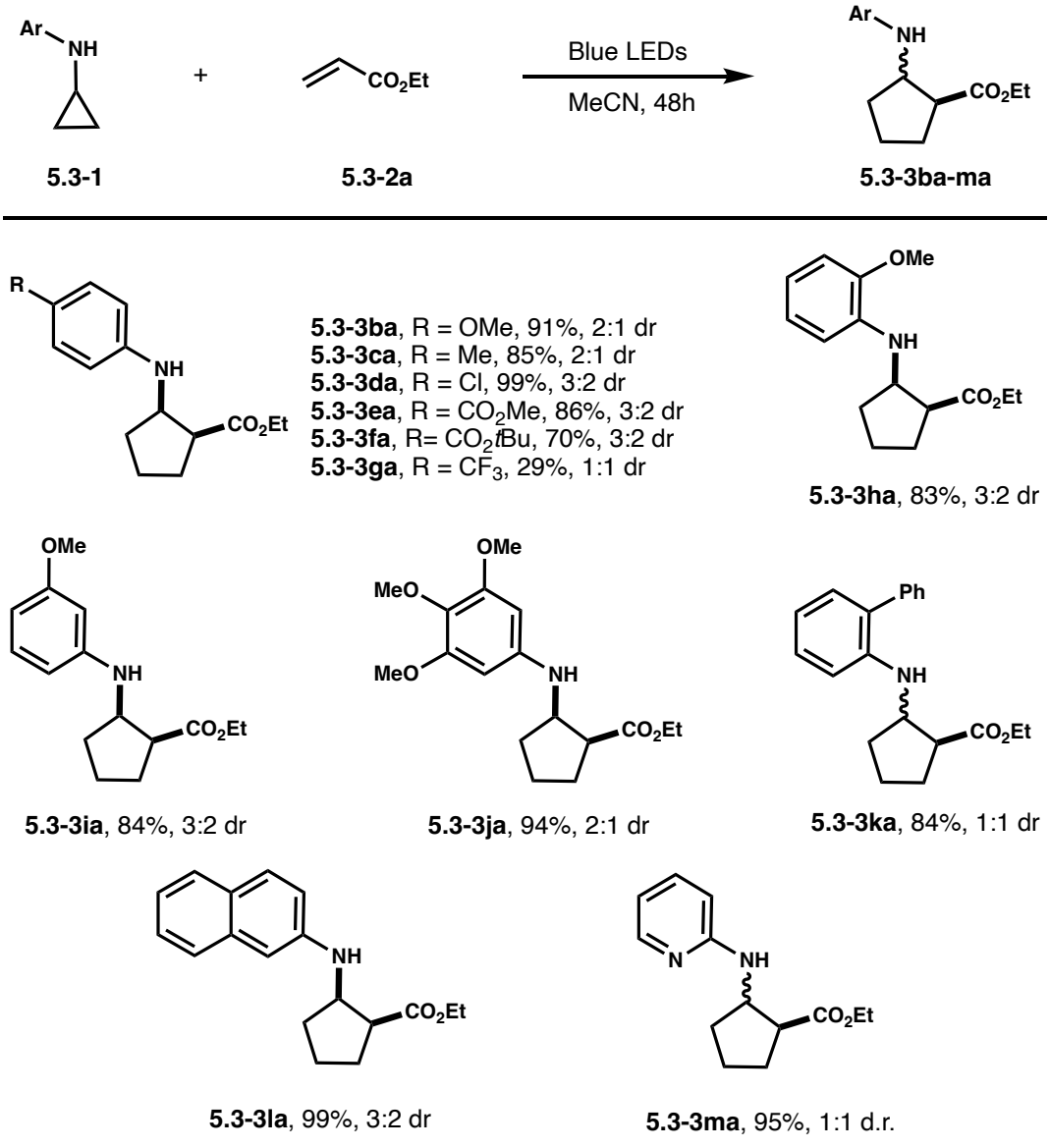
5.3-3an, 75%, 5:1 dr

[a] Isolated with 16% of **5.3-3af'**, Michael addition product

Scheme 5.2- Olefin **5.3-2** substrate scope.

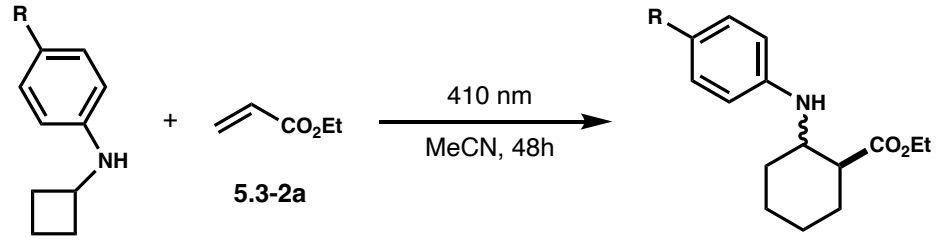
We were wondering if a similar photochemical process could be realized with *N*-arylcyclobutylamine leading to a formal [4 + 2]-cycloaddition (**Scheme 5.4**). Irradiation of *N*-phenyl cyclobutylamine **5.3-1n** and methyl acrylate **5.3-2a** with blue LEDs did not lead to the

complete conversion of the starting product, the desired product was obtained in low yield (<10%). However, performing the same reaction under 410 nm LEDs led to the formation of cyclohexylamine **5.3-3na** in 42% yield (dr = 1:1). We observed an increase in yield with the *p*-methoxy aryl substituent, the formal [4 + 2] cycloaddition product **5.3-3oa** was isolated in 92% yield (dr = 3:2) (**Scheme 5.4**).



Scheme 5.3- Aryl cyclopropylamine **5.3-1** substrate scope.

To gain further mechanistic insight, we performed a series of experiments. We first examined the effect the amine substitution, *N*-methyl-*N*-arylcyclopropylamine **5.3-1p** and carbamate **5.3-1q** were irradiated in the presence of ethyl acrylate **5.3-2a** under standard conditions (**Scheme 5.5A**). After 48h of irradiation using either UVA or blue LEDs, only starting material was recovered in both cases. These results indicates that the *N*-aryl and NH groups are essential for the SET to occur. Based on the results of the cyclization of methyl maleate **5.3-2j** and fumarate **5.3-2k** (**Scheme 5.2**), it can be assumed that the reaction proceeds via a SET process involving the simultaneous formation of cationic and anionic radical intermediates.



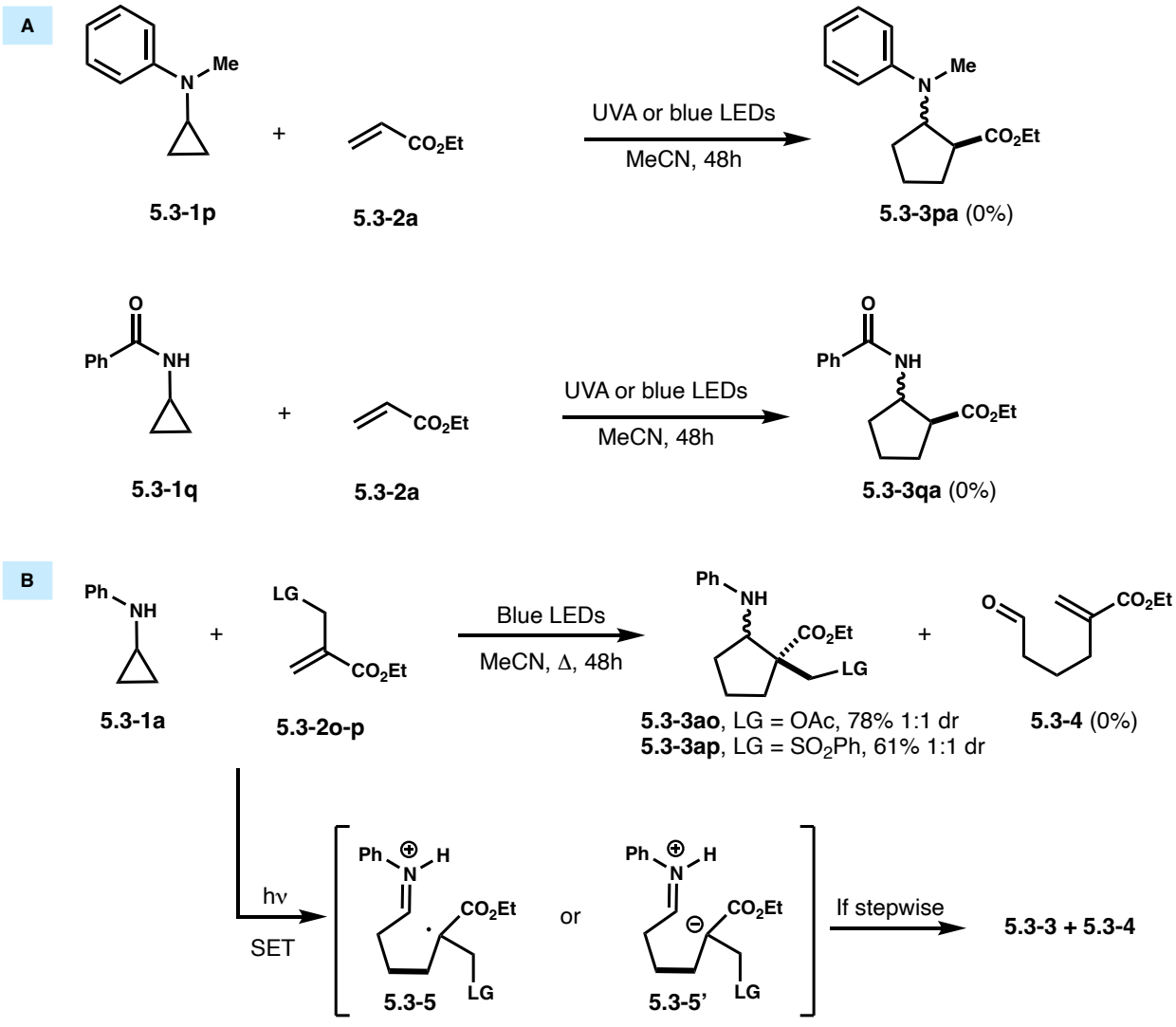
5.3-1n, R = H
5.3-1o, R = OMe

5.3-3na, R = H, 42%, 1:1 dr
5.3-3oa, R = OMe, 92%, 3:2 dr

Scheme 5.4- [4 + 2] cycloaddition of aryl cyclobutylamine.

To examine if the photochemical cycloaddition proceeds through a stepwise or concerted process, cyclopropyl amine **5.3-1a** was irradiated in the presence of allylic acetate **5.3-2p** and allylic sulfone **5.3-2o** (**Scheme 5.5B**). One could reason that if this reaction involves radical or anionic intermediates such **5.3-5** or **5.3-5'**, a mixture of compounds **5.3-3** and **5.3-4** would be observed due to the elimination of the leaving group. In both cases, only the cycloadducts **5.3-3ap** and **5.3-3ao** were isolated in 78% and 61% yields as a mixture of diastereomers. Elimination product such as **5.3-4** or its derivatives were not observed in the crude reaction mixture or nor isolated. Finally, resubmission of ***trans*-5.3-3aa** and ***cis*-5.3-3aa** separately to the reaction conditions in the presence of methyl acrylate **5.3-2b** did not lead to the formation of

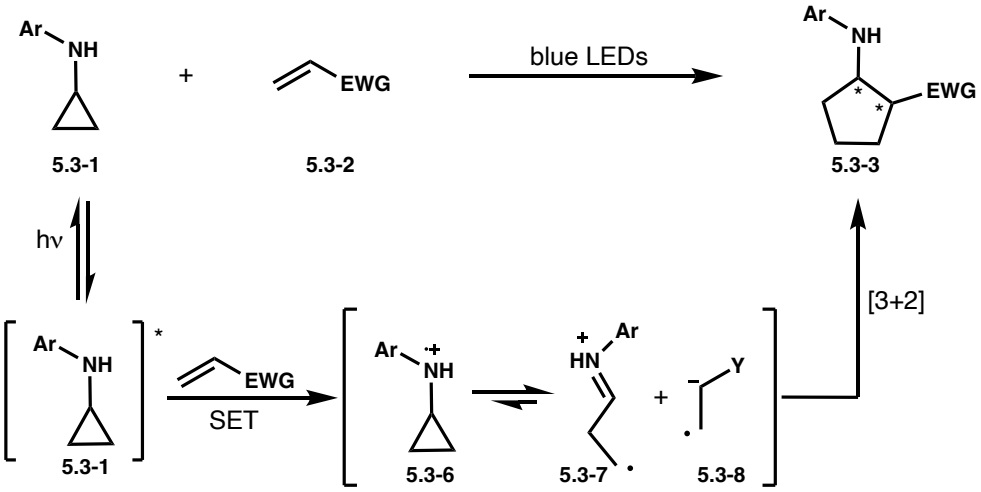
diastereomers, only starting material was recovered. At the outset, these results suggest that the reaction could proceed by a concerted mechanism. However, a stepwise process in which the addition onto the iminium would be faster than the elimination should not be ignored. This is different from previous photoredox-catalyzed [3 + 2] cycloadditions that propose a stepwise radical or anionic cycloaddition.[8-10]



Scheme 5.5- Experiments performed to support proposed mechanism.

With these results in hand, we propose the following mechanism (**Scheme 5.6**). After the photoexcitation of **5.3-1**, one can envisage a SET between **5.3-1** and **5.3-2** promoting the formation of a nitrogen centered radical cation **5.3-6** which under-goes a rapid strain-induced β-

scission ring opening and the radical anion **5.3-8**. The newly formed radical alkyl iminium **5.3-7** would combine with **5.3-8** resulting in the formation of **5.3-3**. The need for secondary aryl cyclopropylamines also supports the formation of a complex bound by hydrogen-bonding, as tertiary amines were not compatible with the methodology. The charge transfer could be facilitated by the H-bonding between **5.3-1** and **5.3-2** by stabilizing the complex and increasing the electrostatic attraction. On the other hand, given the electron rich nature of the *N*-aryl cyclo-propylamine **5.3-1** in the presence of electron accepting compounds such as **5.3-2**, the formation an electron donor-electron (EDA) complex could be at play.[11]



Scheme 5.6- Proposed mechanism of photoactivated [3 + 2] cycloaddition of aryl cyclopropylamines.

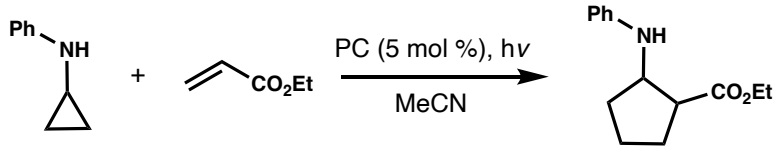
5.4- Conclusions

In summary, we have developed an operationally simple light-mediated formal [3 + 2] cycloaddition of *N*-aryl cyclopropyl amines and electron deficient alkenes to afford amino cyclopentanes in good to excellent yields. The reaction scope is broad including various alkenes and cyclo-propylamines providing key evidence that the reaction mechanism involves a photoinduced SET process. New forays into the use of diverse *N*-aryl cyclobutylamine derivatives including mechanistic investigations are underway and will be reported in due course.

5.5- Further Information

5.5.1- Full Optimization of Reaction Conditions

Table 5.2- Initial experiments of [3 + 2] photo-mediated cycloaddition of aryl cyclopropylamines



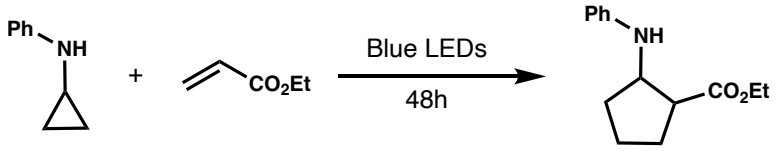
5.3-1a **5.3-2a** **5.2-3aa**

Entry	PC (5 mol %)	hν (nm)	Time (h)	additive	**5.3-1a** conversion (%)	**5.2-3aa** (%)	d.r.
1	$Ru(bpy)_3(PF_6)_2$	465	24	-	100	64	1:1
2	$Ir[dF(ppy)_2(dtbpy)]Cl$	465	24	-	100	68	1:1
3	$Ir[dF(ppy)_2(dtbpy)]PF_6$	465	24	-	100	52	1:1
4	$Ir(ppy)_3$	465	24	-	100	52	1:1
5	$MesAcrClO^-_4$	465	24	-	72	29	1:1
6	$Au_2dppm_2Cl_2$	365	24	-	100	58	1:1
7	$Ru(bpy)_3(PF_6)_2$	465	24	Phosphoric acid[a]	100	68	3:2
8	$Ir[dF(ppy)_2(dtbpy)]Cl$	465	24	Phosphoric acid[a]	100	84	3:2
9	$Ir[dF(ppy)_2(dtbpy)]PF_6$	465	24	Phosphoric acid[a]	100	91	3:2
10	$Ir(ppy)_3$	465	24	Phosphoric acid[a]	100	69	3:2
11	$MesAcrClO^-_4$	465	24	Phosphoric acid[a]	100	23	2:1
12	$Au_2dppm_2Cl_2$	365	24	Phosphoric acida	100	75	3:2
13	$Ru(bpy)_3(PF_6)_2$	465	24	HCl (conc)[b]	59	<10	2:1
14	$Ir[dF(ppy)_2(dtbpy)]Cl$	465	24	HCl (conc)[b]	89	25	2:1
15	$Ir[dF(ppy)_2(dtbpy)]PF_6$	465	24	HCl (conc)[b]	100	40	3:2
16	$Ir(ppy)_3$	465	24	HCl (conc)[b]	100	<10	2:1
17	$Au_2dppm_2Cl_2$	365	24	HCl (conc)[b]	100	34	1:1
18	-	365	24	Phosphoric acid[a]	100	68	1:1
19	-	365	24	Phosphoric acid[c]	100	0	-
20	-	465	24	Phosphoric acid[a]	74	24	1:1
21	-	465	24	Phosphoric acid[c]	100	<5	-

22	$Ru(bpy)_3(PF_6)_2$	465	8	Phosphoric acid[a]	85	53	3:2
23	$Ir[dF(ppy)_2(dtbpy)]Cl$	465	8	Phosphoric acid[a]	84	45	3:2
24	$Ir[dF(ppy)_2(dtbpy)]PF_6$	465	8	Phosphoric acid[a]	100	57	3:2
25	$Ir(ppy)_3$	465	8	Phosphoric acid[a]	100	68	3:2
26	$Au_2dppm_2Cl_2$	365	8	Phosphoric acid[a]	100	41	1:1
27[d]	-	365	24	-	100	88	3:2
28[e]	-	365	24	-	100	69	3:2
29[d]	-	465	24	-	49	46	3:2
30[d]	-	465	48	-	100	>95	3:2
31[d]	-	465	72	-	100	95	3:2

[a] 1,1'-binaphthyl-2,2'-diyl hydrogenphosphate, 15 mol%. [b] HCl (conc), 15 mol%. [c] (S)-(+)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate, 1 equivalent. [d] Heating to 80°C. [e]At room temperature

Table 5.3- Full optimization of reaction conditions of [3 + 2] photo-mediated cycloaddition of aryl cyclopropylamines



5.3-1a **5.3-2a** **5.2-3aa**

Entry	**5.3-2a** (equiv)	Solvent	[M]	**5.3-1a** conversion (%)	**5.3-3aa** (%)	d.r.
1	1	MeCN	0.1	100	72	3:2
2	2	MeCN	0.1	100	56	3:2
3	5	MeCN	0.1	100	45	3:2
4	10	MeCN	0.1	100	95	3:2
5	10	EtOH	0.1	100	78	3:2
6	10	THF	0.1	78	77	3:2
7	10	Cy-H	0.1	100	75	3:2
8	10	DCE	0.1	100	73	3:2
9	10	Ph-H	0.1	100	88	3:2
10	10	EtOAc	0.1	100	82	3:2
11	10	acetone	0.1	100	93	3:2
12	10	$PhCF_3$	0.1	100	93	3:2
13	10	MeCN	0.05	100	79	3:2
14	10	MeCN	0.2	100	98	3:2

15	10	MeCN	0.5	100	85	3:2
16	10	MeCN	Neat	95	<10[a]	-
17	10	MeCN	0.2	100	70	1:1

[a] Could not recover any material as there was complete polymerisation of the reaction medium.

5.5.2- Unsuccessful Substrates

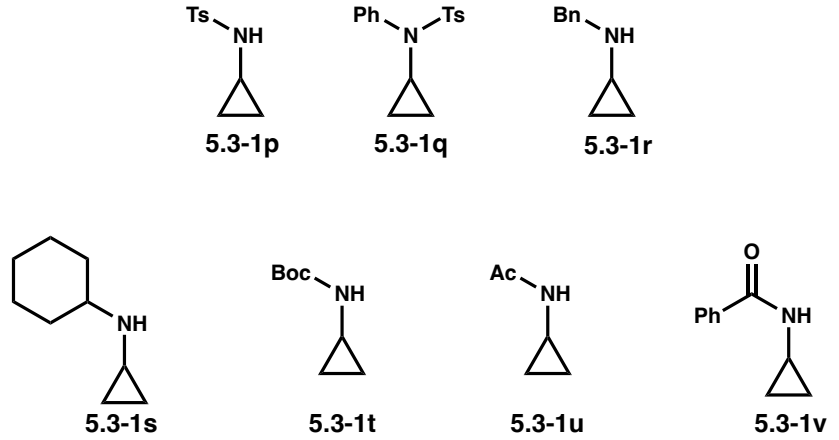


Figure 5.1- Unsuccessful substrates **5.3-1** that were not compatible with the methodology.

5.6- Experimental Procedures

5.6.1- General Information

All reactions were performed under argon atmosphere in Pyrex glassware equipped with a magnetic stir bar, capped with a septum, unless otherwise indicated. All commercial reagents were used without further purification, unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC) analysis. TLC plates were viewed under UV light and stained with potassium permanganate or *p*-anisaldehyde staining solution. Yields refer to products isolated after purification, unless otherwise stated. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AMX 400 MHz. NMR samples were dissolved in deuterated benzene (unless specified otherwise) and chemical shifts are reported in ppm referenced to residual undeuterated solvent. Data are reported as follows: chemical shift, multiplicity, coupling, integration. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on the same Bruker instruments as in proton NMR at 101 MHz. IR spectra were recorded with an Agilent

Technologies Cary 630 FTIR Spectrometer equipped with a diamond ATR module. HRMS were obtained on a Kratos Analytical Concept- Magnetic Sector Electron Impact Mass Spectrometer instrument and Micromass Q-TOF I-TOF Electrospray Ionisation mass spectrometer (University of Ottawa Mass Spectrum Centre).

5.6.2- General Procedures

General Procedure 1 (GP1)- Synthesis of Aryl cyclopropylamines: To an oven-dried round bottom flask Pd(allyl)(BrettPhos)(OTf) (5 mol %), sodium *tert*-butoxide (1.5 equiv) was added. The flask was evacuated and filled with Ar three times. Anhydrous toluene (0.125 M) was added, followed by cyclopropylamine (1.5 equiv), and aryl bromide (1 equiv). The flask was placed in an in an oil bath or aluminum heating block, as a heat source, and was stirred for 4 hours. The flask was removed from heat source and diluted with dichloromethane (0.1 M) and filtered through a pad of celite. The solution was concentrated *in vacuo* and azeotrope with ethanol when needed. Crude mixture was separated *via* column chromatography (0-100 % EtOAc:Hexane) where relevant fractions were combined, concentrated and characterized by proton and carbon NMR (400 and 101 MHz, respectively), HR-MS, and IR (when needed).

General Procedure 2 (GP2)- Synthesis of Aryl cyclopropylamines: An oven-dried round Schlenk tube was charged with CuI (5 mol %), K_2CO_3 (2 equiv), L-proline (20 mol %), cyclopropylamine (2 equiv), iodoarene (1 equiv), anhydrous DMSO (0.5 M) and a stir bar. After purging with Ar, the tube was sealed with a Teflon screw cap. The mixture was heated for 12h, or until full conversion of the starting material. The reaction was cooled down to room temperature, quenched with brine, diluted with Et_2O. The organic layers were separated, dried, and concentrated *in vacuo*. Crude mixture was separated *via* column chromatography (0-100% EtOAc: Hexane) where

relevant fractions were combined, concentrated, and characterized by proton and carbon NMR (400 and 101 MHz, respectively), HR-MS, and IR (when needed).

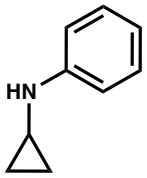
General Procedure 3 (GP3)- Synthesis of Aryl cyclobutylamines: To an oven-dried round flask aniline (1 equiv), cyclobutanone (2 equiv), and anhydrous DCM (0.2 M) was added. After purging with Ar and charged with a stir bar, $NaB(OAc)_3H$ (2 equiv) was added at 0°C. The reaction mixture was allowed to warm up to room temperature and was stirred for 3 hours to overnight. Once the reaction was deemed complete via thin layer chromatography (TLC), it was quenched with $NaHCO_3$ (aq). The organic layer extracted with HCl (1 M) three times. The aqueous phase was then basified with NaOH (1 M) to a pH of 12. The mixture was extracted with DCM. The organic layers were separated, dried, and concentrated *in vacuo* to obtain desired product. Product was characterized by proton and carbon NMR (400 and 101 MHz, respectively), HR-MS, and IR (when needed).

General Procedure 4 (GP4)- [3+2] Cycloaddition of Aryl cyclopropylamines: To an oven dried 8 mL Pyrex screw-top reaction vessel was added the aryl cyclopropylamine (0.2 mmol, 1 equiv), α-β- unsaturated acceptors **5.3-2** (2 mmol, 10 equiv), and MeCN (0.1 M). The reaction vessel was capped, degassed with Argon by sparging for 5 minutes (volatile α-β- unsaturated acceptors were added after sparging), then irradiated with a blue LED light (450 nm; 2-2.4 W; Mouser LED Emitter 897-LZ-400DB00) at an approximate distance of 1 cm for 48 hours. The reaction was removed from the light and concentrated *in vacuo*. Crude mixture was separated *via* column chromatography (0-100 % EtOAc:Hexane) where relevant fractions were combined, concentrated and characterized by proton and carbon NMR (400 and 101 MHz, respectively), HR-MS, and IR (when needed).

Synthetic example: To an oven dried 8 mL Pyrex screw-top reaction vessel was added the arylcyclopropylamine (1 mmol, 1 equiv), α-β- unsaturated acceptors (10 mmol, 10 equiv), and MeCN (0.1 M). The reaction vessel was capped, degassed with Argon by sparging for 5 minutes (volatile α-β- unsaturated acceptors were added after sparging), then irradiated with four blue LED light (450 nm; 2-2.4 W; Mouser LED Emitter 897-LZ-400DB00) at an approximate distance of 1 cm for 72 hours. The reaction was removed from the light and concentrated *in vacuo*. Crude mixture was separated *via* column chromatography (0-100 % EtOAc:Hexane) where relevant fractions were combined, concentrated and characterized by proton and carbon NMR (400 and 101 MHz, respectively), HR-MS, and IR (when needed).

5.7- Characterization Data

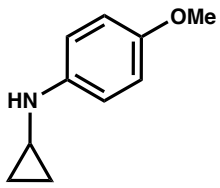
5.7.1- Characterization of 5.3-1 Starting Materials



Phenylcyclopropylamine (5.3-1a)

Synthesized according to GP1. Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[2] Synthesized as a yellow oil. (0.8876 g, 66%)

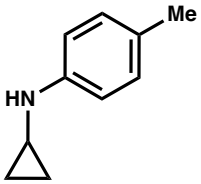
^{1}H NMR (400 MHz, C_6D_6) δ = 7.23 – 7.18 (m, 2H), 6.80 (tt, *J* = 7.3, 1.2 Hz, 1H), 6.69 – 6.63 (m, 2H), 3.45 (s, 1H), 2.06 – 1.99 (m, 1H), 0.36 – 0.30 (m, 2H), 0.25 – 0.19 (m, 2H) ppm; **^{13}C NMR** (101 MHz, C_6D6) δ = 149.1 (C), 129.4 (2 X CH), 118.1 (CH), 113.6 (2 X CH), 25.3 (CH), 7.6 (2 X CH_2) ppm.



4-methoxy-*N*-cyclopropylaniline (5.3-1b)

Synthesized according to GP1. Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[2] Synthesized as a yellow oil. (0.1837 g, 48%)

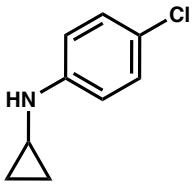
^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.90 – 6.83 (m, 2H), 6.65 – 6.58 (m, 2H), 3.42 (s, 3H), 2.08 – 2.02 (m, 1H), 0.38 – 0.32 (m, 2H), 0.31 – 0.26 (m, 2H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ =153.1 (C), 143.3 (C), 115.1 (2 X CH), 114.5 (2 X CH), 55.4 (CH_3), 26.0 (CH), 7.5 (2 X CH_2) ppm.



4-methyl-*N*-cyclopropylaniline (5.3-1c)

Synthesized according to GP1. Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[2] Synthesized as a yellow oil. (0.1578 g, 55%)

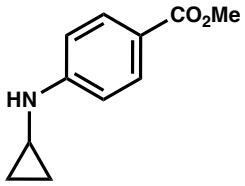
^{1}H NMR (400 MHz, C_6D_6) δ = 7.08 – 7.02 (m, 2H), 6.67 – 6.62 (m, 2H), 2.22 (s, 3H), 2.08 – 2.03 (m, 1H), 0.38 – 0.32 (m, 2H), 0.29 – 0.23 (m, 2H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 147.0 (C), 129.9 (2 X CH), 126.7 (C), 113.7 (2 X CH), 25.6 (CH), 20.7 (CH_3), 7.6 (CH_3) ppm.



_N_-(_p_-chlorophenyl)cyclopropylamine (5.3-1d)

Synthesized according to GP1. Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[2] Synthesized as a yellow oil. (0.2067 g, 53%)

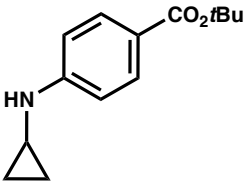
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.17 – 7.08 (m, 2H), 6.79 – 6.64 (m, 2H), 4.31 (s, 1H), 2.40 (tt, *J* = 6.7, 3.6 Hz, 1H), 0.80 – 0.70 (m, 2H), 0.55 – 0.48 (m, 2H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 147.1 (C), 129.2 (C), 128.9 (2 X CH), 114.3 (2 X CH), 25.4 (CH), 7.9 (2 X CH_2) ppm.



Methyl 4-(cyclopropylamino)benzoate (5.3-1e)

Synthesized according to GP2. Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[12] Synthesized as a yellow oil. (0.1837 g, 48%)

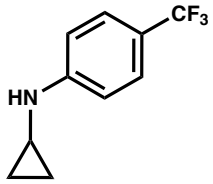
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.28 – 8.14 (m, 2H), 6.53 – 6.42 (m, 2H), 3.71 (s, 1H), 3.59 (s, 3H), 1.87 (dddd, *J* = 10.2, 6.6, 3.6, 1.1 Hz, 1H), 0.31 – 0.22 (m, 2H), 0.12 – 0.05 (m, 2H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 167.1 (C), 152.8 (C), 131.8 (2 X CH), 119.8 (C), 112.4 (2 X CH), 51.2 (CH_3), 24.7 (CH), 7.6 (2 X CH_2) ppm.



Tertbutyl 4-(cyclopropylamino)benzoate (5.3-1f)

Synthesized according to GP2 (By-product of 1f synthesis). Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a yellow oil. (0.1837 g, 48%)

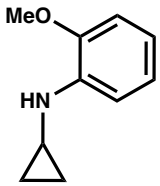
IR (neat, cm^{-1}): 3376 (m), 2977 (m), 1678 (m), 1604 (vs), 1521 (m), 1366 (m), 1292 (vs), 1156 (vs), 1107 (s), 772 (s); **^{1}H NMR** (400 MHz, C_6D_6) δ = 8.28 – 8.20 (m, 2H), 6.51 – 6.44 (m, 2H), 3.56 (s, 1H), 1.87 (dddd, *J* = 10.2, 6.6, 3.6, 1.3 Hz, 1H), 1.54 (s, 9H), 0.25 (td, *J* = 6.7, 4.6 Hz, 2H), 0.13 – 0.03 (m, 2H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 166.1 (C), 152.4 (C), 131.7 (2 X CH), 121.8 (C), 112.3 (2 X CH), 79.4 (C), 28.4 (3 X CH_3), 24.8 (CH), 7.6 (2 X CH_2) ppm; **HRMS** (EI) m/z: [M^+] Calc'd for $C_{14}H_{19}NO_2$ 233.1416; Found 233.1444.



***N*-cyclopropyl-4-(trifluoromethyl)aniline (5.3-1g)**

Synthesized according to GP2. Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[12] Synthesized as a yellow oil. (0.1881 g, 90%)

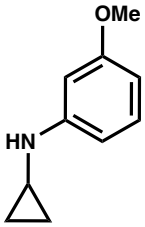
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 – 7.36 (m, 2H), 6.85 – 6.74 (m, 2H), 4.51 (s, 1H), 2.46 (tt, *J* = 6.7, 3.6 Hz, 1H), 0.82 – 0.74 (m, 2H), 0.57 – 0.51 (m, 2H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 151.4 (C), 126.69 (2 X CH, q, *J* = 3.8 Hz), 119.81 – 119.21 (C, m), 114.1 (C), 112.7 (2 X CH), 24.7 (CH), 7.53 (2 X CH_2) ppm.



***N*-cyclopropyl-2-methoxyaniline (5.3-1h)**

Synthesized according to GP1. Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[13] Synthesized as a yellow oil. (0.286 g, 75%)

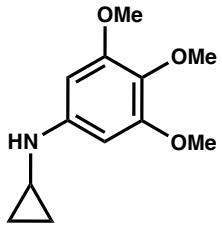
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.09 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.04 (td, *J* = 7.7, 1.3 Hz, 1H), 6.78 (ddd, *J* = 7.9, 7.3, 1.8 Hz, 1H), 6.58 (dd, *J* = 7.9, 1.3 Hz, 1H), 4.60 (s, 1H), 3.32 (s, 3H), 2.16 – 2.09 (m, 1H), 0.39 – 0.29 (m, 4H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 147.1 (C), 139.2 (C), 121.8 (CH), 117.2 (CH), 111.5 (CH), 54.9 (CH_3), 25.1 (CH), 7.44 (2 X CH_2) ppm.



***N*-cyclopropyl-3-methoxyaniline (5.3-1i)**

Synthesized according to GP1. Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[2] Synthesized as a yellow oil. (0.2015 g, 53%)

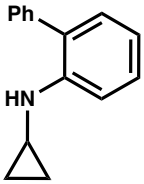
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.12 – 7.03 (m, 1H), 6.41 – 6.35 (m, 2H), 6.34 – 6.28 (m, 1H), 4.24 (s, 1H), 3.79 (s, 3H), 2.42 (tt, *J* = 6.7, 3.6 Hz, 1H), 0.76 – 0.68 (m, 2H), 0.55 – 0.47 (m, 2H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 160.8 (C), 150.1 (C), 129.8 (CH), 106.4 (CH), 102.8 (CH), 99.9 (CH), 55.1 (CH_3), 25.2 (CH), 7.4 (2 X CH_2) ppm.



***N*-cyclopropyl-3,4,5-trimethoxyaniline (5.3-1j)**

Synthesized according to GP1. Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[14] Synthesized as a yellow oil. (0.3288 g, 63%)

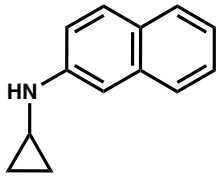
^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.12 – 5.98 (m, 2H), 3.84 (s, 6H), 3.77 (s, 3H), 2.42 (tt, *J* = 6.9, 3.6 Hz, 1H), 0.73 (td, *J* = 6.7, 4.6 Hz, 2H), 0.58 – 0.49 (m, 2H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 153.9 (2 x C), 145.4 (C), 90.6 (2 X CH), 61.1 (CH_3), 55.9 (2 X CH_3), 25.4 (CH), 7.3 (2 X CH_2) ppm.



***N*-cyclopropyl-[1,1'-biphenyl]-2-amine (5.3-1k)**

Synthesized according to GP1. Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[2] Synthesized as a yellow oil. (0.1949 g, 40%)

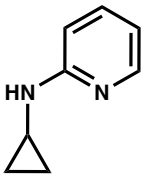
^{1}H NMR (400 MHz, C_6D_6) δ = 7.39 – 7.34 (m, 2H), 7.30 (tdd, *J* = 7.3, 1.6, 0.8 Hz, 1H), 7.20 – 7.13 (m, 5H), 7.11 – 7.05 (m, 1H), 6.87 (td, *J* = 7.4, 1.3 Hz, 1H), 4.30 (s, 1H), 2.02 (dddd, *J* = 10.1, 6.5, 3.6, 1.2 Hz, 1H), 0.31 – 0.24 (m, 2H), 0.20 – 0.12 (m, 2H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 146.0 (C), 140.3 (C), 130.6 (CH), 129.7 (2 X CH), 129.2 (2 X CH), 129.1 (CH), 129.1 (C), 127.4 (CH), 118.1 (CH), 112.3 (CH), 25.6 (CH), 7.7 (2 X CH_2) ppm.



***N*-cyclopropylnaphthalen-2-amine (5.3-1l)**

Synthesized according to GP1. Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[2] Synthesized as a yellow oil. (0.2475 g, 58%)

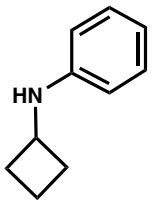
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.71 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.66 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.34 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.20 – 7.17 (m, 1H), 7.13 (d, *J* = 2.3 Hz, 1H), 6.62 (dd, *J* = 8.7, 2.3 Hz, 1H), 3.56 (s, 1H), 2.14 – 2.06 (m, 1H), 0.43 – 0.35 (m, 2H), 0.29 – 0.24 (m, 2H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 146.7 (C), 136.0 (C), 129.1 (CH), 128.5 (C), 128.2 (CH), 126.6 (CH), 126.6 (CH), 122.4 (CH), 118.1 (CH), 106.0 (CH), 25.3 (CH), 7.6 (CH_2) ppm.



***N*-cyclopropylpyridin-2-amine (5.3-1m)**

Synthesized according to GP1. Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[2] Synthesized as a yellow oil. (0.2927 g, 94%)

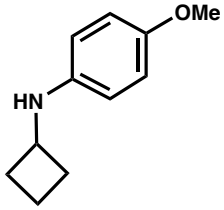
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.24 (ddd, *J* = 5.0, 2.0, 0.9 Hz, 1H), 7.23 – 7.18 (m, 1H), 6.50 (dt, *J* = 8.3, 1.0 Hz, 1H), 6.41 (ddd, *J* = 7.2, 4.9, 1.0 Hz, 1H), 5.23 (s, 1H), 2.13 – 2.03 (m, 1H), 0.33 – 0.27 (m, 2H), 0.22 – 0.16 (m, 2H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 160.6 (C), 148.9 (CH), 137.3 (CH), 113.5 (CH), 106.0 (CH), 24.2 (CH), 7.6 (2 X CH_2) ppm.



***N*-cyclobutylaniline (5.3-1n)**

Synthesized according to GP3 and characterized according to NMR comparison.[15] Synthesized as a clear oil.

^{1}H NMR (400 MHz, C_6D_6) δ = 7.22 – 7.17 (m, 2H), 6.77 (tt, *J* = 7.3, 1.1 Hz, 1H), 6.45 – 6.39 (m, 2H), 3.61 (t, *J* = 7.2 Hz, 1H), 3.26 (s, 1H), 2.16 – 2.06 (m, 2H), 1.56 – 1.40 (m, 4H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 147.7 (C), 129.6 (2 X CH), 117.6 (CH), 113.3 (2 X CH), 49.0 (CH), 31.3 (2 X CH_2), 15.4 (CH_2) ppm.

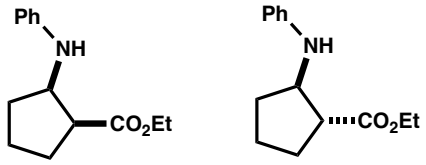


***N*-cyclobutyl-4-methoxyaniline (5.3-1o)**

Synthesized according to GP3 and characterized according to NMR comparison.[15] Synthesized as a clear oil.

^{1}H NMR (400 MHz, C_6D_6) δ = 6.87 – 6.81 (m, 2H), 6.43 – 6.37 (m, 2H), 3.68 – 3.57 (m, 1H), 3.42 (s, CH_3), 2.19 – 2.11 (m, 2H), 1.61 – 1.47 (m, 4H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 152.8 (C), 142.0 (C), 115.3 (2 X CH), 114.6 (2 X CH), 55.4 (CH_3), 49.9 (CH), 31.5 (2 X CH_2), 15.5 (CH_2) ppm.

5.7.2- Characterization of 5.3-3 products



Ethyl 2-(phenylamino)cyclopentanecarboxylate (5.3-3aa)

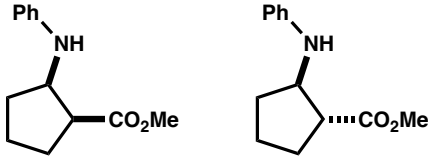
Synthesized according to GP3. Crude mixture was purified by flash chromatography (0-30% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[2] Synthesized as a yellow oil. (41 mg, 88%; 0.2285 g, 98% (1 mmol scale)

(3aa-*cis)*

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.19 – 7.09 (m, 2H), 6.68 (tt, *J* = 7.3, 1.1 Hz, 1H), 6.64 – 6.58 (m, 2H), 4.09 (m, 2H), 4.05 – 3.91 (m, 2H), 3.09 (q, *J* = 7.4 Hz, 1H), 2.17 – 1.83 (m, 4H), 1.83 – 1.71 (m, 1H), 1.71 – 1.54 (m, 1H), 1.08 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ =174.3 (C), 147.3 (C), 129.1 (2 X CH), 117.2 (CH), 113.3 (2 X CH), 60.3 (CH_2), 57.0 (CH), 47.2 (CH), 32.9 (CH_2), 27.8 (CH_2), 22.4 (CH_2), 14.0 (CH_3) ppm.

(3aa-*trans)*

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.20 – 7.13 (m, 2H), 6.70 (tt, *J* = 7.4, 1.1 Hz, 1H), 6.66 – 6.58 (m, 2H), 4.16 – 4.05 (m, 3H), 2.66 (ddd, *J* = 8.5, 7.3, 5.9 Hz, 1H), 2.28 – 2.15 (m, 1H), 2.08 – 1.88 (m, 2H), 1.85 – 1.75 (m, 2H), 1.58 – 1.48 (m, 1H), 1.22 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 175.3 (C), 147.3 (C), 129.2 (2 X CH), 117.5 (CH), 113.4 (2 X CH), 60.6 (CH_2), 58.6 (CH), 51.3 (CH), 33.7 (CH_2), 28.5 (CH_2), 23.5 (CH_2), 14.1 (CH_3) ppm.



Methyl 2-(phenylamino)cyclopentanecarboxylate (5.3-3ab)

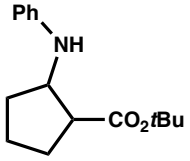
Synthesized according to GP3. Crude mixture was purified by flash chromatography (0-30% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[2] Synthesized as a clear oil. (34 mg, 78%, 3:2 d.r.)

(3ab-*cis- major diastereoisomer)*

^{1}H NMR (400 MHz, C_6D_6) δ = 7.15 – 7.09 (m, 2H), 6.73 (m, 1H), 6.51 – 6.44 (m, 2H,), 3.97 (s, 1H), 3.77 (p, *J* = 6.5 Hz, 1H), 3.20 (s, 3H), 2.81 (q, *J* = 7.4 Hz, 1H), 2.07 – 1.96 (m, 1H), 1.94 – 1.79 (m, 1H), 1.65 – 1.54 (m, 2H), 1.44 – 1.32 (m, 1H), 1.10 (m, 1H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 174.4 (C), 147.9 (C), 129.5 (2 X CH), 117.8 (CH), 113.8 (2 x CH), 57.2 (CH), 51.0 (CH_3), 47.1 (CH), 32.9 (CH_2), 28.1 (CH_2), 22.6 (CH_2) ppm.

(3ab-*trans- minor diastereoisomer)*

^{1}H NMR (400 MHz, C_6D_6) δ = 7.15 – 7.09 (m, 2H), 6.73 (m, 1H), 6.60 – 6.53 (m, 2H), 4.09 (q, *J* = 6.4 Hz, 1H), 3.30 (s, 3H), 3.25 (s, 1H), 2.46 (ddd, *J* = 8.4, 7.1, 5.8 Hz, 1H), 1.75 – 1.65 (m, 1H), 1.65 – 1.54 (m, 2H), 1.55 – 1.45 (m, 1H), 1.29 – 1.15 (m, 2H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 175.3 (C), 147.9 (C), 129.6 (2 X CH), 117.9 (CH,), 113.8 (2 x CH), 58.8 (CH), 51.4 (CH), 51.2 (CH_3), 33.5 (CH_2), 28.8 (CH_2), 23.6 (CH_2), ppm.



***tert*-butyl 2-(phenylamino)cyclopentanecarboxylate (5.3-3ac)**

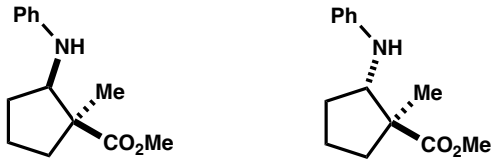
Synthesized according to GP3. Crude mixture was purified by flash chromatography (0-30% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[2] Synthesized as a yellow oil. (37 mg, 70%, 1:1 d.r.)

(3ac-*cis)*

^{1}H NMR (400 MHz, C_6D_6) δ = 7.15 – 7.12 (m, 2H), 6.74 (m, 1H), 6.51 – 6.46 (m, 2H), 3.98 (d, *J* = 7.8 Hz, 1H), 3.74 (dt, *J* = 14.4, 7.2 Hz, 1H), 2.83 (dt, *J* = 8.1, 7.1 Hz, 1H), 1.96 – 1.82 (m, 2H), 1.77 – 1.49 (m, 2H), 1.46 – 1.37 (m, 2H), 1.25 (s, 9H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 173.5 (C), 148.1 (C), 129.4 (2 X CH), 117.5 (CH), 113.7 (2 X CH), 80.0 (C), 57.3 (CH), 48.0 (CH), 33.2 (CH_2), 28.0 (CH_2) 28.0 (3 X CH_3), 22.7 (CH_2) ppm.

(3ac-*trans)*

^{1}H NMR (400 MHz, C_6D_6) δ = 7.20 – 7.17 (m, 2H), 6.74 (m, 1H), 6.64 – 6.56 (m, 2H), 4.07 (q, *J* = 6.4 Hz, 1H), 3.30 (s, 1H), 2.44 (ddd, *J* = 8.6, 6.9, 5.7 Hz, 1H), 2.17 – 2.03 (m, 1H), 1.77 – 1.49 (m, 3H), 1.33 (s, 9H), 1.20 – 1.04 (m, 2H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 174.3 (C), 148.1 (C), 129.5 (2 X CH), 117.8 (CH), 113.9 (2 X CH), 80.0 (C), 58.9 (CH), 52.4 (CH), 33.9 (CH_2), 28.7 (CH_2), 28.0 (3 X CH_3), 23.8 (CH_2) ppm.



Methyl 1-methyl-2-(phenylamino)cyclopentanecarboxylate (5.3-3ad)

Synthesized according to GP3. Crude mixture was purified by flash chromatography (0-30% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[2] Synthesized as a yellow oil. (46 mg, 99%, 3:4 d.r.)

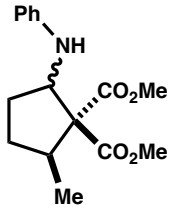
(***cis*-5.3-3ad**-*minor diastereoisomer)*

^{1}H NMR (400 MHz, C_6D_6) δ = 7.15 – 7.10 (m, 2H), 6.71 (m, 1H), 6.55 – 6.49 (m, 1H), 3.49 – 3.39 (m, 2H), 3.35 (d, *J* = 5.2 Hz, 2H), 3.24 (s, 3H), 2.30 – 2.13 (m, 2H), 2.07 (s, 1H), 2.00 – 1.81 (m, 2H), 1.63 – 1.43 (m, 3H), 1.43 – 1.24 (m, 7H), 1.22 (s, 2H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 176.3 (C),

148.4 (C), 129.5 (2 X CH), 117.6 (CH), 113.9 (2 X CH), 64.0 (CH), 51.3 (CH_3), 45.5 (C), 36.2 (CH_2), 31.9 (CH_2), 23.5 (CH_3), 21.1 (CH_2) ppm.

(***trans*-5.3-3ad**-*major diastereoisomer)*

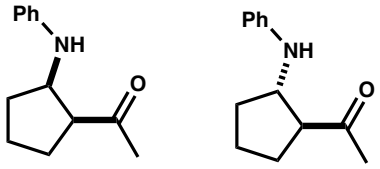
^{1}H NMR (400 MHz, C_6D_6) δ = 7.15 – 7.10 (m, 2H), 6.71 (m, 1H), 6.60 – 6.55 (m, 2H), 4.35 (t, *J* = 8.8 Hz, 1H), 3.49 – 3.39 (m, 2H), 3.35 (d, *J* = 5.2 Hz, 2H), 3.29 (s, 3H), 2.30 – 2.13 (m, 2H), 2.07 (s, 1H), 2.00 – 1.81 (m, 2H), 1.63 – 1.43 (m, 3H), 1.43 – 1.24 (m, 7H), 1.04 (s, 3H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 177.9 (C), 148.2 (C), 129.6 (2 X CH), 117.7 (CH), 113.7 (2 X CH), 61.1 (CH), 51.6 (CH_3),45.2 (C), 37.87 (CH_2), 32.5 (CH_2), 21.1 (CH_2), 17.5 (CH_3) ppm.



(5.3-3ae)

Synthesized according to GP3. Crude mixture was purified by flash chromatography (0-30% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a yellow oil. (33 mg, 57%, 9:1 d.r.)

IR (neat, cm^{-1}): 3395 (bs), 2947 (m), 2873 (m), 1717 (vs), 1601 (vs), 1497 (s), 1432 (m), 1315 (m), 1251 (s), 1146 (vs), 746 (vs), 692 (vs); **^{1}H NMR** (400 MHz, C_6D_6) δ = 7.12 – 7.05 (m, 2H), 6.68 (tt, *J* = 7.3, 1.1 Hz, 1H), 6.63 – 6.54 (m, 2H), 4.89 (q, *J* = 7.3 Hz, 1H), 3.33 (s, 3H), 3.17 (s, 3H), 2.95 – 2.78 (m, 1H), 2.33 – 2.20 (m, 1H), 1.65 – 1.56 (m, 1H), 1.23 – 1.11 (m, 2H), 1.06 (d, *J* = 6.9 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 171.2 (C), 170.3 (C), 147.4 (C), 129.4 (2 X CH), 113.9 (2 X CH), 68.4 (C), 60.5 (CH), 51.5 (2 X CH_3), 40.5 (CH), 33.7 (CH_2), 31.1 (CH_2), 16.7 (CH_3) ppm; **HRMS** (EI) m/z: [M^+] Calc'd for $C_{16}H_{21}NO_4$ 291.1471; Found 291.1471.



1-(phenylamino)-2-acetylcyclopentanone (5.3-3af)

Synthesized according to GP3. Crude mixture was purified by flash chromatography (0-30% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[13] Stereochemistry was determined by NMR comparison.[13] Synthesized as a clear oil. (23 mg, 57%, 1:1 d.r.)

(*cis*-**5.3-3af**)

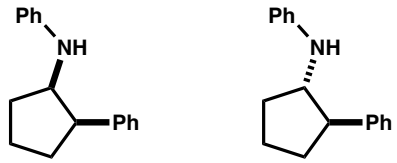
^{1}H NMR (400 MHz, C_6D_6) δ = 7.16 – 7.12 (m, 2H), 6.74 (tt, *J* = 7.4, 1.1 Hz, 1H), 6.49 – 6.44 (m, 2H), 4.00 (dt, *J* = 7.1, 5.6 Hz, 1H), 3.10 (s, 1H), 2.22 (ddd, *J* = 8.8, 6.9, 5.4 Hz, 1H), 1.81 (dq, *J* = 12.7, 7.0 Hz, 1H), 1.74 (s, 3H), 1.59 – 1.47 (m, 2H), 1.47 – 1.30 (m, 2H), 1.17 – 1.04 (m, 1H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 208.1 (C), 147.9 (C), 129.6 (2 X CH), 117.9 (CH), 113.8 (2 X 2H), 58.9 (CH), 57.0 (CH), 33.9 (CH_2), 29.0 (CH_3), 28.4 (CH_2), 24.1 (CH_2) ppm.

(*trans*-**5.3-3af***)* Isolated in a 1:1 mixture with product **5.3-3af'**

^{1}H NMR (400 MHz, C_6D_6) δ = 7.15 – 7.09 (m, 2H), 6.73 (tt, *J* = 7.4, 1.1 Hz, 1H), 6.42 – 6.34 (m, 2H), 3.76 – 3.63 (m, 2H), 2.66 (dt, *J* = 8.4, 6.8 Hz, 1H), 2.01 – 1.94 (m, 1H), 1.69 (s, 3H), 1.66 – 1.56 (m, 2H), 1.54 – 1.50 (m, 1H), 1.50 – 1.36 (m, 1H), 1.32 – 1.22 (m, 1H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 208.9 (C), 147.8 (C), 129.6 (2 X CH), 117.9 (CH), 113.8 (2 X CH), 57.3 (CH), 53.7 (CH), 32.7 (CH_2), 29.8 (CH_3), 26.4 (CH_2), 22.2 (CH_2) ppm.

(**5.3-3af'**)

^{1}H NMR (400 MHz, C_6D_6) δ = 7.30 – 7.21 (m, 2H), 6.96 – 6.89 (m, 2H), 6.83 (tt, *J* = 7.3, 1.1 Hz, 1H), 3.76 – 3.62 (m, 1H), 3.62 – 3.51 (m, 2H), 2.25 – 2.15 (m, 2H), 1.55 (s, 3H), 0.52 – 0.33 (m, 4H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 205.9 (C), 149.3 (C), 129.4 (2 X CH), 118.3 (CH), 115.2 (2 X CH), 45.9 (CH_2), 39.7 (CH_2), 31.6 (CH_3) , 30.7 (CH), 9.4 (2 X CH_2) ppm.



***N*-(2-phenylcyclopentyl)aniline (5.3-3ag)**

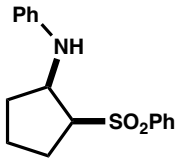
Synthesized according to GP4. Crude mixture was purified by flash chromatography (0-30% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[2] Stereochemistry was determined by NMR comparison.[2] Synthesized as a yellow oil. (40 mg, 84%)

(*cis*-**5.3-3ag**)-Major diastereoisomer

^{1}H NMR (400 MHz, C_6D_6) δ = 7.14 – 7.01 (m, 7H), 6.71 (m, 1H), 6.44 – 6.38 (m, 2H), 3.65 (q, *J* = 7.2 Hz, 1H), 3.35 (s, 1H), 2.63 – 2.50 (m, 1H), 1.82 – 1.65 (m, 1H), 1.65 – 1.42 (m, 4H), 1.42 – 1.26 (m, 1H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 148.5 (C), 144.2 (C), 129.5 (2 X CH), 128.8 (2 X CH), 127.6 (2 X CH), 126.6 (CH), 117.5 (CH), 113.8 (2 X CH), 61.4 (CH), 53.1 (CH), 33.6 (CH_2), 33.5 (CH_2), 23.4 (CH_2) ppm.

(*trans*-**5.3-3ag**)- Minor diastereoisomer

^{1}H NMR (400 MHz, C_6D_6) δ = 7.14 – 7.01 (m, 7H), 6.71 (m, 1H), 6.35 – 6.30 (m, 2H), 3.74 (t, *J* = 5.8 Hz, 1H), 3.14 (m, 2H) 2.09 – 1.99 (m, 1H), 1.96 – 1.82 (m, 2H), 1.65 – 1.42 (m, 3H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 148.3 (C), 141.2 (C), 129.4 (2 X CH), 129.0 (2 X CH), 128.5 (2 X CH), 126.7 (CH), 117.4 (CH), 113.7 (2 X CH), 57.6 (CH), 47.9 (CH), 32.1 (CH_2), 29.2 (CH_2), 22.2 (CH_2) ppm.

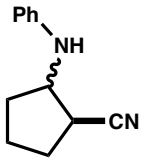


(5.3-3ah)

Synthesized according to GP4. Crude mixture was purified by flash chromatography (0-30% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a yellow oil. (39 mg, 65%, 6:1 d.r.)

(*cis*-**5.3-3ah**) containing 23% of phenyl vinyl sulfone **5.3-2h**

IR (neat, cm^{-1}): 3396 (m), 3370 (m), 3055 (m), 2965 (m), 2938 (m), 2896 (m), 2279 (m), 1601 (s), 1506 (s), 1597 (s), 1306 (s), 1286 (s), 1143 (vs), 1083 (vs), 812 (m), 812 (m), 744 (vs), 688 (vs); **^{1}H NMR** (400 MHz, C_6D_6) δ = 7.76 – 7.70 (m, 2H), 7.13 – 7.06 (m, 2H), 6.97 – 6.84 (m, 3H), 6.73 (tt, *J* = 7.3, 1.1 Hz, 1H), 6.46 – 6.33 (m, 2H), 4.20 (dt, *J* = 7.4, 4.1 Hz, 1H), 3.21 (s, 1H), 3.11 (ddd, *J* = 8.4, 5.9, 4.1 Hz, 1H), 2.08 – 1.93 (m, 2H), 1.55 (dddd, *J* = 15.0, 12.6, 7.6, 3.0 Hz, 2H), 1.36 – 1.13 (m, 2H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 146.9 (C), 139.5 (C), 129.5 (2 X CH), 129.2 (CH), 129.0 (2 X CH), 128.8 (2 X CH), , 118.2 (CH), 113.7 (2 X CH), 69.6 (CH), 56.1 (CH), 33.6 (CH_2), 25.8 (CH_2), 23.4 (CH_2) ppm; **HRMS** (ESI) m/z: [M^+] Calc'd for $C_{17}H_{19}NO_2S$ 301.1136; Found 301.1152.

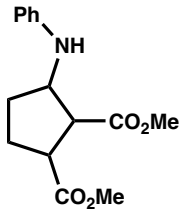


(5.3-3ai)

Synthesized according to GP4. Crude mixture was purified by flash chromatography (0-30% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR

comparison.[8a] Stereochemistry was determined by NMR comparison.[8a] Synthesized as a yellow oil. (37 mg, 99%, 1:2 d.r.)

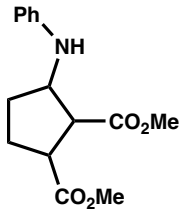
^{1}H NMR (400 MHz, C_6D_6) δ = 7.16 – 7.11 (m, 4H), 6.76 (tdt, *J* = 7.1, 5.9, 1.1 Hz, 2H), 6.51 – 6.46 (m, 1.7H, minor diastereoisomer), 6.44 – 6.32 (m, 2H, major diastereoisomer), 3.72 (m, 1.7H, minor diastereoisomer), 3.27 (tt, *J* = 9.0, 6.7 Hz, 1H, major diastereoisomer), 3.05 (s, 1H, major diastereoisomer), 2.51 – 2.35 (m, 1Hf, major diastereoisomer), 2.03 (ddd, *J* = 8.1, 5.6, 4.4 Hz, 0.7H, minor diastereoisomer), 1.66 (dtd, *J* = 13.4, 7.8, 6.3 Hz, 0.7H, minor diastereoisomer), 1.58 – 1.46 (m, 2H), 1.46 – 1.09 (m, 8H), 1.07 – 0.94 (m, 1H), 0.84 – 0.74 (m, 0.7H, minor diastereoisomer) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 147.3 (C, major diastereoisomer), 146.8 (C, minor diastereoisomer), 129.7 (2 X CH, minor diastereoisomer), 129.6 (2 X CH, major diastereoisomer), 122.1 (C, minor diastereoisomer), 120.1 (C, major diastereoisomer), 118.5 (CH, minor diastereoisomer), 118.5 (CH, major diastereoisomer), 114.0 (2 X CH, major diastereoisomer), 113.8 (2 X CH, minor diastereoisomer), 59.2 (CH, minor diastereoisomer), 56.6 (CH, major diastereoisomer), 35.4 (CH, minor diastereoisomer), 34.1 (CH, major diastereoisomer), 32.8 (CH_2, minor diastereoisomer), 31.1 (CH_2, major diastereoisomer), 29.5 (CH_2, minor diastereoisomer), 28.7 (CH_2, major diastereoisomer), 23.4 (CH_2, minor diastereoisomer), 21.2 (CH_2, major diastereoisomer) ppm.



Dimethyl 3—(phenylamino)cyclopentane-1,2-dicarboxylate (5.3-3aj)

Synthesized according to GP3 using **5.3-2j**. Crude mixture was purified by flash chromatography (0-30% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[2] Synthesized as a yellow oil. (42 mg, 75%, 3:1 d.r.)

^{1}H NMR (400 MHz, C_6D_6) δ = 7.16 – 7.06 (m, 2.6H), 6.72 (m, 1.3H), 6.51 (m, 0.6H, minor diastereoisomer), 6.48 – 6.40 (m, 2H, major diastereoisomer), 4.02 (d, *J* = 6.2 Hz, 0.3H, minor diastereoisomer), 3.95 (m, 1H, major diastereoisomer), 3.68 (m, 1H, major diastereoisomer), 3.51 – 3.43 (m, 2H), 3.30 (s, 3H, major diastereoisomer), 3.27 (s, 0.9H, minor diastereoisomer), 3.24 (s, 0.9H, minor diastereoisomer), 3.16 (s, 3H, major diastereoisomer), 1.97 – 1.82 (m, 1H), 1.85 – 1.69 (m, 1H), 1.68 – 1.52 (m, 2H), 1.46 (m, 1H), 1.35 – 1.23 (m, 1H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ =174.6 (C), 173.1 (C), 147.6 (C, minor diastereoisomer), 147.3 (C, major diastereoisomer), 129.6 (2 X CH, minor diastereoisomer), 129.5 (2 X CH, major diastereoisomer), 118.1 (CH, minor diastereoisomer), 118.1 (CH, major diastereoisomer), 113.9 (2 X CH, minor diastereoisomer), 113.8 (2 X CH, major diastereoisomer), 59.1 (CH, minor diastereoisomer), 56.8 (CH, major diastereoisomer), 54.4 (CH, minor diastereoisomer), 51.7 (CH_3, minor diastereoisomer), 51.6 (CH_3, minor diastereoisomer), 51.6 (CH_3, major diastereoisomer), 51.4 (CH_3, major diastereoisomer), 51.0 (CH, major diastereoisomer), 46.1 (CH, minor diastereoisomer), 46.0 (CH, major diastereoisomer), 33.0 (CH_2, major diastereoisomer), 32.7 (CH_2, minor diastereoisomer), 27.3 (CH_2, minor diastereoisomer), 27.3 (CH_2, major diastereoisomer) ppm.



Dimethyl 3—(phenylamino)cyclopentane-1,2-dicarboxylate (5.3-3aj)

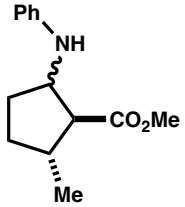
Synthesized according to GP3 using **5.3-2k**. Crude mixture was purified by flash chromatography (0-30% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[2] Synthesized as a yellow oil. (44 mg, 79%, 2:1 d.r.)

Major diastereoisomer:

^{1}H NMR (400 MHz, C_6D_6) δ = 7.14 – 7.07 (m, 2H), 6.78 – 6.68 (m, 1H), 6.55 – 6.49 (m, 2H), 4.00 – 3.90 (m, 1H), 3.74 (d, *J* = 8.3 Hz, 1H), 3.50 – 3.45 (m, 1H), 3.31 (s, 3H), 3.16 (s, 3H), 1.95 – 1.82 (m, 1H), 1.82 – 1.72 (m, 1H), 1.69 – 1.55 (m, 1H), 1.52 – 1.43 (m, 1H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 174.7 (C), 173.1 (C), 147.4 (C), 129.5 (2 x CH), 118.0 (CH), 113.8 (2 X CH), 56.8 (CH), 51.6 (CH_3), 51.3 (CH_3), 51.1 (CH), 45.7 (CH), 33.1 (CH_2), 27.3 (CH_2) ppm.

Minor diastereoisomer:

^{1}H NMR (400 MHz, C_6D_6) δ = 7.14 – 7.07 (m, 2H), 6.78 – 6.68 (m, 1H), 6.50 – 6.43 (m, 2H), 4.06 – 4.01 (m, 1H), 3.61 (d, *J* = 7.9 Hz, 1H), 3.50 – 3.45 (m, 1H), 3.28 (s, 3H), 3.25 (s, 3H), 1.95 – 1.82 (m, 1H), 1.82 – 1.72 (m, 1H), 1.69 – 1.55 (m, 1H), 1.38 – 1.26 (m, 1H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 174.8 (C), 174.0 (C), 147.7 (C), 129.6 (2 X CH), 118.1 (CH) , 113.9 (2 X CH), 59.1 (CH), 54.4 (CH), 51.8 (CH_3), 51.6 (CH_3), 46.2 (CH), 32.7 (CH_2), 27.3 (CH_2) ppm.



Methyl 2-methyl-5-(phenylamino)cyclopentanecarboxylate (5.3-3al)

Synthesized according to GP3. Crude mixture was purified by flash chromatography (0-30% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR

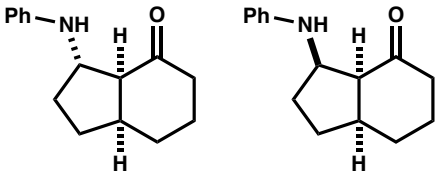
comparison.[2] Stereochemistry was determined by NMR comparison.[2] Synthesized as a yellow oil. (39 mg, 84%), 2:1 d.r.)

Major diastereoisomer:

^{1}H NMR (400 MHz, C_6D_6) δ = 7.15 – 7.10 (m, 2H), 6.90 – 6.85 (m, 1H), 6.54 – 6.48 (m, 2H), 4.01 (s, 1H), 3.93 (d, *J* = 7.0 Hz, 1H), 3.20 (s, 3H), 2.50 – 2.38 (m, 2H), 1.77 (dddd, *J* = 12.7, 8.1, 6.3, 3.5 Hz, 1H), 1.73 – 1.54 (m, 2H), 1.55 – 1.42 (m, 1H), 1.27 – 1.15 (m, 1H), 0.91 (d, *J* = 6.4 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ =, 174.0 (C), 147.7 (C), 129.5 (2 X CH), 118.2 (CH), 113.8 (2 X CH), 56.7 (CH), 55.7 (CH_3), 51.1 (CH), 37.5 (CH), 33.8 (CH_2), 32.1 (CH_2), 19.9 (CH_3) ppm.

Minor diastereoisomer:

^{1}H NMR (400 MHz, C_6D_6) δ = 7.15 – 7.10 (m, 2H), 6.85 – 6.79 (m, 1H), 6.77 – 6.70 (m, 2H), 4.13 (td, *J* = 7.9, 6.1 Hz, 1H), 3.30 (s, 3H), 2.50 – 2.38 (m, 1H), 2.26 – 2.09 (m, 1H), 2.01 (dd, *J* = 9.8, 7.8 Hz, 1H), 1.88 (m, 1H), 1.12 – 1.02 (m, 1H), 0.96 (d, *J* = 6.6 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 174.9 (C), 143.6 (C), 129.6 (2 X CH), 117.7 (CH), 113.81 (2 X CH), 60.0 (CH_3), 59.0 (CH), 51.4 (CH), 38.5 (CH), 32.8 (CH_2), 32.4 (CH_2), 19.7 (CH_3) ppm.



(5.3-3am)

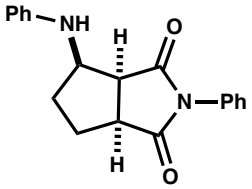
Synthesized according to GP4. Crude mixture was purified by flash chromatography (0-30% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a yellow oil. (14 mg, 31%, 6:1 d.r.)

(*cis,cis,cis*-**5.3-3am***)*

IR (neat, cm^{-1}): 3393 (bs), 2926 (m), 2870 (m), 1696 (vs), 1600 (vs), 1503 (vs), 1437 (s), 1312 (s), 747 (vs), 692 (vs) ; **^{1}H NMR** (400 MHz, C_6D_6) δ = 7.21 – 7.17 (m, 2H), 6.75 (tt, *J* = 7.3, 1.1 Hz, 1H), 6.66 – 6.61 (m, 2H), 5.43 (d, *J* = 10.0 Hz, 1H), 3.71 – 3.55 (m, 1H), 2.30 (dd, *J* = 6.4, 6.4 Hz, 1H no NOESY interaction with 1H @ 5.43 ppm), 2.08 – 1.88 (m, 3H), 1.74 – 1.64 (m, 1H), 1.57 – 1.39 (m, 2H), 1.39 – 1.28 (m, 3H), 1.28 – 1.15 (m, 1H), 1.10 (dddd, *J* = 13.3, 6.5, 5.3, 3.2 Hz, 1H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 213.7 (C), 149.0 (C), 129.6 (2 X CH), 117.6 (CH), 113.9 (2 X CH), 57.5 (CH), 53.4 (CH), 42.7 (CH_2), 41.6 (CH), 29.7 (CH_2), 27.0 (CH_2), 26.1 (CH_2), 23.7 (CH_2) ppm; **HRMS** (EI) m/z: [M^+] Calc'd for $C_{15}H_{19}NO$ 229.1467; Found 229.1444.

(*trans,cis,cis*-**5.3-3am***)*

IR (neat, cm^{-1}): 3393 (bs), 2926 (m), 2870 (m), 1696 (vs), 1600 (vs), 1503 (vs), 1437 (s), 1312 (s), 747 (vs), 692 (vs); **^{1}H NMR** (400 MHz, C_6D_6) δ = 7.21 – 7.17 (m, 2H), 6.75 (tt, *J* = 7.3, 1.0 Hz, 1H), 6.70 – 6.59 (m, 2H), 4.43 (dt, *J* = 8.0, 4.5 Hz, 1H), 3.32 (s, 1H), 2.22 (dd, *J* = 7.9, 4.0 Hz, 1H), 2.10 – 1.88 (m, 3H), 1.88 – 1.78 (m, 1H), 1.48 – 1.22 (m, 3H), 1.22 – 1.13 (m, 1H), 1.09 (ddd, *J* = 12.8, 6.9, 4.0 Hz, 1H), 1.04 – 0.90 (m, 2H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 210.1 (C), 148.2 (C), 129.6 (2 X CH), 117.6 (CH), 113.7 (2 X CH), 58.7 (CH), 54.3 (CH), 41.0 (CH), 40.6 (CH_2), 32.5 (CH_2), 28.8 (CH_2), 27.1 (CH_2), 23.2 (CH_2) ppm; **HRMS** (EI) m/z: [M^+] Calc'd for $C_{15}H_{19}NO$ 229.1467; Found 229.1444.

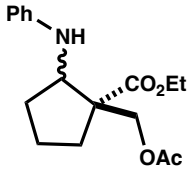


(5.3-3an)

Synthesized according to GP4. Crude mixture was purified by flash chromatography (0-30% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a yellow oil. (46 mg, 75%)

IR (neat, cm^{-1}): 3393 (m), 3052 (m), 2961 (m), 1772 (m), 1698 (vs), 1599 (vs), 1496 (vs), 1376 (s), 1314 (s), 1172 (s), 1163 (s), 747 (vs), 689 (vs); **^{1}H NMR** (400 MHz, C_6D_6) δ = 7.38 – 7.33 (m, 0.6H, minor diastereoisomer), 7.31 – 7.27 (m, 2H), 7.26 – 7.20 (m, 1H), 7.19 (d, *J* = 2.1 Hz, 1H), 7.16 (ddt, *J* = 6.8, 2.7, 1.5 Hz, H), 7.14 – 7.10 (m, 2H), 7.02 (tdt, *J* = 6.8, 6.0, 1.2 Hz, 1H), 6.85 – 6.72 (m, 2H), 6.56 – 6.50 (m, 2H), 4.98 (d, *J* = 6.5 Hz, 1H), 4.01 (d, *J* = 5.5 Hz, 0.2H, minor diastereoisomer), 3.41 (ddt, *J* = 11.7, 8.4, 5.9 Hz, 1H, NOESY with 1H @ 4.98 ppm), 2.81 (d, *J* = 8.0 Hz, 0.2H, minor diastereoisomer), 2.64 – 2.53 (m, 1H), 2.47 (ddd, *J* = 9.3, 7.8, 1.2 Hz, 1H), 1.99 – 1.94 (m, 0.2H, minor diastereoisomer), 1.90 (ddt, *J* = 13.4, 6.6, 1.3 Hz, 1H), 1.80 (dt, *J* = 12.1, 5.8 Hz, 1H), 1.30 (tdd, *J* = 13.4, 9.8, 6.2 Hz, 1H), 1.23 – 1.09 (m, 0.4H, minor diastereoisomer), 0.94 – 0.82 (m, 1H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 178.3 (C, minor diastereoisomer), 178.2 (C, major diastereoisomer), 176.4 (C, major diastereoisomer), 170.1 (C, minor diastereoisomer), 147.8 (C, major diastereoisomer), 146.6 (C, minor diastereoisomer), 133.0 (C, minor diastereoisomer), 132.7 (C, major diastereoisomer), 129.8 (2 X CH, minor diastereoisomer), 129.6 (2 X CH, major diastereoisomer), 129.1 (2 X CH, major diastereoisomer), 129.0 (2 X CH, minor diastereoisomer), 128.4 (CH), 126.6 (CH, major diastereoisomer), 126.5 (CH, minor diastereoisomer), 118.6 (CH, minor diastereoisomer), 118.0 (CH, major diastereoisomer), 113.9 (2 X CH, minor diastereoisomer), 113.6 (2 X CH, major diastereoisomer), 58.7 (CH, minor diastereoisomer), 57.4 (CH, major diastereoisomer), 51.9 (CH, minor diastereoisomer), 45.6 (CH, major diastereoisomer), 44.5 (CH, minor diastereoisomer), 43.5 (CH, major diastereoisomer), 31.2 (CH_2,

minor diastereoisomer), 30.9 (CH_2, major diastereoisomer), 28.8 (CH_2, minor diastereoisomer), 27.4 (CH_2, major diastereoisomer) ppm; **HRMS** (EI) m/z: [M^+] Calc'd for $C_{19}H_{18}N_2O_2$ 306.1368; Found 306.1366.



(5.3-3ao)

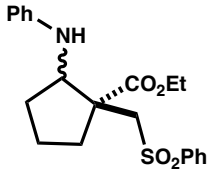
Synthesized according to GP4. Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a clear oil. (48 mg, 78% 1:1 d.r.)

(**5.3-3ao**)- *Diastereoisomer 1*

IR (neat, cm^{-1}): 3379 (m), 3062 (m), 3025 (m), 2978 (m), 2960 (m), 2875 (m), 1715 (vs), 1601 (s), 1517 (s), 1497 (s), 1439 (s), 1371 (s), 1313 (s), 1291 (s), 1257 (vs), 1227 (vs), 1181 (s), 1033 (s), 1019 (s), 746 (vs), 692 (vs); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.18 – 7.10 (m, 2H), 6.68 (tt, *J* = 7.3, 1.1 Hz, 1H), 6.65 – 6.55 (m, 2H), 4.46 (d, *J* = 11.0 Hz, 1H), 4.20 – 4.02 (m, 3H), 3.89 (t, *J* = 7.6 Hz, 1H), 2.34 – 2.24 (m, 1H), 2.24 – 2.12 (m, 1H), 2.00 (s, 3H), 1.92 – 1.83 (m, 1H), 1.82 – 1.72 (m, 1H), 1.72 – 1.62 (m, 2H), 1.17 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 173.5 (C), 170.9 (C), 147.0 (C), 129.2 (2 X CH), 117.7 (CH), 113.4 (2 X CH), 67.0 (CH_2), 61.0 (CH_2), 59.9 (CH), 56.7 (C), 32.8 (CH_2), 31.7 (CH_2), 21.5 (CH_2), 20.8 (CH_3), 14.0 (CH_3) ppm; **HRMS** (EI) m/z: [M^+] Calc'd for $C_{17}H_{23}NO_4$ 305.1627; Found 305.1631.

(**5.3-3ao**)- *Diastereoisomer 2*

IR (neat, cm^{-1}): 3379 (m), 3062 (m), 3025 (m), 2978 (m), 2960 (m), 2875 (m), 1715 (vs), 1601 (s), 1517 (s), 1497 (s), 1439 (s), 1371 (s), 1313 (s), 1291 (s), 1257 (vs), 1227 (vs), 1181 (s), 1033 (s), 1019 (s), 746 (vs), 692 (vs); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.16 – 7.09 (m, 2H), 6.66 (tt, *J* = 7.4, 1.1 Hz, 1H), 6.62 – 6.56 (m, 2H), 4.45 – 4.39 (m, 2H), 4.23 – 4.08 (m, 3H), 2.31 – 2.16 (m, 2H), 1.90 (s, 3H), 1.83 – 1.66 (m, 3H), 1.59 – 1.48 (m, 1H), 1.21 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 175.4 (C), 170.9 (C), 147.2 (C), 129.2 (2 X CH), 117.5 (CH), 113.1 (2 X CH), 65.0 (CH_2), 61.1 (CH_2), 60.2 (CH), 54.7 (C), 34.3 (CH_2), 33.4 (CH_2), 21.7 (CH_2), 20.7 (CH_3), 14.0 (CH_3) ppm; **HRMS** (EI) m/z: [M^+] Calc'd for $C_{17}H_{23}NO_4$ 305.1627; Found 305.1631.

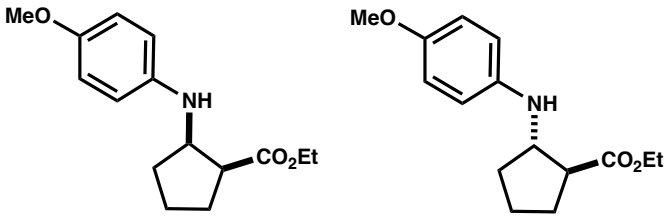


(5.3-3ap)

Synthesized according to GP4. Crude mixture was purified by flash chromatography (0-50% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a clear oil. (47 mg, 61% 1:1 d.r.)

IR (neat, cm^{-1}): 3388 (m), 3056 (m), 2958 (m), 2937 (m), 2874 (m), 1718 (vs), 1600 (vs), 1509 (s), 1497 (s), 1446 (s), 1305 (vs), 1256 (s), 1181 (s), 1142 (vs), 1083 (s), 1024 (s), 731 (vs), 688 (vs); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.93 – 7.80 (m, 2H), 7.68 – 7.57 (m, 1H), 7.57 – 7.48 (m, 2H), 7.15 – 7.06 (m, 2H), 6.73 – 6.64 (m, 1H), 6.59 – 6.49 (m, 2H), 4.18 – 3.98 (m, 4H), 3.93 (d, *J* = 14.4 Hz, 1H, diastereoisomer 1), 3.41 (d, *J* = 14.3 Hz, 1H, diastereoisomer 1), 3.19 (d, *J* = 14.1 Hz, 0.5H, diastereoisomer 2) 2.72 – 2.53 (m, 1H), 2.26 – 2.08 (m, 2H), 1.92 – 1.80 (m, 2H), 1.62 – 1.49 (m, 1H), 1.29 – 1.24 (m, 1.5H, diastereoisomer 2), 1.22 (t, *J* = 7.1 Hz, 3H, diastereoisomer 1) ppm; **^{13}C**

NMR (101 MHz, $CDCl_3$) δ = 174.4 (C, diastereoisomer 1), 172.4 (C, diastereoisomer 2), 146.8 (C), 141.0 (C, diastereoisomer 1), 140.7 (C, diastereoisomer 2), 133.7 (CH, diastereoisomer 2), 133.5 (CH, diastereoisomer 1), 129.3 (2 X CH, diastereoisomer 1), 129.2 (2 X CH, diastereoisomer 2), 129.1 (2 X CH, diastereoisomer 2), 127.7 (2 X CH, diastereoisomer 1), 118.0 (2 X CH, diastereoisomer 2), 117.5 (2 XCH, diastereoisomer 2), 113.0 (2 XCH, diastereoisomer 1), 112.9 (2 XCH, diastereoisomer 1), 63.8 (CH, diastereoisomer 1), 63.3 (CH, diastereoisomer 2), 62.8 (CH_2, diastereoisomer 2), 61.7 (CH_2, diastereoisomer 2), 61.6 (CH_2, diastereoisomer 1), 59.4 (CH_2, diastereoisomer 1), 54.6 (C, diastereoisomer 1), 54.0 (C, diastereoisomer 2), 32.6 (CH_2, diastereoisomer 1), 31.6 (CH_2, diastereoisomer 1), 30.7 (CH_2, diastereoisomer 2), 30.0 (CH_2, diastereoisomer 2), 21.7 (CH_2, diastereoisomer 1), 20.4 (CH_2, diastereoisomer 2), 14.0 (CH_3, diastereoisomer 2), 13.9 (CH_3, diastereoisomer 1) ppm; **HRMS** (EI) m/z: [M^+] Calc'd for $C_{21}H_{25}NO_4S$ 387.1504; Found 387.1488.

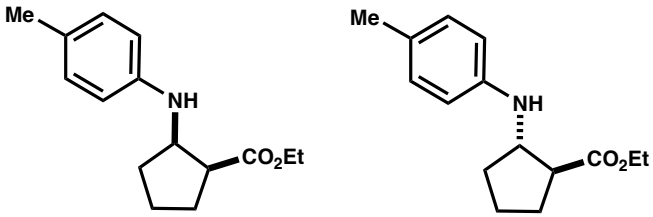


Ethyl 2-((4-methoxyphenyl)amino)cyclopentanecarboxylate (5.3-3ba)

Synthesized according to GP4. Crude mixture was purified by flash chromatography (0-30% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[2] Stereochemistry was determined by NMR comparison.[2] Synthesized as a clear oil. (48 mg, 91% 2:1 d.r.)

^{1}H NMR (400 MHz, C_6D_6) δ = 6.83 – 6.75 (m, 3.2H), 6.60 – 6.52 (m, 1.2H, minor diastereoisomer), 6.49 – 6.43 (m, 2H, major diastereoisomer), 4.10 (q, *J* = 6.1 Hz, 0.6H, minor diastereoisomer), 3.94

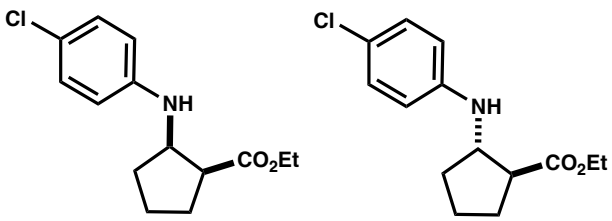
(q, *J* = 7.2 Hz, 1.2H, minor diastereoisomer), 3.85 (q, *J* = 7.2 Hz, 2H, major diastereoisomer), 3.77 (d, *J* = 6.7 Hz, 1H, major diastereoisomer), 3.40 (s, 3H, major diastereoisomer), 3.40 (s, 2H, minor diastereoisomer), 2.87 (q, *J* = 7.4 Hz, major diastereoisomer), 2.53 (ddd, *J* = 8.6, 7.1, 5.8 Hz, 0.6H, minor diastereoisomer), 2.17 – 2.02 (m, 1H), 2.02 – 1.85 (m, 1.2H, minor diastereoisomer), 1.80 – 1.72 (m, 0.6H, minor diastereoisomer), 1.72 – 1.61 (m, 4H), 1.61 – 1.50 (m, 0.6H, minor diastereoisomer), 1.50 – 1.39 (m, 0.6H, minor diastereoisomer), 1.35 – 1.21 (m, 1H), 1.21 – 1.10 (m, 0.6H, minor diastereoisomer), 0.92 (t, *J* = 7.1 Hz, 2H, minor diastereoisomer), 0.84 (t, *J* = 7.1 Hz, 3H, major diastereoisomer) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 175.1 (C, minor diastereoisomer), 174.1 (C, major diastereoisomer), 153.0 (C, minor diastereoisomer), 152.8 (C, major diastereoisomer), 142.2 (C, major diastereoisomer), 142.2 (C, minor diastereoisomer), 115.3 (2 X CH, minor diastereoisomer), 115.2 (2 X CH, minor diastereoisomer), 115.1 (2 X CH, major diastereoisomer), 115.1 (2 X CH, major diastereoisomer), 60.4 (CH_2, minor diastereoisomer), 60.2 (CH_2, major diastereoisomer), 59.8 (CH, minor diastereoisomer), 58.3 (CH, major diastereoisomer), 55.3 (CH_3, major diastereoisomer), 55.3 (CH_3, minor diastereoisomer), 51.5 (CH, minor diastereoisomer) 47.3 (CH, major diastereoisomer), 33.7 (CH_2, minor diastereoisomer), 33.1 (CH_2, major diastereoisomer) 28.9 (CH_2, minor diastereoisomer), 28.1 (CH_2, major diastereoisomer), 23.8 (CH_2, minor diastereoisomer), 22.7 (CH_2, major diastereoisomer), 14.2 (CH_3, minor diastereoisomer), 14.1 (CH_3, major diastereoisomer) ppm.



Ethyl 2-(*p*-tolylamino)cyclopentanecarboxylate (5.3-3ca)

Synthesized according to GP4. Crude mixture was purified by flash chromatography (0-30% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[2] Stereochemistry was determined by NMR comparison.[2] Synthesized as a clear oil. (42 mg, 85% 2:1 d.r.)

^{1}H NMR (400 MHz, C_6D_6) δ = 7.03 – 6.91 (m, 3.4H), 6.60 – 6.52 (m, 1.4H), 6.48 – 6.42 (m, 2H, major diastereoisomer), 3.93 (q, *J* = 7.1 Hz, 2H, minor diastereoisomer), 3.84 (q, *J* = 7.1 Hz, 2H, major diastereoisomer), 3.84 (s, 1H), 2.87 (dt, *J* = 8.2, 7.2 Hz, 1H, major diastereoisomer), 2.51 (ddd, *J* = 8.6, 7.1, 5.8 Hz, 0.7H, minor diastereoisomer), 2.18 (s, 5.1H), 2.13 – 2.03 (m, 1H), 2.00 – 1.84 (m, 1H), 1.77 – 1.70 (m, 0.7H, minor diastereoisomer), 1.70 – 1.59 (m, 4H), 1.59 – 1.50 (m, 0.7H, minor diastereoisomer), 1.50 – 1.34 (m, 1H), 1.28 – 1.08 (m, 2H), 0.91 (t, *J* = 7.1 Hz, 2.1H, minor diastereoisomer), 0.82 (t, *J* = 7.1 Hz, 3H, major diastereoisomer) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 175.1 (C, minor diastereoisomer), 174.1 (C, major diastereoisomer), 145.8 (C, minor diastereoisomer), 145.8 (C, major diastereoisomer), 130.1 (2 X CH, minor diastereoisomer), 130.0 (2 X CH, major diastereoisomer), 126.5 (C, minor diastereoisomer), 126.3 (C, major diastereoisomer), 114.1 (2 X CH, minor diastereoisomer), 114.0 (2 X CH, major diastereoisomer), 60.4 (CH_2, minor diastereoisomer), 60.2 (CH_2, major diastereoisomer), 59.2 (CH, minor diastereoisomer), 57.6 (CH, major diastereoisomer), 51.5 (CH, minor diastereoisomer), 47.2 (CH, major diastereoisomer), 33.7 (CH_2, minor diastereoisomer), 33.0 (CH_2, major diastereoisomer), 28.9 (CH_2, minor diastereoisomer), 28.1 (CH_2, major diastereoisomer), 23.7 (CH_2, minor diastereoisomer), 22.7 (CH_2, major diastereoisomer), 20.6 (2 X CH_3, major and minor diastereoisomer), 14.2 (CH_3, minor diastereoisomer), 14.1 (CH_3, major diastereoisomer) ppm.

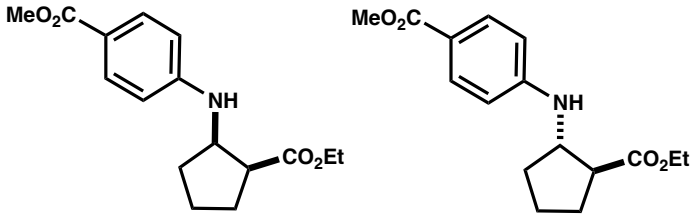


Ethyl 2-(4-chlorophenylamino)-1-cyclopentanecarboxylate (5.3-3da)

Synthesized according to GP4. Crude mixture was purified by flash chromatography (0-30% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[2] Stereochemistry was determined by NMR comparison.[2] Synthesized as a clear oil. (53 mg, 99% 3:2 d.r.)

^{1}H NMR (400 MHz, C_6D_6) = 7.11 – 7.04 (m, 3H), 6.31 – 6.24 (m, 1H, minor diastereoisomer), 6.19 – 6.14 (m, 2H, major diastereoisomer), 4.01 – 3.93 (m, 1H, major diastereoisomer), 3.90 (q, *J* = 7.1 Hz, 1H, minor diastereoisomer), 3.79 (q, *J* = 7.1 Hz, 2H, major diastereoisomer), 3.57 (p, *J* = 7.1 Hz, 1H, major diastereoisomer), 3.20 (s, 0.5H, minor diastereoisomer), 2.75 (dt, *J* = 8.0, 7.2 Hz, 1H, major diastereoisomer), 2.37 (ddd, *J* = 8.7, 7.2, 5.9 Hz, 0.5H), 2.05 – 1.95 (m, 1H, major diastereoisomer), 1.88 – 1.76 (m, 1H), 1.76 – 1.66 (m, 0.5H, minor diastereoisomer), 1.66 – 1.45 (m, 5H), 1.43 – 1.29 (m, 1H), 1.25 – 1.13 (m, 1H), 1.09 – 0.99 (m, 0.5H, minor diastereoisomer), 0.89 (t, *J* = 7.1 Hz, 2H, minor diastereoisomer), 0.79 (t, *J* = 7.1 Hz, 3H, major diastereoisomer) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 174.8 (C, minor diastereoisomer), 174.0 (C, major diastereoisomer), 146. (C), 129.4 (2 X CH, minor diastereoisomer), 129.3 (2 X CH, major diastereoisomer), 122.3 (C, minor diastereoisomer), 122.0 (C, major diastereoisomer), 114.8 (2 X CH, minor diastereoisomer), 114.7 (2 X CH, major diastereoisomer), 60.6 (CH_2, minor diastereoisomer), 60.3 (CH_2, major diastereoisomer), 58.7 (CH, minor diastereoisomer), 57.2 (CH, major diastereoisomer), 51.3 (CH, minor diastereoisomer), 47.0 (CH, major diastereoisomer),

33.4 (CH_2, minor diastereoisomer), 32.9 (CH_2, major diastereoisomer), 28.8 (CH_2, minor diastereoisomer), 28.1 (CH_2, minor diastereoisomer), 23.6 (CH_2, minor diastereoisomer), 22.6 (CH_2, major diastereoisomer), 14.2 (CH_3, minor diastereoisomer), 14.1 (CH_3, major diastereoisomer) ppm.

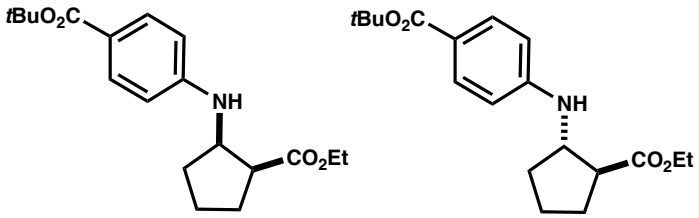


(5.3-3ea)

Synthesized according to GP4. Crude mixture was purified by flash chromatography (0-30% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a clear oil. (50 mg, 86% 3:2 d.r.). Stereochemistry assigned by following trends in similar compounds.

IR (neat, cm^{-1}): 3373 (m, br), 2951 (m), 2872 (m), 1692 (vs), 1706 (vs), 1601 (vs), 1523 (s), 1501 (s), 1433 (s), 1271 (vs), 1101 (vs), 837 (s), 770 (vs), 700 (s) ; **^{1}H NMR** (400 MHz, C_6D_6) δ = 8.20 – 8.08 (m, 3.2H), 6.48 – 6.40 (m, 1.2H, minor diastereoisomer), 6.36 – 6.27 (m, 2H, major diastereoisomer), 4.46 (d, *J* = 8.1 Hz, 1H, major diastereoisomer), 4.04 (p, *J* = 6.8 Hz, 0.6H, minor diastereoisomer), 3.90 (q, *J* = 7.1 Hz, 1.2H, minor diastereoisomer), 3.77 (qd, *J* = 7.2, 0.8 Hz, 2H, major diastereoisomer), 3.67 – 3.60 (m, 1H, major diastereoisomer), 3.58 (s, 3H, major diastereoisomer), 3.58 (s, 2H, minor diastereoisomer), 2.75 (dt, *J* = 8.0, 7.2 Hz, 1H, major diastereoisomer), 2.41 (ddd, *J* = 8.7, 7.3, 5.9 Hz, 0.6H, minor diastereoisomer), 2.07 – 1.95 (m, 1H, major diastereoisomer), 1.89 – 1.76 (m, 1H), 1.76 – 1.65 (m, 1H), 1.65 – 1.53 (m, 3H), 1.53 – 1.43 (m, 2H), 1.41 – 1.33 (m, 0.6H, minor diastereoisomer), 1.27 – 1.14 (m, 1H), 1.07 (ddt, *J* =

13.1, 8.4, 6.6 Hz, 0.6H, minor diastereoisomer), 0.88 (t, *J* = 7.1 Hz, 2H, minor diastereoisomer), 0.75 (t, *J* = 7.1 Hz, 3H, major diastereoisomer) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 174.6 (C, minor diastereoisomer), 173.9 (C, major diastereoisomer), 167.09 (C) 151.6 (C, minor diastereoisomer), 151.6 (C, major diastereoisomer) 132.0 (2 X CH, minor diastereoisomer), 131.9 (2 X CH, major diastereoisomer), 119.3 (C, minor diastereoisomer), 119.1 (C, major diastereoisomer), 112.4 (2 X CH, minor diastereoisomer), 112.4 (2 X CH, minor diastereoisomer), 60.6 (CH_2, minor diastereoisomer), 60.4 (CH_2, major diastereoisomer), 58.1 (CH, minor diastereoisomer), 56.5 (CH, major diastereoisomer), 51.3 (CH, minor diastereoisomer), 51.2 (CH, major diastereoisomer), 47.0 (CH_3), 33.4 (CH_2, minor diastereoisomer), 32.9 (CH_2, major diastereoisomer),, 28.8 (CH_2, minor diastereoisomer), 28.1 (CH_2, major diastereoisomer), 23.6 (CH_2, minor diastereoisomer), 22.6 (CH_2, major diastereoisomer), 14.2 (CH_3, minor diastereoisomer), 14.0 (CH_3, major diastereoisomer) ppm; **HRMS** (EI) m/z: [M^+] Calc'd for $C_{16}H_{21}NO_4$ 291.1471; Found 291.1467

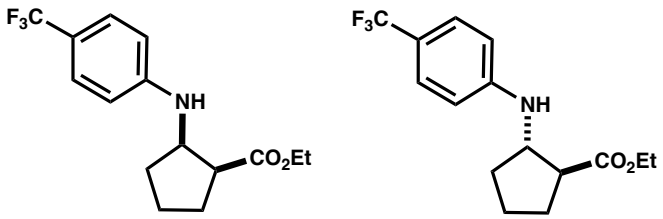


(5.3-3fa)

Synthesized according to GP4. Crude mixture was purified by flash chromatography (0-30% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a clear oil. (48 mg, 70% 3:2 d.r.). Stereochemistry assigned by following trends in similar compounds.

IR (neat, cm^{-1}): 3375 (m, br), 2974 (m), 2875 (m), 1720 (s), 1697 (s), 1681 (s), 1602 (vs), 1523 (s), 1287 (vs), 1255 (s), 1154 (vs), 1104 (vs), 837 (s), 771 (vs); **^{1}H NMR** (400 MHz, C_6D_6) δ = 8.27 – 8.11

(m, 3H), 6.48 – 6.41 (m, 1H, minor diastereoisomer), 6.36 – 6.26 (m, 2H, major diastereoisomer), 4.36 – 4.30 (m, 1H, major diastereoisomer), 4.05 (q, *J* = 6.6 Hz, 0.6H, minor diastereoisomer), 3.89 (qd, *J* = 7.1, 0.8 Hz, 1.2H, minor diastereoisomer), 3.76 (qd, *J* = 7.2, 0.6 Hz, 2H, major diastereoisomer), 3.69 – 3.54 (m, 1H, major diastereoisomer), 2.94 – 2.61 (m, 1H, major diastereoisomer), 2.44 – 2.28 (m, 0.6H, minor diastereoisomer), 2.06 – 1.94 (m, 1H, major diastereoisomer), 1.89 – 1.74 (m, 1H), 1.74 – 1.62 (m, 1H), 1.64 – 1.54 (m, 3H), 1.52 (s, 15H), 1.50 – 1.44 (m, 1H), 1.40 – 1.28 (m, 1H, major diastereoisomer), 1.26 – 1.10 (m, 1H), 1.09 – 0.97 (m, 0.6H, minor diastereoisomer), 0.88 (t, *J* = 7.1 Hz, 2H, minor diastereoisomer), 0.75 (t, *J* = 7.1 Hz, 3H, major diastereoisomer) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ =174.7 (C, minor diastereoisomer), 173.9 (C, major diastereoisomer), 166.0 (C, major diastereoisomer), 166.0 (C, minor diastereoisomer), 151.2 (C), 131.9 (2 X CH, minor diastereoisomer), 131.8 (2 X CH, major diastereoisomer), 121.3 (C, minor diastereoisomer), 121.2 (C, major diastereoisomer), 112.4 (2 X CH, minor diastereoisomer), 112.3 (2 X CH, major diastereoisomer), 79.4 (C), 60.6 (CH_2, minor diastereoisomer), 60.3 (CH_2, major diastereoisomer), 58.1 (CH, minor diastereoisomer), 56.6 (CH, major diastereoisomer), 51.3 (CH, minor diastereoisomer), 46.9 (CH, major diastereoisomer), 33.4 (CH_2, minor diastereoisomer), 32.8 (CH_2, major diastereoisomer), 28.8 (CH_2, minor diastereoisomer), 28.4 (3 X CH_3), 28.1 (CH_2, major diastereoisomer), 23.6 (CH_2, minor diastereoisomer), 22.6 (CH_2, major diastereoisomer), 14.2 (CH_3, minor diastereoisomer), 14.1 (CH_3, major diastereoisomer) ppm; **HRMS** (EI) m/z: [M^+] Calc'd for $C_{19}H_{27}NO_4$ 333.1940; Found 333.1933.



Ethyl 2-((4-(trifluoromethyl)phenyl)amino)cyclopentanecarboxylate (5.3-3ga)

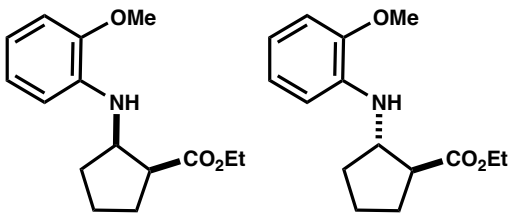
Synthesized according to GP4. Crude mixture was purified by flash chromatography (0-30% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[2] Stereochemistry was determined by NMR comparison.[2] Synthesized as a clear oil. (17 mg, 29% 1:1 d.r.)

(*cis*-**5.3-3ga**)

^{1}H NMR (400 MHz, C_6D_6) δ = 7.39 – 7.29 (m, 2H), 6.14 (d, *J* = 8.5 Hz, 2H), 4.18 (d, *J* = 8.0 Hz, 1H), 3.76 (q, *J* = 7.1 Hz, 2H), 3.54 (p, *J* = 7.1 Hz, 1H), 2.71 (dt, *J* = 8.2, 7.3 Hz, 1H), 2.08 – 1.86 (m, 1H), 1.65 – 1.39 (m, 4H), 1.26 – 1.10 (m, 1H), 0.75 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 173.8 (C), 150.3 (C), 126.78 (C, q, *J* = 3.8 Hz), 112.7 (4 X CH), 60.4 (CH_2), 56.5 (CH), 46.9 (CH), 32.8 (CH_2), 28.1 (CH_2), 22.6 (CH_2), 14.0 (CH_3) ppm.

(*trans*-**5.3-3ga**)

^{1}H NMR (400 MHz, C_6D_6) δ = 7.39 – 7.30 (m, 2H), 6.25 (d, *J* = 8.6 Hz, 2H), 3.96 (q, *J* = 6.5 Hz, 1H), 3.93 – 3.87 (m, 2H), 3.30 (d, *J* = 7.4 Hz, 1H), 2.30 (ddd, *J* = 8.7, 7.3, 6.0 Hz, 1H), 1.90 – 1.61 (m, 3H), 1.52 – 1.39 (m, 1H), 1.40 – 1.26 (m, 2H), 0.95 (ddt, *J* = 12.8, 8.1, 6.4 Hz, 1H), 0.88 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 174.5 (C), 150.2 (C), 126.90 (C, q, *J* = 3.8 Hz), 112.7 (4 X CH), 60.6 (CH_2), 58.1 (CH), 51.3 (CH), 33.3 (CH_2), 28.8 (CH_2), 23.5 (CH_2), 14.1 (CH_3) ppm.

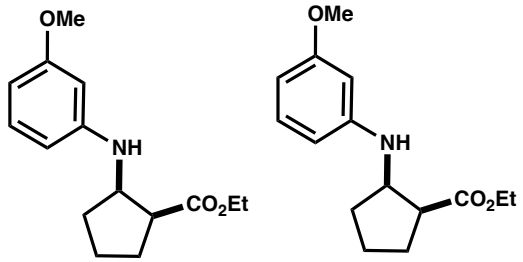


Ethyl 2-((2-methoxyphenyl)amino)cyclopentanecarboxylate (5.3-3ha)

Synthesized according to GP4. Crude mixture was purified by flash chromatography (0-30% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a clear oil. (44 mg, 83% 3:2 d.r.)

IR (neat, cm^{-1}): 3416 (m), 2955 (m), 2871 (m), 2833 (m), 1721 (vs), 1600 (vs), 1510 (vs), 1455 (s), 1430 (s), 1375 (s), 1348 (s), 1303 (m), 1244 (s), 1220 (vs), 1176 (vs), 1150 (vs), 1115 (s), 1048 (s), 1026 (vs), 732 (vs) ; **^{1}H NMR** (400 MHz, C_6D_6) δ = 6.97 (tdd, *J* = 7.6, 3.4, 1.4 Hz, 2H), 6.86 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.72 (td, *J* = 7.7, 1.5 Hz, 2H), 6.68 – 6.64 (m, 1H), 6.58 – 6.53 (m, 2H), 4.89 (d, *J* = 8.2 Hz, 1H, major diastereoisomer), 4.39 (s, 0.6H, minor diastereoisomer), 4.22 (t, *J* = 6.1 Hz, 0.6H, minor diastereoisomer), 3.92 (q, *J* = 7.1 Hz, 2H), 3.90 – 3.83 (m, 3H), 3.33 (s, 2H, minor diastereoisomer), 3.31 (s, 3H, major diastereoisomer), 2.91 (dt, *J* = 8.1, 7.2 Hz, 1H, major diastereoisomer), 2.60 (ddd, *J* = 8.7, 7.0, 5.6 Hz, 0.6H, minor diastereoisomer), 2.20 – 2.12 (m, 1H, major diastereoisomer), 2.02 – 1.85 (m, 1.6H), 1.77 – 1.59 (m, 5H), 1.59 – 1.46 (m, 1H), 1.46 – 1.34 (m, 0.6H. minor diastereoisomer), 1.31 – 1.17 (m, 2H), 0.90 (t, *J* = 7.1 Hz, 2H, minor diastereoisomer), 0.84 (t, *J* = 7.1 Hz, 3H, major diastereoisomer) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 175.1 (C, minor diastereoisomer), 173.8 (C, major diastereoisomer), 147.4 (C, major diastereoisomer), 147.2 (C, minor diastereoisomer), 138.0 (C, major diastereoisomer), 138.0 (C, minor diastereoisomer), 121.9 (CH, minor diastereoisomer), 121.6 (CH, major diastereoisomer), 116.8 (CH, minor diastereoisomer), 116.6 (CH, major diastereoisomer), 111.2 (CH, minor

diastereoisomer), 110.9 (CH, major diastereoisomer) 109.9 (CH, major diastereoisomer), 109.9 (CH, minor diastereoisomer), 60.2 (CH_2, minor diastereoisomer), 58.6 (CH_2, major diastereoisomer), 57.1 (CH, minor diastereoisomer), 55.0 (CH, major diastereoisomer), 54.9 (CH_3, major diastereoisomer), 51.6 (CH_3, minor diastereoisomer), 47.6 (CH, minor diastereoisomer), 33.9 (CH, minor diastereoisomer), 33.0 (CH_2, major diastereoisomer), 28.8 (CH_2, minor diastereoisomer), 27.8 (CH_2, major diastereoisomer), 23.8 (CH_2, minor diastereoisomer), 22.7 (CH_2, major diastereoisomer), 14.2 (CH_3, minor diastereoisomer), 14.0 (CH_3, major diastereoisomer) ppm; **HRMS** (EI) m/z: [M^+] Calc'd for $C_{15}H_{21}NO_3$ 263.1521; Found 263.1547.

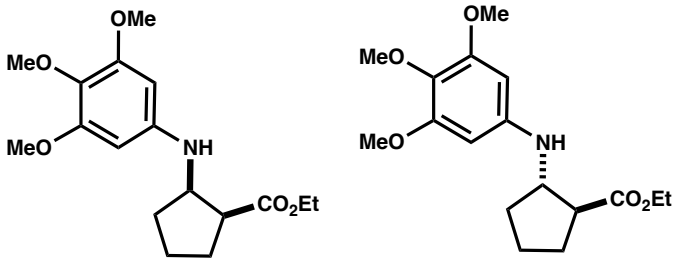


Ethyl 2-((3-methoxyphenyl)amino)cyclopentanecarboxylate (5.3-3ia)

Synthesized according to GP4. Crude mixture was purified by flash chromatography (0-30% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[2] Stereochemistry was determined by NMR comparison.[2] Synthesized as a clear oil. (44 mg, 84% 3:2 d.r.)

^{1}H NMR (400 MHz, C_6D_6) δ = 7.13 – 7.02 (m, 2H), 6.38 – 6.29 (m, 2H), 6.28 – 6.23 (m, 2H), 6.18 (ddd, *J* = 8.1, 2.2, 0.9 Hz, 1H, major diasteroisomer), 4.20 – 4.05 (m, 2H), 3.93 (q, *J* = 7.1 Hz, 1.2H, minor diastereoisomer), 3.89 – 3.81 (m, 2H, major diastereoisomer), 3.81 – 3.71 (m, 0.6H, minor diastereoisomer), 3.44 (s, 2H, minor diastereoisomer), 3.39 (s, 3H, major diastereoisomer), 2.85 (dt, *J* = 8.2, 7.2 Hz, 1H, major diastereoisomer), 2.50 (ddd, *J* = 8.6, 7.0, 5.7 Hz, 1H, minor

diastereoisomer), 2.11 – 1.99 (m, 1H), 1.97 – 1.82 (m, 1H), 1.76 – 1.66 (m, 1H, minor diastereoisomer), 1.66 – 1.56 (m, 4H), 1.58 – 1.45 (m, 1H), 1.44 – 1.35 (m, 1H, minor diastereoisomer), 1.26 – 1.18 (m, 1H), 1.18 – 1.06 (m, 1H), 0.91 (t, *J* = 7.1 Hz, 2H, minor diastereoisomer), 0.83 (t, *J* = 7.1 Hz, 3H, major diastereoisomer) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 175.0 (C, minor diastereoisomer), 174.1 (C, major diastereoisomer), 161.6 (C, minor diastereoisomer), 161.6 (C, major diastereoisomer), 149.4 (C), 130.3 (CH, minor diastereoisomer), 130.1 (CH, major diastereoisomer), 106.9 (CH), 103.2 (CH, minor diastereoisomer), 102.9 (CH, major diastereoisomer), 100.0 (CH, major diastereoisomer), 99.9 (CH, minor diastereoisomer), 60.5 (CH_2, minor diastereoisomer), 60.3 (CH_2, major diastereoisomer), 58.8 (CH, minor diastereoisomer), 57.3 (CH, major diastereoisomer), 54.7 (CH_3, minor diastereoisomer), 54.7 (CH_3, major diastereoisomer), 51.4 (CH, minor diastereoisomer), 47.2 (CH, major diastereoisomer) 33.7 (CH_2, minor diastereoisomer), 33.0 (CH_2, major diastereoisomer), 28.8 (CH_2, minor diastereoisomer), 28.1 (CH_2, major diastereoisomer), 23.7 (CH_2, minor diastereoisomer), 22.7 (CH_2, major diastereoisomer), 14.2 (CH_3, minor diastereoisomer), 14.1 (CH_3, major diastereoisomer) ppm.



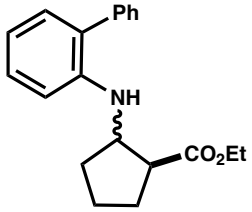
(5.3-3ja)

Synthesized according to GP4. Crude mixture was purified by flash chromatography (0-30% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a

clear oil. (61 mg, 94% 2:1 d.r.). Stereochemistry assigned by following trends in similar compounds.

IR (neat, cm^{-1}): 3385 (bs), 2955 (m), 2939 (m), 2876 (m), 2840 (m), 2825 (m), 1718 (vs), 1605 (vs), 1596 (vs), 1506 (vs), 1449 (s), 1232 (s), 1184 (s), 1121 (vs), 1007 (s), 777 (s), 743 (s) ; **^{1}H NMR** (400 MHz, C_6D_6) δ = 5.92 (s, 1H, minor diastereoisomer), 5.83 (s, 2H, major diastereoisomer), 4.18 (q, *J* = 6.1 Hz, 0.5H, minor diastereoisomer), 4.08 – 3.98 (m, 1H, major diastereoisomer), 3.96 – 3.87 (m, 3H), 3.87 (s, 1.5H, minor diastereoisomer), 3.84 (s, 3H, major diastereoisomer), 3.55 (s, 3H, minor diastereoisomer), 3.47 (s, 6H, major diastereoisomer), 2.94 – 2.85 (m, 1H, major diastereoisomer), 2.61 (ddd, *J* = 8.6, 6.8, 5.4 Hz, 1H, minor diastereoisomer), 2.14 – 2.05 (m, 1H, major diastereoisomer), 2.04 – 1.88 (m, 1H, major diastereoisomer), 1.86 – 1.76 (m, 0.5H, minor diastereoisomer), 1.76 – 1.64 (m, 4H), 1.63 – 1.45 (m, 1H, major diastereoisomer), 1.32 – 1.19 (m, 1.5H), 0.92 – 0.88 (m, 1.5H, minor diastereoisomer), 0.88 – 0.83 (m, 3H, major diastereoisomer) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 175.3 (C, minor diastereoisomer) 174.1 (C, major diastereoisomer), 154.9 (2 X C, minor diastereoisomer), 154.9 (2 X C, major diastereoisomer), 144.5 (C, major diastereoisomer), 144.5 (C, minor diastereoisomer), 131.9 (C, major diastereoisomer), 131.7 (C, minor diastereoisomer), 92.5 (2 X CH, major diastereoisomer) 92.3 (2 X CH, minor diastereoisomer), 60.8 (CH_3), 60.5 (CH_2, minor diastereoisomer), 60.4 (CH_2, major diastereoisomer), 59.2 (CH, minor diastereoisomer), 57.8 (CH, major diastereoisomer), 56.0 (2 X CH_3, major diastereoisomer), 55.9 (2 X CH_3, minor diastereoisomer), 51.5 (CH, minor diastereoisomer), 47.5 (CH, major diastereoisomer), 33.8 (CH_2, minor diastereoisomer), 33.2 (CH_2 major diastereoisomer), 29.0 (CH_2 minor diastereoisomer), 28.3 (CH_2, major diastereoisomer), 23.9 (CH_2, minor diastereoisomer), 22.8 (CH_2, major diastereoisomer), 14.2 (CH_3, minor

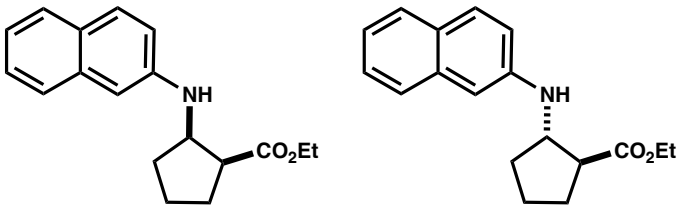
diastereoisomer), 14.1 (CH_3, major diastereoisomer) ppm; **HRMS** (EI) m/z: [M^+] Calc'd for $C_{17}H_{25}NO_5$ 323.1733; Found 323.1705.



Ethyl 2-([1,1'-biphenyl]-2-ylamino)cyclopentanecarboxylate (5.3-3ka)

Synthesized according to GP4. Crude mixture was purified by flash chromatography (0-30% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[2] Synthesized as a clear oil. (52 mg, 84% 1:1 d.r.)

^{1}H NMR (400 MHz, C_6D_6) δ = 7.51 – 7.46 (m, 2H), 7.44 – 7.40 (m, 2H), 7.27 – 7.19 (m, 6H), 7.18 – 7.13 (m, 4H), 7.13 – 7.07 (m, 2H), 6.91 – 6.87 (m, 1H), 6.80 (tdd, *J* = 7.4, 2.7, 1.1 Hz, 2H), 6.70 (dt, *J* = 8.2, 0.8 Hz, 1H), 4.55 (d, *J* = 8.0 Hz, 1H), 4.14 (p, *J* = 6.6 Hz, 1H), 4.08 – 4.00 (m, 1H), 3.91 (qd, *J* = 7.2, 0.6 Hz, 2H), 3.87 – 3.74 (m, 3H), 2.82 (dt, *J* = 8.2, 7.3 Hz, 1H), 2.35 (ddd, *J* = 8.6, 7.4, 6.1 Hz, 1H), 2.03 – 1.79 (m, 3H), 1.64 – 1.41 (m, 6H), 1.32 – 1.12 (m, 2H), 1.02 (ddt, *J* = 13.0, 8.5, 6.6 Hz, 1H), 0.89 (t, *J* = 7.1 Hz, 3H), 0.79 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 174.8 (C), 173.6 (C), 144.8 (2 X C), 144.6 (2 X C), 140.4 (C), 140.2 (C), 130.8 (CH), 130.8 (CH), 129.8 (2 X CH), 129.8 (2 X CH), 129.3 (CH), 129.2 (2 X CH), 129.2 (2 X CH), 128.9 (CH), 127.4 (CH), 117.7 (CH), 117.4 (2 X CH), 112.1 (2 X CH), 111.7 (2 X CH), 60.4 (CH_2), 60.2 (CH_2), 59.1 (CH), 57.1 (CH), 51.3 (CH), 47.5 (CH), 33.6 (CH_2), 32.9 (CH_2), 28.4 (CH_2), 27.9 (CH_2), 23.4 (CH_2), 22.6 (CH_2), 14.2 (CH_3), 14.1 (CH_3) ppm.

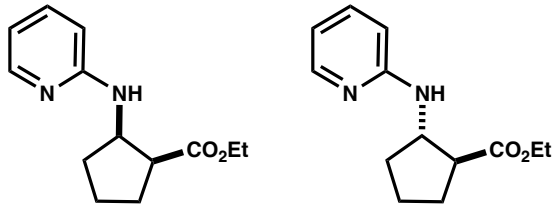


Ethyl 2-(naphthalen-2-ylamino)cyclopentanearboxylate (5.3-3la)

Synthesized according to GP4. Crude mixture was purified by flash chromatography (0-30% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[2] Stereochemistry was determined by NMR comparison.[2] Synthesized as a yellow oil. (56 mg, 99% 3:2 d.r.)

^{1}H NMR (400 MHz, C_6D_6) δ = 7.71 – 7.58 (m, 3H), 7.52 (d, *J* = 8.8 Hz, 0.6H), 7.47 (d, *J* = 8.8 Hz, 1H), 7.32 (dtd, *J* = 8.0, 6.7, 1.3 Hz, 2H), 7.16 – 7.11 (m, 1H), 6.96 (d, *J* = 2.4 Hz, 0.6H), 6.81 (d, *J* = 2.3 Hz, 1H), 6.65 (td, *J* = 8.7, 2.4 Hz, 2H), 4.23 (q, *J* = 6.7 Hz, 1.6H), 3.94 (q, *J* = 7.1 Hz, 1.2H), 3.88 (q, *J* = 6.9 Hz, 1H), 3.79 (q, *J* = 7.1 Hz, 2H), 3.51 (s, 0.6H), 2.90 (dt, *J* = 8.3, 7.4 Hz, 1H), 2.55 (ddd, *J* = 8.6, 7.0, 5.6 Hz, 0.6H), 2.16 – 2.02 (m, 1H), 2.02 – 1.87 (m, 1H), 1.82 – 1.72 (m, 0.6H), 1.72 – 1.61 (m, 4H), 1.61 – 1.52 (m, 0.6H), 1.52 – 1.38 (m, 0.6H), 1.33 – 1.12 (m, 2H), 0.90 (t, *J* = 7.1 Hz, 2H, minor diastereoisomer), 0.73 (t, *J* = 7.1 Hz, 3H, major diastereoisomer) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 175.0 (C, minor diastereoisomer), 174.1 (C, major diastereoisomer), 145.6 (C, major diastereoisomer), 145.5 (C, minor diastereoisomer), 136.1 (C, minor diastereoisomer), 136.0 (C, major diastereoisomer), 129.2 (CH, minor diastereoisomer), 129.2 (CH, major diastereoisomer), 128.2 (C), 128.2 (CH, minor diastereoisomer), 128.1 (CH, major diastereoisomer), 126.7 (CH, minor diastereoisomer), 126.6 (CH, major diastereoisomer), 126.5 (CH, minor diastereoisomer), 126.3 (CH, major diastereoisomer), 122.4 (CH, minor diastereoisomer), 122.3 (CH, major diastereoisomer), 118.6 (CH, major diastereoisomer), 118.6 (CH, minor diastereoisomer), 105.9

(CH, minor diastereoisomer), 105.7 (CH, major diastereoisomer), 60.6 (CH_2, minor diastereoisomer), 60.3 (CH_2, major diastereoisomer), 58.8 (CH, minor diastereoisomer), 57.1 (CH, major diastereoisomer), 51.4 (CH, minor diastereoisomer), 47.2 (CH, major diastereoisomer), 33.6 (CH_2, minor diastereoisomer), 33.0 (CH_2, major diastereoisomer), 28.9 (CH_2, minor diastereoisomer), 28.2 (CH_2, major diastereoisomer), 23.8 (CH_2, minor diastereoisomer), 22.7 (CH_2, major diastereoisomer), 14.2 (CH_3, minor diastereoisomer), 14.0 (CH_3, major diastereoisomer) ppm.



Ethyl 2-(pyridinylamino)cyclopentanearboxylate (5.3-3ma)

Synthesized according to GP4. Crude mixture was purified by flash chromatography (0-30% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a clear oil. (42 mg, 95% 1:1 d.r., isolated with 5% of 1m remaining). Stereochemistry assigned by following trends in similar compounds.

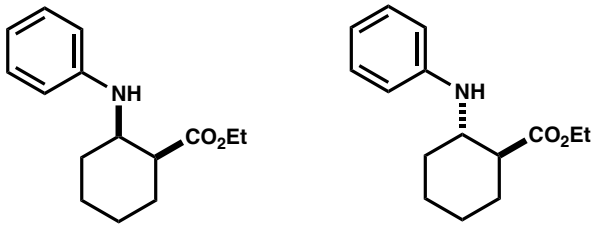
(*cis*-**5.3-3ma**)

IR (neat, cm^{-1}): 3367 (m), 3256 (m), 3085 (m), 2957 (m), 2872 (m), 1717 (vs), 1599 (vs), 1570 (s), 1507 (s), 1482 (s), 1183 (s), 1149 (vs), 856 (m), 768 (vs), 735 (s); **^{1}H NMR** (400 MHz, C_6D_6) δ = 8.22 (ddd, *J* = 5.0, 1.9, 0.9 Hz, 1H), 7.01 (ddd, *J* = 8.4, 7.1, 2.0 Hz, 1H), 6.31 (ddd, *J* = 7.1, 5.0, 1.0 Hz, 1H), 6.00 (dt, *J* = 8.4, 0.9 Hz, 1H), 4.90 (d, *J* = 8.4 Hz, 1H), 4.60 (p, *J* = 7.7 Hz, 1H), 3.83 (qd, *J* = 7.1, 4.1 Hz, 2H), 3.09 – 3.01 (m, 1H), 2.09 – 1.97 (m, 1H), 1.84 – 1.74 (m, 1H), 1.74 – 1.59 (m, 3H), 1.31 – 1.18 (m, 1H), 0.81 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 174.5 (C), 158.7 (C),

148.6 (CH), 136.8 (CH), 112.8 (CH), 108.1 (CH), 60.1 (CH_2), 55.1 (CH), 47.0 (CH), 32.8 (CH_2), 28.2 (CH_2), 22.6 (CH_2), 14.1 (CH_3) ppm; **HRMS** (EI) m/z: [M^+] Calc'd for $C_{13}H_{18}N_2O_2$ 234.1368; Found 234.1387.

(*trans*-**5.3-3ma**)- isolated in a mixture of **5.3-1m**.

IR (neat, cm^{-1}): 3367 (m), 3256 (m), 3085 (m), 2957 (m), 2872 (m), 1717 (vs), 1599 (vs), 1570 (s), 1507 (s), 1482 (s), 1183 (s), 1149 (vs), 856 (m), 768 (vs), 735 (s); **^{1}H NMR** (400 MHz, C_6D_6) δ = 8.25 – 8.17 (m, 2H), 7.09 – 7.04 (m, 1H), 6.32 (ddd, *J* = 7.1, 5.0, 1.0 Hz, 1H), 6.19 (dt, *J* = 8.4, 0.9 Hz, 1H), 4.65 – 4.34 (m, 2H), 3.93 (q, *J* = 7.1 Hz, 2H), 2.51 (ddd, *J* = 8.8, 7.4, 6.3 Hz, 1H), 2.04 – 1.94 (m, 1H), 1.94 – 1.84 (m, 1H), 1.79 – 1.68 (m, 1H), 1.58 – 1.46 (m, 1H), 1.43 – 1.32 (m, 1H), 1.21 – 1.11 (m, 2H), 0.90 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 175.0 (C), 158.9 (C), 148.8 (CH), 137.1 (CH), 113.0 (CH), 107.2 (CH), 60.4 (CH_2), 57.3 (CH), 51.4 (CH), 33.6 (CH_2), 29.0 (CH_2), 23.5 (CH_2), 14.2 (CH_3) ppm; **HRMS** (EI) m/z: [M^+] Calc'd for $C_{13}H_{18}N_2O_2$ 234.1368; Found 234.1387.



2-Anilino-1-carbethoxycyclohexane (5.3-3na)

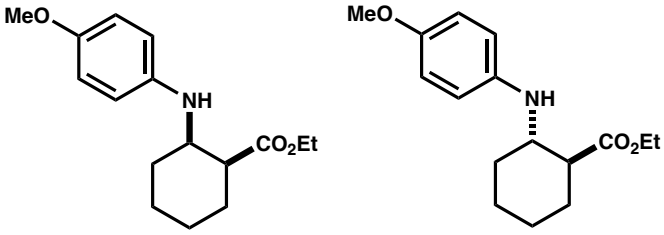
Synthesized according to GP4 using a 410 nm light. Crude mixture was purified by flash chromatography (0-30% EtOAc:Hexane) where relevant fractions were combined and characterized according to NMR comparison.[17] Stereochemistry was determined by NMR comparison.[17] Synthesized as a clear oil. (21 mg, 42%, 1:1 d.r.)

(*cis*-**5.3-3n**)

^{1}H NMR (400 MHz, C_6D_6) δ = 7.15 – 7.10 (m, 2H), 6.72 (tt, *J* = 7.3, 1.1 Hz, 1H), 6.59 – 6.52 (m, 2H), 3.91 (qd, *J* = 7.1, 2.8 Hz, 2H), 3.56 (td, *J* = 10.5, 3.9 Hz, 1H), 3.07 (s, 1H), 2.08 (ddd, *J* = 11.7, 10.3, 3.8 Hz, 1H), 1.97 – 1.87 (m, 1H), 1.84 – 1.76 (m, 1H), 1.67 – 1.55 (m, 1H), 1.49 – 1.33 (m, 2H), 1.09 – 0.93 (m, 2H), 0.89 (t, *J* = 7.1 Hz, 3H), 0.71 – 0.57 (m, 1H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 173.1 (C), 147.4 (C), 129.3 (2 X CH), 117.4 (CH), 113.7 (2 x CH), 59.8 (CH_2), 51.4 (CH), 44.5 (CH), 28.9 (2 X CH_2), 23.2 (2 X CH_2), 13.8 (CH_3) ppm.

(*trans*-**5.3-3n**)

^{1}H NMR (400 MHz, C_6D_6) δ = 7.15 – 7.10 (m, 2H), 6.73 (tt, *J* = 7.3, 1.1 Hz, 1H), 6.56 – 6.50 (m, 2H), 4.27 (s, 1H), 3.87 (qd, *J* = 7.1, 3.8 Hz, 2H), 3.64 (s, 1H), 2.64 (dt, *J* = 8.4, 4.2 Hz, 1H), 1.95 – 1.81 (m, 2H), 1.48 – 1.33 (m, 5H), 1.17 – 1.07 (m, 2H), 0.86 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 174.2 (C), 147.8 (C), 129.6 (2 X CH), 117.9 (CH), 114.2 (2 X CH), 60.3 (CH_2), 54.4 (CH), 51.1 (CH), 32.9 (CH_2), 29.3 (CH_2), 25.0 (2 X CH_2), 14.3 (CH_3) ppm.



(5.3-3oa)

Synthesized according to GP4 using a 410 nm light. Crude mixture was purified by flash chromatography (0-30% EtOAc:Hexane) where relevant fractions were combined and characterized. Synthesized as a clear oil. (51 mg, 92% 3:2 d.r.). Stereochemistry assigned by following trends in similar compounds.

(*cis*-**5.3-3oa**)

^{1}H NMR (400 MHz, C_6D_6) δ = 6.82 – 6.76 (m, 2H), 6.58 – 6.51 (m, 2H), 4.01 – 3.88 (m, 2H), 3.56 – 3.44 (m, 1H), 3.38 (s, 3H), 2.81 (s, 1H), 2.12 (ddd, *J* = 11.7, 10.3, 3.7 Hz, 1H), 2.01 – 1.94 (m, 1H), 1.88 – 1.78 (m, 1H), 1.68 – 1.56 (m, 1H), 1.50 – 1.36 (m, 2H), 1.09 – 0.99 (m, 1H), 0.94 (t, *J* = 7.1 Hz, 4H), 0.91 – 0.82 (m, 1H), 0.70 – 0.58 (m, 1H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 174.4 (C), 153.1 (C), 141.8 (C), 116.0 (2 X CH), 115.1 (2 X CH), 60.2 (CH_2), 55.8 (CH), 55.3 (CH_3), 51.2 (CH), 33.0 (CH_2), 29.4 (CH_2), 25.0 (2 X CH_2), 14.3 (CH_3) ppm; **HRMS** (EI) m/z: [M^+] Calc'd for $C_{16}H_{23}NO_3$ 277.1678; Found 277.1685.

(*cis*-**5.3-3oa**) (isolated in a mixture with **5.3-2o**)

^{1}H NMR (400 MHz, C_6D_6) δ = 6.82 – 6.75 (m, 2H), 6.55 – 6.46 (m, 2H), 3.91 (qd, *J* = 7.2, 2.6 Hz, 2H), 3.67 – 3.58 (m, 2H), 3.39 (s, 3H), 2.73 – 2.59 (m, 1H), 1.96 – 1.80 (m, 2H), 1.63 – 1.31 (m, 8H), 1.20 – 1.09 (m, 2H), 0.94 – 0.85 (m, 3H) ppm; **^{13}C NMR** (101 MHz, C_6D_6) δ = 173.6 (C), 153.0 (C), 141.9 (C), 115.7 (2 X CH), 115.3 (2 X CH), 60.1 (CH_2), 55.3 (CH_3), 53.0 (CH), 45.0 (CH), 31.5 (2 X CH_2), 29.3 CH_2), 23.7 (CH_2), 14.2 (CH_3) ppm; **HRMS** (EI) m/z: [M^+] Calc'd for $C_{16}H_{23}NO_3$ 277.1678; Found 277.1685.

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Chapter 6 – SUMMARY AND FUTURE WORK

6.1- Summary

In summary, the work described in this thesis demonstrates useful synthetic ability of photoredox chemistry in organic synthetic chemistry. Overall, this work shows the utility and diverse reaction that can be achieve with photocatalysts, such as binuclear gold or Ir-based polypyridyl complexes.

In Chapter 2, the alkylation semi-pinacol rearrangement using gold photoredox chemistry and non-activated bromoalkanes was shown to be working *via* an interesting dual photocatalyst/Lewis acid pathway. Using radical clock experiments, it was shown that the reaction mechanism was not solely going through radical pathway. In fact, after the generation of the alkyl radical, the radical will add unto the Au(I)- Au(II) center and form a C-Au bond. This newly formed Lewis acid Au(III) complex will catalyze the semi-pinacol rearrangement. A reductive elimination will occur to give the desired product. This new mode of reactivity of the binuclear gold photocatalyst, $Au_2(dppm)_2X_2$, opens the door for other applications in synthetic organic chemistry.

In Chapter 3, was a direct continuation of the studies performed in chapter 2 to exploit the newfound dual reactivity of $Au_2(dppm)_2X_2$. Atom transfer radical additions (ATRA) reactions often require the use of harsh conditions and the use of strong radical initiators or toxic catalysts such as organotin complexes to go through a chain reaction mechanism. Having mild and simple conditions to perform this reaction proved to be very synthetically useful, as a wide range of non-activated bromoalkanes and iodoarenes are compatible with the reaction. Furthermore, the Br-ATRA reaction can be utilized in intermolecular reactions, clearly demonstrating the synthetic

applications of the reaction. Continued studies to further understand the bimodality and reaction mechanism of the binuclear gold photocatalyst are needed.

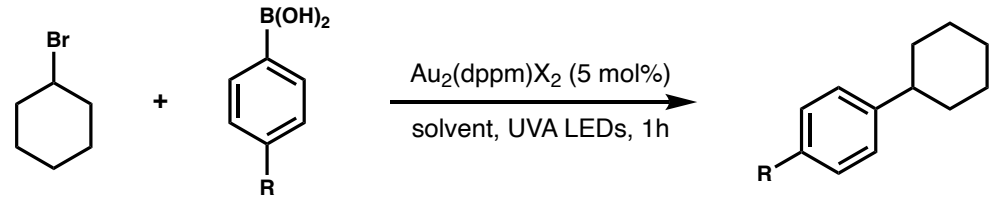
In Chapter 4, another variation on the classic Minisci reaction was presented, this time employing the generation of chlorine *via* the HAT of alcohols. A strong HAT agent is formed by using Ir-based polypyridyl photocatalysts to oxidize chloride to chlorine. After the generation of the α-alkoxy radical, it will alkylate the highly activated heteroarene of primary alcohols or ethers are being used or reduce it when secondary isopropyl alcohol is used. Our methodology highlighted the use of chlorine atom to perform HAT in synthetically useful reactions in fields such as medicinal chemistry. Finally, the versatility of this methodology is highlighted by the different alkylating agents that can be used as cyclic or acyclic ether, and alcohols are compatible with this methodology.

In Chapter 5, photo-mediated [3 + 2] cycloaddition of *N*-aryl cyclopropylamines was demonstrated. Although initially a photoredox catalyzed version was explored, the reaction was self-catalyzing by the excitation of *N*-aryl cyclopropylamine followed by an SET to an acceptor. The newly formed ion pair then performed a [3 + 2] cycloaddition to give the desired functionalized cyclopentane derivative. The scope of the reaction was diverse, demonstrating the applicability of this reaction. Mechanistic questions remain regarding the proposed mechanism and the possibility of an EDA complex being formed. Future work will include further mechanistic and DFT studies to give insight on the mechanism, as well as an expansion of the [4 + 2] cycloaddition scope.

6.2- Future Work

6.2.1- Future Work in Gold Photoredox Catalyzed Reactions

Although extensive work has been done studying the photophysical and electrochemical properties of binuclear gold photocatalyst, $Au_2(dppm)_2X_2$, further studies are needed to understand the newfound dual catalysis that can performed. Unfortunately, the cross-coupling reaction using gold photoredox catalysis did not give positive results using our current conditions but modifying the catalyst could be the key to give the desired compound. Using ^{31}P NMR experiments, the reaction was tracked and the gold photocatalyst's fate was shown (**Figure 3.3**). We have found that either one or both dppm ligands comes off to liberate a coordination site and the metal center. It would be interesting to form $Au_2(dppm)X_2$ catalyst and study the cross-coupling reaction between **6.2.1-1a** and **6.2.1-2**. The photophysical and electrochemical properties of the new photocatalyst will need to be studied as well, to ensure that it can still react as a photocatalyst and reduce non activated bromoalkanes in the same way as the current binuclear gold photocatalyst.



6.2.1-1a

R = H, **6.2.1-2a**
R = OMe, **6.2.1-2b**

R = H, **6.2.1-3ba**
R = OMe, **6.2.1-3bb**

Scheme 6.1- Future work in the C(sp2)-C(sp3) cross-coupling of alkyl bromides and phenyl boronic acids using gold photoredox catalysis.

The ligands that are on the binuclear gold photocatalyst directly impact its electrochemical and photophysical properties. The possibility of using chiral bisphosphines to induce chirality to the desired products needs to be studied as well.

6.2.1- Future Work in photo-mediated [4 + 2] cycloaddition of *N*-aryl cyclopropylamines

Future work in the photo-mediated [3 + 2] and [4 + 2] cycloaddition of *N*-aryl cyclopropylamines and *N*-aryl cyclobutylamines is needed to better understand the mechanism of the reaction. The current proposed mechanism is an excitation of *N*-aryl cyclopropylamine with UVA or blue LEDs (**Scheme 5.6**). Once excited a SET will occur with an α, β-unsaturated acceptor. The newly formed radical cation will force the opening of the highly strained cyclopropyl ring. The cycloaddition will then occur. Studies are needed to determine whether the cycloaddition is performed after excitation of the *N*-aryl cyclopropyl amine or after the formation and excitation of an EDA complex. Preliminary experiments have not ruled out either possibility, therefore further UV-Vis and DFT experiments will be needed. Expanding the scope of the photo-mediated [4 + 2] *N*-aryl cyclobutylamines will also be studied. Adding heterocyclic moieties such as oxetanes or azetidines to the scope will add synthetic utility and diversity. Further studies will also involve applying this methodology in the total synthesis of natural products and pharmaceutical targets.

6.3- Claims to Original Research

- Development of alkylative semi-pinacol rearrangement using gold photoredox catalysis.
- Discovery of alkylative tetrahydrofuran-ring formation using gold photoredox and Lewis acid catalysis.
- Development of mechanistic studies of alkylative tetrahydrofuran-ring formation using gold photoredox catalysis.
- Development of formal bromide and iodide atom transfer radical addition using gold photoredox catalysis.

- Development of intermolecular bromide atom transfer radical addition using gold photoredox catalysis.
- Discovery and development of dual gold photoredox and Lewis acid catalysis: C(sp^3)-C(sp^3) coupling with boronic acids using gold photoredox catalysis.
- Development of alkylation and reduction of heteroarenes with alcohols using photoredox catalysis and hydrogen atom transfer *via* chlorine atom generation.
- Discovery and development of photo-mediated [3 + 2] cycloaddition of *N*-aryl cyclopropylamines.
- Discovery and development of photo-mediated [4 + 2] cycloaddition of *N*-aryl cyclopropylamines.

6.4- Publications

6.4.1- Publications Resulting from Work Presented in this Thesis

[1] Zidan, M.; McCallum, T.; Thai-Savard, L.; Barriault, L., Photoredox meets gold Lewis acid catalysis in the alkylative semipinacol rearrangement: A photocatalyst with a dark side, *Org. Chem. Front.* **2017**, *4*, 2092-2096.

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[3] Zidan, M.; McCallum, T.; Swann, R.; Barriault, L., Formal Bromine Atom Transfer Radical Addition of Nonactivated Bromoalkanes Using Photoredox Gold Catalysis. *Org. Lett.,* **2020**, *22* (21), 8401-8406.

[4] Zidan, M.; Barriault, L. Photoactivated Formal [3 + 2] Cycloaddition of Aryl Cyclopropylamines*. ChemRxiV., Cambridge: Cambridge Open Engage;* **2022***. This content is a preprint and has not been peer-reviewed.* (DOI: 10.26434/chemrxiv-2022-tq6zk)

6.4.2- Publications Not Presented in this Thesis

[1] Zidan, M., Rohe, S., M^{c}Callum, T., Barriault, L. Recent Advances in Mono and Binuclear Gold Photoredox Catalysis. *Catal. Sci. Technol.,* **2018**, *8*, 6019-6028.

[2] Barriault, L.; Zidan, M.; Rohe, S., In *Science of Synthesis: Dual Catalysis in Organic Synthesis,* Molander, G. A., Ed.; Thieme: Stuttgart, (**2019**); Vol. 1, p 377-414.

6.4.3- Presentations of Work in this Thesis
(**Bold denotes Presenting Author**)

[1] **Zidan, M.**; Barriault, L., Photoactivated Formal [3+2] Cycloaddition of *N*-Aryl cyclopropylamines, 2021, *31st Quebec-Ontario Mini-Symposium on Bioorganic and Organic Chemistry*. (Provincial/Oral Presentation)

[2] **Zidan, M.**; Barriault, L., Photoactivated Formal [3+2] Cycloaddition of *N*-Aryl cyclopropylamines, 2021, *IUPAC/CCCE- 103rd Canadian Chemistry Conference and Exhibition,* (International/Oral Presentation)

[3] **Zidan, M.**; McCallum, T.; Swann, R.; Barriault, L., Formal Bromine Atom Transfer Radical Addition of Nonactivated Bromoalkanes Using Photoredox Gold Catalysis*,* 2019, *30th Quebec-Ontario Mini-Symposium on Bioorganic and Organic Chemistry*. (Provincial/Poster Presentation) (Best Poster Prize Awarded by IntellynSyn)

[4] **Zidan, M.**; McCallum, T.; Swann, R.; Barriault, L., Formal Bromine Atom Transfer Radical Addition of Nonactivated Bromoalkanes Using Photoredox Gold Catalysis, 2018,

IUPAC/CCCE- 101st Canadian Chemistry Conference and Exhibition. (International/Poster Presentation)

[5] **Zidan, M.**; McCallum, T.; Barriault, L., Organic Transformations using Gold Photoredox Catalysis, 2018, Ottawa-Carleton Chemistry Institute Research Day. (Regional/Oral Presentation)

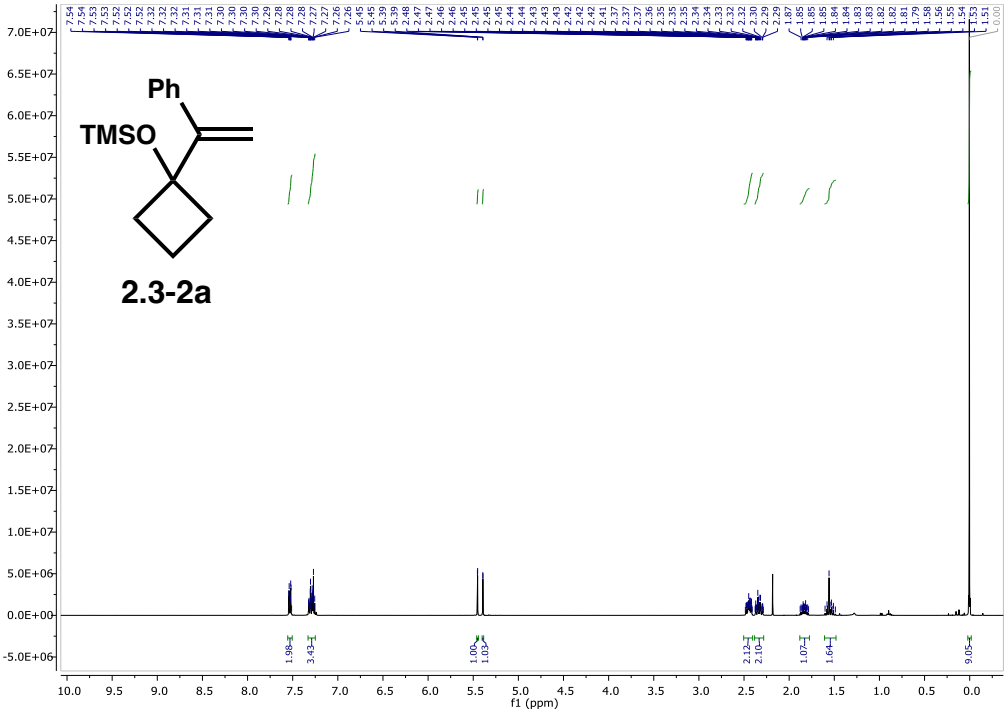
[6] **Zidan, M**.; McCallum, T.; Morris, A. O.; Barriault, L., Photo-mediated Alkylation and Reduction of Heteroarenes, 2017, 28th Quebec-Ontario Mini-Symposium on Bioorganic and Organic Chemistry. (Provincial/Poster Presentation)

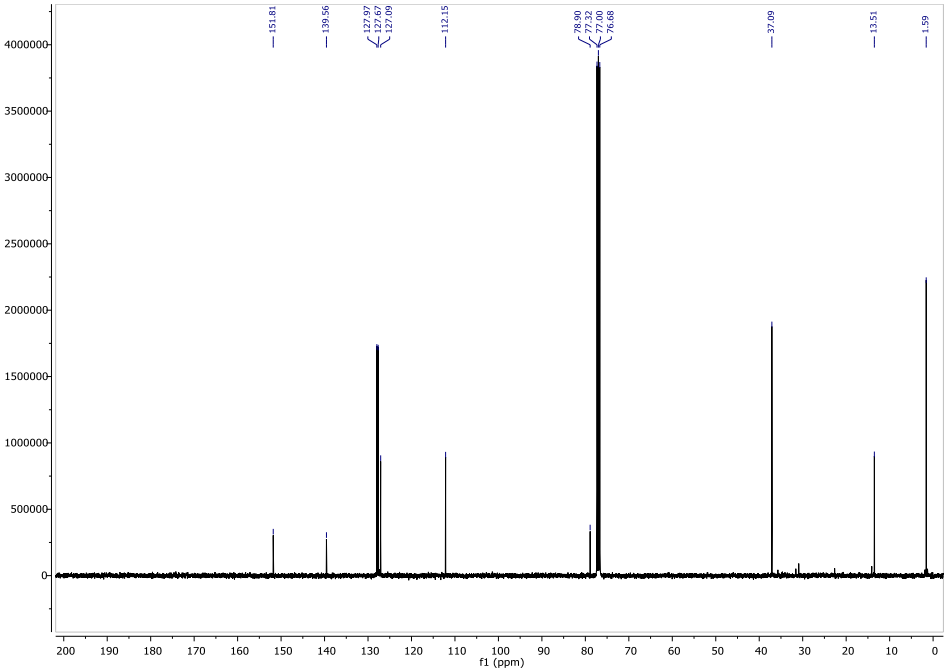
[7] **Zidan, M.**; McCallum, T.; Thai-Savard, L.; Barriault, L., Alkylative Semi-pinacol Rearrangement using Photoredox Gold Catalysis, 2017 Ottawa-Carleton Chemistry Institute Research Day (Regional/Poster Presentation)

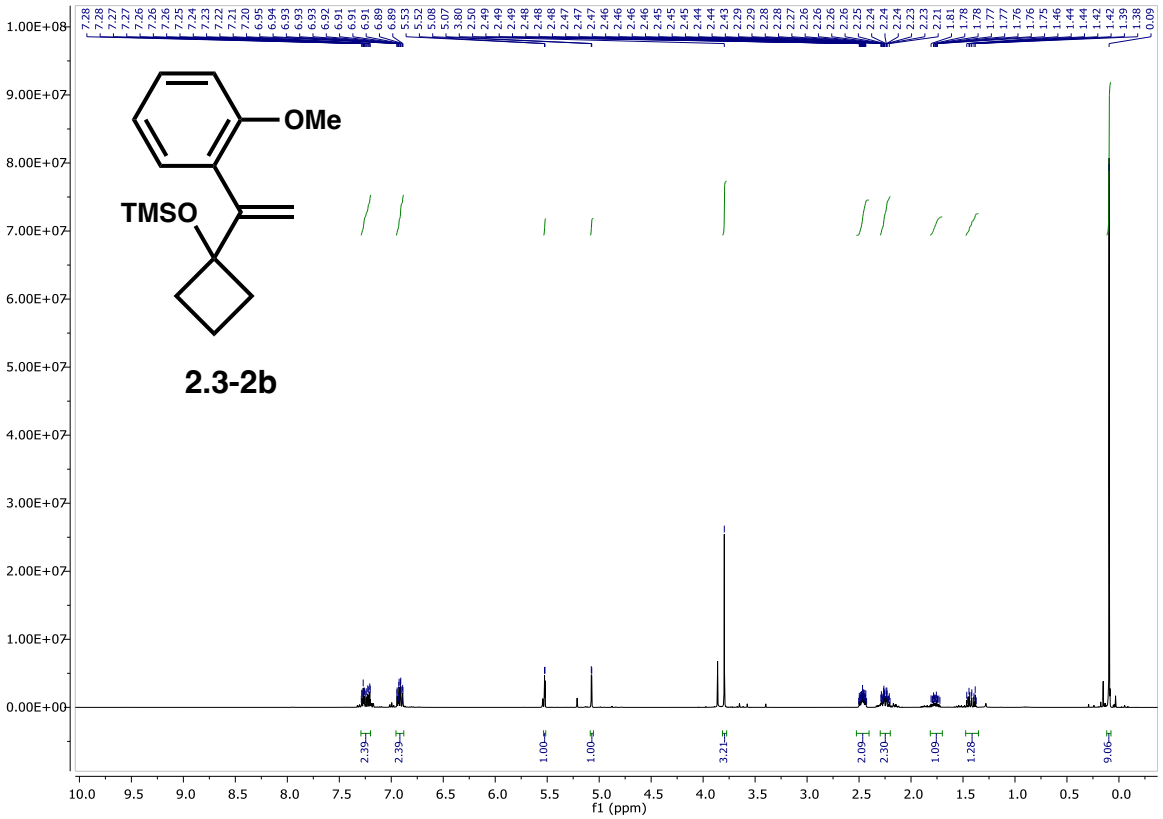
[8] **Zidan, M.**; McCallum, T.; Thai-Savard, L.; Barriault, L., Alkylative Semi-pinacol Rearrangement using Photoredox Gold Catalysis, 2016, 27th Quebec- Ontario Mini-Symposium on Bioorganic and Organic Chemistry. (Provincial/Poster Presentation)

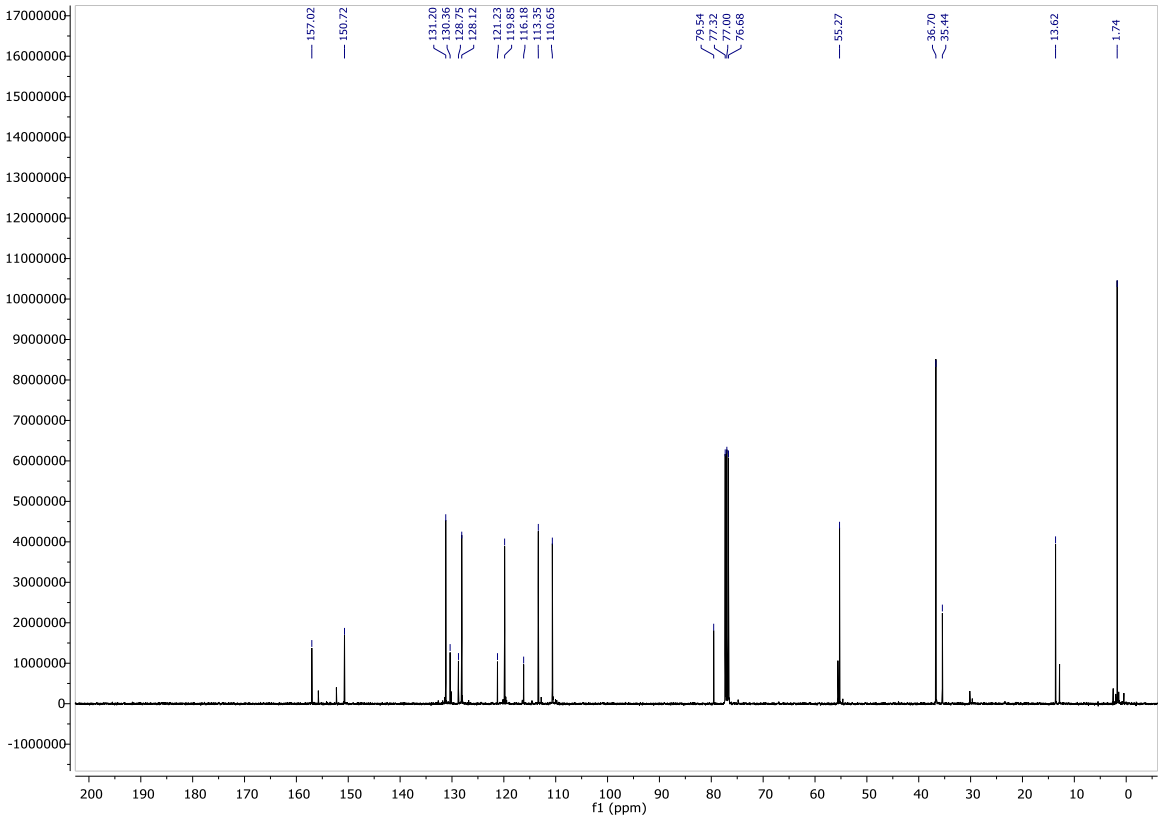
Chapter 7- APPENDIX

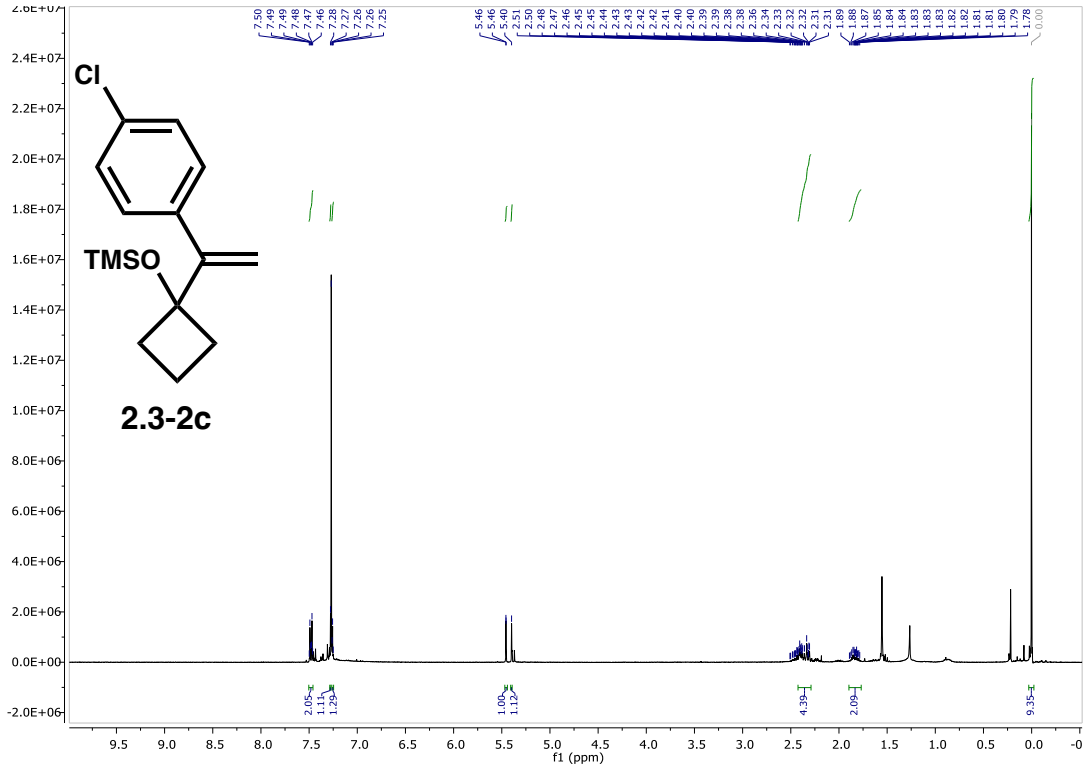
7.1- Spectral Data from Chapter 2: Alkylative Semi-Pinacol Rearrangement using Binuclear Gold Photoredox Catalysis

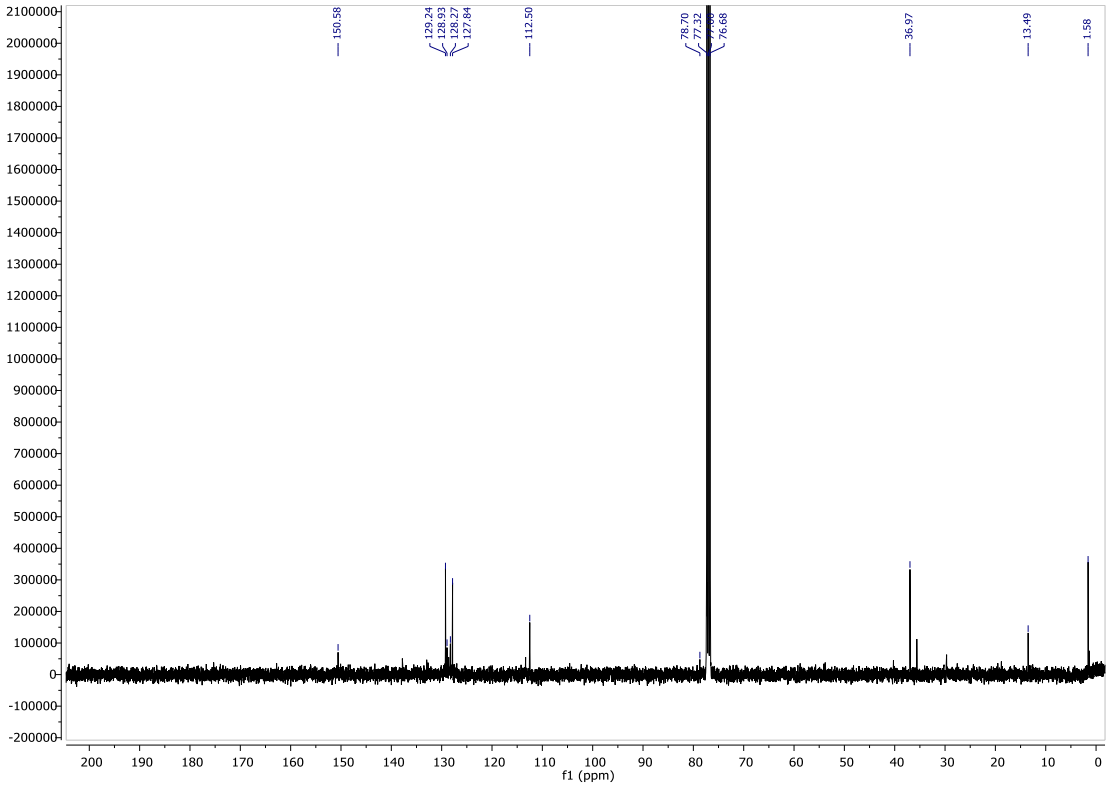


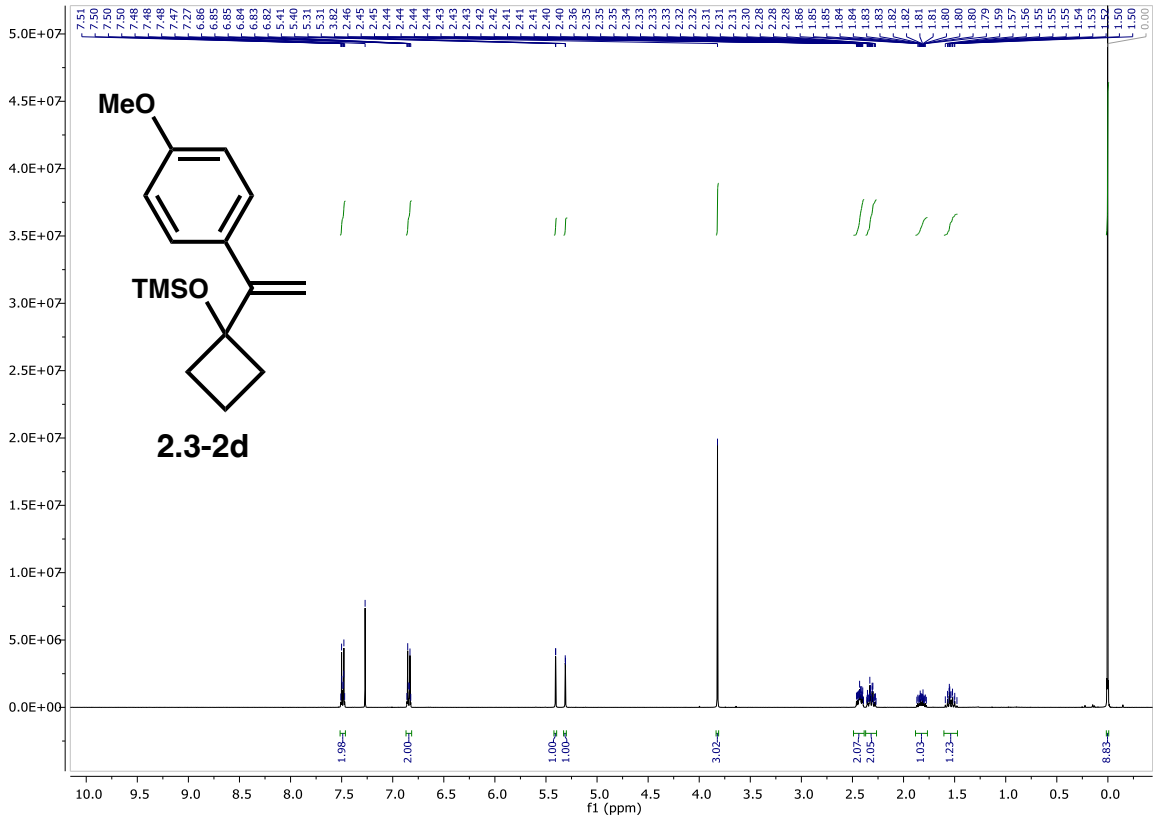


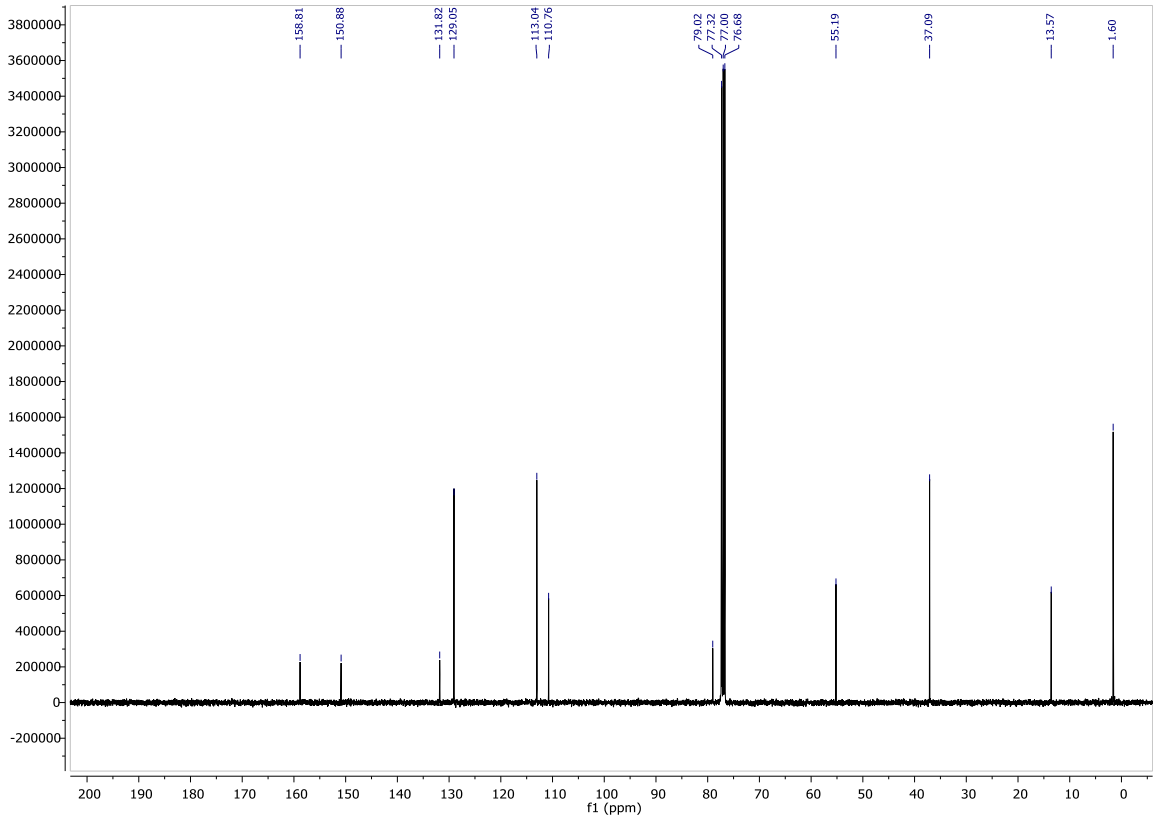

OMe
TMSO
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f1 (ppm)

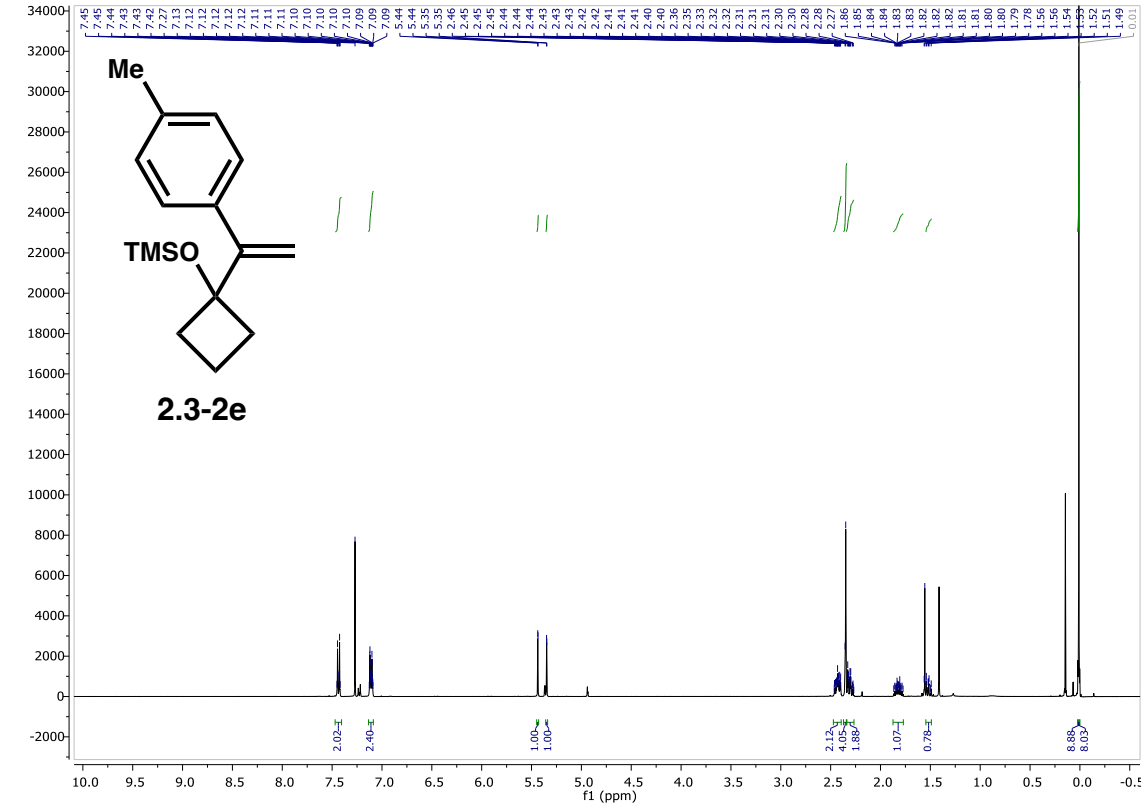

157.02
150.72
131.20
130.36
128.75
128.12
121.23
119.85
116.18
113.35
110.65
79.54
77.32
77.00
76.68
55.27
36.70
35.44
13.62
1.74
f1 (ppm)

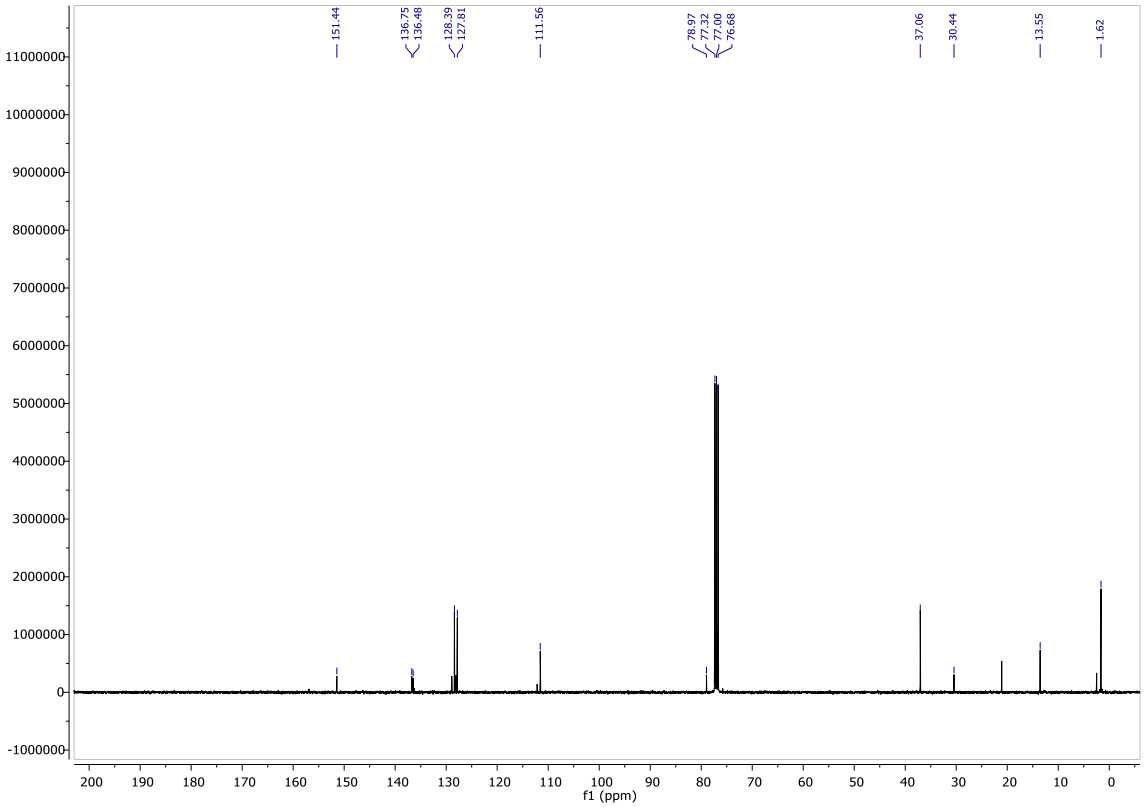

Cl
TMSO
2.3-2c
f1 (ppm)

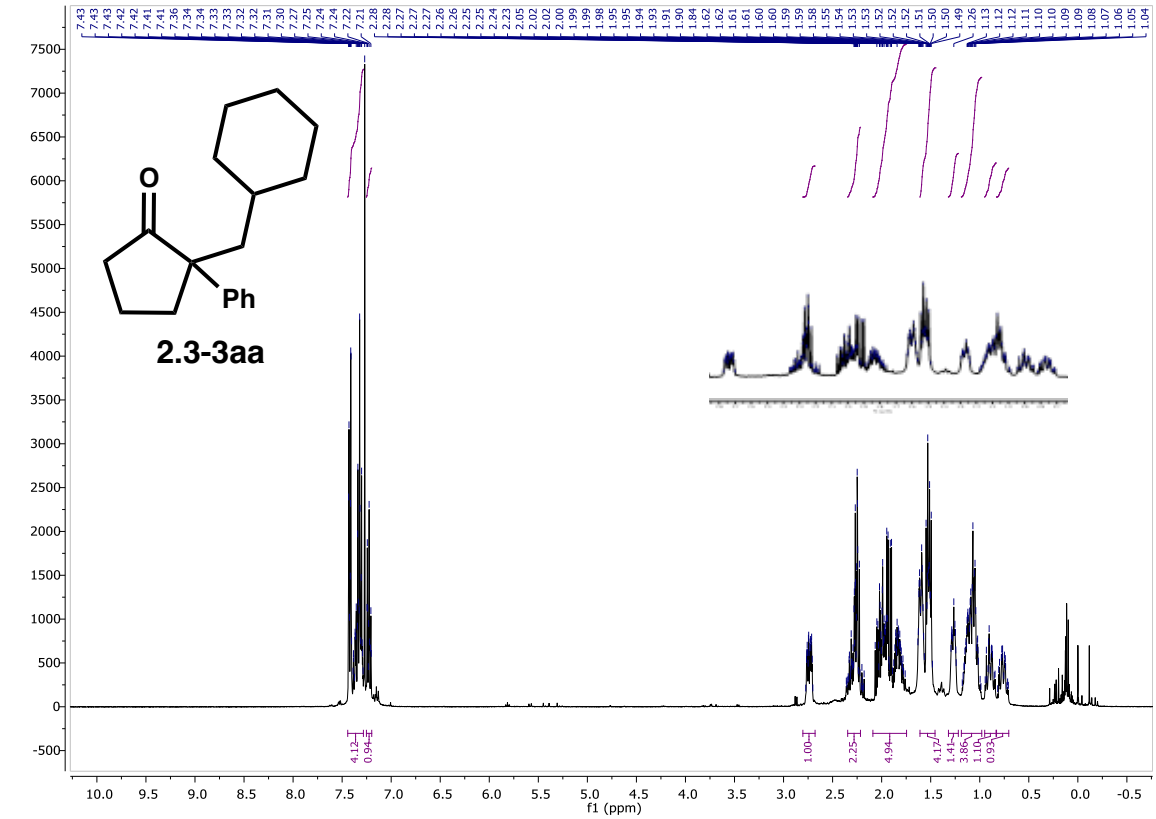

150.58
129.24
128.93
128.27
127.84
112.50
78.70
77.32
76.68
36.97
13.49
1.58
f1 (ppm)

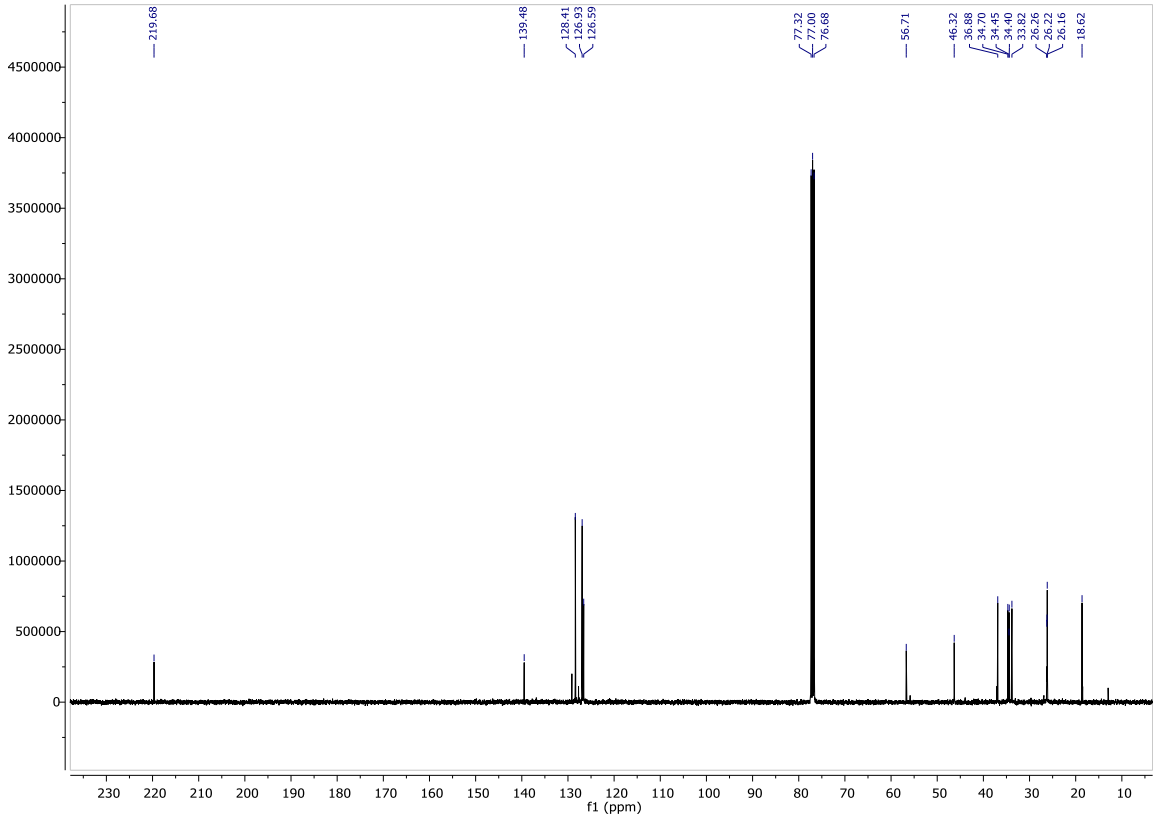

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TMSO
2.3-2d
f1 (ppm)

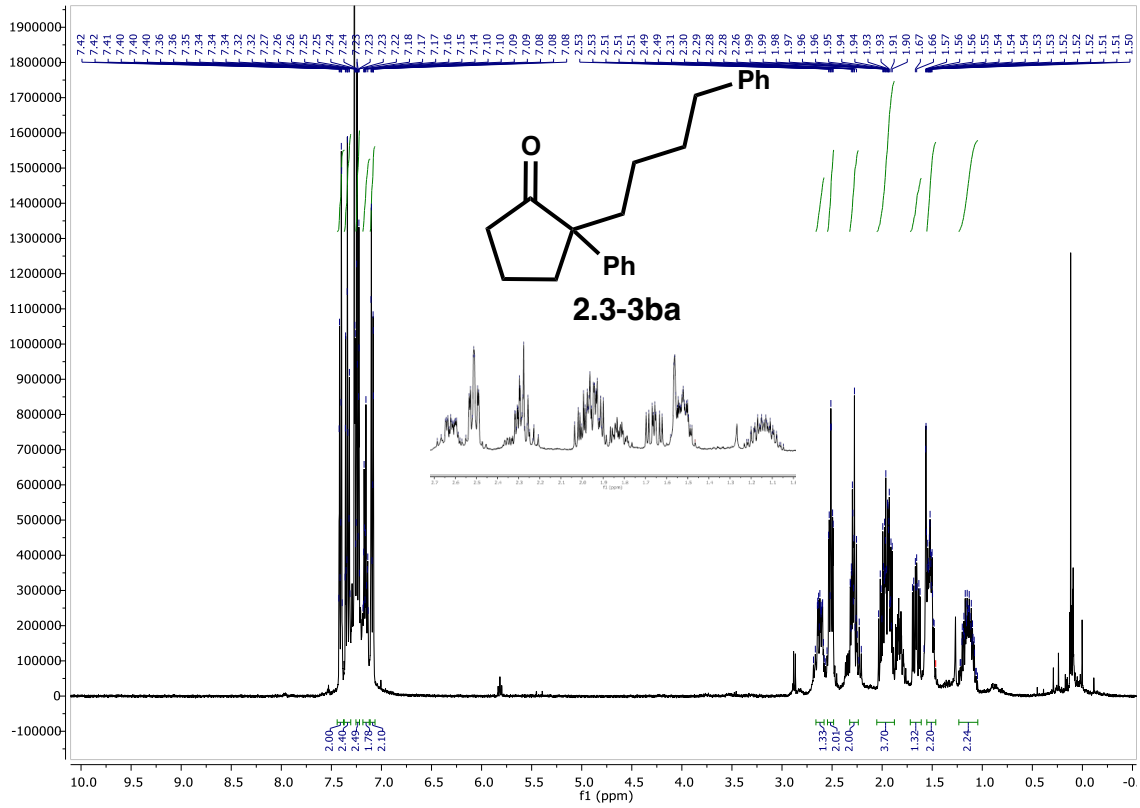

158.81
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131.82
129.05
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77.32
77.00
76.68
55.19
37.09
13.57
1.60
f1 (ppm)

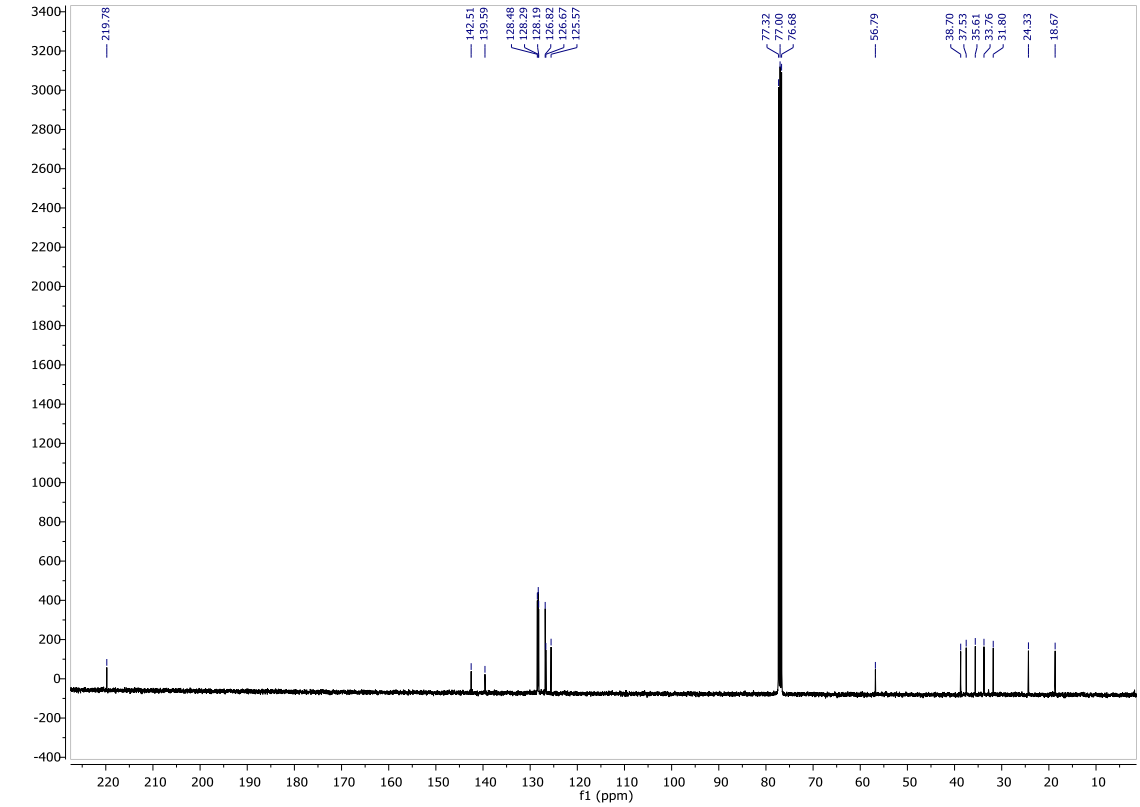

Me
TMSO
2.3-2e
f1 (ppm)

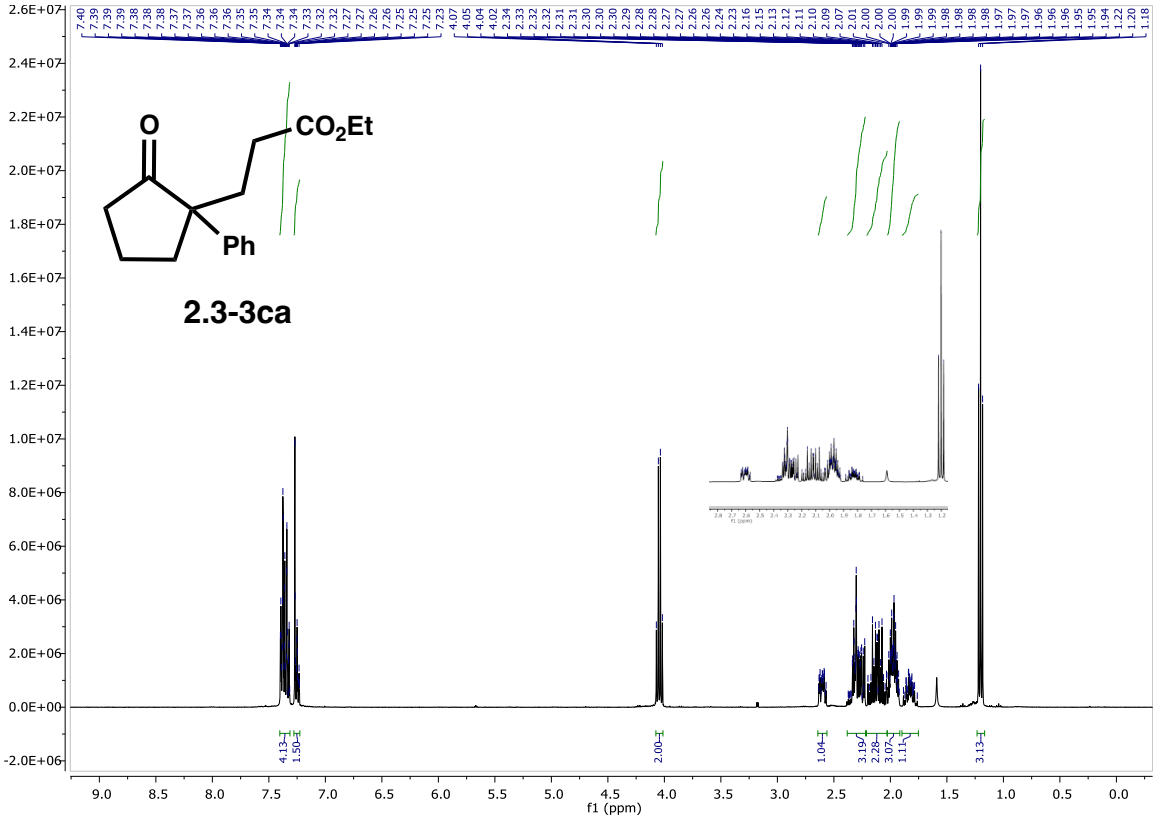

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128.39
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78.97
77.32
77.00
76.68
37.06
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13.55
1.62
f1 (ppm)

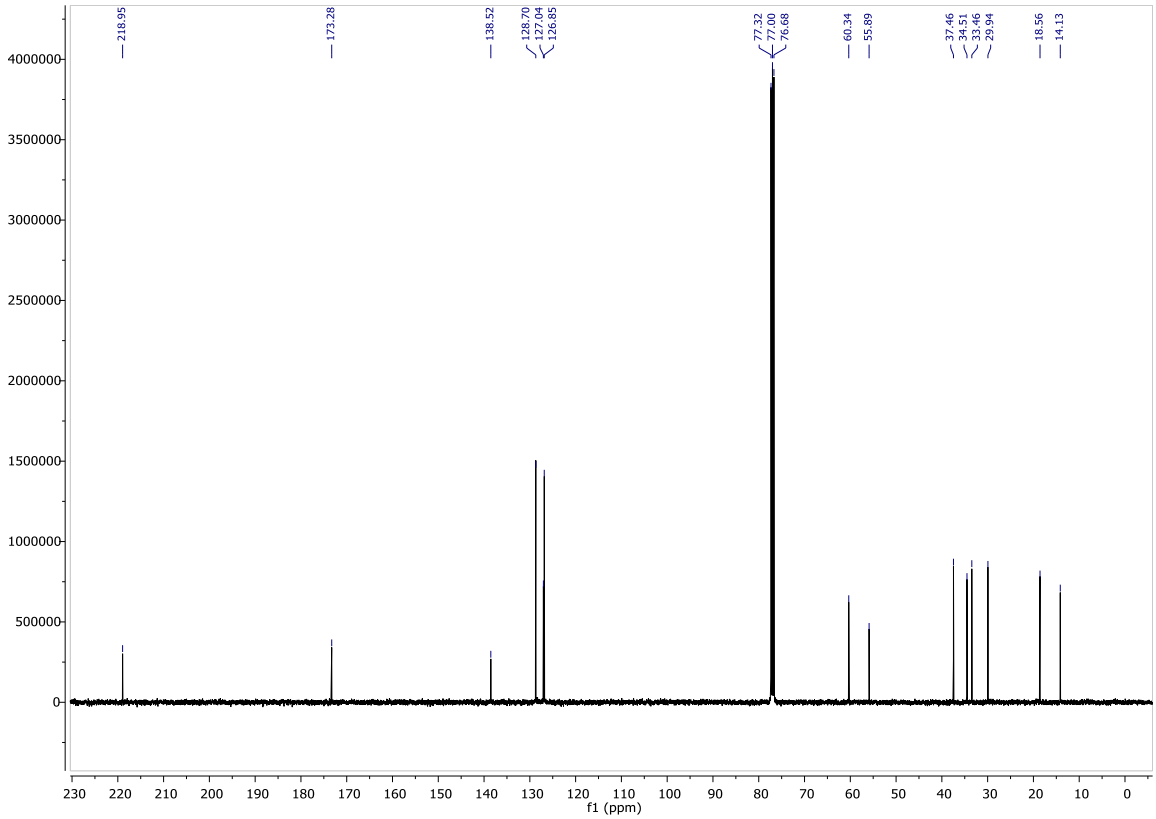

O
Ph
2.3-3aa
f1 (ppm)

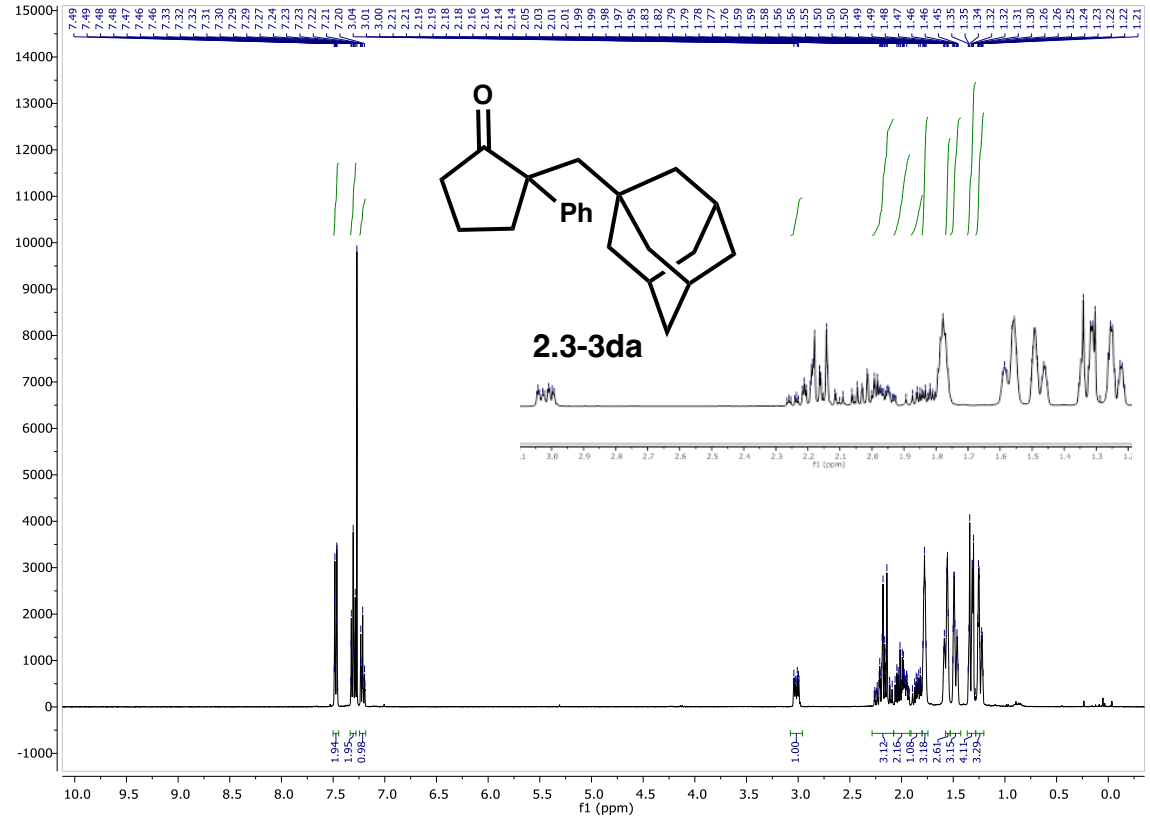

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126.93
126.59
77.32
77.00
76.68
56.71
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34.45
34.40
33.82
26.26
26.22
26.16
18.62
f1 (ppm)

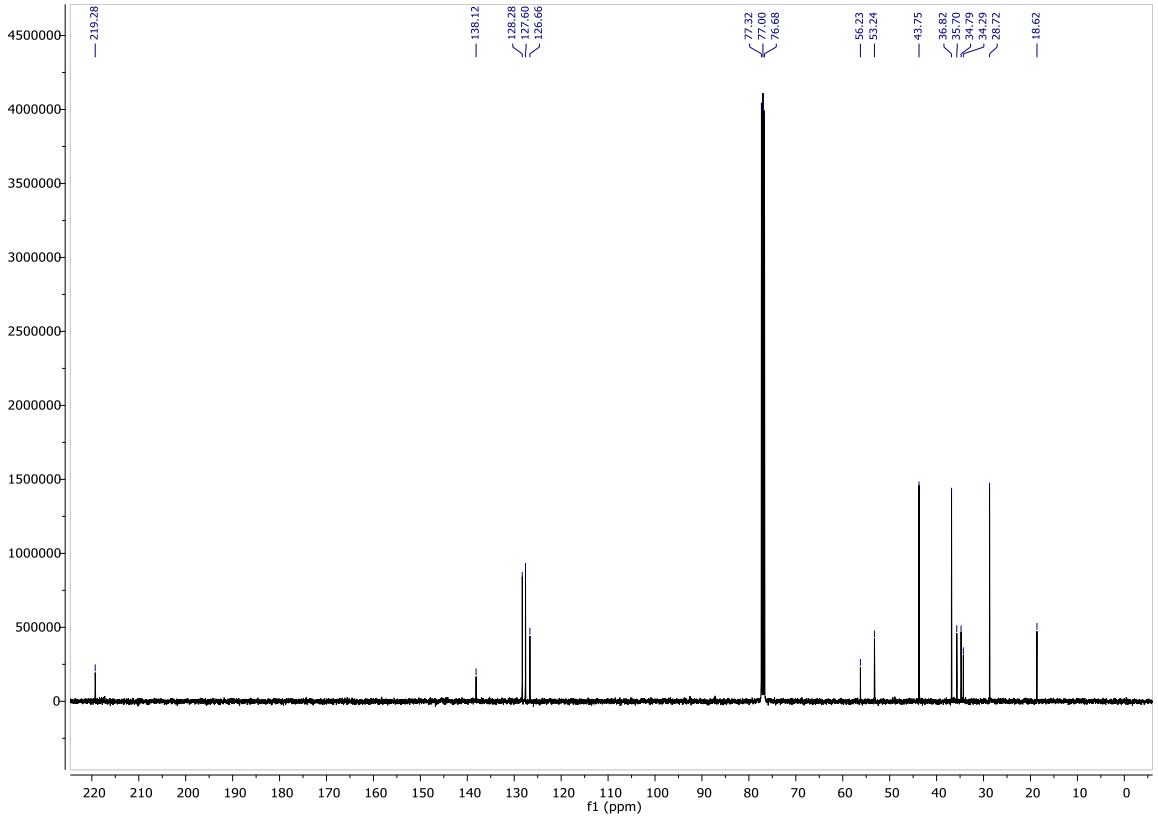

Ph
O
Ph
2.3-3ba
f1 (ppm)

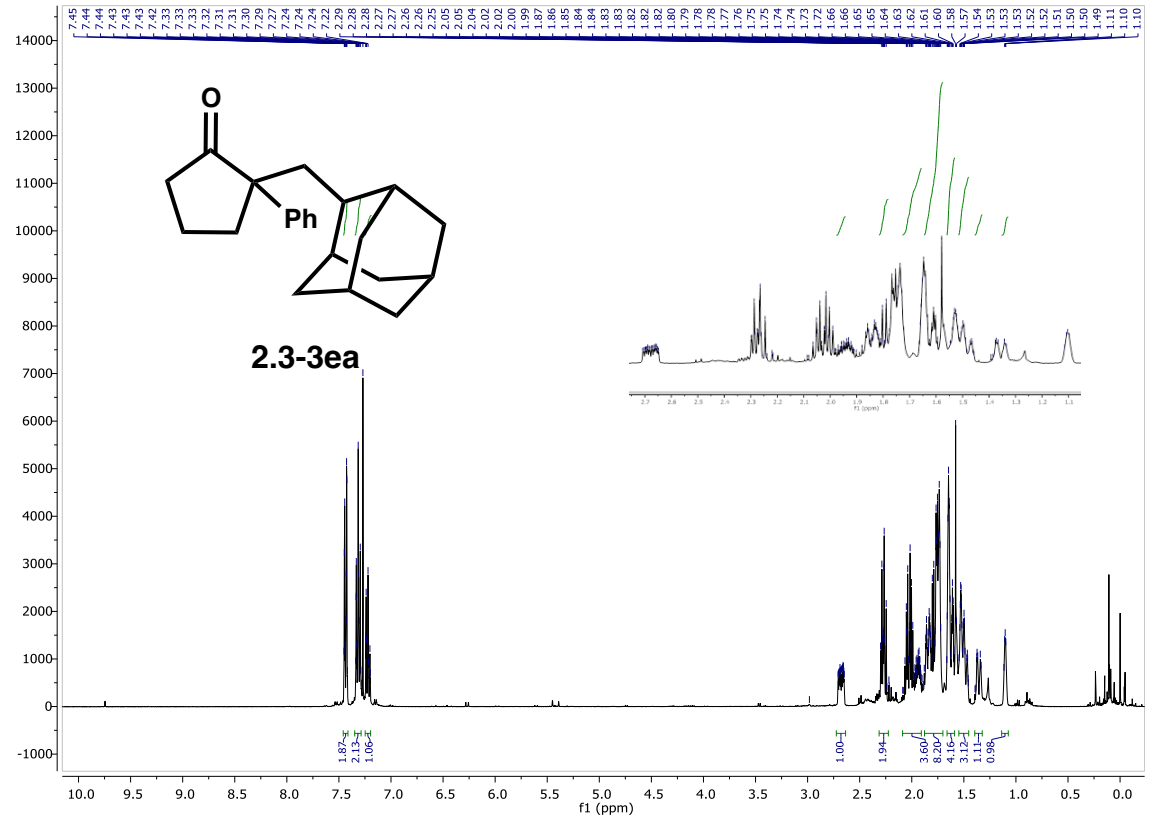

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128.48
128.29
128.19
126.82
126.67
125.57
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31.80
24.33
18.67
f1 (ppm)

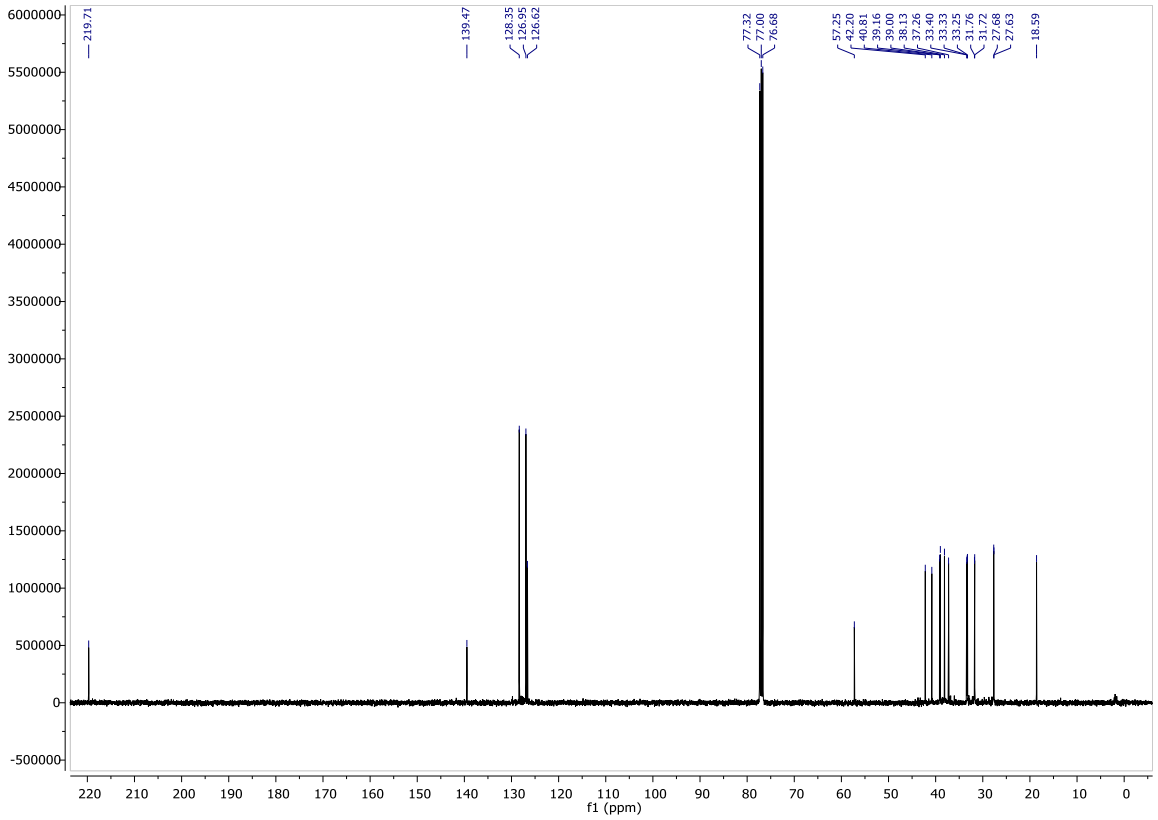

O
CO2Et
Ph
2.3-3ca
f1 (ppm)

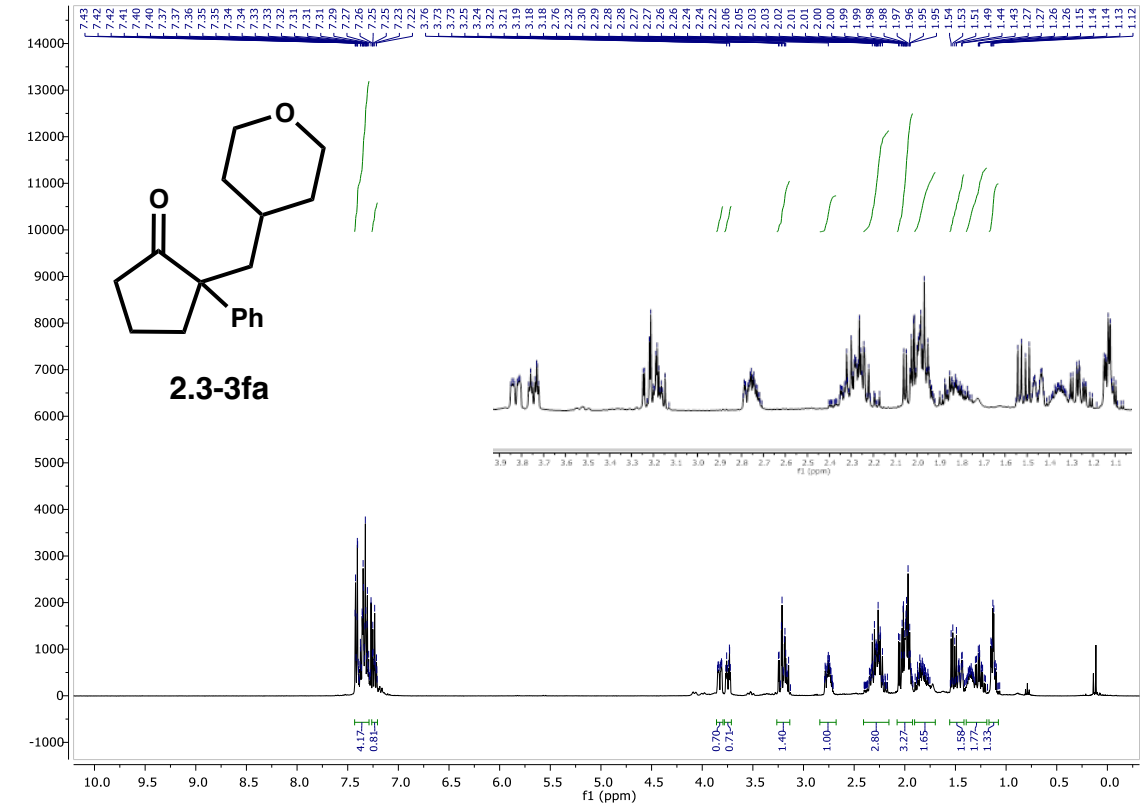

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128.70
127.04
126.85
77.32
77.00
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29.94
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14.13
f1 (ppm)

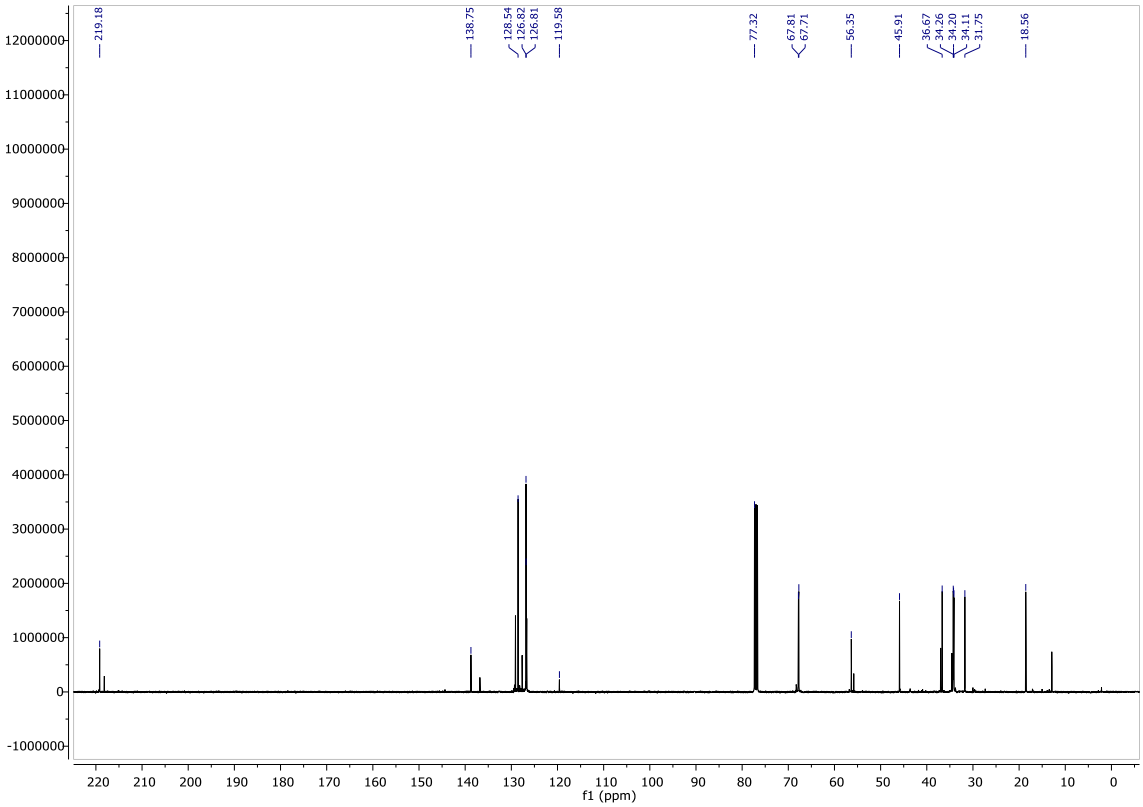

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Ph
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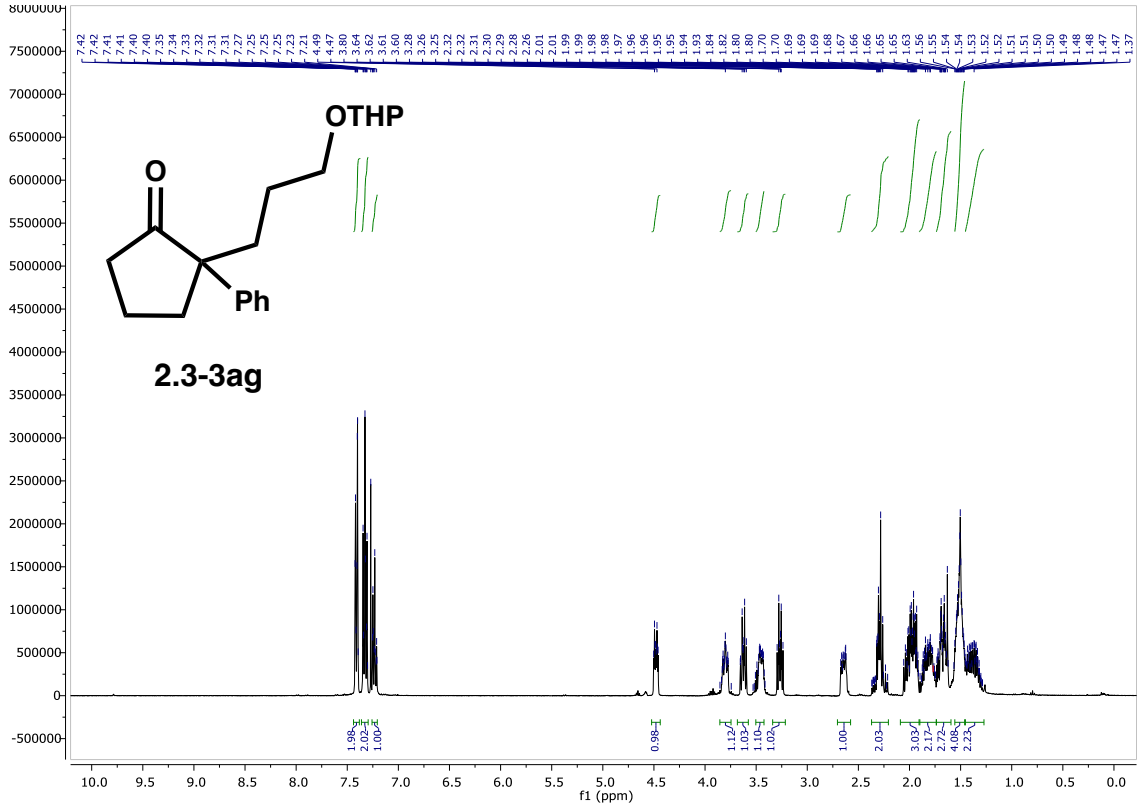

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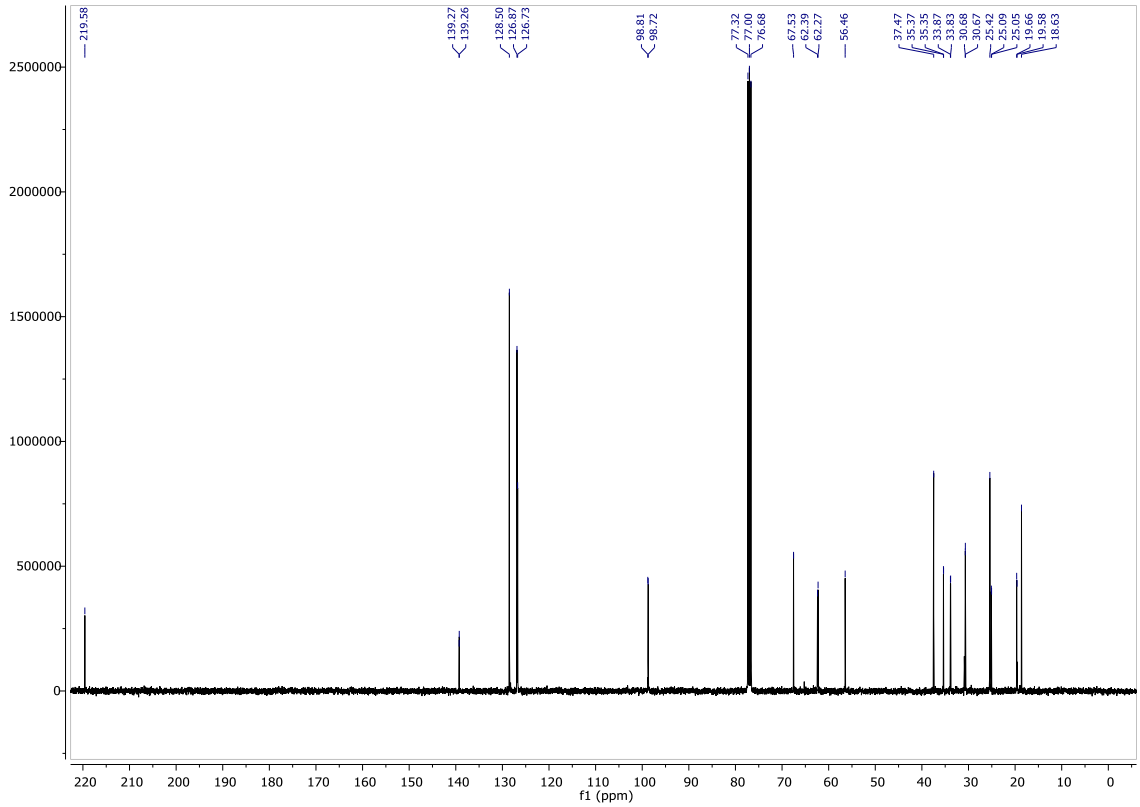

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f1 (ppm)

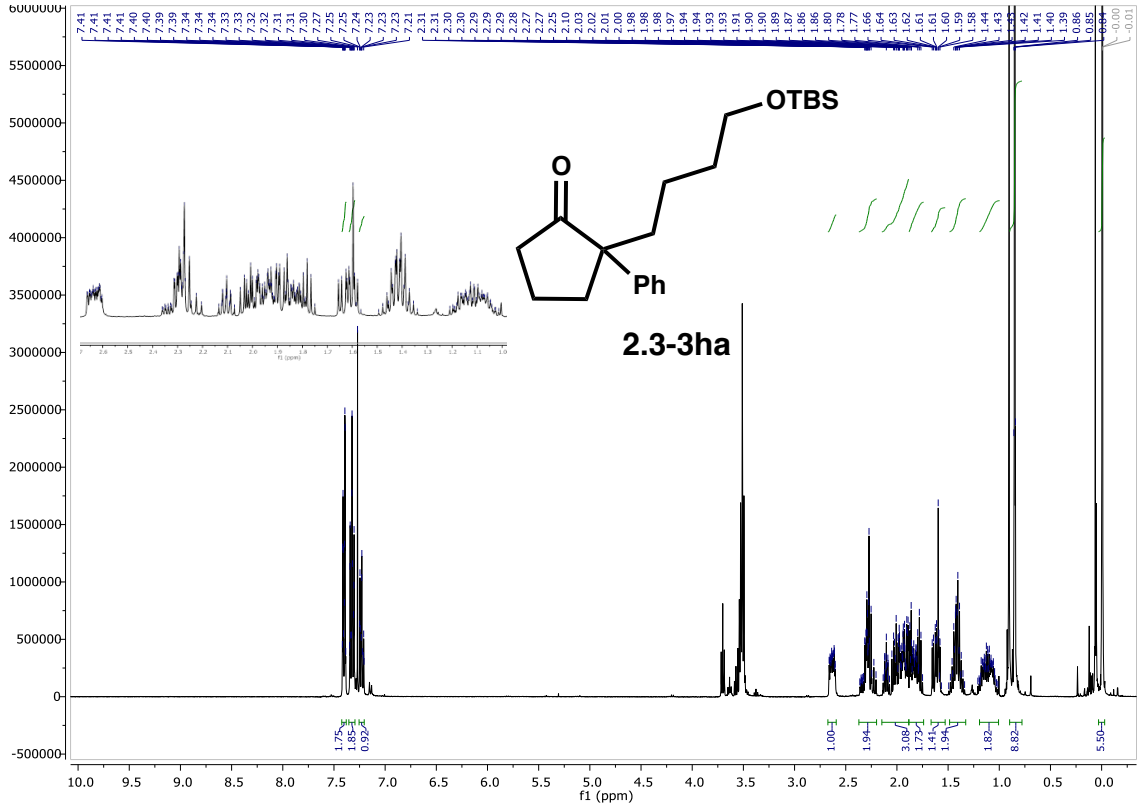

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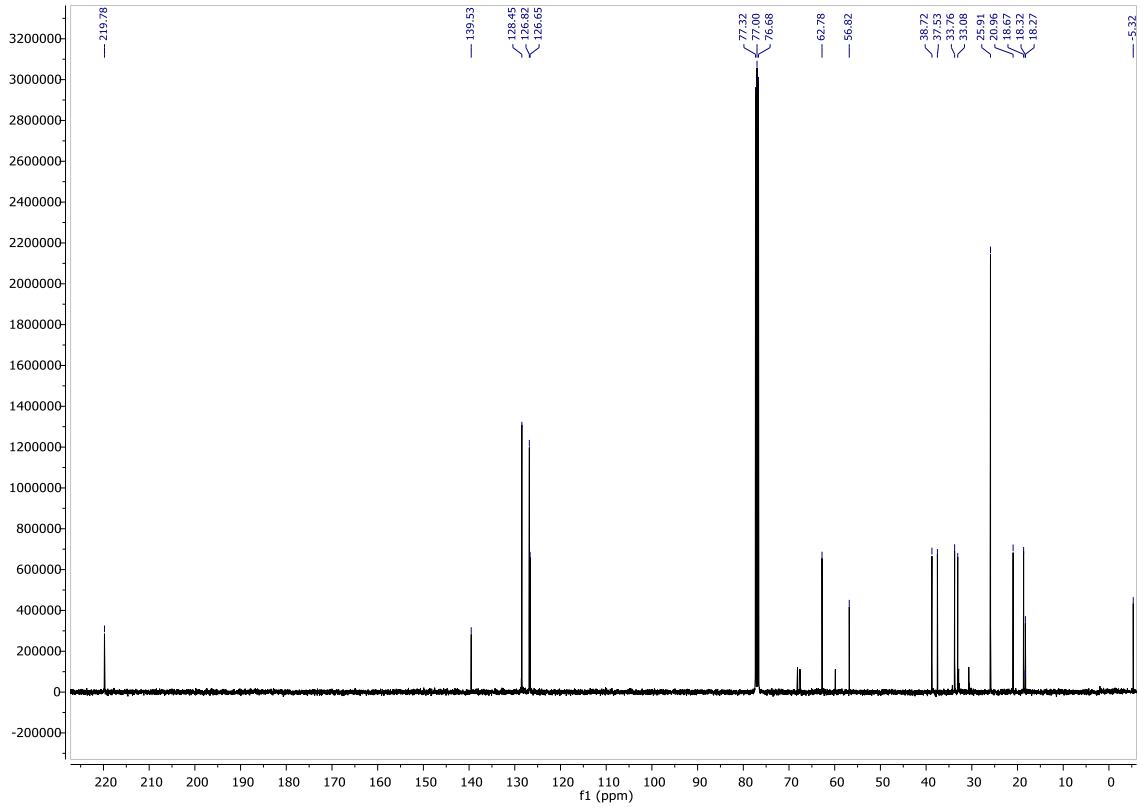

O
O
Ph
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f1 (ppm)

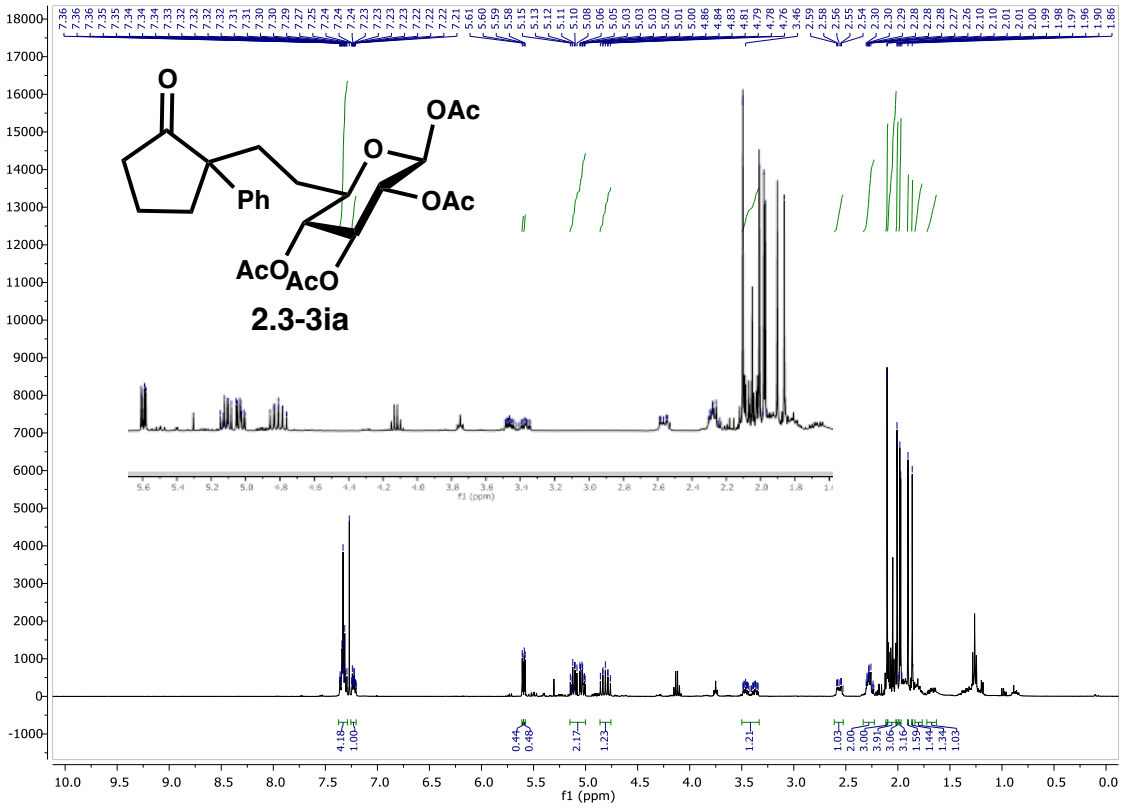

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126.82
126.81
119.58
77.32
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34.11
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18.56
f1 (ppm)

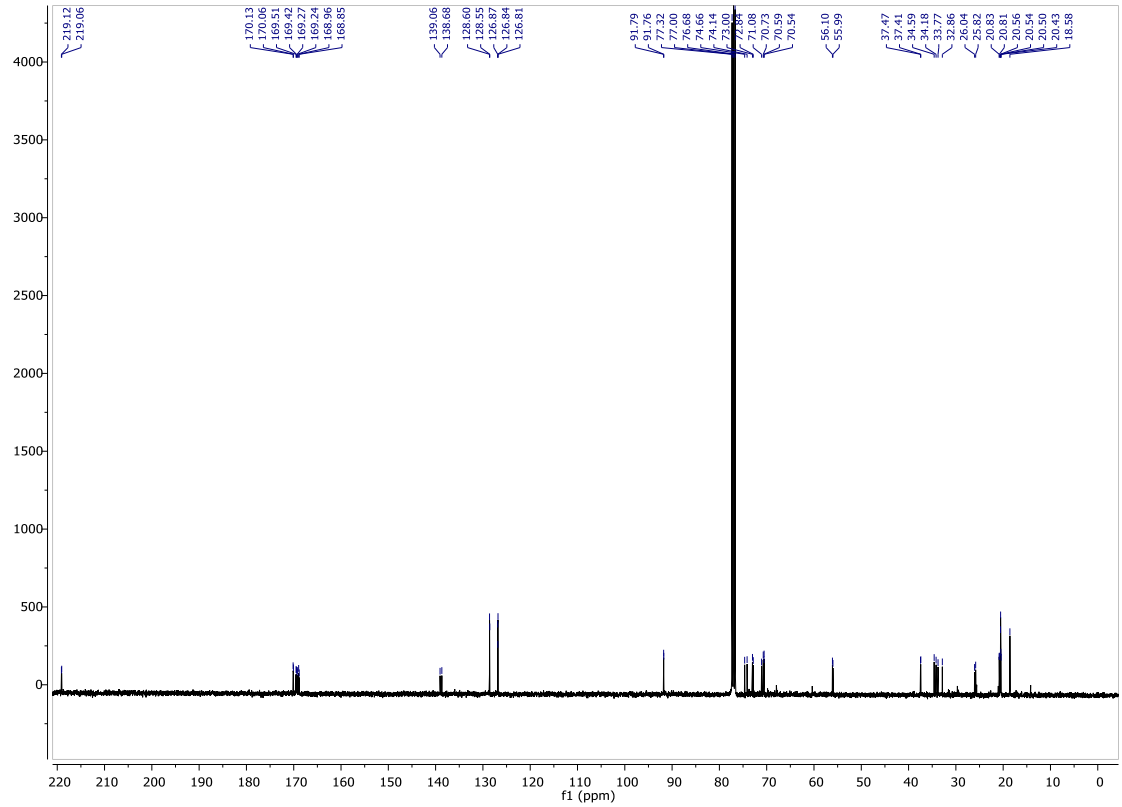

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Ph
2.3-3ag
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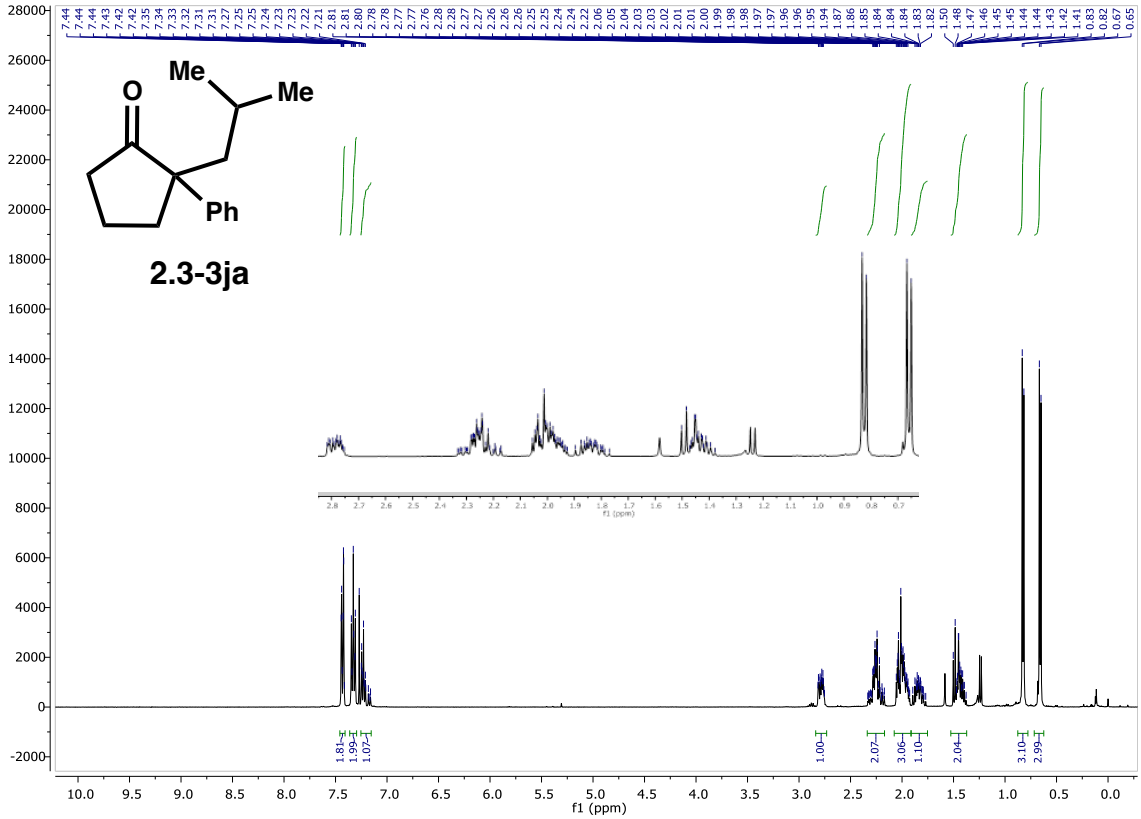

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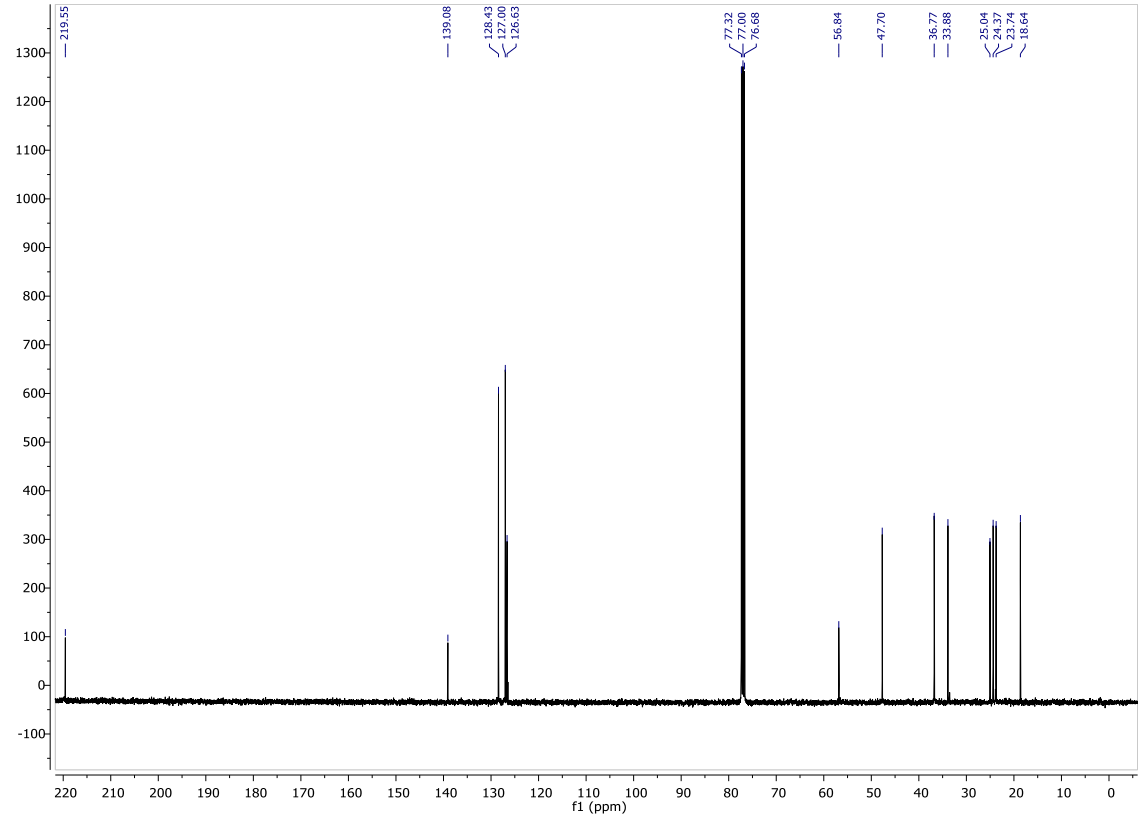

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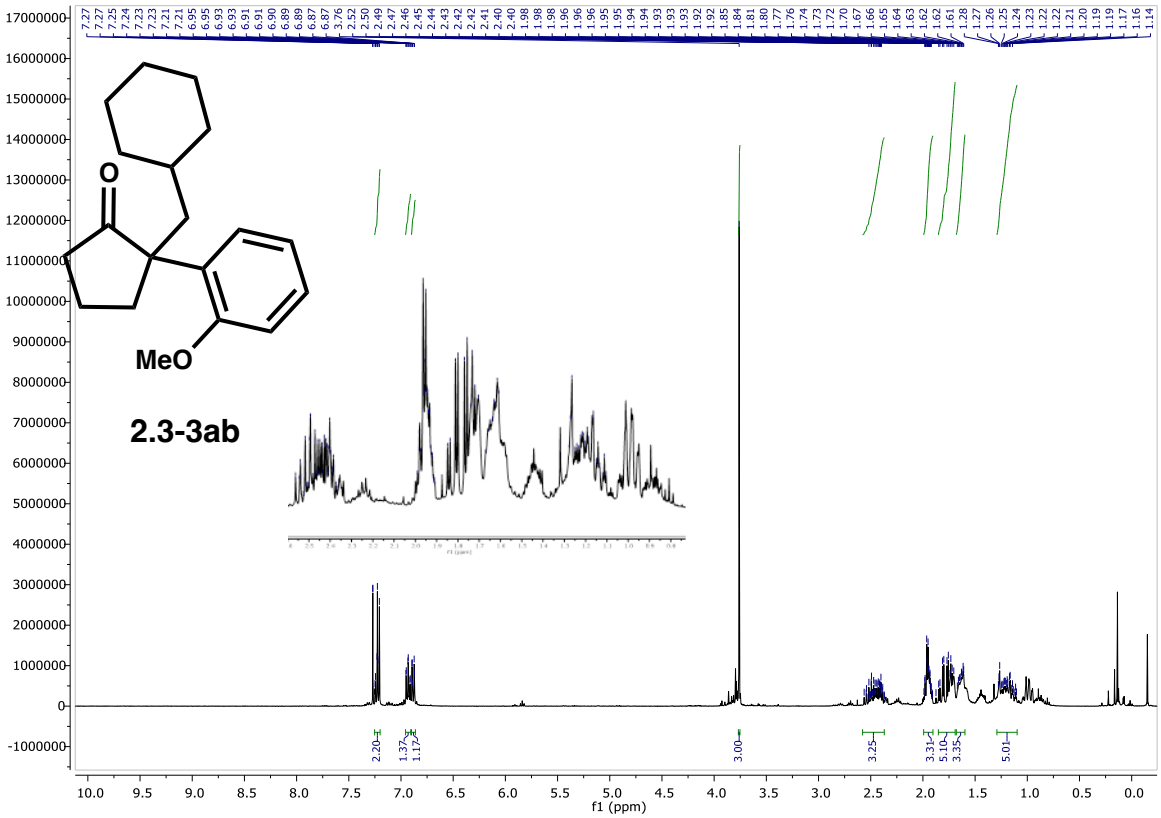

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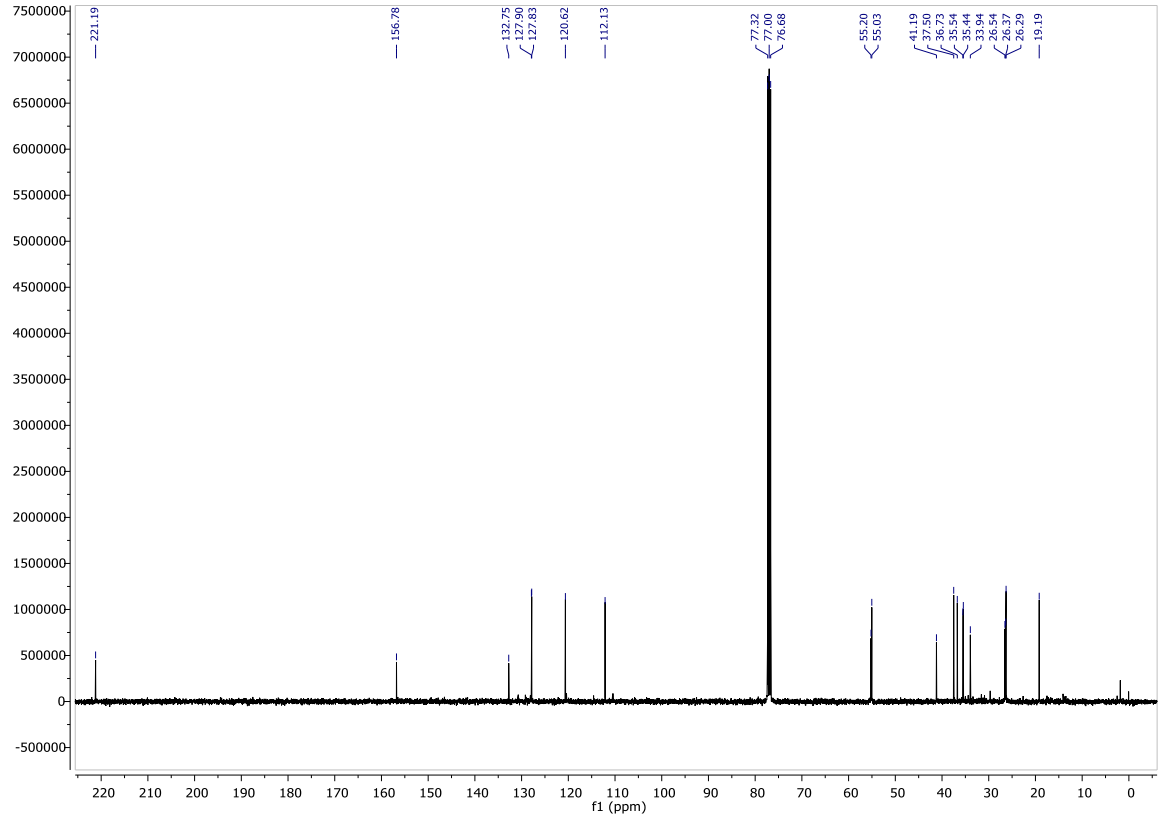

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O
Ph
OAc
AcO
AcO
2.3-3ia
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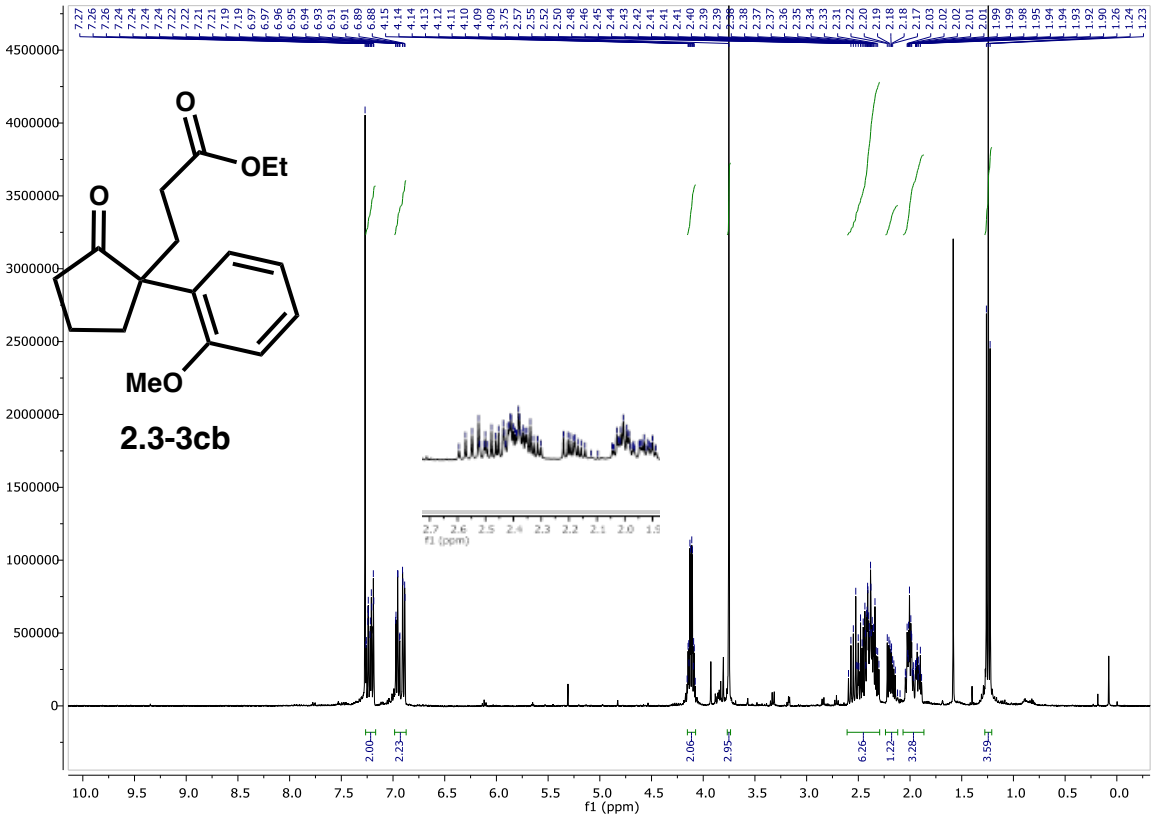

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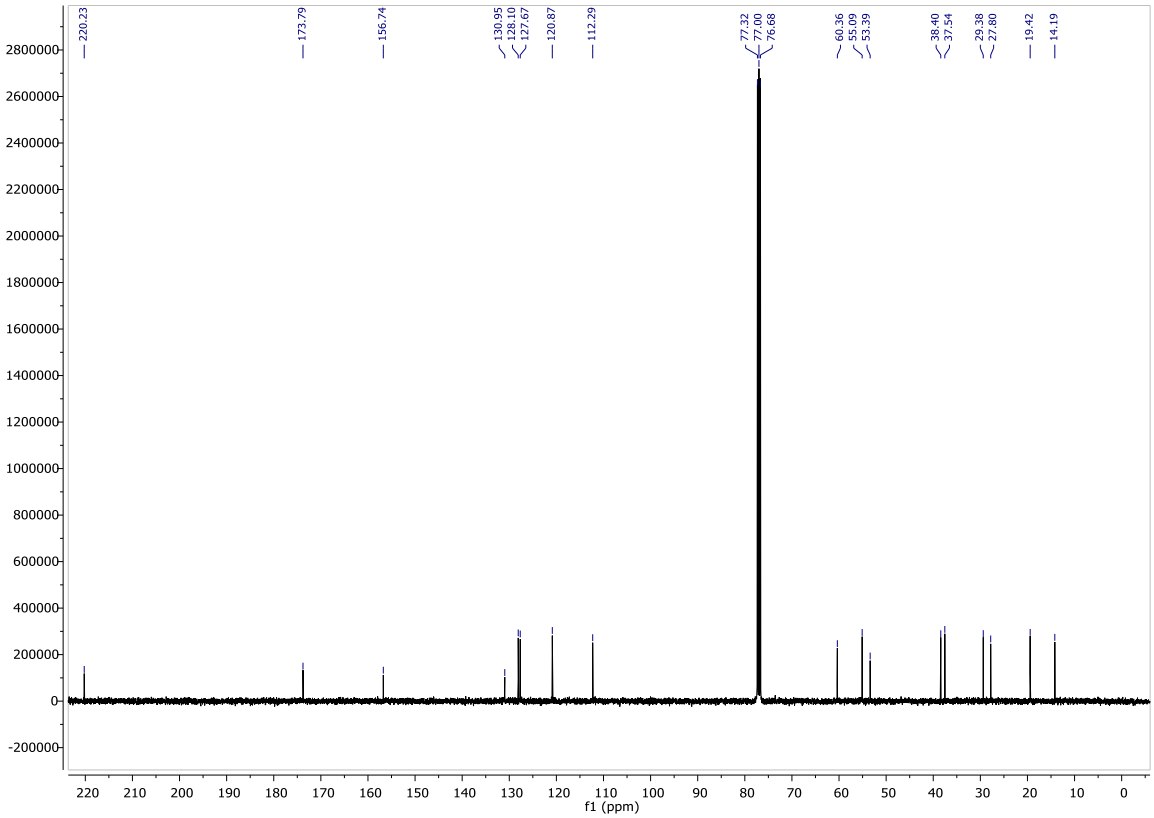

Me
Me
O
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2.3-3ja
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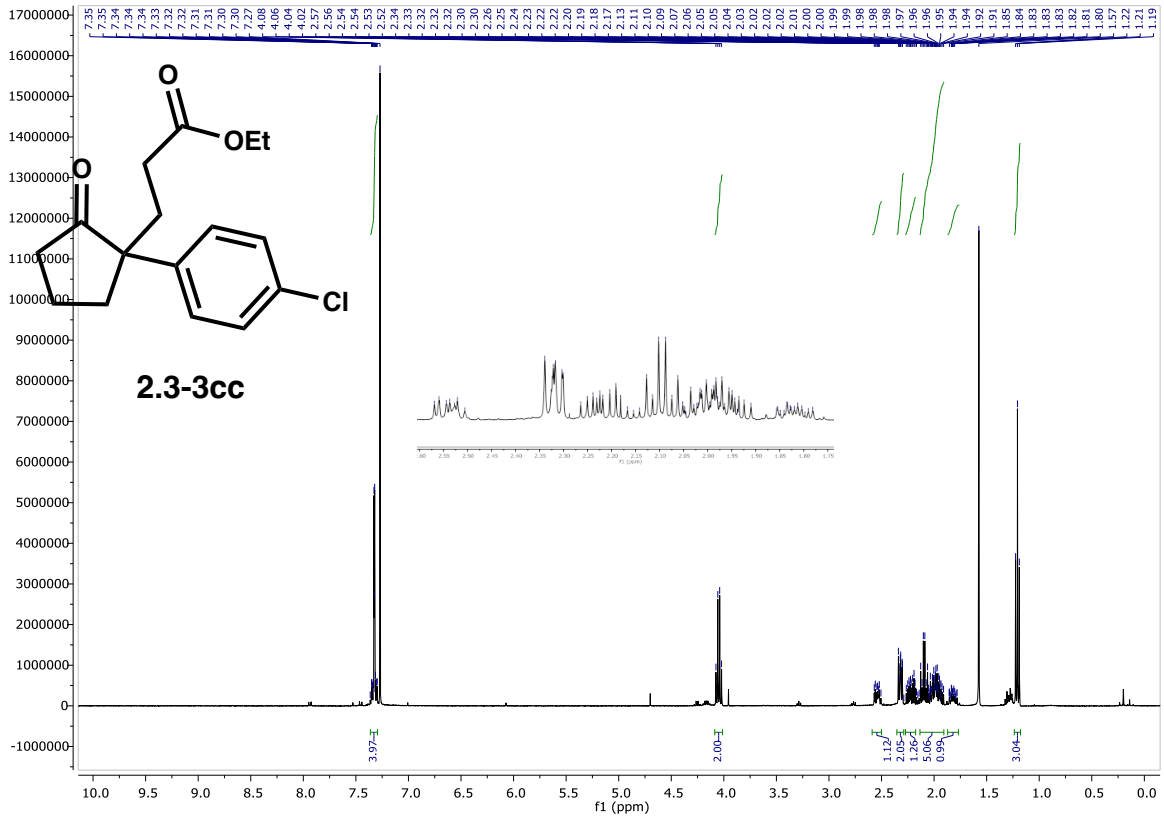

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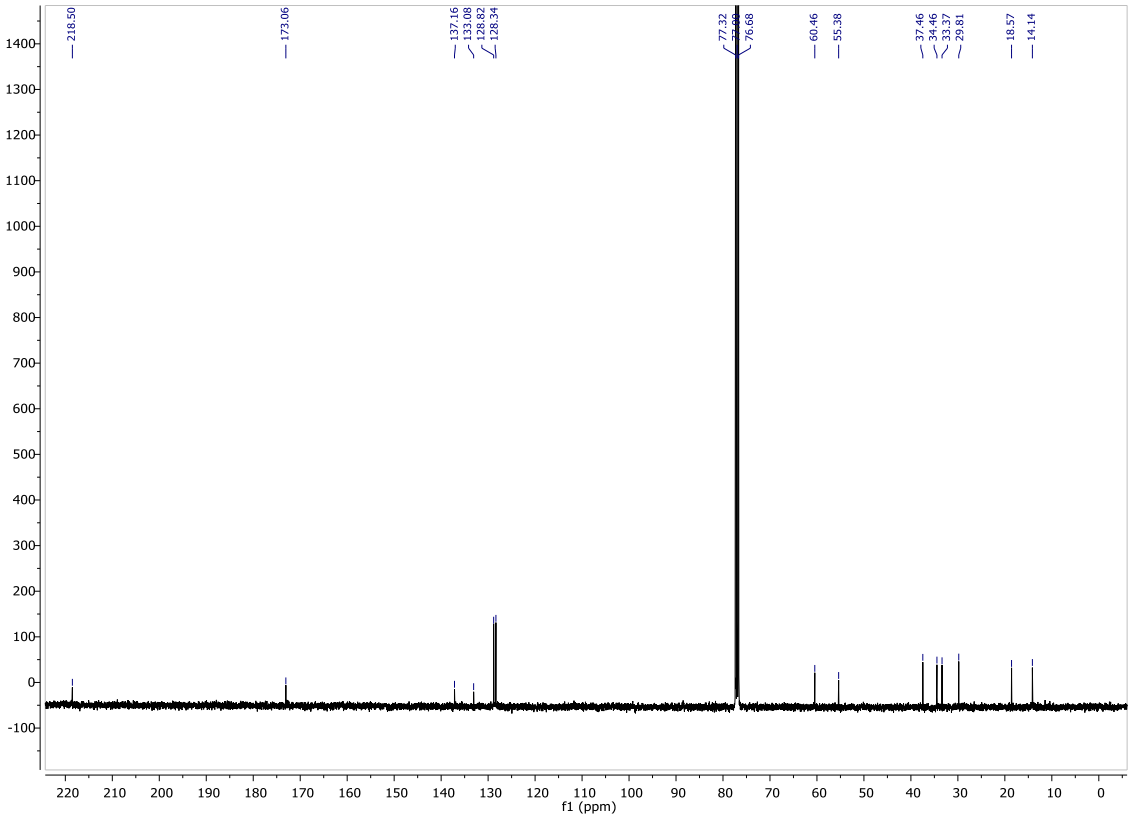

O
MeO
2.3-3ab
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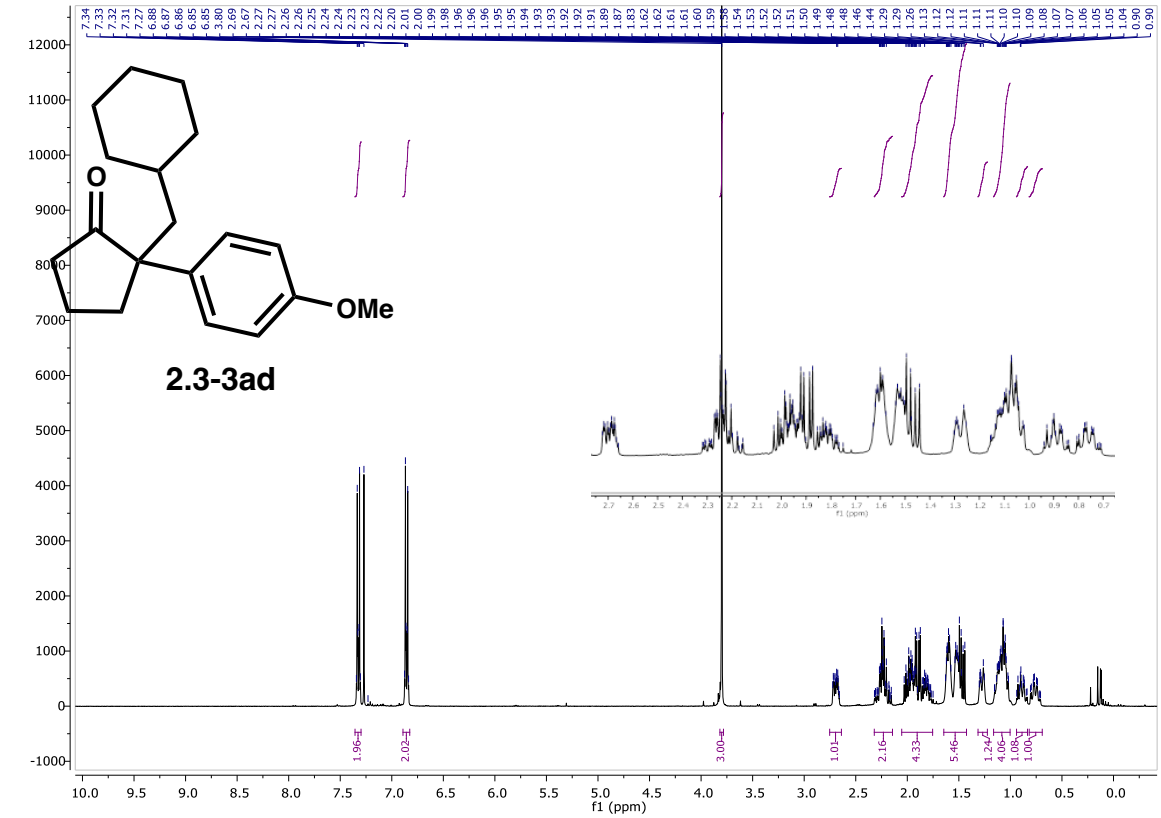

221.19
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127.90
127.83
120.62
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77.32
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76.68
55.20
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26.29
19.19
f1 (ppm)

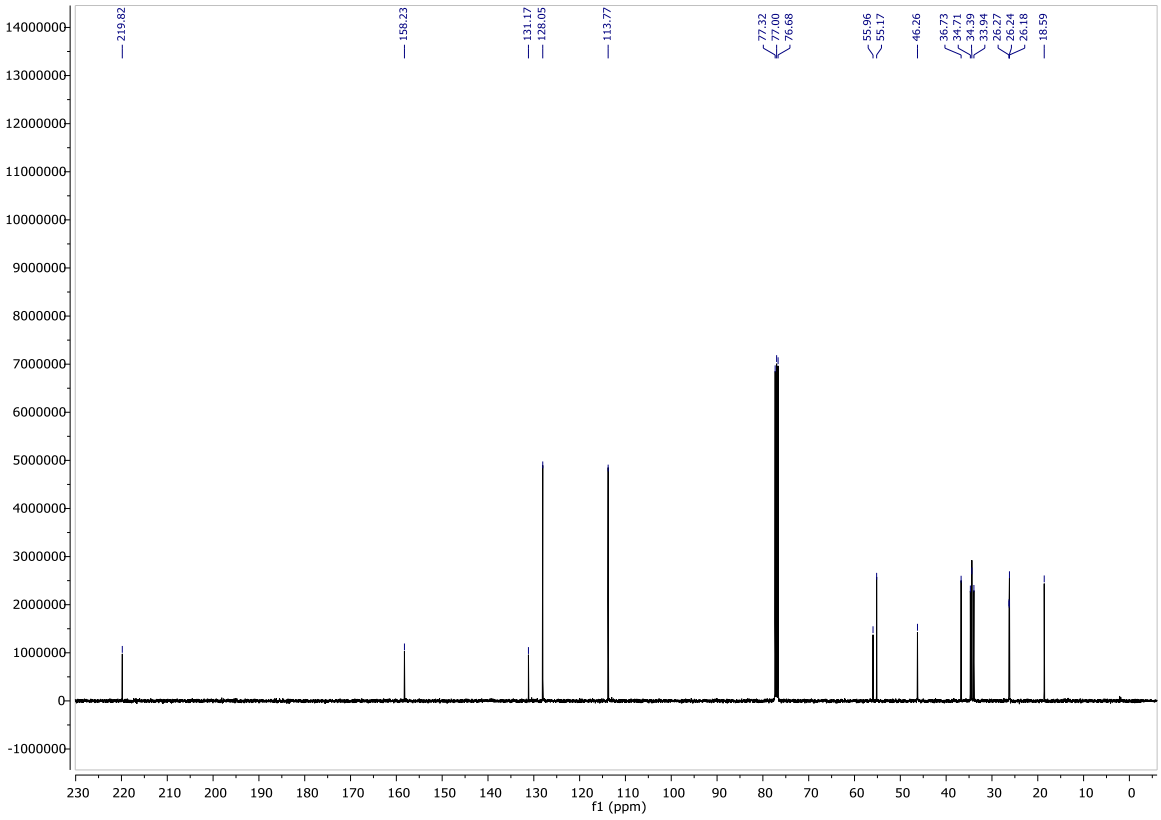

O
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O
MeO
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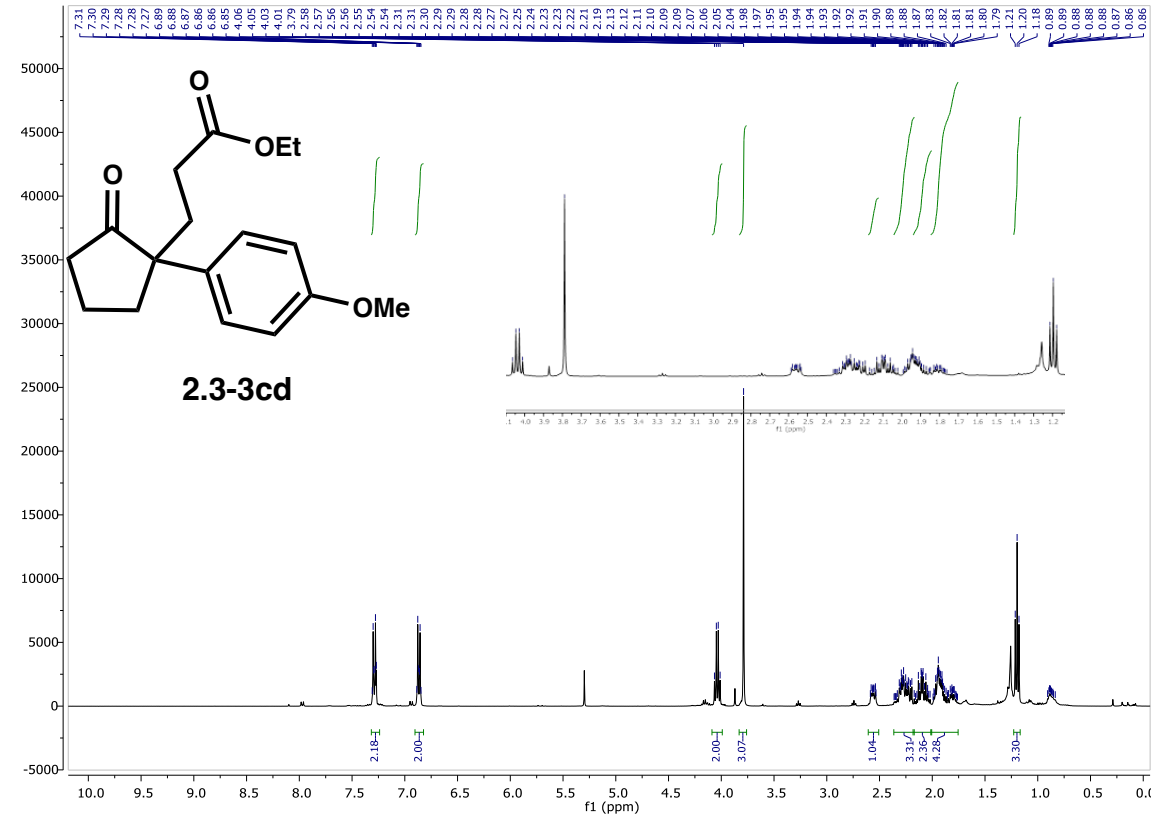

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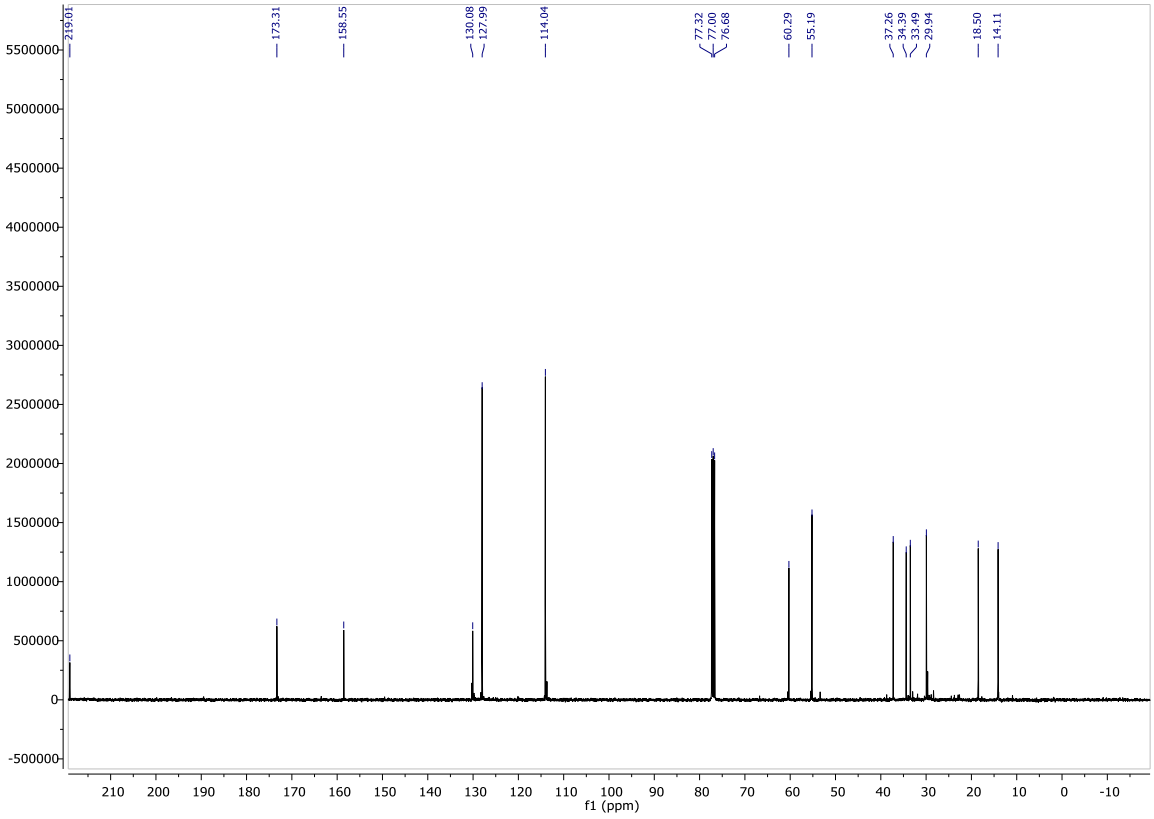

O
OEt
O
Cl
2.3-3cc
f1 (ppm)

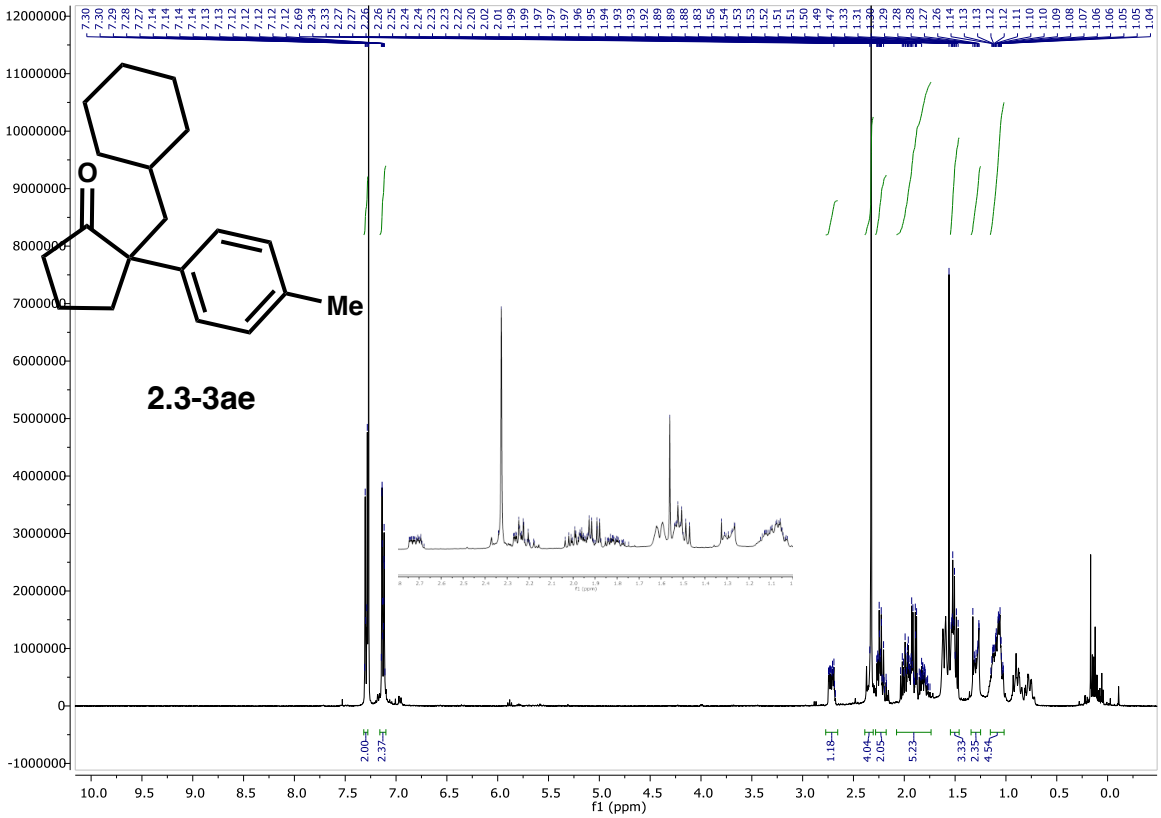

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137.16
133.08
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33.37
29.81
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14.14
f1 (ppm)

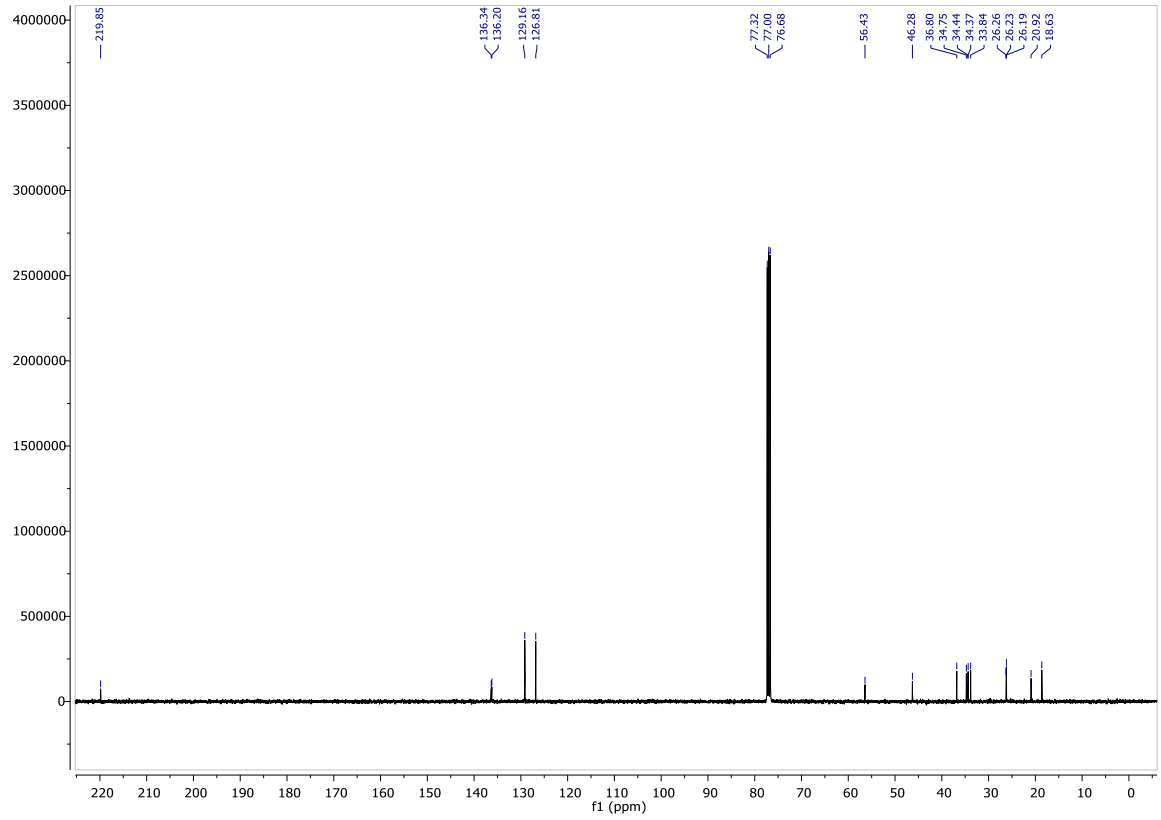

O
OMe
2.3-3ad
f1 (ppm)

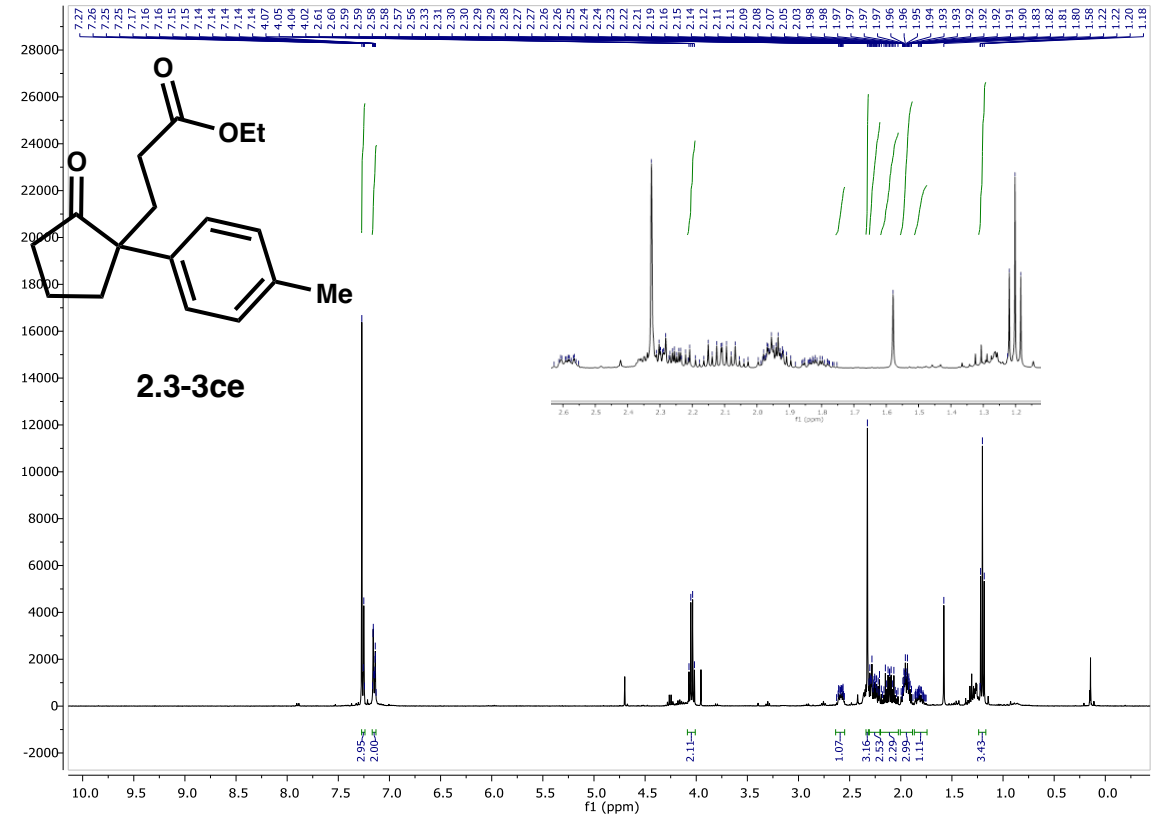

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128.05
113.77
77.32
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76.68
55.96
55.17
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36.73
34.71
34.39
33.94
26.27
26.24
26.18
18.59
f1 (ppm)

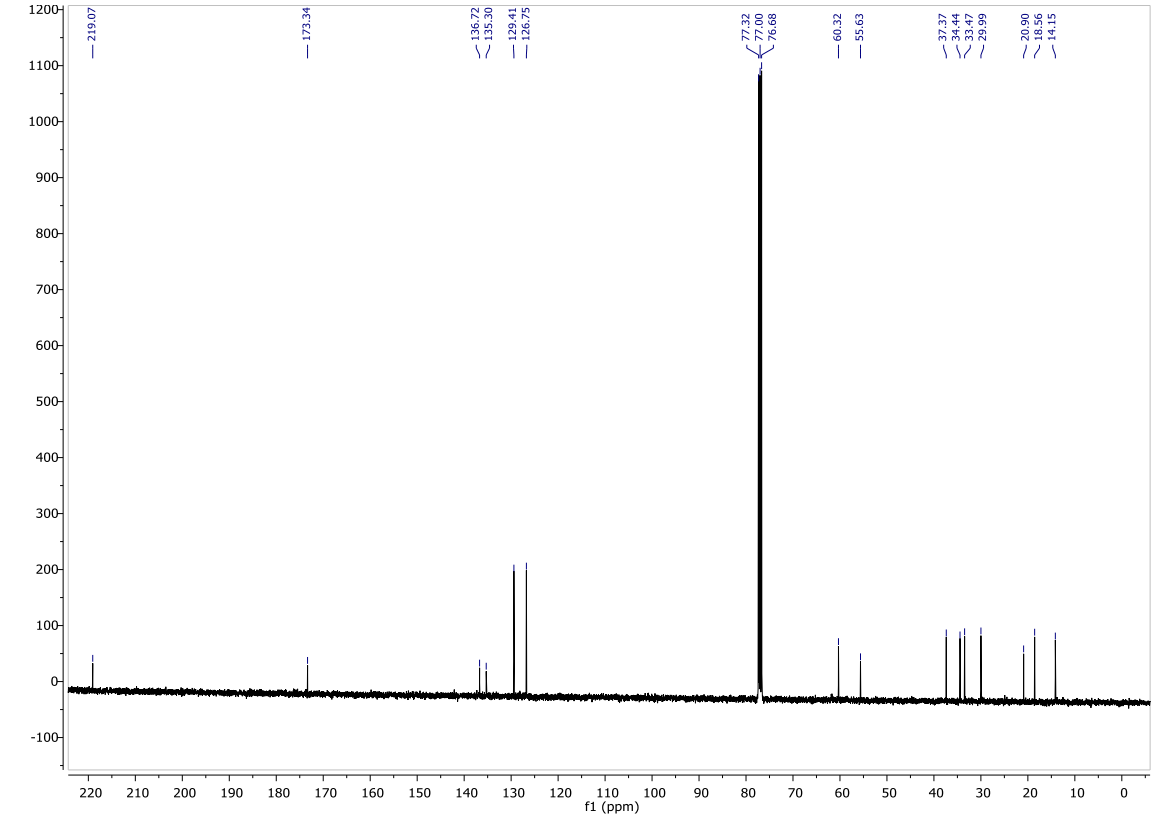

O
OEt
O
OMe
2.3-3cd
f1 (ppm)

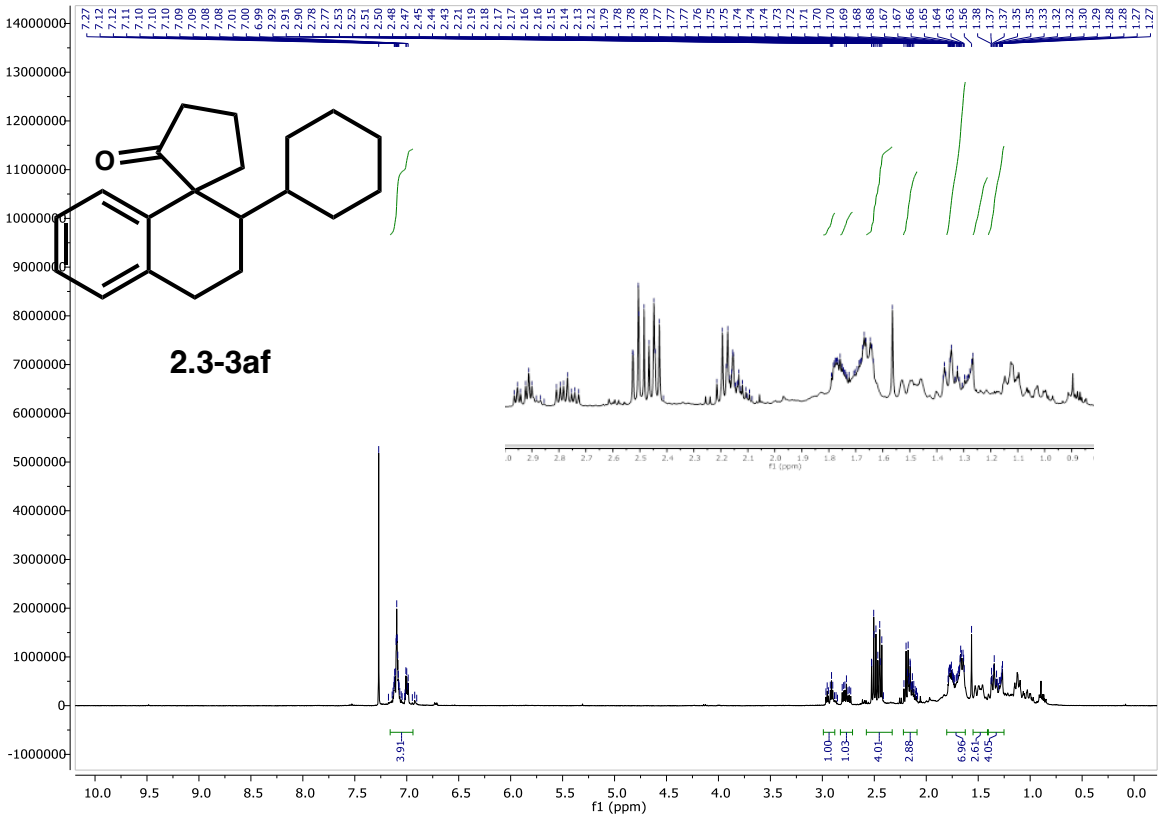

219.01
173.31
158.55
130.08
127.99
114.04
77.32
77.00
76.68
60.29
55.19
37.26
34.39
33.49
29.94
18.50
14.11
f1 (ppm)

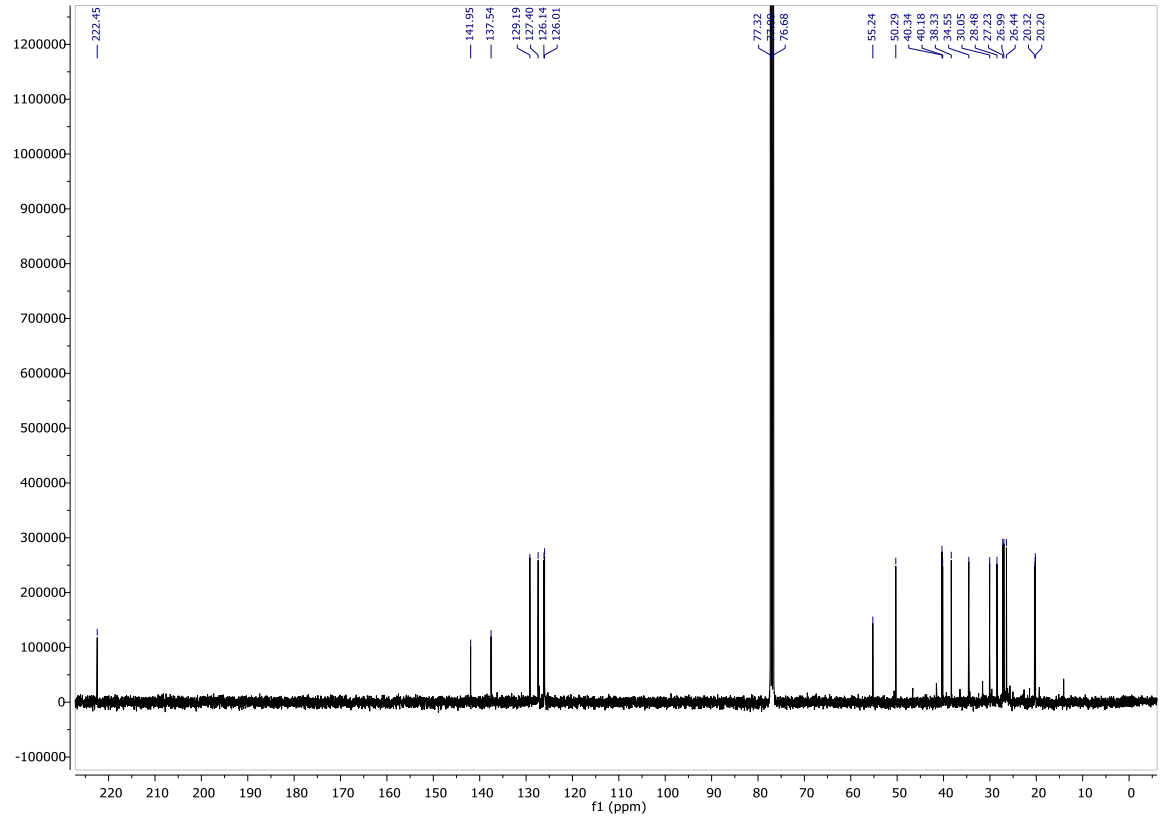

O
Me
2.3-3ae
f1 (ppm)

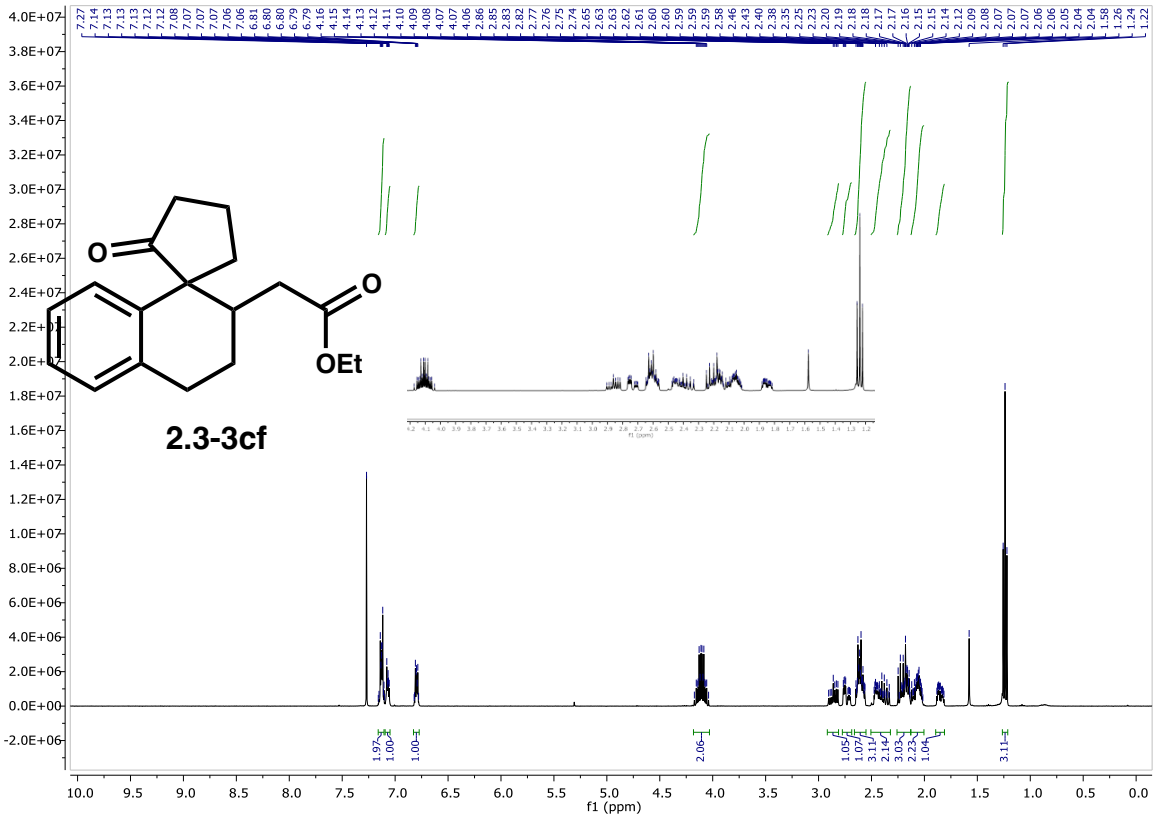

f1 (ppm)

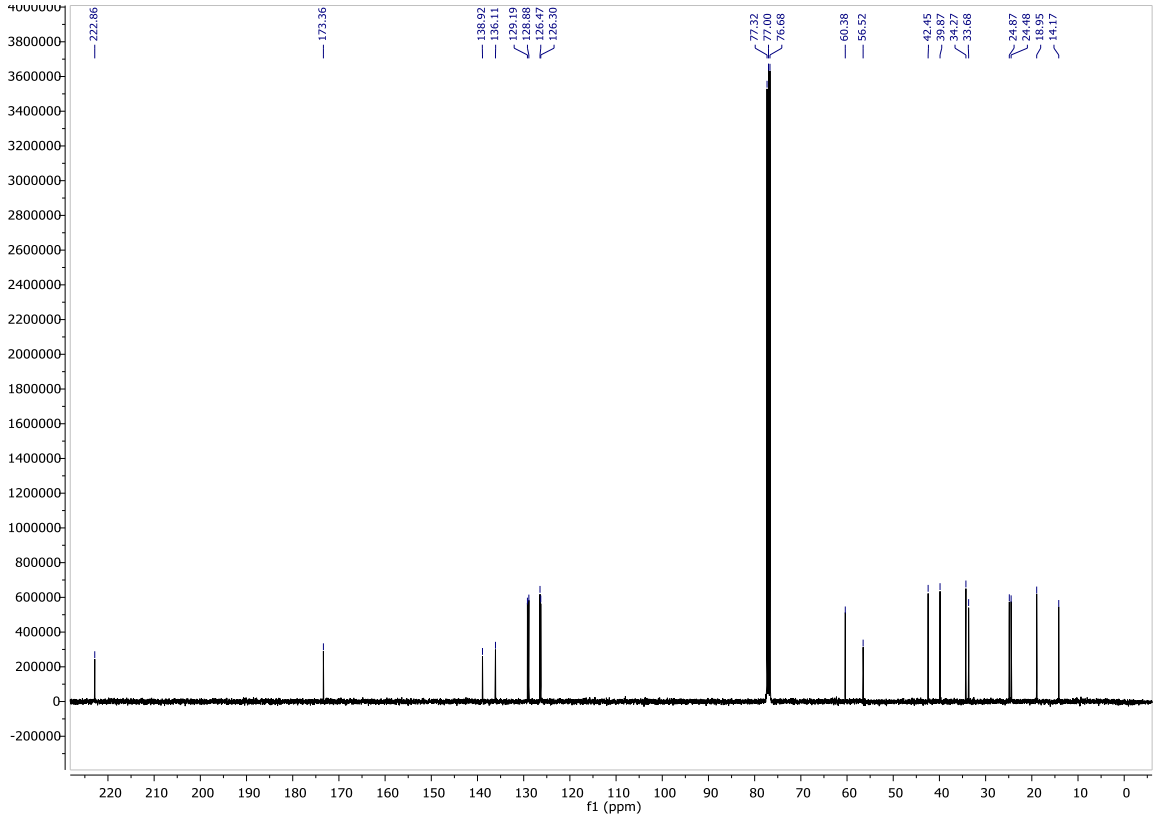

O
OEt
O
Me
2.3-3ce
f1 (ppm)

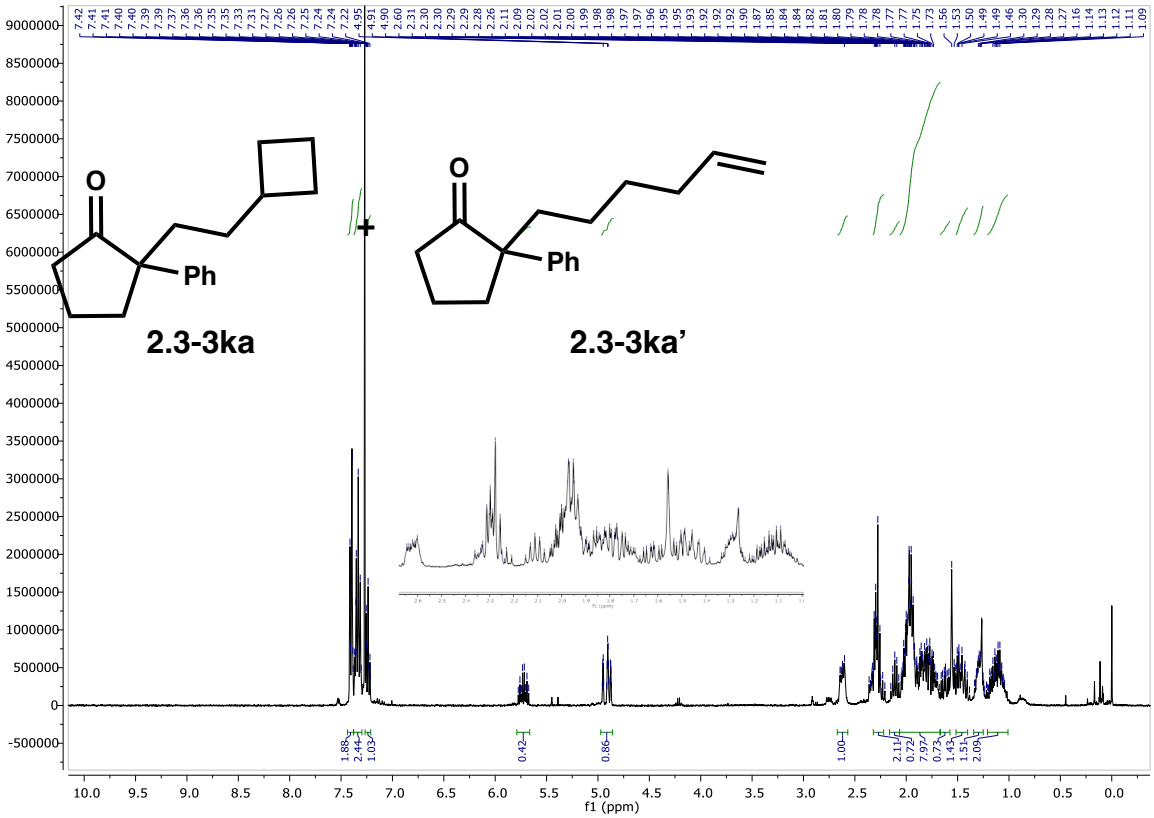

219.07
173.34
136.72
135.30
129.41
126.75
77.32
77.00
76.68
60.32
55.63
37.37
34.44
33.47
29.99
20.90
18.56
14.15
f1 (ppm)

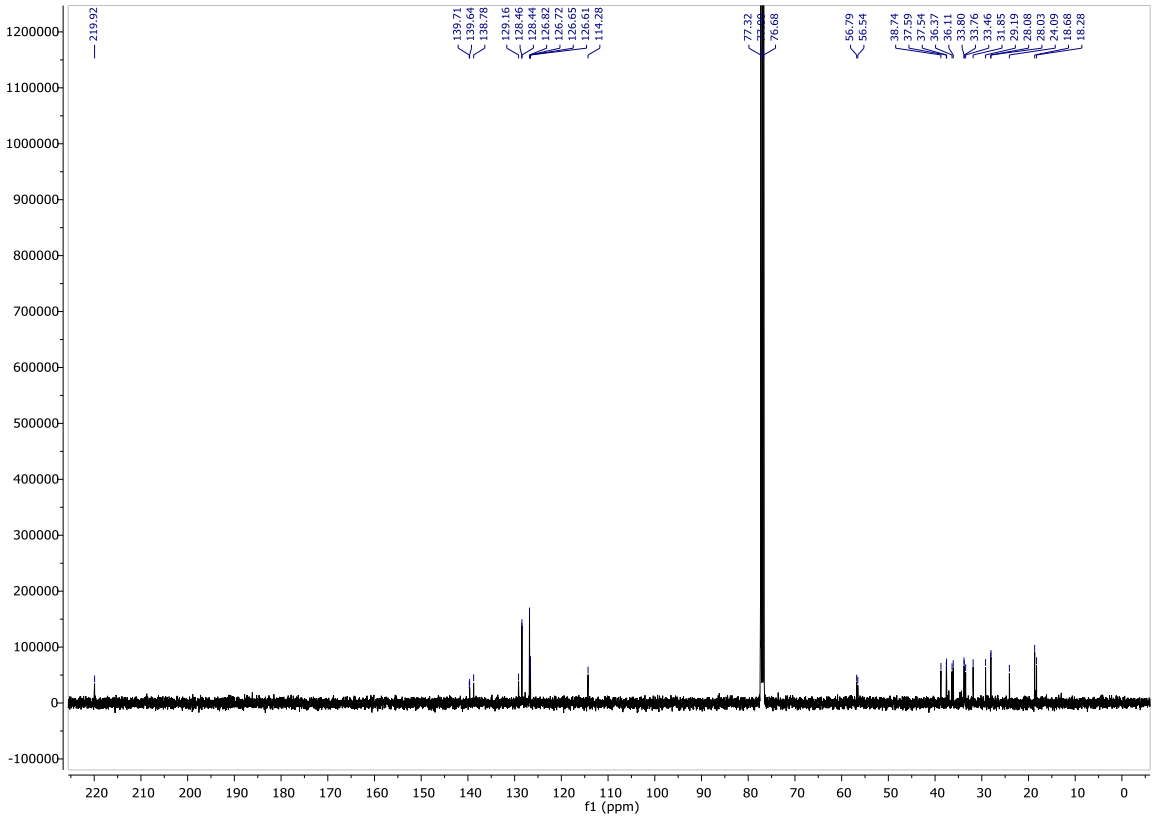

O
2.3-3af
f1 (ppm)

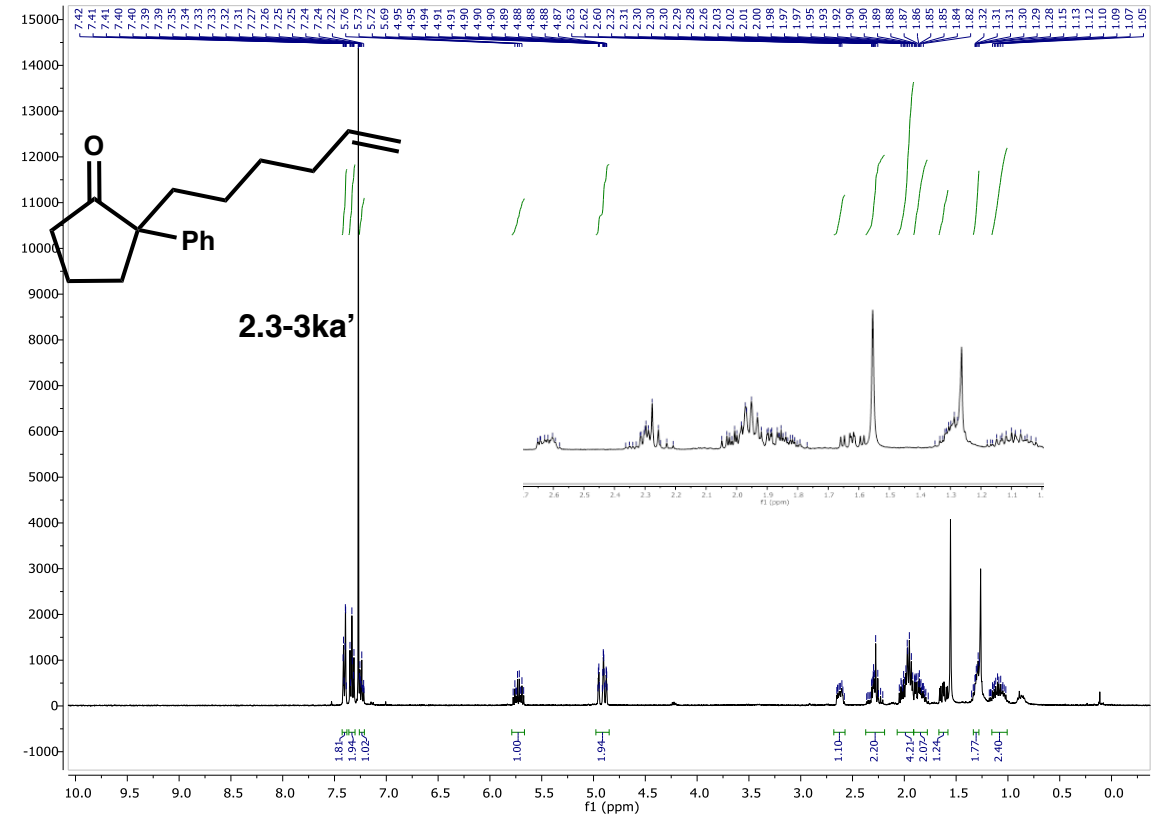

f1 (ppm)

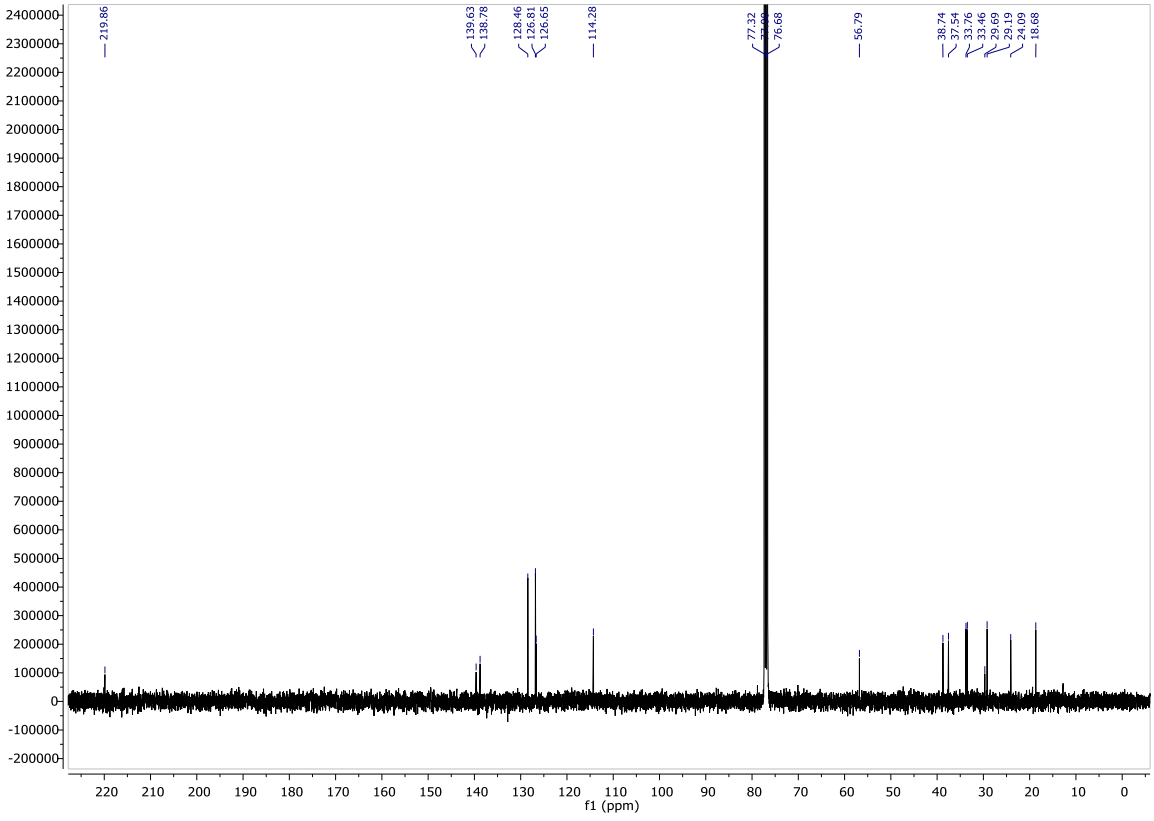

O
O
OEt
2.3-3cf
f1 (ppm)

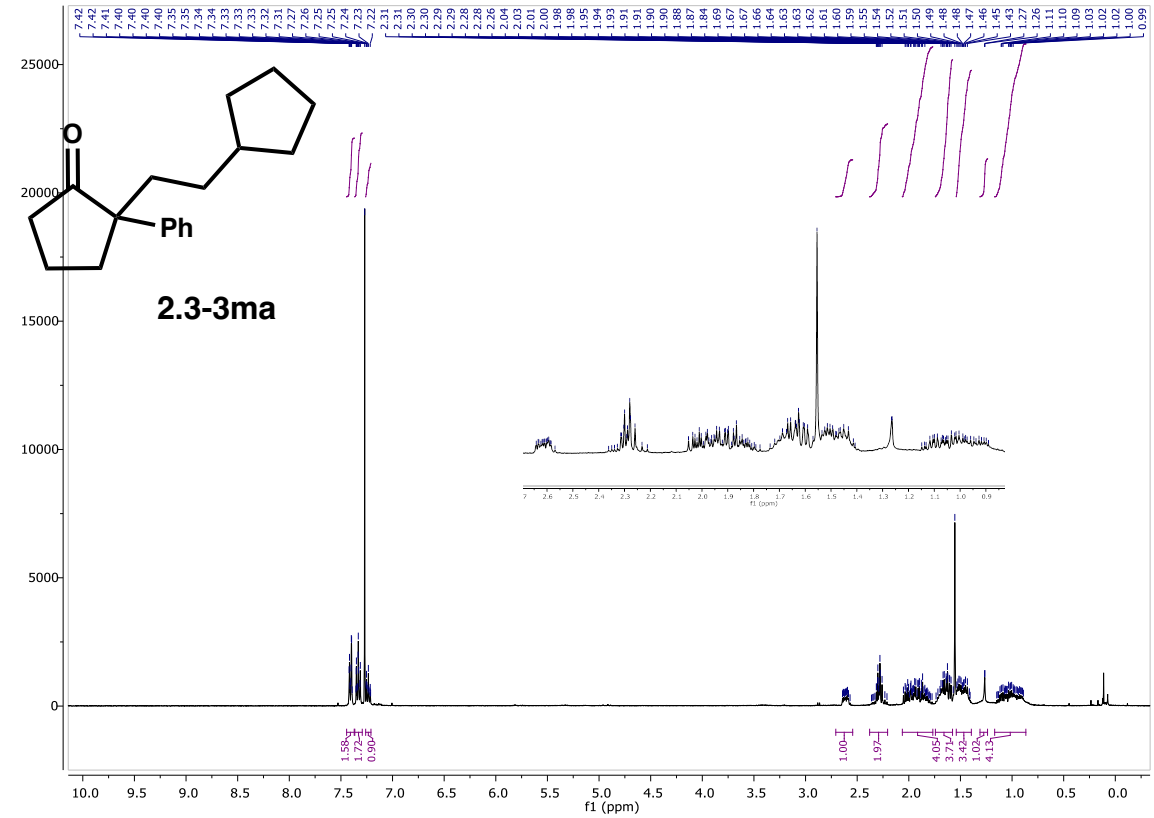

222.86
173.36
138.92
136.11
129.19
128.88
126.47
126.30
77.32
77.00
76.68
60.38
56.52
42.45
39.87
34.27
33.68
24.87
24.48
18.95
14.17
f1 (ppm)

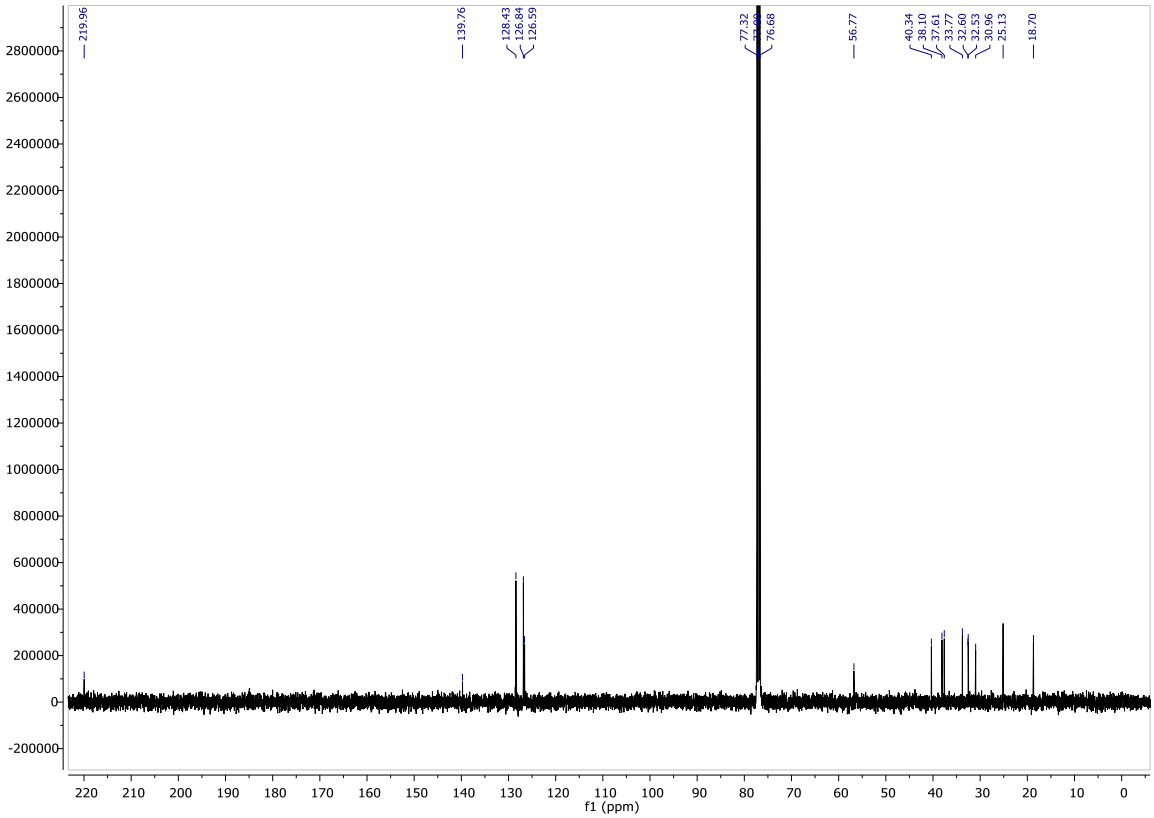

O
Ph
2.3-3ka
+
O
Ph
2.3-3ka'
f1 (ppm)

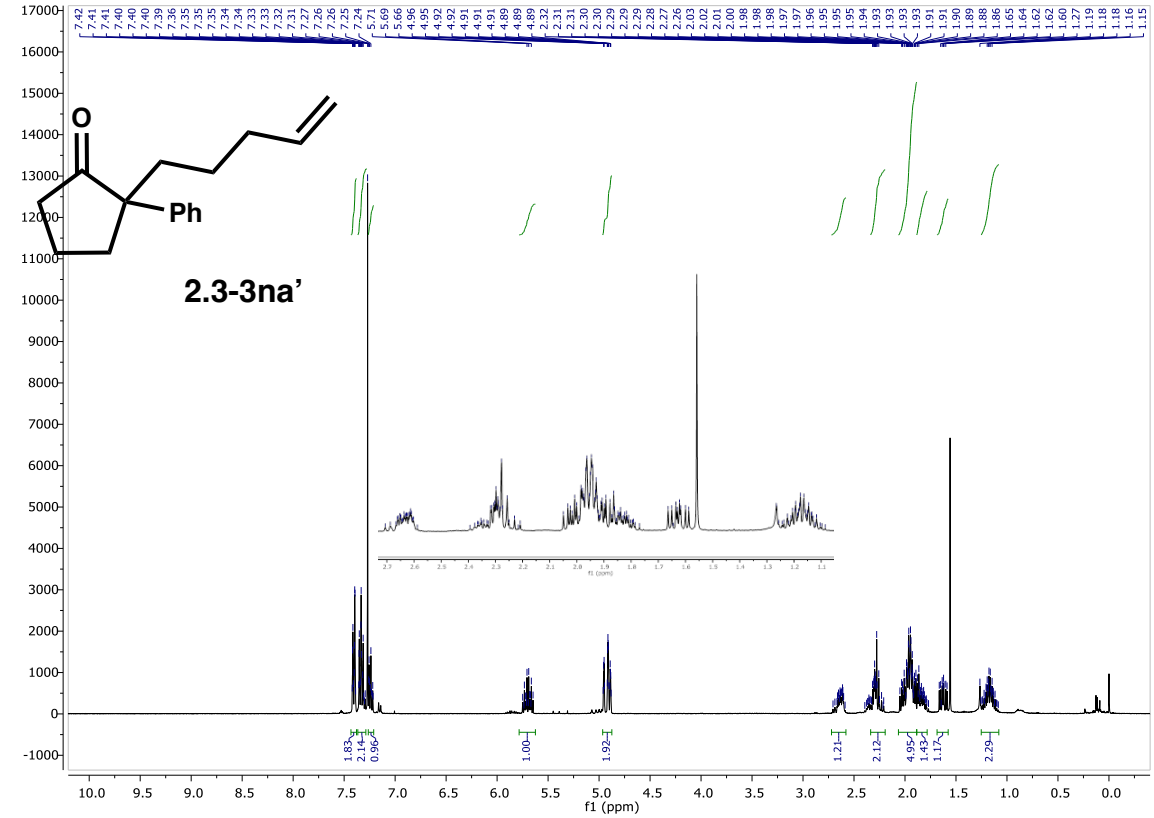

f1 (ppm)

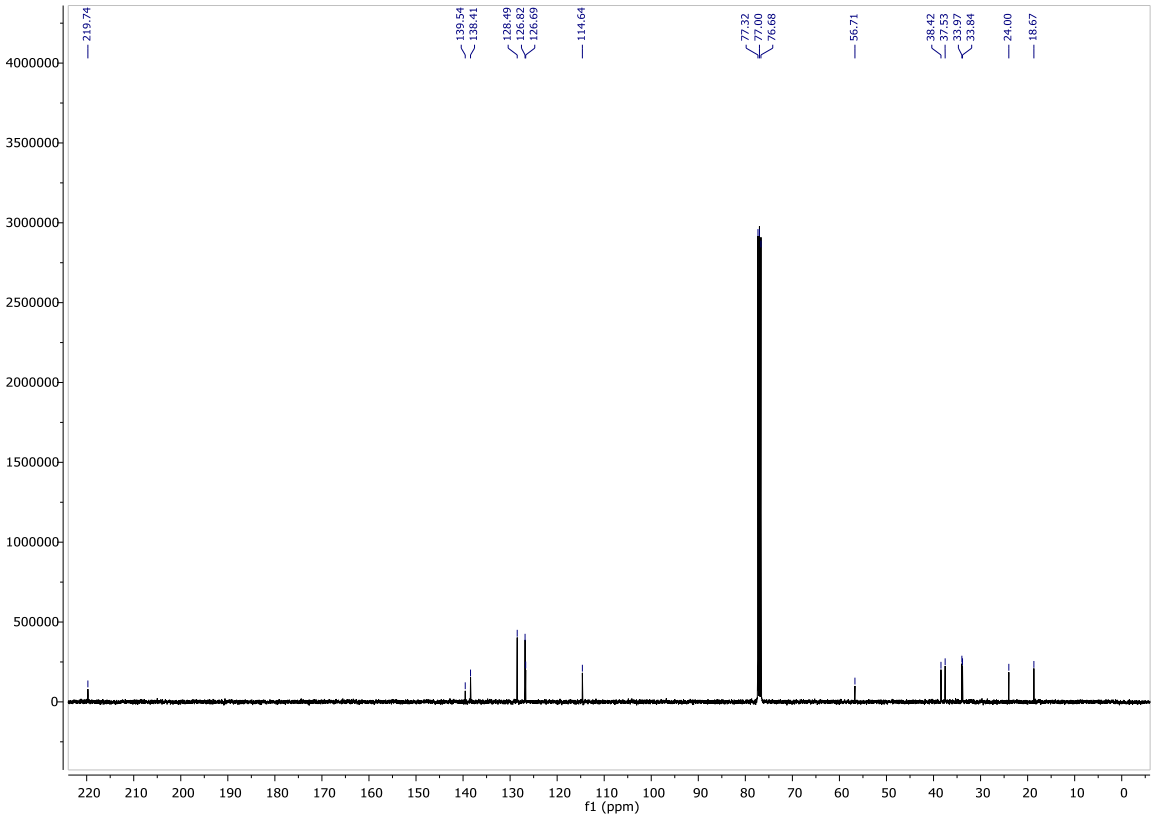

O
Ph
2.3-3ka'
f1 (ppm)


219.86
139.63
138.78
128.46
126.81
126.65
114.28
77.32
76.68
56.79
38.74
37.54
33.76
33.46
29.69
29.19
24.09
18.68
f1 (ppm)

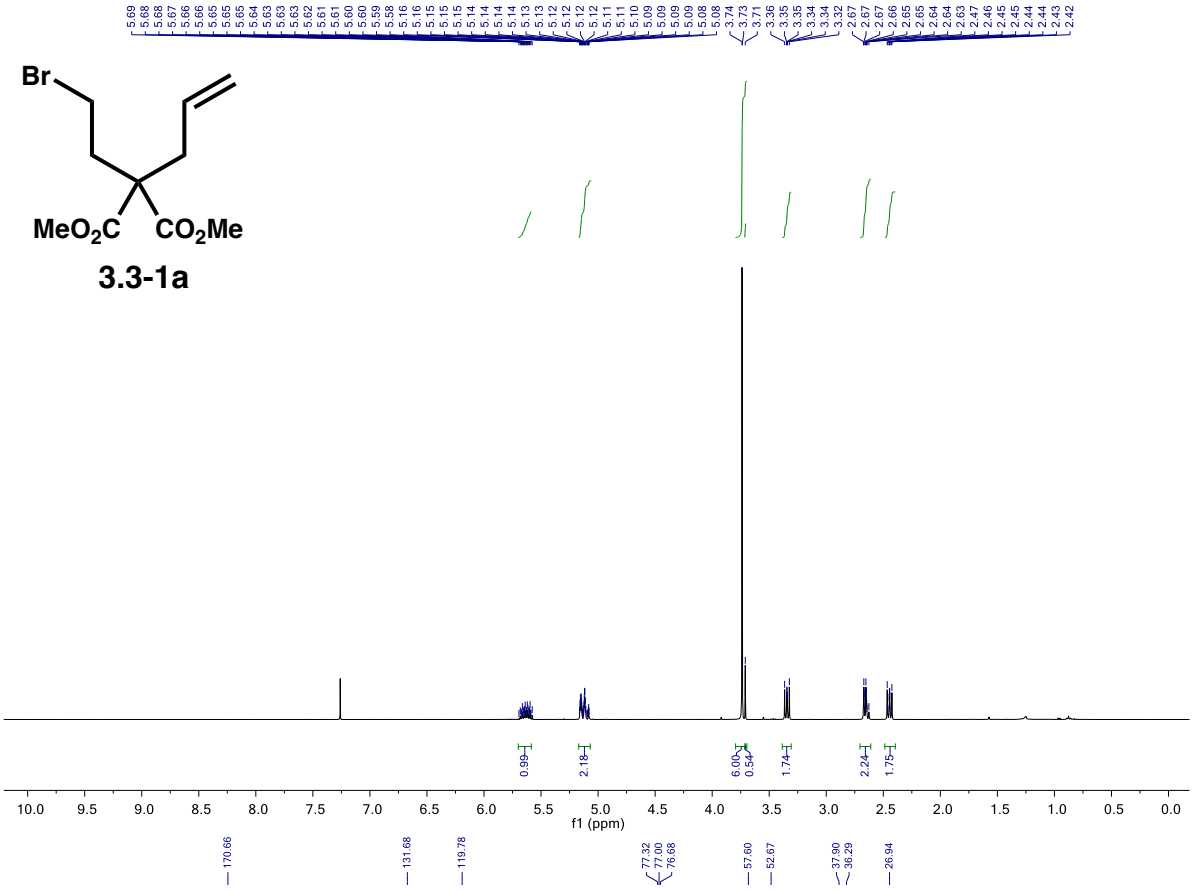

O
Ph
2.3-3ma
f1 (ppm)

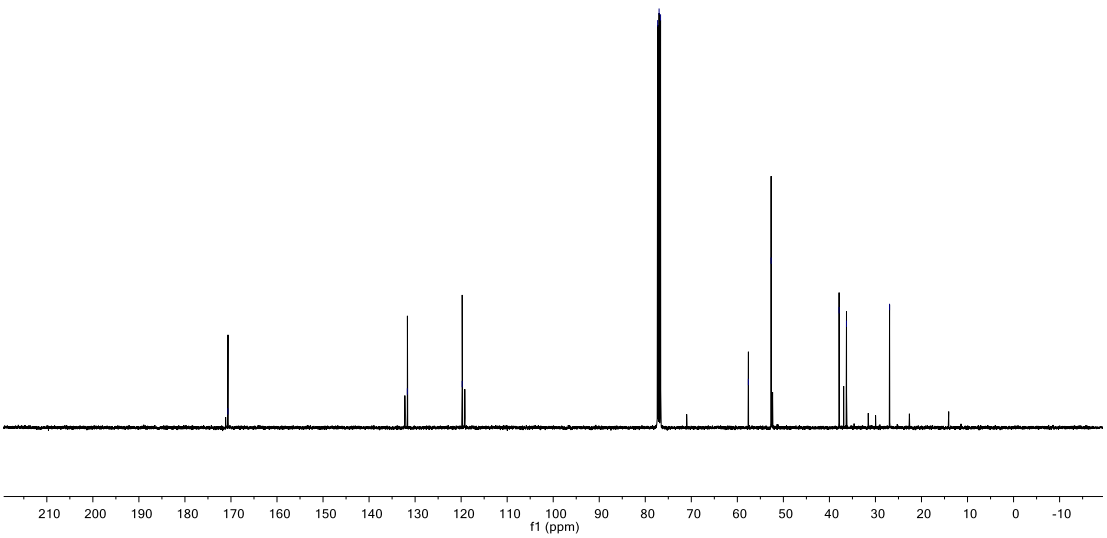

f1 (ppm)

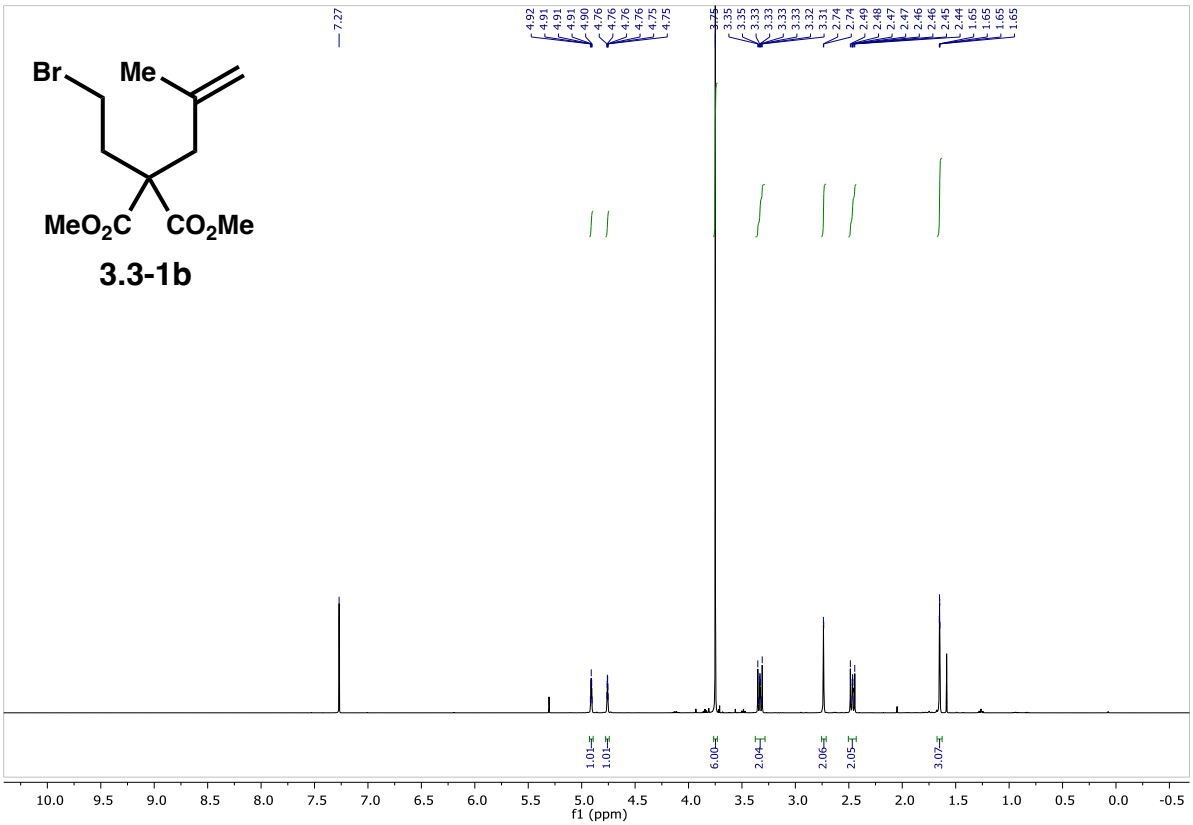

O
Ph
2.3-3na'
f1 (ppm)

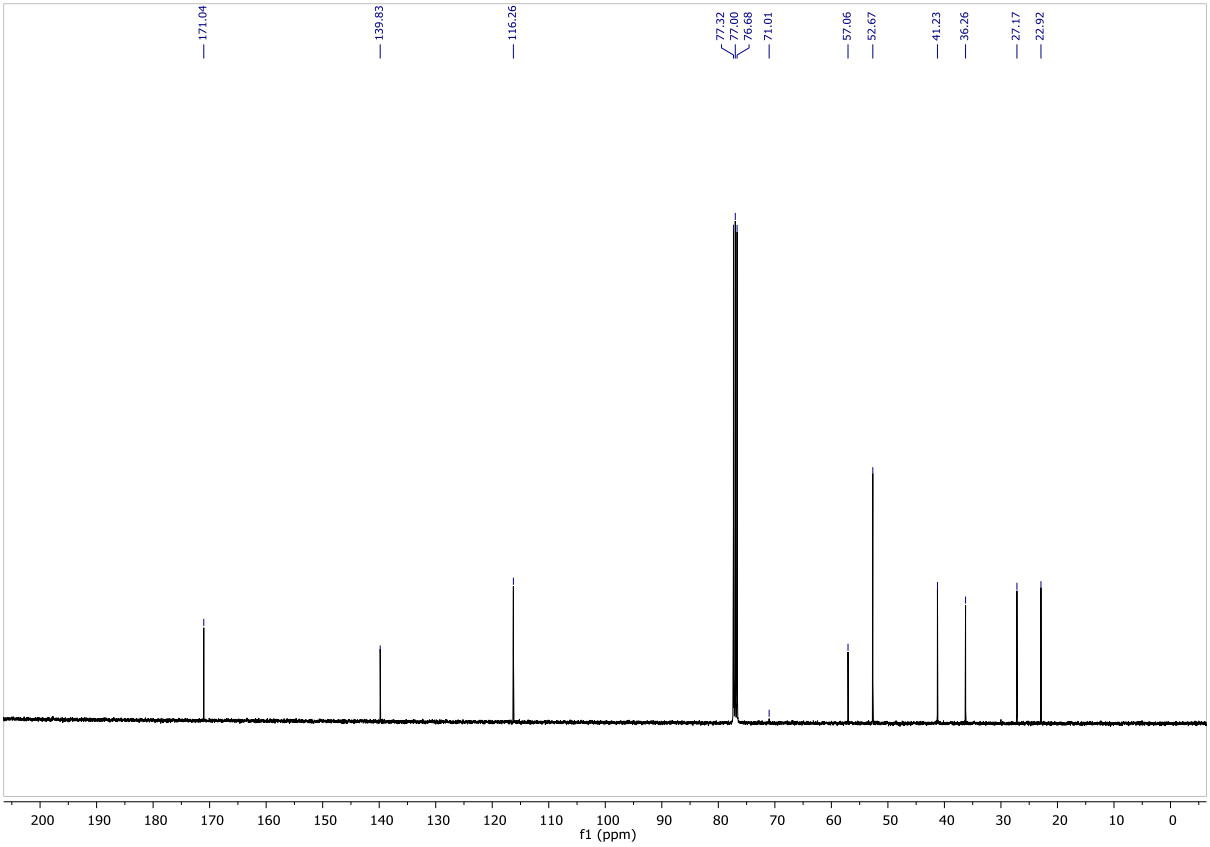

f1 (ppm)

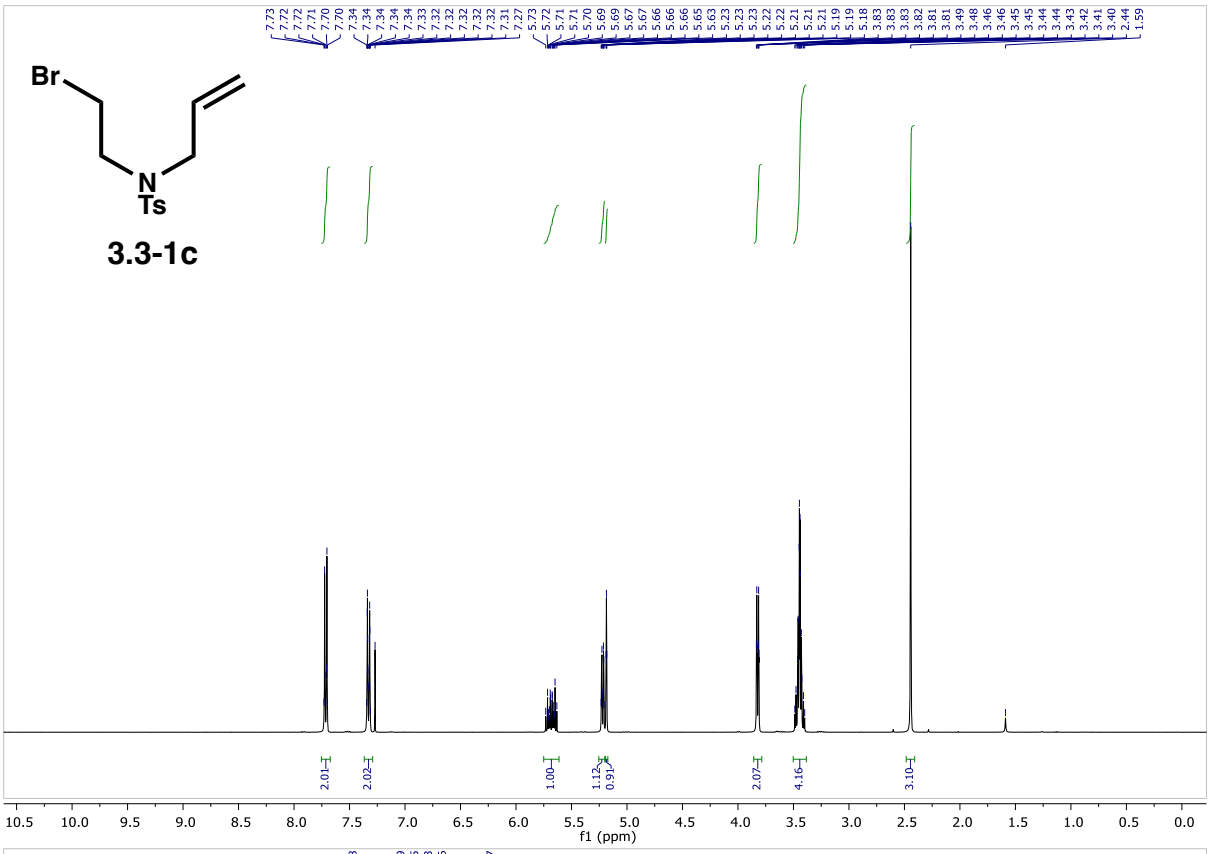
7.2- Spectral Data from Chapter 3: Formal Halogen Atom Transfer Radical Addition using Gold Photoredox Catalysis

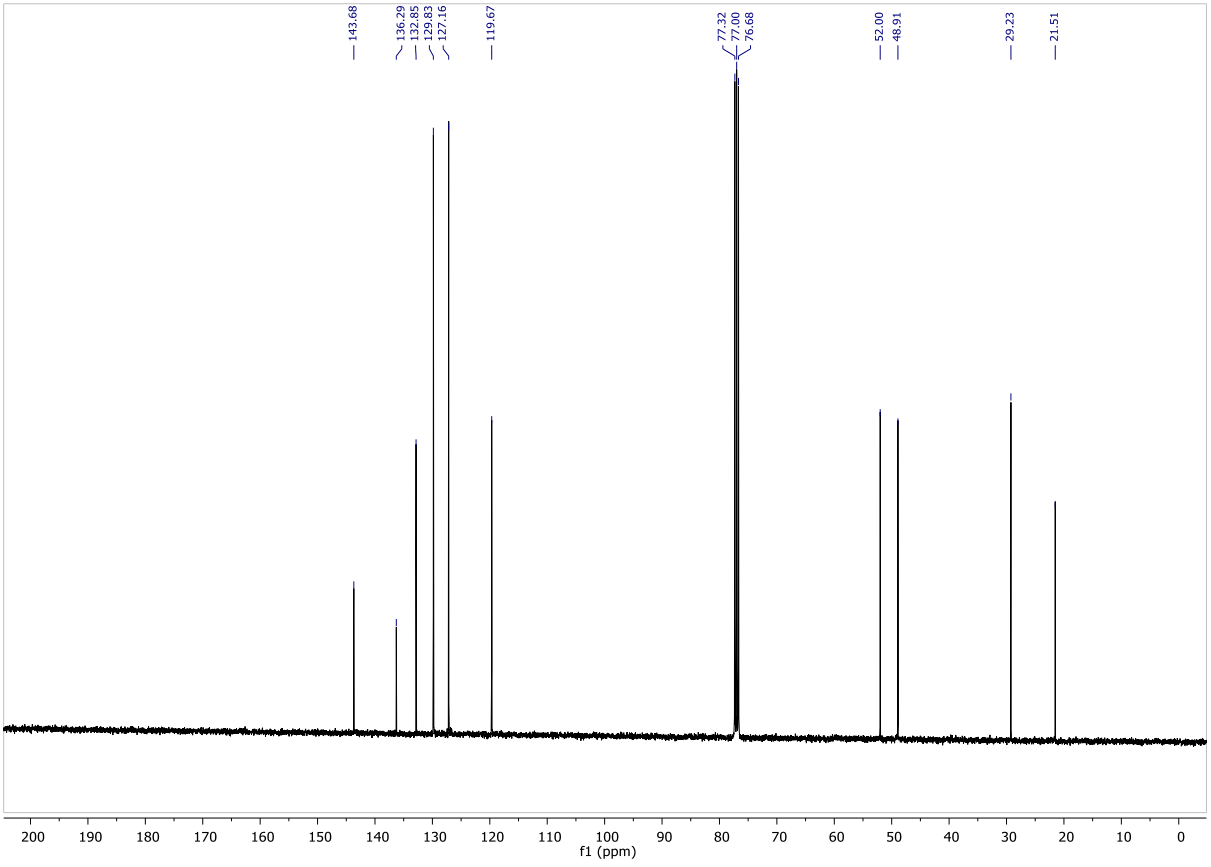


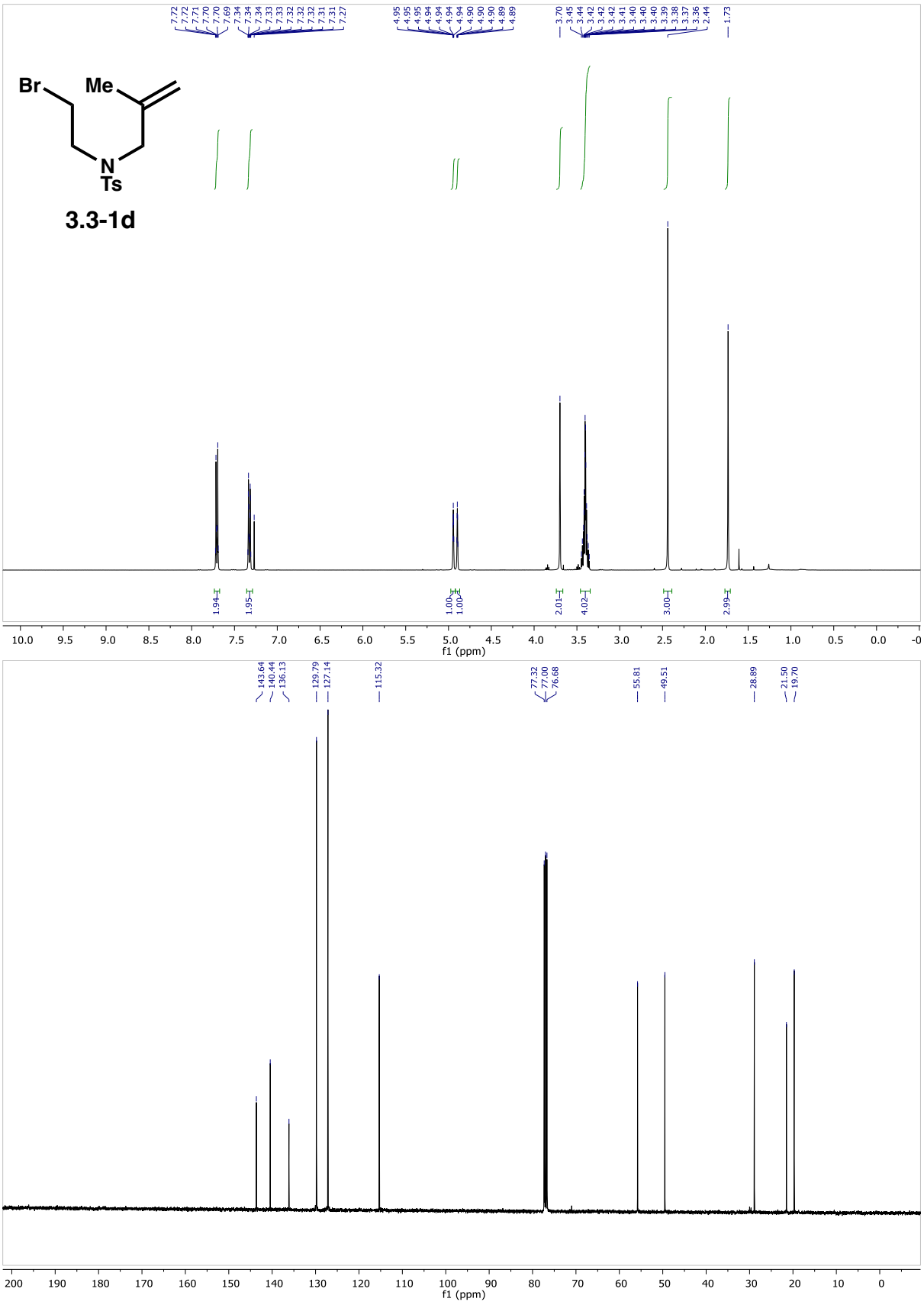


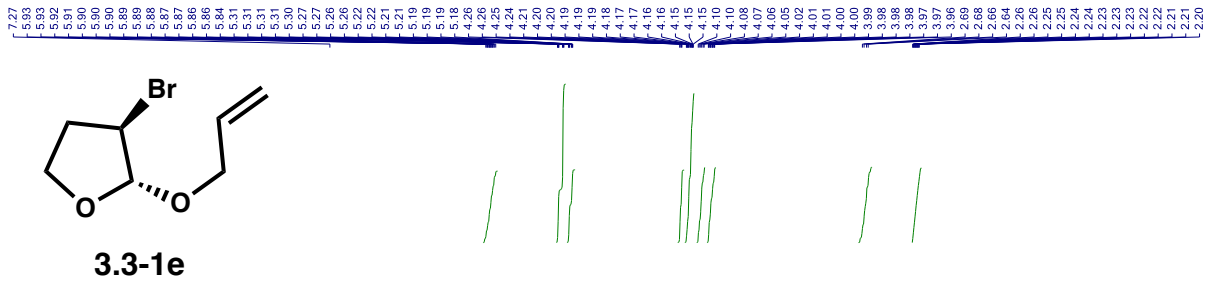

Br
Me
MeO2C
CO2Me
3.3-1b
f1 (ppm)


f1 (ppm)


Br
N
Ts
3.3-1c
f1 (ppm)

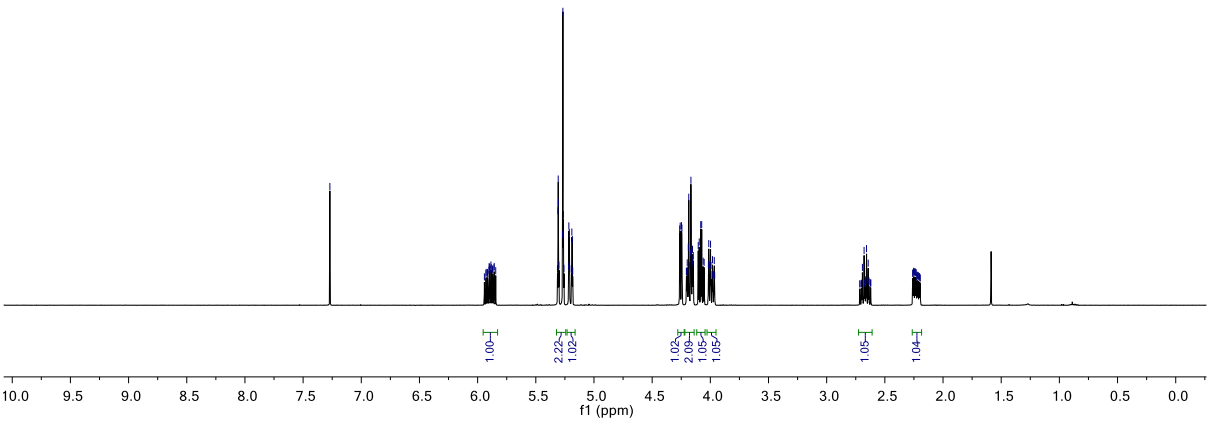

143.68
136.29
132.85
129.83
127.16
119.67
77.32
77.00
76.68
52.00
48.91
29.23
21.51
f1 (ppm)

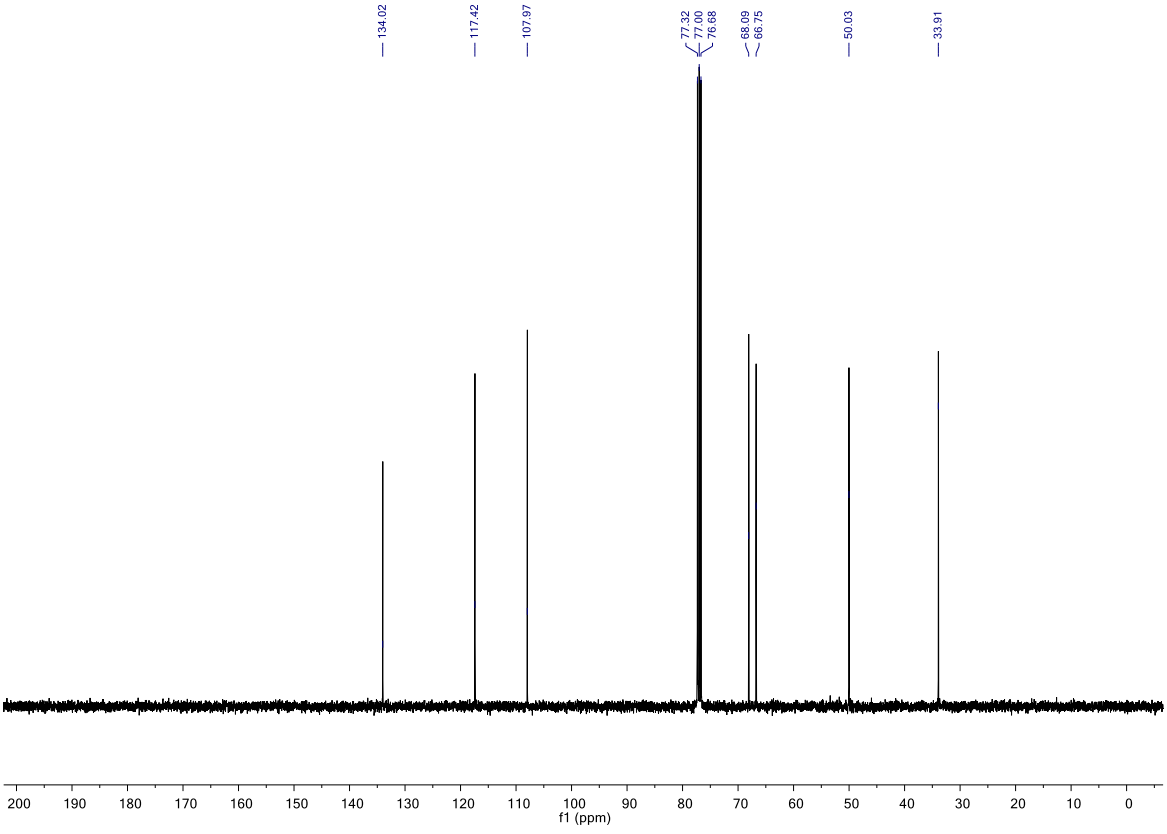

Br
Me
N
Ts
3.3-1d
f1 (ppm)
f1 (ppm)

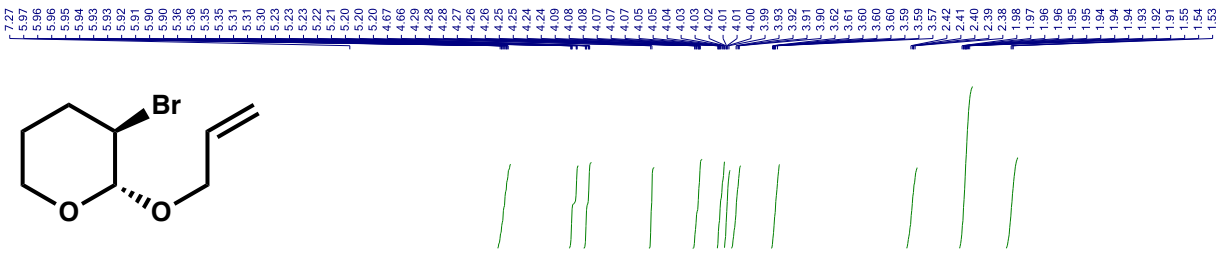


Br
O
O

3.3-1e

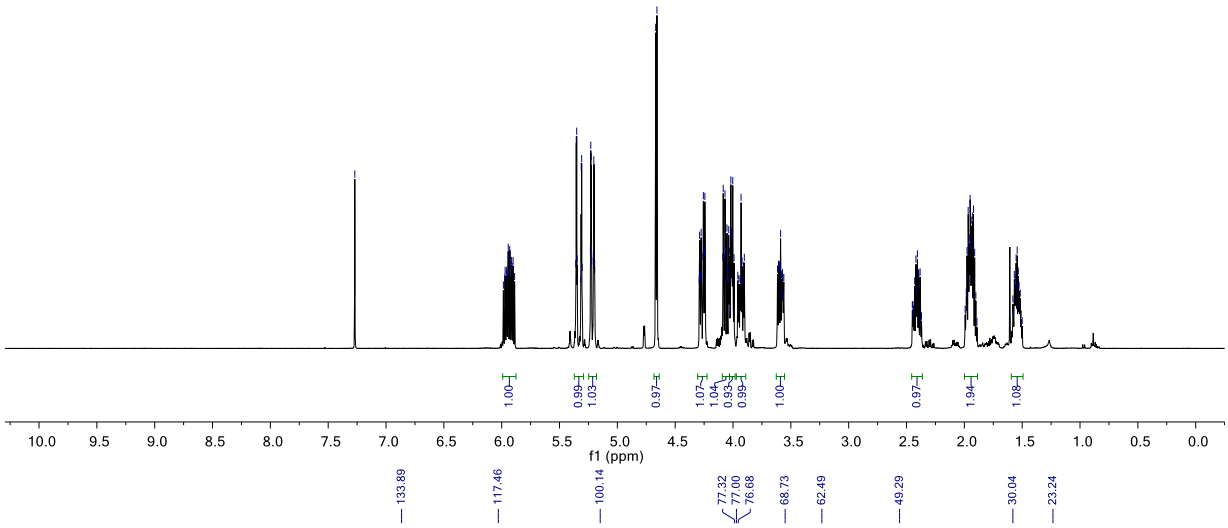

1.00
2.22
1.02
1.02
2.09
1.05
1.05
1.05
1.04
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

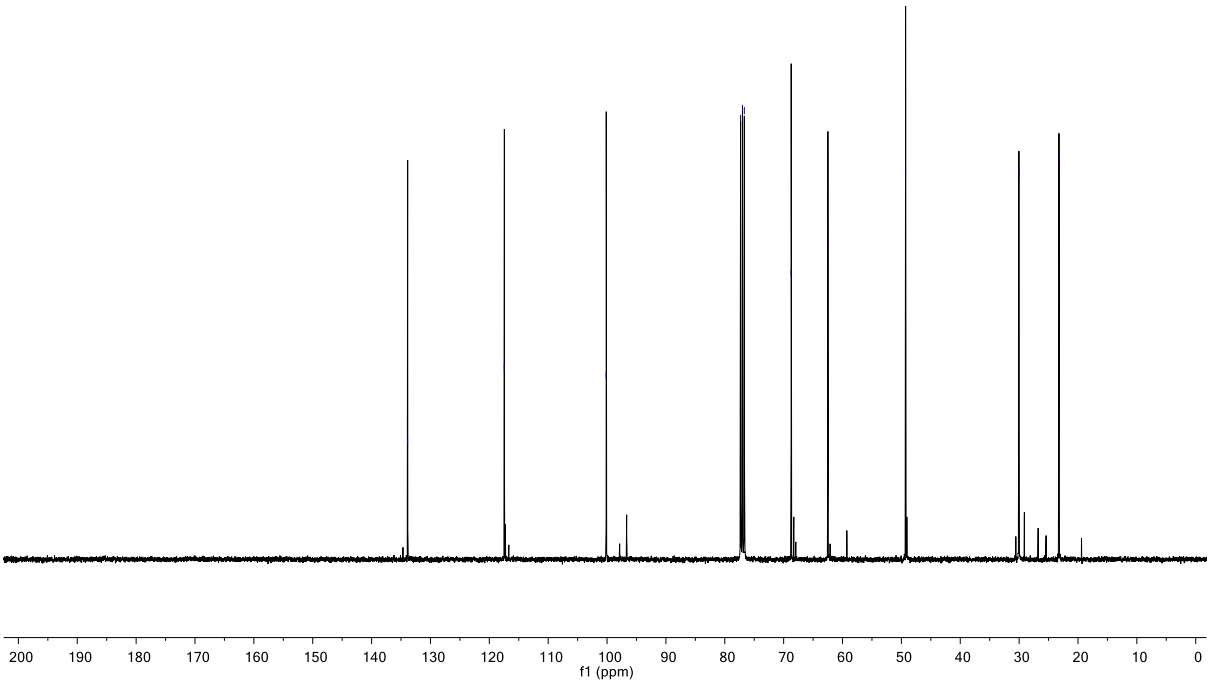

134.02
117.42
107.97
77.32
77.00
76.68
68.09
66.75
50.03
33.91
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

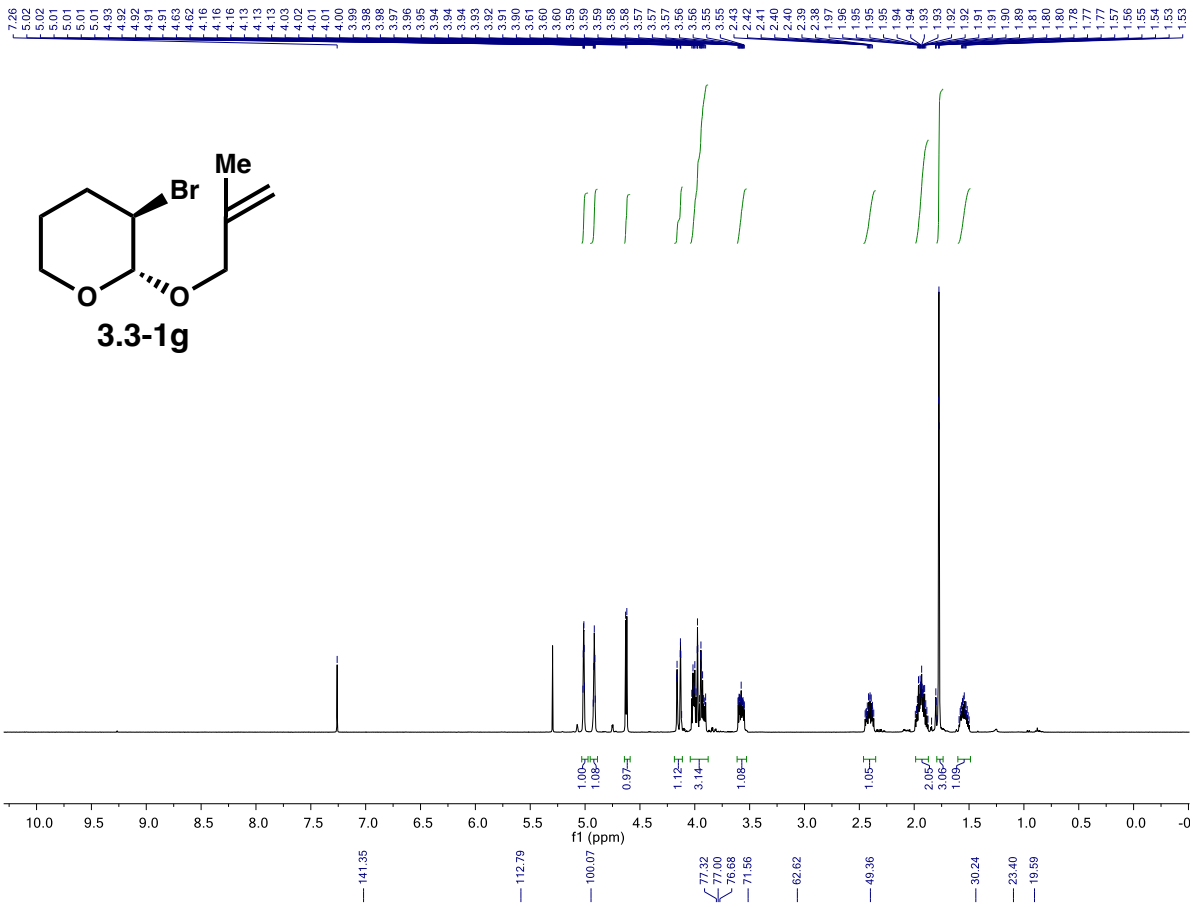


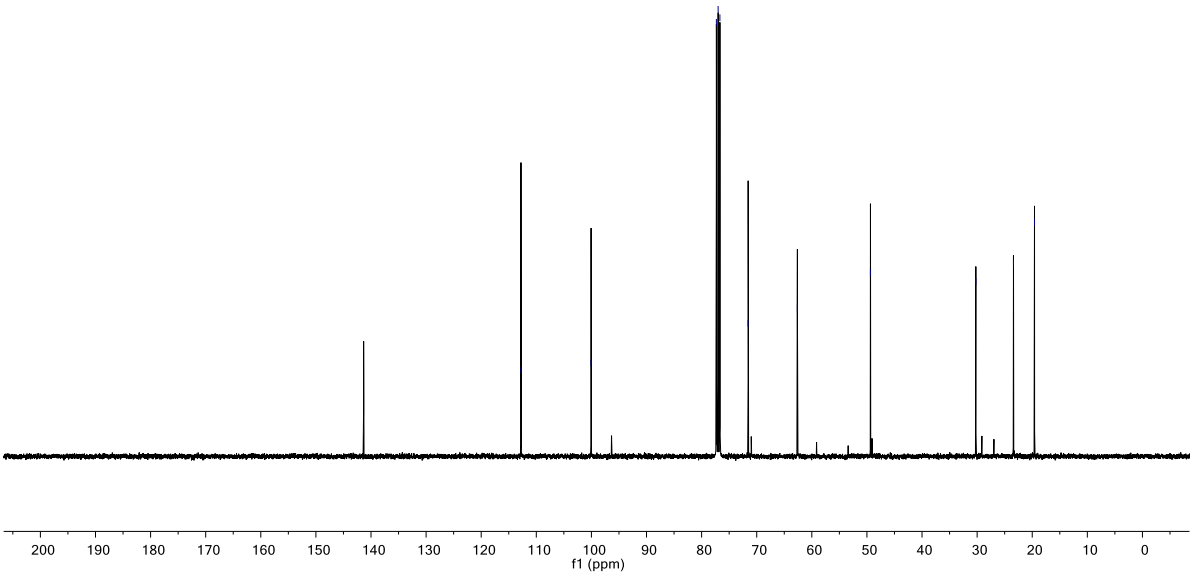
Br
O
O

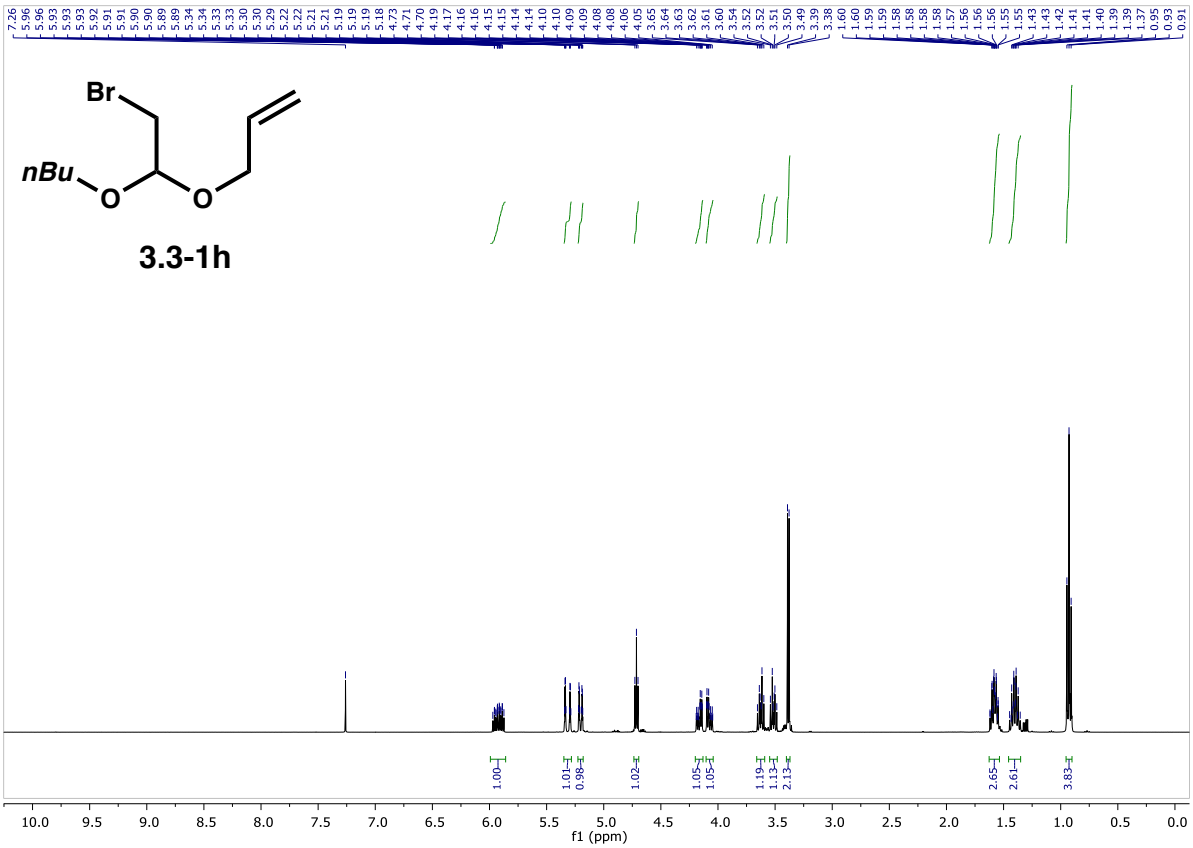
3.3-1f


1.00
0.99
1.03
0.97
1.07
1.04
0.93
0.99
1.00
0.97
1.94
1.08
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

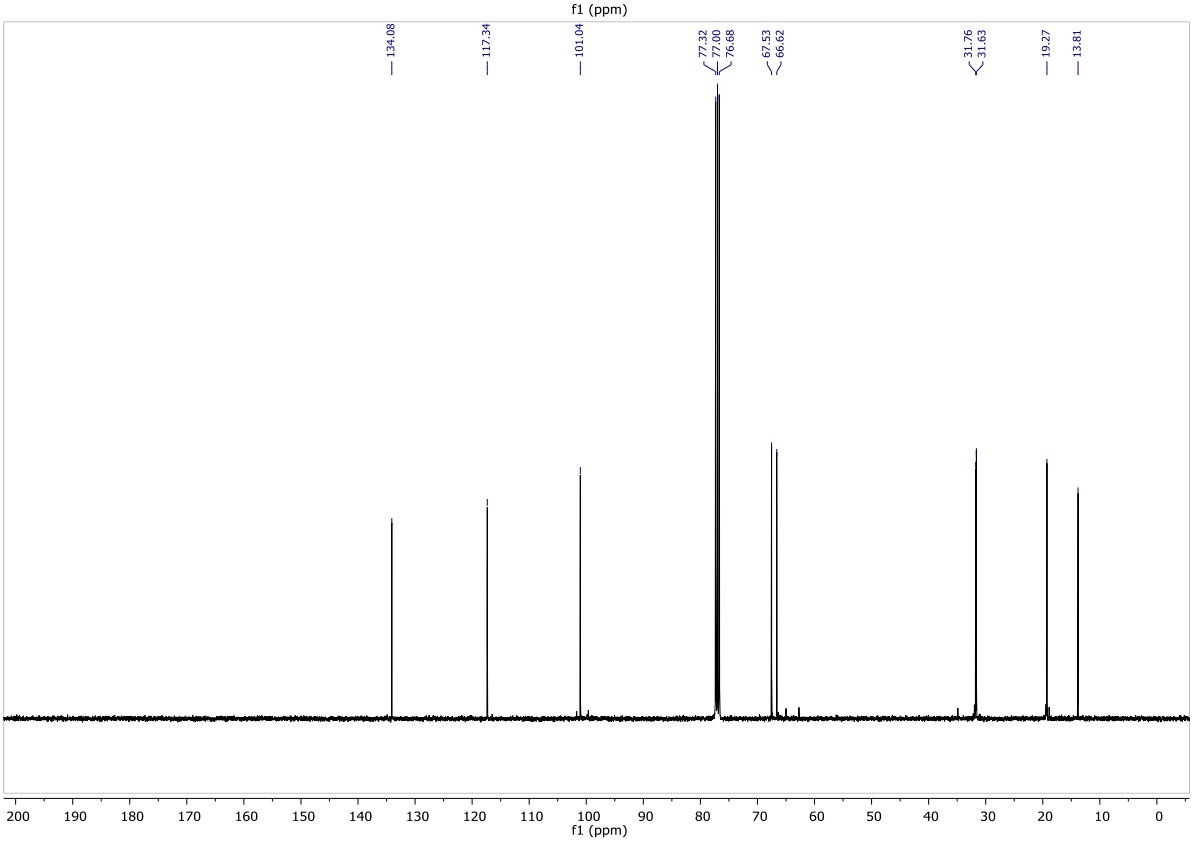

133.89
117.46
100.14
77.32
77.00
76.68
68.73
62.49
49.29
30.04
23.24
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

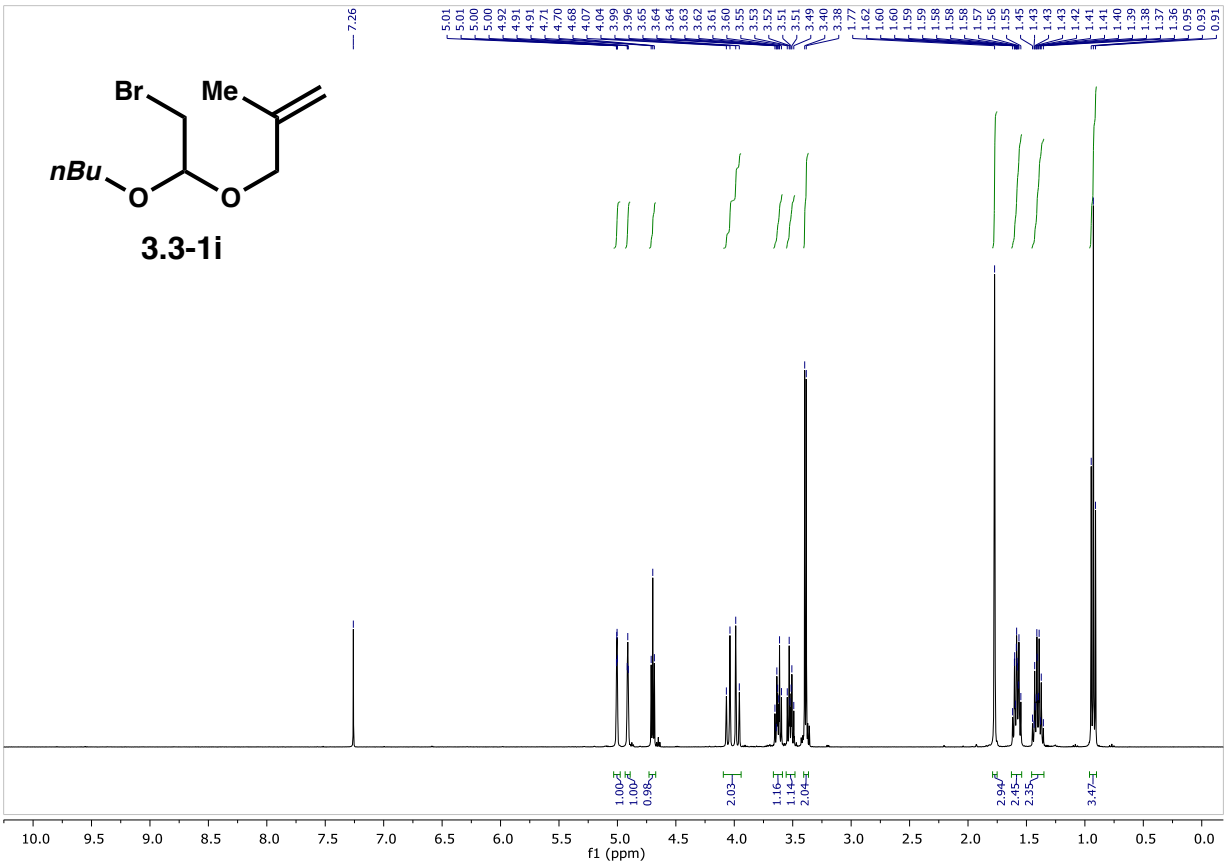

Me
Br
O
O
3.3-1g
f1 (ppm)

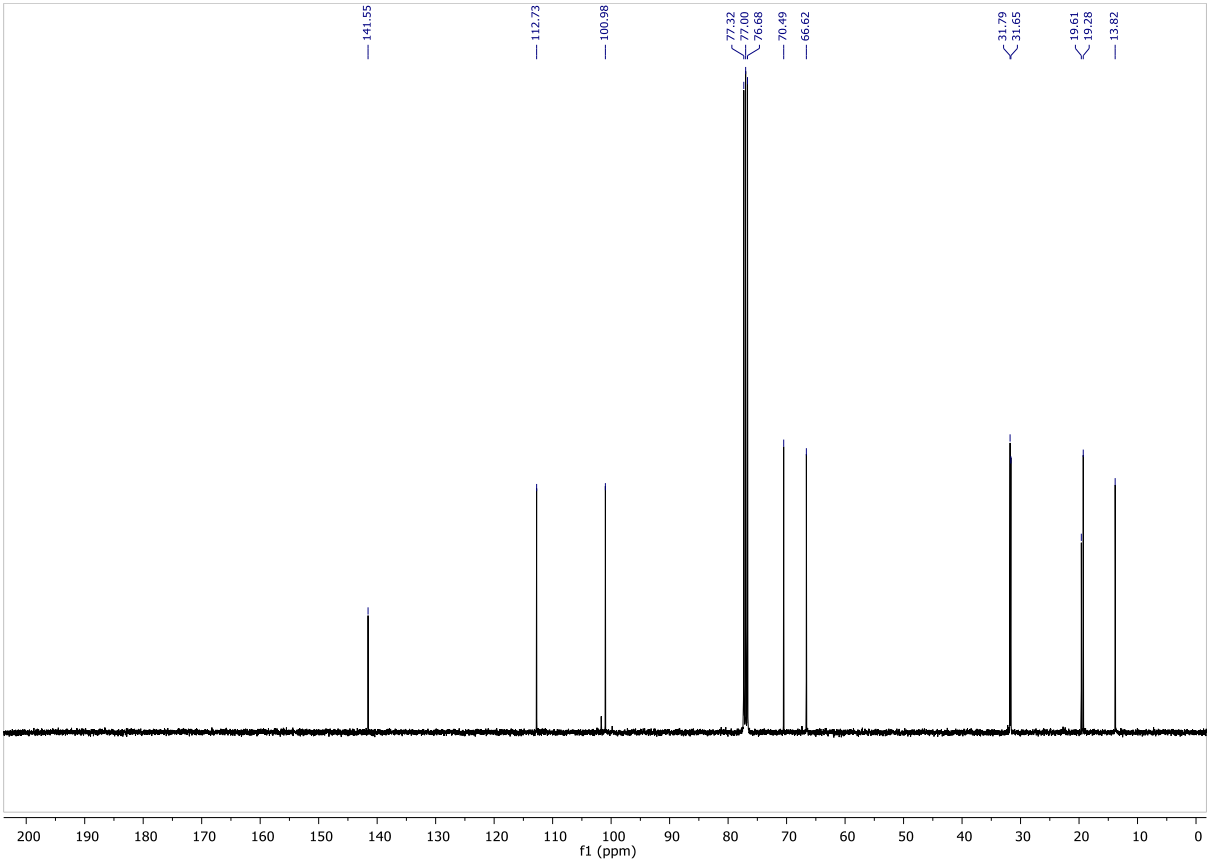

f1 (ppm)

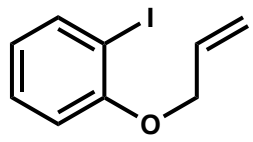


3.3-1h

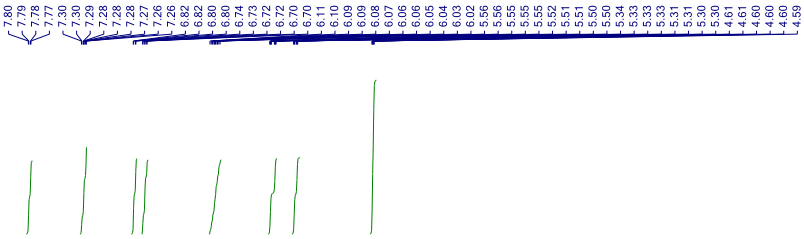


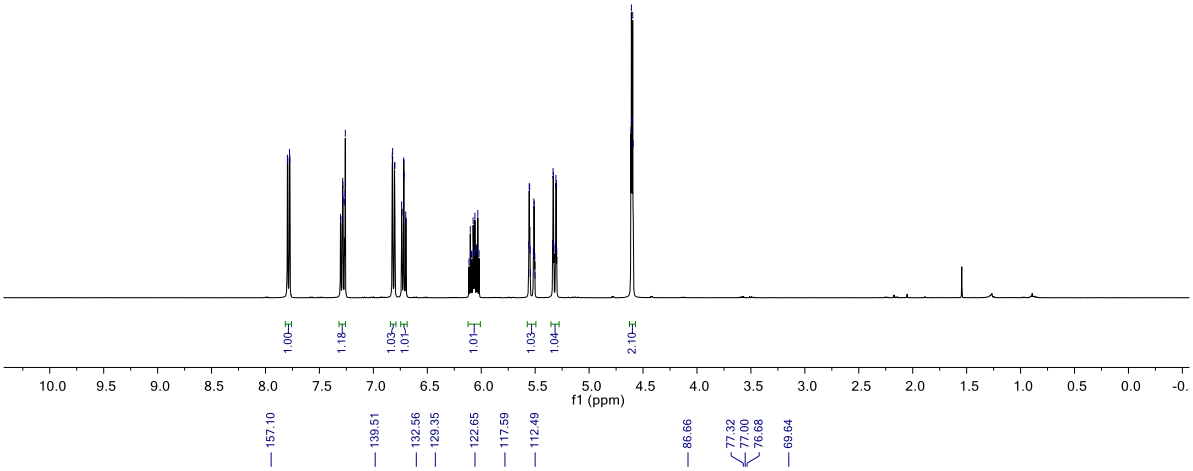

Br
Me
nBu
O
O
3.3-1i
f1 (ppm)

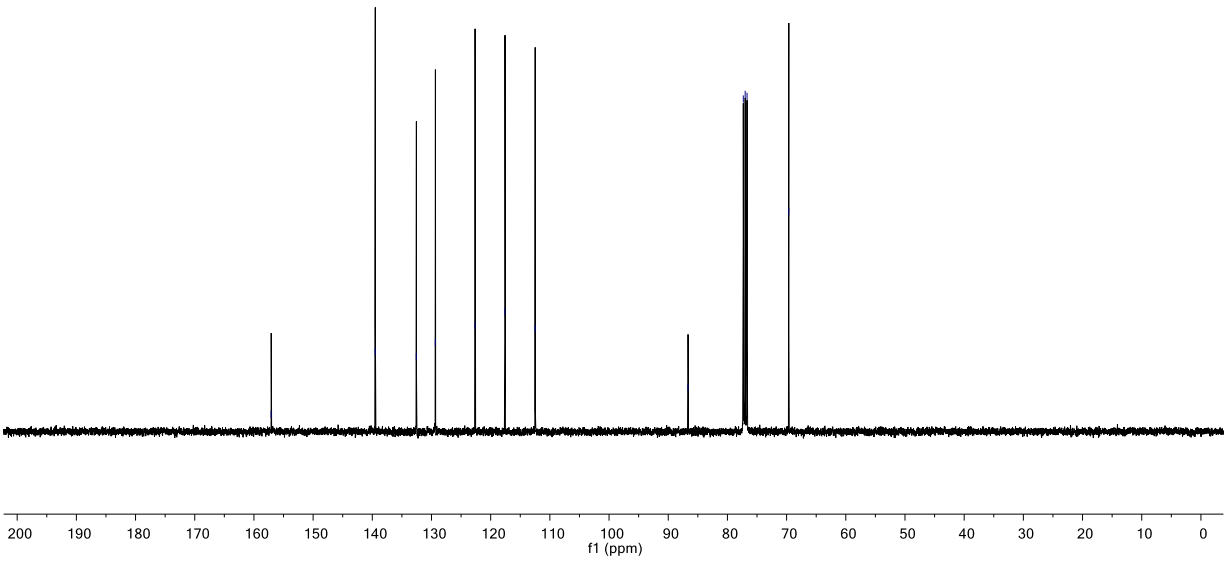

f1 (ppm)

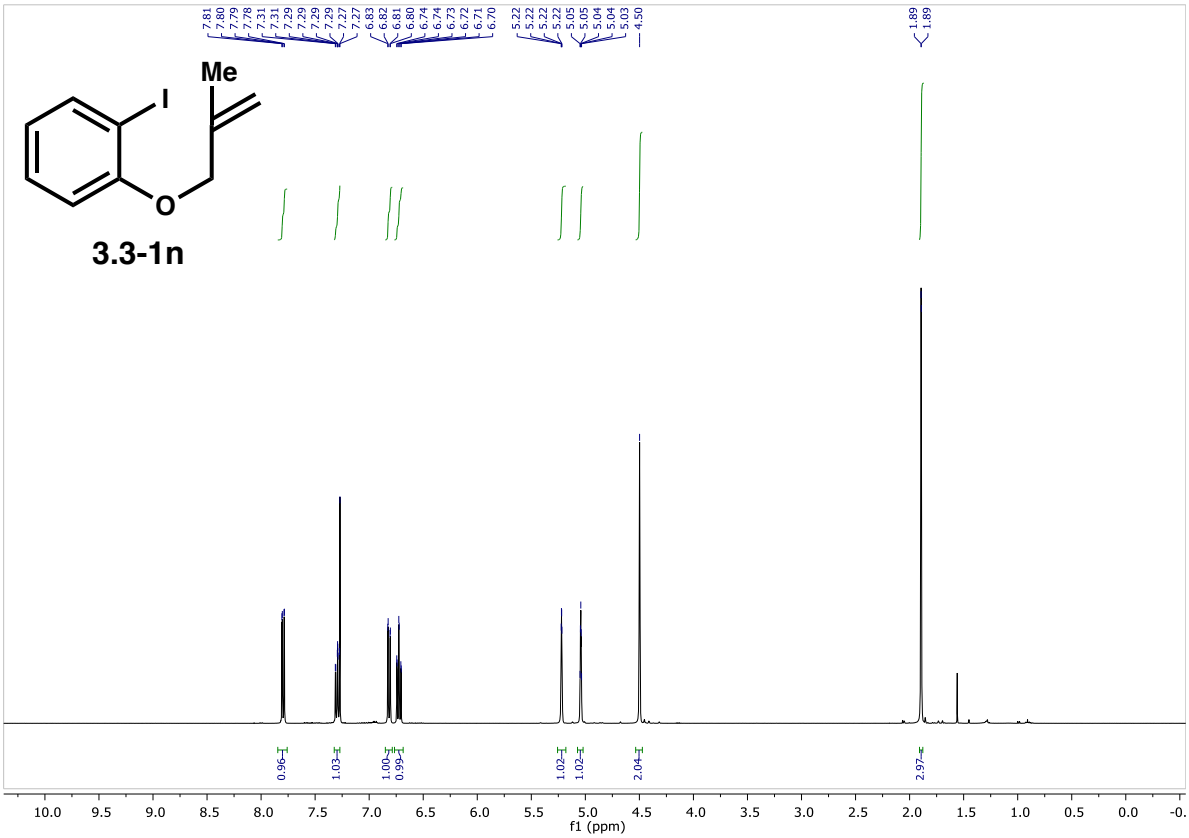


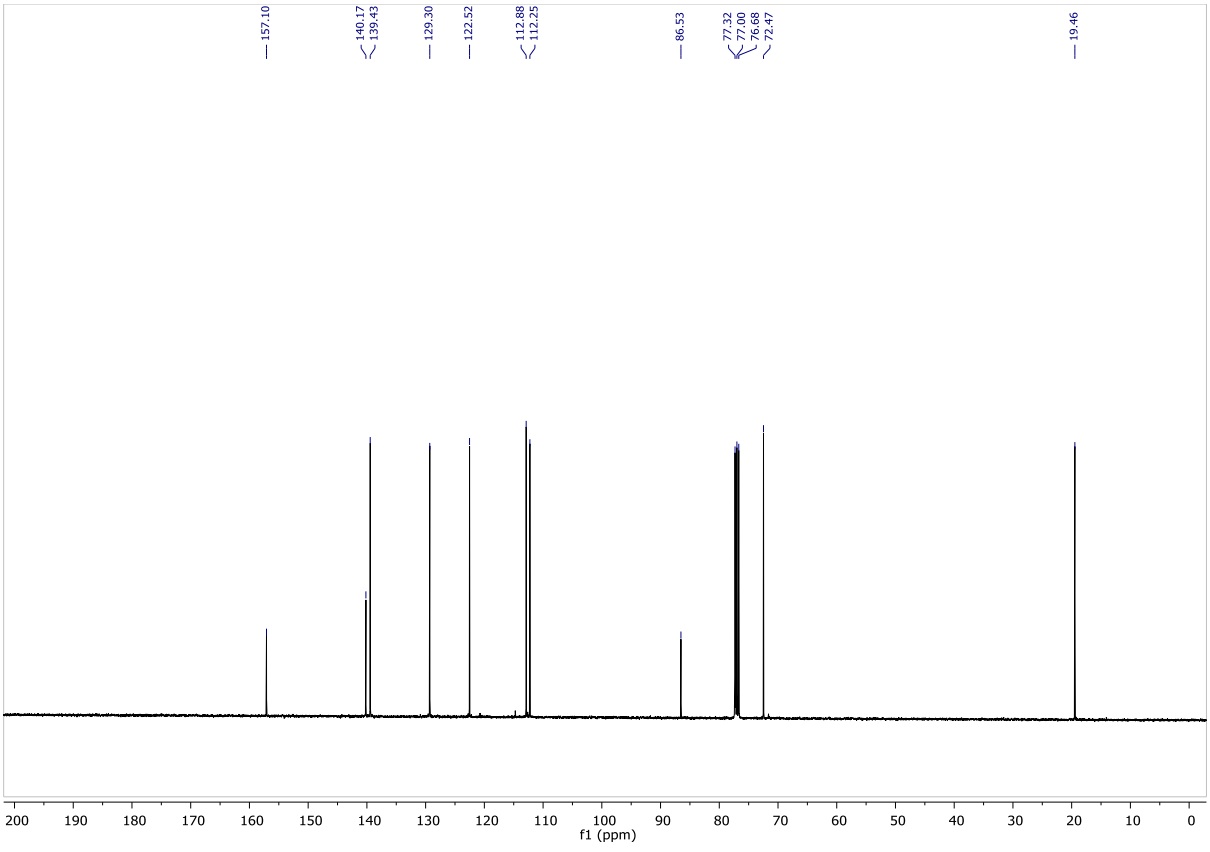
3.3-1m

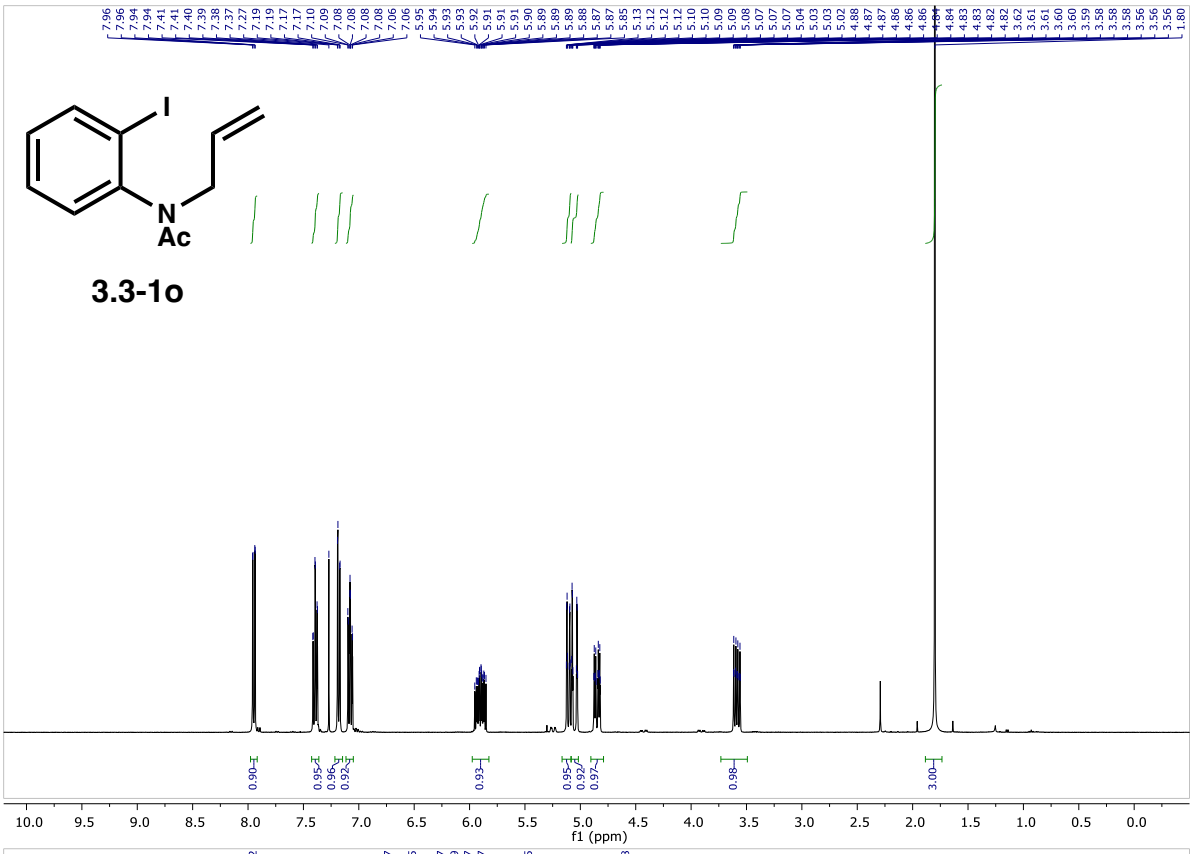




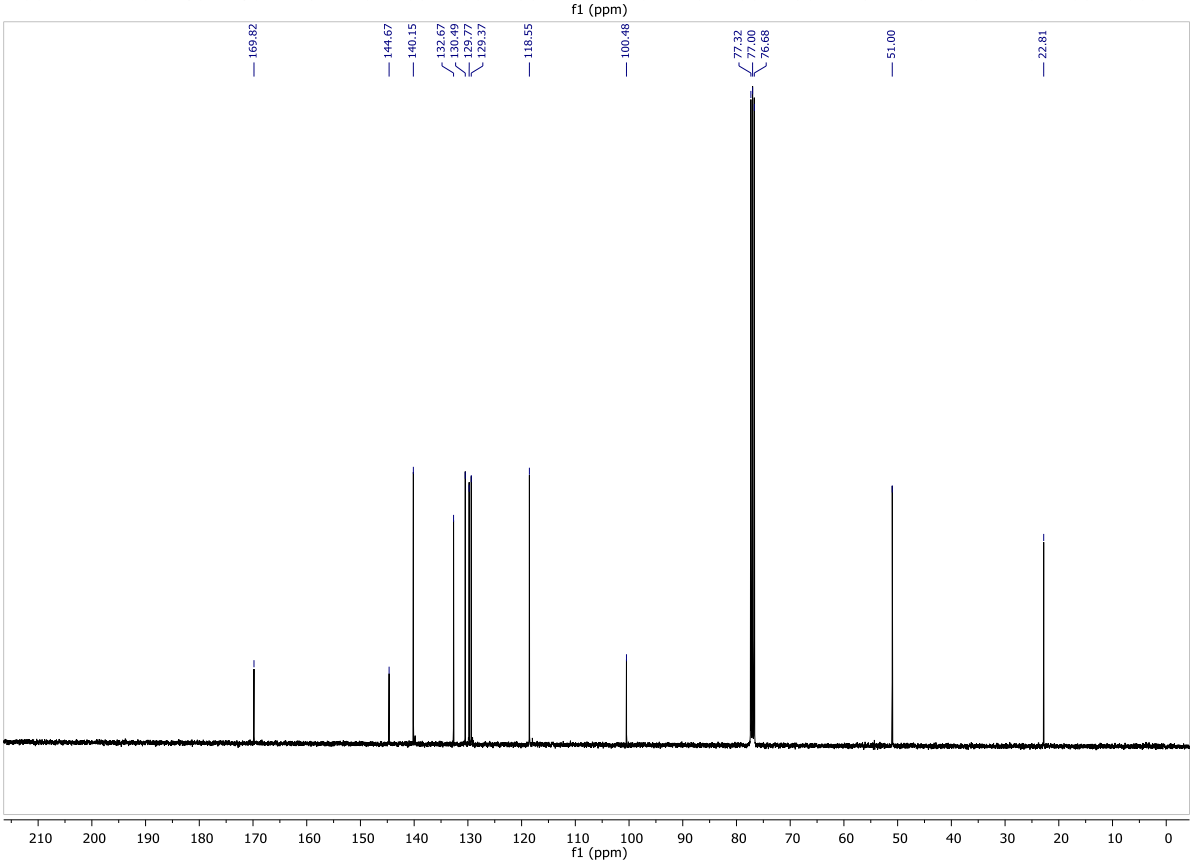


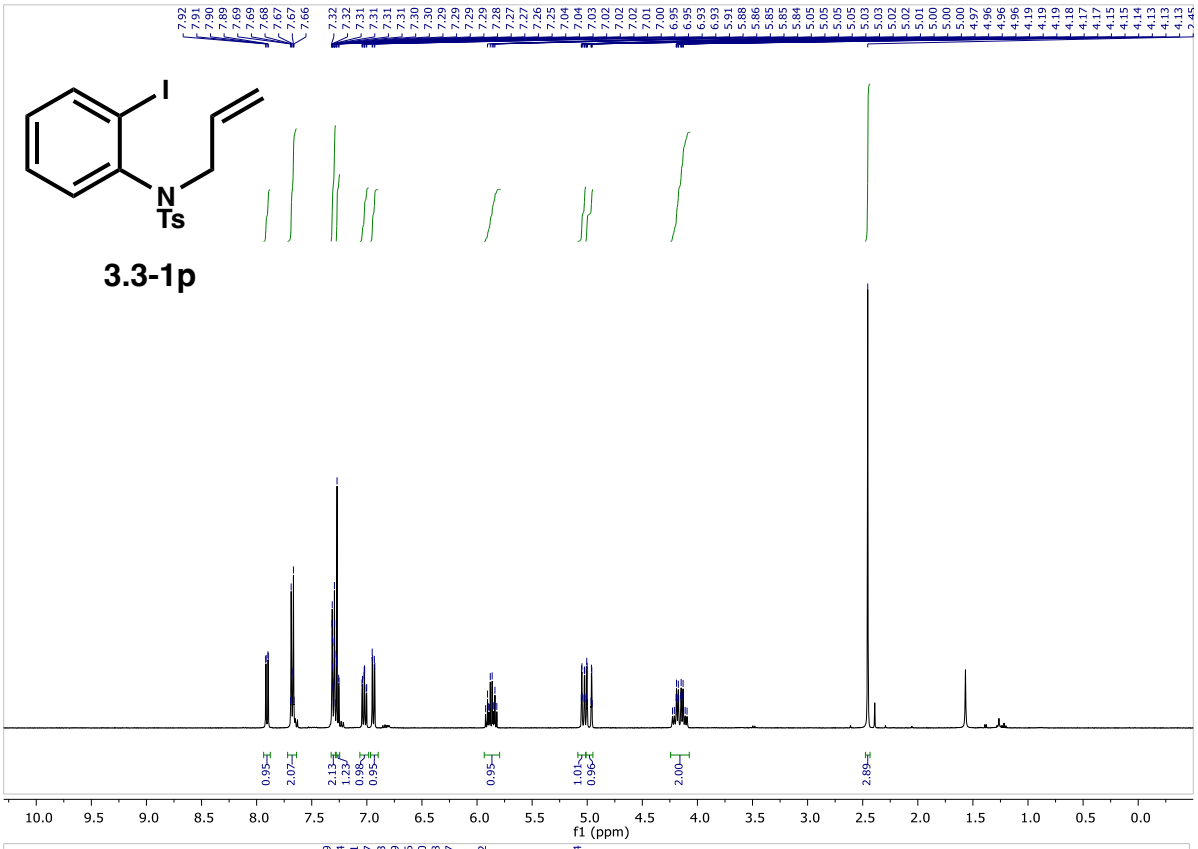

Me
I
O
3.3-1n
7.81
7.80
7.79
7.78
7.31
7.31
7.29
7.29
7.29
7.29
7.27
7.27
6.83
6.82
6.81
6.80
6.74
6.74
6.73
6.72
6.71
6.70
5.22
5.22
5.22
5.05
5.05
5.04
5.04
5.03
4.50
1.89
1.89
0.96
1.03
1.00
0.99
1.02
1.02
2.04
2.97
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.
f1 (ppm)

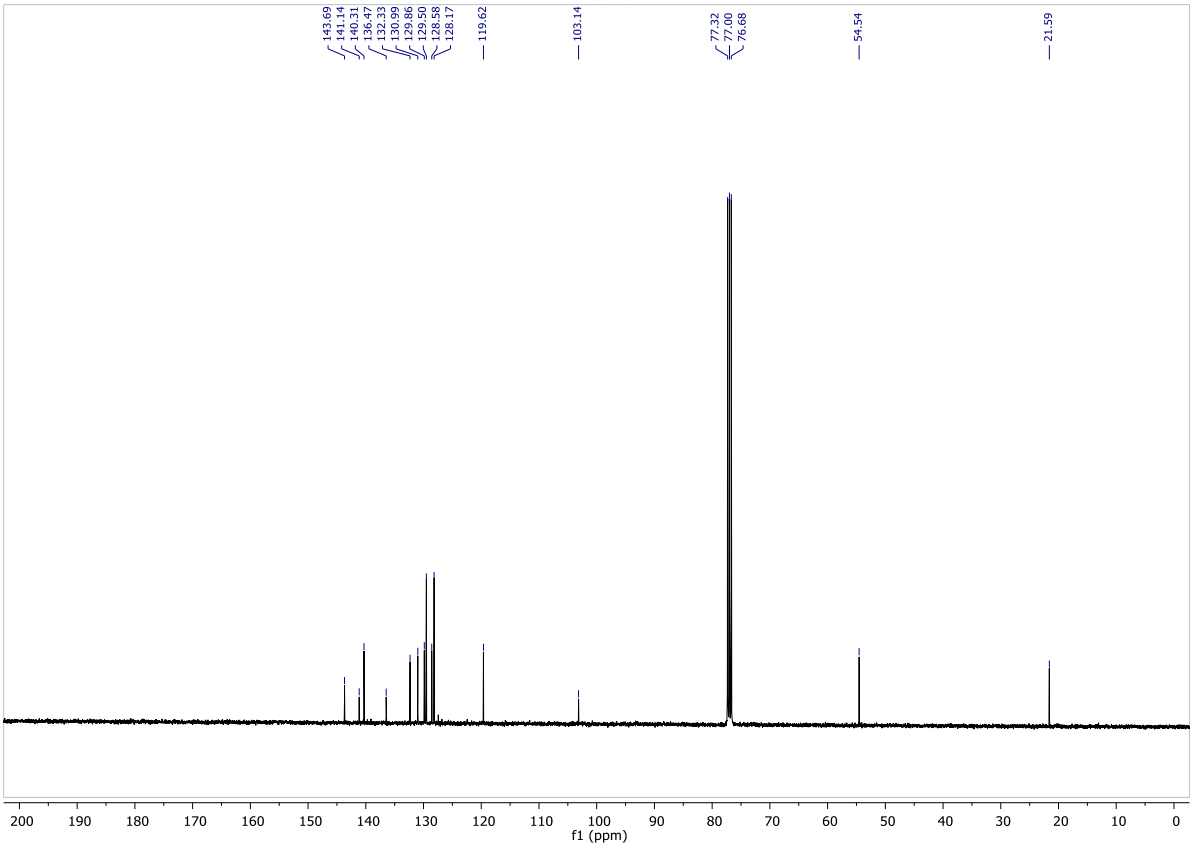

157.10
140.17
139.43
129.30
122.52
112.88
112.25
86.53
77.32
77.00
76.68
72.47
19.46
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

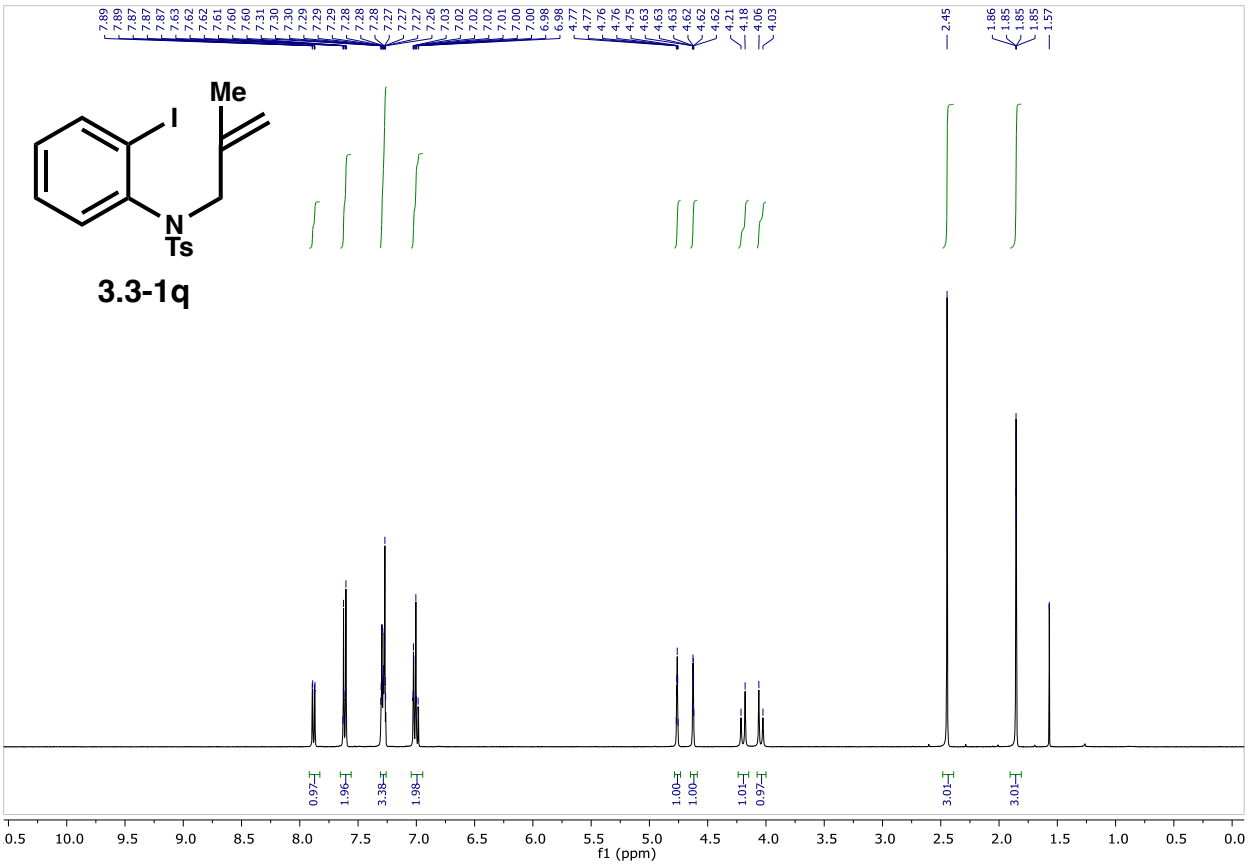


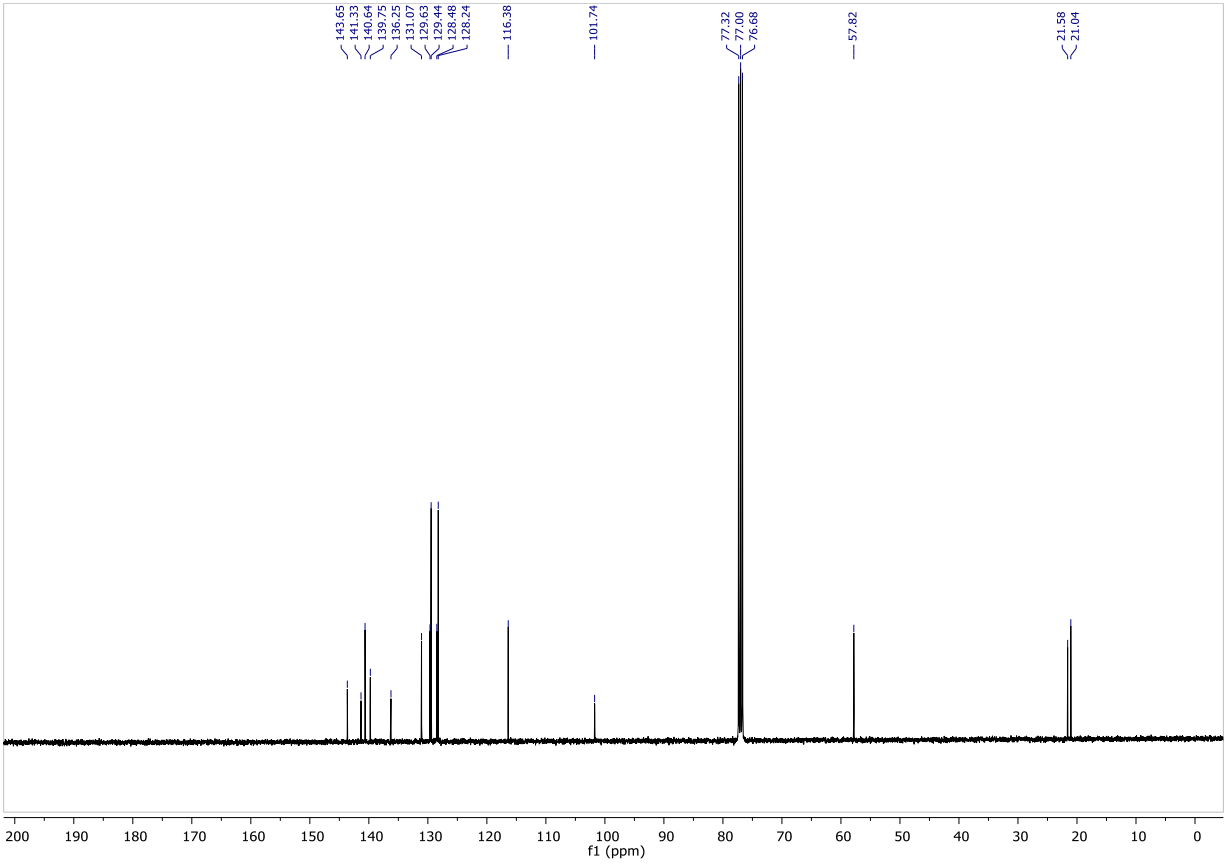
3.3-1o

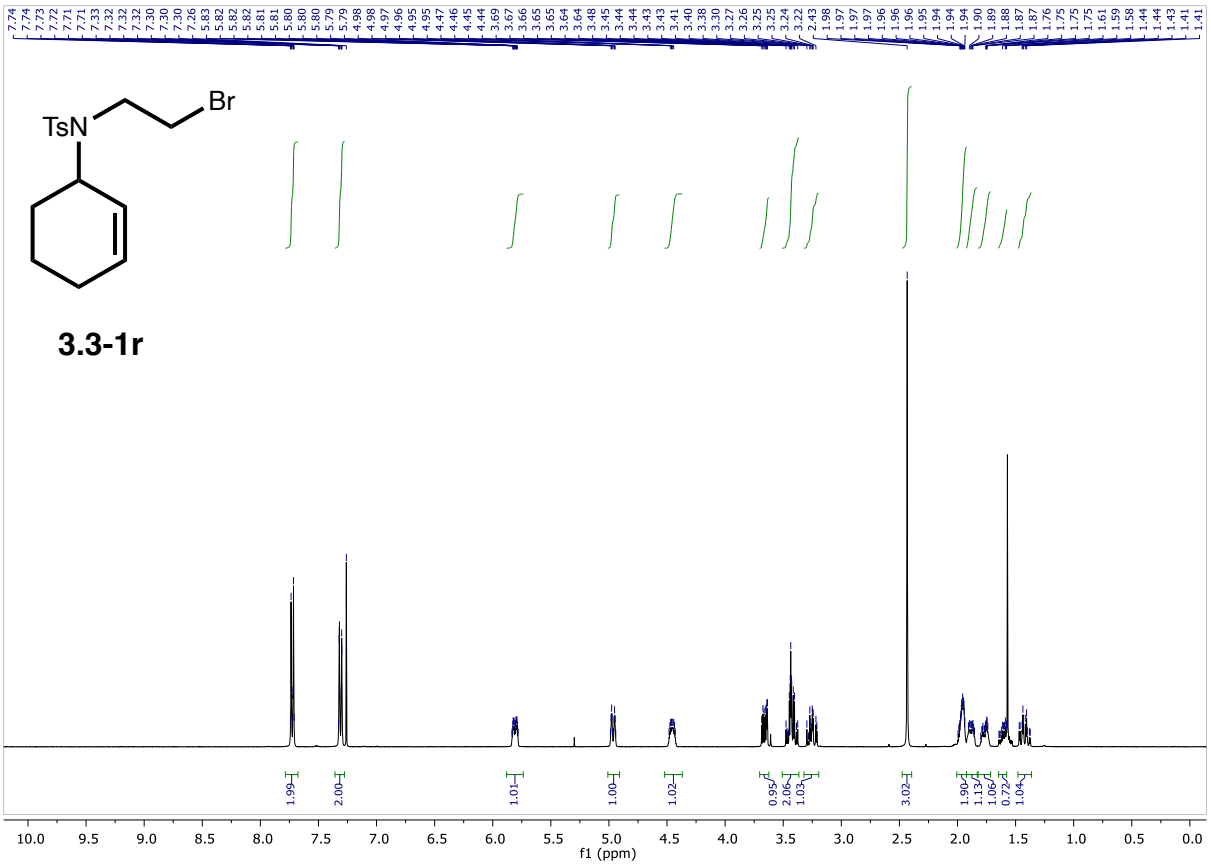


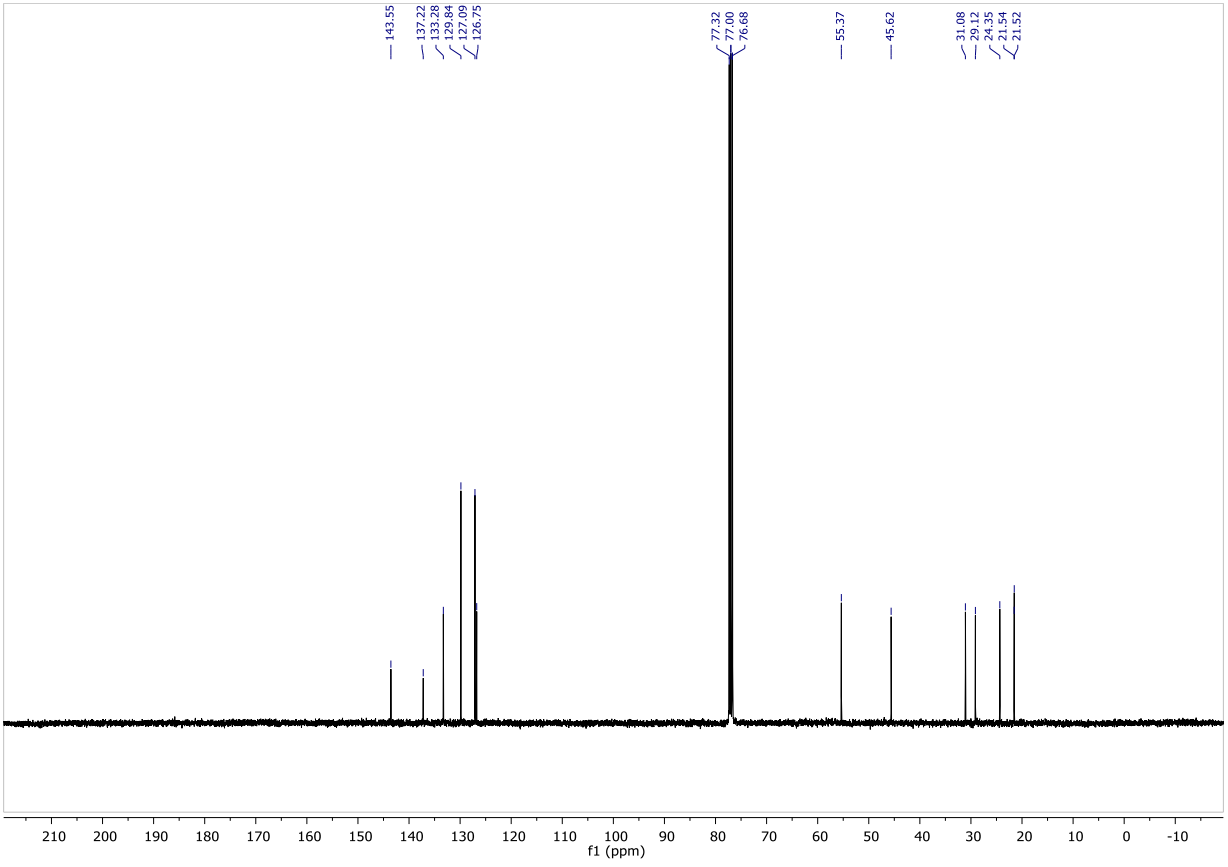

I
N
Ts
3.3-1p
f1 (ppm)

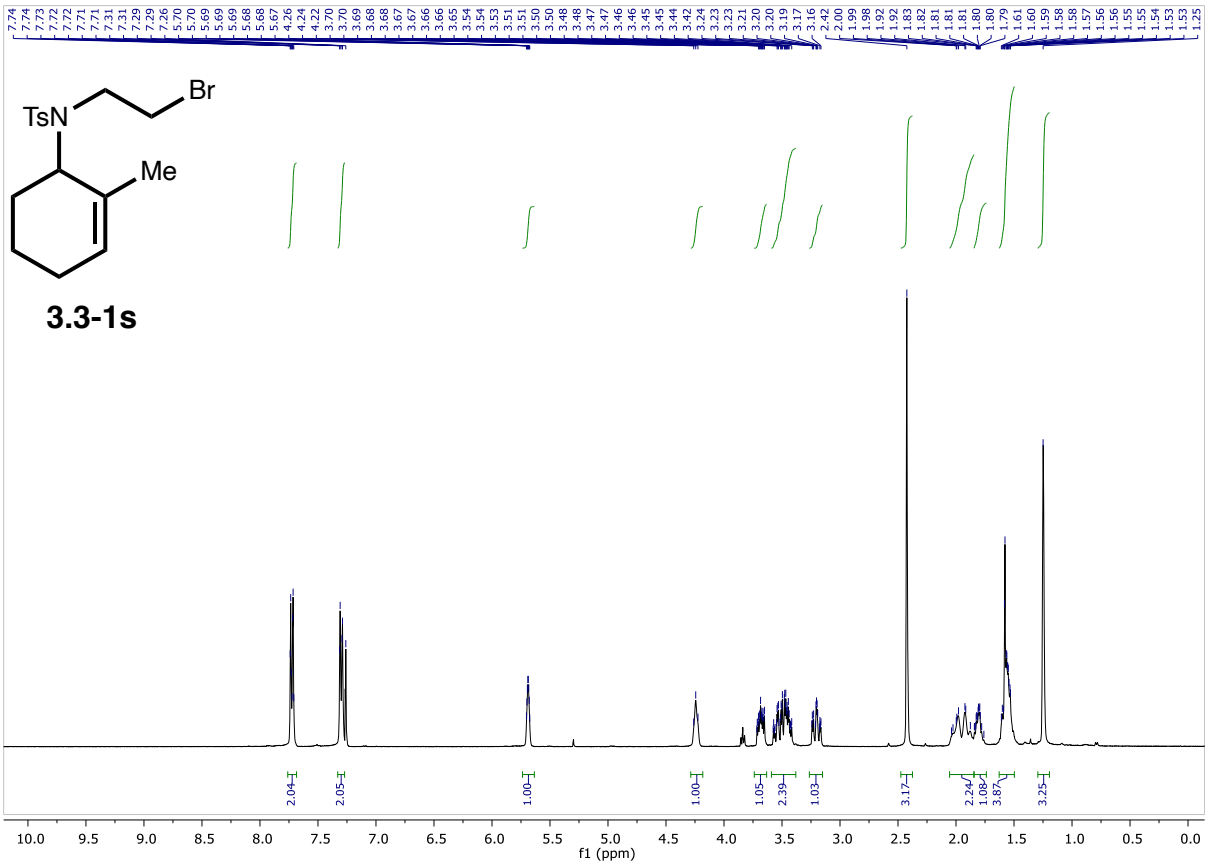

f1 (ppm)

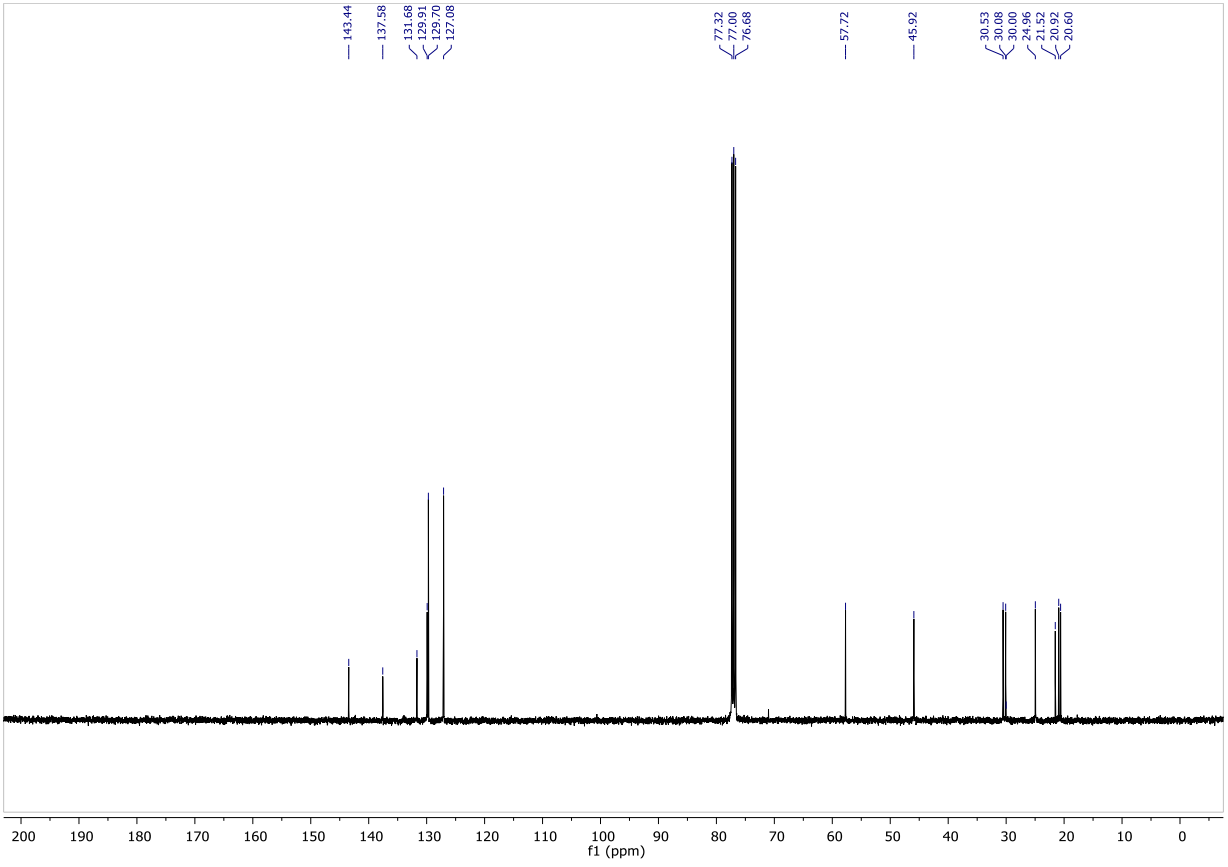

Me
I
N
Ts
3.3-1q
f1 (ppm)

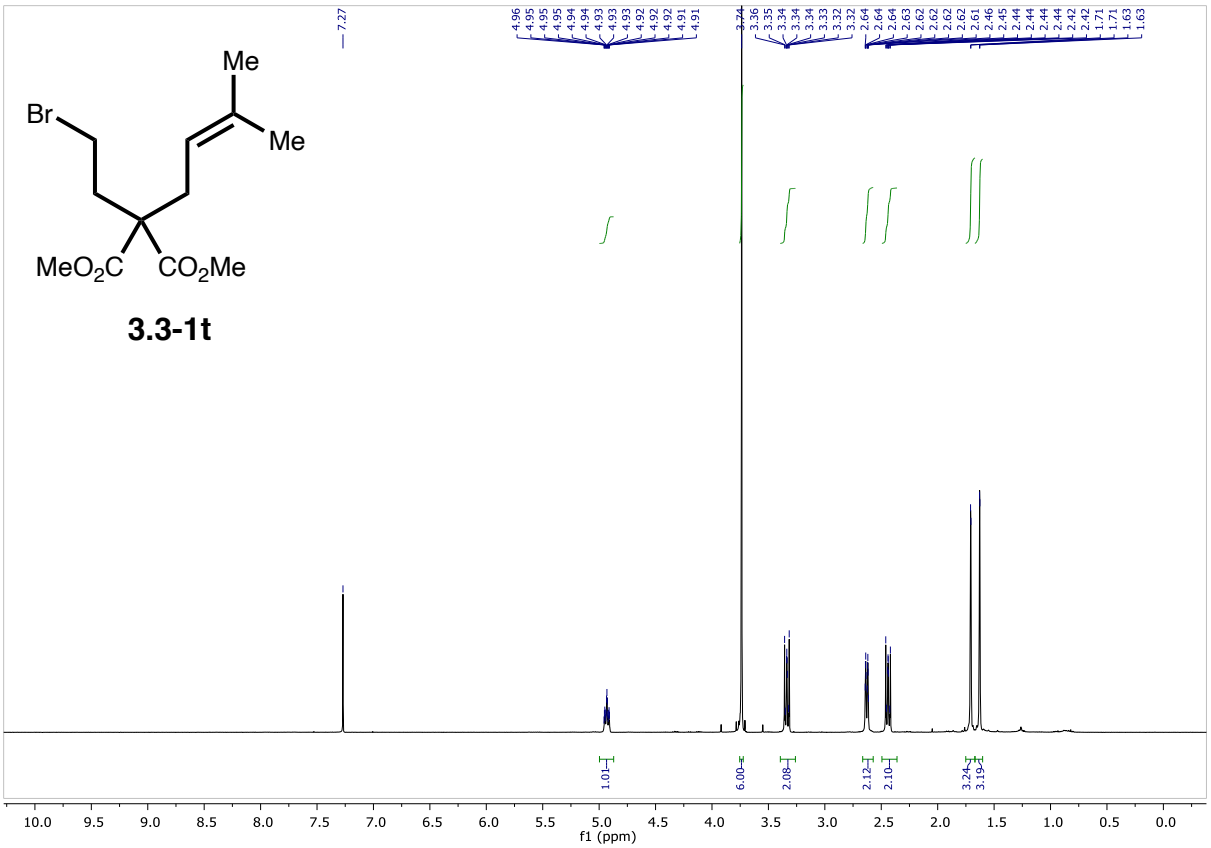

f1 (ppm)

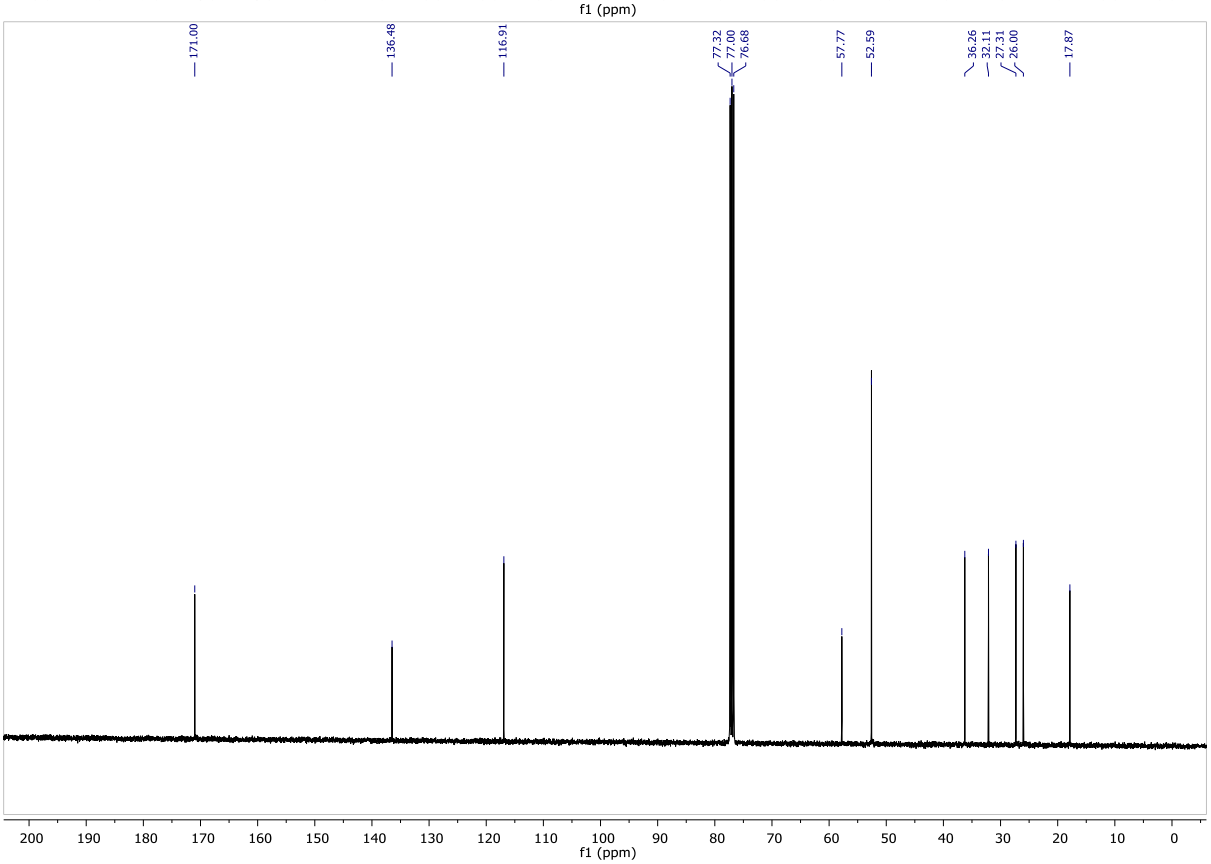

TsN
Br
3.3-1r
f1 (ppm)

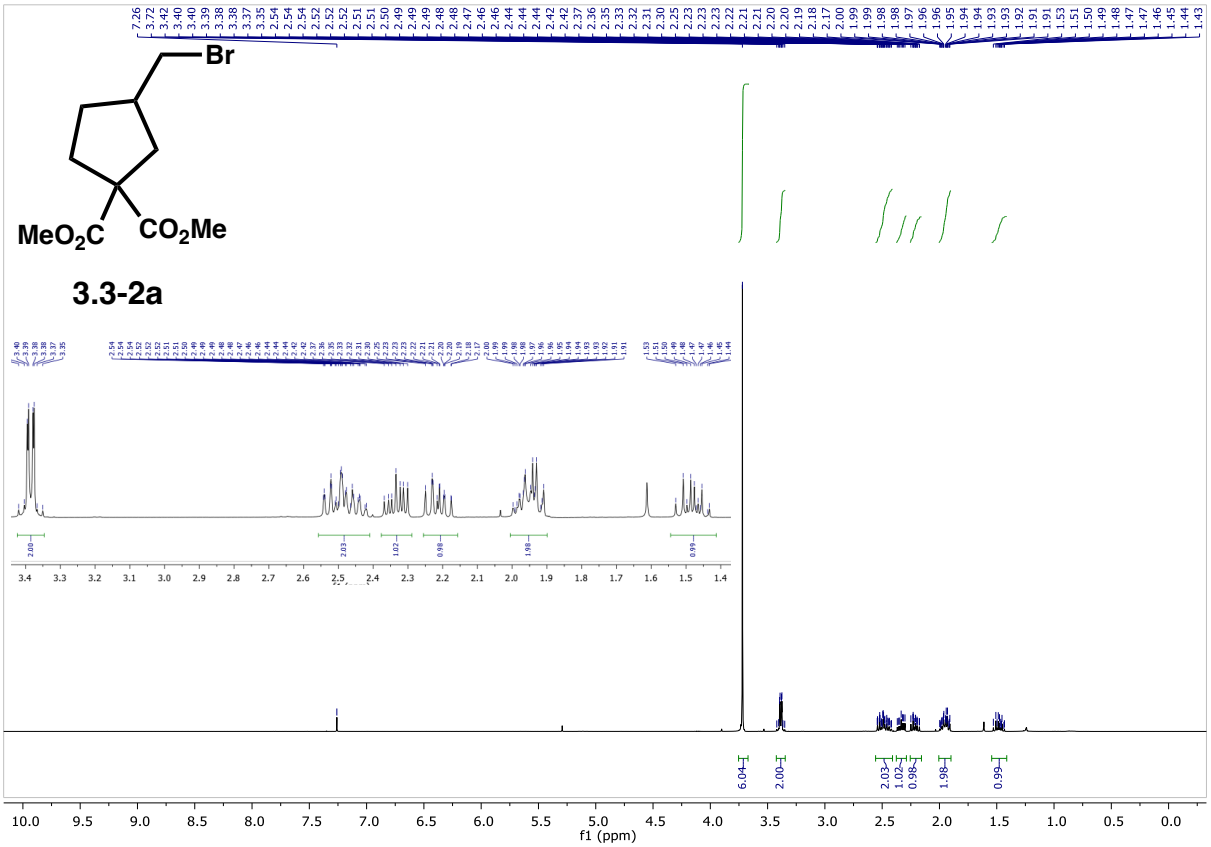

f1 (ppm)

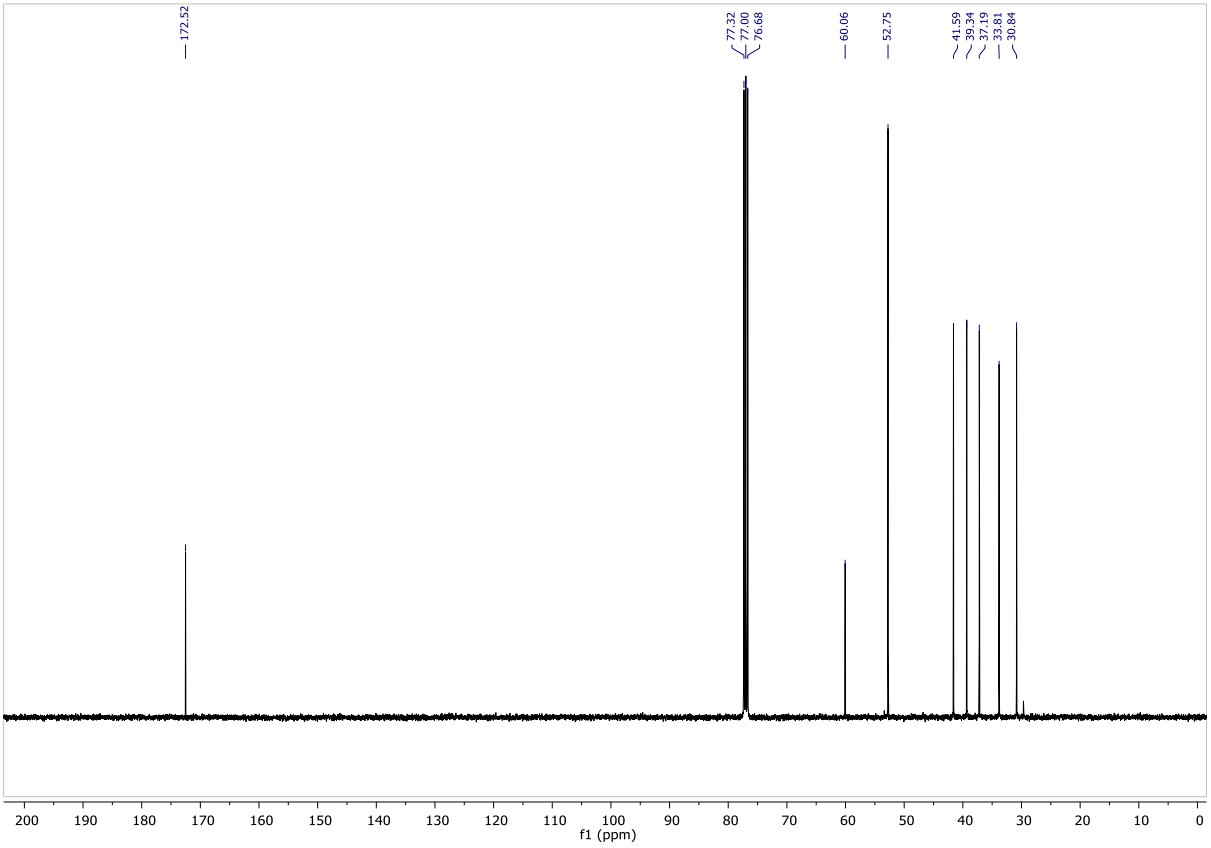

TsN
Br
Me
3.3-1s
f1 (ppm)

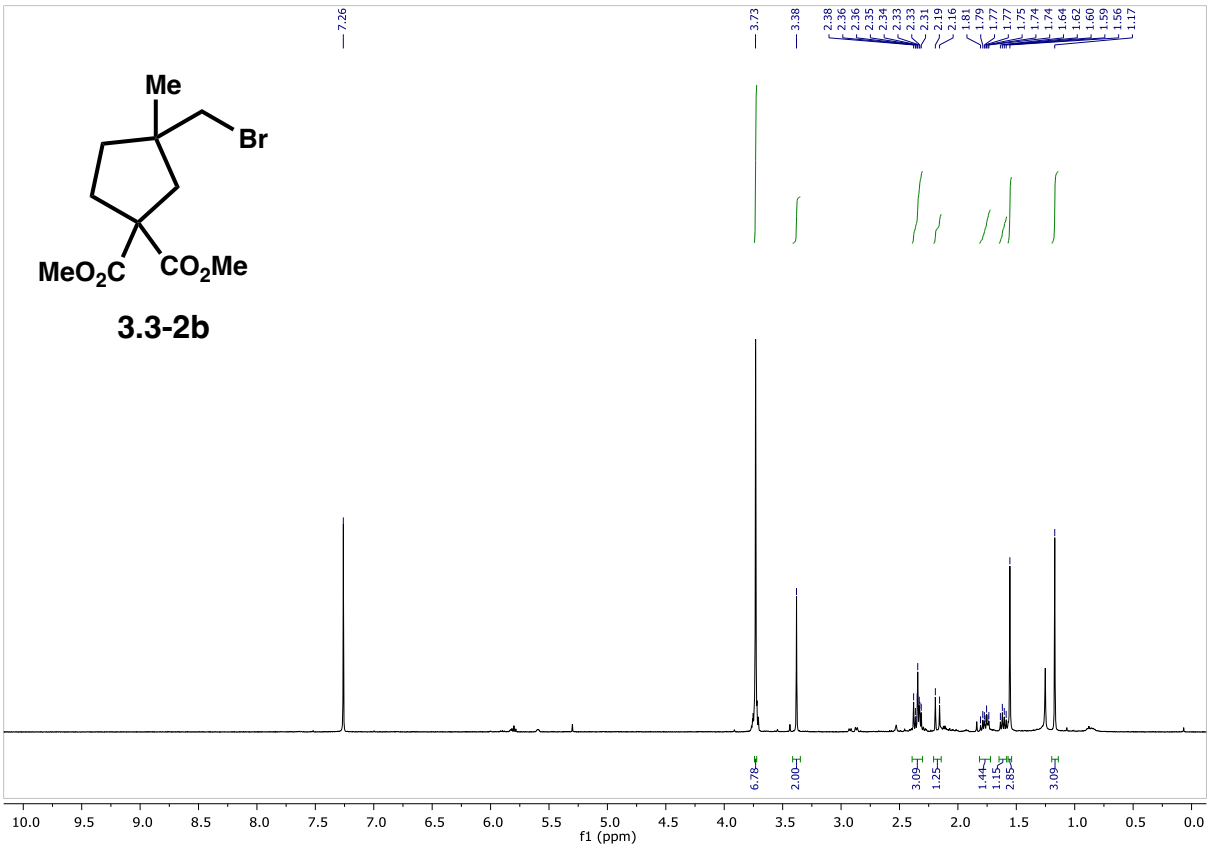

f1 (ppm)

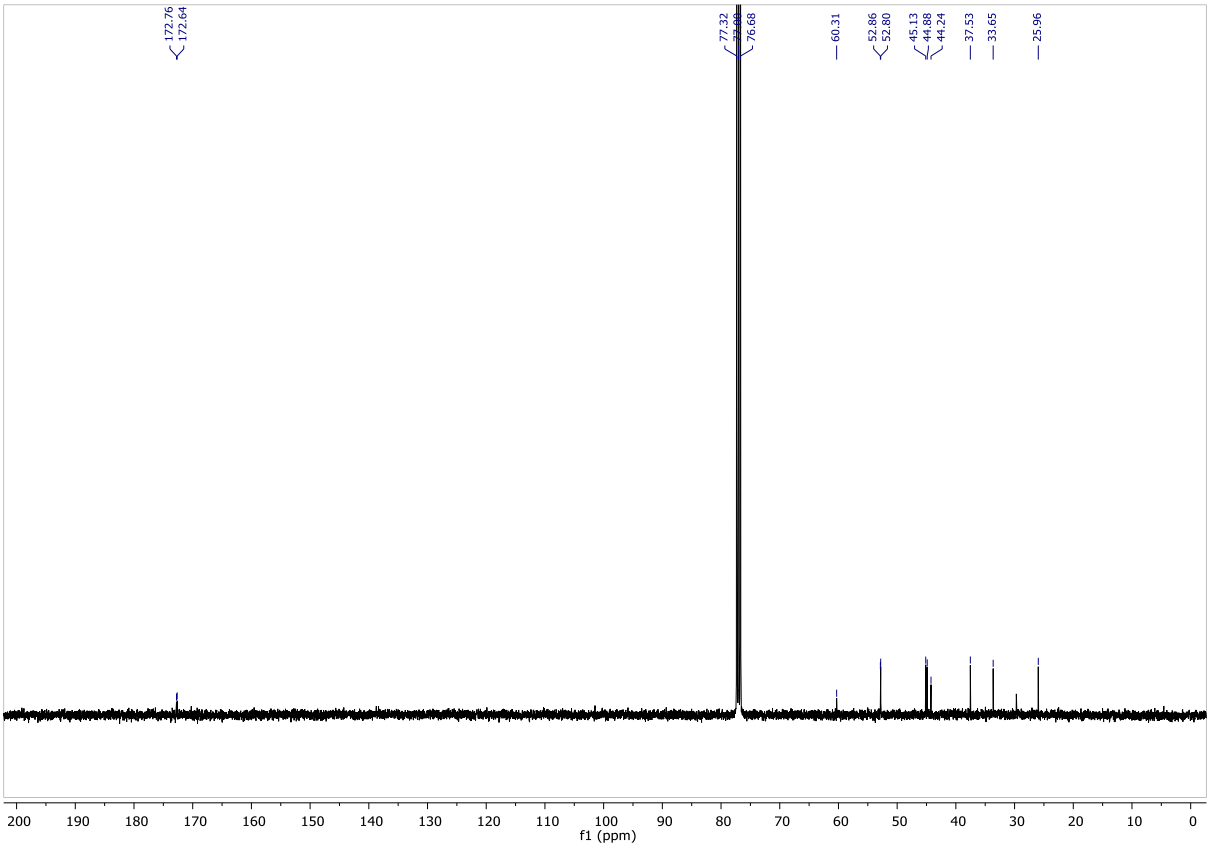

Me
Br
Me
MeO2C
CO2Me
3.3-1t
f1 (ppm)

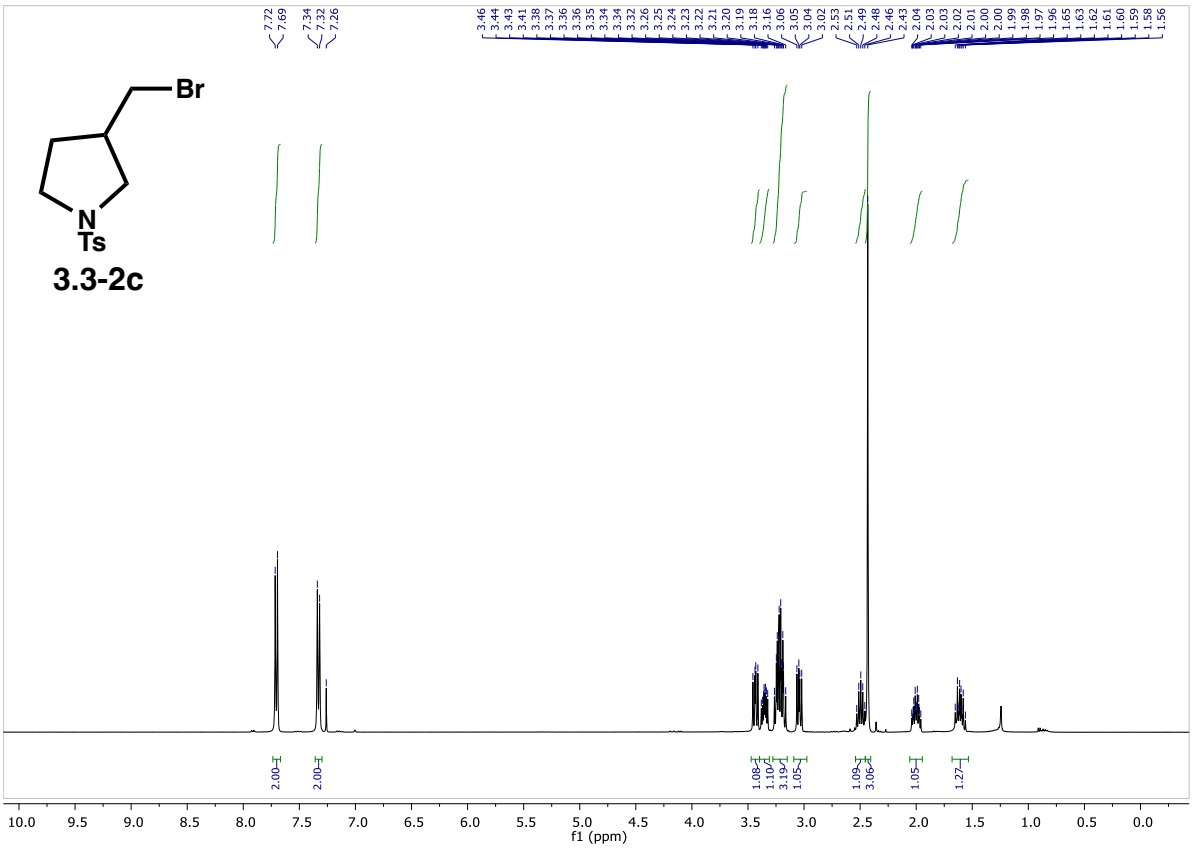

f1 (ppm)

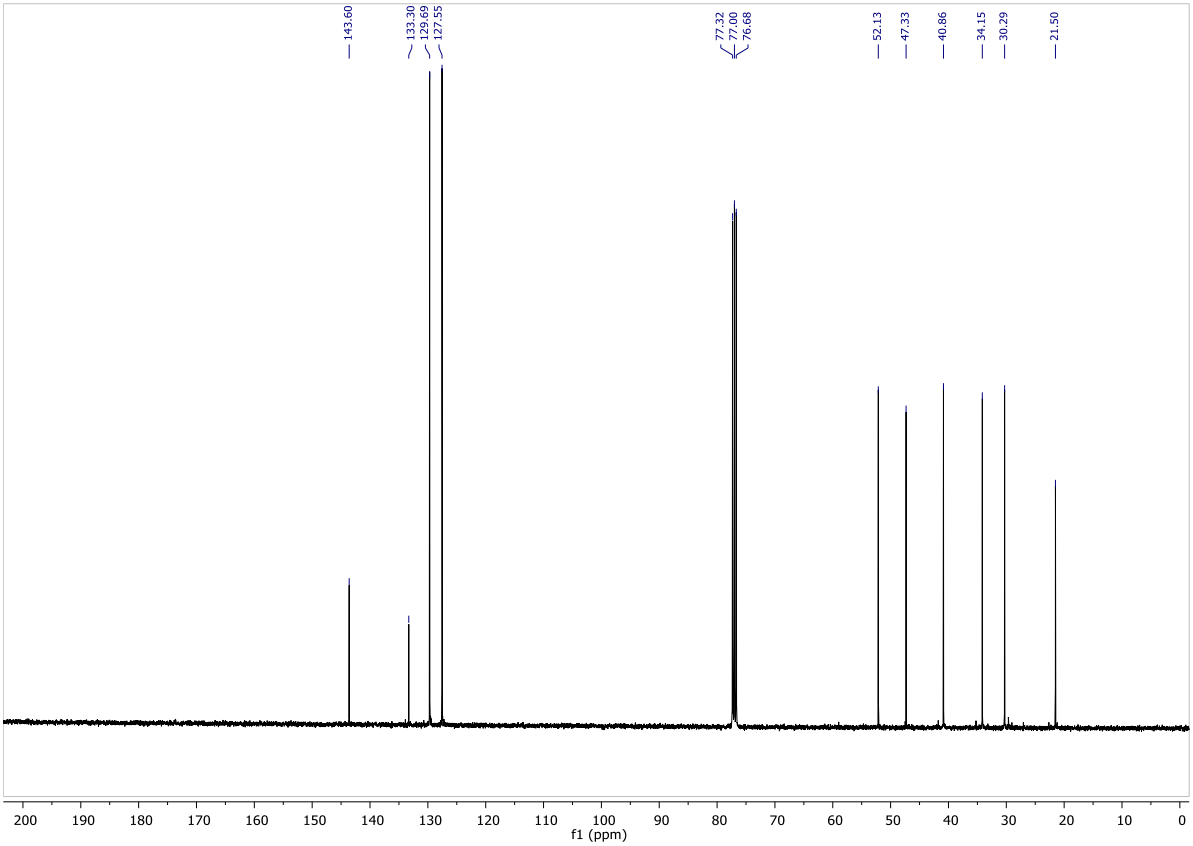

Br
MeO2C
CO2Me
3.3-2a
6.04
2.00
2.03
1.02
0.98
1.98
0.99
f1 (ppm)

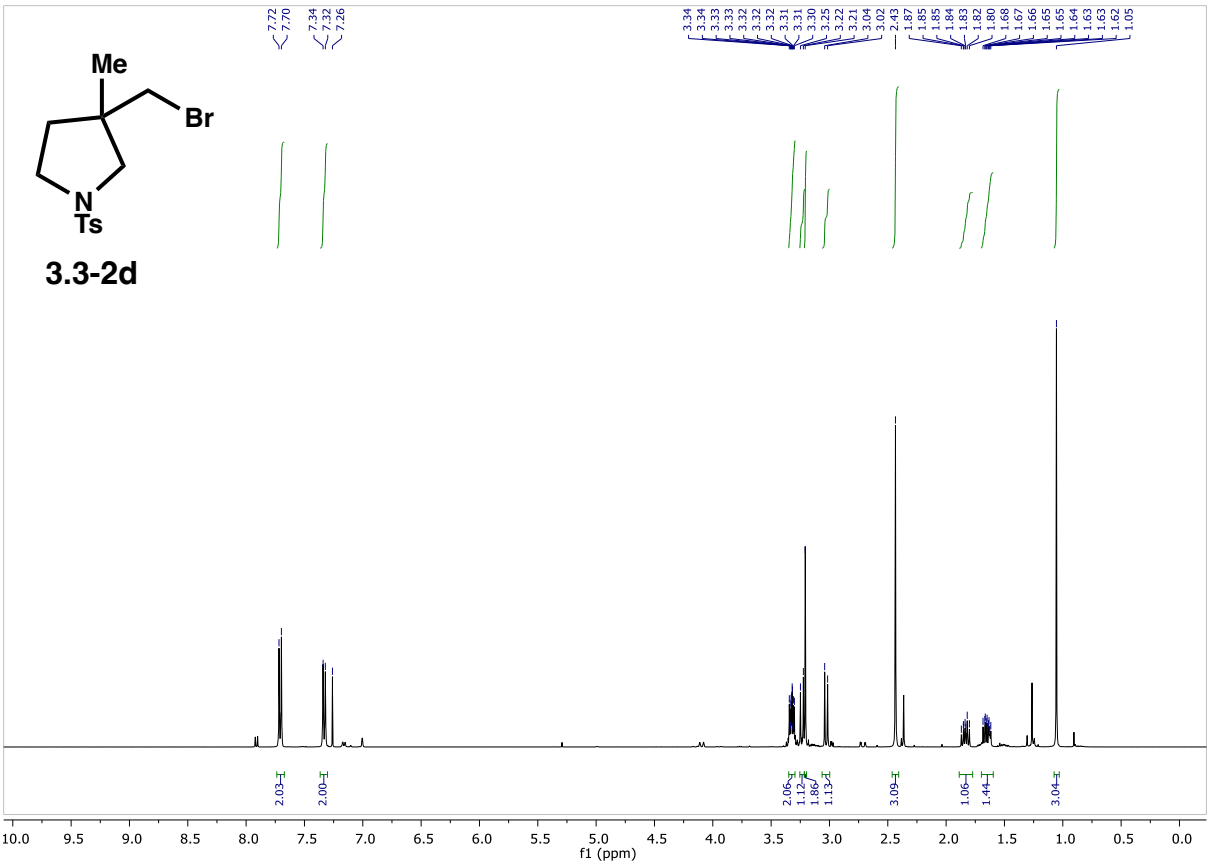

172.52
77.32
77.00
76.68
60.06
52.75
41.59
39.34
37.19
33.81
30.84
f1 (ppm)

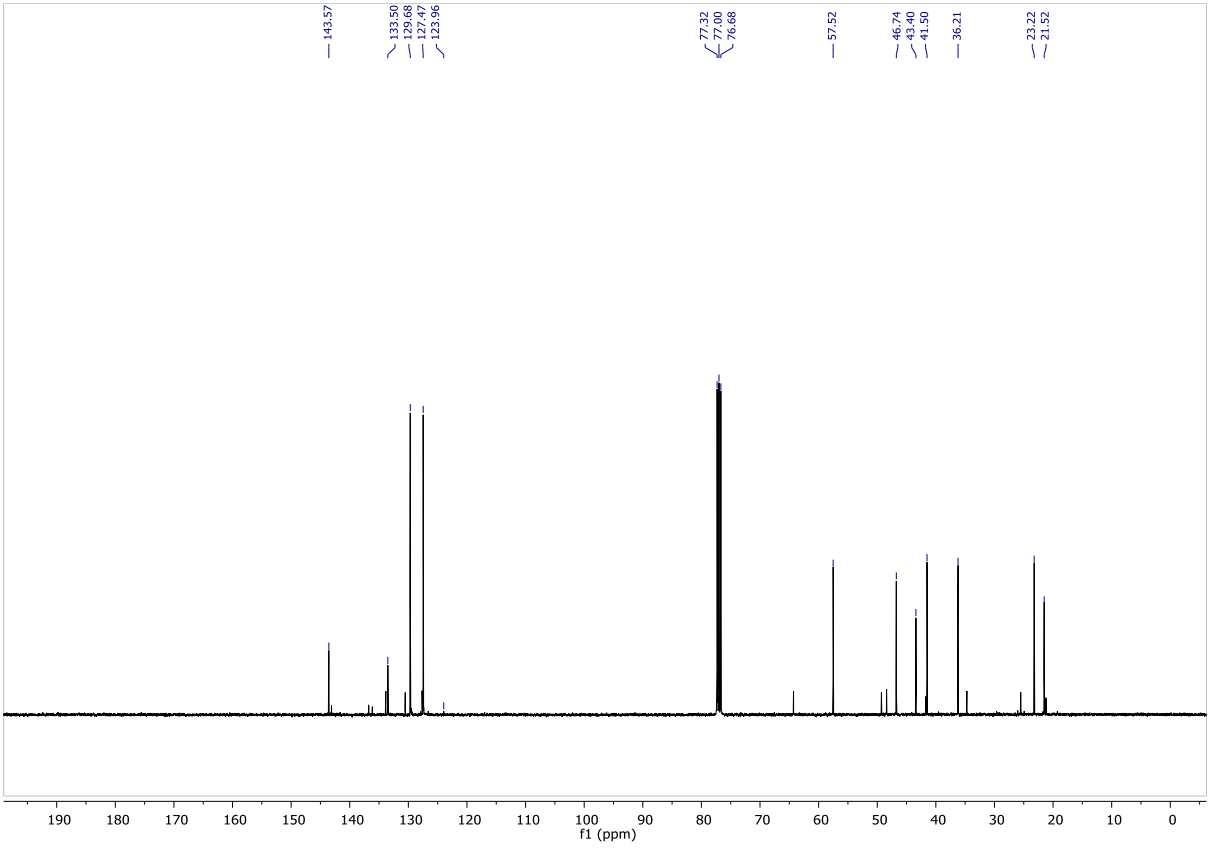

Me
Br
MeO2C
CO2Me
3.3-2b
7.26
3.73
3.38
2.38
2.36
2.36
2.35
2.34
2.33
2.33
2.31
2.19
2.16
1.81
1.79
1.77
1.77
1.75
1.74
1.74
1.64
1.62
1.60
1.59
1.56
1.17
6.78
2.00
3.09
1.25
1.44
1.15
2.85
3.09
f1 (ppm)

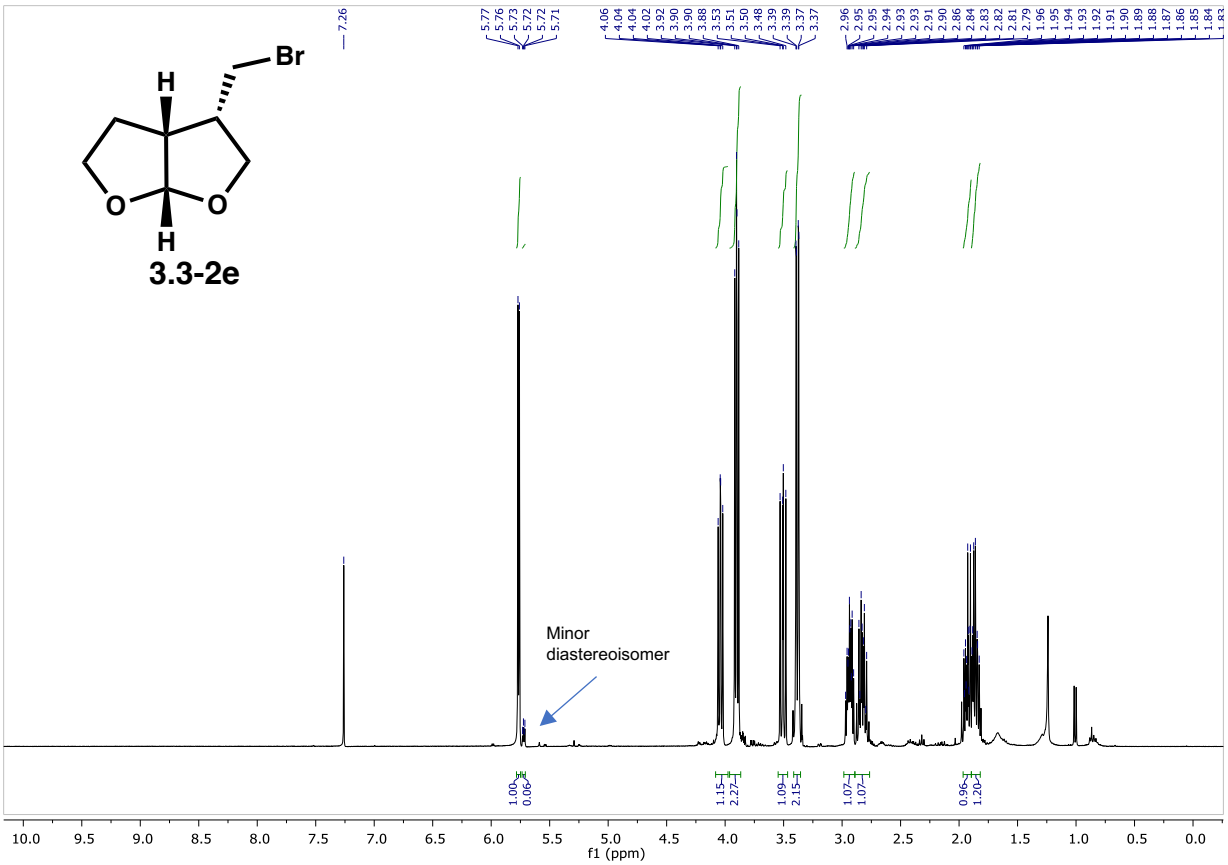

172.76
172.64
77.32
76.68
60.31
52.86
52.80
45.13
44.88
44.24
37.53
33.65
25.96
f1 (ppm)

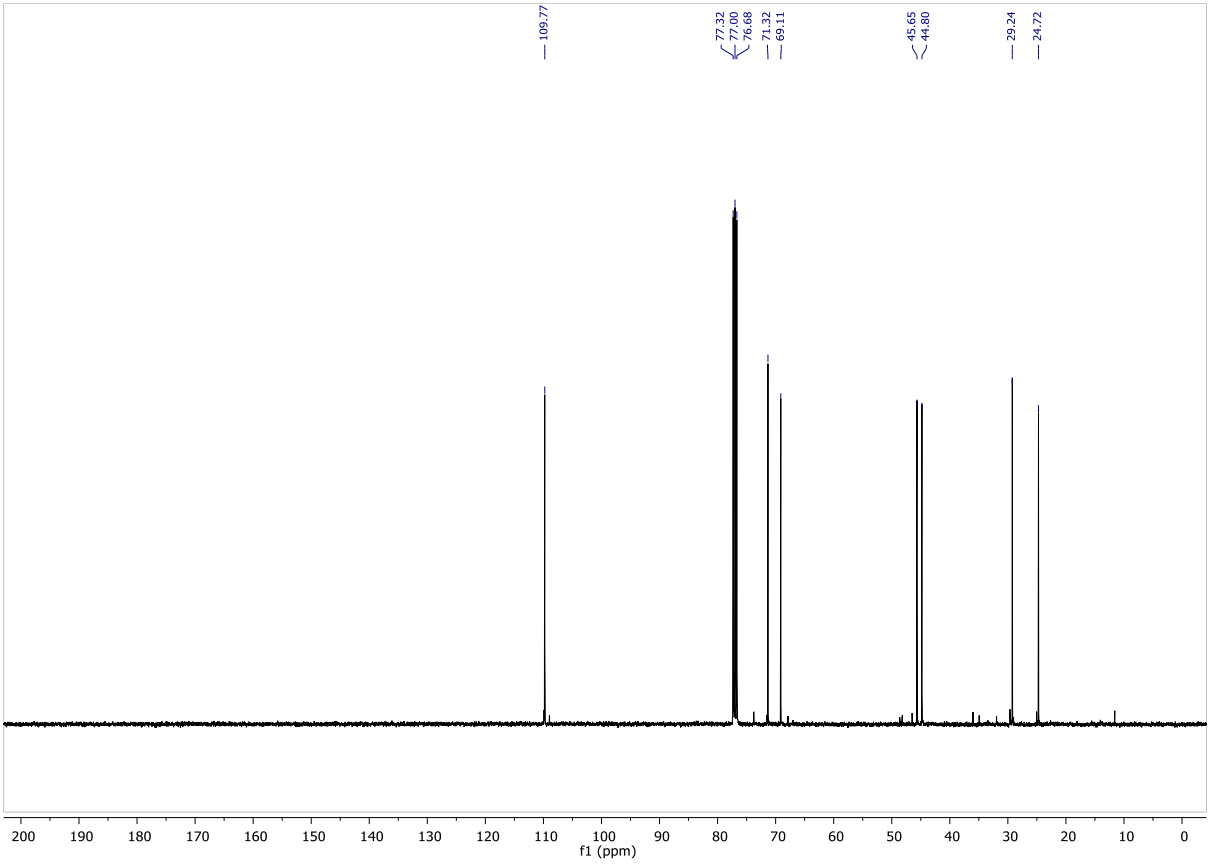

Br
N
Ts
3.3-2c
f1 (ppm)

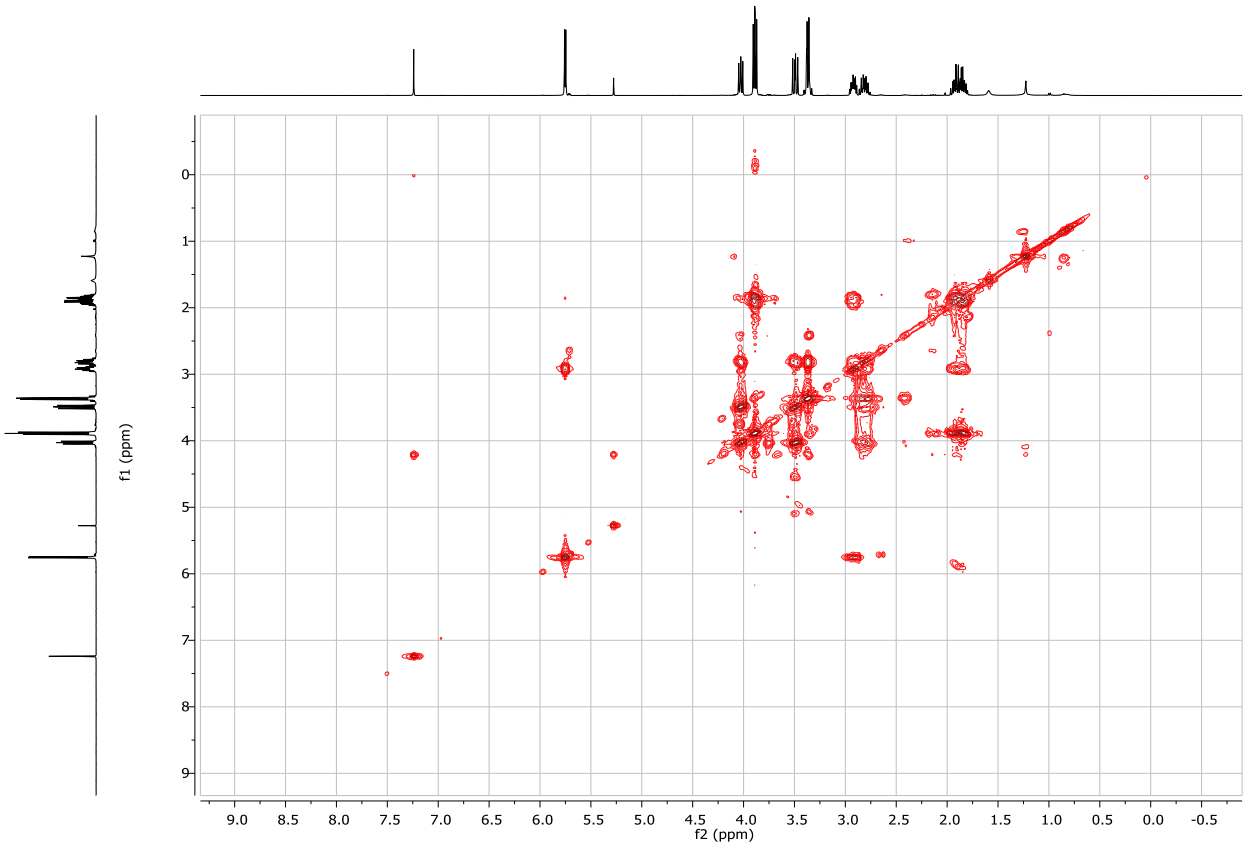

f1 (ppm)

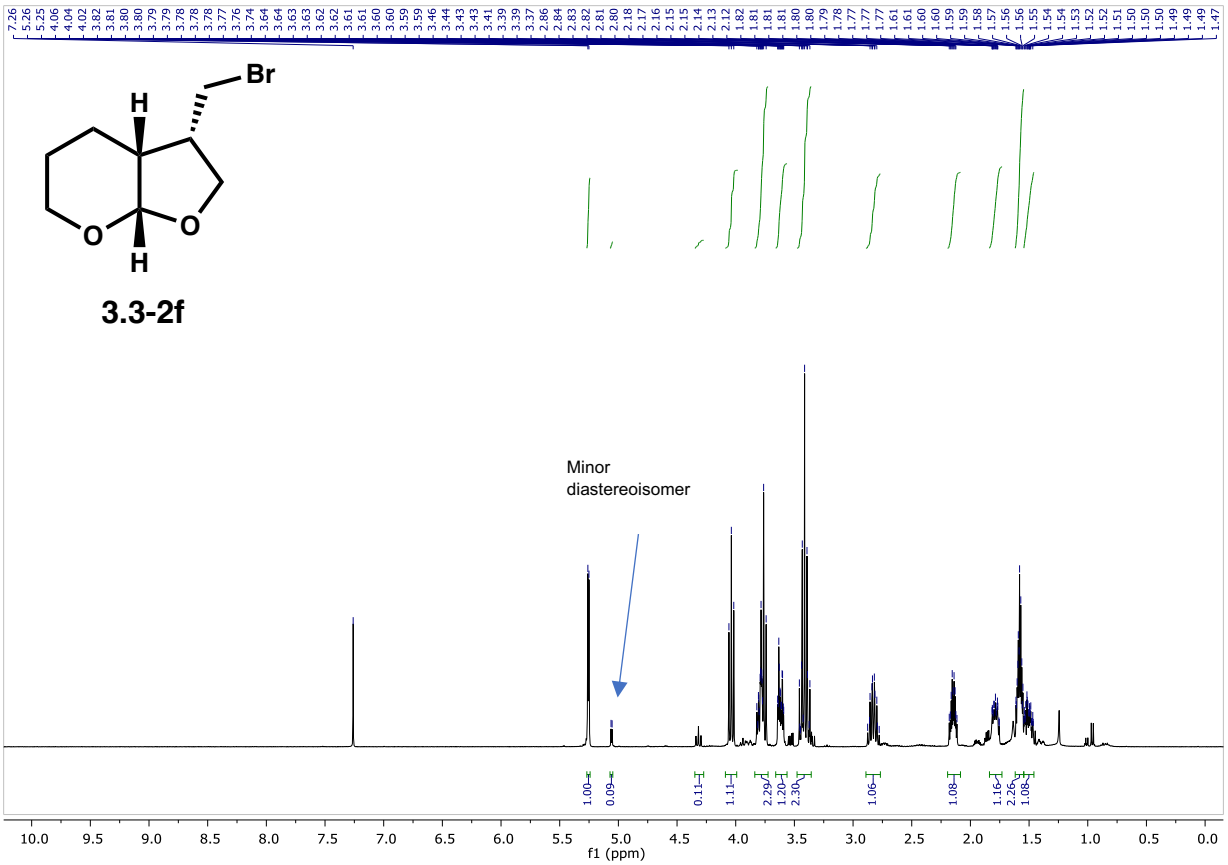

Me
Br
N
Ts
3.3-2d
f1 (ppm)

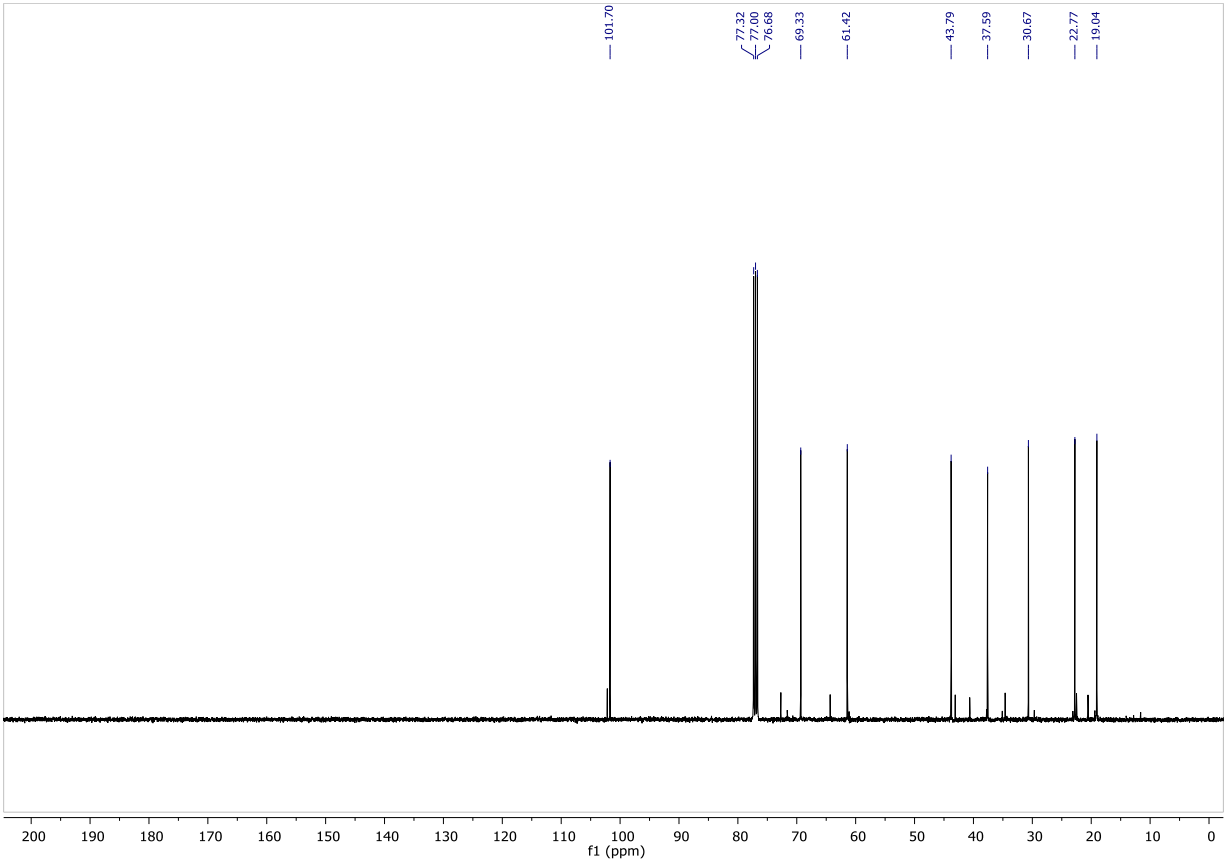

f1 (ppm)

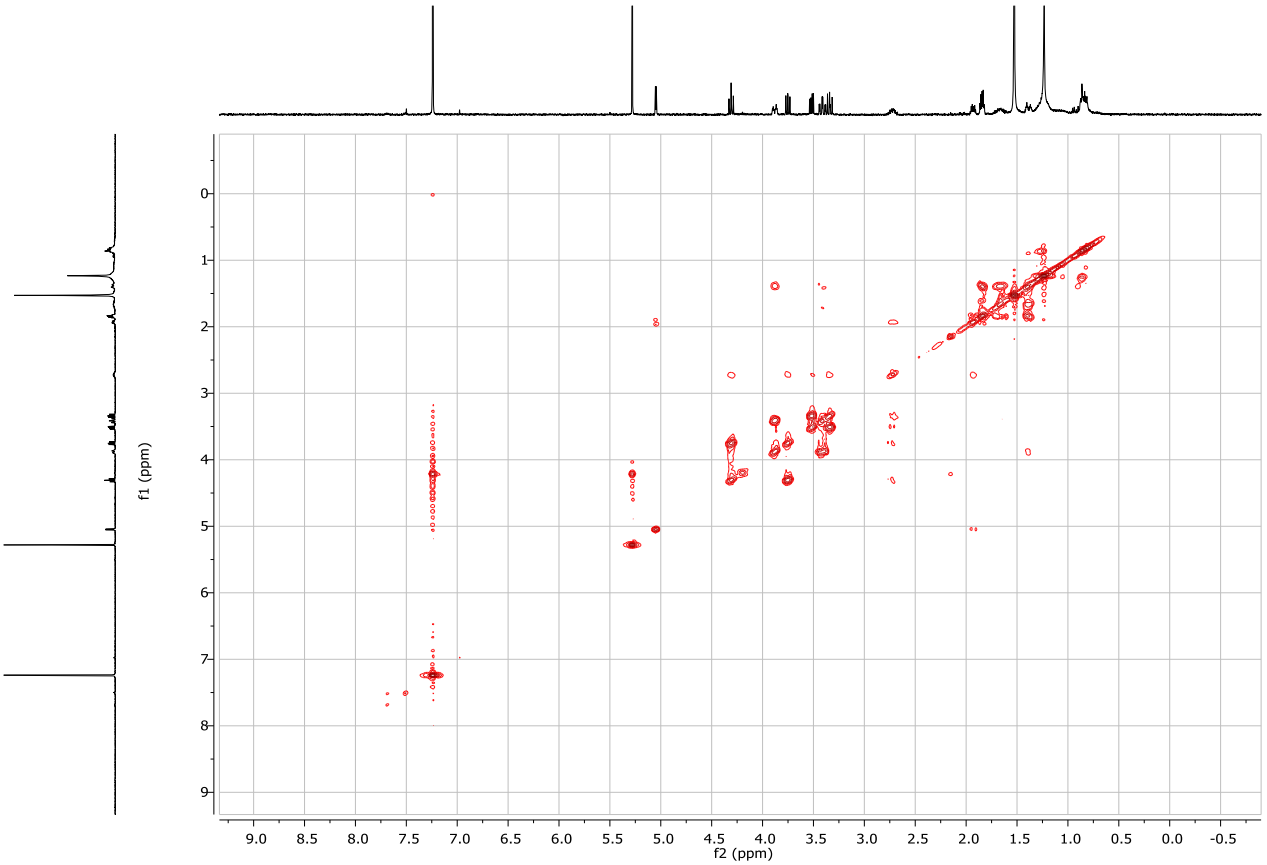

Br
H
O
O
H
3.3-2e
Minor
diastereoisomer
f1 (ppm)

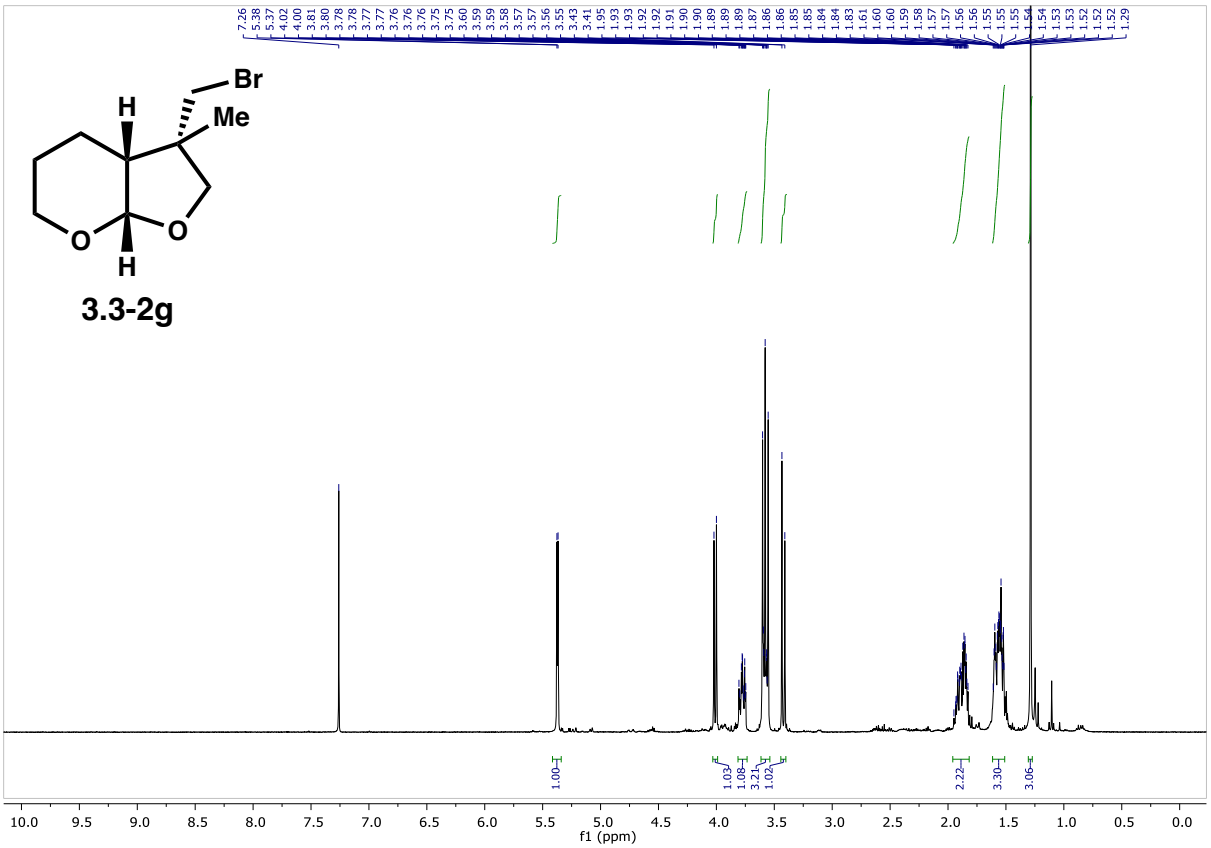

f1 (ppm)

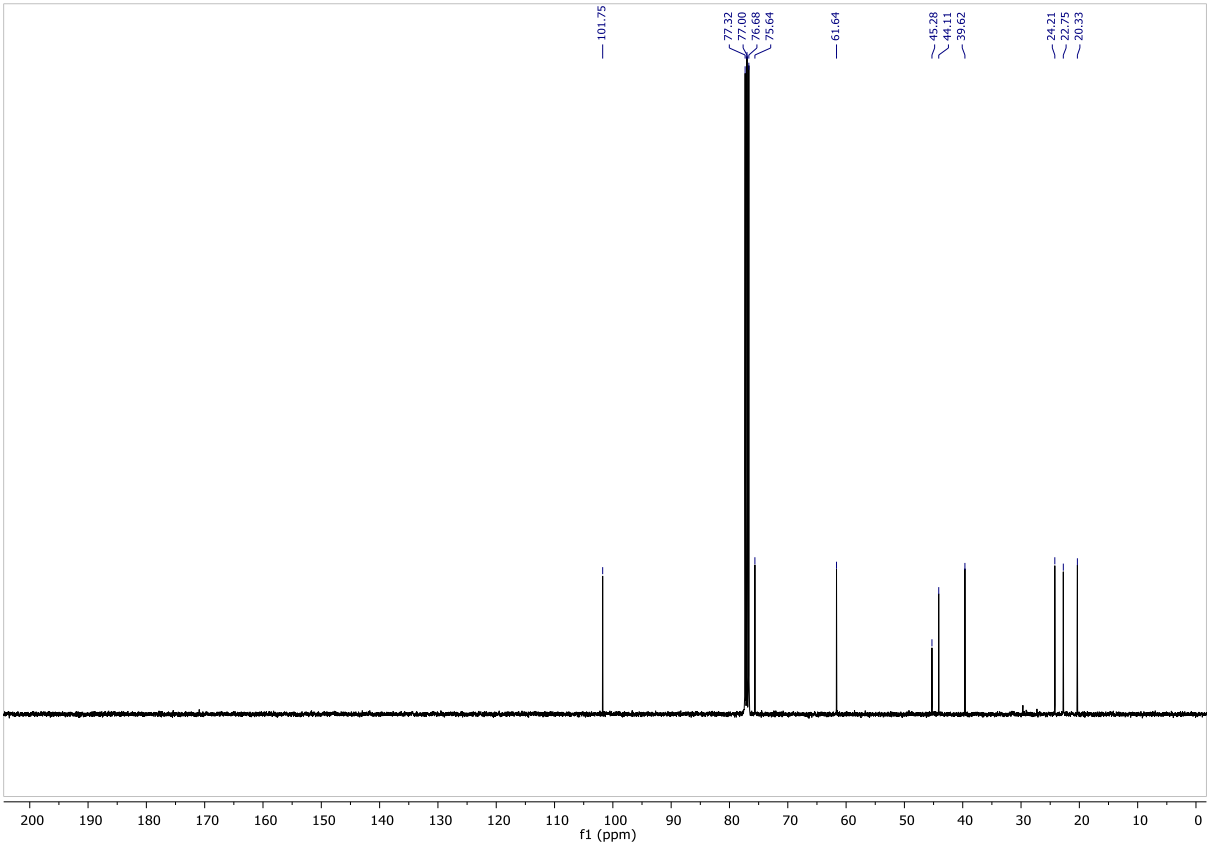

f1 (ppm)
f2 (ppm)
0
1
2
3
4
5
6
7
8
9
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

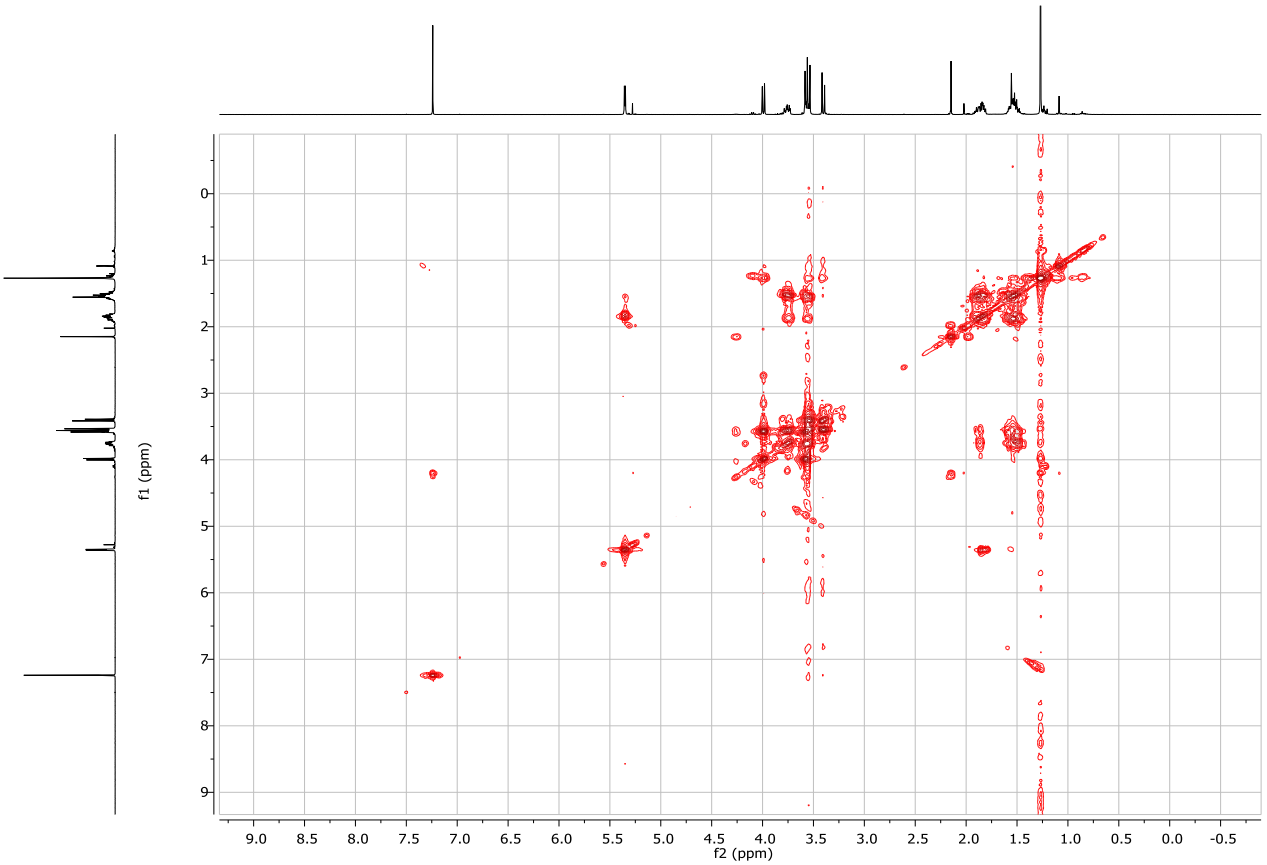

Br
H
O
O
H
3.3-2f
Minor
diastereoisomer
f1 (ppm)

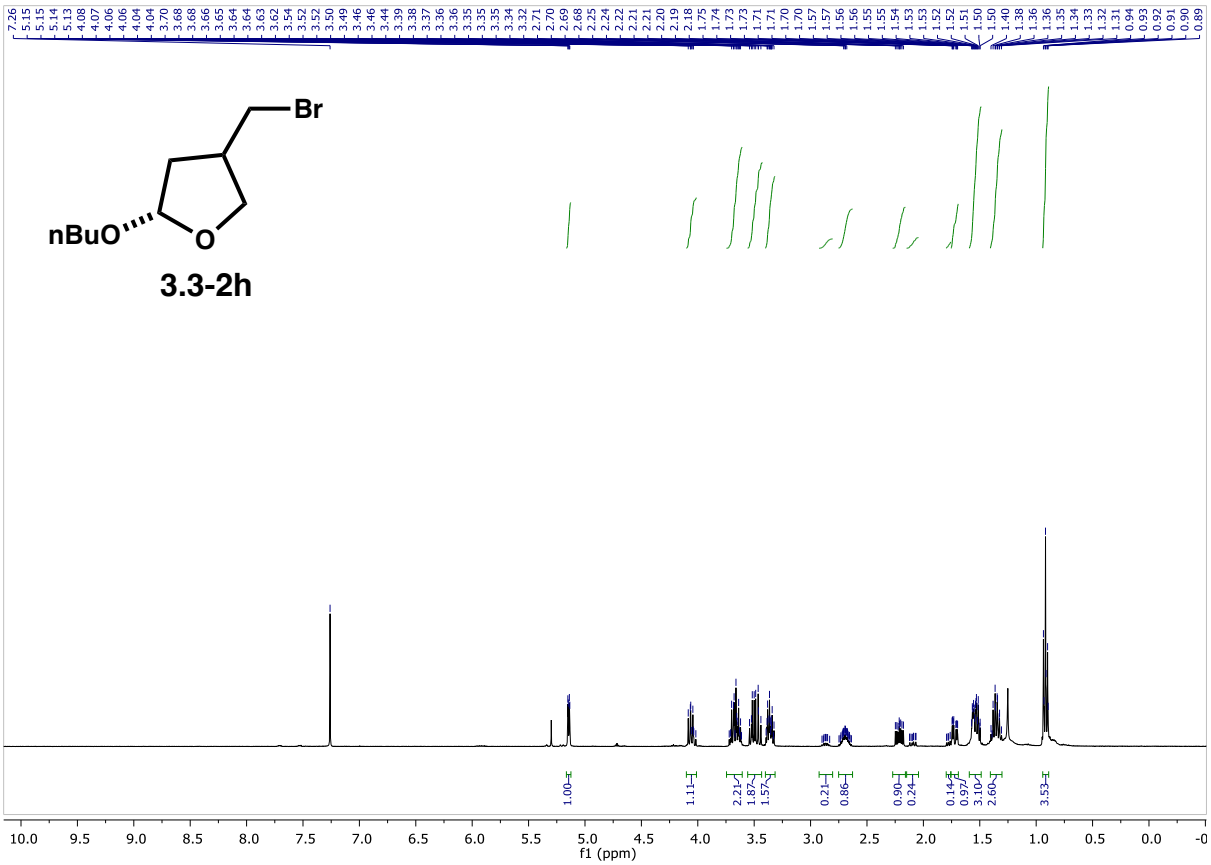

101.70
77.32
77.00
76.68
69.33
61.42
43.79
37.59
30.67
22.77
19.04
f1 (ppm)

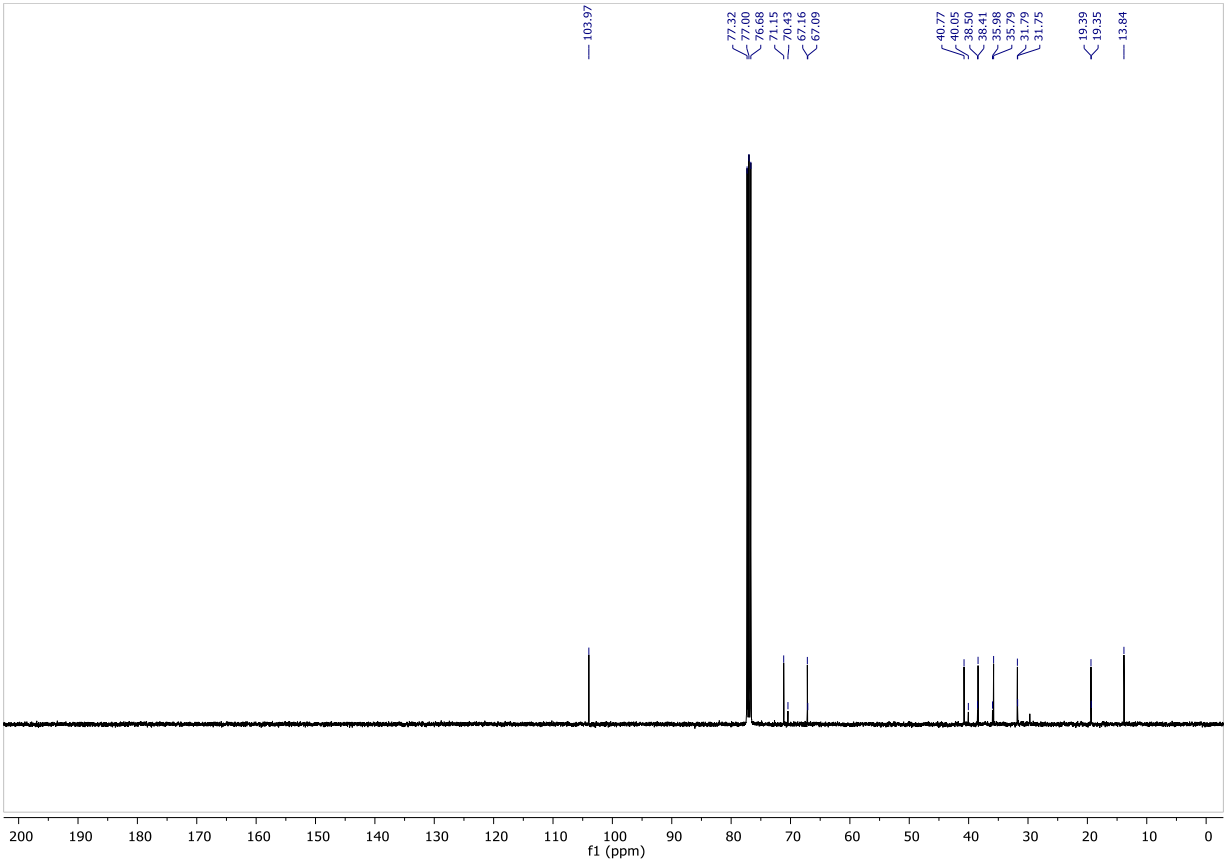

f1 (ppm)
f2 (ppm)
0
1
2
3
4
5
6
7
8
9
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

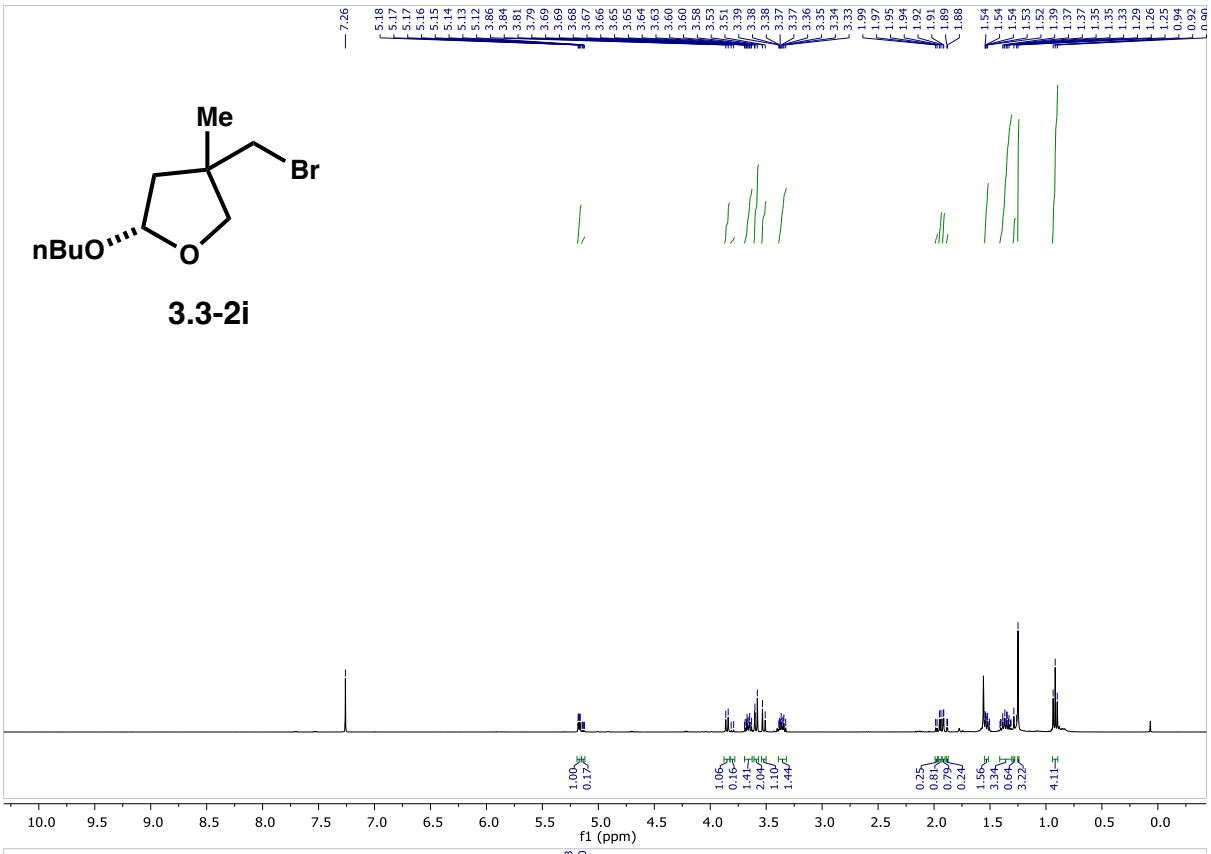

Br
H
Me
O
O
H
3.3-2g
f1 (ppm)

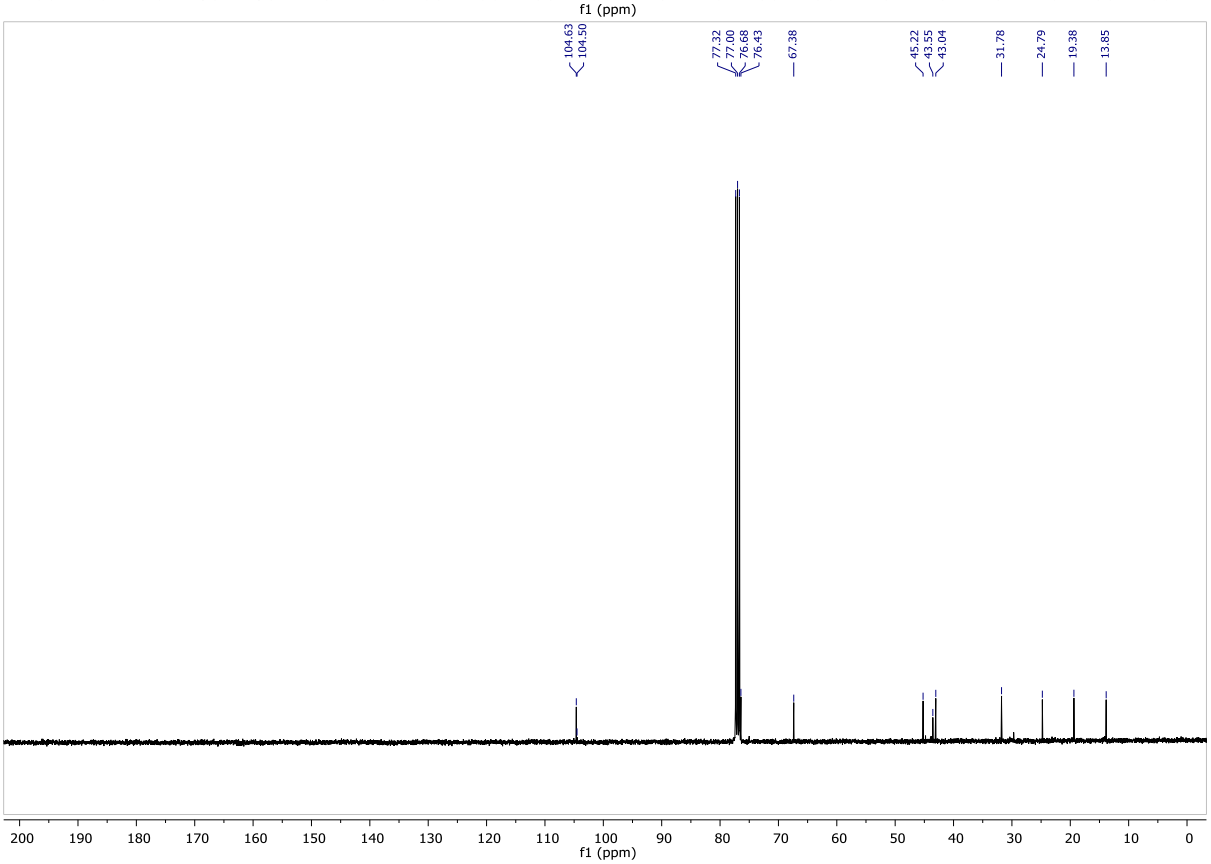

f1 (ppm)

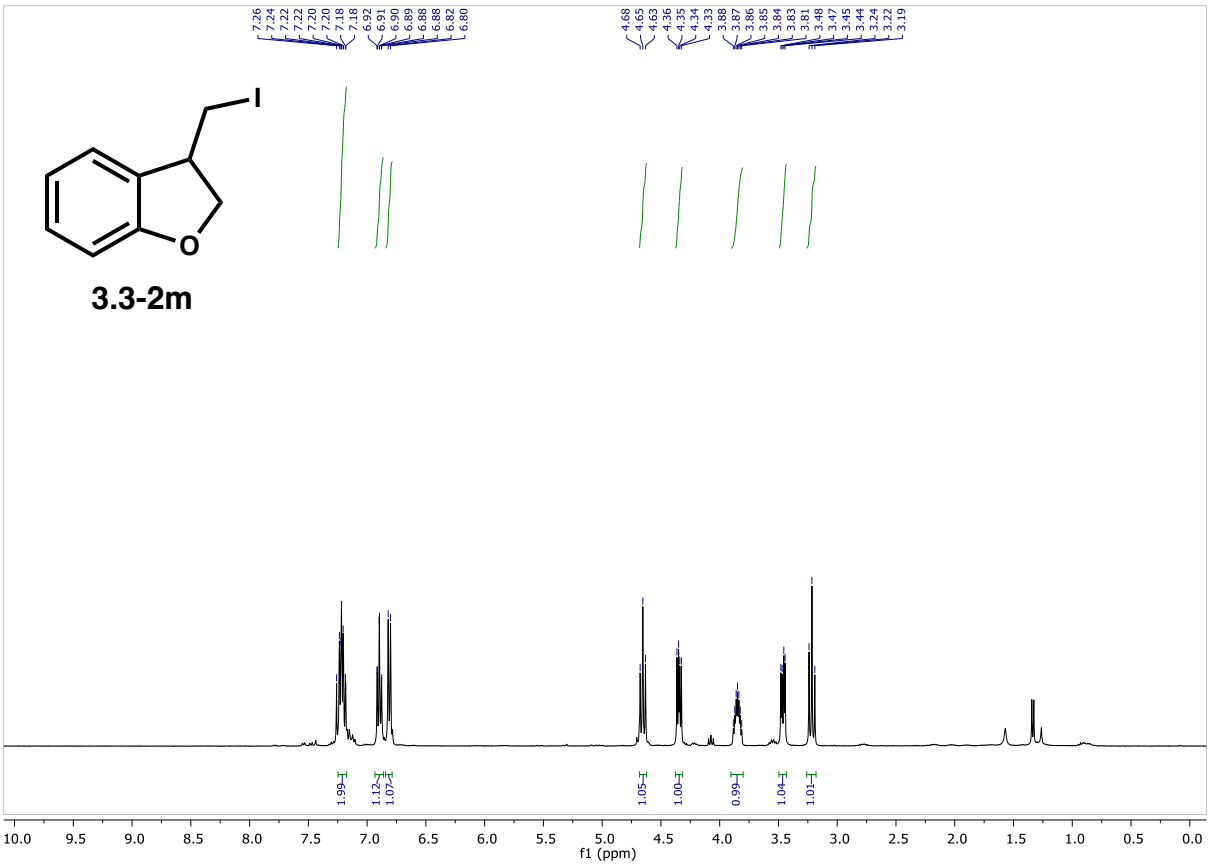

f1 (ppm)
f2 (ppm)
0
1
2
3
4
5
6
7
8
9
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

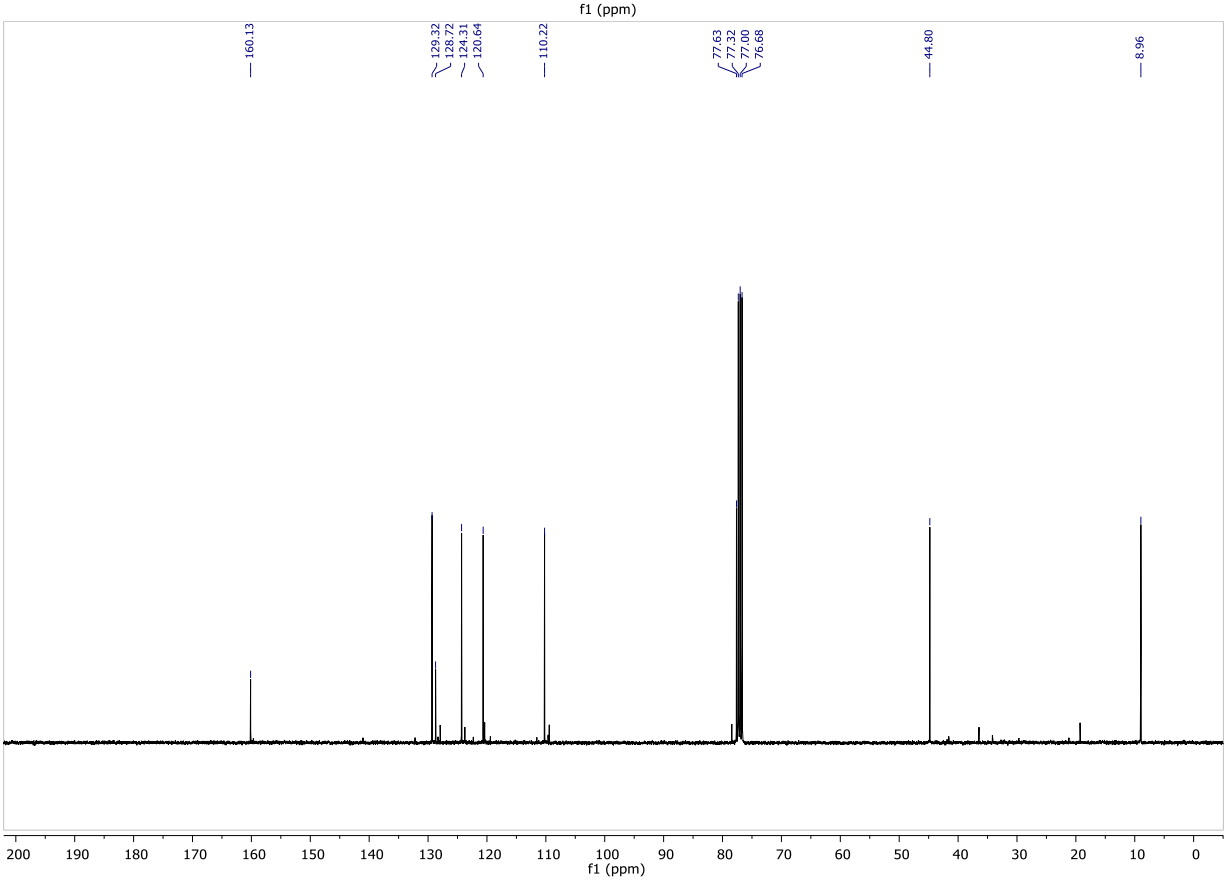

Br
nBuO
O
3.3-2h
f1 (ppm)

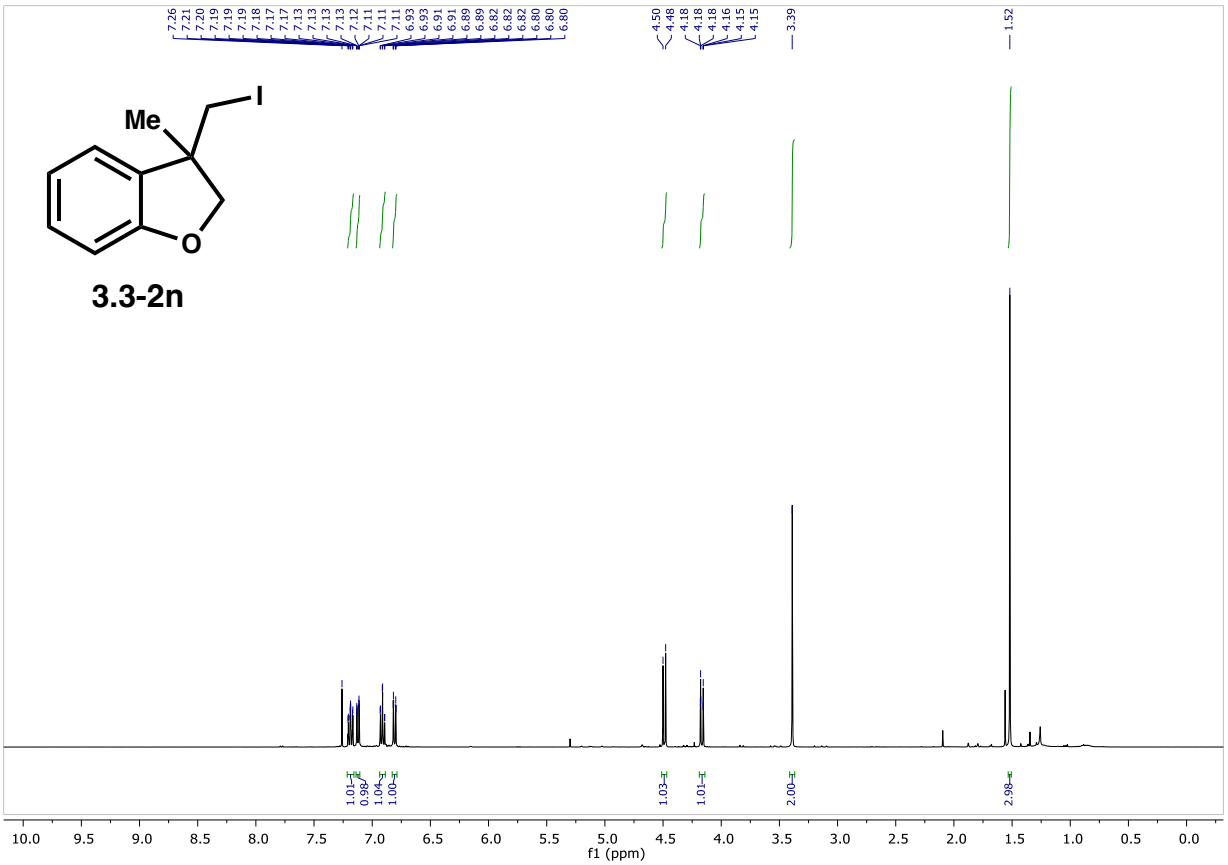

f1 (ppm)

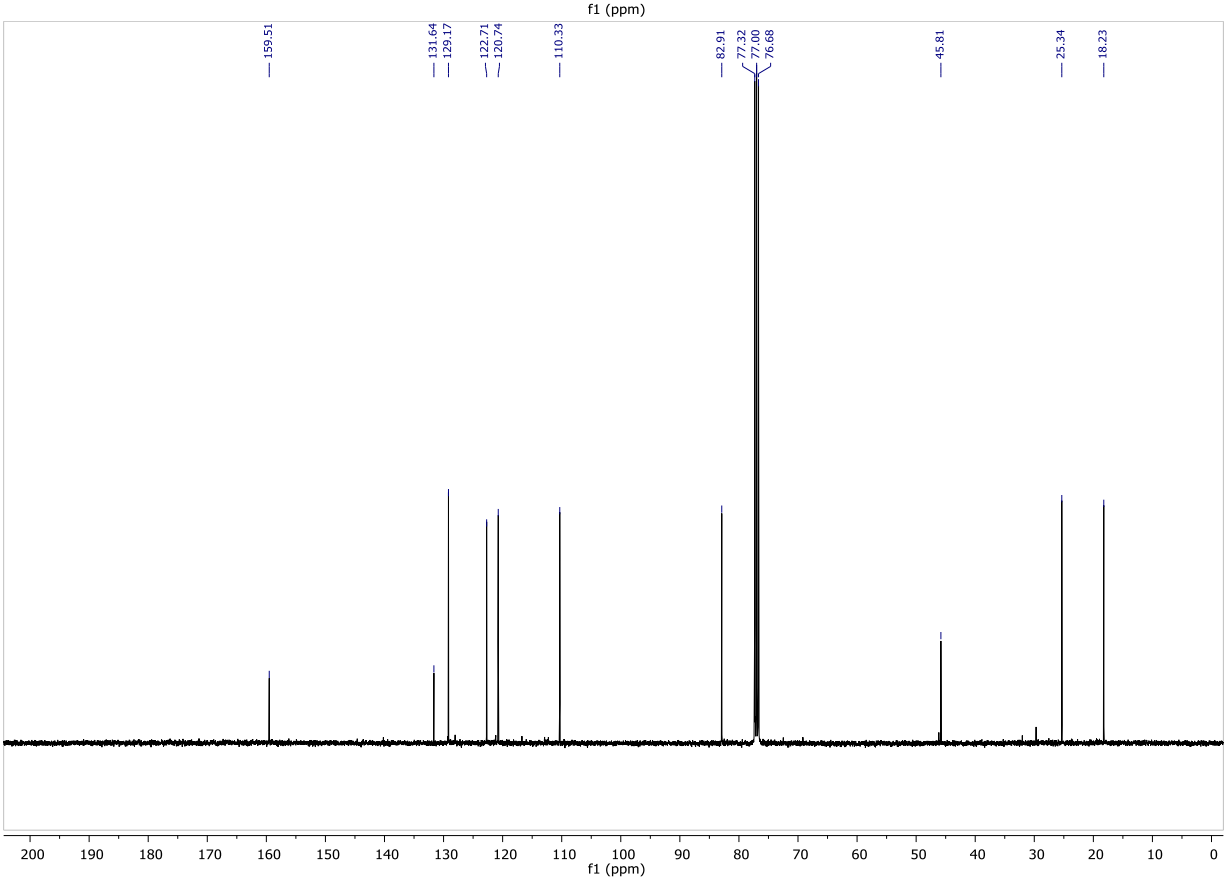

Me
Br
nBuO
O
3.3-2i
f1 (ppm)

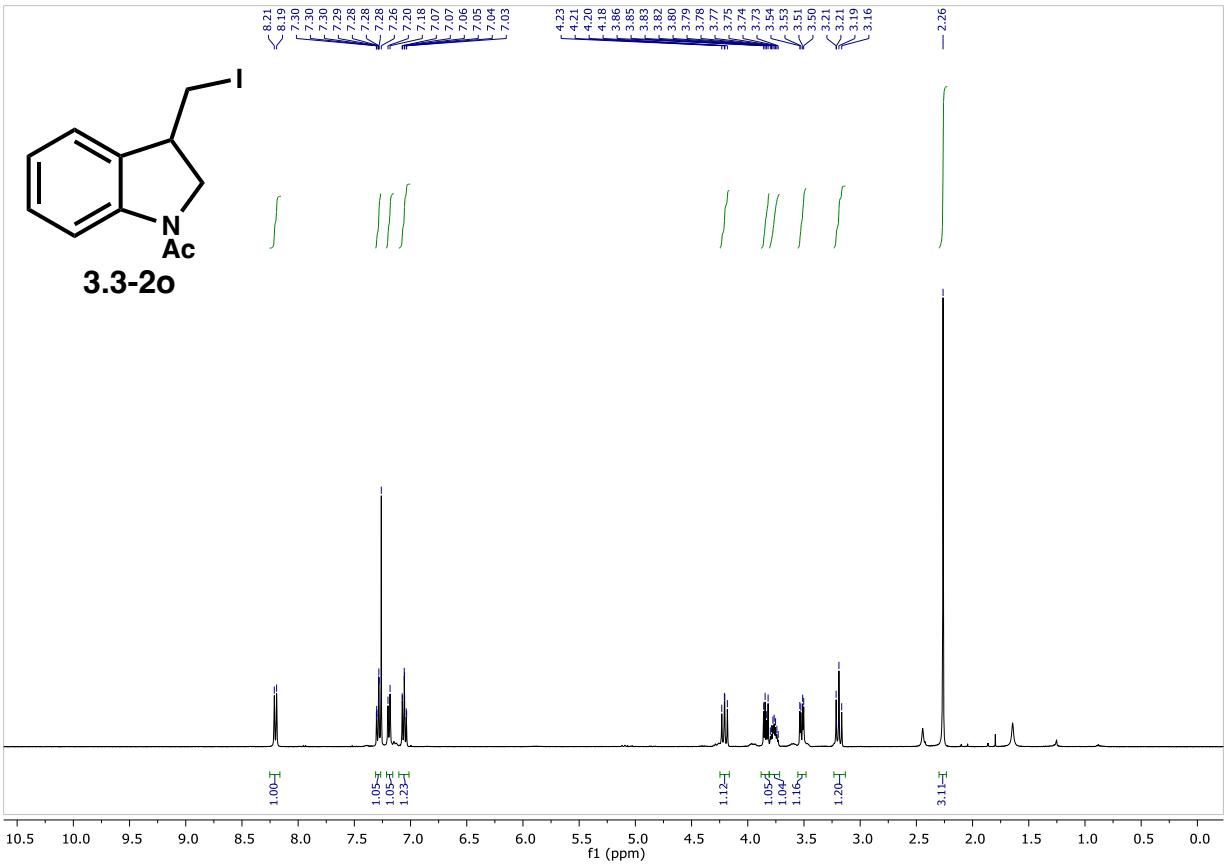

f1 (ppm)

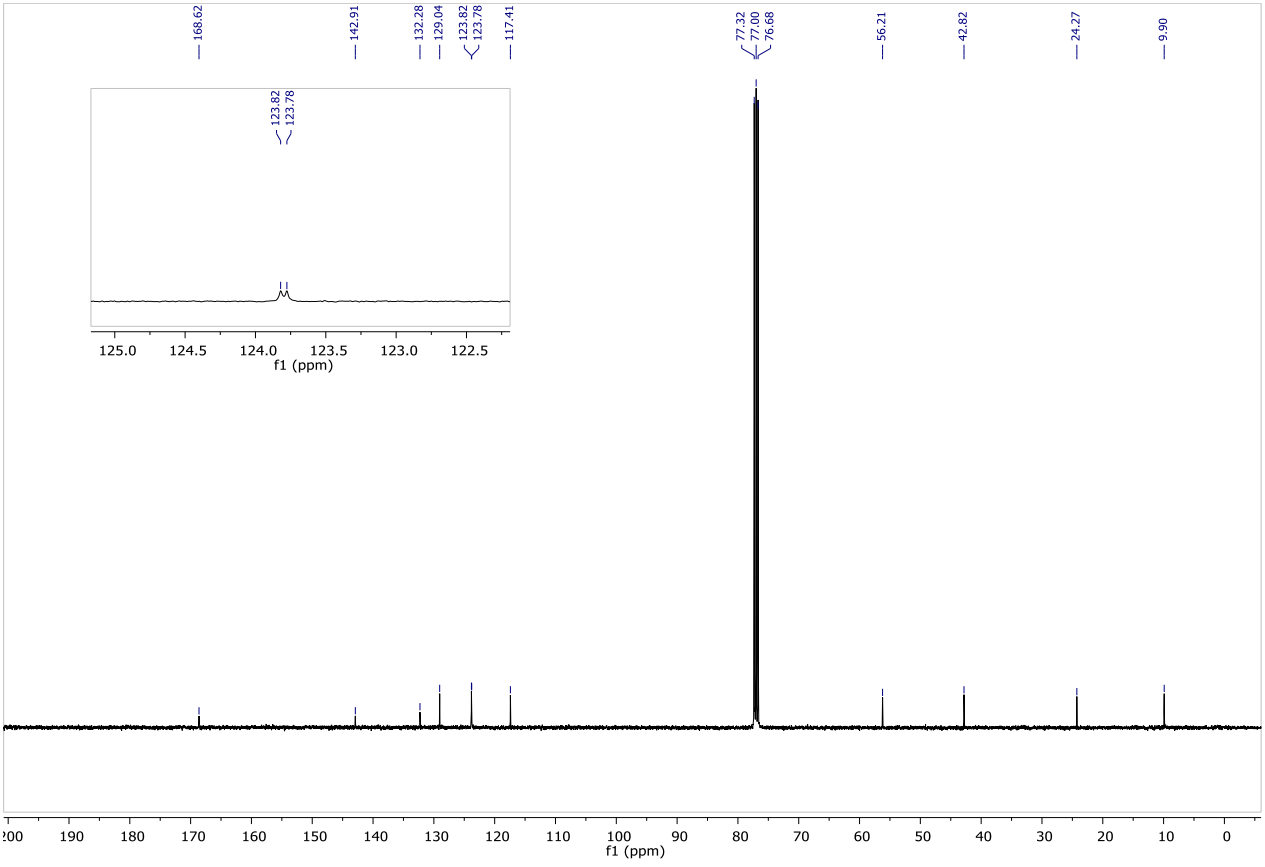

7.26
7.24
7.22
7.22
7.20
7.20
7.18
7.18
6.92
6.91
6.90
6.89
6.88
6.88
6.82
6.80
4.68
4.65
4.63
4.36
4.35
4.34
4.33
3.88
3.87
3.86
3.85
3.84
3.83
3.81
3.48
3.47
3.45
3.44
3.24
3.22
3.19
I
O
3.3-2m
1.99
1.12
1.07
1.05
1.00
0.99
1.04
1.01
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

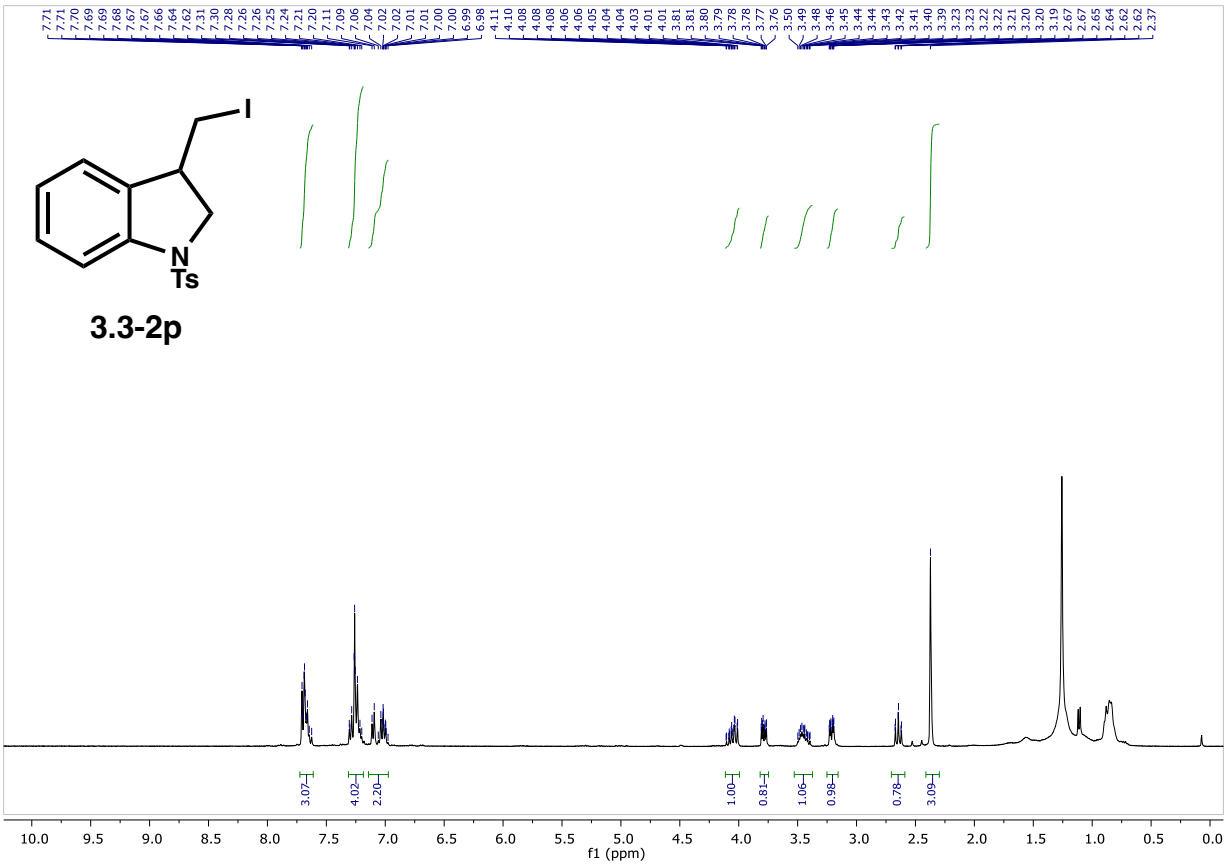

160.13
129.32
128.72
124.31
120.64
110.22
77.63
77.32
77.00
76.68
44.80
8.96
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

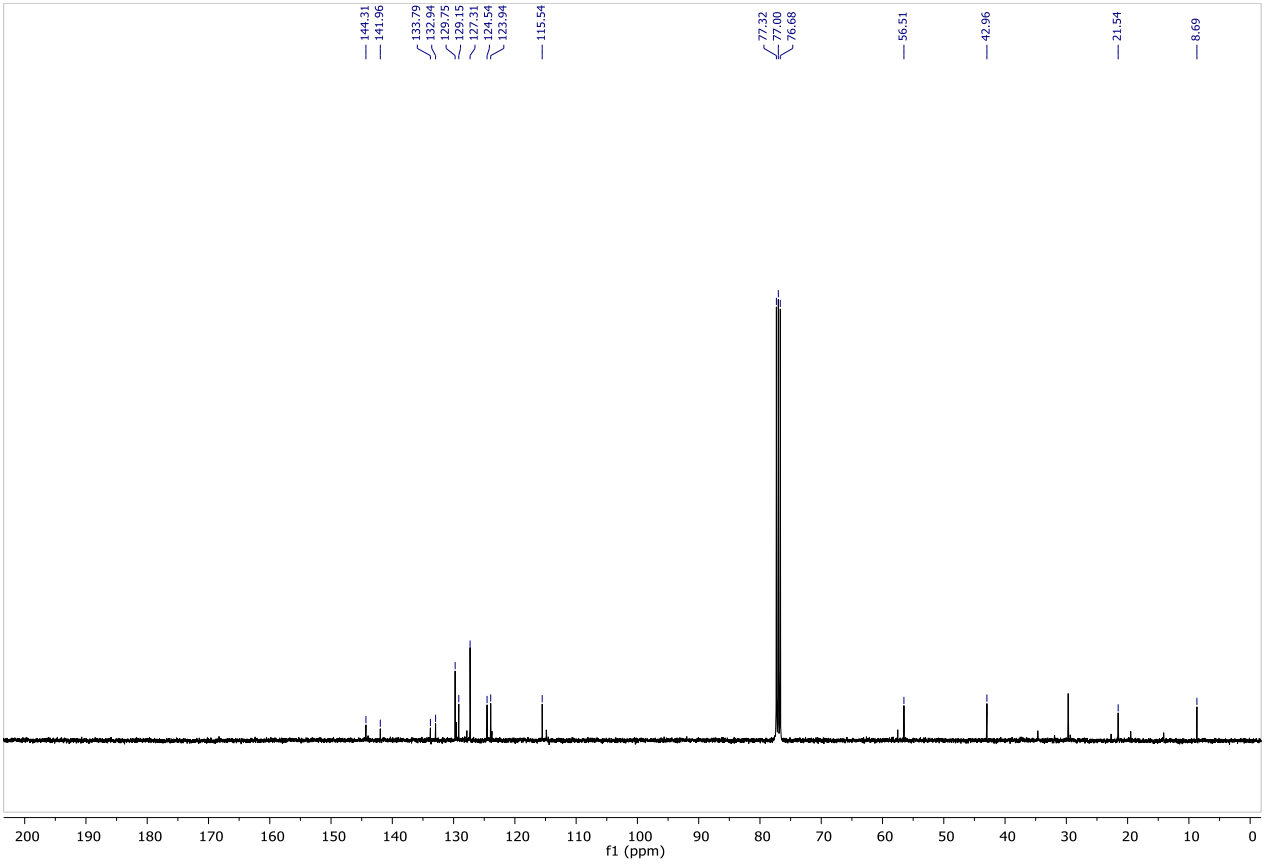

Me
I
O
3.3-2n
f1 (ppm)

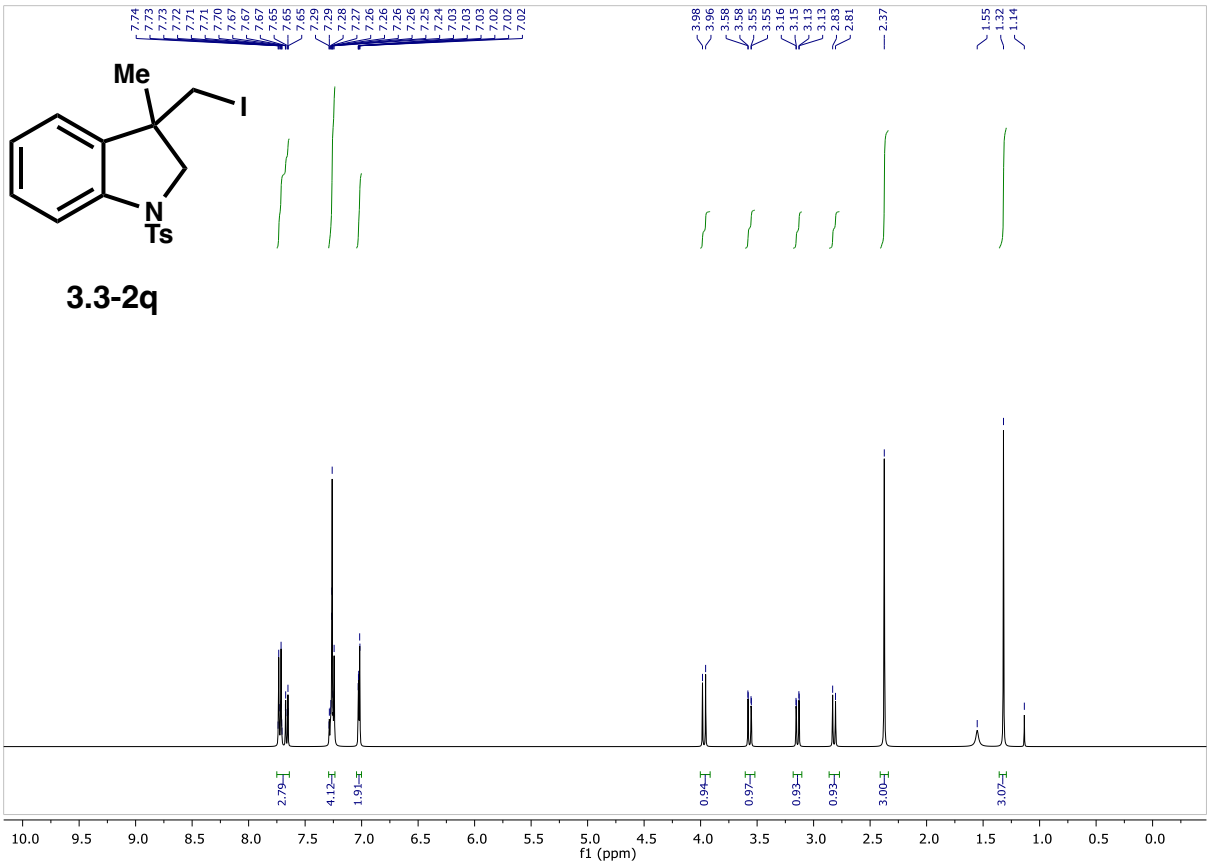

f1 (ppm)

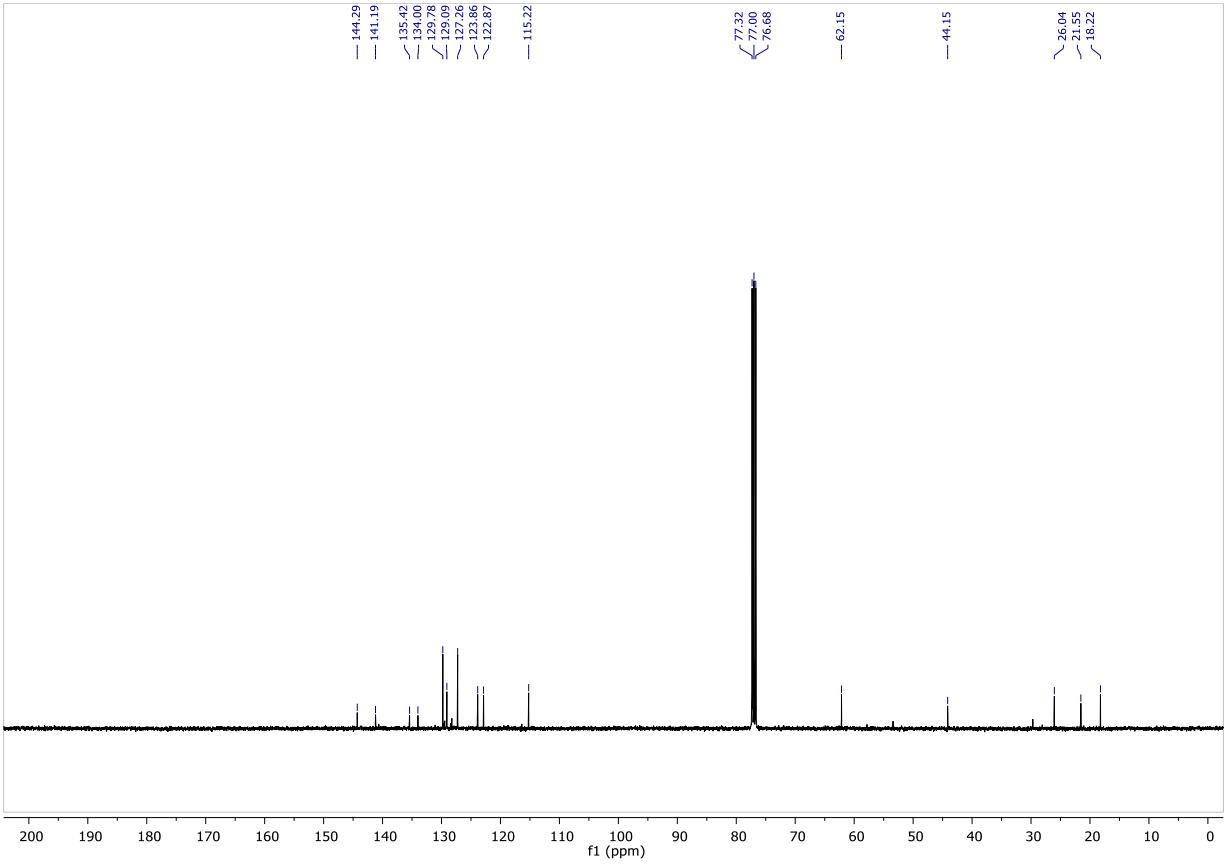

I
N
Ac
3.3-2o
f1 (ppm)

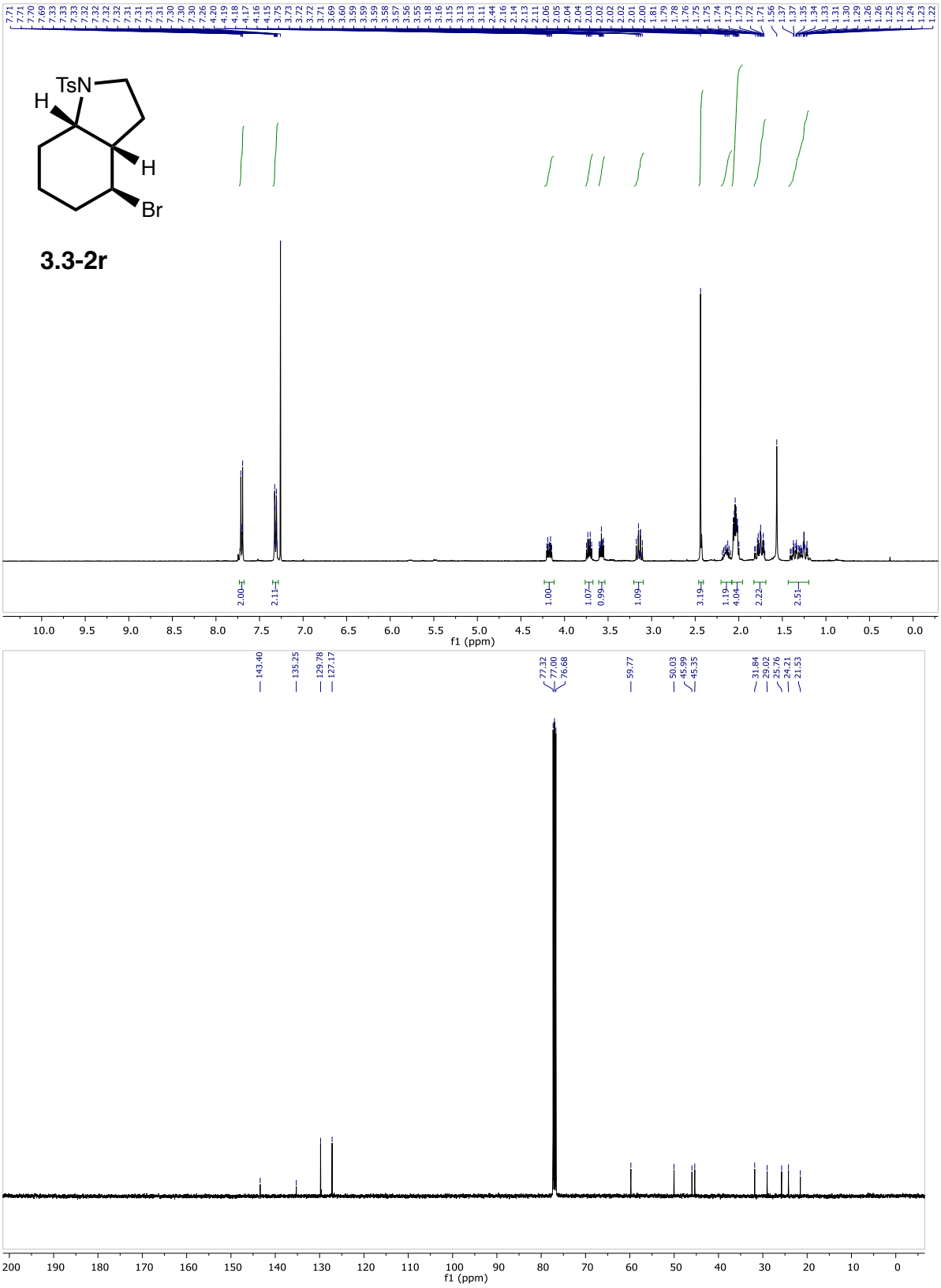

f1 (ppm)
f1 (ppm)

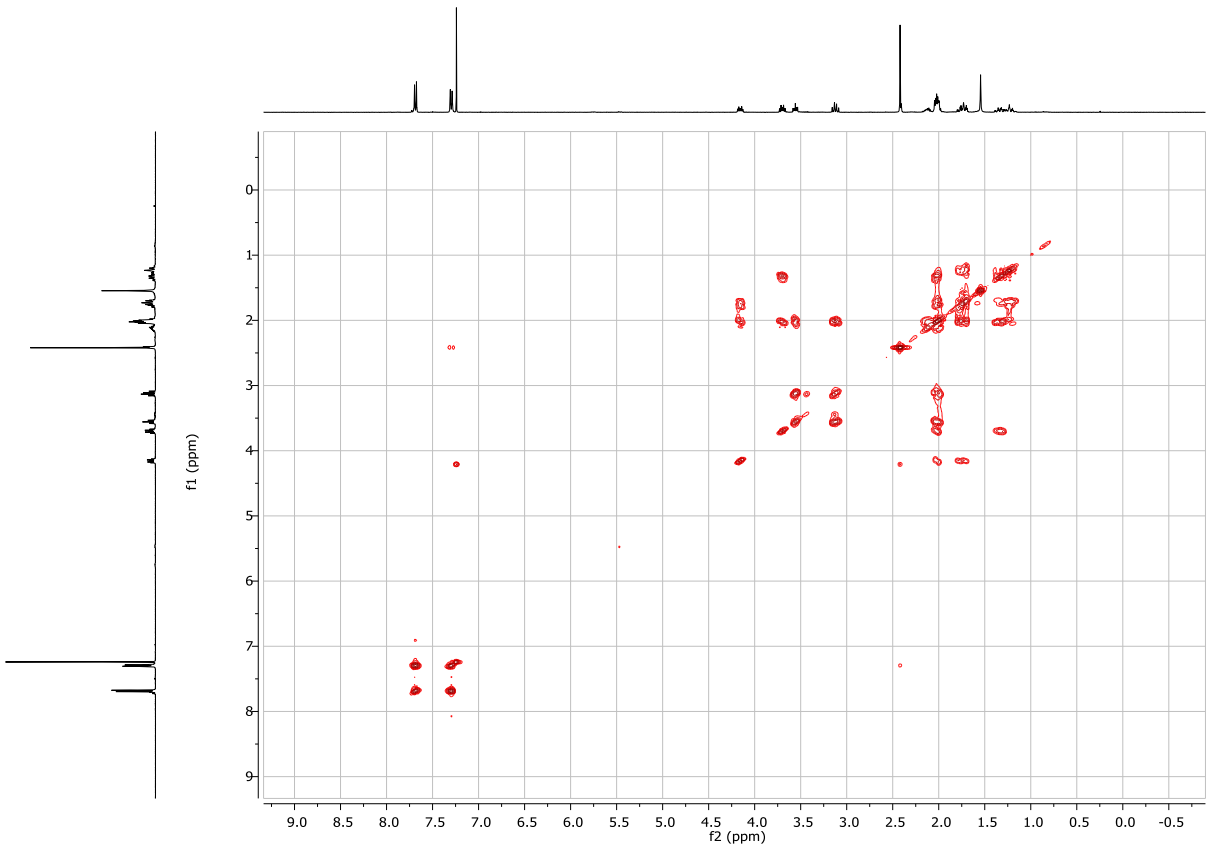

I
N
Ts
3.3-2p
f1 (ppm)

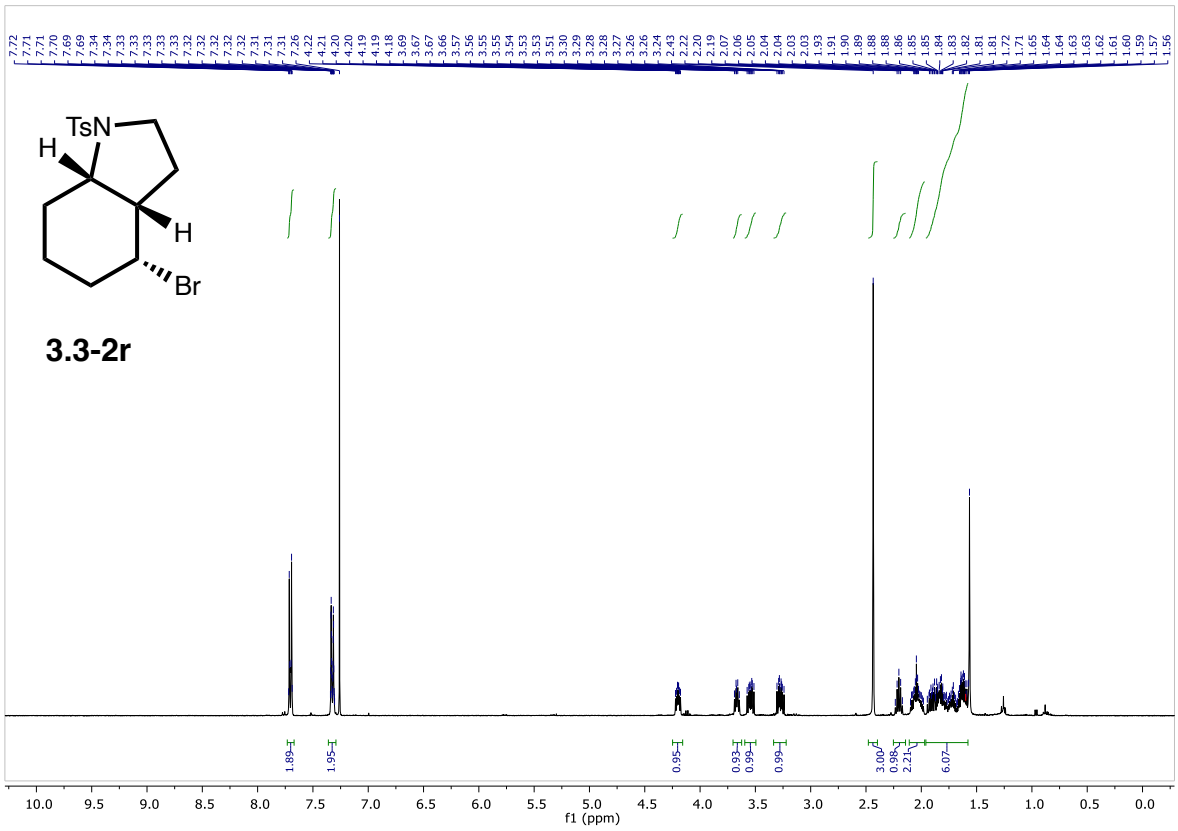

f1 (ppm)

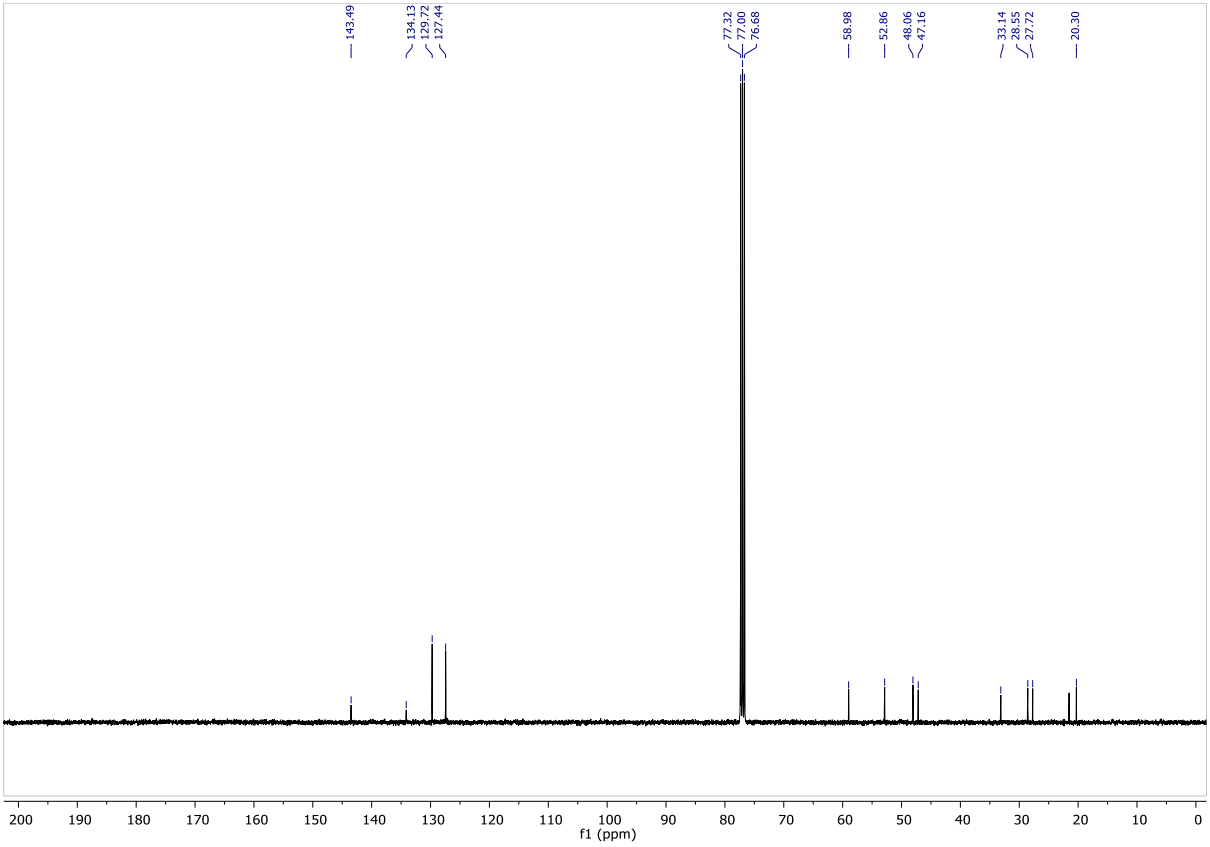

Me
I
N
Ts
3.3-2q
f1 (ppm)

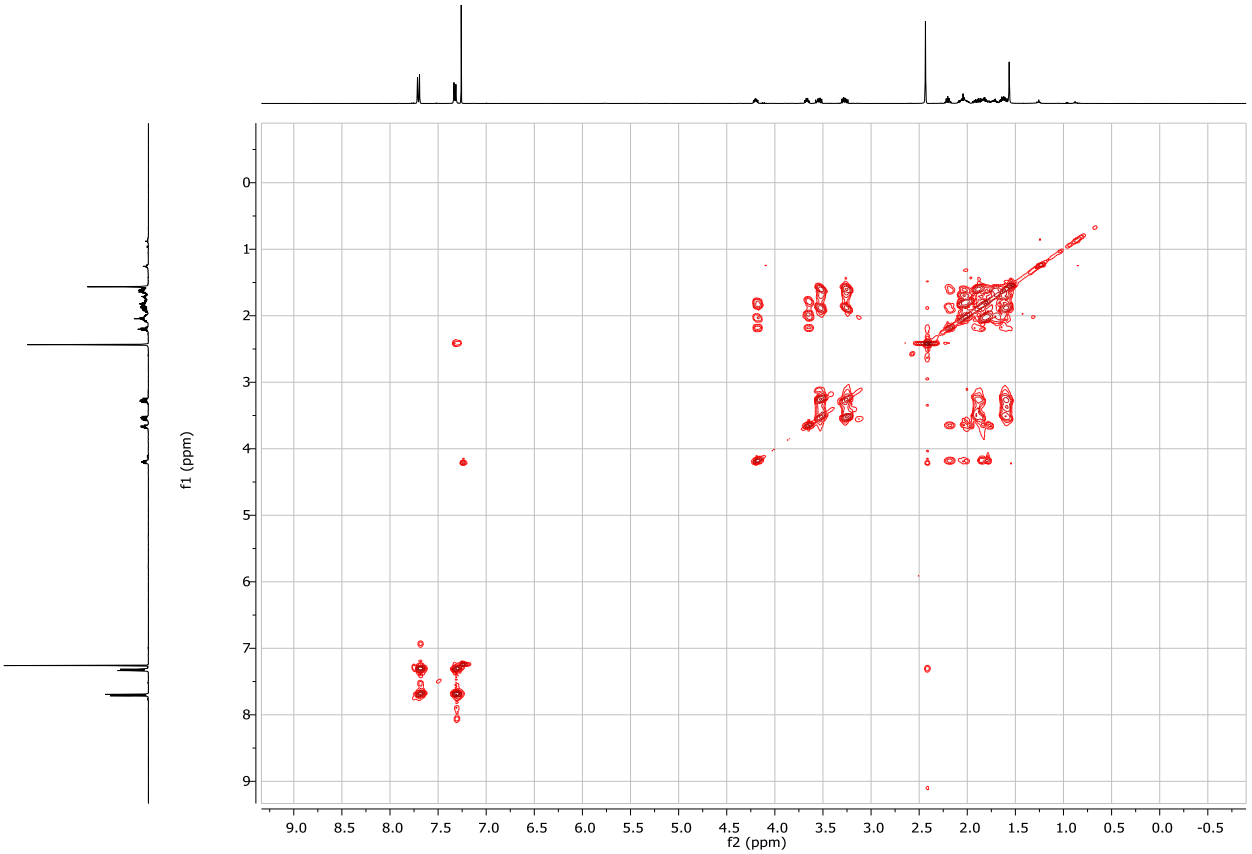

f1 (ppm)

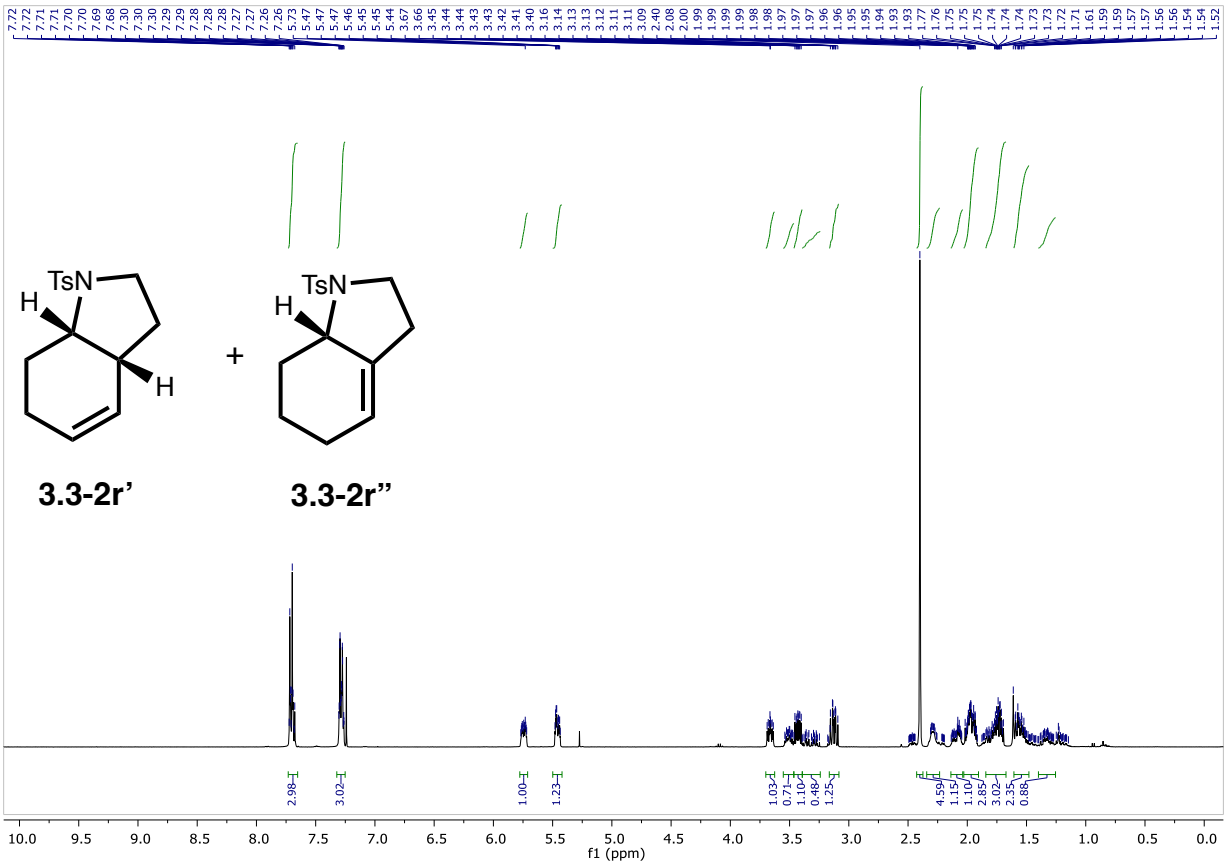

TsN
H
H
Br
3.3-2r
f1 (ppm)
f1 (ppm)

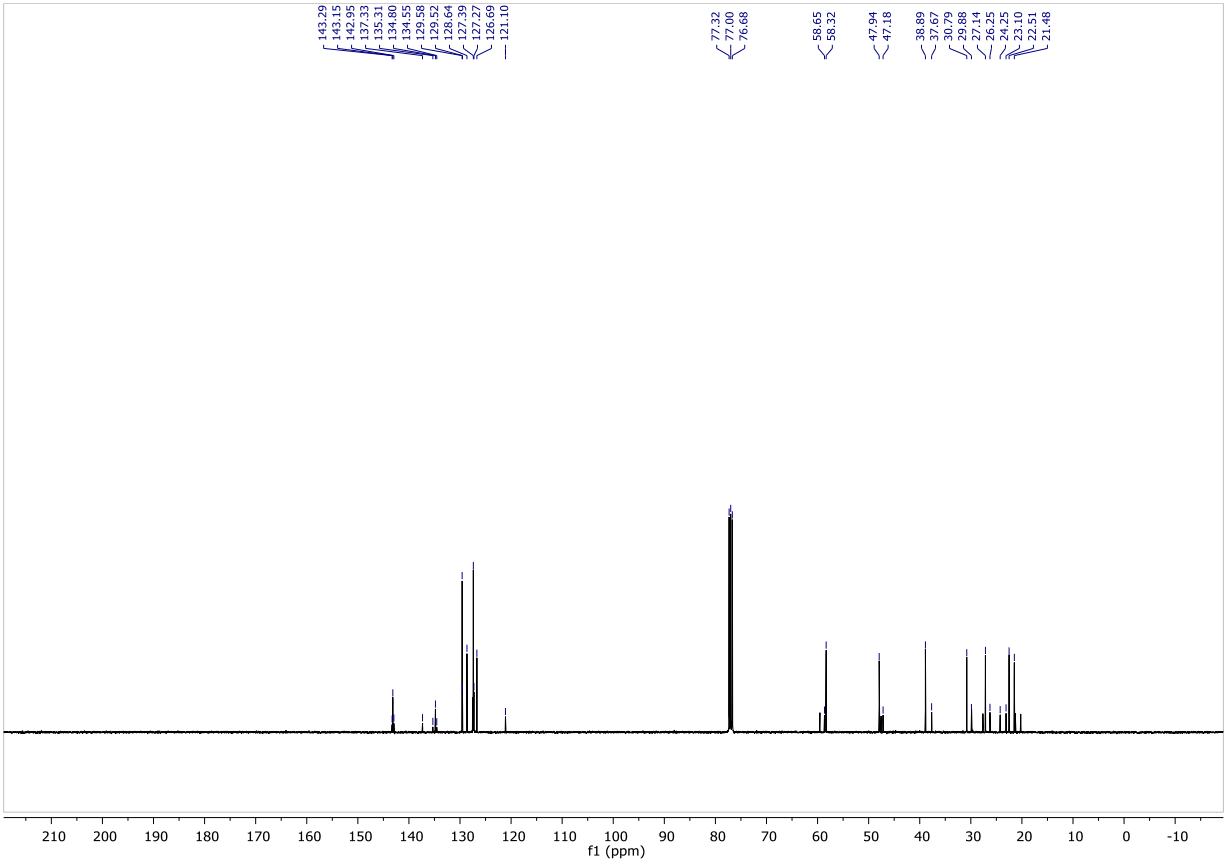

f1 (ppm)
f2 (ppm)
0
1
2
3
4
5
6
7
8
9
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

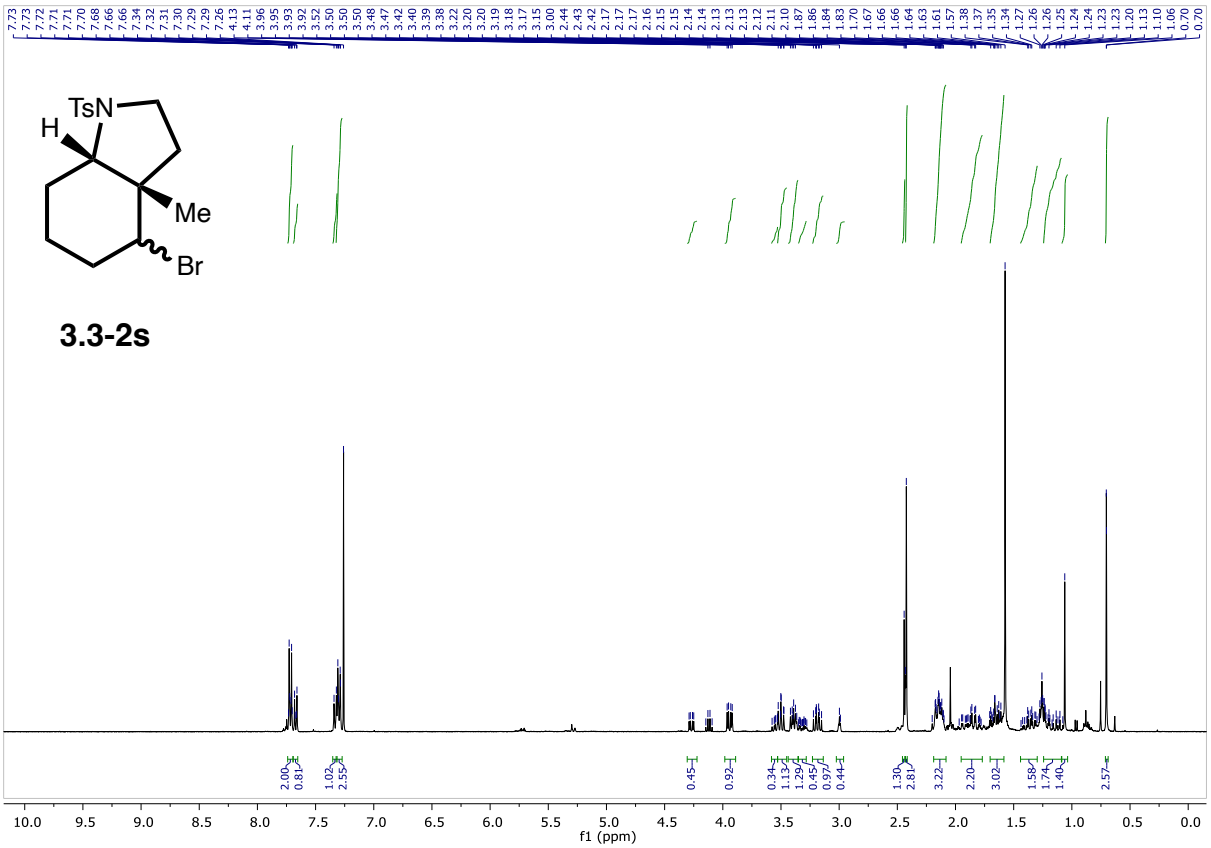

TsN
H
H
Br
3.3-2r
f1 (ppm)

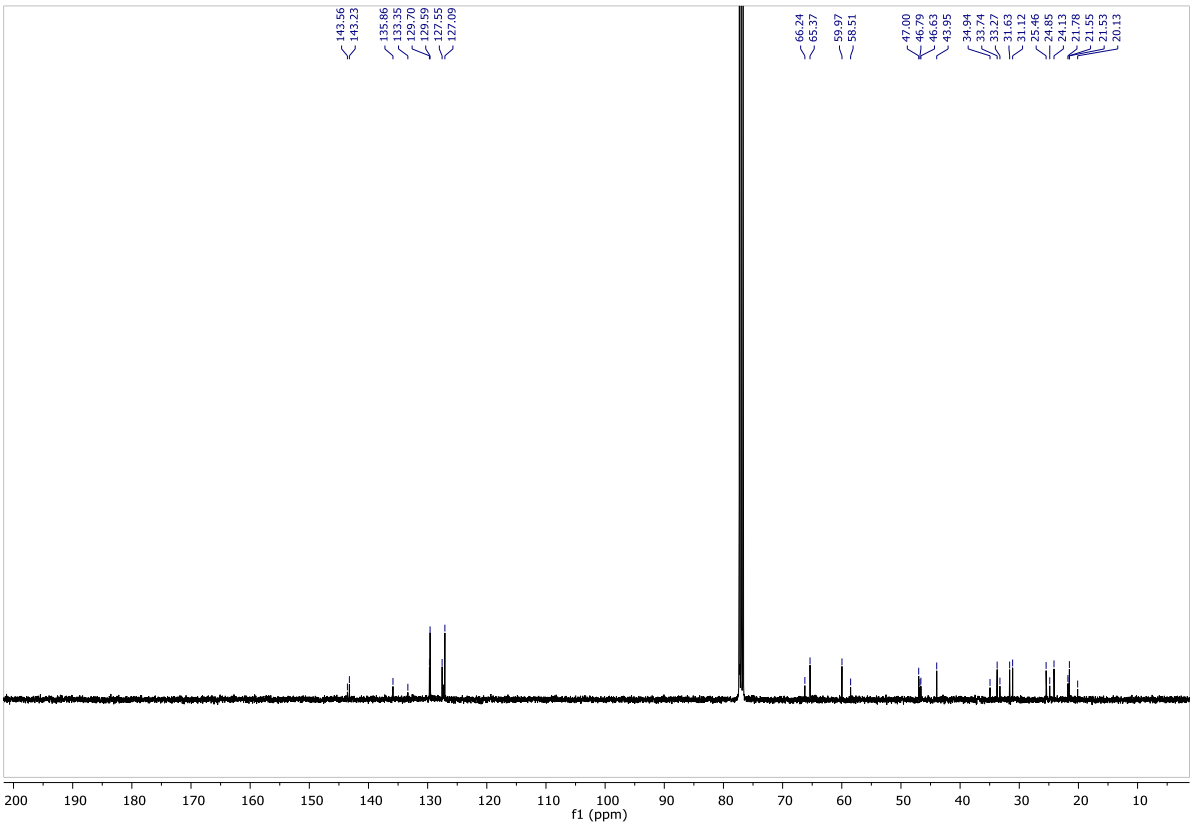

143.49
134.13
129.72
127.44
77.32
77.00
76.68
58.98
52.86
48.06
47.16
33.14
28.55
27.72
20.30
f1 (ppm)

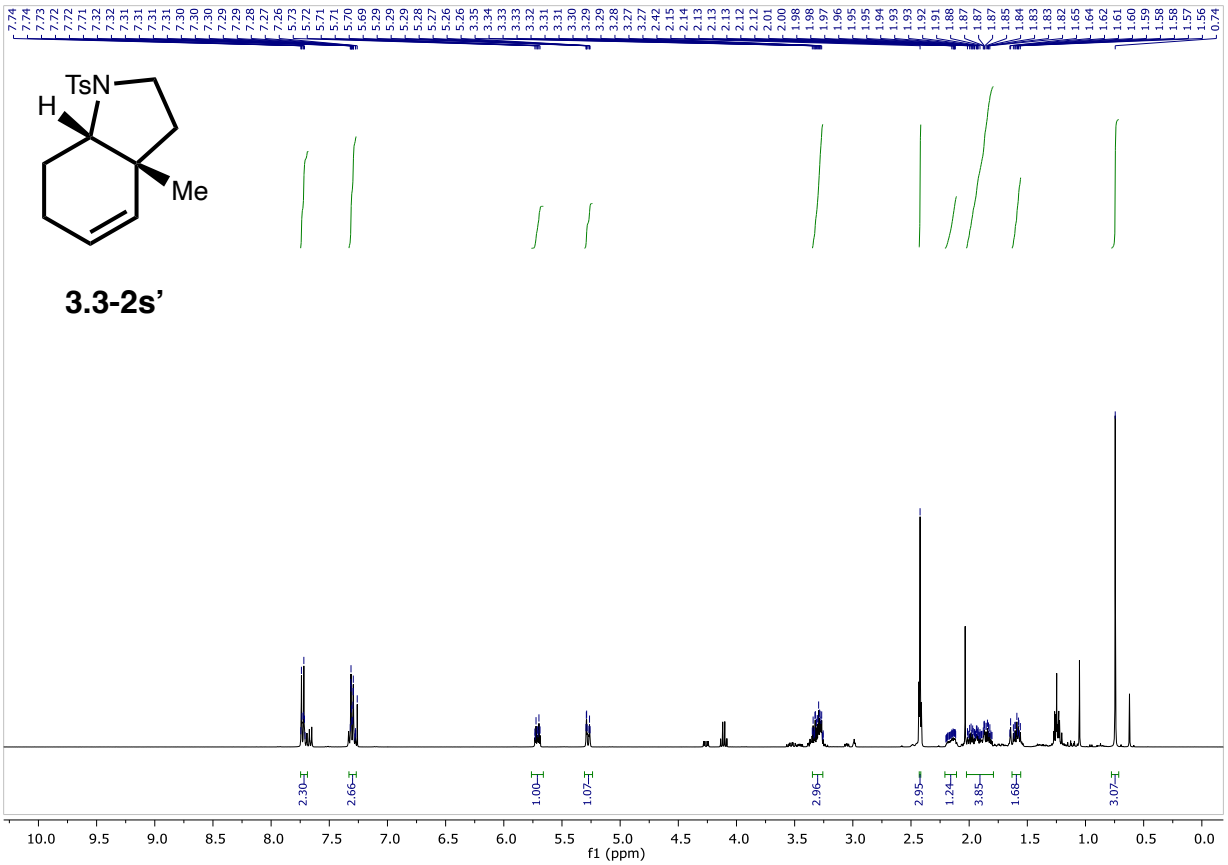

f1 (ppm)
f2 (ppm)
0
1
2
3
4
5
6
7
8
9
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


TsN
H
H
+
TsN
H
3.3-2r'
3.3-2r''
f1 (ppm)

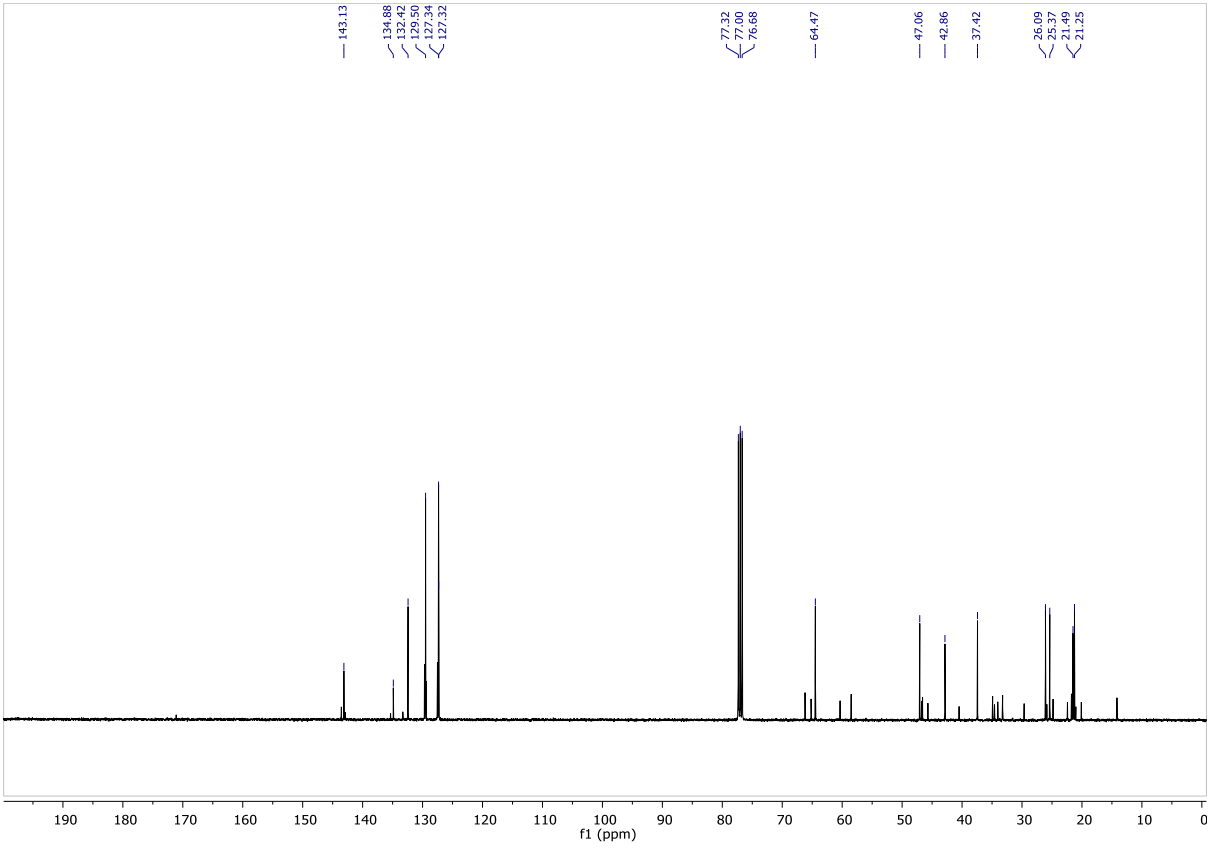

f1 (ppm)

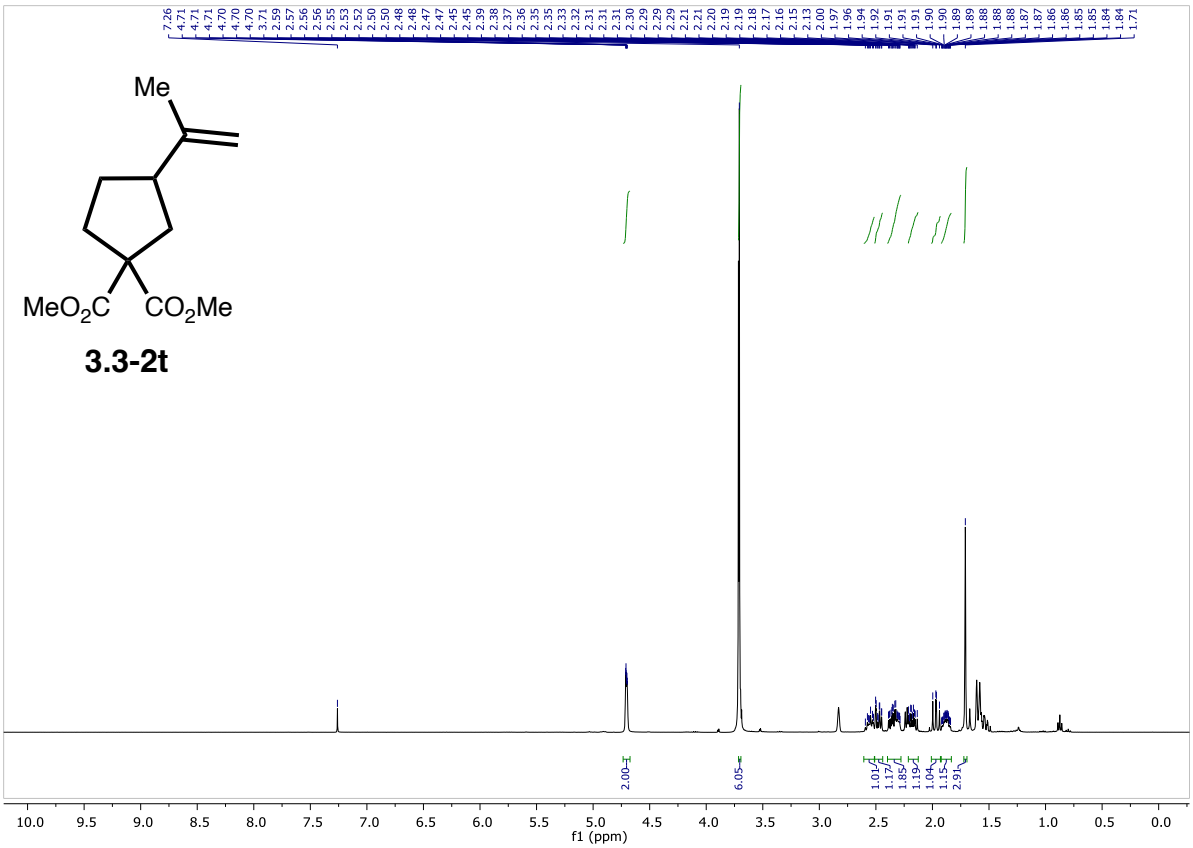

TsN
H
Me
Br
3.3-2s
f1 (ppm)

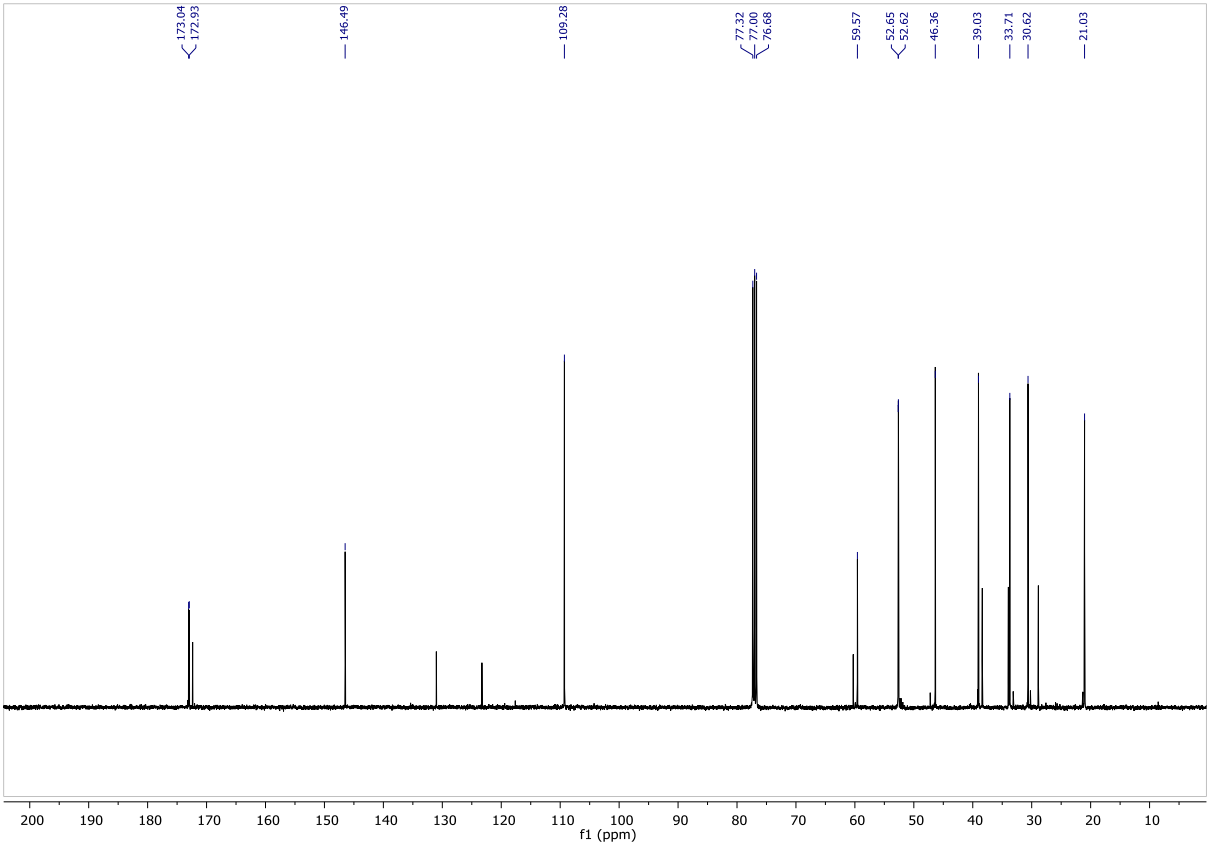

f1 (ppm)

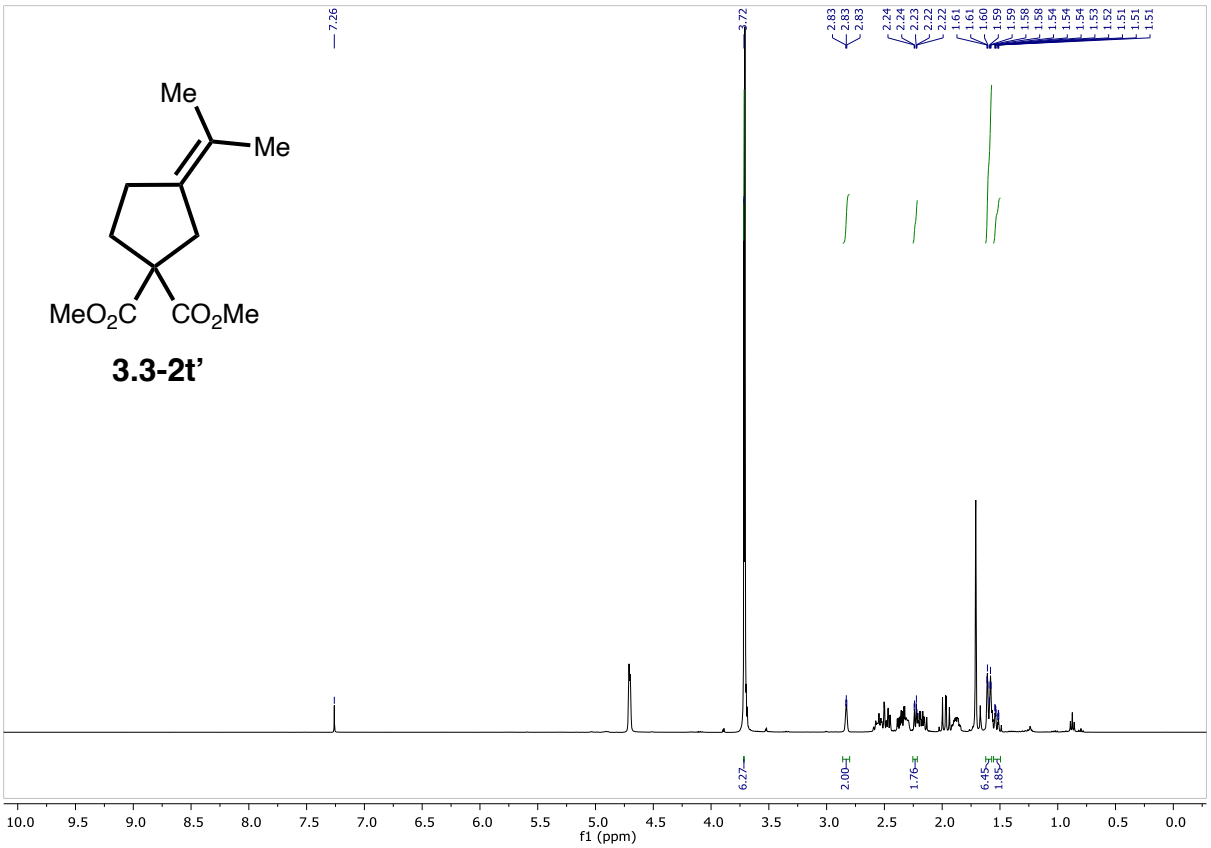


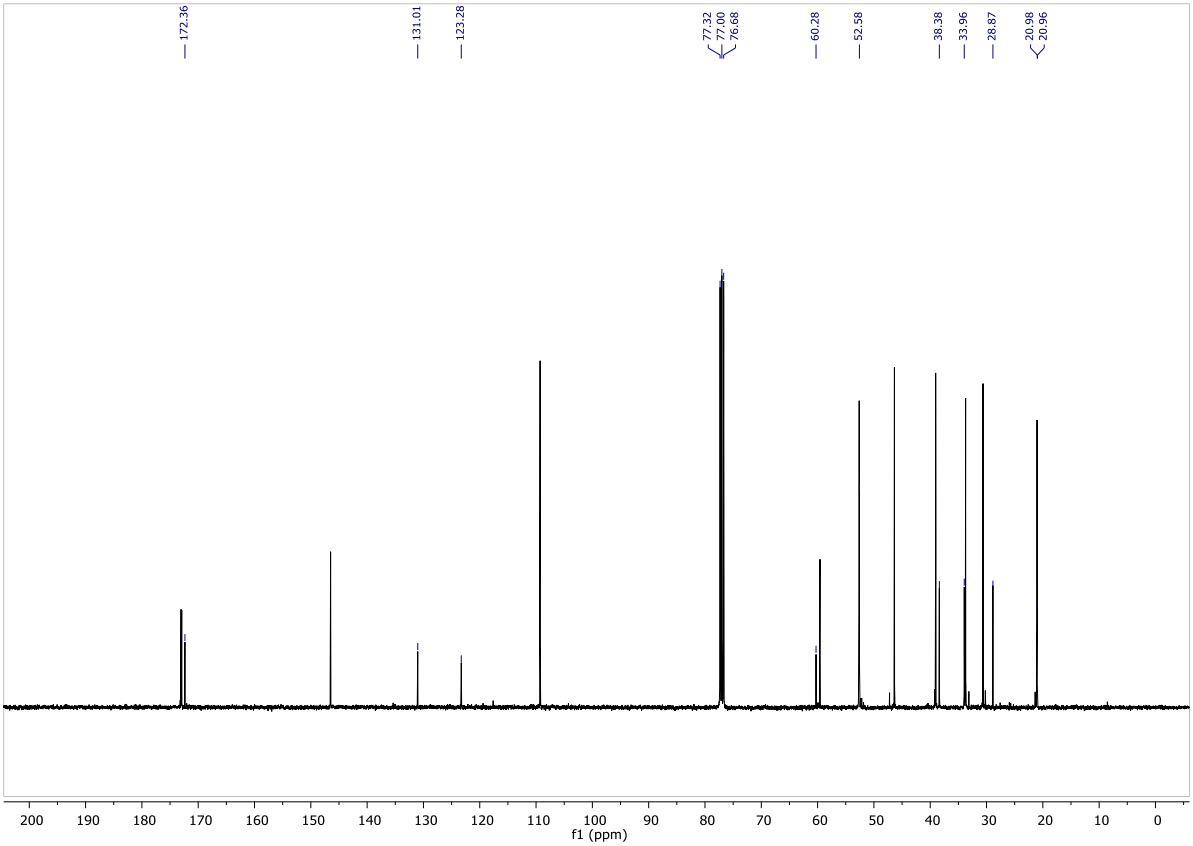
3.3-2s'

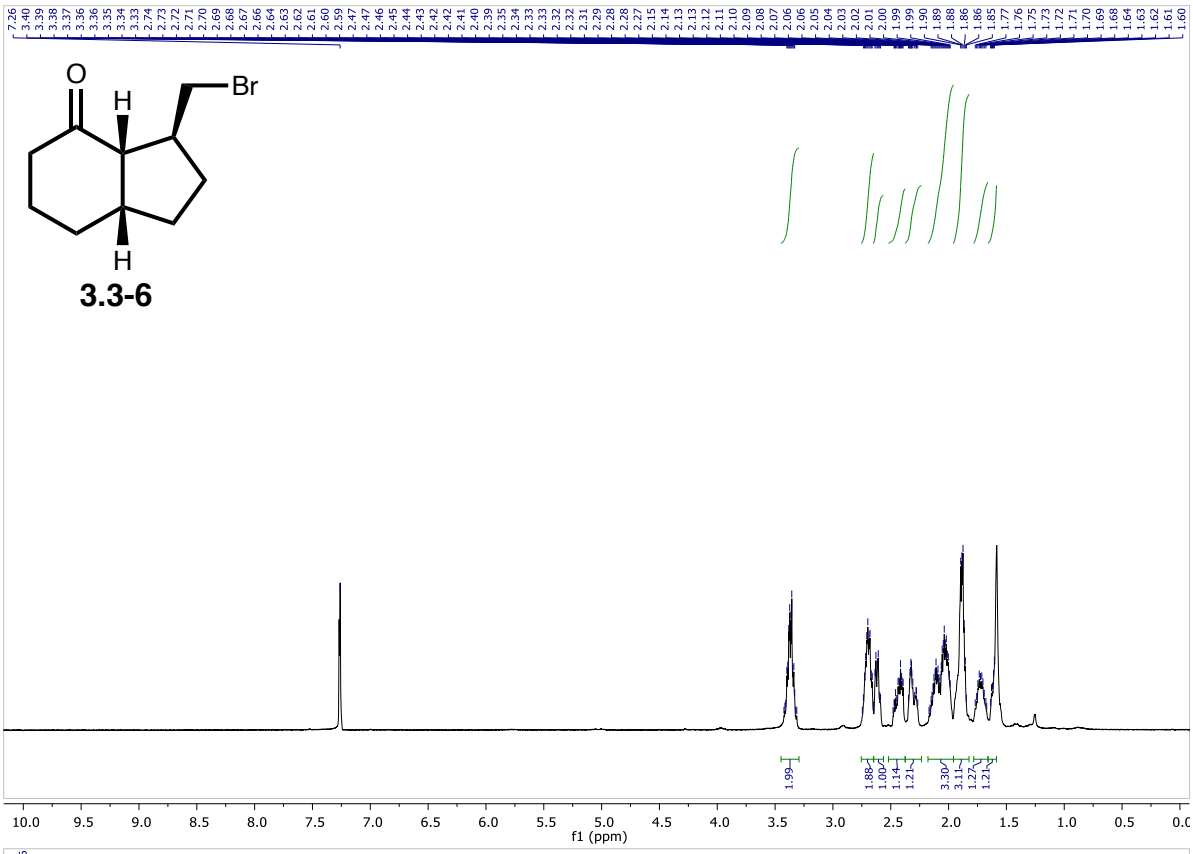


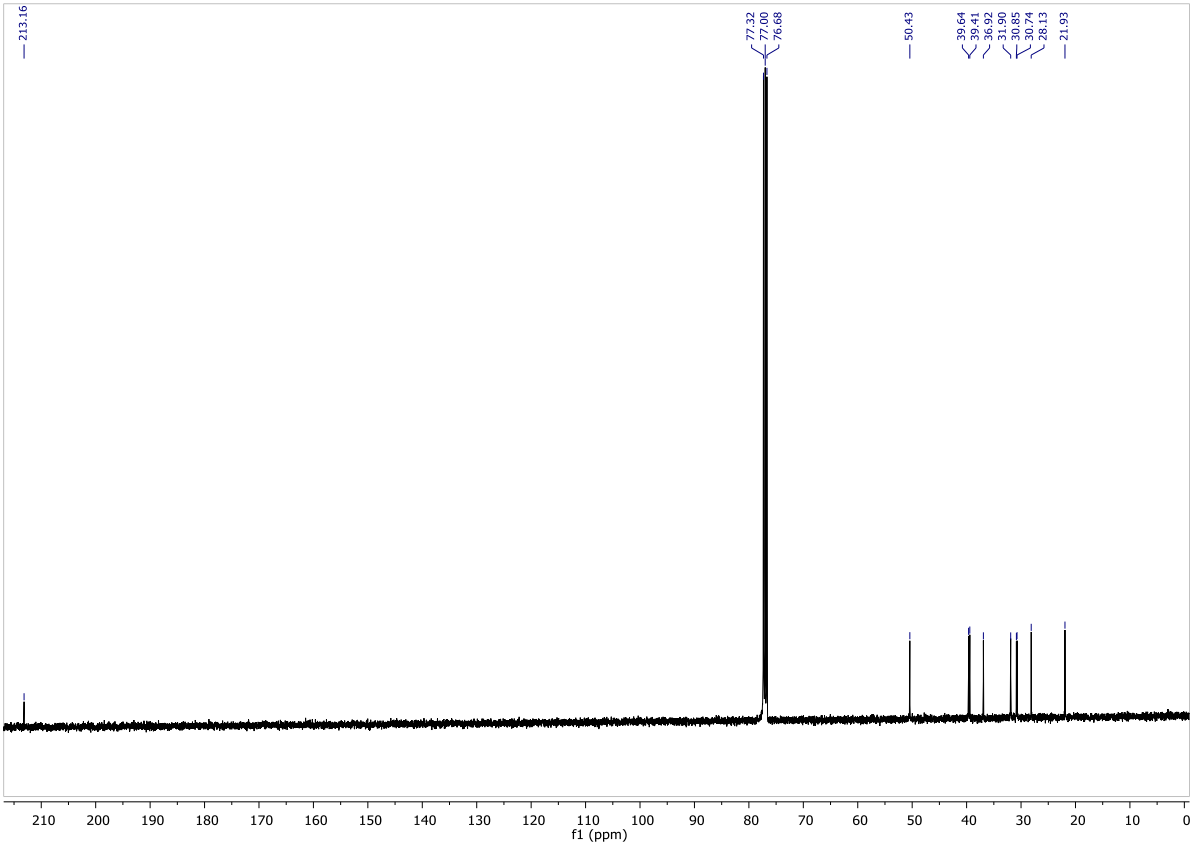

Me
MeO2C
CO2Me
3.3-2t
f1 (ppm)

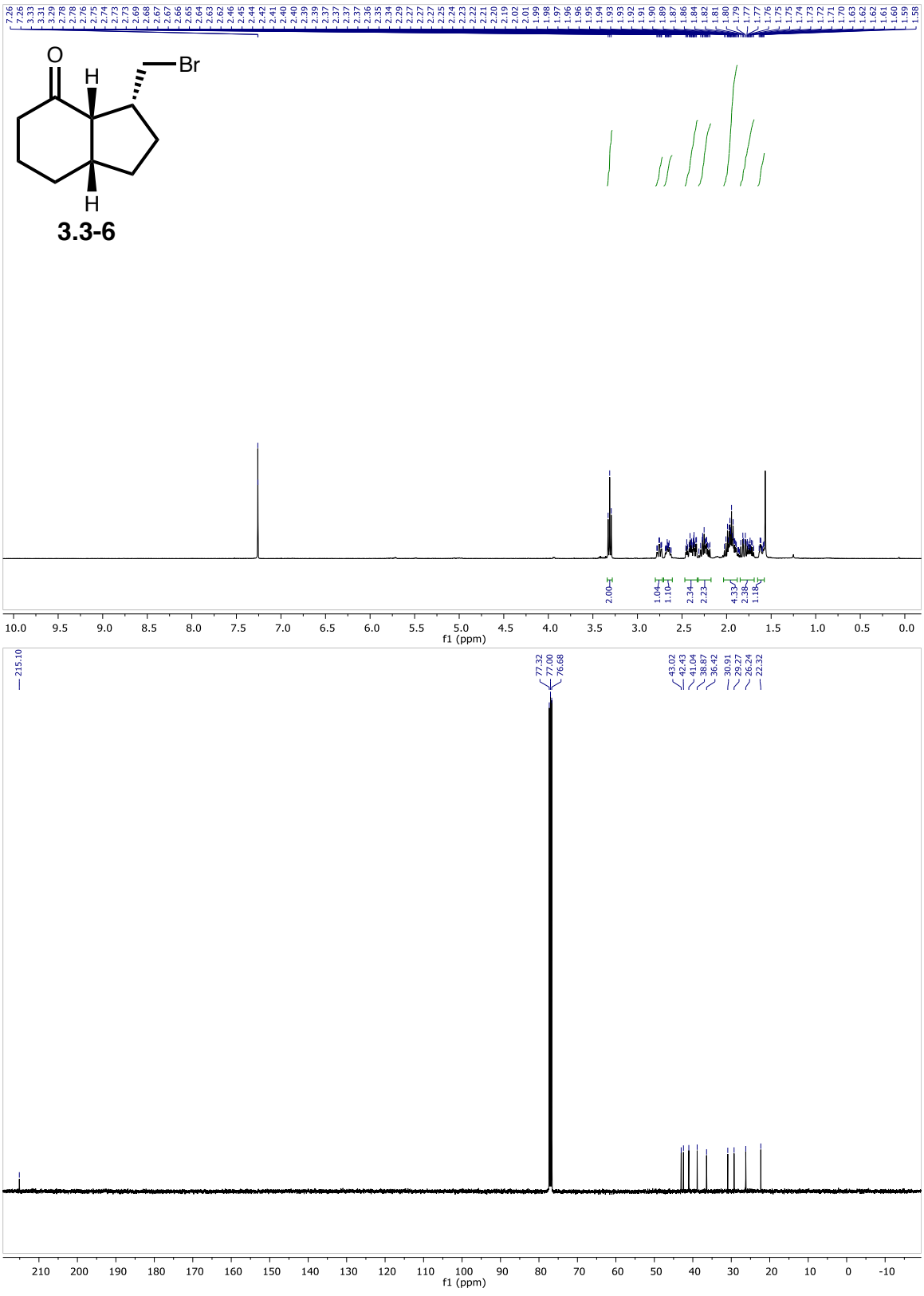

f1 (ppm)


Me
Me
MeO2C
CO2Me
3.3-2t'
7.26
3.72
2.83
2.24
2.23
2.22
1.61
1.60
1.59
1.58
1.54
1.53
1.52
1.51
6.27
2.00
1.76
6.45
1.85
f1 (ppm)

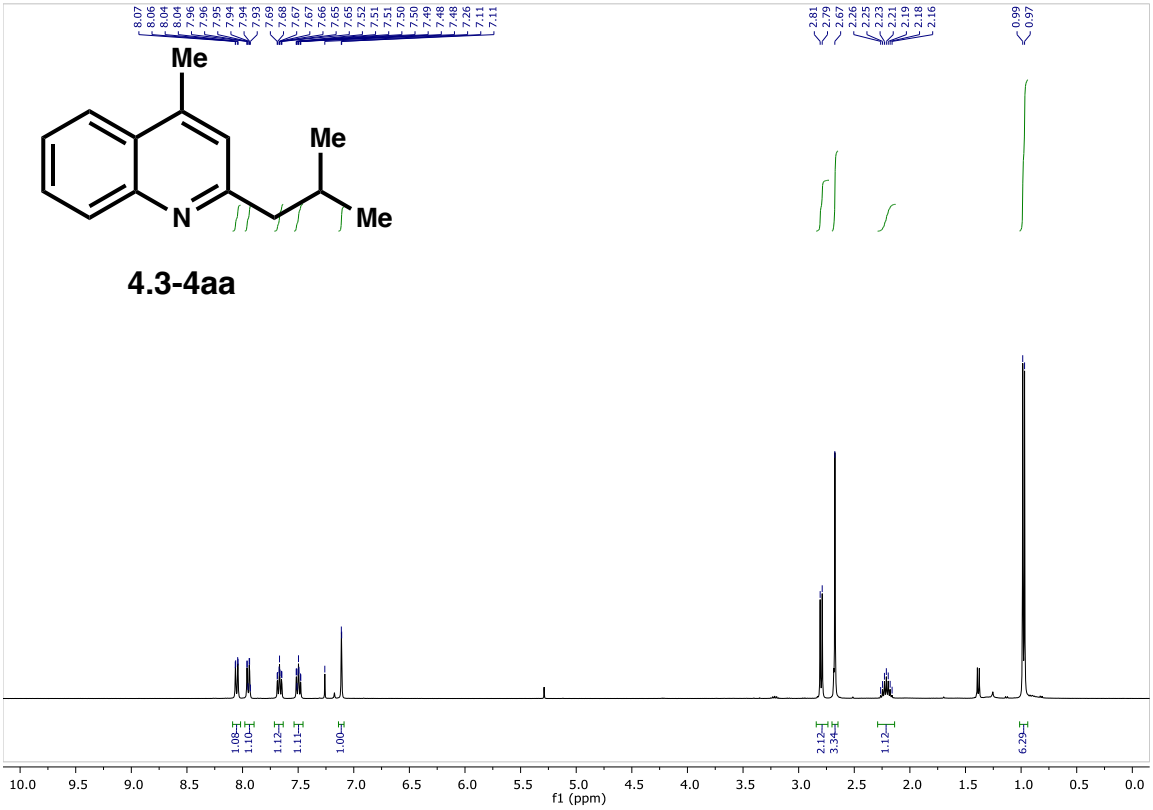

172.36
131.01
123.28
77.32
77.00
76.68
60.28
52.58
38.38
33.96
28.87
20.98
20.96
f1 (ppm)

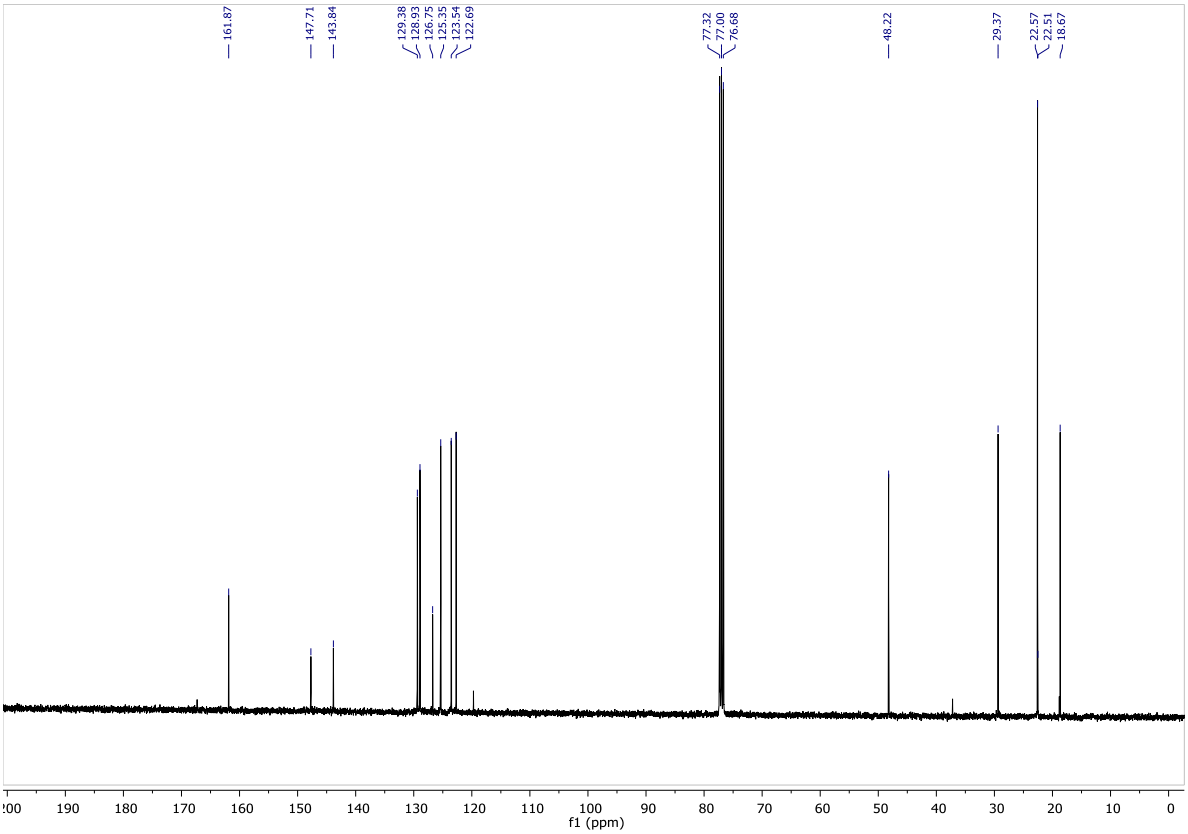

O
H
Br
H
3.3-6
f1 (ppm)

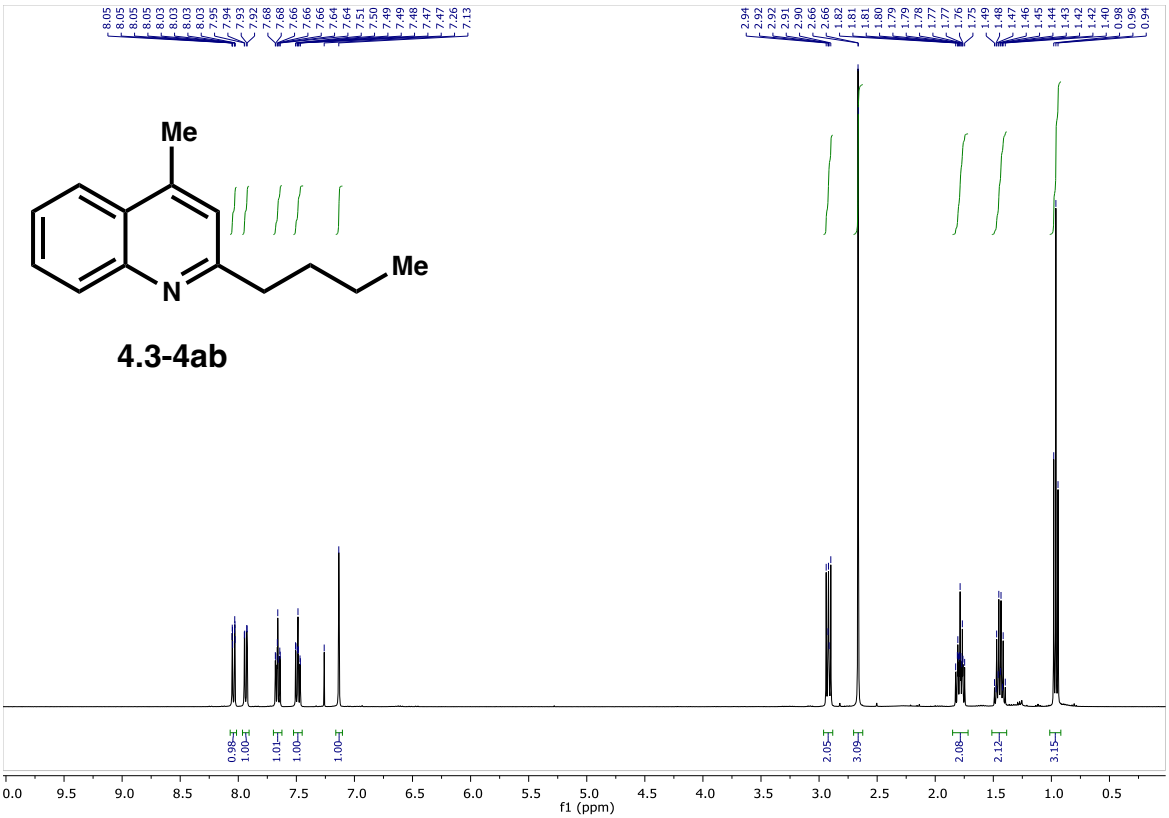

213.16
77.32
77.00
76.68
50.43
39.64
39.41
36.92
31.90
30.85
30.74
28.13
21.93
f1 (ppm)

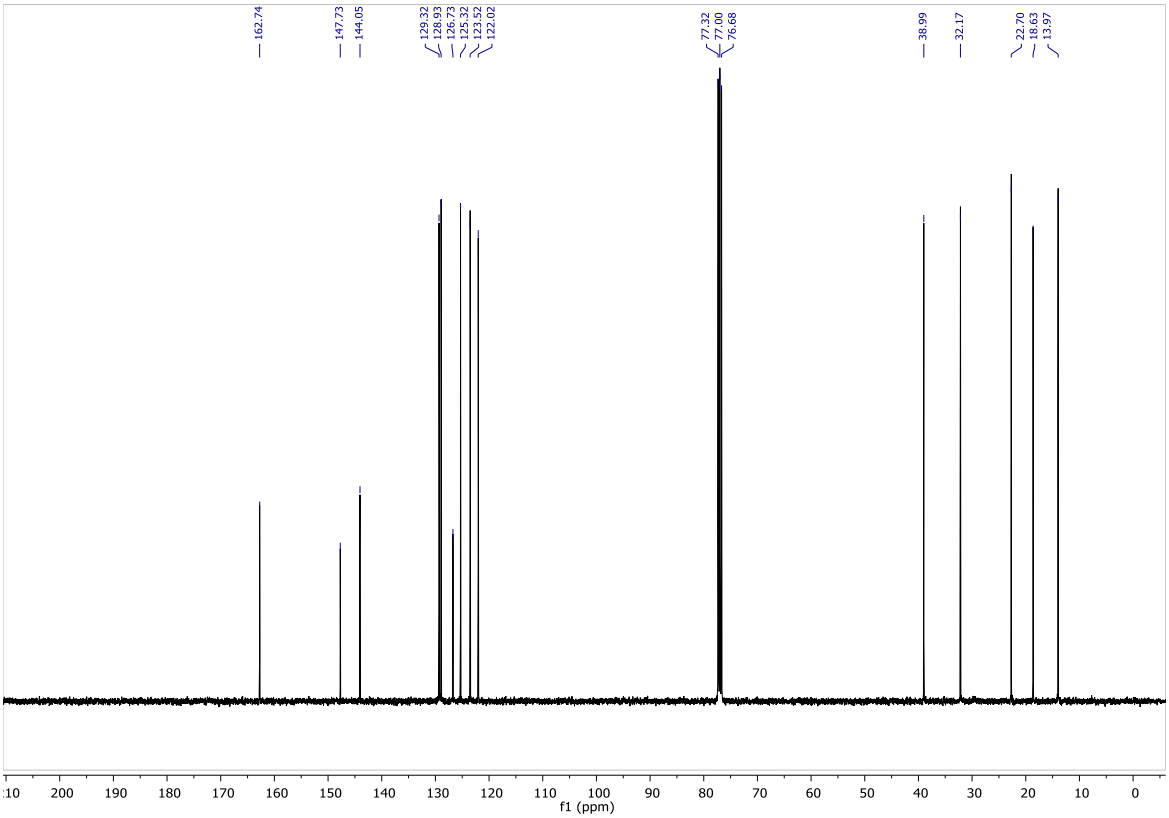

O
H
Br
H
3.3-6
f1 (ppm)
f1 (ppm)

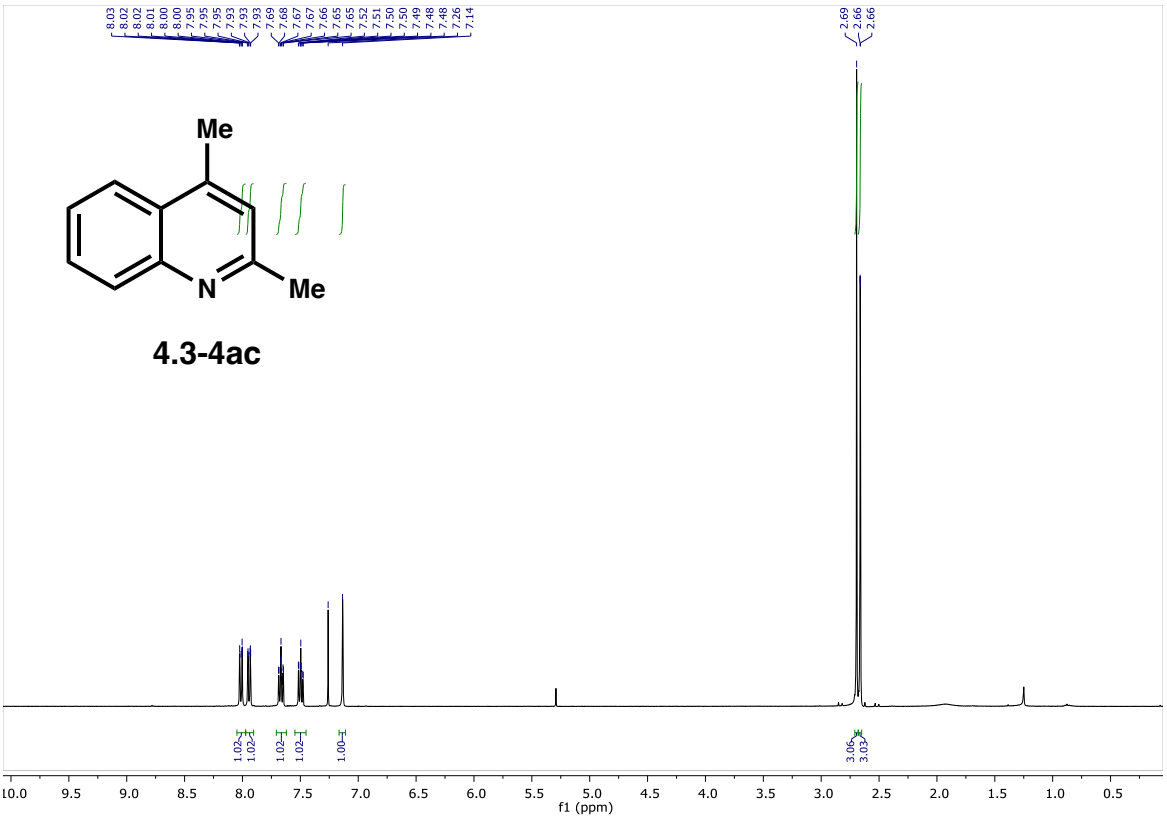
7.3- Spectral Data from Chapter 4: Alkylation and Reduction of Heteroarenes with Alcohols using Photoredox Catalyzed Hydrogen Atom Transfer via Chlorine Radical Generation

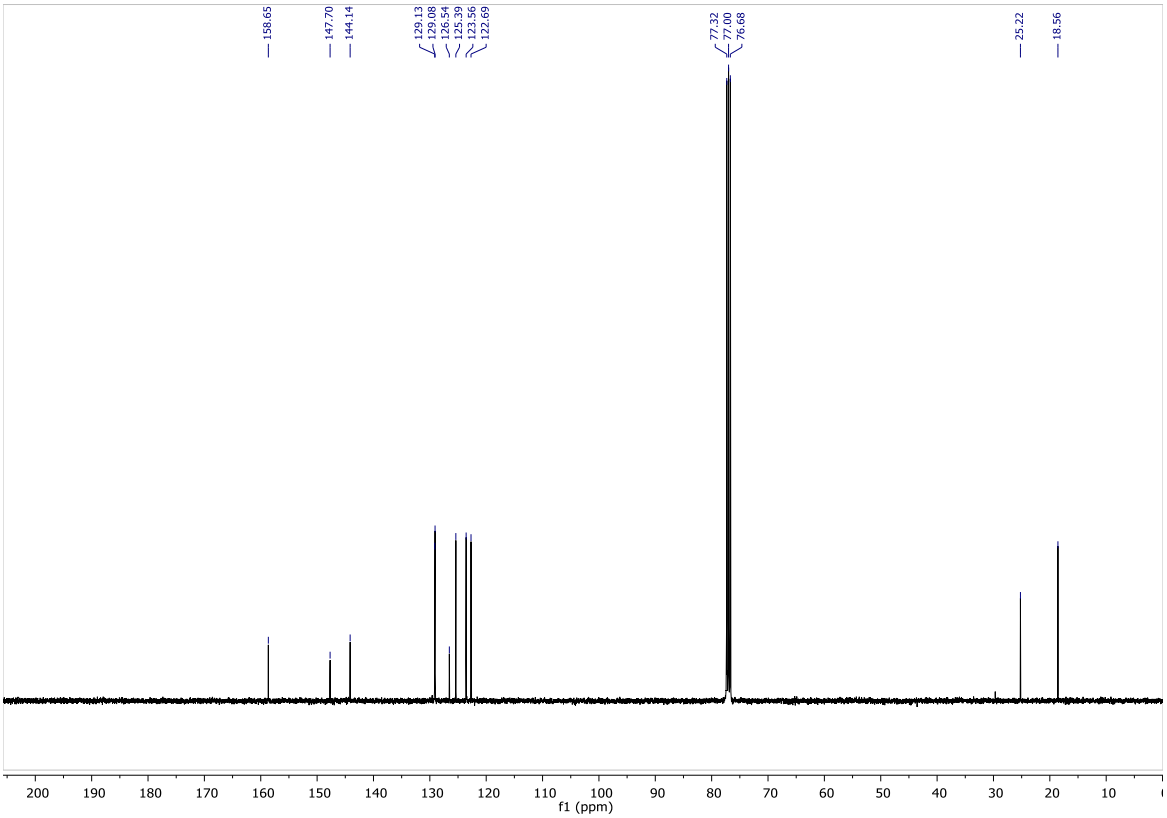


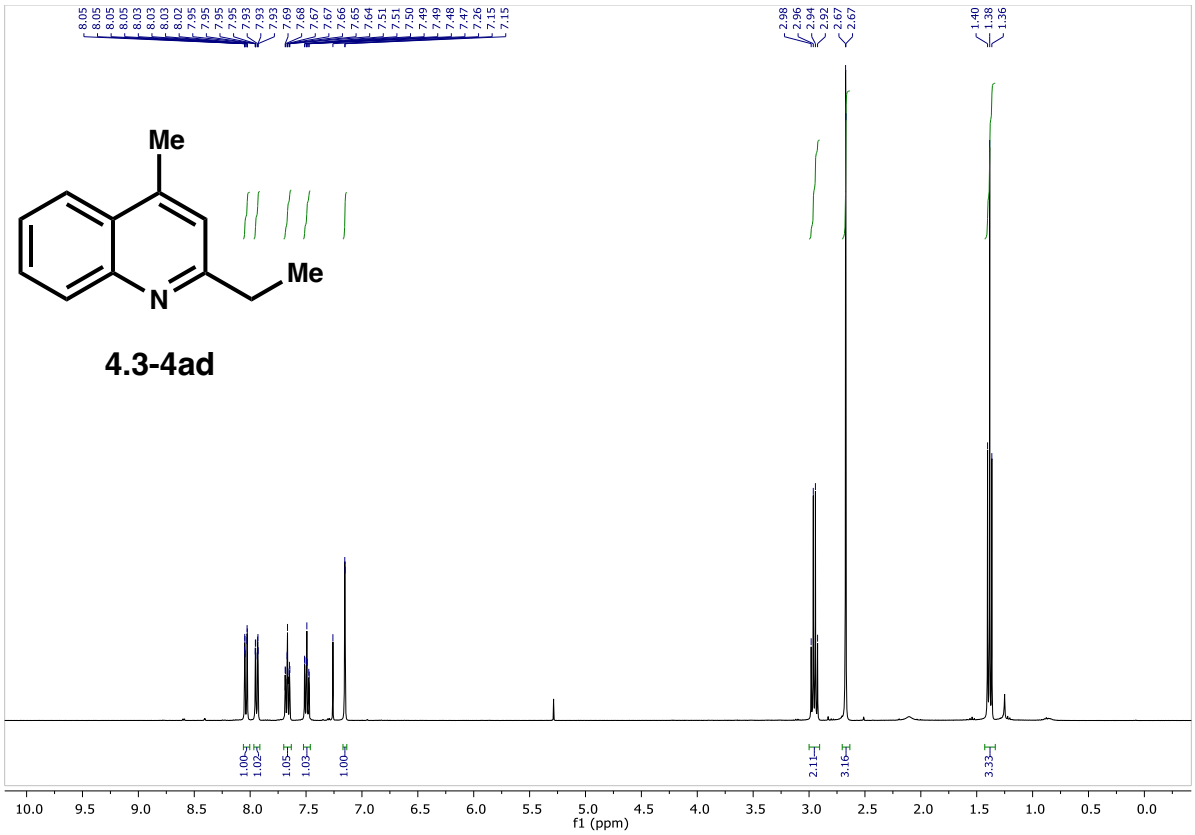


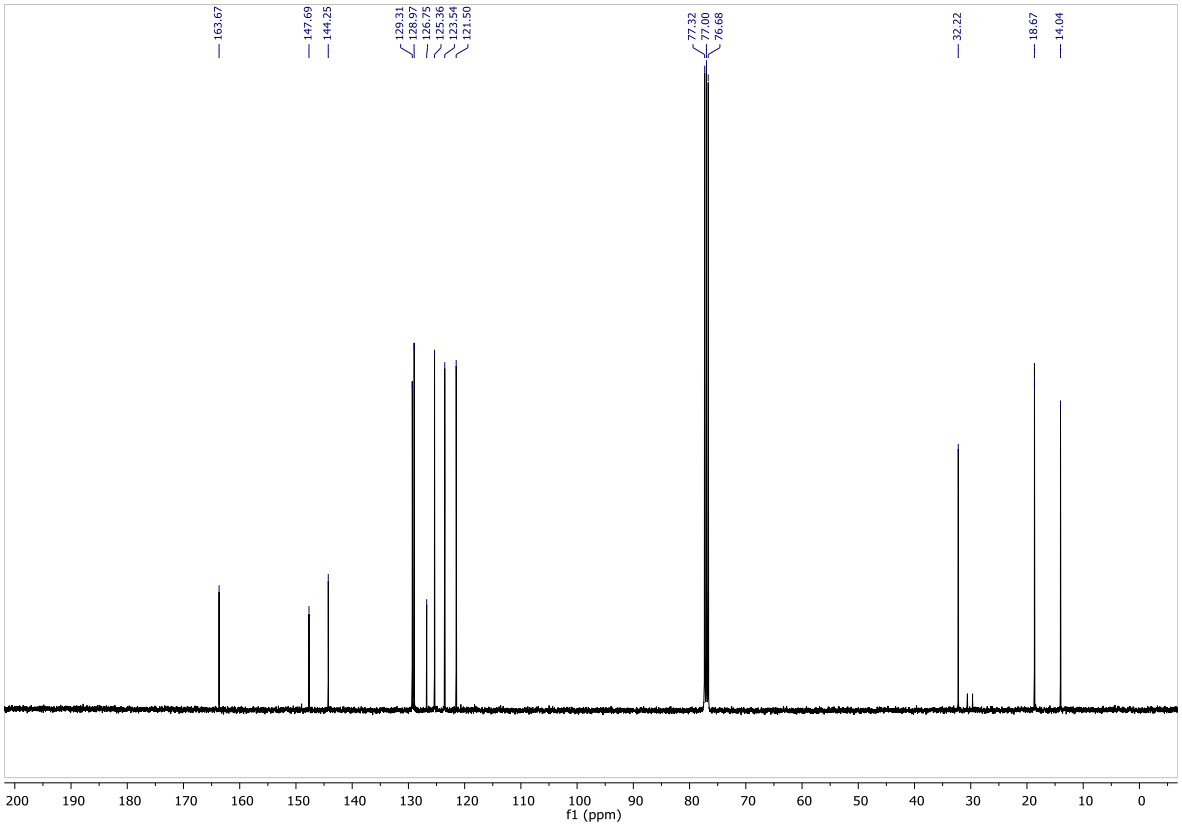

Me
Me
N
4.3-4ab
f1 (ppm)

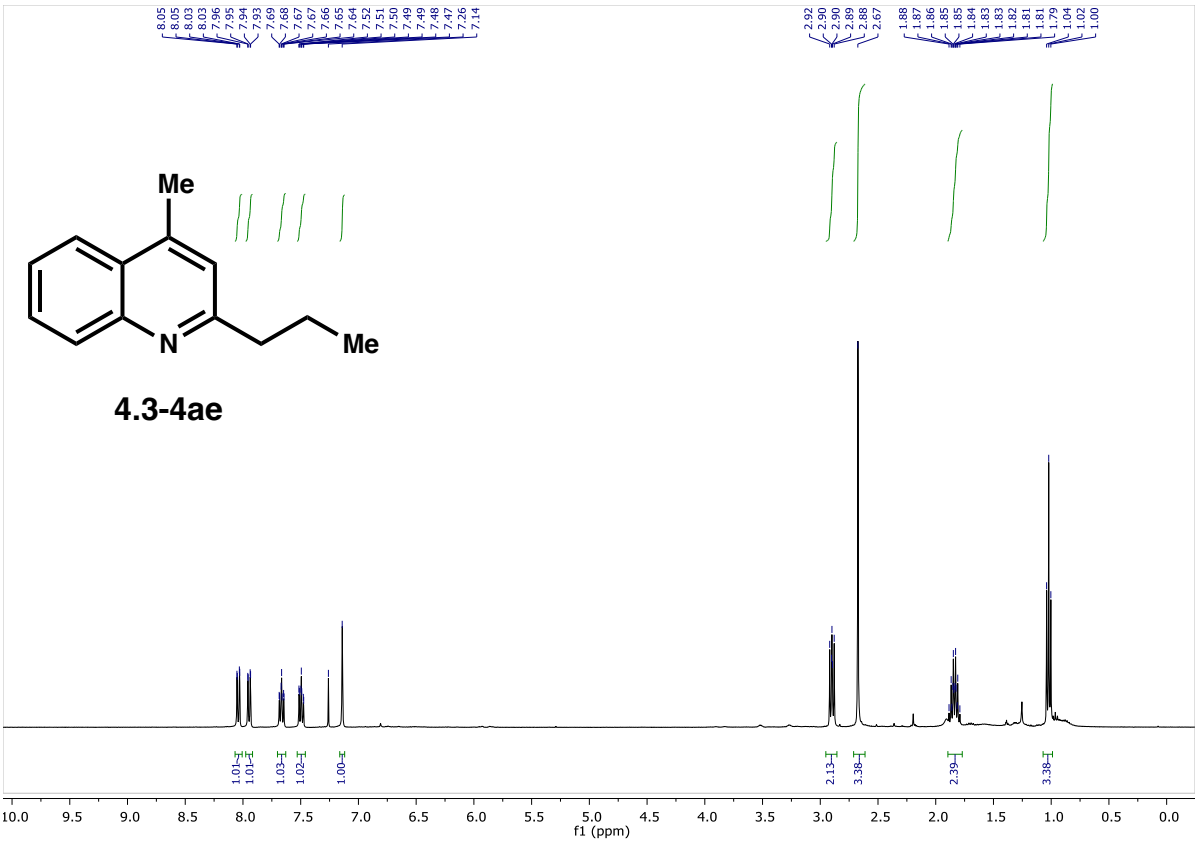

f1 (ppm)

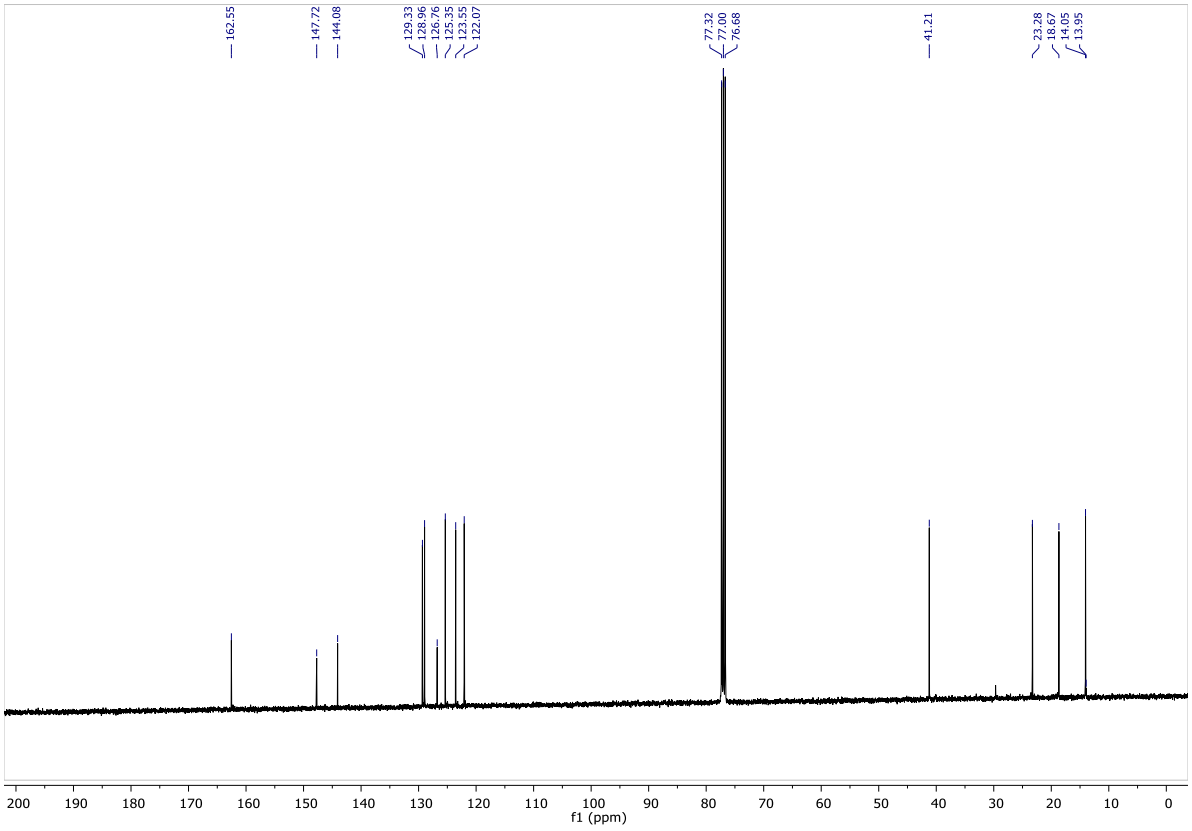

Me
N
Me
4.3-4ac
f1 (ppm)

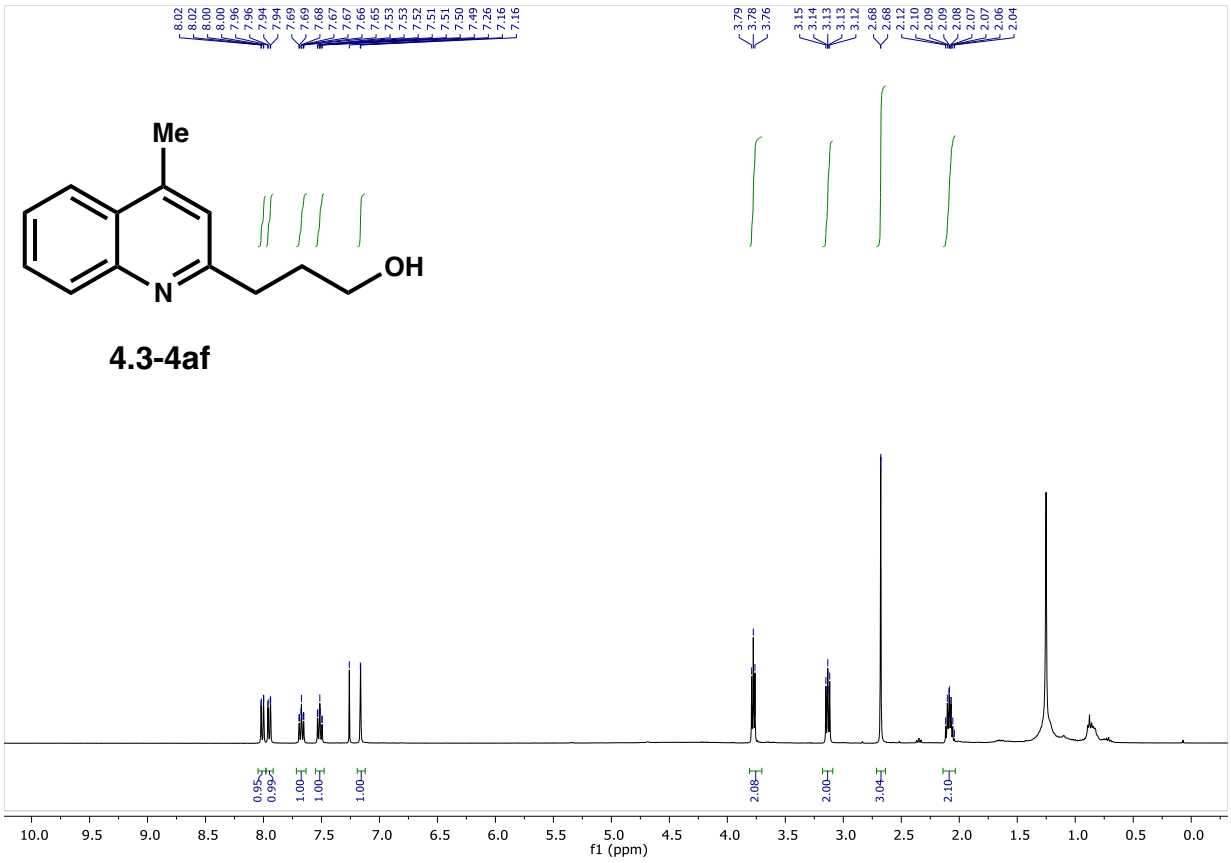

f1 (ppm)

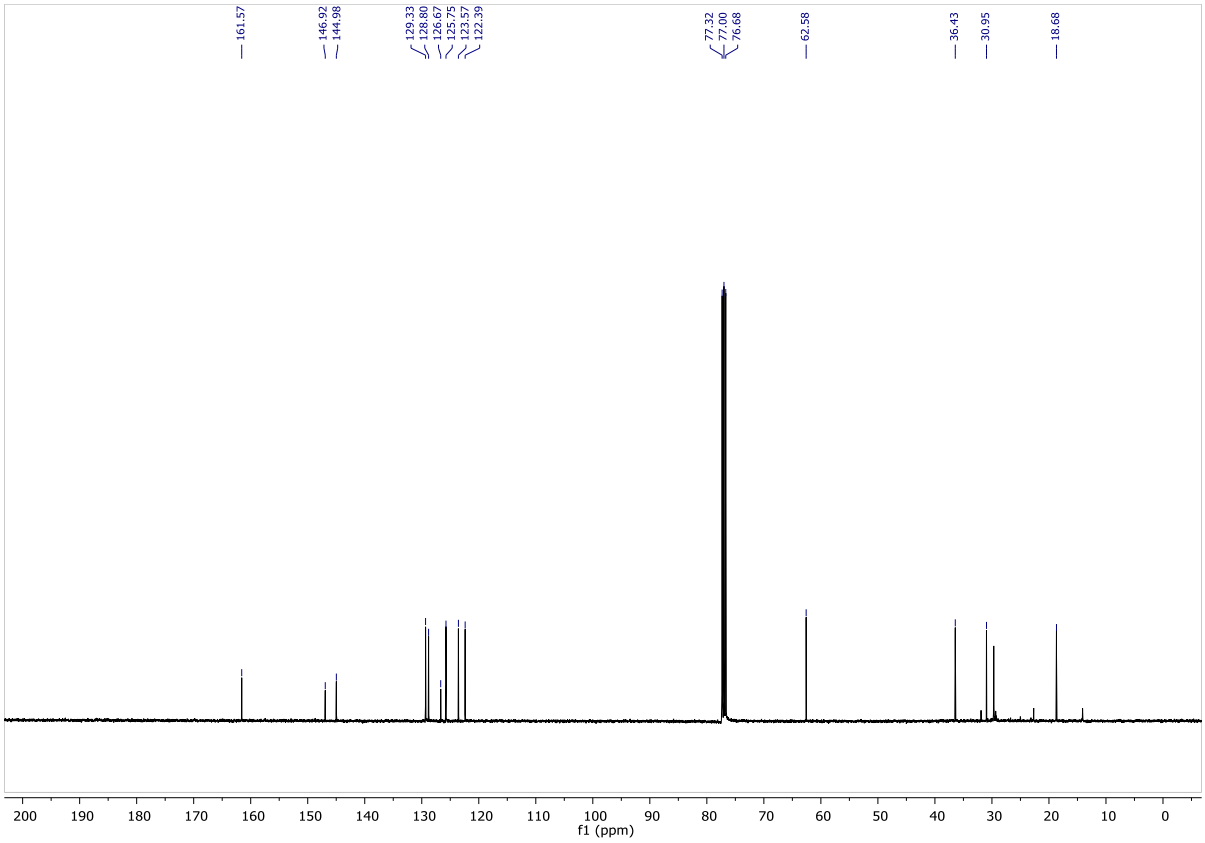

Me
Me
N
4.3-4ad
f1 (ppm)

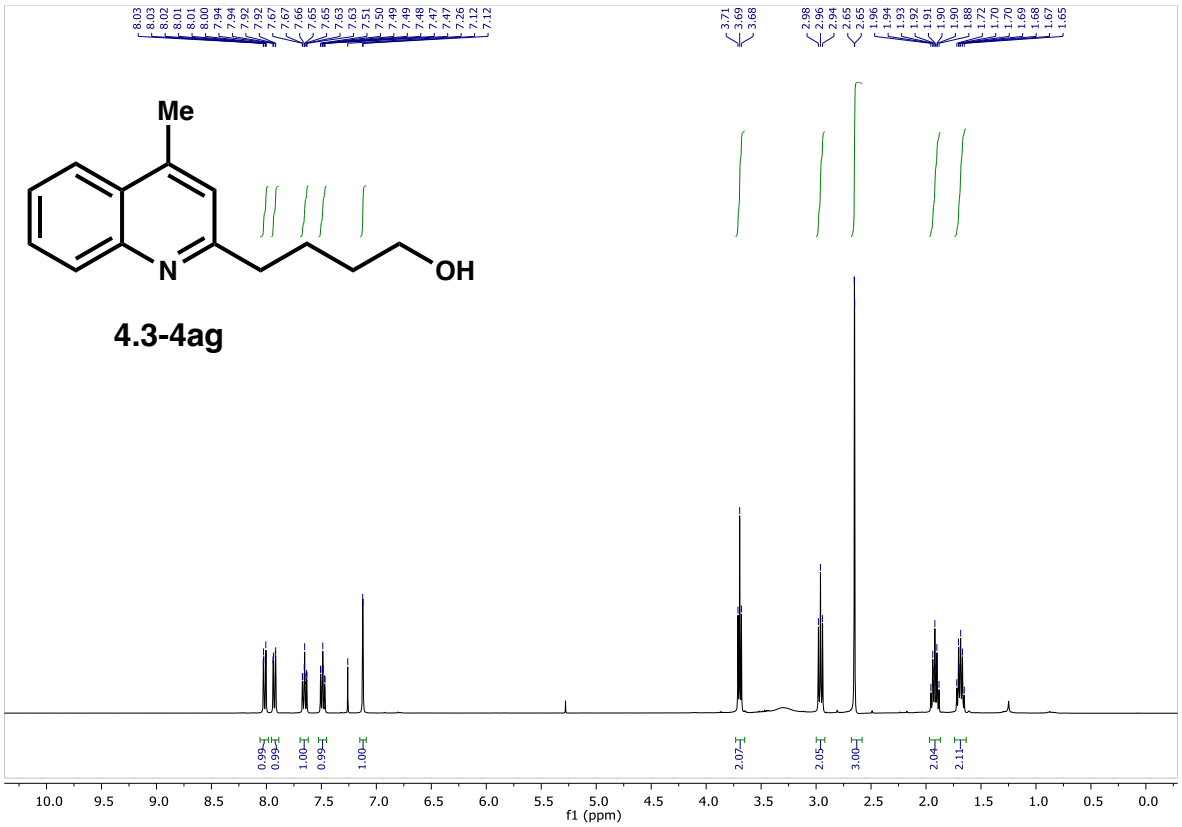

f1 (ppm)

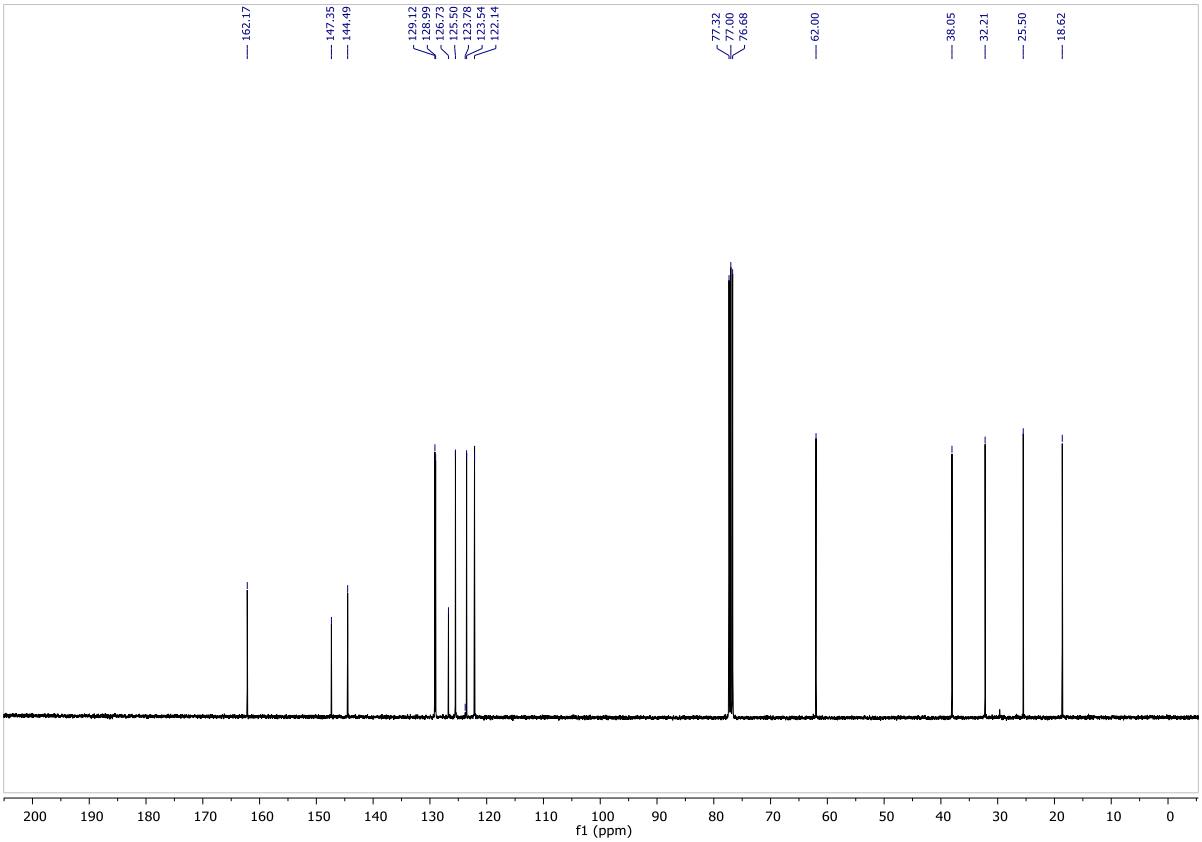

Me
N
Me
4.3-4ae
f1 (ppm)

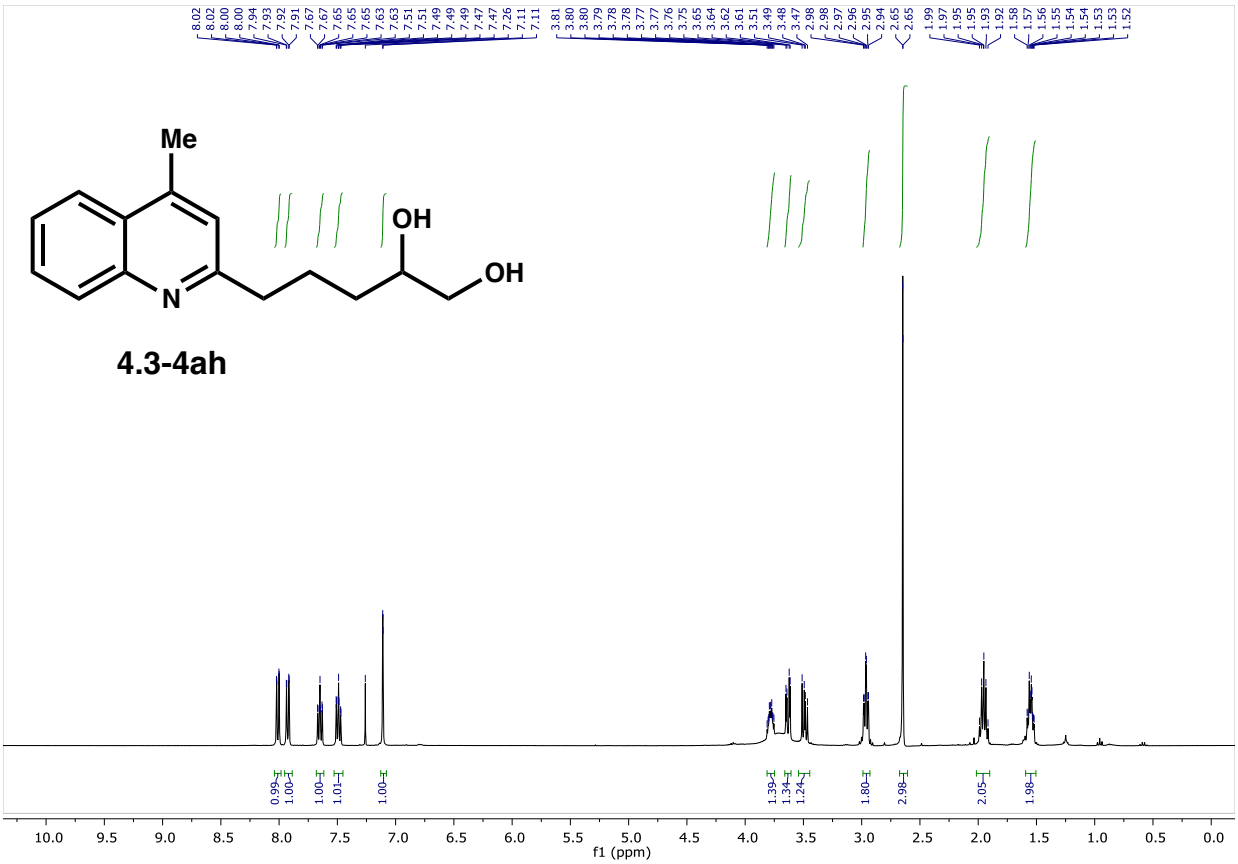

f1 (ppm)

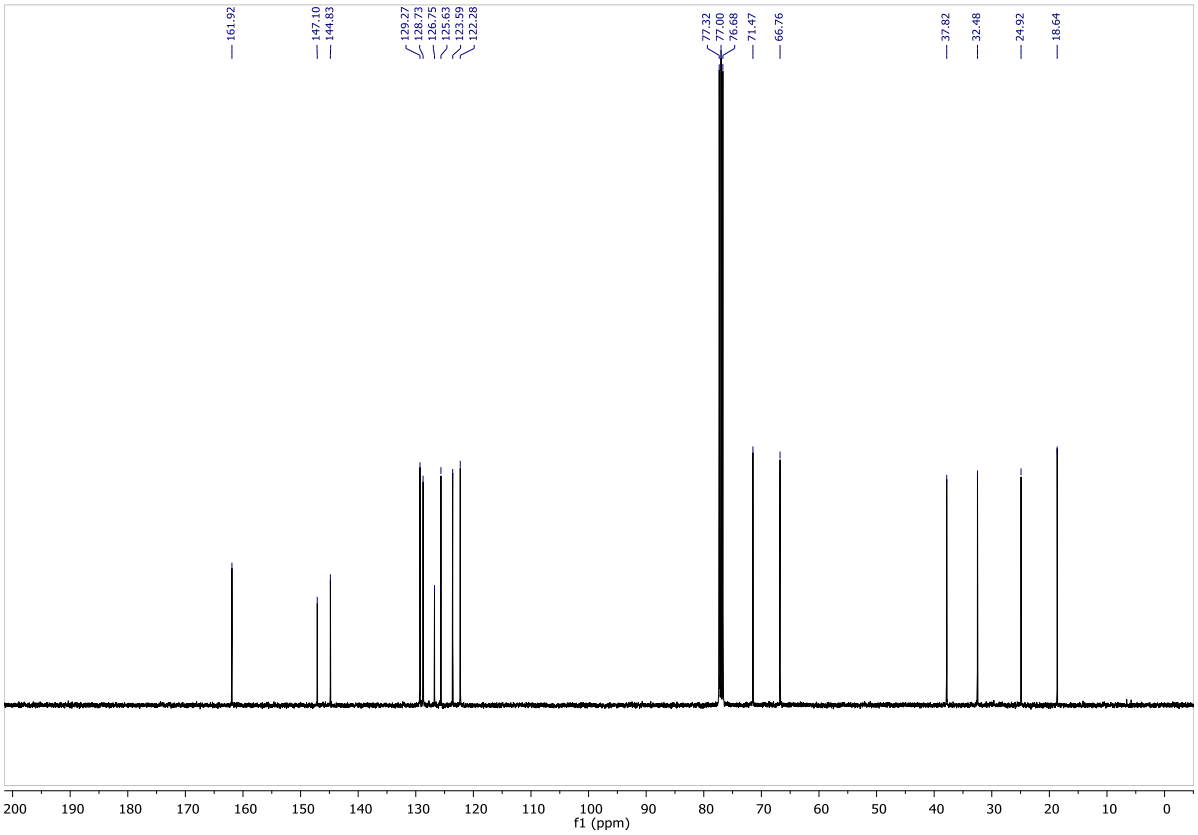

Me
OH
N
4.3-4af
f1 (ppm)

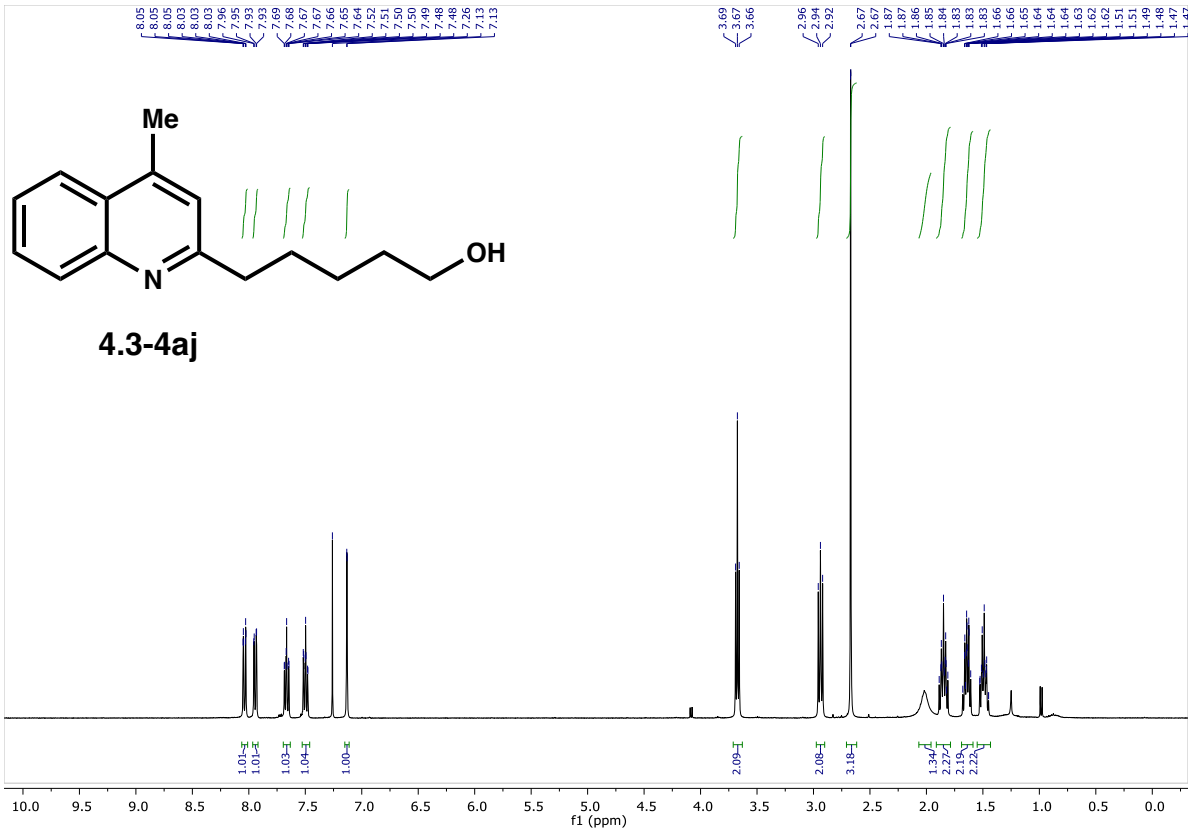

f1 (ppm)

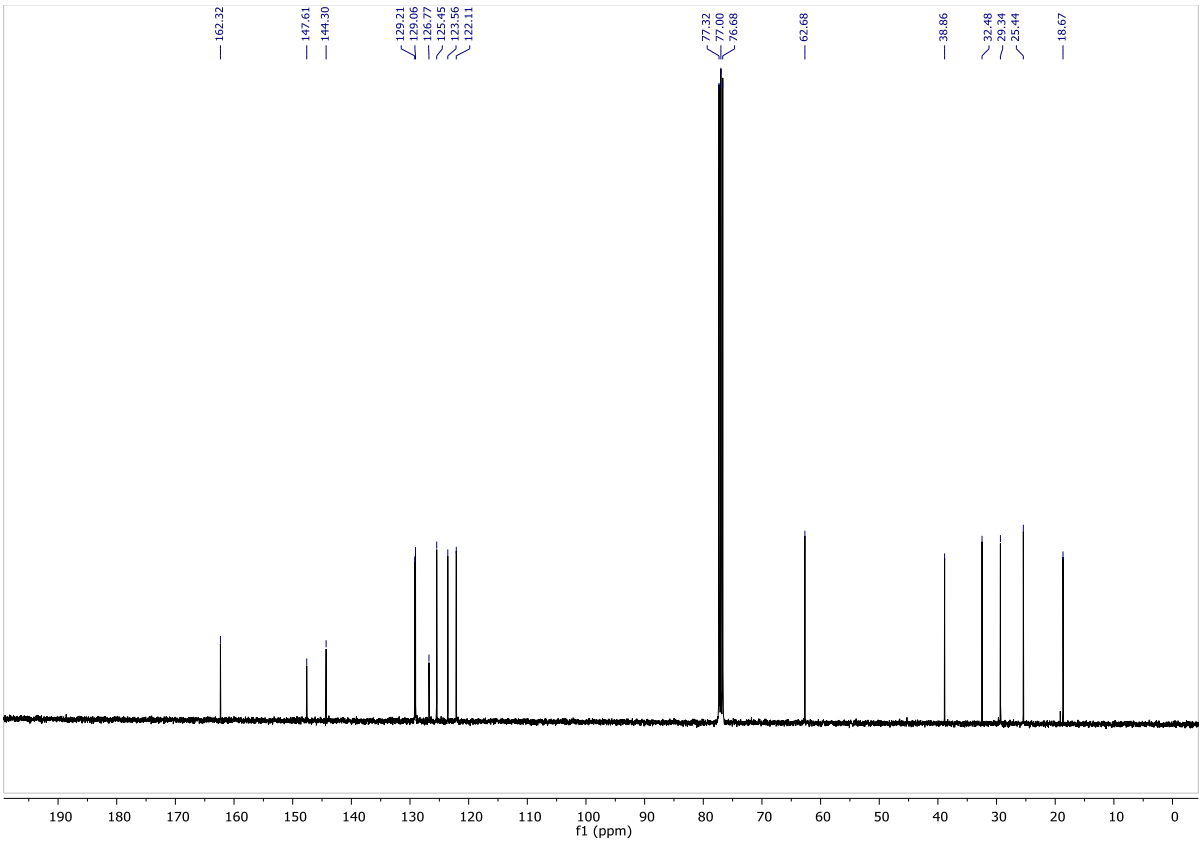

Me
N
OH
4.3-4ag
f1 (ppm)

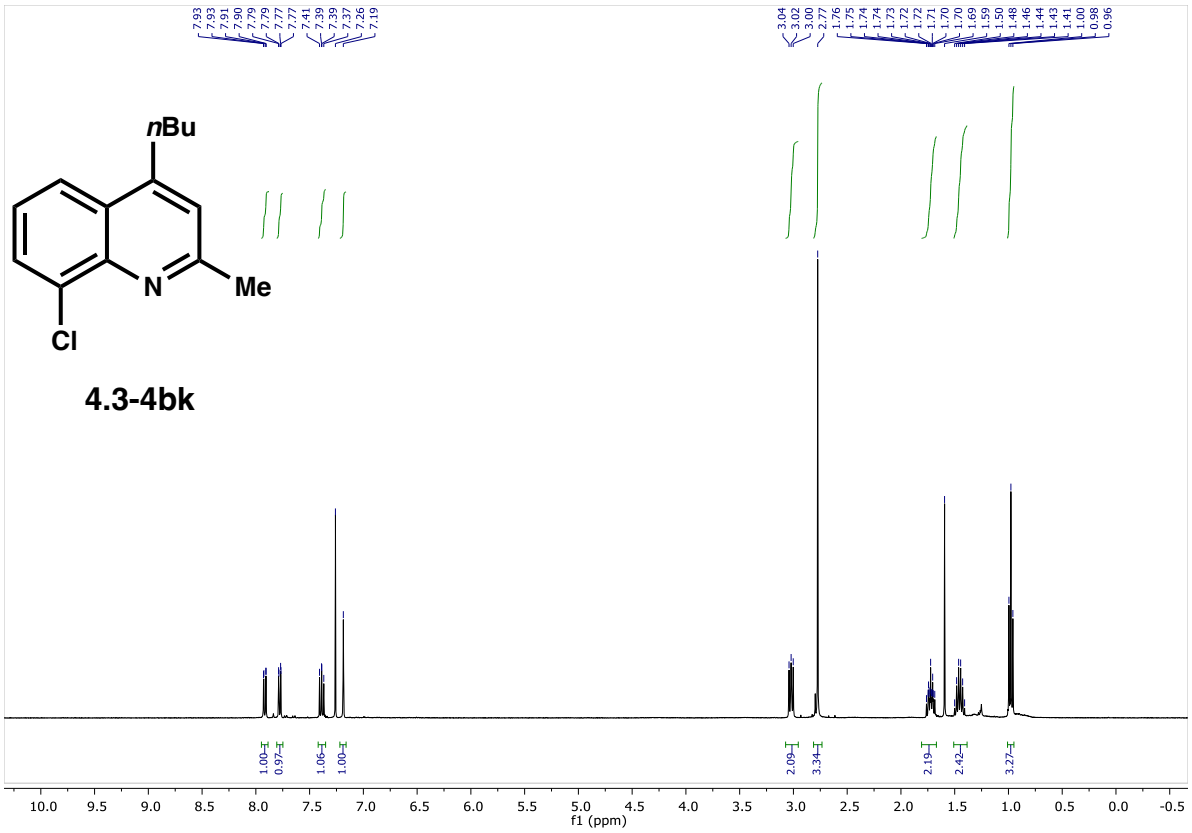

f1 (ppm)

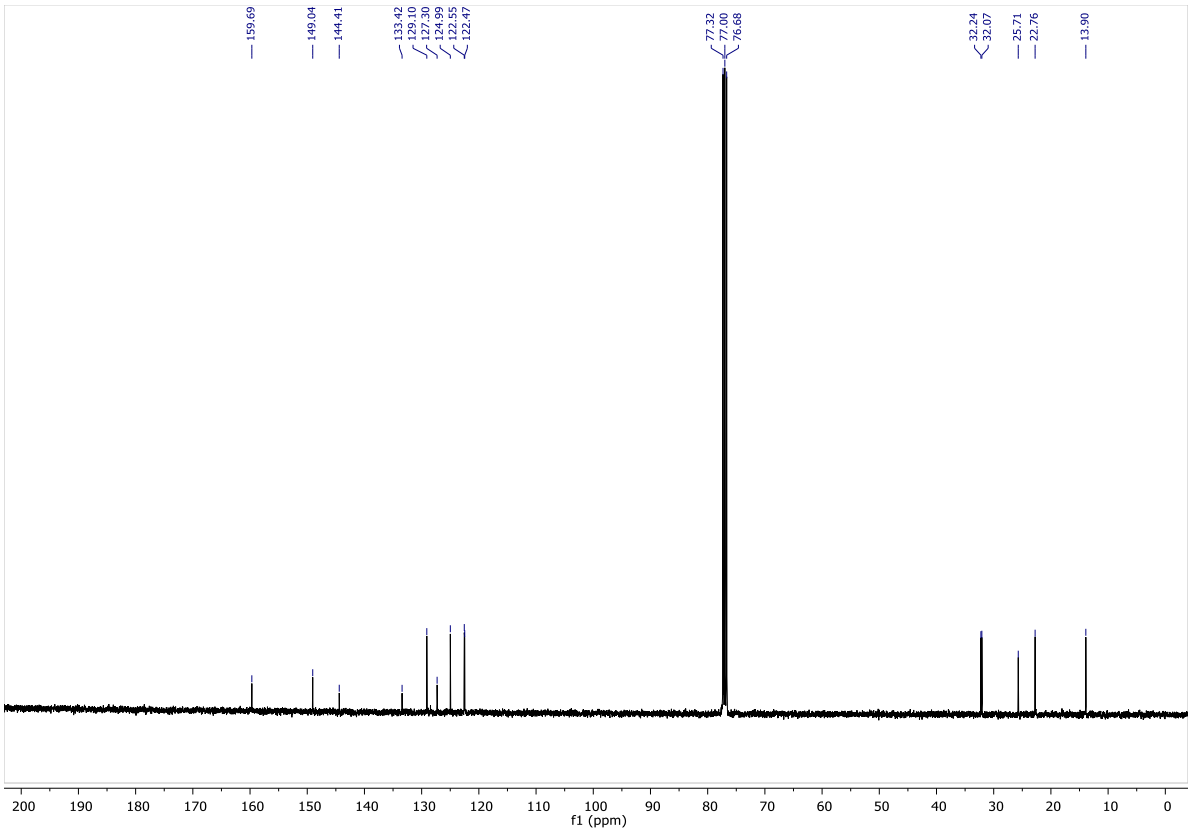

Me
OH
OH
N
4.3-4ah
f1 (ppm)

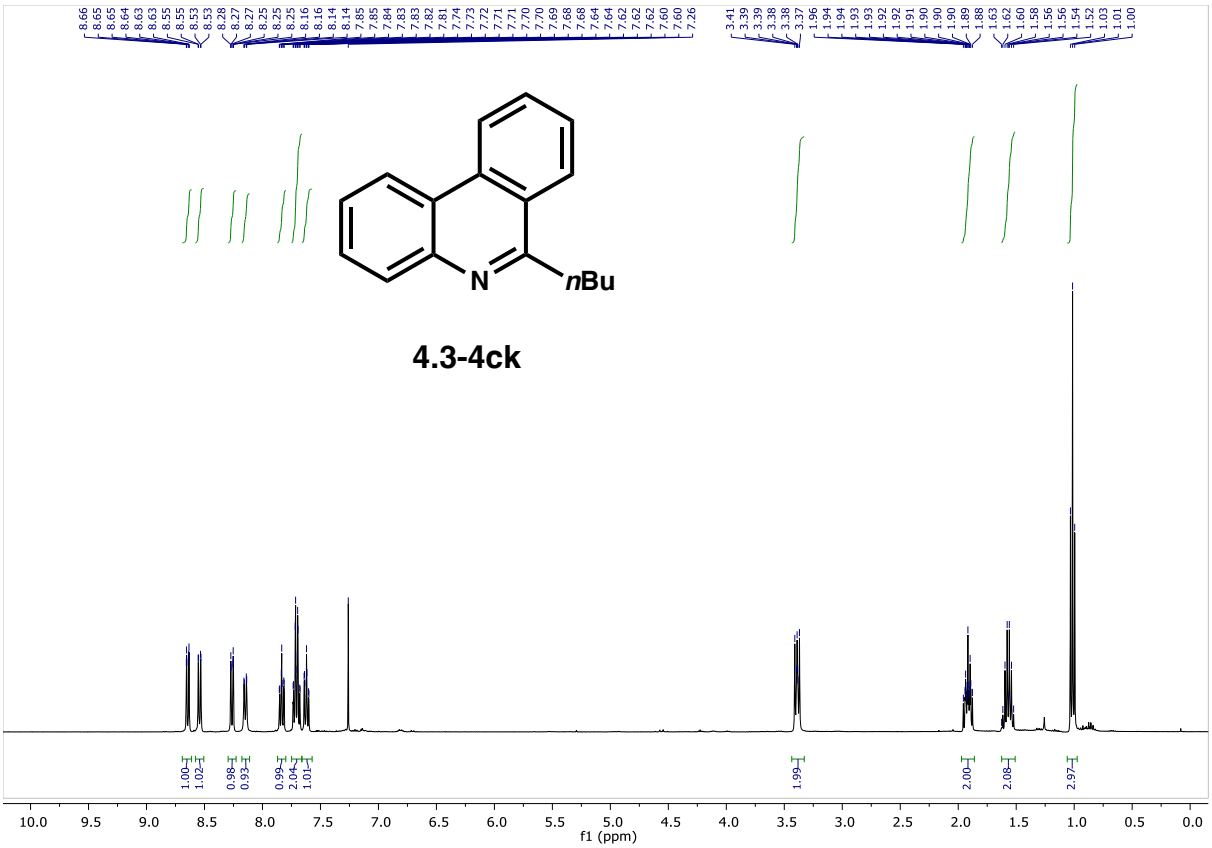

161.92
147.10
144.83
129.27
128.73
126.75
125.63
123.59
122.28
77.32
77.00
76.68
71.47
66.76
37.82
32.48
24.92
18.64
f1 (ppm)

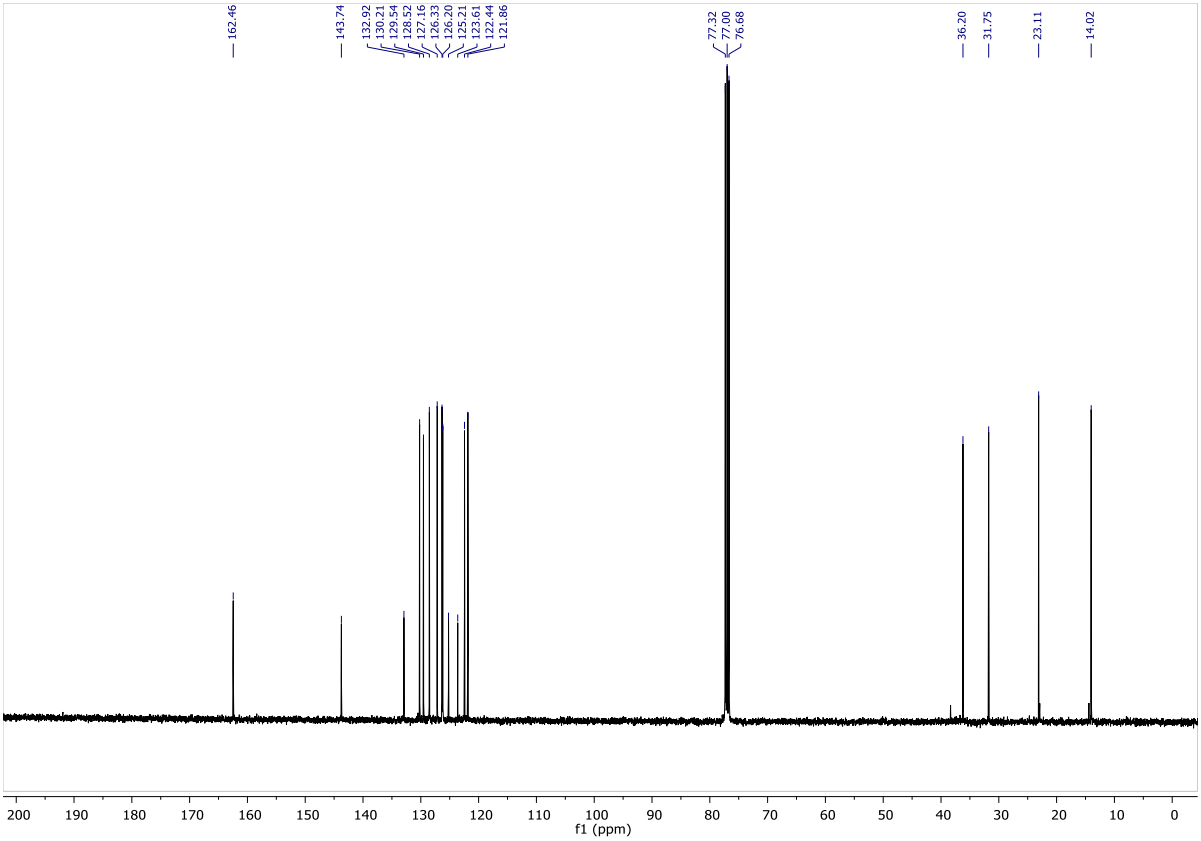

Me
OH
N
4.3-4aj
f1 (ppm)

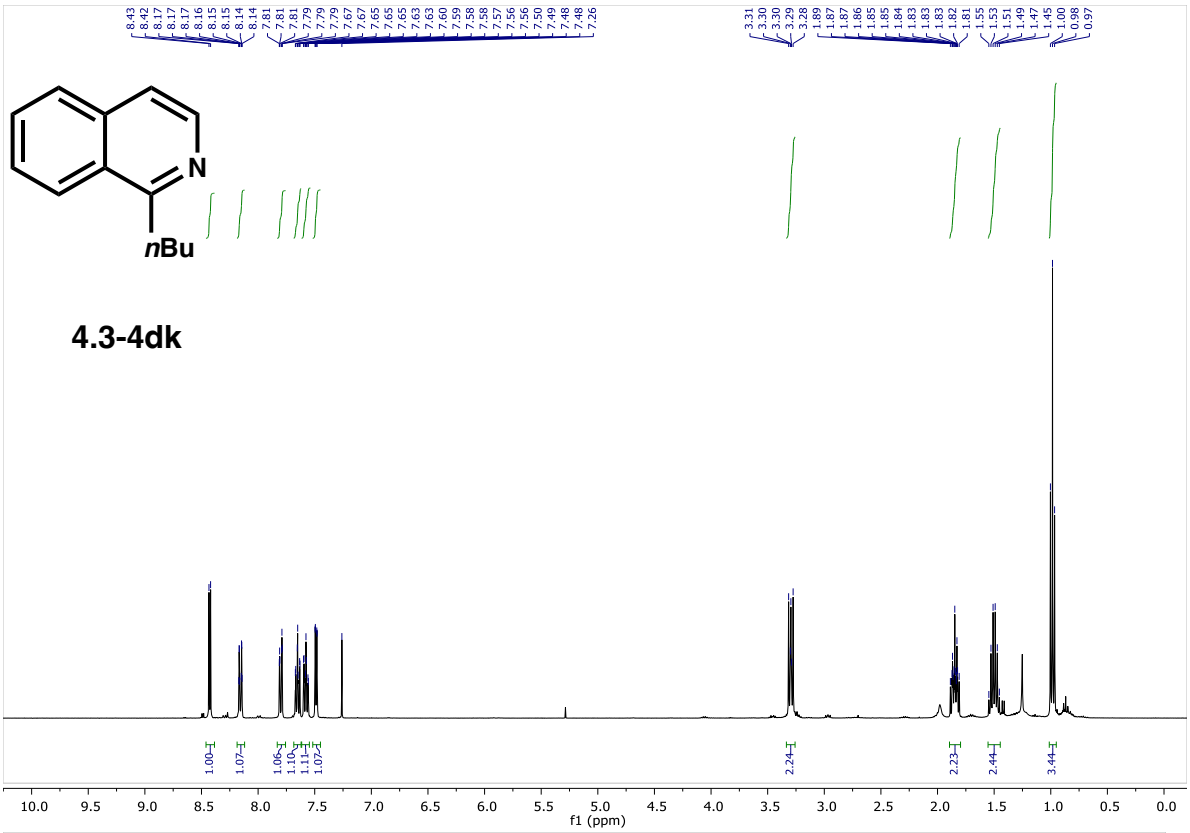

f1 (ppm)

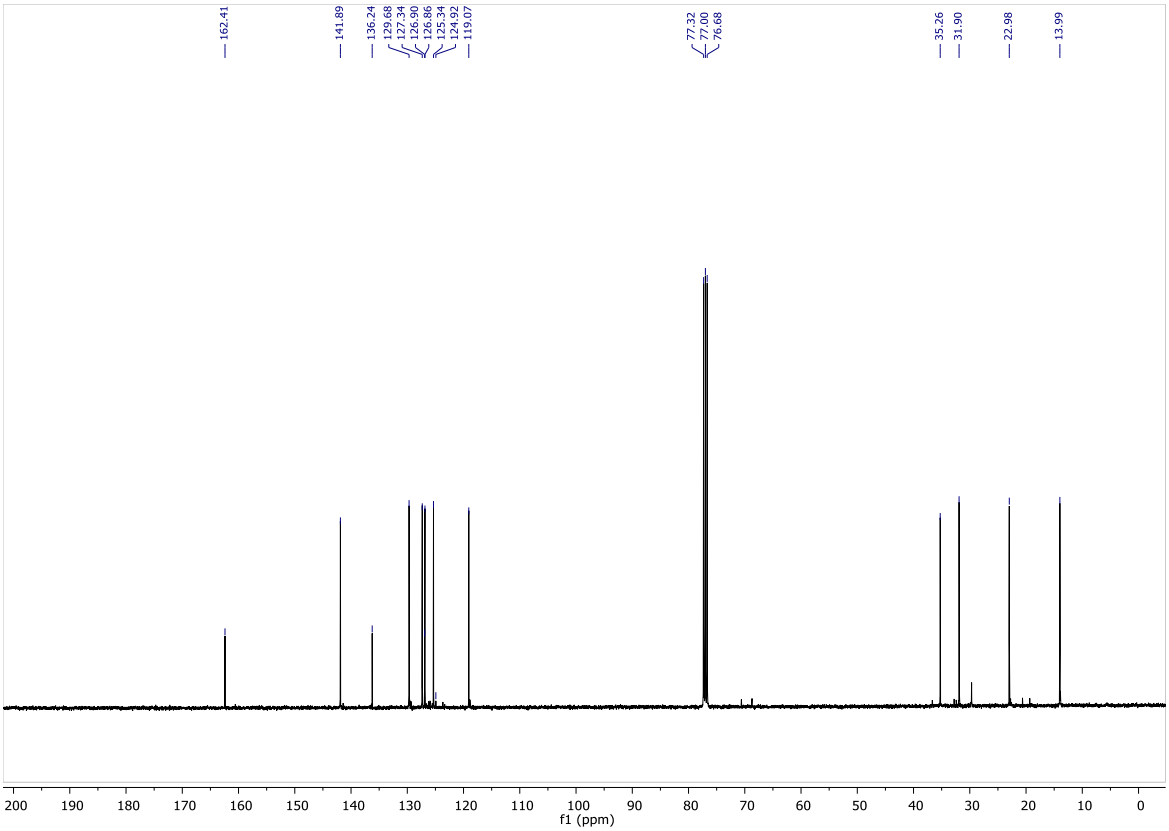

nBu
N
Me
Cl
4.3-4bk
f1 (ppm)

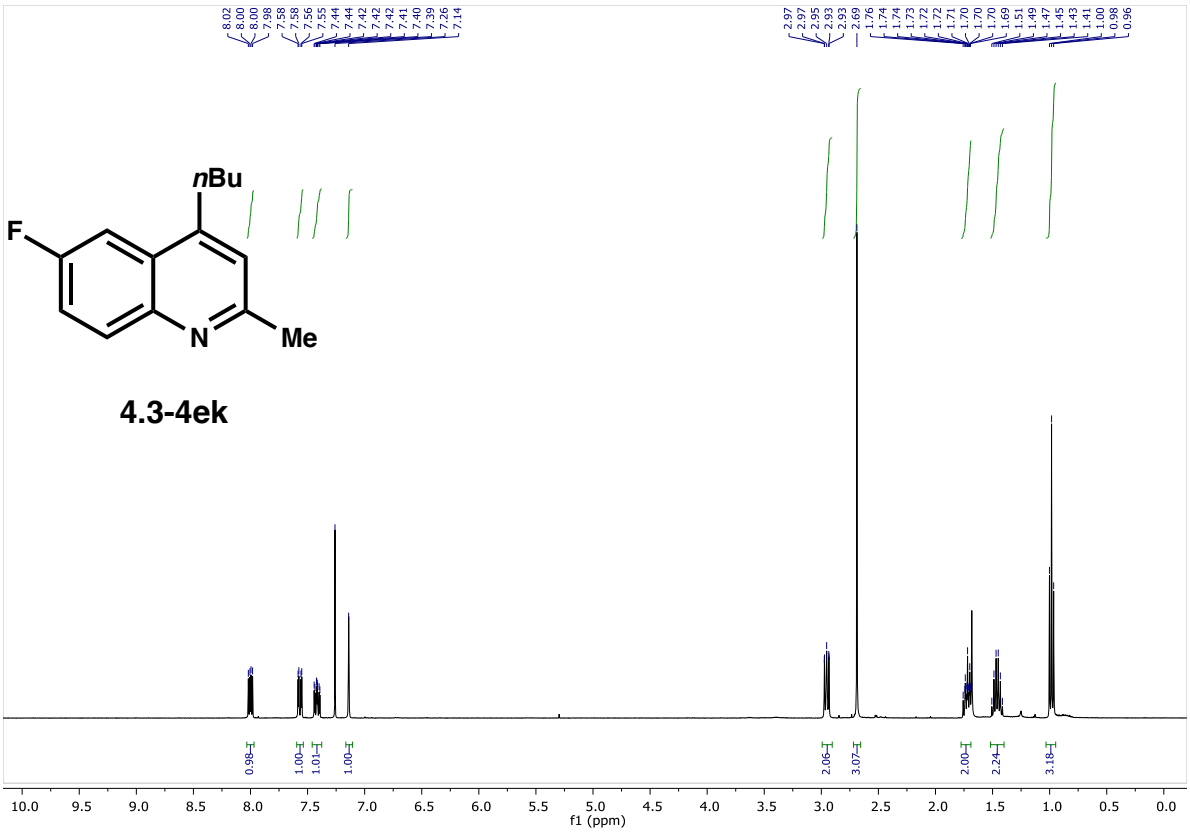

f1 (ppm)


8.66 8.65 8.65 8.64 8.63 8.63 8.55 8.55 8.53 8.53 8.28 8.27 8.27 8.25 8.25 8.25 8.16 8.16 8.14 8.14 7.85 7.85 7.84 7.83 7.83 7.82 7.81 7.74 7.73 7.72 7.71 7.71 7.70 7.70 7.69 7.68 7.68 7.64 7.64 7.62 7.62 7.62 7.60 7.60 7.26
3.41 3.39 3.39 3.38 3.38 3.37 1.96 1.94 1.94 1.93 1.93 1.92 1.92 1.91 1.90 1.90 1.90 1.89 1.88 1.63 1.62 1.60 1.58 1.56 1.56 1.54 1.52 1.03 1.01 1.00
N
nBu
4.3-4ck
1.00 1.02 0.98 0.93 0.99 2.04 1.01 1.99 2.00 2.08 2.97
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

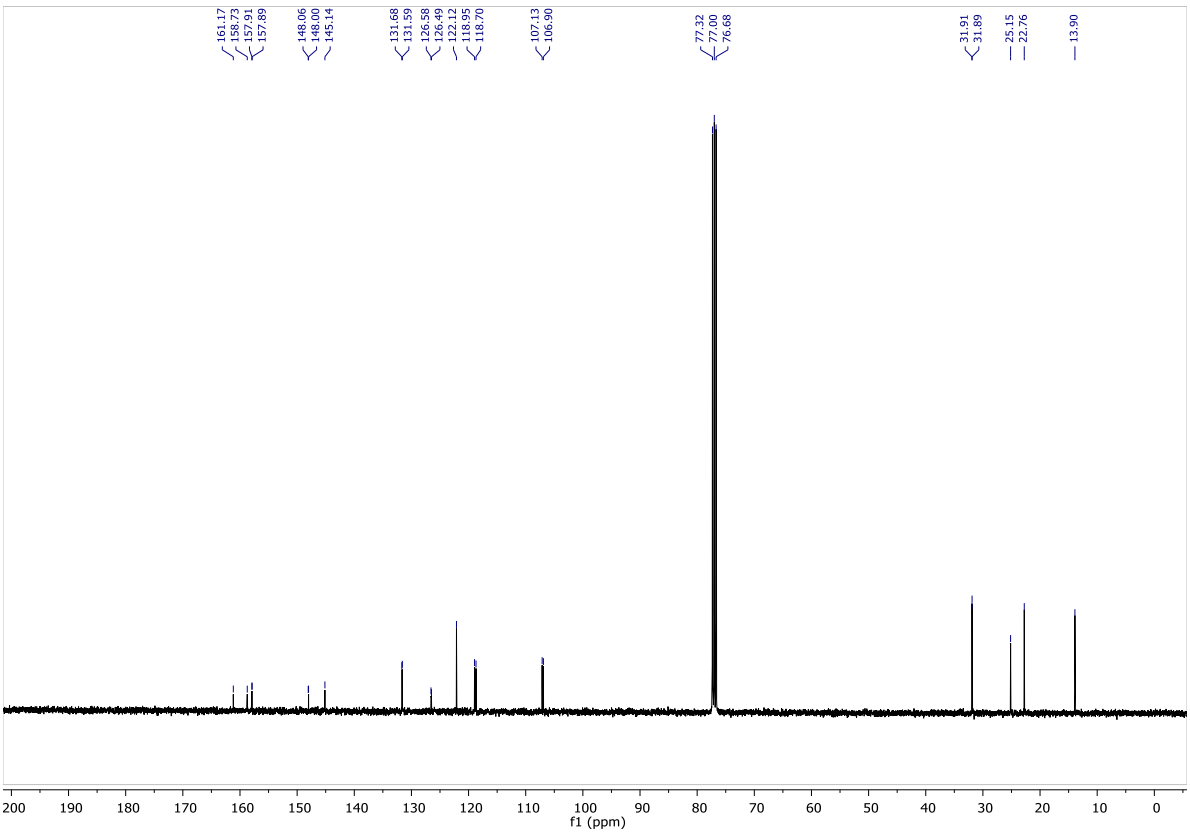

162.46 143.74 132.92 130.21 129.54 128.52 127.16 126.33 126.20 125.21 123.61 122.44 121.86
77.32 77.00 76.68
36.20 31.75 23.11 14.02
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

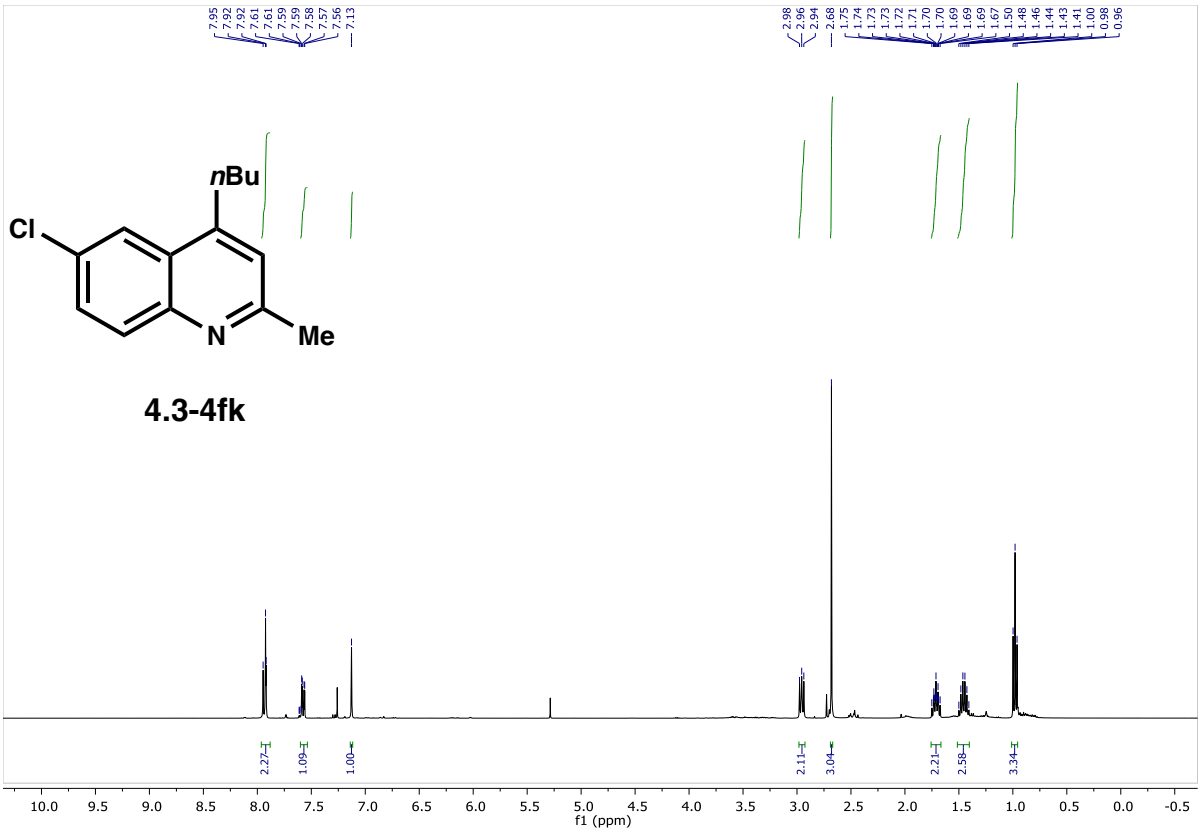

N
nBu
4.3-4dk
f1 (ppm)

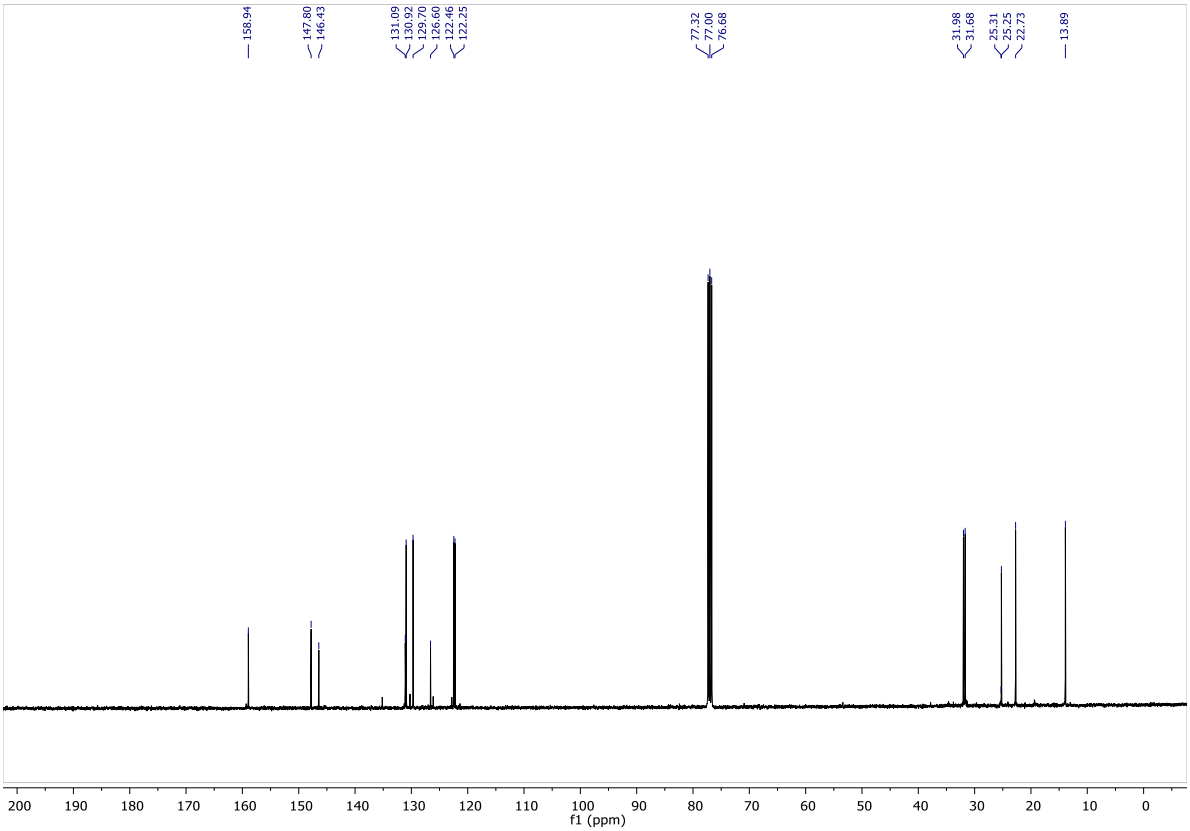

f1 (ppm)

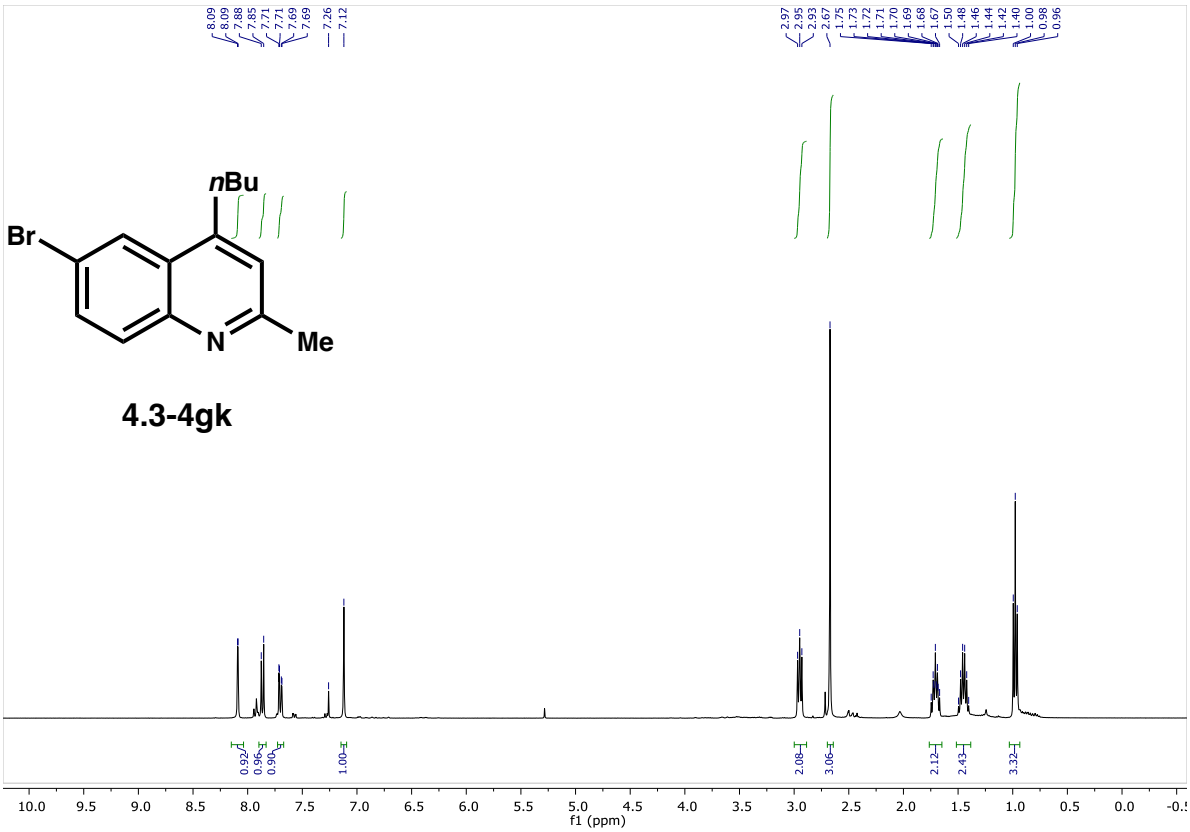


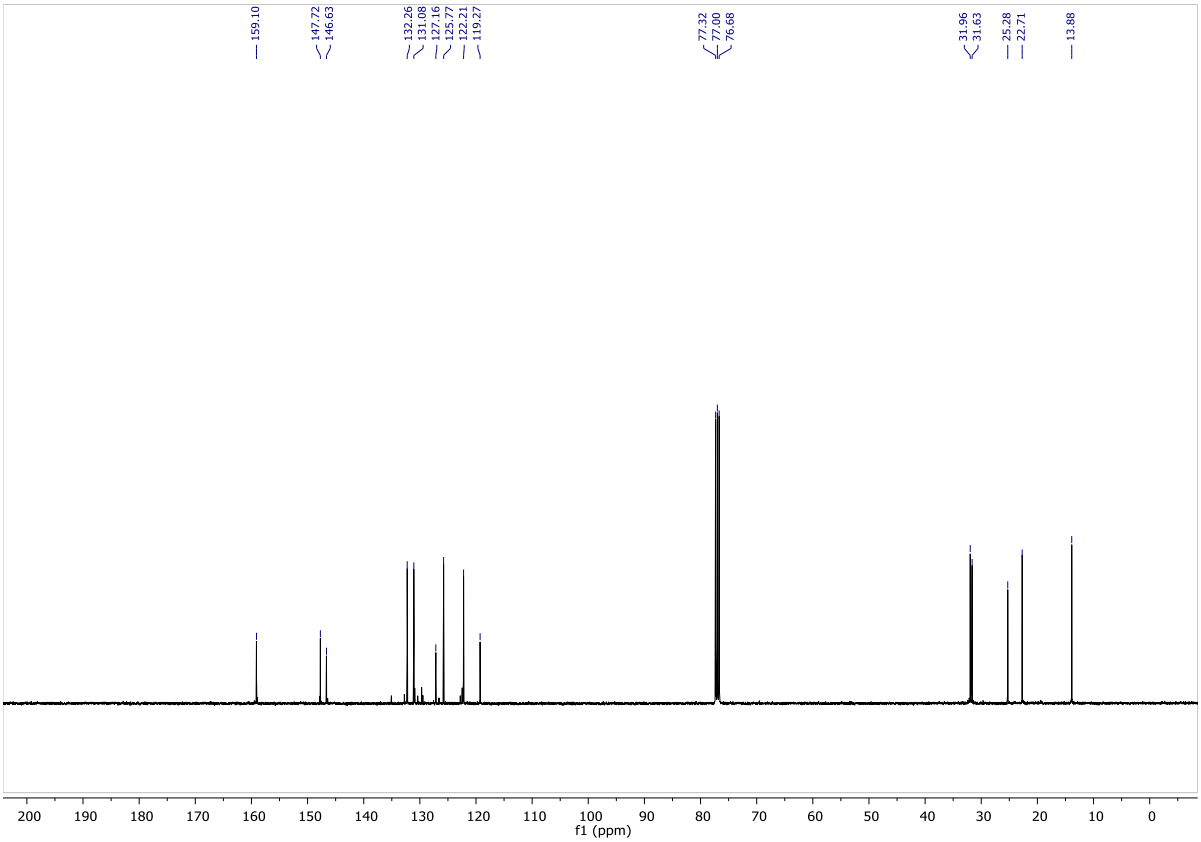
4.3-4ek

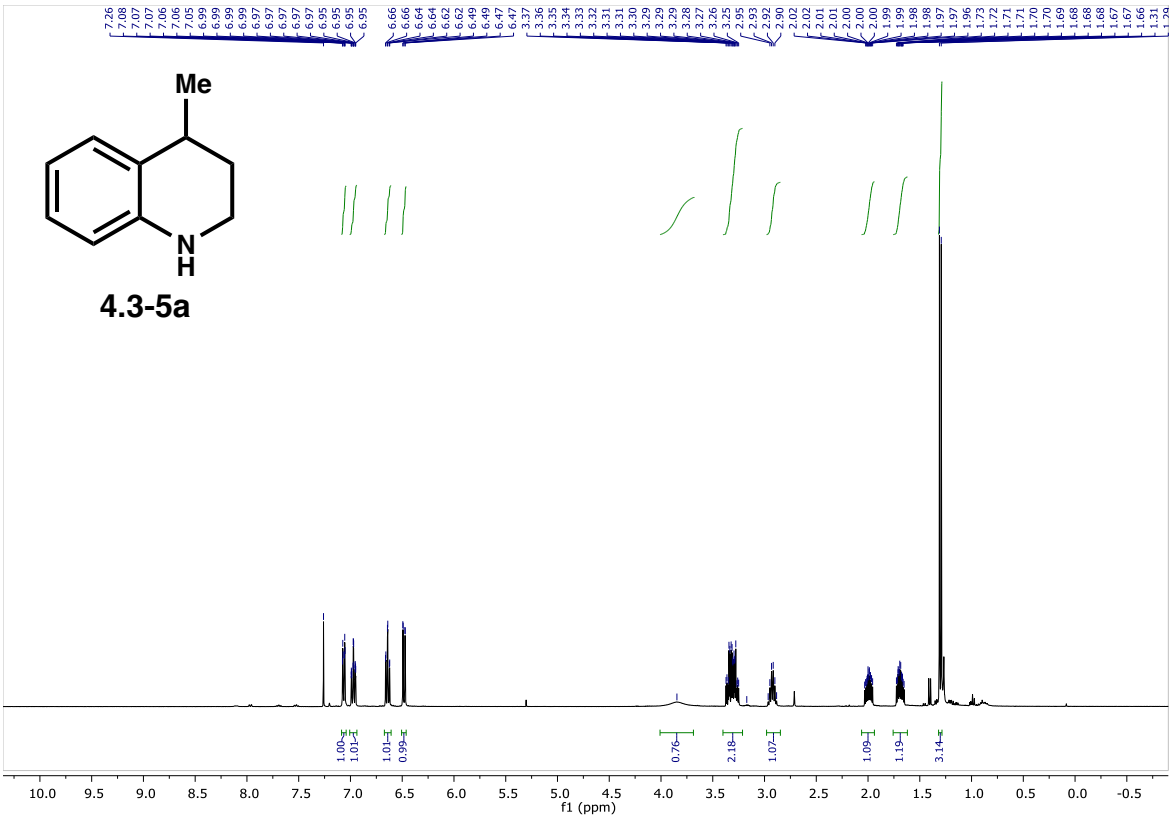


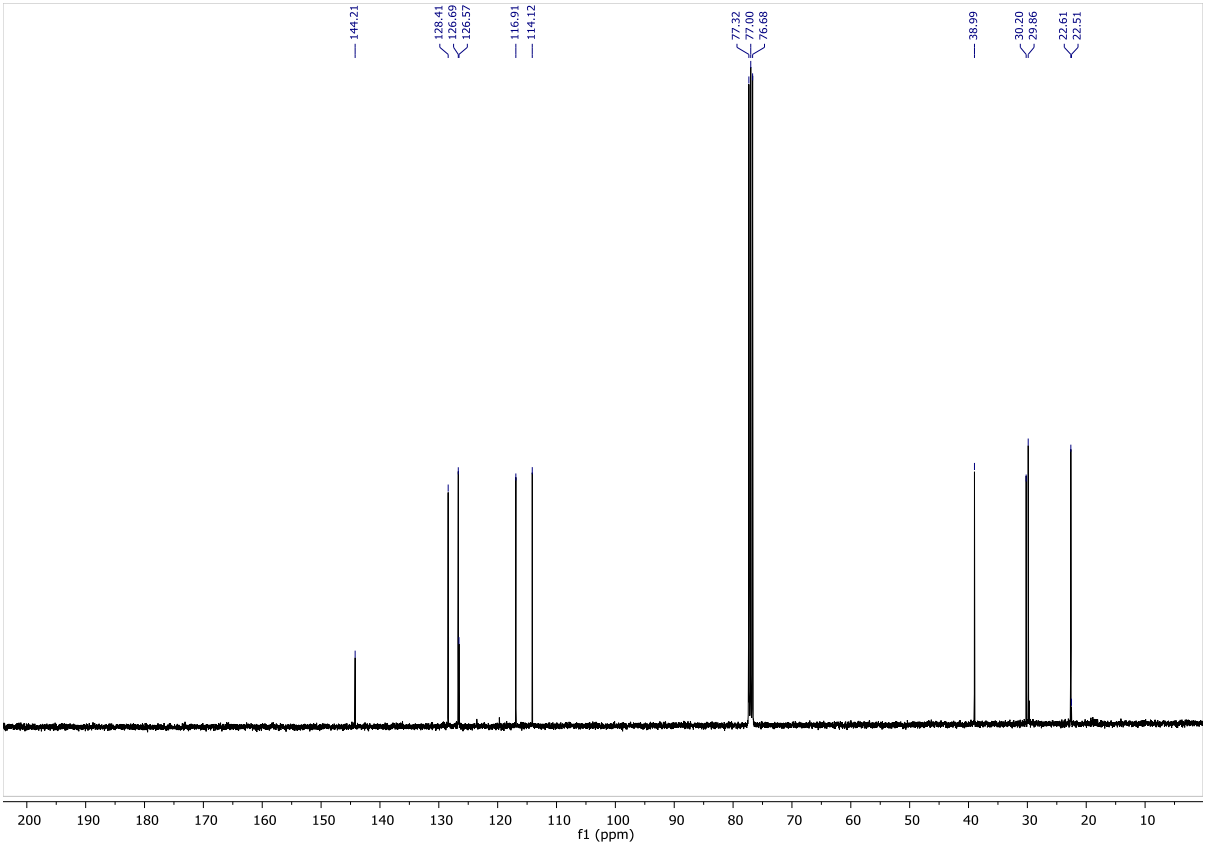

nBu
Cl
N
Me
4.3-4fk
f1 (ppm)

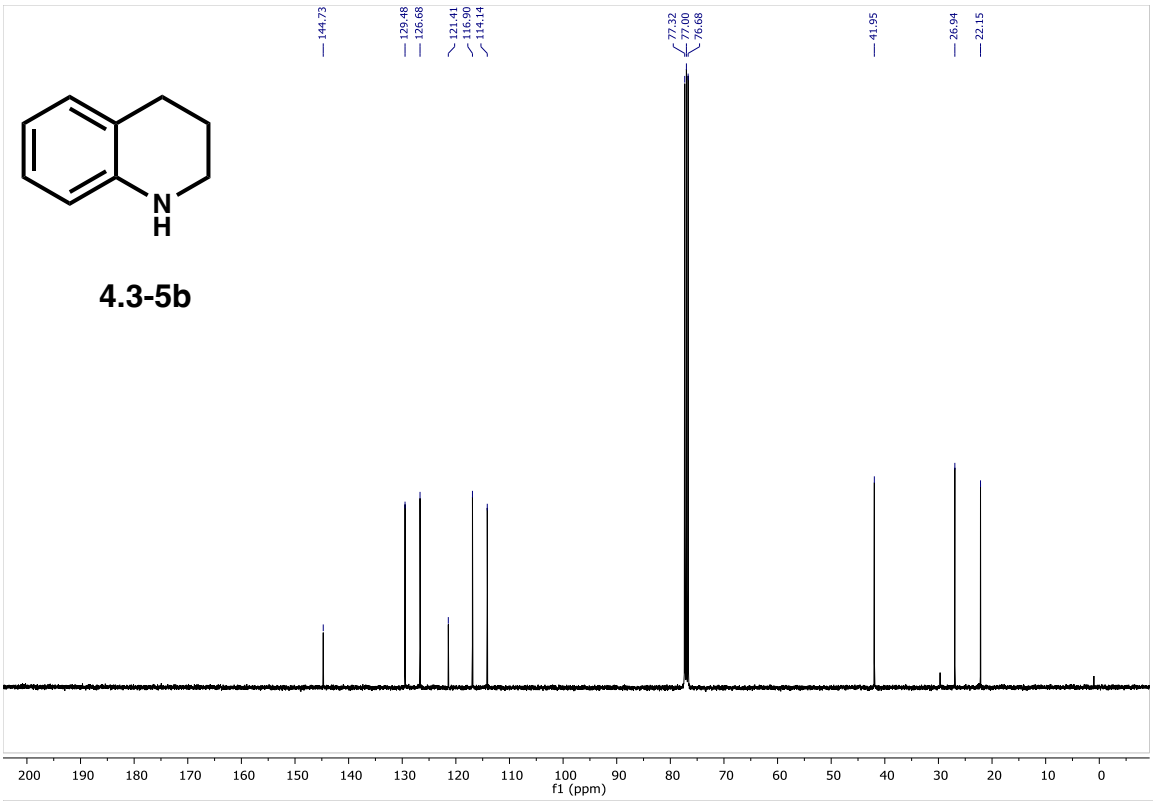

f1 (ppm)

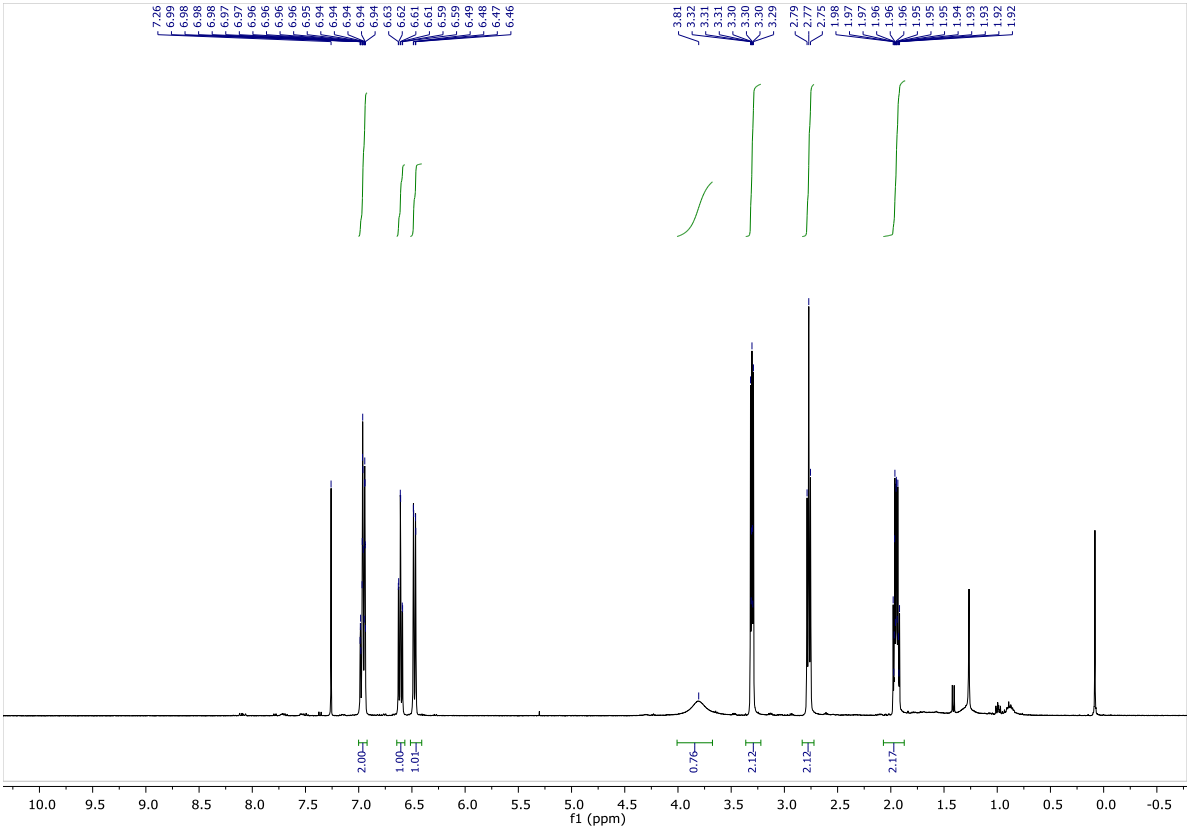

8.09
8.09
7.88
7.85
7.71
7.71
7.69
7.69
7.26
7.12
2.97
2.95
2.93
2.67
1.75
1.73
1.72
1.71
1.70
1.69
1.68
1.67
1.50
1.48
1.46
1.44
1.42
1.40
1.00
0.98
0.96
nBu
Br
N
Me
4.3-4gk
0.92
0.96
0.90
1.00
2.08
3.06
2.12
2.43
3.32
f1 (ppm)

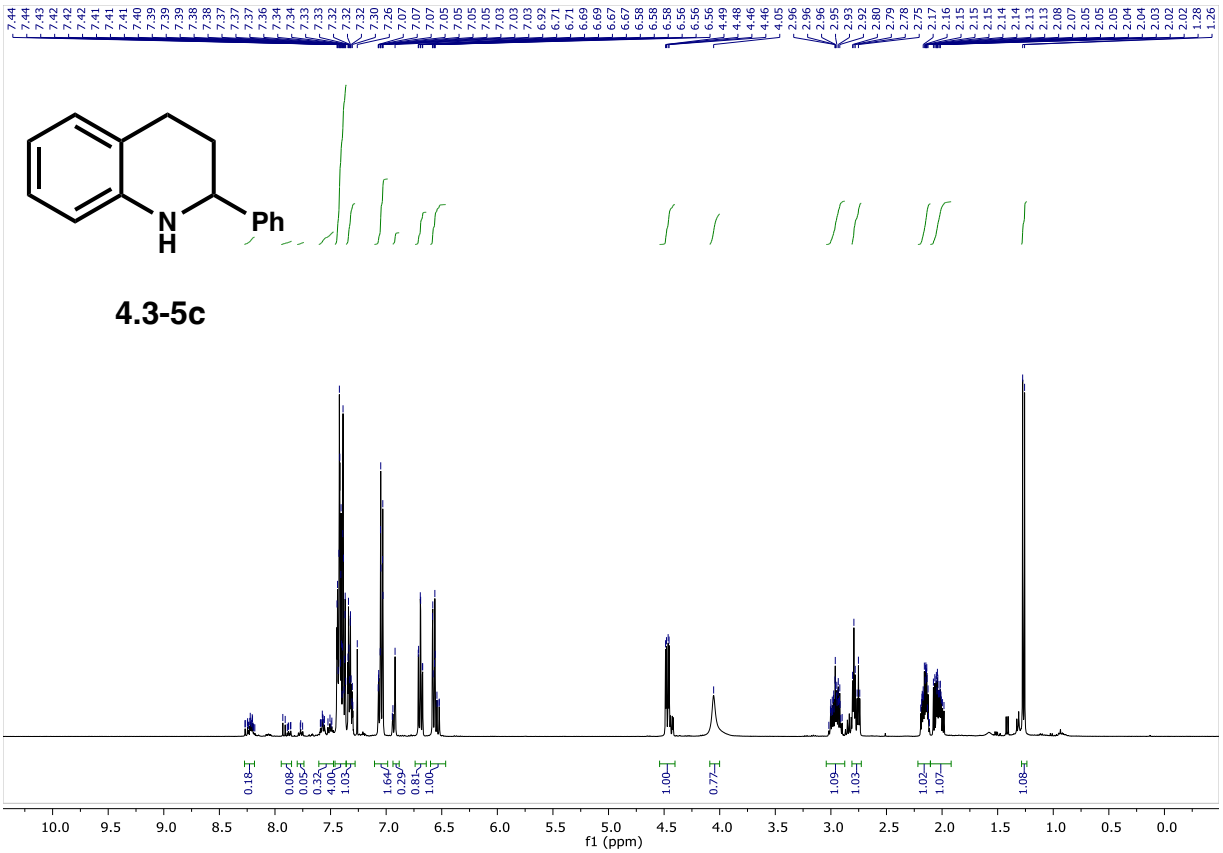

159.10
147.72
146.63
132.26
131.08
127.16
125.77
122.21
119.27
77.32
77.00
76.68
31.96
31.63
25.28
22.71
13.88
f1 (ppm)

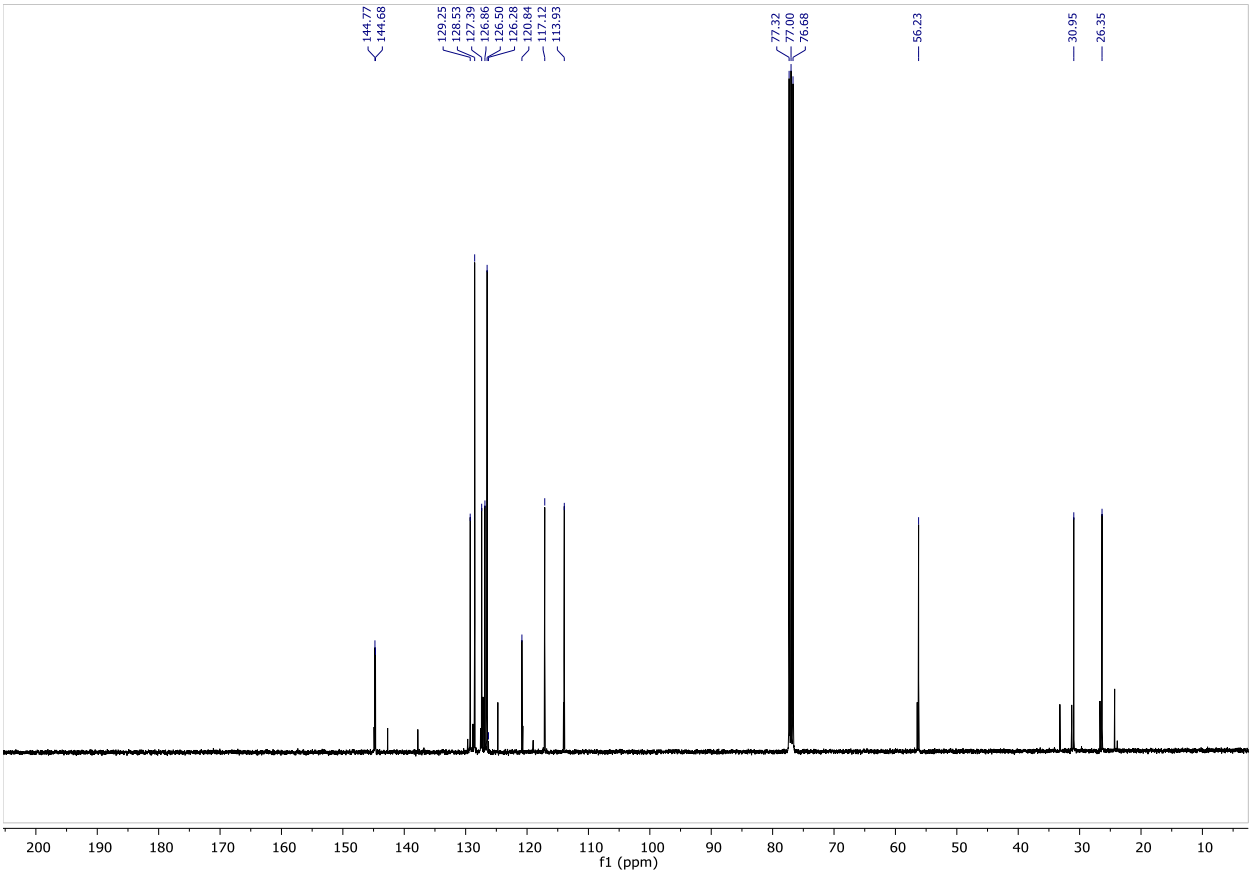

Me
N
H
4.3-5a
f1 (ppm)

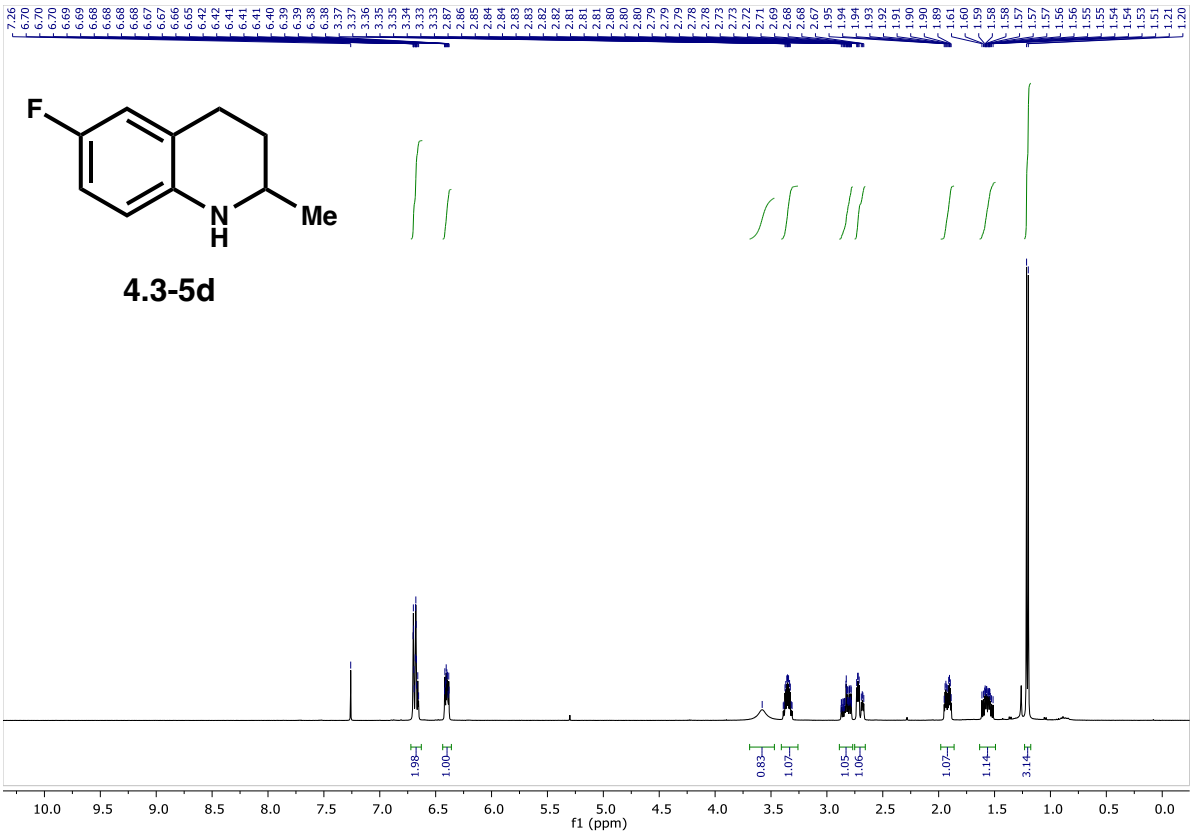

144.21
128.41
126.69
126.57
116.91
114.12
77.32
77.00
76.68
38.99
30.20
29.86
22.61
22.51
f1 (ppm)

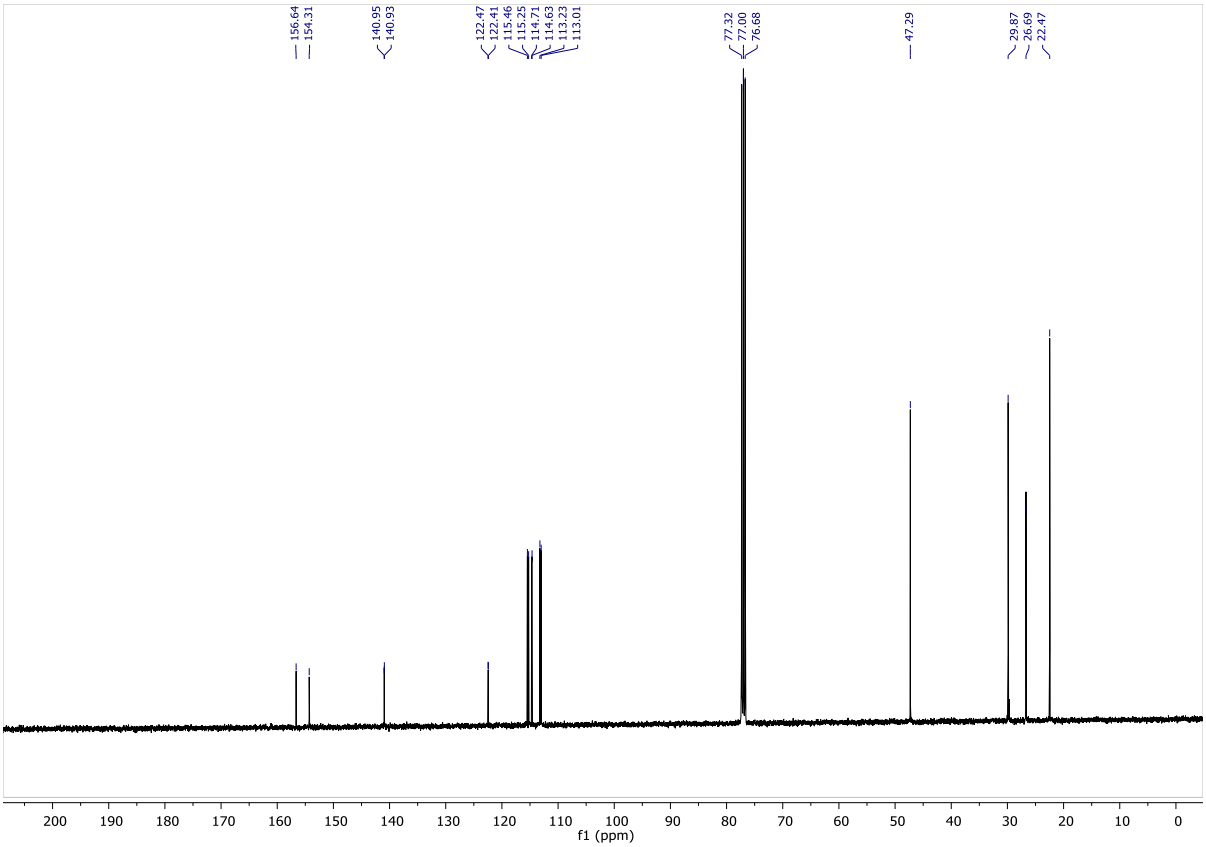

144.73
129.48
126.68
121.41
116.90
114.14
77.32
77.00
76.68
41.95
26.94
22.15
N
H
4.3-5b
f1 (ppm)

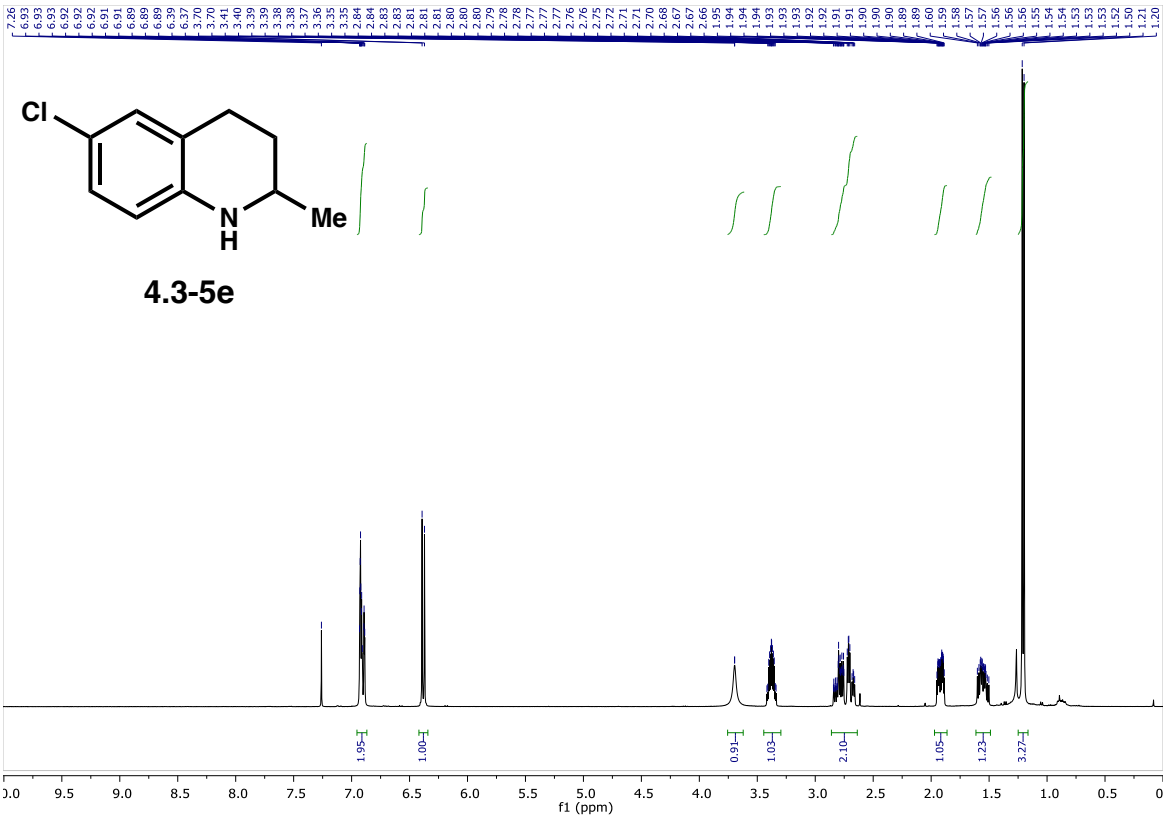

7.26
6.99
6.98
6.98
6.98
6.97
6.97
6.96
6.96
6.96
6.96
6.95
6.94
6.94
6.94
6.94
6.94
6.63
6.62
6.61
6.61
6.59
6.59
6.49
6.48
6.47
6.46
3.81
3.32
3.31
3.31
3.30
3.30
3.30
3.29
2.79
2.77
2.75
1.98
1.97
1.97
1.96
1.96
1.96
1.95
1.95
1.95
1.94
1.93
1.93
1.92
1.92
2.00
1.00
1.01
0.76
2.12
2.12
2.17
f1 (ppm)

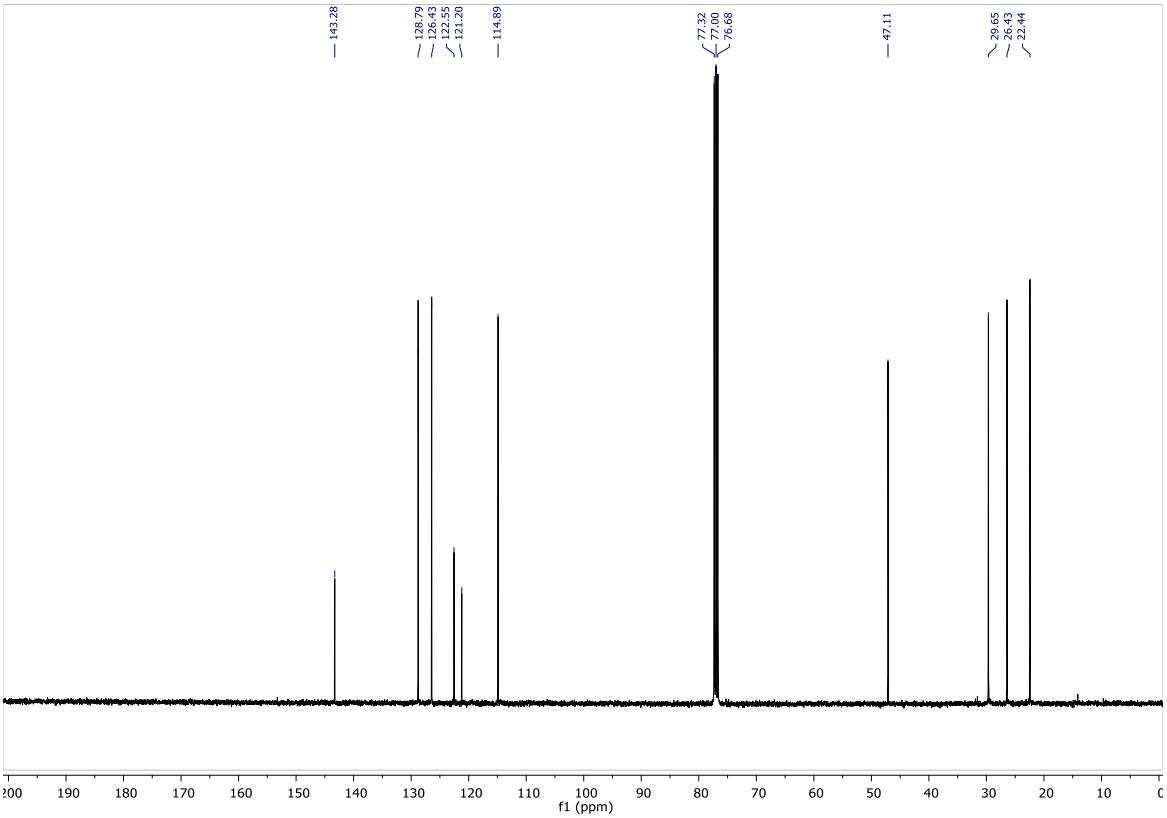

Ph
N
H
4.3-5c
f1 (ppm)

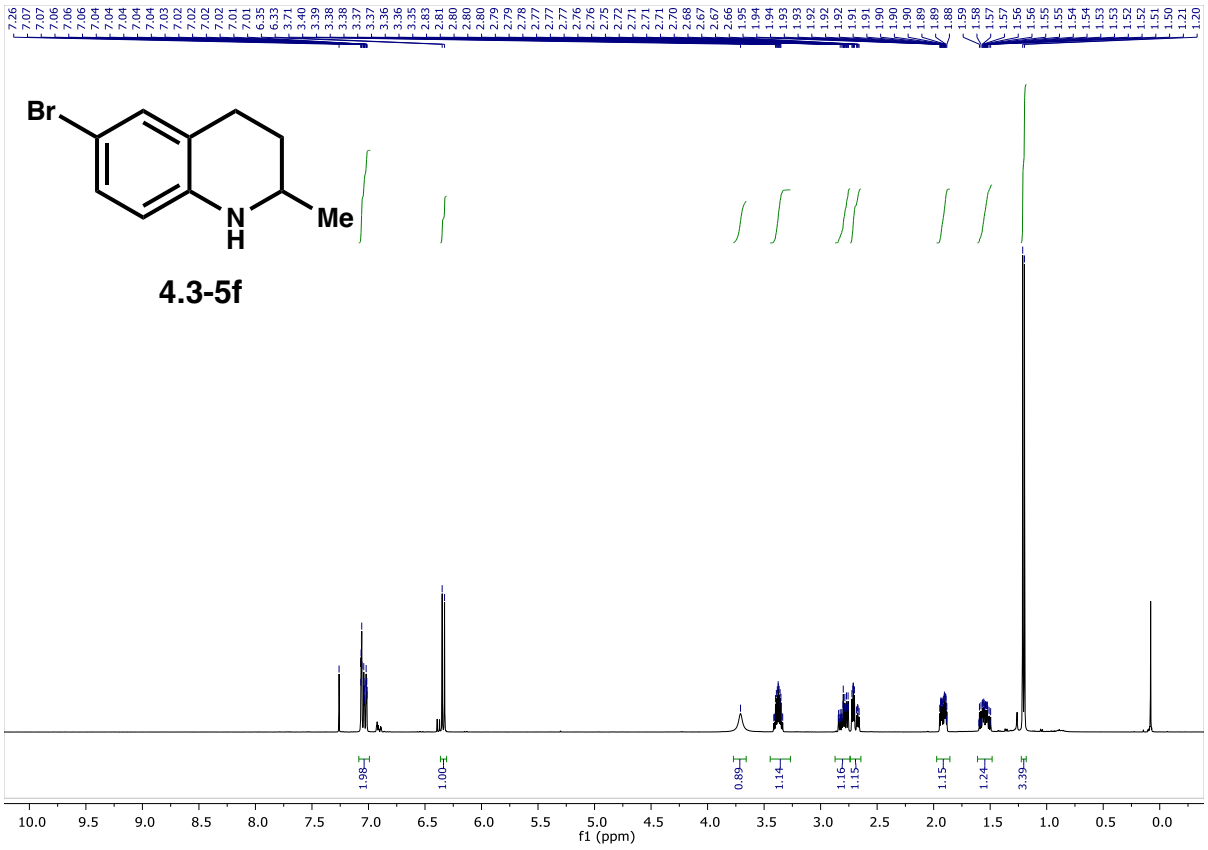

f1 (ppm)

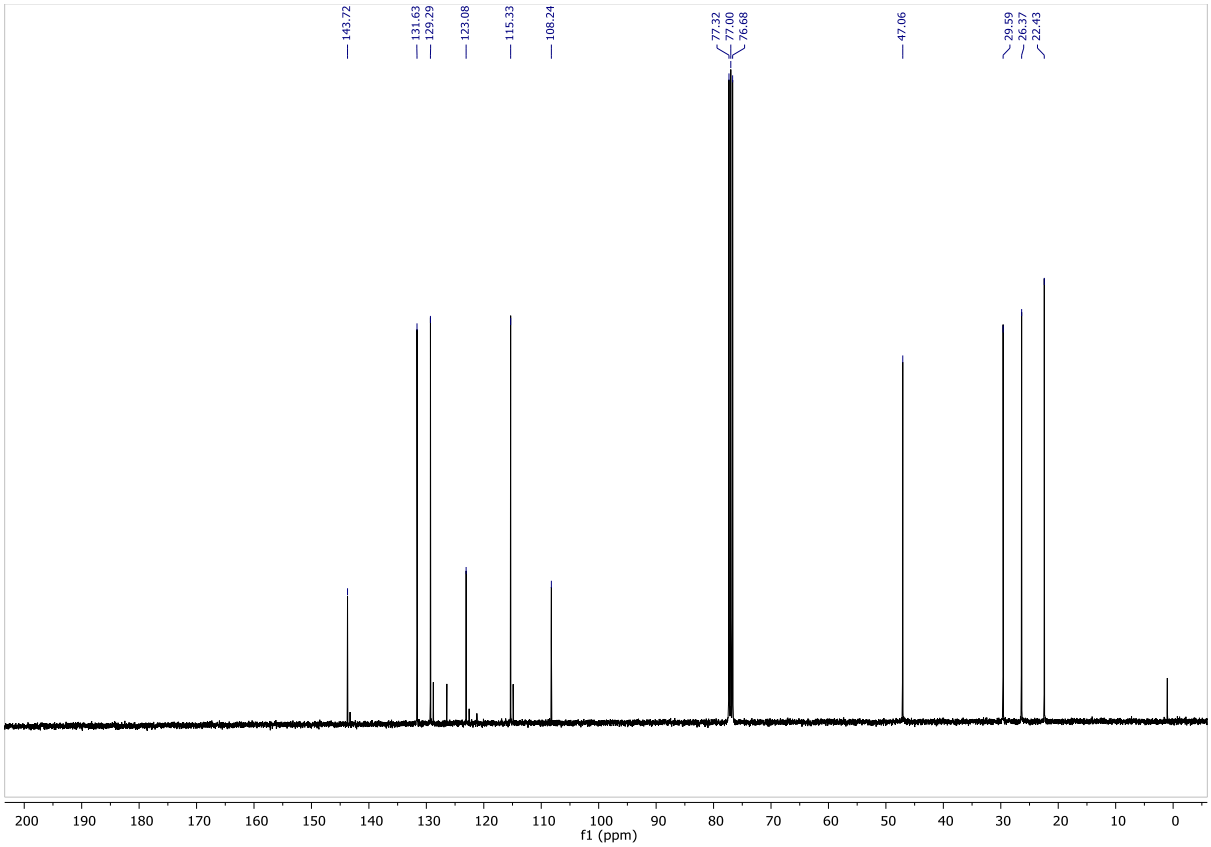

F
N
H
Me
4.3-5d
f1 (ppm)

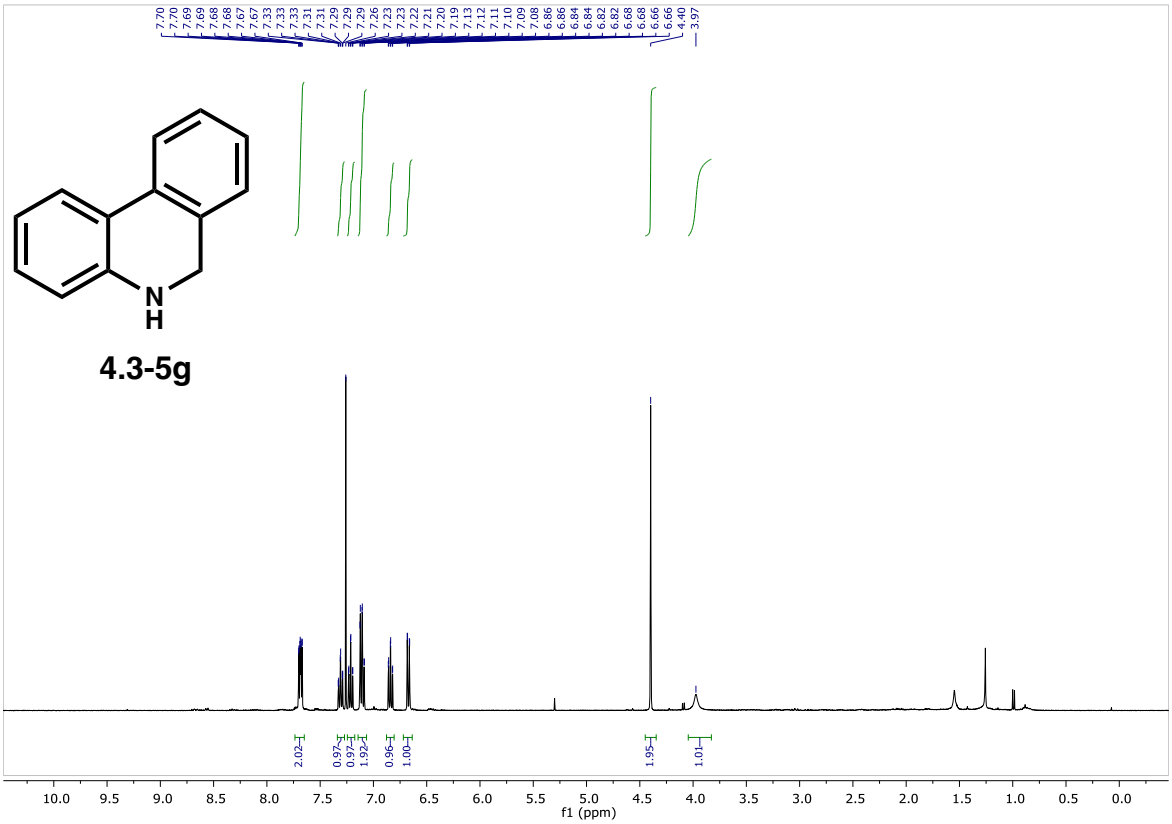

156.64
154.31
140.95
140.93
122.47
122.41
115.46
115.25
114.71
114.63
113.23
113.01
77.32
77.00
76.68
47.29
29.87
26.69
22.47
f1 (ppm)

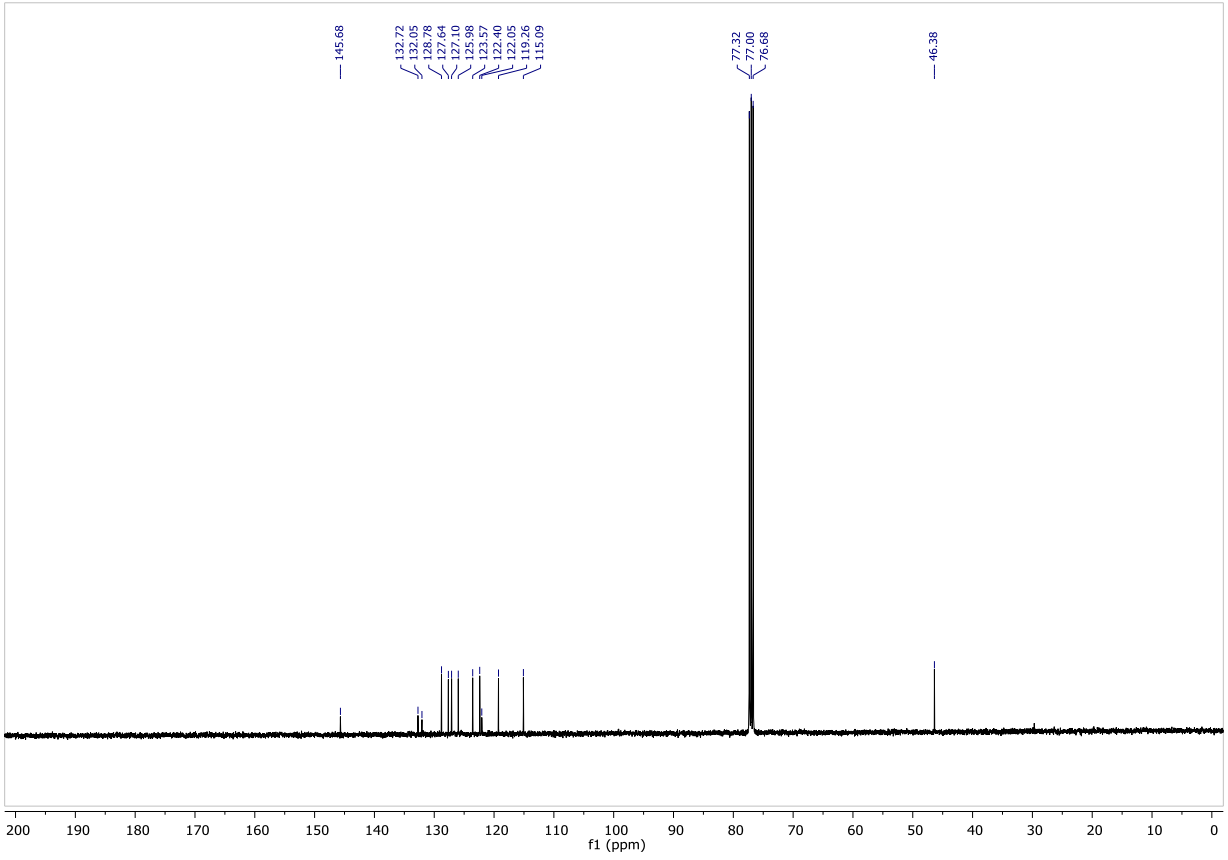

Cl
N
H
Me
4.3-5e
f1 (ppm)

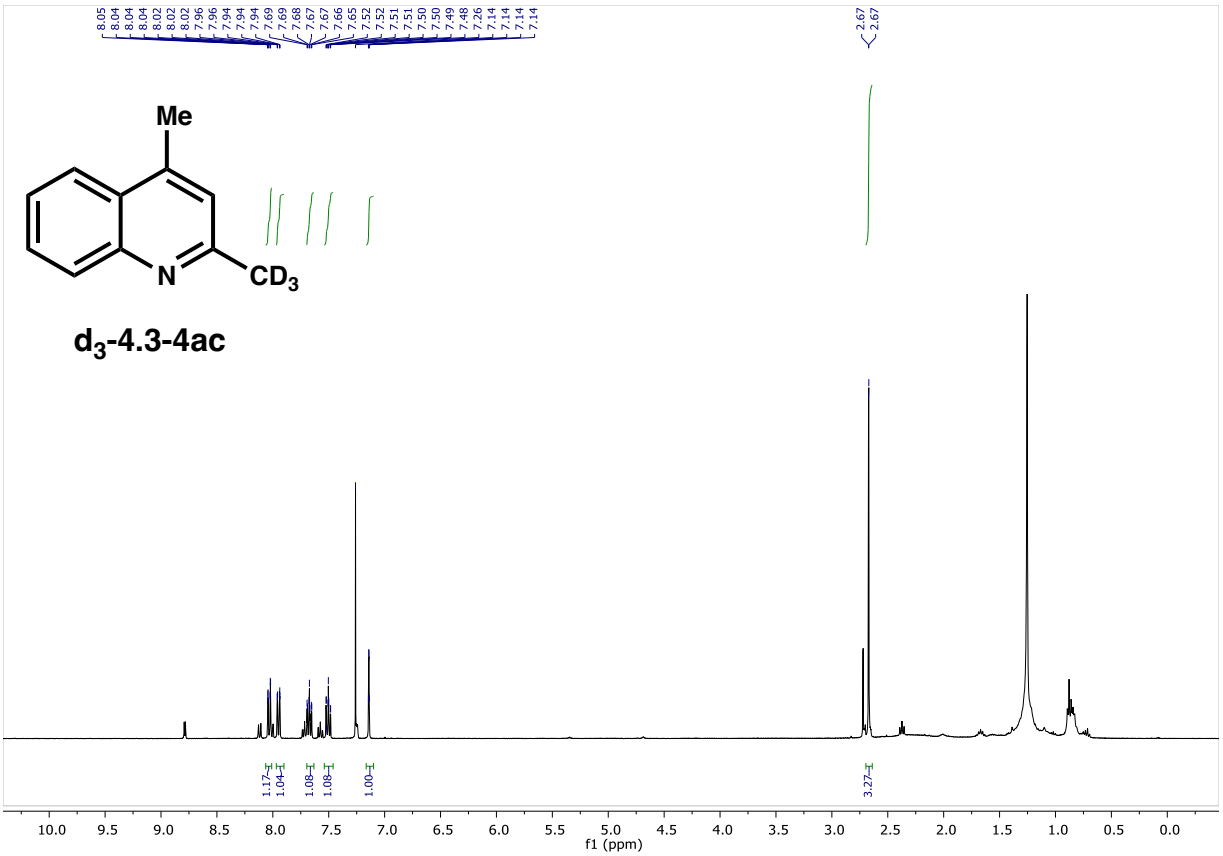

143.28
128.79
126.43
122.55
121.20
114.89
77.32
77.00
76.68
47.11
29.65
26.43
22.44
f1 (ppm)

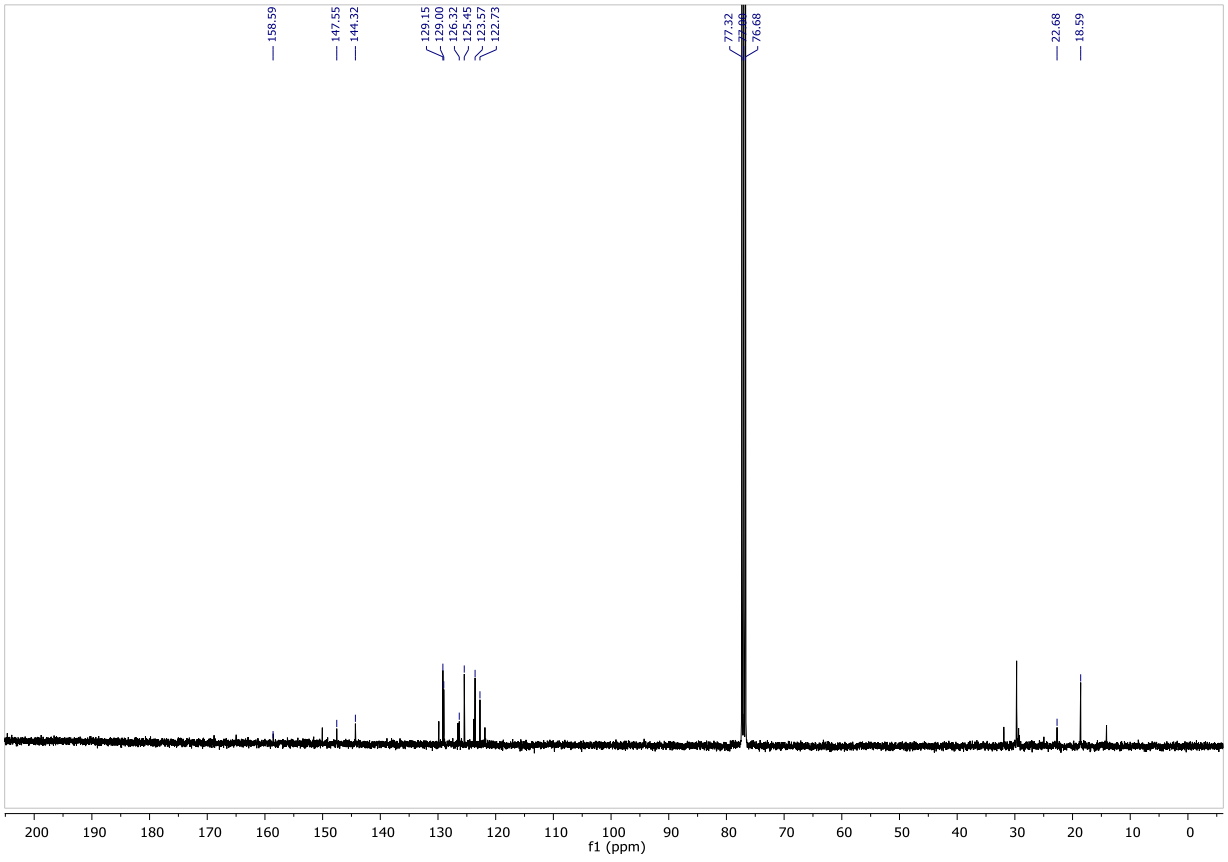

Br
N
H
Me
4.3-5f
f1 (ppm)

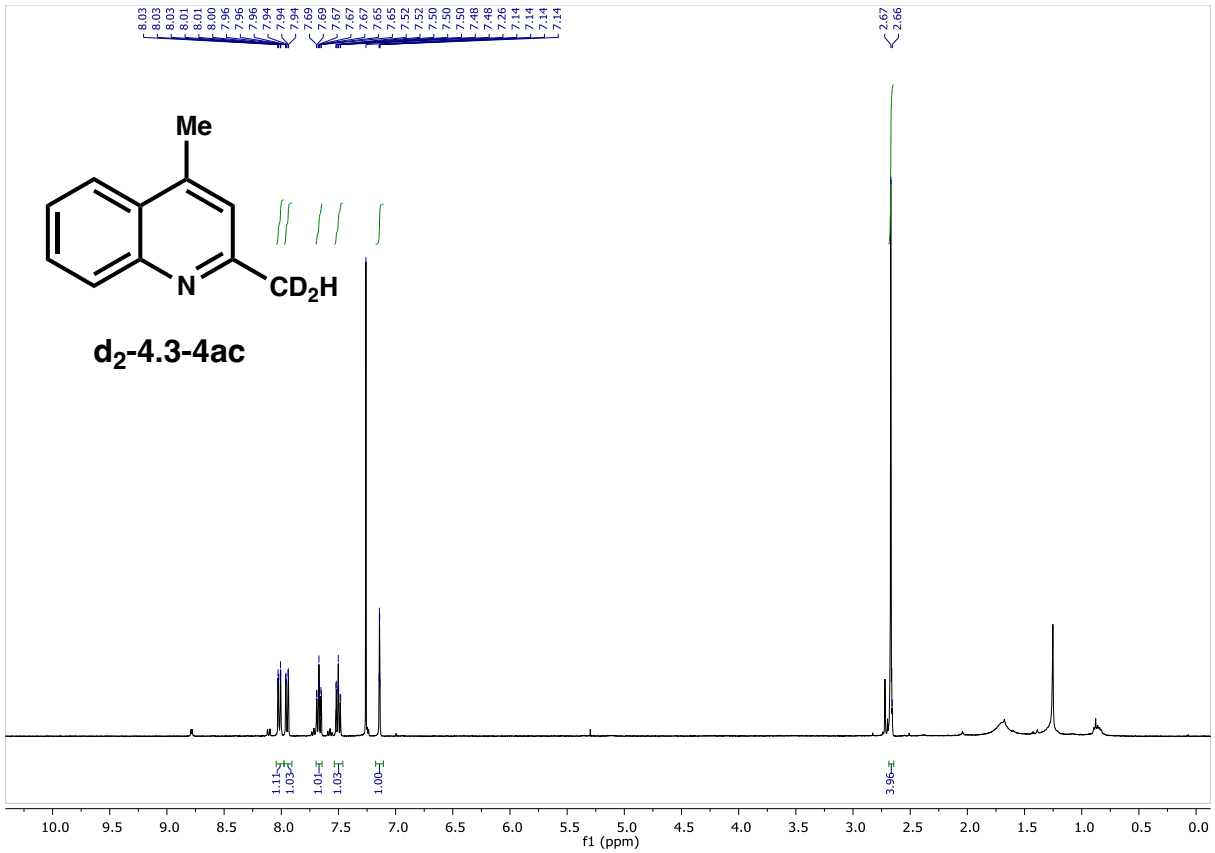

143.72
131.63
129.29
123.08
115.33
108.24
77.32
77.00
76.68
47.06
29.59
26.37
22.43
f1 (ppm)

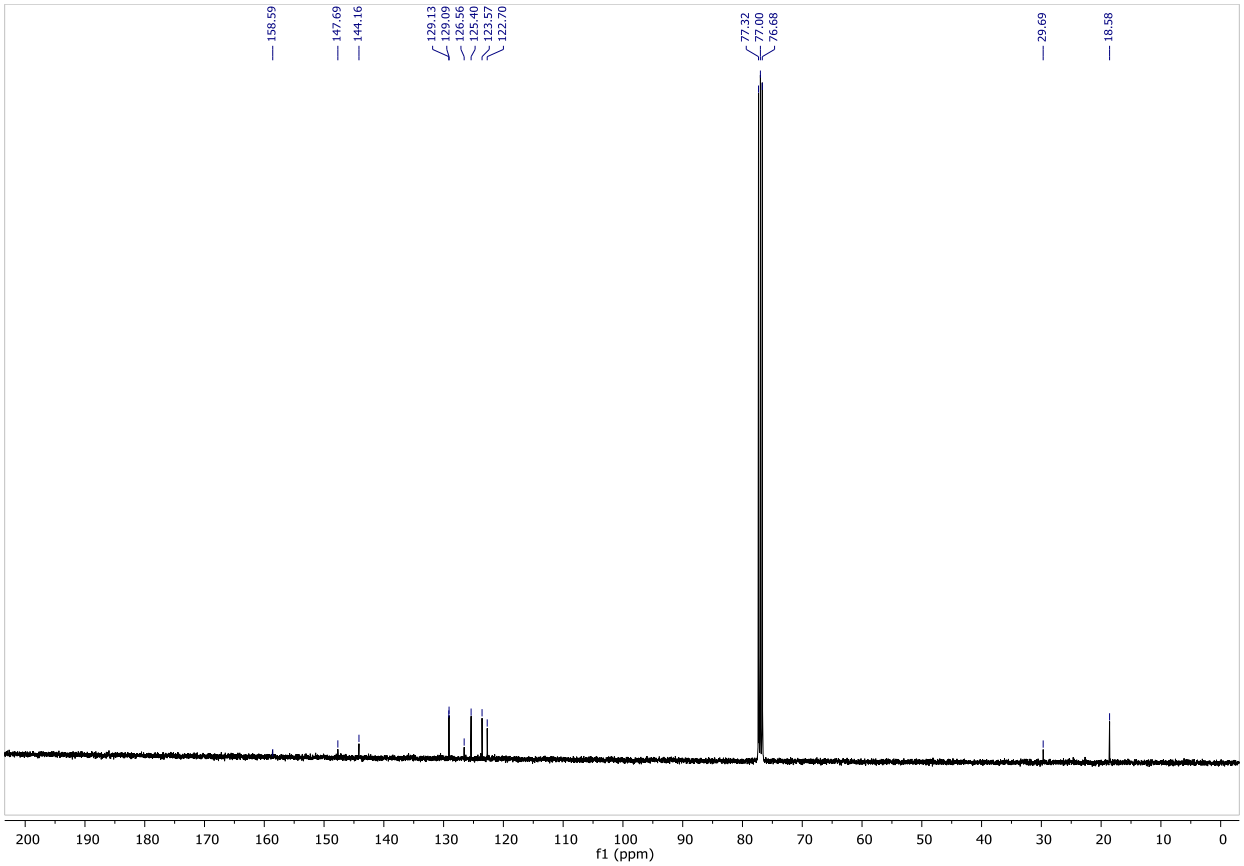

7.70
7.70
7.69
7.69
7.68
7.68
7.67
7.67
7.33
7.33
7.31
7.31
7.29
7.29
7.29
7.26
7.23
7.23
7.22
7.21
7.20
7.19
7.13
7.12
7.11
7.10
7.09
7.08
6.86
6.86
6.84
6.84
6.82
6.82
6.68
6.68
6.66
6.66
4.40
3.97
N
H
4.3-5g
2.02
0.97
0.97
1.92
0.96
1.00
1.95
1.01
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

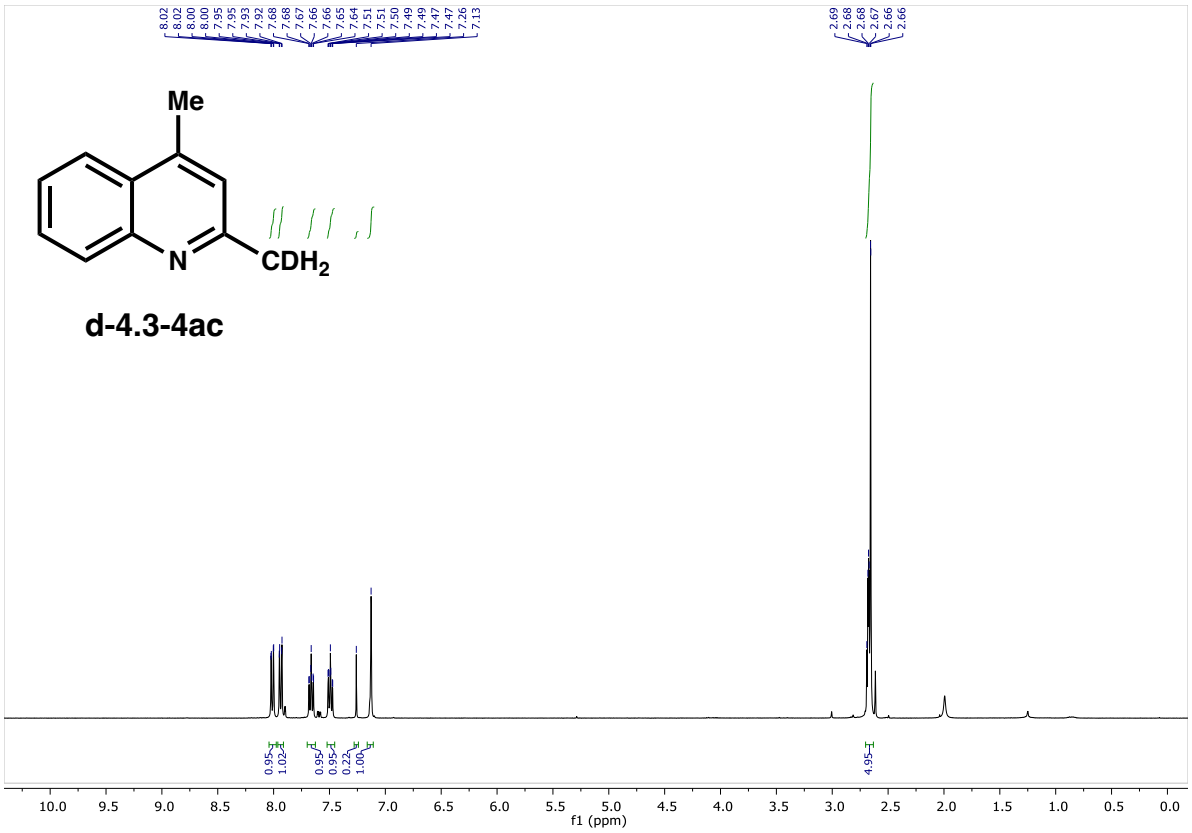

145.68
132.72
132.05
128.78
127.64
127.10
125.98
123.57
122.40
122.05
119.26
115.09
77.32
77.00
76.68
46.38
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

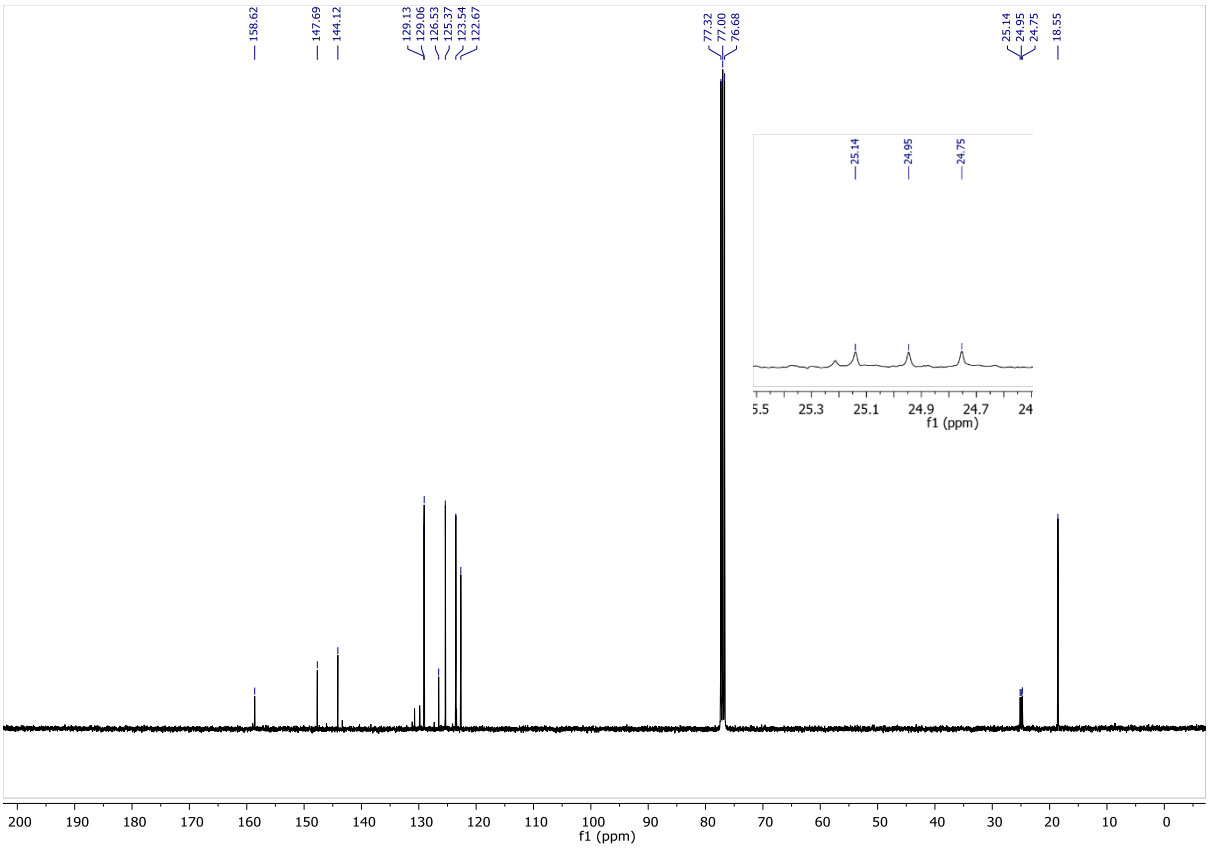

Me
N
CD3
d3-4.3-4ac
f1 (ppm)

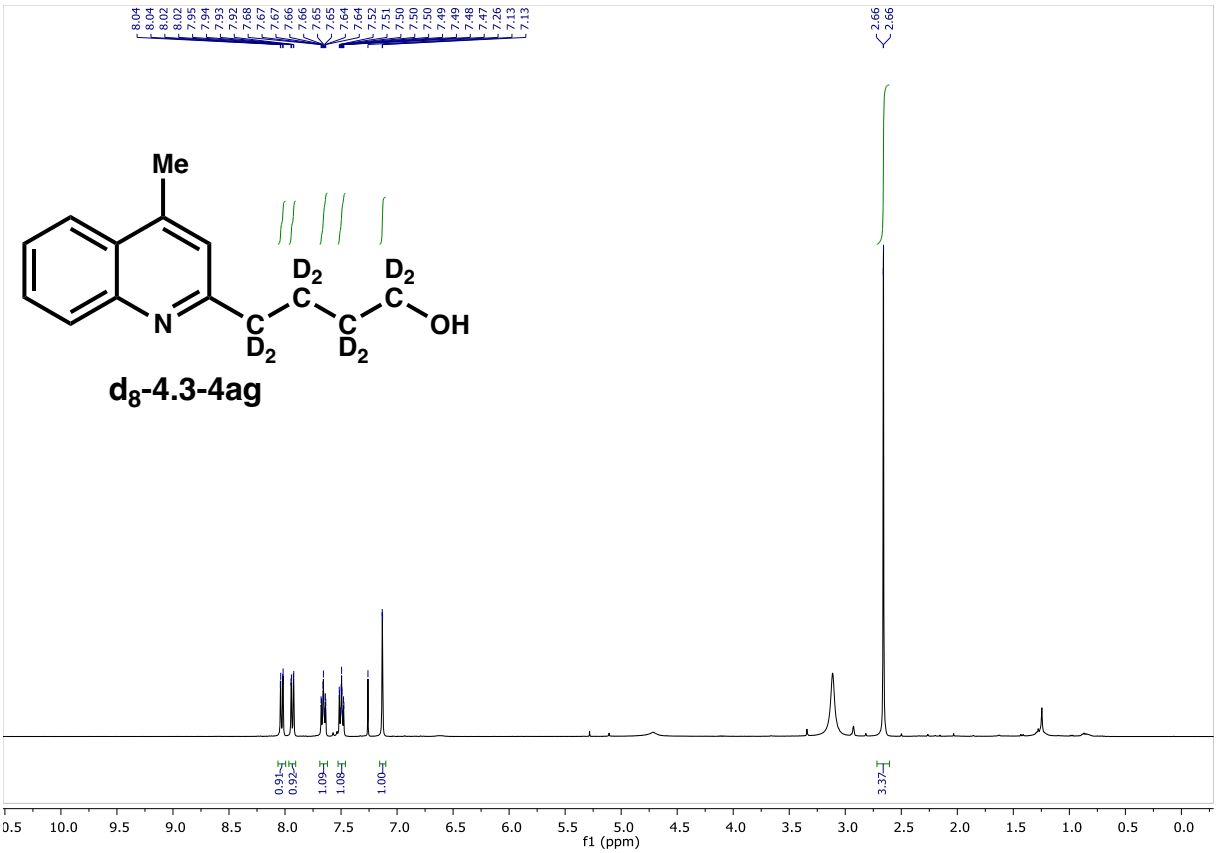

158.59
147.55
144.32
129.15
129.00
126.32
125.45
123.57
122.73
77.32
76.68
22.68
18.59
f1 (ppm)

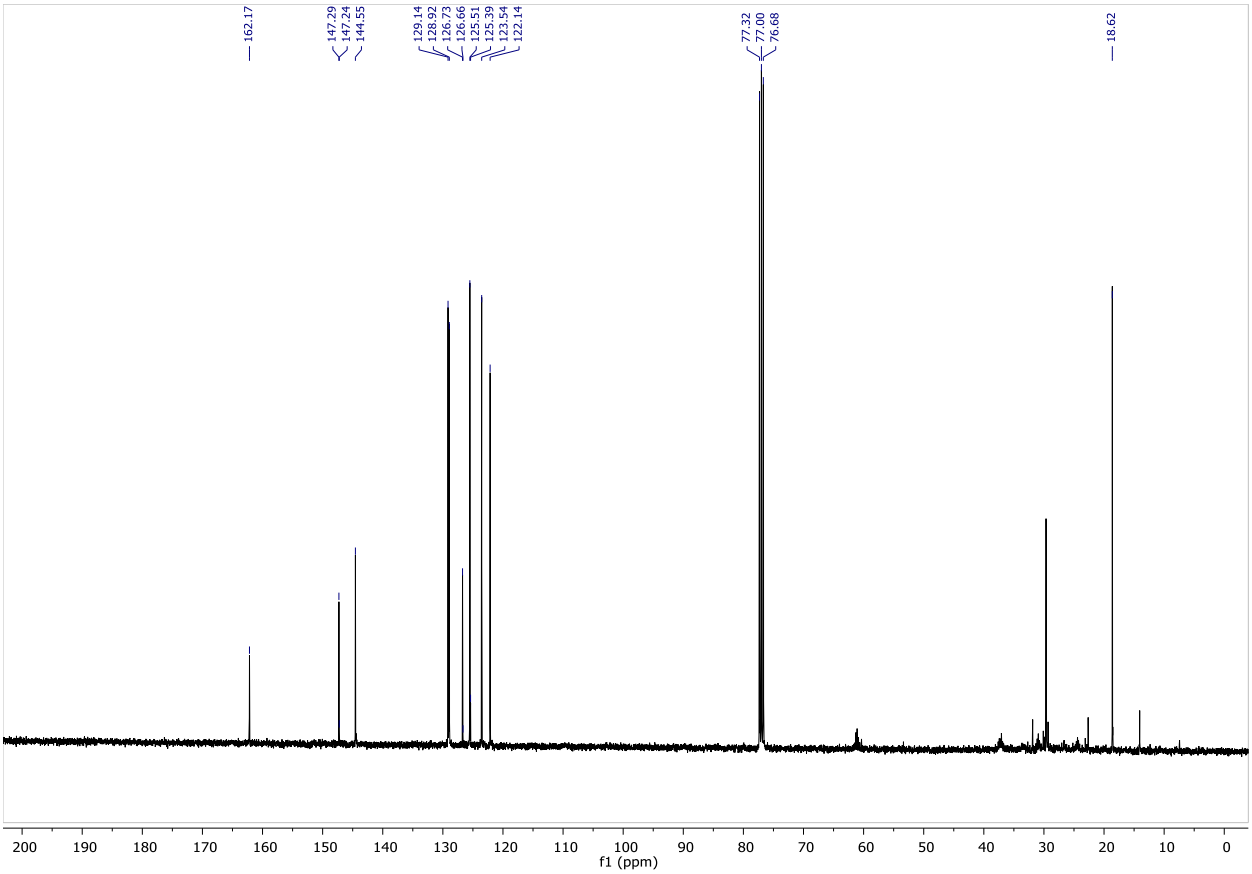

Me
N
CD2H
d2-4.3-4ac
f1 (ppm)

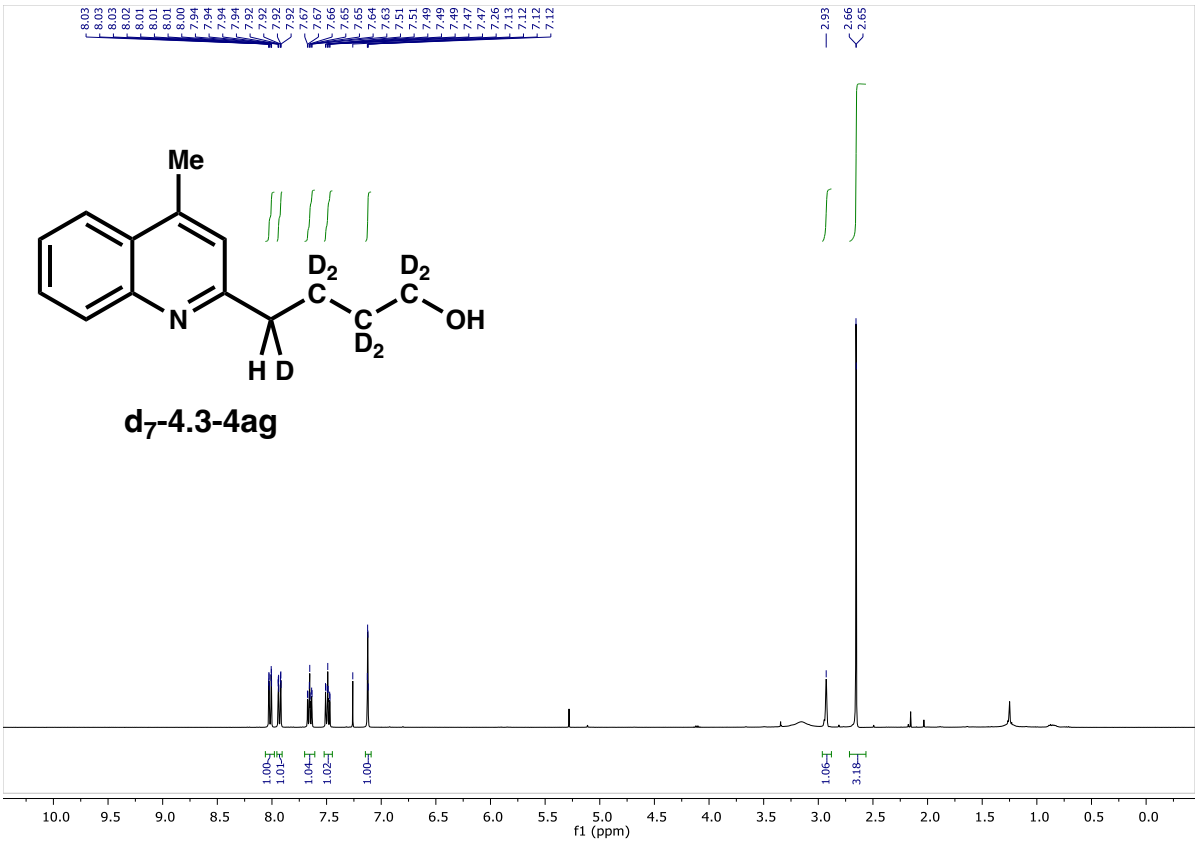

f1 (ppm)


Me
N
CDH2
d-4.3-4ac
f1 (ppm)

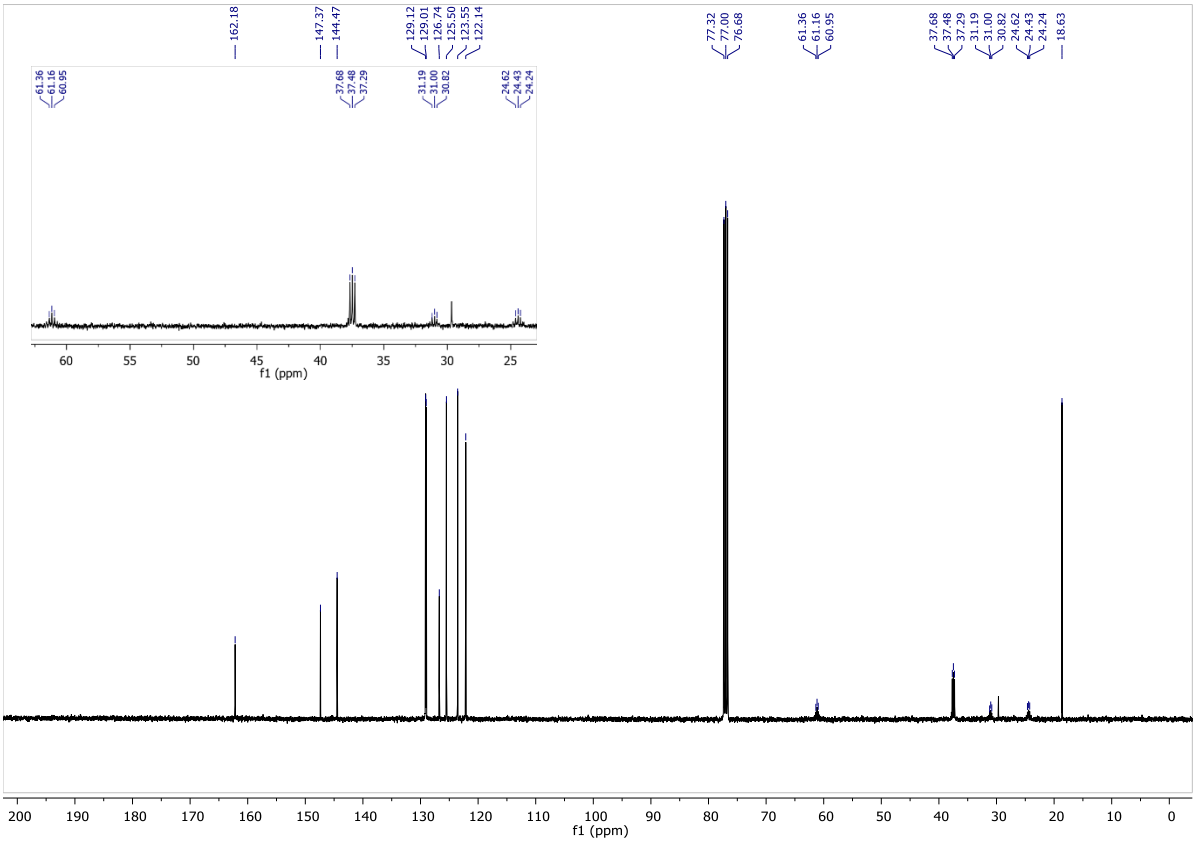

f1 (ppm)

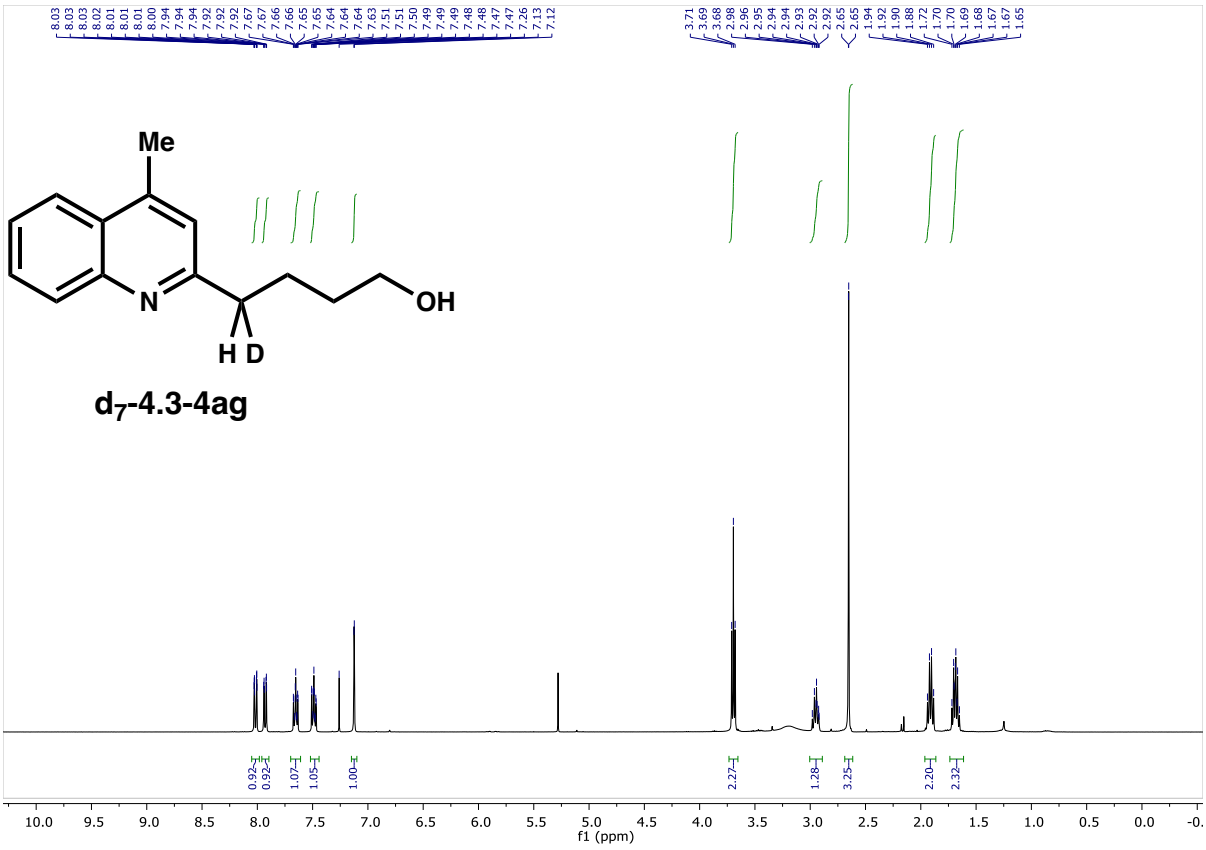

Me
D2
D2
C
C
C
C
N
D2
D2
OH
d8-4.3-4ag
f1 (ppm)

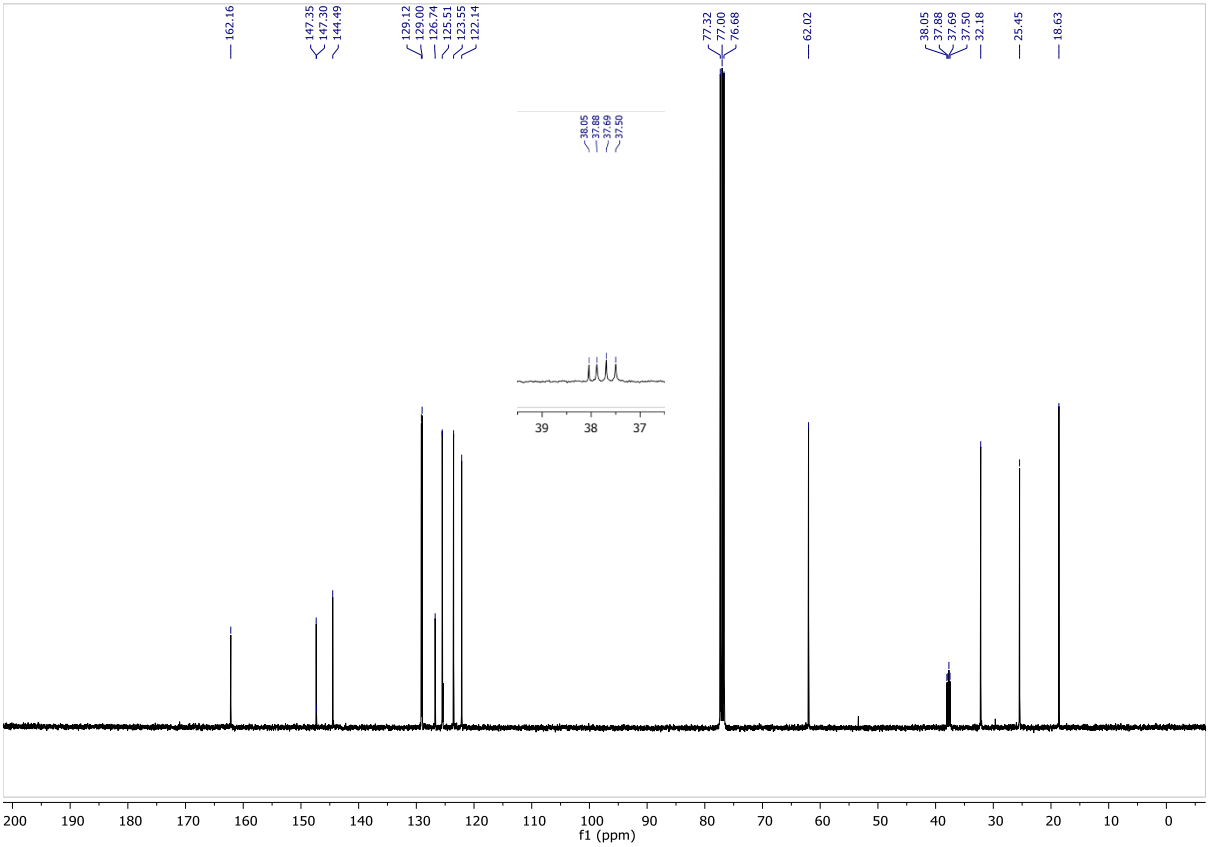

162.17
147.29
147.24
144.55
129.14
128.92
126.73
126.66
125.51
125.39
123.54
122.14
77.32
77.00
76.68
18.62
f1 (ppm)

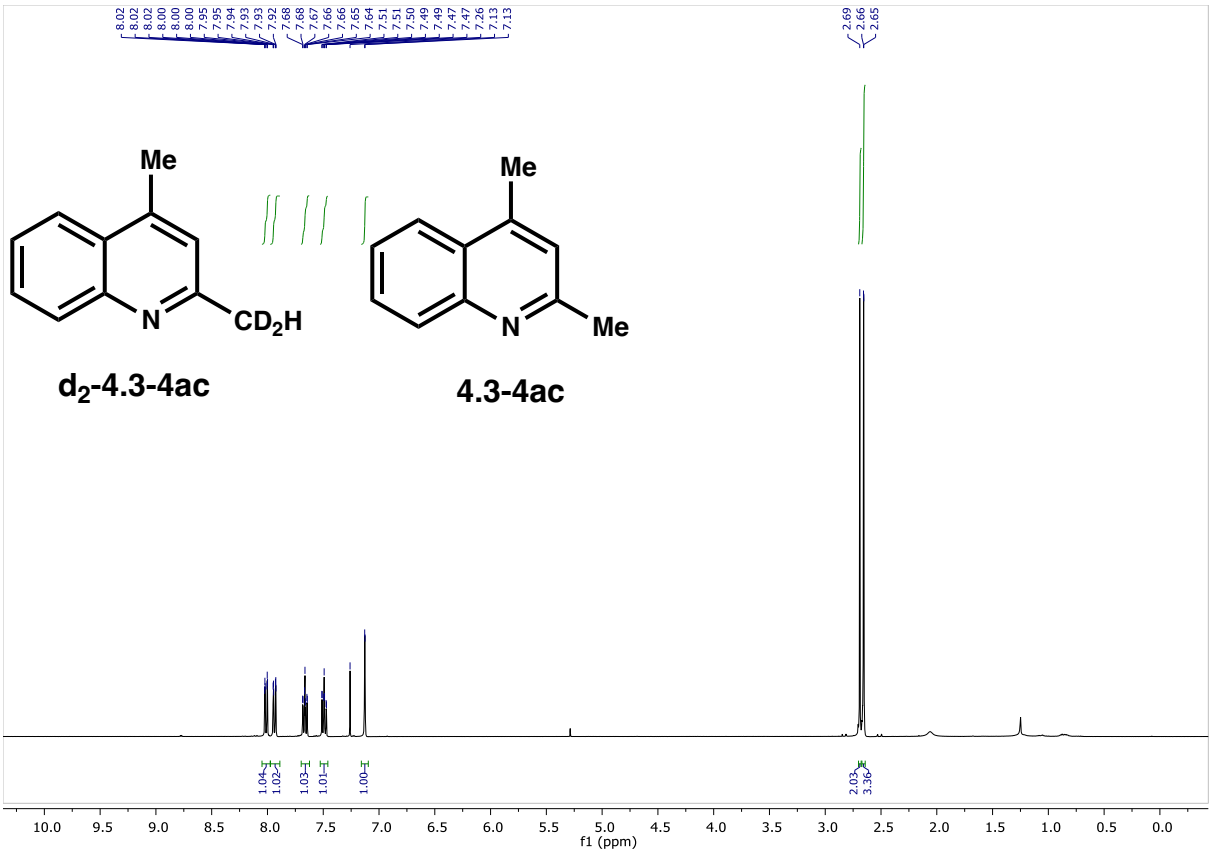


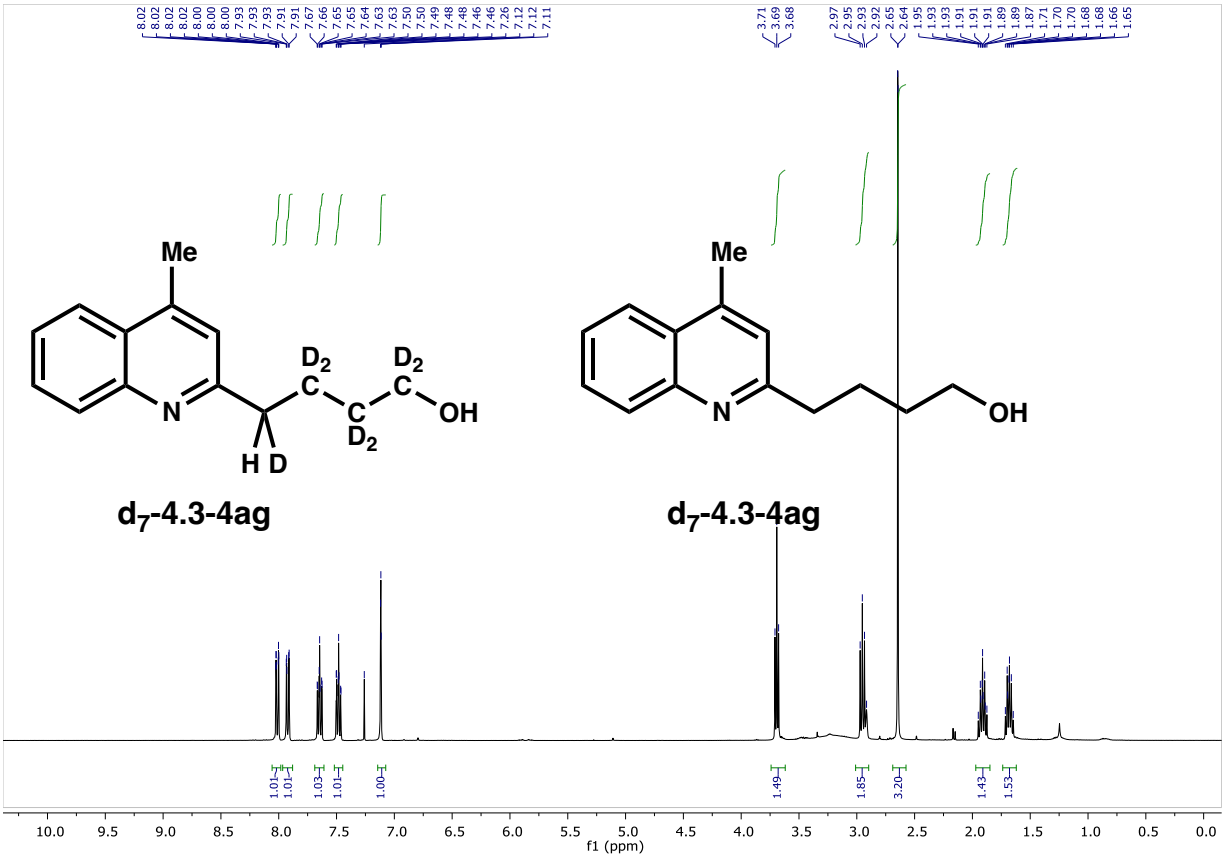
d_7-4.3-4ag



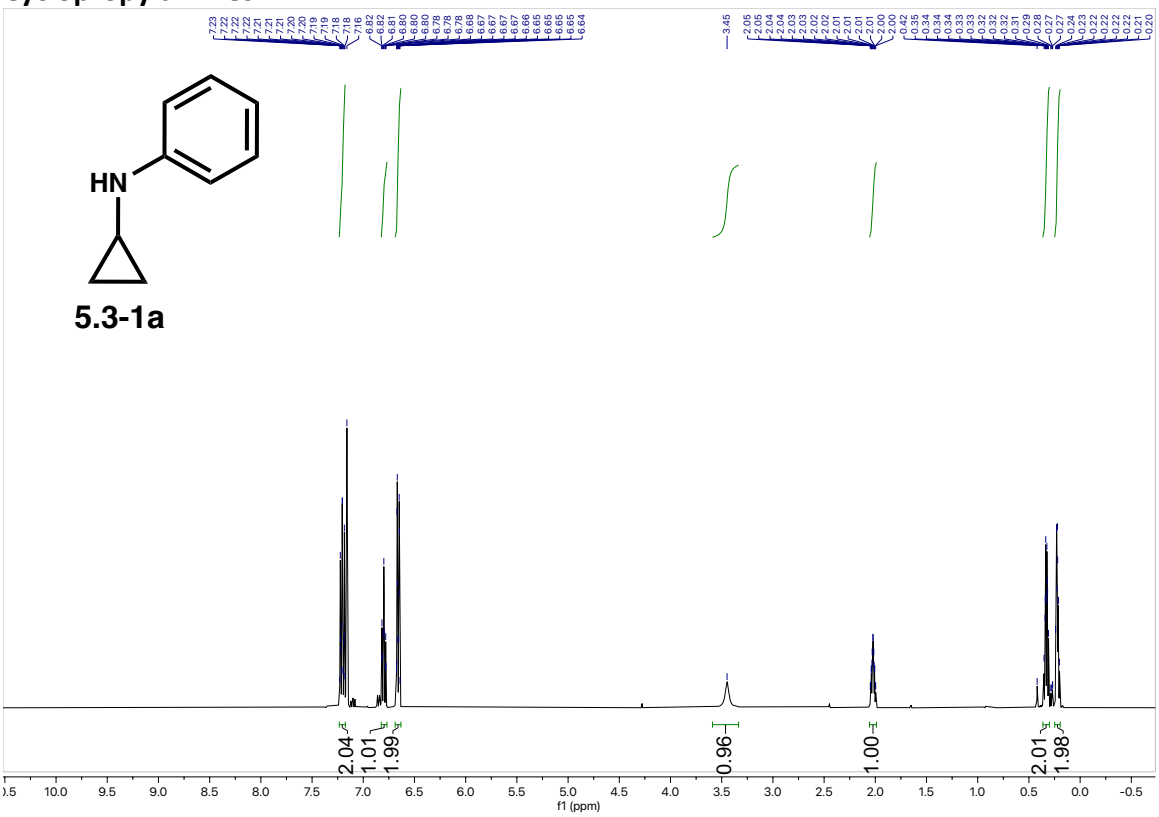

Me
N
OH
H D
d7-4.3-4ag
f1 (ppm)

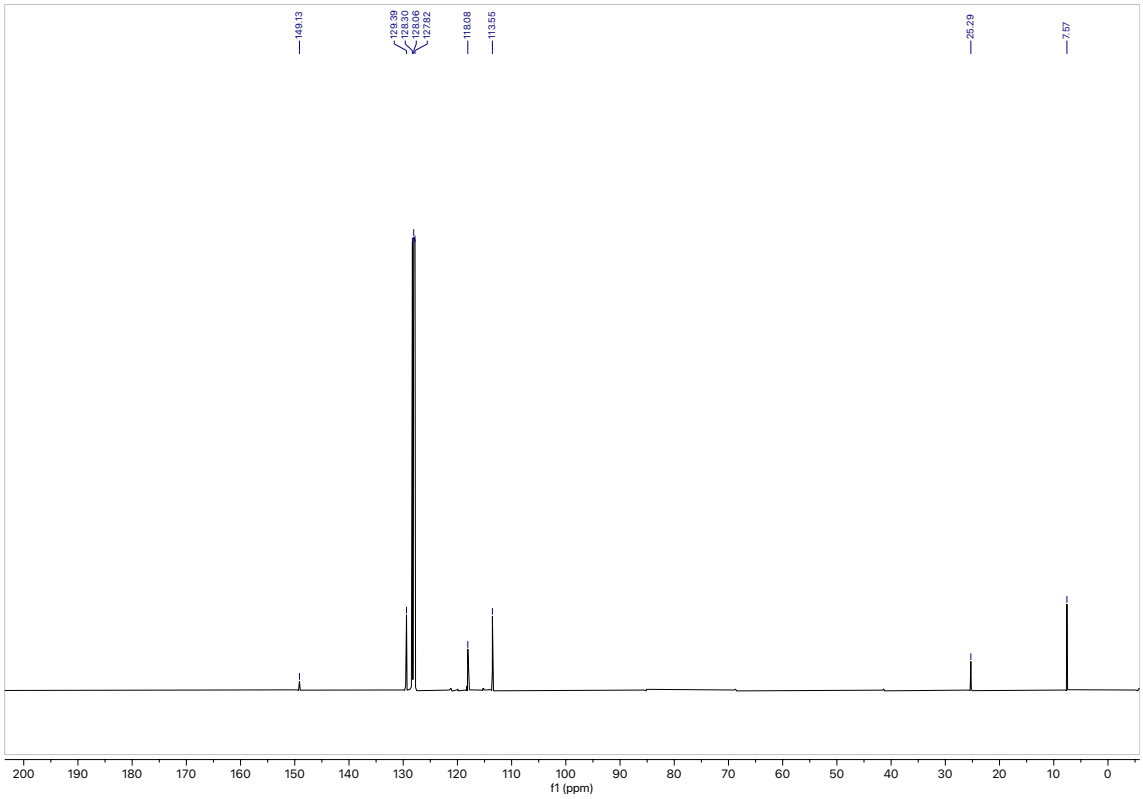

f1 (ppm)

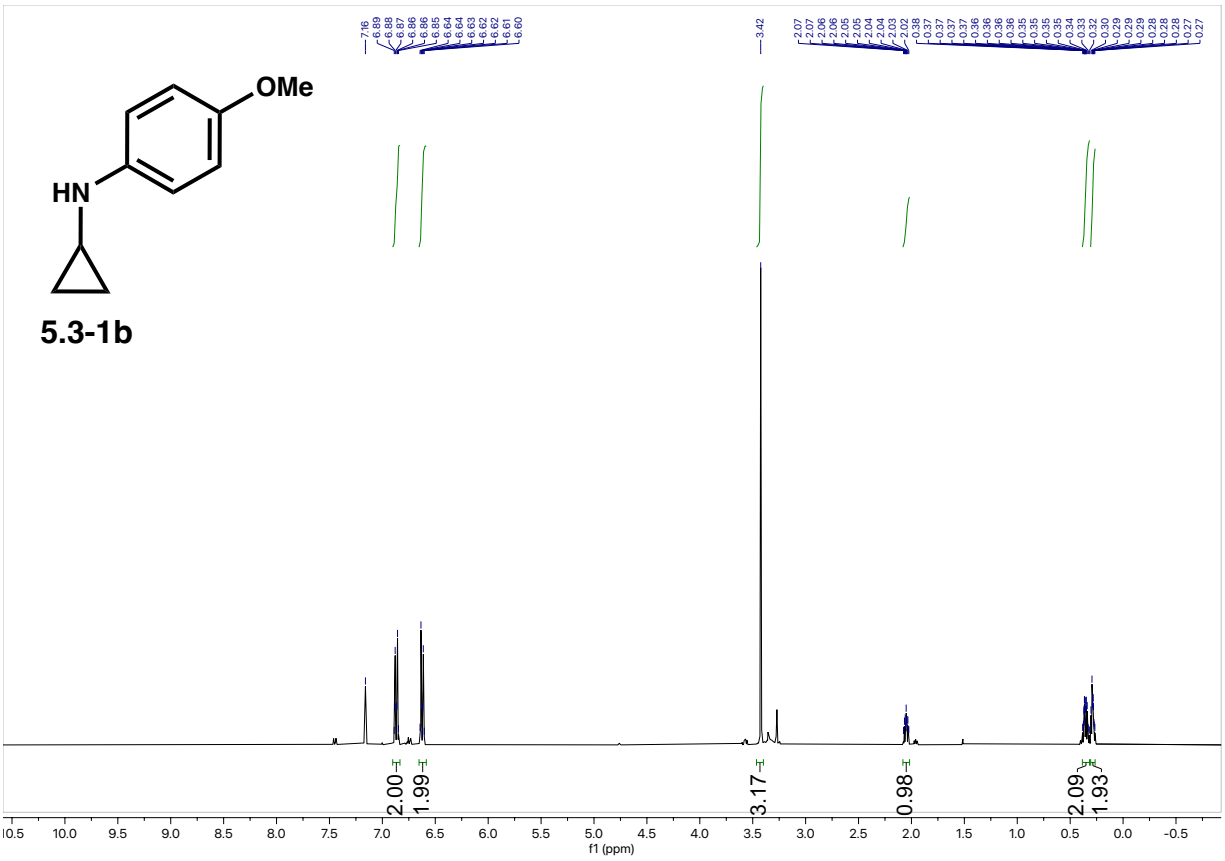

Me
N
CD2H
d2-4.3-4ac
Me
N
Me
4.3-4ac
f1 (ppm)

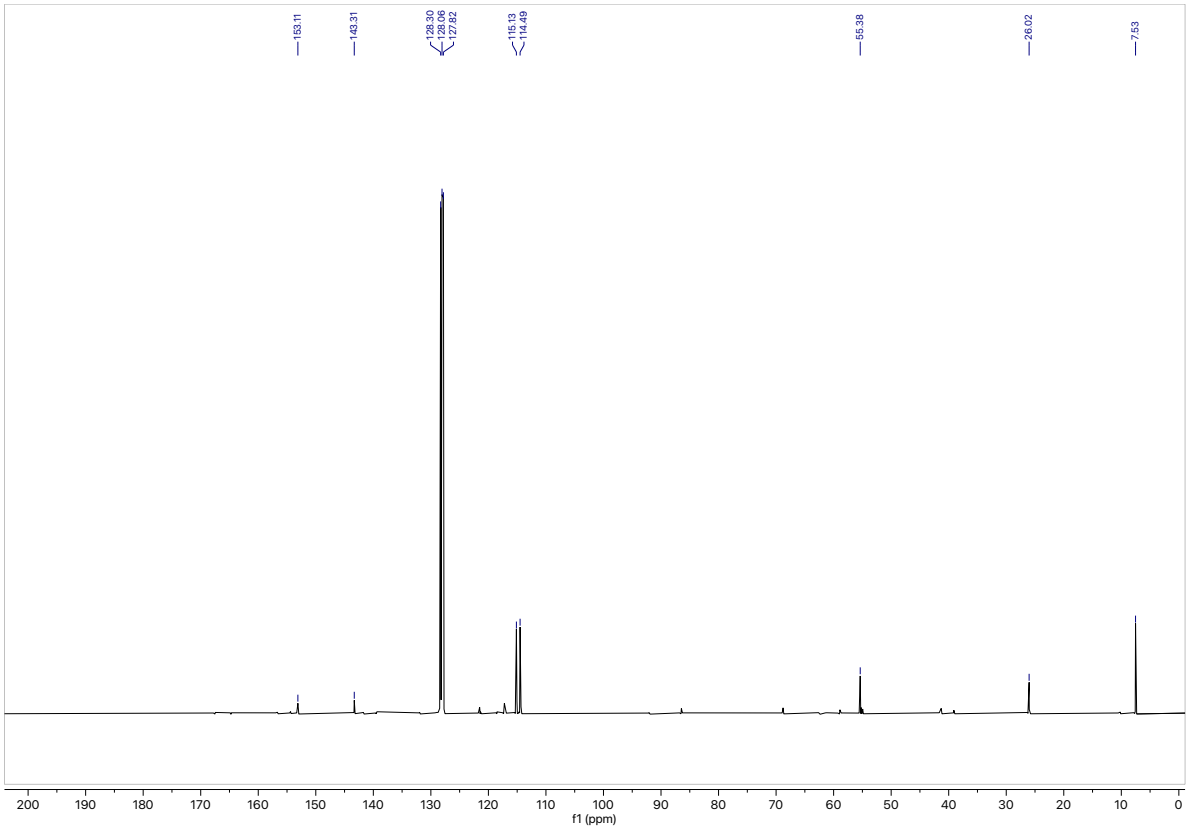

Me
N
D2
C
D2
C
C
OH
D2
H D
d7-4.3-4ag
Me
N
OH
d7-4.3-4ag
f1 (ppm)

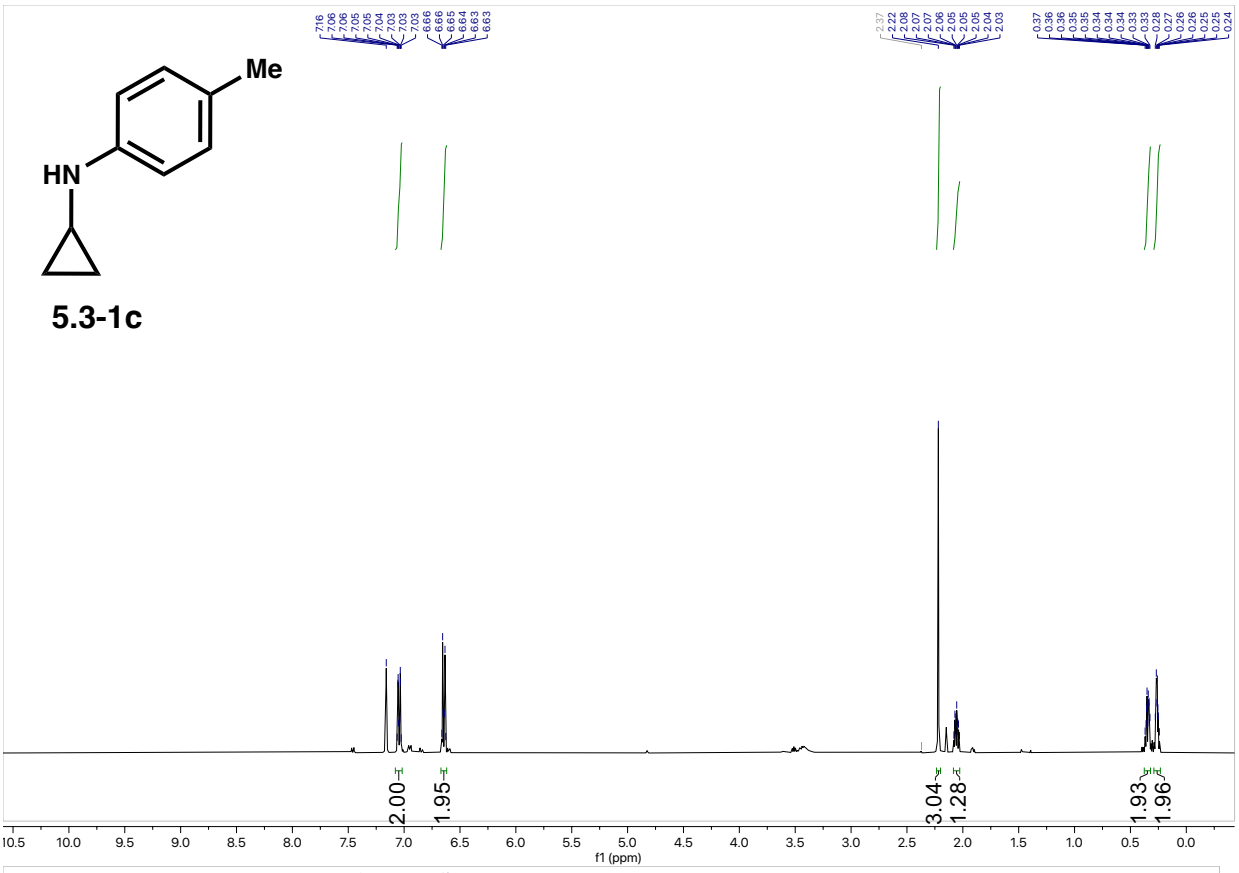
7.4- Spectral Data from Chapter 5: Photoactivated Cycloadditions of *N*-Aryl Cyclopropylamines

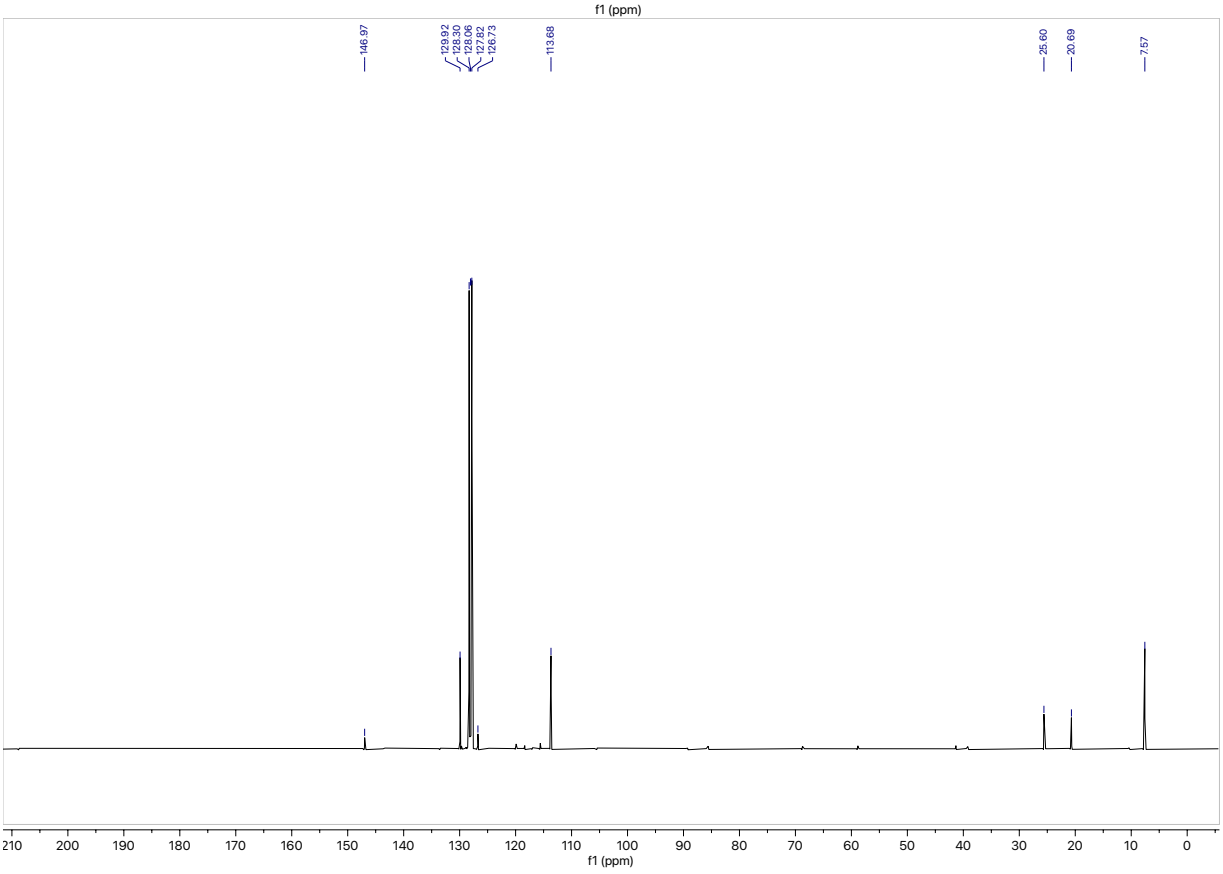


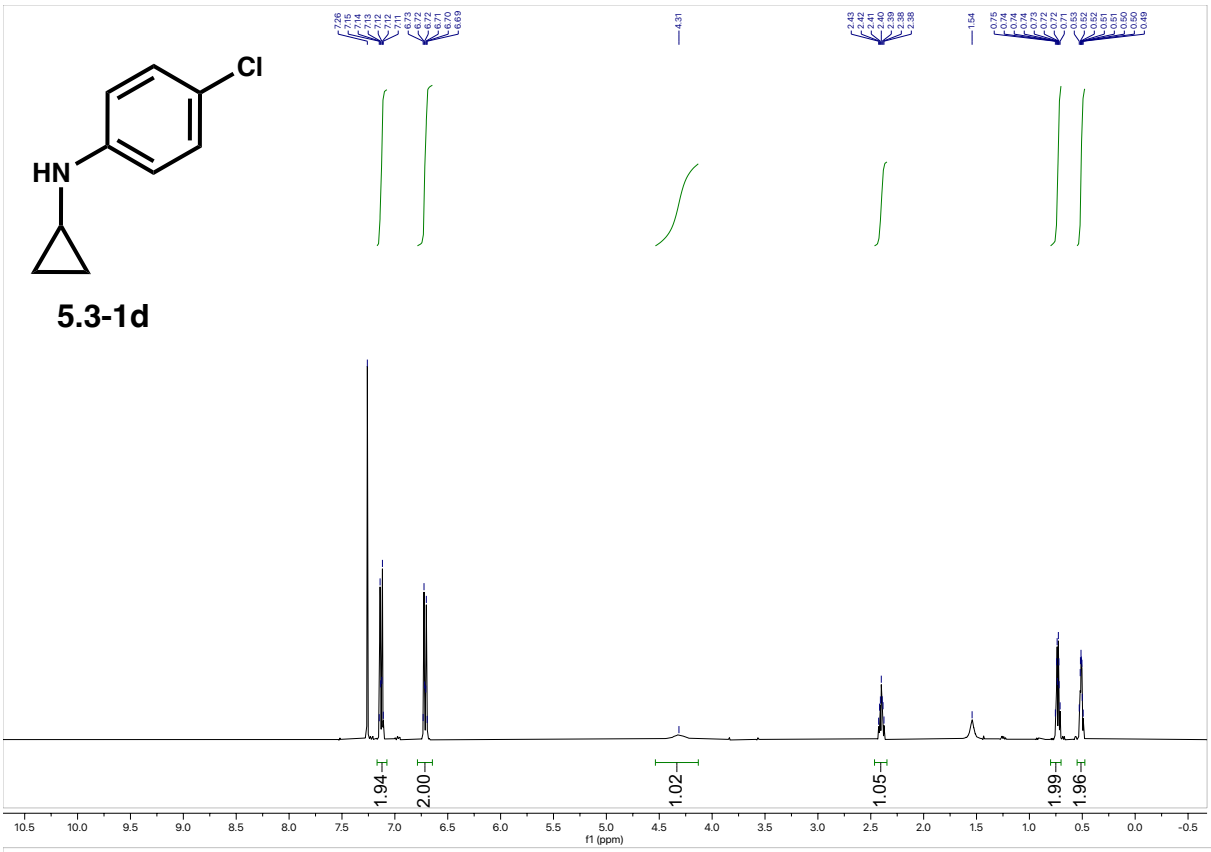


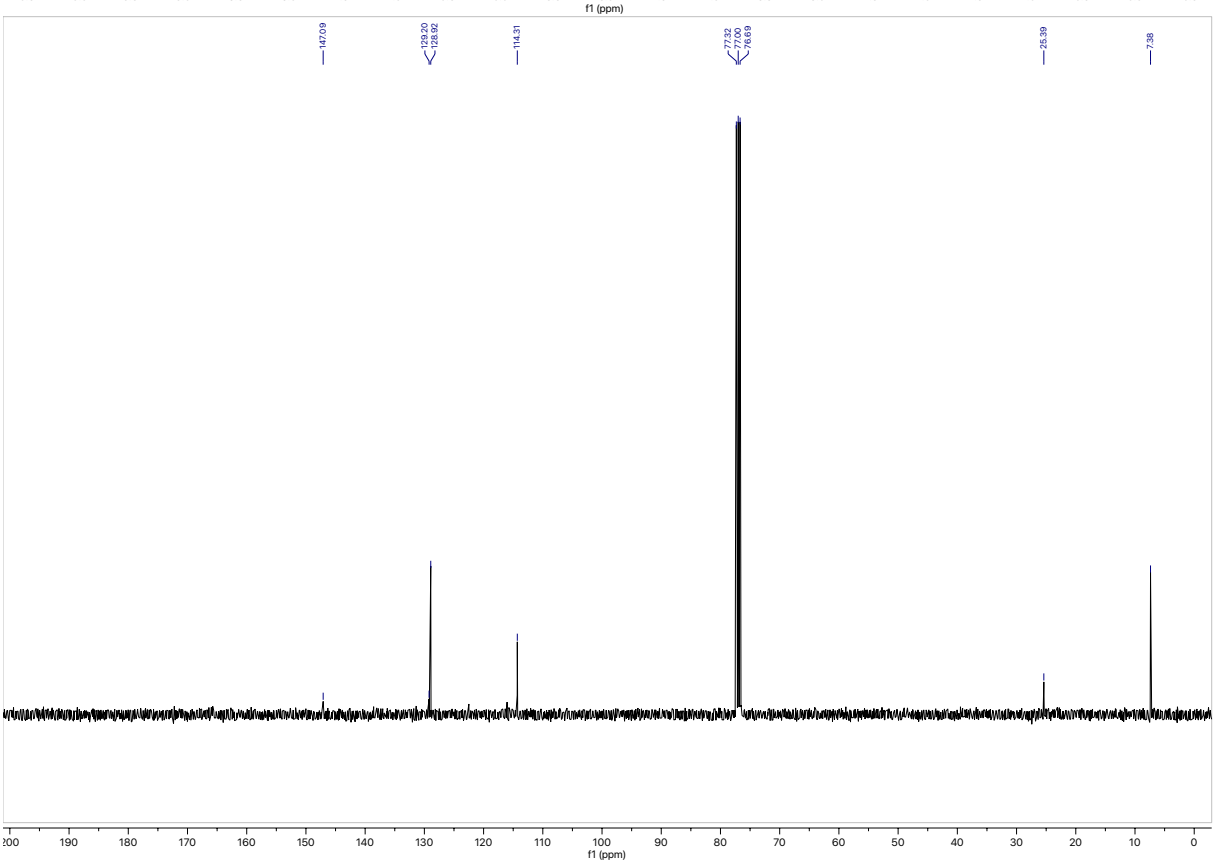

OMe
HN
5.3-1b
f1 (ppm)

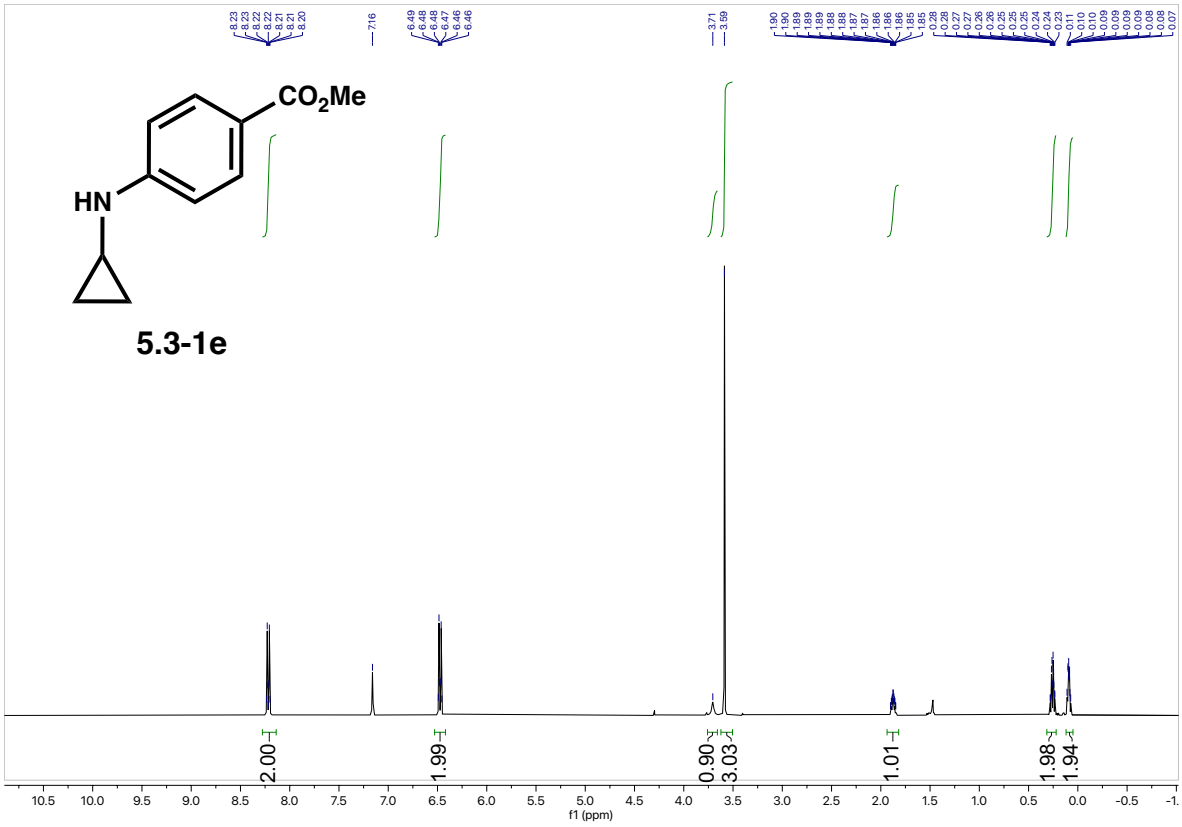

f1 (ppm)

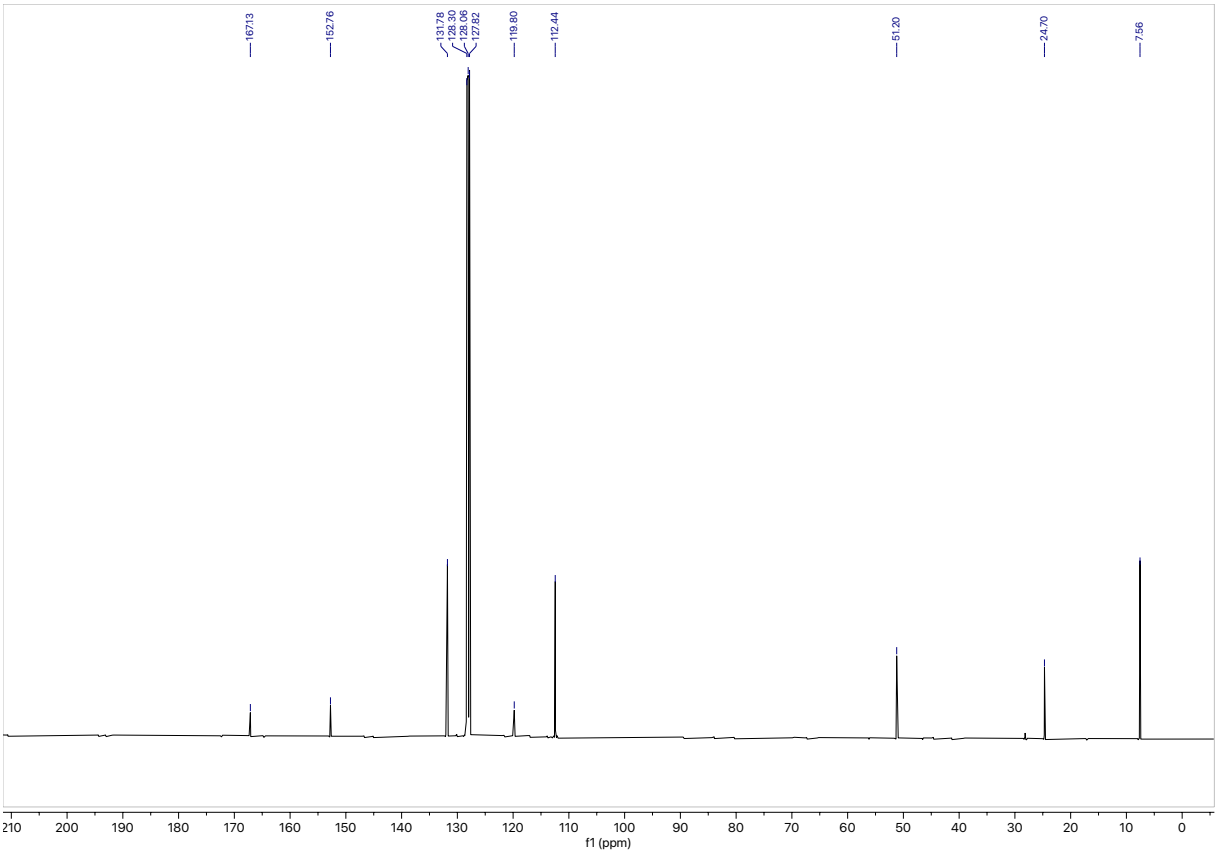

Me
HN
5.3-1c
2.00
1.95
3.04
1.28
1.93
1.96
f1 (ppm)

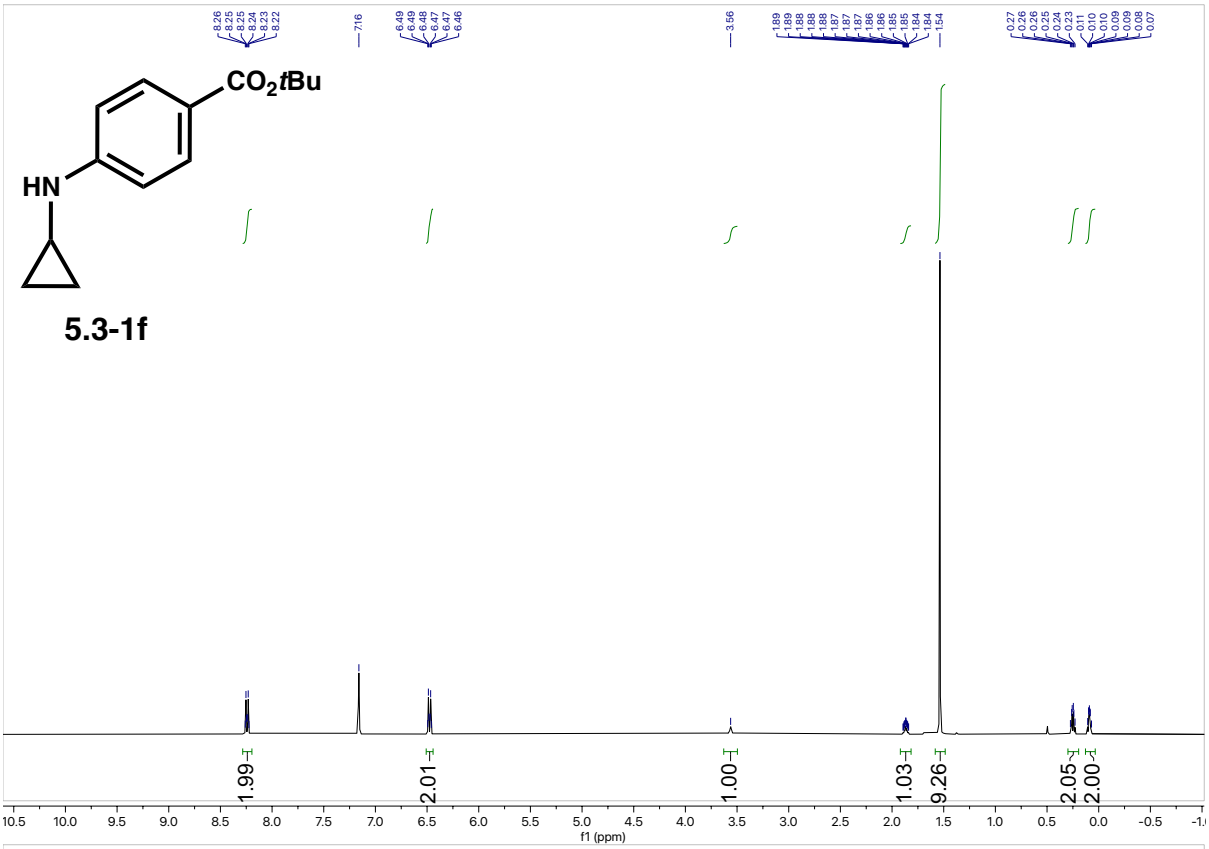

146.97
129.92
128.30
120.66
127.82
126.73
113.68
25.60
20.69
7.57
f1 (ppm)

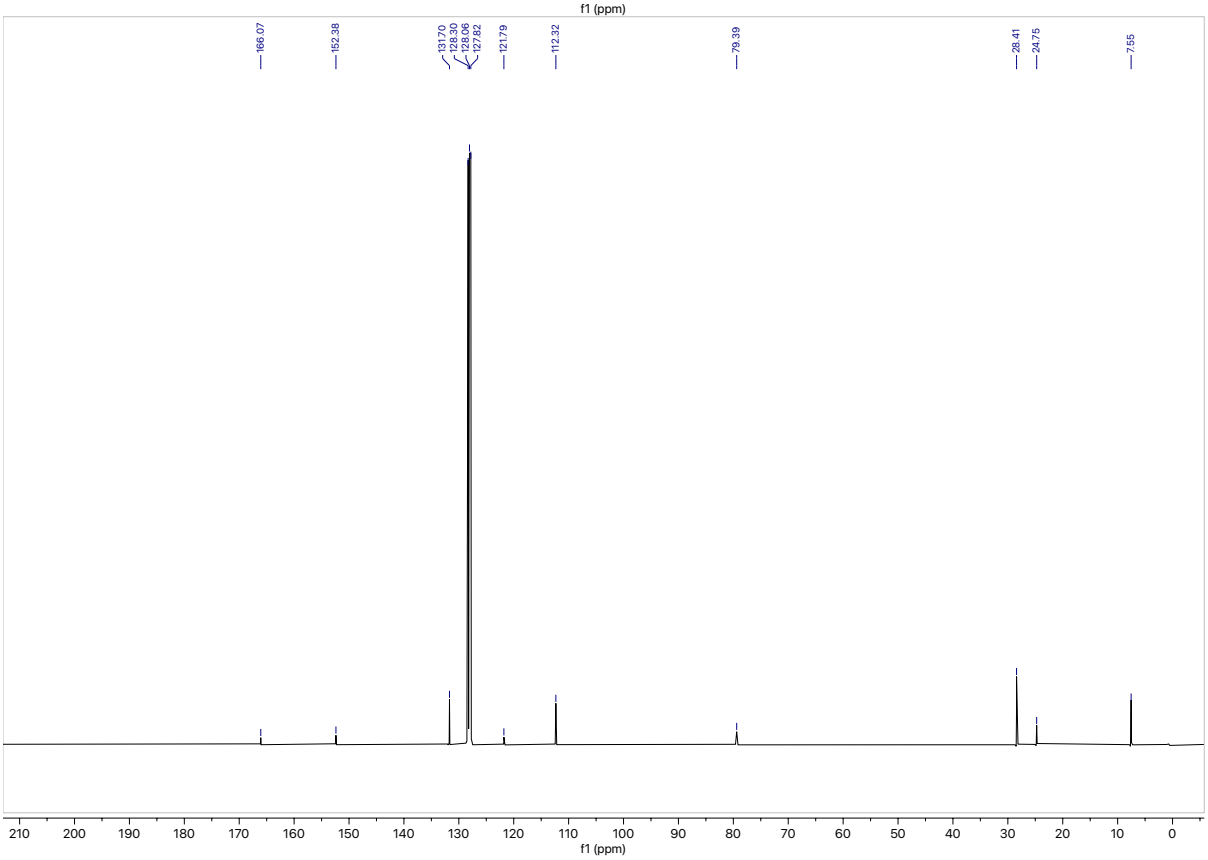

Cl
HN
5.3-1d
7.26
7.15
7.14
7.13
7.12
7.11
6.73
6.72
6.71
6.71
6.70
6.69
4.31
2.43
2.42
2.41
2.40
2.39
2.38
2.38
1.54
0.75
0.74
0.74
0.74
0.73
0.72
0.72
0.71
0.53
0.52
0.52
0.52
0.51
0.51
0.50
0.50
0.49
1.94
2.00
1.02
1.05
1.99
1.96
f1 (ppm)

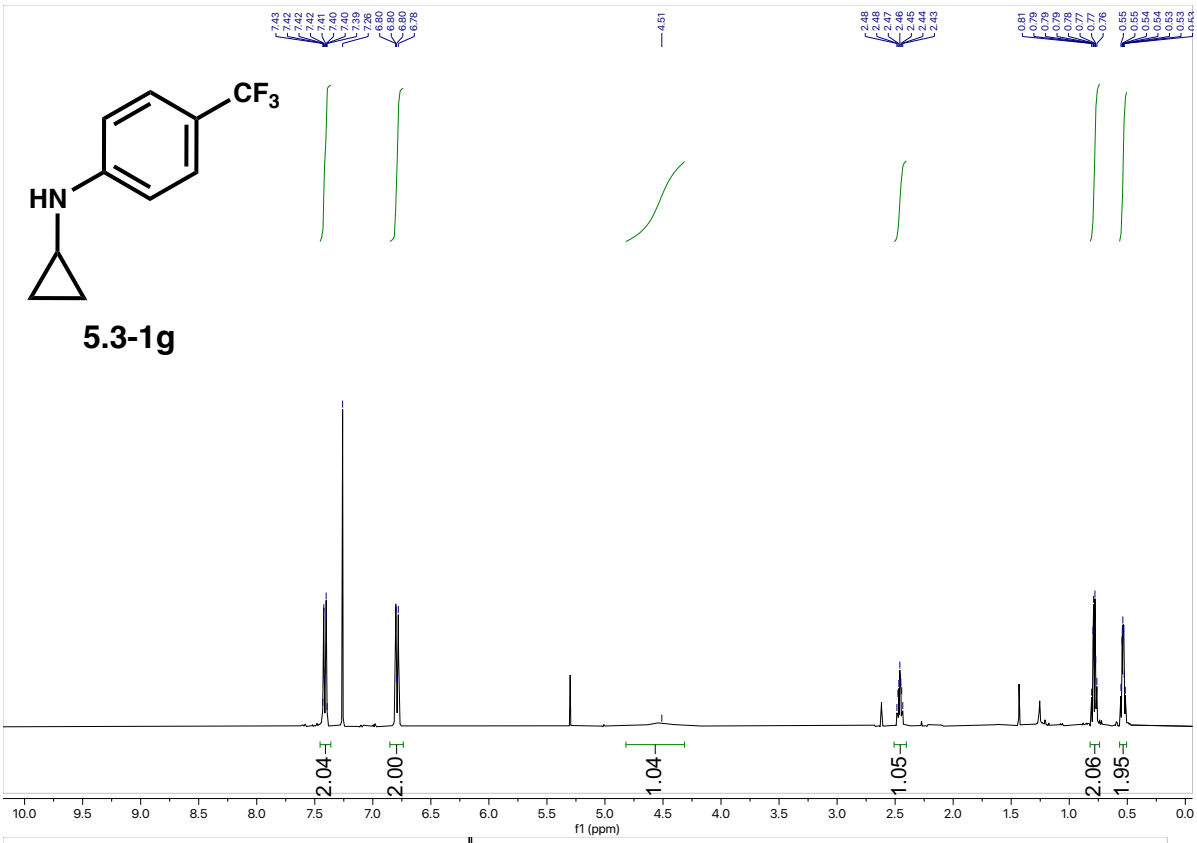

147.09
129.20
128.92
114.31
77.32
77.00
76.69
25.39
7.38
f1 (ppm)

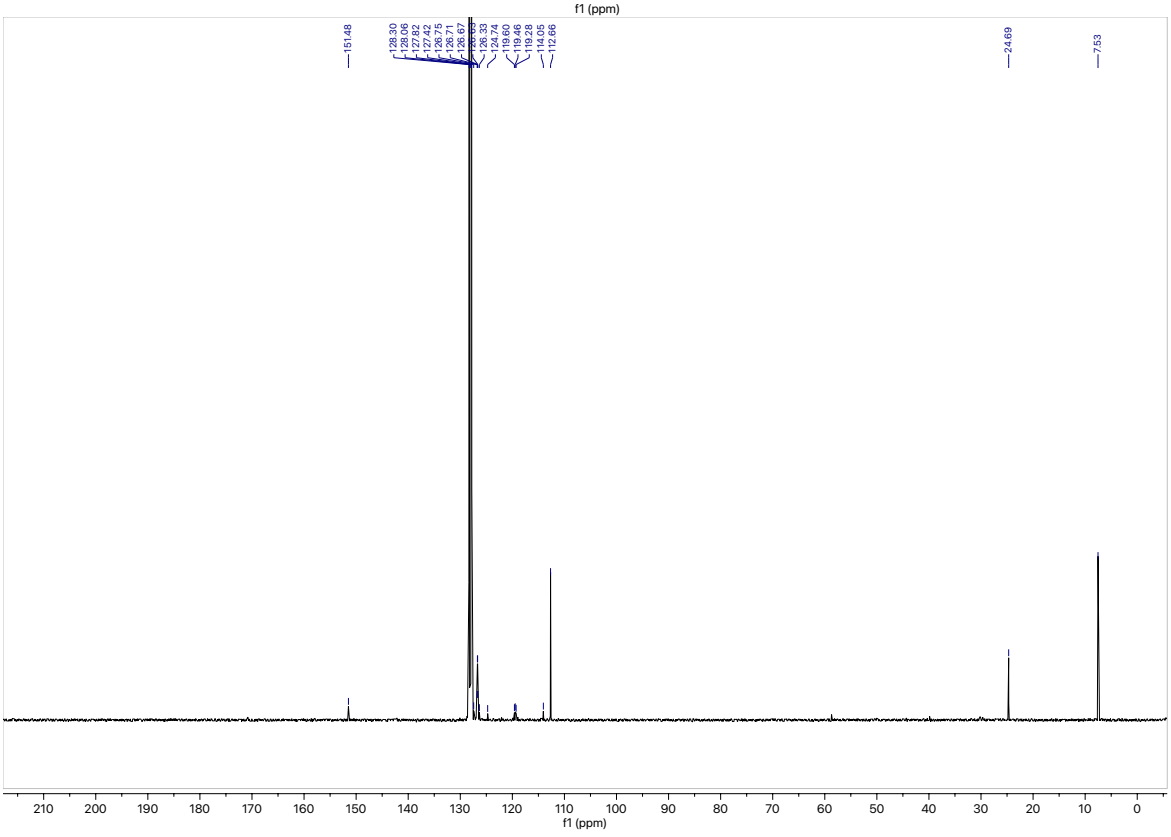

CO2Me
HN
5.3-1e
2.00
1.99
0.90
3.03
1.01
1.98
1.94
f1 (ppm)

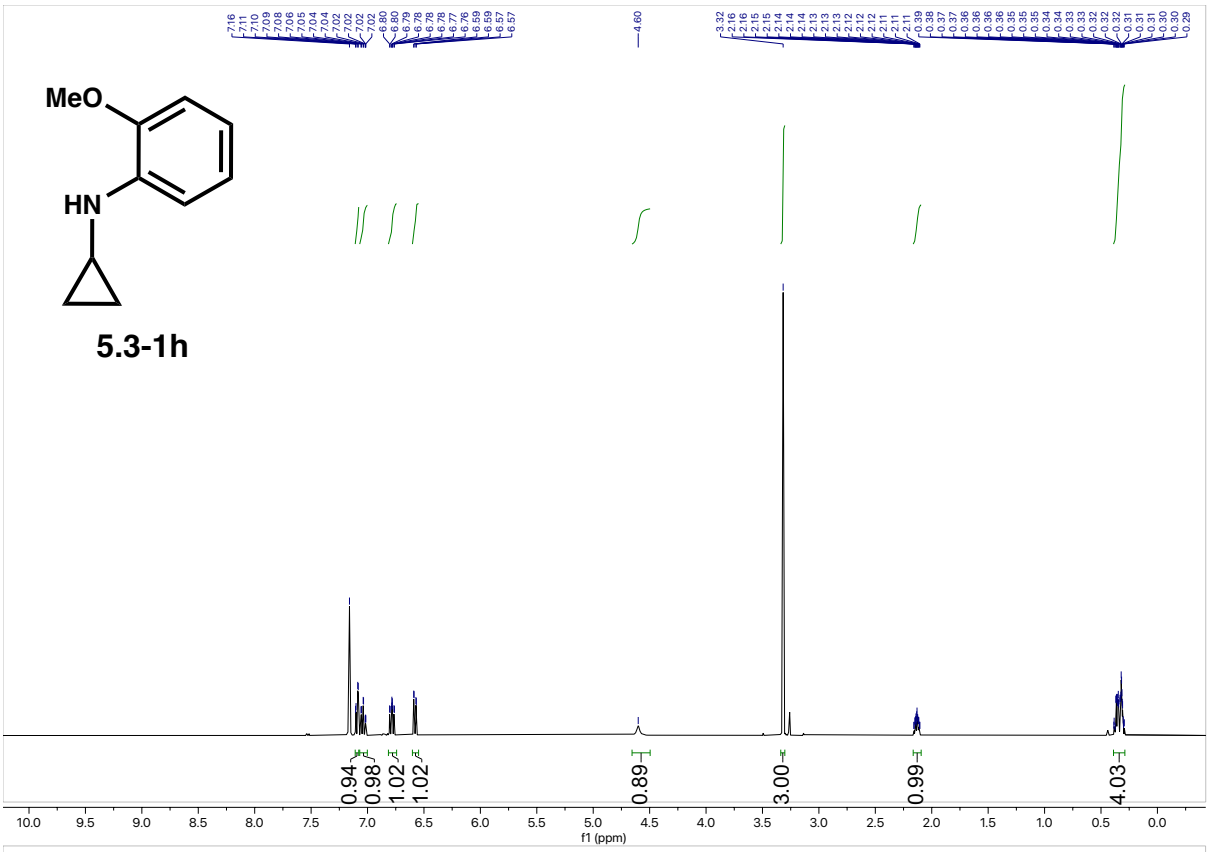

167.13
152.76
131.78
128.30
128.06
127.82
119.80
112.44
51.20
24.70
7.56
f1 (ppm)

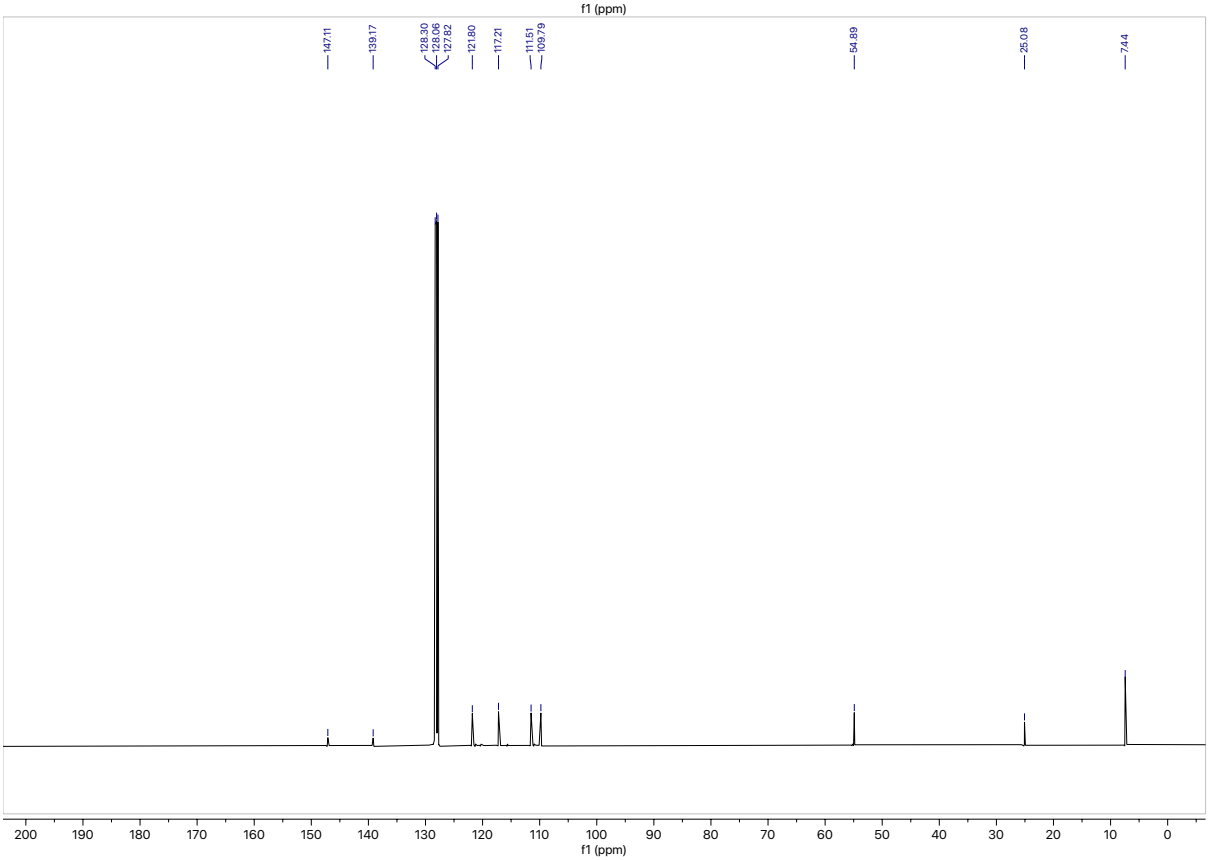

CO2tBu
HN
5.3-1f
f1 (ppm)

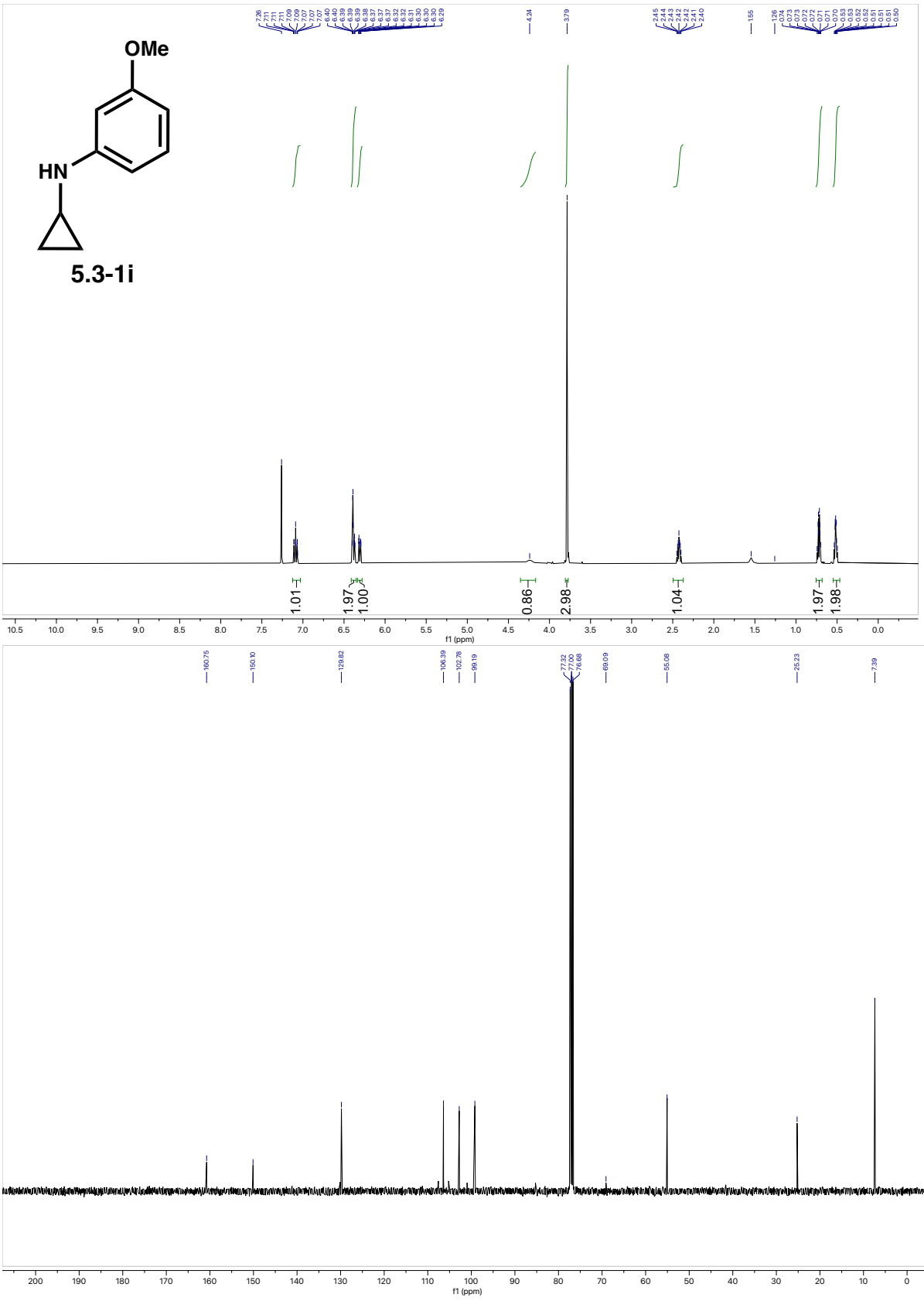

f1 (ppm)

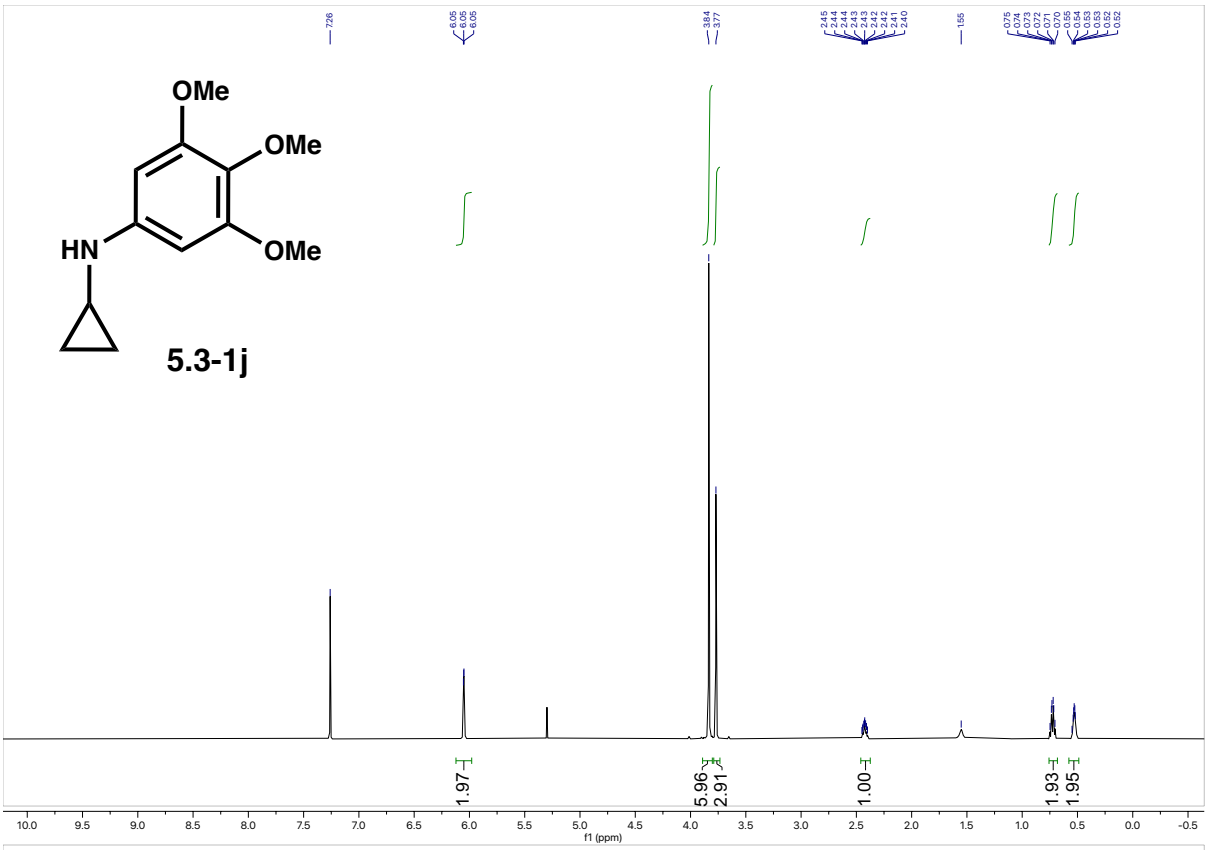

CF3
HN
5.3-1g
2.04
2.00
1.04
1.05
2.06
1.95
f1 (ppm)

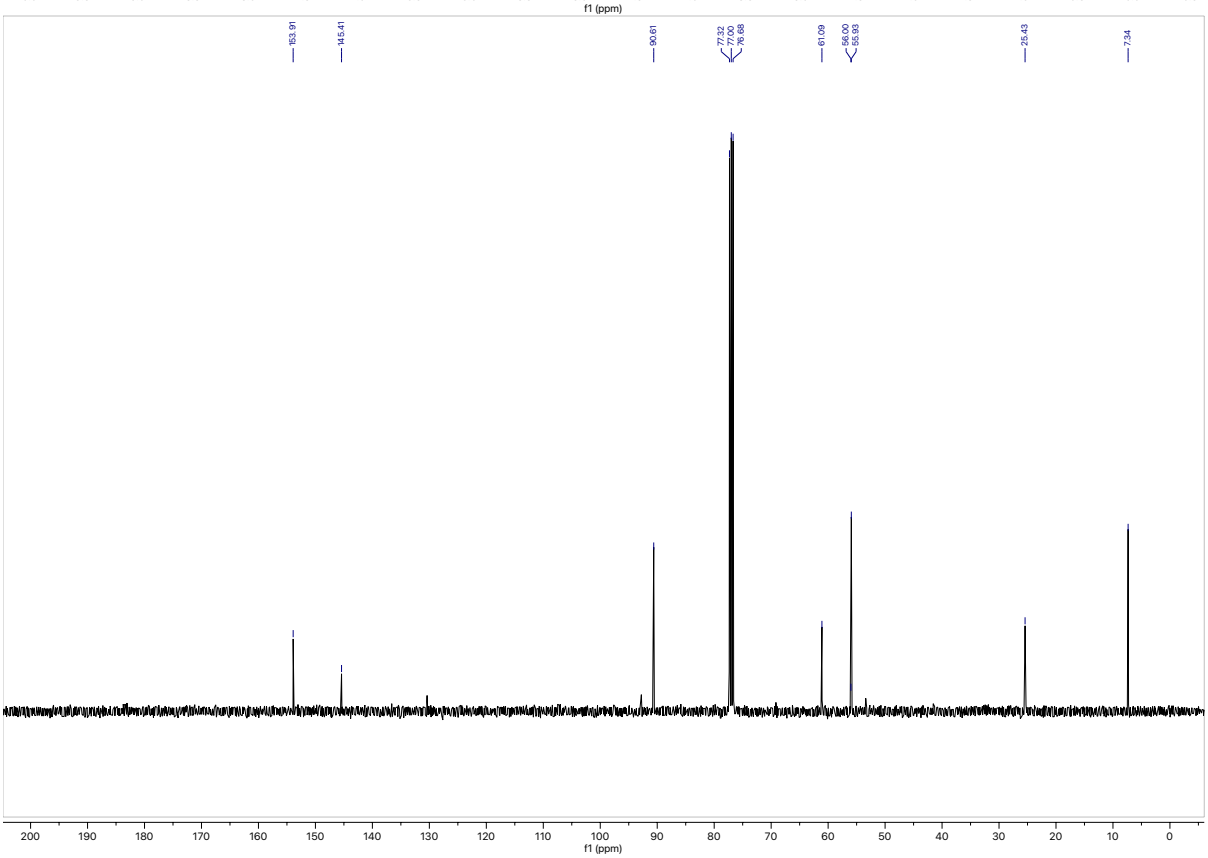

f1 (ppm)

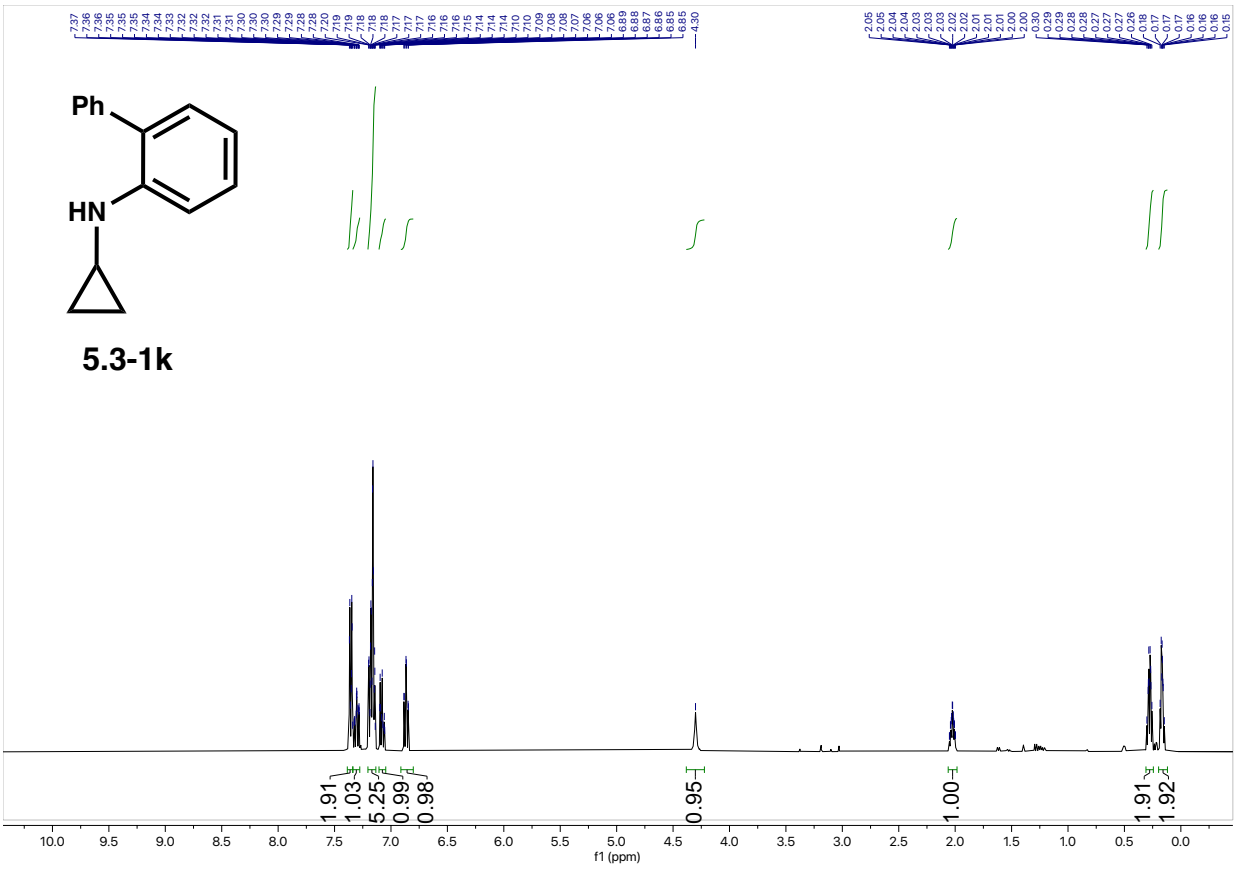

MeO
HN
5.3-1h
0.94
0.98
1.02
1.02
0.89
3.00
0.99
4.03
f1 (ppm)

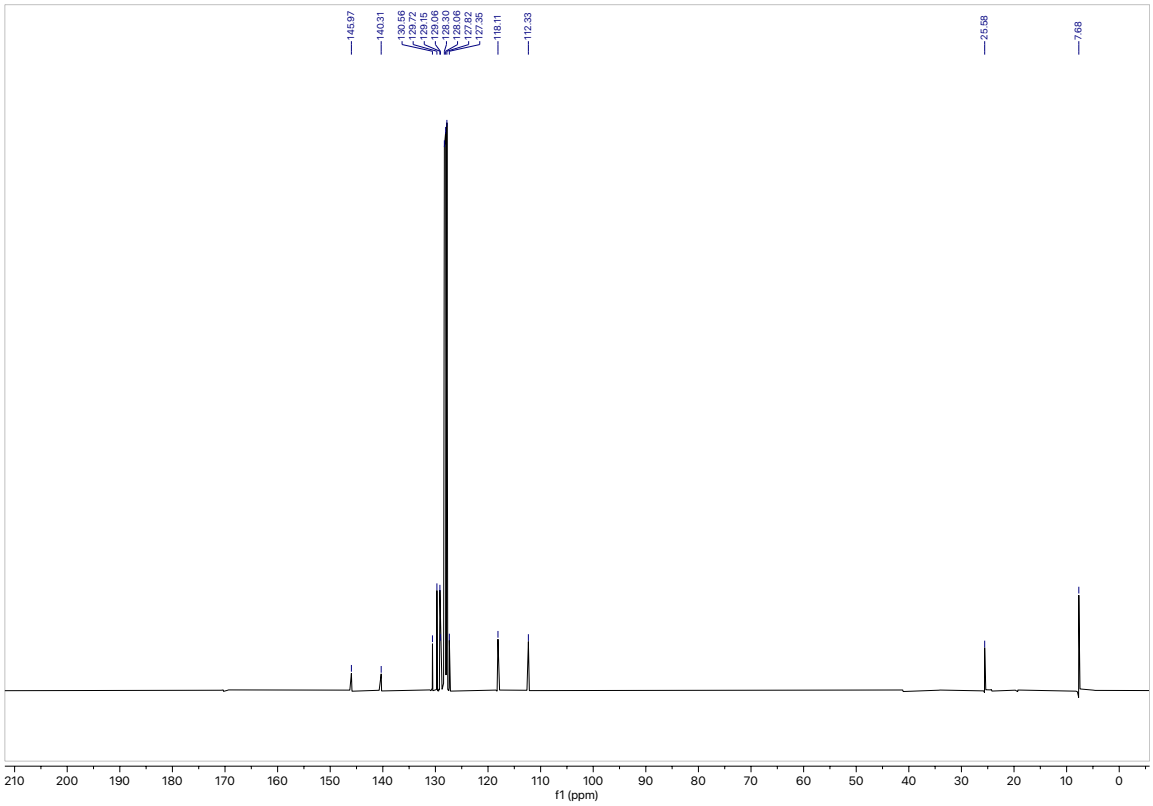

147.11
139.17
128.30
128.06
127.82
121.80
117.21
111.51
109.79
54.89
25.08
7.44
f1 (ppm)

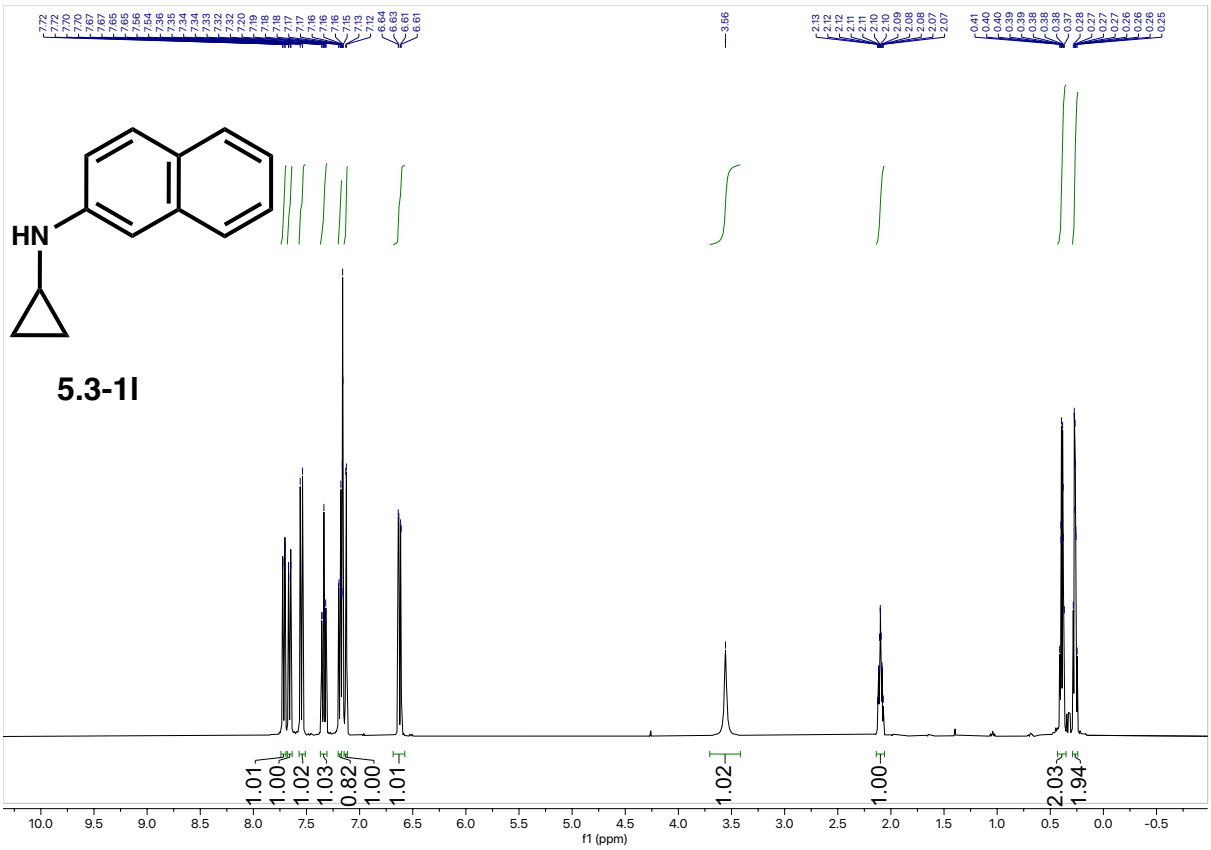

OMe
HN
5.3-1i
f1 (ppm)

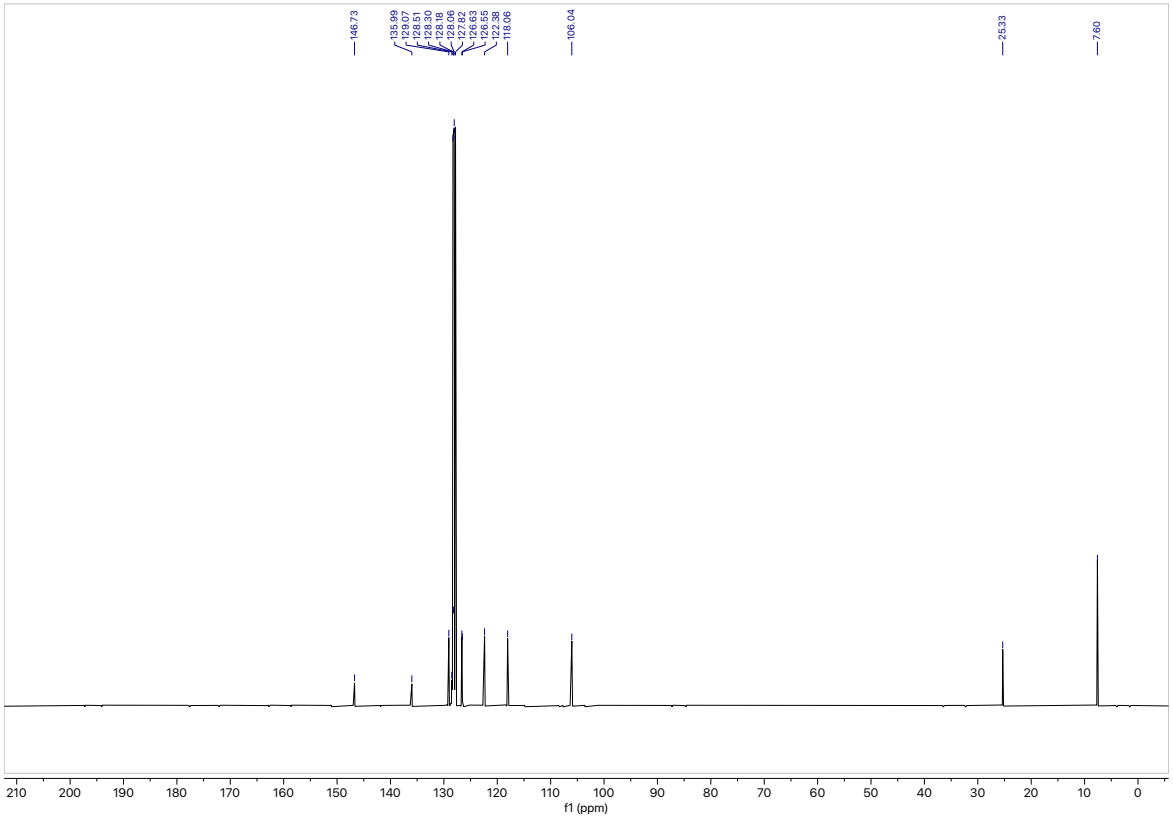

OMe
OMe
OMe
HN
5.3-1j
f1 (ppm)

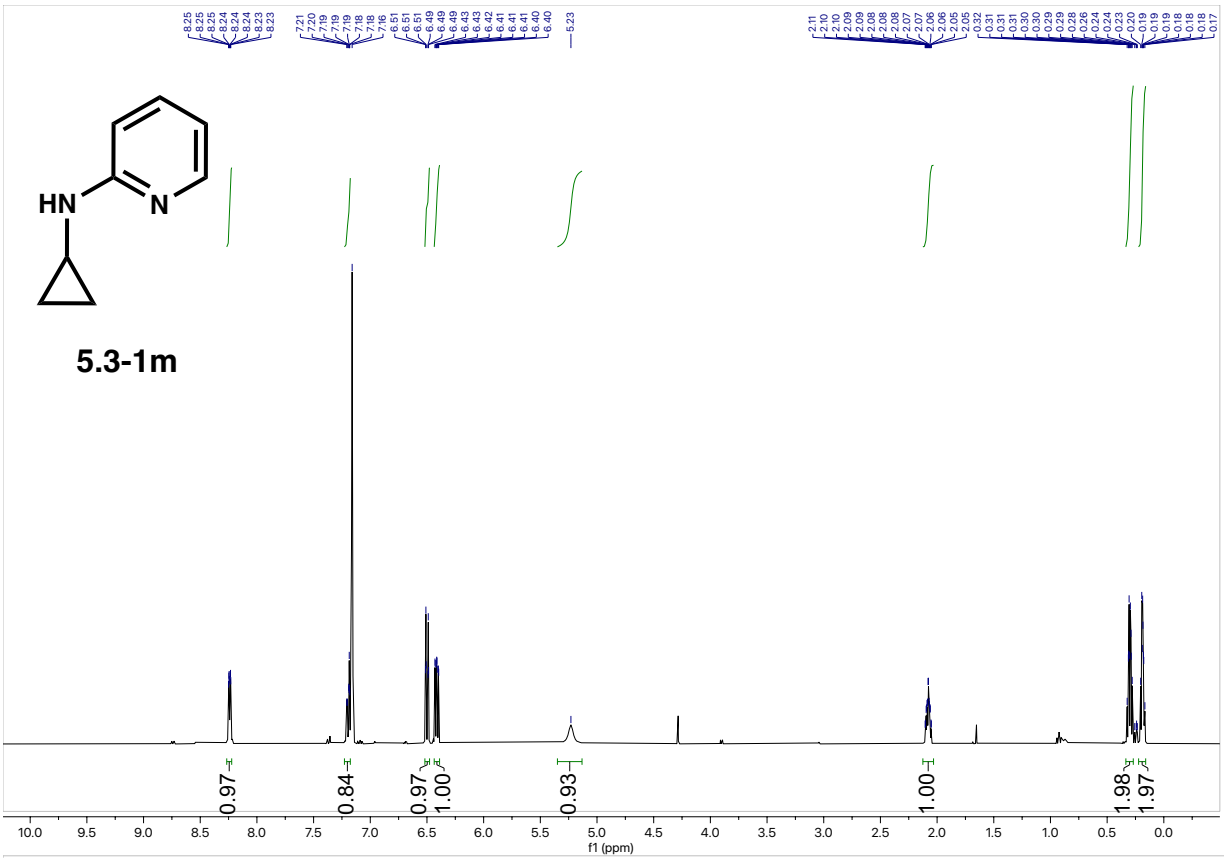

f1 (ppm)

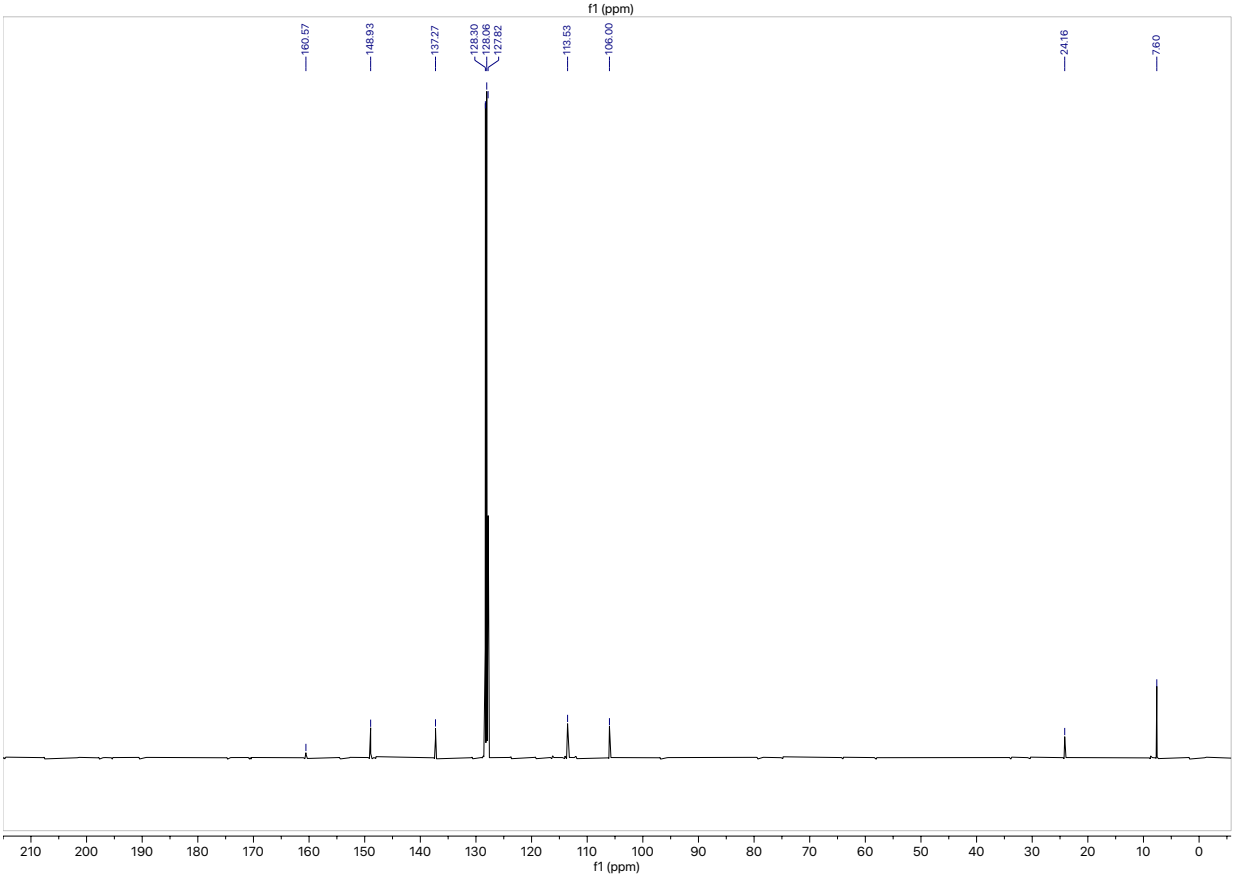

Ph
HN
5.3-1k
1.91
1.03
5.25
0.99
0.98
0.95
1.00
1.91
1.92
f1 (ppm)

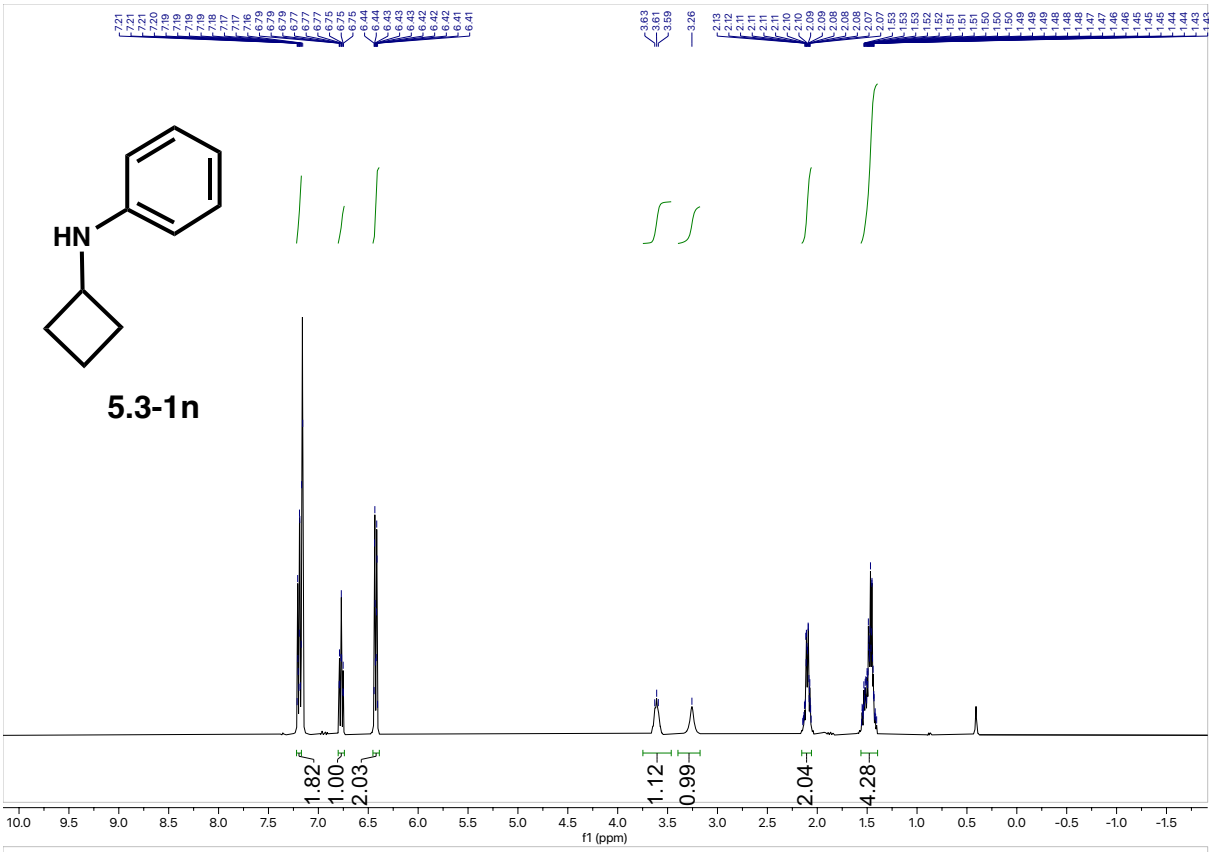

145.97
140.31
130.56
129.72
129.15
128.95
128.30
128.06
127.82
127.35
118.11
112.33
25.58
7.68
f1 (ppm)

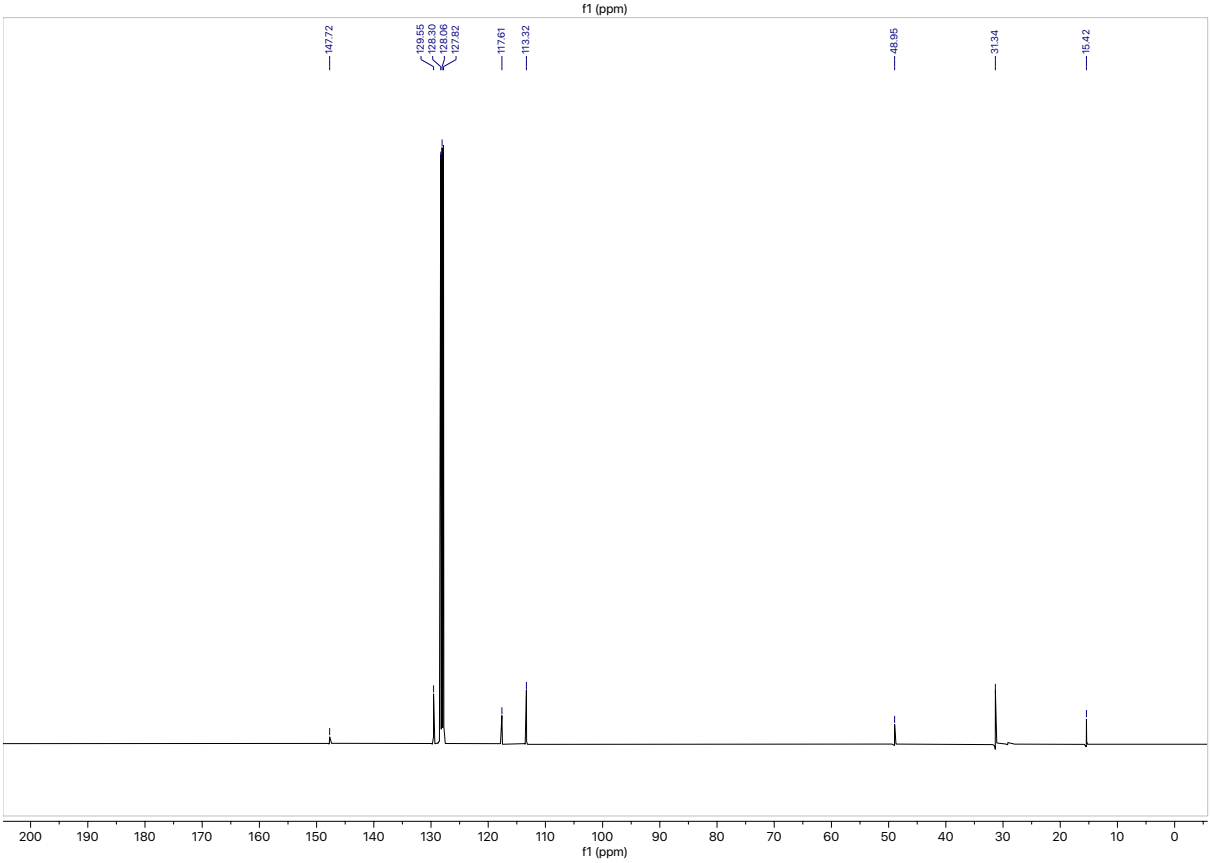

HN
5.3-1l
f1 (ppm)

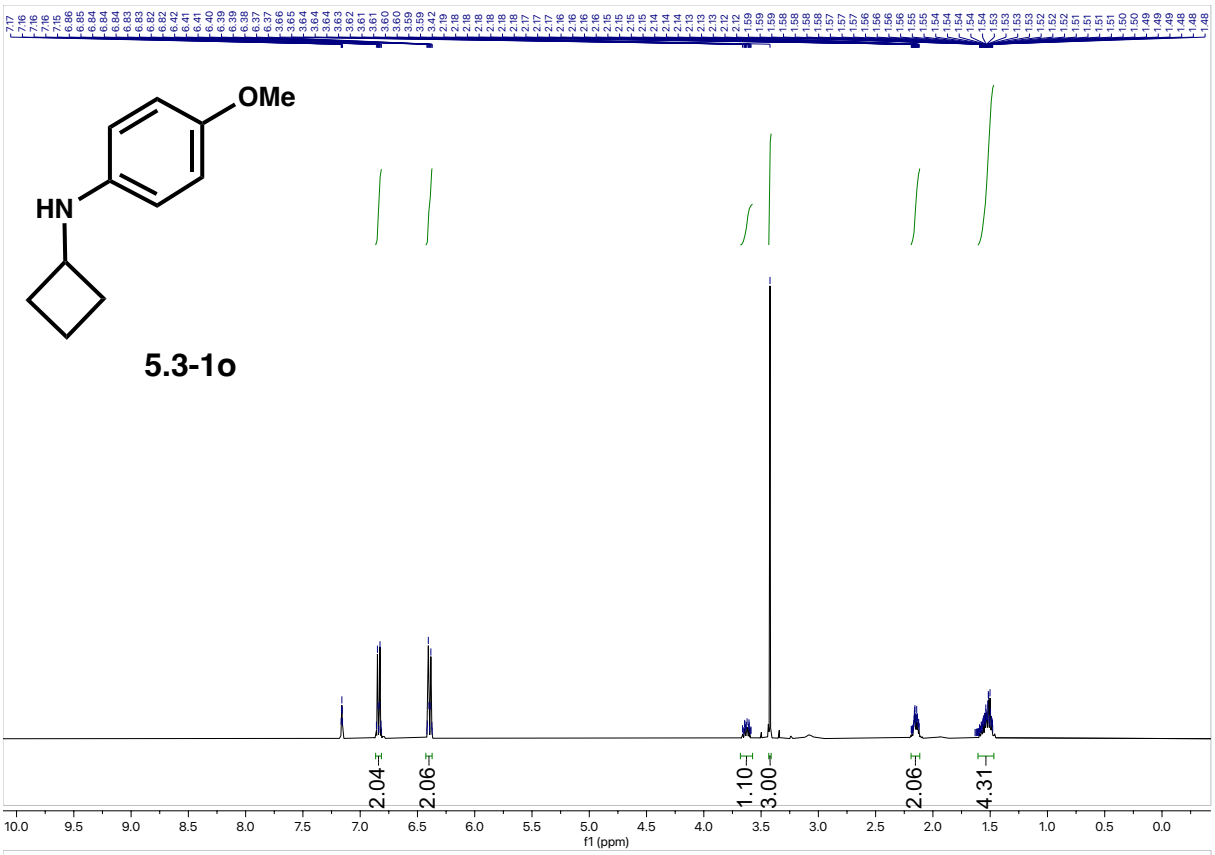

f1 (ppm)

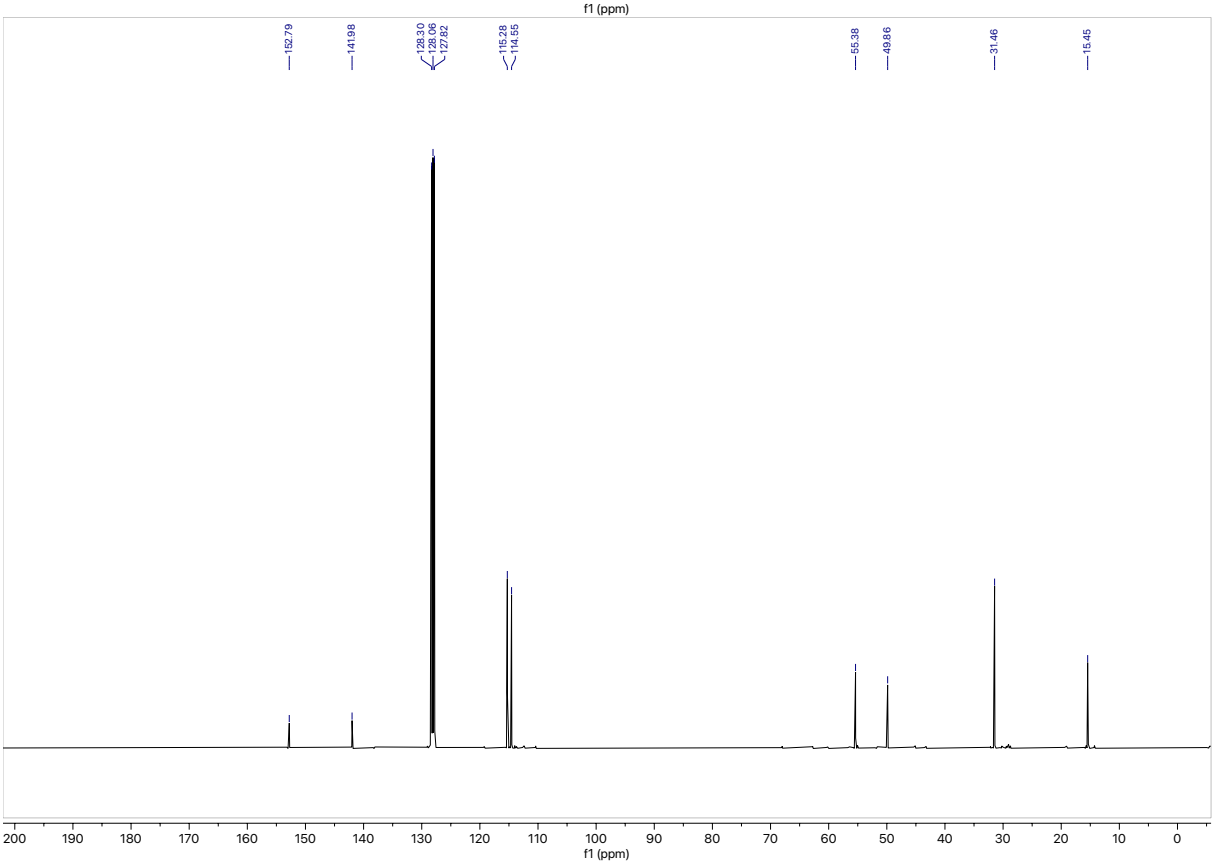

HN
N
5.3-1m
0.97
0.84
0.97
1.00
0.93
1.00
1.98
1.97
f1 (ppm)

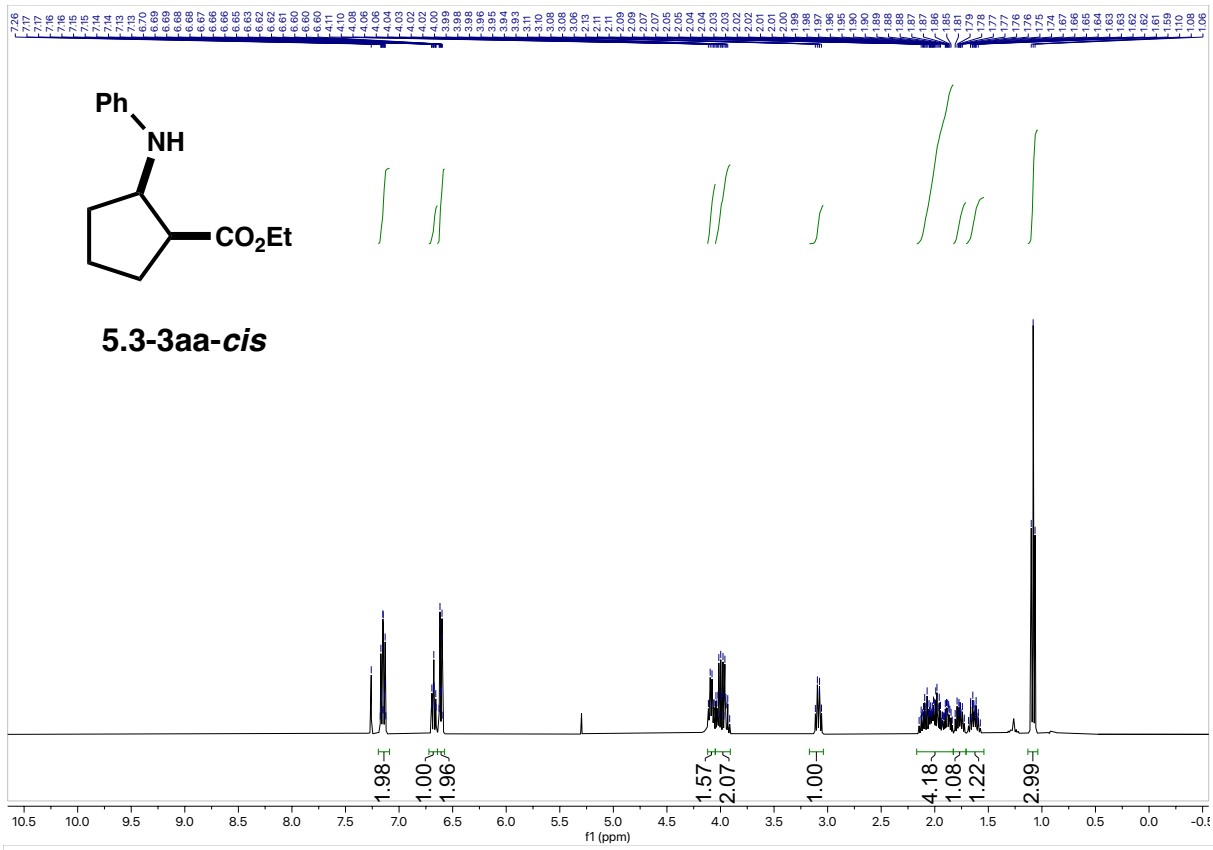

160.57
148.93
137.27
128.30
128.06
127.82
113.53
106.00
24.16
7.60
f1 (ppm)


HN
5.3-1n
1.82
1.00
2.03
1.12
0.99
2.04
4.28
f1 (ppm)

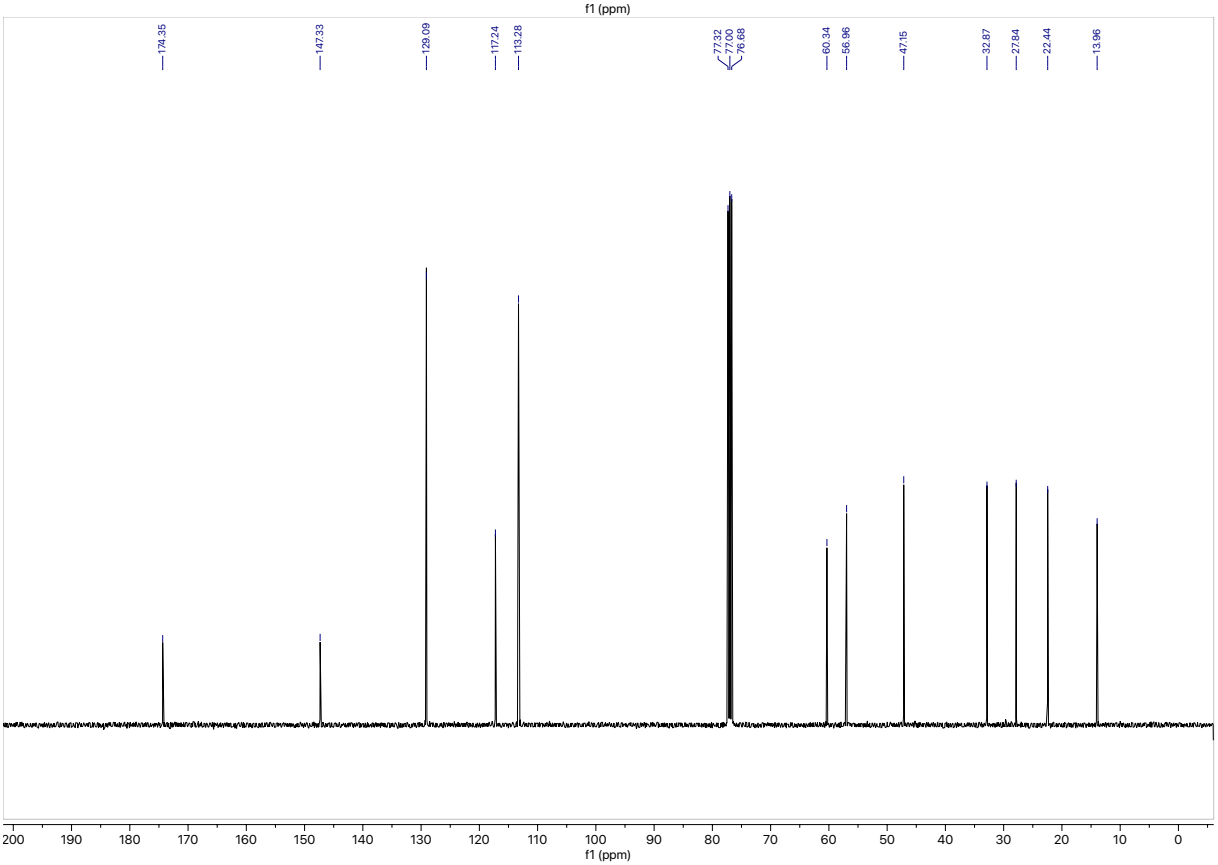

147.72
129.55
128.30
128.06
127.82
117.61
113.32
48.95
31.34
15.42
f1 (ppm)

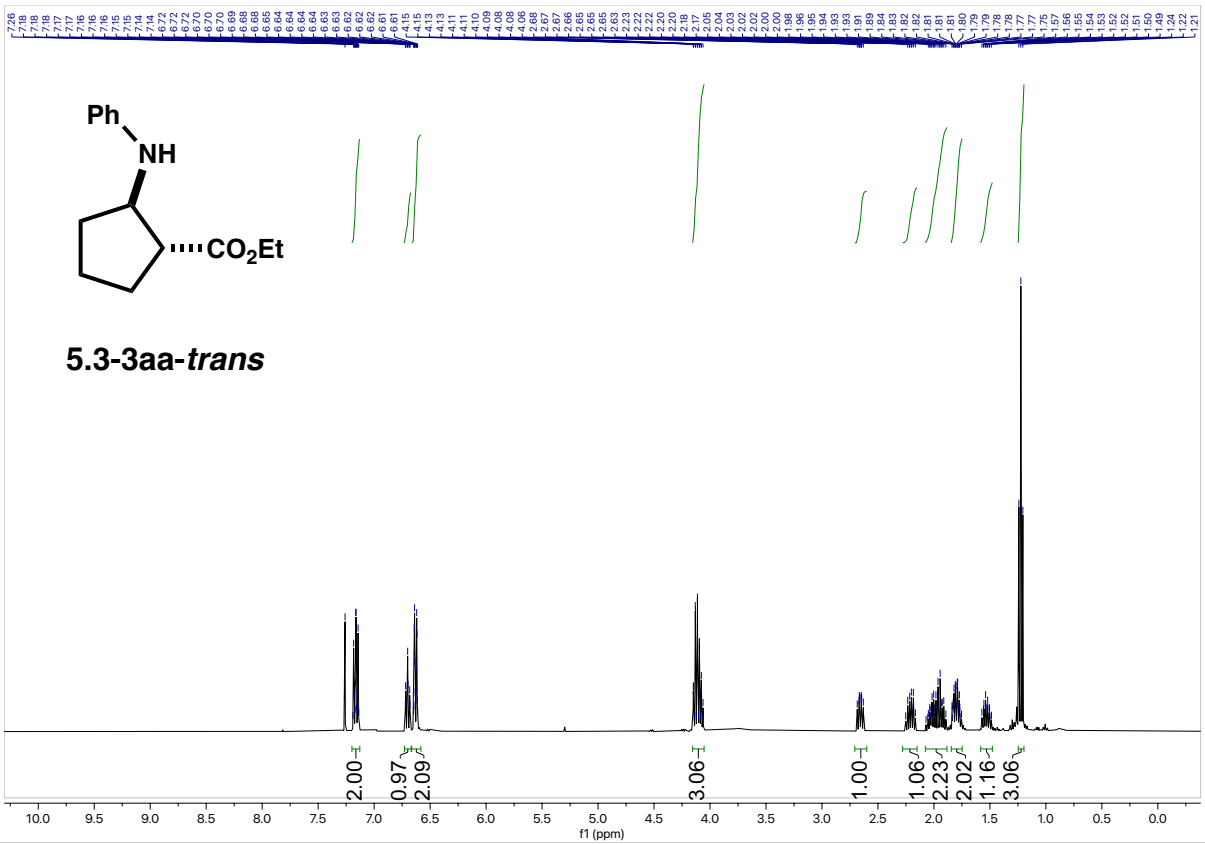

OMe
HN
5.3-1o
2.04
2.06
1.10
3.00
2.06
4.31
f1 (ppm)

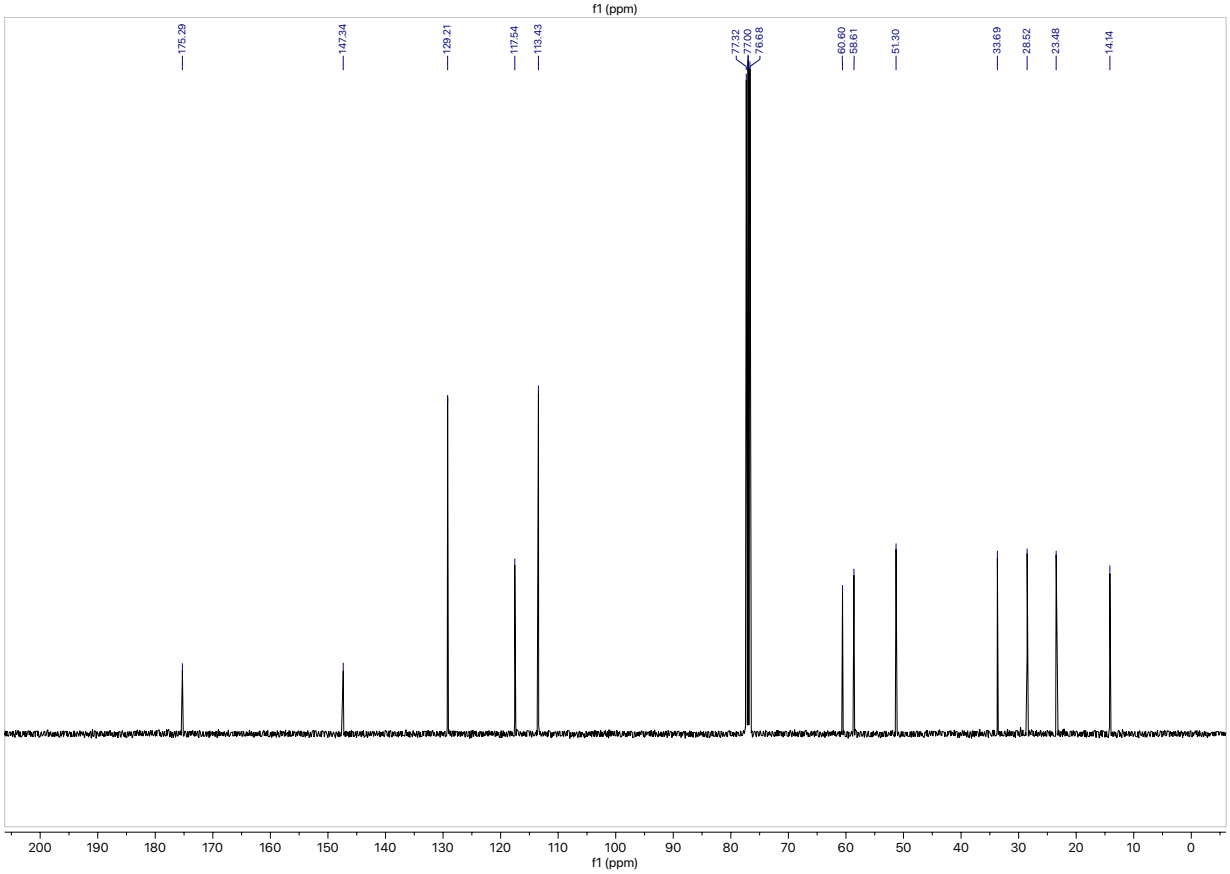

152.79
141.98
128.30
128.06
127.82
115.28
114.55
55.38
49.86
31.46
15.45
f1 (ppm)

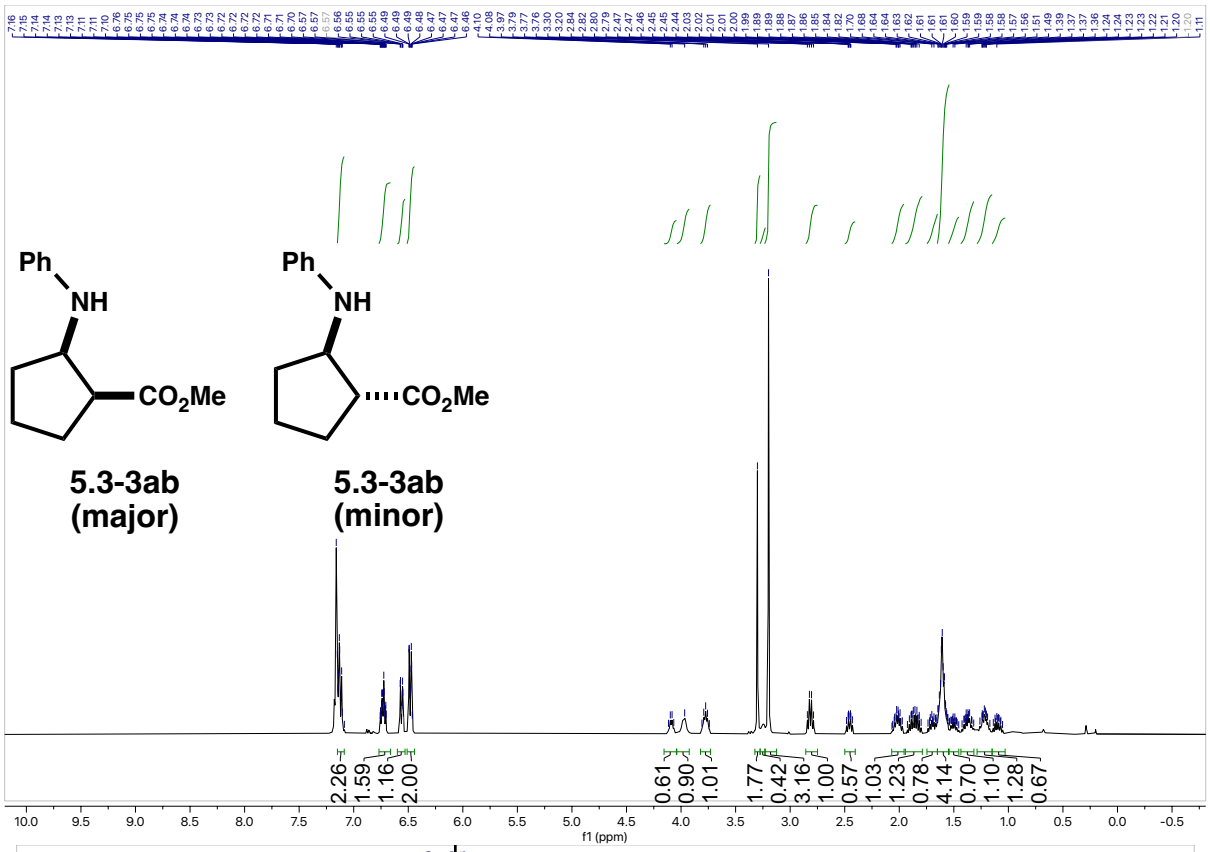

Ph
NH
CO2Et
1.98
1.00
1.96
1.57
2.07
1.00
4.18
1.08
1.22
2.99
f1 (ppm)

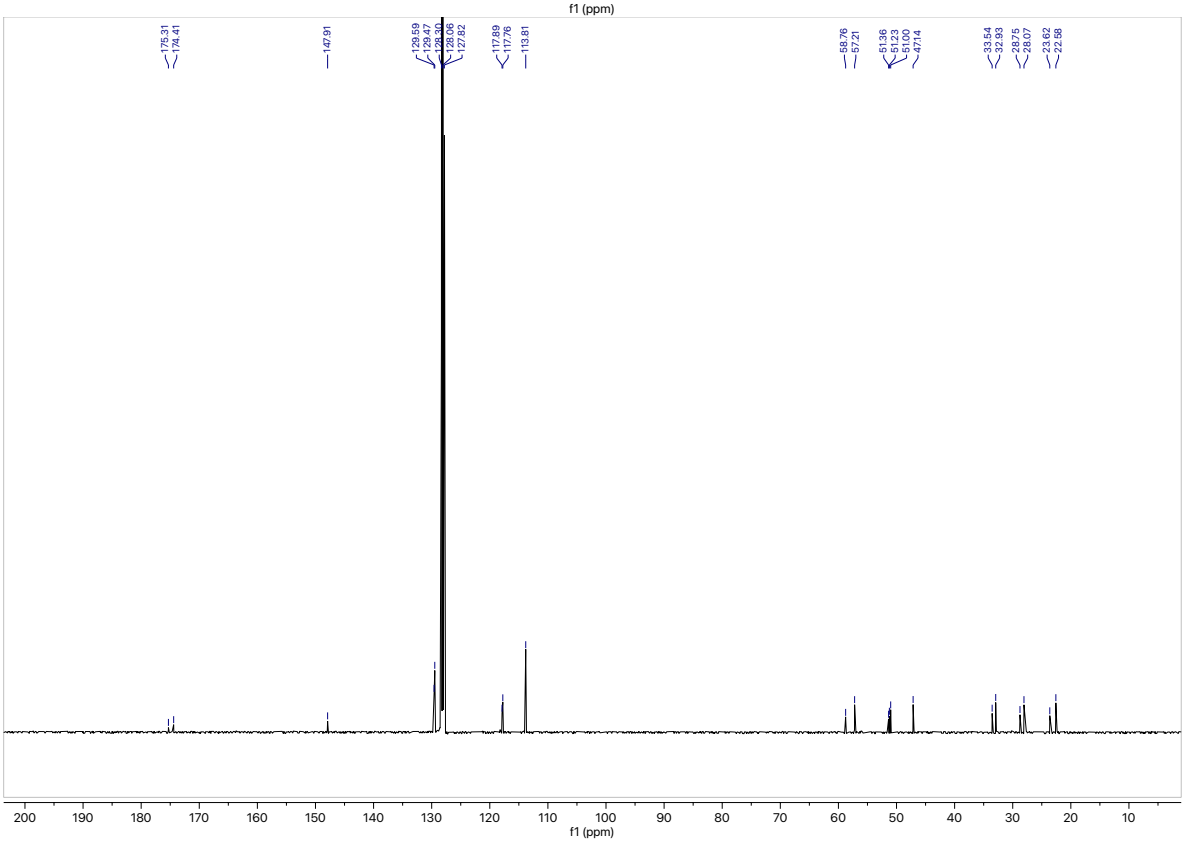
5.3-3aa-*cis*

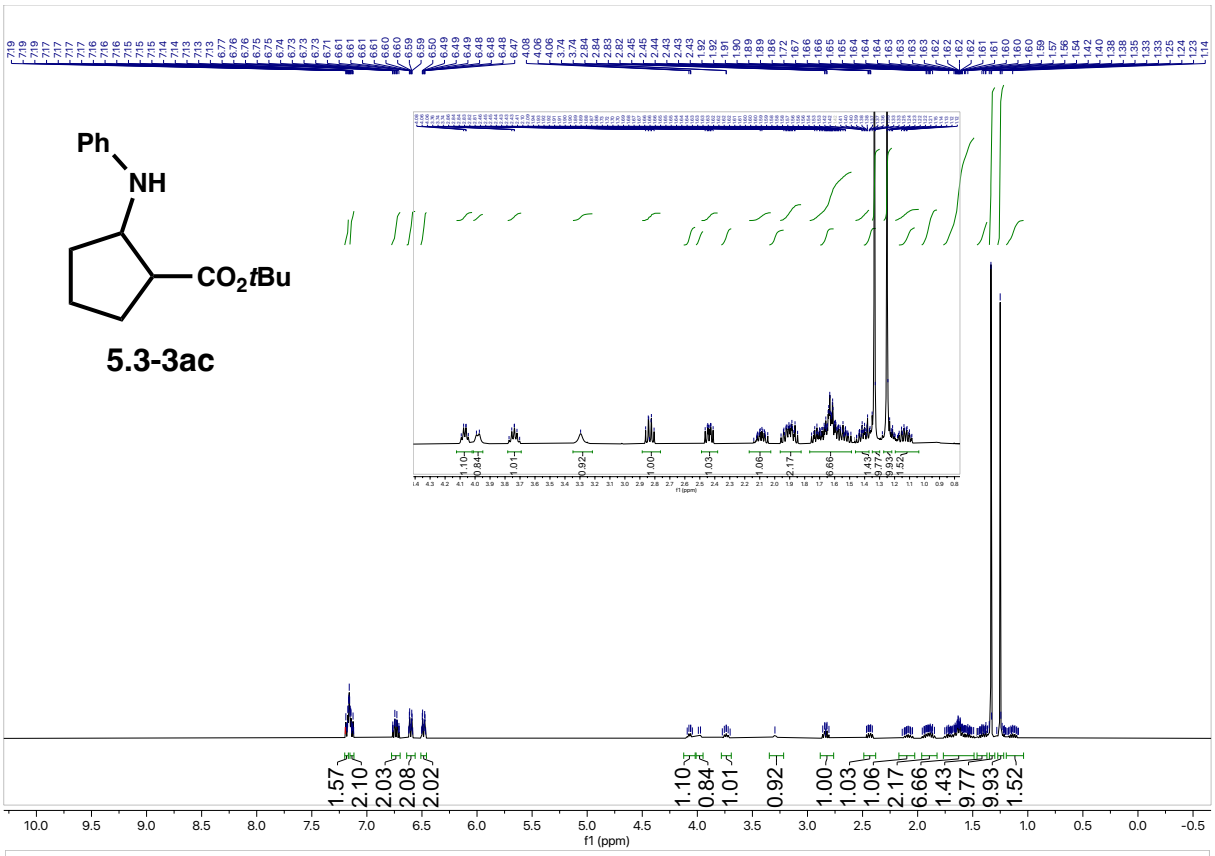

174.35
147.33
129.09
117.24
113.28
77.32
77.00
76.68
60.34
56.96
47.15
32.87
27.84
22.44
13.96
f1 (ppm)

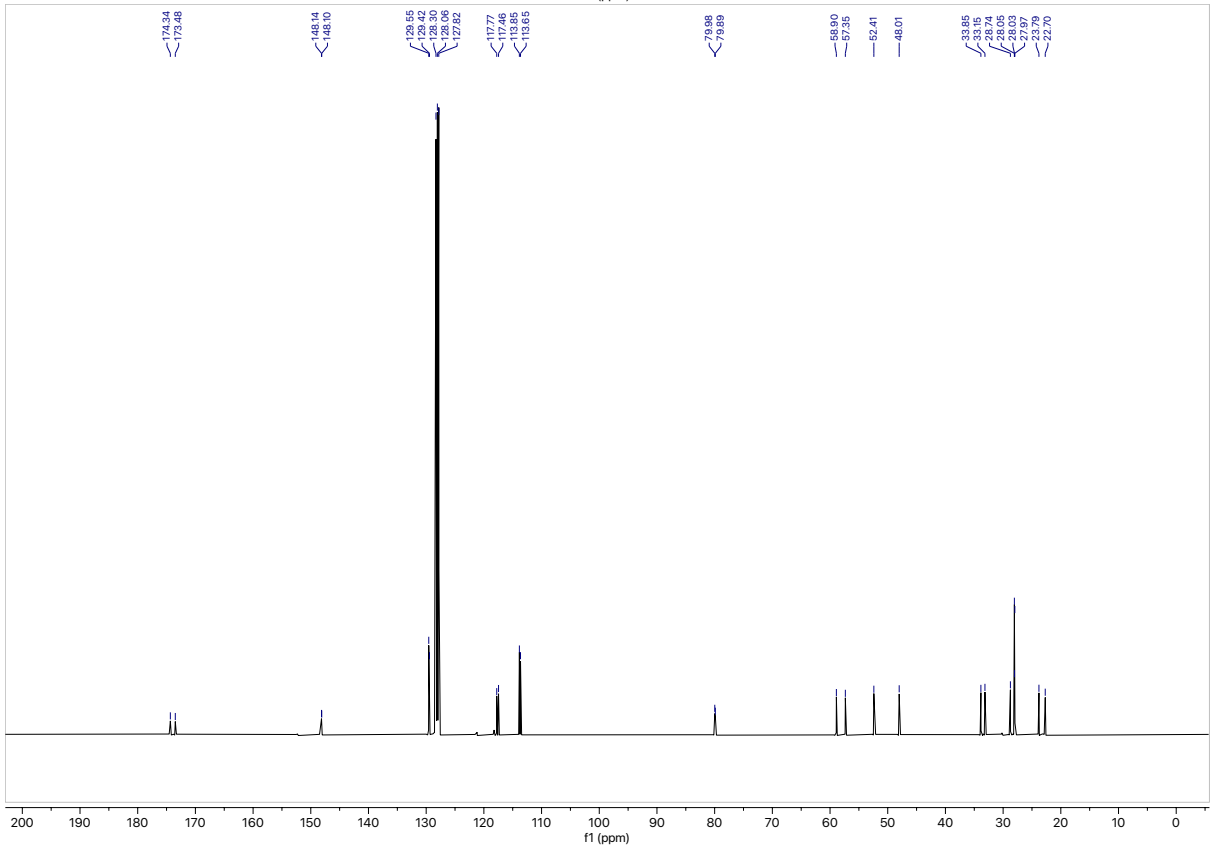

Ph
NH
CO2Et
5.3-3aa-trans
2.00
0.97
2.09
3.06
1.00
1.06
2.23
2.02
1.16
3.06
f1 (ppm)

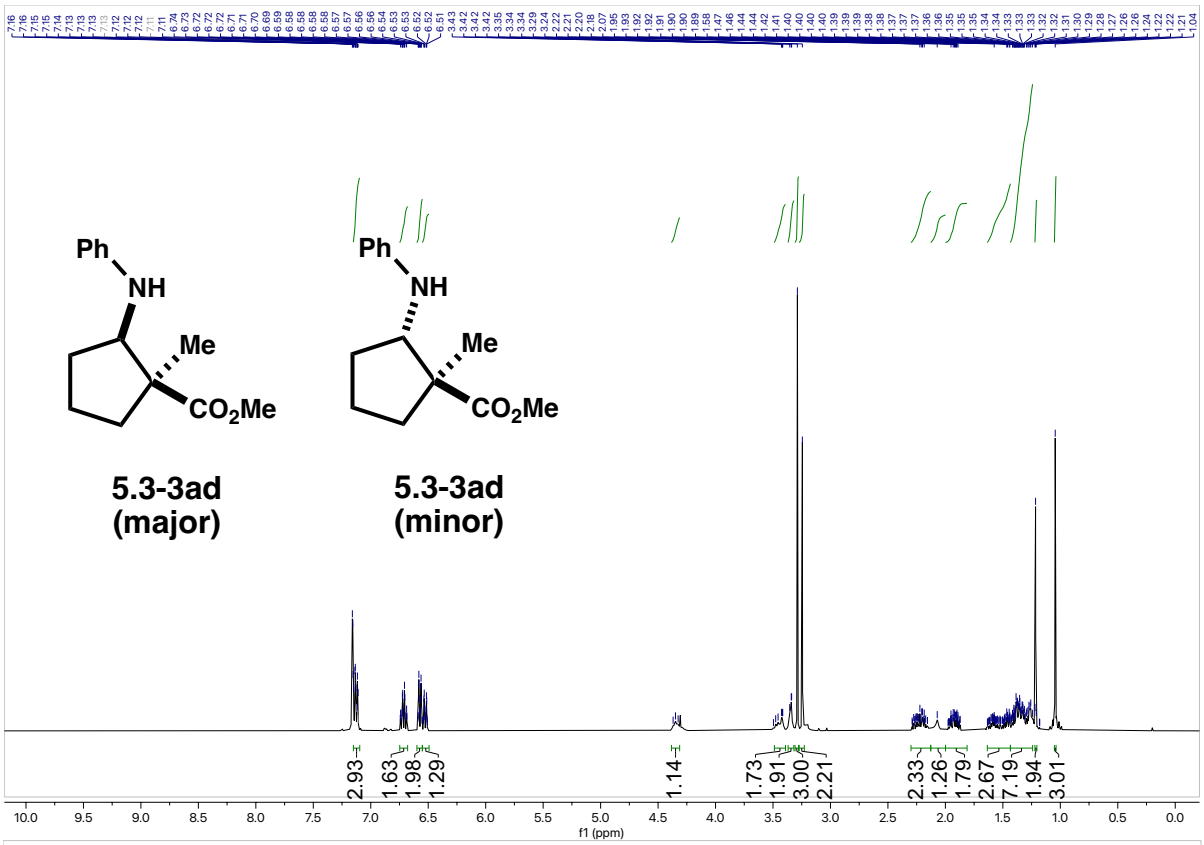

175.29
147.34
129.21
117.54
113.43
77.32
77.00
76.68
60.60
58.61
51.30
33.69
28.52
23.48
14.14
f1 (ppm)

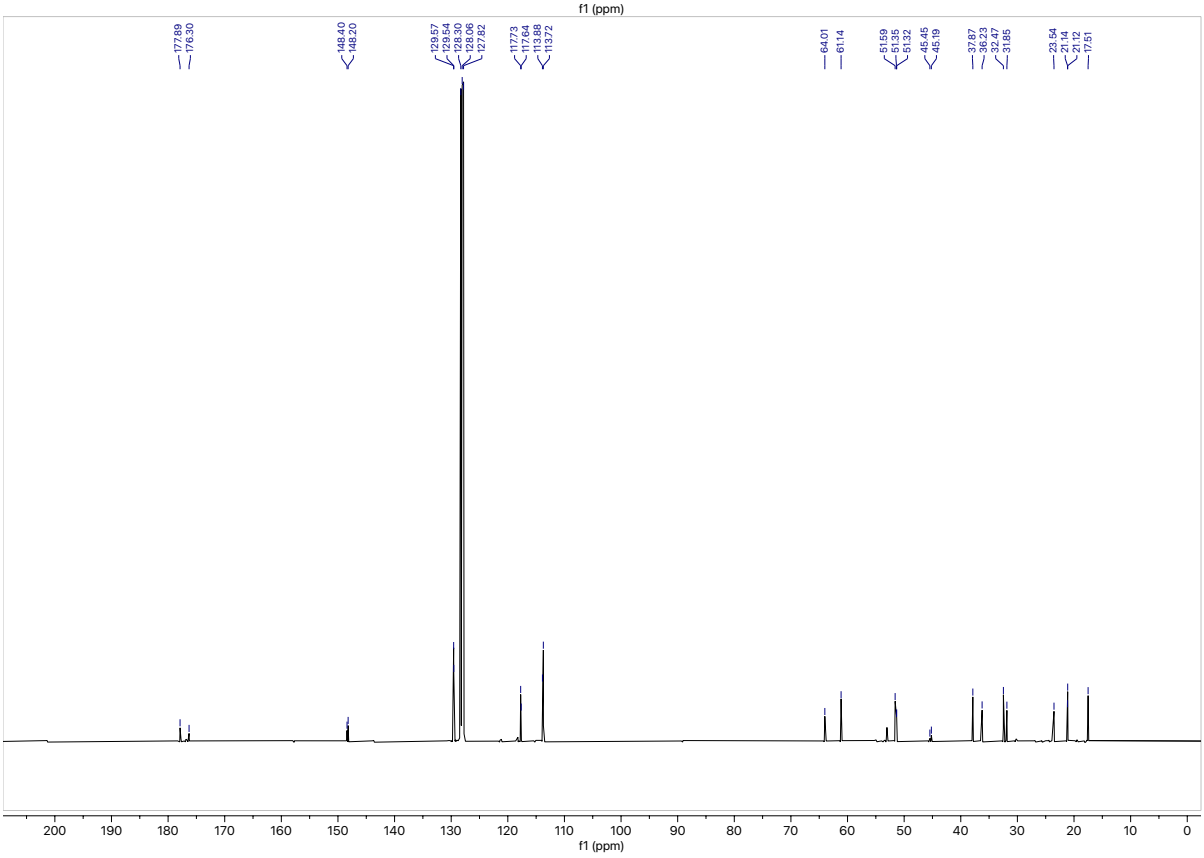

Ph
NH
CO2Me
5.3-3ab
(major)
Ph
NH
CO2Me
5.3-3ab
(minor)
2.26
1.59
1.16
2.00
0.61
0.90
1.01
1.77
0.42
3.16
1.00
0.57
1.03
1.23
0.78
4.14
0.70
1.10
1.28
0.67
f1 (ppm)

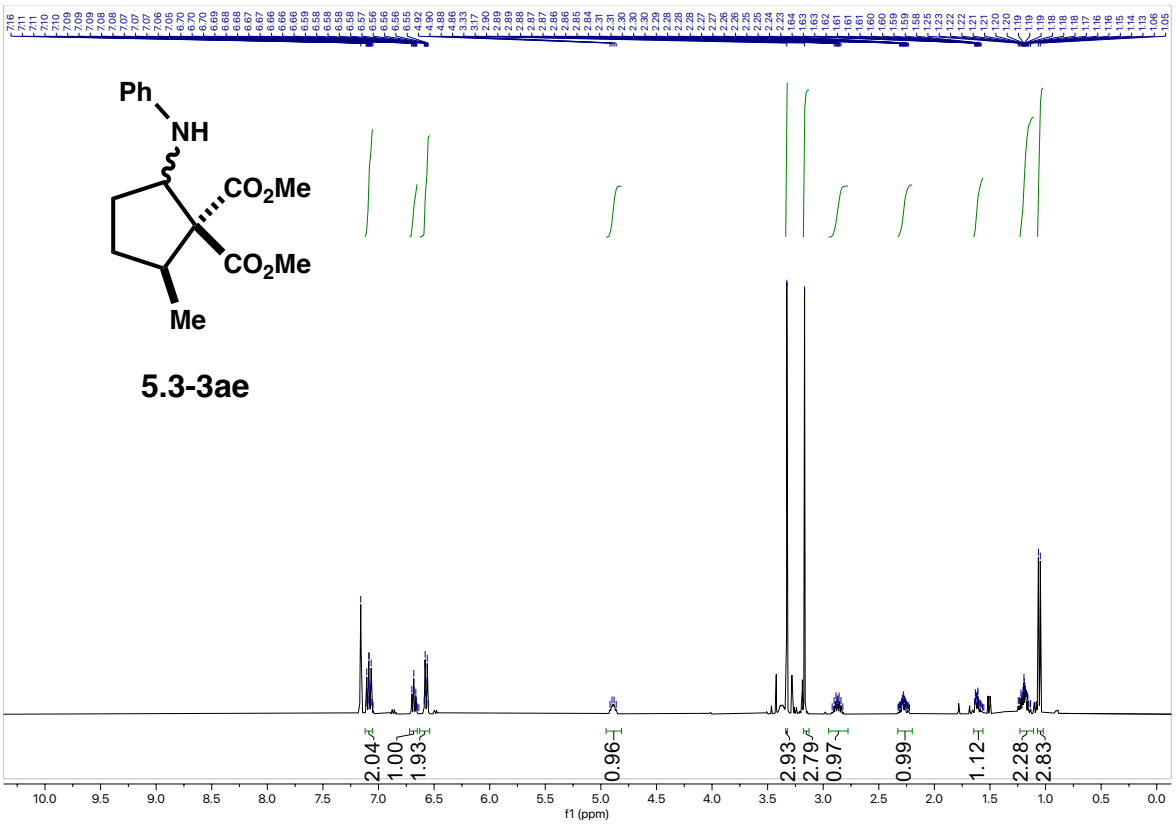

175.31
174.41
147.91
129.59
129.47
128.96
127.92
117.89
117.76
113.81
58.76
57.21
51.36
51.23
51.00
47.14
33.54
32.93
28.75
28.07
23.62
22.88
f1 (ppm)

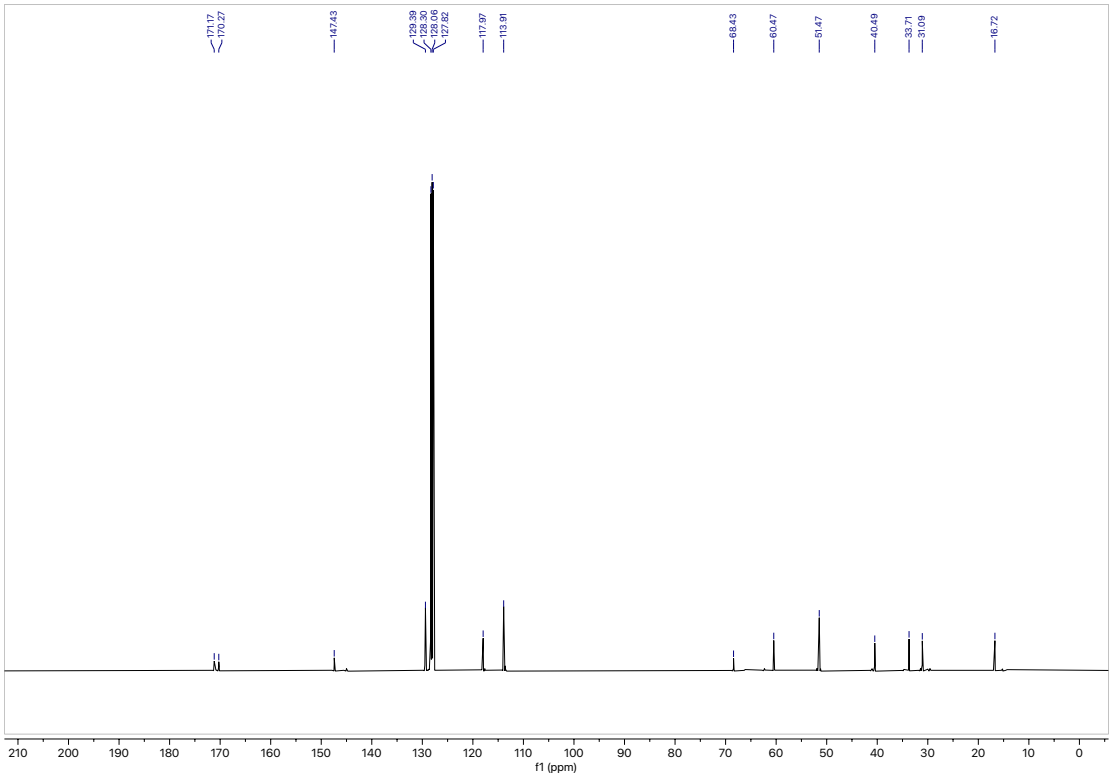

Ph
NH
CO2tBu
5.3-3ac
1.57
2.10
2.03
2.08
2.02
1.10
0.84
1.01
0.92
1.00
1.03
1.06
2.17
6.66
1.43
9.77
9.93
1.52
f1 (ppm)

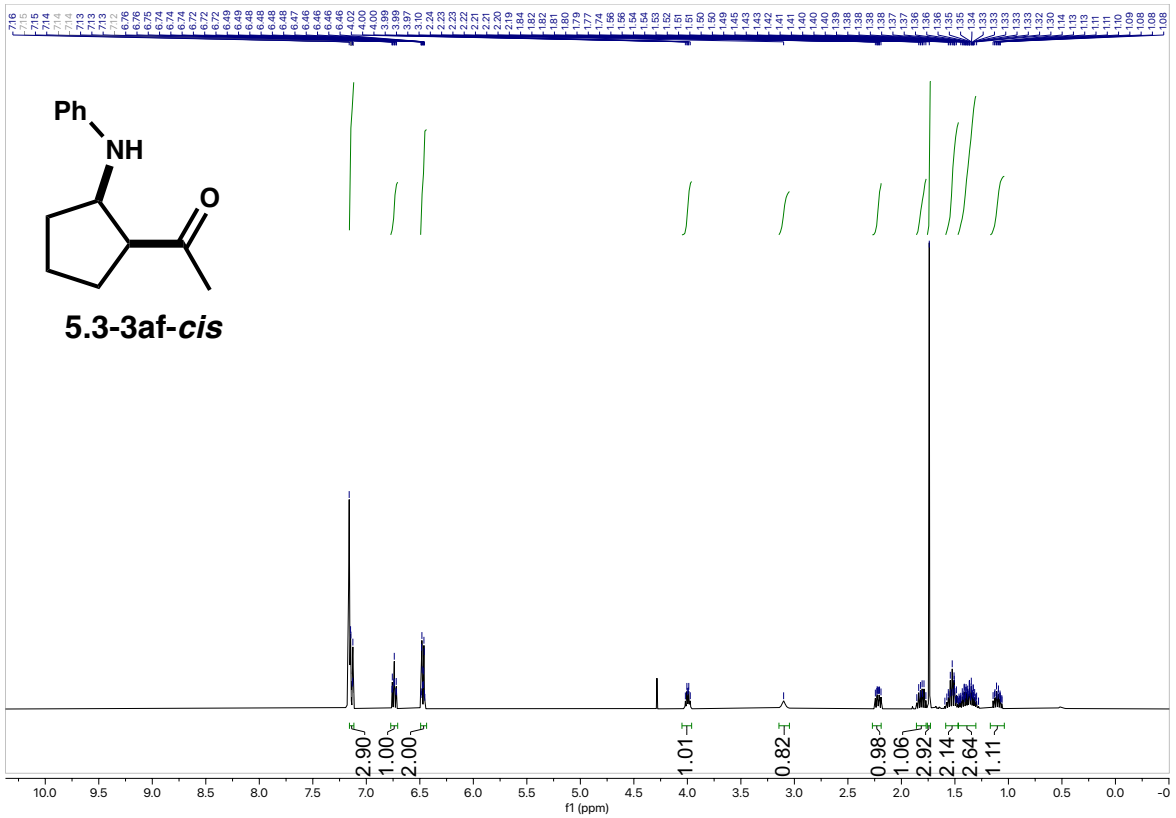

174.34
173.48
148.14
148.10
129.55
129.43
128.30
128.06
127.82
117.77
117.46
113.85
113.65
79.98
79.89
58.90
57.35
52.41
48.01
33.85
33.15
28.74
28.05
28.03
27.97
23.79
22.70
f1 (ppm)

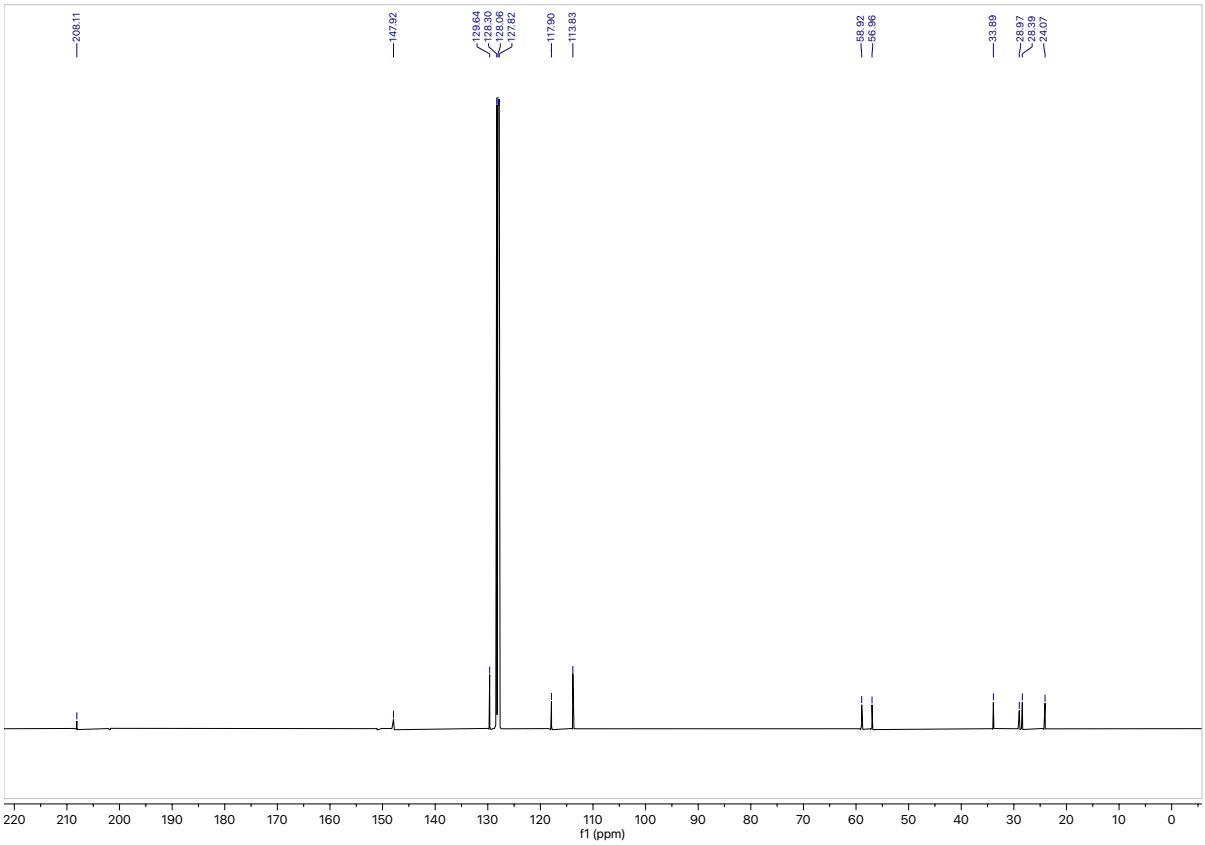

Ph
NH
Me
CO2Me
5.3-3ad
(major)
Ph
NH
Me
CO2Me
5.3-3ad
(minor)
2.93
1.63
1.98
1.29
1.14
1.73
1.91
3.00
2.21
2.33
1.26
1.79
2.67
7.19
1.94
3.01
f1 (ppm)

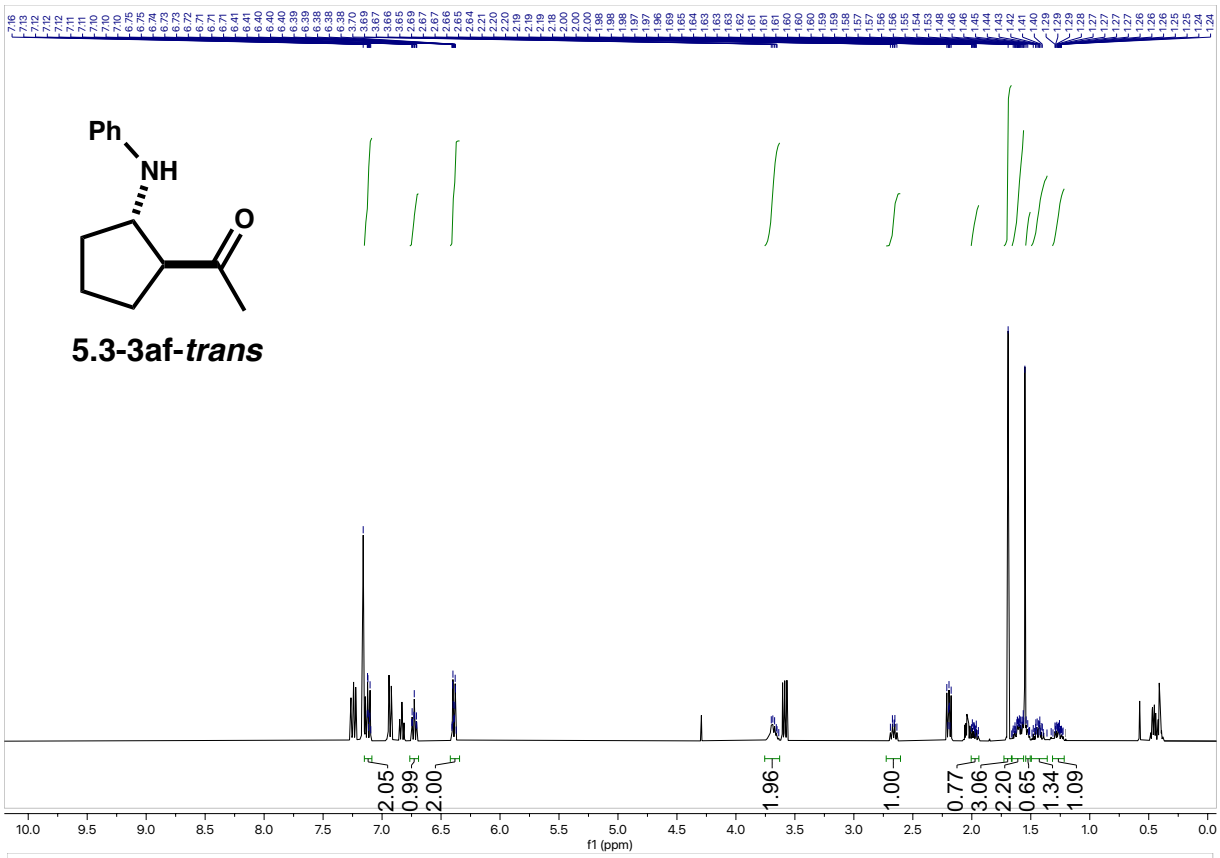

177.89
176.30
148.40
148.20
129.57
129.54
129.30
128.06
127.82
117.73
117.64
113.88
113.72
64.01
61.14
51.59
51.35
51.32
45.45
45.19
37.87
36.23
32.47
31.85
23.54
21.14
21.12
17.51
f1 (ppm)

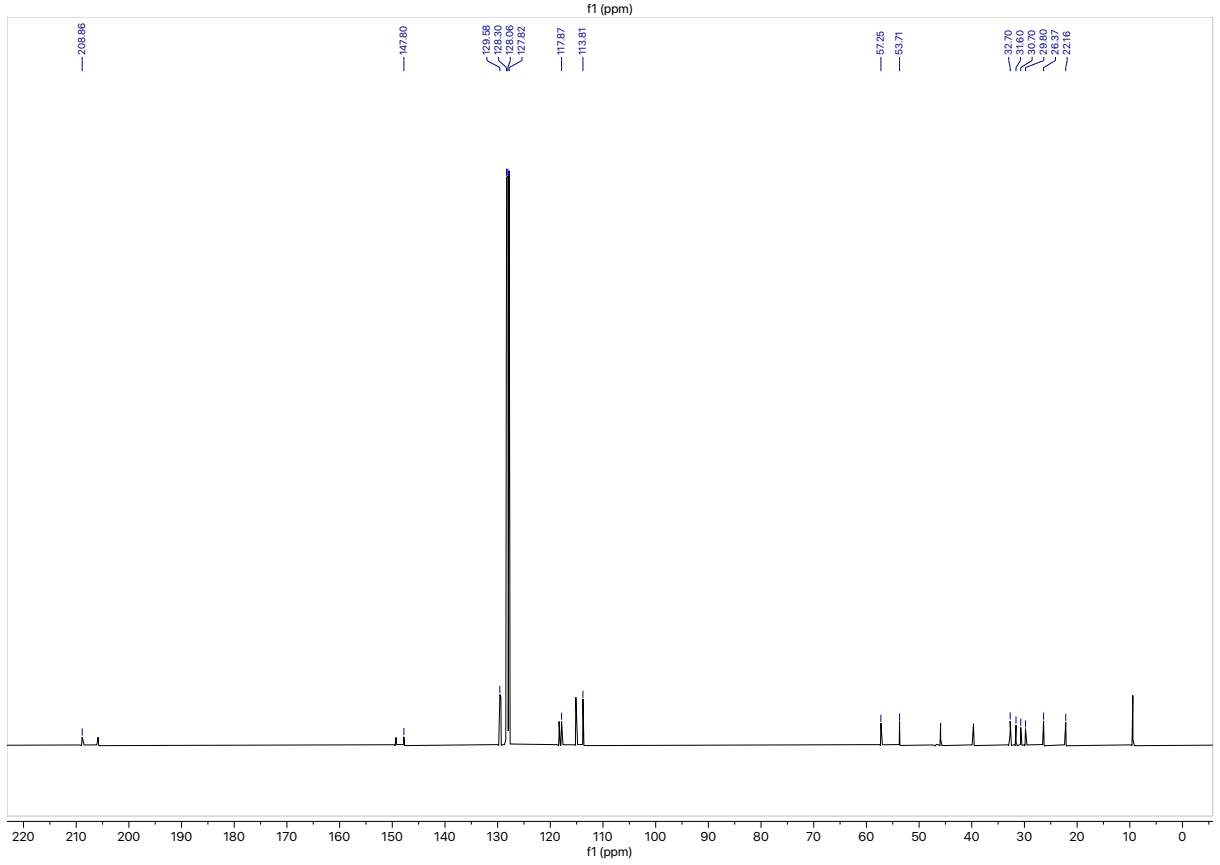

Ph
NH
CO2Me
CO2Me
Me
5.3-3ae
2.04
1.00
1.93
0.96
2.93
2.79
0.97
0.99
1.12
2.28
2.83
f1 (ppm)

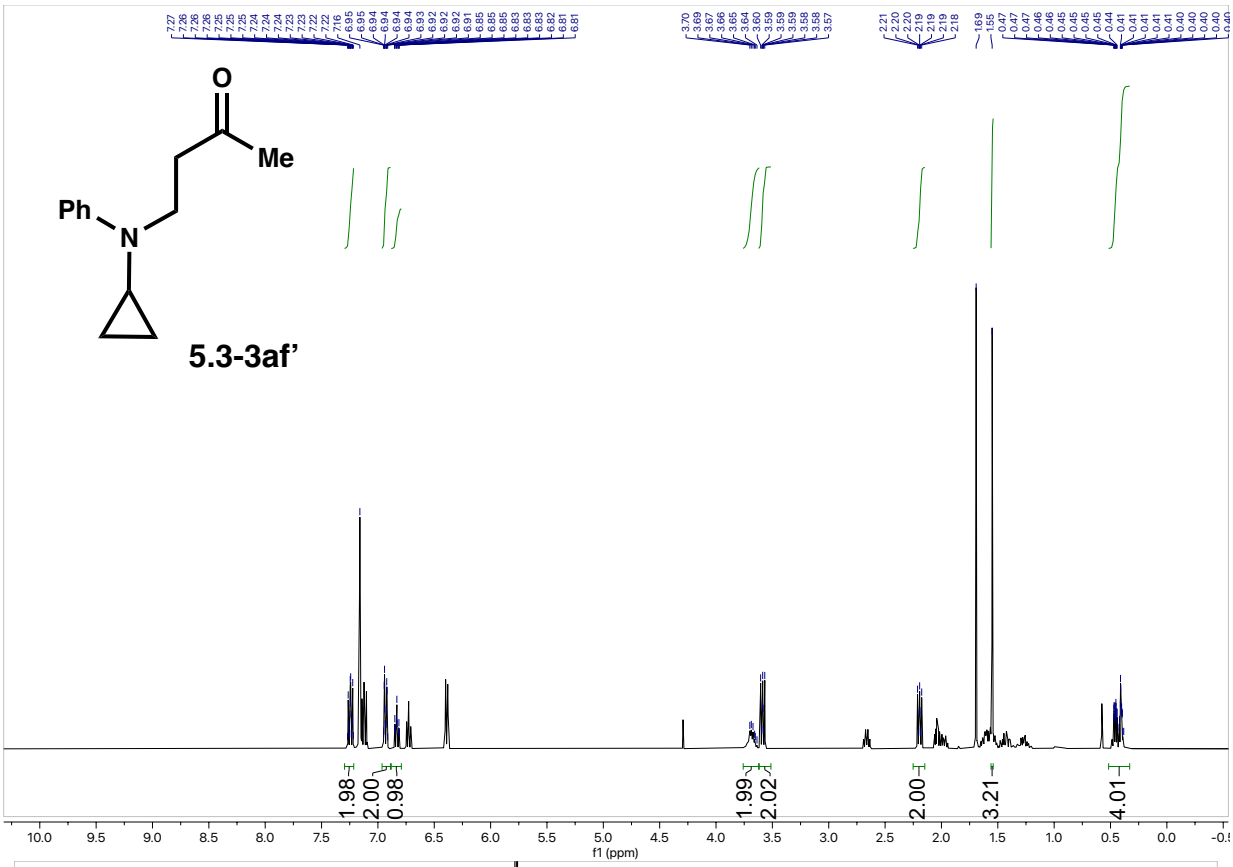

171.17
170.27
147.43
129.39
128.30
128.06
127.82
117.97
113.91
68.43
60.47
51.47
40.49
33.71
31.09
16.72
f1 (ppm)

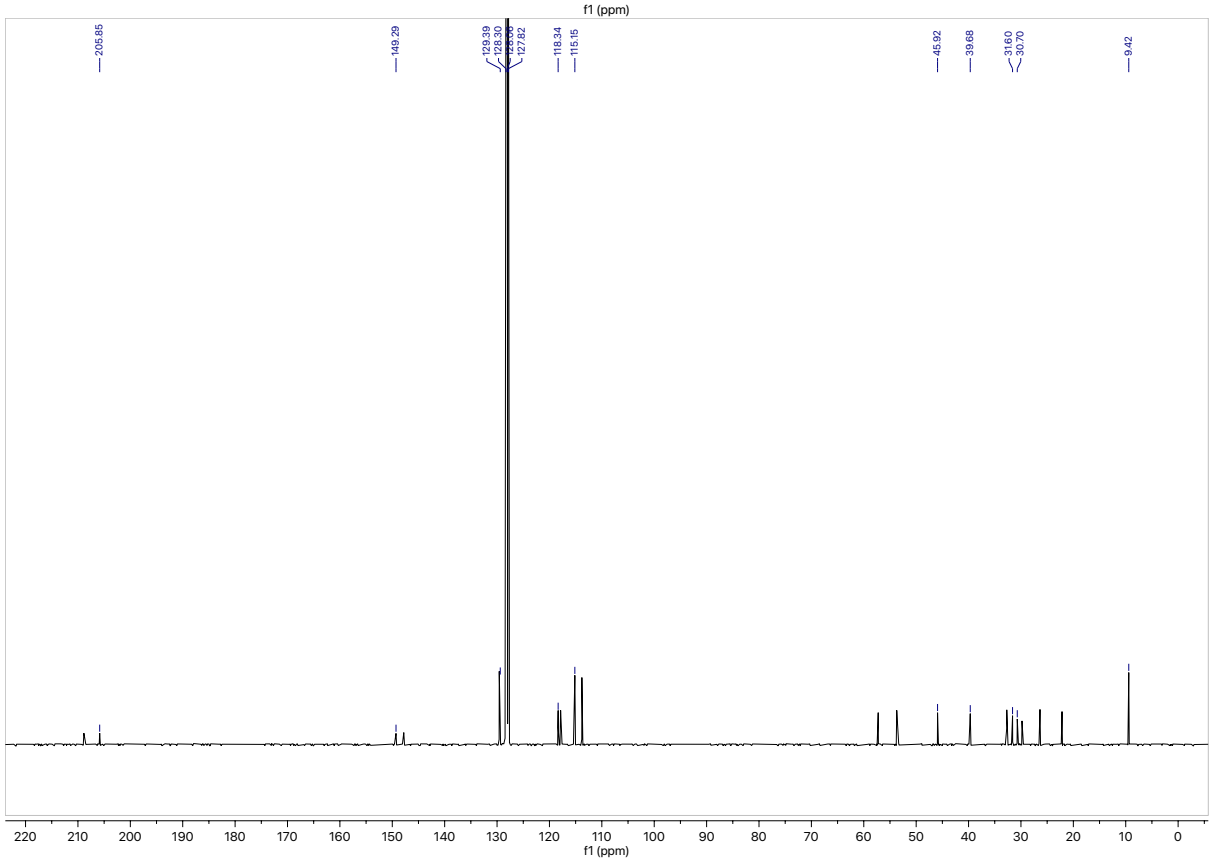

Ph
NH
O
5.3-3af-*cis*
2.90
1.00
2.00
1.01
0.82
0.98
1.06
2.92
2.14
2.64
1.11
f1 (ppm)

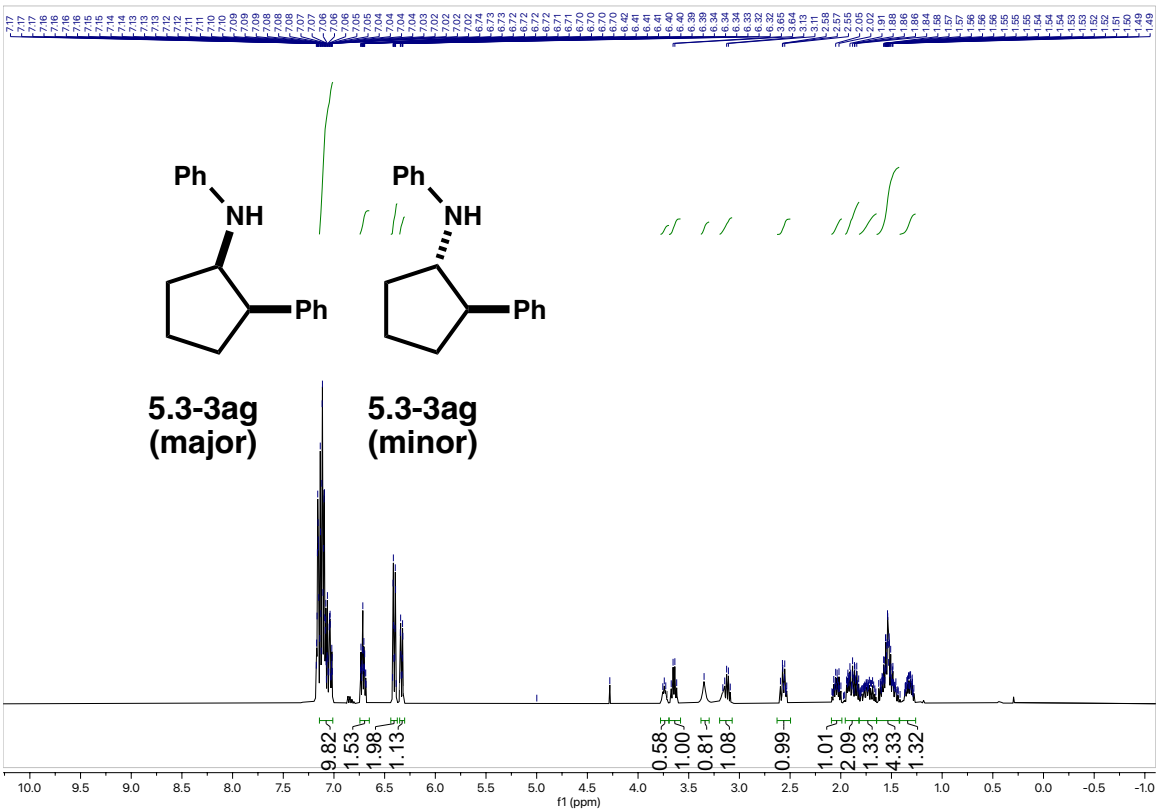

208.11
147.92
129.64
129.30
128.06
127.82
117.90
113.83
58.92
56.96
33.89
28.97
28.39
24.07
f1 (ppm)

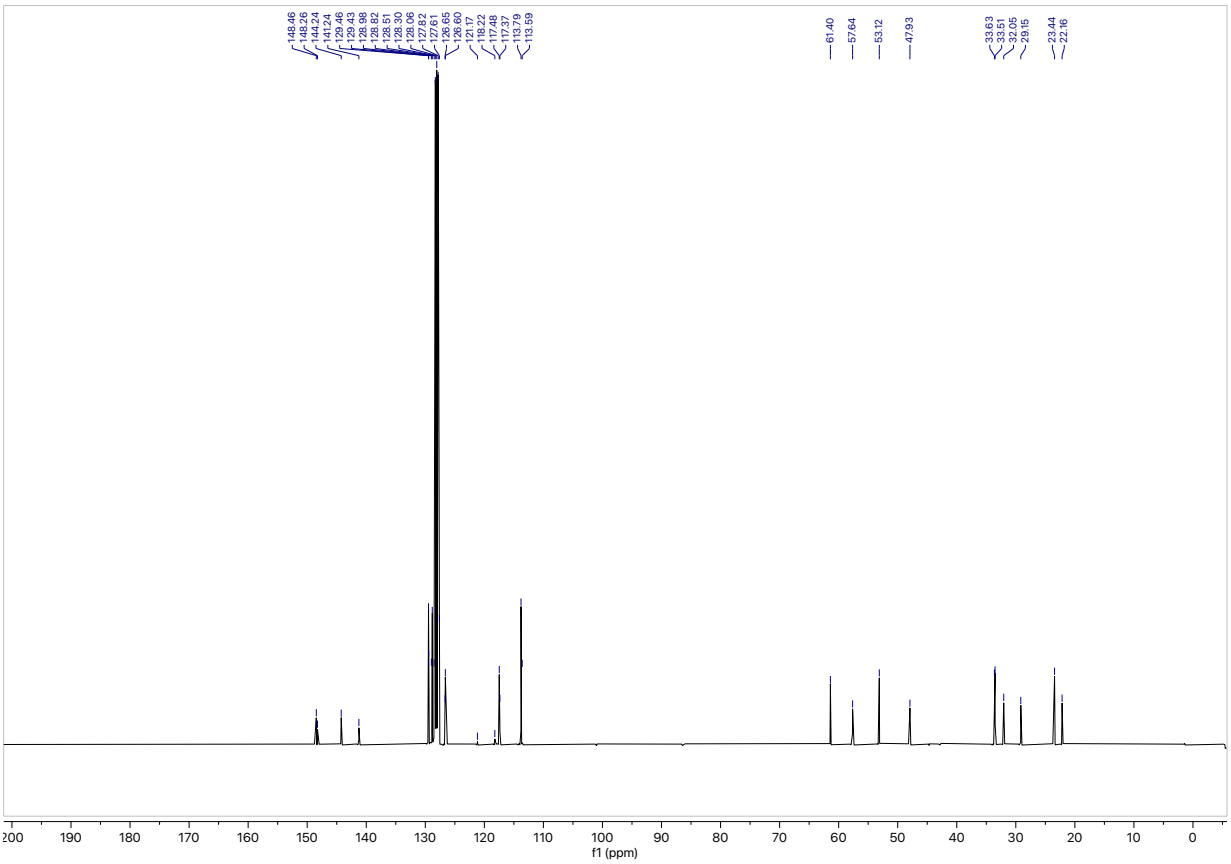

Ph
NH
O
5.3-3af-*trans*
2.05
0.99
2.00
1.96
1.00
0.77
3.06
2.20
0.65
1.34
1.09
f1 (ppm)

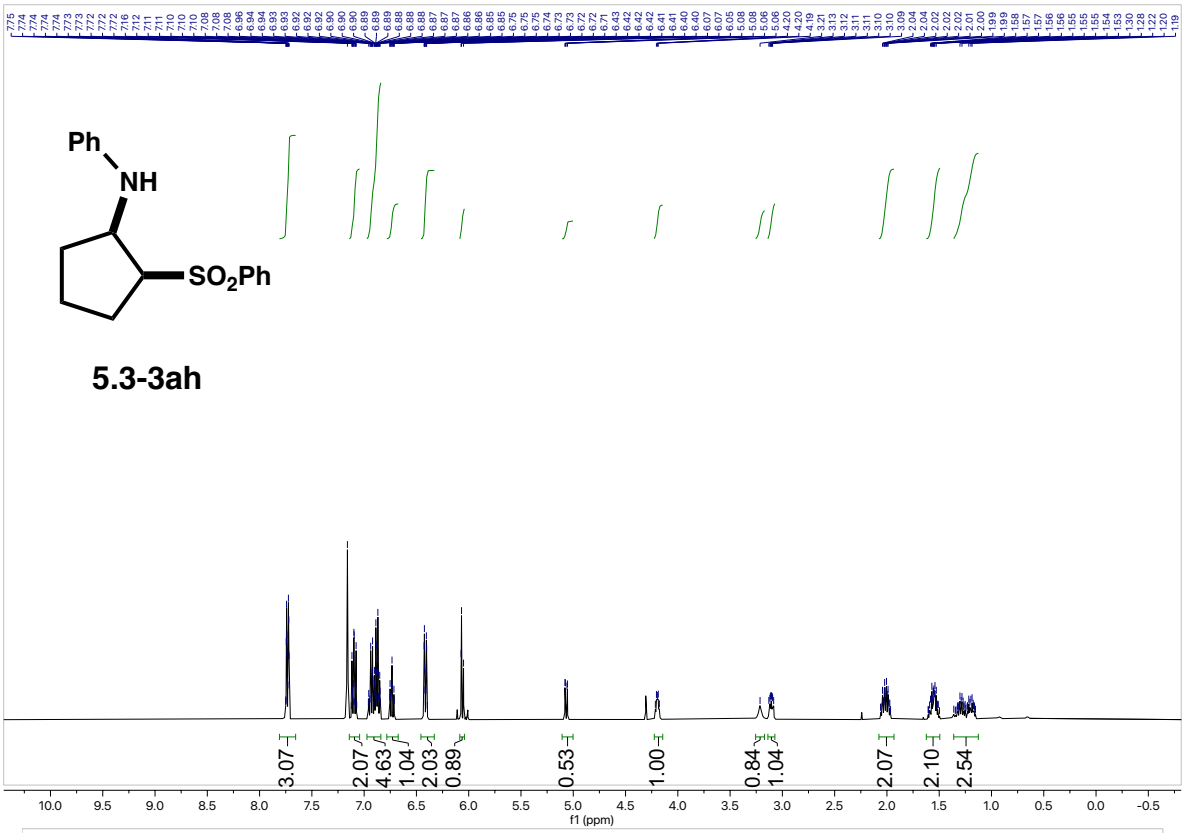

208.86
147.80
129.58
128.30
128.06
127.82
117.87
113.81
57.25
53.71
32.70
31.60
30.70
29.80
26.37
22.16
f1 (ppm)

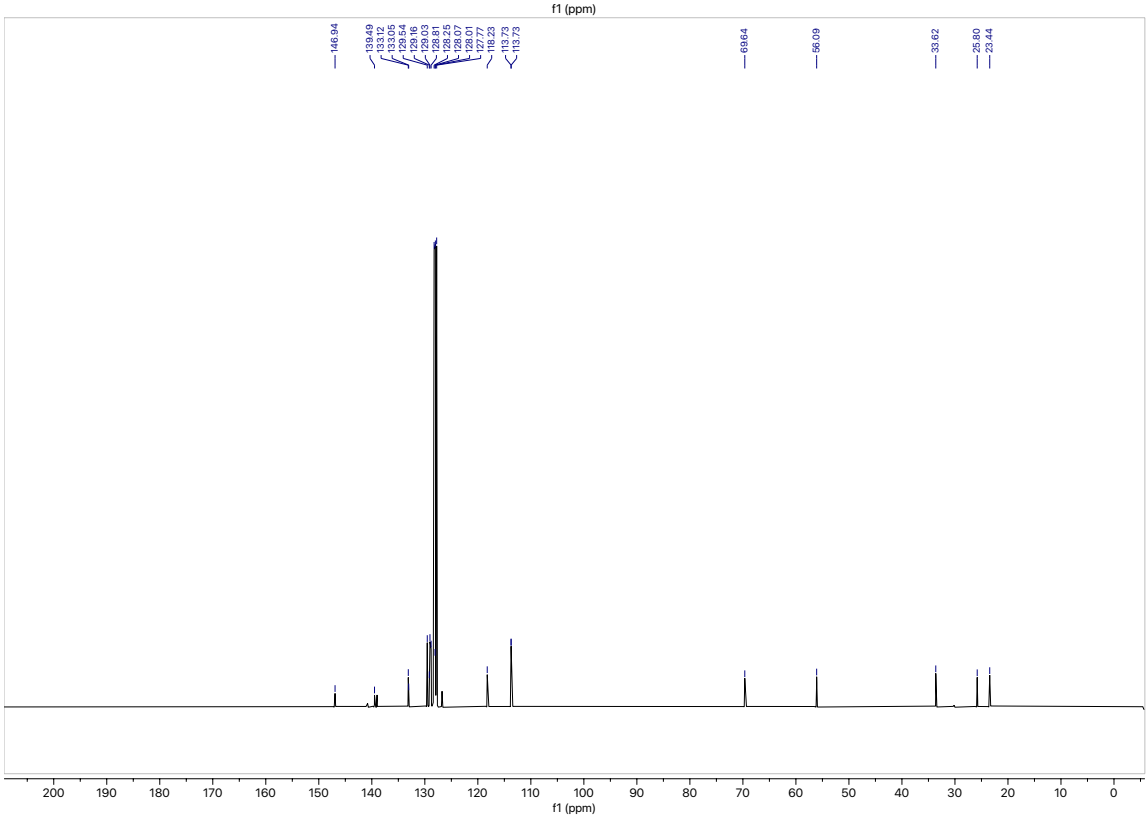

O
Me
Ph
N
5.3-3af'
1.98
2.00
0.98
1.99
2.02
2.00
3.21
4.01
f1 (ppm)

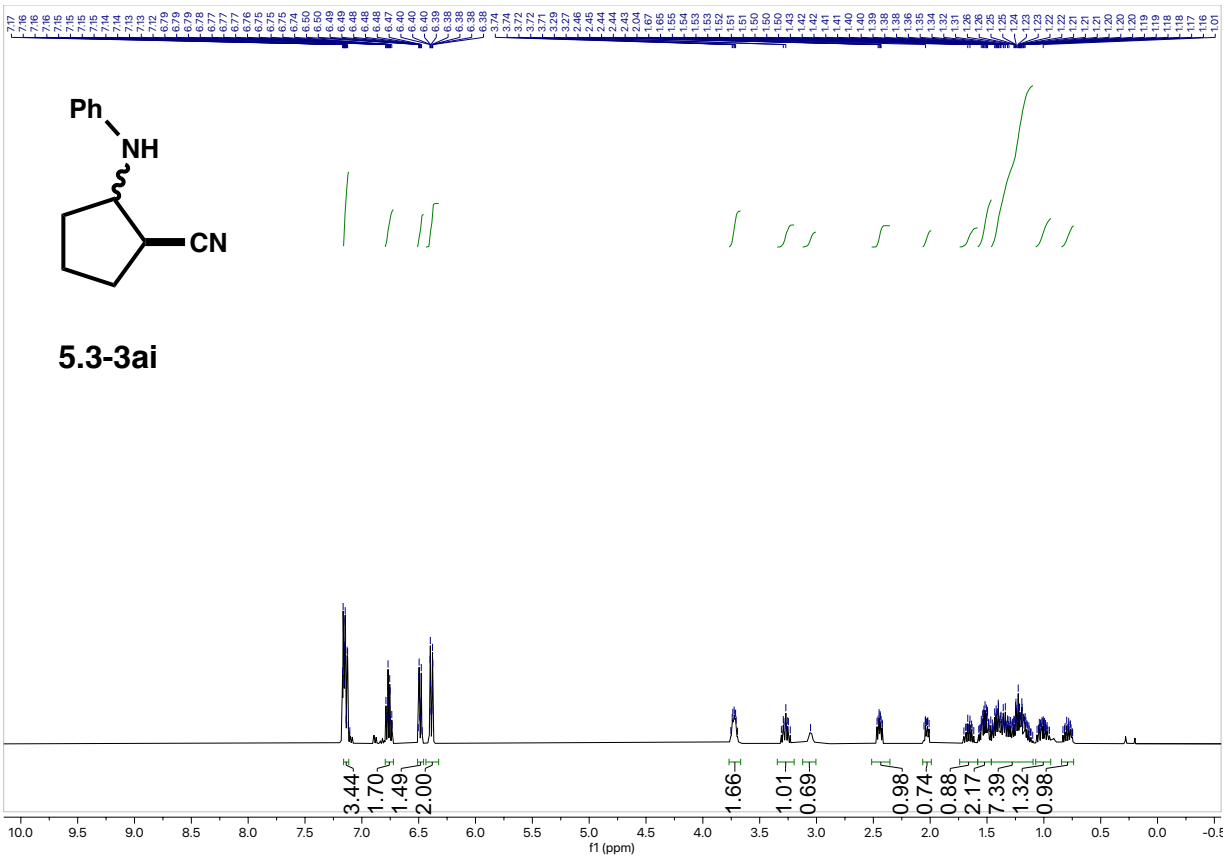

205.85
149.29
129.39
128.30
127.82
118.34
115.15
45.92
39.68
31.60
30.70
9.42
f1 (ppm)

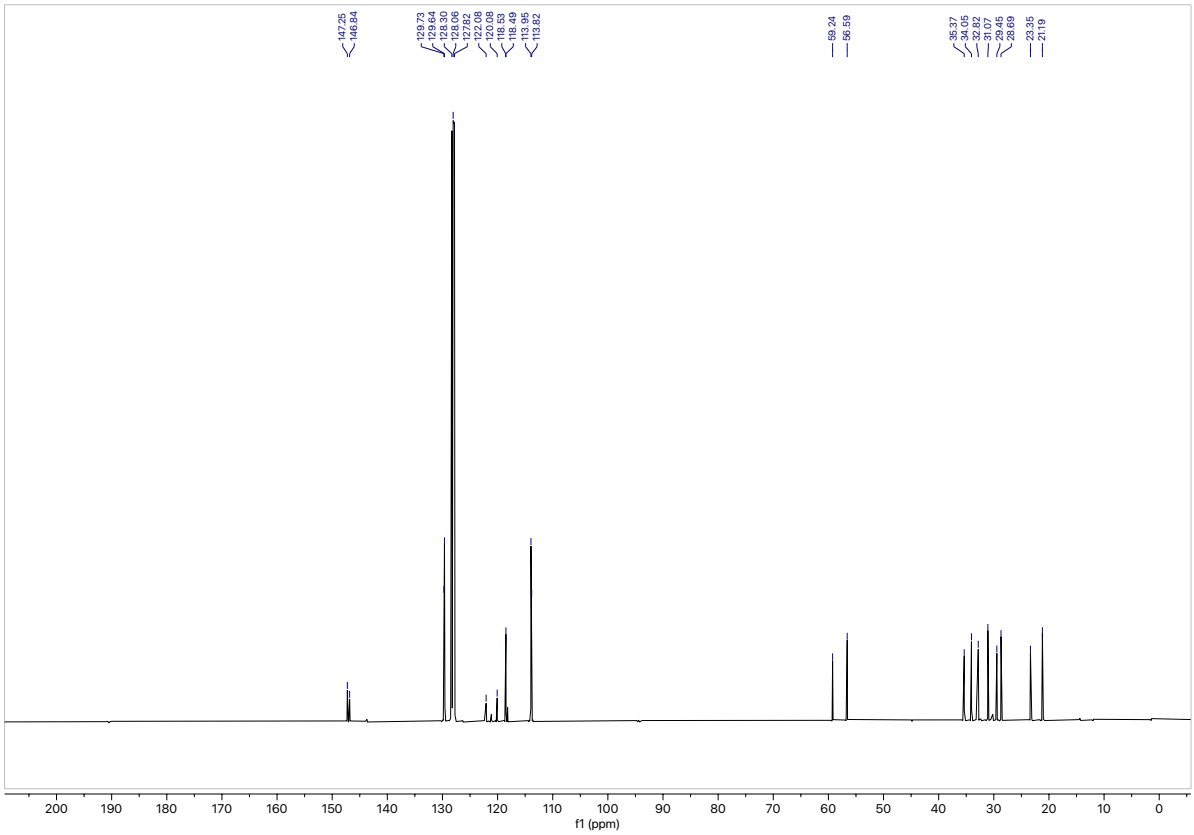

Ph
NH
Ph
Ph
NH
Ph
5.3-3ag
(major)
5.3-3ag
(minor)
9.82
1.53
1.98
1.13
0.58
1.00
0.81
1.08
0.99
1.01
2.09
1.33
4.33
1.32
f1 (ppm)

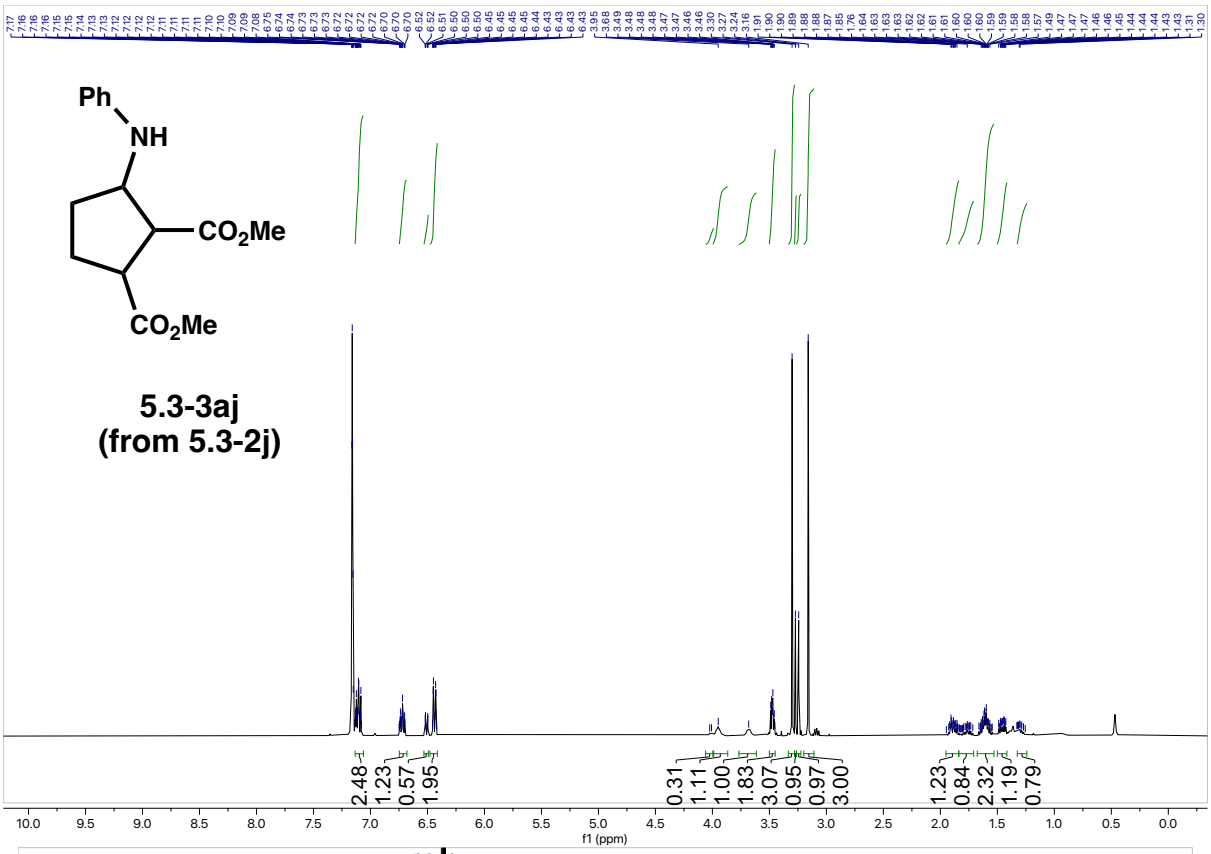

148.46
144.95
144.24
141.24
129.46
129.43
128.98
128.82
128.51
128.30
128.06
127.82
127.61
126.65
126.60
121.17
118.22
117.48
117.37
113.79
113.59
61.40
57.64
53.12
47.93
33.63
33.51
32.05
29.15
23.44
22.16
f1 (ppm)

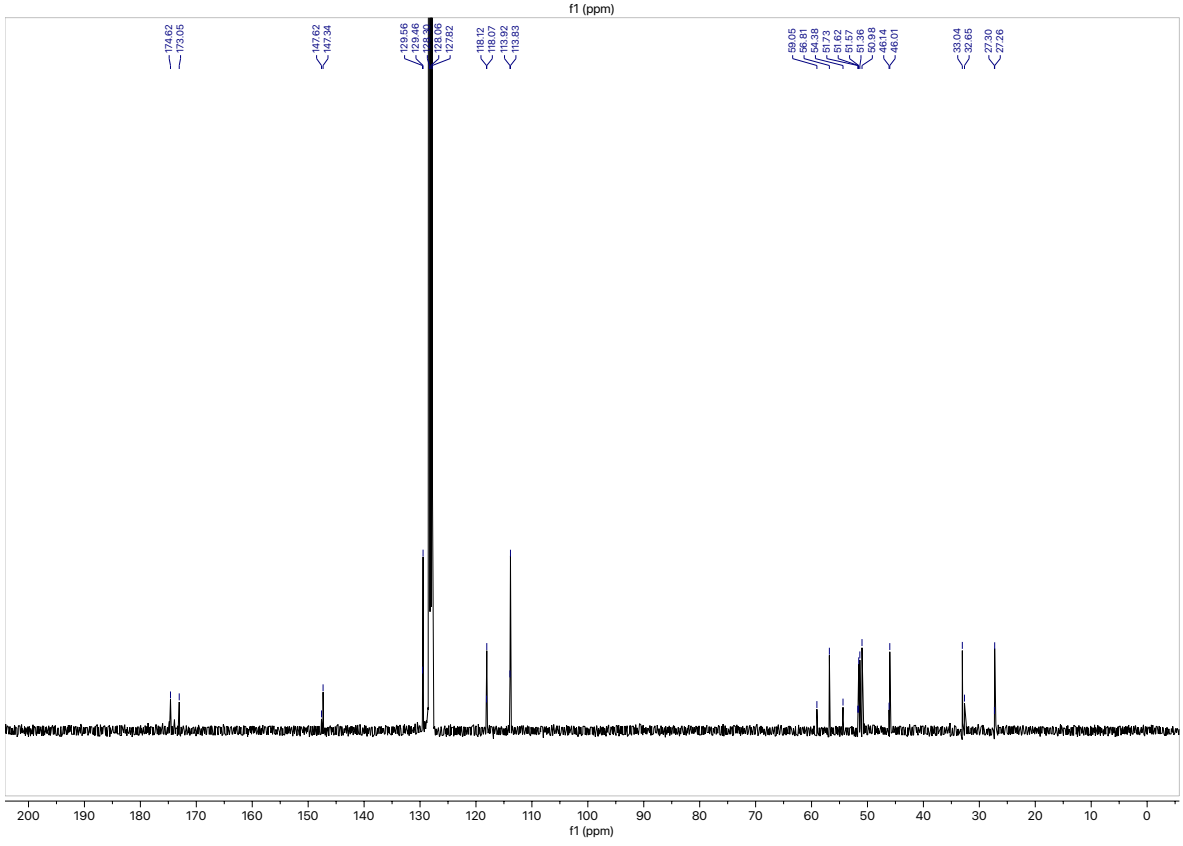

Ph
NH
SO2Ph
5.3-3ah
3.07
2.07
4.63
1.04
2.03
0.89
0.53
1.00
0.84
1.04
2.07
2.10
2.54
f1 (ppm)

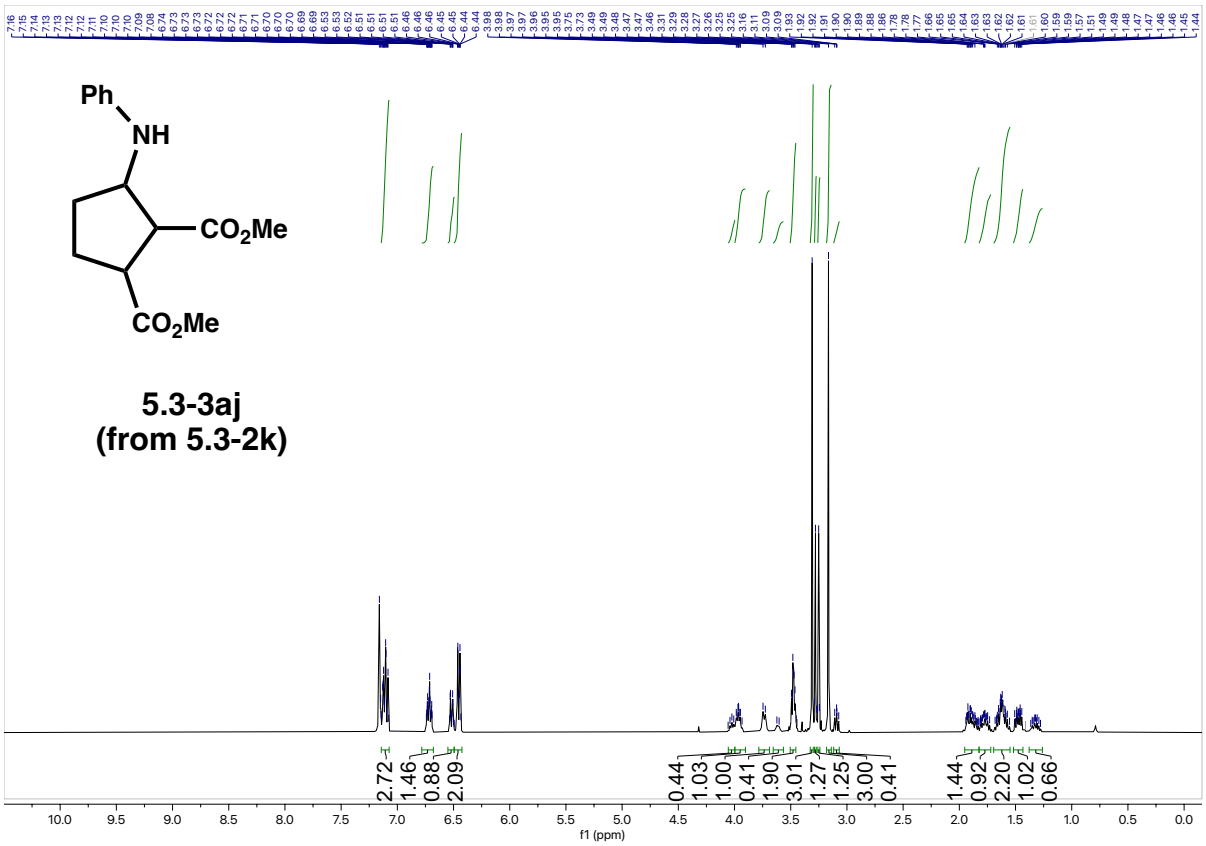

146.94
139.49
133.12
133.05
129.44
129.16
129.03
128.81
128.25
128.07
128.01
127.77
118.23
113.73
113.73
69.64
56.09
33.62
25.80
23.44
f1 (ppm)

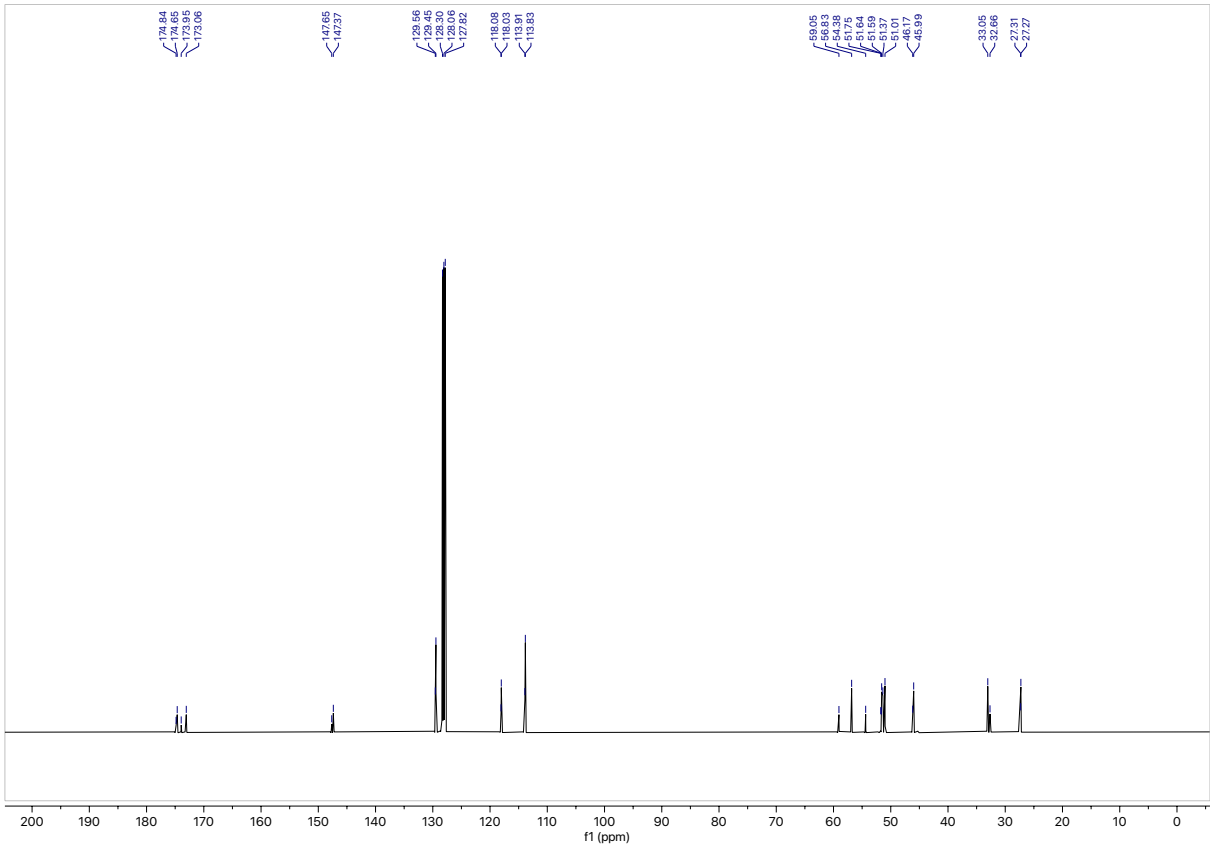

Ph
NH
CN
5.3-3ai
3.44
1.70
1.49
2.00
1.66
1.01
0.69
0.98
0.74
0.88
2.17
7.39
1.32
0.98
f1 (ppm)

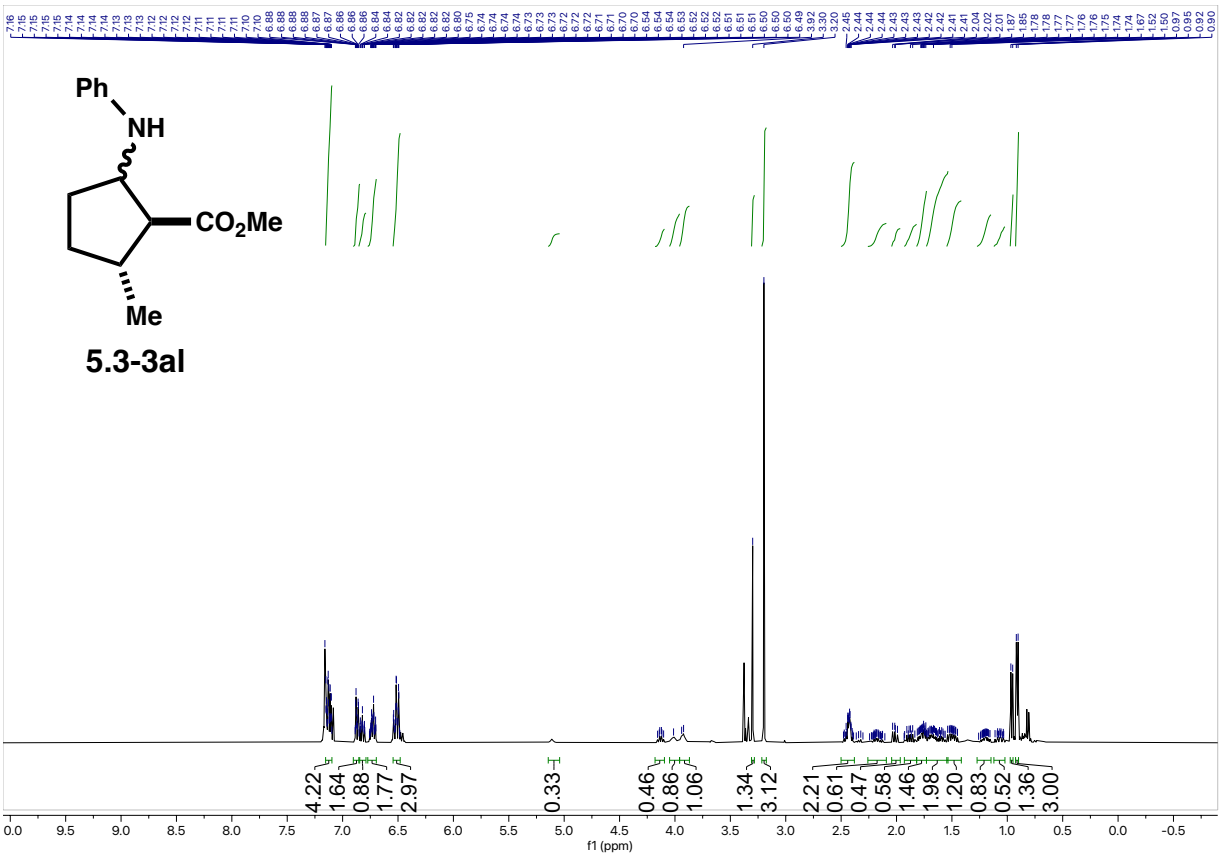

147.25
146.84
129.73
129.64
128.30
128.06
127.82
121.08
120.08
118.53
118.49
113.95
113.82
59.24
56.59
35.37
34.05
32.82
31.07
29.45
28.69
23.35
21.19
f1 (ppm)

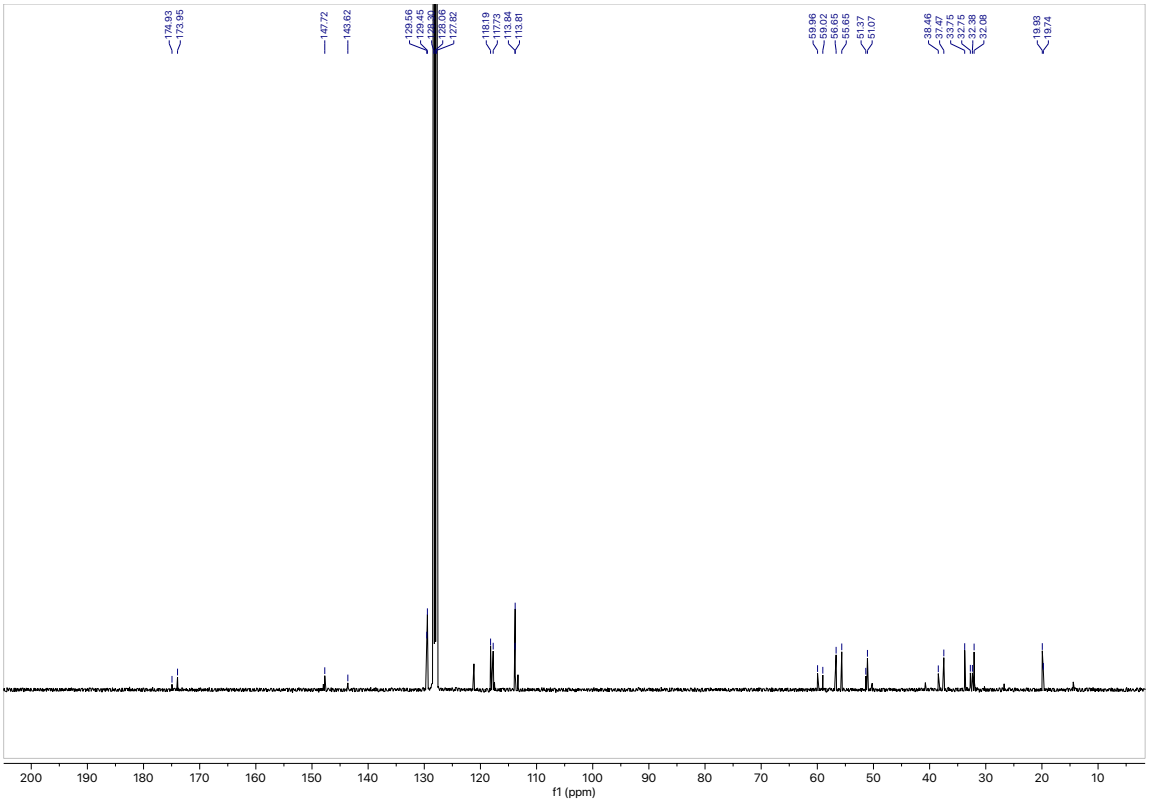

Ph
NH
CO2Me
CO2Me
5.3-3aj
(from 5.3-2j)
2.48
1.23
0.57
1.95
0.31
1.11
1.00
1.83
3.07
0.95
0.97
3.00
1.23
0.84
2.32
1.19
0.79
f1 (ppm)

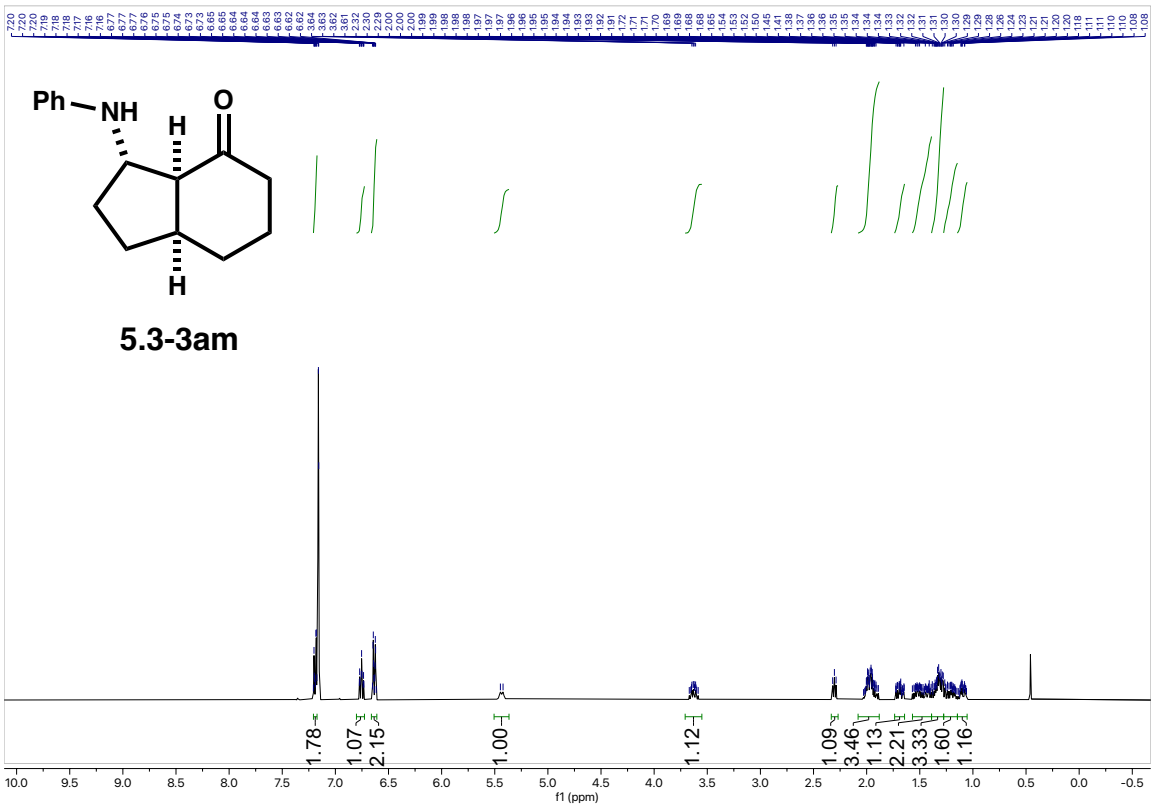

f1 (ppm)

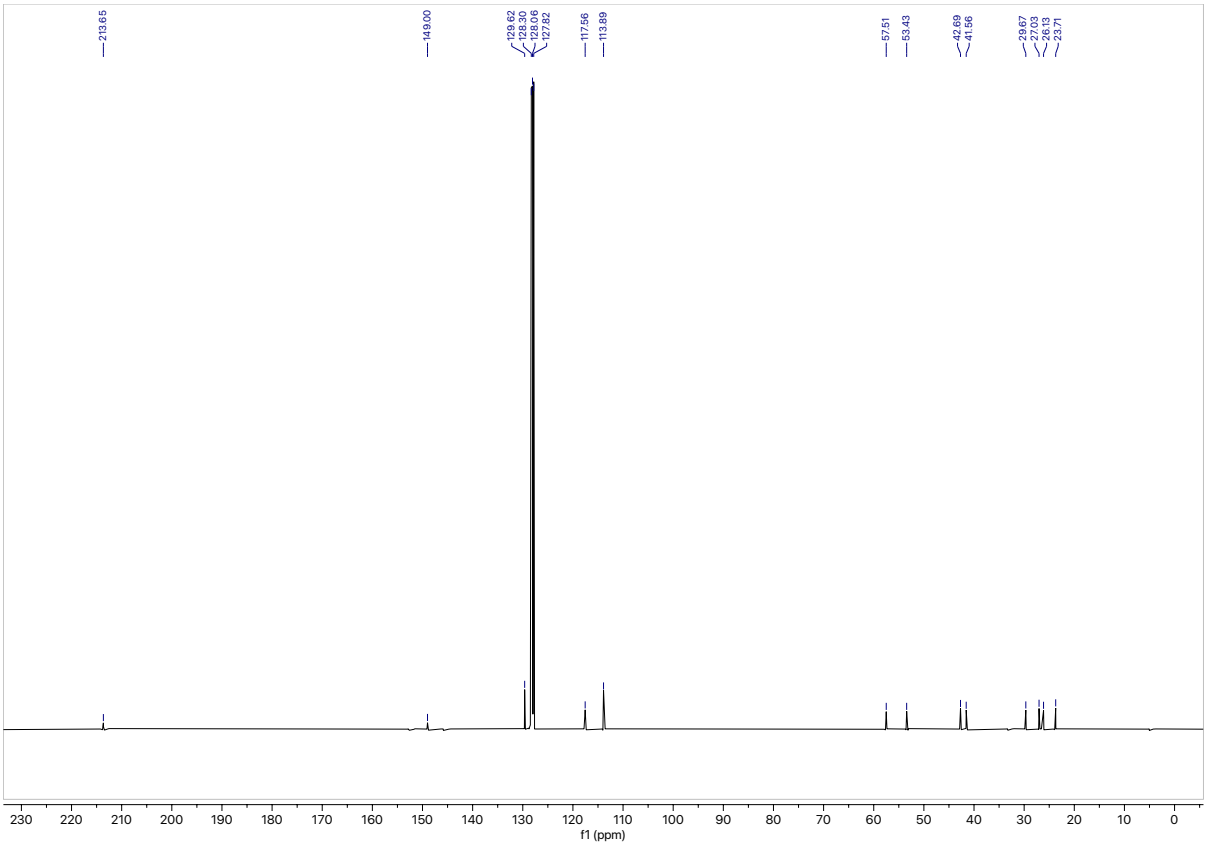

Ph
NH
CO2Me
CO2Me
5.3-3aj
(from 5.3-2k)
2.72
1.46
0.88
2.09
0.44
1.03
1.00
0.41
1.90
3.01
1.27
1.25
3.00
0.41
1.44
0.92
2.20
1.02
0.66
f1 (ppm)

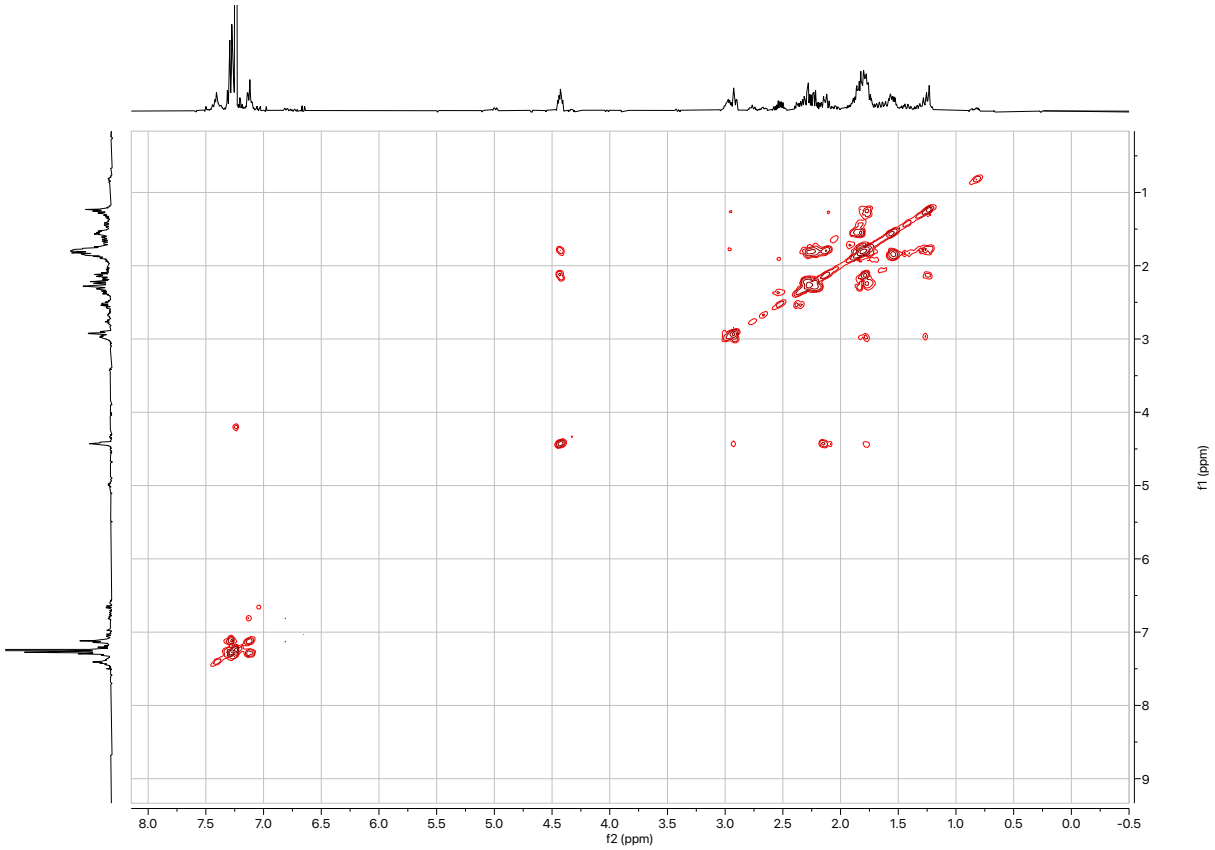

f1 (ppm)

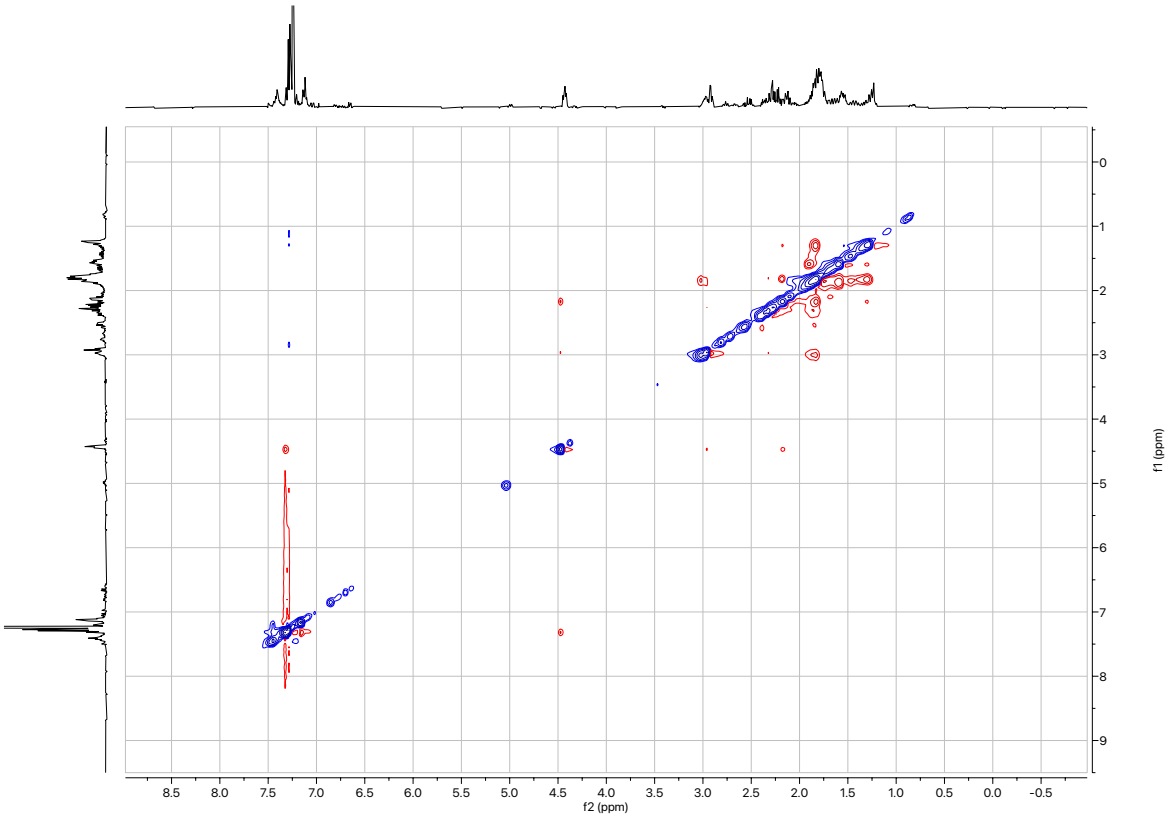

Ph
NH
CO2Me
Me
5.3-3al
4.22
1.64
0.88
1.77
2.97
0.33
0.46
0.86
1.06
1.34
3.12
2.21
0.61
0.47
0.58
1.46
1.98
1.20
0.83
0.52
1.36
3.00
f1 (ppm)

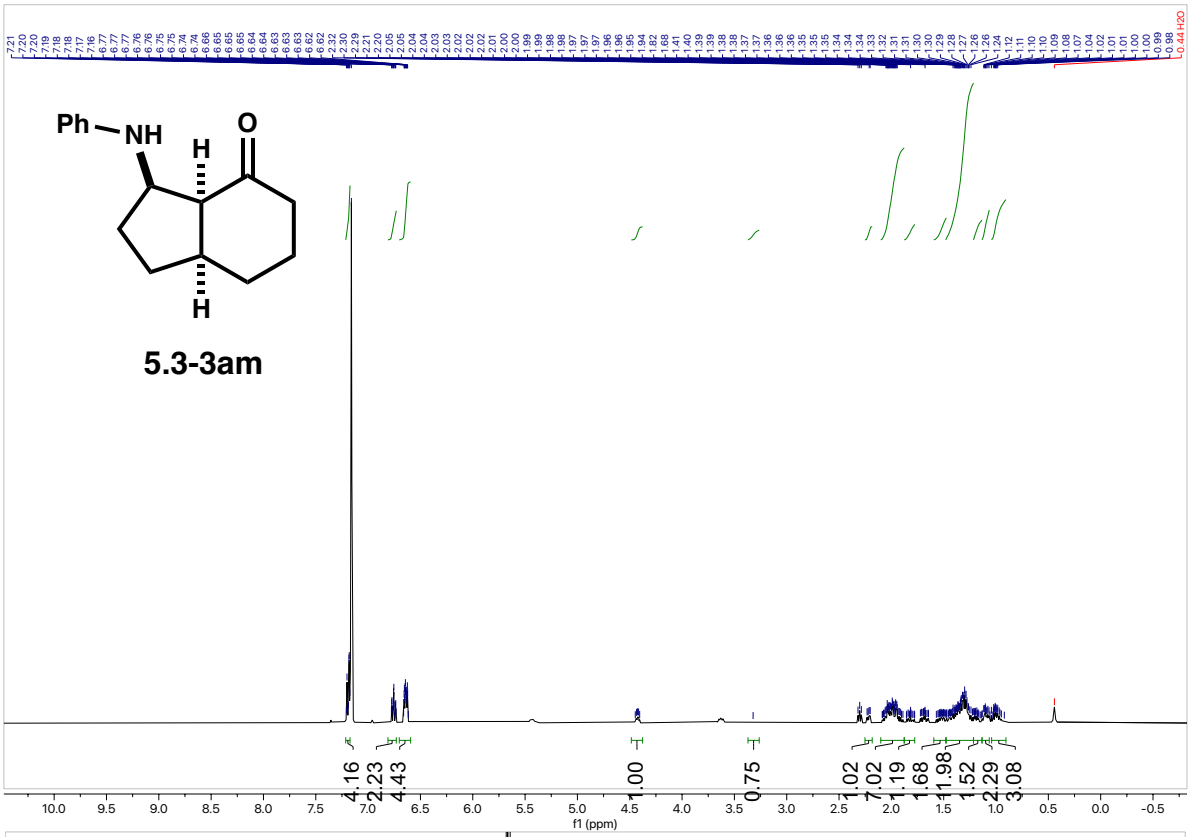

174.93
173.95
147.72
143.62
129.56
129.45
128.96
128.06
127.82
118.19
117.73
113.84
113.81
59.96
59.62
58.65
55.65
51.37
51.07
38.46
37.47
33.75
32.75
32.38
32.08
19.93
19.74
f1 (ppm)

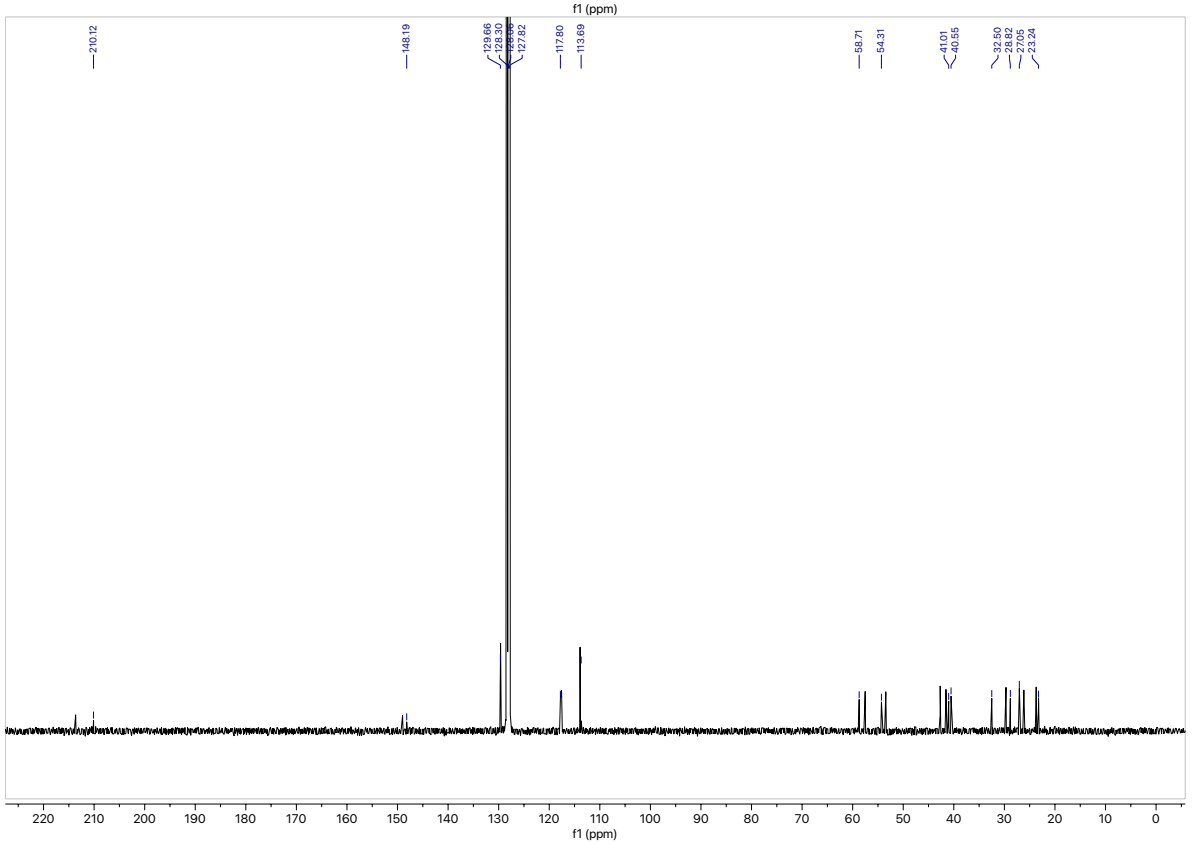

Ph
NH
H
O
H
5.3-3am
1.78
1.07
2.15
1.00
1.12
1.09
3.46
1.13
2.21
3.33
1.60
1.16
f1 (ppm)

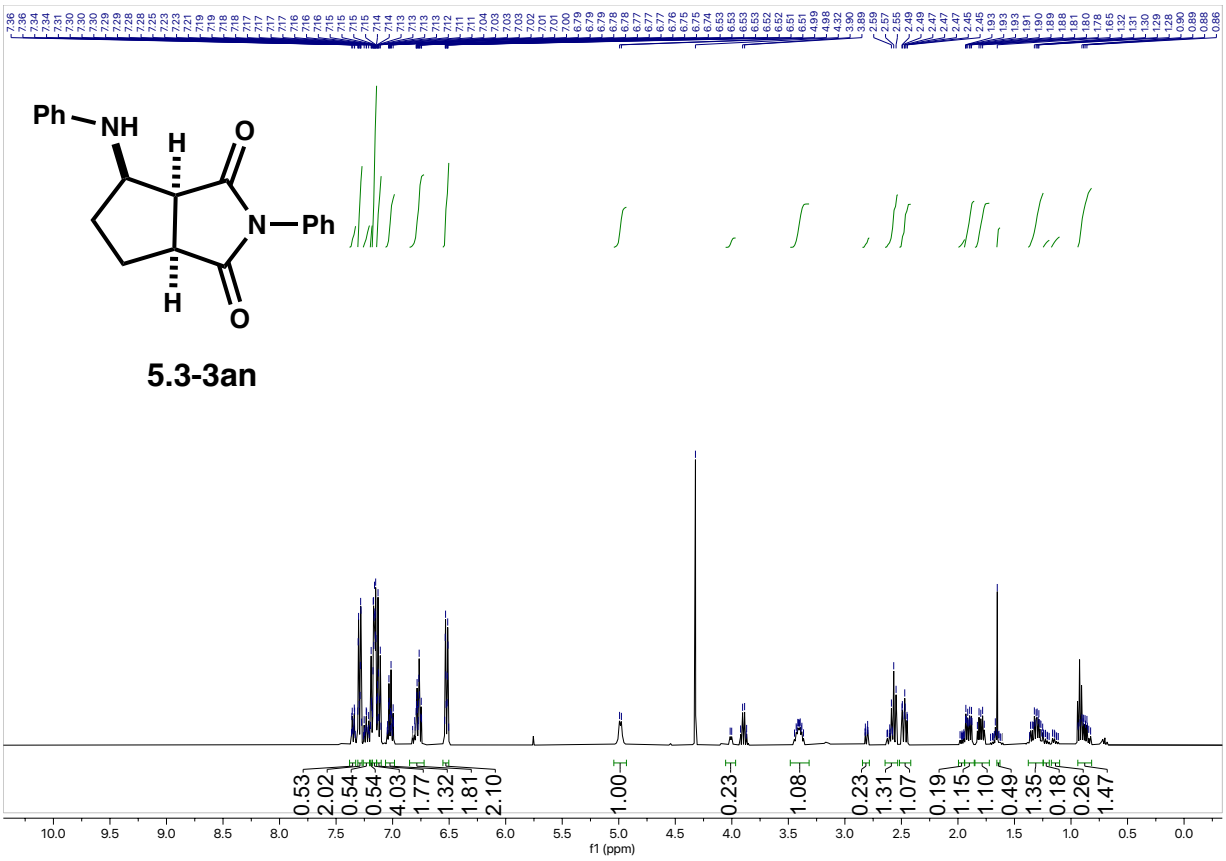

213.65
149.00
129.62
128.30
128.06
127.82
117.56
113.89
57.51
53.43
42.69
41.56
29.67
27.03
26.13
23.71
f1 (ppm)

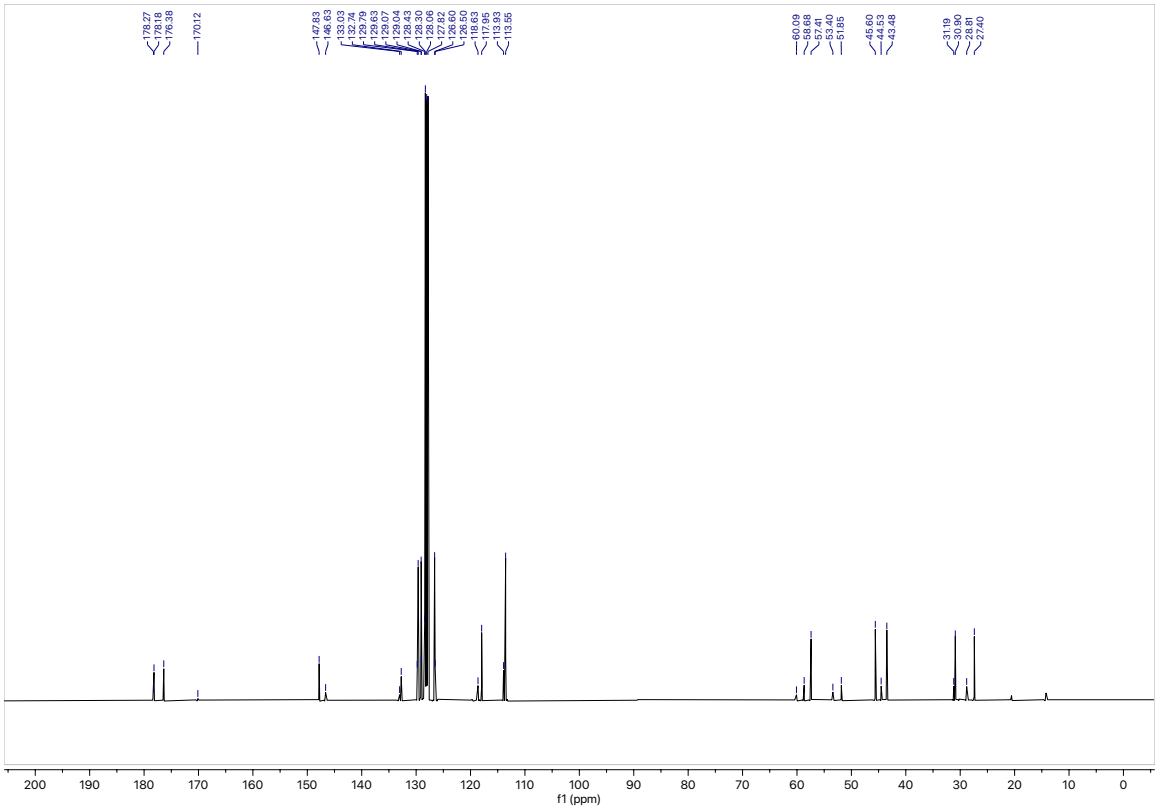

f2 (ppm)
f1 (ppm)


f2 (ppm)
f1 (ppm)

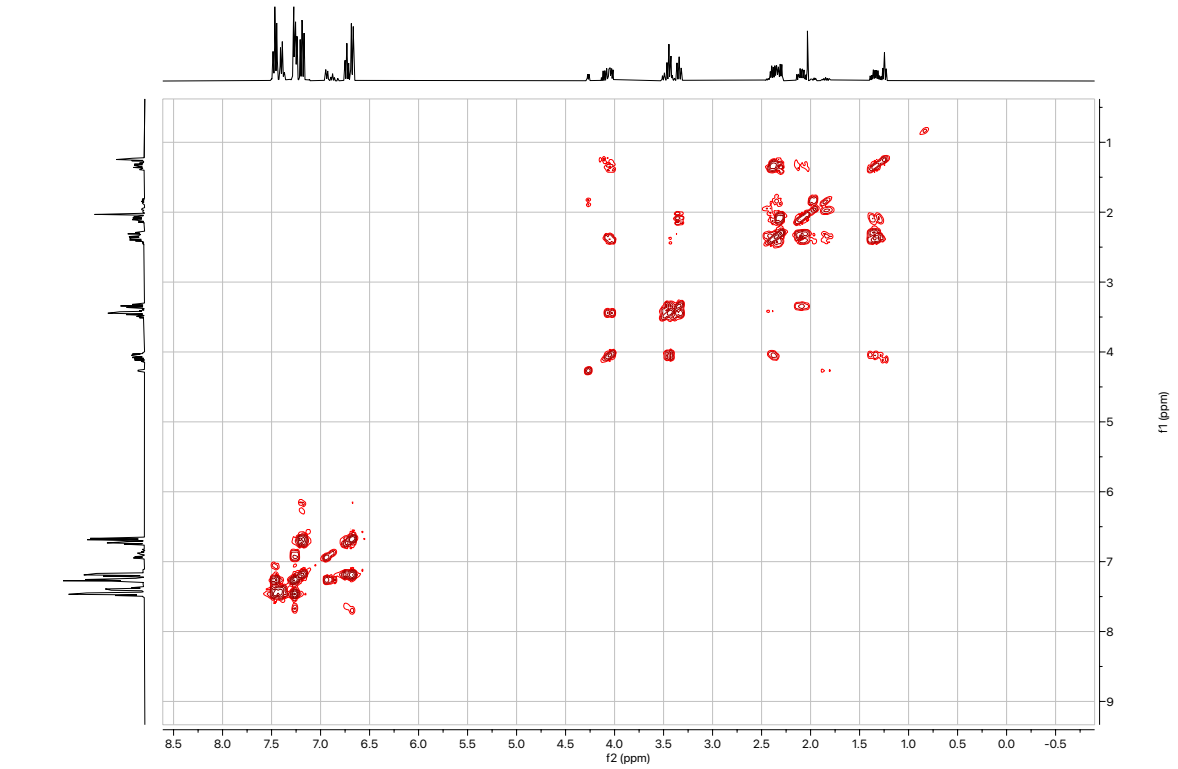

Ph
NH
H
O
H
5.3-3am
4.16
2.23
4.43
1.00
0.75
1.02
7.02
1.19
1.68
11.98
1.52
2.29
3.08
f1 (ppm)

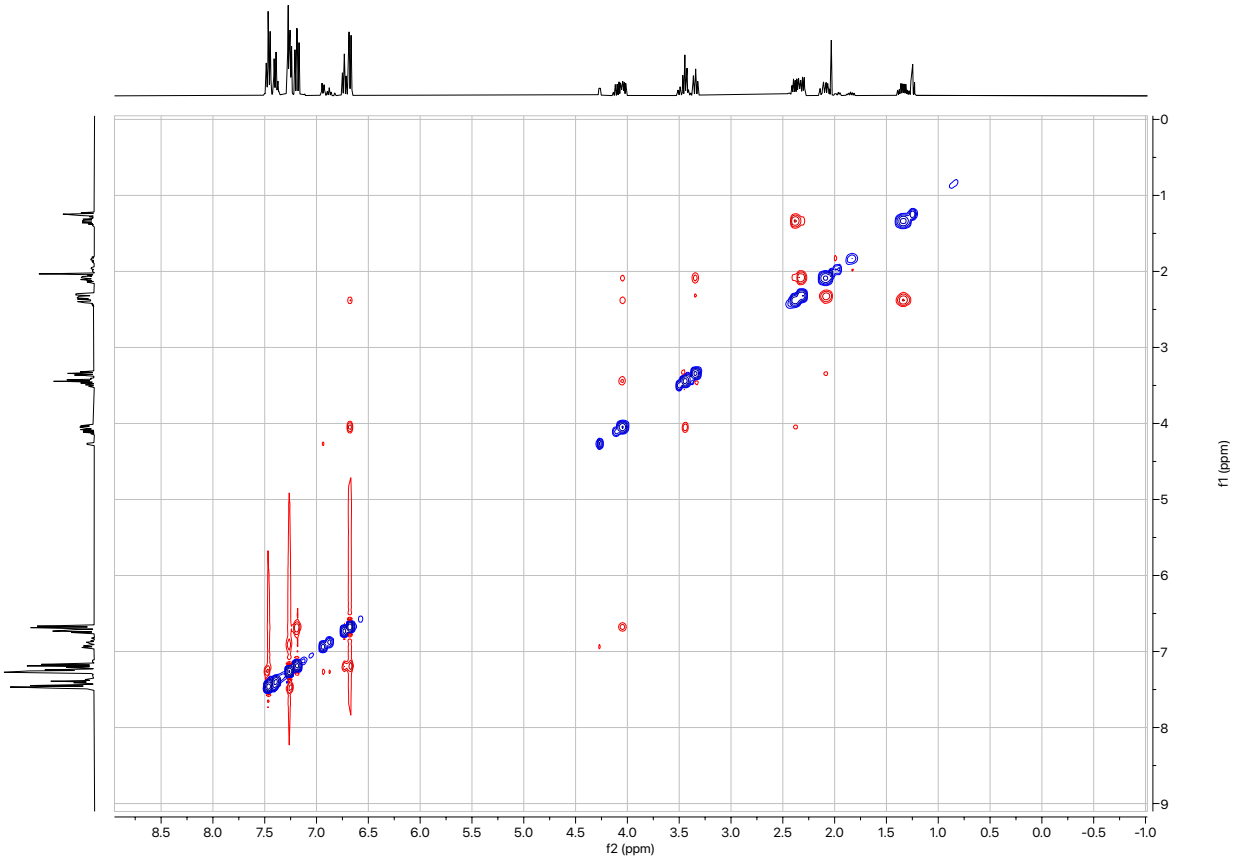

210.12
148.19
129.66
128.30
127.82
117.80
113.69
58.71
54.31
41.01
40.55
32.50
28.82
27.05
23.24
f1 (ppm)

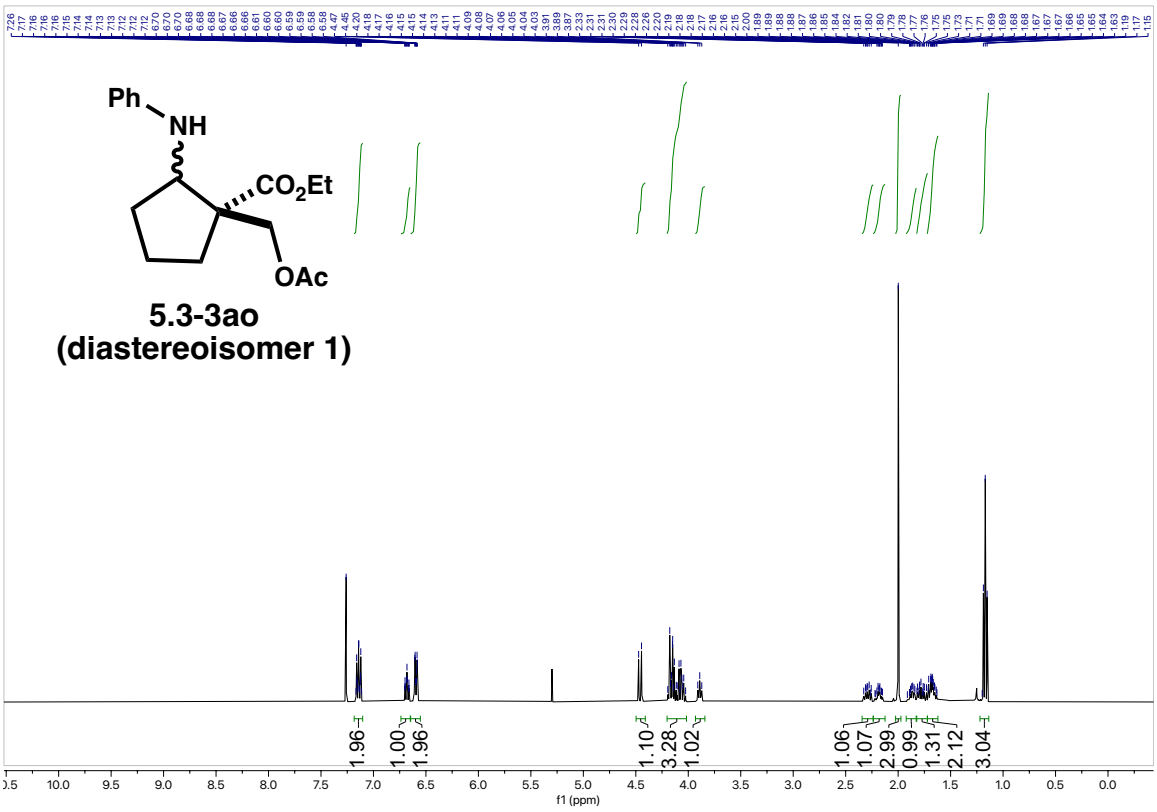

Ph
NH
H
O
N
Ph
H
O
5.3-3an
0.53
2.02
0.54
0.54
4.03
1.77
1.32
1.81
2.10
1.00
0.23
1.08
0.23
1.31
1.07
0.19
1.15
1.10
0.49
1.35
0.18
0.26
1.47
f1 (ppm)

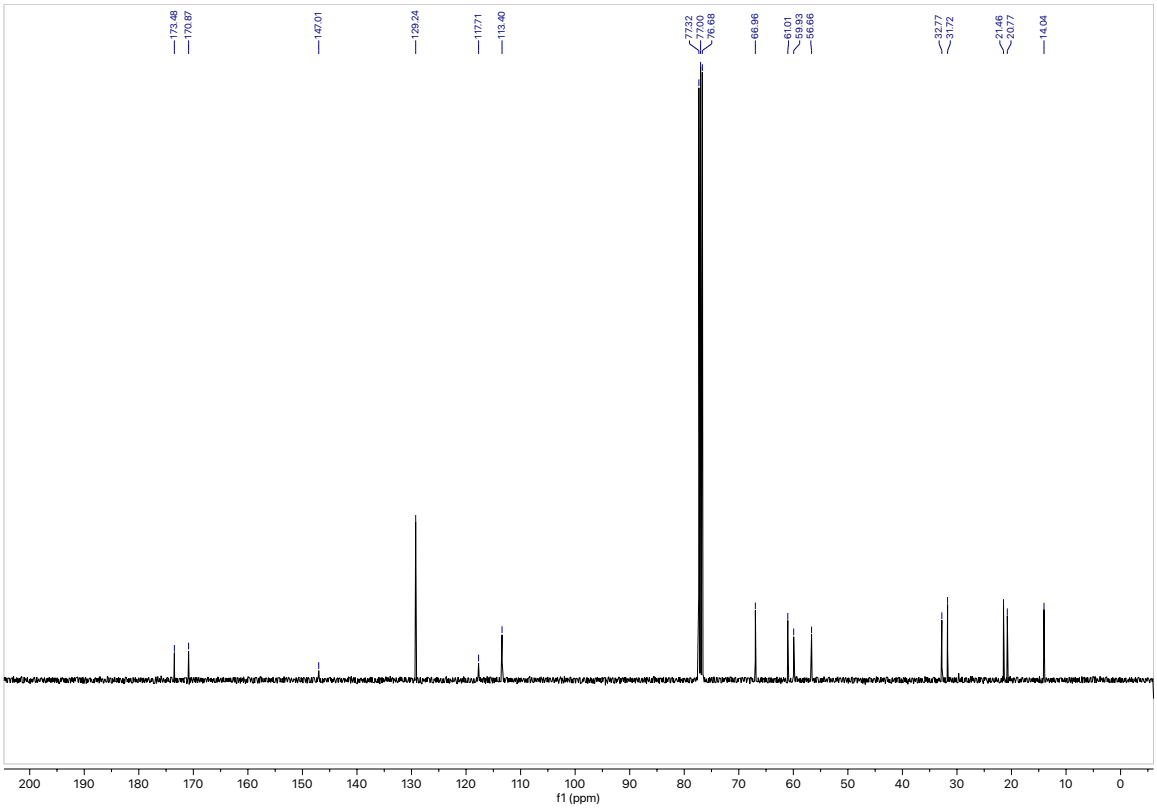

f1 (ppm)

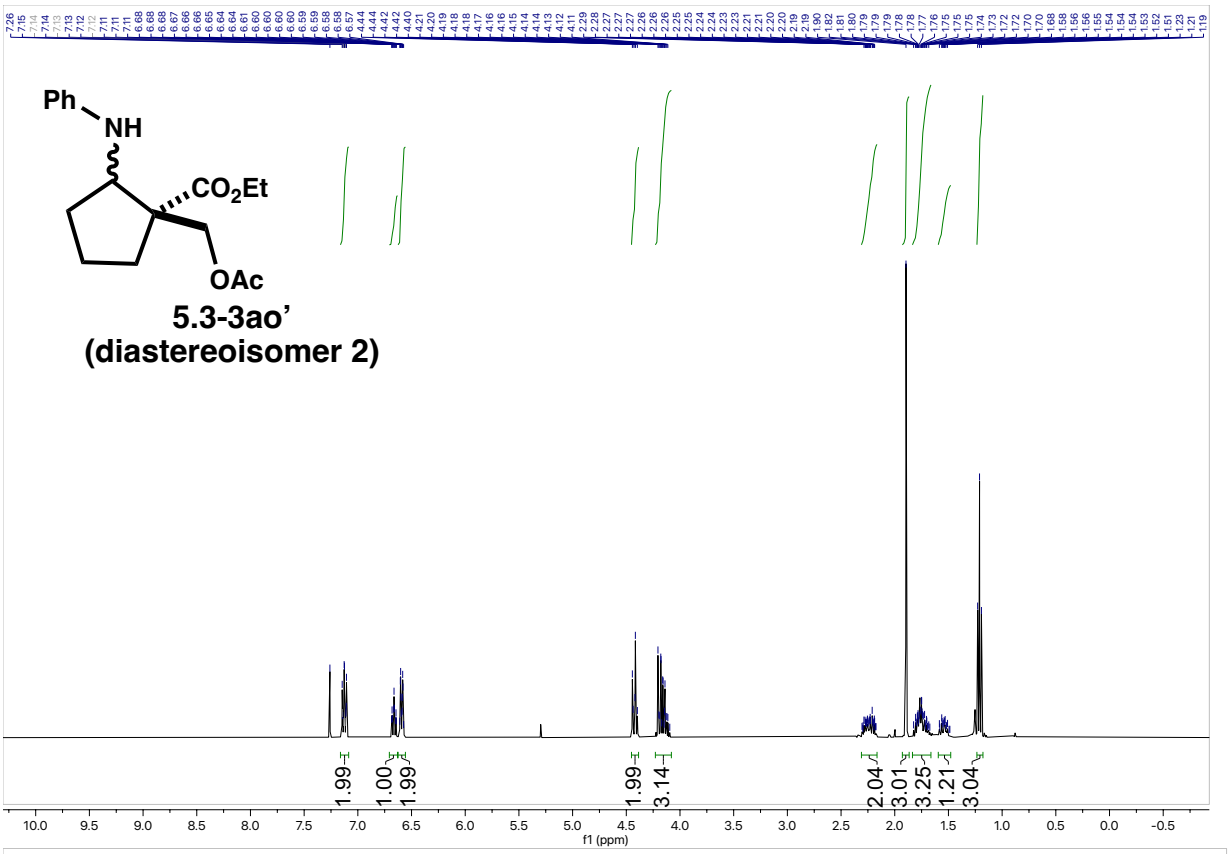
$CDCl_3$, 400 MHZ

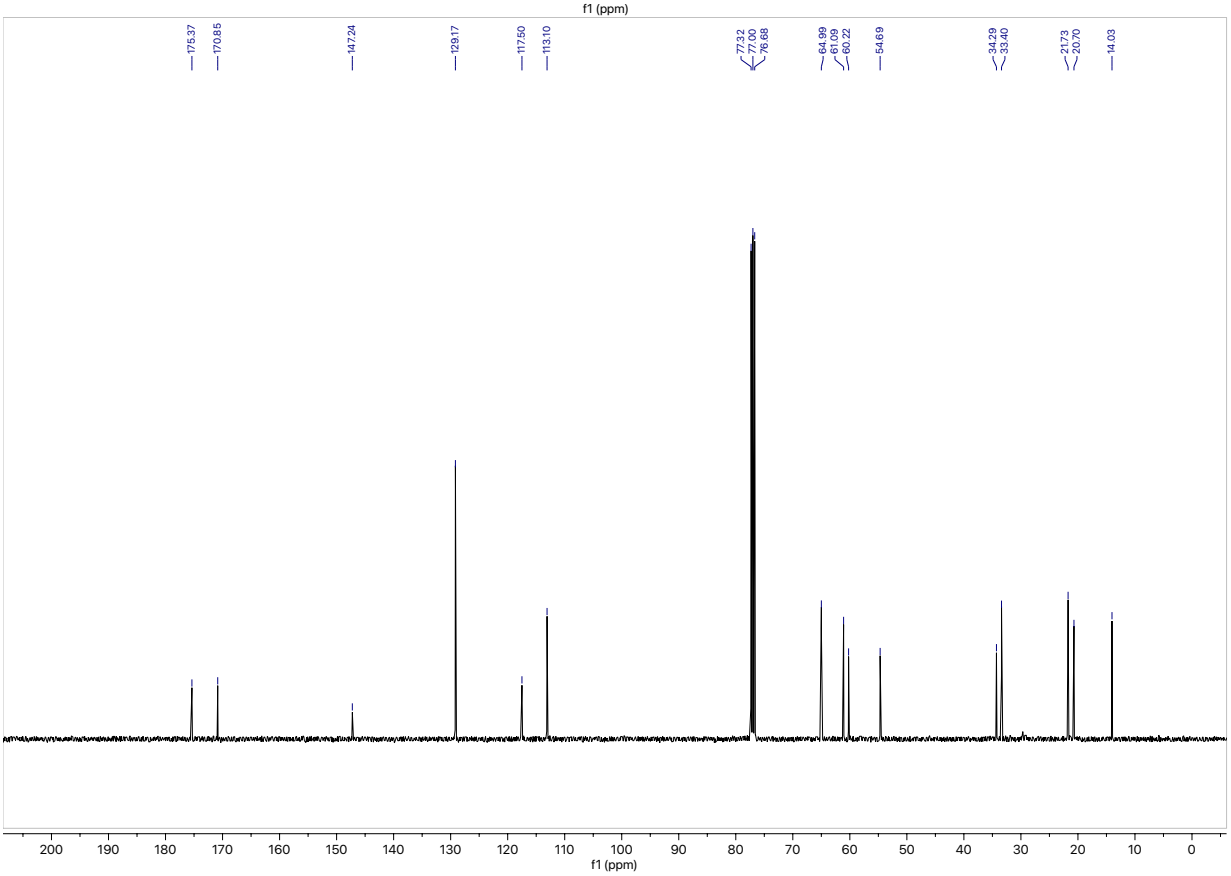


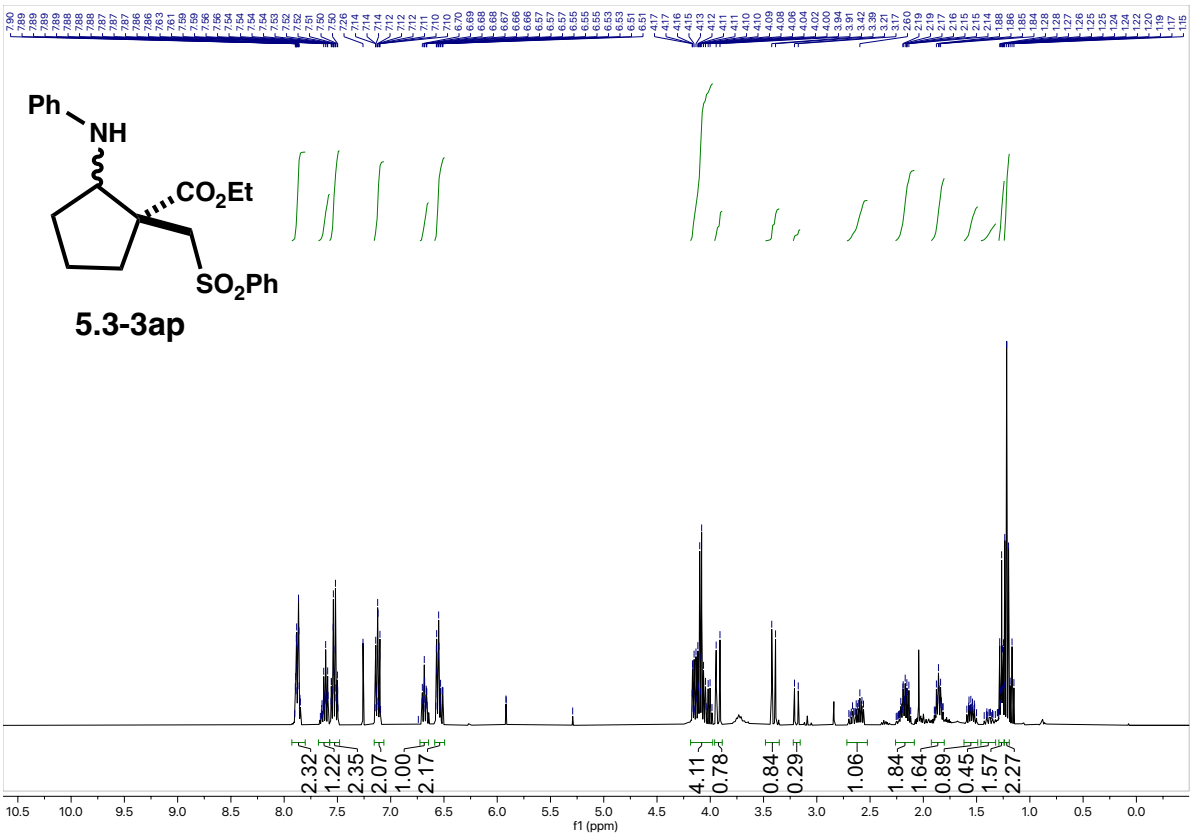


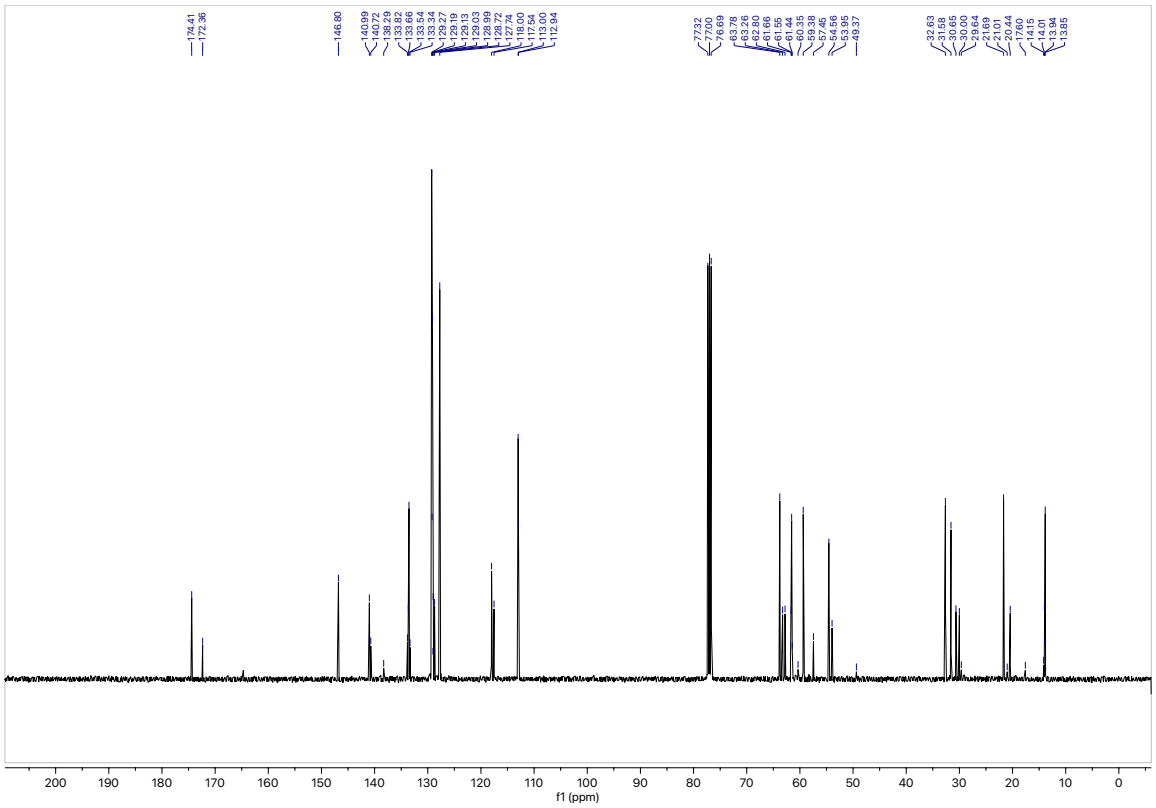

Ph
NH
CO2Et
OAc
5.3-3ao
(diastereoisomer 1)
1.96
1.00
1.96
1.10
3.28
1.02
1.06
1.07
2.99
0.99
1.31
2.12
3.04
f1 (ppm)

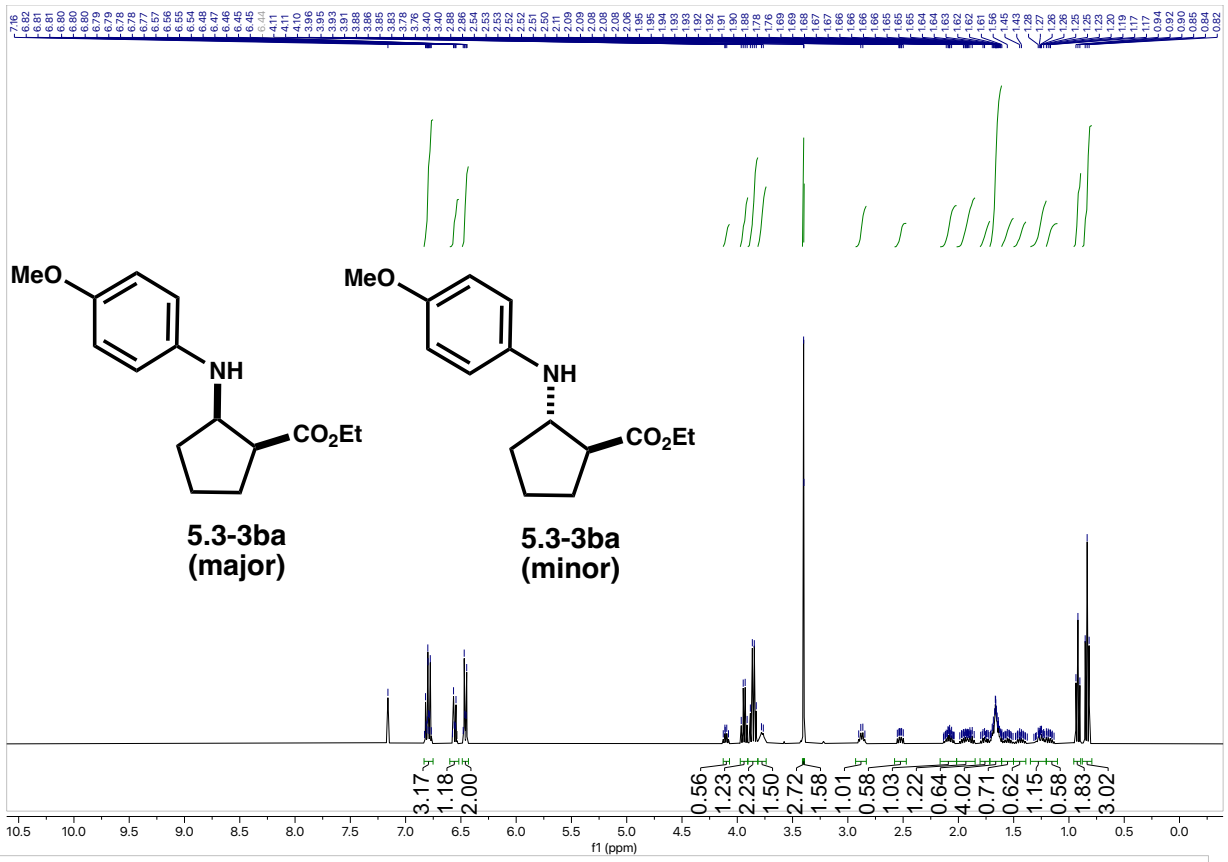

173.48
170.87
147.01
129.24
117.71
113.40
77.32
77.00
76.68
66.96
61.01
59.93
56.66
32.77
31.72
21.46
20.77
14.04
f1 (ppm)

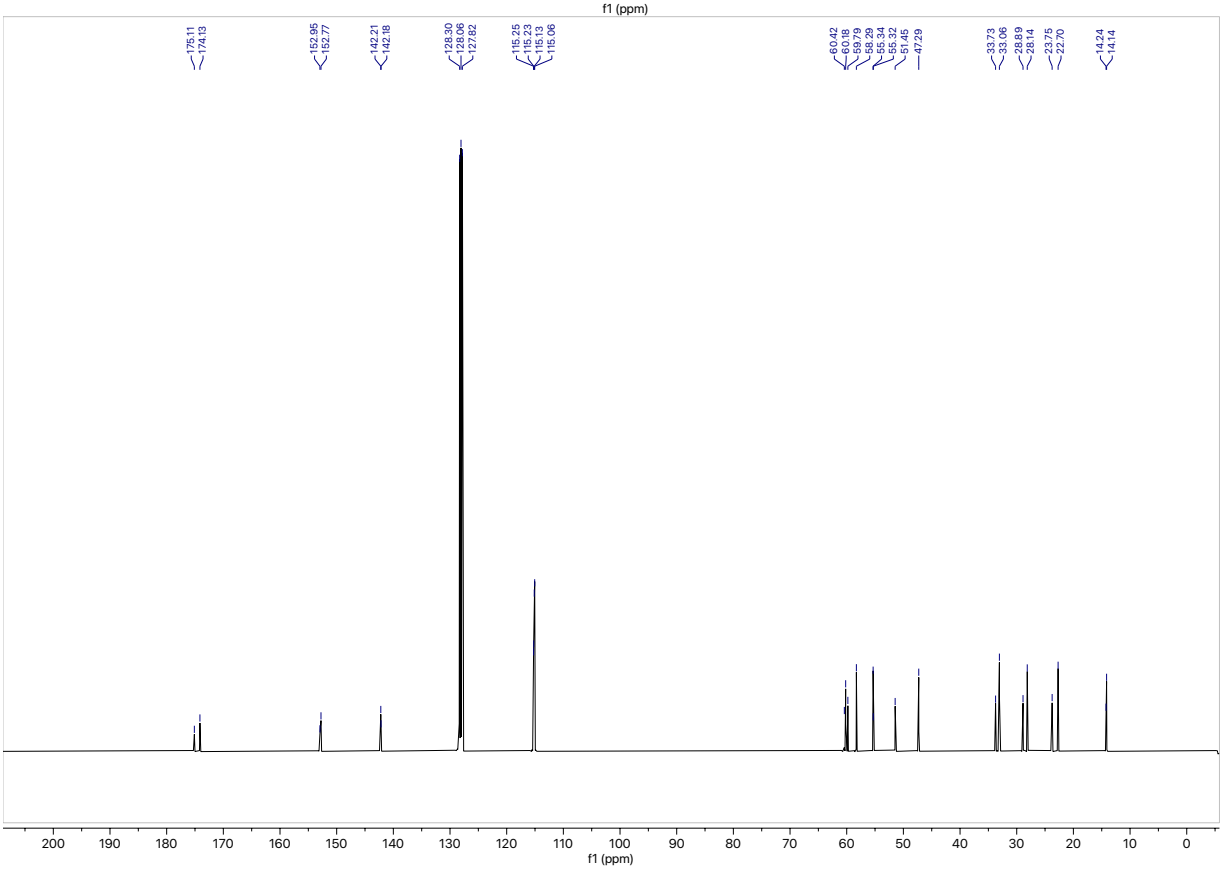

Ph
NH
CO2Et
OAc
5.3-3ao'
(diastereoisomer 2)
1.99
1.00
1.99
1.99
3.14
2.04
3.01
3.25
1.21
3.04
f1 (ppm)

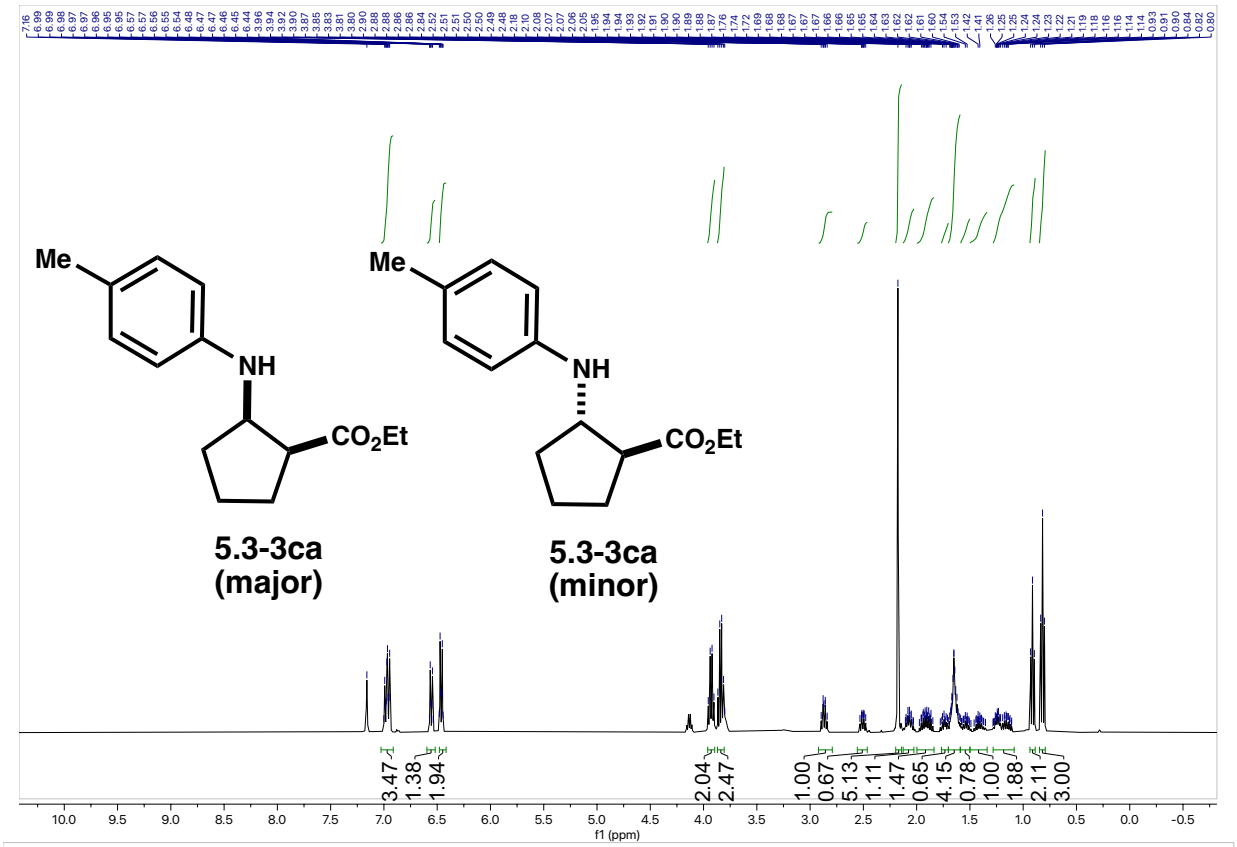

175.37
170.85
147.24
129.17
117.50
113.10
77.32
77.00
76.68
64.99
61.09
60.22
54.69
34.29
33.40
21.73
20.70
14.03
f1 (ppm)

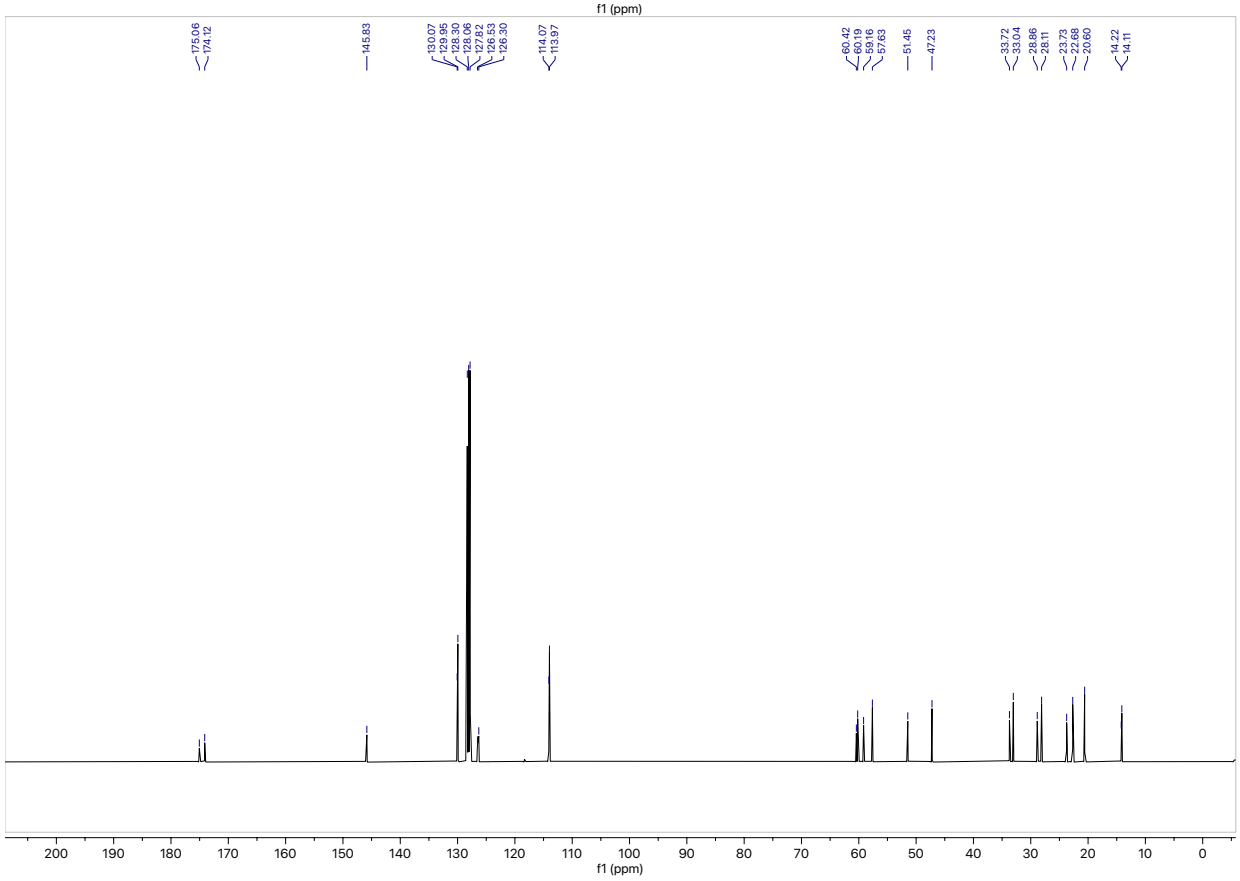

Ph
NH
CO2Et
SO2Ph
5.3-3ap
2.32
1.22
2.35
2.07
1.00
2.17
4.11
0.78
0.84
0.29
1.06
1.84
1.64
0.89
0.45
1.57
2.27
f1 (ppm)

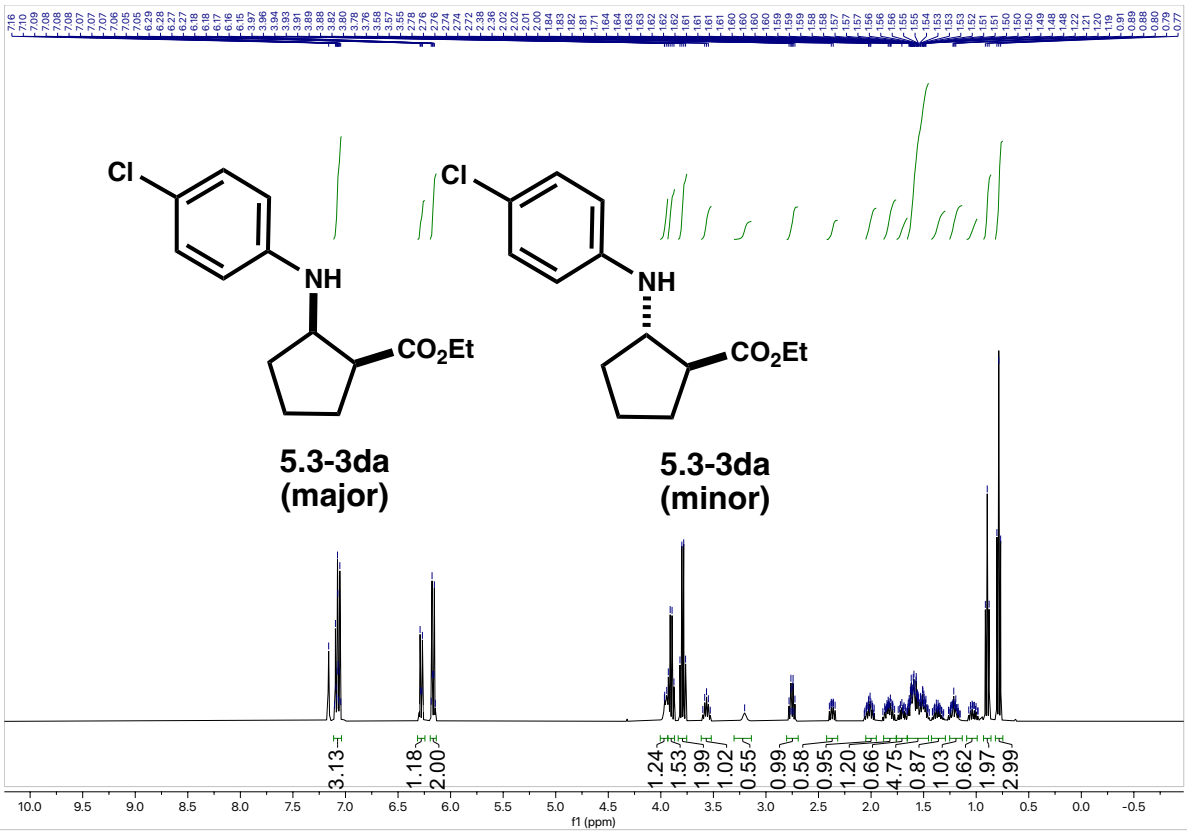

f1 (ppm)

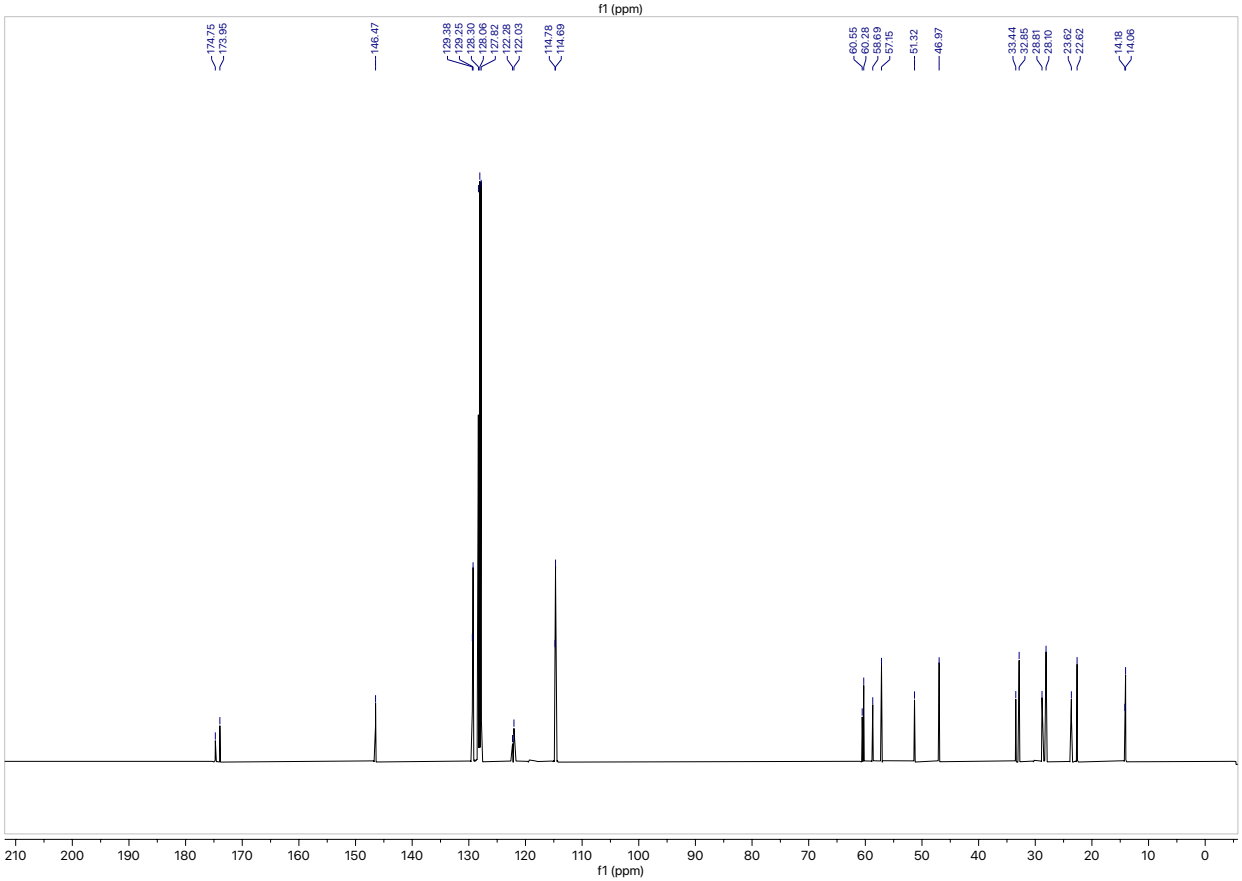

MeO
NH
CO2Et
5.3-3ba
(major)
MeO
NH
CO2Et
5.3-3ba
(minor)
3.17
1.18
2.00
0.56
1.23
2.23
1.50
2.72
1.58
1.01
0.58
1.03
1.22
0.64
4.02
0.71
0.62
1.15
0.58
1.83
3.02
f1 (ppm)

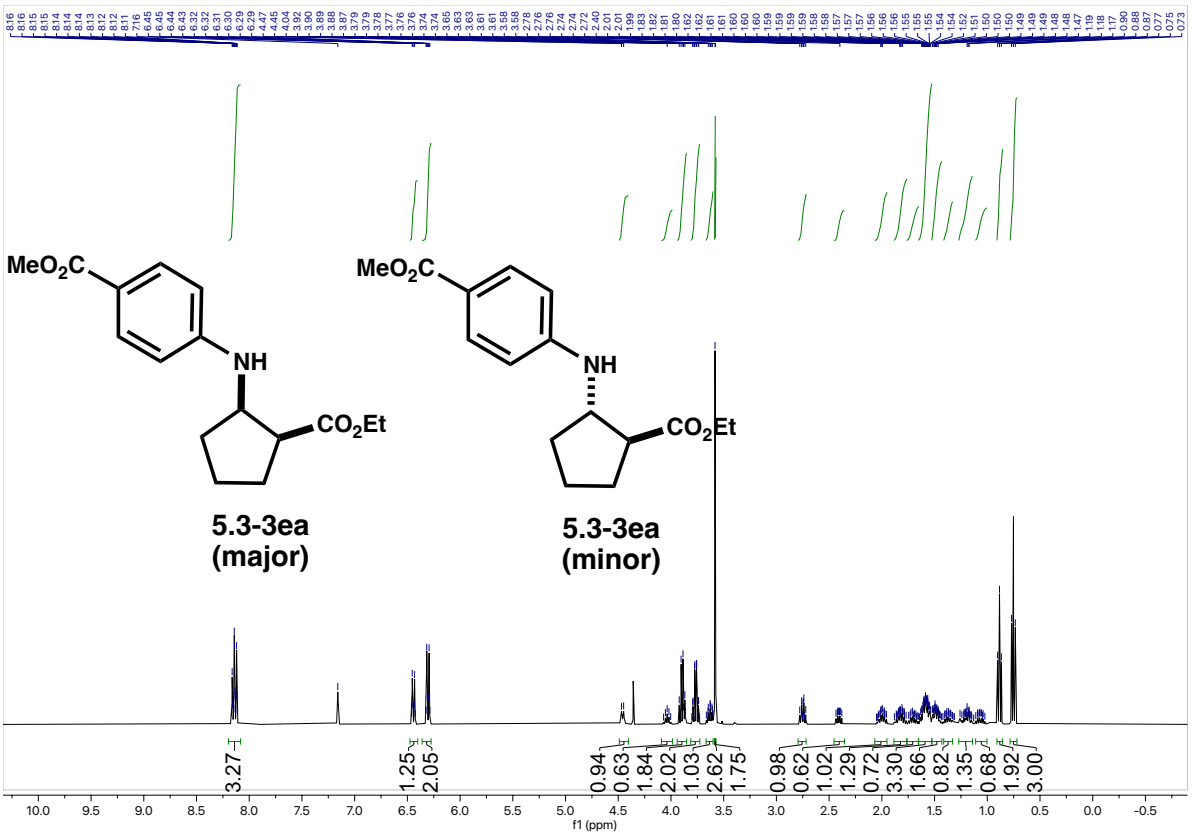

f1 (ppm)

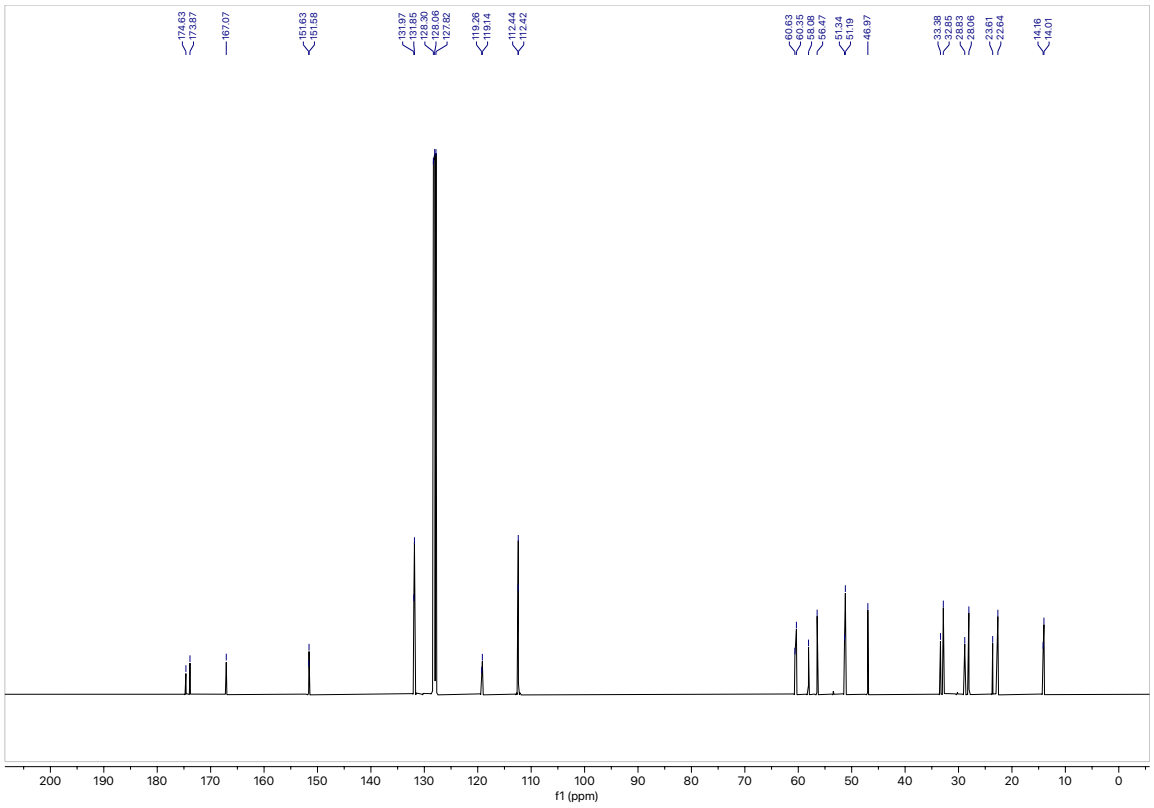

Me
NH
CO2Et
5.3-3ca
(major)
Me
NH
CO2Et
5.3-3ca
(minor)
3.47
1.38
1.94
2.04
2.47
1.00
0.67
5.13
1.11
1.47
0.65
4.15
0.78
1.00
1.88
2.11
3.00
f1 (ppm)

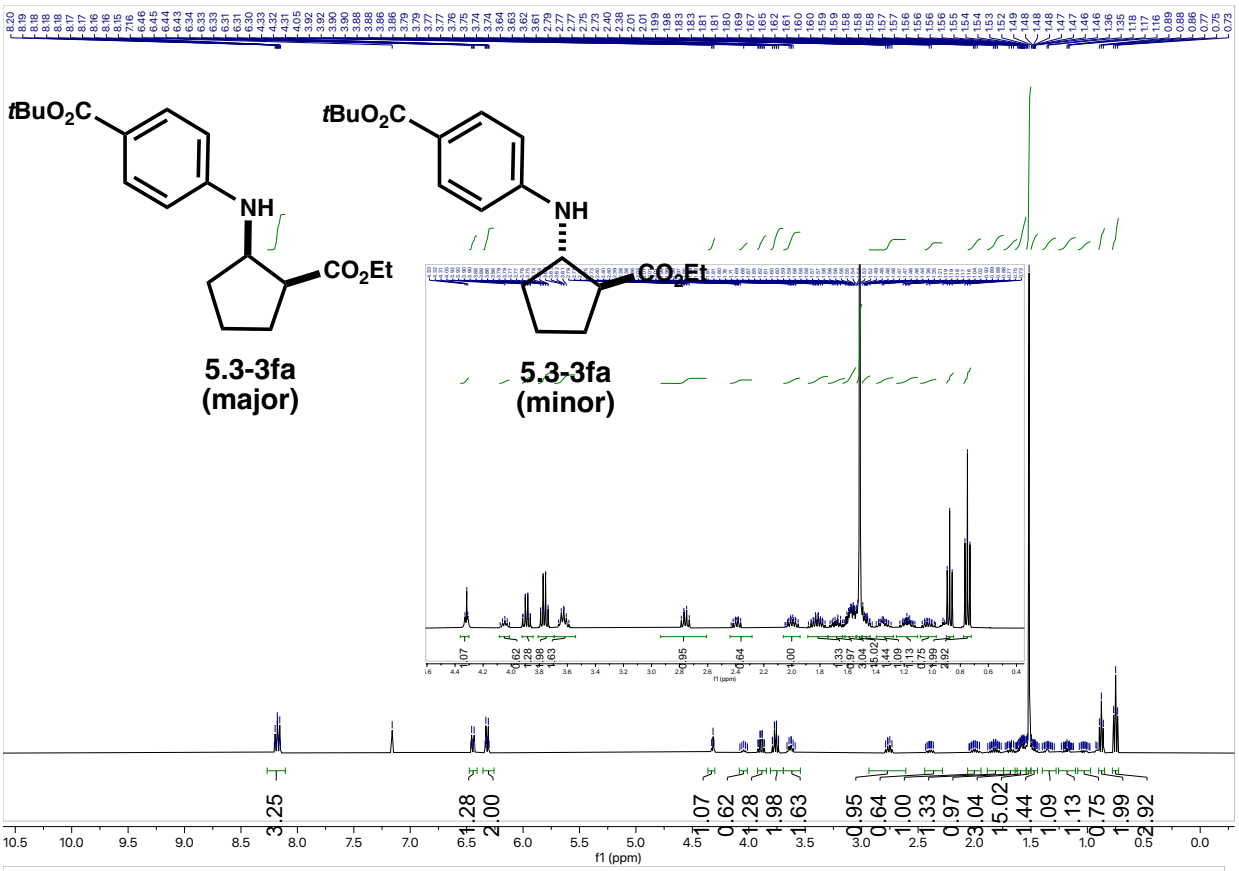

175.06
174.12
145.83
130.07
129.95
128.30
128.06
127.82
126.53
126.30
114.07
113.97
60.42
60.19
59.16
57.83
51.45
47.23
33.72
33.04
28.86
28.11
23.73
22.68
20.60
14.22
14.11
f1 (ppm)

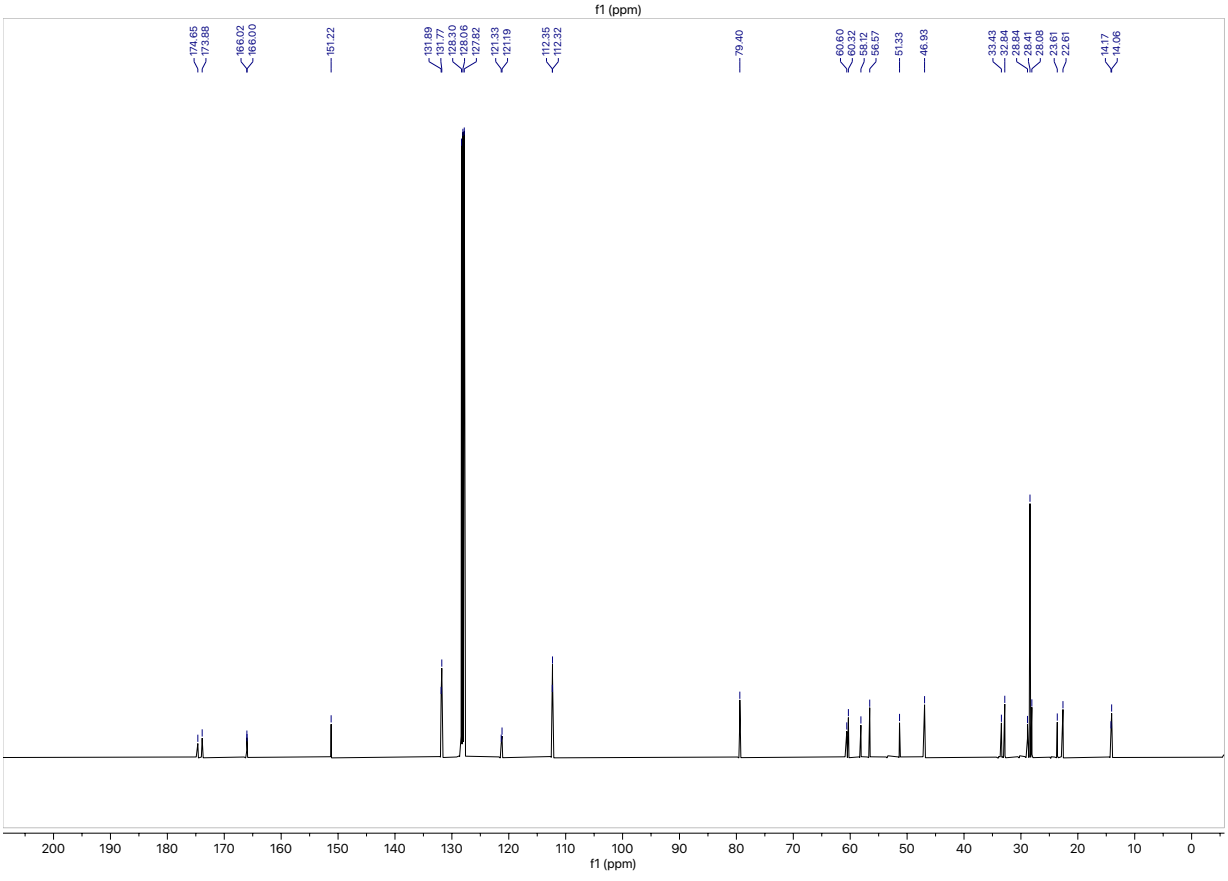

Cl
NH
CO2Et
5.3-3da
(major)
Cl
NH
CO2Et
5.3-3da
(minor)
3.13
1.18
2.00
1.24
1.53
1.99
1.02
0.55
0.99
0.58
0.95
1.20
0.66
4.75
0.87
1.03
0.62
1.97
2.99
f1 (ppm)

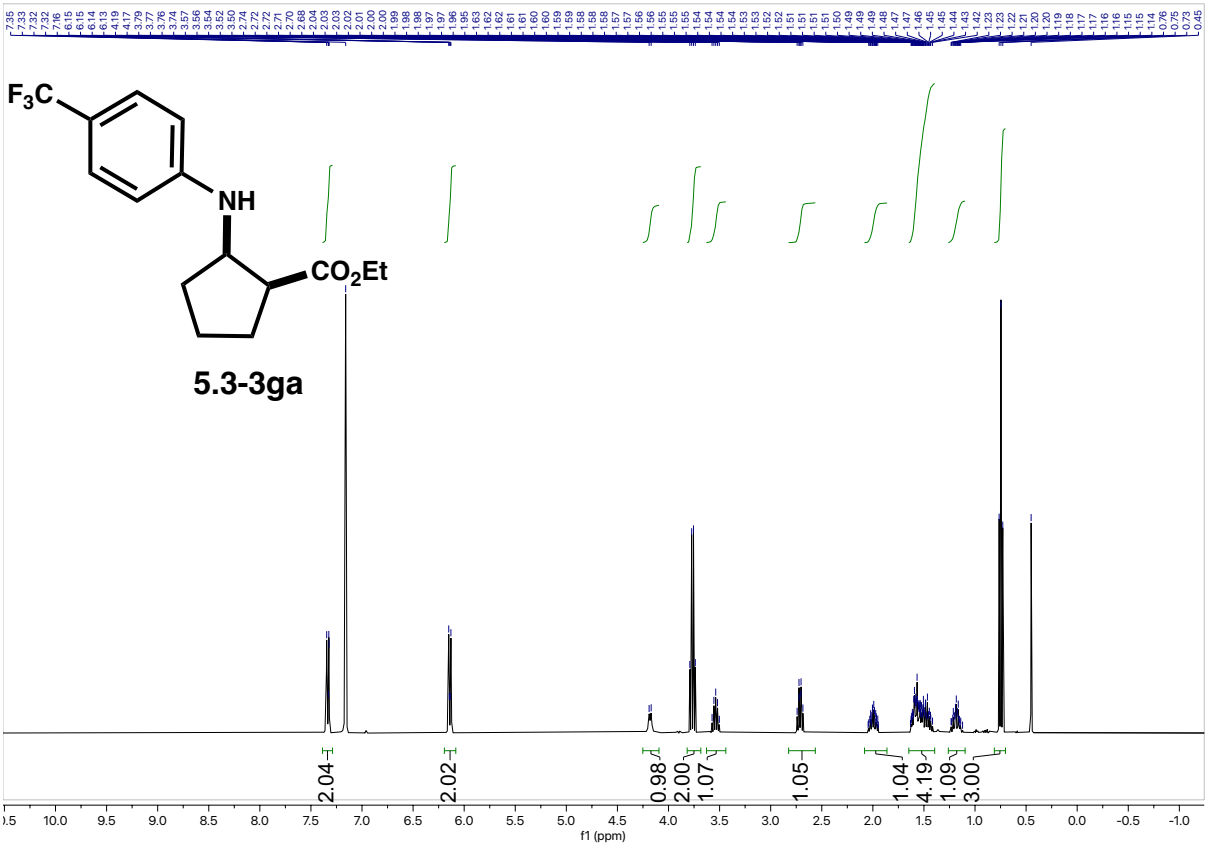

174.75
173.95
146.47
129.38
129.25
128.30
128.06
127.82
122.28
122.03
114.78
114.69
60.55
60.28
58.69
57.15
51.32
46.97
33.44
33.05
28.81
28.10
23.62
22.62
14.18
14.06
f1 (ppm)

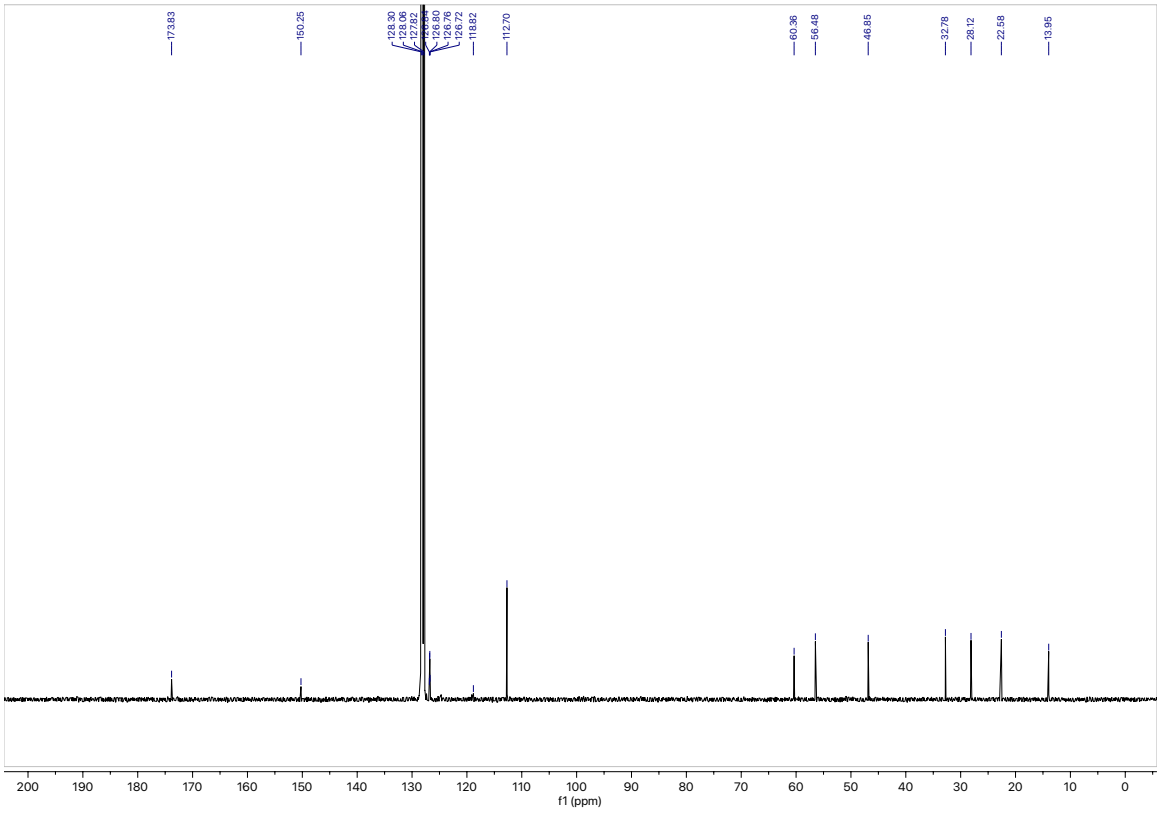

MeO2C
NH
CO2Et
5.3-3ea
(major)
MeO2C
NH
CO2Et
5.3-3ea
(minor)
3.27
1.25
2.05
0.94
0.63
1.84
2.02
1.03
2.62
1.75
0.98
0.62
1.02
1.29
0.72
3.30
1.66
0.82
1.35
0.68
1.92
3.00
f1 (ppm)

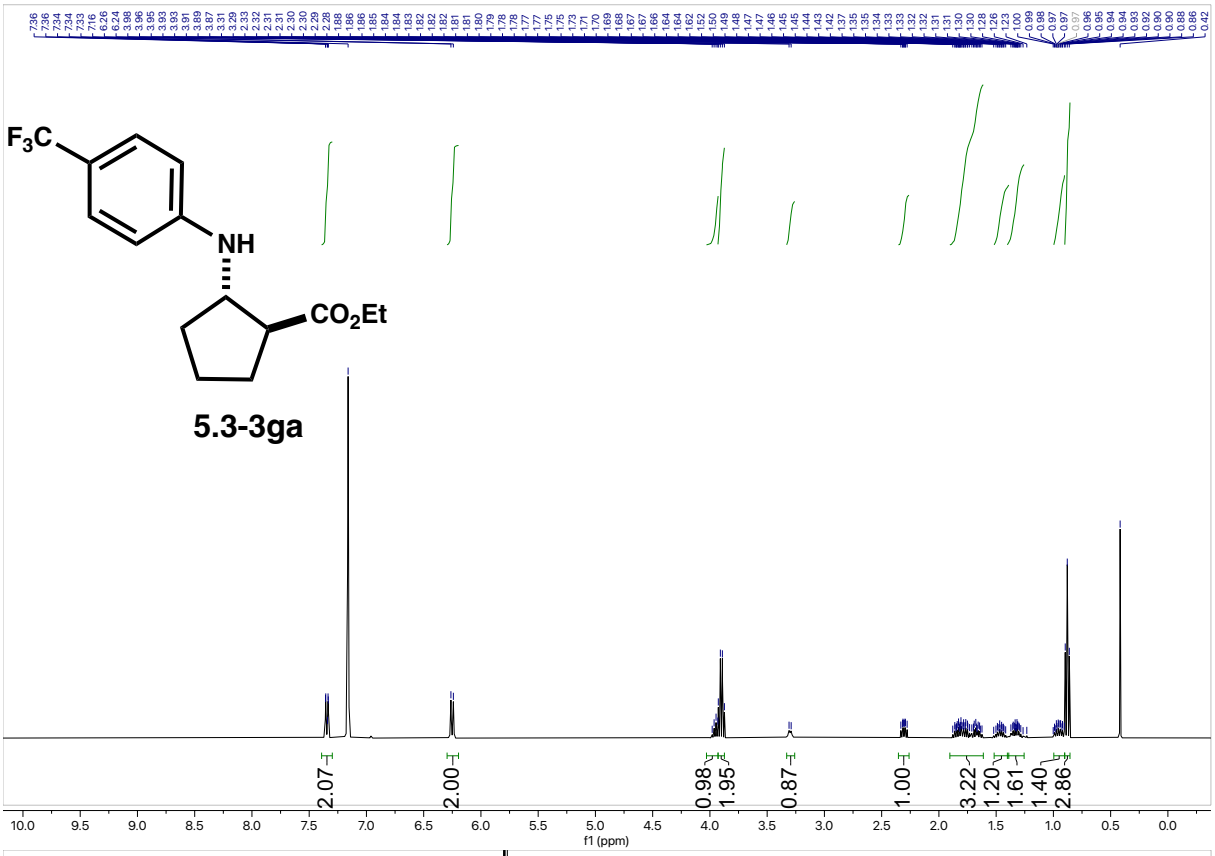

f1 (ppm)

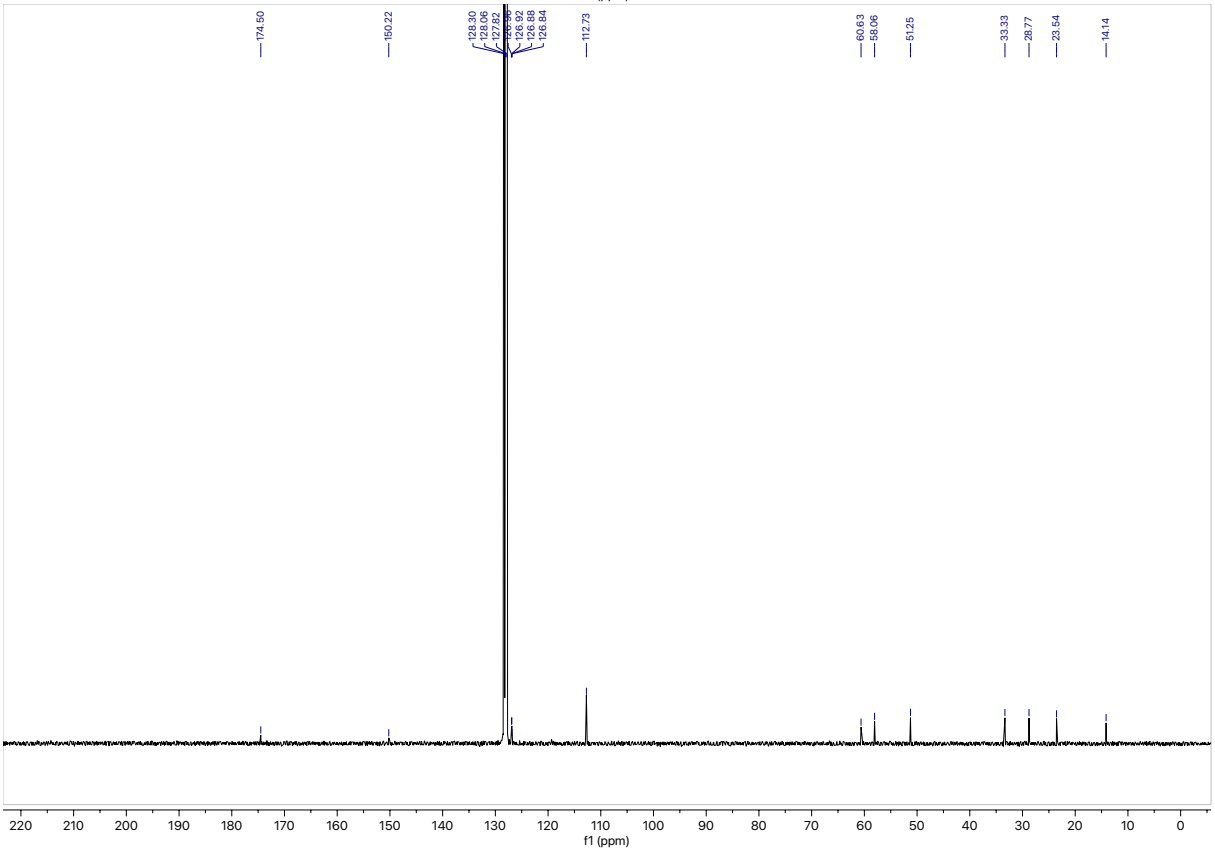

tBuO2C
NH
CO2Et
5.3-3fa
(major)
tBuO2C
NH
CO2Et
5.3-3fa
(minor)
3.25
1.28
2.00
1.07
0.62
1.28
1.98
1.63
0.95
0.64
1.00
1.33
0.97
3.04
15.02
1.44
1.09
1.13
0.75
1.99
2.92
f1 (ppm)

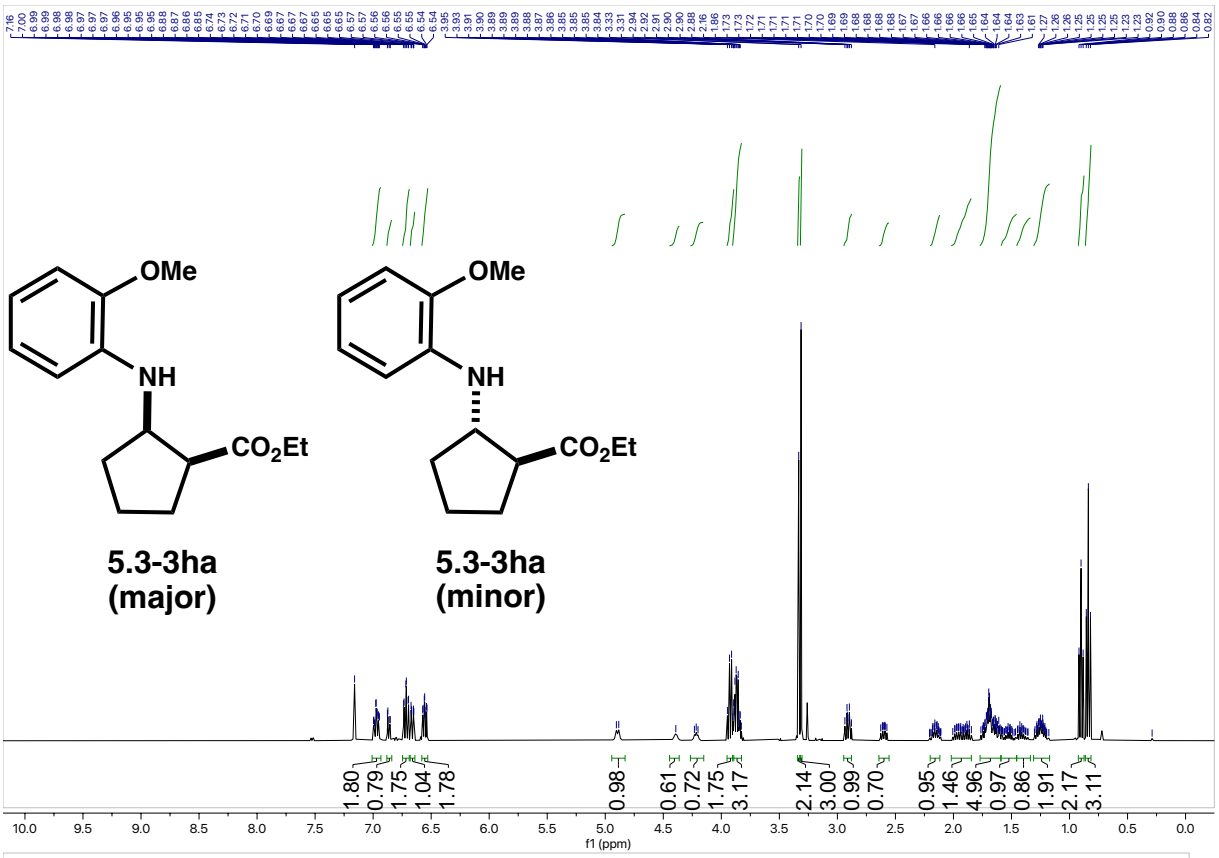

174.65
173.88
166.02
166.00
151.22
131.89
131.77
128.30
128.06
127.82
121.33
121.19
112.35
112.32
79.40
60.60
60.32
58.12
56.57
51.33
46.93
33.43
32.84
28.84
28.41
28.08
23.61
22.61
14.17
14.06
f1 (ppm)

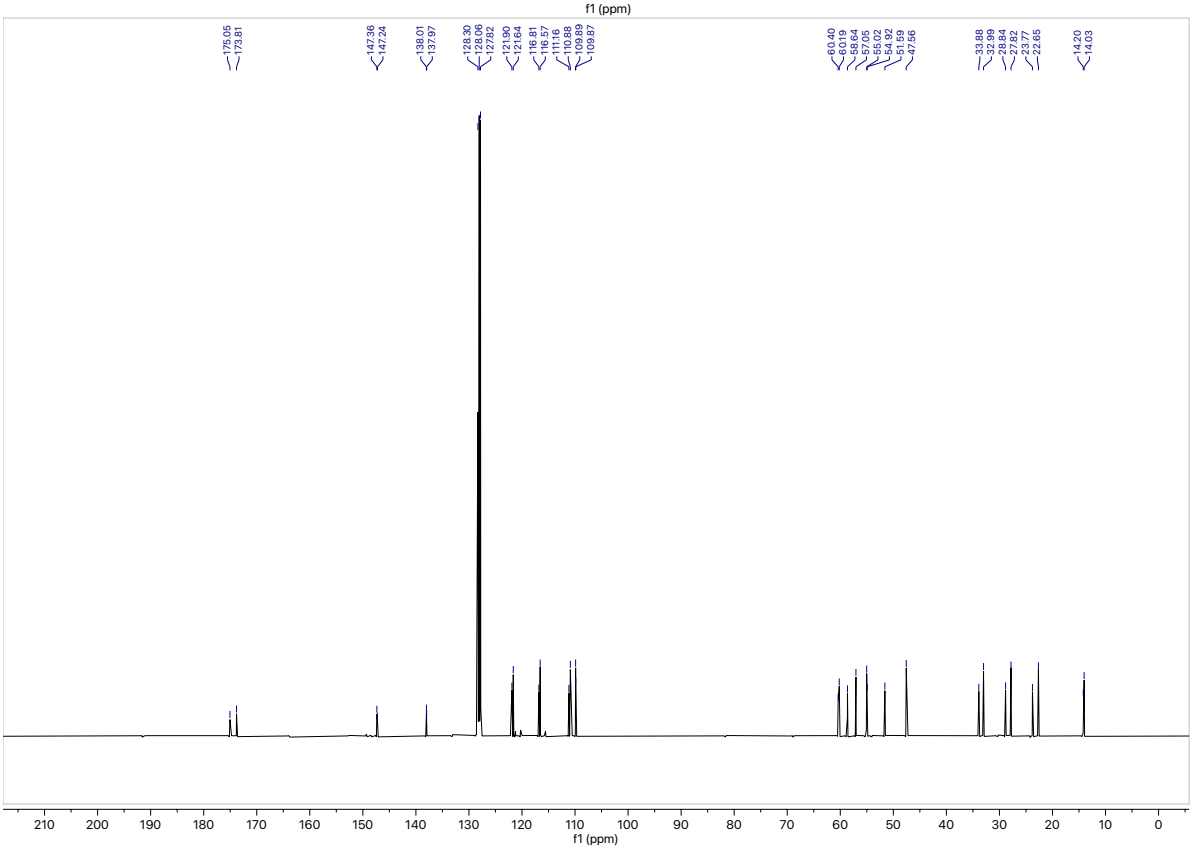

F3C
NH
CO2Et
5.3-3ga
2.04
2.02
0.98
2.00
1.07
1.05
1.04
4.19
1.09
3.00
f1 (ppm)

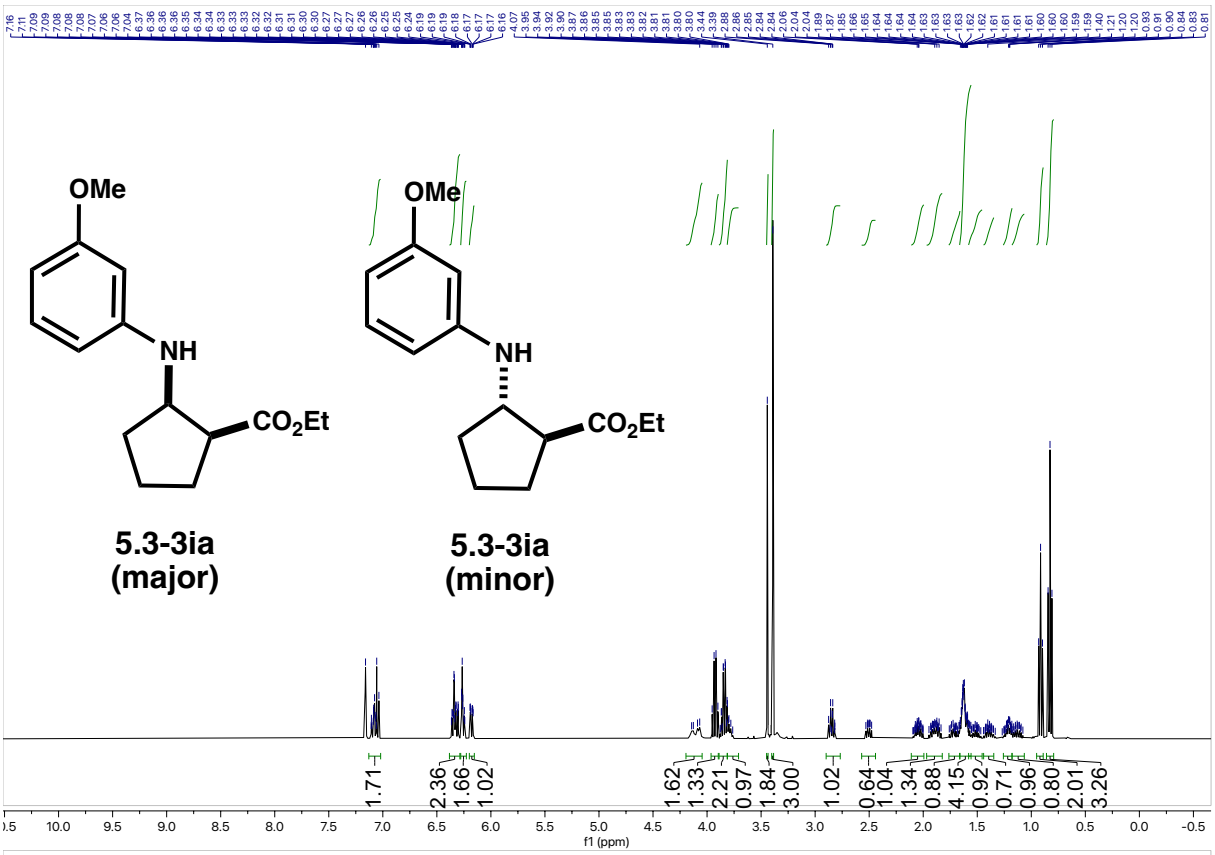

17.383
150.25
128.30
128.06
127.82
126.76
126.72
118.82
112.70
60.36
56.48
46.85
32.78
28.12
22.58
13.95
f1 (ppm)

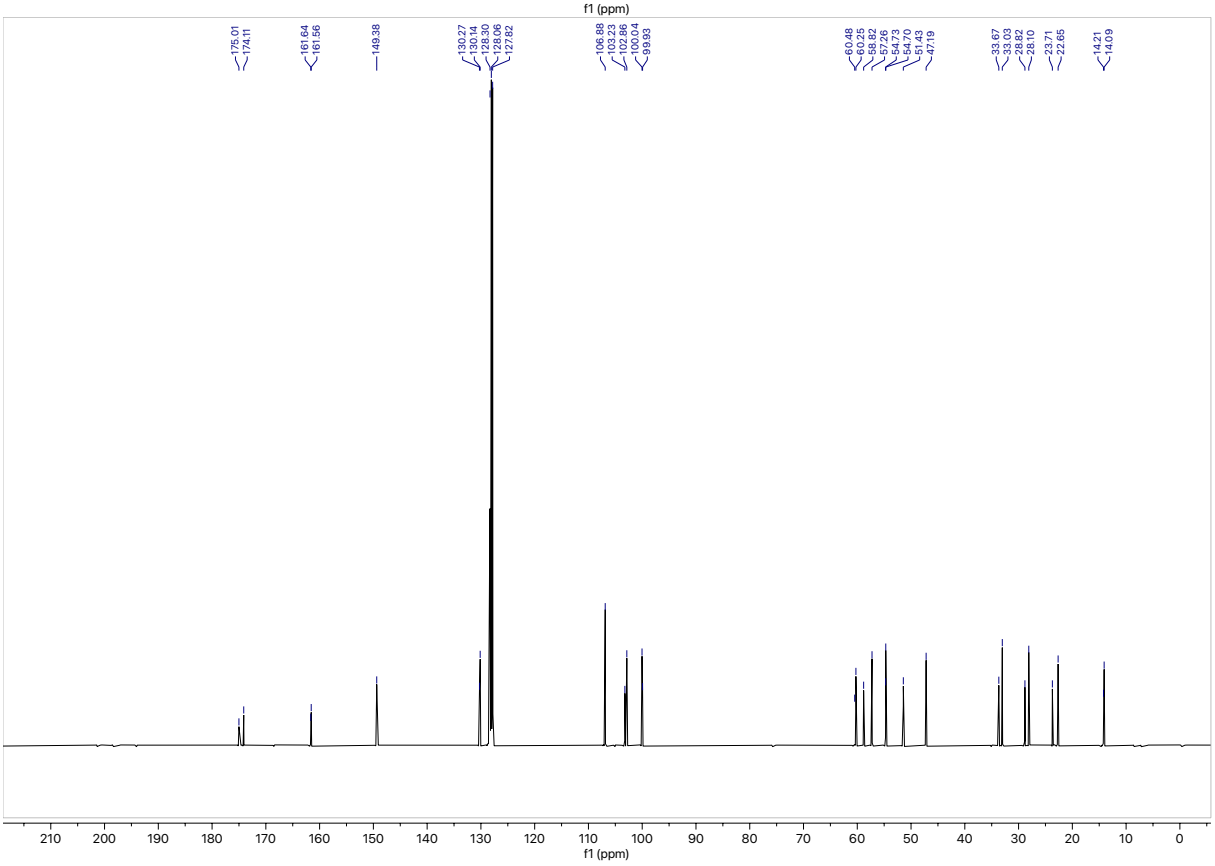

F3C
NH
CO2Et
5.3-3ga
2.07
2.00
0.98
1.95
0.87
1.00
3.22
1.20
1.61
1.40
2.86
f1 (ppm)

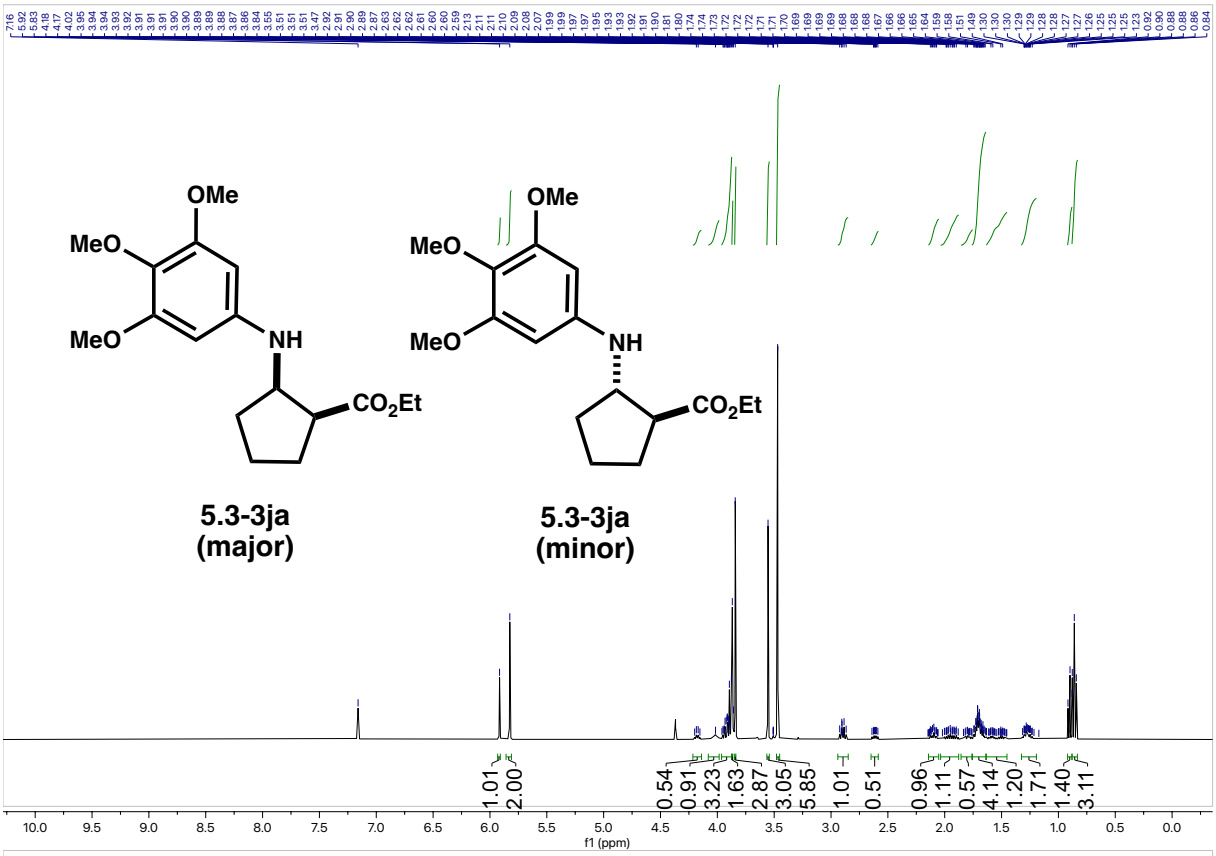

174.50
150.22
128.30
128.06
127.82
126.92
126.88
126.84
112.73
60.63
58.06
51.25
33.33
28.77
23.54
14.14
f1 (ppm)

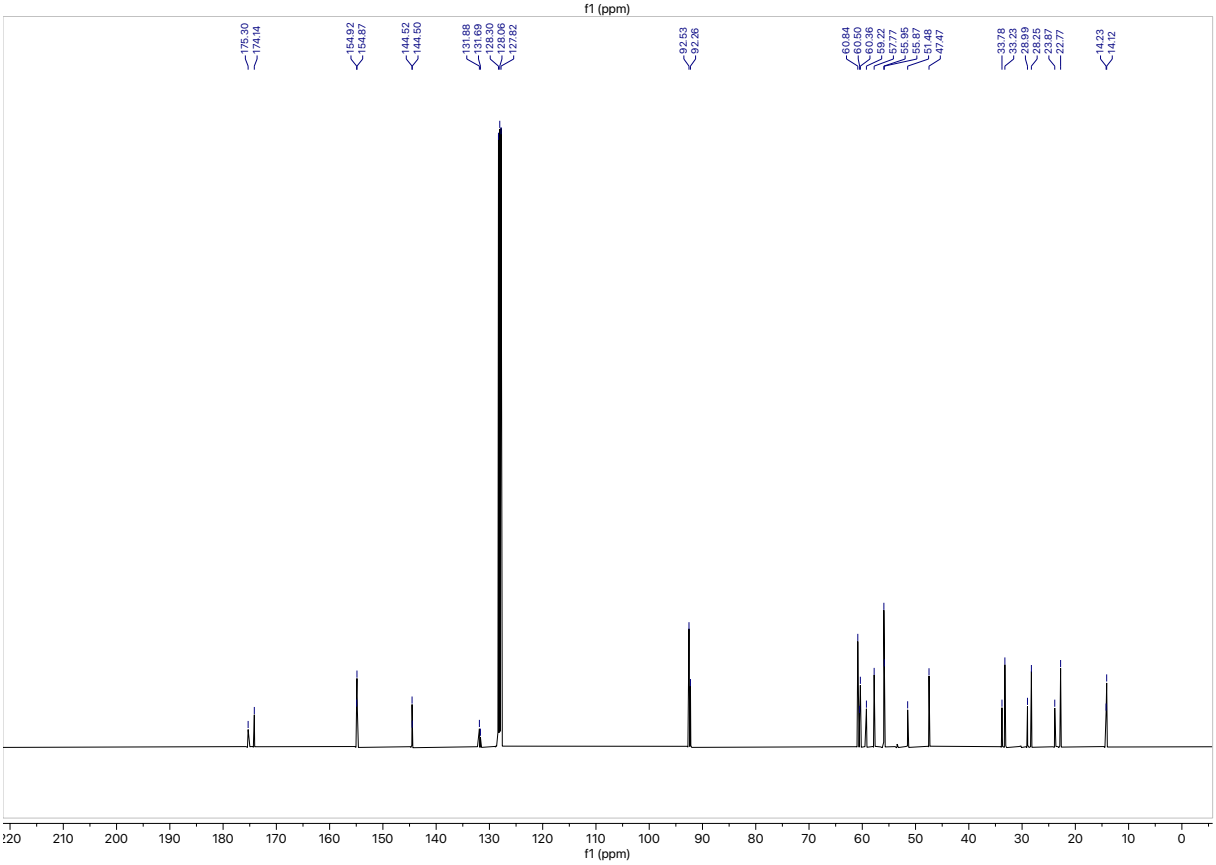

OMe
NH
CO2Et
5.3-3ha
(major)
OMe
NH
CO2Et
5.3-3ha
(minor)
1.80
0.79
1.75
1.04
1.78
0.98
0.61
0.72
1.75
3.17
2.14
3.00
0.99
0.70
0.95
1.46
4.96
0.97
0.86
1.91
2.17
3.11
f1 (ppm)

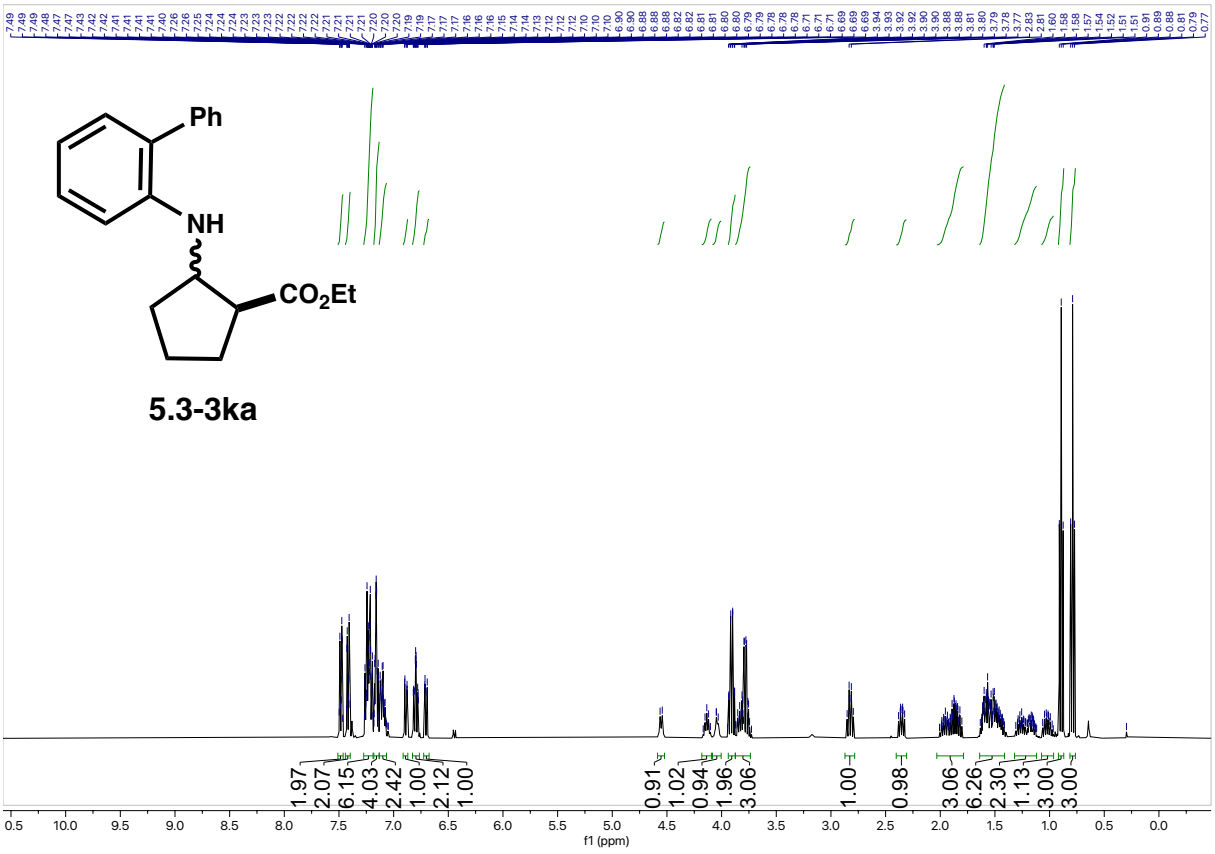

f1 (ppm)

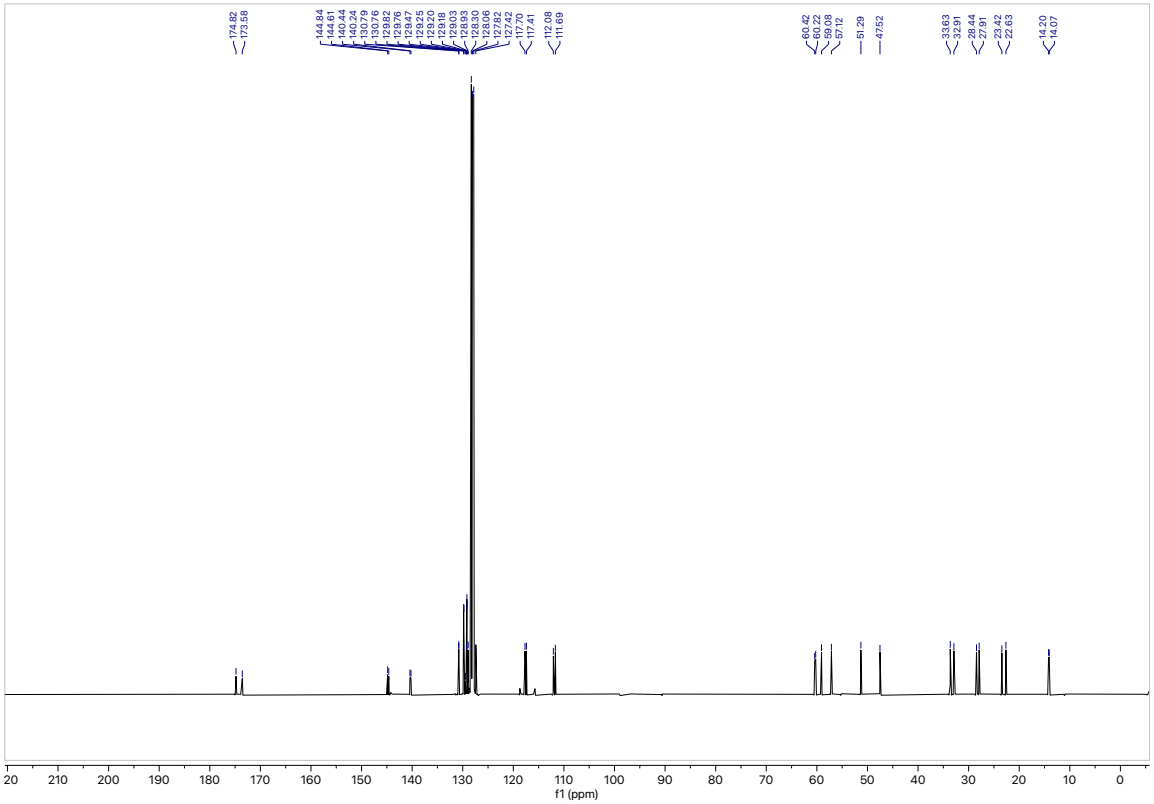

OMe
NH
CO2Et
5.3-3ia
(major)
OMe
NH
CO2Et
5.3-3ia
(minor)
1.71
2.36
1.66
1.02
1.62
1.33
2.21
0.97
1.84
3.00
1.02
0.64
1.04
1.34
0.88
4.15
0.92
0.71
0.96
0.80
2.01
3.26
f1 (ppm)

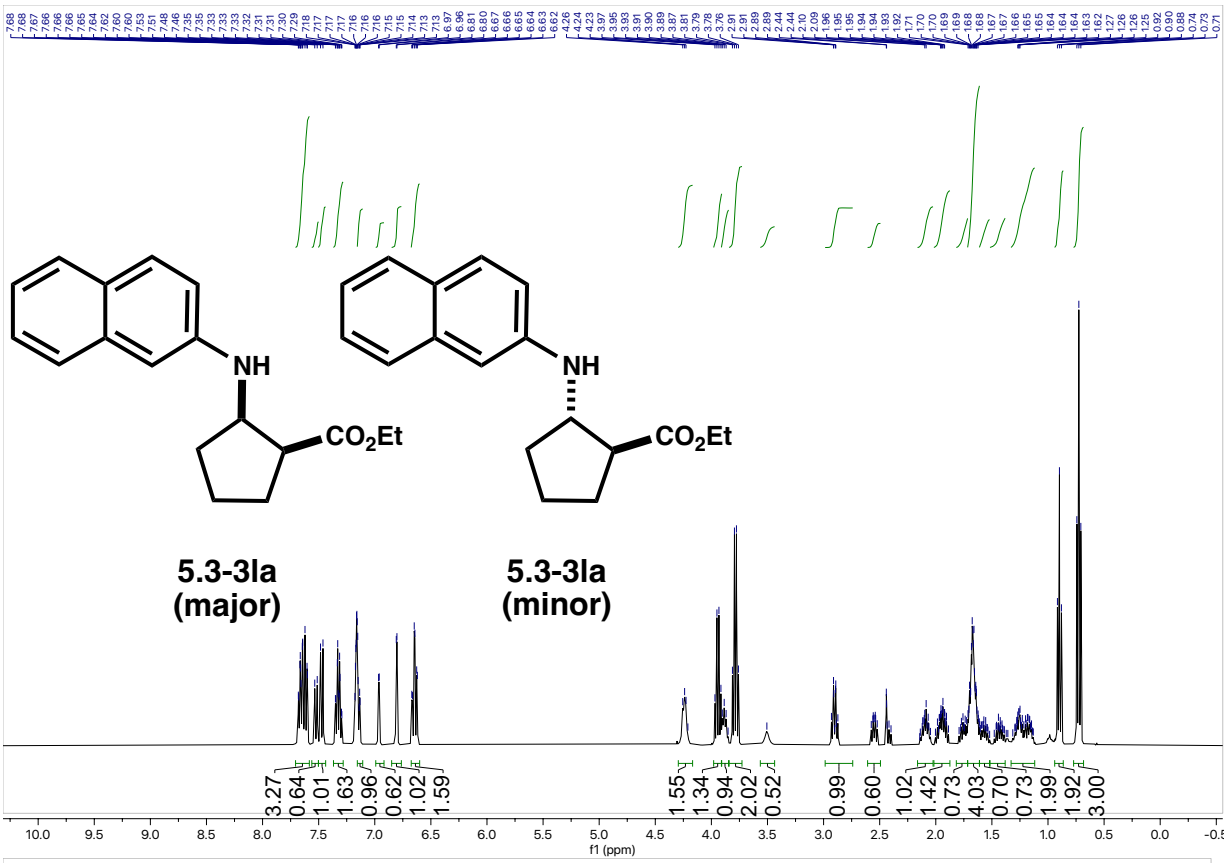

175.01
174.11
161.64
161.56
149.38
130.27
130.14
128.30
128.06
127.82
106.88
103.23
101.56
100.04
99.93
60.48
60.25
58.82
57.26
54.73
54.70
51.43
47.19
33.67
33.03
28.82
28.10
23.71
22.65
14.21
14.09
f1 (ppm)

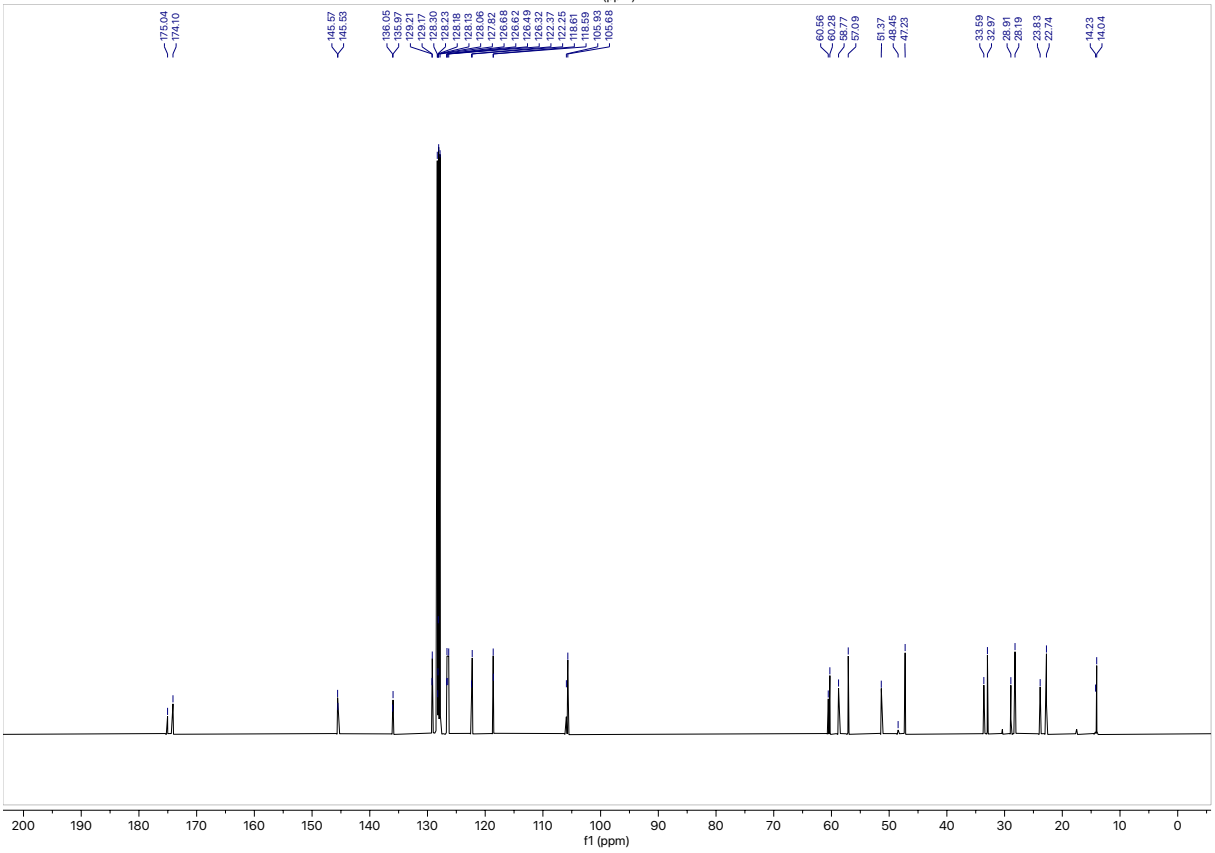

OMe
MeO
MeO
NH
CO2Et
5.3-3ja
(major)
OMe
MeO
MeO
NH
CO2Et
5.3-3ja
(minor)
f1 (ppm)

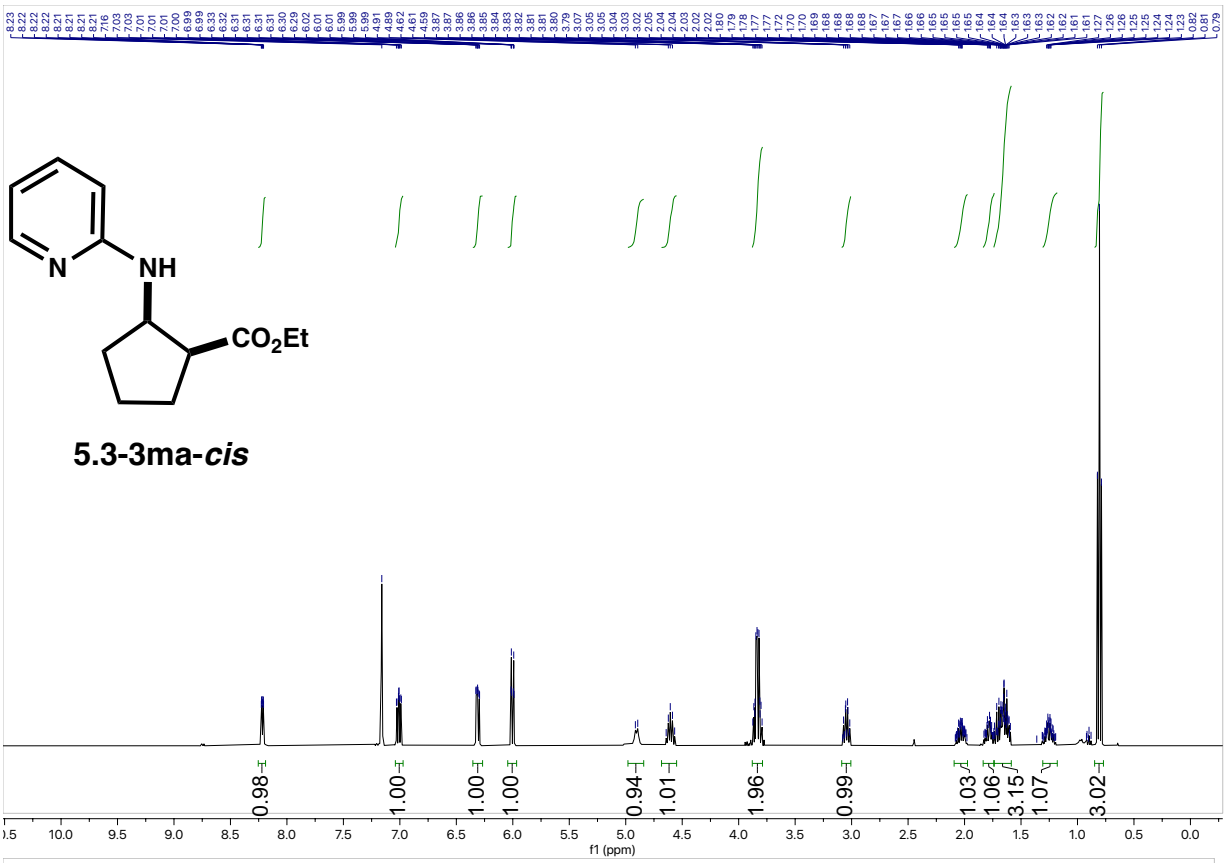

f1 (ppm)


Ph
NH
CO2Et
5.3-3ka
1.97
2.07
6.15
4.03
2.42
1.00
2.12
1.00
0.91
1.02
0.94
1.96
3.06
1.00
0.98
3.06
6.26
2.30
1.13
3.00
3.00
f1 (ppm)

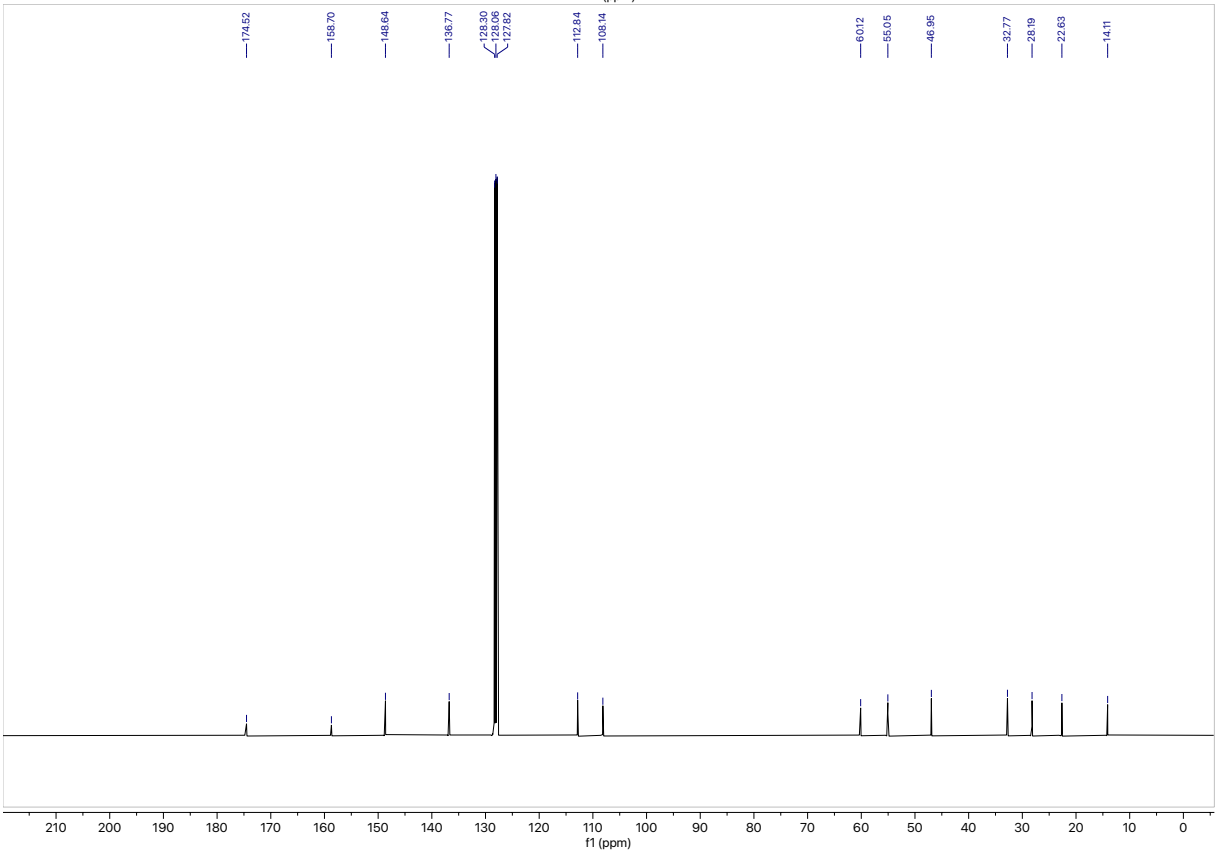

f1 (ppm)

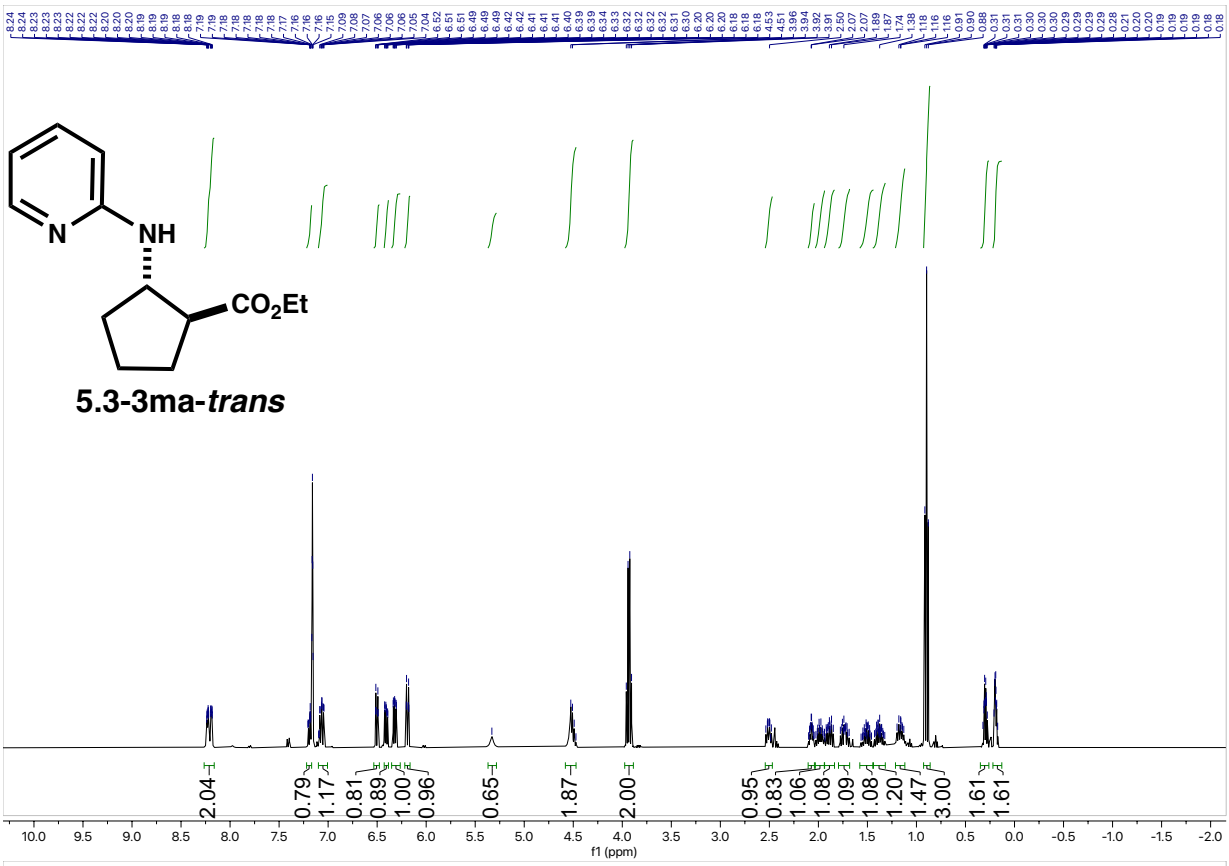

NH
CO2Et
NH
CO2Et
5.3-3la
(major)
5.3-3la
(minor)
3.27
0.64
1.01
1.63
0.96
0.62
1.02
1.59
1.55
1.34
0.94
2.02
0.52
0.99
0.60
1.02
1.42
0.73
4.03
0.70
0.73
1.99
1.92
3.00
f1 (ppm)

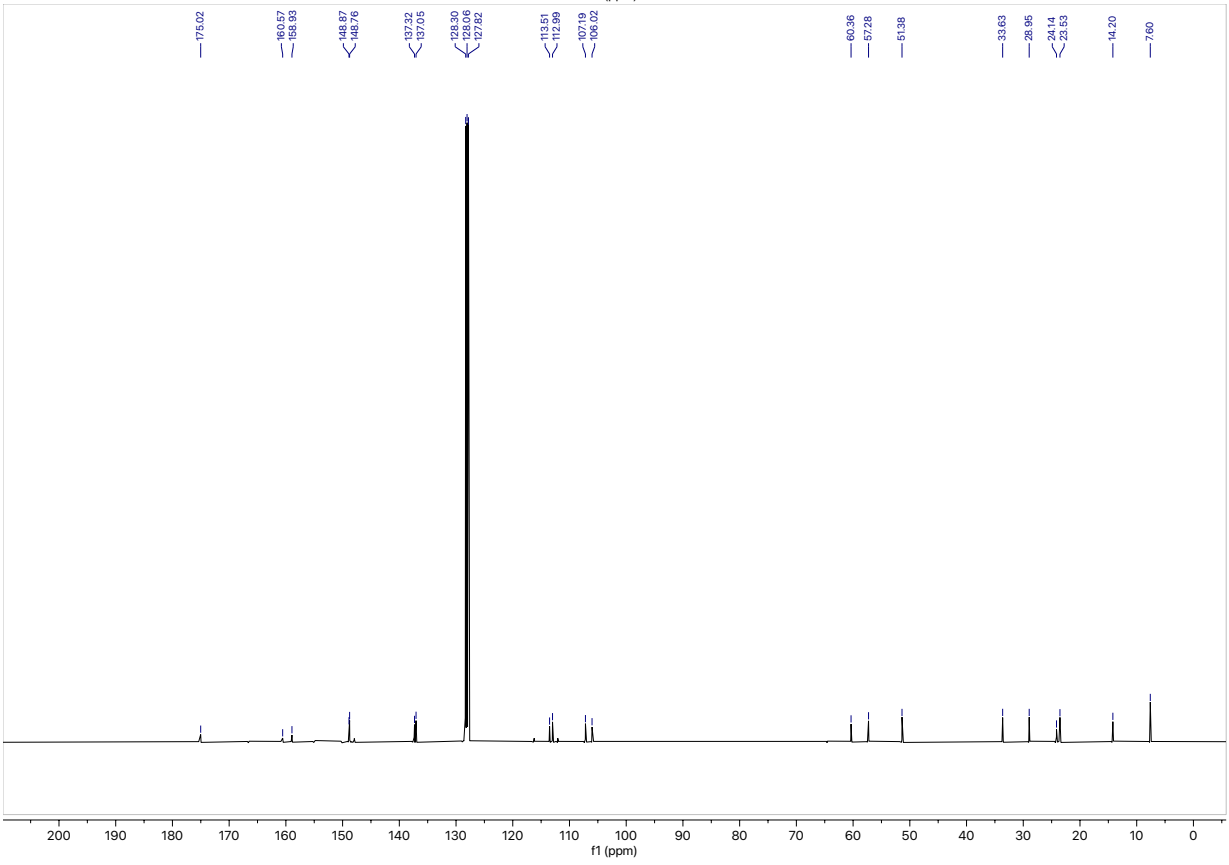

f1 (ppm)

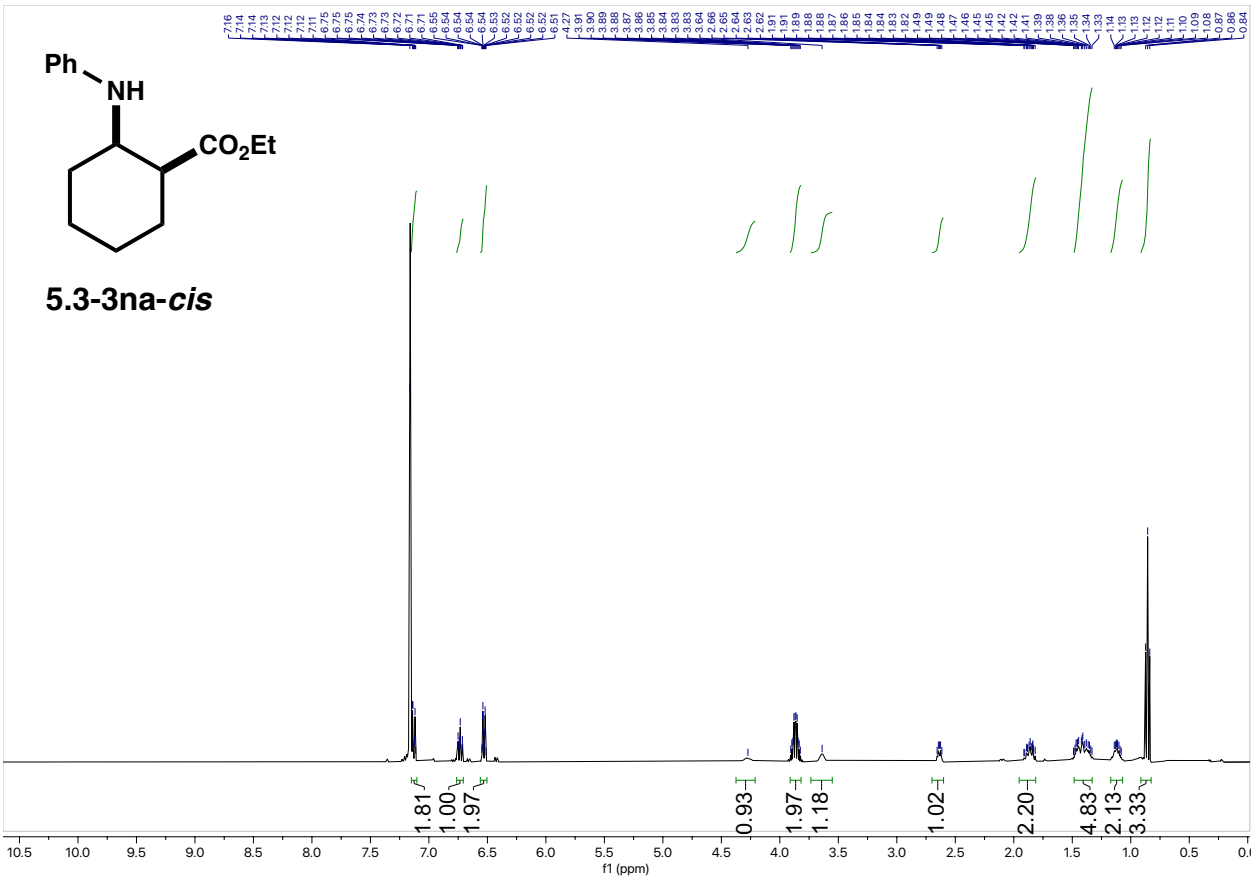

N
NH
CO2Et
0.98
1.00
1.00
1.00
0.94
1.01
1.96
0.99
1.03
1.06
3.15
1.07
3.02
f1 (ppm)

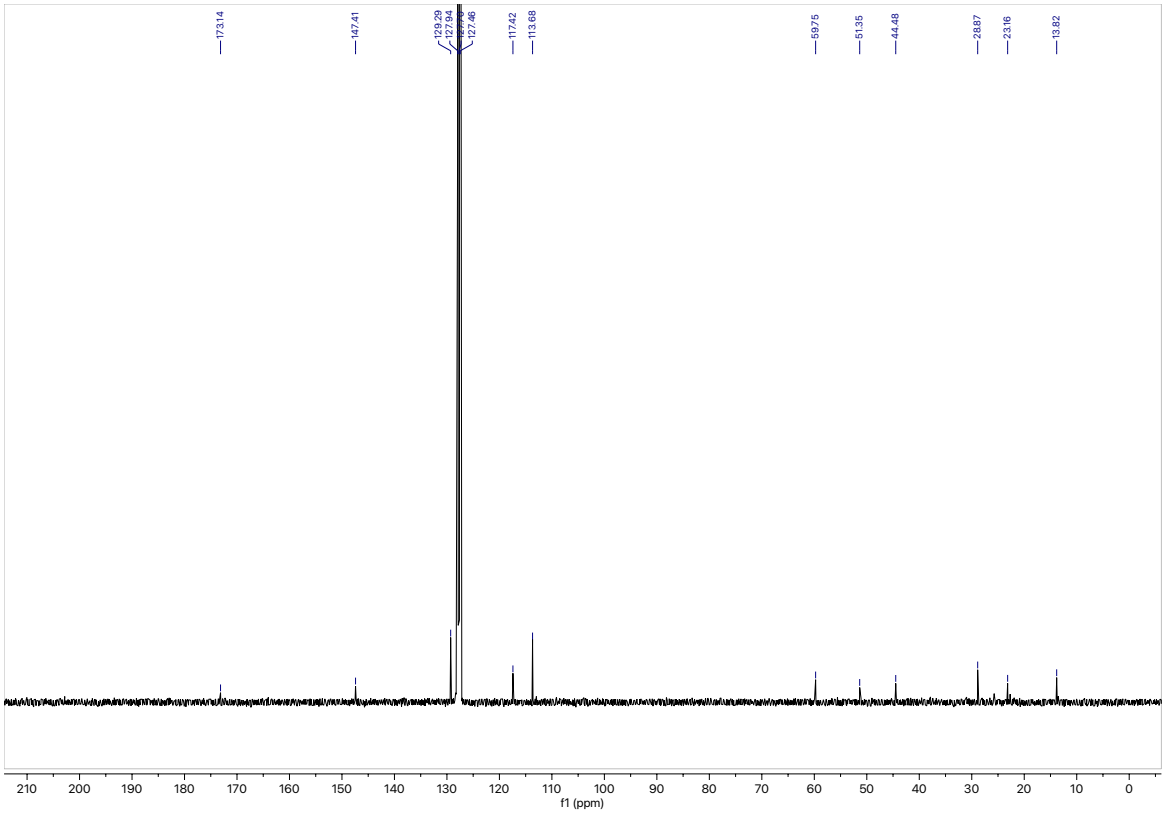
5.3-3ma-*cis*

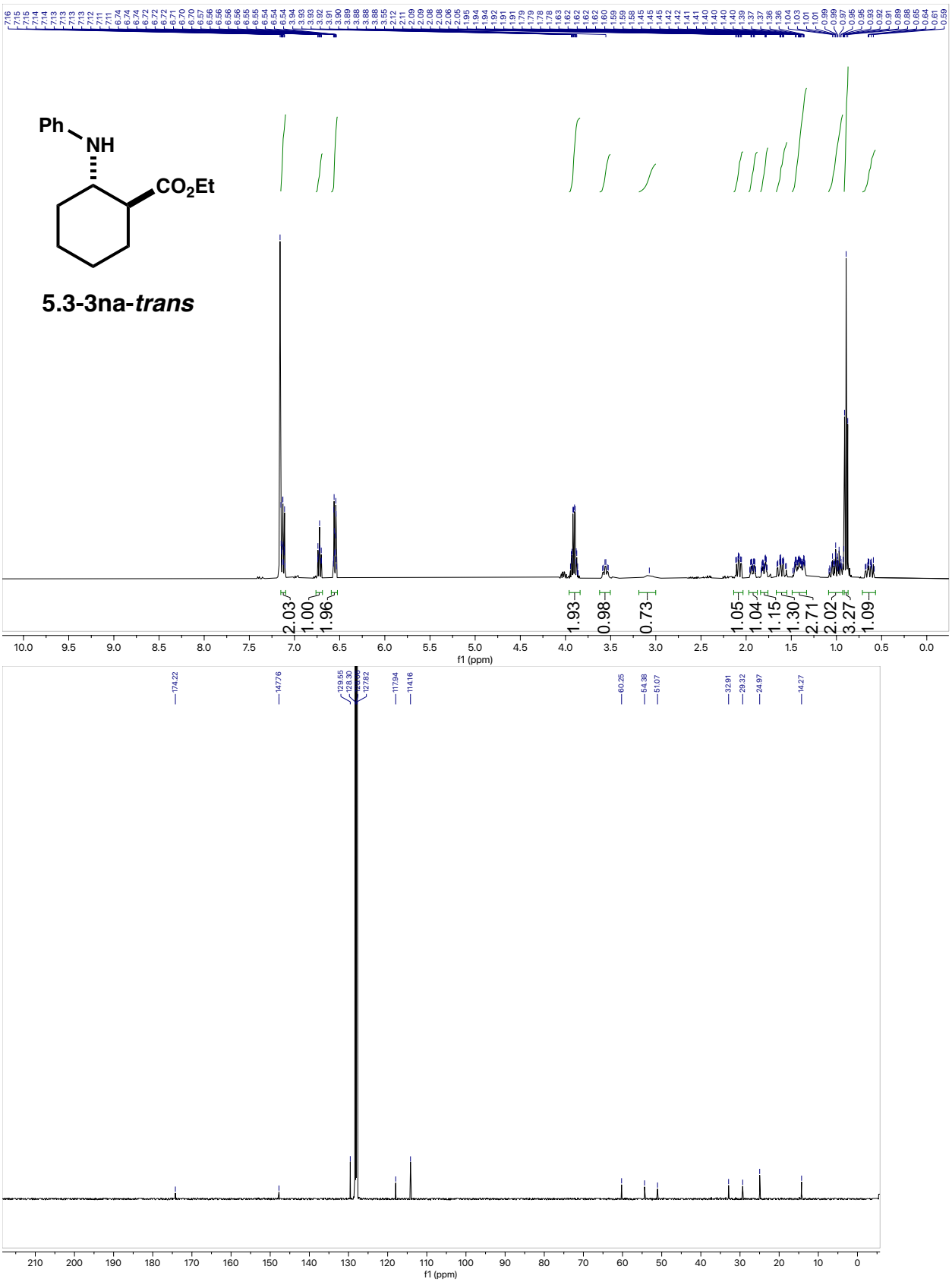

174.52
158.70
148.64
136.77
128.30
128.06
127.82
112.84
108.14
60.12
55.05
46.95
32.77
28.19
22.63
14.11
f1 (ppm)

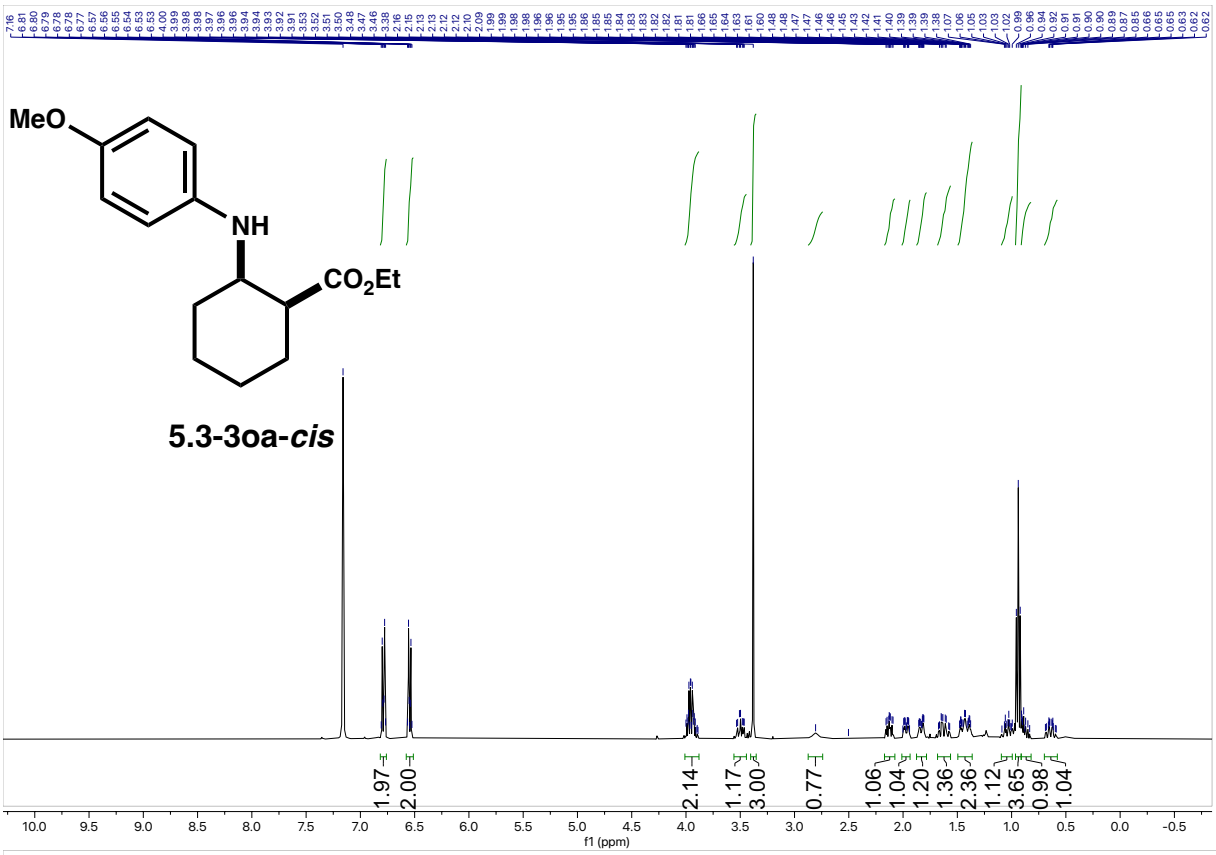

N
NH
CO2Et
5.3-3ma-*trans*
2.04
0.79
1.17
0.81
0.89
1.00
0.96
0.65
1.87
2.00
0.95
0.83
1.06
1.08
1.09
1.08
1.20
1.47
3.00
1.61
1.61
f1 (ppm)

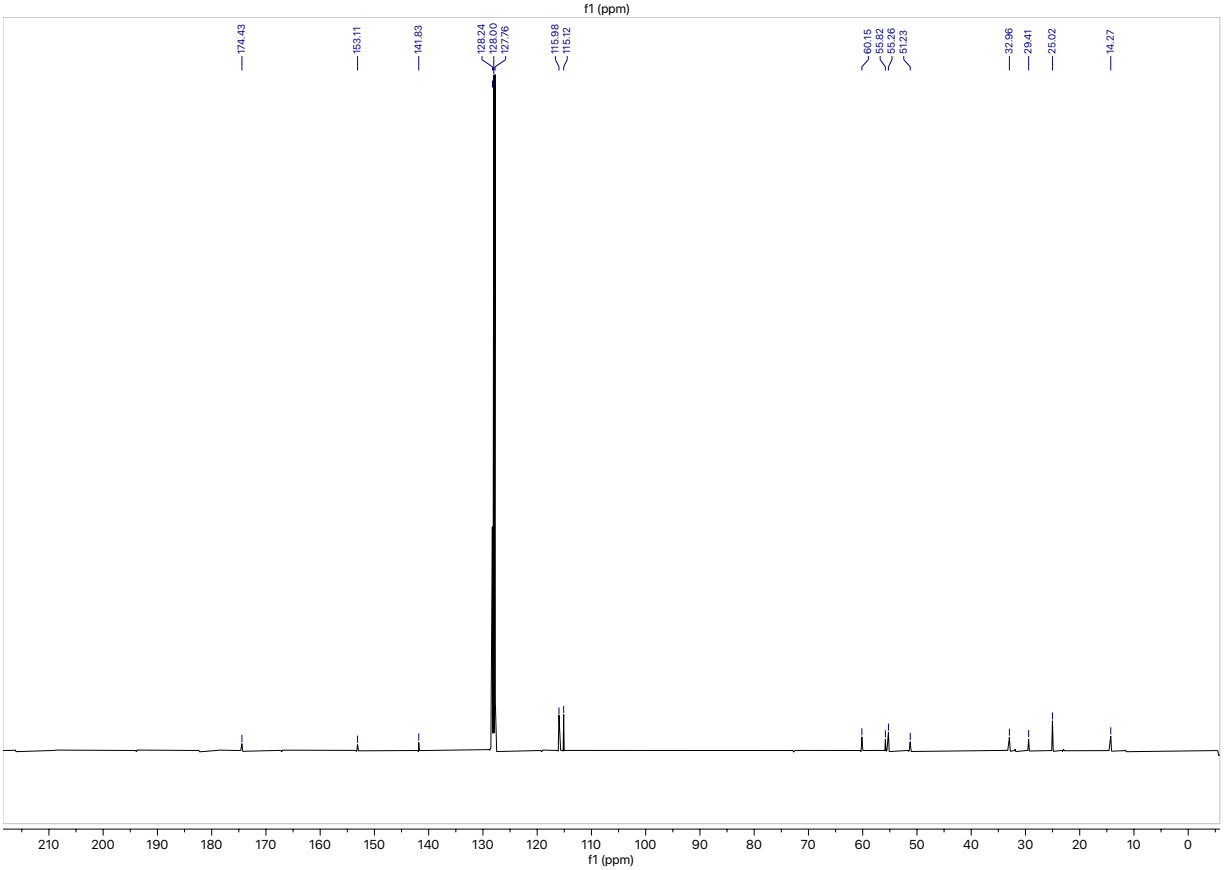

175.02
160.57
158.93
148.87
148.76
137.32
137.05
128.30
128.06
127.82
113.51
112.99
107.19
106.02
60.36
57.28
51.38
33.63
28.95
24.14
23.53
14.20
7.60
f1 (ppm)

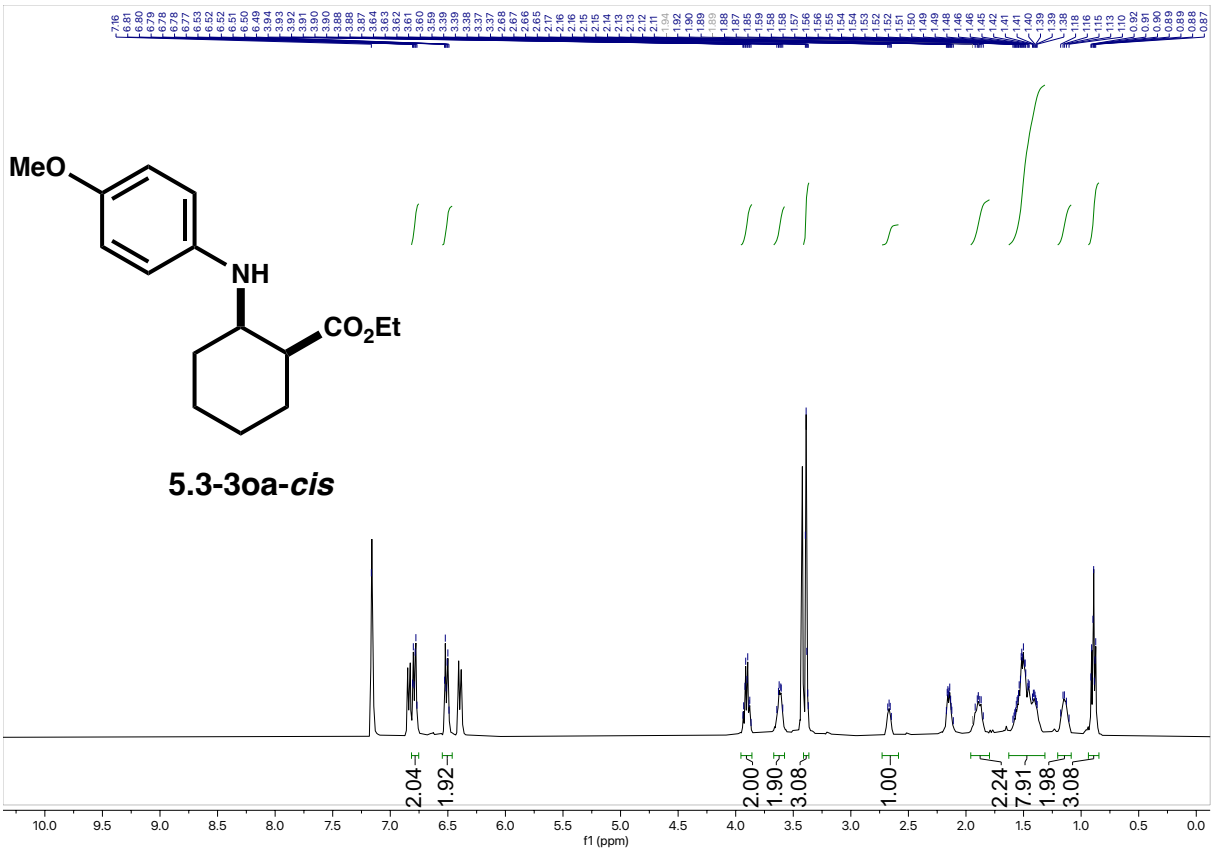

Ph
NH
CO2Et
5.3-3na-cis
1.81
1.00
1.97
0.93
1.97
1.18
1.02
2.20
4.83
2.13
3.33
f1 (ppm)

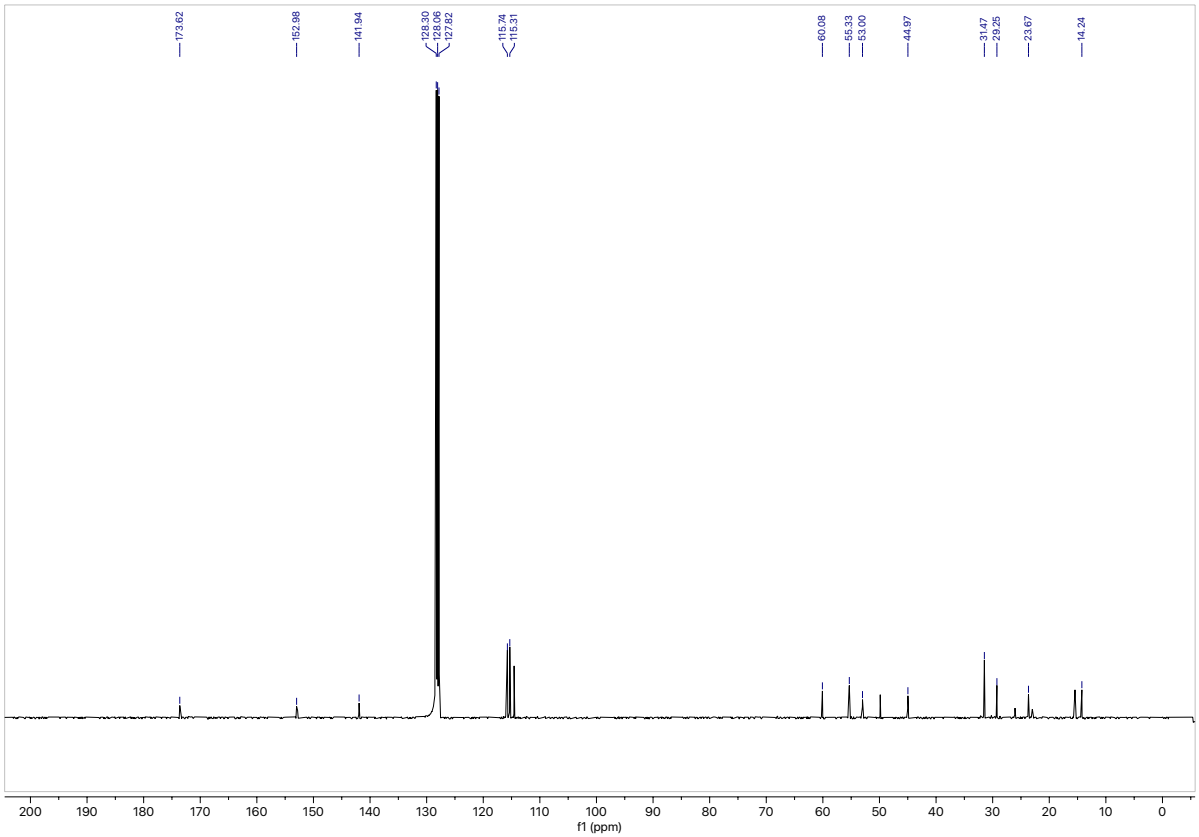

173.14
147.41
129.29
127.94
127.46
117.42
113.68
59.75
51.35
44.48
28.87
23.16
13.82
f1 (ppm)


Ph
NH
CO2Et
5.3-3na-trans
f1 (ppm)
f1 (ppm)


MeO
NH
CO2Et
5.3-3oa-cis
1.97
2.00
2.14
1.17
3.00
0.77
1.06
1.04
1.20
1.36
2.36
1.12
3.65
0.98
1.04
f1 (ppm)


174.43
153.11
141.83
128.24
128.00
127.76
115.98
115.12
60.15
55.82
55.26
51.23
32.96
29.41
25.02
14.27
f1 (ppm)


MeO
NH
CO2Et
5.3-3oa-cis
2.04
1.92
2.00
1.90
3.08
1.00
2.24
7.91
1.98
3.08
f1 (ppm)


173.62
152.98
141.94
128.30
128.06
127.92
115.74
115.31
60.08
55.33
53.00
44.97
31.47
29.25
23.67
14.24
f1 (ppm)