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Mechanistic Studies of Donor-Acceptor Cyclopropanes

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Graduate Program in Chemistry
A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science

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by

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Abstract and Keywords

Cyclopropane 1,1-diesters have been investigated as a source of donor-acceptor cyclopropanes, providing an understanding of the mechanism of reaction between these cyclopropanes and nitrosoarenes, as well as azo dicarboxylates. Cross-over experiments have been utilized to provide key pieces of experimental evidence that help generate a theoretical model of the reactions. By understanding these reactions with precision, the avenue to expand the reaction scope and develop other useful reactions is opened up. This allows the chemistry to be better utilized, providing easier access to important molecules when needed, and contributes to advancing the field of synthetic organic chemistry.

In addition, cyclobutane 1,1-diesters were also investigated as a source of donor-acceptor cyclobutanes. Specifically, their use in cycloaddition reactions has been developed to include the reaction of cyclobutanes with *cis*-diazenes, providing access to hexahydropyridazines. These compounds are synthesized in an efficient manner and are known to contain biologically active properties.

Keywords: donor-acceptor cyclopropane, donor-acceptor cyclobutane, cyclopropane, cyclobutane, tetrahydro-1,2-oxazine

For my parents, Ray and Dianne

Acknowledgements

I would like to acknowledge Dr. Brian L. Pagenkopf for accepting me into his research group, for which I am extremely grateful. I am also thankful to all the students who have worked, and are still working in the Pagenkopf group, especially Naresh Vemula for giving me valuable advice, interesting research ideas, and being a great friend. I would also like to thank Dr. Michael A. Kerr and the Kerr group for interesting research discussions during our shared super group meetings. Dr. Matthew Willians helped with NMR analysis, and Doug Hairsine helped with mass spectrometry and GC-MS data. I would finally like to thank Western University for financial support as a graduate student in the Chemistry Department.

During my time at Western University I had an enjoyable experience taking graduate level classes, which were extremely helpful in advancing my theoretical knowledge in the field of organic chemistry. I was grateful to have enthusiastic professors such as Dr. Hudson who taught me a deeper understanding of mechanisms, and Dr. Kerr who taught me heterocyclic chemistry and total synthesis.

I would like to thank my family for their unconditional love and support throughout my life and throughout my time at the University of Western Ontario. They have contributed so much to my life and I am happy to give back by dedicating this thesis to them.

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Abbreviations

A = Acceptor

Ac = Acetyl

Ar = Aryl

Boc = *tert*-butyloxycarbonyl

D = Donor

d = doublet

dd = doublet of doublets

DA = Donor-Acceptor

DCE = Dichloroethane

DCM = Dichloromethane

DMF = Dimethylformamide

DMSO = Dimethyl Sulfoxide

E = Electrophile

EDG = Electron Donating Group

EWG = Electron Withdrawing Group

GC-MS = Gas Chromatography-Mass Spectrometry

HPLC = High-Performance Liquid Chromatography

HRMS = High-Resolution Mass Spectra

m = multiplet

NMR = Nuclear Magnetic Resonance

Nu = Nucleophile

OTf = Trifluoromethanesulfonate

Ph = Phenyl

ppm = parts per million

^{i}Pr = iso-propyl

PTAD = 4-Phenyl-1,2,4-triazoline-3,5-dione

q = quartet

rt = Room Temperature

R_f = Retention Factor

s = singlet

t = triplet

td = triplet of doublets

TLC = Thin Layer Chromatography

Chapter 1 - General Introduction

The use of cyclopropanes and cyclobutanes in synthetic organic chemistry has received a considerable amount of attention over the years, with multiple applications being continually developed. This chapter serves as an introduction to the chemistry of donor-acceptor (DA) cyclopropanes and cyclobutanes, and their utilization in the synthesis of heterocyclic ring systems. The focus of the reactions is on the use of 1,1-cyclopropanediesters as a source of DA cyclopropanes. The work presented in this thesis was done entirely by me, and the information acquired will be published in peer-reviewed journals in the near future.

Chapter two investigated the reaction of DA cyclopropanes with nitrosoarenes with the use of a cross-over experiment to acquire key experimental data that were used to validate a potential reaction mechanism. The chemistry of DA cyclopropanes with nitrones is well known, but similar products were produced when the nitrone was switched with a nitroso functional group, so a complete mechanism would be valuable for not only understanding this reaction, but in the development of new reactions to come when utilizing DA cyclopropanes.

Chapter three investigated the reaction of DA cyclopropanes with both *cis* and *trans* azo dicarboxylates. The chemistry behind the unusual ring opening reaction of DA cyclopropanes with specifically *cis*-diazenes was a key component of this chapter. The use of cross-over experiments was used to gain a deeper understanding into these reactions and resulted in a new pattern of reactivity which showed similarities to the chemistry presented in chapter two as well.

Chapter four investigated the use of DA cyclobutanes in a new cycloaddition reaction with *cis* azo dicarboxylates. It was shown that DA cyclobutanes are able to react with *cis*-diazenes and form hexahydropyridazines ring systems which are a rare type of heterocycle, which have only a limited number of synthetic procedures available.

The chemistry learned throughout these chapters has shown new procedures to construct heterocyclic compounds from DA cyclopropanes and cyclobutanes, and answer mechanistically related questions into how these compounds form. These experimental observations have shown repeating patterns of reactivity that potentially could be adjusted to include the incorporation of new elements, and hopefully help in the discovery or design of new reactions.

1.1 Introduction

Cyclopropanes and cyclobutanes have been shown to play an important and useful role in synthetic organic chemistry with an array of various reaction partners.[1] Comparison of the properties of carbocycles show cyclopropane and cyclobutane to have a higher ring strain energy due to the distortion of the bond angles away from the ideal 109° angle of the tetrahedron. Figure 1.1 describes the higher ring strain energy of cyclic compounds when the carbon-carbon bond angles in cyclopropane (**1**) and cyclobutane (**2**) are not able to adopt an ideal conformation such as the lower energy chair form of cyclohexane (**4**).[2] When smaller carbocycles are prepared, their inherent ring strain functions as a built-in energy source which can be used as a driving force to produce compounds with various uses in chemical synthesis. The unique properties of cyclopropanes allow for a very useful activation of sp^3 C-C bonds within the cycle, which has contributed to an array of different reaction types. These properties are also useful in biological settings with many cyclopropane ring-opening reactions occurring in nature.

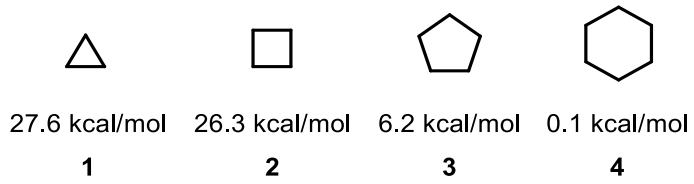
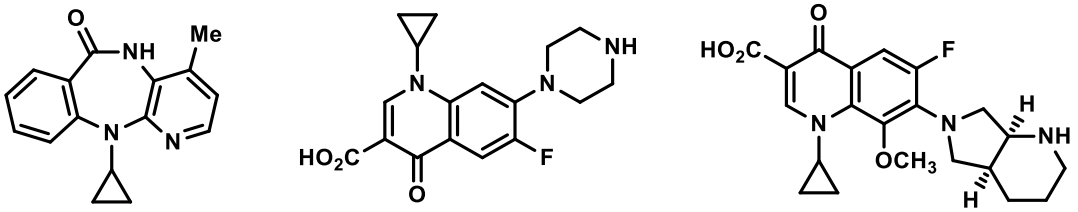


Figure 1.1 Strain energies of small carbocycles

Cyclopropanes are found in natural products and biological settings, including lipids, pheromones, terpenes, and steroids.[3] Examples include the anti-HIV drug Nevirapine (**5**), and the potent antibiotics Ciprofloxacin (**6**) and Vigamox (**7**) as seen in Figure 1.2. Vigamox was ranked in the top 200 brand-name drugs by U.S. retail dollars in 2010 with a profit that year of $0.25 billion.[4]



Nevirapine **5** | Ciprofloxacin **6** | Vigamox **7**

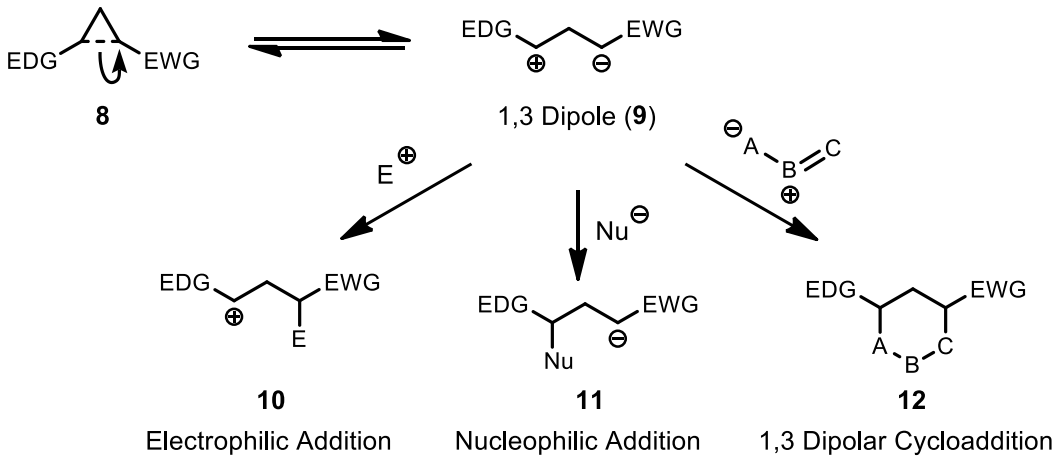
Figure 1.2 Examples of biologically active compounds containing a cyclopropane ring

Cyclopropanes have had many uses in synthetic chemistry, such as in total synthesis, and in the preparation of many useful compounds. In order to make use of the cyclopropane ring and control which bonds will break to undergo reaction, activating groups are strategically used. The cyclopropane ring is reactive due to its high ring strain, but activating groups are commonly present on the ring to selectively increase, and control reactivity. The effects of activating groups can also be enhanced or activated using thermal or catalytic conditions.

1.1.1 Donor-Acceptor (DA) Cyclopropanes

Increased reactivity can be achieved when donor and acceptor groups are arranged in a *vicinal* relationship on the carbocycle to activate the bond between the two groups and allow for different reaction types.[5] Common examples of electron donating groups (EDG) include: alkoxy, amino, aryl, vinyl, and other groups that can stabilize carbocations. Examples of electron withdrawing groups (EWG) commonly include: esters, carbonyls, and other groups that can stabilize carbanions.[6]

Activation of donor-acceptor (DA) cyclopropanes (**8**) and cyclobutanes with Lewis acids allow formation of 1,3-dipole (**9**) and 1,4-dipole intermediates, respectively. Scheme 1.1 shows how DA cyclopropanes are able to react with various electrophiles, nucleophiles, or dipolarophiles.



Scheme 1.1 General reactions of DA cyclopropanes

DA cyclopropanes have been extensively studied over the last 50 years and serve as a synthetically useful 1,3 carbon dipolarophile. This allows for multiple applications such as serving as starting materials for the synthesis of highly substituted 5- and 6-membered carbocycles and heterocycles via annulation (cycloaddition) reactions.

1.1.2 Cycloadditions of DA Cyclopropanes

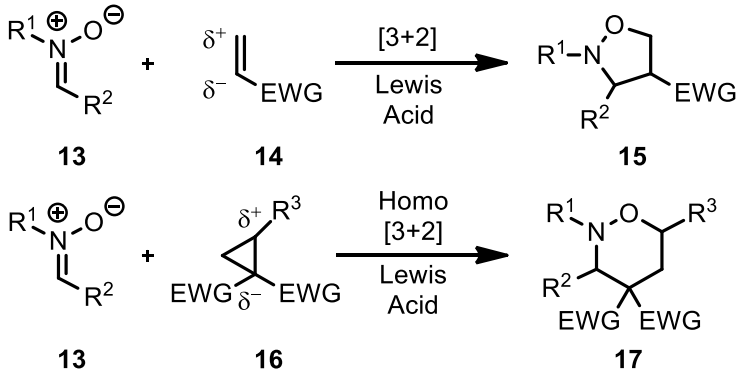
Cycloaddition chemistry has the ability to produce a wide range of molecular architecture often with high levels of control and efficiency.[7] Cycloadditions have also proven to be an effective method for the construction of heterocyclic compounds. The ability to efficiently access different heterocyclic motifs has great importance because of the interesting biological activities that are often associated with the systems when found in living organisms. Active heterocycles have shown considerable biological actions, such as antifungal, anti-inflammatory, antibacterial, anticonvulsant, antiallergic, herbicidal, anticancer activity.[8] A main focus of this thesis is on cycloadditions of DA cyclopropanes with different dipolarophiles, and understanding their mechanism of action in the creation of heterocyclic compounds.

Cycloadditions belong to a broader class of reactions known as pericyclic reactions. Pericyclic reactions are often characterized by a simultaneous event of bond breaking and bond creating in the reaction process. This attribute often provides a way of controlling the

stereochemistry for a specific reaction. In some cases, the stereochemistry of the starting material can control the stereochemical outcome of the product. This type of prediction is made more accurately when a complete understanding of the reaction mechanism and transition states are known.

Typical cycloadditions often occur through tightly held or compact transition states which is governed my maximum orbital overlap between reaction partners.[9] These so-called "closed" transition states are powerful tools in the asymmetric synthesis field for analyzing enantio-selective and diastereo-selective reactions. Acquiring accurate models of transition states is therefore of upmost importance in the understanding of stereo-selective reactions. In addition to understanding transition states, it may also be of equal importance to understand the overall mechanism of a reaction.

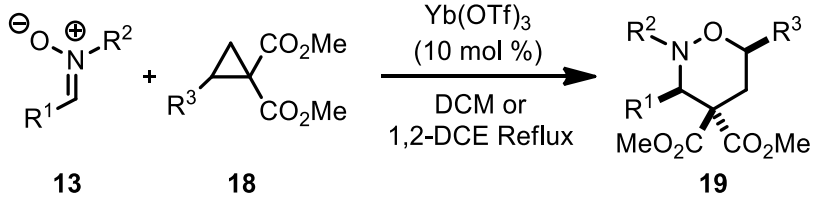
DA cyclopropanes, such as 1,1-cyclopropane diesters react in a similar way to alkenes substituted with an electron withdrawing group (EWG), such as α,β-unsaturated carbonyl systems.[10] The difference is the additional carbon in the cyclopropane ring, which makes the reaction a one carbon homologation as seen in the [3+2], and homo [3+2] cycloaddition (Scheme 1.2).



Scheme 1.2 Cycloaddition of nitrones with α,β-unsaturated systems and cyclopropanes

1.1.3 Cycloadditions of DA Cyclopropanes with Nitrones

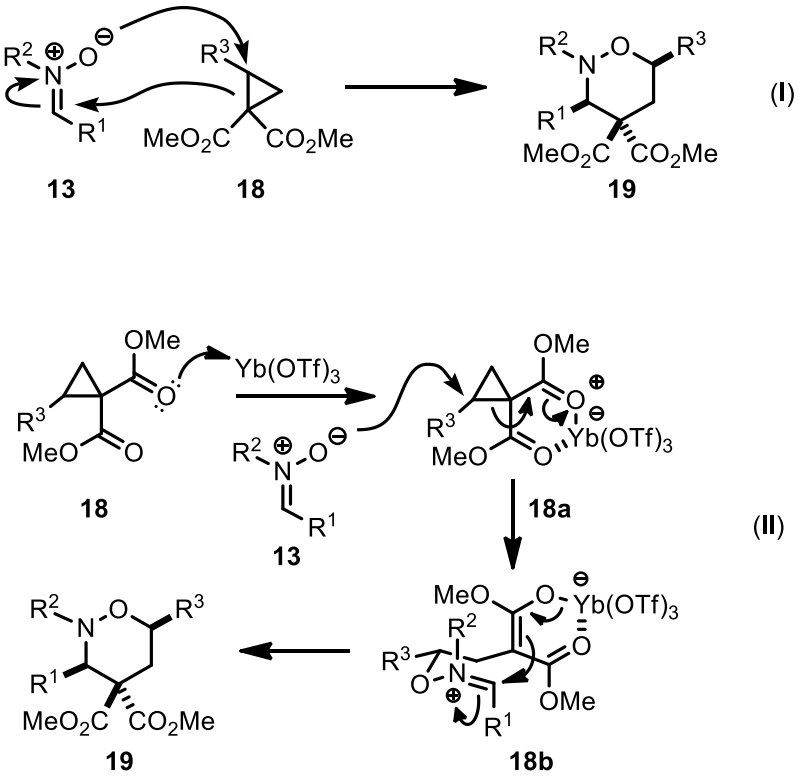
Nitrones (**13**) have been shown to react with 1,1-cyclopropane diesters (**18**) in the presence of $Yb(OTf)_3$ to yield tetrahydro-1,2-oxazines (**19**) with a high degree of regio- and stereo-control, as seen in scheme 1.3.[11]



13 **18** **19**

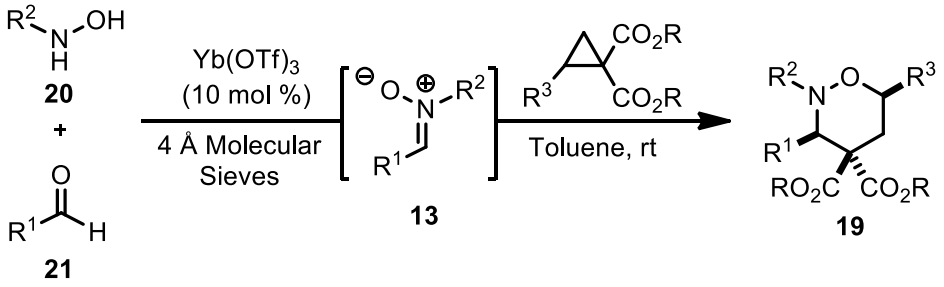
Scheme 1.3 Homo [3+2] cycloaddition of nitrones with DA cyclopropanes

Single-crystal X-Ray analysis has shown that the observed product always forms a single diastereomer in which the substituents at the C3 and C6 position are always in a *cis* relationship. This type of transformation is an example of a dipolar homo [3+2] cycloaddition, but is also considered a 1,3-dipolar cycloaddition, and was first reported by the Kerr group in 2003. Mechanistic studies have been carried out with quantum chemical DFT calculations and indicate that two very similar, but distinct, reaction pathways may account for the transformation, and can be seen in Scheme 1.4.[12] One pathway is an asynchronous concerted mechanism that involves an approximate half-chair-like transition state where the oxygen of the nitrone leads the attack on the cyclopropane ring (**I**). The second pathway is a stepwise mechanism which involves a zwitterionic imminium intermediate, with the oxygen of the nitrone again leading the attack on the cyclopropane ring (**II**). Understanding this transformation in detail has helped discover another transformation, where DA cyclopropanes are capable of reacting with nitrosoarenes.



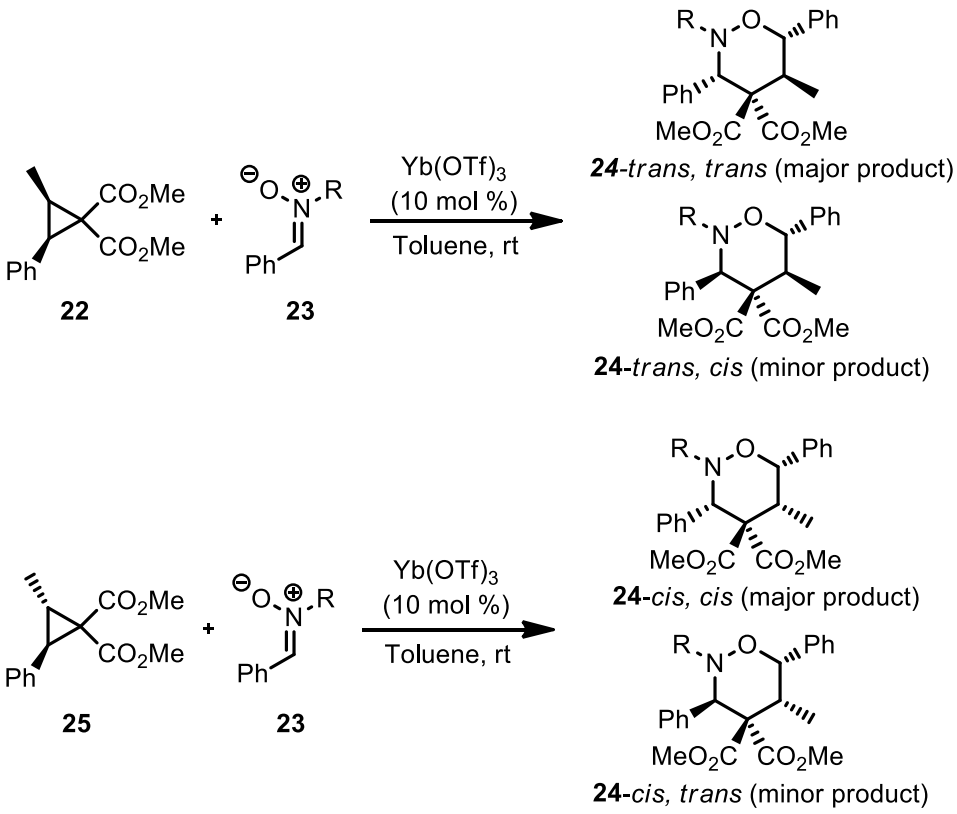
Scheme 1.4 Mechanism of cycloaddition of DA cyclopropanes with nitrones

In 2004 the Kerr group showed that this reaction could be carried out using a three-component coupling strategy between an aldehyde (**21**) and a hydroxylamine (**20**) as seen in Scheme 1.5. In this strategy, the nitrone (**13**) is formed *in situ*, which is useful when dealing with nitrones that are difficult to prepare or are unstable due to oligomerization under the required Lewis acidic conditions.[13]



Scheme 1.5 Three-component homo [3+2] cycloaddition

In order to address the issue as to whether this reaction mechanism is going through a concerted or step-wise pathway, extensive studies were performed using enantio-pure starting materials. Therefore the reaction of enantiomerically enriched 3-methyl-2-phenylcyclopropane-1,1-dicarboxylates with nitrones was performed by Dr. Michael Kerr in 2007[14], as shown in scheme 1.6.



Scheme 1.6 Mechanism studies on cycloadditions of DA cyclopropanes with nitrones

A key piece of information discovered in this study is the inversion of stereochemistry at C2 for both *cis* and *trans* diastereomers of the starting material. The results provided experimental evidence that supports the idea of a step-wise pathway and not a concerted pathway. In the step-wise pathway, there is an inversion of stereochemistry when the oxygen from the nitrone acts as a nucleophile and opens the cyclopropane ring.

Experimental evidence that also helps support the mechanism proposed by Dr. Michael Kerr was provided when optically active cyclopropanes were reacted with nitrones in the presence

of a catalytic amount of $Ni(ClO_4)_2$ without a chiral ligand to give the tetrahydro-1,2-oxazine in a high yield with the same level of enantiomeric purity as that of the starting material.[15]

This work by Tang *et al* shows how understanding the proposed mechanism of a reaction can lead to other discoveries, in this case, applications for kinetic resolution was developed. This was made possible because of the diligent mechanistic studies performed by Dr. Michael Kerr to understand the reaction with a high level of understanding.

1.1.4 Tetrahydro-1,2-Oxazines

The tetrahydro-1,2-oxazine motif is rarely found in nature, appearing in only a small number of natural products. Examples of these natural products include FR900482 (**27**) and FR66979 (**28**) as seen in Figure 1.3, which exhibit antitumor and antibiotic properties.[16] Both of these natural products are structurally similar to the mitomycins, including mitomycin C, which has been in widespread clinical use for more than 20 years. The biological activities of FR900482 and FR66979 are also similar to the mitomycins, which are both reductively activated *in vivo* and covalently cross-link DNA in a fashion analogous to the mitomycins. The difference in structures that ultimately causes a different mechanism of bio-reductive activation between the mitomycins and FR900482, cause FR900482 to not exhibit oxidative strand scission of DNA and to not produce a superoxide radical anion during activation. The FR900482 class of compounds represents a compelling clinical replacement for mitomycin C, given its greatly reduced host toxicity and superior DNA interstrand cross-linking efficacy.

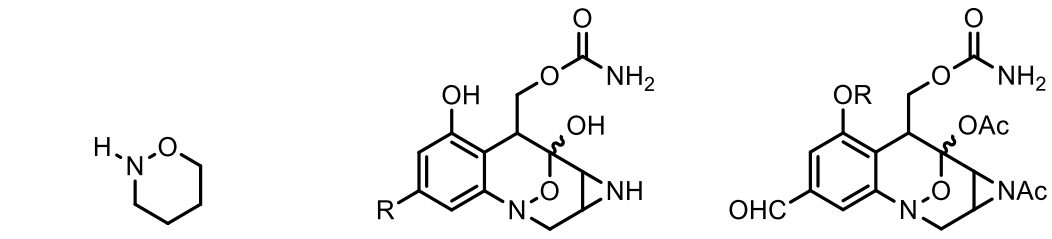


Figure 1.3 Tetrahydro-1,2-oxazine motif in natural and synthetic compounds

FK317 (**29**) and FK973 (**30**) are synthetic analogs of the natural products FR900482 and FR66979, and also contain the tetrahydro-1,2-oxazine system. The antitumor activity of FK317 was found to be equivalent to, or stronger than cisplatin, mitomycin C, and Taxol. Because of compounds such as FR900482 and FR66979 which contain the tetrahydro-1,2-oxazine system and show interesting biological features, new synthetic routes to the tetrahydro-1,2-oxazine core are useful because of the limited ways in which these systems can be created. These limitations have made the tetrahydro-1,2-oxazine ring difficult to synthesize in the past, so having the ability to form the system in a controlled manner is definitely beneficial to the synthetic community. This project looks at how cycloaddition chemistry can be utilized as an effective method for heterocyclic ring construction, and how understanding the process mechanistically may lead to the discovery of other reaction types. It is already know that DA cyclopropanes react with nitrones to form the tetrahydro-1,2-oxazine ring, and a goal of this project is to discover other partners that are compatible with DA cyclopropanes to form these systems as well as other interesting heterocycles.

The post modification of tetrahydro-1,2-oxazines has been examined by Dr. Michael Kerr and has led to some interesting and important uses for the ring system. Selective N-O cleavage of the tetrahydro-1,2-oxazine ring has been utilized in the synthesis of amino alcohols. The amino alcohols have then been used to construct pyrrolidines which has applications in the total synthesis of Nakadomarin A for example.[17] Pyrrole synthesis has also emerged as a tool made possible from post modification of the ring system.[18] These useful applications showcase how important these molecules are, and how important it is to obtain these compounds in an efficient and controllable manner.

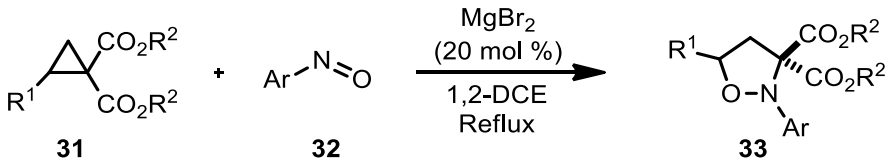
Chapter 2 - Cycloadditions of Donor-Acceptor Cyclopropanes with Nitrosoarenes

2.1 Introduction

Nitrosoarenes have been coupled with DA cyclopropanes in the synthesis of various heterocyclic ring systems.[19] Although reactions of nitrosoarenes and DA cyclopropanes have been reported, their potential has still yet to be reached. The discovery of new reactions utilizing the nitroso functional group is still ongoing and demonstrates the versatility in the construction of heterocyclic systems. The nitrogen-oxygen single bond that forms when nitrosoarenes are used in ring construction, has been shown to be a site of functionalization for the production of important molecules such as amino alcohols.[20]

2.1.1 Cycloadditions of DA Cyclopropanes with Nitrosoarenes

Previous research in the Studer group[21] has shown DA cyclopropanes to be a compatible reaction partner with nitrosoarenes, which undergo a [3+2] cycloaddition forming isoxazolidines when catalyzed with $MgBr_2$ as seen in scheme 2.1. The successful use of DA cyclopropanes with nitrosoarenes in cycloaddition reactions encouraged the Pagenkopf group to determine if these reaction partners were able to undergo other transformations.



Scheme 2.1 [3+2] Cycloaddition of DA cyclopropanes with nitrosoarenes

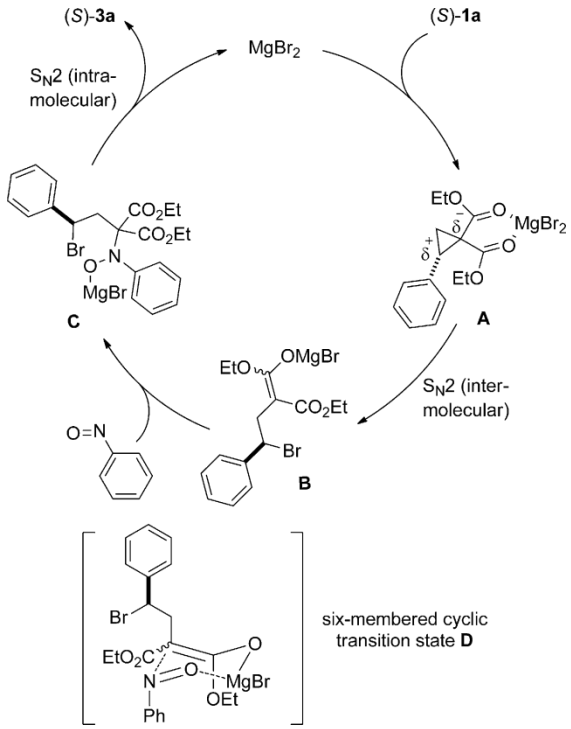


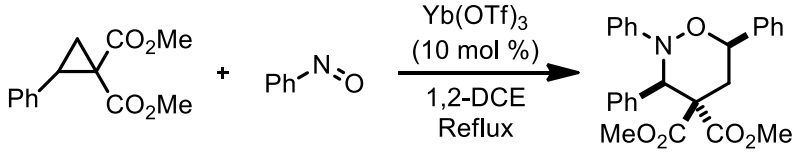
Figure 2.1 Catalytic cycle of [3+2] cycloaddition of DA cyclopropanes with nitrosoarenes

The mechanism (Figure 2.1) shows a bromide ion attacking and opening the cyclopropane ring, which drew my attention because of the Pagenkopf group's interest in $Yb(OTf)_3$ catalyzed DA cyclopropane cycloaddition chemistry. Under $Yb(OTf)_3$ catalytic conditions, only the triflate ion would be present as a counter-ion and would presumably be less nucleophilic towards the cyclopropane, allowing the nitrosoarene a chance to act as the nucleophile and perhaps open the cyclopropane ring in a [3+2] annulation to yield an isooxazolidinine. The initial hope was in opening of the DA cyclopropane in a manner that would yield the opposite *regio*-isomer as the Studer group. Instead of observing an isooxazolidinine, a tetrahydro-1,2-oxazine motif was formed.

2.2 Results and Discussion

Interestingly, it was discovered that when nitrosoarenes were allowed to react with DA cyclopropanes, the tetrahydro-1,2-oxazine motif was formed when catalyzed with $Yb(OTf)_3$ under refluxing conditions. The observed *cis* stereochemical outcome of the tetrahydro-1,2-oxazine ring

is consistent with Kerr's reaction of DA cyclopropanes with nitrones. A nitrone intermediate may account for the formation of the tetrahydro-1,2-oxazine system. This assumption was backed up by experimental evidence when considering the yield of the reaction. When both starting materials were used in a 1:1 ratio of equivalents, a yield of 44% was observed (Scheme 2.2). When using a 2:1 ratio of cyclopropane to nitrosoarene, a yield of 87% was observed. This observation shows how two equivalents of the cyclopropane may be combining to form a nitrone *in situ*, which then reacts with the nitrosoarene. Understanding the mechanics of this unprecedented reaction may lead to the discovery of other reaction types and reaction partners for DA cyclopropanes.



34a	**32a**	**35a**
1 Equiv.	1 Equiv.	44%
2 Equiv.	1 Equiv.	87%

Scheme 2.2 Reaction of DA cyclopropane with nitrosoarene

The physical properties of the tetrahydro-1,2-oxazine produced by this method are an exact match to the tetrahydro-1,2-oxazine produced from Kerr's methodology. The ^{1}H NMR of compound **35a** prepared from DA cyclopropane **34a** and nitrosobenzene **32a** is shown in Figure 2.2.

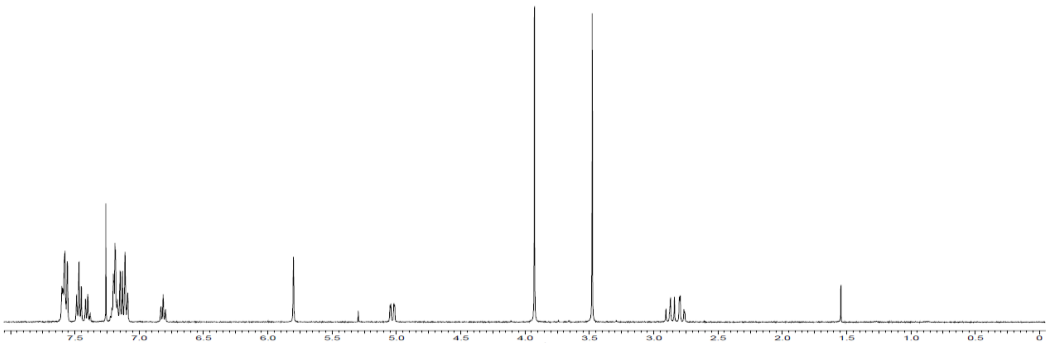
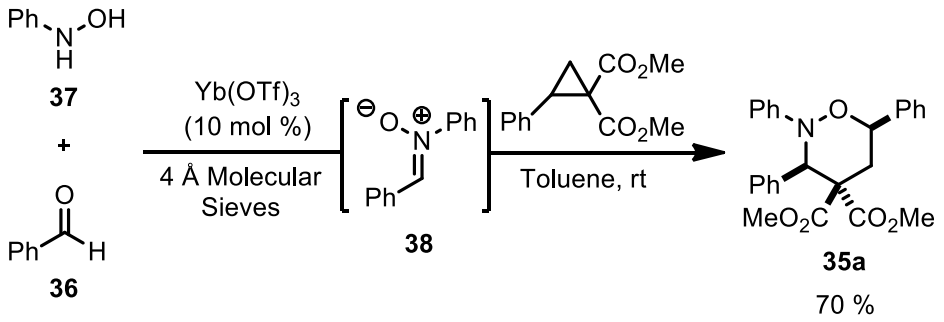


Figure 2.2 ^{1}H NMR of tetrahydro-1,2-oxazine **35a**

The NMR of the product from scheme 2.2 was compared to the identical compound synthesized using Kerr's three-component coupling strategy and is shown in Scheme 2.3 and Figure 2.3.



Scheme 2.3 Three component synthesis of tetrahydro-1,2-oxazine

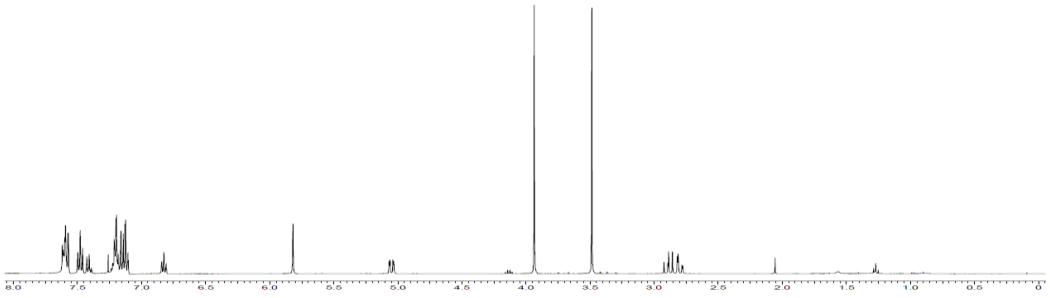
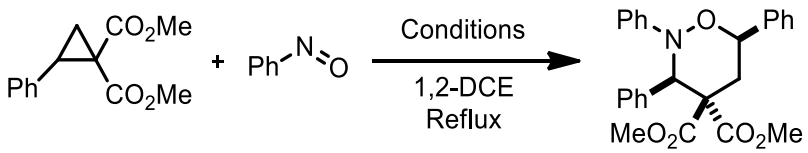


Figure 2.3 ^{1}H NMR of tetrahydro-1,2-oxazine **35a** prepared from Kerr's method

The matching NMR data provided experimental evidence that both methods lead to the same compound and, therefore, access to tetrahydro-1,2-oxazine is possible when reacting 1,1-cyclopropane diesters with nitrosoarene compounds.

To find reaction conditions that produce the highest yields and come to a better understanding of this reaction, an optimization experiment was carried out (Table 2.1). The reaction of DA cyclopropanes with nitrosoarenes was performed under different conditions until the production of tetrahydro-1,2-oxaizine was achieved in an efficient and reproducible manner.

Table 2.1 Optimization of $Yb(OTf)_3$ catalyzed reaction of DA cyclopropanes with nitrosoarene

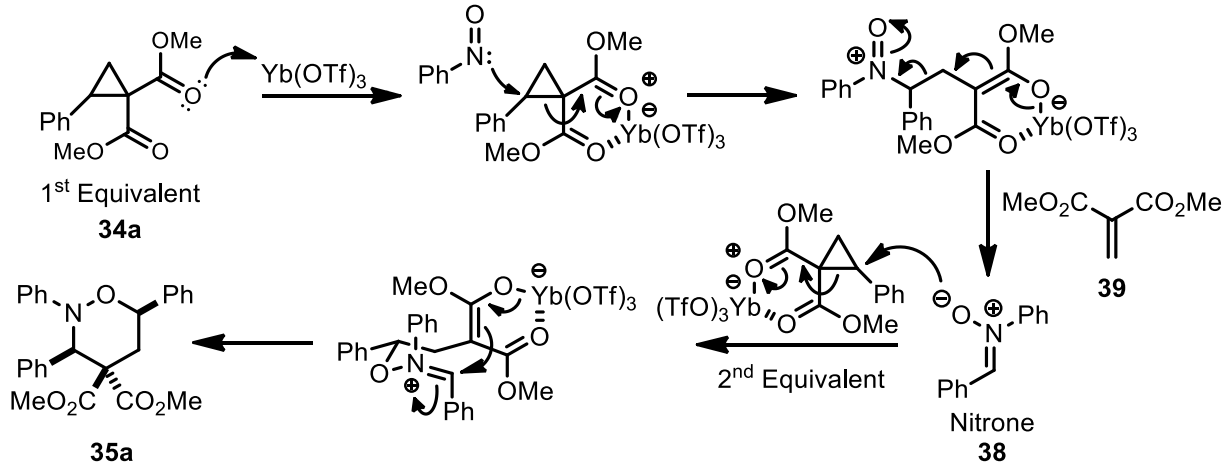


34a **32a** **35a**

Entry[a]	Cyclopropane (Equivalents)	Nitrosoarene (Equivalents)	Time (Hours)	$Yb(OTf)_3$ (mol %)	Yield (%)[b]
1	1	2	20	10	42
2	1	1	20	10	44
3	2	1	18	10	87
4	4	1	16	10	76
5	2	1	15	5	72
6	2	1	9	20	80

[a] Typical reaction conditions: Cyclopropane and nitrosoarene were added to a solution of $Yb(OTf)_3$ in 1,2-DCE (3 mL) at room temperature. Reactions were monitored by thin layer chromatography (TLC) until cyclopropane was consumed. [b] Isolated yield.

A cross-over experiment, which is a method used to study the mechanism of a chemical reaction, was used to address this reaction and the experimental evidence gained would help develop a rational reaction mechanism. A mechanism that would account for this overall transformation is shown in Scheme 2.4, and demonstrates how the nitrosoarene starts by attacking the first equivalent of cyclopropane, then forming a nitrone *in situ*. The nitrone would then react with the second equivalent of cyclopropane, in a known homo [3+2] cycloaddition, shown in a step-wise sequence.



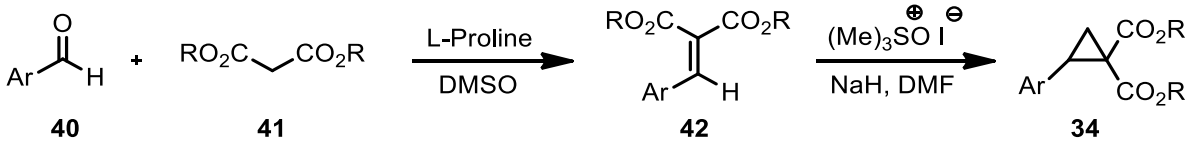
Scheme 2.4 Proposed mechanism for the reaction of DA cyclopropanes with nitrosoarenes

To investigate the proposed reaction mechanism, a cross-over experiment was designed to provide key mechanistic details. The theoretical mechanism can be analyzed by using two different cyclopropanes as the starting materials in a cross-over experiment with nitrosobenzene.

2.2.1 Synthesis of DA cyclopropanes

Cyclopropanes were prepared using a two-step procedure utilizing a Knoevenagel condensation followed by a Corey-Chaykovsky reaction (Table 2.2). Two different cyclopropanes were required for the cross-over experiment and additional cyclopropanes were also prepared to explore the reaction scope for compatibility with various nitrosoarenes.

Table 2.2 Synthesis of DA cyclopropanes



40 **41** **42** **34**

Entry[a]	Cyclopropane	Product	Yield (% over 2 steps)[b]
1	Ar = C_6H_5, R = Me	**34a**	76
2	Ar = 4-MeC_6H_4, R = Me	**34b**	87
3	Ar = C_6H_5, R = Et	**34c**	82
4	Ar = 4-MeC_6H_4, R = Et	**34d**	83
5	Ar = 2-thienyl, R = Me	**34e**	70

[a] Typical reaction conditions: L-Proline (1.88 mmol) was added to a solution of aldehyde (18.8 mmol) in DMSO (6 mL) followed by dialkyl malonate (37.6 mmol) and stirred for 24 h at room temperature. NaH (1.7 mmol) was added to trimethylsulfoxonium iodide (1.7 mmol) in DMF (3 mL) and stirred for 1 h at room temperature before adding the Knoevenagel product (1.4 mmol). Reactions were monitored by TLC until cyclopropane was consumed. [b] Isolated yield.

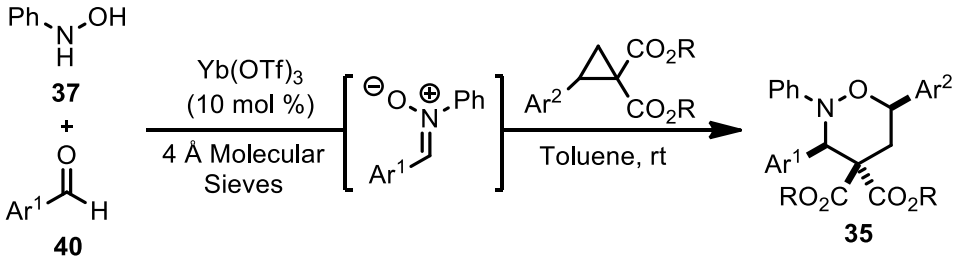
2.2.2 Cross-Over Experiment #1

Using starting material that consisted of two different DA cyclopropanes (**34a**, **34d**) would, in theory, generate two different nitrone intermediates (**38**, **43**) as seen in Scheme 2.5. Nitrone intermediate **38** would react with cyclopropane **34a** and cyclopropane **34d** giving rise to products **35a** and **35c**. The other nitrone intermediate (**43**) would react again with cyclopropane **34a** and cyclopropane **34d**, giving rise to products **35b** and **35d**. Identification of all four products in the reaction mixture would confirm that a reaction is taking place in which there is cross-over between the two different cyclopropanes and the two different nitrone intermediates.

The four expected products were synthesized individually from a three component coupling, homo [3+2] dipolar cycloaddition. Once each tetrahydro-1,2-oxazine product was

synthesized, they were used as standards and compared against the reaction mixture of the cross-over experiment. The three component coupling reaction was performed by making a nitrone *in situ* from the respective aldehyde and hydroxylamine as seen in Table 2.3.

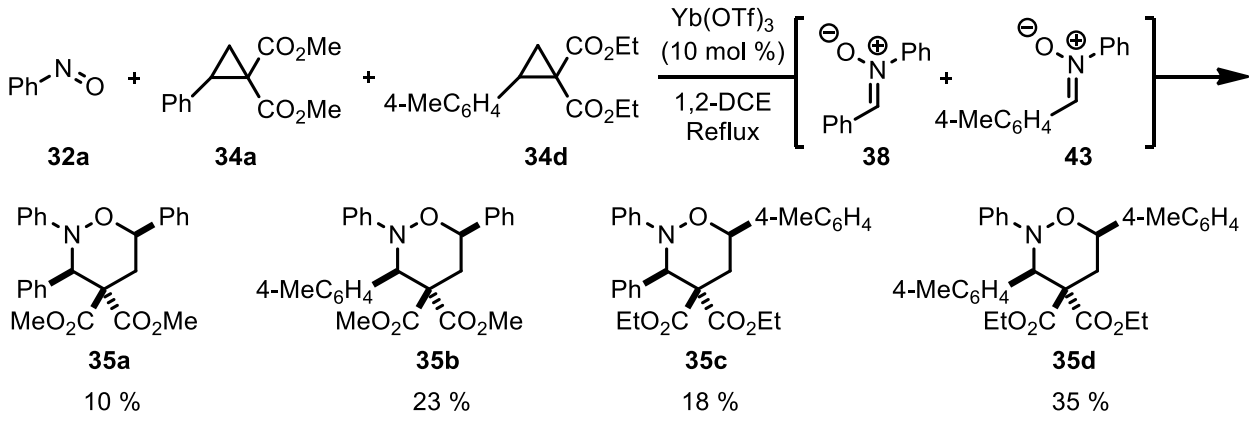
Table 2.3 Synthesis of tetrahydro-1,2-oxazine standards



Entry[a]	Aldehyde	Cyclopropane	Product	Yield (%)[b]
1	$Ar^1 = C_6H_5$	$Ar^2 = C_6H_5$, R= Me	**35a**	64
2	$Ar^1 = 4\text{-}MeC_6H_4$	$Ar^2 = C_6H_5$, R= Me	**35b**	81
3	$Ar^1 = C_6H_5$	$Ar^2 = 4\text{-}MeC_6H_4$, R= Et	**35c**	77
4	$Ar^1 = 4\text{-}MeC_6H_4$	$Ar^2 = 4\text{-}MeC_6H_4$, R= Et	**35d**	63

[a] Typical reaction conditions: To a solution of hydroxylamine (0.46 mmol) and aldehyde (0.50 mmol) in toluene (2 mL) at room temperature, were added $Yb(OTf)_3$ and 4Å molecular sieves. Reactions were monitored by TLC. [b] Isolated yield.

After synthesis and characterization, the standards with their respective R_f values were spotted against the reaction mixture of the cross-over experiment and developed in Hexanes:Ethyl Acetate (3:1) on a TLC plate. All four standards in the reaction mixture were identified. All four tetrahydro-1,2-oxazines (**35a - 35d**) were isolated from the reaction mixture of cross-over experiment #1 to provide isolated yields as seen in Scheme 2.5. All four products in the reaction mixture (from cross-over experiment #1) was verified with NMR and GC-MS data, which were analyzed by comparison to the individual standards produced from Table 2.3

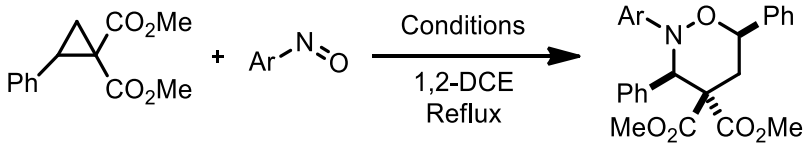


Scheme 2.5 Cross-over experiment for the reaction of DA cyclopropanes with nitrosoarenes

2.2.3 Reaction Scope

After gaining a better understanding and optimizing the reaction of DA cyclopropanes with nitrosoarenes, the optimal conditions were applied to other nitrosoarenes to investigate and expand the reactions scope, as seen in Table 2.4.

Table 2.4 Reaction scope with different nitrosoarenes



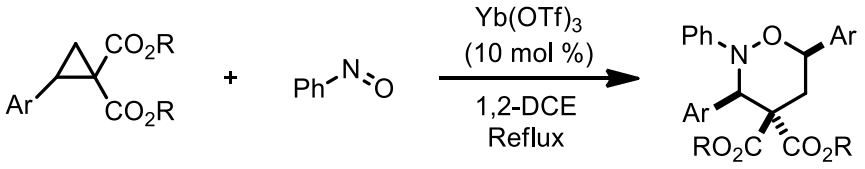
34a **32** **44**

Entry[a]	Nitrosoarene	Product	Yield (%)[b]
1	Ar = 3-BrC_6H_4	**44a**	73
2	Ar = 4-BrC_6H_4	**44b**	75
3	Ar = 3-$CO_2EtC_6H_4$	**44c**	80
4	Ar = 4-$CO_2EtC_6H_4$	**44d**	78
5	Ar = 3,4-$Cl_2C_6H_3$	**44e**	91
6	Ar = 3-$C(O)MeC_6H_4$	**44f**	68
7	Ar = N-Boc-5-Indole	**44g**	55

[a] Typical reaction conditions: To a solution of $Yb(OTf)_3$ in 1,2-DCE (3 mL) at room temperature, was added cyclopropane (0.43 mmol) and nitrosoarene (0.22 mmol). Reactions were monitored by TLC until cyclopropane was consumed. [b] Isolated yield.

After expansion of the reaction scope to include different nitrosoarenes, additional DA cyclopropanes were explored. Table 2.5 shows different DA cyclopropanes that are compatible with the reaction conditions in forming tetrahydro-1,2-oxazines.

Table 2.5 Reaction scope with different DA cyclopropanes



34 **32a** **35**

Entry[a]	Cyclopropane	Product	Yield (%)[b]
1	Ar = C_6H_5, R = Me	**35a**	87
2	Ar = C_6H_5, R = Et	**35e**	62
3	Ar = 4-MeC_6H_4, R = Me	**35f**	46
4	Ar = 4-MeC_6H_4, R = Et	**35d**	70
5	Ar = 2-thienyl, R = Me	**35g**	69

[a] Typical reaction conditions: To a solution of $Yb(OTf)_3$ in 1,2-DCE (3 mL) at room temperature, was added cyclopropane (0.43 mmol) and nitrosoarene (0.22 mmol). Reactions were monitored by TLC until cyclopropane was consumed. [b] Isolated yield.

A new method of synthesizing tetrahydro-1,2-oxazines from DA cyclopropanes and nitrosoarenes under $Yb(OTf)_3$ catalysis has been developed. A mechanism that accounts for this overall transformation has been presented and experimental data obtained from a cross-over experiment provided supporting evidence. The reaction scope was investigated and it was found that the reaction conditions were compatible with different nitrosoarenes and DA cyclopropanes.

2.3 Experimental

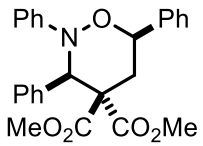
All reactions were performed in an atmosphere of dry argon unless otherwise noted. Flasks were oven-dried at approximately 110 °C overnight and cooled in a desiccator prior to use. Solvents and reagents were purified according to standard procedures. Dichloromethane was purified by passing the solvent through a column of activated alumina. 1,2-Dichloroethane was dried by stirring with CaH_2 for one hour prior to distillation. All other chemicals were of reagent quality and used as obtained from commercial sources unless otherwise noted. The progress of reactions was monitored by TLC performed on F254 silica gel plates. The plates were visualized using UV light (254 nm) or by staining with ceric ammonium molybdate (CAM) or $KMnO_4$. Column chromatography was performed with Silica Flash P60 60 Å silica gel (purchased from Silicycle) using flash column chromatography techniques.

^{1}H and ^{13}C NMR data were obtained on Mercury 400 or Inova 600 MHz spectrometers and chemical shifts were reported in parts per million (ppm). All spectra were obtained in deuterated chloroform and referenced to residual chloroform at δ 7.26 ppm for ^{1}H spectra and the center peak of the triplet at δ 77.0 ppm for ^{13}C spectra. When peak multiplicities are given, abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; m, multiplet. EI high-resolution mass spectra (HRMS) were recorded on a Finnigan MAT 8200 mass spectrometer at an ionizing voltage of 70 eV.

2.4 Supporting Information

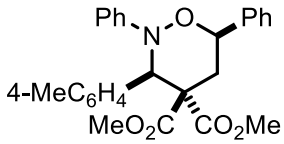
General Three Component Coupling Procedure

To a solution of hydroxylamine (0.46 mmol, 1.3 equiv) and aldehyde (0.50 mmol, 1.4 equiv), in toluene (2 mL) was added 4Å molecular sieves and $Yb(OTf)_3$ (0.04 mmol, 0.1 equiv) and stirred for 30 min. Cyclopropane (0.36 mmol, 1.0 equiv) was then added and stirred for 20 h at rt, then directly loaded onto a packed SiO_2 column. Product was purified by flash chromatography (9:1 hexanes/EtOAc) to afford the corresponding cycloadducts.



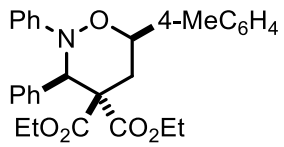
Dimethyl 2,3,6-triphenyl-1,2-oxazinane-4,4-dicarboxylate (35a)

The general three component coupling procedure was followed using hydroxylamine (50 mg, 0.46 mmol), aldehyde (0.05 mL, 0.50 mmol), $Yb(OTf)_3$ (22 mg, 0.036 mmol) and cyclopropane **34a** (84 mg, 0.36 mmol) to yield the compound as a yellow oil. The yellow oil was recrystallized with CH_2Cl_2/Hexane to give a white solid (100 mg, 64%). R_f 0.40 (3:1 Hexanes:EtOAc); ^1H NMR (400 MHz, $CDCl_3$) 7.56 - 7.60 (m, 4 H), 7.47 (app t, J = 7.4 Hz, 2 H), 7.38 - 7.42 (m, 1 H), 7.09 - 7.22 (m, 7 H), 6.81 (app t, J = 7.0 Hz, 1 H), 5.80 (s, 1 H), 5.03 (dd, J = 12.1, 2.3 Hz, 1 H), 3.93 (s, 3 H), 3.48 (s, 3 H), 2.86 (dd, J = 14.5, 12.1 Hz, 1 H), 2.78 (dd, J = 14.5, 2.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.1, 168.3, 148.5, 139.4, 135.0, 130.4, 128.6, 128.5, 128.3, 128.1, 128.0, 126.5, 121.6, 115.8, 78.8, 65.7, 59.5, 53.5, 52.6, 31.6; HRMS $C_{26}H_{25}NO_5$ Calculated = 431.1733, Found = 431.1736



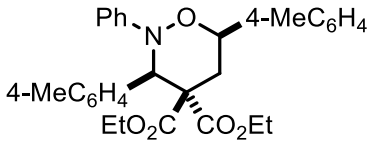
Dimethyl 2,6-diphenyl-3-(p-tolyl)-1,2-oxazinane-4,4-dicarboxylate (35b)

The general three component coupling procedure was followed using hydroxylamine (60 mg, 0.55 mmol), aldehyde (0.07 mL, 0.60 mmol), $Yb(OTf)_3$ (27 mg, 0.043 mmol) and cyclopropane **34a** (100 mg, 0.43 mmol) to yield the compound as a yellow oil. The yellow oil was recrystallized with CH_2Cl_2/Hexane to give a white solid (155 mg, 81%). R_f 0.45 (3:1 Hexanes:EtOAc); ^1H NMR (400 MHz, $CDCl_3$) 7.57 (app d, J = 7.4 Hz, 2 H), 7.45 - 7.49 (m, 4 H), 7.38 - 7.42 (m, 1 H), 7.09 - 7.17 (m, 4 H), 7.00 (app d, J = 7.8 Hz, 2 H), 6.79 - 6.83 (m, 1 H), 5.78 (s, 1 H), 5.03 (dd, J = 12.1, 2.3 Hz, 1 H), 3.92 (s, 3 H), 3.51 (s, 3 H), 2.87 (dd, J = 14.5, 12.1 Hz, 1 H), 2.78 (dd, J = 14.5, 2.3 Hz, 1 H), 2.23 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.1, 168.3, 148.6, 139.5, 137.6, 131.9, 130.3, 121.5, 115.7, 78.8, 77.3, 76.7, 65.4, 59.6, 53.5, 52.7, 31.6, 21.1; HRMS $C_{27}H_{27}NO_5$ Calculated = 445.1889, Found = 445.1882



Diethyl 2,3-diphenyl-6-(p-tolyl)-1,2-oxazinane-4,4-dicarboxylate (35c)

The general three component coupling procedure was followed using hydroxylamine (50 mg, 0.46 mmol), aldehyde (0.05 mL, 0.50 mmol), $Yb(OTf)_3$ (22 mg, 0.036 mmol) and cyclopropane **34d** (100 mg, 0.36 mmol) to yield the compound as a yellow oil. The yellow oil was recrystallized with CH_2Cl_2/Hexane to give a white solid (132 mg, 77%). R_f 0.55 (3:1 Hexanes:EtOAc); ^1H NMR (400 MHz, $CDCl_3$) 7.57 - 7.59 (m, 2 H), 7.45 (app d, J = 8.2 Hz, 2 H), 7.28 (s, 1 H), 7.08 - 7.17 (m, 7 H), 6.80 (app t, J = 7.0 Hz, 1 H), 5.78 (s, 1 H), 5.00 (dd, J = 12.1, 2.3 Hz, 1 H), 4.38 (q, J = 7.0 Hz, 2 H), 3.87 - 3.94 (dddd, J = 7.0, 7.0, 7.0, 10.5 Hz, 2 H), 2.87 (dd, J = 14.5, 12.1 Hz, 1 H), 2.76 (dd, J = 14.5, 2.3 Hz, 1 H), 2.41 (s, 3 H), 1.36 (t, J = 7.2 Hz, 3 H), 1.03 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 169.6, 168.0, 148.7, 138.1, 136.6, 135.1, 130.6, 129.3, 128.5, 128.0, 127.9, 126.5, 121.4, 115.8, 78.7, 65.7, 62.3, 61.8, 59.4, 31.7, 21.3, 14.2, 13.7; HRMS $C_{29}H_{31}NO_5$ Calculated = 473.2202, Found = 473.2195

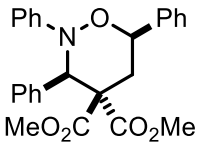


Diethyl 2-phenyl-3,6-di-p-tolyl-1,2-oxazinane-4,4-dicarboxylate (35d)

The general three component coupling procedure was followed using hydroxylamine (50 mg, 0.46 mmol), aldehyde (0.05 mL, 0.50 mmol), $Yb(OTf)_3$ (22 mg, 0.036 mmol) and cyclopropane **34d** (100 mg, 0.36 mmol) to yield the compound as a yellow oil. The yellow oil was recrystallized with CH_2Cl_2/Hexane to give a white solid (190 mg, 63%). R_f 0.58 (3:1 Hexanes:EtOAc); ^1H NMR (400 MHz, $CDCl_3$) 7.44 - 7.47 (app dd, J = 8.2, 6.6 Hz, 4 H), 7.27 (app d, J = 8.2 Hz, 2 H), 7.08 - 7.16 (m, 4 H), 6.97 (app d, J = 8.2 Hz, 2 H), 6.79 (app tt, J = 7.0, 1.6 Hz, 1 H), 5.75 (s, 1 H), 4.98 (dd, J = 14.5, 2.3 Hz, 1 H), 4.38 (q, J = 7.0 Hz, 2 H), 3.85 - 3.99 (dddd, J = 7.0, 7.0, 7.0, 10.5 Hz, 2 H), 2.86 (dd, J = 14.5, 12.5 Hz, 1 H), 2.74 (dd, J = 14.5, 2.3 Hz, 1 H), 2.41 (s, 3 H), 2.21 (s, 3 H), 1.35 (t, J = 7.0 Hz, 3 H), 1.06 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 169.7, 168.0, 148.7, 138.1, 137.5, 136.6, 131.9, 130.5, 129.3, 128.6, 128.5, 126.5, 121.3, 115.7, 78.7, 65.4, 62.2, 61.7, 59.4, 31.7, 21.2, 21.0, 14.2, 13.7; HRMS $C_{30}H_{33}NO_5$ Calculated = 487.2359, Found = 487.2348

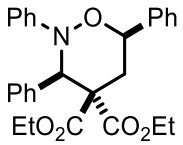
General Lewis Acid Catalyzed Cycloaddition Procedure

To a solution of cyclopropane (0.43 mmol, 2.1 equiv) and nitrosoarene (0.20 mmol, 1.0 equiv) in DCE (3 mL) was added $Yb(OTf)_3$ (0.02 mmol, 0.1 equiv) and stirred for 15 min. The mixture was heated to reflux for 3 h then concentrated after consumption of cyclopropane (as indicated by TLC) and directly loaded onto a packed SiO_2 column. Product was purified by flash chromatography (9:1 hexanes/EtOAc) to afford the corresponding cycloadducts.



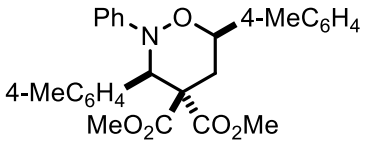
Dimethyl 2,3,6-triphenyl-1,2-oxazinane-4,4-dicarboxylate (35a)

The general Lewis acid cycloaddition procedure was followed using cyclopropane **34a** (100 mg, 0.43 mmol), nitrosobenzene (21 mg, 0.20 mmol) and $Yb(OTf)_3$ (12 mg, 0.020 mmol) to yield the compound as a yellow oil, which was recrystallized with CH_2Cl_2/Hexane to give a white solid (75 mg, 87%). R_f 0.40 (3:1 Hexanes:EtOAc); ^1H NMR (400 MHz, $CDCl_3$) 7.56 - 7.60 (m, 4 H), 7.47 (app t, J = 7.4 Hz, 2 H), 7.38 - 7.42 (m, 1 H), 7.09 - 7.22 (m, 7 H), 6.81 (app t, J = 7.0 Hz, 1 H), 5.80 (s, 1 H), 5.03 (dd, J = 12.1, 2.3 Hz, 1 H), 3.93 (s, 3 H), 3.48 (s, 3 H), 2.86 (dd, J = 14.5, 12.1 Hz, 1 H), 2.78 (dd, J = 14.5, 2.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.1, 168.3, 148.5, 139.4, 135.0, 130.4, 128.6, 128.5, 128.3, 128.1, 128.0, 126.5, 121.6, 115.8, 78.8, 65.7, 59.5, 53.5, 52.6, 31.6; HRMS $C_{26}H_{25}NO_5$ Calculated = 431.1733, Found = 431.1736



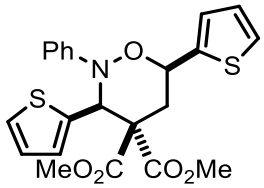
Diethyl 2,3,6-triphenyl-1,2-oxazinane-4,4-dicarboxylate (35e)

The general Lewis acid cycloaddition procedure was followed using cyclopropane **34c** (50 mg, 0.19 mmol), nitrosobenzene (10 mg, 0.095 mmol) and $Yb(OTf)_3$ (12 mg, 0.019 mmol) to yield the compound as a yellow oil, which was recrystallized with CH_2Cl_2/Hexane to give a white solid (28 mg, 62%). R_f 0.46 (3:1 Hexanes:EtOAc); ^1H NMR (400 MHz, $CDCl_3$) 7.55 - 7.60 (m, 4 H), 7.47 (app t, J = 7.2 Hz, 2 H), 7.38 - 7.41 (m, 1 H), 7.09 - 7.20 (m, 7 H), 6.81 (app tt, J = 7.0, 1.6 Hz, 1 H), 5.79 (s, 1 H), 5.03 (dd, J = 12.1, 2.3 Hz, 1 H), 4.40 (q, J = 7.0 Hz, 2 H), 3.83 - 3.99 (dddd, J = 7.0, 7.0, 7.0, 10.5 Hz, 2 H), 2.87 (dd, J = 14.5, 12.1 Hz, 1 H), 2.79 (dd, J = 14.5, 2.3 Hz, 1 H), 1.37 (t, J = 7.2 Hz, 3 H), 1.03 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 169.6, 167.9, 148.6, 139.6, 135.0, 130.6, 128.6, 128.5, 128.2, 128.0, 127.9, 126.4, 121.5, 115.8, 78.8, 65.8, 62.3, 61.8, 59.3, 31.9, 14.2, 13.7; HRMS $C_{28}H_{29}NO_5$ Calculated = 459.2046, Found = 459.2027



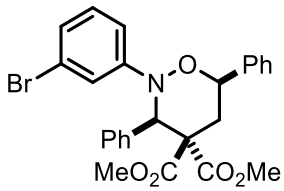
Dimethyl 2-phenyl-3,6-di-p-tolyl-1,2-oxazinane-4,4-dicarboxylate (35f)

The general Lewis acid cycloaddition procedure was followed using cyclopropane **34b** (50 mg, 0.20 mmol), nitrosobenzene (11 mg, 0.10 mmol) and $Yb(OTf)_3$ (12 mg, 0.020 mmol) to yield the compound as a yellow oil, which was recrystallized with CH_2Cl_2/Hexane to give a white solid (21 mg, 46%). R_f 0.60 (3:1 Hexanes:EtOAc); ^1H NMR (400 MHz, $CDCl_3$) 7.45 - 7.48 (m, 4 H), 7.27 (app d, J = 8.2 Hz, 2 H), 7.07 - 7.14 (m, 4 H), 6.99 (app d, J = 7.8 Hz, 2 H), 6.80 (app tt, J = 8.2, 1.2 Hz, 1 H), 5.76 (s, 1 H), 4.98 (dd, J = 12.1, 2.3 Hz, 1 H), 3.91 (s, 3 H), 3.50 (s, 3 H), 2.86 (dd, J = 14.5, 12.1 Hz, 1 H), 2.74 (dd, J = 14.5, 2.3 Hz, 1 H), 2.41 (s, 3 H), 2.22 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.2, 168.4, 148.6, 143.0, 138.2, 137.6, 136.4, 131.9, 130.3, 129.7, 129.5, 129.3, 129.2, 128.7, 128.5, 126.6, 126.5, 121.4, 115.7, 78.7, 65.3, 59.6, 53.4, 52.6, 31.4, 21.3, 21.1; HRMS $C_{28}H_{29}NO_5$ Calculated = 459.2046, Found = 459.2027



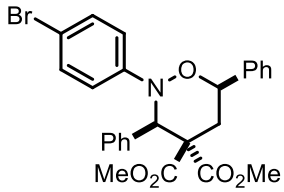
Dimethyl 2-phenyl-3,6-di(thiophen-2-yl)-1,2-oxazinane-4,4-dicarboxylate (35g)

The general Lewis acid cycloaddition procedure was followed using cyclopropane **34e** (100 mg, 0.42 mmol), nitrosobenzene (121 mg, 0.20 mmol) and $Yb(OTf)_3$ (12 mg, 0.020 mmol) to yield the compound as a yellow oil, which was recrystallized with CH_2Cl_2/Hexane to give a white solid (61 mg, 69%). R_f 0.39 (3:1 Hexanes:EtOAc); ^1H NMR (400 MHz, $CDCl_3$) 7.40 (app d, J = 5.1 Hz, 1 H), 7.25 (app d, J = 3.9 Hz, 1 H), 7.15 - 7.20 (m, 3 H), 7.06 - 7.13 (m, 3 H), 6.95 (app d, J = 3.5 Hz, 1 H), 6.88 (app t, J = 7.4 Hz, 1 H), 6.80 - 6.84 (m, 1 H), 6.09 (s, 1 H), 5.27 (dd, J = 12.1, 2.3 Hz, 1 H), 3.92 (s, 3 H), 3.59 (s, 3 H), 2.99 (dd, J = 14.5, 12.1 Hz, 1 H), 2.88 (dd, J = 14.5, 2.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) 169.3, 167.7, 148.1, 141.5, 133.8, 129.2, 128.5, 127.2, 126.7, 126.0, 125.8, 125.4, 122.4, 116.3, 75.0, 64.3, 59.7, 53.6, 52.9, 32.3; HRMS $C_{22}H_{21}NO_5S_2$ Calculated = 443.0861, Found = 443.0864



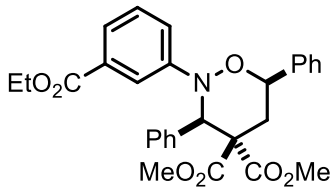
Dimethyl 2-(3-bromophenyl)-3,6-diphenyl-1,2-oxazinane-4,4-dicarboxylate (44a)

The general Lewis acid cycloaddition procedure was followed using cyclopropane **34a** (100 mg, 0.43 mmol), nitrosoarene (20 mg, 0.11 mmol) and $Yb(OTf)_3$ (6 mg, 0.010 mmol) to yield the compound as a yellow oil, which was recrystallized with CH_2Cl_2/Hexane to give a white solid (41 mg, 73%). R_f 0.38 (3:1 Hexanes:EtOAc); ^1H NMR (400 MHz, $CDCl_3$) 7.54 - 7.60 (m, 4 H), 7.46 - 7.50 (m, 2 H), 7.40 - 7.43 (m, 1 H), 7.22 - 7.24 (m, 3 H), 6.99 - 7.01 (m, 2 H), 6.91 - 6.94 (m, 1 H), 5.76 (s, 1 H), 4.99 (dd, J = 12.1, 2.3 Hz, 1 H), 3.92 (s, 3 H), 3.49 (s, 3 H), 2.87 (dd, J = 14.5, 12.1 Hz, 1 H), 2.76 (dd, J = 14.5, 2.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) 169.9, 168.0, 138.9, 134.5, 130.2, 129.9, 128.7, 128.5, 128.3, 128.2, 126.6, 124.4, 122.7, 118.6, 114.0, 79.1, 59.4, 53.6, 52.7; HRMS $C_{26}H_{24}BrNO_5$ Calculated = 509.0838, Found = 509.0823



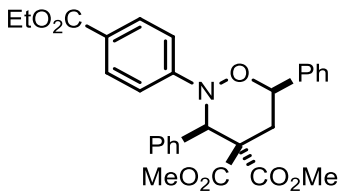
Dimethyl 2-(4-bromophenyl)-3,6-diphenyl-1,2-oxazinane-4,4-dicarboxylate (44b)

The general Lewis acid cycloaddition procedure was followed using cyclopropane **34a** (100 mg, 0.43 mmol), nitrosoarene (37 mg, 0.20 mmol) and $Yb(OTf)_3$ (12 mg, 0.020 mmol) to yield the compound as a yellow oil, which was recrystallized with CH_2Cl_2/Hexane to give a white solid (75 mg, 75%). R_f 0.34 (3:1 Hexanes:EtOAc); ^1H NMR (400 MHz, $CDCl_3$) 7.53 - 7.57 (m, 4 H), 7.45 - 7.47 (m, 2 H), 7.38 - 7.42 (m, 1 H), 7.18 - 7.20 (m, 5 H), 6.96 - 6.98 (m, 2 H), 5.73 (s, 1 H), 5.00 (dd, J = 12.1, 2.7 Hz, 1 H), 3.92 (s, 3 H), 3.48 (s, 3 H), 2.87 (dd, J = 14.5, 12.1 Hz, 1 H), 2.76 (dd, J = 14.5, 2.7 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) 168.1, 147.6, 139.0, 134.6, 131.4, 130.3, 128.7, 128.5, 128.3, 128.1, 126.5, 117.5, 114.1, 79.0, 65.6, 59.4, 53.6, 52.7, 31.5; HRMS $C_{26}H_{24}BrNO_5$ Calculated = 509.0838, Found = 509.0830



Dimethyl 2-(3-(ethoxycarbonyl)phenyl)-3,6-diphenyl-1,2-oxazinane-4,4-dicarboxylate (44c)

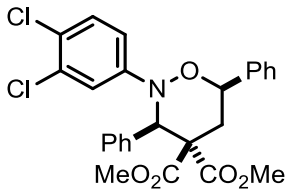
The general Lewis acid cycloaddition procedure was followed using cyclopropane **34a** (100 mg, 0.43 mmol), nitrosoarene (39 mg, 0.22 mmol) and $Yb(OTf)_3$ (12 mg, 0.020 mmol) to yield the compound as a yellow oil, which was recrystallized with CH_2Cl_2/Hexane to give a white solid (88 mg, 80%). R_f 0.29 (3:1 Hexanes:EtOAc); ^1H NMR (400 MHz, $CDCl_3$) 7.75 (app t, J = 1.6 Hz, 1 H), 7.55 - 7.62 (m, 4 H), 7.45 - 7.51 (m, 3 H), 7.39 - 7.43 (m, 1 H), 7.27 - 7.32 (m, 1 H), 7.17 - 7.22 (m, 4 H), 5.85 (s, 1 H), 5.02 (dd, J = 12.1, 2.3 Hz, 1 H), 4.32 (q, J = 7.0 Hz, 2 H), 3.93 (s, 3 H), 3.49 (s, 3 H), 2.90 (dd, J = 14.5, 12.1 Hz, 1 H), 2.77 (dd, J = 14.5, 2.3 Hz, 1 H), 1.35 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.0, 168.1, 166.6, 148.6, 139.1, 134.6, 130.4, 128.7, 128.6, 128.4, 128.2, 128.1, 126.5, 122.6, 120.1, 116.6, 79.0, 65.3, 60.9, 59.4, 53.6, 52.7, 31.6, 14.3; HRMS $C_{29}H_{29}NO_7$ Calculated = 503.1944, Found = 503.1943



Dimethyl 2-(4-(ethoxycarbonyl)phenyl)-3,6-diphenyl-1,2-oxazinane-4,4-dicarboxylate (44d)

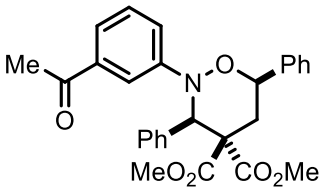
The general Lewis acid cycloaddition procedure was followed using cyclopropane **34a** (106 mg, 0.45 mmol), nitrosoarene (36 mg, 0.20 mmol) and $Yb(OTf)_3$ (17 mg, 0.027 mmol) to yield the compound as a yellow oil, which was recrystallized to give a white solid (78 mg, 78%). R_f 0.28 (3:1 Hexanes:EtOAc); ^1H NMR (400 MHz, $CDCl_3$) 7.82 - 7.86 (m, 2 H), 7.54 - 7.61 (m, 4 H), 7.46 - 7.51 (m, 2 H), 7.40 - 7.45 (m, 1 H), 7.19 - 7.24 (m, 3 H), 7.09 - 7.13 (m, 2 H), 5.91 (s, 1 H), 5.00 (dd, J = 12.1, 2.3 Hz, 1 H), 4.27 (q, J = 7.0 Hz, 2 H), 3.92 (s, 3 H), 3.50 (s, 3 H), 2.90 (dd, J = 14.5, 12.1 Hz, 1 H), 2.77 (dd, J = 14.5, 2.3 Hz, 1 H), 1.32 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 169.9, 168.0, 166.4, 151.9, 138.7, 134.7, 130.6, 130.0, 128.8, 128.6, 128.4, 128.2, 126.6,

122.8, 114.2, 79.1, 64.4, 60.5, 53.6, 52.8, 31.5, 14.3; HRMS $C_{29}H_{29}NO_7$ Calculated = 503.1944, Found = 503.1943



Dimethyl 2-(3,4-dichlorophenyl)-3,6-diphenyl-1,2-oxazinane-4,4-dicarboxylate (44e)

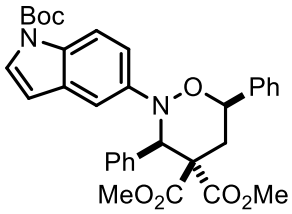
The general Lewis acid cycloaddition procedure was followed using cyclopropane **34a** (57 mg, 0.24 mmol), nitrosoarene (19 mg, 0.11 mmol) and $Yb(OTf)_3$ (6 mg, 0.010 mmol) to yield the compound as a yellow oil, which was recrystallized with CH_2Cl_2/Hexane to give a white solid (50 mg, 91%). R_f 0.55 (3:1 Hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) 7.53 - 7.58 (m, 4 H), 7.46 - 7.50 (m, 2 H), 7.40 - 7.44 (m, 1 H), 7.22 - 7.25 (m, 3 H), 7.17 - 7.19 (m, 2 H), 6.89 - 6.92 (app dd, J = 9.0, 2.7 Hz, 1 H), 5.72 (s, 1 H), 4.98 (dd, J = 12.3, 2.4 Hz, 1 H), 3.92 (s, 3 H), 3.48 (s, 3 H), 2.87 (dd, J = 14.7, 12.3 Hz, 1 H), 2.74 (dd, J = 14.7, 2.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) 167.9, 147.9, 138.7, 134.3, 132.5, 130.2, 130.1, 128.8, 128.7, 128.5, 128.3, 126.6, 124.5, 117.5, 114.9, 79.3, 65.3, 59.2, 53.6, 52.8, 31.4; HRMS $C_{26}H_{23}Cl_2NO_5$ Calculated = 499.0953, Found = 499.0952



Dimethyl 2-(3-acetylphenyl)-3,6-diphenyl-1,2-oxazinane-4,4-dicarboxylate (44f)

The general Lewis acid cycloaddition procedure was followed using cyclopropane **34a** (100 mg, 0.43 mmol), nitrosoarene (32 mg, 0.21 mmol) and $Yb(OTf)_3$ (12 mg, 0.020 mmol) to yield the compound as a yellow oil, which was recrystallized with CH_2Cl_2/Hexane to give a white solid (68 mg, 68%). R_f 0.25 (3:1 Hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) 7.64 - 7.67 (m, 1 H), 7.55 - 7.62 (m, 4 H), 7.46 - 7.50 (m, 2 H), 7.39 - 7.43 (m, 2 H), 7.30 - 7.34 (m, 1 H), 7.24 - 7.26 (m, 1 H), 7.18 - 7.22 (m, 3 H), 5.85 (s, 1 H), 5.03 (dd, J = 12.1, 2.3 Hz, 1 H), 3.93 (s, 3 H), 3.49 (s, 3 H), 2.89 (dd, J = 14.5, 12.1 Hz, 1 H), 2.79 (dd, J = 14.5, 2.3 Hz, 1 H), 2.50 (s, 3 H); ^{13}C NMR (100

MHz, $CDCl_3$) 170.0, 168.1, 148.8, 137.5, 134.6, 130.3, 128.8, 128.7, 128.5, 128.3, 128.1, 126.5, 121.7, 120.5, 115.1, 79.1, 65.3, 59.4, 53.6, 52.7, 31.6, 26.7; HRMS $C_{28}H_{27}NO_6$ Calculated = 473.1838, Found = 473.1829



Dimethyl 2-(1-(tert-butoxycarbonyl)-1H-indol-5-yl)-3,6-diphenyl-1,2-oxazinane-4,4-dicarboxylate (44g)

The general Lewis acid cycloaddition procedure was followed using cyclopropane **34a** (50 mg, 0.21 mmol), nitrosoarene (27 mg, 0.11 mmol) and $Yb(OTf)_3$ (12 mg, 0.020 mmol) to yield the compound as a yellow oil, which was recrystallized with CH_2Cl_2/Hexane to give a white solid (35 mg, 55%). R_f 0.40 (3:1 Hexanes:EtOAc); ^1H NMR (400 MHz, $CDCl_3$) 8.04 - 8.06 (m, 1 H), 7.56 - 7.61 (m, 4 H), 7.46 - 7.50 (m, 4 H), 7.39 - 7.42 (m, 1 H), 7.26 - 7.27 (m, 1 H), 7.14 - 7.18 (m, 2 H), 7.10 - 7.13 (app dd, J = 9.0, 2.3 Hz, 1 H), 6.38 (app d, J = 3.5 Hz, 1 H), 5.78 (s, 1 H), 5.10 (dd, J = 12.1, 2.3 Hz, 1 H), 3.96 (s, 3 H), 3.47 (s, 3 H), 2.90 (dd, J = 14.5, 12.1 Hz, 1 H), 2.80 (dd, J = 14.5, 2.3 Hz, 1 H), 1.61 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.2, 168.3, 166.2, 144.5, 139.6, 134.9, 131.0, 130.5, 128.8, 128.6, 128.4, 128.3, 128.0, 127.9, 126.6, 114.9, 107.4, 78.8, 67.3, 59.6, 53.8, 53.5, 52.6, 31.7, 28.2; HRMS $C_{33}H_{34}N_2O_7$ Calculated = 570.2366, Found = 570.2347

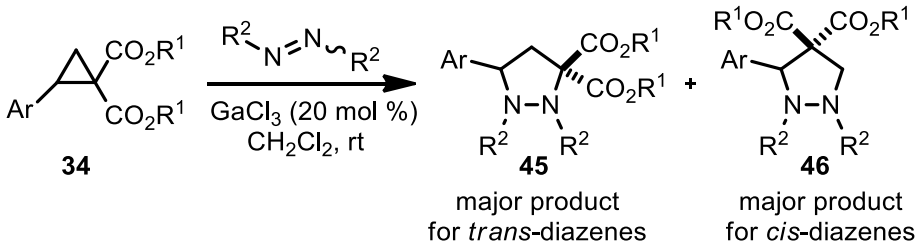
General Lewis Acid Catalyzed Cross-Over Experiment Procedure

To a solution of cyclopropane **34a** (0.43 mmol, 1.0 equiv) and cyclopropane **34d** (0.43 mmol, 1.0 equiv) and nitrosobenzene **32a** (0.43 mmol, 1.0 equiv) in DCE (3 mL) was added $Yb(OTf)_3$ (0.043 mmol, 0.1 equiv) and stirred for 15 min. The mixture was heated to reflux for 3 h then concentrated after consumption of cyclopropane (as indicated by TLC) and directly loaded onto a packed SiO_2 column. The products were purified by flash chromatography (9:1 hexanes/EtOAc).

Chapter 3 - Cycloadditions of Donor-Acceptor Cyclopropanes with Azo Dicarboxylates

3.1 Introduction

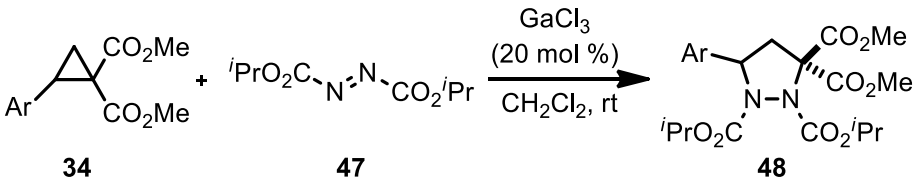
In 2007, Armin de Meijer reported the successful reaction between cyclopropanes and azo dicarboxylates, which give rise to pyrazolidine derivatives (Scheme 3.1). After testing several Lewis acids, $GaCl_3$ was found to catalyze the reaction, and only trace amounts of product were formed using $Yb(OTf)_3$. When *trans*-configured diazenes are used, insertion into the cyclopropane ring proceeds with complete regioselectivity to produce the expected 5-arylpyrazolidine-1,2,3,3-tetracarboxylates. The *trans*-configured diazenes used were naturally existing mixtures of minor amounts of *cis*- and major amounts of the thermodynamically favoured *trans*-diastereomers. The reactivity of cyclopropanes towards a fixed *cis*-configuration of the N,N double bond was also investigated. Interestingly, when 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) was used as a *cis*-configured diazene, two possible regioisomeric pyrazolidine derivatives were formed in ratios varying from 1:1.5 to 1:3.[22]



Scheme 3.1 Cycloaddition of DA cyclopropanes with azo dicarboxylates

3.2 Cycloadditions of DA Cyclopropanes with *trans*-Diazenes

The [3+2] cycloaddition reaction of cyclopropanes with *trans*-configured diazenes as seen in Scheme 3.2 was examined in order to investigate the mechanism and hopefully provide a deeper understanding of how cyclopropanes react with nitrogen-heteroatom double bonded compounds. This mode of reactivity may show resemblance to the opening of cyclopropanes with nitrosoarenes, so a cross-over experiment was performed in order to probe the mechanism of the following reaction.



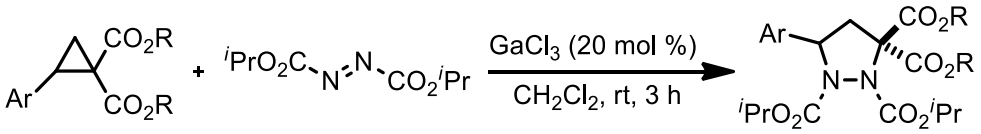
34 **47** **48**

Scheme 3.2 Cycloaddition of DA cyclopropanes with *trans*-diazenes

3.2.1 Cross-Over Experiment #2

To obtain experimental evidence that *trans*-configured diazenes open the cyclopropane ring in a nucleophilic manner, paralleling what happens with nitrosoarenes, a cross-over experiment would have to contain two different cyclopropanes in order to show that a cross-over event occurred. For this cross-over experiment, four different cyclopropanes were used so that four different pyrazolidine standards could be generated, accounting for the possible cross-over based products (Table 3.1). After obtaining the four pyrazolidine standards, the cross-over experiment was performed and the reaction mixture was analyzed.

Table 3.1 Cycloaddition of DA cyclopropanes with *trans*-diazenes

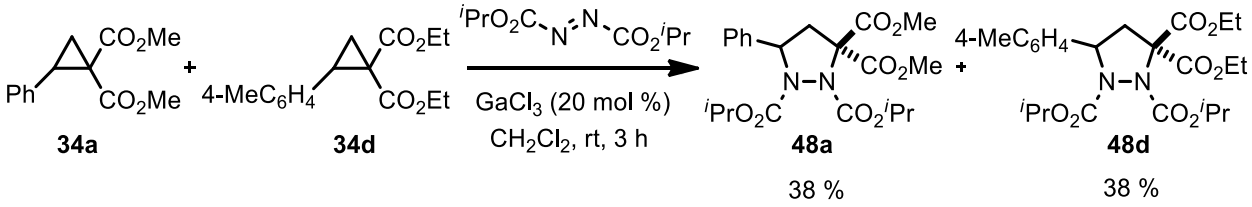


34 **47** **48**

Entry[a]	Cyclopropane	Product	Yield (%)[b]
1	Ar = C_6H_5, R = Me	**48a**	58
2	Ar = 4-MeC_6H_4, R = Me	**48b**	50
3	Ar = C_6H_5, R = Et	**48c**	23
4	Ar = 4-MeC_6H_4, R = Et	**48d**	52

[a] Typical reaction conditions: To a solution of $GaCl_3$ in CH_2Cl_2 (0.8 mL) at room temperature, was added cyclopropane (0.21 mmol) and *trans*-diazene (0.29 mmol). Reactions were monitored by TLC until cyclopropane was consumed. [b] Isolated yield.

Separation of the reaction mixture was performed using column chromatography and only two products had formed, as seen in Scheme 3.3.

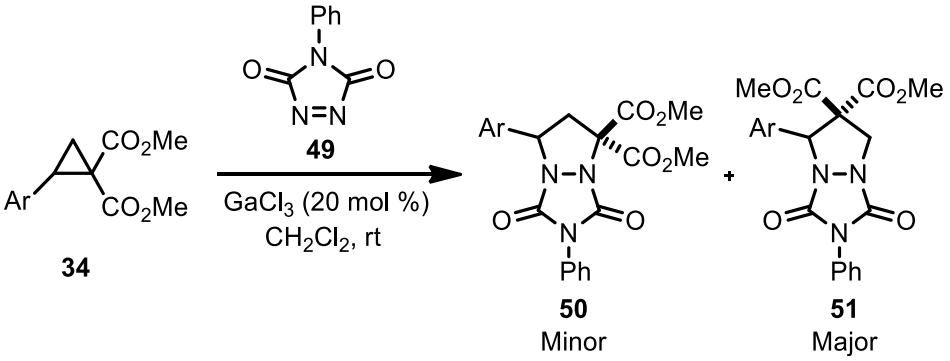


Scheme 3.3 Cross-over experiment of DA cyclopropanes with *trans*-diazenes

The expected [3+2] cycloaddition products were observed with no cross-over. This provides evidence of a straight forward [3+2] cycloaddition with nothing unusual observed with *trans*-diazenes.

3.3 Cycloadditions of DA Cyclopropanes with *cis*-Diazenes

The cycloaddition product from DA cyclopropane and *cis*-configured diazene PTAD produces an unusual pyrazolidine derivative, which may have arisen from insertion into the C(2)-C(3) bond of the cyclopropane (Scheme 3.4). Because of this surprisingly different mode of cyclopropane reactivity, the reaction of DA cyclopropanes with *trans*-diazenes must operate through a different type of mechanism than *cis*-diazenes. A cross-over experiment was performed to investigate how this unusual pyrazolidine derivative product was formed. Understanding how cyclopropanes can undergo this rare insertion into the C(2)-C(3) bond would be useful for its application in synthesis.



Scheme 3.4 Cycloaddition of DA cyclopropanes with *cis*-diazenes

A mechanism was proposed by de Meijer to account for the unusual reactivity of the DA cyclopropane when it encounters the Lewis activated *cis*-diazene (Figure 3.1). It would be very difficult to prove how this reaction proceeds without the use of a cross-over experiment.

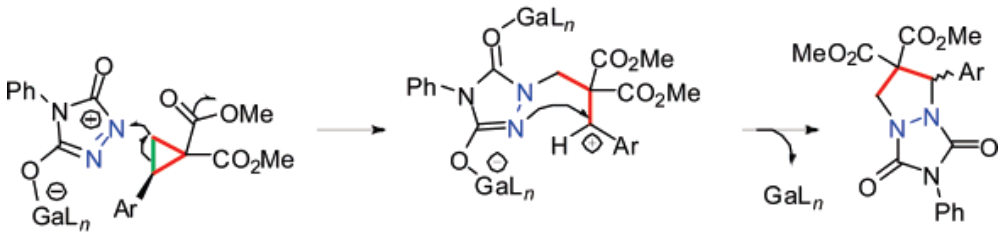
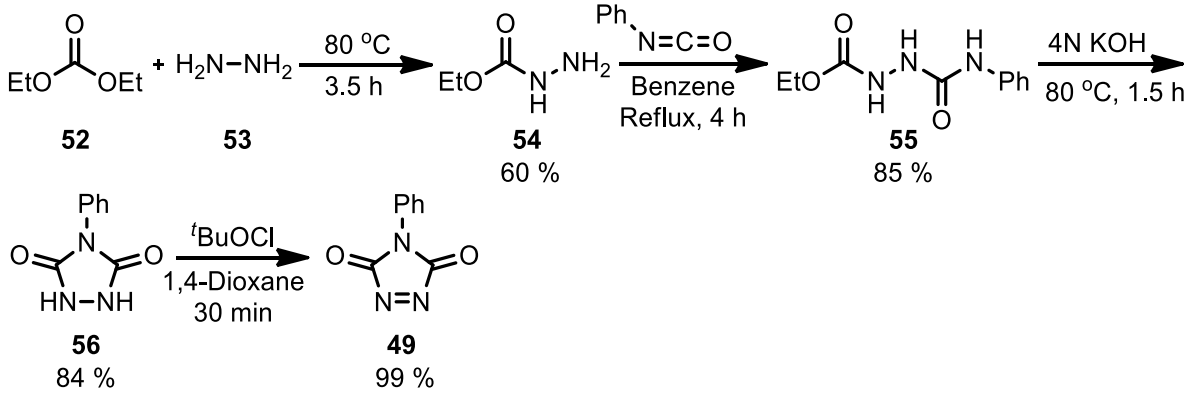


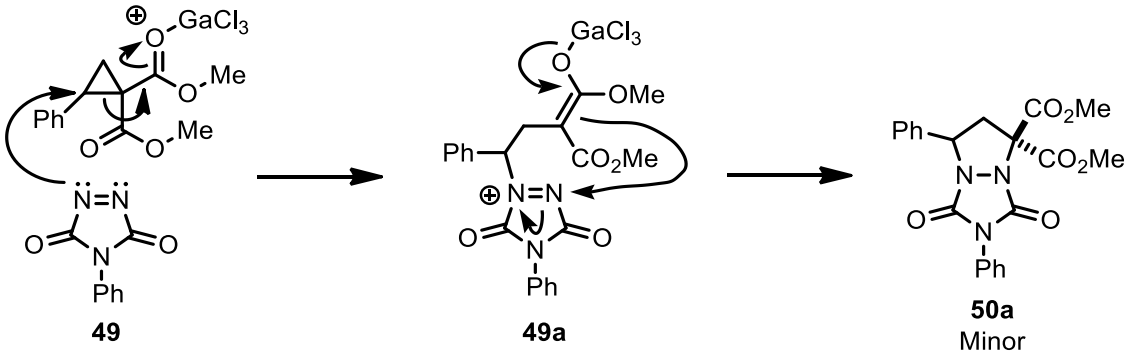
Figure 3.1 Proposed mechanism for the cycloaddition of DA cyclopropane with *cis*-diazene

PTAD was synthesized according to Scheme 3.5 for use in a cross-over experiment and also to generating standards used to analyze the reaction mixture.

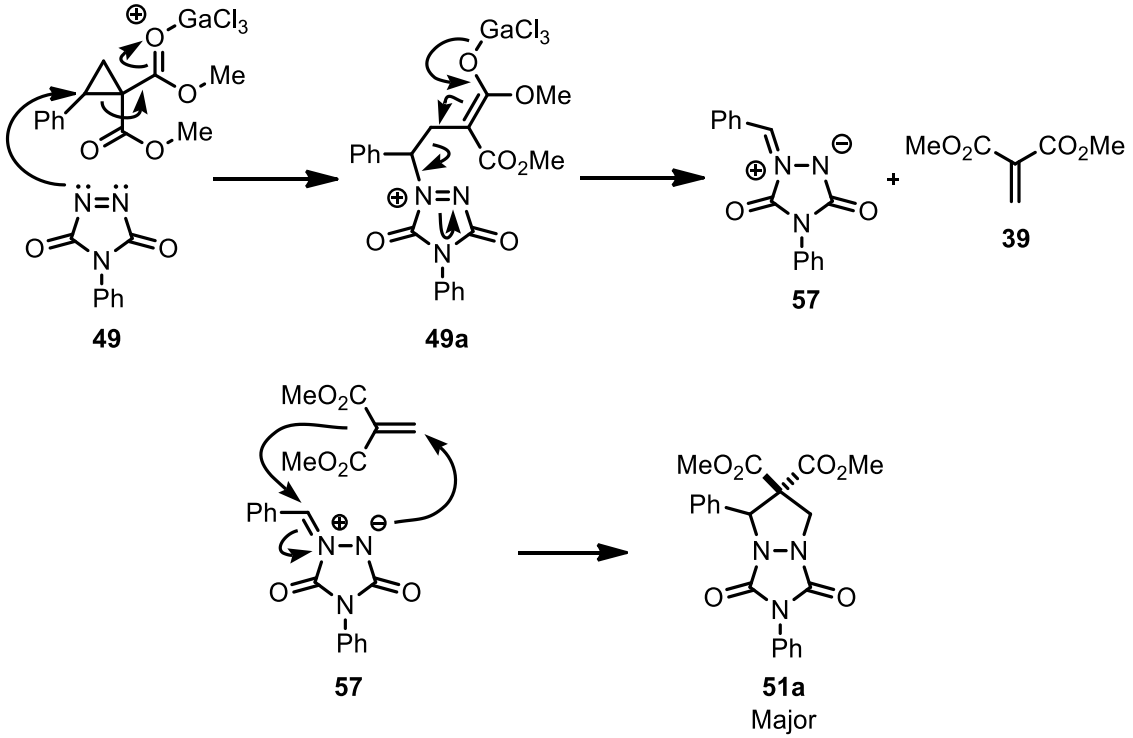


Scheme 3.5 Synthesis of PTAD

The cycloaddition of DA cyclopropanes with *cis*-diazenes was investigated so that it may be applied to understanding and advancing the nitrosoarene chemistry if experimental evidence suggests similarities. Possible reaction mechanisms that accounts for both products are shown in Scheme 3.6 and 3.7, demonstrating a possible resemblance to the cycloaddition of DA cyclopropanes with nitrosoarene mechanism. The first mechanism shows the cycloaddition leading to the minor product operating through a step-wise sequence.



Scheme 3.6 Proposed mechanism for the formation of minor product **50a**

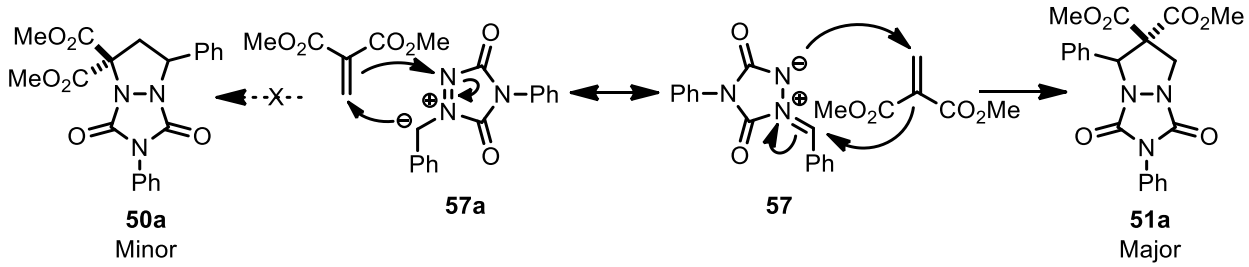


Scheme 3.7 Proposed mechanism for the formation of major product **51a**

Co-ordination of $Yb(OTf)_3$ to the di-ester group on the cyclopropane may allow for a nucleophilic ring opening attack from a nitrogen in PTAD. The mechanism in scheme 3.6 shows formation of the minor product going through a step-wise cyclization, once the acyclic zwitterionic intermediate is formed. Because the presented cyclization is going through a 5-Endo-Trig reaction,

which is disallowed according to Baldwin's rules, the cyclization may be going through a concerted cycloaddition. Scheme 3.7 and 3.8 illustrate that production of the major product may occur through the formation of an azomethine imine intermediate (**57**).

The formation of azomethine imines through the reaction of DA cyclopropanes with *cis*-diazenes has been of interest in the Pagenkopf group and experimental evidence supporting this theory would be of interest not only for understanding the reaction, but in the future development of new reaction types and reaction partners with DA cyclopropanes.



Scheme 3.8 Formation of the two different pyrazolidine *regio*-isomers

Major product **51a** must be coming from azomethine imine **57,** which would have a slightly higher degree of stability or population in comparison to the resonance structure **57a** (Scheme 3.8). The resonance structure, in which the negative charge ends up on nitrogen instead of carbon, would be the more favoured intermediate (**57**) and would therefore contribute to the major product, which is observed to be the case. A resonance structure that places a negative charge on carbon of the azomethine imine (**57a**) is possible, but is not considered to be a nucleophilic centre based on the *regio*-selectivity of other observed azomethine imine reactions. It is therefore highly unlikely that the minor product would be occurring through this type of pathway, and is most likely the result of a formal [3+2] cycloaddition with azomethine imine **57**.

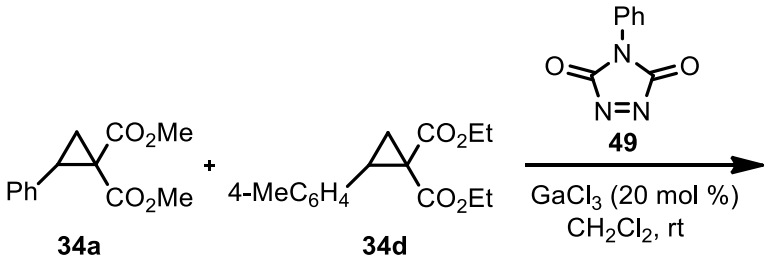
This mode of reactivity would require only one equivalent of DA cyclopropane to one equivalent of the *cis*-diazene because the α,β-unsaturated di-ester may be incorporated into the product. This is slightly different than the nitrosoarene reaction with DA cyclopropanes, because the α,β-unsaturated di-ester is just a by-product and is not incorporated into the tetrahydro-1,2-oxazine product. It is worth determining if the minor product is formed from incorporation of the α,β-unsaturated di-ester unit, or if it is simply a straight-forward cyclization as presented in scheme

2.6. The use of a cross-over experiment would be of great benefit in helping to answer how the two different *regio*-isomers are formed.

Understanding the different ways that DA cyclopropanes react with various dipolarophiles has been undertaken with the hope of developing better and more efficient methods of generating diverse heterocycles. Developing reactions than are able to insert different functional groups into the C(2)-C(3) bond of the cyclopropane ring would have many advantages, and understanding this rare type of reactivity is currently being investigated with the use of cross-over experiments. Being able to open the cyclopropane ring in a controlled manner that allows for different regio-isomers to from is attractive and expands the use of DA cyclopropanes in synthetic chemistry.

3.3.1 Cross-over Experiment #3

Two different cyclopropanes were used as starting material and reacted with PTAD under $GaCl_3$ catalytic conditions (Scheme 3.9). The production of a cross-over based pyrazolidine product would give information about how this reaction mechanism is happening. If results show the presence of a pyrazolidine product, in which cross-over has occurred, then the reaction may be taking place in a way that is similar to the cycloaddition of DA cyclopropanes with nitrosoarenes reaction.



Scheme 3.9 Cross-over experiment of DA cyclopropanes with *cis*-diazenes

The four products shown in Figure 3.2 are expected to be in the reaction mixture of the cross-over experiment. These products would arise from the known reactivity of the two DA cyclopropanes reacting with PTAD, and show no crossing-over.

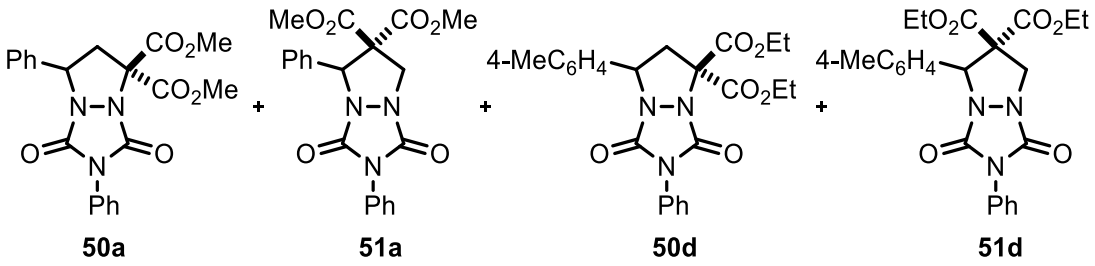


Figure 3.2 Expected products from the cross-over experiment

If additional products are formed, showing that cross-over had occurred, then this provides mechanistic information that would be helpful in generating a theoretical mechanism with supporting evidence. Formation of any of the products shown in Figure 3.3 would be the result of a cross-over event happening in the reaction.

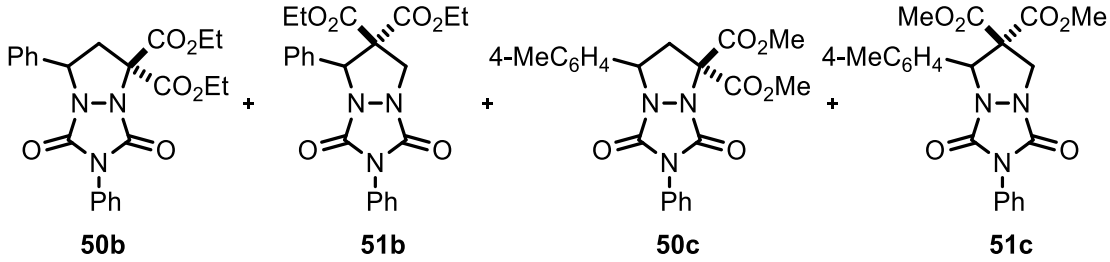
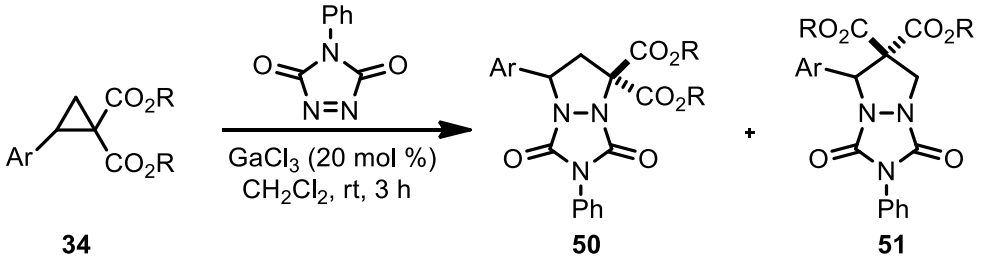


Figure 3.3 Proposed cross-over based products from the cross-over experiment

If DA cyclopropanes react with nitrosoarenes and *cis*-diazenes in a similar fashion, in which a nitrogen-heteroatom double bond opens up the cyclopropane ring, and can be reinforced with experimental evidence, then other reaction types may be discovered by investigating this mode of reactivity. I synthesized the required pyrazolidine standards individually using the methodology presented in de Meijer's study. Table 3.2 shows the synthesis of 8 pyrazolidine standards, which were then used as authentic standards in cross-over experiment #3.

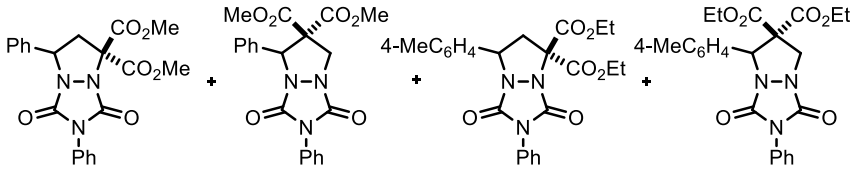
Table 3.2 Synthesis of pyrazolidine standards



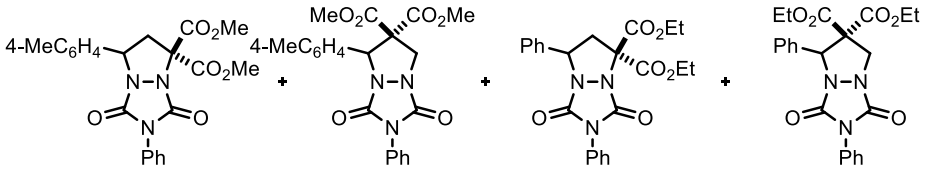
Entry[a]	Cyclopropane	Product	Yield (%)[b]
1	Ar = C_6H_5, R = Me	**50a**	13
2	Ar = C_6H_5, R = Me	**51a**	20
3	Ar = C_6H_5, R = Et	**50b**	19
4	Ar = C_6H_5, R = Et	**51b**	22
5	Ar = 4-MeC_6H_4, R = Me	**50c**	21
6	Ar = 4-MeC_6H_4, R = Me	**51c**	12
7	Ar = 4-MeC_6H_4, R = Et	**50d**	12
8	Ar = 4-MeC_6H_4, R = Et	**51d**	12

[a] Typical reaction conditions: $GaCl_3$ was added to a solution of cyclopropane (0.21 mmol) and PTAD (0.21 mmol) in CH_2Cl_2 (0.2 mL). Reactions were monitored by TLC. [b] Isolated yield.

A detailed analysis of the products from cross-over experiment #3, as seen in Figure 3.4, was achieved with the use of NMR and GC-MS. After carefully analyzing the reaction mixture of the cross-over experiment, it was revealed that all four expected products were formed and, in addition, two of the cross-over products were also formed, yielding six products in total.



Product	**50a**	**51a**	**50d**	**51d**
Retention Time (min): Standard	17.497	17.073	19.438	19.159
Retention Time (min): Cross-Over Exp.	17.572	17.122	19.574	19.267



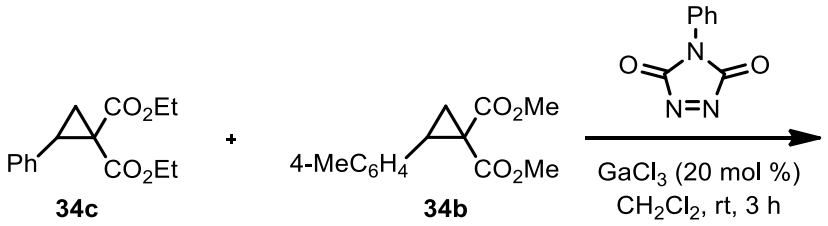
	Not Formed		Not Formed	
Product	**50c**	**51c**	**50b**	**51b**
Retention Time (min): Standard	18.788	18.173	18.297	18.096
Retention Time (min): Cross-Over Exp.	-	18.271	-	18.142

Figure 3.4 Results of cross-over experiment #3

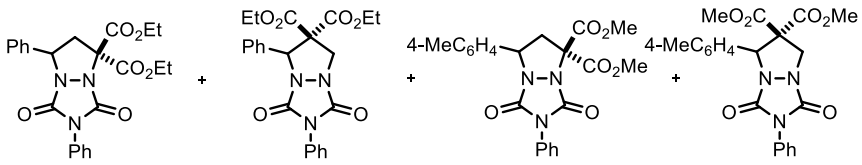
Formation of the cross-over based products provide key mechanistic information that is in agreement with the reaction proceeding via an azomethine imine as illustrated in Scheme 3.7. The azomethine imine can react with either the dimethyl or diethyl α,β-unsaturated ester to yield **51c** or **51b,** respectively. The absence of the other cross-over based products from the reaction mixture is in agreement with the proposed mechanism.

3.3.2 Cross-over Experiment #3 Reversed

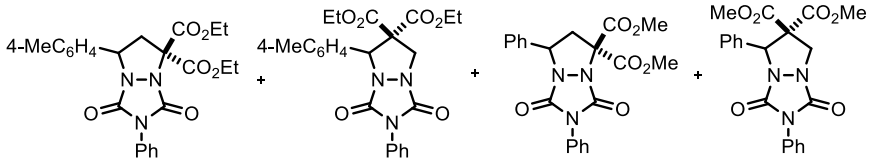
To achieve additional supporting evidence, the reaction was run in reverse, starting with cross-over based cyclopropanes (Scheme 3.10) and observing the reaction mixture to see if cross-over was happening in a reproducible event. The reverse cross-over experiment was repeated three times to provide reinforcing data, as seen in Figure 3.5. This generated reproducible results that are in agreement with the original proposed mechanism.



Scheme 3.10 Reversed cross-over experiment of DA cyclopropanes with *cis*-diazenes



Product	**50b**	**51b**	**50c**	**51c**
Retention Time (min): Cross-Over Exp.	18.2	18.1	18.8	18.3
Run #2	18.230	18.059	18.778	18.230
Run #3	18.196	18.049	18.754	18.196

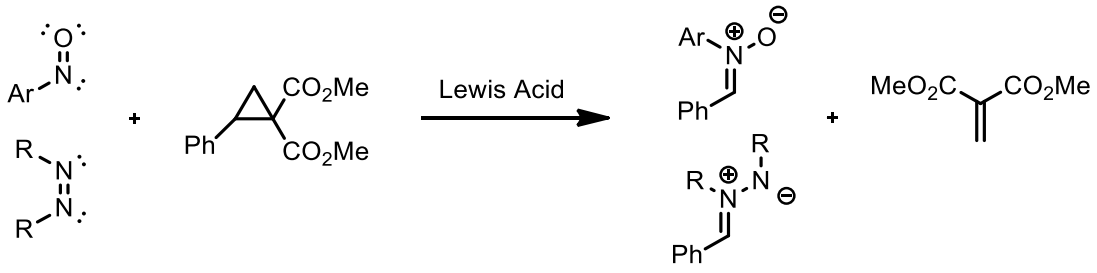


Product	Not Formed	**51d**	Not Formed	**51a**
Retention Time (min): Cross-Over Exp.	**50d**	19.1	**50a**	17.1
Run #2	-	19.118	-	17.038
Run #3	-	19.109	-	17.032

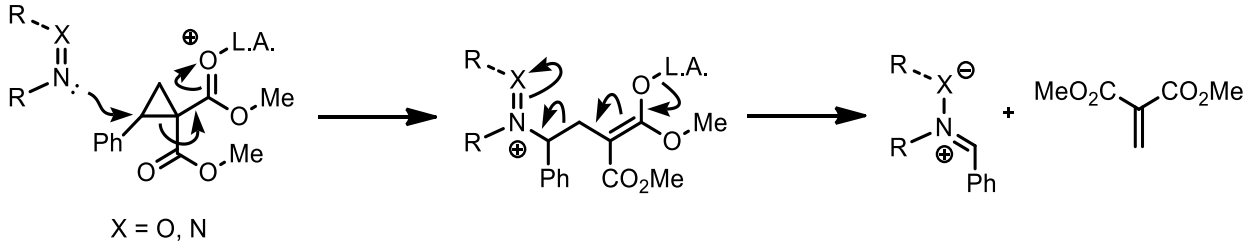
Figure 3.5 Results of reversed cross-over experiment #3

The results from cross-over experiments 1 and 3 (Scheme 3.11 and 3.12) show similarities in the reaction of 1,1-cyclopropane diesters with nitrosoarenes and *cis*-diazenes. The overall pattern of reactivity is the same as both reactions led to the production of a 1,3-dipole intermediate. In the case of nitrosoarenes, a nitrone was produced. In the case of *cis*-diazenes, an azomethine imine was produced. In both cases the functional group is a nitrogen-heteroatom double bond, with a lone pair on nitrogen attacking as a nucleophile to open up the activated DA cyclopropane. The

resulting intermediate undergoes fragmentation forming a 1,3-dipole and an α,β-unsaturated diester.



Scheme 3.11 Reaction of nitrosoarenes and *cis*-diazenes with DA cyclopropanes



Scheme 3.12 Mechanistic formation of 1,3-dipoles

Additional experimentation may show that other heteroatoms could react in a similar fashion, paving the way for new reactions and other reaction partners for DA cyclopropanes. In the case of nitrogen, which is a Group 5 element, trying elements in the same column such as phosphorus, may lead to new reactions because of similarities in the electronic structure of the two elements.

A potential avenue for investigation could include obtaining a compound with a nitrogen-phosphorus double bond and observing the ability of the sp^2 hybridized nitrogen to undergo nucleophilic opening of a DA cyclopropane ring, followed by fragmentation into a 1,3-dipole and an α,β-unsaturated diester. A proper Lewis Acid would be needed to activate the DA cyclopropane, with the idea of undergoing a reaction similar to Scheme 3.12, except using X = phosphorus.

Another experiment could attempt trying elements in the same column as oxygen, such as sulfur. Obtaining a compound with a nitrogen-sulfur double bond would allow for reactions to study the nucleophilicity of the sp^2 hybridized nitrogen towards the opening of DA cyclopropane rings upon activation by Lewis Acids, similar to Scheme 2.12, except using X = sulfur.

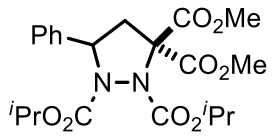
3.4 Experimental

The procedures and conditions were the same as described in section 2.3.

3.5 Supporting Information

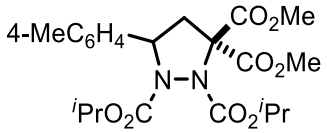
General *trans*-Diazene Cycloaddition Procedure

To a solution of cyclopropane (0.21 mmol, 1.0 equiv) and diisopropyl azodicarboxylate (0.29 mmol, 1.4 equiv) in CH_2Cl_2 (0.2 mL) was added a solution of $GaCl_3$ (0.04 mmol, 0.2 equiv) in CH_2Cl_2 (0.8 mL). After stirring for 3 h, the crude mixture was concentrated and directly loaded onto a packed SiO_2 column. Product was purified by flash chromatography (8:1 hexanes/EtOAc) to afford the corresponding cycloadducts.



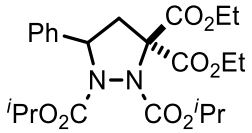
1,2-Diisopropyl 3,3-dimethyl 5-phenylpyrazolidine-1,2,3,3-tetracarboxylate (48a)

The general *trans*-diazene cycloaddition procedure was followed using cyclopropane **34a** (50 mg, 0.21 mmol), diisopropyl azodicarboxylate **47** (59 mg, 0.29 mmol) and $GaCl_3$ (7 mg, 0.040 mmol) to yield the compound as a yellow oil (53 mg, 58%). R_f 0.22 (3:1 Hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) 7.39 (app d, J = 7.8 Hz, 2 H), 7.29 - 7.34 (m, 2 H), 7.22 - 7.26 (m, 1 H), 5.46 (dd, J = 8.2, 3.9 Hz, 1 H), 5.02 (hept, J = 6.3 Hz, 1 H), 4.97 (hept, J = 6.3 Hz, 1 H), 3.82 (s, 3 H), 3.47 (s, 3 H), 3.30 (dd, J = 13.3, 8.2 Hz, 1 H), 2.92 (dd, J = 13.3, 3.9 Hz, 1 H), 1.24 - 1.30 (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) 168.8, 166.5, 156.9, 153.3, 139.5, 128.3, 127.3, 125.8, 72.4, 70.8, 70.5, 61.2, 53.4, 53.0, 44.7, 22.1, 21.9; HRMS $C_{21}H_{28}N_2O_8$ Calculated = 436.1846, Found = 436.1841



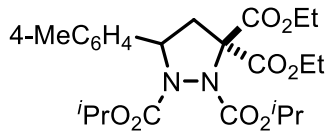
1,2-Diisopropyl 3,3-dimethyl 5-p-tolylpyrazolidine-1,2,3,3-tetracarboxylate (48b)

The general *trans*-diazene cycloaddition procedure was followed using cyclopropane **34b** (55 mg, 0.22 mmol), diisopropyl azodicarboxylate **47** (63 mg, 0.31 mmol) and $GaCl_3$ (7 mg, 0.040 mmol) to yield the compound as a yellow oil (50 mg, 50%). R_f 0.25 (3:1 Hexanes:EtOAc); ^1H NMR (400 MHz, $CDCl_3$) 7.27 (app d, J = 8.2 Hz, 2 H), 7.12 (app d, J = 8.2 Hz, 2 H), 5.40 (dd, J = 8.2, 4.3 Hz, 1 H), 5.01 (hept, J = 6.3 Hz, 1 H), 4.98 (hept, J = 6.3 Hz, 1 H), 3.82 (s, 3 H), 3.51 (s, 3 H), 3.27 (dd, J = 13.3, 8.2 Hz, 1 H), 2.90 (dd, J = 13.3, 4.3 Hz, 1 H), 2.32 (s, 3 H), 1.24 - 1.30 (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) 168.8, 166.4, 156.9, 153.4, 136.9, 136.5, 129.0, 125.8, 72.5, 70.7, 70.5, 61.0, 53.4, 53.0, 44.7, 22.1, 21.9; HRMS $C_{22}H_{30}N_2O_8$ Calculated = 450.2002, Found = 450.1999



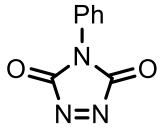
3,3-Diethyl 1,2-diisopropyl 5-phenylpyrazolidine-1,2,3,3-tetracarboxylate (48c)

The general *trans*-diazene cycloaddition procedure was followed using cyclopropane **34c** (50 mg, 0.19 mmol), diisopropyl azodicarboxylate **47** (55 mg, 0.27 mmol) and $GaCl_3$ (7 mg, 0.040 mmol) to yield the compound as a yellow oil (20 mg, 23%). R_f 0.30 (3:1 Hexanes:EtOAc); ^1H NMR (400 MHz, $CDCl_3$) 7.38 - 7.42 (m, 2 H), 7.29 - 7.33 (m, 2 H), 7.22 - 7.25 (m, 1 H), 5.50 (dd, J = 8.2, 3.5 Hz, 1 H), 5.02 (hept, J = 6.3 Hz, 1 H), 4.98 (hept, J = 6.3 Hz, 1 H), 4.29 (dddd, J = 7.0, 7.0, 7.0, 10.5 Hz, 2 H), 3.90 (dddd, J = 7.2, 7.2, 7.2, 10.8 Hz, 2 H), 3.33 (dd, J = 13.3, 8.6 Hz, 1 H), 2.90 (dd, J = 13.3, 3.1 Hz, 1 H), 1.24 - 1.34 (m, 15 H), 0.91 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 168.2, 166.2, 156.9, 153.1, 139.7, 128.3, 127.2, 125.8, 72.3, 70.8, 70.4, 62.4, 62.1, 61.2 44.5, 22.1, 21.9, 21.7, 14.0, 13.3; HRMS $C_{23}H_{32}N_2O_8$ Calculated = 464.2159, Found = 464.2167



3,3-Diethyl 1,2-diisopropyl 5-(p-tolyl)pyrazolidine-1,2,3,3-tetracarboxylate (48d)

The general *trans*-diazene cycloaddition procedure was followed using cyclopropane **34d** (50 mg, 0.18 mmol), diisopropyl azodicarboxylate **47** (51 mg, 0.25 mmol) and $GaCl_3$ (6 mg, 0.036 mmol) to yield the compound as a yellow oil (45 mg, 52%). R_f 0.31 (3:1 Hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) 7.28 (app d, J = 8.2 Hz, 2 H), 7.11 (app d, J = 8.2 Hz, 2 H), 5.45 (dd, J = 8.2, 3.5 Hz, 1 H), 5.01 (hept, J = 6.3 Hz, 1 H), 4.97 (hept, J = 6.3 Hz, 1 H), 4.28 (dddd, J = 7.0, 7.0, 7.0, 10.5 Hz, 2 H), 3.93 (dddd, J = 7.2, 7.2, 7.2, 10.8 Hz, 2 H), 3.29 (dd, J = 13.3, 8.2 Hz, 1 H), 2.88 (dd, J = 13.3, 3.5 Hz, 1 H), 2.31 (s, 3 H), 1.23 - 1.34 (m, 15 H), 0.95 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 168.2, 166.2, 156.9, 153.2, 136.8, 136.7, 128.9, 125.8, 72.4, 70.7, 70.3, 62.4, 62.2, 61.0, 44.5, 22.1, 21.9, 21.0, 14.0, 13.3; HRMS $C_{24}H_{34}N_2O_8$ Calculated = 478.2315, Found = 478.2321

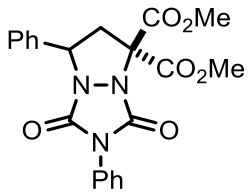


(PTAD) 4-Phenyl-1,2,4-trizaoline-3,5-dione (49)

tert-Butyl hypochlorite (130 mg, 1.2 mmol, 1.1 equiv) was added drop wise with stirring to a solution of 4-phenyl-1,2,4-trizaolidine-3,5-dione (200 mg, 1.1 mmol, 1.0 equiv) in 1,4-dioxane (5 mL). After 30 min the solvent was removed under reduced pressure keeping the temp below 40°C to yield the product as a red solid (200 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) 7.46 - 7.59 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) 129.9, 129.5, 123.9

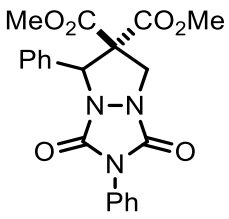
General *cis*-Diazene Cycloaddition Procedure

To a solution of cyclopropane (0.85 mmol, 1.0 equiv) and PTAD (1.7 mmol, 2.0 equiv) in CH_2Cl_2 (4.0 mL) was added a solution of $GaCl_3$ (0.17 mmol, 0.2 equiv) in CH_2Cl_2 (1.0 mL). After stirring for 3 h, the crude mixture was concentrated and directly loaded onto a packed SiO_2 column. Product was purified by flash chromatography (8:1 hexanes/EtOAc) to afford the corresponding cycloadducts.



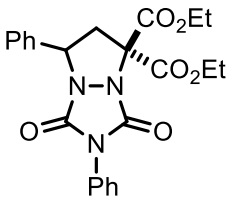
Dimethyl 1,3-dioxo-2,7-diphenyltetrahydropyrazolo[1,2-a][1,2,4]triazole-5,5(1H)-dicarboxylate (50a)

The general *cis*-diazene cycloaddition procedure was followed using cyclopropane **34a** (200 mg, 0.85 mmol), *cis*-diazene **49** (298 mg, 1.7 mmol) and $GaCl_3$ (30 mg, 0.17 mmol) to yield the compound as a white solid (45 mg, 13%). R_f 0.40 (3:1 Hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) 7.51 - 7.55 (m, 2 H), 7.33 - 7.47 (m, 8 H), 5.19 (dd, J = 9.0, 7.4 Hz, 1 H), 3.92 (s, 3 H), 3.87 (s, 3 H), 3.28 (d, J = 3.1 Hz, 1 H), 3.25 (d, J = 5.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) 167.0, 165.7, 153.6, 136.6, 131.5, 129.1, 128.7, 128.3, 126.2, 125.7, 70.7, 59.3, 54.4, 54.0, 46.9; HRMS $C_{21}H_{19}N_3O_6$ Calculated = 409.1274, Found = 409.1264



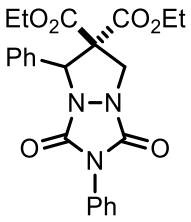
Dimethyl 1,3-dioxo-2,5-diphenyltetrahydropyrazolo[1,2-a][1,2,4]triazole-6,6(1H)-dicarboxylate (51a)

The general *cis*-diazene cycloaddition procedure was followed using cyclopropane **34a** (200 mg, 0.85 mmol), *cis*-diazene **49** (298 mg, 1.7 mmol) and $GaCl_3$ (30 mg, 0.17 mmol) to yield the compound as a white solid (71 mg, 20%). R_f 0.45 (3:1 Hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) 7.48 - 7.50 (m, 4 H), 7.32 - 7.42 (m, 6 H), 5.85 (s, 1 H), 4.46 (d, J = 13.3 Hz, 1 H), 4.28 (d, J = 13.3 H, 1 H), 3.81 (s, 3 H), 3.47 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 169.7, 164.8, 156.6, 156.3, 134.9, 131.6, 129.2, 129.1, 128.7, 128.5, 127.3, 126.0, 66.0, 65.3, 54.1, 52.8, 49.8; HRMS $C_{21}H_{19}N_3O_6$ Calculated = 409.1274, Found = 409.1264



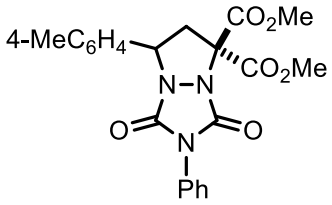
Diethyl 1,3-dioxo-2,7-diphenyltetrahydropyrazolo[1,2-a][1,2,4]triazole-5,5(1H)-dicarboxylate (50b)

The general *cis*-diazene cycloaddition procedure was followed using cyclopropane **34c** (50 mg, 0.19 mmol), *cis*-diazene **49** (67 mg, 0.38 mmol) and $GaCl_3$ (7 mg, 0.040 mmol) to yield the compound as a white solid (16 mg, 19%). R_f 0.60 (1:1 Hexanes:EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) 7.51 - 7.54 (m, 2 H), 7.43 - 7.45 (m, 4 H), 7.39 - 7.41 (m, 2 H), 7.33 - 7.36 (m, 2 H), 5.16 (dd, J = 9.4, 7.6 Hz, 1 H), 4.37 (dddd, J = 7.0, 7.0, 7.0, 10.5 Hz, 2 H), 4.33 (q, J = 7.0 Hz, 2 H), 3.27 (dd, J = 13.5, 7.6 Hz, 1 H), 3.25 (dd, J = 13.5, 8.8 Hz, 1 H), 1.33 (t, J = 7.0 Hz, 3 H), 1.31 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 166.6, 165.1, 153.5, 153.2, 136.8, 131.6, 129.1, 129.0, 128.7, 128.2, 126.2, 125.7, 70.9, 63.8, 63.3, 59.2, 46.8, 14.0, 13.9; HRMS $C_{23}H_{23}N_3O_6$ Calculated = 437.1587, Found = 437.1582



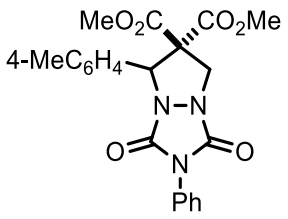
Diethyl 1,3-dioxo-2,5-diphenyltetrahydropyrazolo[1,2-a][1,2,4]triazole-6,6(1H)-dicarboxylate (51b)

The general *cis*-diazene cycloaddition procedure was followed using cyclopropane **34c** (50 mg, 0.19 mmol), *cis*-diazene **49** (67 mg, 0.38 mmol) and $GaCl_3$ (7 mg, 0.040 mmol) to yield the compound as a white solid (18 mg, 22%). R_f 0.70 (1:1 Hexanes:EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) 7.45 - 7.51 (m, 4 H), 7.35 - 7.40 (m, 6 H), 5.84 (s, 1 H), 4.47 (d, J = 12.9 Hz, 1 H), 4.31 (d, J = 12.9 Hz, 1 H), 4.23 - 4.31 (m, 2 H), 3.99 (dddd, J = 7.3, 7.3, 7.3, 10.9 Hz, 1 H), 3.83 (dddd, J = 7.0, 7.0, 7.0, 10.5 Hz, 1 H), 1.25 (t, J = 7.0 Hz, 3 H), 1.07 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 164.4, 156.5, 135.1, 129.2, 129.0, 128.6, 128.4, 127.5, 125.9, 81.3, 65.9, 63.3, 62.2, 49.8, 13.8, 13.6; HRMS $C_{23}H_{23}N_3O_6$ Calculated = 437.1587, Found = 437.1591



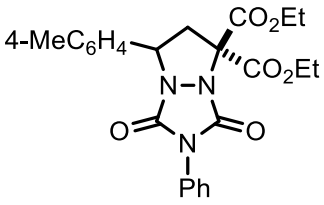
Dimethyl 1,3-dioxo-2-phenyl-7-(p-tolyl)tetrahydropyrazolo[1,2-a][1,2,4]triazole-5,5(1H)-dicarboxylate (50c)

The general *cis*-diazene cycloaddition procedure was followed using cyclopropane **34b** (50 mg, 0.20 mmol), *cis*-diazene **49** (70 mg, 0.40 mmol) and $GaCl_3$ (7 mg, 0.040 mmol) to yield the compound as a white solid (18 mg, 21%). R_f 0.65 (1:1 Hexanes:EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) 7.50 - 7.53 (m, 2 H), 7.42 - 7.45 (m, 2 H), 7.33 - 7.36 (m. 1 H), 7.32 (app d, J = 7.6 Hz, 2 H), 7.20 (app d, J = 7.6 Hz, 2 H), 5.14 (dd, J = 8.2, 8.2 Hz, 1 H), 3.91 (s, 3 H), 3.87 (s, 3 H), 3.25 (d, J = 8.2 Hz, 2 H), 2.35 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 167.0, 165.8, 153.5, 138.6, 131.6, 129.7, 129.0, 128.2, 126.2, 125.7, 70.6, 59.2, 54.3, 54.0, 46.9, 21.1; HRMS $C_{22}H_{21}N_3O_6$ Calculated = 423.1430, Found = 423.1431



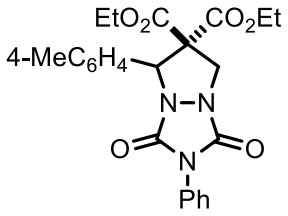
Dimethyl 1,3-dioxo-2-phenyl-5-(p-tolyl)tetrahydropyrazolo[1,2-a][1,2,4]triazole-6,6(1H)-dicarboxylate (51c)

The general *cis*-diazene cycloaddition procedure was followed using cyclopropane **34b** (50 mg, 0.20 mmol), *cis*-diazene **49** (70 mg, 0.40 mmol) and $GaCl_3$ (7 mg, 0.040 mmol) to yield the compound as a white solid (10 mg, 12%). R_f 0.72 (1:1 Hexanes:EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) 7.48 - 7.49 (m, 4 H), 7.38 - 7.41 (m, 1 H), 7.17 - 7.23 (m, 4 H), 5.81 (s, 1 H), 4.46 (d, J = 12.9 Hz, 1 H), 4.30 (d, J = 12.9 Hz, 1 H), 3.80 (s, 3 H), 3.49 (s, 3 H), 2.34 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 169.7, 164.9, 156.2, 139.0, 131.9, 131.6, 129.3, 129.2, 128.4, 127.2, 125.9, 65.9, 65.2, 54.0, 52.8, 49.8, 21.2; HRMS $C_{22}H_{21}N_3O_6$ Calculated = 423.1430, Found = 423.1431



Diethyl 1,3-dioxo-2-phenyl-7-(p-tolyl)tetrahydropyrazolo[1,2-a][1,2,4]triazole-5,5(1H)-dicarboxylate (50d)

The general *cis*-diazene cycloaddition procedure was followed using cyclopropane **34d** (50 mg, 0.18 mmol), *cis*-diazene **49** (63 mg, 0.36 mmol) and $GaCl_3$ (6 mg, 0.036 mmol) to yield the compound as a white solid (10 mg, 12%). R_f 0.60 (5:1 Et_2O:Pentane); ^{1}H NMR (400 MHz, $CDCl_3$) 7.50 - 7.54 (m, 2 H), 7.42 - 7.46 (m, 2 H), 7.33 - 7.37 (m, 3 H), 7.21 (app d, J = 7.8 Hz, 2 H), 5.13 (dd, J = 8.4, 8.4 Hz, 1 H), 4.30 - 4.44 (m, 4 H), 3.24 (d, J = 8.6 Hz, 2 H), 2.35 (s, 3 H), 1.33 (t, J = 7.0 Hz, 3 H), 1.32 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 166.6, 165.2, 153.5, 153.2, 138.6, 133.7, 131.6, 129.7, 129.0, 128.2, 126.2, 125.7, 70.8, 63.8, 63.3, 59.1, 46.8, 21.2, 14.0, 13.9; HRMS $C_{24}H_{25}N_3O_6$ Calculated = 451.1743, Found = 451.1733



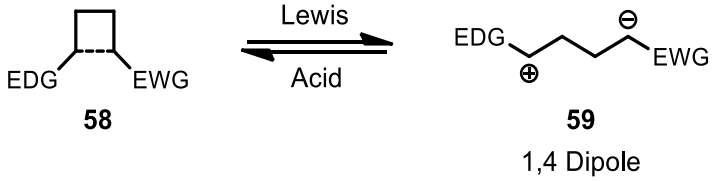
Diethyl 1,3-dioxo-2-phenyl-5-(p-tolyl)tetrahydropyrazolo[1,2-a][1,2,4]triazole-6,6(1H)-dicarboxylate (51d)

The general *cis*-diazene cycloaddition procedure was followed using cyclopropane **34d** (50 mg, 0.18 mmol), *cis*-diazene **49** (63 mg, 0.36 mmol) and $GaCl_3$ (6 mg, 0.036 mmol) to yield the compound as a white solid (10 mg, 12%). R_f 0.70 (5:1 Et_2O:Pentane); ^1H NMR (400 MHz, $CDCl_3$) 7.45 - 7.52 (m, 4 H), 7.34 - 7.41 (m, 1 H), 7.23 - 7.25 (m, 2 H), 7.16 - 7.18 (m, 2 H), 5.81 (s, 1 H), 4.46 (d, J = 13.3 Hz, 1 H), 4.23 - 4.31 (m, 3 H), 3.98 - 4.06 (m, 1 H), 3.80 - 3.88 (m, 1 H), 2.34 (s, 3 H), 1.25 (t, J = 7.0 Hz, 3 H), 1.10 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 169.4, 164.5, 156.5, 156.2, 138.9, 132.0, 131.6, 129.3, 129.2, 128.4, 127.3, 125.9, 120.7, 65.7, 65.4, 63.3, 62.2, 49.8, 21.2, 13.9, 13.6; HRMS $C_{24}H_{25}N_3O_6$ Calculated = 451.1743, Found = 451.1733

Chapter 4 - Cycloadditions of Donor-Acceptor Cyclobutanes with *cis*-Diazenes

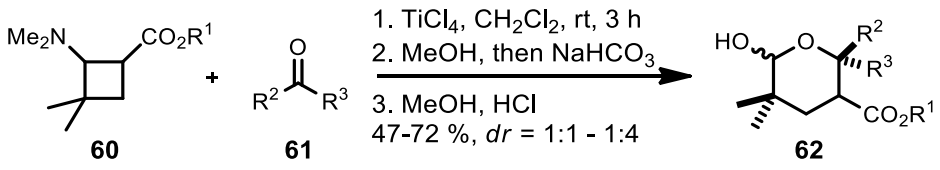
4.1 Introduction

Cyclobutanes have been utilized for various synthetic uses such as ring expansions,[23] metal-catalyzed activation of the carbon-carbon bonds,[24] and Baeyer Villiger oxidations.[25] Because of the unique properties present in cyclobutanes, such as a highly strained ring system, they have been modified into Donor-Acceptor (DA) cyclobutanes in a similar way to DA cyclopropanes. Because the cyclobutane ring system contains four carbon atoms, a 1,4-dipole equivalent (**59**) may be generated under the appropriate conditions as seen in Scheme 4.1.



Scheme 4.1 Reactivity of DA cyclobutanes

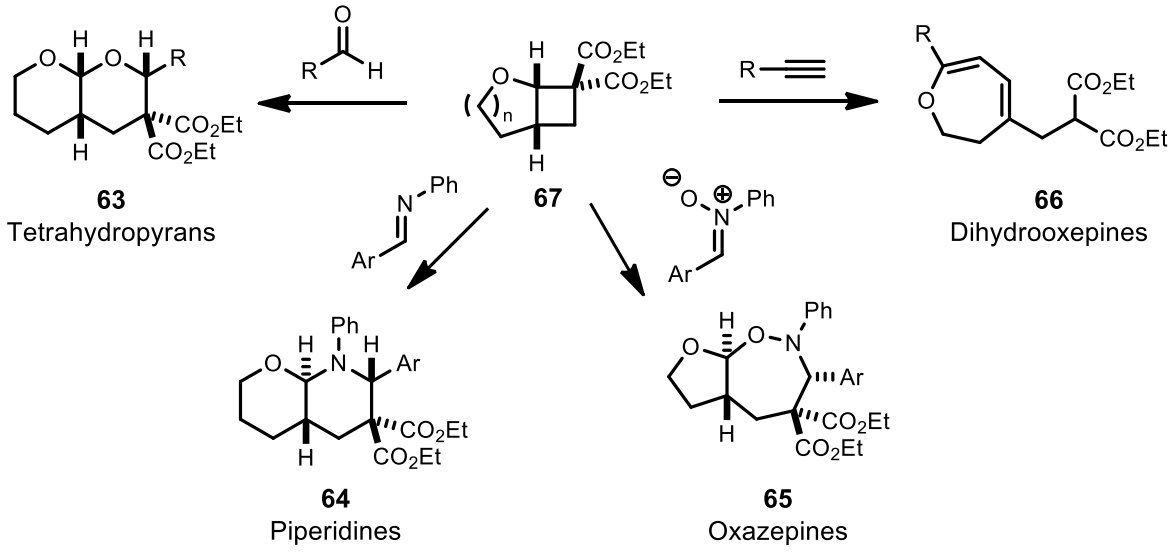
The use of DA cyclobutanes has received less attention than DA cyclopropanes, with the use of DA cyclobutanes starting around 1986.[26] This work later led to the application of DA cyclobutanes in cycloaddition chemistry with seminal work done by Saigo in 1991.[27] Saigo reported that amino-activated cyclobutane mono-ester (**60)** reacted with aldehydes or ketones when treated with $TiCl_4$ to furnish tetrahydropyrans (**62)** in moderate yields and poor diastereoselectivity (Scheme 4.2).



Scheme 4.2 Cycloaddition or DA cyclobutane with aldehydes or ketones

4.1.1 Alkoxy-Activated Cyclobutane Diesters

The Pagenkopf group began experimenting with alkoxy-activated cyclobutane diesters in 2010 because of the similarities to DA cyclopropanes, which have been a focus of interest in the group.[28] Reacting DA cyclobutanes with various dipolarophiles began with first with imines, which was followed by aldehydes. Further work included reacting DA cyclobutanes with acetylenes and nitrones (Scheme 4.3).

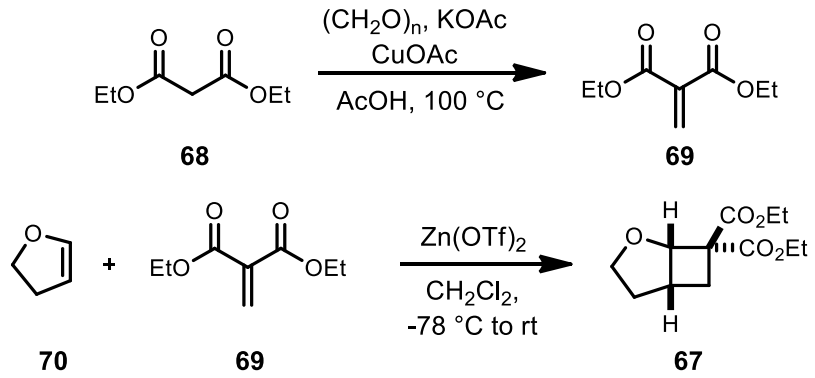


Scheme 4.3 Pagenkopf research of DA cyclobutanes

Under $Yb(OTf)_3$ catalysis, DA cyclobutanes undergo a formal [4+2] cycloaddition with imines to form piperidines (**64**) in a stereoselective manner. A similar type of formal [4+2] cycloaddition is also possible when aldehydes are used as the dipolarophile, and produce tetrahydropyrans (**63**) again in a stereoselective manner.[29] Both of these reactions were discovered in 2010 and it was quickly realized that other dipolarophiles would react in a similar way. In 2011, the formal [4+3] cycloaddition between DA cyclobutanes and nitrones was discovered. This reaction led to oxazepines (**65**) with stereochemistry that can be controlled based on reaction conditions.[30] In the same year it was also discovered that terminal alkynes reacted with DA cyclobutanes in the presence of $BF_3{\cdot}OEt_2$ as the Lewis acid to generate dihydrooxepines (**66**).[31]

4.1.2 Synthesis of DA Cyclobutanes

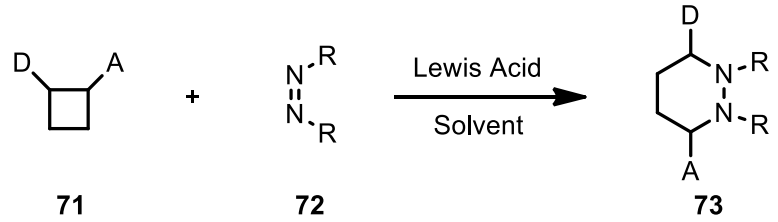
To begin exploring the possibility of cycloadditions occurring between DA cyclobutanes and *cis*-diazenes, it was necessary to work with the appropriate starting materials. The Pagenkopf group's success with alkoxy-activated cyclobutane diesters in other cycloaddition reactions determined them to be a good choice for the DA cyclobutane. The required alkoxy-activated cyclobutane diester was synthesized through a two-step procedure that began with a Knoevenagel condensation of diethyl malonate (**68**) with paraformaldehyde to generate the highly reactive methylidene malonate (**69**). The malonate was then treated with dihydrofuran (**70**) under $Zn(OTf)_2$ catalyzed conditions to afford the desired DA cyclobutane (**67**) as seen in Scheme 4.4.



Scheme 4.4 Two-step synthesis of DA cyclobutanes

4.1.3 Cycloadditions of DA Cyclobutanes with *cis*-Diazenes

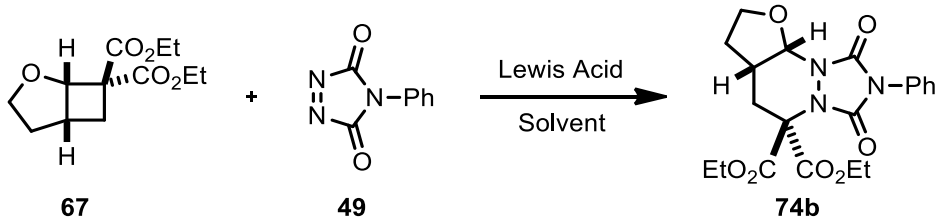
Because the Pagenkopf group was already performing cycloadditions with *cis*-diazenes for DA cyclopropanes, I naturally progressed to trying the same diazene (PTAD) with DA cyclobutanes. PTAD was selected as a desirable *cis*-diazene to work with because of its stability and long shelf-life, and it can be easily synthesized using a straightforward synthetic route. A common problem with other *cis*-diazenes is thermal instability leading to decomposition at room temperature. Finding alternative *cis*-diazenes to undergo cycloaddition reactions with DA cyclobutanes was made difficult due to their instability at room temperature and the limited commercial availability of other *cis*-diazenes.



71 **72** **73**

Scheme 4.5 General cycloaddition of DA cyclobutanes with *cis*-diazenes

The general reaction is shown in scheme 4.5 and the parent molecule generated is a hexahydropyridazine (**73**). Biological assays have shown hexahydropyridazines to exhibit moderate levels of anesthetic, antihistaminic, and anticonvulsive activity.[32] When PTAD is used as the *cis*-diazene, a 5,6,5-ring system is generated through a formal [4+2] cycloaddition with DA cyclobutane (**67**) as seen in Scheme 4.6. These products may potentially serve as a starting point for the synthesis of other useful compounds, and also contain functionality to undergo post-modification.



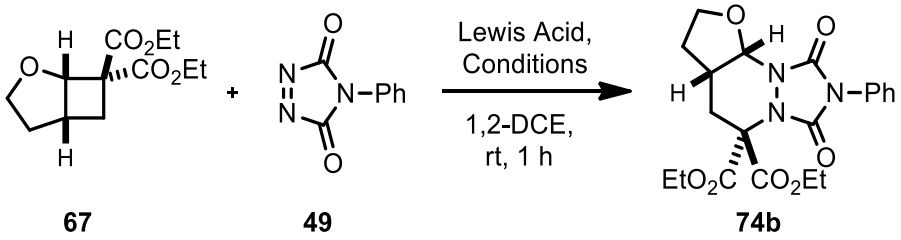
67 **49** **74b**

Scheme 4.6 Cycloaddition of DA cyclobutanes with PTAD

4.2 Results and Discussion

After some experimentation, it was discovered that *cis*-diazenes such as PTAD are indeed a compatible reaction partner for DA cyclobutanes. The [4+2] cycloaddition was achieved using a necessary Lewis acid, and both $GaCl_3$ and $Yb(OTf)_3$ were successful. Optimization of the reaction conditions led to $GaCl_3$ being the better choice for a Lewis acid, with the highest yield occurring at 5 mol % catalytic loading (Table 4.1).

Table 4.1 Cycloaddition of DA cyclobutane with *cis*-diazene



67 **49** **74b**

Entry[a]	Cyclobutane (Equivalents)	*cis*-Diazene (Equivalents)	Lewis Acid	Mol %	Yield (%)[b]
1	1	1	$Yb(OTf)_3$	10	38
2	1	1	$GaCl_3$	10	41
3	1.5	1	$GaCl_3$	10	63
4	2	1	$GaCl_3$	10	79
5[c]	2	1	$GaCl_3$	5	92
6[d]	2	1	$GaCl_3$	2	84

[a] Typical reaction conditions: To a solution of $GaCl_3$ in 1,2-DCE (3 mL) at room temperature, was added cyclobutane (0.44 mmol) and nitrosoarene (0.22 mmol). Reactions were monitored by TLC until cyclobutane was consumed. [b] Isolated yield. [c] 20 min reaction time. [d] 90 min reaction time.

The *cis* stereochemistry of product (**74c**) was deduced from analyzing a crystal structure as seen in Figure 4.1.

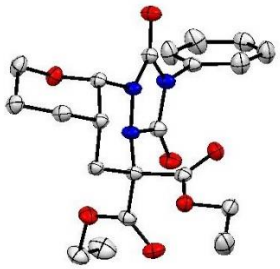


Figure 4.1 Crystal structure of hexahydropyridazine **74c**

4.2.1 Reaction Scope

After obtaining optimal reaction conditions for the cycloaddition, the scope was investigated to see if other DA cyclobutanes were compatible with PTAD. Good yields were obtained using various alkoxy-activated cyclobutane diesters as seen in Figure 4.2.

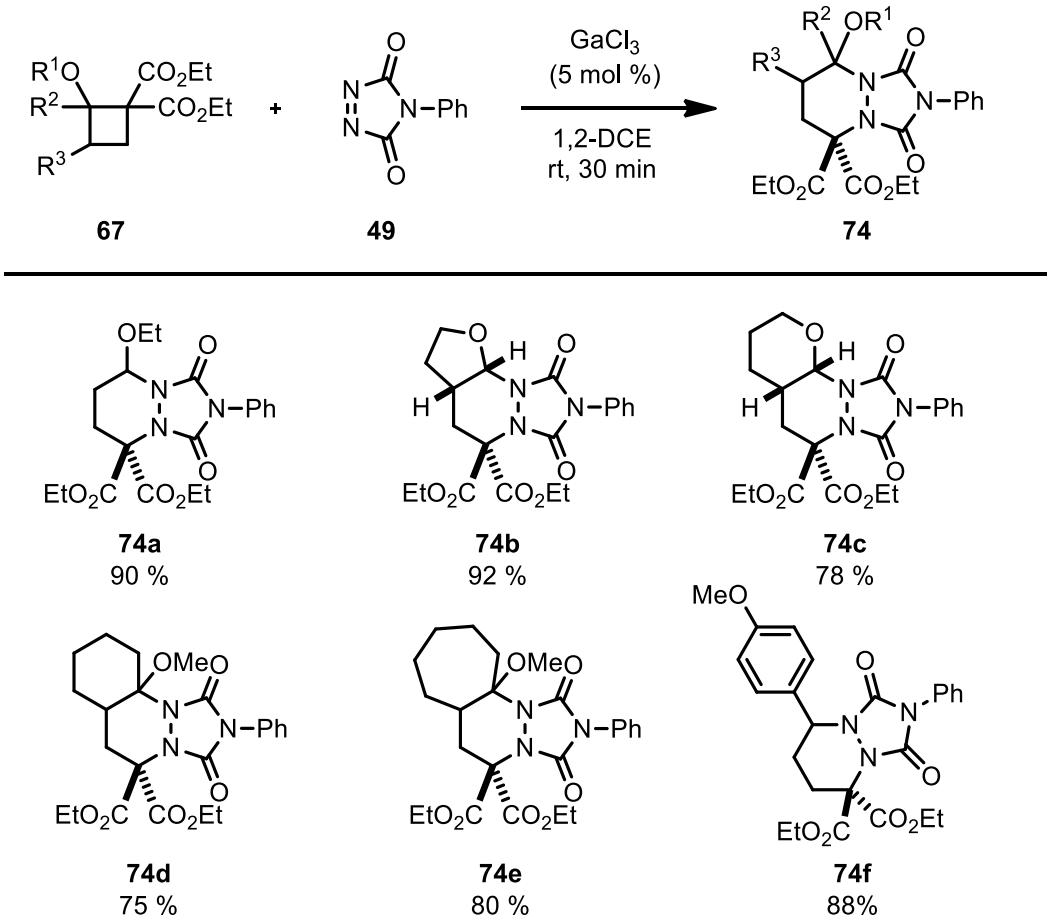
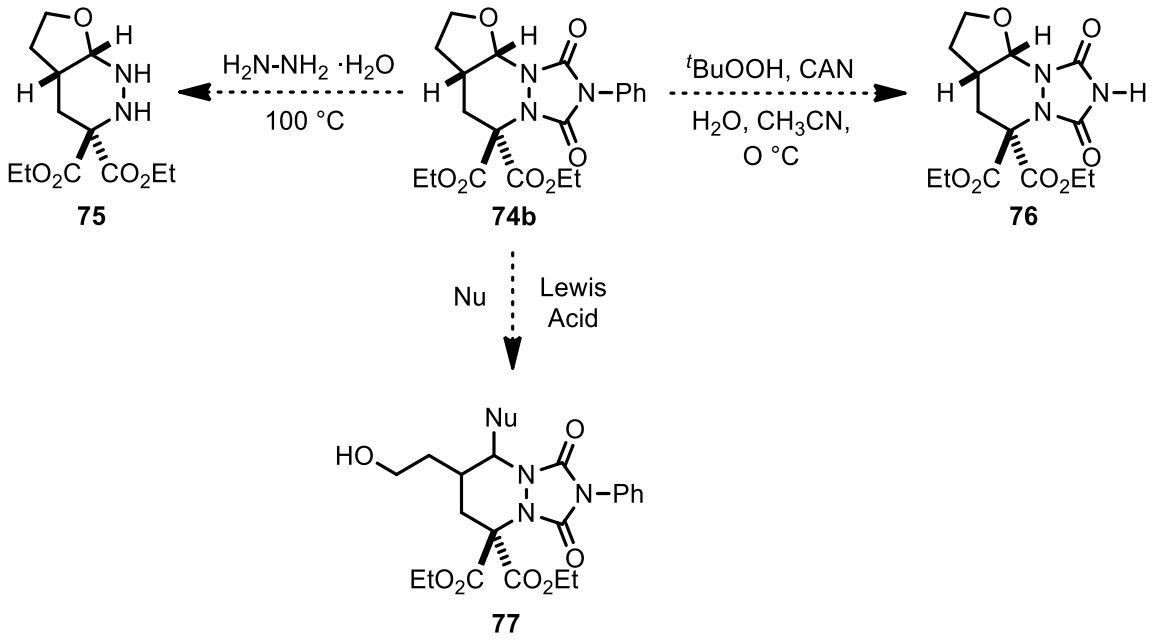


Figure 4.2 Cycloadditions of different DA cyclobutanes with PTAD

Reacting DA cyclobutanes with *trans*-diazenes was attempted but did not result in a cycloaddition. This came as no surprise because of the difference in reactivity between *trans*- and *cis*-diazenes. The difference in reactivity was also observed when working with DA cyclopropanes.

4.3 Post Modification of Hexahydropyridazine Products

The methodology discovered enables easy access to the hexahydropyridazine ring system through an efficient cycloaddition of DA cyclobutanes with *cis*-diazenes. Using specific DA cyclobutanes, the diastereoselectivity can be controlled and can therefore be used in the stereoselective synthesis of hexahydropyridazine systems. These systems contain the appropriate functionality to undergo different post modification reactions (Scheme 4.7). This demonstrates the versatility of the ring system to undergo various transformations to yield different compounds from a single product. The post-modified products can then be potentially useful in the synthesis of other target molecules or serve in other applications.



Scheme 4.7 Potential post modifications of hexahydropyridazine **74b**

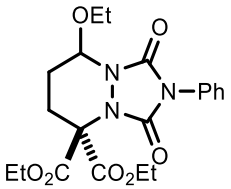
4.4 Experimental

The procedures and conditions were the same as described in section 2.3.

4.5 Supporting Information

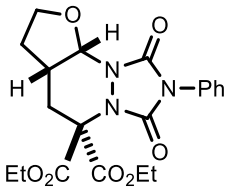
General Procedure for Cycloaddition of *cis*-Diazene with DA Cyclobutane

To a solution of cyclobutane (0.43 mmol, 2.0 equiv) and PTAD (0.22 mmol, 1.0 equiv) in 1,2-DCE (3 mL) was added $GaCl_3$ (0.01 mmol, 0.05 equiv) and stirred for 30 min at rt. The mixture was then concentrated after consumption of cyclobutane (as indicated by TLC) and directly loaded onto a packed SiO_2 column. Product was purified by flash chromatography (1:1 hexanes/EtOAc) to afford the corresponding cycloadducts.



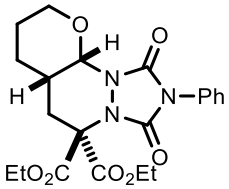
Diethyl 8-ethoxy-1,3-dioxo-2-phenyltetrahydro-1H-[1,2,4]triazolo[1,2-a]pyridazine-5,5(6H)-dicarboxylate (74a)

The general procedure for cycloaddition of *cis*-diazene with DA cyclobutane was followed using cyclobutane (142 mg, 0.58 mmol), *cis*-diazene **49** (50 mg, 0.29 mmol) and $GaCl_3$ (2.6 mg, 0.015 mmol) to yield the compound as a white solid. (109 mg, 90%). R_f 0.20 (3:1 Hexanes:EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) 7.50 (app d, J = 8.2 Hz, 2 H), 7.45 (app t, J = 7.9 Hz, 2 H), 7.34 - 7.38 (m, 1 H), 5.54 (d, J = 1.8 Hz, 1 H), 4.25 - 4.37 (m, 4 H), 3.62 - 3.70 (m, 2 H), 2.69 (ddd, J = 14.1, 14.1, 4.1 Hz, 1 H), 2.47 - 2.51 (m, 1 H), 2.08 (d, J = 14.1 Hz, 1 H), 1.70 (dddd, J = 14.1, 4.1, 4.1, 4.1 Hz, 1 H), 1.27 - 1.33 (m, 6 H), 1.23 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 166.2, 165.8, 153.7, 151.0, 131.0, 129.1, 128.3, 125.7, 77.6, 70.4, 65.0, 63.2, 63.0, 26.5, 25.6, 15.0, 14.1, 13.8; HRMS $C_{20}H_{25}N_3O_7$ Calculated = 419.1693, Found = 419.1699



Diethyl 7,9-dioxo-8-phenylhexahydro-2H-furo[2,3-c][1,2,4]triazolo[1,2-a]pyridazine-5,5(3H)-dicarboxylate (74b)

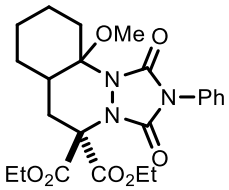
The general procedure for cycloaddition of *cis*-diazene with DA cyclobutane was followed using cyclobutane (141 mg, 0.58 mmol), *cis*-diazene **49** (50 mg, 0.29 mmol) and $GaCl_3$ (2.6 mg, 0.015 mmol) to yield the compound as a white solid. (111 mg, 92%). R_f 0.50 (1:1 Hexanes:EtOAc); ^1H NMR (400 MHz, $CDCl_3$) 7.45 - 7.53 (m, 4 H), 7.38 (app t, J = 7.0 Hz, 1 H), 5.78 (d, J = 4.3 Hz, 1 H), 4.29 - 4.37 (m, 4 H), 4.18 - 4.23 (m, 2 H), 4.08 (td, J = 9.4, 2.0 Hz, 1 H), 2.64 (dd, J = 13.3, 5.9 Hz, 1 H), 2.40 - 2.48 (m, 1 H), 2.28 - 2.36 (m, 1 H), 2.24 (dd, J = 13.3, 12.1 Hz, 1 H), 1.90 (ddd, J = 6.6, 6.6, 2.0 Hz, 1 H), 1.34 (t, J = 7.0 Hz, 3 H), 1.32 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 166.0, 165.6, 153.3, 150.5, 130.9, 129.2, 129.1, 128.4, 125.8, 80.8, 68.9, 66.2, 63.5, 63.1, 32.3, 31.7, 30.2, 14.1, 13.8; HRMS $C_{20}H_{23}N_3O_7$ Calculated = 417.1536, Found = 417.1530



Diethyl 8,10-dioxo-9-phenyloctahydropyrano[2,3-c][1,2,4]triazolo[1,2-a]pyridazine-6,6(2H)-dicarboxylate (74c)

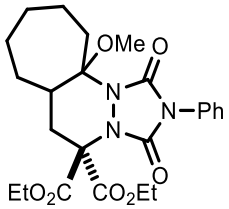
The general procedure for cycloaddition of *cis*-diazene with DA cyclobutane was followed using cyclobutane (149 mg, 0.58 mmol), *cis*-diazene **49** (50 mg, 0.29 mmol) and $GaCl_3$ (2.6 mg, 0.015 mmol) to yield the compound as a white solid. (97 mg, 78%). R_f 0.48 (1:1 Hexanes:EtOAc); ^1H NMR (400 MHz, $CDCl_3$) 7.42 - 7.50 (m, 4 H), 7.36 (app t, J = 7.0 Hz, 1 H), 5.29 - 5.32 (m, 1 H), 4.26 - 4.38 (m, 4 H), 4.09 - 4.14 (m, 1 H), 3.65 (td, J = 12.1, 2.3 Hz, 1 H), 2.76 (dd, J = 13.1, 13.1 Hz, 1 H), 2.37 (dd, J = 13.1, 3.7 Hz, 1 H), 1.90 - 1.95 (m, 2 H), 1.81 - 1.88 (m, 2 H), 1.44 (d, J = 12.5 Hz, 1 H), 1.24 - 1.34 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) 166.3, 165.6, 152.6, 150.7,

131.0, 129.1, 128.3, 125.8, 78.1, 69.6, 67.9, 63.4, 63.0, 30.0, 29.9, 27.1, 19.6, 14.1, 13.8; HRMS $C_{21}H_{25}N_3O_7$ Calculated = 431.1693, Found = 431.1693



Diethyl 10a-methoxy-1,3-dioxo-2-phenyloctahydro-1H-[1,2,4]triazolo[1,2-a]cinnoline-5,5(6H)-dicarboxylate (74d)

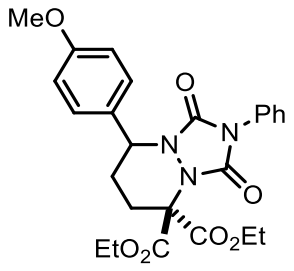
The general procedure for cycloaddition of *cis*-diazene with DA cyclobutane was followed using cyclobutane (165 mg, 0.58 mmol), *cis*-diazene **49** (50 mg, 0.29 mmol) and $GaCl_3$ (2.6 mg, 0.015 mmol) to yield the compound as a white solid. (99 mg, 75%). R_f 0.21 (3:1 Hexanes:EtOAc); ^1H NMR (400 MHz, $CDCl_3$) 7.41 - 7.47 (m, 4 H), 7.31 - 7.35 (app tt, J = 7.0, 1.8 Hz, 1 H), 4.89 (dd, J = 4.1 Hz, 1 H), 4.10 - 4.25 (m, 4 H), 3.85 (dd, J = 6.5, 4.1 Hz, 1 H), 3.45 (s, 3 H), 2.82 (dd, J = 15.3, 6.5 Hz, 1 H), 2.78 (dd, J = 15.3, 4.1 Hz, 1 H), 2.29 - 2.33 (m, 1 H), 2.10 - 2.19 (m, 2 H), 1.91 - 1.95 (m, 1 H), 1.66 - 1.70 (m, 2 H), 1.26 (t, J = 7.0 Hz, 3 H), 1.25 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.1, 169.2, 153.4, 152.2, 151.7, 129.0, 128.1, 125.7, 100.2, 64.7, 61.8, 61.5, 54.0, 48.4, 35.9, 31.9, 23.4, 19.0, 14.1; HRMS $C_{23}H_{29}N_3O_7$ Calculated = 459.2006, Found = 460.2090



Diethyl 11a-methoxy-1,3-dioxo-2-phenyldecahydrocyclohepta[c][1,2,4]triazolo[1,2-a]pyridazine-5,5(1H)-dicarboxylate (74e)

The general procedure for cycloaddition of *cis*-diazene with DA cyclobutane was followed using cyclobutane (173 mg, 0.58 mmol), *cis*-diazene **49** (50 mg, 0.29 mmol) and $GaCl_3$ (2.6 mg, 0.015 mmol) to yield the compound as a white solid. (110 mg, 80%). R_f 0.53 (1:1 Hexanes:EtOAc); ^1H

NMR (400 MHz, $CDCl_3$) 7.48 - 7.50 (m, 2 H), 7.45 (app t, J = 7.9 Hz, 2 H), 7.34 (app t, J = 7.6 Hz, 1 H), 4.58 (app dd, J = 4.5, 2.3 Hz, 1 H), 4.19 - 4.23 (m, 4 H), 3.47 - 3.53 (m, 1 H), 3.34 (s, 3 H), 3.27 (s, 3 H), 2.32 - 2.38 (m, 1 H), 2.03 - 2.08 (m, 1 H), 1.91 - 1.95 (m, 2 H), 1.78 - 1.80 (m, 2 H), 1.53 - 1.65 (m, 5 H), 1.24 - 1.27 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) 169.6, 169.4, 153.3, 129.1, 128.1, 125.4, 105.0, 62.3, 61.5, 61.0, 51.3, 50.3, 48.6, 41.0, 30.3, 27.5, 25.2, 24.6, 24.5, 21.1, 14.1; HRMS $C_{24}H_{31}N_3O_7$ Calculated = 473.2162, Found = 473.2165



Diethyl 8-(4-methoxyphenyl)-1,3-dioxo-2-phenyltetrahydro-1H-[1,2,4]triazolo[1,2-a]pyridazine-5,5(6H)-dicarboxylate (74f)

The general procedure for cycloaddition of *cis*-diazene with DA cyclobutane was followed using cyclobutane (48 mg, 0.16 mmol), *cis*-diazene **49** (14 mg, 0.08 mmol) and $GaCl_3$ (0.7 mg, 0.004 mmol) to yield the compound as a white solid. (34 mg, 88%). R_f 0.45 (1:1 Hexanes:EtOAc); ^1H NMR (400 MHz, $CDCl_3$) 7.39 - 7.47 (m, 5 H), 7.34 (app d, J = 8.6 Hz, 2 H), 6.86 (app d, J = 8.6 Hz, 2 H), 5.11 (dd, J = 11.3, 4.3 Hz, 1 H), 4.20 - 4.31 (m, 4 H), 3.79 (s, 3 H), 3.49 (dd, J = 8.4, 4.5 Hz, 1 H), 2.09 - 2.23 (m, 2 H), 1.80 - 2.04 (m, 2 H), 1.29 (t, J = 7.0 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) 169.7, 169.4, 154.1, 129.0, 128.9, 128.1, 125.5, 114.1, 61.9, 59.7, 55.3, 50.7, 29.0, 26.6, 25.0, 14.1; HRMS $C_{25}H_{27}N_3O_7$ Calculated = 481.1849, Found = 481.1837

Chapter 5 - Conclusions

This thesis has investigated the mechanism of reaction between DA cyclopropanes and nitrosoarenes. The reaction of DA cyclopropanes with azo dicarboxylates was also investigated. These reactions were studied with the use of cross-over experiments. The information learned from these experiments could be used in the development of new reactions. The successful completion of these projects demonstrates the usefulness and versatility of DA cyclopropanes in synthetic organic chemistry.

A breakthrough that was discovered in this thesis included the general pattern of reactivity of nitrogen to open a DA cyclopropane, which undergoes fragmentation and generation of a 1,3-dipole. This reaction type may lead to the discovery of new reactions if further exploration is attempted. This reaction represents a novel way of synthesizing heterocyclic compounds and incorporating new atoms may allow for construction of new heterocycles.

The reaction of DA cyclobutanes with *cis*-diazenes was also accomplished in a highly efficient cycloaddition. The generality of the reaction scope was achieved from the successful coupling of different DA cyclobutanes with *cis*-diazene, PTAD. This project showcased a novel approach to the synthesis of hexahydropyridazine systems. These six-membered ring heterocycles have limited ways to be created, and can now be efficiently synthetized, which demonstrates the usefulness of this chemistry.

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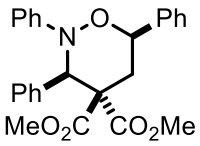
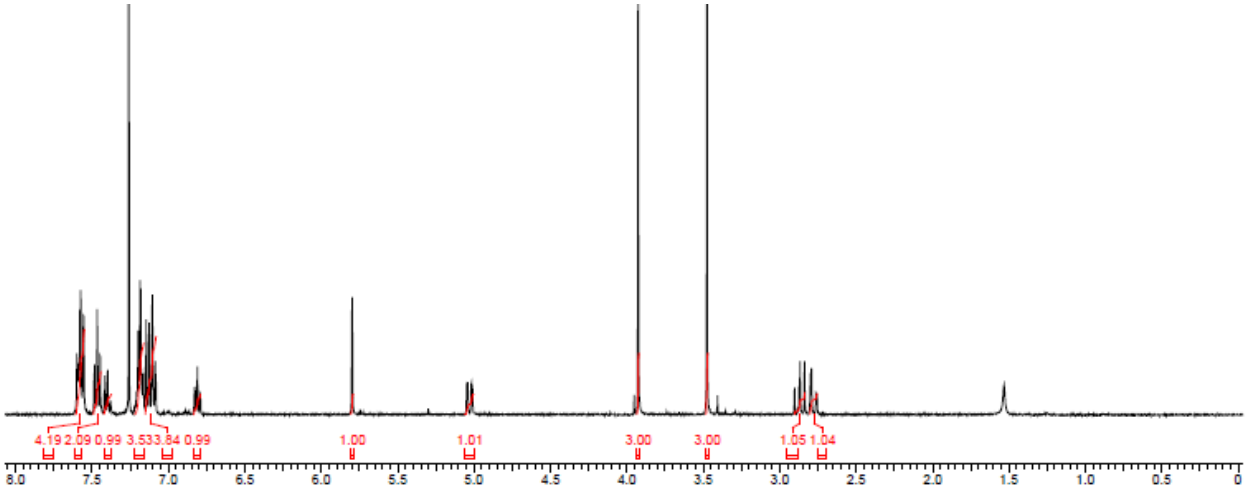
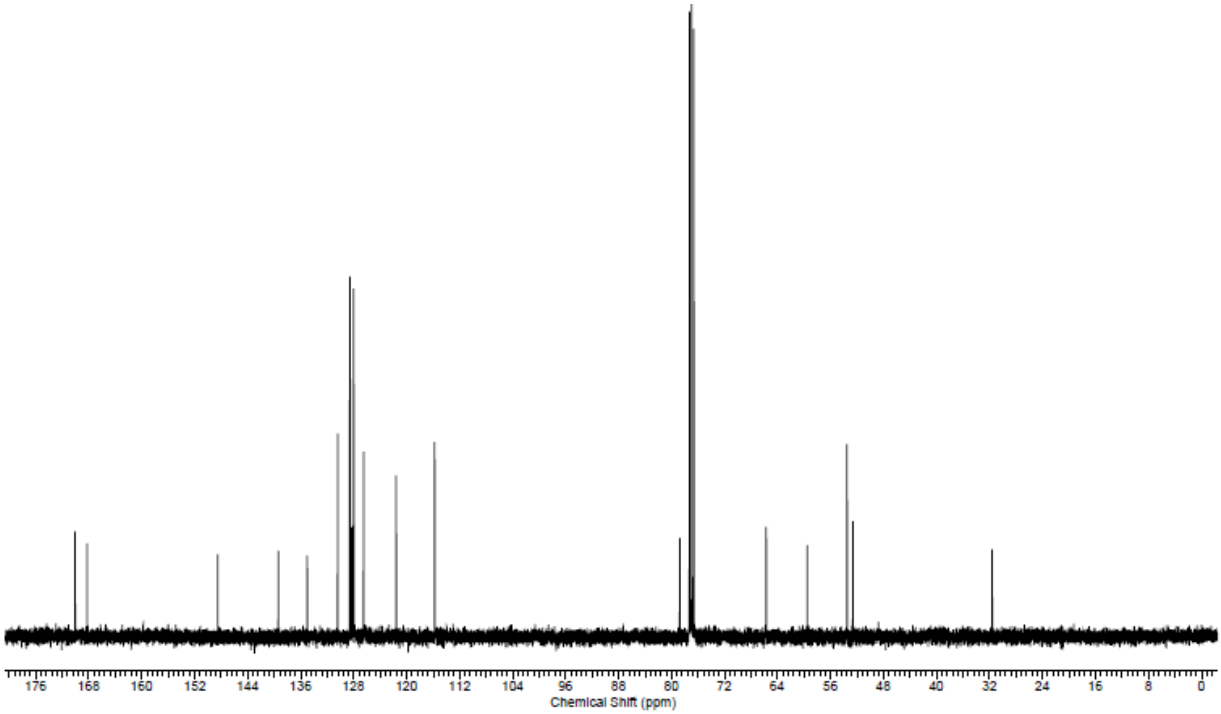
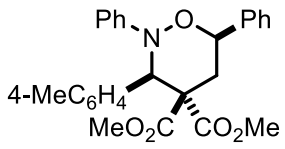
Appendix 1 - NMR Data Chapter 2



35a



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O
Ph
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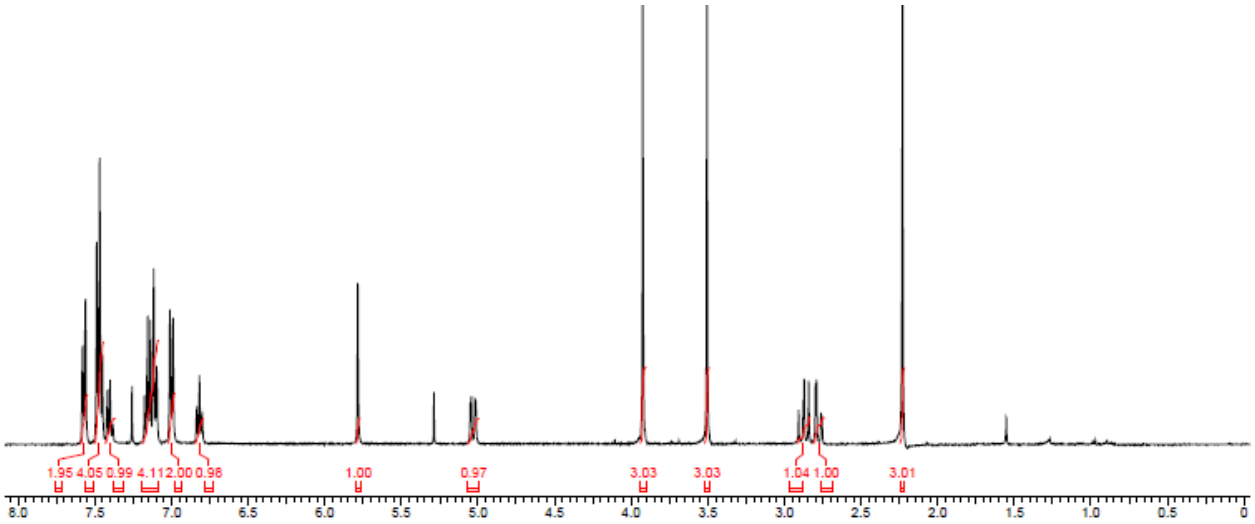
MeO2C
CO2Me

35b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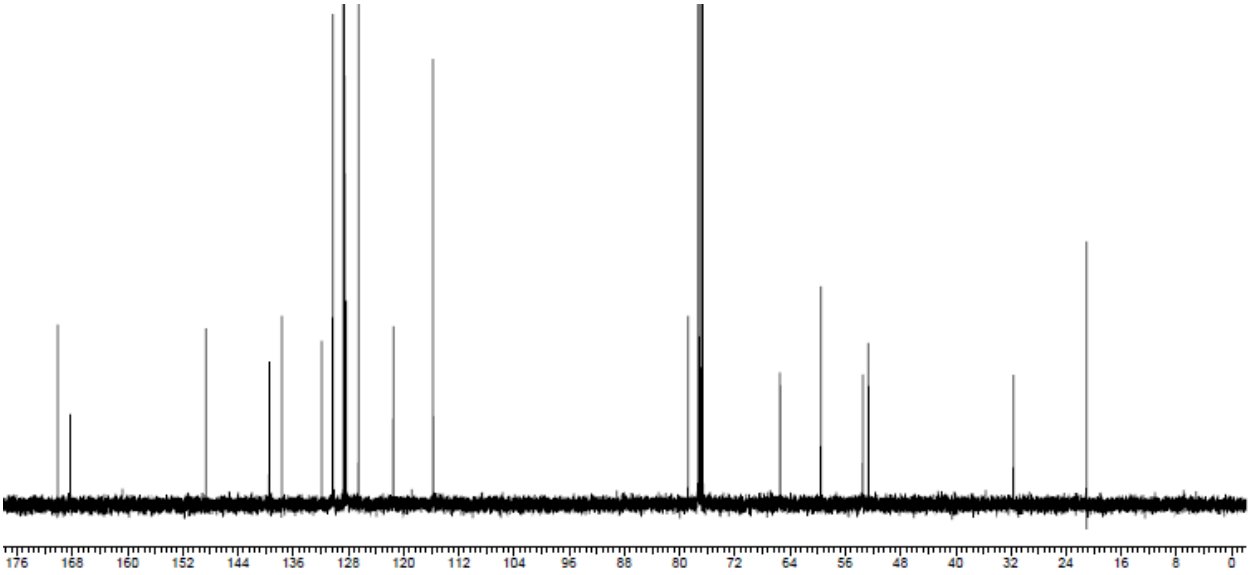
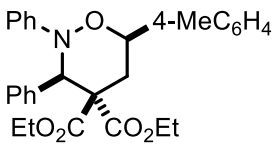
1.00
0.97
3.03
3.03
1.04 1.00
3.01

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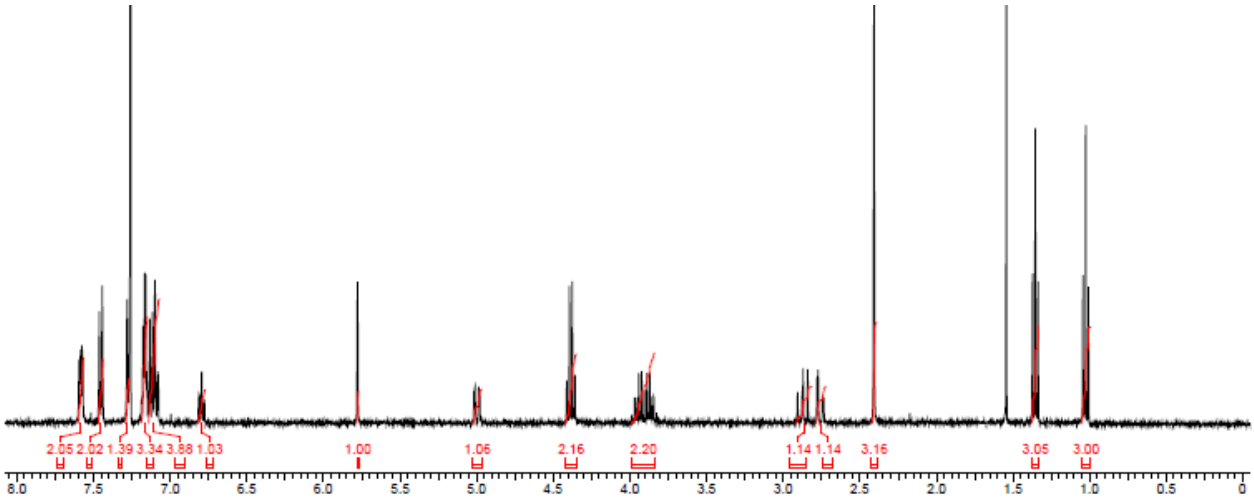
Ph
EtO2C
CO2Et

35c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1.00
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3.16
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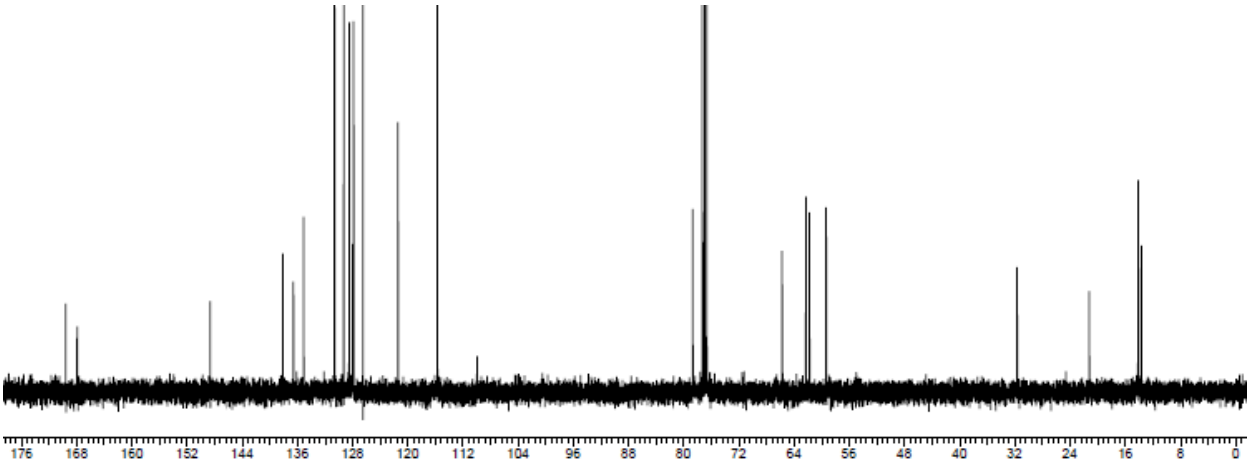
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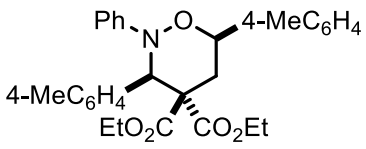
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4-MeC6H4
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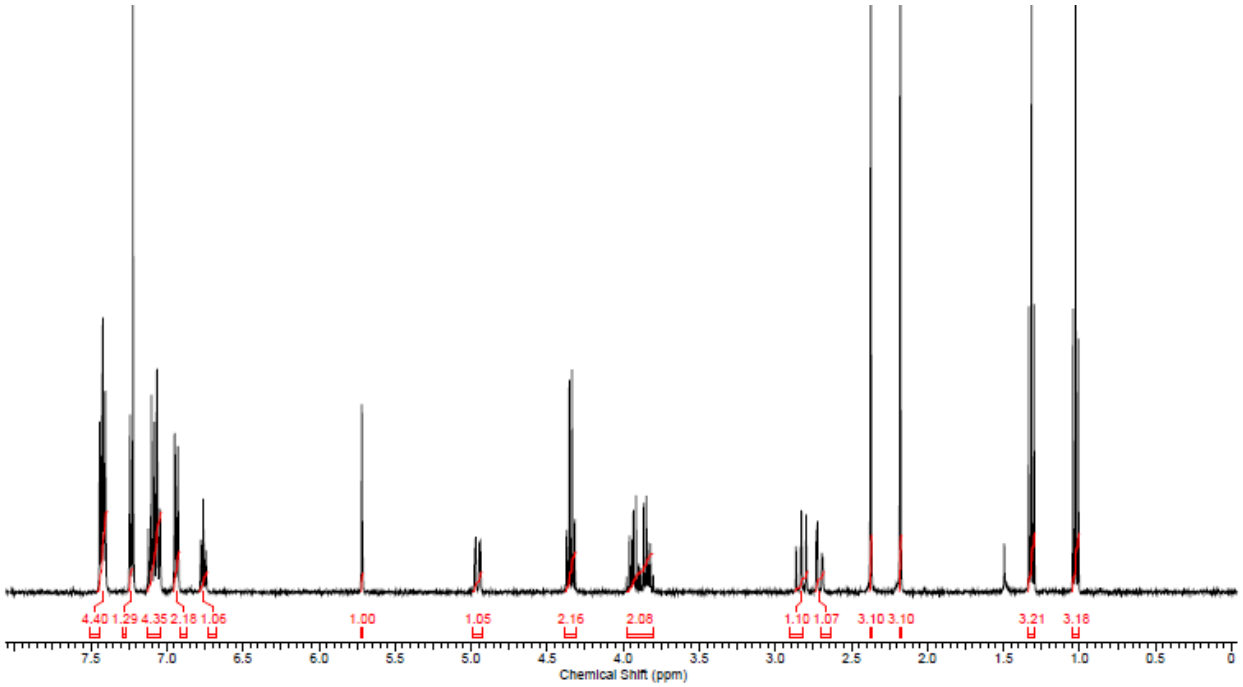
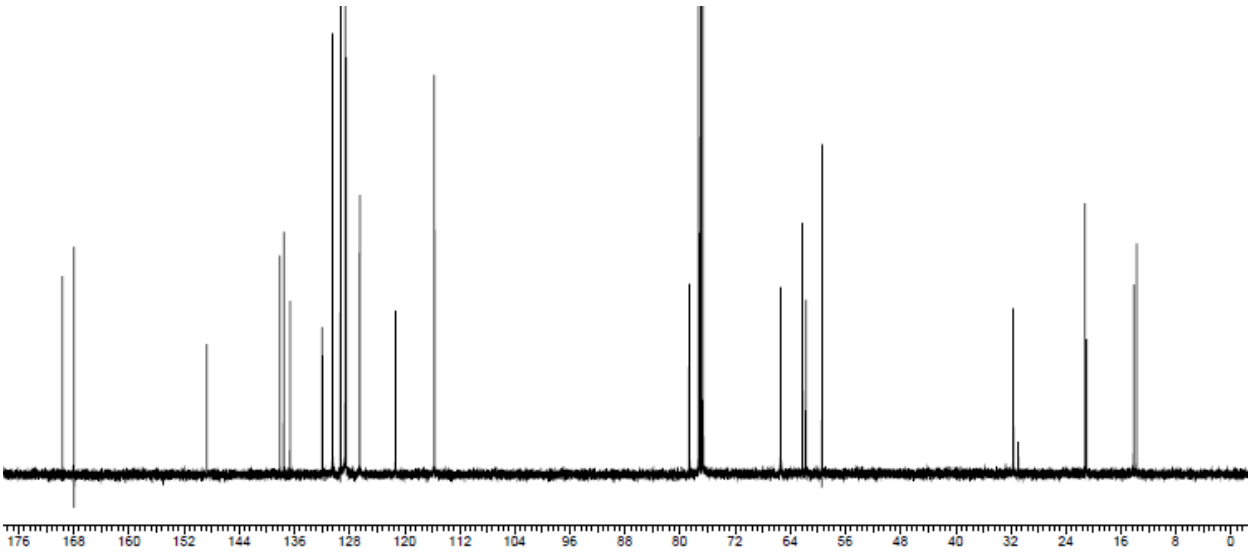
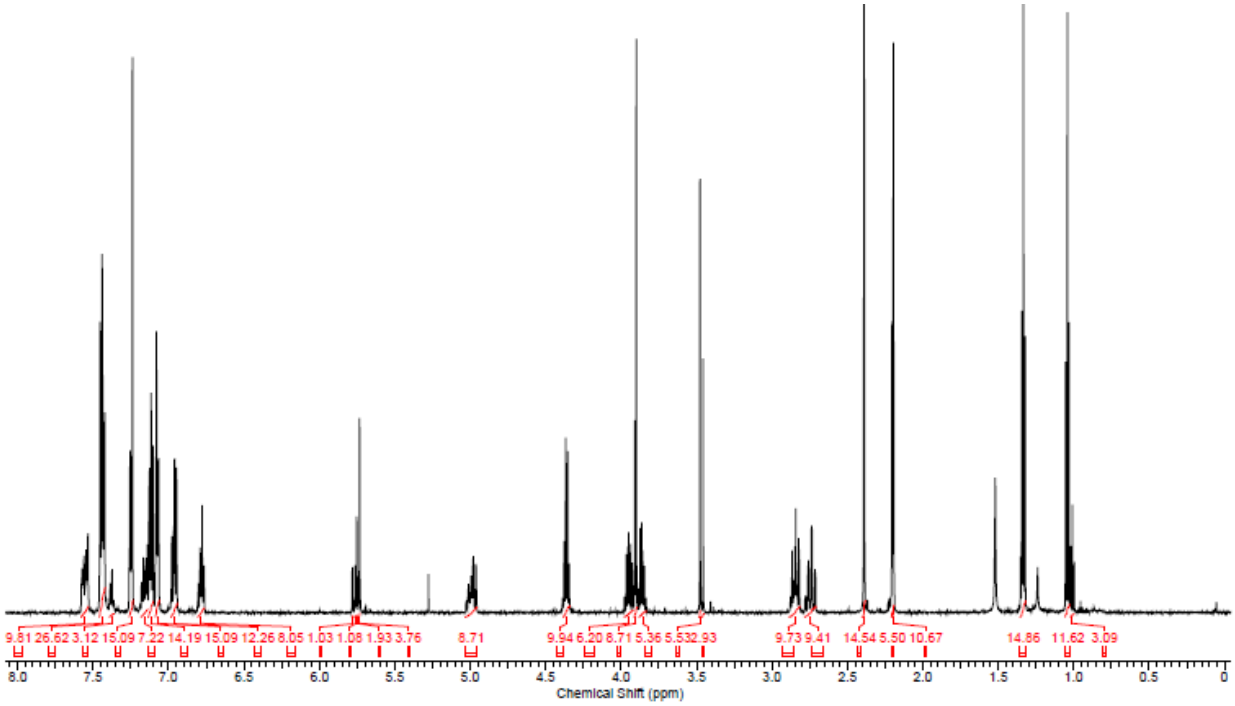
CO2Et

35d

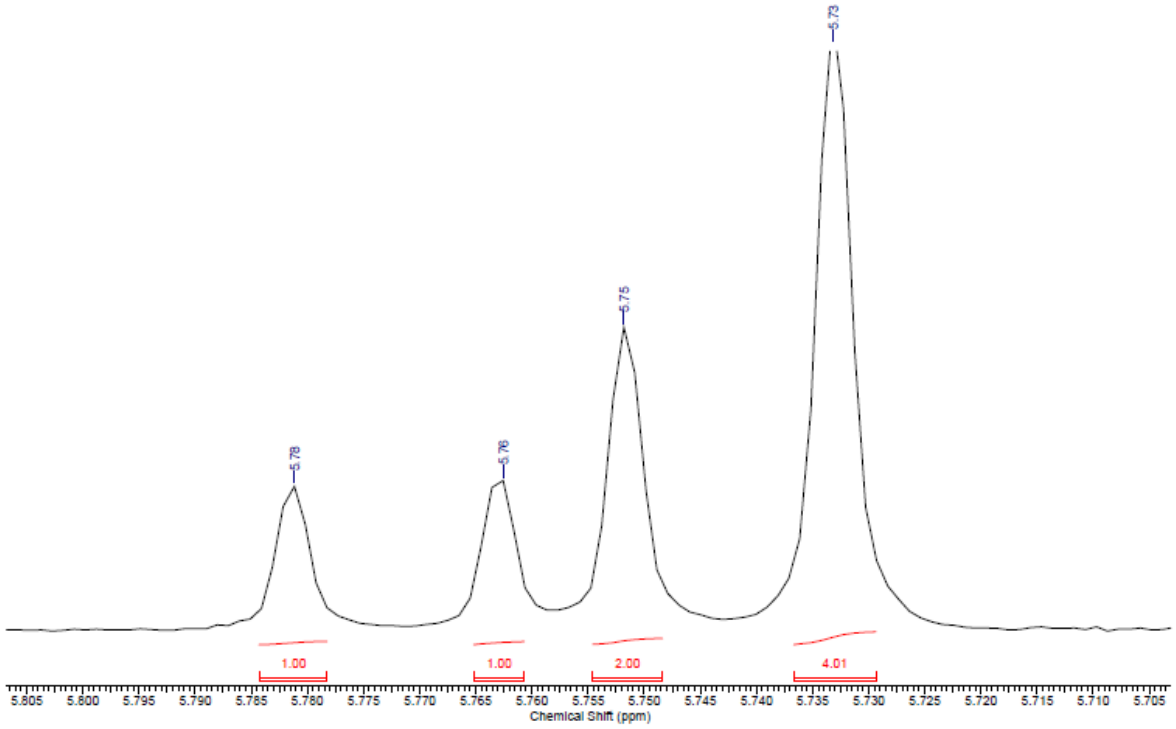

4.40 1.29 4.35 2.18 1.06
1.00
1.05
2.16
2.08
1.10 1.07
3.10 3.10
3.21
3.18
Chemical Shift (ppm)



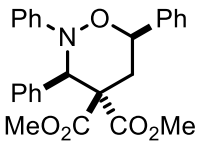
Cross-Over Experiment #1



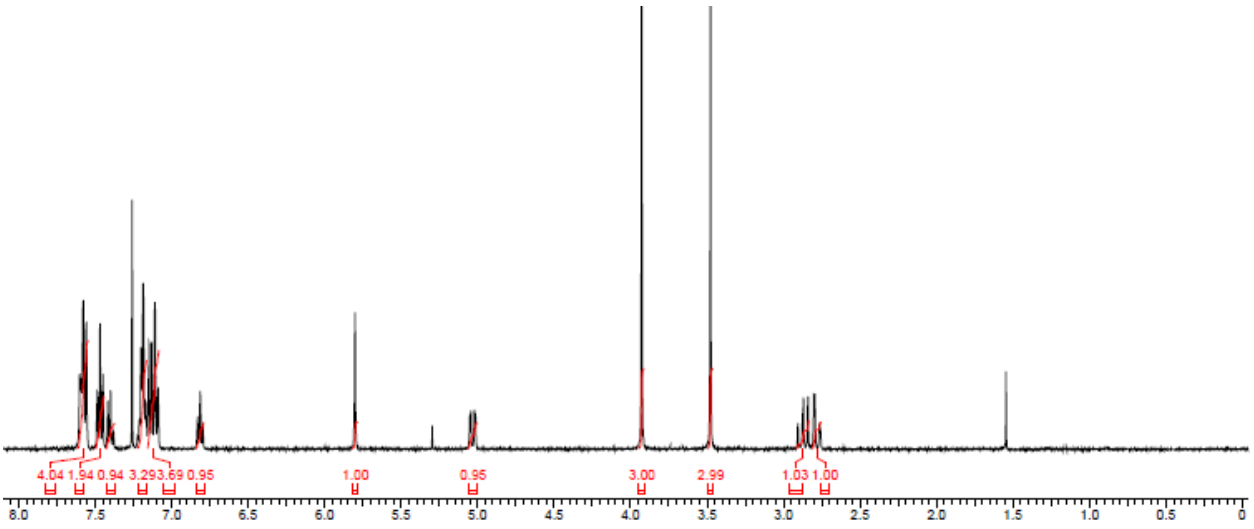
Zoomed into key identifying region

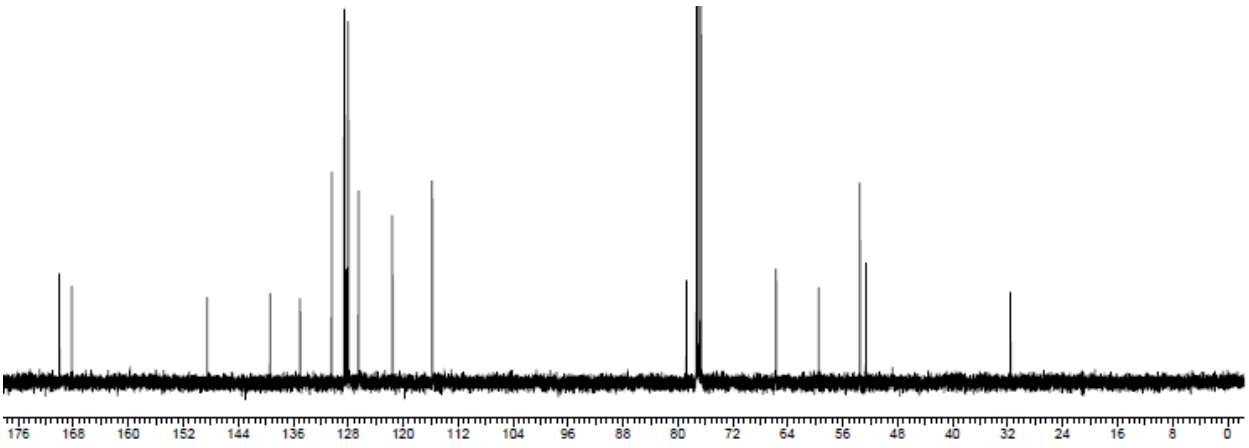


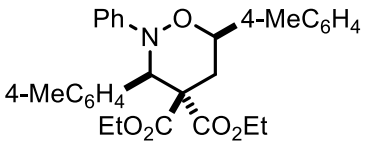
35a **35c** **35b** **35d**


Ph
N
O
Ph
Ph
MeO2C
CO2Me

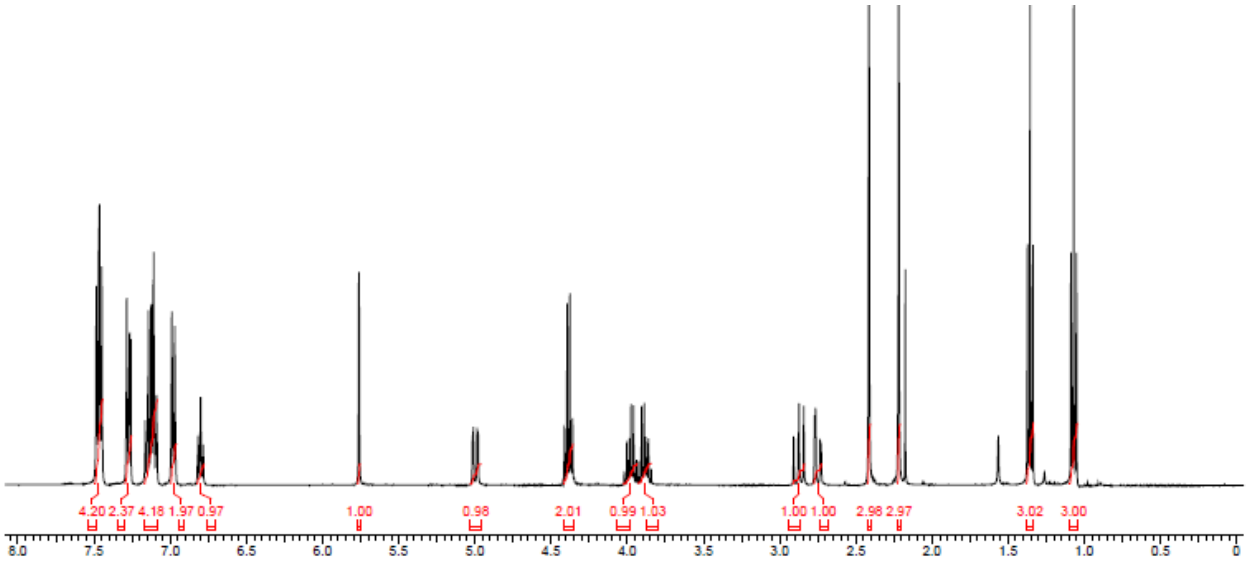
35a

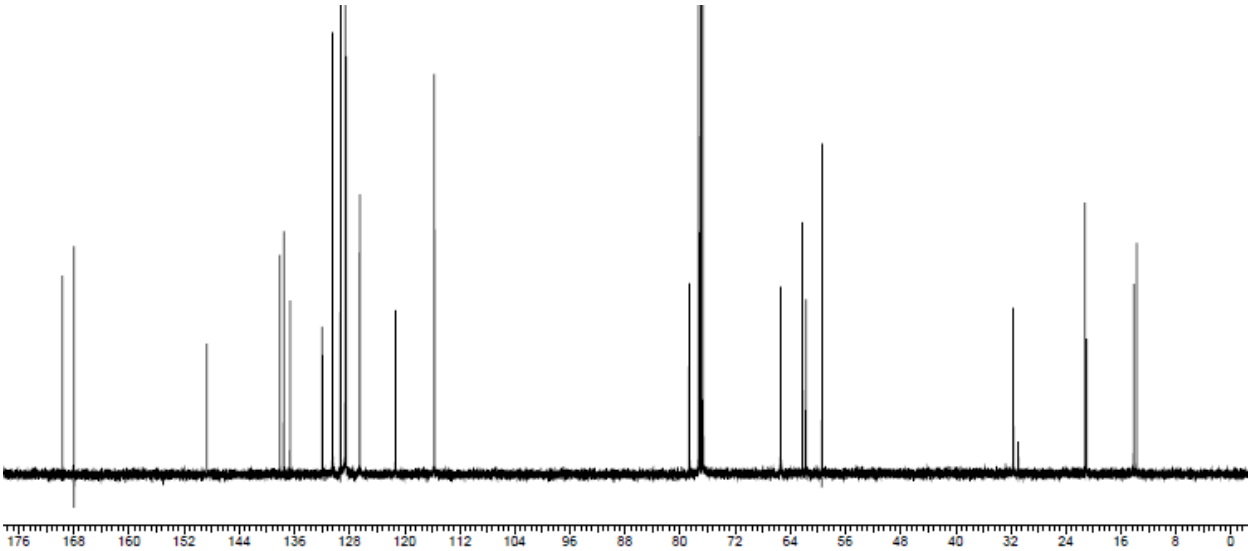

4.04 1.94 0.94 3.29 3.69 0.95
1.00
0.95
3.00
2.99
1.03 1.00

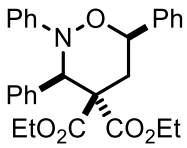



Ph
N
O
4-MeC6H4
4-MeC6H4
EtO2C
CO2Et

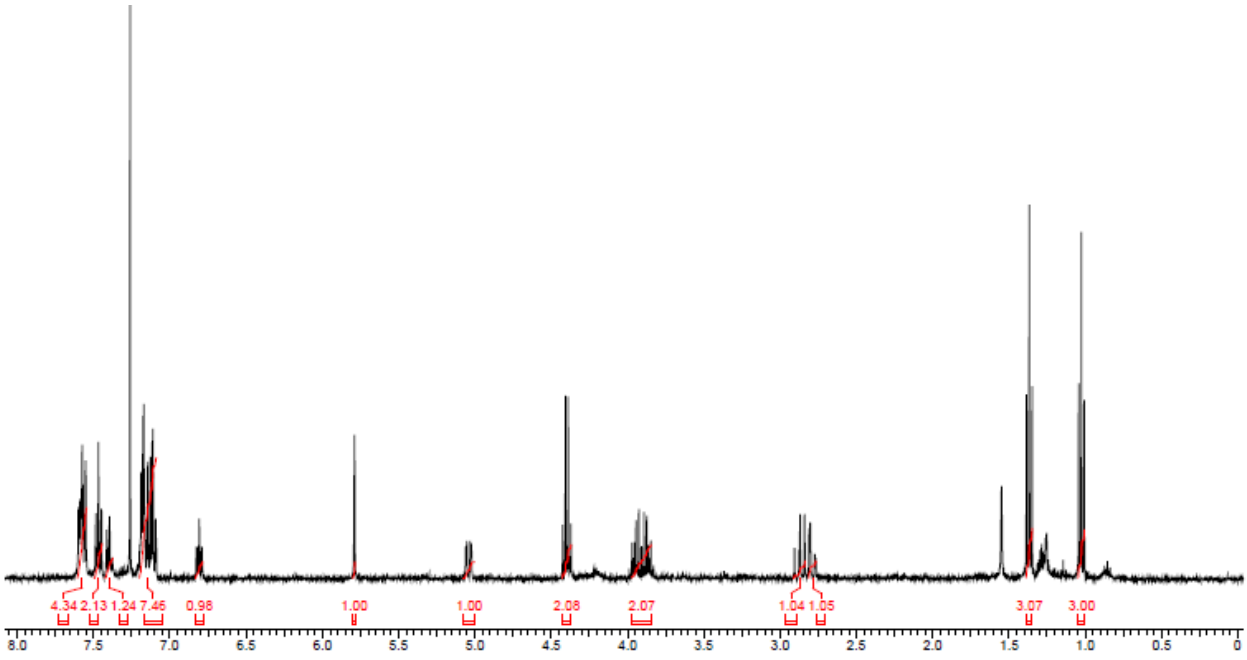
35d

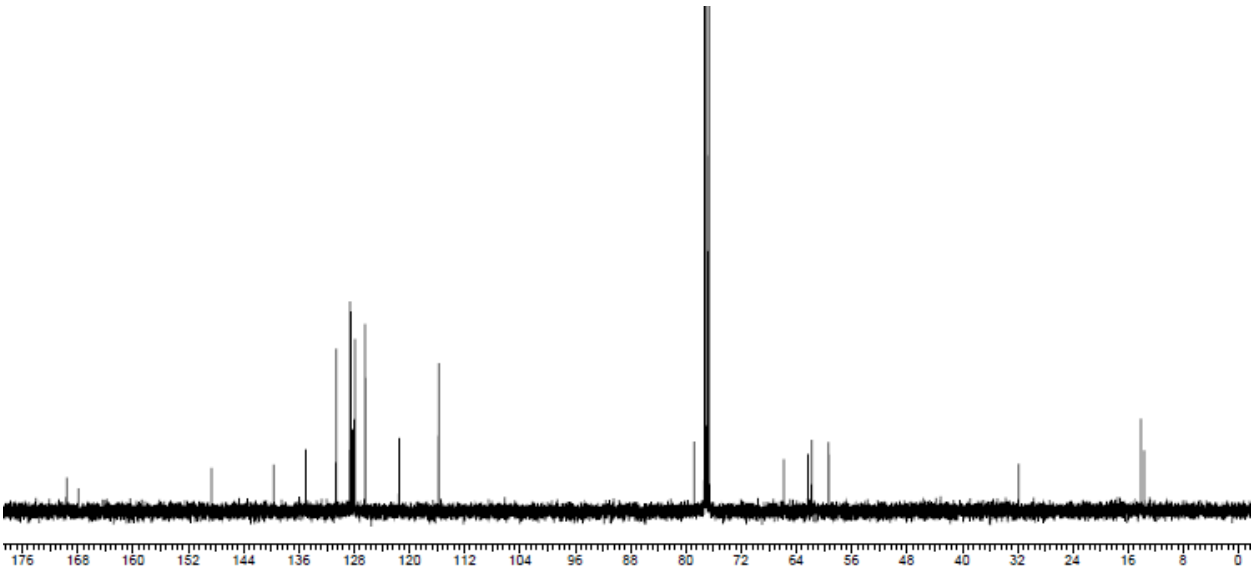

4.20 2.37 4.18 1.97 0.97
1.00
0.98
2.01
0.99 1.03
1.00 1.00
2.98 2.97
3.02
3.00

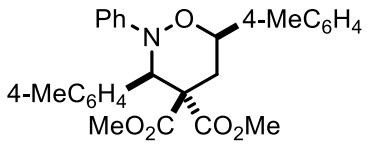



Ph
N
O
Ph
Ph
EtO2C
CO2Et

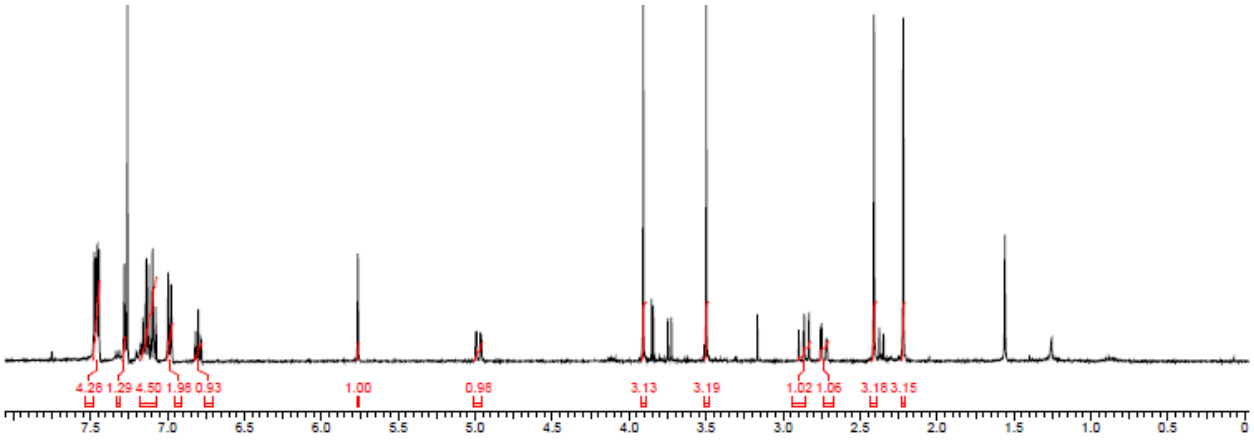
35e

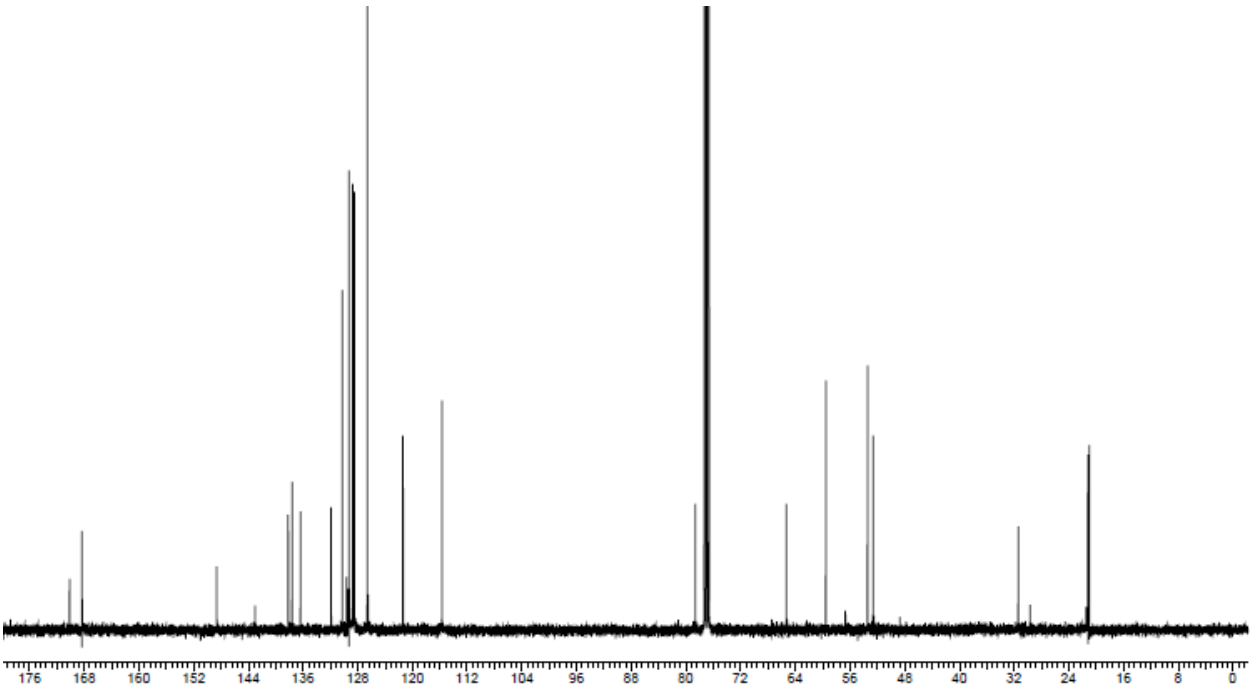

4.34 2.13 1.24 7.46 0.96 1.00 1.00 2.08 2.07 1.04 1.05 3.07 3.00
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0

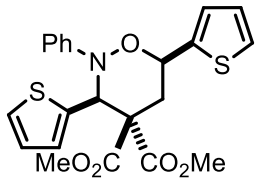

176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0


Ph
N
O
4-MeC6H4
4-MeC6H4
MeO2C
CO2Me

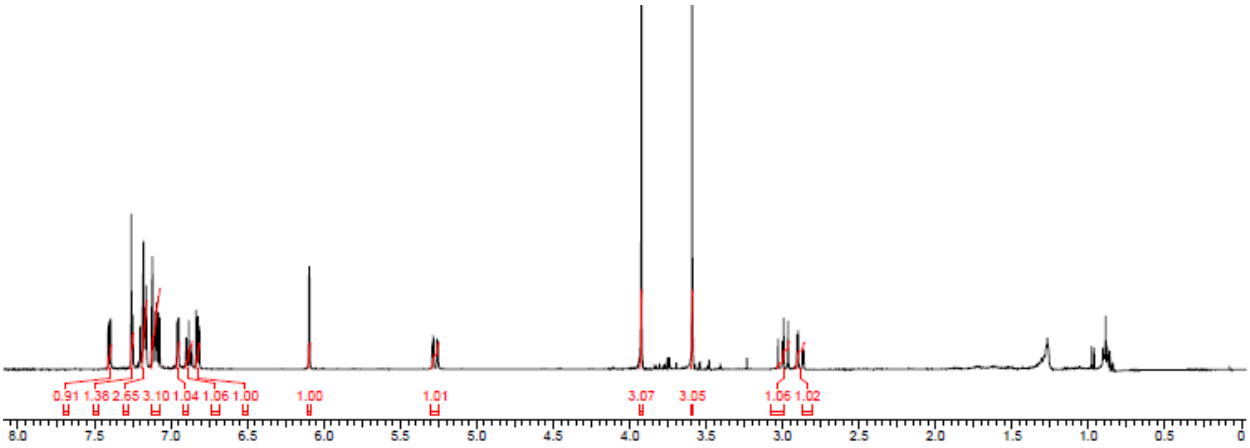
35f

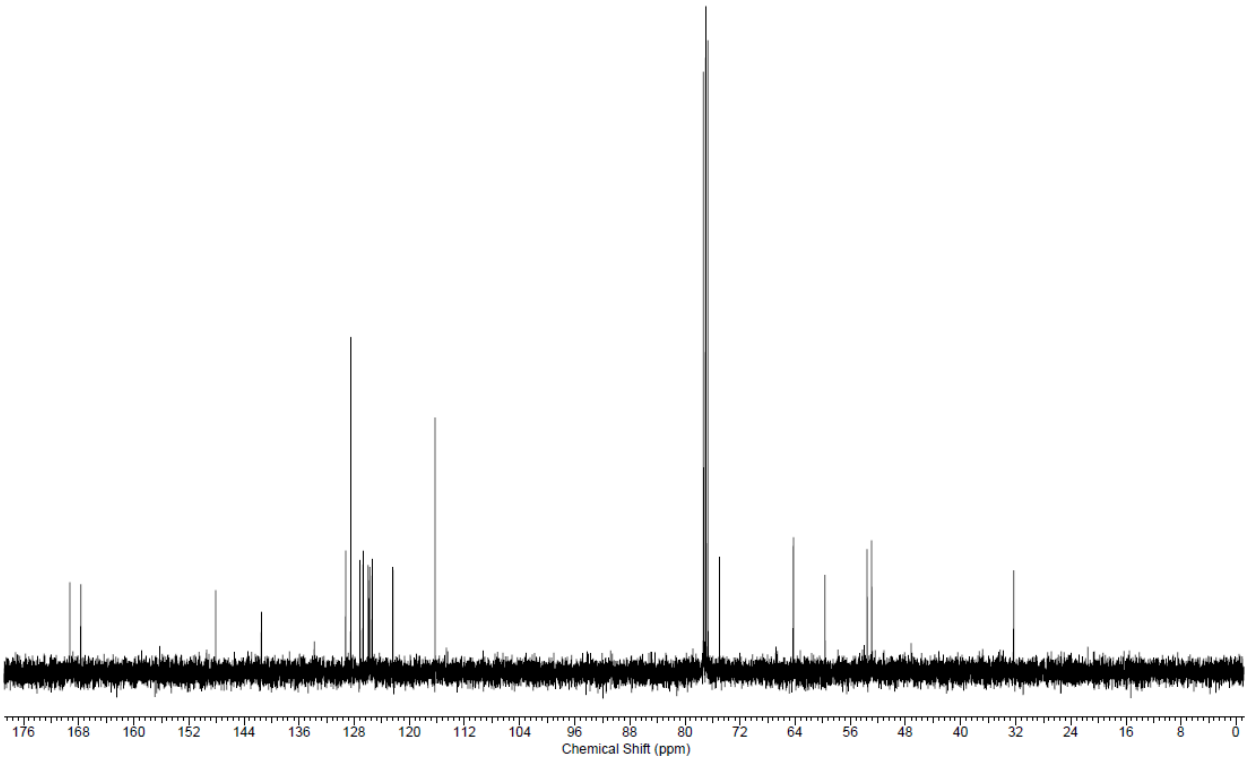

4.28 1.29 4.50 1.98 0.93
1.00
0.98
3.13
3.19
1.02 1.06
3.18 3.15
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0

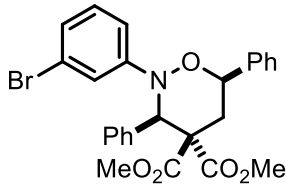

176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0


Ph
N
O
S
S
MeO2C
CO2Me

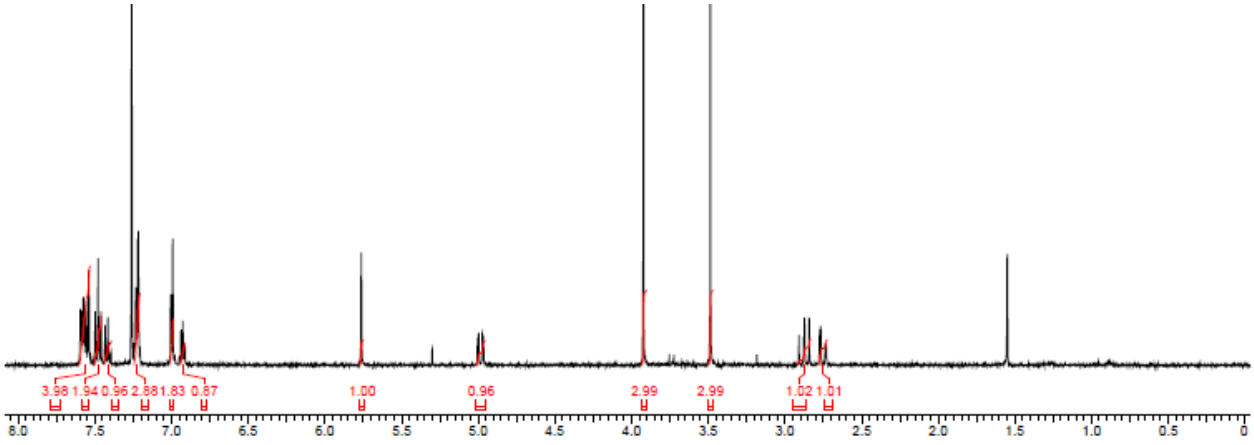
35g

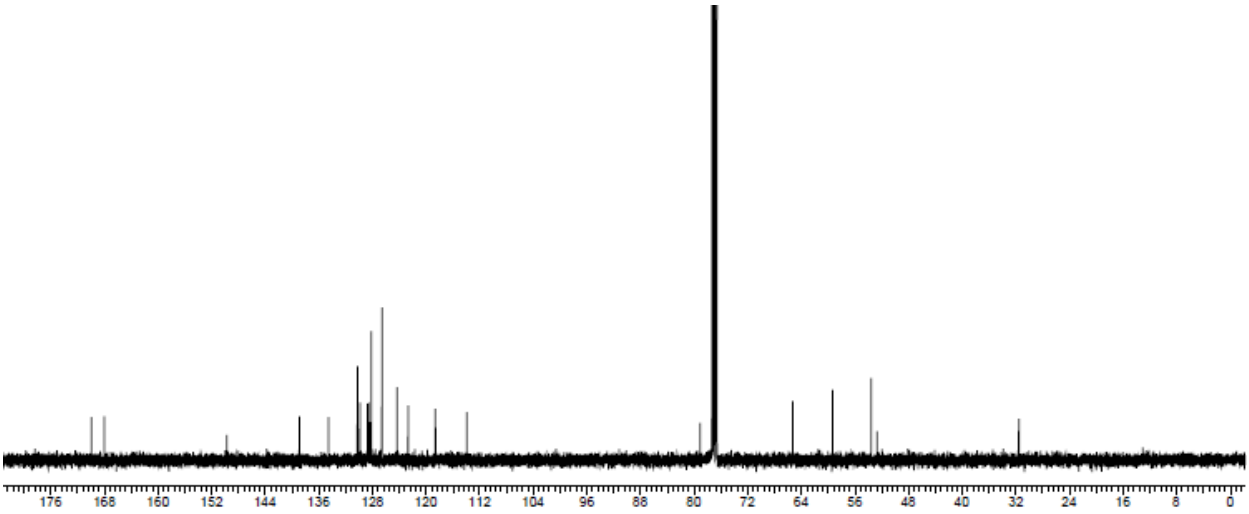

0.91 1.38 2.55 3.10 1.04 1.06 1.00
1.00
1.01
3.07
3.05
1.06 1.02
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0

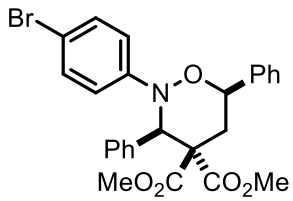

176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)


Br
N
O
Ph
Ph
MeO2C
CO2Me

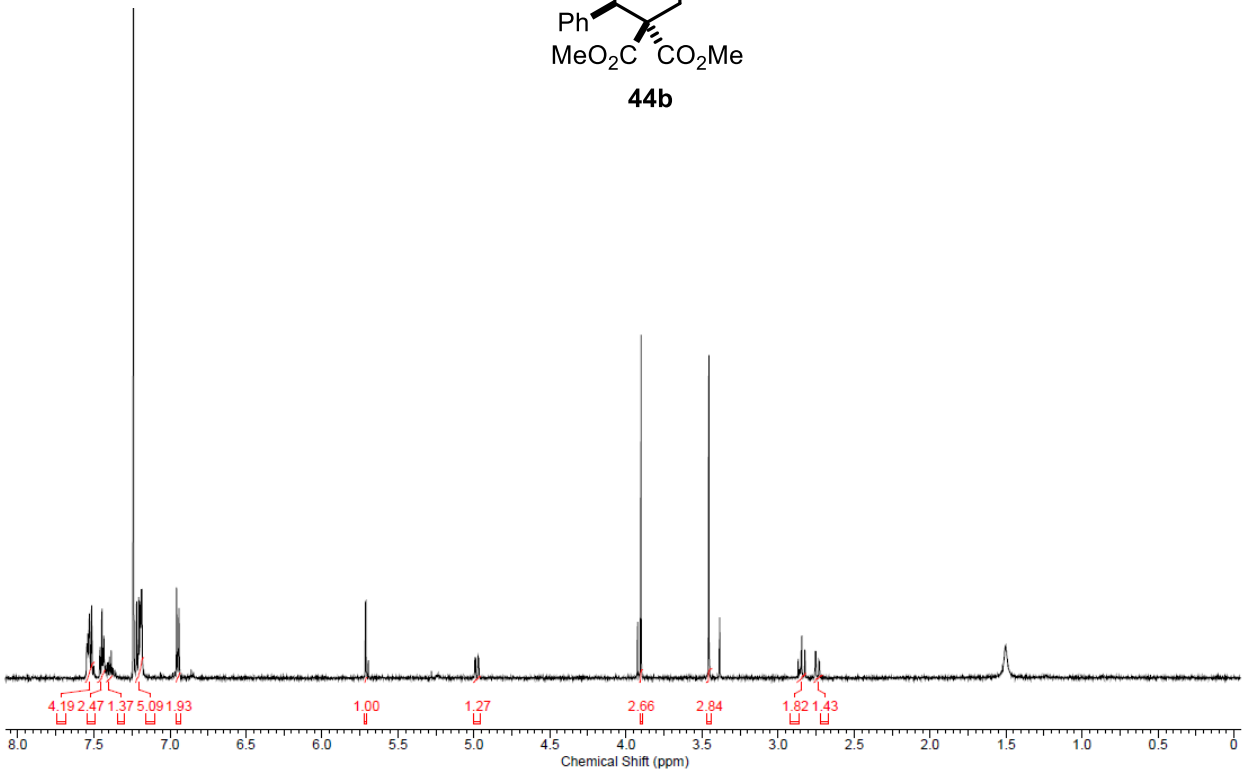
44a

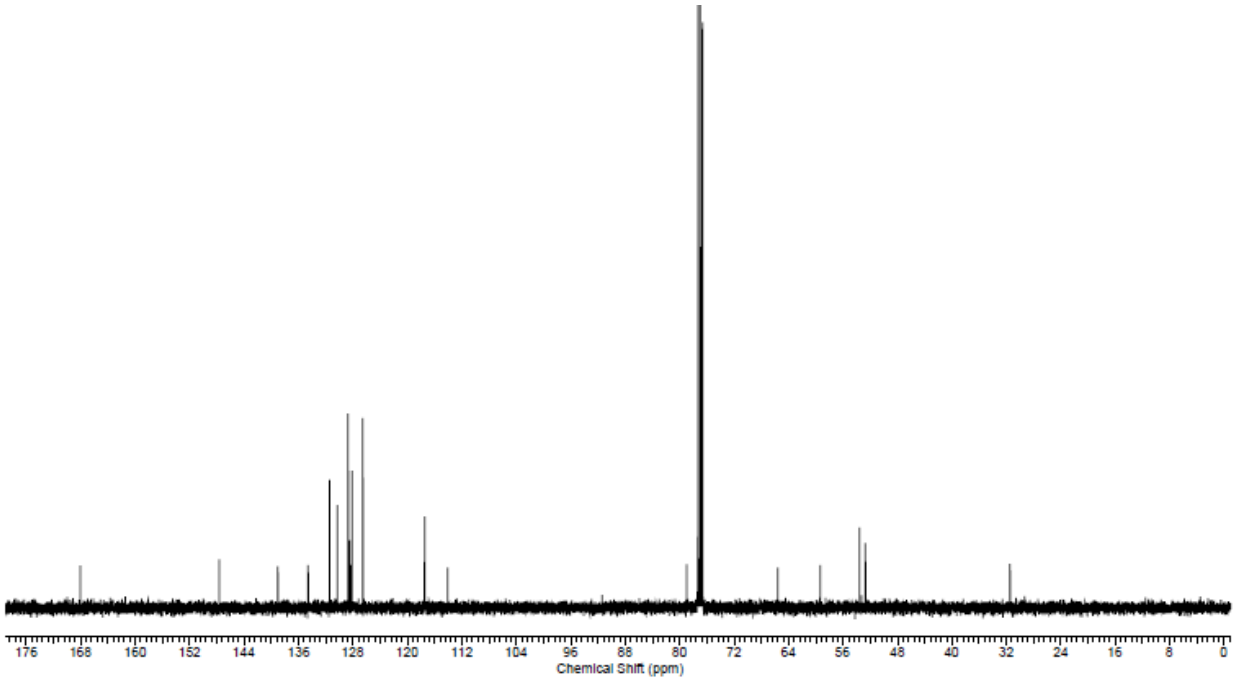

3.98 1.94 0.96 2.88 1.83 0.87
1.00
0.96
2.99
2.99
1.02 1.01

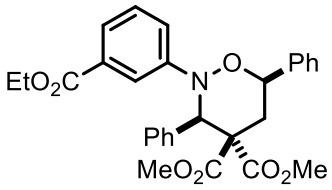



Br
N
O
Ph
Ph
MeO2C
CO2Me

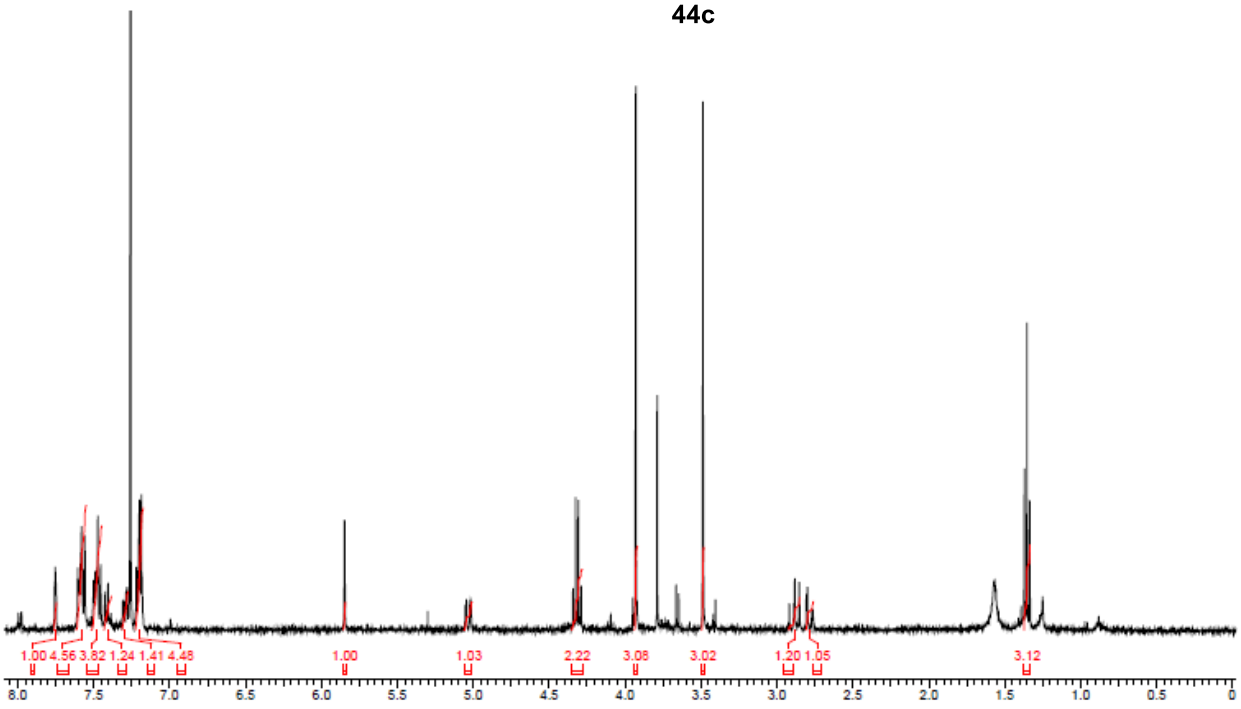
44b

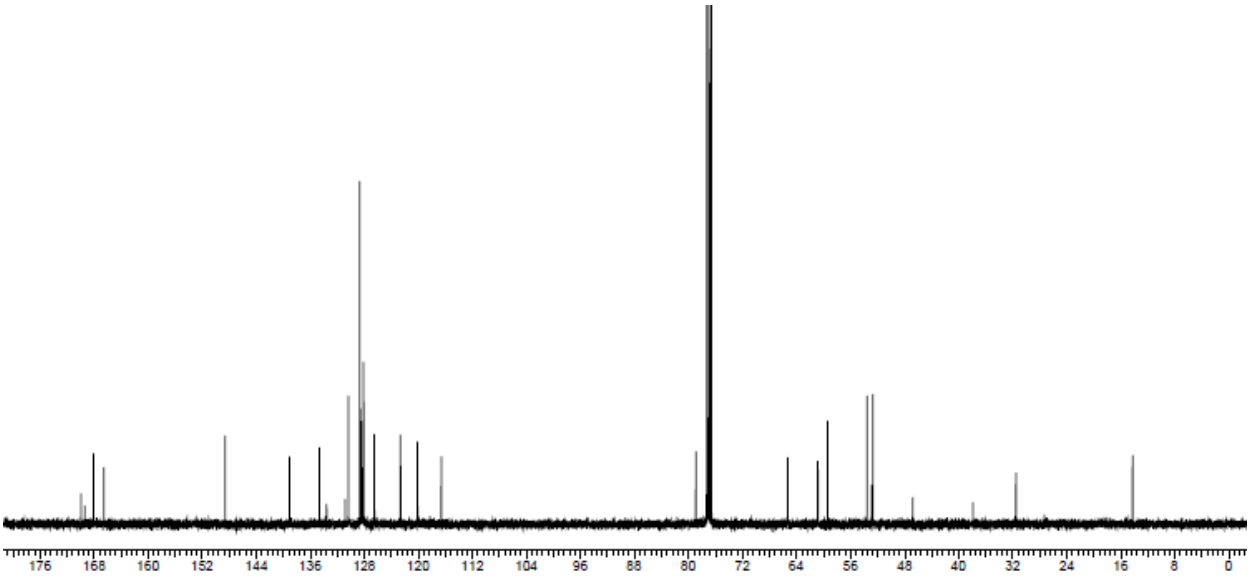

4.19 2.47 1.37 5.09 1.93
1.00
1.27
2.66
2.84
1.82 1.43
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

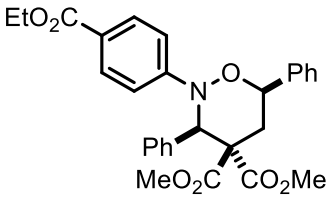

176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)


EtO2C
N
O
Ph
Ph
MeO2C
CO2Me

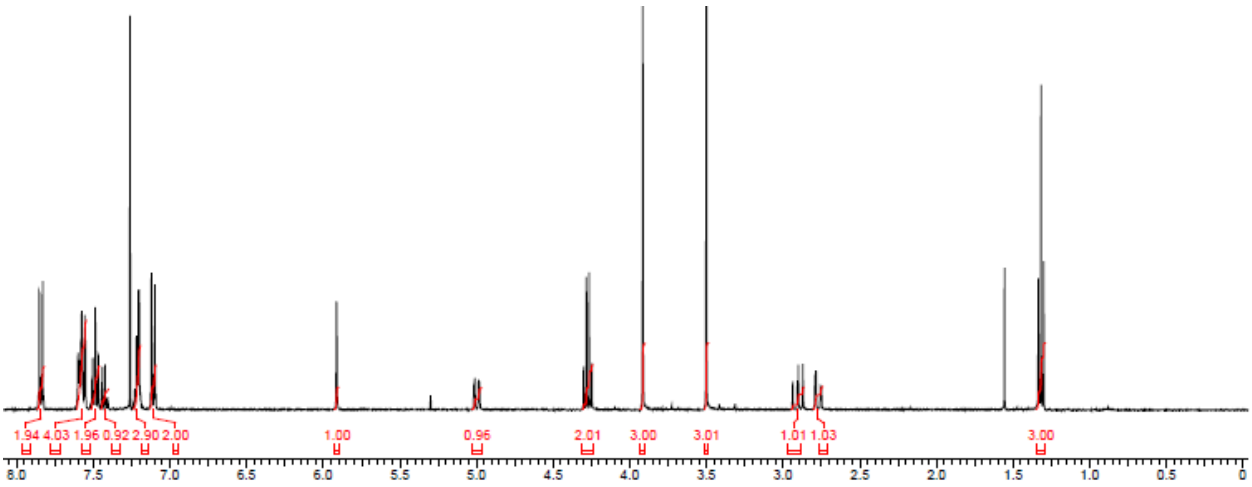
44c

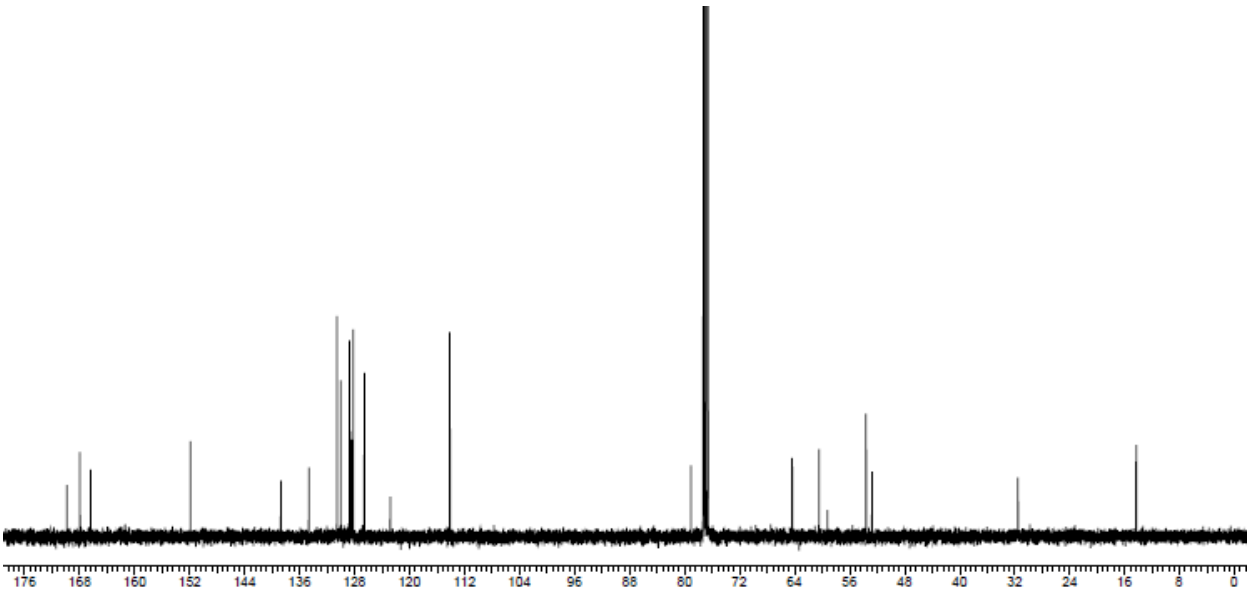

1.00 4.56 3.82 1.24 1.41 4.48
1.00
1.03
2.22
3.08
3.02
1.20 1.05
3.12

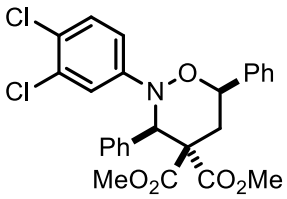



EtO2C
N
O
Ph
Ph
MeO2C
CO2Me

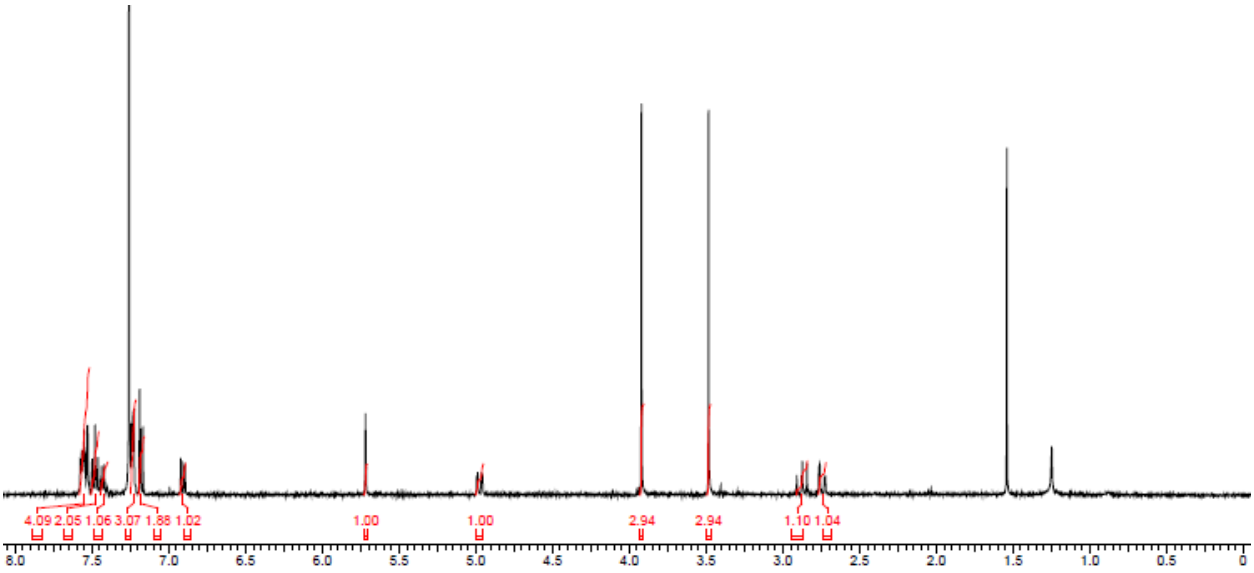
44d

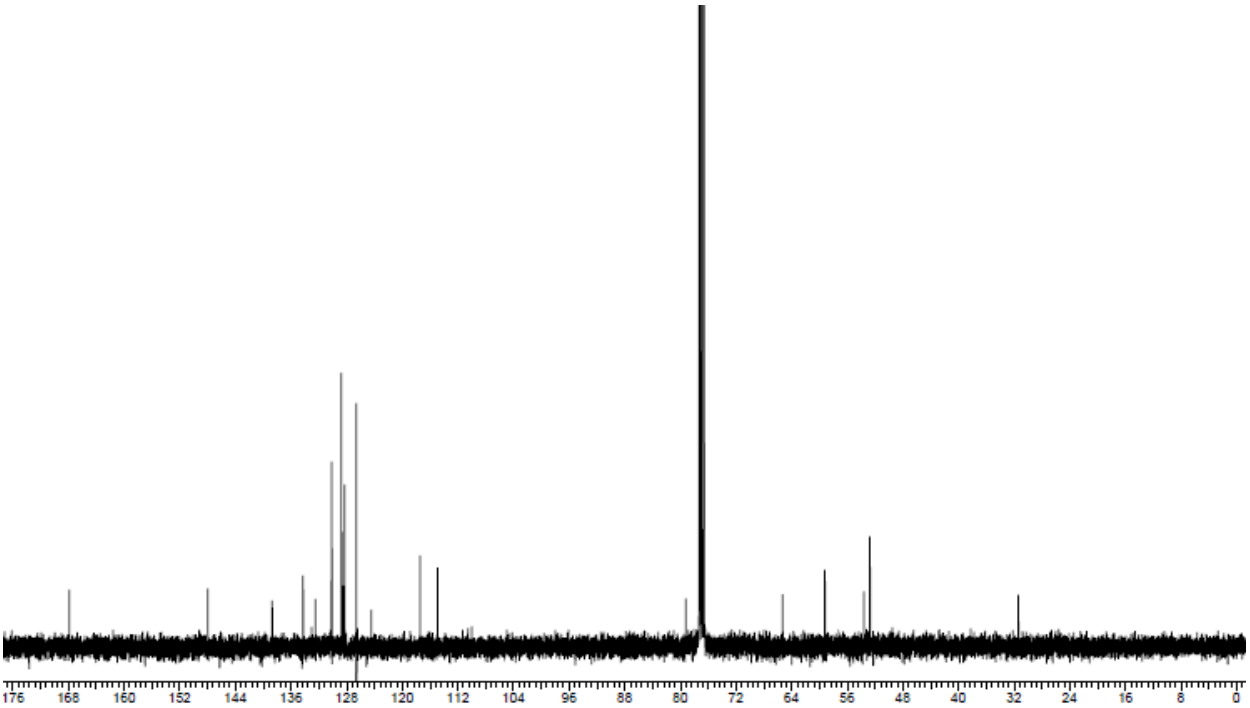

1.94 4.03 1.96 0.92 2.90 2.00
1.00
0.96
2.01
3.00
3.01
1.01 1.03
3.00

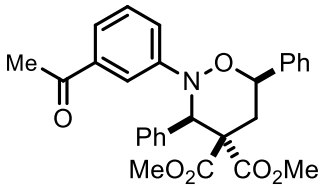



Cl
Cl
N
O
Ph
Ph
MeO2C
CO2Me

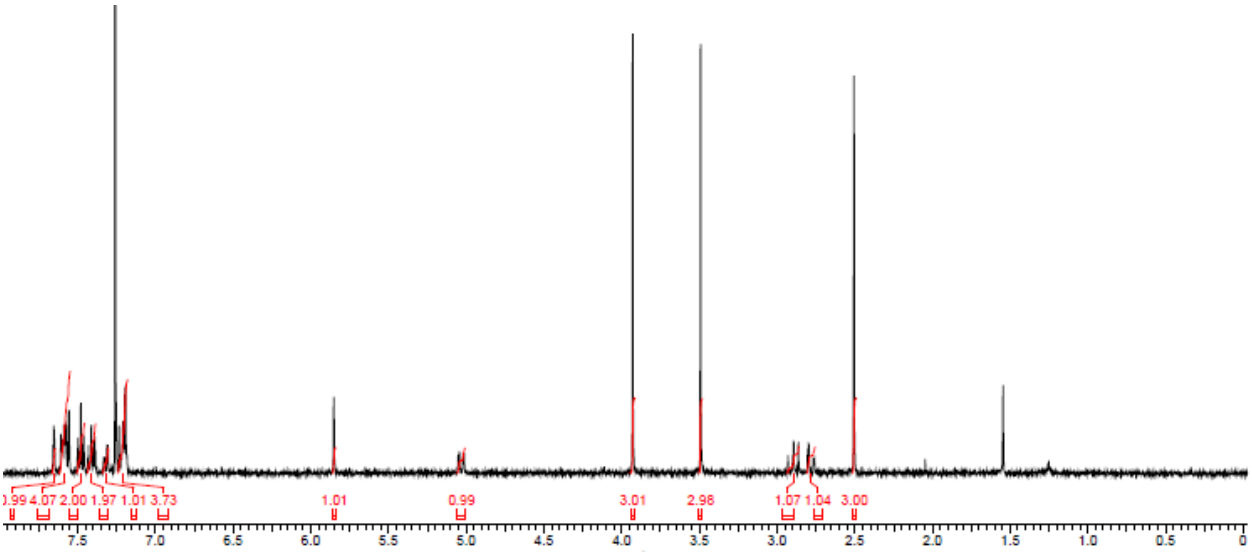
44e

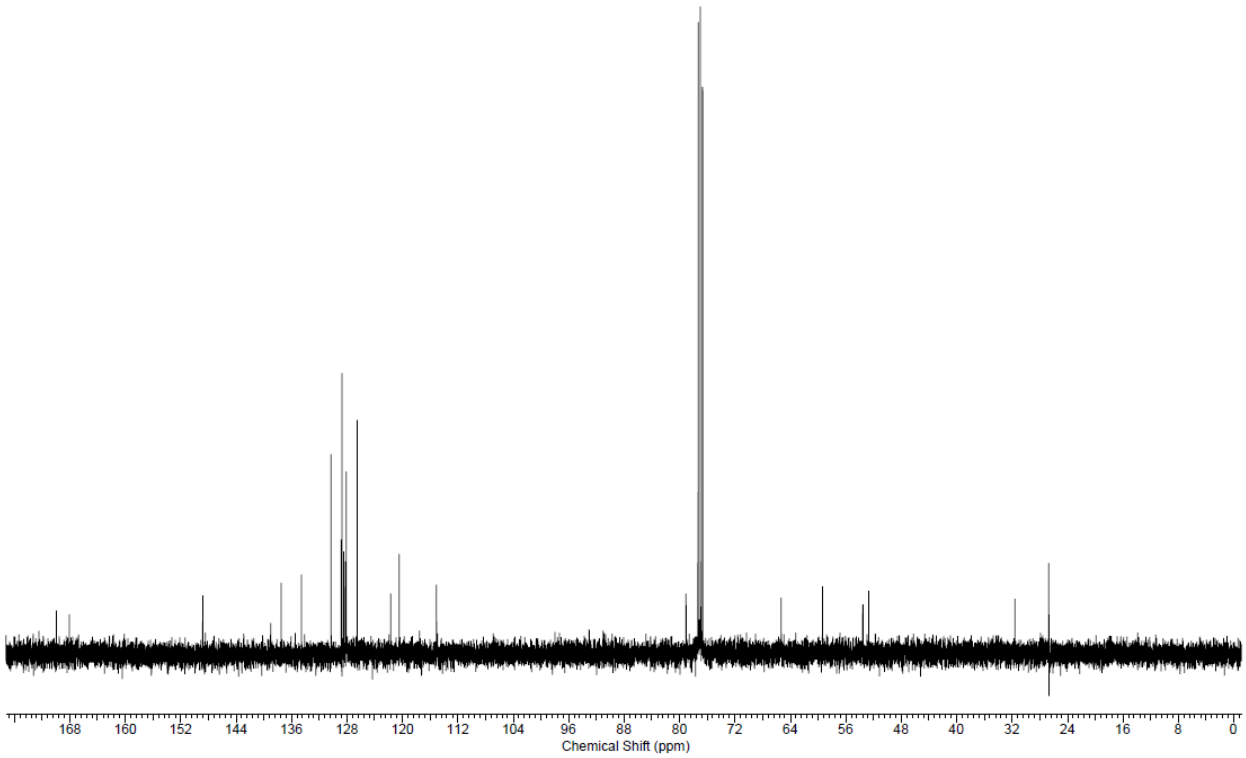

4.09 2.05 1.06 3.07 1.38 1.02
1.00
1.00
2.94
2.94
1.10 1.04
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0

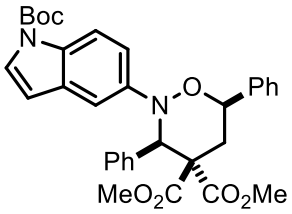

176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0


Me
O
N
O
Ph
Ph
MeO2C
CO2Me

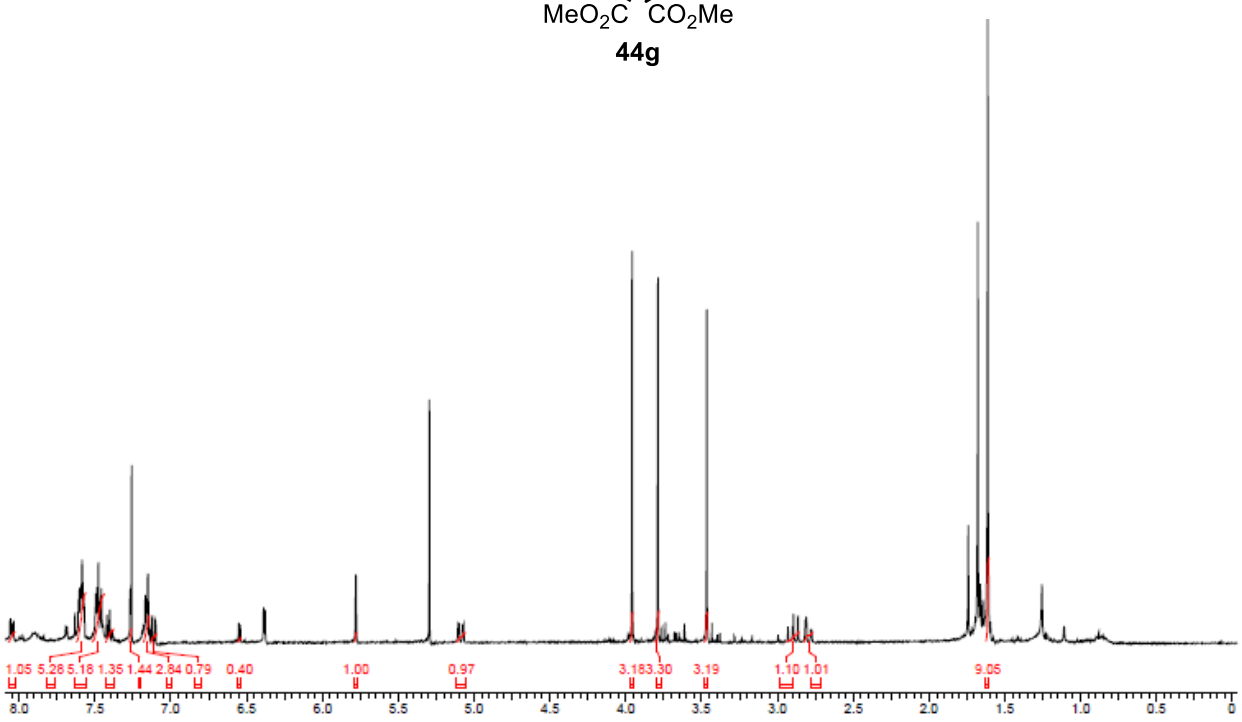
44f

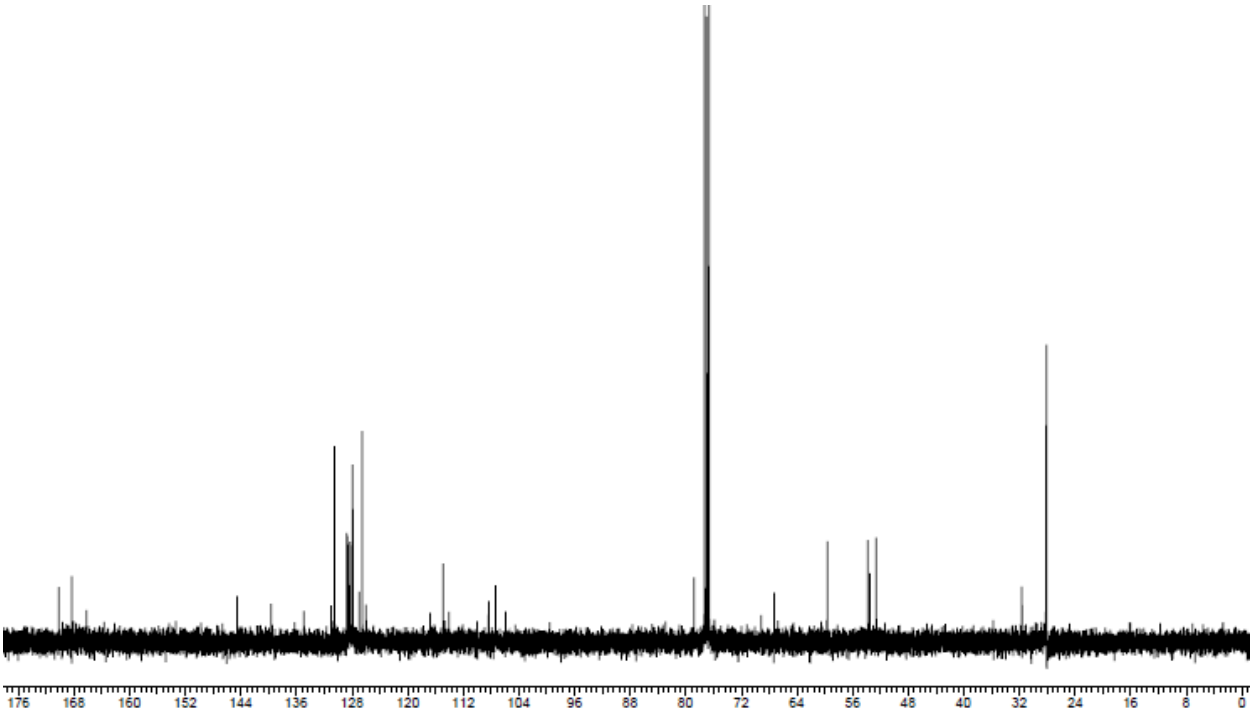

1.99 4.07 2.00 1.97 1.01 3.73
1.01
0.99
3.01
2.98
1.07 1.04
3.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0


168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

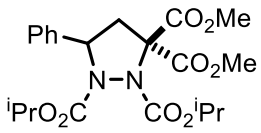

Boc
N
N
O
Ph
Ph
MeO2C
CO2Me

44g

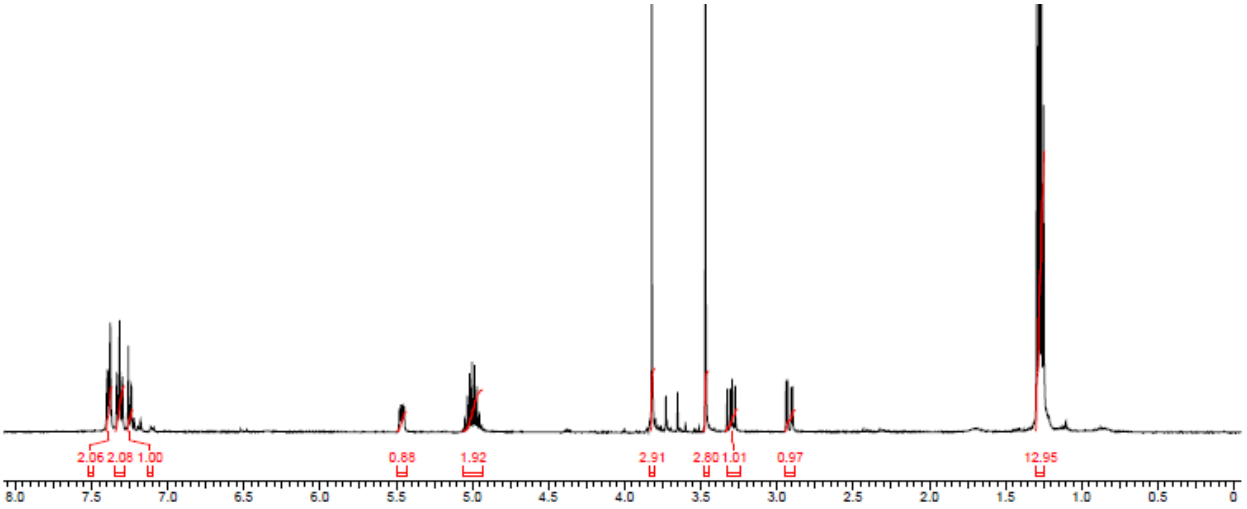

1.05 5.28 5.18 1.35 1.44 2.84 0.79 0.40 1.00 0.97 3.18 3.30 3.19 1.10 1.01 9.05
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0

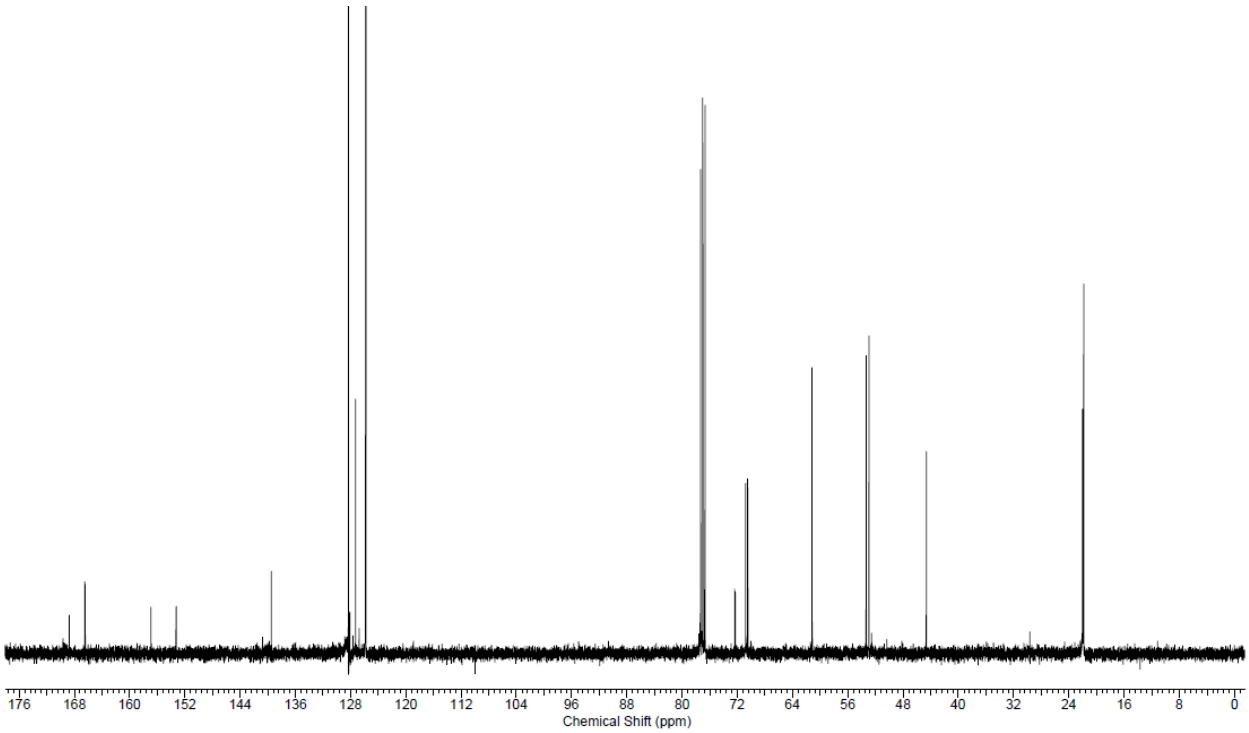

176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0

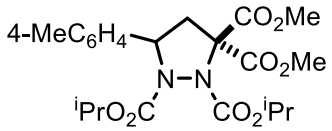
Appendix 2 - NMR Data Chapter 3



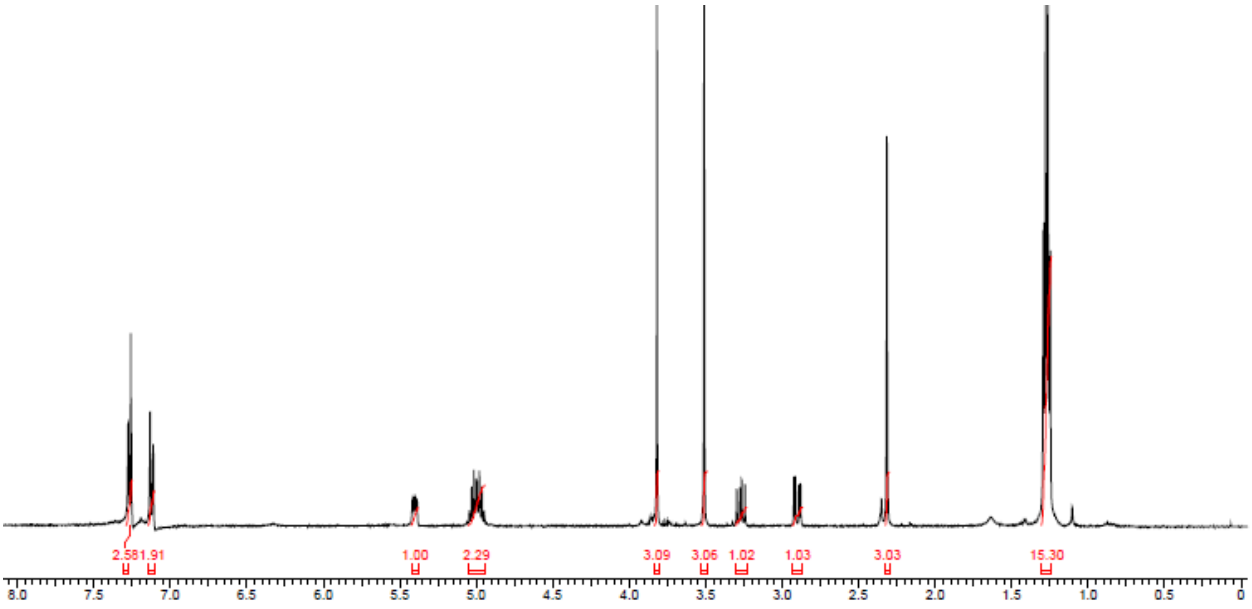
48a

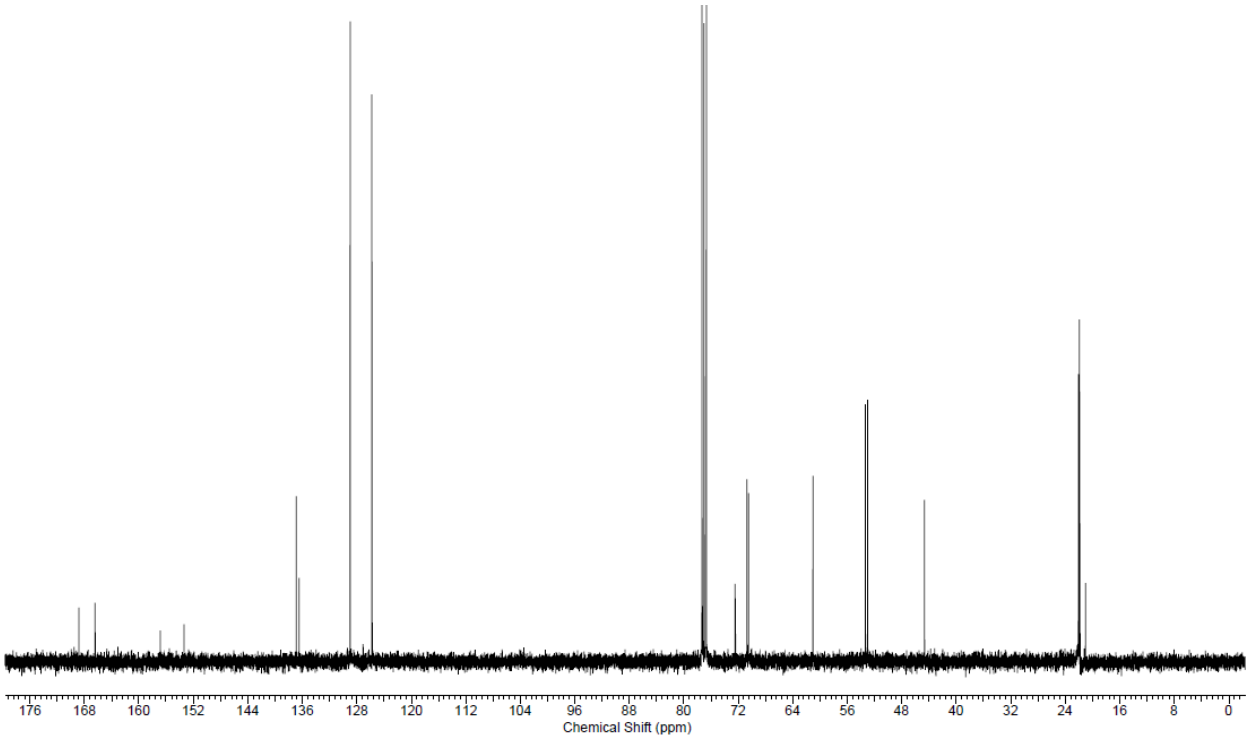


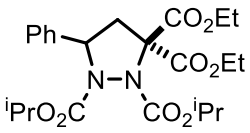



4-MeC6H4
CO2Me
CO2Me
N–N
iPrO2C
CO2iPr

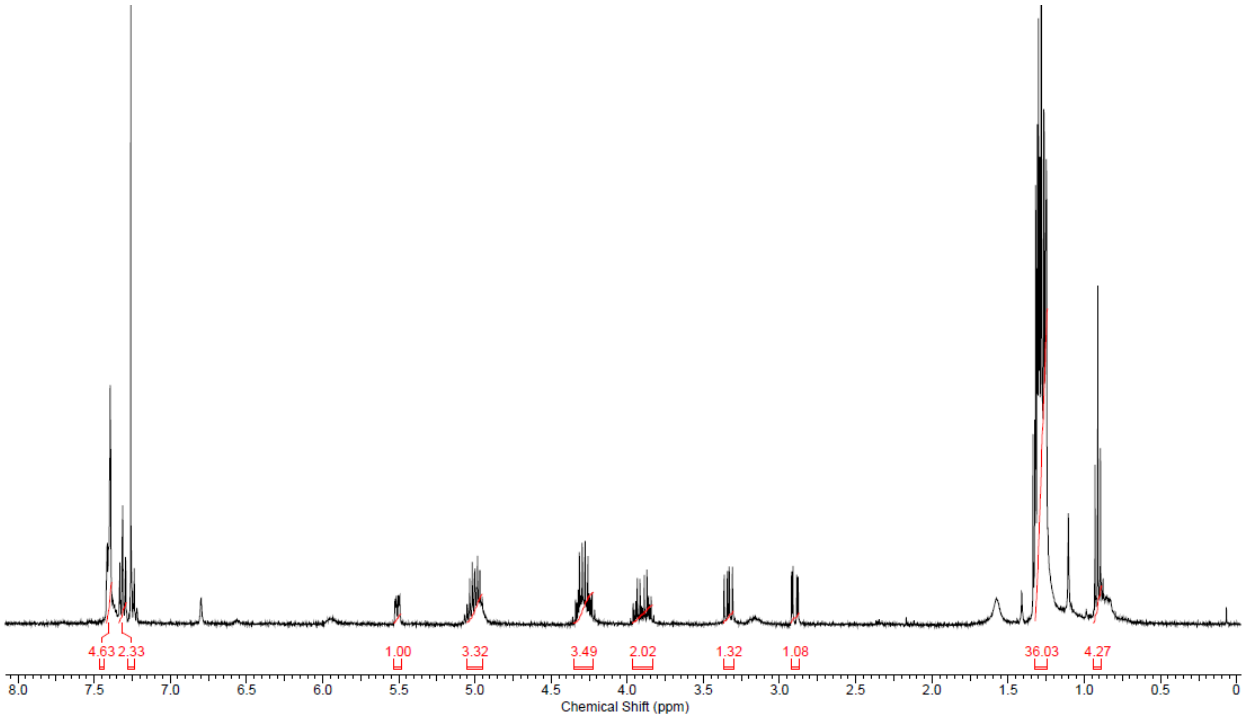
48b

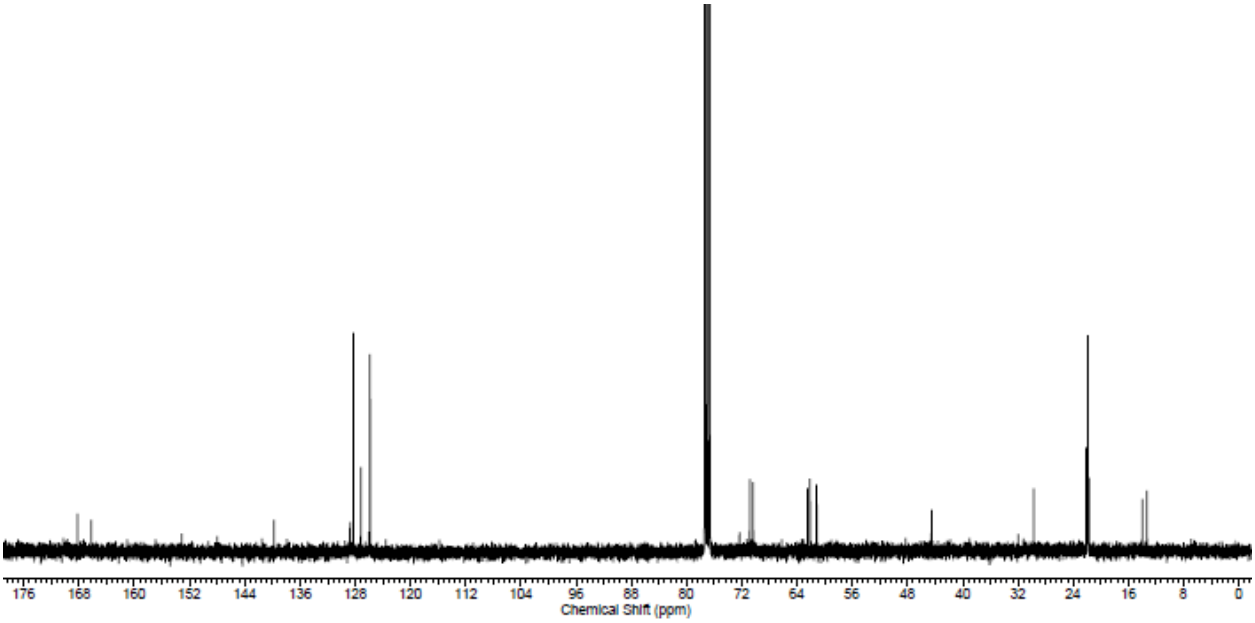

2.58
1.91
1.00
2.29
3.09
3.06
1.02
1.03
3.03
15.30
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0

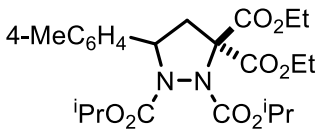

176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)


Ph
CO2Et
CO2Et
N–N
iPrO2C
CO2iPr

48c

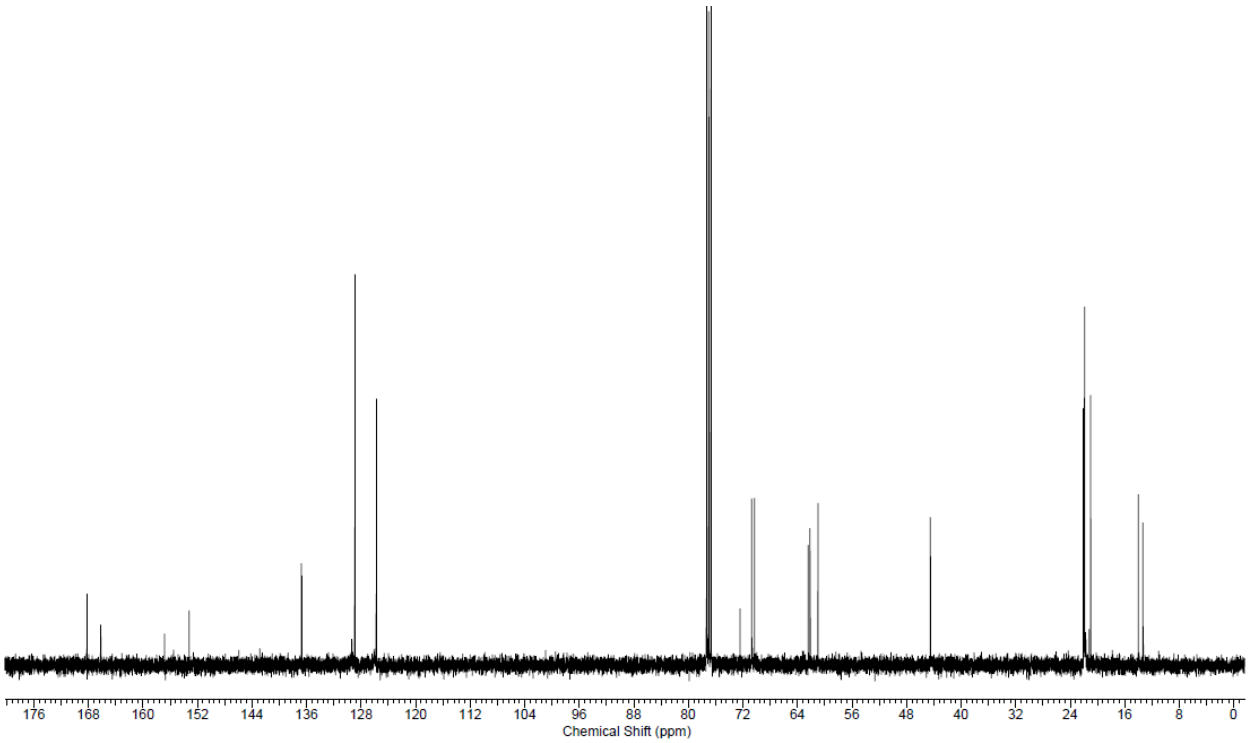

4.63
2.33
1.00
3.32
3.49
2.02
1.32
1.08
36.03
4.27
Chemical Shift (ppm)


Chemical Shift (ppm)


4-MeC6H4
CO2Et
CO2Et
N–N
iPrO2C
CO2iPr

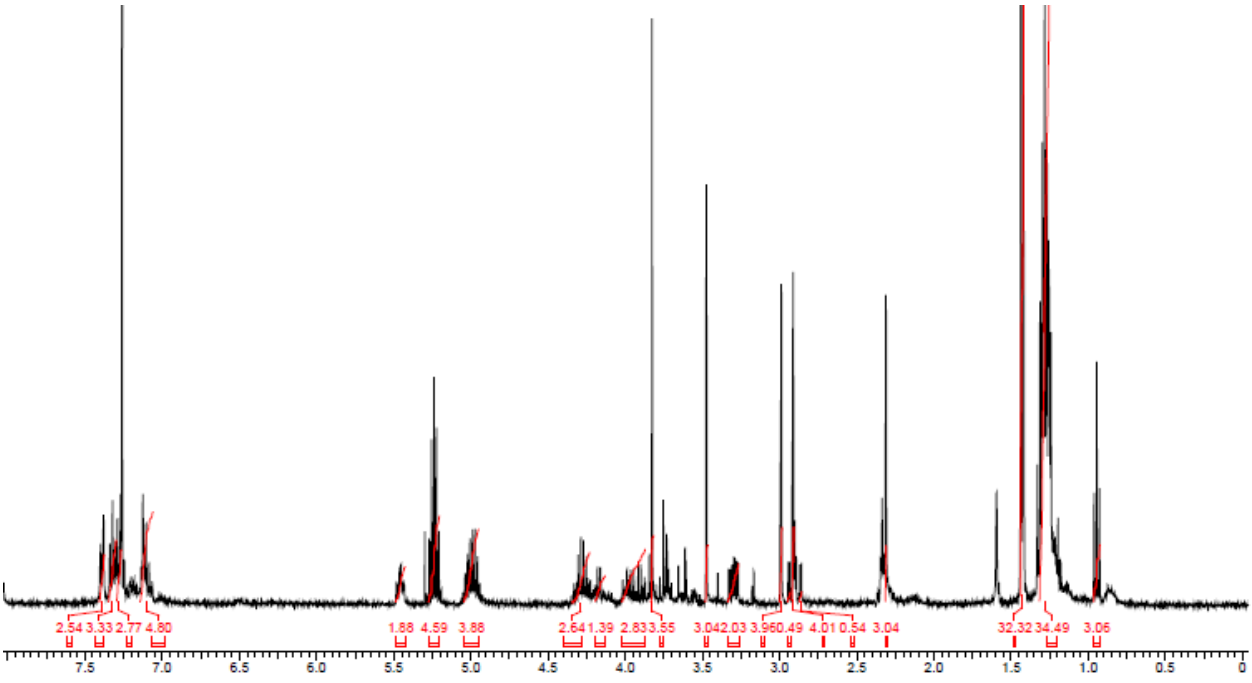
48d

2.55
2.18
1.01
2.64
2.80
2.10
1.23
1.09
3.40
21.68
3.14
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
Chemical Shift (ppm)


176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

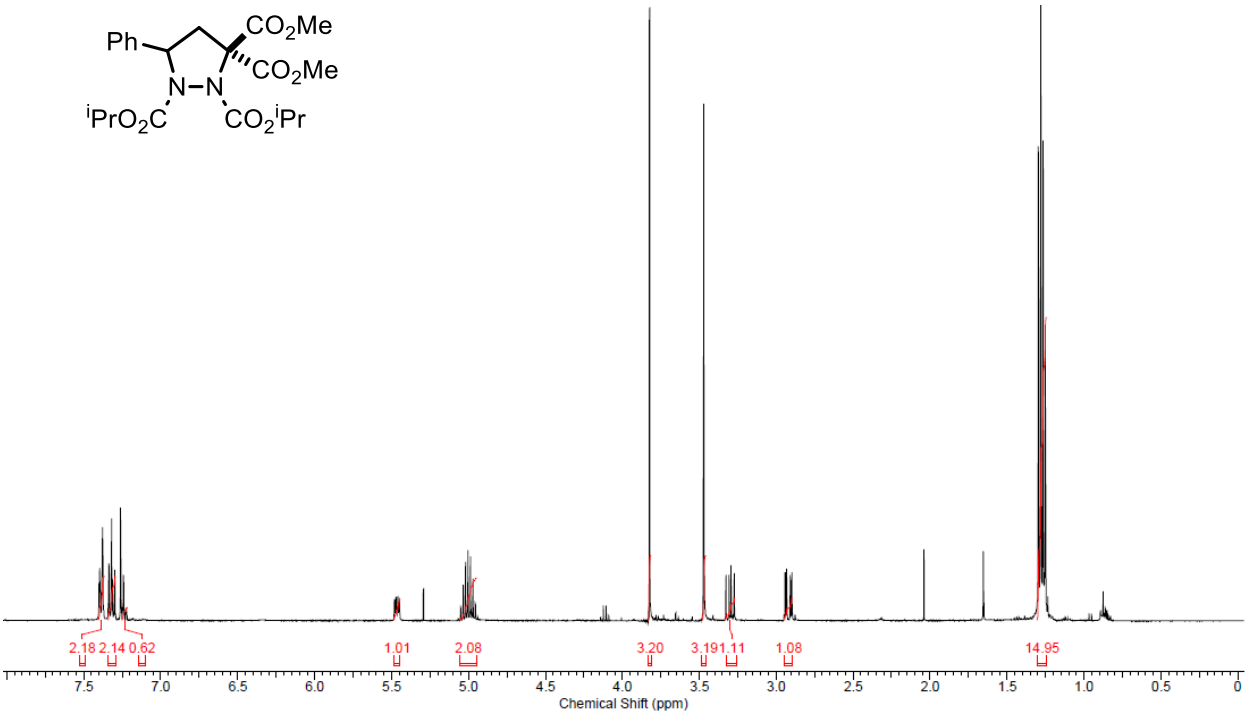
Cross-Over Experiment #2

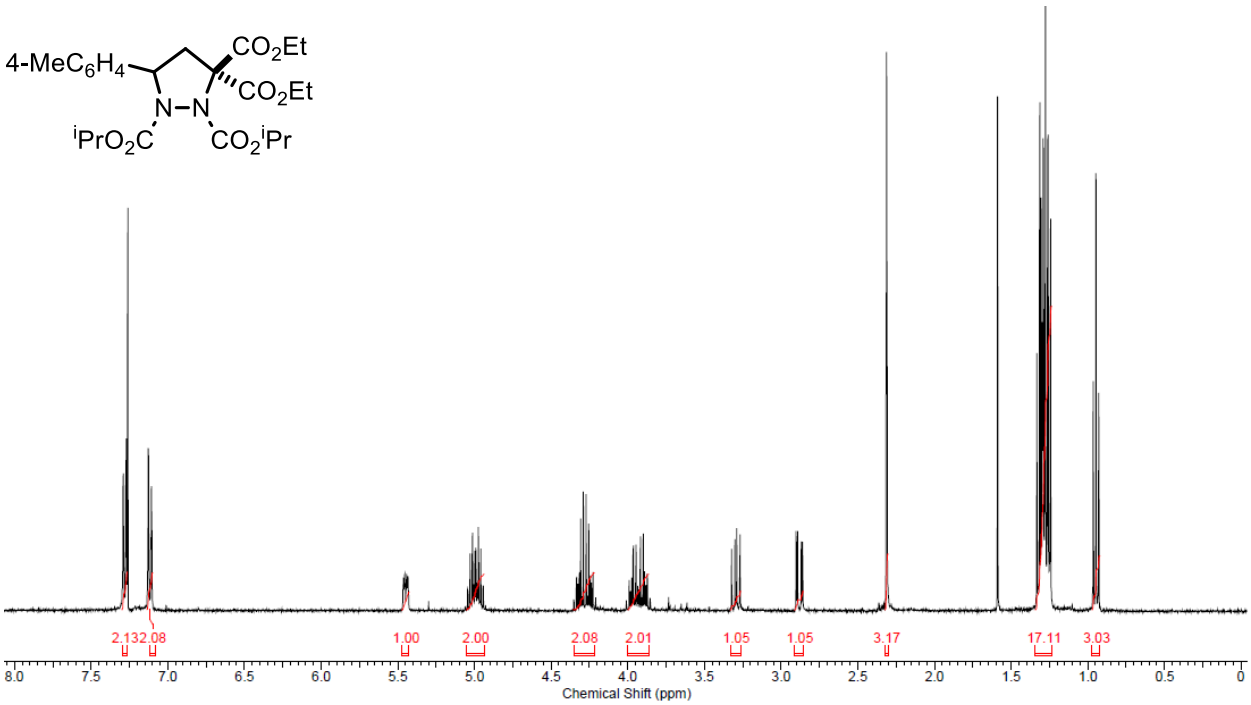
Crude Reaction Mixture

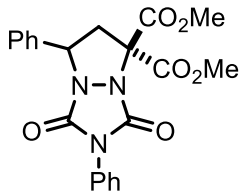


Cross-Over Experiment #2

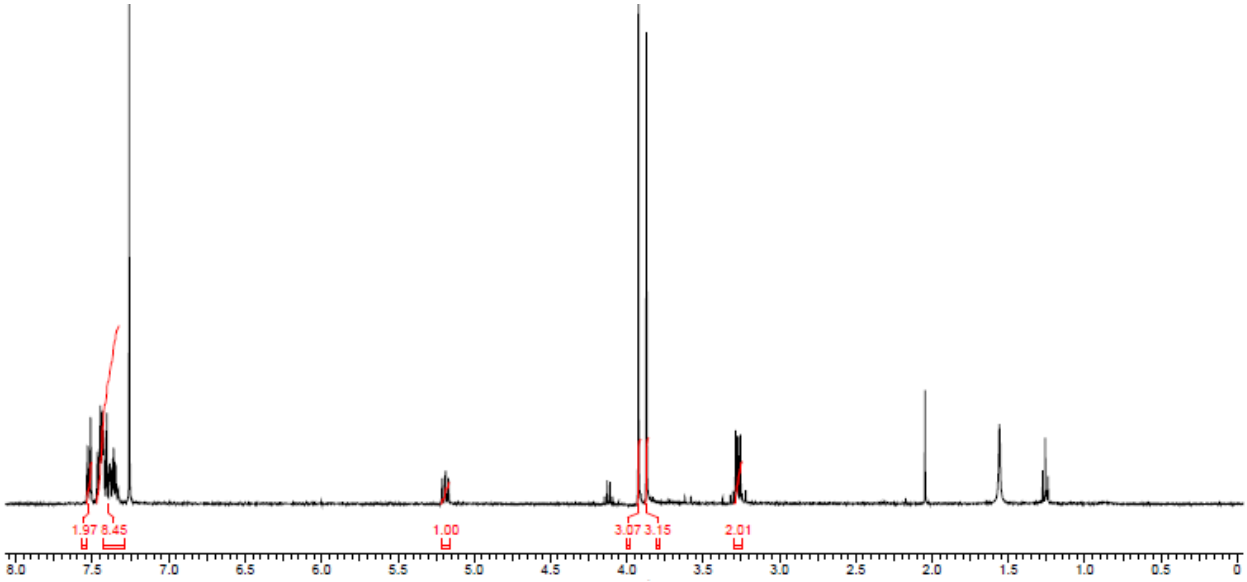
Isolated Products

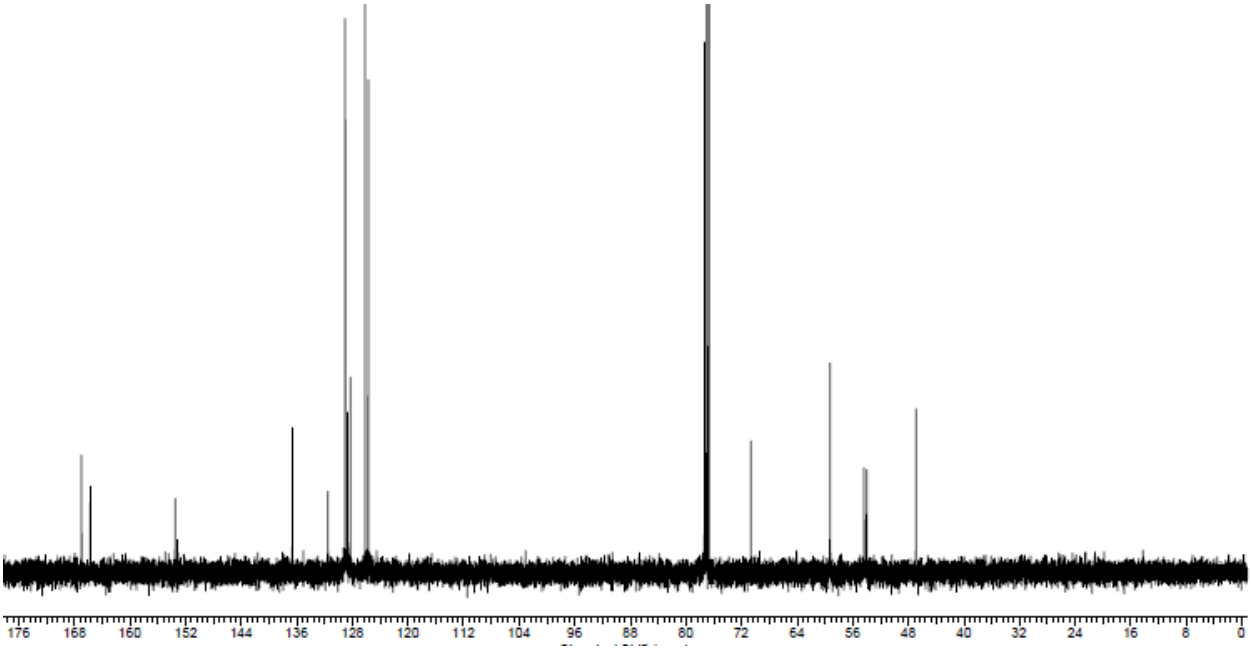


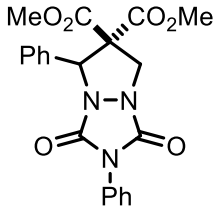



Ph
CO2Me
CO2Me
N
N
O
O
N
Ph

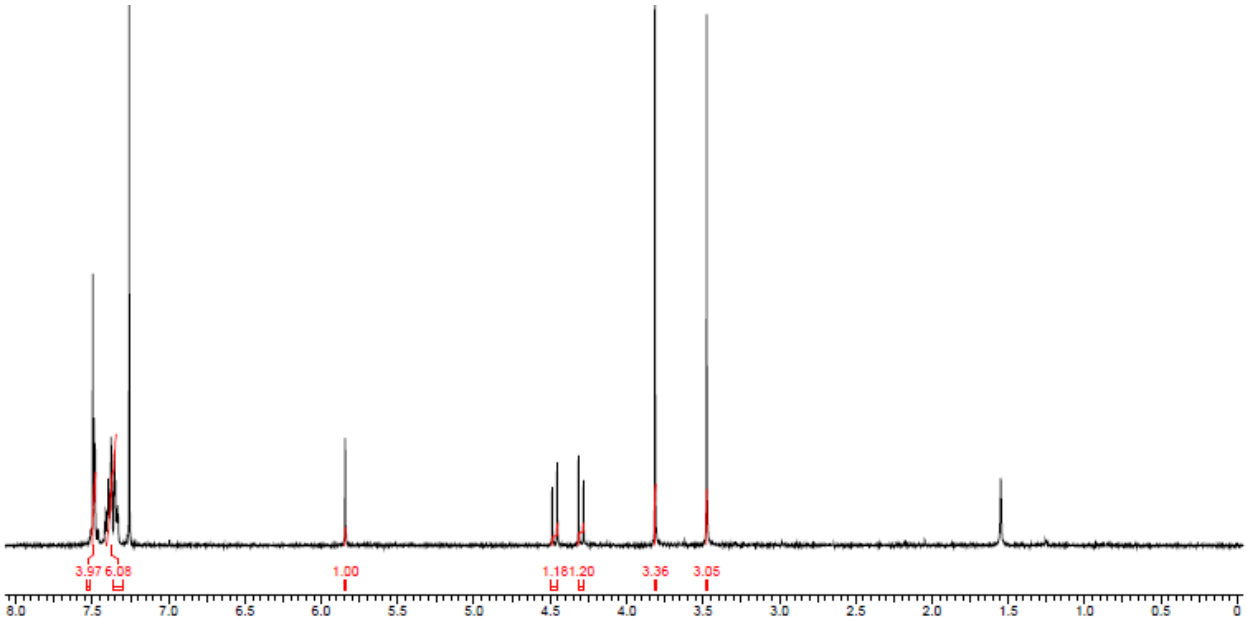
50a

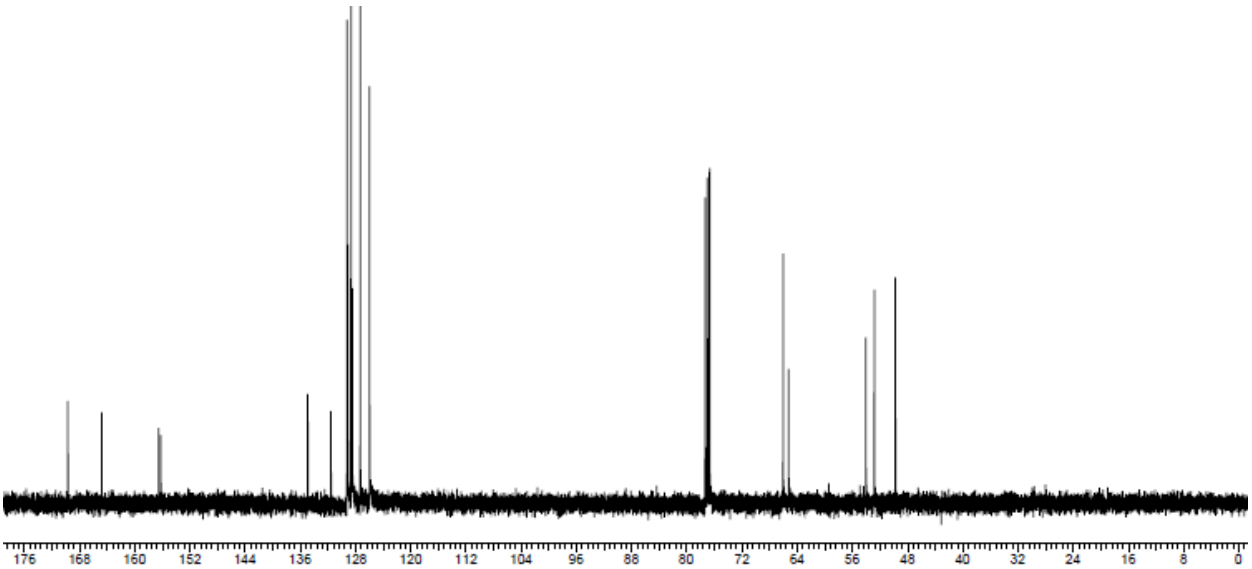

1.97
8.45
1.00
3.07
3.15
2.01
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0

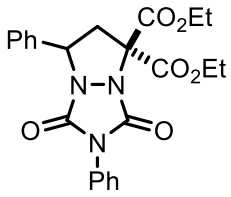

176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0



51a

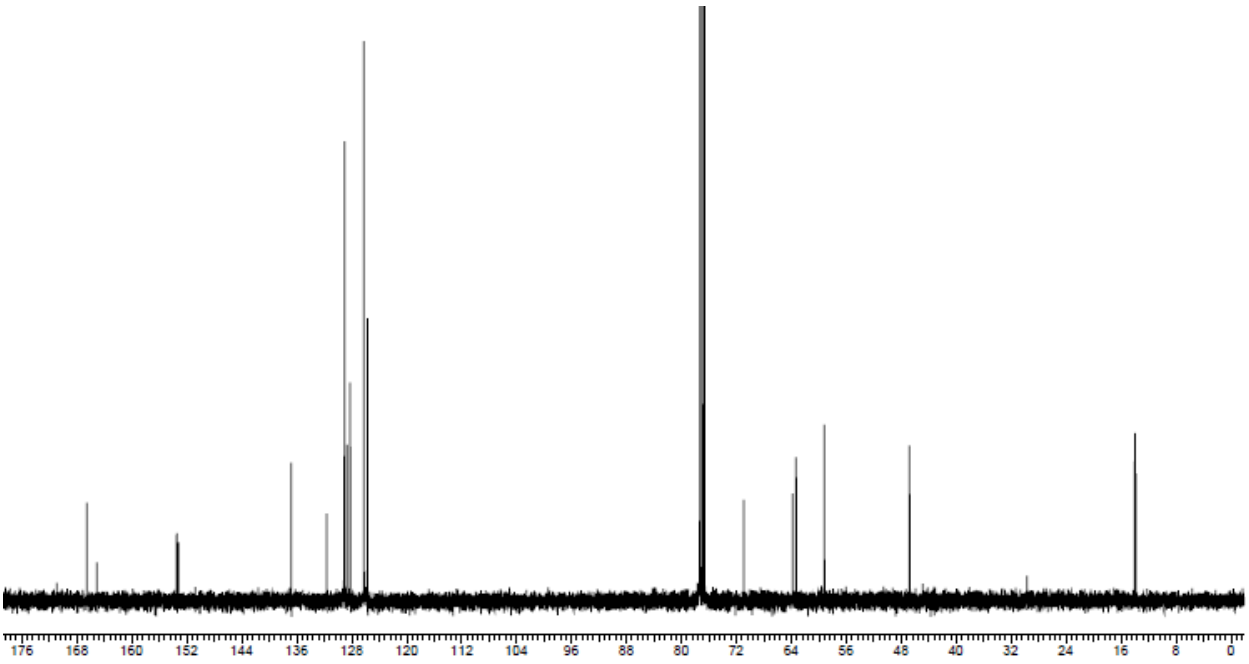


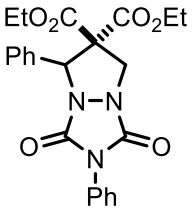



Ph
CO2Et
CO2Et
N
N
O
O
N
Ph

50b

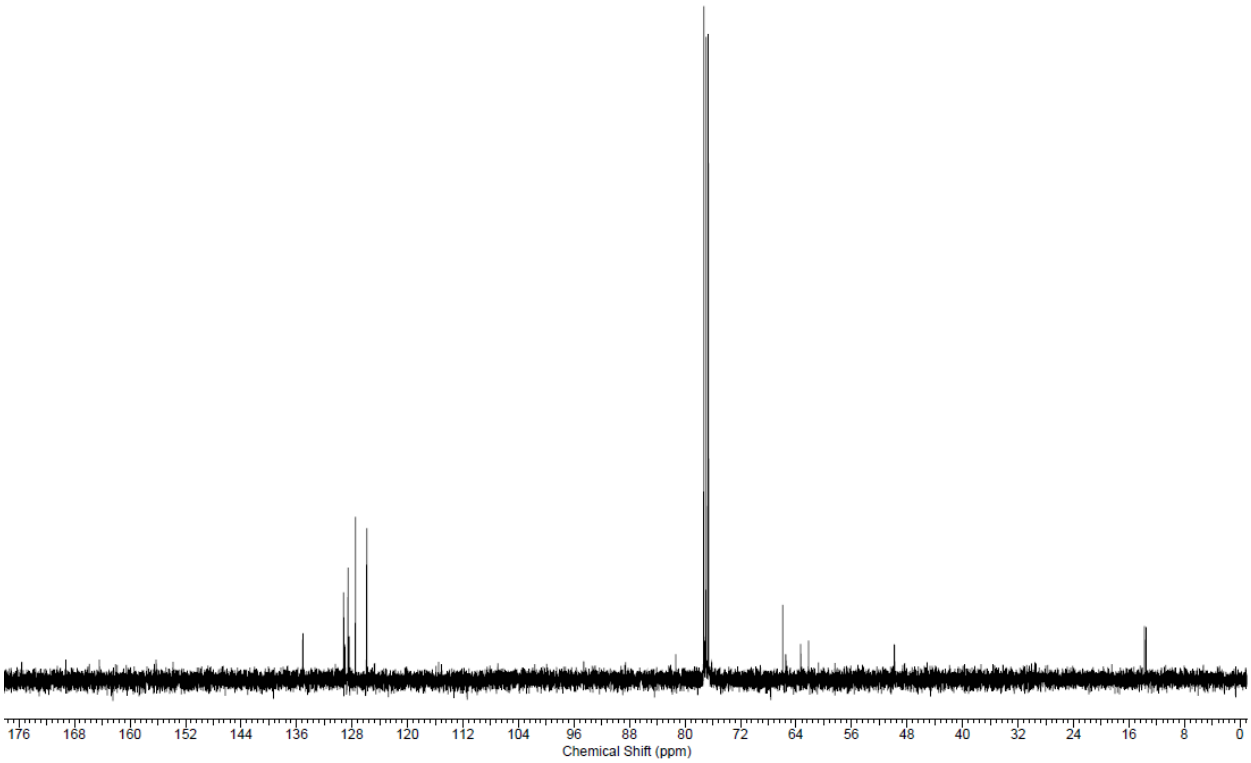
1.50
3.20
1.74
1.60
1.00
3.75
1.83
5.10
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

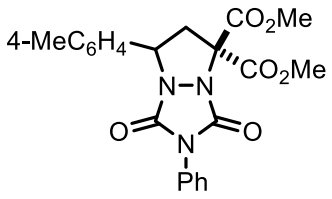

176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0


EtO2C
CO2Et
Ph
N
N
O
O
N
Ph

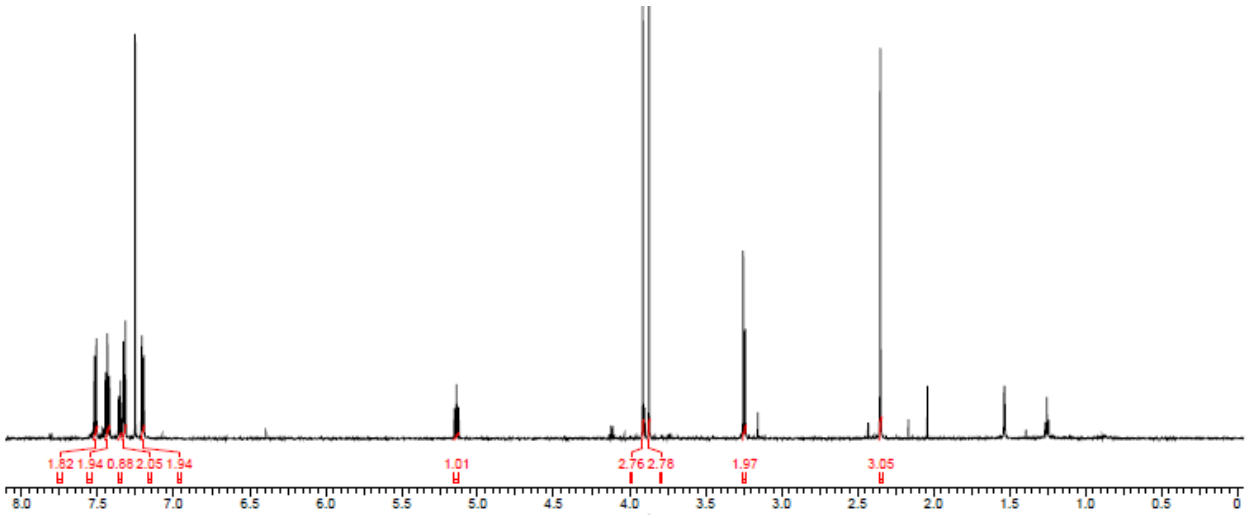
51b

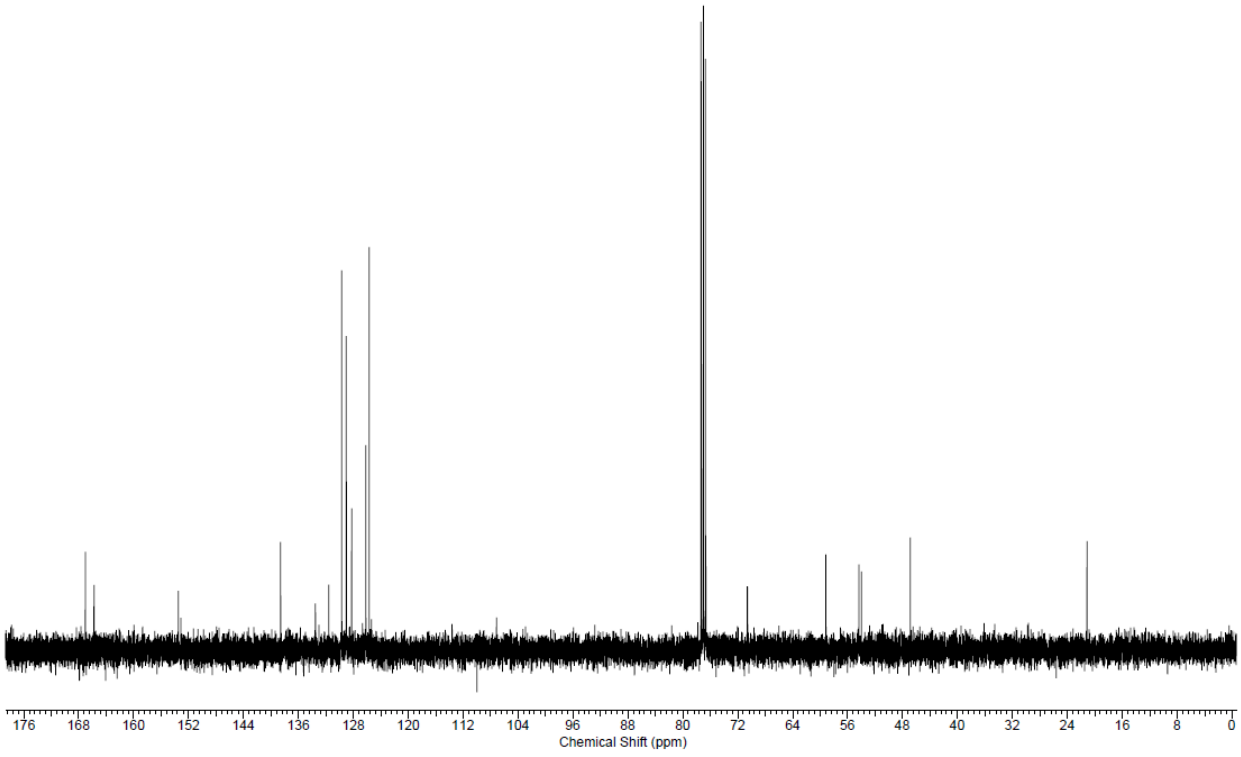
4.37 6.67
1.01
1.28 1.61 2.16 1.36 1.36
4.45 3.40
Chemical Shift (ppm)

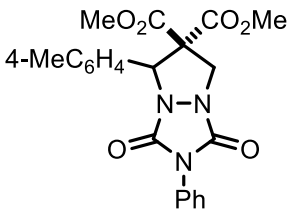

Chemical Shift (ppm)


4-MeC6H4
CO2Me
CO2Me
N
N
O
O
N
O
Ph

50c

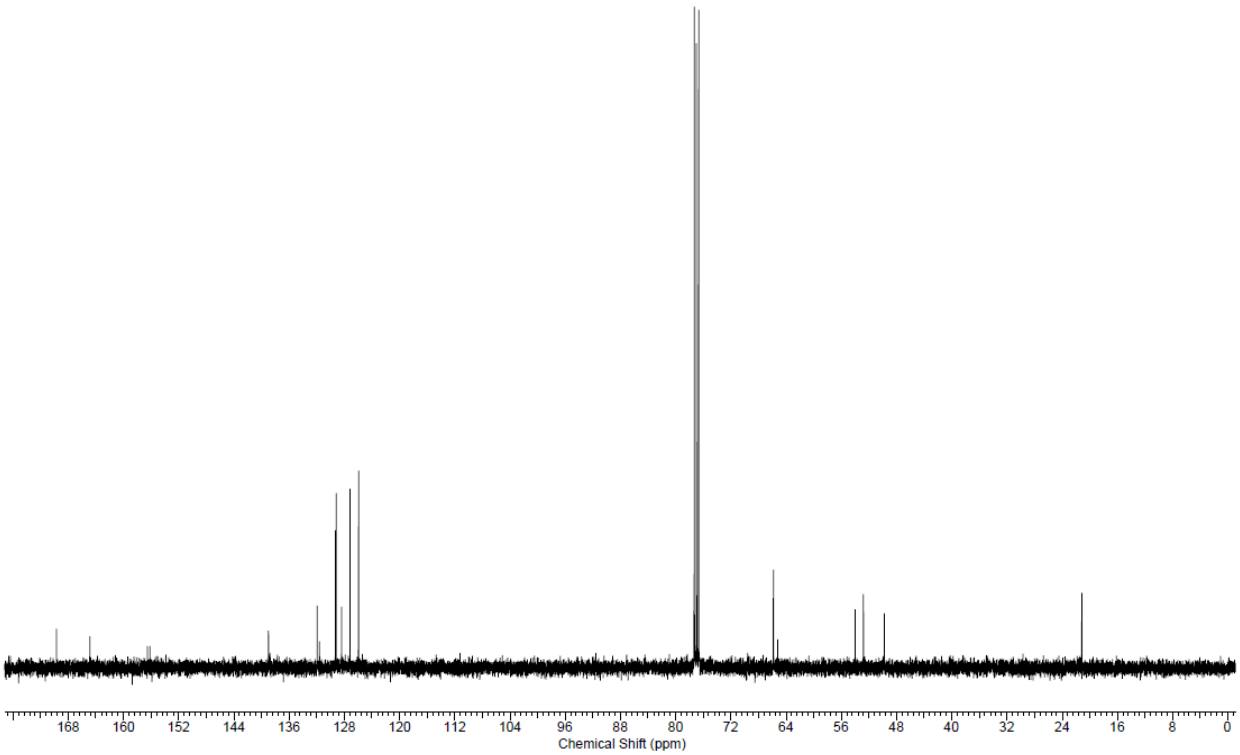

1.82 1.94 0.88 2.05 1.94
1.01
2.76 2.78
1.97
3.05
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0

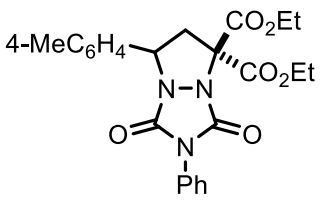

176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)


MeO2C
CO2Me
4-MeC6H4
N
N
O
O
N
Ph

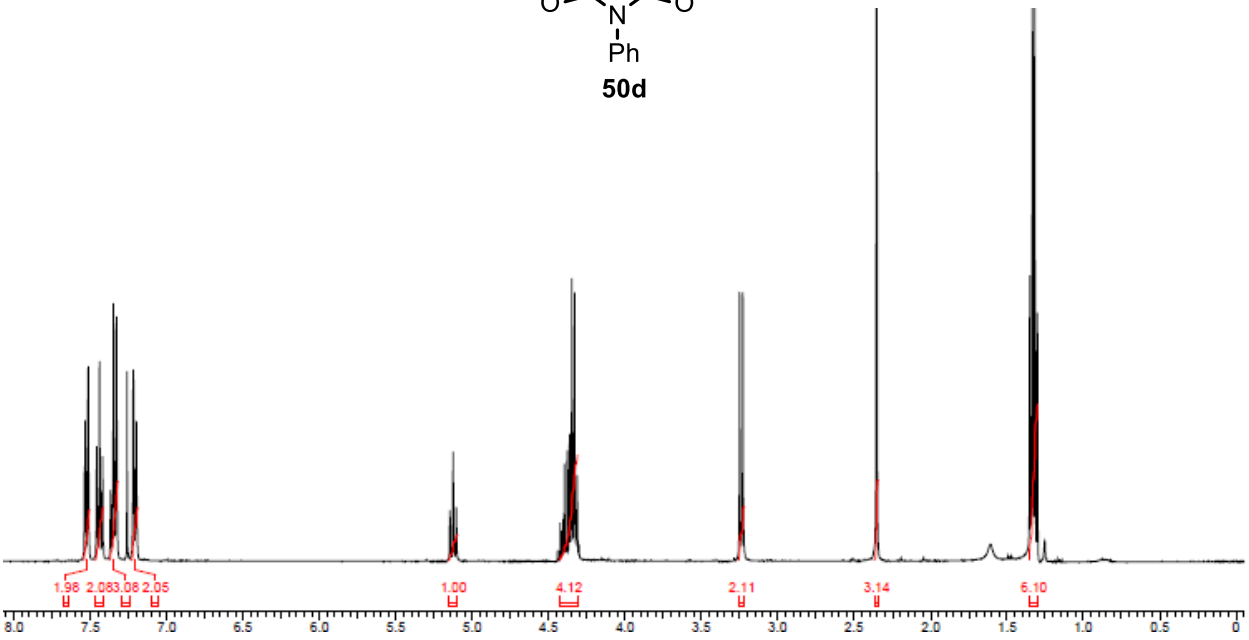
51c

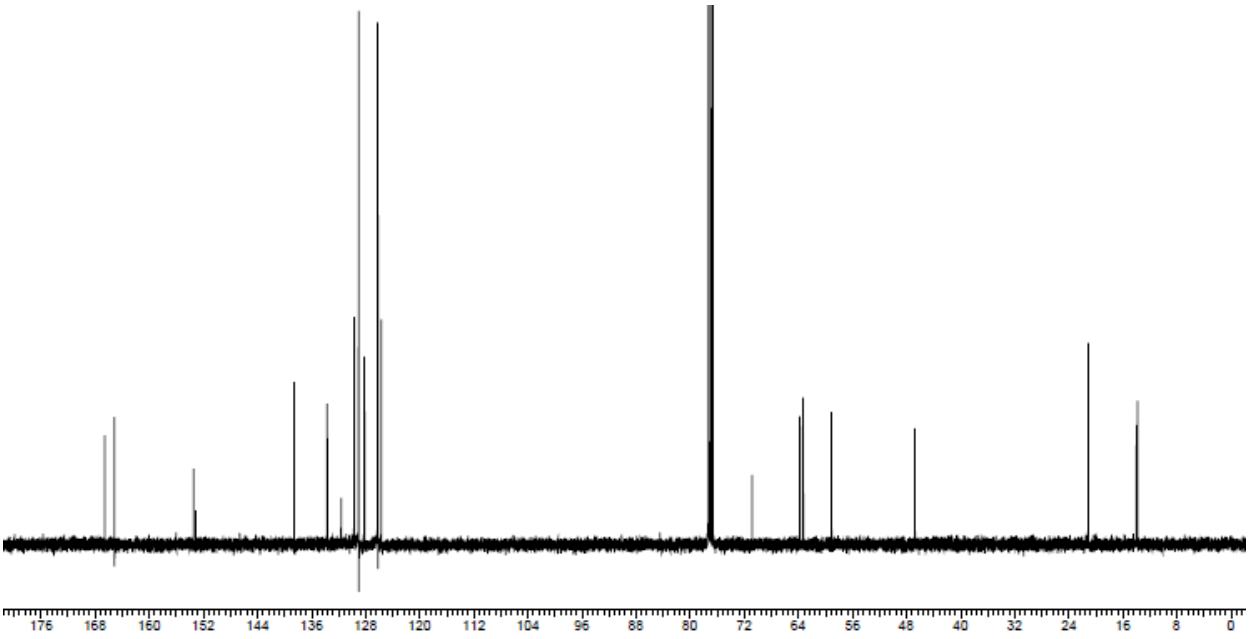
4.18
1.02
5.00
1.00
1.09
1.10
3.10
3.18
3.24
Chemical Shift (ppm)

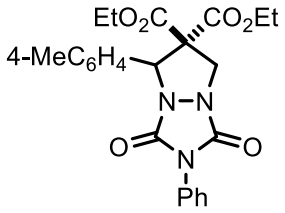

Chemical Shift (ppm)


4-MeC6H4
CO2Et
CO2Et
N
N
O
O
N
Ph

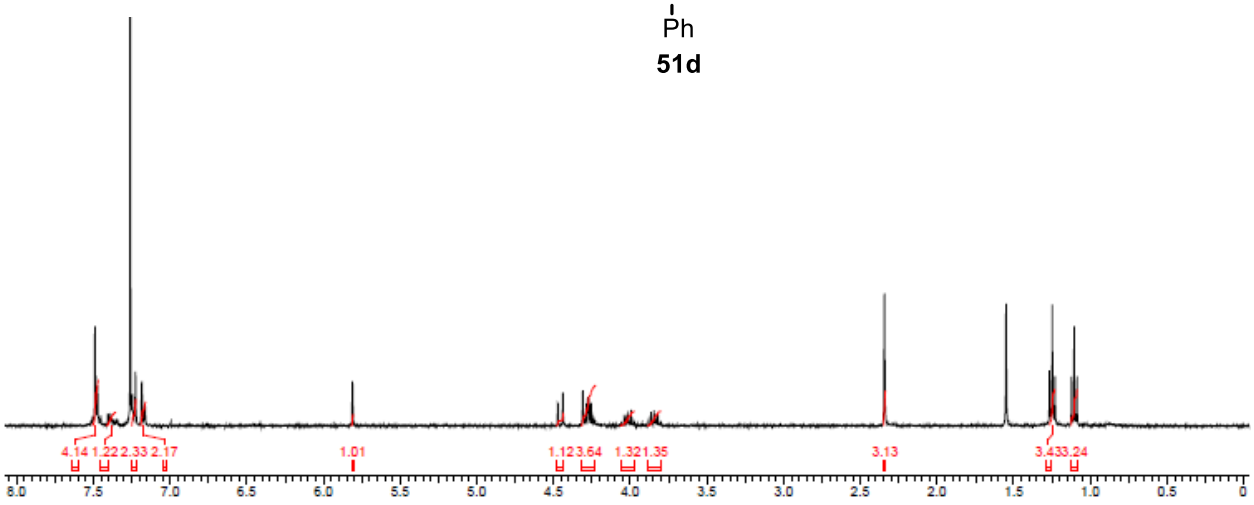
50d

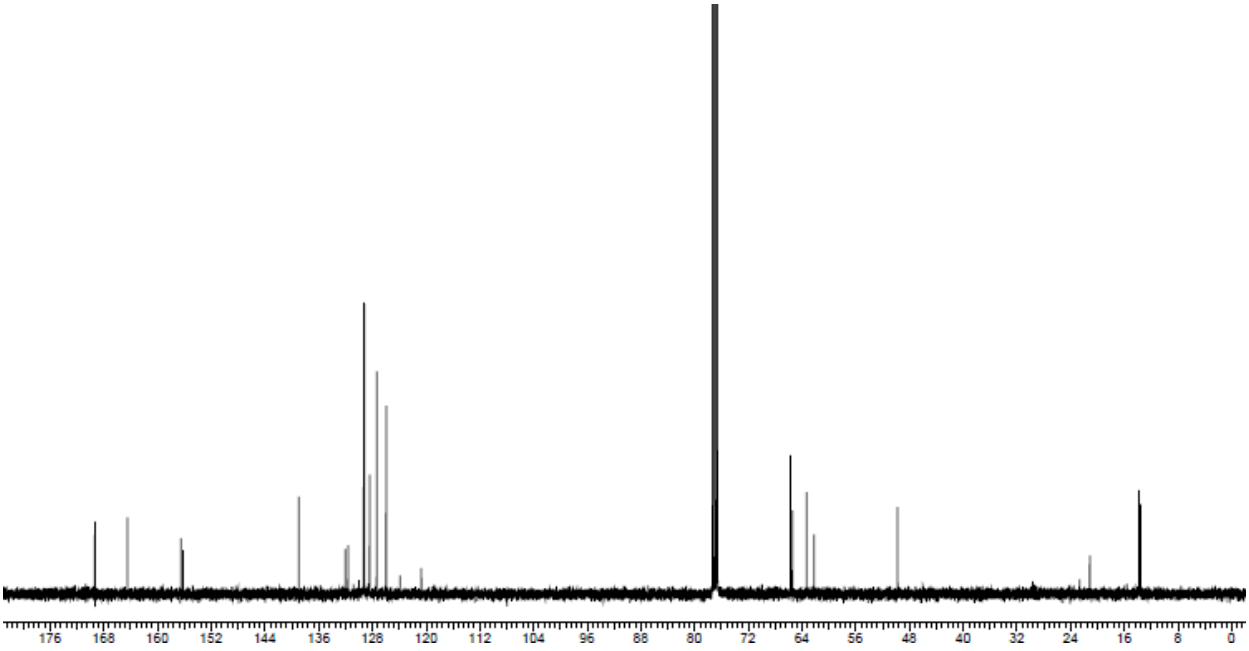

1.98
2.08
3.08
2.05
1.00
4.12
2.11
3.14
6.10



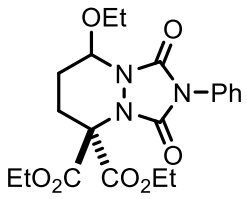

EtO2C
CO2Et
4-MeC6H4
N–N
O
O
N
Ph

51d

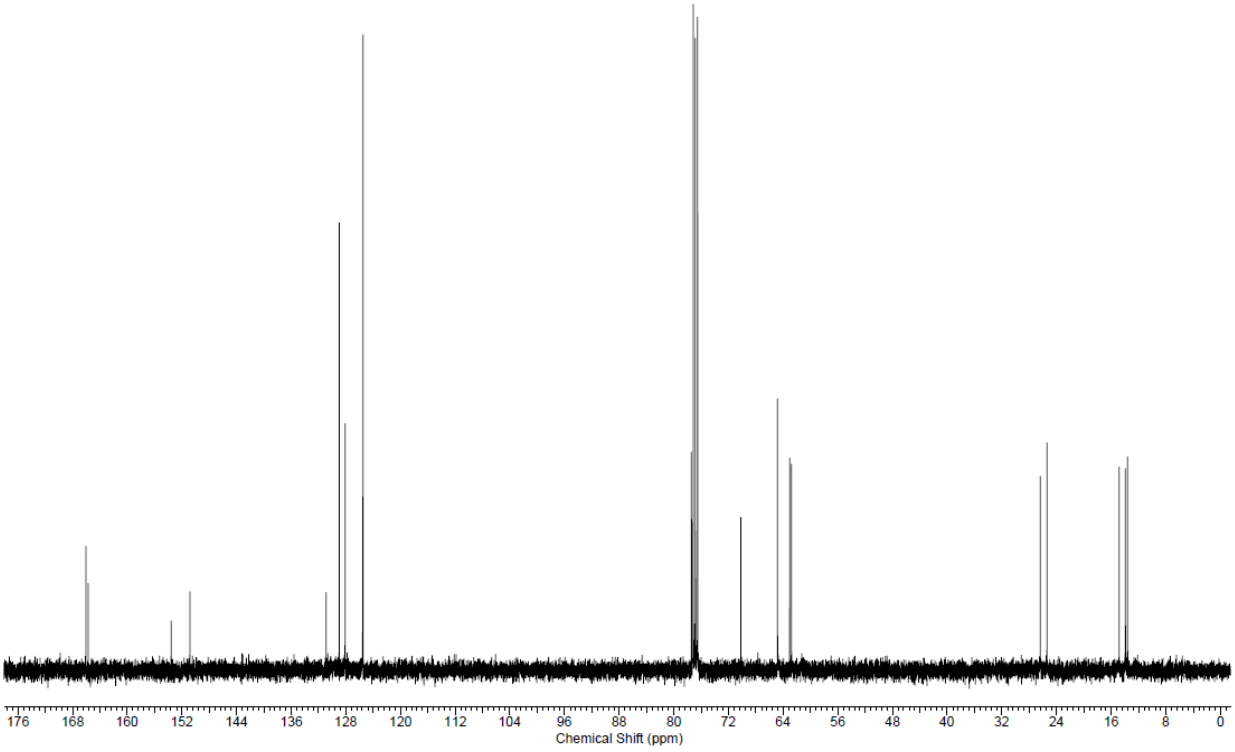

4.14 1.22 2.33 2.17
1.01
1.12 3.64
1.32 1.35
3.13
3.43 3.24

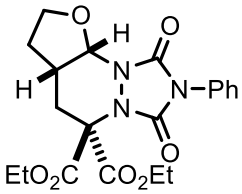


Appendix 3 - NMR Data Chapter 4

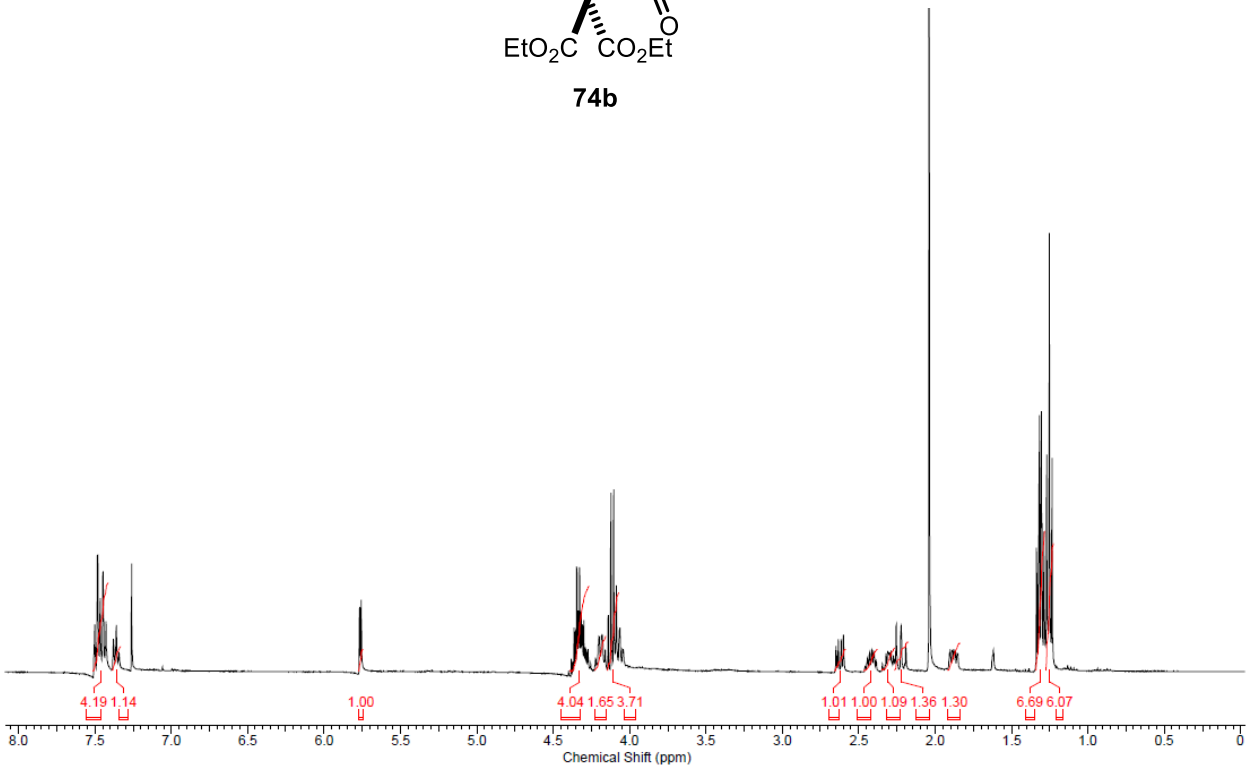


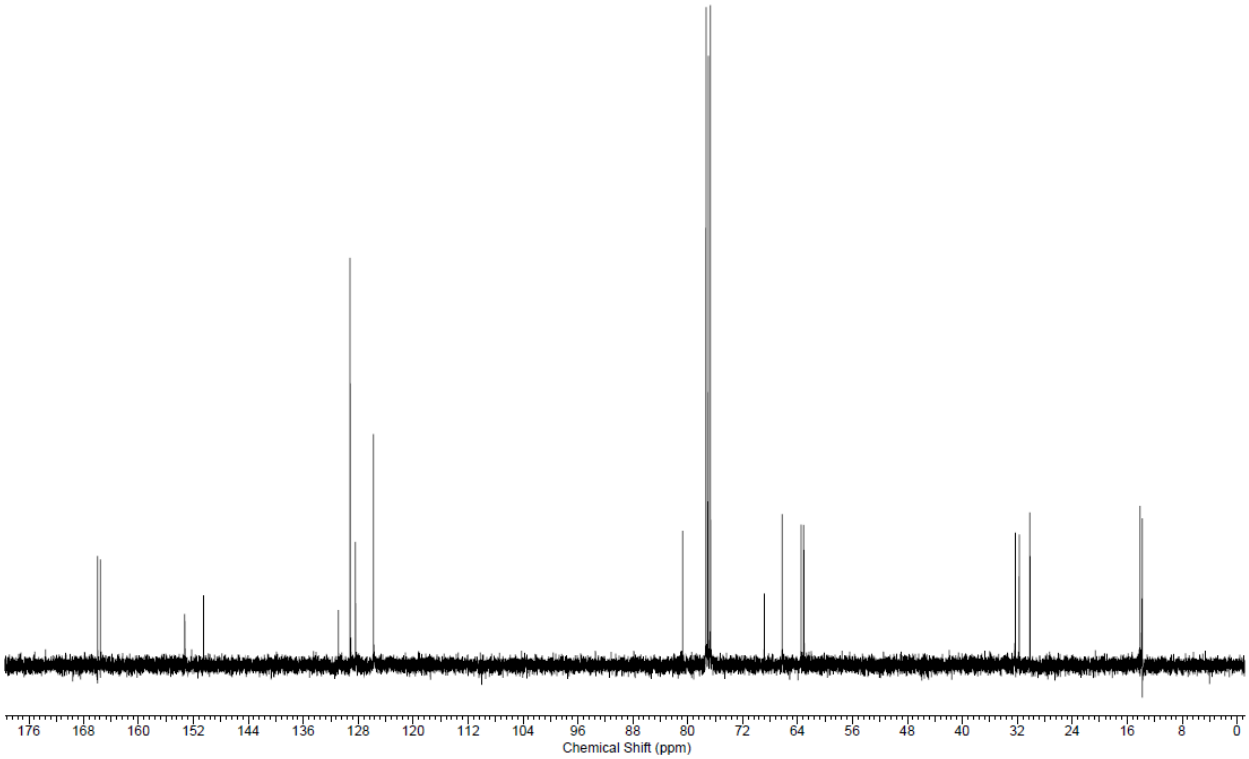
74a

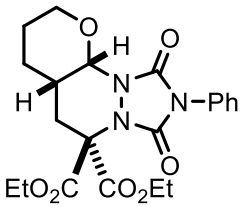



O
H
O
H
N
N–Ph
N
O
EtO2C
CO2Et

74b

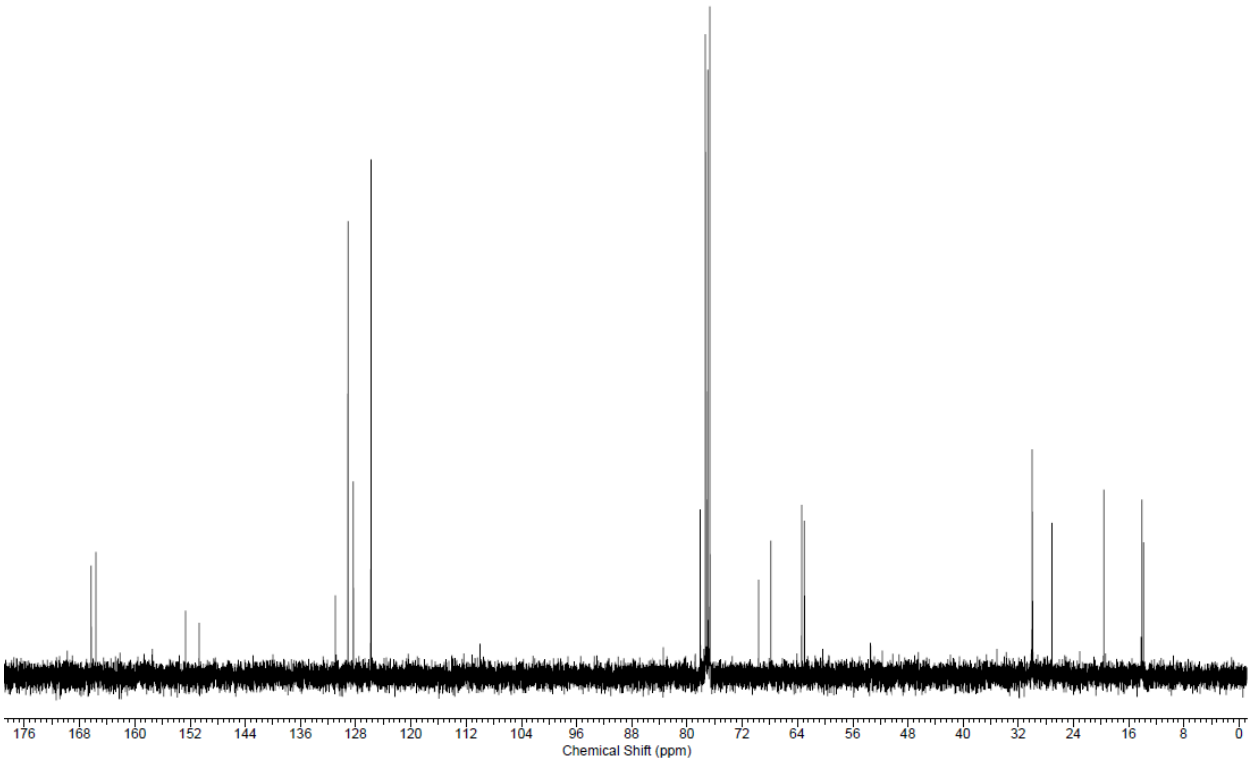

4.19 1.14
1.00
4.04 1.65 3.71
1.01 1.00 1.09 1.36 1.30
6.69 6.07
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

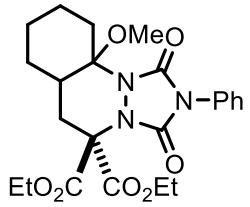

176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)


O
H
O
N
H
N
N–Ph
O
EtO2C
CO2Et

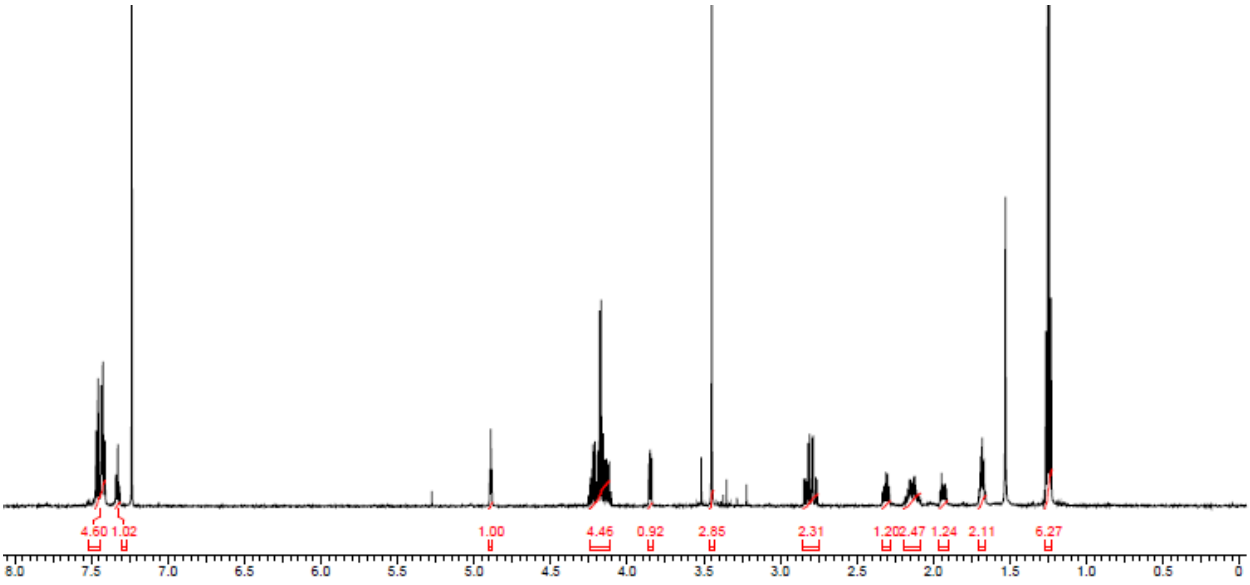
74c

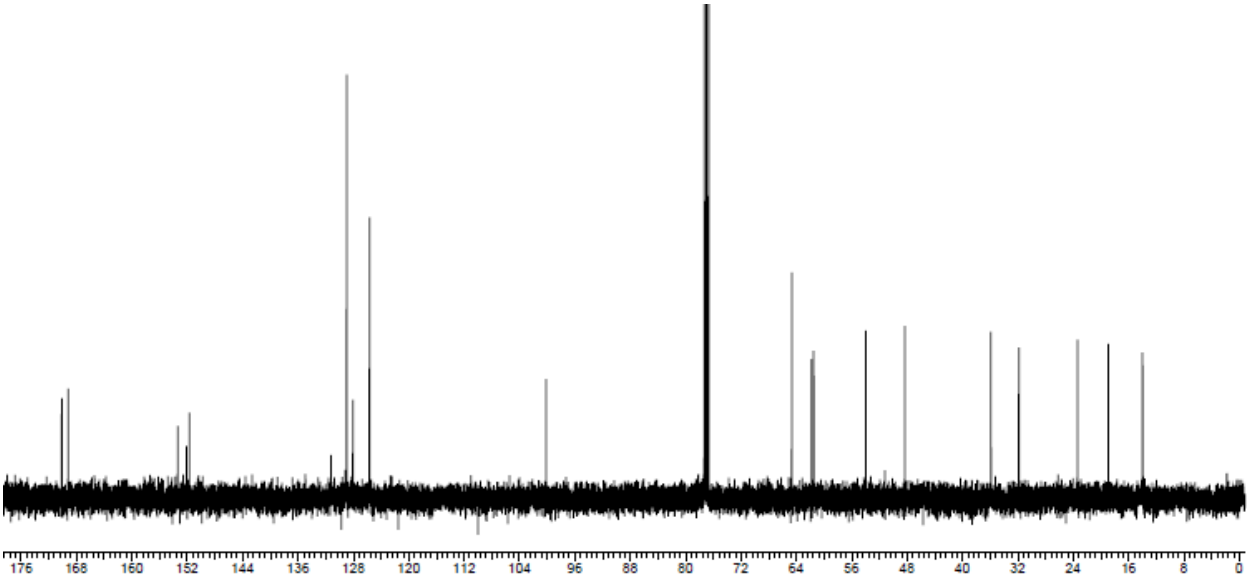
4.20
0.95
0.99
3.52
1.60
1.14
0.98
1.04
2.04
2.31
1.02
6.65
2.08
Chemical Shift (ppm)

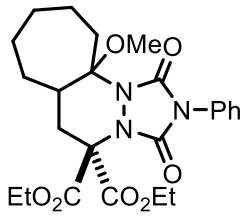

Chemical Shift (ppm)


OMe
O
N
N
N–Ph
O
EtO2C
CO2Et

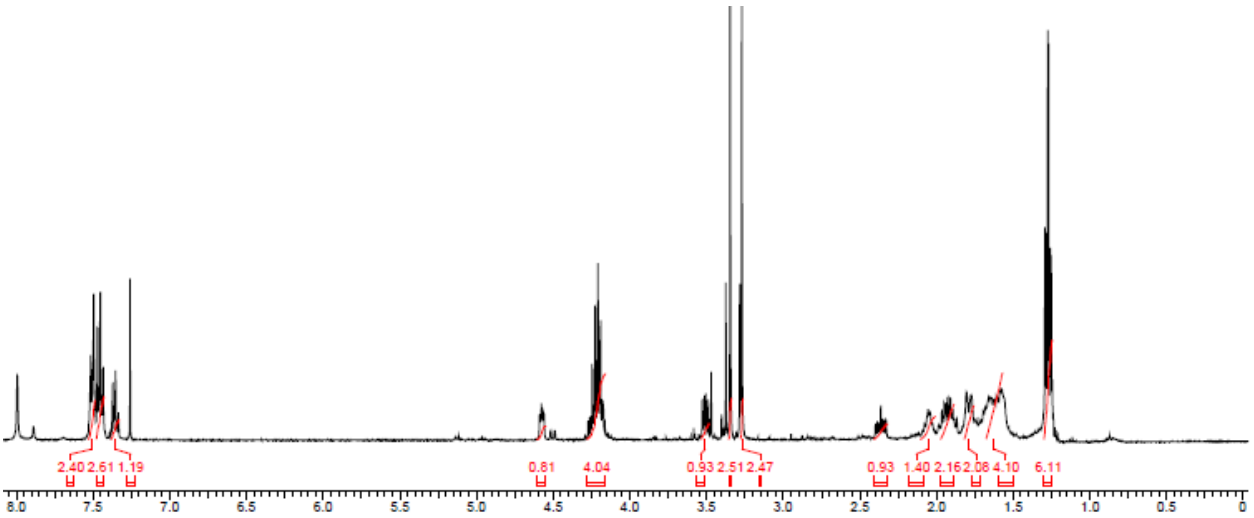
74d

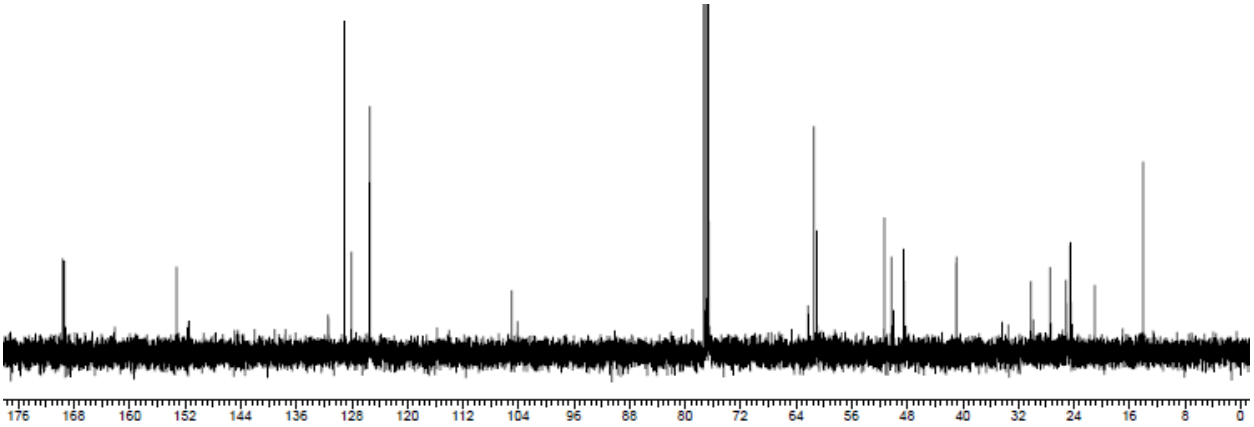

4.60
1.02
1.00
4.46
0.92
2.85
2.31
1.20
2.47
1.24
2.11
6.27

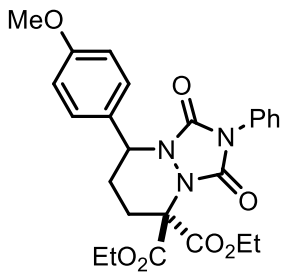



OMe
O
N
N
N–Ph
O
EtO2C
CO2Et

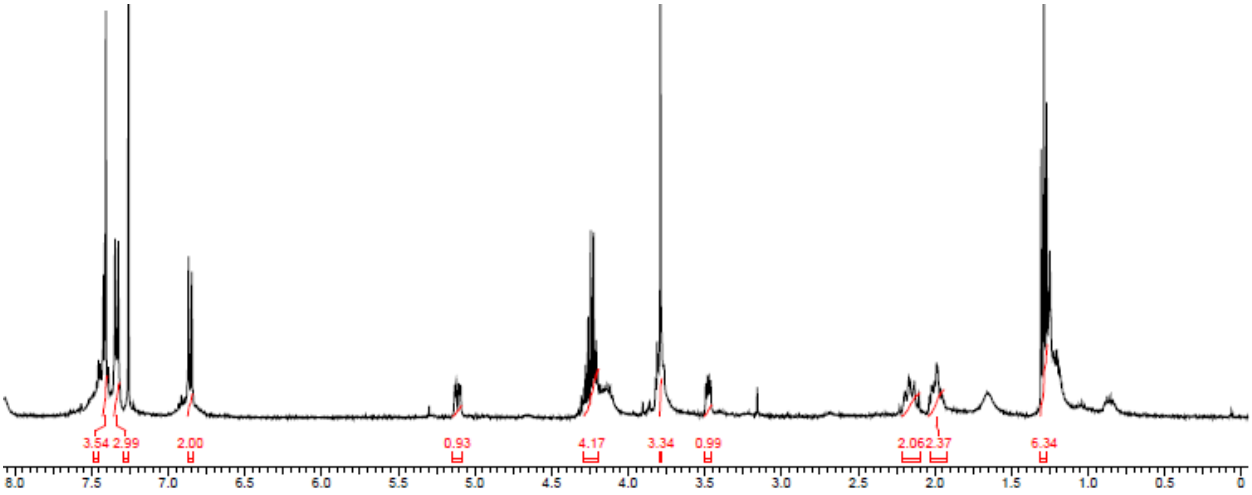
74e

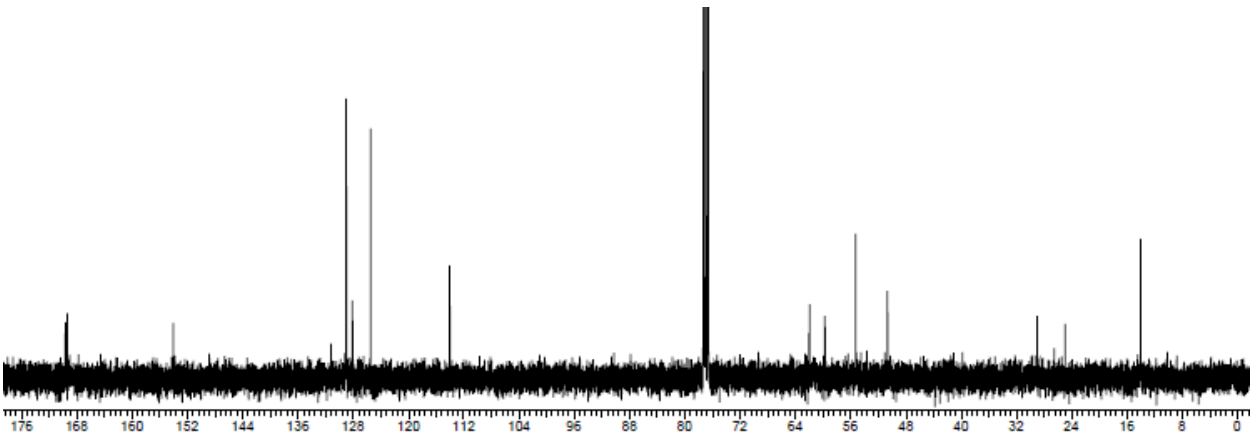

2.40 2.51 1.19
0.81
4.04
0.93 2.51 2.47
0.93 1.40 2.16 2.08 4.10
6.11
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0


176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0


MeO
O
N
Ph
N
N
O
EtO2C
CO2Et

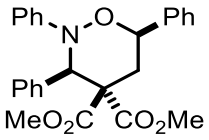
74f


3.54
2.99
2.00
0.93
4.17
3.34
0.99
2.06
2.37
6.34

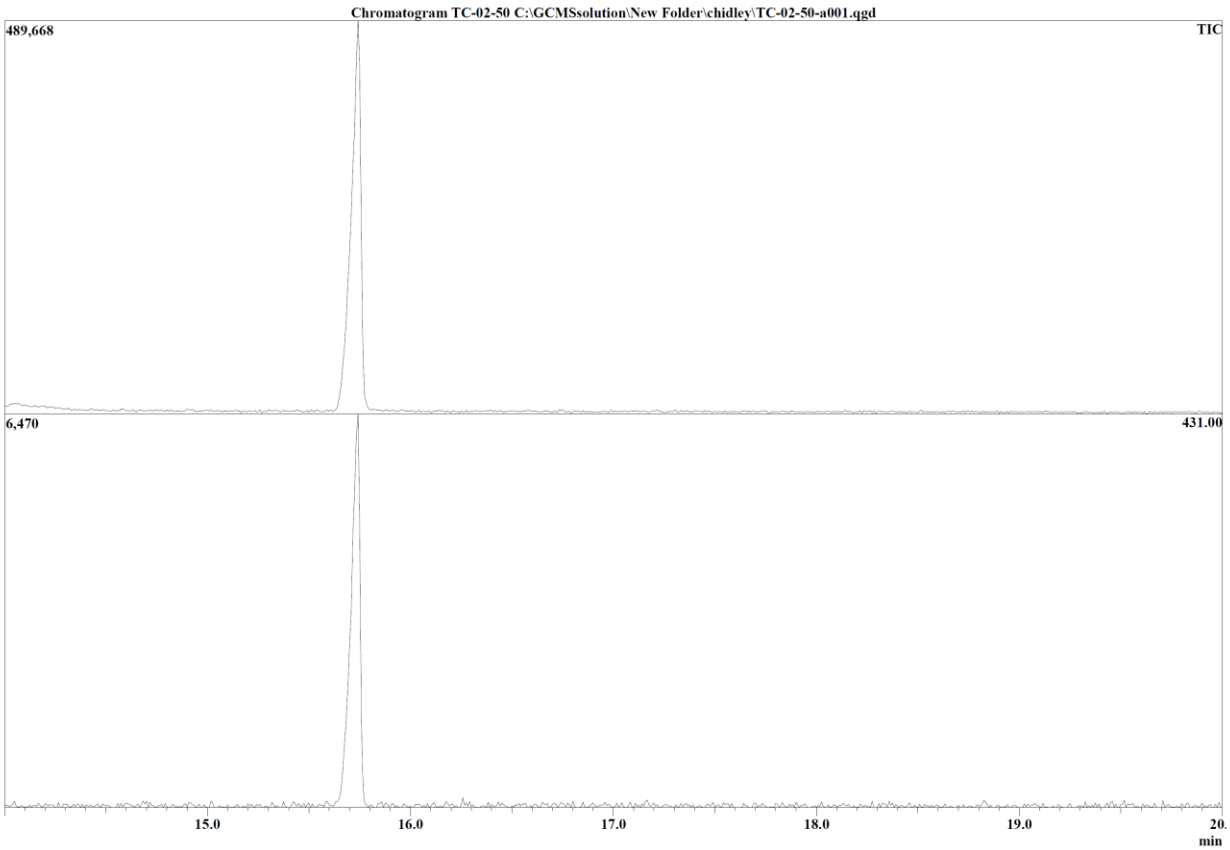


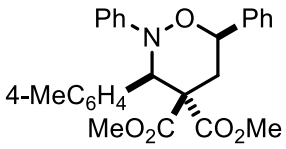
Appendix 4 - GC-MS Data Chapter 2

Standards



35a
431.48 g/mol
15.742 min

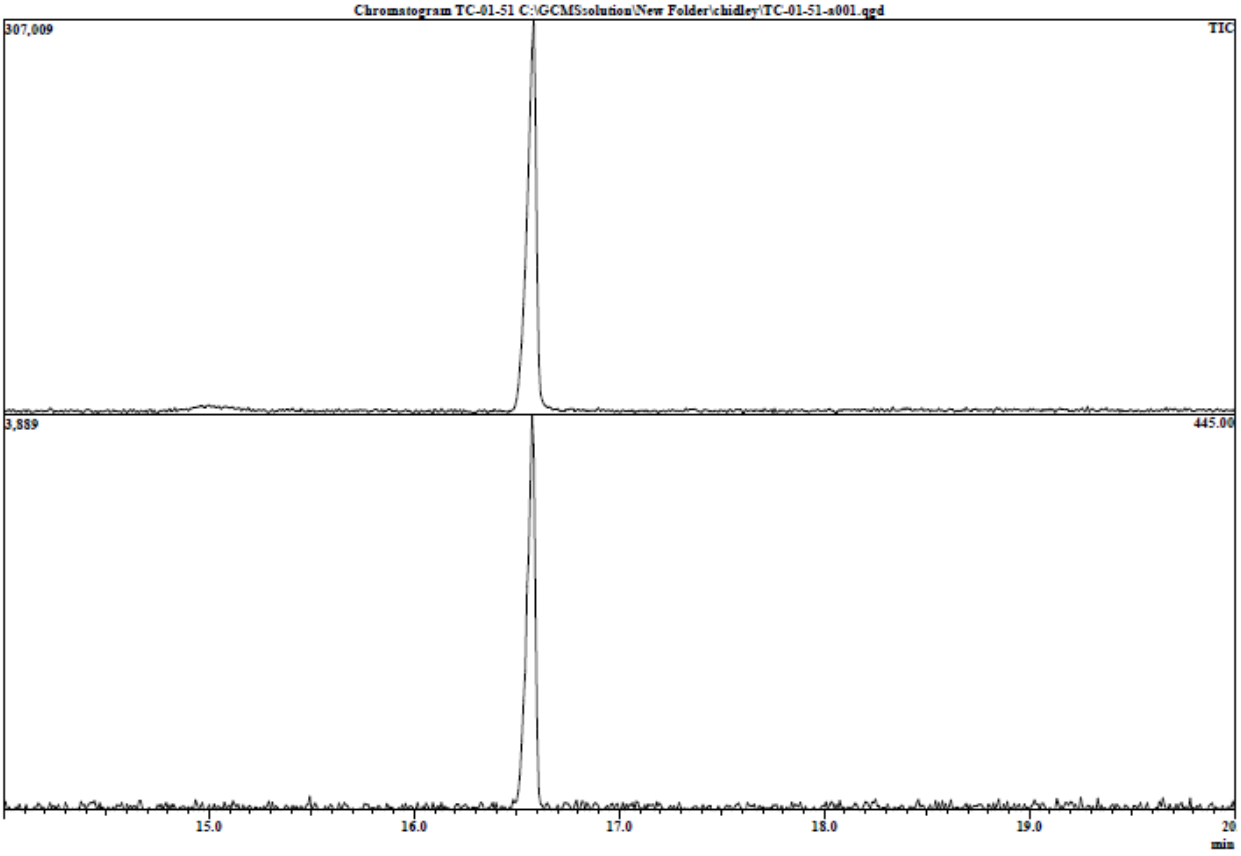


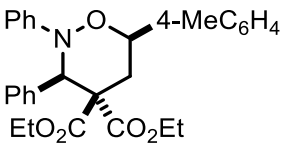


35b

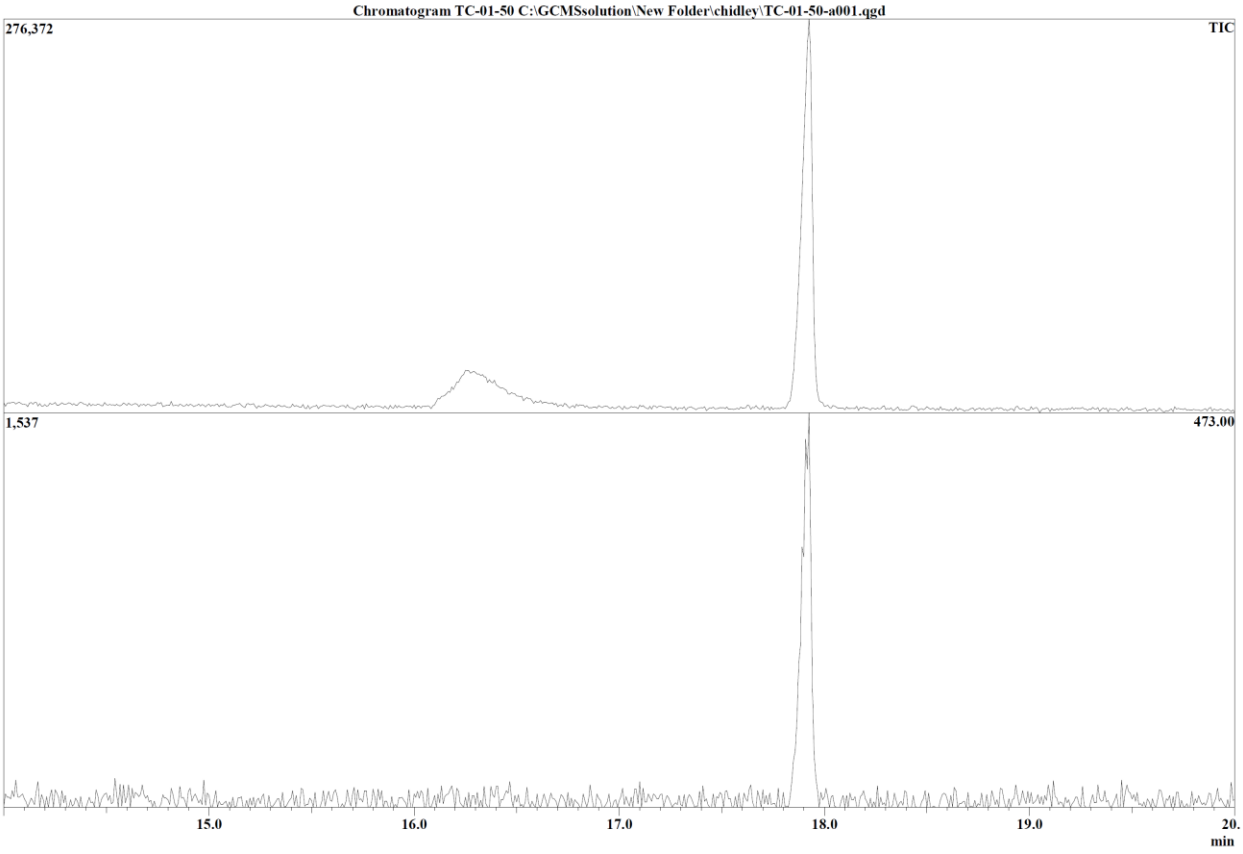
445.51 g/mol

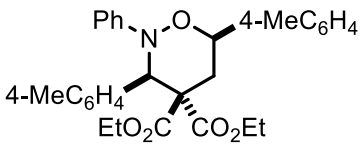
16.581 min



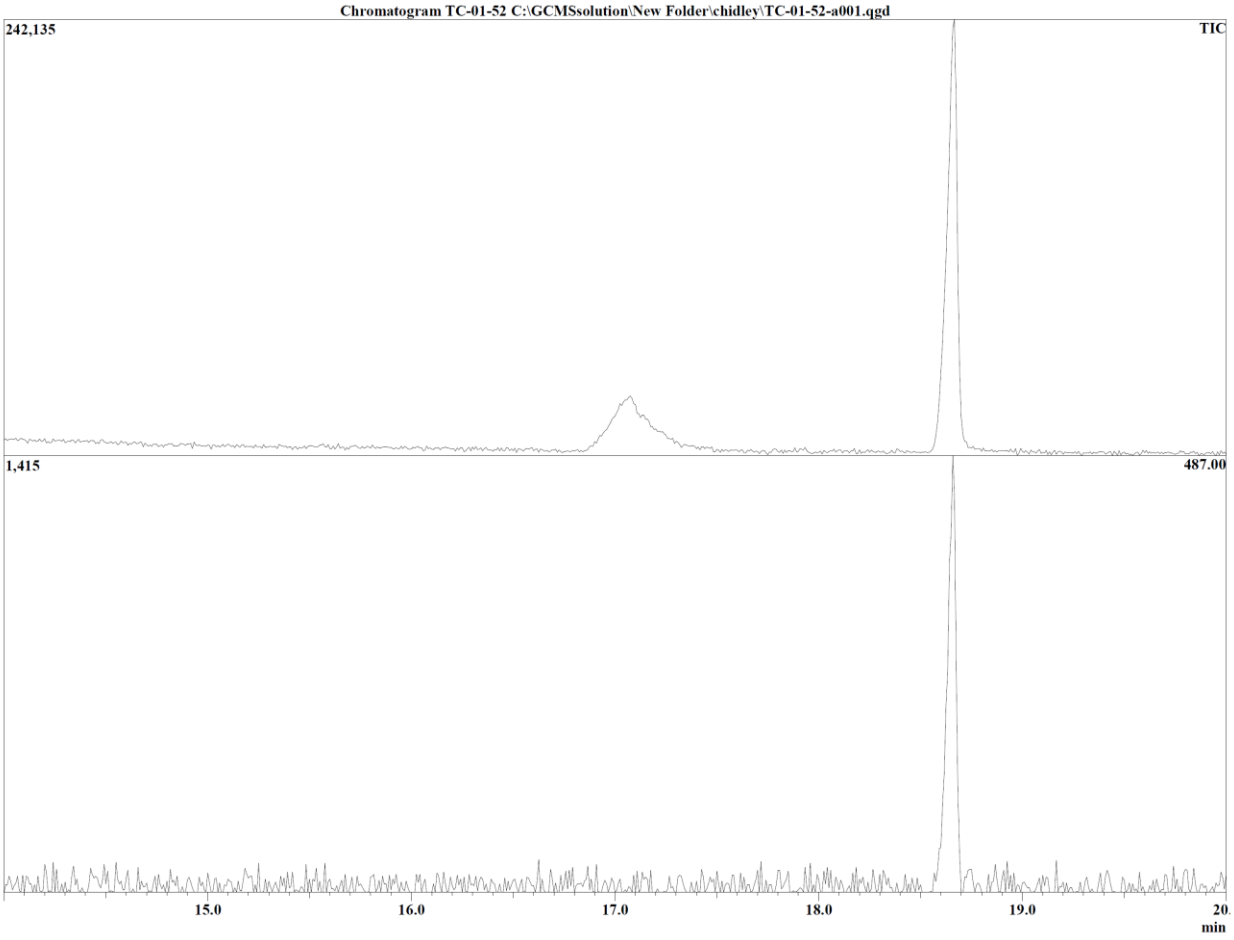


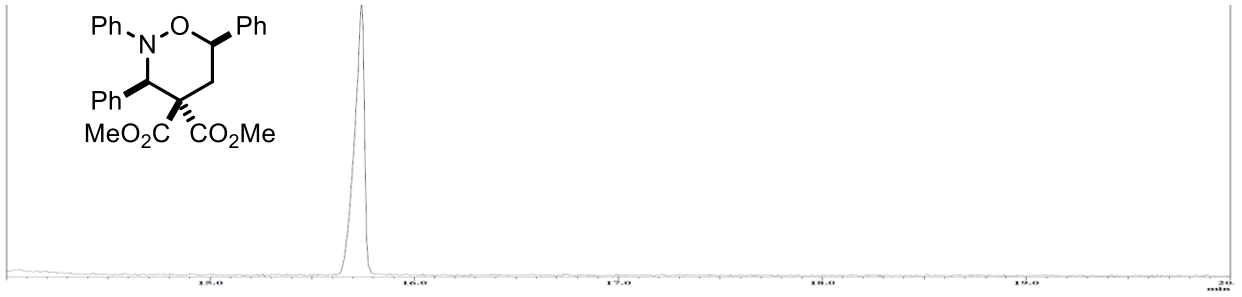
35c
473.56 g/mol
17.925 min

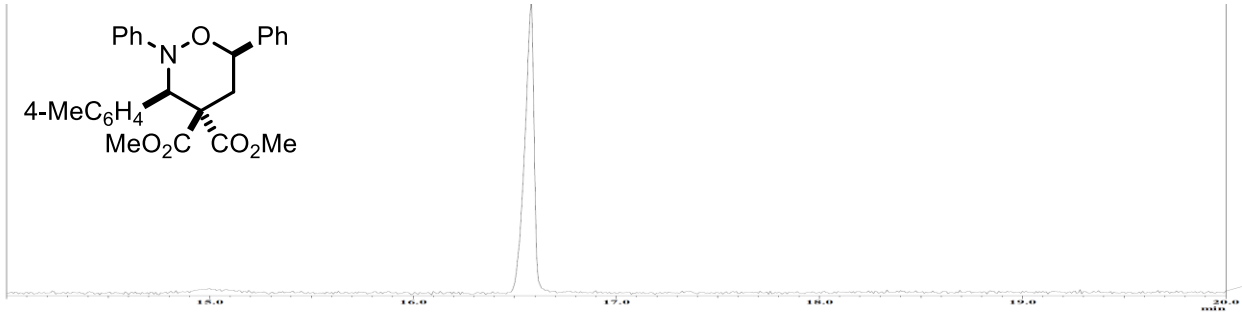


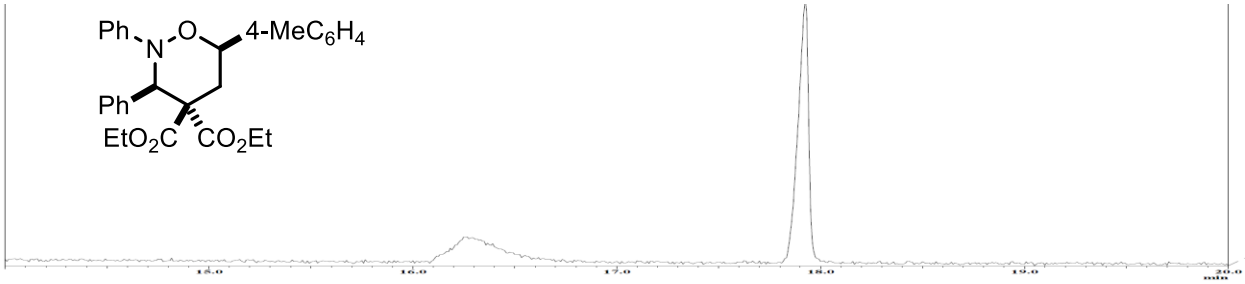


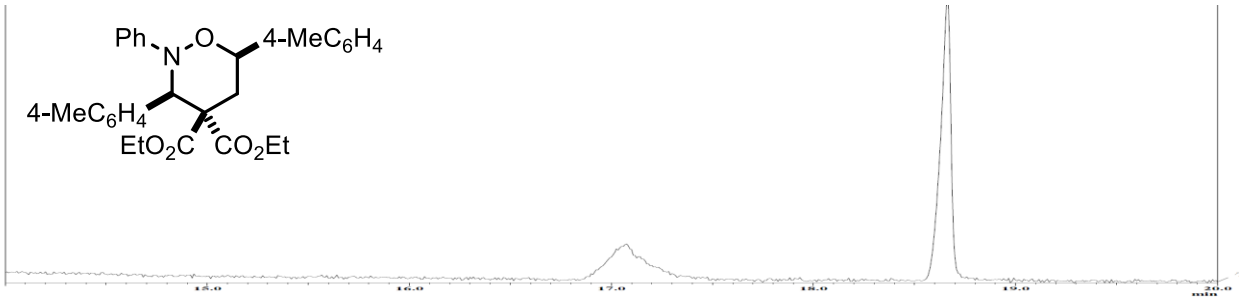
35d
487.59 g/mol
18.663 min



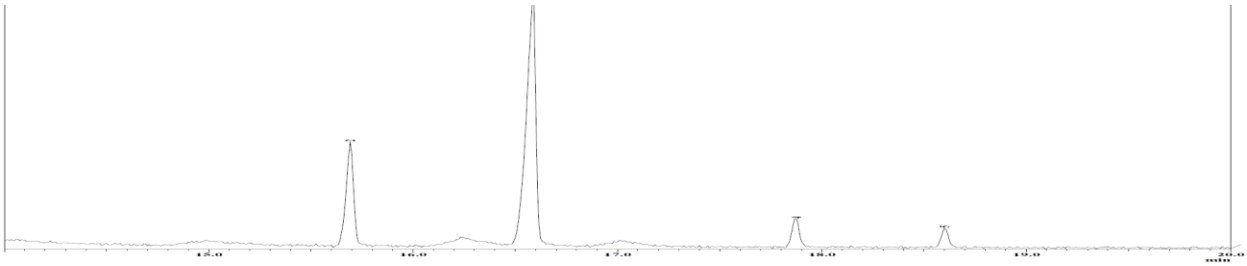






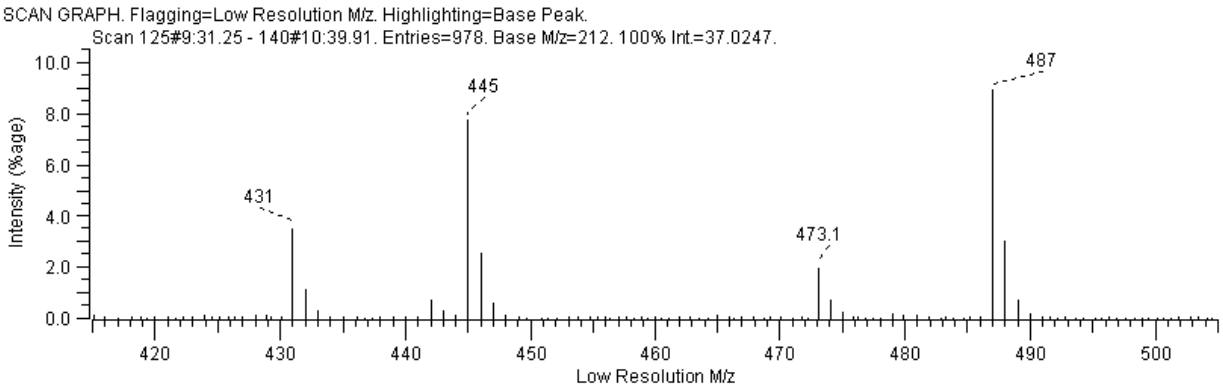


Cross-Over Experiment #1



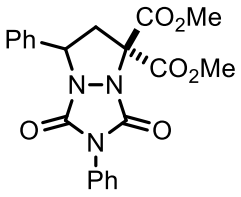
15.692 16.586 17.871 18.602

Cross-Over Experiment #1

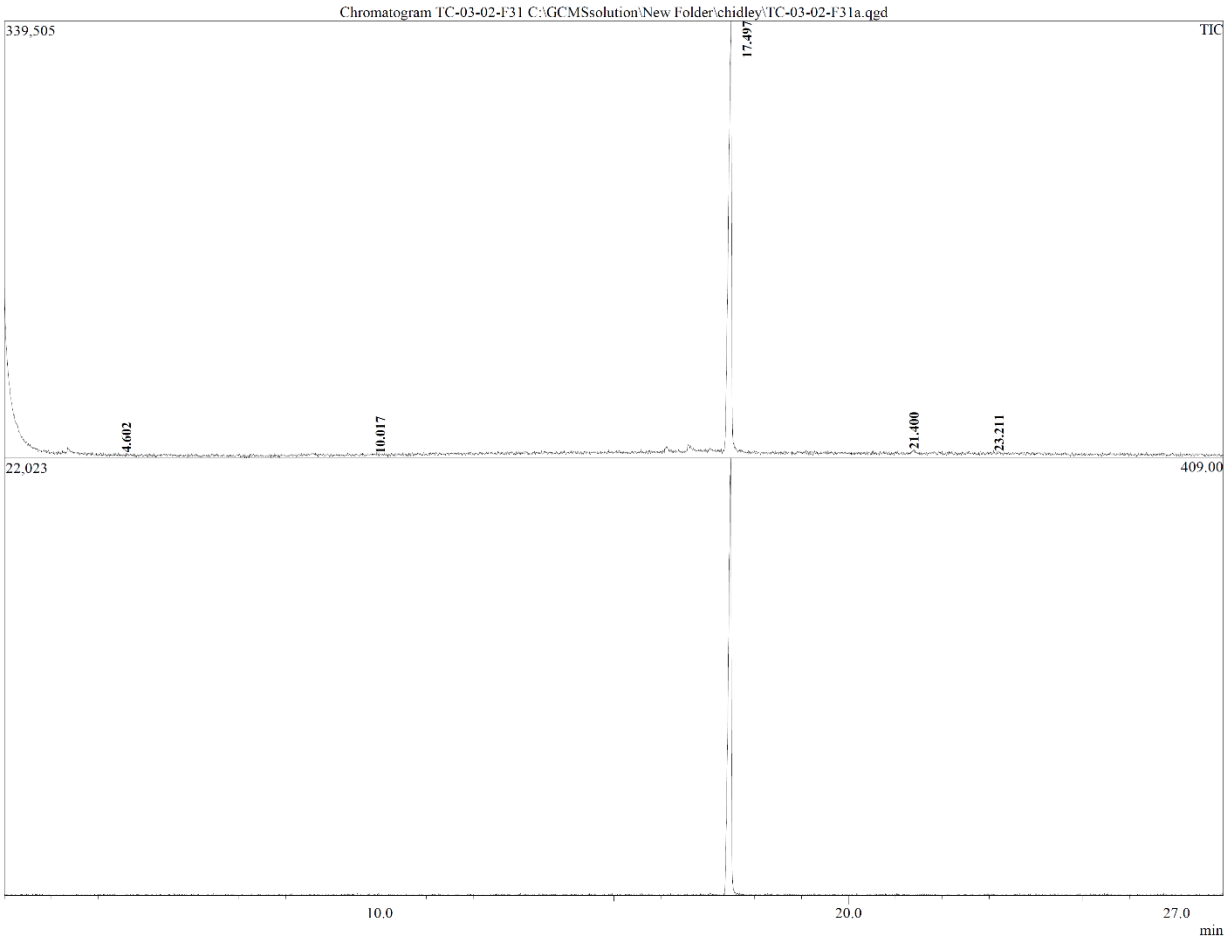


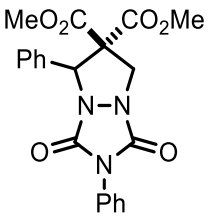
Appendix 5 - GC-MS Data Chapter 3

Standards

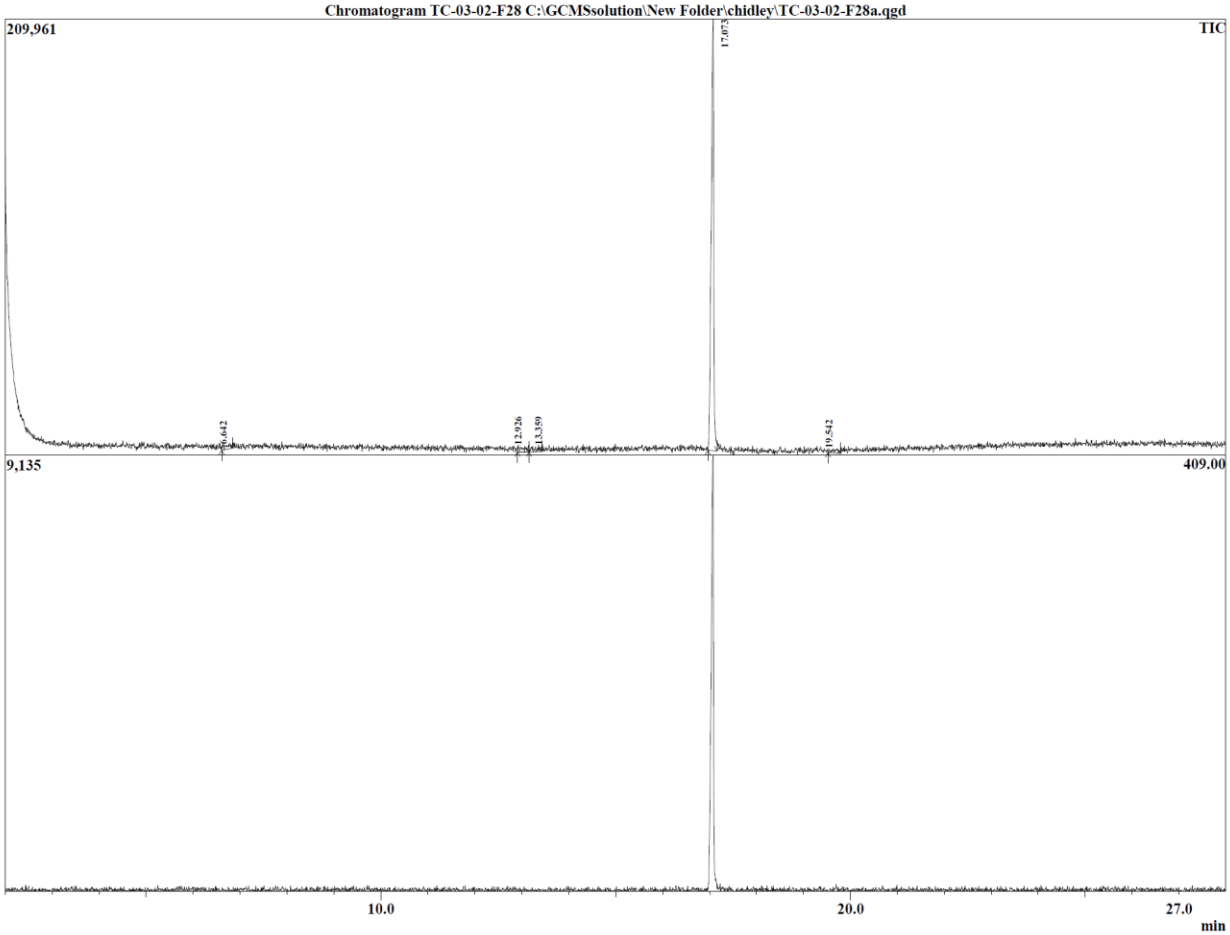


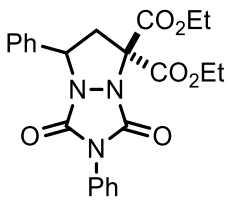
50a
409.39 g/mol
17.497 min



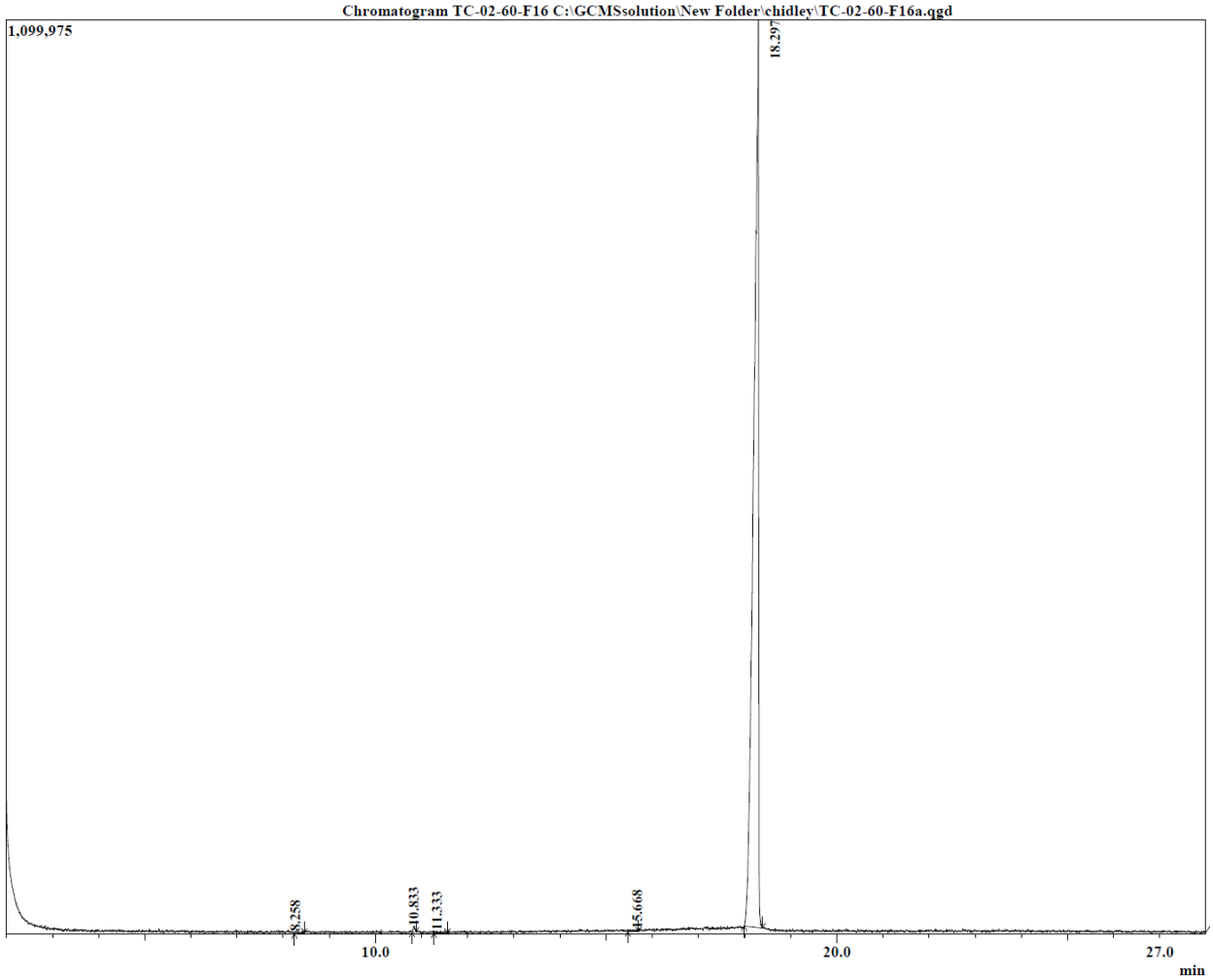


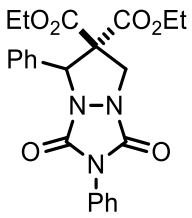
51a
409.39 g/mol
17.073 min



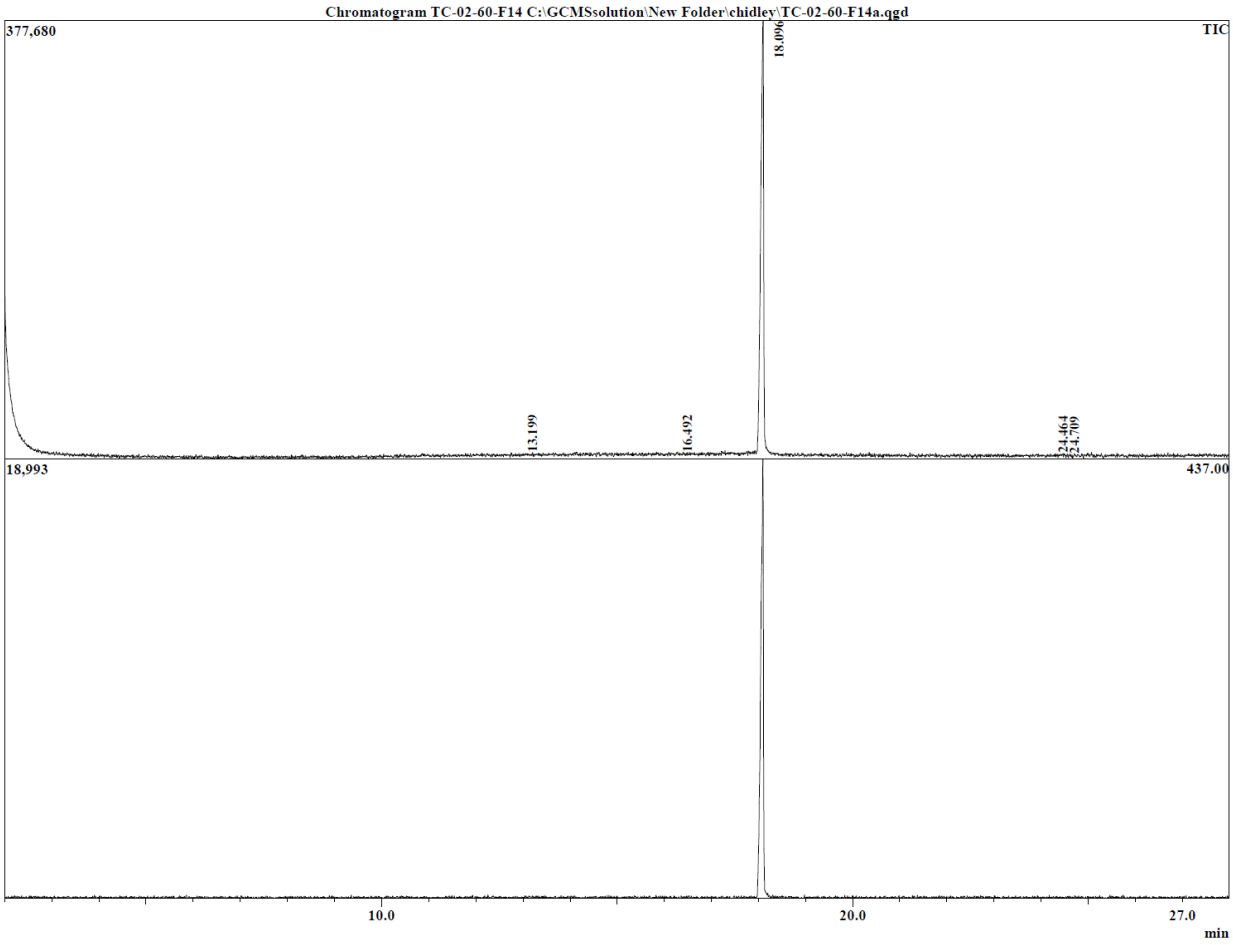


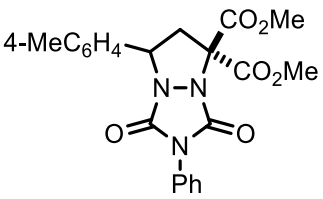
50b
437.45 g/mol
18.297 min



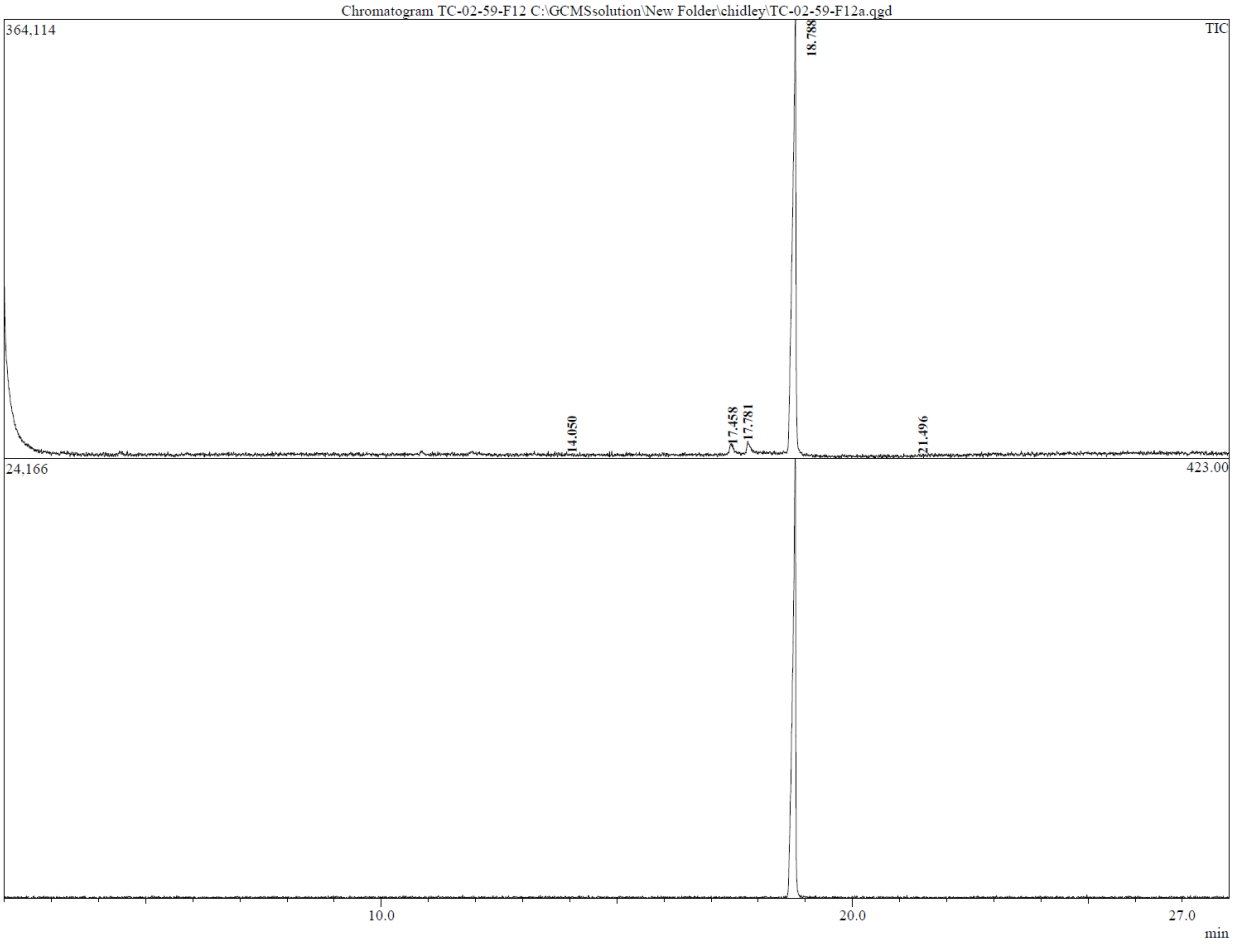


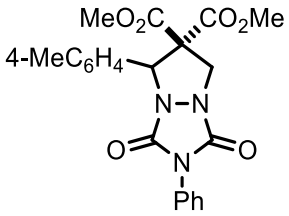
51b
437.45 g/mol
18.096 min



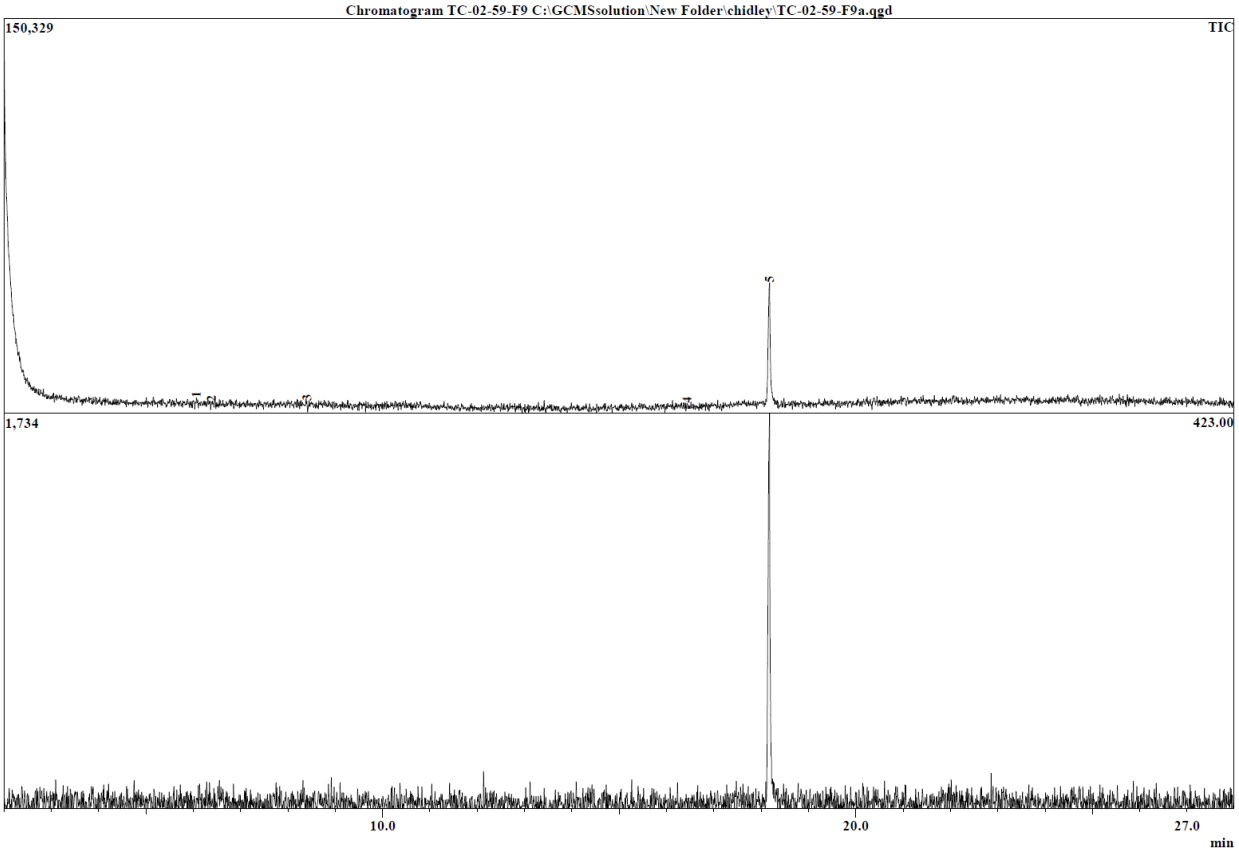


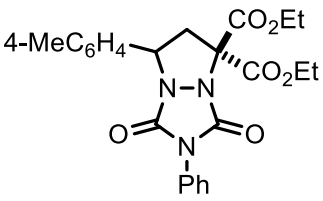
50c
423.42 g/mol
18.788 min



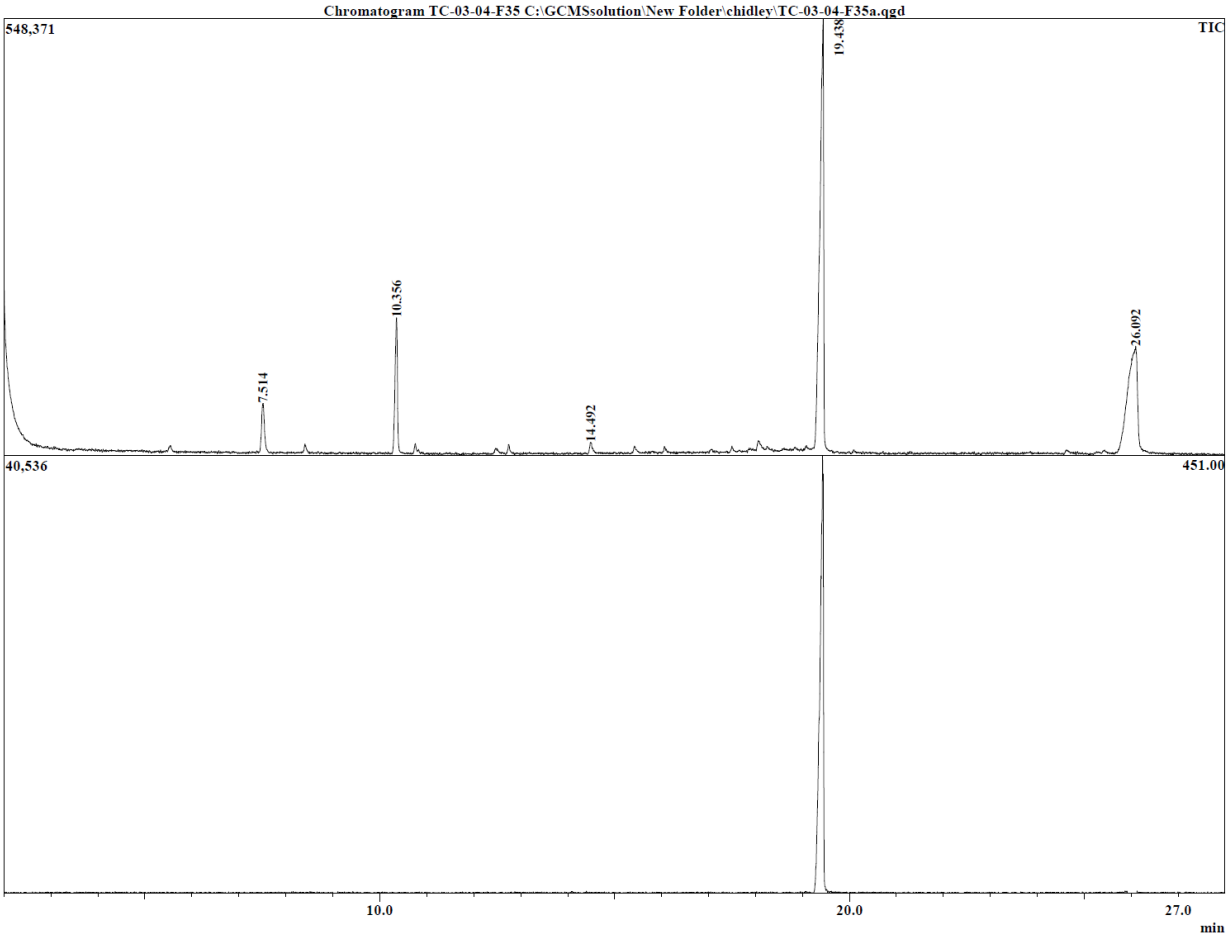


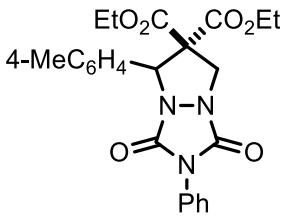
51c
423.42 g/mol
18.173 min



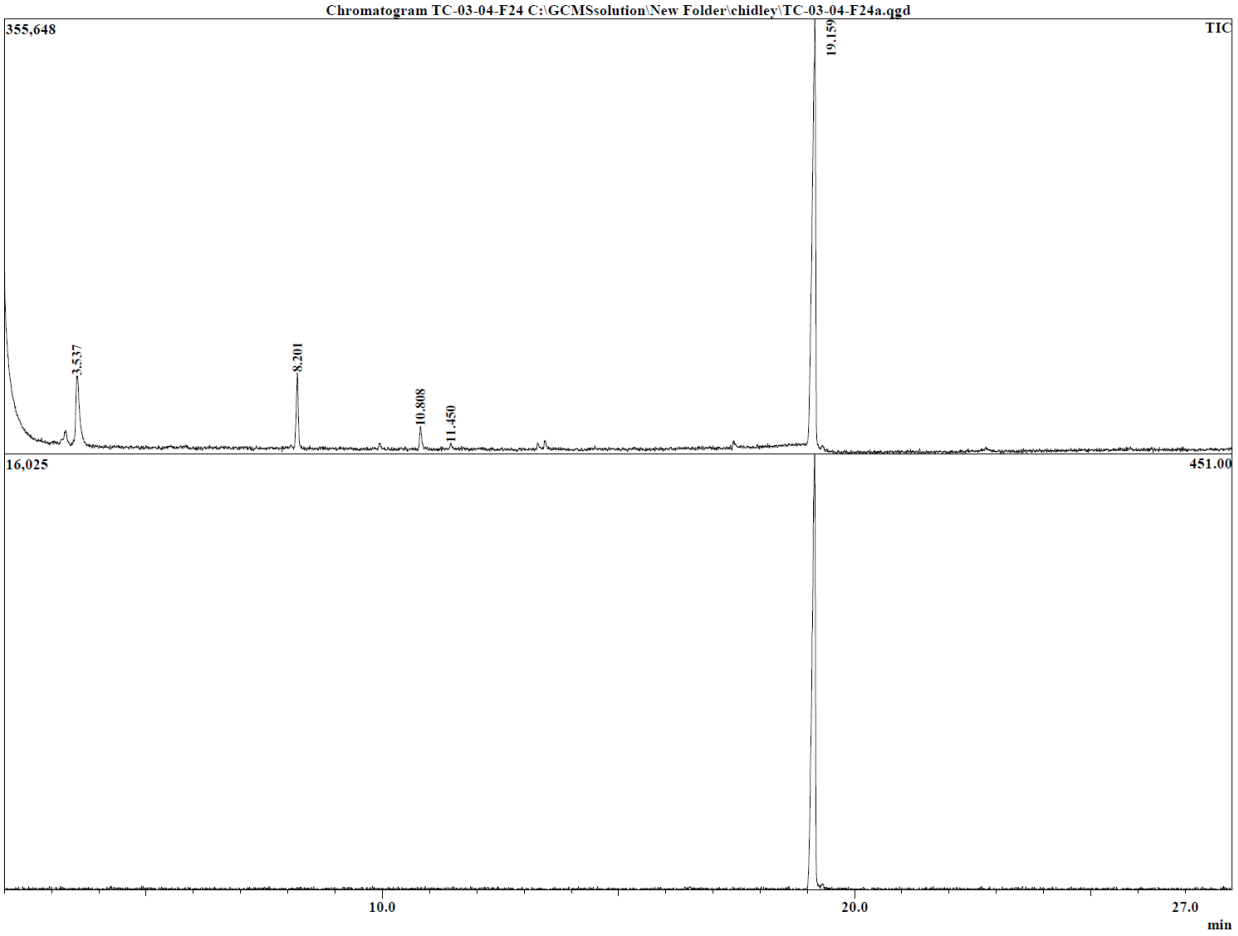


50d
451.47 g/mol
19.438 min

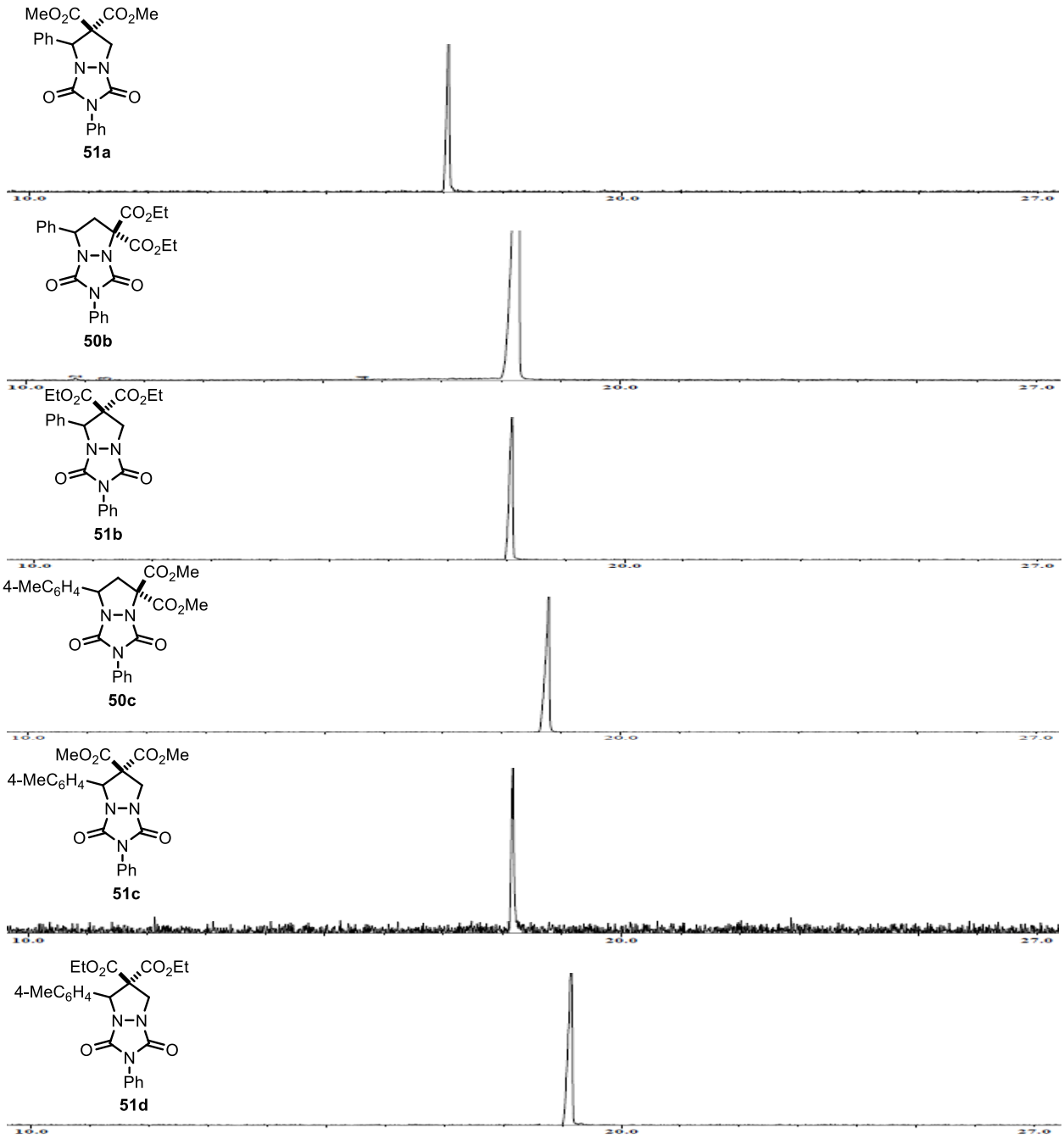




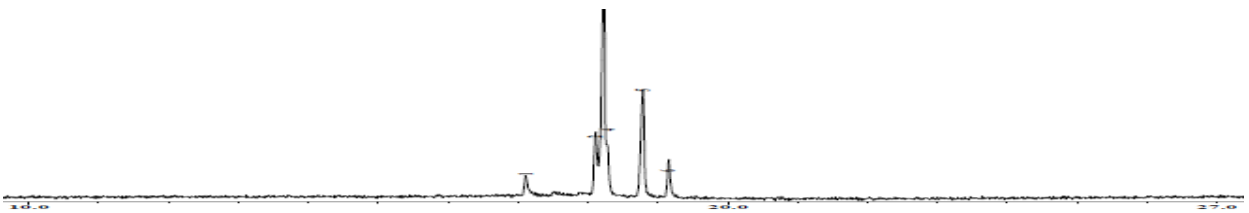
51d
451.47 g/mol
19.159 min



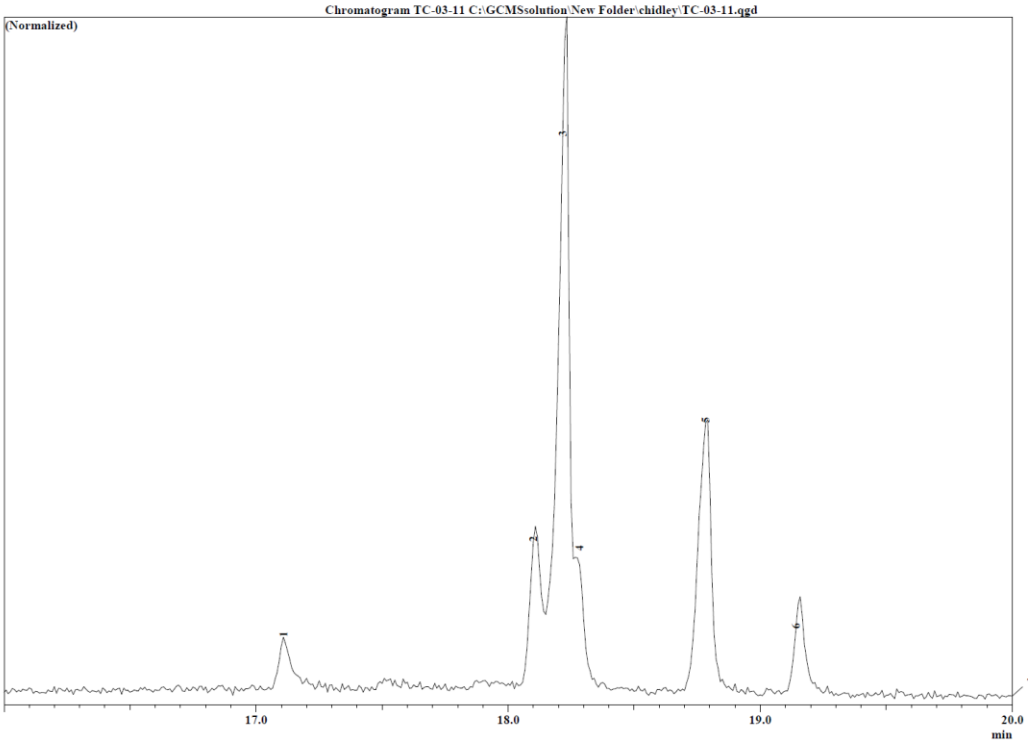
Cross-Over Experiment #3 Standards

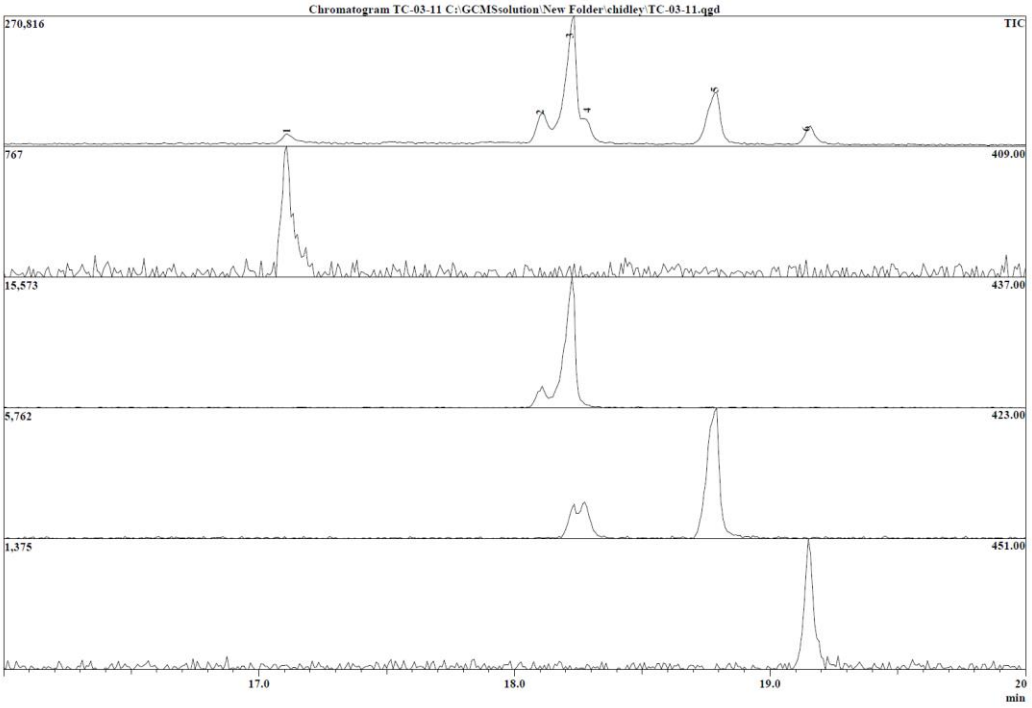


Cross-Over Experiment #3 Reversed (Run #1)



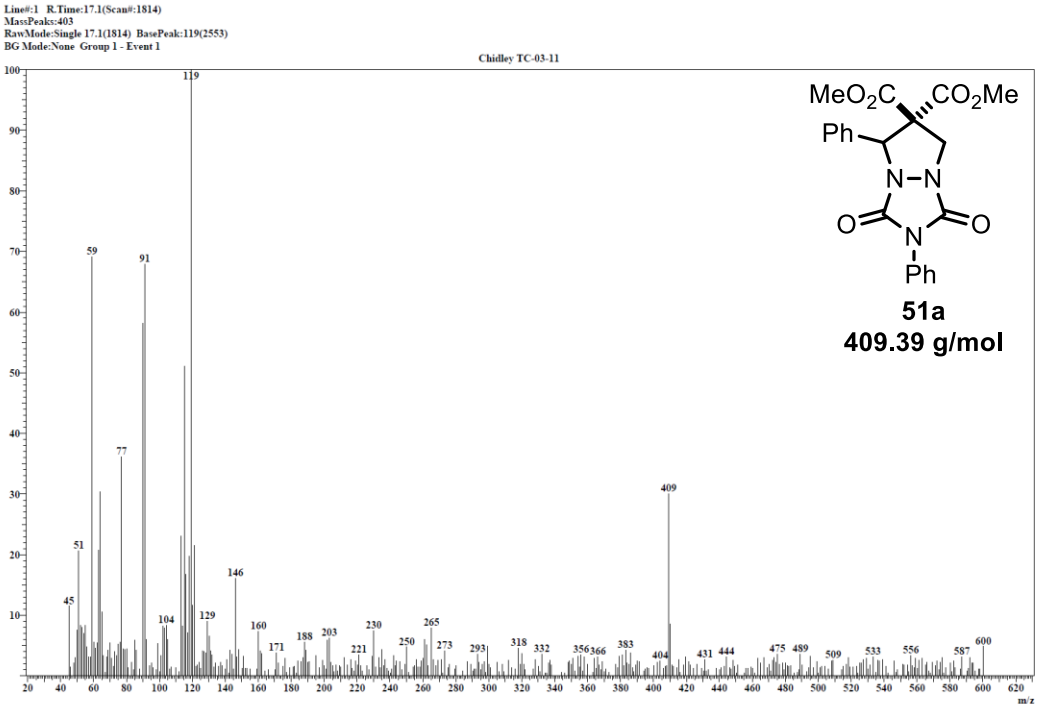
Cross-Over Experiment #3 Reversed (Run #1)



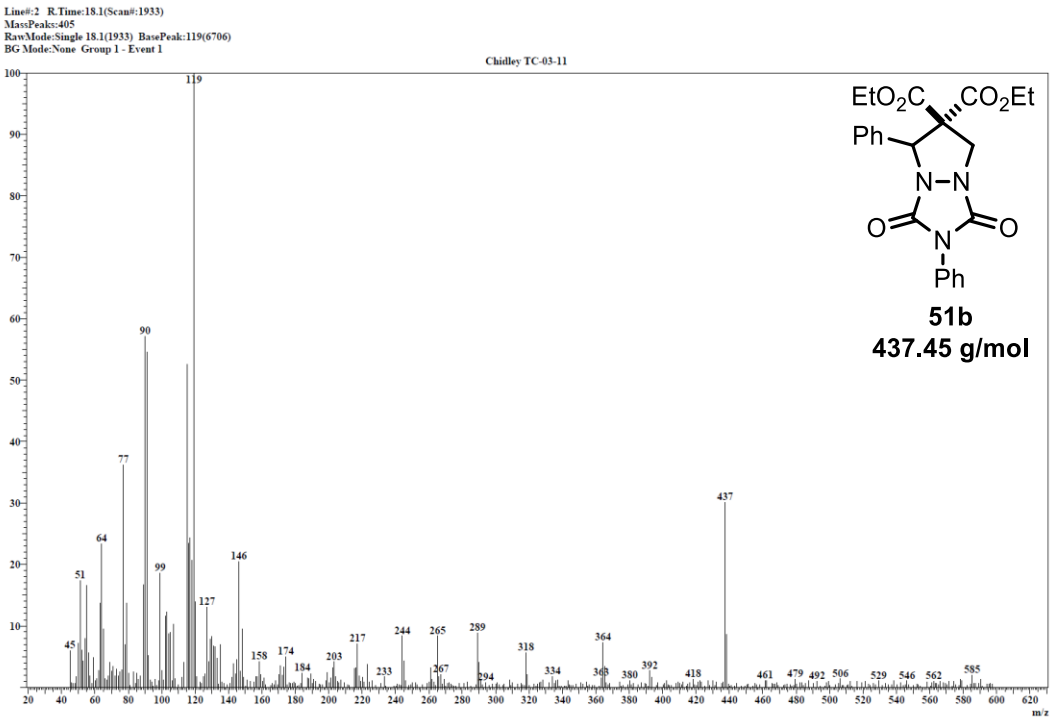


Cross-Over Experiment #3 Reversed (Run #1)

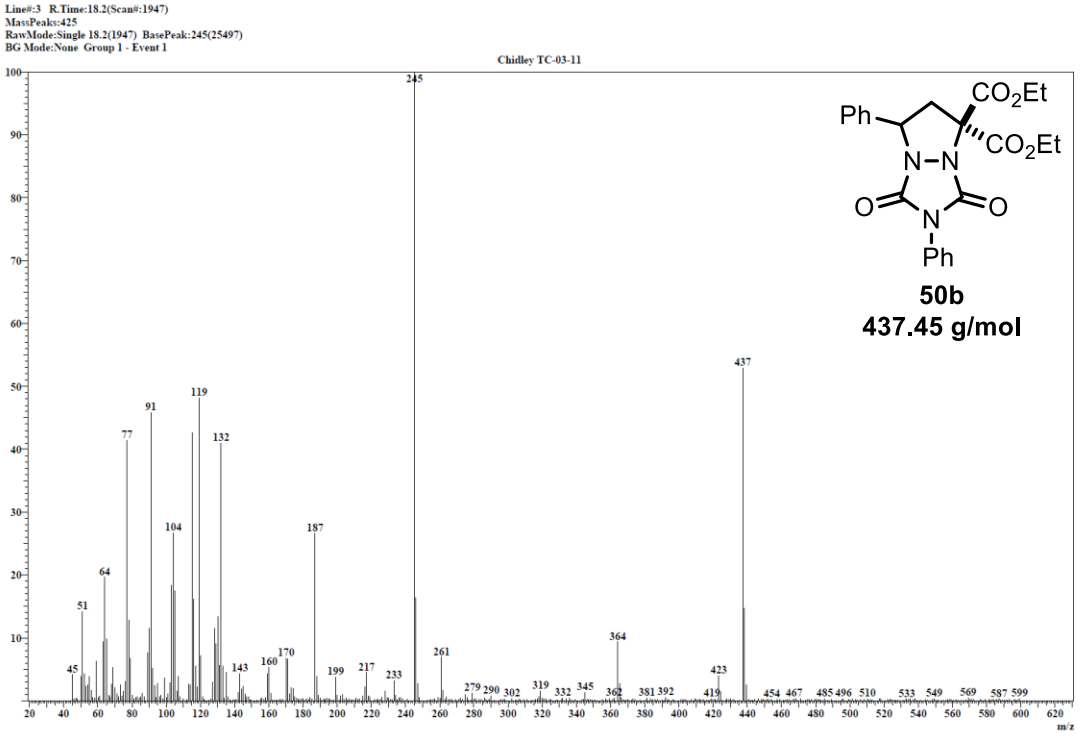
Peak #1



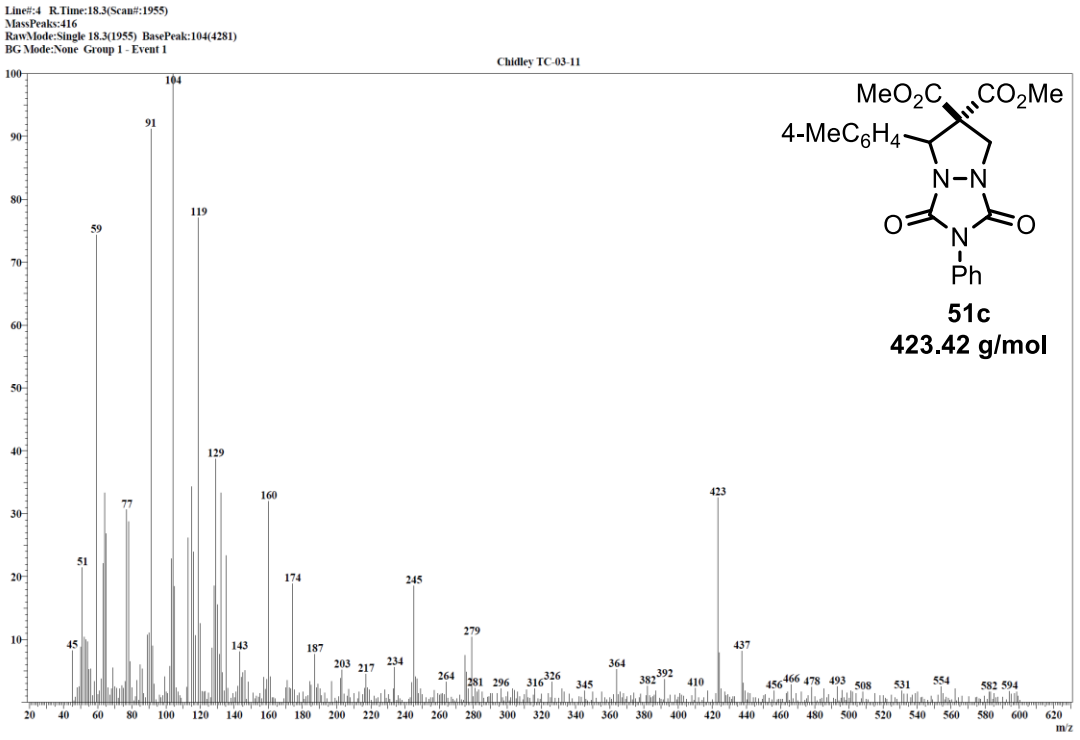
Peak #2



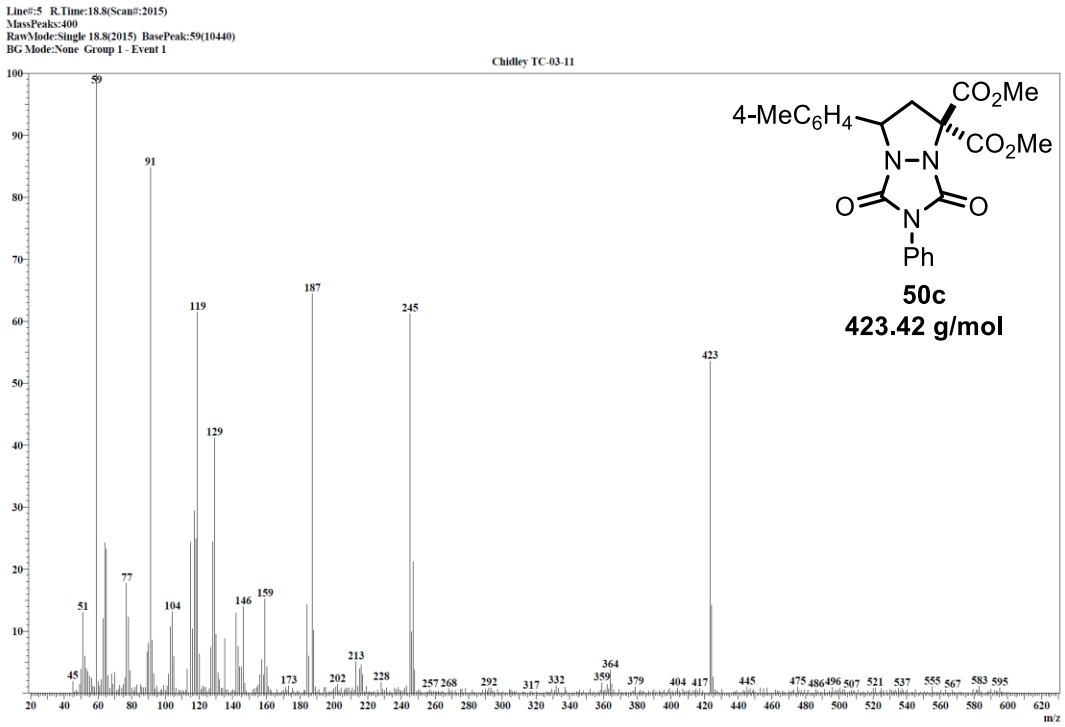
Peak #3


Line#:3 R.Time:18.2(Scan#:1947)
MassPeaks:425
RawMode:Single 18.2(1947) BasePeak:245(25497)
BG Mode:None Group 1 - Event 1
Chidley TC-03-11
m/z
CO2Et
Ph
CO2Et
N–N
O
O
N
Ph
50b
437.45 g/mol

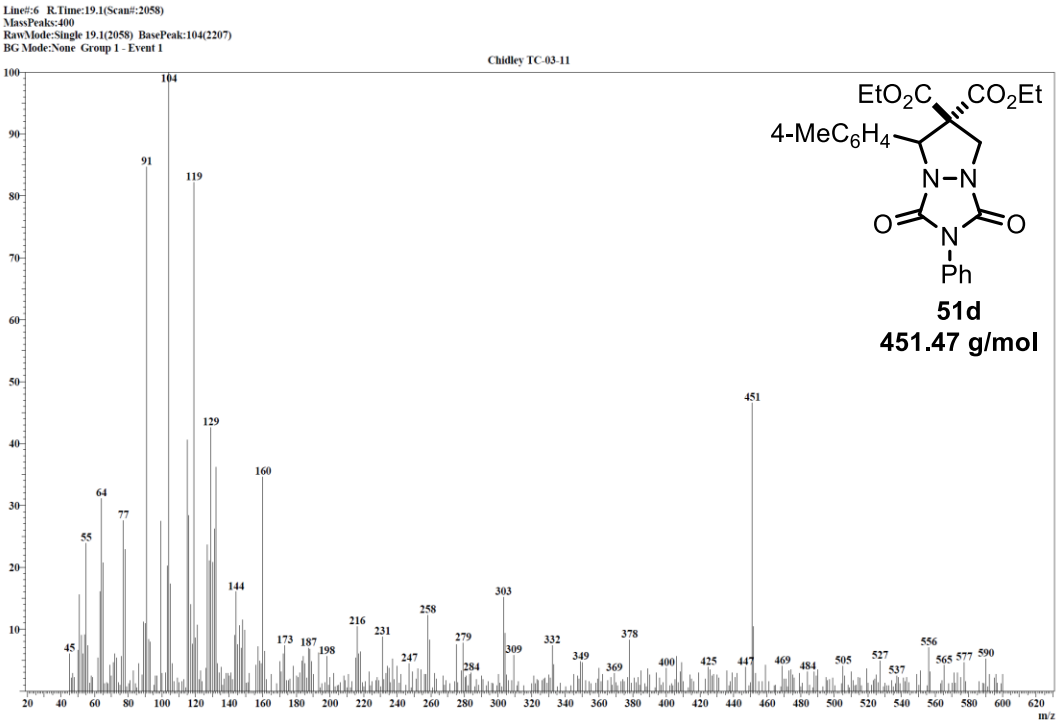
Peak #4


Line#:4 R.Time:18.3(Scan#:1955)
MassPeaks:416
RawMode:Single 18.3(1955) BasePeak:104(4281)
BG Mode:None Group 1 - Event 1
Chidley TC-03-11
m/z
MeO2C
CO2Me
4-MeC6H4
N–N
O
O
N
Ph
51c
423.42 g/mol

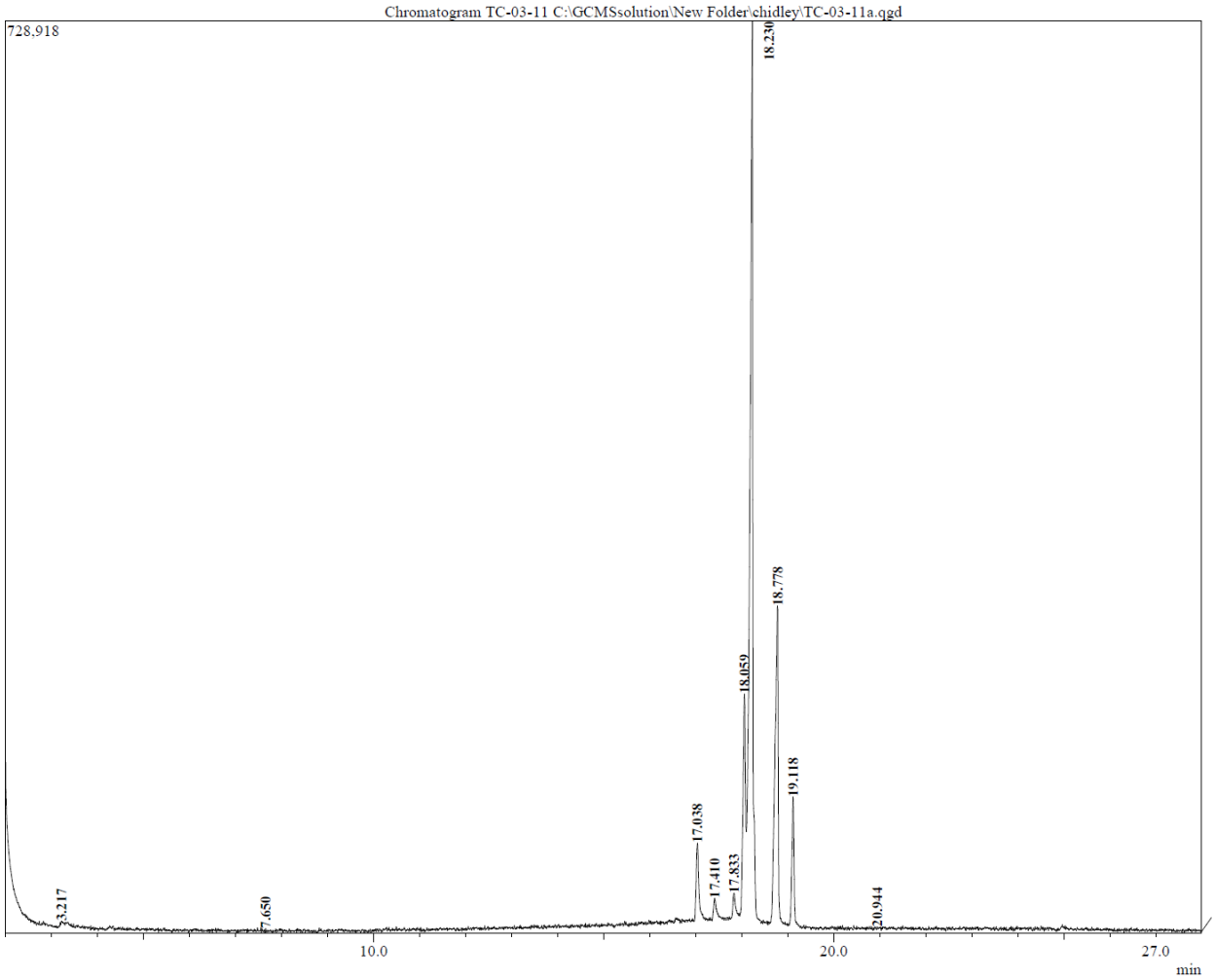
Peak #5


Line#:5 R.Time:18.8(Scan#:2015)
MassPeaks:400
RawMode:Single 18.8(2015) BasePeak:59(10440)
BG Mode:None Group 1 - Event 1
Chidley TC-03-11
4-MeC6H4
CO2Me
CO2Me
N–N
O
O
N
Ph
50c
423.42 g/mol
m/z

Peak #6


Line#:6 R.Time:19.1(Scan#:2058)
MassPeaks:400
RawMode:Single 19.1(2058) BasePeak:104(2207)
BG Mode:None Group 1 - Event 1
Chidley TC-03-11
EtO2C
CO2Et
4-MeC6H4
N–N
O
O
N
Ph
51d
451.47 g/mol
m/z

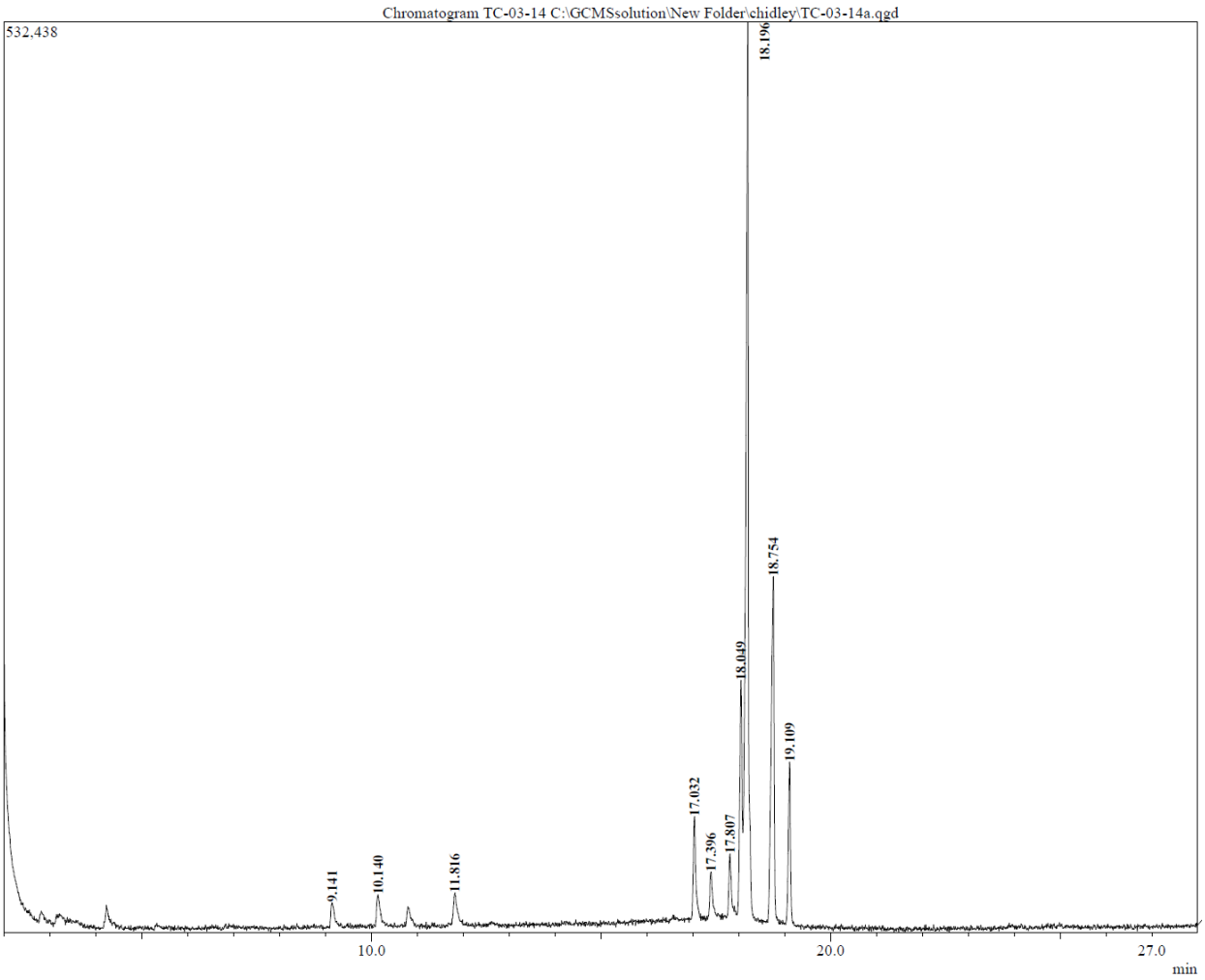
Cross-Over Experiment #3 Reversed (Run #2)



Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	3.217	3.175	3.292	15316	0.26	3900	0.29	3.92		
2	7.650	7.633	7.883	16625	0.28	3303	0.24	5.03		
3	17.038	16.975	17.183	252627	4.32	61958	4.55	4.07	V	
4	17.410	17.333	17.517	64330	1.10	16461	1.21	3.90		
5	17.833	17.775	17.908	76891	1.31	19783	1.45	3.88		
6	18.059	17.908	18.100	712107	12.17	179331	13.17	3.97	V	
7	18.230	18.100	18.358	3158119	53.96	717663	52.72	4.40	V	
8	18.778	18.625	18.900	1218120	20.81	253772	18.64	4.80		
9	19.118	19.033	19.200	320044	5.47	102002	7.49	3.13		
10	20.944	20.875	21.033	18385	0.31	3106	0.23	5.91	V	
				5852564	100.00	1361279	100.00			

Cross-Over Experiment #3 Reversed (Run #3)



Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	9.141	9.083	9.217	60476	1.33	13443	1.19	4.49		
2	10.140	10.083	10.225	82063	1.80	17612	1.55	4.65		
3	11.816	11.758	11.925	70488	1.55	15649	1.38	4.50		
4	17.032	16.958	17.158	232208	5.09	60274	5.32	3.85		
5	17.396	17.292	17.525	137326	3.01	28432	2.51	4.82		
6	17.807	17.758	17.925	157131	3.45	38219	3.37	4.11	V	
7	18.049	17.925	18.092	528048	11.58	139428	12.30	3.78	V	
8	18.196	18.092	18.325	2087367	45.78	524150	46.24	3.98	V	
9	18.754	18.633	18.825	909174	19.94	202577	17.87	4.48		
10	19.109	19.033	19.183	295777	6.49	93759	8.27	3.15		
				4560058	100.00	1133543	100.00			

Curriculum Vitae

Tristan Chidley

Education

M. Sc. Chemistry 2013 - 2015

The University of Western Ontario

Supervisor: Brian L. Pagenkopf

B. Sc. Biochemistry 2001 - 2005

University of Guelph

Graduation with Honours

Related Work Experience

Graduate Research Assistant 2013 - 2015

The University of Western Ontario

Supervisor: Brian L. Pagenkopf

Graduate Teaching Assistant 2013 - 2015

The University of Western Ontario

CHEM 2223b & CHEM 3373

Summary of Course Work

Course Title	Course Code	Instructor	Grade	Credit
Mechanistic Organic Chemistry	9553	Dr. Hudson	92	0.50
Heterocycles	9823	Dr. Kerr	93	0.25
Total Synthesis	9563	Dr. Kerr	91	0.25