THE DEVELOPMENT OF RADICAL CATION CYCLOPROPANATIONS &
CYCLOPENTENE ANNULATIONS WITH DIAZO SPECIES USING PHOTOCATALYSIS

by

FRANCISCO JESUS SARABIA

(Under the Direction of Eric M. Ferreira)

ABSTRACT

Over the past decade, photoredox catalysis has been warmly embraced by the synthetic organic community for its ability to access unique reactivity using mild reaction conditions that harness energy from light. A major drawback in this field of chemistry is that many examples in the current literature use photocatalysts containing precious metals. By utilizing light-activated catalysts based on earth-abundant chromium, our group has been able to cultivate a more sustainable approach in the field of photocatalysis. To this end, a Cr photocatalyzed cyclopropanation using diazo reagents has been developed. The transformation proceeds through a radical cation mechanism that has distinct features from traditional diazo-based cyclopropanations. Furthermore, a direct (3+2) cycloaddition between olefins and vinyldiazo species using photocatalysis has been discovered. This process enables nucleophilic interception of radical cation species by vinyl diazo compounds which traditionally behave as electrophiles. Experimental insights refute a cyclopropanation/rearrangement cascade process and support a direct cycloaddition. Overall, these transformations are able to transform sp^2-rich starting materials to more architecturally complex products containing multiple sp^3 centers.

INDEX WORDS: Visible light photoredox catalysis, Diazo species, Radical cation cycloaddition, Cyclopropanation, Cyclopentene annulation, Sustainable chemistry

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FRANCISCO JESUS SARABIA

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FRANCISCO JESUS SARABIA

Major Professor: Eric M. Ferreira

Committee: Robert Phillips
Vladimir Popik

Electronic Version Approved:

Suzanne Barbour
Dean of the Graduate School
The University of Georgia
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DEDICATION

For my mother, my sister, and my wife/soulmate Indra…

with immense love, admiration, and tremendous appreciation.

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I would like to begin by thanking three of the most important womyn in my life to whom I have dedicated this dissertation to. Amá, thank you for being my number one supporter from day one. I am extremely fortunate to have an angelic mother like yourself and I appreciate all of the hard work you have accomplished and the sacrifices you have made to give my sister and I a better life here in the United States. Vickyta, my one and only sister, thank you for your continuous support and pride in me. I hold your words very close to my heart and I am extremely proud of you as well hermana. Indra, mi media naranja, mi amor eterno, the one I love. Corazon, we started from the border (Chula Vista) and now we are here (both in PhD programs). You made me believe in myself when I did not want to. You filled a deep empty void in my life that I did not know existed until I fell in love with you. I do not think I would have survived graduate school without your undeniable love, support, and empowerment day after day. You make me a better person and make me want to be a better person. Te amo Indra, hoy y siempre, gracias por todo y mas que nada gracias por existir. I cannot wait to move in with you very soon amorcito.

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A special appreciation goes to the beloved mockumentary TV series 'The Office', which I have probably watched over a dozen times and am pretty sure am addicted to (thanks for that

Indra). During times of loneliness, frustration, and sadness, the television show provided company and comic relief in my life, with characters whom I now have a great fondness for.

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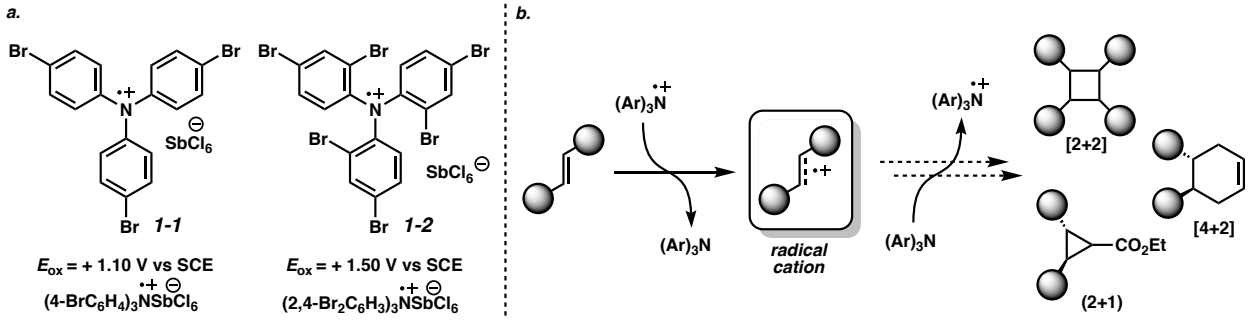
CHAPTER 1

(2+1) CYCLOADDITIONS MEDIATED BY SINGLE ELECTRON TRANSFER EVENTS: FROM AMINIUM SALTS TO PHOTOREDOX CATALYSTS

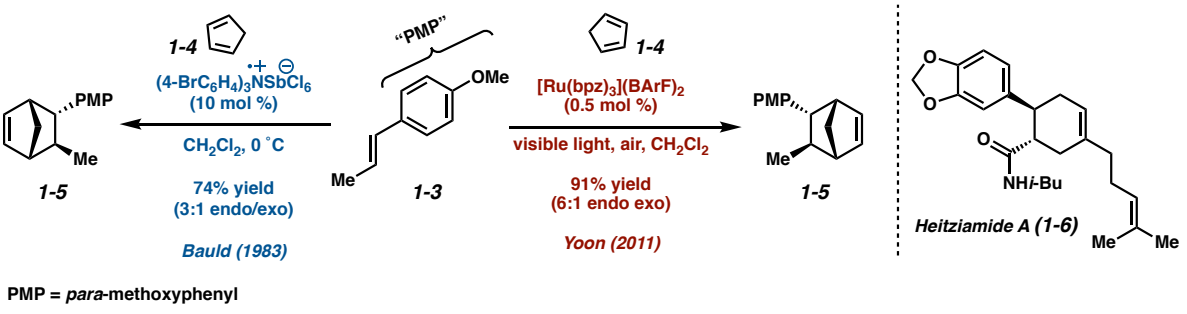
1.1 Introduction: Radical Cation Cycloadditions

In the early 1980s, Bauld and his research group discovered the first radical cation cycloaddition, namely the "cation radical" Diels–Alder.[1] Throughout the late 20th century, Bauld continuously developed, explored, and exploited the radical cation in various transformations.[2,3] Among them are the [4+2] cycloadditions mentioned above, [2+2] cycloadditions, and the radical cation cyclopropanation (Scheme 1.1b). These reactions are catalyzed by one of two bench-stable radical cation bromotriarylaminium hexachloroantimonate salts (Scheme 1.1a). The aminium salt initiators act as highly oxidizing catalysts capable of single electron transfer events. The catalytic aminium salts **1-1** and **1-2** are capable of abstracting a single electron from olefins. This in turn creates a useful radical cation intermediate that is able to undergo a variety of cycloadditions depending on the nucleophile of choice (Scheme 1.1b). The single electron oxidation described can be viewed as an umpolung process, in which the polarity of nucleophilic alkenes is reversed to render them electrophilic.



Scheme 1.1. Oxidizing bromotriarylaminium salts and the general transformations they can accomplish.

More recently, visible light photoredox catalysis has been recognized by synthetic chemists as a unique, efficient, and mild way to generate radical cations through single electron transfer processes.[4] As an example, let us examine the radical cation Diels–Alder reaction. A quarter of a century after Bauld first discovered this cycloaddition, the resuscitation of photochemistry led Yoon and coworkers to further develop the transformation with the use of visible light photoredox catalysis.[5] Rather than employing radical cation aminium salt initiators, the reaction is catalyzed by a ruthenium based photocatalyst $Ru(bpz)_3^{2+}$ ($E^*_{1/2}$ = +1.45 V vs. SCE). In comparison to Bauld's methodology, the photocatalytic method utilizes a much lower catalyst loading, proceeds at room temperature, and provides the Diels–Alder cycloadduct **1-5** from *trans*-anethole (**1-3**) and diene **1-4** in higher yield and with better selectivity (Scheme 1.2). Yoon broadened the scope of this transformation and applied the methodology toward the synthesis of the natural product Heitziamide A (**1-6**).[6]



Scheme 1.2. The radical cation Diels–Alder in 1983 and in 2011, as well as the chemical structure of Heitziamide A.

The radical cation Diels–Alder developed by Yoon relies on the irradiation and consequential excitation of a metal complex which becomes capable of donating or receiving a single electron. Overall, these reactions are considered sustainable or "green", as they use visible light, are environmentally benign, and are easily accessible (without the need of specialized laboratory equipment). Visible light photoredox catalysis also takes advantage of the fact that the majority of organic molecules do not absorb in the visible light region (390-700 nm), avoiding undesired side reactions and substrate decomposition. The processes themselves are thought of as photooxidative or photoreductive, thus leading to the term photoredox (Figure 1.1). Donation to an electron acceptor substrate leads to radical anion intermediates. The abstraction of a single electron from a donor substrate leads to radical cation intermediates. Both radical ions are then capable of undergoing further chemistry. A subsequent oxidation or reduction of the respective transient catalytic species regenerates the ground state photocatalyst, which can reenter the cycle.

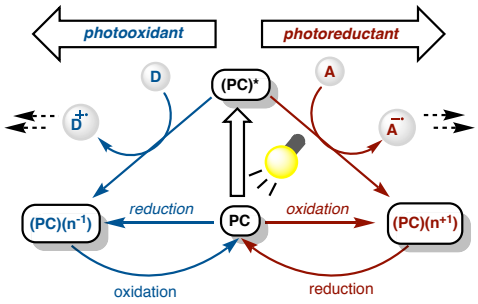
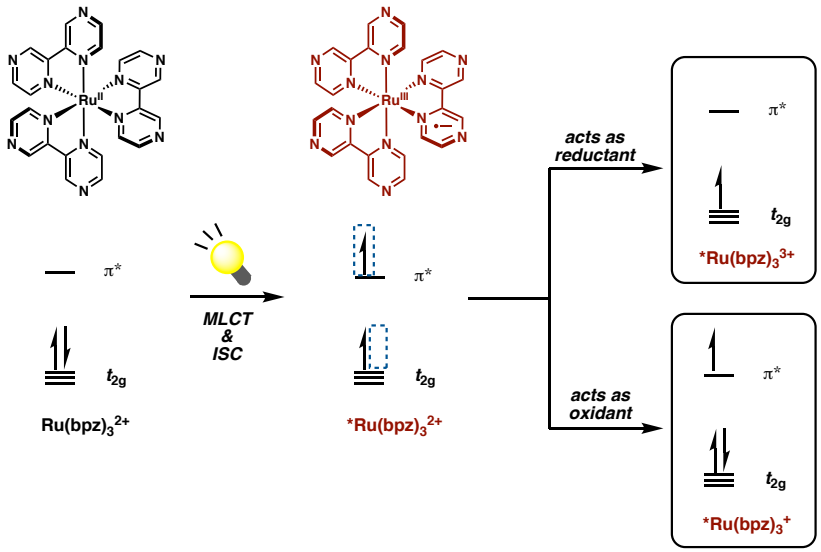


Figure 1.1. Generalized scheme of photoredox catalysis.

To further understand this process on the molecular level, $Ru(bpz)_3^{2+}$ will be used as an example. An oversimplified orbital diagram for $Ru(bpz)_3^{2+}$ is depicted in Scheme 1.3. When the ground state catalyst is irradiated with light, one of the electrons from the metal t_{2g} orbital is excited to the higher energy π^* ligand orbital, a process known as metal-to-ligand charge-transfer (MLCT). MLCT promotes an electron to a singlet state and intersystem crossing (ISC) gives the triplet electron drawn. This overall process allows for single electron transfer events to transpire. In the

photooxidative scenario an electron is abstracted from a donor substrate to fill the empty "hole" in the lower energy orbital; this process furnished radical cations. Alternatively, the higher energy electron can be transferred to an acceptor substrate to create a radical anion.



Scheme 1.3. Simplified molecular orbital diagram of $Ru(bpz)_3^{2+}$.

The main focus of Chapter 1 is to discuss aminium salt catalyzed radical cation net (2+1) cycloadditions and build a bridge toward modern day photoredox catalyzed (2+1) cycloadditions. The synthesis of three-membered heterocyclic or carbocyclic rings using these processes are scarce and underexplored. Thus, cyclopropanations and aziridinations facilitated by single electron transfer events will be thoroughly and chronologically reviewed for both aminium salt- and photoredox-catalyzed methods.[7] Although organic photosensitizers are well represented in a diverse array of transformations,[8] transition metal-based photocatalysts will mainly be discussed. To our knowledge, there is only one example of a (2+1) cycloaddition mediated by single electron transfer processes that uses an organic photosensitizer (*vide infra*).[910]

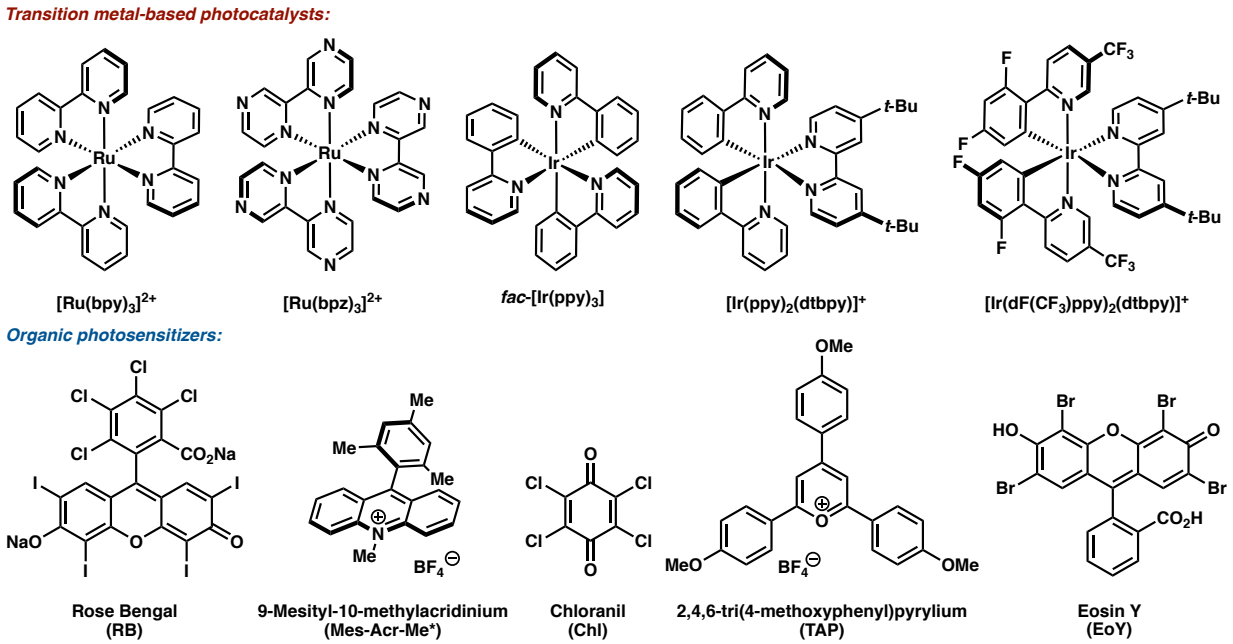
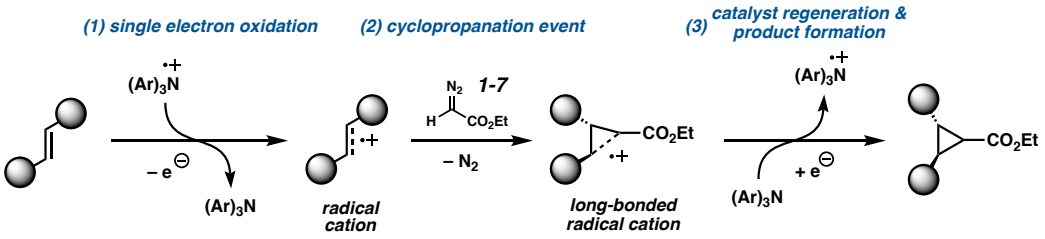


Figure 1.2. Common transition metal-based photocatalysts and organic photosensitizers.

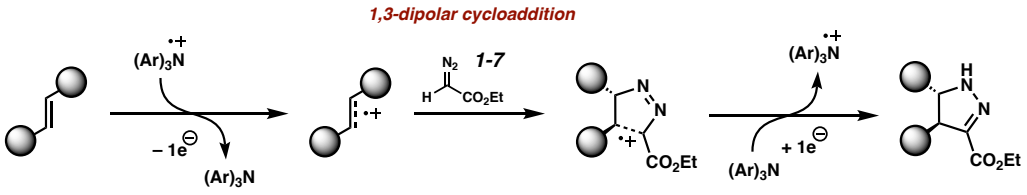
1.2 Aminium Salt Catalyzed Radical Cation Cyclopropanations

In the mid 1980s, Bauld's culmination of work supported the notion that π radical cations have an intrinsic nature to undergo cycloadditions. His reaction platform, which utilized aminium salt catalysts, was highly capable of ionizing a variety of conjugated dienes, styrenes, and electron-rich olefins toward the formation of substituted cyclobutane and cyclohexene adducts.[2] In hopes of further exploiting the radical cation intermediate, Bauld envisioned employing diazo species as the one-carbon component in a radical cation cyclopropanation.[3] A general mechanism for the transformation is illustrated in Scheme 1.4. After a single electron oxidation by an aminium salt initiator, the radical cation generated was envisioned to undergo a (2+1) cycloaddition with ethyl diazoacetate (**1-7**) leading to a "long-bonded" radical cation intermediate after loss of nitrogen gas. Donation of a single electron from the neutral amine regenerates the oxidizing catalyst and simultaneously furnishes the desired cyclopropane adduct.



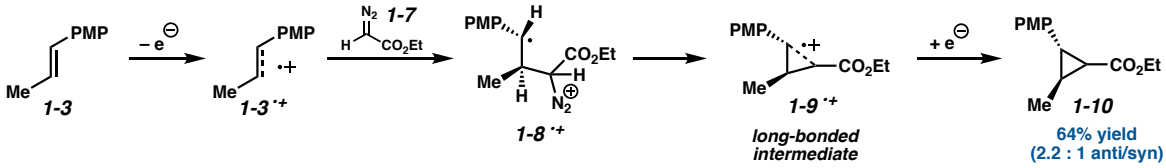
Scheme 1.4. General radical cation cyclopropanation mechanism.

It was believed that the diazo species could act as a nucleophile in this transformation without competing ionization. The aminium salt initiator is more likely to abstract an electron from an olefin substrate such as *trans*-anethole, which has a lower reduction potential (E_{ox} = +1.11 V vs. SCE). The reduction potential value is determined experimentally for individual chemical species and is measured in volts. Specifically, the potential, or tendency, of a chemical species to gain electrons or be reduced is the reduction potential.[11] A compound with a large/higher reduction potential attracts electrons more strongly than a compound with a small reduction potential. Therefore, if a chemical species is less likely to be reduced, it is more likely to be oxidized and experimentally found to have a smaller/lower reduction potential. Further, the higher the potential, the more difficult it becomes to abstract an electron from a substrate. Thus, a single electron abstraction from ethyl diazoacetate (**1-7**) would be more difficult, since its reduction potential is almost 1.0 V higher, placing it outside the range of ionizability (E_{ox} = +2.10 V vs. SCE).[3] Not knowing exactly how the diazo species would react with a radical cation intermediate, an alternate scenario was envisioned by Bauld in which pyrazoline formation could occur via a 1,3-dipolar cycloaddition (Scheme 1.5).



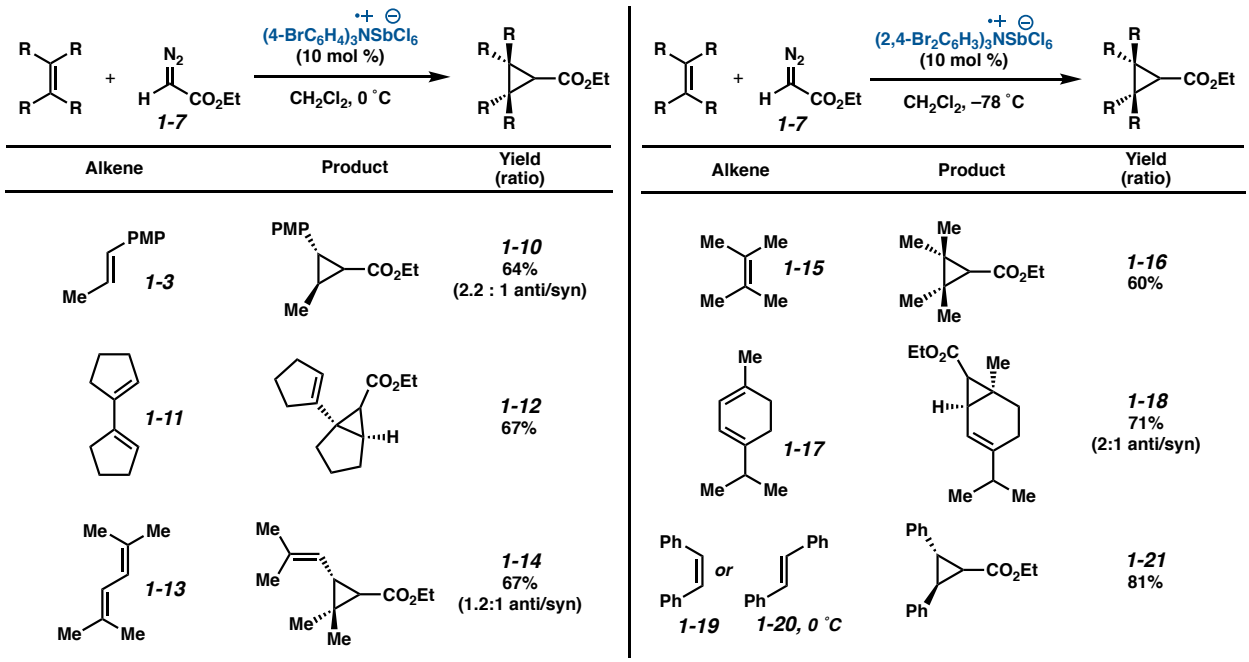
Scheme 1.5. Proposed radical cation pyrazoline formation.

An experiment was performed in order to evaluate the outcome between ethyl diazoacetate and a radical cation intermediate. The reaction employed five equivalents of diazo reagent **1-7** to avoid cyclodimerization of the alkene, and a catalytic loading (10 mol %) of either aminium salt was used. The authors found that when subjecting *trans*-anethole to the reaction conditions, a diastereomeric mixture of cyclopropane **1-10** was indeed observed, presumably arising through their formerly proposed mechanism (Scheme 1.6).



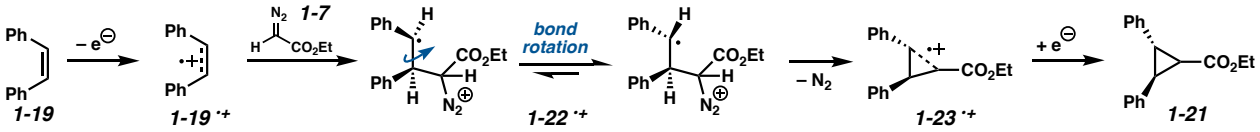
Scheme 1.6. Detailed radical cation cyclopropanation mechanism.

The diazo component was further paired with known ionizable alkenes (Scheme 1.7). 1,1-Bicyclopentenyl **1-11** provided bicycle **1-12** in good yield. Notably, the *anti*-isomer of cyclopropane **1-14**, generated from the hindered *s-trans*-diene 2,5-dimethyl-2,4-hexadiene (**1-13**), is ethyl chrysanthemate, a key intermediate that leads to a potent mammal-safe natural insecticide, pyrethrin I.[12] Catalytic amounts of tris(4-bromophenyl)aminium hexachloroantimonate (E_{ox} = +1.10 V vs. SCE) were unable to oxidize alkenes **1-15**, **1-17**, **1-19**, or **1-20**. However, employing the more powerful single electron acceptor tris(2,4-dibromophenyl)aminium hexachloroantimonate (E_{ox} = +1.47 V vs. SCE) rendered the desired cyclopropanes **1-16**, **1-18**, and **1-21** in respectable yields. The reaction with the stronger single electron oxidant was generally performed at –78 ˚C, which allowed for the chemoselective synthesis of bicycle **1-18**. Specifically, when α-terpinene (**1-17**) is treated with the potent oxidant and ethyl diazoacetate, cyclopropanation occurs exclusively at the less hindered trisubstituted olefin (Me versus *i*-Pr).



Scheme 1.7. Radical cation cyclopropanation scope by Bauld.

Notably, when *cis*-stilbene **1-19** proceeded through the cycloaddition with ethyl diazoacetate only the trans cyclopropane was detected. When *trans*-stilbene is exposed to similar conditions at 0 ˚C, the anti cycloadduct is also obtained in identical yield (81%). The observed stereoconvergency of the stilbene isomers suggests that a free bond rotation occurs during the radical cation mechanism eventually leading to the more stable anti cyclopropane. Presumably, the radical cation generated from *cis*-stilbene undergoes nucleophilic interception by the diazo species **1-7** (Scheme 1.8). Afterward, a free bond rotation leads to a more stable trans intermediate. After loss of nitrogen gas, a "long-bonded" intermediate **1-23**$^{\bullet+}$ is generated and reductively quenched to render the neutral anti cyclopropane **1-21**.

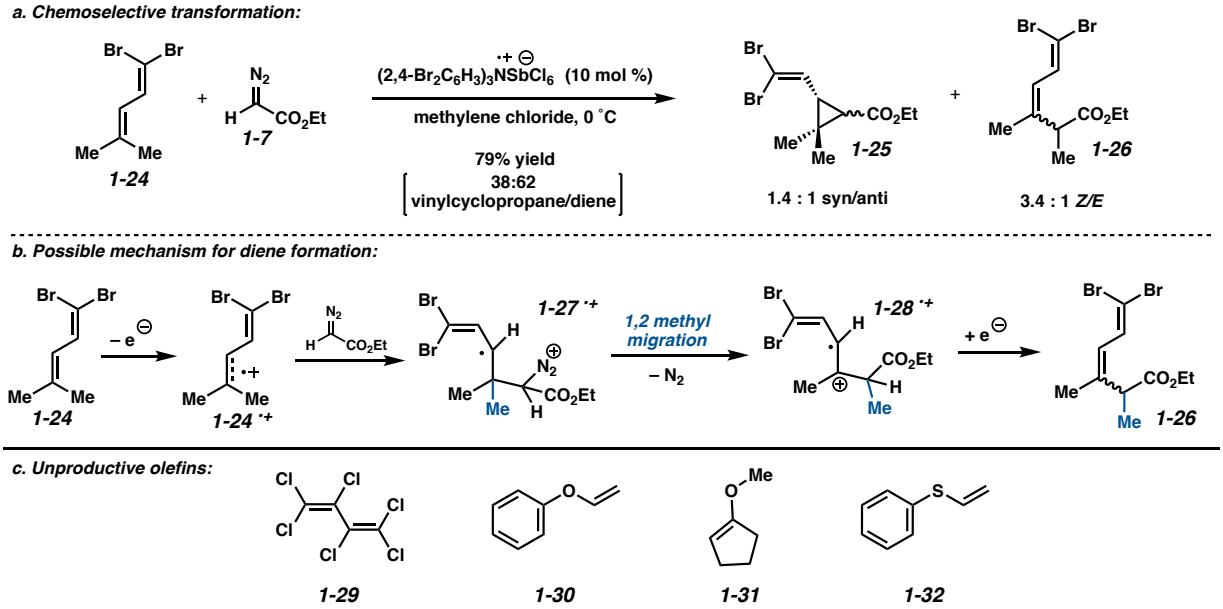


Scheme 1.8. Stereoconvergency of *cis*-stilbene.

Bauld compared the radical cation cyclopropanation method to transition metal catalyzed transformations since they too can combine diazo species and alkenes to construct cyclopropanes.[13] At the time, it was noted that the reaction yields and observed regioselectivities of the radical cation method were comparable to those attained using the rhodium acetate-catalyzed carbenoid procedure.[14] However, the olefin scope of the Rh-catalyzed transformation was more broad, since it is capable of cyclopropanating electronically diverse and more highly strained olefins. Despite this drawback in Bauld's methodology, one of the most powerful aspects of the radical cation cyclopropanation is its chemoselectivity. Assuming the proposed radical cation mechanism is true, the oxidizing catalyst should be able to discriminate between ionizable and non-ionizable olefins. Particularly, cyclopropanation would only occur where radical cation formation is possible. This can allow chemists to design syntheses with the capability of predicting site selective cycloadditions based on the ionizability of the alkenes present.

One example of chemoselectivity is portrayed in the synthesis of an even more potent synthetic pyrethroid insecticide: the *syn*-isomer of vinylcylopropane **1-25**.[15,3] The bromine substituents on diene **1-24** increase its overall reduction potential, yet cyclopropanation was feasible with the stronger oxidant tris(2,4-dibromophenyl)aminium. The desired product, along with its *anti*-isomer, were furnished in a 1.4:1 syn/anti ratio. Indeed, discrimination was accomplished between the brominated and methylated olefin based on the facile formation of the radical cation intermediate. Unfortunately, the reaction suffered greatly in that it favored the formation of byproduct diene mixture **1-26**. A possible mechanistic scenario proposed by Bauld involves a 1,2-alkyl migration leading to the loss of dinitrogen (Scheme 1.9b). The radical cation intermediate is then reduced to render diene **1-26** in a 3.2:1 *Z*/*E* alkene ratio. Even the most potent oxidizing aminium salt, however, was not capable of mediating (2+1) cycloadditions with

hexachloro-1,2-butadiene (**1-29**), phenyl vinyl ether (**1-30**), 1-methoxycyclopentene (**1-31**), or phenyl vinyl sulfide (**1-32**). Enol ethers and vinyl sulfides are thought to act more as nucleophilic partners in radical cation transformations, rather than radical cation precursors themselves. The limited functional group tolerance is also believed to be due, in part, to having a heteroatom directly attached to the olefin.

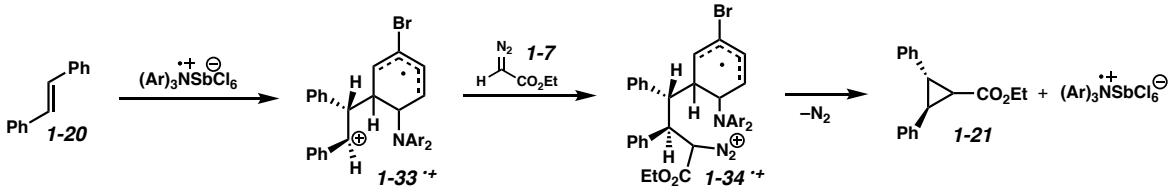


Scheme 1.9. (a) A chemoselective transformation. (b) Proposed mechanism. (c) Failed alkenes.

1.2.1 Radical Cation Mechanisms: Chain versus Catalytic

Several years after the radical cation Diels–Alder was disclosed by Bauld, the aminium salt catalyzed cycloaddition mechanism experienced scrutiny by the chemical community.[1] The criticism arose after a report from a group in Sweden, led by Eberson, proposed an electrophilic mechanism for the Diels–Alder cyclodimerization of 1,3-cyclohexadiene—a reaction which was considered exemplary among radical cation cycloadditions.[16] In order to discern Bauld's reported cyclopropanation method from an electrophilic or even Brønsted acid mediated process, several

criteria that could provide mechanistic evidence for a radical cation pathway were evaluated. The criteria included: (1) testing reactions with a hindered base—a simple test for distinguishing Brønsted acid catalyzed mechanisms from radical cation-based processes, (2) a photosensitized single electron transfer (PET) cycloaddition used to compare and support radical cation mechanisms, (3) detailed kinetic experiments, and (4) an assessment of the transformation's stereochemical outcome. Scheme 1.10 depicts the hypothetical electrophilic mechanism, which invokes the aminium salt initiator as an electrophile as proposed by Eberson.



Scheme 1.10. A hypothetical electrophilic mechanism.

Assessing the first criterion revealed that the hindered base 2-6-di-*tert*-butylpyridine, known to suppress Brønsted acid-catalyzed reactions, did not hinder the cyclopropanation with ethyl diazoacetate. Additionally, the neutral triarylamine, known to be too non-basic to slow Brønsted acid-catalyzed reactions, actually inhibited the (2+1) cycloaddition. These two outcomes ruled out a Brønsted acid-catalyzed mechanism. When a photosensitized single electron transfer (PET) cyclopropanation was performed, the transformation yielded products with similar diastereo- and regioselectivity as with aminium salt conditions. This photosenitized electron-transfer experiment is viewed as authentication of a radical cation mediated cycloaddition. An analogous outcome was observed when evaluating Bauld's radical cation Diels–Alder cycloaddition, further supporting a single electron transfer mechanism involving radical cations.

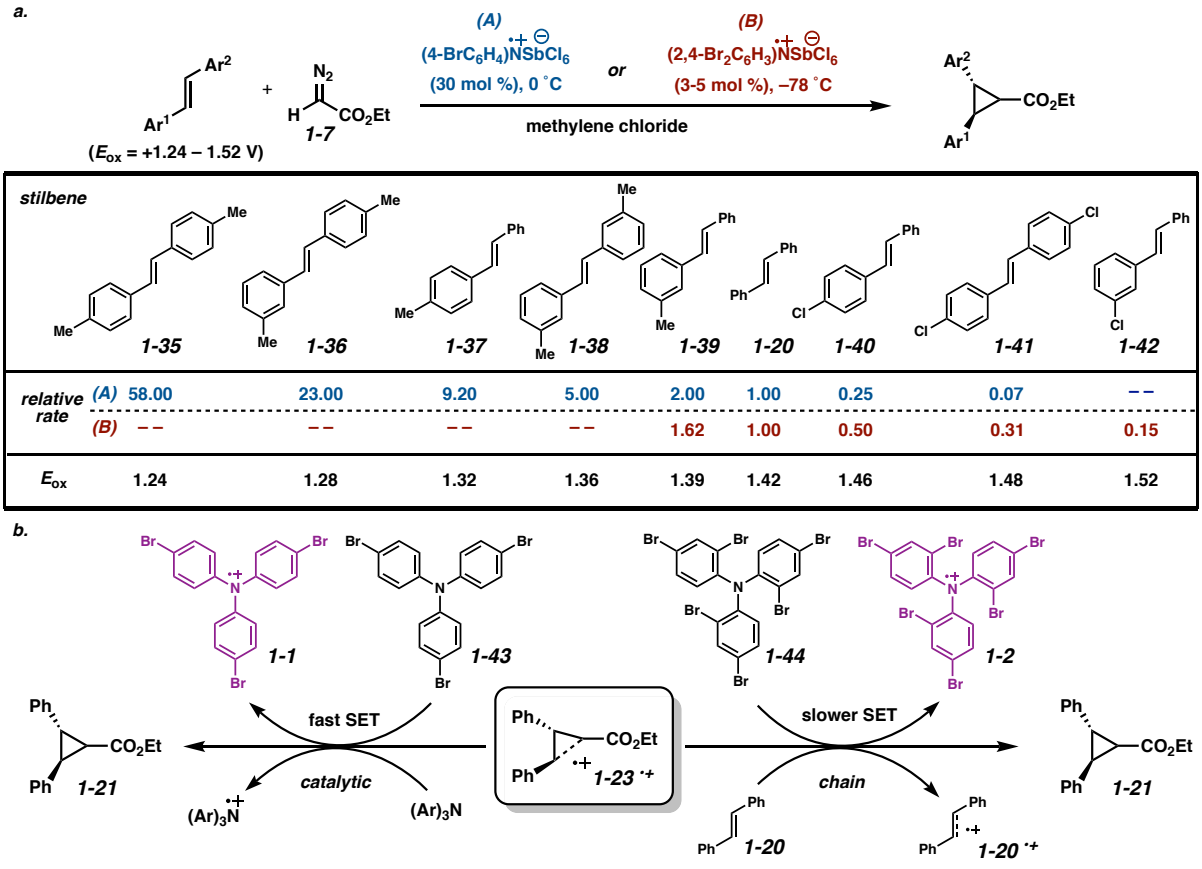
As was previously discussed, the net (2+1) cycloaddition was found to be stereoconvergent. This stereochemical outcome hints at the existence of a radical cation

intermediate that is capable of rotating freely about a bond (Scheme 1.8). Bauld noted that in classical electrophilic additions, *cis*-stilbene is approximately five times more reactive than *trans*-stilbene. If an electrophilic mechanism was indeed operative, the nucleophilic addition of the amine species would be reversible, thus allowing *cis*-stilbene to isomerize to the more stable trans conformer. However, in experiments where ethyl diazoacetate was removed from the reaction mixture, isomerization of *cis*-stilbene was not observed both in the presence and absence of the aminium salt. All of the above experimental observations strongly suggest that a radical cation cyclopropanation mechanism is operative, and neither a Brønsted acid-catalyzed or electrophilic mechanism is functional.

Detailed kinetic experiments by Yueh and Bauld provided further evidence of a radical cation mechanism (Table 1.1).[3] Their studies also made it possible to distinguish between chain and catalytic radical cation processes. By performing Hammett-Brown substituent studies on stilbenes with both triarylaminium salts, it was noted that the ionization step of the stronger catalyst, tris(2,4-dibromophenyl)aminium, was exergonic or "downhill". This signaled that a radical cation chain mechanism was operative and that stilbenes were oxidized by the highly energetic radical cation **1-23**$^{\bullet+}$. When the weaker tris(4-bromophenyl)aminium was examined, an endergonic or "uphill" oxidation step was identified suggestive of a catalytic mechanism.

To further reiterate, it was proposed that both aminium catalysts could not proceed through a radical chain mechanism, and that neutralization of intermediate radical cation **1-23**$^{\bullet+}$ is undeniably much faster with neutral amine **1-43** (E_{ox} = + 1.06 V vs. SCE) than with the weaker reductant **1-44** (E_{ox} = + 1.50 V vs. SCE) (Scheme 1.11b). Thus, transformations with tris(4-bromophenyl)aminium (**1-1**) should be considered catalytic. The more powerful single electron oxidant tris(2,4-dibromophenyl)aminium (**1-2**) proceeds via a radical cation chain mechanism.

These claims were further supported by experimental observations. The cyclopropanations of less reactive stilbenes using tris(2,4-dibromophenyl)aminium **1-2** were much faster (1-2 minutes) in generating the desired 5-10% conversion of starting material. In comparison, the weaker catalyst tris(4-bromophenyl)aminium **1-1**, took several hours in achieving the same result. Furthermore, very small amounts of the stronger oxidizing catalyst tris(2,4-dibromophenyl)aminium **1-2** were required (3-5 mol %) in comparison to (30 mol %) for **1-1**, further pointing toward a radical cation chain mechanism.



Scheme 1.11. (a) Relative rates of cyclopropanation. (b) Distinguishing between chain and catalytic radical cation pathways.

Lastly, Bauld and Yueh inferred that the radical cation cyclopropanation proceeds through an outer-sphere electron-transfer mechanism.[3] This claim was supported by kinetically controlled ionizations of stilbene substrates with both oxidizing aminium salt catalysts. The experiments

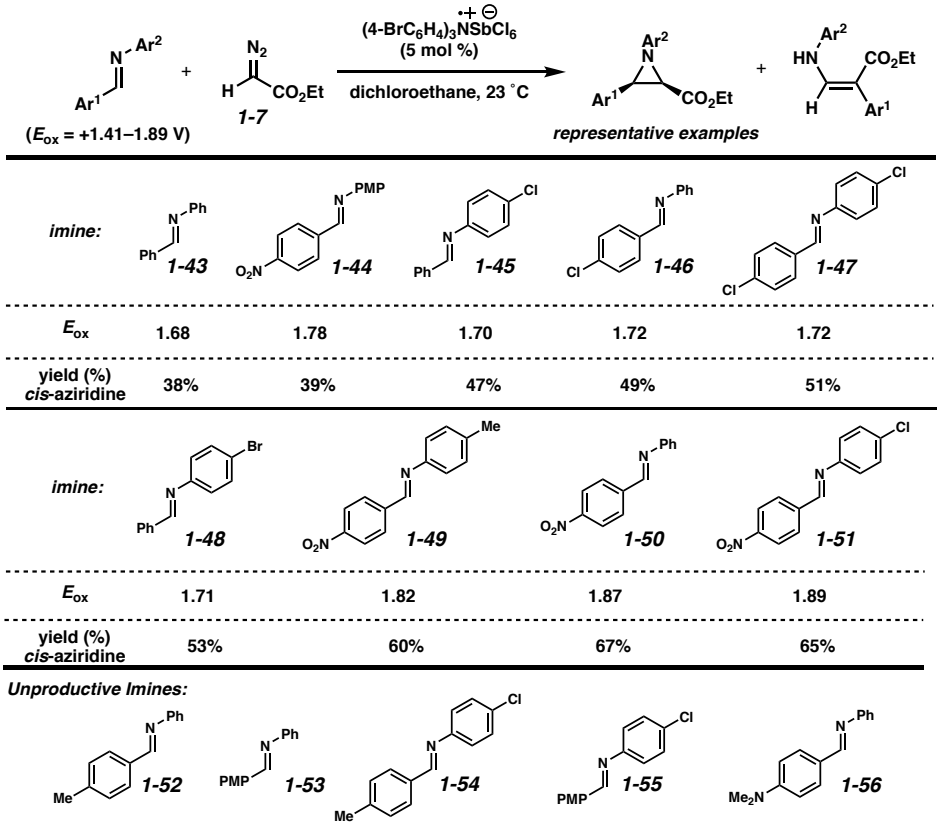
revealed that a symmetrical positive charge accumulated on both aryl rings of the stilbene substrates. This observation is consistent with outer-sphere electron transfer and does not indicate the development of covalent bonding to any one olefinic carbon. If signs of covalent bonding to a specific alkene carbon were observed, they would support the concept of inner-sphere electron transfer, though that was not the case.

1.3 Aminium Salt Catalyzed Radical Cation Aziridinations

For almost three decades, innovative (2+1) radical cation cycloadditions remained absent in the literature. But in 2011, researchers in China led by Huo reported a novel radical cation aziridination between ionizable imines and ethyl diazoacetate. Huo's method furnished a number of aziridines in modest to appreciable yields (Scheme 1.12).[17] The single electron oxidizing reagent tris(4-bromophenyl)aminium hexachloroantimonate was employed throughout the scope of the transformation. The radical cation aziridination process rendered products with exclusive *cis*-stereoselectivity and an enamine byproduct was also observed.

Imines with reduction potentials ranging from +1.41 to 1.89 V vs. SCE were efficient in undergoing the proposed radical cation cycloaddition at room temperature (Scheme 1.12). As imine substrates became more electron-rich, the yield decreased, and no product was observed for the most electron rich imines (**1-52** to **1-56**). The authors cited the work of Steckhan and co-workers which found that in order for a radical cation [4+2] cycloaddition to be successful, the difference in ionization potentials between the diene and dienophile should not surpass 0.50 V.[18] Presumably, this is attributed to a thermodynamic competency that is necessary between the two reactants for an efficient transformation to occur. The difference in electrochemical potential

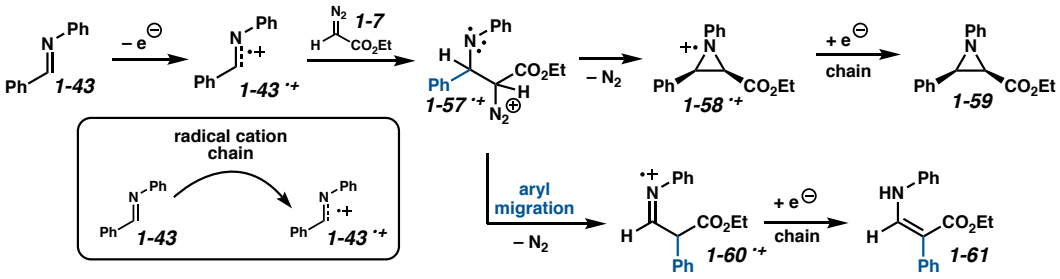
between highly electron rich imines and ethyl diazoacetate (E_{ox} = +2.10 V vs SCE) was too large for an effective transformation. In these unproductive cases, the authors suggest that radical cation formation of the imine substrate does occur but leads to the decomposition of the imine radical cation to generate the corresponding aryl aldehyde and substituted aniline components.[19] The free aniline is then proposed to react with the aminium salt catalyst to displace tris(4-bromophenyl)aminium and form "complex oxidation products". Alternatively, the authors suggest that the imine radical cation can dimerize or oligomerize with neutral arylimines, resulting in complicated reaction mixtures.



Scheme 1.12. Radical cation aziridination scope.

Huo presented a mechanism that is mostly in agreement with that of Bauld's radical cation cycloaddition processes (Scheme 1.13). Initial oxidation of the imine substrate results in polarity reversal to generate radical cation intermediate **1-43**$^{\bullet+}$ that is nucleophilically attacked by ethyl

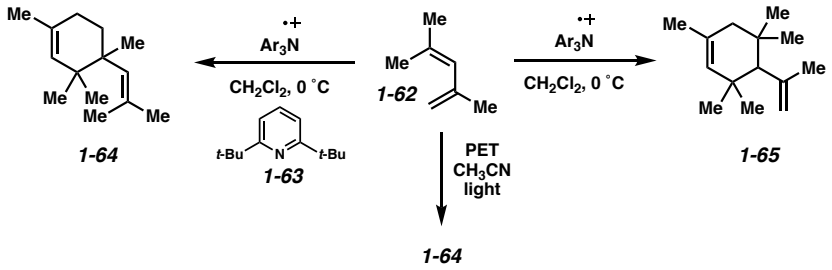
diazoacetate. The resulting radical cation intermediate can then proceed through a ring closure event after loss of dinitrogen to afford radical cation aziridine **1-58**$^{\bullet+}$. **1-58**$^{\bullet+}$ is then reduced by another equivalent of neutral imine to render the *cis*-aziridine product and a radical cation imine that can continue through the cycle. The enamine byproduct **1-61** presumably arises through an aryl migration. Substituent migrations in radical cation intermediates have also been reported by Bauld (Scheme 1.9B).[3] After the proposed aryl migration and loss of nitrogen gas, the radical imine intermediate **1-60**$^{\bullet+}$ formed is reduced and undergoes tautomerization to the conjugated enamine **1-61**. Given the fast reaction time (0.5 h) and low catalyst loading (5 mol %), the authors imply that the transformation proceeds through a radical cation chain mechanism, although no further mechanistic investigations were conducted.



Scheme 1.13. Proposed mechanism for the radical cation aziridination reported by Huo.

In section 1.2.1 we discussed the various criteria assessed when supporting or refuting a radical cation mechanism. One in particular was the evaluation of stereochemical outcome. The *cis*-selectivity that Huo and coworkers observed was a marked difference from Bauld's cyclopropanation with the same tris(4-bromophenyl)aminium salt. The difference in diastereoselectivity may be attributed to the presence of a nitrogen heteroatom, but still we found Huo's stereochemical outcome intriguing. Our curiosity arose from the knowledge that *cis*-aziridines are also generated through a well-known aziridination method known as the Aza-

Darzens reaction.[20] Furthermore, it is a known fact that Aza-Darzens aziridinations can be mediated by Brønsted acids.[21]

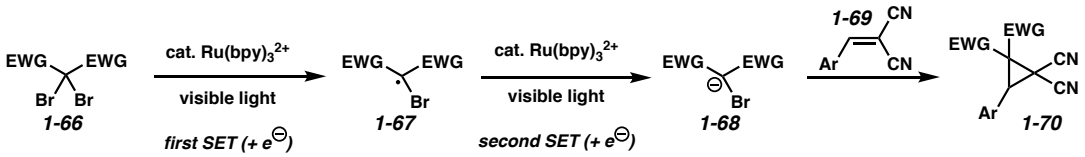


Scheme 1.14. Control experiments for differentiating between radical cation and Brønsted acid mediated pathways.

In order to distinguish between a Brønsted acid and radical cation catalyzed aziridination process, further experiments would need to be performed by Huo or others in order to rule out the former. As an example, in 1984 evidence compiled by Gassman and Singleton suggested that the dimerization of 2,4-dimethyl-1,3-pentadiene (**1-62**) could occur via a Brønsted acid catalyzed mechanism (Scheme 1.14).[22] In order to differentiate between the two mechanistic pathways, Bauld invoked two experiments from their developed criteria that were previously discussed in Section 1.2.1. A photosensitized single electron transfer-initiated reaction was tested. Further, the dimerization in the presence of the hindered base 2,6-di-*tert*-butylpyridine (**1-63**) was assessed. It was found that the single electron transfer photosensitized process yielded the same dimer (**1-64**) as the transformation performed with radical cation aminium salts in the presence of 2,6-di-*tert*-butylpyridine (**1-63**). Furthermore, the standard aminium salt catalyzed process yielded a distinct Diels–Alder cyclodimer (**1-65**). The formation of dimer **1-65** was also suppressed when the identical experiment was conducted in the presence of the hindered base. The bulky base criterion, known to suppress Brønsted acid-catalyzed transformations but not radical cation processes, provided support for the radical cation mechanism.

1.4 Photoredox Catalyzed Cyclopropanation of Arylenemalononitriles

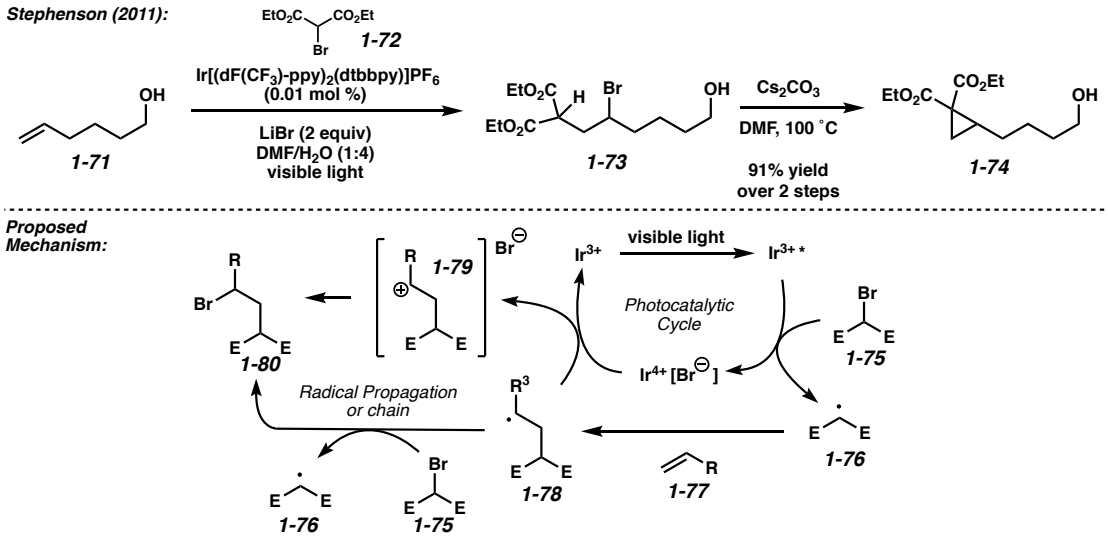
In 2015, Guo and coworkers disclosed a novel cyclopropanation method between a series of dibromomalonates and arylenemalononitriles using $Ru(bpy)_3^{2+}$ and visible light.[23] To our knowledge, this was the first reported cyclopropanation mediated by a photoredox catalyst via single electron transfer events. The authors highlighted the mild reaction conditions, environmental benignness, and easy to handle procedure which utilized a 23 W household lamp or sunlight at room temperature under air or argon. Previous work by Stephenson and coworkers had established that bromomalonates could be converted into their corresponding carbon centered radical after a single electron reduction.[24] Guo hypothesized that a dibromomalonate **1-66** could be reduced in a similar fashion, and that the carbon centered radical **1-67** could undergo a second reduction to reveal a malonate carbanion (**1-68**, Scheme 1.15). An intermolecular Michael addition into malononitrile **1-69** followed by an intramolecular nucleophilic substitution could subsequently render the desired multi-substituted cyclopropane **1-70**.



Scheme 1.15. Guo's conceptualized double single electron transfer process.

The double single electron transfer hypothesis was further supported by a report affirming that benzyl bromide could be converted to its corresponding carbanion through a double single electron reduction using $Ru(bpy)_3^{2+}$.[25] Furthermore, a proof of concept was demonstrated four years earlier by the group of Stephenson (Scheme 1.16). Using the strongly reducing $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ catalyst (Ir(III)*/Ir(IV) = –1.21 V vs. SCE) an atom transfer radical addition of α-halocarbonyls to olefins was accomplished. The initial single electron reduction is

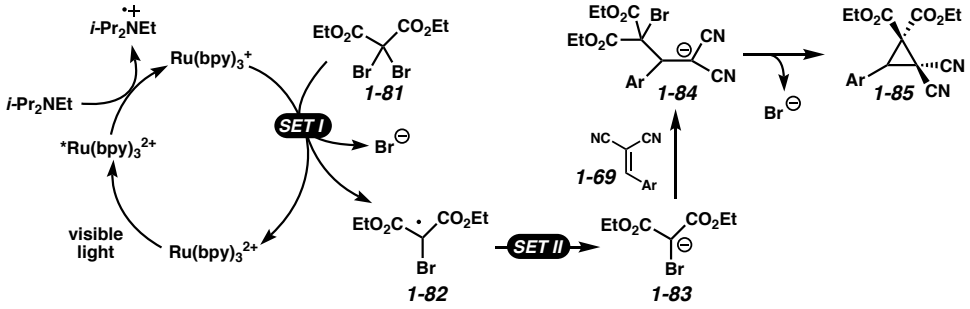
mediated by the excited state Ir(III)* species formed when the ground state Ir(III) complex is exposed to light. Mechanistically, α-halocarbonyls or haloalkanes are believed to be reduced to their radical form **1-76**, afterward combining with an alkene to form key intermediate **1-78**. The observed atom transfer radical addition product **1-80** can be generated through one of two pathways. One path involves the generation of a carbocation through catalyst turnover (Ir(IV)→ Ir(III)), where preassociation to the halide followed by combination results in product formation. Alternatively, a radical chain mechanism could also be functioning, in which the radical bromide source **1-75** couples with intermediate **1-78**, generating the atom transfer radical addition product **1-80** and an equivalent of radical **1-76**, which can proceed through the cycle. To showcase the synthetic utility of these difunctionalized products, in one example Stephenson demonstrated that treating bromoalkyl malonate **1-73** with cesium carbonate at elevated temperatures induced an intramolecular nucleophilic substitution to generate cyclopropane **1-74**.



Scheme 1.16. Stephenson's proof of concept toward cyclopropane generation.

In contrast to Stephenson's methodology, Guo envisioned the formation of an anion capable of intramolecular nucleophilic substitution through mild photoredox mediated single

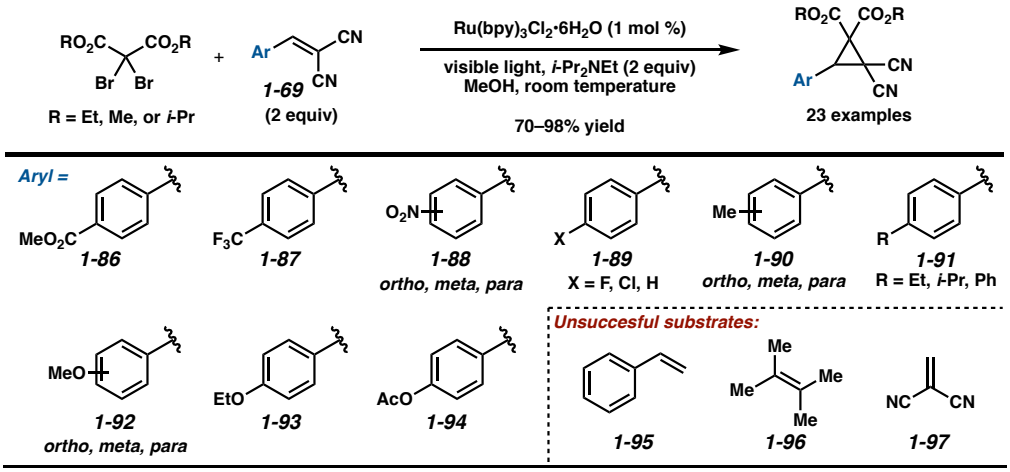
electron transfer, rather than a separate deprotonation event. A full, proposed mechanism is illustrated in Scheme 1.17, with dibromo diethylmalonate **1-81** as the reagent that is being doubly reduced. Irradiation of $Ru(bpy)^{3+}$ with visible light furnishes an excited state species capable of oxidizing Hünig's base to generate the highly reducing $Ru(bpy)_3^{+}$ ($E^*_{1/2}$ = –1.33 V vs. SCE).[26] This species is now capable of donating an electron to dibromomalonate **1-81** generating radical intermediate **1-82**. A sequential single electron transfer reduction, achieved through a similar photocatalytic cycle, generates a bromomalonate anion **1-83** capable of undergoing an intermolecular Michael addition into arylenemalononitriles **1-69**. A final intramolecular nucleophilic ring closure step that displaces bromine renders the desired cyclopropane **1-85**.



Scheme 1.17. Proposed mechanism for cyclopropanation *via* a double SET process.

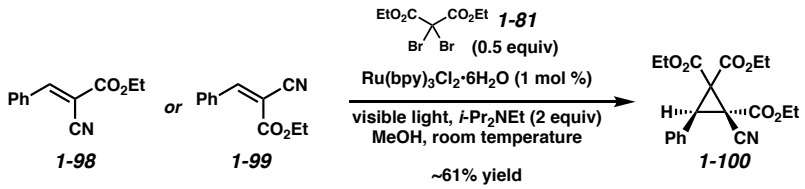
Photoredox catalyzed cyclopropanations were achieved through the reaction design conceived by Guo. Dialkyl 2,2-dibromomalonates and 2-arylenemalonitriles worked in excellent yields ranging from 70–98% (Scheme 1.18). However, the formation of carbanions required the use of electron withdrawing groups on both reaction partners. The electronics of the aryl moiety were easily variable. Diversifying the flanking aryl substituents with electron-donating groups or electron-withdrawing substituents had little to no impact in yield, which was generally maintained above 80%. However, styrene (**1-95**), 1,1-dicyanoethylene (**1-96**), and 2,3-dimethyl-2-butene (**1-97**) were all unsuccessful substrates. This group of failed olefins underscores the importance of

having both aryl and malonolitrile functional groups present on the substrate alkene for an efficient cyclopropanation.



Scheme 1.18. Summarized reaction scope of Guo's photoredox catalyzed cyclopropanations.

To determine if the reaction was stereoconvergent, *E*- and *Z*-trisubstituted alkenes **1-98** and **1-99** were subjected to the optimized reaction conditions individually. Both alkene isomers generated the identical anti cyclopropane **1-100** as the sole product and in comparable yield (Scheme 1.19). The researchers noted that isomerization of the alkene did not occur during the reaction process. Instead, a bond rotation of the proposed carbanion most likely occurs during the reaction mechanism (see Scheme 1.17).

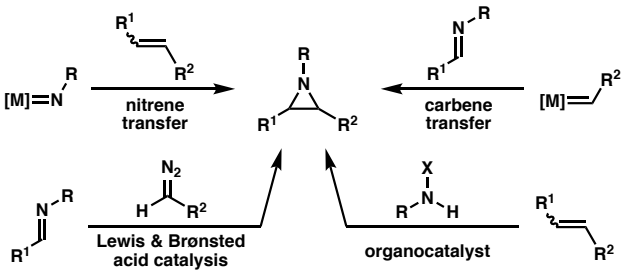


Scheme 1.19. Evaluating the stereoconvergency of Guo's cyclopropanation method.

To gain further insight into the cyclopropanation mechanism, reactions were conducted in the presence of the radical scavengers 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol. Only a slight decrease in cyclopropane yield was observed with no

obvious change in reaction time. Presumably, the radical species **1-82** is not involved in the rate-determining step and reduction of the carbon centered radical **1-82** to the carbanion **1-83** is likely to occur very rapidly (See Scheme 1.17). This may explain why having radical scavengers present in the reaction mixture results in little to no impact on the transformation. An additional experiment was performed to investigate the possibility of a radical chain mechanism. Using the optimized conditions, a reaction tube containing the parent substrates diethyl 2,2-dibromomalonate and 2-phenylenemalononitrile was irradiated for 5 min then placed in the dark for 32 h. The product yield was similar to a reaction that was set up and conducted in the dark. Although, the authors dismissed a radical chain mechanism because of this result, Yoon and Cismesia have argued that these "light/dark" experiments cannot be used to rule out a radical chain process.[27] In all, not much was gained from the further experimentation.

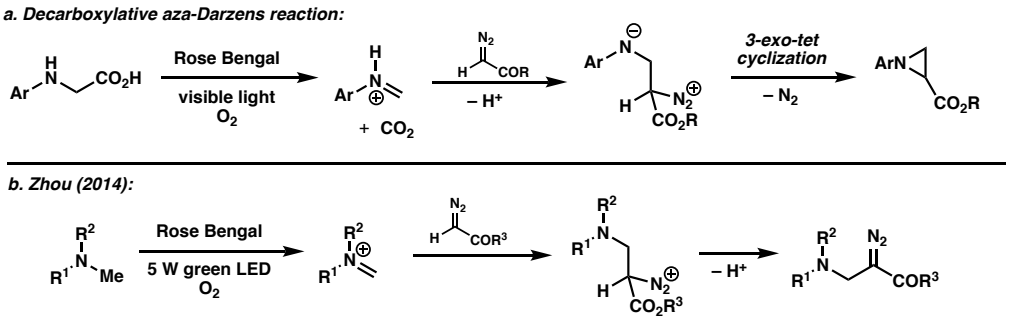
1.5 Rose Bengal Photoredox Catalyzed Aziridinations



Scheme 1.20. Modes of aziridination.

Aziridination reactions can be classified into four distinct approaches, as illustrated in Scheme 1.20. These methods include carbene transfer, organocatalysis, Lewis and Brønsted acid catalysis, and nitrene transfer.[28] Modern photocatalysis has been able to contribute unique, complementary approaches toward the preparation of aziridines. For example, in 2016, Yoon and

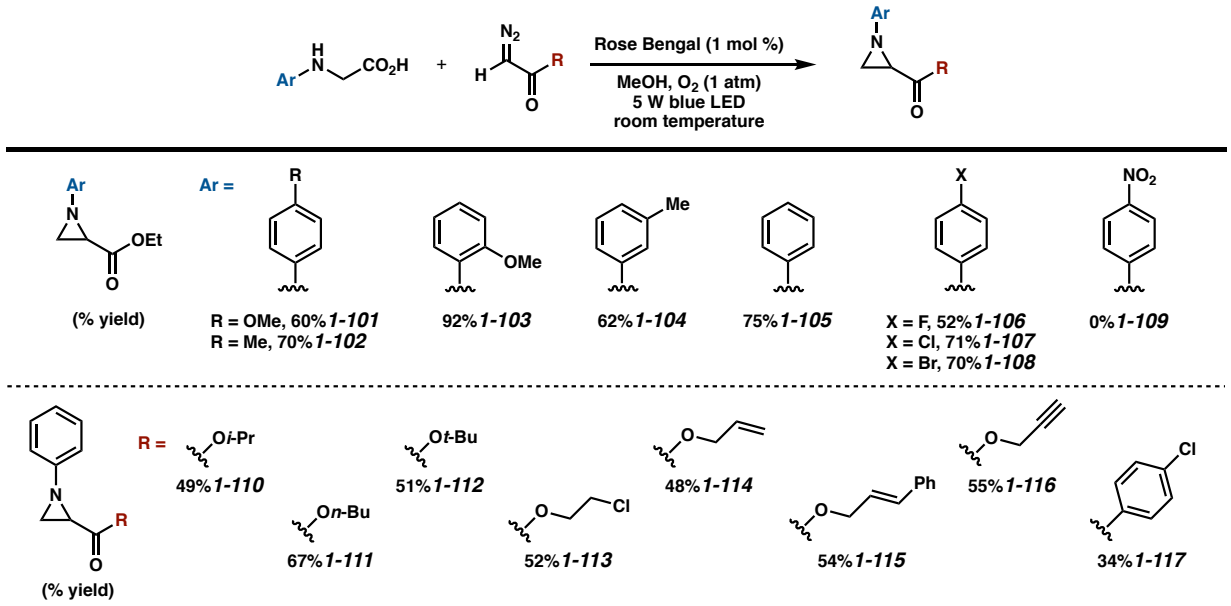
coworkers disclosed a novel approach to olefin aziridination through the generation of triplet nitrenes using visible-light photosensitization with energy-transfer photocatalysts.[29] While this method is interesting and noteworthy, the focus of this chapter is on photoredox catalyzed single electron transfer processes. In 2016, Deng and Zhou disclosed the use of Rose Bengal and visible light to facilitate an aza-Darzens-type reaction between *N*-aryl glycines and diazo reagents.[30] Initially, the authors envisioned photoredox generated iminium ions,[31] through the use of an organic photosensitizer and light, could be susceptible to nucleophilic addition with diazo species (Scheme 1.21a). The intermediate generated after nucleophilic attack could then be deprotonated and positioned to undergo a *3-exo-tet* cyclization with consequential loss of nitrogen gas. This idea stemmed from an earlier study by the group using Rose Bengal and green LEDs to induce a cross-dehydrogenative coupling between tertiary amines and α-diazocarbonyl compounds (Scheme 1.21b).[32] The authors discovered that modifying the light source, solvent, and performing the transformation with Rose Bengal and 1 atm of oxygen successfully generated aziridine products. Because Lewis acids are known to promote aza-Darzens reactions, a control experiment with $Zn(OTf)_2$ was performed, revealing that it was actually detrimental to reactivity.



Scheme 1.21. Zhou's proposed and reported photoredox transformation with diazo species.

With optimized conditions established, the researchers surveyed various α-diazocarbonyl reagents and *N*-aryl glycine derivatives (Scheme 1.22). When the former contained electron-rich

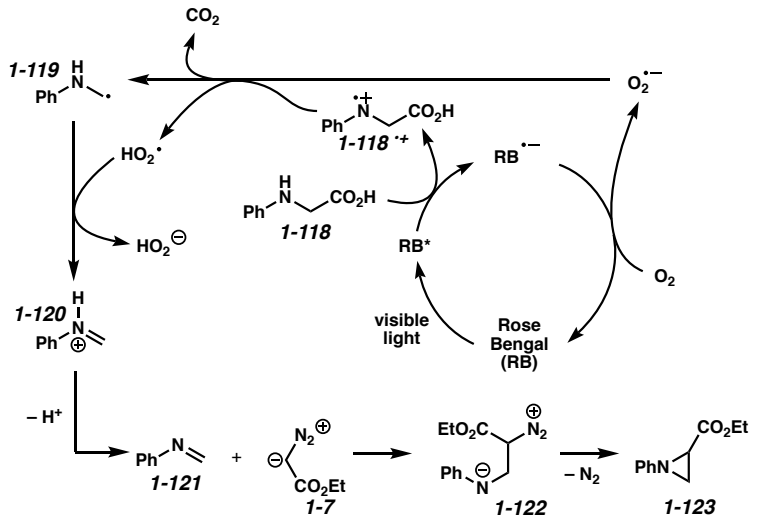
groups (methoxy and methyl) and halides, aziridines were obtained from modest to excellent yields with ethyl diazoacetate as the 1-carbon component. However, when an electron-withdrawing nitro group was present on the aryl moiety (**1-109**), no product was observed. An electron-rich aniline may be necessary for a successful *3-exo-tet* cyclization. In general, photoredox mediated iminium generations seem to necessitate the use of electron neutral/electron rich substituents on the arene.[31] Throughout the exploration of the diazo scope, *N*-phenyl glycine was used as the nitrogen source. Isopropyl **1-110**, *n*-butyl **1-111**, *tert*-butyl **1-112**, allyl **1-114**, cinnamyl **1-115**, and propargyl diazo acetates **1-116** were all compatible, producing aziridines in appreciable yields. Chlorine-tethered diazoester species were also tolerated (**1-113**). Additionally, employing diazo ketone **1-117** with *para*-chloro substitution produced aziridine albeit in low yield. This may be attributed to the weaker nucleophilicity of diazoketones.[33]



Scheme 1.22. Deng and Zhao's photoredox aziridination scope using Rose Bengal.

The mechanism proposed by Deng and Zhou is in line with their previous reports and underscores the important role of oxygen. The plausible mechanism proposed by Deng and Zhou is illustrated in Scheme 1.23 using ethyl diazoacetate (**1-7**) and *N*-phenyl glycine (**1-118**) as model

substrates. Photoexcitation of Rose Bengal (RB) with visible light renders an excited state species capable of oxidizing *N*-phenyl glycine via a single electron transfer process leading to radical cation amine **1-118**$^{\bullet+}$. The Rose Bengal radical anion is oxidized by oxygen to give a superoxide radical anion ($O_2^{\bullet-}$), with this overall process regenerating the photocatalyst.



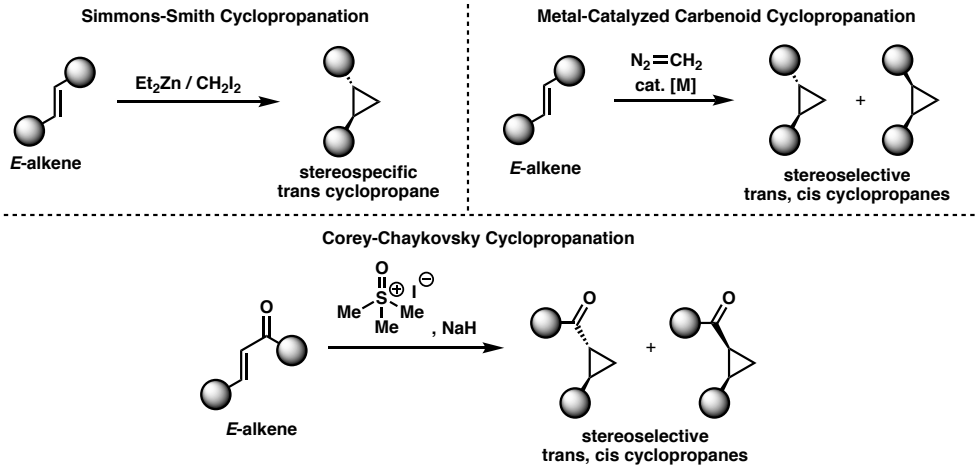
Scheme 1.23. Plausible mechanism employing oxygen and photooxiding Rose Bengal*.

The important role of oxygen was highlighted in a control experiment in which the aziridination of *N*-phenyl glycine (**1-118**) and ethyl diazoacetate (**1-7**) was performed under air. A 16% yield was obtained in comparison to 79% when the reaction is performed with standard conditions. The poor yield was attributed to low oxygen concentration. However, this issue was resolved by performing the aziridinations under an oxygen atmosphere (1 atm). The superoxide radical anion is believed to induce decarboxylation leading to α-amino radical **1-119**, carbon dioxide, and a superoxide radical, which further oxidizes amino radical **1-119** to iminium ion **1-120**. Deprotonation, nucleophilic attack by ethyl diazoacetate (**1-7**), and an intramolecular attack by the nitrogen anion **1-122** leads to monosubstituted aziridine **1-123**. Overall, this metal-free, visible light mediated aziridination that uses easily available aryl glycine derivatives stands as a

useful alternative to Lewis and Brønsted acid catalyzed aziridinations which also employ diazo reagents.

1.6 $Ru(bpy)_3^{2+}$ Photoredox Catalyzed Cyclopropanation of Styrenes

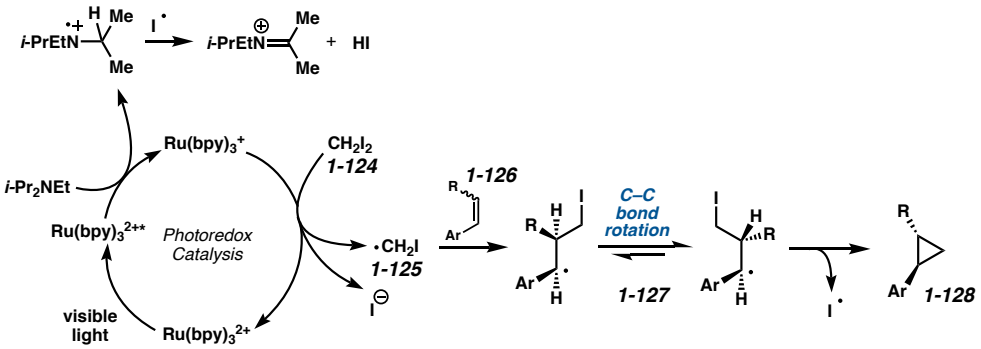
In 2017, Suero and coworkers developed a "gentler" way of transferring a methylene group to alkene substrates through the use of photoredox catalysis. Traditionally, installation of the methylene group has relied on a number of classical transformations including the Simmons-Smith cyclopropanation, which employs iodomethyl-zinc reagents.[34] Diethylzinc, however, is highly pyrophoric and must be handled with care. Diazomethane, infamous for its explosive nature, has also been used to install methylene groups.[35] In combination with metal catalysts, diazomethane is transformed to a metal carbenoid species that can undergo intermolecular metal catalyzed cyclopropanations with olefins. Furthermore, the Corey–Chaykovsky cyclopropanation installs methylenes typically through the use of a bench-stable sulfur ylide. However, the reaction is limited to electron-poor olefins and typically requires the use of strong base.[36]



Scheme 1.24. Traditional methylenation procedures.

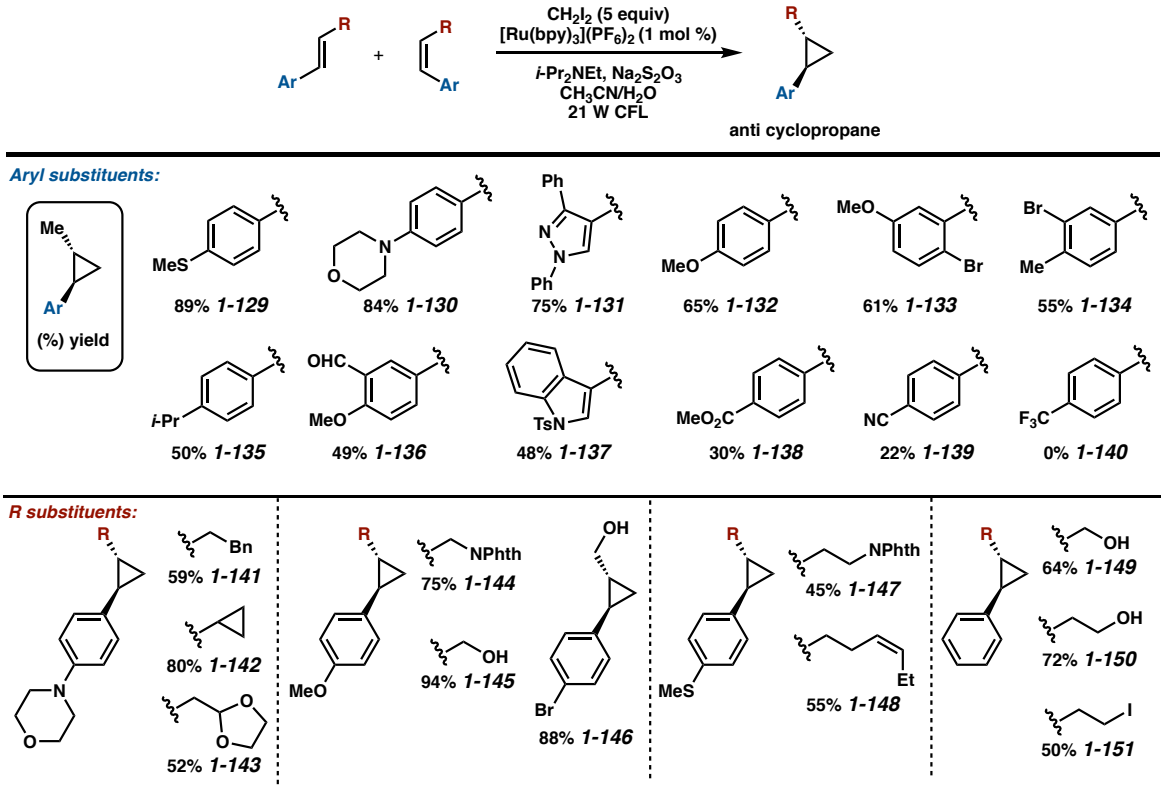
The stereochemical outcome of the Simmons-Smith is stereospecific with respect to the starting alkene geometry. Metal-catalyzed carbenoid and Corey-Chaykovsky cyclopropanations are both stereoselective, typically preferring the trans product regardless of the initial geometry of the olefin. Suero envisioned a mild photoredox catalyzed *stereoconvergent* cyclopropanation that would lead to single trans-isomers regardless of the starting configuration of the alkene precursor. Additionally, rather than using explosive or pyrophoric reagents, commercially available and easy to handle diiodomethane would be the methylene source of choice in their proposed (2+1) cycloaddition with styrenyl analogs.

Pioneering work by Stephenson as well as MacMillan has firmly established that the widely employed ruthenium catalyst $Ru(bpy)_3^{2+}$ is capable of reducing activated halide compounds via single-electron transfer processes.[37] Mechanistically, Suero proposed that the strong reductant, $Ru(bpy)_3^{+}$ ($E^*_{red}{}^{(II)/(I)}$ = –1.33 V vs. SCE), generated from the oxidation of *N,N*-diisopropylethylamine, would be capable of reducing diiodomethane (**1-124**, E_{red} = –1.44 V vs. SCE, Scheme 1.25). Single electron donation would generate a transient radical $CH_2I_2^{\bullet -}$, which is believed to diverge into the iodomethyl radical **1-125** and I^-. The radical intermediate **1-125** can then add into geometrical mixtures of alkenes **1-126** to generate intermediate **1-127** which contains a radical adjacent to a good leaving group (I). In a situation where a *Z*-alkene couples with transient radical **1-125**, a C–C bond rotation would set the neighboring substituents in a favorable trans relationship. Eventual homolytic ring closure would then provide an anti cyclopropane via their desired stereoconvergent pathway.



Scheme 1.25. Suero's proposed mechanism for stereoconvergent cyclopropanation using photoredox catalysis.

For Suero and coworkers, their hypothesis was correct and methylenation was achieved via this process. As illustrated in the above mechanism, the formation of I_2/I_3^- species are possible and could be detrimental to the reaction. These iodine-based byproducts have been reported to quench the photoexcited $Ru(bpy)_3^{2+}*$.[38] Adding water and sodium thiosulfate to the reaction conditions in order to quench unwanted iodine species did in fact increase the overall yield. It was also discovered early on that the anticipated net (2+1) cycloaddition was stereoconvergent, furnishing only anti cyclopropanes when subjecting mixtures of *E/Z*-styrenyl olefins to the reaction. Stereoconvergency has also been observed with other alkene functionalization processes in photoredox catalysis.[39] Additionally, we have seen that Bauld and Guo also observed this phenomenon with at least one olefin substrate.[3,23]



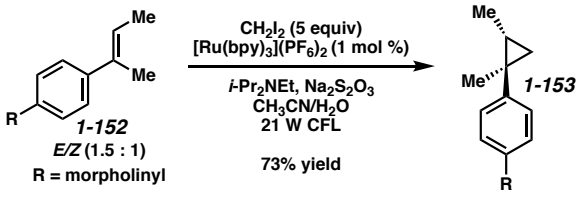
Scheme 1.26. Reaction scope of stereoconvergent cyclopropanations using photoredox catalysis.

After reaction optimization, the scope of the stereoconvergent cyclopropanation was evaluated. When arenes were substituted with electron-rich functionalities, higher yields were observed (Scheme 1.26). Having electron-withdrawing nitrile or ester groups at the 4-position of the phenyl moiety resulted in poor yields. When *para*-trifluoromethyl-β-methyl-styrene was subjected to the reaction conditions, no product was observed at all. The reason why alkenes with moderate to strong electron donating groups performed better could be due to the necessity of a nucleophilic benzylic radical **1-127** to facilitate the radical ring closure event (see Scheme 1.25).

The cyclopropanation of *trans*-anethole could be performed on gram scale without diminishing the yield. Tertiary amines and sulfides, which generally react with iodomethylzinc reagents to generate ylides, were found to be competent functional groups using the photoredox catalyzed conditions. In order to further explore the functional group tolerance of the

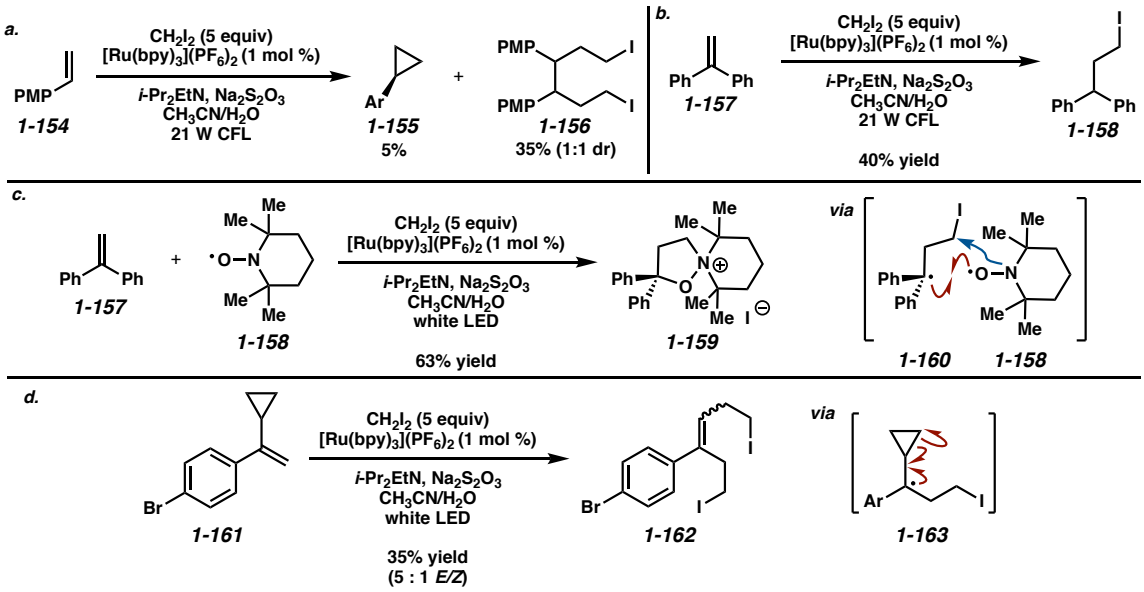
transformation, the alkyl functional group was modified and evaluated. Benzyl groups, cyclopropanes, acetals, free alcohols, imides, alkyl iodides, and alkenes were all tolerated. In an example where a pendant olefin was attached to the styrenyl substrate (**1-148**), only the alkene conjugated to the aromatic group was cyclopropanated. This result highlights the excellent chemoselectivity, a common trend with net (2+1) cycloadditions mediated by single electron transfer processes.

Control experiments confirmed that both light and the ruthenium photocatalyst were necessary for efficient cyclopropanation. Unlike Guo's methodology, oxygen seemed to hamper the reactivity, and degassing the reaction mixture prior to irradiation with visible light benefited the reaction outcome. For example, the cyclopropanation of *trans*-anethole under air afforded the desired cyclopropane in 45% yield. When the identical reaction mixture was degassed prior to irradiation, a 76% yield was observed. Additionally, the stereoconvergency of the cyclopropanation was further inspected. Control experiments confirmed that the mixture of *E/Z*-olefins did not isomerize during the course of the reaction, further supporting the imperative C–C bond rotation that renders cyclopropanes in the anti configuration. The stereoconvergency of a trisubstituted alkene was also examined using the optimized conditions. Initially, the authors believed that the critical C–C bond rotation for a trisubstituted radical intermediate could be difficult or problematic. Much to their surprise and gratification, a single anti diastereomer was observed in good yield (Scheme 1.27).



Scheme 1.27. Stereoconvergent cyclopropanation of a trisubstituted olefin.

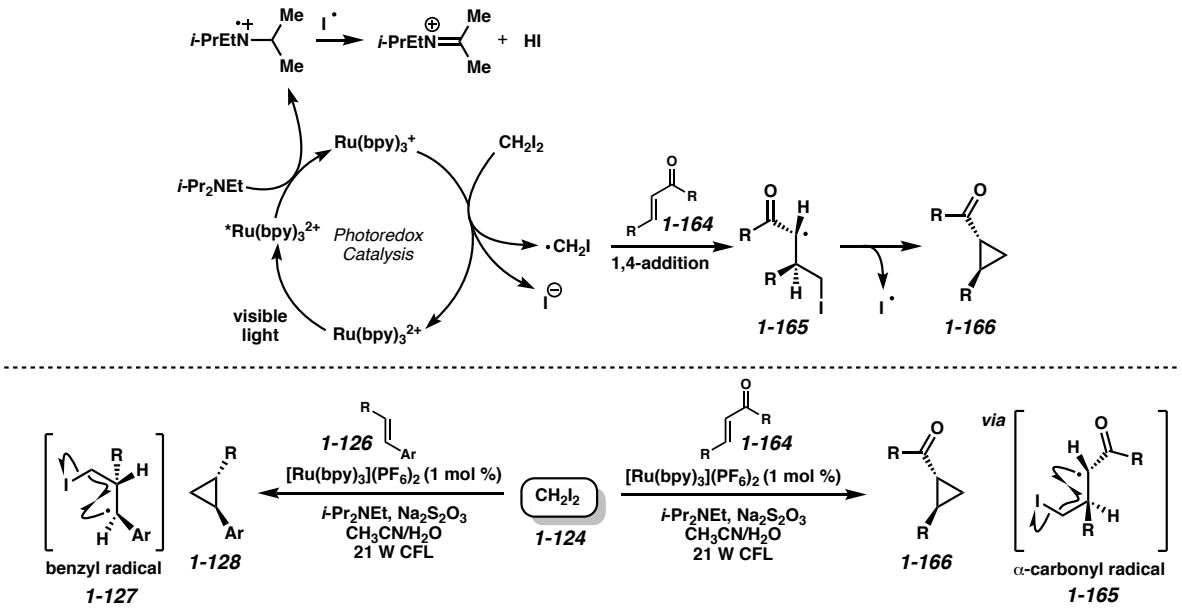
Substituent modification of the starting olefin resulted in differential product outcome which provided further evidence of proposed radical intermediates in the mechanism (Scheme 1.28). When the monosubstituted olefin *para*-methoxy styrene (**1-154**) was subjected to the reaction conditions, a mixture containing small amounts of cyclopropane **1-155** (5% yield) was obtained. The major product was the dimeric species **1-156**. The observation of product **1-156** with a 1:1 diastereomeric ratio suggests that the compound arises from the coupling of two benzylic radicals. When 1,1-diphenylethylene (**1-157**) was subjected to the photocatalytic conditions, the open chain iodoalkane **1-158** was isolated instead. This could be due to an increased stabilization of the doubly benzylic radical, impeding it from undergoing efficient cyclization. When diphenylethylene **1-157** was subjected to the reaction conditions in the presence of TEMPO (**1-158**), a cyclic ammonium iodide salt was isolated (**1-159**). The salt most likely arises from a radical-radical coupling/cyclization between TEMPO and the radical iodine species **1-160**. The radical nature of the proposed intermediates was further supported when vinylcyclopropane **1-161** was subjected to the reaction conditions as a "radical probe". Alkene **1-162** was isolated in 35% yield as a result of a ring-opening event (**1-163**) and subsequent combination with a radical iodine species.



Scheme 1.28. Four separate reactions supporting the generation of radical intermediates.

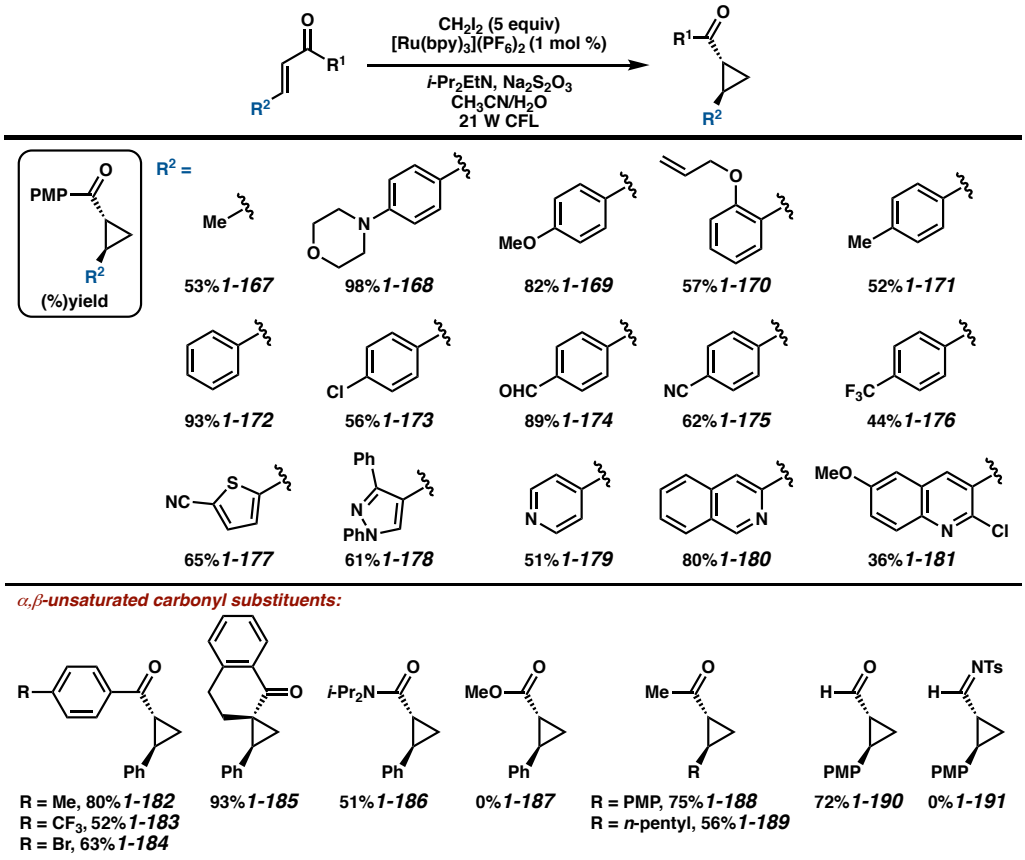
1.7 Photoredox Catalyzed Cyclopropanation of Michael Acceptors

In hopes of further expanding the substrate scope of their cyclopropanation protocol, Suero and del Hoyo explored the photoredox catalyzed cyclopropanation between α,β-unsaturated carbonyl compounds (Michael acceptors) and diiodomethane as a methylene transfer reagent. The reaction conditions were identical to their previous work with styrenyl species, and the cyclopropanation proceeds through a similar reaction mechanism (Scheme 1.29). The main difference is that an α-carbonyl radical intermediate **1-165** is proposed, rather than a benzylic radical **1-127**. A radical 1,4-addition to methyl vinyl ketones to give Michael adducts has been reported,[40] which supports the existence of the alleged α-carbonyl radical in the mechanism.



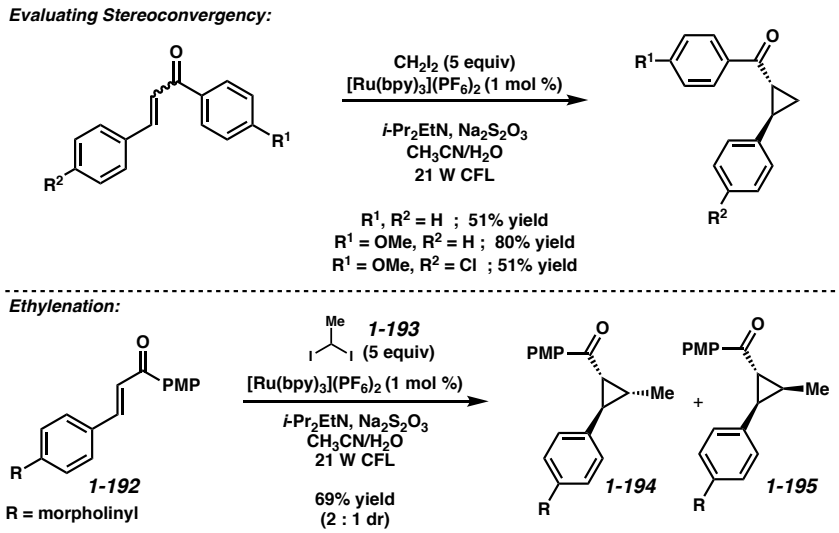
Scheme 1.29. Photoredox catalyzed cyclopropanation mechanism of Michael acceptors.

Using the optimized conditions applied in their previous cyclopropanation report, the scope of the transformation was examined (Scheme 1.30). Various chalcone derivatives with diverse aryl moieties were successful in the reaction conditions. Substituents stemming from one of the aryl moieties included alkyl, *O*-allyl, alkoxy, trisubstituted amines, chlorides, trifluoromethyl, and aldehyde functional groups. Heterocycles such as thiophene, pyrazole, pyridine, quinoline, and isoquinoline were all tolerated in the photocatalytic system. When the aryl moiety at the 2-posiiton was replaced with an alkyl substituent, cyclopropane products **1-167** and **1-189** were also generated. Additionally, a trisubstituted chalcone derivative provided spirocycle **1-185** in excellent yield. With regard to the α,β-unsaturated carbonyl segment, it was noted that apart from phenyl ketones, amides, methyl ketones, and aldehydes were all functional. Unfortunately, α,β-unsaturated imines (**1-191**) and methyl esters (**1-187**) were unable to be methylenated.



Scheme 1.30. Reaction scope of α,β-unsaturated cyclopropanes.

In various cases, low yields were obtained despite full consumption of the starting material alkene. However, no Michael adducts were observed from an incomplete ring-closure event. It was noted that irradiating reactions past the point of completion resulted in a significant drop in yield. For example, subjecting the precursor chalcone of **1-184** to photocatalytic conditions for 30 h resulted in a 22% NMR yield versus the 63% isolated yield obtained after 18 h. The loss in material was mostly attributed to cyclopropane decomposition occurring over time. An unproductive cyclopropane ring-opening event may also be the culprit. The ring-opening proposed is a photoredox process which involves one-electron reduction of the carbonyl group to the corresponding radical anion, and has been exploited by Yoon and coworkers in (3+2) cycloadditions with visible light and $Ru(bpy)_3Cl_2$.[41]



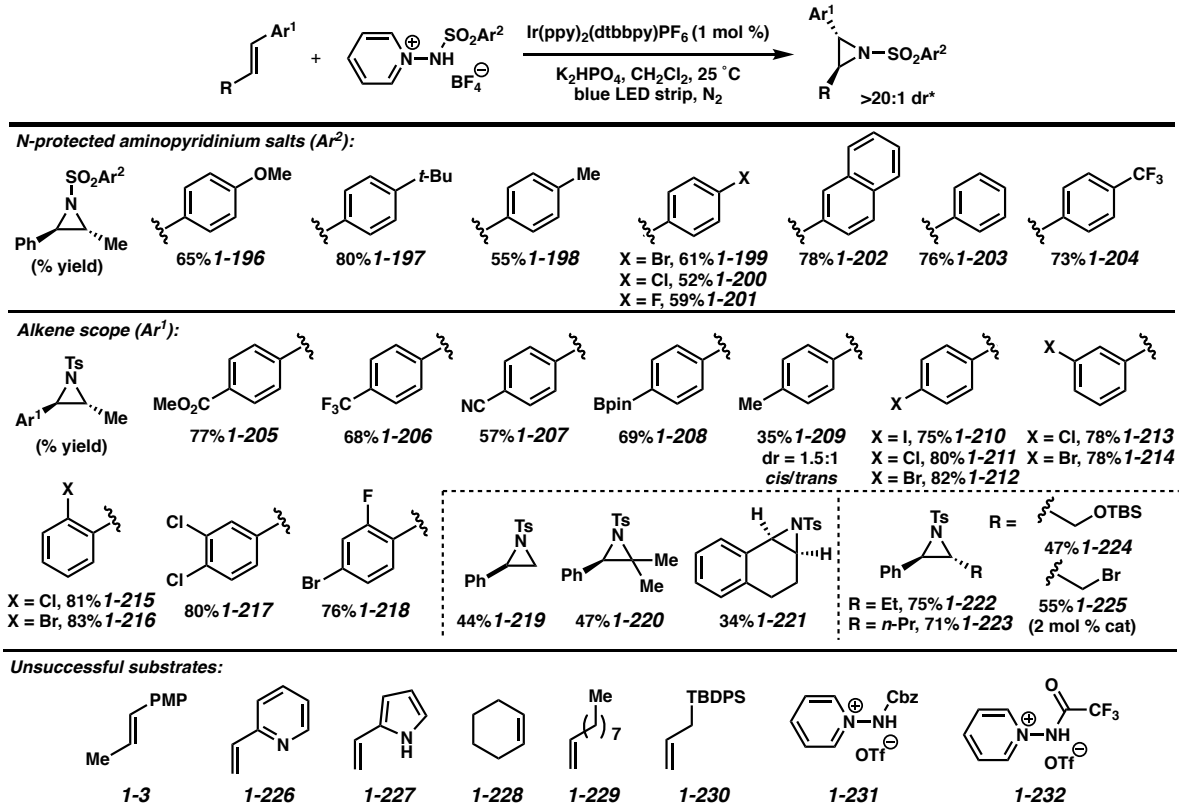
Scheme 1.31. Stereconvergency verification and the ethylenation of a chalcone derivative.

The stereoconvergency of the transformation was also assessed (Scheme 1.31). As in the styrenyl case, trans cyclopropanes were generated despite starting with a mixture of olefin isomers. Furthermore, the authors were curious to see whether other *gem*-diiodoalkanes could be exploited using their novel, catalytic methodology. When 1,1-diiodoethane (**1-193**) was subjected to the reaction conditions, the ethylenated cyclopropane products **1-194** and **1-195** were isolated in 69% yield as a mixture of diastereomers (2:1).

1.8 $Ir(ppy)_2(dtbbpy)PF_6$ Photoredox Catalyzed Aziridination

Xu and coworkers disclosed a distinct approach in the construction of aziridines.[42] The novel method invokes *N*-centered radicals generated *via* photoredox catalysis.[43] The idea stemmed from work reported a few years earlier by Studer and Akita.[44] Both groups unveiled the use of *N*-aminopyridinium salts as precursors for *N*-centered radicals using either $Ru(bpy)_3Cl_2$ or *fac*-$[Ir(ppy)_3]$ in combination with blue LEDs. The group of Xu decided to further exploit this reactivity toward a novel and concise aziridination of various alkenes using photoredox catalysis.

After a photocatalyst screen, it was discovered that $Ir(ppy)_2(dtbbpy)PF_6$ provided the optimal yields for aziridination. Although *fac*-$Ir(ppy)_3$ was a competent catalyst, $Ru(bpy)_3^{2+}$, which was the optimal single electron reductant in Studer's methodology, provided only trace aziridine product. As with Suero's experimental procedure for cyclopropanations, Xu's aziridination methodology also required degassing before irradiation of the reaction mixture. Using the Ir(III)*→Ir(IV) reaction manifold, a variety of styrene derivatives and *N*-protected 1-aminopyridinium salts were tested (Scheme 1.32).

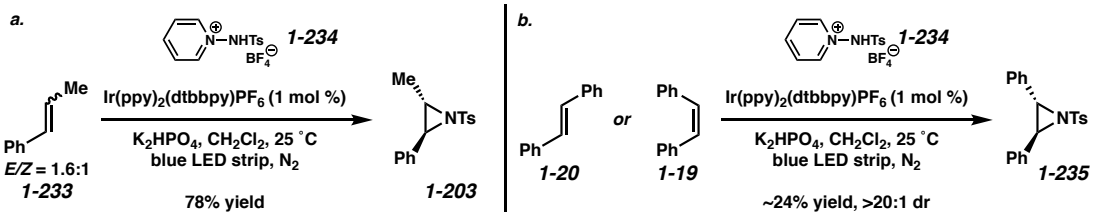


Scheme 1.32. Scope of Xu's photoredox catalyzed aziridination.

Varying the electronics of the pyridinium salts had little to no effect in reactivity, providing aziridine products from β-methyl styrene in modest to good yields (52-80%). However, changing the electronics of the styrene aryl moiety did have an effect on reactivity. Having electron-withdrawing substituents on the aryl moiety gave the best conversions. An electron-donating

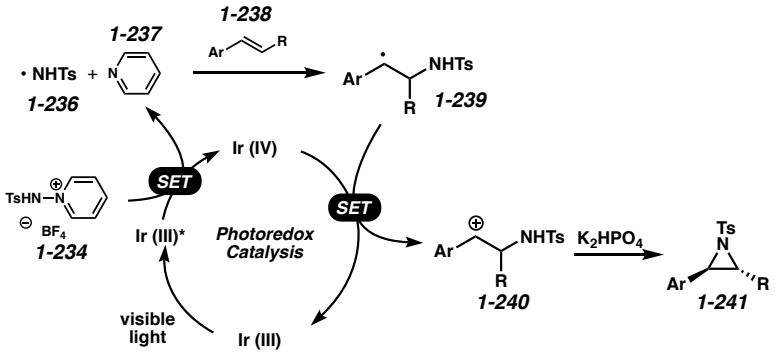
group, such as methyl, not only provided the aziridine in poor yield (35%) but resulted in a 1.5:1 mixture of diastereomers with the *cis*-aziridine as the major product (**1-209**). Attaching a more strongly electron-donating group, such as methoxy, had a major detrimental effect on the reaction outcome (**1-3**). This is a stark difference from Suero's cyclopropanation of styrenes, in which a carbon centered benzylic radical benefited from electron-donating groups on the arene. This is not surprising, however, since Suero's reaction system relies on a *nucleophilic* carbon centered radical, whereas Xu's reaction manifold involves an *electrophilic* carbon centered radical (*vide infra*). On the other hand, ortho, meta, and para mono- and di-substituted aryl halides performed well. Arenes with pendant electron withdrawing groups like nitriles, esters, and boronic esters were also well tolerated. Monosubstituted, trisubstituted, and cyclic alkenes were all compatible in the aziridination, although the products were isolated in lower yields. Modification of the pendant alkyl group revealed that alkenes with tethered silyl ethers, long alkyl chains, and an alkyl bromide (with the use of 2 mol % catalyst) were all efficiently aziridinated.

In general, starting with either *E* or *Z* isomers (or a mixture of both) resulted in the sole formation of *trans*-aziridines (Scheme 1.33a). This is a distinction from the work of Huo in which *cis*-aziridines were exclusively formed. To further support the stereoconvergency of the transformation, the single alkene isomer of *trans*-stilbene **1-20** or *cis*-stilbene **1-19** was subjected to the reaction conditions. In both cases, only the *trans*-aziridine **1-235** was observed in comparable yield and excellent diastereoselectivity (Scheme 1.33b).



Scheme 1.33. Evaluating the stereoconvergency of Xu's aziridinations.

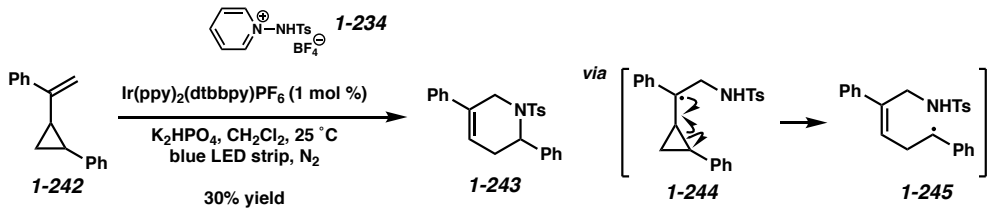
The proposed mechanism is illustrated in Scheme 1.34. When the Ir(III) photocomplex is irradiated with light, a metal-to-ligand charge-transfer (MLCT) occurs to generate the excited state Ir(III)*. This highly reductive species is able to donate a single electron to the *N*-Ts-protected 1-aminopyridinium **1-234**, consequentially generating an electrophilic nitrogen-centered radical **1-236** and one equivalent of pyridine. After radical combination with a substrate alkene, a stable benzylic radical intermediate is furnished (**1-239**). Subsequent oxidation of the radical renders a stabilized carbocation intermediate **1-240**, simultaneously regenerating the ground state Ir(III) photocatalyst. A final deprotonation and intramolecular nucleophilic addition renders the anti-aziridine **1-241**.



Scheme 1.34. Proposed mechanism for Xu's photoredox catalyzed aziridination.

A control experiment with styrene using the optimized reaction conditions and the radical scavenger TEMPO (2 equiv) resulted in no aziridine formation, indicating that the reaction does proceed through radical processes. A "radical clock" substrate further supported this notion (Scheme 1.35). When vinylcyclopropane **1-242** was subjected to the reaction conditions, the six-membered tetrahydropyridine derivative **1-243** was formed in appreciable yield. Presumably, the product arises via a radical ring opening event of **1-242** resulting in the stable benzylic radical **1-245**. One can then imagine a second SET event to form a different, yet stable benzylic carbocation

intermediate, which can undergo intramolecular nucleophilic ring closure in the presence of base to render tetrahydropyridine **1-243**.



Scheme 1.35. Tetrahydropyridine formation.

1.9 Conclusion

Net (2+1) cycloadditions mediated by aminium salts via single electron transfer events have been known since 1984. The renaissance of photoredox catalysis over the past decade has provided a unique reaction platform for single electron processes. A major drawback in this young and emerging field of chemistry is the fact that many examples in the current literature use photocatalysts which contain precious ruthenium and iridium metal centers.[45] These two transition metals are among the nine rarest elements on earth as depicted in a figure created by Generalić (Figure 1.3).[46] Thus, there is a dire need to develop and apply novel, earth-abundant metal photocatalysts to further broaden synthetic applications in a more sustainable fashion.

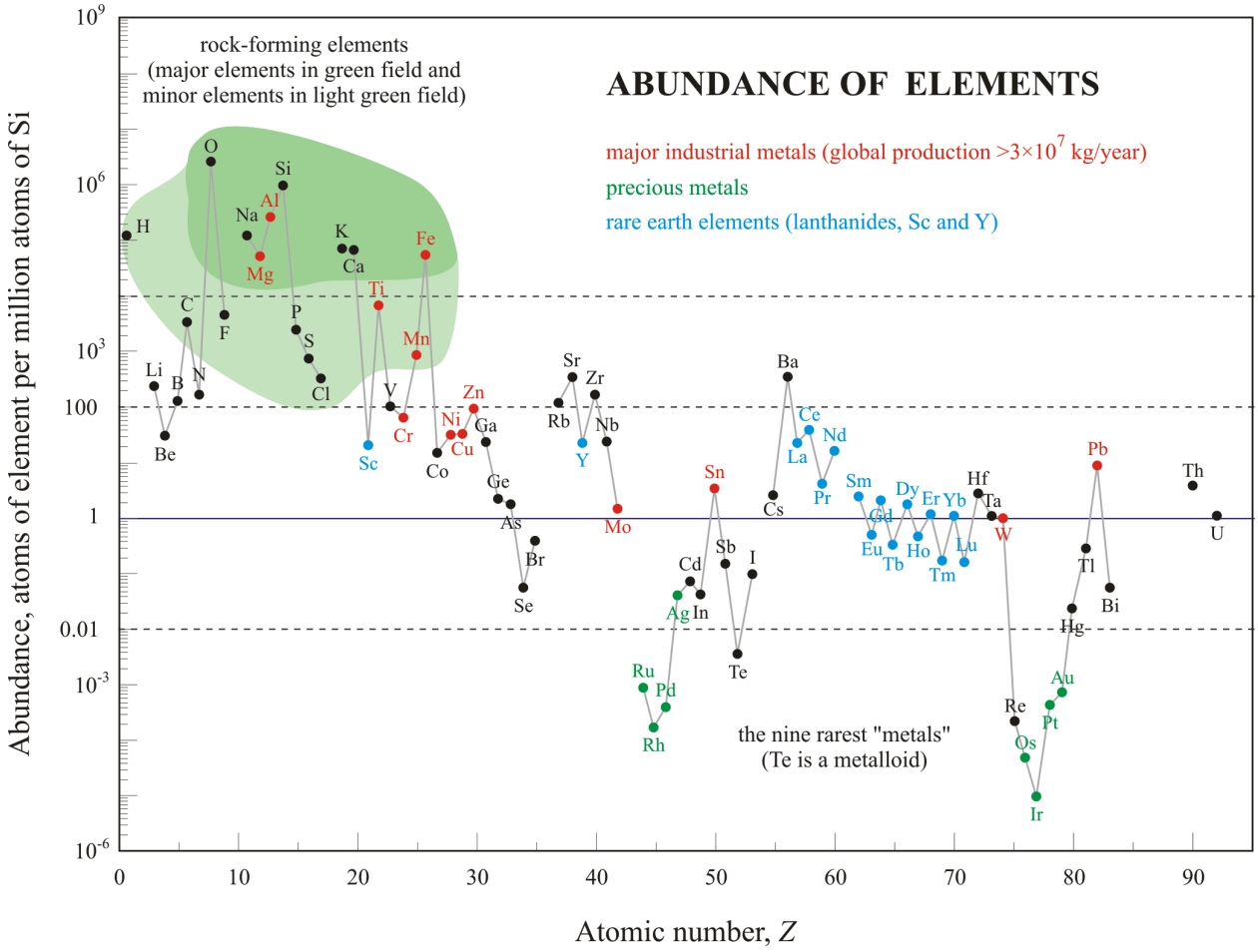


Figure 1.3. Abundance of elements organized by atomic number (Image from Eni Generalić, University of Split, Croatia)

As a result of this major disadvantage in photoredox catalysis, in 2013 the Catalysis Collaboratory for Light-activated Earth Abundant Reagents (C-CLEAR) was formed in one of the first National Science Foundation and Environmental Protection Agency funded Networks for Sustainable Molecular Design and Synthesis (CHE-1339674). This collaboratory, whose goal is to develop photocatalysts of earth-abundant metals, consists of Prof. Anthony Rappé (Colorado State University), Prof. Matthew Shores, (Colorado State University), Prof. Niels Damrauer (University of Colorado Boulder), Prof. Tomislav Rovis (Columbia University), and Prof. Eric Ferreira (University of Georgia). Others in the chemistry community have also taken notice of the downside, to the current photocatalysts governing the field, and have developed photoactive

complexes of Cr(III), Fe(II),[47] Ni(II),[48] Cu(I),[49] Zn(II), Zr(IV), Mo(0), and U(VI).[50] Our group has focused on developing and understanding transformations using photooxidizing chromium catalysts. By exploiting light-activated catalysts based on earth-abundant chromium, which is several orders of magnitude more abundant than Ru,[51] our group has been able to cultivate a more sustainable approach in the field of photoredox catalysis.[52] Over the past five years, my role in C-CLEAR began in the development of novel Zn(II) photocatalysts and transitioned toward the discovery of new transformations using Cr(III) photooxiding catalysts. The latter efforts will be discussed in this dissertation.

1.10 Chapter 1 Notes and References

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CHAPTER 2

THE DEVELOPMENT OF RADICAL CATION CYCLOPROPANATIONS USING PHOTOOXIDIZING CHROMIUM CATALYSIS AND DIAZO REAGENTS

2.1 Introduction: The Discovery and Application of Cr Photocatalysts

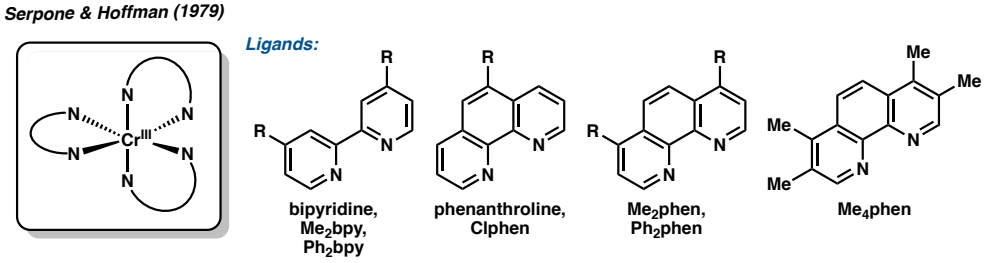


Figure 2.1. Cr(III) polypyridyl complexes studied photophysically.

Nearly four decades ago, dipyridyl and phenanthrolinyl chromium(III) complexes created by Serpone and Hoffman were investigated for their photooxidizing properties (Figure 2.1).[1] The excited-state behaviors of these earth-abundant metal-based complexes were evaluated and distinguished for their valuable features. When compared to their Ru(II) counterparts, the excited state lifetimes of the Cr compounds were found to be two to three orders of magnitude longer (*vide infra*). It was also noted that varying the substitution of the dipyridyl and phenanthrolinyl ligands strongly affected the complexes' redox potentials and absorption spectra. Potentially, this feature could give chemists the ability to finely tune the properties of the chromium complexes to their liking. For example, the addition of phenyl substituents on the examined ligands significantly increased the absorption of the Cr(III) species into the visible region. Furthermore, the ligands on

the chromium complexes were generally substitution inert in acidic solutions and devoid of photochemical loss.

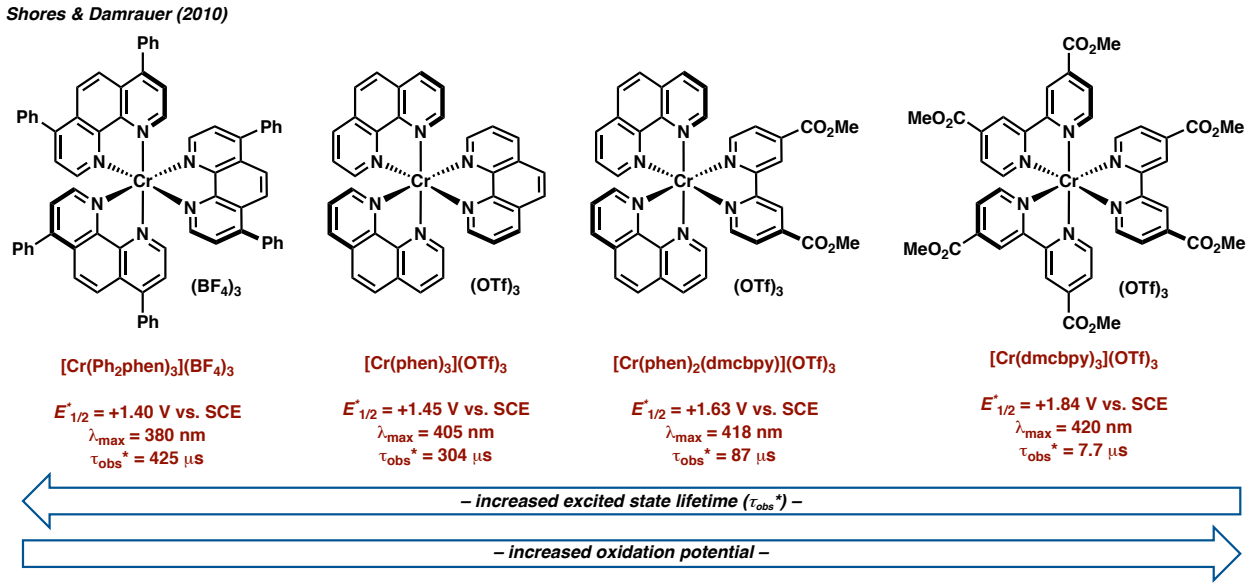


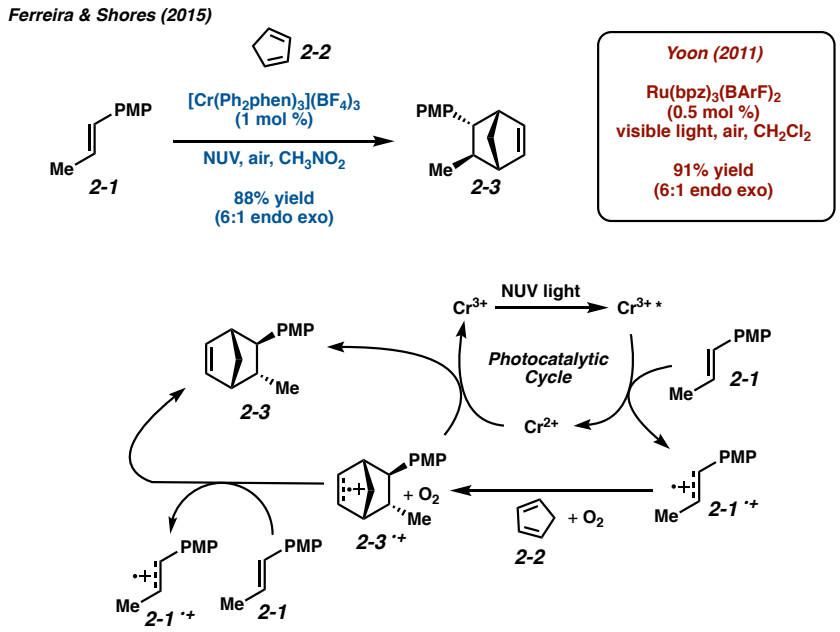
Figure 2.2. Selected chromium(III) complexes.

In 2010, Shores and Damrauer continued investigating the photooxidizing properties of related homo- as well as heteroleptic Cr complexes.[2] Prior to this study, the syntheses of Cr(III) dipyridyl complexes were considered inefficient. Issues partly arose from attempting to activate the inert chromium metal center which often led to ligand scrambling.[3] By employing previously reported methodology,[4] the preparations of novel homo- and heteroleptic Cr complexes were completed, allowing for further electrochemical and photophysical investigations (Figure 2.2). Their properties were explored to better understand the chromium compounds' long-lived excited-states. It was believed that long excited state lifetimes could ensure, to some part, the ability for electron hole transfer photochemistry. The chromium species were found to absorb in the near-ultraviolet (NUV) and visible region. The homo- and heteroleptic dipyridyl Cr complexes possessed relatively high excited state reduction potentials ($E^*_{1/2}$ = +1.40 to +1.84 V vs. SCE) and exhibited the capacity to undergo reversible 1e$^-$ reductions. The accrued data appeared to indicate

that these Cr(III) complexes could be employed in organic synthesis as alternatives to precious-metal centered photooxidizing catalysts.

As a proof of concept, in 2015 our group disclosed the use of polypyridinyl and phenanthrolinyl ligated chromium photocatalysts for mediating radical cation Diels–Alder cycloadditions via single electron transfer processes.[5] The conditions were very mild: reaction mixtures were irradiated with NUV and performed under air with catalytic amounts of $[Cr(Ph_2phen)_3](BF_4)_3$. The scope of the transformation was thoroughly evaluated and found to be stereoconvergent. Subjecting mixtures of cis- and trans-alkenes only rendered anti-cyclohexenes (*vide infra*). The radical cation (4+2) cycloaddition between cyclopentadiene and *trans*-anethole with $[Cr(Ph_2phen)_3](BF_4)_3$ provided a comparable yield and ratio to Yoon's $[Ru(bpz)_3](BArF)_2$ catalyzed procedure (Scheme 2.1).[6] To our knowledge, this was the first report in which a Cr(III) complex functioned as a photocatalyst in an organic transformation.

Our initially proposed radical cation cycloaddition mechanism is illustrated in Scheme 2.1 with *trans*-anethole (**2-1**) and cyclopentadiene (**2-2)**. Irradiation of the Cr(III) catalyst generates an excited state species with a high reduction potential capable of oxidizing olefin **2-1**. The resulting radical cation is situated to undergo a radical cation Diels–Alder with cyclopentadiene (**2-2**) to furnish intermediate **2-3**$^{\bullet+}$. Two separate quenching pathways exist at this point. In a chain propagation pathway, a single electron transfer with another alkene equivalent renders the product and propagates the process. Alternatively, in a catalytic pathway, cyclohexene **2-3** is furnished by oxidizing the transient Cr(II) intermediate which regenerates the ground-state catalyst. Like Bauld, who judiciously investigated mechanistic criteria for characterizing aminium-salt initiated radial cation processes,[7] future experiments would elucidate the predominant mechanistic pathway (i.e. radical cation chain vs. catalytic).

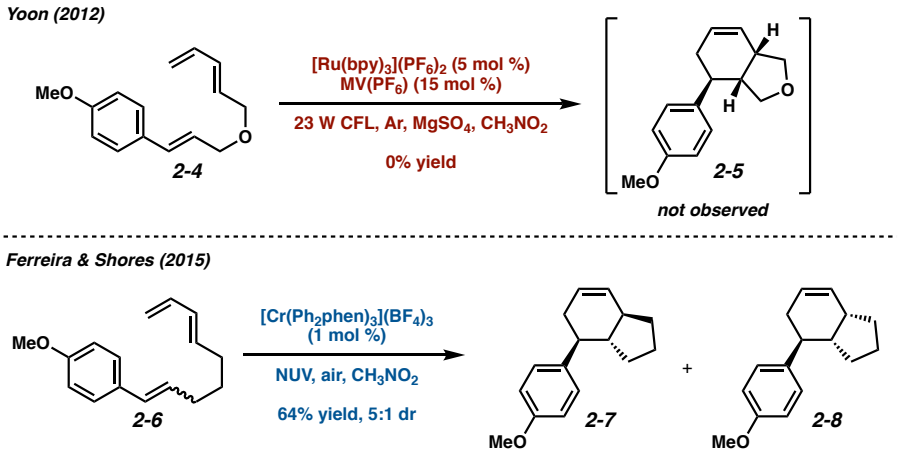


Scheme 2.1. Cr-photocatalyzed radical cation Diels–Alder and its initially proposed mechanism.

Differences in reactivity between the Cr and Ru systems indicated that a distinct mechanism was operative. Oxygen, for example, was found to be crucial in order for cycloadditions with *trans*-anethole to succeed when using Cr photocatalysis. When the reaction mixture was thoroughly degassed and performed under an inert atmosphere, only trace Diels–Alder cycloadduct was observed in the chromium photocatalyzed process. In comparison, the transformation catalyzed by $Ru(bpz)_3^{2+}$ under similar anaerobic conditions produced the Diels–Alder cycloadduct in measurable yield but did not go to completion. Yoon proposed that oxygen may be facilitating catalyst turnover and lack thereof could contribute to the poor reactivity.[6] The authors reasoned that this observation may indicate an operative chain propagation mechanism with Ru, citing studies of radical cation cycloadditions by Ledwith.[8] Through experimental and theoretical analyses, our group and collaborators from Colorado elucidated several roles of O_2 in the radical cation-mediated Diels–Alder with Cr.[9] It was ascertained that oxygen was vital for catalyst protection, product formation, as well as catalyst regeneration. The collaborative studies

further demonstrated that the Cr photocatalyst appears to proceed through a catalytic turnover while Ru based photocatalysts proceeds via radical chain propagation, as Yoon had inferred.

Before a distinct operating mechanism was identified, differential reaction outcomes were observed between Ru and Cr photocatalyzed processes. When the intramolecular (4+2) cycloaddition of monosubstituted diene **2-4** was attempted with catalytic $Ru(bpy)_3^{2+}$, the reaction failed and only gave a complicated mixture of undesired byproducts (Scheme 2.2).[10] Subjecting an analogous intramolecular substrate **2-6** to chromium photocatalyzed conditions resulted in a fruitful outcome. (2+2) cycloadducts, previously detected by Yoon, were not observed in the Cr case, and bicycles **2-7** and **2-8** were obtained in good yield and diastereoselectivity.



Scheme 2.2. Successful intramolecular (4+2) cycloaddition using a tethered monosubstituted diene.

These experiments underscore the importance of designing and developing new photocatalysts based on first-row transition metals. Molecules formerly considered inaccessible can be constructed with mild and "green" conditions that utilize a simple and infinite energy source (i.e., light). Additionally, differences in reactivity to rare-metal centered photocatalysts allow for continuing mechanistic investigations to further our understanding in this young and exciting field of chemistry. We hoped to further expand our chemical intuition of Cr(III) photocatalysis through the development of useful synthetic organic transformations.

2.2 Experimental Design

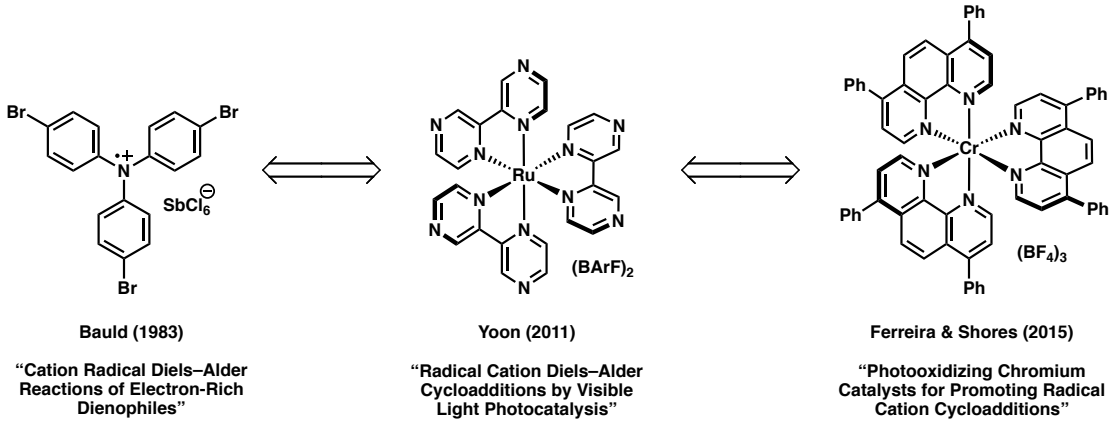


Figure 2.3. The radical cation Diels–Alder: translation over time.

We were inspired by Yoon's conceptual method of translating Bauld's radical cation Diels–Alder reaction (originally mediated by aminium salts) into a photoredox system that employs $Ru(bpz)_3^{2+}$ and visible light.[6] Our group further translated this transformation into one that can now be mediated by $Cr(Ph_2phen)_3^{3+}$ and NUV light. Given the sparse examples of photoredox catalyzed cyclopropanations in the current literature, and the fact that the majority are performed using photocatalysts embedded with rare metals (i.e., Ru and Ir), we decided to investigate Bauld's original aminium salt catalyzed radical cation cyclopropanation.[11] By employing our chromium photooxiding catalysts, we envisioned that the method by Bauld could be directly translated using our Cr mediated methodology (Figure 2.4).

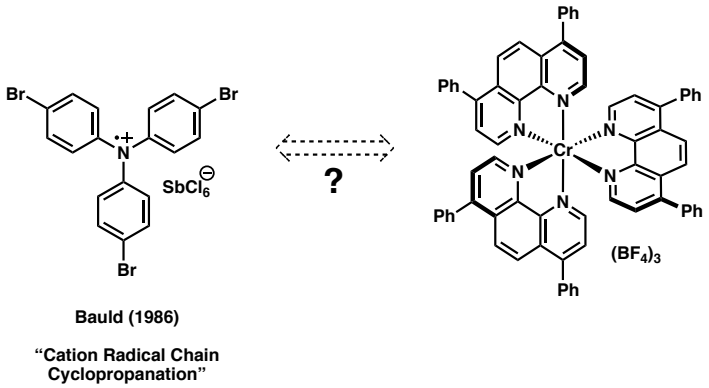
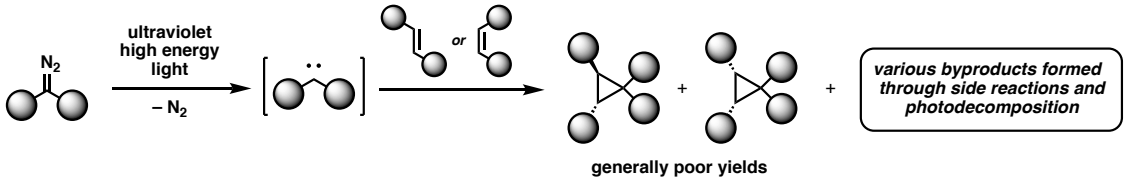


Figure 2.4. The radical cation cyclopropanation: a conceptual translation.

2.3 Diazos in Photochemistry: Cyclopropanations

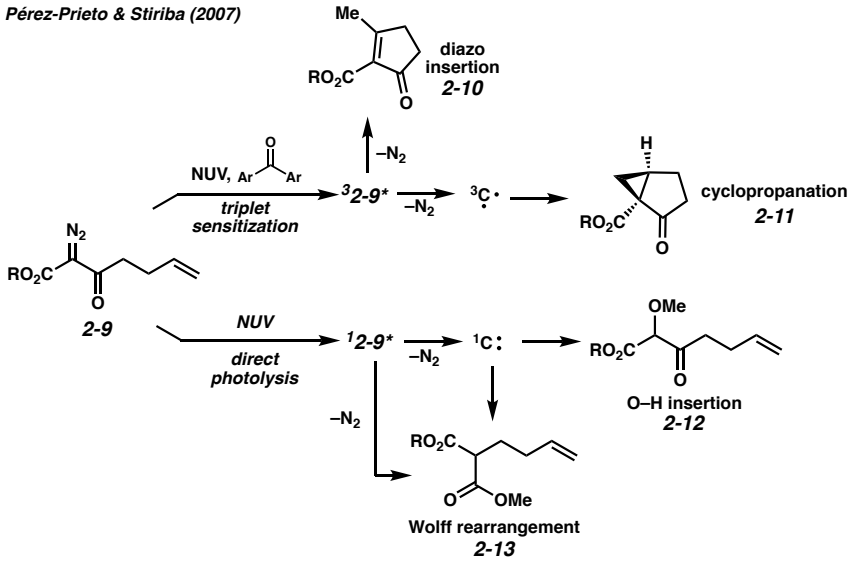
Because the radical cation cyclopropanation employs diazo reagents as the 1-carbon component, an initial consideration was the stability of diazos when exposed to light in the presence of olefins.[12] Throughout the 1970s, chemists around the globe investigated both direct and sensitized UV-light-mediated diazo decomposition as a means to cyclopropanate alkenes (Scheme 2.3).[13] Though various classes of diazo species were successfully decomposed, cyclopropanation yields were poor and a variety of undesired byproducts were also formed. Apart from cyclopropanation, nonstereospecific addition to olefins, Wolff Rearrangements,[14] O–H insertions into alkenols, diazo self-dimerizations and eliminations, and even diazirine formation could be observed. The overall inefficiency is mainly attributed to the high energy direct photolysis that employs ultraviolet light to generate singlet state species.



Scheme 2.3. Cyclopropanations via diazo photolysis.

Unlike direct photolysis, triplet sensitized UV or NUV-light-mediated transformations can be favorable toward cyclopropanation. About a decade ago, Pérez-Prieto and Stiriba exploited a cyclopropanation method first reported by Kirmse and Fien in 1998.[15] This intramolecular (2+1) cycloaddition uses catalytic amounts of diarylketones for the triplet sensitization of diazo ketoesters **2-9** (Scheme 2.4). By using substituted benzophenones as sensitizers, it was found that the triplet excited state ^{3}**2-9*** is selectively populated, thus favoring intramolecular

cyclopropanation. Most importantly, O–H insertion (from MeOH solvent) and Wolff Rearrangement products **2-12** and **2-13** respectively, were diminished.

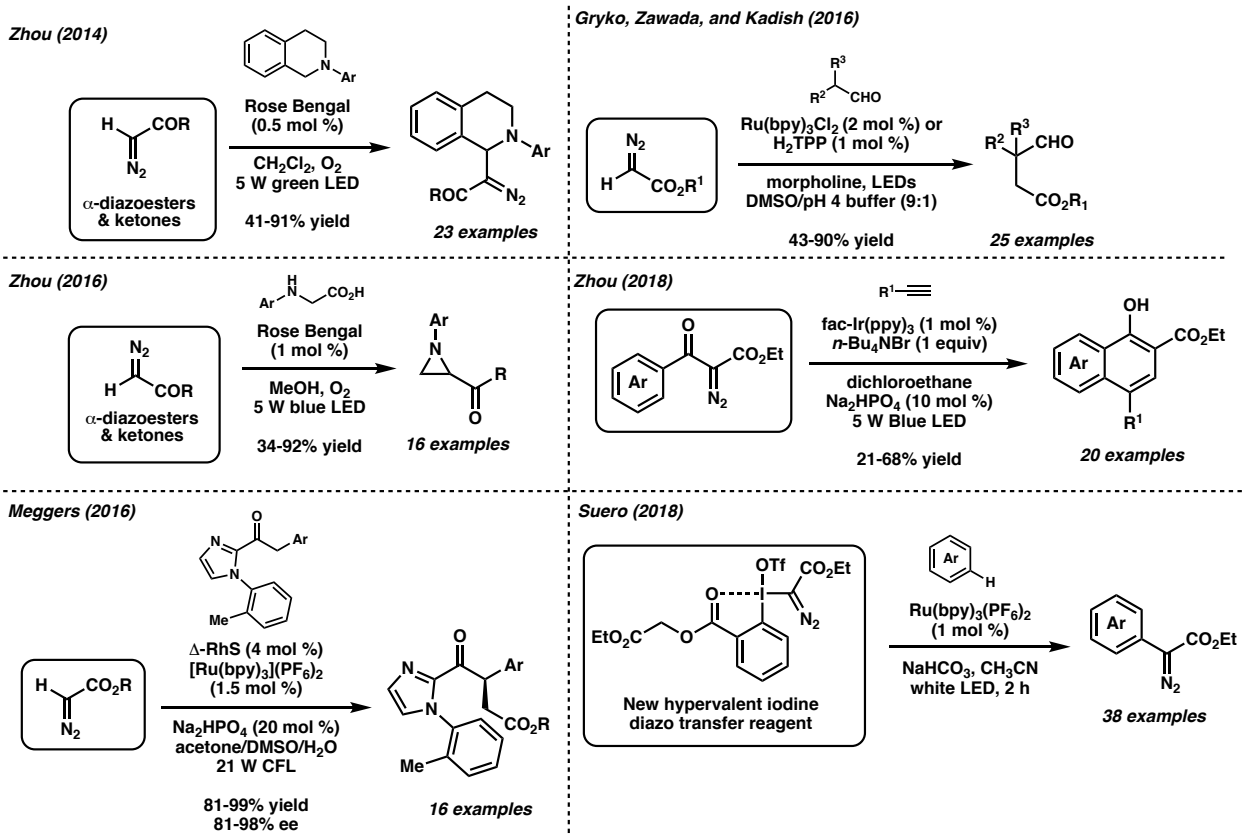


Scheme 2.4. Triplet versus direct photolysis of α-ketone diazoesters.

Interestingly, a triplet-photosensitized diazo insertion furnished cyclopentenone **2-10**; a process known previously to be mediated by Pd(II) catalysis.[16] Although most byproducts were lessened through this alternate pathway an additional byproduct also arose and the cyclopropanation only worked intramolecularly, with specific substrates, and with major restrictions (i.e., choice of solvent, photosensitizer, tether length, etc.). The use of visible light in modern photoreactions has greatly circumvented these issues and aided in expanding reaction scopes.[17] Fortunately, the majority of transition metal photocatalysts (including ours) are excited by visible light.

2.4 Diazos in Photoredox Catalysis

Over the past several years, Zhou, Gryko, Meggers, and Suero have all shown the compatibility of diazos in photoredox catalysis (Scheme 2.5). Though diazo ketones are known to undergo Wolff Rearrangement, Zhou demonstrated their ability to undertake productive transformations using Rose Bengal and green or blue light-emitting diodes (LEDs).[18] In 2016, Meggers, as well as Gryko, employed $Ru(bpy)_3^{2+}$ in the α-alkylation of carbonyl compounds; Meggers was able to achieve this transformation enantioselectively.[19] That same year, Gryko in collaboration with Zawada and Kadish used free base tetraphenylporphyrin (H_2TPP) as a photoreductive organic sensitizer as an alternative to $Ru(bpy)_3^{2+}$.[20] Recently, Zhou revealed that in the presence of strongly reducing *fac*-$Ir(ppy)_3$ and blue LED, phenyl diazoketones undergo radical benzannulations with alkynes to render polysubstituted naphthols.[21,22] This year Suero and coworkers designed a unique diazo transfer reagent. The hypervalent iodine species impregnated with ethyl diazoacetate performs elegant C–H diazomethylations using white LED and $Ru(bpy)_3^{2+}$.[23] Notably, many of these examples appeared during or after our studies described in this chapter. Initially, like many of the authors mentioned above, we explored our hypothesis with little knowledge of how diazo species would react under single electron transfer processes mediated by transition metal photocatalysts. Overall, the aforementioned examples support the compatibility, efficiency, and versatility of diazo species in photoredox processes.

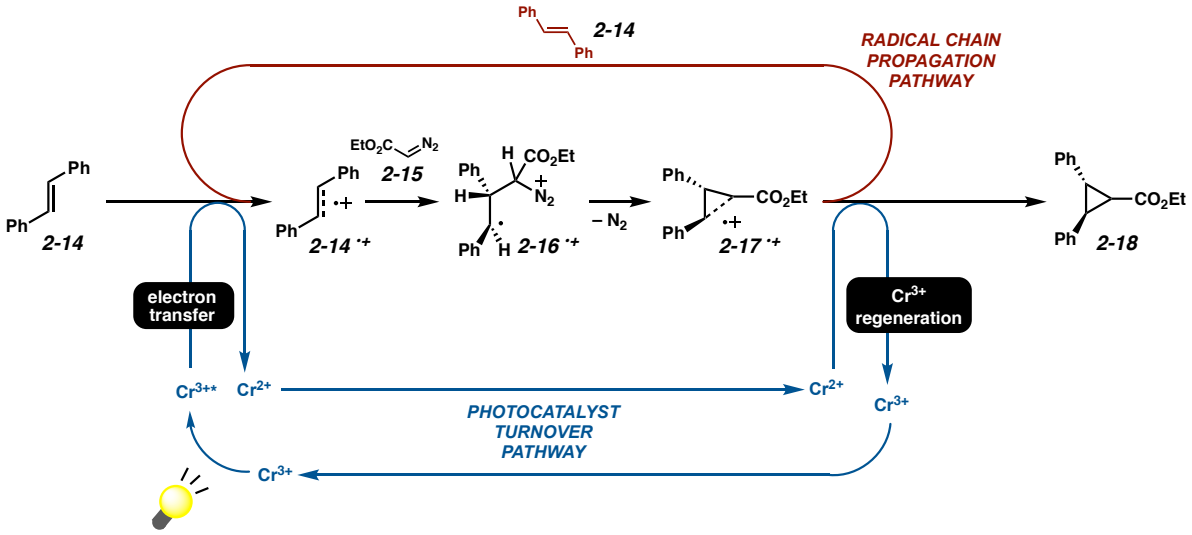


Scheme 2.5. Examples of diazo reagents used in photoredox catalysis.

2.5 Preliminary Experiments

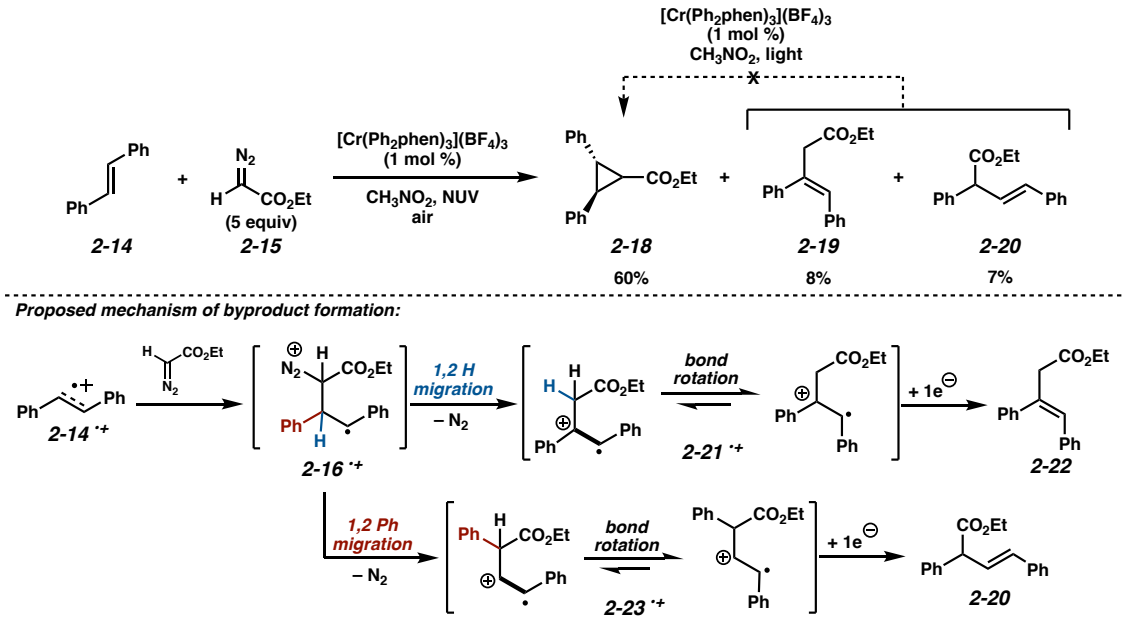
By combining Bauld's proposed radical cation cyclopropanation mechanism with aspects of our original Cr-catalyzed report, we hypothesized that a photocatalytic cycle could be viable in facilitating a net (2+1) radical cation cycloaddition. Our proposed mechanism using *trans*-stilbene, ethyl diazoacetate, and a chromium(III) photooxidative catalyst is shown in Scheme 2.6. Here, *trans*-stilbene (**2-14**) and ethyl diazoacetate (**2-15**) are used as the model substrates. Irradiation of the Cr(III) complex generates an excited state $Cr(III)^*$ species highly capable of oxidizing *trans*-stilbene (**2-14**) through a single electron transfer event; a transient Cr(II) species is generated as a result. The resulting radical cation **2-14**$^{\bullet+}$ undergoes nucleophilic attack by the

diazo species (**2-15**) affording intermediate **2-16**$^{\bullet+}$, consistent with Bauld's proposed mechanism. After loss of dinitrogen, a "long-bonded" radical cation intermediate **2-17**$^{\bullet+}$ is formed and neutralized with an electron transfer from either the reduced-state Cr(II) complex (catalytic) or an equivalent of *trans*-stilbene (chain). Turnover occurs via reentry of the ground state Cr(III) catalyst or radical chain propagation.



Scheme 2.6. Proposed Cr photocatalyzed radical cation cyclopropanation mechanism.

Our experimental studies began by interrogating the feasibility of our proposed mechanism. Subjecting *trans*-stilbene and commercially available ethyl diazoacetate (5 equiv) to our chromium catalyst $[Cr(Ph_2phen)_3](BF_4)_3$ (1 mol %) with NUV irradiation in nitromethane solvent resulted in complete consumption of the alkene starting material. The desired cyclopropane was formed in good yield, in addition to two unexpected alkene byproducts (**2-19** and **2-20**). This validated our conceptualized hypothesis: Cr photooxidizing catalysts could directly induce the process originally reported by Bauld.



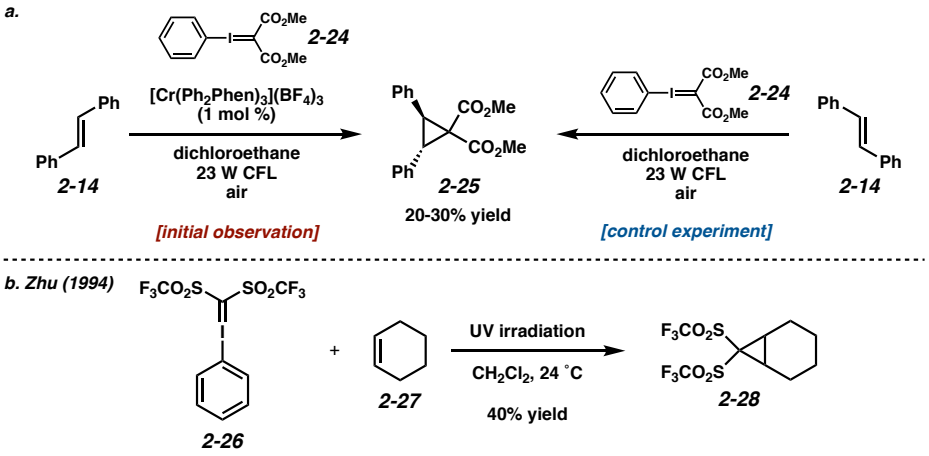
Scheme 2.7. Initial result and a possible mechanism for alkene byproduct generation.

The formation of the byproduct olefins **2-19** and **2-20** was further evaluated. When a mixture of the byproduct olefins was treated with catalytic Cr photoconditions, cyclopropane formation did not occur. This strongly suggested that the alkenes are not intermediates toward the cyclopropane product and presumably proceed through a distinct pathway. We believe byproducts **2-19** and **2-20** arise from the central intermediate **2-16**$^{\bullet+}$ after loss of N_2 either through hydrogen or phenyl migrations, respectively (Scheme 2.7). Bauld has observed similar migrations of radical cation intermediates in his work.[11] Subsequent bond rotations of intermediates **2-21**$^{\bullet+}$ and/or **2-23**$^{\bullet+}$ followed by a single electron reduction furnishes the alkene byproducts **2-22** and **2-20**.

2.5.1 Exploration of Alternative Carbene Precursors

Carcinogenic, toxic, explosive, shock sensitive, dangerous– these are common terms often associated with diazo compounds.[24] Despite the augmented safety and health risks associated with working with these reagents, diazo species have found a niche in synthetic organic chemistry and

are here to stay. Diazos have proven to be versatile reagents; their level of interest has persisted for almost a century and continues to grow.[25] However, in an effort to evaluate whether other carbene precursors could be used to cyclopropanate radical cations, various safer alternatives were explored. *N*-Sulfonyl 1,2,3-triazoles[26] and sulfur ylides[27] did not work. Further, the in-situ formation of diazo species was attempted since these reagents are typically more stable once in solution. Common procedures include the oxidation of hydrazones with MnO_2,[28] or application of the Bamford-Stevens reaction in which treatment of tosylhydrazones and/or their respective salts with base prompts diazo formation.[29] All these attempts were unsuccessful when applied with our chromium photoconditions. We were excited to see that phenyliodonium ylides[30] did in fact provide cyclopropane product **2-25** (Scheme 2.8a). However, when we performed a control experiment with light, in the absence of our Cr catalyst, **2-25** was observed in comparable yield. It was light itself, and not our photocatalyst, that facilitated the observed cycloaddition.



Scheme 2.8. (a) Attempted cyclopropanations with a phenyliodonium reagent (b) Precedence of cyclopropanations with phenyliodonium species using UV irradiation.

Iodonium ylides are known to decompose under thermal, catalytic, and photochemical processes; these scenarios have been reviewed thoroughly by Stang and Zhdankin.[31] When phenyliodonium ylides are irradiated with light, loss of iodobenzene (analogous to loss of

dinitrogen in diazo and diazonium species) leads to carbene intermediates capable of undergoing a variety of transformations.[32] However, to our knowledge, only one example of cyclopropanation has been reported with these organic polyvalent iodine reagents and light. In 1994, Zhu prepared phenyliodonium bis(perfluoroalkanesulfonyl) methides such as **2-26** and examined their reactivity (Scheme 2.8b).[33] When Zhu's ylide was irradiated with ultraviolet light in the presence of cyclohexene (**2-27**), cyclopropanation occurred to furnish bicycle **2-28**. It is possible that our result is the first that uses visible light irradiation to decompose aryliodonium ylides toward the formation of cyclopropanes.

2.5.2 Safety Discussion of Diazo Reagents

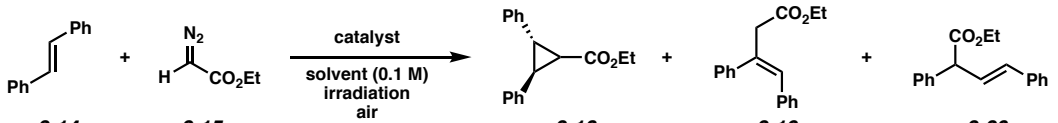
As a word of warning to the reader: diazo species should always be treated with extreme care, but so should the syntheses of these dangerous yet highly versatile reagents. Several examples will be discussed in hopes that they can provide some insight to those planning to pursue the synthesis and/or application of diazo chemistry. To begin, it is important to note that sodium azide, a common source for the synthesis of diazotization reagents, is recognized as an explosive hazard and is also acutely toxic. As a point of reference, NaN_3 is nearly as poisonous to mammals as sodium cyanide.[34] (Trimethylsilyl)diazomethane,[35] initially developed commercially as a safer alternative to diazomethane, was found to be less explosive and more stable to increased temperatures. However, its oral toxicity, like that of sodium azide, is commonly overlooked. Lamentably, in 2008 and 2009 the chemistry community lost two researchers in two separate incidents while handling TMS diazomethane due to delayed respiratory fatality.[36] Additional accidents with TMS diazomethane and a separate crystalline and stable benzotriazolsulfonyl azide

led to more mindfulness when handling these precarious compounds.[37] For example, labelling a diazo precursor or alternative as "safe" should not be correlated with it being nontoxic. Additionally, thermal stability, shock sensitivity, and explosiveness are in fact related, but not directly. This means that just because a certain diazo precursor melts at elevated temperatures does not necessarily signify that it is not shock-sensitive or explosive. There are cases where compounds are shock-sensitive but not explosive, and others where compounds can explode but are only mildly shock sensitive.[38] These dangers have led scientists to come up with innovative solutions. In particular, the generation of diazo compounds in continuous-flow reactors is a young but very important and major development that deserves both attention and praise.[39] With the goal of maximizing safety and minimizing health risks, sophisticated continuous-flow systems have been created with the aim of generating diazo compounds in situ; these and other innovative approaches have recently been reviewed.[24] This young field continues to blossom through the design of state-of-the art synthetic methods and physical apparatuses, all in hopes of accessing diazo reagents safely and consistently. Unfortunately, the novelty and complexity of certain organic reactors can render them unattractive to synthetic organic chemists, despite offering various advantages.[40] Overall, awareness and the continuous distribution of knowledge are crucial toward keeping researchers safe.

We decided to continue our study with diazo reagents. In particular, commercially available ethyl diazoacetate was used as the parent nucleophile in our optimization studies. In a sense, we were fortunate in that ethyl diazoacetate is very stable and can be stored in a freezer for prolonged periods of time. Additionally, in 2002 ethyl diazoacetate was evaluated with United Nation guidelines for standard detonation studies and was discovered to be non-explosive.[41]

2.5.3 Optimization Studies

Table 2.1. Cr photocatalyzed radical cation cyclopropanation optimization.



Entry	Catalyst (mol %)	Solvent	Irradiation	Equiv *2-15*	Time (h)	NMR yield (%)[a] *2-18*	*2-19*	*2-20*
1	$[Cr(Ph_2phen)_3](BF_4)_3$ (1)	CH_3NO_2	NUV[b]	5	24	60	8	7
2	$[Cr(Ph_2phen)_3](BF_4)_3$ (1)	CH_3NO_2	23 W CFL	5	24	61	10	8
3	$[Cr(Ph_2phen)_3](BF_4)_3$ (1)	CH_3NO_2	23 W CFL	1.1	40	60	8	11
4	$[Cr(4\text{-}dmcbpy)_3](BF_4)_3$ (1)	CH_3NO_2	23 W CFL	1.1	40	5	1	1
5	$[Cr(phen)_2(dmcbpy)](OTf)_3$ (1)	CH_3NO_2	23 W CFL	1.1	40	40	8	7
6	$[Cr(phen)_3](OTf)_3$ (1)	CH_3NO_2	23 W CFL	1.1	40	50	9	8
7	$Ru(bpz)_3(PF_6)_2$ (1)	CH_3NO_2	23 W CFL	1.1	24	3	0	0
8	$Ru(bpz)_3(PF_6)_2$ (1)	CH_3NO_2	23 W CFL	5	14	9	4	5
9	$Ru(bpy)_3(PF_6)_2$ (5) + MV (15)[c]	CH_3NO_2	23 W CFL	5	21	12	2	2
10	$Ru(bpy)_3(PF_6)_2$ (5)	CH_3NO_2	23 W CFL	5	21	0	0	0
11	$[Cr(Ph_2phen)_3](BF_4)_3$ (1)	$CHCl_3$	23 W CFL	1.1	24	18	1	2
12	$[Cr(Ph_2phen)_3](BF_4)_3$ (1)	acetone	23 W CFL	1.1	24	57	5	8
13	$[Cr(Ph_2phen)_3](BF_4)_3$ (1)	CH_2Cl_2	23 W CFL	1.1	24	73	2	7
14	$[Cr(Ph_2phen)_3](BF_4)_3$ (1)	CH_3CN	23 W CFL	1.1	24	67	8	10
15	$[Cr(Ph_2phen)_3](BF_4)_3$ (1)	DCE	23 W CFL	1.1	24	73	0	5
16	none	DCE	23 W CFL	1.1	14	0	0	0
17	$CrCl_3$ (10)	DCE	23 W CFL	1.1	49	0	0	0
18	$[Cr(Ph_2phen)_3](BF_4)_3$ (1)	DCE	none[d]	1.1	49	0	0	0

[a] Determined using veratraldehyde as a standard.
[b] Near UV light (bulbs at 300, 350, and 419 nm) used instead of 23 W CFL.
[c] MV: methyl viologen$^{2+}\cdot(PF_6)_2$.
[d] Reaction performed in dark (foil wrapped).

Once we settled on the use of diazo species as the 1-carbon component for our chromium photocatalyzed radical cation cyclopropanation, we sought to optimize the transformation. Originally, Bauld had carried out the cycloadditions with excess diazo reagent in order to suppress alkene cyclodimerization. Lowering the diazo equivalents to 1.1 and switching to a 23 W compact fluorescent lightbulb (CFL) gave a yield similar to the first conditions attempted. No cyclodimerization was observed. The three other chromium catalysts previously described furnished our desired product albeit in lower yield. Interestingly, the yield followed a trend with

oxidation potential and excited state lifetime. As the excited state lifetime increased and the oxidation potential decreased, the yield increased. However, correlation does not necessarily imply causation and this phenomenon would need further exploration to fully understand it.

When oxidizing Ru(II) catalysts were invoked, low reaction yields were observed, and *cis*-stilbene was identified as the major product. It seemed as though trans- to cis-isomerization was preferred over cyclopropanation. Furthermore, *cis*-stilbene becomes more challenging to cyclopropanate. Bauld previously noted that the cyclopropanation of *cis*-stilbene (E_{ox} = +1.70 V vs. SCE) is more difficult in comparison to *trans*-stilbene (E_{ox} = +1.59 V vs. SCE) due to its increased reduction potential.[7] In 2014, Weaver and coworkers exploited this phenomenon in the synthesis of *Z*-alkenes using *fac*-[Ir(ppy)$_3$] and blue LEDs via "uphill catalysis".[42] They propose the isomerization occurs through a "photochemical pumping mechanism" in which the excited state photocatalyst is quenched by *E*-alkenes which eventually leads to buildup of the *Z*-isomer. When we increased the amount of diazo in entries 8-10 to boost the chances of cyclopropanation, still both Ru(bpz)$_3^{2+}$ and Ru(bpy)$_3^{2+}$ failed to facilitate the cycloaddition of *trans*-stilbene. A short solvent screen led us to our optimized solvent dichloroethane which provided the highest yield, no product **2-19**, and minimum formation of **2-20**. Reactions in methylene chloride and acetonitrile provided slightly lower yields but greater amounts of byproducts (Entries 13 and 14). Control experiments were also informative and helped rule out visible light decomposition of the diazo reagent. Reactions were performed without the catalyst and light, with the catalyst in the dark, and in the presence of a Cr Lewis acid; none rendered any of the initially observed products. This further validated that both light and our chromium catalyst were essential for a productive outcome.

2.6 Alkene Scope

Given that the chemoselectivity of our transformation is governed partly by the ionization of the alkene, we evaluated a series of aryl alkenes to gauge the reactivity window. Most of the olefins in this frame consisted of symmetrical stilbenes whose reduction potential had been reported.[7,43] This allowed us to easily measure an electrochemical range by testing an array of stilbene substrates varying from electron poor to electron rich. Stilbene derivatives with reduction potentials ranging from +1.11 to 1.80 V vs SCE were found to be productive in the radical cation cycloaddition. The highly electron rich stilbene **2-29** (E_{ox} = +0.99 V) and the most electron poor stilbene **2-33** (E_{ox} = +1.94 V) were unsuccessful in this transformation. Stilbene **2-33** may be too difficult to ionize due to its high reduction potential. In the case of stilbene **2-29**, oxidation is most likely occurring, but the radical cation intermediate may be less reactive due to dual stabilization of the methoxy substituents. Presumably, this leads to lowered radical cation electrophilicity (less cationic character, more radical character) and electron back transfer may preferentially occur, overall hindering the reactivity. In order for a reaction to be successful, olefins must have the appropriate ionization capacity for $[Cr(Ph_2phen)_3]^{3+}$ ($E^*_{1/2}$ = +1.33 V vs SCE) to mediate the transformation.

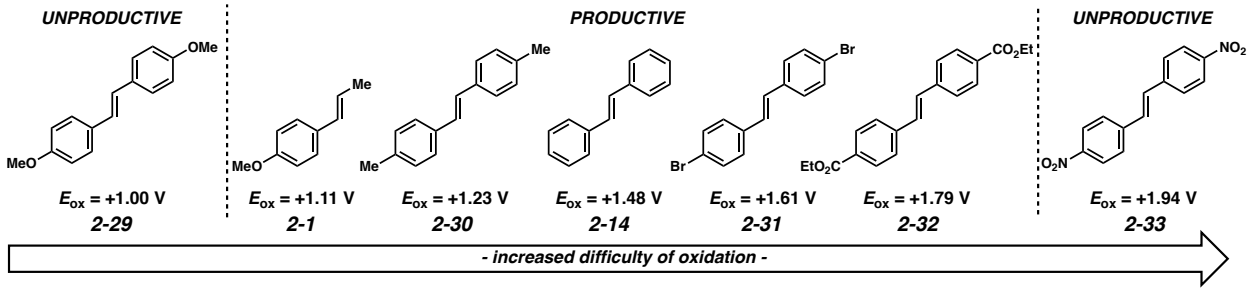
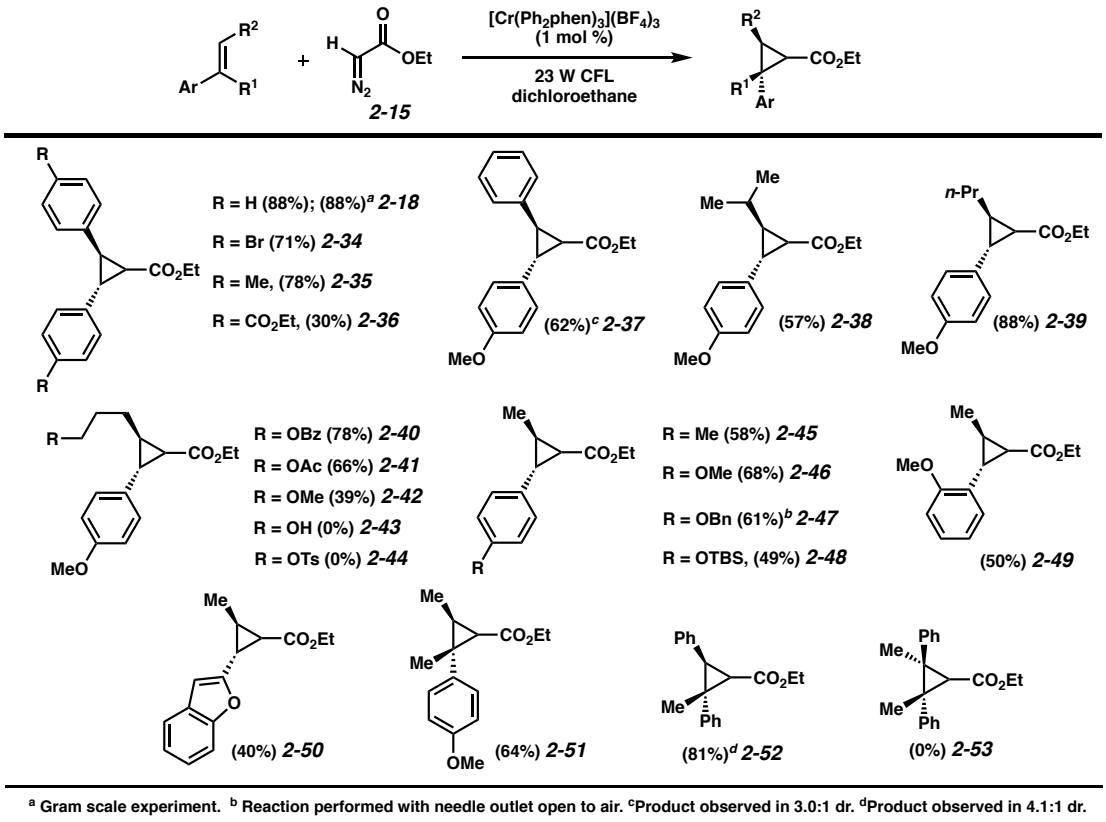


Figure 2.5. Alkene reactivity range based on ionization potential.

We continued our investigations to establish the olefin scope of the Cr photooxidized cyclopropanation. The range of *trans*-stilbenes discussed furnished products in generally high yields. The exception was the more difficult to ionize 4,4'-bis(carboethoxy)stilbene (**2-32**), which produced cyclopropane **2-36** in 30% yield. This electron deficient symmetrical stilbene had the highest reduction potential of those evaluated, second to 4,4'-bis(nitro)stilbene (**2-33**), which did not undergo cyclopropanation. We also evaluated the unsymmetrical 4-methoxy-*trans*-stilbene, whose reduction potential is comparable to that of 4,4-dimethylstilbene (**2-30**).[44] We predicted, based on our ionization compatibility window, that this substrate should undergo the (2+1) radical cation cycloaddition efficiently. Indeed, cyclopropane **2-37** was isolated in good yield with an observed diastereoselectivity of 3.0:1. Notably, the radical cation cyclopropanation of *trans*-stilbene could be performed on gram scale without diminishing the yield or altering the reaction conditions.

Apart from tolerating bromine and ester functionality on stilbenes, in surveying aryl alkenes it was revealed that ethers, esters, and sulfonates were also acceptable functional groups. We wanted to explore an alternative aryl group besides phenyl and were inspired by work from Steckhan, in which he reported a cross (4+2) cycloaddition of dienes with vinylbenzofurans achieved through radical cation processes.[45] To our good fortune we were able to construct cyclopropane **2-50** containing a benzofuran moiety, albeit in modest yield. Gratifyingly, trisubstituted olefins, which were not reactive in our reported (4+2) process, yielded tetrasubstituted cyclopropanes **2-51** and **2-52**. Tetrasubstituted alkenes however, were incompatible (**2-53**), presumably due to increased steric hindrance, making nucleophilic attack by the diazo species increasingly difficult. Overall, the yields were good although the observed diastereoselectivity was approximately 1:1 with a couple of exceptions. The stereochemical

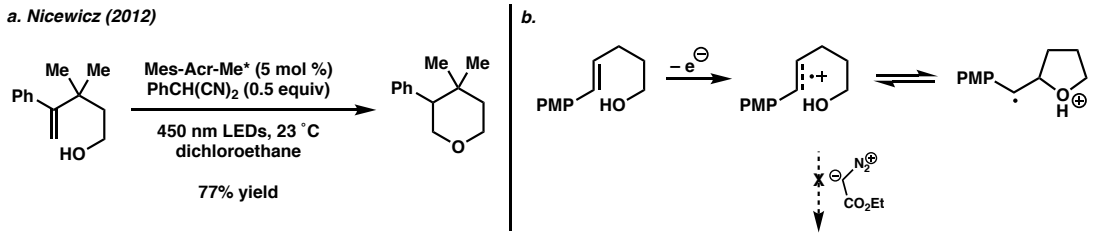
outcome, a criterion used to assess radical cation processes, is in agreement with that of Bauld's aminium salt catalyzed method.[11]



Scheme 2.9. Alkene scope.

For compounds **2-40** to **2-44**, electron-withdrawing groups on the pendant oxygen atom became necessary for a prosperous reaction outcome (-OAc or -OBz). Having a pendant electron-rich methyl ether (**2-42**) resulted in diminished yield and the alcohol completely shut down the reactivity (**2-43**). These observations somewhat mirror that of our previously developed (4+2) cycloaddition. Donation into the proposed radical cation intermediate by these electron-rich functional groups presumably debilitates the transformation. Alcohols adding into radical cations have been documented for over four decades with some of the most recent examples disclosed by Nicewicz (Scheme 2.10a).[46e] In our case, it is believed that radical cation formation does occur, but a kinetically favored intramolecular formal *5-exo* cyclization may be preferred over

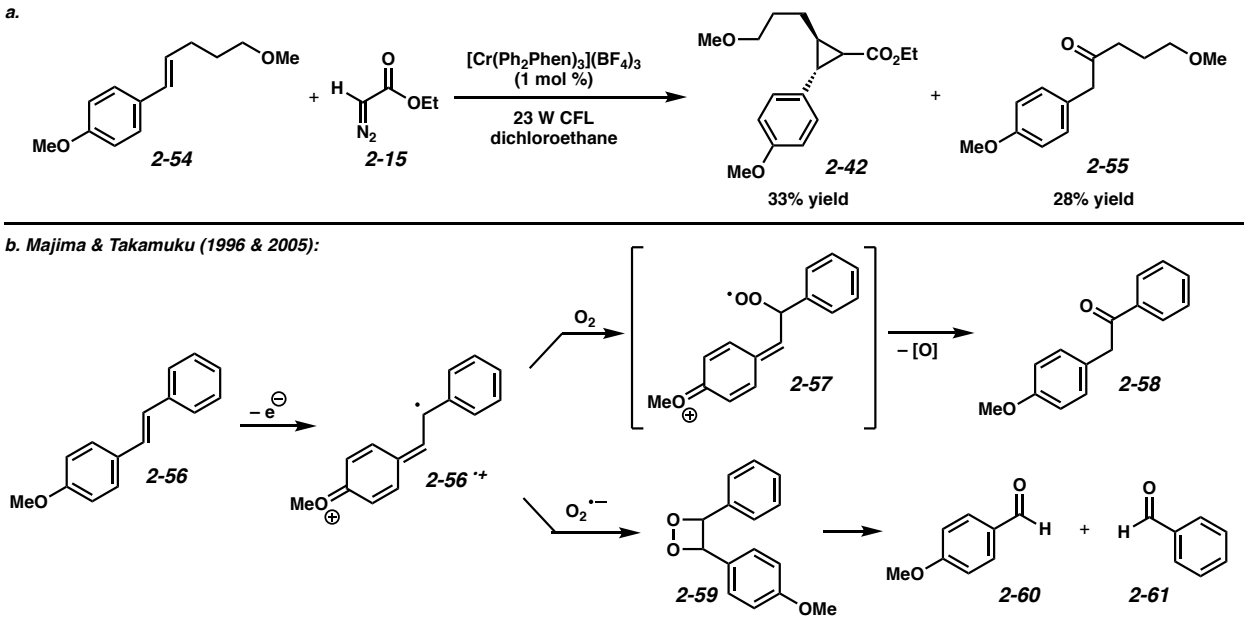
intermolecular cycloaddition with ethyl diazoacetate (Scheme 2.10b). Although a tetrahydrofuran derivative was not detected, this was expected as we did not include an H-atom transfer reagent (i.e., $PhCH(CN)_2$) which aids in generating the neutral cyclic ether product.



Scheme 2.10. (a) Photocatalytic anti-Markovnikov hydroetherification (b) Hypothetical impeding cyclization.

As noted, we saw a decrease in yield when an anethole derivative with a tethered methoxy group was subjected to our cyclopropanation conditions. Apart from the desired cyclopropane, ketone product **2-55** was generated in comparable yield (Scheme 2.11). This result was unexpected and not seen for any of the other styrenyl or stilbene analogs. A similar oxidative outcome has been observed and reported by Majima and Takamuku.[47] When an oxygen-saturated solution containing stilbene **2-56** is irradiated (high energy mercury lamp or two-photon ionization) in the presence of an organic photosensitizer like chloranil, radical cation **2-56**$^{\bullet+}$ is believed to be generated. A second radical cation intermediate **2-57** is proposed to arise after a nucleophilic addition by oxygen. The loss of an oxygen atom and a presumable 1,2-hydrogen shift renders the observed stable phenyl ketone **2-58**. Superoxide anion $O_2^{\bullet-}$ is also an alleged reactive intermediate, as a result of these radical processes. An alternative pathway is proposed, in which radical cation stilbene **2-56**$^{\bullet+}$ undergoes radical combination with $O_2^{\bullet-}$ leading to oxetane **2-59**, which decomposes to furnishes *para*-anisaldehyde (**2-60**) and benzaldehyde (**2-61**).[48] Trace amounts of anisaldehyde and derivatives thereof were often seen in our crude reaction mixtures. Notably, we and our collaborators judiciously probed the Cr radical cation (4+2) cycloadditions

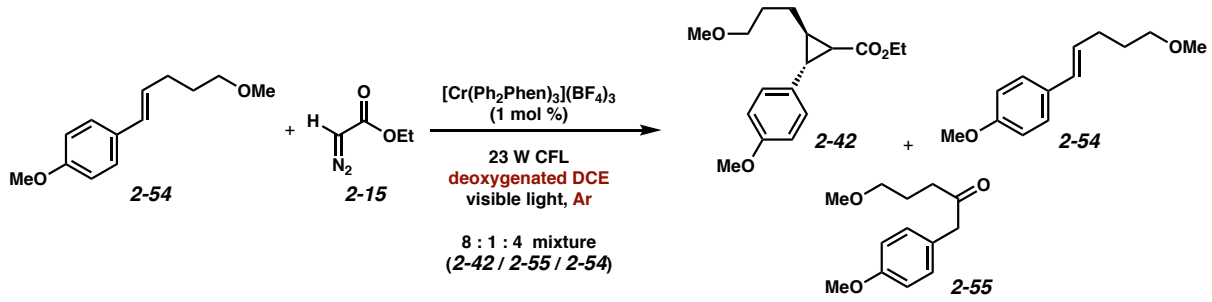
with various experiments that suggested the presence of superoxide.[9] Our chromium catalyst and oxygen may be active in certain cyclopropanations, although we do not understand yet why that is. It is a bit perplexing that in the chromium photooxidative cyclopropanation with Majima and Takamuku's model substrate, *p*-methoxy *trans*-stilbene (**2-56**), the cyclopropane was observed in good yield and phenyl ketone **2-58** was not identified.



Scheme 2.11. Ketone observation and potential explanation using oxygen.

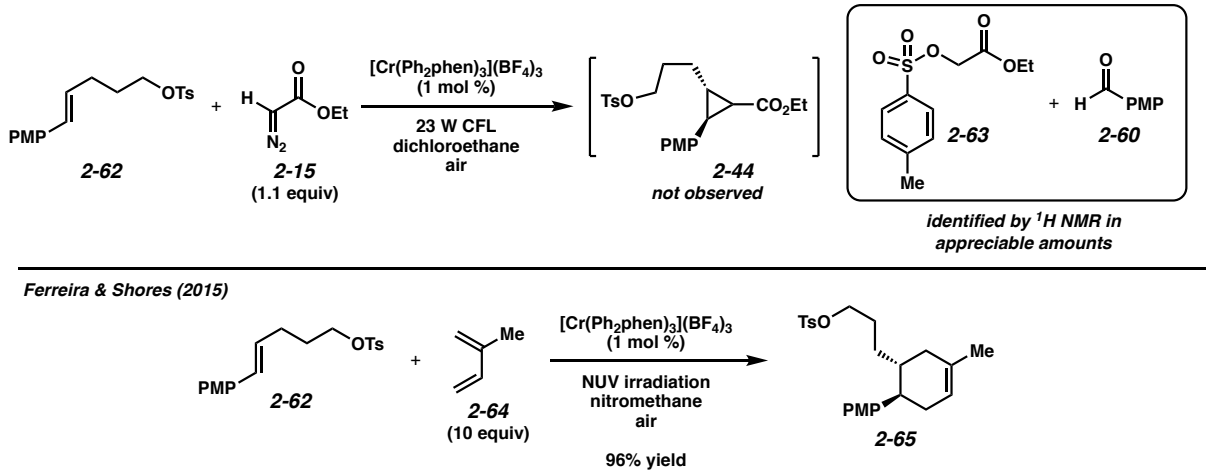
In order to further investigate the formation of ketone byproduct **2-55** and determine whether oxygen was indeed playing a role, a separate experiment was conducted in deoxygenated DCE under an inert environment. Through ^{1}H NMR analysis about a 2:1 ratio of desired product to starting material was observed, with ketone **2-55** as the minor product. It appeared as though the absence of oxygen diminished ketone formation but also retarded the cyclopropanation. This implied that oxygen is partially needed for efficient cyclopropane formation but is also detrimental to the reaction as it aids in generating ketone **2-55**. Further mechanistic investigations would be

necessary in order to elucidate the role of oxygen and this particular substrate in promoting this process.



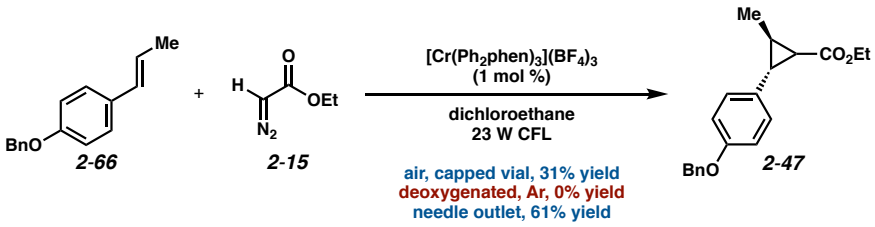
Scheme 2.12. "Air-free" experiment supporting oxygens role in generating ketone **2-55**.

Curiously yet unfortunately, the presence of a pendant alkyl tosylate encumbered the formation of cyclopropane **2-44**. This came to us as a surprise, for the previously reported (4+2) radical cation cycloaddition between alkene **2-62** and isoprene (**2-64**) furnished cyclohexene **2-65** in excellent yield.[5] When this specific substrate was subjected to cyclopropanation conditions, appreciable amounts of *p*-anisaldehyde (**2-60**) was observed in addition to the unexpected ester tosylate **2-63**. This byproduct presumably arises as a result of sulfonyloxy transfer to the diazoacetate.[49] Control experiments later determined that the catalyst was not necessary in generating compound **2-63**, but both oxygen and light were imperative.



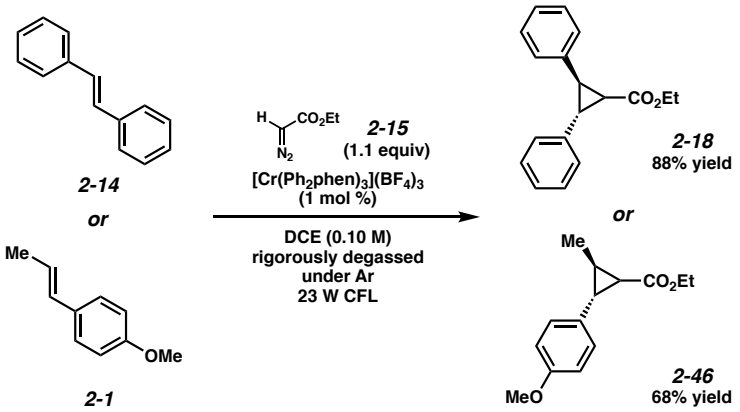
Scheme 2.13. Unexpected sulfonyloxy transfer to ethyl diazoacetate compared to a successful radical cation Diels–Alder.

In our group's previous work with chromium photocatalyzed Diels–Alder cycloadditions it was found that certain substrates necessitated bubbling O_2 into the reaction mixture or performing transformations with a needle outlet. We found that this was the case with *para*-benzyloxy β-methyl styrene. When we subjected this olefin to our optimized cyclopropanation conditions in a closed vial, the reaction did not go completion and cyclopropane **2-47** was isolated in 31% yield. To determine whether oxygen was crucial to the transformation we conducted the reaction under anaerobic conditions and no product was observed. Gratifyingly, performing the radical cation cyclopropanation with a needle outlet increased the yield by almost two-fold from the initial conditions.



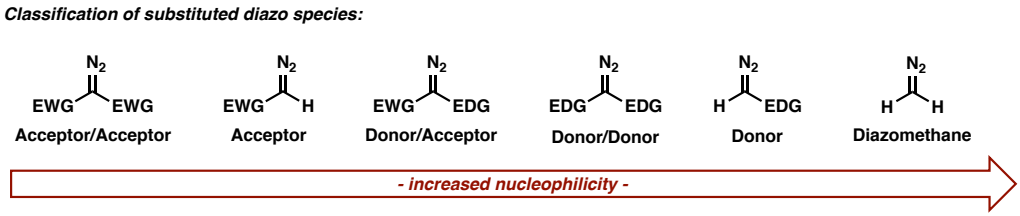
Scheme 2.14. Brief cyclopropane optimization of **2-47.**

It seemed as though oxygen had modest but unclear roles in our cyclopropanation method with specific substrates. To further explore the role of oxygen, radical cation cyclopropanations were attempted with both *trans*-stilbene or *trans*-anethole under strictly anaerobic conditions (Scheme 2.15). In both cases, the (2+1) cycloadducts were isolated in yields comparable to the aerobic conditions. Furthermore, no significant rate retardation was observed in the absence of oxygen. In our (4+2) studies, we noted a vital O_2 dependence that was consistent with a radical cation photocatalytic turnover. This was used to rule out a turnover from radical cation chain propagation. The observation of differential reactivities indicate that a more thorough analysis of the mechanism will be necessary for full elucidation.



Scheme 2.15. Anaerobic cyclopropanations.

2.7 Diazo Scope

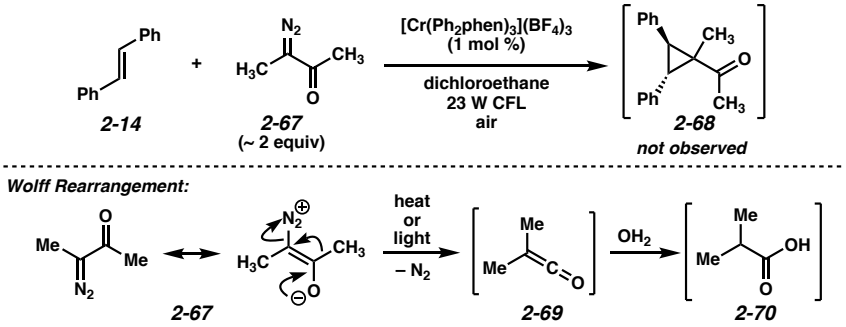


Scheme 2.16. Diazo species organized by increasing nucleophilicity.

When acceptor–acceptor, donor–donor, and donor diazo reagents were examined using our optimized reactions they were found to be ineffective nucleophilic partners. Assuming our mechanism is similar to that of Bauld's, acceptor diazo reagents may not be sufficiently nucleophilic to attack radical cation intermediates.[50] In the case where a donor-donor species was subjected to the reaction conditions, no product was observed. In this scenario, the addition of electron-donating groups to the diazo species lowers its oxidation potential making it easier to oxidize. Thus, competing ionization between the alkene and diazo reagent may be occurring. In this case, oxidation and electron back transfer hinder the reactivity.

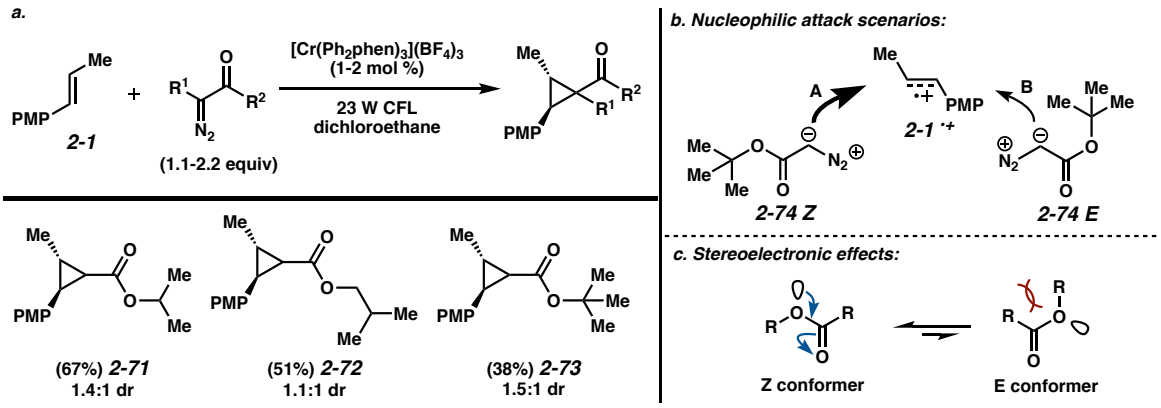
When donor acceptor α-diazo ketone **2-67** was subjected as a potential 1-carbon component to install alkyl ketones, cyclopropane **2-68** was not furnished (Scheme 2.17). Instead,

a carboxylic acid signal was identified by ^{1}H NMR, reminiscent of a Wolff Rearrangement byproduct. Wolff Rearrangement, loss of nitrogen gas, and nucleophilic addition of adventitious water into the ketene intermediate **2-69** is a possible pathway to the observed byproduct.



Scheme 2.17. Experimental failure of a donor acceptor α-diazo methyl ketone.

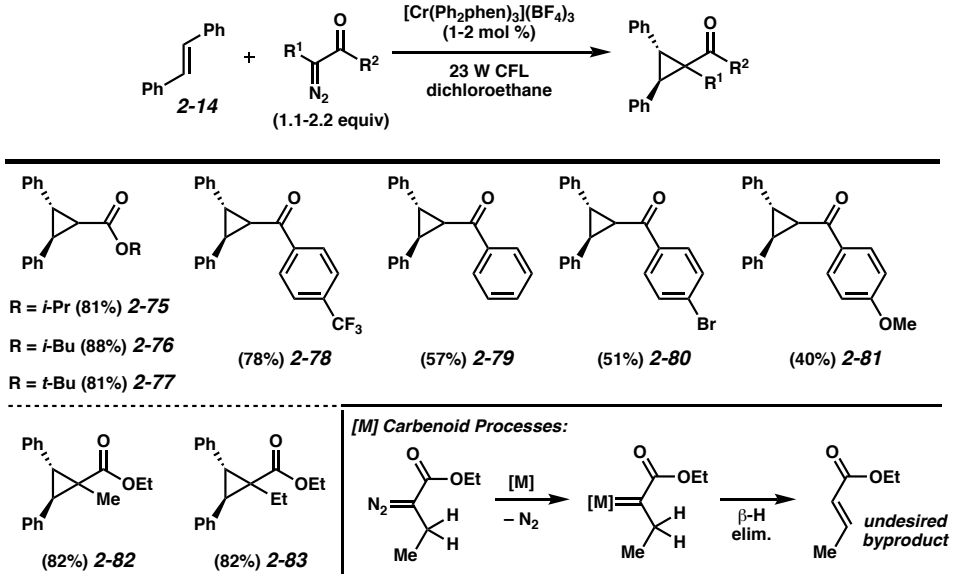
Given the low diastereoselectivity of the (2+1) cycloaddition, we assessed early on whether bulky α-diazo esters could have an impact in the diastereomeric outcome with *trans*-anethole. Unfortunately this was not the case, and instead we only observed a decrease in yield as sterics increased. We can envision two nucleophilic scenarios: one in which the diazo ester is in the E conformer **2-74 E** and another in which the Z conformer **2-74 Z** is operational during interception of the radical cation **2-1**$^{\bullet+}$. Due to both steric and electronic effects, the Z conformer is the predominant configuration of most esters (Scheme 2.15c). The interactions between nonbonding electrons to antibonding orbitals are especially strong when the centers involved are π-bonded, such as a carbonyl. This is because the interatomic distances are shorter and thus overlap more efficiently. The lone pair on the O-alkyl oxygen of an ester stabilizes the antibonding orbital of the carbonyl, specifically σ*. In the E conformer, this stabilizing interaction is not observed.[51]



Scheme 2.18. (a) Diazo scope with *trans*-anethole. (b) Two nucleophilic scenarios. (c) Stabilizing (left/blue) and destabilizing (right/red) stereoelectronic effects.

When the diazo scope with *trans*-stilbene was explored, increasing the sterics on the diazo ester had little impact in yield, and cyclopropanes were obtained in very good yields (Scheme 2.19). Furthermore, aryl diazoketones provided cyclopropanes in appreciable to good yields (40-78%), with no detection of a Wolff rearrangement occurring whatsoever. This came as a bit of a surprise to us, as aryl diazoketones are known to undergo this rearrangement with compact fluorescent lightbulbs with similar wattage.[52] We also observed somewhat of a trend with these reagents. Cyclopropane **2-81** obtained when subjecting the more nucleophilic α-*p*-OMe(C_6H_4) resulted in the lowest yield, while cyclopropane **2-78** obtained by using the electron-deficient trifluoromethylated aryl diazo reagent provided the highest. Although one may expect the more nucleophilic species to also be the most effective based on our proposed mechanism, it is important not to forget the importance of having appropriate reduction potentials for an effective transformation. As aryl diazo ketones become more electron rich, it is safe to assume that their reduction potential lowers as well. It is possible that the reduction potential of the electron-rich *para*-methoxy substituted aryl diazoketone may be close to our ionization window. Competitive ionization between *trans*-stilbene and the diazo species may be occurring, leading to electron back transfer from the oxidized diazo species and hampering the reactivity. In the case of α-*p*-

$CF_3(C_6H_4)$ diazoketone it is a very electron poor diazo, which presumably has a higher reduction potential that is most likely outside our ionization window thus leading to an efficient reaction outcome. Notably, diazo ketones were not compatible in radical cation cycloadditions using *trans*-anethole as the 2-carbon unit.

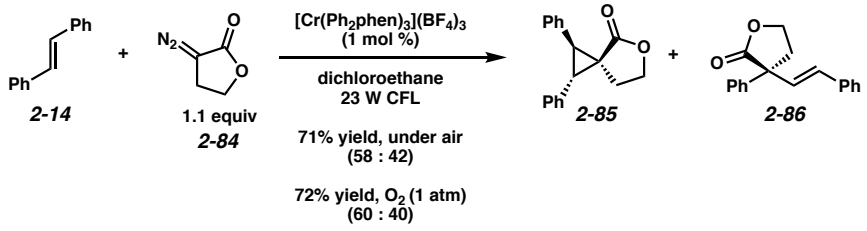


Scheme 2.19. Diazo scope with *trans*-stilbene.

When α-alkyl diazoesters were subjected to our optimized conditions tetrasubstituted cyclopropanes **2-82** and **2-83** were rendered in very good yields. These donor-acceptor diazo species typically undergo β-hydride elimination in diazo decomposition cyclopropanations involving metal carbenoids (see Scheme 2.19).[53] To circumvent this issue, chemists typically use excess diazo reagent or olefin, which can be very wasteful. Another undesired side reaction that is common in transition-metal catalyzed cyclopropanations is diazo dimerization, which was not detected when surveying the scope of diazo reagents. Slow addition protocols that require the use of a syringe pump can aid in diminishing diazo dimerization, although excess reagent is still required. The radical cation pathway avoids both of these undesired processes as a result of the mechanistic differences. In our optimized protocol we generally found that ~1.1-2.2 equivalents

of the diazo reagent were sufficient for effective reactivity, without the necessity of slow addition. These aspects of our Cr photoredox catalyzed cyclopropanation further highlight the feasibility and sustainability of our reaction methodology.

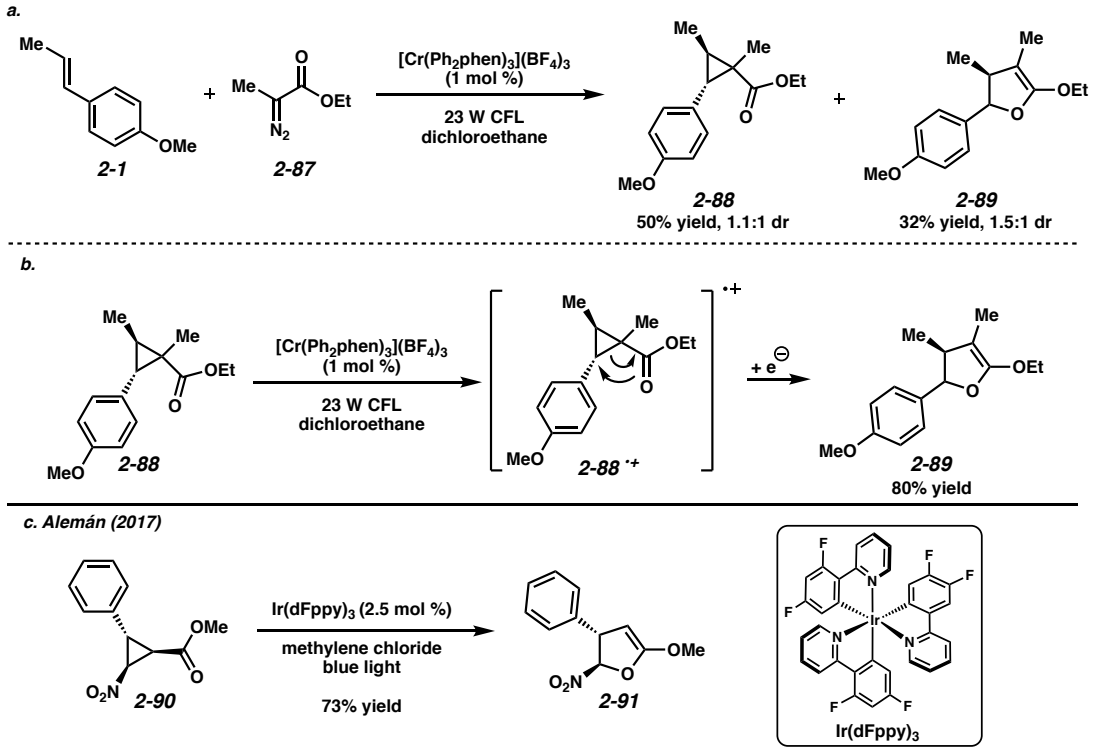
Differential outcomes were observed depending on the combination of alkene and diazo reagent. When *trans*-stilbene (**2-14**) and α-diazolactone **2-84** were subjected to our optimized Cr photocatalyzed conditions the formation of the aryl migration product **2-86**, which was typically observed in small quantities, increased significantly. We were curious to see if we could optimize for this interesting byproduct. When *trans*-stilbene was subjected to anaerobic cyclopropanation conditions, the alkene arising from a phenyl migration was not observed. We questioned whether oxygen had some role in the formation of the aryl migration product and whether we could exploit this property. Unfortunately, when we performed the transformation with 1 atm of O_2, similar results were observed. Further analyses may be necessary to understand the aryl migration and why it is enhanced in this particular case.



Scheme 2.20. Increased aryl migration observation.

A distinct anomaly was noticed in the reaction between *trans*-anethole (**2-1**) and diazopropionate **2-87** (Scheme 2.21a). Apart from the expected cyclopropane **2-88**, a byproduct dihydrofuran **2-89** was also isolated in measurable yield. It was hypothesized that **2-89** arose from cyclopropyl ester **2-88**. This type of ring expansion is known as a Cloke-Wilson Rearrangement, but is normally observed with cyclopropylketones and cyclopropylaldehydes.[54] However, there are isolated reports of donor-acceptor based cyclopropylester Cloke Wilson Rearrangements that

are typically mediated by Lewis acids and/or heat.[55] In order to rule out a Lewis acid or even light catalyzed mechanism, several control experiments were performed. Subjecting the cyclopropylester to $CrCl_3$ and light did not promote dihydrofuran formation. We did not see product when the ester was treated with our Cr photocatalyst in the dark either. When cyclopropane **2-88** was subjected to visible light and $[Cr(Ph_2phen)_3](BF_4)_3$ dihydrofuran **2-89** was isolated in very good yield (Scheme 2.21b). While radical cation vinylcyclobutane and vinylcyclopropane rearrangements have been reported in the past, to our knowledge this is the first report of a radical cation Cloke-Wilson Rearrangement.[56] Furthermore, the rearrangement was not observed with any of the stilbene derived cyclopropanes. Notably, in 2017 Alemán and coworkers observed a diastereoselective Cloke-Wilson Rearrangement through a divergent energy-transfer process using catalytic $Ir(dFppy)_3$ and blue light (Scheme 2.21c).[57]



Scheme 2.21. (a) Unexpected outcome. (b) Radical cation Cloke-Wilson Rearrangement. (c) Energy transfer-induced Cloke-Wilson Rearrangement.

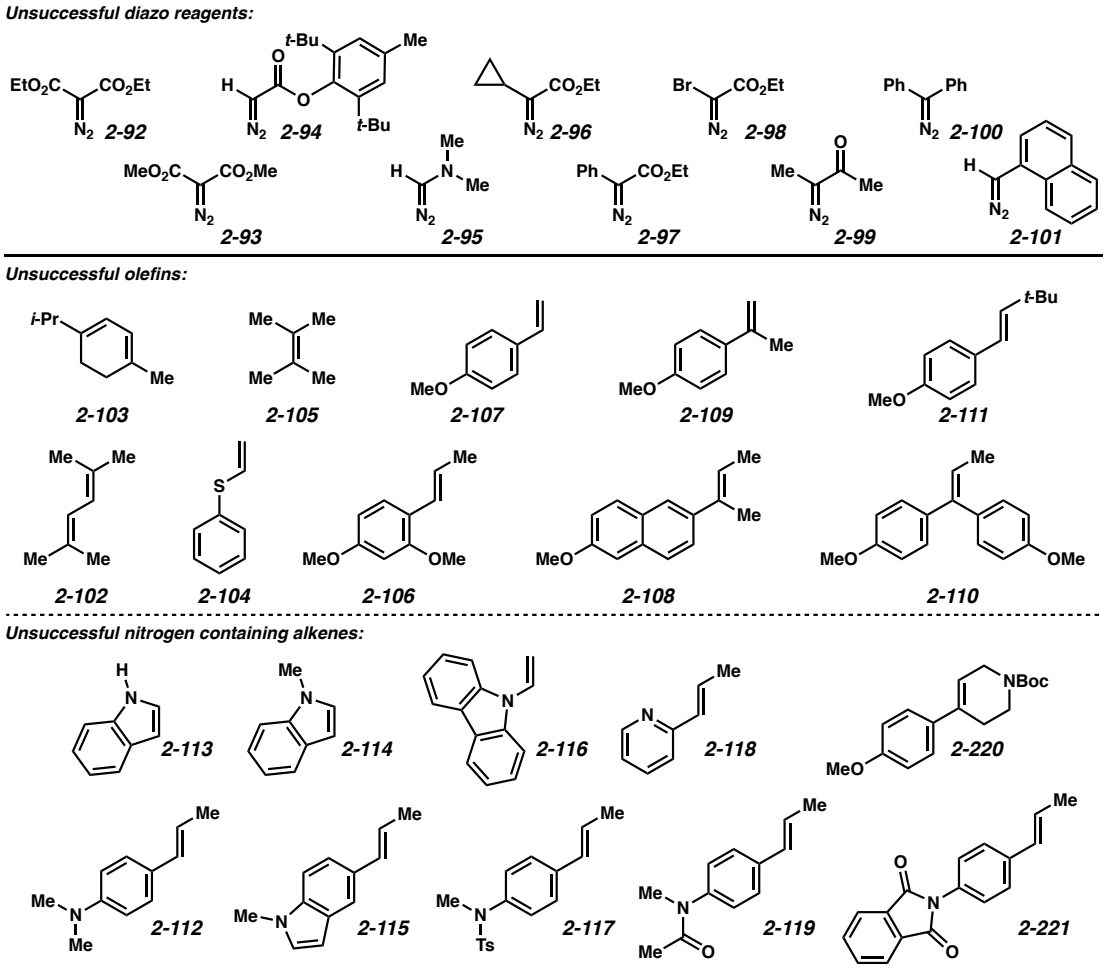
2.8 Unsuccessful Substrates

All unsuccessful substrates are compiled in Scheme 2.22. Many of the failed diazo species have been discussed but a few more are worth noting. Donor acceptor diazo **2-96** was not successful and was found to decompose into cyclobutene products when irradiated with light. Cyclopropanation with α-bromo diazo ester **2-98** was attempted but found to decompose readily as reported in the literature[58] When the bulky diazo ester **2-94** was subjected to our conditions no product was observed, most likely due to unfavorable steric interactions which impede nucleophilic attack into presumed radical cation intermediates. Diazoamide **2-95** was also incompatible in our reaction scope.

Alkenes **2-102**, **2-103**, and **2-15** that were reported by Bauld as efficient radical cation cyclopropanation substrates were unsuccessful.[11] Alkenes **2-106**, **2-108**, and **2-110** also failed most likely due to their electron rich nature, which places them outside our productive electrochemical window for ionization. Substitution at the β-position was deemed necessary, as styrenes **2-107** or **2-109** did not undergo the (2+1) cycloaddition. Having a *tert*-butyl group at the 2-position of olefin **2-111** also impeded reactivity, presumably due to steric hindrance.

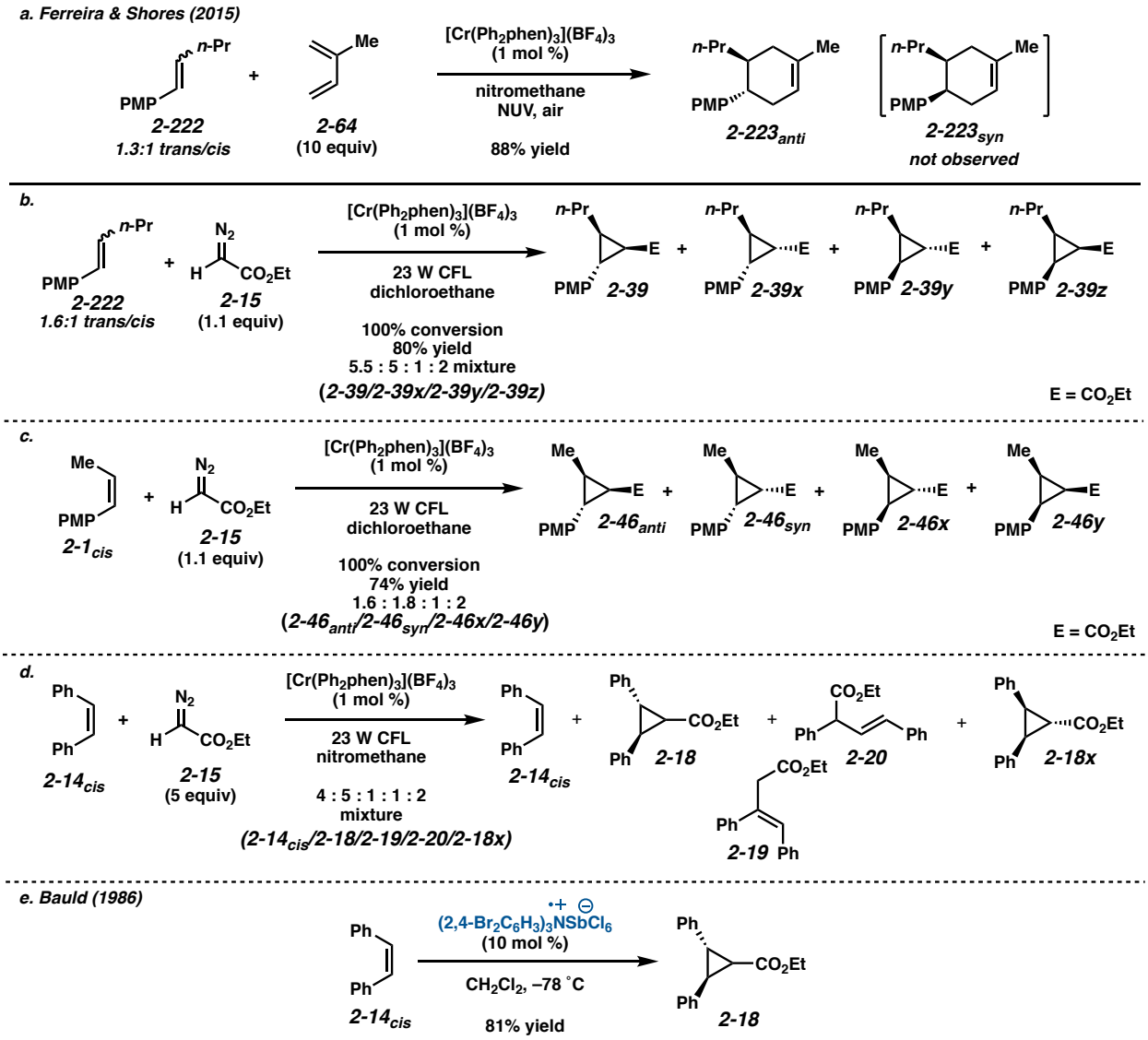
Nitrogen containing olefins were also explored. We began by evaluating those that had precedence in other radical cation cycloadditions. Indole and *N*-methyl indole, which were reported in Steckhan's radical cation Diels–Alder studies, did not work in our transformation.[59] *N*-Vinylcarbazole (**2-116**), shown to be a compatible substrate in radical cation cycloadditions by Bauld as well as Yoon, failed in undergoing our (2+1) cycloaddition.[60,6] A range of *para*-substituted aniline alkenes were synthesized to vary electronics from the very electron rich dimethylamino group (**2-112**) to the more electron withdrawing phthalimide derivative **2-221**, but

all proved incompatible. Photooxidizing catalysts are also known to ionize amines to generate reactive radical cation nitrogen species, and this process has been thoroughly reviewed by Zheng.[61] Presumably, even nitrogen containing compounds that fall within our ionization window fail because of radical cation amine formation and back electron transfer to our photooxidizing Cr catalyst. This is exemplified by the failure of trisubstituted alkene **2-220**. Perhaps in the near future, we may be able to harness the reactivity of nitrogen containing substrates with our chromium catalyzed photoredox chemistry, rather than avoiding it.



Scheme 2.22. Failed substrates.

2.9 Evaluation of Stereoconvergency



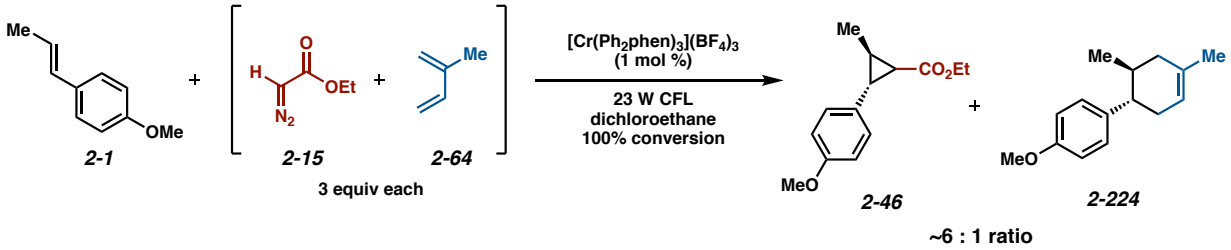
Scheme 2.23. Experiments attempted to evaluate stereoconvergency.

Early on in our method development we noticed the lack of stereoconvergency in the radical cation cyclopropanation. Subjecting a 1.6:1 mixture of *E* and *Z*-alkenes resulted in the formation of all four cyclopropane diastereomers (Scheme 2.23b). Their structural assignment was validated by analogy to a related cyclopropyl compound.[62] This was a striking difference to the Cr photocatalyzed Diels–Alder cycloaddition which generated anti-cyclohexenes despite

subjecting geometrical mixtures of alkenes (Scheme 2.23a).[5] As a consequence, all alkene mixtures that were synthesized were subjected to a known radical isomerization method to yield the sole *trans*-isomer for the cyclopropanation.[63] We continued to evaluate the stereoconvergency and subjected *cis*-anethole to our optimized reaction conditions. A good yield was observed but all four diastereomers were identified through ^{1}H NMR analysis. Bauld had previously shown that the radical cation cyclopropanation was stereconvergent for *cis*-anethole using arylaminium salts (Scheme 2.23e).[11] In our attempted cyclopropanation of *cis*-stilbene using Cr photoconditions both anti and syn cyclopropanes (**2-18** and **2-18x**) were identified. Additionally, the mixture contained the previously observed alkene byproducts and an appreciable amount of *cis*-stilbene was left unreacted.

2.10 Competition Experiments

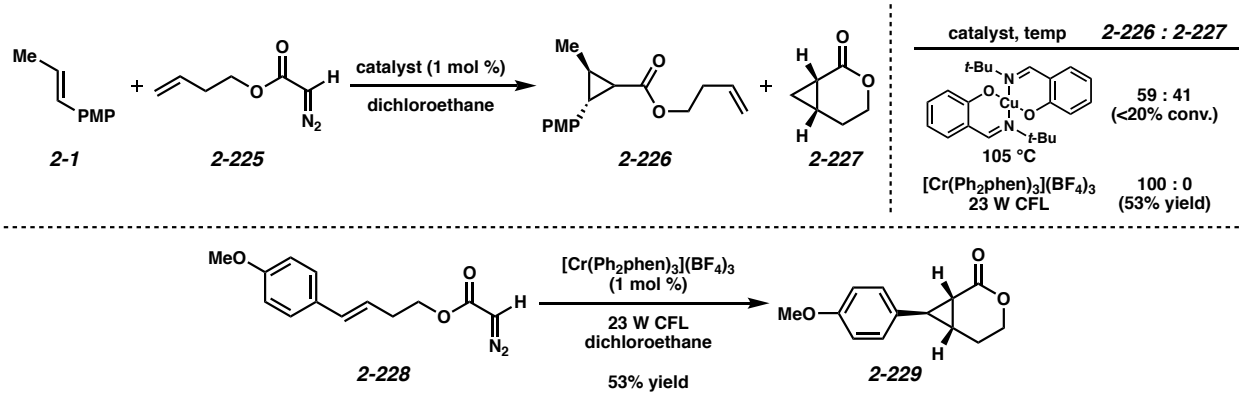
Assuming our proposed radical cation mechanism is true both ethyl diazoacetate and isoprene should be competent nucleophiles. A competition experiment showed that it was the cyclopropane that was the predominantly observed product. This experiment highlighted the increased nucleophilicity of the diazo species in intercepting the radical cation of *trans*-anethole.



Scheme 2.24. Competition experiment between a diazo and diene.

2.11 Chemoselectivity Highlighted

The chemoselectivity of the radical cation cyclopropanation, dictated by electronics, is a unique and important aspect. In comparison to the more commonly employed Rh or Cu catalyzed cyclopropanation of diazo compounds, our method may stand out in this regard. To exemplify this powerful attribute, we compared the reactivity of Cr photoredox catalyzed cyclopropanation to a classical Cu-catalyzed process.[64] *trans*-anethole (**2-1**) and diazoacetate **2-225** were subjected to two separate reaction conditions. The Cu-catalyzed reaction provided, in low conversion, a mixture of **2-226** and **2-227**, arising from both inter- and intramolecular cyclopropanation events. Employing Cr(III) photoconditions exclusively yielded the intermolecular cyclopropane adduct **2-226**. Furthermore, our ability to predict a successful cycloaddition on the basis of feasible alkene oxidation steered us to build diazo species **2-228**, which was subjected to our chromium conditions, successfully leading to lactone **2-229**. This last example adds to the synthetic toolbox of intramolecular radical cation cycloadditions: (2+2),[65] (4+2),[10b] and now (2+1) intramolecular cycloadditions can be achieved.



Scheme 2.25. Explored chemoselectivity.

2.12 Conclusion

In summary, we were able to successfully translate the radical cation cyclopropanation method initially developed by Bauld into our chromium photoredox catalyzed system. Examination of the reaction scope through the testing of diverse alkene and diazo substrates yielded information on the chemoselectivity, diastereoselectivity, and functional group tolerance. Differences in reactivity were observed and noted from both Bauld's work and our previously reported radical cation (4+2) cycloaddition. The formation of polysubstituted cyclopropanes through this method could offer an attractive and facile alternative to Rh or Cu mediated diazo decomposition reactions. Selected work discussed in this chapter was published in *Organic Letters* in 2017.[66]

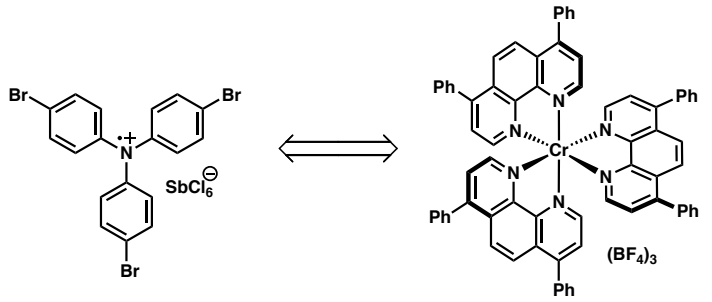


Figure 2.6. Conceptual translation achieved via chromium photoredox catalysis.

2.13 Experimental Section

2.13.1 Materials and Methods

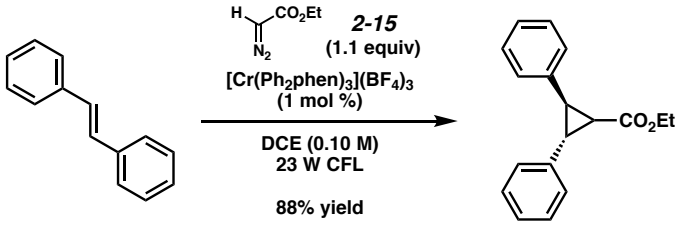
Cr(III) catalysts were synthesized as described by Shores and Damrauer.[67] $Ru(bpz)_3(PF_6)_2$ and

$Ru(bpy)_3Cl_2$ were purchased from Sigma-Aldrich. $Ru(bpy)_3(PF_6)_2$ and methyl viologen bis(hexafluorophosphate) were prepared according to the procedures by Yoon and coworkers.[68] All solvents, excluding nitromethane and 1,2-dichloroethane, were purified by passing through activated alumina columns. All reagents were used as received unless otherwise noted. Commercially available chemicals were purchased from Alfa Aesar (Ward Hill, MA), Sigma-Aldrich (St. Louis, MO), Oakwood Products (West Columbia, SC), Strem (Newburport, MA), and TCI America (Portland, OR). Qualitative TLC analysis was performed on 250 mm thick, 60 Å, glass backed, F254 silica (Silicycle, Quebec City, Canada). Visualization was accomplished with UV light and exposure to *p*-anisaldehyde or $KMnO_4$ stain solutions followed by heating. Flash chromatography was performed using Silicycle silica gel (230-400 mesh). Reactions under near-UV irradiation (NUV) were performed in a Luzchem photoreactor (LZC-ORG) equipped with 10 lamps of wavelengths 419, 350, and 300 nm. Irradiation with visible light was performed in a closed box using a 23 W compact fluorescent light bulb (EcoSmart 23 W bright white CFL spiral light bulb, 1600 lumens). The temperature of this closed box when operating was measured at approximately 35-40 °C. Cycloadditions using all modes of irradiation were performed using borosilicate vials. ^1H NMR spectra were acquired on a Varian Mercury Plus 400 MHz NMR and are reported relative to $SiMe_4$ (δ 0.00). ^{13}C NMR spectra were acquired on a Varian Mercury Plus NMR (at 100 MHz) or a Varian Unity Inova NMR (at 125 MHz) and are reported relative to $SiMe_4$ (δ 0.0). IR spectra were obtained on a Nicolet 380 FT-IR. High-resolution mass spectrometry data was acquired by the University of Georgia Proteomics and Mass Spectrometry Core Facility on a Bruker Esquire 3000 Plus Ion Trap Spectrophotometer.

2.13.2 Radical Cation Cyclopropanations

General Procedure for the photocatalyzed cyclopropanation: A solution of (*E*)-alkene (1 equiv), diazo species (1.1-2.2 equiv), and $[Cr(Ph_2phen)_3](BF_4)_3$ (1-2 mol %) in DCE (0.10 M) was prepared in a flame-dried borosilicate vial open to air. The vial was then capped and placed on a stir plate in a closed box lined with aluminum foil and equipped with a 23 W compact fluorescent light bulb. The reaction mixture was irradiated with stirring until consumption of the alkene was complete, as determined by TLC. Once finished, the reaction mixture was concentrated via rotary evaporation and purified by flash column chromatography to afford the desired product.

2.13.3 Alkene Scope



Cyclopropane 2-18. Prepared according to the *General Procedure* using 18.0 mg *trans*-stilbene (0.0999 mmol), 14.7 mg ethyl diazoacetate (85% wt. solution in CH_2Cl_2, 0.110 mmol), 1.3 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (0.999 μmol), and 1.0 mL DCE. The reaction mixture was irradiated for 14 h. The crude product was purified by flash chromatography (100% hexanes → 19:1 hexanes/acetone eluent) to afford cyclopropane **2-18** (23.5 mg, 88% yield) as a colorless oil.

TLC: R_f = 0.32 in 19:1 hexanes/acetone, visualized by UV.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.36-7.21 (comp. m, 10H), 3.95 (dq, *J* = 7.2, 1.8 Hz, 2H), 3.22

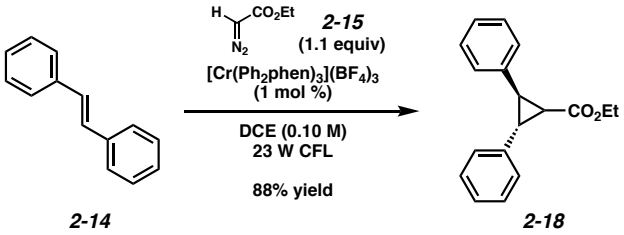
(dd, J = 7.0, 5.2 Hz, 1H), 2.94 (dd, J = 9.4, 7.0 Hz, 1H), 2.42 (dd, J = 9.4, 5.2 Hz, 1H), 1.04 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 170.1, 139.8, 136.3, 129.3, 128.8, 128.2, 127.1, 126.8, 60.6, 34.6, 31.4, 29.4, 14.2.

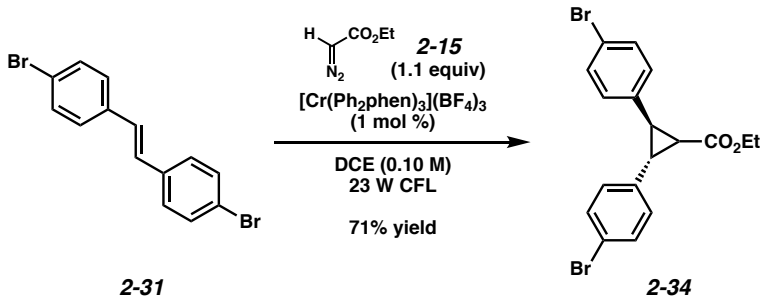
IR (ATR, neat): 3050, 3997, 1729, 1948, 1177, 752, 696 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M+H)^+$ $[C_{18}H_{18}O_2 + H]^+$: 267.1380 found 267.1381.

(Gram Scale Experiment)



Inside a flame-dried round bottom flask open to air, a solution containing 1.00 g *trans*-stilbene (5.55 mmol), 820 mg ethyl diazoacetate (85% solution in CH_2Cl_2, 6.11 mmol), and 72.7 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (0.0555 mmol) in 56 mL DCE was prepared. The flask was then fitted with a rubber septa and needle outlet open to air and placed in a closed box, lined with aluminum foil, and equipped with a 23 W compact fluorescent light bulb. The reaction mixture was irradiated with stirring until consumption of the alkene was complete (43 h), as determined by TLC. The reaction was concentrated via rotary evaporation, and the crude product was purified by flash chromatography (100% hexanes → 19:1 hexanes/acetone eluent) to afford *trans*-cyclopropane **2-18** (1.30 g, 88% yield) as a colorless oil.



2-31 *2-34*

Cyclopropane 2-34. Prepared according to the *General Procedure* using 34.0 mg *trans*-4,4'-dibromostilbene (0.101 mmol), 15.0 mg ethyl diazoacetate (85% wt. solution in CH_2Cl_2, 0.111 mmol), 1.3 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (1.01 μmol), and 1.0 mL DCE. The reaction mixture was irradiated for 14 h. The crude product was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford cyclopropane **2-34** (30.3 mg, 71% yield) as a white solid.

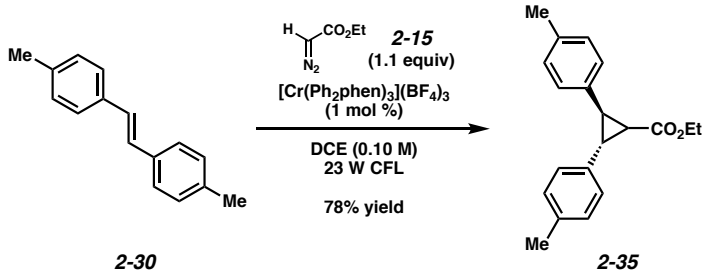
TLC: R_f = 0.34 in 9:1 hexanes/Et_2O, visualized by UV.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.45 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H) 7.20 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 3.98 (dq, *J* = 7.2, 2.4 Hz, 2H), 3.12 (dd, *J* = 7.0, 5.2 Hz, 1H), 2.81 (dd, *J* = 9.6, 7.0 Hz, 1H), 2.38 (dd, *J* = 9.6, 5.2 Hz, 1H), 1.09 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 169.6, 138.3, 134.9, 131.9, 131.4, 130.9, 128.5, 121.1, 120.7, 60.9, 33.8, 31.3, 28.9, 14.3.

IR (ATR, neat): 1724, 1490, 1178, 1073, 1010, 817 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M+H)^+$ $[C_{18}H_{16}Br_2O_2 + H]^+$: 424.9569, found 424.9572.



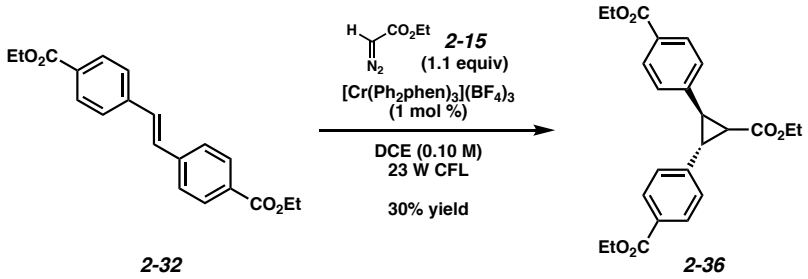
2-30 *2-35*

Cyclopropane 2-35. Prepared according to the *General Procedure* using 21.1 mg 4,4'-dimethyl-*trans*-stilbene (0.101 mmol), 15.0 mg ethyl diazoacetate (85% wt. solution in CH_2Cl_2, 0.111

mmol), 1.3 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (1.01 μmol), and 1.0 mL DCE. The reaction mixture was irradiated for 24 h. The crude product was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford cyclopropane **2-35** (23.3 mg, 78% yield) as a colorless oil.

TLC: R_f = 0.37 in 9:1 hexanes/Et_2O, visualized by UV.

Spectroscopic data were in accordance with the published values.[69]



2-32 *2-36*

Cyclopropane 2-36. Prepared according to the *General Procedure* using 32.0 mg *E*-alkene **2-32** (0.0986 mmol), 14.6 mg ethyl diazoacetate (85% wt. solution in CH_2Cl_2, 0.109 mmol), 1.3 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (0.986 μmol), and 1.0 mL DCE. The reaction mixture was irradiated for 72 h. The crude product was purified by flash chromatography (3:2 hexanes/Et_2O as eluent) to afford cyclopropane **2-36** (12.0 mg, 30% yield) as a colorless oil.

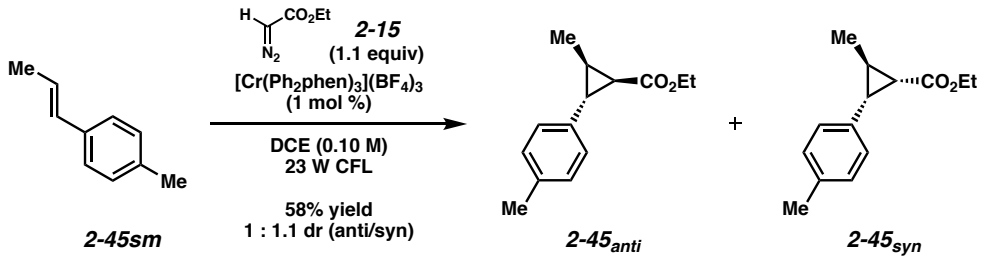
TLC: R_f = 0.33 in 3:2 hexanes/Et_2O, visualized by UV.

^{1}H NMR (400 MHz; $CDCl_3$): δ 8.01 (d, *J* = 8.4 Hz, 2H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 4.40-4.34 (comp. m, 4H), 3.96 (q, *J* = 7.0 Hz, 1H), 3.28 (dd, *J* = 7.0, 5.2 Hz, 1H), 2.98 (dd, *J* = 9.8, 7.0 Hz, 1H), 2.52 (dd, *J* = 9.8, 5.2 Hz, 1H), 1.40 (t, *J* = 7.2 Hz, 3H), 1.39 (t, *J* = 7.2 Hz, 3H), 1.06 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 169.4, 166.5, 166.4, 144.5, 141.0, 130.1, 129.6, 129.4, 129.3, 129.2, 126.6, 61.13, 61.06, 61.0, 34.7, 32.0, 29.5, 14.5, 14.3.

IR (ATR, neat): 2984, 1717, 1275, 1180, 1104, 1020 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M+H)^+$ $[C_{24}H_{26}O_6 + H]^+$: 411.1802, found 411.1804.



Cyclopropane 2-45. Prepared according to the *General Procedure* using 13.5 mg *E*-alkene **2-45sm** (0.102 mmol), 15.1 mg ethyl diazoacetate (85% wt. solution in CH_2Cl_2, 0.112 mmol), 1.3 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (1.02 μmol), and 1.0 mL DCE. The reaction mixture was irradiated for 24 h. The crude product was purified by flash chromatography (100% hexanes → 19:1 hexanes/EtOAc eluent) to afford *trans*-cyclopropane **2-45** (13.0 mg, 58% yield) as a colorless oil. Diastereomeric ratio (1:1.1 anti/syn) was determined by ^{1}H NMR analysis of the crude mixture.

TLC: R_f = 0.36 in 9:1 hexanes/Et_2O, visualized by UV. Stained purple by *p*-anisaldehyde.

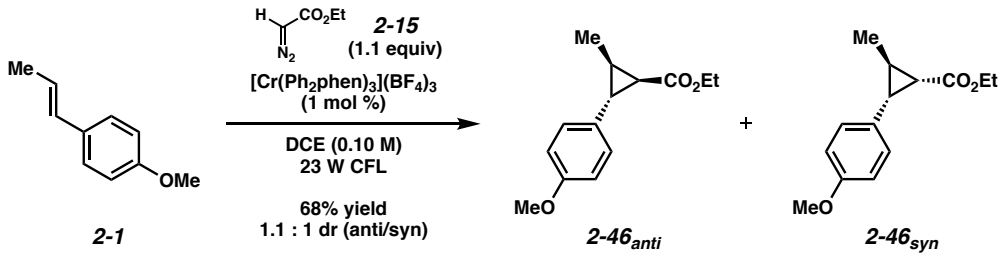
^{1}H NMR (400 MHz; $CDCl_3$): Major (syn): δ 7.12 (d, *J* = 8.2 Hz, 2H), 7.05 (d, *J* = 8.2 Hz, 2H), 4.16 (dq, *J* = 7.2, 4.4 Hz, 2H), 2.34-2.33 (m, 1H), 2.29 (s, 3H), 2.04 (app. quintet, *J* = 6.0 Hz, 1H), 1.78 (dd, *J* = 9.2, 5.2 Hz, 1H), 1.26 (d, *J* = 6.0 Hz, 3H), 1.02 (t, *J* = 7.2 Hz, 3H).

Minor (anti): δ 6.97 (d, *J* = 7.8 Hz, 2H), 7.08 (d, *J* = 7.8 Hz, 2H), 3.89 (dq, *J* = 7.2, 2.8 Hz, 2H), 2.37 (dd, *J* = 6.4, 5.2 Hz, 1H), 2.31 (s, 3H), 1.97 (dd, *J* = 9.2, 5.2 Hz, 1H), 1.67-1.62 (comp. m, 1H), 1.34 (d, *J* = 6.0 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz; $CDCl_3$): δ 171.9, 171.2, 137.7, 136.1, 133.7, 129.4, 129.2, 129.1, 128.7, 126.1, 60.6, 60.2, 34.1, 32.2, 30.1, 29.4, 25.6, 21.2, 21.1, 19.9, 17.9, 14.5, 14.2, 12.2.

IR (ATR, neat): 2981, 1731, 1439, 1375, 1181, 1163, 1047 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + Na)^+$ $[C_{14}H_{18}O_2 + Na]^+$: 241.1199, found 241.1200.



Cyclopropane 2-46. Prepared according to the *General Procedure* using 14.7 mg *trans*-anethole (0.0992 mmol), 14.6 mg ethyl diazoacetate (85% wt. solution in CH_2Cl_2, 0.109 mmol), 1.3 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (0.992 μmol), and 1.0 mL DCE. The reaction mixture was irradiated for 25 h. The crude product was purified by flash chromatography (100% hexanes → 9:1 hexanes/EtOAc eluent) to afford cyclopropane **2-46** (15.8 mg, 68% yield) as a colorless oil. Diastereomeric ratio (1.1:1 anti/syn) was determined by ^{1}H NMR analysis of the crude mixture.

TLC: R_f = 0.45 in 9:1 hexanes/EtOAc, visualized by UV.

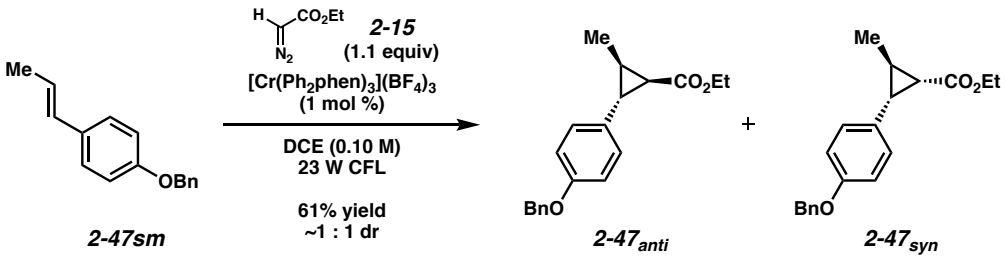
^{1}H NMR (400 MHz; $CDCl_3$): Major (anti): δ 7.01 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 4.17 (dq, *J* = 7.2, 1.6 Hz, 2H), 3.78 (s, 3H), 2.36 (dd, *J* = 6.2, 5.2 Hz, 1H), 1.93 (dd, *J* = 9.0, 5.2 Hz, 1H), 1.65-1.59 (comp. m, 1H), 1.34 (d, *J* = 6.4 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H).

Minor (syn): δ 7.16 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 3.89 (dq, *J* = 7.2, 1.2 Hz, 2H), 3.77 (s, 3H), 2.29 (dd, *J* = 8.8, 7.2 Hz, 1H), 2.02 (app. sextet, *J* = 6.0 Hz, 1H), 1.77 (dd, *J* = 8.8, 5.2 Hz, 1H), 1.26 (d, *J* = 6.0 Hz, 3H), 1.03 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 171.9, 171.1, 158.32, 158.27, 132.7, 130.2, 128.8, 127.3, 114.0, 113.4, 60.5, 60.2, 55.4, 55.3, 33.7, 31.9, 30.1, 29.2, 25.3, 20.0, 17.9, 14.5, 14.3, 12.1.

IR (ATR, neat): 2959, 1722, 1518, 1246, 1163, 1035, 829 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + Na)^+$ $[C_{14}H_{18}O_3 + Na]^+$: 257.1154, found 257.1149.



Cyclopropane 2-47. Prepared with a slight modification to the *General Procedure* using 22.5 mg *E*-alkene **2-47sm** (0.100 mmol), 14.8 mg ethyl diazoacetate (85% wt. solution in CH_2Cl_2, 0.110 mmol), 1.3 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (1.00 μmol), and 1.0 mL DCE. The reaction mixture was irradiated for 42 h *with a needle outlet open to air*. The crude product was purified by flash chromatography (100% hexanes → 9:1 hexanes/EtOAc eluent) to afford cyclopropane **3-47** (19.1 mg, 61% yield) as a white solid. Diastereomeric ratio (~1:1 anti/syn) was determined by ^{1}H NMR analysis of the crude mixture.

TLC: R_f = 0.44 in 9:1 hexanes/EtOAc, visualized by UV.

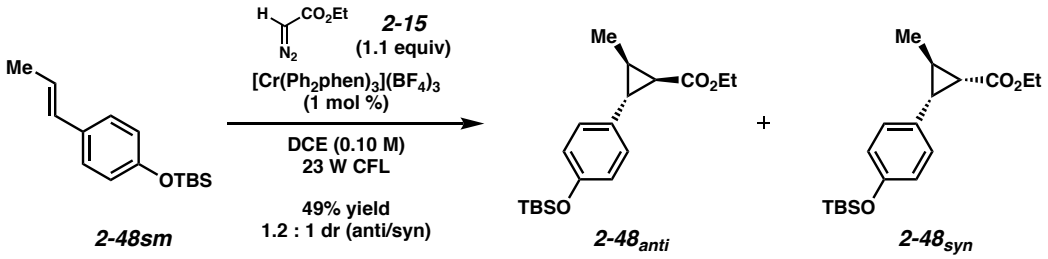
^{1}H NMR (400 MHz; $CDCl_3$): Anti: δ 7.43-7.30 (comp. m, 5H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 5.04 (s, 2H), 4.17 (qd, *J* = 7.0, 2.0 Hz, 2H), 2.37 (dd, *J* = 6.4, 5.0 Hz, 1H), 1.94 (dd, *J* = 9.2, 5.0 Hz, 1H), 1.65-1.59 (comp. m, 1H), 1.34 (d, *J* = 6.0 Hz, 3H), 1.29 (t, *J* = 7.0 Hz, 3H).

Syn: δ 7.43-7.30 (comp. m, 5H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.03 (s, 3H), 3.89 (qd, *J* = 7.2, 1.2 Hz, 2H), 2.30 (dd, *J* = 9.2, 7.0 Hz, 1H), 2.03 (app. sextet, *J* = 6.0 Hz, 1H), 1.78 (dd, *J* = 9.2, 5.2 Hz, 1H), 1.26 (d, *J* = 6.0 Hz, 3H), 1.02 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 171.9, 171.1, 157.6, 157.5, 137.3, 137.2, 133.0, 130.2, 129.2, 128.70, 128.67, 128.1, 128.0, 127.6, 127.5, 127.3, 115.0, 114.4, 70.2, 70.1, 60.5, 60.2, 33.8, 31.9, 30.1, 29.3, 25.3, 20.0, 17.9, 14.5, 14.3, 12.1.

IR (ATR, neat): 2980, 1721, 1514, 1454, 1371, 1242, 1175, 1026 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M+H)^+$ $[C_{20}H_{22}O_3 + H]^+$: 311.1647, found 311.1643.



Cyclopropane 2-48. Prepared according to the *General Procedure* using 26.4 mg *E*-alkene **2-48sm** (0.106 mmol), 15.7 mg ethyl diazoacetate (85% wt. solution in CH_2Cl_2, 0.117 mmol), 1.4 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (1.06 μmol), and 1.1 mL DCE. The reaction mixture was irradiated for 25 h. The crude product was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford cyclopropane **2-48** (17.4 mg, 49% yield) as a colorless oil. Diastereomeric ratio (1.2:1 anti/syn) was determined by ^{1}H NMR analysis of the crude mixture.

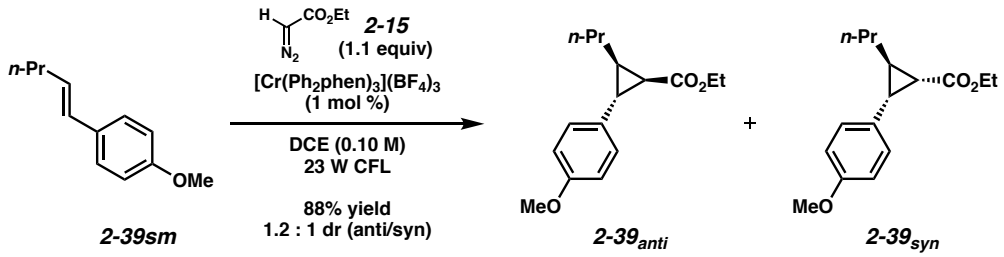
TLC: R_f = 0.40 in 9:1 hexanes/Et_2O, visualized by UV.

^{1}H NMR (400 MHz; $CDCl_3$): Major (anti): δ 6.93 (d, *J* = 7.8 Hz, 2H), 6.74 (d, *J* = 7.8 Hz, 2H), 4.16 (qd, *J* = 7.2, 1.6 Hz, 2H), 2.34 (dd, *J* = 6.2, 5.1 Hz, 1H), 1.93 (dd, *J* = 9.2, 5.1 Hz, 1H), 1.64-1.59 (comp. m, 1H), 1.33 (d, *J* = 6.0 Hz, 3H), 0.98 (t, *J* = 7.2 Hz, 3H), 0.98 (s, 9H), 0.17 (s, 6H). Minor (syn): δ 7.09 (d, *J* = 8.4 Hz, 2H), 6.72 (d, *J* = 8.4 Hz, 2H), 3.86 (qd, *J* = 7.2, 3.0 Hz, 2H), 2.27 (dd, *J* = 9.2, 7.0 Hz, 1H), 2.02 (app. sextet, *J* = 6.0 Hz, 1H), 1.76 (dd, *J* = 9.2, 5.2 Hz, 1H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.24 (d, *J* = 6.0 Hz, 3H), 0.96 (s, 9H), 0.16 (s, 6H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 171.9, 171.0, 154.4, 154.2, 133.3, 130.1, 129.5, 127.1, 120.2, 119.6, 60.5, 60.1, 33.8, 32.0, 30.4, 29.4, 25.8, 25.7, 25.4, 19.7, 18.4, 17.9, 14.5, 14.3, 12.2, -4.3.

IR (ATR, neat): 2957, 2856, 1724, 1512, 1254, 1175, 914, 837, 781 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{19}H_{30}O_3Si + H]^+$: 335.2037, found 335.2033.



Cyclopropane 2-39. Prepared according to the *General Procedure* using 18.4 mg *E*-alkene **2-39sm** (0.104 mmol), 15.4 mg ethyl diazoacetate (85% wt. solution in CH_2Cl_2, 0.115 mmol), 1.4 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (1.04 μmol), and 1.0 mL DCE. The reaction mixture was irradiated for 14 h. The crude product was purified by flash chromatography (100% hexanes → 9:1 hexanes/EtOAc eluent) to afford cyclopropane **2-39** (24.0 mg, 88% yield) as a colorless oil. Diastereomeric ratio (1.2:1 anti/syn) was determined by ^{1}H NMR analysis of the crude mixture.

TLC: R_f = 0.45 in 9:1 hexanes/EtOAc, visualized by UV.

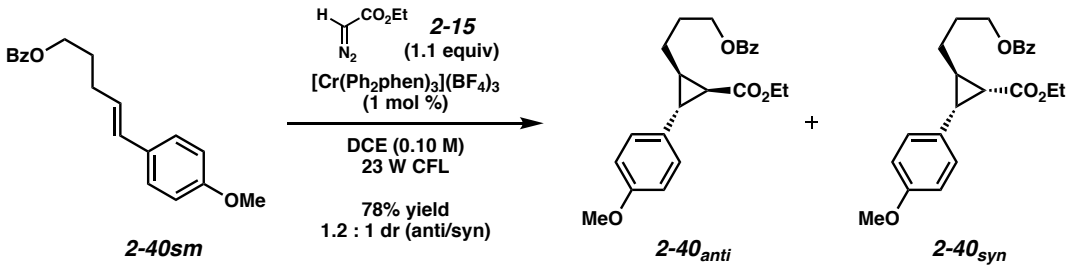
^{1}H NMR (400 MHz; $CDCl_3$): Major (anti): δ 7.02 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.78 (s, 3H), 2.41 (dd, *J* = 6.4, 5.1 Hz, 1H), 1.94 (dd, *J* = 9.0, 5.1 Hz, 1H), 1.74-1.40 (comp. m, 5H), 1.28 (t, *J* = 7.2 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H).

Minor (syn): δ 7.16 (d, *J* = 8.2 Hz, 2H), 6.80 (d, *J* = 8.2 Hz, 2H), 3.90 (qd, *J* = 7.2, 1.2 Hz, 2H), 3.77 (s, 3H), 2.31 (dd, *J* = 9.2, 7.0 Hz, 1H), 2.01-1.98 (comp. m, 1H), 1.79 (dd, *J* = 9.2, 4.8 Hz, 1H), 1.74-1.40 (comp. m, 4H), 1.03 (t, *J* = 7.2 Hz, 3H), 0.98 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 172.1, 171.2, 158.34, 158.27, 132.8, 130.3, 129.0, 127.4, 114.0, 113.4, 60.5, 60.2, 55.4, 55.3, 35.1, 32.7, 31.1, 31.0, 29.0, 28.9, 28.6, 25.6, 22.8, 22.3, 14.5, 14.3, 14.03, 13.96.

IR (ATR, neat): 2959, 1721, 1516, 1246, 1175, 1036, 843 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M+H)^+$ $[C_{16}H_{22}O_3 + H]^+$: 263.1642, found 262.1638.



Cyclopropane 2-40. Prepared according to the *General Procedure* using 24.0 mg *E*-alkene **2-40sm** (0.0810 mmol), 12.0 mg ethyl diazoacetate (85% wt. solution in CH_2Cl_2, 0.0891 mmol), 1.1 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (0.810 μmol), and 0.8 mL DCE. The reaction mixture was irradiated for 9 h. The crude product was purified by flash chromatography (100% hexanes → 4:1 hexanes/EtOAc eluent) to afford cyclopropane **2-40** (24.1 mg, 78% yield) as a colorless oil. Diastereomeric ratio (1.2:1 anti/syn) was determined by ^{1}H NMR analysis of the crude mixture.

TLC: R_f = 0.47 in 4:1 hexanes/EtOAc, visualized by UV.

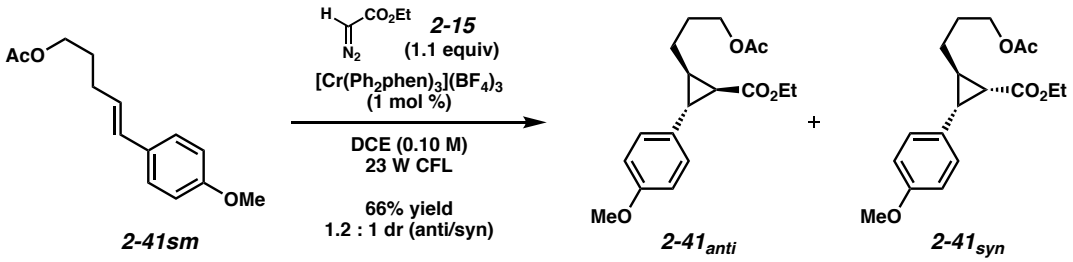
^{1}H NMR (400 MHz; $CDCl_3$): Major (anti): δ 8.05 (d, *J* = 7.2 Hz, 2H), 7.58-7.54 (m, 1H), 7.47-7.42 (m, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 4.39 (t, *J* = 6.4 Hz, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.78 (s, 3H), 2.45 (dd, *J* = 6.4, 5.6 Hz, 1H), 2.10-1.52 (comp. m, 6H), 1.27 (t, *J* = 7.2 Hz, 3H).

Minor (syn): δ 8.05 (d, *J* = 7.2 Hz, 2H), 7.58-7.54 (m, 1H), 7.47-7.42 (m, 2H), 7.16 (d, *J* = 8.2 Hz, 2H), 6.79 (d, *J* = 8.2 Hz, 2H), 4.35 (t, *J* = 5.8 Hz, 2H), 3.90 (qd, *J* = 7.2, 0.8 Hz, 2H), 3.77 (s, 3H), 2.36 (dd, *J* = 9.2, 7.0 Hz, 1H), 2.10-1.52 (comp. m, 6H), 1.02 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 171.9, 170.9, 166.7, 158.45, 158.38, 133.1, 133.0, 132.3, 130.7, 130.5, 130.4, 130.2, 129.7, 128.50, 128.46, 127.4, 114.1, 113.5, 97.5, 64.63, 64.58, 60.7, 60.3, 55.5, 55.3, 32.6, 31.1, 30.6, 29.6, 29.0, 28.7, 28.54, 28.46, 25.1, 23.6, 14.5, 14.3, 11.4.

IR (ATR, neat): 2935, 1717, 1515, 1452, 1272, 1247, 1175, 1111, 1026, 830, 711 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M+H)^+$ $[C_{23}H_{26}O_5 + H]^+$: 383.1853, found 383.1847.



Cyclopropane 2-41. Prepared according to the *General Procedure* using 41.5 mg *E*-alkene **2-41sm** (0.177 mmol), 26.1 mg ethyl diazoacetate (85% wt. solution in CH_2Cl_2, 0.195 mmol), 2.3 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (1.77 μmol), and 1.8 mL DCE. The reaction mixture was irradiated for 48 h. The crude product was purified by flash chromatography (1:1 hexanes/Et_2O eluent) to afford cyclopropane **2-41** (37.6 mg, 66% yield) as a colorless oil. Diastereomeric ratio (1.2:1 anti/syn) was determined by ^{1}H NMR analysis of the crude mixture.

TLC: R_f = 0.43 in 1:1 hexanes/Et_2O, visualized by UV.

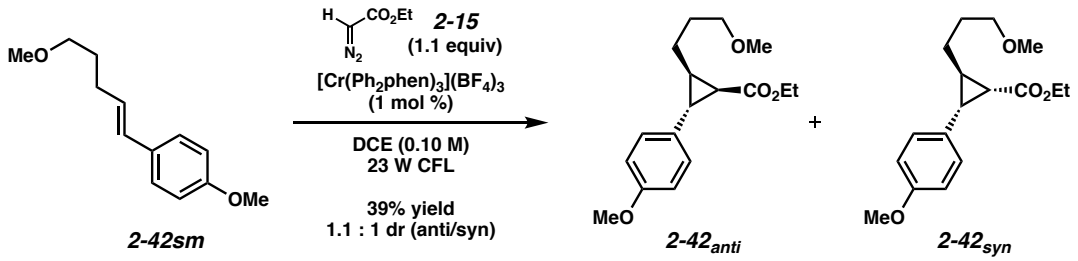
^{1}H NMR (400 MHz; $CDCl_3$): Major (anti): δ 7.01 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 4.16 (qd, *J* = 7.2, 0.8 Hz, 2H), 4.13 (t, *J* = 6.4 Hz, 2H), 3.78 (s, 3H), 2.42 (dd, *J* = 6.6, 5.0 Hz, 1H), 2.03 (s, 3H), 1.97 (dd, *J* = 9.0, 5.0 Hz, 1H), 1.86-1.80 (comp. m, 3H), 1.63-1.55 (comp. m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H).

Minor (syn): δ 7.15 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 2H), 4.09 (t, *J* = 6.0 Hz, 2H), 3.90 (qd, *J* = 7.2, 0.8 Hz, 2H), 3.77 (s, 3H), 2.33 (dd, *J* = 9.0, 7.0 Hz, 1H), 2.05 (s, 3H), 2.02-1.97 (comp. m, 1H), 1.80-1.71 (comp. m, 3H), 1.50-1.43 (comp. m, 2H), 1.02 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 171.8, 171.2, 170.8, 158.42, 158.36, 132.3, 130.2, 128.5, 127.4, 114.0, 113.5, 64.13, 64.11, 60.6, 60.3, 55.4, 55.3, 32.6, 31.1, 30.5, 29.5, 28.9, 28.6, 28.5, 28.2, 25.1, 23.4, 21.1, 14.4, 14.2.

IR (ATR, neat): 2963, 1729, 1517, 1454, 1368, 1244, 1174, 1033, 830 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M+H)^+$ $[C_{18}H_{24}O_5 + H]^+$: 321.1697, found 321.1693.



Cyclopropane 2-42. Prepared according to the *General Procedure* using 21.2 mg *E*-alkene **2-42sm** (0.103 mmol), 15.2 mg ethyl diazoacetate (85% wt. solution in CH_2Cl_2, 0.113 mmol), 1.3 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (1.03 μmol), and 1.0 mL DCE. The reaction mixture was irradiated for 42 h. The crude product was purified by flash chromatography (100% hexanes → 7:1:1:1 hexanes/EtOAc/Et_2O/CH_2Cl_2 eluent) to afford cyclopropane **2-42** (11.7 mg, 39% yield) as a pale yellow oil. Diastereomeric ratio (1.1:1 anti/syn) was determined by ^{1}H NMR analysis of the crude mixture.

TLC: R_f = 0.51 in 7:1:1:1 hexanes/EtOAc/Et_2O/CH_2Cl_2, visualized by UV.

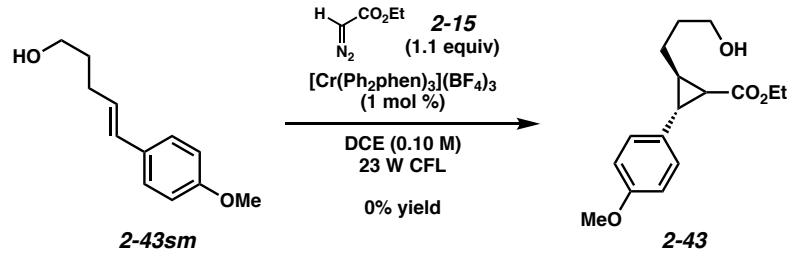
^{1}H NMR (400 MHz; $CDCl_3$): Major (anti): δ 7.02 (d, *J* = 8.4 Hz, 2H), 6.81 (d, *J* = 8.4 Hz, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.78 (s, 3H), 3.44 (t, *J* = 6.2 Hz, 2H), 3.33 (s, 3H), 2.41 (dd, *J* = 6.2, 5.2 Hz, 1H), 1.95 (dd, *J* = 9.2, 5.2 Hz, 1H), 1.83-1.57 (comp. m, 5H), 1.28 (t, *J* = 7.2 Hz, 3H).

Minor (syn): δ 7.15 (d, *J* = 8.4 Hz, 2H), 6.80 (d, *J* = 8.4 Hz, 2H), 3.90 (qd, *J* = 7.2, 1.2 Hz, 2H), 3.77 (s, 3H), 3.39 (t, *J*= 6.0 Hz, 2H), 3.32 (s, 3H), 2.33 (dd, *J* = 9.2, 7.2 Hz, 1H), 2.00-1.94 (comp. m, 1H), 1.83-1.57 (comp. m, 4H), 1.52-1.43 (comp. m, 1H), 1.03 (t, *J* = 7.2 Hz, 3H).

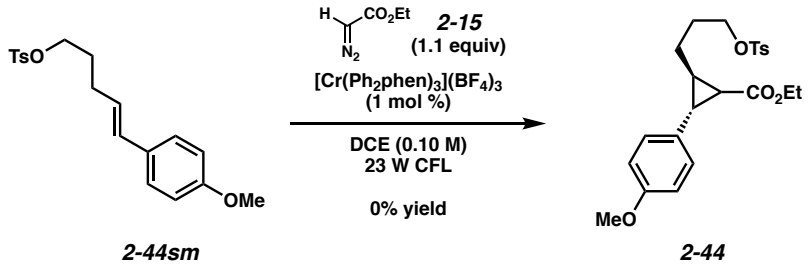
^{13}C NMR (100 MHz; $CDCl_3$): δ 172.0, 171.1, 158.4, 143.5, 132.6, 130.3, 128.8, 127.4, 114.0, 113.5, 72.5, 72.2, 60.6, 60.3, 58.74, 58.68, 55.5, 55.3, 32.7, 31.2, 30.9, 29.59, 29.57, 29.2, 28.9, 28.6, 25.4, 23.6, 14.5, 14.3.

IR (ATR, neat): 2934, 1724, 1516, 1449, 1377, 1248, 1175, 1117, 1036 cm^{-1}.

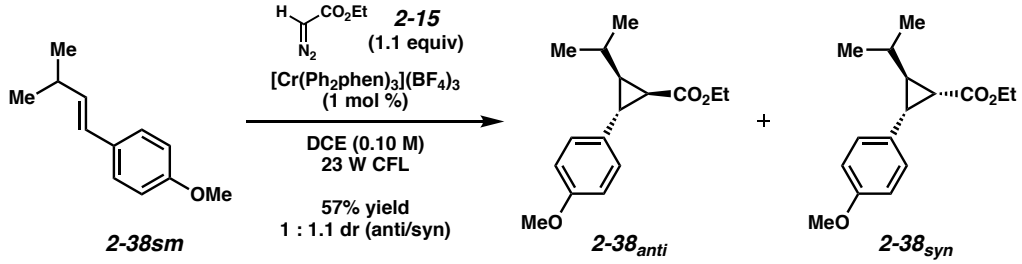
HRMS (ESI+): *m/z* calc'd for $(M+H)^+$ $[C_{17}H_{24}O_4 + H]^+$: 293.1747, found 293.1746.



Cyclopropane 2-43. Reaction performed according to the *General Procedure* using 19.2 mg of *E*-alkene **2-43sm** (0.0999 mmol), 14.7 mg ethyl diazoacetate (85% wt. solution in CH_2Cl_2, 0.113 mmol), 1.3 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (0.999 μmol), and 1.0 mL DCE. The reaction mixture was irradiated for 40 h. Cyclopropane **2-43** was not observed.



Cyclopropane 2-44. Reaction performed according to the *General Procedure* using 35.6 mg of *E*-alkene **2-44sm** (0.103 mmol), 15.2 mg ethyl diazoacetate (85% wt. solution in CH_2Cl_2, 0.113 mmol), 1.3 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (1.03 μmol), and 1.0 mL DCE. The reaction mixture was irradiated for 43 h. Cyclopropane **2-44** was not observed. Instead, a product resulting from a tosyloxy transfer to ethyl diazoacetate[70] was observed.



Cyclopropane 2-38. Prepared according to the *General Procedure* using 18.8 mg *E*-alkene **2-38sm** (0.107 mmol), 15.8 mg ethyl diazoacetate (85% wt. solution in CH_2Cl_2, 0.118 mmol), 1.4

mg $[Cr(Ph_2phen)_3](BF_4)_3$ (0.999 μmol), and 1.1 mL DCE. The reaction mixture was irradiated for 17 h. The crude product was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford *trans*-cyclopropane **2-38** (15.9 mg, 57% yield) as a colorless oil. Diastereomeric ratio (1:1.1 anti/syn) was determined by ^1H NMR analysis of the crude mixture.

TLC: R_f = 0.29 in 9:1 hexanes/Et_2O, visualized by UV. Stained blue by *p*-anisaldehyde.

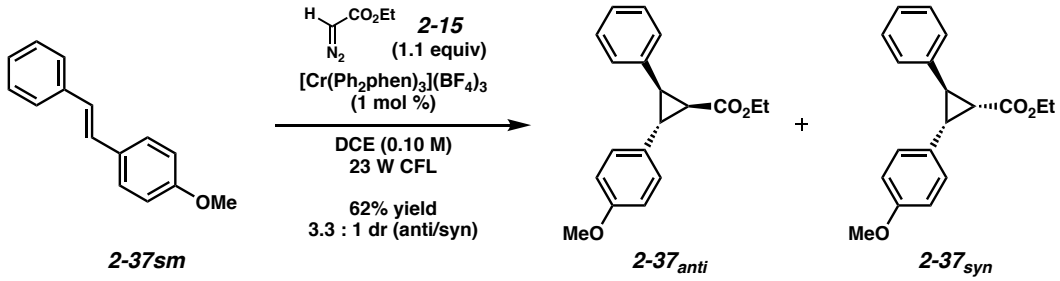
^1H NMR (400 MHz; $CDCl_3$): Major (syn): δ 7.03 (d, *J* = 8.4 Hz, 2H), 6.81 (d, *J* = 8.4 Hz, 2H), 4.17 (qd, *J* = 5.4, 7.0 Hz, 2H), 3.77 (s, 3H), 2.36 (app. t, *J* = 8.0 Hz, 1H), 1.88-1.80 (comp. m, 3H), 1.28 (t, *J* = 7.0 Hz, 3H), 1.09 (d, *J* = 6.4 Hz, 6H).

Minor (anti): δ 7.15 (d, *J* = 8.6 Hz, 2H), 6.80 (d, *J* = 8.6 Hz, 2H), 3.90 (q, *J* = 7.2 Hz, 2H), 3.78 (s, 3H), 2.46 (dd, *J* = 6.4, 5.1 Hz, 1H), 1.95 (dd, *J* = 9.4, 5.1 Hz, 1H), 1.34-1.20 (comp. m, 2H), 1.06 (d, *J* = 6.8 Hz, 3H), 1.02 (t, *J* = 7.2 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (125 MHz; $CDCl_3$): δ 172.2, 171.3, 158.4, 158.3, 132.8, 130.3, 129.1, 127.6, 114.0, 113.5, 60.6, 60.2, 55.5, 55.3, 39.3, 33.7, 32.2, 31.8, 30.9, 28.7, 28.0, 26.8, 22.7, 22.3, 21.9, 21.7, 14.5, 14.3.

IR (ATR, neat): 2959, 1731, 1518, 1247, 1178, 1159, 1038 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + Na)^+$ $[C_{16}H_{22}O_3 + Na]^+$: 285.1461, found 285.1461.



Cyclopropane 2-37. Prepared according to the *General Procedure* using 20.8 mg *E*-alkene **2-37sm** (0.0989 mmol), 14.6 mg ethyl diazoacetate (85% wt. solution in CH_2Cl_2, 0.109 mmol), 1.3 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (0.989 μmol), and 1.0 mL DCE. The reaction mixture was irradiated for

72 h. The crude product was purified by flash chromatography (100% hexanes → 9:1 hexanes/EtOAc eluent) to afford cyclopropane **2-37** (18.2 mg, 62% yield) as a colorless oil. Diastereomeric ratio (3.3:1 anti/syn) was determined by ^{1}H NMR analysis of the crude mixture.

TLC: R_f = 0.21 in 9:1 hexanes/Et_2O, visualized by UV.

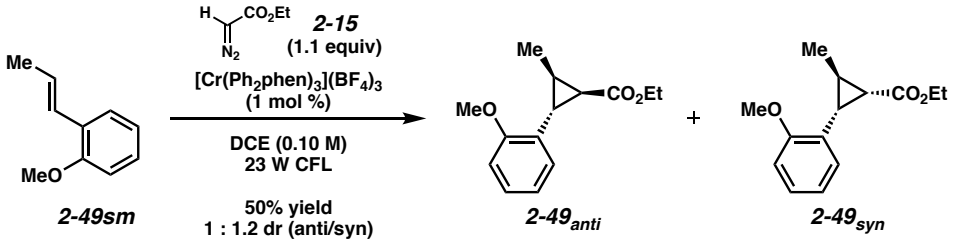
^{1}H NMR (400 MHz; $CDCl_3$): Major (anti): δ 7.38-6.83 (comp. m, 9H), 4.00-3.90 (comp. m, 2H), 3.80 (s, 3H), 3.18 (dd, *J* = 7.2, 5.2 Hz, 1H), 2.88 (dd, *J* = 7.2, 5.2 Hz, 1H), 2.39-2.32 (comp. m, 1H), 1.10-1.02 (comp. m, 3H).

Minor (syn): δ 7.85-6.83 (comp. m, 9H), 4.00-3.90 (comp. m. 2H), 3.79 (s, 3H), 3.19 (dd, *J* = 7.2, 5.2 Hz, 1H), 2.88 (dd, *J* = 7.2, 5.2 Hz, 1H), 2.39-2.32 (comp. m, 1H), 1.10-1.02 (comp. m, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 170.3, 158.6, 143.5, 136.4, 132.7, 131.7, 130.3, 129.3, 128.7, 128.3, 128.2, 128.0, 127.0, 126.7, 114.6, 114.2, 113.7, 113.6, 60.60, 60.56, 55.5, 55.3, 34.3, 34.0, 31.4, 31.2, 29.6, 28.8, 14.3, 14.2.

IR (ATR, neat): 2980, 1724, 1516, 1248, 1177, 1036, 827, 696 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M+H)^+$ $[C_{19}H_{20}O_3 + H]^+$: 297.1485, found 297.1482.



Cyclopropane 2-49. Prepared according to the *General Procedure* using 16.5 mg *E*-alkene **2-49sm** (0.111 mmol), 16.4 mg ethyl diazoacetate (85% wt. solution in CH_2Cl_2, 0.122 mmol), 1.5 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (1.11 μmol), and 1.10 mL DCE. The reaction mixture was irradiated for 27 h. The crude product was purified by flash chromatography (100% hexanes → 3:1 hexanes/Et_2O eluent) to afford cyclopropane **2-49** (18.2 mg, 50% yield) as a colorless oil. Diastereomeric ratio (1:1.2 anti/syn) was determined by ^{1}H NMR analysis of the crude mixture.

TLC: R_f = 0.55 in 3:1 hexanes/Et_2O, visualized by UV.

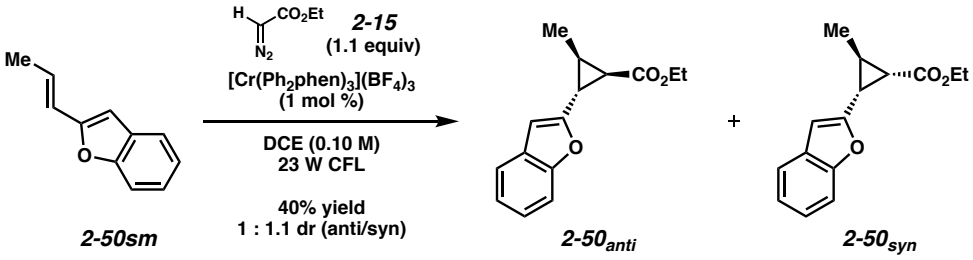
^{1}H NMR (400 MHz; $CDCl_3$): Major (syn): δ 7.21-7.17 (comp. m, 2H), 6.88 (app. td, *J* = 7.6, 2.4 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 3.88 (q, *J* = 7.2 Hz, 2H), 3.80 (s, 3H), 2.29 (dd, *J* = 9.2, 7.2 Hz, 1H), 2.00-1.92 (comp. m, 1H), 1.84 (dd, *J* = 9.2, 5.2 Hz, 1H), 1.28 (d, *J* = 6.0 Hz, 3H), 1.00 (t, *J* = 7.2 Hz, 3H).

Minor (anti): δ 7.17 (ddd, *J* = 8.4, 6.8, 2.6 Hz, 1H), 6.90-6.83 (comp. m, 3H), 4.18 (m, 2H), 3.83 (s, 3H), 2.63 (dd, *J* = 6.8, 5.2 Hz, 1H), 1.97 (dd, *J* = 9.2, 5.2 Hz, 1H), 1.67-1.61 (comp. m, 1H), 1.36 (d, *J* = 6.0 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 172.3, 171.6, 158.7, 130.3, 129.0, 127.9, 127.4, 126.0, 125.5, 120.5, 120.1, 110.5, 109.9, 60.4, 59.9, 55.6, 55.4, 31.7, 27.4, 24.5, 18.0, 14.6, 14.2, 12.3.

IR (ATR, neat): 2978, 1724, 1497, 1248, 1180, 1163, 1030, 750 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M+H)^+$ $[C_{14}H_{18}O_3 + H]^+$: 235.1329, found 235.1330.



Cyclopropane 2-50. Prepared according to the *General Procedure* using 17.3 mg alkene **2-50sm** (0.109 mmol, 9:1 *E/Z* mixture), 16.1 mg ethyl diazoacetate (85% wt. solution in CH_2Cl_2, 0.120 mmol), 1.4 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (1.09 μmol), and 1.1 mL DCE. The reaction mixture was irradiated for 36 h. The crude product was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford *trans*-cyclopropane **2-50** (10.7 mg, 40% yield) as a colorless oil. Diastereomeric ratio (1:1.1 anti/syn) was determined by ^{1}H NMR analysis of the crude mixture.

TLC: R_f = 0.47 in 9:1 hexanes/EtOAc, visualized by UV. Stained pink by *p*-anisaldehyde.

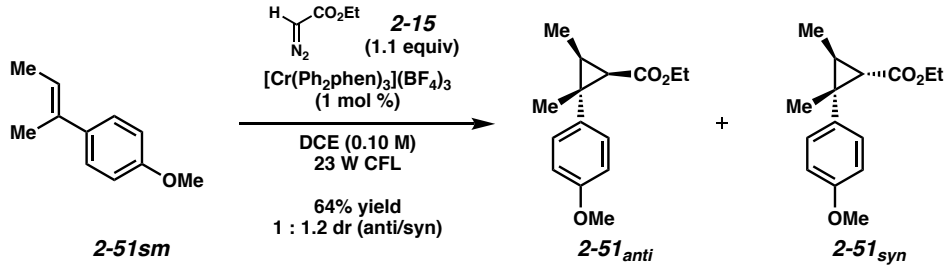
^{1}H NMR (400 MHz; $CDCl_3$): Major (syn): δ 7.48-7.44 (m, 1H), 7.39-7.34 (m, 1H) 7.21-7.15 (m, 2H), 6.50 (s, 1H), 4.18 (dq, *J* = 7.2, 5.2 Hz, 2H), 2.34 (dd, *J* = 8.6, 6.6 Hz, 1H), 2.12 (app. quintet, *J* = 6.0 Hz, 1H), 1.92-1.89 (m, 1H), 1.31 (d, *J* = 6.4 Hz, 3H), 1.03 (t, *J* = 7.2 Hz, 3H).

Minor (anti): δ 7.48-7.44 (m, 1H), 7.39-7.34 (m, 2H), 7.21-7.15 (m, 2H), 6.44 (s, 1H), 3.95 (dq, *J* = 7.2, 3.6 Hz, 2H), 2.53 (dd, *J* = 6.2, 5.0 Hz, 1H), 2.28 (dd, *J* = 9.6, 5.0 Hz, 1H), 1.96-1.92 (m, 1H), 1.36 (d, *J* = 6.4 Hz, 3H), 1.29 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz; $CDCl_3$): δ 171.1, 170.3, 156.8, 154.7, 154.5, 154.4, 128.9, 123.6, 123.5, 122.8, 122.6, 120.7, 120.3, 111.0, 110.83, 110.81, 104.3, 102.0, 60.9, 60.6, 29.9, 27.8, 26.5, 25.7, 23.6, 20.6, 17.5, 14.5, 14.2, 11.7.

IR (ATR, neat): 2961, 1728, 1454, 1257, 1184, 750 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + Na)^+$ $[C_{15}H_{16}O_3 + Na]^+$: 267.0992, found 267.0993.



Cyclopropane 2-51. Prepared according to the *General Procedure* using 16.2 mg (*E*)-alkene **2-51sm** (0.0999 mmol), 14.7 mg ethyl diazoacetate (85% wt. solution in CH_2Cl_2, 0.110 mmol), 1.3 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (0.999 μmol), and 1.0 mL DCE. The reaction mixture was irradiated for 14 h. The crude product was purified by flash chromatography (100% hexanes → 9:1 hexanes/EtOAc eluent) to afford *trans*-cyclopropane **2-51** (15.9 mg, 64% yield) as a colorless oil. Diastereomeric ratio (1:1.2 anti/syn) was determined by ^{1}H NMR analysis of the crude mixture.

TLC: R_f = 0.41 in 9:1 hexanes/EtOAc, visualized by UV.

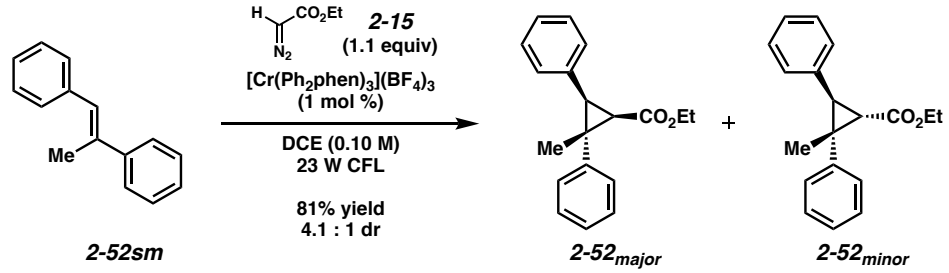
^{1}H NMR (400 MHz; $CDCl_3$): Major (syn): δ 7.14 (d, *J* = 8.6 Hz, 2H), 6.80 (d, *J* = 8.6 Hz, 2H), 3.91-3.84 (m, 2H), 3.77 (s, 3H), 2.05 (app. quintet, *J* = 6.3 Hz, 1H), 1.49 (d, *J* = 5.6 Hz, 1H), 1.41 (s, 3H), 1.28 (d, *J* = 6.3 Hz, 3H), 1.02 (t, *J* = 7.0 Hz, 3H).

Minor (anti): δ 7.20 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 4.18-4.12 (dq, *J* = 7.2, 1.2 Hz, 2H), 3.79 (s, 3H), 1.87 (d, *J* = 8.8 Hz, 1H), 1.71-1.63 (comp. m, 1H), 1.48 (s, 3H), 1.38 (d, *J* = 6.8 Hz, 3H), 1.29 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 171.82, 171.77, 158.2, 158.1, 140.5, 136.2, 129.8, 128.6, 113.9, 113.7, 60.2, 60.0, 55.4, 55.3, 36.1, 35.5, 33.2, 29.0, 26.4, 24.7, 23.0, 15.7, 14.6, 14.3, 12.8, 8.4.

IR (ATR, neat): 2976, 1724, 1516, 1244, 1171, 1036, 831 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{15}H_{20}O_3 + H]^+$: 249.1485, found 249.1488.



Cyclopropane 2-52. Prepared according to the *General Procedure* using 19.5 mg *E*-alkene **2-52sm** (0.100 mmol), 14.8 mg ethyl diazoacetate (85% wt. solution in CH_2Cl_2, 0.110 mmol), 1.3 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (1.00 μmol), and 1.0 mL DCE. The reaction mixture was irradiated for 14 h. The crude product was purified by flash chromatography (100% petroleum ether → 9:1 petroleum ether/EtOAc eluent) to afford cyclopropane **2-52** (22.9 mg, 81% yield) as a colorless oil. Diastereomeric ratio (4.1:1 major/minor) was determined by ^{1}H NMR analysis of the crude mixture.

TLC: R_f = 0.47 in 9:1 hexanes/Et_2O, visualized by UV.

^{1}H NMR (400 MHz; $CDCl_3$): Major: δ 7.43-7.17 (m, 10H), 4.19-4.10 (m, 2H), 2.97 (d, *J* = 9.6

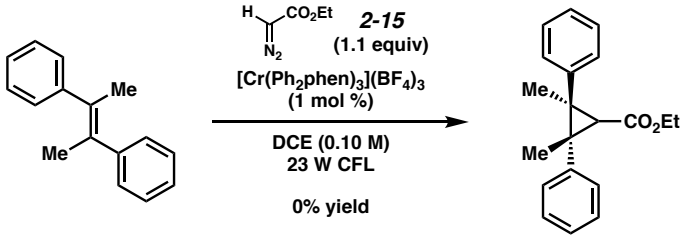
Hz, 1H), 2.37 (d, J = 9.6 Hz, 1H), 1.54 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H).

Minor: δ 7.43-7.17 (m, 10H), 3.98-3.88 (m, 2H), 3.40 (d, J = 5.8 Hz, 1H), 2.33 (d, J = 5.8 Hz, 1H), 1.20 (s, 3H), 1.01 (t, J = 7.2 Hz, 3H).

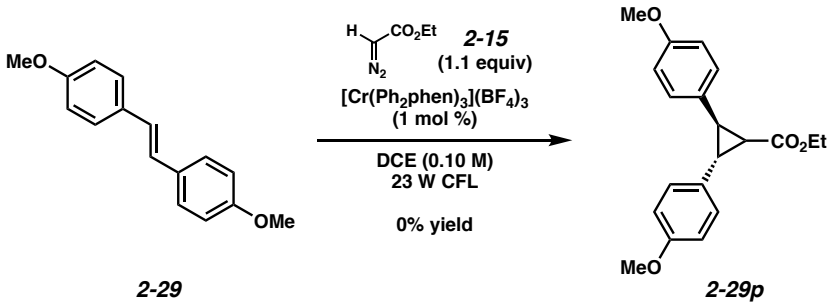
^{13}C NMR (100 MHz; $CDCl_3$): δ 170.6, 147.6, 136.8, 135.1, 130.5, 129.2, 128.8, 128.5, 128.2, 127.8, 126.8, 60.5, 60.3, 38.3, 35.6, 35.1, 35.0, 33.0, 30.4, 24.0, 18.4, 14.5, 14.2.

IR (ATR, neat): 2980, 1732, 1445, 1152, 1053, 764, 698 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{19}H_{20}O_2 + H]^+$: 281.1536, found 281.1537.

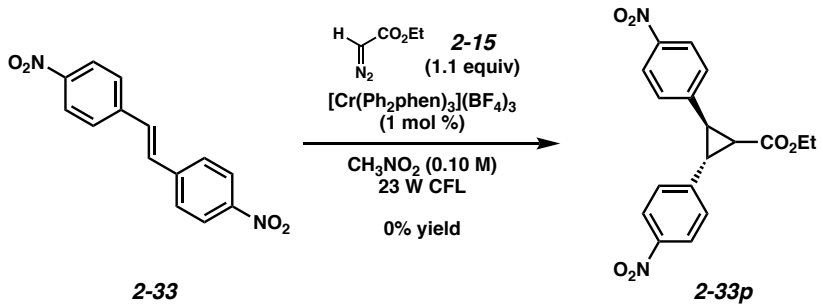


Cyclopropane 2-53. Reaction performed according to the *General Procedure* using 21.5 mg of alkene **2-53sm** (0.103 mmol), 15.2 mg ethyl diazoacetate (85% wt. solution in CH_2Cl_2, 0.114 mmol), 1.3 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (1.03 μmol), and 1.0 mL DCE. The reaction mixture was irradiated for 72 h. Cyclopropane **2-53** was not observed.



Cyclopropane 2-29p. Reaction performed according to the *General Procedure* using 24.0 mg of *E*-alkene **2-29** (0.0999 mmol), 14.7 mg ethyl diazoacetate (85% wt. solution in CH_2Cl_2, 0.113

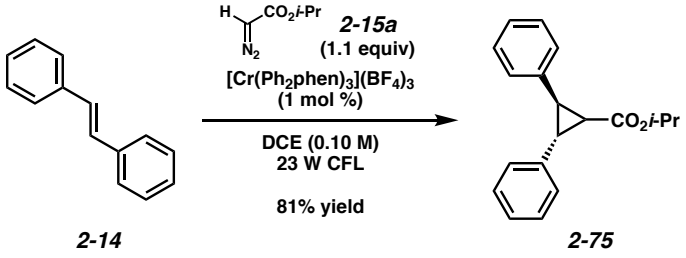
mmol), 1.3 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (0.999 μmol), and 1.0 mL DCE. The reaction mixture was irradiated for 53 h. Cyclopropane **2-29p** was not observed.



2-33 *2-33p*

Cyclopropane 2-33p. Reaction performed according to the *General Procedure* using 27.0 mg of *E*-alkene **2-33** (0.0999 mmol), 14.7 mg ethyl diazoacetate (85% wt. solution in CH_2Cl_2, 0.113 mmol), 1.3 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (0.999 μmol), and 1.0 mL CH_3NO_2. The reaction mixture was irradiated for 24 h. Cyclopropane **2-33p** was not observed.

2.13.4 Diazo Scope



2-14 *2-75*

Cyclopropane 2-75. Prepared according to the *General Procedure* using 18.1 mg *trans*-stilbene (0.100 mmol), 14.8 mg diazoacetate **2-15a** (0.110 mmol), 1.3 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (1.00 μmol), and 1.0 mL DCE. The reaction mixture was irradiated for 24 h. The crude product was purified by flash chromatography (100% hexanes → 9:1 hexanes/acetone eluent) to afford cyclopropane **2-75** (22.7 mg, 81% yield) as a colorless oil.

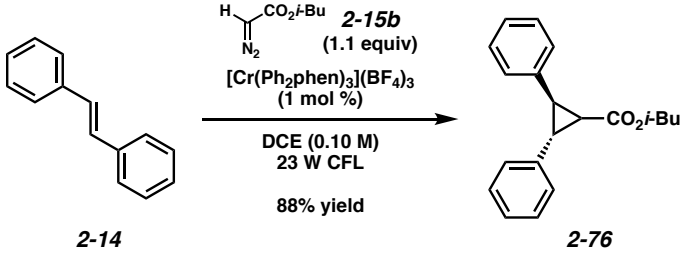
TLC: R_f = 0.52 in 9:1 hexanes/acetone, visualized by UV.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.35-7.21 (m, 10H), 4.84-4.75 (app. septet, *J* = 6.2 Hz, 1H), 3.21 (dd, *J* = 6.8, 5.2 Hz, 1H), 2.92 (dd, *J* = 9.6, 6.8 Hz, 1H), 2.40 (dd, *J* = 9.6, 5.2 Hz, 1H), 1.04 (d, *J* = 6.4 Hz, 3H), 0.97 (d, *J* = 6.0 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 169.6, 139.8, 136.3, 129.3, 128.7, 128.2, 127.0, 126.8, 68.0, 34.5, 31.6, 29.0, 22.0, 21.6.

IR (ATR, neat): 2978, 1721, 1179, 1105, 750, 696 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{19}H_{20}O_2 + H]^+$: 281.1536, found 281.1536.



Cyclopropane 2-76. Prepared according to the *General Procedure* using 18.1 mg *trans*-stilbene (0.100 mmol), 15.7 mg diazoacetate **2-15b** (0.110 mmol), 1.3 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (1.00 μmol), and 1.0 mL DCE. The reaction mixture was irradiated for 60 h. The crude product was purified by flash chromatography (100% hexanes → 19:1 hexanes/acetone eluent) to afford cyclopropane **2-76** (25.9 mg, 88% yield) as a colorless oil.

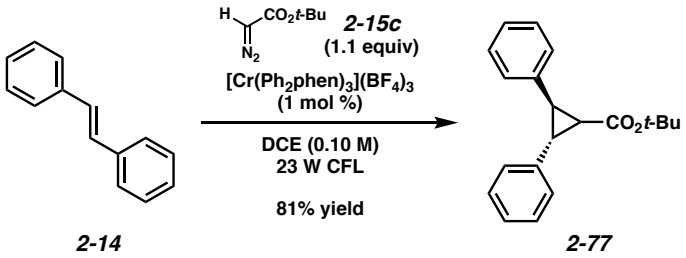
TLC: R_f = 0.28 in hexanes/Et_2O, visualized by UV.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.40-7.23 (m, 10H), 3.74-3.62 (m, 2H), 3.21 (dd, *J* = 7.0, 5.2 Hz, 1H), 2.94 (dd, *J* = 9.6, 7.0 Hz, 1H), 2.44 (dd, *J* = 9.6, 5.2 Hz, 1H), 1.71 (app. septet, *J* = 6.6 Hz, 1H), 0.79 (d, *J* = 6.4 Hz, 6H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 170.2, 139.8, 136.3, 129.3, 128.8, 128.3, 127.1, 126.82, 126.77, 70.9, 34.6, 31.5, 29.4, 27.7, 19.12, 19.10.

IR (ATR, neat): 2961, 1728, 1171, 752, 696 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{20}H_{22}O_2 + H]^+$: 295.1693, found 295.1693.



Cyclopropane 2-77. Prepared according to the *General Procedure* using 17.7 mg *trans*-stilbene (0.0982 mmol), 15.4 mg diazoacetate **2-15c** (0.108 mmol), 1.3 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (0.982 μmol), and 1.0 mL DCE. The reaction mixture was irradiated for 48 h. The crude product was purified by flash chromatography (100% hexanes → 19:1 hexanes/acetone eluent) to afford *trans*-cyclopropane **2-77** (20.2 mg, 70% yield) as a colorless oil.

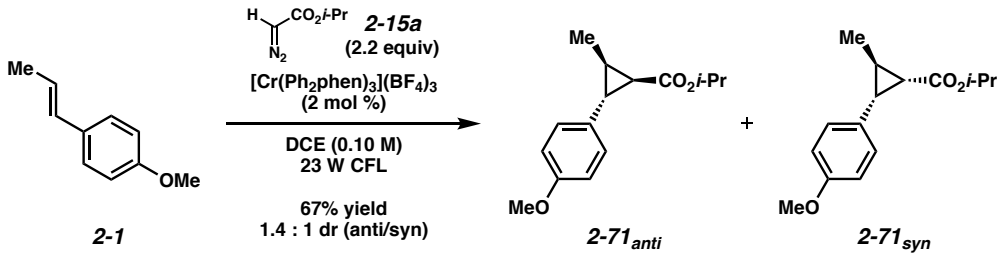
TLC: R_f = 0.32 in 19:1 hexanes/acetone, visualized by UV.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.37-7.23 (m, 10H), 3.15 (dd, *J* = 6.8, 5.2 Hz, 1H), 2.88 (dd, *J* = 9.6, 6.8 Hz, 1H), 2.35 (dd, *J* = 9.6, 5.2 Hz, 1H), 1.21 (s, 9H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 169.2, 140.1, 136.5, 129.5, 128.7, 128.1, 126.9, 126.8, 126.7, 80.7, 34.4, 32.4, 28.8, 28.0.

IR (ATR, neat): 2976, 1724, 1497, 1366, 1144, 741, 696 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{20}H_{22}O_2 + H]^+$: 295.1693, found 295.1693.



Cyclopropane 2-71. Prepared with a modification to the *General Procedure* using 15.4 mg *trans*-anethole (0.104 mmol), 14.6 mg diazoacetate **2-15a** (0.114 mmol), 1.4 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (1.04 μmol), and 1.0 mL DCE. The reaction mixture was irradiated for 36 h. Then, an additional

1.3 mg (1.04 μmol) of catalyst and 14.6 mg (0.114 mmol) of diazoacetate were added to the mixture, and the reaction mixture was irradiated for another 33 h. The crude product was purified by flash chromatography (100% hexanes → 9:1 hexanes/EtOAc eluent) to afford cyclopropane **2-71** (17.3 mg, 67% yield) as a colorless oil. Diastereomeric ratio (1.4:1 anti/syn) was determined by ^{1}H NMR analysis of the crude mixture.

TLC: R_f = 0.41 in 9:1 hexanes/EtOAc, visualized by UV.

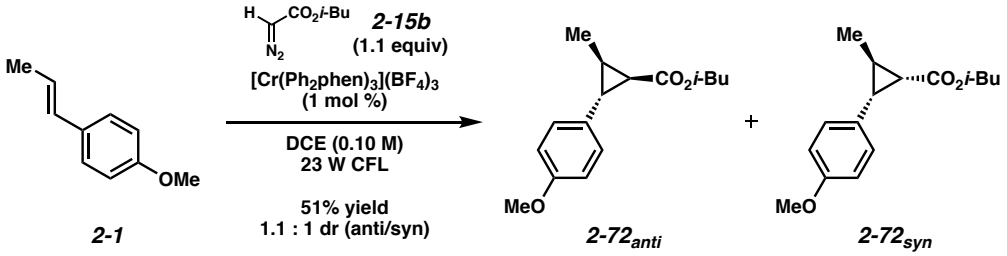
^{1}H NMR (400 MHz; $CDCl_3$): Major (anti): δ 7.01 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 5.04 (app. septet, *J* = 6.4 Hz, 1H), 3.78 (s, 3H), 2.35 (dd, *J* = 6.2, 5.0 Hz, 1H), 1.91 (dd, *J* = 9.2, 5.0 Hz, 1H), 1.62-1.58 (comp. m, 1H), 1.33 (d, *J* = 6.4 Hz, 3H), 1.25 (d, *J* = 6.4 Hz, 6H).

Minor (syn): δ 7.15 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 4.74 (app. septet, *J* = 6.1 Hz, 1H), 3.77 (s, 3H), 2.28 (dd, *J* = 9.2, 6.8 Hz, 1H), 2.01 (app. sextet, *J* = 6.2 Hz, 1H), 1.74 (dd, *J* = 9.2, 5.2 Hz, 1H), 1.25 (d, *J* = 6.2 Hz, 3H), 1.00 (d, *J* = 6.1 Hz, 3H), 0.97 (d, *J* = 6.1 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 171.4, 158.2, 136.6, 132.9, 130.3, 129.5, 129.0, 127.7, 127.2, 114.0, 113.4, 67.9, 67.4, 55.5, 55.3, 33.6, 31.6, 30.3, 29.6, 25.3, 22.2, 22.1, 21.6, 19.6, 17.9, 12.1.

IR (ATR, neat): 2980, 1721, 1516, 1248, 1175, 1146, 1109, 1038 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{15}H_{20}O_3 + H]^+$: 249.1485, found 249.1486.



Cyclopropane 2-72. Prepared according to the *General Procedure* using 15.5 mg *trans*-anethole (0.105 mmol), 16.4 mg diazoacetate **2-15b** (0.115 mmol), 1.4 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (1.05 μmol), and 1.1 mL DCE. The reaction mixture was irradiated for 60 h. The crude product was

purified by flash chromatography (100% hexanes → 9:1 hexanes/EtOAc eluent) to afford *trans*-cyclopropane **2-72** (14.0 mg, 51% yield) as a colorless oil. Diastereomeric ratio (1.1:1 anti/syn) was determined by ^{1}H NMR analysis of the crude mixture.

TLC: R_f = 0.33 in 9:1 hexanes/Et_2O, visualized by UV.

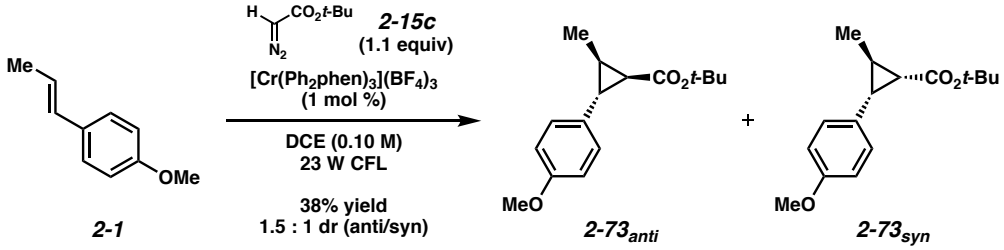
^{1}H NMR (400 MHz; $CDCl_3$): Major (anti): δ 7.01 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 3.94-3.87 (m, 2H), 3.78 (s, 3H), 2.37 (dd, *J* = 6.0, 5.2 Hz, 1H), 1.98-1.91 (comp. m, 2H), 1.64-1.60 (comp. m, 1H), 1.34 (d, *J* = 6.4 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 6H).

Minor (syn): δ 7.15 (d, *J*= 8.8 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 3.77 (m, 3H), 3.68-3.56 (m, 2H), 2.29 (dd, *J* = 9.2, 7.0 Hz, 1H), 2.03-1.99 (m, 1H), 1.79 (dd, *J* = 9.2, 5.2 Hz, 1H), 1.72-1.65 (m, 1H), 1.26 (d, *J* = 6.0 Hz, 3H), 0.77 (d, *J* = 6.4 Hz, 6H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 172.0, 171.3, 158.4, 158.3, 132.8, 130.2, 128.9, 127.3, 125.4, 114.0, 113.5, 70.8, 70.5, 55.5, 55.3, 33.7, 31.9, 30.1, 29.3, 27.9, 27.7, 25.3, 20.0, 19.3, 19.13, 19.12, 17.9, 12.2.

IR (ATR, neat): 2959, 1724, 1516, 1285, 1248, 1171, 1038 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{16}H_{22}O_3 + H]^+$: 263.1642, found 263.1638.



Cyclopropane 2-73. Prepared according to the *General Procedure* using 14.8 mg *trans*-anethole (0.0999 mmol), 15.6 mg diazoacetate **2-15c** (0.110 mmol) 1.3 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (0.999 μmol), and 1.0 mL DCE. The reaction mixture was irradiated for 69 h. The crude product was purified by flash chromatography (100% hexanes → 9:1 hexanes/EtOAc eluent) to afford

cyclopropane **2-73** (10.0 mg, 38% yield) as a colorless oil. Diastereomeric ratio (1.5:1 anti/syn) was determined by ^{1}H NMR analysis of the crude mixture.

TLC: R_f = 0.52 in 9:1 hexanes/EtOAc, visualized by UV.

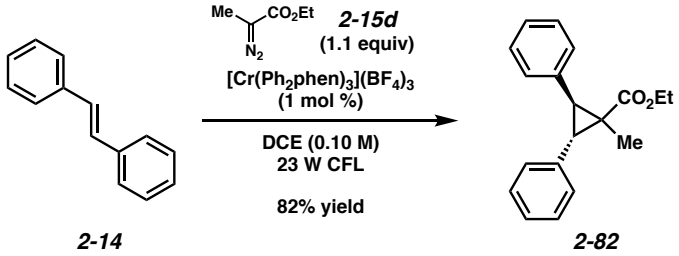
^{1}H NMR (400 MHz; $CDCl_3$): Major (anti): δ 7.00 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 3.78 (s, 3H), 2.29 (dd, *J* = 6.0, 5.3 Hz, 1H), 1.87 (dd, *J* = 9.4, 5.3 Hz, 1H), 1.56-1.50 (comp. m, 1H), 1.47 (s, 9H), 1.31 (d, *J* = 6.4 Hz, 3H).

Minor (syn): δ 7.15 (d, *J* = 8.2 Hz, 2H), 6.79 (d, *J* = 8.2 Hz, 2H), 3.77 (s, 3H), 2.24 (dd, *J* = 9.2, 6.8 Hz, 1H), 1.94 (app. sextet, *J* = 6.0 Hz, 1H), 1.68 (dd, *J* = 9.2, 5.0 Hz, 1H), 1.23 (d, *J* = 6.0 Hz, 3H), 1.18 (s, 9H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 171.1, 158.3, 158.2, 133.1, 130.4, 129.3, 127.2, 114.0, 113.4, 80.6, 80.0, 55.5, 55.4, 33.3, 31.2, 31.1, 30.4, 28.4, 28.0, 25.2, 19.2, 17.8, 12.1.

IR (ATR, neat): 2976, 1717, 1516, 1366, 1248, 1152, 1038 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + Na)^+$ $[C_{16}H_{22}O_3 + Na]^+$: 285.1461, found 285.1463.



Cyclopropane 2-82. Prepared with a slight modification to the *General Procedure* using 17.9 mg *trans*-stilbene (0.0993 mmol), 14.0 mg diazoacetate **2-15d** (0.109 mmol), 1.3 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (0.993 μmol), and 1.0 mL DCE. The reaction mixture was irradiated for 48 h. The crude product was purified by flash chromatography (100% hexanes → 19:1 hexanes/EtOAc as eluent) to afford cyclopropane **2-82** (22.8 mg, 82% yield) as a colorless oil.

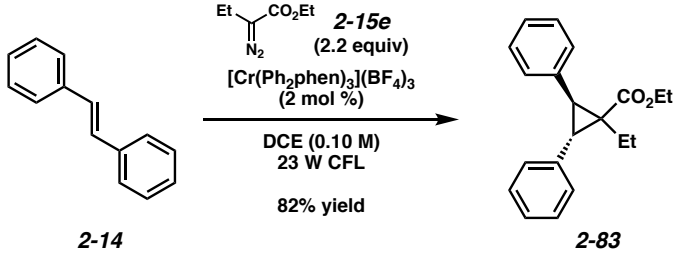
TLC: R_f = 0.37 in 19:1 hexanes/EtOAc, visualized by UV.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.36-7.22 (m, 10H), 3.87-3.84 (m, 2H), 3.60 (d, *J* = 7.4 Hz, 1H), 2.78 (d, *J* = 7.4 Hz, 1H), 1.21 (s, 3H), 0.88 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 172.3, 137.3, 137.2, 129.4, 129.2, 128.5, 128.1, 127.0, 126.8, 60.6, 37.3, 33.9, 33.7, 16.5, 14.0.

IR (ATR, neat): 2981, 1717, 1498, 1447, 1260, 1243, 1145, 1029, 749, 697 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M+H)^+$ $[C_{19}H_{20}O_2 + H]^+$: 281.1536, found 281.1522**.**



Cyclopropane 2-83. Prepared with a modification to the *General Procedure* using 17.8 mg *trans*-stilbene (0.0988 mmol), 15.5 mg diazoacetate **2-15e** (0.109 mmol), 1.3 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (0.988 μmol), and 1.0 mL DCE. The reaction mixture was irradiated for 48 h, at which point an additional 1.3 mg (0.988 μmol) of catalyst and 15.5 mg (0.109 mmol) of diazoacetate were added, and the reaction mixture was irradiated for another 24 h. The crude product was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford cyclopropane **2-83** (23.8 mg, 82% yield) as a colorless oil.

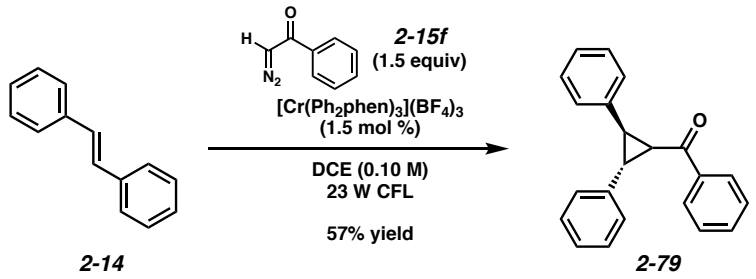
TLC: R_f = 0.52 in 9:1 hexanes/Et_2O, visualized by UV.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.34-7.21 (m, 10H), 3.91-3.83 (m, 2H), 3.64 (d, *J* = 7.6 Hz, 1H), 2.84 (d, *J* = 7.6 Hz, 1H), 1.66 (dq, *J* = 14.4, 7.3 Hz, 1H), 1.43 (dq, *J* = 14.4, 7.1 Hz, 1H), 0.94-0.88 (m, 6H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 171.6, 137.3, 137.0, 129.4, 129.1, 128.4, 128.1, 126.9, 126.7, 60.4, 40.3, 35.6, 34.4, 23.5, 14.0, 12.0.

IR (ATR, neat): 2976, 1721, 1497 1246, 1148, 745, 696 cm^{-1}.

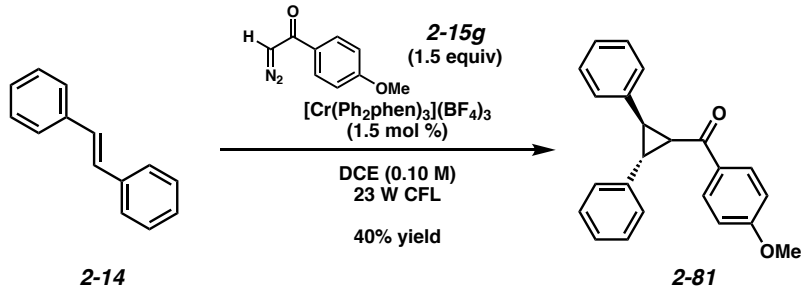
HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{20}H_{22}O_2 + H]^+$: 295.1693, found 295.1694.



Cyclopropane 2-79. Prepared according to the *General Procedure* using 18.0 mg *trans*-stilbene (0.0999 mmol), 16.0 mg diazoketone **2-15f** (0.150 mmol), 2.0 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (1.50 μmol), and 1.0 mL DCE. The reaction mixture was irradiated for 48 h. The crude product was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford *trans*-cyclopropane **2-79** (16.9 mg, 57% yield) as a white solid.

TLC: R_f = 0.36 in 9:1 hexanes/Et_2O, visualized by UV.

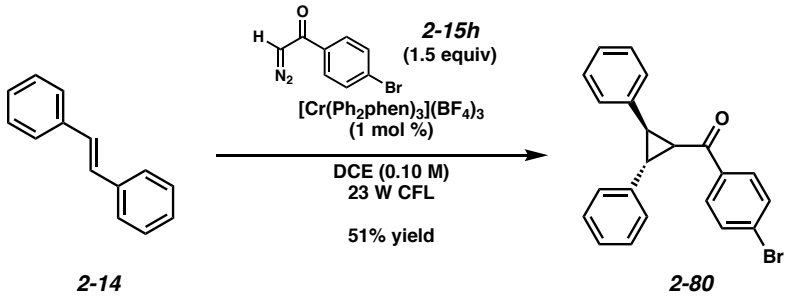
All spectroscopic data were in accordance with the published values.[71]



Cyclopropane 2-81. Prepared according to the *General Procedure* using 18.0 mg *trans*-stilbene (0.0999 mmol), 26.4 mg diazoketone **2-15g** (0.150 mmol), 1.3 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (0.999 μmol), and 1.0 mL DCE. The reaction mixture was irradiated for 48 h. The crude product was purified by flash chromatography (100% hexanes → 4:1 hexanes/Et_2O eluent) to afford *trans*-cyclopropane **2-81** (13.2 mg, 40% yield) as a white solid.

TLC: R_f = 0.26 in 4:1 hexanes/Et_2O, visualized by UV.

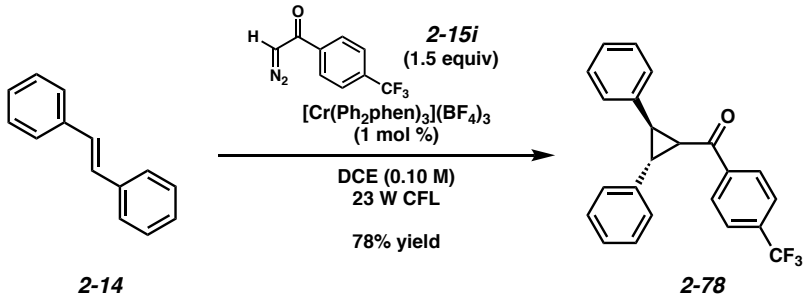
All spectroscopic data were in accordance with the published values.71



Cyclopropane 2-80. Prepared according to the *General Procedure* using 18.0 mg *trans*-stilbene (0.0999 mmol), 33.8 mg diazoketone **2-15h** (0.150 mmol), 1.3 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (0.999 μmol), and 1.0 mL DCE. The reaction mixture was irradiated for 48 h. The crude product was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford *trans*-cyclopropane **2-80** (19.1 mg, 51% yield) as a pale yellow solid.

TLC: R_f = 0.41 in 9:1 hexanes/Et_2O, visualized by UV.

All spectroscopic data were in accordance with the published values.71



Cyclopropane 2-78. Prepared according to the *General Procedure* using 18.1 mg *trans*-stilbene (0.100 mmol), 32.0 mg diazoketone **2-15i** (0.110 mmol), 1.3 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (1.00 μmol), and 1.0 mL DCE. The reaction mixture was irradiated for 13 h. The crude product was purified by flash chromatography (100% hexanes → 19:1 hexanes/EtOAc eluent) to afford *trans*-cyclopropane **2-78** (28.6 mg, 78% yield) as a colorless oil that solidified upon standing.

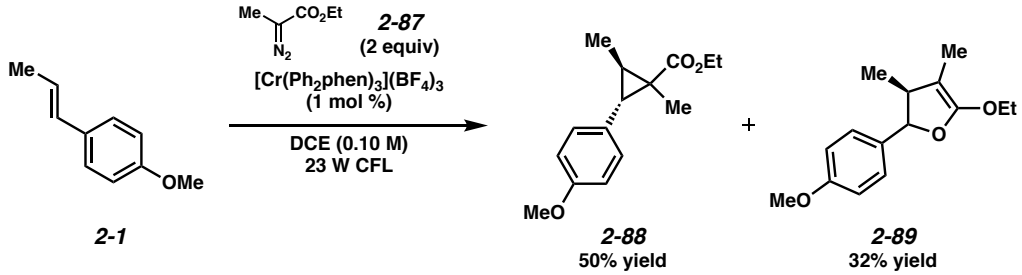
TLC: R_f = 0.35 in 19:1 hexanes/EtOAc, visualized by UV.

^{1}H NMR (400 MHz; $CDCl_3$): δ 8.04 (d, *J* = 8.3 Hz, 2H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.38-7.19 (comp. m, 10H), 3.66 (app. t, *J* = 6.2 Hz, 1H), 3.35 (app. d, *J* = 6.0 Hz, 2H).

^{13}C NMR (125 MHz; $CDCl_3$): δ 194.3, 141.1, 139.6, 135.2, 129.2, 128.8, 128.5, 128.4 127.3, 127.1, 127.0, 126.6, 125.8 (q, $J_{C\text{-}F}$ = 15 Hz), 125.7, 38.4, 36.9, 30.4.

IR (ATR, neat): 3054, 1577, 1324, 1170, 1128, 1067, 1016, 756, 696 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M+H)^+$ $[C_{23}H_{17}F_3O + H]^+$: 367.1304, found 367.1306**.**



Cyclopropane 2-88. Prepared according to the *General Procedure* using 14.7 mg *trans*-anethole (0.0992 mmol), 14.0 mg diazoacetate **2-87** (0.109 mmol), 1.3 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (0.992 μmol), and 1.0 mL DCE. The reaction mixture was irradiated for 48 h. The crude products were purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O → 9:1 hexanes/EtOAc eluent) to afford 12.3 mg of cyclopropane **2-88** (50% yield) and 7.8 mg of dihydrofuran **2-89** (32% yield). Diastereomeric ratio (1.1:1 anti/syn) was determined by ^{1}H NMR analysis of the crude mixture.

TLC: R_f = 0.43 in 9:1 hexanes/EtOAc, visualized by UV and stained purple with *p*-anisaldehyde.

^{1}H NMR (400 MHz; $CDCl_3$): <u>Major (anti):</u> δ 7.09 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.79 (s, 3H), 2.72 (d, *J* = 7.2 Hz, 1H), 2.21 (app. q, *J* = 6.4 Hz, 1H), 1.31 (d, *J* = 6.4 Hz, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 0.97 (s, 3H).

<u>Minor (syn):</u> δ 7.11 (d, *J* = 8.6 Hz, 2H), 6.77 (d, *J* = 8.6 Hz, 2H), 3.81-3.77 (comp m., 2H), 3.77 (s, 3H), 1.92 (d, *J* = 7.2 Hz, 1H), 1.46-1.40 (m, 1H), 1.43 (s, 3H), 1.26 (d, *J* = 6.4 Hz, 3H), 0.89 (t,

J = 7.0 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 174.0, 173.1, 158.3, 158.2, 130.2, 130.0, 129.8, 113.6, 113.3, 60.6, 60.2, 55.4, 40.7, 36.4, 31.7, 30.6, 28.3, 23.3, 16.2, 15.3, 14.5, 14.1, 13.4, 12.7.

IR (ATR, neat): 2975, 1719, 1515, 1474, 1247, 1174, 1158, 1033 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M+Na)^+$ $[C_{15}H_{20}O_3 + Na]^+$: 271.1305, found 271.1305.

Dihydrofuran 2-89.

Diastereomeric ratio (1.5:1 major/minor) was determined by ^{1}H NMR analysis of the crude mixture.

TLC: R_f = 0.31 in 17:3 hexanes/EtOAc, visualized by UV and stained gray with *p*-anisaldehyde.

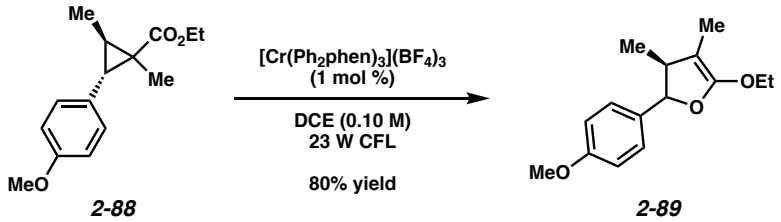
^{1}H NMR (400 MHz; $CDCl_3$): Major: δ 7.31 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 4.89 (d, J = 9.6 Hz, 1H), 4.35-4.25 (comp. m, 2H), 3.81 (s, 3H), 2.69 (dq, J = 9.6, 7.0 Hz, 1H), 1.65 (s, 3H), 1.36 (t, J = 7.2 Hz, 3H), 1.03 (d, J = 7.0 Hz, 3H).

Minor: δ 7.29 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 4.68 (d, J = 8.4 Hz, 1H), 4.35-4.25 (comp. m, 2H), 3.80 (s, 3H), 3.25 (qd, J = 8.4 Hz, 7.2 Hz, 1H), 1.46 (s, 3H), 1.34 (t, J = 6.4 Hz, 3H), 1.12 (d, J = 7.2 Hz, 3H).

^{13}C NMR (125 MHz; $CDCl_3$): δ 173.8, 171.3, 160.4, 160.3, 129.2, 128.8, 127.0, 126.7, 114.4, 114.3, 90.9, 88.6, 88.4, 87.9, 61.9, 61.7, 61.1, 55.4, 54.6, 21.8, 17.4, 14.5, 14.3, 12.5, 11.5.

IR (ATR, neat): 2981, 1733, 1612, 1516, 1462, 1251, 1177, 1109, 1030, 829 cm^{-1}.

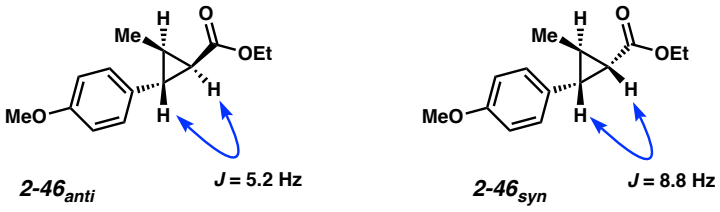
HRMS (ESI+): *m/z* calc'd for $(M+H)^+$ $[C_{15}H_{20}O_3 + H]^+$: 249.1485, found 249.1485.



Cyclopropane to Dihydrofuran Rearrangement. A solution of cyclopropane **2-88** (7.7 mg (0.0310 mmol) and $[Cr(Ph_2phen)_3](BF_4)_3$ (0.4 mg) in DCE (0.5 mL) was prepared in a flame-dried borosilicate vial open to air. The vial was then capped and placed in a closed box, lined with aluminum foil, and equipped with a 23 W compact fluorescent light bulb. The reaction mixture was irradiated for 45 h. The reaction mixture was concentrated via rotary evaporation and purified by flash column chromatography (100% hexanes → 17:3 hexanes/EtOAc eluent) to afford 6.1 mg of dihydrofuran **2-89** (80% yield).

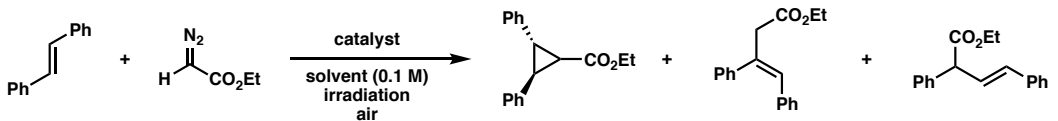
2.13.5 Diastereomer Assignments

For the cyclopropane products where diastereomers were formed, their stereochemistry was assigned by analysis of NMR data. Specifically, coupling constants for two of the cyclopropyl protons could be identified and evaluated, and their relative values gave a strong indication of relative positioning. An anti relationship of the two protons would have a smaller coupling constant than the corresponding syn relationship. An example using compound **2-46** is depicted below.



2.13.6 Optimization Studies

Table 2.1. (*Reproduction*) Optimization of Cr-catalyzed cyclopropanation.



2-14 *2-15* *2-18* *2-19* *2-20*

Entry	Catalyst (mol %)	Solvent	Irradiation	Equiv *2-15*	Time (h)	NMR yield (%)[a] *2-18*	*2-19*	*2-20*
1	$[Cr(Ph_2phen)_3](BF_4)_3$ (1)	CH_3NO_2	NUV[b]	5	24	60	8	7
2	$[Cr(Ph_2phen)_3](BF_4)_3$ (1)	CH_3NO_2	23 W CFL	5	24	61	10	8
3	$[Cr(Ph_2phen)_3](BF_4)_3$ (1)	CH_3NO_2	23 W CFL	1.1	40	60	8	11
4	$[Cr(4\text{-}dmcbpy)_3](BF_4)_3$ (1)	CH_3NO_2	23 W CFL	1.1	40	5	1	1
5	$[Cr(phen)_2(dmcbpy)](OTf)_3$ (1)	CH_3NO_2	23 W CFL	1.1	40	40	8	7
6	$[Cr(phen)_3](OTf)_3$ (1)	CH_3NO_2	23 W CFL	1.1	40	50	9	8
7	$Ru(bpz)_3(PF_6)_2$ (1)	CH_3NO_2	23 W CFL	1.1	24	3	0	0
8	$Ru(bpz)_3(PF_6)_2$ (1)	CH_3NO_2	23 W CFL	5	14	9	4	5
9	$Ru(bpy)_3(PF_6)_2$ (5) + MV (15)[c]	CH_3NO_2	23 W CFL	5	21	12	2	2
10	$Ru(bpy)_3(PF_6)_2$ (5)	CH_3NO_2	23 W CFL	5	21	0	0	0
11	$[Cr(Ph_2phen)_3](BF_4)_3$ (1)	$CHCl_3$	23 W CFL	1.1	24	18	1	2
12	$[Cr(Ph_2phen)_3](BF_4)_3$ (1)	acetone	23 W CFL	1.1	24	57	5	8
13	$[Cr(Ph_2phen)_3](BF_4)_3$ (1)	CH_2Cl_2	23 W CFL	1.1	24	73	2	7
14	$[Cr(Ph_2phen)_3](BF_4)_3$ (1)	CH_3CN	23 W CFL	1.1	24	67	8	10
15	$[Cr(Ph_2phen)_3](BF_4)_3$ (1)	DCE	23 W CFL	1.1	24	73	0	5
16	none	DCE	23 W CFL	1.1	14	0	0	0
17	$CrCl_3$ (10)	DCE	23 W CFL	1.1	49	0	0	0
18	$[Cr(Ph_2phen)_3](BF_4)_3$ (1)	DCE	none[d]	1.1	49	0	0	0

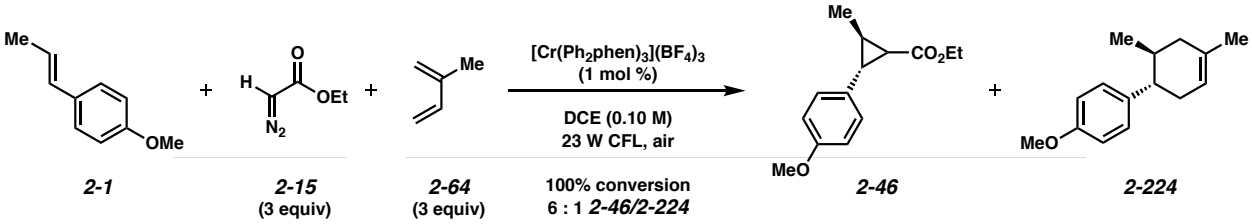
[a] Determined using veratraldehyde as a standard.
[b] Near UV light (bulbs at 300, 350, and 419 nm) used instead of 23 W CFL.
[c] MV: methyl viologen^{2+}·$(PF_6)_2$.
[d] Reaction performed in dark (foil wrapped).

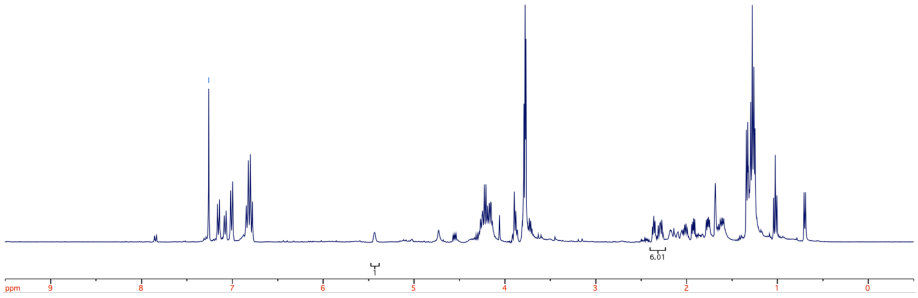
General Procedure for Optimization Experiments: A flame-dried 1-dram borosilicate vial open to air was charged with *trans*-stilbene (18.0 mg, 0.0999 mmol), ethyl diazoacetate (1.1 or 5.0 equiv), catalyst, and 1.0 mL solvent (0.1 M). The vial was then capped. The solution was irradiated with the indicated light source, stirring for the indicated time and then concentrated via rotary evaporation. The resulting crude product was analyzed by ^{1}H NMR, using veratraldehyde

as a standard. Compounds **2-19** and **2-20** were identified by comparison to compounds reported in the literature.[72]

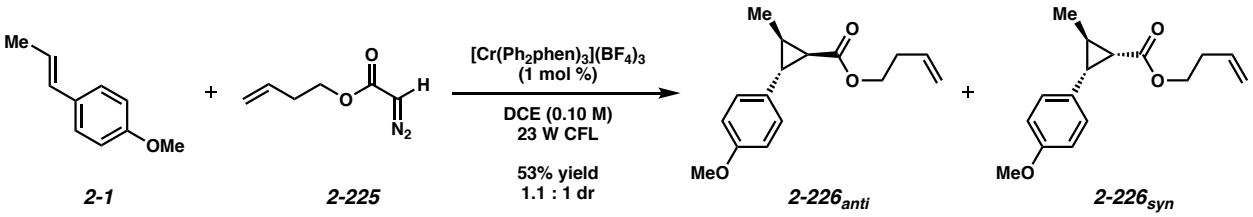
2.13.7 Nucleophile Competition Experiment

A solution containing 14.8 mg *trans*-anethole (0.0999 mmol, 1 equiv), 37.3 µL ethyl diazoacetate (85% wt. solution in CH_2Cl_2, 0.300 mmol, 3 equiv), 30.0 µL isoprene (0.300 mmol, 3 equiv), and 1.3 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (0.999 µmol, 1 mol %) in 1.0 mL DCE was prepared in a flame-dried borosilicate vial open to air. The vial was then capped and placed in a closed box, lined with aluminum foil, and equipped with a 23 W compact fluorescent light bulb. The mixture was irradiated for 48 h at which point it was concentrated *via* rotary evaporation. The crude product was analyzed by ^1H NMR to determine the ratio of product distribution.





2.13.8 Chemoselectivity Experiments



2-1 *2-225* *2-226$_{anti}$* *2-226$_{syn}$*

Cyclopropane 2-226. Prepared according to the *General Procedure* using 14.8 mg *trans*-anethole (0.0999 mmol), 15.4 mg diazoacetate **2-225** (0.110 mmol), 1.3 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (0.999 μmol), and 1.0 mL DCE. The reaction mixture was irradiated for 72 h. The crude product was purified by flash chromatography (100% hexanes → 9:1 hexanes/EtOAc eluent) to afford *trans*-cyclopropane **2-226** (13.9 mg, 53% yield) as a colorless oil. Diastereomeric ratio (1.1:1 anti/syn) was determined by ^{1}H NMR analysis of the crude mixture.

TLC: R_f = 0.29 in 9:1 hexanes/Et_2O, visualized by UV. Stained blue by *p*-anisaldehyde.

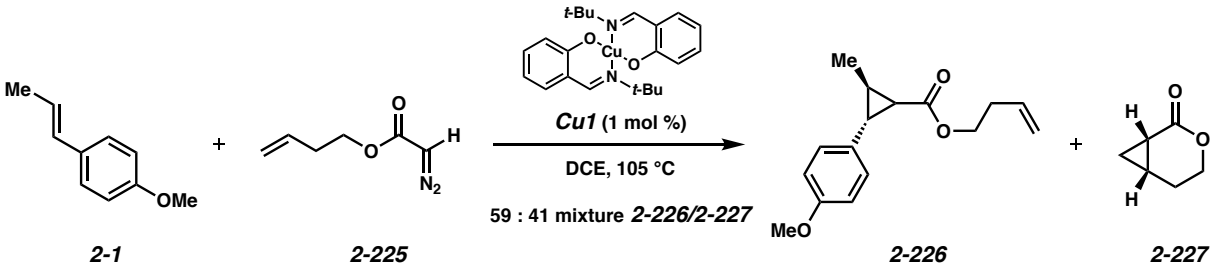
^{1}H NMR (400 MHz; $CDCl_3$): Major (anti): δ 7.01 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 5.81 (ddt, *J* = 17.0, 10.3, 6.8 Hz, 1H), 5.15-4.98 (comp. m, 2H), 4.17 (dt, *J* = 6.8, 1.5 Hz, 2H), 3.78 (s, 3H), 2.41 (app. q, *J* = 6.8 Hz, 2H), 2.36 (dd, *J* = 6.6, 5.0 Hz, 1H), 1.93 (dd, *J* = 9.2, 5.0 Hz, 1H), 1.67-1.58 (comp. m, 1H), 1.33 (d, *J* = 6.4 Hz, 3H).

Minor (syn): δ 7.15 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 2H), 5.63 (ddt, *J* = 17.0, 10.5, 6.6 Hz, 1H), 5.15-4.98 (comp. m, 2H), 3.95-3.84 (comp. m, 2H), 3.77 (s, 3H), 2.30 (dd, *J* = 9.2, 7.0 Hz, 1H), 2.15 (app. qd, *J* = 6.8, 1.2 Hz, 2H), 2.01 (app. sextet, *J* = 6.0 Hz, 1H), 1.78 (dd, *J* = 9.2, 5.2 Hz, 1H), 1.26 (d, *J* = 6.0 Hz, 3H).

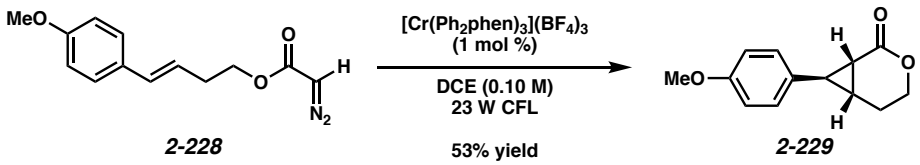
^{13}C NMR (100 MHz; $CDCl_3$): δ 171.9, 171.1, 158.4, 158.3, 134.31, 134.27, 132.7, 130.2, 128.8, 127.3, 117.3, 117.0, 114.0, 113.5, 63.7, 63.4, 55.5, 55.3, 33.9, 33.4, 33.1, 32.0, 30.0, 29.2, 25.4, 20.1, 17.9, 12.2.

IR (ATR, neat): 2960, 1724, 1517, 1248, 1168, 1037, 917, 829 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{16}H_{20}O_3 + H]^+$: 261.1485, found 261.1472.



Cu-Catalyzed Experiment. To a flame-dried round bottom flask was added *trans*-anethole (**2-1**, 0.150 mL, 1.01 mmol), copper catalyst **Cu1**[73] (4.2 mg, 0.0101 mmol), and 3.0 mL of DCE. The flask was fitted with a reflux condenser and placed in an oil bath that was subsequently heated to 105 ˚C. To this reaction mixture, a solution of diazo **2-225** (1.10 mL, 1.0 M solution in CH_2Cl_2, 1.10 mmol) in 2.0 mL of DCE, was added *via* syringe pump at a rate of 500 μL/h. After ~6 h, the reaction mixture was allowed to cool to room temperature. The reaction mixture was concentrated via rotary evaporation and the crude reaction mixture was analyzed by ^1H NMR. Through ^1H NMR analysis, it was determined that a 59:41 ratio was obtained of **2-226:2-227**, with <20% consumption of either **2-1** or **2-225**. Compound **2-227** was confirmed by comparison to literature data.[74] Unreacted *trans*-anethole was observed, as were diazo dimerization products (assigned by comparison to dimethyl fumarate and maleate).



Cyclopropane 2-229. Prepared using 25.7 mg diazo ester **2-228** (0.104 mmol), 1.3 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (1.04 μmol), and 1.0 mL DCE. The reaction mixture was irradiated for 48 h. The crude product was purified by flash chromatography (3:1 → 1:1 hexanes/EtOAc eluent) to

afford cyclopropane **2-229** (12.1 mg, 53% yield) as a colorless oil. The stereochemical assignment of cyclopropane **2-229** was determined by analogy to a similar lactone compound.74

TLC: R_f = 0.40 in 1:1 hexanes/EtOAc, visualized by UV and stained blue with *p*-anisaldehyde.

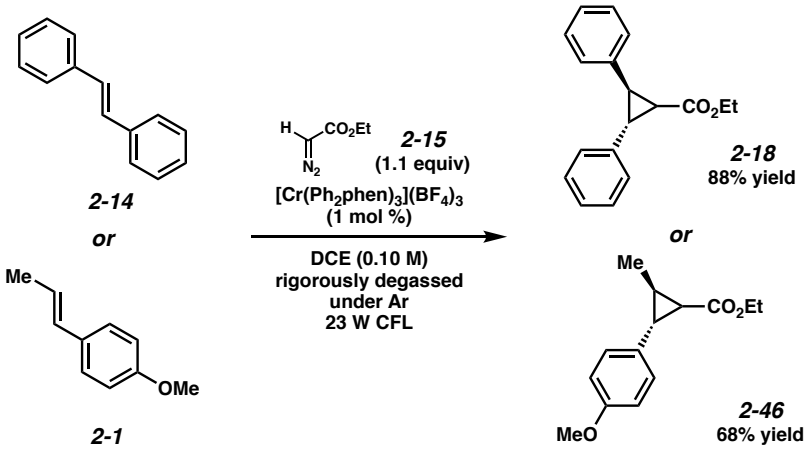
^{1}H NMR (400 MHz; $CDCl_3$): δ 7.04 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 4.34 (dd, *J* = 12.3, 6.2 Hz, 1H), 4.25 (app. td, *J* = 12.3, 4.1 Hz, 1H), 3.79 (s, 3H), 2.90 (app. t, *J* = 4.1 Hz, 1H), 2.25 (app. td, *J* = 13.0, 6.2 Hz, 1H), 2.14-2.10 (comp. m, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 169.9, 158.8, 130.1, 127.6, 114.3, 64.7, 55.5, 26.5, 24.6, 23.5, 20.6.

IR (ATR, neat): 2934, 1721, 1516, 1248, 1082, 1034, 806 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{13}H_{14}O_3 + H]^+$: 219.1016, found 219.1016.

2.13.9 Oxygen-Free Experiments



Cyclopropane 2-18. A solution containing 18.0 mg *trans*-stilbene (0.0999 mmol), 14.7 mg ethyl diazoacetate (0.110 mmmol, 85% wt. solution in CH_2Cl_2, 1.1 equiv), and 1.3 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (0.999 μmol, 1 mol %) in 1.0 mL of deoxygenated DCE was prepared in a flame-dried schlenk flask under argon. The reaction mixture was degassed by freeze-pump-thaw

method (3x) and kept under argon. The flask was placed above a stir plate, surrounded with aluminum foil, and irradiated with a 23 W compact fluorescent light bulb. The mixture was irradiated for 60 h at which point it was concentrated *via* rotary evaporation. The crude product was purified by flash column chromatography (100% hexanes → 19:1 hexanes/acetone eluent) to afford cyclopropane **2-18** (23.5 mg, 88% yield) as a colorless oil.

Cyclopropane 2-46. A solution containing 14.7 mg *trans*-anethole (0.0992 mmol), 14.6 mg ethyl diazoacetate (0.110 mmol, 85% wt. solution in CH_2Cl_2, 1.1 equiv), and 1.3 mg $[Cr(Ph_2phen)_3](BF_4)_3$ (0.992 μmol, 1 mol %) in 1.00 mL of deoxygenated DCE was prepared in a flame-dried schlenk flask under argon. The reaction mixture was degassed by freeze-pump-thaw method (3x) and kept under argon. The flask was placed above a stir plate, surrounded with aluminum foil, and irradiated with a 23 W compact fluorescent light bulb. The mixture was irradiated for 60 h at which point it was concentrated *via* rotary evaporation. The crude product was purified by flash column chromatography (100% hexanes → 9:1 hexanes/EtOAc eluent) to afford cyclopropane **2-46** (15.8mg, 68% yield) as a colorless oil.

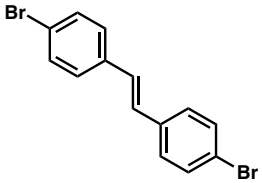
2.13.10 Substrate Synthesis

General Notes: All reactions were performed in flame-dried glassware under argon. Aldehydes were used directly from commercial sources with no further purification. Alkyltriphenylphosphonium halides for Wittig reactions were dried under vacuum at 105 ˚C overnight prior to use. Alkenes were prepared from the reported procedures in the literature and

the pure *E* isomer was subjected to the *General Procedure.* Where relevant, all spectroscopic data were consistent with the published values.

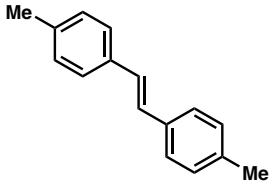
Alkene Substrates

General Procedure for alkene geometry enrichment: When mixtures of *E* and *Z* isomers could be improved to greatly favor the *E* isomer, the protocol as previously described by Yoon[75] was followed. The mixture of isomers was dissolved in benzene (0.25 M), AIBN (0.15 equiv), and PhSH (0.5 equiv) were added, and the reaction was heated at reflux for 1 h. Upon cooling to room temperature, the mixture was washed sequentially with 1 M aq. NaOH and brine, dried over $MgSO_4$, and concentrated using rotary evaporation. The residue was purified by flash column chromatography to afford the desired product as a single *E* isomer.



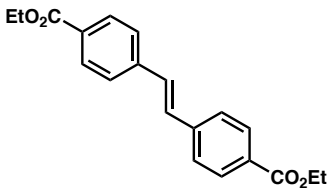
2-31

Stilbene 2-31. Stilbene **2-31** was synthesized according to the procedure described by Winter.[76]



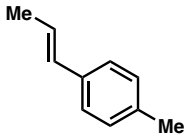
2-30

Stilbene 2-30. Stilbene **2-30** was synthesized according to the procedure described by Batey.[77]



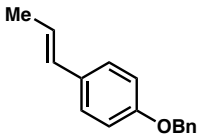
2-32

Stilbene 2-32. Stilbene **2-32** was synthesized in two steps from the corresponding dicarboxylic acid via reported procedures.[78]



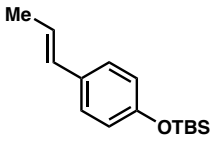
2-45sm

Alkene 2-45m. Alkene **2-45m** was prepared according to the procedure described by Nicewicz and coworkers.[79] To improve the isomeric ratio, the *E/Z* mixture was dissolved in benzene (0.25 M), AIBN (0.10 equiv) and PhSH (0.10 equiv) were added, and the reaction was heated at reflux overnight. The mixture was cooled to room temperature, diluted with Et_2O, and washed sequentially with sat. aq. $NaHCO_3$, then brine. The organic layer was dried over $MgSO_4$, filtered, concentrated via rotary evaporation, and purified by flash column chromatography to afford alkene **2-45m** as a single *E* isomer.



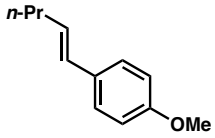
2-47sm

Alkene 2-47sm. Alkene **2-47sm** was prepared according to our reported procedure,[80] and the alkene geometry was enriched according to the above General Procedure.



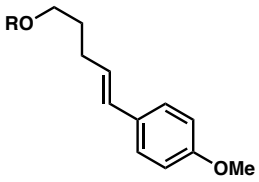
2-48sm

Alkene 2-48sm. Alkene **2-48sm** was prepared according to the procedure described by Yoon.[81]



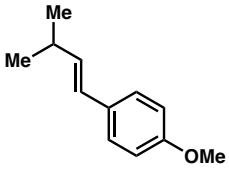
2-39sm

Alkene 2-39sm. Alkene **2-39sm** was prepared according to our reported procedure,80 and the alkene geometry was enriched according to the above General Procedure.



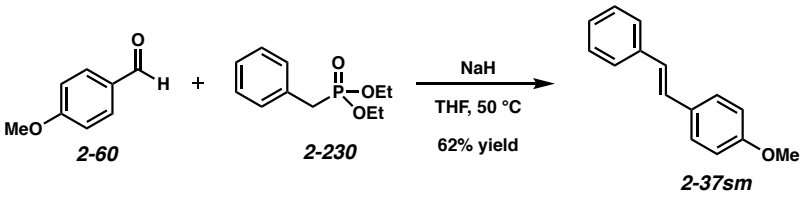
2-40sm (R = Bz)
2-41sm (R = Ac)
2-42sm (R = Me)
2-43sm (R = H)
2-44sm (R = Ts)

Alkenes 2-30sm to 2-44sm. Alkenes **2-40sm** to **2-44sm** were prepared according to our reported procedures,80 and the alkene geometry was enriched according to the above General Procedure.



2-38sm

Alkene 2-38sm. Alkene **2-38sm** was prepared according to the procedure described by Yoon, and the alkene geometry was enriched according to the above General Procedure.75[a]

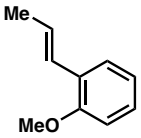


2-60 *2-230* *2-37sm*

Stilbene 2-37sm. Under an argon atmosphere, NaH (792 mg, 60% dispersion in mineral oil, 19.8 mmol, 3.0 equiv) was added to a solution of *p*-anisaldehyde (**2-60**) (0.80 mL, 6.60 mmol, 1.0 equiv) and diethyl benzylphosphonate (**2-230**) (1.40 mL, 6.60 mmol, 1.0 equiv) in THF (22.0 mL, 0.3 M) at room temperature. The resulting mixture was stirred at 50 ˚C for 30 min. The reaction mixture was cooled to room temperature and H_2O (25 mL) was added, which caused a white solid to precipitate. The reaction mixture was filtered, and the white precipitate was washed with water. The crude product was recrystallized from hot EtOH, filtered, washed with cold EtOH, and dried in vacuo to yield alkene **2-37sm** (857 mg, 62% yield) as fine white crystals.

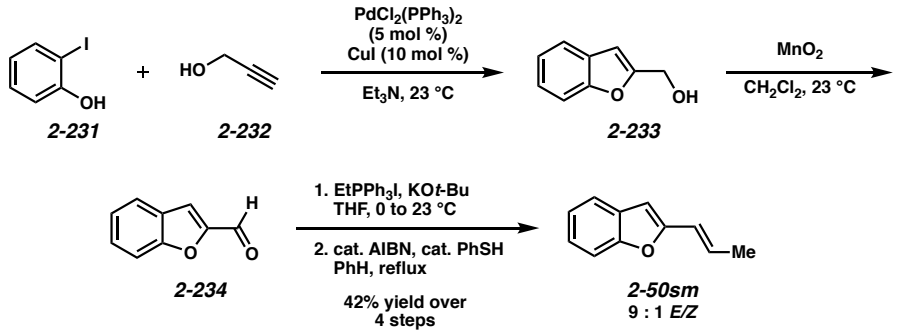
TLC: R_f = 0.63 in 9:1 hexanes/EtOAc, visualized by UV.

All spectroscopic data were in accordance with the published values.[82]



2-49sm

Alkene 2-49sm. Alkene **2-49sm** was prepared according to our reported procedure,80 and the alkene geometry was enriched according to the above General Procedure.



2-231 *2-232* *2-233* *2-234* *2-50sm*
9 : 1 *E/Z*

Alkene 2-50sm. Alkene **2-50sm** was synthesized in 4 steps from 2-iodophenol. A solution of 2-iodophenol (500 mg, 2.27 mmol) and propargyl alcohol (0.144 mL, 2.50 mmol) in triethylamine (5.0 mL, 0.454 M) at 23 ˚C was degassed with argon via bubbling for 15 min. CuI (43.0 mg, 0.227 mmol) was added followed by $PdCl_2(PPh_3)_2$ (80.0 mg, 0.114 mmol), and the mixture was stirred at 23 ˚C overnight. Upon completion, the mixture was filtered through a SiO_2 plug, washing with EtOAc (25 mL). The filtrate was concentrated under reduced pressure and carried directly to the next transformation without further purification. The crude carbinol (**2-233**) was dissolved in 13.6 mL CH_2Cl_2 (0.484 M), and 1.90 g (10 equiv) of MnO_2 was added to the mixture. After stirring overnight, the mixture was filtered through a celite plug using CH_2Cl_2 as the eluent (25 mL). The filtrate was concentrated under reduced pressure to give crude aldehyde **2-234**, which was carried directly to the next transformation without further purification. In a dry round bottom flask, 1.11 g of $EtPPh_3I$ (2.66 mmol, 1.4 equiv) and KO*t*-Bu (2.47 mmol, 1.3 equiv) were added. The reaction flask was placed in an ice-water bath, and THF (5 mL, 0.4 M) was added to the mixture. The solution was stirred at 0 ˚C for 0.5 h, at which point a solution of aldehyde **2-234** in 1.0 mL THF was added dropwise via syringe. The mixture was allowed to warm to room temperature and stirred overnight. Once complete, the mixture was quenched with sat. aq. NH_4Cl (10 mL) and H_2O (5 mL), and it was extracted with Et_2O (3 x 25 mL). The combined organic layers were washed with brine (40 mL) and dried over $MgSO_4$. The $MgSO_4$ was filtered, and the solvent was removed via rotary evaporation to give an amorphous residue that was purified by silica gel chromatography (100% hexanes $\rightarrow$ 19:1 hexanes/Et_2O) to afford alkene **2-50sm** (253 mg, 4:1 *E/Z* mixture, 70% yield over 3 steps) as a colorless oil. To further enrich the *E* geometry, 250 mg (1.58 mmol) of alkene **2-50sm** was dissolved in 6.4 mL of benzene (0.25 M). To the solution was added 26.0 mg AIBN (0.158 mmol) and 0.02 mL PhSH (0.158 mmol), and the mixture was heated to reflux and

stirred overnight. After cooling to room temperature, the mixture was diluted with Et_2O (15 mL), transferred to a separatory funnel and washed with sat. aq. $NaHCO_3$ (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated via rotary evaporation to afford a cloudy oil that was purified by flash column chromatography (100% hexanes → 19:1 hexanes/Et_2O) to afford alkene **2-50sm** (152 mg, 60% yield, ~9:1 trans/cis) as a colorless oil.

TLC: R_f = 0.79 in 9:1 hexanes/Et_2O, visualized by UV, stained yellow by $KMnO_4$.

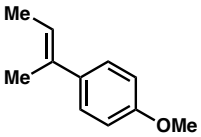
(Note: NMR spectroscopic data reported is for the E isomer only.)

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.49 (d, *J* = 7.6 Hz, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.23-7.15 (m, 2H), 6.49 (dd, *J* = 15.6, 6.8 Hz, 1H), 6.45 (br s, 1H), 6.34 (dd, *J* = 15.6, 1.6 Hz, 1H), 1.94 (dd, *J* = 6.8, 1.2 Hz, 3H).

^{13}C NMR (125 MHz; $CDCl_3$): δ 155.3, 154.7, 129.2, 128.7, 124.0, 122.8, 120.7, 120.1, 110.9, 102.6, 18.7.

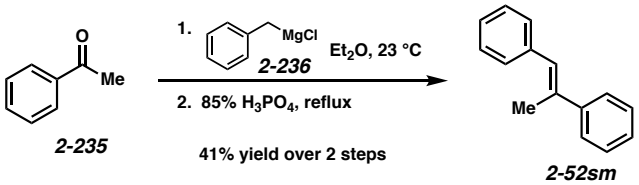
IR (ATR, neat): 2932, 1652, 1453, 1254, 959, 748 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M^{\bullet})^+$ $[C_{11}H_{10}O^{\bullet}]^+$: 158.0726, found 158.0726.



2-51sm

Alkene 2-51sm. Alkene **2-51sm** was prepared according to the procedure described by Castle.[83]



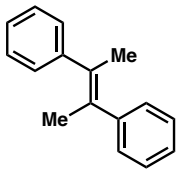
2-235 ***2-52sm***

Stilbene 2-52sm. A suspension of magnesium turnings (560 mg, 23.0 mmol, 2.3 equiv) in dry Et_2O (11.1 mL) was prepared in a flame-dried round bottom flask fitted with a reflux condenser. A solution of benzyl chloride (2.30 mL, 20.0 mmol, 2.0 equiv) in dry Et_2O (11.1 mL) was added

dropwise at room temperature, and bubbling indicated the formation of benzyl magnesium chloride. Once bubbling ceased, the mixture was set to a gentle reflux at 35 ˚C for approximately 15 min, and then cooled to room temperature. To this freshly prepared Grignard solution was added acetophenone (1.17 mL, 10.0 mmol, 1.0 equiv) dropwise at ambient temperature. The reaction mixture was stirred at room temperature until determined complete by TLC (~1 h). The reaction mixture was quenched with sat. aq. NH_4Cl (25 mL) and extracted with Et_2O (3 x 25 mL). The combined organic phases were washed with brine (60 mL), dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The crude product was then refluxed in 85% phosphoric acid (17.0 mL, 0.6 M) for 12 h. After cooling to room temperature, the reaction mixture was poured into H_2O (25 mL) and extracted with Et_2O (3 x 25 mL). The combined organic phases were then washed with H_2O (60 mL), then brine (60 mL), dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The crude product was recrystallized from hot EtOH. The crystals were collected by filtration, washed with cold EtOH, and dried in vacuo to provide alkene **2-52sm** (800 mg, 41% yield over two steps) as white crystals.

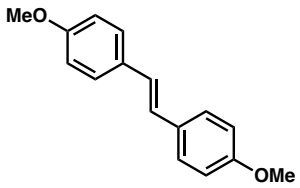
TLC: R_f = 0.77 in 9:1 hexanes/Et_2O, visualized by UV.

All spectroscopic data were consistent with previously reported values.[84]



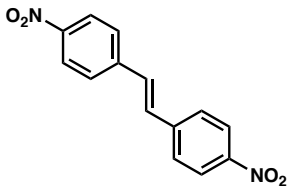
2-53sm
(~1:1 *E/Z*)

Alkene 2-53sm. Alkene **2-53sm** was prepared according to the procedure described by Konwar and Dutta.[85]



2-29

Stilbene 2-29. Stilbene **2-29** was synthesized according to the procedure described by Kam.[86]

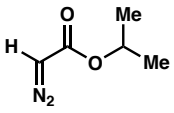


2-33

Stilbene 2-33. Stilbene **2-33** was synthesized according to the procedure described by Bendig.[87]

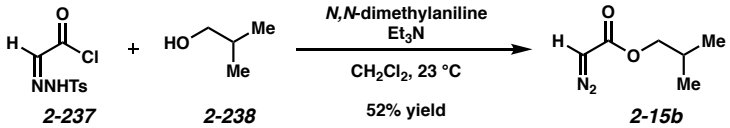
Diazo Substrates

General Notes: *Diazo compounds are toxic, irritants, and many compounds are explosive. Care should be taken when handling and synthesizing diazo compounds.*



2-15a

Diazoacetate 2-15a. Diazoacetate **2-15a** was synthesized according to the procedure described by Hodgson.[88]



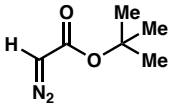
2-237 *2-238* *2-15b*

Diazoacetate 2-15b. To synthesize diazoacetate **2-15b**, a modified procedure by Corey and Myers[89] was followed. At room temperature, *N,N*-dimethylaniline (0.600 mL, 4.60 mmol, 1.2

equiv) was added dropwise to a solution of dry dichloromethane (6.30 mL) containing glyoxalyl chloride tosylhydrazone (1.00 g, 3.80 mmol) and 2-methyl-1-propanol (0.530 mL, 5.70 mmol, 1.5 equiv). The resulting mixture was stirred at room temperature for 1 h. Triethylamine (2.70 mL, 19.0 mmol, 5.0 equiv) was added, and the resulting mixture was stirred for 30 min, before being poured into water (10 mL). The resulting mixture was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed once with brine (40 mL) and dried over $MgSO_4$. The $MgSO_4$ was filtered, and the solvent removed via rotary evaporation to give a yellow oil, which was purified by silica gel flash chromatography (9:1 hexanes/Et_2O eluent) to give diazoacetate **2-15b** (280 mg, 52% yield) as a yellow oil.

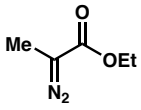
TLC: R_f = 0.52 in 9:1 hexanes/EtOAc, visualized by UV.

All spectroscopic data were in accordance with the published values.[90]



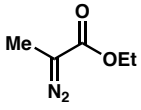
2-15c

Diazoacetate 2-15c. Diazoacetate **2-15c** was synthesized according to the procedure described by Johnson.[91]



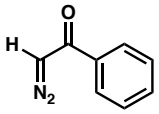
2-15d

Diazopropionate 2-15d. Diazopropionate **2-15d** was synthesized according to the procedure described by Wang and Lin.[92]



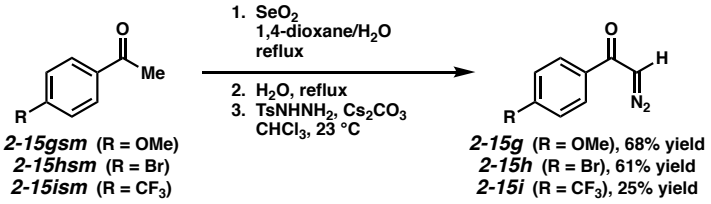
2-15e

Diazobutyrate 2-15e. Diazobutyrate **2-15e** was synthesized according to the procedure described by Wulff.[93]



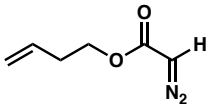
2-15f

Diazoketone 2-15f. Diazoketone **2-15f** was synthesized according to the procedure described by Wu.[94]



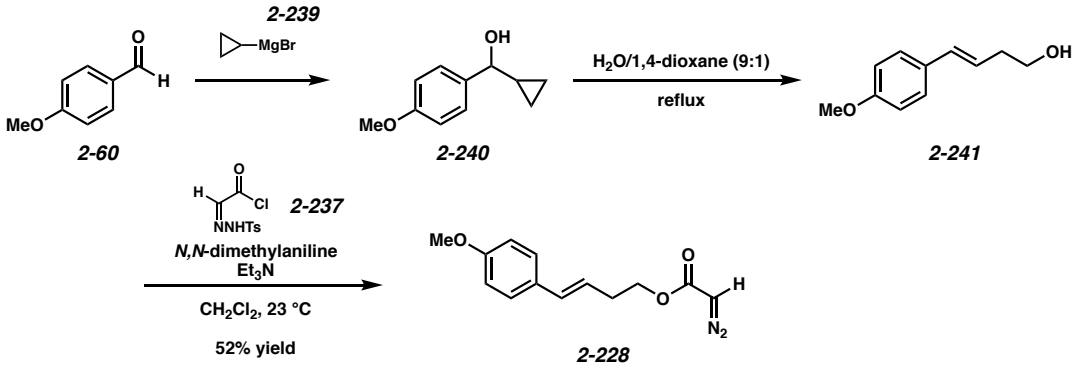
Diazoketones 2-15g to 2-15i. Diazoketones **215g** to **2-15i** were synthesized from their respective, commercially available, *para*-substituted acetophenone precursors. Employing a reported α-oxidation procedure,[95] to a round bottom flask containing 333 mg of SeO_2 (3.00 mmol, 1 equiv), 1.5 mL of 1,4-dioxane (1.98 M) and 0.1 mL of H_2O (41.6 M) was added *p*-substituted acetophenone (3.00 mmol, 1 equiv). The mixture was refluxed overnight and after cooling to room temperature, the solvent was removed via rotary evaporation. 7.2 mL of H_2O (0.416 M) was added to the crude residue, and the mixture was refluxed for another 5 h. The mixture was allowed to cool to room temperature then placed in an ice-water bath to give an off-white precipitate that was filtered and dried in vacuo. Employing a reported diazotization procedure,94 approximately 1 mmol of the crude solid was dissolved in 2.0 mL of $CHCl_3$ (0.5 M) along with 186 mg of $TsNHNH_2$ (0.999 mmol, 1 equiv) and 977 mg of Cs_2CO_3 (3.00 mmol, 3 equiv). The mixture was stirred for 5 min at room temperature. 50 mL of H_2O was added, and the mixture was extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine (50 mL) and dried over $MgSO_4$. The $MgSO_4$ was filtered, and the solvent was removed via rotary evaporation to

give a yellow amorphous residue that was purified by silica gel flash chromatography to give pure diazoketone (R = OCH_3 (68%), Br (61%), CF_3 (25%) yields over three steps). All spectroscopic data were in accordance with the published values (–OCH_3,95 –Br,95 and –CF_3[96]).



2-225

Diazoester 2-225. Diazoester **2-225** was synthesized according to the procedure described by Moody.[97]



Diazoacetate 2-228. To synthesize diazoacetate **2-228**, the procedure of McCormick procedure was followed to synthesize carbinol **2-240**,[98] which was rearranged to homoallylic alcohol **2-241** using the conditions reported by Qu.[99] A modification of the Corey and Myers protocol[89] for the synthesis of diazoacetates was then followed to furnish diazoacetate **2-228**. At room temperature, *N,N*-dimethylaniline (0.150 mL, 1.20 mmol, 1.2 equiv) was added dropwise to a solution of dry dichloromethane (1.60 mL) containing glyoxalyl chloride tosylhydrazone (287 mg, 1.10 mmol, 1.1 equiv) and alcohol **2-241** (178 mg, 1.00 mmol). The resulting mixture was stirred at room temperature for 1 h. Triethylamine (0.700 mL, 5.00 mmol, 5.0 equiv) was added, and the resulting mixture was stirred for 30 min, before being poured into water (5.0 mL). The resulting mixture was extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed once with brine (15 mL) and dried over $MgSO_4$. The $MgSO_4$ was filtered and the solvent removed via rotary

evaporation to give a yellow oil, which was purified by silica gel flash chromatography (9:1 hexanes/EtOAc eluent) to give diazoacetate **2-228** (118 mg, 48% yield) as a yellow oil that solidified upon cooling.

TLC: R_f = 0.28 in 9:1 hexanes/EtOAc, visualized by UV.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.28 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.41 (d, *J* = 16.0 Hz, 1H), 6.01 (dt, *J* = 16.0, 7.2 Hz, 1H), 4.75 (br. s, 1H), 4.26 (t, *J* = 6.6 Hz, 2H), 3.80 (s, 3H), 2.54 (app. qd, *J* = 6.8, 1.2 Hz, 2H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 159.1, 132.1, 130.2, 127.4, 125.4, 123.2, 114.1, 64.4, 55.4, 46.4, 32.7.

IR (ATR, neat): 2109, 1692, 1608, 1511, 1395, 1359, 1246, 1175, 1033 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + Na)^+$ $[C_{13}H_{14}N_2O_3 + Na]^+$: 269.0897, found 269.0898.

2.14 Chapter 2 Notes and References

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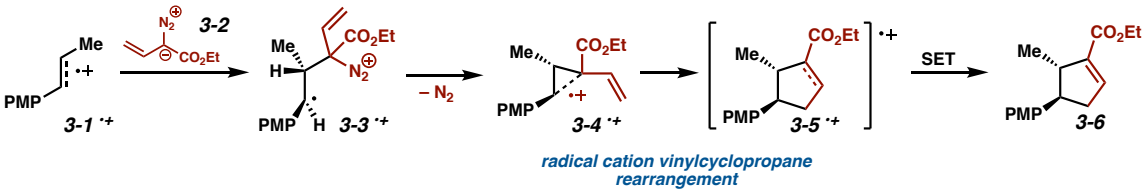
CHAPTER 3

MODERN PHOTOCATALYTIC METHODS TOWARD CYCLOPENTENE FORMATION AND AN EVALUATION OF VINYLDIAZO NUCLEOPHILICITY

3.1 Introduction: Project Proposal and Precedence

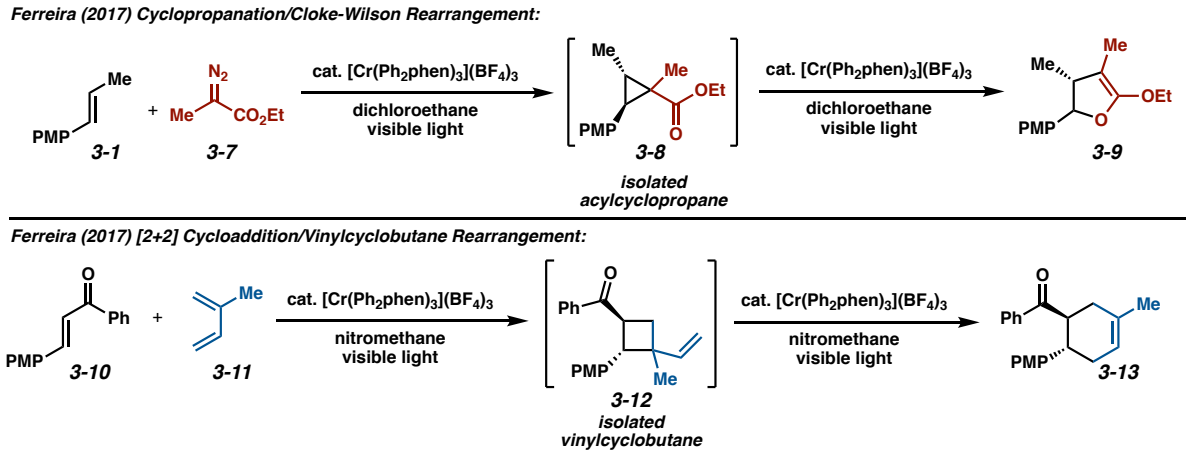
The emergence of photoredox catalysis in organic synthesis has been well recognized for their diverse transformations and intriguing mechanistic pathways. As part of our goal in exploiting chromium(III) photocatalysts in useful organic reaction development, last year we disclosed the Cr-catalyzed cyclopropanation using diazocarbonyl compounds in *Organic Letters*.[1] We were curious to see if we could further manipulate this reaction platform to render cyclopentene products. In comparison to cyclohexene construction via (4+2) cycloadditions, such as the revered Diels–Alder reaction, examples of direct (3+2) pathways to access cyclopentenes are much more limited.[2] Initially, we envisioned taking advantage of our established reaction method in which excited state Cr complexes oxidize olefins to render valuable radical cation intermediates **3-1**$^{\bullet+}$ (Scheme 3.1). A subsequent attack by a vinyldiazo species **3-2**, acting as the 3-carbon component, would furnish radical cation vinylcyclopropane intermediate **3-4**$^{\bullet+}$, poised to undergo a rearrangement to eventually yield cyclopentene **3-6**. However, examples in the literature using photocatalysis to construct cyclopentenes are scarce. Furthermore, although vinyldiazo species are useful reagents in transition metal-mediated (3+2) cycloadditions, in these scenarios they rarely act as nucleophiles (*vide infra*). Additionally, vinyldiazos have not yet been

employed in photocatalytic transformations. The objective of this chapter is to provide the necessary background and basic principles concerning our conceptualized proposal.



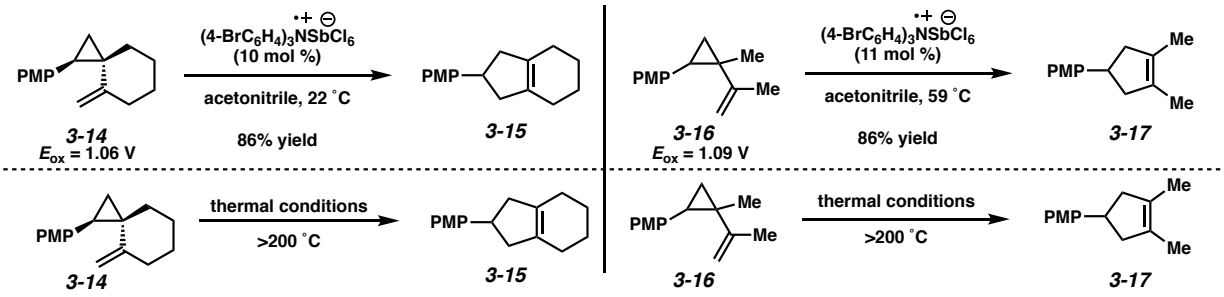
Scheme 3.1. Proposed Cr-photocatalyzed cyclopropanation/rearrangement cascade process.

The anticipated cyclopropanation/rearrangement cascade process was inspired from related transformations explored in our laboratory. The reactions themselves were found to involve strained intermediates (i.e., cyclopropanes and cyclobutanes) and proceeded through rearrangements that were catalyzed by our chromium photocatalyst (Scheme 3.2). Our studies on Cr photocatalyzed radical cation cyclopropanations revealed that acylcyclopropanes underwent Cloke-Wilson rearrangement to furnish dihydrofurans (**3-9**). During these investigations, our group also reported a net (4+2)-cycloaddition process that expanded the reaction scope beyond the realm of oxidizable alkenes.[3] Electron-poor olefins, such as *para*-methoxy chalcone **3-10** (E_{ox} = +2.00 V vs. SCE), were subjected to catalytic $[Cr(Ph_2phen)_3](BF_4)_3$ ($E^*_{1/2}$ = +1.40 V vs. SCE) in the presence of isoprene (**3-11**). A distinct mechanistic pathway yielded cyclohexene products with opposite regiochemistry of what would be obtained through a normal electron-demand Diels–Alder reaction. It was discovered that a cascade [2+2] cycloaddition/vinylcyclobutane rearrangement was an active reaction pathway leading to the observed cycloadducts.



Scheme 3.2. Precedence for rearrangement cascade processes mediated by Cr photocatalysis.

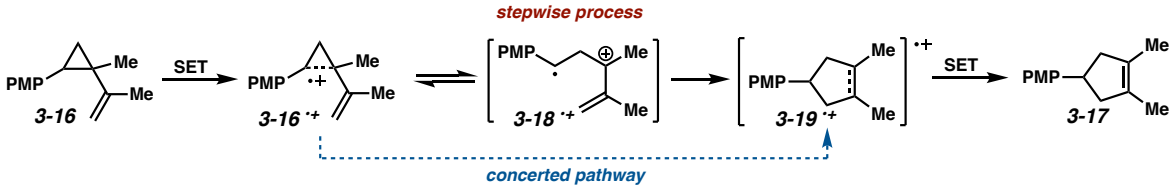
Although we have experimentally confirmed that chromium(III) photoredox catalysis can achieve cyclopropanation, we had not investigated our systems' ability to induce vinylcyclopropane (VCP) rearrangements. Fortunately, beginning more than 30 years ago, Dinnocenzo and his research group studied the vinylcyclopropane → cyclopentene radical cation rearrangement using the one-electron oxidant tris(4-bromophenyl)aminium hexachloroantimonate (E_{ox} = +1.10 V vs. SCE).[4] Vinycyclopropane rearrangements which required extreme temperatures were found to be catalyzed by the aminium salt initiator at room temperature or with mild heat (59 ˚C) (Scheme 3.3).[5]



Scheme 3.3. Experiments conducted by Dinnocenzo, evaluating the radical cation VCP rearrangement.

Given that triarylaminium salts in solution can lead to Brønsted acid-catalyzed transformations,[6] a control experiment was performed to rule out this process and possibly support

a radical cation route. By attempting the rearrangements of **3-14** and **3-16** in an aminium ion solution containing ~20 mol % of 2,6-di-*tert*-butylpyridine, known to suppress Brønsted acid-catalyzed processeses, cyclopentenes **3-15** and **3-17** were furnished in comparable yields, thus refuting a Brønsted acid-catalyzed scenario. At the time, however, discerning between a stepwise or concerted rearrangement was challenging (Scheme 3.4). Eight years after their original report, the mechanism of the radical cation vinylcyclopropane → cyclopentene rearrangement was further investigated. Dinnocenzo revealed that the process could be catalyzed by triarylaminum ions, oxidizing $Fe(phen)_3^{3+}$ salts, and excited state electron acceptors.[7] These experimental insights were proposed to be in line with a stepwise, radical cation pathway. The mechanism was later found to be intriguing by Wiest, who performed computational experiments, only to discover that the activation energy of the two potential pathways (concerted vs. stepwise) was very close and thus competitive.[8] With the established knowledge that $[Cr(Ph_2phen)_3](BF_4)_3$ can perform transformations somewhat analogously to tris(4-bromophenyl)aminium, Dinnocenzo's studies provided further insight into our reaction design.

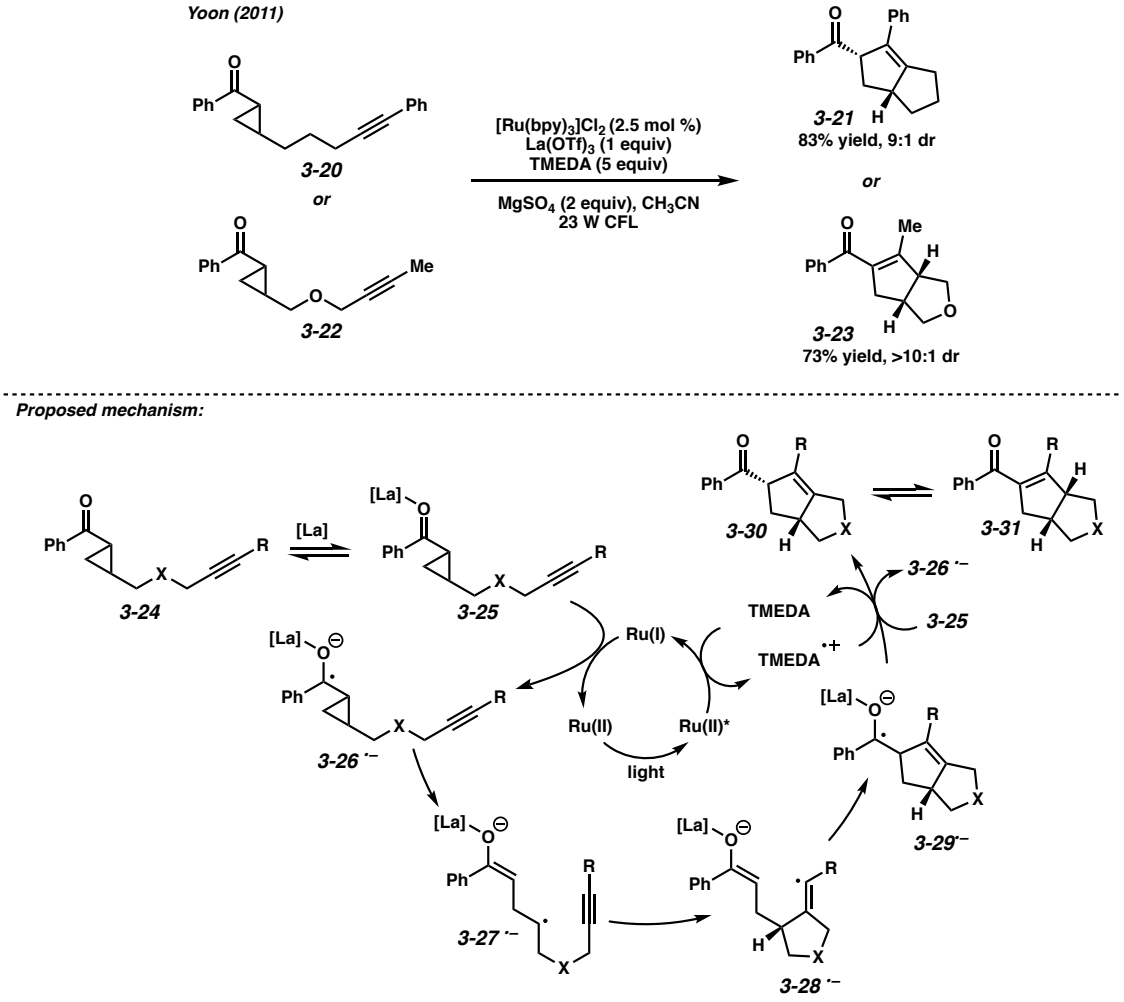


Scheme 3.4. The two possible pathways for radical cation VCP rearrangement.

3.2 Modern Photocatalyzed Cyclopentene Formation

3.2.1 Intramolecular [3+2] Using Visible Light and $Ru(bpy)_3^{2+}$

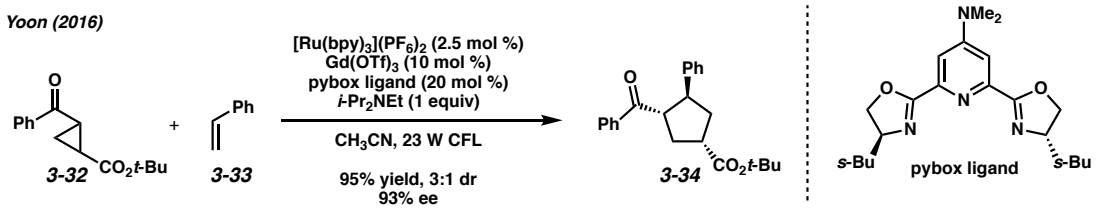
In 2011, Yoon and coworkers disclosed a new and mechanistically novel intramolecular [3+2]-cycloaddition to generate highly substituted [5-5]-bicyclic ring systems.[9] Aryl cyclopropyl ketones operated as the 3-carbon component in intramolecular cycloadditions with alkenes to furnish cyclopentanes. Additionally, two isolated examples of cyclopentene construction were also reported (Scheme 3.5). When aryl and aliphatic alkynes were tethered to phenyl cyclopropyl ketones, cyclopentenes **3-21** and **3-23** were observed, in which the latter product underwent alkene migration into conjugation with the aryl ketone.



Scheme 3.5. Cyclopentene formation using Ru photoredox catalysis.

At the time of Yoon's report, cyclopropyl ketones had not yet been examined as intermediates in (3+2) cycloadditions. However, reported strategies for radical anion formation using visible light photocatalysis led to the proposition in which radical anion cyclopropyl ketones **3-26**$^{\bullet -}$ could undergo a ring-opening event with the aid of stochiometric amounts of a Lewis acid ($La(OTf)_3$) (Scheme 3.5). This in turn would lead to a distonic radical anion **3-27**$^{\bullet -}$ capable of sequential (3+2) radical cyclizations ultimately leading to their observed products.

Eventually, Yoon was able to perform this transformation intermolecularly and enantioselectively (Scheme 3.6).[10] The transformation was accomplished through the combination of catalytic amounts of a gadolinium Lewis acid in the presence of a pybox ligand and photoredox catalyst. While this was only demonstrated for cyclopentane generation, it shows promise in that these types of (3+2) photocatalyzed transformations (and potentially others) can be further developed to render them asymmetric.

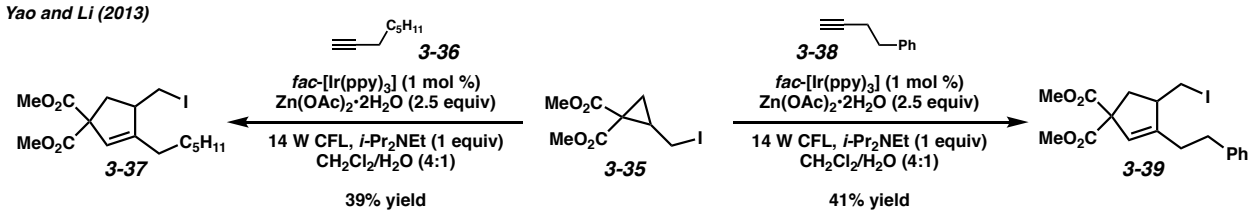


Scheme 3.6. Intermolecular and enantioselective (3+2) cycloaddition.

3.2.2 Intermolecular (3+2) ATR Cycloadditions Using Visible Light & *fac*-[Ir(ppy)$_3$]

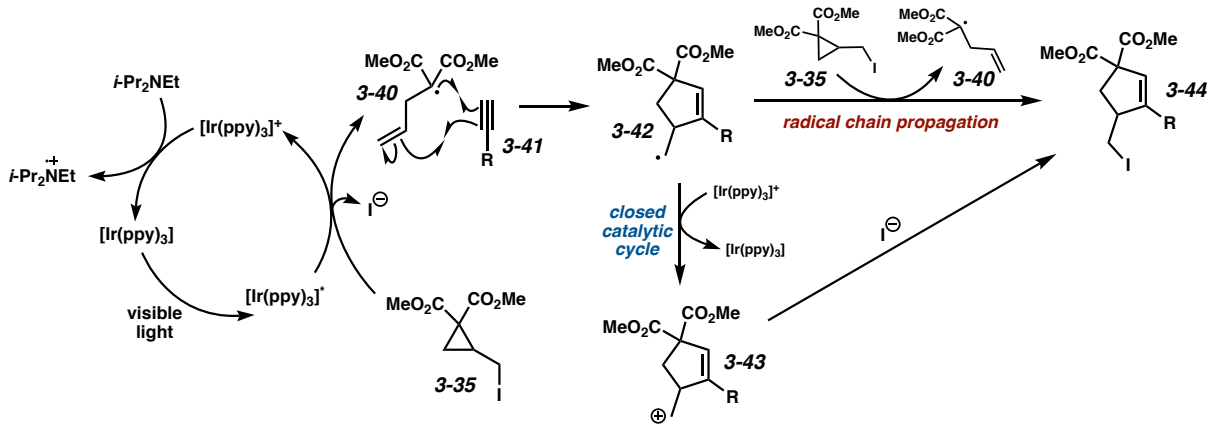
Two years later, an intermolecular (3+2) cycloaddition was reported by Yao and Li to furnish cyclopentanes and cyclopentenes. As in Yoon's previously described example, cyclopentanes were the main products but two examples were presented in which cyclopentene formation was successful (Scheme 3.7). Atom-transfer radical (ATR) cyclizations were efficient between dimethyl-2-(iodomethyl) cyclopropane-1,1-dicarboxylate and alkynes albeit in low

yields. The strongly reducing *fac*-[Ir(ppy)$_3$], Hünig's base, and a Lewis acid (Zn(OAc)$_2$•2H$_2$O) facilitated the formal (3+2) cycloaddition. The researchers implemented the Lewis acid given its beneficial effect reported in the literature.[11] Specifically, it was believed that the coordination of Zn(OAc)$_2$ to the ester carbonyl groups of the cyclopropyl intermediate may enhance the electrophilicity of the proposed homoallylic radical intermediate necessary for an efficient cycloaddition (*vide infra*).[12]



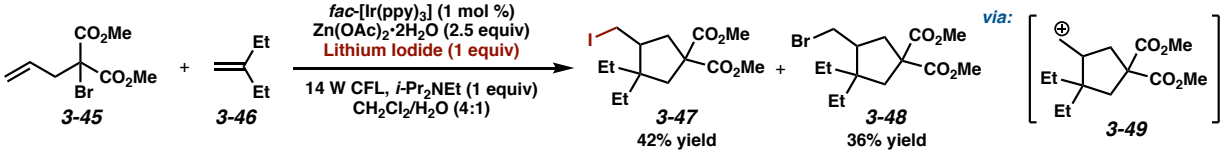
Scheme 3.7. ATR cycloadditions with alkynes to furnish cyclopentenes.

Mechanistically, the excited species [Ir(ppy)]* reduces cyclopropyl iodide **3-35** to promote a ring-opening event leading to the homoallylic radical **3-40** (Scheme 3.8). This reactive intermediate is proposed to undergo a (3+2) cyclization event with an alkyne to generate the radical cyclopentene intermediate **3-42**. Two distinct pathways, a closed catalytic cycle or radical chain propagation, are proposed to lead to the final product. In the former, the intermediate radical **3-42** is believed to be oxidized by [Ir(ppy)$_3$]$^+$ to furnish carbocation **3-43**, which reacts with an iodine atom to provide the final product (**3-44**). In the radical chain propagation pathway, radical intermediate **3-42** is thought to abstract an iodine atom directly from the starting material **3-35**, generating the homoallylic radical **3-40** as well as the cyclopentene product.



Scheme 3.8. Proposed photocatalyzed ATR cyclization mechanism.

The mechanism was first interrogated with a "light on/lights off" experiment to evaluate the existence of a radical chain reaction mechanism but was found to be inconclusive. In order to support or refute the closed catalytic cycle that generates a carbocation intermediate, a separate reaction was performed in the presence of LiI (1 equiv) with 3-methylenepentane (**3-46**) and dimethyl 2-allyl-2-bromomalonate (**3-45**) under the optimized conditions (Scheme 3.9). The addition of LiI led to a mixture of products in which bromine or iodide was incorporated. This outcome supported the formation of the cyclopentyl carbinyl carbocation intermediate **3-49**.

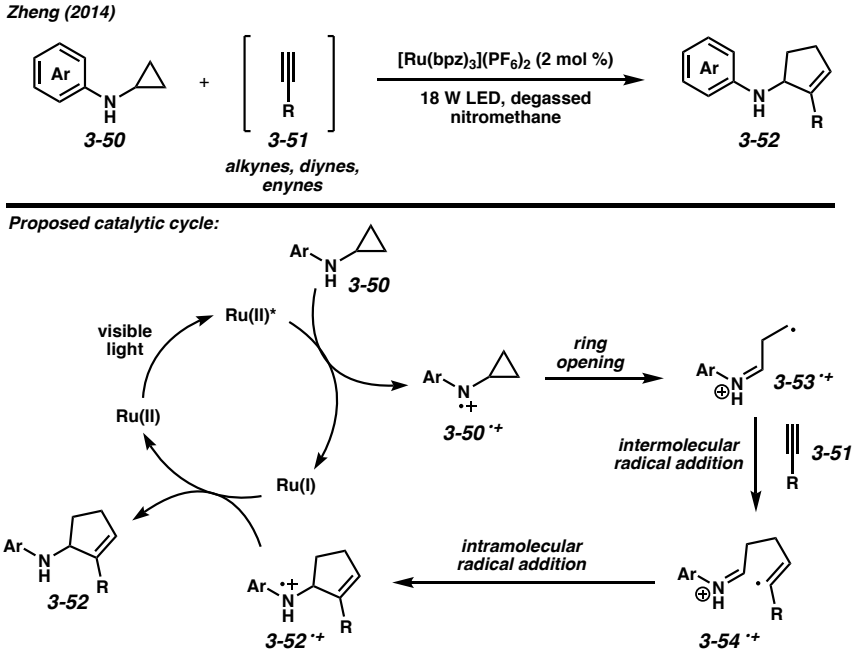


Scheme 3.9. Control experiment supporting carbocation existence in mechanism.

3.2.3 Intermolecular [3+2] Cycloaddition with Cyclopropylanilines using $Ru(bpz)_3^{2+}$ and Visible Light

Thus far, we have witnessed that the exploitation of radical anion intermediates can be useful toward the construction of cyclopentene products. In 2014, Zheng took advantage of radical

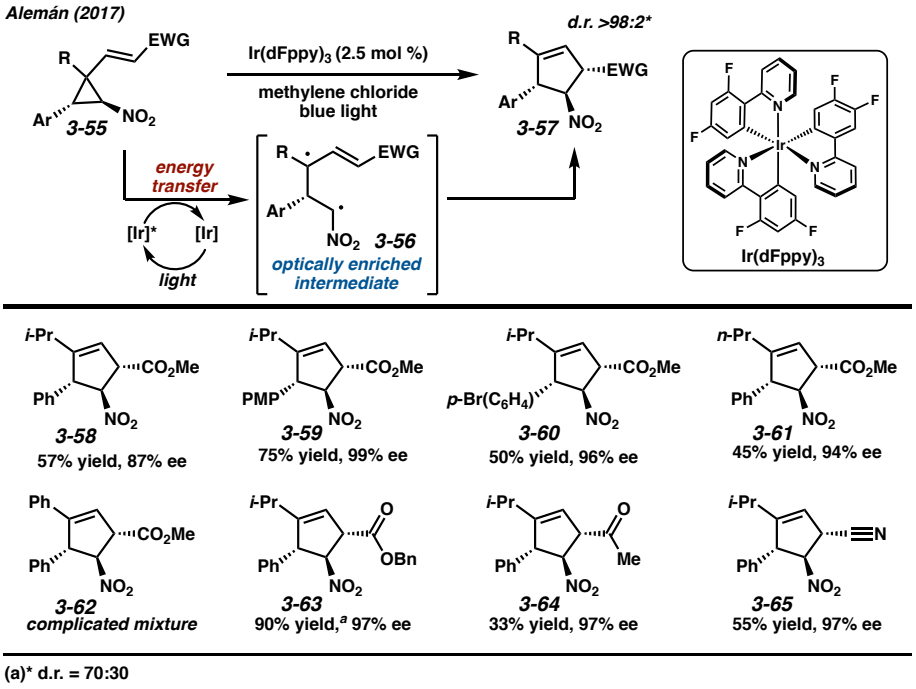
cation intermediates for the synthesis of cyclopentenes.[13] Specifically, an intermolecular (3+2) annulation between cyclopropylanilines and alkynes was achieved using catalytic $[Ru(bpz)_3](PF_6)_2$ and visible light (Scheme 3.10). In a subsequent report that same year, diynes, enynes, substituted cyclopropylanilines and heteroarylamines were further evaluated. Mechanistically, the cycloaddition with alkynes is believed to commence when excited state species $Ru(bpz)_3$* oxidizes cyclopropylaniline **3-50** to the amine radical cation **3-50**$^{\bullet+}$. This single electron transfer process then triggers a cyclopropyl ring opening to generate the distonic radical cation **3-53**$^{\bullet+}$, capable of undergoing an intermolecular radical addition with alkyne substrates to furnish a vinyl radical iminium intermediate **3-54**$^{\bullet+}$. An intramolecular radical addition results in a ring closure to generate the five-membered ring radical cation amine **3-52**$^{\bullet+}$. A closed photocatalytic cycle is proposed in which $Ru(bpz)_3^{1+}$ reduces amine radical cation **3-52**$^{\bullet+}$ to simultaneously generate the ground state $Ru(bpz)_3^{2+}$ and the observed cyclopentene adduct.



Scheme 3.10. Cyclopentene synthesis through a photooxidative pathway.

3.2.4 Chirality Preserved Photocatalytic Ring Expansion via Energy Transfer

In 2017, inspired by the elegant work of Yoon, the group of Alemán envisioned that enantiomerically enriched cyclopropanes could perhaps undergo an intramolecular visible-light photocatalytic mediated ring expansion.[14] This process was hypothesized to form an optically enriched intermediate that could preserve the chiral information throughout the mechanism, leading to optically enriched products. After a thorough catalyst screen, it was found that $Ir(dFppy)_3$ did in fact promote this process. Acylcyclopropanes, specifically aldehydic cyclopropanes, were found to furnish dihydrofurans with high chiral preservation. The cyclopropyl aldehydic partners were easily converted to α,β-unsaturated esters, ketones, and nitriles and found to undergo vinylcyclopropane rearrangement with excellent chirality transfer (Scheme 3.11).



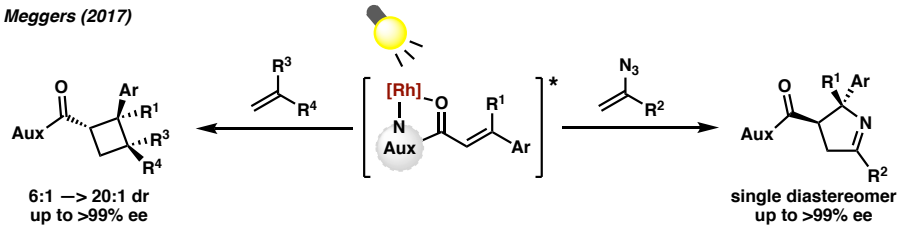
Scheme 3.11. Scope of optically enriched cyclopentenes.

To further understand this unique process, DFT (density functional theory) computational calculations were performed in combination with further experimentation. Electrochemical studies aided in ruling out a photocatalytic oxidation mechanism, as no oxidation features were observed when a cyclopropyl starting material was evaluated. A photocatalytic reduction was deemed possible, but when the highly reducing *fac*-[Ir(ppy)$_3$] ($E^*_{4+/3+} = -1.67$ V vs. Ag/AgCl) was employed as a catalyst in one of the rearrangements, only 27% versus >98% conversion was observed. When an ester cyclopropane was irradiated with UV light (λ_{max} = 365 nm), Cloke-Wilson Rearrangement was observed with moderate conversion (23%) after prolonged irradiation. Lastly, the quantum yield was measured and observed to be ($\Phi = 0.05$). It was suggested that because of the low value, a radical chain propagation is not taking place. In all, these experiments combined suggested that an energy transfer process was facilitating the transformation, a stark difference from the reactions evaluated thus far.[15]

3.2.5 Asymmetric Cyclopentene Annulation via Visible Light Excitation of Catalyst Bound Substrates

To our knowledge, the most recent example of cyclopentene construction using photocatalysis was reported by Meggers this year.[16] Based on the reports disclosed by Yoon and Alemán, acceptor substituted cyclopropanes were distinguished by Meggers to be useful building blocks for photoexcited state or photoinduced electron transfer induced ring opening. Rather than using dual catalysis like Yoon's system which combines a chiral Lewis acid and a Ru photocatalyst, Meggers has developed a more simplified catalytic system. By using a single rhodium based chiral Lewis acid and visible light, asymmetric [2+2] cycloadditions with olefins

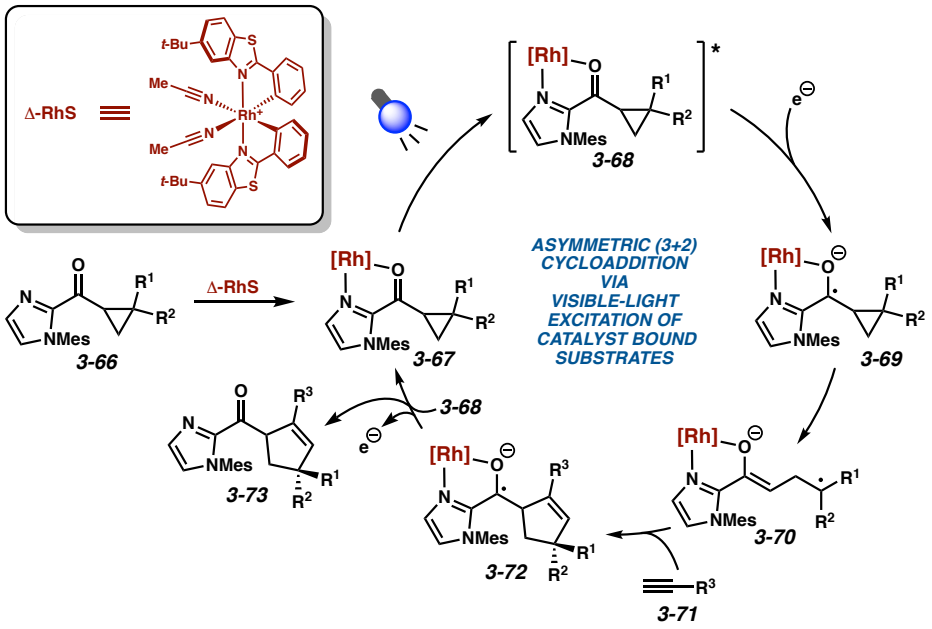
to furnish chiral cyclobutanes[17] and a net (2+3) cycloaddition using vinylazides to generate chiral 1-pyrrolines[18] have been accomplished (Scheme 3.12).



Scheme 3.12. Visible-light-activated catalytic asymmetric cycloadditions via direct excitation of Rh-substrate complex.

In hopes of expanding their methodology toward other chiral cyclic scaffolds, Meggers envisioned exploiting acylcyclopropanes with their reaction manifold in combination with alkenes or alkynes. As a result, this feat was successful with Meggers' chiral-at-metal rhodium Lewis acid photocatalyst,[19] and non-racemic cyclopentanes and cyclopentenes were directly obtained. The proposed mechanism depicted in Scheme 3.13 was supported by investigations of the photophysical and photoredox properties of a Rh-coordinated acylcyclopropane. The chiral Rh Lewis acid photocatalyst is believed to have three main roles: enabling direct excitation, lowering the reduction potential, and inducing excellent asymmetry. Initial bidentate coordination of the cyclopropane starting material to the rhodium complex generates catalyst/intermediate **3-67**. Irradiation of **3-67** results in a highly oxidizing photooexcited species capable of abstracting an electron from triethylamine. This in turn causes a ring opening event leading to the rhodium enolate radical intermediate **3-70**. It is believed that during this ring opening, all initial chiral information of the starting material cyclopropane disappears and only the helical chirality of the Rh-complex remains. At this point the asymmetric (3+2) photocycloaddition occurs with alkynes leading to the ketyl radical intermediate **3-72**. **3-72** is thought of as a potent reducing agent, which can either donate an electron to the previously oxidized Et_3N or to another equivalent of the photoexcited intermediate **3-68** thus propagating a chain mechanism. Lastly, ligand exchange

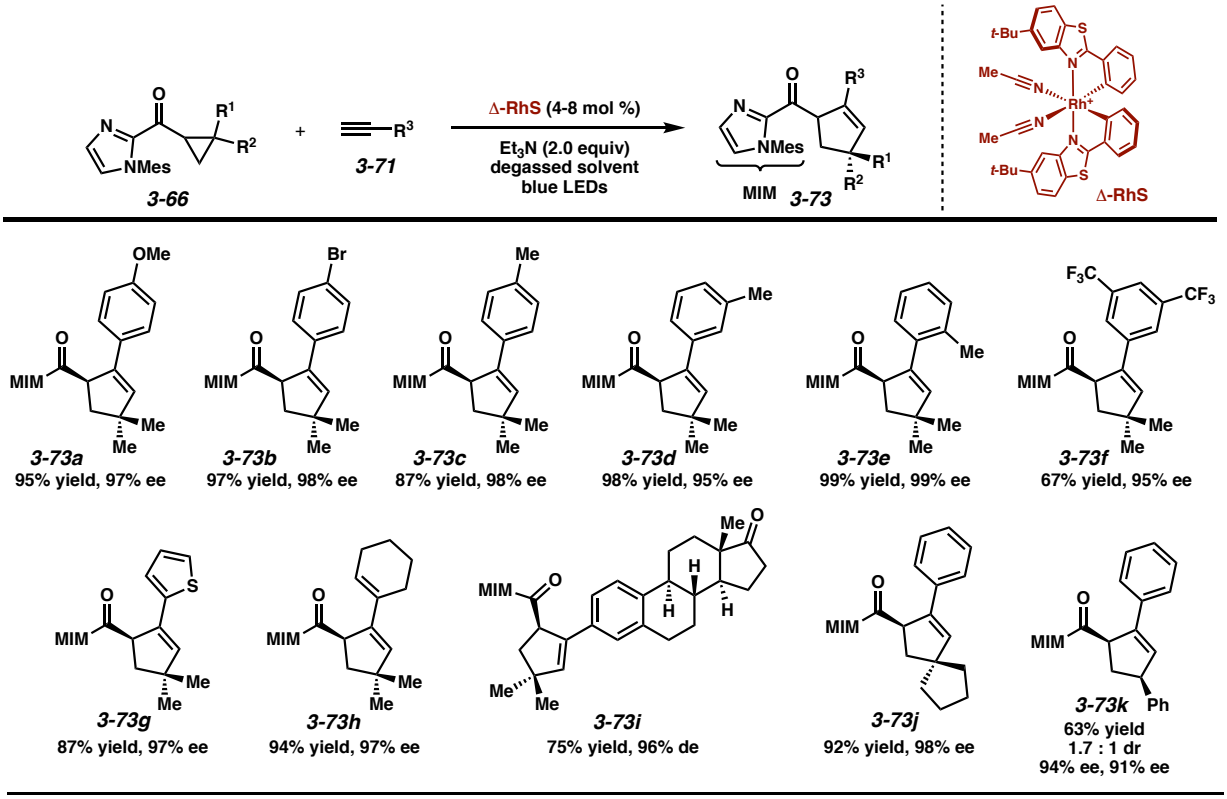
occurs to regenerate the catalyst/substrate complex and release the cycloaddition product(s). Assessment of the quantum yield was determined to be 0.11, which disfavors a chain propagation mechanism.



Scheme 3.13. Proposed mechanism of a photocatalyzed asymmetric (3+2) cycloaddition to furnish cyclopentenes.

The cyclopentene scope for this transformation is presented in Scheme 3.14. Notably, phenylacetylenes were suitable for accessing asymmetric cyclopentenes. It was noted that before Meggers' report, these alkyne substrates had not been successful in intermolecular catalytic asymmetric photocycloadditions. Electron-neutral and electron-rich arylacetylenes were tolerated, and products were obtained in excellent yields and enantioselectivity. A decrease in yield was observed with the electron-poor arylacetylene **3-73f**, but regardless it was still obtained in an appreciable amount and excellent enantioselectivity. Additionally, subjecting a thiophene alkyne (**3-73g**), enyne (**3-73h**), or estrone derivative alkyne (**3-73i**) to the reaction conditions resulted in efficacious outcomes. Modifying the cyclopropyl ketone led to spirocycle **3-73j** in excellent yield

and enantioselectivity. For product **3-73k**, although a 1.7:1 dr and decrease in yield was observed, both diastereomers were obtained in high enantioselectivity.



Scheme 3.14. Asymmetric cyclopentene scope.

3.3 Evaluation of Vinyldiazo Reagent Nucleophilicity

Over the past two decades, vinyldiazo compounds have become popular building blocks for the synthetic organic chemistry community. These reagents provide mild, efficient, and highly selective modes of access to heterocycles and carbocycles.[20] In particular, stabilized vinyldiazo acetate compounds have been recognized as versatile species that offer diverse reaction outcomes. Slight modification of the substitutional environment of a vinyldiazo reagent can lead to unique and differential pathways toward accessing an array of synthetically useful compounds. This

ability is heavily due to the presence of two very valuable functional groups, the vinyl and the diazo, which in combination can lead to elegant and powerful transformations (*vide infra*).

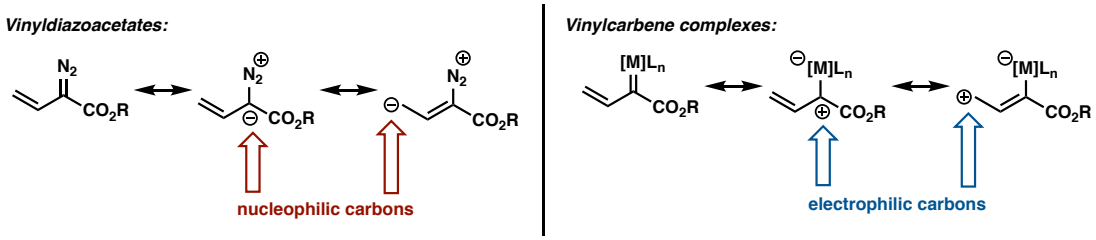


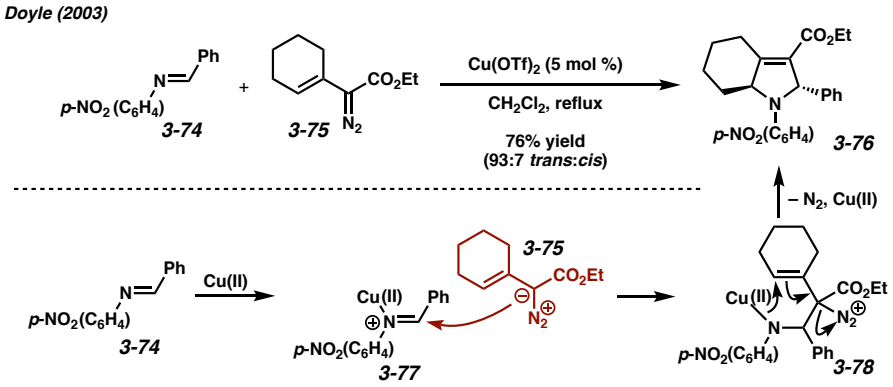
Figure 3.1 General reactivity patterns of vinyldiazoacetates and metal vinylcarbene complexes.

The potential reactivity sites of vinyldiazoacetate and metal vinylcarbene complexes are portrayed in Figure 3.1. By inspecting the two resonance contributing structures it is clear that naked vinyldiazoacetates contain two nucleophilic sites at C(α) and the vinylogous C(γ). In general, the exact opposite is observed when metal vinyl carbene species are invoked, leading to two sites of electrophilicity, C(γ) and C(α). The latter reactivity has been heavily exploited in the construction of cyclopentenes via (3+2) cycloadditions. Davies,[21] Doyle,[22] and López[23] have been major contributors to this area of metal catalyzed cyclization reactions with vinyldiazo reagents to construct useful cyclopentene products. The reactivity is typically mediated by carbene/carbenoid intermediacy, where diazo decomposition using Rh, Cu, or Au leads to an electrophilic metal vinylcarbene species, typically undergoing addition with nucleophilic C=C partners. In order for efficient cyclizations to occur, 2-carbon components for effective cyclizations have included enol ethers, indoles, vinyl azides, as well as allenes.

Conversely, in our projected proposal, we envisioned the vinyldiazoacetate species acting as a *nucleophile*, in order to efficiently attack our 2-carbon radical cation intermediate. The exploration of different transformations using vinyl diazo reagents and metal catalysts have revealed that although rare, vinyl diazo compounds can in fact function as nucleophilic partners.

The isolated examples in the literature that document this uncommon nucleophilic behavior will be reviewed chronologically, focusing on the mechanistic behavior of the vinyldiazo species in each transformation in order to provide the necessary background and basic principles for our conceptualized proposal.

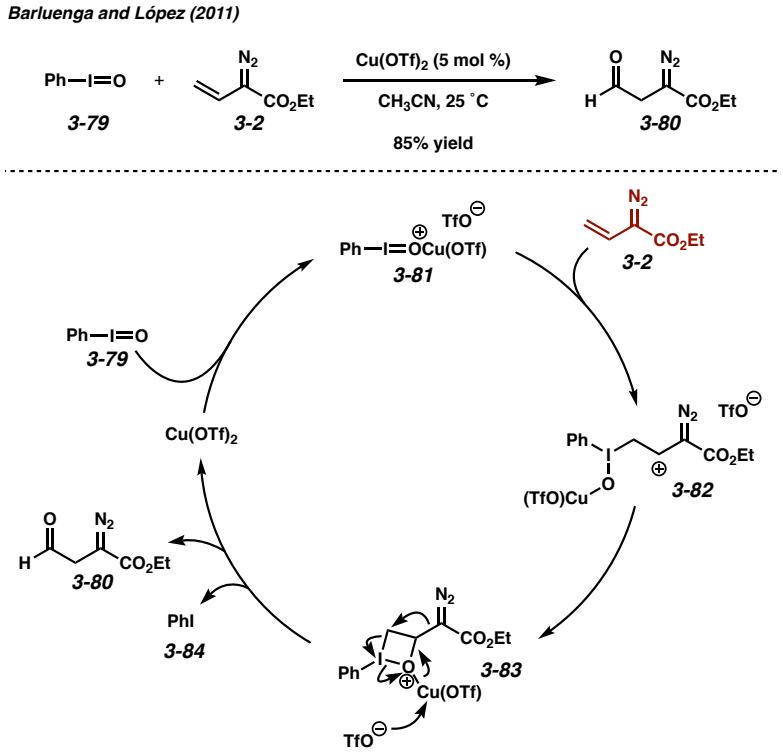
In 2003, Doyle reported a copper catalyzed synthesis of dihydropyrroles from vinyldiazoacetates and imine starting materials (Scheme 3.15).[24] Mechanistically, it is believed that $Cu(OTf)_2$ acts as a Lewis acid by activating imine **3-74**. This activation results in a highly electrophilic species that experiences a direct C(α) nucleophilic attack by the aliphatic vinyldiazo reagent **3-75**. The resulting intermediate **3-78** is then poised to undergo an S_N2' displacement of dinitrogen, leading to dihydropyrrole **3-76**. The desired product was only formed by $Cu(OTf)_2$ catalysis and was not catalyzed by $Rh_2(OAc)_4$. Their proposed mechanism was supported by work from Jørgensen, Gevorgyan, and Lee at the time, which demonstrated the use of copper salts for the activation of imines in cycloaddition reactions.[25]



Scheme 3.15. Dihydropyrrole synthesis using vinyldiazoacetates and aryl imines.

In an alternative transformation employing $Cu(OTf)_2$ and vinyldiazo reagents, Barluenga and López disclosed a novel method to access *β*-oxodiazo compounds using iodosylbenzene (Scheme 3.16).[26] Notably, these products arose from an unprecedented oxidation/1,2-shift of the diazoacetate moiety (*vide infra*). First, it is believed that copper triflate coordinates with

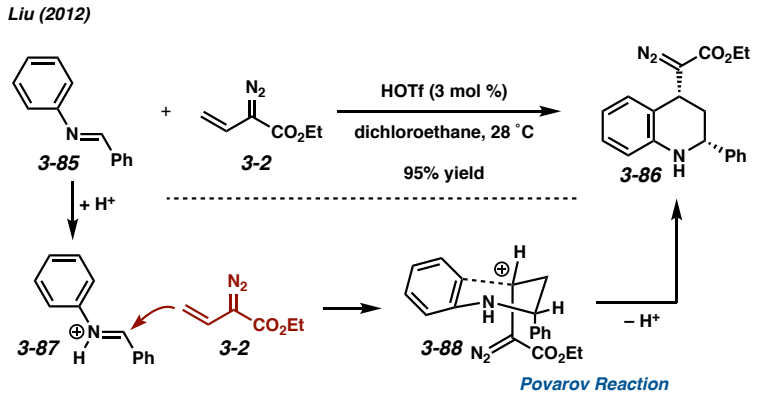
iodosylbenzene **3-79** to generate the electrophilic species **3-81**.[27] A vinylogous attack by ethyl vinyldiazoacetate **3-2** into intermediate **3-81** generates **3-82**, which cyclizes to the oxonium species **3-83**. At this stage, a pinacol-like migration of diazo acetate results in reductive elimination of iodobenzene **3-84** and the Cu(II) catalyst to furnish the observed oxodiazo product **3-80**.



Scheme 3.16. Synthesis of β-oxodiazo compounds.

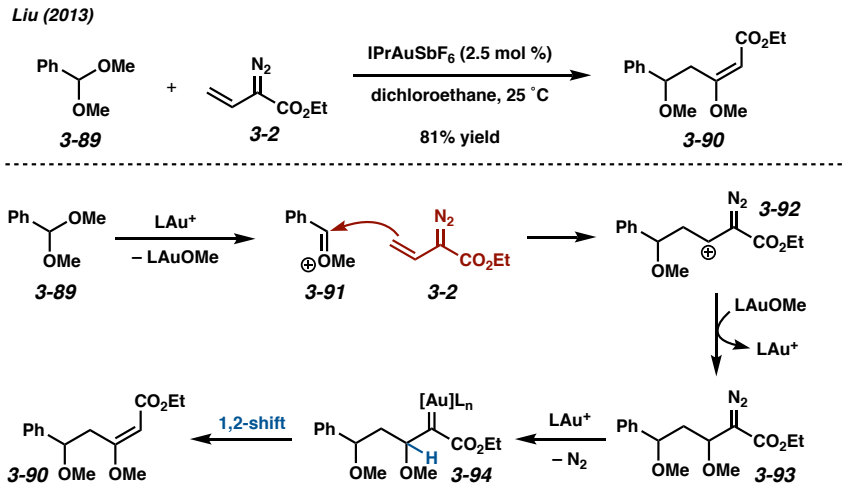
Rather than employing a metal catalyst, in 2012 Liu demonstrated the efficiency of a Brønsted acid to facilitate formal (4+2) cycloadditions between aromatic imines and vinyldiazo species (Scheme 3.17).[28] This transformation, typically known as a Povarov Reaction when employing a suitable alkene (here the vinyl group of the diazo reagent), allowed for the efficient synthesis of useful six-membered diazo containing azacycles. Initial protonation of the imine renders the highly electrophilic species **3-87** susceptible to a vinylogous attack by vinyldiazoacetate **3-2**. The formation of the initial C–C bond is then proposed to generate a

chairlike transition-state in which a Povarov Reaction occurs, resulting in the regeneration of catalytic acid and the versatile diazo product **3-86**.



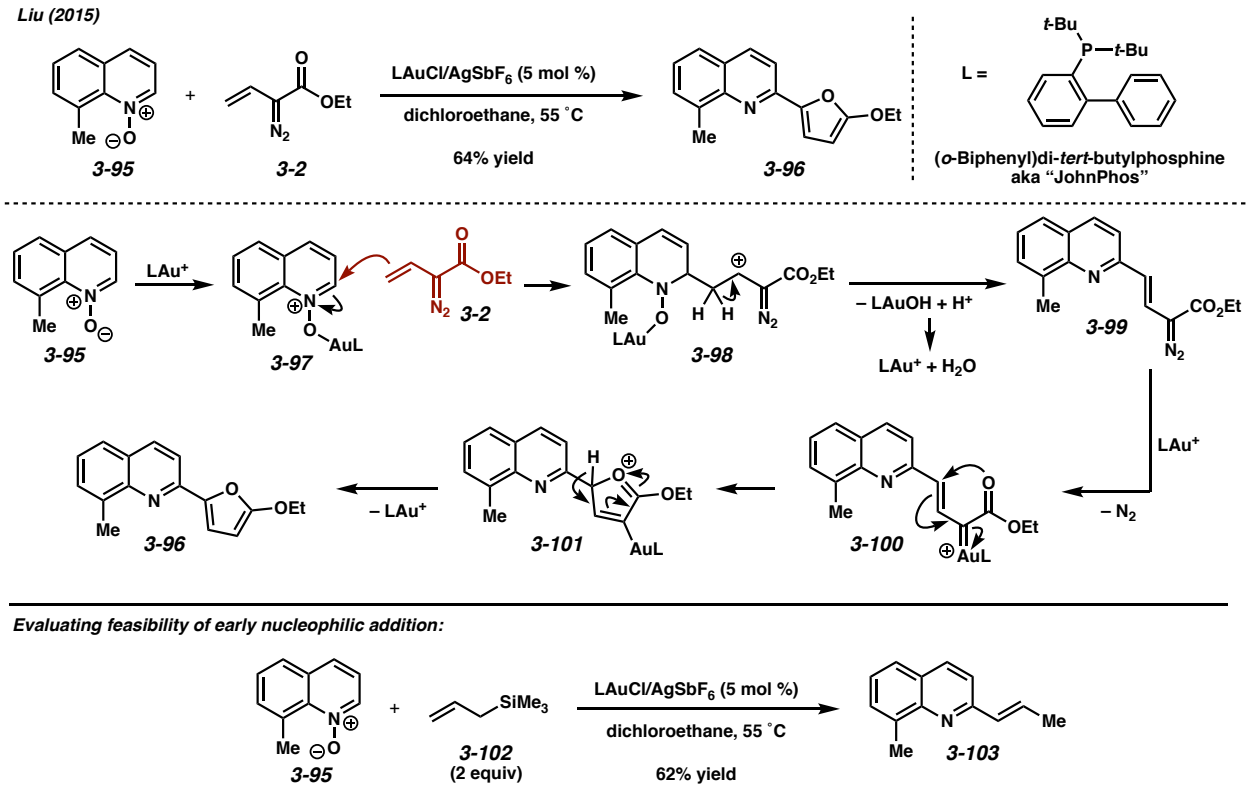
Scheme 3.17. Synthesis of diazo azacycles.

A year later, Liu continued exploring alkenyldiazo carbonyl species in a gold-catalyzed reaction with acetals to render *E*-selective alkyl 3,5-dimethoxy-5-pent-2-enoates in good yields.[29] Mechanistically, it is believed that the $IPrAuSbF_6$ (IPr = 1,3-bis(diisopropylphenyl)imidazole-2-ylidene) catalyst facilitates rapid methoxy exchange with acetals to generate oxonium intermediate **3-91**. This electrophile readily undergoes a nucleophilic attack by the γ-carbon of the vinyldiazo reagent to render carbocation **3-92** stabilized by the neighboring diazo functionality. A subsequent methoxy exchange leads to intermediate **3-93**, and the regeneration of the Au-catalyst subsequently furnishes carbene intermediate **3-94**. At this point in the mechanism a 1,2-hydrogen shift, supported by deuterium labeling experiments, leads to excellent *E*-selectivity in the product. The *trans*-selectivity further supports the proposed mechanism as it is a feature that is substantially indicative of gold carbene species.



Scheme 3.18. Synthesis of *E*-alkenes.

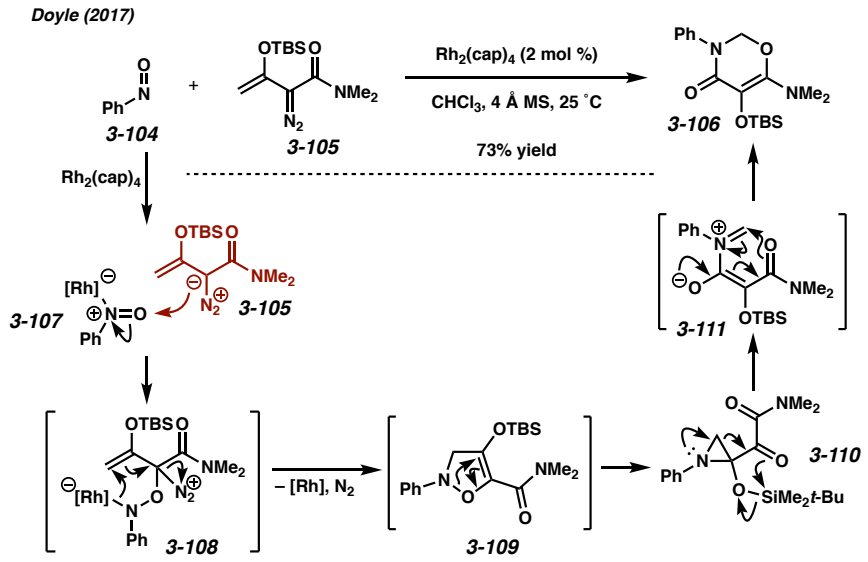
In an additional transformation reported by Liu and mediated by cationic gold catalysis, the α-furanylation of quinoline *N*-oxides with vinyldiazo carbonyl species was achieved.[30] A speculative mechanism was presented by Liu and is illustrated in Scheme 3.19. Initially, the gold complex is believed to coordinate with the oxygen of 8-methylquinoline *N*-oxide, thus increasing its electrophilicity. A control experiment to verify this first step was conducted in which a solution of methylquinoline *N*-oxide in the presence of the LAuCl/$AgSbF_6$ was treated with allyl trimethylsilane. As a result, the nucleophilic addition was observed in good yield. Continuing with the mechanism, a subsequent loss of H_2O is believed to generate γ-quinoline substituted diazo ester **3-99**. At this stage, diazo decomposition leads to a gold carbene poised to undergo an "oxa-Nazarov" cyclization to yield the furanylium cation **3-101**. Deuterium labelling studies supports a closing protodeauration, leading to the furanylated quinoline product **3-96**.



Scheme 3.19. Furanylation of quinoline *N*-oxides: proposed mechanism and control experiment.

Apart from the early example by Doyle which reported a *direct* addition of a vinyldiazo reagent, *vinylogous* additions have predominated the nucleophilic examples discussed thus far. However, as it was noted earlier, modifying the substitution of vinyldiazo species can result in differential reaction outcomes. In 2017, Doyle reported an elegant rhodium-catalyzed cyclization reaction employing enoldiazoacetamides and nitrosoarenes.[31] Enoldiazo carbonyl reagents are a subclass of vinyldiazo species in which the enol subunit has generally been exploited as an efficient nucleophile in transformations involving vinylogous additions (e.g., Mukaiyama aldol-type, etc.).[20a] Interestingly, in the example disclosed by Doyle, the enoldiazoacetamide is proposed to undergo a direct addition with nucleophilic C(α) rather than a vinylogous addition (*vide infra*). Multiple experiments were conducted in order to support/refute the proposed mechanism in Scheme 3.20. Initial coordination of $Rh_2(cap)_4$ is believed to activate the nitrosoarene for a direct

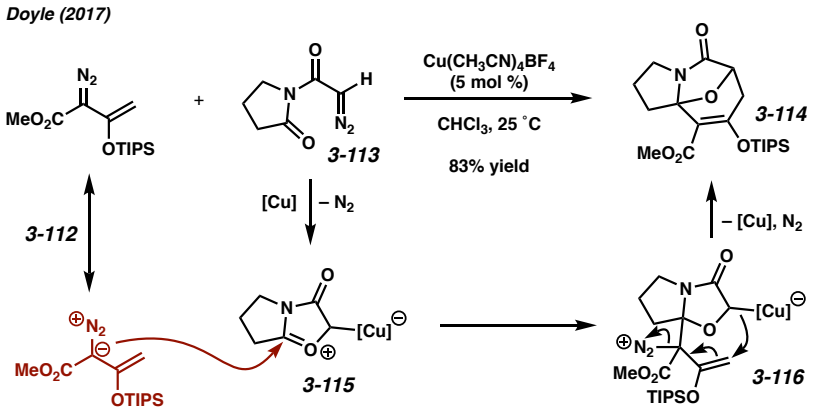
nucleophilic attack by the vinyldiazo reagent rendering diazonium intermediate **3-108**, which proceeds through an intramolecular nucleophilic addition into the vinylogous position furnishing intermediate **3-109**. The early coordination of nitrosobenzene was supported by NMR experiments. Intermediate **3-109** is believed to rearrange generating 2-acylaziridine **3-110**, an intermediate that was identified via NMR monitoring. Literature precedence supported both the generation of isoxazoline **3-109**, as well as its proposed rearrangement. Ring cleavage results in ring expansion of the acyl aziridine **3-110** followed by silyl migration. A final six-membered ring closure of **3-111** affords the product in what is defined as an overall (5+1) cycloaddition.



Scheme 3.20. A formal (5+1) cycloaddition.

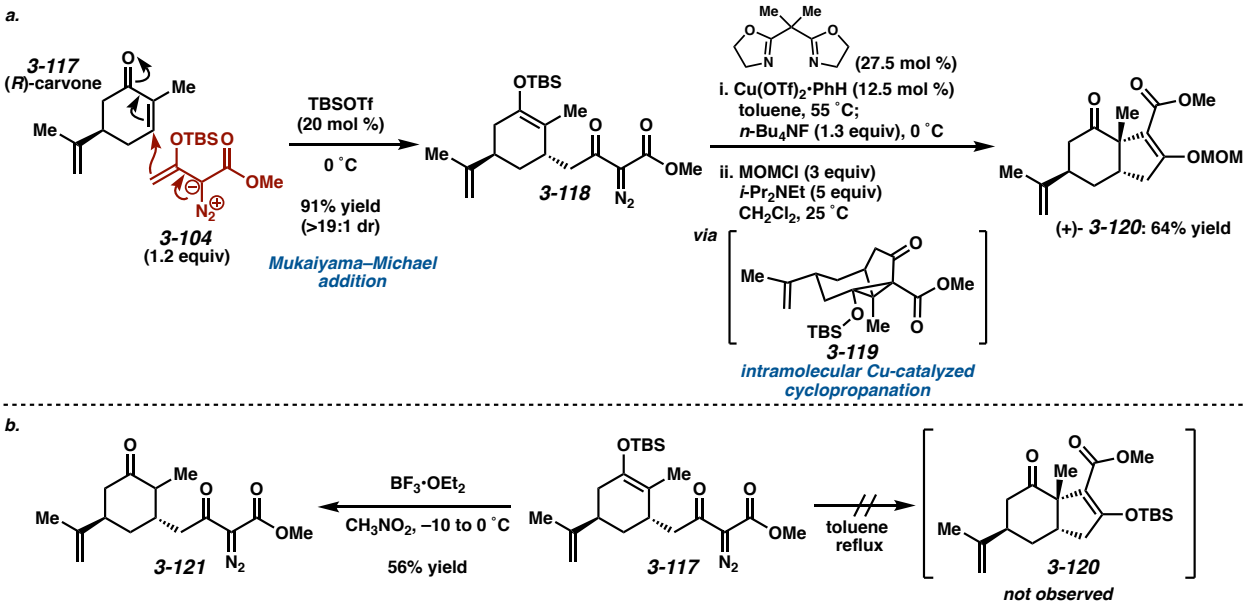
Recent reports in the literature have revealed that two distinct diazo species can be discriminated from one another in cycloaddition reactions.[32] Given that these examples are synthetically attractive yet rare, Doyle developed a novel and useful Cu catalyzed [3+3]-cycloaddition to furnish multicyclic heterocycles of the epoxypyrrolo[1,2-*a*]azepine class.[33] In this Cu catalyzed mechanism, it is believed that diazocarboximide **3-113** is selectively decomposed, resulting in a copper associated cyclic carbonyl ylide **3-115**. A direct nucleophilic

attack by the vinyldiazo species **3-112** followed by a cyclization event renders the formal (3+3) cycloadduct **3-114**.



Scheme 3.21. Diazo discrimination exploited.

All of these isolated examples show promise in that a vinyldiazo reagent may behave as a nucleophile in our proposed photoredox catalyzed process. They also imply that a vinylogous addition may occur, in addition to our hypothetical direct C(α) addition. The former scenario is encouraging given an example by Guerrero and coworkers, who reported a two-step sequence for the cyclopentannulation of conjugate acceptors using a vinyldiazomethane-based reagent.[34] The annulation is illustrated in Scheme 3.22a with (*R*)-carvone **3-117** as the conjugated enone. The procedure begins with a vinylogous addition of enol diazoacetate **3-104** via a Mukaiyama-Michael addition to render diazo ketoester **3-118**. A subsequent Cu-catalyzed cyclopropanation/ring opening cascade leads to the cyclopentene unit **3-120**. Further control experiments ruled out a thermal or Lewis acid promoted cyclization (Scheme 3.22b).



Scheme 3.22 (a) Two step synthesis of cyclopentene products. (b) Control experiments.

To date however, a direct cyclopentene annulation using vinyl diazocarbonyl species as nucleophiles via metal-catalyzed carbene/carbenoid processes or photocatalyzed procedures has not yet been accomplished. Our studies in this area will be described in Chapter 4.

3.4 Chapter 3 Notes and References

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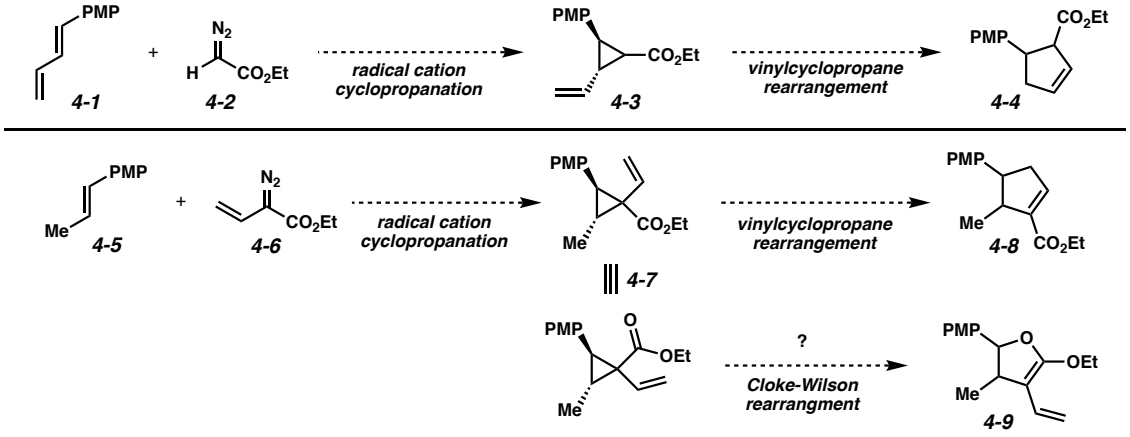
CHAPTER 4

THE DISCOVERY OF RADICAL CATION CYCLOPENTENE ANNULATIONS WITH VINYLDIAZO SPECIES USING PHOTOCATALYSIS

4.1 Introduction: From Cyclopropanes to Cyclopentenes

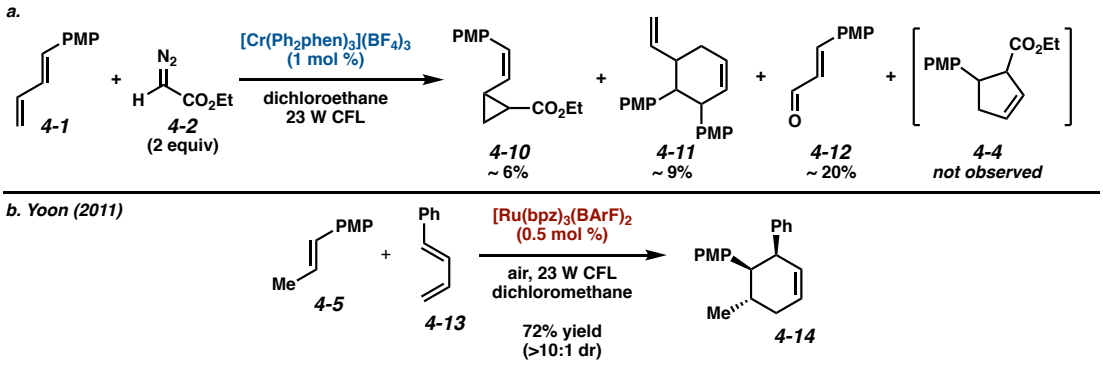
Vinycyclopropane rearrangements have a rich history in their use toward forming 5-membered carbocycles via the vinylcyclopropane → cyclopentene rearrangement.[1] During our investigations of radical cation cyclopropanations, we envisioned a process that could exploit our method to generate vinylcyclopropane intermediates capable of rearranging to cyclopentenes. Initially we evaluated two transformations that could lead to donor-acceptor vinylcyclopropanes (Scheme 4.1). The first reaction used diene **4-1** and ethyl diazoacetate (**4-2**), the latter which had already been established as a useful and efficient nucleophile in radical cation cycloadditions.[2] The second test reaction employed *trans*-anethole (**4-5**), ensuring that radical cation formation would occur due to the proven ionizability of the alkene. The proposed nucleophile, which had not been employed in any photoreactions, was vinyldiazoacetate **4-6**. As covered in Chapter 3, vinyldiazo reagents traditionally behave as electrophilic species but in isolated cases can act as nucleophiles; here we were hoping for the latter. Regardless, both methods could potentially lead to donor-acceptor cyclopropanes, which are useful building blocks that facilitate ring opening rearrangements.[3] An additional product that was anticipated for the second method was dihydrofuran **4-9**, arising from a Cloke-Wilson Rearrangement. In our previous work, we had

observed that cyclopropyl esters can undergo this ring expansion.[2] Using our most successful photooxidizing chromium catalyst $[Cr(Ph_2phen)_3](BF_4)_3$ we proceeded to investigate both theories.



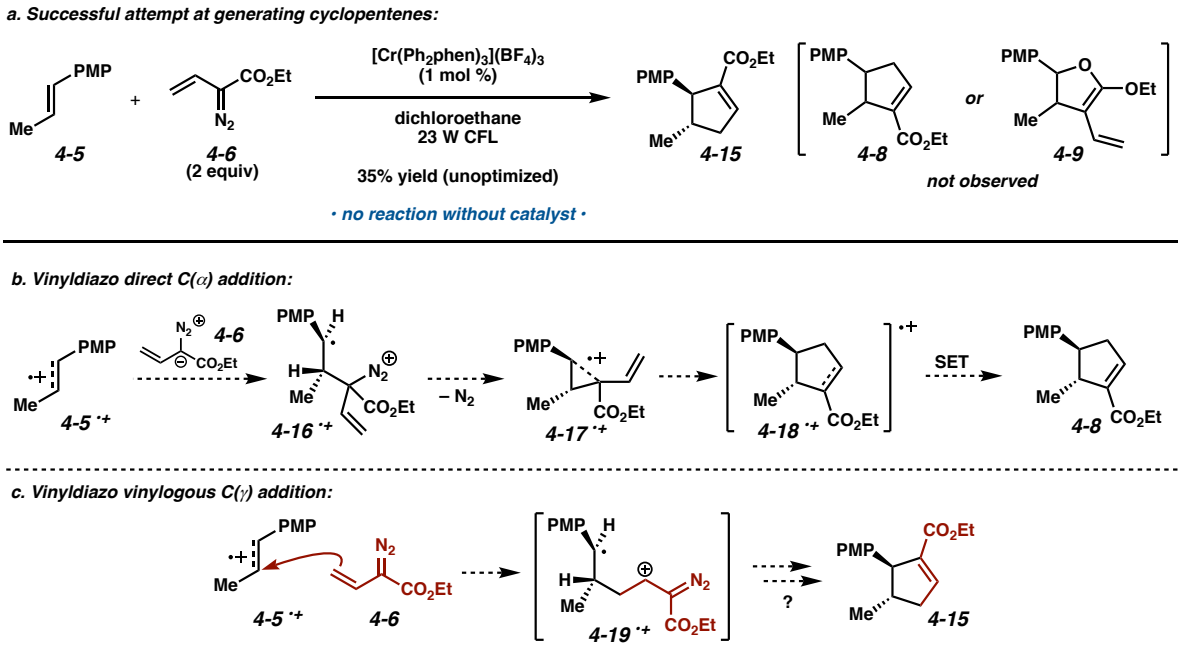
Scheme 4.1. Possible pathways to vinylcyclopropane intermediates.

The results of our initial attempt are displayed in Scheme 4.2a, in which a mixture of products was identified. Cyclopropanation had occurred unexpectedly at the terminal olefin of the diene starting material to generate a distinct vinylcyclopropane (**4-10**). Additionally, the cyclohexene product **4-11** arising from either a direct radical cation Diels-Alder or a [2+2]/vinylcyclobutane cascade process was furnished. In 2011, Yoon reported a similar phenyl diene **4-13** undergoing a successful radical cation (4+2) cycloaddition with *trans*-anethole (Scheme 4.2b).[4] Additionally, a cinnamaldehyde derivative **4-12** was isolated from our reaction mixture, presumably due to oxidative cleavage of the terminal double bond with oxygen.



Scheme 4.2. (a) Initial attempt at generating cyclopentenes (b) Yoon (4+2) cycloaddition using styrenyl alkenes

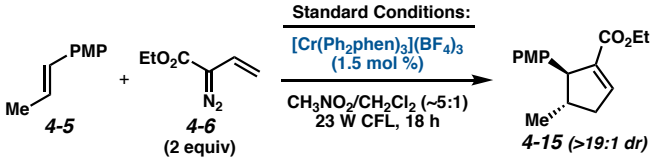
Given the failure of our first endeavor, we continued with plan B, which invoked a vinyldiazo reagent. Although not commercially available, ethyl vinyldiazoacetate (**4-6**) is readily synthesized in three straightforward steps from ethyl acetoacetate, a commodity chemical. It is worth recognizing that the conceptualization of the vinyldiazo approach came from a postdoctoral fellow in our group Dr. Qiankun Li. When the vinyldiazo reagent was subjected to our optimal reported conditions for radical cation cyclopropanation, much to our great fortune, cyclopentene **4-15** was observed as a single diastereomer in 35% yield (Scheme 4.3a). However, NMR experiments revealed that the excellent regioselectivity was not what we had initially inferred. This led us to doubt our initially proposed vinylcyclopropane → cyclopentene cascade process, which in turn raised further questions about our initially proposed mechanism (Scheme 4.3b). Based on the position of the methylene group and ester moiety in the resulting carbon framework, we thought it would be reasonable to suggest that a vinylogous rather than direct addition is occurring (Scheme 4.3c). Further mechanistic investigations would need to be conducted in order to elucidate this proposal and the potential intermediates that eventually lead to the observed cycloadduct (*vide infra*).



Scheme 4.3. (a) Successful cyclopentene annulation attempt (b) Previously proposed mechanism (c) Updated mechanistic proposal involving a vinylogous addition

4.2 Cyclopentene Optimization with *trans*-Anethole

Our successful Cr-photocatalyzed cyclopentene annulation of the *trans*-anethole radical cation with vinyldiazoacetate encouraged us to rapidly optimize the unique transformation (Scheme 4.4). A short solvent screen led us to use nitromethane, which dramatically increased the yield. This was also the optimal solvent for our previously reported radical cation (4+2)-cycloadditions.[5] In order to keep our vinyldiazo reagent stable for longer periods of time, we stored it at low temperatures in a 1 M solution of methylene chloride. The small amount of methylene chloride in the reaction mixture did not hamper the reactivity, although performing the transformation in CH_2Cl_2 did (Entry 3) Performing the reaction with a slight increased catalyst loading (1 to 1.5 mol %) generated cyclopentene **4-15** in excellent yield (92%).



Entry	Deviation from Standard Conditions	NMR yield (%)[a]	Entry	Deviation from Standard Conditions	NMR yield (%)[a]
1	NONE	89 (92[b,c])	13	10 mol % $CrCl_3$	0
2	DCE as solvent	32	14	no catalyst	0
3	CH_2Cl_2 as solvent	22	15	no light	0
4	acetone as solvent	25	16	1.5 mol % $[Ru(bpz)_3](PF_6)_2$, 1 h	99 (93[b])
5	CH_3CN as solvent	67	17	0.2 mol % $[Ru(bpz)_3](PF_6)_2$, 1.5 h	88
6	1 equiv *4-6*	57	18	5 mol % $[IPr(CH_3CN)Au]BF_4$ CH_2Cl_2, 23 °C, 24 h	23
7	3 equiv *4-6*	84	19	2 mol % $Rh_2(OAc)_4$ CH_2Cl_2, 40 °C, 5 h	0
8	NUV[d]	87	20	10 mol % $AgSbF_6$ CH_2Cl_2, 40 °C, 4 h[e]	19
9	blue LED, 37 h	75	21	1.5 mol % Cu(*t*-BuSal)$_2$[f] DCE, 84 °C, 4 h	0
10	white LED, 37 h	74			
11	1 mol % $[Cr(Ph_2phen)_3](BF_4)_3$	86			
12	0.2 mol % $[Cr(Ph_2phen)_3](BF_4)_3$, 42 h	24			

PMP: *para*-methoxyphenyl. [a] ^{1}H NMR yields determined using 2-naphthaldehyde as a standard. [b] Isolated yield in parentheses. [c] 16 h. [d] Near-UV light (bulbs at 300, 350, and 419 nm). [e] 4.9:1 stoichiometry of *4-5*:*4-6* used. [f] Cu(*t*-BuSal)$_2$: copper bis(*N*-*t*-butylsalicylaldimine).

Scheme 4.4. Cyclopentene optimization scope.

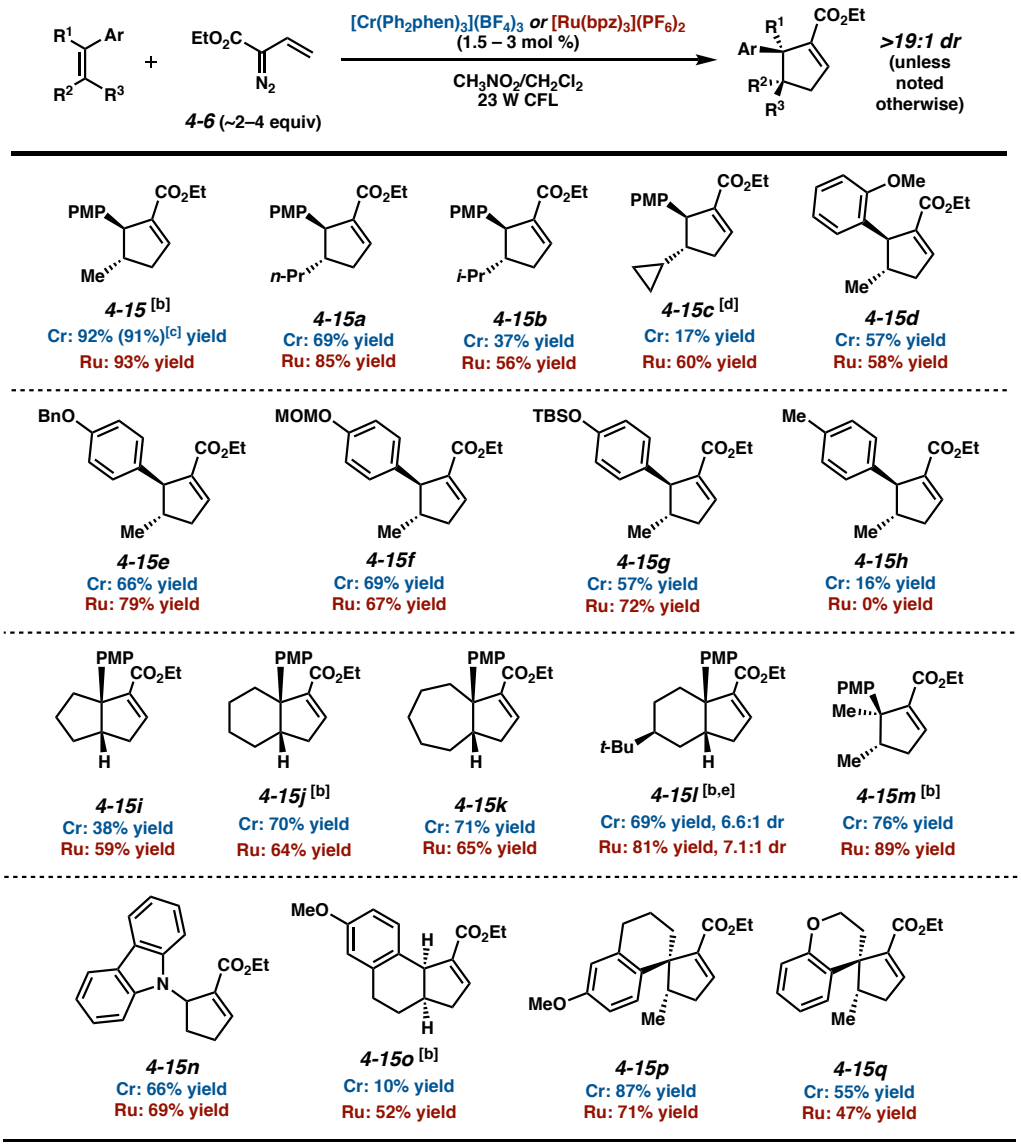
We further evaluated the reaction parameters with our chromium catalyst by deviating from the standard conditions. Two equivalents of the diazo reagent were found to be necessary for an efficient reaction outcome. As in our radical cation cyclopropanations and (4+2) cycloadditions NUV irradiation was acceptable. Switching light sources to blue or white LEDs afforded diminished yields and necessitated longer reaction times. A substantially lower catalyst loading (0.2 mol %) severely hampered the cycloaddition yield. Control experiments supported the vital role of both the photoredox catalyst and light in order for the reaction to occur. Employing a simple $CrCl_3$ salt did not facilitate the reaction at all. Notably, when we replaced our Cr catalyst with the highly oxidizing Ru photocatalyst $[Ru(bpz)_3](PF_6)_2$, the transformation was significantly accelerated, yielding the cyclopentene product in comparable yield but with shorter reaction times. With the Ru photocatalyst, cycloadditions were successful with significantly lower catalyst loading (0.2 mol %), an attractive feature for process chemists. Given the voluminous examples

of metal carbene/carbenoid mediated (3+2) cycloadditions employing alkenyl diazo carbonyl reagents,[6,7,8,9] we evaluated Au, Rh, Ag, and Cu catalysts. Although some reactivity was observed, the transformations typically resulted in complicated mixtures, and were inferior (0-23% yield) to our optimized photocatalyzed method. With huge success employing either Cr and Ru photocatalysts, we decided to pursue both in evaluating our reaction scope. We also viewed this as a comparison study since differences in reactivity between the two oxidizing photocatalysts have been observed and reported in the past.[10] With these goals in mind I surveyed and established the scope with Cr photoredox conditions and Dr. Li assessed the reactivity with the Ru photocatalyst.

4.3 Olefin Scope

Eighteen cyclopentenes with varied substitution were synthesized from a diverse array of olefins using our Cr and/or Ru photocatalyzed (3+2) cycloaddition methodology (Scheme 4.5). The transformation was also performed on gram scale, using *trans*-anethole, without hindering the reaction outcome. It was revealed that ~2-4 equivalents of the diazo reagent and a 1.5-3 mol % catalyst loading led to successful cycloadditions. The main requirement for an effective transformation is the ability to ionize alkenes to form electrophilic radical cation intermediates. As a result, this obligates the presence of an electron-rich arene moiety to allow for facile single electron oxidation. For example, when an alkyl arene was employed, cyclopentene **4-15h** resulted in low yield (16%) with the Cr photocatalyst. However, no product was observed in the Ru case, which may suggest that $[Cr(Ph_2phen)_3](BF_4)_3$ is a more potent single electron acceptor. Therefore, oxygenated arenes provided the best results and could be substituted with alkyl ethers, silyl ethers,

benzyl ethers, and acetals. *N*-Vinyl carbazole, demonstrated by Yoon and Bauld to be a competent ionizable olefin in radical cation cycloadditions,[4,11] proved compatible in our system as well to afford nitrogenated cyclopentene **4-15n**. Architecturally appealing fused ring systems and spirocycles were constructed with excellent diastereoselectivities. An acyclic trisubstituted olefin also rendered product **4-15m** in good yields with both Ru and Cr photocatalysts. Notably, these last three classes of carbocycles contain newly formed quaternary centers. Additionally, cyclopentene **4-15l** was formed in good diastereoselectivity, presumably due to preferential facial attack of the vinyldiazo reagent opposite the large *tert*-butyl substituent.

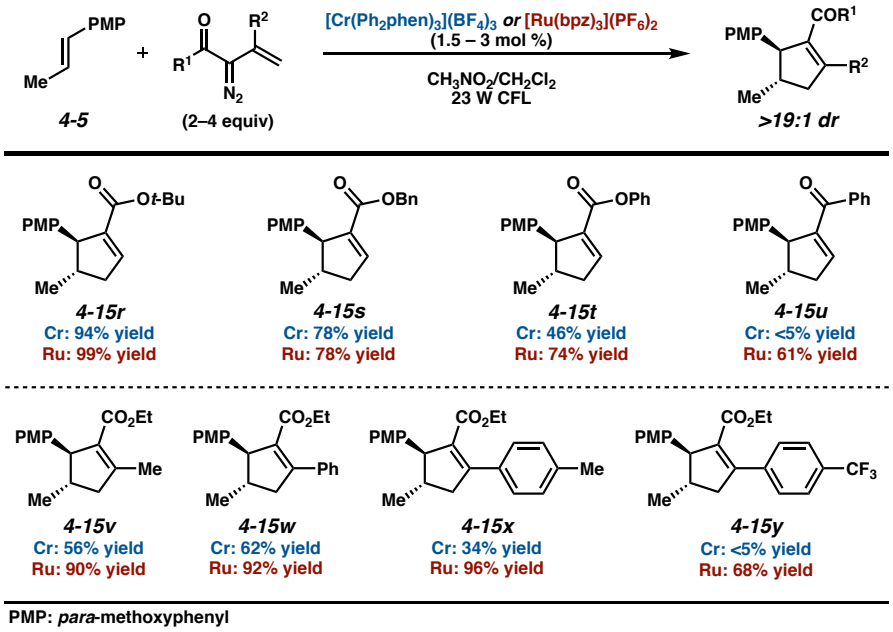


Scheme 4.5. Olefin scope of photocatalyzed (3+2) cycloaddition

4.4 Vinyldiazo Carbonyl Scope

The ester moiety of the vinyldiazo reagent was altered, and it was discovered that *tert*-butyl, benzyl, and activated phenyl esters were all compatible (Scheme 4.6). A diazoketone was also effective using the Ru photocatalyst (**4-15u**). Substitution on the C(β) and C(γ) of the

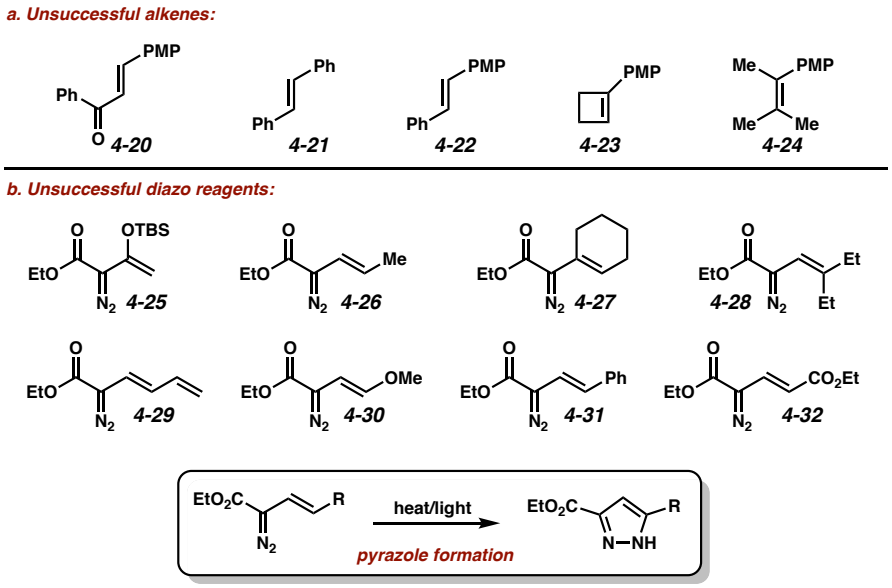
vinyldiazo species was evaluated, but only β-alkyl and β-aryl substituents were successful. When γ-substituted alkenyl diazo reagents were employed, cyclopentene products were not generated. We see this being caused by two possible reasons. First, diazo reagents with γ-substitution may be less likely to undergo a vinylogous nucleophlic addition into radical cation species due to steric considerations. Second, during the course of this project we noted that pyrazole formation mediated by heat/light occurred as an unwanted background reaction.[12] In cases where vinyldiazo reagents lacked γ-substitution, trace amounts of pyrazole formation were also observed. We found that by keeping our reaction mixtures cool and adding the alkenyl diazo reagent in portions, pyrazole formation was usually diminished.



Scheme 4.6. Vinyldiazo scope of (3+2) cycloaddition.

4.4.1 Unproductive Substrates

When surveying the scope of our reaction manifold several limitations were noted (Scheme 4.7). First, tetrasubstituted alkenes such as **4-24** and stilbene substrates **4-21** and **4-22** were not reactive, presumably due to steric hindrance. Enol diazoacetate **4-25** was also unproductive, and instead competitive enol oxidation was observed. An array of γ-substituted vinyldiazo reagents were found to be ineffective due to steric constraints and/or the pyrazole background reaction.

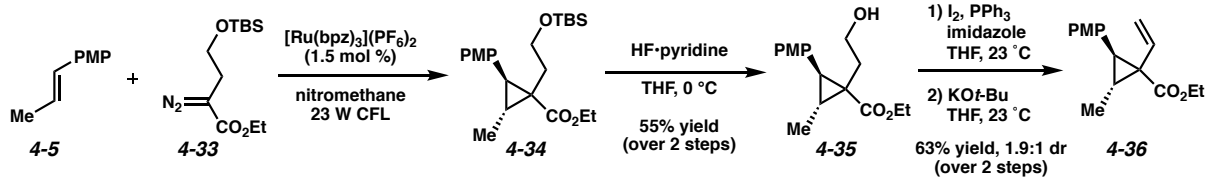


Scheme 4.7. Unsuccessful substrates.

4.5 Mechanistic Investigations

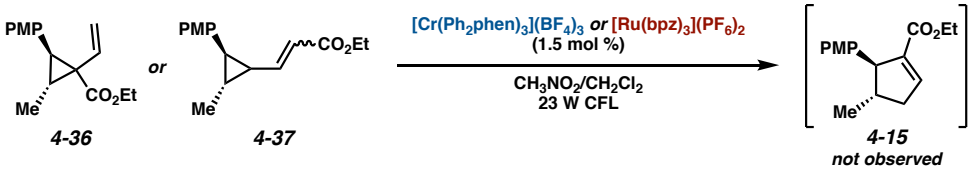
Given the novelty of this transformation, we became highly interested in elucidating the reaction pathway(s) involved. Working together, Dr. Li and I constructed various substrates to probe the mechanistic aspects of the radical cation cyclopentene annulation. To begin, we sought out to synthesize two potential vinylcyclopropanes that could arise from a direct C(α) or

vinylogous C(γ) addition by the diazo reagent. The synthesis of the former is worth addressing (Scheme 4.8). We attempted approximately half a dozen cyclopropanation conditions toward the intermediate cyclopropane, but discovered that only a radical cation cyclopropanation optimized with $[Ru(bpz)_3](PF_6)_2$ was successful. *trans*-Anethole proceeded through a radical cation (2+1) cycloaddition with donor/acceptor diazo **4-33**. Subsequent TBS deprotection with HF•pyridine led to the free alcohol **4-35** in 55% yield over those two steps. Afterward, conversion of the alcohol into a good leaving group (iodine), allowed for an efficient elimination with potassium *tert*-butoxide to render a diastereomeric mixture of vinyclyclopropane **4-36** in 63% yield over two steps. Notably, it was our previous investigations in radical cation cyclopropanations that facilitated the synthesis of **4-36**.[2]



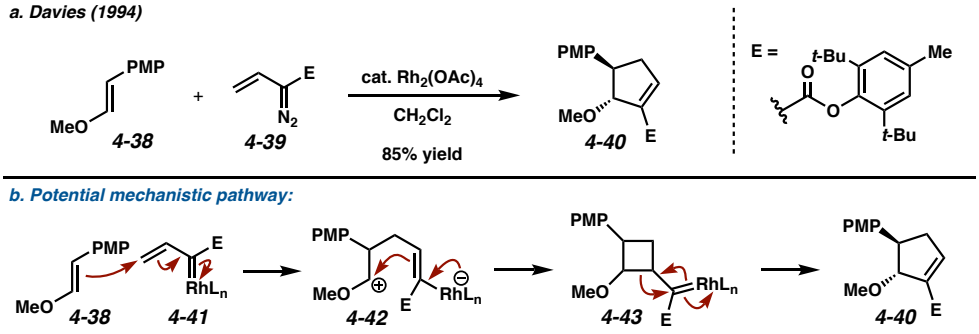
Scheme 4.8. Synthesis of vinylcyclopropane **4-36**.

Both alkene isomers of vinylcyclopropane **4-37** arising from a potential vinylogous addition were synthesized using alternative Cu catalyzed carbene/carbenoid chemistry to set the cyclopropyl backbone.[13] Once these two substrates were formed they were exposed to both Cr and Ru photocatalysts (Scheme 4.9). Cyclopentene **4-15** rearrangement was not generated from either **4-36** or **4-37**. This refuted a process in which an initial cyclopropanation followed by vinylcyclopropane rearrangement leads to our observed cycloadduct.



Scheme 4.9. Attempted vinylcyclopropane → cyclopentene rearrangements.

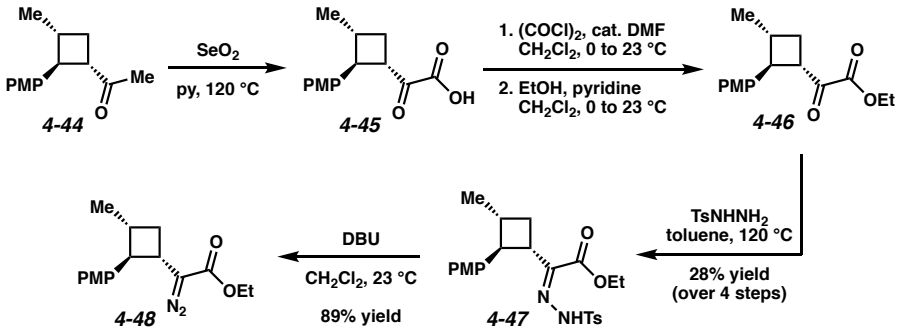
We further pondered whether other transient intermediates could be formed in our photocatalytic system that could potentially lead to our observed cyclopentene. We were inspired by an early report by Davies in which (3+2) cycloadditions between vinyldiazo reagents and vinyl or styrenyl ethers were accomplished (Scheme 4.10a).[7b] In comparison to our (3+2) process which summons vinyldiazo species as nucleophiles, Davies' rhodium vinylcarbene intermediate generated after diazo decomposition acted as an electrophile (Scheme 4.10b). A subsequent attack by styrenyl ether **4-38** to the electrophilic vinylogous carbon of vinylcarbenoid species **4-41** results in a zwitterionic intermediate (**4-42**). Ring closure to form cyclobutyl carbenoid **4-43** followed by ring expansion via a 1,2-alkyl shift renders the observed cyclopentene compound **4-40**.



Scheme 4.10. (3+2) cycloaddition with electrophilic vinyl metal carbene species and enol ethers.

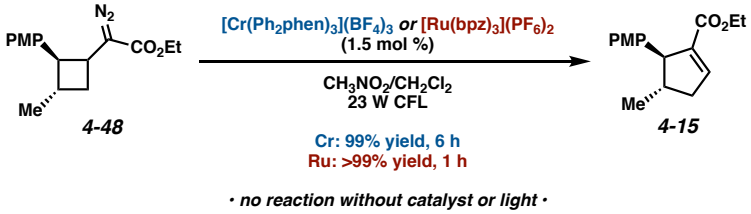
Previous research in our laboratory has confirmed that strained vinylcyclobutane intermediates can be generated through Cr photocatalysis.[14] A subsequent vinylcyclobutane rearrangement mediated by the photocatalyst leads to cyclohexene adducts. Therefore we had to wonder whether a diazo cyclobutane intermediate, analogous to the one proposed by Davies, could be a potential intermediate in our net (3+2) radical cation cycloaddition. The pursued synthesis of cyclobutane intermediate **4-48** is illustrated in Scheme 4.11. The initial cyclobutyl methylketone was generated using a known procedure,[15] and subsequently oxidized with selenium dioxide to furnish α-keto acid **4-45**. Next, acyl chloride generation followed by treatment with ethanol in the

presence of base rendered α-keto ester **4-46**. Lastly, a condensation with tosyl hydrazide to form tosylhydrazone **4-47** was treated with DBU to reveal the diazo functionality in cyclobutane **4-48**.



Scheme 4.11. Synthesis of cyclobutane diazo test substrate.

With our independently synthesized cyclobutyl diazo test substrate on hand, we subjected it to both Ru and Cr photocatalyzed conditions (Scheme 4.12). Surprisingly, cyclopentene **4-15** was formed in near quantitative yield. Further control experiments established that both light and the photooxidative catalysts were necessary, suggesting that a radical cation mechanism mediates the observed ring expansion. Although we did not detect the diazo cyclobutane **4-48** in any of our reaction mixtures, we cannot definitely refute its presence in a mechanistic pathway.



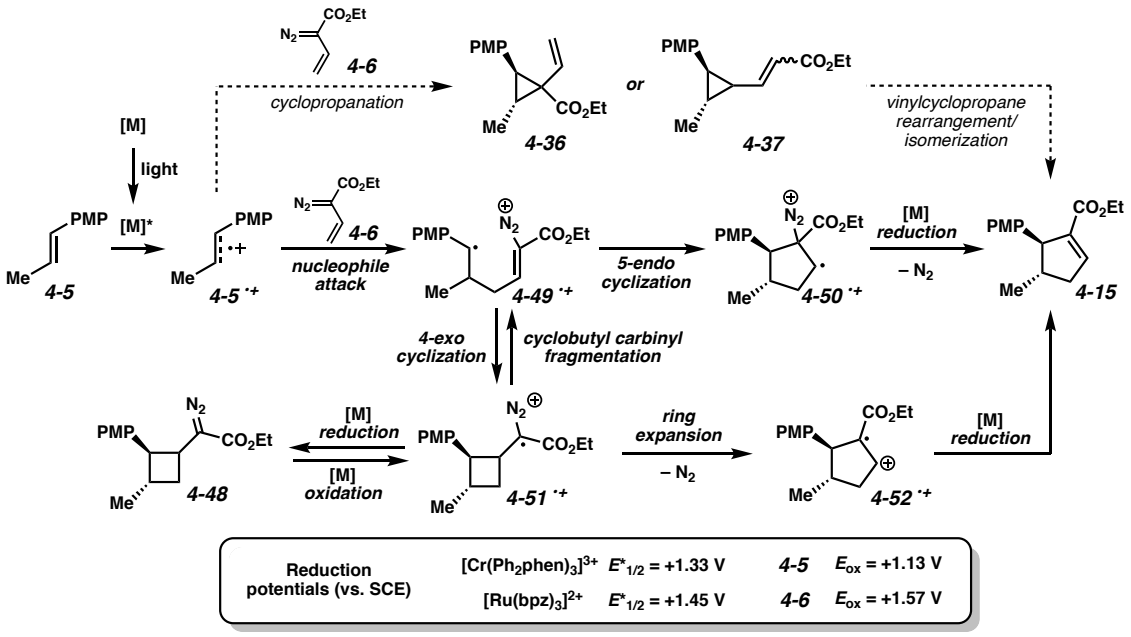
Scheme 4.12. Observed diazo cyclobutane → cyclopentene photocatalyzed rearrangement.

By combining these experimental observations, as well as our previous studies exploiting radical cations for carbocyclic construction, a proposed mechanism using *trans*-anethole and ethyl vinlyldiazoacetate as model reagents is shown in Scheme 4.13. The vinylcyclopropane → cyclopentene scenario is included for completeness sake but can be disregarded. Irradiation of either $[Cr(Ph_2phen)_3]^{3+}$ or $[Ru(bpz)_3]^{2+}$ with visible light forms an excited state catalyst that

performs a single electron transfer with *trans*-anethole to generate radical cation intermediate **4-5**$^{\bullet+}$. The alternative possibility of ethyl vinyldiazoacetate being ionized by either photooxidizing catalyst was assessed by measuring its reduction potential (E_{ox} = +1.57 V vs. SCE). The ionization potential was found to be higher than both catalysts and almost 0.5 V higher than the more easily oxidizable *trans*-anethole (E_{ox} = +1.13 V vs. SCE). Thus, the feasibility of oxidizing the diazo species was deemed improbable.

Once the formation of the electrophilic intermediate **4-5**$^{\bullet+}$ occurs, a vinylogous attack from the diazo reagent is proposed to furnish intermediate **4-49**$^{\bullet+}$. Benzylic radical stabilization of intermediate **4-49**$^{\bullet+}$ may rationalize the excellent regioselectivity of our cycloaddition. At this stage in the mechanism, two potential pathways eventually lead to the cyclopentene product. One scenario would involve a 5-endo radical cyclization that generates intermediate **4-50**$^{\bullet+}$. A subsequent single electron reduction and loss of dinitrogen would produce the observed cyclopentene. An alternative pathway from key intermediate **4-49**$^{\bullet+}$ would invoke a 4-exo cyclization to furnish cyclobutyl species **4-51**$^{\bullet+}$. Hypothetically, an off-cycle reduction of intermediate **4-51**$^{\bullet+}$ would generate the independently synthezied cyclobutane diazo **4-48**. This scenario would support its involvement as an intermediate toward cyclopentene formation. Oxidation of **4-48** would render intermediate **4-51**$^{\bullet+}$ which can undergo ring expansion with simultaneous loss of N_2 to furnish **4-52**$^{\bullet+}$, and reduction would generate cyclopentene **4-15**. Although the radical cation is drawn on the diazo motif of **4-51**$^{\bullet+}$, we believe the radical ion generated from the oxidation of **4-48** resides on the arene, not the diazo functionality. Furthermore we cannot disregard the possibility of a "long-bonded intermediate"—similar to what Bauld has proposed in the radical cation cyclopropanation. The cyclobutanation pathway better adheres to Baldwin's Rules of radical cyclization, but the lack of observation of the cyclobutane intermediate

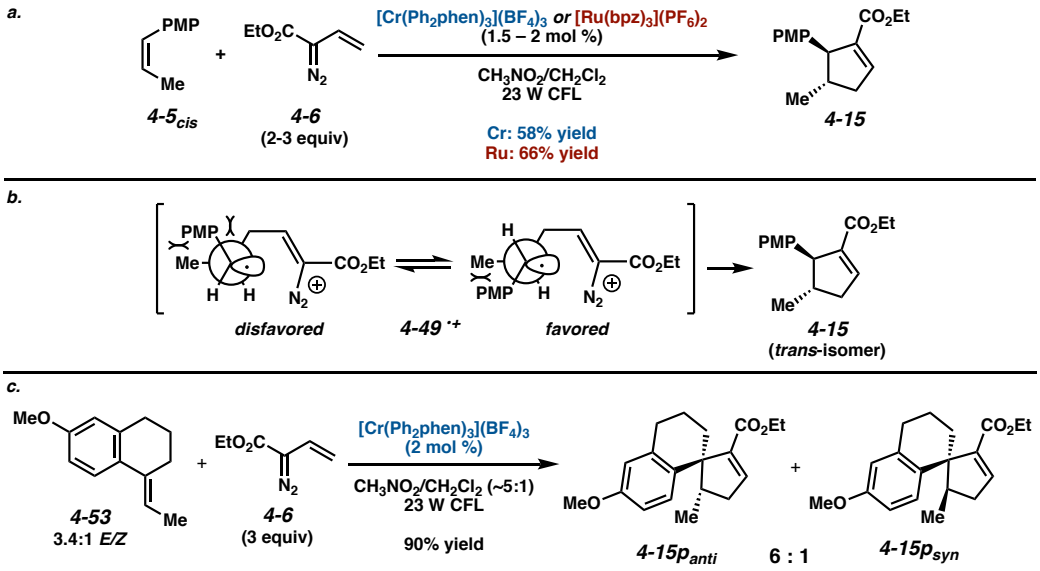
makes us favor the former mechanism. Further mechanistic studies (e.g., computational, kinetics) may provide more insight into the proposed intermediates and elucidate which is the more favorable pathway.



Scheme 4.13. Mechanistic analysis for our photocatalyzed (3+2) radical cation cycloaddition.

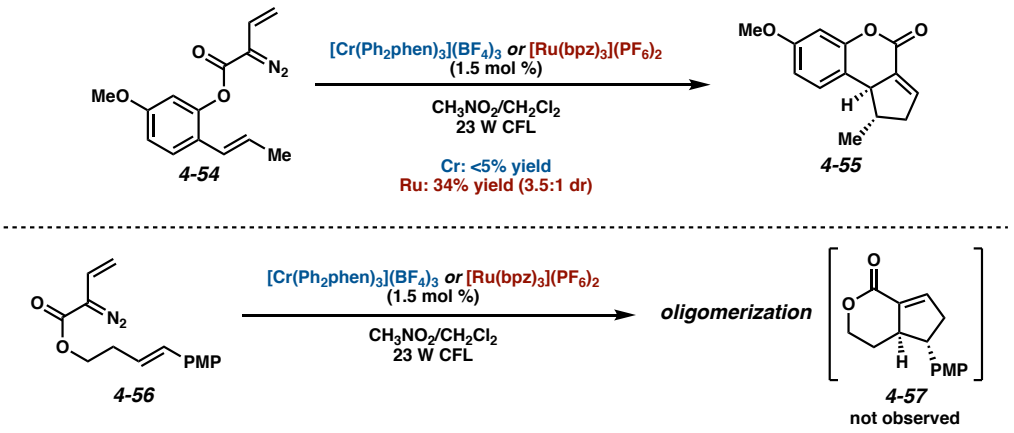
The existence of central intermediate **4-49**$^{\bullet+}$, which is the key precursor to the diverging pathways, is further supported by the stereoconvergent synthesis of our observed *anti*-cyclopentene from *cis*-anethole (Scheme 4.14a). Additionally, when running the (3+2) cycloaddition with *cis*-anethole partway and monitoring it by NMR, isomerization to *trans*-anethole was not observed. These experimental results suggest that a bond rotation occurs along the reaction pathway to render a more stable *anti*-conformer. Furthermore, the validity of intermediate **4-49**$^{\bullet+}$ may explain the excellent diastereoselectivity observed, which presumably arises from the second bond forming event via each respective cyclization pathway (4-exo vs. 5-endo). Scheme 4.14b illustrates the favorability of the trans substituted product through key intermediate **4-49**$^{\bullet+}$. In the favored conformation, the *para*-methoxy phenyl moiety has only one

gauche interaction, whereas the unfavored conformer has two. We further investigated whether the cyclopentene annulation of a mixture of isomeric trisubstituted alkenes would be stereoconvergent (Scheme 4.14c). Subjecting a 3.4:1 trans/cis isomeric mixture of alkene **4-53** led to a 6:1 anti/syn diastereomeric ratio of cyclopentene products in excellent yield. It seems that in the case of trisubstituted alkenes, the critical C–C bond rotation prior to cyclization is more arduous, in comparison to disubstituted olefins. Nevertheless, the increase in trans distribution (3.4:1 → 6:1) as a result of the cycloaddition, may further support the involvement of a C–C bond rotation prior to cyclization. Notably, stereoconvergent transformations with trisubstituted olefin mixtures are generally uncommon.[16]



Scheme 4.14 (a) Example of stereoconvergency. (b) Conformational analysis of key intermediate. (c) Testing the stereoconvergency of an alkene mixture of trisubstituted alkene **4-53**.

Interestingly, the opposite regioisomer cannot be formed even with forced intramolecular restrictions (Scheme 4.15). Ester **4-54** rendered lactone **4-55** via a macrocyclic ring closure event, whereas vinyldiazo **4-56** furnished apparent oligomerization products. This dichotomy underscores the nucleophilic behavior from the vinylogous carbon of the alkenyl diazo species.

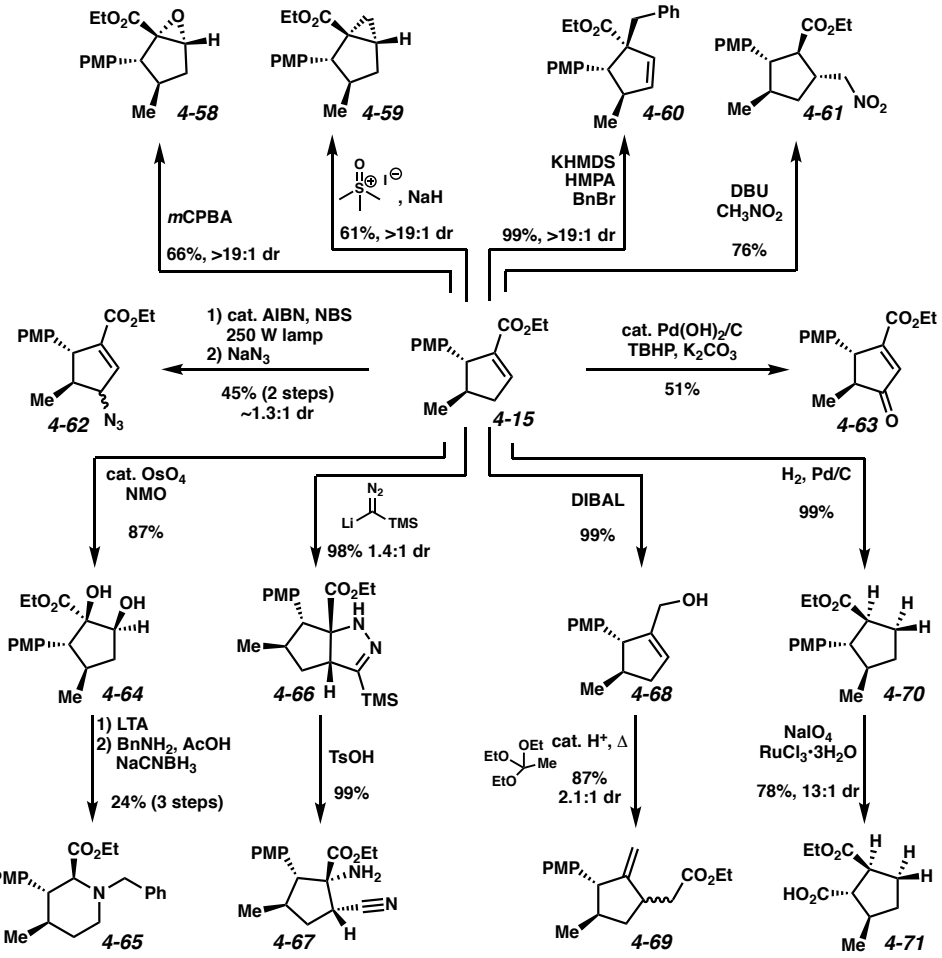


Scheme 4.15. Attempted intramolecular transformations.

4.6 Product Diversification

We wanted to purposefully showcase the versatility of intermediate cyclopentene **4-15** to highlight the synthetic potential of our products. After Dr. Li returned to his native China,[17] I successfully synthesized fourteen distinct carbocycles from **4-15**, and these efforts are depicted in Scheme 4.16. Given that γ-substituted vinyldiazo reagents were not tolerated, the allylic oxidation[18] and halogenation/azidation enables post-cycloaddition functionalization at the γ-methylene. Michael addition, deconjugative alkylation, Corey-Chaykovsky cyclopropanation, epoxidation with *m*CPBA, and even hydrogenation with catalytic Pd/C all occurred in excellent diastereoselectivity. The origin of the high stereoselectivity observed is due to "torsional steering" and has been discussed in detail by Houk and coworkers.[19] Dihydroxylation leads to diol **4-64**, which can be further transformed into piperidine **4-65** via oxidative cleavage and reductive amination. A distinct (3+2) cycloaddition using TMS-diazomethane works well and a subsequent desilylative elimination renders aminonitrile **4-67**.[20] Generation of the useful allylic alcohol **4-68** followed by Johnson orthoester Claisen rearrangement affords methylene cyclopentane **4-69**.

Most importantly, the electron rich arene, deemed necessary for radical cation formation, can be oxidatively cleaved to reveal a carboxylic acid functional group handle (**4-71**). Thus, requirements for radical cation formation are not necessarily restrictive to accessing product diversity. We believe the catalysis and synthetic community at large will be appreciative of our diversification analysis.

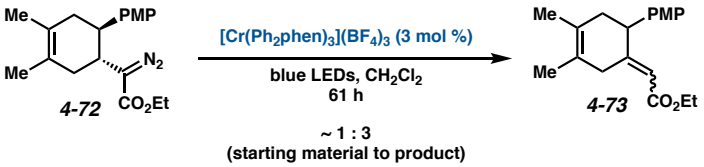


Scheme 4.16. Product elaborations.

4.7 Unusual Cr-Photocatalyzed β-Hydride Elimination

We spent some effort trying to exploit the cyclic diazo ester expansion observed for cylobutane diazo **4-48**. Interestingly, when we synthesized cyclohexene diazo **4-72** we noted that

our chromium catalyst mediated a β-hydride elimination (Scheme 4.17). Control experiments verified that both the catalyst and light were needed for the elimination to occur. This striked us as an unusual transformation to be mediated by our photooxidizing catalyst. Perhaps this reactivity can be exploited in the future through novel cascade processes.



Scheme 4.17. Cr-photocatalyzed β-Hydride Elimination.

4.8 Conclusion

In conclusion, the first example of a direct cyclopentene annulation using vinyldiazo carbonyl compounds as nucleophiles is described. The method exploits a radical cation intermediate that can be generated with both Ru and Cr photocomplexes. In general, the cycloadditions occurred more rapidly with the ruthenium catalysts than the chromium complexes. The comparable reduction potential of the two photocatalysts would suggest that they should behave similarly. However, differential mechanistic turnover pathways (closed photocatalytic cycle versus radical chain propagation) may explain the observed differences in reaction time and substrate scope. Further mechanistic elucidation through computational and/or kinetic studies would be necessary to establish each photocatalyst's function. Overall, excellent regio- and diastereoselectivities are obtained for an array of cyclopentene products that can be readily diversified. Five-membered carbocycles are common cores in many bioactive and functional molecules (Figure 4.1).[21] We envision that our methodology will serve as a useful platform for accessing cyclopentene- and cyclopentane-based compounds. To our knowledge, this is the first

example of vinyldiazo reagents reacting with radical cation species. This contribution adds to the synthetic toolbox of valuable radical cation cycloadditions and the majority of the work discussed in this chapter was recently published in *Angewandte Chemie International Edition*.[22]

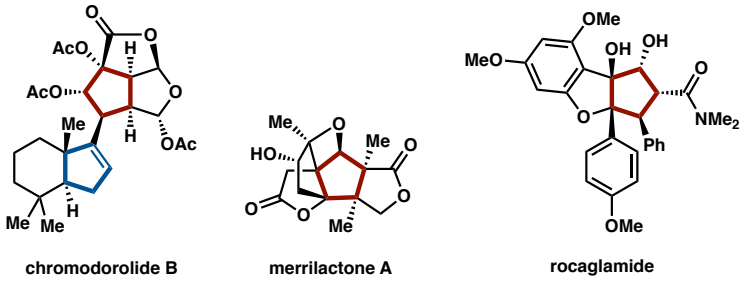


Figure 4.1. Five-membered carbocycle containing natural products with significant bioactivity.

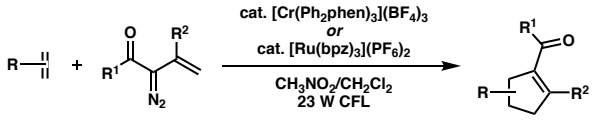
4.9 Experimental Section

4.9.1 Materials and Methods

Cr(III) catalysts were synthesized as described by Shores and Damrauer.[23] $Ru(bpz)_3(PF_6)_2$ was purchased from Sigma-Aldrich. THF, Et_2O, toluene and CH_2Cl_2 were purified by passing through activated alumina columns. Benzene and MeOH were dried over molecular sieves before use. All other solvents were used as received. All reagents were used as received unless otherwise noted. Commercially available chemicals were purchased from Alfa Aesar (Ward Hill, MA), Sigma-Aldrich (St. Louis, MO), Oakwood Products (West Columbia, SC), Strem (Newburport, MA), and TCI America (Portland, OR). Qualitative TLC analysis was performed on 250 mm thick, 60 Å, glass backed, F254 silica (Silicycle, Quebec City, Canada). Visualization was accomplished with UV light and exposure to *p*-anisaldehyde, $KMnO_4$, or Seebach's stain solution followed by heating. Flash chromatography was performed using Silicycle silica gel (230-400 mesh). Reactions under near-UV irradiation (NUV) were performed in a Luzchem photoreactor (LZC-ORG) equipped with 10 lamps of wavelengths 419, 350, and 300 nm. Irradiation with visible light was performed in a closed box using a 23 W compact fluorescent light bulb (EcoSmart 23 W bright white CFL spiral light bulb, 1600 lumens). Cycloadditions using all modes of irradiation were performed using borosilicate vials. ^1H NMR spectra were acquired on a Varian Mercury Plus NMR (at 400 MHz) or a Varian Unity Inova (at 500 MHz) and are reported relative to $SiMe_4$ (δ 0.00). ^{13}C NMR spectra were acquired on a Varian Mercury Plus NMR (at 100 MHz) or a Varian Unity Inova NMR (at 125 MHz) and are reported relative to $SiMe_4$ (δ 0.0). ^{19}F NMR spectra were acquired on a Varian Mercury Plus NMR (at 376 MHz) and are reported relative to $CFCl_3$ (δ 0.0).

IR spectra were obtained on a Nicolet 380 or iS10 FT-IR Spectrophotometer. High-resolution mass spectrometry data was acquired by the University of Georgia Proteomics and Mass Spectrometry Core Facility on a Bruker Esquire 3000 Plus Ion Trap Spectrophotometer. Cyclic voltammetry (CV) measurements were performed with a μAutolab Type III potentiostat/galvanostat using a nonaqeous Ag/Ag^+ (0.01 M $AgNO_3$/0.1 M Bu_4NPF_6 in CH_3CN) reference electrode, Pt wire counter electrode, and a glassy-carbon working milli-electrode (2 mm diameter). Measurements were performed at ambient temperature using 5 mM analyte in CH_3NO_2 under Ar containing 0.1M Bu_4NPF_6 as the supporting electrolyte. Analyte potentials were referenced against 2.4 mM ferrocene internal standard under identical conditions, where $E_{1/2}$ = 0.067 V in CH_3NO_2 vs. the reported nonaqueous Ag/Ag^+ electrode. Potential is referenced to Fc^+/Fc. Scans were performed at 100 mV/s scan rates in 0.1 M Bu_4NPF_6. To convert the potentials from V vs. Fc^+/Fc to V vs. SCE, 0.35 was added to the potentials taken in CH_3NO_2.

4.9.2 Chromium and Ruthenium Catalyzed (3+2) Cycloadditions



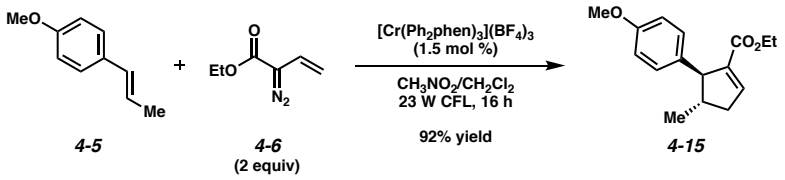
General Procedure for the Cr- or Ru-photocatalyzed (3+2) cycloaddition: A solution of alkene (1.0 equiv), diazo species (2.0 - 4.0 equiv, 1.0 M solution in CH_2Cl_2), and the respective [Cr] or [Ru] photocatalyst (1.5 - 3.0 mol %) in CH_3NO_2 (0.10 M) was prepared in a flame-dried borosilicate vial open to air. The vial was capped and placed on a stirplate in a closed box lined with aluminum foil and equipped with a 23 W compact fluorescent light bulb. The reaction mixture was irradiated while stirring until consumption of the alkene was complete, as determined by TLC. The temperature of the irradiation box was approx. 35 °C during the reaction. Extra charges of the diazo species and photocatalyst were added as necessary. (Small amounts of the diazo species were converted to pyrazole over the course of the reaction, while the remaining excess was either unreactive or underwent nonspecific decomposition. Dimerization was not observed.) Once the reaction was complete, the solvent was removed via rotary evaporation, and the residue was purified by flash chromatography to afford the desired cyclopentene.

Note on alkene geometry: In general, the alkene substrates could be isolated in isomeric purity, and pure E isomers of the alkene substrates were used in the cycloaddition. In one exception (**4-15csm**), the alkene isomer could not be purified, but the trans isomer of the cycloaddition product (**4-15c**) was still observed. Unless otherwise noted, the diastereoselectivity was >19:1, as

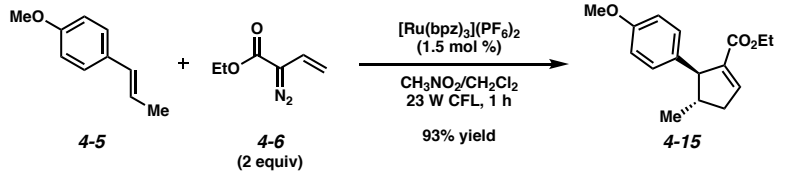
determined by analysis of the crude ^{1}H NMR. The relative stereochemistry of the diastereomeric cycloadducts were determined by NOE studies (see below), or by analogy to those confirmed.

4.9.2a Alkene Scope

Cyclopentene 4-15.



Cr-catalyzed cycloaddition: Prepared according to the *General Procedure* using *trans*-anethole (**4-5**, 15.9 mg, 0.107 mmol), diazoester **4-6** (0.210 mL, 1.0 M solution in CH_2Cl_2, 0.210 mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.1 mg, 0.00161 mmol) in CH_3NO_2 (1.00 mL). The reaction mixture was irradiated for 16 h. The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford cyclopentene **4-15** (25.7 mg, 92% yield) as a colorless oil.



Ru-catalyzed cycloaddition: Prepared according to the *General Procedure* using *trans*-anethole (**4-5**, 15.2 mg, 0.103 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Ru(bpz)_3](PF_6)_2$ (1.3 mg, 0.00155 mmol) in CH_3NO_2 (1.00 mL). The reaction mixture was irradiated for 1 h. The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (20:1 hexanes/EtOAc eluent) to afford cyclopentene **4-15** (24.9 mg, 93% yield) as a colorless oil.

TLC: R_f = 0.34 in 10:1 hexanes/EtOAc, visualized by UV. Stained blue with *p*-anisaldehyde.

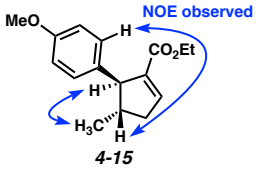
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (d, J = 8.6 Hz, 2H), 6.87 (dd, J = 4.4, 2.4 Hz, 1H), 6.81 (d, J = 8.6 Hz, 2H), 4.11-3.96 (comp. m, 2H), 3.78 (s, 3H), 3.59-3.55 (m, 1H), 2.83 (app. ddt, J = 18.4, 8.0, 2.4 Hz, 1H), 2.26 (app. septet, J = 6.8 Hz, 1H), 2.13 (app. ddt, J = 18.4, 5.0, 2.4 Hz, 1H), 1.13 (d, J = 6.8 Hz, 3H), 1.12 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 158.1, 143.2, 139.0, 136.9, 128.1, 113.8, 60.1, 58.1, 55.3, 43.5, 40.4, 21.0, 14.2.

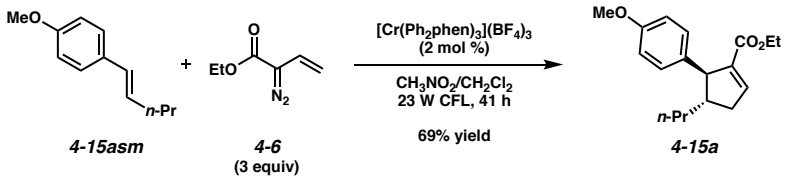
IR (ATR, neat): 1716, 1511, 1240, 1176, 1095 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{16}H_{20}O_3 + H]^+$: 261.1485, found 261.1507.

The relative stereochemistry of cyclopentene **4-15** was confirmed by 2D NOESY NMR analysis.

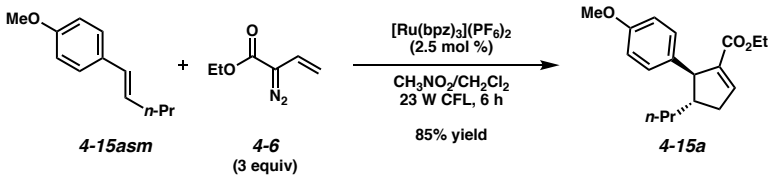


Cyclopentene 4-15a.



Cr-catalyzed cycloaddition: Prepared according to the *General Procedure* using alkene **4-15asm** (17.6 mg, 0.0999 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). After 36 h, another charge of diazoester **4-6** (0.100 mL, 1.0 M solution in CH_2Cl_2, 0.100 mmol) and $[Cr(Ph_2phen)_3](BF_4)_3$ (0.7 mg, 0.000500 mmol) was added. The reaction mixture was irradiated for an additional 5 h (41 h total). The solvent was removed by rotary evaporation and the resulting residue was purified

by flash chromatography (100% hexanes → 9:1 hexanes/EtOAc eluent) to afford cyclopentene **4-15a** (19.8 mg, 69% yield) as a colorless oil.



Ru-catalyzed cycloaddition: Prepared according to the *General Procedure* using alkene **4-15sm** (18.0 mg, 0.102 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Ru(bpz)_3](PF_6)_2$ (1.4 mg, 0.00162 mmol) in CH_3NO_2 (1.00 mL). After 4.5 h, another charge of diazoester **4-6** (0.100 mL, 1.0 M solution in CH_2Cl_2, 0.100 mmol) and $[Ru(bpz)_3](PF_6)_2$ (0.9 mg, 0.00104 mmol) was added. The reaction mixture was irradiated for an additional 1.5 h (6 h total). The solvent was removed by rotary evaporation and the resulting residue was purified by flash chromatography (20:1 hexanes/EtOAc eluent) to afford cyclopentene **4-15a** (24.9 mg, 85% yield) as a colorless oil.

TLC: R_f = 0.41 in 10:1 hexanes/EtOAc, visualized by UV. Stains blue with *p*-anisaldehyde.

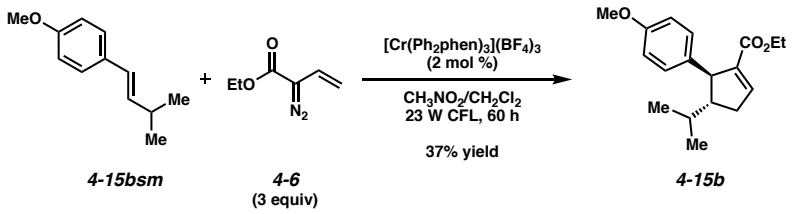
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07 (d, *J* = 8.4 Hz, 2H), 6.87 (dd, *J* = 4.8, 2.8 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 2H), 4.11-3.95 (comp. m, 2H), 3.78 (s, 3H), 3.68-3.65 (m, 1H), 2.80 (app. ddt, *J* = 20.0, 10.0, 2.8 Hz, 1H), 2.21-2.12 (comp. m, 2H), 1.60-1.49 (m, 1H), 1.42-1.24 (comp. m, 3H), 1.11 (t, *J* = 7.0 Hz, 3H), 0.86 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 158.0, 143.3, 139.0, 137.3, 128.3, 113.8, 60.1, 56.4, 55.3, 48.6, 38.6, 38.2, 21.0, 14.3, 14.2.

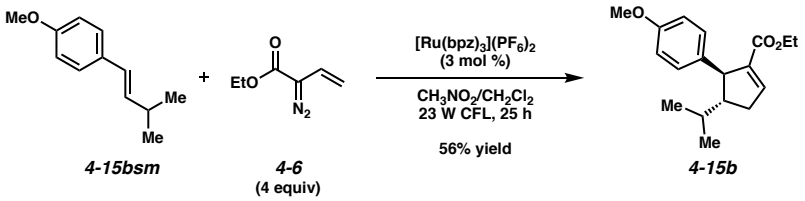
IR (ATR, neat): 2929, 1717, 1511, 1246, 1097 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{18}H_{24}O_3 + H]^+$: 289.1798, found 289.1801.

Cyclopentene 4-15b.



Cr-catalyzed cycloaddition: Prepared according to the *General Procedure* using alkene **4-15bsm** (18.3 mg, 0.104 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). After 24 h, another charge of diazoester **4-6** (0.100 mL, 1.0 M solution in CH_2Cl_2, 0.100 mmol) and $[Cr(Ph_2phen)_3](BF_4)_3$ (0.7 mg, 0.000500 mmol) was added. The reaction mixture was irradiated for an additional 36 h (60 h total). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford cyclopentene **4-15b** (11.2 mg, 37% yield) as a colorless oil.



Ru-catalyzed cycloaddition: Prepared according to the *General Procedure* using alkene **4-15bsm** (17.5 mg, 0.0993 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Ru(bpz)_3](PF_6)_2$ (1.3 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). After 6 h, a second charge of diazoester **4-6** (0.100 mL, 1.0 M solution in CH_2Cl_2, 0.100 mmol) and $[Ru(bpz)_3](PF_6)_2$ (0.9 mg, 0.00104 mmol) was added. After an additional 12 h, another charge of diazoester **4-6** (0.100 mL, 1.0 M solution in CH_2Cl_2, 0.100 mmol) and $[Ru(bpz)_3](PF_6)_2$ (0.4 mg, 0.000462 mmol) was added The reaction mixture was irradiated for an additional 7 h (25 h total). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (100%

hexanes → 9:1 hexanes/Et_2O eluent) to afford cyclopentene **4-15b** (15.9 mg, 56% yield) as a colorless oil.

TLC: R_f = 0.24 in 9:1 hexanes/Et_2O, visualized by UV. Stained blue with *p*-anisaldehyde.

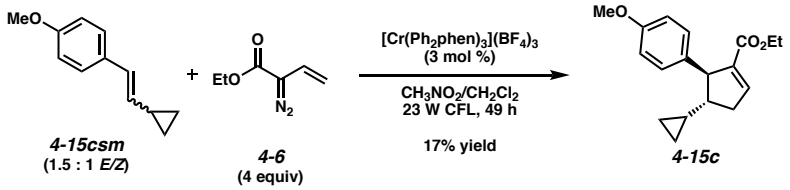
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (d, *J* = 8.8 Hz, 2H), 6.85 (app. q, *J* = 2.2 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 2H), 4.10-3.94 (comp. m, 2H), 3.83-3.80 (m, 1H), 3.77 (s, 3H), 2.71 (app. ddt, *J* = 19.0, 8.9, 2.7 Hz, 1H), 2.32-2.23 (m, 1H), 2.15 (app. dq, *J* = 8.8, 5.8 Hz, 1H), 1.74 (app. octet, *J* = 6.6 Hz, 1H), 1.11 (t, *J* = 7.2 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.0, 157.9, 143.1, 139.3, 138.1, 128.5, 113.8, 60.1, 55.3, 54.7, 53.5, 35.3, 32.1, 20.5, 19.3, 14.2.

IR (ATR, neat): 2953, 1710, 1511, 1247, 1097 cm^{-1}.

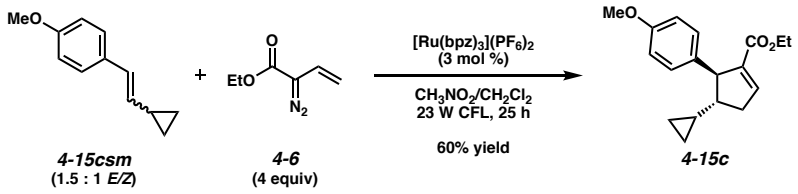
HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{18}H_{24}O_3 + H]^+$: 289.1798, found 289.1799.

Cyclopentene 4-15c.



Cr-catalyzed cycloaddition: Prepared according to the *General Procedure* using alkene **4-15csm** (~1.5:1 *E/Z*, 17.2 mg, 0.0987 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). After 12 h, a second charge of diazoester **4-6** (0.100 mL, 1.0 M solution in CH_2Cl_2, 0.100 mmol) and $[Cr(Ph_2phen)_3](BF_4)_3$ (0.7 mg, 0.000500 mmol) was added. After an additional 24 h, another charge of diazoester **4-6** (0.100 mL, 1.0 M solution in CH_2Cl_2, 0.100 mmol) and $[Cr(Ph_2phen)_3](BF_4)_3$ (1.3 mg, 0.00100 mmol) was added. The reaction mixture was irradiated for

an additional 13 h (49 h total). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O → 9:1 hexanes/EtOAc eluent) to afford cyclopentene **4-15c** (4.8 mg, 17% yield) as a colorless oil. Approximately 30% of unreacted alkene **4-15csm** (still ~1.5:1 E/Z) was observed by crude ^{1}H NMR.



Ru-catalyzed cycloaddition: Prepared according to the *General Procedure* using alkene **4-15csm** (1.5:1 *E/Z*, 17.4 mg, 0.0999 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Ru(bpz)_3](PF_6)_2$ (1.3 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). After 5 h, a second charge of diazoester **4-6** (0.100 mL, 1.0 M solution in CH_2Cl_2, 0.100 mmol) and $[Ru(bpz)_3](PF_6)_2$ (0.4 mg, 0.000462 mmol) was added. After an additional 14 h, another charge of diazoester **4-6** (0.100 mL, 1.0 M solution in CH_2Cl_2, 0.100 mmol) and $[Ru(bpz)_3](PF_6)_2$ (0.9 mg, 0.00104 mmol) was added. The reaction mixture was irradiated for an additional 9 h (28 h total). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O → 9:1 hexanes/EtOAc eluent) to afford cyclopentene **4-15c** (17.2 mg, 60% yield) as a colorless oil. All of alkene **4-15csm** had been consumed by analysis of the crude ^{1}H NMR.

TLC: R_f = 0.29 in 10:1 hexanes/EtOAc, visualized by UV. Stained aqua blue with *p*-anisaldehyde.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (d, *J* = 8.6 Hz, 2H), 6.91 (app. q, *J* = 2.1 Hz, 1H), 6.79 (d, *J* = 8.6 Hz, 2H), 4.13-3.98 (comp. m, 2H), 3.97-3.95 (m, 1H), 3.77 (s, 3H), 2.80 (app. ddt, *J* = 18.8,

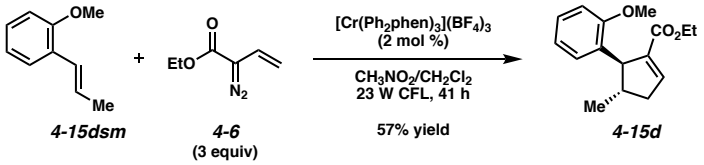
8.2, 2.6 Hz, 1H), 2.40-2.33 (m, 1H), 1.55-1.59 (m, 1H), 1.14 (t, J = 7.0 Hz, 3H), 0.92-0.85 (m, 1H), 0.49-0.39 (m, 2H), 0.11-0.01 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.1, 158.0, 143.3, 138.9, 137.2, 128.0, 113.8, 60.1, 56.5, 55.3, 53.7, 38.4, 17.4, 14.2, 3.8, 3.6.

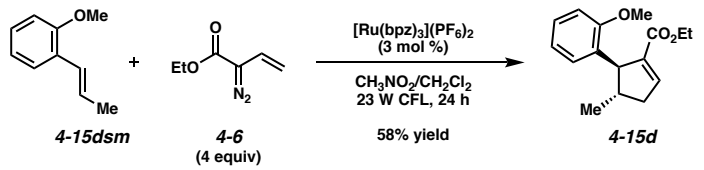
IR (ATR, neat): 2924, 1715, 1511, 1238, 1095, 1037 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{18}H_{22}O_3 + H]^+$: 287.1642, found 287.1641.

Cyclopentene 4-15d.



Cr-catalyzed cycloaddition: Prepared according to the *General Procedure* using alkene **4-15dsm** (14.7 mg, 0.0992 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00150 mmol) in CH_3NO_2 (1.0 mL). After 36 h, another charge of diazoester **4-6** (0.100 mL, 1.0 M solution in CH_2Cl_2, 0.100 mmol) and $[Cr(Ph_2phen)_3](BF_4)_3$ (0.7 mg, 0.000500 mmol) was added. The reaction mixture was irradiated for an additional 5 h (41 h total). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford cyclopentene **4-15d** (14.8 mg, 57% yield) as a colorless oil.



Ru-catalyzed cycloaddition: Prepared according to the *General Procedure* using alkene **4-15dsm** (14.7 mg, 0.0992 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and

$[Ru(bpz)_3](PF_6)_2$ (1.3 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). After 7 h, another charge of diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol) and $[Ru(bpz)_3](PF_6)_2$ (1.3 mg, 0.00150 mmol) was added. The reaction mixture was irradiated for an additional 17 h (24 h total). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (20:1 hexanes/EtOAc eluent) to afford cyclopentene **4-15d** (15.2 mg, 58% yield) as a colorless oil.

TLC: R_f = 0.41 in 10:1 hexanes/EtOAc, visualized by UV. Stained orange with *p*-anisaldehyde.

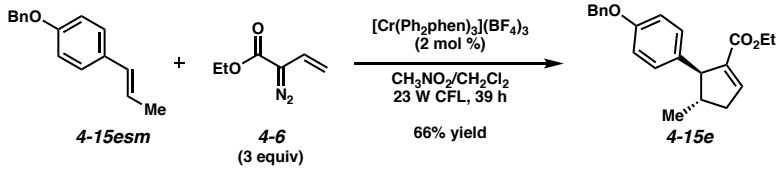
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18-7.13 (m, 1H), 6.95-6.92 (comp. m, 2H), 6.88-6.82 (comp. m, 2H), 4.13-3.98 (comp. m, 3H), 3.84 (s, 3H), 2.75 (app. ddt, *J* = 18.3, 7.9, 2.4 Hz, 1H), 2.27-2.18 (m, 1H), 2.13-2.02 (m, 1H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.11 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 157.3, 143.9, 138.0, 132.8, 127.1, 127.0, 120.5, 110.7, 60.0, 55.6, 51.6, 42.3, 40.2, 21.6, 14.2.

IR (ATR, neat): 1716, 1491, 1278, 1242, 753 cm^{-1}.

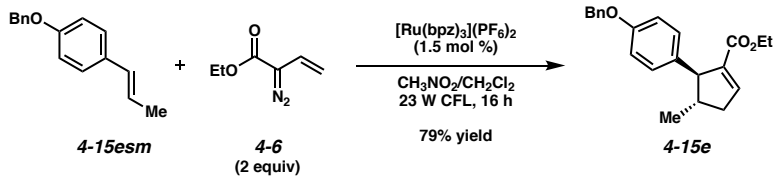
HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{16}H_{20}O_3 + H]^+$: 261.1485, found 261.1487.

Cyclopentene 4-15e.



Cr-catalyzed cycloaddition: Prepared according to the *General Procedure* using alkene **4-15esm** (22.2 mg, 0.0990 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). After 24 h, another charge of diazoester **4-6** (0.100 mL, 1.0 M solution in CH_2Cl_2, 0.100 mmol) and $[Cr(Ph_2phen)_3](BF_4)_3$ (0.7 mg, 0.000500 mmol) was added. The reaction mixture was irradiated for an additional 15 h

(39 h total). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/EtOAc eluent) to afford cyclopentene **4-15e** (21.9 mg, 66% yield) as a colorless oil.



Ru-catalyzed cycloaddition: Prepared according to the *General Procedure* using alkene **4-15esm** (22.8 mg, 0.102 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Ru(bpz)_3](PF_6)_2$ (1.3 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). The reaction mixture was irradiated for 16 h. The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (20:1 hexanes/EtOAc eluent) to afford cyclopentene **4-15e** (27.0 mg, 79% yield) as a colorless oil.

TLC: R_f = 0.36 in 10:1 hexanes/EtOAc, visualized by UV. Stains orange with *p*-anisaldehyde.

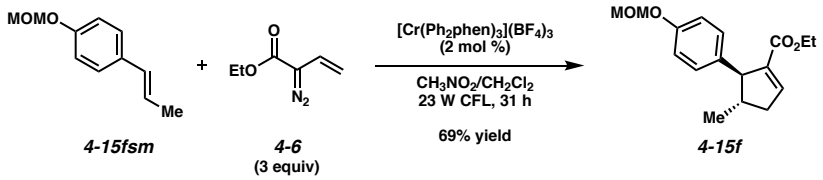
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.31 (comp. m, 5H), 7.07 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.88-6.66 (m, 1H), 5.03 (s, 2H), 4.12-3.95 (comp. m, 2H), 3.59-3.55 (m, 1H), 2.83 (app. ddt, *J* = 18.4, 7.6, 2.4 Hz, 1H), 2.26 (app. septet, *J* = 6.8 Hz, 1H), 2.16-2.08 (m, 1H), 1.13 (d, *J* = 7.2 Hz, 3H), 1.11 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.1, 157.4, 143.3, 139.0, 137.4, 137.2, 128.7, 128.2, 128.0, 127.7, 114.8, 70.1, 60.1, 58.1, 43.4, 40.4, 21.0, 14.2.

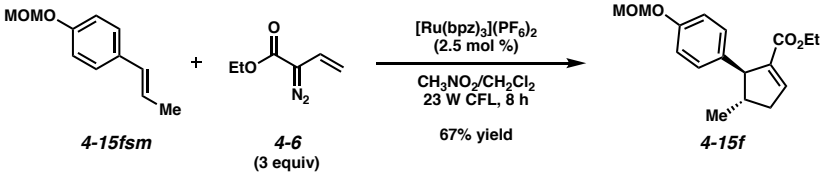
IR (ATR, neat): 1715, 1510, 1238, 1176, 739 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{22}H_{24}O_3 + H]^+$: 337.1798, found 337.1802.

Cyclopentene 4-15f.



Cr-catalyzed cycloaddition: Prepared according to the *General Procedure* using alkene **4-15fsm** (18.2 mg, 0.102 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). After 23 h, another charge of diazoester **4-6** (0.100 mL, 1.0 M solution in CH_2Cl_2, 0.100 mmol) and $[Cr(Ph_2phen)_3](BF_4)_3$ (0.7 mg, 0.000500 mmol) was added. The reaction mixture was irradiated for an additional 8 h (31 h total). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/EtOAc eluent) to afford cyclopentene **4-15f** (20.4 mg, 69% yield) as a colorless oil.



Ru-catalyzed cycloaddition: Prepared according to the *General Procedure* using alkene **4-15fsm** (17.5 mg, 0.0982 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Ru(bpz)_3](PF_6)_2$ (1.3 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). After 4 h, another charge of diazoester **4-6** (0.100 mL, 1.0 M solution in CH_2Cl_2, 0.100 mmol) and $[Ru(bpz)_3](PF_6)_2$ (0.9 mg, 0.00104 mmol) was added. The reaction mixture was irradiated for an additional 4 h (8 h total). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (20:1 hexanes/EtOAc eluent) to afford cyclopentene **4-15f** (19.1 mg, 67% yield) as a colorless oil.

TLC: R_f = 0.27 in 10:1 hexanes/EtOAc, visualized by UV. Stained orange with *p*-anisaldehyde.

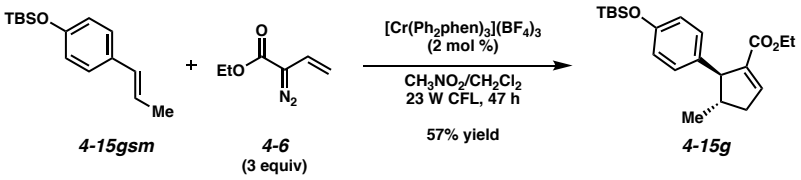
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 6.88 (dd, *J* = 4.4, 2.4 Hz, 1H), 5.14 (s, 2H), 4.12-3.96 (comp. m, 2H), 3.59-3.55 (m, 1H), 3.47 (s, 3H), 2.83 (app. ddt, *J* = 18.4, 8.0, 2.6 Hz, 1H), 2.25 (app. septet, *J* = 6.5 Hz, 1H), 2.12 (app. ddt, *J* = 18.4, 5.0, 2.0 Hz, 1H), 1.13 (d, *J* = 6.8 Hz, 3H), 1.12 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 155.8, 143.4, 138.9, 138.3, 128.2, 116.3, 94.7, 60.1, 58.1, 56.1, 43.4, 40.4, 21.0, 14.2.

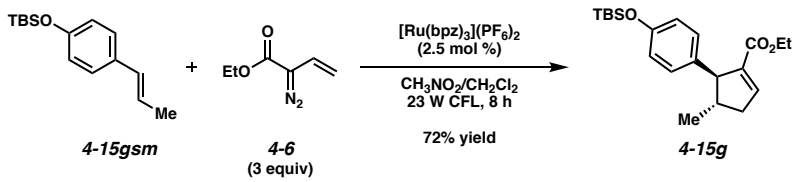
IR (ATR, neat): 1716, 1510, 1233, 1152, 1079 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{17}H_{22}O_4 + H]^+$: 291.1591, found 291.1593.

Cyclopentene 4-15g.



Cr-catalyzed cycloaddition: Prepared according to the *General Procedure* using alkene **4-15gsm** (24.6 mg, 0.0990 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). After 36 h, another charge of diazoester **4-6** (0.100 mL, 1.0 M solution in CH_2Cl_2, 0.100 mmol) and $[Cr(Ph_2phen)_3](BF_4)_3$ (0.7 mg, 0.000500 mmol) was added. The reaction mixture was irradiated for an additional 11 h (47 h total). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford cyclopentene **4-15g** (20.3 mg, 57% yield) as a colorless oil.



Ru-catalyzed cycloaddition: Prepared according to the *General Procedure* using alkene **4-15gsm** (24.9 mg, 0.100 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Ru(bpz)_3](PF_6)_2$ (1.4 mg, 0.00162 mmol) in CH_3NO_2 (1.00 mL). After 4 h, another charge of diazoester **4-6** (0.100 mL, 1.0 M solution in CH_2Cl_2, 0.100 mmol) and $[Ru(bpz)_3](PF_6)_2$ (0.9 mg, 0.00104 mmol) was added. The reaction mixture was irradiated for an additional 4 h (8 h total). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (30:1 hexanes/EtOAc eluent) to afford cyclopentene **4-15g** (26.1 mg, 72% yield) as a colorless oil.

TLC: R_f = 0.48 in 10:1 hexanes/EtOAc, visualized by UV. Stains maroon with *p*-anisaldehyde.

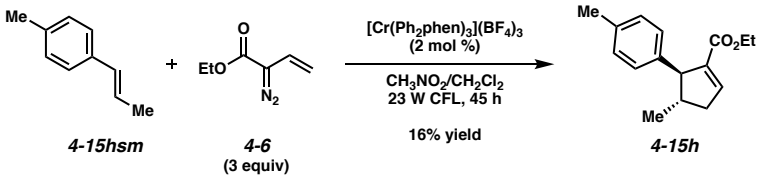
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98 (d, *J* = 8.4 Hz, 2H), 6.87 (dd, *J* = 4.4, 2.4 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 2H), 4.11-3.94 (comp. m, 2H), 3.56-3.53 (m, 1H), 2.82 (app. ddt, *J* = 18.4, 8.2, 2.6 Hz, 1H), 2.31-2.20 (m, 1H), 2.11 (app. ddt, *J* = 18.4, 5.2, 2.4 Hz, 1H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.08 (t, *J* = 7.0 Hz, 3H), 0.96 (s, 9H), 0.17 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 154.0, 143.2, 139.1, 137.5, 128.1, 119.9, 60.0, 58.2, 43.4, 40.4, 25.8, 21.0, 18.3, 14.2, -4.3.

IR (ATR, neat): 2957, 1718, 1509, 1259, 917 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{21}H_{32}O_3Si + H]^+$: 361.2193, found 361.2196.

Cyclopentene 4-15h.



Cr-catalyzed cycloaddition: Prepared according to the *General Procedure* using alkene **4-15hsm** (13.2 mg, 0.0998 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and

$[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). After 26 h, another charge of diazoester **4-6** (0.100 mL, 1.0 M solution in CH_2Cl_2, 0.100 mmol) and $[Cr(Ph_2phen)_3](BF_4)_3$ (0.7 mg, 0.000500 mmol) was added. The reaction mixture was irradiated for an additional 19 h (45 h total). The solvent was removed by rotary evaporation and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O → 9:1 hexanes/EtOAc eluent) to afford cyclopentene **4-15h** (4.0 mg, 16% yield) as a colorless oil.

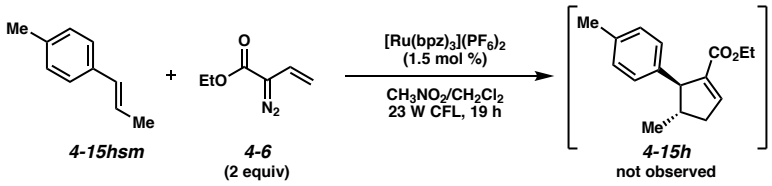
TLC: R_f = 0.55 in 9:1 hexanes/EtOAc, visualized by UV. Stained yellow with $KMnO_4$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.88 (dd, *J* = 4.0, 2.4 Hz, 1H), 4.11-3.97 (comp. m, 2H), 3.59-3.58 (m, 1H), 2.83 (app. ddt, *J* = 18.4, 8.0, 2.6 Hz, 1H), 2.31 (s, 3H), 2.30-2.22 (m, 1H), 2.13 (app. ddt, *J* = 18.4, 4.8, 2.4 H, 1H), 1.13 (d, *J* = 7.2 Hz, 3H), 1.12 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 143.4, 141.8, 138.9, 135.7, 129.2, 127.1, 60.1, 58.5, 43.5, 40.5, 21.2, 21.0, 14.2.

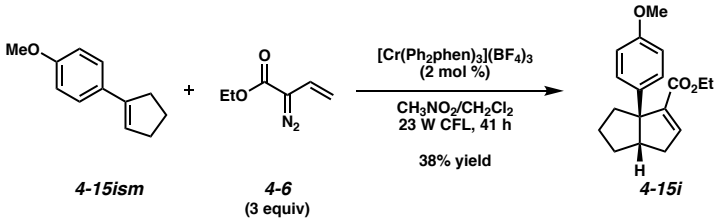
IR (ATR, neat): 2929, 1720, 1275, 1258, 1096 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{16}H_{20}O_2 + H]^+$: 245.1536, found 245.1536.

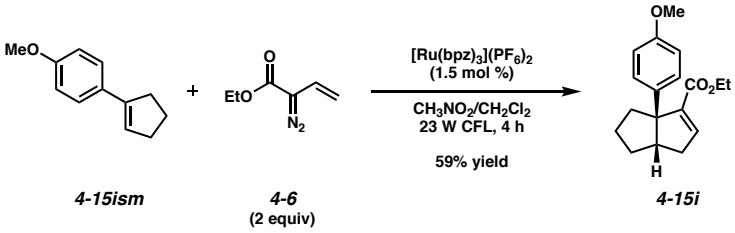


Attempted Ru-catalyzed cycloaddition: A solution of alkene **4-15hsm** (12.7 mg, 0.0961 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Ru(bpz)_3](PF_6)_2$ (1.0 mg, 0.00116 mmol) in CH_3NO_2 (1.00 mL) was prepared in a flame-dried borosilicate vial open to air. The reaction mixture was irradiated for 19 h. The solvent was removed by rotary evaporation, and no product was observed by ^{1}H NMR.

Cyclopentene 4-15i.



Cr-catalyzed cycloaddition: Prepared according to the *General Procedure* using alkene **4-15ism** (17.2 mg, 0.0987 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). After 17 h, another charge of diazoester **4-6** (0.100 mL, 1.0 M solution in CH_2Cl_2, 0.100 mmol) and $[Cr(Ph_2phen)_3](BF_4)_3$ (0.7 mg, 0.000500 mmol) was added. The reaction mixture was irradiated for an additional 24 h (41 h total). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford cyclopentene **4-15i** (10.8 mg, 38% yield) as a colorless oil.



Ru-catalyzed cycloaddition: Prepared according to the *General Procedure* using alkene **4-15ism** (17.3 mg, 0.0993 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Ru(bpz)_3](PF_6)_2$ (1.3 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). The reaction mixture was irradiated for 4 h. The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford cyclopentene **4-15i** (16.9 mg, 59% yield) as a colorless oil.

TLC: R_f = 0.26 in 10:1 hexanes/Et_2O, visualized by UV. Stained olive-green with *p*-anisaldehyde.

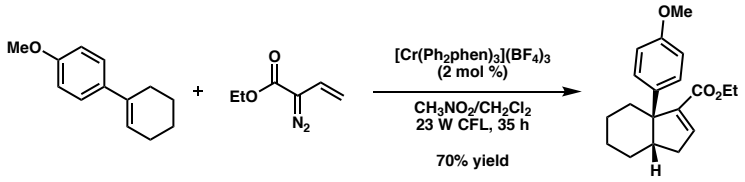
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (d, *J* = 8.8 Hz, 2H), 6.86 (app. t, *J* = 2.6 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 2H), 4.06 (app. q, *J* = 7.1 Hz, 2H), 3.78 (s, 3H), 2.90 (ddd, *J* = 19.2, 8.8, 2.4 Hz, 1H), 2.69-2.60 (m, 1H), 2.33-2.18 (comp. m, 3H), 1.97 (app. dtd, *J* = 12.4, 8.4, 6.0 Hz, 1H), 1.73 (app. dquintet *J* = 11.8, 5.9 Hz, 1H), 1.68-1.56 (m, 1H), 1.41 (app. dq, *J* = 11.8, 5.8 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 164.6, 157.6, 143.5, 141.5, 140.4, 127.3, 113.4, 64.2, 60.0, 55.3, 52.7, 40.0, 37.1, 36.7, 26.5, 14.3

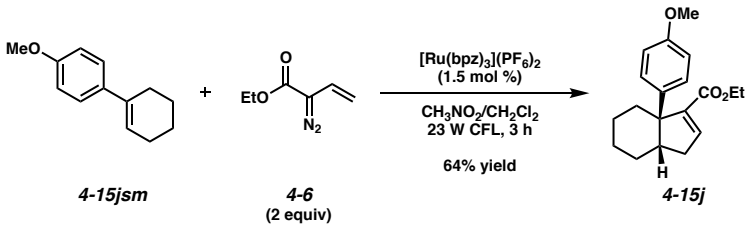
IR (ATR, neat): 2958, 1715, 1512, 1289, 1248 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{18}H_{22}O_3 + H]^+$: 287.1642, found 287.1642.

Cyclopentene 4-15j.



Cr-catalyzed cycloaddition: Prepared according to the *General Procedure* using alkene **4-15jsm** (18.8 mg, 0.0999 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). After 12 h, another charge of diazoester **4-6** (0.100 mL, 1.0 M solution in CH_2Cl_2, 0.100 mmol) and $[Cr(Ph_2phen)_3](BF_4)_3$ (0.7 mg, 0.000500 mmol) was added. The reaction mixture was irradiated for an additional 23 h (35 h total). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford cyclopentene **4-15j** (21.0 mg, 70% yield) as a colorless oil.



Ru-catalyzed cycloaddition: Prepared according to the *General Procedure* using alkene **4-15jsm** (19.3 mg, 0.103 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Ru(bpz)_3](PF_6)_2$ (1.3 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). The reaction mixture was irradiated for 3 h. The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (20:1 → 10:1 hexanes/EtOAc eluent) to afford cyclopentene **4-15j** (19.7 mg, 64% yield) as a colorless oil.

TLC: R_f = 0.41 in 10:1 hexanes/EtOAc, visualized by UV. Stained teal with *p*-anisaldehyde.

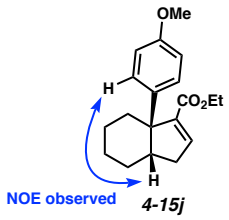
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.8 Hz, 2H), 6.87 (app. t, *J* = 2.4 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 2H), 4.07-3.93 (comp. m, 2H), 3.78 (s, 3H), 2.58-2.50 (m, 1H), 2.49-2.37 (m, 2H), 2.31 (ddd, *J* = 17.6, 8.4, 2.4 Hz, 1H), 1.81-1.72 (m, 1H), 1.62-1.42 (comp. m, 6H), 1.08 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 157.5, 145.5, 143.0, 139.0, 128.2, 113.3, 59.8, 55.3, 53.1, 48.3, 35.4, 31.9, 26.1, 22.4, 21.8, 14.2.

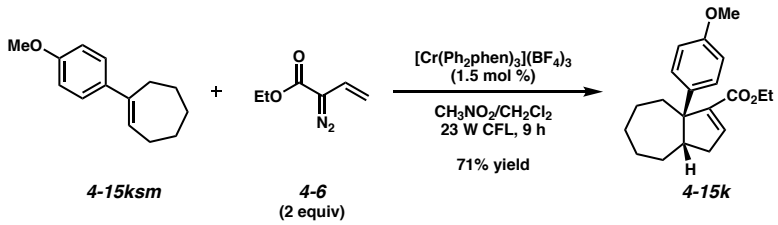
IR (ATR, neat): 2932, 1714, 1512, 1251, 1109 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{19}H_{24}O_3 + Na]^+$: 323.1618, found 323.1625.

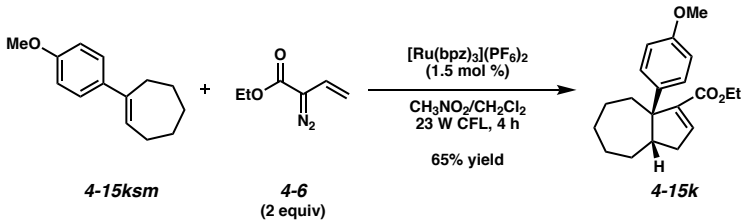
The relative stereochemistry of cyclopentene **4-15j** was confirmed by 2D NOESY NMR analysis.



Cyclopentene 4-15k.



Cr-catalyzed cycloaddition: Prepared according to the *General Procedure* using alkene **4-15ksm** (20.2 mg, 0.0999 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). The reaction mixture was irradiated for 9 h. The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford cyclopentene **4-15k** (22.4 mg, 71% yield) as a colorless oil.



Ru-catalyzed cycloaddition: Prepared according to the *General Procedure* using alkene **4-15ksm** (20.8 mg, 0.103 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Ru(bpz)_3](PF_6)_2$ (1.3 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). The reaction mixture was irradiated for 4 h. The solvent was removed by rotary evaporation and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford cyclopentene **4-15k** (21.2 mg, 65% yield) as a colorless oil.

TLC: R_f = 0.24 in 10:1 hexanes/Et_2O, visualized by UV. Stained blue with *p*-anisaldehyde.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (d, *J* = 8.9 Hz, 2H), 7.04 (app. t, *J* = 2.8 Hz, 1H), 6.80 (d, *J* = 8.9 Hz, 2H), 4.07 (app. q, *J* = 7.2 Hz, 2H), 3.77 (s, 3H), 2.73 (ddd, *J* = 19.2, 9.6, 2.4 Hz, 1H),

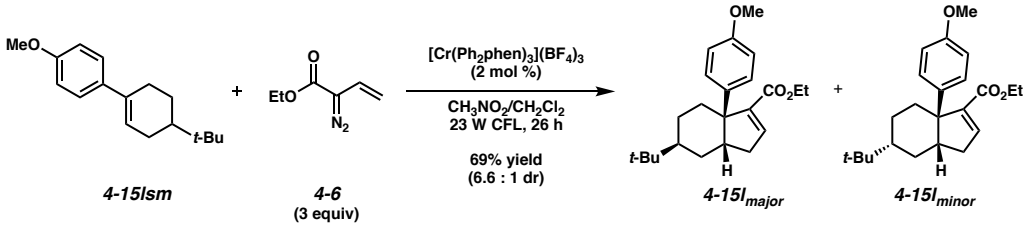
2.67-2.59 (m, 1H), 2.41-2.24 (comp. m, 3H), 1.77-1.57 (comp. m, 5H), 1.52-1.20 (comp. m, 3H), 1.18 (t, J = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 164.8, 157.4, 144.3, 143.0, 141.4, 126.7, 113.4, 59.9, 59.5, 55.3, 51.4, 37.3, 34.0, 31.6, 31.4, 25.3, 25.2, 14.3.

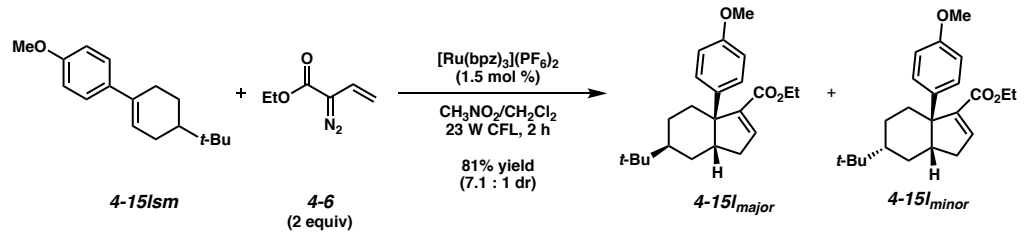
IR (ATR, neat) 2932, 1716, 1511, 1247, 1230 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{20}H_{26}O_3 + H]^+$: 315.1955, found 315.1953.

Cyclopentene 4-15l.



Cr-catalyzed cycloaddition: Prepared according to the *General Procedure* using alkene **4-15lsm** (24.6 mg, 0.101 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). After 23 h, another charge of diazoester **4-6** (0.100 mL, 1.0 M solution in CH_2Cl_2, 0.100 mmol) and $[Cr(Ph_2phen)_3](BF_4)_3$ (0.7 mg, 0.000500 mmol) was added. The reaction mixture was irradiated for an additional 3 h (26 h total). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/EtOAc eluent) to afford cyclopentene **4-15l** (25.0 mg, 69% yield, 6.6:1 dr) as a colorless oil.



Ru-catalyzed cycloaddition: Prepared according to the *General Procedure* using alkene **4-15lsm** (24.6 mg, 0.101 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Ru(bpz)_3](PF_6)_2$ (1.3 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). The reaction mixture was irradiated for 2 h. The solvent was removed by rotary evaporation, and the resulting residue was purified by preparative TLC (30:1 hexanes/EtOAc eluent) to afford cyclopentene **4-15l$_{major}$** as a colorless oil (25.5 mg, 71% yield, major isomer) and cyclopentene **4-15l$_{minor}$** as a colorless oil (3.5 mg, 10% yield, minor isomer).

TLC: *Major isomer*: R_f = 0.48 in 10:1 hexanes/EtOAc. *Minor isomer*: R_f = 0.41 in 10:1 hexanes/EtOAc. Both isomers visualized by UV, and stained pink with *p*-anisaldehyde.

Major diastereomer

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.82-6.77 (m, 1H), 4.02-3.84 (comp. m, 2H), 3.78 (s, 3H), 2.81-2.72 (m, 1H), 2.72-2.63 (m, 1H), 2.57-2.39 (comp. m, 2H), 1.75-1.45 (comp. m, 3H), 1.36-1.09 (comp. m, 3H), 1.01 (t, *J* = 7.0 Hz, 3H), 0.83 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.0, 157.4, 147.0, 141.4, 138.8, 128.3, 113.2, 59.7, 55.2, 51.8, 49.9, 42.0, 35.5, 32.4, 31.6, 27.6, 25.9, 23.2, 14.1.

IR (ATR, neat): 2938, 1717, 1513, 1256, 1109 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{23}H_{32}O_3 + H]^+$: 357.2424, found 357.2426.

Minor diastereomer

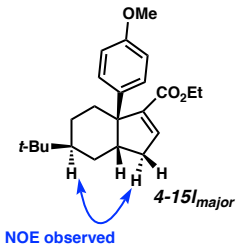
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.6 Hz, 2H), 7.01 (s, 1H), 6.79 (d, *J* = 8.6 Hz, 2H), 4.29-4.15 (comp. m, 2H), 3.77 (s, 3H), 2.75-2.64 (m, 1H), 2.52-2.42 (m, 1H), 2.42-2.31 (m, 1H), 1.94-1.65 (comp. m, 3H), 1.29 (t, *J* = 7.0 Hz, 3H), 1.17-0.86 (comp. m, 3H), 0.84 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.8, 157.7, 146.9, 140.1, 139.9, 127.7, 113.3, 60.1, 55.8, 55.3, 48.1, 46.3, 38.0, 34.6, 32.6, 32.1, 27.6, 24.5, 14.4.

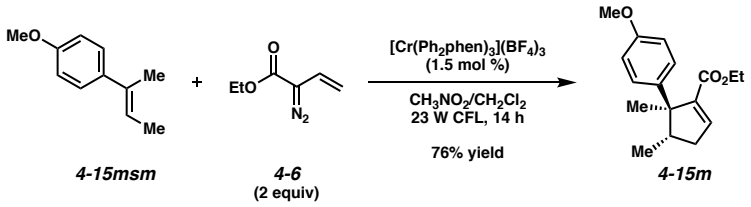
IR (ATR, neat): 2934, 1713, 1510, 1295, 1251 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{23}H_{32}O_3 + H]^+$: 357.2424, found 357.2429.

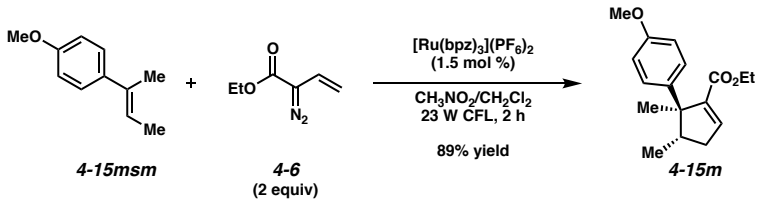
The relative stereochemistry of the major diastereomer of cyclopentene **4-15l** was confirmed by 2D NOESY NMR analysis.



Cyclopentene 4-15m.



Cr-catalyzed cycloaddition: Prepared according to the *General Procedure* using alkene **4-15msm** (16.2 mg, 0.0999 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). The reaction mixture was irradiated for 14 h. The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/EtOAc eluent) to afford cyclopentene **4-15m** (20.7 mg, 76% yield) as a colorless oil.



Ru-catalyzed cycloaddition: Prepared according to the *General Procedure* using alkene **4-15msm** (15.9 mg, 0.0980 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Ru(bpz)_3](PF_6)_2$ (1.3 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). The reaction mixture was irradiated for 2 h. The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (20:1 hexanes/EtOAc eluent) to afford cyclopentene **4-15m** (23.9 mg, 89% yield) as a colorless oil.

TLC: R_f = 0.39 in 10:1 hexanes/EtOAc, visualized by UV. Stains blue with *p*-anisaldehyde.

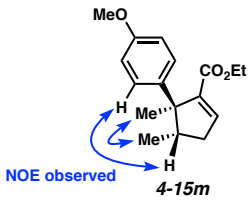
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (d, *J* = 8.8 Hz, 2H), 6.90 (dd, *J* = 3.0, 2.0 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 2H), 4.08-3.92 (comp. m, 2H), 3.78 (s, 3H), 2.60 (ddd, *J* = 17.6, 7.6, 3.0 Hz, 1H), 2.36-2.25 (m, 1H), 2.11 (ddd, *J* = 17.6, 10.0, 2.0 Hz, 1H), 1.39 (s, 3H), 1.06 (t, *J* = 7.2 Hz, 3H), 0.91 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 157.6, 145.3, 143.2, 140.5, 127.1, 113.4, 59.8, 55.3, 53.5, 48.8, 38.5, 16.9, 14.2, 13.3.

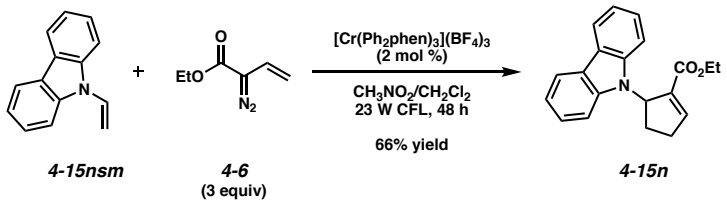
IR (ATR, neat): 1717, 1512, 1252, 1049, 759 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{17}H_{22}O_3 + Na]^+$: 297.1461, found 297.1469.

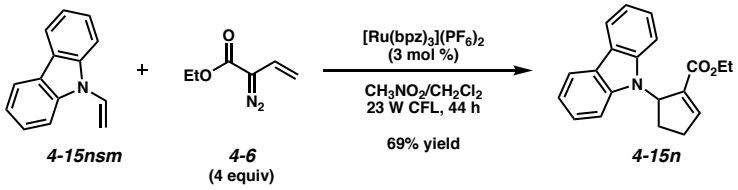
The relative stereochemistry of cyclopentene **4-15m** was confirmed by 2D NOESY NMR analysis.



Cyclopentene 4-15n.



Cr-catalyzed cycloaddition: Prepared according to the *General Procedure* using enamine **4-15nsm** (19.3 mg, 0.0999 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). After 17 h, a second charge of diazoester **4-6** (0.100 mL, 1.0 M solution in CH_2Cl_2, 0.100 mmol) was added. After an additional 23 h, another charge of diazoester **4-6** (0.100 mL, 1.0 M solution in CH_2Cl_2, 0.100 mmol) and $[Cr(Ph_2phen)_3](BF_4)_3$ (0.7 mg, 0.000500 mmol) was added. The reaction mixture was irradiated for an additional 8 h (48 h total). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/EtOAc eluent) to afford cyclopentene **4-15n** (20.1 mg, 66% yield) as a colorless oil.



Ru-catalyzed cycloaddition: Prepared according to the *General Procedure* using enamine **4-15nsm** (19.9 mg, 0.103 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Ru(bpz)_3](PF_6)_2$ (1.3 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). After 2.5 h, another charge of diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol) and $[Ru(bpz)_3](PF_6)_2$ (1.3 mg, 0.00150 mmol) was added. The reaction mixture was irradiated for an additional 1.5 h (4 h total). The solvent was removed by rotary evaporation, and the resulting residue was purified by

flash chromatography (20:1 hexanes/EtOAc eluent) to afford cyclopentene **4-15n** (21.7 mg, 69% yield) as a colorless oil.

TLC: R_f = 0.30 in 10:1 hexanes/EtOAc, visualized by UV. Stained blue with *p*-anisaldehyde.

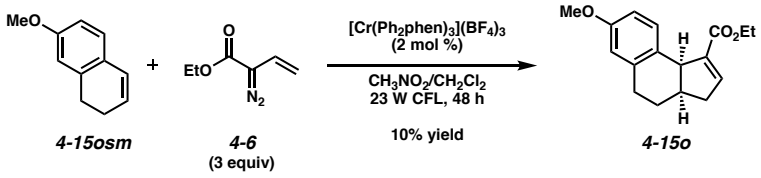
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (d, *J* = 8.0 Hz, 2H), 7.61-7.16 (comp. m, 7H), 6.18-6.10 (m, 1H), 3.86-3.73 (comp. m, 2H), 3.07-2.95 (m, 1H), 2.86-2.67 (comp. m, 2H), 2.51-2.38 (m, 1H), 0.69 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 163.8, 146.6, 138.8, 136.1, 125.7, 125.4, 120.5, 120.2, 118.9, 111.2, 110.5, 109.1, 60.3, 59.2, 31.8, 28.4, 13.6.

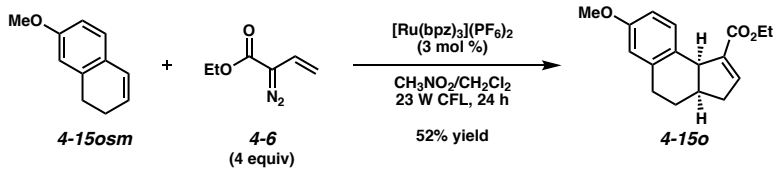
IR (ATR, neat): 1716, 1453, 1285, 1223, 749 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^{2+}$ $[C_{20}H_{19}NO_2 + H]^{2+}$: 306.1483, found 306.1486.

Cyclopentene 4-15o.



Cr-catalyzed cycloaddition: Prepared according to the *General Procedure* using alkene **4-15osm** (16.3 mg, 0.102 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). After 24 h, another charge of diazoester **4-6** (0.100 mL, 1.0 M solution in CH_2Cl_2, 0.100 mmol) and $[Cr(Ph_2phen)_3](BF_4)_3$ (0.7 mg, 0.000500 mmol) was added. The reaction mixture was irradiated for an additional 24 h (48 h total). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford cyclopentene **4-15o** (2.8 mg, 10% yield) as a colorless oil.



Ru-catalyzed cycloaddition: Prepared according to the *General Procedure* using alkene **4-15osm** (15.9 mg, 0.0992 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Ru(bpz)_3](PF_6)_2$ (1.3 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). After 6 h, another charge of diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol) and $[Ru(bpz)_3](PF_6)_2$ (1.3 mg, 0.00150 mmol) was added. The reaction mixture was irradiated for an additional 18 h (24 h total). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (20:1 hexanes/EtOAc eluent) to afford cyclopentene **4-15o** (14.1 mg, 52% yield) as a colorless oil.

TLC: R_f = 0.45 in 10:1 hexanes/EtOAc, visualized by UV. Stained blue with *p*-anisaldehyde.

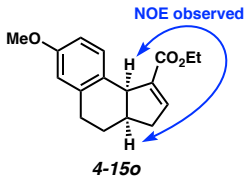
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 8.5 Hz, 1H), 6.77-6.73 (m, 1H), 6.69 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.62 (d, *J* = 2.7 Hz, 1H), 4.26-4.10 (comp. m, 3H), 3.76 (s, 3H), 2.96 (app. qt, *J* = 8.4, 4.3 Hz, 1H), 2.73 (app. quintet, *J* = 7.8 Hz, 1H), 2.65 (ddd, *J* = 18.4, 9.2, 2.8 Hz, 1H), 2.56 (app. dt, *J* = 15.6, 4.2 Hz, 1H), 2.39 (app. ddt, *J* = 18.8, 7.6, 2.5 Hz, 1H), 1.78 (app. q, *J* = 4.5 Hz, 1H), 1.77 (app. q, *J* = 4.5 Hz, 1H), 1.28 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.8, 157.6, 143.6, 140.1, 139.7, 131.2, 129.4, 113.3, 111.8, 60.3, 55.3, 45.8, 37.6, 37.0, 27.6, 26.8, 14.4.

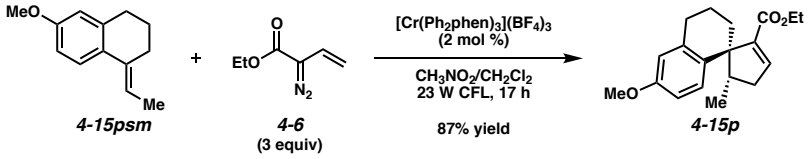
IR (ATR, neat): 1712, 1500, 1265, 1238, 1095 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{17}H_{20}O_3 + H]^+$: 273.1485, found 273.1487.

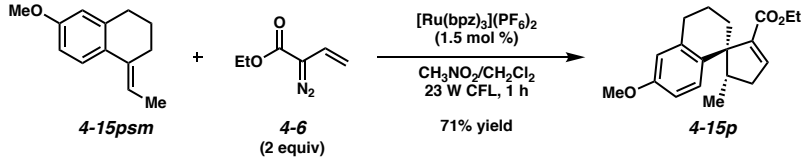
The relative stereochemistry of cyclopentene **4-15o** was confirmed by 2D NOESY NMR analysis.



Cyclopentene 4-15p.



Cr-catalyzed cycloaddition: Prepared according to the *General Procedure* using alkene **4-15psm** (19.7 mg, 0.105 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). After 13 h, another charge of diazoester **4-6** (0.100 mL, 1.0 M solution in CH_2Cl_2, 0.100 mmol) and $[Cr(Ph_2phen)_3](BF_4)_3$ (0.7 mg, 0.000500 mmol) was added. The reaction mixture was irradiated for an additional 4 h (17 h total). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford cyclopentene **4-15p** (27.3 mg, 87% yield) as a colorless oil.



Ru-catalyzed cycloaddition: Prepared according to the *General Procedure* using alkene **4-15psm** (19.0 mg, 0.101 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Ru(bpz)_3](PF_6)_2$ (1.3 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). The reaction mixture was irradiated for 1 h. The solvent was removed by rotary evaporation, and the resulting residue was

purified by flash chromatography (20:1 hexanes/EtOAc eluent) to afford cyclopentene **4-15p** (21.6 mg, 71% yield) as a colorless oil.

TLC: R_f = 0.33 in 10:1 hexanes/EtOAc, visualized by UV. Stained blue with *p*-anisaldehyde.

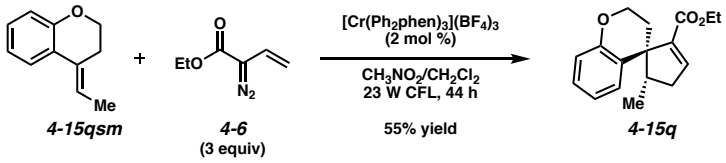
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.04 (d, *J* = 8.6 Hz, 1H), 6.87 (app. t, *J* = 2.2 Hz, 1H), 6.66 (app. dd, *J* = 8.6, 2.7 Hz, 1H), 6.58 (app. d, *J* = 2.7 Hz, 1H), 4.00-3.88 (comp. m, 2H), 3.76 (s, 3H), 2.84-2.69 (comp. m, 2H), 2.59-2.50 (comp. m, 2H), 2.17 (ddd, *J* = 19.8, 12.3, 1.8 Hz, 1H), 1.98-1.92 (m, 1H), 1.88-1.76 (comp. m, 3H), 1.05 (d, *J* = 6.7 Hz, 3H), 1.02 (t, *J* = 7.9 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 164.7, 157.2, 146.0, 142.5, 139.6, 134.6, 128.5, 112.8, 112.3, 59.7, 55.2, 51.8, 50.0, 38.2, 30.6, 27.2, 20.6, 14.9, 14.1.

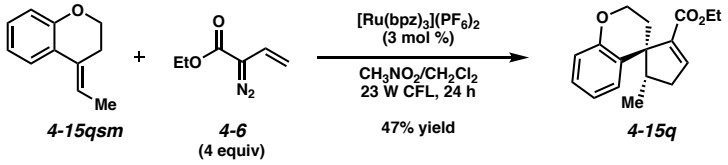
IR (ATR, neat): 2930, 1716, 1500, 1255, 1239 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{19}H_{24}O_3 + H]^+$: 323.1618, found 323.1625.

Cyclopentene 4-15q.



Cr-catalyzed cycloaddition: Prepared according to the *General Procedure* using alkene **4-15qsm** (17.3 mg, 0.108 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). After 24 h, another charge of diazoester **4-6** (0.100 mL, 1.0 M solution in CH_2Cl_2, 0.100 mmol) and $[Cr(Ph_2phen)_3](BF_4)_3$ (0.7 mg, 0.000500 mmol) was added. The reaction mixture was irradiated for an additional 20 h (44 h total). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/EtOAc eluent) to afford cyclopentene **4-15q** (16.1 mg, 55% yield) as a colorless oil.



Ru-catalyzed cycloaddition: Prepared according to the *General Procedure* using alkene **4-15qsm** (16.5 mg, 0.103 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Ru(bpz)_3](PF_6)_2$ (1.4 mg, 0.00162 mmol) in CH_3NO_2 (1.00 mL). After 7.5 h, another charge of diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol) and $[Ru(bpz)_3](PF_6)_2$ (1.3 mg, 0.00150 mmol) was added. The reaction mixture was irradiated for an additional 16.5 h (24 h total). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (30:1 hexanes/EtOAc eluent) to afford cyclopentene **4-15q** (13.1 mg, 47% yield) as a colorless oil.

TLC: R_f = 0.41 in 10:1 hexanes/EtOAc, visualized by UV. Stained pink with *p*-anisaldehyde.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (comp. m, 2H), 6.98-6.94 (m, 1H), 6.83 (comp. m, 2H), 4.28 (ddd, *J* = 11.0, 4.4, 3.3 Hz, 1H), 4.09 (app. td, *J* = 11.7, 1.9 Hz, 1H), 4.00 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.89 (dq, *J* = 10.8, 7.1 Hz, 1H), 2.71-2.58 (comp. m, 2H), 2.33-2.14 (comp. m, 2H), 1.99 (app. dt, *J* = 14.4, 2.6 Hz, 1H), 1.09 (d, *J* = 6.8 Hz, 3H), 0.98 (t, *J* = 7.1 Hz, 3H).

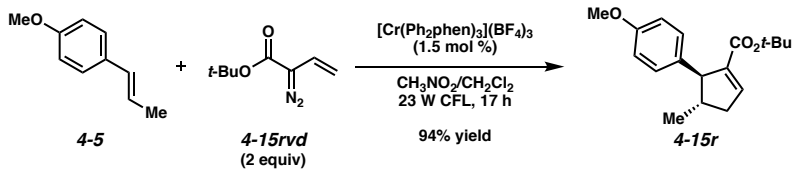
^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 155.6, 144.2, 143.7, 128.3, 127.8, 127.4, 120.7, 116.8, 63.8, 60.0, 48.9, 48.3, 37.9, 26.6, 14.7, 14.0.

IR (ATR, neat): 1716, 1489, 1259, 1222, 755 cm^{-1}.

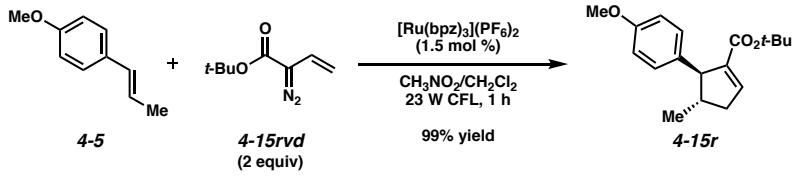
HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{17}H_{20}O_3 + H]^+$: 273.1485, found 273.1488.

4.9.2b Diazo Scope

Cyclopentene 4-15r.



Cr-catalyzed cycloaddition: Prepared according to the *General Procedure* using *trans*-anethole (**4-5**, 14.7 mg, 0.0992 mmol), diazoester **4-15rvd** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). The reaction mixture was irradiated for 17 h. The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/EtOAc eluent) to afford cyclopentene **4-15r** (26.8 mg, 94% yield) as a colorless oil.



Ru-catalyzed cycloaddition: Prepared according to the *General Procedure* using *trans*-anethole (**4-5**, 14.9 mg, 0.101 mmol), diazoester **4-15rvd** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Ru(bpz)_3](PF_6)_2$ (1.3 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). The reaction mixture was irradiated for 1 h. The solvent was removed by rotary evaporation and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/EtOAc eluent) to afford cyclopentene **4-15r** (28.9 mg, 99% yield) as a colorless oil.

TLC: R_f = 0.42 in 10:1 hexanes/EtOAc, visualized by UV. Stained blue with *p*-anisaldehyde.

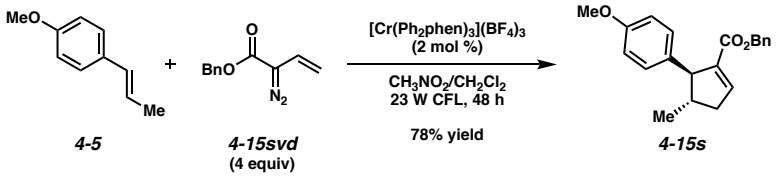
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.81-6.79 (m, 1H), 3.78 (s, 3H), 3.52-3.47 (m, 1H), 2.77 (app. ddt, *J* = 18.0, 8.2, 2.6 Hz, 1H), 2.22 (app. septet, *J* = 6.8 Hz, 1H), 2.10 (ddt, *J* = 18.0, 6.0, 2.4 Hz, 1H), 1.26 (s, 9H), 1.12 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 164.7, 158.0, 142.5, 140.6, 137.4, 128.2, 113.7, 80.1, 58.2, 55.3, 43.9, 40.2, 28.0, 20.5.

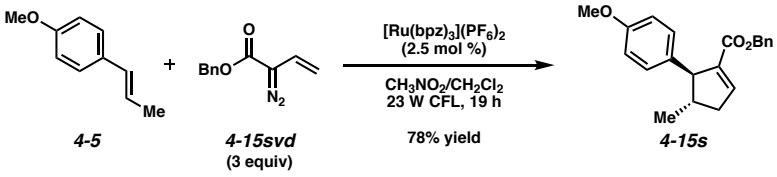
IR (ATR, neat): 2968, 1708, 1512, 1246, 1167 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{18}H_{24}O_3 + H]^+$: 289.1798, found 289.1797.

Cyclopentene 4-15s.



Cr-catalyzed cycloaddition: Prepared according to the *General Procedure* using *trans*-anethole (**4-5**, 16.1 mg, 0.109 mmol), diazoester **4-15svd** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). After 24 h, another charge of diazoester **4-15svd** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol) and $[Cr(Ph_2phen)_3](BF_4)_3$ (0.7 mg, 0.000500 mmol) was added. The reaction mixture was irradiated for an additional 10 h (46 h total). The reaction mixture was irradiated for 48 h. The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford cyclopentene **4-15s** (27.5 mg, 78% yield) as a colorless oil.



Ru-catalyzed cycloaddition: Prepared according to the *General Procedure* using *trans*-anethole (**4-5**, 14.4 mg, 0.0972 mmol), diazoester **4-15svd** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Ru(bpz)_3](PF_6)_2$ (1.3 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). After 3 h, another charge of diazoester **4-15svd** (0.100 mL, 1.0 M solution in CH_2Cl_2, 0.100 mmol) and $[Ru(bpz)_3](PF_6)_2$ (0.9 mg, 0.00104 mmol) was added. The reaction mixture was irradiated for an additional 16 h (19 h total). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (20:1 hexanes/EtOAc eluent) to afford cyclopentene **4-15s** (24.3 mg, 78% yield) as a colorless oil.

TLC: R_f = 0.37 in 10:1 hexanes/EtOAc, visualized by UV. Stained blue with *p*-anisaldehyde.

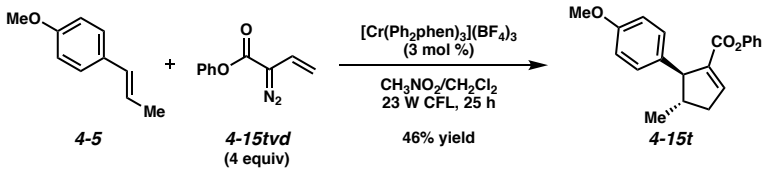
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.23 (comp. m, 3H), 7.10-7.03 (comp. m, 4H), 6.95 (dd, *J* = 4.0, 2.0 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 2H), 5.13 (d, *J* = 12.8 Hz, 1H), 4.94 (d, *J* = 12.8 Hz, 1H), 3.79 (s, 3H), 3.62-3.57 (m, 1H), 2.83 (app. ddt, *J* = 18.4, 8.0, 2.6 Hz, 1H), 2.26 (app. septet, *J* = 7.2 Hz, 1H), 2.13 (app. ddt, *J* = 18.4, 5.2, 2.4, 1H), 1.13 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 164.9, 158.2, 144.3, 138.6, 136.9, 136.2, 128.4, 128.2, 127.9, 127.8, 113.9, 65.8, 58.0, 55.3, 43.7, 40.4, 20.8.

IR (ATR, neat): 1716, 1511, 1260, 1247, 1177 cm^{-1}.

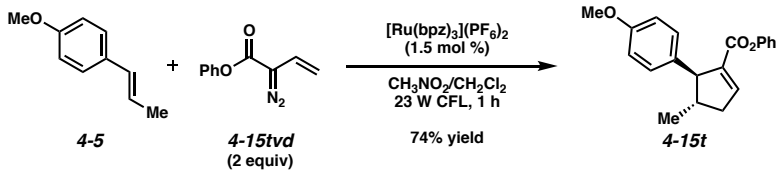
HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{21}H_{22}O_3 + Na]^+$: 345.1461, found 345.1463.

Cyclopentene 4-15t.



Cr-catalyzed cycloaddition: Prepared according to the *General Procedure* using *trans*-anethole (**4-5**, 14.6 mg, 0.0985 mmol), diazoester **4-15tvd** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200

mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). After 24 h, a second charge of diazoester **4-15tvd** (0.100 mL, 1.0 M solution in CH_2Cl_2, 0.100 mmol) and $[Cr(Ph_2phen)_3](BF_4)_3$ (0.7 mg, 0.000500 mmol) was added. After an additional 24 h, another charge of diazoester **4-15tvd** (0.100 mL, 1.0 M solution in CH_2Cl_2, 0.100 mmol) and $[Cr(Ph_2phen)_3](BF_4)_3$ (1.3 mg, 0.00100 mmol) was added. The reaction mixture was irradiated for an additional 24 h (72 h total). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford cyclopentene **4-15t** (14.0 mg, 46% yield) as a colorless oil.



Ru-catalyzed cycloaddition: Prepared according to the *General Procedure* using *trans*-anethole (**4-5**, 14.8 mg, 0.0999 mmol), diazoester **4-15tvd** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Ru(bpz)_3](PF_6)_2$ (1.3 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). The reaction mixture was irradiated for 1 h. The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford cyclopentene **4-15t** (22.9 mg, 74% yield) as a colorless oil.

TLC: R_f = 0.32 in 10:1 hexanes/Et_2O, visualized by UV. Stained orange with *p*-anisaldehyde.

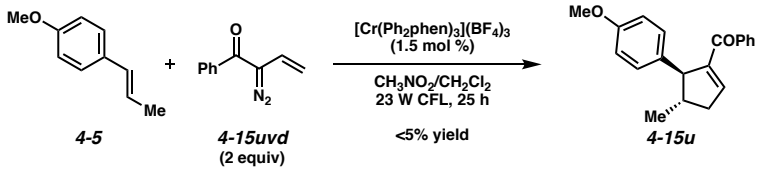
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.26 (comp. m, 2H), 7.18-7.10 (comp. m, 3H), 6.89 (d, *J* = 7.6 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 3.79 (s, 3H), 3.72-3.67 (m, 1H), 2.91 (app. ddt, *J* = 18.4, 8.0, 2.4 Hz, 1H), 2.35 (app. septet, *J* = 7.0 Hz, 1H), 2.22 (app. ddt, *J* = 18.4, 5.4, 2.4 Hz, 1H), 1.19 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 163.4, 158.2, 150.7, 145.8, 138.4, 136.7, 129.3, 128.3, 125.6, 121.7, 114.0, 58.1, 55.4, 43.6, 40.7, 20.8.

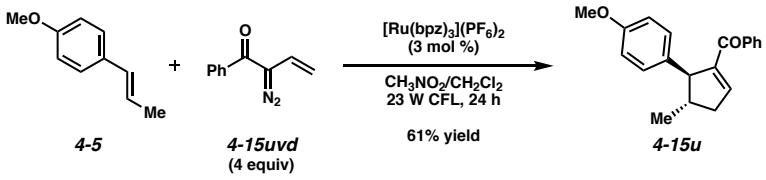
IR (ATR, neat): 2960, 1735, 1511, 1244, 1192, 1036 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{20}H_{20}O_3 + H]^+$: 309.1485, found 309.1485.

Cyclopentene 4-15u.



Cr-catalyzed cycloaddition: A solution of *trans*-anethole (**4-5**, 14.3 mg, 0.0965 mmol), diazoketone **4-15uvd** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (1.9 mg, 0.00145 mmol) in CH_3NO_2 (1.00 mL) was prepared in a flame-dried borosilicate vial open to air. The reaction mixture was irradiated for 25 h. The solvent was removed by rotary evaporation, and the resulting residue was analyzed by crude ^1H NMR with CH_2Br_2 as the internal standard. Cyclopentene **4-15u** was observed in trace amounts (<5% yield, 52% recovery of *trans*-anethole).



Ru-catalyzed cycloaddition: Prepared according to the *General Procedure* using *trans*-anethole (**4-5**, 14.9 mg, 0.101 mmol), diazoketone **4-15uvd** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Ru(bpz)_3](PF_6)_2$ (1.3 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). After 15.5 h, another charge of diazoketone **4-15uvd** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol) and $[Ru(bpz)_3](PF_6)_2$ (1.3 mg, 0.00150 mmol) was added. The reaction mixture was irradiated for an additional 8.5 h (24 h total). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (20:1 hexanes/EtOAc eluent) to afford cyclopentene

4-15u (18.0 mg, 61% yield) as a colorless oil. (12% yield of recovered alkene **4-5** was also isolated.)

TLC: R_f = 0.25 in 10:1 hexanes/EtOAc, visualized by UV. Stained yellow with $KMnO_4$.

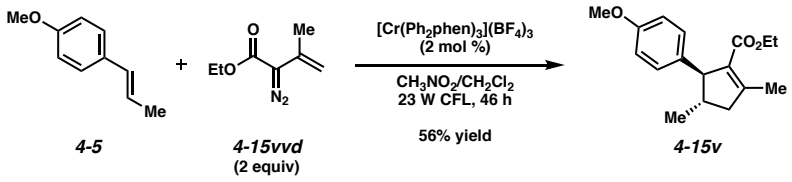
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 7.5 Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.42 (app. t, *J* = 7.6 Hz, 2H), 7.15 (d, *J* = 8.6 Hz, 2H), 6.80 (d, *J* = 8.6 Hz, 2H), 6.57-6.54 (m, 1H), 3.90-3.82 (m, 1H), 3.74 (s, 3H), 2.94 (app. ddt, *J* = 18.2, 7.8, 2.4 Hz, 1H), 2.41-2.28 (m, 1H), 2.23 (app. ddt, *J* = 18.2, 6.9, 2.4 Hz, 1H), 1.18 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 193.7, 158.1, 146.8, 145.0, 138.6, 136.3, 132.3, 129.2, 128.31, 128.29, 114.0, 58.5, 55.3, 43.4, 41.3, 20.0.

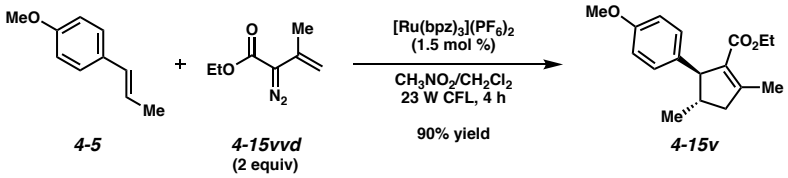
IR (ATR, neat): 1648, 1611, 1511, 1244, 709 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{20}H_{20}O_2 + H]^+$: 293.1536, found 293.1539.

Cyclopentene 4-15v.



Cr-catalyzed cycloaddition: Prepared according to the *General Procedure* using *trans*-anethole (**4-5**, 15.8 mg, 0.107 mmol), diazoester **4-15vvd** (0.100 mL, 1.0 M solution in CH_2Cl_2, 0.100 mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (1.3 mg, 0.00100 mmol) in CH_3NO_2 (1.00 mL). After 36 h, another charge of diazoester **4-15vvd** (0.100 mL, 1.0 M solution in CH_2Cl_2, 0.100 mmol) and $[Cr(Ph_2phen)_3](BF_4)_3$ (1.3 mg, 0.00100 mmol) was added. The reaction mixture was irradiated for an additional 10 h (46 h total). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford cyclopentene **4-15v** (16.4 mg, 56% yield) as a colorless oil.



Ru-catalyzed cycloaddition: Prepared according to the *General Procedure* using *trans*-anethole (**4-5**, 14.6 mg, 0.0986 mmol), diazoester **4-15vvd** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Ru(bpz)_3](PF_6)_2$ (1.3 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). The reaction mixture was irradiated for 4 h. The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (20:1 hexanes/EtOAc eluent) to afford cyclopentene **4-15v** (24.3 mg, 90% yield) as a colorless oil.

TLC: R_f = 0.40 in 10:1 hexanes/EtOAc, visualized by UV. Stained blue with *p*-anisaldehyde.

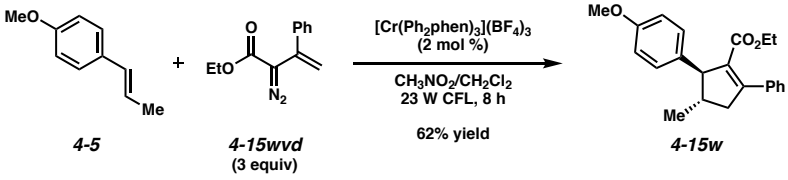
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04 (d, *J* = 8.5 Hz, 2H), 6.80 (d, *J* = 8.5 Hz, 2 H), 4.08-3.98 (m, 1H), 3.98-3.87 (m, 1H), 3.77 (s, 3H), 3.64-3.56 (m, 1H), 2.79 (dd, *J* = 18.9, 9.4 Hz, 1H), 2.19-2.02 (comp. m, 5H), 1.09 (d, *J* = 6.5 Hz, 3H), 1.02 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2, 158.0, 154.8, 137.9, 130.5, 128.1, 113.7, 60.0, 59.6, 55.4, 47.5, 41.5, 20.6, 16.6, 14.2.

IR (ATR, neat): 1708, 1512, 1273, 1244, 1114 cm^{-1}.

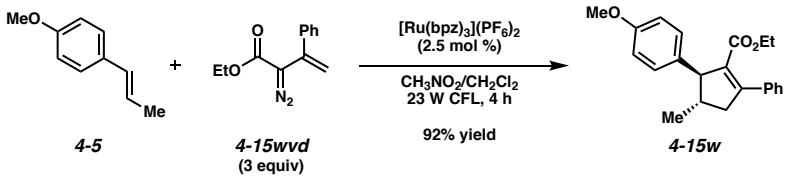
HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{17}H_{22}O_3 + H]^+$: 275.1642, found 275.1643.

Cyclopentene 4-15w.



Cr-catalyzed cycloaddition: Prepared according to the *General Procedure* using *trans*-anethole (**4-5**, 14.9 mg, 0.101 mmol), diazoester **4-15wvd** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200

mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). After 5 h, another charge of diazoester **4-15wvd** (0.100 mL, 1.0 M solution in CH_2Cl_2, 0.100 mmol) and $[Cr(Ph_2phen)_3](BF_4)_3$ (0.7 mg, 0.000500 mmol) was added. The reaction mixture was irradiated for an additional 3 h (8 h total). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford cyclopentene **4-15w** (20.9 mg, 62% yield) as a colorless oil.



Ru-catalyzed cycloaddition: Prepared according to the *General Procedure* using *trans*-anethole (**4-5**, 14.4 mg, 0.0972 mmol), diazoester **4-15wvd** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Ru(bpz)_3](PF_6)_2$ (1.3 mg 0.00150 mmol) in CH_3NO_2 (1.00 mL). After 2 h, another charge of diazoester **4-15wvd** (0.100 mL, 1.0 M solution in CH_2Cl_2, 0.100 mmol) and $[Ru(bpz)_3](PF_6)_2$ (0.9 mg, 0.00104 mmol) was added. The reaction mixture was irradiated for an additional 2 h (4 h total). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (20:1 hexanes/EtOAc eluent) to afford cyclopentene **4-15w** (30.1 mg, 92% yield) as a colorless oil.

TLC: R_f = 0.36 in 10:1 hexanes/EtOAc, visualized by UV. Stained blue with *p*-anisaldehyde.

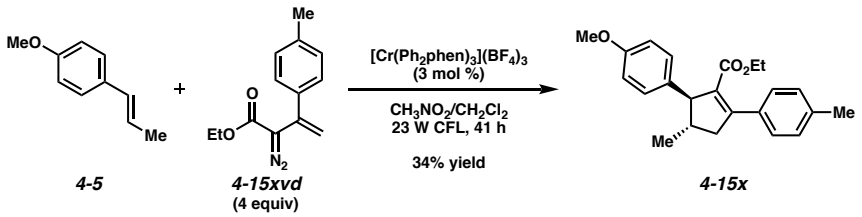
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 7.1 Hz, 2H), 7.41-7.28 (m, 3H), 7.17 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2 H), 4.01-3.81 (comp. m, 3H), 3.80 (s, 3H), 3.17 (ddd, *J* = 17.1, 8.0, 2.0 Hz, 1H), 2.52 (ddd, *J* = 17.1, 7.0, 2.3 Hz, 1H), 2.35-2.22 (app. septet, *J* = 7.0 Hz, 1H), 1.19 (d, *J* = 6.8 Hz, 3H), 0.90 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 158.3, 151.0, 136.7, 136.4, 132.7, 128.5, 128.2, 128.01, 127.97, 113.9, 61.3, 60.0, 55.4, 46.3, 42.2, 19.8, 13.9.

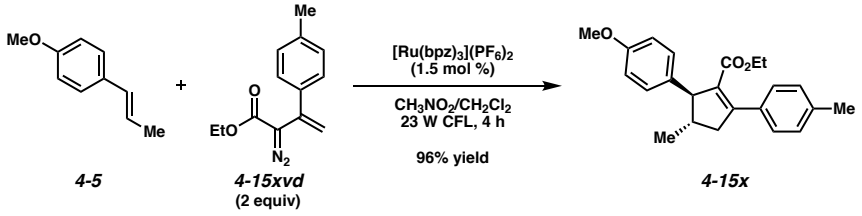
IR (ATR, neat): 1715, 1512, 1247, 1176, 1035 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{22}H_{24}O_3 + H]^+$: 337.1798, found 337.1797.

Cyclopentene 4-15x.



Cr-catalyzed cycloaddition: Prepared according to the *General Procedure* using *trans*-anethole (**4-5**, 14.4 mg, 0.0972 mmol), diazoester **4-15xvd** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). After 17 h, another charge of diazoester **4-15xvd** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol) and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00150 mmol) was added. The reaction mixture was irradiated for an additional 24 h (41 h total). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (20:1 hexanes/EtOAc eluent) to afford cyclopentene **4-15x** (11.7 mg, 34% yield) as a colorless oil.



Ru-catalyzed cycloaddition: Prepared according to the *General Procedure* using *trans*-anethole (**4-5**, 14.5 mg, 0.0978 mmol), diazoester **4-15xvd** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Ru(bpz)_3](PF_6)_2$ (1.3 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). The reaction mixture was irradiated for 4 h. The solvent was removed by rotary evaporation, and the resulting residue

was purified by flash chromatography (20:1 hexanes/EtOAc eluent) to afford cyclopentene **4-15x** (33.0 mg, 96% yield) as a colorless oil.

TLC: R_f = 0.24 in 10:1 hexanes/EtOAc, visualized by UV. Stained yellow with $KMnO_4$.

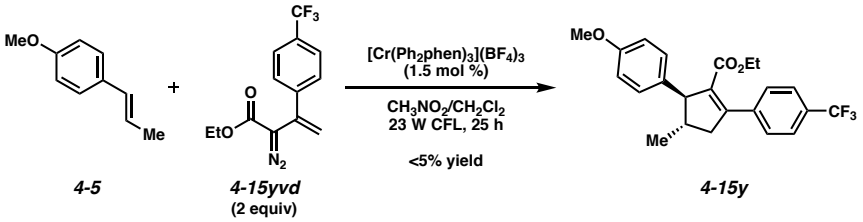
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.2 Hz, 2H), 7.17 (d, *J* = 8.2, 2H), 7.16 (d, *J* = 8.7, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 3.99-3.84 (comp. m, 2H), 3.82 (app. dt, *J* = 6.8, 2.2 Hz, 1H), 3.79 (s, 3H), 3.14 (ddd, *J* = 17.1, 8.0, 2.2 Hz, 1H), 2.49 (ddd, *J* = 17.1, 7.1, 2.3 Hz, 1H), 2.36 (s, 3H), 2.30-2.18 (m, 1H), 1.18 (d, *J* = 6.8 Hz, 3H), 0.91 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.6, 158.2, 150.9, 138.2, 136.6, 133.6, 132.0, 128.7, 128.5, 128.0, 113.8, 61.4, 60.0, 55.3, 46.1, 42.1, 21.4, 19.7, 13.9.

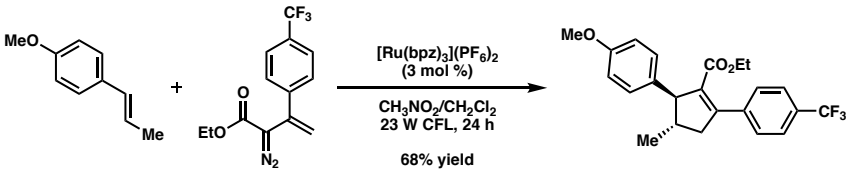
IR (ATR, neat): 1714, 1512, 1247, 1176, 816 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{23}H_{26}O_3 + H]^+$: 351.1955, found 351.1958.

Cyclopentene 4-15y.



Cr-catalyzed cycloaddition: A solution of *trans*-anethole (**4-5**, 15.3 mg, 0.103 mmol), diazoester **4-15yvd** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00153 mmol) in CH_3NO_2 (1.00 mL) was prepared in a flame-dried borosilicate vial open to air. The reaction mixture was irradiated for 25 h. The solvent was removed by rotary evaporation, and the resulting residue was analyzed by crude ^{1}H NMR with CH_2Br_2 as the internal standard. Cyclopentene **4-15y** was observed in trace amounts (<5% NMR yield, 69% recovery of *trans*-anethole).



4-5 *4-15yvd* (4 equiv) *4-15y*

Ru-catalyzed cycloaddition: Prepared according to the *General Procedure* using *trans*-anethole (**4-5**, 15.2 mg, 0.103 mmol), diazoester **4-15yvd** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Ru(bpz)_3](PF_6)_2$ (1.3 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). After 4 h, another charge of diazoester **4-15yvd** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol) and $[Ru(bpz)_3](PF_6)_2$ (1.3 mg, 0.00150 mmol) was added. The reaction mixture was irradiated for an additional 20 h (24 h total). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (20:1 hexanes/EtOAc eluent) to afford cyclopentene **4-15y** (28.2 mg, 68% yield) as a colorless oil.

TLC: R_f = 0.29 in 10:1 hexanes/EtOAc, visualized by UV. Stained yellow with $KMnO_4$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2 H), 4.00-3.81 (comp. m, 3H), 3.79 (s, 3H), 3.14 (ddd, *J* = 17.2, 8.0, 2.2 Hz, 1H), 2.52 (ddd, *J* = 17.2, 7.0, 2.4 Hz, 1H), 2.30 (app. septet, 7.0 Hz, 1H), 1.20 (d, *J* = 6.8 Hz, 3H), 0.88 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.9, 158.4, 149.7, 140.5, 136.0, 134.5, 130.0 (q, J_{C-F} = 32.7 Hz), 128.5, 128.3, 125.0 (q, J_{C-F} = 3.7 Hz), 124.2 (q, J_{C-F} = 272.9 Hz), 114.0, 61.2, 60.2, 55.3, 46.3, 42.2, 19.7, 13.8.

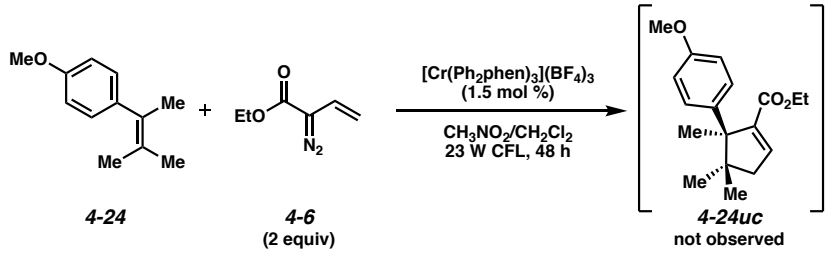
^{19}F NMR (376 MHz, $CDCl_3$): δ -62.7.

IR (ATR, neat): 1716, 1512, 1236, 1248, 1126 cm^{-1}.

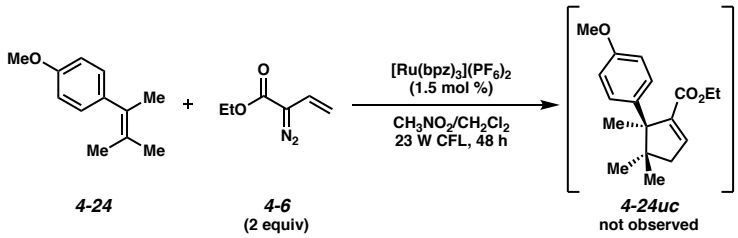
HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{23}H_{23}F_3O_3 + H]^+$: 405.1672, found 405.1675.

4.9.3 Unsuccessful cycloadditions

Tetrasubstituted alkene

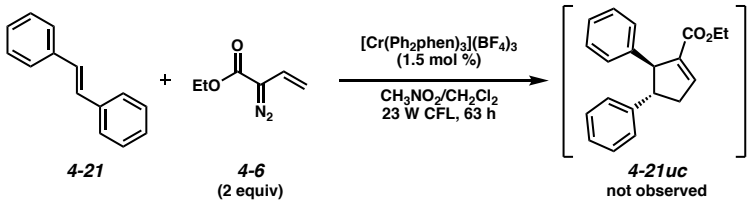


Attempted Cr-catalyzed cycloaddition: A solution of tetrasubstituted alkene **4-24** (18.2 mg, 0.103 mmol), diazoester **4-6** (0.210 mL, 1.0 M solution in CH_2Cl_2, 0.210 mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00155 mmol) in CH_3NO_2 (1.00 mL) was prepared in a flame-dried borosilicate vial open to air. The reaction mixture was irradiated for 48 h. The solvent was removed by rotary evaporation, and cyclopentene **4-24uc** was not observed in the crude ^{1}H NMR spectrum.

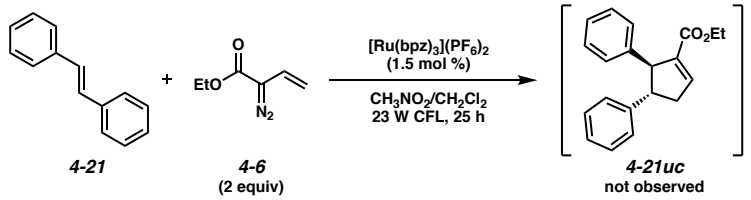


Attempted Ru-catalyzed cycloaddition: A solution of tetrasubstituted alkene **4-24** (19.8 mg, 0.112 mmol), diazoester **4-6** (0.220 mL, 1.0 M solution in CH_2Cl_2, 0.220 mmol), and $[Ru(bpz)_3](PF_6)_2$ (1.5 mg, 0.00168 mmol) in CH_3NO_2 (1.10 mL) was prepared in a flame-dried borosilicate vial open to air. The reaction mixture was irradiated for 48 h. The solvent was removed by rotary evaporation, and cyclopentene **4-24uc** was not observed in the crude ^{1}H NMR spectrum.

Stilbene

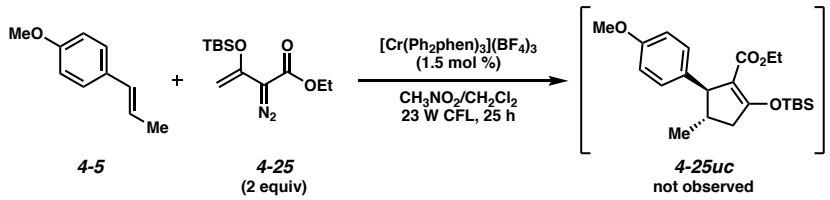


Attempted Cr-catalyzed cycloaddition: A solution of *trans*-stilbene (**4-21**, 18.0 mg, 0.0998 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00153 mmol) in CH_3NO_2 (1.00 mL) was prepared in a flame-dried borosilicate vial open to air. The reaction mixture was irradiated for 63 h. The solvent was removed by rotary evaporation, and cyclopentene **4-21uc** was not observed by ^1H NMR.

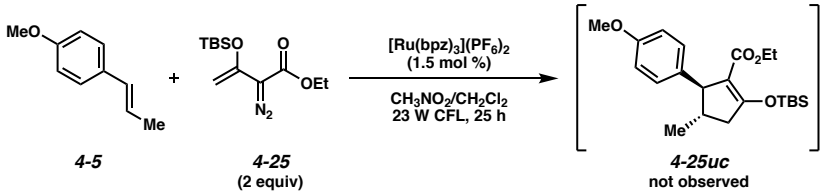


Attempted Ru-catalyzed cycloaddition: A solution of *trans*-stilbene (**4-21**, 18.0 mg, 0.0961 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Ru(bpz)_3](PF_6)_2$ (1.3 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL) was prepared in a flame-dried borosilicate vial open to air. The reaction mixture was irradiated for 25 h. The solvent was removed by rotary evaporation, and cyclopentene **4-21uc** was not observed by ^1H NMR.

Enol diazoacetate

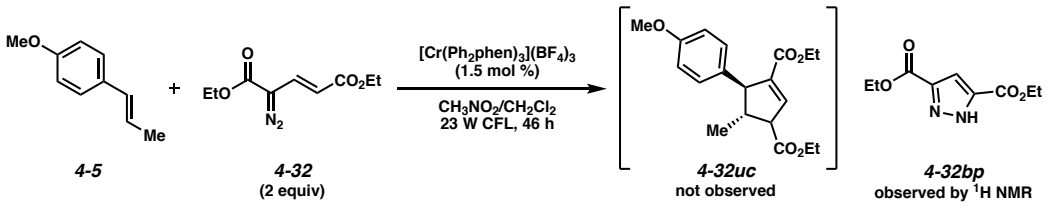


Attempted Cr-catalyzed cycloaddition: A solution of *trans*-anethole (**4-5**, 14.8 mg, 0.0999 mmol), diazoester **4-25** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00153 mmol) in CH_3NO_2 (1.00 mL) was prepared in a flame-dried borosilicate vial open to air. The reaction mixture was irradiated for 25 h. The solvent was removed by rotary evaporation, and cyclopentene **4-25uc** was not observed in the crude ^{1}H NMR spectrum.



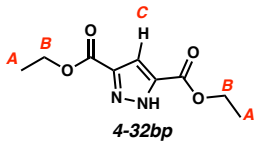
Attempted Ru-catalyzed cycloaddition: A solution of *trans*-anethole (**4-5**, 14.8 mg, 0.0999 mmol), diazoester **4-25** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Ru(bpz)_3](PF_6)_2$ (1.3 mg, 0.00150 mmol) in CH_3NO_2 (1.10 mL) was prepared in a flame-dried borosilicate vial open to air. The reaction mixture was irradiated for 25 h. The solvent was removed by rotary evaporation, and cyclopentene **4-25uc** was not observed in the crude ^{1}H NMR spectrum.

Gamma-substituted vinyl diazos

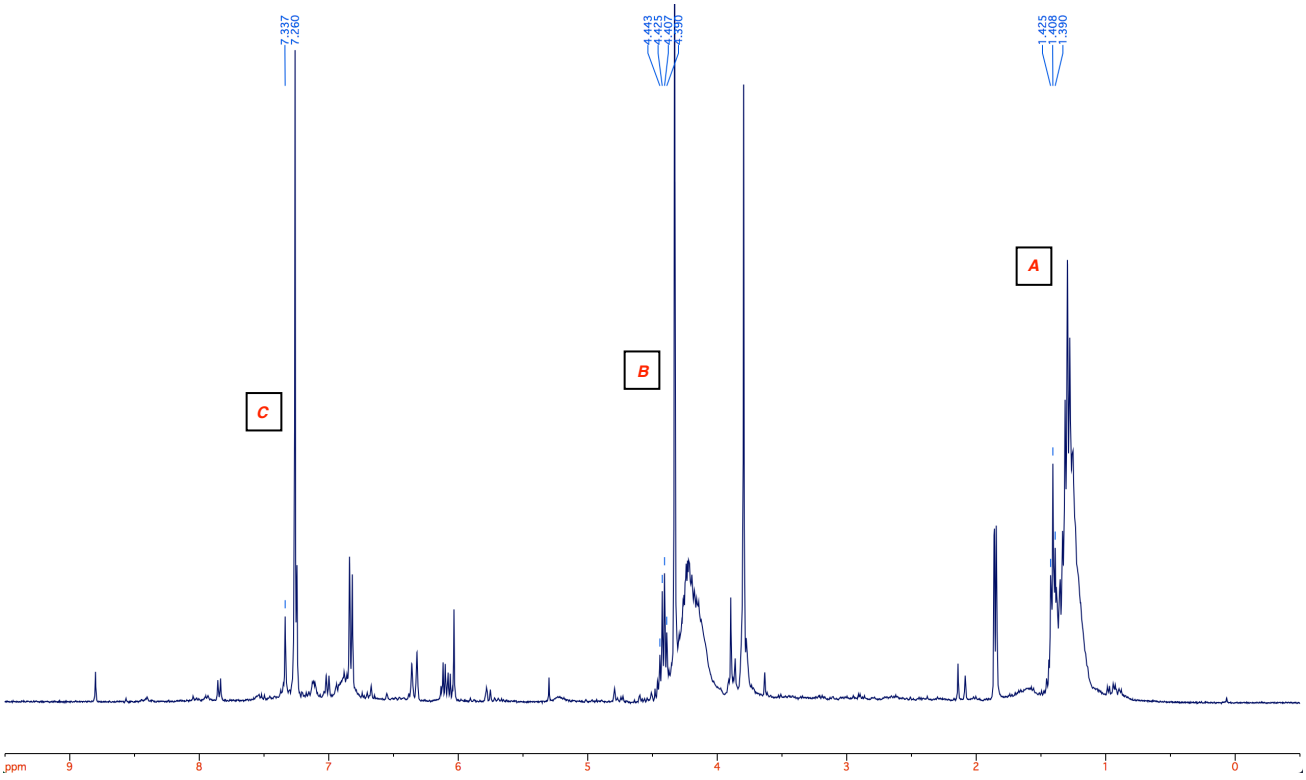


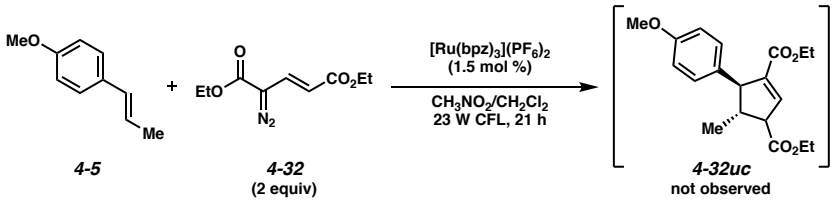
Attempted Cr-catalyzed cycloaddition: A solution of *trans*-anethole (**4-5**, 15.1 mg, 0.102 mmol), diazoester **4-32** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00153 mmol) in CH_3NO_2 (1.00 mL) was prepared in a flame-dried borosilicate vial open to air. The reaction mixture was irradiated for 46 h. The solvent was removed by rotary evaporation, and cyclopentene **4-32uc** was not observed in the crude ^{1}H NMR spectrum. Pyrazole **4-32bp** was

observed in the crude ^{1}H NMR spectrum (below), consistent with reported data on this compound.[24]



4-32bp

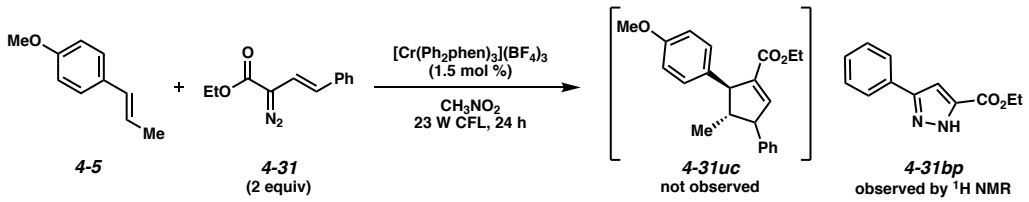




4-5 | *4-32* (2 equiv) | *4-32uc* not observed

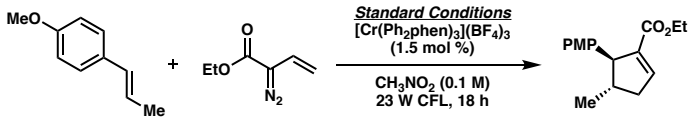
Attempted Ru-catalyzed cycloaddition: A solution of *trans*-anethole (**4-5**, 15.2 mg, 0.103 mmol), diazoester **4-32** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Ru(bpz)_3](PF_6)_2$ (1.4 mg, 0.00155 mmol) in CH_3NO_2 (1.00 mL) was prepared in a flame-dried borosilicate vial open to air.

The reaction mixture was irradiated for 21 h. The solvent was removed by rotary evaporation, and cyclopentene **4-32uc** was not observed in the crude ^{1}H NMR spectrum.



Attempted Cr-catalyzed cycloaddition: A solution of *trans*-anethole (**4-5**, 14.9 mg, 0.101 mmol), diazoester **4-31** (44.0 mg, 0.203 mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00153 mmol) in CH_3NO_2 (1.00 mL) was prepared in a flame-dried borosilicate vial open to air. The reaction mixture was irradiated for 24 h. The solvent was removed by rotary evaporation, and cyclopentene **4-31uc** was not observed in the crude ^{1}H NMR spectrum. Pyrazole **4-31bp** was observed in the crude ^{1}H NMR spectrum, identified by signals consistent with reported values.[25]

4.9.4 Cycloaddition Optimization



4-5 + *4-6* (2 equiv)[a] → *4-15*

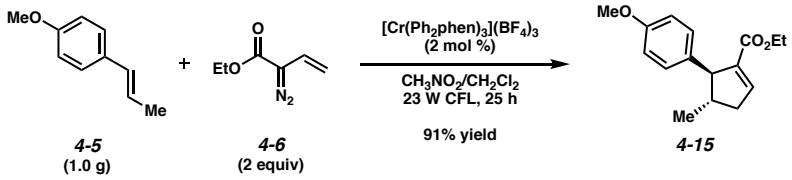
Deviation from "Standard Conditions"	NMR yield (%)[b]
None	89
1 equiv *4-6*	57
3 equiv *4-6*	84
NUV irradiation[c]	87
blue LED irradiation, 37 h	75
white LED irradiation, 37 h	74
CH_3CN as solvent	67
dichloroethane as solvent	32
acetone as solvent	25
CH_2Cl_2 as solvent	22
1 mol % $[Cr(Ph_2phen)_3](BF_4)_3$	86
0.2 mol % $[Cr(Ph_2phen)_3](BF_4)_3$, 42 h	24
$CrCl_3$ (10 mol %) instead of Cr complex	0
no catalyst added	0
no irradiation	0
$[Ru(bpz)_3](PF_6)_2$ instead of Cr complex, 1 h	99
0.2 mol % $[Ru(bpz)_3](PF_6)_2$ instead of Cr complex, 1.5 h	88

[a] Reagent *4-6* was added as a 1.0 M solution in CH_2Cl_2. [b] ^1H NMR yields determined using 2-naphthaldehyde as a standard. *c* Near-UV light (bulbs at 300, 350, and 419 nm).

General Procedure for optimization experiments: A flame-dried 1-dram borosilicate vial open to air was charged with *trans*-anethole (**4-5**, 0.100 mmol, 1.0 equiv), vinyl diazoacetate **4-6** (1.0, 2.0, or 3.0 equiv, 1.0 M solution in CH_2Cl_2), the respective [Cr] or [Ru] photocatalyst (0.2, 1.0 or 1.5 mol %), and 1.0 mL of solvent (0.1 M). The vial was then capped. The solution was irradiated with the indicated light source, stirring for the indicated time and then concentrated via rotary evaporation. The resulting crude product was analyzed by ^1H NMR, using 2-naphthaldehyde as a standard.

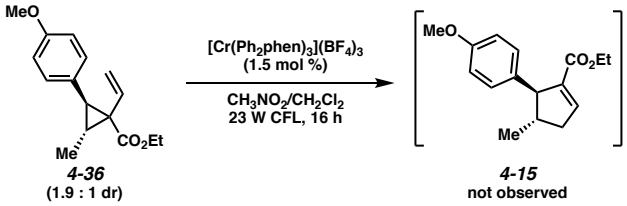
4.9.5 Additional Experiments

Gram-scale experiment



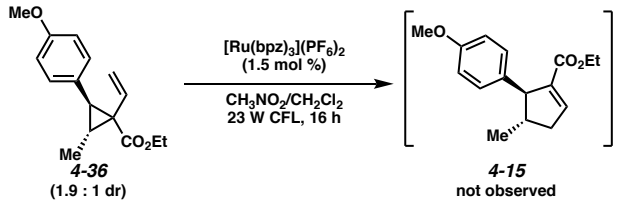
A solution of *trans*-anethole (**4-5**, 1.00 g, 6.75 mmol), diazoester **4-6** (6.80 mL, 1.0 M solution in CH_2Cl_2, 6.80 mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (177 mg, 0.135 mmol) in CH_3NO_2 (67.0 mL) was prepared in a flame-dried round bottom flask. The flask was fitted with a rubber septum and needle outlet (for N_2 formation) and placed into a room-temperature water bath (in recrystallizing dish) on a stirplate in a closed box lined with aluminum foil and equipped with two 23 W compact fluorescent light bulbs. The reaction mixture was irradiated for 10 h, at which point a second equivalent of diazoester **4-6** (6.80 mL, 1.0 M solution in CH_2Cl_2, 6.80 mmol) was added. The mixture was irradiated for an additional 15 h (25 h total). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford cyclopentene **4-15** (1.60 g, 91% yield) as a colorless oil.

Vinylcyclopropane analyses

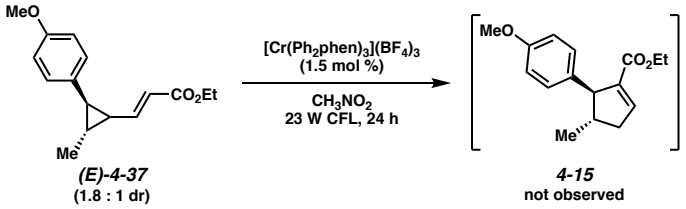


Cr-catalyzed experiment: A solution of vinylcyclopropane **4-36** (9.4 mg, 0.0361 mmol) and $Cr(Ph_2Phen)_3(BF_4)_3$ (0.7 mg, 0.000542 mmol) in CH_3NO_2 (0.360 mL) and CH_2Cl_2 (0.0700 mL)

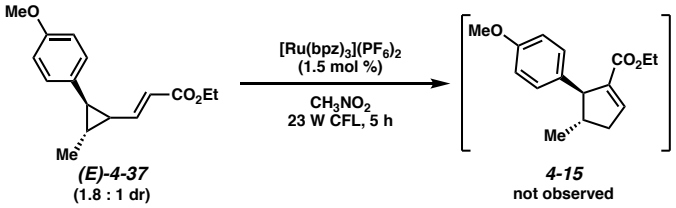
was prepared in a flame-dried borosilicate vial open to air. The vial was capped and placed on a stirplate in a closed box lined with aluminum foil and equipped with a 23 W compact fluorescent light bulb. The reaction mixture was irradiated while stirring for 16 h. The solvent was removed via rotary evaporation. ^{1}H NMR analysis of the residue showed no cyclopentene product **4-15**.



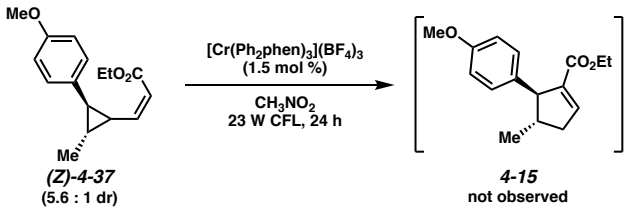
Ru-catalyzed experiment: A solution of vinylcyclopropane **4-36** (17.7 mg, 0.0680 mmol) and $[Ru(bpz)_3](PF_6)_2$ (0.9 mg, 0.00102 mmol) in CH_3NO_2 (0.680 mL) and CH_2Cl_2 (0.140 mL) was prepared in a flame-dried borosilicate vial open to air. The vial was capped and placed on a stirplate in a closed box lined with aluminum foil and equipped with a 23 W compact fluorescent light bulb. The reaction mixture was irradiated while stirring for 16 h. The solvent was removed via rotary evaporation. ^{1}H NMR analysis of the residue showed no cyclopentene product **4-15**.



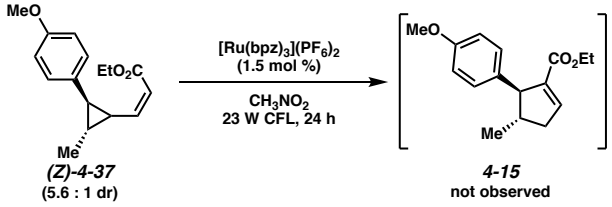
Cr-catalyzed experiment: A solution of vinycyclopropane **(*E*)-4-37** (26.4 mg, 0.101 mmol) and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00152 mmol) in CH_3NO_2 (1.00 mL) was prepared in a flame-dried borosilicate vial open to air. The reaction mixture was irradiated for 24 h. The solvent was removed by rotary evaporation, and cyclopentene **4-15** was not observed in the crude ^{1}H NMR spectrum.



Ru-catalyzed experiment: A solution of vinylcyclopropane **(*E*)-4-37** (26.0 mg, 0.0999 mmol) and $[Ru(bpz)_3](PF_6)_2$ (1.3 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL) was prepared in a flame-dried borosilicate vial open to air. The reaction mixture was irradiated for 5 h. The solvent was removed by rotary evaporation, and cyclopentene **4-15** was not observed in the crude ^{1}H NMR spectrum.



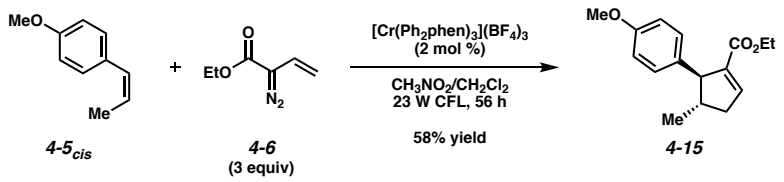
Cr-catalyzed experiment: A solution of vinylcyclopropane **(*Z*)-4-37** (26.0 mg, 0.0999 mmol) and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL) was prepared in a flame-dried borosilicate vial open to air. The reaction mixture was irradiated for 24 h. The solvent was removed by rotary evaporation, cyclopentene **4-15** was not observed in the crude ^{1}H NMR spectrum.



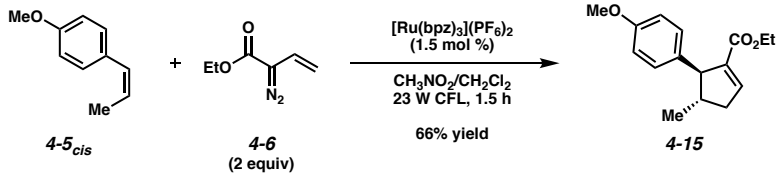
Ru-catalyzed experiment: A solution of vinylcyclopropane **(*Z*)-4-37** (28.0 mg, 0.108 mmol) and $[Ru(bpz)_3](PF_6)_2$ (1.4 mg, 0.00162 mmol) in CH_3NO_2 (1.00 mL) was prepared in a flame-dried borosilicate vial open to air. The reaction mixture was irradiated for 24 h. The solvent was

removed by rotary evaporation, cyclopentene **4-15** was not observed in the crude ^{1}H NMR spectrum.

Cycloaddition using cis-anethole

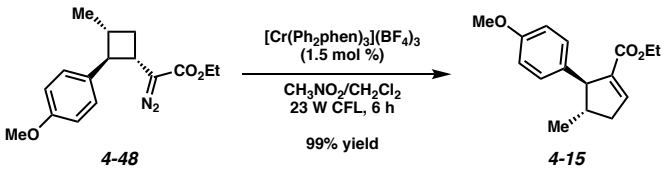


Cr-catalyzed cycloaddition: Prepared according to the *General Procedure* using *cis*-anethole (**4-5$_{cis}$**, 14.8 mg, 0.0999 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL). After 36 h, another charge of diazoester **4-6** (0.100 mL, 1.0 M solution in CH_2Cl_2, 0.100 mmol) and $[Cr(Ph_2phen)_3](BF_4)_3$ (0.7 mg, 0.000500 mmol) was added. The reaction mixture was irradiated for an additional 20 h (56 h total). The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford cyclopentene **4-15** (15.2 mg, 58% yield) as a colorless oil.

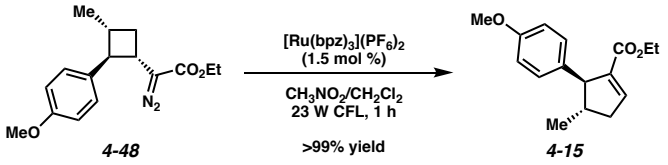


Ru-catalyzed cycloaddition: Prepared according to the *General Procedure* using *cis*-anethole (**4-5$_{cis}$**, 15.9 mg, 0.107 mmol), diazoester **4-8** (0.210 mL, 1.0 M solution in CH_2Cl_2, 0.210 mmol), and $[Ru(bpz)_3](PF_6)_2$ (1.4 mg, 0.00161 mmol) in CH_3NO_2 (1.00 mL). The reaction mixture was irradiated for 1.5 h. The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford cyclopentene **4-15** (18.4 mg, 66% yield) as a colorless oil.

Diazo cyclobutane rearrangement

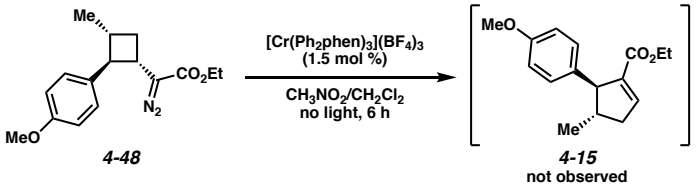


Cr-catalyzed experiment: A solution of cyclobutyl diazoester **4-48** (28.0 mg, 0.0971 mmol) and $Cr(Ph_2Phen)_3(BF_4)_3$ (2.0 mg, 0.00153 mmol) in CH_3NO_2 (1.00 mL) and CH_2Cl_2 (0.200 mL) was prepared in a flame-dried borosilicate vial open to air. The vial was capped and placed on a stirplate in a closed box lined with aluminum foil and equipped with a 23 W compact fluorescent light bulb. The reaction mixture was irradiated while stirring for 6 h. The solvent was removed via rotary evaporation. The crude product was passed through a short plug of silica (Et_2O eluent) to afford cyclopentene **4-15** (25.1 mg, 99% yield) as a yellow oil.

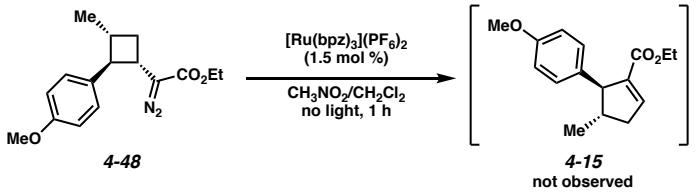


Ru-catalyzed experiment: A solution of cyclobutyl diazoester **4-48** (29.4 mg, 0.102 mmol) and $[Ru(bpz)_3](PF_6)_2$ (1.3 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL) and CH_2Cl_2 (0.200 mL) was prepared in a flame-dried borosilicate vial open to air. The vial was capped and placed on a stirplate in a closed box lined with aluminum foil and equipped with a 23 W compact fluorescent light bulb. The reaction mixture was irradiated while stirring for 1 h. The solvent was removed via rotary evaporation. The crude product was passed through a short plug of silica (Et_2O eluent) to afford cyclopentene **4-15** (27.2 mg, >99% yield) as a yellow oil.

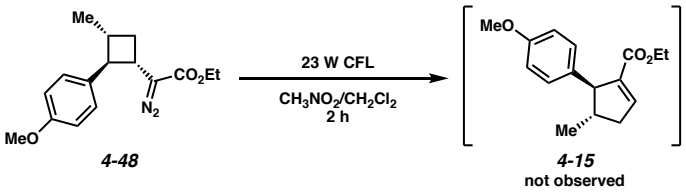
Diazo cyclobutane - related control experiments



Cr-catalyzed experiment (dark): A solution of cyclobutyl diazoester **4-48** (13.5 mg, 0.0468 mmol) and $Cr(Ph_2Phen)_3(BF_4)_3$ (1.0 mg, 0.000763 mmol) in CH_3NO_2 (0.500 mL) and CH_2Cl_2 (0.100 mL) was prepared in a flame-dried borosilicate vial open to air. The vial was capped, wrapped with aluminum foil, and placed on a stirplate in a closed box lined with aluminum foil and equipped with a 23 W compact fluorescent light bulb. After 6 h, the reaction mixture was concentrated via rotary evaporation. The residue was analyzed by crude ^1H NMR with CH_2Br_2 as the internal standard. Cyclopentene **4-15** was not observed.

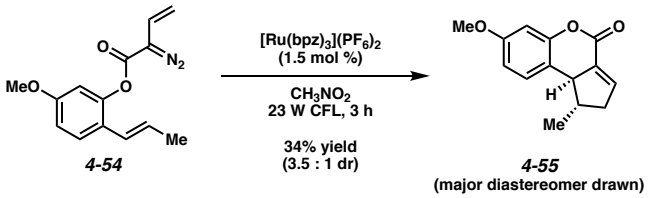


Ru-catalyzed experiment (dark): A solution of cyclobutyl diazoester **4-48** (13.7 mg, 0.0475 mmol) and $[Ru(bpz)_3](PF_6)_2$ (0.7 mg, 0.000809 mmol) in CH_3NO_2 (0.500 mL) and CH_2Cl_2 (0.100 mL) was prepared in a flame-dried borosilicate vial open to air. The vial was capped, wrapped with aluminum foil, and placed on a stirplate in a closed box lined with aluminum foil and equipped with a 23 W compact fluorescent light bulb. After 1 h, the reaction mixture was concentrated via rotary evaporation, and the residue was analyzed by crude ^1H NMR with CH_2Br_2 as the internal standard. Cyclopentene **4-15** was not observed.



Catalyst-free experiment: A solution of cyclobutyl diazoester **4-48** (13.7 mg, 0.0476 mmol) in CH_3NO_2 (0.500 mL) and CH_2Cl_2 (0.100 mL) was prepared in a flame-dried borosilicate vial open to air. The vial was capped and placed on a stirplate in a closed box lined with aluminum foil and equipped with a 23 W compact fluorescent light bulb. The reaction mixture was irradiated while stirring for 2 h. The solvent was removed via rotary evaporation, and the residue was analyzed by crude ^{1}H NMR with CH_2Br_2 as the internal standard. Cyclopentene **4-15** was not observed.

Intramolecular Cyclopentenannulation



Cyclopentene 4-55. A solution of diazoester **4-54** (38.3 mg, 0.148 mmol) and $[Ru(bpz)_3](PF_6)_2$ (1.9 mg, 0.00222 mmol) in CH_3NO_2 (1.00 mL) was prepared in a flame-dried borosilicate vial open to air. The vial was capped and placed on a stirplate in a closed box lined with aluminum foil, and it was irradiated with a 23 W compact fluorescent light bulb. The reaction mixture was irradiated while stirring for 3 h. The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (100% hexanes → 3:1 hexanes/EtOAc eluent) to afford cyclopentene **4-55** (11.5 mg, 34% yield, 3.5:1 inseparable mixture of diastereomers) as a white solid.

TLC: R_f = 0.37 in 3:1 hexanes/EtOAc, visualized by UV. Stained red with *p*-anisaldehyde.

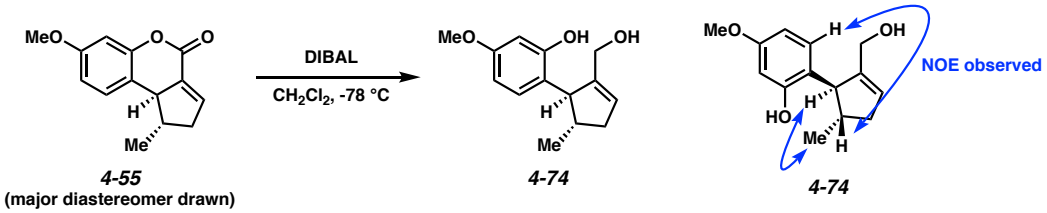
^{1}H NMR (400 MHz, $CDCl_3$): [Major diastereomer] δ 7.11 (d, *J* = 8.4 Hz, 1H), 6.76-6.72 (m, 1H), 6.72-6.65 (comp m, 2H), 3.71 (s, 3H), 3.65-3.56 (m, 1H), 2.77 (app. ddt, *J* = 17.7, 7.7, 2.4 Hz, 1H), 2.49-2.37 (m, 1H), 2.29-2.17 (m, 1H), 1.16 (d, *J* = 6.4 Hz, 3H); [Minor diastereomer] δ 7.07 (d, *J* = 8.4 Hz, 1H), 7.02-6.99 (m, 1H), 6.72-6.65 (comp m, 2H), 3.87-3.82 (m, 1H), 3.72 (s, 3H), 2.93 (app. ddt, *J* = 18.5, 7.8, 2.6 Hz, 1H), 2.39-2.30 (m, 1H), 2.29-2.17 (m, 1H), 1.10 (d, *J* = 6.8 Hz, 3H).

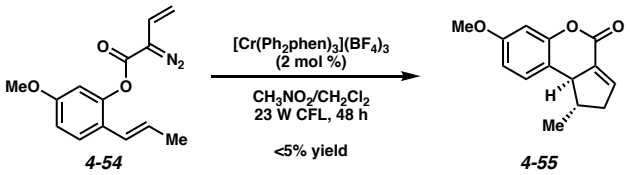
^{13}C NMR (125 MHz, $CDCl_3$, characterized as mixture of the major and minor diastereomers): δ 164.1, 162.2, 158.6, 158.4, 149.3, 148.2, 144.1, 141.4, 139.7, 139.5, 131.6, 129.7, 126.0, 112.2, 112.0, 110.2, 108.9, 56.7, 55.5, 55.4, 52.5, 43.6, 43.0, 40.7, 40.4, 29.8, 20.6, 18.1.

IR (ATR, neat): 2954, 1743, 1616, 1504, 1235, 1114 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{14}H_{14}O_3 + H]^+$: 231.1016, found 231.1016.

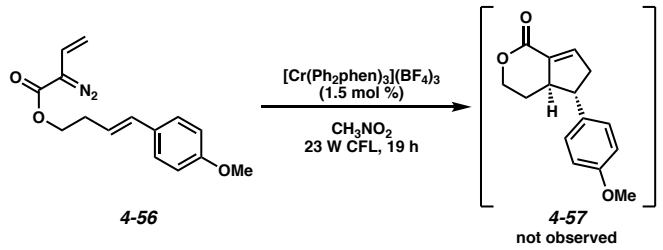
The relative stereochemistry of the major diastereomer of lactone **4-55** was confirmed by 2D NOESY NMR analysis of the corresponding reduction product (**4-74**).





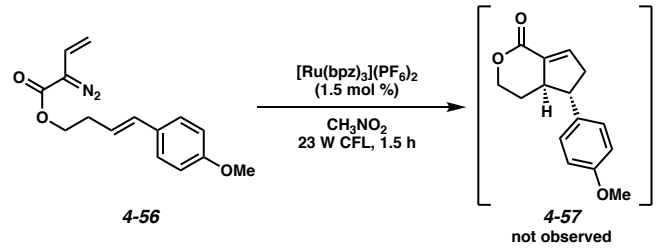
Attempted Cr-catalyzed cycloaddition: A solution of diazoester **4-54** (26.3 mg, 0.102 mmol) and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL) and CH_2Cl_2 (0.200 mL) was prepared in a flame-dried borosilicate vial open to air. The vial was capped and placed on a

stirplate in a closed box lined with aluminum foil, and it was irradiated with a 23 W compact fluorescent light bulb. After 24 h, another charge of $[Cr(Ph_2phen)_3](BF_4)_3$ (0.7 mg, 0.000500 mmol) was added. The reaction mixture was irradiated for an additional 24 h (48 h total). The solvent was removed by rotary evaporation. Traces of product **4-55** (<5% yield) were observed by ^{1}H NMR.



4-56 *4-57* not observed

Attempted Cr-catalyzed cycloaddition: A solution of diazoester **4-56** (27.4 mg, 0.101 mmol) and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL) was prepared in a flame-dried borosilicate vial open to air. The vial was capped and placed on a stirplate in a closed box lined with aluminum foil and equipped with a 23 W compact fluorescent light bulb. The reaction mixture was irradiated while stirring for 19 h. The solvent was removed via rotary evaporation. Broad peaks, suggestive of oligomer formation, were observed by ^{1}H NMR. Cyclopentene **4-57** was not observed.

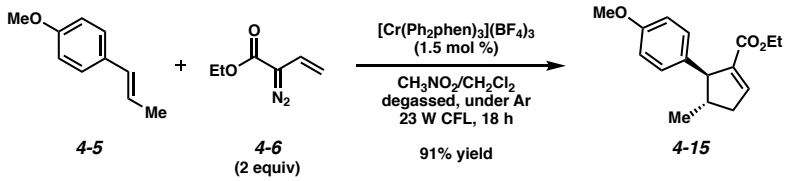


4-56 *4-57* not observed

Attempted Ru-catalyzed cycloaddition: A solution of diazoester **4-56** (9.0 mg, 0.0331 mmol) and $[Ru(bpz)_3](PF_6)_2$ (0.4 mg, 0.497 μmol) in CH_3NO_2 (0.33 mL) was prepared in a flame-dried borosilicate vial open to air. The vial was capped and placed on a stirplate in a closed box lined

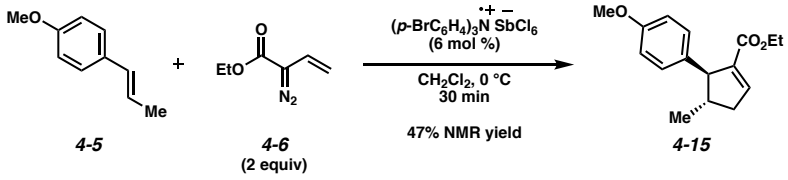
with aluminum foil and equipped with a 23 W compact fluorescent light bulb. The reaction mixture was irradiated while stirring for 1.5 h. The solvent was removed via rotary evaporation. Broad peaks, suggestive of oligomer formation, were observed by ^{1}H NMR. Cyclopentene **4-57** was not observed.

Oxygen-Free Experiments



A solution containing *trans*-anethole (**4-5**, 15.0 mg, 0.101 mmol), diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol), and $[Cr(Ph_2phen)_3](BF_4)_3$ (2.0 mg, 0.00150 mmol) in CH_3NO_2 (1.00 mL) was prepared in a flame-dried schlenk flask under argon. The reaction mixture was degassed by freeze-pump-thaw method (3x) and kept under argon. The flask was placed on a stirplate in a closed box lined with aluminum foil, and irradiated with a 23 W compact fluorescent light bulb. The mixture was irradiated for 18 h, at which point it was concentrated via rotary evaporation. The crude product was purified by flash column chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford cyclopentene **4-15** (24.0 mg, 91% yield) as a colorless oil.

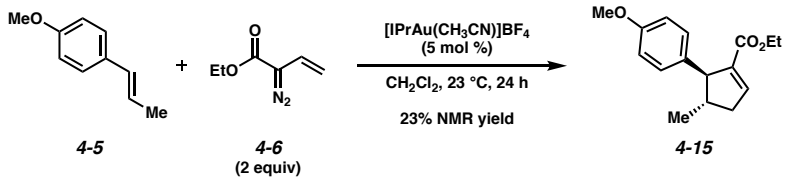
Bauld Aminium Catalyst Experiment



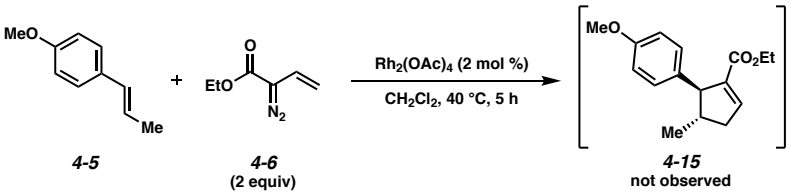
To an oven-dried vial was added $(p\text{-}BrC_6H_4)_3NSbCl_6$ (5.5 mg, 0.00673 mmol) and CH_2Cl_2 (1.00 mL) under Ar. The mixture was then cooled to 0 °C, *trans*-anethole (**4-5**, 15.1 mg, 0.102 mmol)

and diazoester **4-6** (0.200 mL, 1.0 M solution in CH_2Cl_2, 0.200 mmol) was added at this temperature. After 0.5 h at 0 °C, the solvent was removed by rotary evaporation, and the crude residue was analyzed by ^1H NMR. Cyclopentene **4-15** was observed in 47% NMR yield using 2-naphthaldehyde as a standard.

Other metal catalysts examination

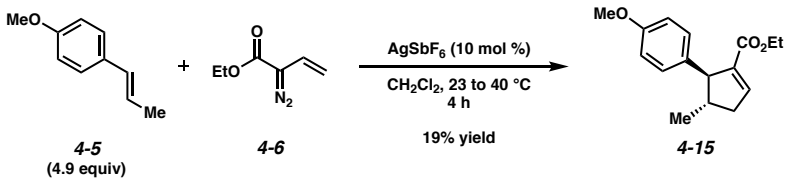


Au-Catalyzed Experiment: A procedure similar to the protocol of López was followed.[26] In a glovebox under Ar, $[IPrAu(CH_3CN)]BF_4$ (4.0 mg, 0.00555 mmol) was added to a solution of diazoester **4-6** (0.220 mL, 1.0 M solution in CH_2Cl_2, degassed, 0.220 mmol) and *trans*-anethole (**4-5**, 16.5 mg, 0.111 mmol) in CH_2Cl_2 (1.10 mL). The sealed mixture was removed from the glovebox and stirred at room temperature for 24 h. The reaction mixture was passed through a short silica plug (EtOAc eluent), and the solvent was removed under reduced pressure. The crude residue was analyzed by ^1H NMR. Cyclopentene **4-15** was observed in 23% NMR yield using 2-naphthaldehyde as a standard.

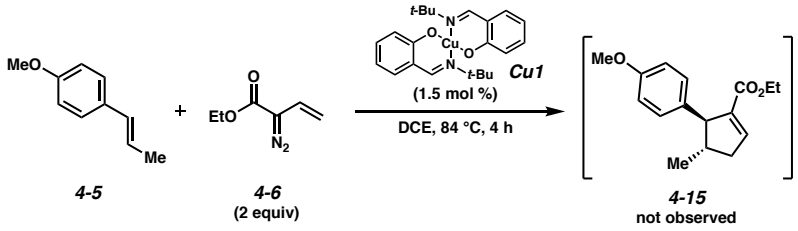


Rh-Catalyzed Experiment: A solution containing *trans*-anethole (**4-5**, 52.0 mg, 0.351 mmol), $Rh_2(OAc)_4$ (3.1 mg, 0.00300 mmol, 2 mol %), and 1.6 mL CH_2Cl_2 was prepared in a flame-dried round bottom flask, and it was heated to 40 °C. To this reaction mixture, a solution of diazoester

4-6 (0.700 mL, 1.0 M solution in CH_2Cl_2, 0.700 mmol) in 4.2 mL CH_2Cl_2 was added via syringe pump at a rate of 500 μL/h over 5 h. The reaction mixture was cooled to room temperature, concentrated via rotary evaporation, and the crude reaction mixture was analyzed by ^1H NMR. Cyclopentene **4-15** was not observed.



Ag-Catalyzed Experiment: The transformation was performed following a procedure described by Davies and Thompson.[27] In a rigorously dried round bottom flask covered in aluminum foil to exclude light, a mixture of $AgSbF_6$ (10.3 mg, 0.0300 mmol, 10 mol %) in 8.0 mL of CH_2Cl_2 at 23 °C under argon was prepared, and to this mixture was added *trans*-anethole (**4-5**, 0.220 mL, 1.48 mmol). The resulting mixture was heated to reflux. A solution of diazoester **4-6** (0.300 mL, 1.0 M solution in CH_2Cl_2, 0.300 mmol) in 3.0 mL CH_2Cl_2 was added to the mixture over 3 h via syringe pump. The mixture was refluxed after addition was complete, and after 1 h vinyldiazoacetate had been consumed. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, and the residue was purified by flash column chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to yield cyclopentene **4-15** (15.2 mg, 19% yield) as a colorless oil.

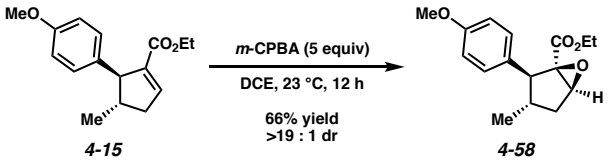


Cu-Catalyzed Experiment: A solution containing *trans*-anethole (**4-5**, 29.6 mg, 0.200 mmol), copper catalyst **Cu1**[28] (1.3 mg, 0.00300 mmol), and 1.0 mL DCE was prepared in a flame-dried

round bottom flask and heated to 84 ˚C. A solution of diazoester **4-6** (0.400 mL, 1.0 M solution in CH_2Cl_2, 0.400 mmol) in 0.5 mL DCE was added via syringe pump at a rate of 500 μL/h. After 4 h, the reaction mixture was cooled to room temperature, concentrated via rotary evaporation, and the crude reaction mixture was analyzed by ^{1}H NMR. Cyclopentene **4-15** was not observed.

4.9.6 Cycloaddition Product Diversifications

Epoxidation



Epoxide 4-58. Following the procedure described by Xiao, Guo and coworkers,[29] a mixture of cyclopentene **4-15** (108 mg, 0.416 mmol) and *m*-CPBA (512 mg, 70%, 2.08 mmol) in 5.50 mL of DCE at room temperature under argon was stirred for 12 h. The solution was then quenched with sat. aq. Na_2SO_3 (5 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 6 mL). The combined organic extracts were washed with saturated aqueous Na_2SO_4 (12 mL), saturated aqueous $NaHCO_3$ (12 mL), and brine (12 mL), dried over Na_2SO_4, filtered, and concentrated via rotary evaporation. The crude material was purified by flash chromatography (100% hexanes → 6:1 hexanes/EtOAc eluent) to afford epoxide **4-58** (75.7 mg, 66% yield, >19:1 dr) as a colorless oil.

TLC: R_f = 0.36 in 6:1 hexanes/EtOAc, visualized by UV, stained by Seebach's stain.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 4.19-4.03 (comp. m, 2H), 3.79 (s, 3H), 3.69 (app. s, 1H), 3.06 (d, J = 9.7 Hz, 1H), 2.38 (app. dd, J = 14.2, 7.1 Hz,

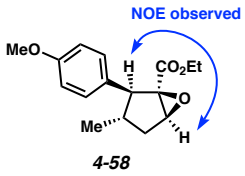
1H), 1.88 (app. tquintet, J = 9.8, 6.8 Hz, 1H), 1.53 (app. dd, J = 14.2, 10.2 Hz, 1H), 1.17 (t, J = 7.1 Hz, 3H), 0.95 (d, J = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 158.7, 131.5, 129.5, 113.9, 66.1, 61.6, 61.5, 55.3, 52.6, 36.8, 36.2, 17.2, 14.2.

IR (film): 2957, 2931, 2871, 1731, 1514, 1302, 1240, 1034, 826 cm^{-1}.

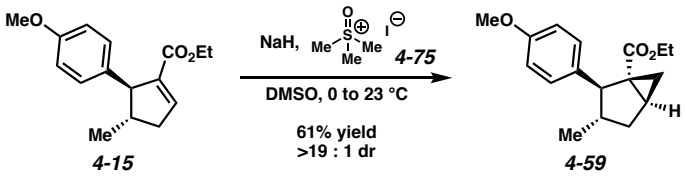
HRMS (ESI+) m/z calc'd for $(M + Na)^+$ $[C_{16}H_{20}O_4 + Na]^+$: 299.1254, found 299.1253.

The relative stereochemistry of epoxide **4-58** was confirmed through 1D NOESY NMR analysis.



4-58

Cyclopropanation



4-15 *4-59*

Cyclopropane 4-59. Following a procedure described by Tiefenbacher and coworkers,[30] to a flame-dried flask charged with NaH (14.5 mg, 60% dispersion in mineral oil, 0.361 mmol) and trimethylsulfoxonium iodide (**4-75**, 79.5 mg, 0.361 mmol) at 0 °C was added anhydrous DMSO (1.0 mL) dropwise over 5 min. After stirring for 10 min at 0 °C, cyclopentene **4-15** (78.4 mg, 0.301 mmol) in DMSO (1.0 mL) was added via syringe. The mixture was allowed to warm to room temperature and stirred for 40 min, at which point it was diluted with Et_2O (5.0 mL), followed by the addition of sat. aq. NH_4Cl (5 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic layers were washed sequentially with water (15 mL), then brine (15 mL), dried over $MgSO_4$, filtered, and concentrated via rotary

evaporation. The crude material was purified by flash chromatography (100% hexanes → 19:1 hexanes/EtOAc) to give cyclopropane **4-59** (50.2 mg, 61% yield, >19:1 dr) as a colorless oil.

TLC: R_f = 0.22 in 95:5 hexanes/EtOAc, stained blue with *p*-anisaldehyde stain.

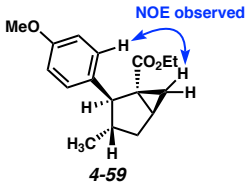
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 4.08-3.96 (comp. m, 2H), 3.79 (s, 3H), 3.17 (d, *J* = 10.2 Hz, 1H), 2.03 (app. dd, *J* = 12.1, 6.3 Hz, 1H), 1.80 (app. dt, *J* = 8.7, 4.5 Hz, 1H), 1.74-1.66 (m, 1H), 1.63 (app. td, *J* = 11.4, 4.5 Hz, 1H), 1.51 (dd, *J* = 8.4, 5.0 Hz, 1H), 1.38 (app. t, *J* = 5.0 Hz, 1H), 1.15 (t, *J* = 7.1 Hz, 3H), 0.92 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2, 158.2, 134.5, 129.0, 113.6, 60.3, 55.2, 52.0, 37.2, 36.1, 35.6, 27.8, 17.7, 15.1, 14.2.

IR (film): 2955, 2928, 2869, 1716, 1513, 1245, 1149, 1037 cm^{-1}.

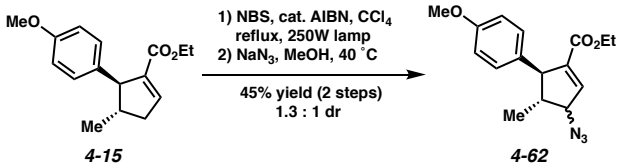
HRMS (ESI+) m/z calc'd for $(M + H)^+$ $[C_{17}H_{22}O_3 + H]^+$: 275.1642, found 275.1640.

The relative stereochemistry of cyclopropane **4-59** was confirmed through 2D NOESY NMR analysis.



4-59

Allylic Bromination/Azidation



4-15 *4-62*

Azide 4-62. A mixture containing cyclopentene **4-15** (64.3 mg, 0.247 mmol), *N*-bromosuccinimide (48.0 mg, 0.270 mmol), AIBN (3.0 mg, 0.0183 mmol) and carbon tetrachloride (3.00 mL) was heated to reflux and irradiated with a 250 W lamp for 0.5 h. The reaction mixture

was allowed to cool to room temperature and filtered through a short celite plug (carbon tetrachloride eluent). The solvent was removed via rotary evaporation, and the resulting residue was carried directly to the next transformation without further purification. The crude bromide was dissolved in methanol (2.50 mL) and treated with sodium azide (18.0 mg, 0.277 mmol). The mixture was heated at 40 °C for 24 h. The reaction mixture was allowed to cool to room temperature and partitioned between chloroform (5 mL) and water (7 mL). The aqueous layer was extracted with chloroform (3 x 5 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, and concentrated via rotary evaporation. The resulting residue was purified by flash chromatography (100% hexanes → 20:1 hexanes/EtOAc eluent) to afford azide **4-62** (33.5 mg, 45% yield over 2 steps, 1.3:1 inseparable mixture of diastereomers) as a colorless oil.

TLC: R_f = 0.25 in 9:1 hexanes/EtOAc, stained with Seebach's stain.

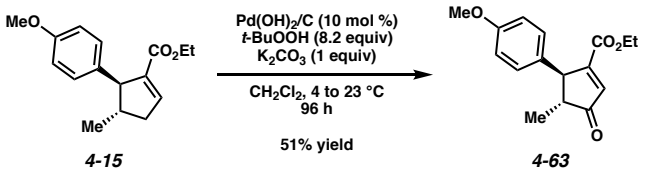
^{1}H NMR (400 MHz, $CDCl_3$): [Major diastereomer] δ 7.08 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.82 (app. t, *J* = 2.1 Hz, 1H), 4.14-3.95 (comp. m, 3H), 3.79 (s, 3H), 3.52 (app. dt, *J* = 7.0, 2.2 Hz, 1H), 2.13 (app. sextet, *J* = 6.9 Hz, 1H), 1.24 (d, *J* = 6.9 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H); [Minor diastereomer] δ 7.02 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.73 (app. t, *J* = 2.1 Hz, 1H), 4.49 (app. dt, *J* = 7.0 Hz, 1H), 4.14-3.95 (comp. m, 2H), 3.78 (s, 3H), 3.70 (app. dt, *J* = 7.2, 2.0 Hz, 1H), 2.38 (app. sextet, *J* = 7.1 Hz, 1H), 1.16 (d, *J* = 7.1 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, characterized as mixture of the major and minor diastereomers): δ 164.3, 164.2, 158.6, 158.5, 144.5, 141.8, 139.0, 138.3, 134.9, 134.2, 128.5, 128.2, 114.07, 114.05, 77.4, 71.9, 68.4, 60.72, 60.67, 56.73, 56.66, 55.4, 50.9, 17.5, 14.10, 14.09, 13.3.

IR (film): 2962, 2093, 1721, 1513, 1249 cm^{-1}.

HRMS (ESI+) m/z calc'd for $(M + H)^+$ $[C_{16}H_{19}N_3O_3 + H]^+$: 302.1502, found 302.1499.

Allylic Oxidation



Enone 4-63. Following the procedure described by Corey and Yu,[31] a 25 mL round-bottom flask equipped with a stirbar was charged with 20% $Pd(OH)_2/C$ (11.2 mg, 0.0160 mmol Pd), K_2CO_3 (11.1 mg, 0.0808 mmol), 1.50 mL of CH_2Cl_2, and cyclopentene **4-15** (84.0 mg, 0.323 mmol). The mixture was cooled to 4 °C, maintained in a water bath with ice cooling, and *t*-BuOOH (0.300 mL, ~5 M solution in CH_2Cl_2, 1.50 mmol) was added with vigorous stirring. The flask was sealed (without removal of air) with a rubber septum and allowed to warm to room temperature, and the contents were stirred for 24 h, at which time additional 20% $Pd(OH_2)/C$ (11.2 mg, 0.0160 mmol Pd), K_2CO_3 (11.1 mg, 0.0808 mmol), and *t*-BuOOH (0.300 mL, ~5 M solution in CH_2Cl_2, 1.50 mmol) were added. The reaction mixture was stirred at room temperature for another 24 h, at which point TLC analysis indicated that the reaction was complete. Filtration through a short plug of silica, removal of solvent via rotary evaporation, and flash chromatography (1:1 hexanes/Et_2O eluent) afforded enone **4-63** (44.9 mg, 51% yield) as a pale yellow oil.

TLC: R_f = 0.41 in 1:1 hexanes/Et_2O, visualized by UV, stained with Seebach's stain.

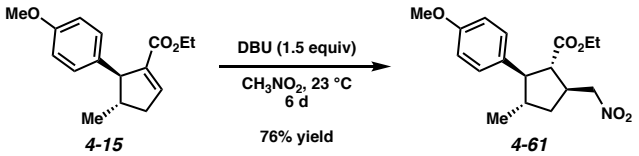
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.80 (d, *J* = 1.6 Hz, 1H), 4.22-4.07 (comp. m, 2H), 3.84 (m, 1H), 3.79 (s, 3H), 2.42 (qd, *J* = 7.4, 2.5 Hz, 1H), 1.28 (d, *J* = 7.4 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 211.1, 164.4, 164.0, 158.8, 136.4, 132.6, 128.2, 114.3, 61.6, 55.3, 54.0, 52.6, 15.1, 14.0.

IR (film): 2979, 2934, 1720, 1612, 1513, 1250, 1215, 1034 cm^{-1}.

HRMS (ESI+) m/z calc'd for $(M + H)^+$ $[C_{16}H_{18}O_4 + H]^+$: 275.1278, found 275.1282.

Michael Addition



Cyclopentane 4-61. To a solution of cyclopentene **4-15** (52.7 mg, 0.202 mmol) in CH_3NO_2 (0.70 mL) at room temperature was added DBU (15.1 μL, 0.101 mmol) dropwise. After 60 h, another portion of DBU (15.1 μL, 0.101 mmol) was added. After 24 h, a final charge of DBU (15.1 μL, 0.101 mmol) was added, and the mixture was allowed to stir for another 48 h (132 h total, ~5.5 days). The reaction mixture was then concentrated via rotary evaporation. Analysis of the crude ^{1}H NMR showed a diastereoselective ratio of ~80:20 (major diastereomer : two minor diastereomers). The residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/EtOAc eluent) to afford the major diastereomeric cyclopentane **4-61** (49.6 mg, 76% yield) as a colorless oil.

TLC: R_f = 0.25 in 9:1 hexanes/EtOAc, stained blue with *p*-anisaldehyde.

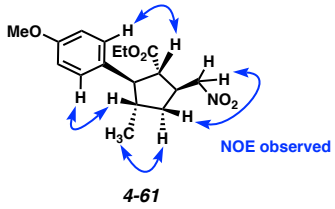
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 4.58 (dd, *J* = 12.9, 8.6 Hz, 1H), 4.48 (dd, *J* = 12.9, 6.9 Hz, 1H), 3.86 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.78 (s, 3H), 3.74 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.20 (app. t, *J* = 6.7 Hz, 1H), 3.15-3.02 (m, 1H), 2.98 (dd, *J* = 11.4, 6.8 Hz, 1H), 2.90-2.77 (m, 1H), 2.14 (ddd, *J* = 13.2, 10.1, 8.8 Hz, 1H), 1.71 (ddd, *J* = 13.2, 10.2, 6.7 Hz, 1H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 158.7, 130.4, 129.1, 113.8, 76.9, 60.2, 56.8, 55.4, 54.3, 39.2, 36.0, 34.9, 19.6, 13.9.

IR (film): 2957, 1720, 1552, 1514, 1381, 1248, 1184, 1033 cm^{-1}.

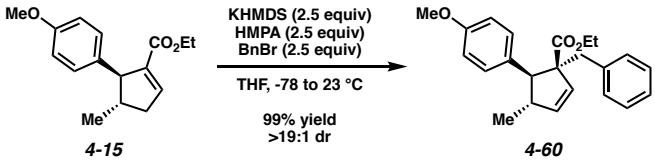
HRMS (ESI+) m/z calc'd for $(M + H)^+$ $[C_{17}H_{23}NO_5 + H]^+$: 322.1649, found 322.1649.

The relative stereochemistry of cyclopentane **4-61** was confirmed through 2D NOESY NMR analysis.



4-61

Deconjugative Alkylation



4-15 *4-60*

Cyclopentene 4-60. To a solution of cyclopentene **4-15** (26.0 mg, 0.0999 mmol) in dry THF (1.0 mL) at -78 °C was added a mixture of KHMDS (36.0 μL, 0.7 M solution in toluene, 0.250 mmol) and HMPA (43.0 μL, 0.250 mmol) dropwise. The reaction mixture was stirred for 1 h at -78 °C, and a solution of benzyl bromide (30.0 μL, 0.250 mmol) in THF (0.25 mL) was then added dropwise. The mixture was stirred at -78 °C for 1 h. The cooling bath was then removed, and the reaction mixture allowed to warm to room temperature over another hour. Brine (2 mL) was added to the mixture, and the mixture was partitioned between water (5 mL) and Et_2O (5 mL). The aqueous mixture was extracted with Et_2O (3 x 5 mL). The combined organic layers were washed sequentially with water (10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated via rotary evaporation. The crude residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford cyclopentene **4-60** (35.0 mg, 99% yield, >19:1 dr) as a colorless oil.

TLC: R_f= 0.31 in 9:1 hexanes/EtOAc, stained blue with *p*-anisaldehyde.

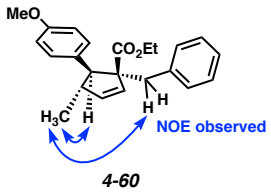
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.17 (comp. m, 5H), 7.15 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 5.92 (dd, J = 5.9, 2.0 Hz, 1H), 5.64 (dd, J = 5.9, 2.2 Hz), 3.80 (s, 3H), 3.74 (dq, J = 10.8, 7.2 Hz, 1H), 3.61 (dq, J = 10.8, 7.2 Hz, 1H), 3.53 (d, J = 13.3 Hz, 1H), 3.16-3.07 (m, 1H), 2.86 (d, J = 7.1 Hz, 1H), 2.82 (d, J = 13.3 Hz, 1H), 1.03 (d, J = 7.0 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 158.6, 138.6, 138.2, 133.1, 131.3, 130.6, 129.6, 128.1, 126.5, 113.6, 67.0, 62.5, 60.5, 55.4, 47.0, 45.2, 20.0, 13.9.

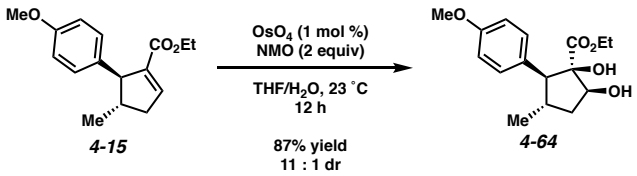
IR (film): 3030, 2955, 2927, 1723, 1513, 1249, 1181, 1037 cm^{-1}.

HRMS (ESI+) m/z calc'd for $(M + H)^+$ $[C_{23}H_{26}O_3 + H]^+$: 351.1956, found 351.1955.

The relative stereochemistry of cyclopentene **4-60** was confirmed through 2D NOESY NMR analysis.



Dihydroxylation/Oxidative Cleavage/Reductive Amination



Diol 4-64. Following a modification of a procedure described by Kumar and Waldmann,[32] to a solution of cyclopentene **4-15** (79.3 mg, 0.305 mmol) in THF (3.0 mL) at room temperature was added sequentially a solution of NMO (71.3 mg, 0.609 mmol) in H_2O (3.0 mL), followed by a solution of OsO_4 (38.0 μL, 2.5% w/w in *t*-BuOH, 0.00305 mmol). After 12 h, the reaction mixture was quenched with sat. aq. $NaHSO_3$ (6.0 mL), and the mixture was stirred for an additional hour at ambient temperature. The organic layer was separated, and the aqueous layer was extracted

with EtOAc (3 x 6 mL). The combined organic layers were washed sequentially with water (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated via rotary evaporation. The crude material was purified by flash chromatography (5:2 hexanes/EtOAc eluent) to give diol **4-64** (77.9 mg, 87% yield, 11:1 dr) as a colorless oil.

TLC: R_f = 0.33 in 5:2 hexanes/EtOAc, stained by Seebach's stain.

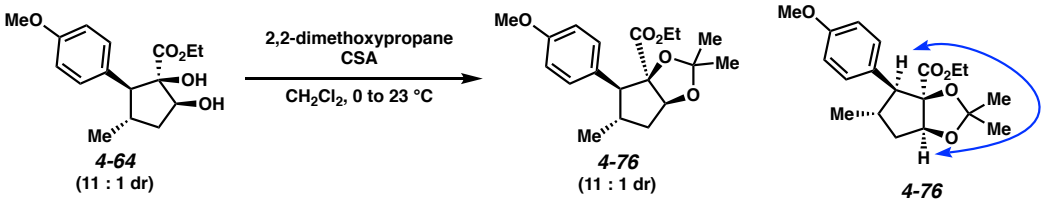
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 4.56 (app. td, J = 9.2, 6.7 Hz, 1H), 4.30-4.13 (comp. m, 2H), 3.78 (s, 3H), 3.32 (s, 1H), 2.92 (d, J = 11.5 Hz, 1H), 2.68 (d, J = 10.2 Hz, 1H), 2.67-2.57 (m, 1H), 2.01-1.87 (comp. m, 2H), 1.29 (t, J = 7.1 Hz, 3H), 0.94 (d, J = 6.7 Hz, 3H).

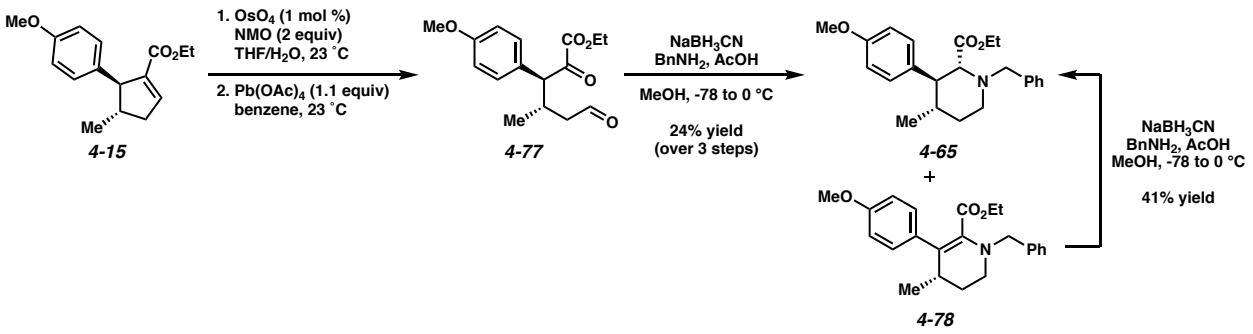
^{13}C NMR (100 MHz, $CDCl_3$): δ 174.5, 158.9, 130.2, 128.6, 113.7, 84.0, 76.3, 62.3, 59.3, 55.3, 40.9, 35.9, 19.2, 14.4.

IR (film): 3479, 2957, 1727, 1514, 1248, 1147, 1038 cm-1.

HRMS (ESI+) m/z calc'd for $(M + H)^+$ $[C_{16}H_{22}O_5 + H]^+$: 295.1540, found 295.1541.

The relative stereochemistry of the major diastereomeric product was determined by 1D NOESY of the related acetal (**4-76**).





Piperidine 4-65. To a solution of cyclopentene **4-15** (131 mg, 0.503 mmol) in THF (5.0 mL) at 23 °C was added sequentially a solution of NMO (118 mg, 1.01 mmol) in H_2O (5.0 mL) and OsO_4 (63.0 μL, 2.5% w/w in *t*-BuOH, 5.03 μmol). After 12 h, the reaction mixture was quenched with sat. aq. $NaHSO_3$ (10.0 mL), and the mixture was stirred for an additional hour at ambient temperature. The mixture was diluted with EtOAc (12 mL), the organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 12 mL). The combined organic layers were washed sequentially with water (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated via rotary evaporation. The resulting residue was carried directly to the next transformation without further purification. The crude diol was dissolved in benzene (5.00 mL) at 23 °C, and it was treated with $Pb(OAc)_4$ (256 mg, 96% (dry wt.), stab. with 5-10% glacial acetic acid, 0.553 mmol). The reaction mixture was allowed to stir for 1 h at room temperature, and then it was filtered through a short plug of celite (benzene eluent). The solvent was removed via rotary evaporation, and the resulting residue was carried directly to the next transformation without further purification. Aldehyde **4-77** was dissolved in methanol (1.00 mL), and the solution was cooled to -78 °C. A solution of benzylamine (60.0 μL, 0.553 mmol) and glacial acetic acid (29.0 μL, 0.503 mmol) in MeOH (0.70 mL), and a separate solution of $NaBH_3CN$ (35.0 mg, 0.557 mmol) in MeOH (0.70 mL) were added simultaneously dropwise via syringe. The reaction mixture was stirred for 0.5 h at -78 °C, then warmed to 0 °C. The mixture was stirred for 24 h at 0 °C. The

solvent was removed via rotary evaporation, and the crude residue was partitioned between sat. aq. $NaHCO_3$ (5 mL) and CH_2Cl_2 (5 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated via rotary evaporation. ^{1}H NMR analysis of the crude mixture suggested a highly diastereoselective reaction, but exact dr could not be obtained. The crude material was purified by flash chromatography (100% hexanes → 9:1 hexanes/EtOAc eluent) to afford the major diastereomeric piperidine (**4-65**, 44.3 mg, 24% yield over 3 steps, >19:1 dr) as a light yellow oil that solidified upon standing. In addition to piperidine **4-65**, tetrahydropyridine **4-78** (56.1 mg, 30% yield) was isolated as a light yellow oil. Subjecting this tetrahydropyridine to the reductive amination conditions afforded additional piperidine **4-65** (23.1 mg, 41% yield). Collectively, piperidine **4-65** could be obtained in 36% yield overall (24% + 12%).

TLC: R_f = 0.16 in 9:1 hexanes/EtOAc, stained with Seebach's stain.

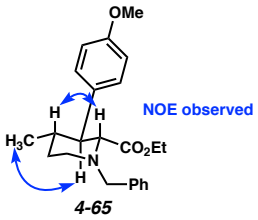
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.24 (comp. m, 5H), 7.07 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 3.93-3.83 (comp. m, 2H), 3.78 (s, 3H), 3.76 (d, *J* = 13.1 Hz, 1H), 3.19 (d, *J* = 13.1 Hz, 1H), 3.03 (d, *J* = 10.4 Hz, 1H), 2.96-2.89 (m, 1H), 2.58 (app. t, *J* = 10.7 Hz, 1H), 2.05 (app. td, *J* = 12.0, 2.4 Hz, 1H), 1.72-1.58 (comp. m, 2H), 1.44 (app. qd, *J* = 12.0, 3.9 Hz, 1H), 0.93 (t, *J* = 7.1 Hz, 3H), 0.67 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 158.6, 137.6, 132.7, 129.7, 128.3, 127.3, 113.8, 77.4, 74.1, 61.0, 60.5, 55.4, 53.4, 51.9, 35.8, 33.7, 19.8, 14.1.

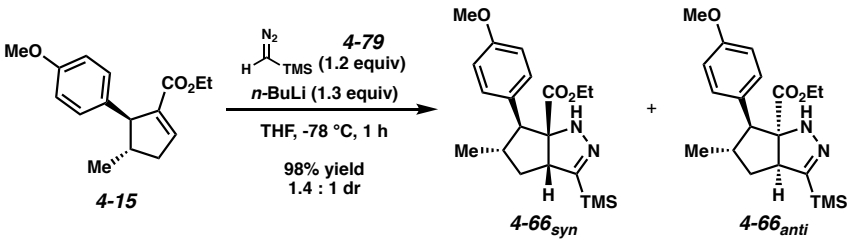
IR (film): 2925, 2834, 1737, 1513, 1249, 1177, 1033 cm^{-1}.

HRMS (ESI+) m/z calc'd for $(M + H)^+$ $[C_{23}H_{29}NO_3 + H]^+$: 368.2223, found 368.2220.

The relative stereochemistry of piperidine **4-65** was confirmed through 2D NOESY ^{1}H NMR analysis.



TMS-Diazomethane Cycloaddition/Elimination



Pyrazoline 4-66. Following the procedure described by Lee and coworkers,[33] to a stirred solution of trimethylsilyldiazomethane[1] (**4-79**, 0.100 mL, 2.0 M solution in Et_2O, 0.400 mmol) in anhydrous THF (1.3 mL) under argon at -78 °C was added *n*-BuLi (0.180 mL, 2.5 M solution in hexanes, 0.650 mmol, 1.3 equiv) dropwise over 1 min. The solution went pale yellow, and it was allowed to stir for an additional 30 min at -78 °C. A solution of enoate **4-15** (86.8 mg, 0.333 mmol) in THF (1.3 mL) was then added dropwise over 30 s, and the reaction was allowed to stir for a further 30 min, when TLC showed the full consumption of the starting material. The reaction mixture was quenched with sat. aq. NH_4Cl (5 mL) and allowed to warm to ambient temperature. The phases were separated, and the aqueous layer was further extracted with Et_2O (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated via rotary evaporation.

[1] Caution! Trimethylsilyldiazomethane should be regarded extremely toxic and all operations must on carried out only in a well-ventilated fume hood and all skin contact should be avoided, see: (a) Shioiri, T.; Aoyama, T.; Mori, S. *Org. Synth. Coll.* Vol. 8, 1993, 612. (b) Barnhart, R.; Dale, D. J.; Ironside, M. D.; Vogt, P. F. *Org. Process Res. Dev.* **2009**, *13*, 1388. (c) Kemsley, J. *Chem. Eng. News* **2011**, *89*(*19*), 15.

The crude material was purified by flash chromatography (20:1 hexanes/EtOAc → 6:1 hexanes/EtOAc eluent) to give a mixture of pyrazoline diastereomers **4-66$_{syn}$** and **4-66$_{anti}$** (121 mg, 98% yield). Diastereomeric ratio (1.4:1) was determined by ^{1}H NMR analysis of the crude mixture. The diastereomers could be separated by column chromatography for isomeric purity and further transformations.

Major diastereomer 4-66$_{syn}$: off white powder.

TLC: R_f = 0.49 in 4:1 hexanes/EtOAc, visualized with $KMnO_4$ stain.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.11 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 3.86 (dd, *J* = 10.2, 8.5 Hz, 1H), 3.78 (s, 3H), 3.76-3.65 (comp. m, 2H), 2.86 (d, *J* = 12.2 Hz, 1H), 2.57 (app. septet, *J* = 6.0 Hz, 1H), 2.41 (ddd, *J* = 12.0, 8.5, 5.9 Hz, 1H), 1.29 (app. q, *J* = 11.1 Hz, 1H), 0.934 (t, *J* = 7.1 Hz, 3H), 0.931 (d, *J* = 6.3 Hz, 3H), 0.22 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 173.4, 161.6, 158.8, 129.9, 129.5, 113.7, 81.9, 66.3, 61.32, 61.30, 55.4, 39.8, 38.5, 17.2, 13.9, -1.5.

IR (film): 3344, 2956, 1727, 1514, 1248, 841 cm^{-1}.

HRMS (ESI+) m/z calc'd for $(M + H)^+$ $[C_{20}H_{30}N_2O_3Si + H]^+$: 375.2098, found 375.2100.

Minor diastereomer 4-66$_{anti}$: pale yellow oil.

TLC: R_f = 0.54 in 4:1 hexanes/EtOAc, visualized with $KMnO_4$ stain.

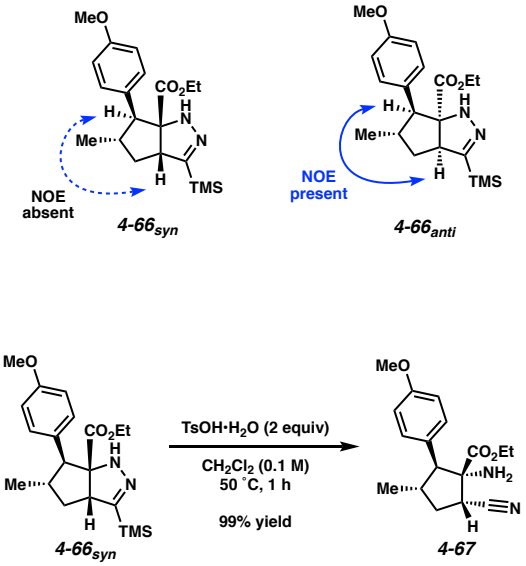
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 6.00 (br. s, 1H), 4.16 (dq, *J* = 7.1, 1.1 Hz, 2H), 3.79 (s, 3H), 3.72 (dd, *J* = 10.0, 1.3 Hz, 1H), 3.05 (d, *J* = 11.9 Hz, 1H), 2.21 (app. tquintet, *J* = 12.2, 6.1 Hz, 1H), 1.94 (ddd, *J* = 12.8, 6.5, 1.3 Hz, 1H), 1.78 (app. td, *J* = 12.3, 10.2 Hz, 1H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.87 (d, *J* = 6.5 Hz, 3H), 0.22 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 174.9, 160.7, 158.9, 130.2, 129.6, 113.7, 79.6, 61.6, 61.3, 60.1, 55.3, 39.2, 38.0, 16.9, 14.4, -1.3

IR (film): 3355, 2955, 1728, 1513, 1248, 1228, 841 cm^{-1}.

HRMS (ESI+) m/z calc'd for $(M + H)^+$ $[C_{20}H_{30}N_2O_3Si + H]^+$: 375.2098, found 375.2107.

The relative stereochemistry of pyrazoles **4-66$_{syn}$** and **4-66$_{anti}$** was confirmed through 1D NOESY NMR analysis.



Aminonitrile 4-67. Following the procedure described by Lee and coworkers,[33] a solution of pyrazoline **4-66$_{syn}$** (37.5 mg, 0.100 mmol) in 1.0 mL CH_2Cl_2 at room temperature was treated with TsOH•H_2O (38.0 mg, 0.200 mmol), and the reaction mixture was heated to reflux (50 °C) and stirred until the TLC indicated the full consumption of the starting material (1 h). The mixture was cooled to room temperature, and sat. aq. $NaHCO_3$ solution (2 mL) was carefully added to neutralize the reaction. The organic layer was separated, and the aqueous later was extracted with CH_2Cl_2 (3 x 2 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated via rotary evaporation to afford analytically pure aminonitrile **4-67** (30.1 mg, 99% yield).

TLC: R_f = 0.14 in 4:1 hexanes/EtOAc, visualized by UV, stained by $KMnO_4$ or Seebach's stain.

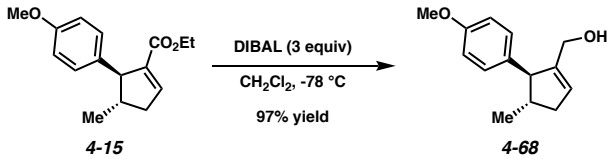
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 3.83-3.67 (comp. m, 3H), 3.78 (s, 3H), 2.62 (d, *J* = 11.1 Hz, 1H), 2.54-2.40 (comp. m, 2H), 1.91 (app. q, *J* = 10.9 Hz, 1H), 0.98 (d, *J* = 6.2 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 173.3, 159.3, 129.6, 129.0, 119.8, 114.0, 70.4, 66.2, 61.9, 55.4, 38.0, 37.9, 37.6, 17.9, 13.8.

IR (film): 2959, 1725, 1514, 1249, 1181, 1035, 845 cm^{-1}.

HRMS (ESI+) m/z calc'd for $(M + H)^+$ $[C_{17}H_{22}N_2O_3 + H]^+$: 303.1703, found 303.1705.

Reduction/Johnson Orthoester Claisen Rearrangement



4-15 *4-68*

Alcohol 4-68. To a solution of cyclopentene **4-15** (155 mg, 0.595 mmol) in CH_2Cl_2 (6.30 mL) at -78 °C was added DIBAL (1.80 mL, 1.0 M in toluene, 1.80 mmol) dropwise. The reaction mixture was stirred for 1 h and then quenched with sat. aq. sodium potassium tartrate (10 mL). The resulting mixture was warmed to room temperature and stirred for 30 min. The layers were then separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash chromatography (100% hexanes → 6:1 hexanes/EtOAc eluent) to give allylic alcohol **4-68** (126 mg, 97% yield) as a colorless oil.

TLC: R_f = 0.37 in 4:1 hexanes/EtOAc, stained by $KMnO_4$, stained blue with *p*-anisaldehyde.

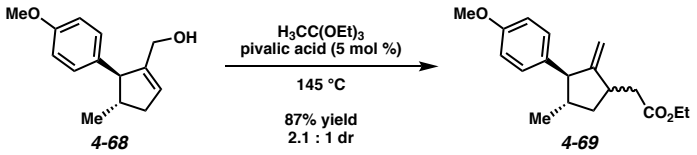
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 5.80-5.75 (m, 1H), 4.01 (br. d, *J* = 14.0 Hz, 1H), 3.92 (br. d, *J* = 14.0 Hz, 1H), 3.79 (s, 3H), 3.29 (app. dt, *J* =

6.4, 1.0 Hz, 1H), 2.66 (app. ddquintet, J = 16.3, 8.1, 2.1 Hz, 1H), 2.23 (app. septet, 6.7 Hz, 1H), 2.02 (app. dddt, J = 16.3, 6.6, 4.4, 2.2 Hz, 1H), 1.29-1.19 (br. s, 1H), 1.10 (d, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3, 146.0, 136.2, 128.8, 126.2, 114.1, 61.3, 59.3, 55.4, 44.3, 39.7, 20.4.

IR (film): 3349, 2951, 2835, 1611, 1511, 1245, 1037, 821 cm^{-1}.

HRMS (ESI+) m/z calc'd for $(M + Na)^+$ $[C_{14}H_{18}O_2 + Na]^+$: 241.1199, found 241.1191.



Ester 4-69. To a solution of alcohol **4-68** (22.0 mg, 0.101 mmol) in triethyl orthoacetate (0.50 mL) at room temperature was added pivalic acid (0.5 mg, 0.00505 mmol). The resulting mixture was heated to 145 °C and stirred for 3 h. It was then cooled to room temperature, sat. aq. NH_4Cl was added (3 mL), and the mixture was extracted with Et_2O (3 x 3 mL). The combined organic layers were washed with brine (6 mL) and dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford ester **4-69** (25.2 mg, 87% yield, 2.1:1 inseparable mixture of diastereomers) as a colorless oil.

TLC: R_f = 0.50 in 9:1 hexanes/EtOAc, stained blue with *p*-anisaldehyde.

^{1}H NMR (400 MHz, $CDCl_3$): [Major diastereomer] δ 7.10 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 4.89 (app. t, J = 2.6 Hz, 1H), 4.56 (app. t, J = 2.6 Hz, 1H), 4.19 (app. q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 3.13-3.03 (m, 1H), 3.04-2.96 (m, 1H), 2.72 (dd, J = 15.3, 5.2 Hz, 1H), 2.37 (dd, J = 15.3, 9.1 Hz, 1H), 2.24 (app. quint, J = 6.3 Hz, 1H), 2.03-1.88 (m, 1H), 1.31 (t, J = 7.1 Hz, 3H), 1.13 (app. q, J = 11.6 Hz, 1H), 0.95 (d, J = 6.4 Hz, 3H); [Minor diastereomer] δ 7.08 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 4.94 (app. t, J = 2.1 Hz, 1H), 4.53 (app. t, J = 2.1 Hz, 1H), 4.19 (app.

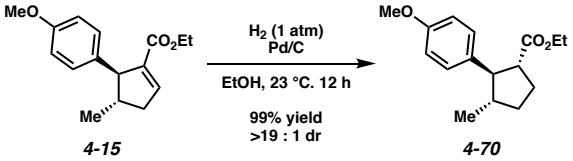
q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 3.21-3.12 (m, 1H), 3.04-2.96 (m, 1H), 2.58 (dd, J = 15.3, 5.5 Hz, 1H), 2.46 (dd, J = 15.3, 9.9 Hz, 1H), 2.10-1.97 (m, 1H), 1.84-1.76 (m, 1H), 1.69-1.59 (m, 1H), 1.31 (t, J = 7.1 Hz, 3H), 0.95 (d, J = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, characterized as mixture of the major and minor diastereomers): δ 173.1, 173.0, 160.0, 159.8, 158.17, 158.15, 135.6, 135.0, 129.9, 129.8, 113.8, 108.1, 107.4, 60.48, 60.45, 59.6, 59.1, 55.3, 42.4, 41.1, 40.74, 40.73, 40.6, 40.1, 39.1, 39.0, 18.4, 18.0, 14.4.

IR (film): 2953, 1734, 1512, 1247, 1175, 1036, 825 cm^{-1}.

HRMS (ESI+) m/z calc'd for $(M + H)^+$ $[C_{18}H_{24}O_3 + H]^+$: 289.1793, found 289.1798.

Hydrogenation/Arene Oxidation



Cyclopentane 4-70. H_2 gas was bubbled through a mixture of cyclopentene **4-15** (131 mg, 0.503 mmol) and Pd/C (53.6 mg, 10% w/w) in EtOH (5.60 mL) at 23 °C for 30 s using a balloon of H_2 and a needle outlet. The needle outlet was removed, and the reaction mixture was left under positive pressure of H_2 and stirred for 12 h. The reaction mixture was then passed through a short plug of celite to afford cyclopentane **4-70** (131 mg, 99% yield, >19:1 dr) as a pale yellow oil.

TLC: R_f = 0.41 in 9:1 hexanes/EtOAc, visualized by UV. Stained pink with *p*-anisaldehyde.

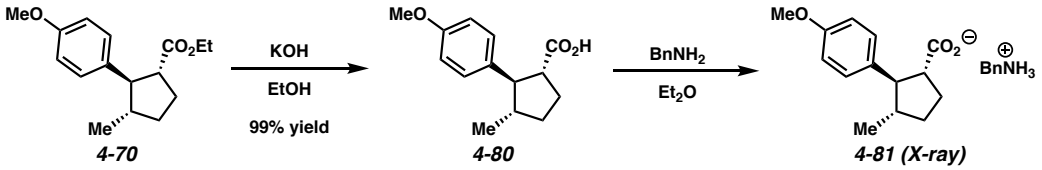
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 4.03 (app. q, J = 7.1 Hz, 2H), 3.79 (s, 3H), 2.84 (app. dt, J = 9.9, 7.2 Hz, 1H), 2.69 (app. t, J = 10.2 Hz, 1H), 2.15-1.89 (comp. m, 4H), 1.53-1.39 (m, 1H), 1.12 (t, J = 7.1 Hz, 3H), 0.91 (d, J = 6.1 Hz, 3H).

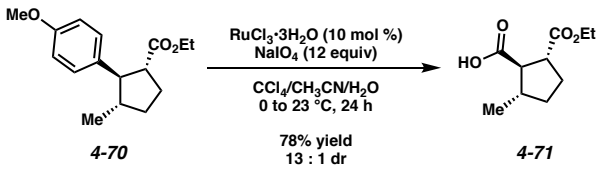
^{13}C NMR (125 MHz, $CDCl_3$): δ 176.1, 158.3, 134.6, 128.7, 113.9, 60.3, 57.4, 55.3, 52.7, 43.0, 33.6, 28.6, 18.2, 14.3.

IR (film): 2954, 1730, 1514, 1246, 1177, 1037 cm^{-1}.

HRMS (ESI+) m/z calc'd for $(M + Na)^+$ $[C_{16}H_{22}O_3 + Na]^+$: 285.1461, found 285.1465.

The relative stereochemistry of ester **4-70** was determined via X-ray of the benzylamine salt **4-81**. The salt was recrystallized from deionized water by slow evaporation. The observed diastereoselectivity is consistent with a similar reductive process described by Scheidt and coworkers,[34] and can be readily explained by torsional steering effects.[35]





Carboxylic acid 4-71. To a solution of cyclopentane **4-70** (69.5 mg, 0.265 mmol) in CCl_4 (1.6 mL), acetonitrile (1.6 mL), and H_2O (2.4 mL) at 0 °C was sequentially added $NaIO_4$ (680 mg, 3.18 mmol, 12 equiv) and $RuCl_3•3H_2O$ (5.5 mg, 0.0270 mmol, 10 mol %). After 0.5 h, the ice-water bath was removed, and the reaction mixture was stirred vigorously. The reaction mixture turned from orange to yellow to dark brown over 10 h. Reaction progress was monitored by TLC. After 24 h, the reaction mixture was diluted with H_2O (7 mL) and CH_2Cl_2 (7 mL), and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed sequentially with 10% aq. $Na_2S_2O_3$ (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated via rotary evaporation. The crude product was passed through a short plug of silica (EtOAc eluent) to afford carboxylic acid **4-71** (41.2 mg, 78% yield, 13:1 dr) as a pale yellow oil. The NMR spectroscopic data of the major diastereomer is reported.

(It is unclear which stereocenter may be epimerizing to lead to modest erosion of the diastereoenrichment.)

TLC: R_f = 0.39 in 4:1 hexanes/EtOAc, visualized as a light pink stain with *p*-anisaldehyde.

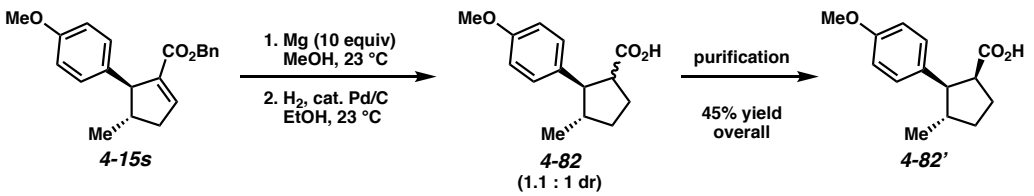
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.16 (app. dq, *J* = 7.1, 1.2 Hz, 2H), 3.17 (app. dt, *J* = 9.4, 7.0 Hz, 1H), 2.66 (app. t, *J* = 9.4 Hz, 1H), 2.27-2.17 (m, 1H), 2.10-1.87 (comp. m, 3H), 1.44-1.32 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.15 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 180.7, 175.0, 61.0, 54.8, 47.7, 40.0, 34.1, 28.6, 19.3, 14.3.

IR (film): 2960, 1706, 1185, 911, 734 cm^{-1}.

HRMS (ESI+) m/z calc'd for $(M - H)^-$ $[C_{10}H_{16}O_4 - H]^-$: 199.0976, found 199.0978.

Alternative reduction method - accessing opposite diastereomer



Carboxylic Acid S11'. To a solution of cyclopentene **4-15s** (50.0 mg, 0.155 mmol) in MeOH (1.30 mL) at room temperature was added magnesium turnings (38.0 mg, 1.56 mmol). The suspension was stirred at room temperature for 4 h. 3.0 N aq. HCl (~2.0 mL) was carefully added until excess Mg was dissolved. The mixture was extracted with Et_2O (3 x 5 mL). The combined organic layers were washed sequentially with water (10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated via rotary evaporation. The crude cyclopentane (R_f = 0.42, 9:1 hexanes/EtOAc, stained blue with *p*-anisaldehyde) was carried directly to the next transformation without further purification. To a solution of cyclopentane in ethanol (2 mL) was added Pd/C (3.5 mg, 7% w/w). H_2 gas was bubbled through the mixture at 23 °C for 30 s using a balloon of H_2 and a needle outlet.

The needle outlet was removed, and the reaction mixture was left under positive pressure of H_2 and stirred for 6 days. The reaction mixture was then passed through a short plug of celite (ethyl acetate eluent). The solvent was removed via rotary evaporation, and the crude material (1.1:1 dr) was purified by flash chromatography (100% hexanes → 2:1 hexanes/MTBE eluent) twice sequentially to obtain a single diastereomer of the carboxylic acid (**4-82'**, 16.3 mg, 45% yield over 2 steps) as a colorless oil that solidified upon standing.

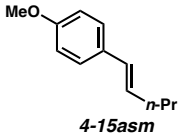
TLC: R_f = 0.34 in 1:1 hexanes/Et_2O, stained with Seebach's stain.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 3.78 (s, 3H), 3.12 (app. q, *J* = 7.2 Hz, 1H), 2.82 (app. t, *J* = 10.1 Hz, 1H), 2.41 (app. tquintet, *J* = 10.3, 6.6 Hz, 1H), 2.17-1.89 (comp. m, 3H), 1.38-1.26 (m, 1H), 0.93 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3, 132.0, 129.5, 113.7, 56.4, 55.3, 38.7, 34.0, 28.7, 27.8, 18.6.

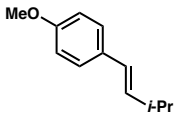
4.9.7 Substrate Synthesis

Alkene Syntheses



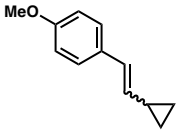
4-15asm

Alkene 4-15asm. Prepared according to our previously reported procedure.[36] The compound was isomerized to the pure *E* isomer according to the previously reported procedures (PhSH, AIBN, PhH, reflux).[37]



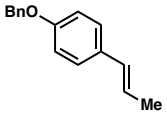
4-15bsm

Alkene 4-14bsm. Prepared according to the procedure reported by Yoon and coworkers.[37b] The compound was isomerized to the pure *E* isomer according to the previously reported procedures (PhSH, AIBN, PhH, reflux).[37]



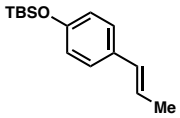
4-15csm
(1.5:1 *E/Z*)

Alkene 4-15csm. Prepared according to the procedure reported by Tantillo and coworkers.[38]



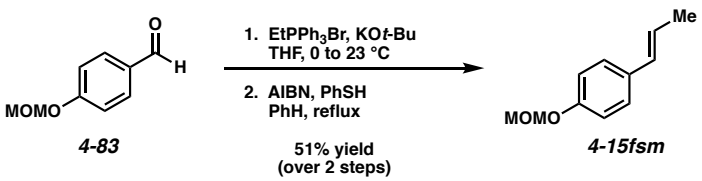
4-15esm

Alkene 4-15esm. Prepared according to the procedure reported by Nicewicz and coworkers.[39] The compound was isomerized to the pure *E* isomer according to the previously reported procedures (PhSH, AIBN, PhH, reflux).[37]



4-15gsm

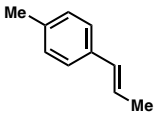
Alkene 4-15gsm. Prepared according to the procedure reported by Yoon and coworkers.[40]



4-83 *4-15fsm*

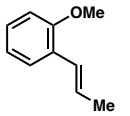
Alkene 4-15fsm. Ethyltriphenylphosphonium iodide (1.76 g, 4.20 mmol) and potassium *tert*-butoxide (438 mg, 3.90 mmol) were added to a flame-dried round bottom flask equipped with a magnetic stirbar. The flask was cooled to 0 °C, and THF (7.5 mL) was added slowly. The suspension was stirred at 0 °C for 0.5 h, after which aldehyde **4-83**[41] (499 mg, 3.00 mmol) was added dropwise to the mixture. The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature and stirred overnight. The next day, the reaction mixture was quenched with sat. aq. NH_4Cl (5 mL), diluted with Et_2O (8 mL) and H_2O (8 mL), and the phases were separated. The aqueous layer was extracted with Et_2O (2 x 15 mL), and the organic layers were then combined, washed with brine (40 mL), dried over $MgSO_4$, and concentrated via rotary evaporation. The residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford alkene **4-15fsm** (372 mg, 70%) as a colorless oil. To improve the isomeric ratio, alkene **4-15fsm** (370 mg, 2.08 mmol) was dissolved in benzene (8.35 mL), AIBN (34.0 mg, 0.208 mmol, 0.1 equiv) and PhSH (0.020 mL, 0.209 mmol, 0.1 equiv) were added, and the reaction was heated at reflux and stirred overnight. The mixture was cooled to room temperature, diluted with Et_2O (10 mL), and washed sequentially with sat. aq. $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$ and concentrated via rotary evaporation. The residue was purified by flash column chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford alkene **4-15fsm** (270 mg, 73% yield, R_f = 0.60 in 9:1 hexanes/Et_2O) as a single *E* isomer.

All spectroscopic data were in accordance with the published values.[42]



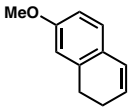
4-15hsm

Alkene 4-15hsm. Prepared according to the procedure reported by Nicewicz and coworkers.[43]



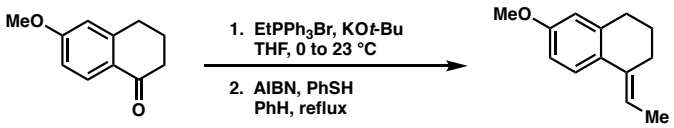
4-15dsm

Alkene 4-15dsm. Prepared according to our previously reported procedure.[36] The compound was isomerized to the pure *E* isomer according to the previously reported procedures (PhSH, AIBN, PhH, reflux).[37]



4-15osm

Alkene 4-15osm. Prepared according to the procedure reported by Gaunt and coworkers.[44]



4-84 *4-15psm*

Alkene 4-15psm. Ethyltriphenylphosphonium bromide (1.34 g, 3.60 mmol) and potassium *tert*-butoxide (404 mg, 3.60 mmol) were added to a flame-dried round bottom flask equipped with a magnetic stirbar. The flask was cooled to 0 °C, and THF (5.0 mL) was added slowly. The suspension was stirred at 0 °C for 0.5 h, after which 6-methoxy tetralone (**4-84**, 529 mg, 3.00 mmol) dissolved in THF (2.1 mL) was added dropwise to the mixture. The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature and stirred overnight. The next day, the reaction mixture was quenched with sat. aq. NH_4Cl (5.0 mL), diluted with Et_2O (8 mL) and H_2O (8 mL), and the phases were separated. The aqueous layer was extracted with

Et_2O (2 x 15 mL), and the organic layers were then combined, washed with brine (40 mL), dried over $MgSO_4$, and concentrated via rotary evaporation. The residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford alkene **4-15psm** (480 mg, 85%) as a colorless oil. To improve the isomeric ratio, alkene **4-15psm** (460 mg, 2.44 mmol) was dissolved in benzene (9.8 mL), AIBN (40.0 mg, 0.244 mmol, 0.1 equiv) and PhSH (0.0250 mL, 0.244 mmol, 0.1 equiv) were added, and the reaction mixture was heated at reflux and stirred overnight. The mixture was cooled to room temperature, diluted with Et_2O (10 mL), and washed sequentially with sat. aq. $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$ and concentrated via rotary evaporation. The residue was purified by flash column chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford alkene **4-15psm** (333 mg, 72% yield) as a single *E* isomer.

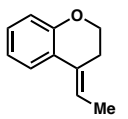
TLC: R_f = 0.86 in 9:1 hexanes/EtOAc, visualized by UV. Stained yellow with $KMnO_4$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J* = 8.6 Hz, 1H), 6.72 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.61 (d, *J* = 2.6 Hz, 1H), 5.97 (q, *J* = 7.2 Hz, 1H), 3.79 (s, 3H), 2.73 (t, *J* = 6.4 Hz, 2H), 2.47 (t, *J* = 6.4 Hz, 2H), 1.81 (app. quintet, 6.4 Hz, 2H), 1.76 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 158.2, 138.6, 134.5, 129.4, 124.8, 116.4, 113.2, 112.5, 55.3, 31.1, 26.4, 23.2, 13.7.

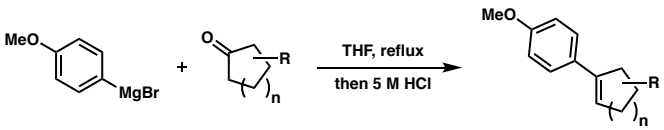
IR (ATR, neat): 2924, 1605, 1496, 1231, 1041, 805 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{13}H_{14}O + H]^+$: 189.1274, found 189.1274.

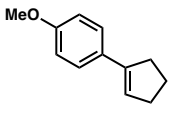


4-15qsm

Alkene 4-15qsm. Prepared according to the procedure reported by Maddaluno and coworkers.[45]

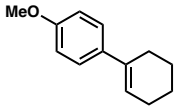


General Procedure for Cyclic Alkene Synthesis: In a flame-dried round bottom flask equipped with a stirbar, a 4.4 M suspension of Mg turnings (1.10 equiv) in THF was prepared. To the Mg turnings suspension was added a 3.7 M solution of 4-bromoanisole (1.05 equiv) in dry THF dropwise at room temperature. After the addition was complete, the flask was fitted with a reflux condenser, and the reaction mixture was heated to reflux and stirred for 1 h. The reaction mixture was removed from the oil bath and allowed to cool to room temperature. The fresh Grignard reagent was further cooled to 0 °C in an ice-water bath, and a 1.3 M solution of cyclic ketone (1.00 equiv) in dry THF was then added dropwise. After the addition was complete, the reaction mixture was heated to reflux and stirred for 1 h. The reaction mixture was removed from the oil bath and allowed to cool to room temperature. The suspension was further cooled to 0 °C in an ice-water bath, and an equal volume of 5 M aq. HCl was slowly added. The reaction mixture was stirred for 30 min, and then subsequently diluted with H_2O. The crude mixture was partitioned between EtOAc and H_2O, and the phases were separated. The aqueous phase was extracted with EtOAc (3x), and the combined organic layers were washed sequentially with water (2x), then brine (1x). The organic layer was dried over $MgSO_4$, filtered, and concentrated via rotary evaporation. The residue was then purified by column chromatography to afford alkenes **4-15ism** to **4-15lsm** (yields ranged from 50-70%).



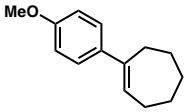
4-15ism

Alkene 4-15ism. Prepared in 50% yield. All spectroscopic data were in accordance with the published values.[46]



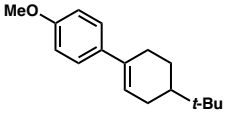
4-15jsm

Alkene 4-15jsm. Prepared in 62% yield. All spectroscopic data were in accordance with the published values.[46]



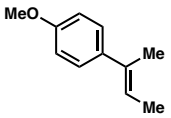
4-15ksm

Alkene 4-15ksm. Prepared in 70% yield. All spectroscopic data were in accordance with the published values.[46]



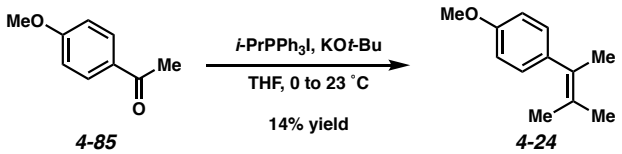
4-15lsm

Alkene 4-15lsm. Prepared in 57% yield. All spectroscopic data were in accordance with the published values.[47]



4-15msm

Alkene 4-15msm. Prepared according to the procedure reported by Castle and coworkers.[48] The compound was isomerized to the pure *E* isomer according to our previously reported procedure (PhSH, AIBN, PhH, reflux).[37]

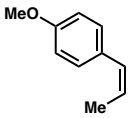


4-85 *4-24*

Tetrasubstituted alkene 4-24. To a flame-dried flask charged with isopropyltriphenylphosphonium iodide (3.03 g, 7.00 mmol) and potassium *tert*-butoxide (730 mg, 6.50 mmol) was added THF (8 mL) at 0 °C. The suspension was stirred for 1.5 h at 0 °C, and a

solution of 4-acetylanisole (**4-85**, 751 mg, 5.00 mmol) in THF (2 mL) was then added dropwise. The resulting mixture was allowed to warm to room temperature and stirred for 48 h. The mixture was diluted with sat. aq. NH_4Cl (10 mL), and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by flash chromatography (100% hexanes → 20:1 hexanes/Et_2O eluent) to yield tetrasubstituted alkene **4-24** (118 mg, 14% yield, R_f = 0.63 in 9:1 hexanes/Et_2O) as a colorless oil.

All spectroscopic data were in accordance with the published values.[49]

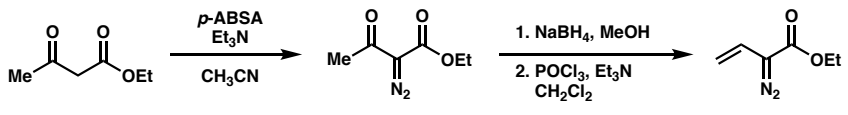


***4-5*$_{cis}$**

***Cis*-anethole (4-5$_{cis}$)**. Prepared according to the procedure reported by Yoon and coworkers.[37b]

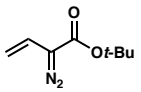
Diazocarbonyl Syntheses

General Notes: After synthesizing, vinyl diazocarbonyl compounds were stored in a -20 °C freezer as a 1.0 M solution in CH_2Cl_2. Diazo compounds are toxic, irritants, and many compounds are explosive. Care should be taken when handling and synthesizing diazo compounds. For several of these compounds, the ^{13}C NMR signal for the CN_2 carbon atom was not observed; this phenomenon is common and is due to the long relaxation time due to the enhanced negative partial charge on this atom.[50]



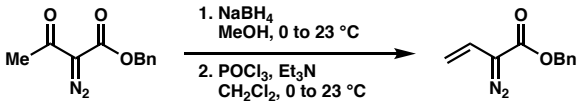
4-86 ***4-87*** ***4-6***

Diazoester 4-6. Prepared in three steps from commercially available ethyl acetoacetate (**4-86**). For the initial diazo transfer step, *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) was synthesized and utilized by following Davies's protocols[51], to afford α-diazo-β-ketoester **4-87**. Following a separate procedure described by Davies[52], a subsequent reduction with $NaBH_4$, followed by an elimination with phosphorus oxychloride yielded diazoester **4-6**. All spectroscopic data were in accordance with the published values.[53]



4-15rvd

Diazoester 4-15rvd. Prepared by following the procedure reported by Williams and coworkers.[54]



4-88 *4-15svd*

Diazoester 4-15svd. To a solution of ketone diazoester **4-88**[55] (873 mg, 4.00 mmol) in MeOH (6.30 mL) at 0 °C was added $NaBH_4$ (182 mg, 4.81 mmol, 1.2 equiv) portionwise. After the addition, the reaction mixture was allowed to warm to room temperature. Reaction progress was monitored by TLC. After 0.5 h, the reaction mixture was diluted with H_2O (15 mL) and extracted with EtOAc (3 x 15 mL). The organic extracts were combined and washed with brine (30 mL). The organic layer was dried over $MgSO_4$, concentrated via rotary evaporation, and the crude alcohol (R_f = 0.37 in 3:1 hexanes/EtOAc) was carried directly to the next transformation without further purification. The yellow crude alcohol was dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C. Triethylamine (2.20 mL, 16.0 mmol, 4.0 equiv) was added in one portion, and a solution of $POCl_3$ (0.560 mL, 6.00 mmol, 1.5 equiv) in CH_2Cl_2 (5.20 mL) was added slowly dropwise via an

addition funnel. The reaction mixture was allowed to gradually warm to room temperature, and progress was monitored by TLC. After 2 h, the reaction mixture was diluted with H_2O (20 mL), and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (40 mL) and dried over Na_2SO_4. The solvent was removed via rotary evaporation, and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford vinyl diazoester **4-15svd** (501 mg, 62% yield over two steps) as a yellow oil.

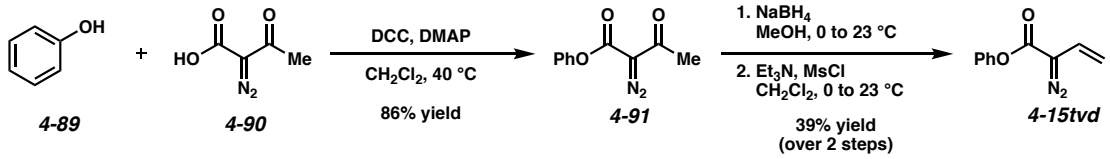
TLC: R_f = 0.80 in 4:1 hexanes/EtOAc, visualized by UV. Stained yellow with $KMnO_4$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.31 (comp. m, 5H), 6.18 (dd, *J* = 17.2, 11.0 Hz, 1H), 5.25 (s, 2H), 5.12 (d, *J* = 11.0 Hz, 1H), 4.86 (d, *J* = 17.2 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 138.9, 135.9, 128.7, 128.5, 128.3, 120.5, 107.7, 66.8. (Diazo carbon not observed.)

IR (ATR, neat): 2083, 1708, 1304, 1265, 1192, 1102, 742, 696 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{11}H_{10}N_2O_2 + H]^+$: 203.0815, found 203.0816.



4-89 *4-90* *4-91* *4-15tvd*

Ketone diazoester S20. Following the procedure reported by Stoltz and coworkers,[55] to a solution of phenol (96.0 mg, 1.02 mmol), diazo acetoacetic acid **4-90** (315 mg, 2.46 mmol, 2.4 equiv), and DMAP (12.5 mg, 0.102 mmol, 0.1 equiv) in CH_2Cl_2 (6.80 mL) at 40 °C was added in one portion DCC (421 mg, 2.04 mmol, 2.0 equiv). The reaction was monitored by TLC. After 2 h, the reaction mixture was filtered through a plug of celite (Et_2O eluent), and the resulting filtrate was partitioned between H_2O (15 mL) and Et_2O (15 mL). The aqueous layer was extracted with Et_2O (2 x 15 mL).

The organic extracts were combined and washed sequentially with sat. aq. $NaHCO_3$ (30 mL) and brine (30 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/EtOAc eluent) to afford ketone diazoester **4-91** (179 mg, 86% yield) as a cream colored solid.

TLC: R_f = 0.55 in 4:1 hexanes/EtOAc, visualized by UV.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (app. t, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 2H), 2.53 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 189.9, 160.2, 149.7, 129.8, 126.6, 121.7, 28.5. (Diazo carbon not observed).

IR (ATR, neat): 2139, 1731, 1657, 1315, 1188 cm^{-1}.

Diazoester 4-15tvd. To a solution of ketone diazoester **4-91** (511 mg, 2.50 mmol) in MeOH (3.90 mL) at 0 °C was added $NaBH_4$ (114 mg, 3.01 mmol, 1.2 equiv) portionwise. After the addition, the ice-water bath was removed, and the reaction mixture was allowed to warm to room temperature. Reaction progress was monitored by TLC. After 1 h, the reaction mixture was diluted with H_2O (20 mL), and extracted with EtOAc (3 x 20 mL). The organic extracts were combined and washed with brine (40 mL). The organic layer was dried over $MgSO_4$, concentrated via rotary evaporation, and the crude alcohol (R_f = 0.30 in 3:1 hexanes/EtOAc) was carried directly to the next transformation without further purification. The yellow crude alcohol was dissolved in CH_2Cl_2 (14.6 mL) and cooled to 0 °C. Triethylamine (1.70 mL, 12.5 mmol, 5.00 equiv), and MsCl (0.220 mL, 2.90 mmol, 1.16 equiv) were added subsequently. The reaction flask was allowed to gradually warm to room temperature. The reaction was monitored by TLC, and the alcohol was consumed after 2 h. The solvent was removed via rotary evaporation, and the resulting residue

was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford vinyl diazoester **4-15tvd** (183.3 mg, 39% yield over two steps) as a yellow oil.

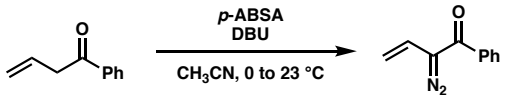
TLC: R_f = 0.48 in 9:1 hexanes/Et_2O, visualized by UV.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (app. t, *J* = 7.6 Hz, 2H), 7.25 (t, *J* = 7.6, 1H), 7.14 (d, *J* = 7.6 Hz, 2H), 6.26 (dd, *J* = 17.2, 11.0 Hz, 1H), 5.20 (d, *J* = 11.0 Hz, 1H), 4.97 (d, *J* = 17.2 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 150.4, 148.0, 129.6, 126.1, 121.7, 120.2, 108.3. (Diazo carbon not observed).

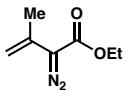
IR (ATR, neat): 2086, 1715, 1307, 1265, 1190, 1163, 1058 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{10}H_8N_2O_2 + H]^+$: 189.0659, found 189.0661.



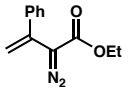
4-92 *4-15uvd*

Diazoketone 4-15uvd. To a solution of phenyl ketone **3-92**[56] (730 mg, 5.00 mmol) and DBU (836 mg, 5.50 mmol) in CH_3CN at 0 °C was added *p*-acetamidobenzenesulfonyl azide (1.32 g, 5.50 mmol). The reaction mixture was allowed to warm to room temperature and monitored by TLC. After 1.5 h, the solvent was removed via rotary evaporation. The crude residue was purified by flash chromatography (20:1 hexanes/EtOAc eluent) to afford diazoketone **4-15uvd** (394 mg, 46% yield, R_f = 0.54 in 10:1 hexanes/EtOAc) as a yellow oil. All spectroscopic data were in agreement with the published values.[53]



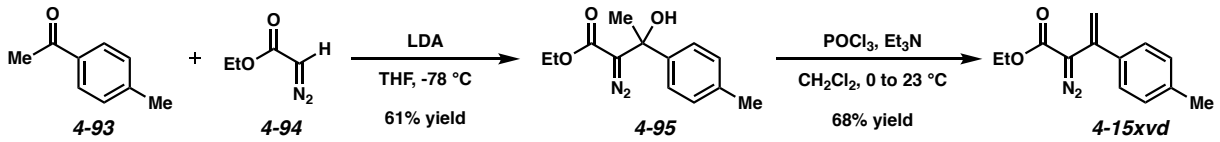
4-15vvd

Diazoester 4-15vvd. Prepared following the procedure reported by Liu and coworkers.[53]



4-15wvd

Diazoester 4-15wvd. Prepared following the procedure reported by Liu and coworkers.[53]



Diazoester 4-15xvd. To a solution of 1-(*p*-tolyl)ethanone (**4-93**, 1.35 g, 10.1 mmol) and ethyl diazoacetate (**4-94**, 1.38 g, 12.1 mmol) in anhydrous THF (10 mL) at -78 °C was added LDA (freshly generated, 12.5 mmol in 10 mL THF/hexanes (1:1)) over 20 min. The resulting solution was stirred at -78 °C for 2.5 h, and then quenched by addition of 1 N HCl (25 mL) after completion. The resulting mixture was extracted with Et_2O (3 x 25 mL), and the combined organic layers were washed with sat. aq. $NaHCO_3$ (20 mL), then brine (25 mL), and dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation, and the crude product was purified by column chromatography (5:1 hexanes/EtOAc eluent) to give alcohol **4-95** (1.52 g, 61% yield, R_f = 0.15 in 5:1 hexanes/EtOAc) as a yellow oil, which was carried directly to the next transformation without further purification. To a solution of alcohol **4-95** (247 mg, 0.996 mmol) and Et_3N (0.560 mL, 4.03 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C was slowly added $POCl_3$ (0.140 mL, 1.51 mmol). The resulting solution was warmed to room temperature and stirred for 2 h. Water (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were sequentially washed with water (15 mL) and brine (15 mL), and then dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation, and the crude product was purified by flash chromatography (30:1 hexanes/EtOAc eluent) to give alkenyl diazoester **4-15xvd** (156 mg, 68% yield) as a yellow oil.

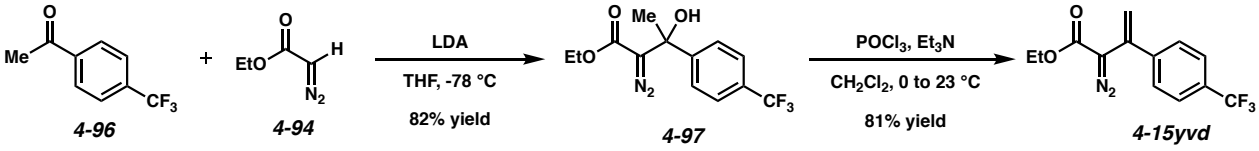
TLC: R_f = 0.48 in 10/1 hexane/ethyl acetate. Visualized by UV and $KMnO_4$ stain.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 5.70 (s, 1H), 5.27 (s, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 2.35 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.6, 138.4, 135.5, 133.7, 129.4, 127.4, 114.2, 61.1, 21.3, 14.6. (Diazo carbon not observed.)

IR (film): 2088, 1707, 1248, 1124, 1061 cm^{-1}.

HRMS (ESI+) m/z calc'd for $(M + H)^+$ $[C_{13}H_{14}N_2O_2 + H]^+$: 231.1128, found 231.1136.



Diazoester 4-15yvd. To a solution of 1-(4-(trifluoromethyl)phenyl)ethanone (**4-96**, 1.89 g, 10.1 mmol) and ethyl diazoacetate (**4-94**, 1.38 g, 12.1 mmol) in anhydrous THF (10 mL) at -78 °C was added LDA (freshly generated solution, 12.5 mmol in 10 mL THF/hexanes (1:1)) over 20 min. The resulting mixture was stirred at -78 °C for 2.5 h, and then quenched by addition of 1 N HCl (25 mL) after completion. The resulting mixture was extracted with Et_2O (3 x 25 mL), and the combined organic layers were washed with brine (25 mL) and dried over anhydrous Na_2SO_4. The solvent was removed via rotary evaporation, and the crude product was purified by column chromatography (10:1 hexanes/EtOAc → 5:1 hexanes/EtOAc eluent) to give alcohol **4-97** (2.49 g, 82% yield, R_f = 0.25 in 5:1 hexanes/EtOAc) as a yellow oil, which was carried directly to the next transformation without further purification. To a solution of alcohol **4-97** (305 mg, 1.01 mmol) and Et_3N (0.560 mL, 4.03 mmol) in CH_2Cl_2 (2 mL) at 0 °C was slowly added $POCl_3$ (0.140 mL, 1.51 mmol). The resulting solution was warmed to room temperature and stirred for 2 h. Water (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 x 15 mL). The combined

organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed via rotary evaporation, and the crude product was purified by flash chromatography (30:1 hexane/EtOAc eluent) to give alkenyl diazoester **4-15yvd** (233 mg, 81% yield) as a yellow oil.

TLC: R_f = 0.38 in 10:1 hexane/EtOAc. Visualized by UV and $KMnO_4$ stain.

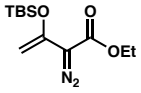
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J*= 8.2 Hz, 2H), 5.76 (s, 1H), 5.37 (s, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.2, 141.9, 133.2, 130.6 (q, *J* = 32.6 Hz), 127.8, 125.7 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 272.4 Hz), 116.2, 61.3, 14.5. (Diazo carbon not observed.)

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.7.

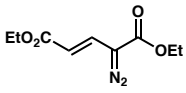
IR (film): 2095, 1704, 1321, 1123, 1064 cm^{-1}.

HRMS (ESI+) m/z calc'd for $(M + H)^+$ $[C_{13}H_{11}F_3N_2O_2 + H]^+$: 285.0845, found 285.0844.



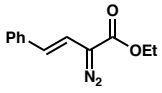
4-25

Diazoester 4-25. Prepared following the procedure reported by Doyle and coworkers.[57]



4-32

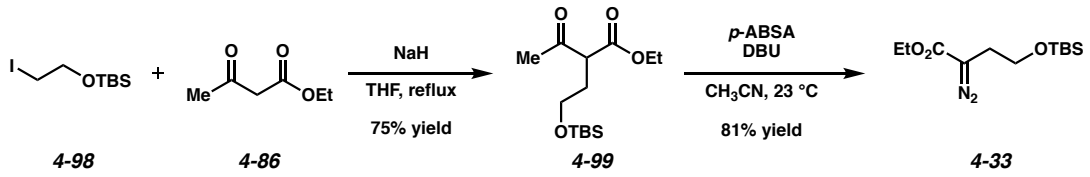
Diazoester 4-32. Prepared following the procedure reported by Davies and coworkers.[58]



4-31

Diazoester 4-31. Prepared following the procedure reported by Padwa and coworkers.[59]

Vinylcyclopropane Synthesis



Diazoester 4-33. To a suspension of NaH (1.21 g, 60% dispersion in mineral oil, 30.3 mmol) in THF (10.0 mL) at 23 °C was added a solution of ethyl acetoacetate (**4-86**, 3.80 mL, 30.1 mmol) in THF (10.0 mL) dropwise over 15 min. After 40 min of stirring at room temperature, a solution of *tert*-butyl(2-iodoethoxy)dimethylsilane (**4-98**, 5.76 g, 20.1 mmol) in THF (10 mL) was added dropwise to the reaction mixture over 5 min. The resulting mixture was then heated to reflux for 64 h, and then cooled to room temperature. Water (20 mL) was added, and the mixture was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed via rotary evaporation, and the resulting residue was purified by flash chromatography (20:1 hexanes/EtOAc eluent) to afford ketoester **4-99** (4.33 g, 75% yield, R_f = 0.36 in 10:1 hexanes/EtOAc) as a colorless oil, which was carried directly to the next transformation. To a solution of ketoester **4-99** (2.88 g, 10.0 mmol) and DBU (2.29 g, 15.1 mmol) in CH_3CN (20 mL) at 23 °C was added *para*-acetamidobenzenesulfonyl azide (*p*-ABSA) (3.13 g, 13.0 mmol). Reaction progress was monitored by TLC. After 1 h, the solvent was removed via rotary evaporation, and the residue was purified by column chromatography (20:1 hexanes/EtOAc eluent) to afford diazoester **4-33** (2.22 g, 81% yield) as a yellow liquid.

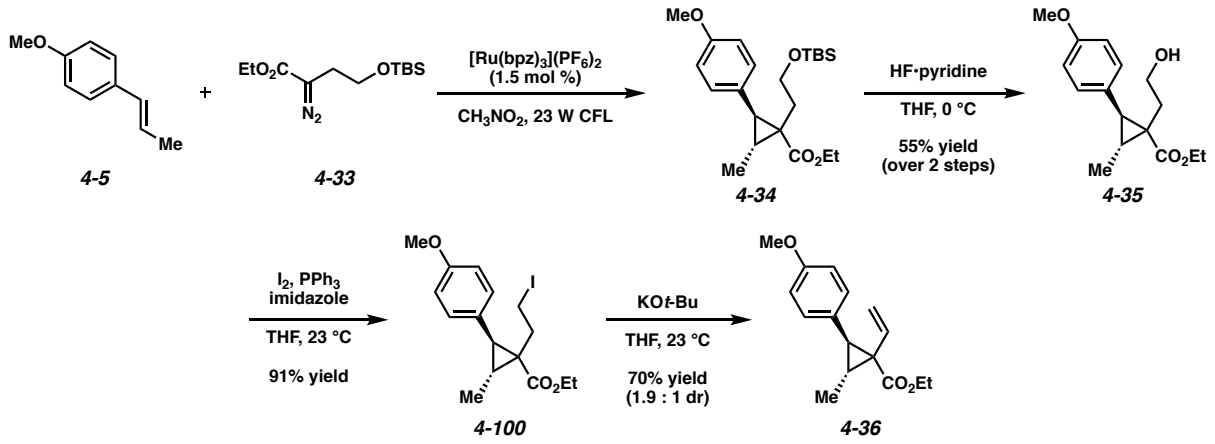
TLC: R_f = 0.39 in 10:1 hexanes/EtOAc, visualized by UV.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.21 (q, *J* = 7.1 Hz, 2H), 3.76 (t, *J* = 5.7 Hz, 2H), 2.46 (t, *J* = 5.7 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 61.8, 60.8, 27.2, 25.9, 18.3, 14.7, -5.4. (Diazo carbon not observed.)

IR (film): 2088, 1692, 1122, 1098, 835 cm^{-1}.

HRMS (ESI+) m/z calc'd for $(M + Na)^+$ $[C_{12}H_{24}N_2O_3Si + Na]^+$: 295.1448, found 295.1451.



Vinylcyclopropane 4-36. A flame-dried 5-dram borosilicate vial open to air was charged with *trans*-anethole (**4-5**, 177 mg, 1.20 mmol), diazoester **4-33** (273 mg, 1.00 mmol), $[Ru(bpz)_3](PF_6)_2$ (12.8 mg, 0.0148 mmol), and CH_3NO_2 (10.0 mL). The vial was then capped and placed in front of a 23 W compact fluorescent light bulb in a closed box lined with aluminum foil. After 21 h, the mixture was concentrated by rotary evaporation, and the resulting residue was carried directly to the next transformation without further purification. To a solution of crude cyclopropane **4-34** in THF (10.0 mL) was added HF·pyridine (1.00 mL, ~38.5 mmol) at 0 °C. After 20 min, the mixture was poured into sat. aq. $NaHCO_3$ (30 mL) and extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The solvent was removed via rotary evaporation, and the resulting residue was purified by flash chromatography (2:1 hexanes/EtOAc eluent) to afford alcohol **4-35** (153 mg, 55% yield over two steps, R_f = 0.16 in 2:1 hexanes/EtOAc) as a colorless oil.

Alcohol **4-35** (84.9 mg, 0.305 mmol) was dissolved in THF (6.0 mL) at 23 °C. To this solution was sequentially added PPh_3 (156 mg, 0.595 mmol), imidazole (82.0 mg, 1.21 mmol), and I_2 (153 mg, 0.602 mmol). The resulting mixture was stirred at room temperature for 40 min. The solvent was removed via rotary evaporation, and the residue was purified by flash chromatography (5:1 hexanes/EtOAc eluent) to afford iodide **4-100** as a yellow liquid (108 mg, 91% yield, R_f = 0.68 in 2:1 hexanes/EtOAc).

To a solution of iodide **4-100** (59.7 mg, 0.154 mmol) in THF (4.5 mL) at 23 °C was added solid KO*t*-Bu (21.5 mg, 0.192 mmol). After 5.5 h, another portion of KO*t*-Bu was added (12.3 mg, 0.110 mmol). After 19 h, sat. aq. NH_4Cl (10.0 mL) was added, and the reaction mixture was extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over anhydrous Na_2SO_4. The solvent was removed via rotary evaporation, and the residue was purified by flash chromatography (10:1 hexanes/EtOAc eluent) to afford vinylcyclopropane **4-36** (28.1 mg, 70% yield, 1.9:1 inseparable mixture of diastereomers) as a colorless oil.

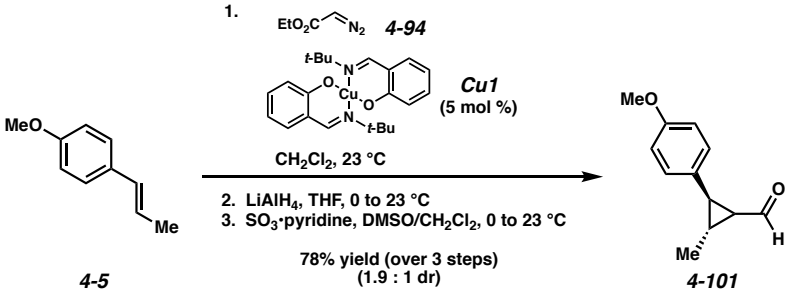
TLC: R_f = 0.38, 0.42 in 10:1 hexanes/EtOAc, visualized by UV.

^{1}H NMR (400 MHz, $CDCl_3$): [Major diastereomer] δ 7.14 (d, *J* = 8.7 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 6.09 (dd, *J* = 17.3, 10.7 Hz, 1H), 5.34 (d, *J* = 10.7 Hz, 1H), 5.27 (d, *J* = 17.3 Hz, 1H), 3.89-3.80 (comp. m, 2H), 3.77 (s, 3H), 2.48 (d, *J* = 7.5 Hz, 1H), 2.39 (app. quintet, *J* = 6.6 Hz, 1H), 1.18 (d, *J* = 6.2 Hz, 3H), 0.92 (t, *J* = 7.1 Hz, 3H); [Minor diastereomer] δ 7.04 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 5.60 (dd, *J* = 17.3, 10.8 Hz, 1H), 5.00 (d, *J* = 10.8 Hz, 1H), 4.97 (d, *J* = 17.3 Hz, 1H), 4.27-4.19 (comp. m, 2H), 3.78 (s, 3H), 2.92 (d, *J* = 7.6 Hz, 1H), 1.98 (app. quintet, *J* = 6.7 Hz, 1H), 1.36 (d, *J* = 6.3 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, characterized as mixture of the major and minor diastereomers): δ 171.8, 171.1, 158.4, 158.3, 134.0, 133.7, 130.3, 130.1, 129.0, 128.6, 117.3, 116.5, 113.5, 113.4, 61.1, 60.7, 55.35, 55.32, 39.8, 38.5, 37.3, 30.4, 26.1, 25.7, 14.5, 14.1, 13.2, 12.9.

IR (film): 1719, 1516, 1245, 1175, 1032 cm^{-1}.

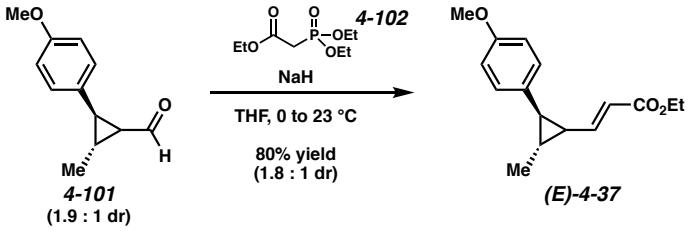
HRMS (ESI+) m/z calc'd for $(M + H)^+$ $[C_{16}H_{20}O_3 + H]^+$: 261.1485, found 261.1487.



Aldehyde S30. To a solution of *trans*-anethole (**4-5**, 1.50 mL, 10.1 mmol) and Cu catalyst **Cu1**[28] (210 mg, 0.505 mmol) in CH_2Cl_2 (10.0 mL) at room temperature was added ethyl diazoacetate (**4-94**, 8.50 mL, ≥13 wt. % in CH_2Cl_2, 70.7 mmol) in CH_2Cl_2 (60 mL) over 6 h via an addition funnel. The reaction mixture was concentrated via rotary evaporation, and the crude residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to give a mixture of cyclopropane diastereomers (R_f = 0.33, 0.22 in 9:1 hexanes/Et_2O, visualized by UV, stained purple with *p*-anisaldehyde stain) in the presence of inseparable diethyl maleate and diethyl fumarate byproducts. This mixture was dissolved in 10 mL THF, and the solution was added dropwise to a suspension of LAH (1.15 g, 30.3 mmol) in THF (10 mL) at 0 °C. After 3 h at 0 ˚C, the reaction was complete by TLC. The reaction mixture was diluted with Et_2O (10 mL) at 0 °C, and to the mixture was slowly and sequentially added H_2O (1.2 mL), 15% aq. NaOH solution (1.2 mL), and water (3.5 mL). The resulting mixture was warmed to room temperature and stirred for 15 min. $MgSO_4$ was added, the mixture was stirred 15 min, and then it was filtered to remove the solids

(Et_2O eluent). The filtrate was concentrated in vacuo, and the crude residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) to yield pure cyclopropyl alcohol (1.80 g, 93% yield over 2 steps, R_f = 0.26 in 4:1 hexanes/EtOAc, visualized by UV, stained purple with *p*-anisaldehyde) as a white solid.

To a solution of the cyclopropyl alcohol (769 mg, 4.00 mmol) in DMSO (5.0 mL) and CH_2Cl_2 (10 mL) was added Et_3N (1.67 mL, 12.0 mmol) at 0 °C. To this reaction mixture, a solution of SO_3•pyridine complex (955 mg, 6.00 mmol) in DMSO (5.0 mL) was added via syringe. The mixture was stirred at 0 °C for 10 min, and then it was warmed to room temperature. After 1 h, the solution was cooled to 0 °C, diluted with H_2O (40 mL), and the mixture was extracted with Et_2O (3 x 40 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated via rotary evaporation. The crude residue was purified by flash chromatography (4:1 hexanes/Et_2O eluent) to yield cyclopropyl aldehyde **4-101** (638 mg, 84% yield, 1.9:1 inseparable mixture of diastereomers, R_f= 0.54 in 4:1 hexanes/EtOAc, stained blue by *p*-anisaldehyde) as a colorless oil that solidified upon standing.



Vinylcyclopropane (*E*)-4-37. To a suspension of NaH (44.0 mg, 60% dispersion in mineral oil, 1.10 mmol) in dry THF (1.5 mL) at 0 °C was added triethylphosphonoacetate (**4-102**, 0.210 mL, 1.05 mmol) dropwise, and the reaction mixture was stirred for 1 h. A solution of cyclopropyl aldehyde **4-101** (1.9:1 dr, 190 mg, 1.00 mmol) in THF (1.5 mL) was then added to the mixture at 0 °C, and the resulting mixture was allowed to warm to room temperature. The reaction was complete after 1 h by TLC, and the mixture was quenched with H_2O (5 mL) and diluted with Et_2O

(5 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated via rotary evaporation. The crude residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/EtOAc eluent) to yield vinylcyclopropane **(*E*)-4-37** (209 mg, 80% yield, 1.8:1 inseparable mixture of diastereomers) as a colorless oil that solidified upon standing. (*Note*: The diagnostic J couplings and the differences in compound mixtures between this and the subsequent reaction indicated that this mixture was of the two diastereomers of the (*E*)-enoates.)

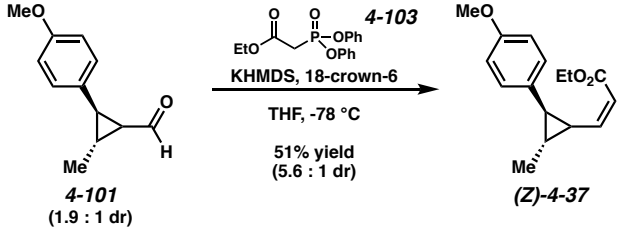
TLC: R_f = 0.30 in 4:1 hexanes/EtOAc, visualized by UV, stained with $KMnO_4$ stain.

^{1}H NMR (400 MHz, $CDCl_3$): [Major diastereomer] δ 6.98 (d, *J* = 8.8 Hz, 2H), 6.83-6.78 (m, 1H), 6.82 (d, *J* = 8.8 Hz, 2H), 5.94 (d, *J* = 15.3 Hz, 1H), 4.19 (app. q, *J* = 7.1 Hz, 2H), 3.781 (s, 3H), 1.93 (app. t, *J* = 5.2 Hz, 1H), 1.83 (ddd, *J* = 10.3, 9.0, 4.5 Hz, 1H), 1.67-1.62 (m, 1H), 1.31-1.26 (m, 6H); [Minor diastereomer] δ 7.10 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.29 (dd, *J* = 15.4, 10.6 Hz, 1H), 5.86 (d, *J* = 15.4 Hz, 1H), 4.09 (app. q, *J* = 7.1 Hz, 2H), 3.784 (s, 3H), 2.26 (dd, *J* = 8.4, 6.3 Hz, 1H), 1.70-1.66 (m, 1H). 1.61-1.56 (m, 1H), 1.30-1.26 (m, 3H), 1.21 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, characterized as mixture of the diastereomeric isomers): δ 166.8, 166.5, 158.3, 158.1, 150.2, 148.9, 133.4, 130.0, 129.8, 127.0, 120.6, 119.6, 114.0, 113.9, 60.2, 60.0, 55.5, 55.4, 34.4, 33.7, 32.0, 31.3, 25.0, 22.6, 18.5, 14.5, 14.4, 14.2.

IR (film): 2957, 1711, 1639, 1515, 1250, 1146, 1037 cm^{-1}.

HRMS (ESI+) m/z calc'd for $(M + H)^+$ $[C_{16}H_{20}O_3 + H]^+$: 261.1485, found 261.1488.



Vinylcyclopropane (*Z*)-4-37. To a solution of Ando's reagent[60] (**4-103**, 450 mg, 1.40 mmol) and 18-crown-6 (1.85 g, 7.00 mmol) in 28 mL THF at -78 °C under argon was added KHMDS (1.54 mL, 0.91 M solution in THF, 1.40 mmol). A solution of cyclopropyl aldehyde **4-101** (1.9:1 dr, 266 mg, 1.40 mmol) in 2 mL of THF was added, and the resulting mixture was stirred for 8 h at -78 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (30 mL), and diluted with H_2O (5 mL) and Et_2O (20 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 x 35 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated via rotary evaporation. The crude residue was purified by flash chromatography (100% hexanes → 20:1 hexanes/EtOAc eluent) to yield vinylcyclopropane **(*Z*)-4-37** (185 mg, 51% yield, 5.6:1 inseparable mixture of diastereomers) as a colorless oil. (*Note*: The diagnostic J couplings and the differences in compound mixtures between this and the previous reaction indicated that this mixture was of the two diastereomers of the (*Z*)-enoates.)

TLC: R_f = 0.21 in 20:1 hexanes/EtOAc, visualized by UV, stained with $KMnO_4$ stain.

The spectroscopic data is reported for the major diastereomer only.

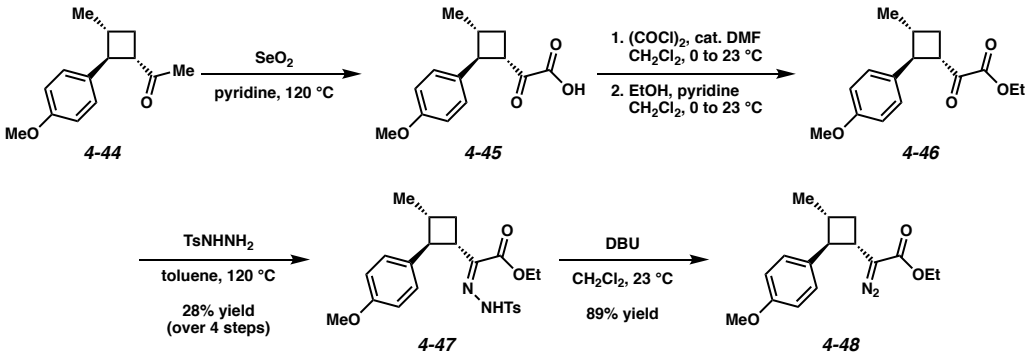
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 5.98 (app. t, *J* = 11.2 Hz, 1H), 5.82 (d, *J* = 11.6 Hz, 1H), 4.16 (dq, *J* = 7.1, 1.5 Hz, 2H), 3.78 (s, 3H), 3.28-3.19 (m, 1H), 1.85 (app. t, *J* = 5.2 Hz, 1H), 1.69-1.58 (m, 1H), 1.28 (d, *J* = 6.4 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 158.0, 149.7, 133.7, 127.1, 118.9, 114.0, 59.9, 55.5, 35.7, 28.7, 25.7, 14.4, 14.2.

IR (film): 2958, 1713, 1515, 1247, 1183, 1035 cm^{-1}.

HRMS (ESI+) m/z calc'd for $(M + H)^+$ $[C_{16}H_{20}O_3 + H]^+$: 261.1485, found 261.1489.

Cyclobutyl Diazoester Synthesis



Cyclobutyl diazoester 4-48. To a solution of cyclobutyl methyl ketone **4-44**[61] (604 mg, 2.99 mmol) in dry pyridine (1.50 mL) at 23 °C was added SeO_2 (669 mg, 6.03 mmol). The mixture was heated to 120 °C in an oil bath and stirred 2 h. After cooling to room temperature, the solvent was removed via rotary evaporation. The residue was dissolved in EtOAc (30 mL) and washed sequentially with 1 N HCl (2 x 15 mL) and brine (15 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give crude α-ketoacid **4-45**, which was carried directly to the next transformation without further purification. To a solution of crude α-ketoacid **4-45** in dry CH_2Cl_2 (6.00 mL) at 0 °C was added two drops of dry DMF. Then, $(COCl)_2$ (0.260 mL, 3.07 mmol) was added at 0 °C over 5 min, and the mixture was warmed to room temperature. After 1.5 h, the solvent was removed via rotary evaporation. The residue was dissolved in CH_2Cl_2 (6.00 mL), then EtOH (0.35 mL, 6.00 mmol) and pyridine (0.25 mL, 3.10 mmol) were added to the solution at 0 °C. After stirring for 70 min at room temperature, water (20 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (15 mL) and dried over anhydrous Na_2SO_4. The solvent was removed via rotary evaporation, and the residue was dissolved in toluene (45 mL). To the solution was added $TsNHNH_2$ (615 mg, 3.31 mmol), and the reaction mixture was heated to 120 °C and stirred 3 h. The solvent was removed via rotary evaporaton, and the residue was purified by flash chromatography (10:1

hexanes/EtOAc → 5:1 hexanes/EtOAc) to give tosylhydrazone **4-47** (378 mg, 28% yield over 3 steps, R_f = 0.22 in 5:1 hexanes/EtOAc) as a yellow oil. To a solution of tosylhydrazone **4-47** in CH_2Cl_2 (6.00 mL) at 23 °C was added DBU (244 mg, 1.61 mmol), and the reaction mixture was stirred at room temperature for 18 h. The solvent was removed via rotary evaporation, and the residue was purified by flash chromatography (20:1 hexanes/EtOAc eluent) to give cyclobutyl diazoester **4-48** (103 mg, 89% yield) as a yellow oil.

TLC: R_f = 0.60 in 3:1 hexanes/EtOAc, visualized by UV.

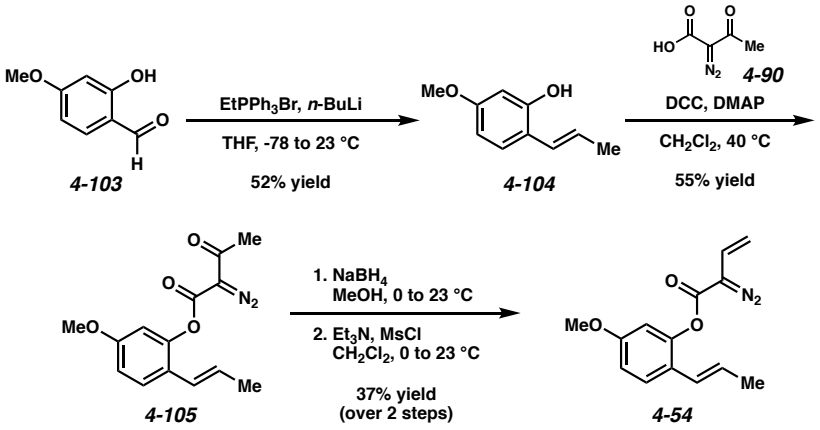
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.17 (app. dq, *J* = 7.1, 2.4 Hz, 2H), 3.79 (s, 3H), 3.08 (app. td, *J* = 10.0, 7.9 Hz, 1H), 2.77 (app. t, *J* = 9.6 Hz, 1H), 2.40 (app. dt, *J* = 10.3, 7.7 Hz, 1H), 2.28-2.15 (m, 1H), 1.49 (app. q, *J* = 10.1 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.15 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 158.4, 134.2, 127.8, 114.0, 60.8, 55.4, 53.0, 35.5, 32.4, 32.3, 20.5, 14.6. (Diazo carbon not observed.)

IR (film): 2077, 1689, 1513, 1249, 1133 cm^{-1}.

HRMS (ESI+) m/z calc'd for $(M + Na)^+$ $[C_{16}H_{20}N_2O_3 + Na]^+$: 311.1366, found 311.1366.

Intramolecular Substrates Synthesis



Alkene 4-104. To a suspension of ethyltriphenylphophonium bromide (2.12 g, 5.71 mmol) in THF (36.0 mL) at -78 °C in a flame-dried flask under argon was added *n*-BuLi (2.28 mL, 2.5 M in hexanes, 5.71 mmol) dropwise. The mixture was warmed to 0 °C. After 1 h, the reaction mixture was cooled back to -78 °C, and aldehyde **4-103**[62] (456 mg, 3.00 mmol) in THF (3.00 mL) was added dropwise. The suspension was allowed to warm to room temperature and stirred overnight. The next morning, the reaction mixture was quenched with sat. aq. NH_4Cl (15 mL), diluted with H_2O (30 mL), and the phases were separated. The aqueous layer was further extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated via rotary evaporation. The residue was purified by flash chromatography (100% hexanes → 6:1 hexanes/EtOAc eluent) to afford *trans*-alkene **4-104** (255 mg, 52% yield) as an oil that solidified upon standing into off-white crystals. All spectroscopic data were in accordance with the published values.[63]

Ketone diazoester 4-105. Following the procedure reported by Stoltz and coworkers,[55] to a solution of phenol **4-104** (367 mg, 2.24 mmol), diazo acetoacetic acid (685 mg, 5.35 mmol, 2.4 equiv), and DMAP (27.0 mg, 0.221 mmol, 0.1 equiv) in CH_2Cl_2 (15.0 mL) at 40 °C was added in one portion DCC (920 mg, 4.46 mmol, 2.0 equiv). Reaction progress was monitored by TLC. After 2 h, the reaction mixture was filtered through a plug of celite (Et_2O eluent), and the resulting filtrate was partitioned between H_2O (30 mL) and Et_2O (30 mL). The aqueous layer was extracted with Et_2O (2 x 30 mL). The organic extracts were combined and washed sequentially with sat. aq. $NaHCO_3$ (60 mL) and brine (60 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (100% hexanes → 6:1

hexanes/EtOAc eluent) to afford ketone diazoester **4-105** (614 mg, 55% yield) as a cream colored solid.

TLC: R_f = 0.33 in 6:1 hexanes/EtOAc, visualized by UV.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.7 Hz, 1H), 6.81 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.63 (d, *J* = 2.6 Hz, 1H), 6.29 (dd, *J* = 15.7, 1.6 Hz, 1H), 6.13 (dq, *J* = 15.7, 6.5 Hz, 1H), 3.80 (s, 3H), 2.54 (s, 3H), 1.88 (dd, *J* = 6.5, 1.6 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 190.0, 159.9, 159.3, 147.0, 127.4, 127.1, 123.41, 123.39, 113.3, 107.9, 55.7, 28.5, 19.0. (Diazo carbon not observed.)

IR (ATR, neat): 2945, 2140, 1733, 1318, 1244, 1152, 1107, 1028, 963 cm^{-1}.

Diazoester 4-54. To a solution of ketone diazoester **4-105** (111 mg, 0.405 mmol) in MeOH (1.00 mL) at 0 °C was added $NaBH_4$ (18.3 mg, 0.486 mmol, 1.2 equiv) portionwise. After the addition, the ice-water bath was removed, and the reaction mixture was allowed to warm to ambient temperature. Reaction progress was monitored by TLC. After 0.5 h, the reaction mixture was diluted with H_2O (5 mL), and extracted with EtOAc (3 x 5 mL). The organic extracts were combined and washed with brine (10 mL). The organic layer was dried over $MgSO_4$ and concentrated via rotary evaporation, and the crude alcohol (R_f = 0.17 in 3:1 hexanes/EtOAc) was carried directly to the next transformation without further purification. The yellow crude alcohol was dissolved in CH_2Cl_2 (2.50 mL) and cooled to 0 °C in an ice-water bath. Triethylamine (0.280 mL, 2.03 mmol, 5.0 equiv) and MsCl (36.0 μL, 0.470 mmol, 1.16 equiv) were added. The reaction mixture was allowed to gradually warm to room temperature. Reaction progress was monitored by TLC. After 2 h, the solvent was removed via rotary evaporation, and the resulting residue was

purified by flash chromatography (100% hexanes → 9:1 hexanes/Et_2O eluent) to afford vinyl diazoester **4-54** (38.3 mg, 37% yield over two steps) as a pale orange solid.

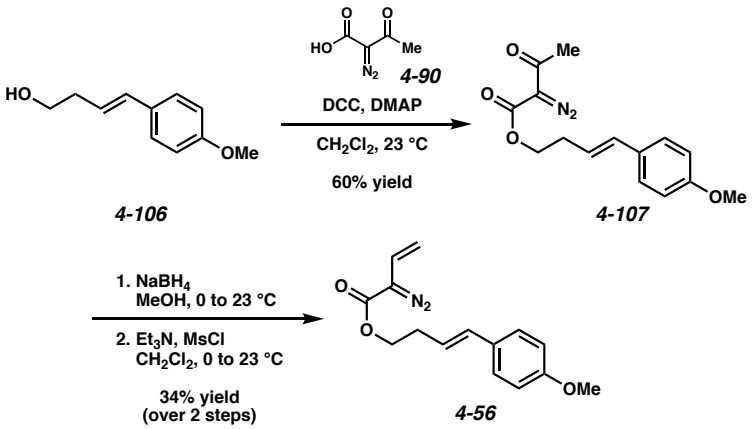
TLC: R_f = 0.36 in 9:1 hexanes/Et_2O, visualized by UV. Stained yellow with $KMnO_4$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.7 Hz, 1H), 6.77 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.63 (d, *J* = 2.6 Hz, 1H), 6.35-6.22 (comp. m, 2H), 6.11 (dq, *J* = 15.7 Hz, 6.6 Hz, 1H), 5.22 (d, *J* = 11.0 Hz, 1H), 4.98 (d, *J* = 17.4 Hz, 1H), 3.78 (s, 3H), 1.86 (dd, *J* = 6.6, 1.6 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 147.7, 127.2, 126.5, 123.7, 123.4, 120.2, 113.1, 108.3, 107.9, 55.6, 19.0. (Diazo carbon not observed.)

IR (ATR, neat): 2946, 2087, 1715, 1615, 1503, 1304, 1253, 1153, 1107 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + Na)^+$ $[C_{14}H_{14}N_2O_3 + Na]^+$: 281.0897, found 281.0897.



Ketone diazoester 4-107. Following the procedure reported by Stoltz and coworkers,[55] to a solution of alcohol **4-106**[64] (178 mg, 0.999 mmol), diazo acetoacetic acid (307 mg, 2.40 mmol, 2.4 equiv), and DMAP (12.2 mg, 0.0999 mmol, 0.1 equiv) in CH_2Cl_2 (6.70 mL) at 23 °C was added in one portion DCC (413 mg, 2.00 mmol, 2.0 equiv). Reaction progress was monitored by TLC. After 3 h, the reaction mixture was filtered through a plug of celite (Et_2O eluent), and the filtrate was partitioned between H_2O (15 mL) and Et_2O (15 mL). The aqueous layer was extracted with Et_2O (2 x 15 mL). The organic extracts were combined and washed sequentially with sat. aq.

$NaHCO_3$ (30 mL) and brine (30 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (100% hexanes → 6:1 hexanes/EtOAc eluent) to afford ketone diazoester **4-107** (172 mg, 60% yield) as a pale yellow solid.

TLC: R_f = 0.47 in 3:1 hexanes/EtOAc, visualized by UV.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.42 (app. d, *J* = 15.8 Hz, 1H), 6.00 (dt, *J* = 15.8, 7.1 Hz, 1H), 4.34 (t, *J* = 6.7 Hz, 2H), 3.80 (s, 3H), 2.58 (app. qd, *J* = 6.8, 1.1 Hz, 2H), 2.47 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 190.3, 161.5, 159.2, 132.5, 129.9, 127.4, 122.6, 114.1, 64.8, 55.4, 32.6, 28.4. (Diazo carbon not observed.)

IR (ATR, neat): 2959, 2138, 1719, 1656, 1511, 1314 cm^{-1}.

Diazoester 4-56. To a solution of ketone diazoester **4-107** (161 mg, 0.558 mmol) in MeOH (1.00 mL) at 0 °C was added $NaBH_4$ (25.4 mg, 0.671 mmol, 1.2 equiv) portionwise. After the addition, the ice-water bath was removed, and the reaction mixture was allowed to warm to ambient temperature. Reaction progress was monitored by TLC. After 0.5 h, the reaction mixture was diluted with H_2O (5 mL), and extracted with EtOAc (3 x 5 mL). The organic extracts were combined and washed with brine (10 mL). The organic layer was dried over $MgSO_4$ and concentrated via rotary evaporation, and the crude alcohol (R_f = 0.22 in 3:1 hexanes/EtOAc) was carried directly to the next transformation without further purification. The yellow crude alcohol was dissolved in CH_2Cl_2 (3.40 mL) and cooled to 0 °C in an ice-water bath. Triethylamine (0.390 mL, 2.80 mmol, 5.0 equiv) and MsCl (50.0 μL, 0.647 mmol, 1.16 equiv) were added. The reaction mixture was allowed to gradually warm to room temperature, and reaction progress was monitored

by TLC. After 5 h, the solvent was removed via rotary evaporation, and the resulting residue was purified by flash chromatography (100% hexanes → 9:1 hexanes/EtOAc eluent) to afford vinyl diazoester **4-56** (51.5 mg, 34% yield over two steps) as a pale orange solid.

TLC: R_f = 0.31 in 9:1 hexanes/EtOAc, visualized by UV. Stained yellow with $KMnO_4$.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.42 (app. d, *J* = 15.8 Hz, 1H), 6.16 (dd, *J* = 17.4, 11.0 Hz, 1H), 6.01 (dt, *J* = 15.8, 7.1 Hz, 1H), 5.11 (d, *J* = 11.0 Hz, 1H), 4.86 (d, *J* = 17.4 Hz, 1H), 4.32 (t, *J* = 6.8 Hz, 2H), 3.81 (s, 3H), 2.56 (app. qd, *J* = 6.8, 1.0 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1, 132.2, 130.2, 127.4, 123.0, 120.5, 114.1, 107.6, 64.6, 55.4, 32.7. (Diazo carbon not observed.)

IR (ATR, neat): 2085, 1697, 1608, 1511, 1305, 1246, 1108 cm^{-1}.

HRMS (ESI+): *m/z* calc'd for $(M + Na)^+$ $[C_{15}H_{16}N_2O_3 + Na]^+$: 295.1053, found 295.1053.

4.9.8 Cyclic Voltammetry Measurement of Compound 4-6

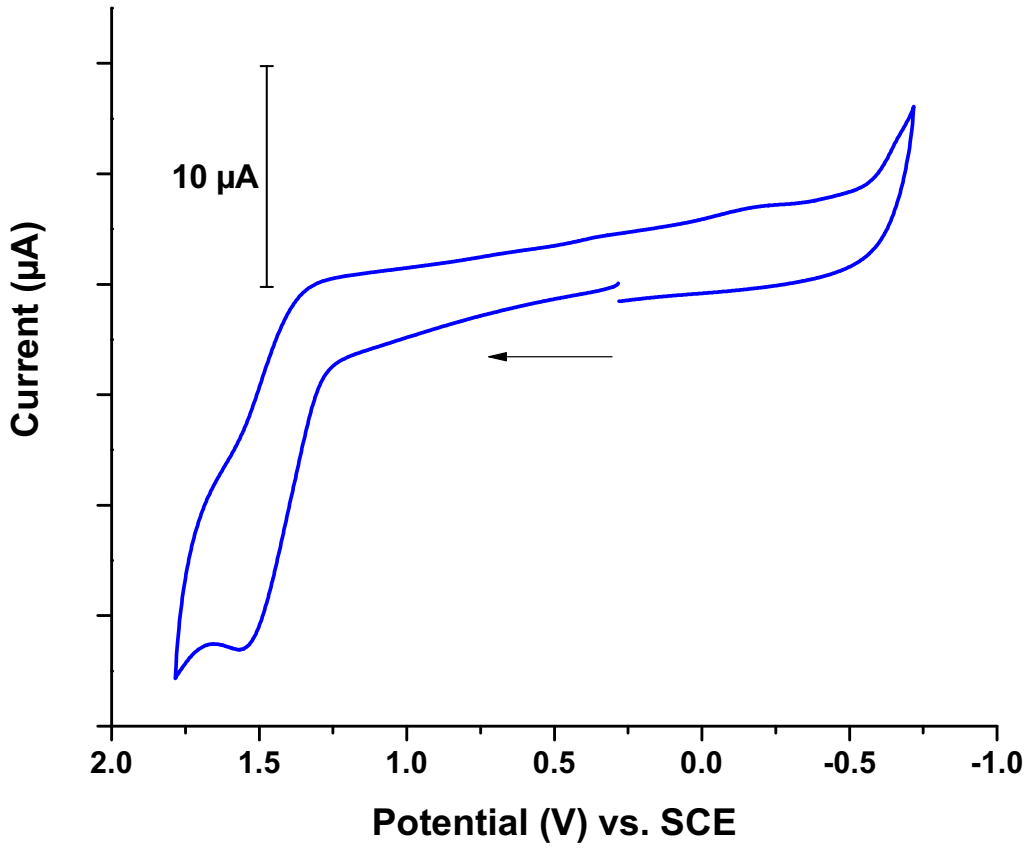


Figure 4.2. Cyclic voltammogram of vinyldiazo **4-6** (5 mM) recorded at ambient temperature in CH_3NO_2 containing 0.1 M Bu_4NPF_6 supporting electrolyte, glassy carbon working electrode measured at a scan rate of 100 mV/s. The arrow displays scan direction.

4.10 Chapter 4 Notes and References

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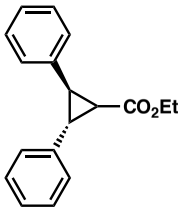
APPENDIX A

NMR SPECTRA RELEVANT TO CHAPTER 2



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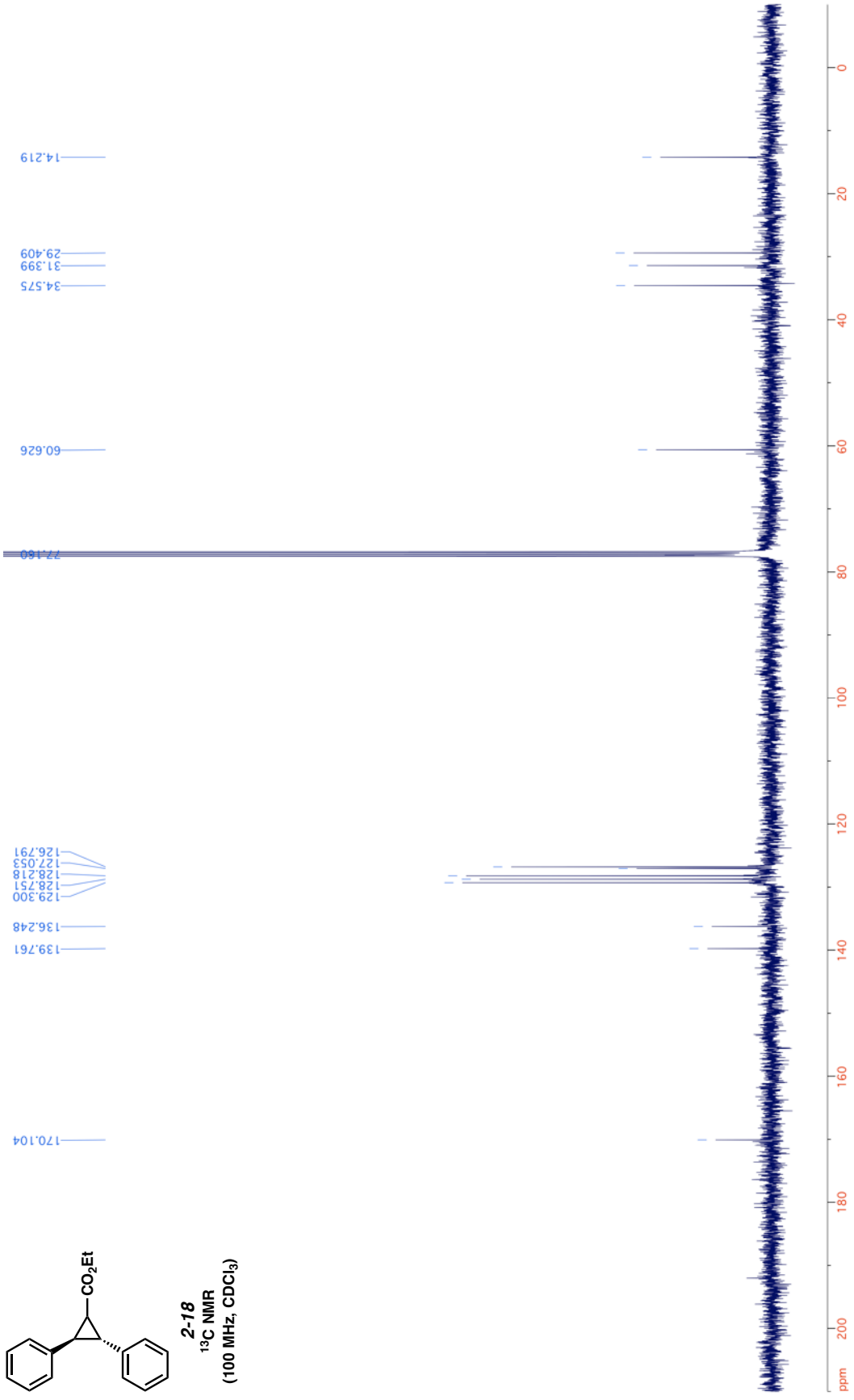
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170.104
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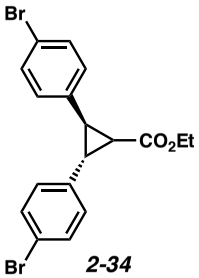
CO2Et
2-18
13C NMR
(100 MHz, CDCl3)



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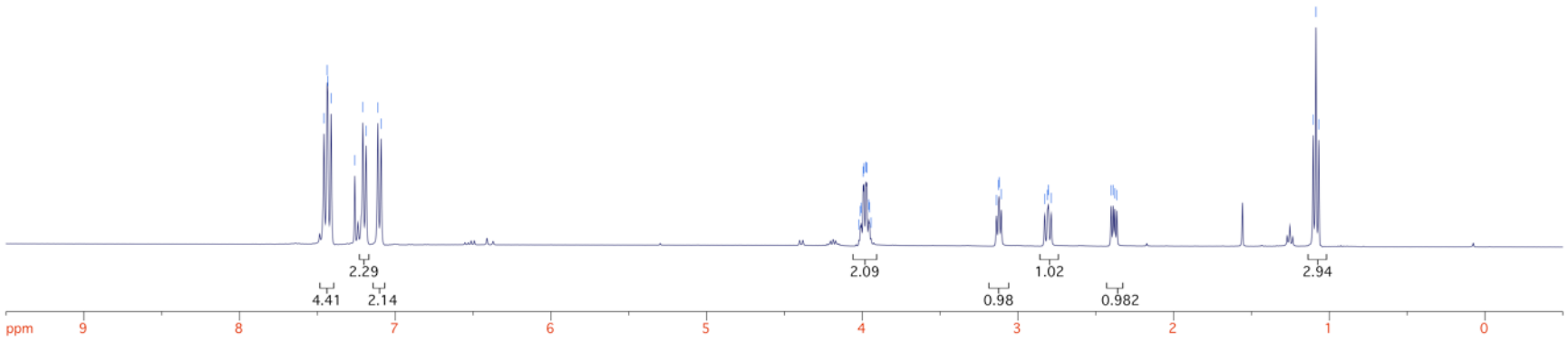
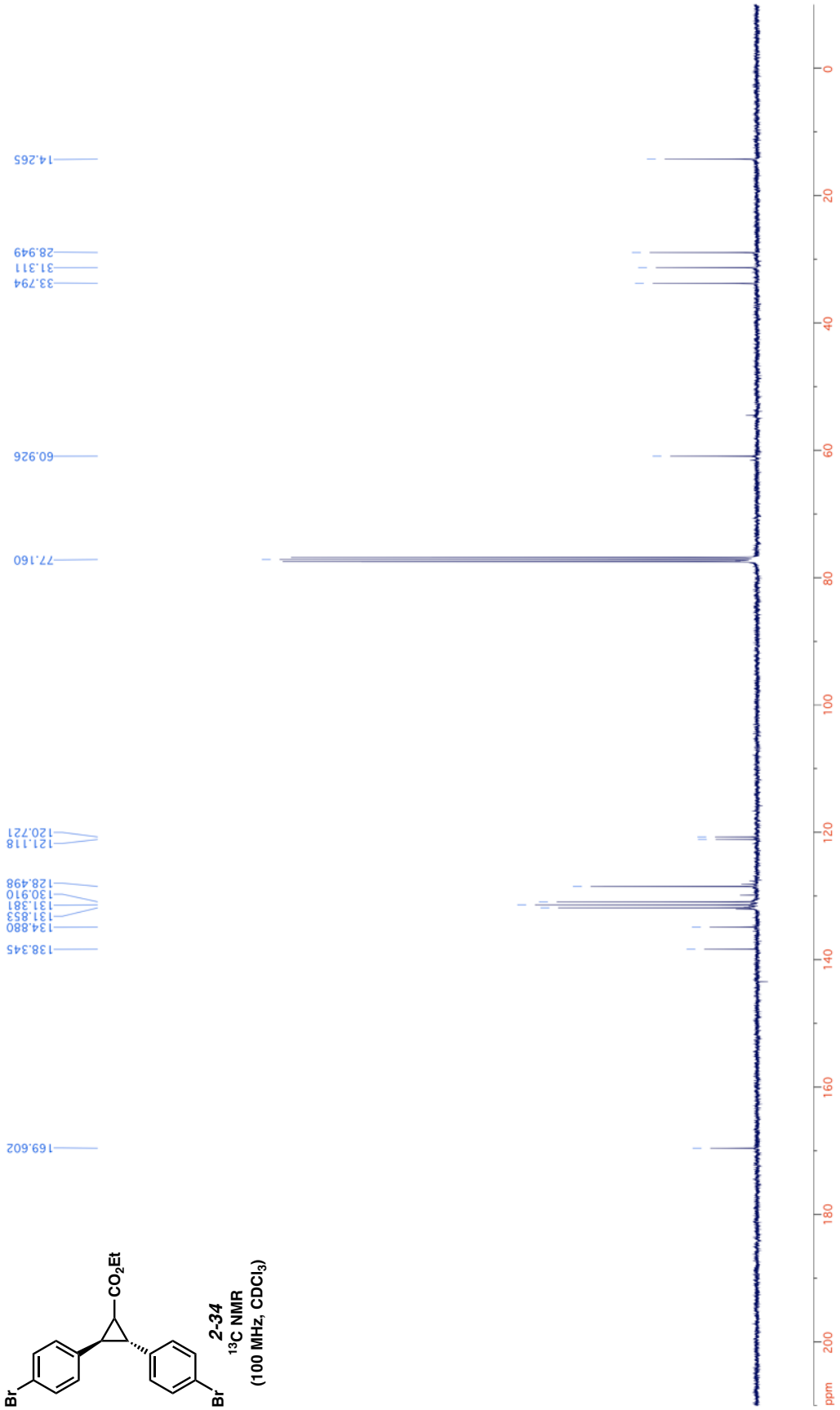
^{1}H NMR
(400 MHz, $CDCl_3$)





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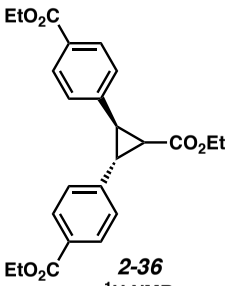
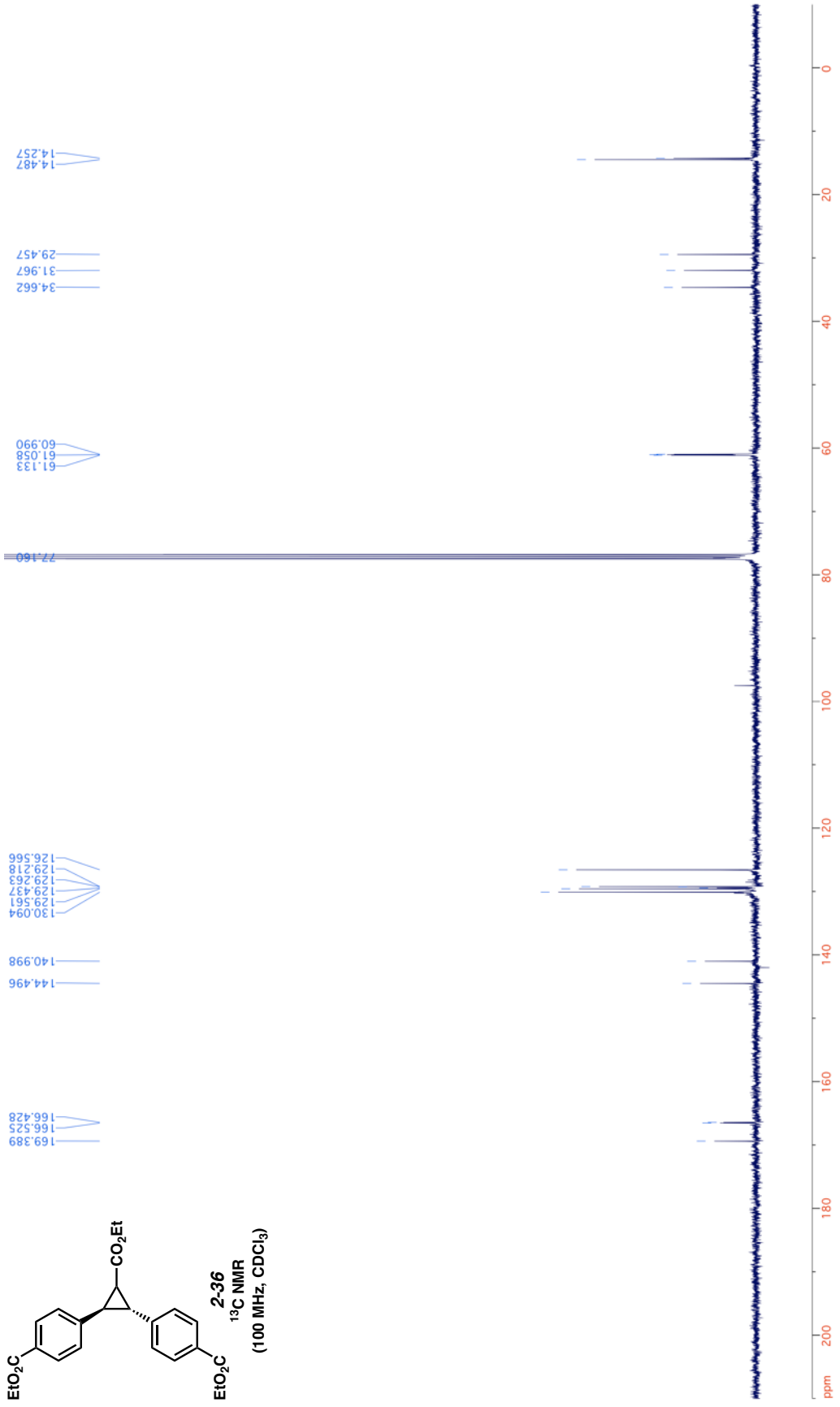


2-36

^{1}H NMR

(400 MHz, $CDCl_3$)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129.561
130.094
140.998
144.496
166.428
166.525
169.389
ppm
0
20
40
60
80
100
120
140
160
180
200
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CO2Et
EtO2C
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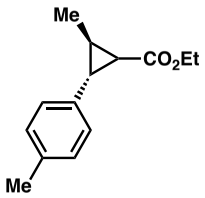
13C NMR
(100 MHz, CDCl3)



2-45
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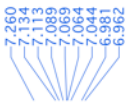
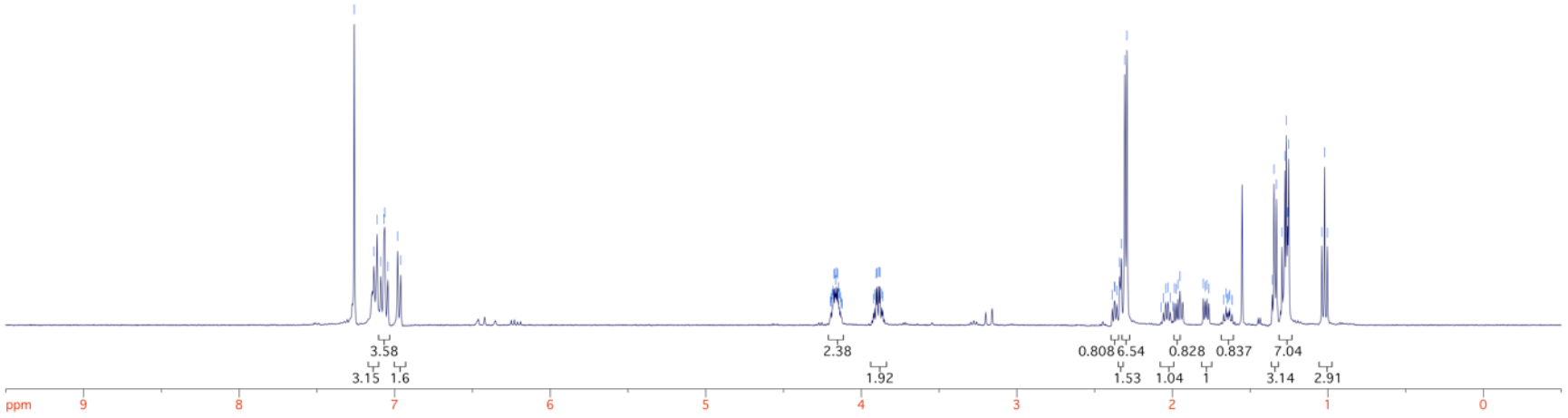
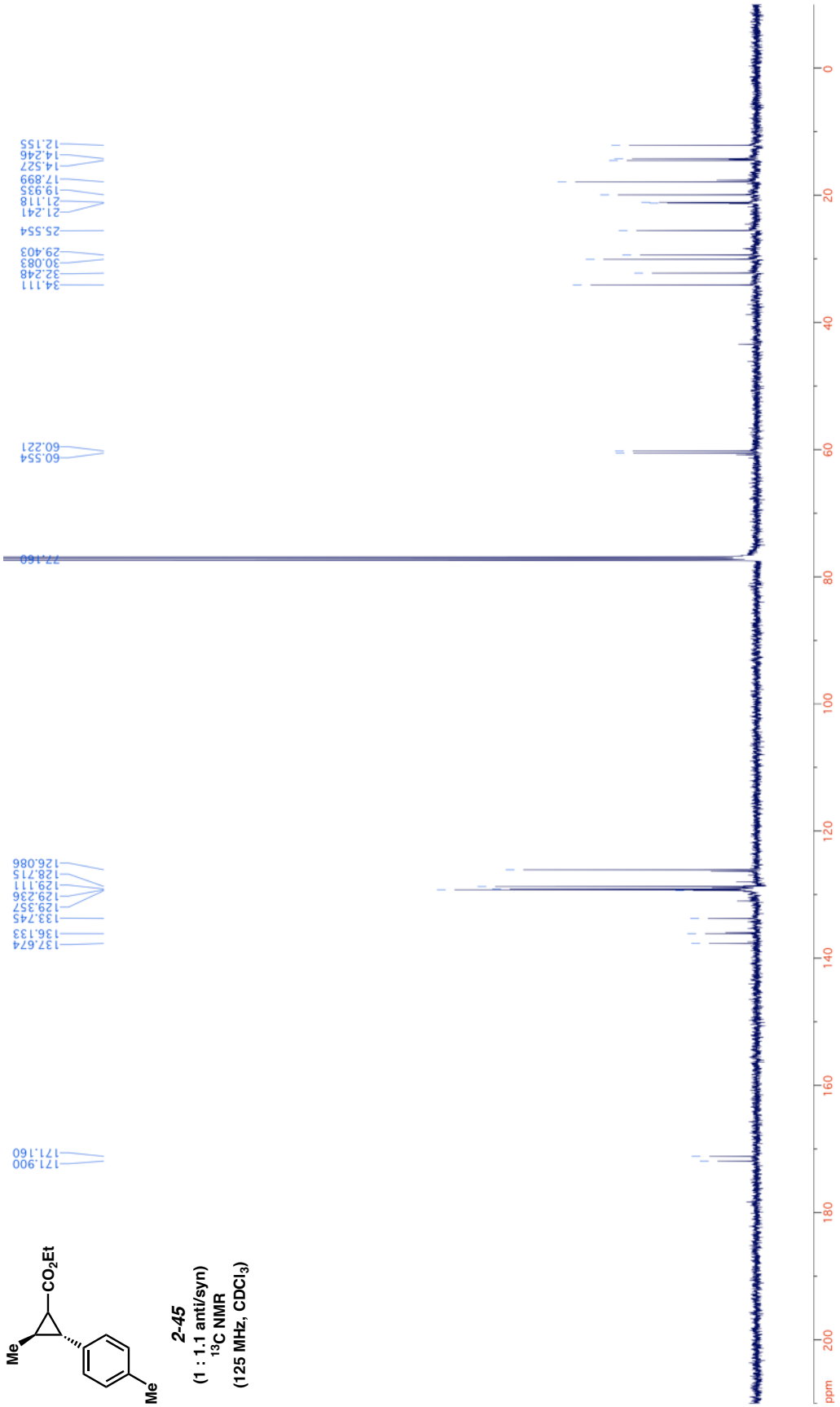
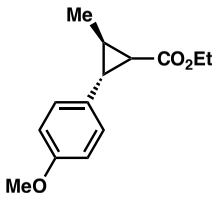
^{1}H NMR
(400 MHz, $CDCl_3$)

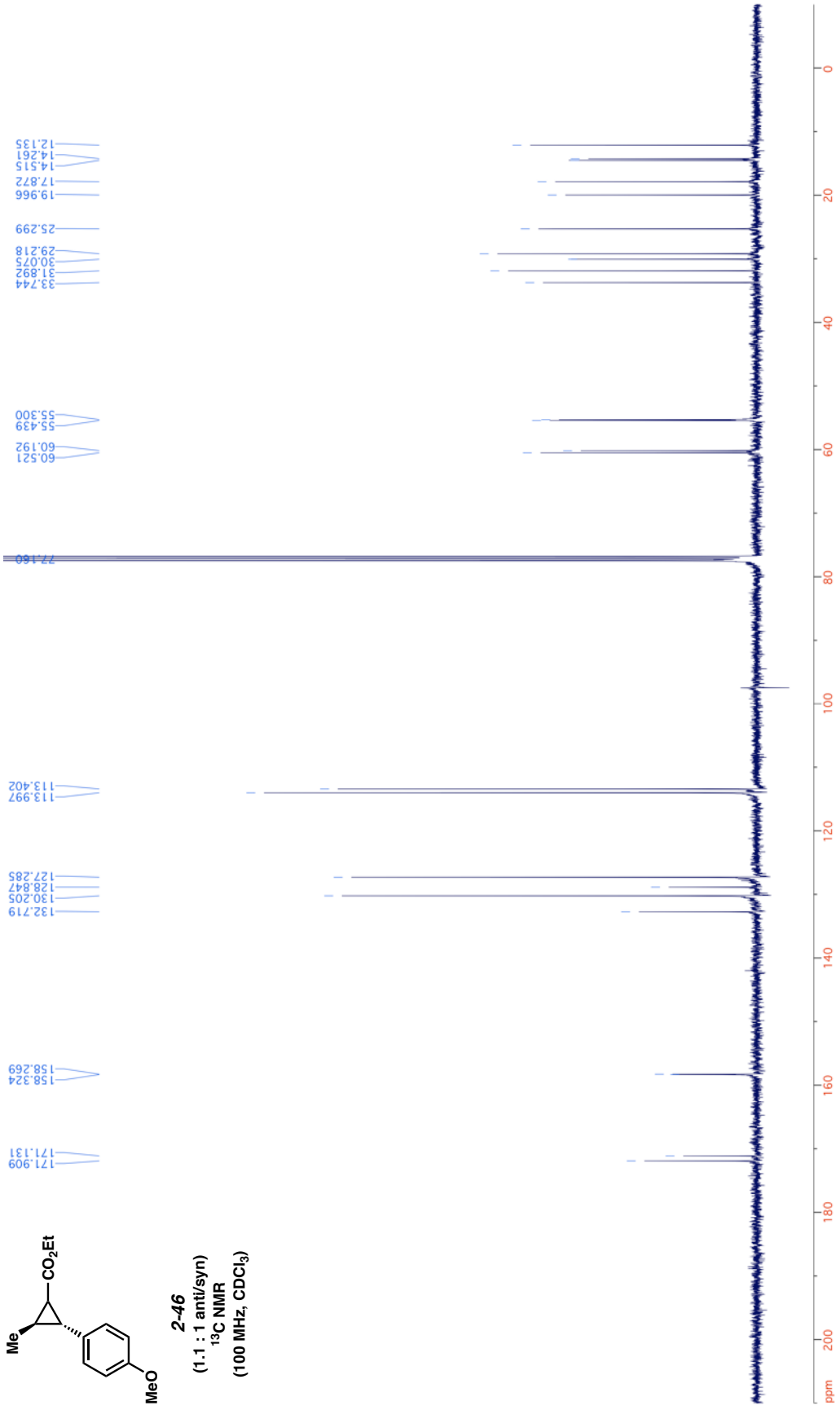




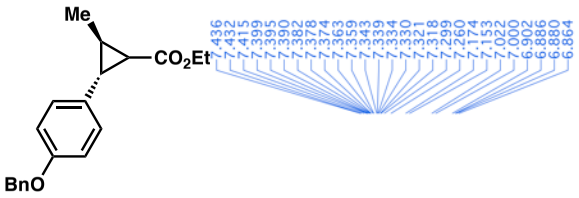

CO2Et
Me
Me
2-45
(1 : 1.1 anti/syn)
13C NMR
(125 MHz, CDCl3)
171.900
171.160
137.674
136.133
133.745
129.357
129.236
129.111
128.715
126.086
77.160
60.554
60.221
34.111
32.248
30.083
29.403
25.554
21.241
21.118
19.935
17.899
14.527
14.246
12.155
0
20
40
60
80
100
120
140
160
180
200
ppm



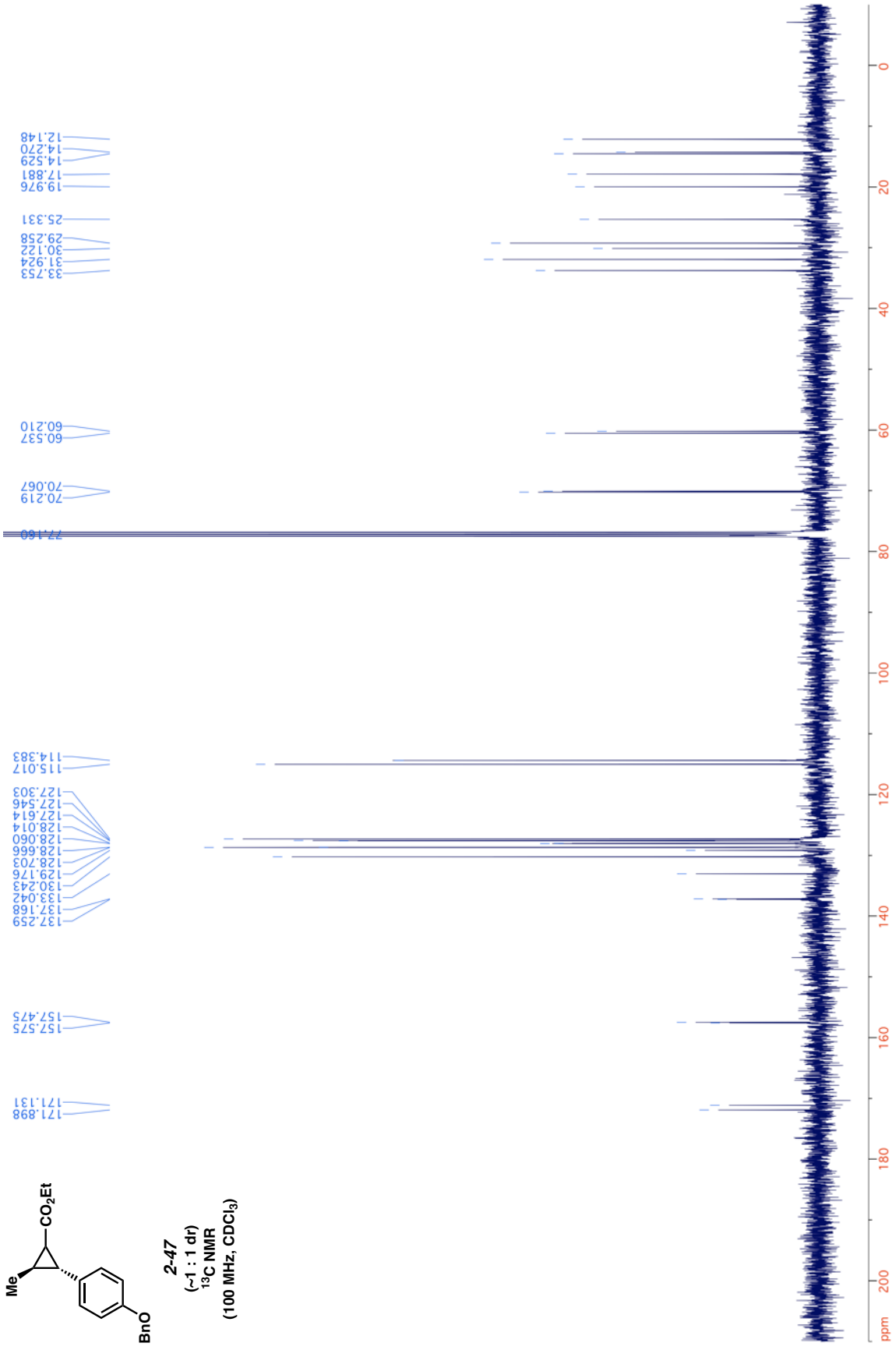
2-46
(1.1 : 1 anti/syn)
^{1}H NMR
(400 MHz, $CDCl_3$)

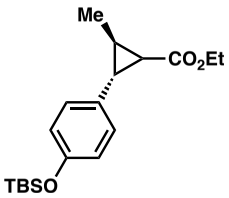


2-46
(1.1 : 1 anti/syn)
^{13}C NMR
(100 MHz, $CDCl_3$)

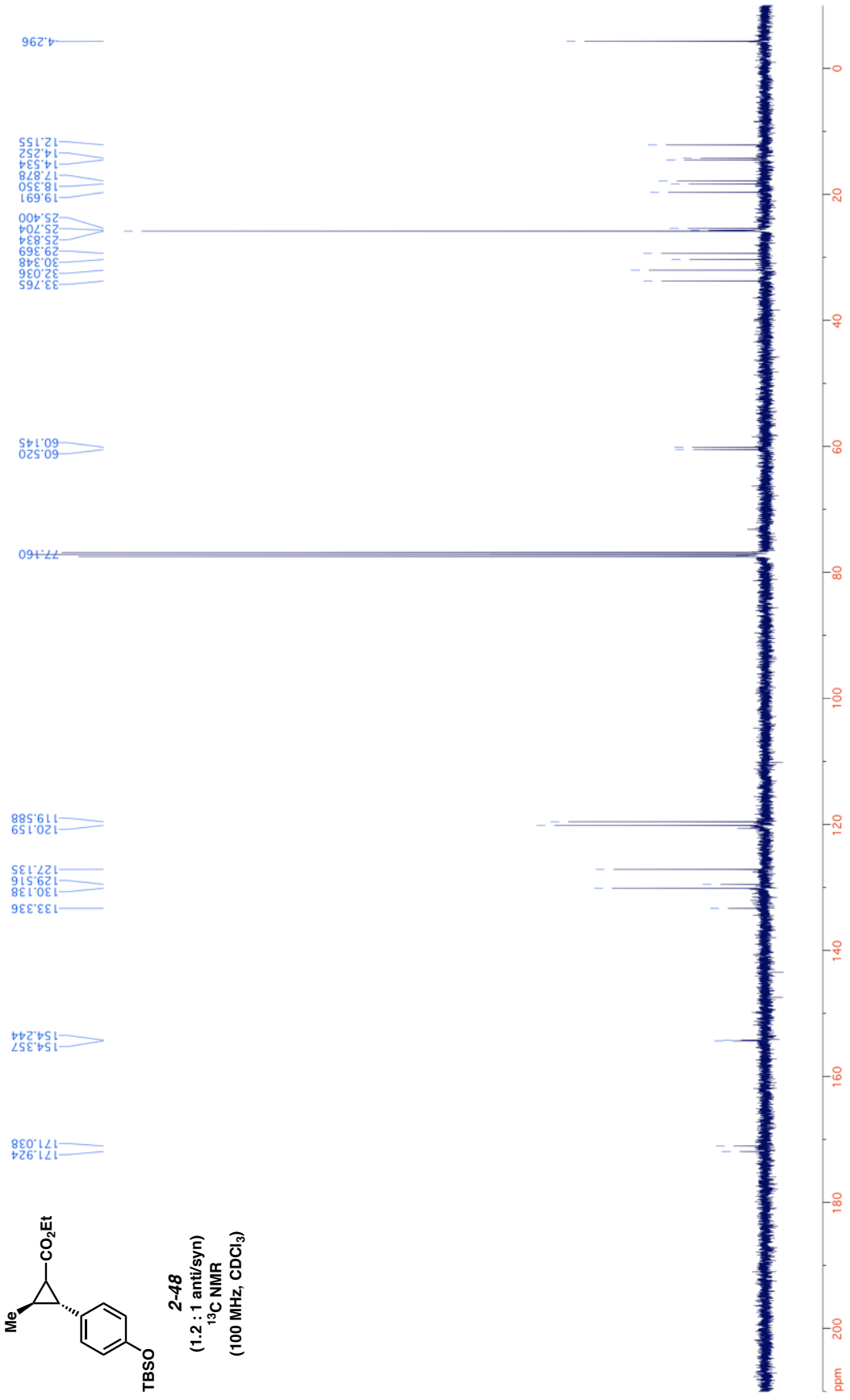


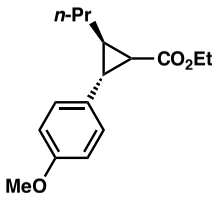
2-47
(~1 : 1 dr)
^{1}H NMR
(400 MHz, $CDCl_3$)


Me
CO2Et
BnO
2-47
(~1 : 1 dr)
13C NMR
(100 MHz, CDCl3)
171.898
171.131
157.575
157.475
137.259
137.168
133.042
130.243
129.176
128.703
128.666
128.060
128.014
127.614
127.546
127.303
115.017
114.383
77.160
70.219
70.067
60.537
60.210
33.753
31.924
30.122
29.258
25.331
19.976
17.881
14.529
14.270
12.148
ppm

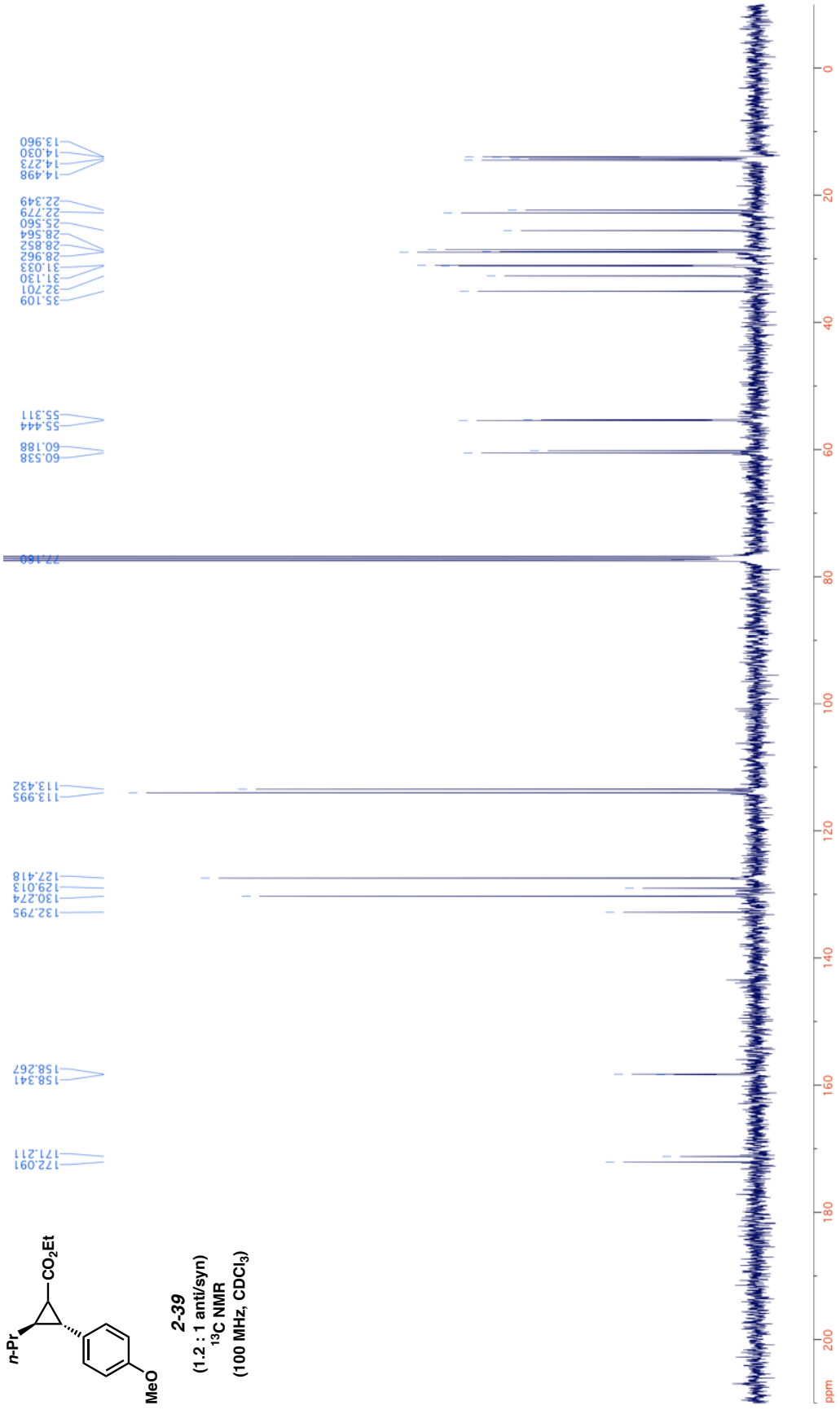


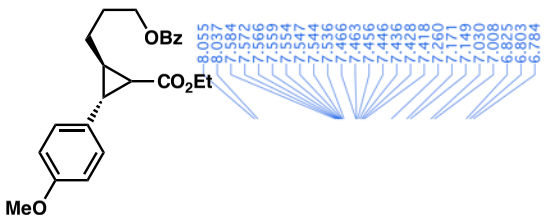
2-48
(1.2 : 1 anti/syn)
^{1}H NMR
(400 MHz, $CDCl_3$)


4.296
12.155
14.252
14.534
17.878
18.350
19.691
25.400
25.704
25.834
29.369
30.348
32.036
33.765
60.520
60.145
77.160
119.588
120.159
127.135
129.516
130.138
133.336
154.357
154.244
171.038
171.924
Me
CO2Et
TBSO
2-48
(1.2 : 1 anti/syn)
13C NMR
(100 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm

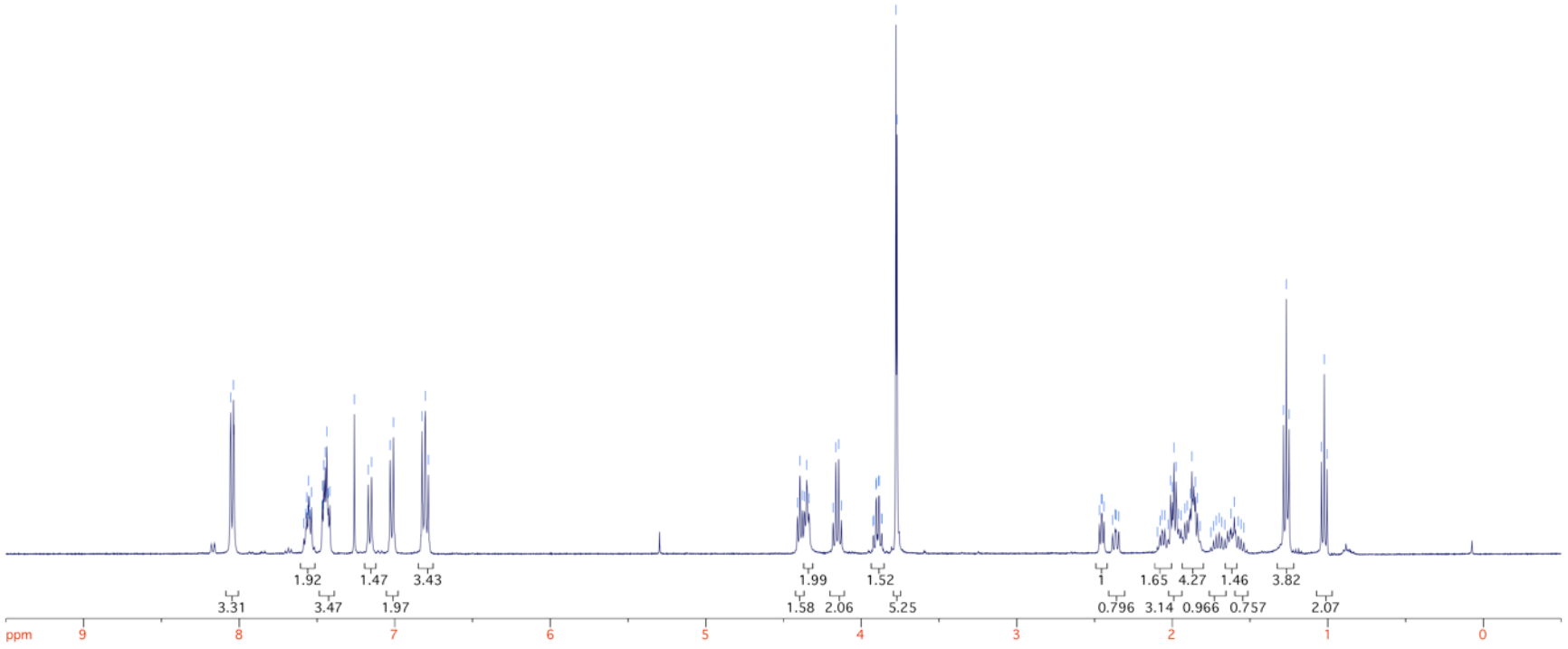


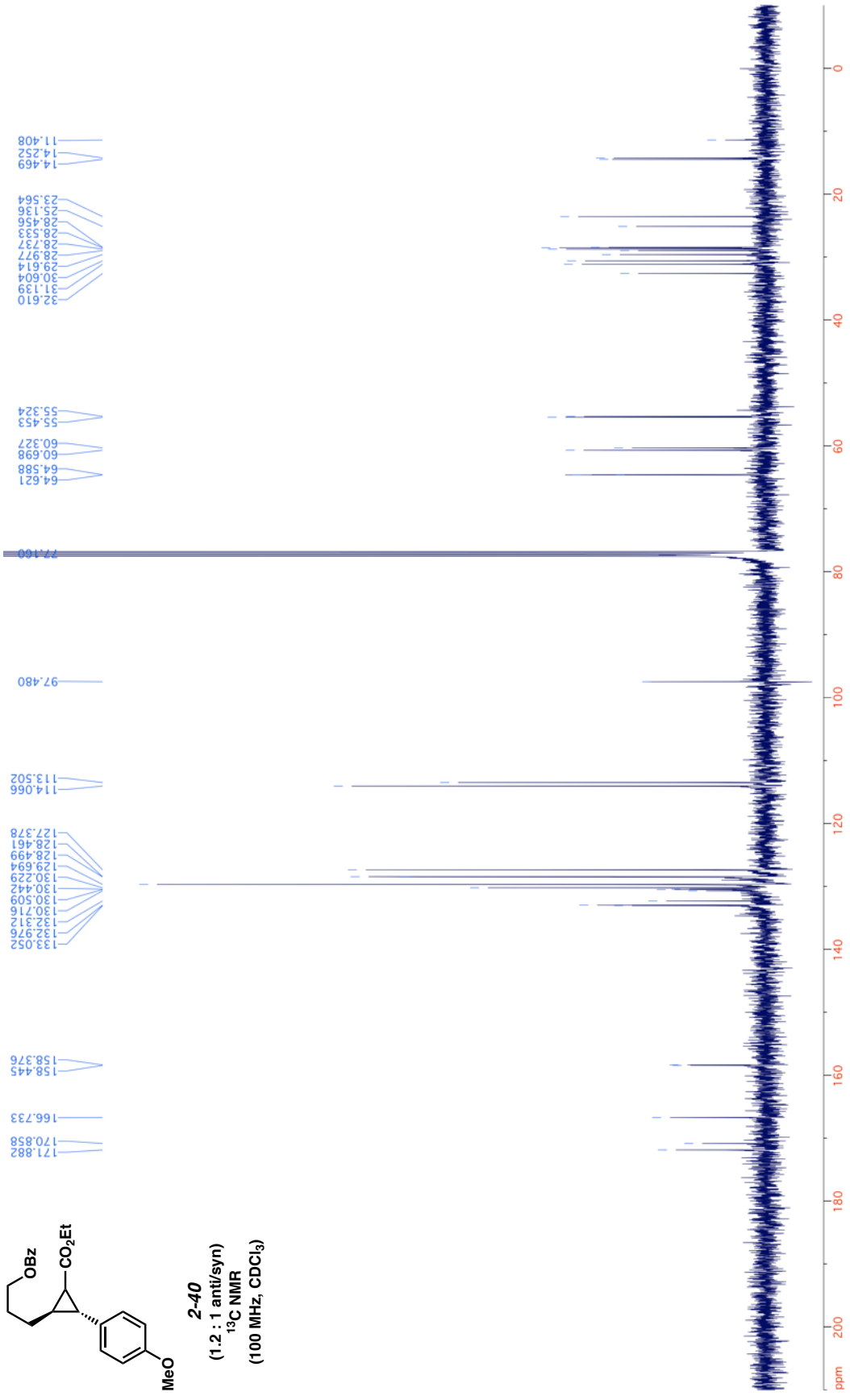
2-39
(1.2 : 1 anti/syn)
^{1}H NMR
(400 MHz, $CDCl_3$)

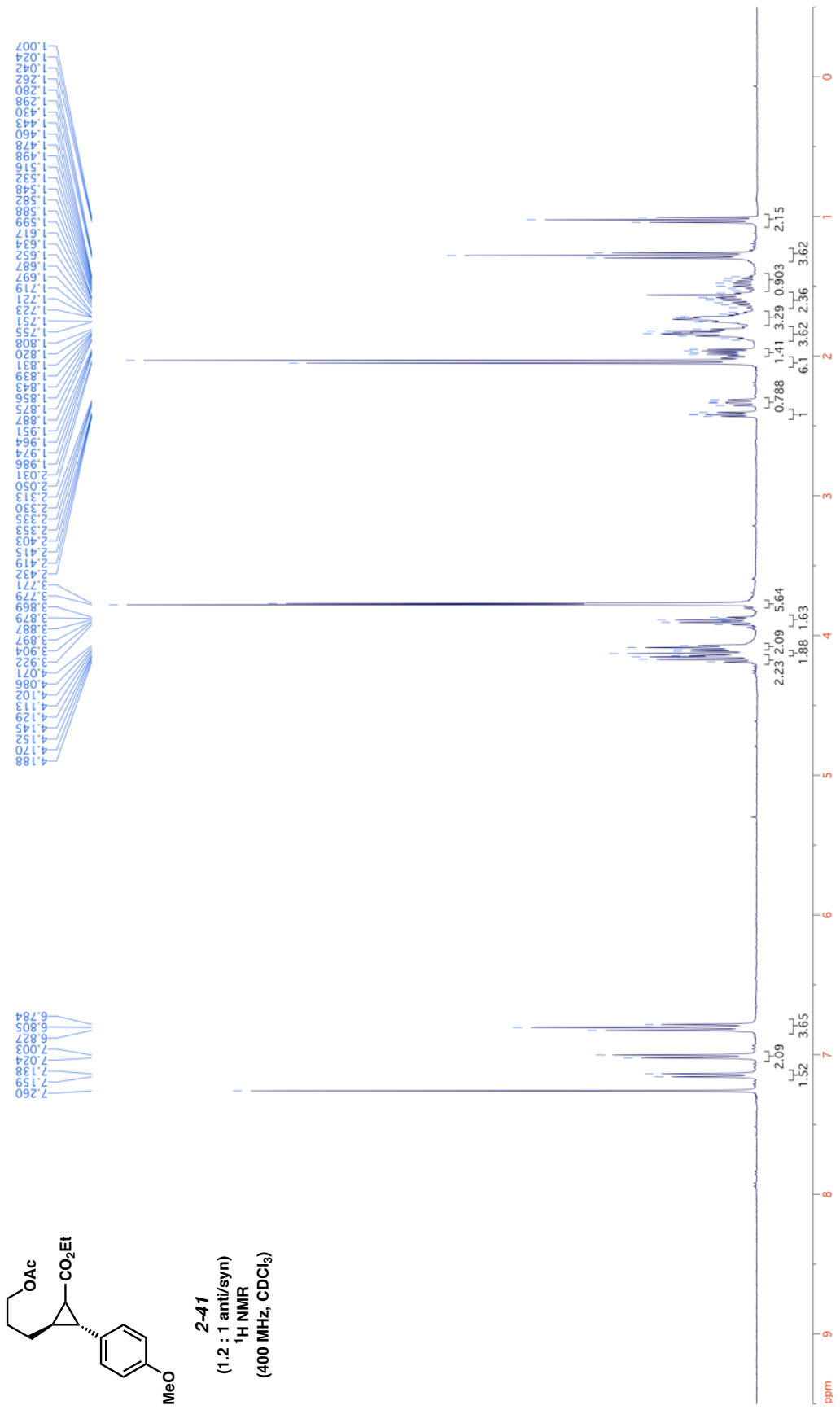

13.960
14.030
14.273
14.498
22.349
22.779
25.560
28.564
28.852
28.962
31.033
31.130
32.701
35.109
55.311
55.444
60.188
60.538
77.160
113.432
113.995
127.418
129.013
130.274
132.795
158.267
158.341
171.211
172.091
0
20
40
60
80
100
120
140
160
180
200
ppm
CO2Et
n-Pr
MeO
2-39
(1.2 : 1 anti/syn)
13C NMR
(100 MHz, CDCl3)

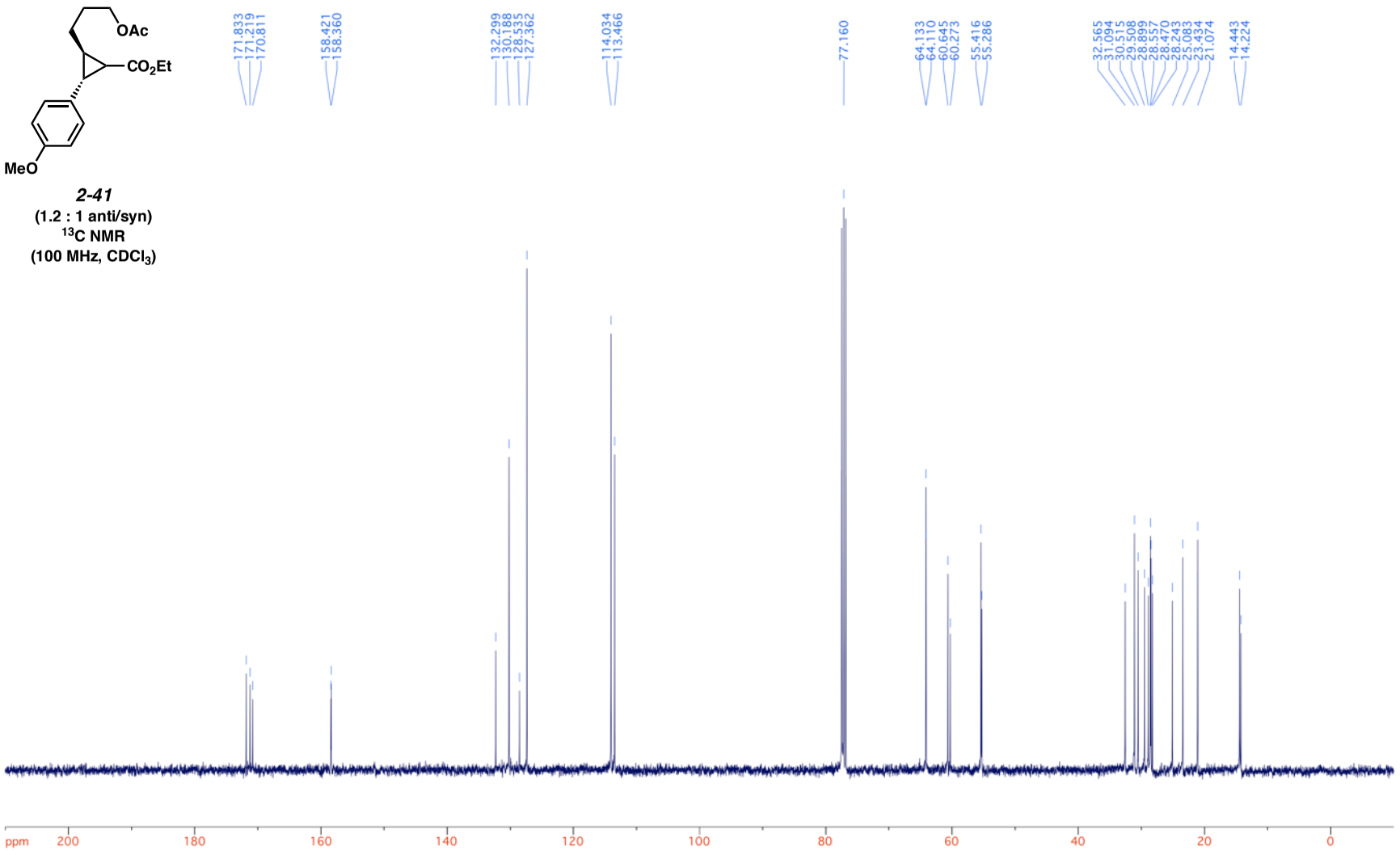


2-40
(1.2 : 1 anti/syn)
^{1}H NMR
(400 MHz, $CDCl_3$)

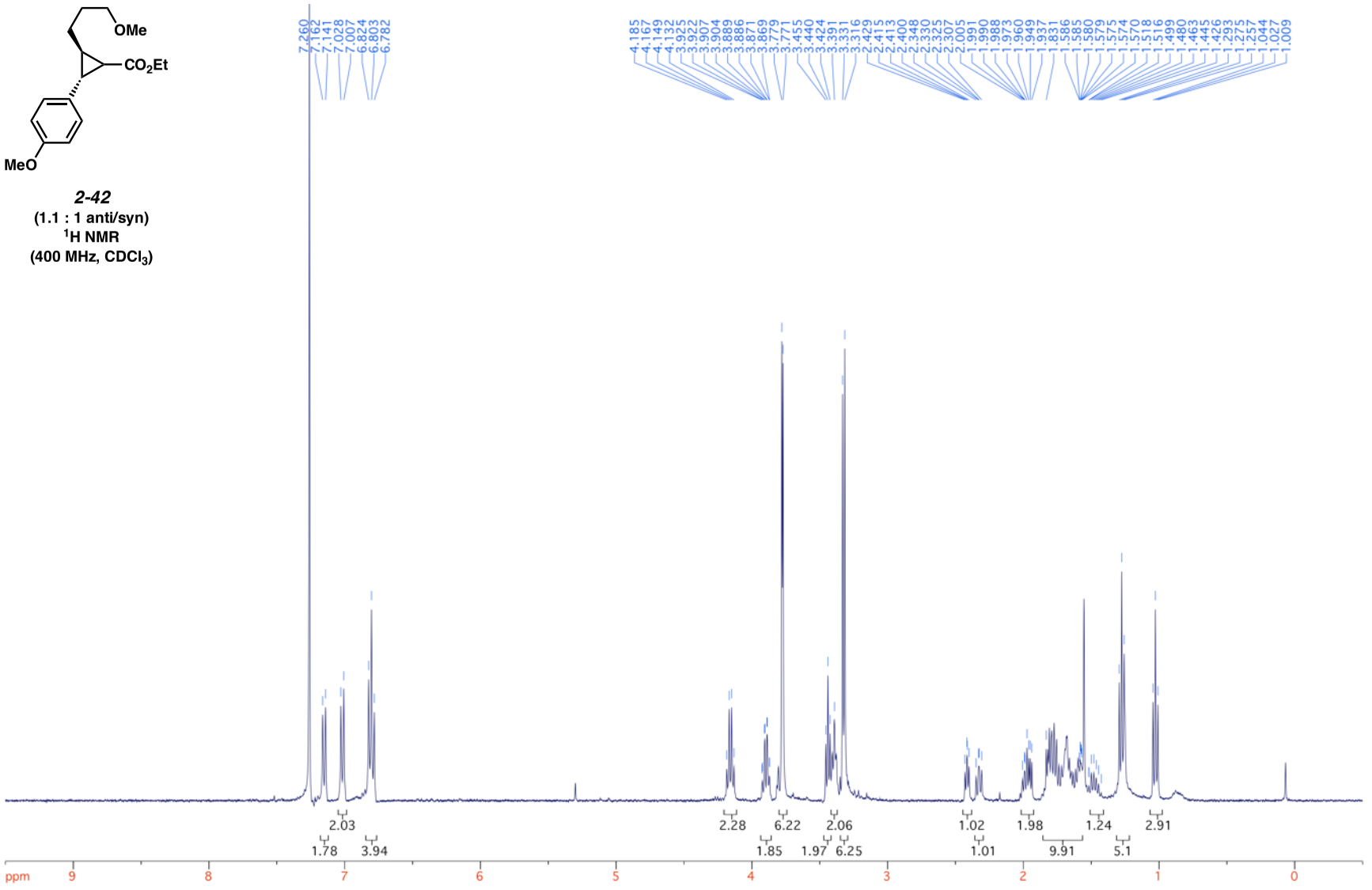


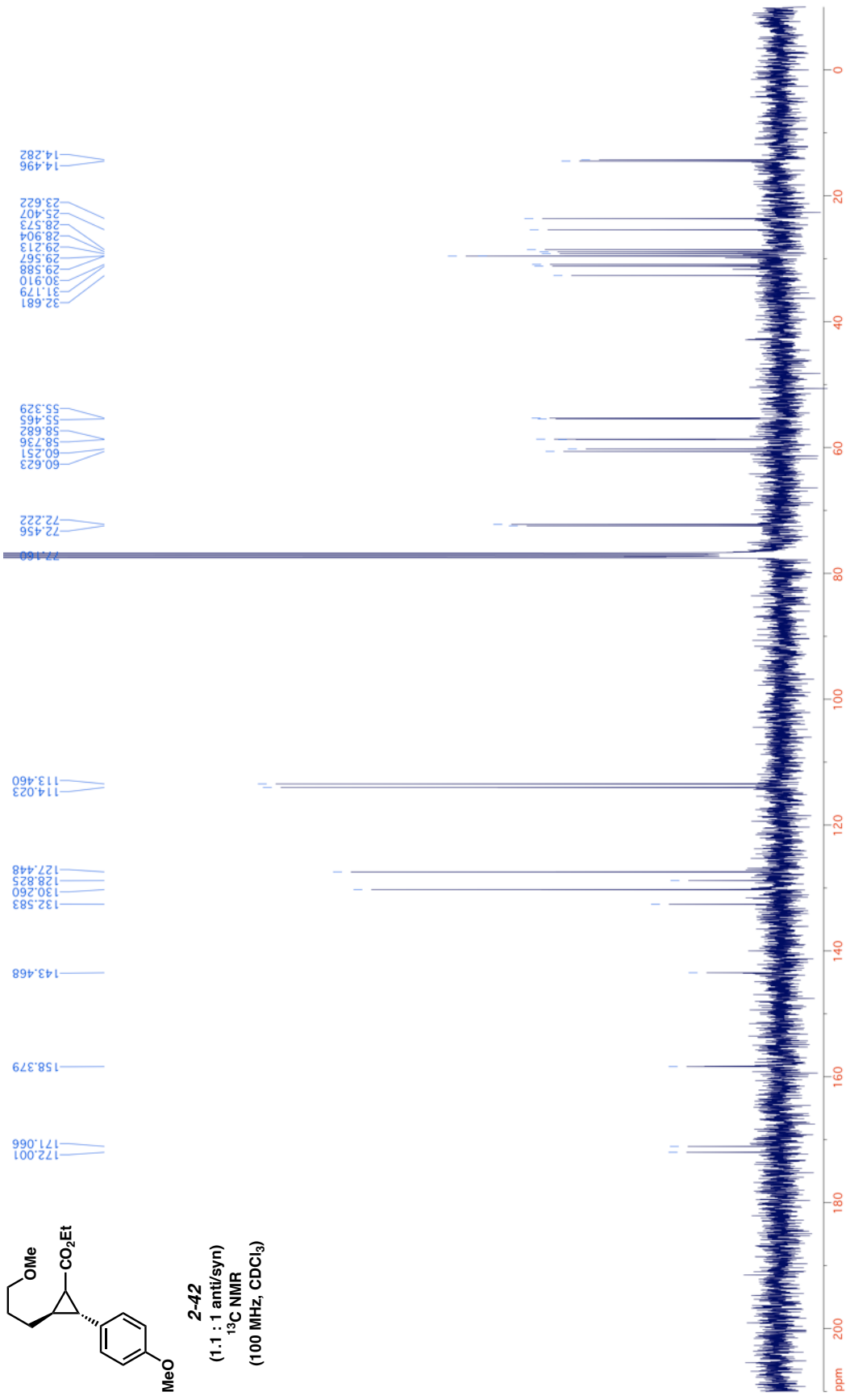

OBz
CO2Et
MeO
2-40
(1.2 : 1 anti/syn)
13C NMR
(100 MHz, CDCl3)
11.408
14.252
14.469
23.564
25.136
28.456
28.533
28.737
28.977
29.614
30.604
31.139
32.610
55.324
55.453
60.327
60.698
64.588
64.621
77.160
97.480
113.502
114.066
127.378
128.461
128.499
129.694
130.229
130.442
130.509
130.716
132.312
132.976
133.052
158.445
158.376
166.733
170.858
171.882
0
20
40
60
80
100
120
140
160
180
200
ppm

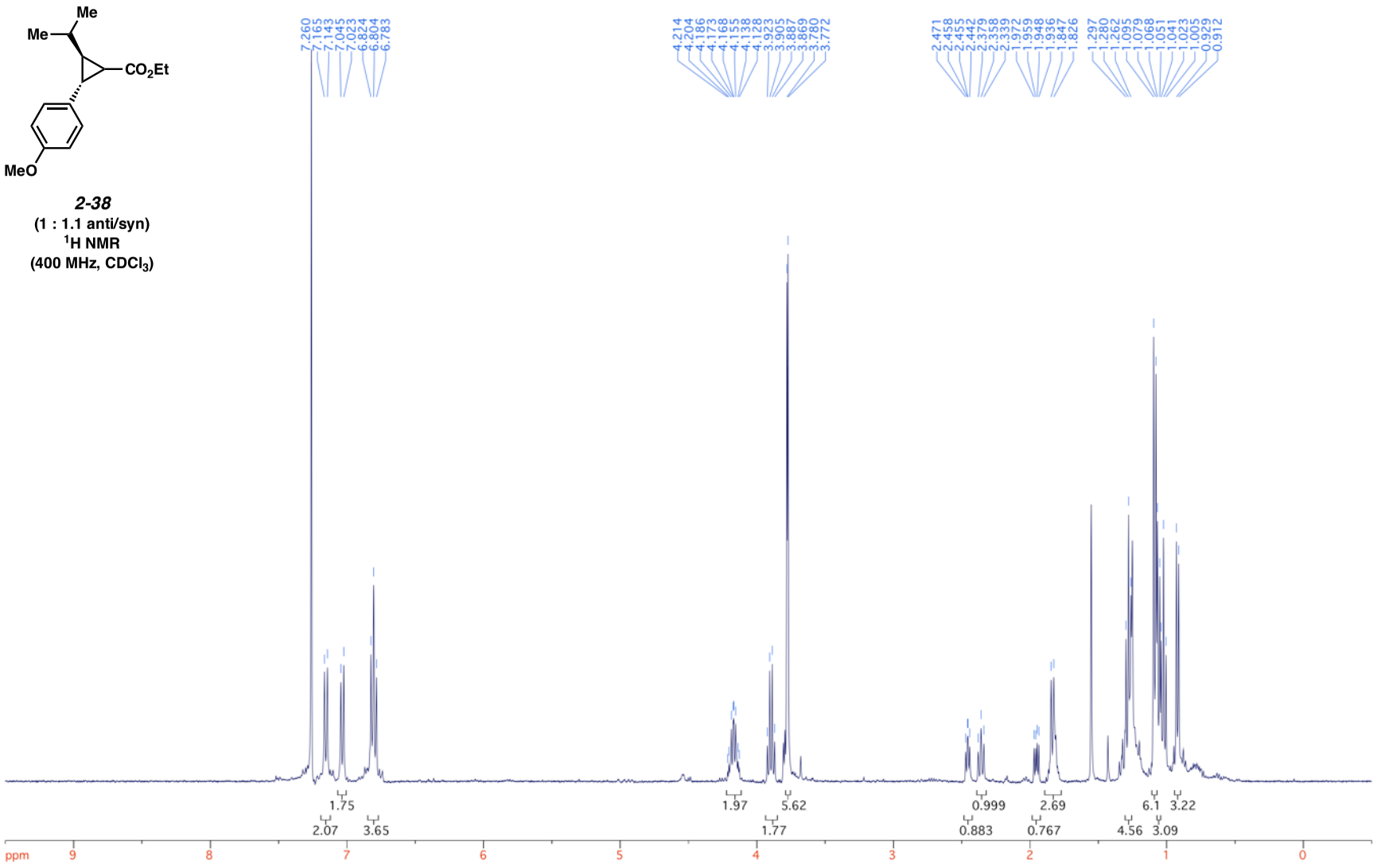

OAc
CO2Et
MeO
2-41
(1.2 : 1 anti/syn)
1H NMR
(400 MHz, CDCl3)
ppm

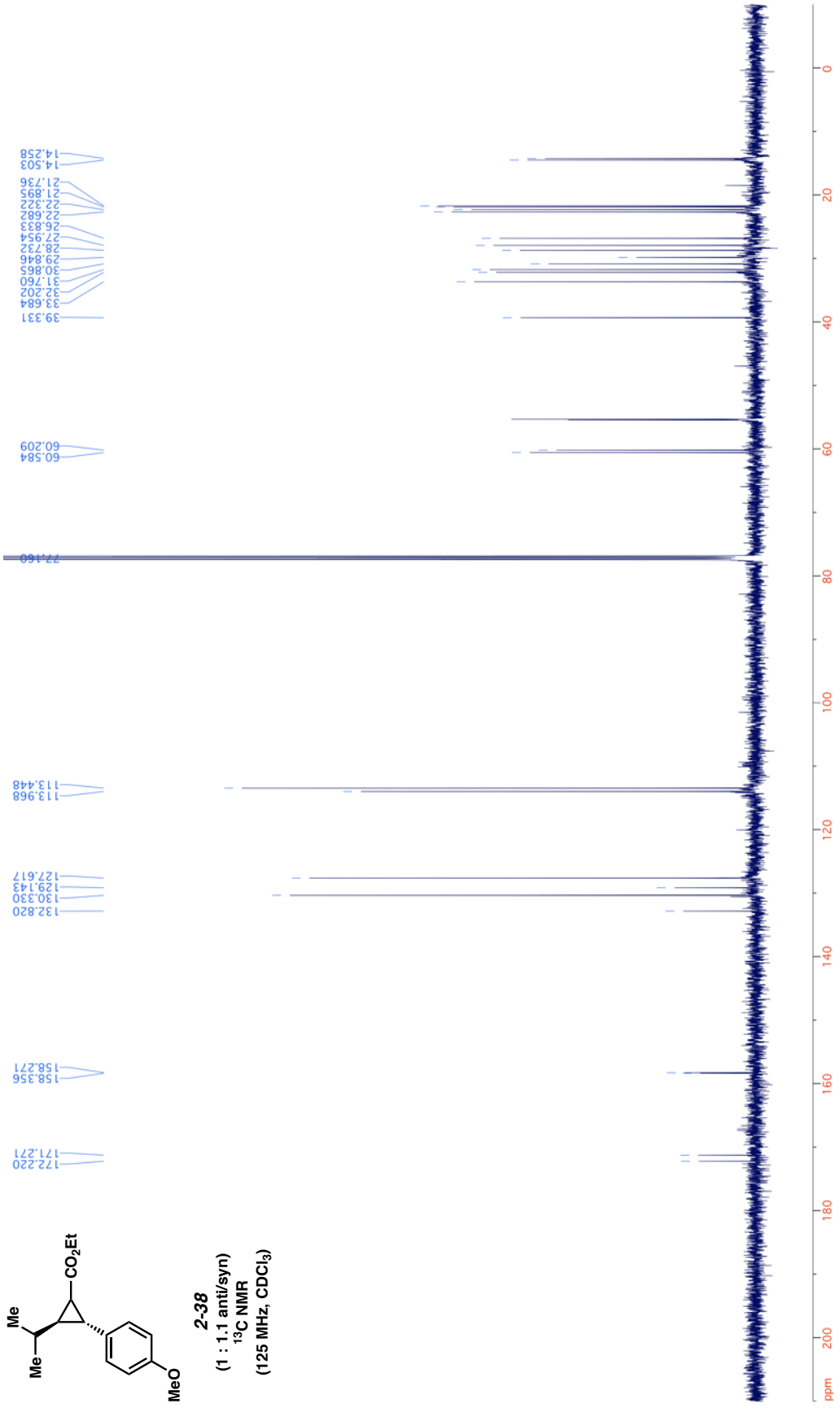


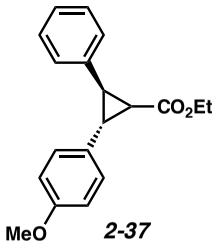
2-41
(1.2 : 1 anti/syn)
^{13}C NMR
(100 MHz, $CDCl_3$)


OMe
CO2Et
MeO
2-42
(1.1 : 1 anti/syn)
1H NMR
(400 MHz, CDCl3)
7.260
7.162
7.141
7.028
7.007
6.824
6.803
6.782
4.185
4.167
4.149
4.132
3.925
3.922
3.907
3.904
3.889
3.886
3.871
3.869
3.779
3.771
3.455
3.440
3.424
3.391
3.331
3.316
2.429
2.415
2.413
2.400
2.348
2.330
2.325
2.307
2.005
1.991
1.990
1.988
1.973
1.960
1.949
1.937
1.831
1.586
1.585
1.580
1.579
1.575
1.574
1.570
1.518
1.516
1.499
1.480
1.463
1.445
1.426
1.293
1.275
1.257
1.044
1.027
1.009
2.03
1.78
3.94
2.28
6.22
1.85
2.06
1.97
6.25
1.02
1.01
1.98
9.91
1.24
5.1
2.91
ppm
9
8
7
6
5
4
3
2
1
0


14.282
14.496
23.622
25.407
28.573
28.904
29.213
29.567
29.588
30.910
31.179
32.681
55.329
55.465
58.682
58.736
60.251
60.623
72.222
72.456
77.160
113.460
114.023
127.448
128.825
130.260
132.583
143.468
158.379
171.066
172.001
OMe
CO2Et
MeO
2-42
(1.1 : 1 anti/syn)
13C NMR
(100 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm


Me
Me
CO2Et
MeO
2-38
(1 : 1.1 anti/syn)
1H NMR
(400 MHz, CDCl3)
7.260
7.165
7.143
7.045
7.023
6.824
6.804
6.783
4.214
4.204
4.186
4.173
4.168
4.155
4.138
4.128
3.923
3.905
3.887
3.869
3.780
3.772
2.471
2.458
2.455
2.442
2.379
2.358
2.339
1.972
1.959
1.948
1.936
1.847
1.826
1.297
1.280
1.262
1.095
1.079
1.068
1.051
1.041
1.023
1.005
0.929
0.912
1.75
2.07
3.65
1.97
1.77
5.62
0.999
0.883
2.69
0.767
6.1
4.56
3.22
3.09
ppm
9
8
7
6
5
4
3
2
1
0


14.258
14.503
21.736
21.895
22.322
22.682
26.833
27.954
28.732
29.846
30.865
31.760
32.202
33.684
39.331
60.584
60.209
77.160
113.968
113.448
127.617
129.143
130.330
132.820
158.356
158.271
172.220
171.271
Me
Me
CO2Et
MeO
2-38
(1 : 1.1 anti/syn)
13C NMR
(125 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm

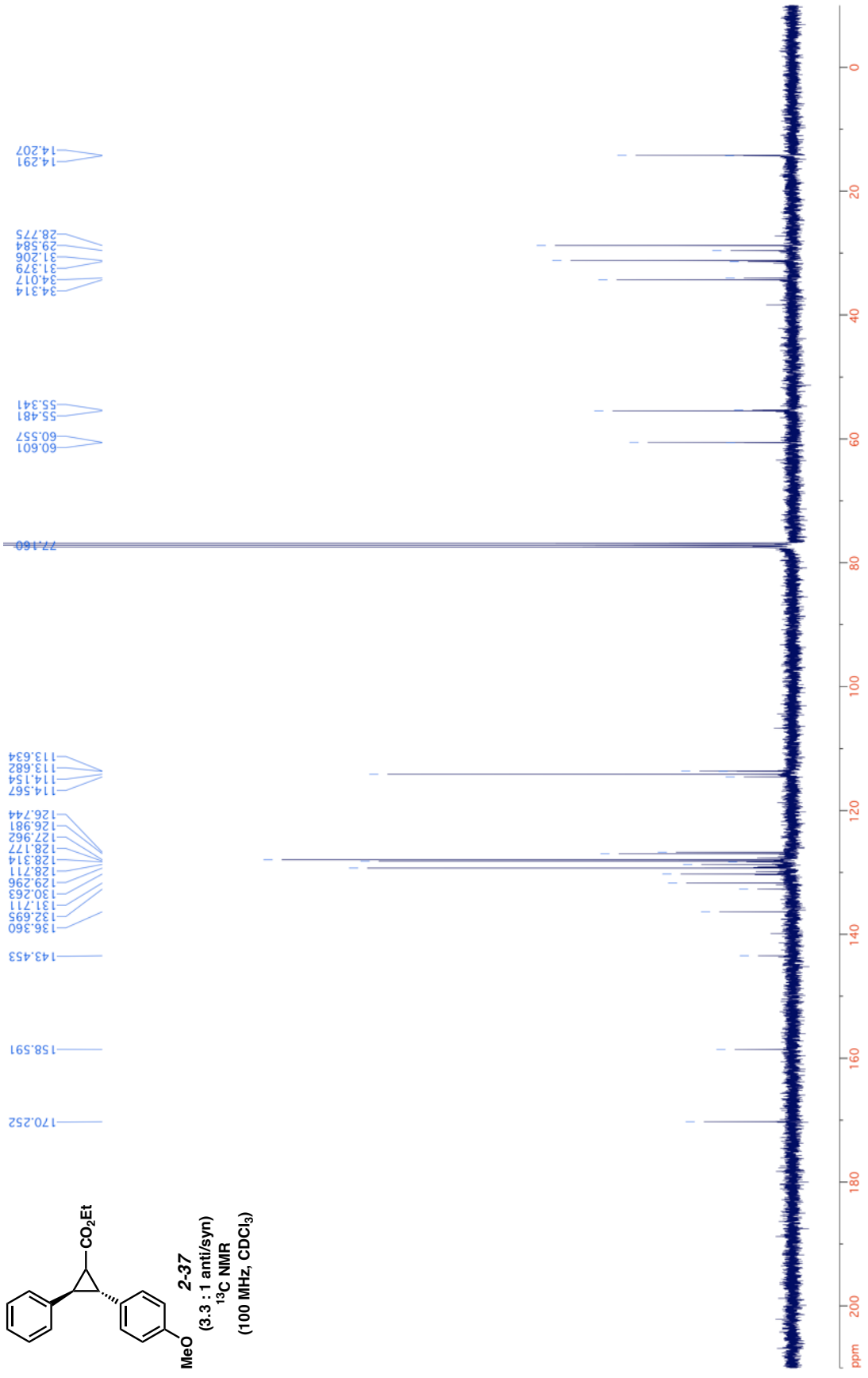


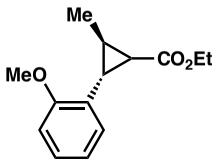
2-37

(3.3 : 1 anti/syn)

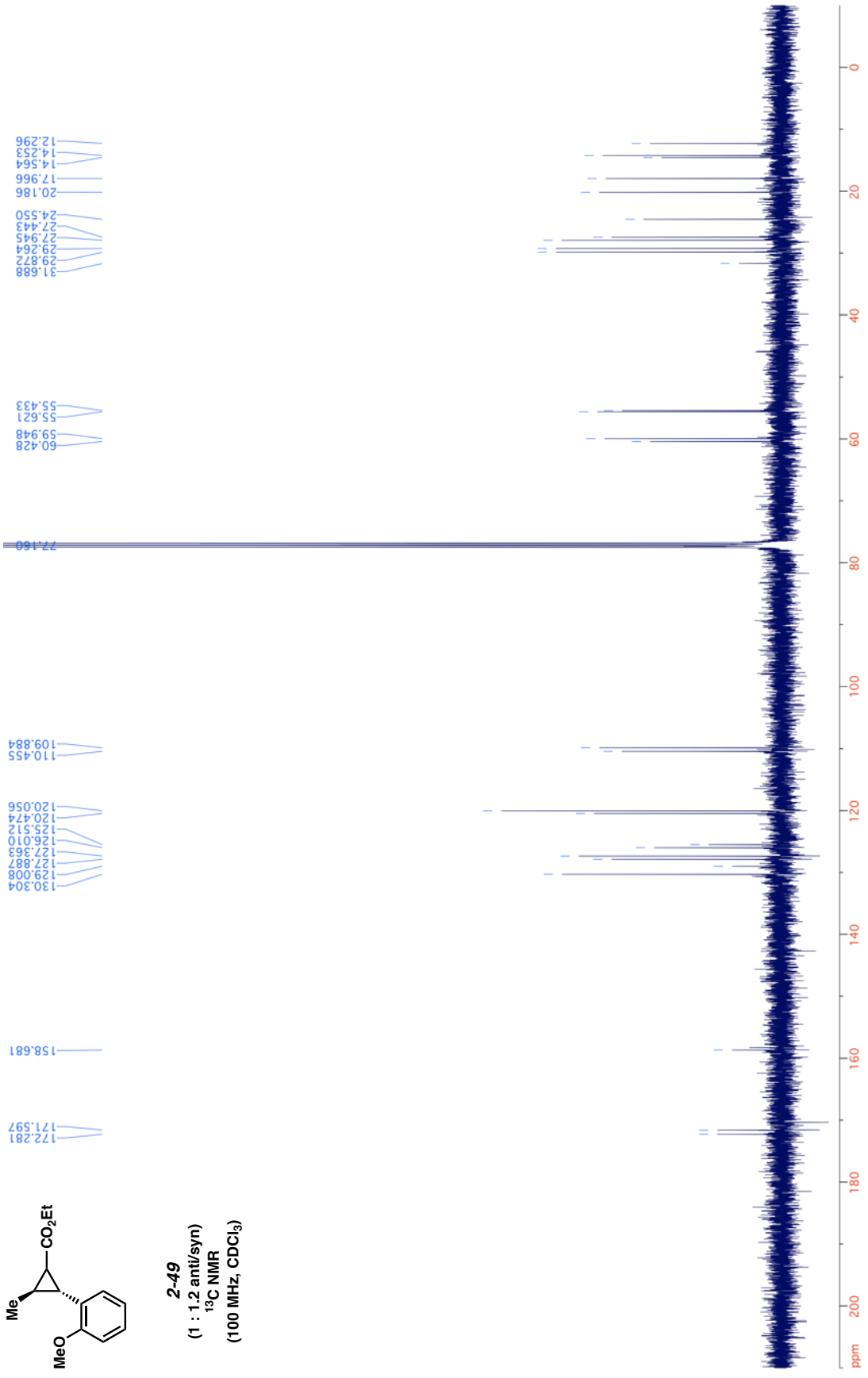
^{1}H NMR

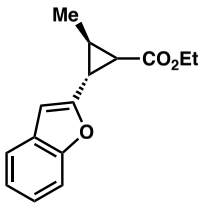
(400 MHz, $CDCl_3$)


14.291
14.207
28.775
29.584
31.206
31.379
34.017
34.314
55.481
55.341
60.601
60.557
77.160
113.634
113.682
114.154
114.567
126.744
126.981
127.962
128.177
128.314
128.711
129.296
130.263
131.711
132.695
136.360
143.453
158.591
170.252
0
20
40
60
80
100
120
140
160
180
200
ppm
CO2Et
MeO
2-37
(3.3 : 1 anti/syn)
13C NMR
(100 MHz, CDCl3)

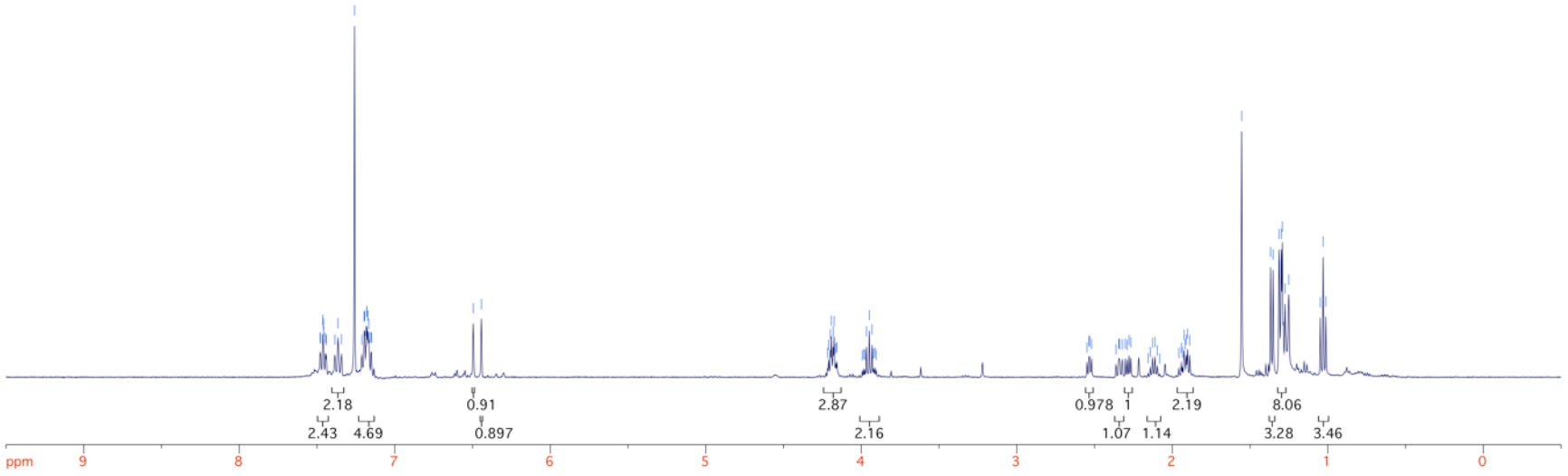


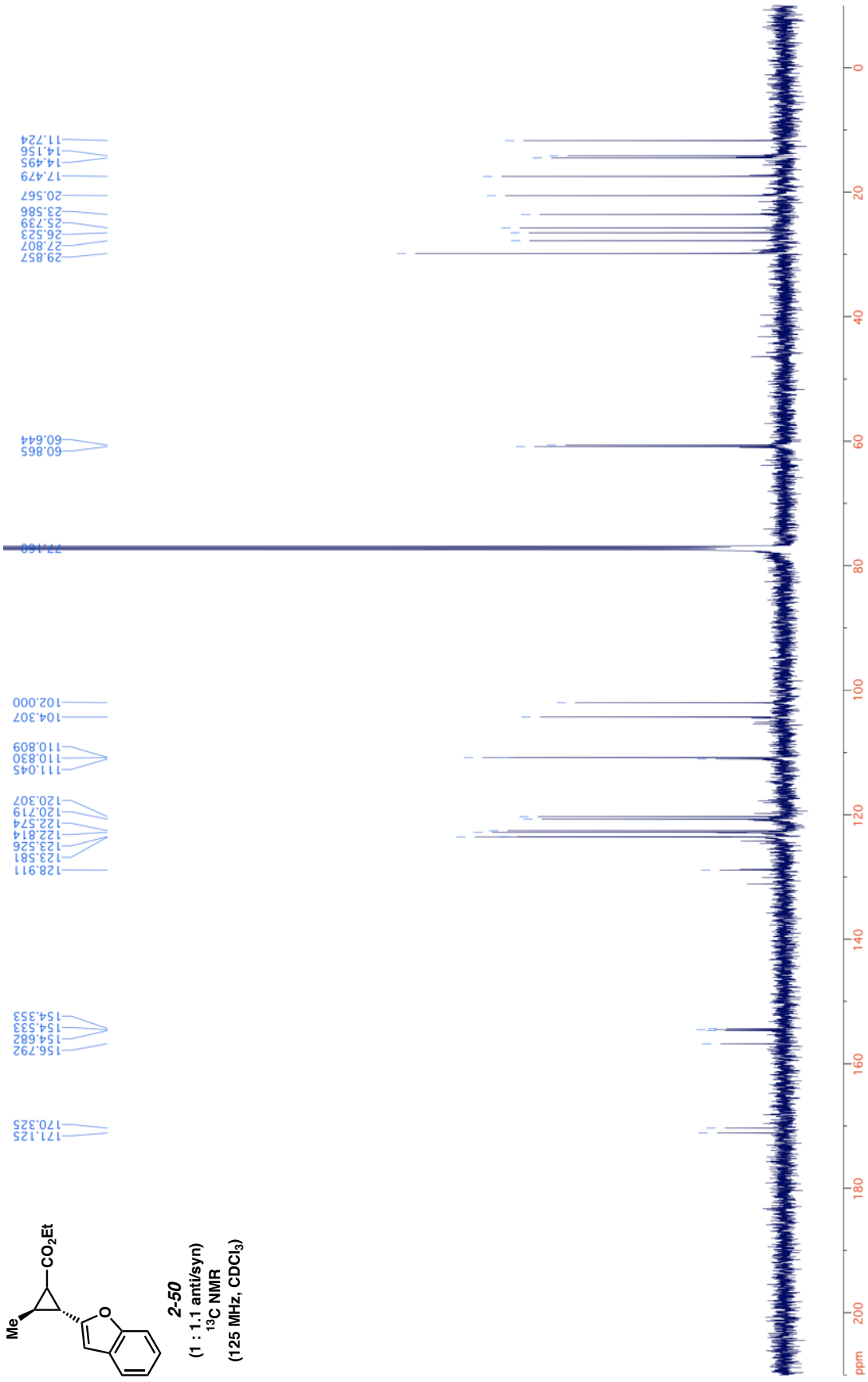
2-49
(1 : 1.2 anti/syn)
^{1}H NMR
(400 MHz, $CDCl_3$)

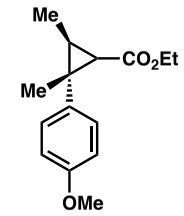

Me
CO2Et
MeO
2-49
(1 : 1.2 anti/syn)
13C NMR
(100 MHz, CDCl3)
172.281
171.597
158.681
130.304
129.008
127.887
127.363
126.010
125.512
120.474
120.056
110.455
109.884
77.160
60.428
59.948
55.621
55.433
31.688
29.872
29.264
27.945
27.443
24.550
20.186
17.966
14.564
14.253
12.296
0
20
40
60
80
100
120
140
160
180
200
ppm



2-50
(1 : 1.1 anti/syn)
^{1}H NMR
(400 MHz, $CDCl_3$)




Me
CO2Et
O
2-50
(1 : 1.1 anti/syn)
13C NMR
(125 MHz, CDCl3)
171.125
170.325
156.792
154.682
154.533
154.353
128.911
123.581
123.526
122.814
122.574
120.719
120.307
111.045
110.830
110.809
104.307
102.000
77.160
60.865
60.644
29.857
27.807
26.523
25.739
23.586
20.567
17.479
14.495
14.156
11.724
ppm
0
20
40
60
80
100
120
140
160
180
200

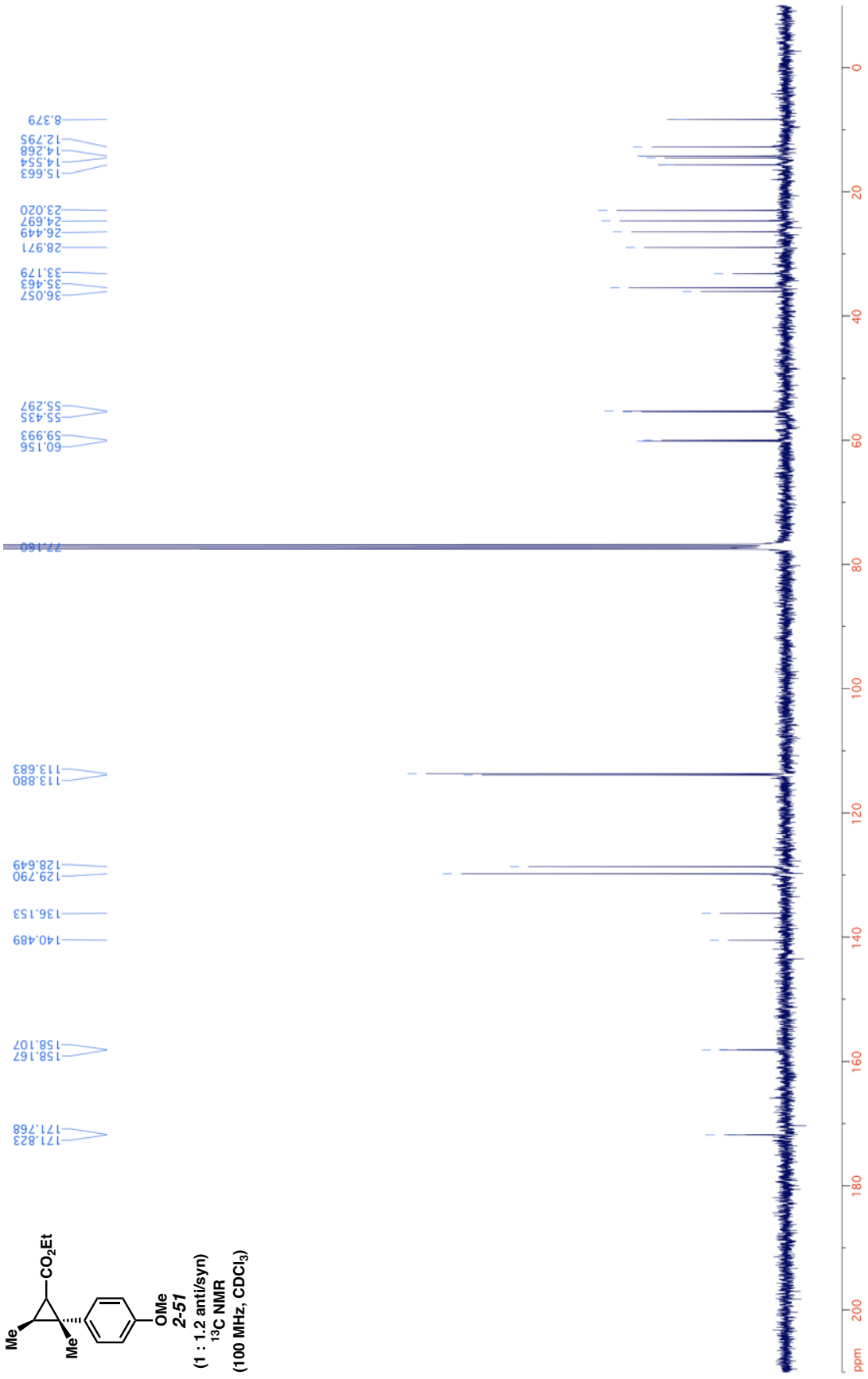


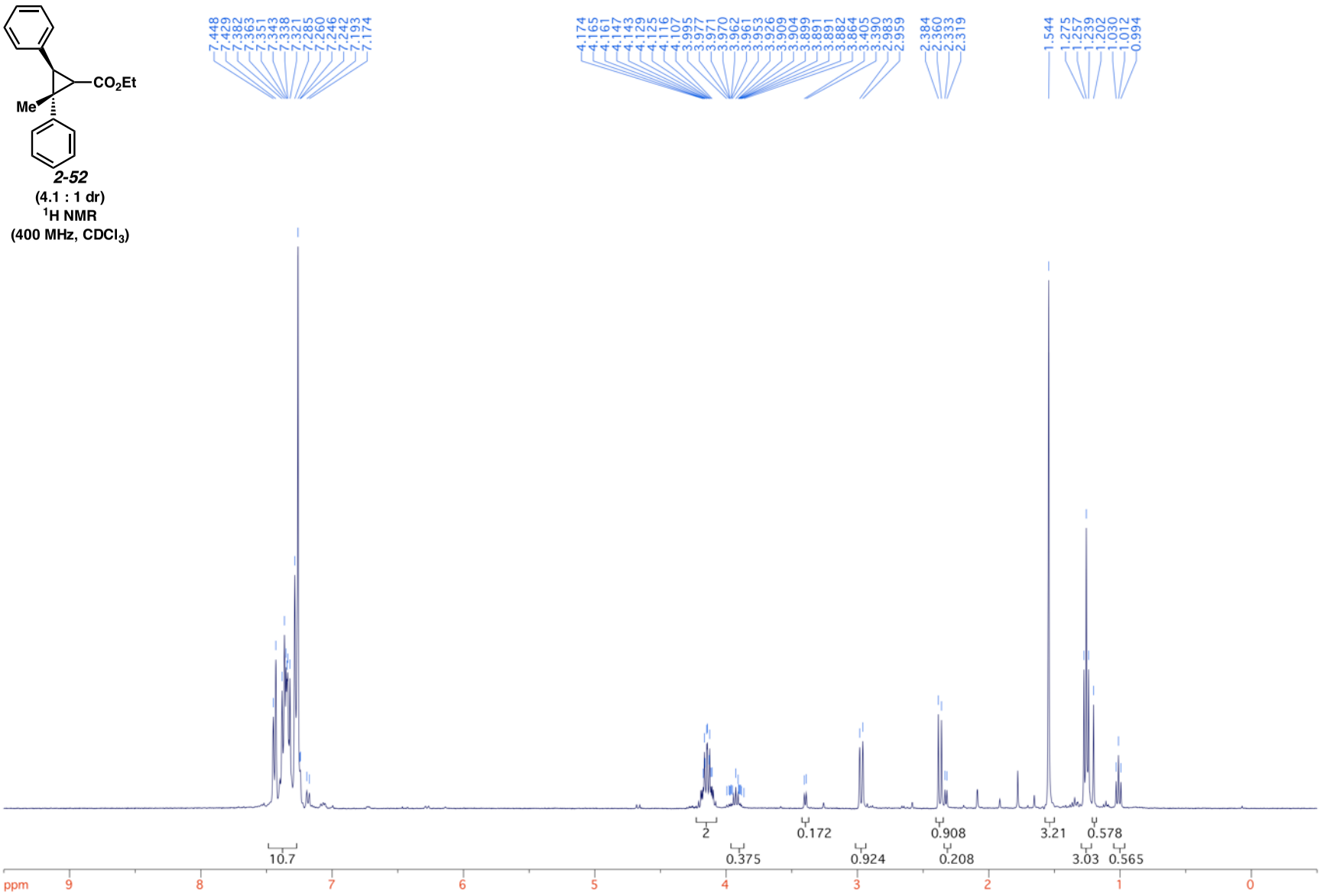
2-51

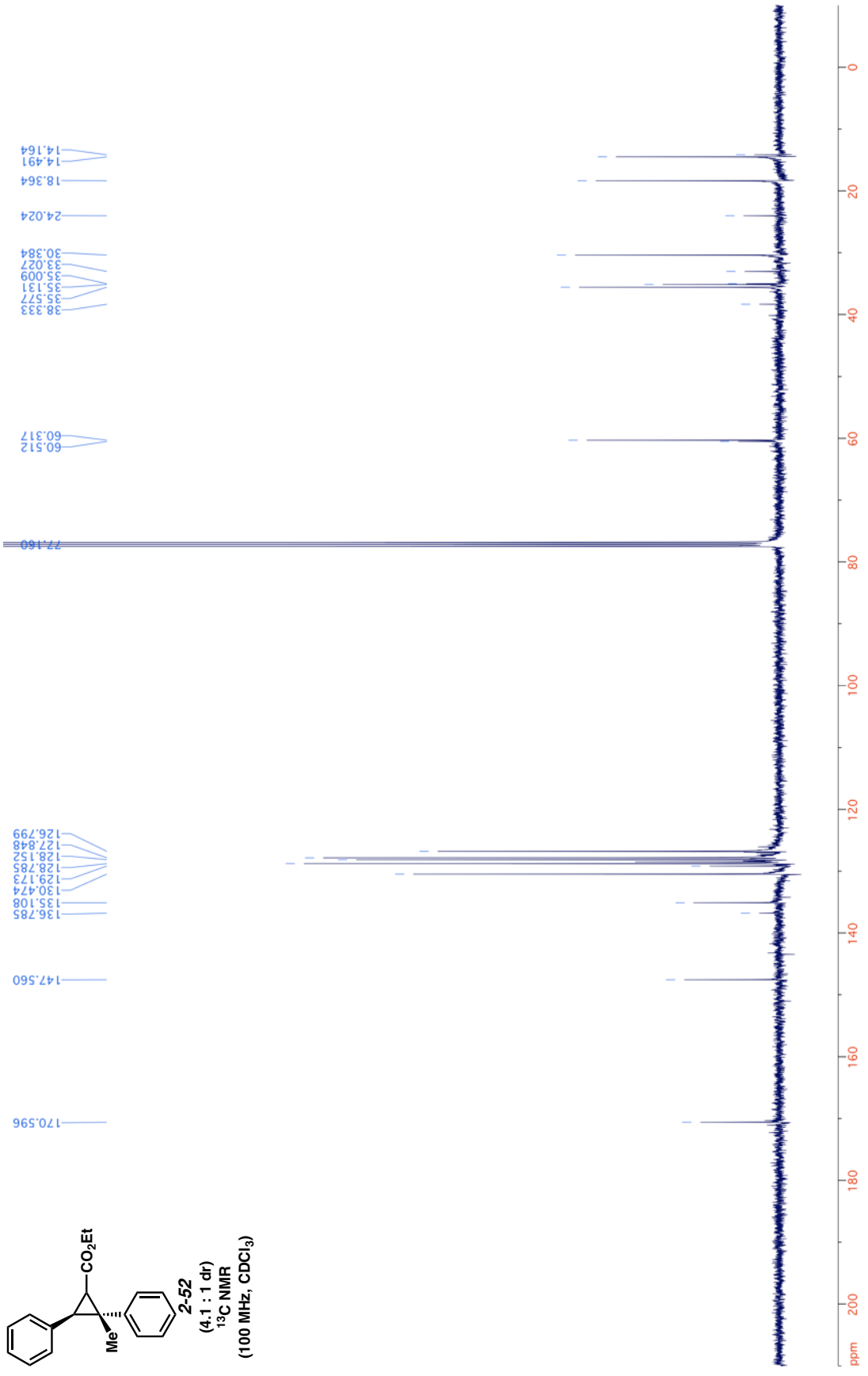
(1 : 1.2 anti/syn)

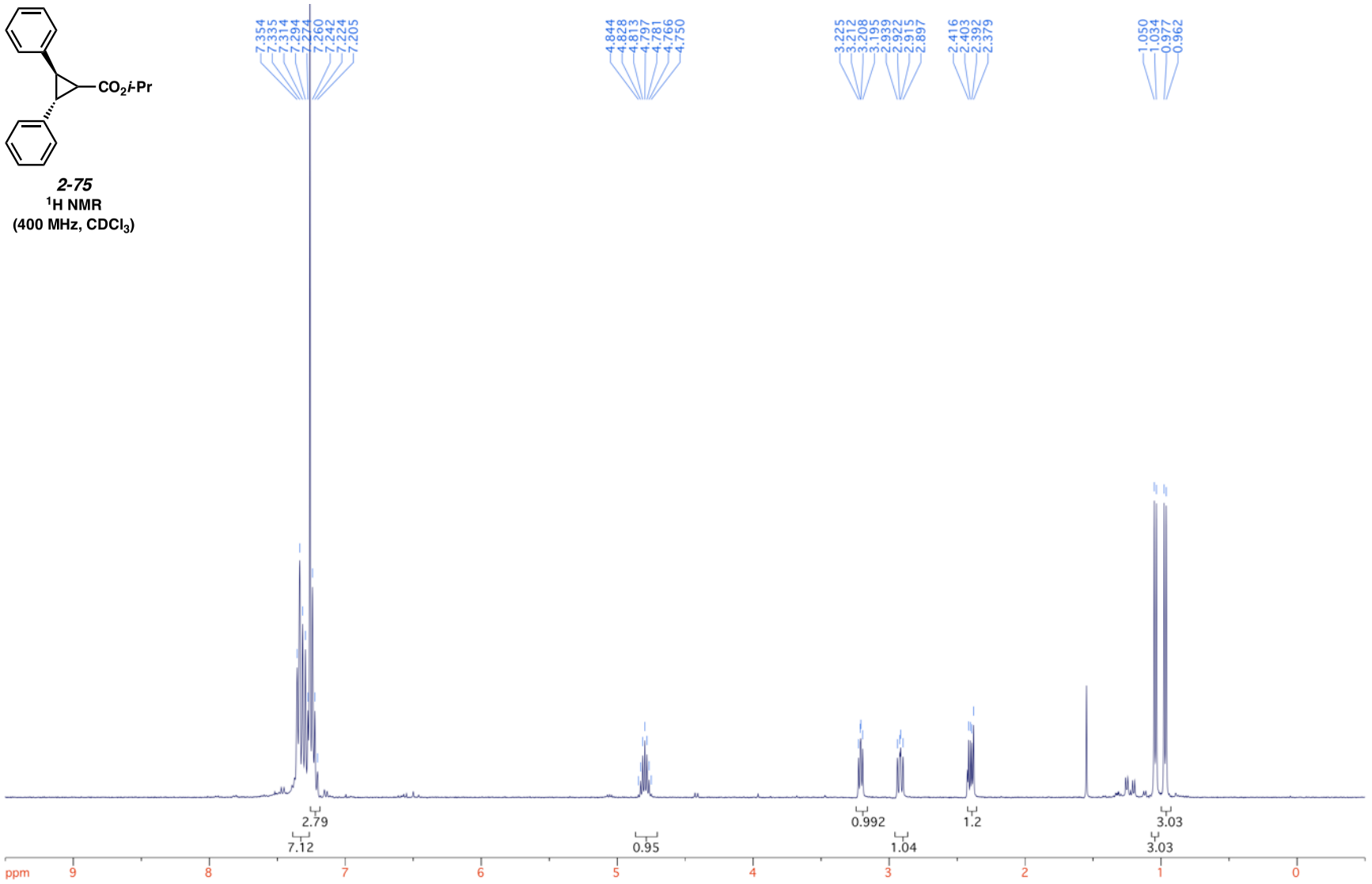
^{1}H NMR

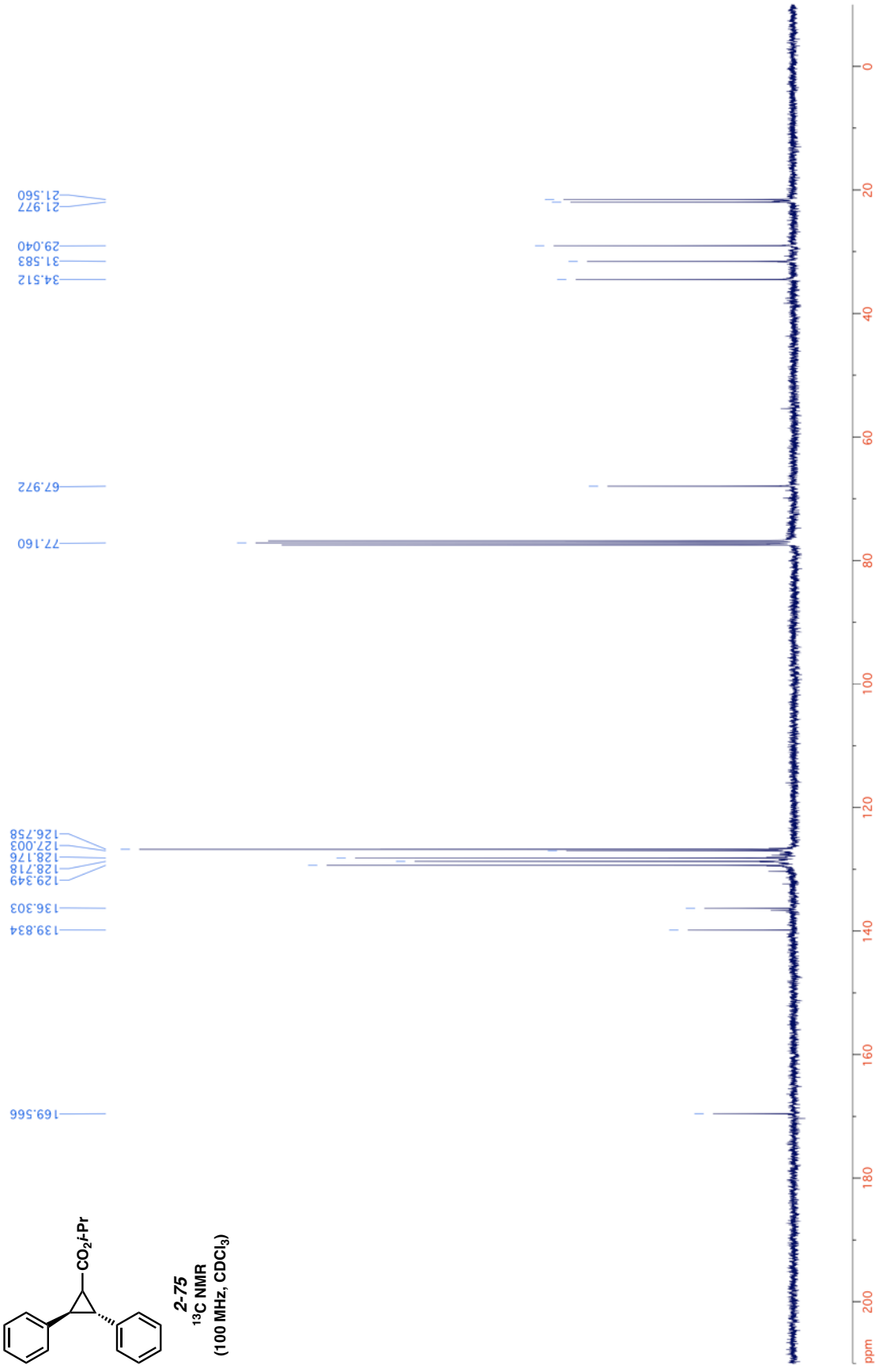
(400 MHz, $CDCl_3$)

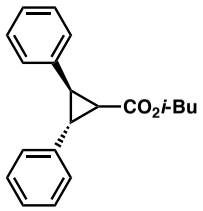

8.379
12.795
14.268
14.554
15.663
23.020
24.697
26.449
28.971
33.179
35.463
36.057
55.297
55.435
59.993
60.156
77.160
113.683
113.880
128.649
129.790
136.153
140.489
158.107
158.167
171.768
171.823
ppm
0
20
40
60
80
100
120
140
160
180
200
CO2Et
Me
Me
OMe
2-51
(1 : 1.2 anti/syn)
13C NMR
(100 MHz, CDCl3)


CO2Et
Me
2-52
(4.1 : 1 dr)
1H NMR
(400 MHz, CDCl3)
7.448
7.429
7.382
7.363
7.351
7.343
7.338
7.321
7.285
7.260
7.246
7.242
7.193
7.174
4.174
4.165
4.161
4.147
4.143
4.129
4.125
4.116
4.107
3.995
3.977
3.971
3.970
3.962
3.961
3.953
3.926
3.909
3.904
3.899
3.891
3.891
3.882
3.864
3.405
3.390
2.983
2.959
2.384
2.360
2.333
2.319
1.544
1.275
1.257
1.239
1.202
1.030
1.012
0.994
10.7
2
0.375
0.172
0.924
0.908
0.208
3.21
3.03
0.578
0.565
ppm
9
8
7
6
5
4
3
2
1
0

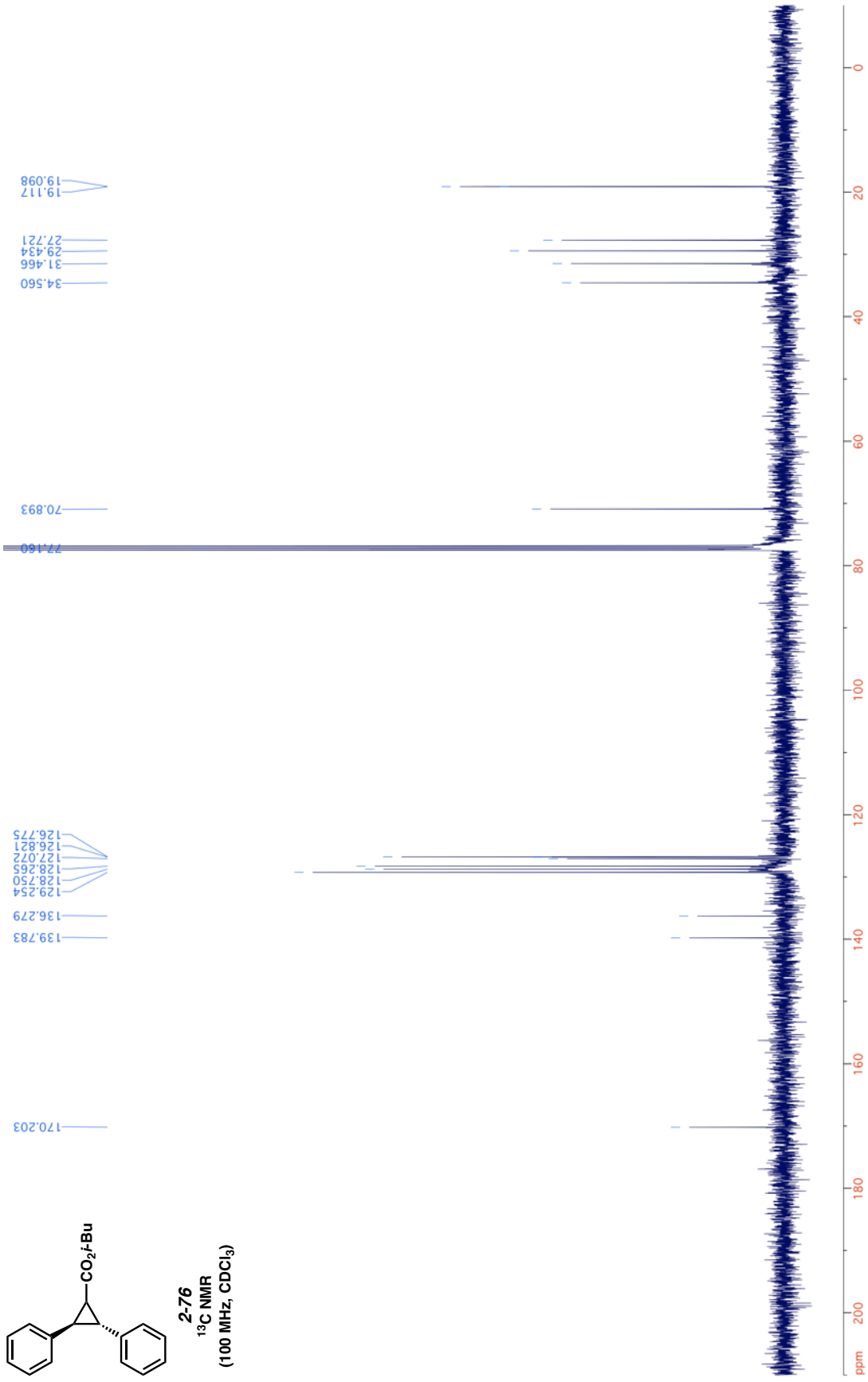

14.164
14.491
18.364
24.024
30.384
33.027
35.009
35.131
35.577
38.333
60.317
60.512
77.160
126.799
127.848
128.152
128.785
129.173
130.474
135.108
136.785
147.560
170.596
CO2Et
Me
2-52
(4.1 : 1 dr)
13C NMR
(100 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm

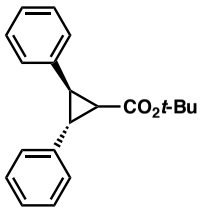

CO2i-Pr
2-75
1H NMR
(400 MHz, CDCl3)
7.354
7.335
7.314
7.294
7.274
7.260
7.242
7.224
7.205
4.844
4.828
4.813
4.797
4.781
4.766
4.750
3.225
3.212
3.208
3.195
2.939
2.922
2.915
2.897
2.416
2.403
2.392
2.379
1.050
1.034
0.977
0.962
2.79
7.12
0.95
0.992
1.04
1.2
3.03
3.03
ppm
9
8
7
6
5
4
3
2
1
0


21.560
21.977
29.040
31.583
34.512
67.972
77.160
126.758
127.003
128.176
128.718
129.349
136.303
139.834
169.566
ppm
0
20
40
60
80
100
120
140
160
180
200
CO2i-Pr
2-75
13C NMR
(100 MHz, CDCl3)

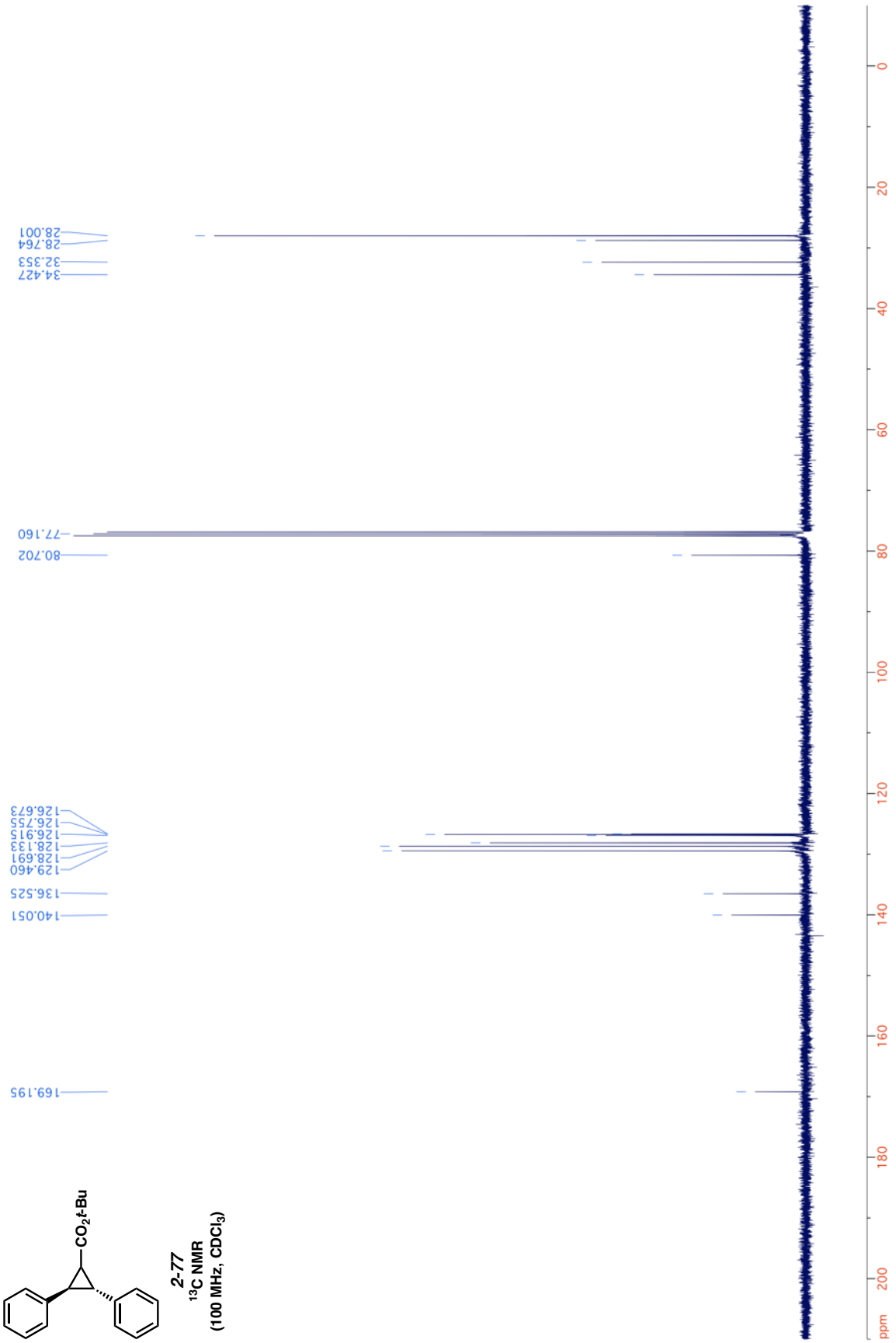


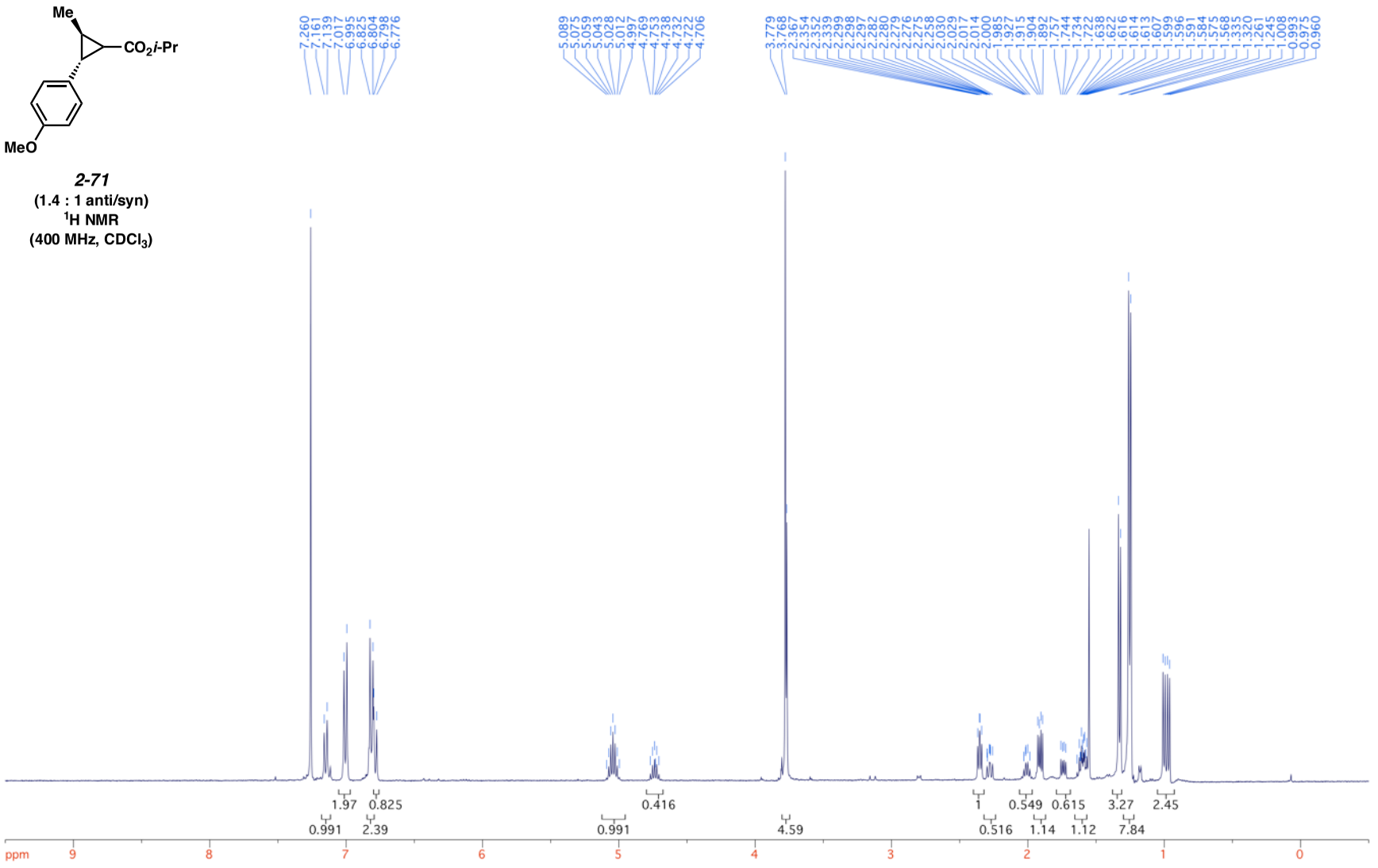
2-76
^{1}H NMR
(400 MHz, $CDCl_3$)

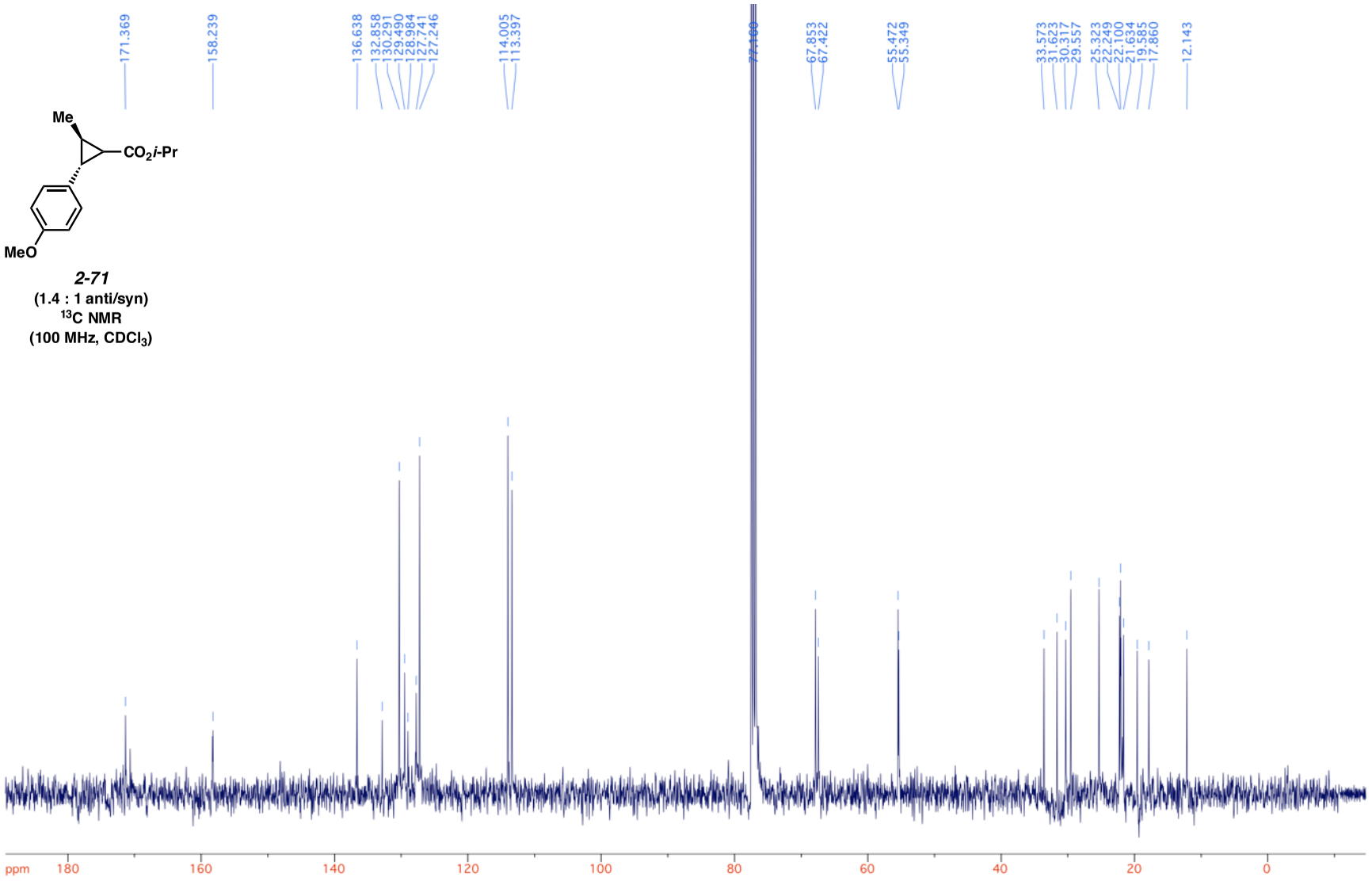

19.098
19.117
27.721
29.434
31.466
34.560
70.893
77.160
126.775
126.821
127.072
128.265
128.750
129.254
136.279
139.783
170.203
0
20
40
60
80
100
120
140
160
180
200
ppm
CO2i-Bu
2-76
13C NMR
(100 MHz, CDCl3)

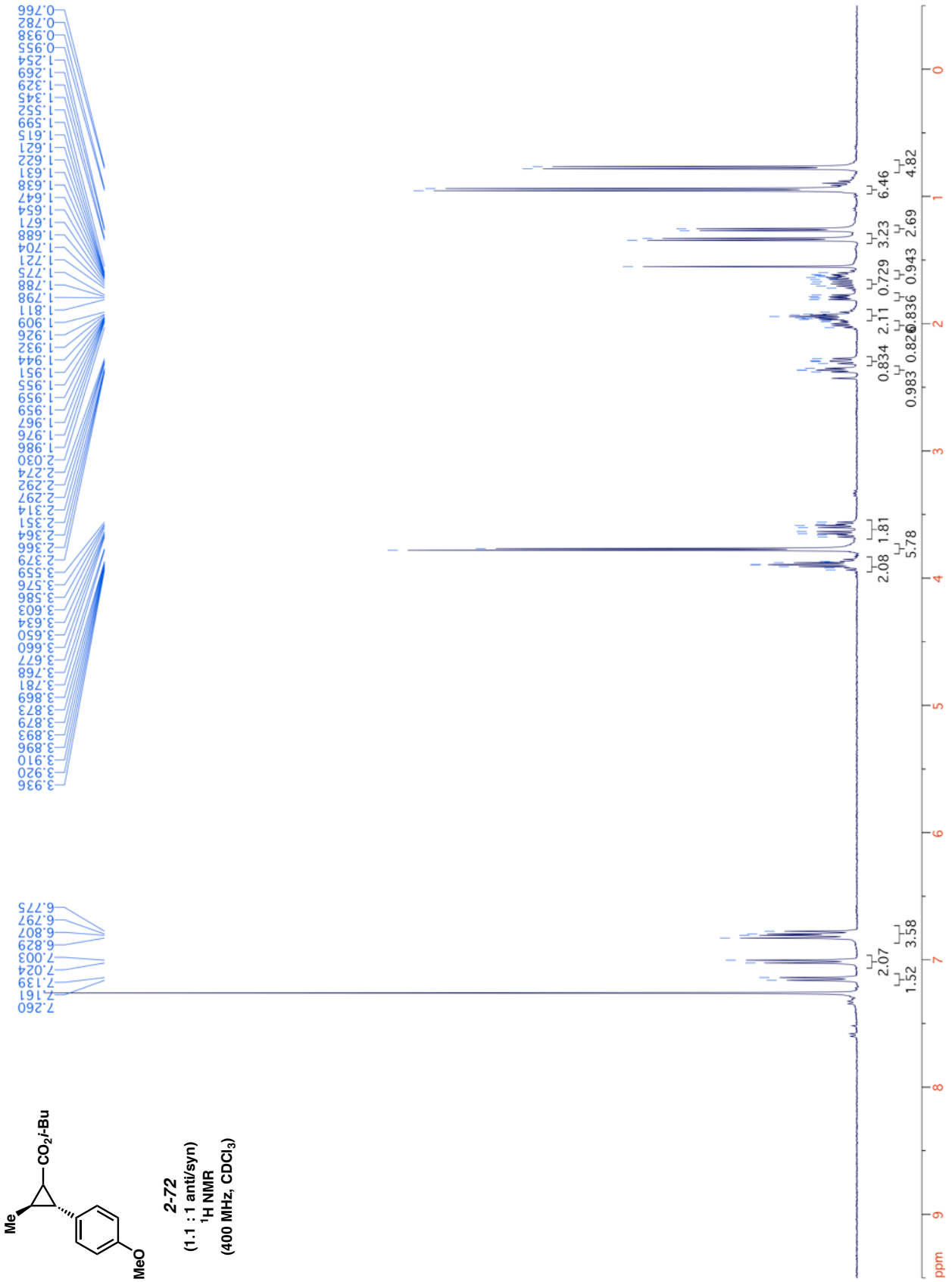


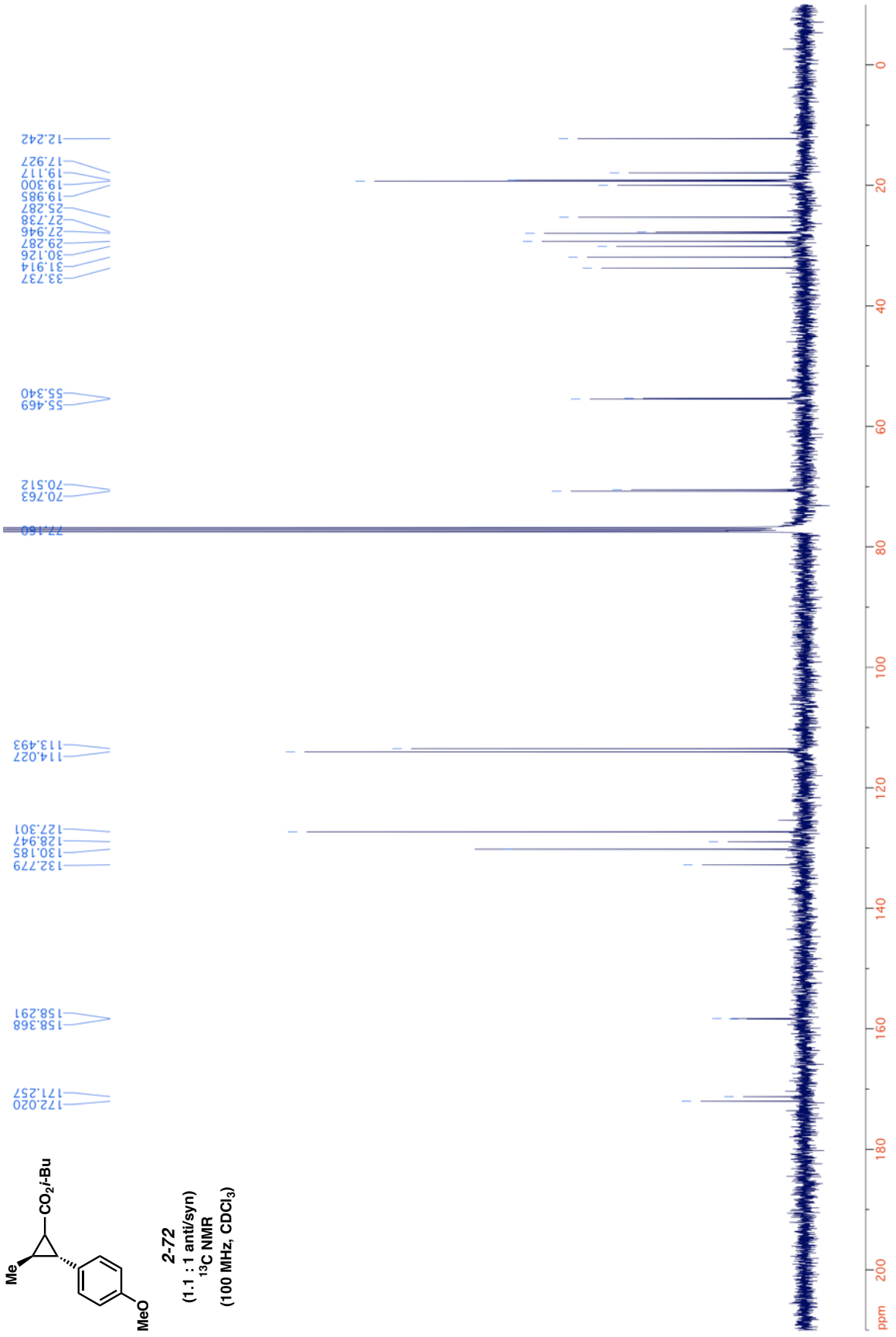
2-77
^{1}H NMR
(400 MHz, $CDCl_3$)

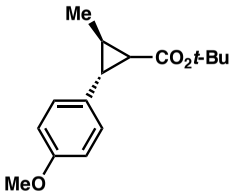

CO2t-Bu
2-77
13C NMR
(100 MHz, CDCl3)
169.195
140.051
136.525
129.460
128.691
128.133
126.915
126.755
126.673
80.702
77.160
34.427
32.353
28.764
28.001
ppm
0
20
40
60
80
100
120
140
160
180
200


Me
CO2i-Pr
MeO
2-71
(1.4 : 1 anti/syn)
1H NMR
(400 MHz, CDCl3)
7.260
7.161
7.139
7.017
6.995
6.825
6.804
6.798
6.776
5.089
5.075
5.059
5.043
5.028
5.012
4.997
4.769
4.753
4.738
4.732
4.722
4.706
3.779
3.768
3.367
2.354
2.352
2.339
2.299
2.298
2.297
2.282
2.280
2.279
2.276
2.275
2.258
2.030
2.029
2.017
2.014
2.000
1.985
1.927
1.915
1.904
1.892
1.757
1.744
1.734
1.722
1.638
1.622
1.616
1.614
1.613
1.607
1.599
1.596
1.591
1.584
1.575
1.568
1.335
1.320
1.261
1.245
1.008
0.993
0.975
0.960
1.97
0.825
0.991
2.39
0.991
0.416
4.59
1
0.549
0.615
3.27
2.45
0.516
1.14
1.12
7.84
ppm
9
8
7
6
5
4
3
2
1
0

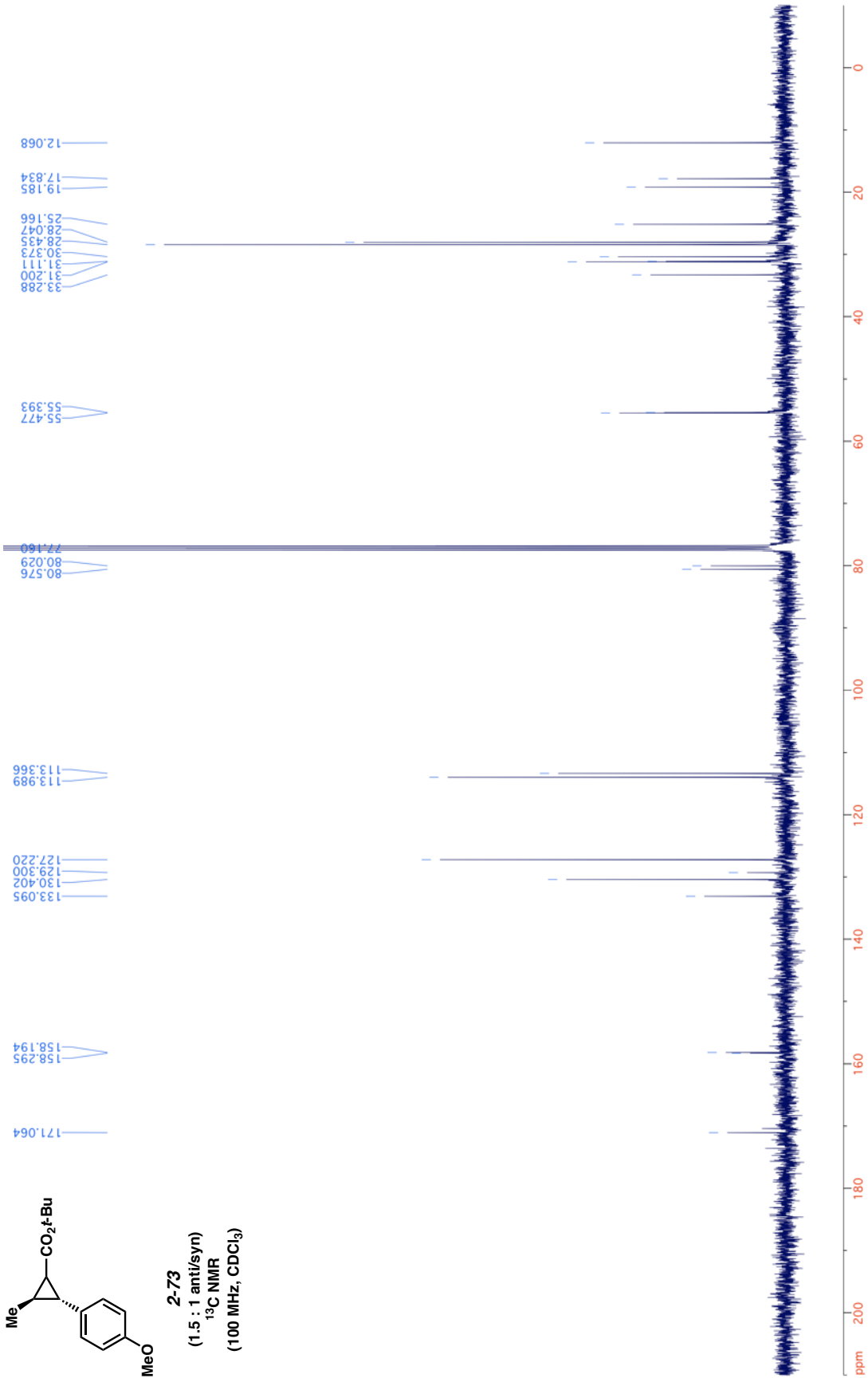

171.369
158.239
136.638
132.858
130.291
129.490
128.984
127.741
127.246
114.005
113.397
77.160
67.853
67.422
55.472
55.349
33.573
31.623
30.317
29.557
25.323
22.249
22.100
21.634
19.585
17.860
12.143
Me
CO2i-Pr
MeO
2-71
(1.4 : 1 anti/syn)
13C NMR
(100 MHz, CDCl3)
ppm
180
160
140
120
100
80
60
40
20
0

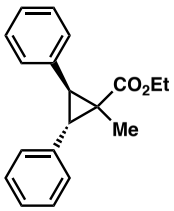

Me
CO2i-Bu
MeO
2-72
(1.1 : 1 anti/syn)
1H NMR
(400 MHz, CDCl3)
ppm


12.242
17.927
19.117
19.300
19.985
25.287
27.738
27.946
29.287
30.126
31.914
33.737
55.469
55.340
70.763
70.512
77.160
113.493
114.027
127.301
128.947
130.185
132.779
158.291
158.368
171.257
172.020
ppm
0
20
40
60
80
100
120
140
160
180
200
Me
CO2i-Bu
MeO
2-72
(1.1 : 1 anti/syn)
13C NMR
(100 MHz, CDCl3)

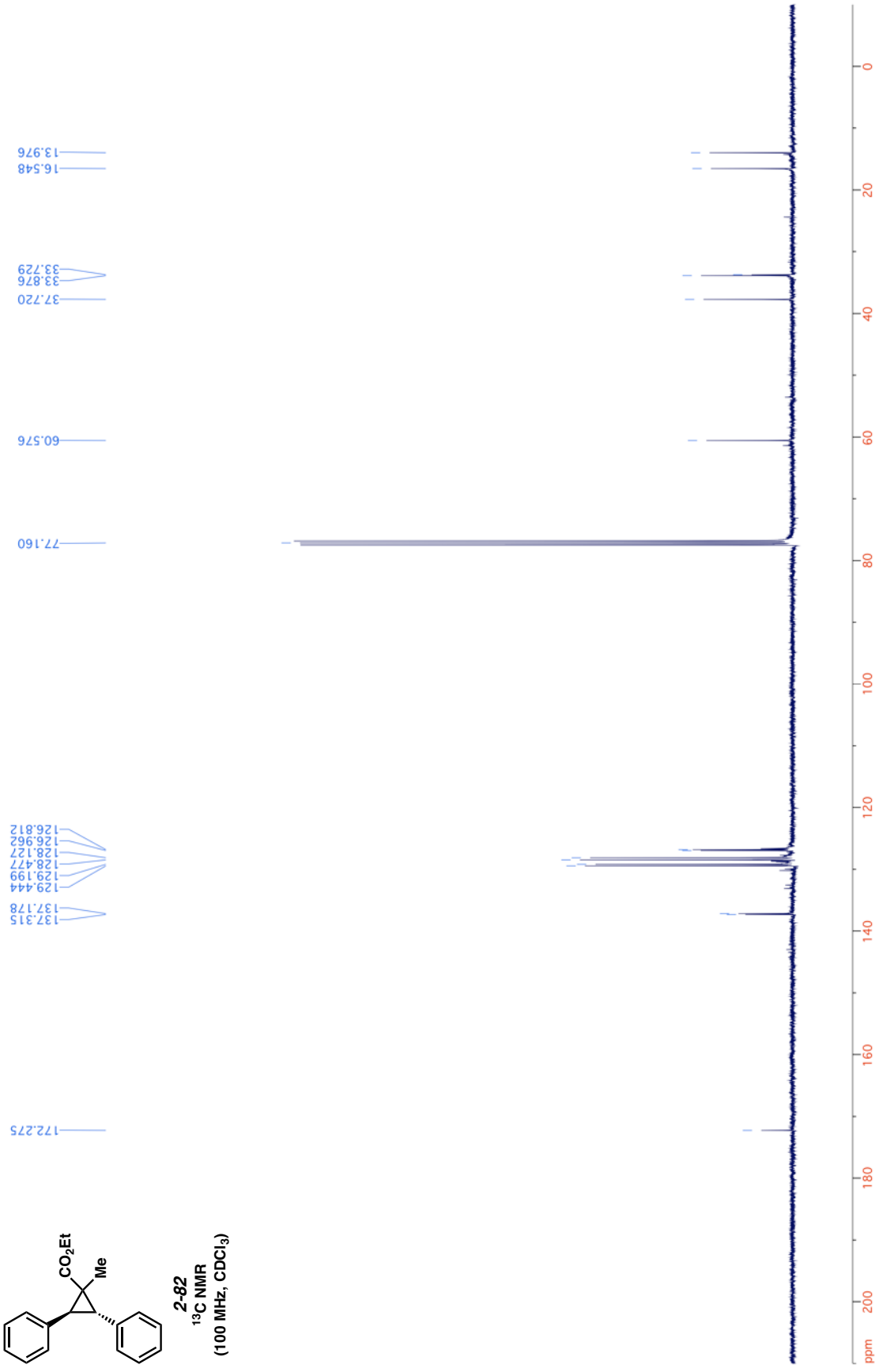


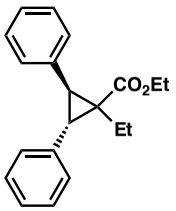
2-73
(1.5 : 1 anti/syn)
^{1}H NMR
(400 MHz, $CDCl_3$)


12.068
17.834
19.185
25.166
28.435
28.047
30.373
31.111
31.200
33.288
55.477
55.393
77.160
80.576
80.029
113.989
113.366
127.220
129.300
130.402
133.095
158.295
158.194
171.064
0
20
40
60
80
100
120
140
160
180
200
ppm
Me
CO2t-Bu
MeO
2-73
(1.5 : 1 anti/syn)
13C NMR
(100 MHz, CDCl3)

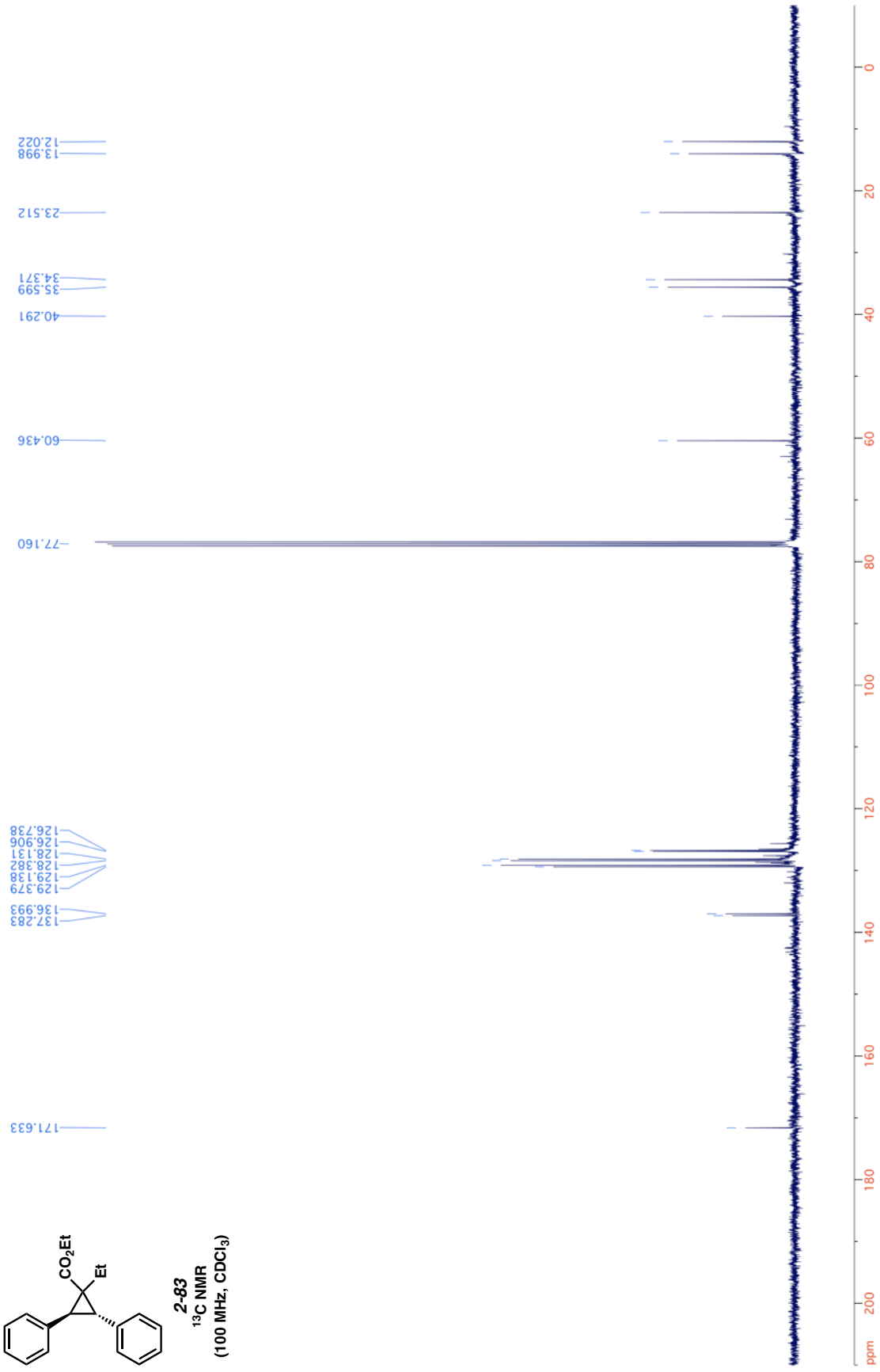


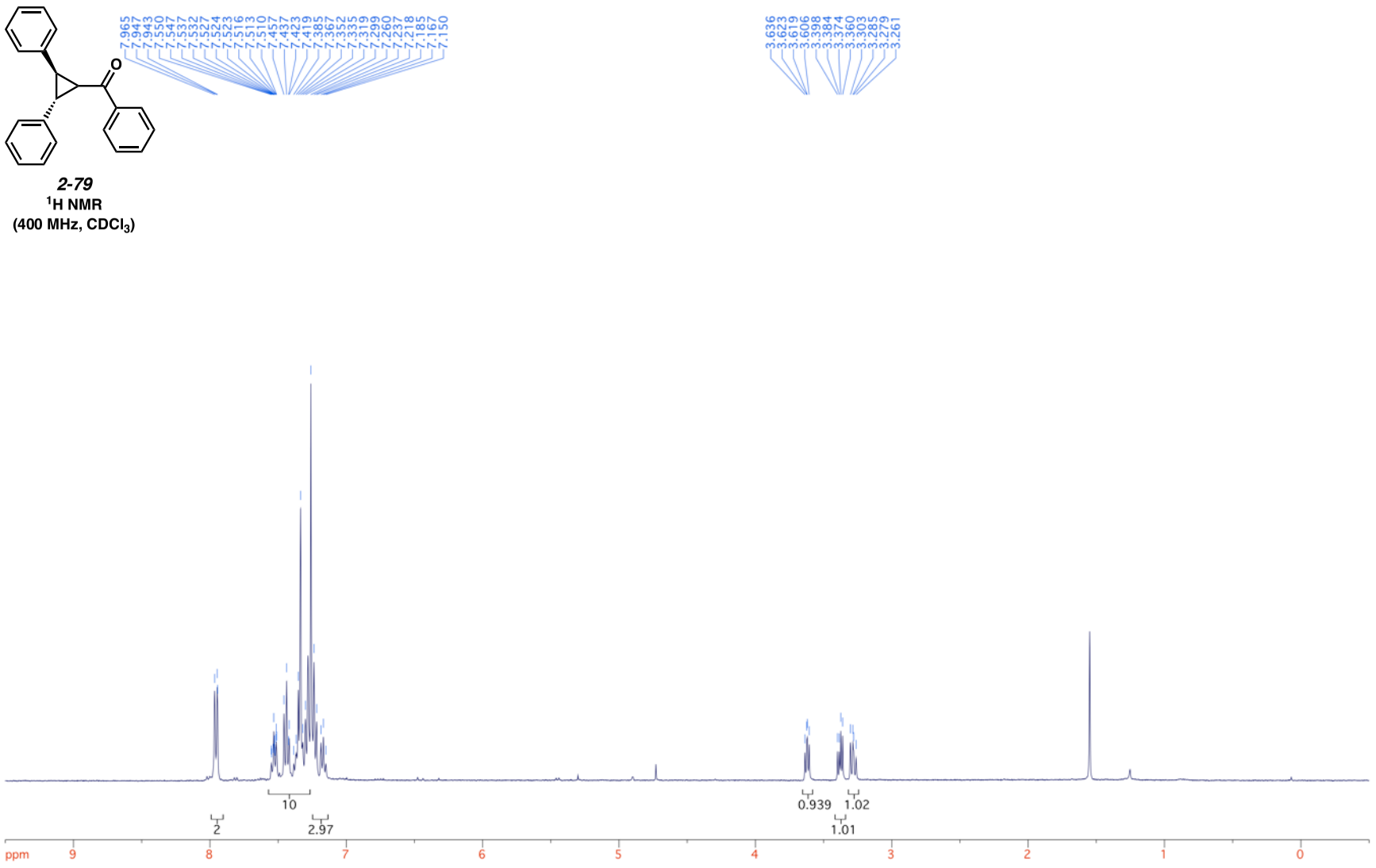
2-82
^{1}H NMR
(400 MHz, $CDCl_3$)


13.976
16.548
33.729
33.876
37.720
60.576
77.160
126.812
126.962
128.127
128.477
129.199
129.444
137.178
137.315
172.275
ppm
0
20
40
60
80
100
120
140
160
180
200
CO2Et
Me
2-82
13C NMR
(100 MHz, CDCl3)

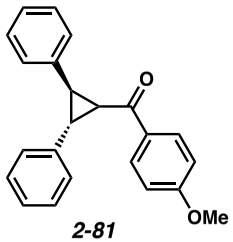


2-83
^{1}H NMR
(400 MHz, $CDCl_3$)

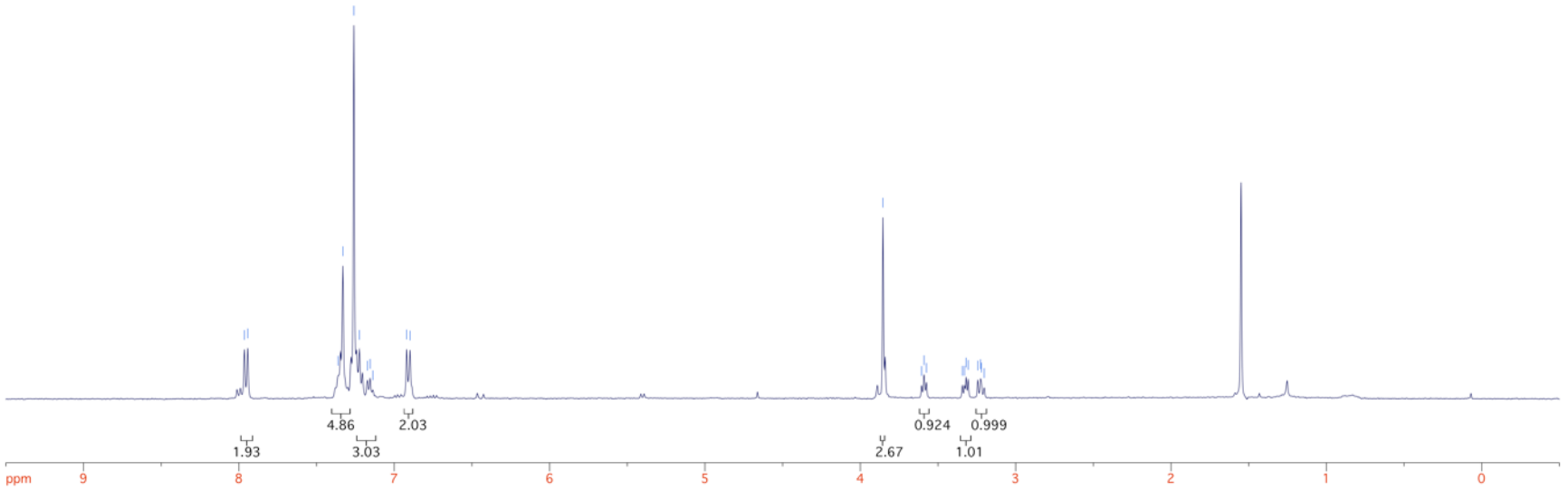

CO2Et
Et
2-83
13C NMR
(100 MHz, CDCl3)
12.022
13.998
23.512
34.371
35.599
40.291
60.436
77.160
126.738
126.906
128.131
128.382
129.379
129.138
136.993
137.283
171.633
ppm

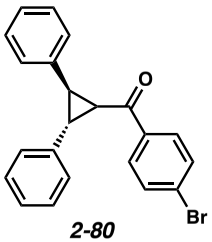


2-79
^{1}H NMR
(400 MHz, $CDCl_3$)

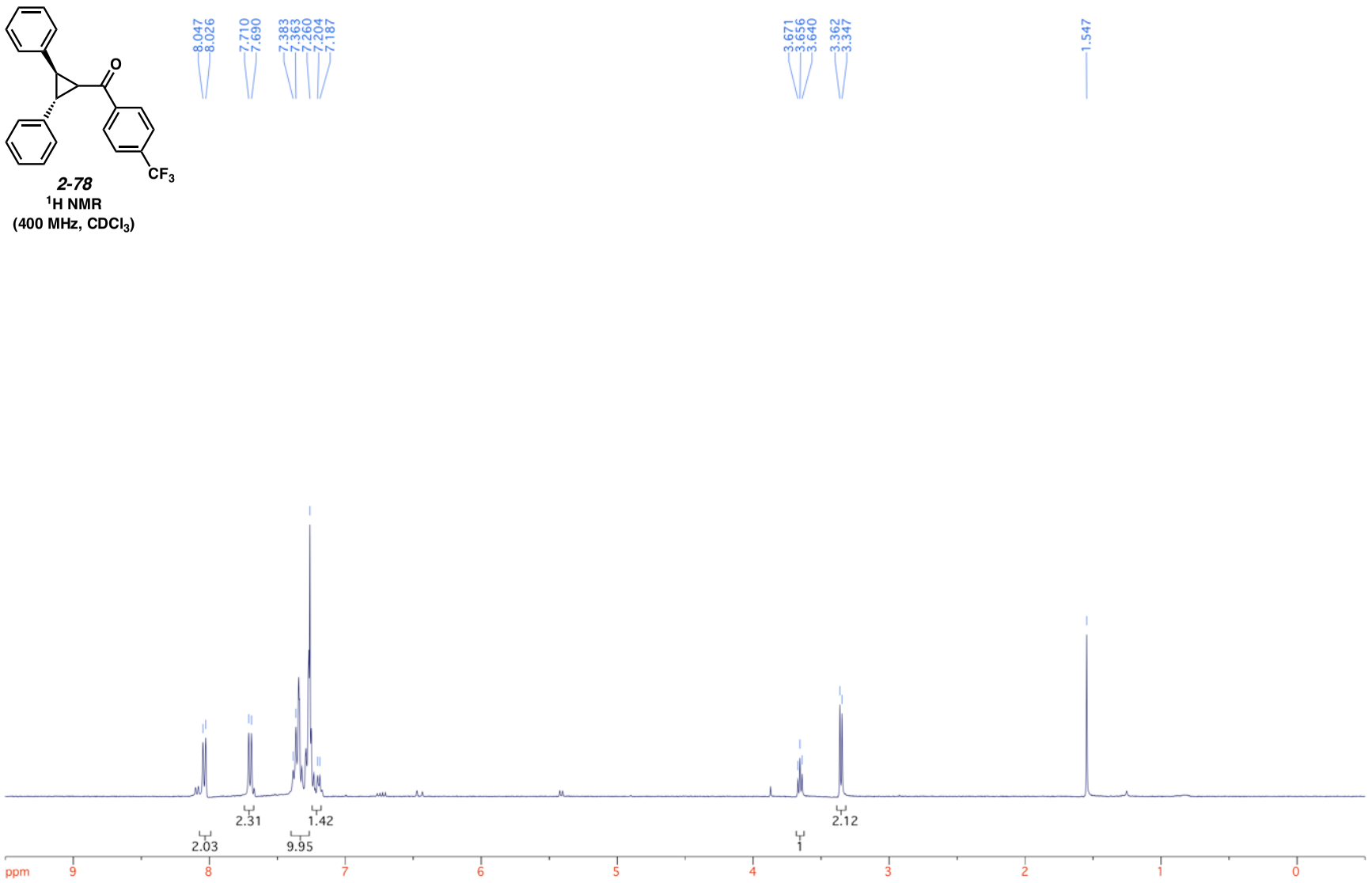


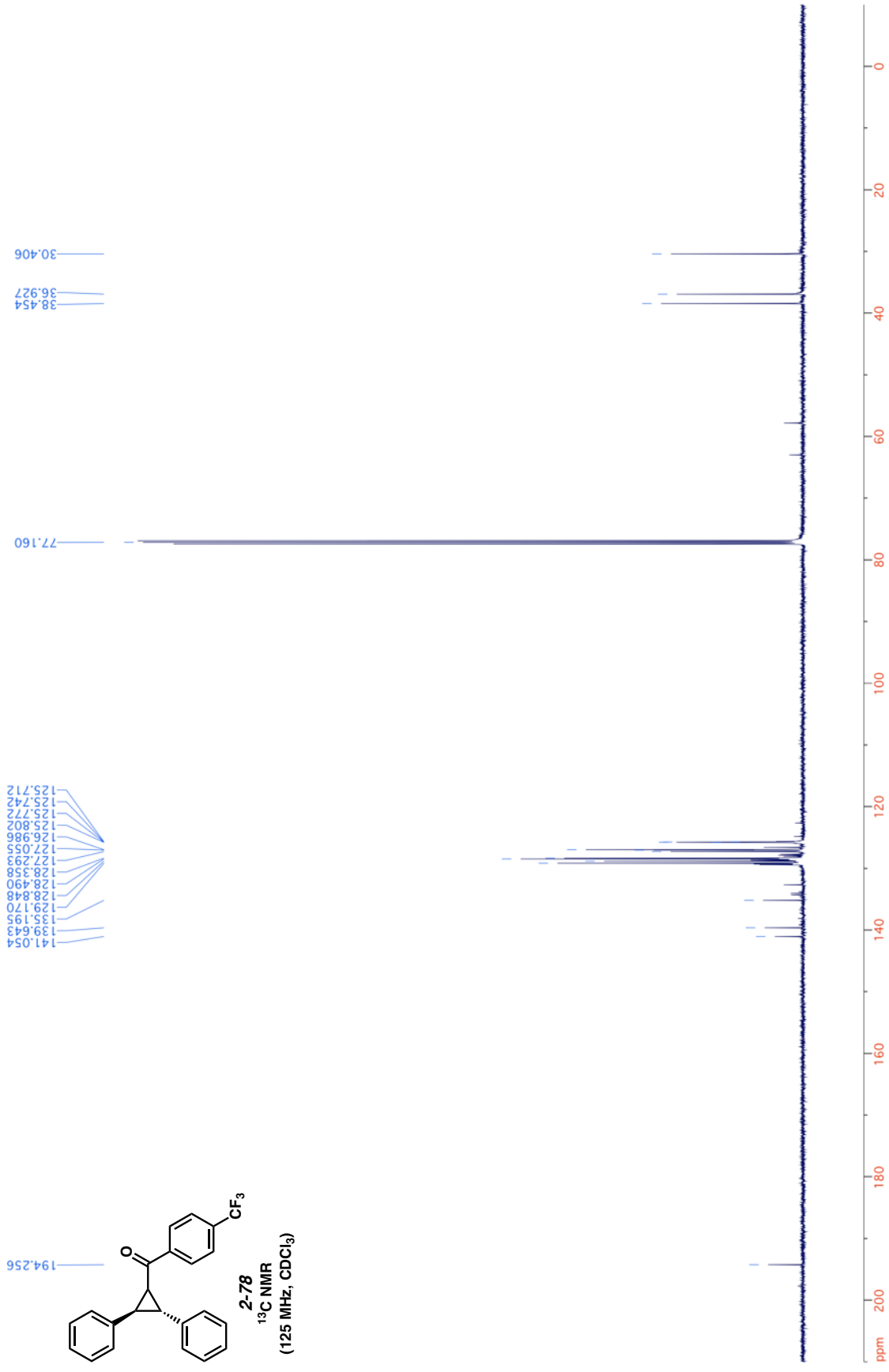
2-81
^{1}H NMR
(400 MHz, $CDCl_3$)

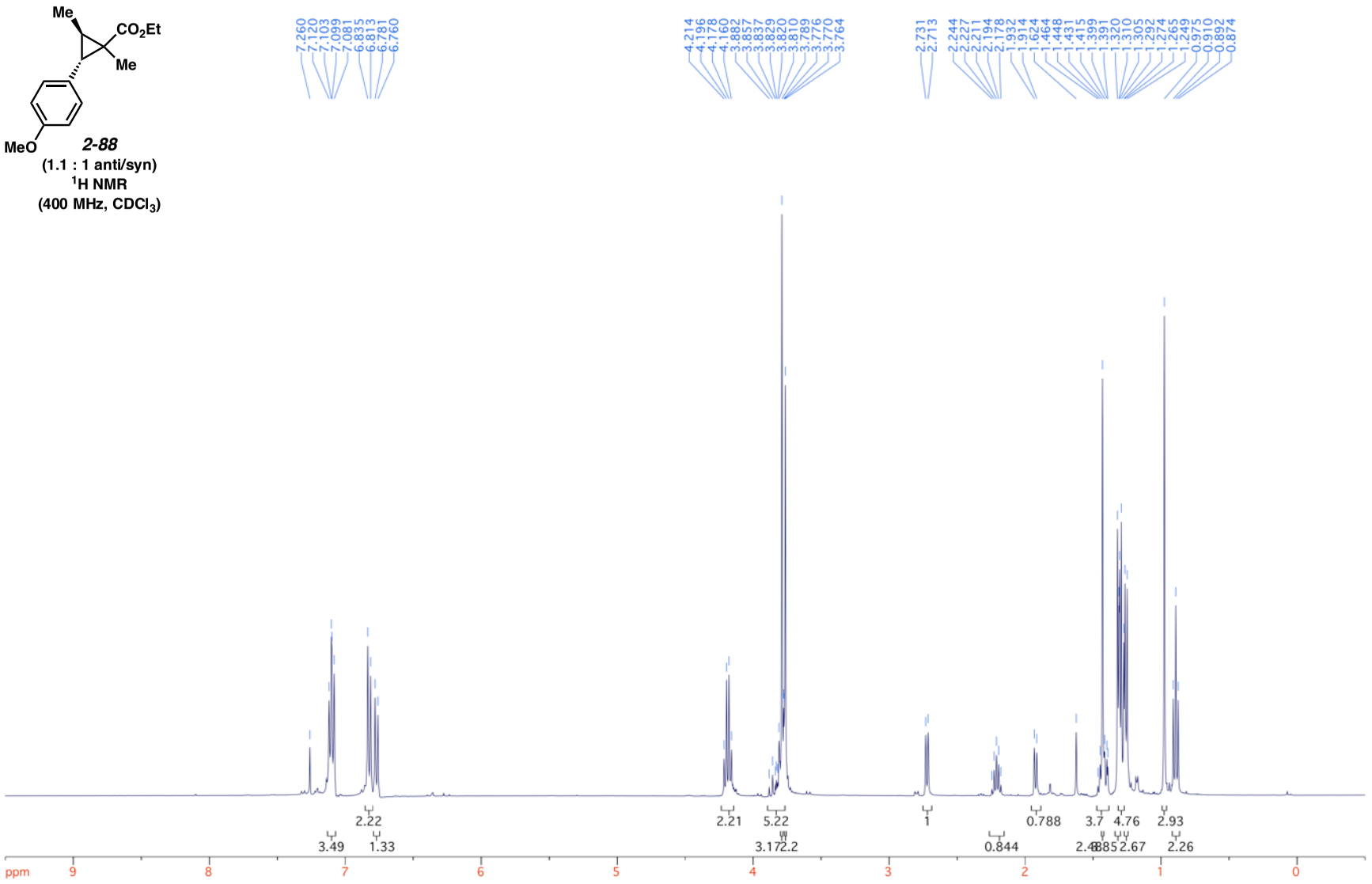


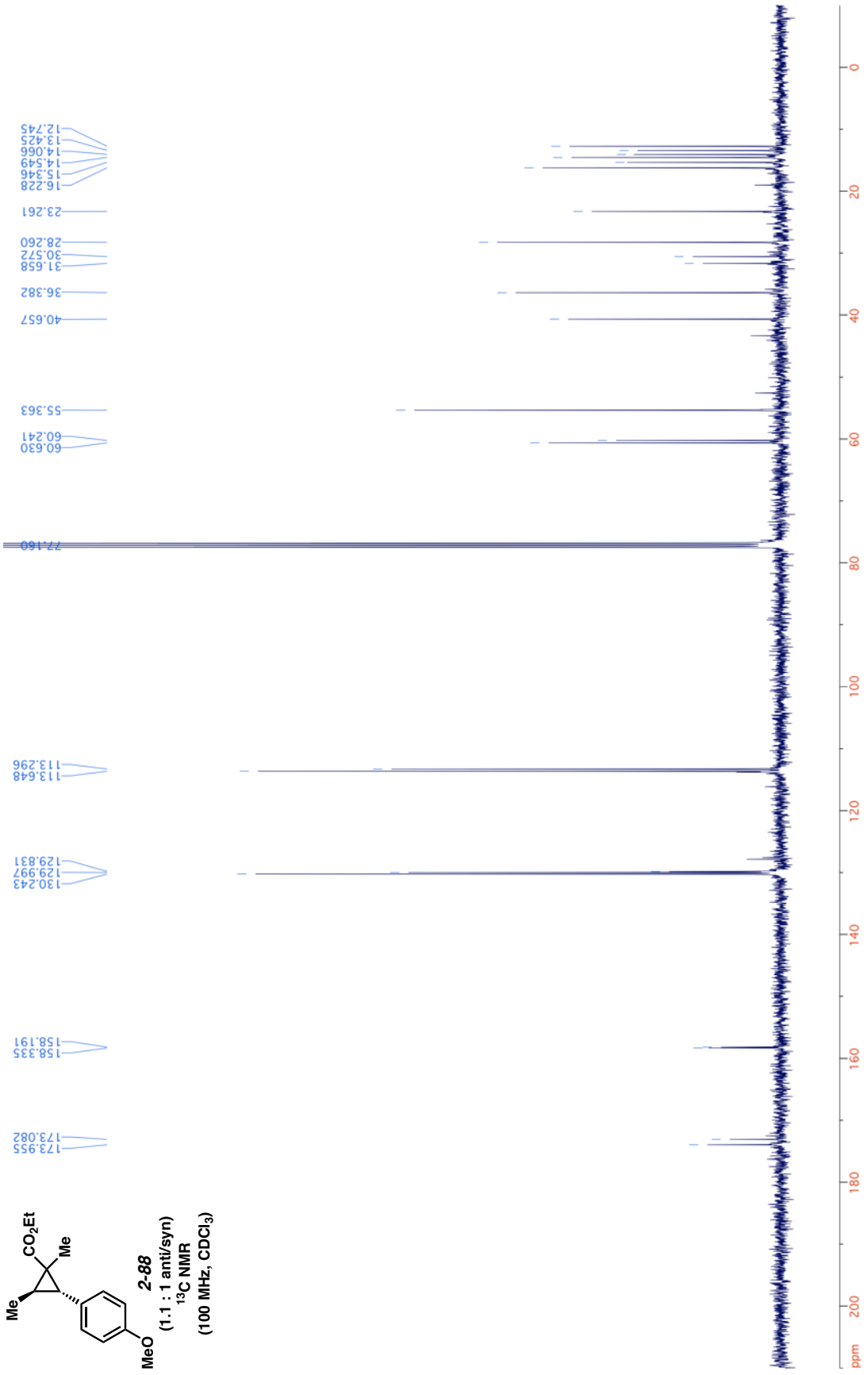


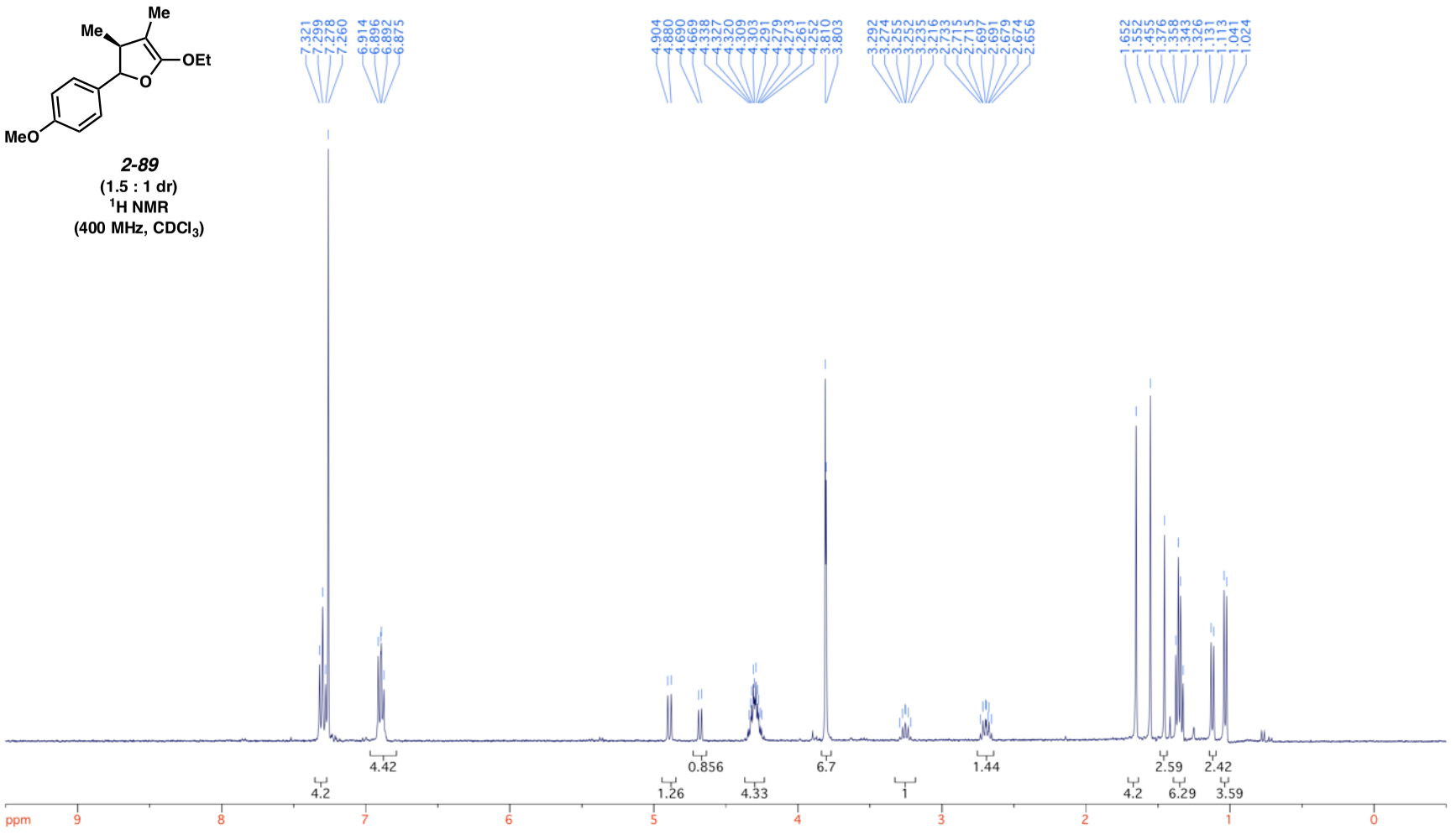
2-80
^{1}H NMR
(400 MHz, $CDCl_3$)

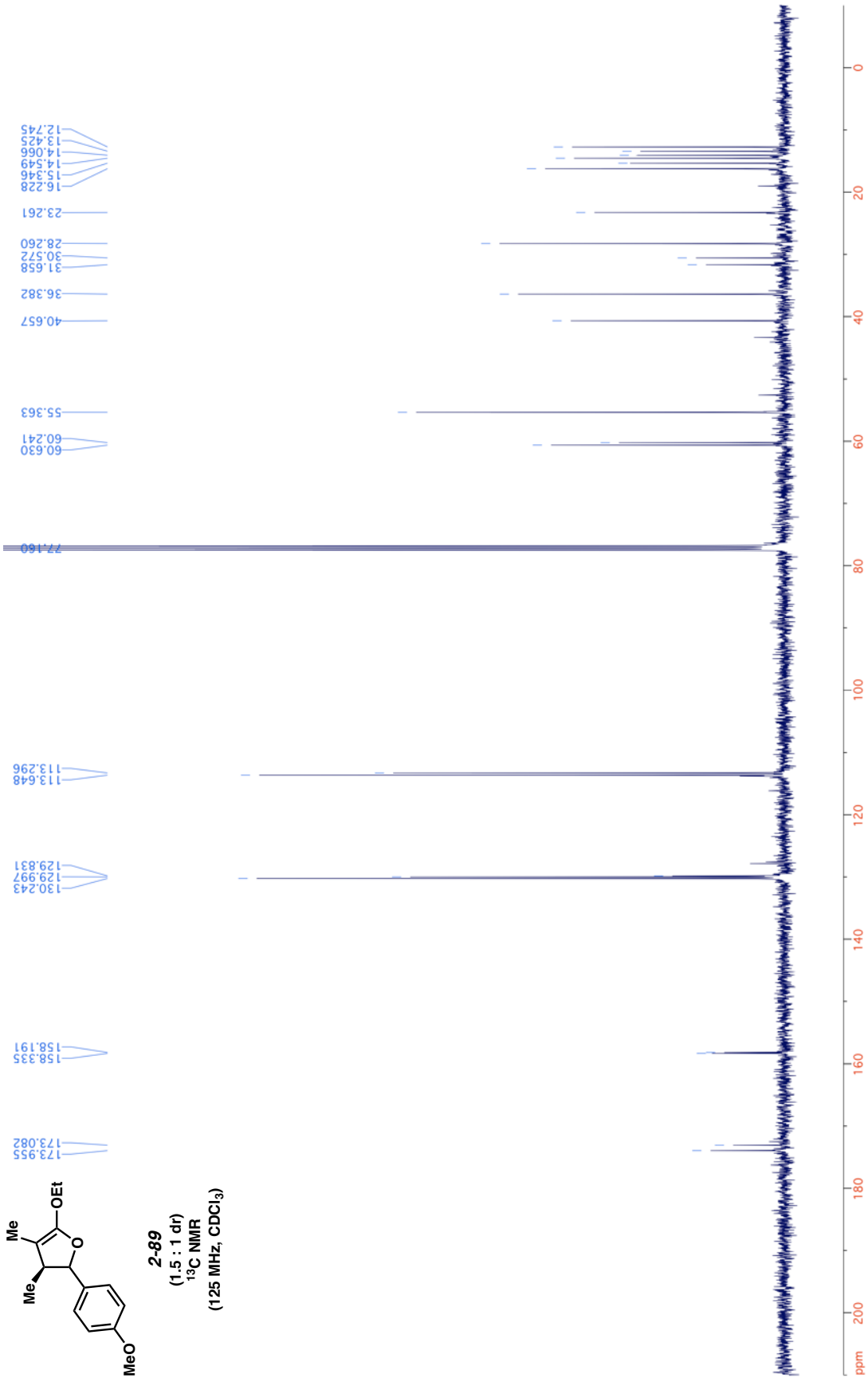

8.047
8.026
7.710
7.690
7.383
7.363
7.260
7.204
7.187
3.671
3.656
3.640
3.362
3.347
1.547
O
CF3
2-78
1H NMR
(400 MHz, CDCl3)
2.03
2.31
9.95
1.42
1
2.12
ppm
9
8
7
6
5
4
3
2
1
0

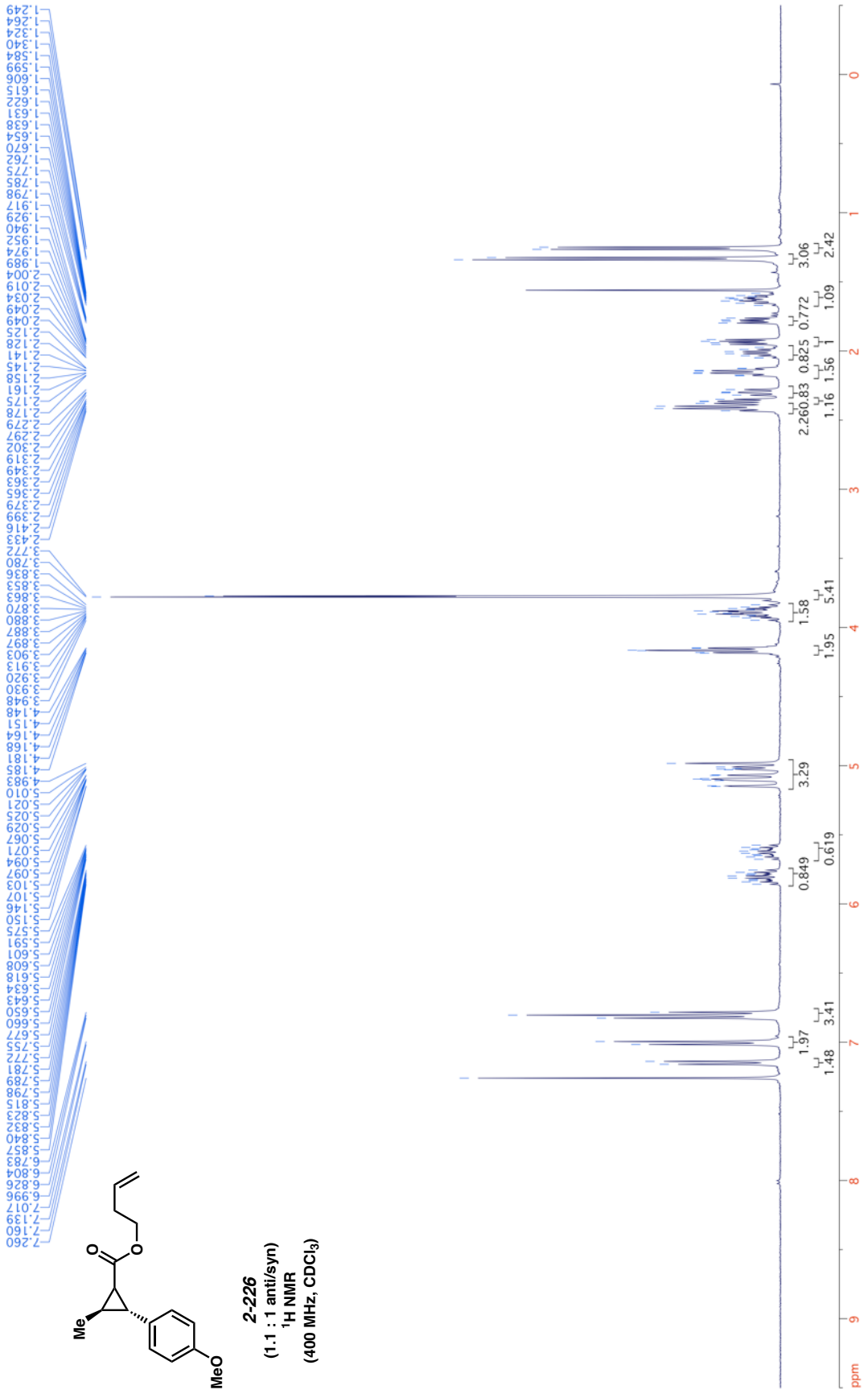

194.256
141.054
139.643
135.195
129.170
128.848
128.490
128.358
127.293
127.055
126.986
125.802
125.772
125.742
125.712
77.160
38.454
36.927
30.406
O
CF3
2-78
13C NMR
(125 MHz, CDCl3)
ppm
0
20
40
60
80
100
120
140
160
180
200

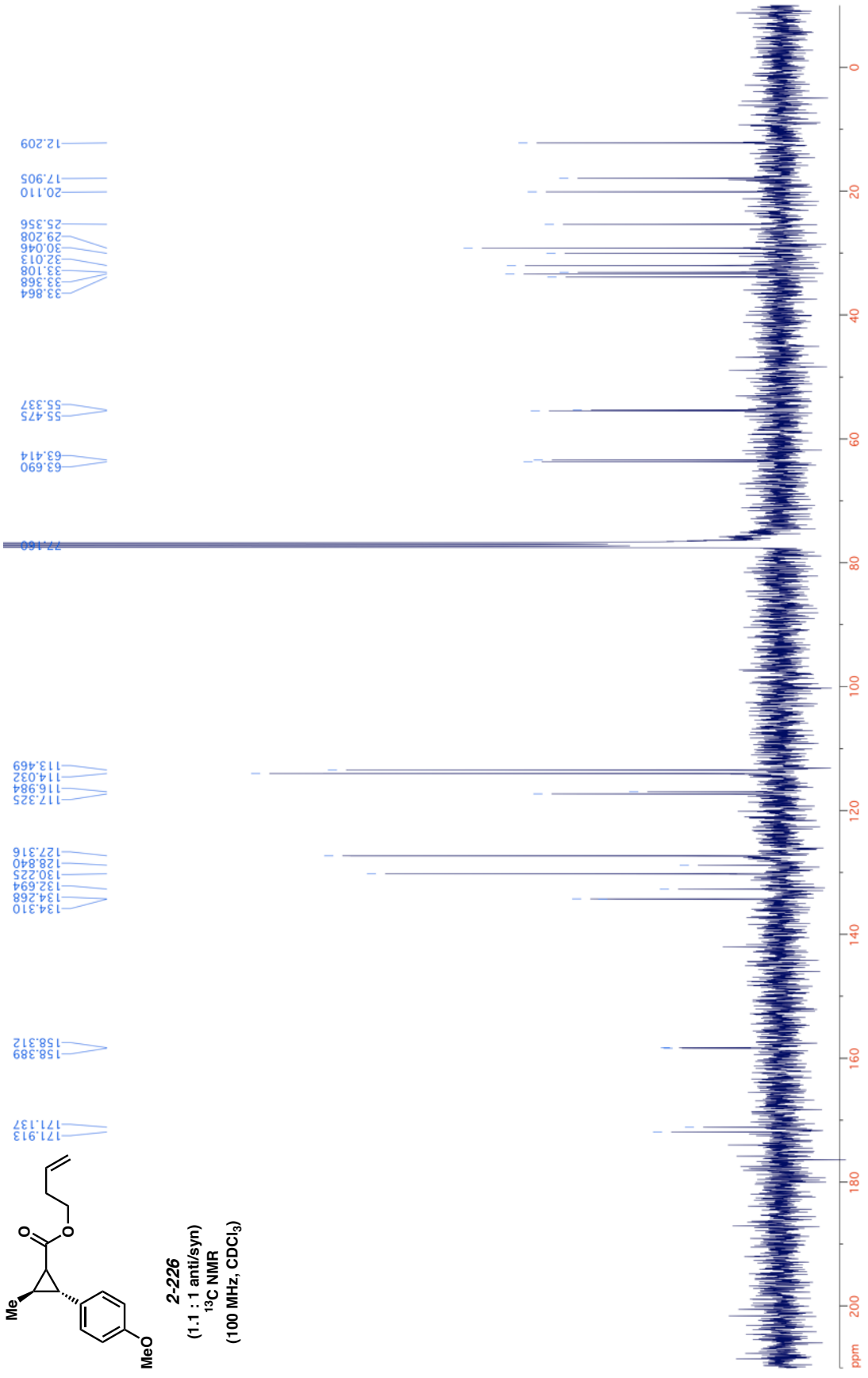

Me
CO2Et
Me
MeO
2-88
(1.1 : 1 anti/syn)
1H NMR
(400 MHz, CDCl3)
7.260
7.120
7.103
7.099
7.081
6.835
6.813
6.781
6.760
4.214
4.196
4.178
4.160
3.882
3.857
3.837
3.829
3.820
3.810
3.789
3.776
3.770
3.764
2.731
2.713
2.244
2.227
2.211
2.194
2.178
1.932
1.914
1.624
1.464
1.448
1.431
1.415
1.399
1.391
1.320
1.310
1.305
1.292
1.274
1.265
1.249
0.975
0.910
0.892
0.874
2.22
3.49
1.33
2.21
5.22
3.17
2.2
1
0.788
0.844
3.7
4.76
2.93
2.67
2.26
ppm
9
8
7
6
5
4
3
2
1
0


12.745
13.425
14.066
14.549
15.346
16.228
23.261
28.260
30.572
31.658
36.382
40.657
55.363
60.241
60.630
77.160
113.296
113.648
129.831
129.997
130.243
158.191
158.335
173.082
173.955
0
20
40
60
80
100
120
140
160
180
200
ppm
Me
CO2Et
Me
MeO
2-88
(1:1 : 1 anti/syn)
13C NMR
(100 MHz, CDCl3)


Me
Me
OEt
O
MeO
2-89
(1.5 : 1 dr)
1H NMR
(400 MHz, CDCl3)
7.321
7.299
7.278
7.260
6.914
6.896
6.892
6.875
4.904
4.880
4.690
4.669
4.338
4.327
4.320
4.309
4.303
4.291
4.279
4.273
4.261
4.252
3.810
3.803
3.292
3.274
3.255
3.252
3.235
3.216
2.733
2.715
2.715
2.697
2.691
2.679
2.674
2.656
1.652
1.552
1.455
1.376
1.358
1.343
1.326
1.131
1.113
1.041
1.024
4.42
0.856
6.7
1.44
2.59
2.42
4.2
1.26
4.33
1
4.2
6.29
3.59
ppm
9
8
7
6
5
4
3
2
1
0


12.745
13.425
14.066
14.549
15.346
16.228
23.261
28.260
30.572
31.658
36.382
40.657
55.363
60.241
60.630
77.160
113.296
113.648
129.831
129.997
130.243
158.191
158.335
173.082
173.955
OEt
Me
Me
O
MeO
2-89
(1.5 : 1 dr)
13C NMR
(125 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm


Me
O
O
MeO
2-226
(1.1 : 1 anti/syn)
^{1}H NMR
(400 MHz, $CDCl_3$)
ppm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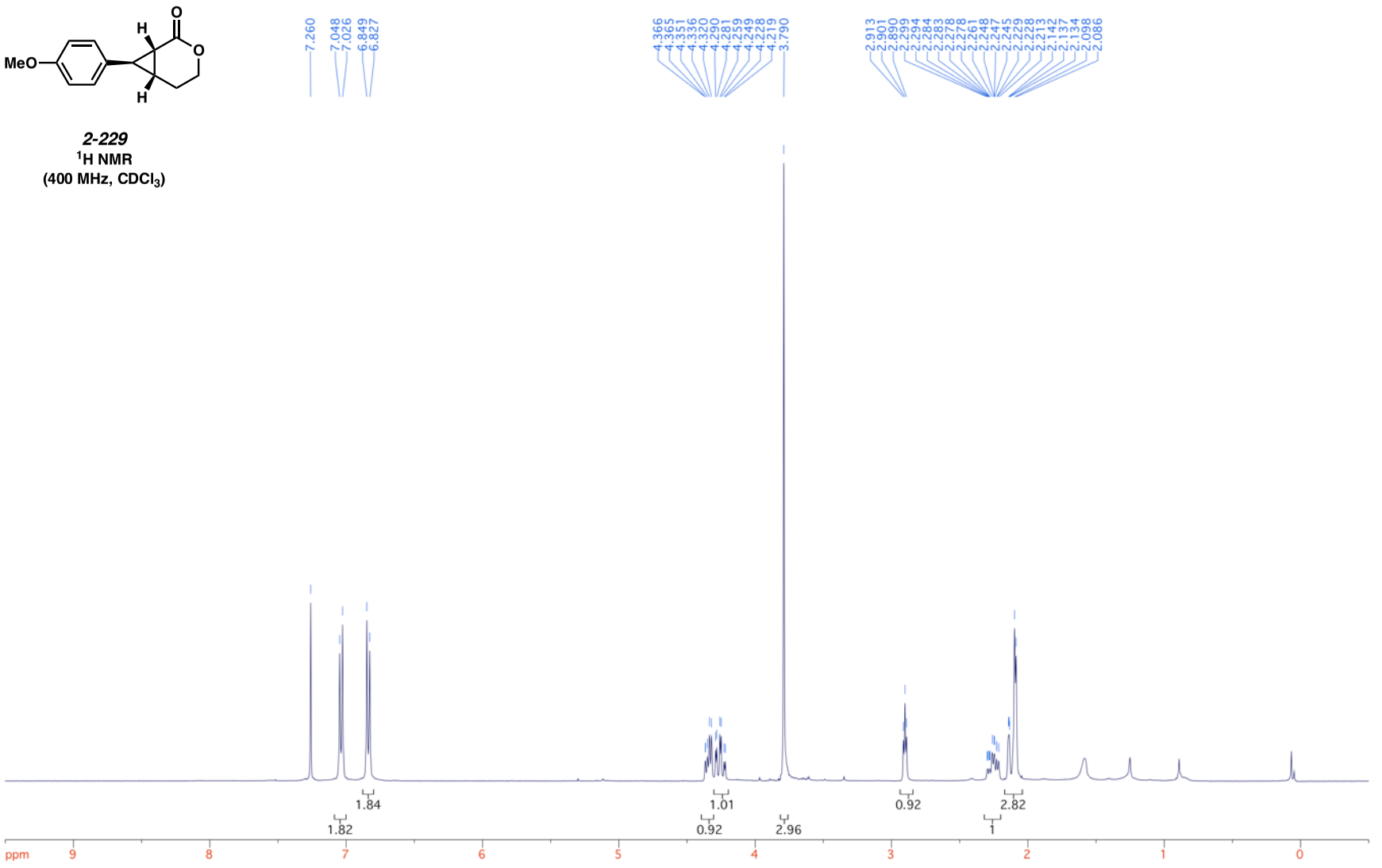
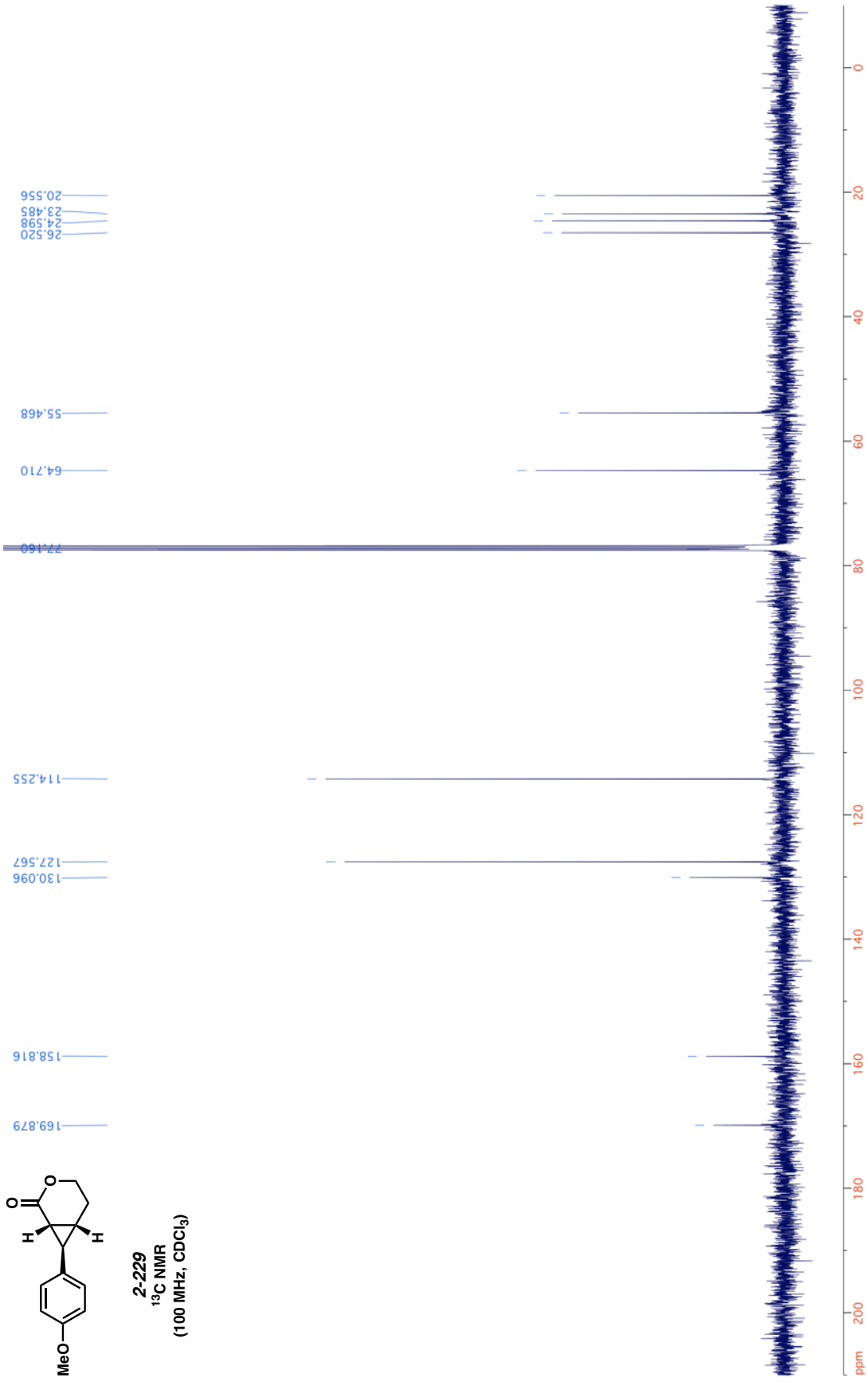
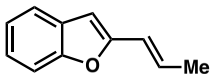
17.905
20.110
25.356
29.208
30.046
32.013
33.108
33.368
33.864
55.337
55.475
63.414
63.690
77.160
113.469
114.032
116.984
117.325
127.316
128.840
130.225
132.694
134.268
134.310
158.312
158.389
171.137
171.913
Me
O
O
MeO
2-226
(1.1 : 1 anti/syn)
13C NMR
(100 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm



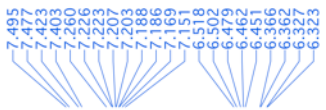
2-229
^{1}H NMR
(400 MHz, $CDCl_3$)

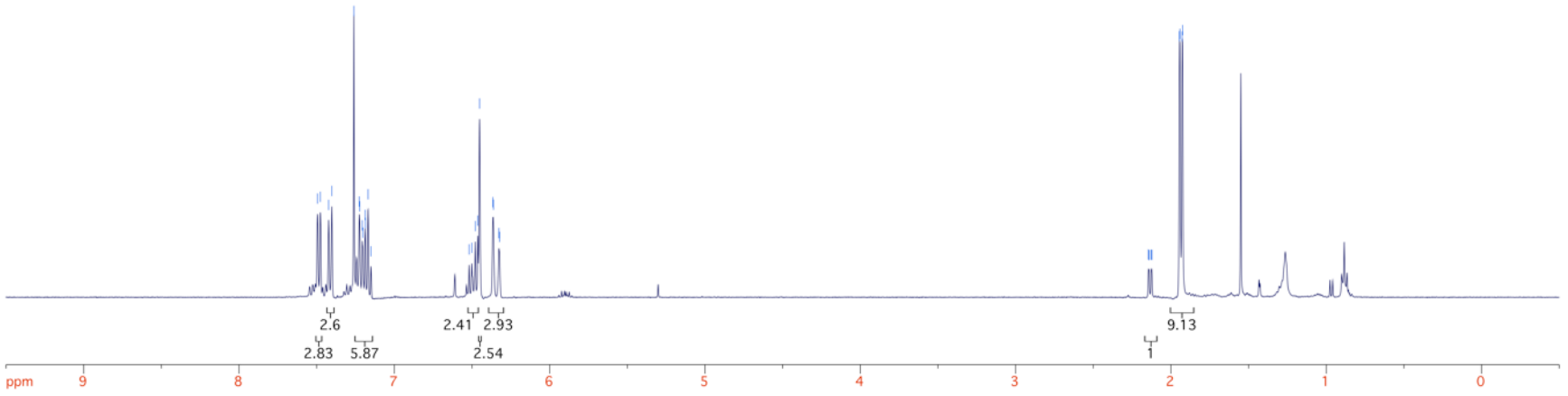


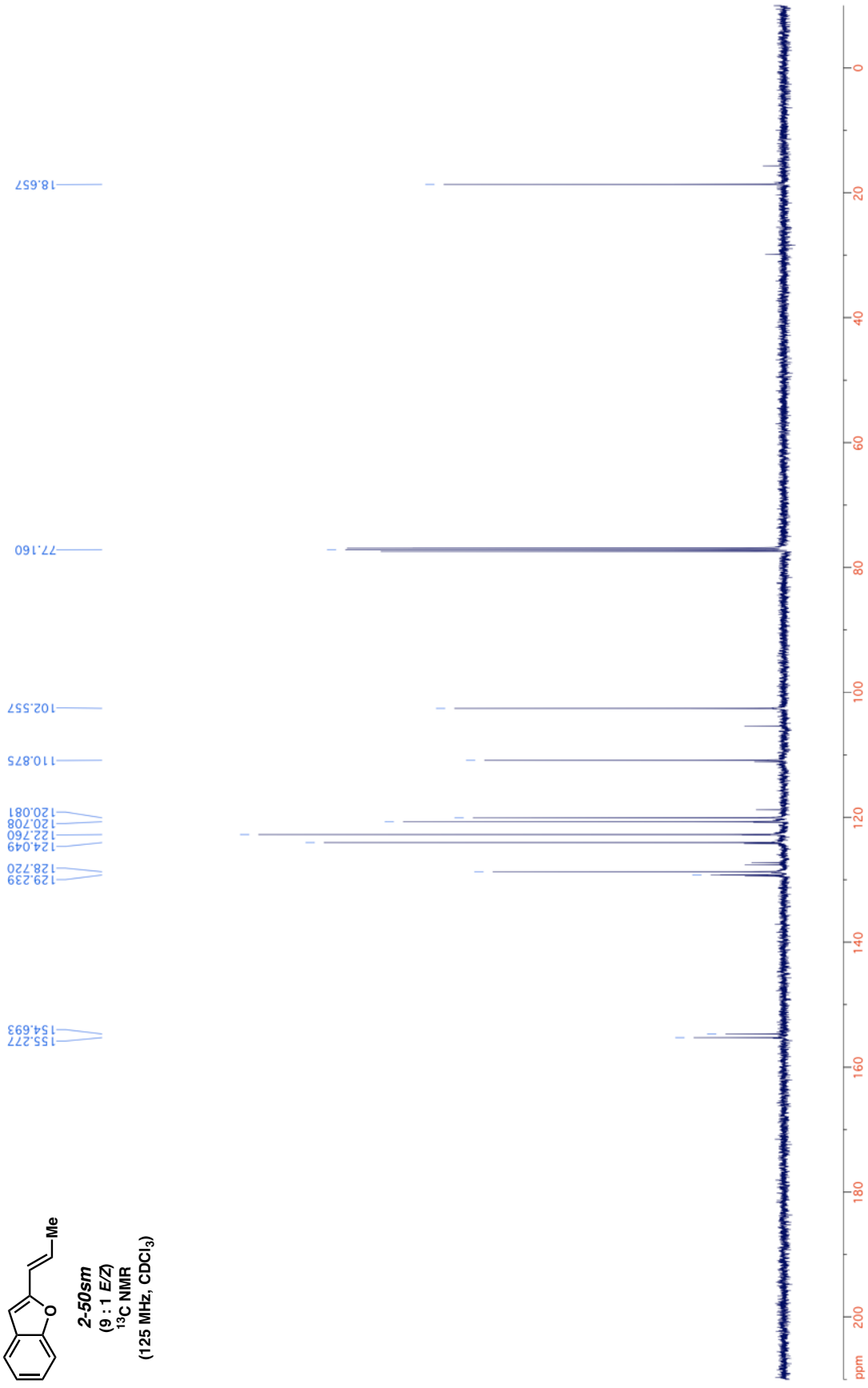
2-229
^{13}C NMR
(100 MHz, $CDCl_3$)

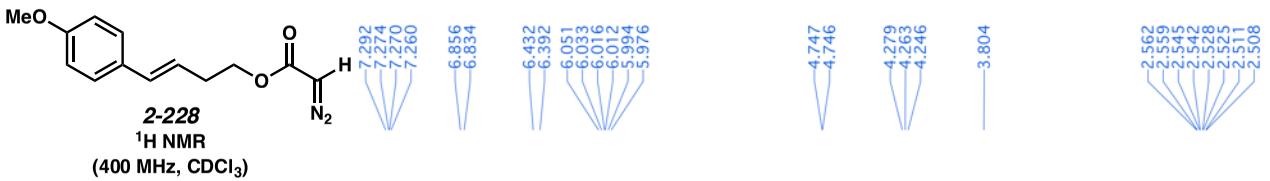


2-50sm
(9 : 1 *E/Z*)
^{1}H NMR
(400 MHz, $CDCl_3$)





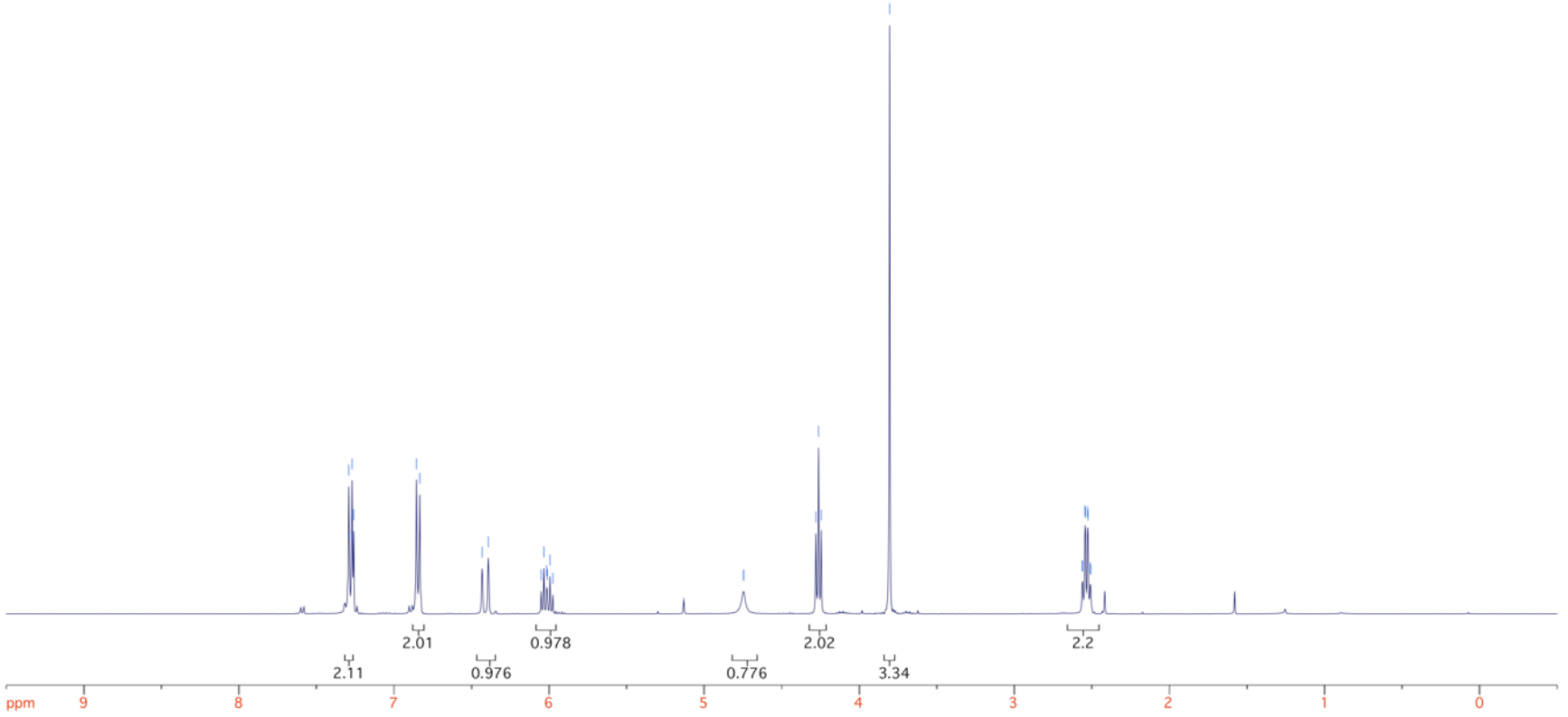

Me
O
2-50sm
(9 : 1 E/Z)
13C NMR
(125 MHz, CDCl3)
18.657
77.160
102.557
110.875
120.081
120.708
122.760
124.049
128.720
129.239
154.693
155.277
0
20
40
60
80
100
120
140
160
180
200
ppm

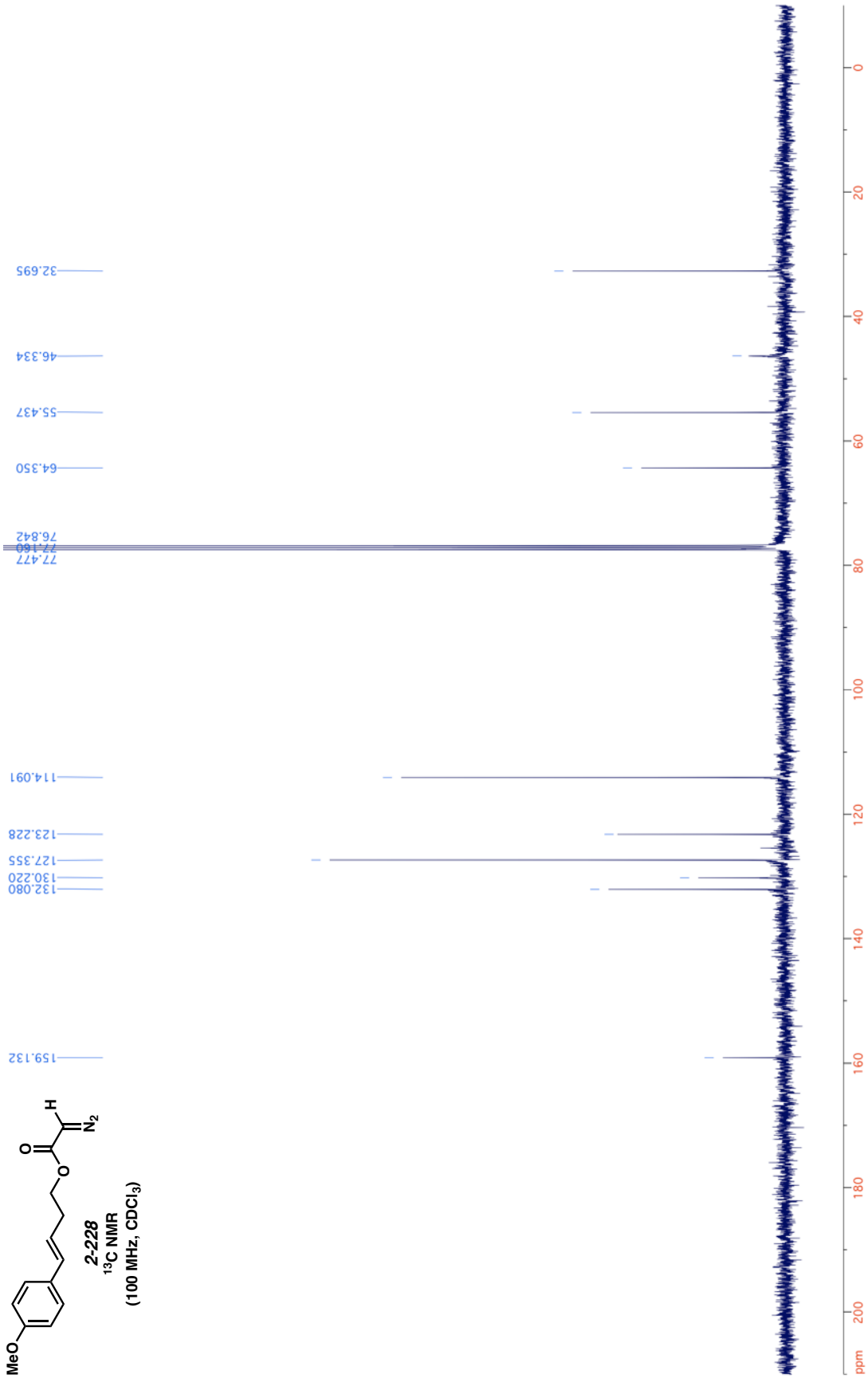


2-228

^{1}H NMR

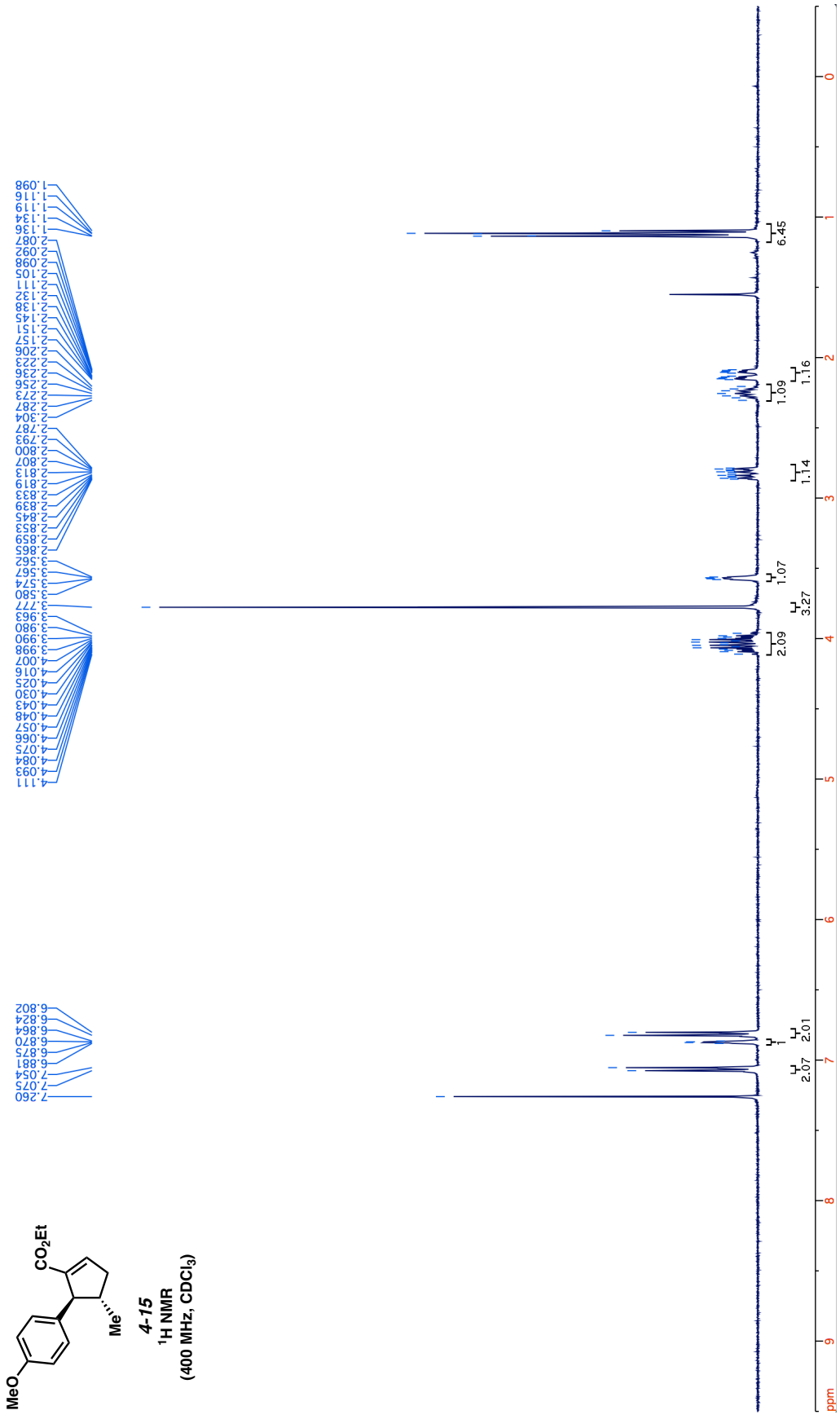
(400 MHz, $CDCl_3$)

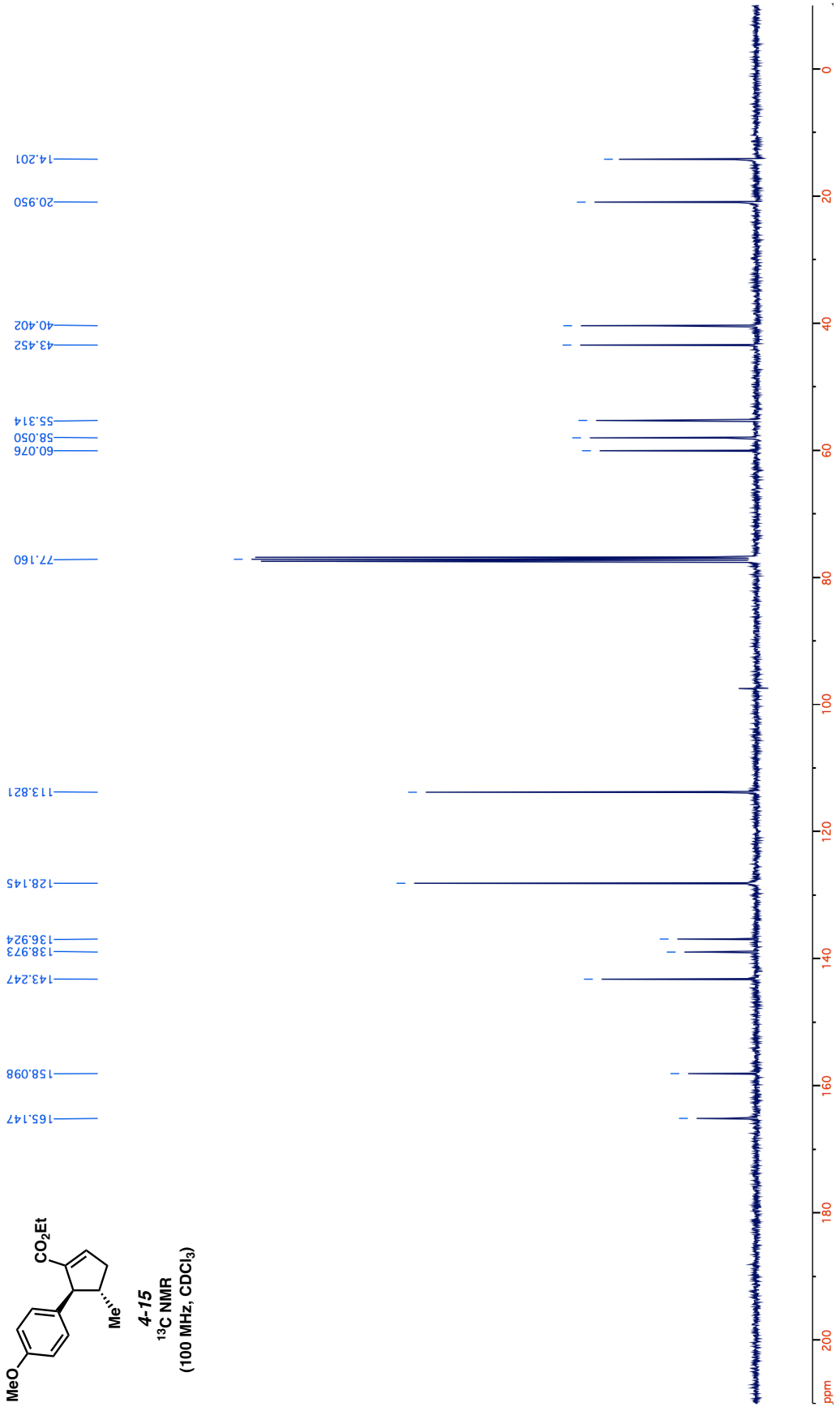


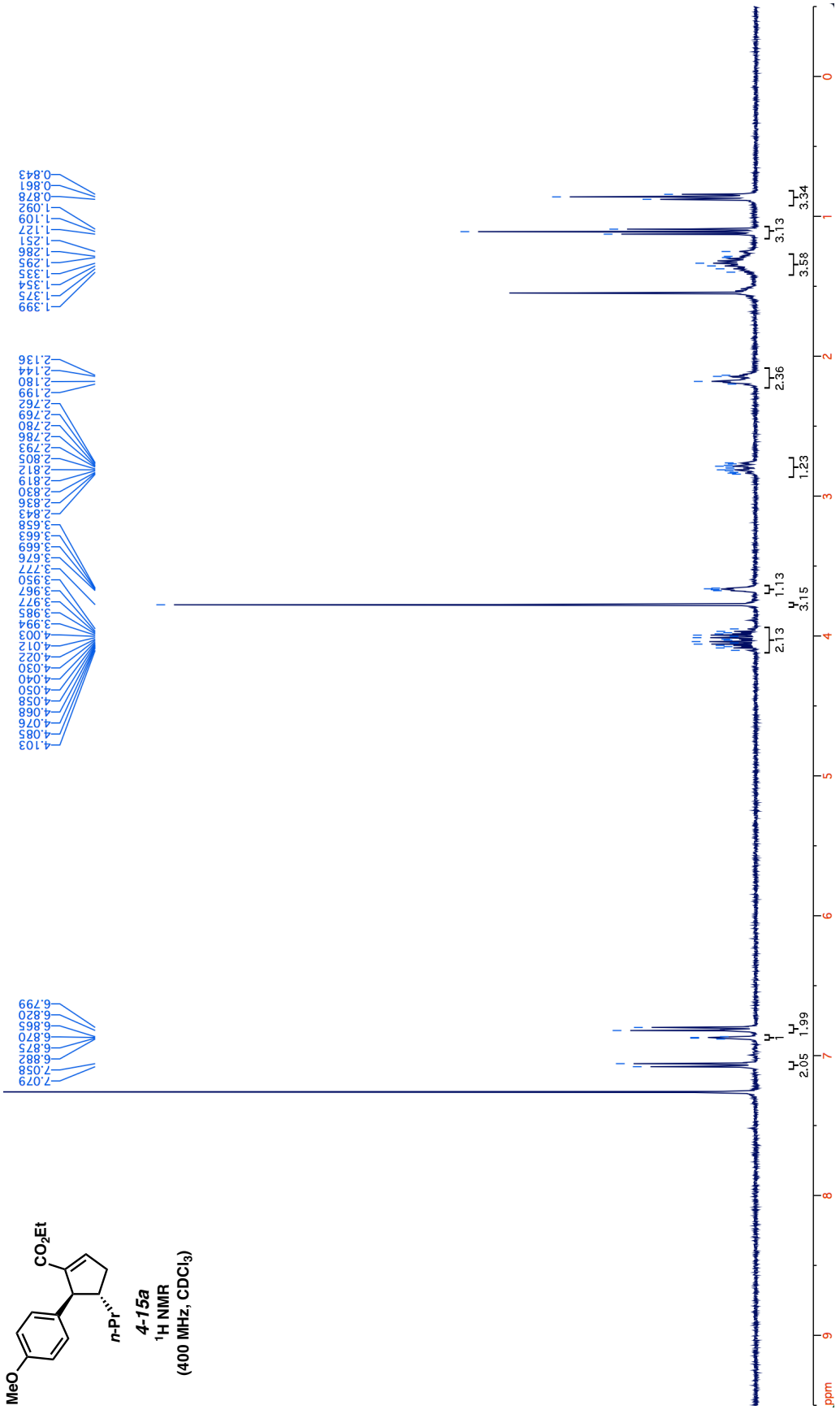

32.695
46.334
55.437
64.350
76.842
77.160
77.477
114.091
123.228
127.355
130.220
132.080
159.132
ppm
0
20
40
60
80
100
120
140
160
180
200
MeO
O
O
H
N2
2-228
13C NMR
(100 MHz, CDCl3)

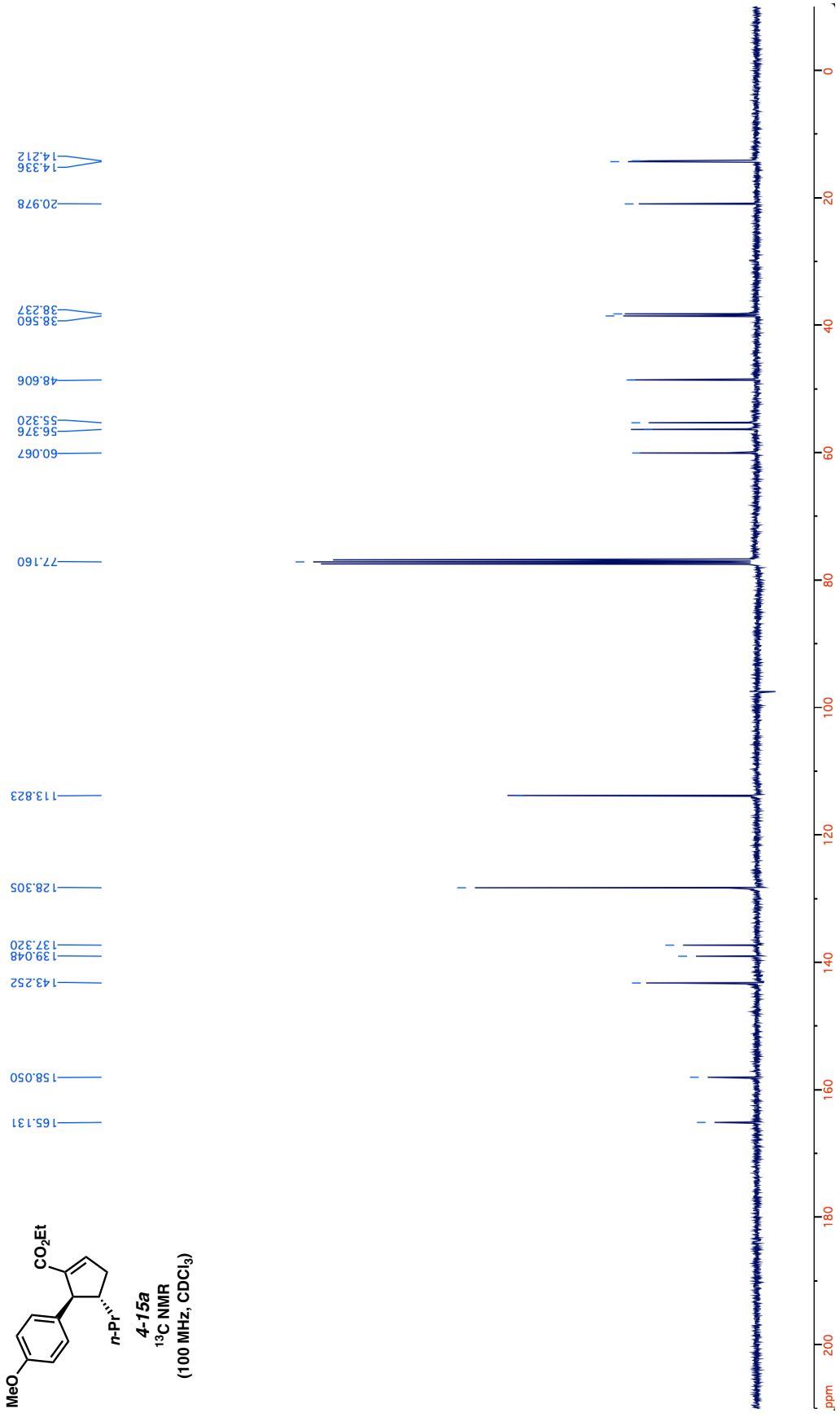
APPENDIX B

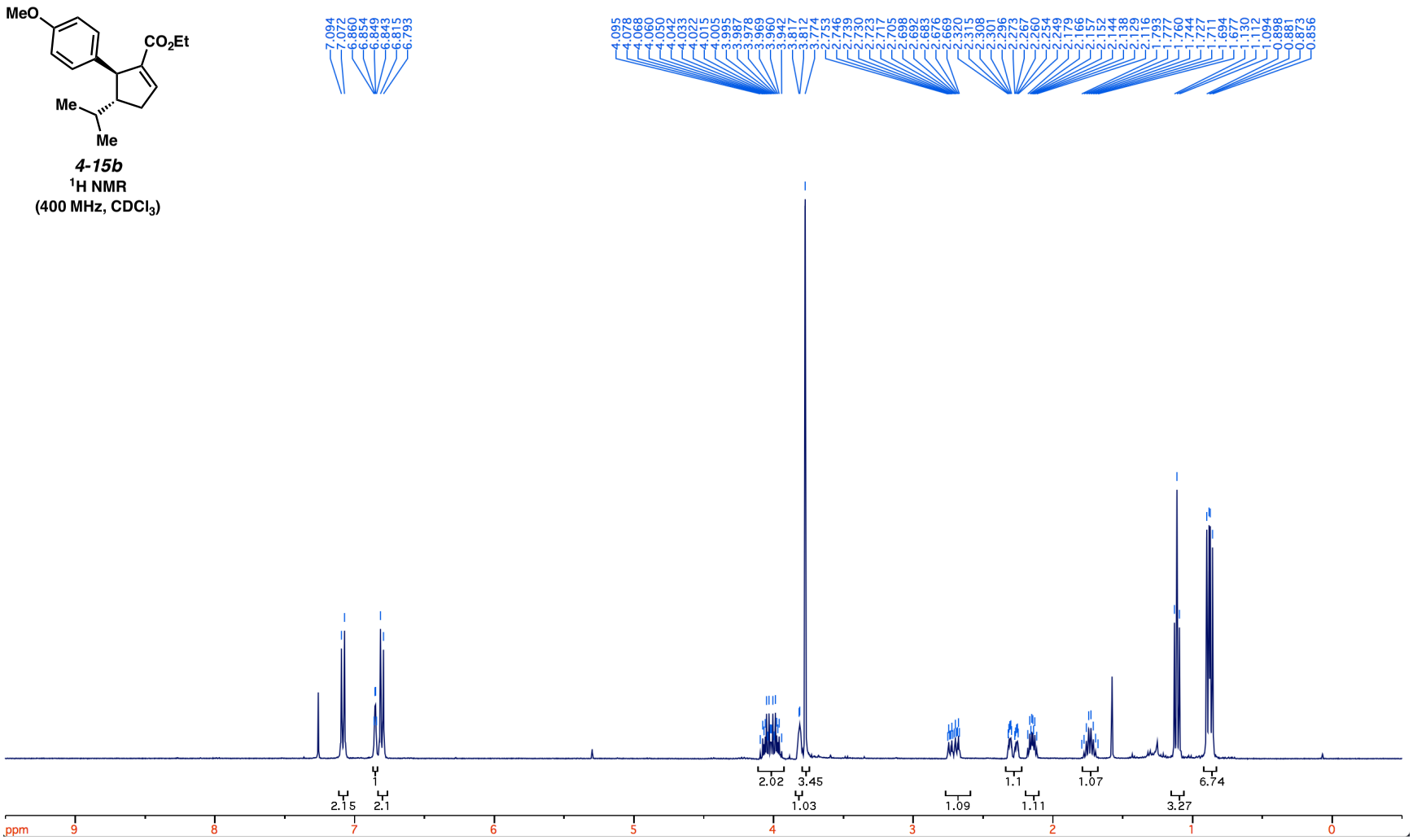
NMR SPECTRA RELEVANT TO CHAPTER 4

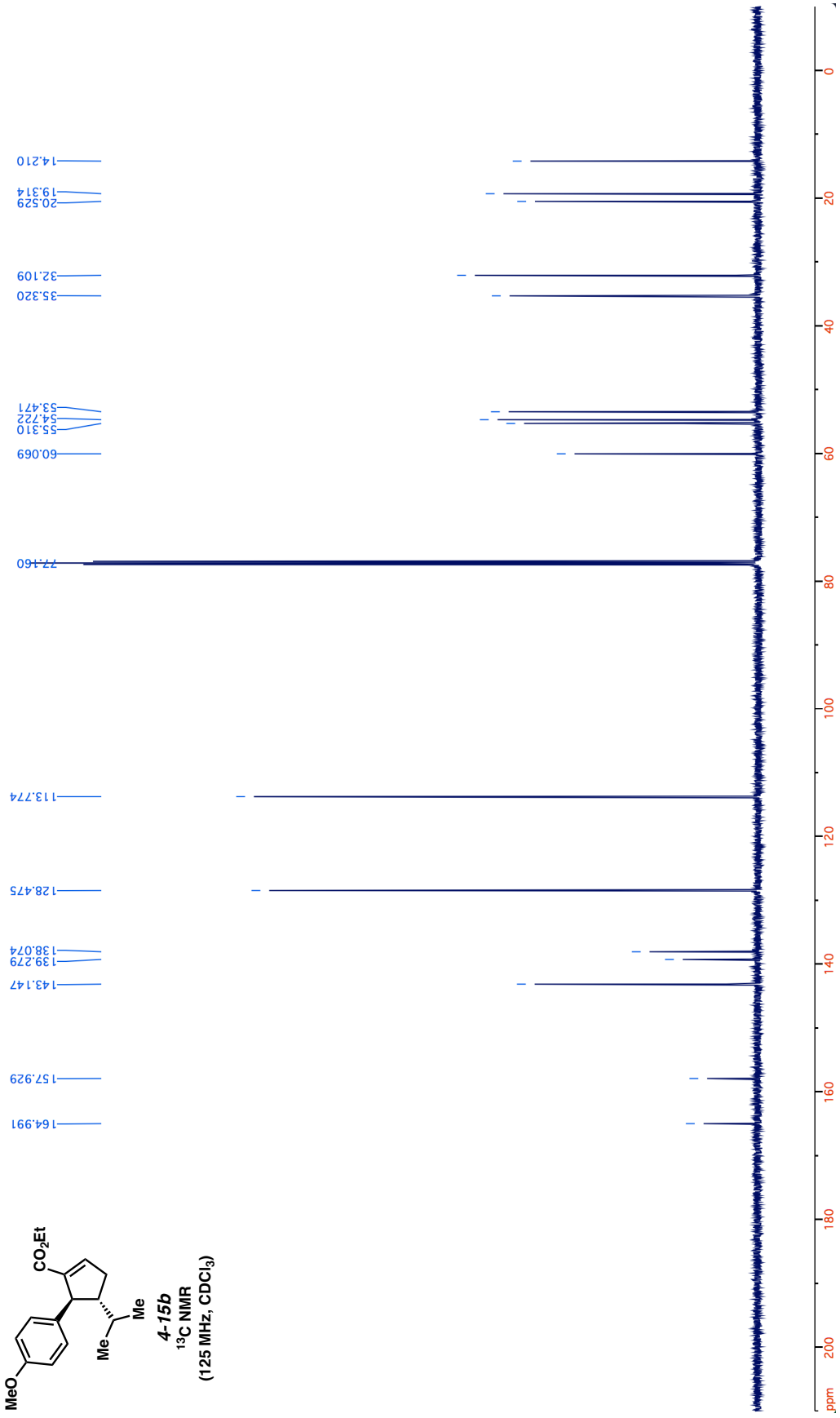

MeO
CO2Et
Me
4-15
1H NMR
(400 MHz, CDCl3)
ppm

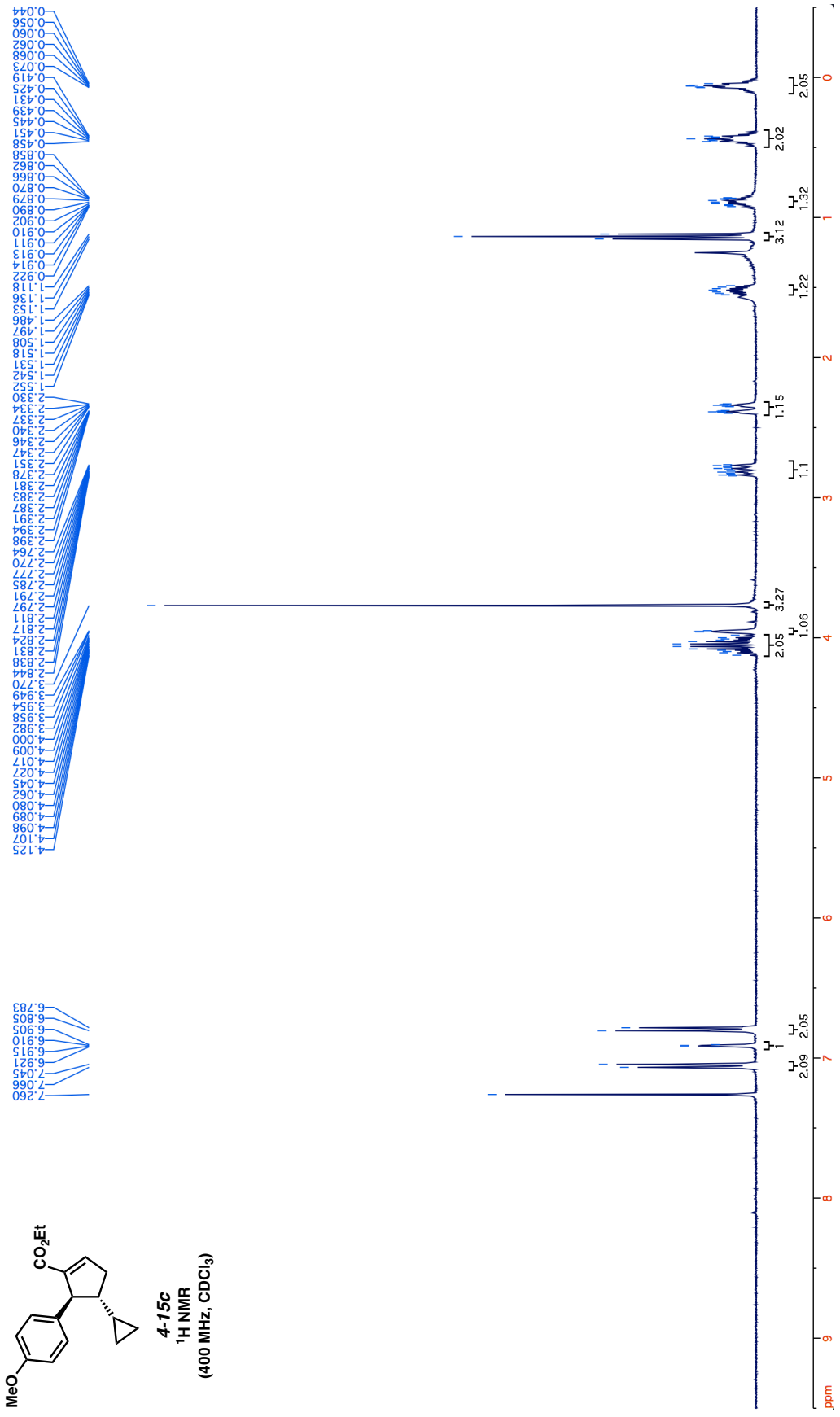

14.201
20.950
40.402
43.452
55.314
58.050
60.076
77.160
113.821
128.145
136.924
138.973
143.247
158.098
165.147
MeO
Me
CO2Et
4-15
13C NMR
(100 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm

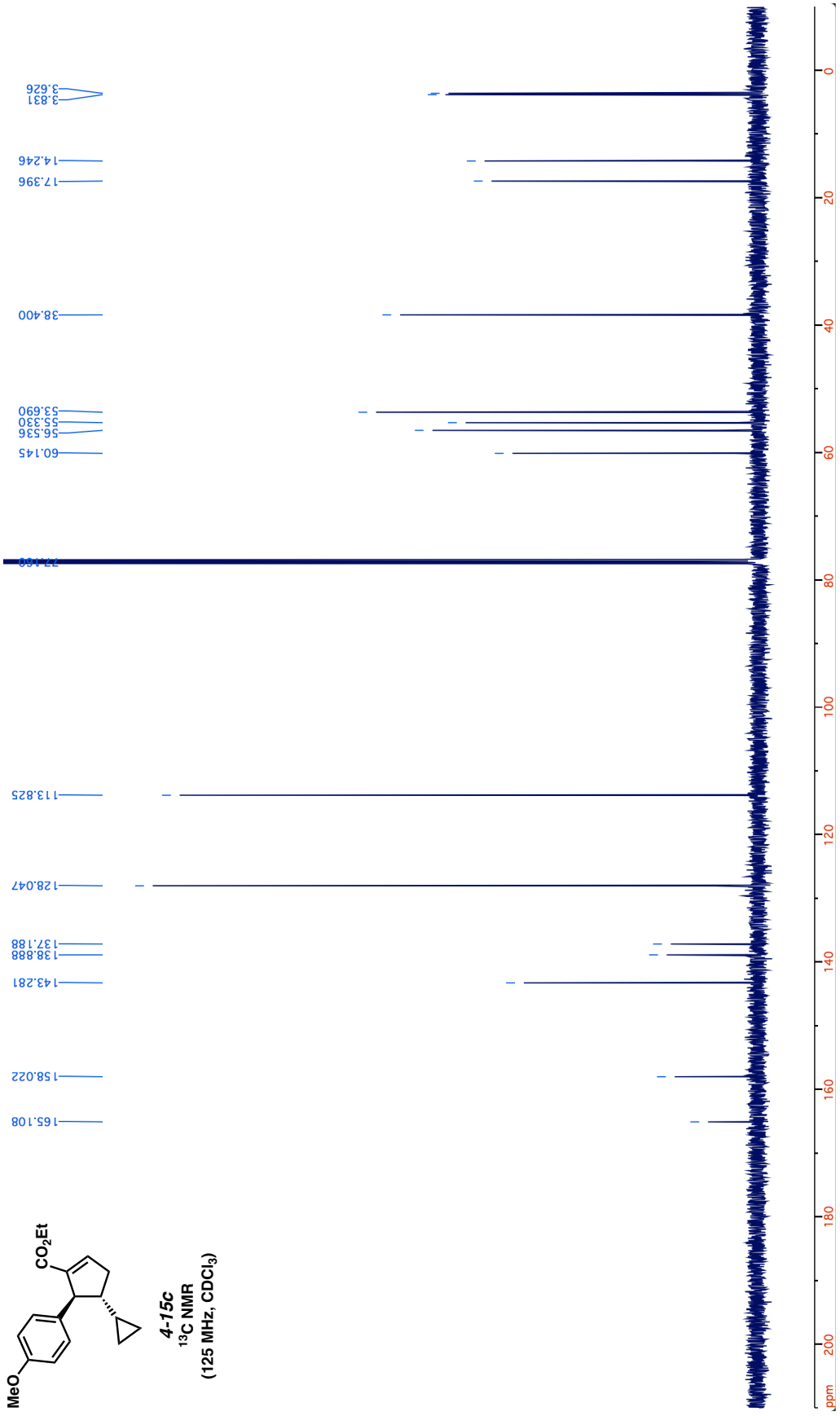

MeO
n-Pr
CO2Et
4-15a
1H NMR
(400 MHz, CDCl3)
7.079
7.058
6.882
6.875
6.870
6.865
6.820
6.799
4.103
4.085
4.076
4.068
4.058
4.050
4.040
4.030
4.012
4.002
3.994
3.985
3.977
3.967
3.950
3.777
3.676
3.669
3.663
3.658
2.843
2.836
2.830
2.812
2.805
2.793
2.786
2.780
2.769
2.762
2.199
2.180
2.144
2.136
1.399
1.375
1.354
1.335
1.295
1.286
1.251
1.127
1.109
1.092
0.878
0.861
0.843
1
1.99
2.05
2.13
1.13
3.15
2.36
1.23
3.13
3.58
3.34
ppm


14.212
14.336
20.978
38.237
38.560
48.606
55.320
56.376
60.067
77.160
113.823
128.305
137.320
139.048
143.252
158.050
165.131
MeO
n-Pr
CO2Et
4-15a
13C NMR
(100 MHz, CDCl3)
ppm

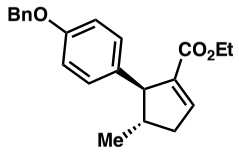

MeO
CO2Et
Me
Me
4-15b
1H NMR
(400 MHz, CDCl3)
7.094
7.072
6.860
6.854
6.849
6.843
6.815
6.793
4.095
4.078
4.068
4.060
4.050
4.042
4.033
4.022
4.015
4.005
3.995
3.987
3.978
3.969
3.960
3.942
3.817
3.812
3.774
3.753
2.746
2.739
2.730
2.723
2.707
2.705
2.698
2.692
2.683
2.676
2.669
2.320
2.315
2.308
2.301
2.296
2.273
2.267
2.260
2.254
2.249
2.179
2.166
2.157
2.152
2.144
2.138
2.129
2.116
1.793
1.777
1.760
1.744
1.727
1.711
1.694
1.677
1.170
1.112
1.094
0.898
0.881
0.873
0.856
1
2.15
2.1
2.02
3.45
1.03
1.09
1.1
1.11
1.07
3.27
6.74
ppm
9
8
7
6
5
4
3
2
1
0


14.210
19.314
20.529
32.109
35.320
53.471
54.722
55.310
60.069
77.160
113.774
128.475
138.074
139.279
143.147
157.929
164.991
ppm
0
20
40
60
80
100
120
140
160
180
200
MeO
Me
Me
CO2Et
4-15b
13C NMR
(125 MHz, CDCl3)

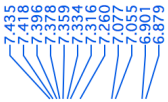

CO2Et
MeO
4-15c
1H NMR
(400 MHz, CDCl3)
ppm

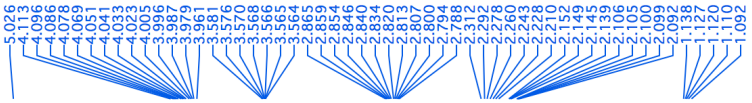


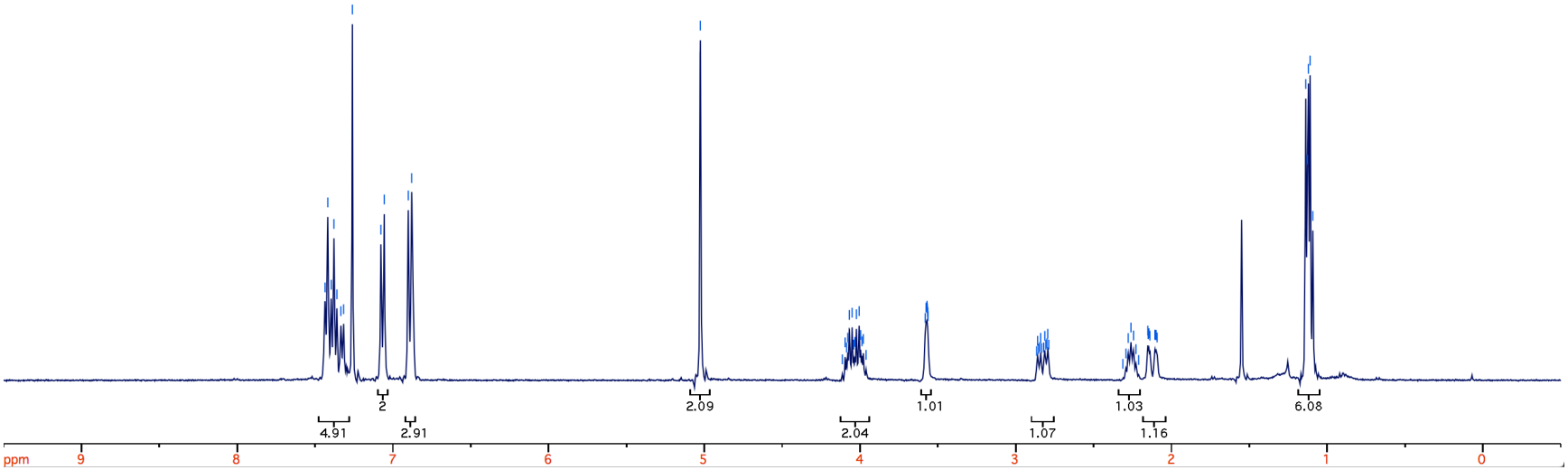
4-15c
^{13}C NMR
(125 MHz, $CDCl_3$)

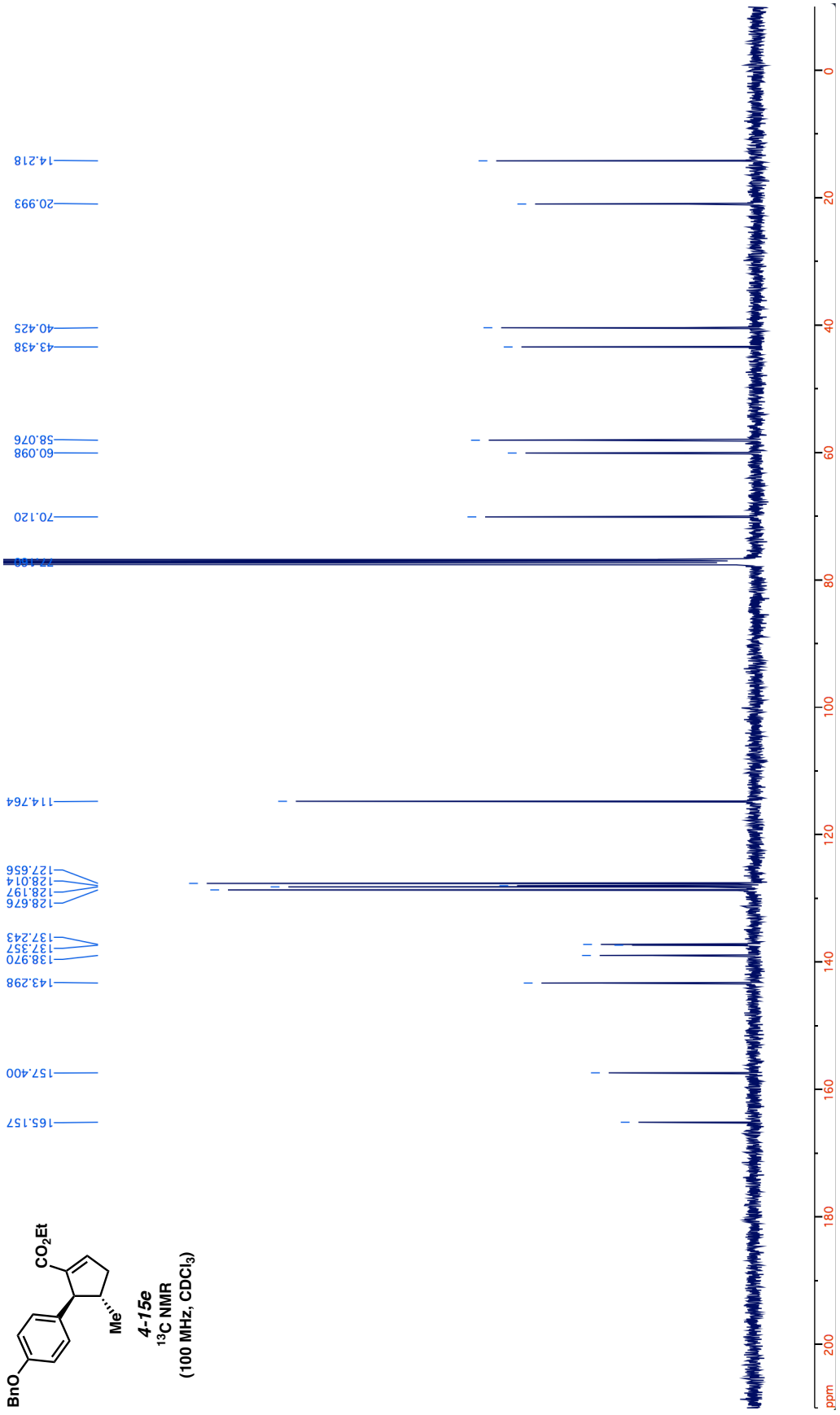


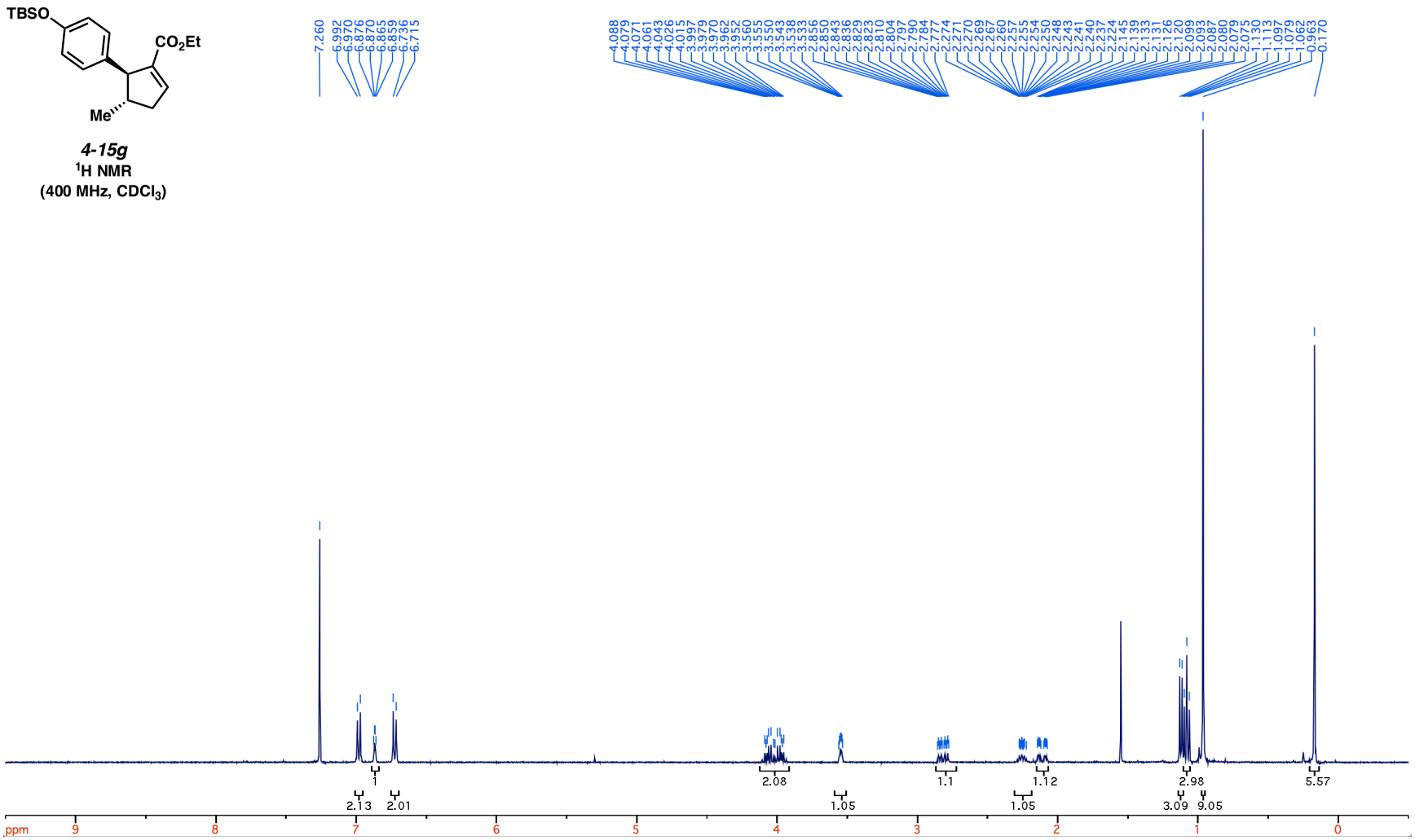
4-15e
^{1}H NMR
(400 MHz, $CDCl_3$)








14.218
20.993
40.425
43.438
58.076
60.098
70.120
114.764
127.656
128.014
128.197
128.676
137.243
137.357
138.970
143.298
157.400
165.157
BnO
Me
CO2Et
4-15e
13C NMR
(100 MHz, CDCl3)
ppm


TBSO
CO2Et
Me
4-15g
1H NMR
(400 MHz, CDCl3)
7.260
6.992
6.970
6.876
6.870
6.865
6.659
6.736
6.715
4.088
4.079
4.071
4.061
4.043
4.026
4.015
3.997
3.979
3.970
3.962
3.952
3.560
3.555
3.550
3.543
3.538
3.353
3.356
2.850
2.843
2.836
2.829
2.823
2.810
2.804
2.797
2.790
2.784
2.777
2.274
2.271
2.270
2.269
2.267
2.260
2.257
2.255
2.254
2.250
2.248
2.243
2.241
2.240
2.237
2.224
2.145
2.139
2.133
2.131
2.126
2.120
2.093
2.087
2.080
2.079
2.075
1.130
1.113
1.097
1.079
1.062
0.963
0.170
1
2.13
2.01
2.08
1.05
1.1
1.05
1.12
2.98
3.09
9.05
5.57
ppm
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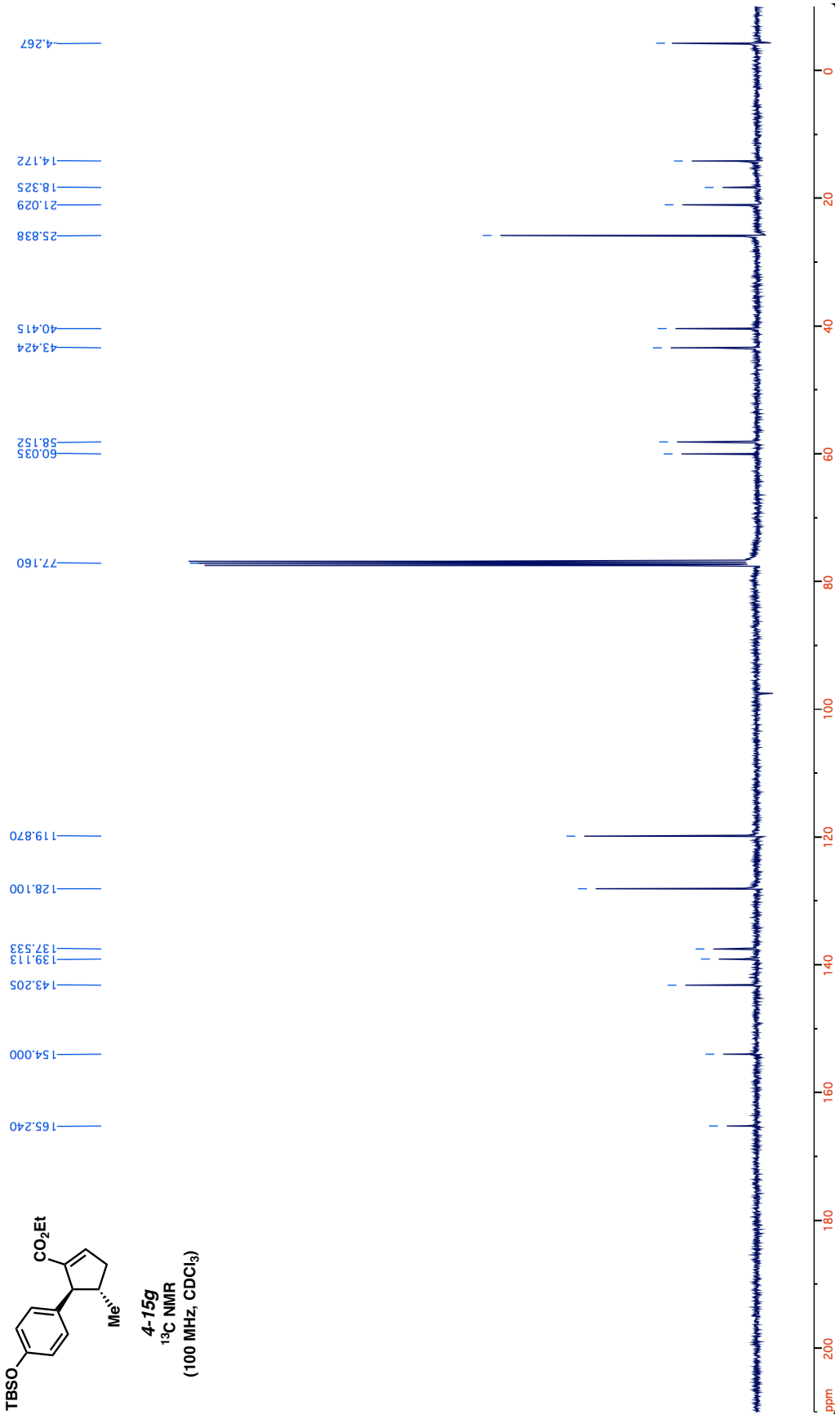
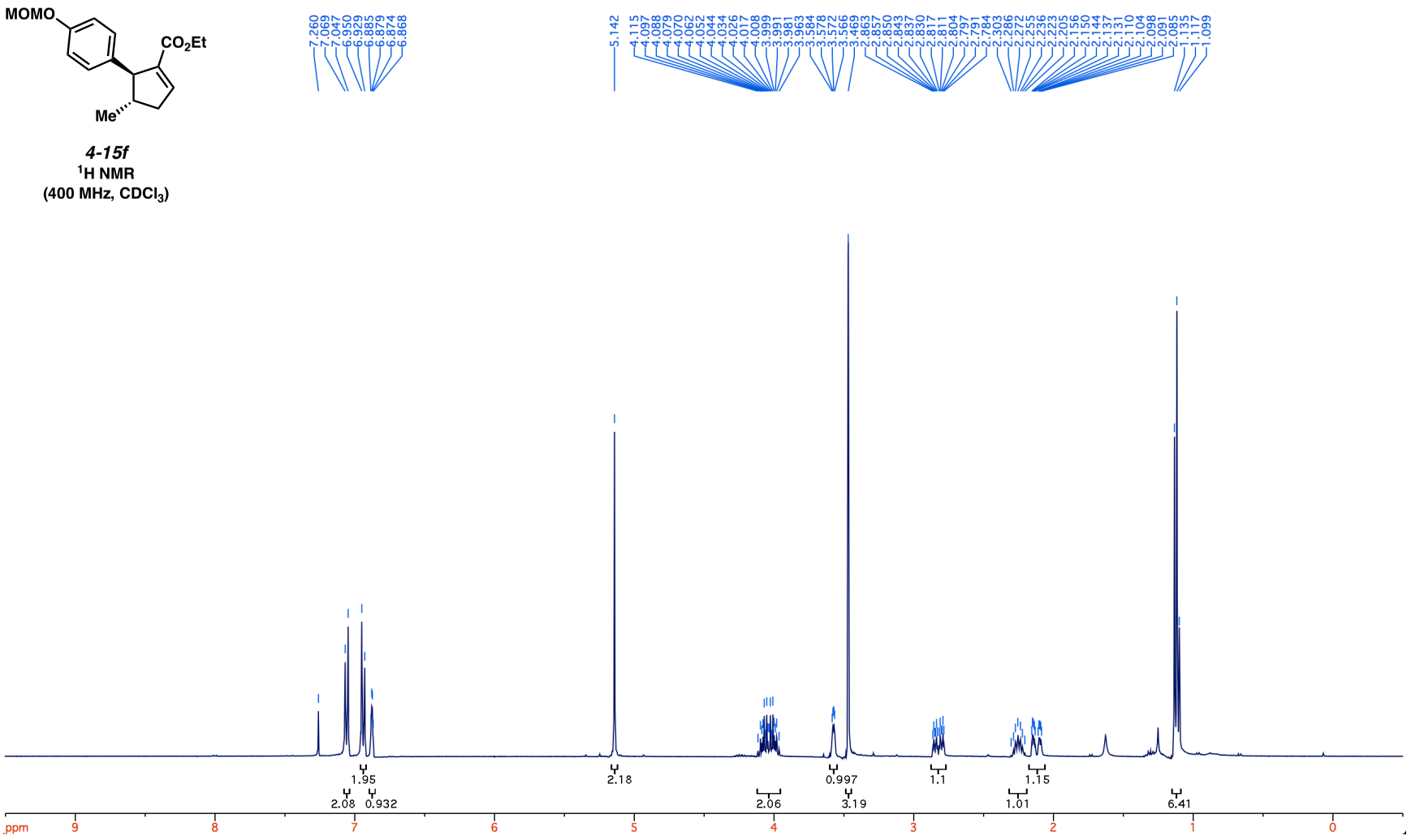
8
7
6
5
4
3
2
1
0


TBSO
CO2Et
Me
4-15g
13C NMR
(100 MHz, CDCl3)
4.267
14.172
18.325
21.029
25.838
40.415
43.424
58.152
60.035
77.160
119.870
128.100
137.533
139.113
143.205
154.000
165.240
ppm


MOMO
CO2Et
Me
4-15f
1H NMR
(400 MHz, CDCl3)
7.260
7.069
7.047
6.950
6.929
6.885
6.879
6.874
6.868
5.142
4.115
4.097
4.088
4.079
4.070
4.062
4.052
4.044
4.034
4.026
4.017
4.008
3.999
3.991
3.981
3.963
3.584
3.578
3.572
3.566
3.469
2.863
2.857
2.850
2.843
2.837
2.830
2.817
2.811
2.804
2.797
2.791
2.784
2.303
2.286
2.272
2.255
2.236
2.223
2.205
2.156
2.150
2.144
2.137
2.131
2.110
2.104
2.098
2.091
1.135
1.117
1.099
1.95
2.08
0.932
2.18
2.06
0.997
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1.01
1.15
6.41
ppm
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7
6
5
4
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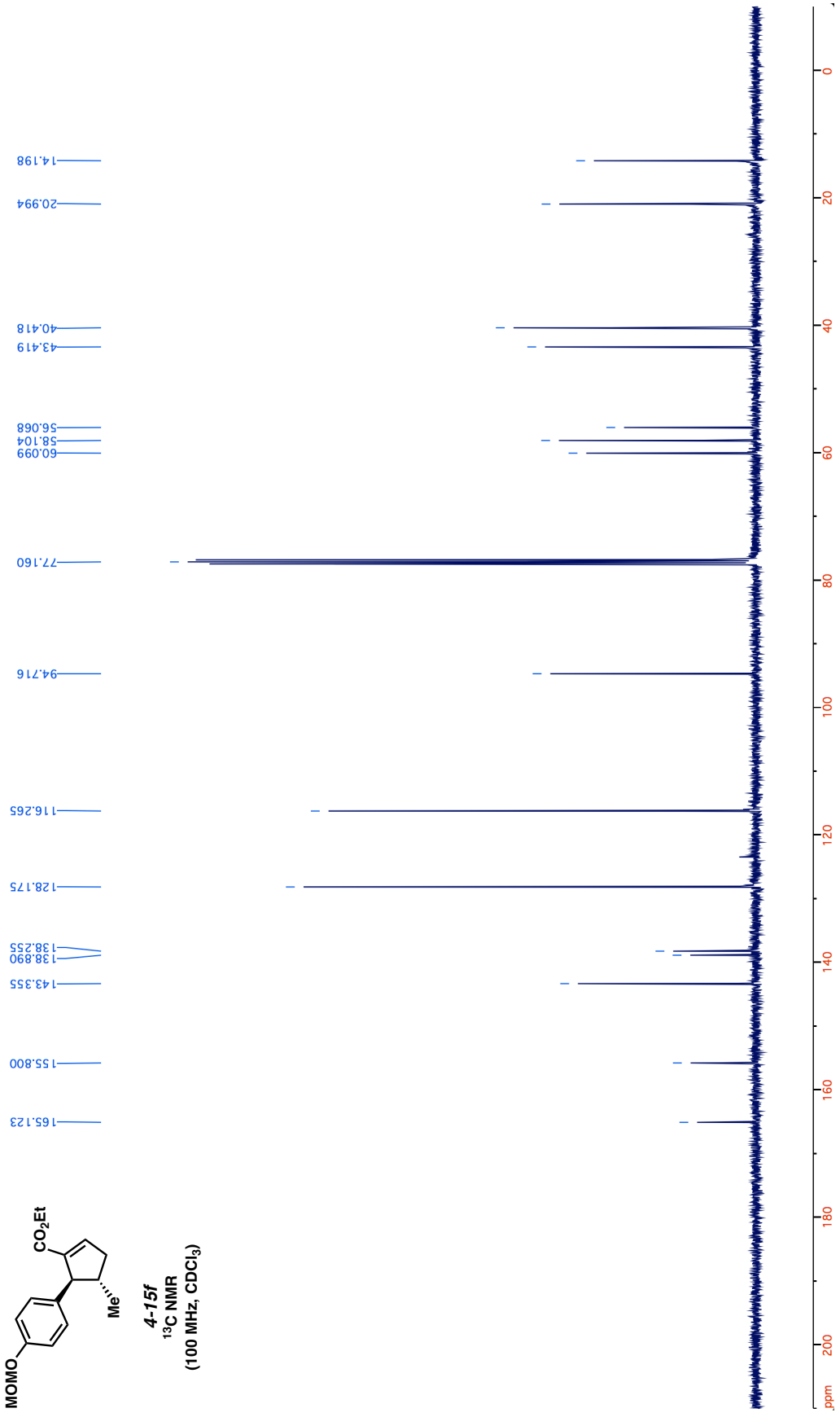
2
1
0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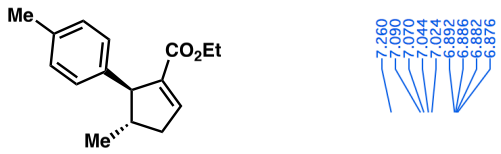
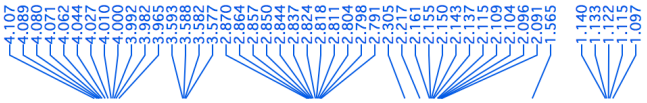
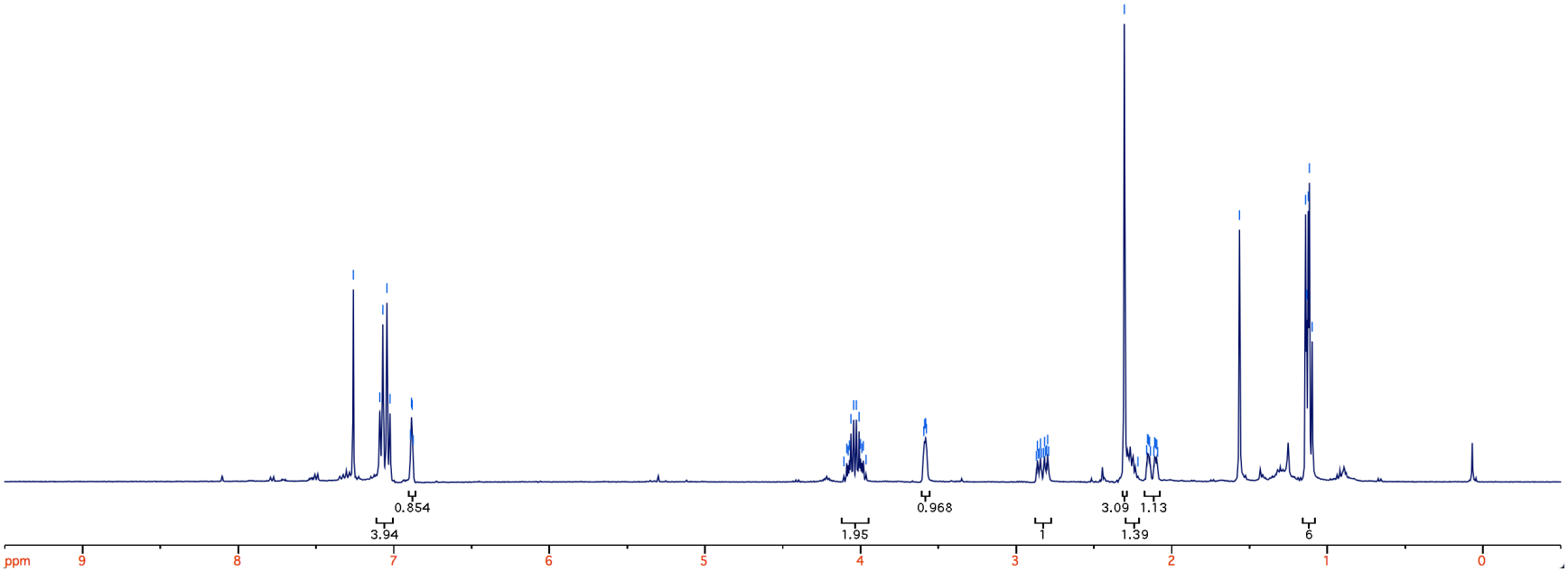
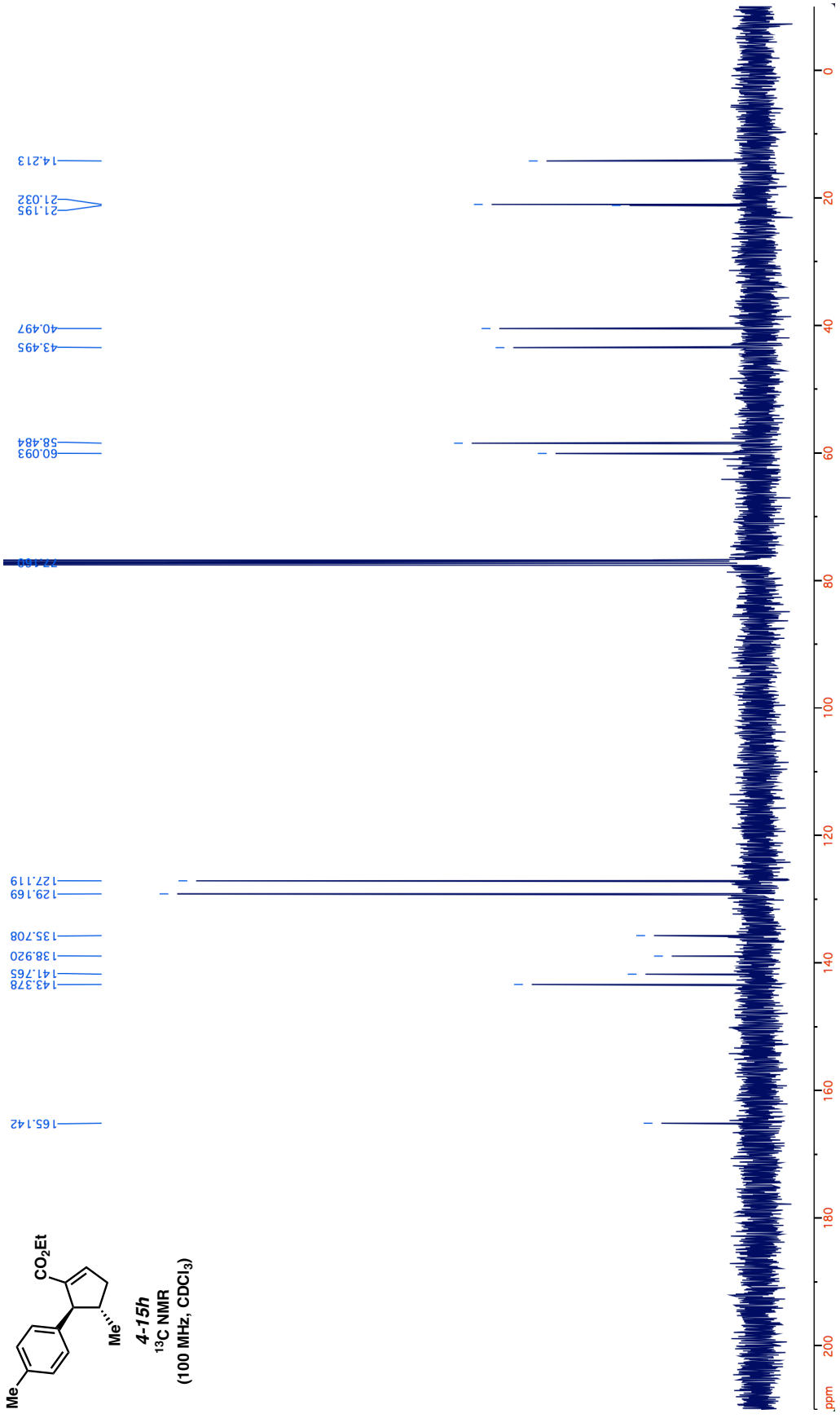
40.418
43.419
56.068
58.104
60.099
77.160
94.716
116.265
128.175
138.255
138.890
143.355
155.800
165.123
MOMO
CO2Et
Me
4-15f
13C NMR
(100 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm



4-15h
^{1}H NMR
(400 MHz, $CDCl_3$)



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21.032
21.195
40.497
43.495
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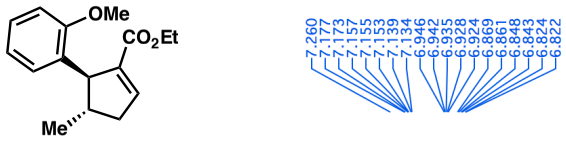
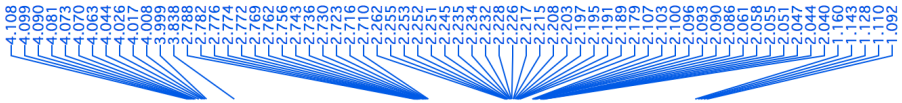
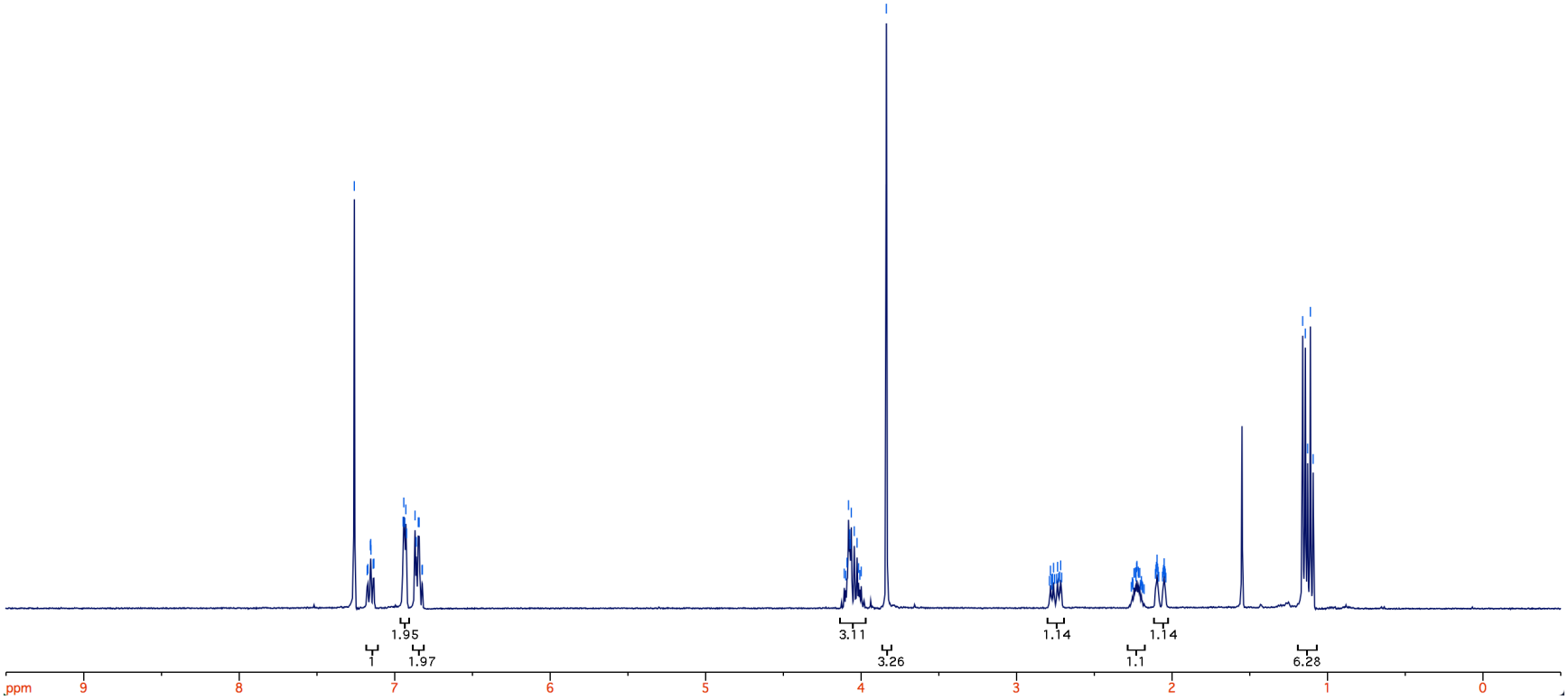
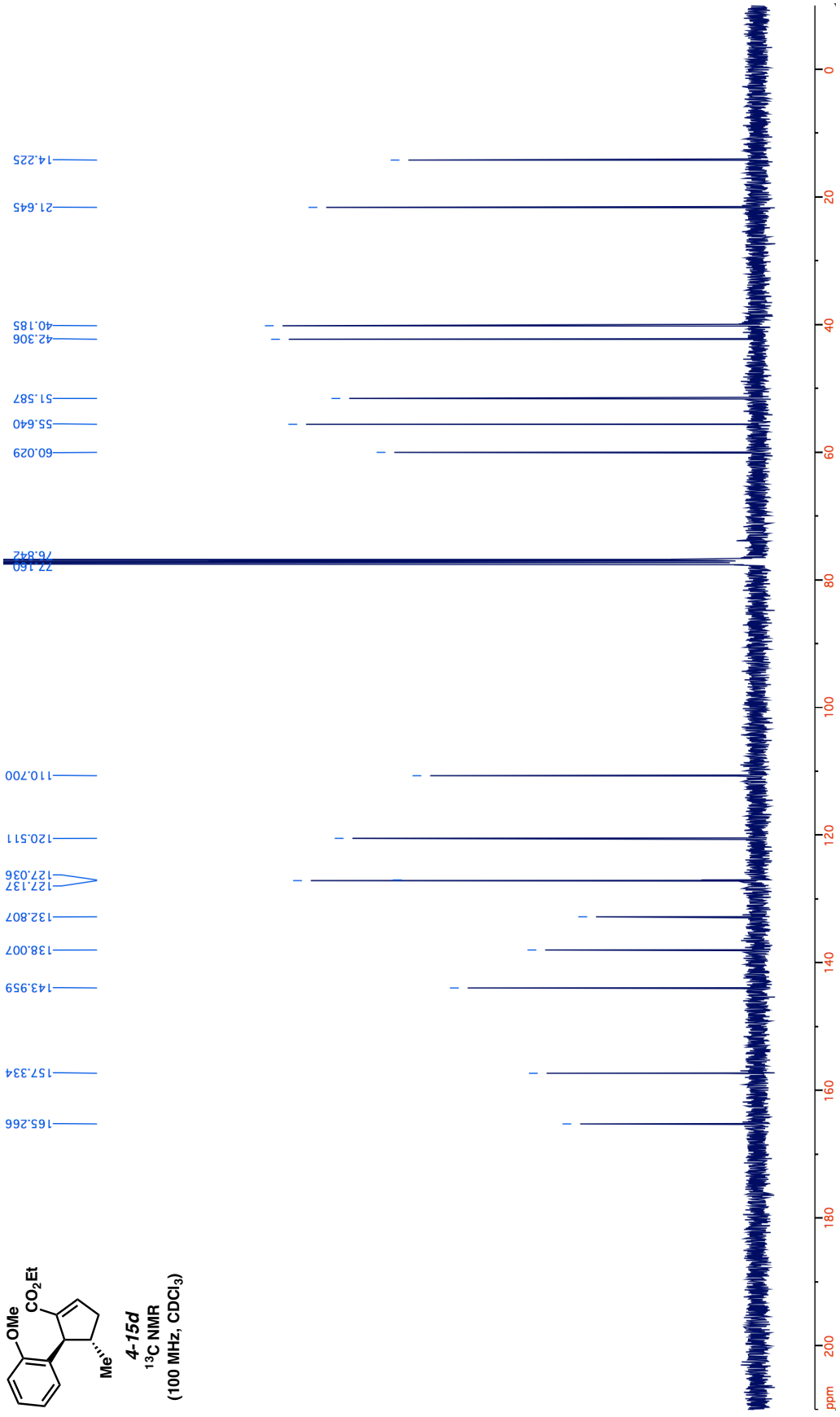
60.093
77.488
127.119
129.169
135.708
138.920
141.765
143.378
165.142
ppm
0
20
40
60
80
100
120
140
160
180
200
Me
Me
CO2Et
4-15h
13C NMR
(100 MHz, CDCl3)



4-15d
^{1}H NMR
(400 MHz, $CDCl_3$)



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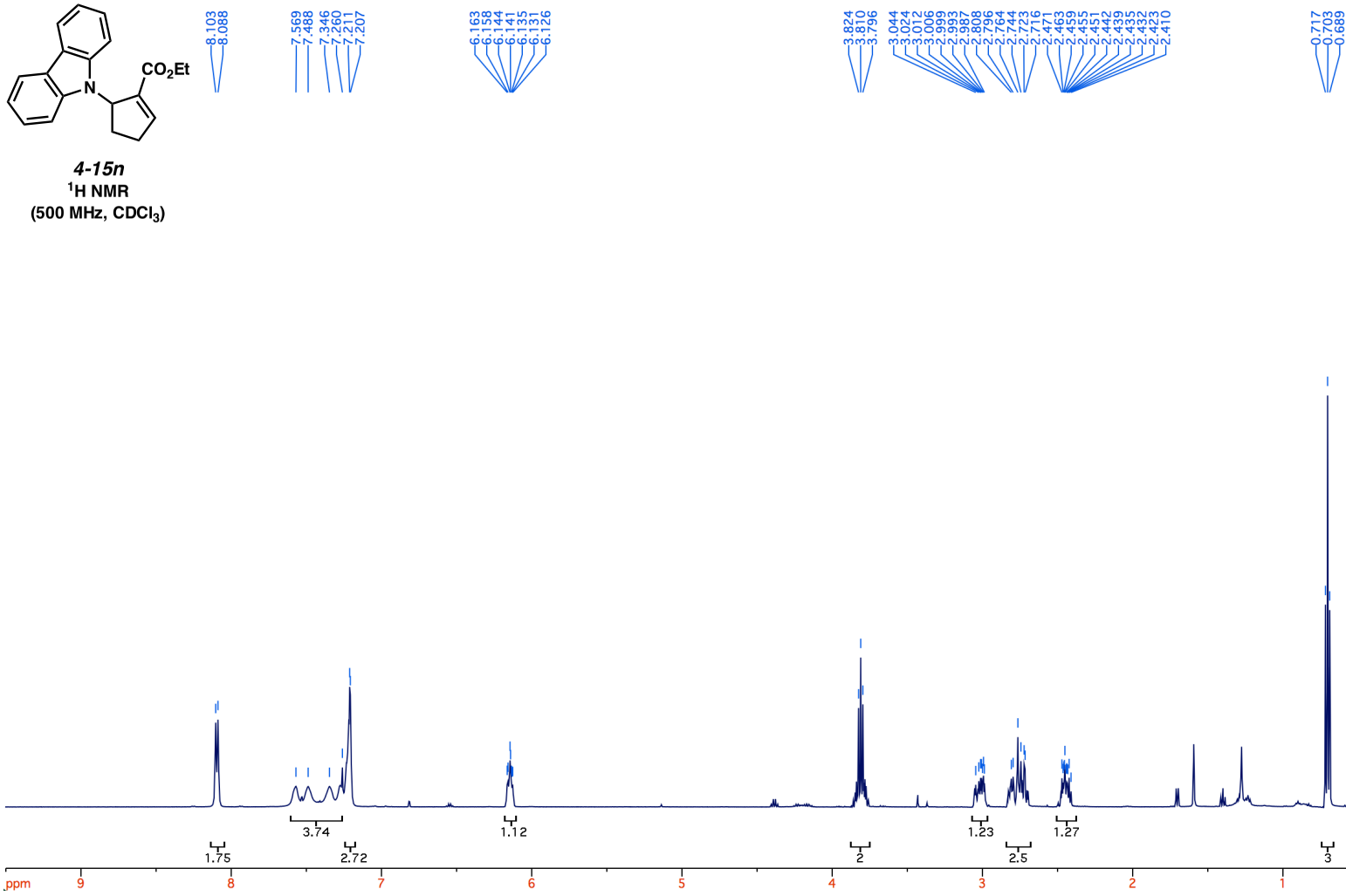
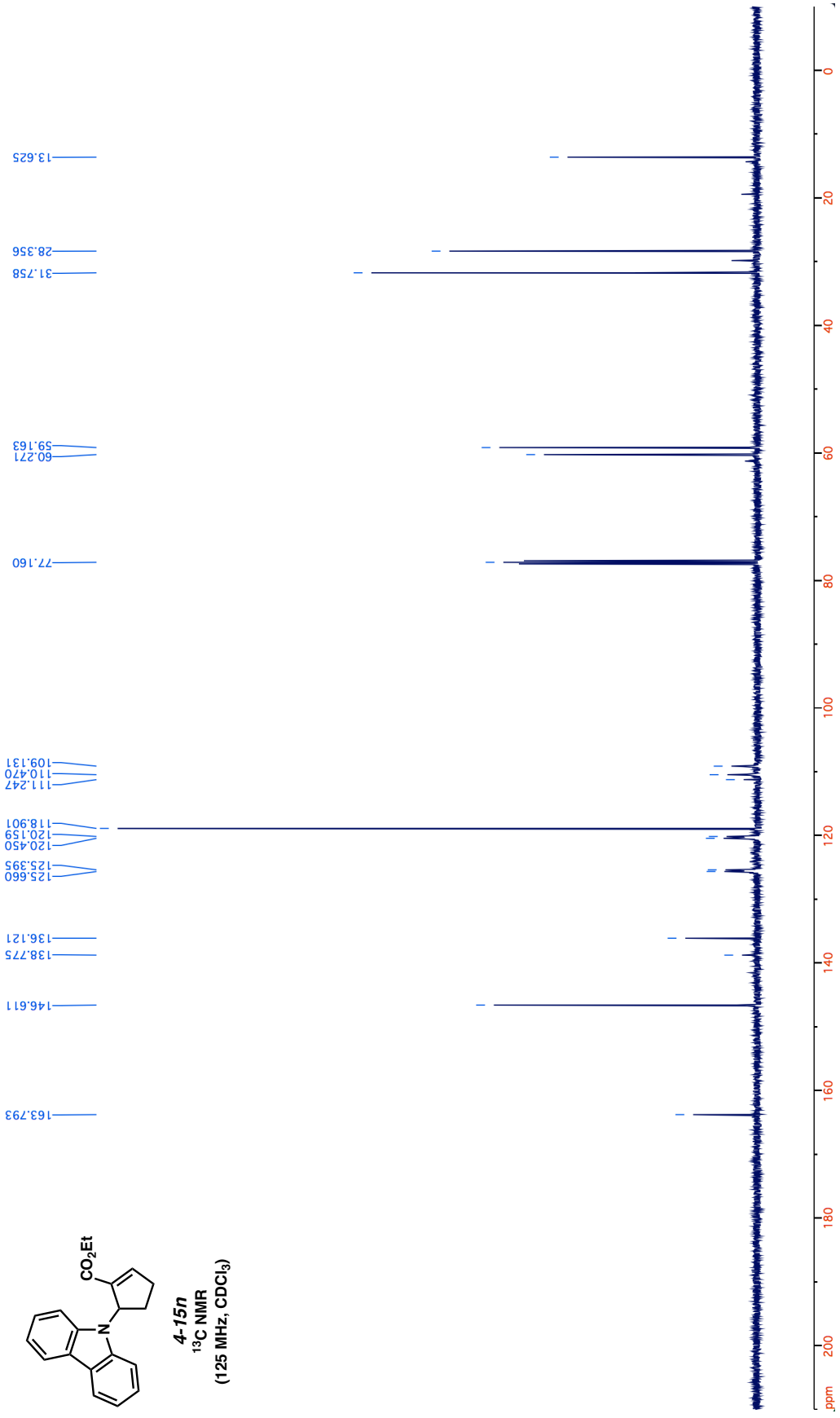
21.645
40.185
42.306
51.587
55.640
60.029
77.160
76.842
110.700
120.511
127.137
127.036
132.807
138.007
143.959
157.334
165.266
ppm
0
20
40
60
80
100
120
140
160
180
200
OMe
CO2Et
Me
4-15d
13C NMR
(100 MHz, CDCl3)



4-15n
^{1}H NMR
(500 MHz, $CDCl_3$)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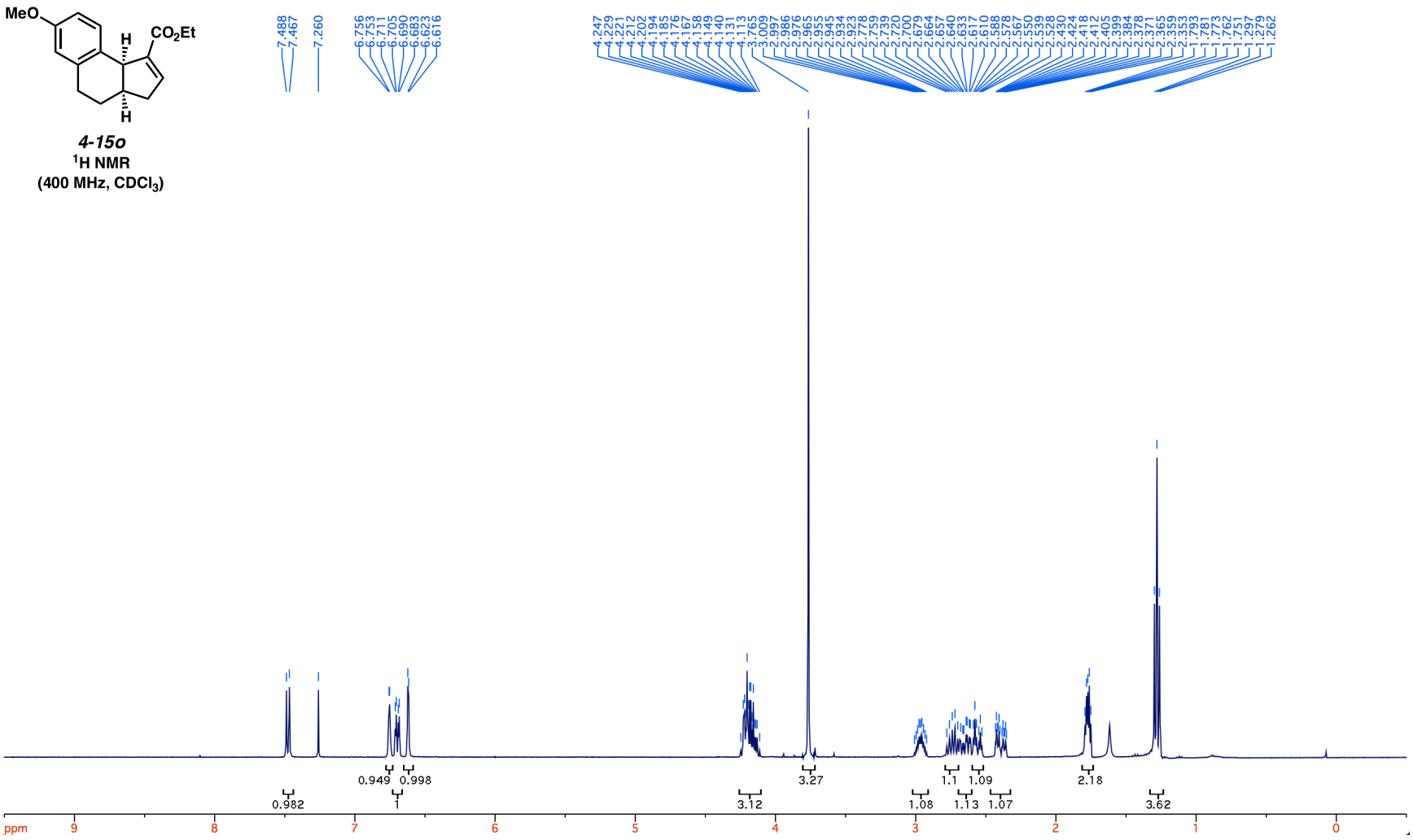
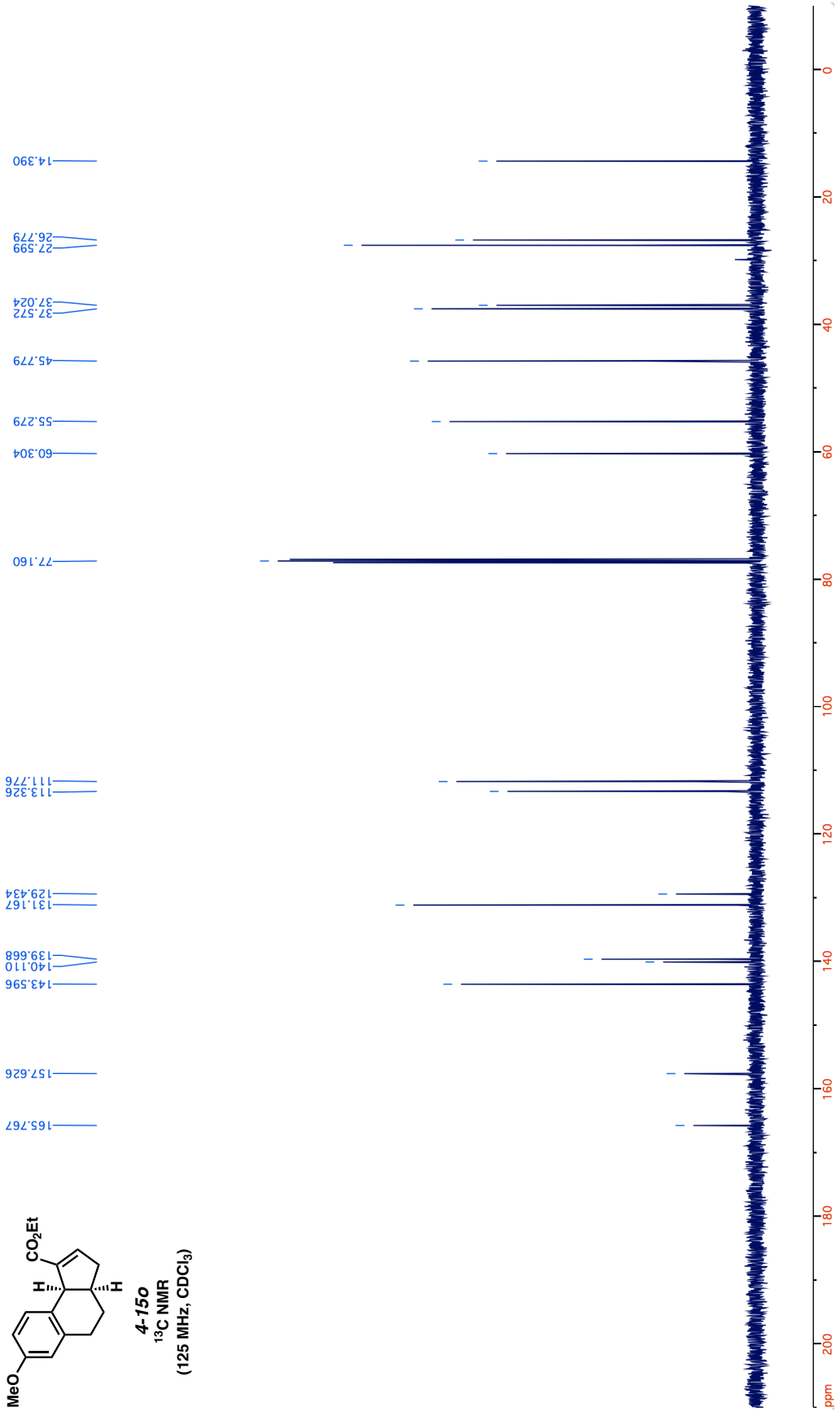
28.356
31.758
59.163
60.271
77.160
109.131
110.470
111.247
118.901
120.159
120.450
125.395
125.660
136.121
138.775
146.611
163.793
CO2Et
N
4-15n
13C NMR
(125 MHz, CDCl3)
ppm


MeO
CO2Et
H
H
4-15o
1H NMR
(400 MHz, CDCl3)
7.488
7.467
7.260
6.756
6.753
6.711
6.705
6.690
6.683
6.623
6.616
4.247
4.229
4.221
4.212
4.202
4.194
4.175
4.167
4.158
4.149
4.140
4.131
4.113
3.765
3.009
2.997
2.986
2.976
2.965
2.955
2.945
2.934
2.923
2.778
2.759
2.739
2.720
2.700
2.679
2.664
2.657
2.640
2.633
2.617
2.610
2.588
2.578
2.567
2.550
2.539
2.528
2.430
2.424
2.418
2.412
2.405
2.399
2.384
2.378
2.371
2.365
2.359
2.353
1.793
1.781
1.773
1.762
1.751
1.297
1.279
1.262
0.982
0.949
0.998
1
3.12
3.27
1.08
1.1
1.13
1.09
1.07
2.18
3.62
ppm
9
8
7
6
5
4
3
2
1
0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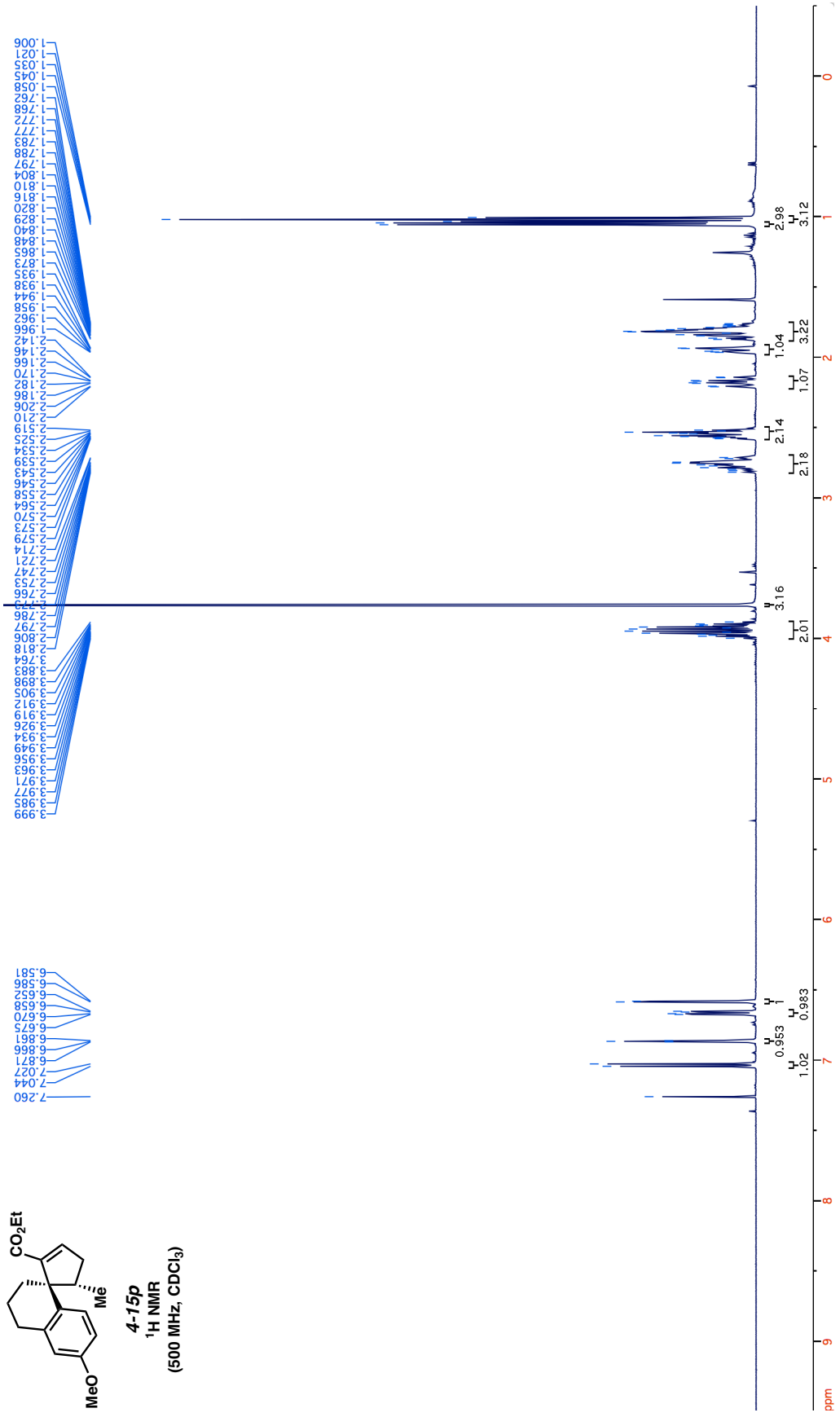
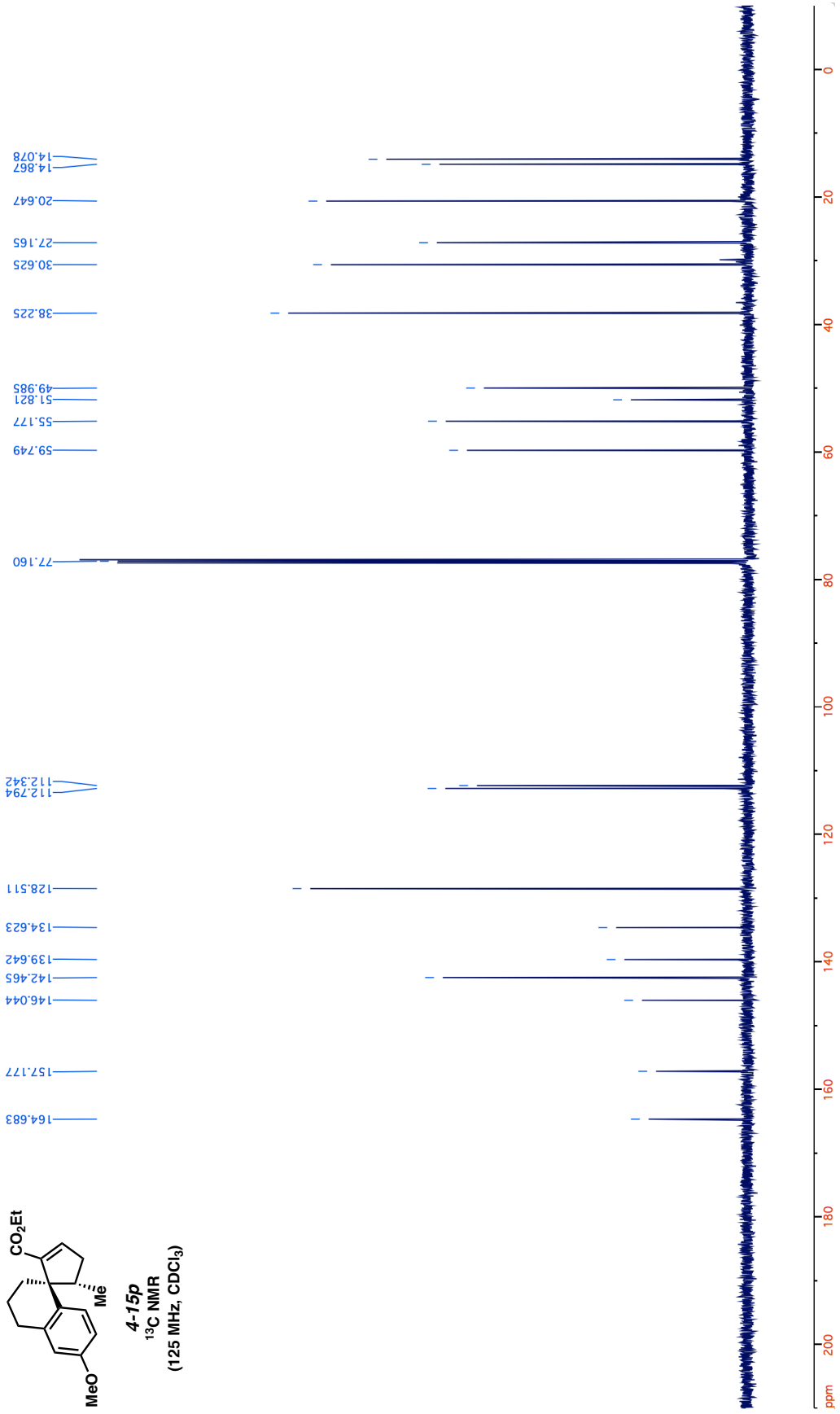
26.779
27.599
37.024
37.572
45.779
55.279
60.304
77.160
111.776
113.326
129.434
131.167
139.668
140.110
143.596
157.626
165.767
MeO
H
H
CO2Et
4-15o
13C NMR
(125 MHz, CDCl3)
ppm
0
20
40
60
80
100
120
140
160
180
200


CO2Et
Me
MeO
4-15p
1H NMR
(500 MHz, CDCl3)
ppm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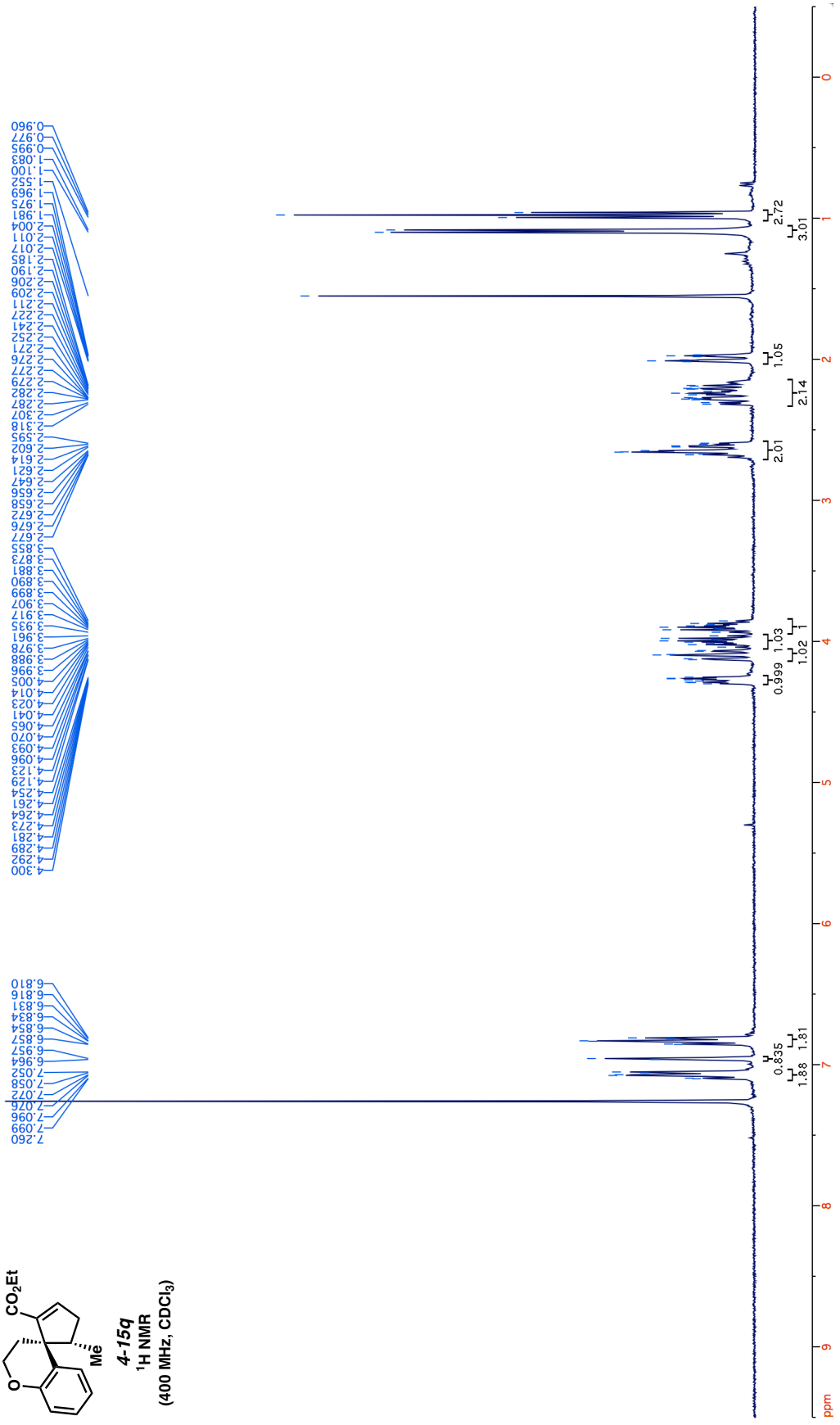
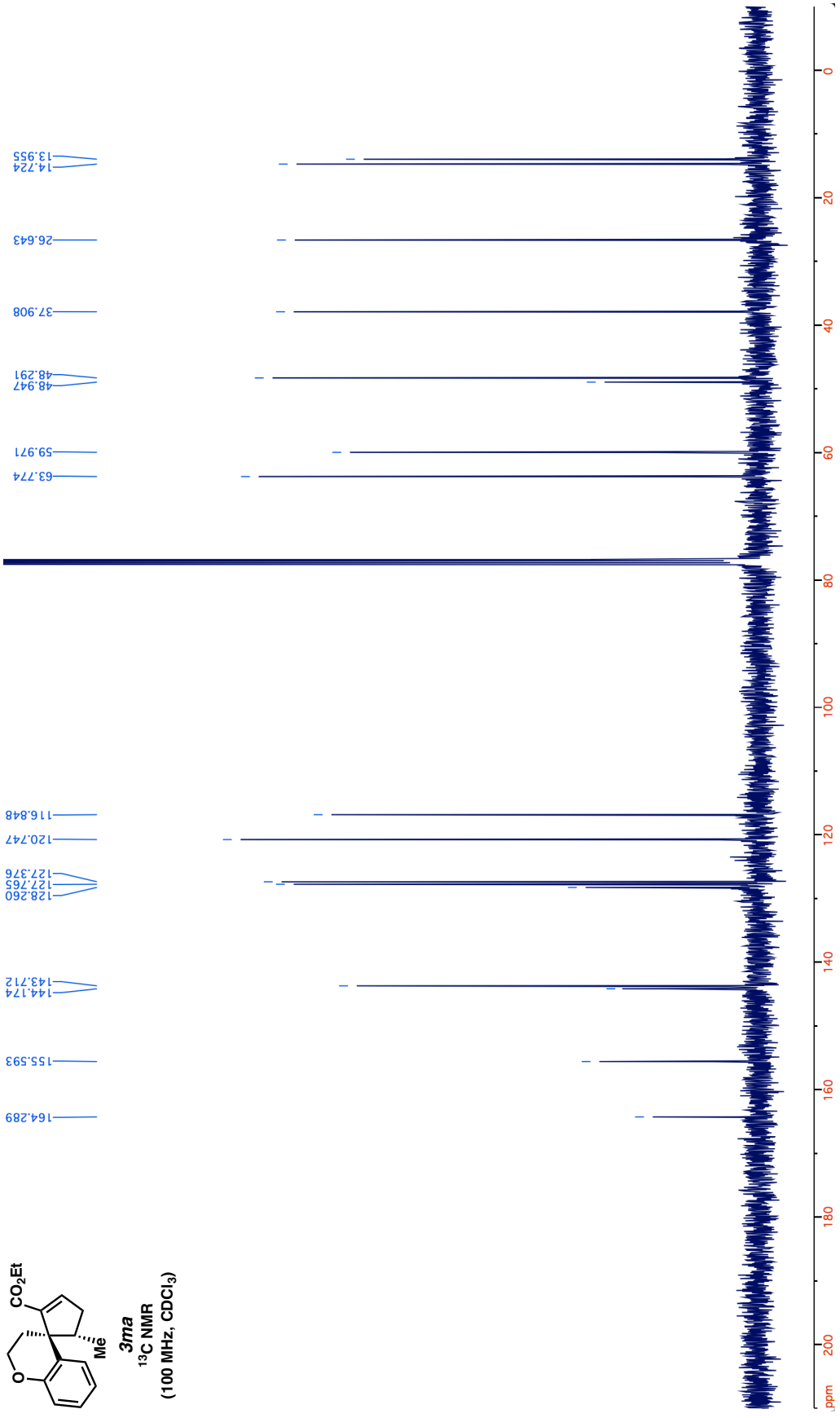
14.867
20.647
27.165
30.625
38.225
49.985
51.821
55.177
59.749
77.160
112.794
112.342
128.511
134.623
139.642
142.465
146.044
157.177
164.683
ppm
0
20
40
60
80
100
120
140
160
180
200
CO2Et
Me
MeO
4-15p
13C NMR
(125 MHz, CDCl3)


CO2Et
Me
O
4-15q
1H NMR
(400 MHz, CDCl3)
7.260
7.099
7.096
7.076
7.072
7.058
7.052
6.964
6.957
6.857
6.854
6.834
6.831
6.816
6.810
4.300
4.292
4.289
4.281
4.273
4.264
4.261
4.254
4.129
4.123
4.096
4.093
4.070
4.065
4.041
4.023
4.014
4.005
3.996
3.988
3.978
3.961
3.935
3.917
3.907
3.899
3.890
3.881
3.873
3.855
2.677
2.676
2.672
2.658
2.656
2.647
2.621
2.614
2.602
2.595
2.318
2.307
2.287
2.282
2.279
2.277
2.276
2.271
2.252
2.241
2.227
2.211
2.209
2.206
2.190
2.185
2.017
2.011
2.004
1.981
1.975
1.969
1.552
1.100
1.083
0.995
0.977
0.960
0.835
1.88
1.81
0.999
1.03
1.02
1
2.01
1.05
2.14
2.72
3.01
ppm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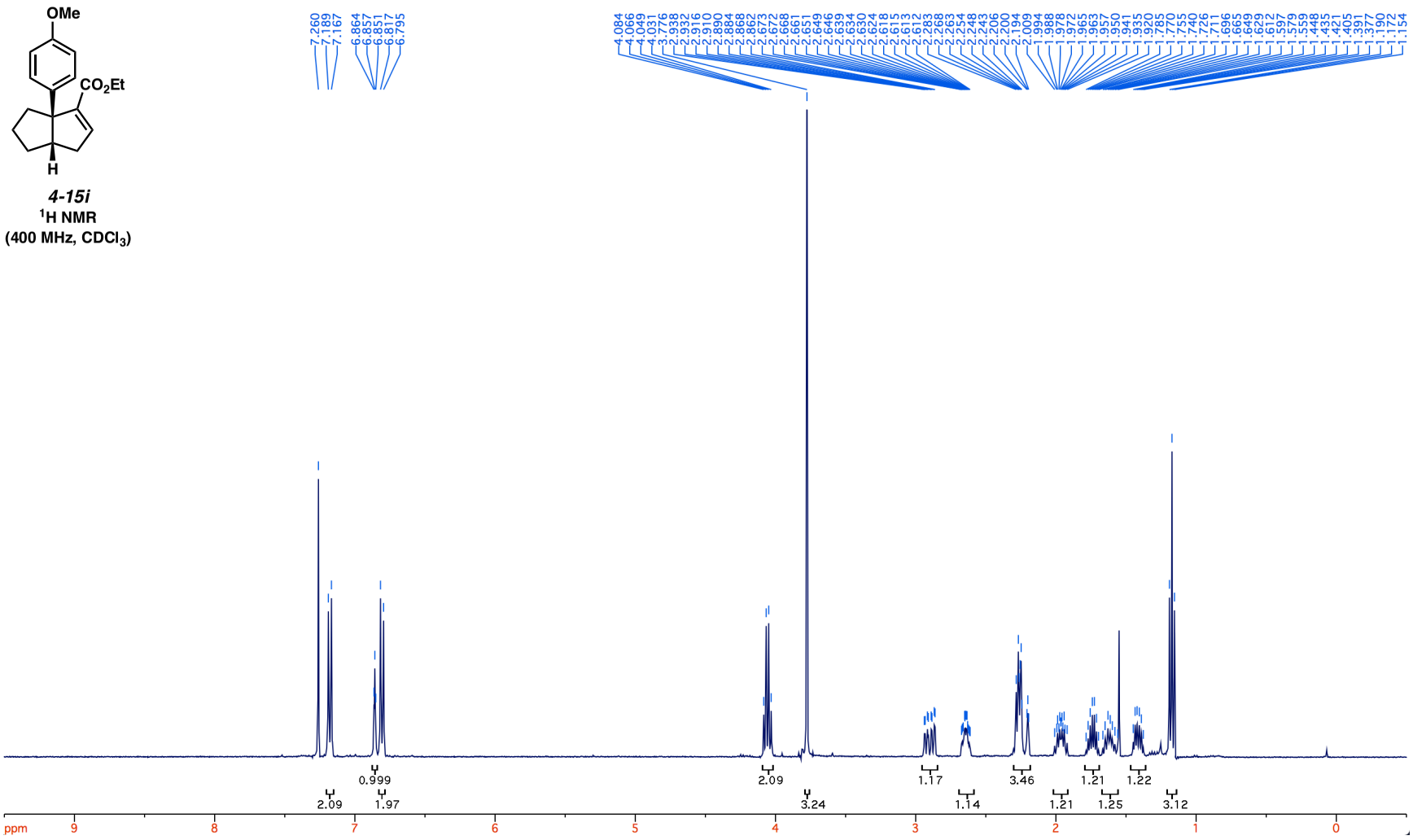
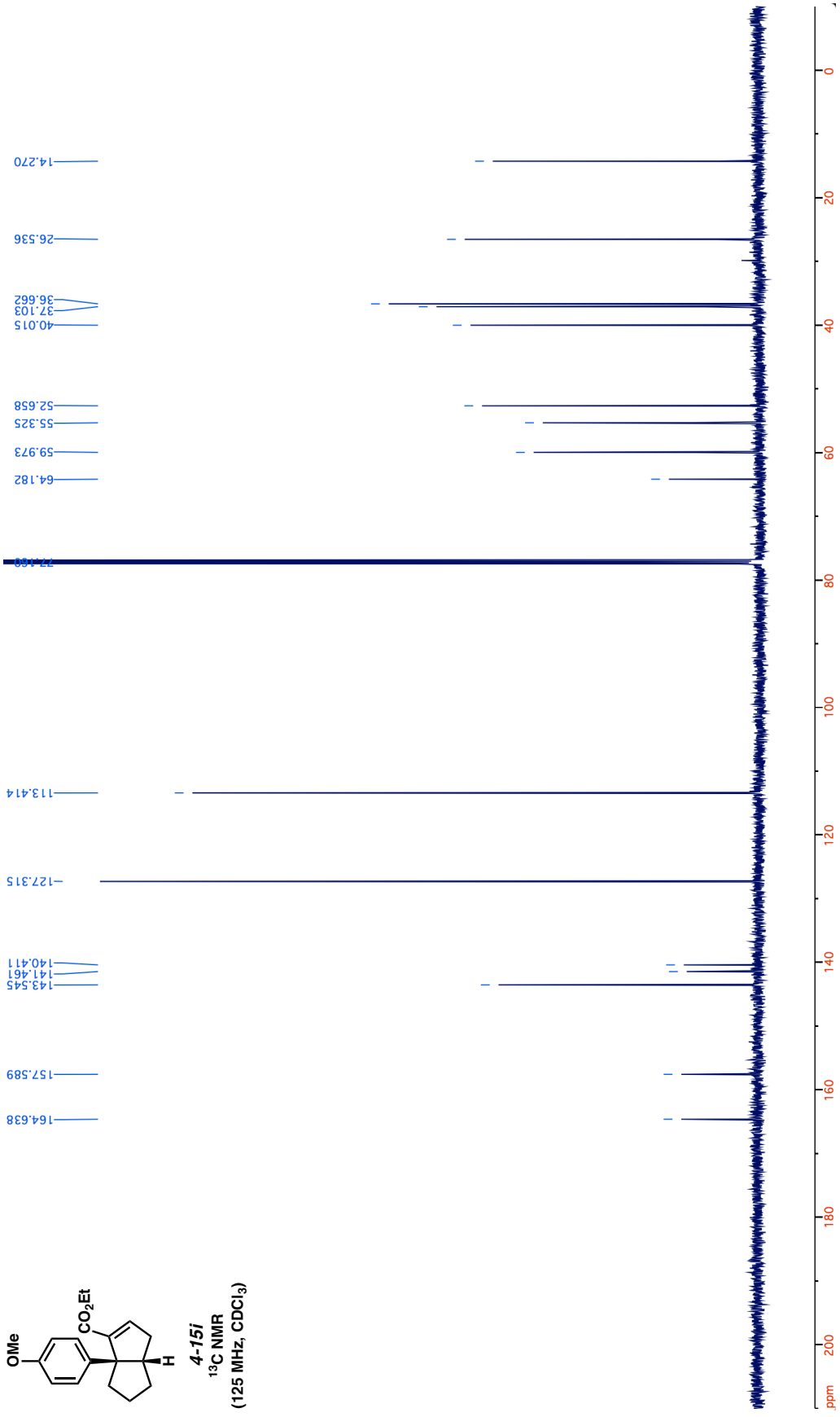
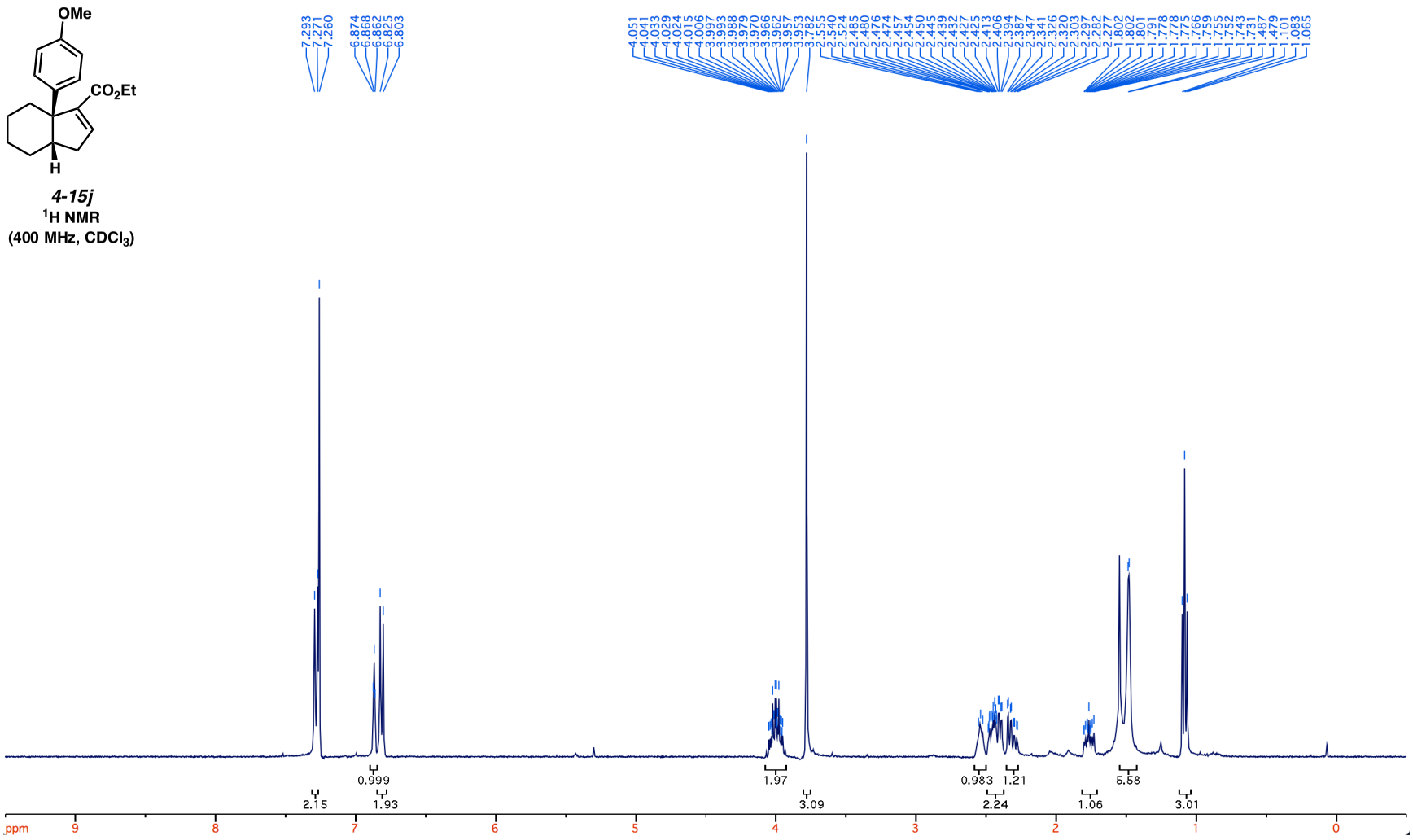
26.643
37.908
48.291
48.947
59.971
63.774
116.848
120.747
127.376
127.765
128.260
143.712
144.174
155.593
164.289
ppm
0
20
40
60
80
100
120
140
160
180
200
CO2Et
Me
O
3ma
13C NMR
(100 MHz, CDCl3)


OMe
CO2Et
H
4-15i
1H NMR
(400 MHz, CDCl3)
7.260
7.189
7.167
6.864
6.857
6.851
6.817
6.795
4.084
4.066
4.049
4.031
3.776
2.938
2.933
2.916
2.910
2.890
2.884
2.868
2.862
2.673
2.672
2.668
2.661
2.651
2.649
2.646
2.639
2.634
2.630
2.624
2.618
2.615
2.613
2.612
2.283
2.268
2.263
2.254
2.248
2.243
2.206
2.200
2.194
2.009
1.994
1.988
1.978
1.972
1.965
1.963
1.957
1.950
1.941
1.935
1.920
1.785
1.770
1.755
1.740
1.726
1.711
1.696
1.665
1.649
1.629
1.612
1.597
1.579
1.559
1.448
1.435
1.421
1.415
1.391
1.377
1.190
1.172
1.154
2.09
0.999
1.97
2.09
3.24
1.17
1.14
3.46
1.21
1.21
1.25
1.22
3.12
ppm
9
8
7
6
5
4
3
2
1
0


14.270
26.536
36.662
37.103
40.015
52.658
55.325
59.973
64.182
77.168
113.414
127.315
140.411
141.461
143.545
157.589
164.638
0
20
40
60
80
100
120
140
160
180
200
ppm
OMe
CO2Et
H
4-15i
13C NMR
(125 MHz, CDCl3)


OMe
CO2Et
H
4-15j
1H NMR
(400 MHz, CDCl3)
7.293
7.271
7.260
6.874
6.868
6.862
6.825
6.803
4.051
4.041
4.033
4.029
4.024
4.015
4.006
3.997
3.993
3.988
3.979
3.970
3.966
3.962
3.957
3.953
3.782
2.555
2.540
2.524
2.485
2.480
2.476
2.474
2.457
2.454
2.450
2.445
2.439
2.432
2.427
2.425
2.413
2.406
2.394
2.387
2.347
2.341
2.326
2.320
2.303
2.297
2.282
2.277
1.802
1.801
1.791
1.778
1.775
1.766
1.759
1.755
1.752
1.743
1.731
1.487
1.479
1.101
1.083
1.065
2.15
0.999
1.93
1.97
3.09
0.983
1.21
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1.06
5.58
3.01
ppm
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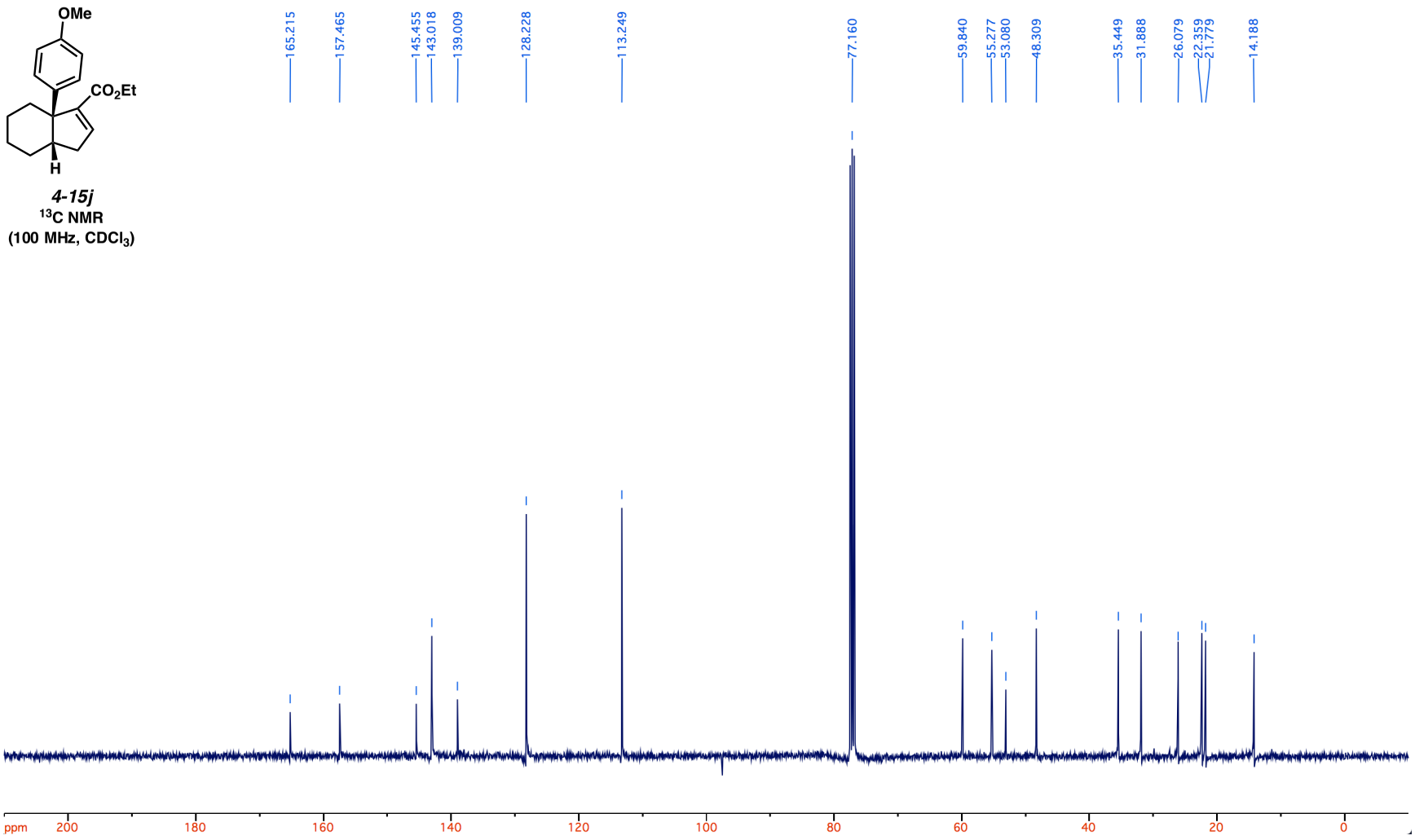
8
7
6
5
4
3
2
1
0


OMe
CO2Et
H
4-15j
13C NMR
(100 MHz, CDCl3)
165.215
157.465
145.455
143.018
139.009
128.228
113.249
77.160
59.840
55.277
53.080
48.309
35.449
31.888
26.079
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21.779
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ppm
200
180
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140
120
100
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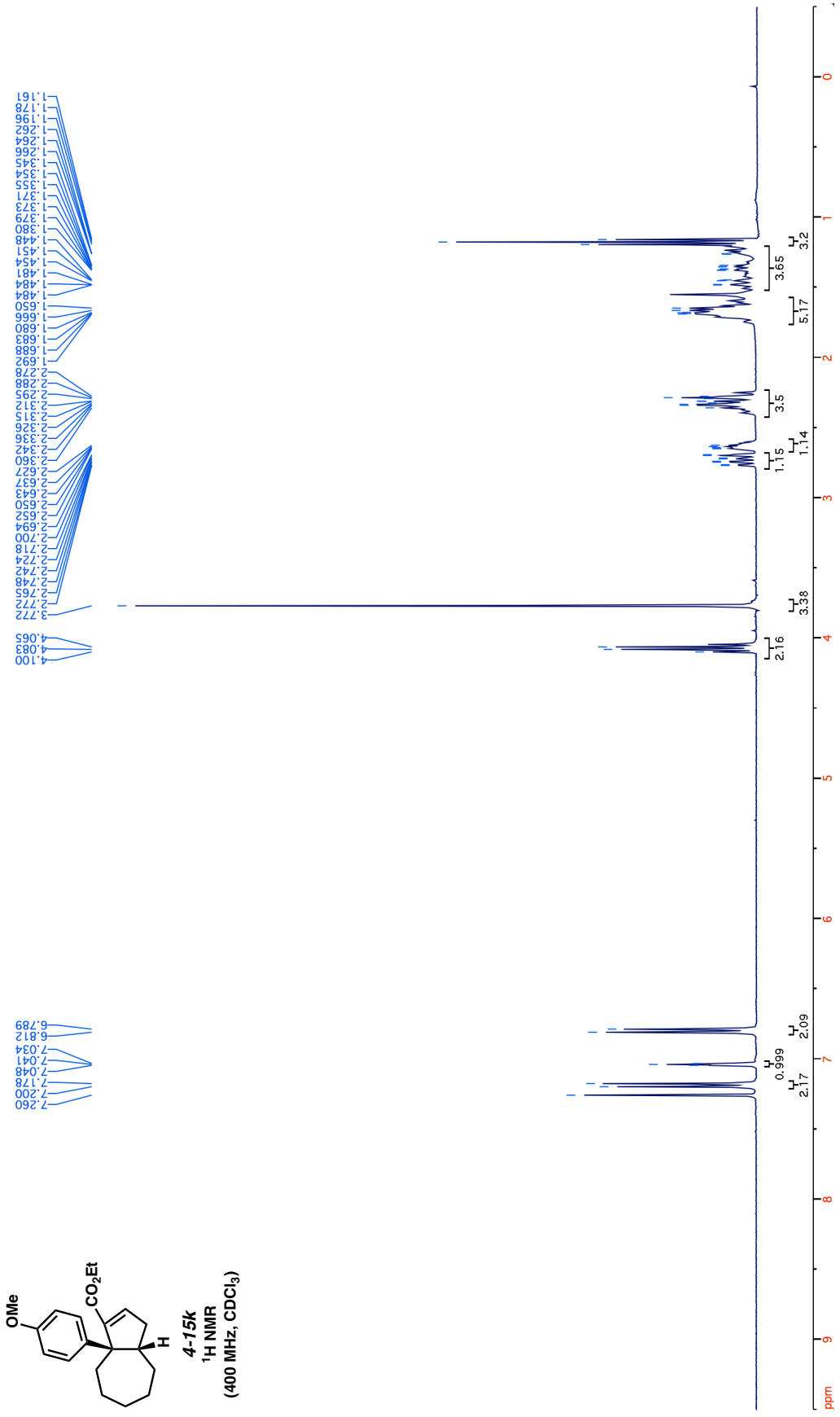
60
40
20
0


OMe
CO2Et
H
4-15k
1H NMR
(400 MHz, CDCl3)
7.260
7.200
7.178
7.048
7.041
7.034
6.812
6.789
4.100
4.083
4.065
3.772
2.772
2.765
2.748
2.742
2.724
2.718
2.700
2.694
2.652
2.650
2.643
2.637
2.627
2.360
2.342
2.336
2.326
2.315
2.312
2.295
2.288
2.278
1.692
1.688
1.683
1.680
1.666
1.650
1.484
1.481
1.454
1.451
1.448
1.380
1.379
1.373
1.371
1.355
1.354
1.345
1.266
1.264
1.262
1.196
1.178
1.161
2.16
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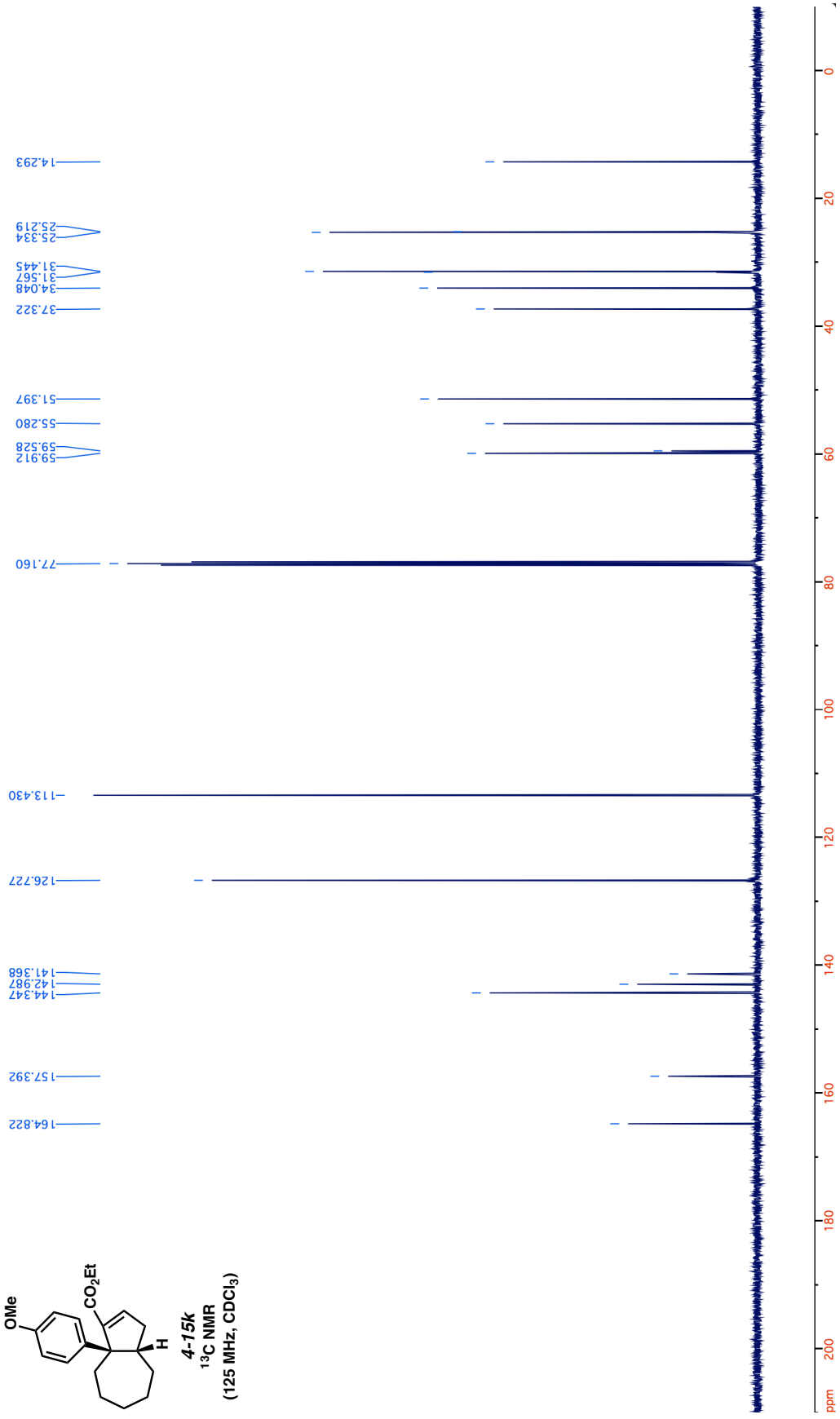
1.15
1.14
3.5
3.65
5.17
3.2
0.999
2.09
2.17
ppm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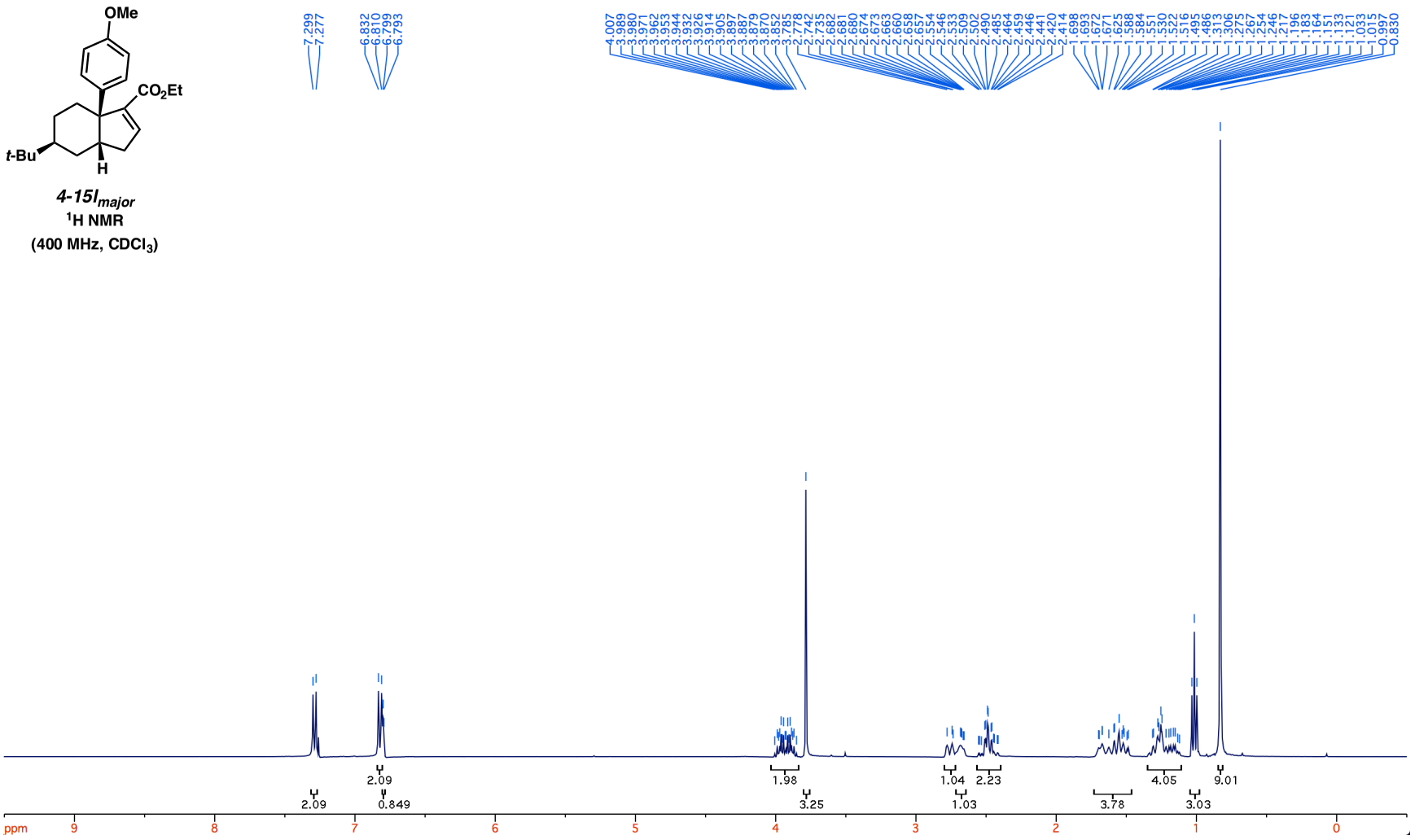
25.219
25.334
31.445
31.567
34.048
37.322
51.397
55.280
59.528
59.912
77.160
113.430
126.727
141.368
142.987
144.347
157.392
164.822
OMe
CO2Et
H
4-15k
13C NMR
(125 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm


OMe
CO2Et
t-Bu
H
4-15I major
1H NMR
(400 MHz, CDCl3)
7.299
7.277
6.832
6.810
6.799
6.793
4.007
3.989
3.980
3.971
3.962
3.953
3.944
3.932
3.926
3.914
3.905
3.897
3.887
3.879
3.870
3.852
3.785
2.778
2.742
2.735
2.682
2.681
2.680
2.674
2.673
2.663
2.660
2.658
2.657
2.554
2.546
2.533
2.509
2.502
2.490
2.485
2.464
2.459
2.446
2.441
2.420
2.414
1.698
1.693
1.672
1.671
1.625
1.588
1.584
1.551
1.530
1.522
1.516
1.495
1.486
1.313
1.306
1.275
1.267
1.254
1.246
1.217
1.196
1.183
1.164
1.151
1.133
1.121
1.033
1.015
0.997
0.830
2.09
2.09
0.849
1.98
3.25
1.04
2.23
1.03
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4.05
3.03
9.01
ppm
9
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7
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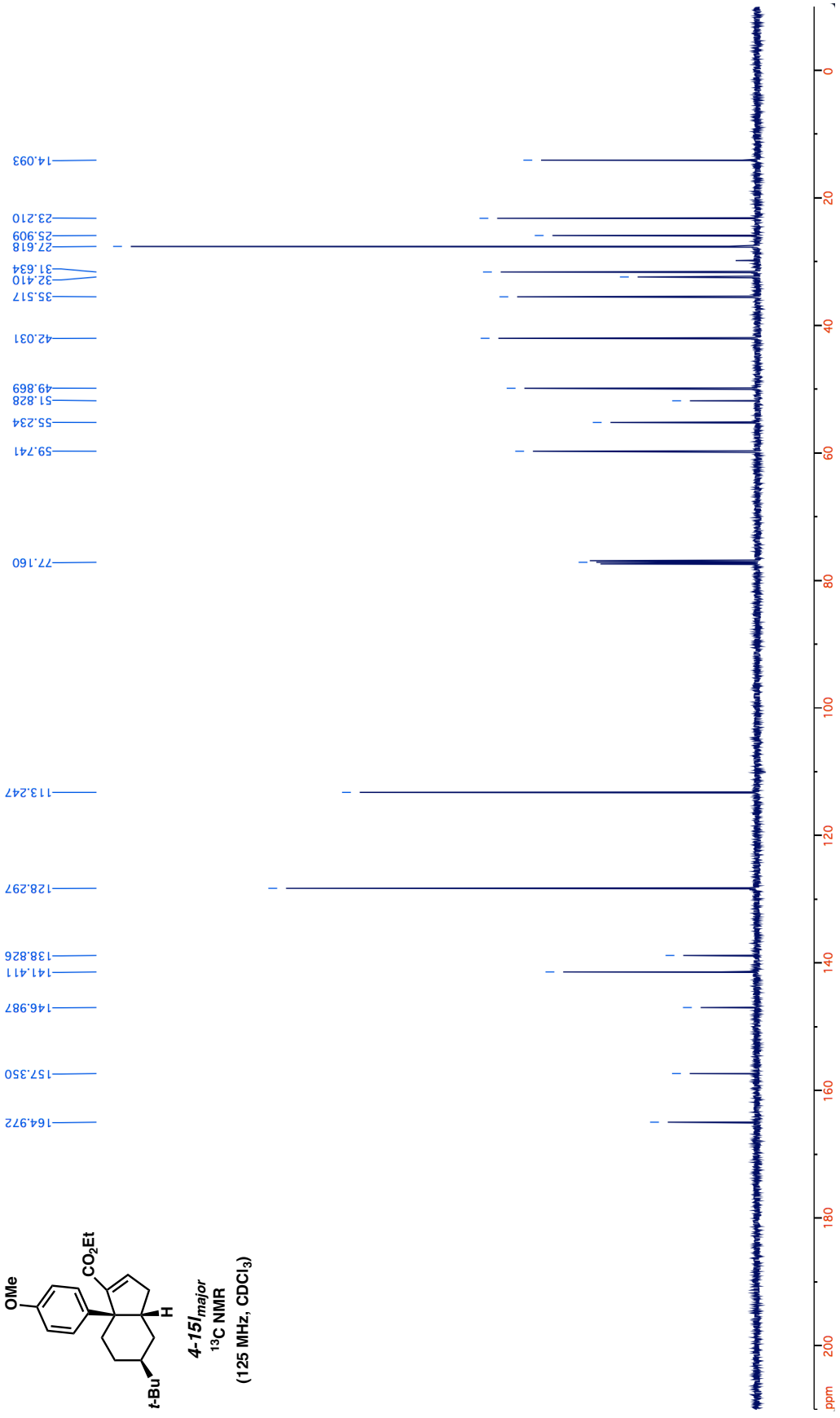
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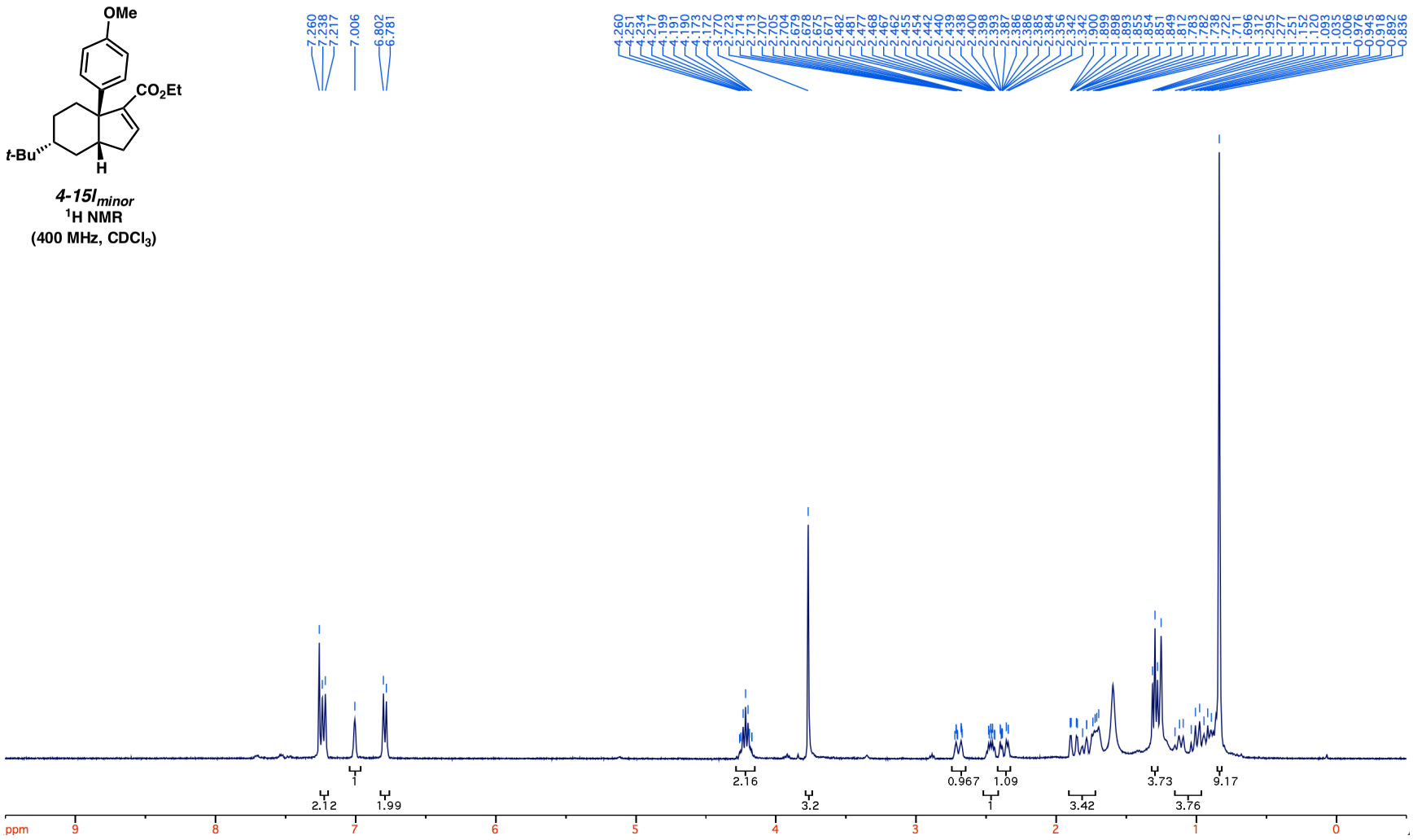
23.210
25.909
27.618
31.634
32.410
35.517
42.031
49.869
51.828
55.234
59.741
77.160
113.247
128.297
138.826
141.411
146.987
157.350
164.972
ppm
0
20
40
60
80
100
120
140
160
180
200
OMe
CO2Et
H
t-Bu
4-15l major
13C NMR
(125 MHz, CDCl3)


OMe
CO2Et
t-Bu
H
4-15I minor
1H NMR
(400 MHz, CDCl3)
7.260
7.238
7.217
7.006
6.802
6.781
4.260
4.251
4.234
4.217
4.199
4.191
4.190
4.173
4.172
3.770
2.723
2.714
2.713
2.707
2.705
2.704
2.679
2.678
2.675
2.671
2.482
2.481
2.477
2.468
2.467
2.462
2.455
2.454
2.442
2.440
2.439
2.438
2.400
2.398
2.393
2.387
2.386
2.386
2.385
2.384
2.356
2.342
2.342
1.900
1.899
1.898
1.893
1.855
1.854
1.851
1.849
1.812
1.783
1.782
1.738
1.722
1.711
1.696
1.312
1.295
1.277
1.251
1.152
1.120
1.033
1.006
0.976
0.945
0.918
0.892
0.836
2.12
1
1.99
2.16
3.2
0.967
1.09
1
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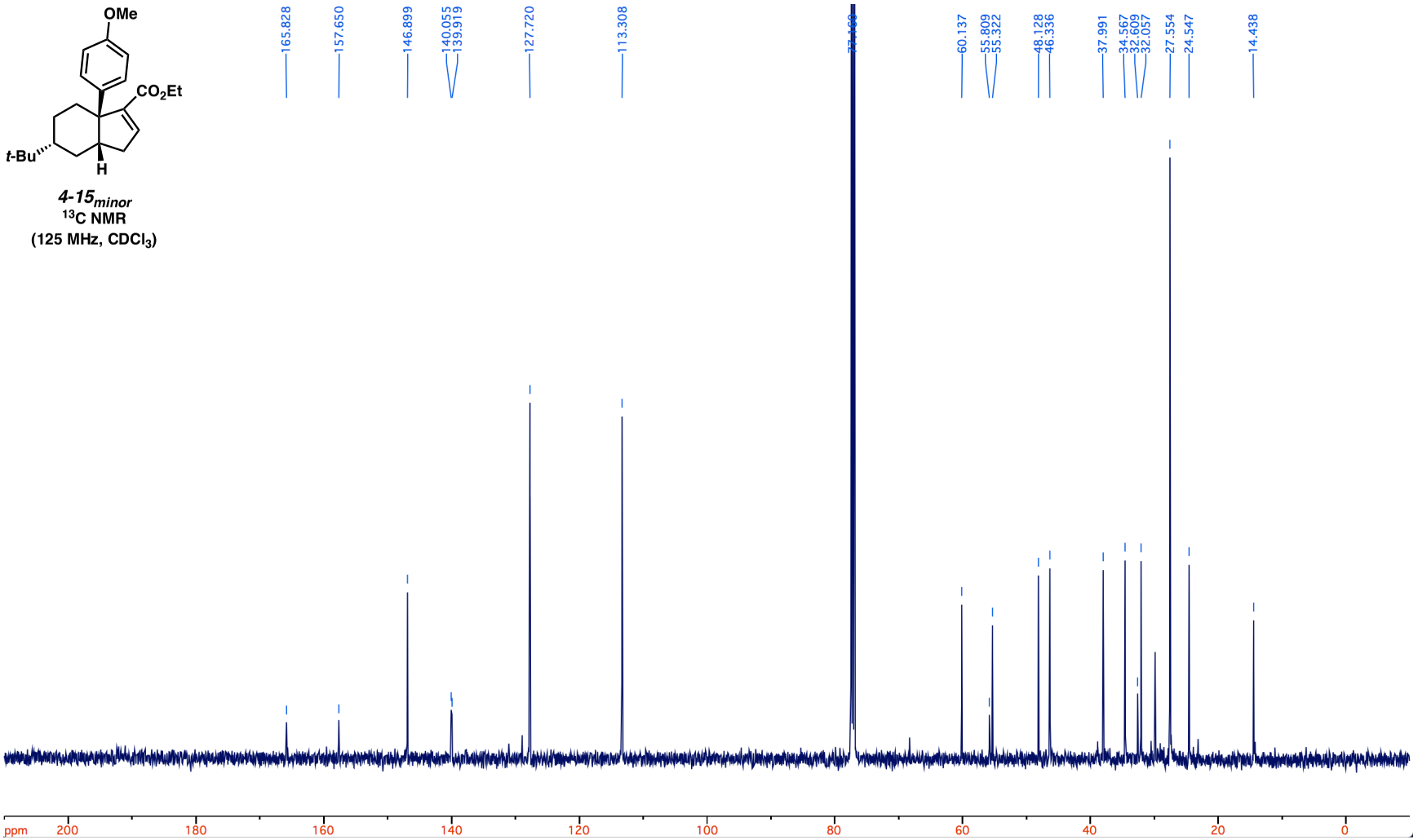
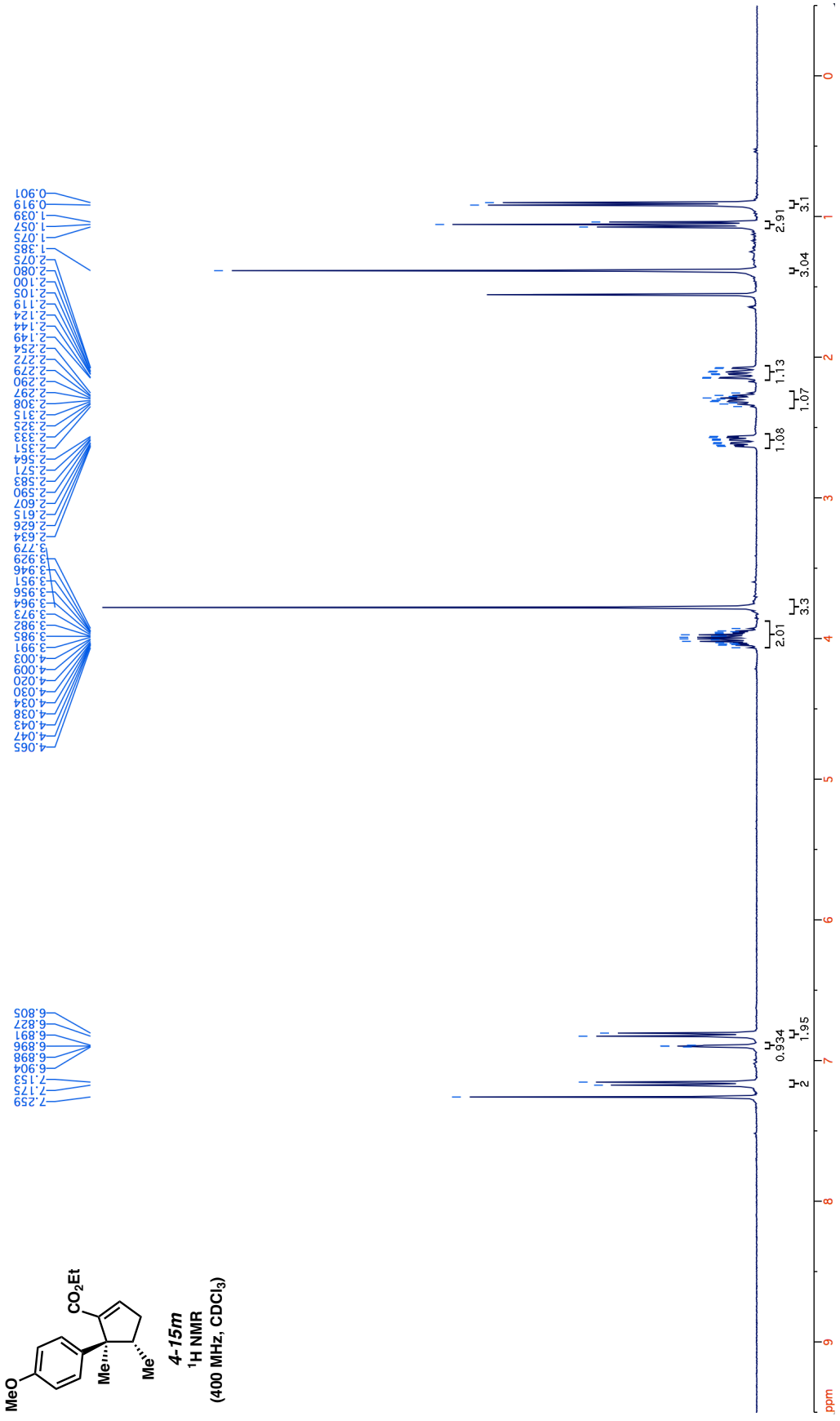
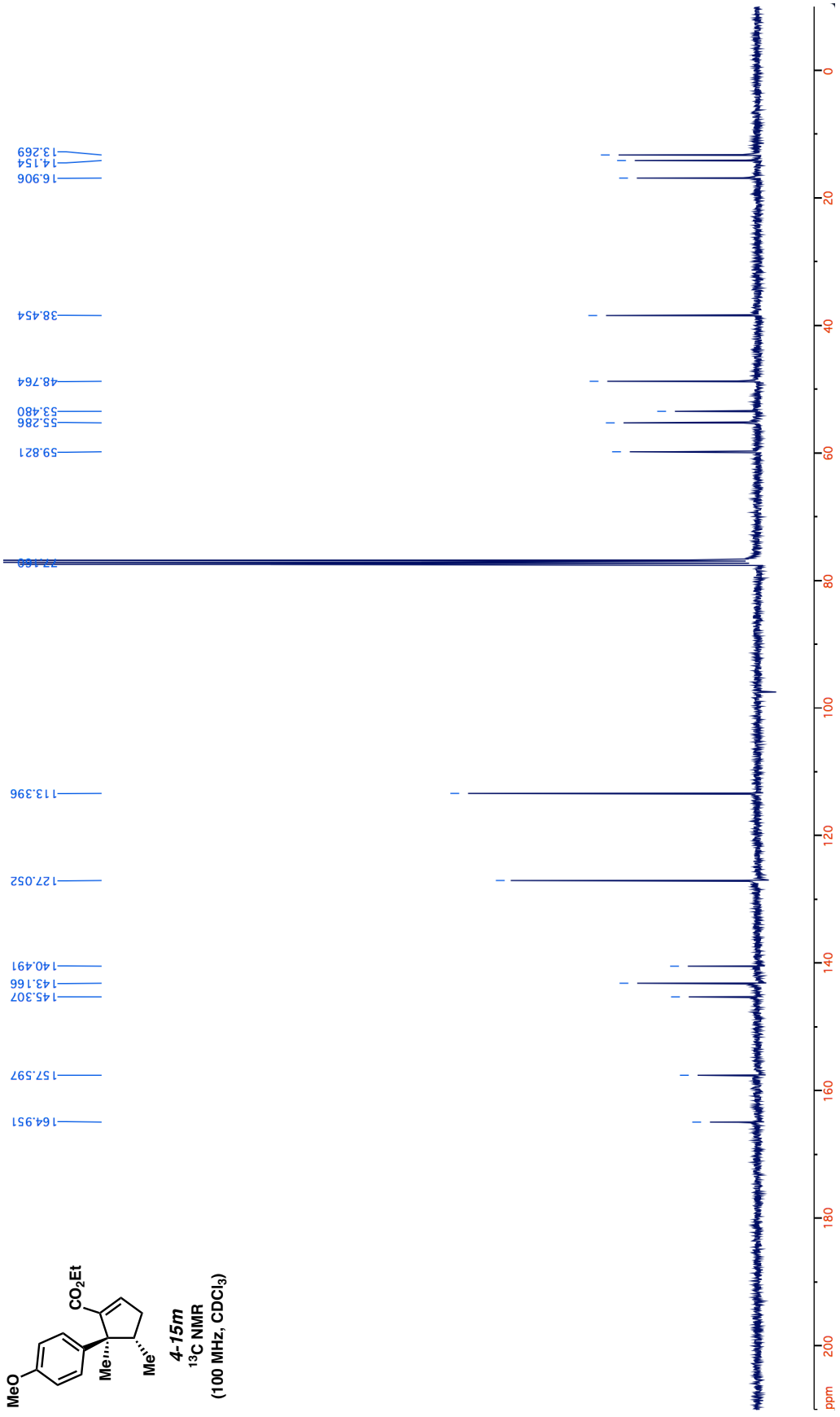
3.73
3.76
9.17
ppm
9
8
7
6
5
4
3
2
1
0


OMe
CO2Et
t-Bu
H
4-15minor
13C NMR
(125 MHz, CDCl3)
165.828
157.650
146.899
140.055
139.919
127.720
113.308
77.160
60.137
55.809
55.322
48.128
46.336
37.991
34.567
32.609
32.057
27.554
24.547
14.438
ppm
200
180
160
140
120
100
80
60
40
20
0


MeO
CO2Et
Me
Me
4-15m
1H NMR
(400 MHz, CDCl3)
ppm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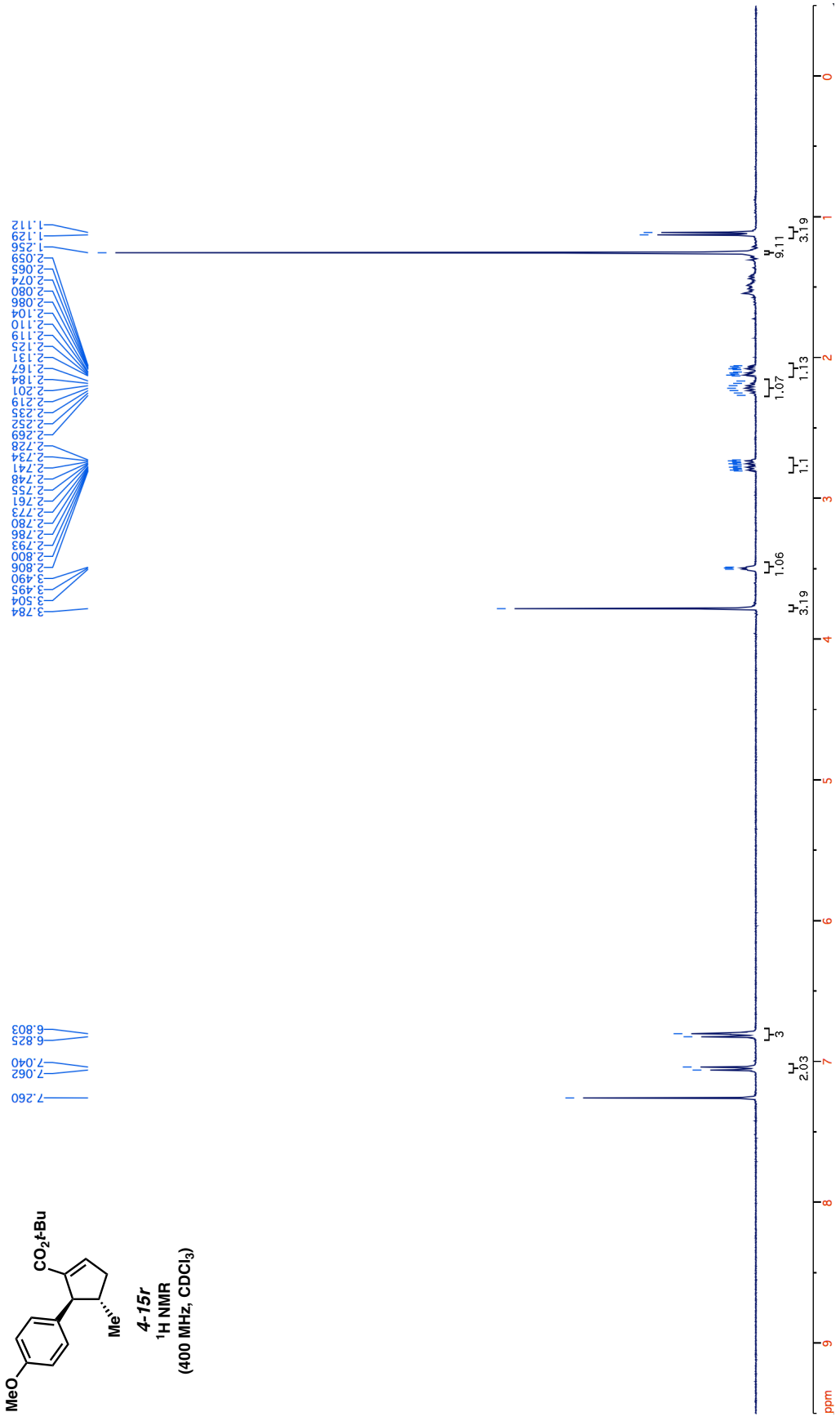
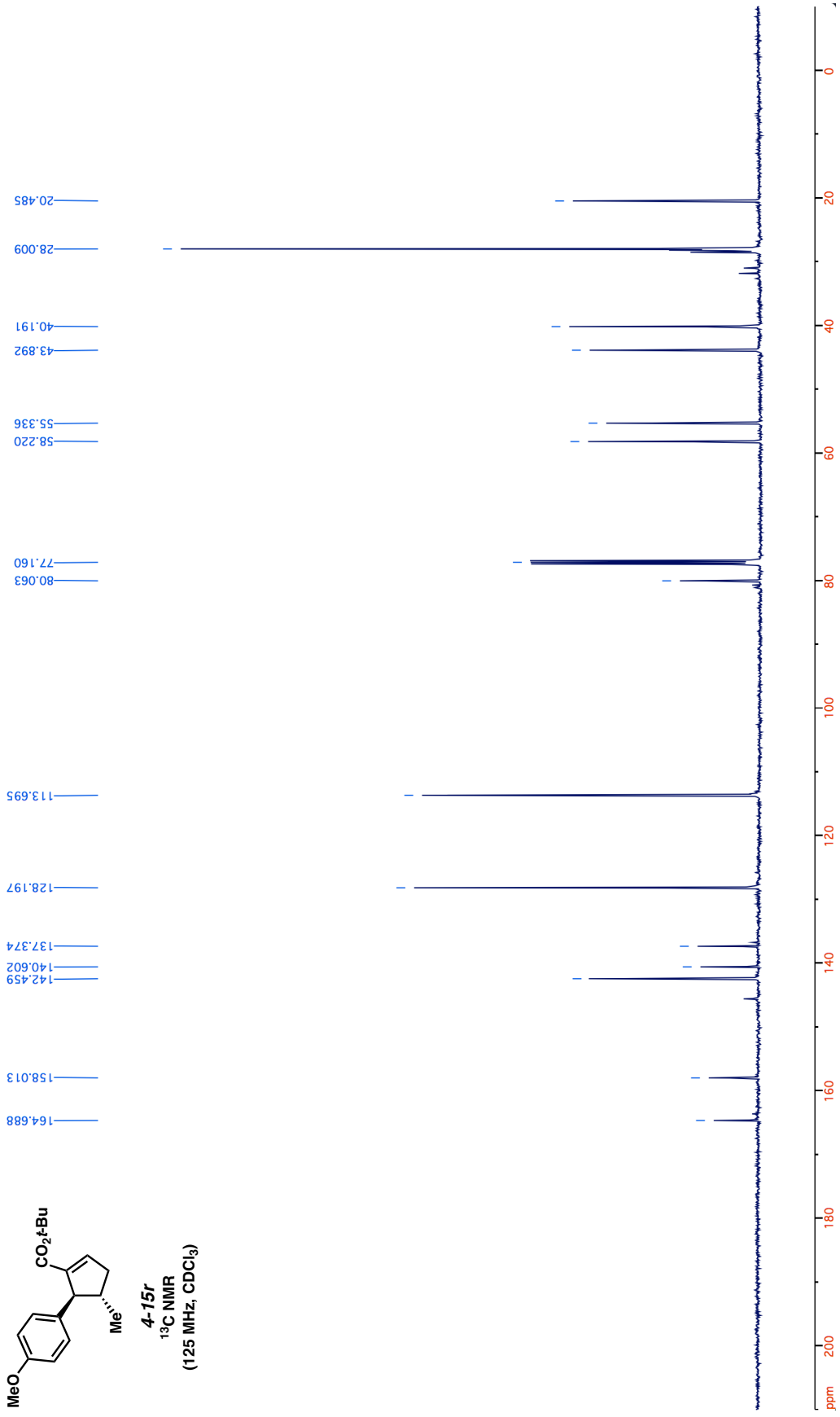
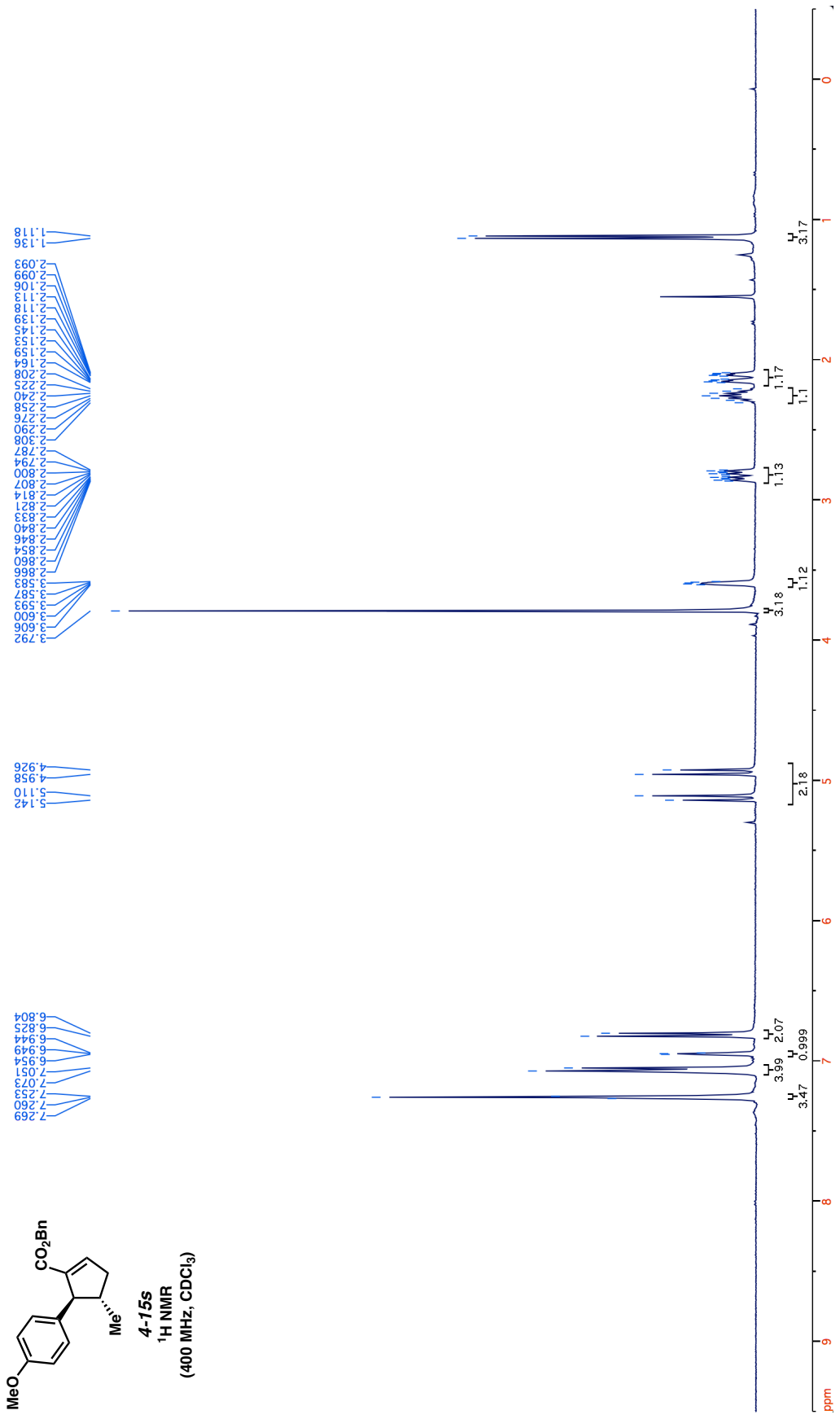
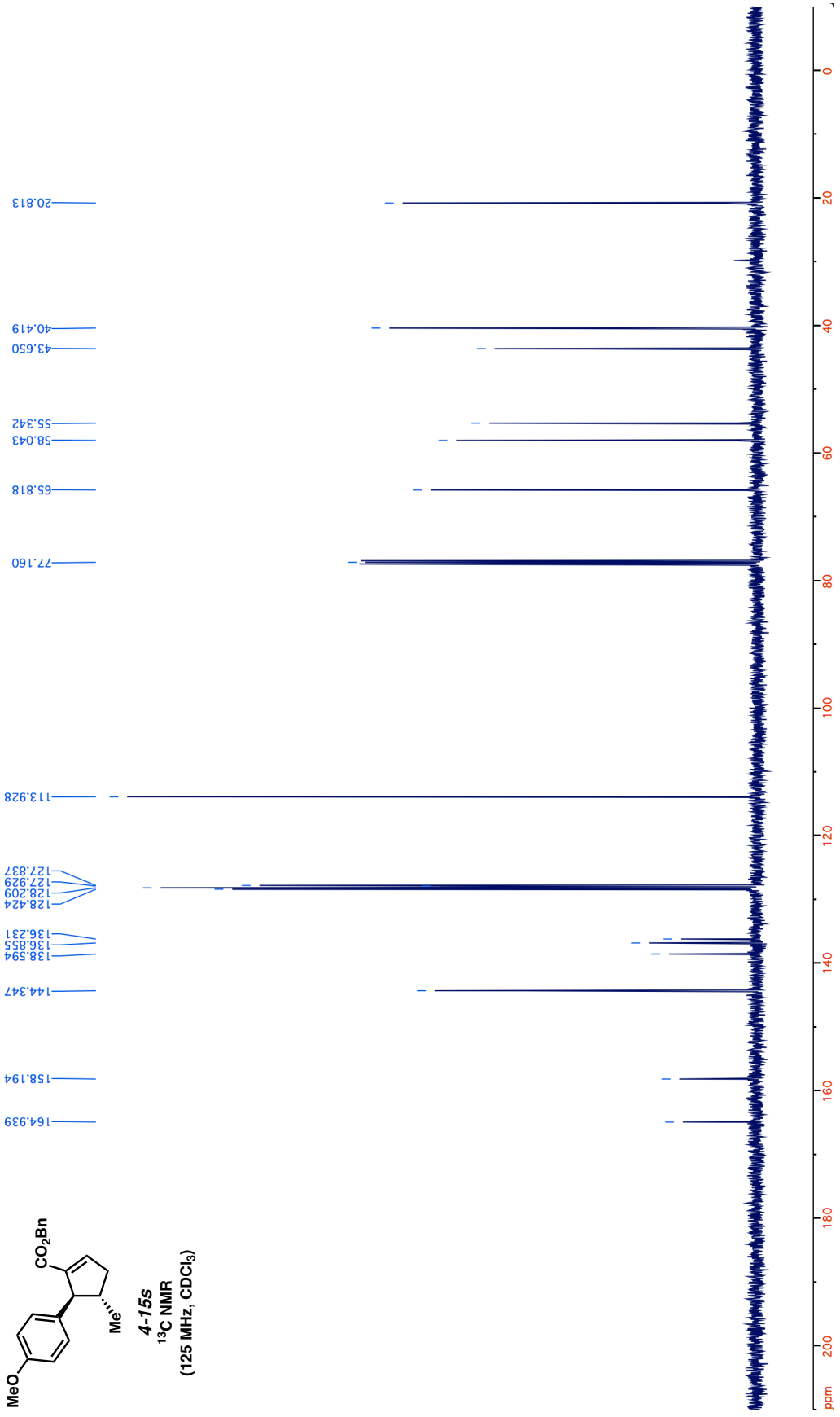
14.154
16.906
38.454
48.764
53.480
55.286
59.821
77.188
113.396
127.052
140.491
143.166
145.307
157.597
164.951
MeO
CO2Et
Me
Me
4-15m
13C NMR
(100 MHz, CDCl3)
ppm

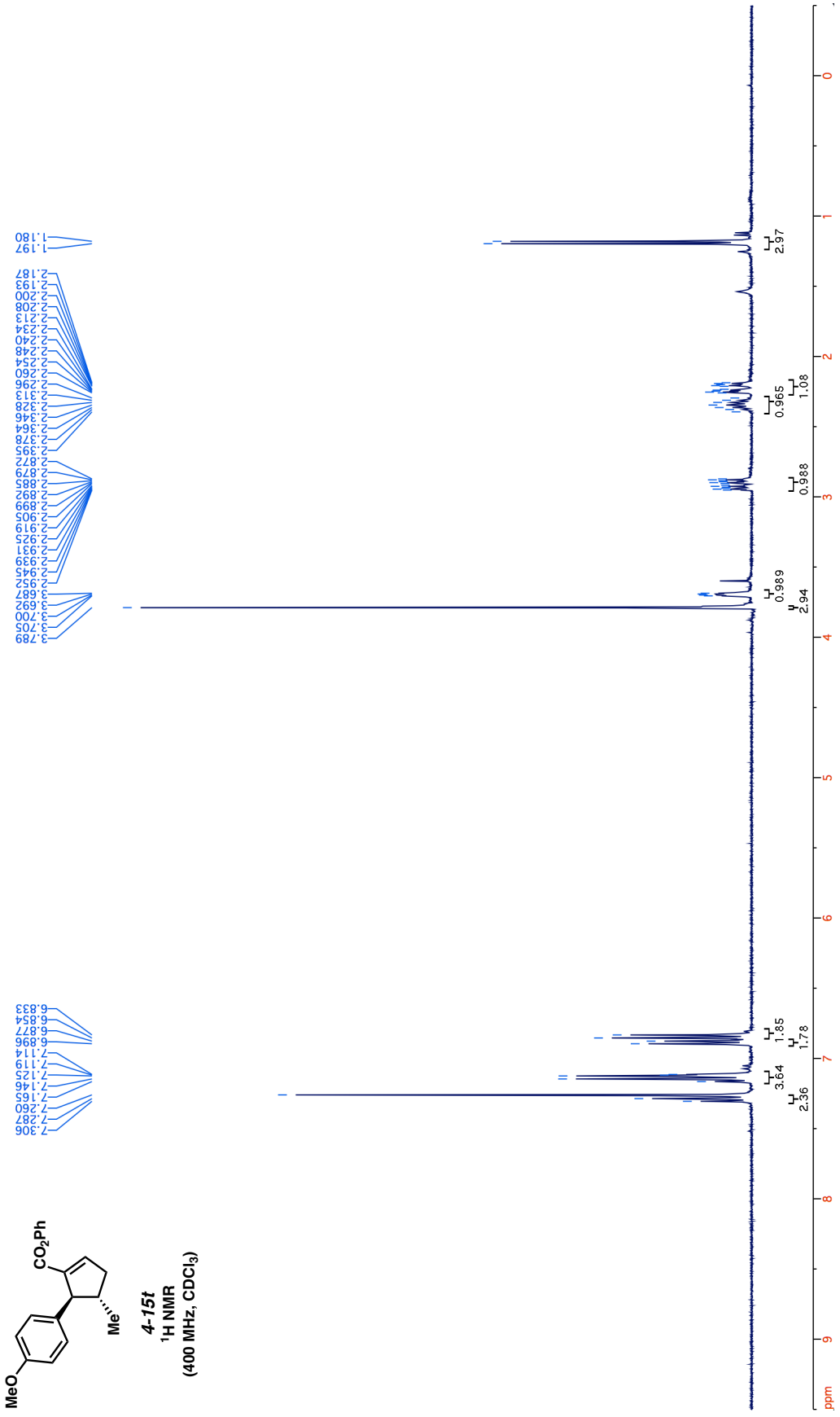

MeO
CO2t-Bu
Me
4-15r
1H NMR
(400 MHz, CDCl3)
7.260
7.062
7.040
6.825
6.803
3.784
3.504
3.495
3.490
2.806
2.800
2.793
2.786
2.780
2.773
2.761
2.755
2.748
2.741
2.734
2.728
2.269
2.252
2.235
2.219
2.201
2.184
2.167
2.131
2.125
2.119
2.110
2.104
2.086
2.080
2.074
2.065
2.059
1.729
1.256
1.112
3
2.03
1.06
3.19
1.1
1.07
1.13
9.11
3.19
ppm

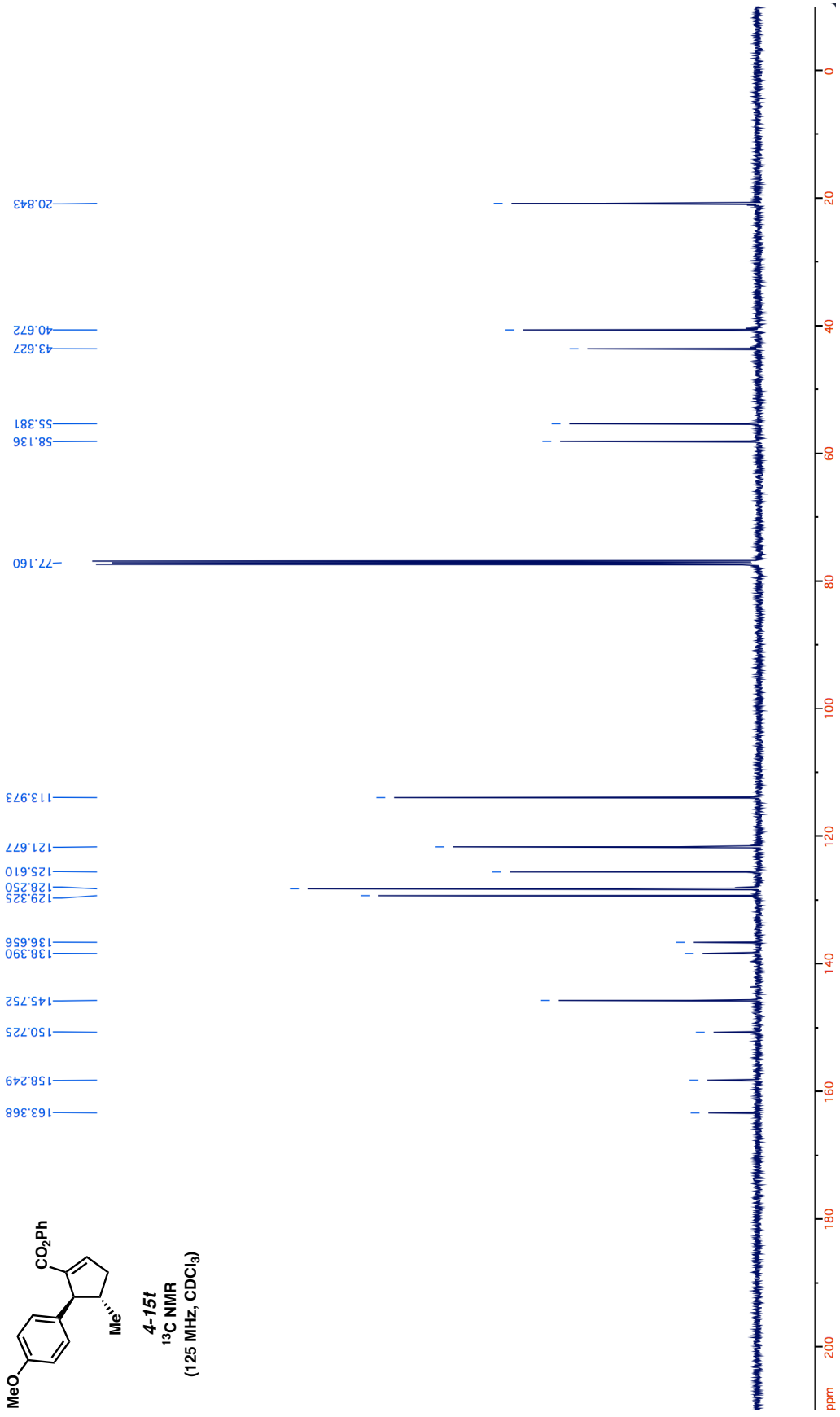


4-15r
^{13}C NMR
(125 MHz, $CDCl_3$)

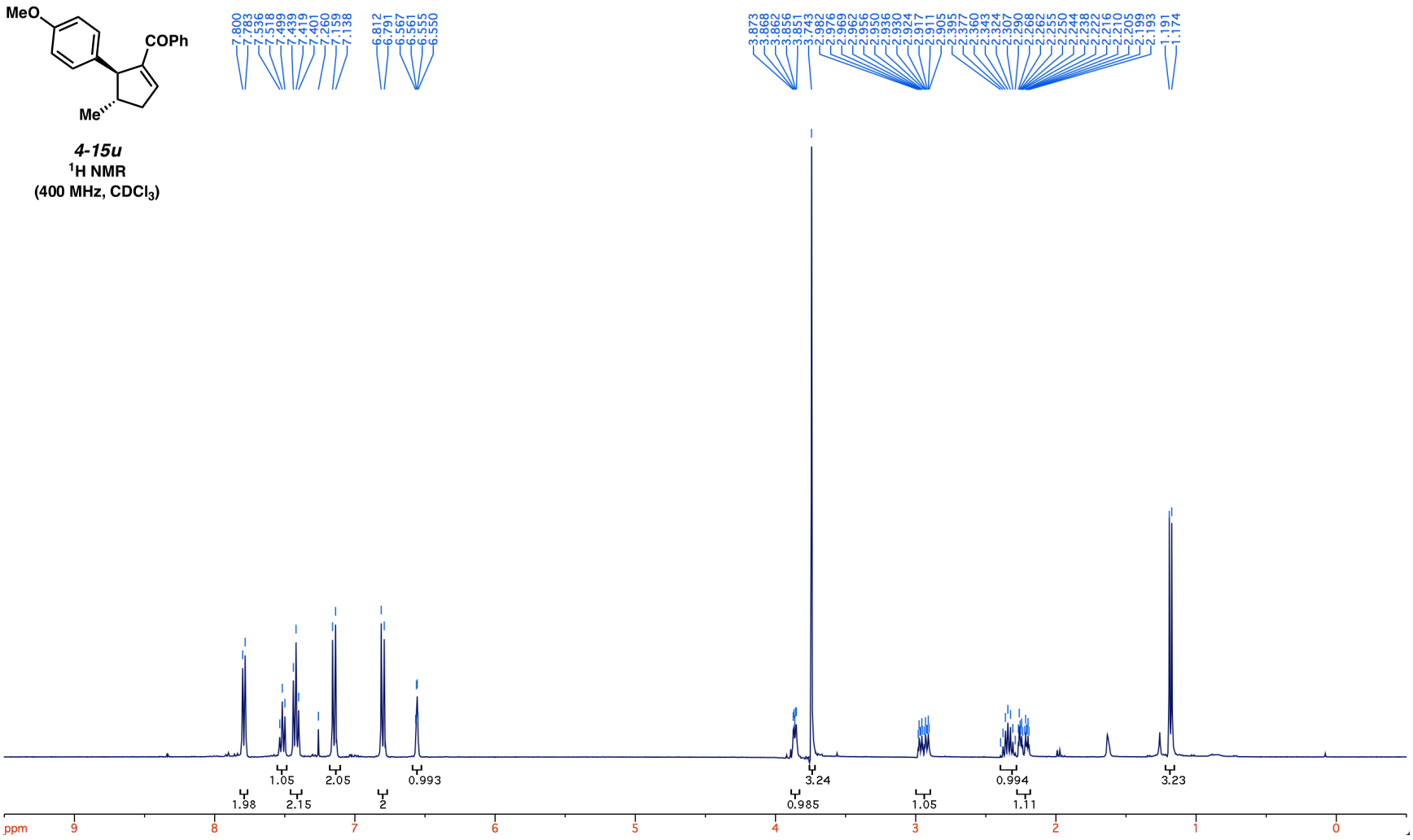

MeO
CO2Bn
Me
4-15s
1H NMR
(400 MHz, CDCl3)
7.269
7.260
7.253
7.073
7.051
6.954
6.949
6.944
6.825
6.804
5.142
5.110
4.958
4.926
3.792
3.606
3.600
3.593
3.587
3.583
2.866
2.860
2.854
2.846
2.840
2.833
2.821
2.814
2.807
2.800
2.794
2.787
2.308
2.290
2.276
2.258
2.240
2.225
2.208
2.164
2.159
2.153
2.145
2.139
2.118
2.113
2.106
2.099
2.093
1.136
1.118
3.99
2.07
0.999
3.47
2.18
3.18
1.12
1.13
1.17
1.1
3.17
ppm


20.813
40.419
43.650
55.342
58.043
65.818
77.160
113.928
127.837
127.929
128.209
128.424
136.231
136.855
138.594
144.347
158.194
164.939
MeO
CO2Bn
Me
4-15s
13C NMR
(125 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm

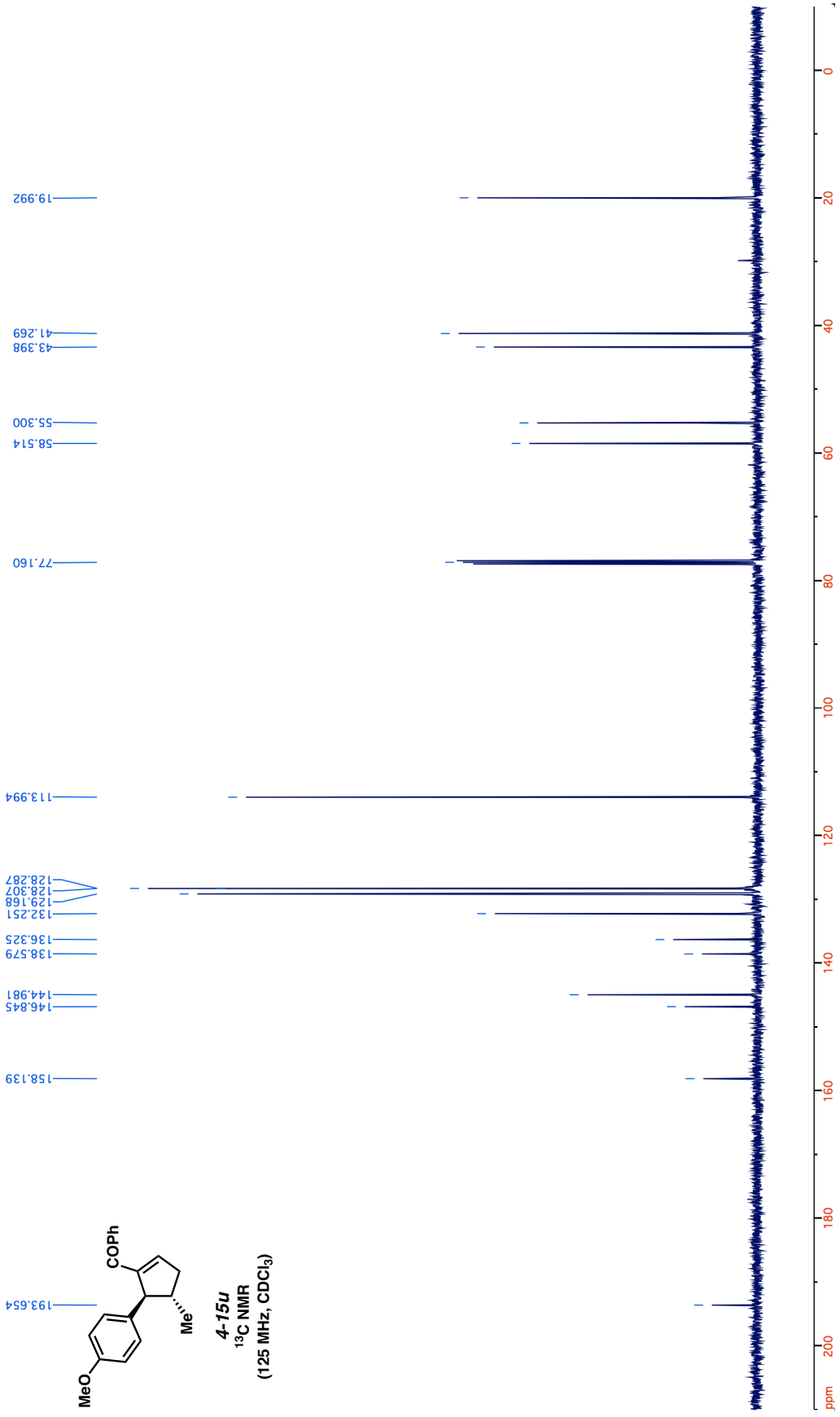

MeO
CO2Ph
Me
4-15t
1H NMR
(400 MHz, CDCl3)
7.306
7.287
7.260
7.165
7.146
7.125
7.119
7.114
6.896
6.877
6.854
6.833
3.789
3.705
3.700
3.692
3.687
2.952
2.945
2.939
2.931
2.925
2.919
2.905
2.899
2.892
2.885
2.879
2.872
2.395
2.378
2.364
2.346
2.328
2.313
2.296
2.260
2.254
2.248
2.240
2.234
2.213
2.208
2.200
2.193
2.187
1.197
1.180
2.97
1.08
0.965
0.988
0.989
2.94
1.85
1.78
3.64
2.36
ppm

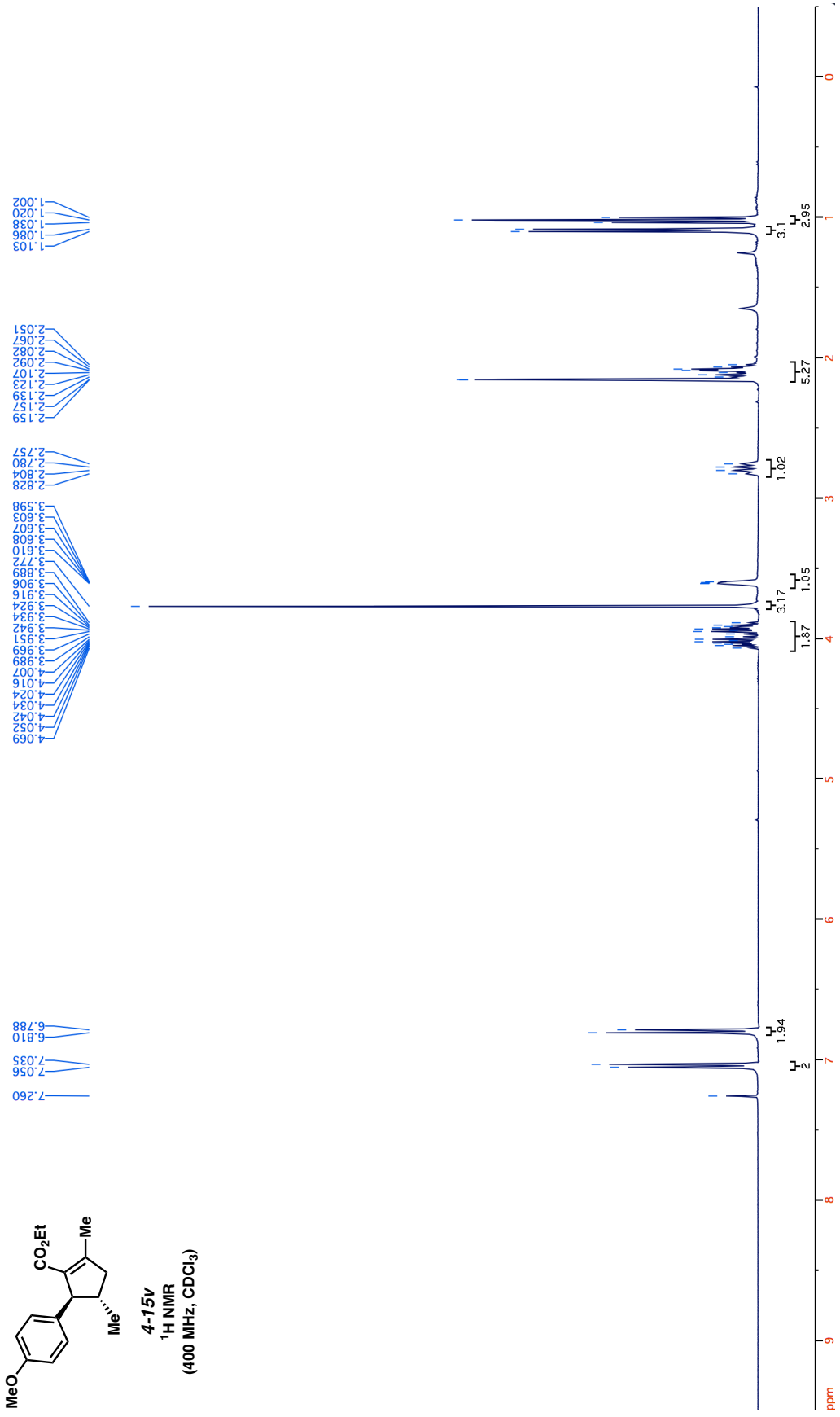


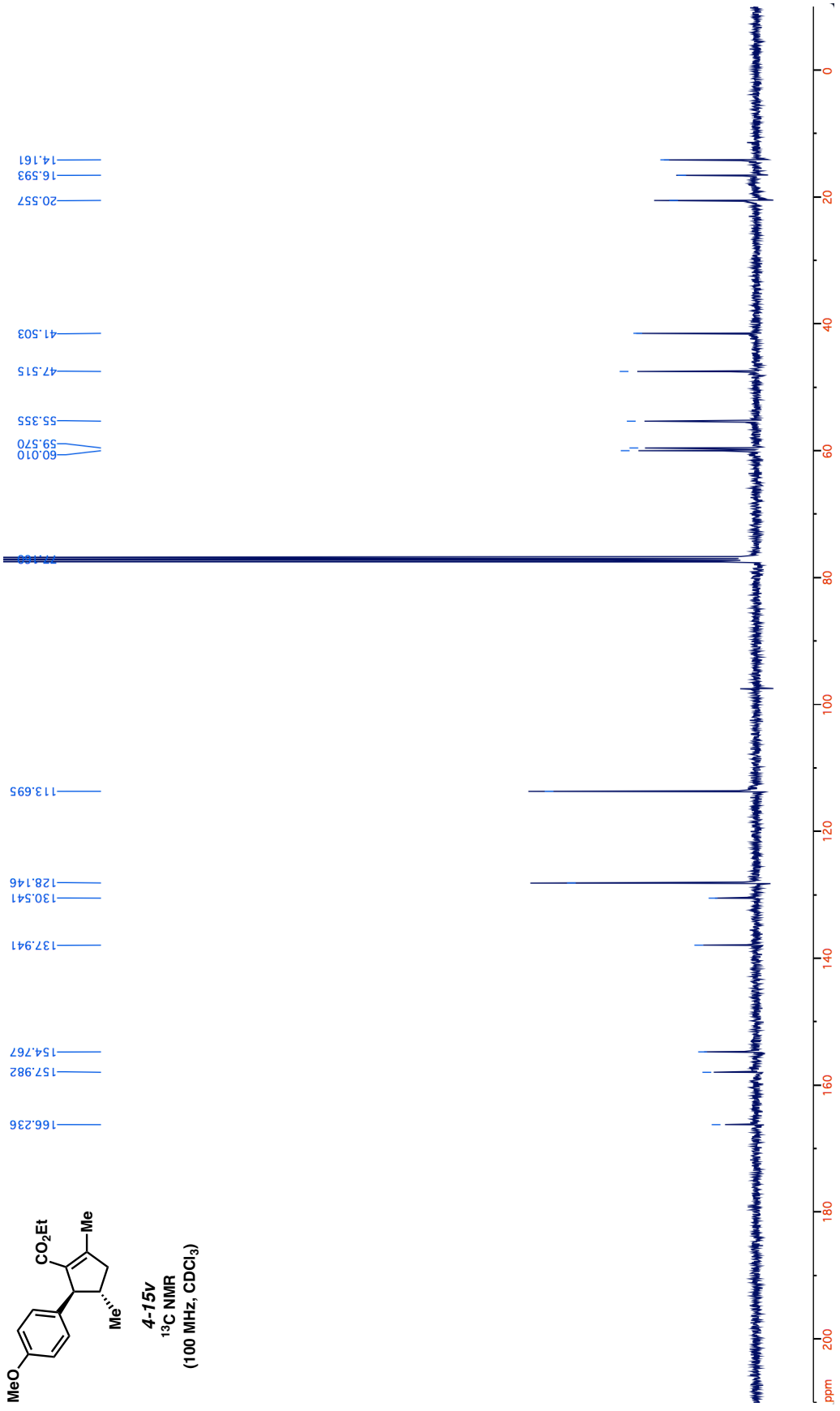
4-15t
^{13}C NMR
(125 MHz, $CDCl_3$)

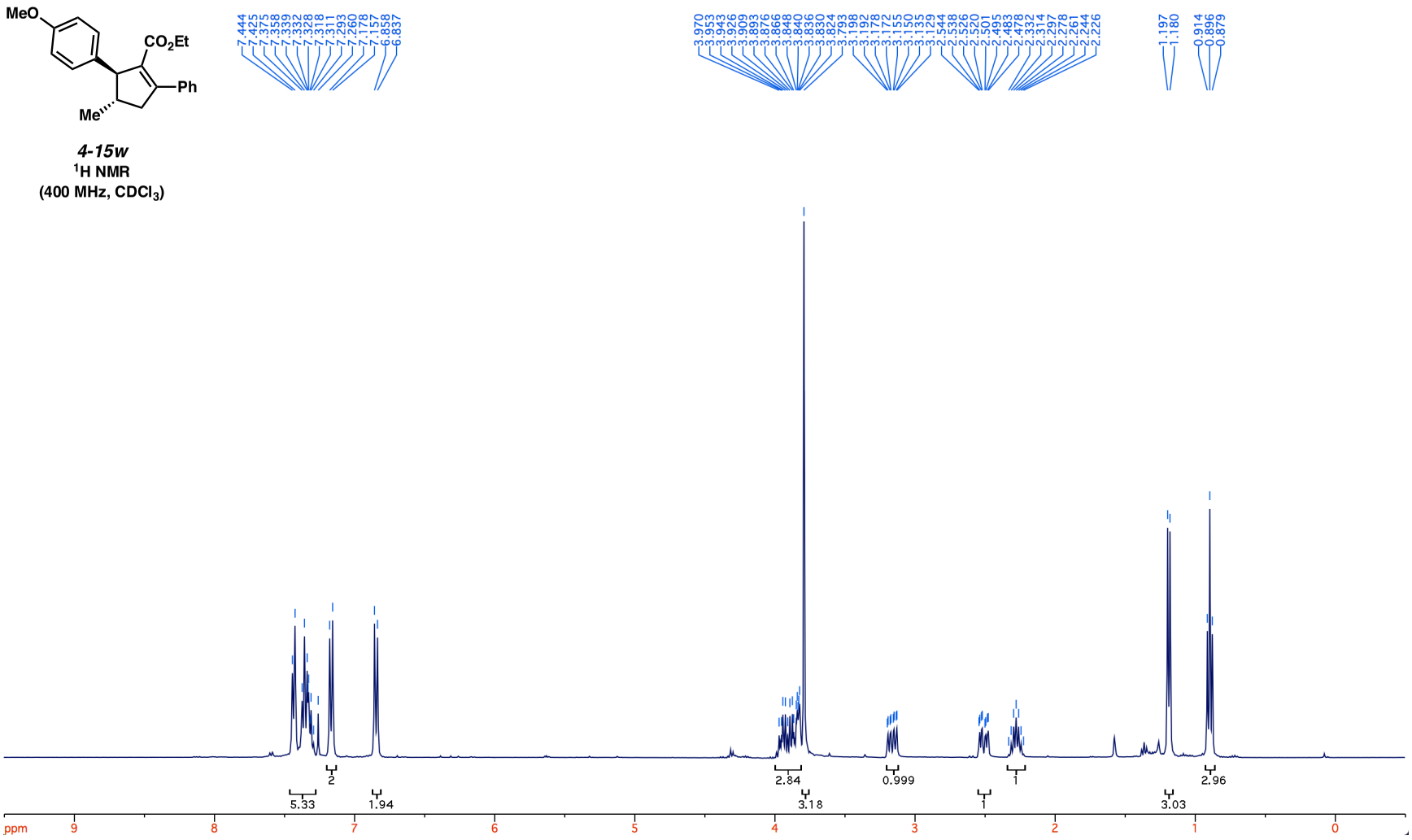


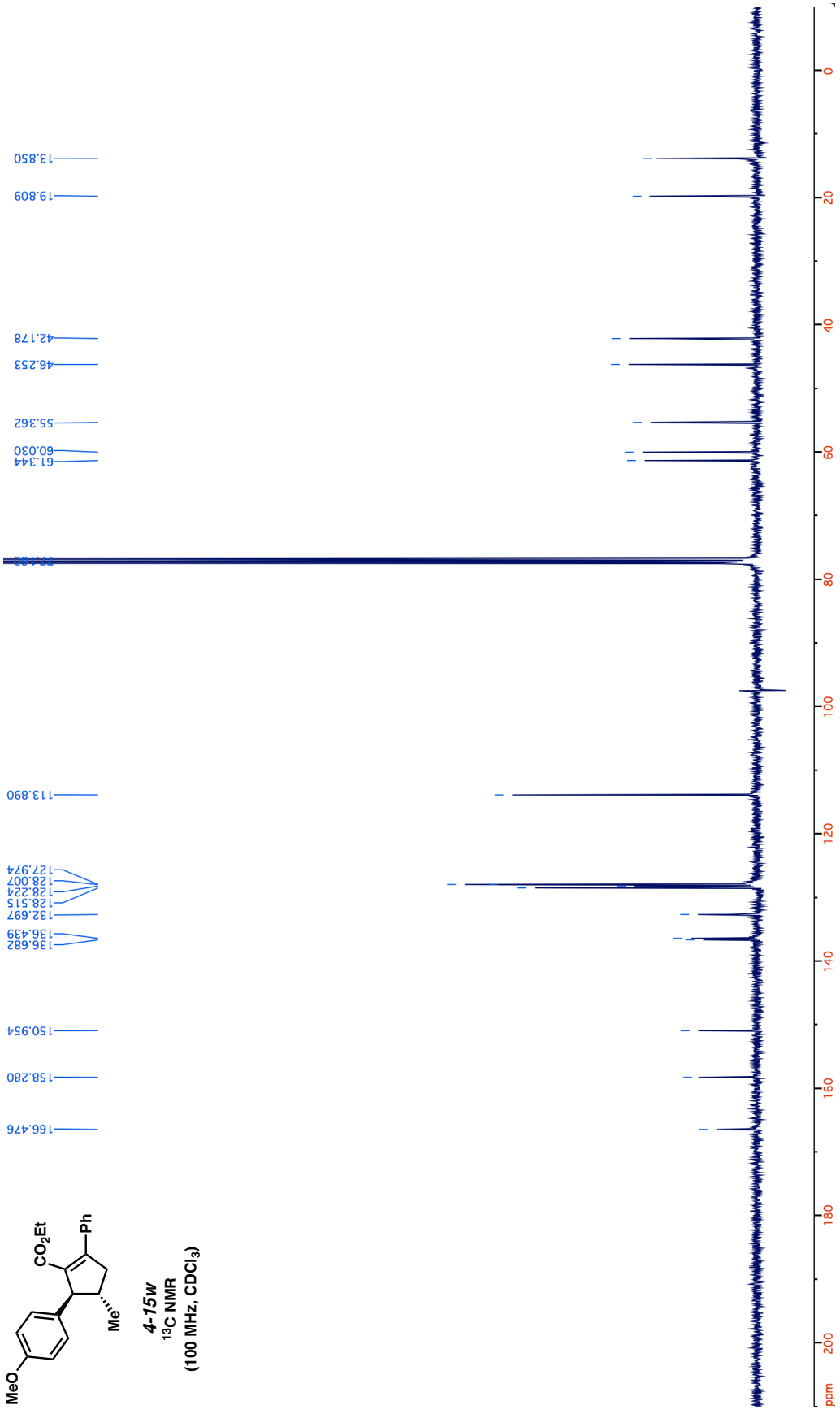
4-15u
^{1}H NMR
(400 MHz, $CDCl_3$)


19.992
41.269
43.398
55.300
58.514
77.160
113.994
128.287
128.307
129.168
132.251
136.325
138.579
144.981
146.845
158.139
193.654
COPh
Me
MeO
4-15u
13C NMR
(125 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm


MeO
CO2Et
Me
Me
4-15v
1H NMR
(400 MHz, CDCl3)
7.260
7.056
7.035
6.810
6.788
4.069
4.052
4.042
4.034
4.024
4.016
4.007
3.989
3.969
3.951
3.942
3.934
3.924
3.916
3.906
3.889
3.772
3.610
3.608
3.607
3.603
3.598
2.828
2.804
2.780
2.757
2.159
2.157
2.139
2.123
2.107
2.092
2.082
2.067
2.051
1.103
1.086
1.038
1.020
1.002
2
1.94
1.87
3.17
1.05
1.02
5.27
3.1
2.95
ppm


14.161
16.593
20.557
41.503
47.515
55.355
59.570
60.010
77.488
113.695
128.146
130.541
137.941
154.767
157.982
166.236
0
20
40
60
80
100
120
140
160
180
200
ppm
CO2Et
Me
Me
MeO
4-15v
13C NMR
(100 MHz, CDCl3)


MeO
CO2Et
Ph
Me
4-15w
1H NMR
(400 MHz, CDCl3)
7.444
7.425
7.375
7.358
7.339
7.332
7.328
7.318
7.311
7.293
7.260
7.178
7.157
6.858
6.837
3.970
3.953
3.943
3.926
3.909
3.893
3.876
3.866
3.848
3.840
3.836
3.830
3.824
3.793
3.198
3.192
3.178
3.172
3.155
3.150
3.135
3.129
2.544
2.538
2.526
2.520
2.501
2.495
2.483
2.478
2.332
2.314
2.297
2.278
2.261
2.244
2.226
1.197
1.180
0.914
0.896
0.879
2
5.33
1.94
2.84
3.18
0.999
1
1
1
3.03
2.96
ppm
9
8
7
6
5
4
3
2
1
0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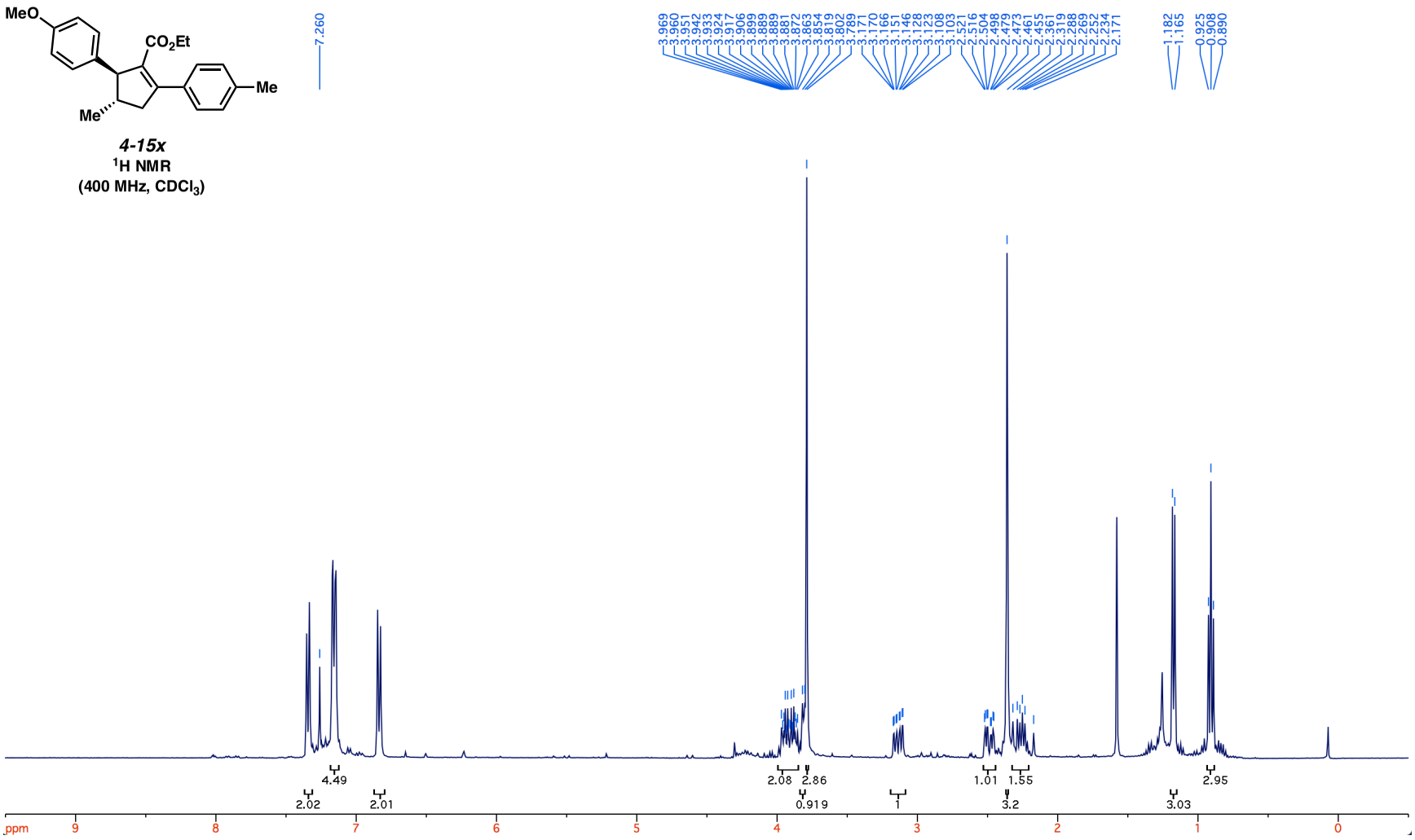
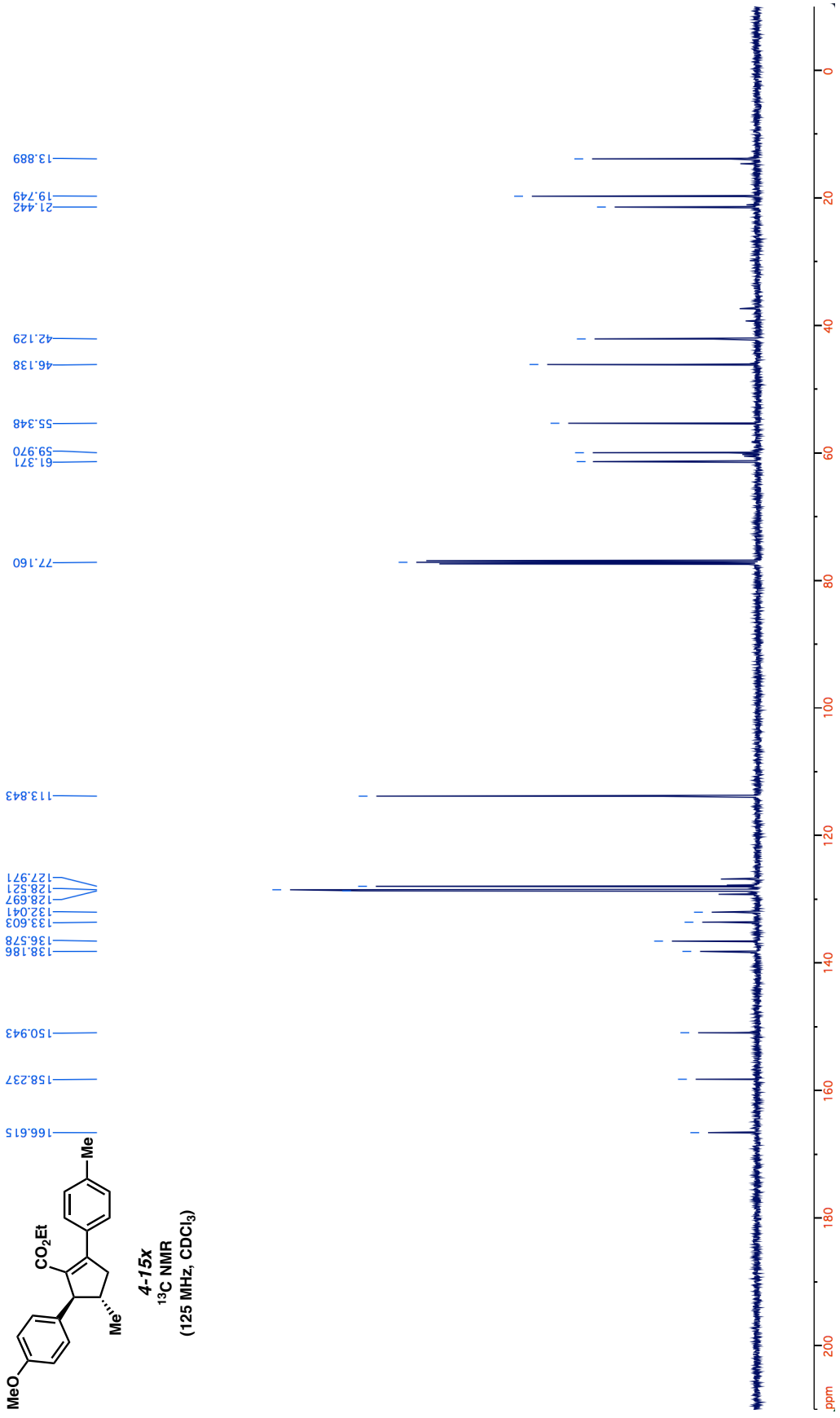
19.809
42.178
46.253
55.362
60.030
61.344
113.890
127.974
128.007
128.224
128.515
132.697
136.439
136.682
150.954
158.280
166.476
ppm
0
20
40
60
80
100
120
140
160
180
200
CO2Et
Ph
Me
MeO
4-15w
13C NMR
(100 MHz, CDCl3)


MeO
CO2Et
Me
Me
4-15x
1H NMR
(400 MHz, CDCl3)
7.260
3.969
3.960
3.951
3.942
3.933
3.924
3.917
3.906
3.899
3.889
3.889
3.881
3.872
3.863
3.854
3.819
3.802
3.789
3.171
3.170
3.166
3.151
3.146
3.128
3.123
3.108
3.103
2.521
2.516
2.504
2.498
2.479
2.473
2.461
2.455
2.361
2.319
2.288
2.269
2.252
2.234
2.171
1.182
1.165
0.925
0.908
0.890
4.49
2.02
2.01
2.08
2.86
0.919
1
1.01
1.55
3.2
2.95
3.03
ppm
9
8
7
6
5
4
3
2
1
0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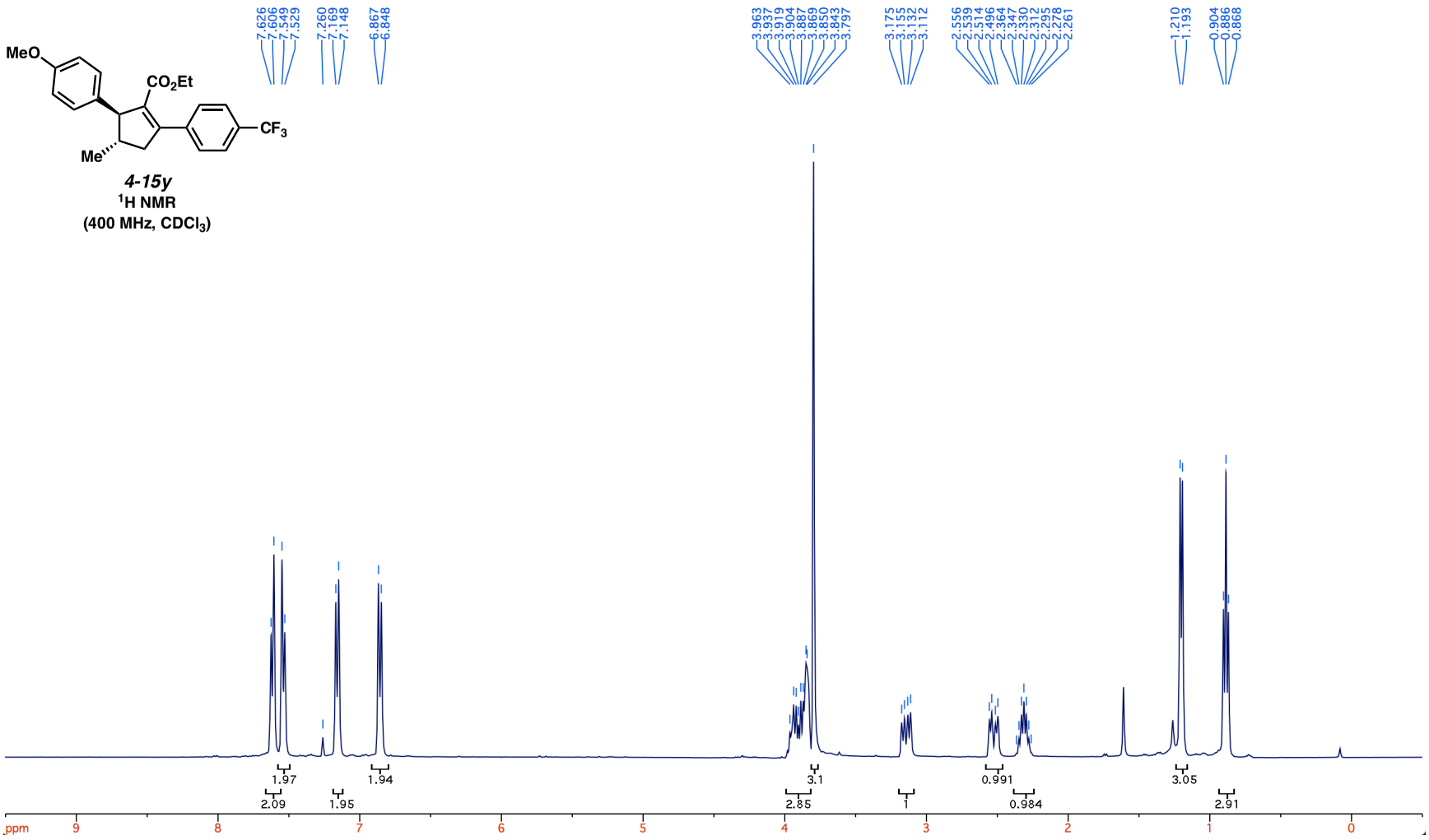
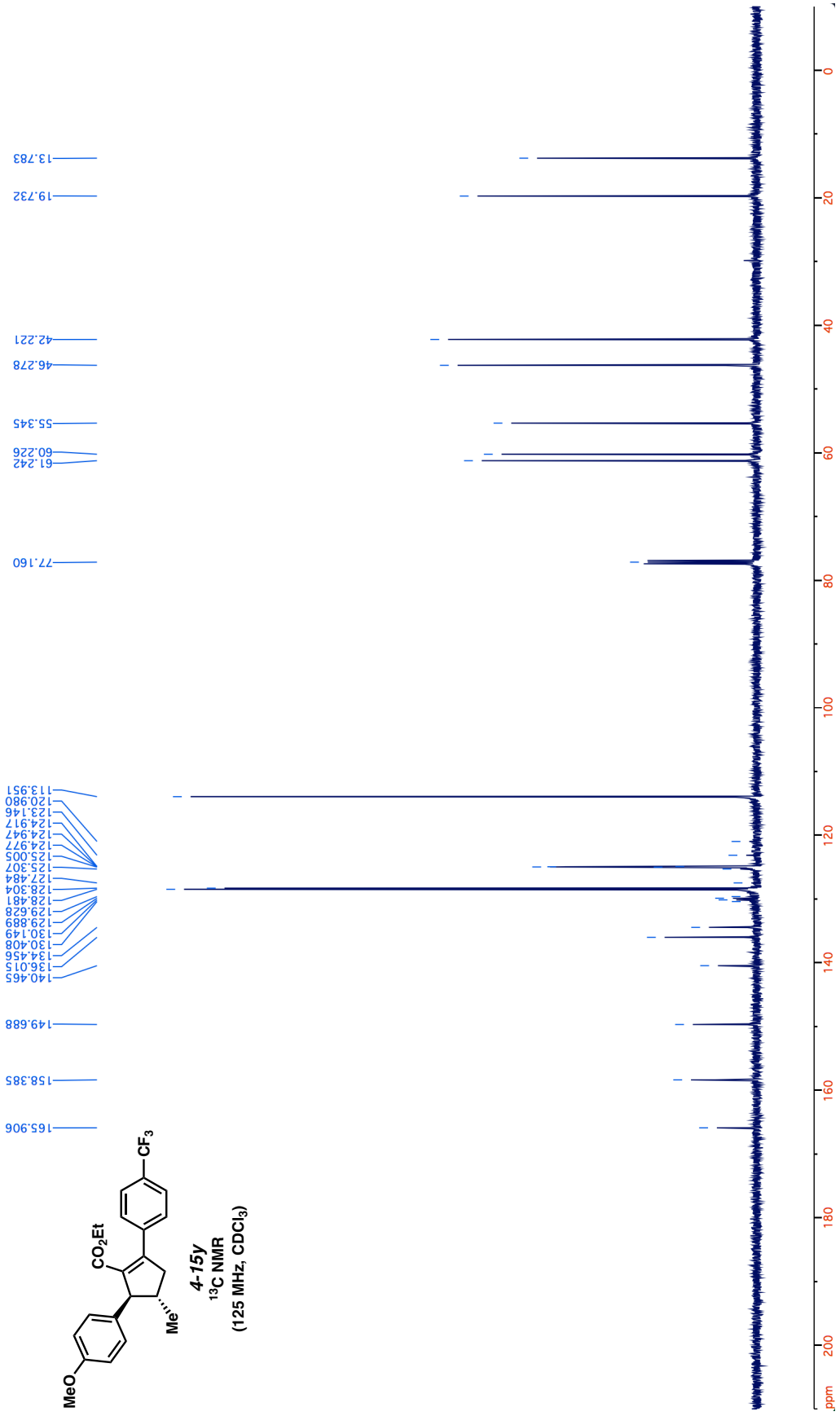
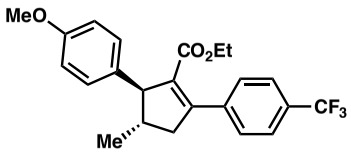
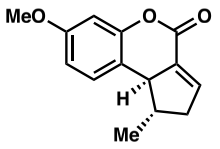
19.749
21.442
42.129
46.138
55.348
59.970
61.371
77.160
113.843
127.971
128.521
128.697
132.041
133.603
136.578
138.186
150.943
158.237
166.615
Me
CO2Et
Me
MeO
4-15x
13C NMR
(125 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm


MeO
CO2Et
CF3
Me
4-15y
1H NMR
(400 MHz, CDCl3)
7.626
7.606
7.549
7.529
7.260
7.169
7.148
6.867
6.848
3.963
3.937
3.919
3.904
3.887
3.869
3.850
3.843
3.797
3.175
3.155
3.132
3.112
2.556
2.539
2.514
2.496
2.364
2.347
2.330
2.312
2.295
2.278
2.261
1.210
1.193
0.904
0.886
0.868
1.97
2.09
1.95
1.94
3.1
2.85
1
0.991
0.984
3.05
2.91
ppm
9
8
7
6
5
4
3
2
1
0

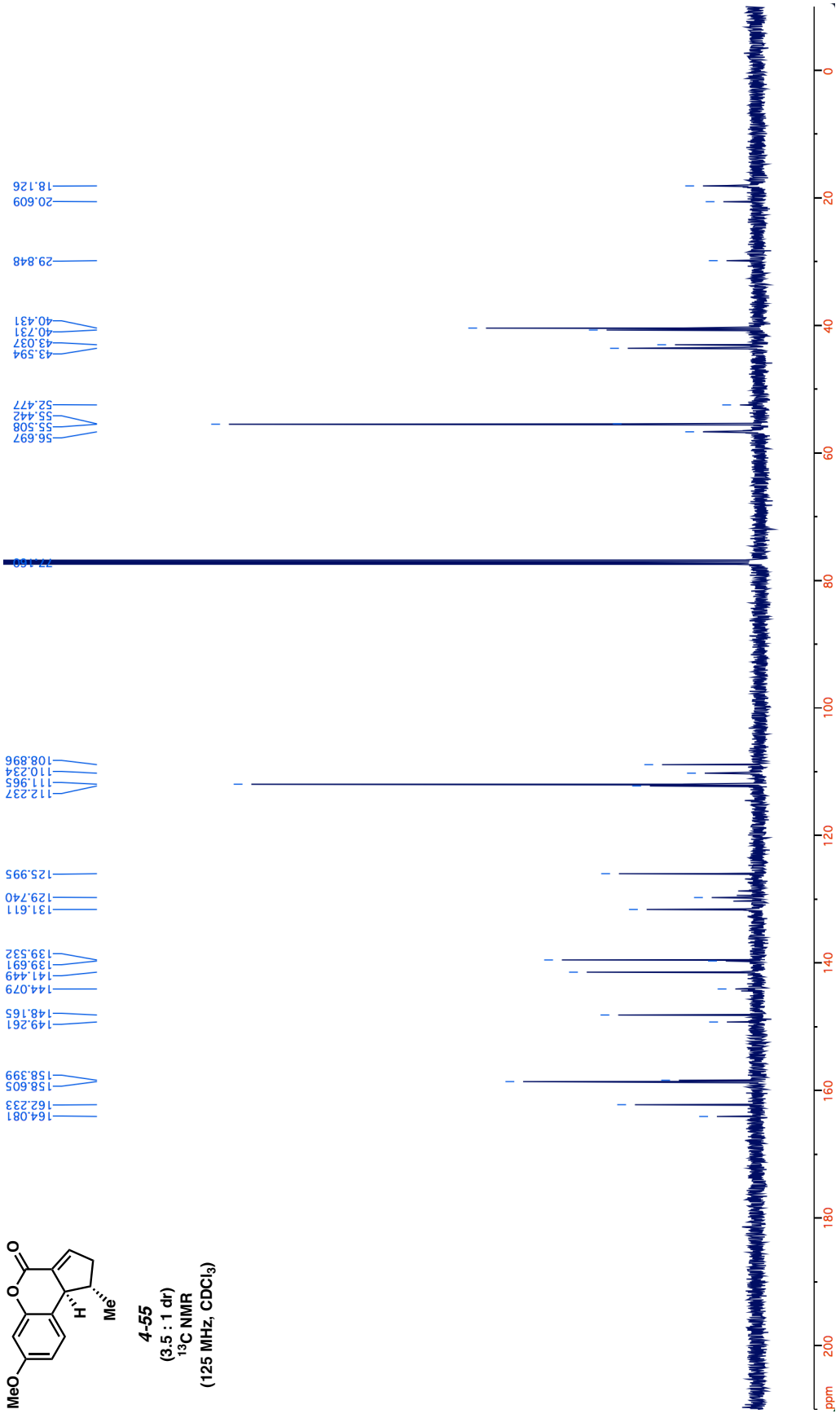

13.783
19.732
42.221
46.278
55.345
60.226
61.242
77.160
113.951
120.980
123.146
124.917
124.947
124.977
125.005
125.307
127.484
128.304
128.481
129.628
129.889
130.149
130.408
134.456
136.015
140.465
149.688
158.385
165.906
MeO
Me
CO2Et
CF3
4-15y
13C NMR
(125 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm

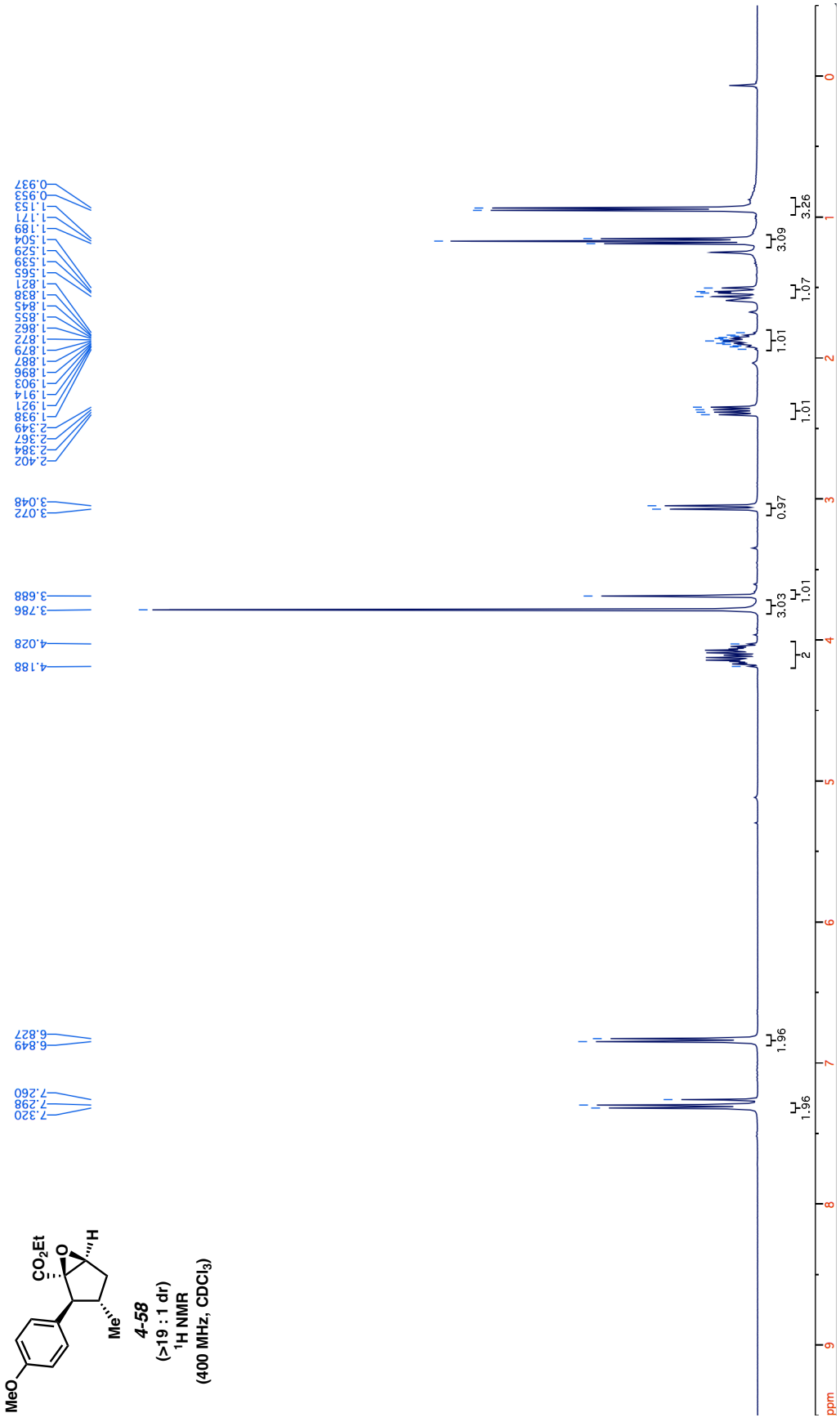


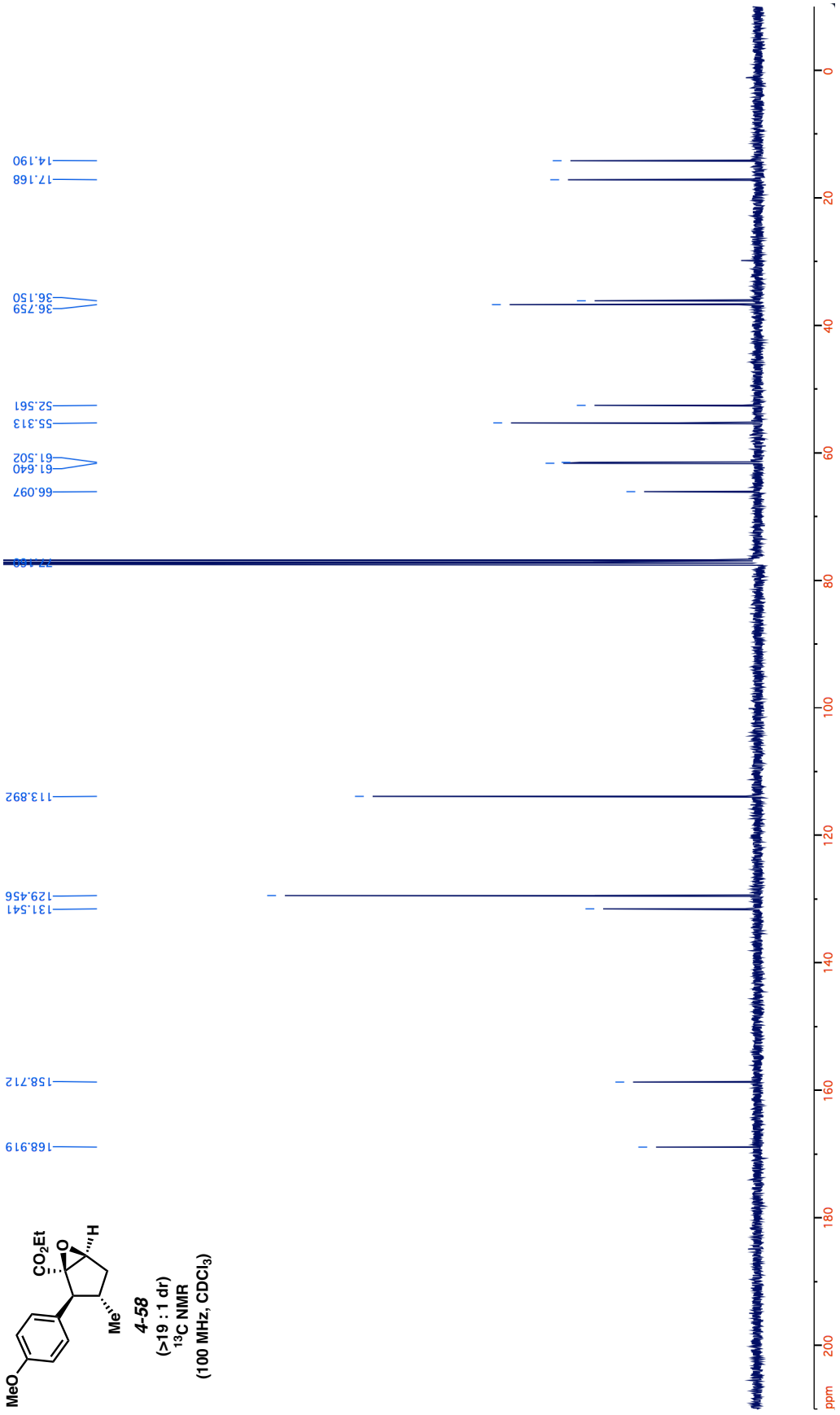
4-15y
^{19}F NMR
(376 MHz, $CDCl_3$)

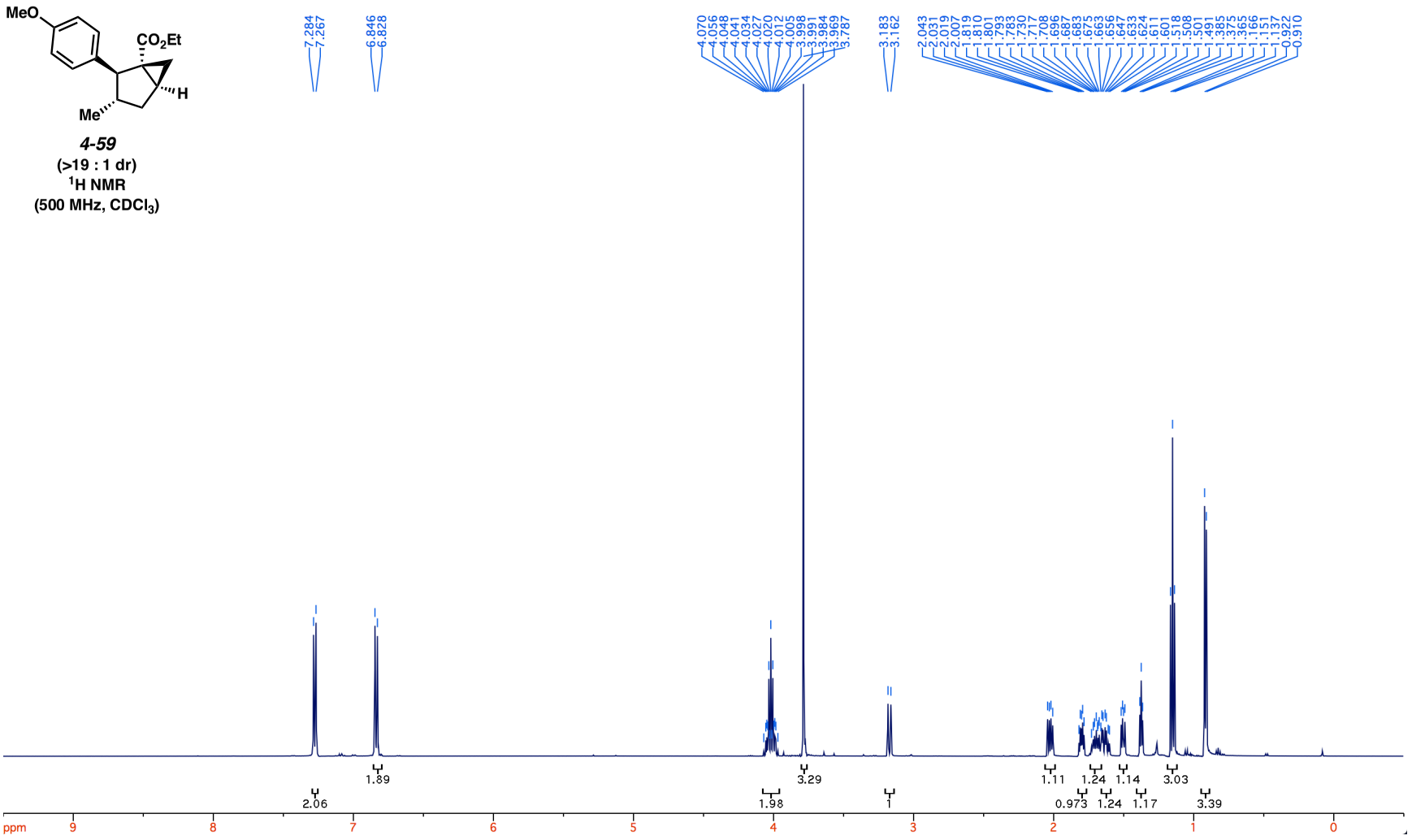


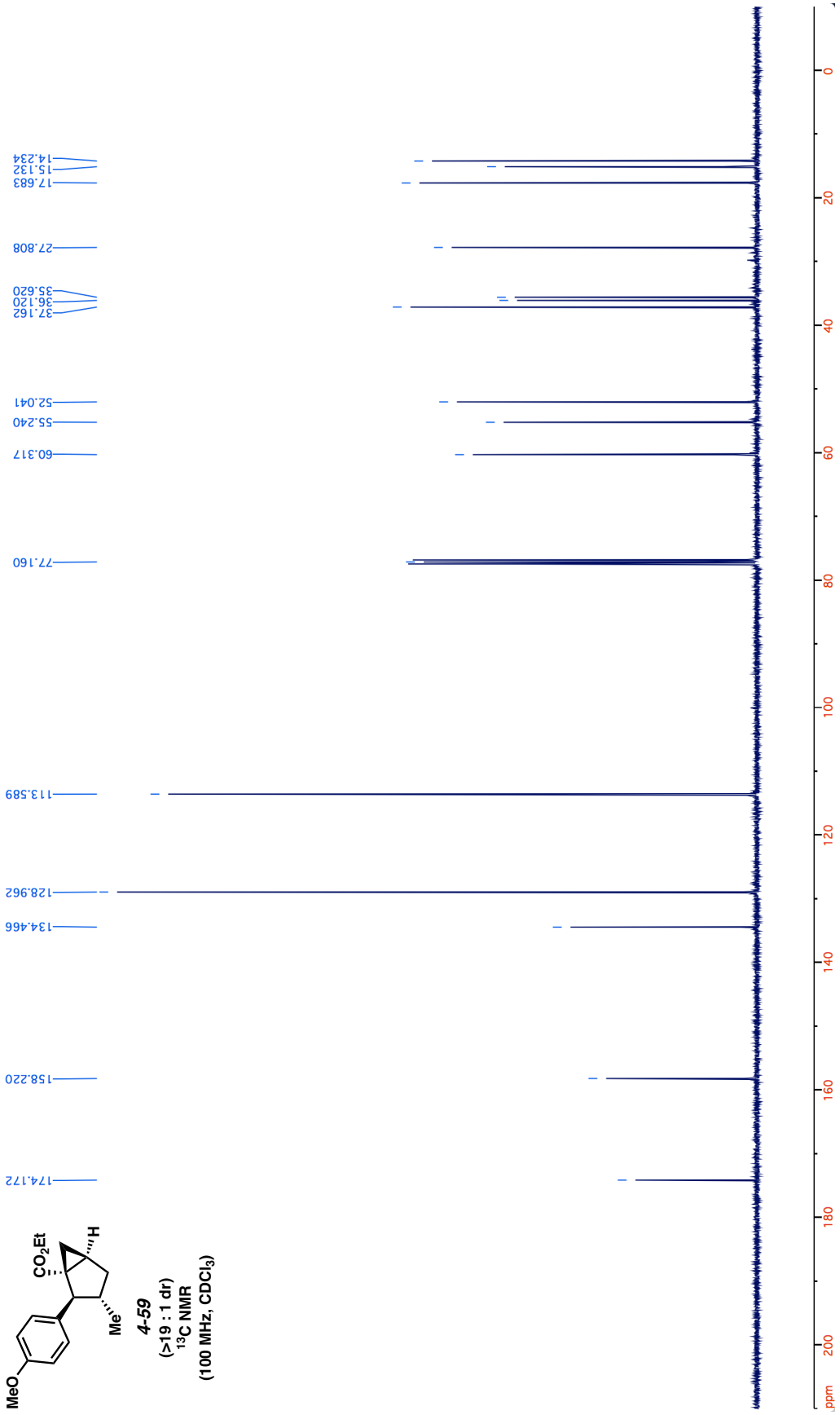
4-55
(3.5 : 1 dr)
^{1}H NMR
(400 MHz, $CDCl_3$)

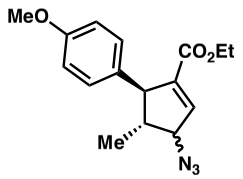

18.126
20.609
29.848
40.431
40.731
43.037
43.594
52.477
55.442
55.508
56.697
77.468
108.896
110.234
111.965
112.237
125.995
129.740
131.611
139.532
139.691
141.449
144.079
148.165
149.261
158.399
158.605
162.233
164.081
MeO
H
Me
O
O
O
4-55
(3.5 : 1 dr)
13C NMR
(125 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm


MeO
CO2Et
O
H
Me
4-58
(>19 : 1 dr)
1H NMR
(400 MHz, CDCl3)
7.320
7.298
7.260
6.849
6.827
4.188
4.028
3.786
3.688
3.072
3.048
2.402
2.384
2.367
2.349
1.938
1.921
1.914
1.903
1.896
1.887
1.879
1.872
1.866
1.855
1.845
1.838
1.821
1.565
1.539
1.529
1.504
1.189
1.171
1.153
0.953
0.937
1.96
1.56
0.97
3.03
1.01
1.01
1.01
1.07
3.09
3.26
ppm

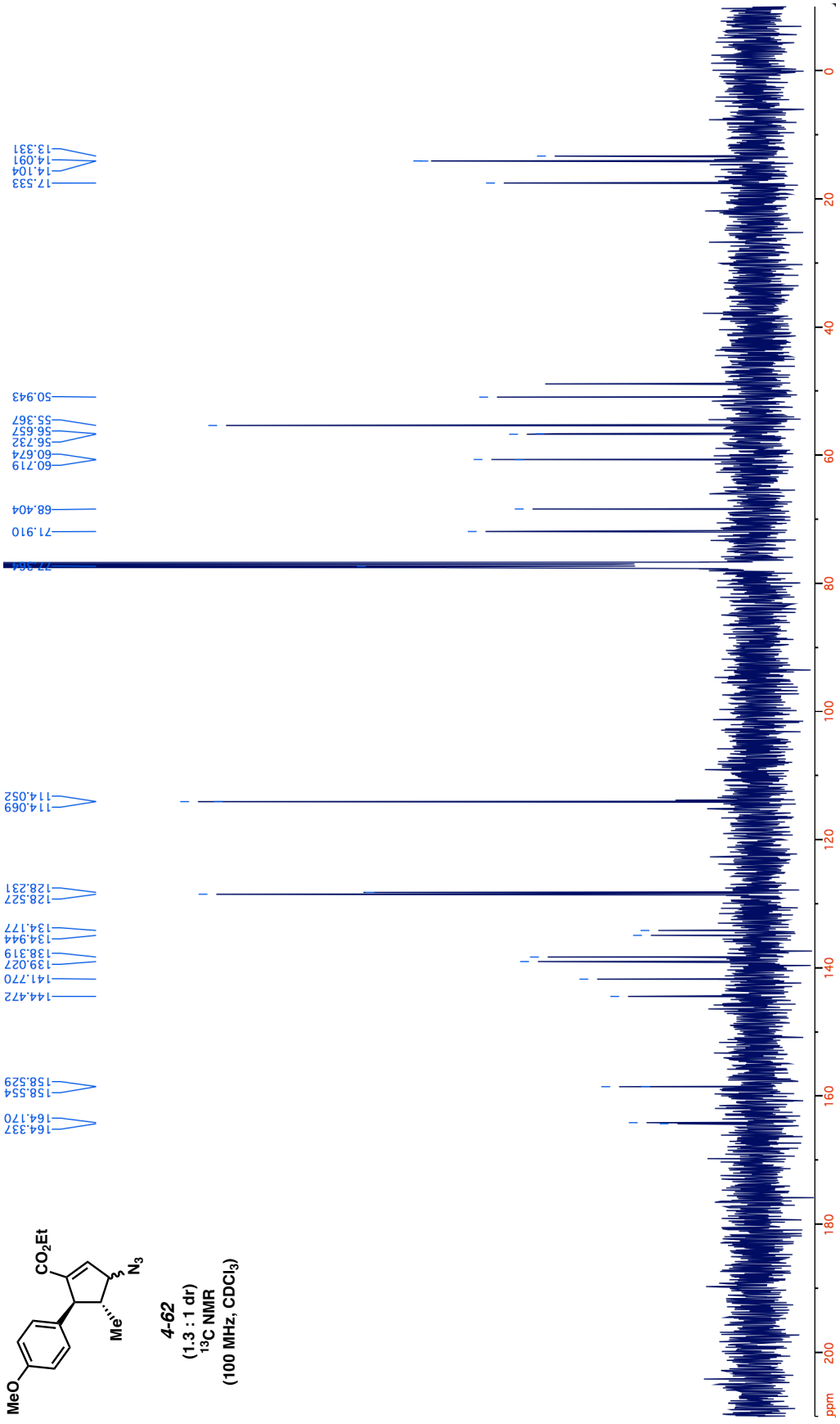

14.190
17.168
36.150
36.759
52.561
55.313
61.502
61.640
66.097
77.488
113.892
129.456
131.541
158.712
168.919
MeO
CO2Et
O
H
Me
4-58
(>19 : 1 dr)
13C NMR
(100 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm

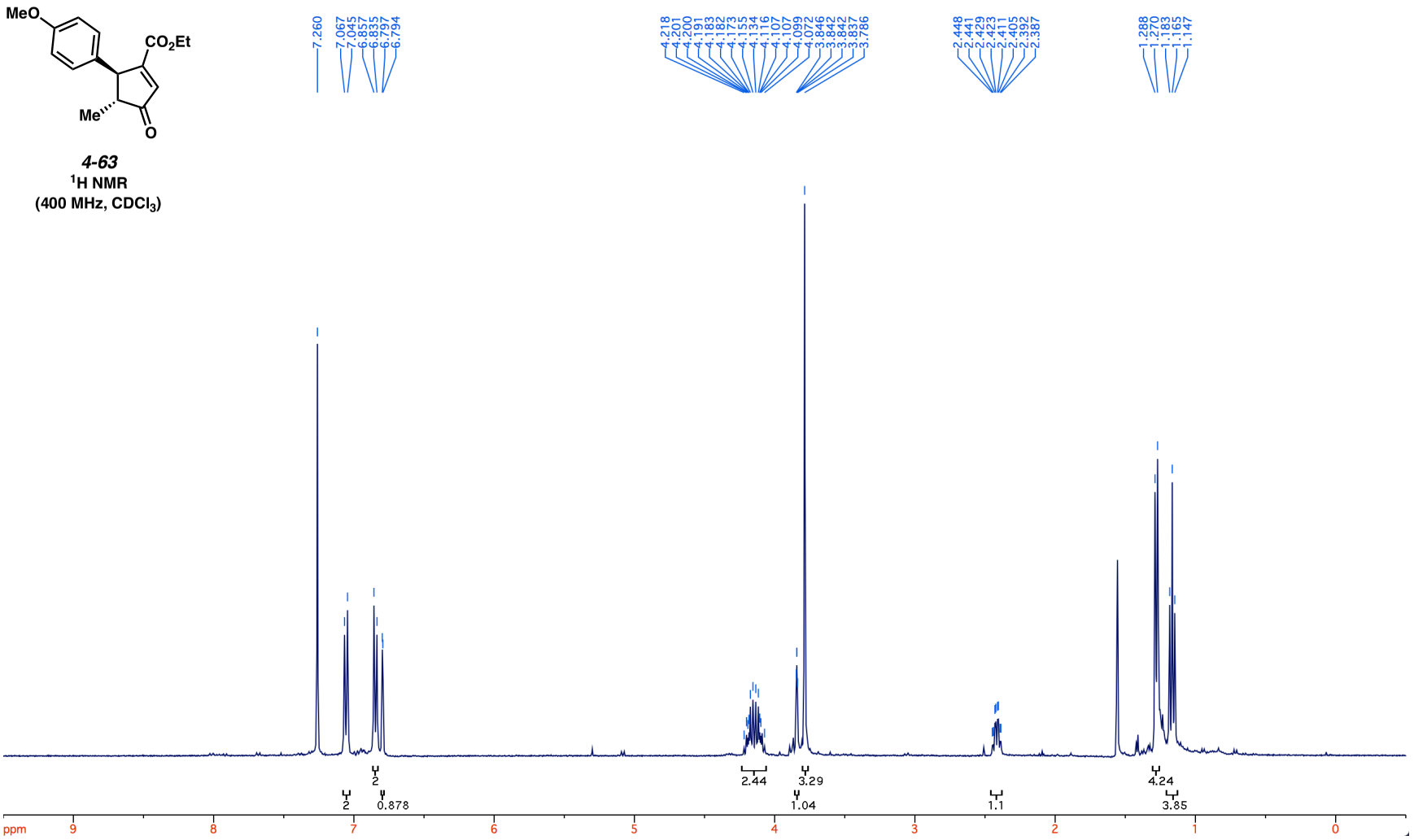

MeO
CO2Et
H
Me
4-59
(>19 : 1 dr)
1H NMR
(500 MHz, CDCl3)
7.284
7.267
6.846
6.828
4.070
4.056
4.048
4.041
4.034
4.027
4.020
4.012
4.005
3.998
3.991
3.984
3.989
3.787
3.183
3.162
2.043
2.031
2.019
2.007
1.819
1.810
1.801
1.793
1.783
1.730
1.717
1.708
1.696
1.687
1.683
1.675
1.663
1.656
1.647
1.633
1.624
1.611
1.601
1.518
1.508
1.501
1.491
1.375
1.365
1.166
1.151
1.137
0.922
0.910
2.06
1.89
1.98
3.29
1
1.11
0.973
1.24
1.24
1.14
1.17
3.03
3.39
ppm
9
8
7
6
5
4
3
2
1
0

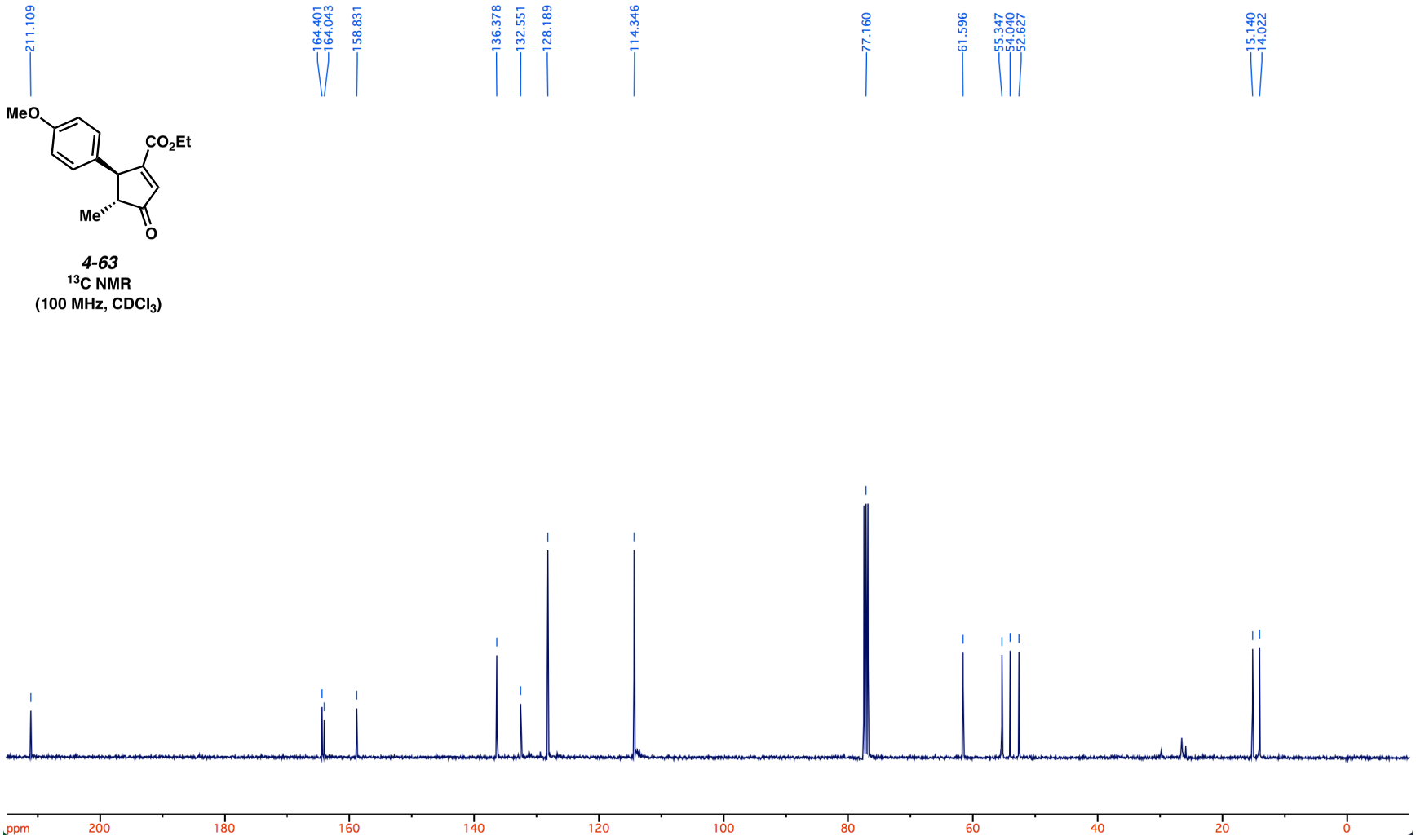

14.234
15.132
17.683
27.808
35.620
36.120
37.162
52.041
55.240
60.317
77.160
113.589
128.962
134.466
158.220
174.172
MeO
Me
CO2Et
H
4-59
(>19 : 1 dr)
13C NMR
(100 MHz, CDCl3)
ppm

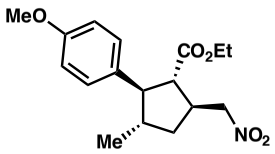


4-62
(1.3 : 1 dr)
^{1}H NMR
(400 MHz, $CDCl_3$)

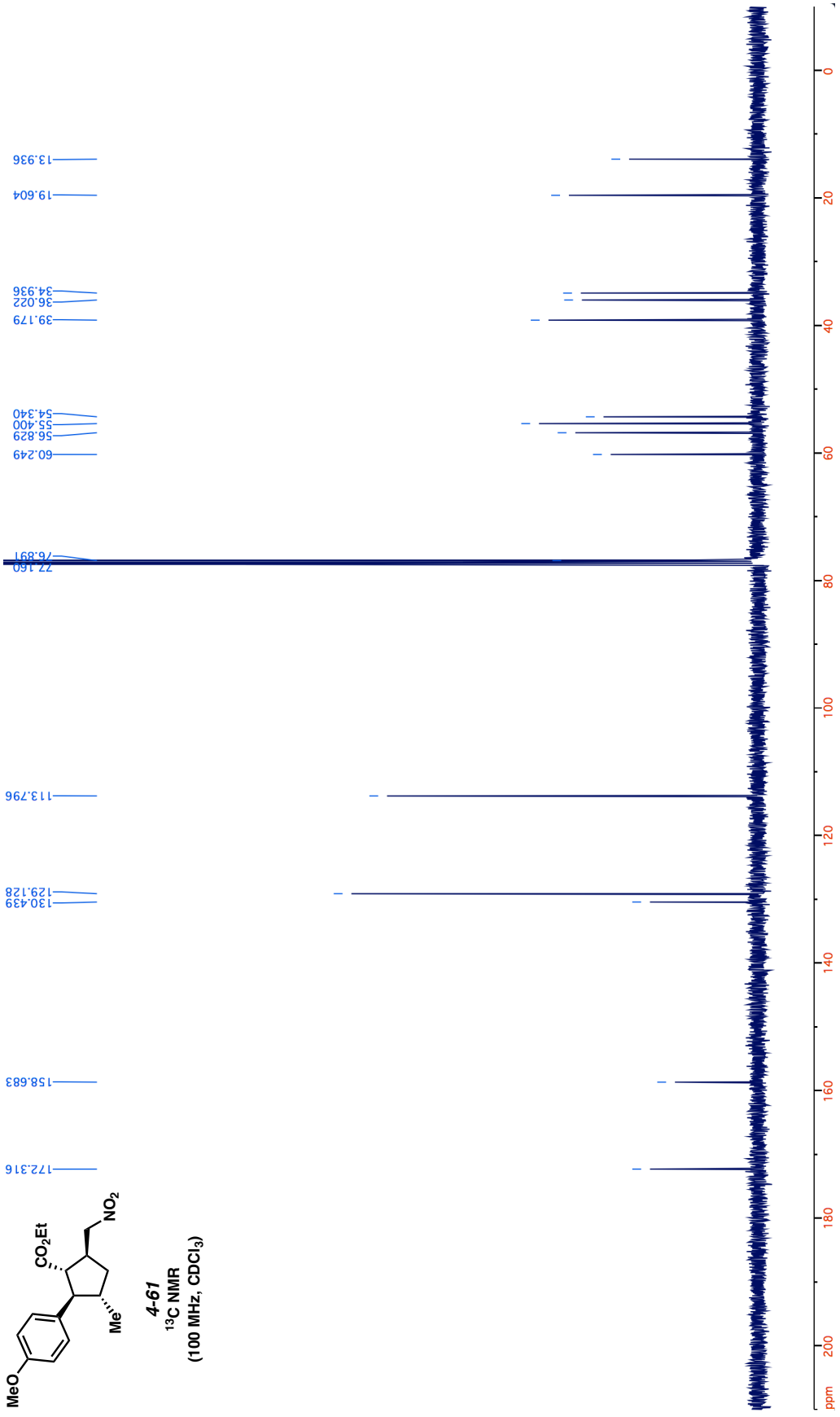

13.331
14.091
14.104
17.533
50.943
55.367
56.657
56.732
60.674
60.719
68.404
71.910
77.384
114.052
114.069
128.231
128.527
134.177
134.944
138.319
139.027
141.770
144.472
158.529
158.554
164.170
164.337
MeO
Me
N3
CO2Et
4-62
(1.3 : 1 dr)
13C NMR
(100 MHz, CDCl3)
ppm

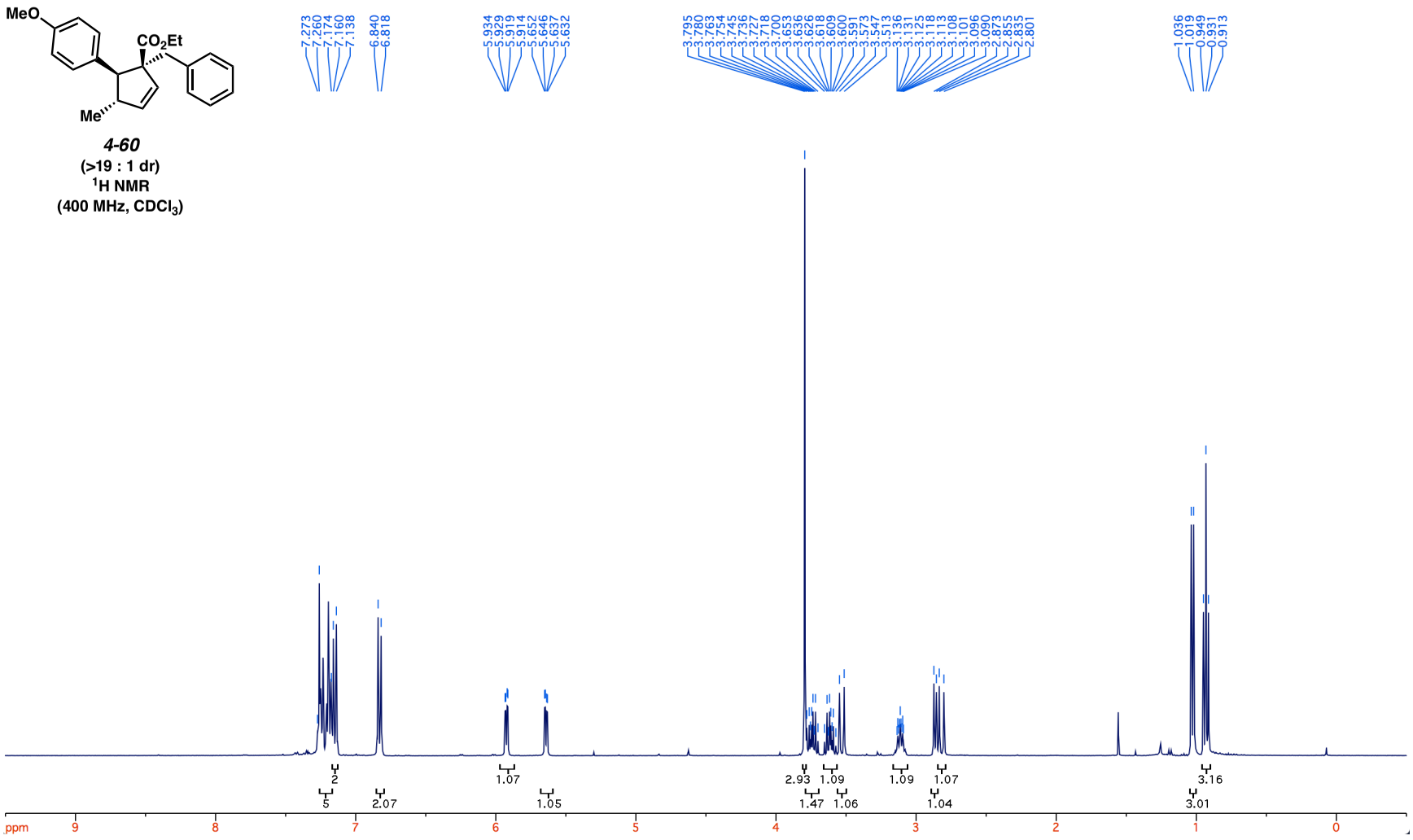

MeO
CO2Et
Me
O
4-63
1H NMR
(400 MHz, CDCl3)
7.260
7.067
7.045
6.857
6.835
6.797
6.794
4.218
4.201
4.200
4.191
4.183
4.182
4.173
4.155
4.134
4.116
4.107
4.099
4.072
3.846
3.842
3.842
3.837
3.786
2.448
2.441
2.429
2.423
2.411
2.405
2.392
2.387
1.288
1.270
1.183
1.165
1.147
2
2
0.878
2.44
3.29
1.04
1.1
4.24
3.85
ppm
9
8
7
6
5
4
3
2
1
0


211.109
164.401
164.043
158.831
136.378
132.551
128.189
114.346
77.160
61.596
55.347
54.040
52.627
15.140
14.022
MeO
CO2Et
Me
O
4-63
13C NMR
(100 MHz, CDCl3)
ppm
200
180
160
140
120
100
80
60
40
20
0

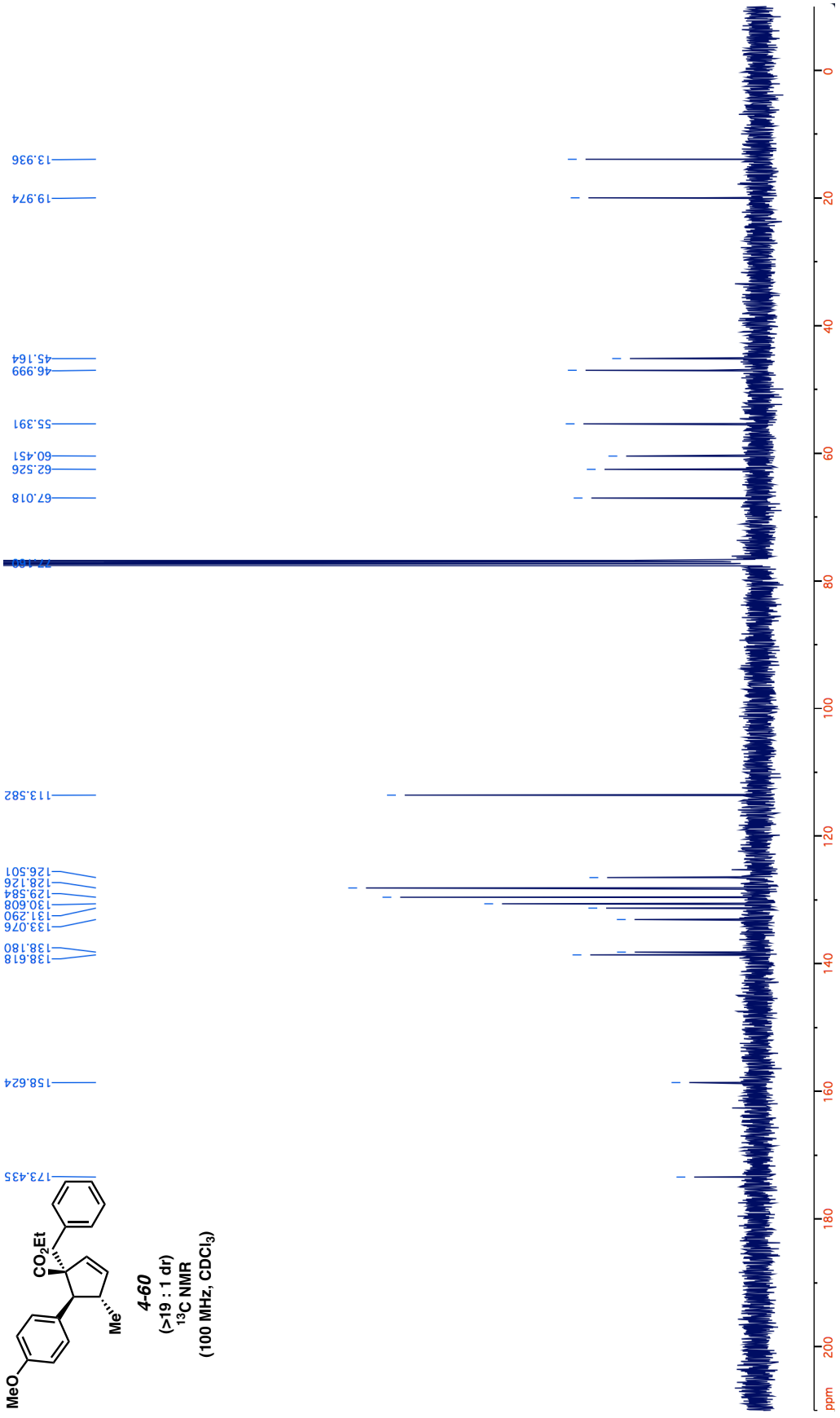


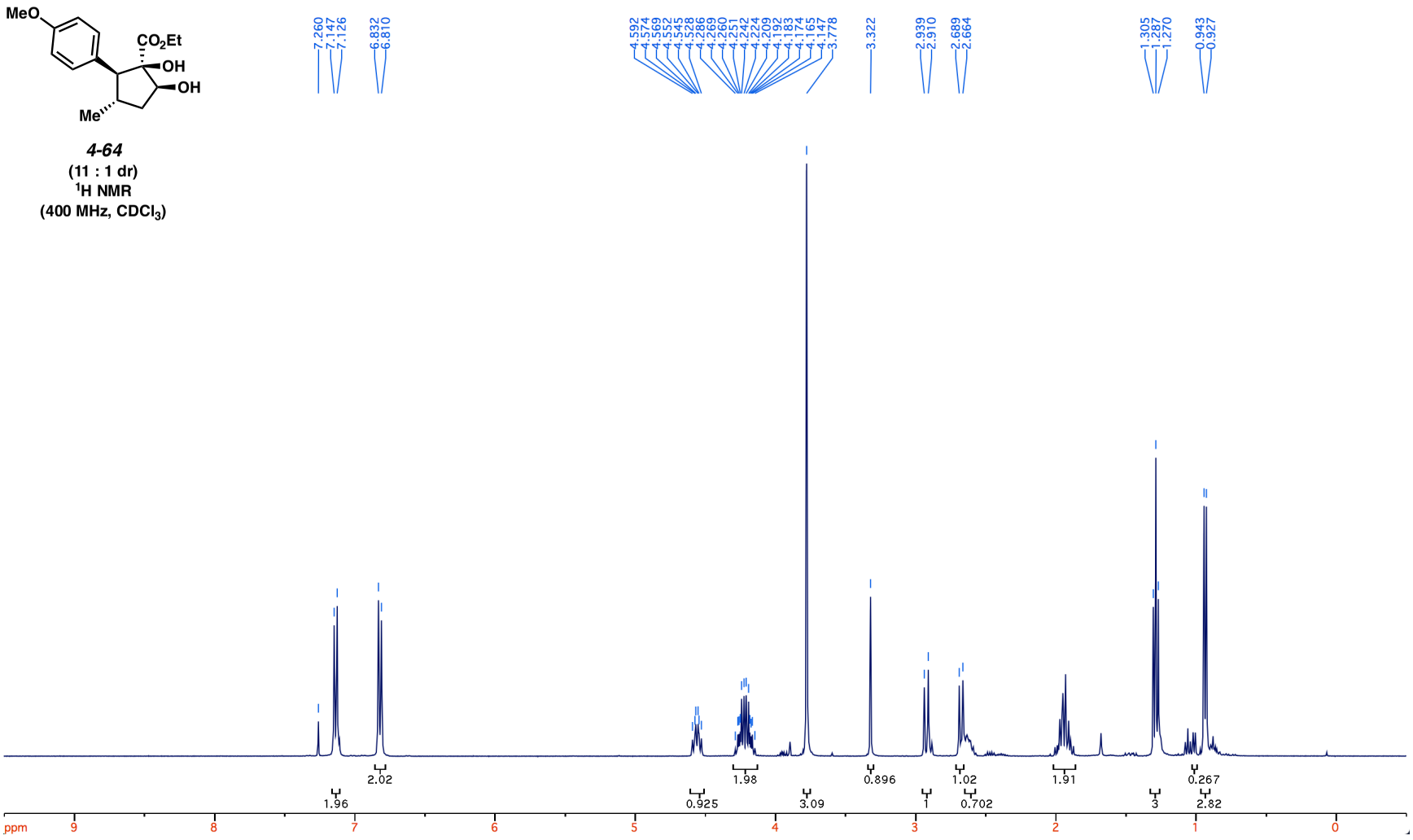
4-61
^{1}H NMR
(400 MHz, $CDCl_3$)

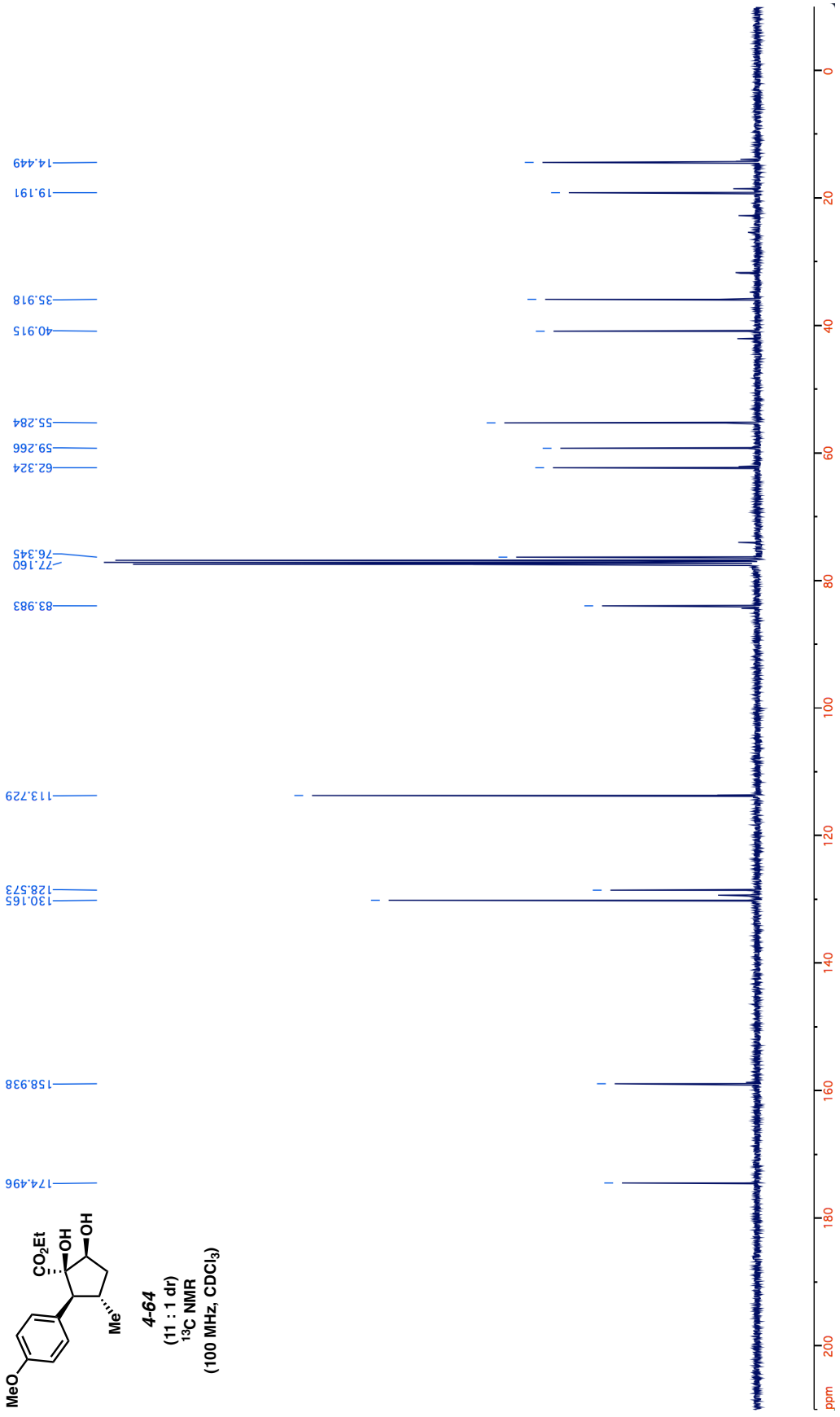

13.936
19.604
34.936
36.022
39.179
54.340
55.400
56.829
60.249
76.891
77.160
113.796
129.128
130.439
158.683
172.316
MeO
Me
CO2Et
NO2
4-61
13C NMR
(100 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm

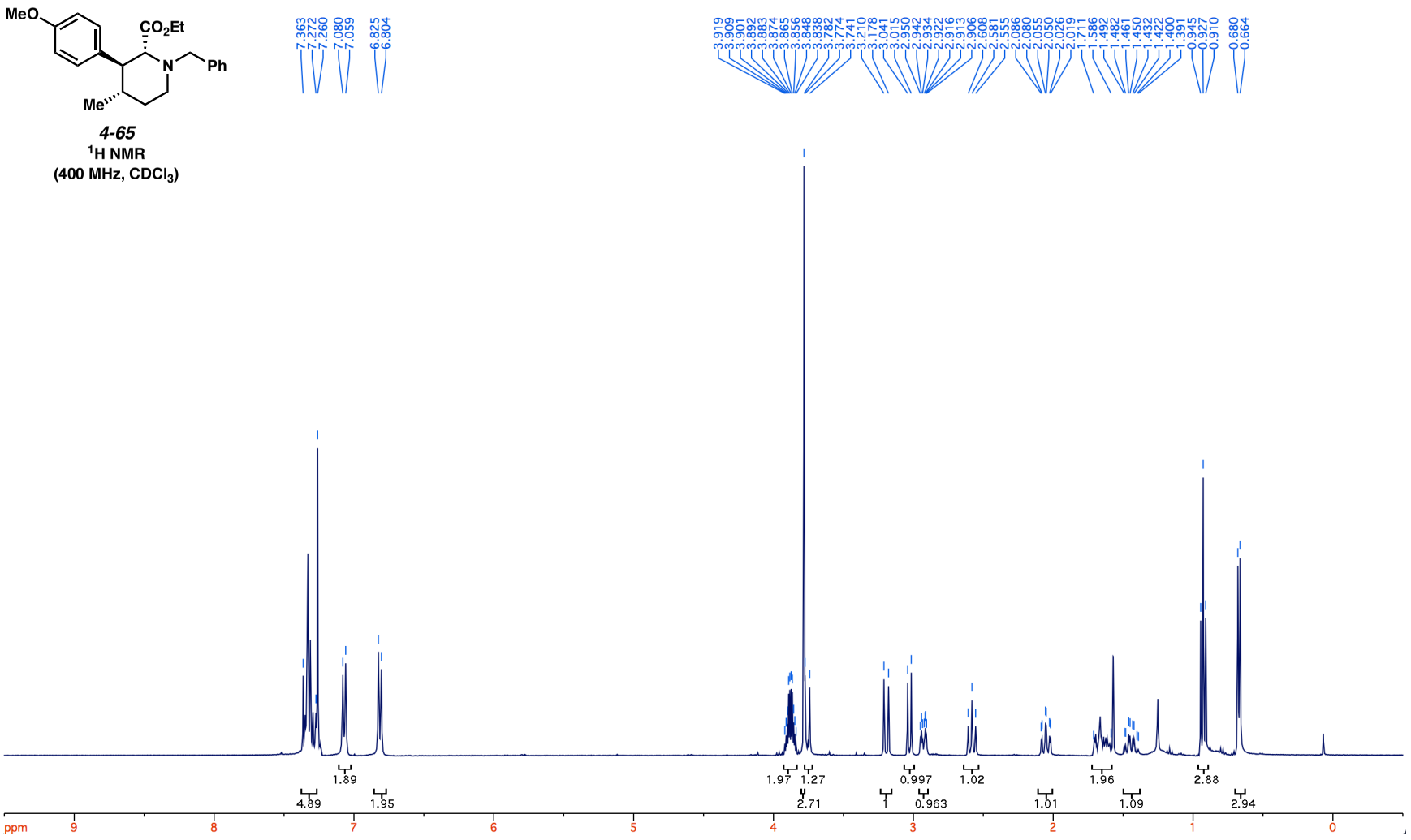


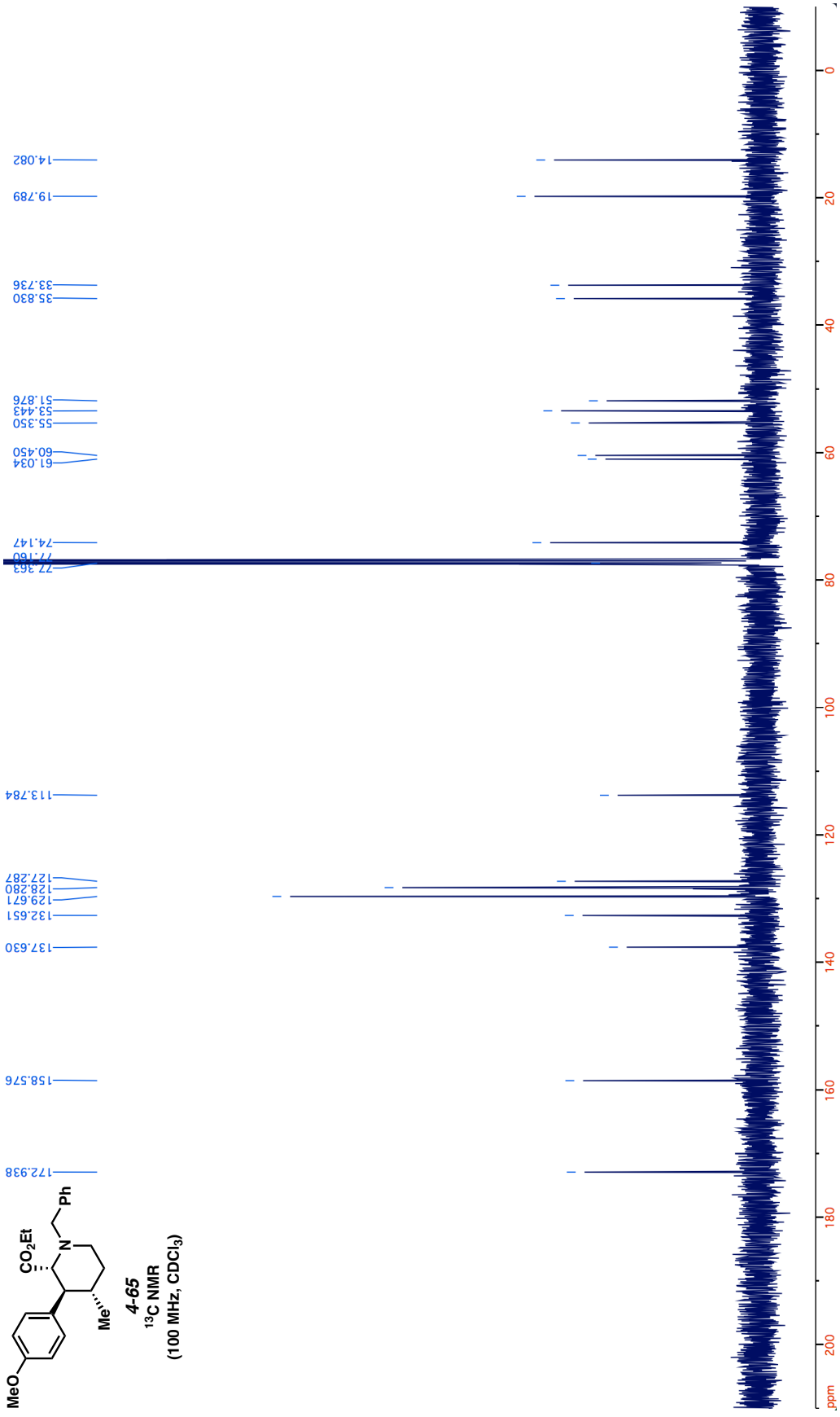
4-60
(>19 : 1 dr)
^{1}H NMR
(400 MHz, $CDCl_3$)

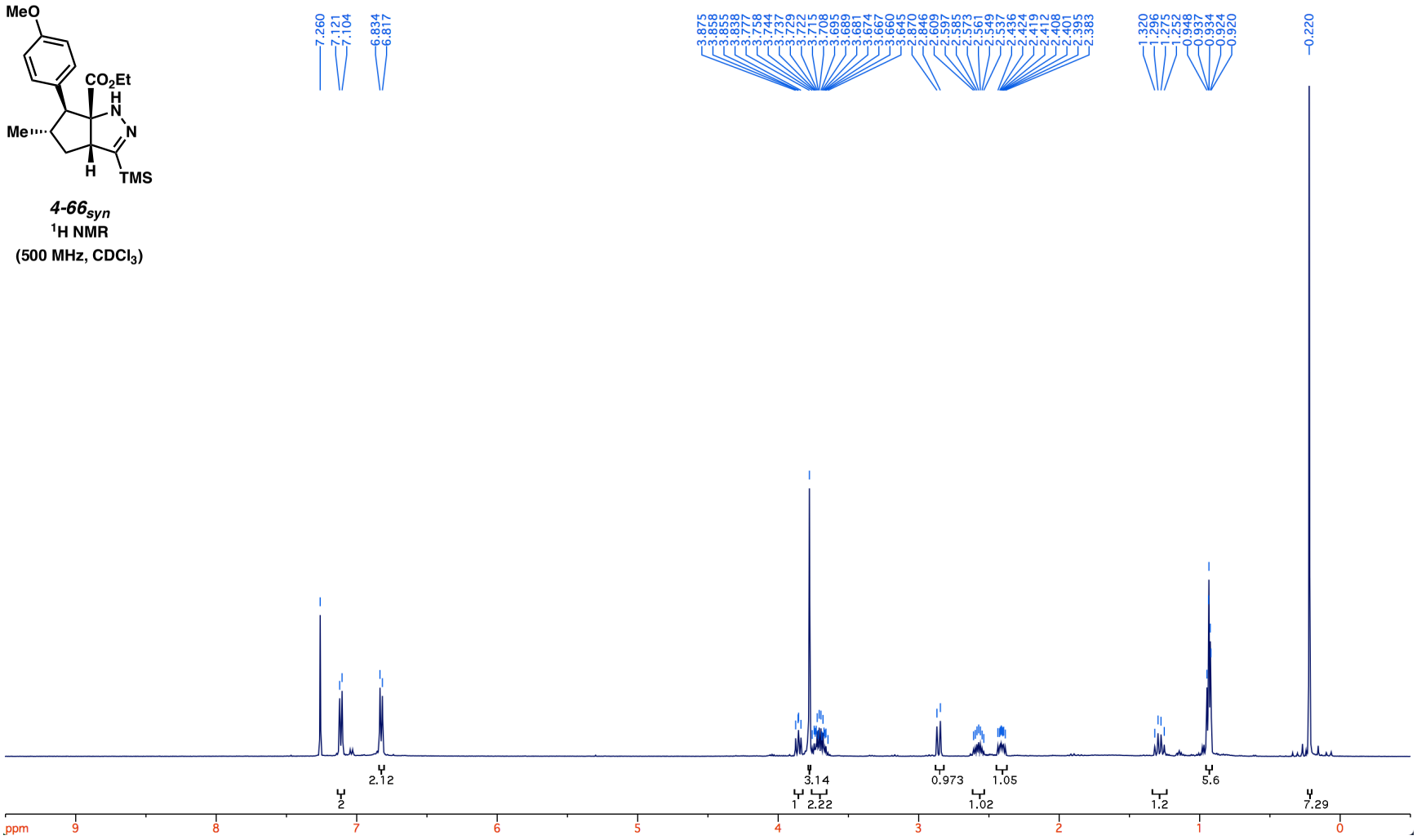

MeO
CO2Et
Me
4-60
(>19 : 1 dr)
13C NMR
(100 MHz, CDCl3)
173.435
158.624
138.618
138.180
133.076
131.290
130.608
129.584
128.126
126.501
113.582
77.488
67.018
62.526
60.451
55.391
46.999
45.164
19.974
13.936
ppm

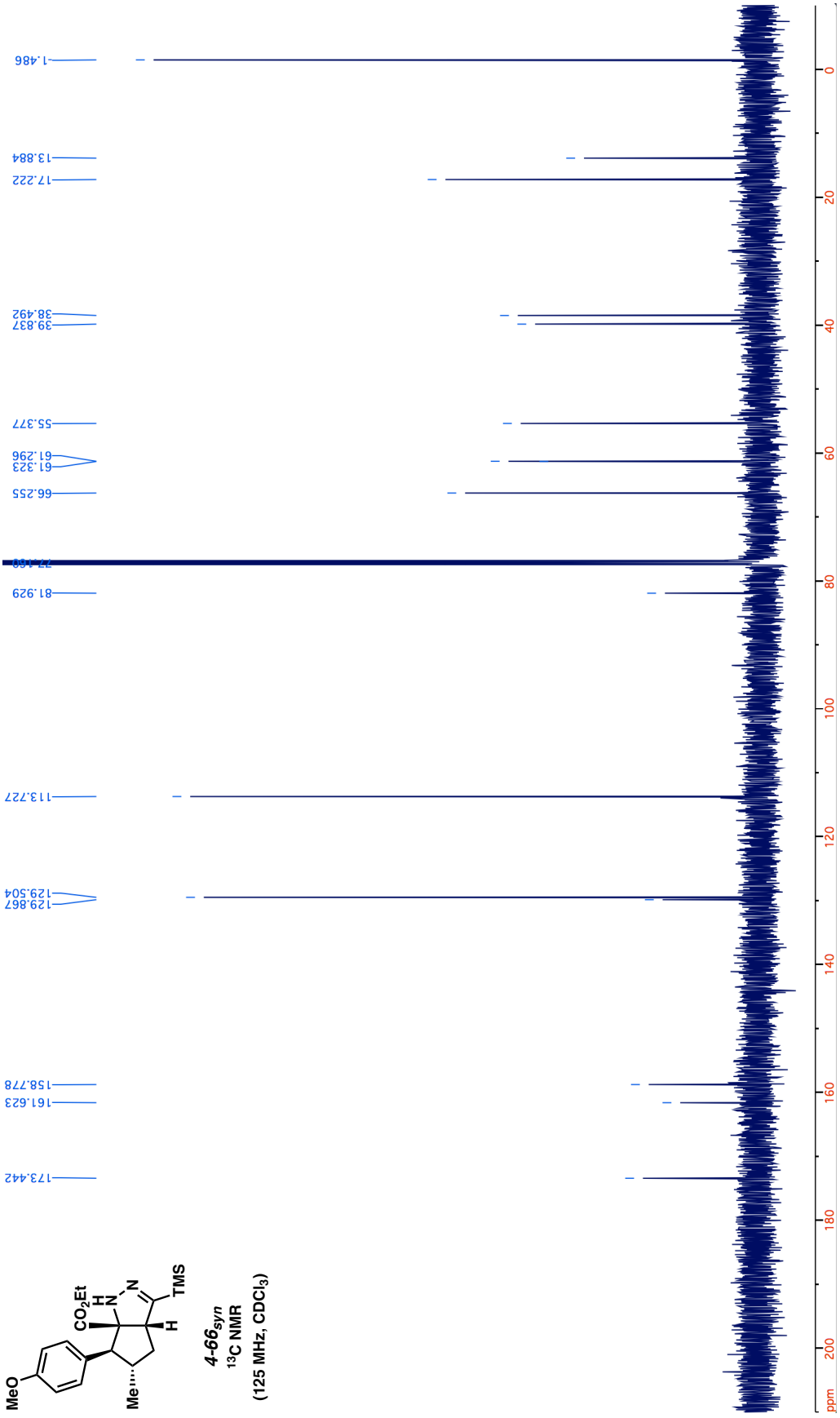

MeO
CO2Et
OH
OH
Me
4-64
(11 : 1 dr)
1H NMR
(400 MHz, CDCl3)
7.260
7.147
7.126
6.832
6.810
4.592
4.574
4.569
4.552
4.545
4.528
4.286
4.269
4.260
4.231
4.222
4.224
4.209
4.192
4.183
4.174
4.165
4.147
3.778
3.322
2.939
2.910
2.689
2.664
1.305
1.287
1.270
0.943
0.927
2.02
1.98
0.896
1.02
1.91
0.267
1.96
0.925
3.09
1
0.702
3
2.82
ppm
9
8
7
6
5
4
3
2
1
0

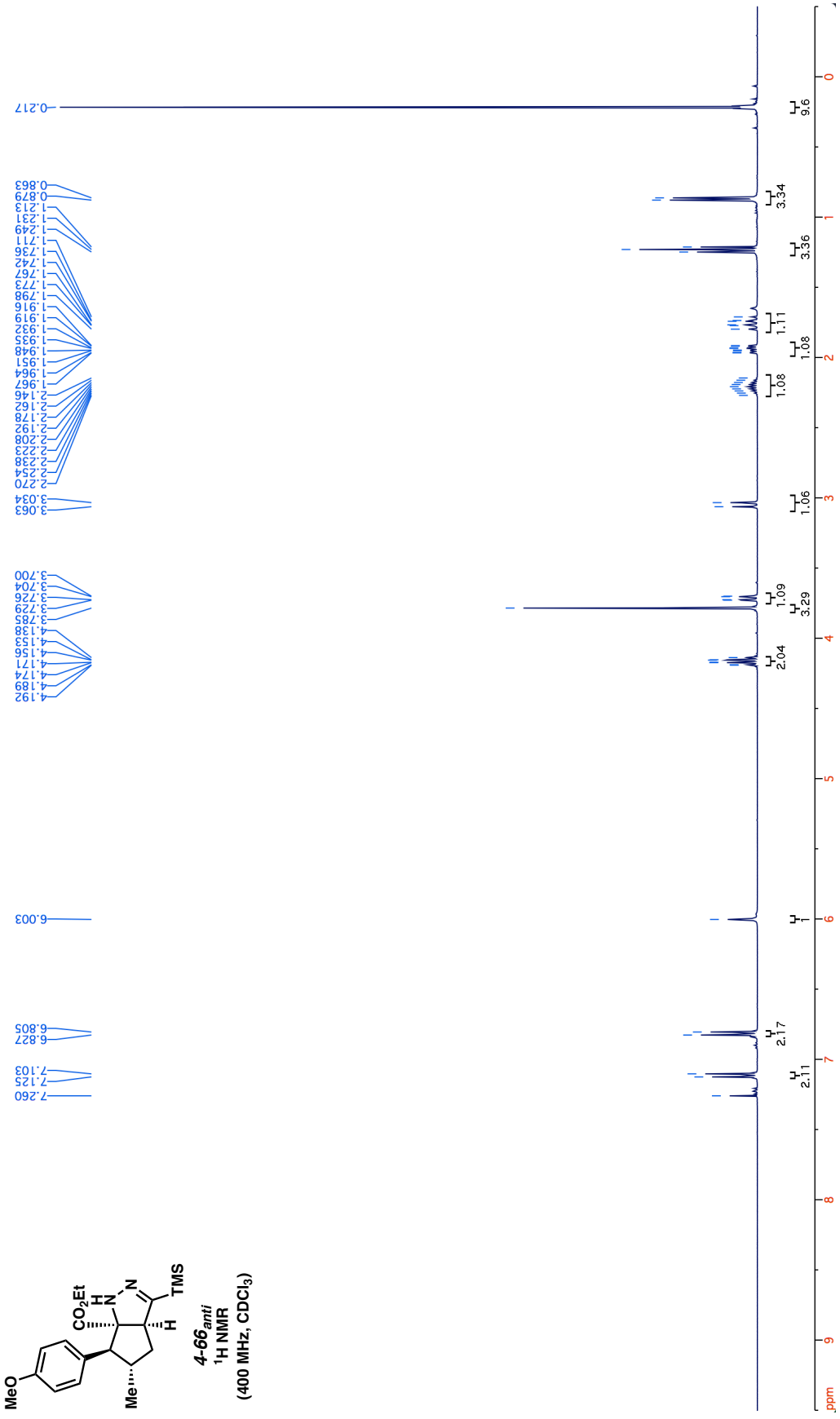

14.449
19.191
35.918
40.915
55.284
59.266
62.324
76.345
77.160
83.983
113.729
128.573
130.165
158.938
174.496
MeO
CO2Et
OH
OH
Me
4-64
(11 : 1 dr)
13C NMR
(100 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm

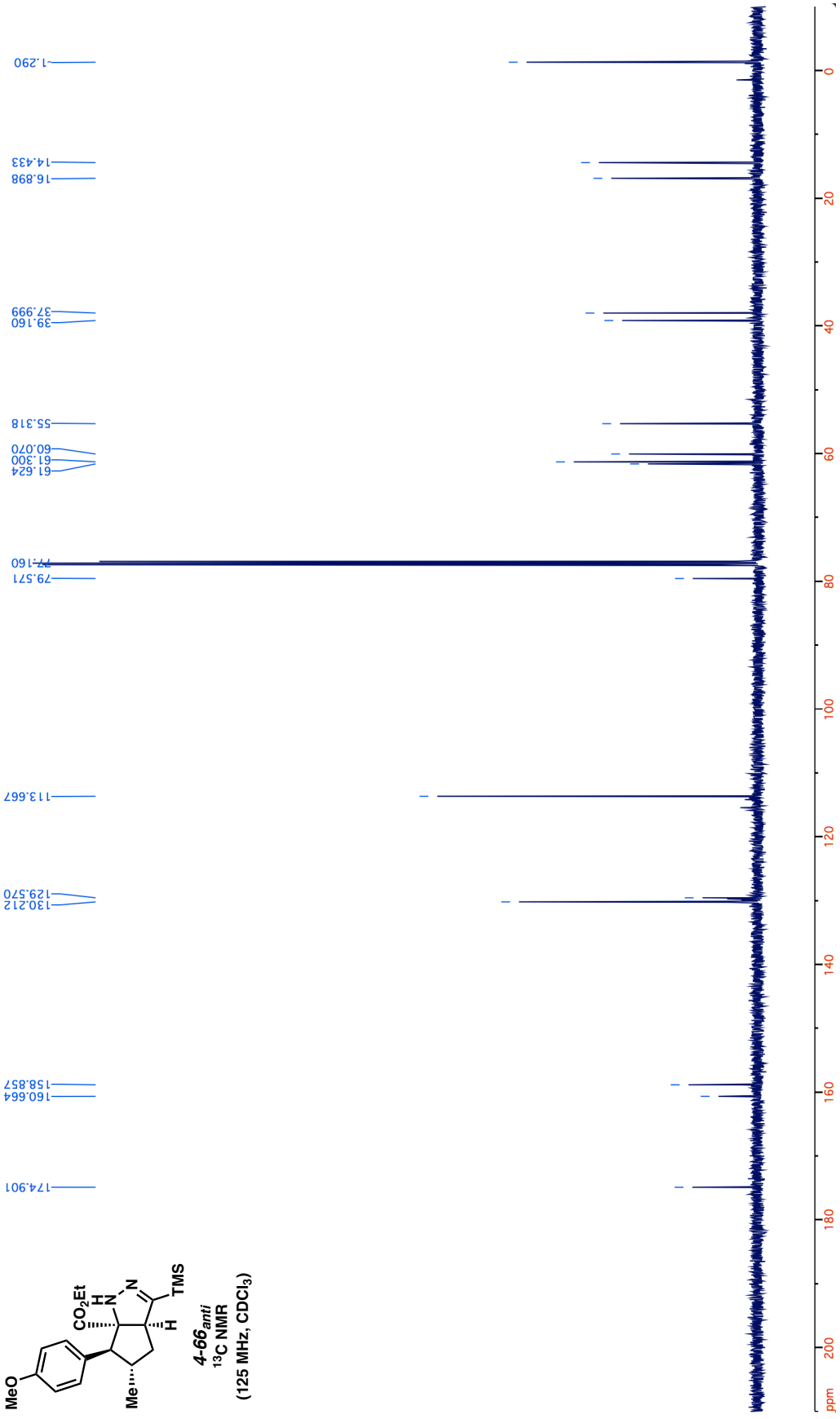

MeO
CO2Et
N
Ph
Me
4-65
1H NMR
(400 MHz, CDCl3)
7.363
7.272
7.260
7.080
7.059
6.825
6.804
3.919
3.909
3.901
3.892
3.883
3.874
3.865
3.856
3.848
3.838
3.782
3.774
3.741
3.210
3.178
3.041
3.015
2.950
2.942
2.934
2.922
2.916
2.913
2.906
2.608
2.581
2.555
2.086
2.060
2.055
2.030
2.026
2.019
1.711
1.586
1.492
1.482
1.461
1.450
1.432
1.422
1.400
1.391
0.945
0.927
0.910
0.680
0.664
1.89
4.89
1.95
1.97
1.27
2.71
1
0.997
0.963
1.02
1.01
1.96
1.09
2.88
2.94
ppm
9
8
7
6
5
4
3
2
1
0


14.082
19.789
33.736
35.830
51.876
53.443
55.350
60.450
61.034
74.147
77.363
77.760
113.784
127.287
128.280
129.671
132.651
137.630
158.576
172.938
ppm
0
20
40
60
80
100
120
140
160
180
200
MeO
CO2Et
Ph
Me
4-65
13C NMR
(100 MHz, CDCl3)

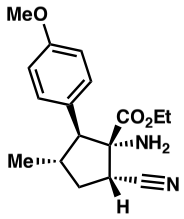

MeO
CO2Et
H
N
N
Me
H
TMS
4-66syn
1H NMR
(500 MHz, CDCl3)
7.260
7.121
7.104
6.834
6.817
3.875
3.858
3.855
3.838
3.778
3.755
3.744
3.737
3.729
3.722
3.715
3.708
3.695
3.689
3.681
3.674
3.667
3.660
3.645
2.870
2.846
2.609
2.597
2.585
2.573
2.561
2.549
2.537
2.436
2.424
2.419
2.412
2.408
2.401
2.395
2.383
1.320
1.296
1.275
1.252
0.948
0.937
0.934
0.924
0.920
-0.220
2.12
3.14
0.973
1.05
5.6
2
1
2.22
1.02
1.2
7.29
ppm
9
8
7
6
5
4
3
2
1
0


1.486
13.884
17.222
38.492
39.837
55.377
61.296
61.323
66.255
77.168
81.929
113.727
129.504
129.867
158.778
161.623
173.442
ppm
0
20
40
60
80
100
120
140
160
180
200
MeO
Me
CO2Et
H
N
N
H
TMS
4-66syn
13C NMR
(125 MHz, CDCl3)


MeO
CO2Et
H
N
N
TMS
H
Me
4-66anti
1H NMR
(400 MHz, CDCl3)
0.217
0.863
0.879
1.213
1.231
1.249
1.711
1.736
1.742
1.767
1.773
1.798
1.916
1.919
1.932
1.935
1.948
1.951
1.964
1.967
2.146
2.162
2.178
2.192
2.208
2.223
2.238
2.254
2.270
3.034
3.063
3.700
3.704
3.726
3.729
3.785
4.138
4.153
4.156
4.171
4.174
4.189
4.192
6.003
6.805
6.827
7.103
7.125
7.260
9.6
3.34
3.36
1.11
1.08
1.08
1.06
1.09
3.29
2.04
1
2.17
2.11
ppm



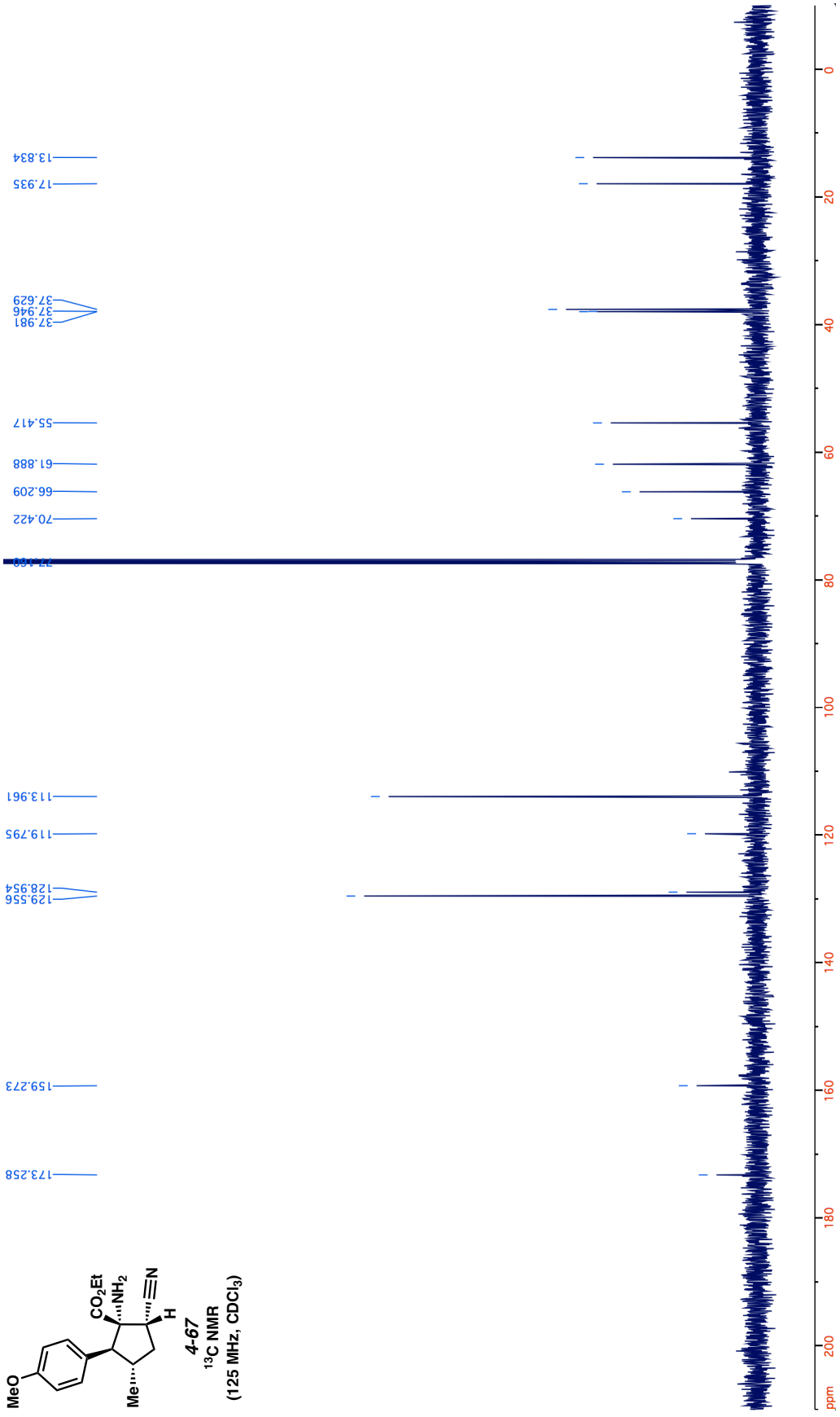
4-66*anti*
^{13}C NMR
(125 MHz, $CDCl_3$)

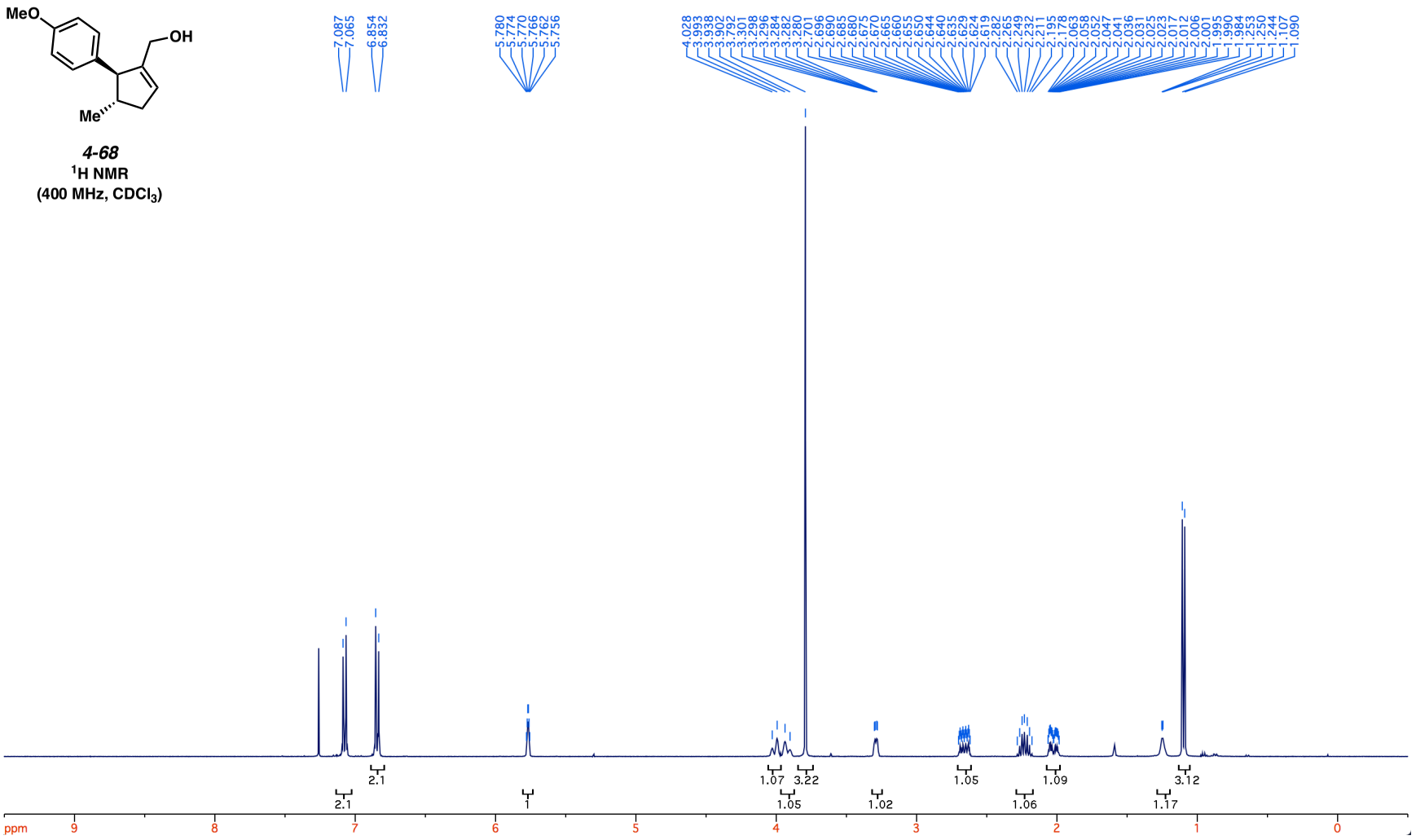


4-67

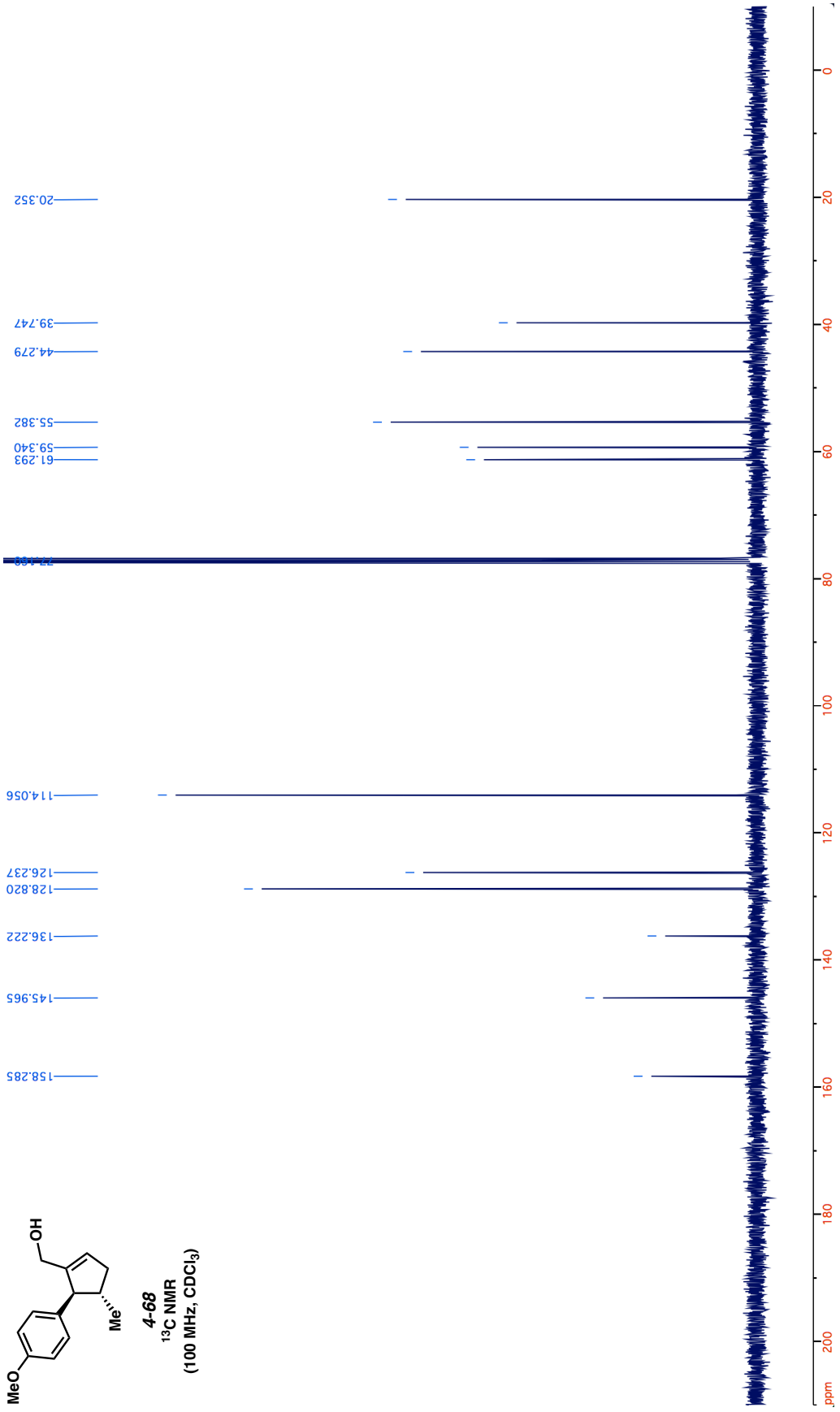
^{1}H NMR

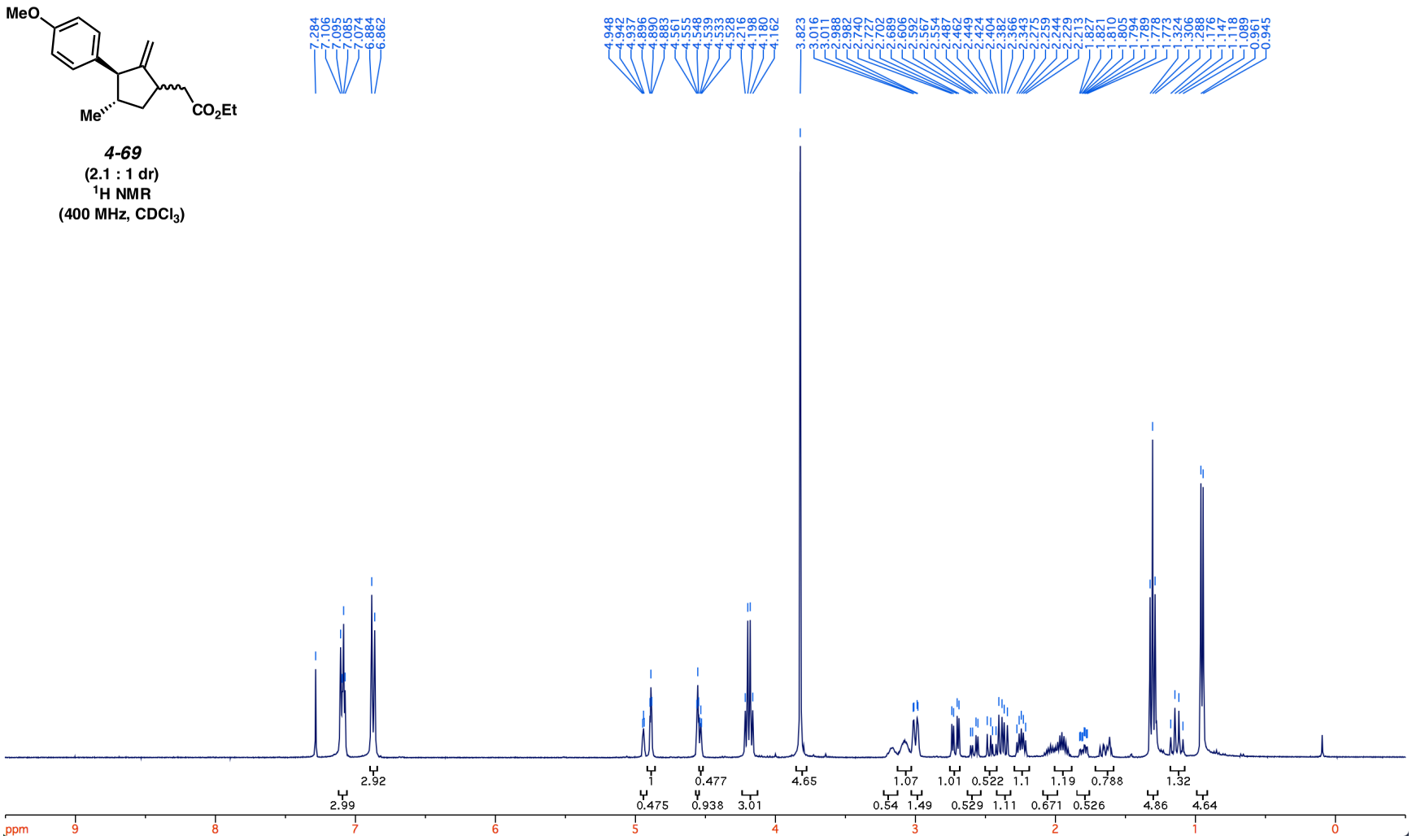
(400 MHz, $CDCl_3$)

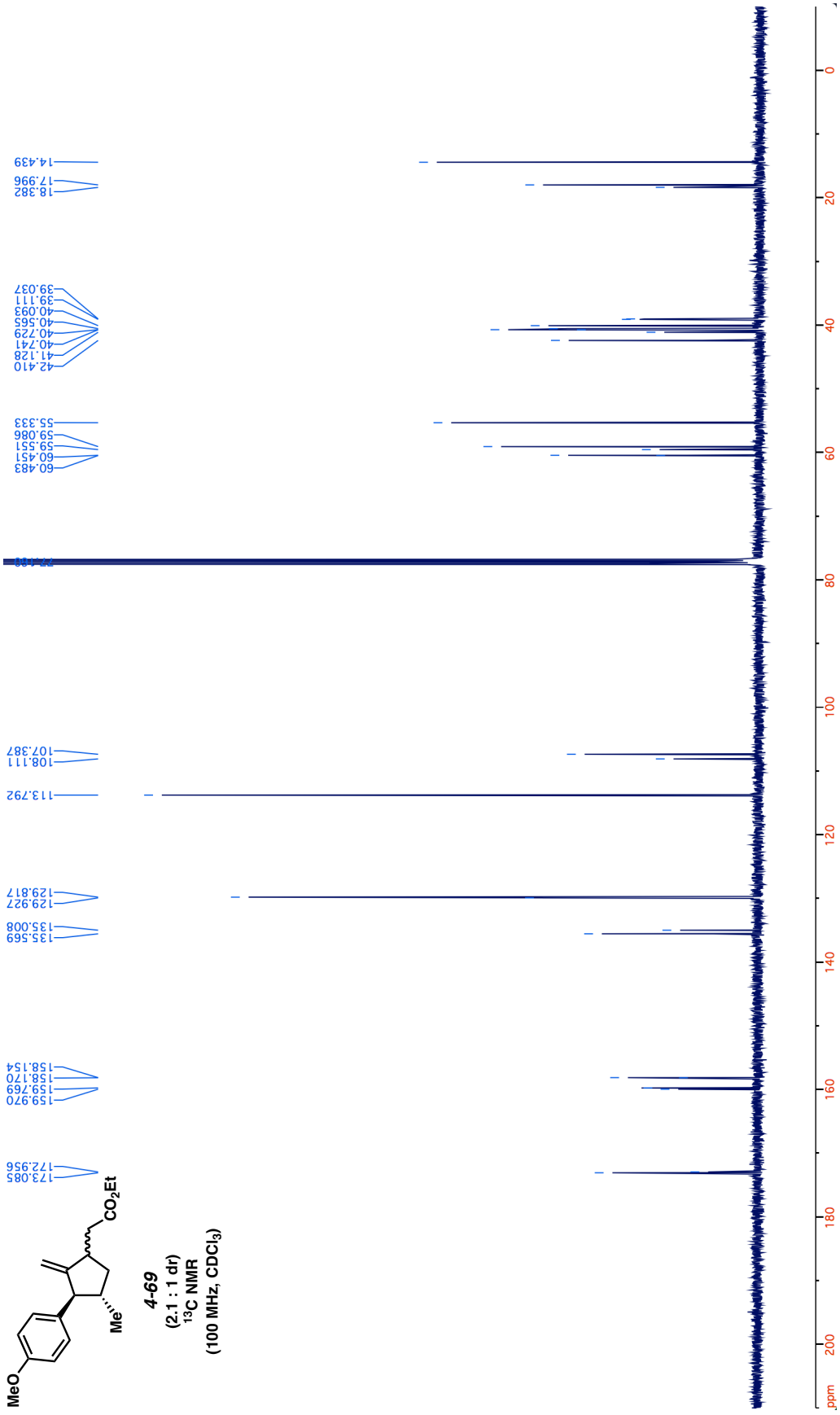

13.834
17.935
37.629
37.946
37.981
55.417
61.888
66.209
70.422
77.488
113.961
119.795
128.954
129.556
159.273
173.258
MeO
Me
CO2Et
NH2
N
H
4-67
13C NMR
(125 MHz, CDCl3)
ppm

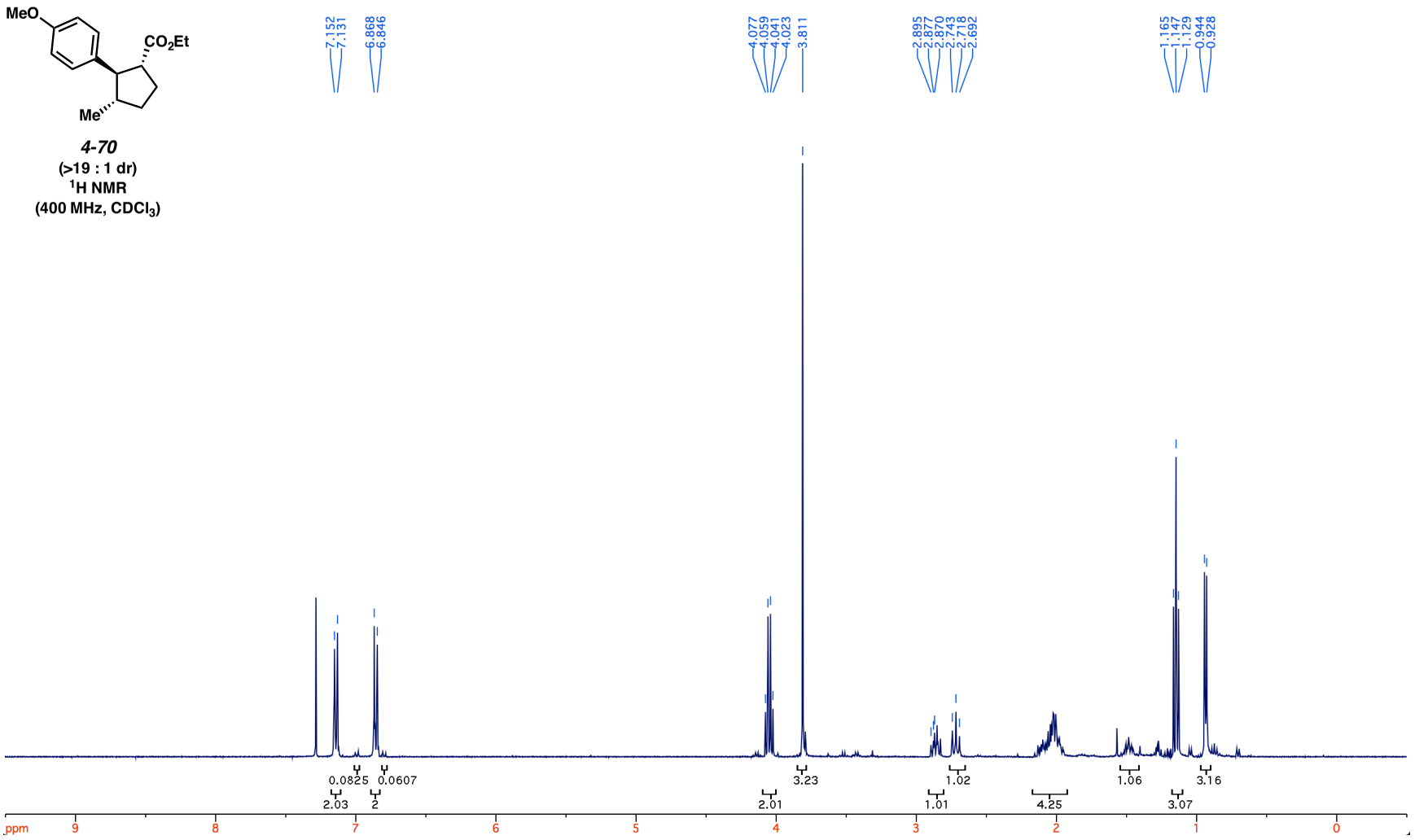


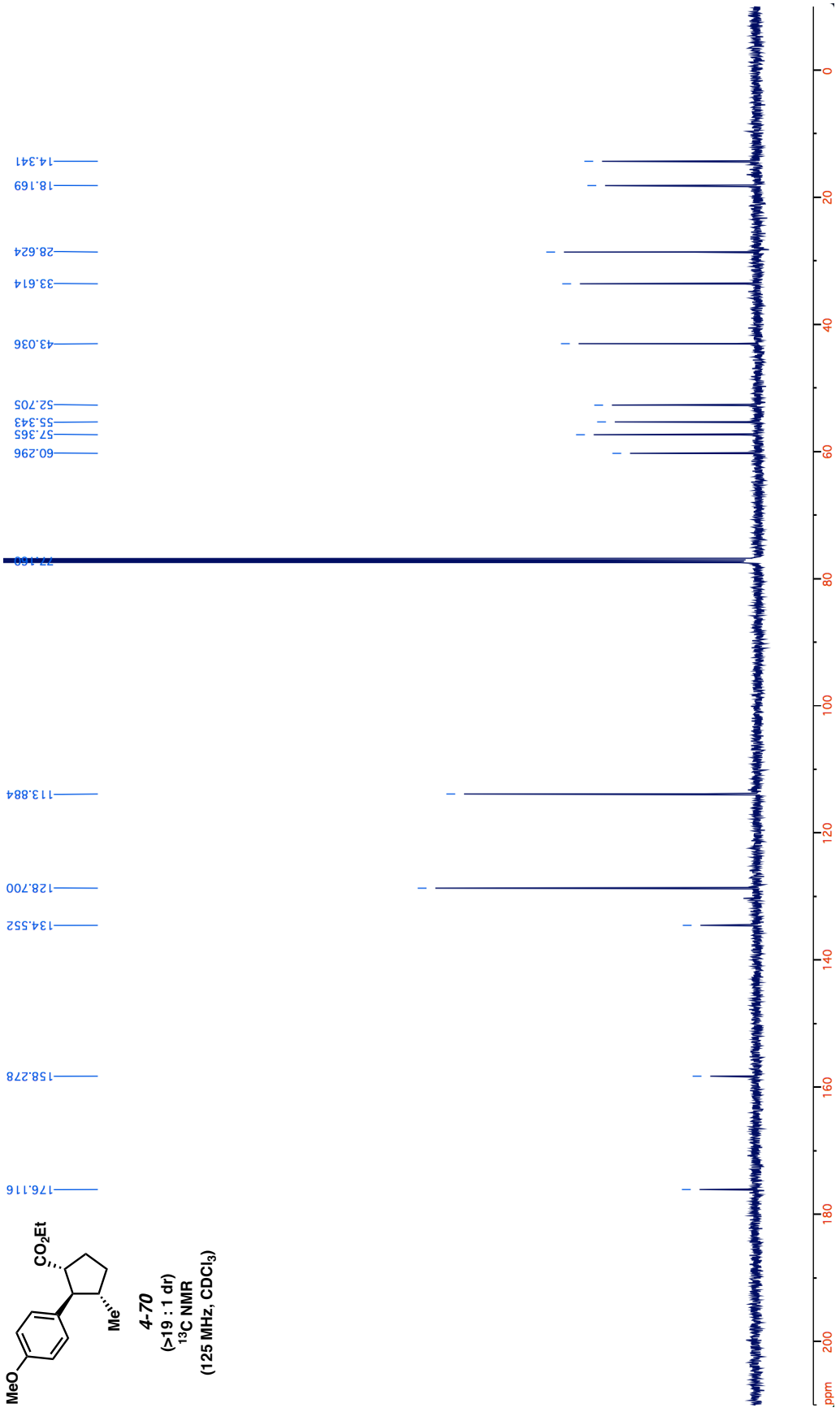
4-68
^{1}H NMR
(400 MHz, $CDCl_3$)

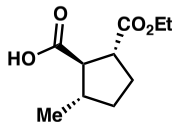

20.352
39.747
44.279
55.382
59.340
61.293
114.056
126.237
128.820
136.222
145.965
158.285
ppm
0
20
40
60
80
100
120
140
160
180
200
OH
Me
MeO
4-68
13C NMR
(100 MHz, CDCl3)


MeO
Me
CO2Et
4-69
(2.1 : 1 dr)
1H NMR
(400 MHz, CDCl3)
7.284
7.106
7.095
7.085
7.074
6.884
6.862
4.948
4.942
4.937
4.896
4.890
4.863
4.561
4.555
4.548
4.539
4.533
4.528
4.216
4.198
4.180
4.162
3.823
3.016
3.011
2.988
2.982
2.940
2.767
2.762
2.689
2.696
2.592
2.567
2.554
2.487
2.462
2.449
2.424
2.404
2.382
2.366
2.343
2.275
2.259
2.244
2.229
2.213
1.827
1.821
1.810
1.805
1.794
1.789
1.778
1.773
1.324
1.306
1.288
1.176
1.147
1.118
1.089
0.961
0.945
2.99
2.92
0.475
1
0.938
0.477
3.01
4.65
0.54
1.07
1.49
1.01
0.529
0.522
1.11
1.1
0.671
1.19
0.526
0.788
4.86
1.32
4.64
ppm
9
8
7
6
5
4
3
2
1
0

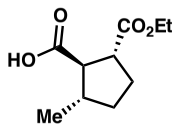

MeO
Me
CO2Et
4-69
(2.1 : 1 dr)
13C NMR
(100 MHz, CDCl3)
173.085
172.956
159.970
159.769
158.170
158.154
135.569
135.008
129.927
129.817
113.792
108.111
107.387
60.483
60.451
59.551
59.086
55.333
42.410
41.128
40.741
40.729
40.565
40.093
39.111
39.037
18.382
17.996
14.439
ppm


MeO
CO2Et
Me
4-70
(>19 : 1 dr)
1H NMR
(400 MHz, CDCl3)
7.152
7.131
6.868
6.846
4.077
4.059
4.041
4.023
3.811
2.895
2.877
2.870
2.743
2.718
2.692
1.165
1.147
1.129
0.944
0.928
0.0825
0.0607
3.23
1.02
1.06
3.16
2.03
2
2.01
1.01
4.25
3.07
ppm
9
8
7
6
5
4
3
2
1
0

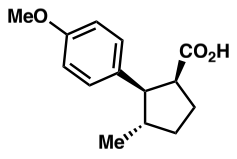

14.341
18.169
28.624
33.614
43.036
52.705
55.343
57.365
60.296
77.158
113.884
128.700
134.552
158.278
176.116
ppm
0
20
40
60
80
100
120
140
160
180
200
MeO
CO2Et
Me
4-70
(>19 : 1 dr)
13C NMR
(125 MHz, CDCl3)



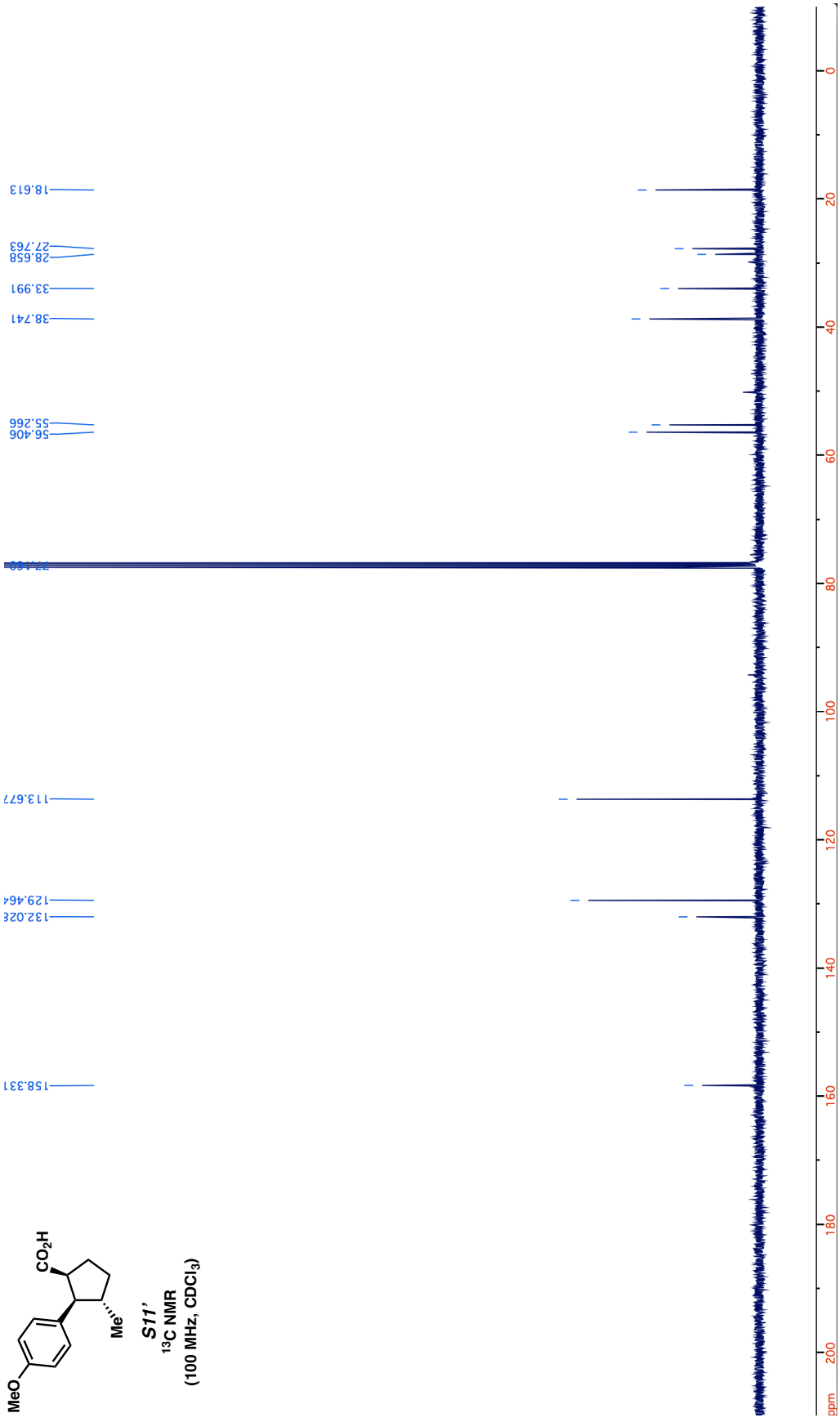
4-71
(13 : 1 dr)
^{1}H NMR
(400 MHz, $CDCl_3$)

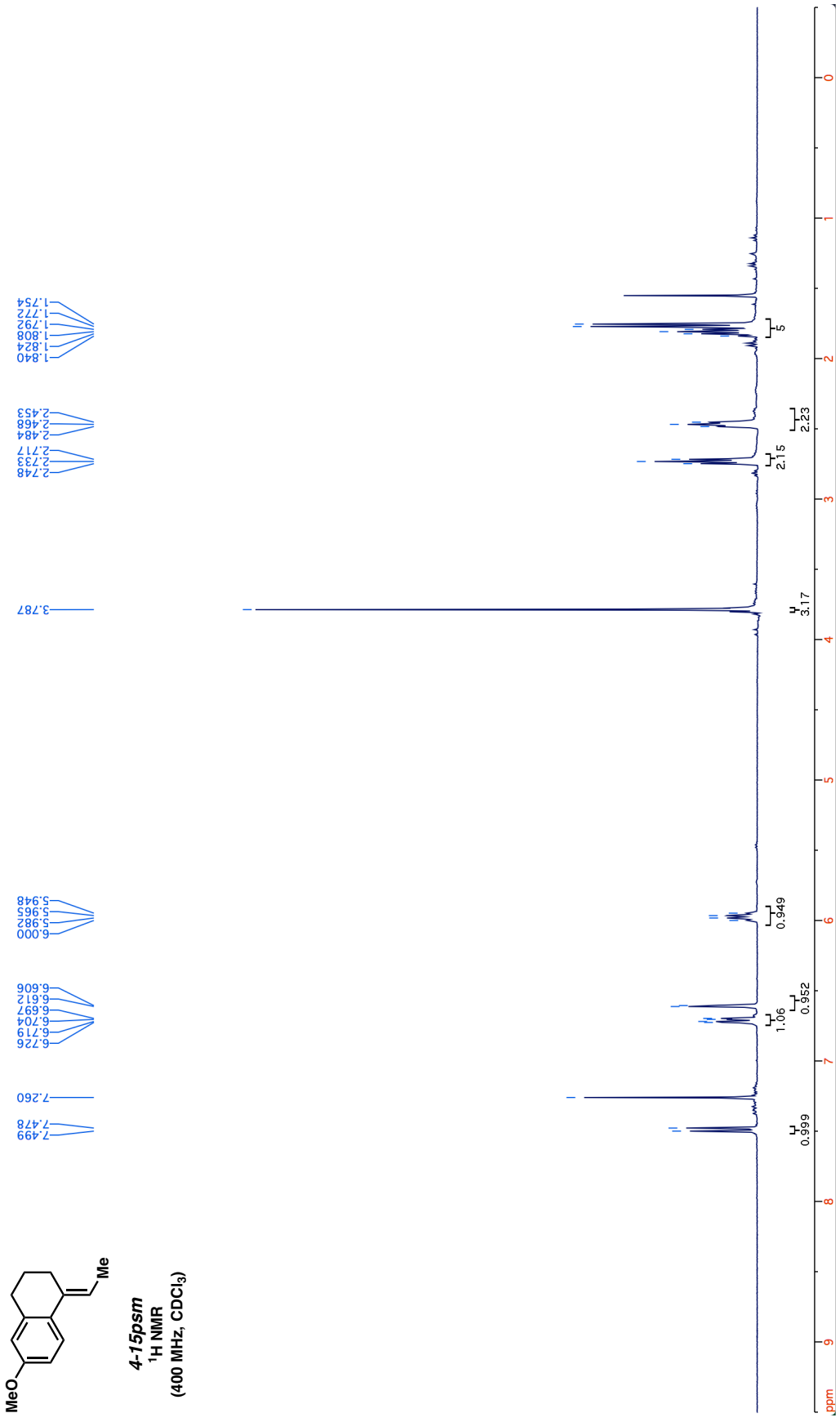


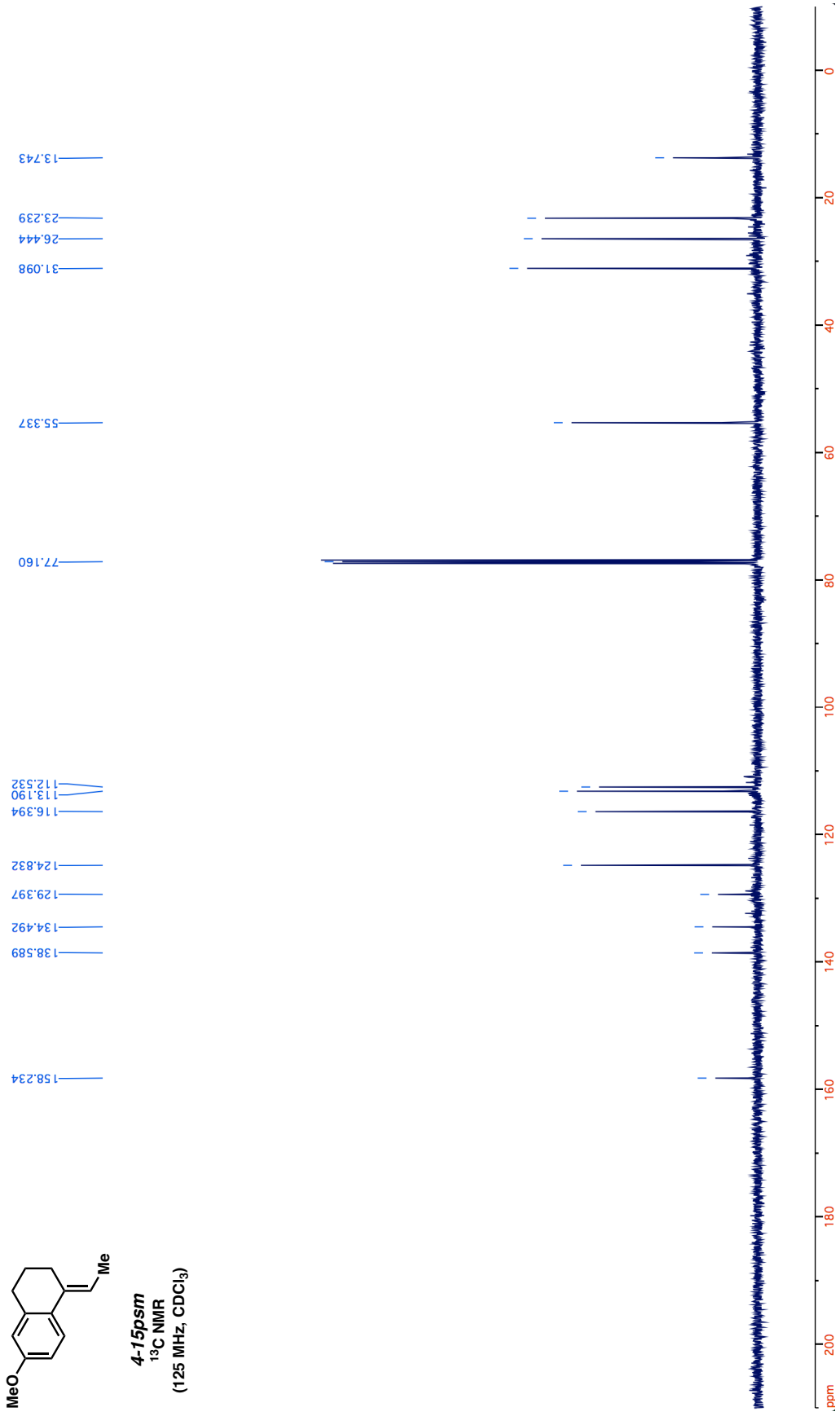
4-71
(13 : 1 dr)
^{13}C NMR
(125 MHz, $CDCl_3$)

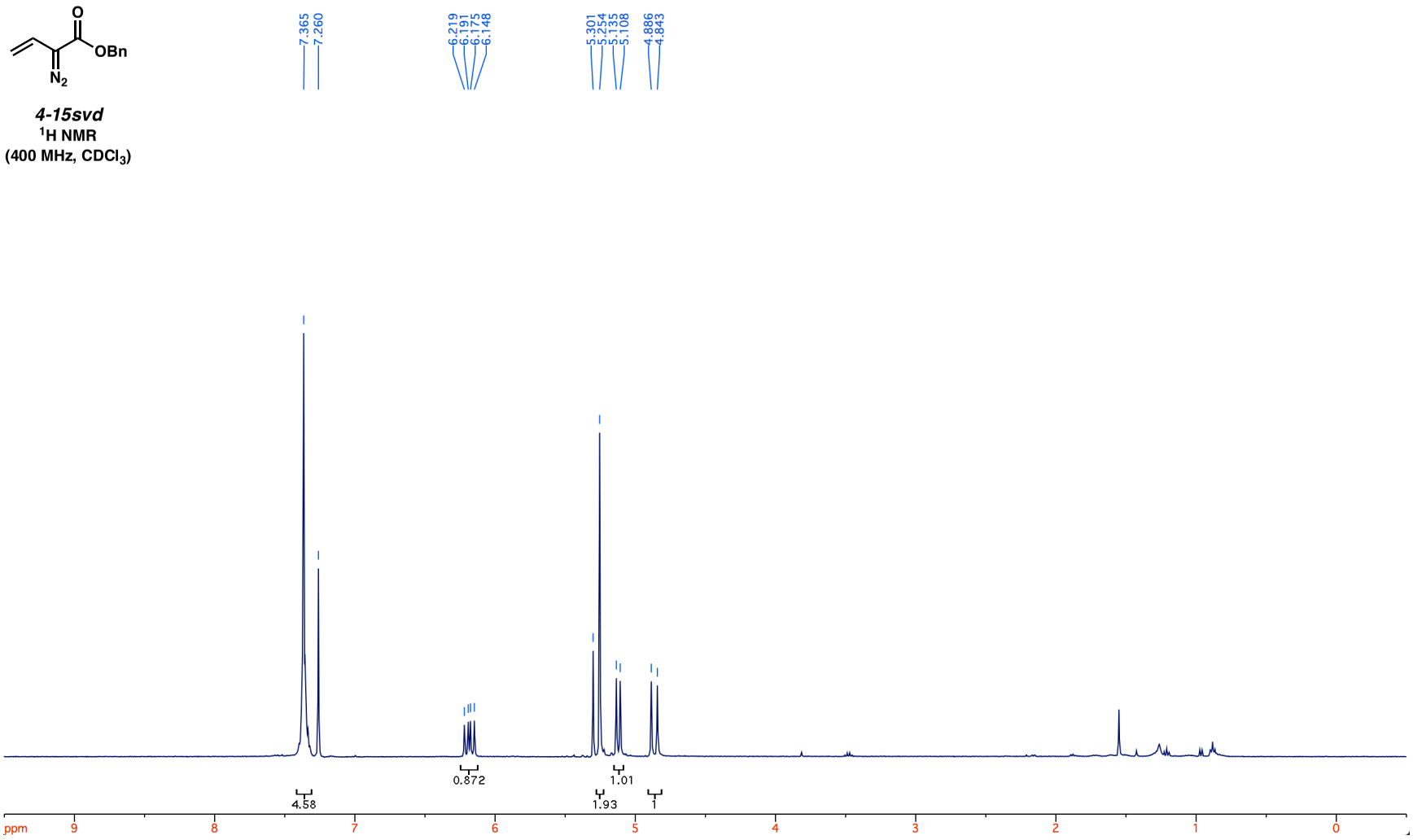


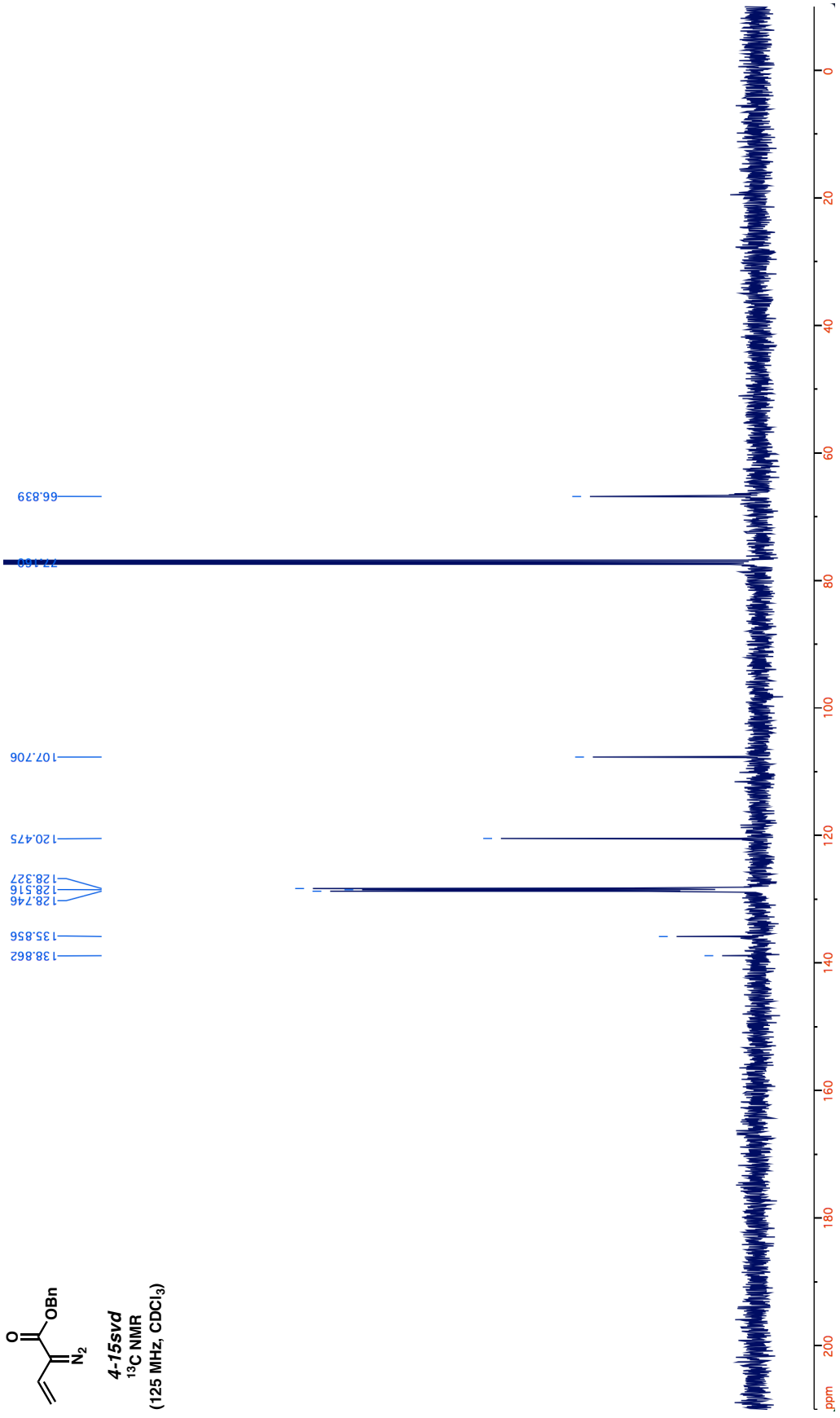
S11'
^{1}H NMR
(400 MHz, $CDCl_3$)

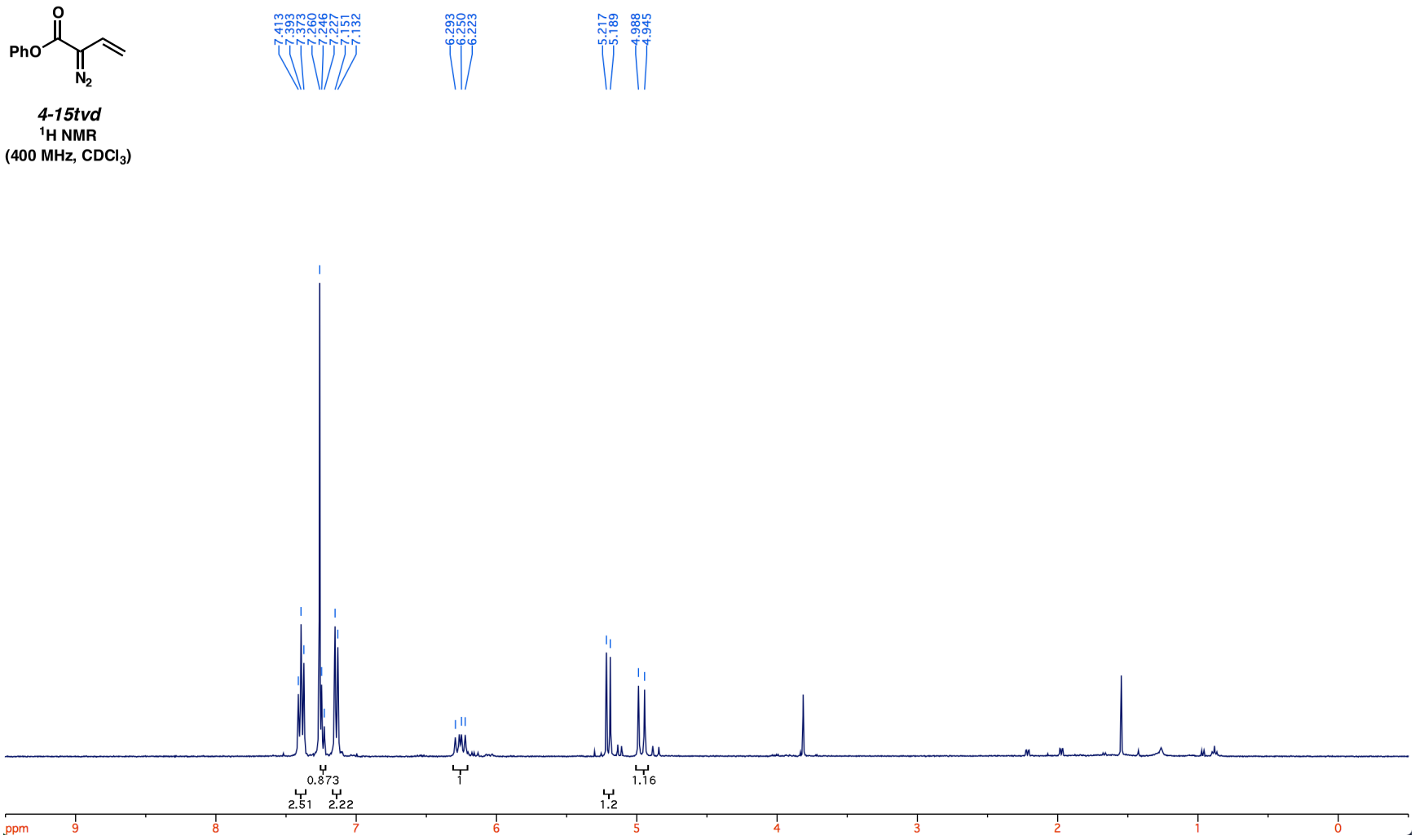

18.613
27.763
28.658
33.991
38.741
55.266
56.406
113.677
129.464
132.026
158.331
MeO
Me
CO2H
S11'
13C NMR
(100 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm


MeO
Me
4-15psm
1H NMR
(400 MHz, CDCl3)
7.499
7.478
7.260
6.726
6.719
6.704
6.697
6.612
6.606
6.000
5.982
5.965
5.948
3.787
2.748
2.733
2.717
2.484
2.468
2.453
1.840
1.824
1.808
1.792
1.772
1.754
0.999
1.06
0.952
0.949
3.17
2.15
2.23
5
ppm

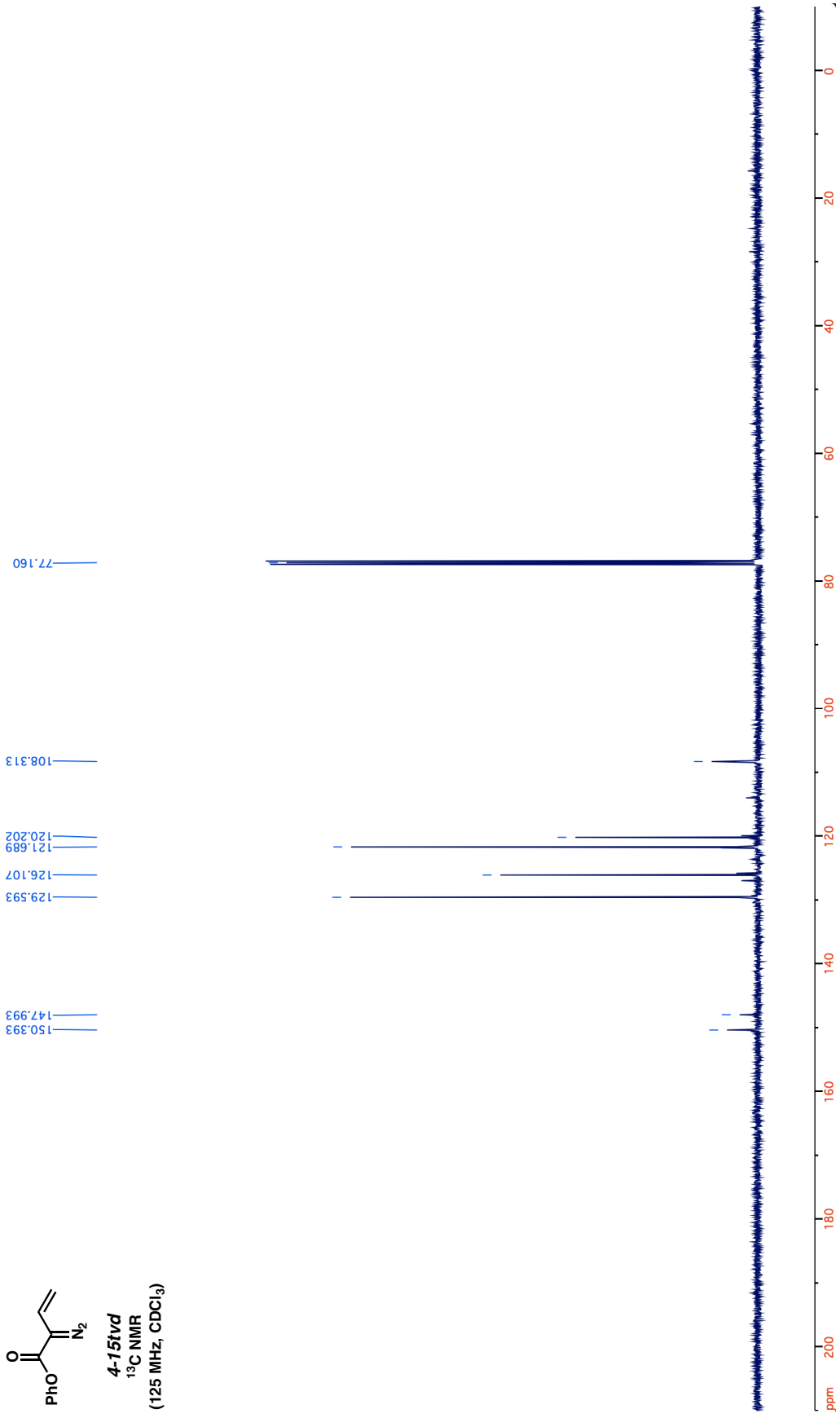

MeO
Me
4-15psm
13C NMR
(125 MHz, CDCl3)
158.234
138.589
134.492
129.397
124.832
116.394
113.190
112.532
77.160
55.337
31.098
26.444
23.239
13.743
ppm

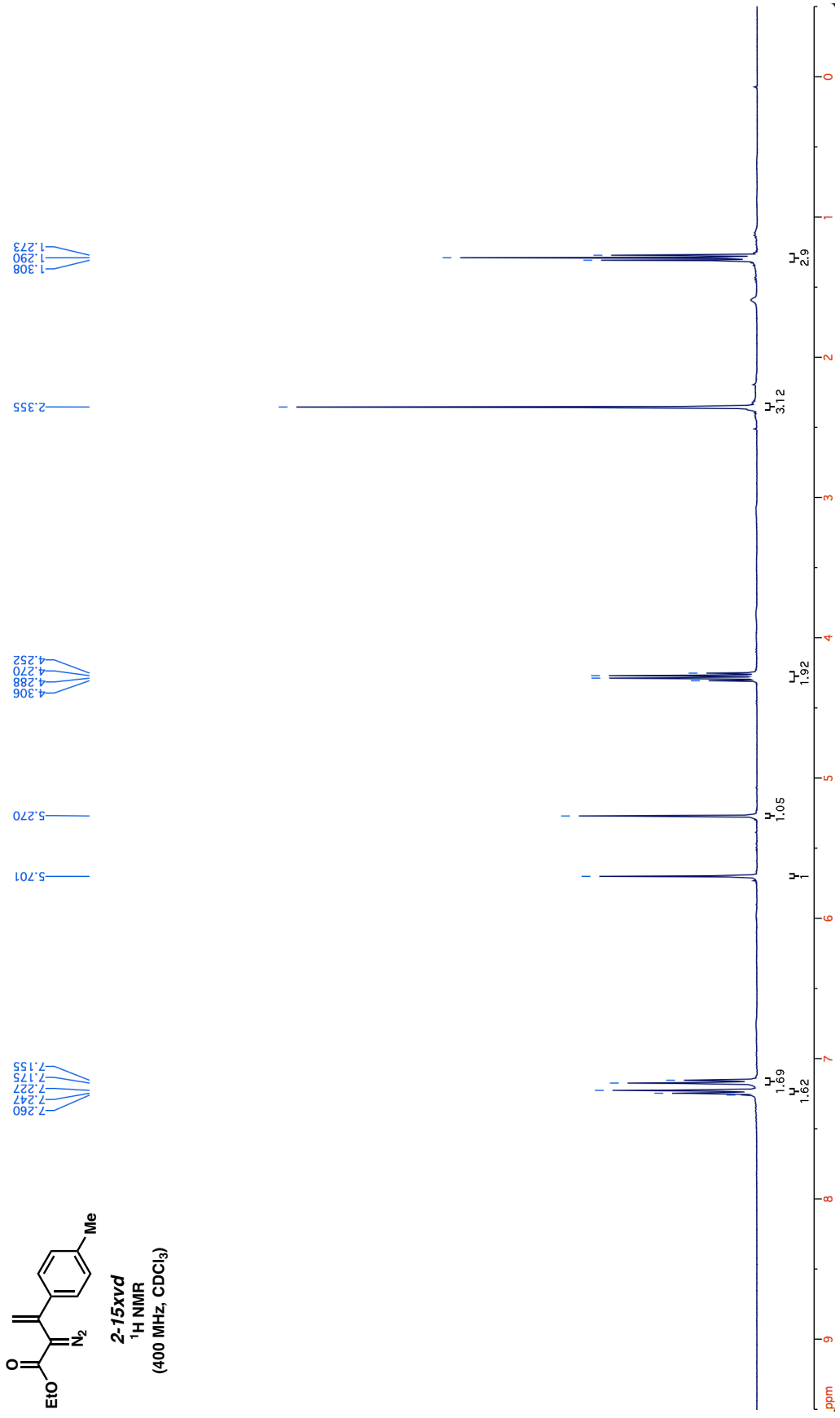

O
OBn
N2
4-15svd
1H NMR
(400 MHz, CDCl3)
7.365
7.260
6.219
6.191
6.175
6.148
5.301
5.254
5.135
5.108
4.886
4.843
4.58
0.872
1.93
1.01
1
ppm
9
8
7
6
5
4
3
2
1
0

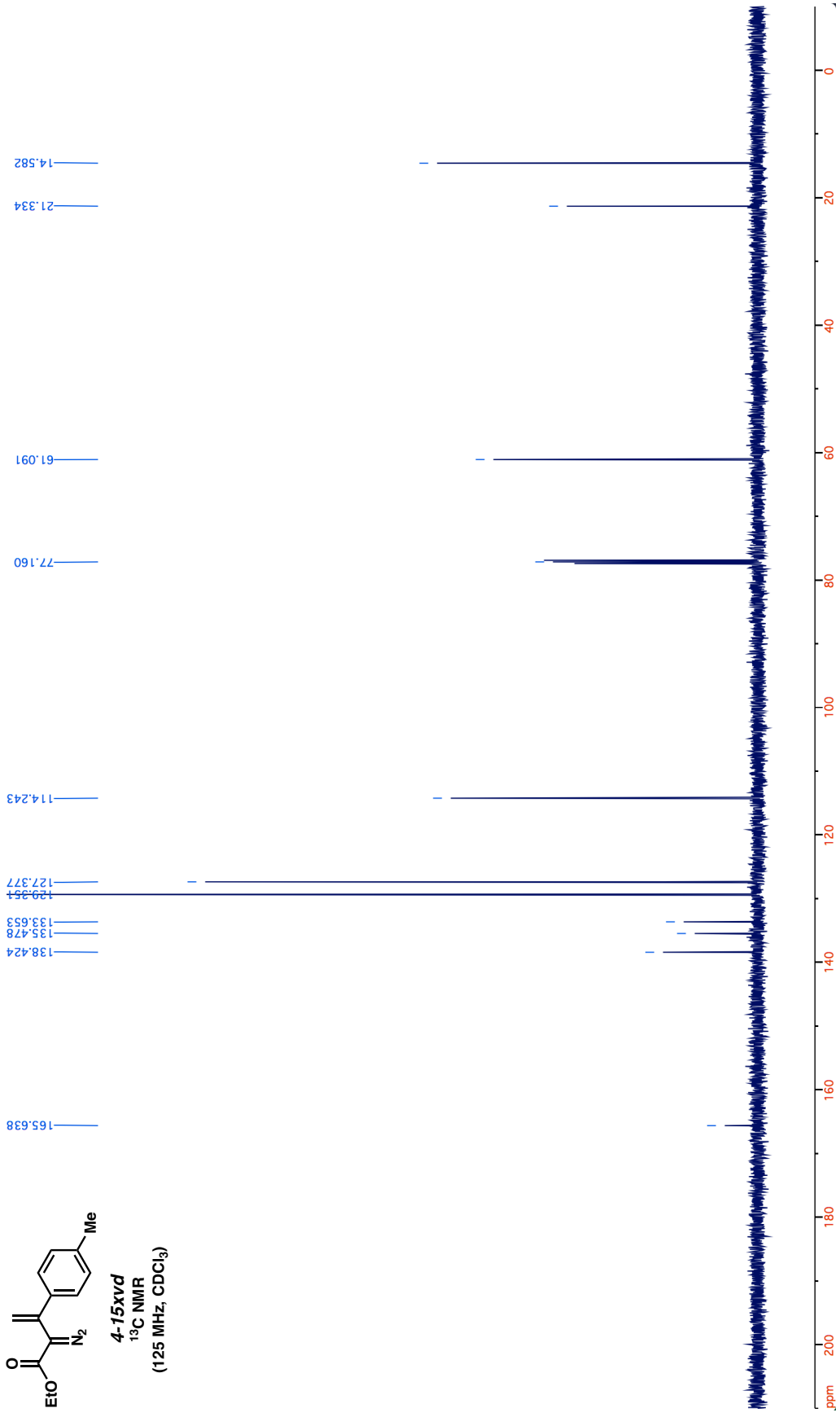

O
OBn
N2
4-15svd
13C NMR
(125 MHz, CDCl3)
66.839
27.458
107.706
120.475
128.327
128.516
128.746
135.856
138.862
0
20
40
60
80
100
120
140
160
180
200
ppm

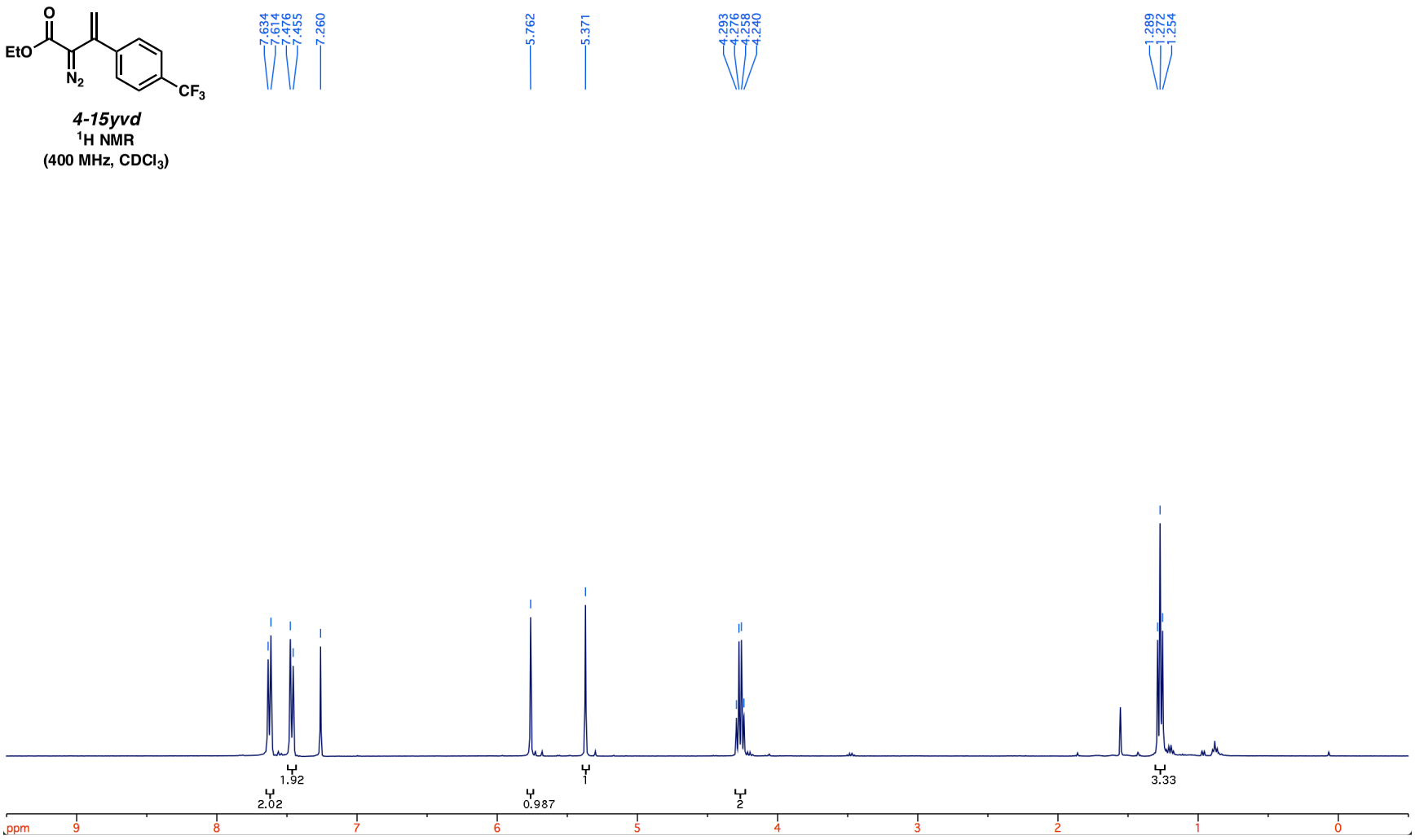


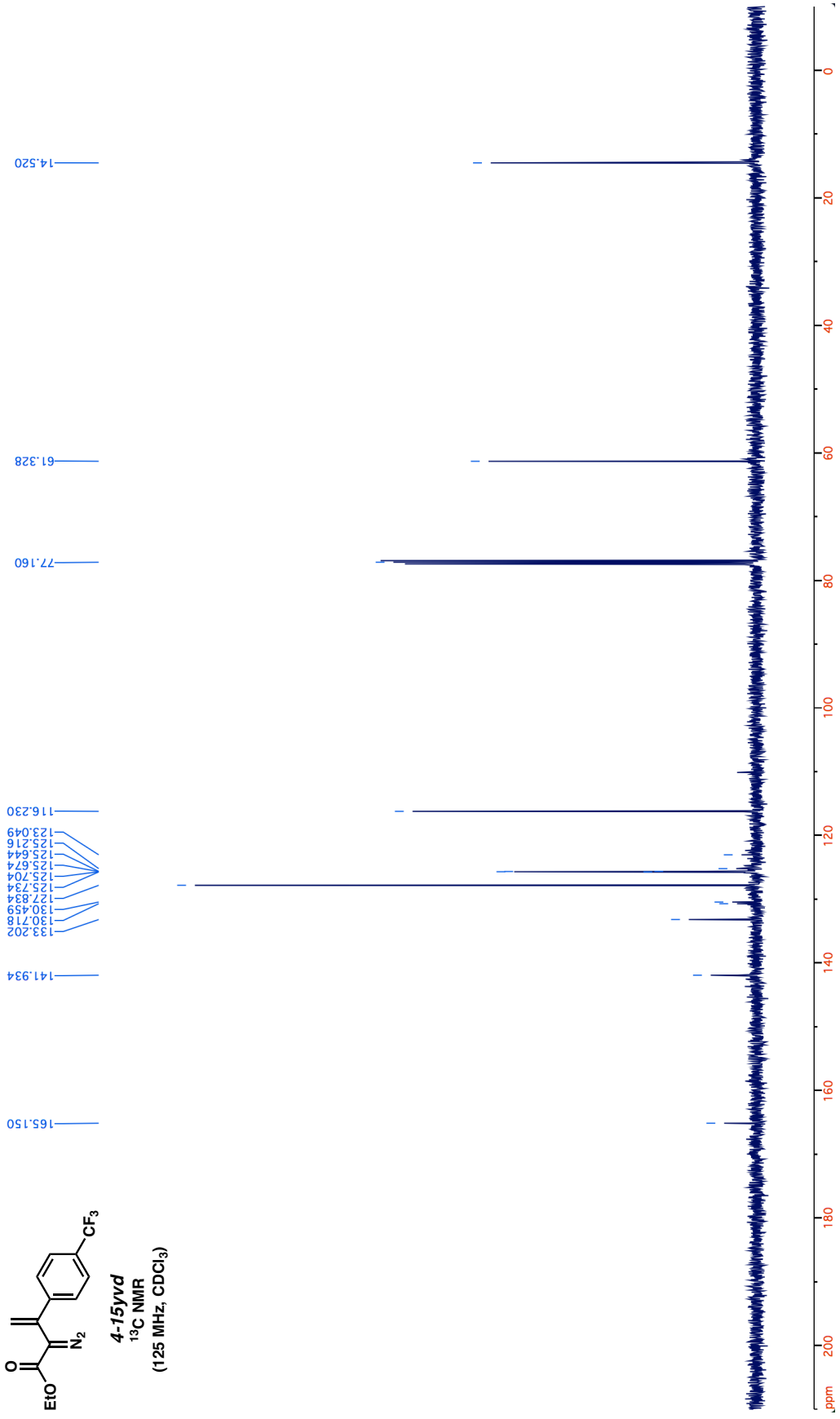
4-15tvd
^{1}H NMR
(400 MHz, $CDCl_3$)

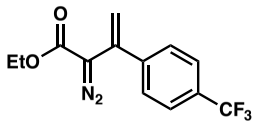

PhO
O
N2
4-15tvd
13C NMR
(125 MHz, CDCl3)
77.160
108.313
120.202
121.689
126.107
129.593
147.993
150.393
0
20
40
60
80
100
120
140
160
180
200
ppm


Me
N2
O
EtO
2-15xvd
1H NMR
(400 MHz, CDCl3)
7.260
7.247
7.227
7.175
7.155
5.701
5.270
4.306
4.288
4.270
4.252
2.355
1.308
1.290
1.273
1.59
1.62
1
1.05
1.92
3.12
2.9
ppm

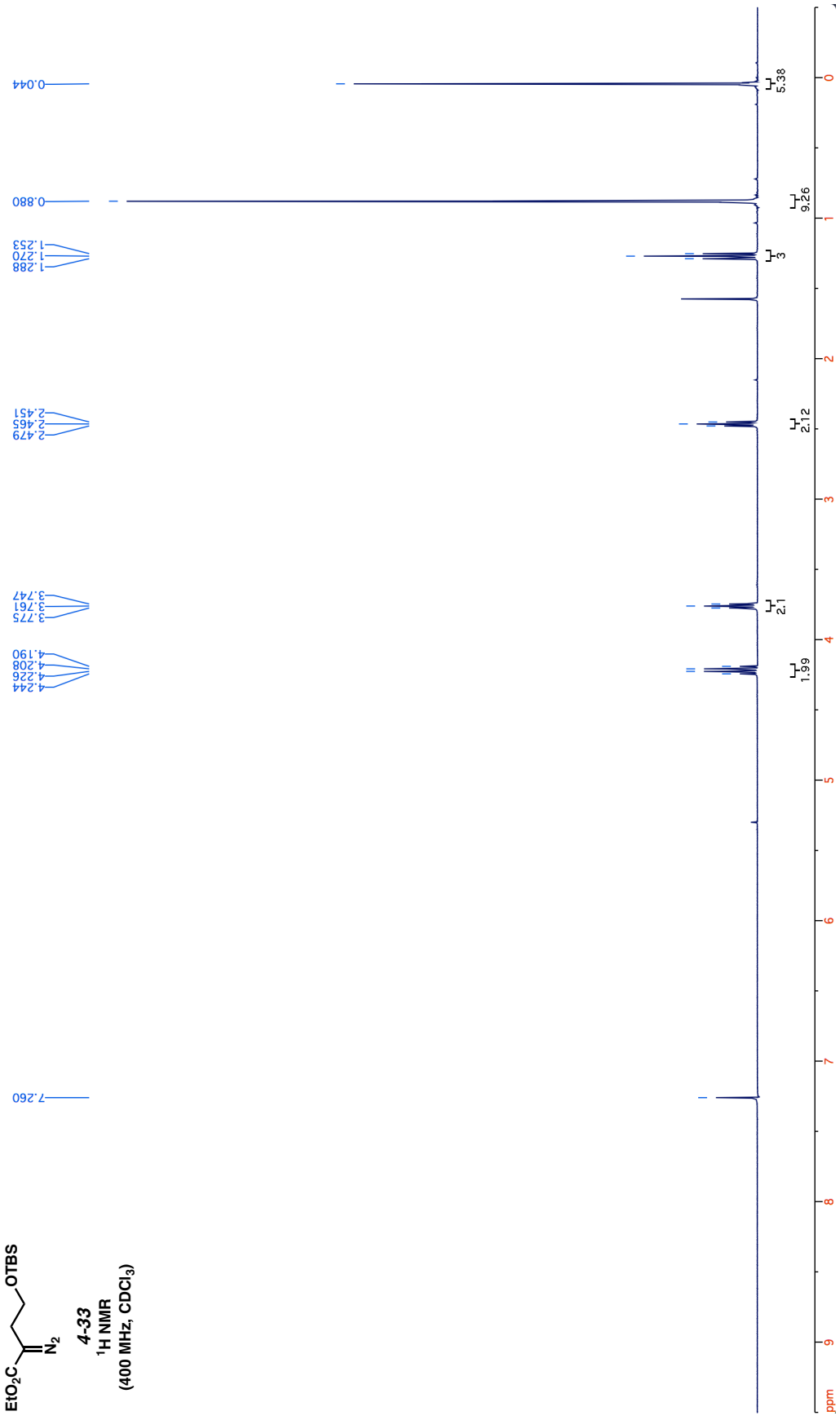

14.582
21.334
61.091
77.160
114.243
127.377
129.351
133.653
135.478
138.424
165.638
ppm
0
20
40
60
80
100
120
140
160
180
200
Me
N2
O
EtO
4-15xvd
13C NMR
(125 MHz, CDCl3)

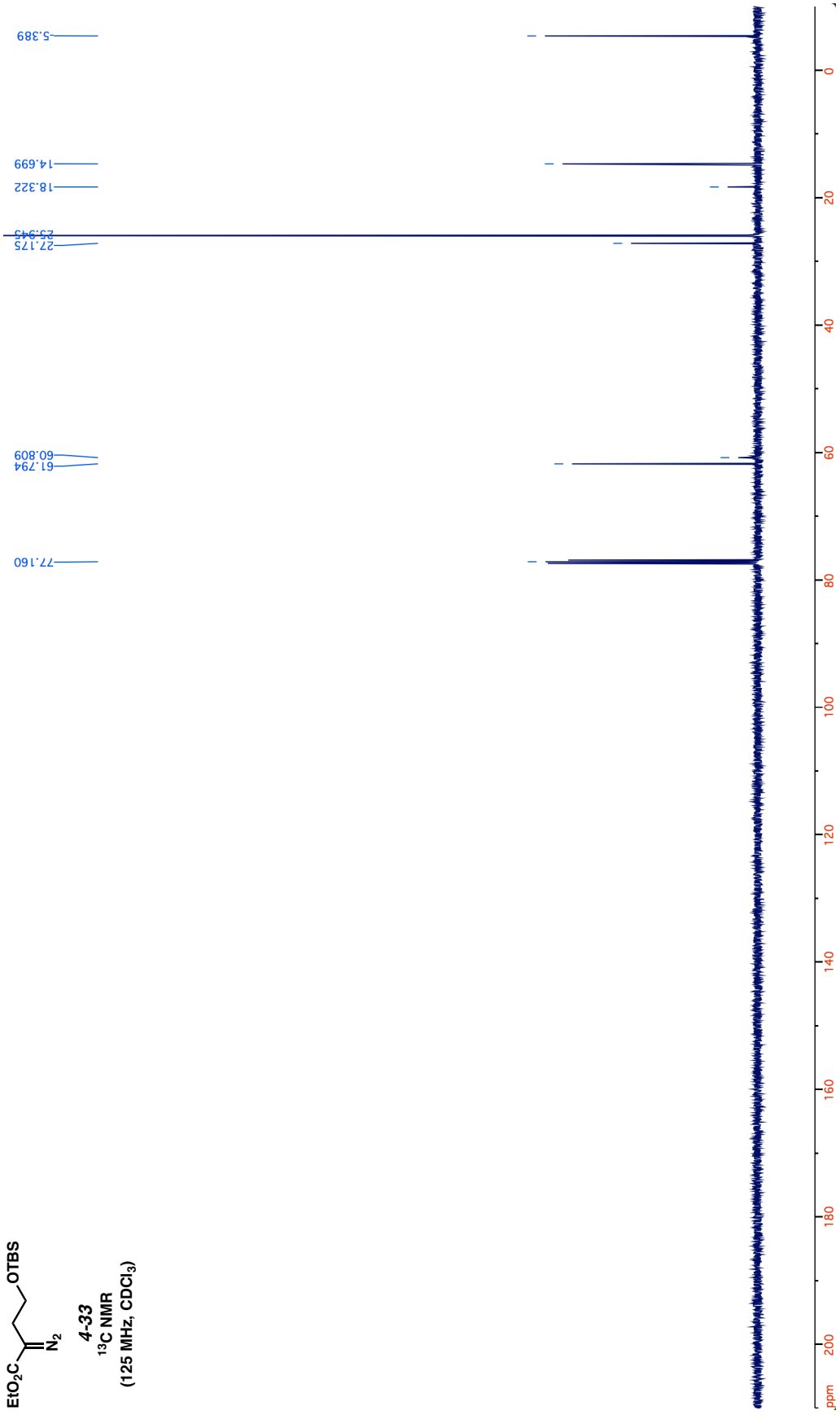

EtO
O
N2
CF3
4-15yvd
1H NMR
(400 MHz, CDCl3)
7.634
7.614
7.476
7.455
7.260
5.762
5.371
4.293
4.276
4.258
4.240
1.289
1.272
1.254
2.02
1.92
0.987
1
2
3.33
ppm
9
8
7
6
5
4
3
2
1
0

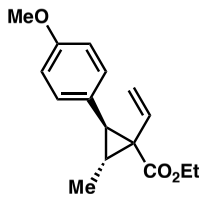

4-15yvd
13C NMR
(125 MHz, CDCl3)
EtO
O
N2
CF3
14.520
61.328
77.160
116.230
123.049
125.216
125.644
125.674
125.704
125.734
127.834
130.459
130.718
133.202
141.934
165.150
0
20
40
60
80
100
120
140
160
180
200
ppm



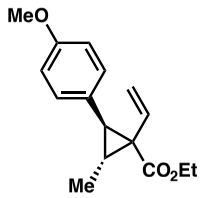
4-15yvd
^{19}F NMR
(376 MHz, $CDCl_3$)


EtO2C
OTBS
N2
4-33
1H NMR
(400 MHz, CDCl3)
0.044
0.880
1.253
1.270
1.288
2.451
2.465
2.479
3.747
3.761
3.775
4.190
4.208
4.226
4.244
7.260
5.38
9.26
3
2.12
2.1
1.99
ppm

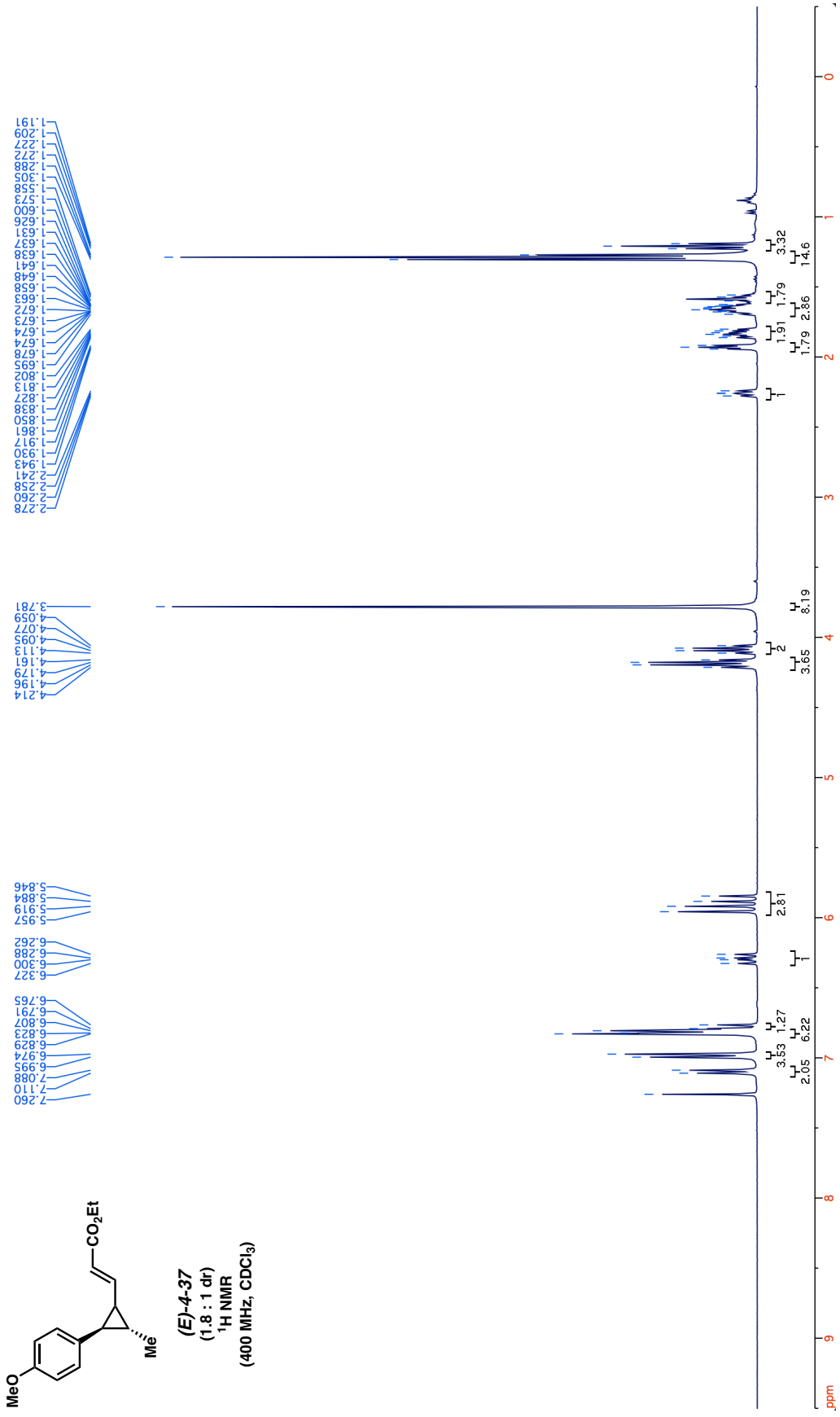

OTBS
N2
EtO2C
4-33
13C NMR
(125 MHz, CDCl3)
5.389
14.699
18.322
25.945
27.175
60.809
61.794
77.160
0
20
40
60
80
100
120
140
160
180
200
ppm

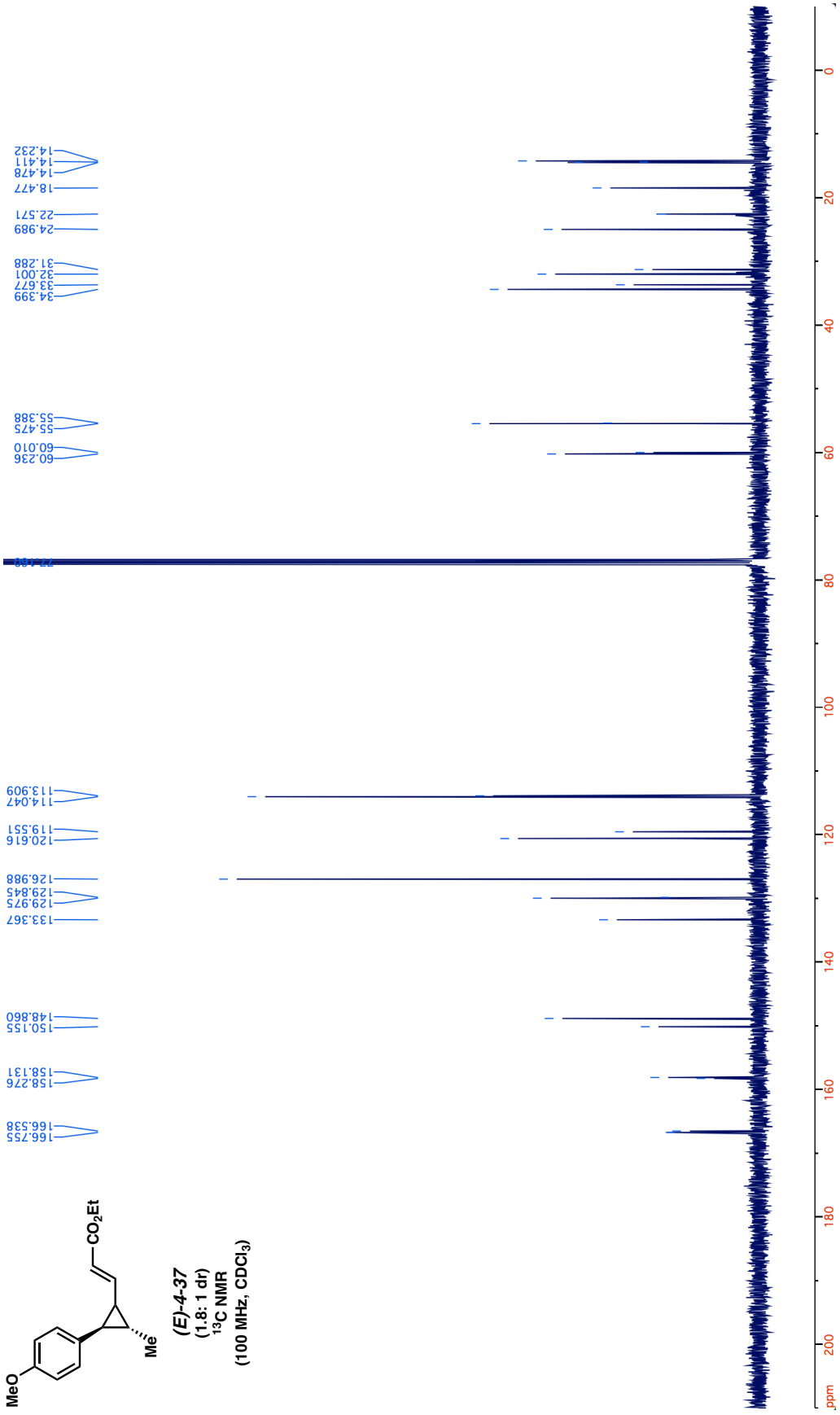


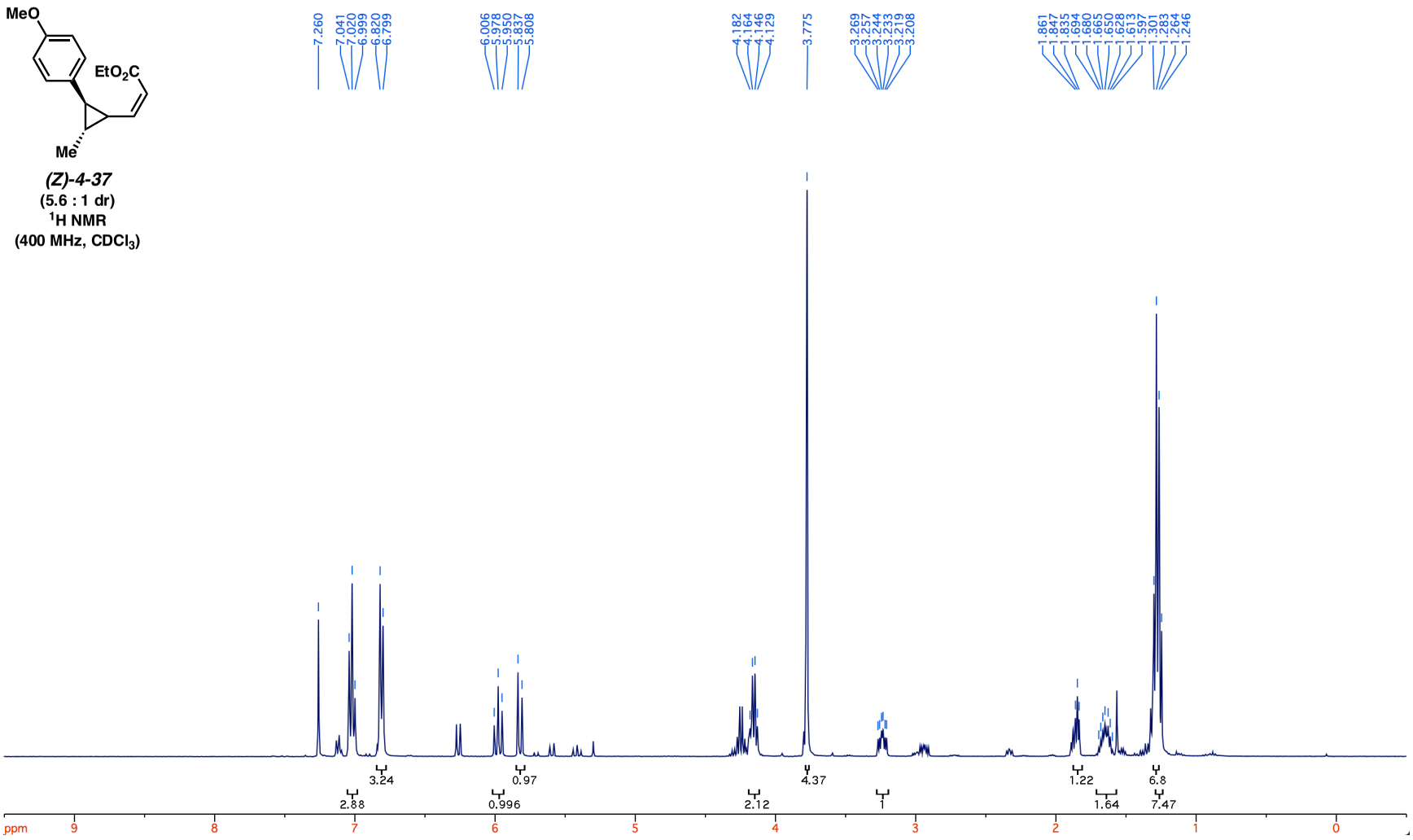
4-36
(1.9 : 1 dr)
^{1}H NMR
(400 MHz, $CDCl_3$)

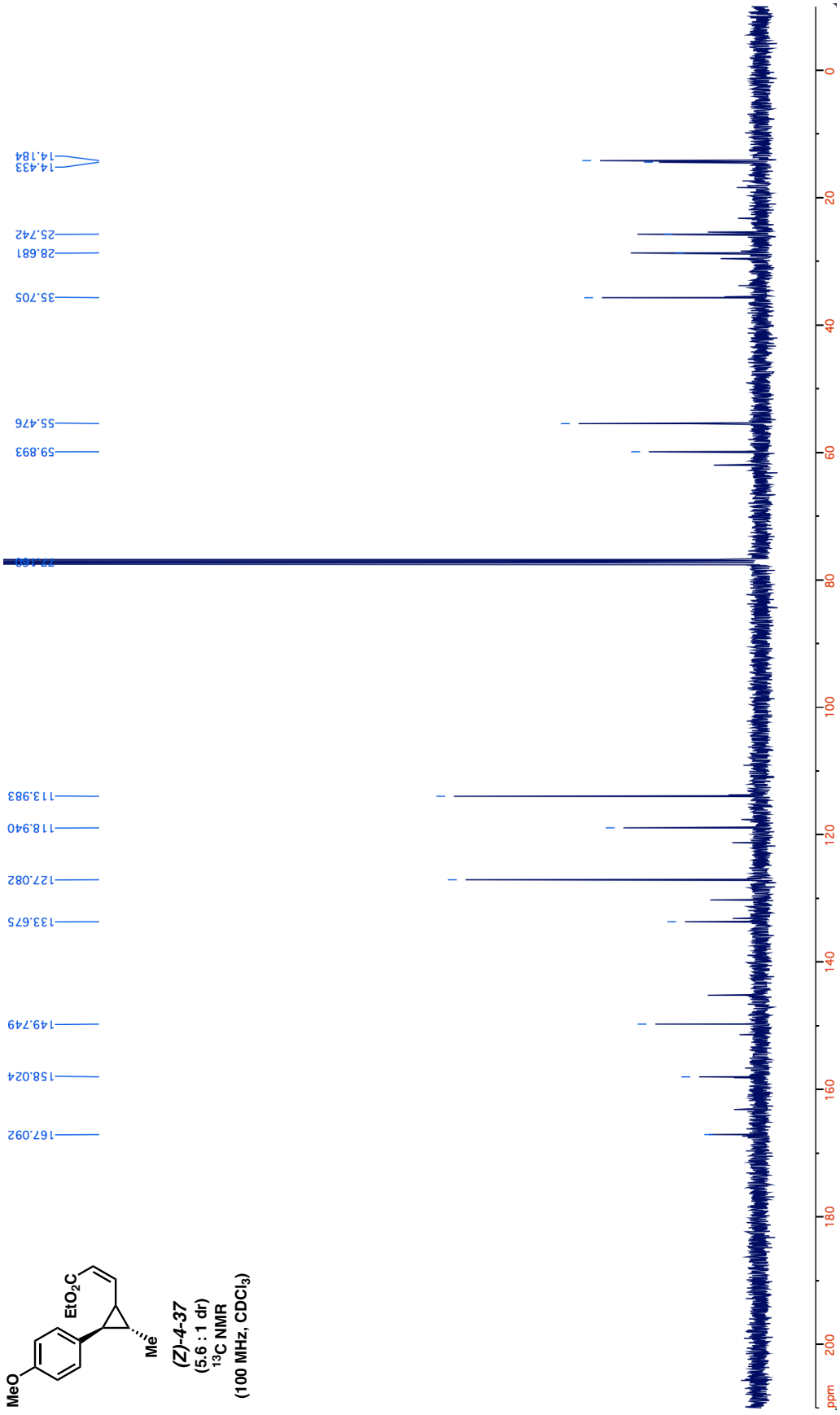


4-36
(1.9 : 1 dr)
^{13}C NMR
(125 MHz, $CDCl_3$)


MeO
CO2Et
Me
(E)-4-37
(1.8 : 1 dr)
1H NMR
(400 MHz, CDCl3)
ppm


14.232
14.411
14.478
18.477
22.571
24.989
31.288
32.001
33.677
34.399
55.475
55.388
60.236
60.010
77.408
113.909
114.047
119.551
120.616
126.988
129.845
129.975
133.367
148.860
150.155
158.131
158.276
166.538
166.755
MeO
Me
CO2Et
(E)-4-37
(1.8: 1 dr)
13C NMR
(100 MHz, CDCl3)
ppm


MeO
EtO2C
Me
(Z)-4-37
(5.6 : 1 dr)
1H NMR
(400 MHz, CDCl3)
7.260
7.041
7.020
6.999
6.820
6.799
6.006
5.978
5.950
5.837
5.808
4.182
4.164
4.146
4.129
3.775
3.269
3.257
3.244
3.233
3.219
3.208
1.861
1.847
1.835
1.694
1.680
1.665
1.650
1.628
1.613
1.597
1.301
1.283
1.264
1.246
3.24
0.97
4.37
1.22
6.8
2.88
0.996
2.12
1
1.64
7.47
ppm
9
8
7
6
5
4
3
2
1
0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14.433
25.742
28.681
35.705
55.476
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77.488
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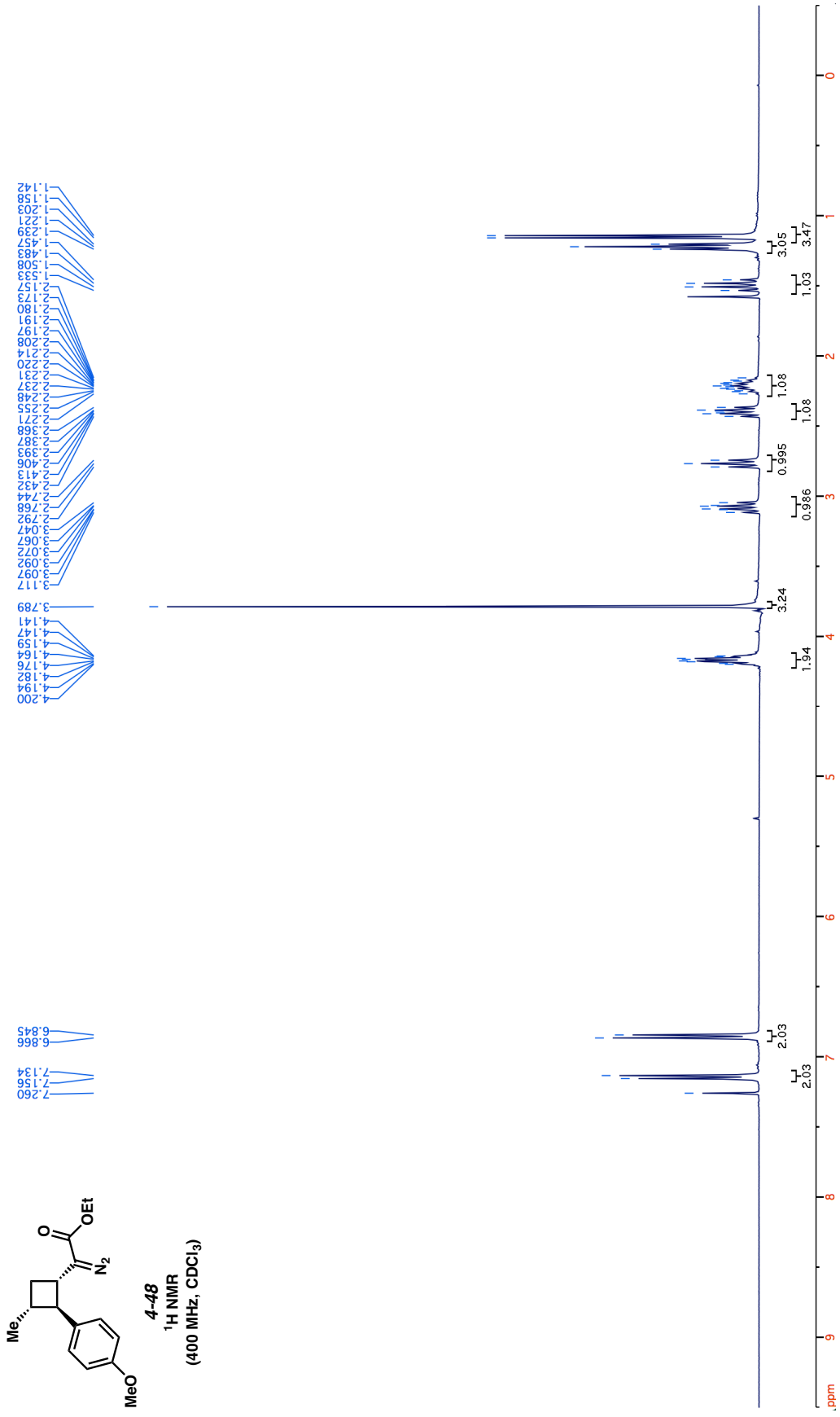
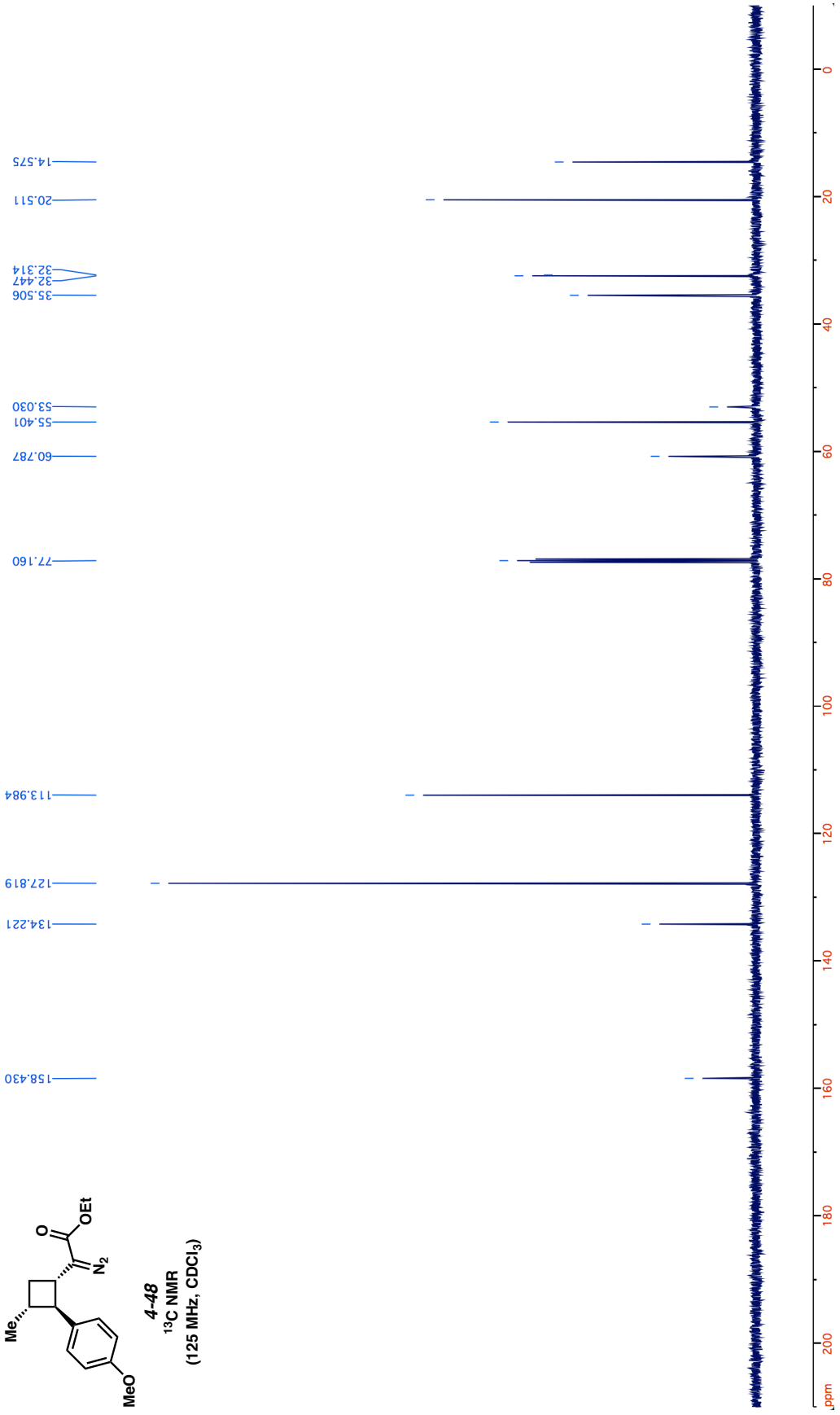
118.940
127.082
133.675
149.749
158.024
167.092
ppm
0
20
40
60
80
100
120
140
160
180
200
MeO
Me
EtO2C
(Z)-4-37
(5.6 : 1 dr)
13C NMR
(100 MHz, CDCl3)


Me
MeO
O
OEt
N2
4-48
1H NMR
(400 MHz, CDCl3)
7.260
7.156
7.134
6.866
6.845
4.200
4.194
4.182
4.176
4.164
4.159
4.147
4.141
3.789
3.117
3.097
3.092
3.072
3.067
3.047
2.792
2.768
2.744
2.432
2.413
2.406
2.393
2.387
2.368
2.271
2.255
2.248
2.237
2.231
2.220
2.214
2.208
2.197
2.191
2.180
2.173
2.157
1.533
1.508
1.483
1.457
1.239
1.221
1.203
1.158
1.142
2.03
2.03
1.94
3.24
0.986
0.995
1.08
1.08
1.03
3.05
3.47
ppm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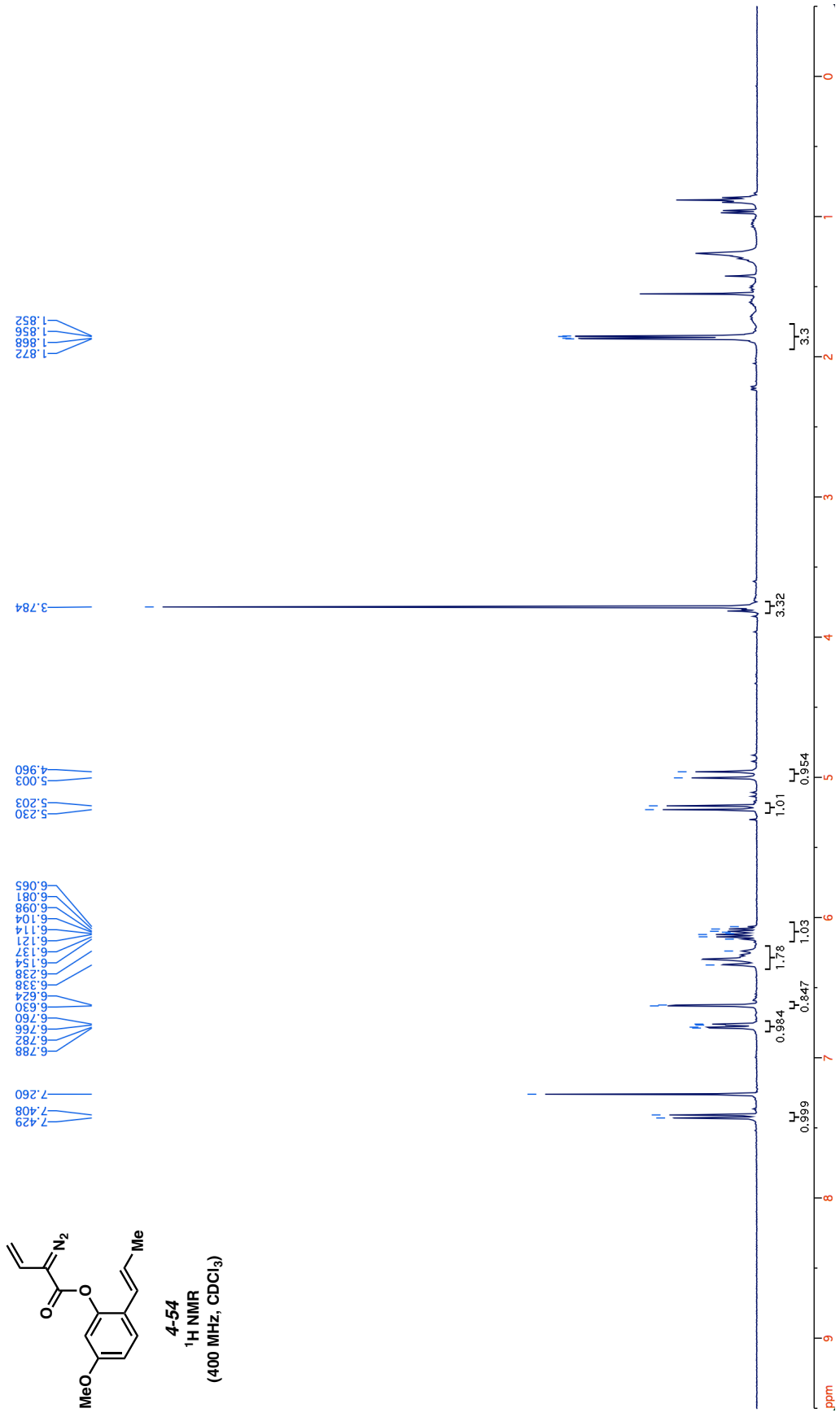
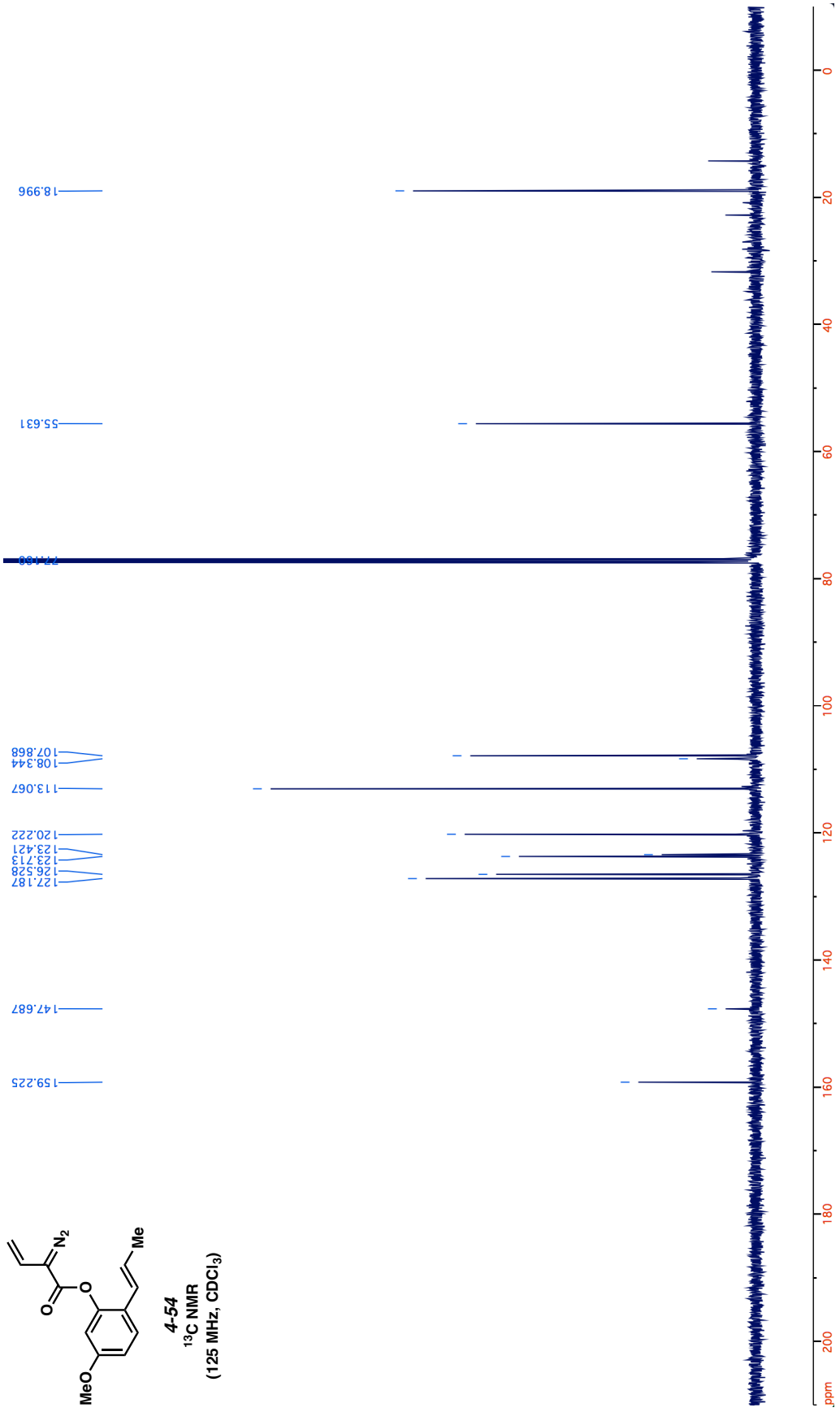
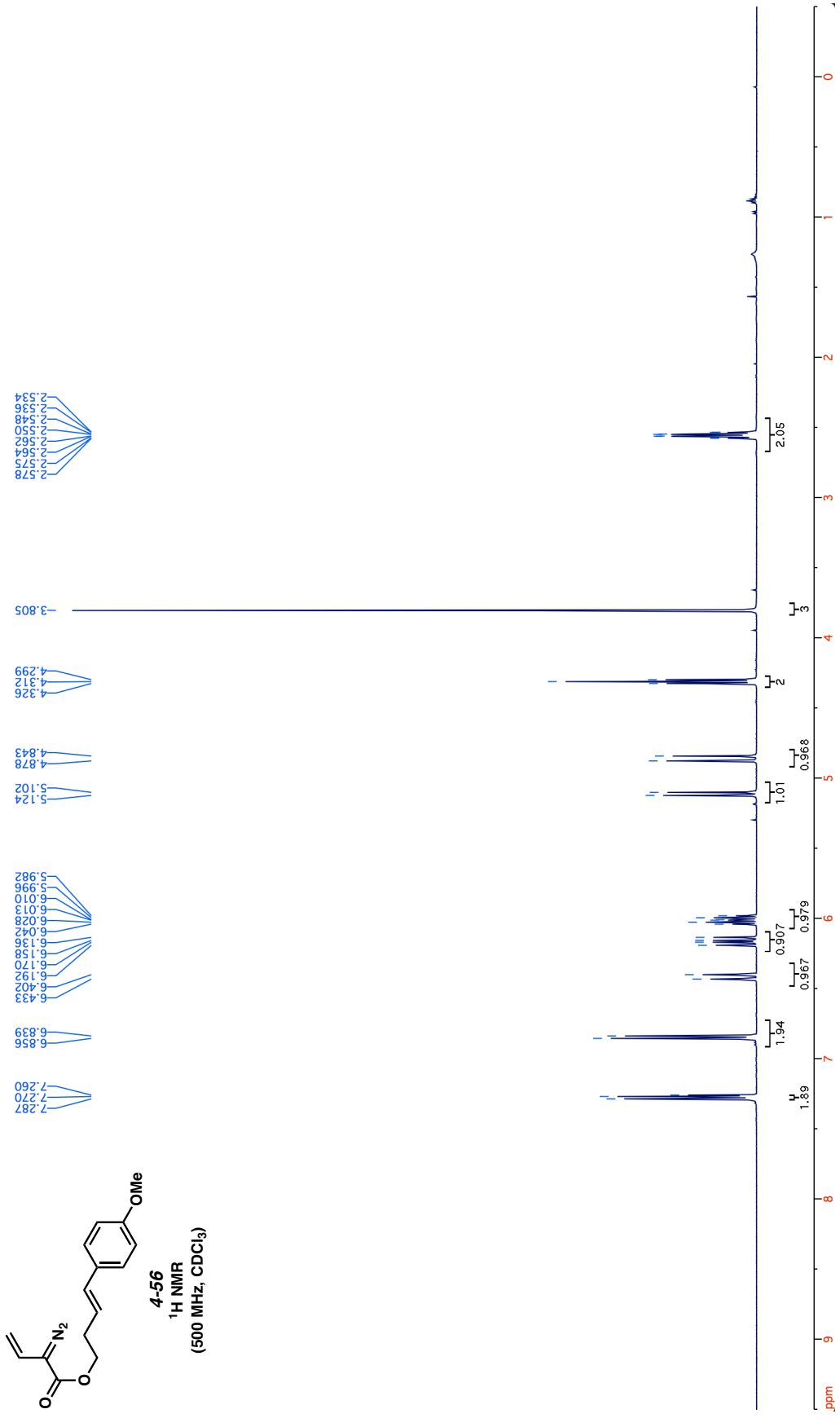
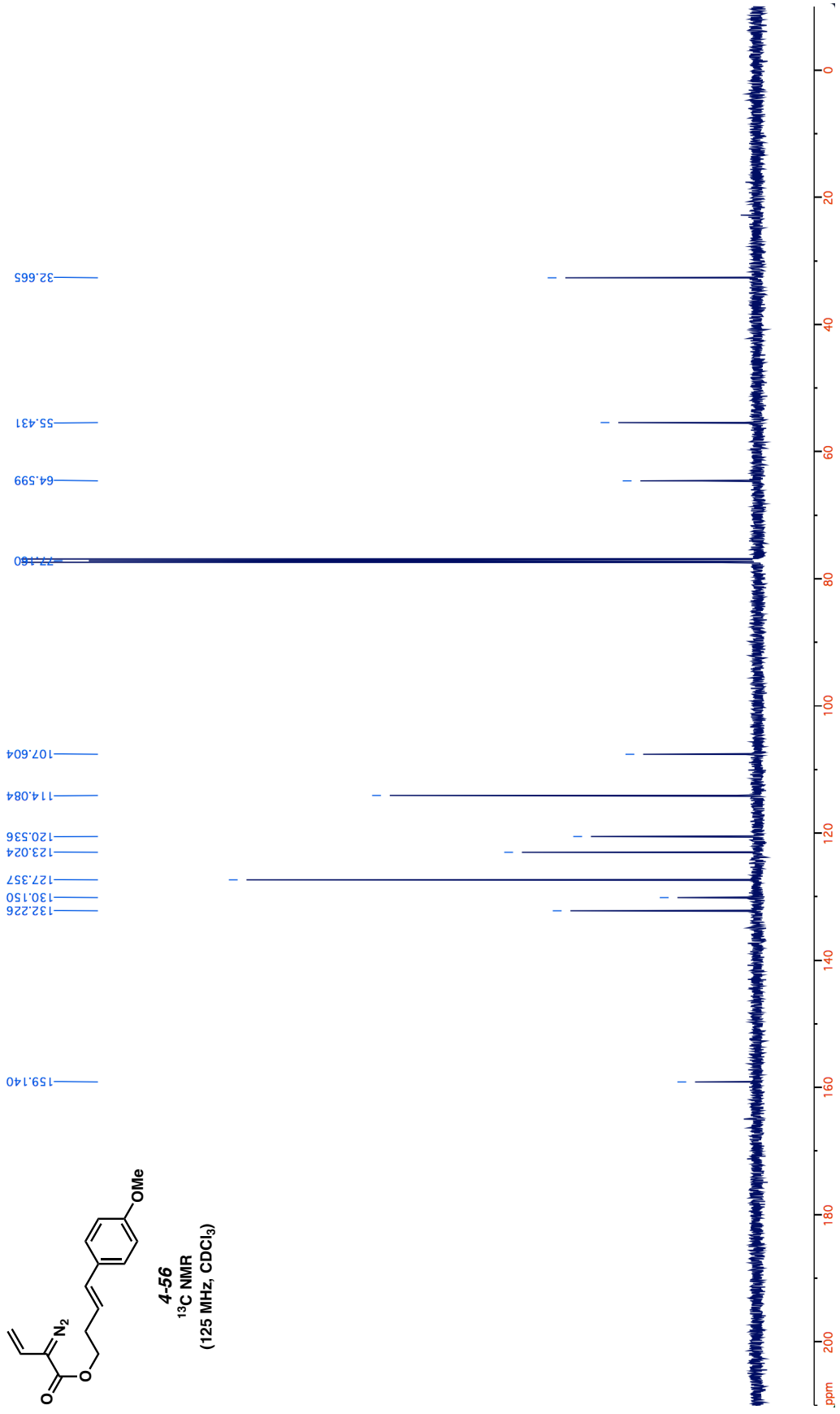
20.511
32.314
32.447
35.506
53.030
55.401
60.787
77.160
113.984
127.819
134.221
158.430
Me
O
OEt
N2
MeO
4-48
13C NMR
(125 MHz, CDCl3)
0
20
40
60
80
100
120
140
160
180
200
ppm


MeO
O
O
N2
Me
4-54
1H NMR
(400 MHz, CDCl3)
1.872
1.868
1.856
1.852
7.429
7.408
7.260
6.788
6.782
6.766
6.760
6.630
6.624
6.338
6.238
6.154
6.137
6.121
6.114
6.104
6.098
6.081
6.065
5.230
5.203
5.003
4.960
3.784
3.3
3.32
0.954
1.01
1.03
1.78
0.847
0.984
0.999
ppm



4-54
^{13}C NMR
(125 MHz, $CDCl_3$)


OMe
N2
O
O
4-56
1H NMR
(500 MHz, CDCl3)
7.287
7.270
7.260
6.856
6.839
6.433
6.402
6.192
6.170
6.158
6.136
6.042
6.028
6.013
6.010
5.996
5.982
5.124
5.102
4.878
4.843
4.326
4.312
4.299
3.805
2.578
2.575
2.564
2.562
2.550
2.548
2.536
2.534
1.89
1.94
0.967
0.907
0.979
1.01
2
0.968
3
2.05
ppm


159.140
132.226
130.150
127.357
123.024
120.536
114.084
107.604
77.180
64.599
55.431
32.665
0
20
40
60
80
100
120
140
160
180
200
ppm
OMe
N2
O
O
4-56
13C NMR
(125 MHz, CDCl3)

APPENDIX C

CRYSTALLOGRAPHIC DATA FOR COMPOUND **4-81**

Table 1. Crystal data and structure refinement for compound **4-81**.

Identification code	j1_a
Empirical formula	C21 H27 N O3
Formula weight	341.43
Temperature	100(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)/c
Unit cell dimensions	a = 12.4477(7) A alpha = 90 deg.
	b = 6.0026(3) A beta = 99.514(2) deg.
	c = 25.7550(14) A gamma = 90 deg.
Volume	1897.91(18) A^3
Z, Calculated density	4, 1.195 Mg/m^3
Absorption coefficient	0.079 mm^-1
F(000)	736
Crystal size	0.386 x 0.378 x 0.246 mm
Theta range for data collection	3.208 to 29.999 deg.
Limiting indices	-17<=h<=17, -8<=k<=8, -36<=l<=36

Reflections collected / unique	61552 / 5543 [R(int) = 0.0277]
Completeness to theta = 25.242	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7470 and 0.7164
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5543 / 0 / 238
Goodness-of-fit on F^2	1.077
Final R indices [I>2sigma(I)]	R1 = 0.0512, wR2 = 0.1392
R indices (all data)	R1 = 0.0556, wR2 = 0.1426
Extinction coefficient	n/a
Largest diff. peak and hole	0.541 and -0.277 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **4-81**.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	5361(1)	5065(1)	3143(1)	20(1)
O(2)	6485(1)	2345(2)	3473(1)	27(1)
C(1)	6217(1)	4351(2)	3435(1)	18(1)
C(2)	6930(1)	6075(2)	3761(1)	20(1)
C(3)	8135(1)	5952(2)	3698(1)	18(1)
C(4)	8690(1)	7400(2)	4163(1)	24(1)
C(5)	8068(1)	6756(3)	4613(1)	37(1)
C(6)	6973(1)	5786(3)	4357(1)	38(1)
C(7)	8343(1)	6640(2)	3159(1)	16(1)
C(8)	8070(1)	8773(2)	2954(1)	19(1)
C(9)	8210(1)	9327(2)	2446(1)	20(1)
C(10)	8622(1)	7766(2)	2129(1)	18(1)
C(11)	8926(1)	5673(2)	2330(1)	19(1)

C(12)	8784(1)	5145(2)	2841(1)	18(1)
O(3)	8687(1)	8464(2)	1629(1)	26(1)
C(13)	9001(1)	6840(3)	1279(1)	31(1)
C(14)	9909(1)	7052(3)	4297(1)	35(1)
C(15)	3745(1)	9675(2)	3596(1)	19(1)
C(16)	3368(1)	7678(2)	3776(1)	25(1)
C(17)	3273(1)	7441(2)	4304(1)	32(1)
C(18)	3560(1)	9177(3)	4653(1)	35(1)
C(19)	3943(1)	11160(2)	4474(1)	33(1)
C(20)	4030(1)	11412(2)	3949(1)	25(1)
C(21)	3850(1)	9962(2)	3026(1)	23(1)
N(1)	4977(1)	9470(2)	2937(1)	18(1)

Table 3. Bond lengths [A] and angles [deg] for **4-81**.

O(1)-C(1)	1.2730(14)
O(2)-C(1)	1.2488(14)
C(1)-C(2)	1.5218(16)
C(2)-C(6)	1.5374(17)
C(2)-C(3)	1.5380(16)
C(2)-H(2A)	1.0000
C(3)-C(7)	1.5097(15)
C(3)-C(4)	1.5470(16)
C(3)-H(3A)	1.0000
C(4)-C(14)	1.5145(18)
C(4)-C(5)	1.545(2)
C(4)-H(4A)	1.0000
C(5)-C(6)	1.528(2)
C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-C(12)	1.3878(15)
C(7)-C(8)	1.4054(16)

C(8)-C(9)	1.3874(16)
C(8)-H(8A)	0.9500
C(9)-C(10)	1.3963(16)
C(9)-H(9A)	0.9500
C(10)-O(3)	1.3692(13)
C(10)-C(11)	1.3873(16)
C(11)-C(12)	1.3942(15)
C(11)-H(11A)	0.9500
C(12)-H(12A)	0.9500
O(3)-C(13)	1.4256(17)
C(13)-H(13A)	0.9800
C(13)-H(13B)	0.9800
C(13)-H(13C)	0.9800
C(14)-H(14A)	0.9800
C(14)-H(14B)	0.9800
C(14)-H(14C)	0.9800
C(15)-C(20)	1.3904(17)
C(15)-C(16)	1.3948(17)
C(15)-C(21)	1.5039(15)
C(16)-C(17)	1.3918(18)
C(16)-H(16A)	0.9500
C(17)-C(18)	1.384(2)
C(17)-H(17A)	0.9500

C(18)-C(19)	1.388(2)
C(18)-H(18A)	0.9500
C(19)-C(20)	1.3847(18)
C(19)-H(19A)	0.9500
C(20)-H(20A)	0.9500
C(21)-N(1)	1.4891(15)
C(21)-H(21A)	0.9900
C(21)-H(21B)	0.9900
N(1)-H(1A)	0.92(2)
N(1)-H(1B)	0.95(2)
N(1)-H(1C)	0.914(19)

O(2)-C(1)-O(1)	123.86(11)
O(2)-C(1)-C(2)	119.30(10)
O(1)-C(1)-C(2)	116.83(10)
C(1)-C(2)-C(6)	113.26(10)
C(1)-C(2)-C(3)	113.54(9)
C(6)-C(2)-C(3)	103.07(10)
C(1)-C(2)-H(2A)	108.9
C(6)-C(2)-H(2A)	108.9
C(3)-C(2)-H(2A)	108.9
C(7)-C(3)-C(2)	113.68(9)
C(7)-C(3)-C(4)	115.82(10)

C(2)-C(3)-C(4)	102.11(9)
C(7)-C(3)-H(3A)	108.3
C(2)-C(3)-H(3A)	108.3
C(4)-C(3)-H(3A)	108.3
C(14)-C(4)-C(5)	113.68(11)
C(14)-C(4)-C(3)	113.65(11)
C(5)-C(4)-C(3)	103.01(11)
C(14)-C(4)-H(4A)	108.8
C(5)-C(4)-H(4A)	108.8
C(3)-C(4)-H(4A)	108.8
C(6)-C(5)-C(4)	107.11(10)
C(6)-C(5)-H(5A)	110.3
C(4)-C(5)-H(5A)	110.3
C(6)-C(5)-H(5B)	110.3
C(4)-C(5)-H(5B)	110.3
H(5A)-C(5)-H(5B)	108.5
C(5)-C(6)-C(2)	105.60(11)
C(5)-C(6)-H(6A)	110.6
C(2)-C(6)-H(6A)	110.6
C(5)-C(6)-H(6B)	110.6
C(2)-C(6)-H(6B)	110.6
H(6A)-C(6)-H(6B)	108.8
C(12)-C(7)-C(8)	117.49(10)

C(12)-C(7)-C(3)	120.64(10)
C(8)-C(7)-C(3)	121.85(10)
C(9)-C(8)-C(7)	120.84(10)
C(9)-C(8)-H(8A)	119.6
C(7)-C(8)-H(8A)	119.6
C(8)-C(9)-C(10)	120.46(11)
C(8)-C(9)-H(9A)	119.8
C(10)-C(9)-H(9A)	119.8
O(3)-C(10)-C(11)	125.00(11)
O(3)-C(10)-C(9)	115.49(10)
C(11)-C(10)-C(9)	119.51(10)
C(10)-C(11)-C(12)	119.32(10)
C(10)-C(11)-H(11A)	120.3
C(12)-C(11)-H(11A)	120.3
C(7)-C(12)-C(11)	122.32(10)
C(7)-C(12)-H(12A)	118.8
C(11)-C(12)-H(12A)	118.8
C(10)-O(3)-C(13)	116.75(10)
O(3)-C(13)-H(13A)	109.5
O(3)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5
O(3)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5

H(13B)-C(13)-H(13C)	109.5
C(4)-C(14)-H(14A)	109.5
C(4)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	109.5
C(4)-C(14)-H(14C)	109.5
H(14A)-C(14)-H(14C)	109.5
H(14B)-C(14)-H(14C)	109.5
C(20)-C(15)-C(16)	119.34(11)
C(20)-C(15)-C(21)	119.85(11)
C(16)-C(15)-C(21)	120.81(11)
C(17)-C(16)-C(15)	120.09(12)
C(17)-C(16)-H(16A)	120.0
C(15)-C(16)-H(16A)	120.0
C(18)-C(17)-C(16)	120.18(13)
C(18)-C(17)-H(17A)	119.9
C(16)-C(17)-H(17A)	119.9
C(17)-C(18)-C(19)	119.77(12)
C(17)-C(18)-H(18A)	120.1
C(19)-C(18)-H(18A)	120.1
C(20)-C(19)-C(18)	120.30(13)
C(20)-C(19)-H(19A)	119.8
C(18)-C(19)-H(19A)	119.8
C(19)-C(20)-C(15)	120.31(12)

C(19)-C(20)-H(20A)	119.8
C(15)-C(20)-H(20A)	119.8
N(1)-C(21)-C(15)	111.32(9)
N(1)-C(21)-H(21A)	109.4
C(15)-C(21)-H(21A)	109.4
N(1)-C(21)-H(21B)	109.4
C(15)-C(21)-H(21B)	109.4
H(21A)-C(21)-H(21B)	108.0
C(21)-N(1)-H(1A)	110.4(11)
C(21)-N(1)-H(1B)	113.2(11)
H(1A)-N(1)-H(1B)	107.6(16)
C(21)-N(1)-H(1C)	107.6(12)
H(1A)-N(1)-H(1C)	109.2(16)
H(1B)-N(1)-H(1C)	108.8(16)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for **4-81**.

The anisotropic displacement factor exponent takes the form:

-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O(1)	25(1)	17(1)	19(1)	1(1)	6(1)	1(1)
O(2)	21(1)	20(1)	40(1)	0(1)	3(1)	3(1)
C(1)	19(1)	18(1)	17(1)	-2(1)	9(1)	-3(1)
C(2)	21(1)	20(1)	18(1)	-3(1)	4(1)	0(1)
C(3)	19(1)	21(1)	15(1)	0(1)	1(1)	2(1)
C(4)	25(1)	28(1)	18(1)	-5(1)	-4(1)	2(1)
C(5)	35(1)	59(1)	16(1)	-6(1)	1(1)	6(1)
C(6)	48(1)	51(1)	17(1)	-7(1)	13(1)	-12(1)
C(7)	13(1)	21(1)	15(1)	-2(1)	0(1)	-2(1)
C(8)	18(1)	18(1)	20(1)	-4(1)	2(1)	-1(1)
C(9)	21(1)	16(1)	22(1)	0(1)	0(1)	-2(1)
C(10)	16(1)	22(1)	16(1)	0(1)	2(1)	-5(1)
C(11)	15(1)	22(1)	19(1)	-3(1)	3(1)	1(1)

C(12)	15(1)	20(1)	19(1)	0(1)	0(1)	1(1)
O(3)	33(1)	29(1)	16(1)	2(1)	5(1)	-7(1)
C(13)	33(1)	41(1)	19(1)	-6(1)	9(1)	-10(1)
C(14)	28(1)	43(1)	31(1)	-4(1)	-6(1)	-1(1)
C(15)	17(1)	22(1)	20(1)	4(1)	4(1)	5(1)
C(16)	29(1)	21(1)	26(1)	4(1)	4(1)	2(1)
C(17)	41(1)	25(1)	32(1)	12(1)	12(1)	5(1)
C(18)	48(1)	36(1)	23(1)	6(1)	15(1)	10(1)
C(19)	44(1)	30(1)	26(1)	-5(1)	12(1)	3(1)
C(20)	27(1)	22(1)	27(1)	1(1)	10(1)	2(1)
C(21)	19(1)	30(1)	19(1)	6(1)	3(1)	5(1)
N(1)	21(1)	16(1)	19(1)	2(1)	5(1)	3(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for **4-81**.

	x	y	z	U(eq)
H(2A)	6645	7596	3656	23
H(3A)	8388	4380	3762	22
H(4A)	8545	9005	4073	29
H(5A)	8487	5639	4847	44
H(5B)	7955	8084	4825	44
H(6A)	6365	6596	4476	45
H(6B)	6924	4190	4448	45
H(8A)	7787	9850	3166	23
H(9A)	8024	10778	2314	24
H(11A)	9227	4611	2121	22
H(12A)	8997	3711	2977	22
H(13A)	9020	7526	935	46
H(13B)	9726	6262	1423	46
H(13C)	8474	5614	1238	46

H(14A)	10252	7491	3996	52
H(14B)	10203	7963	4604	52
H(14C)	10062	5477	4378	52
H(16A)	3176	6478	3539	30
H(17A)	3009	6084	4426	38
H(18A)	3496	9013	5014	41
H(19A)	4146	12349	4714	39
H(20A)	4286	12779	3829	30
H(21A)	3332	8951	2807	27
H(21B)	3657	11511	2916	27
H(1A)	5174(15)	8040(30)	3044(7)	33(4)
H(1B)	5506(16)	10450(30)	3120(7)	34(5)
H(1C)	4985(16)	9600(30)	2584(8)	33(4)

Table 6. Torsion angles [deg] for **4-81**.

O(2)-C(1)-C(2)-C(6)	-64.56(15)
O(1)-C(1)-C(2)-C(6)	114.39(12)
O(2)-C(1)-C(2)-C(3)	52.55(14)
O(1)-C(1)-C(2)-C(3)	-128.50(10)
C(1)-C(2)-C(3)-C(7)	68.44(13)
C(6)-C(2)-C(3)-C(7)	-168.65(11)
C(1)-C(2)-C(3)-C(4)	-166.07(10)
C(6)-C(2)-C(3)-C(4)	-43.16(12)
C(7)-C(3)-C(4)-C(14)	-72.77(14)
C(2)-C(3)-C(4)-C(14)	163.17(11)
C(7)-C(3)-C(4)-C(5)	163.79(10)
C(2)-C(3)-C(4)-C(5)	39.72(12)
C(14)-C(4)-C(5)-C(6)	-144.99(14)
C(3)-C(4)-C(5)-C(6)	-21.55(15)
C(4)-C(5)-C(6)-C(2)	-4.99(17)
C(1)-C(2)-C(6)-C(5)	152.91(12)
C(3)-C(2)-C(6)-C(5)	29.82(15)
C(2)-C(3)-C(7)-C(12)	-118.57(11)
C(4)-C(3)-C(7)-C(12)	123.61(11)

C(2)-C(3)-C(7)-C(8)	59.49(14)
C(4)-C(3)-C(7)-C(8)	-58.33(14)
C(12)-C(7)-C(8)-C(9)	1.86(15)
C(3)-C(7)-C(8)-C(9)	-176.26(10)
C(7)-C(8)-C(9)-C(10)	0.22(17)
C(8)-C(9)-C(10)-O(3)	177.65(10)
C(8)-C(9)-C(10)-C(11)	-2.12(16)
O(3)-C(10)-C(11)-C(12)	-177.88(10)
C(9)-C(10)-C(11)-C(12)	1.87(16)
C(8)-C(7)-C(12)-C(11)	-2.13(16)
C(3)-C(7)-C(12)-C(11)	176.01(10)
C(10)-C(11)-C(12)-C(7)	0.28(16)
C(11)-C(10)-O(3)-C(13)	5.83(16)
C(9)-C(10)-O(3)-C(13)	-173.92(10)
C(20)-C(15)-C(16)-C(17)	0.43(18)
C(21)-C(15)-C(16)-C(17)	-179.82(12)
C(15)-C(16)-C(17)-C(18)	-0.6(2)
C(16)-C(17)-C(18)-C(19)	0.1(2)
C(17)-C(18)-C(19)-C(20)	0.5(2)
C(18)-C(19)-C(20)-C(15)	-0.6(2)
C(16)-C(15)-C(20)-C(19)	0.16(18)
C(21)-C(15)-C(20)-C(19)	-179.60(12)
C(20)-C(15)-C(21)-N(1)	84.55(14)

C(16)-C(15)-C(21)-N(1)	-95.20(13)

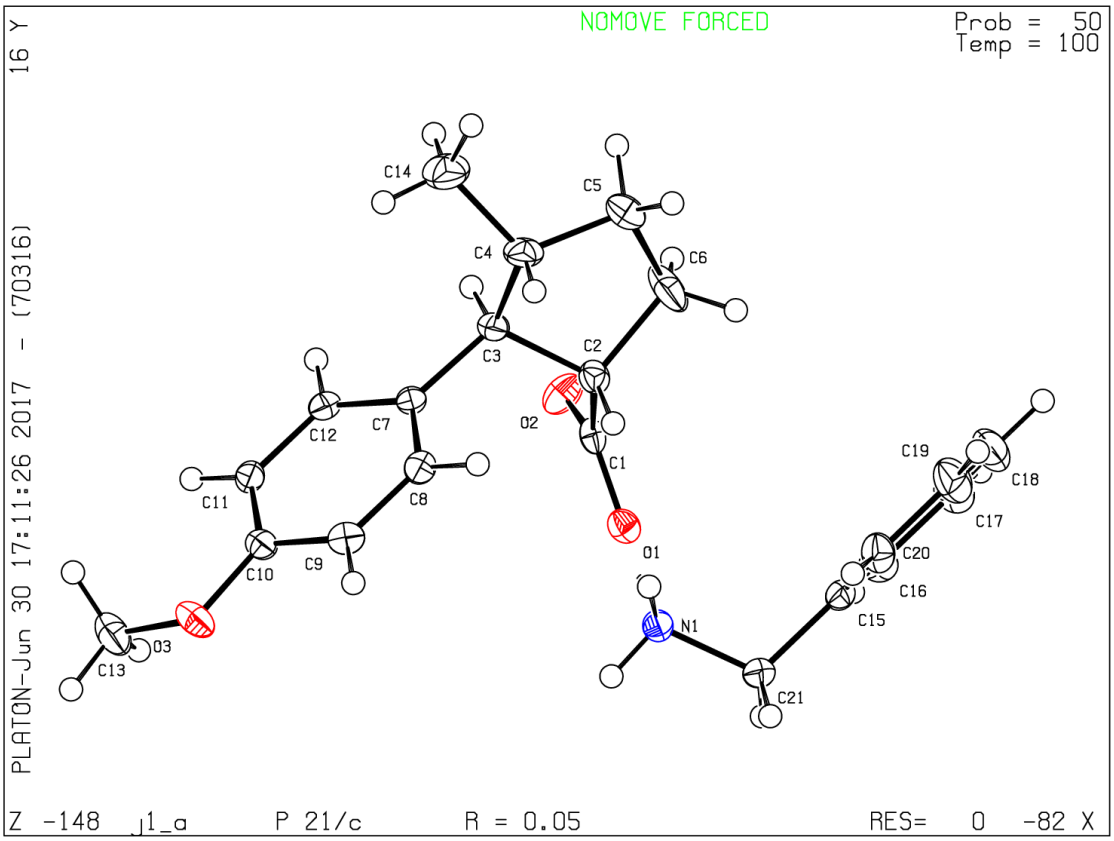
Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for **4-81** [A and deg.].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1A)...O(1)	0.92(2)	1.81(2)	2.7233(13)	168.6(17)
N(1)-H(1B)...O(2)#1	0.95(2)	1.80(2)	2.7468(14)	178.8(18)
N(1)-H(1C)...O(1)#2	0.914(19)	1.87(2)	2.7661(13)	165.7(18)

Symmetry transformations used to generate equivalent atoms:

#1 x,y+1,z #2 -x+1,y+1/2,-z+1/2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16 Y
PLATON-Jun 30 17:11:26 2017 - (70316)
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C5
C4
C6
C3
C2
O2
C12
C7
C1
C19
C18
C11
C8
C17
O1
C20
C10
C9
C16
C15
N1
O3
C13
C21
Z -148 j1_a P 21/c R = 0.05 RES= 0 -82 X