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Exploration of Spirocyclic Topology: Reaction Discovery En Route to Total Synthesis of
Urceoloids & B

By

Karan Goyal

A dissertation submitted in partial satisfaction of the
requirements for the degree of
Doctor of Philosophy
in
Chemistry
in the
Graduate Division
of the
University of California, Berkeley

Committee in charge:

Professor Richmond Sarpong, Chair

Professor F. Dean Toste

Professor Gregory W. Aponte

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Abstract

Exploration of Spirocyclic Topology: Reaction Discovery En Route to Total Synthesis of Urceoloids A & B

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Karan Goyal

Doctor of Philosophy in Chemistry

University of California, Berkeley

Professor Richmond Sarpong, Chair

This dissertation describes efforts toward the total synthesis of urceoloids A & B as a means to gain insight into the reactivity and synthetic utility of spiro[4.4]nonenes, an underexplored class of compounds.

Chapter 1 introduces the field of total synthesis and highlights its growth, specifically noting the theme of exploration which carries through from its inception. We then discuss spirocyclic motifs in natural products and the strategies used to construct spirocyclic scaffolds. A brief history of spiro[4.4]nonenes is then provided, showcasing the limited investigations regarding their reactivity.

Chapter 2 introduces urceoloids A & B and our motivation for total synthesis efforts toward these compounds. Additionally, we discuss our initial synthetic strategy which centers around an oxidative-Heck fragment coupling. Attempts at this fragment coupling led to the discovery of unexpected reactivity, which is the subject of Chapter 3.

Chapter 3 outlines investigation of the unexpected rearrangement of a spirononene to enantioenriched, aryl-substituted annulated fulvenes. This work includes mechanistic insights which were performed in collaboration with the Houk group at UCLA.

Chapter 4 captures the remainder of our total synthesis efforts toward urceoloids A & B. This work includes multiple revisions in strategy in order to ultimately achieve a successful fragment coupling between a spiro[4.4]nonene and cyclopentyl coupling partner. In the process of arriving at this success, we examined the reactivity of various spirocyclic intermediates and initiated investigations into the synthesis of enantioenriched spirocycles through an asymmetric iodolactonization. Overall, this combined body of work highlights how total synthesis may be used as a platform for exploration of underexplored structures and their reactivity.

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Chapter 1: An Overview of Total Synthesis and Spirononenes

1.1 Total Synthesis: A Field Rooted in Serendipity

The field of total synthesis has its purported beginning in serendipity in Wöhler's accidental synthesis of urea in the pursuit of making ammonium cyanate (Figure 1).¹ At the time, this was a vital study in disproving the theory of vitalism by synthesizing an organic compound from inorganic matter. Since that time, the study of total synthesis has undergone much evolution in not only the complexity of the target structures but also in serving a variety of purposes.² The broadest goal of total synthesis is synthetic access to naturally occurring compounds, which may be difficult to obtain through isolation³ from natural sources alone. More specifically, synthesis served as a means of structural determination prior to the invention of advanced analytical techniques such as nuclear magnetic resonance (NMR) spectroscopy.⁴ Despite the advancements in analytical techniques, total synthesis still leads to structural revisions in modern times.⁵ Synthesis also facilitates investigation of bioactive natural products,⁶ as well as their derivatives⁷ which may possess altered bioactivities. This motivation is often rooted in the necessity to discover therapeutics which can solve problems of human health.⁸

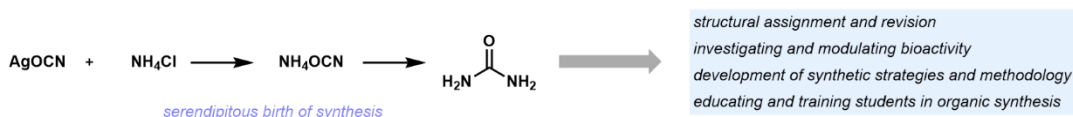


Figure 1. Wöhler's synthesis of urea and the roles of synthesis in the modern era.

Beyond the end goal of the natural product itself, the journey of a synthesis is also valuable.⁹ The process of designing and carrying out a synthetic route toward a complex target requires the development of both creative strategies and innovative methodologies.¹⁰ These developments expand the field of chemistry and allow chemists to synthesize increasingly complex molecules, feeding back into the cycle of development. This process also provides a rich education for students to learn not just synthesis, but also problem-solving strategies.¹¹ Often, syntheses are justified by the bioactivity of a natural product, a unique synthetic strategy, or the ability to showcase a methodology. While these are, indeed, prominent aspects of synthesis, it is important to bear in mind the serendipitous roots of synthesis. That is, in the journey of a synthesis, one must traverse uncharted chemical space and, in the process, be open to the discovery of something new. This idea is eloquently stated by Nicolau's comments⁹ on natural product total synthesis:

"At its core, in its most essential form, natural product total synthesis is a vehicle for discovery, one that is perhaps unparalleled by any other endeavor in the realm of chemical synthesis."

1.2 Spiro[4.4.0]nonenes in Natural Products

The greatest potential for discovery arises from access to underexplored areas of science. A relatively underexplored scaffold in natural products is the spiro[4.4.0]nonane or spiro[4.4.0]nonene core. Among natural products bearing a general spiro[4.4.0]nonane, the nonane core is often heterocyclic, containing a spiro-lactone, spiro-ether, spiro-acetal/aminal, or spiro-indole-derived motif.¹² Fully carbocyclic spiro[4.4.0]nonanes, which are not embedded within a more intricate polycyclic system,¹³ are much rarer.¹⁴ An extensive literature survey has revealed only five natural products (and families thereof) which possess this spiro[4.4.0]nonane core that have been isolated and synthesized: fredericamycin A,^{15–17} acutumine (and its derivatives),^{18,19}

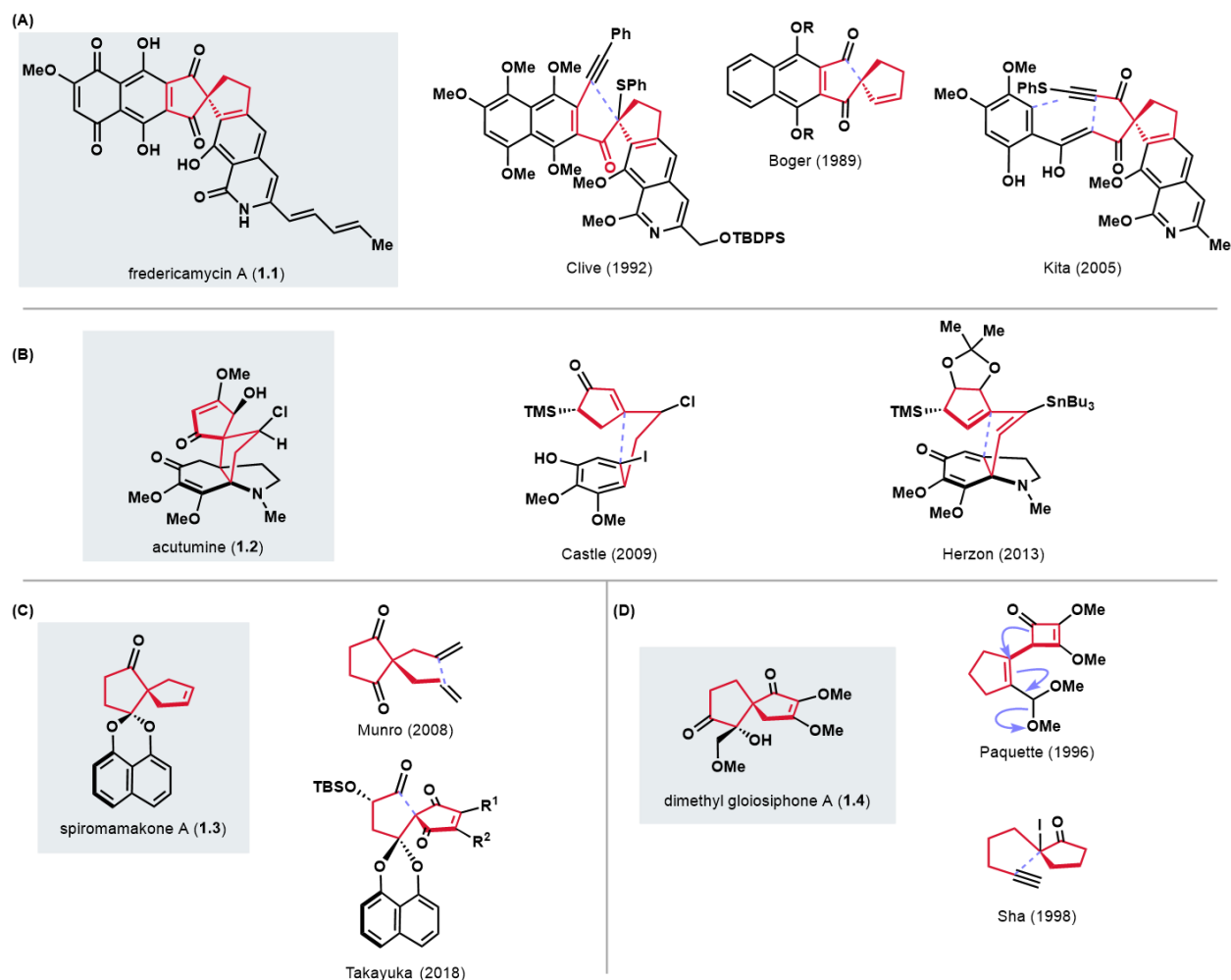


Figure 2. Natural products bearing a carbocyclic spiro[4.4]nonene core and reported approaches to the construction of the spirocyclic core.

dimethyl gloiosiphone A,²⁰ and spiromamakone A.²¹ The spiro[4.4.0]nonane core for all of these natural products has some degree of unsaturation, rendering it a spiro[4.4.0]nonene core. While other spirononenes exist (e.g. a spiro[5.3.0]nonene²²), the shorthand “spirononene” will exclusively refer to the spiro[4.4.0]nonenes for the remainder of this dissertation.

A brief examination of the synthetic approaches for the aforementioned natural products shows a general trend where the spirononene core is constructed at a late-stage from a complex intermediate (Figure 2). Clive's²³ synthesis of fredericamycin A (**1.1**) involves a late-stage intramolecular 5-exo-dig radical spirocyclization which furnishes the spirononene moiety (Figure 2A). Boger's synthesis of the core²⁴ and eventually, the natural product²⁵, forms the same bond from a complex intermediate through an intramolecular aldol reaction. Kita's²⁶ approach was different, in that it used a Diels–Alder cycloaddition to construct a six-membered ring and the western bond of the spirononene structure simultaneously, but was still similar in that the spirocycle is forged late in the synthesis. This strategy of late-stage spirocyclization is also used in Herzon's²⁷ synthesis of acutumine (**1.2**), in which the spirononene core is forged through a Sakurai reaction (Figure 2B). Castle's^{28,29} synthesis of the **1.2** forms the spirononene earlier, but the remaining synthesis largely focused on chemistry of the aromatic ring rather than the spirononene structure. While these disconnections are strategic in producing the targeted natural products, they limit the exploration of reactivity of the spirononene structure.

The strategy of late-stage spirocyclization is also used in Takayuki's synthesis of spiromamakone A (**1.3**). Paquette's synthesis of dimethyl gloiosiphone (**1.4**) also forms the spirocycle at a late stage, albeit through a more unique cyclobutene rearrangement. These two natural products both bear a more central spirononene motif relative to the entirety of their structures, as compared to the natural products noted above. This potentially allows for an earlier-stage construction of the spirononene core to be synthetically strategic, as is shown by Munro's³⁰ synthesis of spiromamakone A (Figure 2C) and Sha's³¹ synthesis of dimethyl gloiosiphone A (Figure 2D). Sha shows that a radical spirocyclization similar to Kita's can be used to furnish the spirononene early in the synthesis toward dimethyl gloiosiphone A. Similarly, Munro rapidly constructed the spirononene core of mamakone A in only two steps, using a di-allylation of cyclopentane-1,3-dione, followed by a ring closing metathesis. In both Munro and Sha's work, early assembly of the spirononene core allowed for the evaluation of various redox chemistry around the spirocycle. However, intermolecular C–C bond formations using such spirononenes was not shown and remains an unexplored area of spirononene chemistry, which is one point of motivation for the work which will be discussed in the next chapters.

1.3 Spiroconjugation in Spirononenes

Spirononenes were first investigated in the late 20th century by Semmelhack³⁴ and others.^{35,36} These molecules were of particular interest due to their potential to exhibit spiroconjugation, which was a theory first proposed in contemporary reports in 1967 by Fukunaga and Simmons,³⁷ as well as Hoffman, Imamura, and Zeiss.³⁸ This theory holds that mutually perpendicular π -orbital systems which have sufficient overlap, proper symmetry, and matching energies may have a through-space interaction and form new, spiroconjugated molecular orbitals (MO's). While spirononene derivatives had been

previously prepared,^{35,36} the parent, unsubstituted spirononatetraene (**1.9**) and its more saturated variants (**1.5–1.8**) were first synthesized by Semmelhack and coworkers (Figure 3).³⁴ The synthesis of **1.9** was challenging as the molecule was found to undergo thermal rearrangement to the 5-6 fused ring system of an indene when exposed to elevated temperatures (e.g. pyrolysis at 150 °C). Successful synthesis of **1.9** was, however, achieved and allowed for investigation of spiroconjugation through photoelectron spectroscopy (PES).³⁹

Evidence for spiroconjugation was found when the PES of spirononatetraene **1.9** was compared against reference spirononenes **1.5–1.8** (Figure 3). Spiroonene **1.5** has only one π -band arising from the single filled π -MO of the lone alkene. Spiroonadiene **1.8** exhibits two π -bands which result from the single 4π MO system of the diene moiety, as expected. Spiroonatrienes **1.6** and **1.7** exhibit PES bands similar to each other, indicating the location of the double bond in the eastern ring does not significantly impact the overall electronic structure of spiroonatrienes. In these PES spectra, π -bands of an isolated alkene (as in **1.5**) and an isolated diene (as in **1.8**) are observed. Evaluation of the PES spectra for spirononatetraene **1.9**, however, indicates a unique MO system. In the absence of a significant interaction between the two 4π moieties in **1.9**, one would expect two sets of degenerate diene-type MO's, resulting in a PES with two sets of π -bands similar to spiroonadiene **1.8**. However, the PES shows three distinct π -bands as a result of spiroconjugation between the two 4π units, splitting the degeneracy of one set of the filled MO's. This also affects the UV spectrum of **1.9**, as compared to **1.8** or **1.7**. Spiroonadiene **1.8** and spiroonatriene **1.7** both only have a singular absorption at 254 nm, corresponding to the HOMO of the 4π unit. However, spirononatetraene **1.9** shows two distinct absorptions at 276 nm and 218 nm, further indicating the orbital splitting.

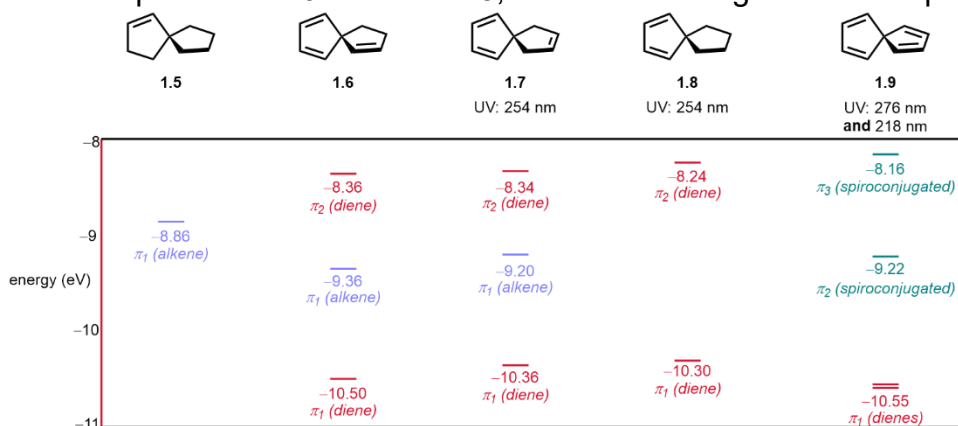


Figure 3. Depiction of reported PES data, showing the averaged energies of π bands, recreated from ref. 39.

The theory^{37,38} behind spiroconjugation denotes that spiroconjugation not only requires proper overlap, enforced by the rigid geometry of these spirononenes, but also requires orbitals to have proper symmetry (Figure 4A). Insight into this facet of spiroconjugation can be gained through an in-depth frontier molecular orbital (FMO)

analysis of two 4π MO's arranged perpendicular to each other.⁴⁰ These orbital interactions can be more clearly understood in examining the Newman projection model of **1.9** through the spirocyclic axis (Figure 4). First, we examine the HOMO–1 of the 4π units (Figure 4B). There are constructive (in-phase) interactions at the periphery of the C4–C5 lobes and C1–C8 lobes. Additionally, there are destructive (out-of-phase) interactions between the lobes at the radial positions (i.e. through the spiro-junction) of C5–C8 and C1–C5. An equal number of constructive and destructive interactions result in a net nonbonding interaction and thus, no spiroconjugation. Inverting the phasing of one of these 4π units inverts these interactions and the same analysis indicates there is no spiroconjugation for the HOMO–1.

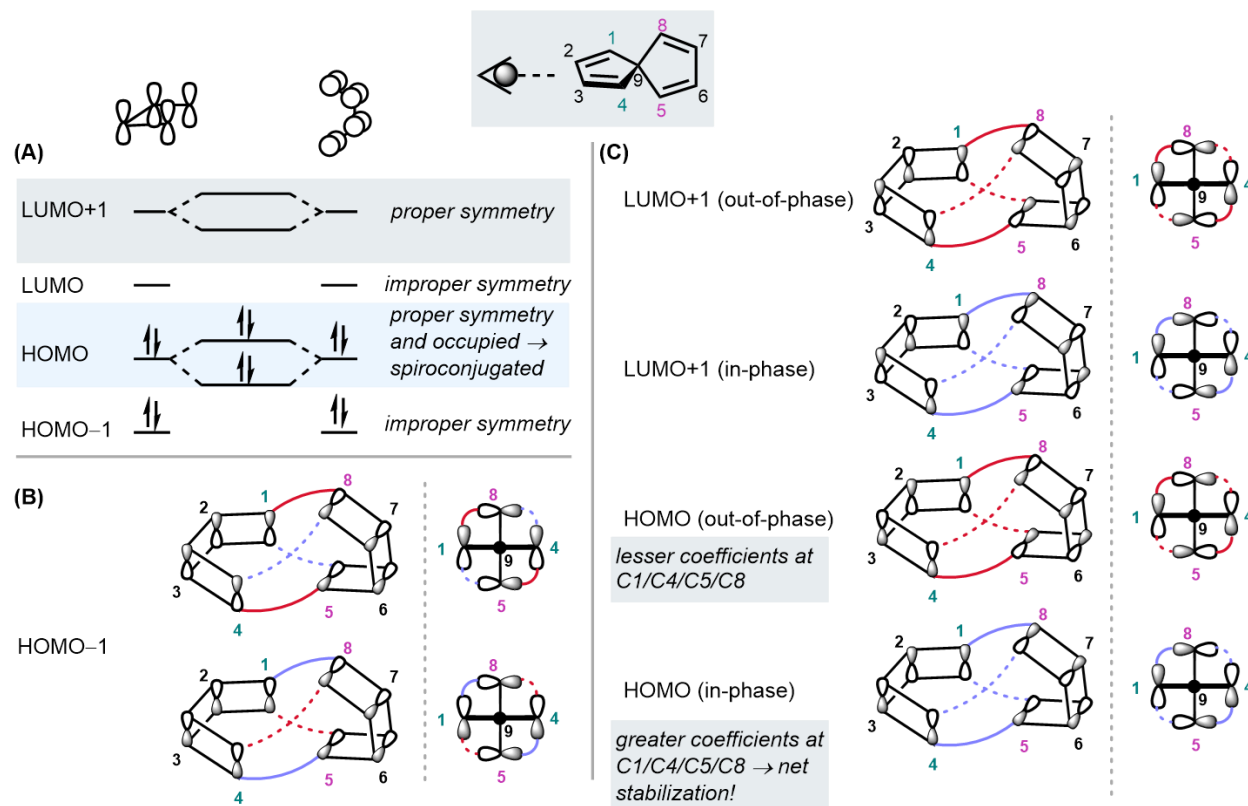


Figure 4. Frontier molecular orbital analysis of spiroconjugation in spirononatetraene **1.9**. Figure inspired by those in refs. 37 and 40. Constructive interactions are indicated by blue lines between orbital lobes, and destructive interactions are indicated by red lines between orbital lobes.

The HOMO of these perpendicular 4π units can be analyzed in the same manner (Figure 4C). We can see that, in this case, the peripheral lobes at C4–C5 and C1–C8 now interact in a constructive (in-phase) manner. The radial lobes at C1–C5 and C4–C8 also interact constructively, giving an overall new bonding MO that is of lower energy. An inversion in the phasing of one of these 4π units results in an inversion of all the constructive interactions to destructive (out-of-phase or destabilizing) interactions, which results in the formation of a new antibonding MO that is of higher energy. This splitting of

previously degenerate orbitals is the result of spiroconjugation. This analysis also extends to the LUMO+1, which has proper symmetry for spiroconjugation, but is of less significance due to its unfilled nature. A point of interest is that although this is an 8π system, which maybe be considered “anti-aromatic” by Hückel’s rules, the spiroconjugation in spirononatetraene is actually stabilizing overall. This is due to a rearrangement of atomic orbital (AO) coefficients in the new MO’s.⁴¹ In the new bonding MO, the carbons participating in spiroconjugation (C1,C4,C5,C8) have higher AO coefficients so the in-phase interactions are more stabilizing. Conversely, for the new antibonding MO, the carbons participating in this destabilizing interaction have lower AO coefficients so the out-of-phase interactions are less destabilizing.

Spiroconjugation has shown to be more than just a curiosity of chemistry and is a useful design element for charge-transfer dyes and optoelectronic materials.⁴² In these types of systems, spiroconjugation allows for the tuning of absorption bands⁴³ and promoting electron transport.⁴⁴ While Semmelhack³⁴ and Simmons⁴¹ have investigated the effects of spiroconjugation on reactivity through limited studies of Diels–Alder reactions, spiroconjugation has been largely unexplored in modern synthetic contexts. The potential to access spiroconjugated intermediates and learn more about their reactivity has been a second point of motivation for the total synthesis endeavor described in subsequent chapters.

1.4 Conclusion

Total synthesis is a versatile field which has enabled the investigation of a myriad of scientific pursuits, but at its heart, is an avenue for exploration. Reported syntheses of natural products with a spirononene core have either centered on late-stage construction of the spirononene core or have mostly explored redox chemistry of an early-stage spirononene intermediate. This provides a niche of unexplored chemical space, that is examining how spirocyclic topology may impact and enable the construction of a natural product. Additionally, such an effort has the potential to access spiroconjugated intermediates which may provide additional insights into the physical organic phenomenon. These motivations have led me to explore spirocyclic topology through the total synthesis of urceoloids A & B, spirocyclic natural products which will be elaborated upon in the next chapter. This work has occurred with an open mind, guided by serendipity in an unknown reaction space.

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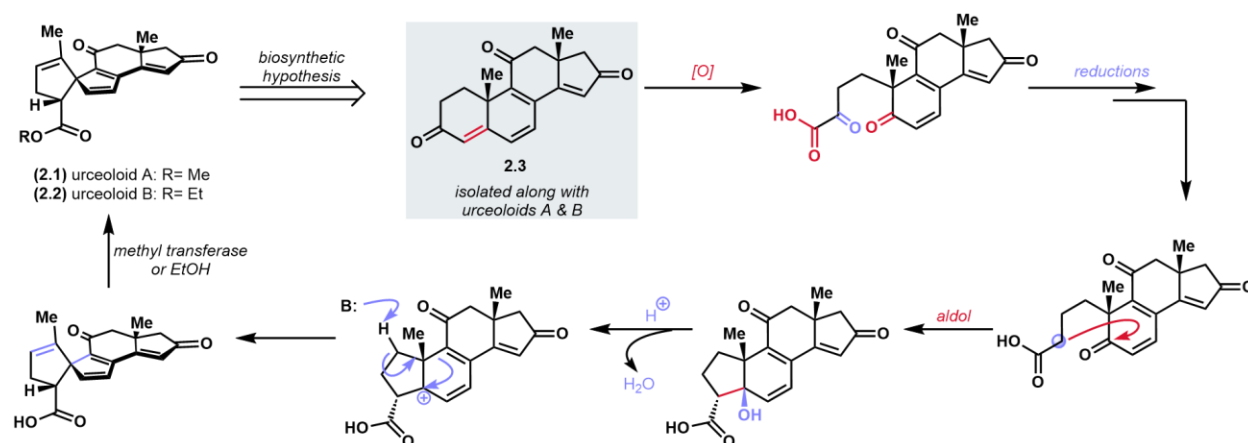
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Chapter 2: Introduction to Urceoloids A & B and Initial Synthetic Route

2.1 Introduction to Urceoloids A & B

Urceoloids A & B (**2.1** and **2.2**) are rearranged C19 steroid natural products, possessing a unique spirononatriene core, which were reported in 2019 (Scheme 2.1).¹ Urceoloid B was shown to have weak immunosuppressive bioactivity against B and T lymphocytes. However, the IC₅₀ values for inhibition of B and T cell proliferation were both 35 μ M which is well below state-of-the-art immunosuppressive therapeutics such as cyclosporin which has a reported IC₅₀ value of approximately 10 nM.²

While the biosynthesis for the urceoloids has not yet been studied, steroid **2.3** was isolated from the same extract alongside urceoloids A & B.¹ On the basis of the structural similarities between **2.3** and the urceoloids (**2.1** & **2.2**), Yue and coworkers propose a biosynthetic hypothesis wherein the urceoloids originate from steroid **2.3** (Scheme 2.1). This involves initial oxidative cleavage of the A-ring, potentially mediated by p450 enzymes through an alkene epoxidation and hydration to a diol,³ followed by oxidative cleavage.⁴ Following this C–C cleaving oxidation, the α -carboxy ketone may undergo a reduction to a hydroxy group⁵ and subsequent elimination, followed by hydrogenation to give a net deoxygenation.⁶ This would set the stage for an enzymatic aldol reaction⁷ to form a new five-membered A ring bearing a hydroxy group. The newly formed hydroxy group could then undergo ionization and cationic ring contraction⁷ to forge the key spirononene core of urceoloids A & B. A methyltransferase⁸ could then install the methyl group required for urceoloid A (**2.1**). Urceoloid B (**2.2**) is hypothesized to exist as an artifact of isolation⁹ from an ethanolic extract.¹



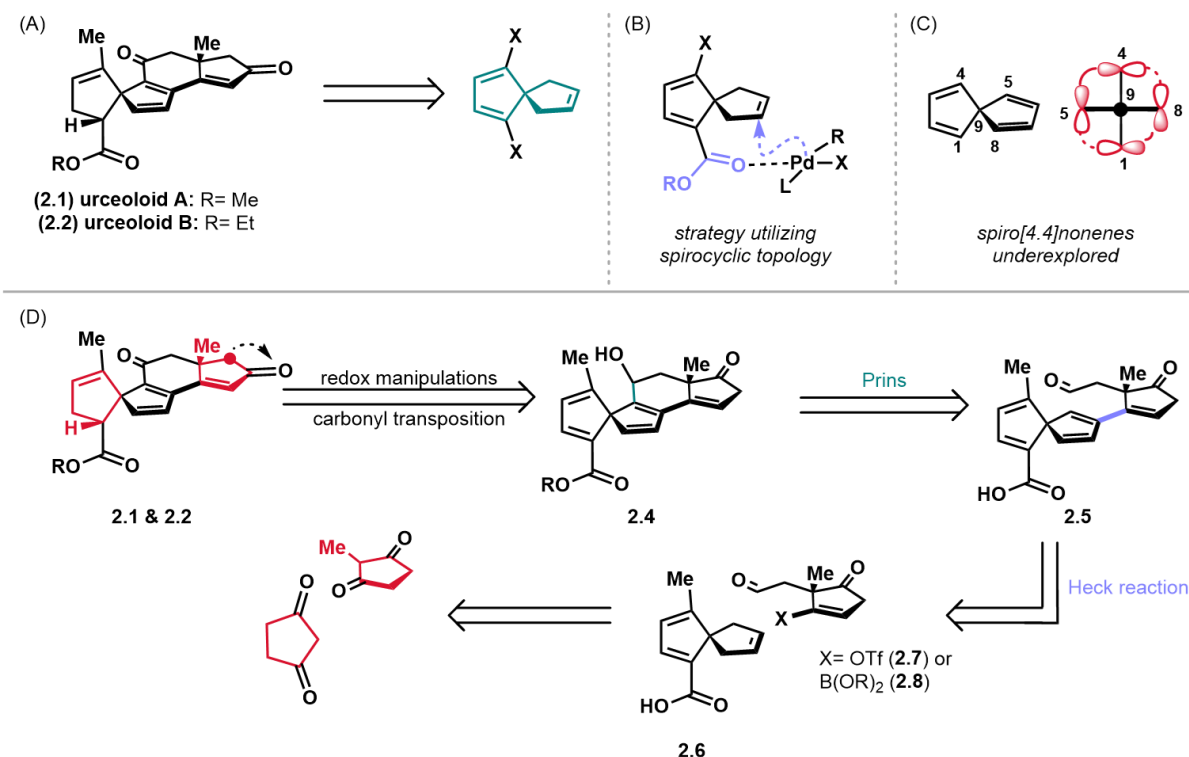
Scheme 2.1. Yue's hypothesis for the biosynthesis of **2.1** & **2.2** from **2.3** is shown above.

2.2 Motivation for Total Synthesis and Retrosynthesis

Our motivation for a total synthesis of the urceoloids (**2.1** & **2.2**) stems from an interest in the unique spirononene core (Scheme 2.2A). As stated in Chapter 1, the all-carbon spirononene core is fairly rare in natural products and to date, no syntheses have

forged an early-stage spirononene intermediate in order to explore its chemistry in C–C bond formation reactions. Specifically, we envisioned that we could use the topology of the spironone system for a directing group effect^{10,11}. Since the two rigid five-membered rings occupy nearly perpendicular planes, we envisioned using an ester or carboxylate directing group on one ring to effect a transformation on the opposite ring in a diastereo- or potentially enantioselective fashion (Scheme 2.2B). Furthermore, a synthesis targeting these underexplored spirononene intermediates may lead to more insights about their reactivity and provide a platform to probe properties of spiroconjugation (Scheme 2.2C).

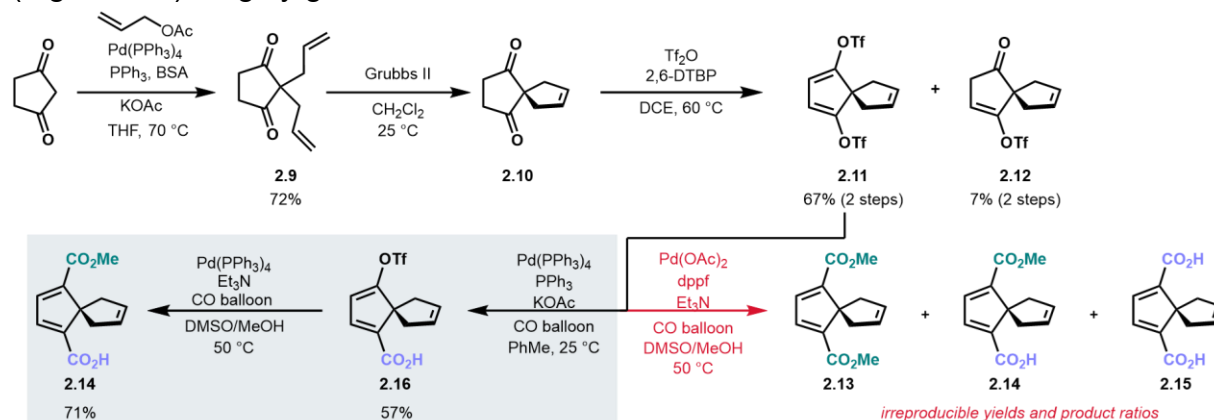
With these motivations in mind, we designed a retrosynthesis focused on a key spirononatriene intermediate (**2.6**, see Scheme 2.2D). In a retrosynthetic fashion, the natural products **2.1** and **2.2** could arise from penultimate intermediate **2.4** through redox manipulations involving a 1,4-reduction, alcohol oxidation, and late-stage carbonyl transposition.¹⁰ The six-membered ring could be forged from a Prins reaction¹¹ of an alkene and pendant aldehyde in intermediate **2.5**. This requisite Prins precursor could arise from a key Heck-type¹² fragment coupling of spirononatriene **2.6** and some cyclopentenyl coupling partner (**2.7** or **2.8**). Both coupling partners could be accessed from a commercially available cyclopentanone starting material, highlighting the element of symmetry within the natural product scaffold.



Scheme 2.2. (A) General retrosynthetic plan for urceoloids A & B. (B) Motivation in using spirocyclic topology. (C) Motivation in learning about underexplored spirononenes. (D) Initial retrosynthesis for urceoloids A & B.

2.3 Forward Progress

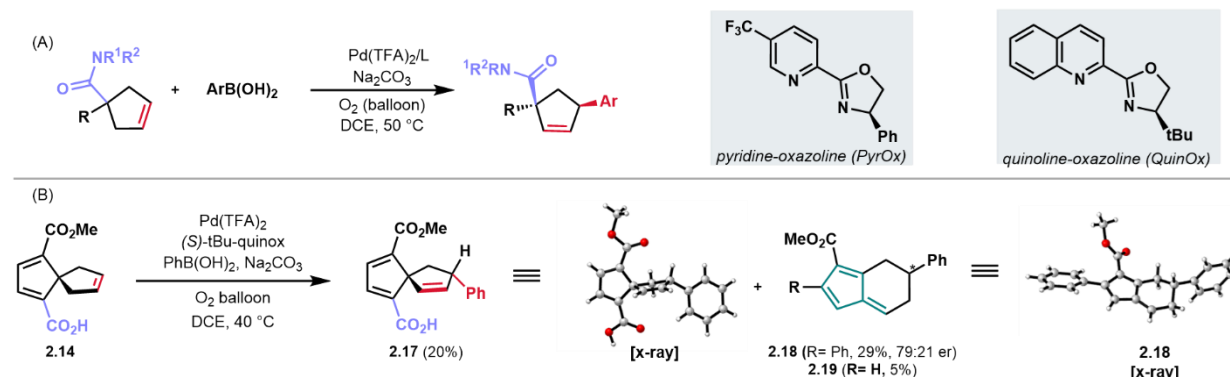
The forward route was aimed at rapid access to a diversifiable spirononene core, as that was the focal point of the synthetic design. We were able to quickly access spirodione **2.10** by adapting a two-step procedure reported by Munro (Scheme 2.3).¹³ First, cyclopentanedione was subjected to Tsuji-Trost-type allylation¹⁴ conditions to give diallyl cyclopentanedione¹⁵ **2.9** in 72% yield. This di-allylated compound could then undergo ring-closing metathesis mediated by Grubbs II catalyst to give spirodione **2.10**.¹³ This dione was used without further purification and gave bis-triflate **2.11** and trace amounts of mono-triflate **2.12** upon treatment with a set of conditions reported by Stang and co-workers.¹⁶ The use of the bulky pyridine base (2,6-di-*tert*-butylpyridine) was crucial as other soft bases, such as alkylamines, or hard deprotonation conditions, such as hexamethyldisilazane anionic bases, were unsuccessful. Additionally, elevated temperature was necessary for successful bis-triflation as reactions at lower temperature (e.g., 25 °C), largely gave monotriflate **2.12**.



Scheme 2.3. Synthetic route to access substituted spironones.

Bis-triflate **2.11** presented an opportunity for diverse functionalizations.¹⁷ However, control of mono-functionalization presented a distinct challenge. In order to access a difunctionalized model-system for further studies, methoxycarbonylation¹⁸ reactions of bis-triflate **2.11** were carried out in order to obtain spirononene diester **2.13**. However, treatment with methoxycarbonylation conditions using Pd(OAc)_2 and dppf¹⁹ gave a mixture of di-ester (**2.13**), ester-acid (**2.14**), and di-acid (**2.15**) products (Scheme 2.3). While it was initially assumed that **2.14** and **2.15** arose from hydrolysis of **2.13**, a report by Cacchi²⁰ suggests that trapping of an acyl-palladium species by an acetate anion and hydrolysis of the resultant anhydride may be another pathway for the formation of **2.14** and **2.15**. Spiroonene **2.14** was a promising compound for further studies owing to the desymmetrized western ring, but this methoxycarbonylation reaction from **2.11** to **2.14** suffered from challenges in reproducibility and purification of the product mixtures. Instead, compound **2.14** could be more reliably accessed by a sequence of initial hydroxycarbonylation (to give **2.16**) using Cacchi's conditions,²⁰ followed by methoxycarbonylation. Compound **2.14** is a useful intermediate in testing the directing

group hypothesis suggested earlier, by allowing us to probe the effects of a strongly coordinating carboxylate²¹ vs. a weakly coordinating²² ester carbonyl group.



Scheme 2.4. (A) Zhu's desymmetrization of cyclopentenones through an asymmetric oxidative Heck reaction. (B) Results of the oxidative Heck reaction of **2.14** using Zhu's conditions.

Following successful functionalization of the western ring, we sought to desymmetrize the eastern ring. We were inspired by a report from Zhu²³ and coworkers in which they accomplished the desymmetrization of cyclopentenones bearing amide directing groups through an oxidative Heck reaction with arylboronic acids (Scheme 2.4A). This desymmetrization was accomplished in high yields and enantiomeric excess (ee's) through the use of pyridine- or quinoline-oxazoline (PyrOx or QuinOx) ligands. While the spatial relationship of the alkene and directing group system of spirononene **2.14** differs from the cyclopentenones used by Zhu, we hypothesized that the reported conditions would suffice as a starting point for further optimization. Importantly, we would be utilizing a carboxylic acid directing group rather than amide, which may be more distal by carbon count but held in relatively close proximity to the alkene due to the topology of the spirocyclic system.

Since the desired cyclopentenyl coupling partner (**2.7** or **2.8**) had not yet been synthesized, we decided to test whether spirononene **2.14** could be a competent coupling partner under the reported conditions with simple phenylboronic acid. Upon treatment of **2.14** with phenylboronic acid and Zhu's oxidative Heck conditions, the expected arylated spirononene product (**2.17**) was indeed isolated in 20% yield as a single diastereomer (Scheme 2.4B). A single crystal of this compound was grown for analysis by x-ray diffraction. Analysis of the resulting crystal structure showed that the newly installed aryl group is positioned "syn" to the carboxylic acid moiety, rather than the ester group. This observation supports for the directing group hypothesis discussed previously. However, alongside the expected product **2.17**, unexpected products (**2.18** and **2.19**) were also isolated. The discovery of these products led to an investigation of new reactivity for spirononene systems, which was studied in a collaborative effort with the Houk group at UCLA. A full report of our studies on the formation of **2.18** and **2.19** is presented in the next chapter.

2.4 Conclusion

Urceoloids A & B (**2.1** & **2.2**) are rearranged steroid natural products which possess a rare spirononatriene core. This core has inspired us to design a synthetic route revolving around the exploration of spirocyclic intermediates. In doing so, we can learn more about their reactivity and study how they may be leveraged in total synthesis. Specifically, on the basis of conditions developed by Jieping Zhu and coworkers,²³ we used a carboxylate directing group to achieve an asymmetric oxidative Heck reaction. In applying these conditions to a reaction of spirononene **2.14** and phenylboronic acid, we did, indeed, observe evidence which supports the use of carboxylates as directing groups in this spirocyclic system. However, we have also discovered new, unexpected reactivity for spirononene **2.14**, which is the subject of interest for the next chapter.

2.5 Experimental Contributors

Project design and development was carried out by Prof. Richmond Sarpong (R.S.) and Karan Goyal (K.G.). Experimentation was largely conducted by K.G with guidance from R.S. Rafael Rippel (R.R.) and Nico Homfeldt (N.H.) assisted with scale-up and reaction optimization with guidance from K.G. and R.S.

2.6 Experimental Information

2.6.1 General Information

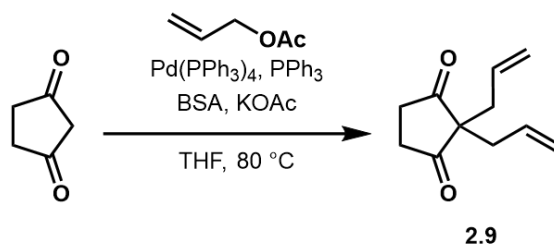
Unless otherwise stated, commercial reagents were purchased and used without purification. Solvents including tetrahydrofuran (THF), diethylether (Et₂O), methanol (MeOH), and benzene (PhH) were dried by passage through activated alumina columns using argon in a Glass Contour solvent purification system. Dichloroethane (DCE, dry and packaged under nitrogen) and dimethylsulfoxide (DMSO, dry and packaged under nitrogen) were used without purification. Dichloromethane (DCM) was freshly distilled over calcium hydride under a N₂ atmosphere. Deuterated solvents were purchased from Cambridge Isotope Laboratories and were used without further purification unless otherwise specified. Deuterated acetic acid was purchased from Sigma Aldrich.

Unless otherwise stated, all reactions were performed in flame-dried or oven-dried glassware under an atmosphere of positive nitrogen pressure using Teflon-coated stir bars. Air and moisture-sensitive liquids were transferred via syringe through rubber septa. Solids were added under inert gas or were dissolved in the appropriate solvent and added via syringe and needle. Reactions ran above room temperature (20–25 °C) were heated in a metal block or oil bath with a thermocouple. Low temperature reactions were carried out in a Dewar flask filled with isopropanol/dry ice (–78 °C) or water/ice (0 °C). Organic solutions were concentrated under reduced pressure on an IKA temperature-controlled rotary evaporator equipped with a dry ice/isopropanol condenser. Reaction progress was monitored by thin layer chromatography (TLC). TLC and preparative TLC were performed on glass-backed Silicycle SiliaPlate 250 µm thickness, 60 Å porosity F-254 precoated plates. Flash column chromatography was performed with either glass columns using Silicycle silica gel (40– 63 µm particle size) or with a Yamazen Smart Flash EPCLC W-Prep 2XY (dual channel) automated flash chromatography system on prefilled, premium, universal columns using ACS grade solvents. Compounds were visualized with UV light (254 nm) and stained with aqueous potassium permanganate (KMnO₄) or *p*-anisaldehyde and heat.

NMR spectral data were obtained using deuterated solvents, obtained from Cambridge Isotope Laboratories, Inc. ¹H NMR, proton-decoupled ¹³C NMR, and ¹⁹F NMR data were recorded on Bruker AV-300, AVQ-400, AVB-400, NEO-500, AV-600 and AV-700 spectrometers using CDCl₃ as solvent at 20–23 °C. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal (δ 7.26 for ¹H NMR & δ 77.16 for ¹³C NMR in CDCl₃). Data for ¹H, ¹³C, and ¹⁹F spectroscopy are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent), coupling constant (Hz), integration. All raw FID files were processed, and the spectra analyzed, using the program MestReNOVA 11.0 from Mestrelab Research S. L. High-resolution mass spectra (HRMS) were obtained from the Mass Spectral Facility at the University of California, Berkeley, on a Finnigan/Thermo LTQ-FT instrument (ESI). Data acquisition and processing were performed using the Xcalibur™ software. Chiral HPLC analysis was conducted using a Waters Alliance e2695

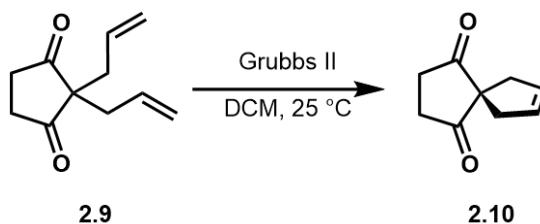
Separations Module equipped with ChiralPak® columns. Data was processed and analyzed using Empower®3 software. HPLC grade isopropanol (IPA) and hexanes were used for HPLC analysis.

2.6.2 Experimental Procedures and Characterization Data



2,2-Diallylcyclopentane-1,3-dione (2.9): This procedure was adapted from Poli et. al.¹⁴ To a flame-dried two-neck flask equipped with a stir bar was added 1,3-cyclopentanone (10.0 g, 102 mmol, 1.0 equiv) and THF (255 mL, 0.4 M). One neck of the flask was sealed with a septum and the other was fitted with a septum-sealed reflux condenser under a N₂ atmosphere. Allyl acetate (23.1 mL, 214 mmol, 2.1 equiv) and bis-trimethylsilyl acetamide (BSA, 24.9 mL, 102 mmol, 1.0 equiv) were then added by syringe. The septum was removed and the following solid reagents were quickly added before re-capping the flask: oven-dried KOAc (1.00 g, 10.2 mmol, 0.10 equiv), Pd(PPh₃)₄ (11.8 g, 10.2 mmol, 0.10 equiv), and then PPh₃ (2.67 g, 10.2 mmol, 0.10 equiv). The reaction mixture was stirred at reflux (heating to 70 °C) for 22 h, then cooled to room temperature, quenched with sat. aq. NH₄Cl (50 mL), and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na₂SO₄, filtered, and then concentrated under reduced pressure to afford the crude product as a brown oil. This oil was then purified by silica gel flash column chromatography (5–15% EtOAc/hexanes gradient) to afford **2.9** (13.1 g, 72%) as a yellow oil. The ¹H NMR spectrum was consistent with results reported in the literature.¹⁵

¹H NMR: (300 MHz, CDCl₃) δ 5.55 (ddt, J = 17.2, 9.7, 7.5 Hz, 2H), 5.12 – 4.99 (m, 4H), 2.62 (s, 4H), 2.37 (dt, J = 7.5, 1.0 Hz, 4H).



Spiro[4.4]non-7-ene-1,4-dione (2.10): This procedure was adapted from a report in the literature.¹³ To a flame-dried flask equipped with a stir bar was added diallylated diketone **2.9** (13.1 g, 73.4 mmol, 1.0 equiv), DCM (223 mL, 0.33M), and Grubbs' G2 catalyst (312

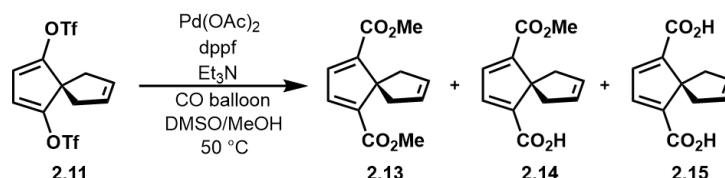
Characterization data for **4-oxospiro[4.4]nona-1,7-dien-1-yl trifluoromethanesulfonate (2.12)**

¹H NMR (500 MHz, CDCl₃) δ 5.92 (t, J = 2.4 Hz, 1H), 5.67 – 5.63 (m, 2H), 3.14 (dd, J = 2.6, 1.0 Hz, 2H), 2.75 – 2.56 (m, 4H).

¹³C NMR (126 MHz, CDCl₃) δ 212.9, 151.7, 128.1, 118.57 (q, J = 320.4 Hz), 109.9, 56.9, 41.2, 41.0.

¹⁹F NMR (471 MHz, CDCl₃) δ –73.57.

HRMS (EI): Calcd for ([M], C₁₀H₉F₃O₄S)⁺: m/z= 282.0168, found 282.0175



dimethyl spiro[4.4]nona-1,3,7-triene-1,4-dicarboxylate (2.13) and **4-(methoxycarbonyl)spiro[4.4]nona-1,3,7-triene-1-carboxylic acid (2.14)** and **spiro[4.4]nona-1,3,7-triene-1,4-dicarboxylic acid (2.15)**: This procedure was adapted from a report in the literature.¹⁹ To a flame-dried vial with a stir bar was added **2.11** (1.82 g, 4.39 mmol, 1 equiv), Pd(OAc)₂ (197 mg, 0.88 mmol, 0.2 equiv), and dppf (487 mg, 0.88 mmol, 0.2 equiv). To this mixture was added DMSO (35 mL, 0.13 M), MeOH (23 mL, 0.19 M), and Et₃N (1.2 mL, 8.8 mmol, 2 equiv). The resulting solution was sparged with a CO balloon for 5 mins and then stirred at 50 °C for 12 h. 1 M HCl (100 mL) was then added, and the resulting mixture was filtered through a celite pad. The filtrate was transferred to a separatory funnel and extracted with Et₂O (3 x 100 mL). The organic layers were combined and washed with brine (3 x 100 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (20% EtOAc/2% AcOH/hexanes to 30% EtOAc/2% AcOH/hexanes) to give diester **2.13** (141 mg, 14%) as a pale-brown solid, ester-acid **2.14** (402 mg, 42%) as an off-white solid, and diacid **2.15** (73 mg, 8%) as pale-brown solid. While this procedure led to the initial synthesis of these compounds, it gave irreproducible yields and was not used, in favor of the two-step procedure reported below.

Characterization data for **dimethyl spiro[4.4]nona-1,3,7-triene-1,4-dicarboxylate (2.13)**:

¹H NMR (400 MHz, CDCl₃) δ 7.18 (s, 2H), 5.88 (s, 2H), 3.77 (s, 6H), 2.73 (s, 4H).

¹³C NMR (126 MHz, CDCl₃) δ 163.4, 152.7, 137.6, 129.5, 59.4, 51.6, 38.9.

HRMS (ESI): Calcd for ([M+Na], C₁₃H₁₄O₄Na)⁺: m/z= 257.0784, found 257.0784

Characterization data for **4-(methoxycarbonyl)spiro[4.4]nona-1,3,7-triene-1-carboxylic acid (2.14)**:

¹H NMR (500 MHz, CDCl₃) δ 7.33 (d, *J* = 2.5 Hz, 1H), 7.19 (d, *J* = 2.5 Hz, 1H), 5.87 (s, 2H), 3.78 (s, 3H), 2.82 – 2.70 (m, 4H).

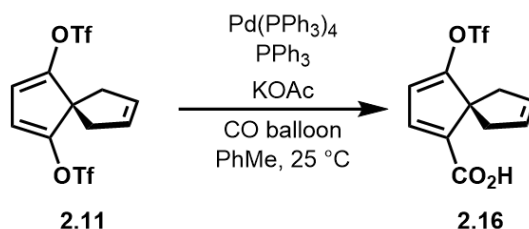
¹³C NMR (126 MHz, CDCl₃) δ 167.8, 163.3, 154.0, 151.8, 140.3, 137.3, 129.5, 59.3, 51.7, 38.7.

HRMS (ESI): Calcd for ([M-H], C₁₂H₁₁O₄)⁻: *m/z* = 219.0663, found 219.0664

Characterization data for **spiro[4.4]nona-1,3,7-triene-1,4-dicarboxylic acid (2.15)**:

¹H NMR (500 MHz, MeOD) δ 7.18 (s, 2H), 5.77 (s, 1H), 2.72 (s, 2H).

¹³C NMR (126 MHz, H₂O+D₂O_salt) δ 166.1, 154.8, 138.9, 130.3, 60.3, 39.6.



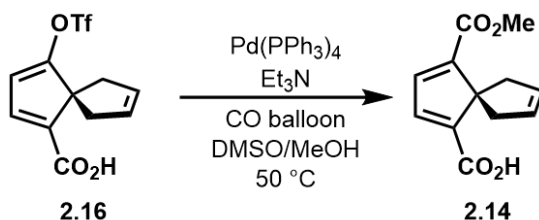
4-(((trifluoromethyl)sulfonyl)oxy)spiro[4.4]nona-1,3,7-triene-1-carboxylic acid (2.16): This procedure was adapted from a report in the literature.²⁰ To a flame-dried flask with a stir bar was added **2.11** (10.0 g, 24.1 mmol, 1.0 equiv), which was dissolved in toluene (142 mL, 0.17 M). To this solution was added oven-dried KOAc (2.6 g, 26.6 mmol, 1.1 equiv), PPh₃ (1.3 g, 4.8 mmol, 0.2 equiv), and Pd(PPh₃)₄ (1.4 g, 1.2 mmol, 0.05 equiv). The mixture was sparged with a CO balloon and the reaction mixture was stirred under a continuously sparging CO atmosphere at 25 °C. The balloon was refilled with CO as needed throughout the duration of the reaction. Reaction progress was monitored by ¹H NMR analysis of aliquots of the reaction mixture which were worked up. At the following varying time points, additional Pd(PPh₃)₄ was added to the reaction mixture and it was allowed to continue stirring under continuous CO sparging: 21 h (450 mg, 0.4 mmol, 0.33 equiv added), 43 h (950 mg, 0.8 mmol, 0.67 equiv added). After 75 h of total reaction time, the mixture was diluted with Et₂O (50 mL) and poured into a separatory funnel containing ice. The mixture was acidified to pH=1 with 1M HCl, and extracted with Et₂O (5 x 100 mL). The organic layers were combined, washed with brine (3 x 100 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (15% EtOAc/2% AcOH/hexanes) to give 4.3 g (58%) of **2.16** as a pale-yellow solid.

¹H NMR (600 MHz, CDCl₃) δ 7.32 (d, *J* = 2.9 Hz, 1H), 6.14 (d, *J* = 2.9 Hz, 1H), 5.82 (s, 2H), 3.04 (d, *J* = 14.9 Hz, 2H), 2.53 (d, *J* = 14.5 Hz, 1H).

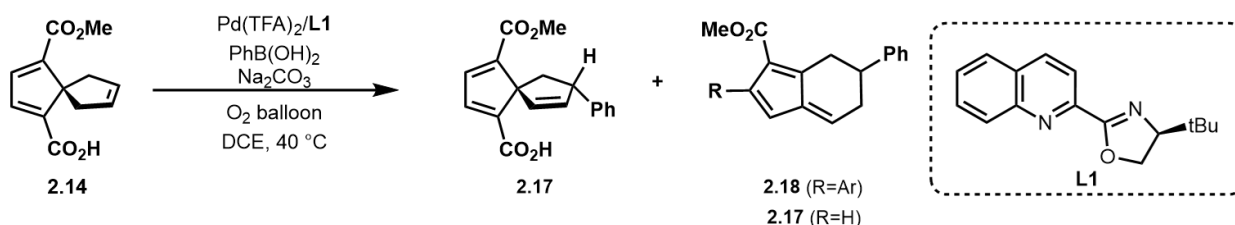
^{13}C NMR (151 MHz, CDCl_3) δ 167.6, 166.4, 141.3, 138.0, 129.3, 118.60 (q, $J = 320.7$ Hz), 110.9, 57.9, 37.5.

^{19}F NMR (470 MHz, CDCl_3) δ -73.28 (s).

HRMS (ESI): Calcd for $([\text{M}-\text{H}], \text{C}_{11}\text{H}_8\text{F}_3\text{O}_5\text{S})^-$: $m/z = 309.0050$, found 309.0051

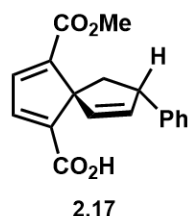


4-(methoxycarbonyl)spiro[4.4]nona-1,3,7-triene-1-carboxylic acid (2.14): This procedure was adapted from the literature.²⁴ To a flame-dried flask with a stir bar was added **2.16** (720 mg, 2.32 mmol, 1.0 equiv) under air, which was dissolved in DMSO (62.8 mL, 0.037 M) and MeOH (113 mL, 0.021 M). Et_3N (0.97 mL, 3.90 mmol, 3 equiv) was then added, followed by $\text{Pd}(\text{PPh}_3)_4$ (134 mg, 0.116 mmol, 0.05 equiv). The mixture was sparged with CO for 5 min and then stirred under a CO atmosphere at 50 °C for 4 h. The reaction mixture was cooled to 25 °C and then poured into a separatory funnel with ice. The mixture was acidified to pH=1 with 1M HCl and extracted with Et_2O (3 x 100 mL). The organic layers were combined, washed with brine (3 x 50 mL), dried over Mg_2SO_4 , filtered, and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (20% EtOAc /2% AcOH /hexanes) to give 419 mg (82%) of **2.14** as a white to off-white solid. A single crystal of **2.14** was grown by slow evaporation from a solution in 30% EtOAc /hexanes. See above for complete characterization data.



The rearrangement of spirononatrienes to annulated fulvenes was initially discovered by application of Zhu's conditions to **2.14**.²³ To a flame-dried vial equipped with a stir bar was added Pd(II) trifluoroacetate ($\text{Pd}(\text{TFA})_2$, 0.10 equiv), **L1** (0.10 equiv), and DCE (0.90 mL, 0.05 M). The vial was sealed with a septum cap and the mixture was stirred at 25 °C for 30 min. Sequentially, spirononatriene **2.14** (10.0 mg, 0.045 mmol, 1.0 equiv), $\text{PhB}(\text{OH})_2$ (6.6 mg, 0.054 mmol, 1.2 equiv), and Na_2CO_3 (9.6 mg, 0.091 mmol, 2.0 equiv) were added and, then the mixture was sparged with an O_2 balloon for 2 min. The reaction mixture was stirred under an O_2 atmosphere at 40 °C for 23 h, then cooled to 25 °C and filtered through a celite pad, eluting with DCM. The mixture was concentrated under reduced pressure

and purified by preparatory TLC (95% DCM/hexanes) to give 3.3 mg (29%) of diaryl fulvene **2.18** as an orange solid (79:21 er) and 0.7 mg of monoaryl fulvene **2.19** as a yellow solid (5%). A mixture of starting material **2.14** and arylated product **2.17** were isolated from the baseline band and separated through an additional preparatory TLC plate (35% EtOAc/2% AcOH/hexanes). This gave 2.8 mg of **2.17** (20%) as an off-white powder.



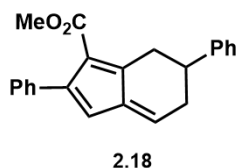
Characterization data for **4-(methoxycarbonyl)-8-phenylspiro[4.4]nona-1,3,6-triene-1-carboxylic acid (2.16)**:

¹H NMR (600 MHz, CDCl₃) δ 7.50 – 7.47 (m, 2H), 7.44 (d, *J* = 2.5 Hz, 1H), 7.31 (td, *J* = 7.7, 3.0 Hz, 2H), 7.25 (d, *J* = 2.5 Hz, 1H), 7.22 – 7.17 (m, 1H), 6.18 (dt, *J* = 5.4, 2.1 Hz, 1H), 5.22 (ddd, *J* = 4.7, 2.7, 1.8 Hz, 1H), 4.68 (tt, *J* = 8.3, 2.4 Hz, 1H), 3.83 (s, 3H), 2.63 – 2.53 (m, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 167.1, 163.2, 151.3, 148.5, 148.5, 145.5, 141.7, 141.6, 140.3, 140.3, 138.4, 129.7, 129.7, 128.6, 128.4, 126.5, 69.7, 53.9, 51.7, 38.6.

HRMS (ESI): Calcd for ([M+Na], C₁₈H₁₆O₂Na)⁺: *m/z* = 319.0941, found 319.0939

Note: a single crystal of **2.17** was grown by slow evaporation from a solution in DCM.



Characterization data for **methyl 2,5-diphenyl-5,6-dihydro-4H-indene-3-carboxylate (2.17)**:

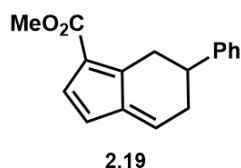
¹H NMR (500 MHz, CDCl₃) δ 7.41 – 7.35 (m, 4H), 7.35 – 7.32 (m, 4H), 7.31 – 7.27 (m, 2H), 7.01 (dd, *J* = 6.0, 3.0 Hz, 1H), 6.20 (s, 1H), 3.68 (s, 3H), 3.51 (ddd, *J* = 17.5, 4.3, 1.1 Hz, 1H), 3.29 – 3.19 (m, 1H), 2.90 (dd, *J* = 17.5, 13.0 Hz, 1H), 2.81 (dt, *J* = 19.5, 5.4 Hz, 1H), 2.73 (ddd, *J* = 19.5, 10.9, 3.0 Hz, 1H).

^{13}C NMR (151 MHz, CDCl_3) δ 165.9, 147.1, 144.7, 143.8, 143.7, 142.9, 136.8, 128.8, 128.0, 127.8, 127.4, 127.3, 127.2, 127.0, 118.5, 51.2, 43.4, 35.1, 32.4.

HRMS (EI): Calcd for $([\text{M}], \text{C}_{23}\text{H}_{20}\text{O}_2)^+$: m/z = 328.1458, found 328.1460

Chiral HPLC data: AD3 chiral column, 1% IPA/hexanes 2 mL/min, $t_R(\text{minor})$ = 11.9 min, $t_R(\text{major})$ = 14.1 min, λ = 254 nm

Note: a single crystal of **2.18** was grown by slow evaporation from a solution in THF.



Characterization data for **methyl 5-phenyl-5,6-dihydro-4H-indene-3-carboxylate (2.18)**:

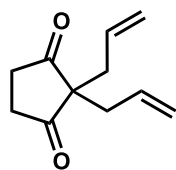
^1H NMR (500 MHz, CDCl_3) δ 7.37 – 7.27 (m, 5H), 7.01 (dd, J = 6.0, 2.9 Hz, 1H), 6.80 (d, J = 5.4 Hz, 1H), 6.17 (dd, J = 5.3, 1.0 Hz, 1H), 3.78 (s, 3H), 3.60 (ddd, J = 17.8, 4.4, 1.0 Hz, 1H), 3.20 (ddt, J = 12.9, 10.8, 4.4 Hz, 1H), 2.86 (dd, J = 17.8, 12.9 Hz, 1H), 2.79 (dt, J = 19.2, 5.3 Hz, 1H), 2.69 (ddd, J = 19.4, 10.9, 2.9 Hz, 1H).

^{13}C NMR (126 MHz, CDCl_3) δ 165.6, 145.5, 144.7, 143.7, 143.1, 132.5, 128.7, 127.3, 127.2, 126.9, 119.5, 51.3, 43.4, 35.0, 32.2.

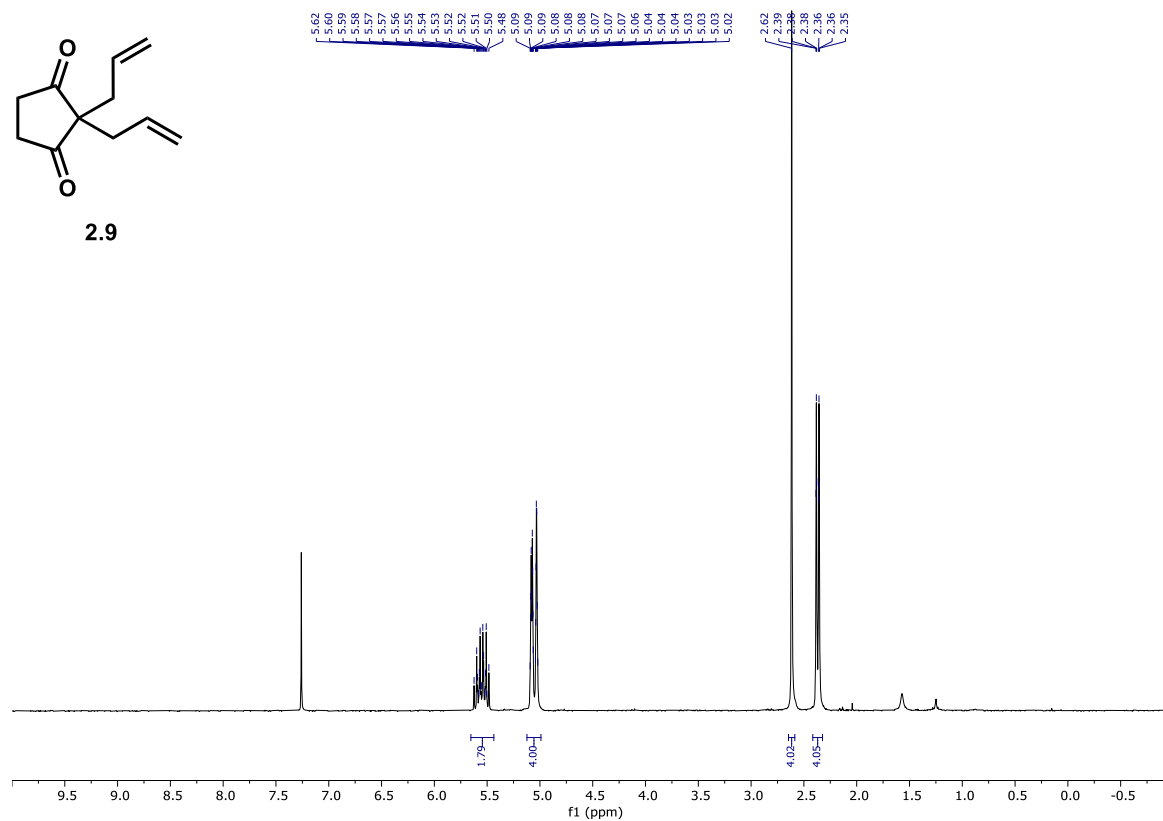
HRMS (EI): Calcd for $([\text{M}], \text{C}_{17}\text{H}_{16}\text{O}_2)^+$: m/z = 252.1145, found 252.1151

2.6.3 NMR Spectra

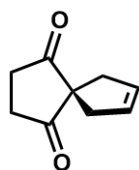
^1H NMR (300 MHz, CDCl_3)



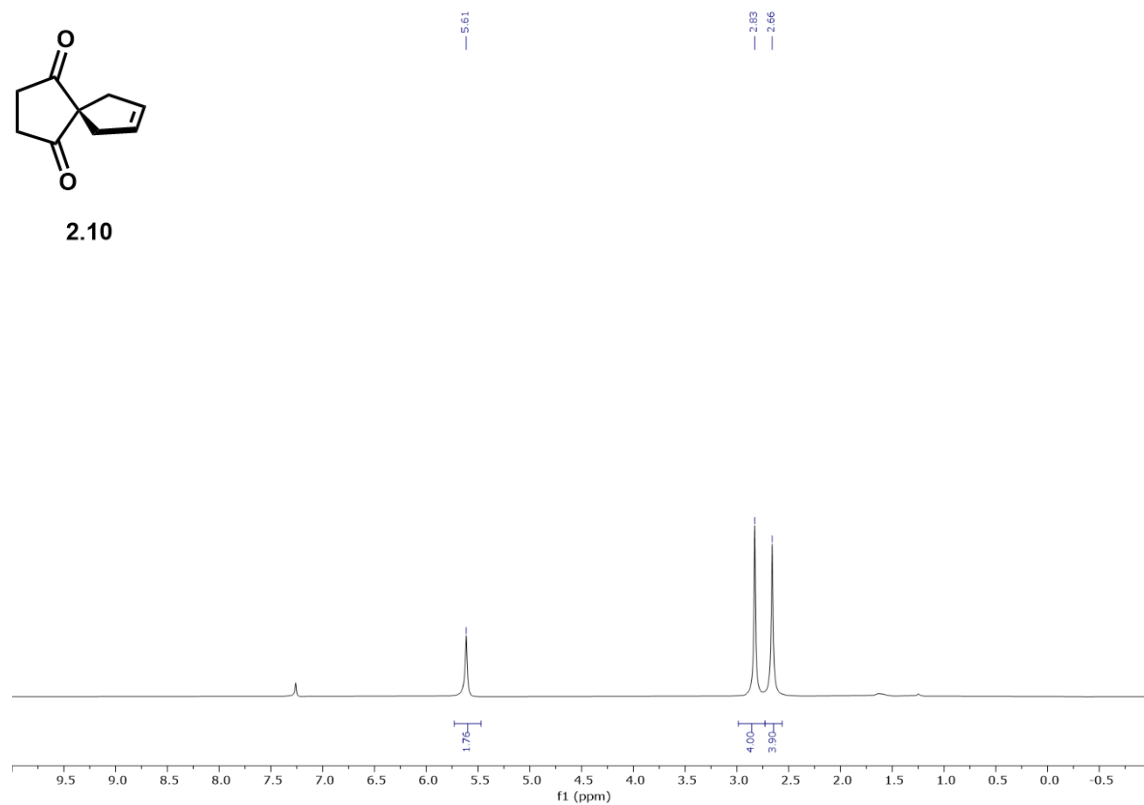
2.9



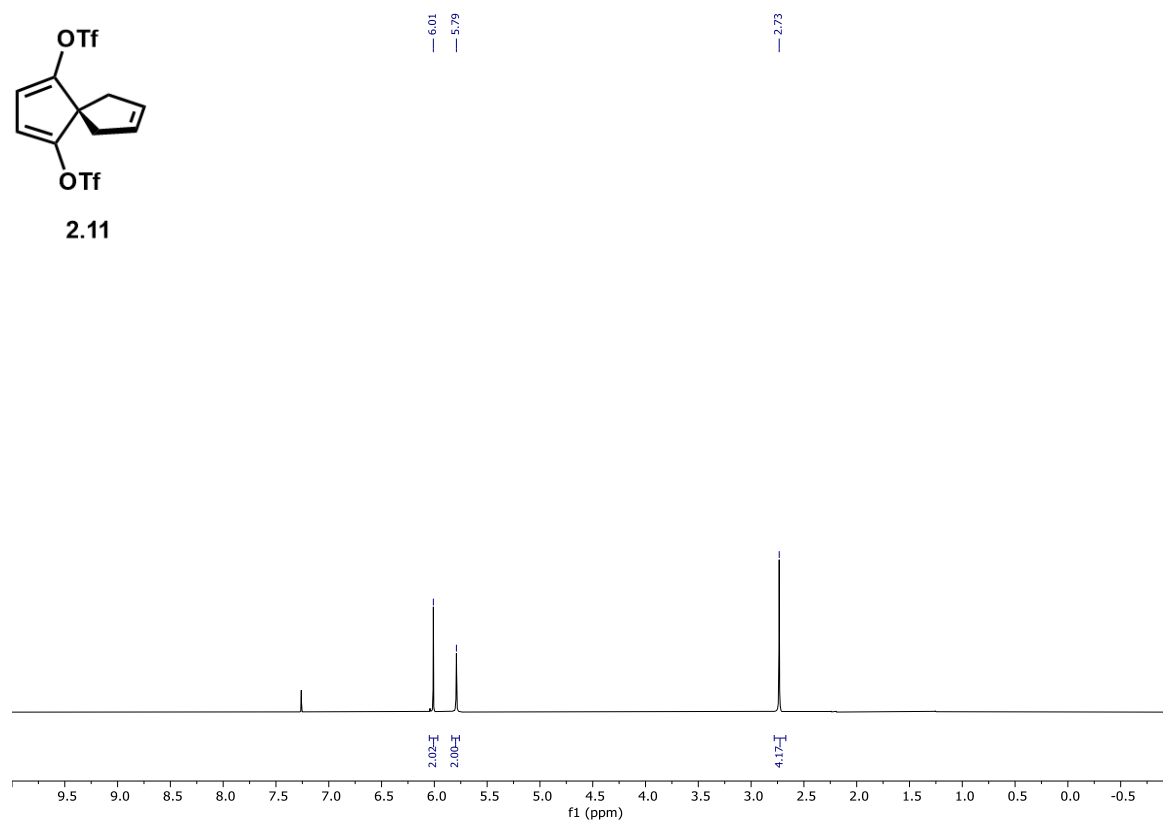
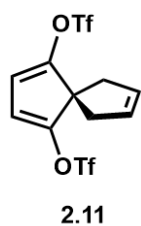
^1H NMR (300 MHz, CDCl_3)



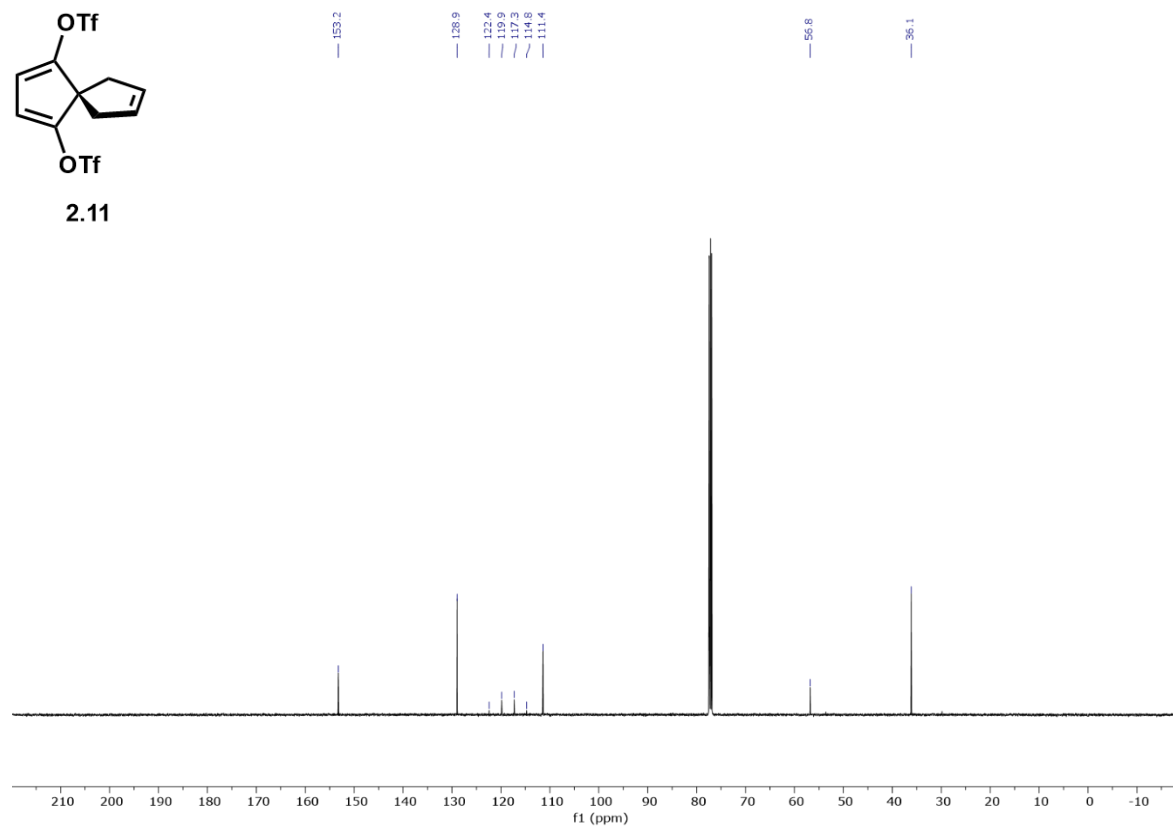
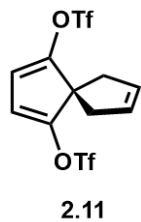
2.10



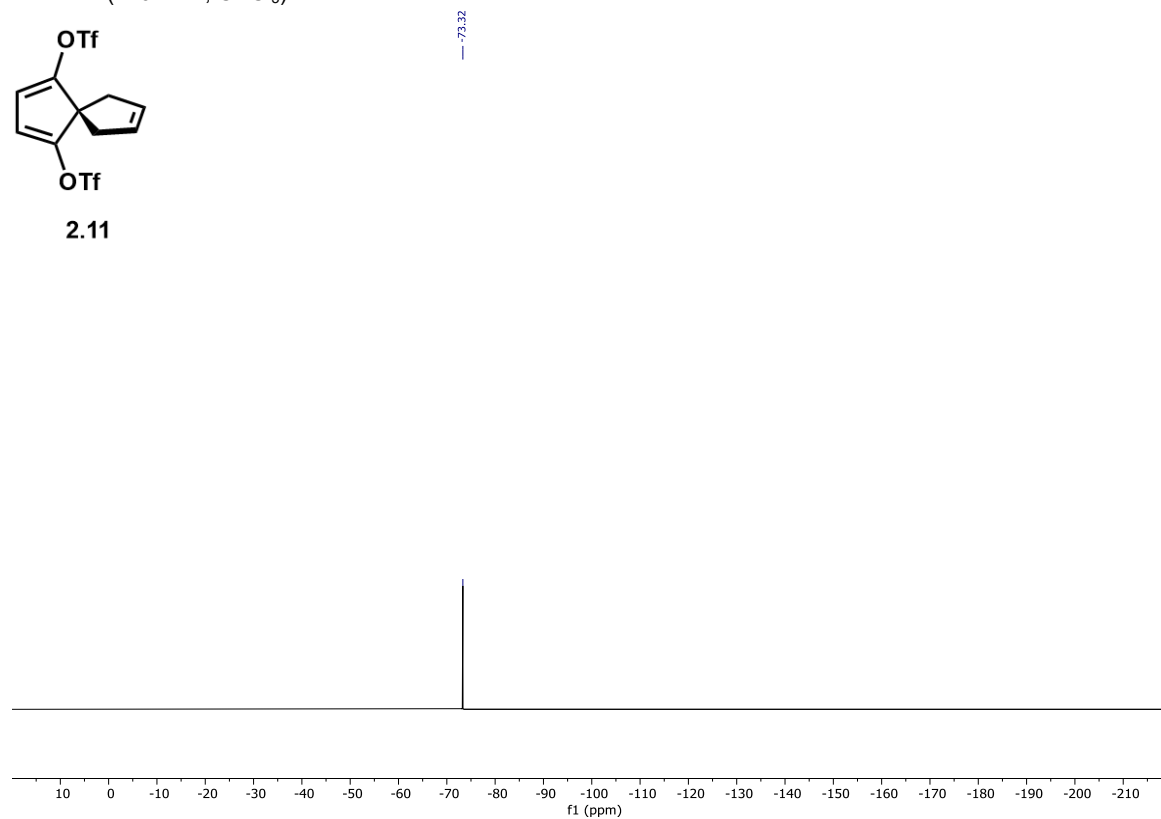
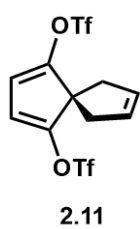
¹H NMR (500 MHz, CDCl₃)



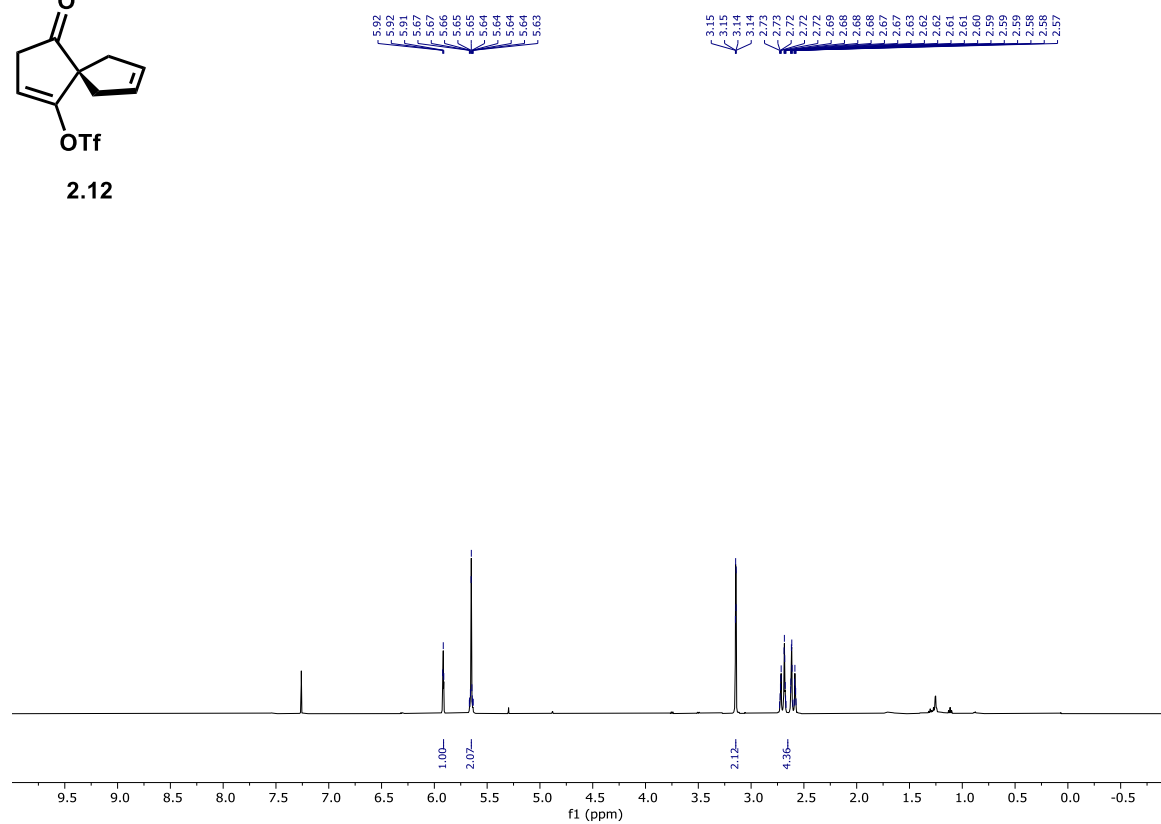
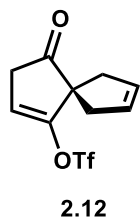
¹³C NMR (126 MHz, CDCl₃)



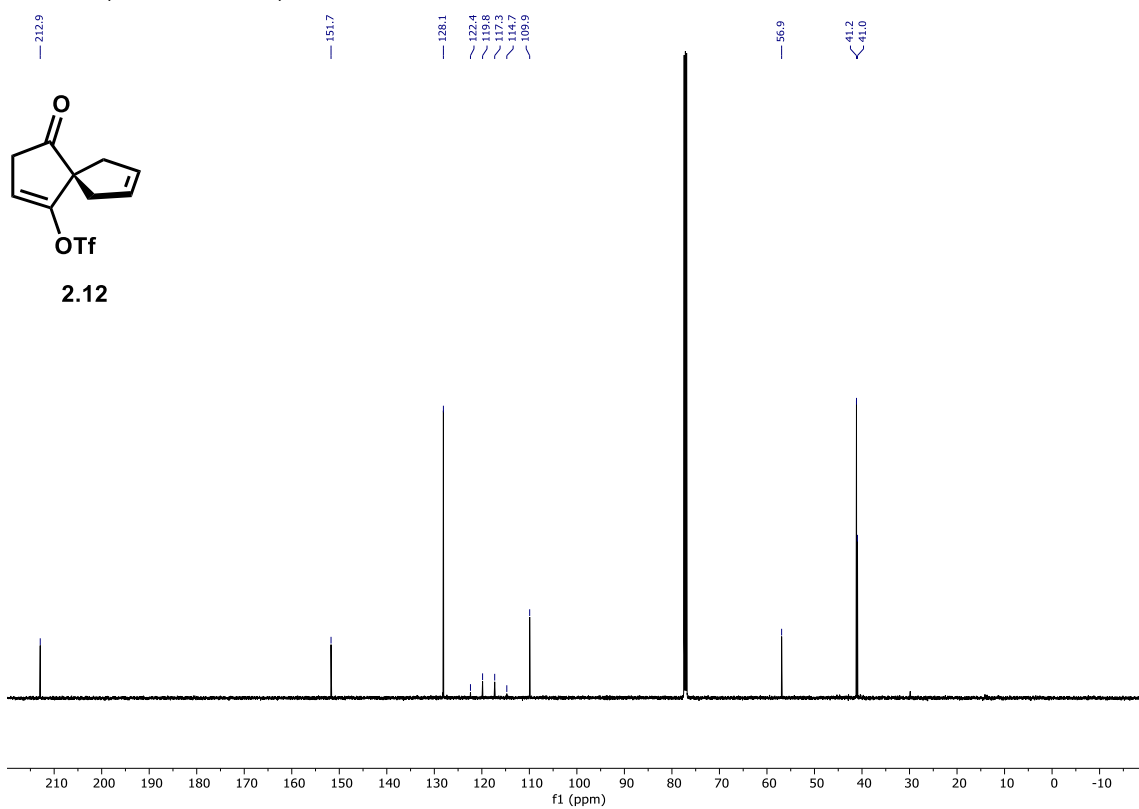
^{19}F NMR (470 MHz, CDCl_3)



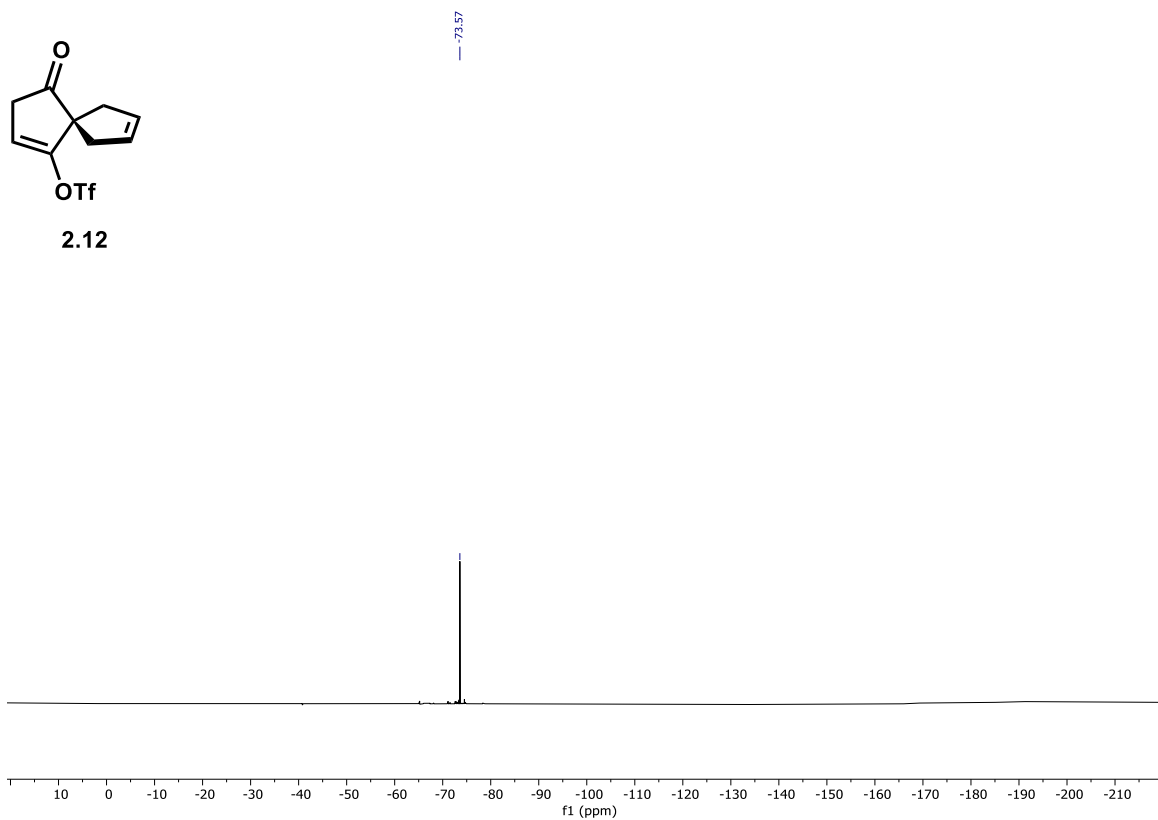
^1H NMR (500 MHz, CDCl_3)



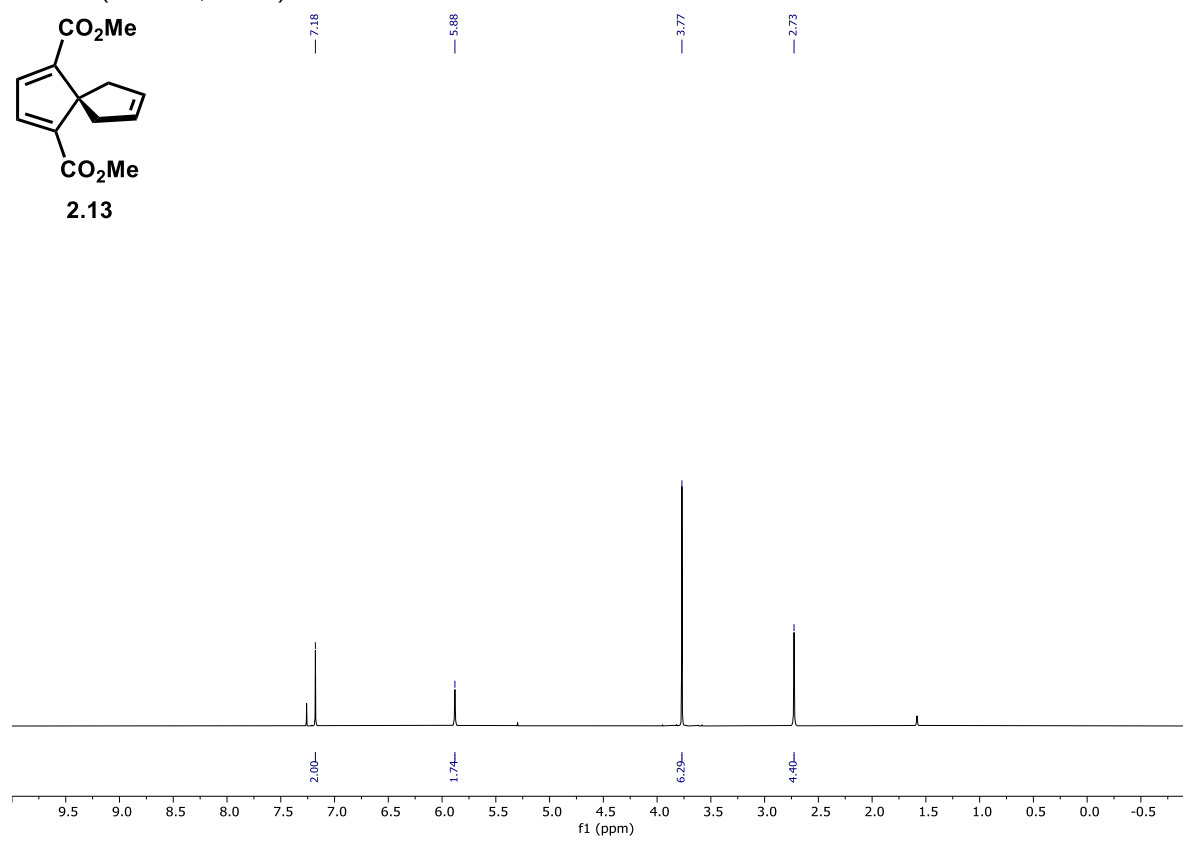
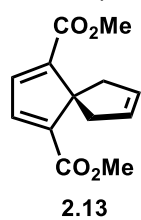
^{13}C NMR (126 MHz, CDCl_3)



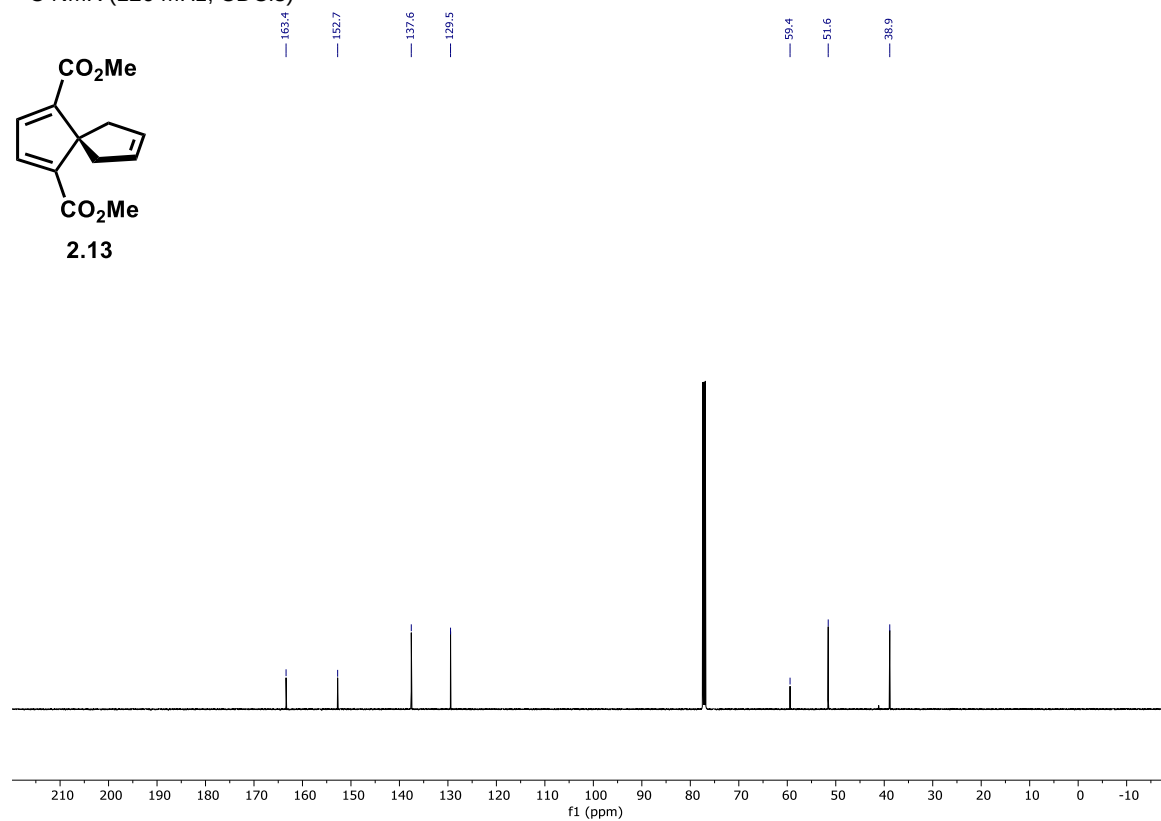
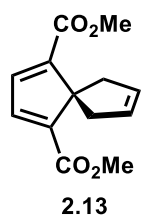
^{19}F NMR (470 MHz, CDCl_3)



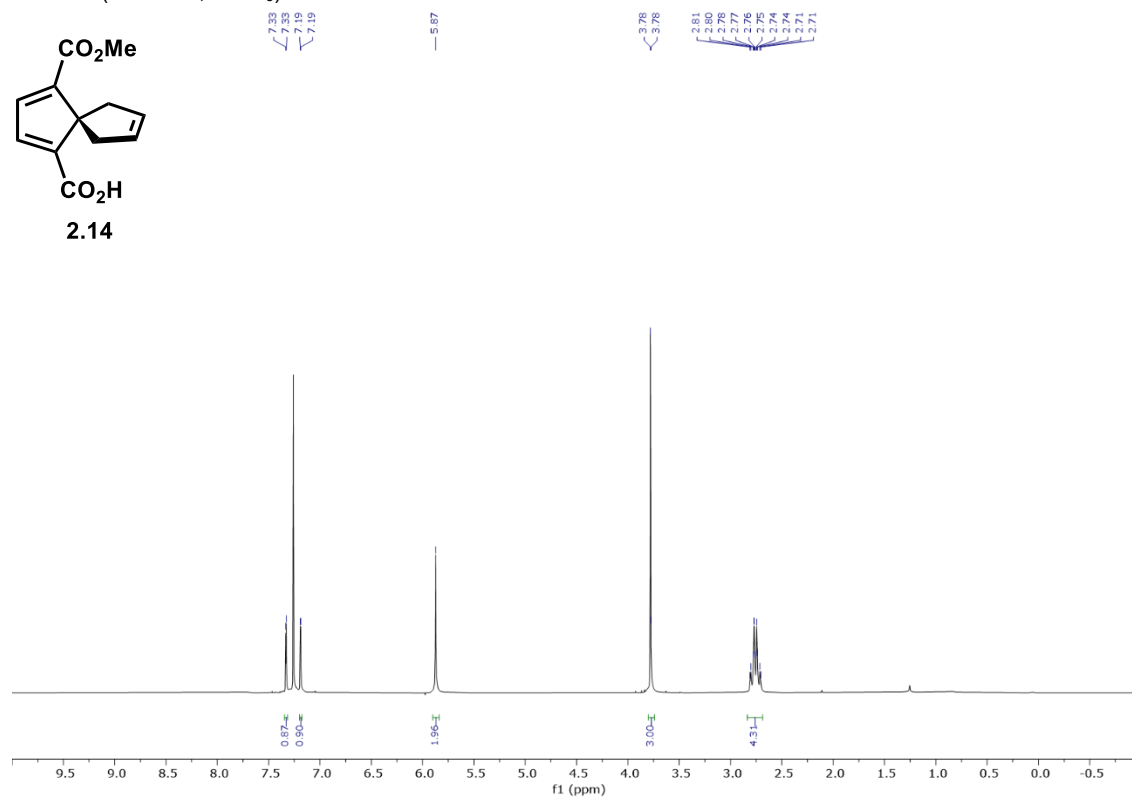
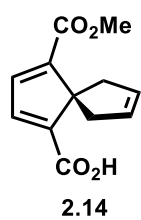
^1H NMR (400 MHz, CDCl_3)



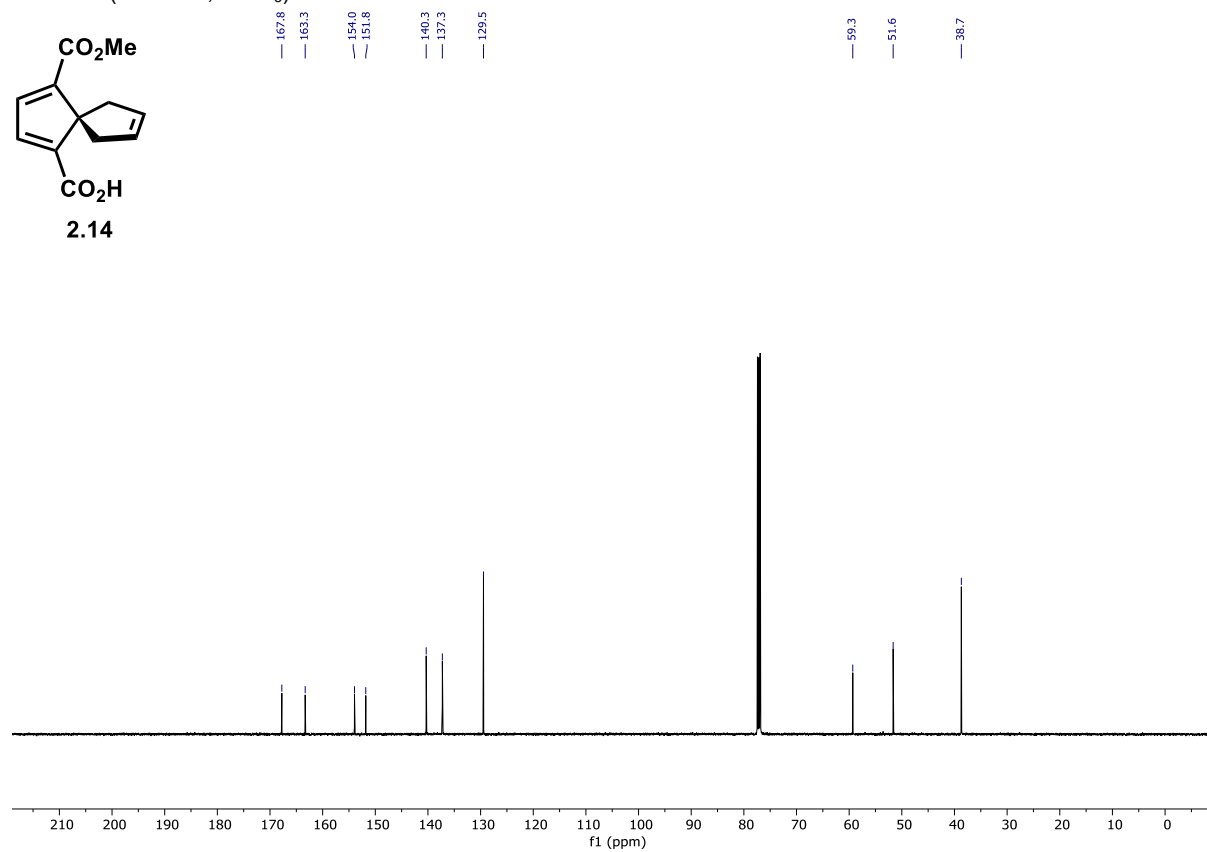
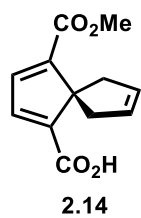
^{13}C NMR (126 MHz, CDCl_3)



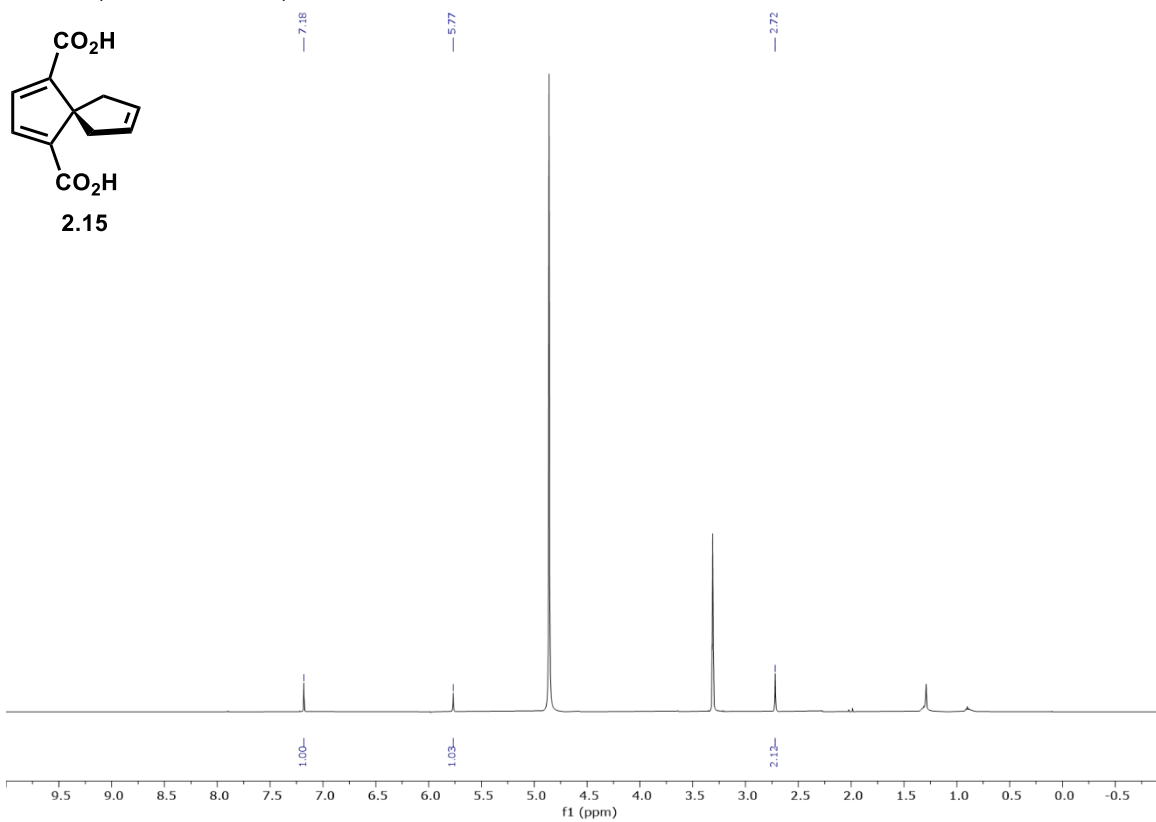
^1H NMR (500 MHz, CDCl_3)



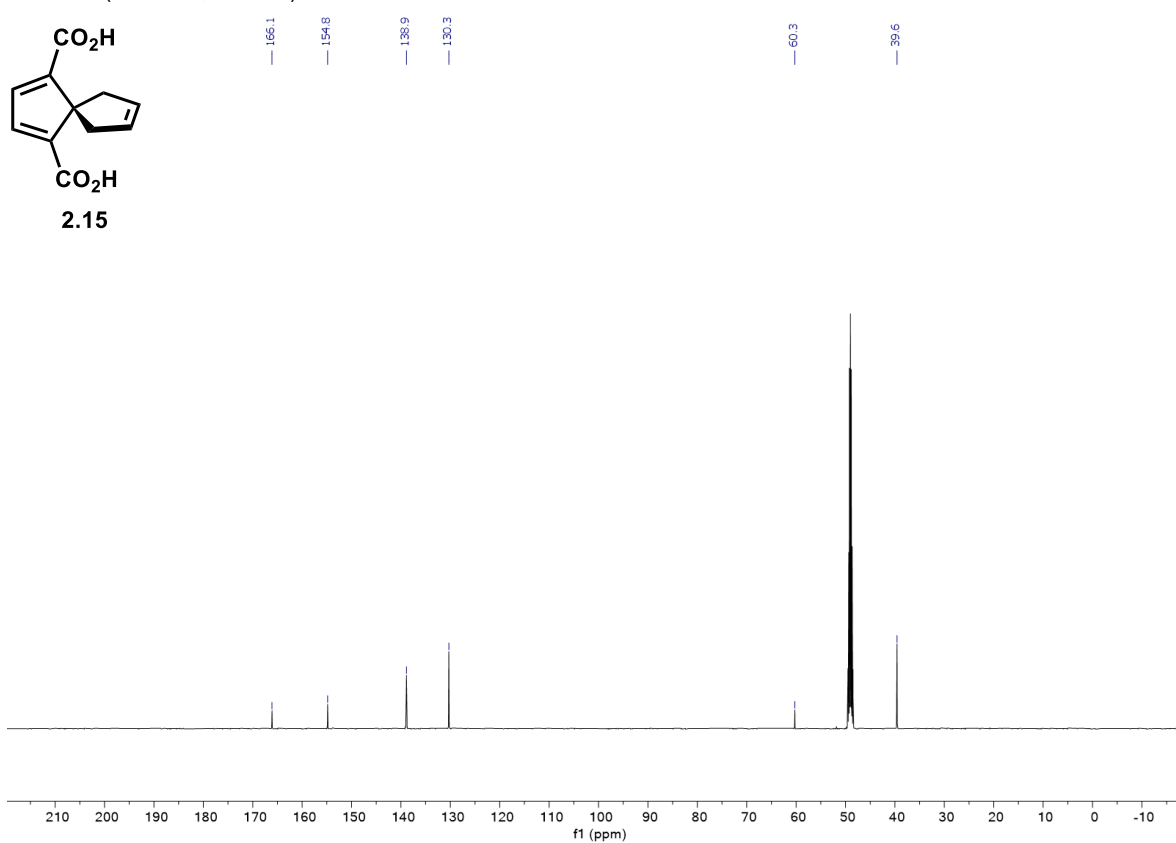
^{13}C NMR (126 MHz, CDCl_3)



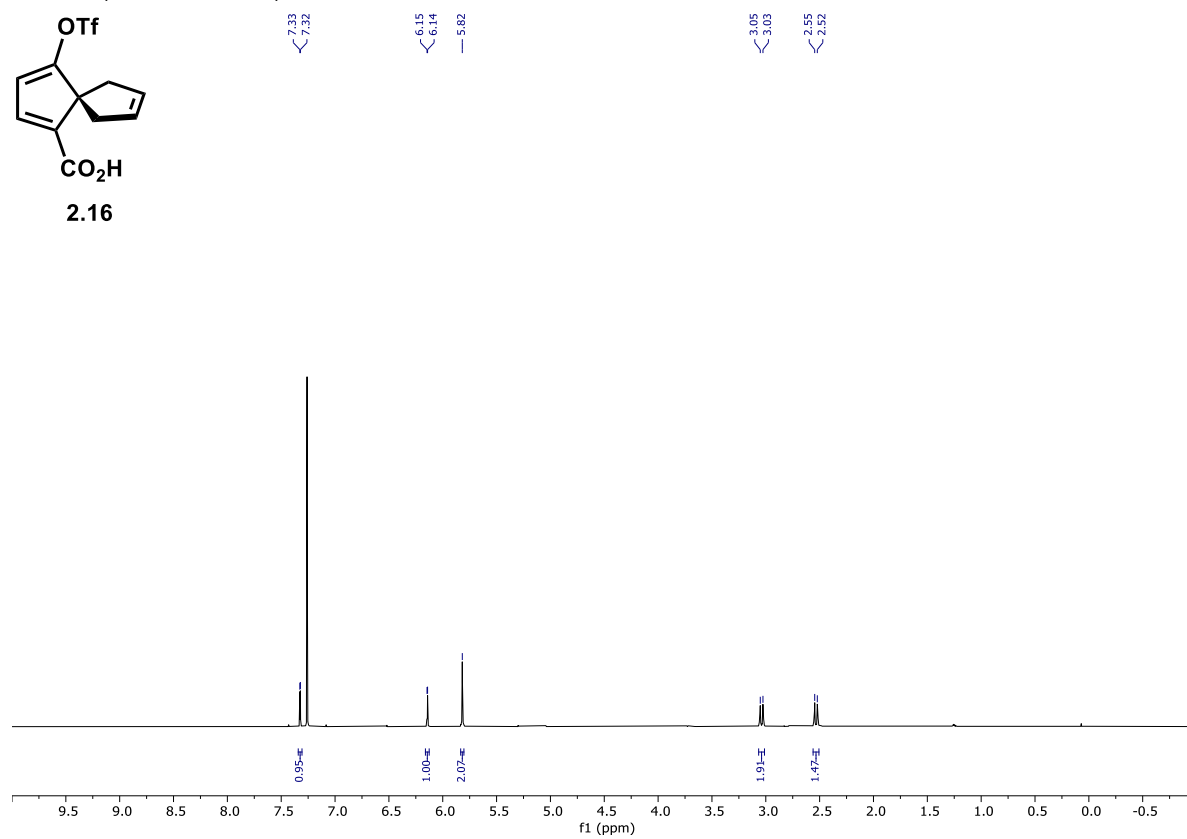
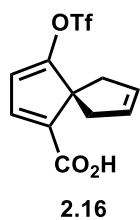
^1H NMR (500 MHz, CD_3OD)



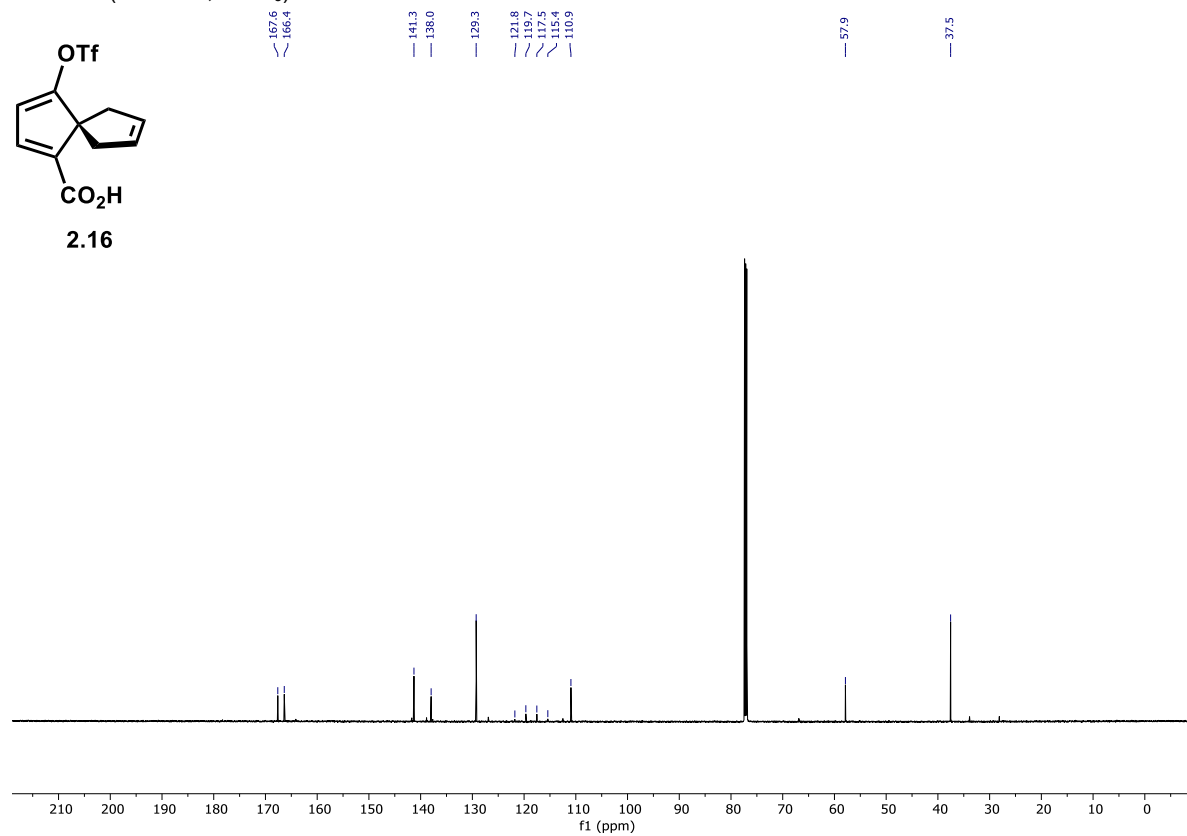
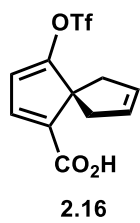
^{13}C NMR (500 MHz, CD_3OD)



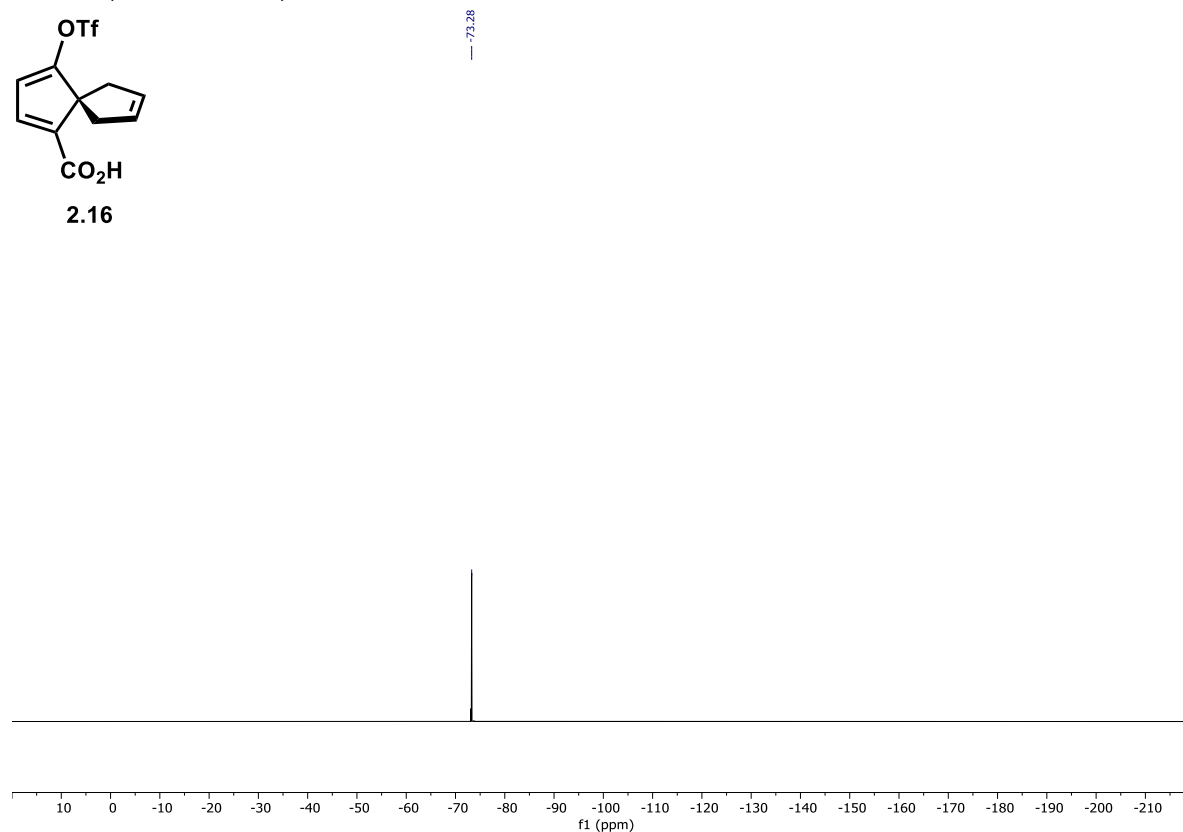
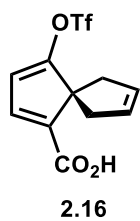
^1H NMR (600 MHz, CDCl_3)



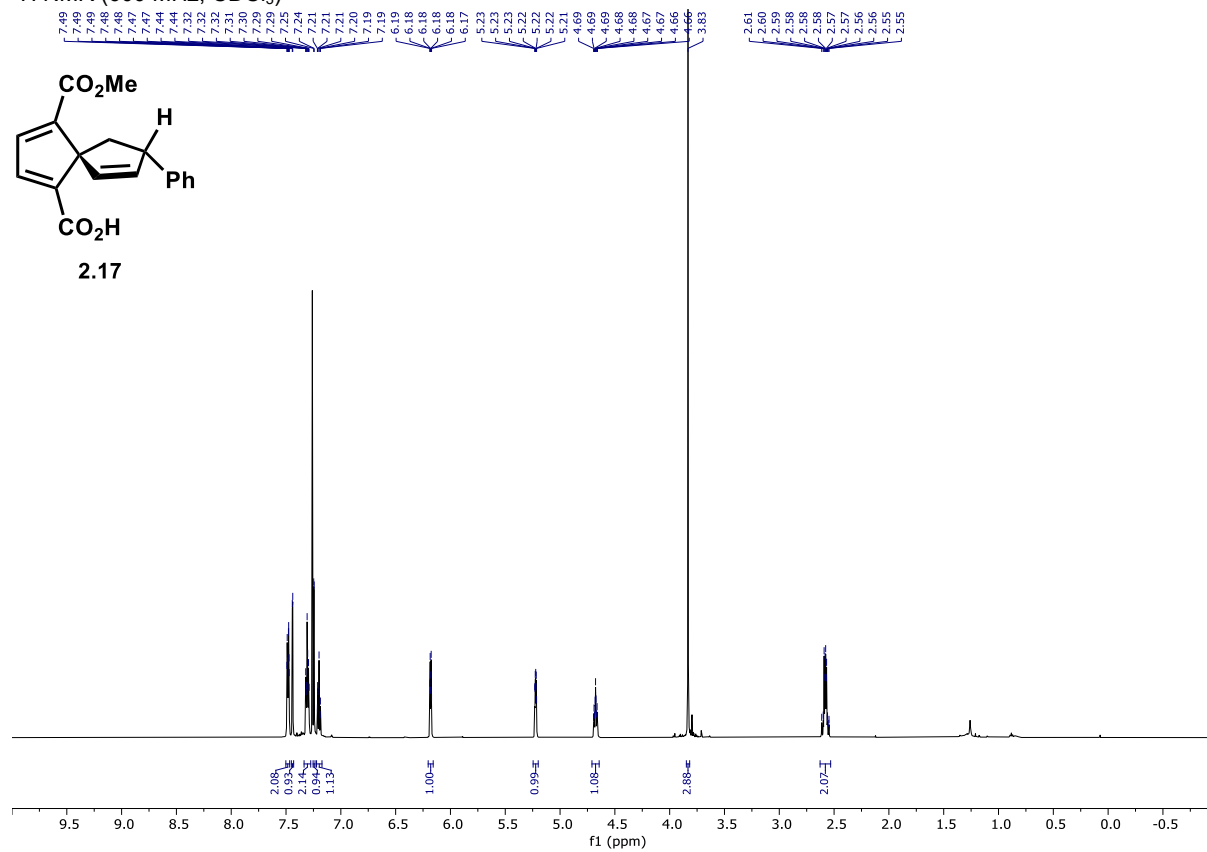
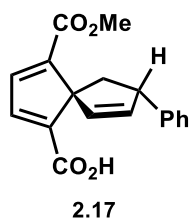
^{13}C NMR (151 MHz, CDCl_3)



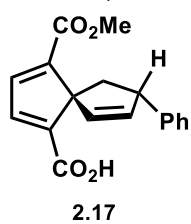
^{19}F NMR (470 MHz, CDCl_3)



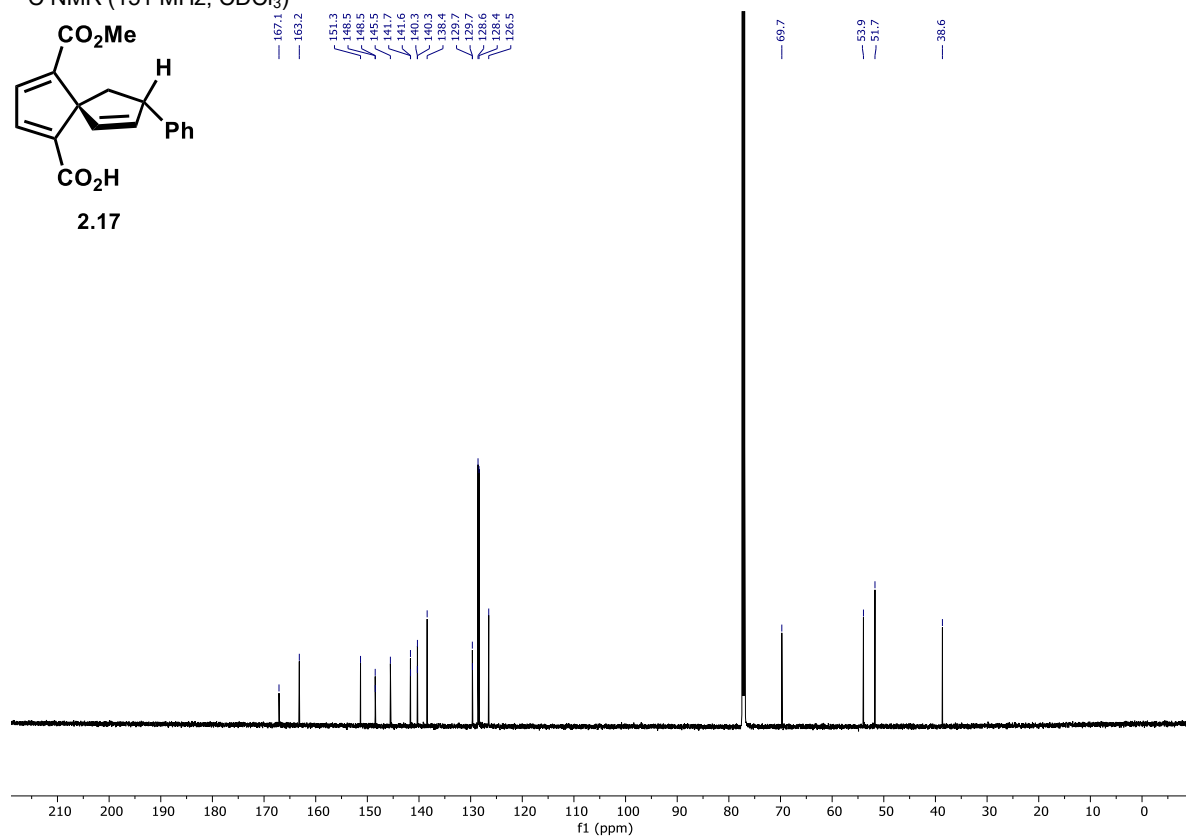
^1H NMR (600 MHz, CDCl_3)



¹³C NMR (151 MHz, CDCl₃)

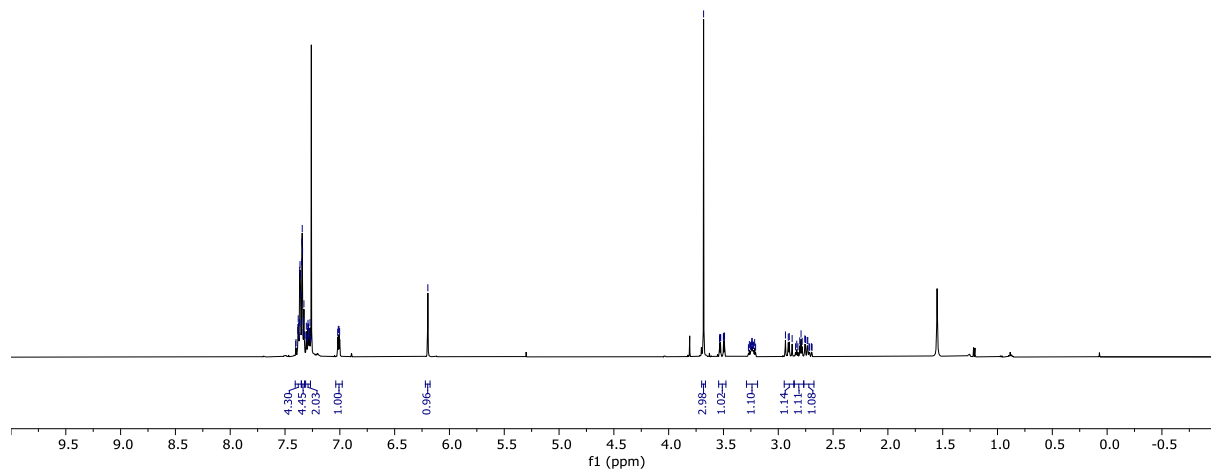
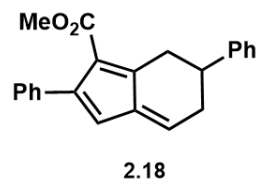


167.1
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141.6
140.3
138.3
138.3
129.7
128.6
128.4
126.5

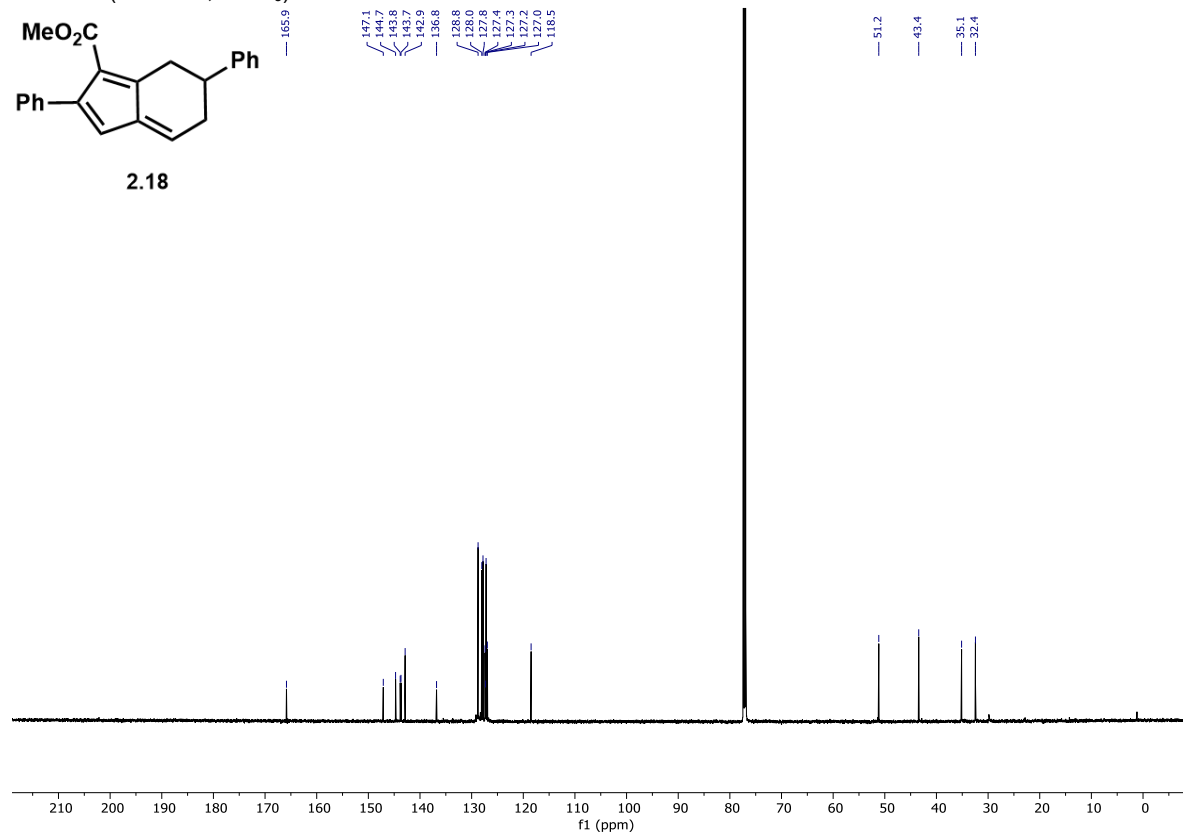
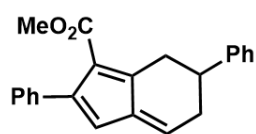


¹H NMR (500 MHz, CDCl₃)

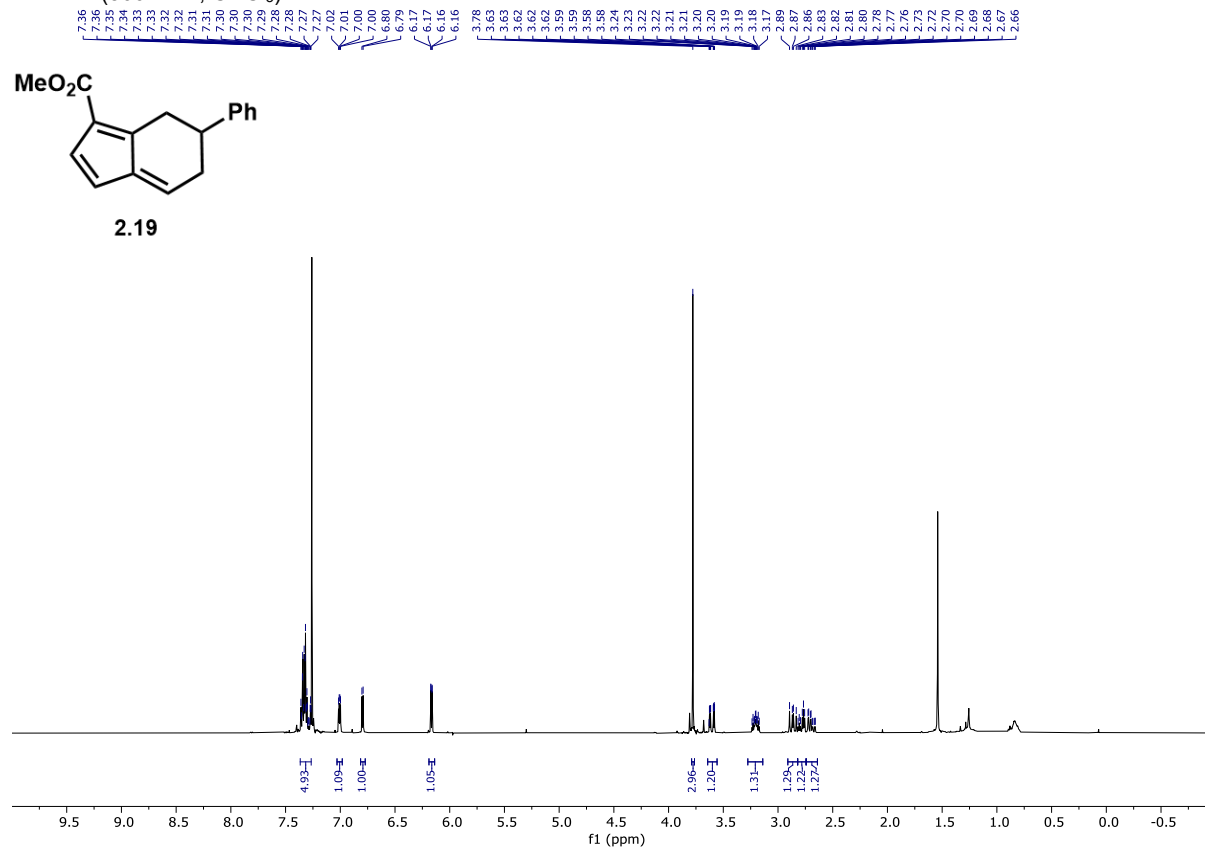
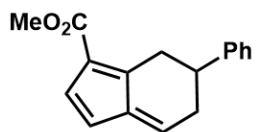
7.38
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2.69



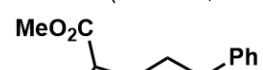
^{13}C NMR (126 MHz, CDCl_3)



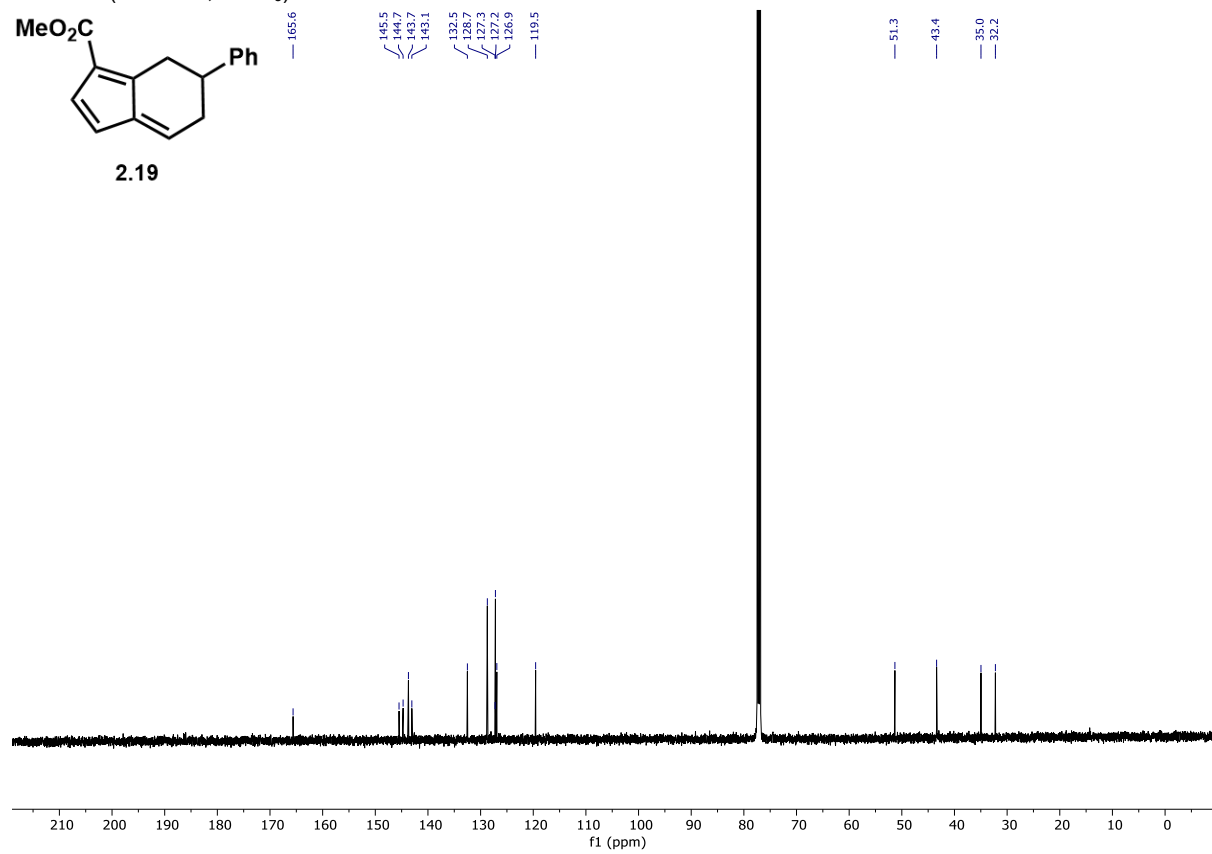
^1H NMR (500 MHz, CDCl_3)



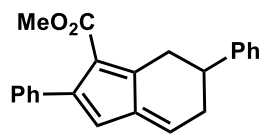
^{13}C NMR (126 MHz, CDCl_3)



2.19



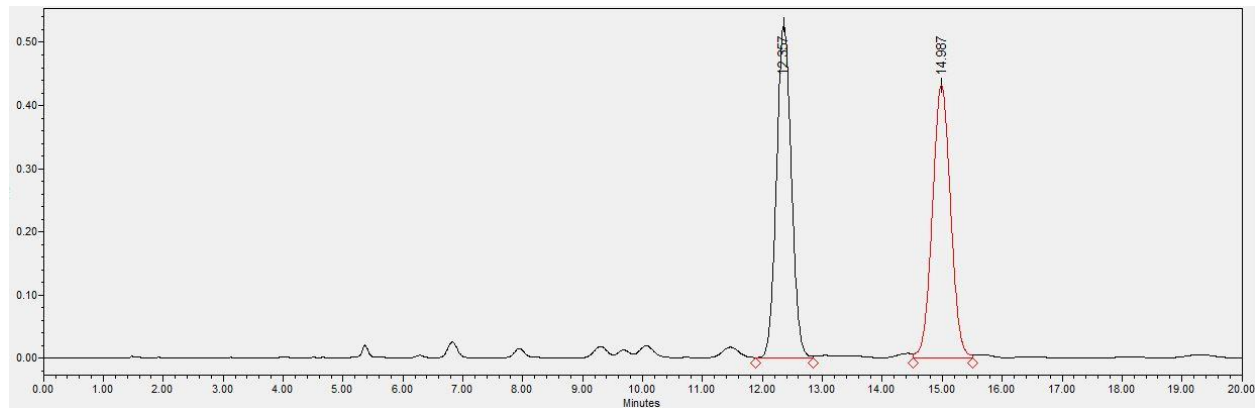
Section 2.6.4 Chiral HPLC Traces



2a

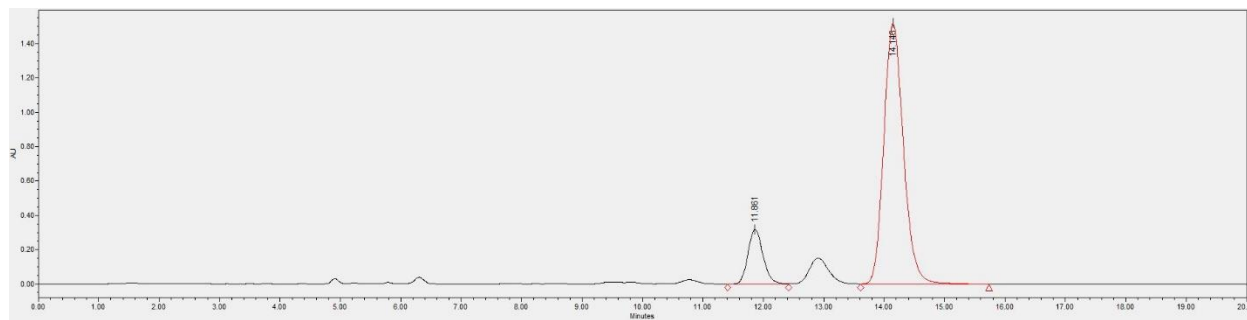
Method: AD3 chiral column, 1% IPA/hexanes 2 mL/min, λ = 254 nm

Racemic:



retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
12.357	9093061	49.93
14.987	9118099	50.07

Enantioenriched (1 mmol scale):



retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
11.861	5528729	13.84
14.146	34423325	86.16

Section 2.6.4 Crystallography Data

X-ray Analysis of 2.14

A colorless block 0.37 x 0.24 x 0.12 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using omega scans. Crystal-to-detector distance was 40 mm and exposure time was 0.50 seconds per frame at low angles and 2.50 seconds at high angles, using a scan width of 0.5°. Data collection was 99% complete to 74.000° in θ . A total of 26165 reflections were collected covering the indices $-21 \leq h \leq 21$, $-9 \leq k \leq 10$, $-39 \leq l \leq 39$. 4271 reflections were founded to be symmetry independent, with an R_{int} of 0.0410. Indexing and unit cell refinement indicated a centered, monoclinic lattice. The space group was found to be C 2/c (No. 15). The data were integrated using the CrysAlis^{Pro} 1.171.40.84a software program and scaled using the SCALE3 ABSPACK scaling algorithm. Solution by intrinsic phasing (SHELXT-2015) produced a heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

[Note: The instruments are supported by an NIH Shared Instrument Grant S10-RR027172.]

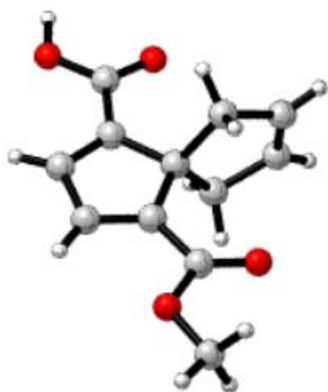


Figure S2.1. CYLview representation of **2.14**.

This crystal structure has been deposited at the Cambridge Crystallographic Data Center under CCDC 2245692.

Table S2.1. Crystal data and structure refinement for KGoyal001_Sarpong.

Identification code	KGoyal001_Sarpong	
Empirical formula	C ₁₂ H ₁₂ O ₄	
Formula weight	220.22	
Temperature	100(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	C 2/c	
Unit cell dimensions	a = 17.1400(2) Å	a = 90°.
	b = 8.09620(10) Å	b = 105.1660(10)°.
	c = 31.5007(4) Å	g = 90°.
Volume	4219.07(9) Å ³	

Z	16
Density (calculated)	1.387 Mg/m ³
Absorption coefficient	0.873 mm ⁻¹
F(000)	1856
Crystal size	0.370 x 0.240 x 0.120 mm ³
Theta range for data collection	5.348 to 74.480°.
Index ranges	-21<=h<=21, -9<=k<=10, -39<=l<=39
Reflections collected	26165
Independent reflections	4271 [R(int) = 0.0410]
Completeness to theta = 74.000°	99.1 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.89090
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	4271 / 0 / 299
Goodness-of-fit on F ²	1.083
Final R indices [I>2sigma(I)]	R1 = 0.0423, wR2 = 0.1139
R indices (all data)	R1 = 0.0451, wR2 = 0.1168
Extinction coefficient	n/a
Largest diff. peak and hole	0.277 and -0.240 e.Å ⁻³

X-ray Analysis of 2.17

A colorless block 0.20 x 0.11 x 0.08 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using omega scans. Crystal-to-detector distance was 33.00 mm and exposure time was 0.50 seconds per frame at

low and high angles, using a scan width of 0.5°. Data collection was 98% complete to 74.000° in θ . A total of 33501 reflections were collected covering the indices $-12 \leq h \leq 12$, $-13 \leq k \leq 17$, $-25 \leq l \leq 26$. 6110 reflections were founded to be symmetry independent, with an R_{int} of 0.0295. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21/n (No. 14). The data were integrated using the CrysAlis^{Pro} 1.171.41.112a software program and scaled using the SCALE3 ABSPACK scaling algorithm. Solution by intrinsic phasing (SHELXT-2015) produced a heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

[Note: The instruments are supported by an NIH Shared Instrument Grant S10-RR027172.]

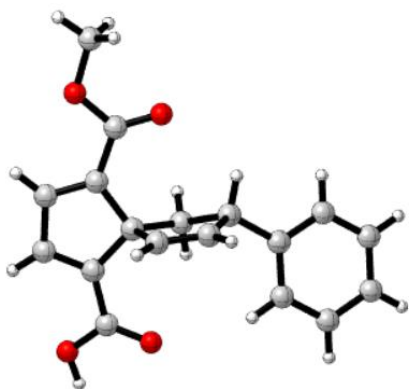


Figure S2.2. CYLview representation of **2.17**.

This crystal structure has been deposited at the Cambridge Crystallographic Data Center under CCDC 2245677.

Table S2.2. Crystal data and structure refinement for KGoyal03_Sarpong.

Identification code	KGoyal03_Sarpong	
Empirical formula	C ₁₈ H ₁₆ O ₄	
Formula weight	296.31	
Temperature	100(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 2 ₁ /n	
Unit cell dimensions	a = 10.18740(10) Å	a = 90°.
	b = 13.9611(2) Å	b = 93.5000(10)°.
	c = 21.4180(3) Å	g = 90°.
Volume	3040.54(7) Å ³	
Z	8	
Density (calculated)	1.295 Mg/m ³	
Absorption coefficient	0.748 mm ⁻¹	
F(000)	1248	
Crystal size	0.200 x 0.110 x 0.080 mm ³	
Theta range for data collection	3.781 to 74.502°.	
Index ranges	-12 ≤ h ≤ 12, -13 ≤ k ≤ 17, -25 ≤ l ≤ 26	
Reflections collected	33501	
Independent reflections	6110 [R(int) = 0.0295]	
Completeness to theta = 74.000°	98.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.85005	
Refinement method	Full-matrix least-squares on F ²	

Data / restraints / parameters	6110 / 0 / 407
Goodness-of-fit on F^2	1.031
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0351, wR2 = 0.0884
R indices (all data)	R1 = 0.0405, wR2 = 0.0936
Extinction coefficient	n/a
Largest diff. peak and hole	0.240 and -0.222 e. $\text{\AA}^{-3}$

X-Ray Analysis of 2.18

An orange block 0.33 x 0.19 x 0.12 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using omega scans. Crystal-to-detector distance was 33.00 mm and exposure time was 0.50 seconds per frame using a scan width of 0.5°. Data collection was 100% complete to 74.000° in θ . A total of 31264 reflections were collected covering the indices $-16 \leq h \leq 16$, $-10 \leq k \leq 10$, $-20 \leq l \leq 20$. 6878 reflections were found to be symmetry independent, with an R_{int} of 0.0434. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21 (No. 4). The data were integrated using the CrysAlis^{Pro} 1.172.42.72a software program and scaled using the SCALE3 ABSPACK scaling algorithm. Solution by intrinsic phasing (SHELXT-2015) produced a heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Although a solution was found in P21/n, the presence of an ordered molecule alongside a disordered molecule in the P21 solution likely

indicates that P21 is the correct space group, as we would expect both molecules to have the same disorder in the P21 solution if it was meant to be P21/n. However, the Flack parameter is ill-determined due to a lack of noticeable difference in the Friedel pairs, and thus the presence of a single enantiomer cannot be definitively stated.

[Note: The instruments are supported by an NIH Shared Instrument Grant S10-RR027172.]

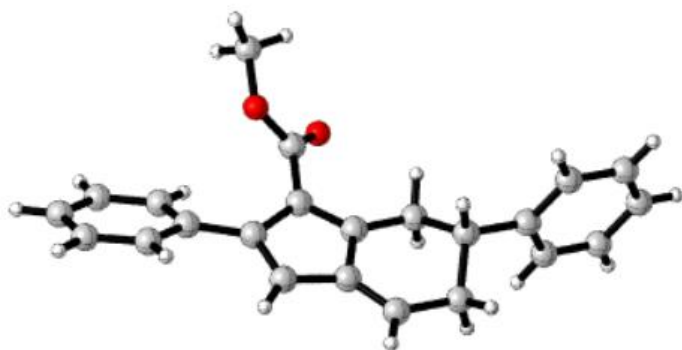


Figure S2.3. CYLview representation of **2.18**.

This crystal structure has been deposited at the Cambridge Crystallographic Data Center under CCDC 2245684.

Table S13. Crystal data and structure refinement for KGoyal06_Sarpong.

Identification code	KGoyal06_Sarpong
Empirical formula	C ₂₃ H ₂₀ O ₂
Formula weight	328.39
Temperature	100(2) K
Wavelength	1.54184 Å
Crystal system	Monoclinic
Space group	P 21

Unit cell dimensions	a = 12.9522(3) Å	a = 90°.
	b = 8.0449(2) Å	b = 98.837(2)°.
	c = 16.5583(4) Å	g = 90°.
Volume	1704.88(7) Å ³	
Z	4	
Density (calculated)	1.279 Mg/m ³	
Absorption coefficient	0.631 mm ⁻¹	
F(000)	696	
Crystal size	0.330 x 0.190 x 0.120 mm ³	
Theta range for data collection	3.453 to 74.502°.	
Index ranges	-16 ≤ h ≤ 16, -10 ≤ k ≤ 10, -20 ≤ l ≤ 20	
Reflections collected	31264	
Independent reflections	6878 [R(int) = 0.0434]	
Completeness to theta = 74.000°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.89267	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	6878 / 79 / 527	
Goodness-of-fit on F ²	1.049	
Final R indices [I > 2σ(I)]	R1 = 0.0513, wR2 = 0.1356	
R indices (all data)	R1 = 0.0533, wR2 = 0.1372	
Absolute structure parameter	-0.12(17)	
Extinction coefficient	0.0036(6)	
Largest diff. peak and hole	0.287 and -0.258 e.Å ⁻³	

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Chapter 3: Investigations into an Unexpected Rearrangement of a Spiroonatriene

3.1 Introduction to (Penta)fulvenes

Chapter 1 discussed how the distinct topology of spirononenes can give rise to π -orbital overlap, resulting in spiroconjugation. Fulvenes, such as the pentafulvenes, are another class of molecules that possess unique π orbital systems (Figure 3.1A, left).¹ The arrangement of p-orbitals in these systems confers some aromatic character, as well as versatile reactivity — both of which can be affected by substituent changes.² Unlike spiro[4.4]nonenes, however, pentafulvenes have found much broader application in synthesis. These structural motifs are not only featured in polymers³ and dyes^{4,5} due to their tunable electronic properties, but are also found in some natural products such as the illudin family (e.g., see acylfulvene and irofulven in Figure 3.1A, middle).⁶ Furthermore, the reactivity of fulvenes with nucleophiles and with other π systems as diverse cycloaddition partners has made them synthetically attractive (Figure 3.2B, right), as demonstrated by Carreira and coworkers in the total synthesis of the pallambin natural products.⁷

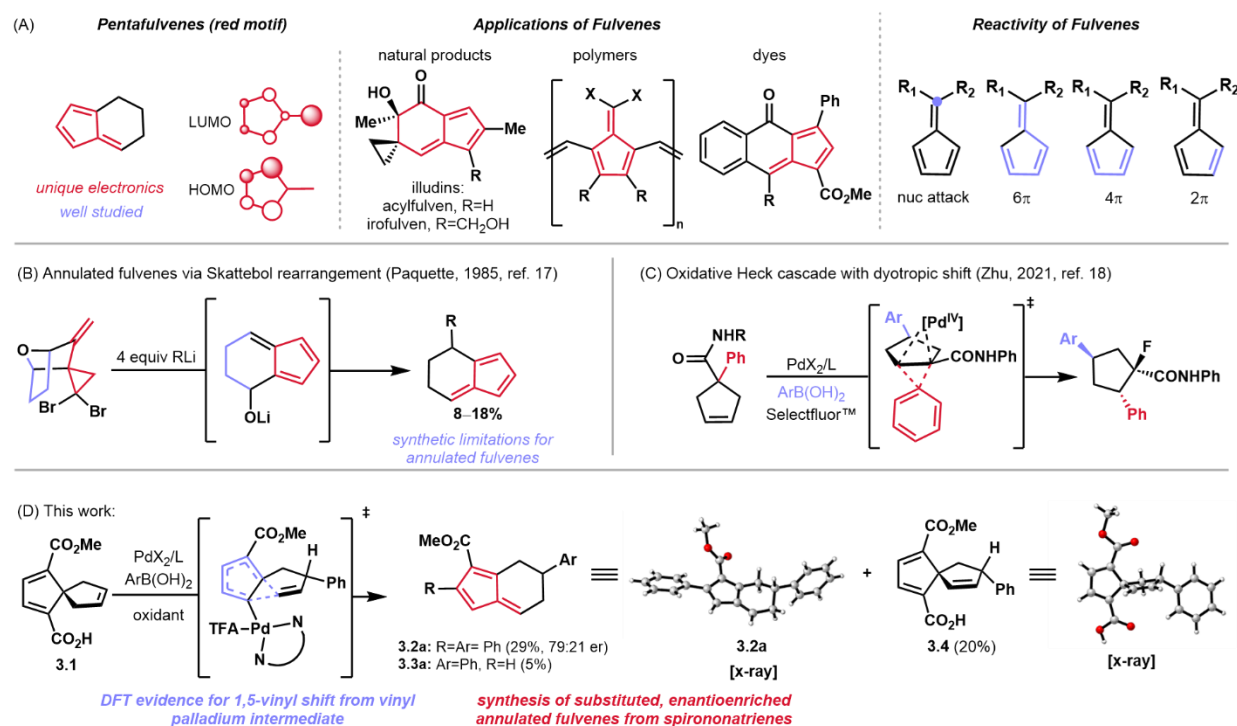


Figure 3.1. (A) Electronics, applications, and reactivity of pentafulvenes. (B) Synthesis of annulated fulvenes reported by Paquette. (C) Oxidative Heck reactions and dyotropic shift reported by Zhu (D) This work: rearrangement of a spiro[4.4]nonatriene to annulated fulvenes through an oxidative Heck cascade.

A subset of fulvenes, known as annulated fulvenes, were first synthesized by Paquette and coworkers in 1985 and used as intermediates toward conformationally restricted methylenenorbornadiene derivatives. (Figure 3.1B).⁸ While the Paquette approach yielded the desired molecules, it proceeded in low yield. Specifically, treatment

of a gem-dibromocyclopropane with four equivalents of an organolithium reagent resulted in a Skattebøl rearrangement⁹ followed by nucleophilic attack to give the substituted annulated fulvenes in low yields alongside indene and ring-opened aryl alkyne side products. Notably, this synthesis only allowed for substitution at a single position and afforded racemic products.

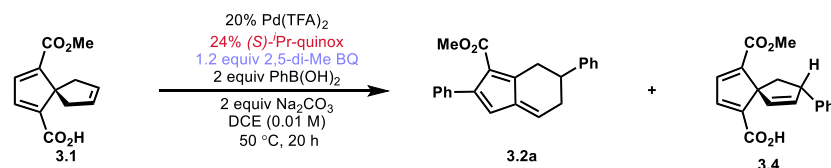
Herein, we report the development of a method which results in the synthesis of enantioenriched, substituted annulated fulvenes in moderate to good yields and enantiomeric ratios (er's) through an intercepted oxidative Heck reaction of a carboxy-substituted spiro[4.4]nonatriene (Figure 3.1D). This discovery points to an intriguing mechanism in which a C–C cleavage occurs at low temperature and under weakly oxidative conditions. Recently, Zhu and coworkers demonstrated a cleavage of unstrained C–C bonds in related five-membered ring systems through an oxidative Heck reaction followed by a dyotropic shift (Figure 3.1C).¹⁰ We reasoned that a similar pathway might be operative in this spirononatriene system. Our mechanistic investigations using a combination of DFT and empirical insights have led to a mechanistic hypothesis involving C–C cleavage from a key vinyl palladium species. The net coupling/rearrangement transformation of **3.1** to **3.2a** (Figure 3.1D) occurs with a range of commercially available arylboronic acids. Overall, this work expands the chemistry of spirononenes by showcasing their transformation to annulated fulvenes and provides evidence for a novel mechanism of C–C cleavage and migration — a Pd (II)-mediated 1,5 vinyl shift.

3.2 Reaction Discovery and Optimization

As discussed in Chapter 2, an oxidative Heck reaction of spirononatriene **3.1** to synthesize **3.4** was desired. Upon applying the oxidative Heck conditions reported by Zhu¹¹ to this spirononatriene system, the desired Heck product (**3.4**) was indeed isolated in 20% yield. However, diaryl fulvene **3.2a** was obtained as the major product in 29% yield, alongside a small amount of monoaryl fulvene **3.3a** in 5% yield (Figure 3.1D). Extensive optimization of different parameters led to reaction conditions which gave diaryl fulvene **3.2a** as the major in 59% isolated yield and 87:13 enantiomeric ratio (er) (Table 3.1, entry 1; see section 3.8 for the full optimization tables). Deviation from these conditions, as illustrated in Table 3.1, inform our overall mechanistic understanding (vide infra). As described in the optimized conditions, pyridine oxazoline (PyrOx) and quinoline oxazoline (Quinox) ligands emerged as the best performers with (S)-isopropyl quinoline oxazoline ((S)-Pr-quinox) giving the highest yields and er's.

While the reaction was shown to work well under neutral, basic, or acidic conditions (Table 3.1, entries 1–3), basic conditions proved most suitable for a range of electron-rich and -deficient arylboronic acids (see section 3.8, Table S3.6). Protodeboronation became

more pronounced under more acidic conditions.¹² Additionally, the presence of acetate, either from the added base or in the form of Pd(OAc)₂, favored formation of Heck



entry	deviation	results ^[a]
1	none	76 (59%) 3.2a , 87:13 er
2	5% (v/v) AcOH instead of base	88% (46%) 3.2a , 84:16 er
3	no base	65 % (53%) 3.2a , 84:16 er
4	KOAc instead of Na ₂ CO ₃	43% 3.2a , 44% 3.4
5	Pd(OAc) ₂ instead of Pd(TFA) ₂ ; no base	45% 3.2a , 34% 3.4
6	5% AcOH (v/v), no base; 0.4 equiv Ag ₂ O	28% 3.2a , 24% 3.4 , 21% 3.1
7	1 equiv PhB(OH) ₂	46% 3.2a , 43% 3.1
8	BQ instead of 2,5-dimethyl BQ	49% 3.2a , 39% 3.4
9	0.1M instead of 0.01	47% 3.2a , 12% 3.4

^aNMR yields determined by integration using pyrazine as an internal standard; isolated yields in parentheses

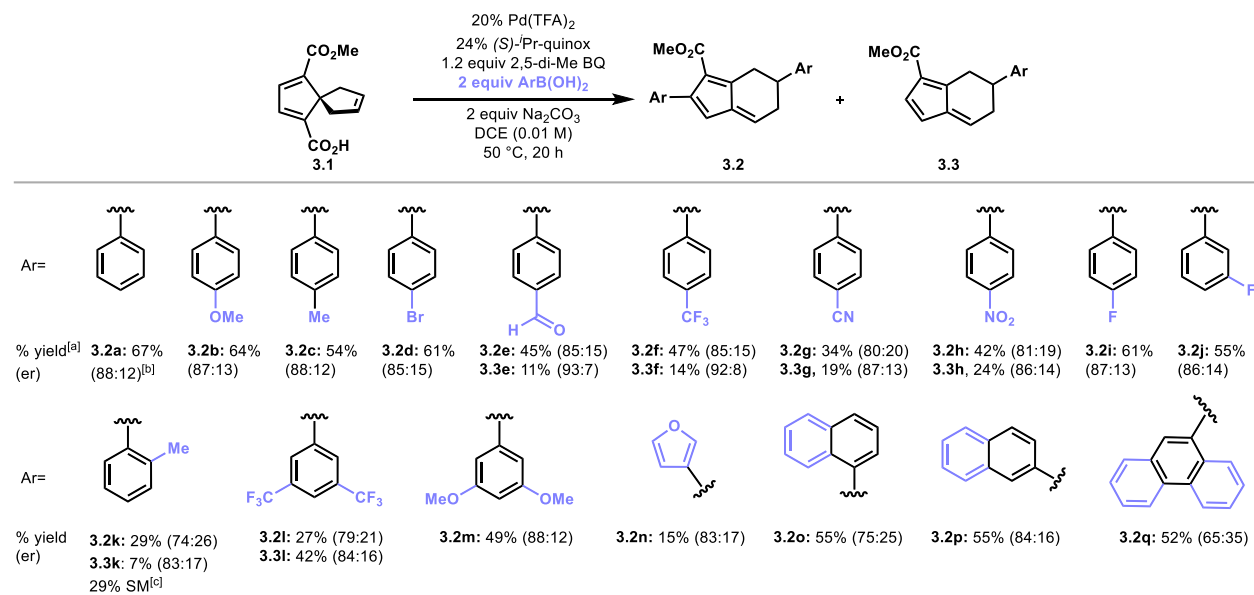
Table 3.1. Deviations from optimized reaction conditions.

product **4** (Table 3.1, entries 4–5). The use of silver salts to promote decarboxylation¹³ and favor fulvene product **3.2a** had no such effect and led to lower overall conversion and nearly equal amounts of the two products (Table 3.1, compare entries 2 and 6). The choice of oxidant was found to be crucial with 2,5-dimethyl-*para*-benzoquinone outperforming *p*-benzoquinone (Table 3.1, entry 7). The use of two equivalents of boronic acid was found to be necessary to obtain high yields. Using only one equivalent of the boronic acid coupling partner still led primarily to products that had incorporated two of the boronic acid units, albeit in low overall conversion (Table 3.1, entry 8). Finally, the reaction yield was highest at a concentration of 0.01 M (Table 3.1, entry 9).

3.3 Arylboronic Acid Substrate Scope

With optimized conditions established, we first sought to evaluate the scope of arylboronic acids (Scheme 3.1). 4-Substituted arylboronic acids performed well regardless of the electronic nature of the substituents, giving fulvene products in 50–60% yield and approximately 85:15 er's. More electron-deficient arylboronic acids such as 4-NO₂, 4-CF₃, and 4-CHO phenylboronic acids gave greater amounts of monoaryl fulvenes (**3**) as compared to the reaction profile of more electron-neutral or electron-rich arylboronic acids. The monoaryl fulvene products were generally formed in higher er's as compared to the corresponding diaryl fulvenes. 3-Substituted arylboronic acids performed analogously to give monoaryl fulvene and diaryl fulvene products in similar yields, er's, and ratios. 2-Substituted arylboronic acids, however, did not perform well likely due to

pronounced steric hindrance that could impede migratory insertion of the aryl-palladium intermediate across the spirononatriene olefin group.



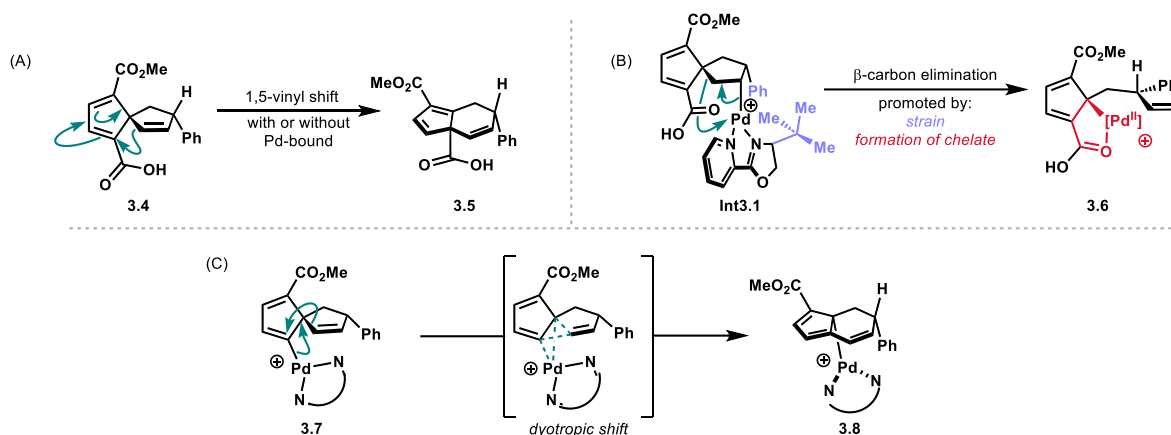
Scheme 3.1. Substrate scope for arylboronic acids. ^a All yields shown are isolated yields for reactions run with 0.05 mmol (11 mg) of **1**. ^b Reaction was run on 1.0 mmol scale. ^c Remaining starting material (SM) was determined by ¹H NMR analysis of the crude reaction mixture with pyrazine as an internal standard.

Arylboronic acids with extended aromatic systems also gave fulvene products such as **3.2o–3.2q** in moderate yields, albeit with diminished enantiomeric ratios. Finally, heterocyclic arylboronic acids performed poorly as coupling partners under the optimal conditions that we have identified. Nonetheless, 3-furanyl-boronic acid gave a 15% isolated yield of fulvene product **3.2n**. While low-yielding, this result suggests the potential for optimization of this method for heteroarylboronic acid coupling partners. Vinyl boronic acids and arylboronic pinacol esters did not participate in the coupling/rearrangement transformation, presumably due to inefficient transmetalation to the organo-palladium intermediate as well as competing decomposition of the vinyl boronic acid coupling partner (see section 3.8, Table S3.7).^{14,15}

3.4 Mechanistic Hypotheses

A focal point of our mechanistic studies has been the C–C cleavage of the spirononatriene to afford the fused 5,6-bicycle. DFT calculations, in conjunction with experiments, were used to gain insight into this transformation. Three hypotheses were initially considered (Scheme 3.2). The first pathway that was considered was a 1,5-vinyl shift from isolable Heck product **3.4**. Semmelhack and coworkers have proposed that simple, unsubstituted spirononatetraenes and trienes similar to **3.4** undergo rearrangement to 5,6-fused ring systems through such a mechanism but have high

barriers that require temperatures over 100 °C.^{25,26} However, it may be that the presence of substituents on **3.4** or coordination of the spirononatriene to a palladium complex may lead to lower barriers, giving rise to **3.5** (Scheme 3.2A).



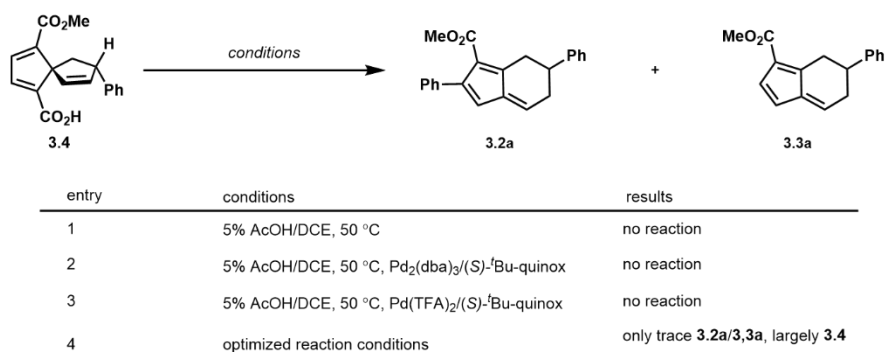
Scheme 3.2. Proposed pathways for C-C cleavage: (A) 1,5-vinyl shift from **3.4** (B) β -carbon elimination from alkyl palladium species **Int3.1** (C) dyotropic shift from vinyl palladium species **3.7**.

A second proposed pathway involves a β -carbon elimination from the intermediate alkyl palladium species generated after migratory insertion into the spirononatriene olefin (see **Int3.1**, Scheme 3.2B). β -Carbon eliminations in relatively unstrained systems of this type are rare due to the higher kinetic barriers and thermodynamic considerations.¹⁶ However, Lautens and coworkers have reported a Heck cascade in which a β -carbon elimination is driven by the relief of strain arising from bulky ortho-aryl substituents.¹⁷ We hypothesized that in our system, analogous relief of developing strain between the newly introduced phenyl group and bulky substituent on the ligand may serve as a driving force (see **Int3.1**, Scheme 3.2B). Additionally, enthalpic gain through formation of a chelate with the pendant carboxylic acid could further facilitate this rearrangement to **3.6** (Scheme 3.2B).

Finally, a dyotropic shift pathway could be operative. Here, concerted migration of two bonds across a stationary scaffold could occur from vinyl palladium species **7** (Scheme 3.2C).¹⁸ In this case, such a rearrangement would furnish the observed 5,6-fused ring system of the annulated fulvene. The dyotropic shifts that have been invoked for transition metal intermediates generally involve high oxidation state metal centers such as putative Cu(III) or Pd(IV) intermediates.¹⁹ In a related report, a possible dyotropic rearrangement in a Heck reaction with Pd(II) is proposed, albeit without sufficient supporting data.²⁰ Under our reaction conditions, accessing a Pd(IV) intermediate appears unlikely and so a Pd(II)-mediated dyotropic shift was considered.

3.5 Mechanistic Investigations

Initial mechanistic insight was obtained through a series of experiments as summarized in Table 3.2. Proposed Pathway A was examined by subjecting Heck product **3.4** to a variety of reaction conditions that may facilitate rearrangement to the 5,6-fused bicycle and checking for formation of annulated fulvenes **3.2a** or **3.3a**. Simply heating **3.4** in a DCE/AcOH mixture only returned the starting spirononatriene (Table 3.2, entry 1).



*fulvene products (**3.2a** and **3.3a**) do not readily form from Heck product (**3.4**)*

Table 3.2. Probing conversion of Heck product **3.4** to fulvenes (**3.2a/3.3a**).

While no reports of Pd-mediated 1,5-vinyl shifts are known, it has been shown that coordination of Pd(II) to 1,5-hexadienes can catalyze [3,3]-sigmatropic rearrangements.²¹ To test for a possible effect of Pd(II) or Pd(0)-coordination on the vinyl-shift, **3.4** was added to pre-stirred mixtures of either a Pd(0) or Pd(II) precatalyst and ligand (Table 3.2, entries 2–3). Only starting material (**4**) was recovered in both of these cases as well. Additionally, re-subjecting **4** to the optimized reaction conditions only gave trace amounts of annulated fulvene products as determined by ¹H NMR of the crude product mixture (Table 3.2, entry 4). This observation indicates that **4** itself may not rearrange to the fulvene products but rather, rearrangement likely occurs through an intermediate related to **3.4** along the oxidative Heck pathway.

These empirical observations are supported by DFT calculations. For all calculations involving Pd, alkyl palladium species **Int3.1** was used as the starting point (i.e., $\Delta G = 0$ kcal/mol). The energies of all cationic structures include the energy of a trifluoroacetate (TFA) anion at an infinite distance from the Pd-complex. Pathway A was initially considered with coordination of palladium (Figure 3.2A). In this scenario, **9**, which may be accessed through vinyl shift of the Pd-bound alkene (**Int2**), was determined to be uphill by 15.9 kcal/mol (ΔG) and has a transition state (TS) energy, $\Delta G^\ddagger$, of 44.8 kcal/mol (see the section 3.8 for the structure of **TS3.1**). This value is unlikely for a transformation that occurs at 50 °C (approximate maximum of 28 kcal/mol accessible).²² In considering Pathway A without the involvement of Pd(II), **3.4** was used as the thermodynamic starting point (Figure 3.2B). Overall, while this transformation was found to be more kinetically and thermodynamically accessible, it was still unlikely to occur under the reaction conditions that had been employed. This reaction was endergonic by 1.0 kcal/mol with an activation barrier of 29.4 kcal/mol (Figure 3.2B, see the section 3.8 for the structure of

TS3.2). Altogether, these computational and experimental results do not support Pathway A as a viable reaction path for the formation of the annulated fulvene products from the precursor spirononatriene.

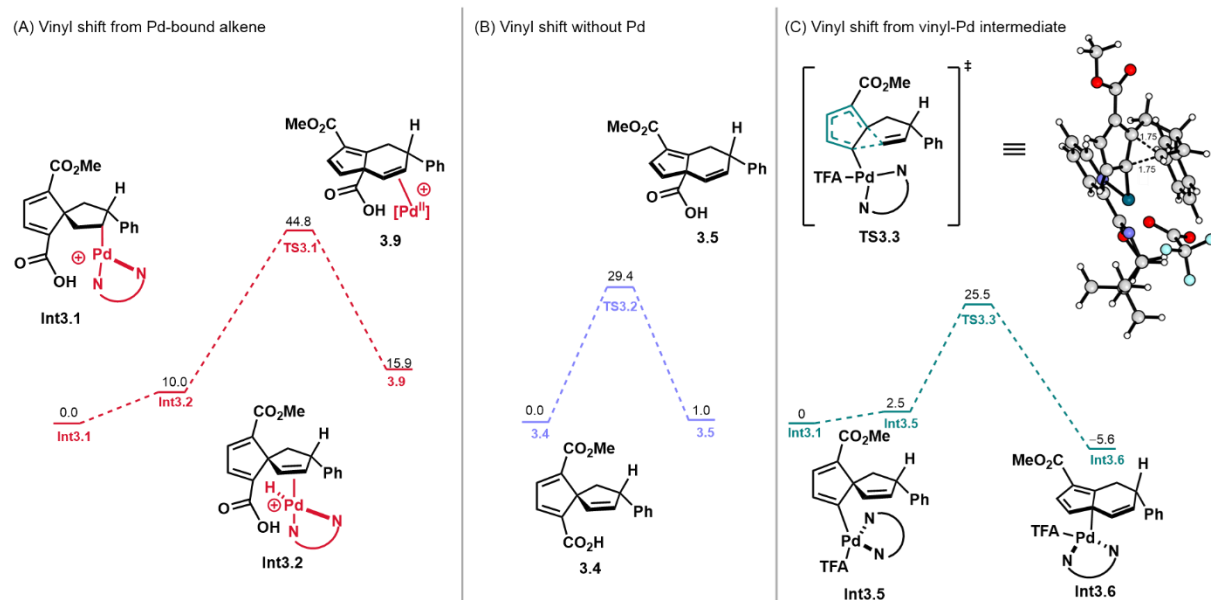


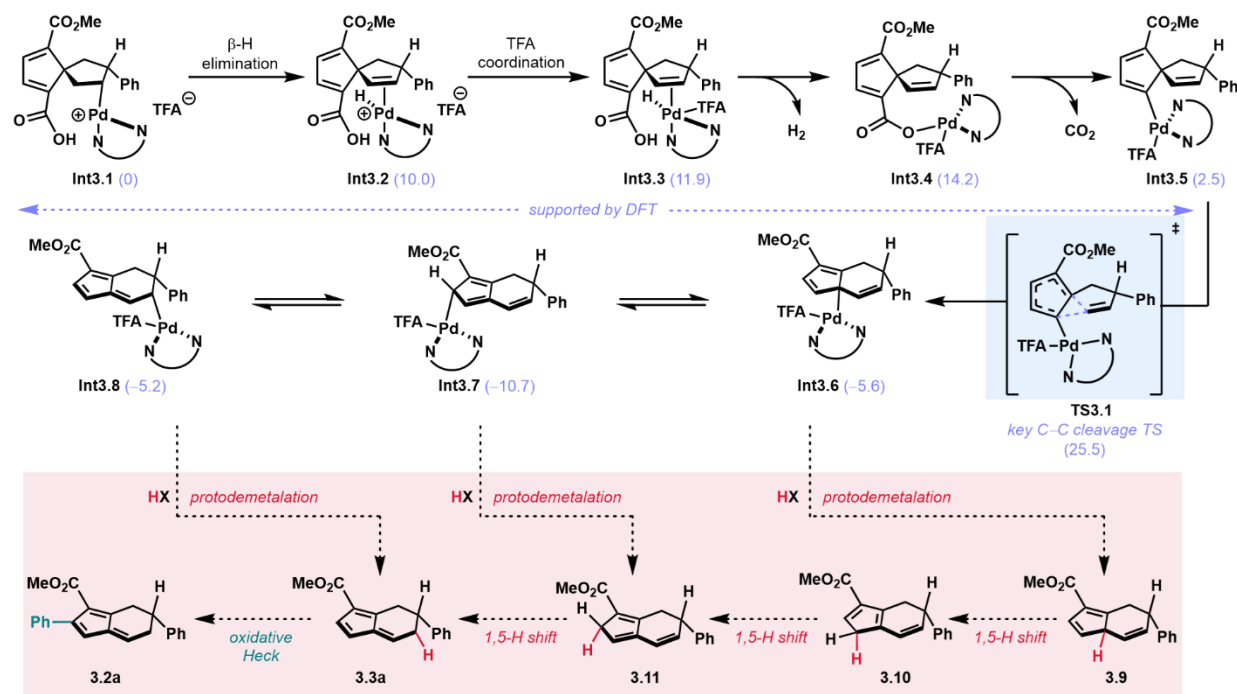
Figure 3.2. Calculated energies (in kcal/mol) of transition states and intermediates for pathways involving vinyl shifts. A trifluoroacetate (TFA) counter-anion at infinite distance is implied for all cationic species.

Next, the β -carbon elimination pathway (Scheme 3.2B) was investigated using DFT calculations. A transition state for β -carbon elimination was found with a TS energy of 38.7 kcal/mol (see section 3.8.3.1, Scheme S3.1). The reaction itself was also found to be endergonic, giving a product that lies 11.6 kcal/mol higher. On the basis of these initial results, we concluded that the β -carbon elimination pathway was unlikely and additional mechanistic studies and calculations to support or refute this possibility were not pursued.

Finally, Pathway C (Scheme 3.2C), which involves a dyotropic shift, was investigated computationally. Following an extensive search, a dyotropic shift transition state was not found. However, searches for this transition state converged to one where the C–C bond migrates but the C–Pd bond remains stationary, constituting a 1,5-vinyl shift from vinyl-Pd species Int5 (Figure 3.2C). Since transition state optimizations of geometries constituting a dyotropic rearrangement converged to this Pd(II)-mediated 1,5-vinyl shift transition state, we conclude that this pathway must be lower in energy than the proposed dyotropic rearrangement. Initial searches furnished a 1,5-vinyl shift transition state involving a cationic Pd(II) intermediate. It was then found that coordination of TFA reduces the energy of this transition state, resulting in a sufficiently low transition state energy of 25.5 kcal/mol and an exergonic reaction which places Int6 at –5.6 kcal/mol

(Figure 3.2C). On the basis of these calculations, the 1,5-vinyl shift pathway from vinyl palladium species Int5 was then deemed as a plausible pathway and the energies of intermediates leading to Int5 were calculated (Scheme 3).

The immediate step following formation of alkyl Pd-species Int1 (Scheme 3) is expected to be a β -hydride elimination to give the spirononatriene-bound Pd–H species **Int3.2** at



Scheme 3.3. Intermediates en route to and following key **TS3.3** are shown above. Calculated energies for intermediates are shown in parentheses in units of kcal/mol. The remaining hypothesized steps for this pathway are shown in a red box and further discussed below.

10.0 kcal/mol. Subsequently, a TFA anion coordinates to the cationic Pd(II)-complex to give a neutral trigonal bipyramidal complex (Int3 at 11.9 kcal/mol). In **Int3.3**, the Pd–H is positioned such that the hydride is proximal to the pendant carboxylic acid. At this stage, we propose a deprotonation-palladation sequence which results in the loss of H₂ and the formation of a palladated carboxylate. Pd(II)-hydrides have been reported to be basic enough to deprotonate phenols.²³ As such, we posit that the deprotonation of a more acidic carboxylic acid should be possible under these conditions. Calculations show this transformation from **Int3.3** to **Int3.4** to be thermodynamically feasible with the palladated carboxylate at 14.2 kcal/mol. Furthermore, it has been shown in the context of organolithium systems that complex-induced proximity effects (CIPE) can be leveraged for selective deprotonation.²⁴ Due to the observation that **3.4** does not form any rearranged products when subjected to the reaction conditions (Table 3.2, entry 4), we hypothesize that CIPE may be operative in this intramolecular deprotonation to form **Int3.4**, and that **Int3.4** does not form from intermolecular palladation of **3.4**. This direct

palladation of **3.4** is likely impeded by steric hindrance between the newly installed aryl group and bulky palladium complex.

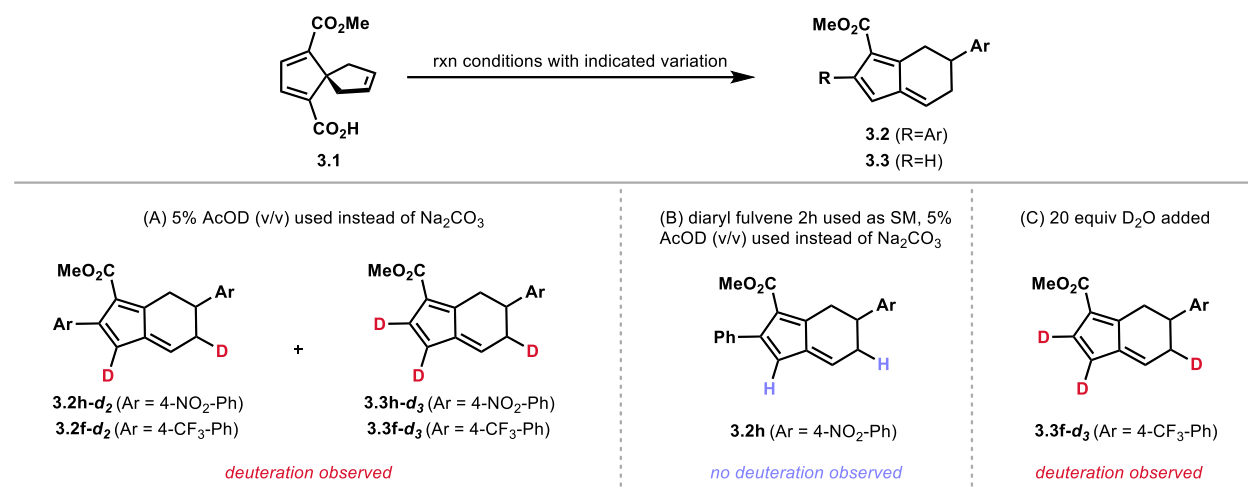


Figure 3.3. The results of investigating protodemetalation are shown above.

From **Int3.4**, we propose that a Pd(II)-mediated decarboxylation,^{25–27} which is calculated to be exergonic by 12.3 kcal/mol, furnishes an initial vinyl Pd species at 5.8 kcal/mol (see section 3.8, **Int-S3.1**). Due to the difficulty in finding a feasible transition state for the decarboxylation using DFT calculations, it is possible that the decarboxylation and 1,5-vinyl shift are concerted (see Section 3.8 for more details). A slight conformational change to pre-reaction complex **Int3.5** at 2.5 kcal/mol then leads to C–C cleavage through a kinetically feasible and exergonic Pd(II)-mediated 1,5-vinyl shift (with a TS energy of 25.5 kcal/mol) to give cyclopentadienyl Pd-complex **Int3.6** at –5.6 kcal/mol. The η -1 bound palladium isomers **Int3.7** and **Int3.8** were calculated to have energies of –10.7 and –5.2 kcal/mol, respectively (Scheme 3.3). At this stage, the catalytic cycle could terminate in protodemetalation from any of these intermediates (**Int3.6**–**Int3.8**). Direct protodemetalation from **Int3.8**, or protodemetalation from **Int3.6** and **Int3.7** followed by 1,5-hydride shifts, could furnish monoaryl fulvene **3.3a** (Scheme 3.3, red box). A subsequent oxidative Heck reaction would then yield diaryl fulvene **3.2a**.

Our hypotheses regarding protodemetalation and second oxidative Heck reaction were both investigated experimentally. The protodemetalation step was tested through a series of deuterium-labeling studies (Figure 3.3). First, spirononatriene **3.1** was subjected to the standard reaction conditions in the absence of base with an added 5% (v/v) of deuterated acetic acid (AcOD). For reactions with both 4-NO₂ and 4-CF₃ phenylboronic acids, the mono- and diaryl fulvene products were obtained with partial deuterium incorporation at multiple positions (Figure 3.3A). This outcome not only provides evidence for protodemetalation but the observation of deuteration at multiple sites provides

additional mechanistic insight. Specifically, it is likely that alkyl palladium intermediates that result from the Pd(II)-mediated vinyl shift (e.g., **Int3.6–Int3.8**, Scheme 3.3) equilibrate prior to protodemetalation. Suprafacial 1,5-hydride shifts may ultimately give the fulvenyl π system. This rationale is in line with Semmelhack's proposal of rapid 1,5-hydride shifts following the vinyl shift in spiro[4.4]nonenes to the 5,6-fused bicycles under high temperature conditions.²⁸ To support the proposal that deuteration results from protodemetalation en route to the fulvene, and not after fulvene formation, diaryl fulvene **3.2h** was subjected to the conditions with added deuterated acetic acid (Figure 3.3B). In this case, deuterium incorporation was not observed, supporting our initial hypothesis.

Because the standard reaction conditions use base, we sought to determine the source of the proton that terminates the transformation. We hypothesized that adventitious water might be the source of the proton. Addition of D₂O to the reaction conditions did, indeed, lead to partial deuterium incorporation (Figure 3.3C). Additionally, on the basis of the pK_a's of aryl boronic acids (pK_a=4.2–9.0),²⁹ which tend to be lower than the pK_a of H₂O (pK_a=14),³⁰ the proton involved in protodemetalation might arise from the boronic acid coupling partner or a by-product of boronic acid transmetalation. These observations provide strong support for a terminating protodemetalation and 1,5-hydride shifts in the formation of the initial monoaryl fulvene product (**3.3a**). On the basis of these results, we hypothesize that 1,5-hydride shifts of the benzylic hydrogen in intermediates similar to **12** (Scheme 3.3) may also be responsible for the lower *er*'s observed for diaryl fulvenes as compared to the corresponding monoaryl fulvenes (i.e. **3.2h** vs. **3.3h**).

Subjecting 4-NO₂ monoaryl fulvene **3.3h** to the reaction conditions cleanly gives diaryl fulvene **3.2h** in 73% yield, consistent with the second aryl group arising through a second oxidative Heck reaction. On the basis of the observation that monoaryl fulvenes are only formed in isolable quantities when electron-deficient boronic acids are used (e.g. 4-CN, 4-NO₂, 4-CN arylboronic acids), the rate of the migratory insertion for more electron-deficient aryl palladium intermediates across the fulvene alkene is likely slower than for more electron-rich arylboronic acids. Measuring the product distribution of **3.2h** vs. **3.3h** over the course of the reaction provides further support for this second oxidative Heck reaction. An initial increase in monoaryl fulvene **3.3h** is observed, followed by a decrease in **3.3h** as a simultaneous increase in the amount of diarylfulvene **3.2h** is observed (see section 3.8.5). Overall, these experiments provide support for the hypothesis for conversion of alkyl palladium intermediates **Int3.6–Int3.8** to fulvenes **3.2a** and **3.3a** (Scheme 3.3, red box).

Collectively, these findings support the mechanistic picture illustrated in Scheme 3.3, which is consistent with our empirical observations and calculations. Additional insight may be provided by some observations made during the process of reaction optimization. DFT calculations indicate that the key transition state (**TS3.3**) bearing

acetate instead of trifluoroacetate as the X-type ligand is lower in energy (18.2 kcal/mol, see section 3.8.3.2, Scheme S3.2) despite the observation that addition of acetate results in reduction in the amount of fulvene product (**3.2a**) and greater amounts of the Heck product (**3.4**; see section 3.8.3.2, Table S3.8). In this case, it may be that acetate competitively binds the Pd(II) center, displacing arylated spirononatriene **4** from either the Pd(II)-bound alkene (**Int3.3**) or palladated carboxylate (**Int4**). Silver salts might serve an analogous role due to their ability to bind carboxylates.³¹

3.6 Conclusion

In conclusion, we have developed a new oxidative Heck cascade reaction which results in the rearrangement of 1-carboxy-4-methyl-ester-spiro[4.4]nonatriene to enantioenriched, aryl-substituted annulated fulvenes. The products are obtained in moderate to good yields and enantiomeric ratios. Overall, this transformation expands the reactivity of spirononatrienes and provides a complementary synthesis of annulated fulvenes. In this way, the work reported here connects these two classes of π -conjugated molecules which have a rich history in physical organic chemistry. Our mechanistic investigations, bolstered by DFT calculations, support a pathway where cleavage of a relatively unstrained C–C bond occurs through a novel palladium-mediated 1,5-vinyl shift. This work expands the known reactivity of spirononenes and shows how total synthesis can act as a platform for exploration of under-explored scaffolds. Following this, the project re-focused on the total synthesis, which will be the subject of discussion for the remainder of this dissertation.

3.7 Experimental Contributors

K.G. and R.S. made the original discovery, conceived the project, and formulated the initial mechanistic hypotheses. K.G. performed all experimental work under the guidance of R.S. G.A.K., A.T., and X.C. performed all computational work under the guidance of K.N.H.

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3.8 Experimental Information

3.8.1 General Information

Unless otherwise stated, commercial reagents were purchased and used without purification. Solvents including tetrahydrofuran (THF), diethylether (Et₂O), methanol (MeOH), and benzene (PhH) were dried by passage through activated alumina columns using argon in a Glass Contour solvent purification system. Dichloroethane (DCE, dry and packaged under nitrogen) and dimethylsulfoxide (DMSO, dry and packaged under nitrogen) were used without purification. Dichloromethane (DCM) was freshly distilled over calcium hydride under a N₂ atmosphere. Deuterated solvents were purchased from Cambridge Isotope Laboratories and were used without further purification unless otherwise specified. Deuterated acetic acid was purchased from Sigma Aldrich.

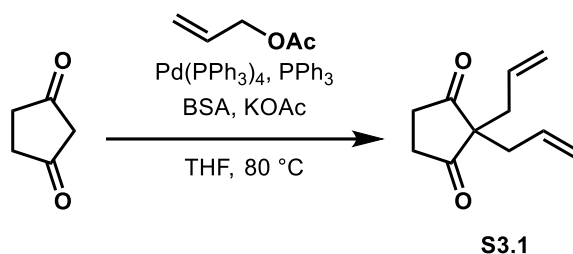
Unless otherwise stated, all reactions were performed in flame-dried or oven-dried glassware under an atmosphere of positive nitrogen pressure using Teflon-coated stir bars. Air and moisture-sensitive liquids were transferred via syringe through rubber septa. Solids were added under inert gas or were dissolved in the appropriate solvent and added via syringe and needle. Reactions ran above room temperature (20–25 °C) were heated in a metal block or oil bath with a thermocouple. Low temperature reactions were carried out in a Dewar flask filled with isopropanol/dry ice (–78 °C) or water/ice (0 °C). Organic solutions were concentrated under reduced pressure on an IKA temperature-controlled rotary evaporator equipped with a dry ice/isopropanol condenser. Reaction progress was monitored by thin layer chromatography (TLC). TLC and preparative TLC were performed on glass-backed Silicycle SiliaPlate 250 µm thickness, 60 Å porosity F-254 precoated plates. Flash column chromatography was performed with either glass columns using Silicycle silica gel (40– 63 µm particle size) or with a Yamazen Smart Flash EPCLC W-Prep 2XY (dual channel) automated flash chromatography system on prefilled, premium, universal columns using ACS grade solvents. Compounds were visualized with UV light (254 nm) and stained with aqueous potassium permanganate (KMnO₄) or *p*-anisaldehyde and heat.

NMR spectral data were obtained using deuterated solvents, obtained from Cambridge Isotope Laboratories, Inc. ¹H NMR, proton-decoupled ¹³C NMR, and ¹⁹F NMR data were recorded on Bruker AV-300, AVQ-400, AVB-400, NEO-500, AV-600 and AV-700 spectrometers using CDCl₃ as solvent at 20–23 °C. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal (δ 7.26 for ¹H NMR & δ 77.16 for ¹³C NMR in CDCl₃). Data for ¹H, ¹³C, and ¹⁹F spectroscopy are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent), coupling constant (Hz), integration. All raw FID files were processed, and the spectra analyzed, using the program MestReNOVA 11.0 from Mestrelab Research S. L. High-resolution mass spectra (HRMS) were obtained from the Mass

Spectral Facility at the University of California, Berkeley, on a Finnigan/Thermo LTQ-FT instrument (ESI). Data acquisition and processing were performed using the XcaliburTM software. Chiral HPLC analysis was conducted using a Waters Alliance e2695 Separations Module equipped with ChiralPak[®] columns. Data was processed and analyzed using Empower[®]3 software. HPLC grade isopropanol (IPA) and hexanes were used for HPLC analysis.

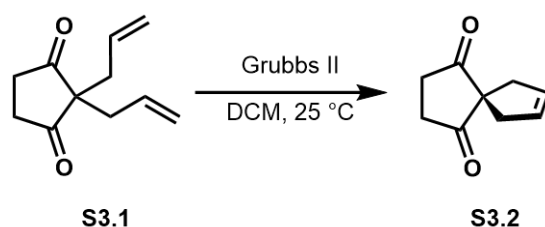
3.8.2 Experimental Procedures and Characterization Data

3.8.2.1 Preparation of Spiro[4.4]nonatriene Substrate



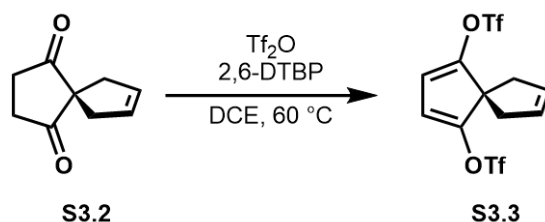
2,2-Diallylcyclopentane-1,3-dione (S3.1): This procedure was adapted from Poli et. al.³² To a flame-dried two-neck flask equipped with a stir bar was added 1,3-cyclopentanedione (10.0 g, 102 mmol, 1.0 equiv) and THF (255 mL, 0.4 M). One neck of the flask was sealed with a septum and the other was fitted with a septum-sealed reflux condenser under a N₂ atmosphere. Allyl acetate (23.1 mL, 214 mmol, 2.1 equiv) and bis-trimethylsilyl acetamide (BSA, 24.9 mL, 102 mmol, 1.0 equiv) were then added by syringe. The septum was removed and the following solid reagents were quickly added before re-capping the flask: oven-dried KOAc (1.00 g, 10.2 mmol, 0.10 equiv), Pd(PPh₃)₄ (11.8 g, 10.2 mmol, 0.10 equiv), and then PPh₃ (2.67 g, 10.2 mmol, 0.10 equiv). The reaction mixture was stirred at reflux (heating to 70 °C) for 22 h, then cooled to room temperature, quenched with sat. aq. NH₄Cl (50 mL), and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na₂SO₄, filtered, and then concentrated under reduced pressure to afford the crude product as a brown oil. This oil was then purified by silica gel flash column chromatography (5–15% EtOAc/hexanes gradient) to afford **S3.1** (13.1 g, 72%) as a yellow oil. The ¹H NMR spectrum was consistent with results reported in the literature.³³

¹H NMR: (300 MHz, CDCl₃) δ 5.55 (ddt, J = 17.2, 9.7, 7.5 Hz, 2H), 5.12 – 4.99 (m, 4H), 2.62 (s, 4H), 2.37 (dt, J = 7.5, 1.0 Hz, 4H).



Spiro[4.4]non-7-ene-1,4-dione (S3.2): This procedure was adapted from a report in the literature.³⁴ To a flame-dried flask equipped with a stir bar was added diallylated diketone **S3.1** (13.1 g, 73.4 mmol, 1.0 equiv), DCM (223 mL, 0.33M), and Grubbs' G2 catalyst (312 mg, 0.367 mmol, 0.05 mol % under air. The flask was sealed with a septum and placed under a slow stream of N₂. The resulting solution was stirred at 25 °C until consumption of starting material (4 h). The reaction mixture was then concentrated under reduced pressure to give a brown solid which was used without further purification. The ¹H NMR spectrum was consistent with results reported in the literature.³⁴

¹H NMR: (300 MHz, CDCl₃) δ 5.61 (br s, 2H), 2.83 (br s, 4H), 2.66 (br s, 4H).



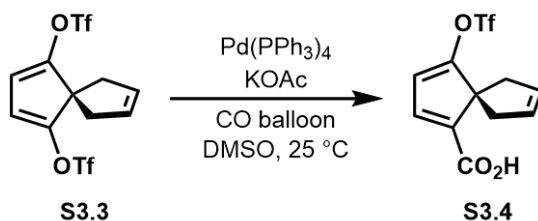
Spiro[4.4]nona-1,3,7-triene-1,4-diyl bis(trifluoromethanesulfonate) (S3.3). This procedure was modified from a report by Stang et. al.³⁵ To a flame-dried flask equipped with a stir bar was added spiro-diketone **S3.2** (4.0 g, 27 mmol, 1.0 equiv). The flask was evacuated and refilled with N₂ three times. Under a N₂ atmosphere, DCE (130 mL, 0.20 M) and 2,6-di-*tert*-butyl pyridine (DTBP, 60 mL, 270 mmol, 10 equiv) were added. Then triflic anhydride (45 mL, 270 mmol, 10 equiv) was slowly added. The reaction mixture was heated to 60 °C and stirred for 24 h at this temperature. The reaction mixture was then cooled to 25 °C, transferred to an Erlenmeyer flask, and then further cooled to 0 °C. Water (200 mL) was slowly added until bubbling ceased. Hexanes (400 mL) were then added and a brown solid formed. The resulting biphasic mixture was filtered through a celite pad. The organic layer was separated and washed with 4 M HCl (3 x 200 mL) and then brine (200 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure to yield a crude, black oil which was then purified by silica gel flash column chromatography (0–8% EtOAc/hexanes gradient) to give 6.6 g (60%) of **S3.3** as an orange oil.

¹H NMR (500 MHz, CDCl₃) δ 6.01 (s, 2H), 5.79 (s, 2H), 2.73 (s, 4H).

¹³C NMR (126 MHz, CDCl₃) δ 153.2, 129.0, 118.6 (q, *J* = 320.7 Hz), 111.4, 56.8, 36.1.

¹⁹F NMR (470 MHz, CDCl₃) δ –73.32 (s).

HRMS (EI): Calcd for ([M], C₁₁H₈F₆O₆S₂)⁺: *m/z* = 413.9661, found 413.9673



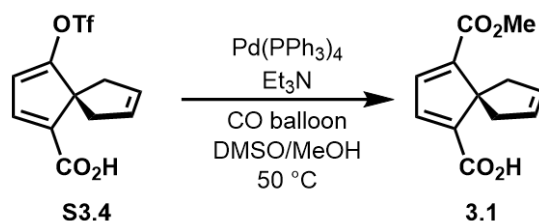
4-(((trifluoromethyl)sulfonyl)oxy)spiro[4.4]nona-1,3,7-triene-1-carboxylic acid (S3.4). This procedure was adapted from a report in the literature.³⁶ To a flame-dried flask with a stir bar was added **S3** (2.00 g, 4.83 mmol, 1.0 equiv), which was dissolved in DMSO (28.4 mL, 0.17 M). To this solution was added oven-dried KOAc (497 mg, 5.07 mmol, 1.05 equiv) and Pd(PPh₃)₄ (279 mg, 0.241 mmol, 0.05 equiv). The mixture was sparged with CO for 5 min and the reaction mixture was stirred under a CO atmosphere at 25 °C. Reaction progress was monitored by ¹HNMR analysis of aliquots of the reaction mixture which were worked up. At the following varying time points, 279 mg (0.05 equiv) of additional Pd(PPh₃)₄ was added and the reaction mixture was sparged with CO for 5 mins and allowed to continue stirring: 22 h, 34 h, 46 h, 59 h (0.025 equiv of PdP(Ph)₃ added this time). After 66 h of total reaction time, the mixture was diluted with DCM (20 mL), acidified to pH=1 with 1M HCl, and extracted with DCM (3 x 30 mL). The organic layers were combined, washed with brine (3 x 30 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (15% EtOAc/2% AcOH/hexanes) to give 541 mg (36%) of **S3.4** as a pale-yellow solid.

¹H NMR (600 MHz, CDCl₃) δ 7.32 (d, *J* = 2.9 Hz, 1H), 6.14 (d, *J* = 2.9 Hz, 1H), 5.82 (s, 2H), 3.04 (d, *J* = 14.9 Hz, 2H), 2.53 (d, *J* = 14.5 Hz, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 167.6, 166.4, 141.3, 138.0, 129.3, 118.60 (q, *J* = 320.7 Hz), 110.9, 57.9, 37.5.

¹⁹F NMR (470 MHz, CDCl₃) δ -73.28 (s).

HRMS (ESI): Calcd for ([M-H], C₁₁H₈F₃O₅S)⁻: *m/z* = 309.0050, found 309.0051



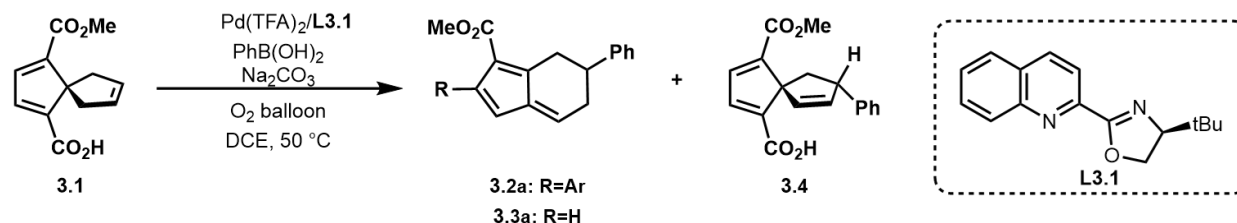
4-(methoxycarbonyl)spiro[4.4]nona-1,3,7-triene-1-carboxylic acid (3.1): This procedure was adapted from the literature.³⁷ To a flame-dried flask with a stir bar was added **S3.4** (720 mg, 2.32 mmol, 1.0 equiv) under air, which was dissolved in DMSO (62.8 mL, 0.037 M) and MeOH (113 mL, 0.021 M). Et₃N (0.97 mL, 3.90 mmol, 3 equiv) was then added, followed by Pd(PPh₃)₄ (134 mg, 0.116 mmol, 0.05 equiv). The mixture was sparged with CO for 5 min and then stirred under a CO atmosphere at 50 °C for 4 h. The reaction mixture was cooled to 25 °C and then poured into a separatory funnel with ice. The mixture was acidified to pH=1 with 1M HCl and extracted with Et₂O (3 x 100 mL). The organic layers were combined, washed with brine (3 x 50 mL), dried over Mg₂SO₄, filtered, and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (20% EtOAc/2% AcOH/hexanes) to give 419 mg (82%) of **1** as a white to off-white solid. A single crystal of **1** was grown by slow evaporation from a solution in 30% EtOAc/hexanes.

¹H NMR (500 MHz, CDCl₃) δ 7.33 (d, *J* = 2.5 Hz, 1H), 7.19 (d, *J* = 2.5 Hz, 1H), 5.87 (s, 2H), 3.78 (s, 3H), 2.82 – 2.70 (m, 4H).

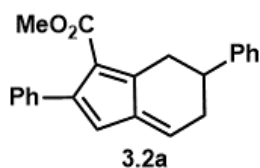
¹³C NMR (126 MHz, CDCl₃) δ 167.8, 163.3, 154.0, 151.8, 140.3, 137.3, 129.5, 59.3, 51.7, 38.7.

HRMS (ESI): Calcd for $[\text{M-H}]^-$, $\text{C}_{12}\text{H}_{11}\text{O}_4$: $m/z = 219.0663$, found 219.0664

3.8.2.2. Discovery and Optimization of Oxidative Heck Reaction Conditions



Initial Reaction Discovery: The rearrangement of spirononatrienes to annulated fulvenes was initially discovered by application of Zhu's conditions to **3.1**.¹¹ To a flame-dried vial equipped with a stir bar was added $\text{Pd}(\text{II})$ trifluoroacetate ($\text{Pd}(\text{TFA})_2$, 0.10 equiv), **L3.1** (0.10 equiv), and DCE (0.90 mL, 0.05 M). The vial was sealed with a septum cap and the mixture was stirred at 25°C for 30 min. Sequentially, spirononatriene **3.1** (10.0 mg, 0.045 mmol, 1.0 equiv), $\text{PhB}(\text{OH})_2$ (6.6 mg, 0.054 mmol, 1.2 equiv), and Na_2CO_3 (9.6 mg, 0.091 mmol, 2.0 equiv) were added and, then the mixture was sparged with an O_2 balloon for 2 min. The reaction mixture was stirred under an O_2 atmosphere at 40°C for 23 h, then cooled to 25°C and filtered through a celite pad, eluting with DCM. The mixture was concentrated under reduced pressure and purified by preparatory TLC (95% DCM/hexanes) to give 3.3 mg (29%) of diaryl fulvene **3.2a** as an orange solid (79:21 er) and 0.7 mg of monoaryl fulvene **3.3a** as a yellow solid (5%). A mixture of starting material **3.1** and arylated product **3.4** were isolated from the baseline band and separated through an additional preparatory TLC plate (35% EtOAc/2% AcOH/hexanes). This gave 2.8 mg of **3.4** (20%) as an off-white powder.



Characterization data for **methyl 2,5-diphenyl-5,6-dihydro-4H-indene-3-carboxylate (3.2a)**:

^1H NMR (500 MHz, CDCl_3) δ 7.41 – 7.35 (m, 4H), 7.35 – 7.32 (m, 4H), 7.31 – 7.27 (m, 2H), 7.01 (dd, $J = 6.0, 3.0$ Hz, 1H), 6.20 (s, 1H), 3.68 (s, 3H), 3.51 (ddd, $J = 17.5, 4.3, 1.1$

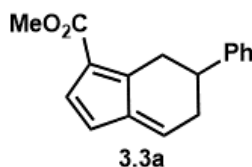
Hz, 1H), 3.29 – 3.19 (m, 1H), 2.90 (dd, $J = 17.5, 13.0$ Hz, 1H), 2.81 (dt, $J = 19.5, 5.4$ Hz, 1H), 2.73 (ddd, $J = 19.5, 10.9, 3.0$ Hz, 1H).

^{13}C NMR (151 MHz, CDCl_3) δ 165.9, 147.1, 144.7, 143.8, 143.7, 142.9, 136.8, 128.8, 128.0, 127.8, 127.4, 127.3, 127.2, 127.0, 118.5, 51.2, 43.4, 35.1, 32.4.

HRMS (EI): Calcd for $([\text{M}], \text{C}_{23}\text{H}_{20}\text{O}_2)^+$: $m/z = 328.1458$, found 328.1460

Chiral HPLC data: AD3 chiral column, 1% IPA/hexanes 2 mL/min, $t_R(\text{minor}) = 11.9$ min, $t_R(\text{major}) = 14.1$ min, $\lambda = 254$ nm

Note: a single crystal of **3.2a** was grown by slow evaporation from a solution in THF.

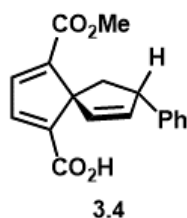


Characterization data for **methyl 5-phenyl-5,6-dihydro-4H-indene-3-carboxylate (3.3a)**:

^1H NMR (500 MHz, CDCl_3) δ 7.37 – 7.27 (m, 5H), 7.01 (dd, $J = 6.0, 2.9$ Hz, 1H), 6.80 (d, $J = 5.4$ Hz, 1H), 6.17 (dd, $J = 5.3, 1.0$ Hz, 1H), 3.78 (s, 3H), 3.60 (ddd, $J = 17.8, 4.4, 1.0$ Hz, 1H), 3.20 (ddt, $J = 12.9, 10.8, 4.4$ Hz, 1H), 2.86 (dd, $J = 17.8, 12.9$ Hz, 1H), 2.79 (dt, $J = 19.2, 5.3$ Hz, 1H), 2.69 (ddd, $J = 19.4, 10.9, 2.9$ Hz, 1H).

^{13}C NMR (126 MHz, CDCl_3) δ 165.6, 145.5, 144.7, 143.7, 143.1, 132.5, 128.7, 127.3, 127.2, 126.9, 119.5, 51.3, 43.4, 35.0, 32.2.

HRMS (EI): Calcd for $([\text{M}], \text{C}_{17}\text{H}_{16}\text{O}_2)^+$: $m/z = 252.1145$, found 252.1151



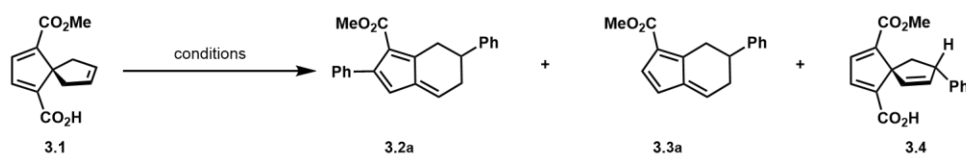
Characterization data for **4-(methoxycarbonyl)-8-phenylspiro[4.4]nona-1,3,6-triene-1-carboxylic acid (3.4)**:

^1H NMR (600 MHz, CDCl_3) δ 7.50 – 7.47 (m, 2H), 7.44 (d, J = 2.5 Hz, 1H), 7.31 (td, J = 7.7, 3.0 Hz, 2H), 7.25 (d, J = 2.5 Hz, 1H), 7.22 – 7.17 (m, 1H), 6.18 (dt, J = 5.4, 2.1 Hz, 1H), 5.22 (ddd, J = 4.7, 2.7, 1.8 Hz, 1H), 4.68 (tt, J = 8.3, 2.4 Hz, 1H), 3.83 (s, 3H), 2.63 – 2.53 (m, 2H).

^{13}C NMR (151 MHz, CDCl_3) δ 167.1, 163.2, 151.3, 148.5, 148.5, 145.5, 141.7, 141.6, 140.3, 140.3, 138.4, 129.7, 129.7, 128.6, 128.4, 126.5, 69.7, 53.9, 51.7, 38.6.

HRMS (ESI): Calcd for $[\text{M}+\text{Na}]$, $\text{C}_{18}\text{H}_{16}\text{O}_2\text{Na}^+$: m/z = 319.0941, found 319.0939

Note: a single crystal of **3.4** was grown by slow evaporation from a solution in DCM.

Table S3.1. Initial Exploration of Reaction Conditions

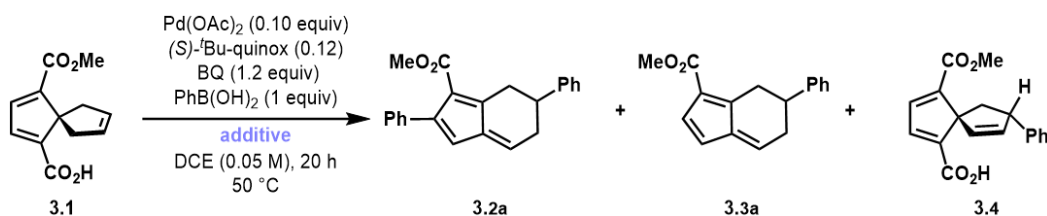
entry	[Pd] (equiv)	ligand (equiv)	ArB(OH) ₂ (equiv)	oxidant (equiv)	additive (equiv)	temp. (°C)	solvent (M)	results ^[a]
1	Pd(TFA) ₂ (0.10)	^t Bu-quinox (0.12)	PhB(OH) ₂ (1.2)	O ₂ balloon	Na ₂ CO ₃ (1.2)	50-80	DCE (0.05)	19% 3.2a+3.3a , trace 3.4 , 40% 3.1
2	Pd(TFA) ₂ (0.10)	^t Bu-pyrox (0.12)	PhB(OH) ₂ (1.2)	O ₂ balloon	Na ₂ CO ₃ (1.2)	75	DCE (0.05)	12% 3.2a+3.3a , 21% 3.4 , 19% 3.1
3	Pd(TFA) ₂ (0.10)	^t Bu-pyrox (0.12)	PhB(OH) ₂ (1.2)	O ₂ balloon	Li ₂ CO ₃ (1.2)	75	DCE (0.05)	25% 3.2a+3.3a , 11% 3.4 , 47% 3.1
4 ^[b]	Pd(TFA) ₂ (0.10)	^t Bu-pyrox (0.7)	PhB(OH) ₂ (1.2)	O ₂ balloon	Li ₂ CO ₃ (1.2)	40	DCE (0.05)	23% 3.2a+3.3a , 10% 3.4 , 47% 3.1
5	Pd(TFA) ₂ (0.10)	^t Bu-pyrox (0.12)	PhB(OH) ₂ (1.2)	BQ (1.2)	Li ₂ CO ₃ (1.2)	50	DCE (0.05)	4% 3.2a+3.3a , 15% 3.4 ,
6	Pd(TFA) ₂ (0.10)	^t Bu-pyrox (0.12)	PhB(OH) ₂ (1.2)	2,6-di-Me BQ (1.2)	Li ₂ CO ₃ (1.2)	50	DCE (0.05)	14% 3.2a+3.3a , 23% 3.4
7	Pd(OAc) ₂ (0.10)	^t Bu-quinox (0.12)	PhB(OH) ₂ (1.2)	2,6-di-Me BQ (1.2)	--	50	DCE (0.05)	28% 3.2a+3.3a , 22% 3.4 , 34% 3.1
8	Pd(OAc) ₂ (0.10)	^t Bu-quinox (0.12)	PhB(OH) ₂ (1.2)	BQ (1.2)	--	50	DCE (0.05)	28% 3.2a+3.3a , 24% 3.4 , 19% 3.1

^[a]All yields reported are calculated by integration of ¹HNMR of crude reaction mixtures relative to pyrazine as an internal standard. All reactions were run for 20 h unless otherwise noted. ^[b]This reaction was run for three days.

Initial exploration of various reaction parameters indicated the following for further optimization:

- Both Pd(OAc)₂ and Pd(TFA)₂ showed promise in promoting the reaction.
- Benzoquinones were superior oxidants to molecular O₂.
- 50 °C was an ideal temperature as higher temperatures led to lower conversions.
- 20 h was a sufficient reaction time.

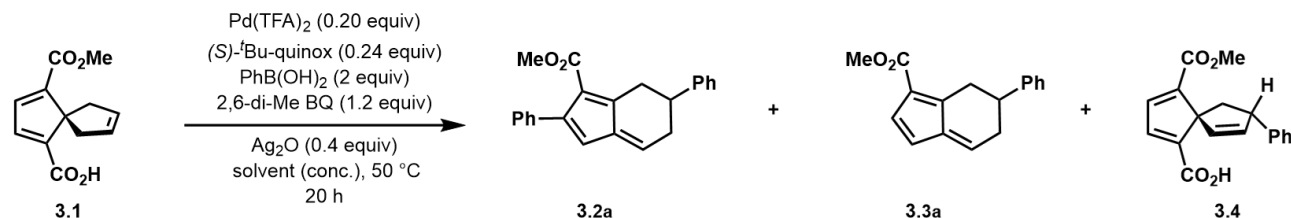
Table S3.2. Effect of Additives



entry	additive (equiv)	results ^[a]
1	AcOH (9)	14% 3.2a , 6% 3.3a , 30% 3.4 , 52% 3.1
2	PivOH (9)	19% 3.2a , 11% 3.3a , 30% 3.4 , 45% 3.1
3	AdCO ₂ H (9)	22% 3.2a , 6% 3.3a , 32% 3.4 , 43% 3.1
4	Ag ₂ CO ₃ (0.2)	15% 3.2a , 13% 3.3a , 31% 3.4 , 41% 3.1
5	Ag ₂ O (0.4)	18% 3.2a , 1% 3.3a , 54% 3.4 , 16% 3.1
6	CuF ₂ (0.2)	14% 3.2a , 12% 3.3a , 32% 3.4 , 47% 3.1
7	Cu ₂ O	16% 3.2a , 13% 3.3a , 32% 3.4 , 45% 3.1
8	none	17% 3.2a , 12% 3.3a , 35% 3.4 , 41% 3.1
g ^[b]	Ag ₂ O (0.4)	30% 3.2a , 3% 3.3a , 55% 3.4

^[a]All yields reported are calculated by integration of ¹HNMR of crude reaction mixtures relative to pyrazine as an internal standard. ^[b]Pd(TFA)₂ (0.10 equiv) used instead of Pd(OAc)₂.

Exploring various additives indicated that addition of Ag₂O afforded higher overall conversions. Additionally, Pd(TFA)₂ resulted in higher yield of desired product **3.2a**.

Table S3.3. Effects of Solvents, Concentration, and Ag₂O

entry	solvent (M)	other variation	results ^[a]
1	DCE (0.05)		40% 3.2a , 7% 3.3a , 36% 3.4 , 4% 3.1
2	DMSO (0.05)		37% 3.2a , 4% 3.3a , 39% 3.4 , 2% 3.1
3	o-DCB (0.05)		14% 3.4
4	PhMe (0.05)		23% 3.2a , 63% 3.4
5	THF (0.05)		19% 3.2a , 52% 3.4
6	5% AcOH/DCE (0.05)		40% 3.2a , 2% 3.3a , 31% 3.4
7	5% AcOH/DCE (0.01)		28% 3.2a , 4% 3.3a , 24% 3.4 , 21% 3.1
8	5% AcOH/DCE (0.05)	no Ag ₂ O	59% (46%) ^[b] 3.2a , 8% 3.3a , 12% 3.4 , 10% 3.1
9	5% AcOH/DCE (0.025)	no Ag ₂ O	65% 3.2a , 2% 3.3a , 14% 3.4 , 8% 3.1
10	5% AcOH/DCE (0.01)	no Ag ₂ O	72% (59%) ^[b] 3.2a , 2% 3.3a , 19% 3.4 , 5% 3.4
11	DCE (0.05)	no Ag ₂ O	66% 3.2a , 3% 3.3a , 10% 3.4

^[a]All yields reported are calculated by integration of ¹H NMR of crude reaction mixtures relative to pyrazine as an internal standard. ^[b]Isolated yield.

Higher loadings of Pd/L and greater amounts of PhB(OH)₂ were shown to give higher yields of **3.2a** (compare Table S3.2, entry 9 and Table S3, entry 1). DCE and 5% AcOH/DCE were shown to be optimal solvents for yield of **3.2a**. Comparing entries 7 and 9, DCE without AcOH seemed to perform slightly better. Additionally, dilute conditions gave higher yields of **3.2a** (compare entries 8–9). At more dilute conditions, Ag₂O showed a detrimental effect on yield of **3.2a** (compare entries 7 and 10). With these conditions in mind, ligands, benzoquinones, and the effect of acid could be more extensively evaluated (see below).

Table S3.4. Ligand Optimization

 (S)-CF ₃ - ^t Bu-pyrox 25% 3.2a , 35% 3.1	 (S)- ^t Bu-pyrox 18% 3.2a , 13% 3.3a , 5% 3.4 , 35% 3.1	 (S)-Ph-pyrox 17% 3.2a , 23% 3.3a , 12% 3.4 , 23% 3.1	 (S)-Bn-quinox 64% 3.2a , 10% 3.4	 H-quinox 42% 3.2a , 19% 3.4
 (S)-di-Ph-quinox 63% 3.2a , 5% 3.4 , 5% 3.1	 (S)- ^t Bu-quinox 57% 3.2a , 10% 3.4 9% 3.1 er: 76:24	 (S)-Ph-quinox 68% 3.2a er: 66:34	 (S)- ⁱ Pr-quinox 68% 3.2a er: 84:16	

All yields reported are calculated by integration of ¹H NMR of crude reaction mixtures relative to pyrazine as an internal standard. Yield was the initial consideration for optimization, er's were measured for product **3.2a** of reactions with ligands that gave a promising yield.

Table S3.5. Oxidant Optimization

 BQ 49% 3.2a , 39% 3.4	 2,6-di-Me BQ 55% 3.2a , 6% 3.1	 2,6-di- ^t Bu BQ 37% 3.2a , 5% 3.3a , 6% 3.4 , 27% 3.1	 2,6-di-OMe BQ 60% 3.2a , 12% 3.4 , 13% 3.1	 2,6-di-Cl BQ 42% 3.2a , 43% 3.4
 O ₂ oxygen (1 atm) 8% 3.2a , 50% 3.1	 2,5-di-Me BQ 66% 3.2a , 10% 3.4 , 6% 3.1	 2,5-di- ^t Bu BQ 29% 3.2a , 5% 3.3a , 5% 3.4 , 45% 3.1	 duroquinone 12% 3.2a , 50% 3.1	 DDQ no reaction

All yields reported are calculated by integration of ¹H NMR of crude reaction mixtures relative to pyrazine as an internal standard. Yields <5% are not shown.

While the role of the benzoquinone (BQ) in this reaction is to oxidize Pd(0) back to Pd(II) to allow for catalyst turnover, as illustrated in the table, there may be other subtle effects which affect the product ratios of **3.2a** vs. **3.4**. Interestingly, there is little correlation of product ratio to the oxidation potential of the benzoquinone. We hypothesize that steric effects control the product ratio through the binding of the substituted benzoquinone or the resulting hydroquinone to **Int3.2** or **Int3.3**, which may displace the spirononatriene

olefin, resulting in the dissociation of **3.4** as the product. Unsubstituted benzoquinone gives a nearly 1:1 ratio of **3.2a** : **3.4** whereas all of the substituted benzoquinones, except for 2,6-dichlorobenzoquinone, give predominantly **3.2a**. This may be because the substituents hinder the binding of the BQ to **Int3.2** or **Int3.3**. Note that severely hindered quinones (2,6-di-tert-butyl and duroquinone) give the highest ratios of **3.2a** : **3.4**. However, these also give low conversion, likely due to the low binding to the palladium (0) complex, impeding its oxidation and catalytic turnover.

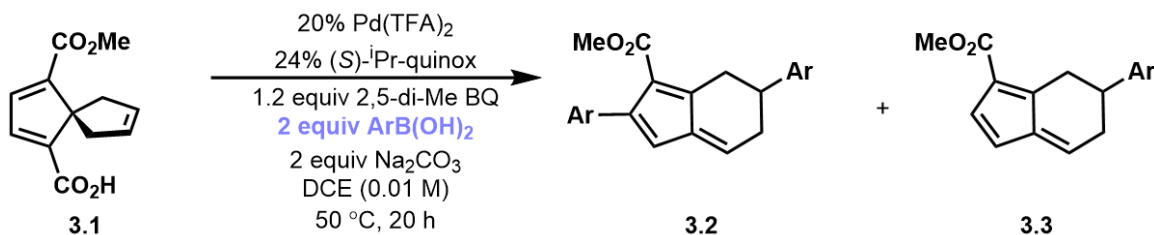
Table S3.6. Effects of Acidic or Basic Conditions

entry	variation	% yield ^[a]	er
1	PhB(OH) ₂ , no additive	65 (53)	84:16
2	4-OMe-PhB(OH) ₂ , no additive	55 (39)	
3	4-CN-PhB(OH) ₂ , no additive	53 (30)	
4	PhB(OH) ₂ ; 5% (v/v) AcOH	88 (46)	84:16
5	4-OMe-PhB(OH) ₂ ; 5% (v/v) AcOH	mostly SM	
6	4-CN-PhB(OH) ₂ ; 5% (v/v) AcOH	65	
7	PhB(OH) ₂ ; 2 equiv Na ₂ CO ₃	76 (59)	87:13
8	4-OMe-PhB(OH) ₂ ; 2 equiv Na ₂ CO ₃	74 (26)	
9	4-CN-PhB(OH) ₂ ; 2 equiv Na ₂ CO ₃	61 (40)	

^[a]NMR yields with pyrazine as internal standard, isolated yields in parentheses

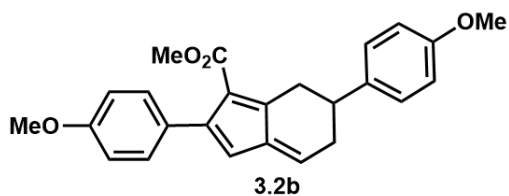
Electron-deficient and -neutral arylboronic acids were shown to tolerate acidic, basic, and neutral conditions. However, electron-rich aryl boronic acids performed poorly under acidic conditions, likely due to protodeboronation.¹² On the basis of the higher yield and enantiomeric ratio, basic conditions were chosen as optimal conditions for a range of substituted arylboronic acids.

3.8.2.3 Substrate Scope for Arylboronic Acids



Procedure for 1 mmol reaction with PhB(OH)₂: To a flame-dried flask equipped with a stir bar was added Pd(TFA)₂ (65.2 mg, 0.196 mmol, 0.2 equiv), (S)-ⁱPr-quinox (56.6 mg, 0.235 mmol, 0.24 equiv), and DCE (98.1 mL, 0.01M) under air. The vial was sealed with a septum and the mixture was stirred at 25 °C for approximately 30 min. Then 2,5-di-Me BQ (160 mg, 1.18 mmol, 1.2 equiv), Na₂CO₃ (208 mg, 1.96 mmol, 2 equiv), spirononatriene **3.1** (216 mg, 0.981 mmol, 1.0 equiv), and phenylboronic acid (239 mg, 1.96 mmol, 2.0 equiv) were added. The vial was then sealed and stirred at 50 °C for 20 h. The vial was allowed to cool to 25 °C and then filtered through a silica pad, eluting with DCM. The mixture was concentrated under reduced pressure and the resulting residue was purified using silica gel flash column chromatography (70–80% DCM/hexanes) to give 232 mg (72%) of **3.2a** as an orange solid (86:14 er, see above for characterization data).

General Procedure A: To a 20 mL scintillation vial equipped with a stir bar was added Pd(TFA)₂ (3.3 mg, 0.010 mmol, 0.2 equiv), (S)-ⁱPr-quinox (2.9 mg, 0.012 mmol, 0.24 equiv), and DCE (5.0 mL, 0.1 M) under air. The vial was sealed with a PTFE-lined screw cap and the mixture was stirred at r.t. for approximately 30 mins. Then, 2,5-di-Me BQ (8.2 mg, 0.060 mmol, 1.2 equiv), Na₂CO₃ (10.6 mg, 0.10 mmol, 2 equiv), spirononatriene **3.1** (11.0 mg, 0.050 mmol, 1.0 equiv), and varying arylboronic acids (2 equiv) were added. The vial was then sealed and stirred at 50 °C for 20 h. The vial was allowed to cool to 25 °C and then filtered through a silica pad, eluting with DCM. The mixture was concentrated under reduced pressure and the resulting residue was purified using preparatory TLC. Compounds which were obtained as sticky residues after purification could be reconstituted as solids by addition of 10% ⁱPrOH/hexanes and concentration under reduced pressure.



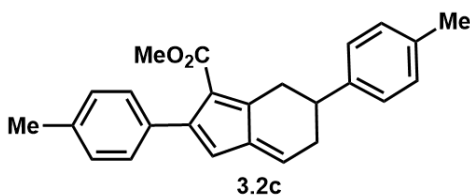
methyl 2,5-bis(4-methoxyphenyl)-5,6-dihydro-4H-indene-3-carboxylate (3.2b) was prepared according to General Procedure A using 15.2 mg (0.10 mmol, 2 equiv) of 4-(methoxy)phenylboronic acid. The crude mixture was purified by preparatory TLC (5% Et₂O/PhMe, run twice) to give 12.4 mg (64%) of a waxy orange solid (87:13 er).

¹H NMR (500 MHz, CDCl₃) δ 7.34 – 7.29 (m, 2H), 7.24 (d, *J* = 2.2 Hz, 2H), 6.96 (dd, *J* = 6.1, 2.9 Hz, 1H), 6.92 – 6.85 (m, 4H), 6.13 (s, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.70 (s, 3H), 3.46 (ddd, *J* = 17.4, 4.3, 1.0 Hz, 1H), 3.18 (ddt, *J* = 12.9, 11.0, 4.3 Hz, 1H), 2.85 (dd, *J* = 17.5, 13.0 Hz, 1H), 2.82 – 2.72 (m, 1H), 2.66 (ddd, *J* = 19.3, 11.1, 3.0 Hz, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 166.0, 159.2, 158.5, 146.6, 144.0, 143.7, 142.3, 137.0, 129.3, 129.3, 128.1, 127.2, 117.4, 114.1, 114.1, 113.3, 55.5, 55.4, 51.2, 42.6, 35.4, 32.7.

HRMS (ESI): Calcd for ([M+H], C₂₅H₂₅O₄)⁺: *m/z* = 389.1747, found 389.1751

Chiral HPLC data: AD3 chiral column, 5% IPA/hexanes 1 mL/min, *t_R*(minor) = 28.6 min, *t_R*(major) = 33.7 min, λ = 254 nm



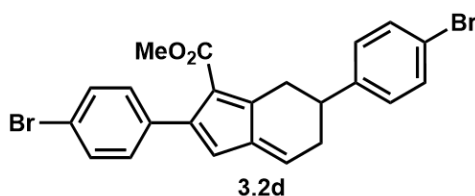
methyl 2,5-di-p-tolyl-5,6-dihydro-4H-indene-3-carboxylate (3.2c) was prepared according to General Procedure A using 13.6 mg (0.10 mmol, 2 equiv) of *para*-tolylboronic acid. The crude mixture was purified by preparatory TLC (5% Et₂O/PhMe, run twice) to give 9.9 mg (54%) of **3.2c** as an orange foam (88:12 er).

¹H NMR (500 MHz, CDCl₃) δ 7.29 – 7.26 (m, 2H), 7.24 – 7.21 (m, 2H), 7.18 – 7.13 (m, 4H), 6.97 (dd, *J* = 6.0, 3.0 Hz, 1H), 6.16 (s, 1H), 3.69 (s, 3H), 3.47 (ddd, *J* = 17.4, 4.3, 1.0 Hz, 1H), 3.19 (ddt, *J* = 13.1, 10.8, 4.5 Hz, 1H), 2.87 (dd, *J* = 17.5, 13.0 Hz, 1H), 2.78 (dddd, *J* = 19.4, 5.9, 4.7, 1.1 Hz, 1H), 2.69 (ddd, *J* = 19.3, 11.1, 3.0 Hz, 1H), 2.37 (s, 3H), 2.36 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 165.9, 147.0, 143.8, 143.7, 142.6, 141.8, 137.2, 136.5, 133.8, 129.4, 128.6, 127.9, 127.3, 127.1, 117.9, 51.2, 43.1, 35.2, 32.6, 21.4, 21.2.

HRMS (EI): Calcd for ([M], C₂₅H₂₄O₂)⁺: *m/z* = 356.1771, found 356.1777

Chiral HPLC data: AD3 chiral column, 1% IPA/hexanes 2 mL/min, *t_R*(minor) = 11.5 min, *t_R*(major) = 14.7 min, λ = 254 nm



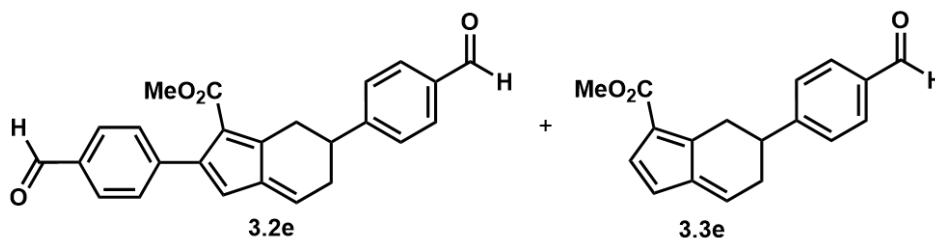
methyl 2,5-bis(4-bromophenyl)-5,6-dihydro-4H-indene-3-carboxylate (3.2d) was prepared according to General Procedure A using 20.1 mg (0.10 mmol, 2 equiv) of 4-(bromo)phenylboronic acid. The crude mixture was purified by preparatory TLC (80% DCM/hexanes) to give 14.7 mg (61%) of **3.2d** as a waxy yellow solid (85:15 er).

¹H NMR (600 MHz, CDCl₃) δ 7.49 – 7.44 (m, 4H), 7.22 (app dd, *J* = 19.8, 8.3 Hz, 4H), 7.01 (dd, *J* = 6.1, 2.9 Hz, 1H), 6.18 (s, 1H), 3.69 (s, 3H), 3.52 – 3.45 (m, 1H), 3.20 (ddt, *J* = 15.6, 11.0, 4.4 Hz, 1H), 2.87 (dd, *J* = 17.6, 12.8 Hz, 1H), 2.82 – 2.74 (m, 1H), 2.67 (ddd, *J* = 19.5, 11.0, 2.9 Hz, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 165.6, 146.0, 143.8, 143.6, 143.5, 143.1, 135.7, 131.8, 130.9, 129.7, 128.9, 127.1, 121.5, 120.7, 118.9, 51.3, 42.7, 34.9, 32.3.

HRMS (ESI): Calcd for ([M+H], C₂₃H₁₉Br₂O₂)⁺: *m/z* = 484.9746, found 484.9746

Chiral HPLC data: AD3 chiral column, 5% IPA/hexanes 1 mL/min, $t_R(\text{minor}) = 22.0$ min, $t_R(\text{major}) = 27.7$ min, $\lambda = 254$ nm



methyl 2,5-bis(4-formylphenyl)-5,6-dihydro-4H-indene-3-carboxylate (3.2e) and **methyl 5-(4-formylphenyl)-5,6-dihydro-4H-indene-3-carboxylate (3.3e)** were prepared according to General Procedure A using 15.0 mg (0.10 mmol, 2 equiv) of 4-(formyl)phenylboronic acid. The crude mixture was first purified by preparatory TLC (10% Et₂O/PhMe) to give 8.6 mg (41%) of **3.2e** as a waxy orange solid (85:15 er). A yellow band from this preparative TLC plate was isolated and further purified through a second preparative TLC plate (80% DCM/hexanes) to give 1.6 mg (11%) of **3.3e** as a waxy yellow solid (93:7 er).

Characterization data for **methyl 2,5-bis(4-formylphenyl)-5,6-dihydro-4H-indene-3-carboxylate (3.2e)**:

¹H NMR (500 MHz, CDCl₃) δ 10.02 (s, 1H), 10.02 (s, 1H), 7.90 – 7.85 (m, 4H), 7.55 – 7.48 (m, 4H), 7.09 (dd, $J = 5.9, 3.0$ Hz, 1H), 6.31 (s, 1H), 3.69 (s, 3H), 3.56 (ddd, $J = 17.6, 4.4, 1.1$ Hz, 1H), 3.35 (ddt, $J = 12.5, 10.8, 4.4$ Hz, 1H), 2.96 (dd, $J = 17.5, 12.8$ Hz, 1H), 2.87 (dddd, $J = 19.3, 5.8, 4.5, 1.1$ Hz, 1H), 2.78 (ddd, $J = 19.3, 10.8, 3.1$ Hz, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 192.1, 191.9, 165.4, 151.4, 146.0, 143.8, 143.6, 143.6, 143.1, 135.5, 135.4, 130.3, 129.4, 128.7, 127.9, 127.2, 120.3, 51.3, 43.3, 34.7, 32.0.

HRMS (EI): Calcd for ([M], C₂₅H₂₀O₄)⁺: $m/z = 384.1356$, found 384.1359

Chiral HPLC data: AD3 chiral column, 30% IPA/hexanes 1 mL/min, $t_R(\text{minor}) = 36.6$, $t_R(\text{major}) = 42.3$ min, $\lambda = 254$ nm

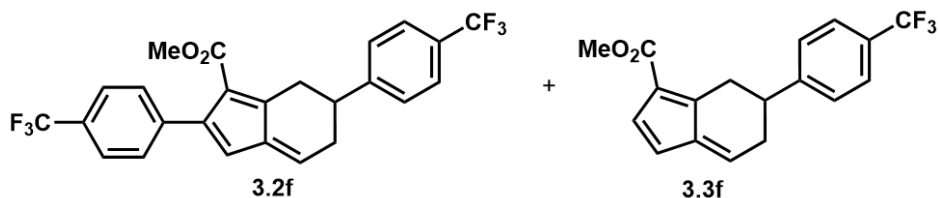
Characterization data for **methyl 5-(4-formylphenyl)-5,6-dihydro-4H-indene-3-carboxylate (3.3e):**

^1H NMR (600 MHz, CDCl_3) δ 10.01 (s, 1H), 7.87 – 7.85 (m, 2H), 7.50 – 7.46 (m, 2H), 6.99 (dd, $J = 5.9, 2.9$ Hz, 1H), 6.80 (d, $J = 5.4$ Hz, 1H), 6.18 (dd, $J = 5.4, 1.0$ Hz, 1H), 3.79 (s, 3H), 3.62 (ddd, $J = 17.6, 4.4, 1.1$ Hz, 1H), 3.30 (ddd, $J = 15.5, 11.2, 4.4$ Hz, 1H), 2.91 (dd, $J = 17.7, 12.7$ Hz, 1H), 2.81 (dt, $J = 19.2, 5.2$ Hz, 1H), 2.72 (ddd, $J = 19.3, 10.7, 2.9$ Hz, 1H).

^{13}C NMR (151 MHz, CDCl_3) δ 192.0, 165.5, 151.7, 145.6, 142.7, 142.2, 135.4, 132.6, 130.3, 127.9, 127.7, 119.7, 51.4, 43.4, 34.5, 31.7.

HRMS (EI): Calcd for $([\text{M}], \text{C}_{18}\text{H}_{16}\text{O}_3)^+$: $m/z = 280.1094$, found 280.1099

Chiral HPLC data: IC3 chiral column, 20% IPA/hexanes 1 mL/min, $t_R(\text{minor}) = 48.1$, $t_R(\text{major}) = 36.5$ min, $\lambda = 254$ nm



methyl 2,5-bis(4-(trifluoromethyl)phenyl)-5,6-dihydro-4H-indene-3-carboxylate (3.2f) and methyl 5-(4-(trifluoromethyl)phenyl)-5,6-dihydro-4H-indene-3-carboxylate (3.3f)

(3.3f) were prepared according to General Procedure A using 19.0 mg (0.10 mmol, 2 equiv) of 4-(trifluoromethyl)phenylboronic acid. The crude mixture was purified by preparatory TLC (80% DCM/hexanes) to give 11.0 mg (47%) of **3.2f** as a yellow solid (85:15 er) and 2.3 mg (14%) of **3.3f** as a yellow solid (92:8 er).

Characterization data for **methyl 2,5-bis(4-(trifluoromethyl)phenyl)-5,6-dihydro-4H-indene-3-carboxylate (3.2f)**:

¹H NMR (500 MHz, CDCl₃) δ 7.61 (app dd, *J* = 12.5, 8.0 Hz, 4H), 7.46 (app t, *J* = 8.6 Hz, 4H), 7.07 (dd, *J* = 5.9, 3.0 Hz, 1H), 6.25 (s, 1H), 3.70 (s, 3H), 3.54 (ddd, *J* = 17.5, 4.4, 1.1 Hz, 1H), 3.32 (ddt, *J* = 12.7, 10.8, 4.4 Hz, 1H), 2.94 (dd, *J* = 17.5, 12.8 Hz, 1H), 2.85 (dddd, *J* = 19.4, 5.8, 4.6, 1.1 Hz, 1H), 2.75 (ddd, *J* = 19.4, 10.8, 3.0 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 165.4, 148.4, 145.9, 143.6, 143.6, 140.4, 129.4 (q, *J* = 32.2 Hz), 128.4, 127.6, 127.1, 125.8 (q, *J* = 3.7 Hz), 125.6, 125.4, 124.7 f(q, *J* = 3.7 Hz), 123.4, 123.2, 119.9, 51.3, 43.0, 34.8, 32.2.

¹⁹F NMR (470 MHz, CDCl₃) δ −62.42 (br s), −62.43 (br s).

HRMS (ESI): Calcd for ([M+Na], C₂₅H₁₈F₆O₂Na)⁺: *m/z* = 487.1103, found 487.1101

Chiral HPLC data: AD3 chiral column, 3% IPA/hexanes 1 mL/min, *t_R*(minor) = 9.9 min, *t_R*(major) = 11.9 min, λ = 254 nm

Characterization data for **methyl 5-(4-(trifluoromethyl)phenyl)-5,6-dihydro-4H-indene-3-carboxylate (3.3f)**:

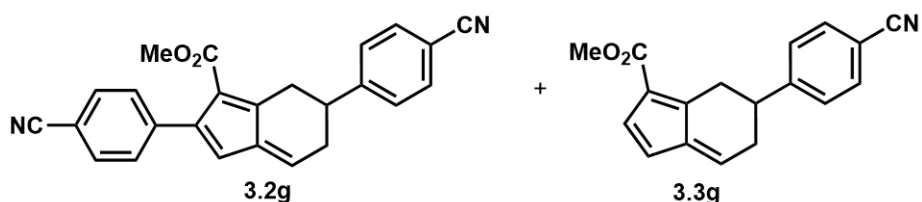
¹H NMR (600 MHz, CDCl₃) δ 7.60 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 6.99 (dd, *J* = 6.0, 2.9 Hz, 1H), 6.80 (d, *J* = 5.4 Hz, 1H), 6.17 (dd, *J* = 5.4, 1.0 Hz, 1H), 3.79 (s, 3H), 3.60 (ddd, *J* = 17.6, 4.4, 1.1 Hz, 1H), 3.32 – 3.23 (m, 1H), 2.89 (dd, *J* = 17.7, 12.7 Hz, 1H), 2.80 (dt, *J* = 19.3, 5.2 Hz, 1H), 2.70 (ddd, *J* = 19.2, 10.9, 2.9 Hz, 1H).

^{13}C NMR (151 MHz, CDCl_3) δ 165.5, 148.6, 145.6, 142.8, 142.2, 132.6, 129.3 (d, J = 32.6 Hz), 127.6, 127.6, 125.7 (q, J = 3.7 Hz), 119.7, 51.4, 43.0, 34.6, 31.8.

^{19}F NMR (565 MHz, CDCl_3) δ -62.43 (br s)

HRMS (EI): Calcd for $([\text{M}], \text{C}_{18}\text{H}_{15}\text{F}_3\text{O}_2)^+$: m/z = 320.1019, found 320.1031

Chiral HPLC data: AD3 chiral column, 1% IPA/hexanes 1 mL/min, $t_{\text{R}}(\text{minor})$ = 11.6 min, $t_{\text{R}}(\text{major})$ = 12.5 min, λ = 254 nm



methyl 2,5-bis(4-cyanophenyl)-5,6-dihydro-4H-indene-3-carboxylate (3.2g) and **methyl 5-(4-cyanophenyl)-5,6-dihydro-4H-indene-3-carboxylate (3.3g)** were prepared according to General Procedure A using 14.7 mg (0.10 mmol, 2 equiv) of 4-(cyano)phenylboronic acid. The crude mixture was purified by preparatory TLC (10% Et_2O /hexanes) to give 6.5 mg (34%) of **3.2g** as an orange solid (80:20 er). A band containing **3.3g** was isolated and further purified through a second preparatory TLC (10% Et_2O /Hexanes) to give 2.6 mg (19%) of **3.3g** as an orange solid (87:13 er).

Characterization data for **methyl 2,5-bis(4-cyanophenyl)-5,6-dihydro-4H-indene-3-carboxylate (3.2g)**:

^1H NMR (600 MHz, CDCl_3) δ 7.68 – 7.60 (m, 4H), 7.47 – 7.42 (m, 4H), 7.08 (dd, J = 6.0, 3.0 Hz, 1H), 6.26 (d, J = 0.8 Hz, 1H), 3.69 (s, 3H), 3.53 (ddd, J = 17.5, 4.4, 1.1 Hz, 1H), 3.31 (ddt, J = 12.4, 10.8, 4.4 Hz, 1H), 2.92 (ddt, J = 17.6, 12.7, 0.9 Hz, 1H), 2.85 (dddd, J = 19.4, 5.8, 4.5, 1.1 Hz, 1H), 2.74 (ddd, J = 19.2, 10.8, 2.7 Hz, 1H).

^{13}C NMR (151 MHz, CDCl_3) δ 165.2, 149.6, 145.6, 143.9, 143.5, 143.5, 141.5, 132.7, 131.6, 128.8, 128.1, 127.0, 120.5, 119.2, 118.9, 111.1, 110.9, 51.4, 43.1, 34.5, 31.9.

HRMS (EI): Calcd for ([M], C₂₅H₁₈N₂O₂)⁺: m/z= 378.1363, found 378.1369

Chiral HPLC data: AD3 chiral column, 30% IPA/hexanes 1 mL/min, t_R(minor)= 30.3 min, t_R(major)= 38.4 min, λ= 254 nm

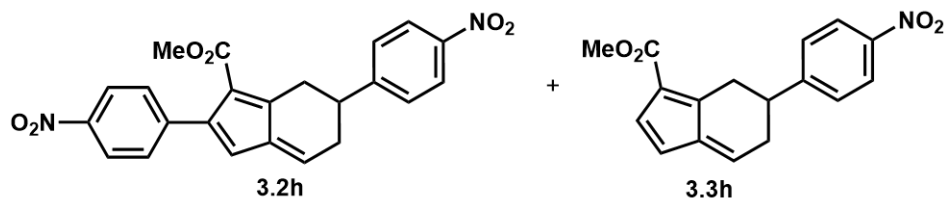
Characterization data for **methyl 5-(4-cyanophenyl)-5,6-dihydro-4H-indene-3-carboxylate (3.3g)**:

¹H NMR (500 MHz, CDCl₃) δ 7.66 – 7.60 (m, 2H), 7.48 – 7.37 (m, 2H), 6.98 (dd, *J* = 5.9, 2.9 Hz, 1H), 6.79 (d, *J* = 5.4 Hz, 1H), 6.17 (d, *J* = 5.4 Hz, 1H), 3.79 (s, 3H), 3.59 (dd, *J* = 17.9, 4.2 Hz, 1H), 3.32 – 3.22 (m, 1H), 2.87 (dd, *J* = 17.6, 12.5 Hz, 1H), 2.79 (dt, *J* = 19.3, 5.2 Hz, 1H), 2.68 (dd, *J* = 19.2, 10.7 Hz, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 165.4, 150.0, 145.6, 142.4, 141.8, 132.7, 132.6, 128.1, 127.8, 119.8, 119.0, 110.9, 51.4, 43.2, 34.3, 31.6.

HRMS (EI): Calcd for ([M], C₁₈H₁₅NO₂)⁺: m/z= 277.1097, found 277.1102

Chiral HPLC data: AD3 chiral column, 3% IPA/hexanes 1 mL/min, t_R(minor)= 39.0 min, t_R(major)= 45.1 min, λ= 254 nm



methyl 2,5-bis(4-nitrophenyl)-5,6-dihydro-4H-indene-3-carboxylate (3.2h) and **methyl 5-(4-nitrophenyl)-5,6-dihydro-4H-indene-3-carboxylate (3.3h)** were prepared according to General Procedure A using 16.7 mg (0.10 mmol, 2 equiv) of 4-(nitro)phenylboronic acid. The crude mixture was purified by preparatory TLC (70% DCM/hexanes) to give 8.7 mg (42%) of **3.2h** as an orange solid (81:19 er) and 3.6 mg (24%) of **3.3h** as a yellow solid (86:14 er).

Characterization data for **methyl 2,5-bis(4-nitrophenyl)-5,6-dihydro-4H-indene-3-carboxylate (3.3h)**:

^1H NMR (600 MHz, CDCl_3) δ 8.25 – 8.18 (m, 4H), 7.52 – 7.47 (m, 4H), 7.12 (dd, J = 6.0, 2.9 Hz, 1H), 6.32 (s, 1H), 3.70 (s, 3H), 3.57 (ddd, J = 17.5, 4.3, 1.1 Hz, 1H), 3.39 (ddt, J = 12.4, 10.6, 4.4 Hz, 1H), 2.97 (dd, J = 17.6, 12.6 Hz, 1H), 2.89 (dddd, J = 19.4, 5.8, 4.5, 1.1 Hz, 1H), 2.78 (ddd, J = 19.5, 10.8, 3.0 Hz, 1H).

^{13}C NMR (151 MHz, CDCl_3) δ 165.1, 151.6, 147.1, 147.1, 145.2, 144.2, 143.5, 143.5, 143.5, 128.9, 128.1, 127.1, 124.2, 123.2, 120.9, 51.4, 42.9, 34.6, 31.9.

HRMS (ESI): Calcd for $([\text{M}+\text{Na}], \text{C}_{23}\text{H}_{18}\text{N}_2\text{O}_6\text{Na})^+$: m/z = 441.1057, found 441.1058

Chiral HPLC data: AD3 chiral column, 20% IPA/hexanes 1 mL/min, $t_R(\text{minor})$ = 36.5 min, $t_R(\text{major})$ = 41.1 min, λ = 300 nm

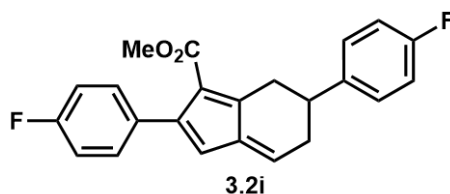
Characterization data for **methyl 5-(4-nitrophenyl)-5,6-dihydro-4H-indene-3-carboxylate (3.3h)**:

¹H NMR (600 MHz, CDCl₃) δ 8.23 – 8.18 (m, 2H), 7.50 – 7.44 (m, 2H), 6.98 (dd, *J* = 5.9, 3.0 Hz, 1H), 6.80 (d, *J* = 5.4 Hz, 1H), 6.18 (dd, *J* = 5.5, 0.9 Hz, 1H), 3.79 (s, 3H), 3.61 (ddd, *J* = 17.6, 4.4, 1.1 Hz, 1H), 3.37 – 3.29 (m, 1H), 2.91 (dd, *J* = 17.6, 12.5 Hz, 1H), 2.82 (dt, *J* = 19.2, 5.2 Hz, 1H), 2.71 (ddd, *J* = 19.1, 10.7, 3.0 Hz, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 165.4, 152.1, 147.0, 145.6, 142.2, 141.7, 132.7, 128.1, 127.9, 124.1, 119.8, 51.4, 43.0, 34.3, 31.6.

HRMS (EI): Calcd for ([M], C₁₇H₁₅NO₄)⁺: *m/z* = 297.0996, found 297.0999

Chiral HPLC data: IC3 chiral column, 10% IPA/hexanes 1 mL/min, *t_R*(minor) = 64.6 min, *t_R*(major) = 53.6 min, λ = 300 nm



methyl 2,5-bis(4-fluorophenyl)-5,6-dihydro-4H-indene-3-carboxylate (3.2i) was prepared according to General Procedure A using 14.0 mg (0.10 mmol, 2 equiv) of 4-(fluoro)phenylboronic acid. The crude mixture was purified by preparatory TLC (35% EtOAc/2% AcOH/hexanes) to give 11.2 mg (61%) of **2i** as an orange solid (87:13 er).

Characterization data for **methyl 2,5-bis(4-fluorophenyl)-5,6-dihydro-4H-indene-3-carboxylate (3.2i)**:

¹H NMR (600 MHz, CDCl₃) δ 7.36 – 7.31 (m, 2H), 7.30 – 7.27 (m, 2H), 7.06 – 7.01 (m, 4H), 7.00 (dd, *J* = 6.1, 2.9 Hz, 1H), 6.16 (s, 1H), 3.69 (s, 3H), 3.49 (ddd, *J* = 17.5, 4.3, 1.1 Hz, 1H), 3.22 (ddt, *J* = 12.4, 10.8, 4.4 Hz, 1H), 2.86 (dd, *J* = 17.6, 12.9 Hz, 1H), 2.79 (dddd, *J* = 19.4, 5.9, 4.5, 1.1 Hz, 1H), 2.68 (ddd, *J* = 19.4, 10.9, 2.9 Hz, 1H).

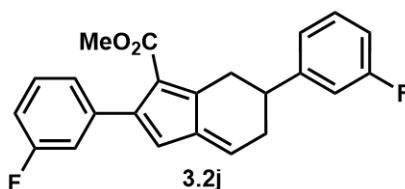
¹³C NMR (151 MHz, CDCl₃) δ 165.7, 162.4 (d, *J* = 246.1 Hz), 161.8 (d, *J* = 244.9 Hz), 146.1, 143.9, 143.6, 142.9, 140.3 (d, *J* = 2.8 Hz), 132.8 (d, *J* = 3.3 Hz), 129.7 (d, *J* = 8.0

Hz), 128.6 (d, $J = 7.8$ Hz), 127.2, 118.5, 115.5 (d, $J = 21.1$ Hz), 114.7 (d, $J = 21.5$ Hz), 51.2, 42.6, 35.2, 32.6.

^{19}F NMR (565 MHz, CDCl_3) δ -115.08 – -115.20 (m), -116.08 (dt, $J = 8.0, 3.8$ Hz).

HRMS (EI): Calcd for $([\text{M}], \text{C}_{23}\text{H}_{18}\text{F}_2\text{O}_2)^+$: $m/z = 364.1269$, found 364.1275

Chiral HPLC data: AD3 chiral column, 1% IPA/hexanes 2 mL/min, $t_R(\text{minor}) = 14.2$ min, $t_R(\text{major}) = 19.3$ min, $\lambda = 254$ nm



methyl 2,5-bis(3-fluorophenyl)-5,6-dihydro-4H-indene-3-carboxylate (3.2j) was prepared according to General Procedure A using 14.0 mg (0.10 mmol, 2 equiv) of 3-(fluoro)phenylboronic acid. The crude mixture was purified by preparatory TLC (15% Et_2O /hexanes, run three times) to give 10.0 mg (55%) of **3.2j** as a yellow solid (86:14 er).

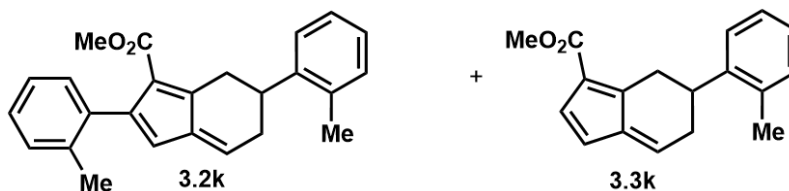
^1H NMR (600 MHz, CDCl_3) δ 7.33–7.27 (m, 2H), 7.13 (ddd, $J = 7.7, 1.6, 1.0$ Hz, 1H), 7.10 (ddt, $J = 7.6, 1.6, 0.7$ Hz, 1H), 7.07 (ddd, $J = 10.1, 2.6, 1.6$ Hz, 1H), 7.02–7.04 (m, 2H), 6.95–7.00 (m, 2H), 6.21 (d, $J = 0.8$ Hz, 1H), 3.70 (s, 3H), 3.52 (ddd, $J = 17.5, 4.3, 1.1$ Hz, 1H), 3.24 (ddt, $J = 15.5, 12.2, 4.4$ Hz, 1H), 2.91 – 2.85 (m, 1H), 2.82 (dddd, $J = 19.4, 5.9, 4.5, 1.1$ Hz, 1H), 2.70 (ddd, $J = 19.4, 11.0, 2.9$ Hz, 1H).

^{13}C NMR (151 MHz, CDCl_3) δ 165.5, 163.1 (d, $J = 246.0$ Hz), 162.5 (d, $J = 244.5$ Hz), 147.1 (d, $J = 6.7$ Hz), 146.0 (d, $J = 2.5$ Hz), 143.6 (d, $J = 8.3$ Hz), 143.3, 139.0 (d, $J = 8.2$ Hz), 130.3 (d, $J = 8.3$ Hz), 129.2 (d, $J = 8.4$ Hz), 127.2, 123.8 (d, $J = 2.8$ Hz), 122.9 (d, $J = 2.8$ Hz), 119.3, 115.0 (d, $J = 22.0$ Hz), 114.2, 114.2 (d, $J = 21.1$ Hz), 114.1, 113.9 (d, $J = 21.0$ Hz), 51.3, 43.0, 34.9, 32.2

^{19}F NMR (565 MHz, CDCl_3) δ -112.82 (q, $J = 8.7$ Hz), -114.37 (q, $J = 8.5$ Hz).

HRMS (EI): Calcd for $([M], C_{23}H_{18}F_2O_2)^+$: $m/z = 364.1269$, found 364.1270

Chiral HPLC data: AD3 chiral column, 1% IPA/hexanes 1 mL/min, $t_R(\text{minor}) = 24.4$ min, $t_R(\text{major}) = 27.0$ min, $\lambda = 254$ nm



methyl 2,5-di-o-tolyl-5,6-dihydro-4H-indene-3-carboxylate (3.2k) and **methyl 5-(o-tolyl)-5,6-dihydro-4H-indene-3-carboxylate (3.3k)** were prepared according to General Procedure A using 13.6 mg (0.10 mmol, 2 equiv) of *o*-tolylboronic acid. The crude mixture was purified by preparatory TLC (80% DCM/hexanes) to give 5.1 mg (29%) of **3.2k** as a yellow solid (74:26 er). A band containing **3.3k** was isolated and further purified through a second preparatory TLC plate (70% DCM/hexanes) to give 0.9 mg (7%) of **3.3k** as a yellow solid (83:17 er).

Characterization data for **methyl 2,5-di-o-tolyl-5,6-dihydro-4H-indene-3-carboxylate (3.2k)**:

^1H NMR (600 MHz, $CDCl_3$) δ 7.40 (dd, $J = 7.7, 1.4$ Hz, 1H), 7.25 – 7.19 (m, 4H), 7.19 – 7.15 (m, 3H), 7.02 (dd, $J = 5.1, 3.7$ Hz, 1H), 6.05 (d, $J = 0.9$ Hz, 1H), 3.57 (s, 2H), 3.55 – 3.48 (m, 2H), 2.92 (dd, $J = 18.4, 13.7$ Hz, 1H), 2.74 – 2.71 (m, 2H), 2.39 (s, 3H), 2.22 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 165.5, 147.2, 143.8, 143.8, 143.1, 142.7, 137.7, 136.3, 135.8, 130.9, 129.4, 128.8, 128.0, 127.3, 126.7, 126.4, 125.8, 125.2, 118.8, 51.1, 39.1, 34.3, 32.0, 20.5, 19.7.

HRMS (ESI): Calcd for $([M+Na], C_{25}H_{24}O_2Na)^+$: $m/z = 379.1669$, found 379.1667

Chiral HPLC data: AD3 chiral column, 1% IPA/hexanes 2 mL/min, $t_R(\text{minor}) = 4.8$ min, $t_R(\text{major}) = 5.7$ min, $\lambda = 254$ nm

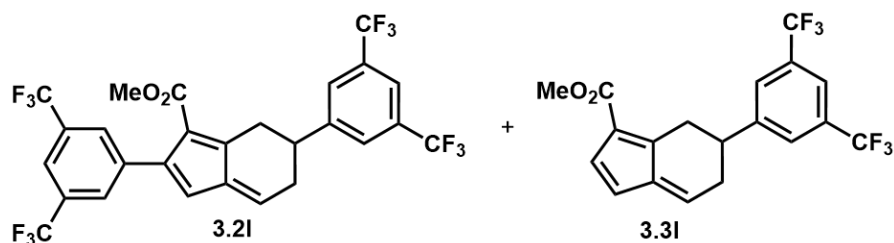
Characterization data for **methyl 5-(o-tolyl)-5,6-dihydro-4H-indene-3-carboxylate (3.3k)**:

^1H NMR (600 MHz, CDCl_3) δ 7.39 – 7.35 (m, 1H), 7.23 – 7.18 (m, 2H), 7.15 (td, $J = 7.3, 1.4$ Hz, 1H), 7.03 (dd, $J = 5.3, 3.5$ Hz, 1H), 6.80 (d, $J = 5.4$ Hz, 1H), 6.18 (dd, $J = 5.4, 1.0$ Hz, 1H), 3.77 (s, 3H), 3.57 – 3.50 (m, 1H), 3.45 (dddd, $J = 13.5, 9.7, 5.9, 4.2$ Hz, 1H), 2.85 (dd, $J = 17.6, 13.0$ Hz, 1H), 2.71 – 2.66 (m, 2H), 2.35 (s, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 165.6, 145.4, 144.1, 143.3, 142.6, 135.7, 132.5, 130.8, 127.3, 126.6, 126.3, 125.8, 119.5, 51.3, 39.1, 34.2, 31.6, 19.6.

HRMS (EI): Calcd for $([\text{M}], \text{C}_{18}\text{H}_{18}\text{O}_2)^+$: $m/z = 266.1301$, found 266.1308

Chiral HPLC data: AD3 chiral column, 1% IPA/hexanes 2 mL/min, $t_R(\text{minor}) = 4.3$ min, $t_R(\text{major}) = 5.0$ min, $\lambda = 254$ nm



methyl 2,5-bis(3,5-bis(trifluoromethyl)phenyl)-5,6-dihydro-4H-indene-3-carboxylate (3.2I) and **methyl 5-(3,5-bis(trifluoromethyl)phenyl)-5,6-dihydro-4H-indene-3-carboxylate (3.3I)** were prepared according to General Procedure A using 25.8 mg (0.10 mmol, 2 equiv) of 3,5-bis(trifluoromethyl)phenylboronic acid. The crude mixture was purified by preparatory TLC (60% DCM/hexanes) to give 7.2 mg (27%) of **3.2I** as a yellow solid (79:21 er) and 8.2 mg (42%) of **3.3I** as a yellow solid (84:16 er)

Characterization data for **methyl 2,5-bis(3,5-bis(trifluoromethyl)phenyl)-5,6-dihydro-4H-indene-3-carboxylate (3.2I)**:

¹H NMR (600 MHz, CDCl₃) δ 7.82 – 7.81 (m, 4H), 7.79 (s, 2H), 7.13 (dd, *J* = 6.0, 2.8 Hz, 1H), 6.33 (s, 1H), 3.68 (s, 3H), 3.65 (ddd, *J* = 17.6, 4.3, 1.0 Hz, 1H), 3.40 (ddt, *J* = 12.7, 11.0, 4.4 Hz, 1H), 2.97 (dd, *J* = 17.6, 13.0 Hz, 1H), 2.91 (dddd, *J* = 19.4, 5.9, 4.5, 1.1 Hz, 1H), 2.80 (ddd, *J* = 19.4, 11.1, 2.9 Hz, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 164.9, 146.6, 144.4, 144.1, 143.9, 143.4, 138.7, 132.2 (q, *J* = 33.3 Hz, 2CF₃), 131.0 (q, *J* = 33.1 Hz, 2CF₃), 128.5 (app d, *J* = 4.1 Hz), 127.5 (app d, *J* = 4.0 Hz), 126.9, 124.4 (app d, *J* = 24.0 Hz), 122.61 (app d, *J* = 24.3 Hz), 121.3 (app dt, *J* = 7.2, 3.5 Hz), 121.0 (app dt, *J* = 7.3, 3.1 Hz), 120.9, 51.3, 42.9, 34.7, 32.0.

¹⁹F NMR (565 MHz, CDCl₃) δ –62.79 (br s), –62.83 (br s).

HRMS (ESI): Calcd for ([M+Na], C₂₇H₁₆F₁₂O₂Na)⁺: *m/z* = 623.0847, found 623.0847

Chiral HPLC data: AD3 chiral column, 0.1% IPA/hexanes 2 mL/min, *t_R*(minor) = 8.2 min, *t_R*(major) = 10.0 min, λ = 254 nm

Characterization data for **methyl 5-(3,5-bis(trifluoromethyl)phenyl)-5,6-dihydro-4H-indene-3-carboxylate (3.3I)**:

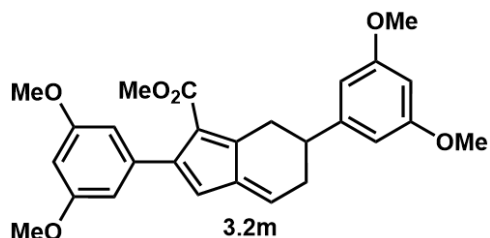
¹H NMR (600 MHz, CDCl₃) δ 7.79 (s, 1H), 7.76 (s, 1H), 6.98 (dd, *J* = 6.0, 2.8 Hz, 1H), 6.80 (d, *J* = 5.4 Hz, 1H), 6.19 (dd, *J* = 5.4, 1.0 Hz, 1H), 3.80 (s, 3H), 3.65 (ddd, *J* = 17.4, 4.3, 1.1 Hz, 1H), 3.35 (ddt, *J* = 12.3, 10.9, 4.4 Hz, 1H), 2.89 (dd, *J* = 17.6, 12.9 Hz, 1H), 2.83 (dt, *J* = 19.1, 5.3 Hz, 1H), 2.72 (ddd, *J* = 19.2, 11.0, 2.8 Hz, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 165.4, 147.0, 145.6, 142.0, 141.4, 132.7, δ 132.1 (q, *J* = 33.2 Hz), 128.0, 127.5 (d, *J* = 3.8 Hz), 124.4, 122.6, 121.09 (p, *J* = 3.9 Hz), 119.8, 51.4, 43.0, 34.4, 31.7.

^{19}F NMR (565 MHz, CDCl_3) δ -62.80 (br s).

HRMS (ESI): Calcd for $([\text{M}+\text{Na}], \text{C}_{27}\text{H}_{16}\text{F}_{12}\text{O}_2\text{Na})^+$: m/z = 623.0847, found 623.0847

Chiral HPLC data: AD3 chiral column, 1% IPA/hexanes 2 mL/min, $t_R(\text{minor})$ = 4.9 min, $t_R(\text{major})$ = 5.5 min, λ = 254 nm



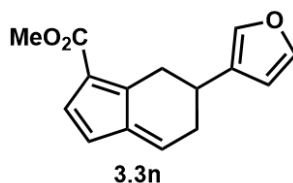
methyl 2,5-bis(3,5-dimethoxyphenyl)-5,6-dihydro-4H-indene-3-carboxylate (3.2m) was prepared according to General Procedure A using 18.2 mg (0.10 mmol, 2 equiv) of 3,5-(dimethoxy)phenylboronic acid. The crude mixture was purified by preparatory TLC (5% $\text{Et}_2\text{O}/\text{PhMe}$) to give 10.9 mg (49%) of **3.2m** as a waxy yellow solid (88:12 er).

^1H NMR (500 MHz, CDCl_3) δ 6.99 (dd, J = 6.0, 2.9 Hz, 1H), 6.53 (d, J = 2.3 Hz, 2H), 6.48 (d, J = 2.3 Hz, 2H), 6.42 (t, J = 2.3 Hz, 1H), 6.37 (t, J = 2.2 Hz, 1H), 6.20 (s, 1H), 3.81 (s, 6H), 3.79 (s, 6H), 3.70 (s, 3H), 3.47 (dd, J = 17.4, 4.2 Hz, 1H), 3.22 – 3.10 (m, 1H), 2.86 (dd, J = 17.5, 13.0 Hz, 1H), 2.79 (dt, J = 19.4, 5.3 Hz, 1H), 2.70 (ddd, J = 19.4, 10.9, 3.0 Hz, 1H).

^{13}C NMR (151 MHz, CDCl_3) δ 165.8, 161.1, 160.3, 147.2, 146.9, 143.5, 143.4, 143.0, 138.7, 127.5, 118.6, 106.2, 105.5, 99.9, 98.5, 55.5, 55.5, 51.3, 43.8, 35.1, 32.2

HRMS (ESI): Calcd for $([\text{M}+\text{Na}], \text{C}_{27}\text{H}_{28}\text{O}_6\text{Na})^+$: m/z = 471.1778, found 471.1772

Chiral HPLC data: AD3 chiral column, 10% IPA/hexanes 0.5 mL/min, $t_R(\text{minor})$ = 52.3 min, $t_R(\text{major})$ = 47.9 min, λ = 254 nm



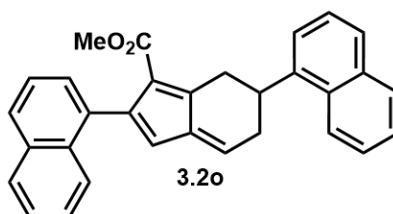
methyl 5-(furan-3-yl)-5,6-dihydro-4H-indene-3-carboxylate (3.3n) was prepared according to General Procedure A using 11.2 mg (0.10 mmol, 2 equiv) of 3-furanylboronic acid. The crude mixture was purified by preparatory TLC (30% DCM/PhMe) to give 1.8 mg (15%) of **3.3n** as a waxy yellow solid (83:17 er).

¹H NMR (600 MHz, CDCl₃) δ 7.38 (t, *J* = 1.7 Hz, 1H), 7.30 (dt, *J* = 1.7, 0.9 Hz, 1H), 6.97 (dd, *J* = 5.8, 3.1 Hz, 1H), 6.78 (d, *J* = 5.4 Hz, 1H), 6.36 (dd, *J* = 1.9, 0.9 Hz, 1H), 6.15 (dd, *J* = 5.3, 0.9 Hz, 1H), 3.80 (s, 3H), 3.59 (ddd, *J* = 17.6, 4.4, 1.1 Hz, 1H), 3.12 (tt, *J* = 9.9, 4.4 Hz, 1H), 2.86 – 2.73 (m, 2H), 2.55 (ddd, *J* = 19.2, 10.1, 2.8 Hz, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 165.6, 145.6, 143.3, 143.1, 142.8, 138.6, 132.3, 128.7, 127.4, 119.6, 109.7, 51.3, 34.2, 33.5, 31.5.

HRMS (EI): Calcd for ([M], C₁₅H₁₄O₃)⁺: *m/z* = 242.0937, found 242.0942

Chiral HPLC data: AD3 chiral column, 3% IPA/hexanes 1 mL/min, *t_R*(minor) = 10.7 min, *t_R*(major) = 11.2 min, λ = 254 nm



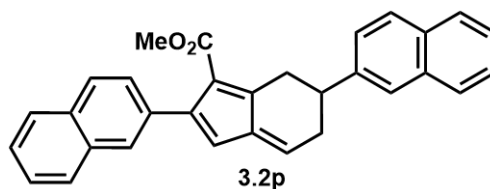
methyl 2,5-di(naphthalen-1-yl)-5,6-dihydro-4H-indene-3-carboxylate (3.2o) was prepared according to General Procedure A using 17.2 mg (0.10 mmol, 2 equiv) of 1-naphthylboronic acid. The crude mixture was purified by preparatory TLC (70% DCM/hexanes) to give 11.7 mg (55%) of **3.2o** as a waxy yellow solid (75:25 er).

¹H NMR (600 MHz, CDCl₃) δ 8.18 (d, *J* = 8.5 Hz, 1H), 7.91 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.88 – 7.85 (m, 2H), 7.84 – 7.77 (m, 2H), 7.61 (d, *J* = 7.4 Hz, 1H), 7.56 (ddd, *J* = 8.4, 6.7, 1.5 Hz, 1H), 7.53 – 7.49 (m, 2H), 7.49 – 7.40 (m, 4H), 7.15 (dd, *J* = 6.0, 2.8 Hz, 1H), 6.30 (d, *J* = 0.8 Hz, 1H), 4.25 – 4.15 (m, 1H), 3.77 (dd, *J* = 17.4, 3.9 Hz, 1H), 3.30 (s, 3H), 3.17 (dd, *J* = 17.5, 12.8 Hz, 1H), 3.02 (dddd, *J* = 19.4, 5.8, 4.3, 1.2 Hz, 1H), 2.91 (ddd, *J* = 19.2, 11.0, 2.9 Hz, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 165.4, 146.0, 144.0, 143.9, 143.5, 140.5, 136.0, 134.2, 133.4, 132.6, 131.5, 129.3, 128.9, 128.3, 127.7, 127.5, 126.4, 126.3, 125.8 (2C), 125.8, 125.6, 125.6, 125.3, 123.3, 123.0, 120.1, 50.9, 38.4, 35.0, 32.2

HRMS (EI): Calcd for ([M], C₃₁H₂₄O₂)⁺: *m/z* = 428.1771, found 428.1778

Chiral HPLC data: IC3 chiral column, 5% IPA/hexanes 1 mL/min, *t_R*(minor) = 14.7 min, *t_R*(major) = 9.8 min, λ = 254 nm



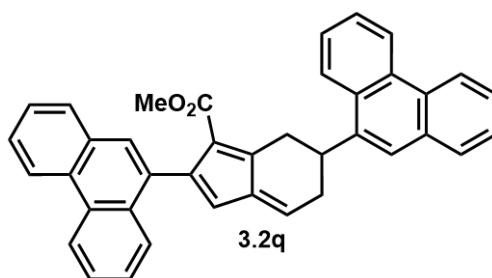
methyl 2,5-di(naphthalen-2-yl)-5,6-dihydro-4H-indene-3-carboxylate (3.2p) was prepared according to General Procedure A using 17.2 mg (0.10 mmol, 2 equiv) of 2-naphthylboronic acid. The crude mixture was purified by preparatory TLC (70% DCM/hexanes) to give 11.8 mg (55%) of **3.2p** as an orange solid (84:16 er).

¹H NMR (500 MHz, CDCl₃) δ 7.88 – 7.83 (m, 6H), 7.82 – 7.77 (m, 2H), 7.53 – 7.49 (m, 2H), 7.48 – 7.45 (m, 4H), 7.08 (dd, *J* = 5.8, 3.1 Hz, 1H), 6.33 (s, 1H), 3.67 (s, 3H), 3.67 – 3.62 (m, 1H), 3.44 (ddt, *J* = 17.6, 9.4, 4.5 Hz, 1H), 3.05 (dd, *J* = 17.5, 13.0 Hz, 1H), 2.92 (dt, *J* = 19.3, 5.3 Hz, 1H), 2.85 (ddd, *J* = 19.5, 10.7, 3.2 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 165.9, 147.1, 144.1, 143.8, 143.0, 142.1, 134.5, 133.7, 133.3, 132.9, 132.6, 128.4, 128.2, 127.9, 127.8, 127.8, 127.4, 127.0, 126.8, 126.4, 126.3, 126.1, 125.9, 125.8, 125.8, 125.5, 118.9, 51.2, 43.5, 35.2, 32.4.

HRMS (EI): Calcd for ([M], C₃₁H₂₄O₂)⁺: m/z= 428.1771, found 428.1775

Chiral HPLC data: IC3 chiral column, 10% IPA/hexanes 0.5 mL/min, t_R(minor)= 37.4 min, t_R(major)= 35.2 min, λ= 254 nm



methyl 2,5-di(phenanthren-9-yl)-5,6-dihydro-4H-indene-3-carboxylate (3.2q) was prepared according to General Procedure A using 22.2 mg (0.10 mmol, 2 equiv) of 9-phenanthracenylboronic acid. The crude mixture was purified by preparatory TLC (70% DCM/hexanes) to give 13.7 mg (52%) of **3.2q** a yellow solid (65:35 er).

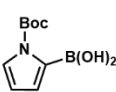
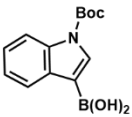
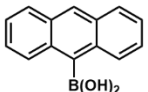
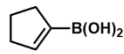
¹H NMR (600 MHz, CDCl₃) δ 8.84 – 8.78 (m, 1H), 8.75 – 8.72 (m, 1H), 8.71 (dd, *J* = 8.2, 3.4 Hz, 2H), 8.27 – 8.22 (m, 1H), 7.94 – 7.88 (m, 3H), 7.87 (s, 1H), 7.73 (s, 1H), 7.73 – 7.58 (m, 7H), 7.55 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.20 (dd, *J* = 6.1, 2.8 Hz, 1H), 6.40 (s, 1H), 4.27 – 4.17 (m, 1H), 3.90 (d, *J* = 17.4 Hz, 1H), 3.29 (dd, *J* = 17.5, 12.6 Hz, 1H), 3.24 (s, 3H), 3.17 – 3.08 (m, 1H), 2.96 (dd, *J* = 19.3, 10.9 Hz, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 165.4, 146.3, 144.3, 144.1, 143.6, 138.6, 135.0, 132.1, 131.9, 131.7, 131.1, 130.6, 130.4, 130.1, 129.9, 129.0, 128.8, 128.7, 127.0, 127.0 (2C), 126.7, 126.7, 126.5, 126.5, 126.5, 126.3, 126.2, 124.1, 123.7, 123.7, 122.9, 122.7, 122.6, 120.1, 50.9, 38.5, 35.0, 31.9.

HRMS (ESI): Calcd for ([M+H], C₃₉H₂₉O₂)⁺: m/z= 529.2162, found 529.2161

Chiral HPLC data: AD3 chiral column, 10% IPA/hexanes 1.0 mL/min, $t_R(\text{minor}) = 42.9$ min, $t_R(\text{major}) = 23.2$ min, $\lambda = 254$ nm

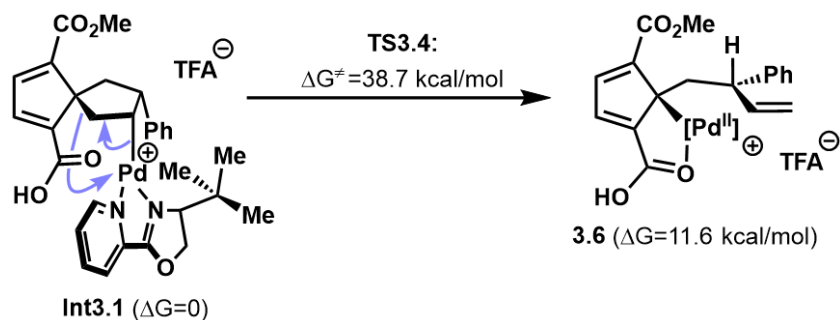
Table S3.7. Substrate Scope of Arylboronic Acids- Unsuccessful Substrates

					
30% SM ^[a] , 15% Heck product ^[b]	mostly SM	only SM	only SM	only SM	only SM

^[a]Determined by integration of ¹H NMR of crude reaction mixture relative to pyrazine internal standard. ^[b]The likely Heck product was determined by analogy to known diagnostic peaks of **3.4**, NMR yield was determined with pyrazine as internal standard.

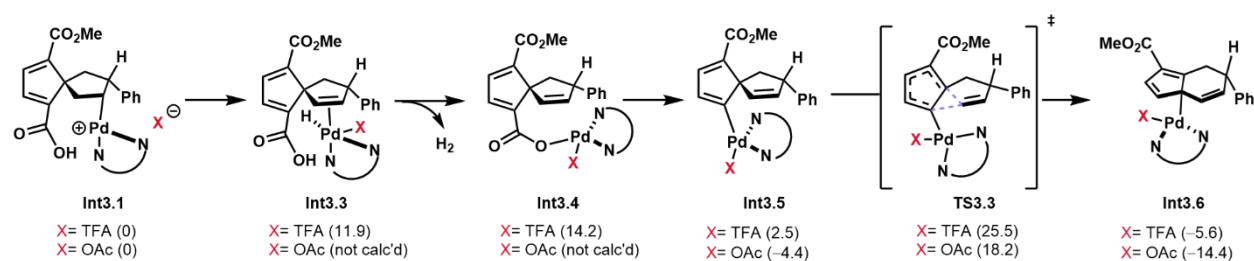
3.8.3 Additional Mechanistic Insight and Discussion

3.8.3.1 β -Carbon Elimination

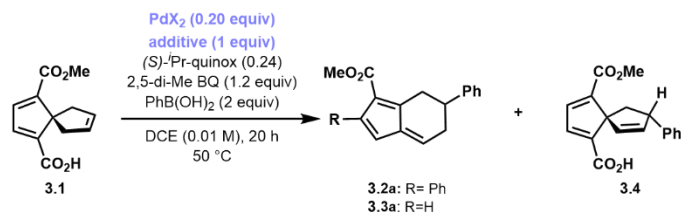


Scheme S3.1. Calculated thermodynamic and TS energies (in units of kcal/mol) are shown for the proposed β -carbon elimination pathway.

3.8.3.2 Effects of Acetate vs. Trifluoroacetate Coordination



Scheme S3.2. Calculated energies for TFA and OAc as X-type ligands are shown in parentheses in units of kcal/mol. For cationic structure **Int3.1**, the energy of the respective anion (OAc or TFA) at infinite distance was added. The acetate bound versions of **Int3.5**, **TS3.3**, and **Int3.6** are labeled as **Int3.5-OAc**, **TS3.3-OAc**, and **Int3.6-OAc** in the SI.



entry	PdX ₂	additive	ratio of fulvenes (3.2a+3.3a) to 3.4 ^[a]
1	Pd(TFA) ₂	KTFA	11.9 : 1
2	Pd(TFA) ₂	KOAc	1 : 1
3	Pd(OAc) ₂	KTFA	1 : 1.1
4	Pd(OAc) ₂	KOAc	1 : 2

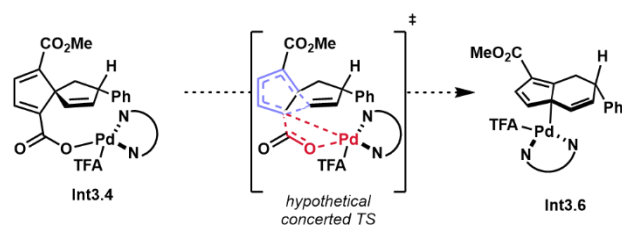
^[a]Ratios are calculated by integration of peaks in the ¹HNMR of the crude reaction mixtures.

Table S8. Effects of Acetate and Trifluoroacetate on product ratio

DFT calculations indicate that OAc as an X-type ligand gives lower energies for key vinyl palladium intermediate **Int3.5**, key transition state **TS3.3**, and product **Int3.6**, as opposed to having TFA as an X-type ligand (Scheme S3.2.) However, empirical observations suggest that the presence of OAc results in lower amounts of fulvene products **3.2a/3.3a** versus Heck product **3.4** (Table S3.5). We hypothesize this is because OAc can more strongly bind the palladium center, as opposed to TFA. This may result in OAc displacing the spirononene in **Int3.3** or the pendant carboxylate in **Int3.4**, hindering the formation of key intermediate **Int3.5**.

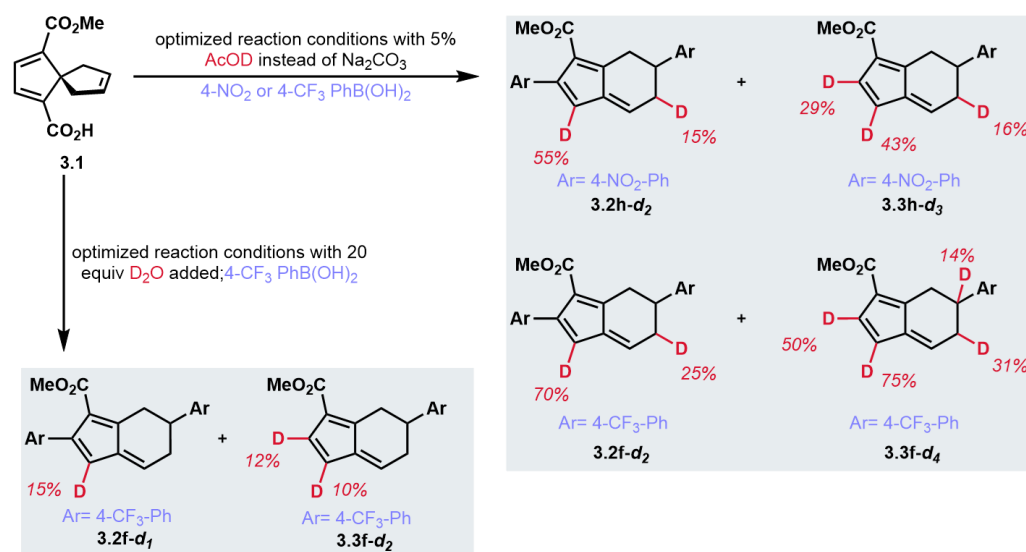
3.8.3.3 Discussion of Decarboxylation Step

Palladium-mediated decarboxylations of aryl, vinyl, and alkynyl carboxylic acids are well-documented in the literature.¹³ While many of these reports employ high temperatures (100 – 200 °C), there are indeed reports of lower temperature decarboxylations (room temperature or 70 °C).^{25–27} DFT calculations to identify a feasible TS for the decarboxylation of **Int3.4** to form **Int3.5** were conducted but were not successful. However, the existing precedents referenced above suggest a decarboxylation at 50 °C is, indeed, a feasible mechanistic step. It may be that this decarboxylation is slower than the 1,5-vinyl shift of **Int3.5**. We have observed that upon the addition of acetate to the reaction mixture (see Table S3.8), a reduced amount of fulvene (**3.2a**) is formed. This is likely because **Int3.3** and **Int3.4** persist long enough such that acetate anion can displace the spirononatriene carboxylate, releasing product **3.4**. If the 1,5-vinyl shift (see **TS3.3**) was slower than the decarboxylation, we might expect **Int3.5** to persist for enough time for other pathways to become competitive (e.g. protodemetalation). However, no such products from **Int3.5** were observed. Additionally, there is a possibility that the proposed decarboxylation and 1,5-vinyl shift are concerted (see Scheme S3.3).



Scheme S3.3. A hypothetical TS for a concerted Pd-mediated decarboxylation and 1,5-vinyl shift step is shown above.

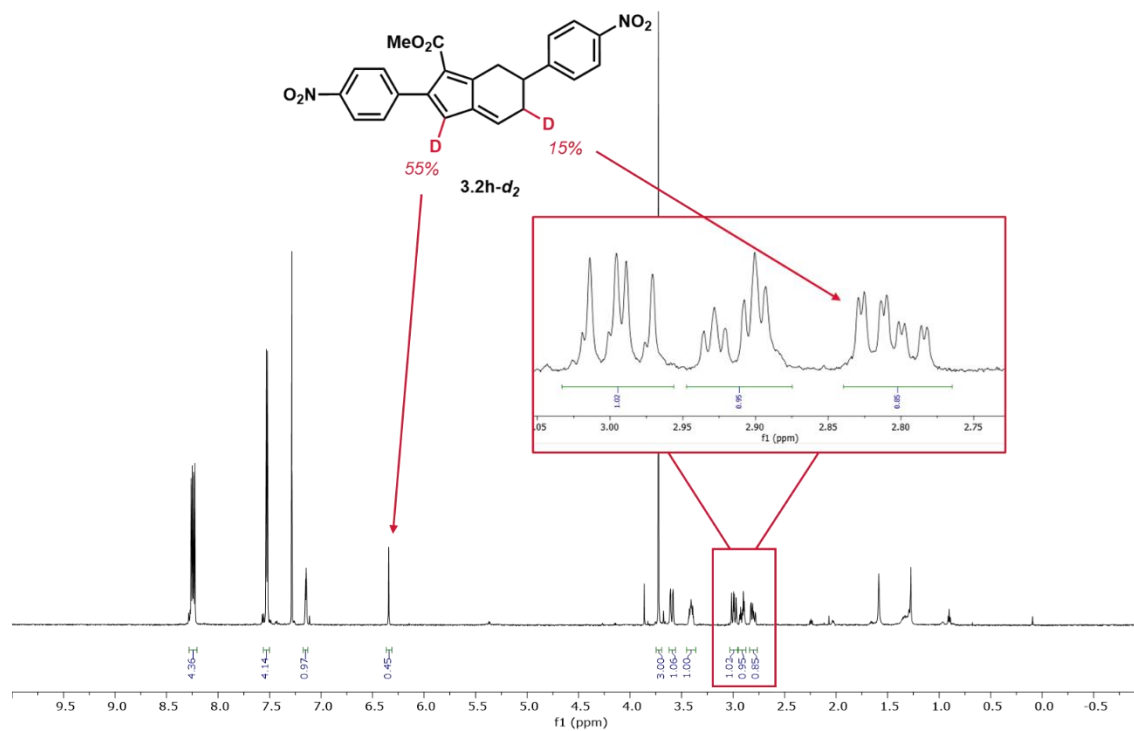
3.8.3.4 Protodemetalation Studies and ^1H NMR Spectra for Deuterated Compounds



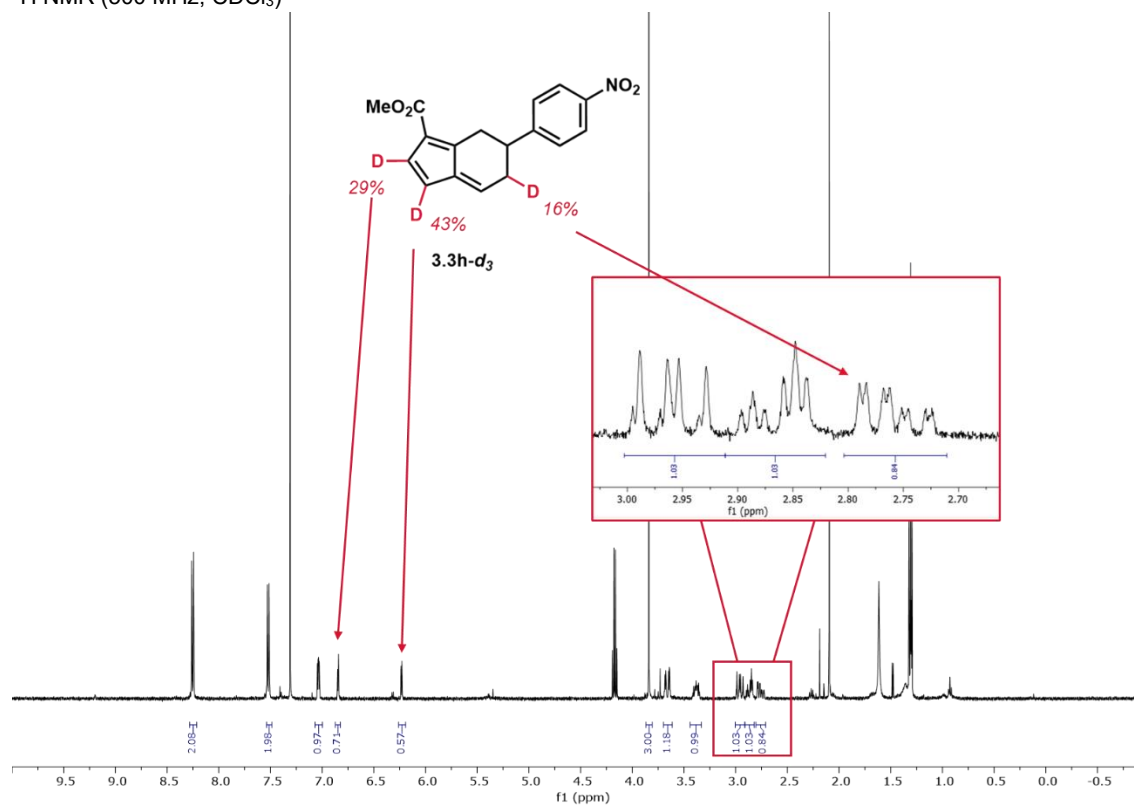
Scheme S3.4. The results of protodemetalation investigations are shown above.

Percent deuteration for the above compounds was determined by ^1H NMR integration with the methyl of the methyl ester group standardized to 3H. The spectra for these compounds are shown below. The ^1H identity was determined by analogy to those of **3.3a**, for which COESY and NOESY spectra are reported in the NMR spectra section.

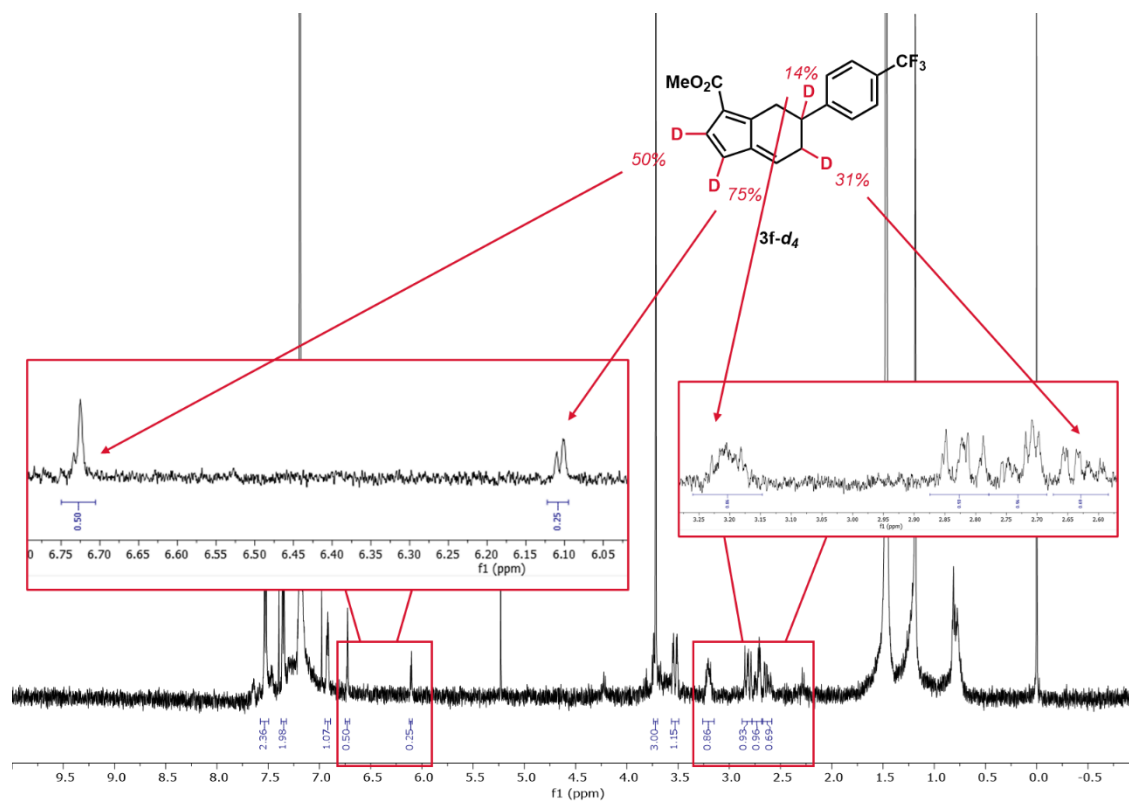
^1H NMR (700 MHz, CDCl_3)



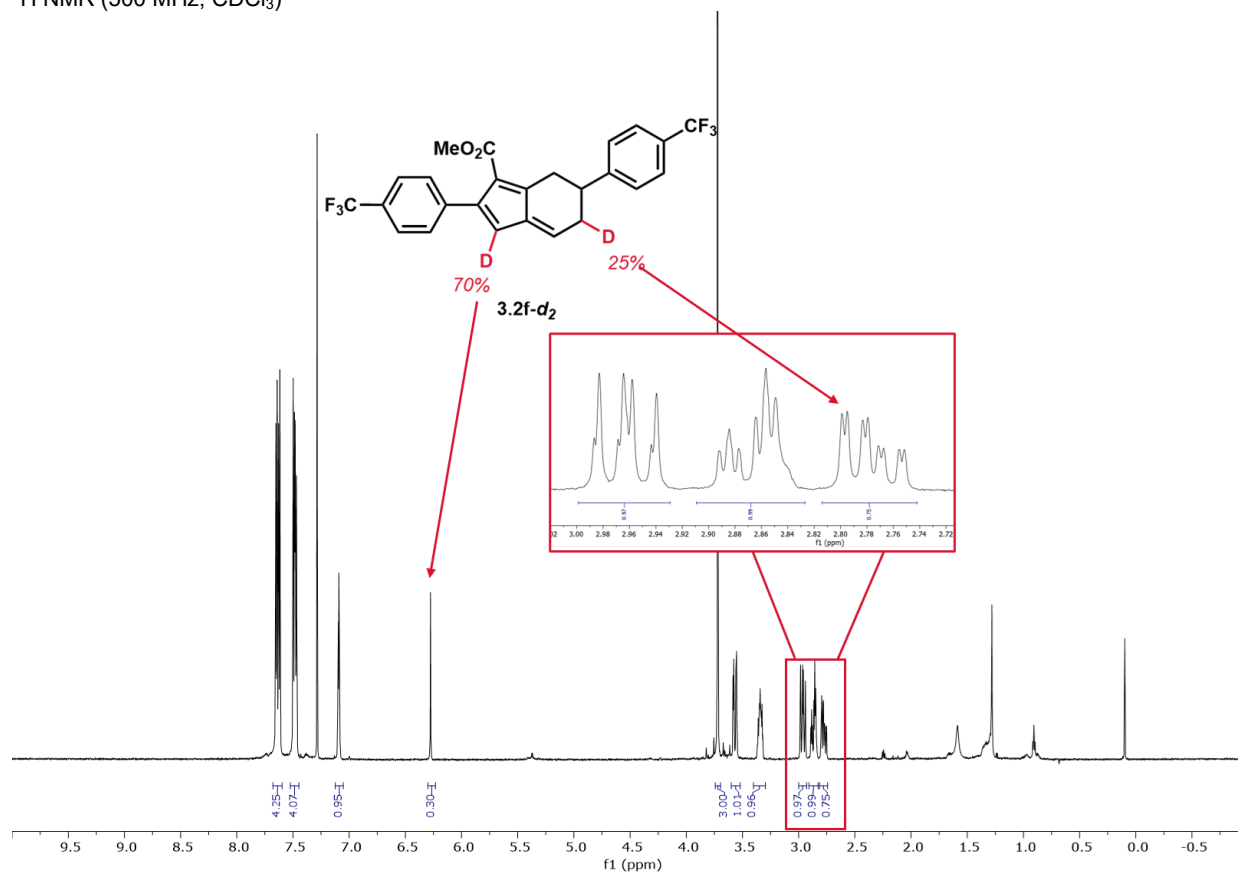
^1H NMR (500 MHz, CDCl_3)



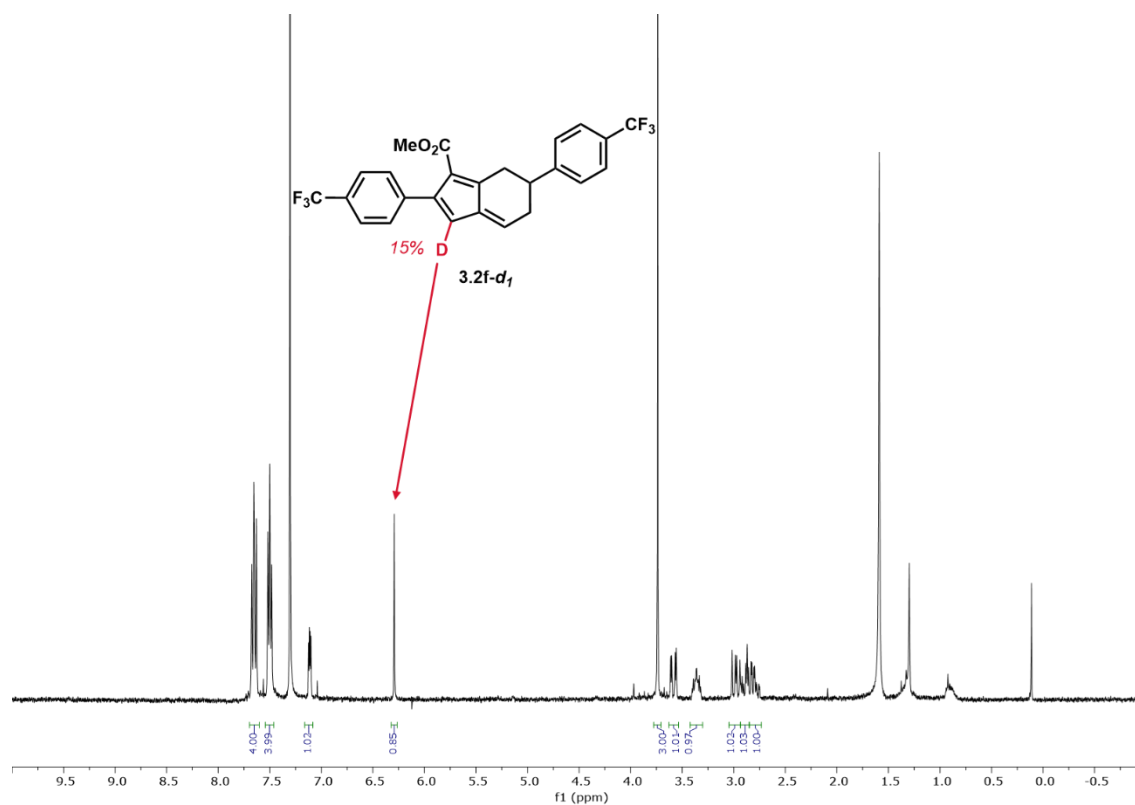
^1H NMR (500 MHz, CDCl_3)



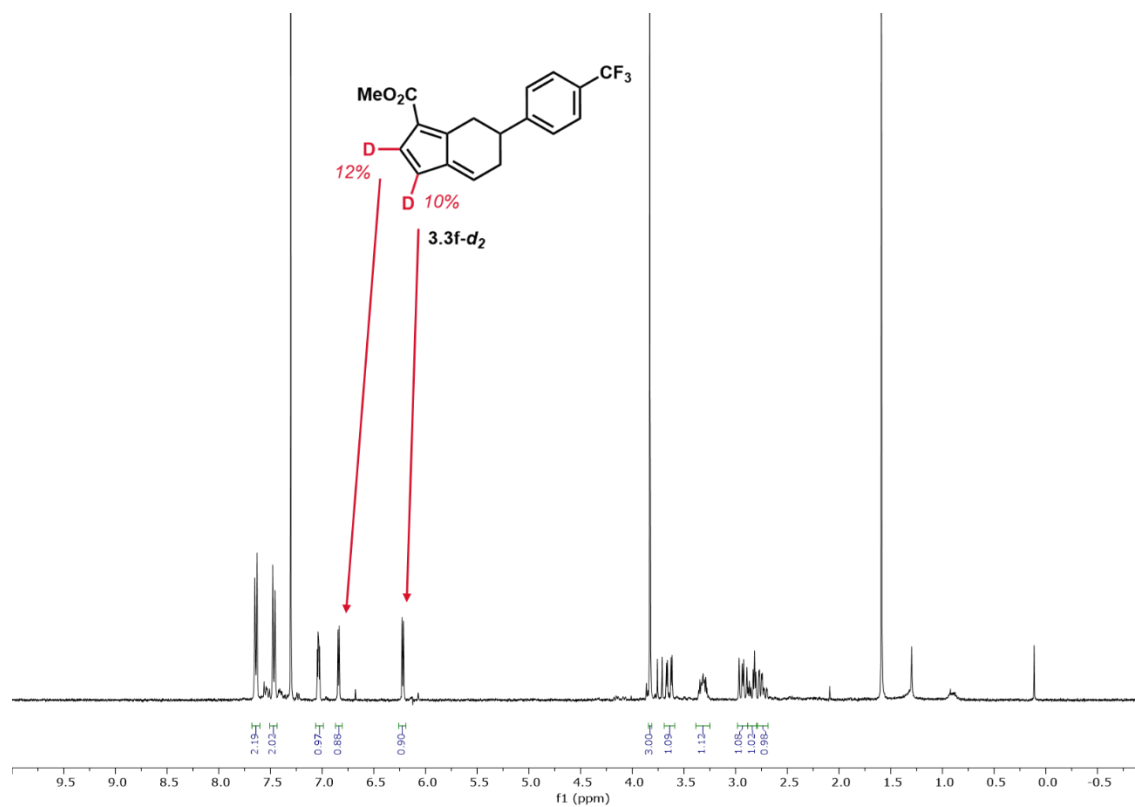
^1H NMR (500 MHz, CDCl_3)



^1H NMR (500 MHz, CDCl_3)



^1H NMR (400 MHz, CDCl_3)



3.8.3.5 Monitoring Product Distribution of 3.2h vs. 3.3h Over Time

Procedure for Reaction Monitoring:

General Procedure A was followed for the reaction of **1** with 4-NO₂-phenylboronic acid to give diaryl fulvene **2h** and monoaryl fulvene **3h**. Na₂CO₃ was omitted from this reaction in order to maintain homogeneity of aliquots removed for ¹H NMR analysis. For each time point taken, the reaction mixture was allowed to cool for 10 minutes. Then, a 450 microliter aliquot of the reaction mixture was removed and filtered through a silica plug (approximately 1 inch of silica in a glass pipette) with 7 mL of EtOAc as the eluent. The resulting solution was then concentrated under reduced pressure. The crude residue was analyzed by ¹H NMR analysis with pyrazine as an internal standard (δ 8.64 ppm (s, 4H) for pyrazine, δ 6.32 ppm (s, 1H) for **2h**, and δ 6.19 (d, 1H) for **3h**).

Results:

time (h)	% 3.2h	% 3.3h	ratio 3.2h:3.3h
1	0	4	--
2	0	14	--
3	1	20	1:20
4	3	27	1:9
5	4	32	1:8
6	4	33	1:8.3
7	7	43	1:6.1
8	9	43	1:4.8
9	11	47	1:4.3
10	15	51	1:3.4
11	17	51	1:3
23	40	42	1:1
49	46	33	1.4:1

Table S3.9. % Yields of **3.2h** and **3.3h** determined by ¹H NMR analysis are shown above, along with the ratio of **3.2h:3.3h**.

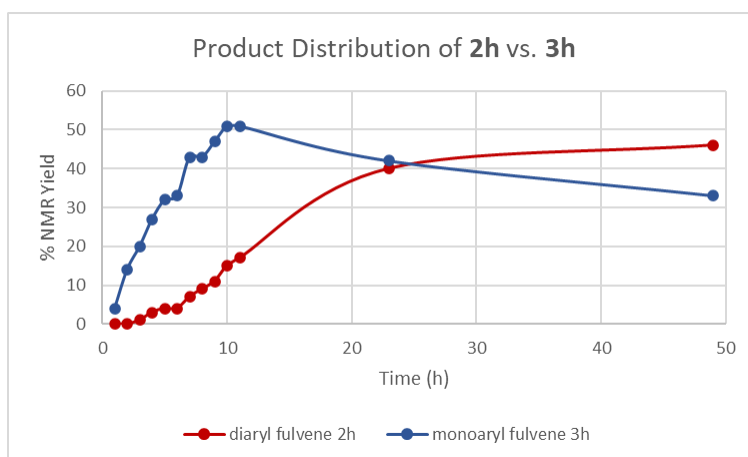


Figure S3.1. % Yields of **3.2h** (red) and **3.3h** (blue) determined by ¹H NMR analysis are graphed above.

Discussion:

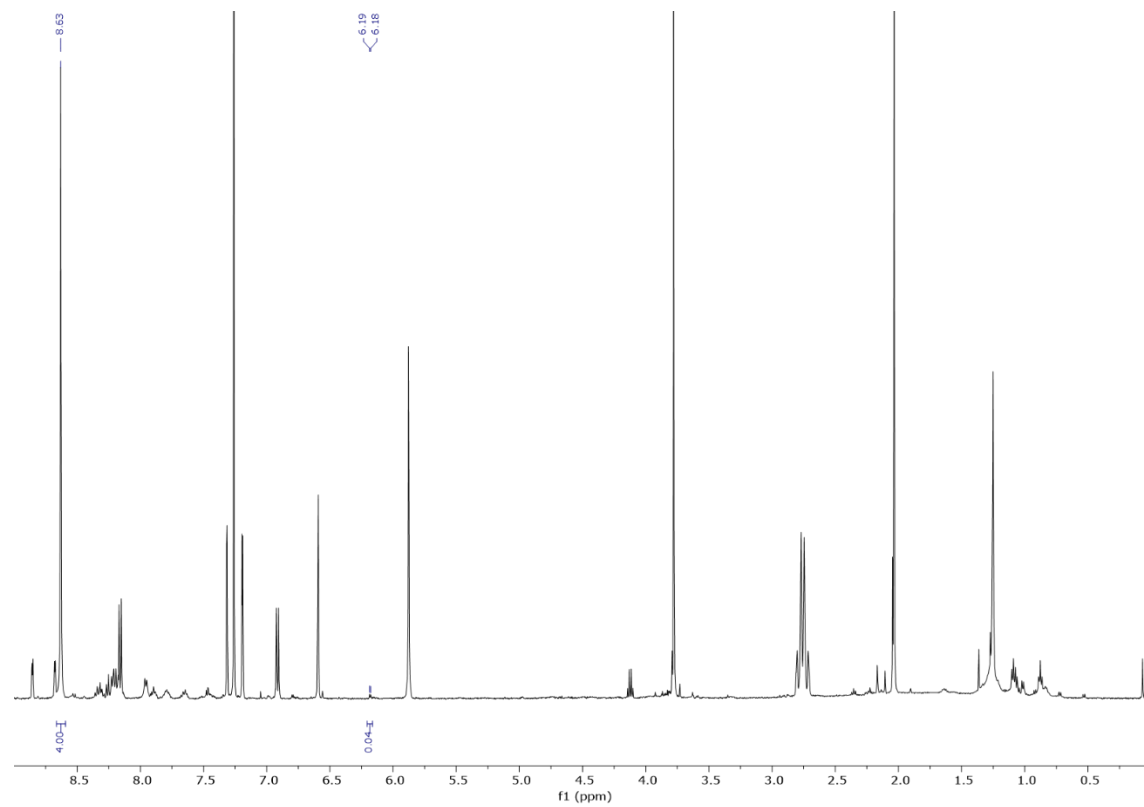
The oxidative Heck reaction of **3.1** with 4-NO₂-phenylboronic acid was monitored over a 49 hour period in order to test the hypothesis that 4-NO₂-Ph monoaryl fulvene (**3.3h**) forms initially and is then converted to 4-NO₂-Ph diaryl fulvene (**3.2h**). After two hours of reaction, only monoaryl fulvene **3.3h** is detected and no diaryl fulvene **3.2h** is observed, indicating that the monoarylfulvene is, indeed formed first. Trace amounts of **3.2h** (1%) are first detected after three hours of reaction time. The NMR yield of **3.3h** continues to increase faster than that of **3.2h** with the mixture containing 51% **3.3h** and 17% **3.2h** (a ratio of 3:1, **3.3h:3.2h**) at 11 hours of reaction time. After 23 hours of total reaction time, the amount of **3.3h** is reduced to 42% while the amount of **3.2h** is increased 40% (approximately 1:1 ratio). Extended reaction time to 49 hours results in a further

increase in the amount of diaryl fulvene **3.2h** (46%), accompanied by a further decrease in the amount of monoaryl fulvene **3.3h** (33%). The initial increase in monoaryl fulvene **3.3h**, followed by a decrease in **3.3h** and concurrent increase in **3.2h** supports the initial hypothesis that monoaryl fulvene is formed first and then converted to diaryl fulvene. For electron deficient arylboronic acids, the second oxidative Heck to give diaryl fulvene is likely slow enough such that monoaryl fulvenes are present in isolable quantities after 20 hours of reaction time. For electron-rich or -neutral arylboronic, the second oxidative Heck reaction is likely fast such that little monoaryl fulvene remains after the standard reaction time of 20 hours.

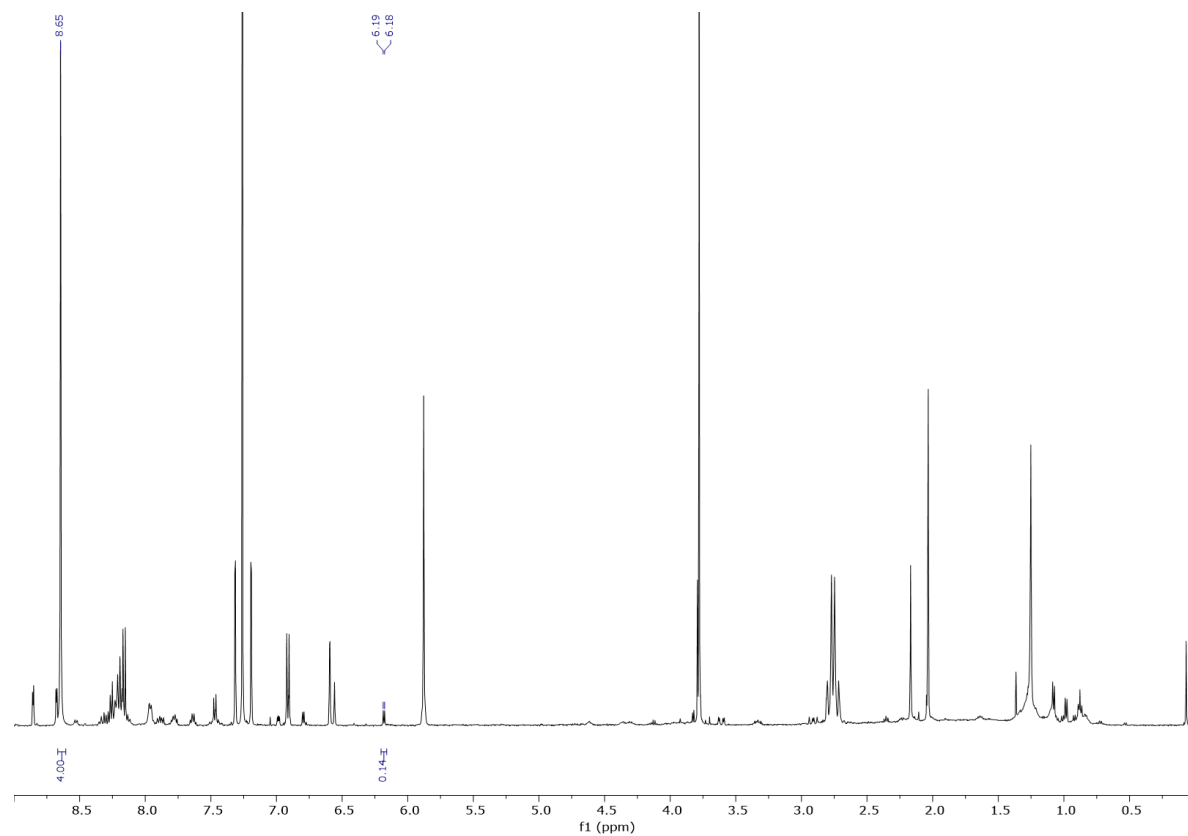
¹H NMR Spectra Used to Determine Product Distribution

All spectra shown in this section are ¹H NMRs (500 MHz, CDCl₃). Insets around diagnostic peaks for **3.2h** and **3.3h** for t=3h, t=11h, t=23h, and t=49h are shown for clarity.

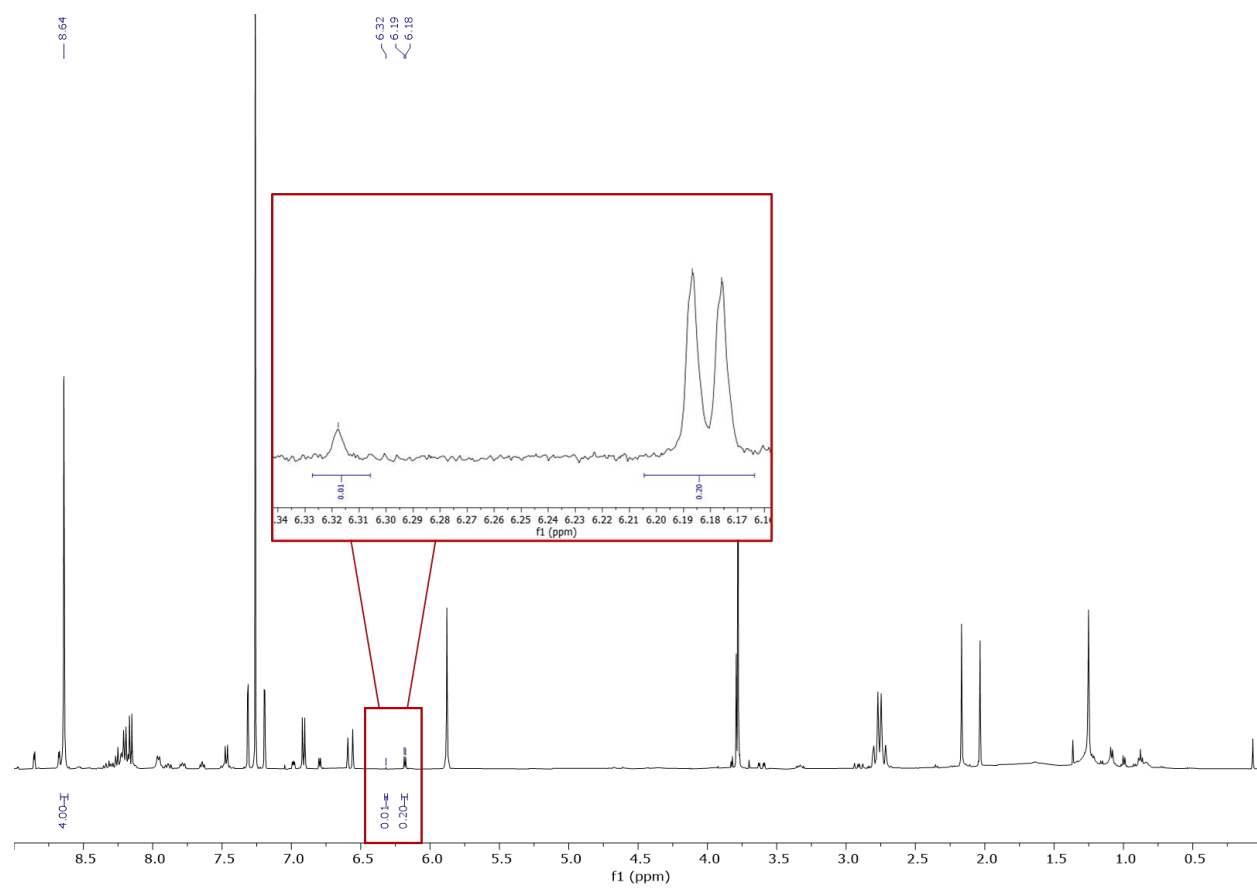
t = 1 h



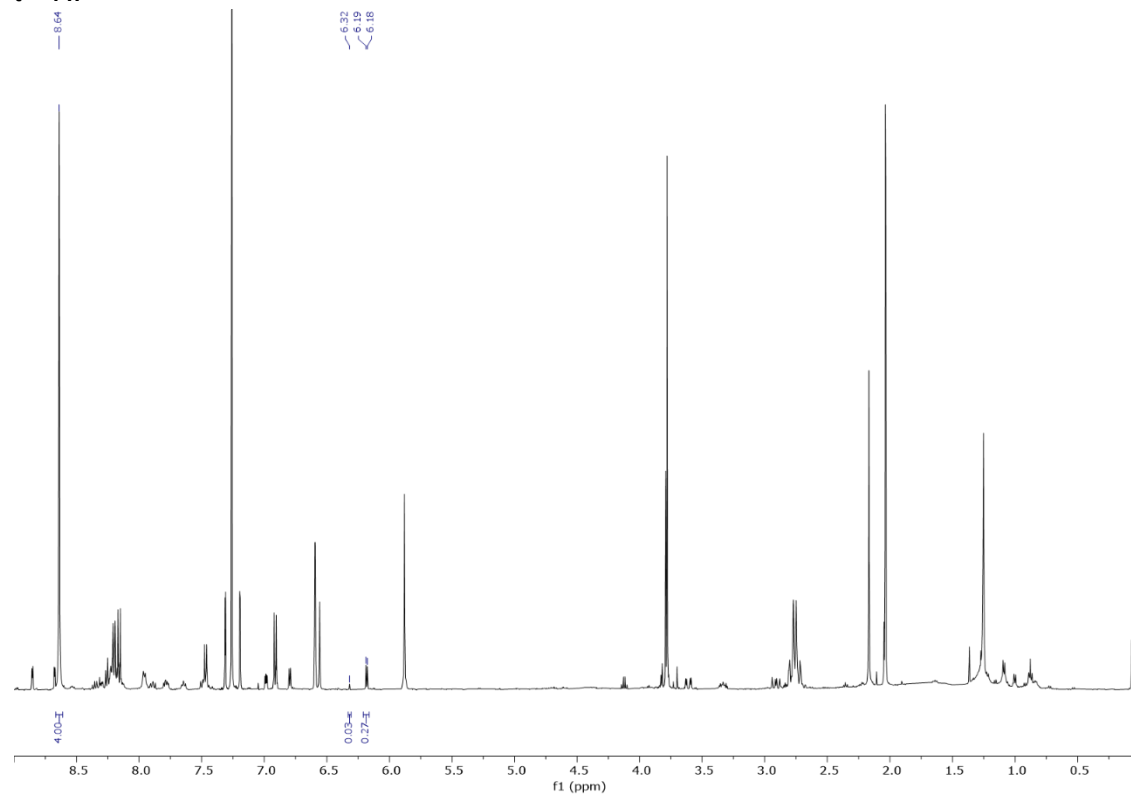
t = 2 h



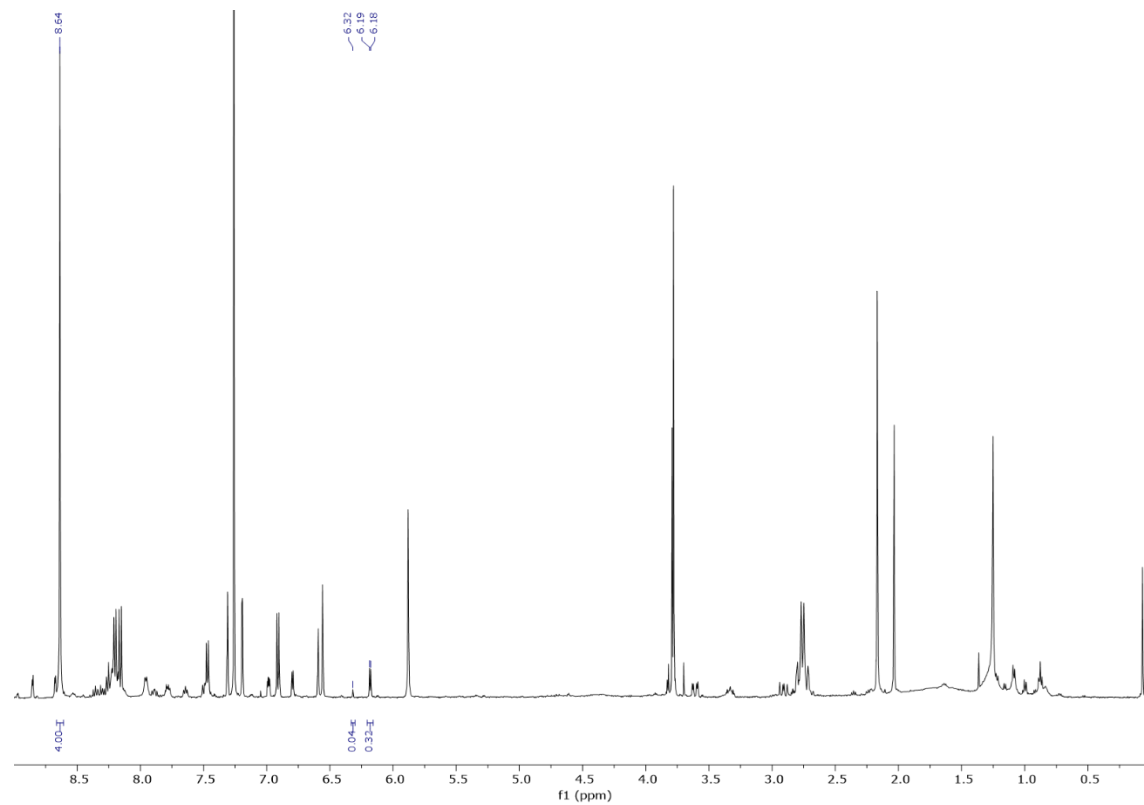
t = 3 h



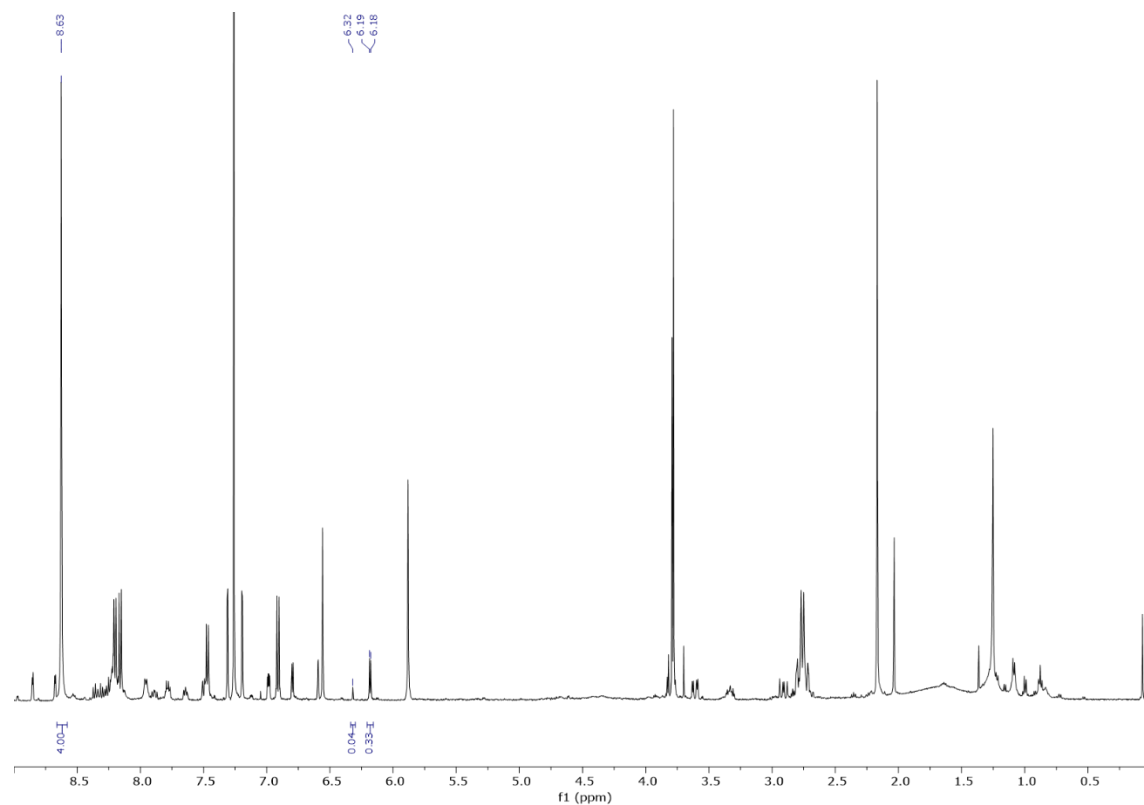
t = 4 h



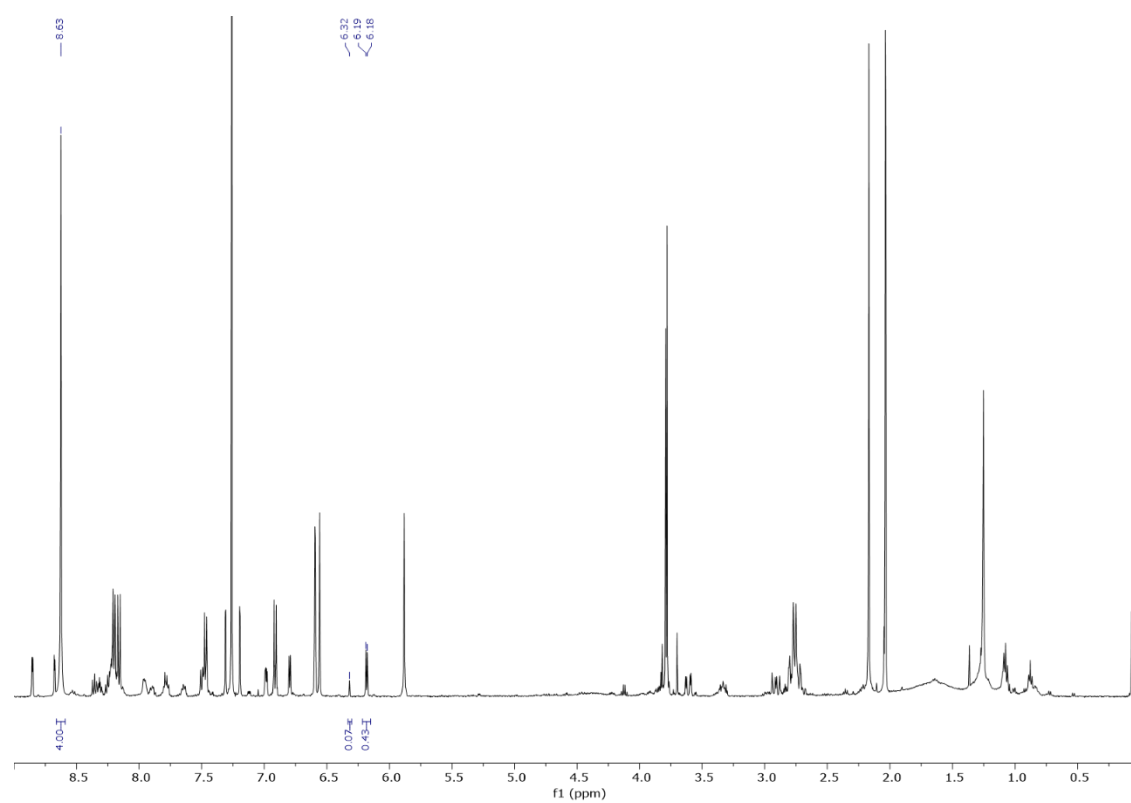
t = 5 h



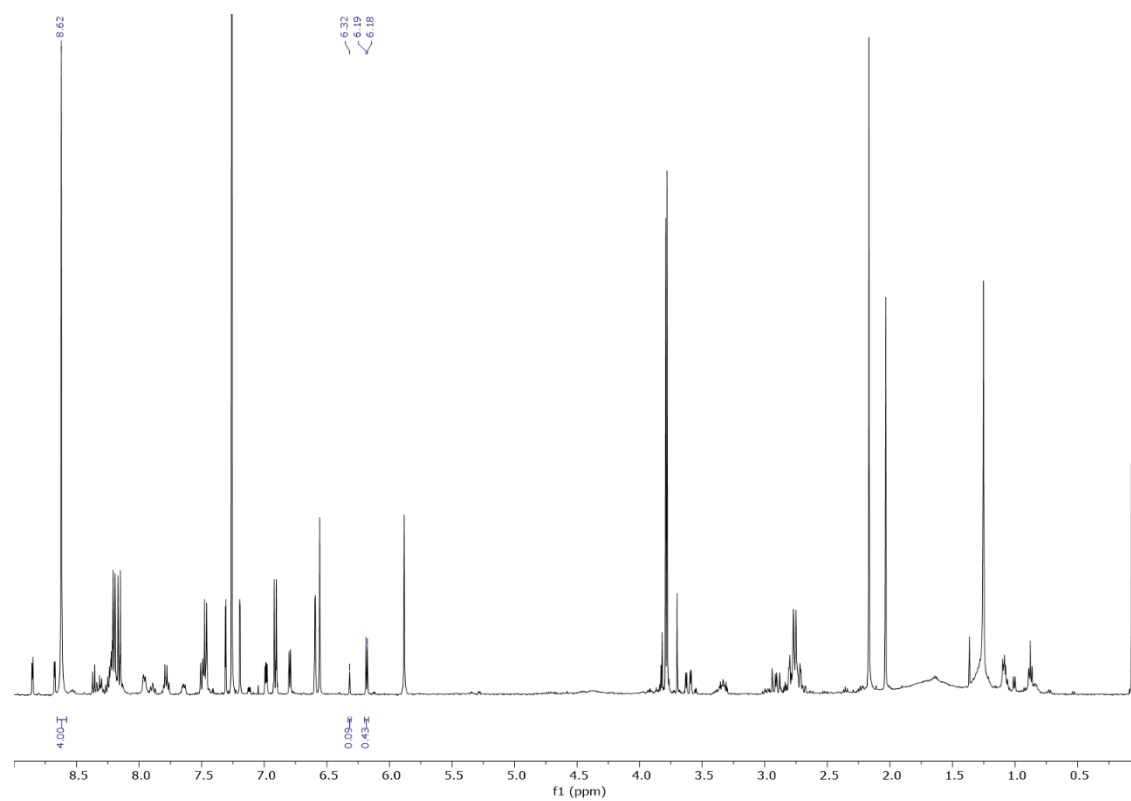
t = 6 h



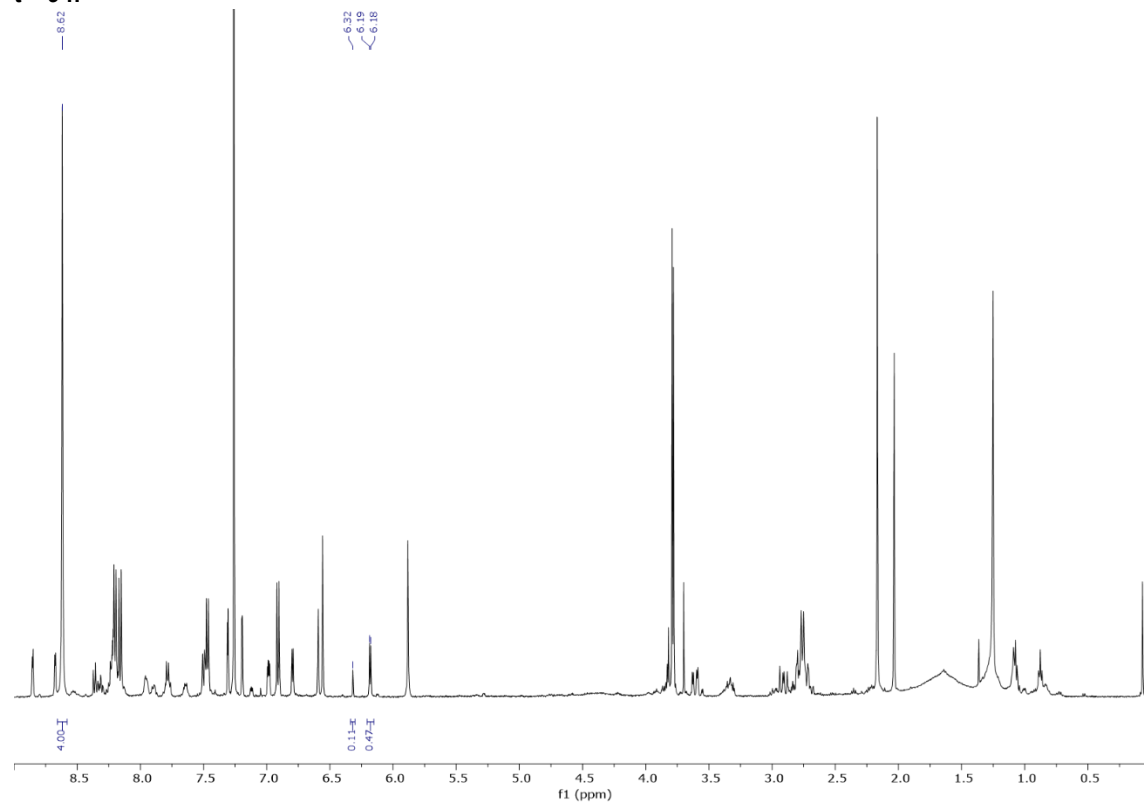
t = 7 h



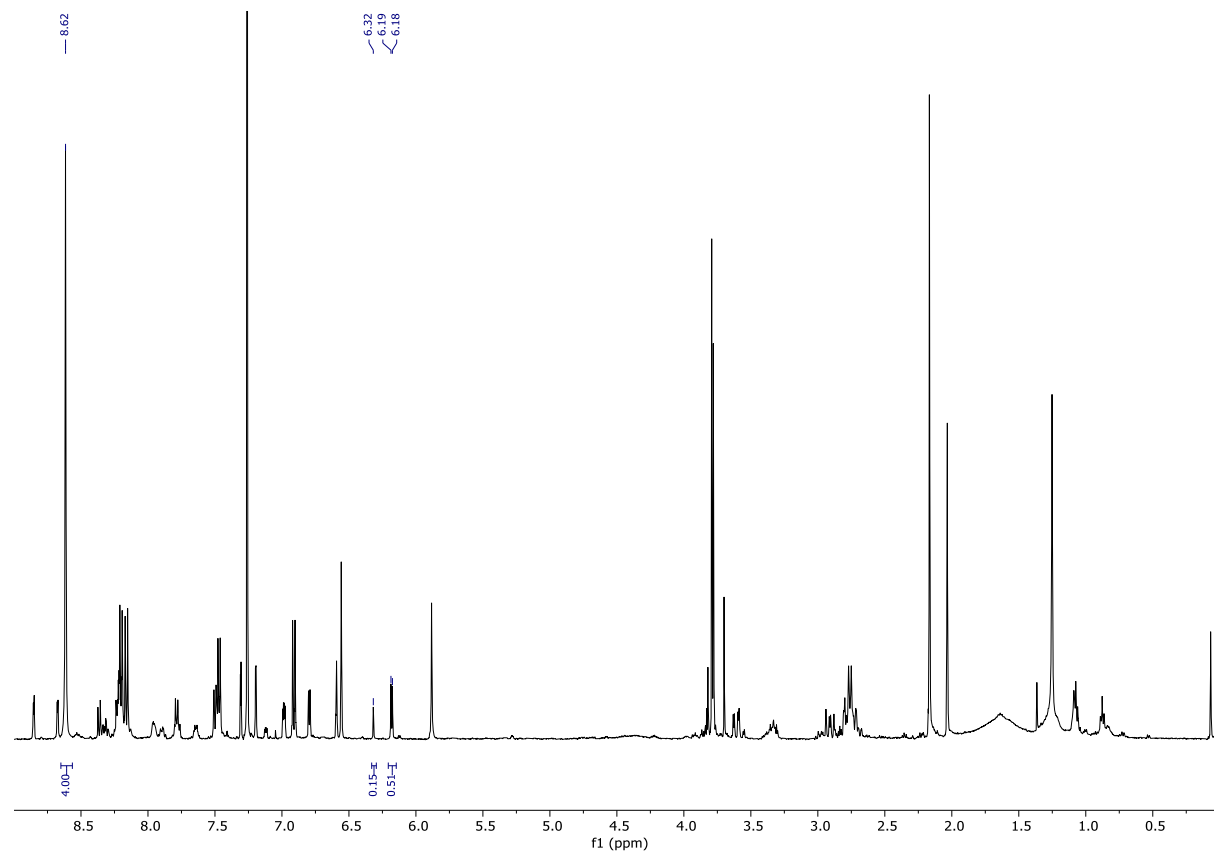
t = 8 h



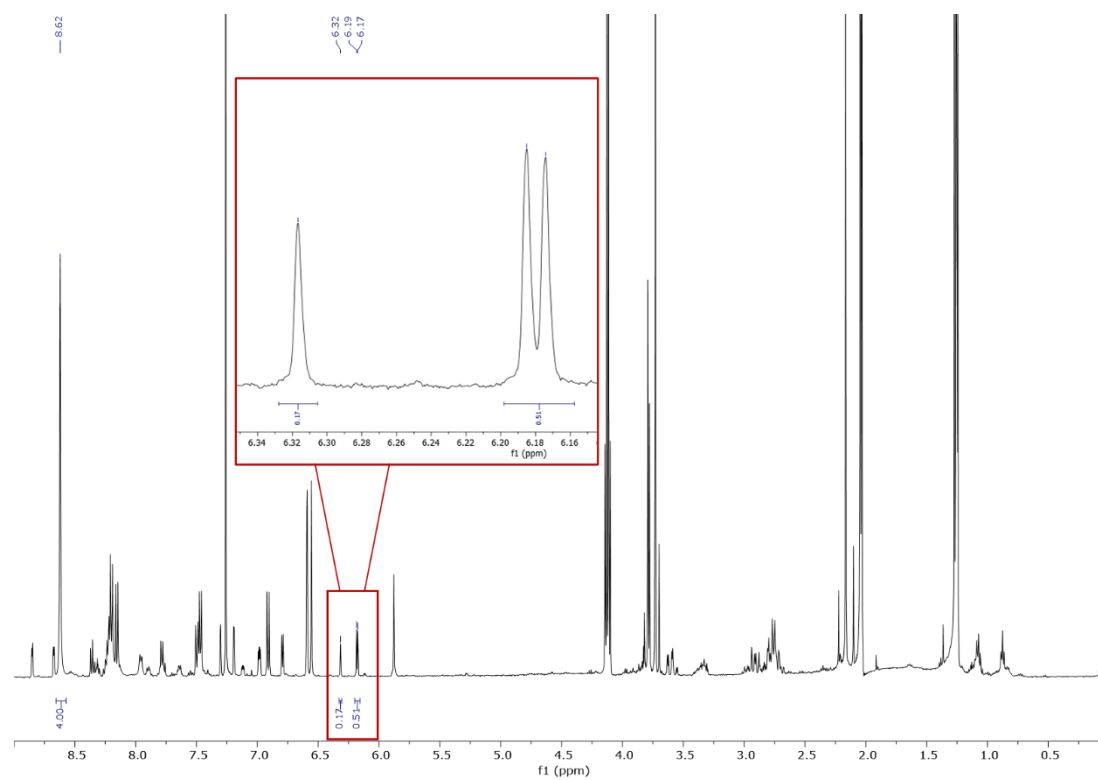
t = 9 h



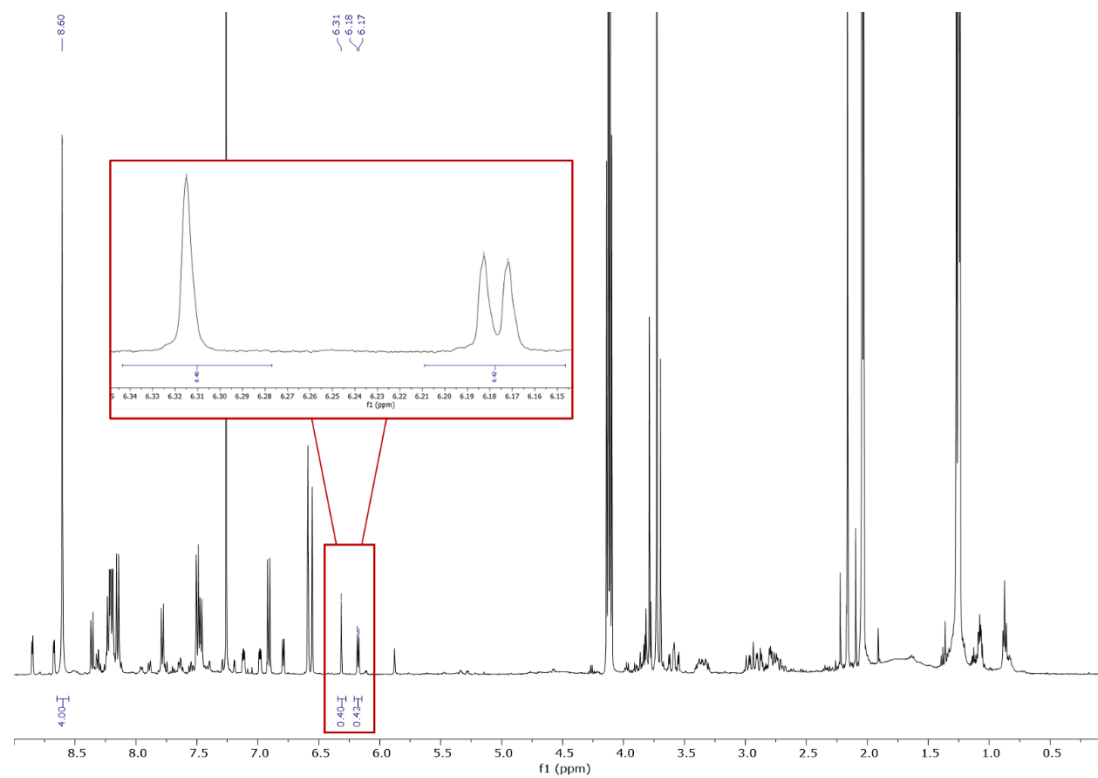
t = 10 h



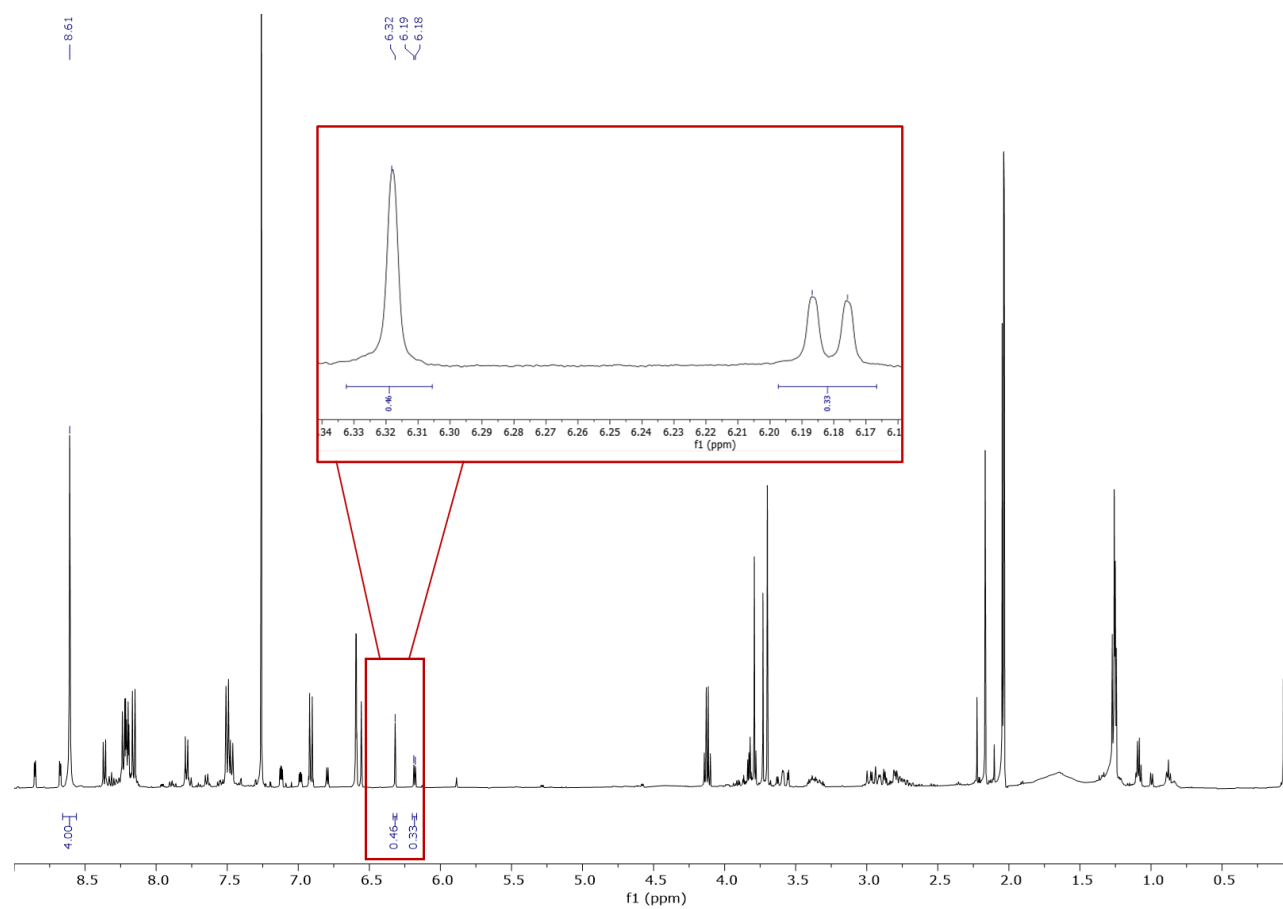
t = 11 h



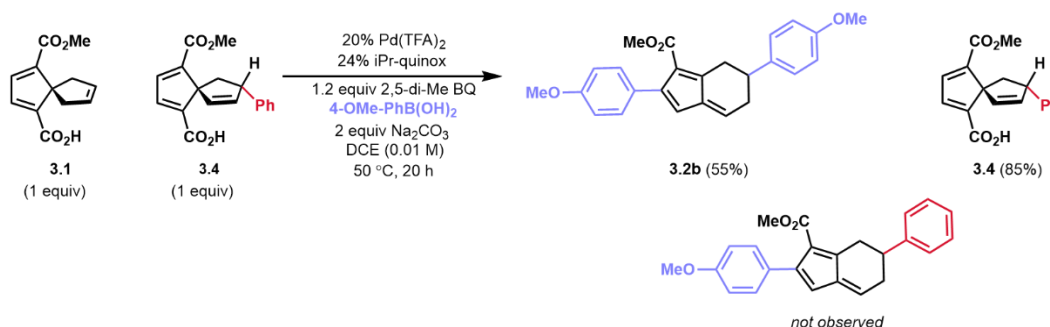
t = 23 h



t = 49 h



3.8.3.6 Resubjecting Heck Product (3.4) to Reaction Conditions with SM (3.1)

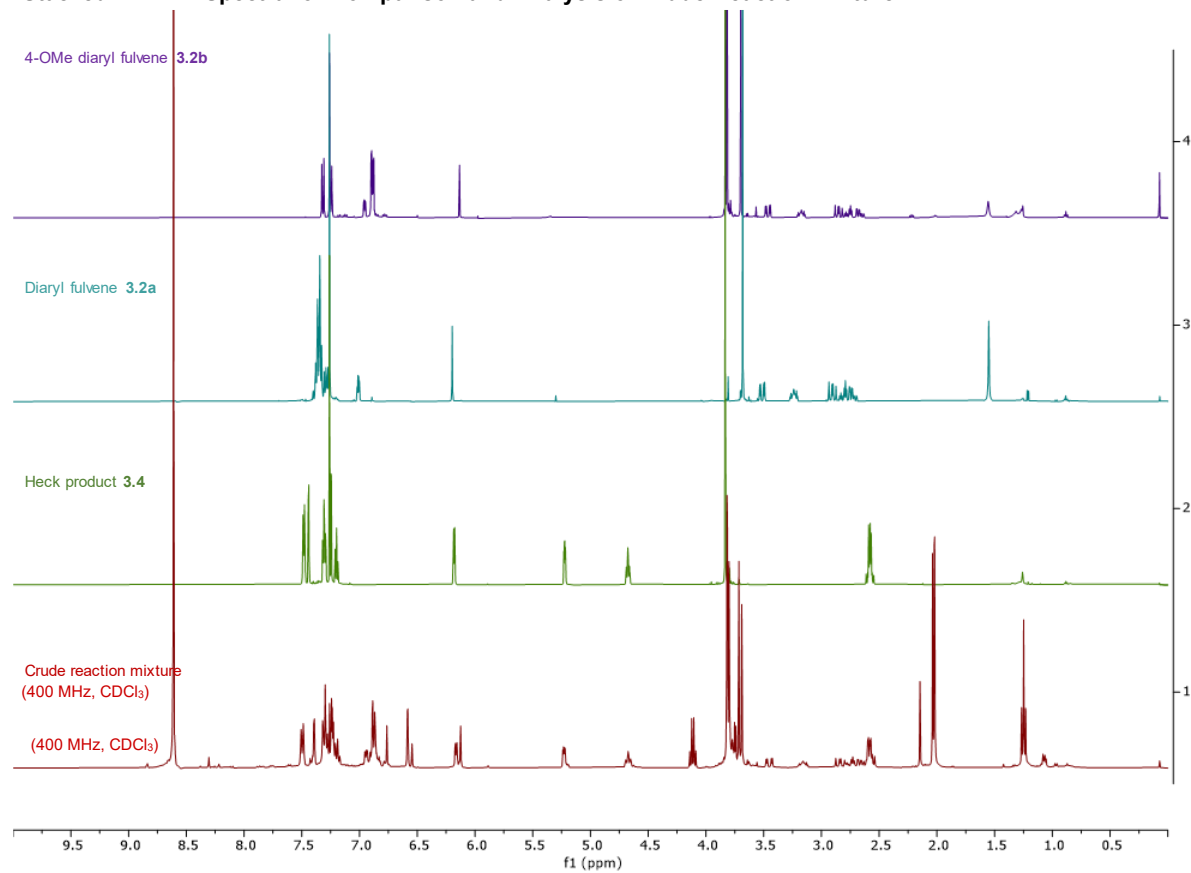


Scheme S5. Heck product (**3.4**) was subjected to the reaction conditions, along with starting material (**3.1**).

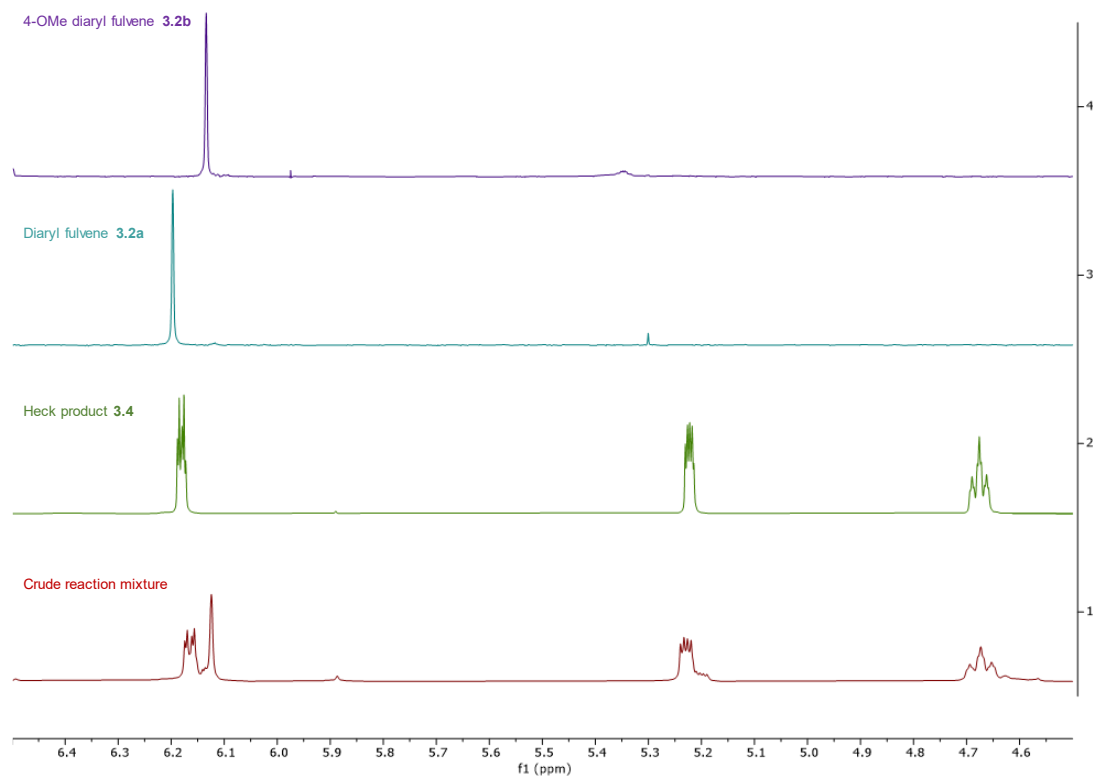
The reaction shown in Scheme S5 was conducted according to General Procedure A, with the addition of a solution of **4** in DCE prior to the addition of arylboronic acid.

This experiment offers additional support for the Heck product (**3.4**) not being transformed to fulvene products under the reaction conditions. While the results presented in Table 3.3 indicate that **3.4** does not rearrange to fulvene products when subjected to the reaction conditions, those experiments do not account for any transient species that may be formed from the reaction of **3.1**. It could be that such a transient species may react intermolecularly with **3.4** to facilitate its rearrangement to a fulvene product. We tested this hypothesis by subjecting a mixture of both **3.4** and **3.1** to the reaction conditions with 4-OMe-PhB(OH)₂. If **3.4** is, in fact, transformed to a fulvene product by reaction with some transient species formed due to the presence of **3.1**, we would expect significant consumption of **3.4**, along with the observation of a new diaryl fulvene bearing an unsubstituted phenyl group conserved from **3.4** and a newly installed 4-OMe-phenyl group. ¹H analysis of the crude reaction mixture with an internal standard indicates that diaryl fulvene **2b** was obtained and in 55% yield and **3.4** was recovered in 85% yield. Moreover, no new diaryl fulvene bearing both a phenyl group and 4-OMe-phenyl group was observed (by comparison to diagnostic regions of **3.2a** and **3.2b**; see stacked spectra below). This experiment provides additional support that Heck product (**3.4**) is not converted to fulvene products.

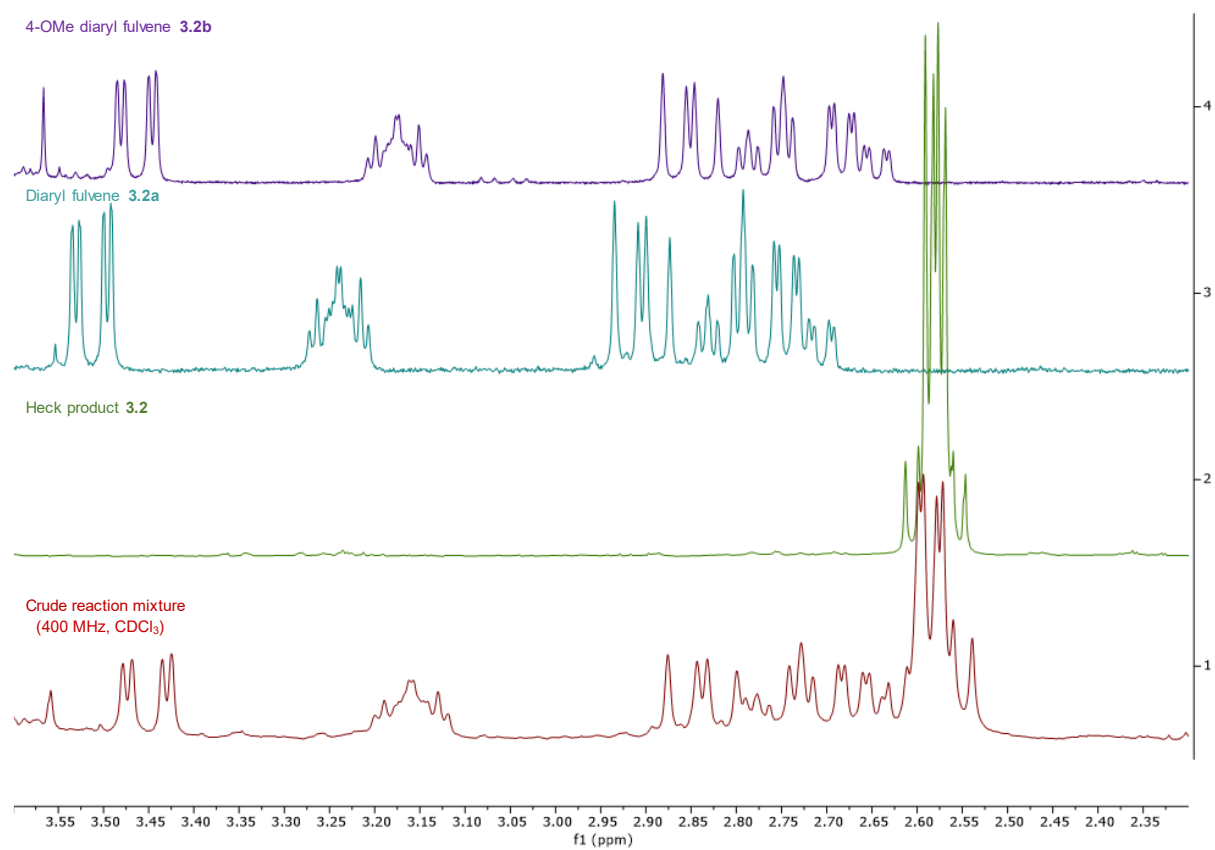
Stacked ¹H NMR Spectra for Comparison and Analysis of Crude Reaction Mixture



Stacked ¹H NMR Spectra for Comparison and Analysis of Crude Reaction Mixture (4.5–6.5 ppm)

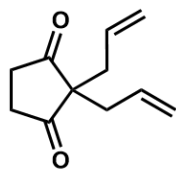


Stacked ^1H NMR Spectra for Comparison and Analysis of Crude Reaction Mixture

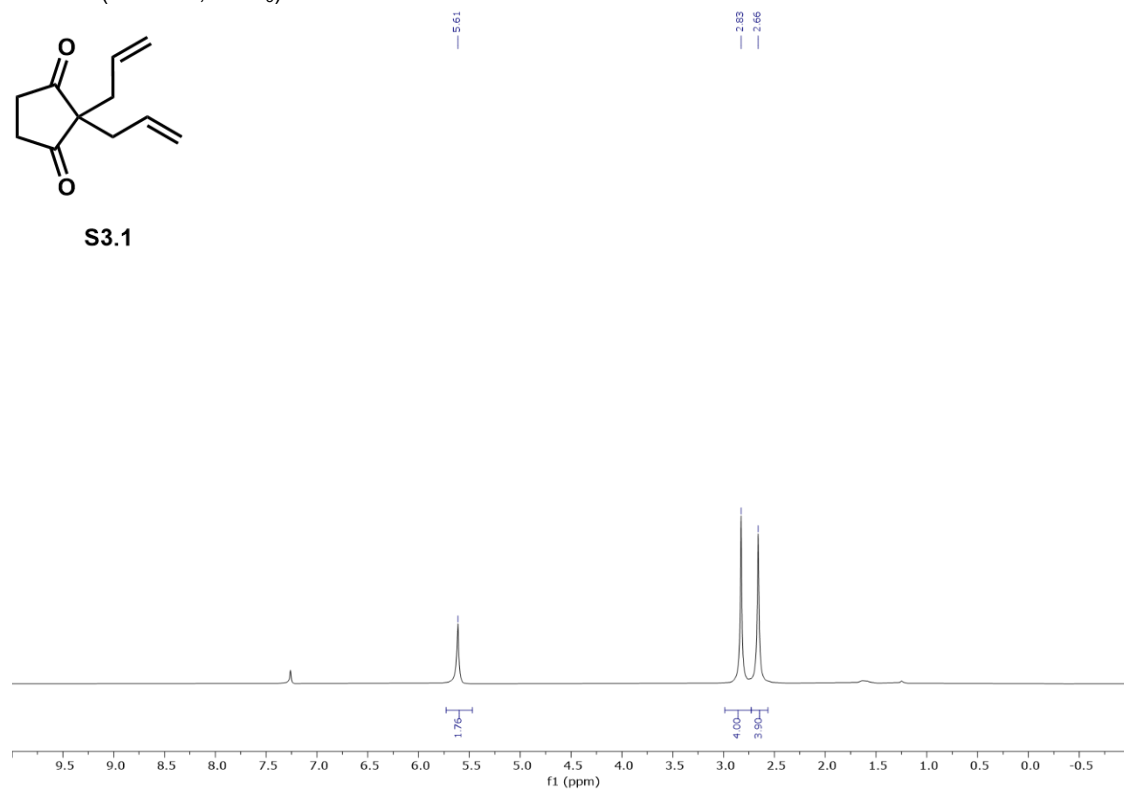


3.8.4 NMR Spectra

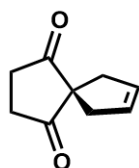
^1H NMR (300 MHz, CDCl_3)



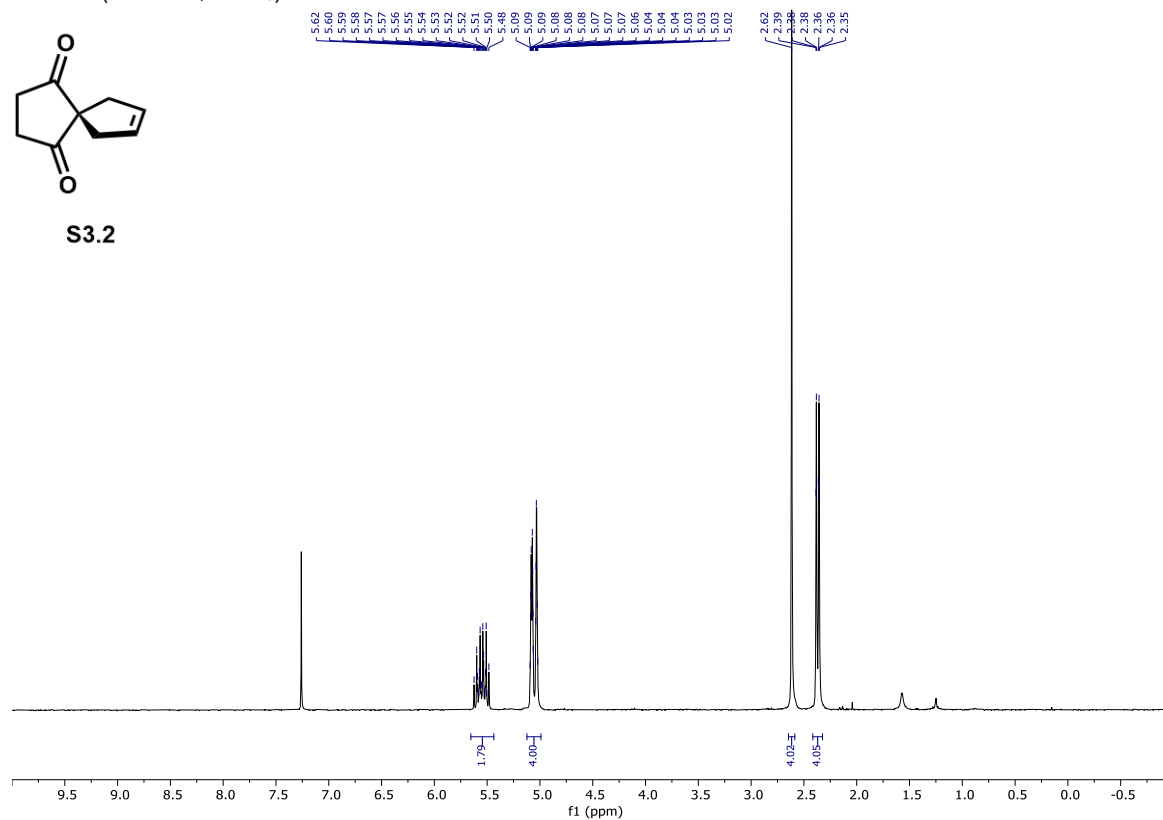
S3.1



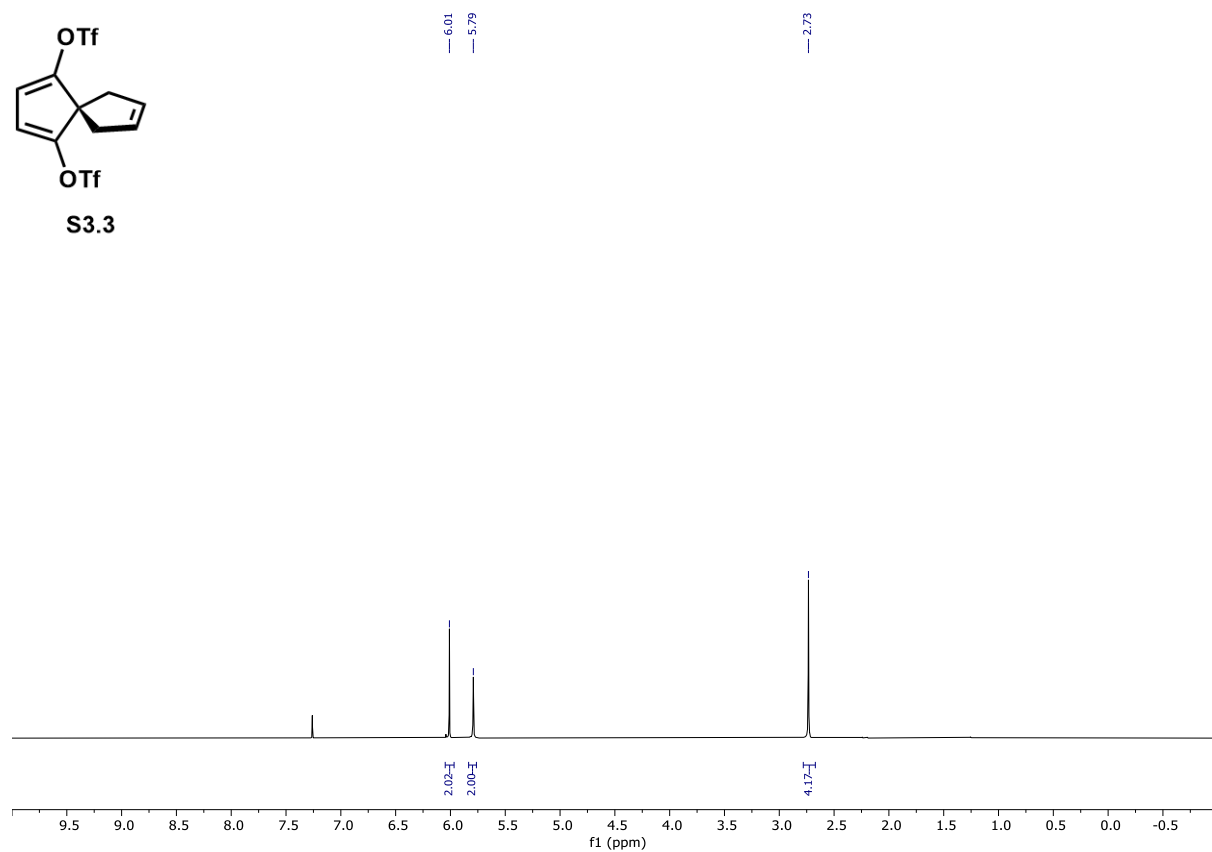
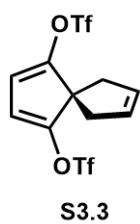
^1H NMR (300 MHz, CDCl_3)



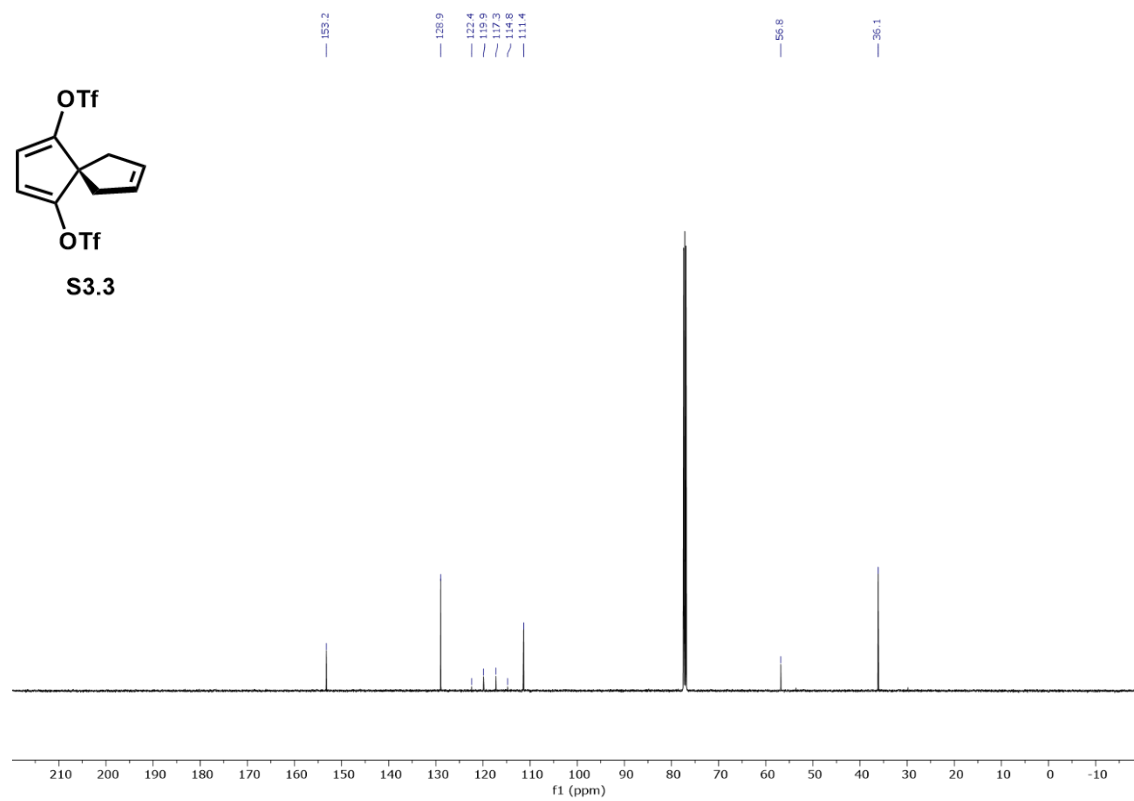
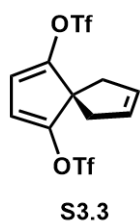
S3.2



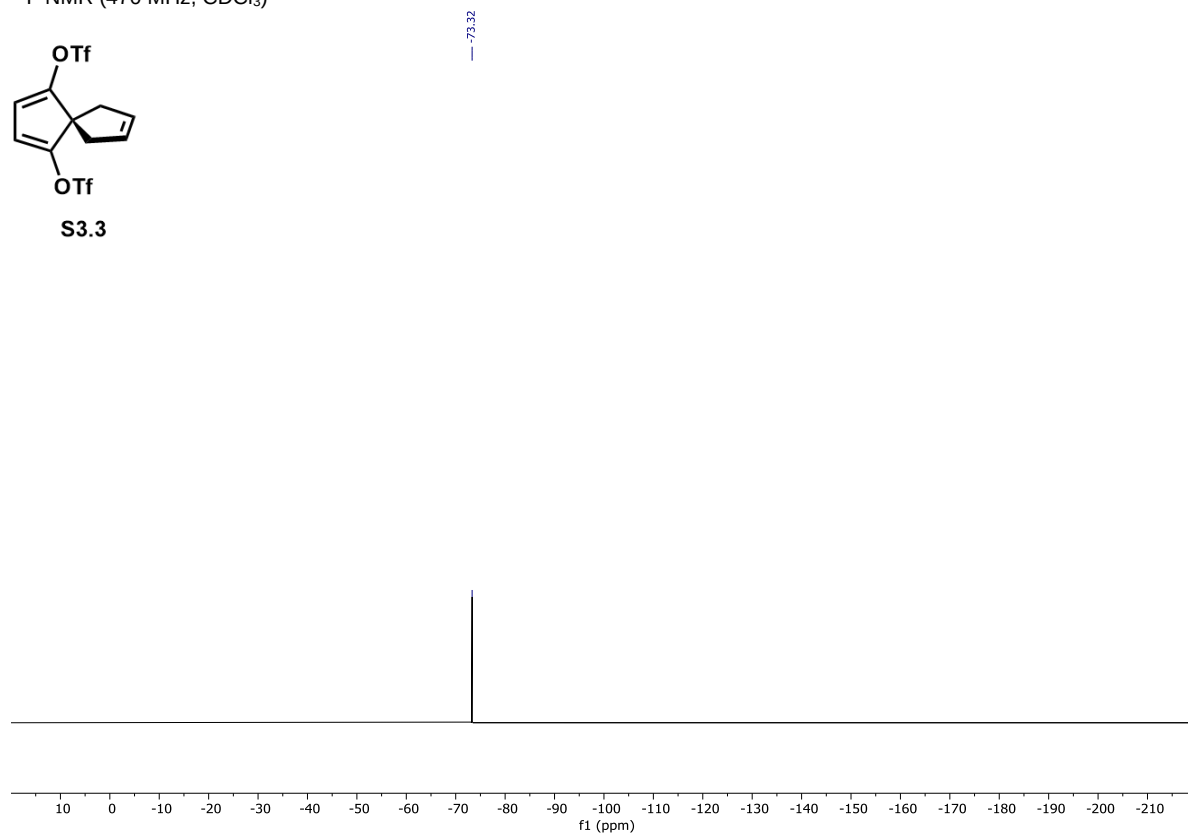
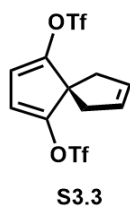
^1H NMR (500 MHz, CDCl_3)



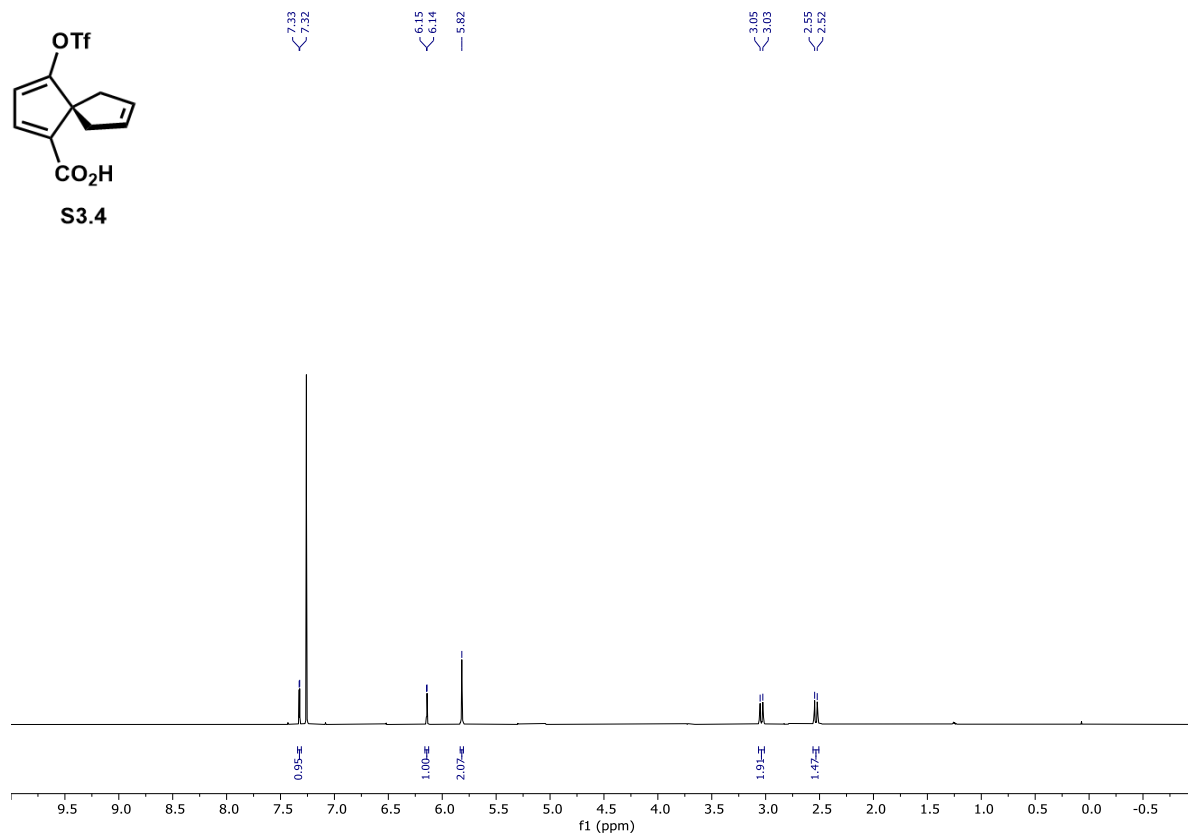
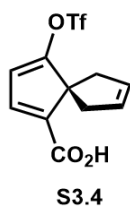
^{13}C NMR (126 MHz, CDCl_3)



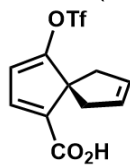
^{19}F NMR (470 MHz, CDCl_3)



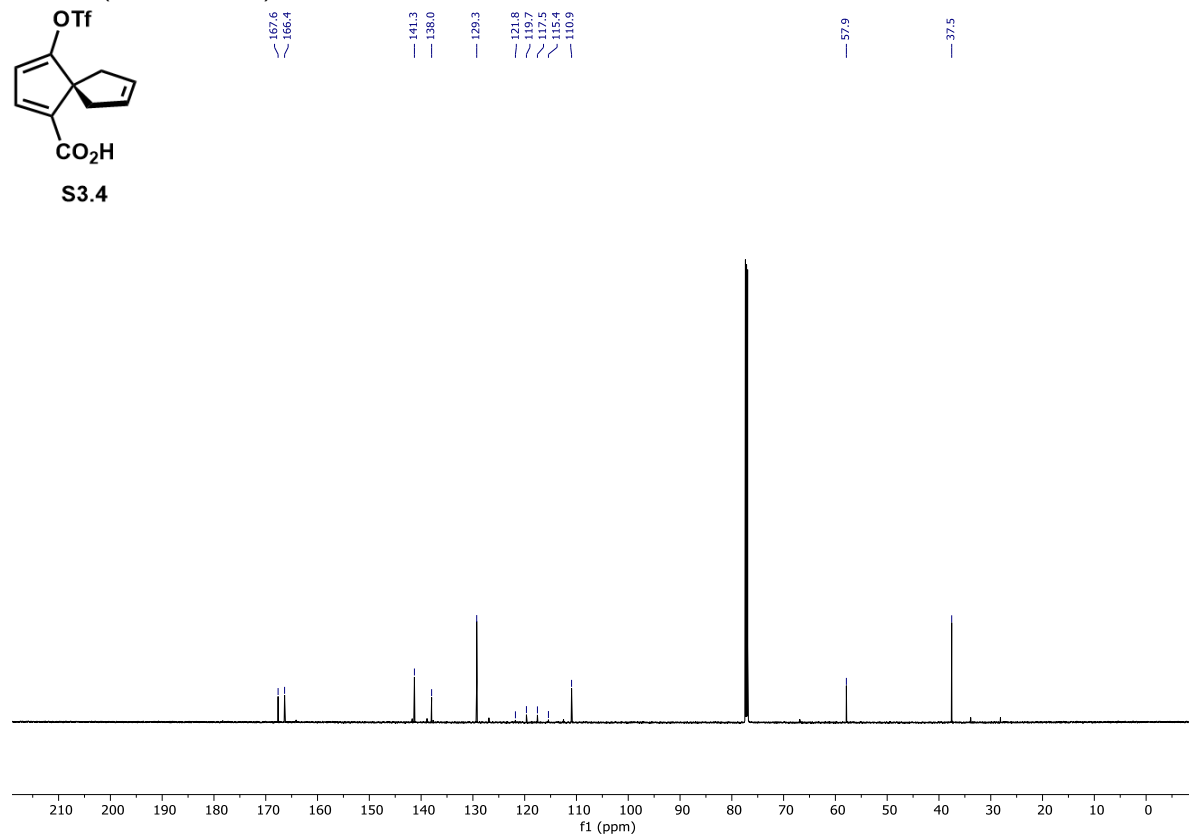
^1H NMR (600 MHz, CDCl_3)



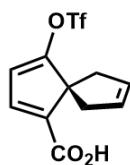
¹³C NMR (151 MHz, CDCl₃)



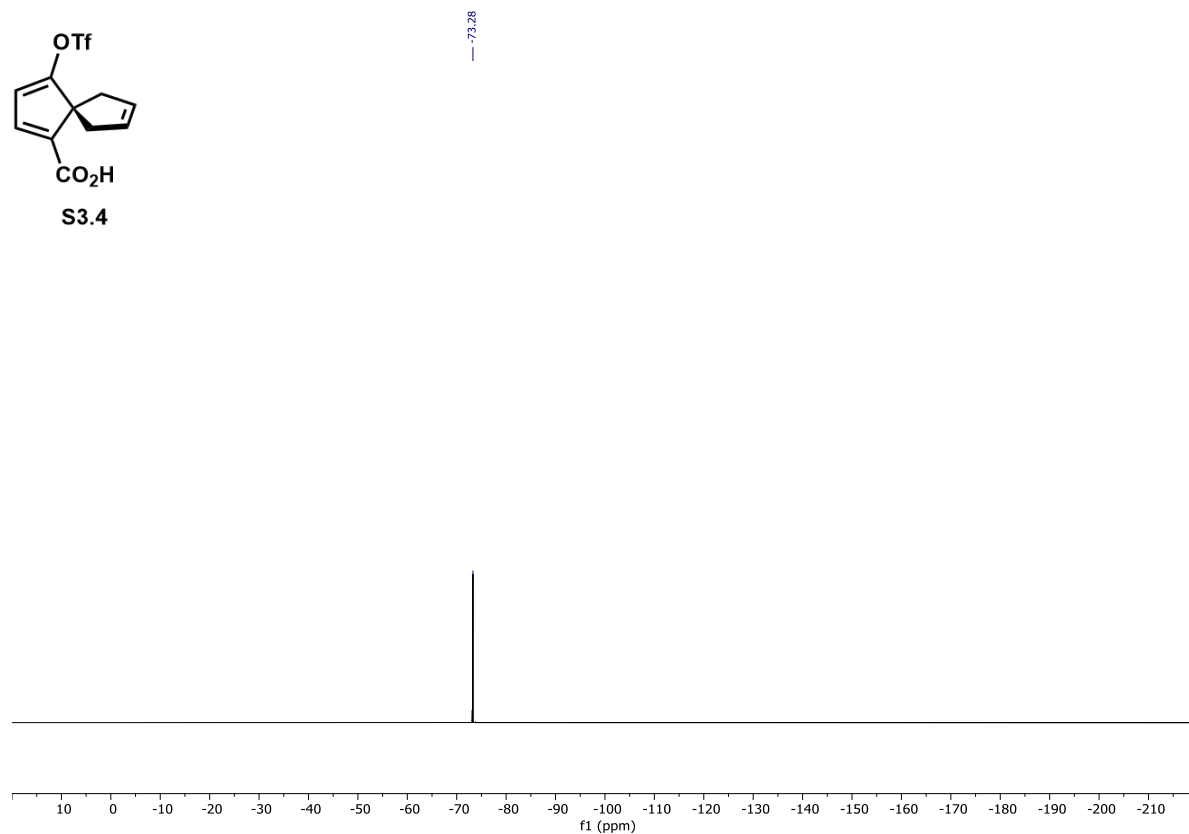
S3.4



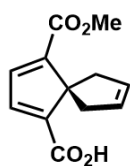
¹⁹F NMR (470 MHz, CDCl₃)



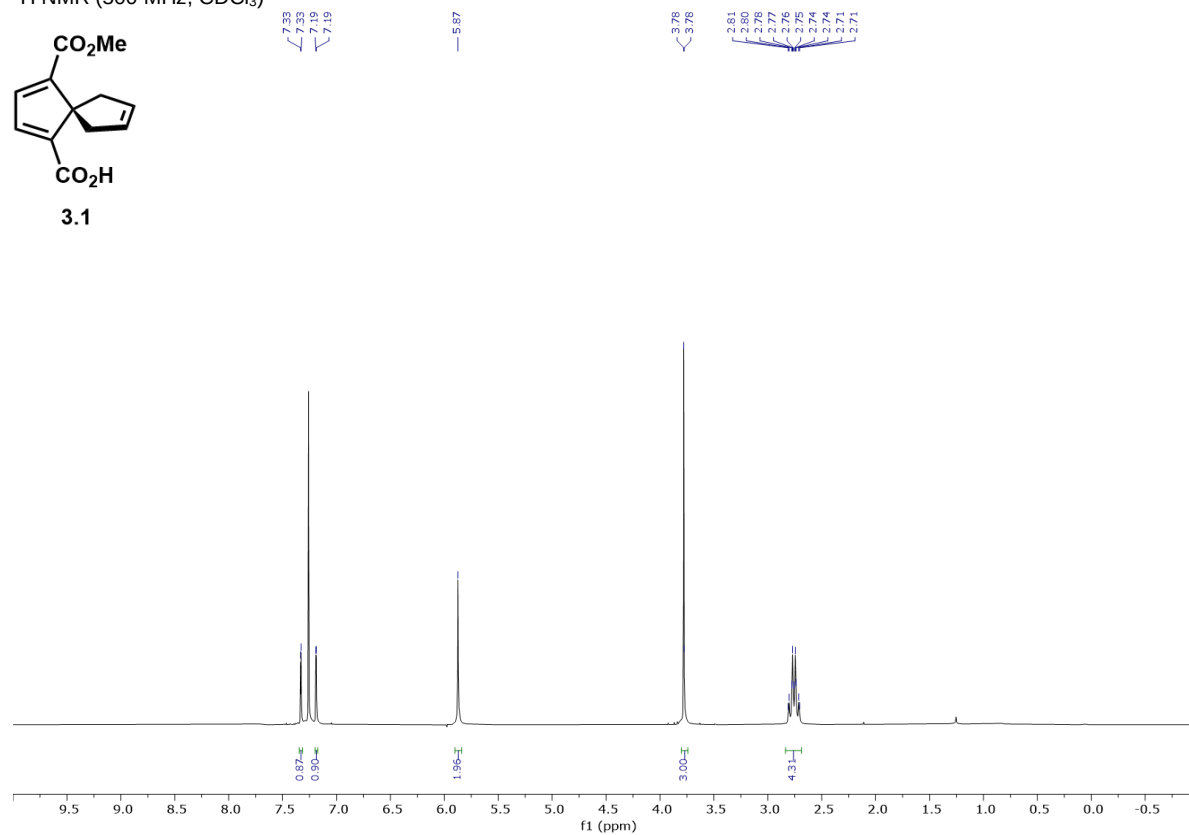
S3.4



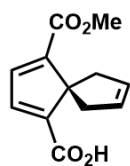
¹H NMR (500 MHz, CDCl₃)



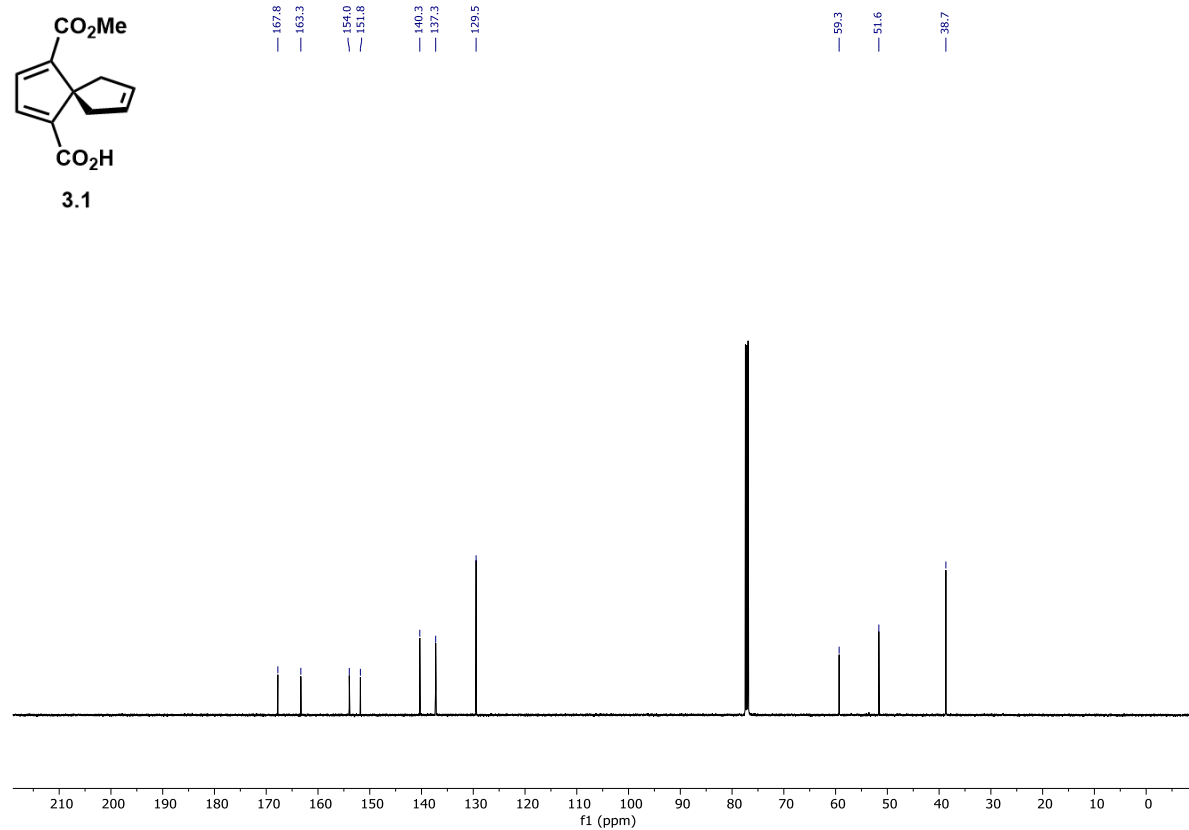
3.1



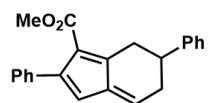
¹³C NMR (126 MHz, CDCl₃)



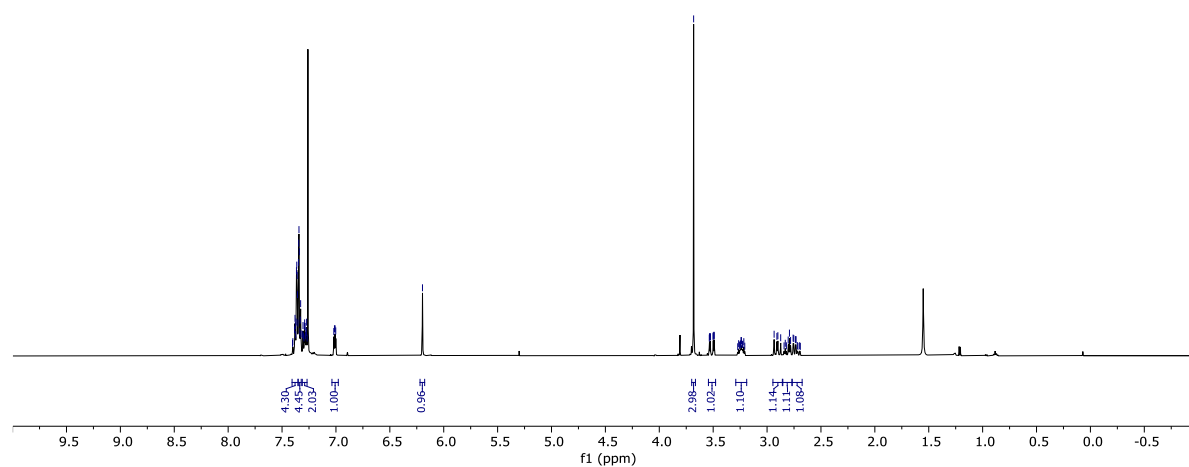
3.1



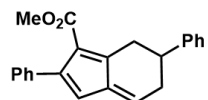
¹H NMR (500 MHz, CDCl₃)



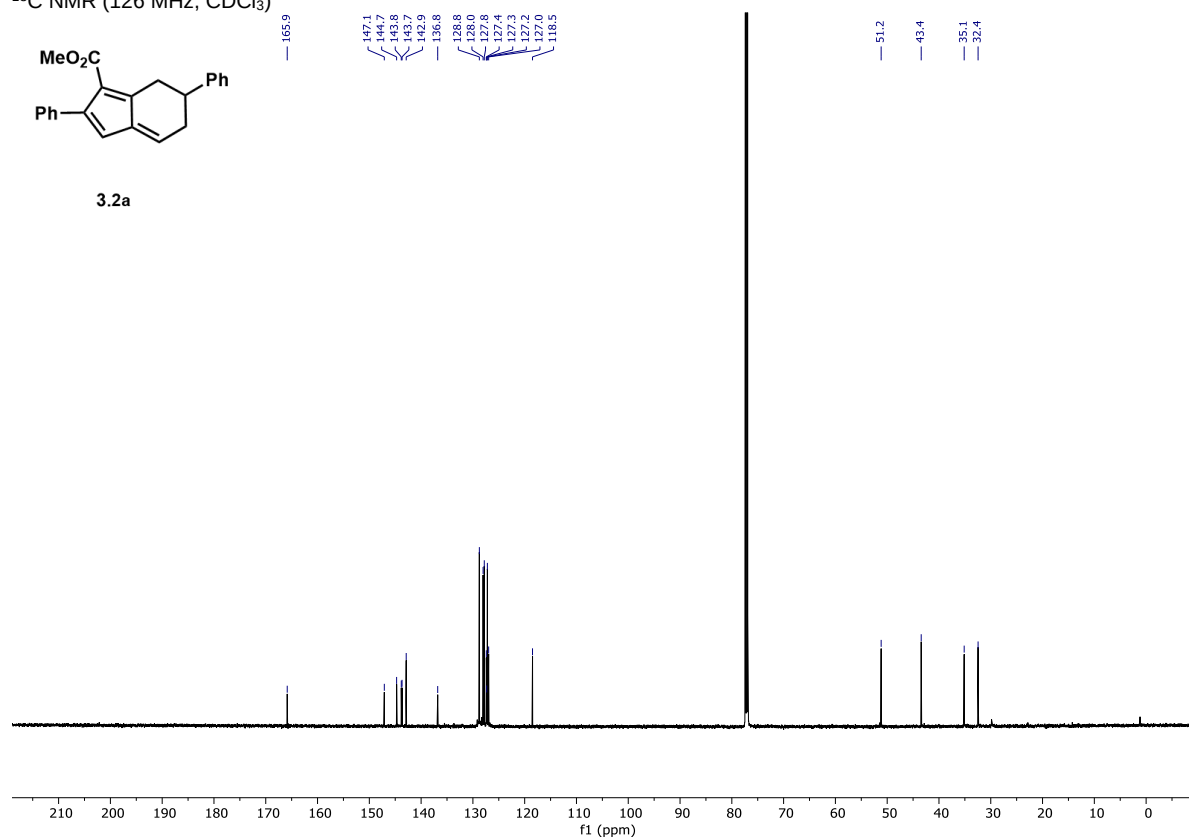
3.2a



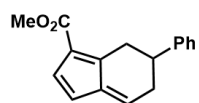
¹³C NMR (126 MHz, CDCl₃)



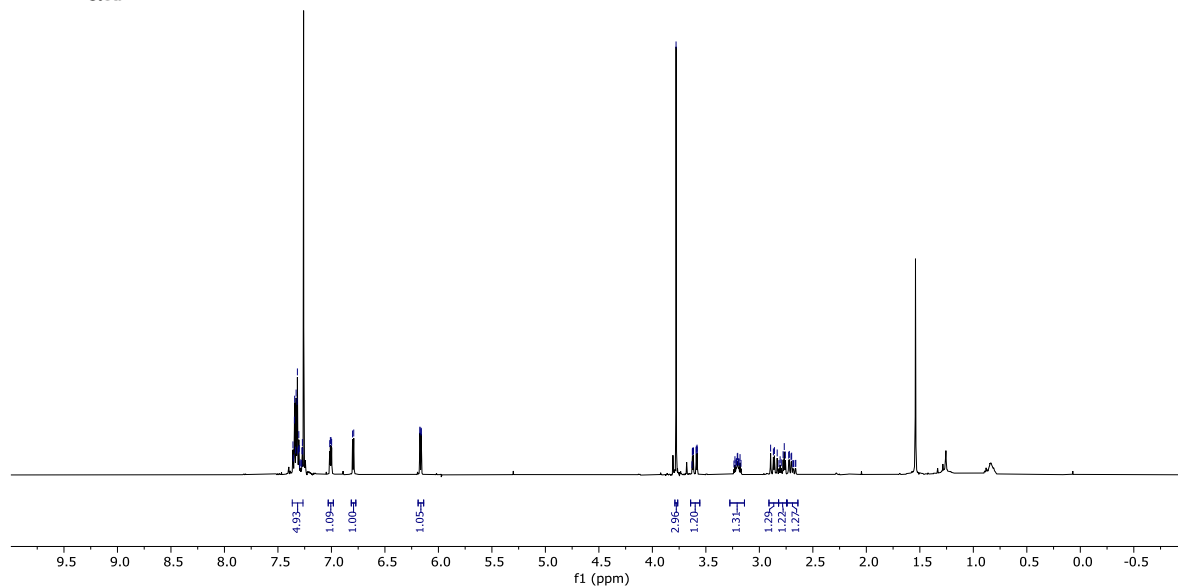
3.2a



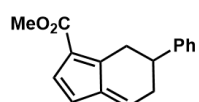
^1H NMR (500 MHz, CDCl_3)



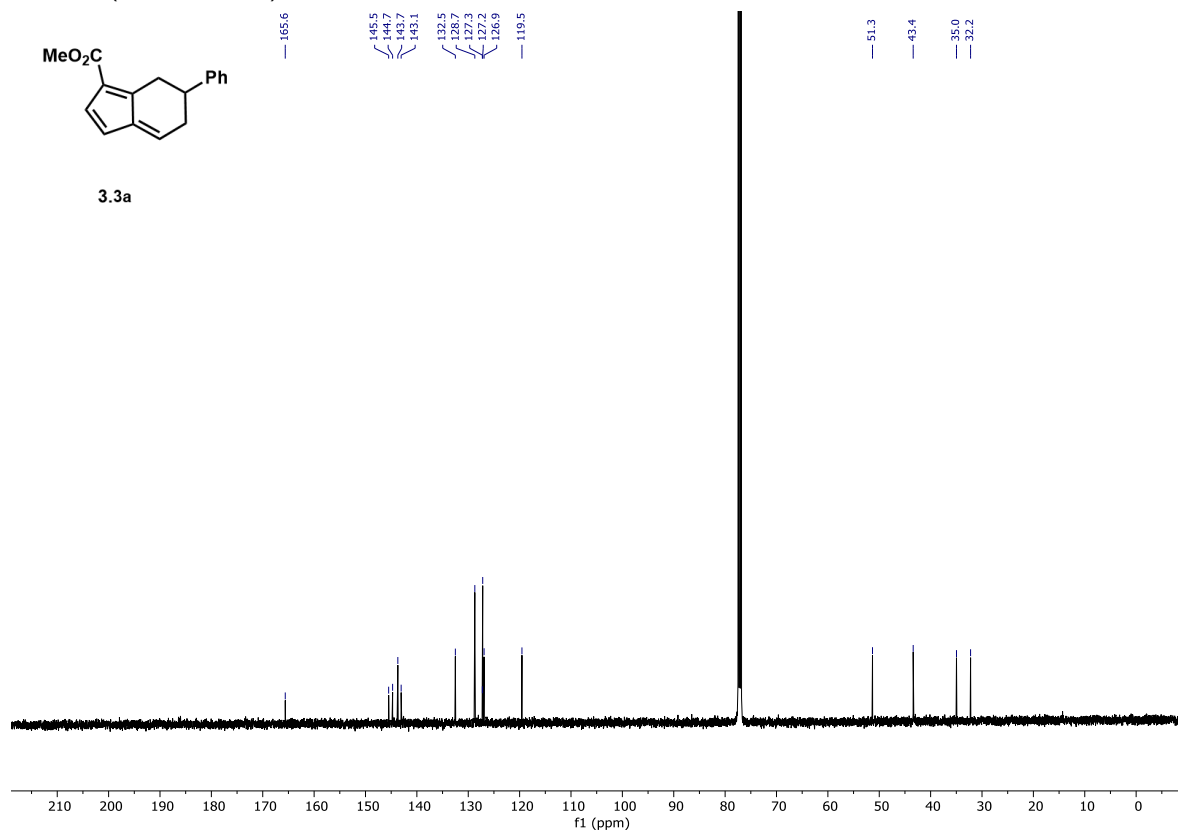
3.3a



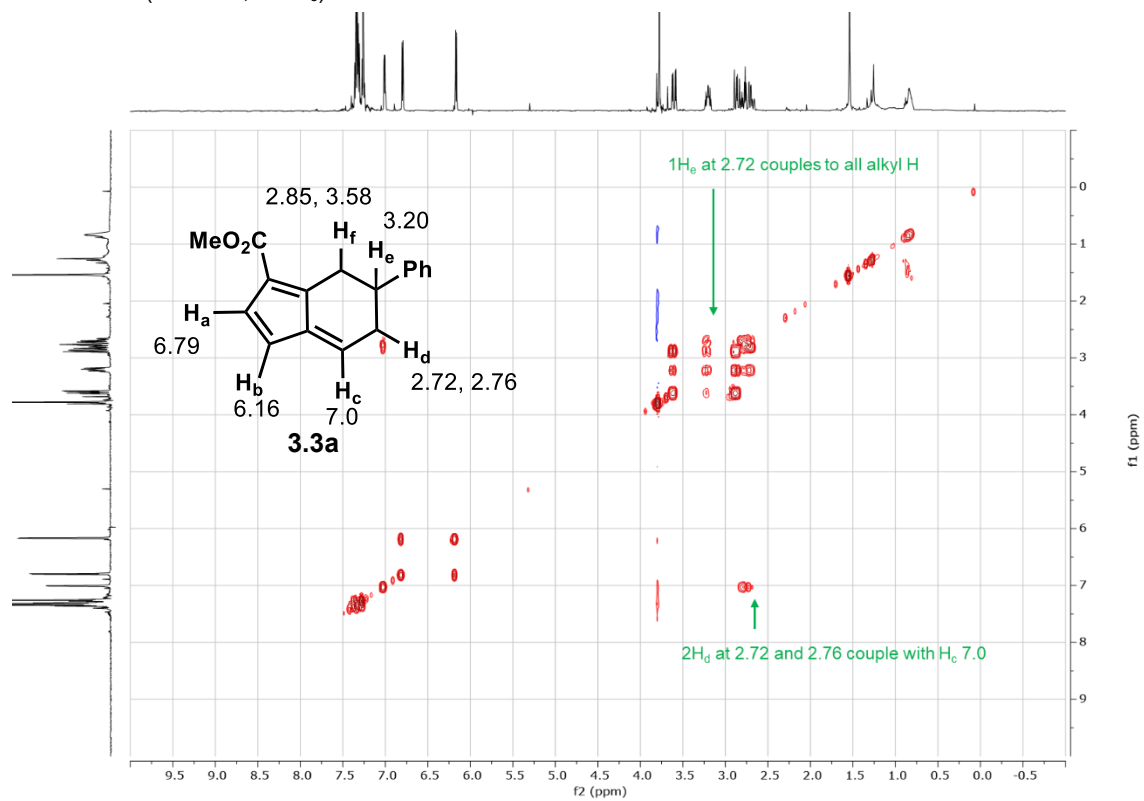
^{13}C NMR (126 MHz, CDCl_3)



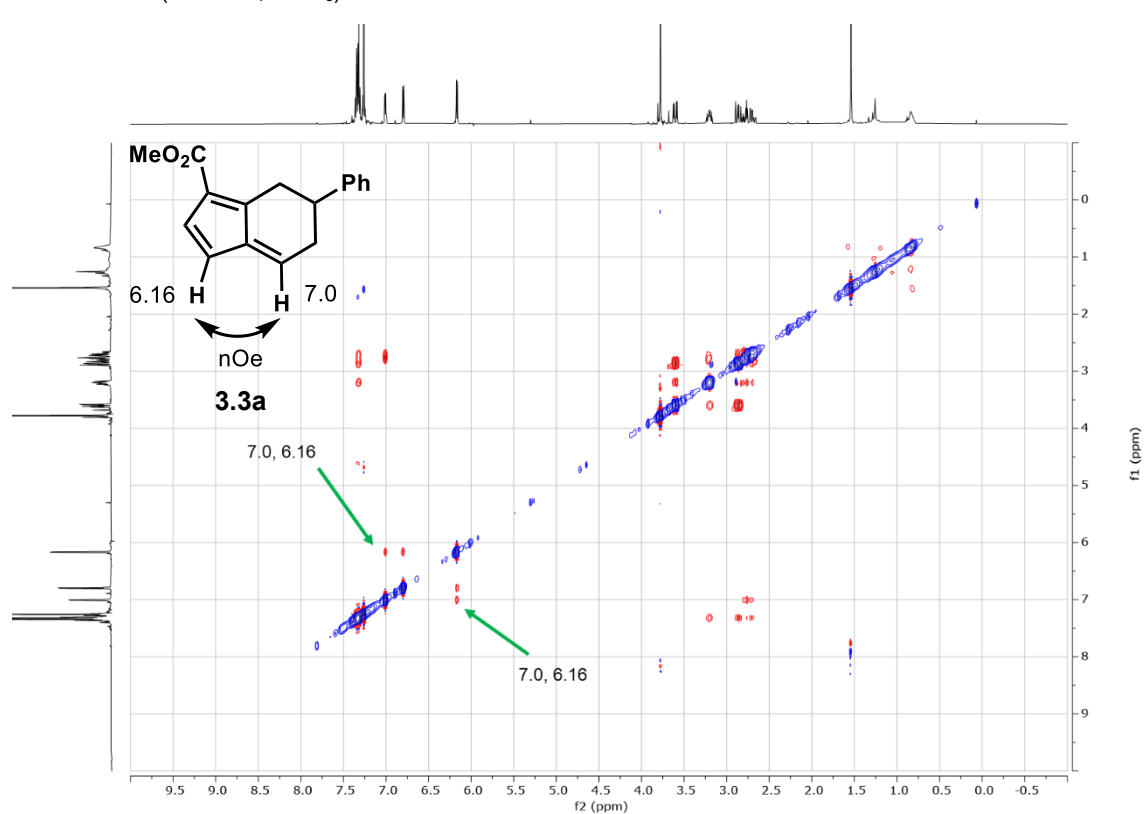
3.3a



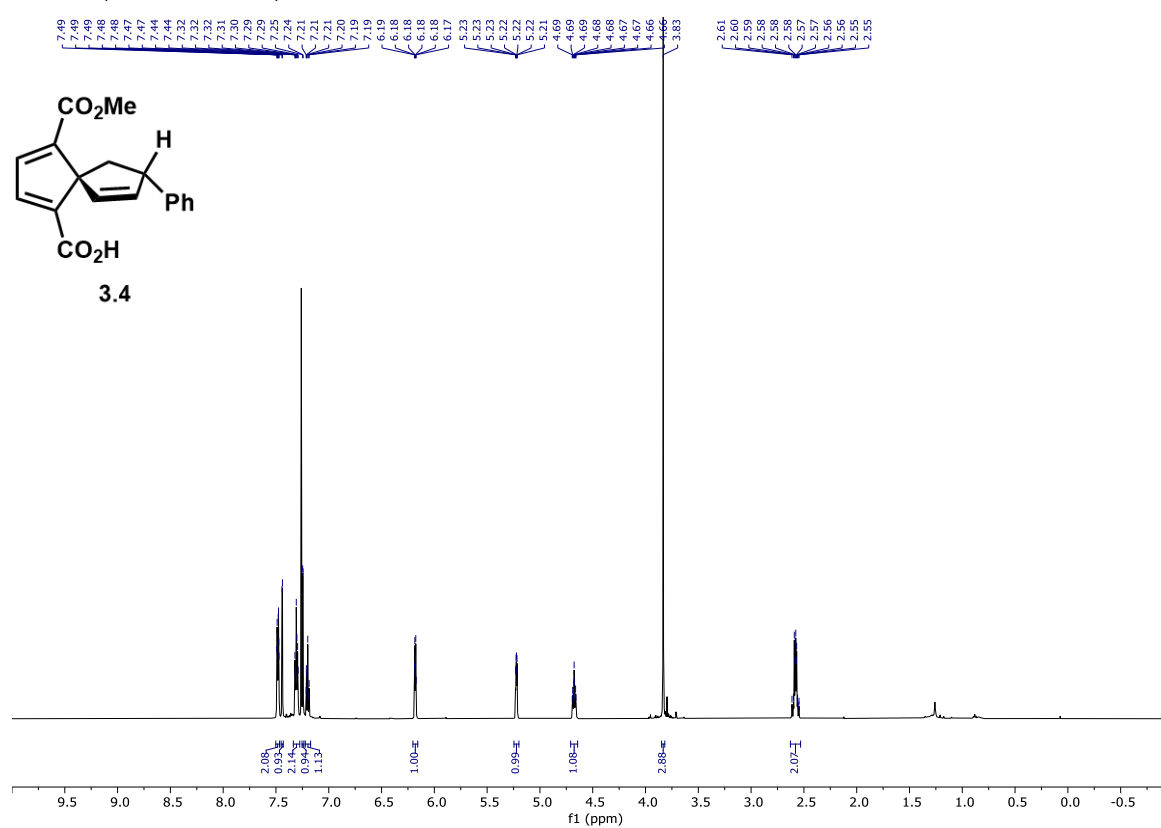
^1H - ^1H COSY (500 MHz, CDCl_3)



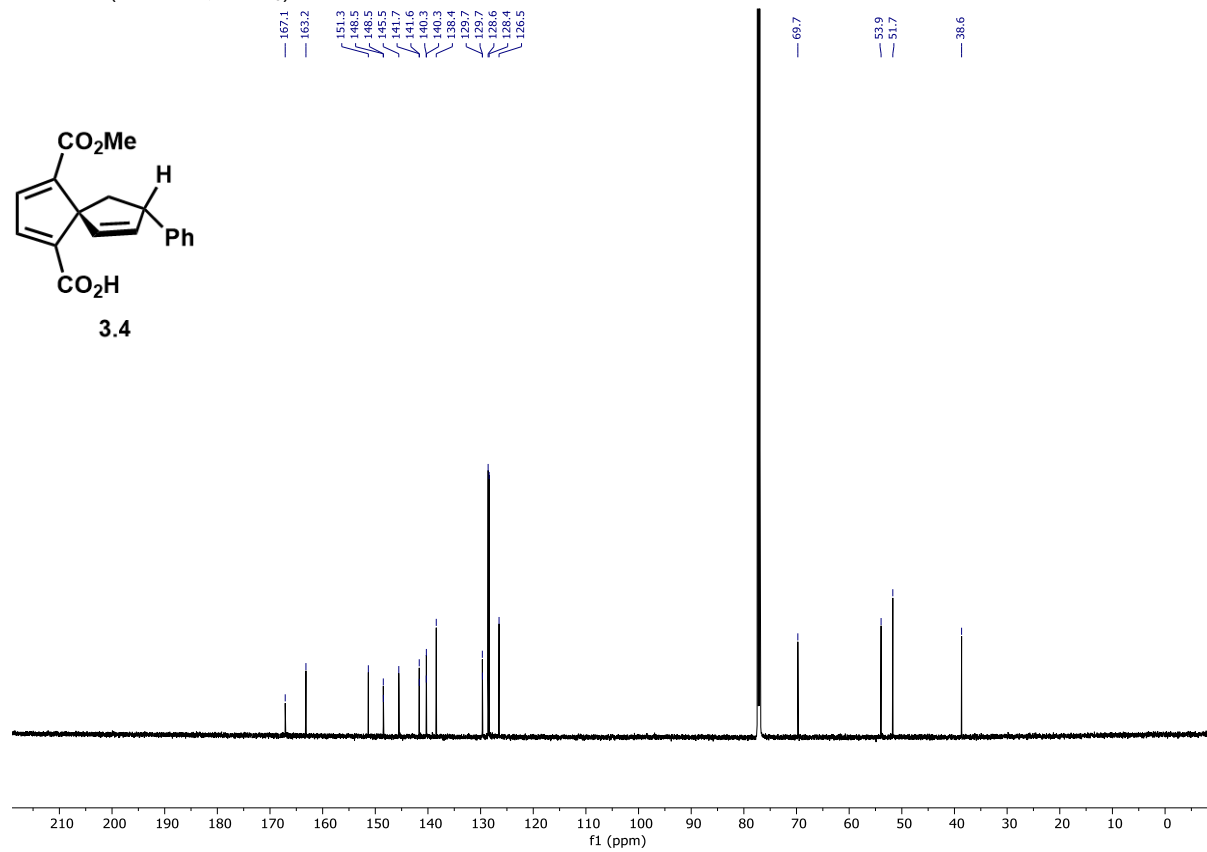
^1H - ^1H NOESY (500 MHz, CDCl_3)



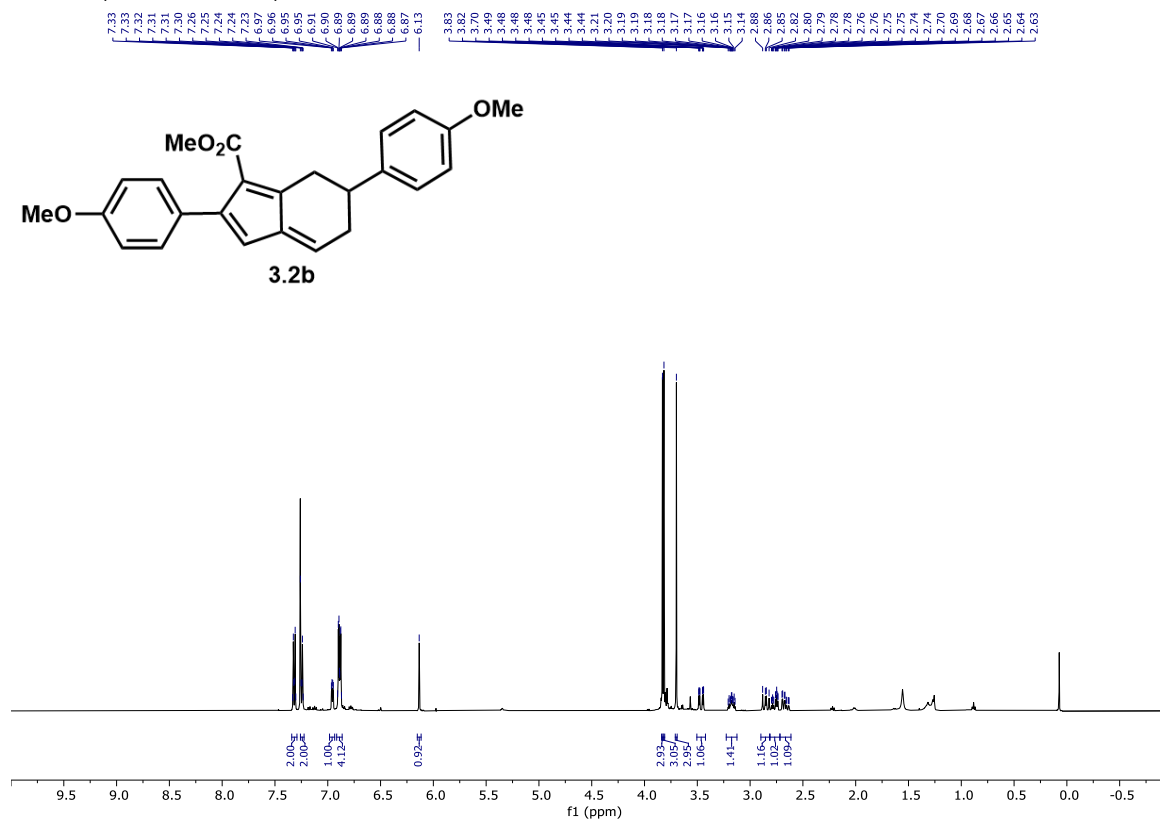
¹H NMR (600 MHz, CDCl₃)



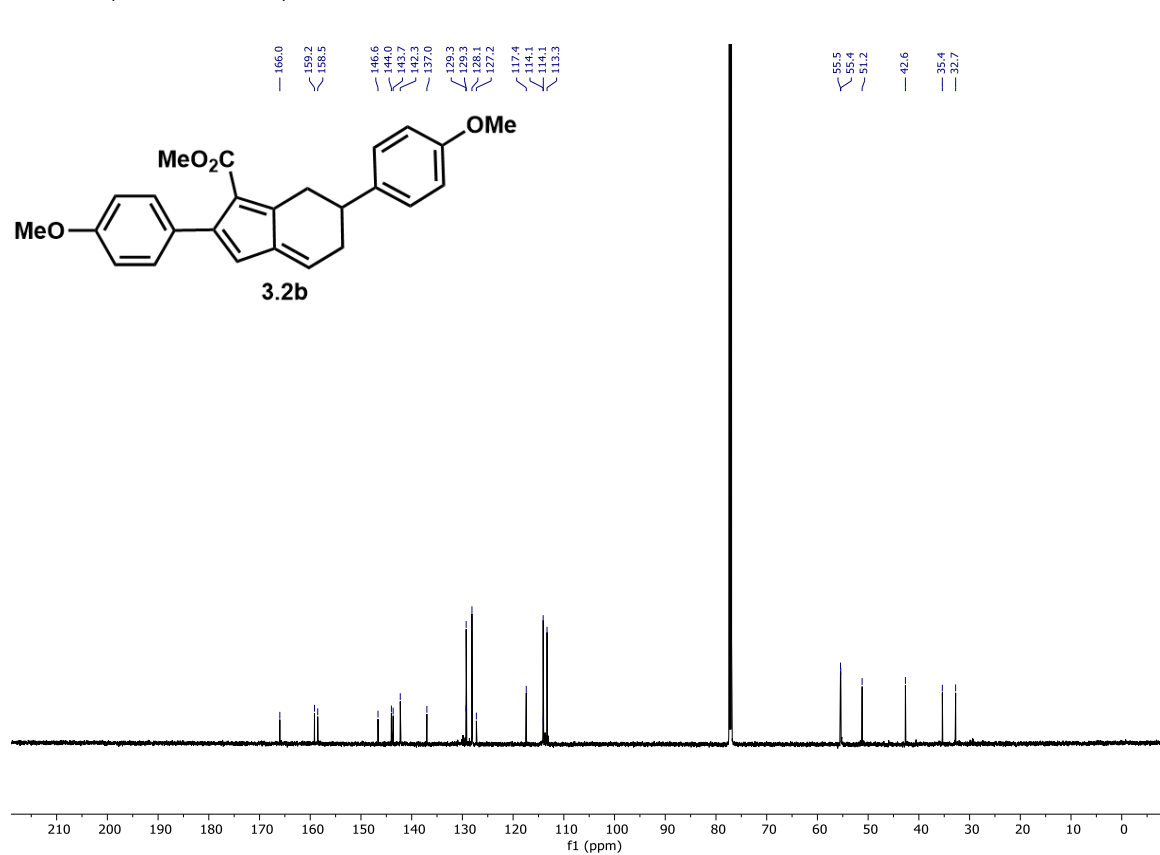
¹³C NMR (151 MHz, CDCl₃)



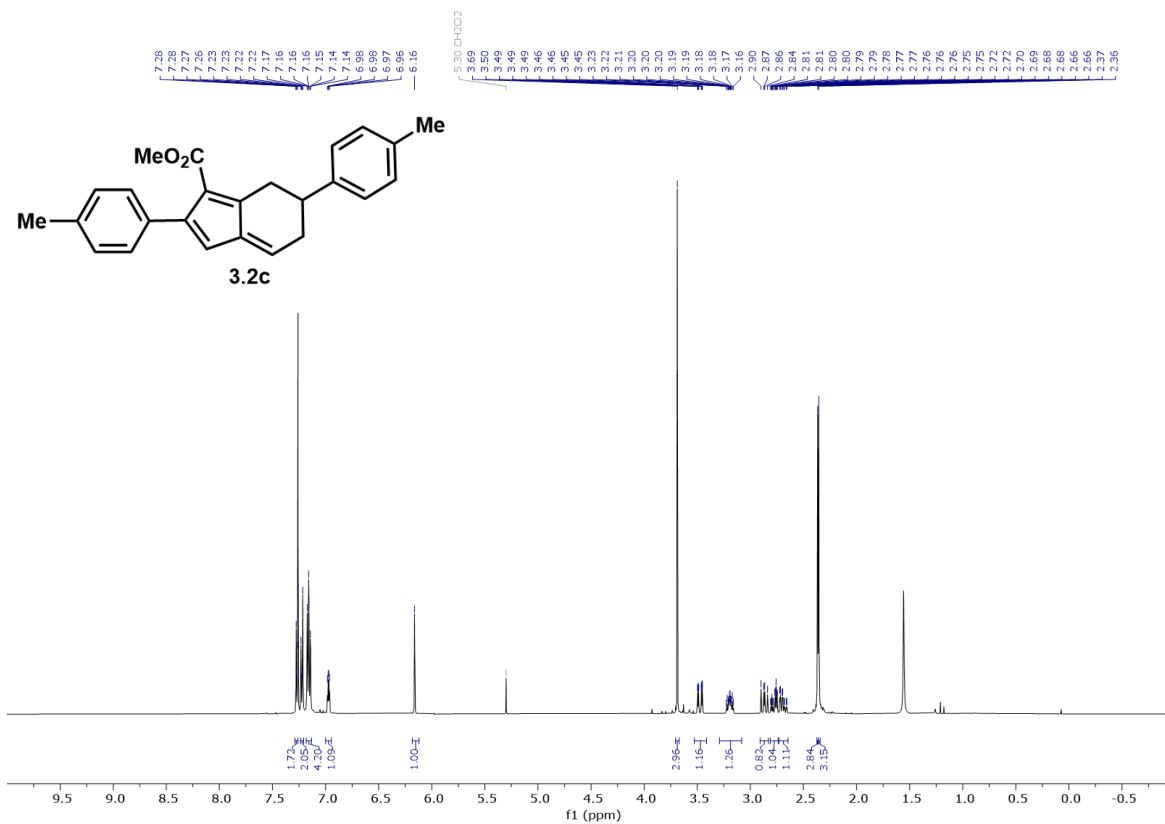
¹H NMR (500 MHz, CDCl₃)



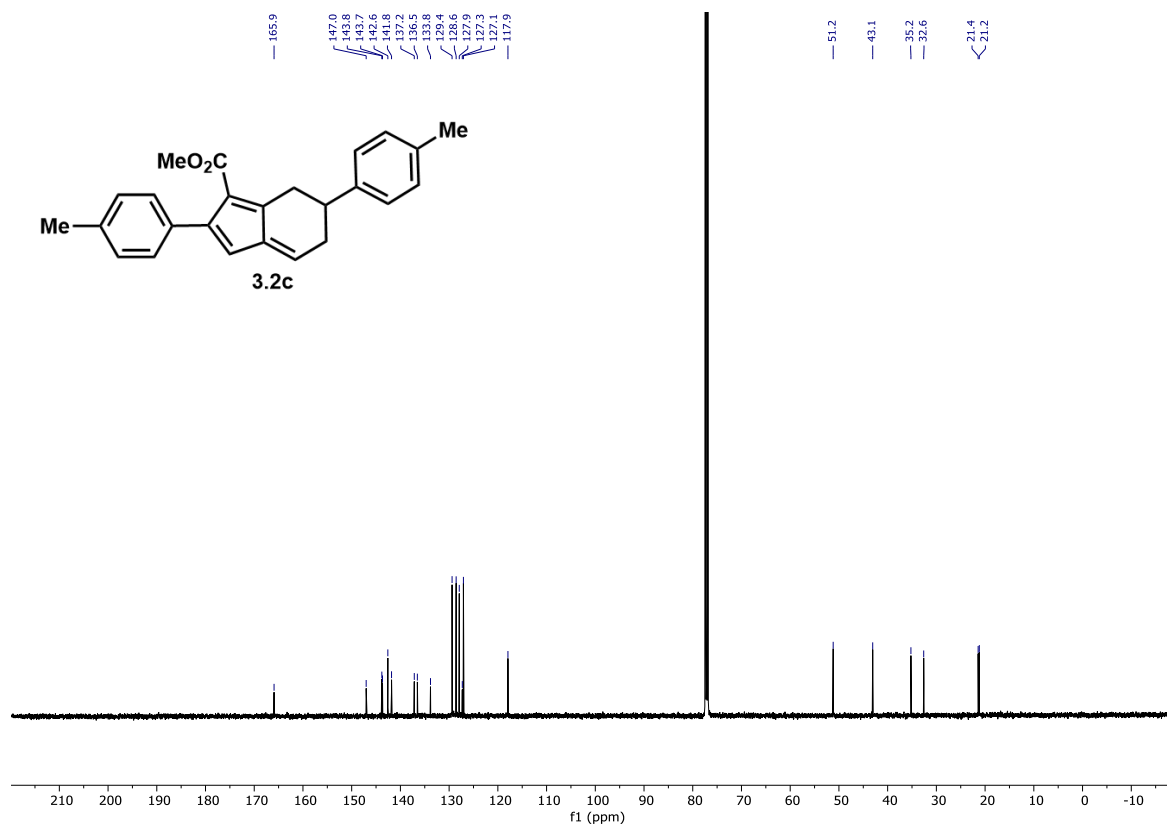
¹³C NMR (151 MHz, CDCl₃)



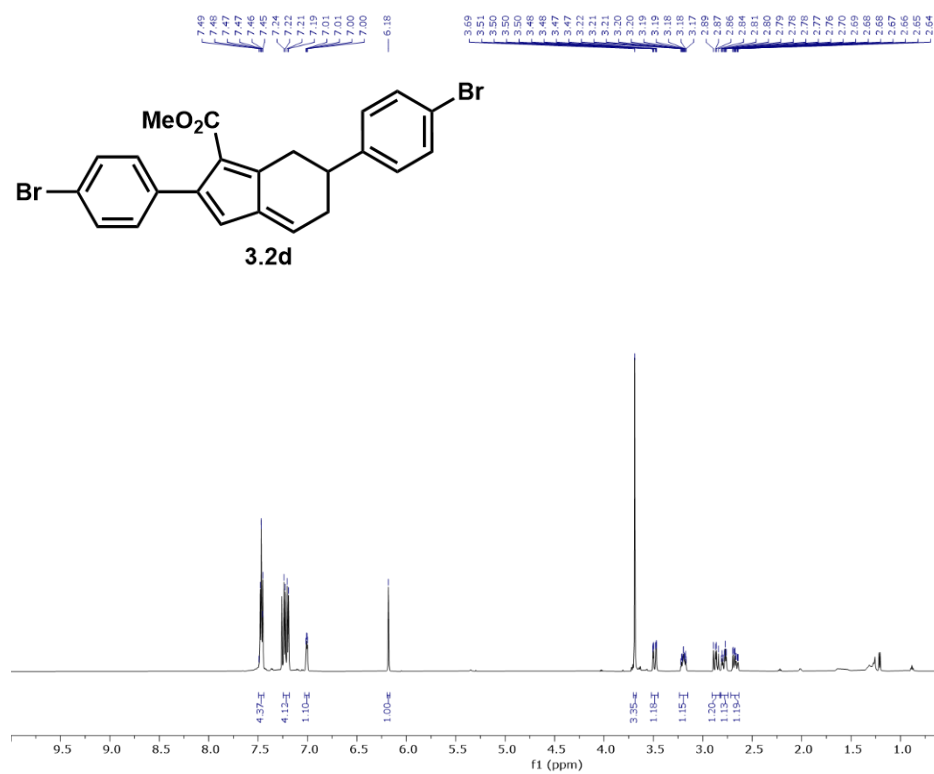
^1H NMR (500 MHz, CDCl_3)



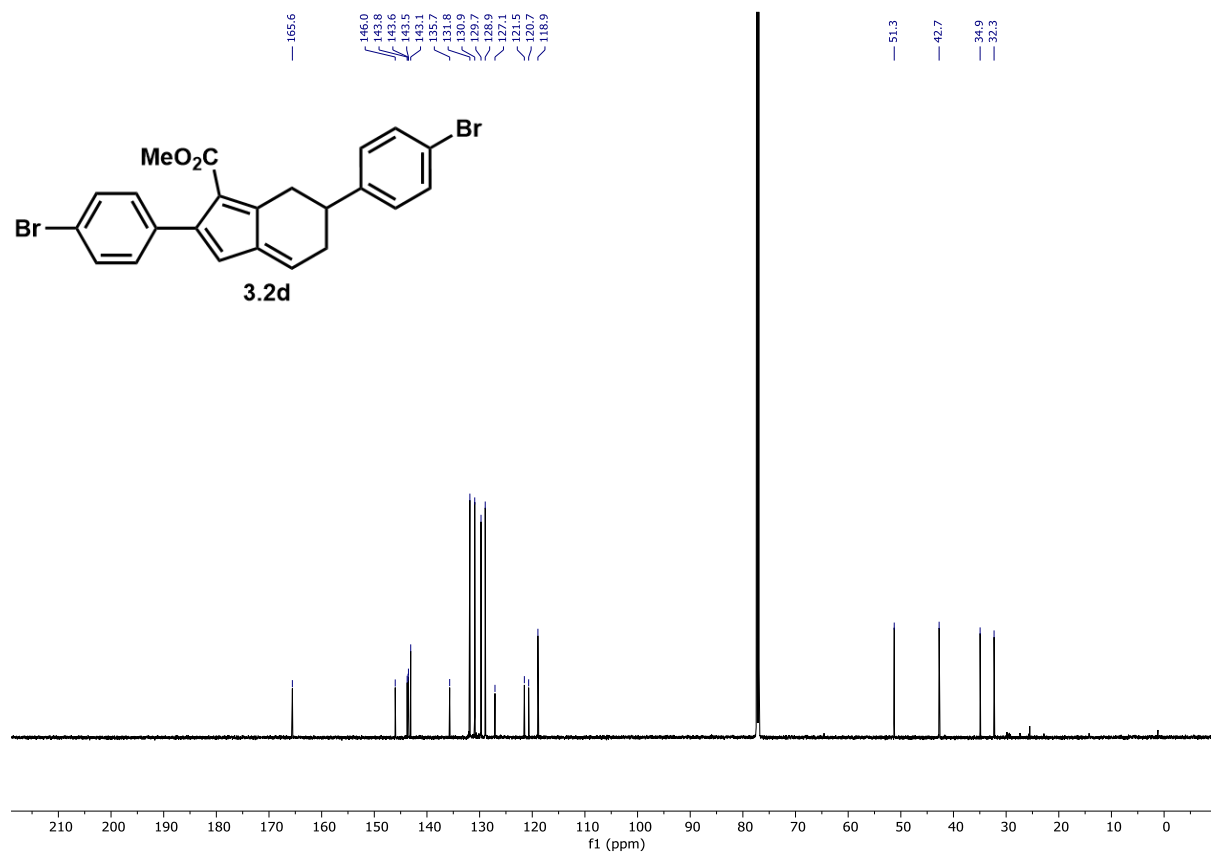
^{13}C NMR (126 MHz, CDCl_3)



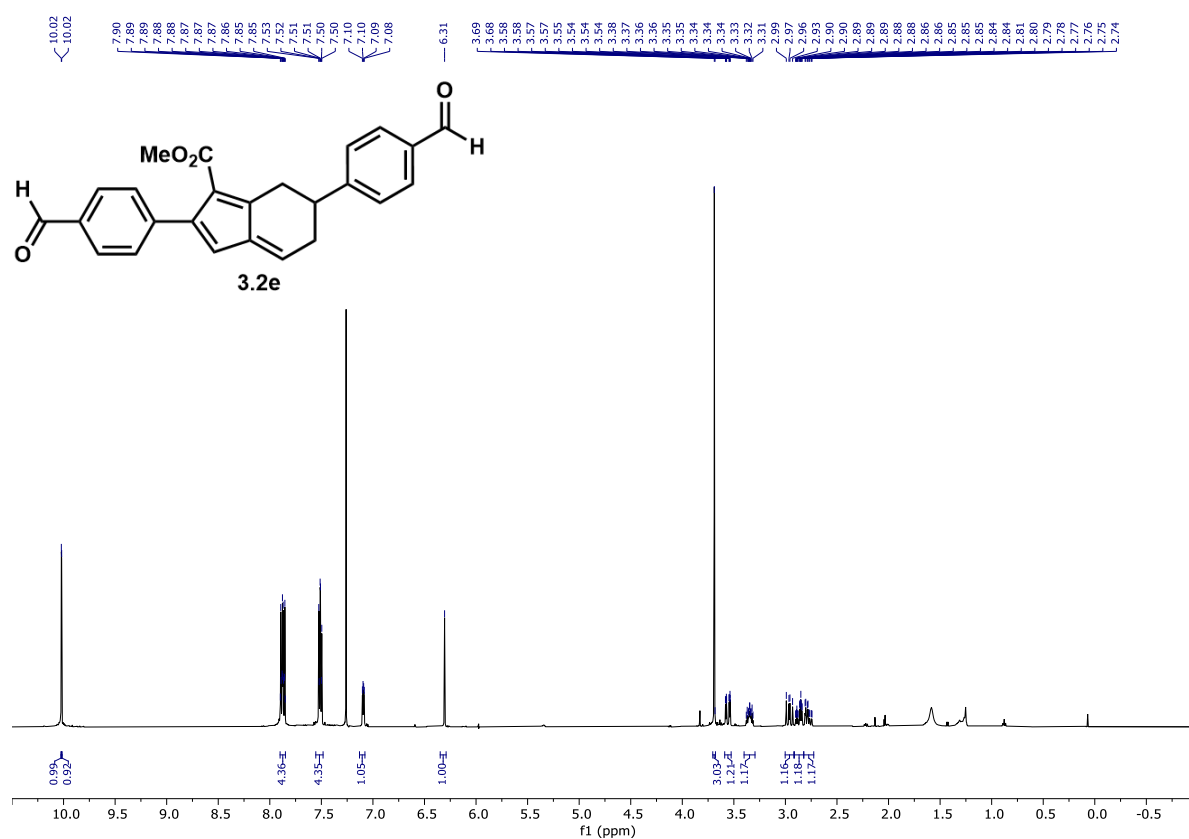
^1H NMR (600 MHz, CDCl_3)



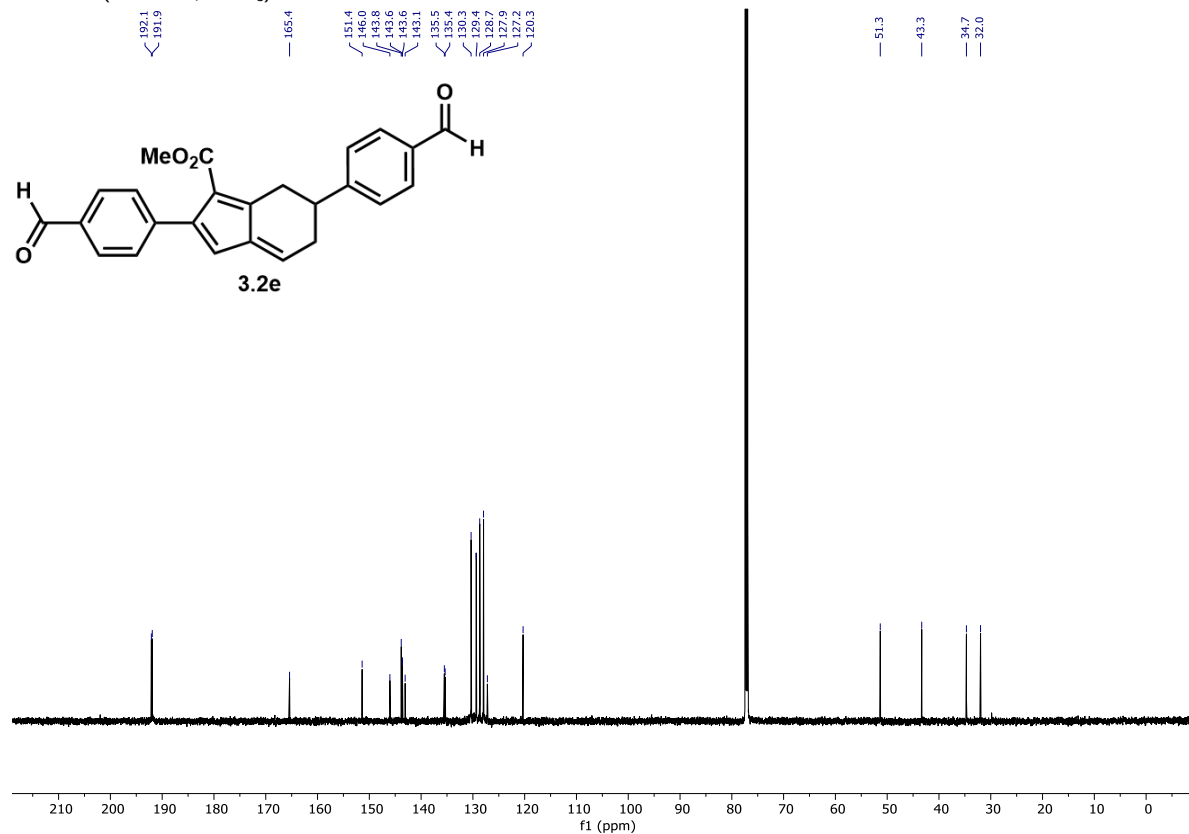
^{13}C NMR (126 MHz, CDCl_3)



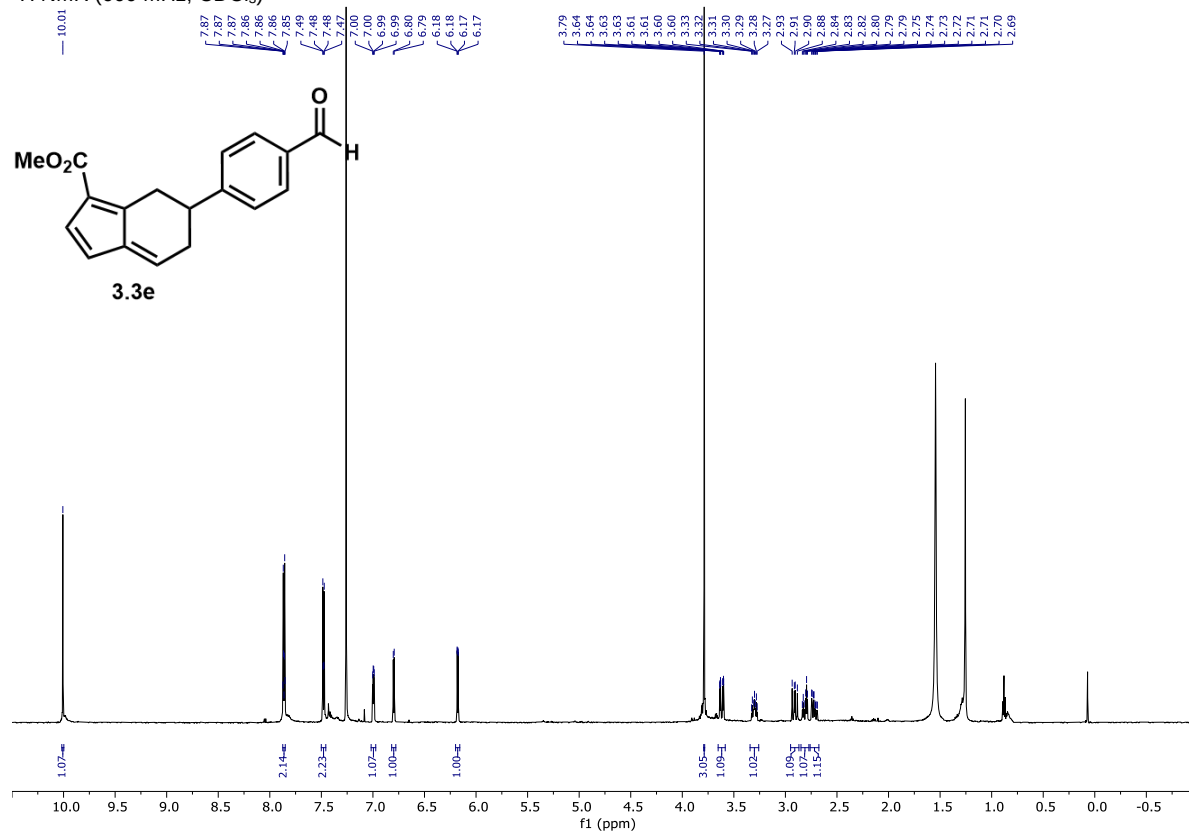
^1H NMR (500 MHz, CDCl_3)



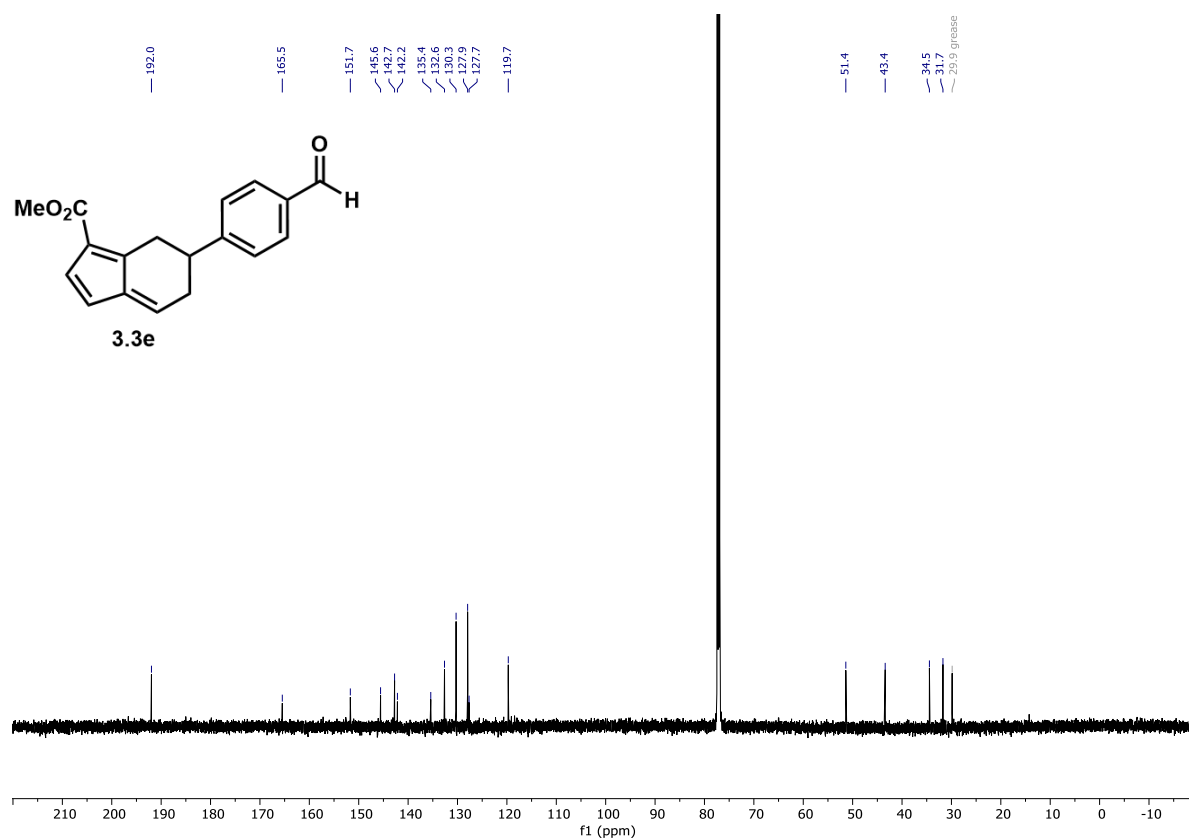
^{13}C NMR (151 MHz, CDCl_3)



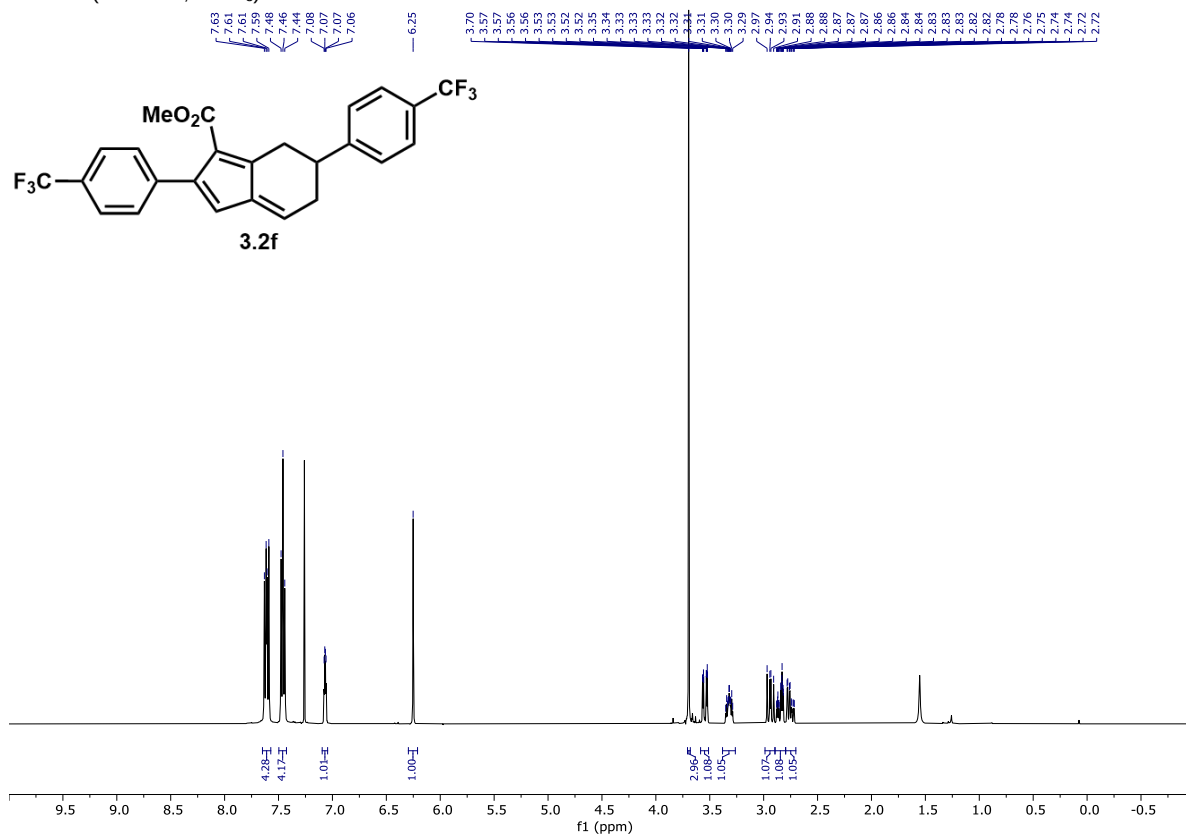
¹H NMR (600 MHz, CDCl₃)



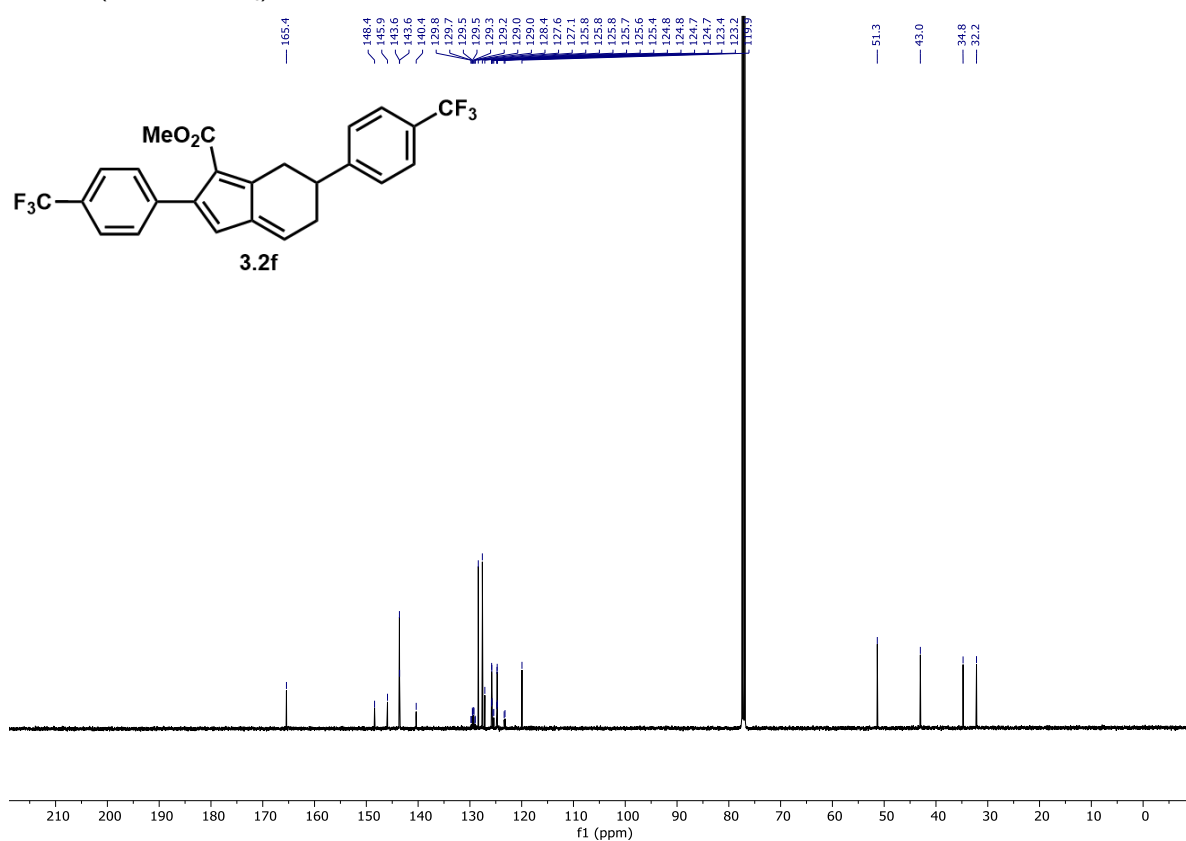
¹³C NMR (151 MHz, CDCl₃)



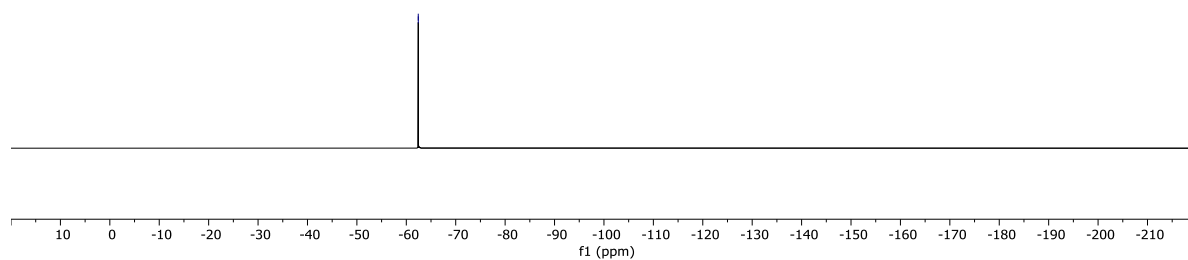
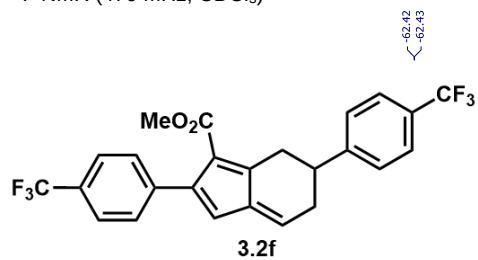
^1H NMR (600 MHz, CDCl_3)



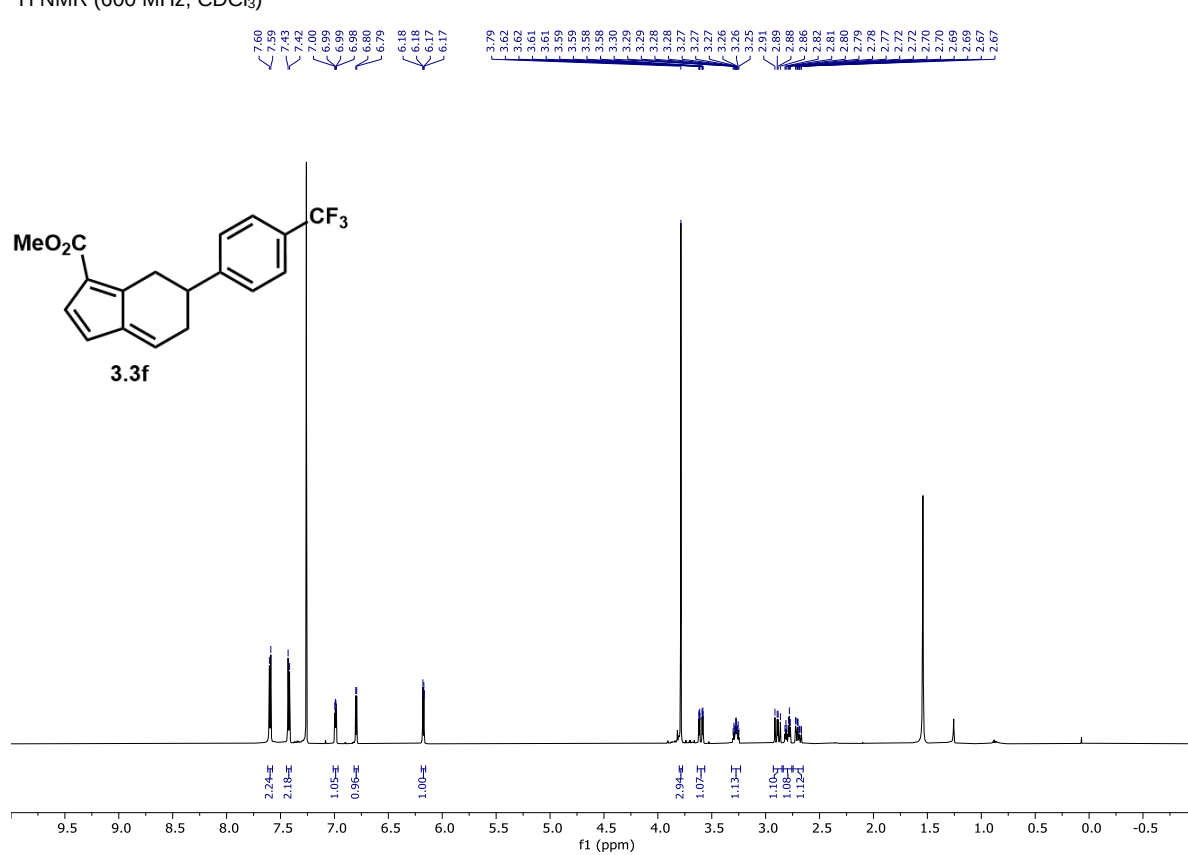
^{13}C NMR (126 MHz, CDCl_3)



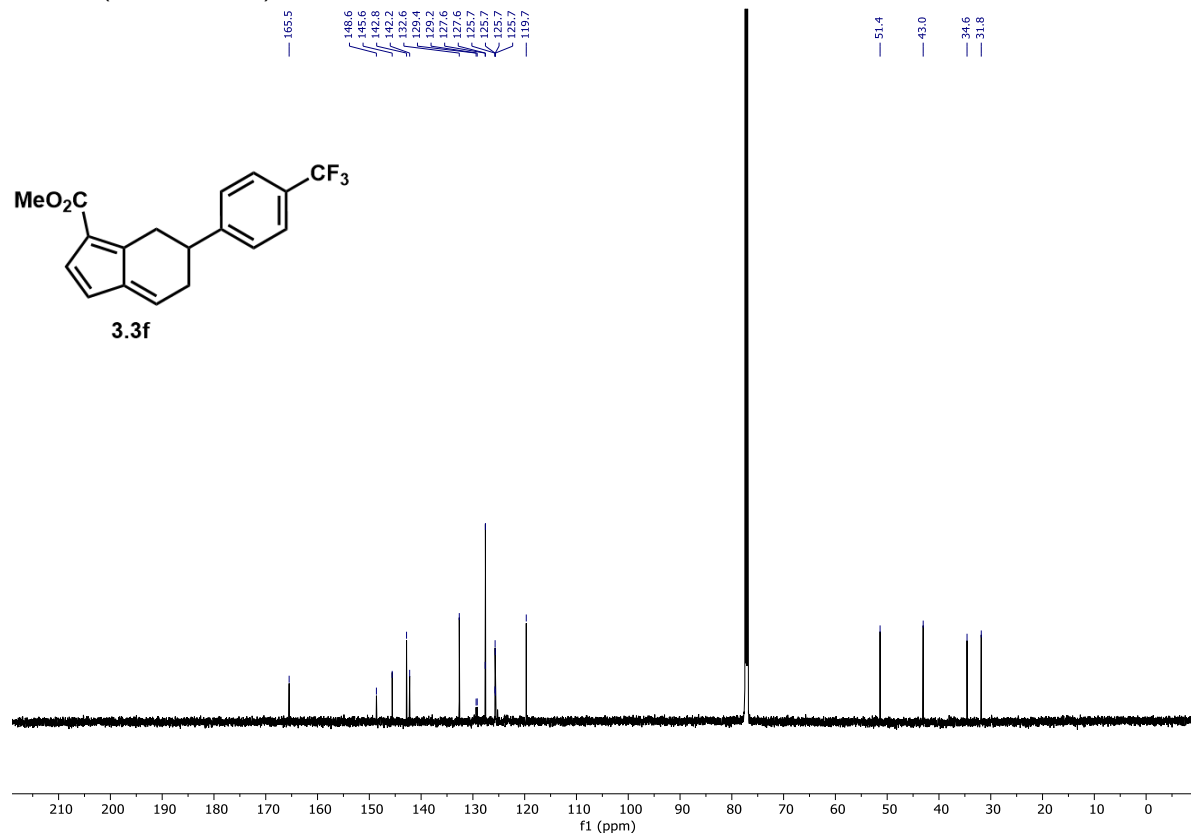
^{19}F NMR (470 MHz, CDCl_3)



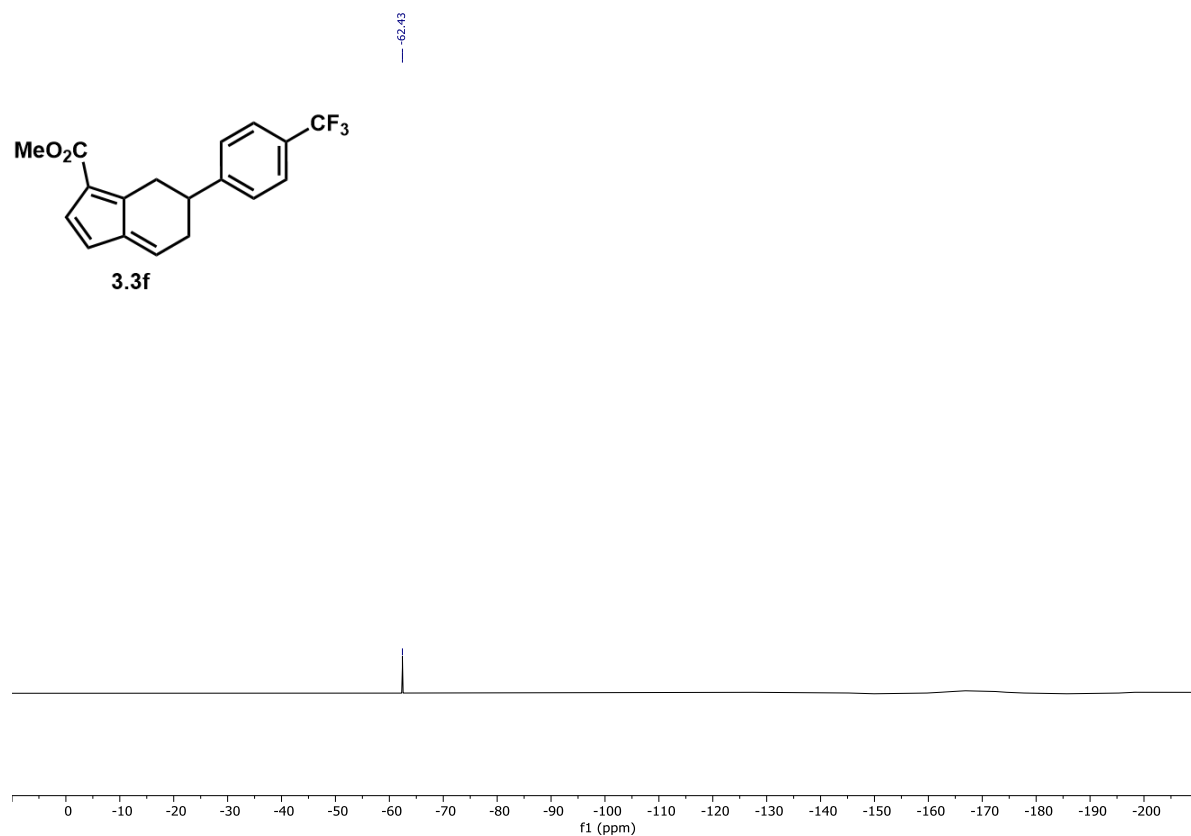
^1H NMR (600 MHz, CDCl_3)



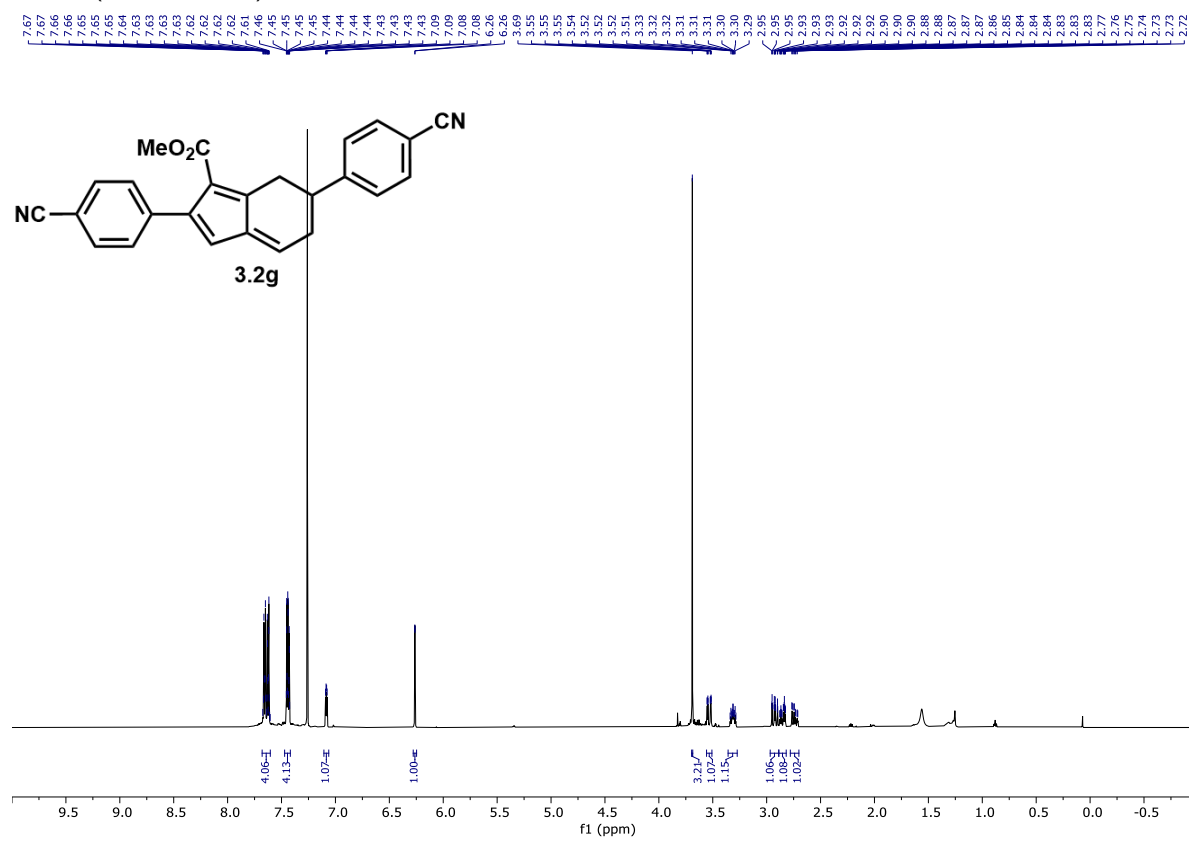
¹³C NMR (151 MHz, CDCl₃)



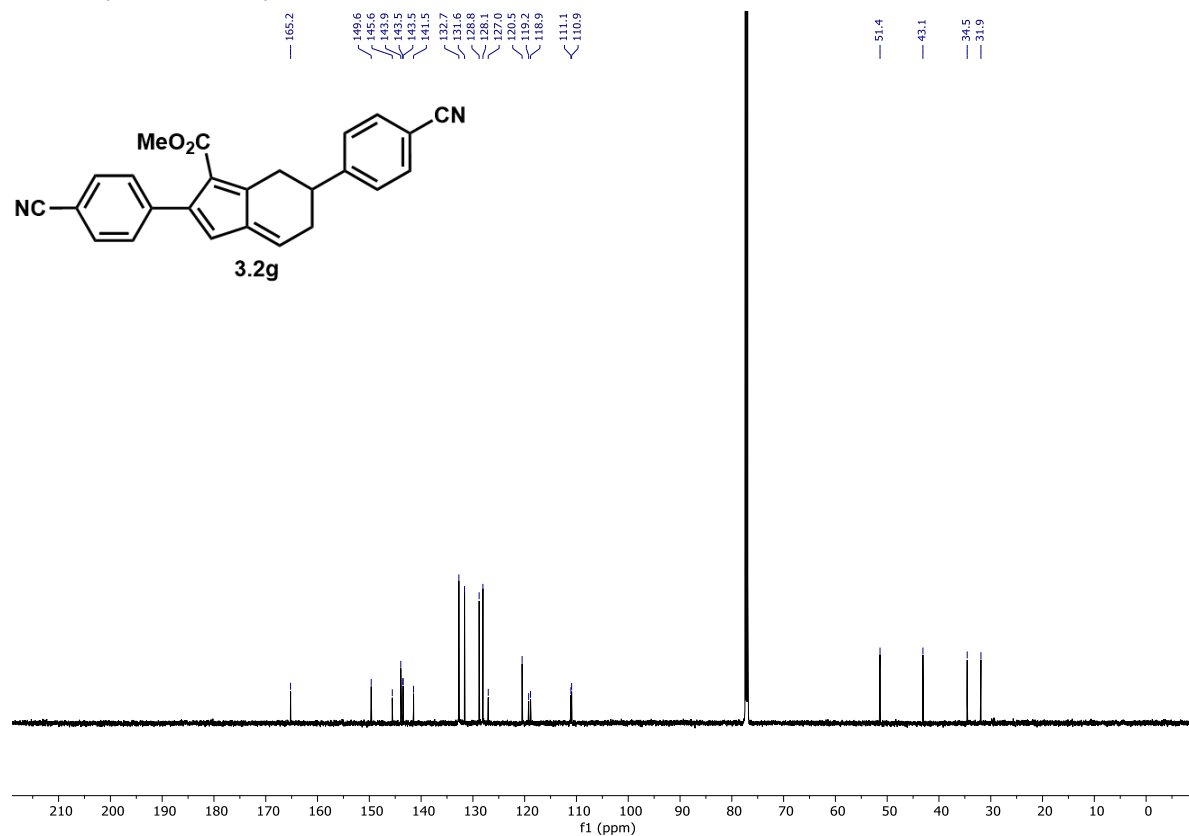
¹⁹F NMR (565 MHz, CDCl₃)



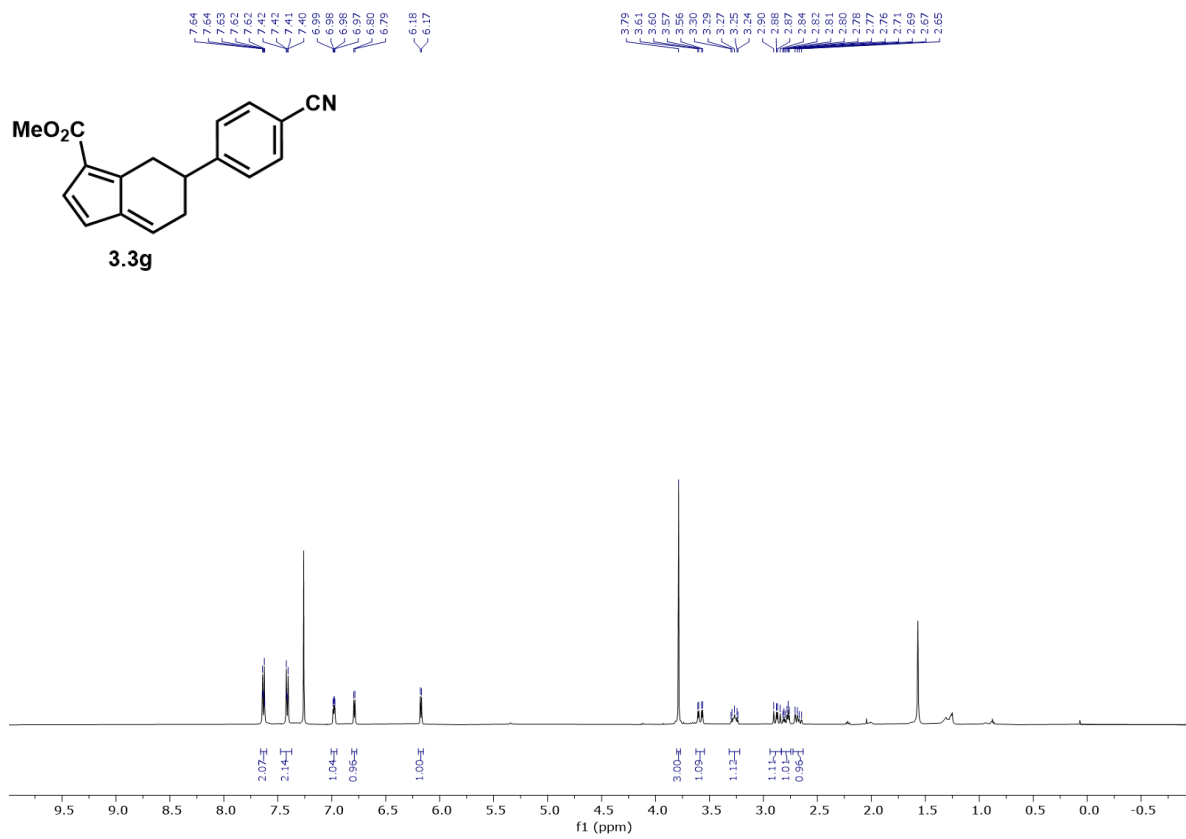
^1H NMR (600 MHz, CDCl_3)



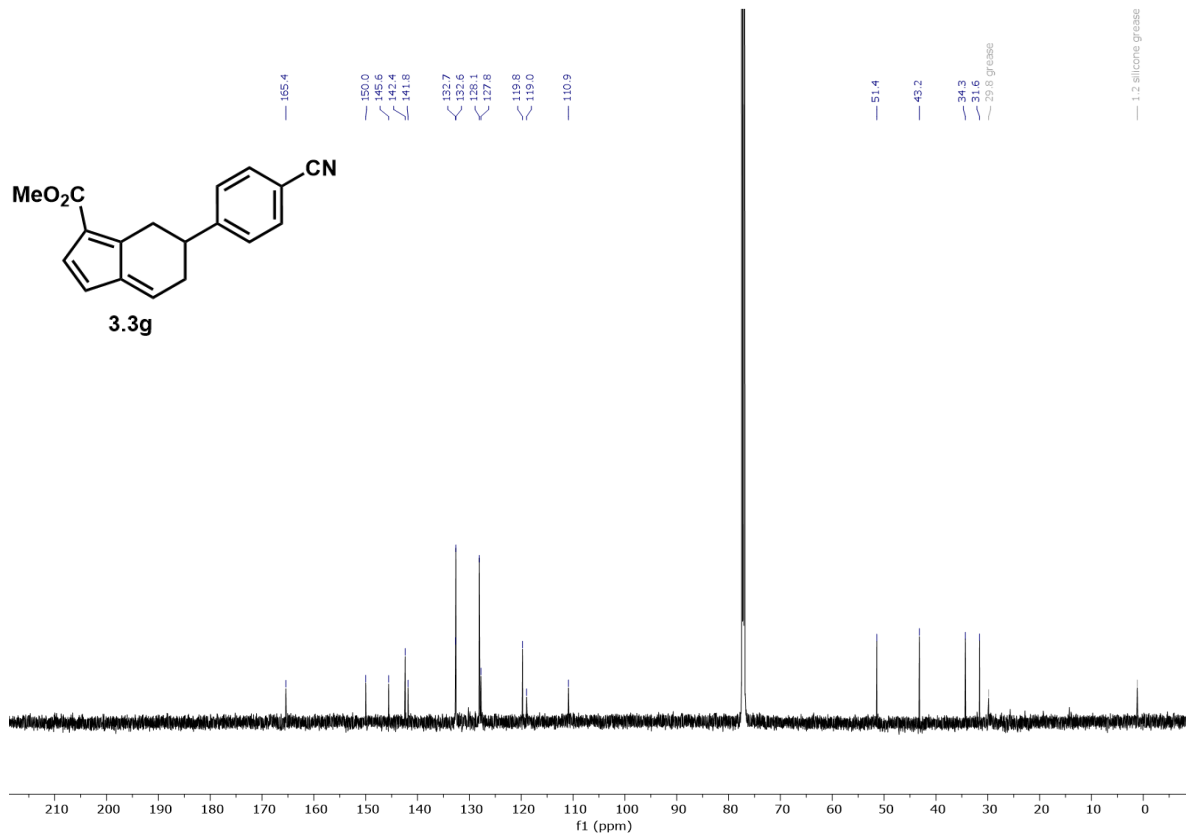
^{13}C NMR (151 MHz, CDCl_3)



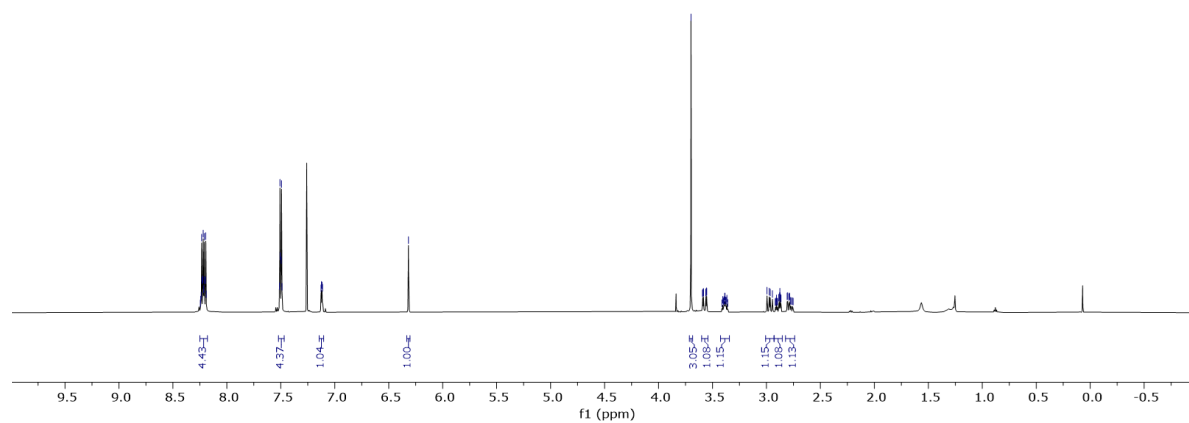
^1H NMR (500 MHz, CDCl_3)



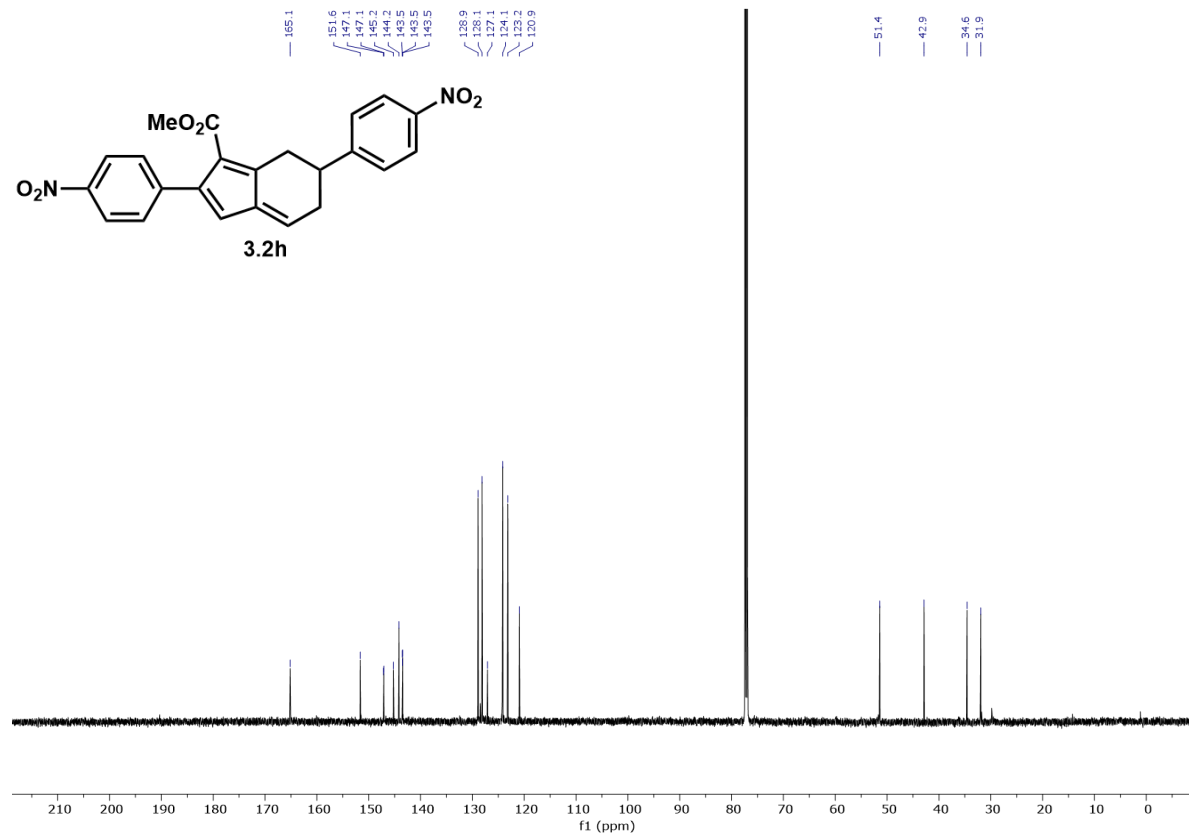
^{13}C NMR (151 MHz, CDCl_3)



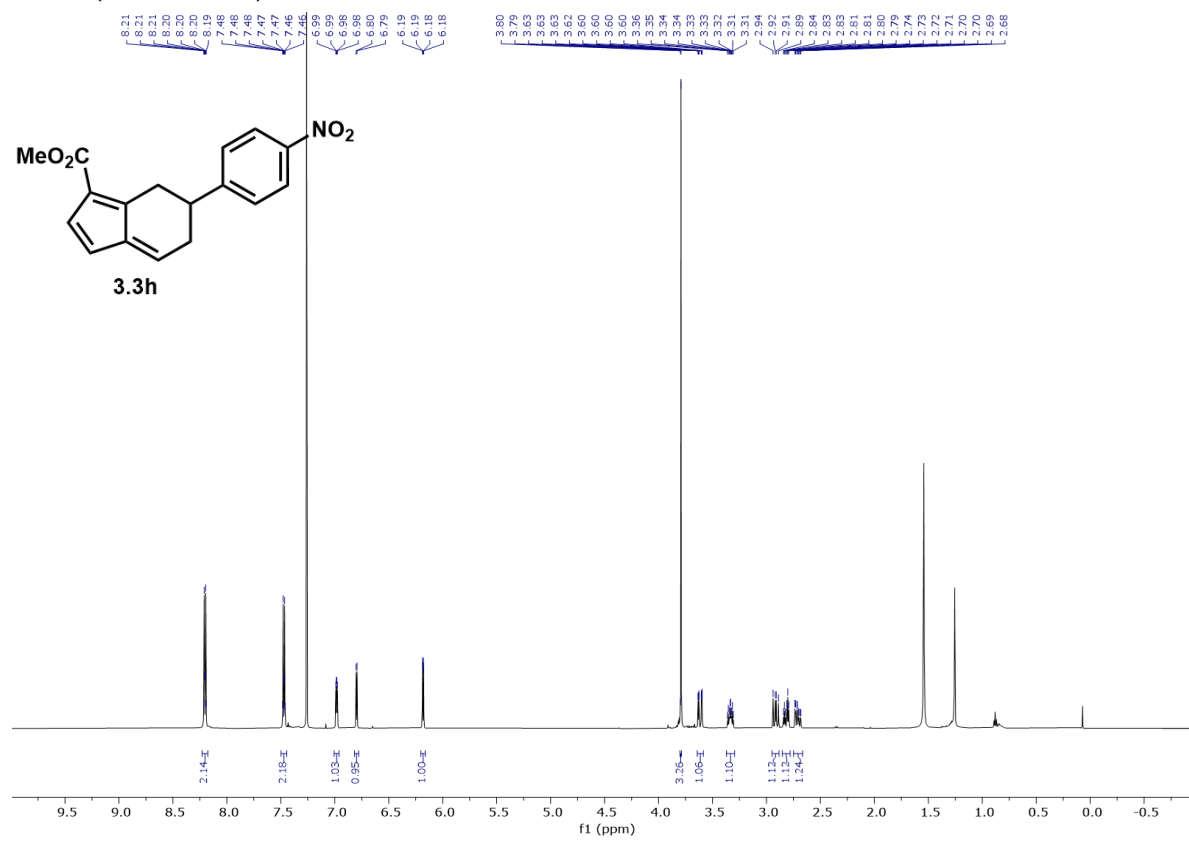
8.24
8.24
8.23
8.23
8.22
8.22
8.22
8.21
8.21
8.21
8.20
8.20
8.20
8.20
7.75
7.75
7.75
7.75
7.49
7.49
7.13
7.13
7.12
7.12
7.11
7.11
6.92
3.70
3.59
3.59
3.58
3.58
3.58
3.56
3.56
3.56
3.55
3.55
3.41
3.41
3.40
3.40
3.39
3.39
3.39
3.38
3.38
3.38
3.37
3.37
3.37
2.97
2.97
2.97
2.95
2.95
2.92
2.91
2.91
2.91
2.90
2.89
2.88
2.88
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2.81
2.80
2.79
2.79
2.77
2.77
2.76
2.75



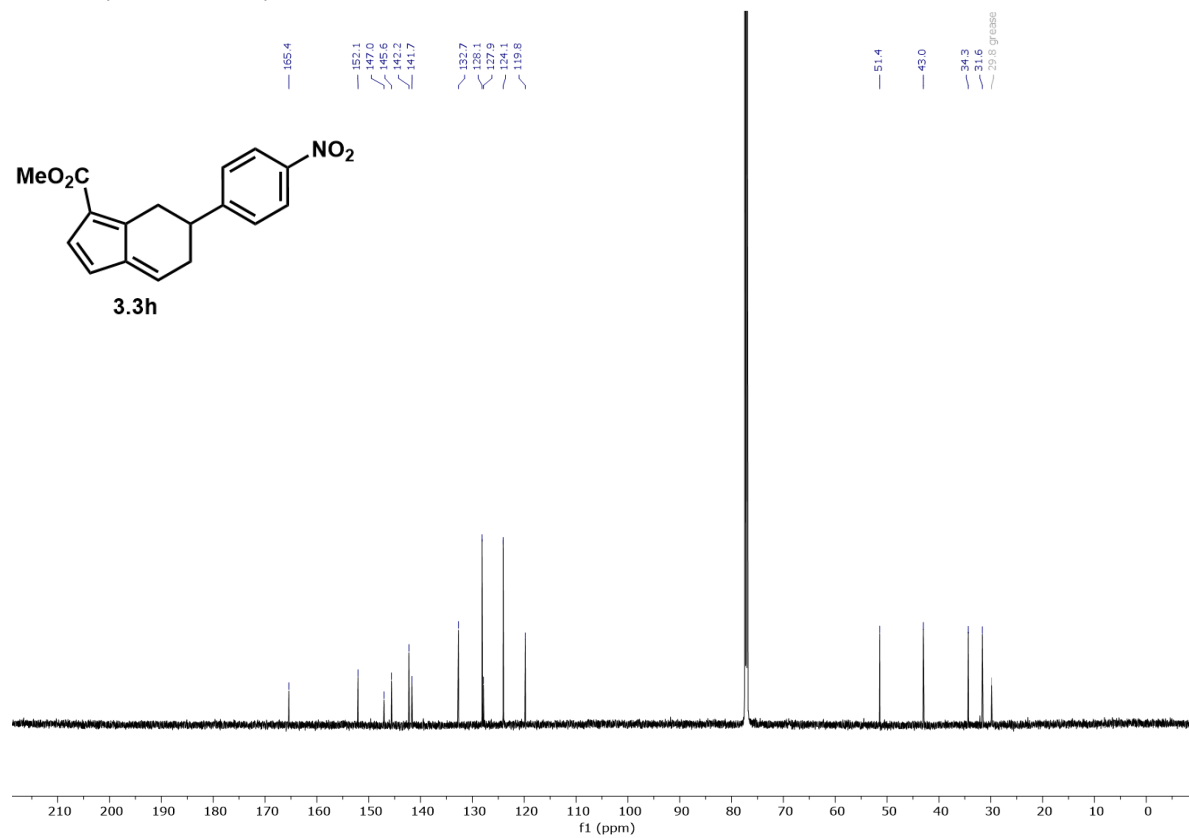
151.6
147.1
147.1
145.2
144.2
143.5
143.5
143.5
128.9
128.1
127.1
124.1
123.2
120.9



^1H NMR (600 MHz, CDCl_3)



^{13}C NMR (151 MHz, CDCl_3)

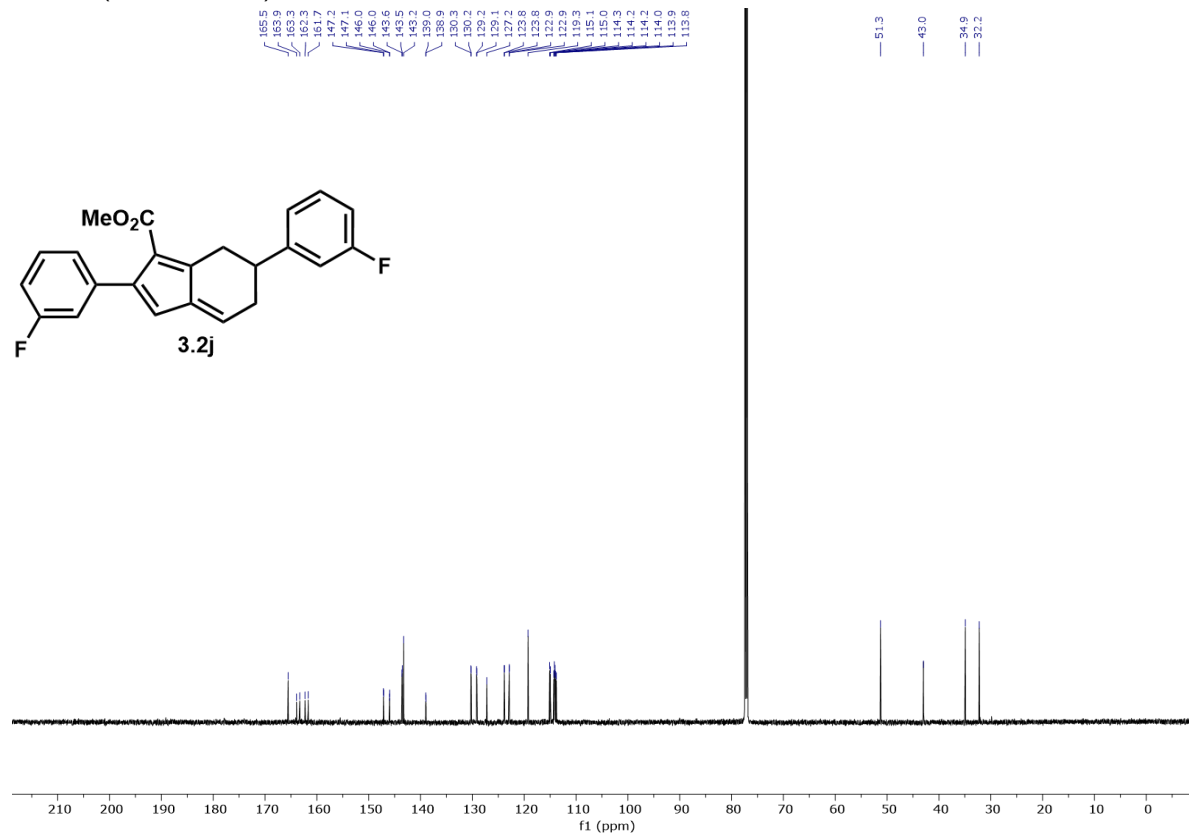


Chemical structure of compound **3.2i** is shown, which is a fluorene derivative. It features a methyl ester group (MeO_2C) at position 9, a 4-fluorophenyl group at position 2, and a 4-fluorophenyl group at position 7.

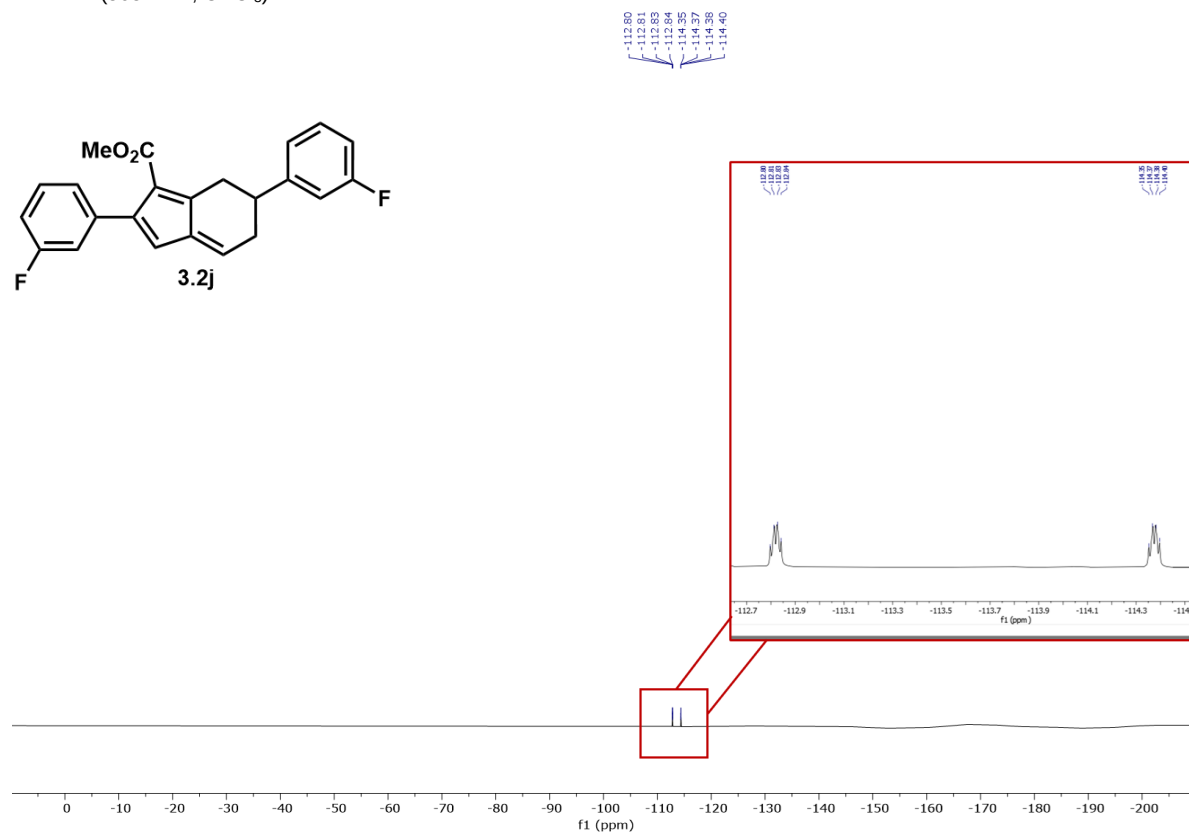
The ^{13}C NMR spectrum (f1 (ppm)) displays peaks corresponding to the structure. The spectrum shows a broad peak around -115.5 ppm and a sharp peak around -115.1 ppm. An inset provides a detailed view of the region from 115.0 to 116.2 ppm, showing two distinct doublets.

[illegible]

¹³C NMR (151 MHz, CDCl₃)



¹⁹F NMR (565 MHz, CDCl₃)



Chemical structure of **3.2k** is shown above the spectrum.

¹H NMR spectrum (CDCl₃) of **3.2k** is displayed below the structure. The x-axis represents the chemical shift in ppm (f1), ranging from -0.5 to 10.0. The spectrum shows several peaks, with integration values indicated below the baseline.

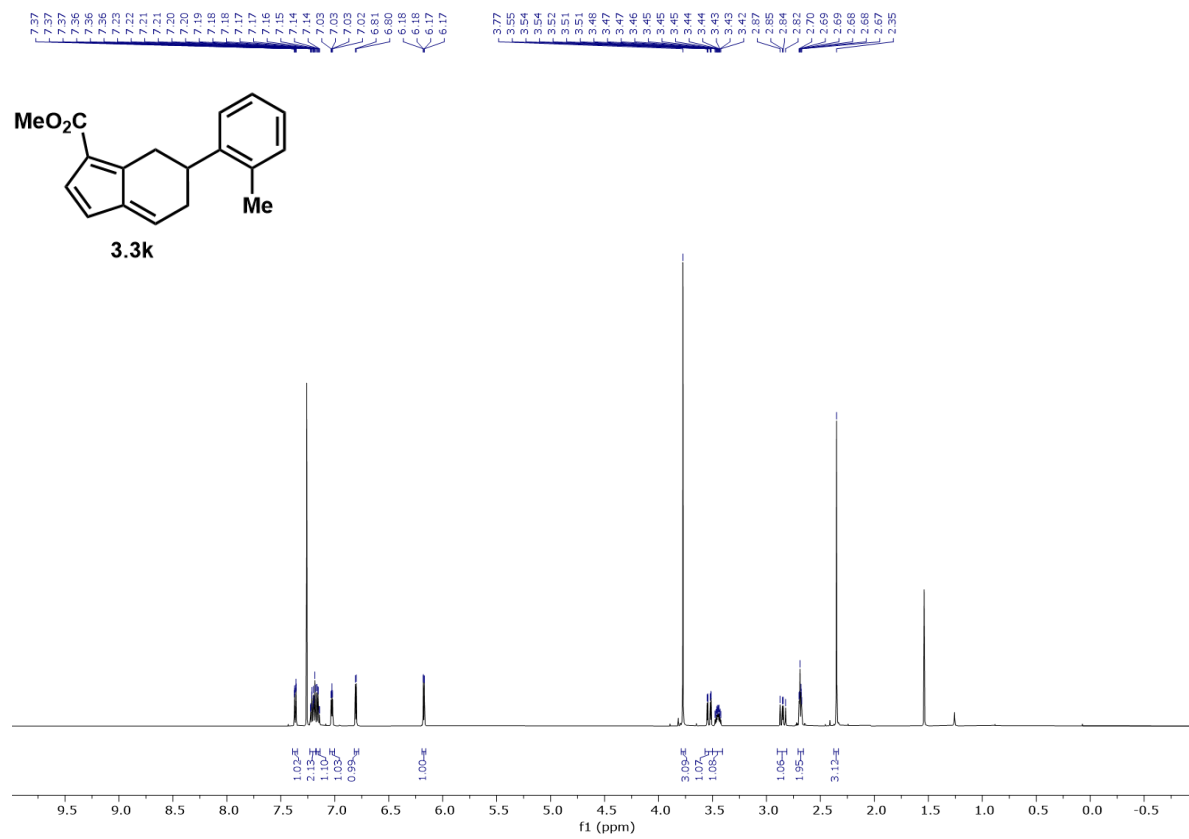
Integration values (from left to right): 1.02, 4.02, 3.34, 1.04, 0.98, 3.05, 2.14, 1.06, 1.99, 3.12, 3.08.

Chemical structure of **3.2k** is shown. The structure is a 1-methyl-2-(4-methylphenyl)-3-(4-methoxyphenyl)hexahydroindene.

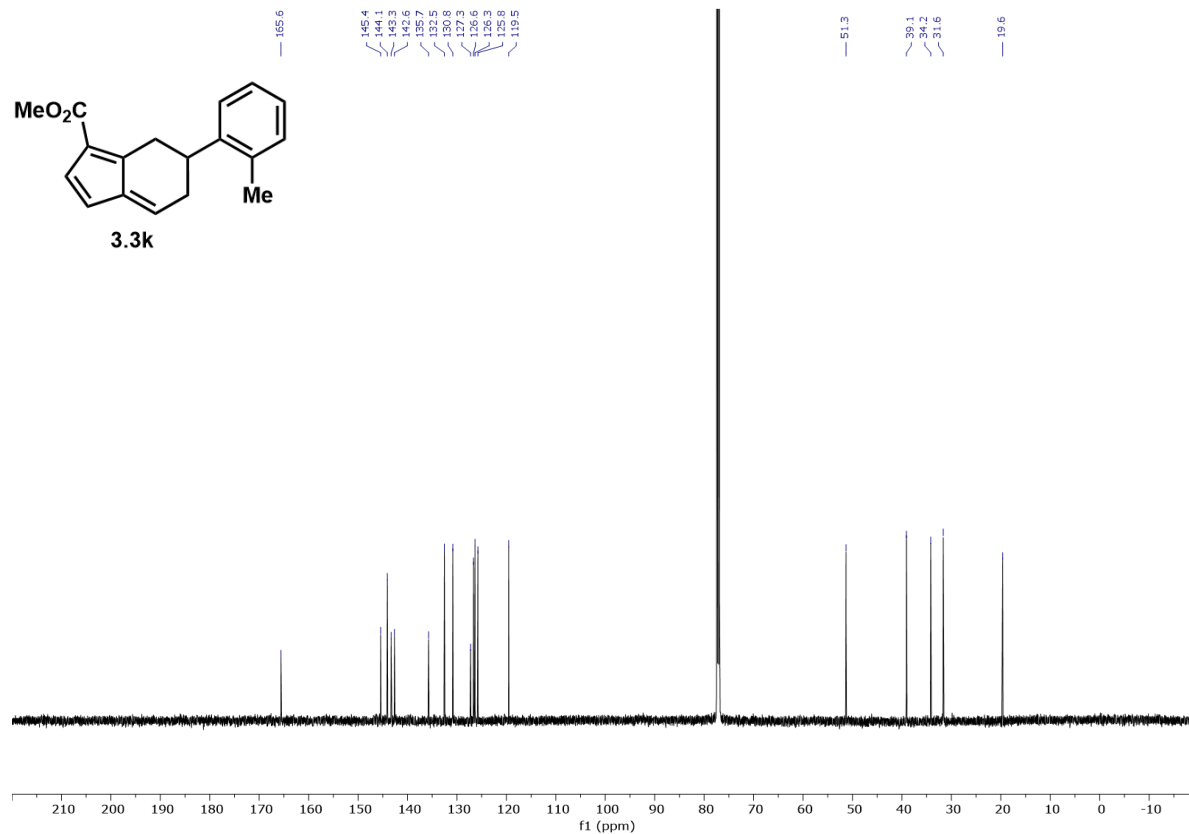
¹³C NMR spectrum (f1 (ppm)) is displayed. The spectrum shows peaks corresponding to the structure, with the following chemical shifts (ppm) listed:

- 165.5
- 145.5
- 143.8
- 143.8
- 143.1
- 142.7
- 137.7
- 136.5
- 136.8
- 136.9
- 130.9
- 129.4
- 128.8
- 128.0
- 127.3
- 127.2
- 126.4
- 125.8
- 125.2
- 118.8
- 51.1
- 39.1
- 34.3
- 32.0
- 20.5
- 19.7

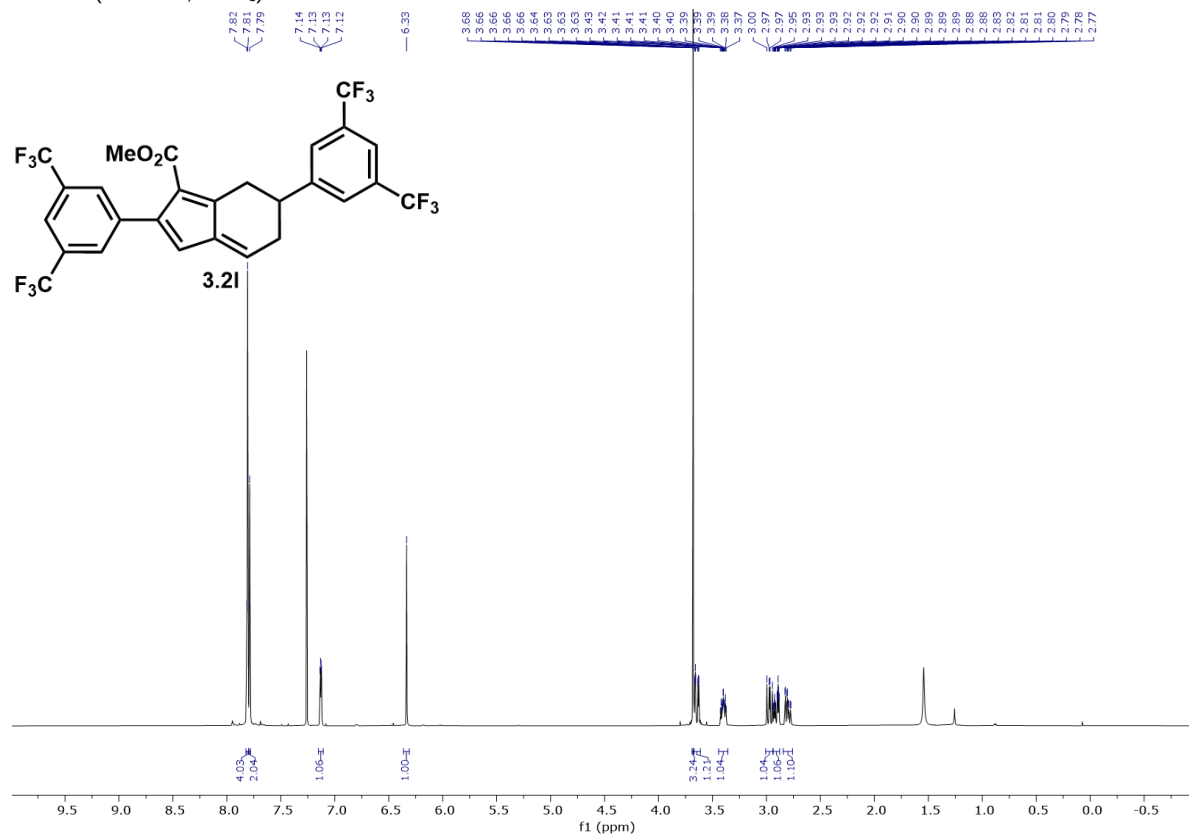
^1H NMR (600 MHz, CDCl_3)



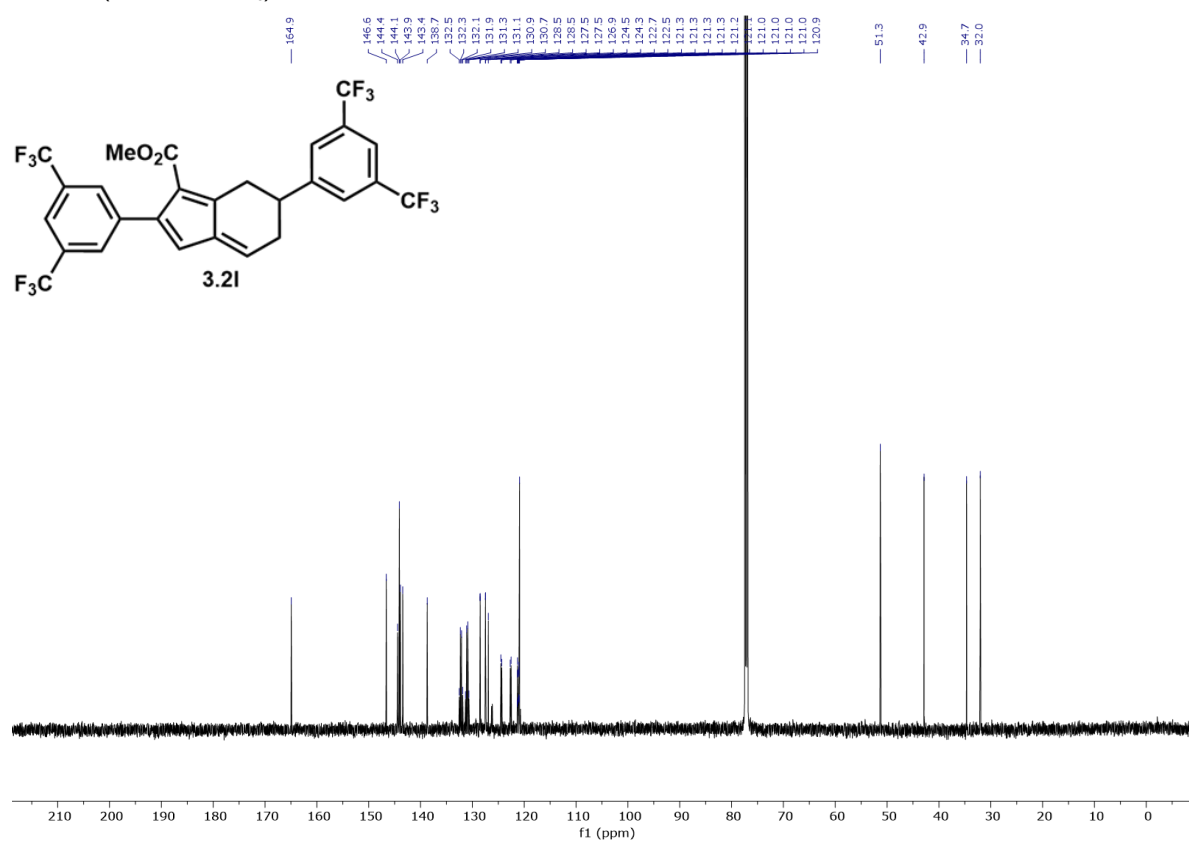
^{13}C NMR (151 MHz, CDCl_3)



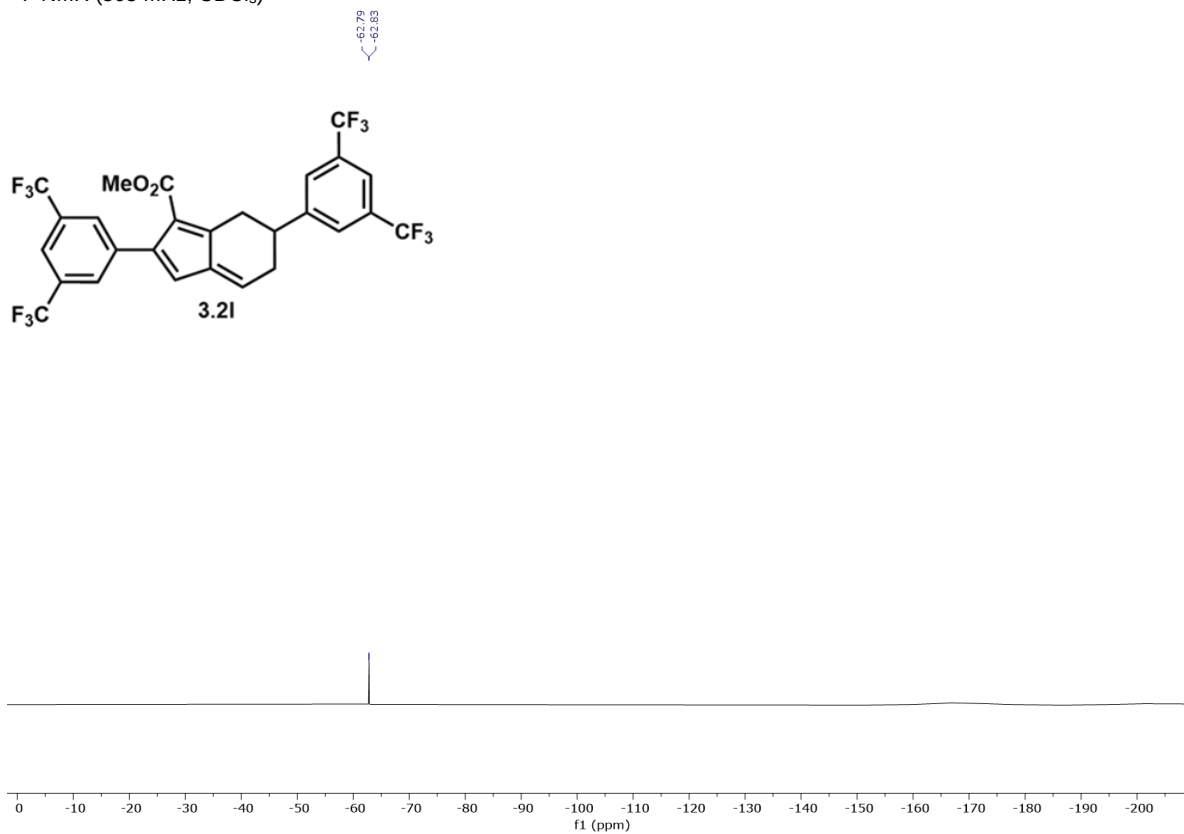
^1H NMR (600 MHz, CDCl_3)



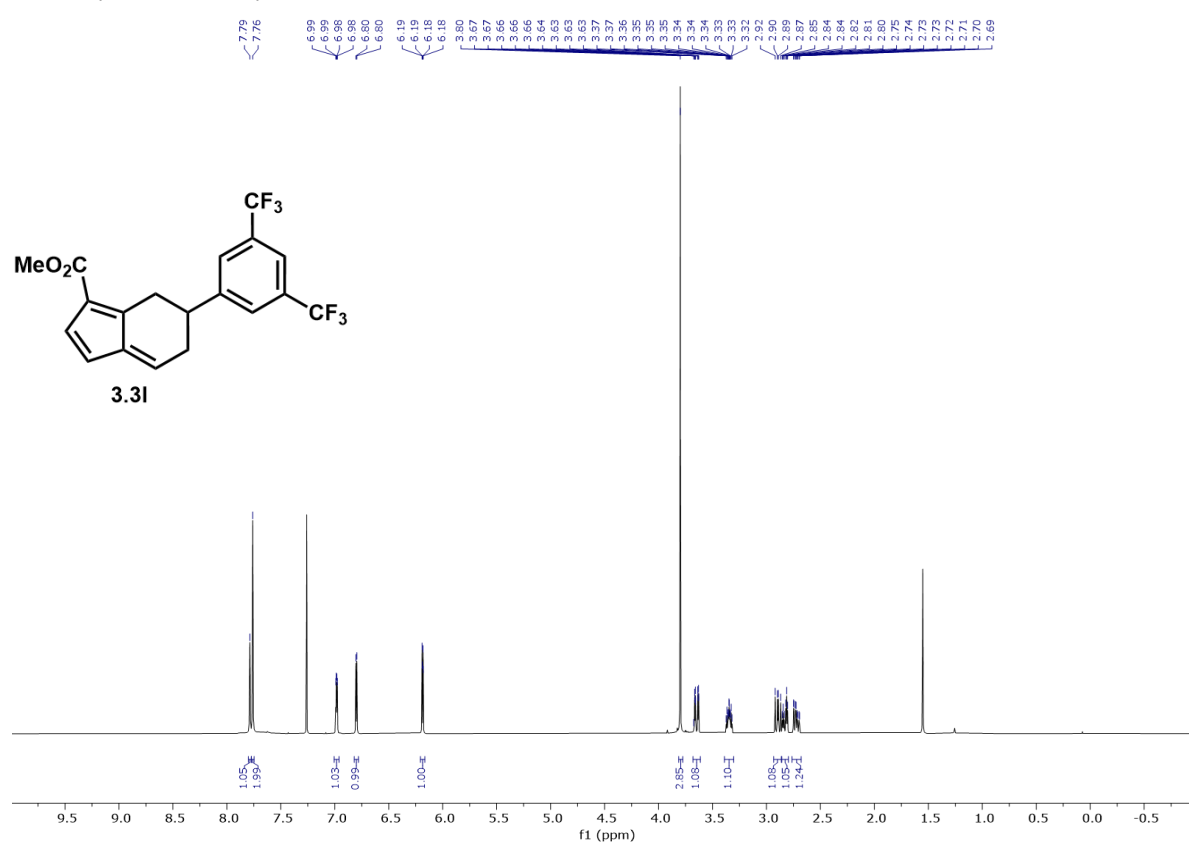
^{13}C NMR (151 MHz, CDCl_3)



^{19}F NMR (565 MHz, CDCl_3)



^1H NMR (600 MHz, CDCl_3)



COC(=O)c1ccc2ccccc2c1-c1ccc(C(F)(F)F)c(C(F)(F)F)c1

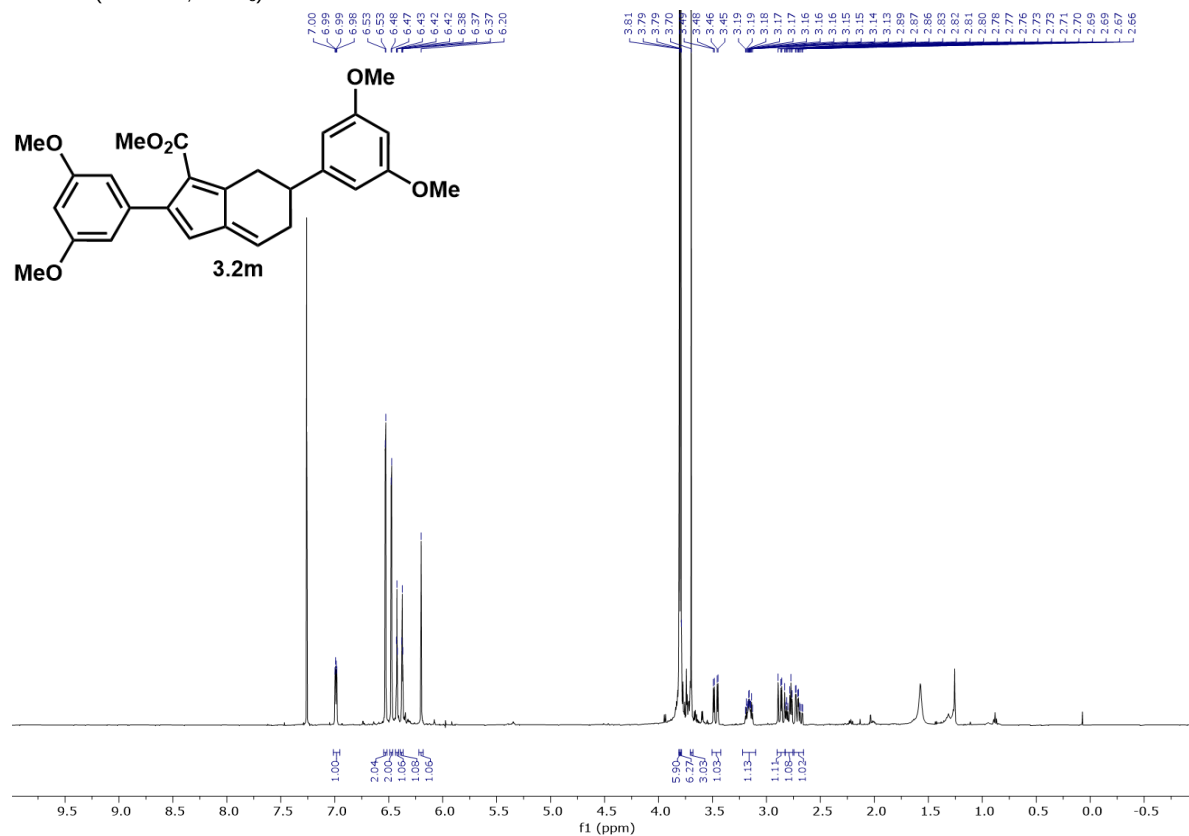
3.3l

13C NMR spectrum (CDCl₃) of compound **3.3l**. The x-axis is labeled "f1 (ppm)" and ranges from -10 to 210. The spectrum shows a large solvent peak at 77.0 ppm. Other peaks are observed in the aromatic region (119.8-147.0 ppm) and aliphatic region (31.7-51.4 ppm).

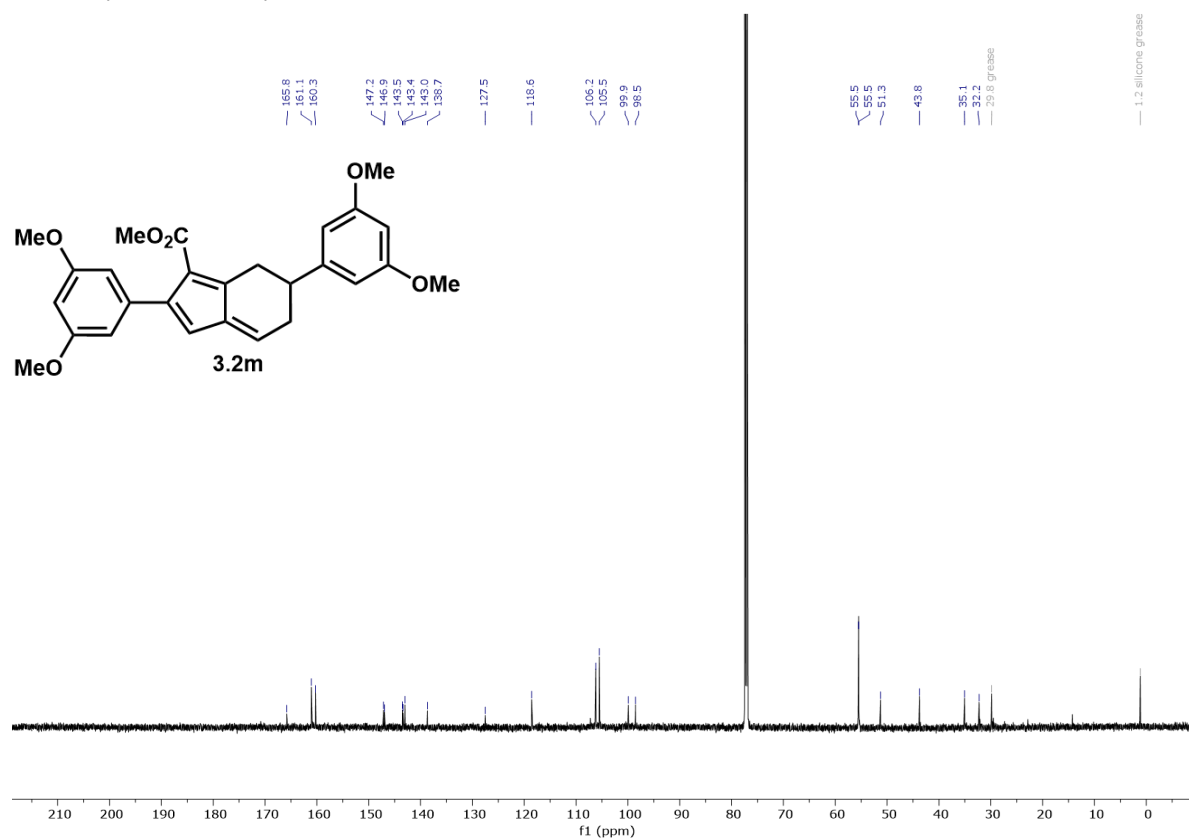
Chemical Shift (ppm)
165.4
147.0
145.6
142.0
141.4
137.4
132.4
132.2
131.9
131.7
128.0
127.5
125.2
124.4
122.6
121.1
121.1
121.1
121.1
121.1
119.8
51.4
43.0
34.4
31.7

Chemical structure of compound 3.31 is shown above the spectrum. The structure is a bicyclic compound consisting of a cyclohexene ring fused to a cyclopentene ring, substituted with a methoxycarbonyl group (MeO_2C) and a 2,4-difluorophenyl group.

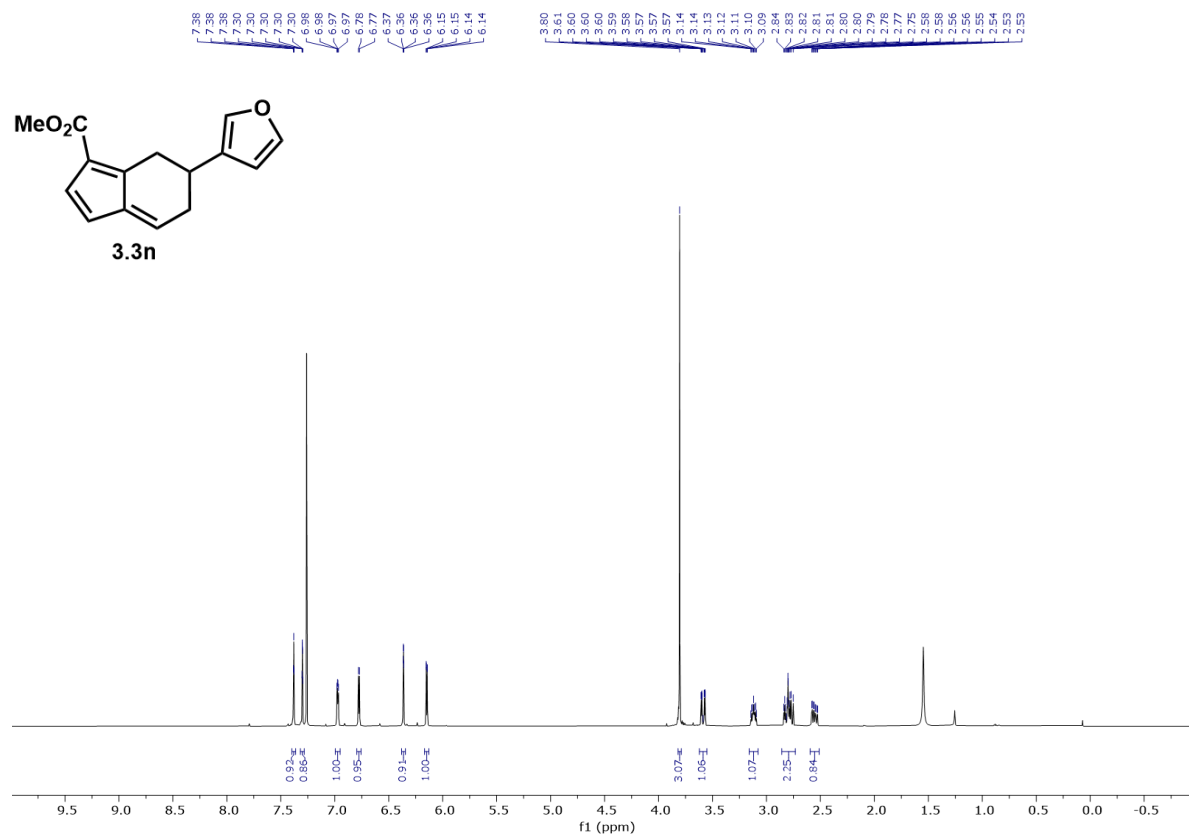
^1H NMR (500 MHz, CDCl_3)



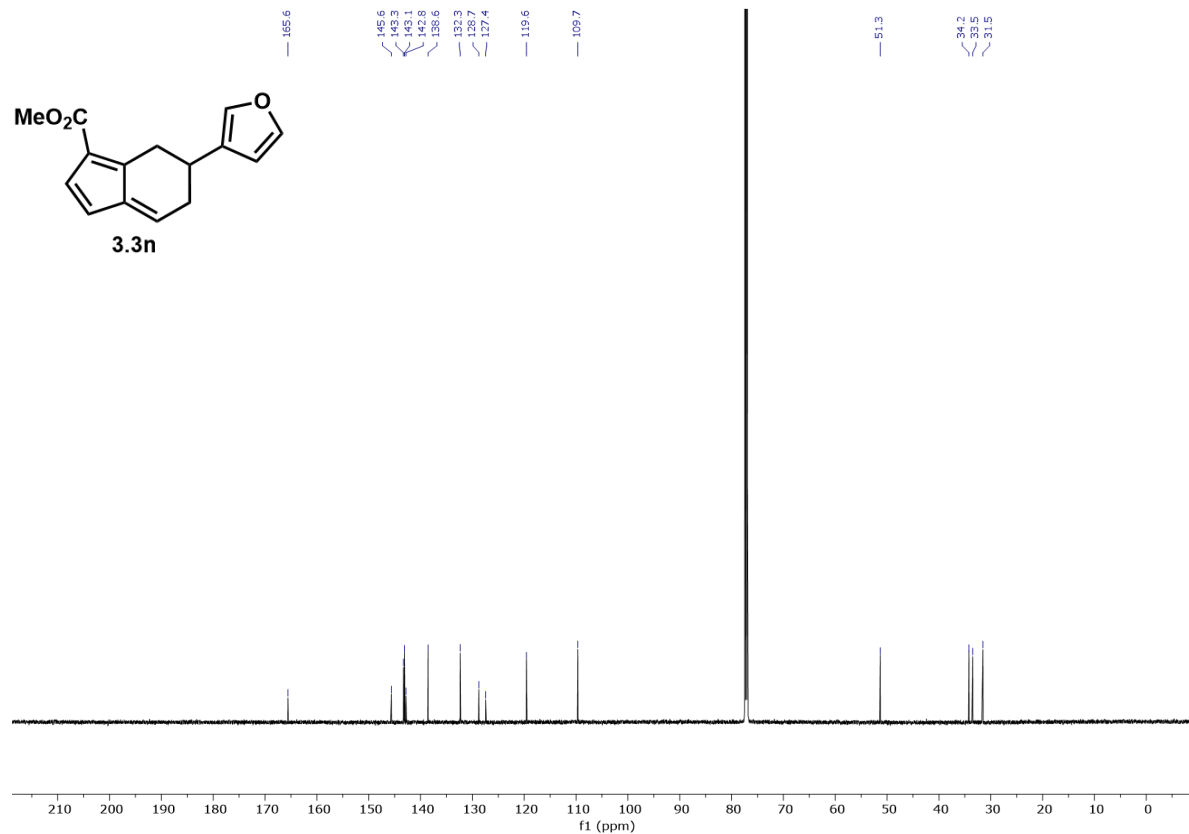
^{13}C NMR (151 MHz, CDCl_3)



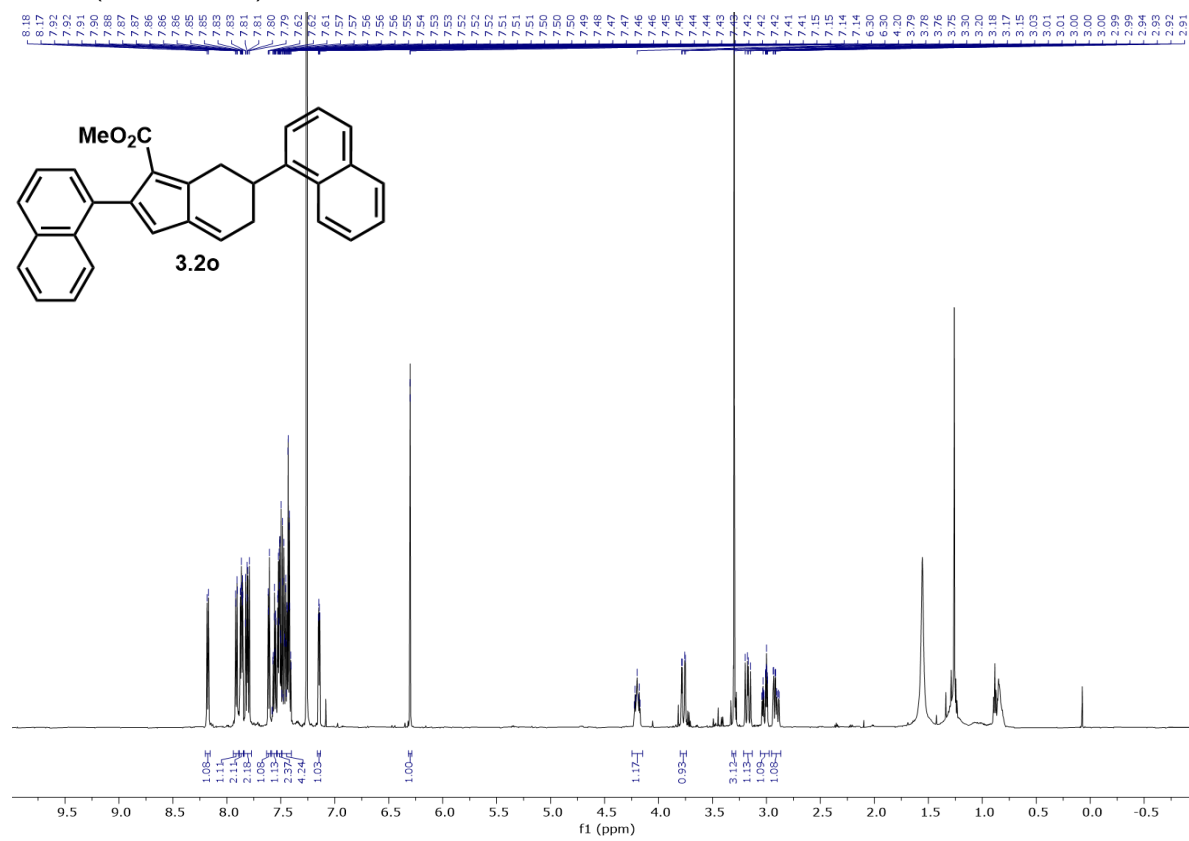
^1H NMR (600 MHz, CDCl_3)



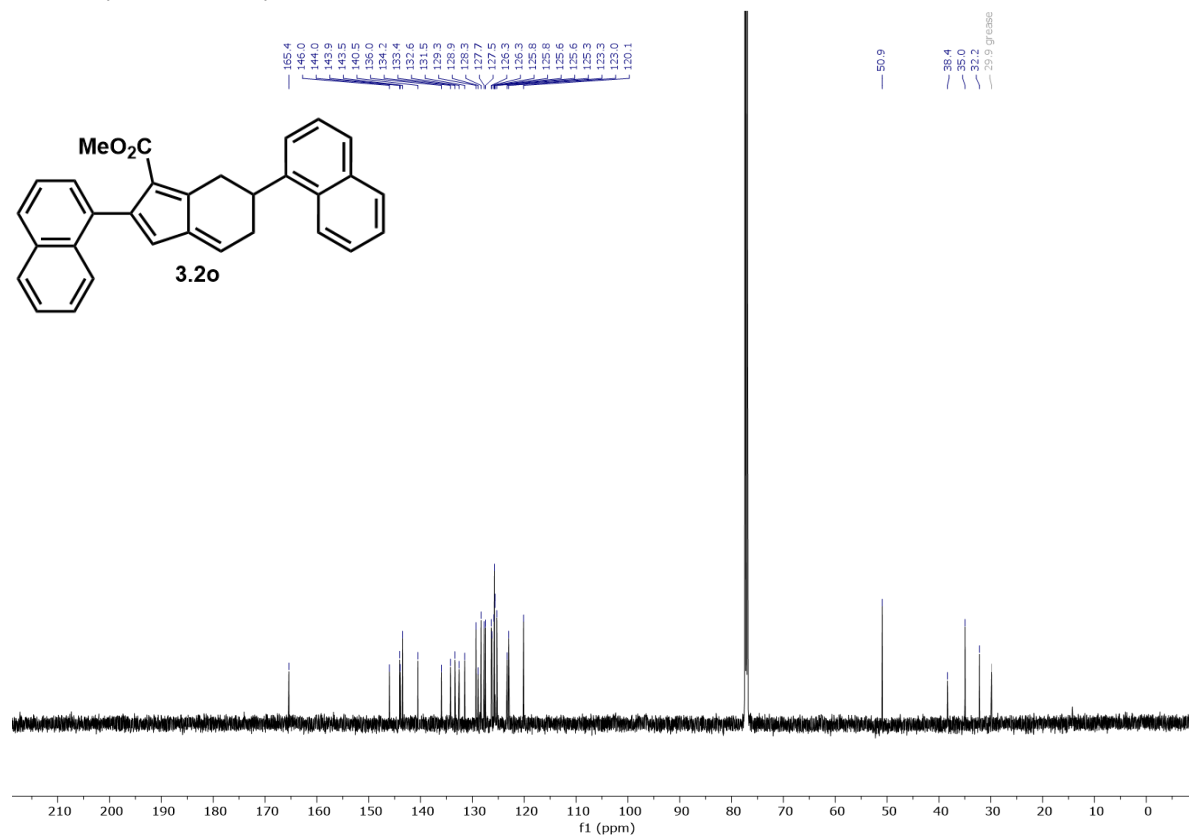
^{13}C NMR (151 MHz, CDCl_3)



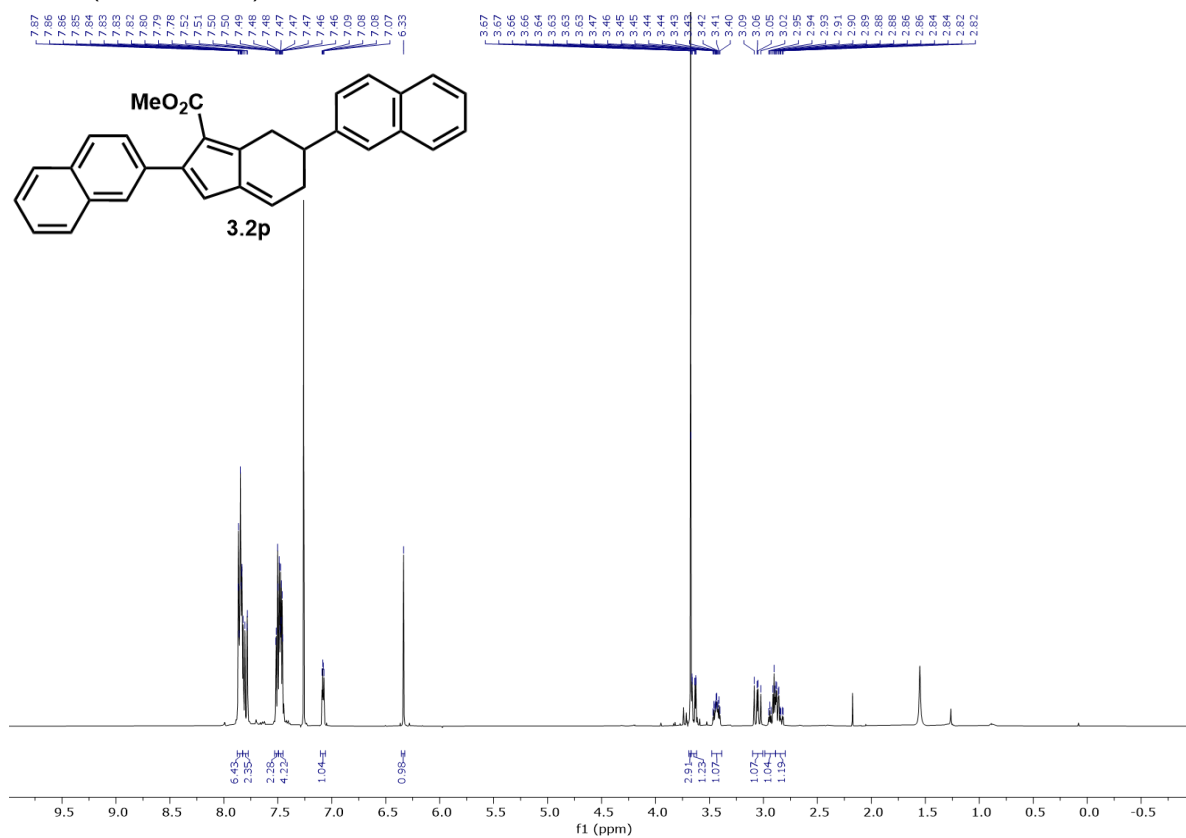
¹H NMR (600 MHz, CDCl₃)



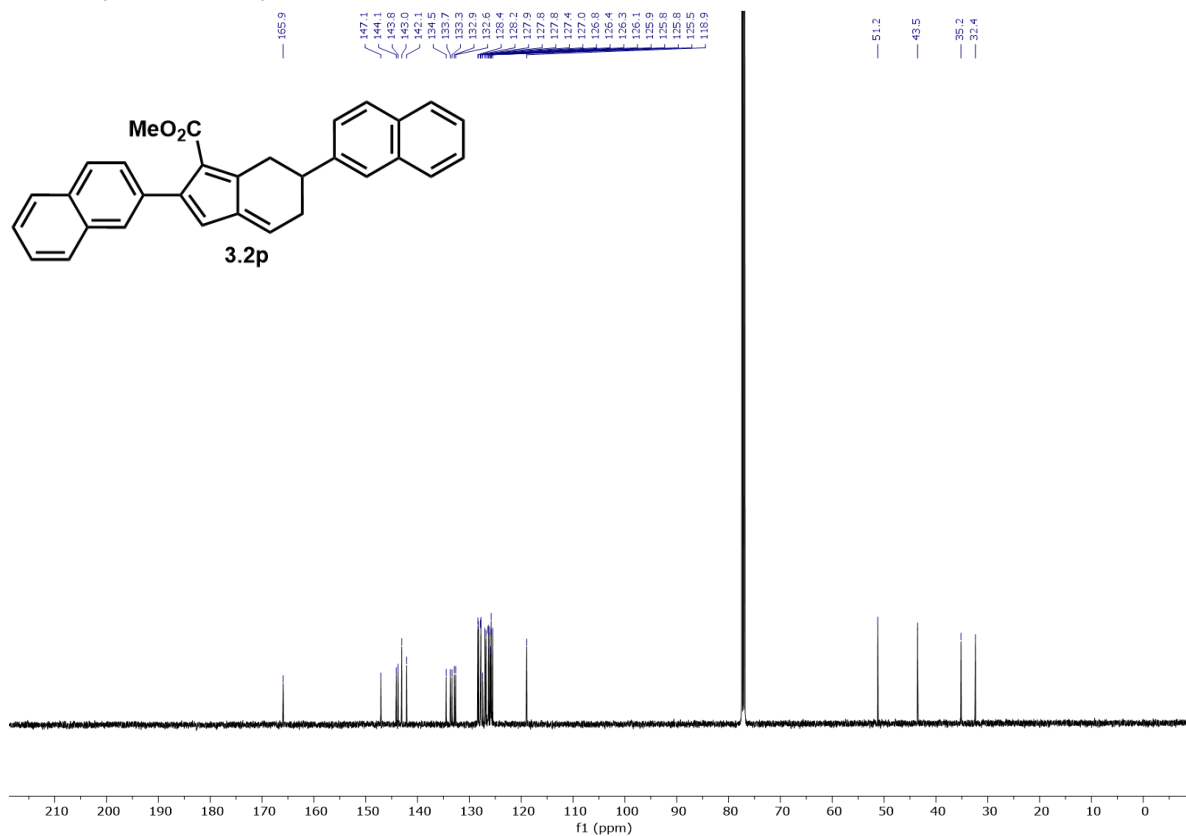
¹³C NMR (151 MHz, CDCl₃)



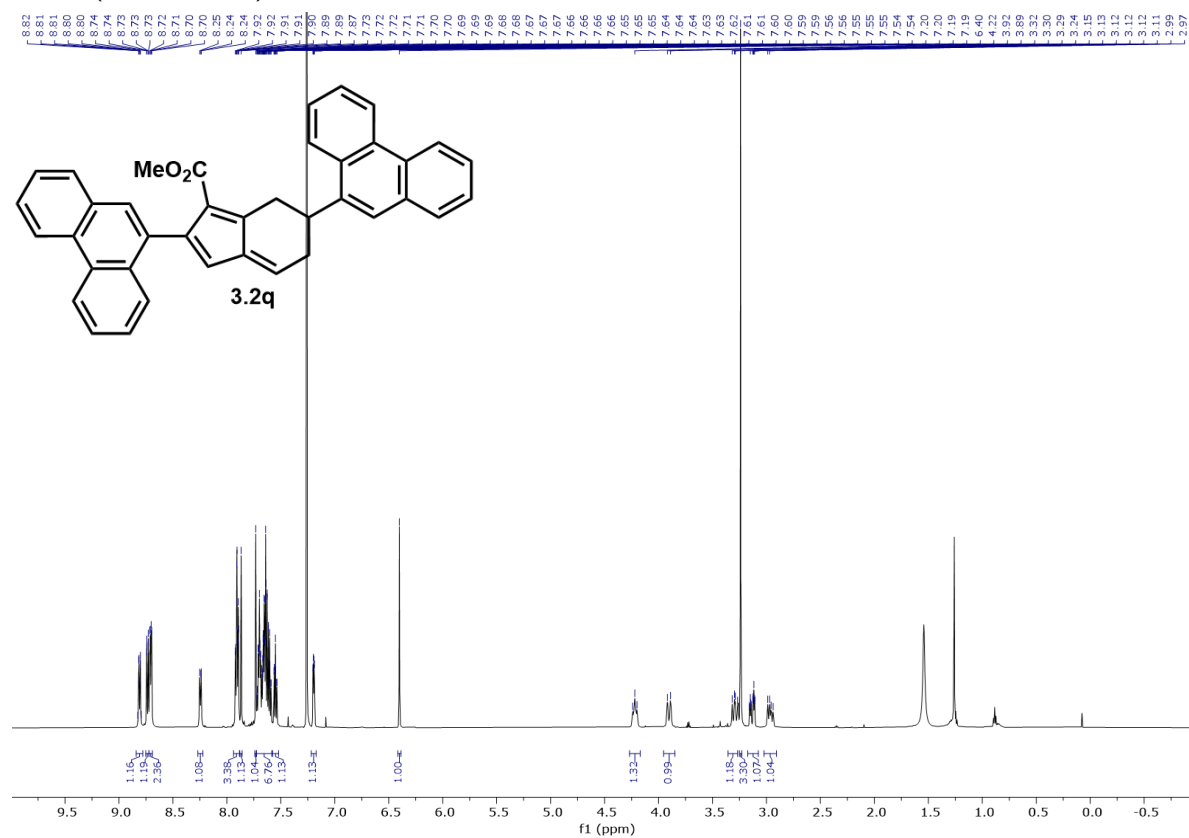
^1H NMR (500 MHz, CDCl_3)



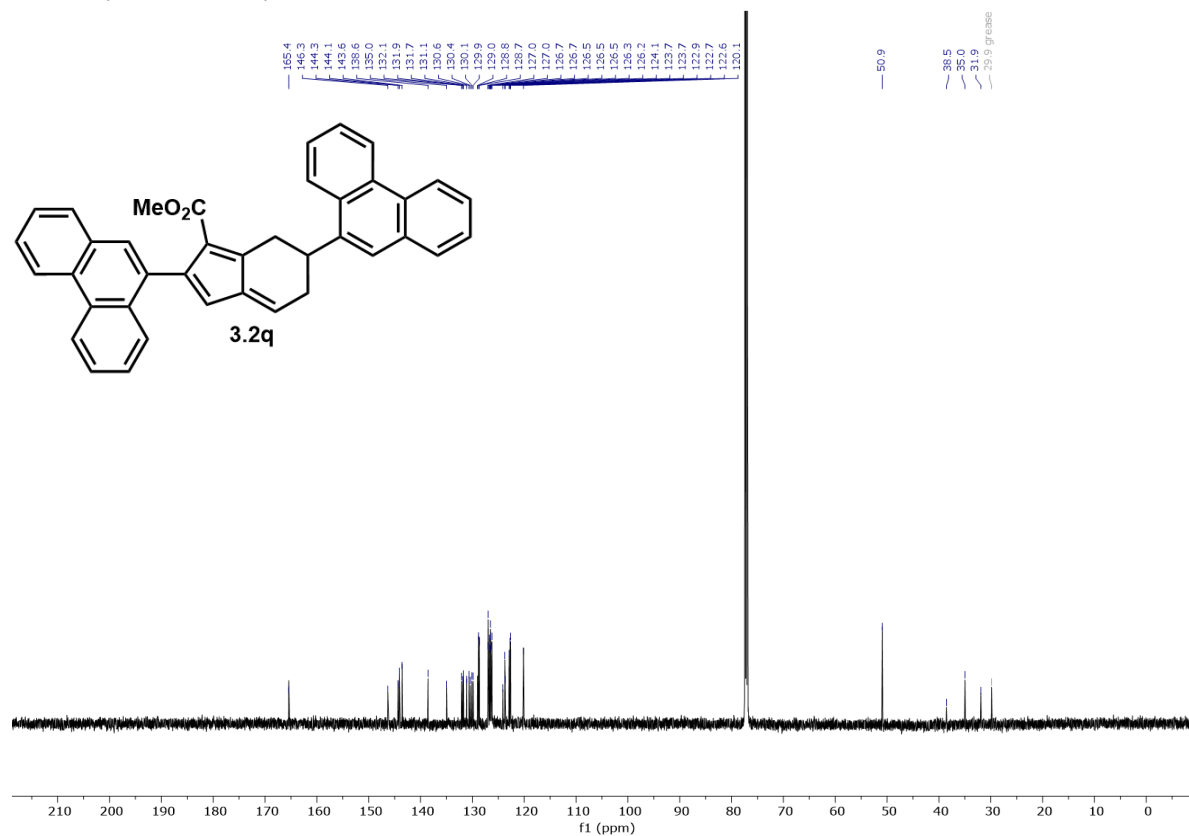
^{13}C NMR (126 MHz, CDCl_3)



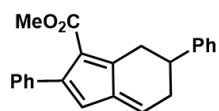
^1H NMR (600 MHz, CDCl_3)



^{13}C NMR (151 MHz, CDCl_3)



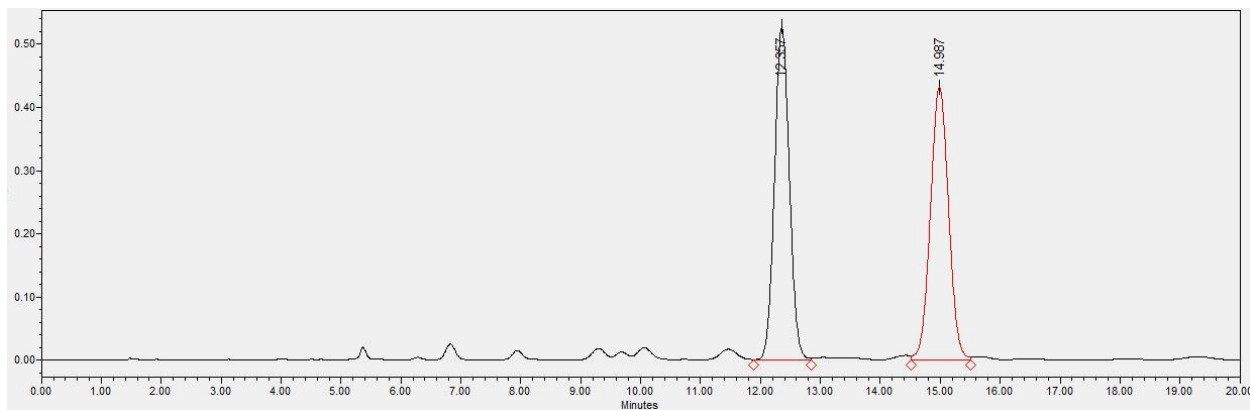
3.8.5 Chiral HPLC Traces



3.2a

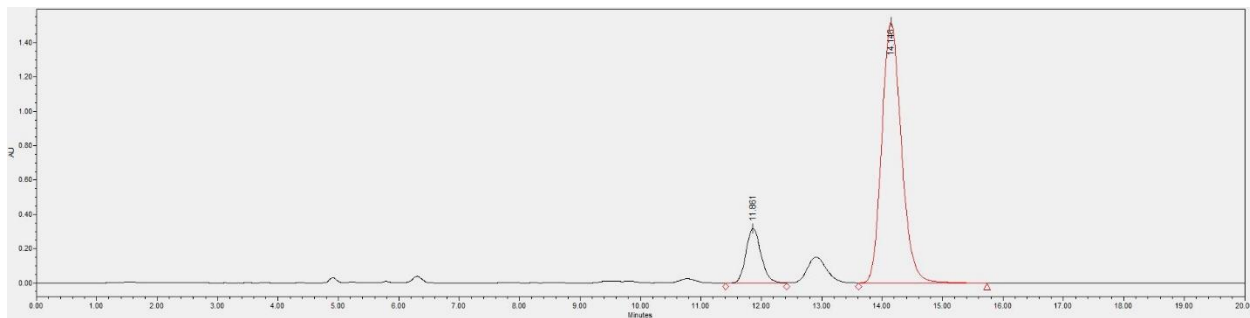
Method: AD3 chiral column, 1% IPA/hexanes 2 mL/min, λ = 254 nm

Racemic:

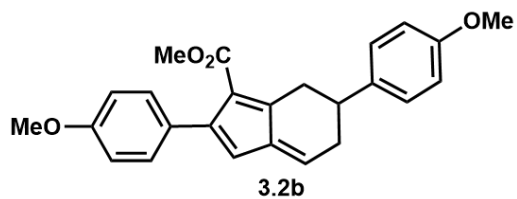


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
12.357	9093061	49.93
14.987	9118099	50.07

Enantioenriched (1 mmol scale):

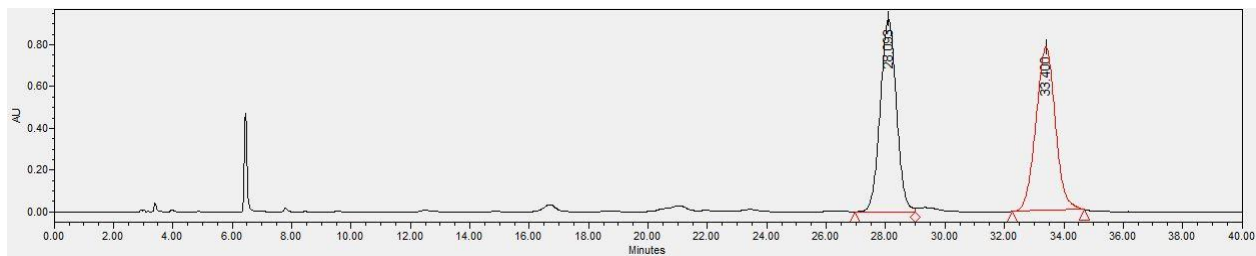


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
11.861	5528729	13.84
14.146	34423325	86.16



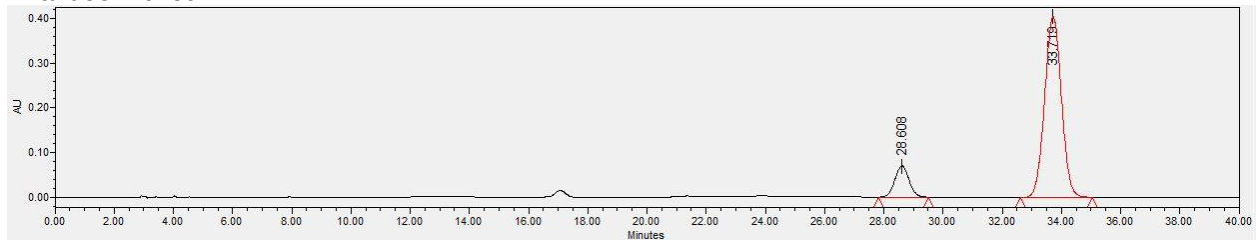
Method: AD3 chiral column, 5% IPA/hexanes 1 mL/min, λ = 254 nm

Racemic:

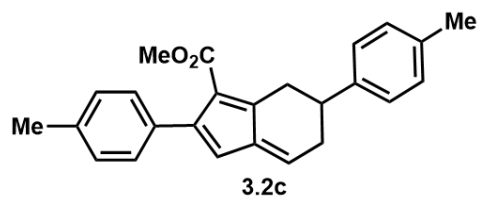


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
28.093	34869206	49.41
33.400	35708050	50.59

Enantioenriched:

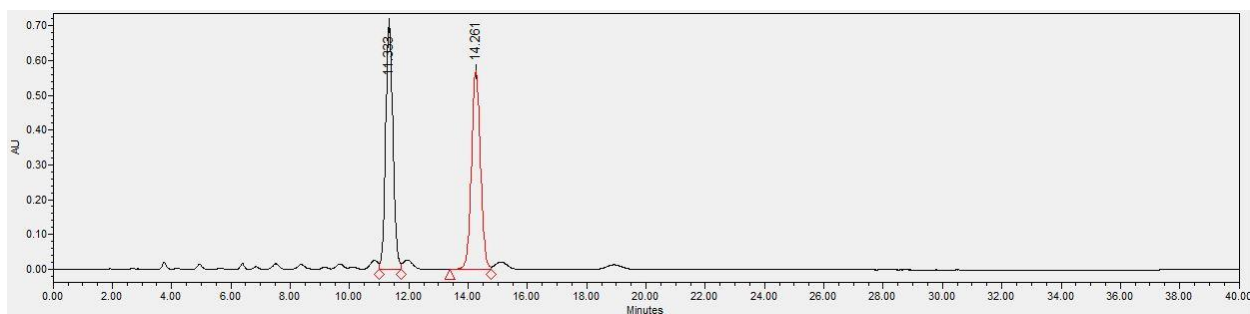


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
28.608	2301910	12.61
33.719	15949113	87.39



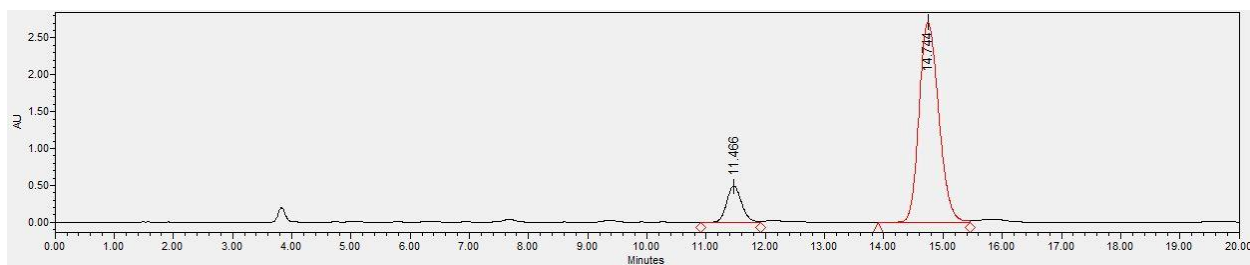
Method: AD3 chiral column, 1% IPA/hexanes 2 mL/min, λ = 254 nm

Racemic:

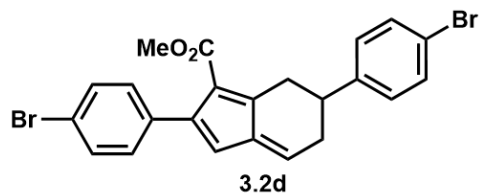


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
11.333	12021951	49.88
14.261	12080718	50.12

Enantioenriched:

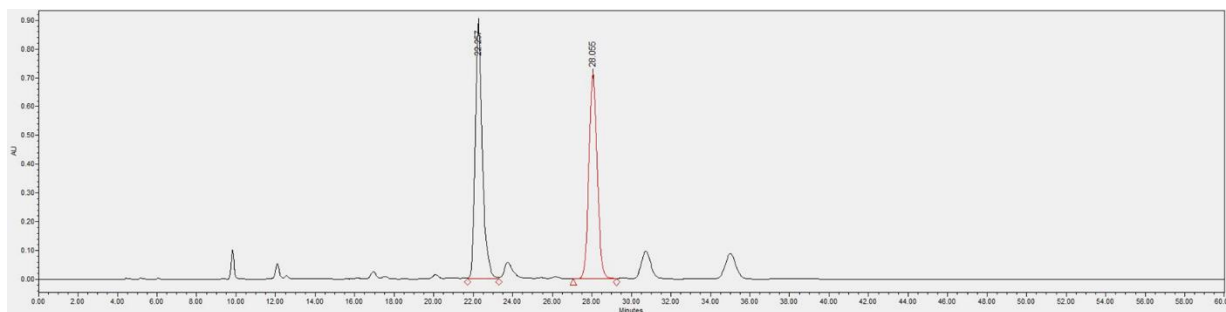


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
11.466	8515477	12.02
14.744	62326780	87.98



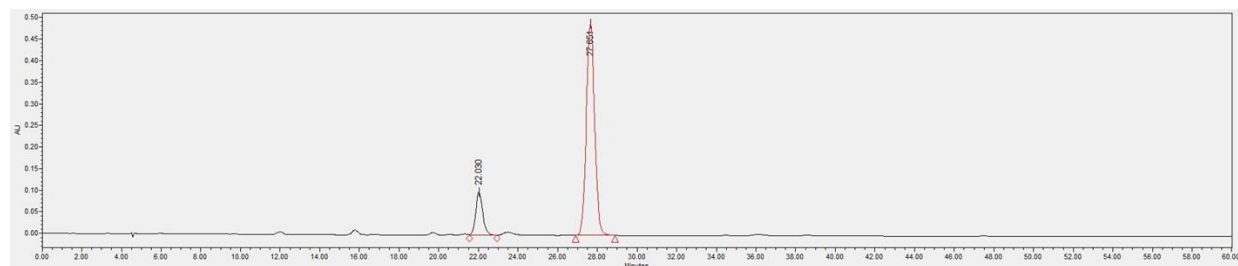
Method: AD3 chiral column, 5% IPA/hexanes 1 mL/min, λ = 254 nm

Racemic:

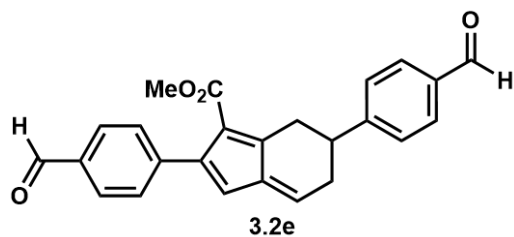


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
22.257	22193296	51.48
28.055	20918567	48.52

Enantioenriched:

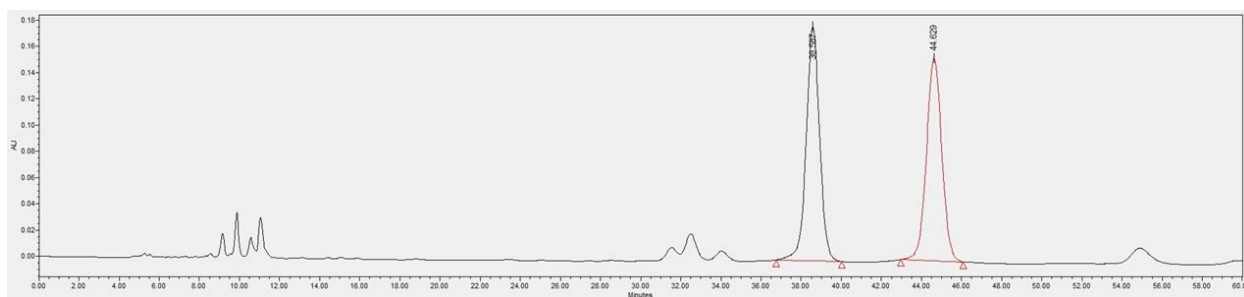


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
22.030	2437316	14.57
27.651	14291891	85.43



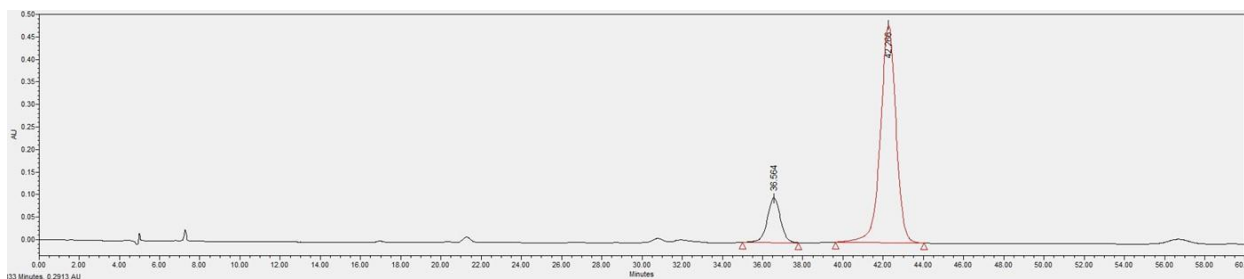
Method: AD3 chiral column, 30% IPA/hexanes 1 mL/min, λ = 254 nm

Racemic:

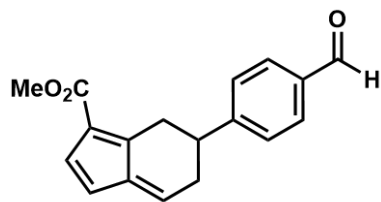


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
38.587	8322196	50.33
44.629	8214296	49.67

Enantioenriched:



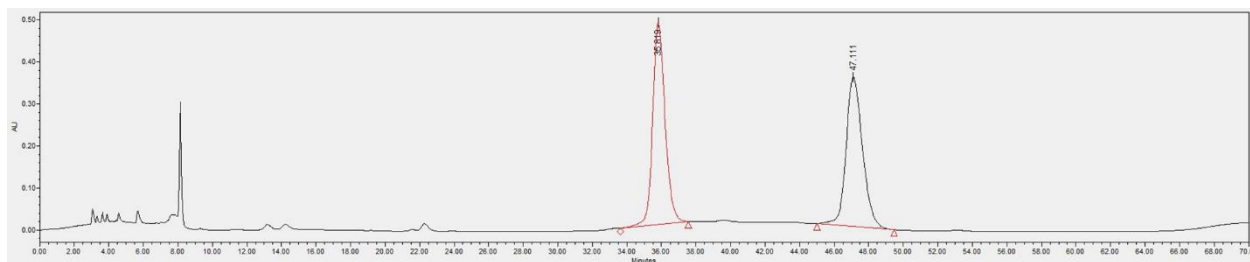
retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
36.564	4520051	14.79
42.266	26041114	85.21



3.3e

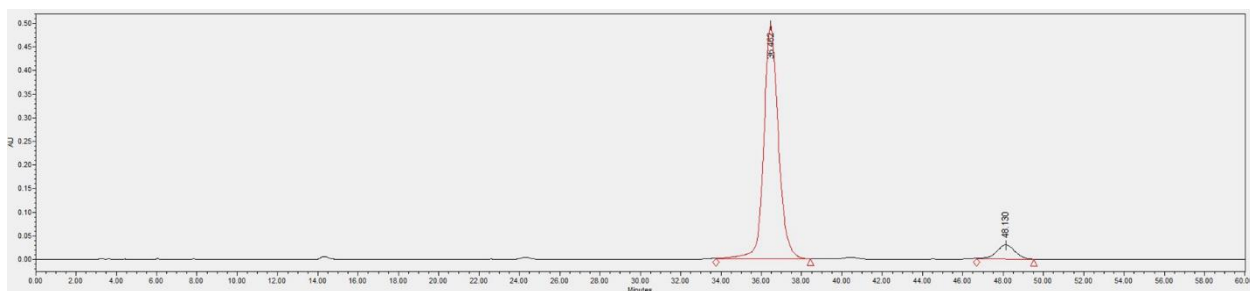
Method: IC3 chiral column, 20% IPA/hexanes 1 mL/min, λ = 254 nm

Racemic:

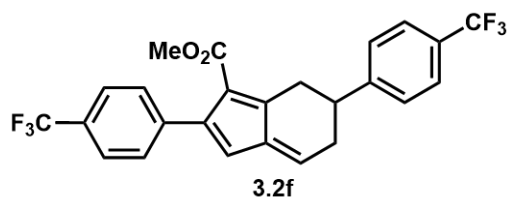


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
35.819	23869218	50.37
47.111	23514074	49.63

Enantioenriched:

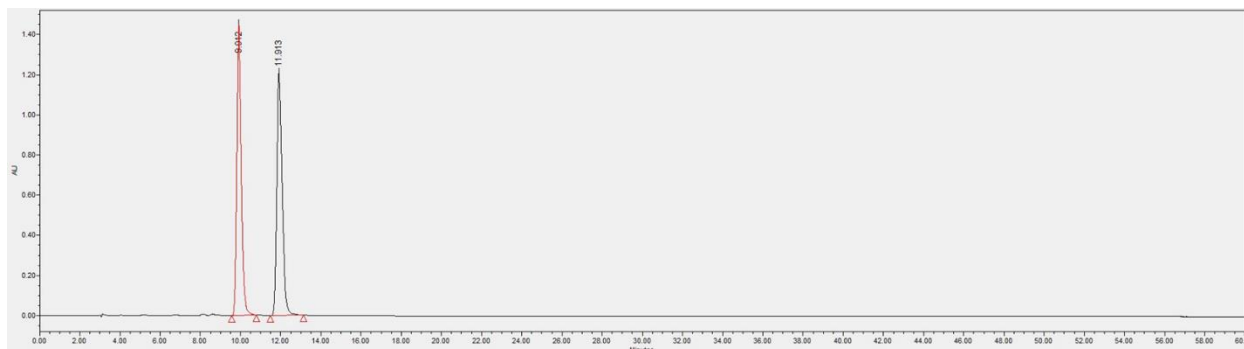


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
36.462	25041887	92.76
48.130	1954341	7.24



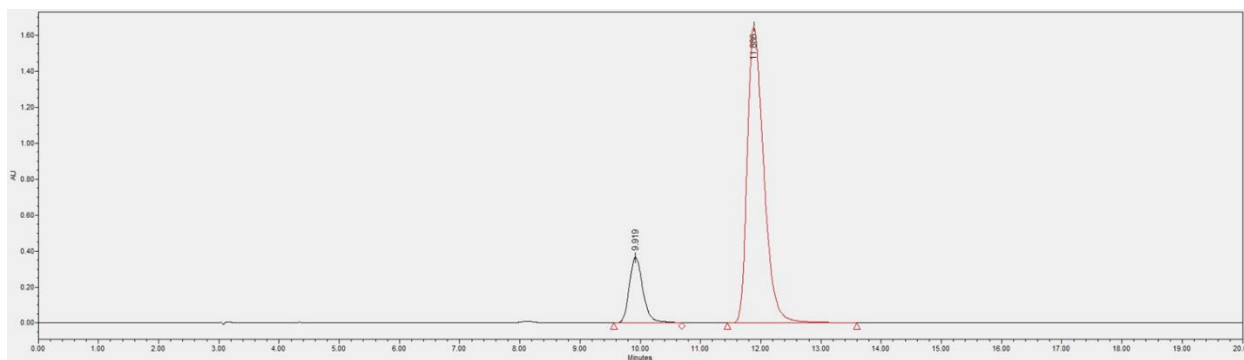
Method: AD3 chiral column, 3% IPA/hexanes 1 mL/min, λ = 254 nm

Racemic:

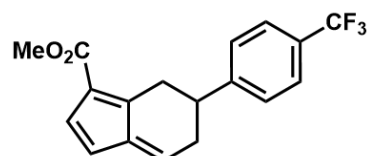


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
9.912	22549545	49.85
11.913	22681739	50.15

Enantioenriched:



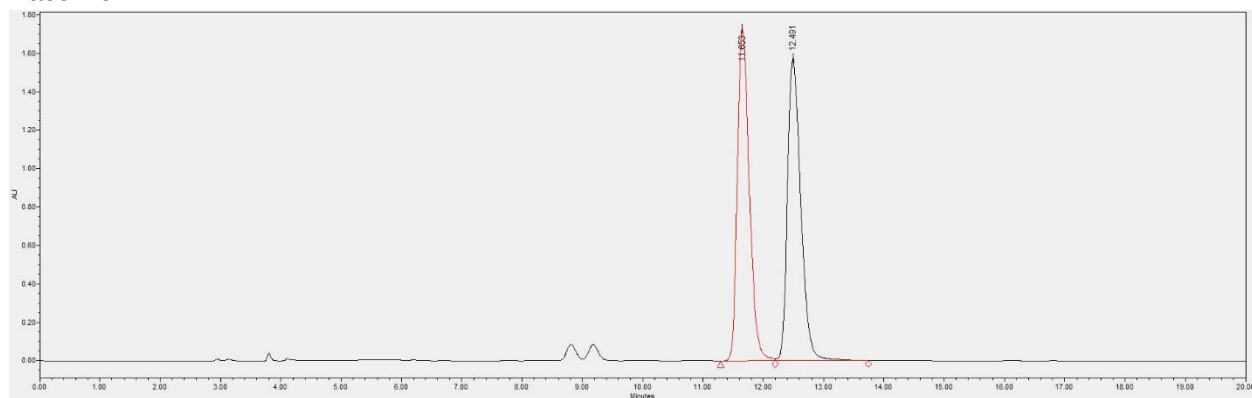
retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
9.919	5696403	15.42
11.886	31240884	84.58



3.3f

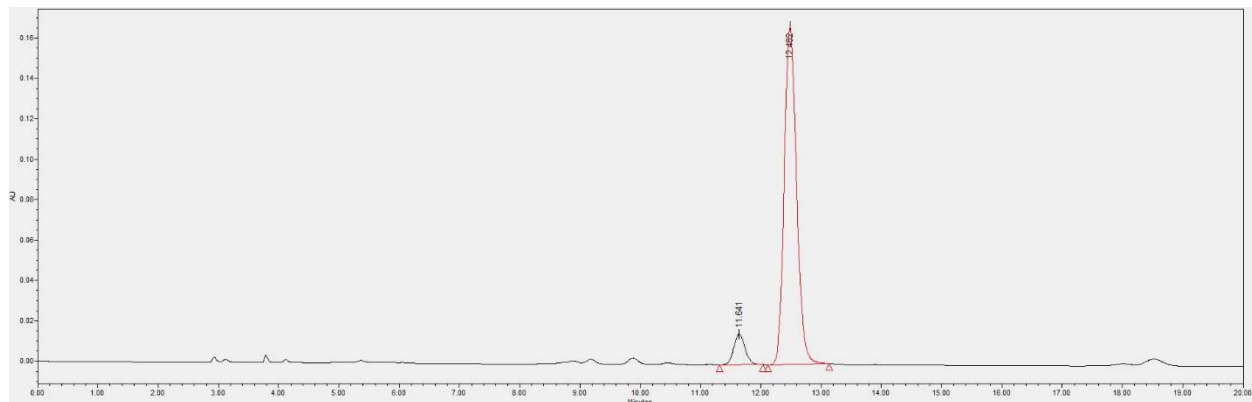
Method: AD3 chiral column, 1% IPA/hexanes 1 mL/min, $\lambda = 254$ nm

Racemic:

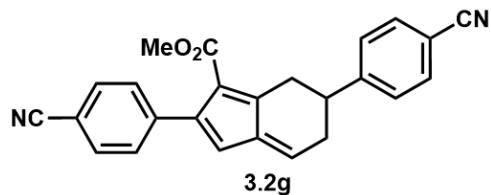


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
11.653	23846934	49.70
12.491	24132775	50.30

Enantioenriched:

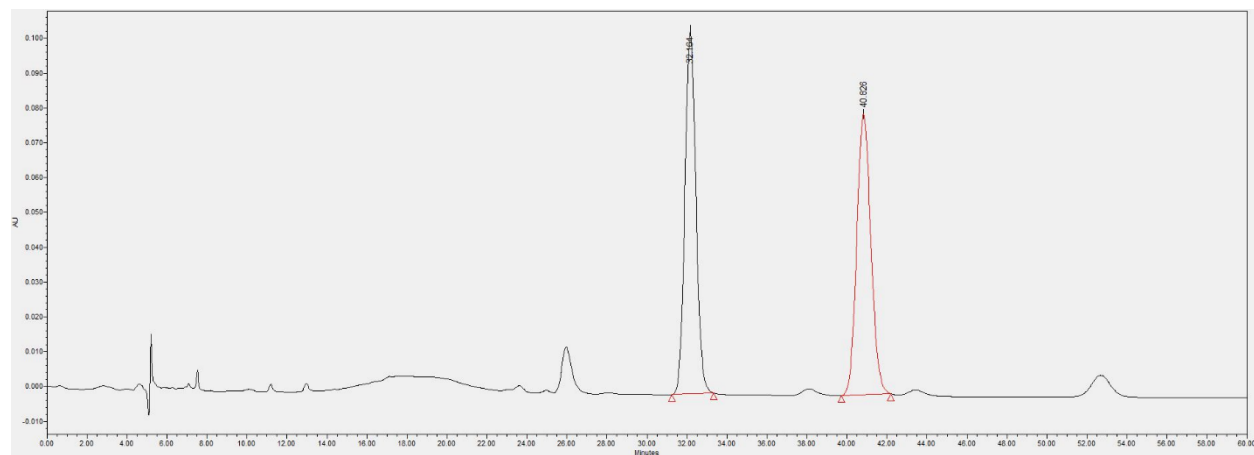


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
11.641	197838	7.69
12.482	2374692	92.31



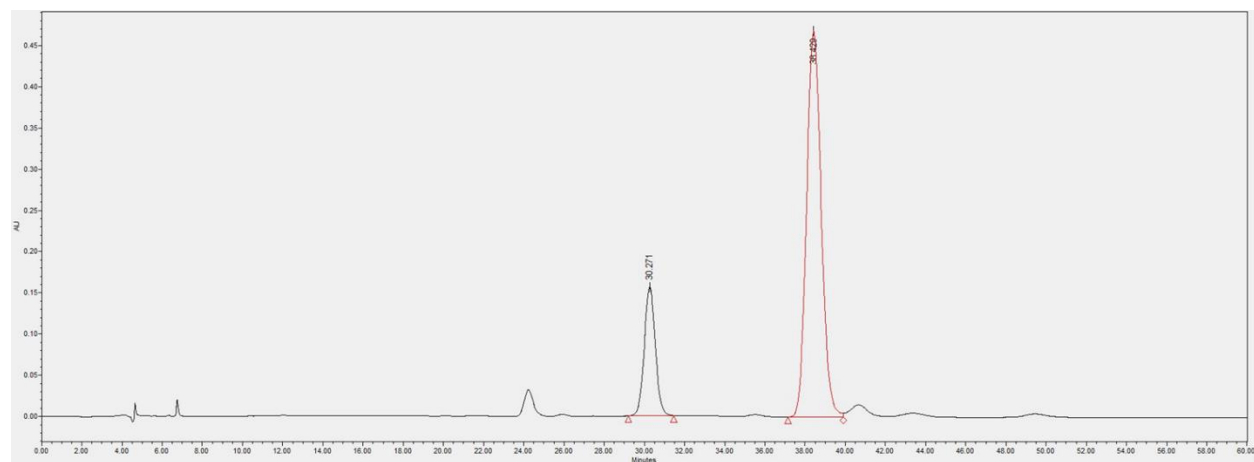
Method: AD3 chiral column, 30% IPA/hexanes 1 mL/min, λ = 254 nm

Racemic:

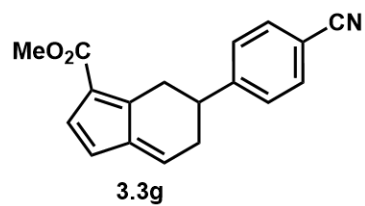


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
32.164	3981262	50.15
40.826	3957668	49.85

Enantioenriched:

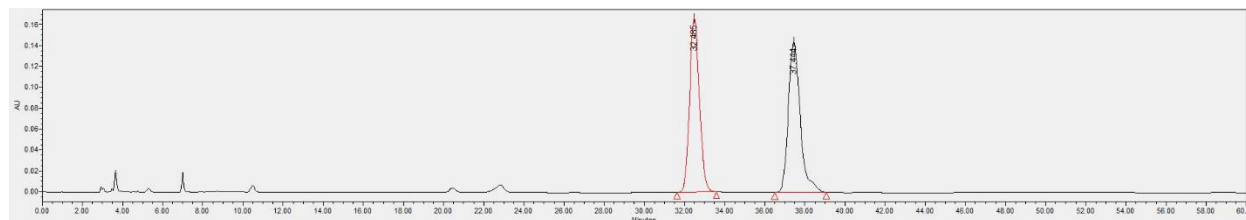


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
30.271	5978424	20.14
38.429	23710119	79.86



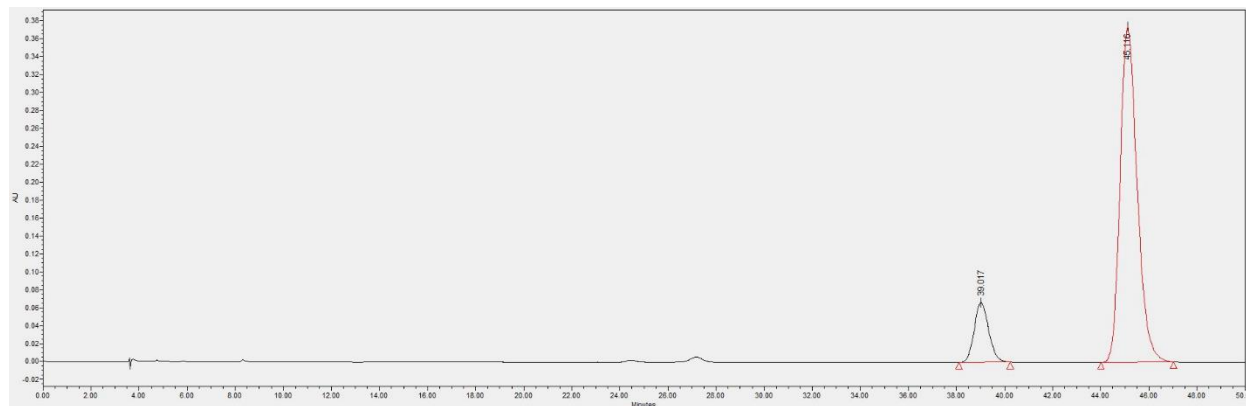
Method: AD3 chiral column, 3% IPA/hexanes 1 mL/min, $\lambda = 254$ nm

Racemic:

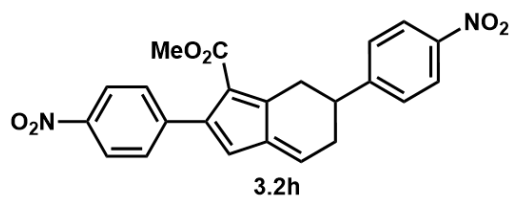


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
32.485	5649874	48.67
37.444	5957878	51.33

Enantioenriched:

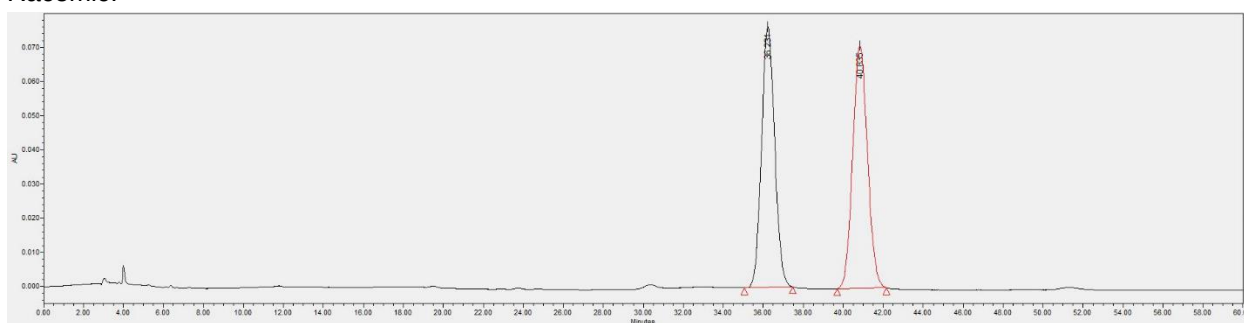


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
39.017	2782198	13.14
45.116	18385501	86.86



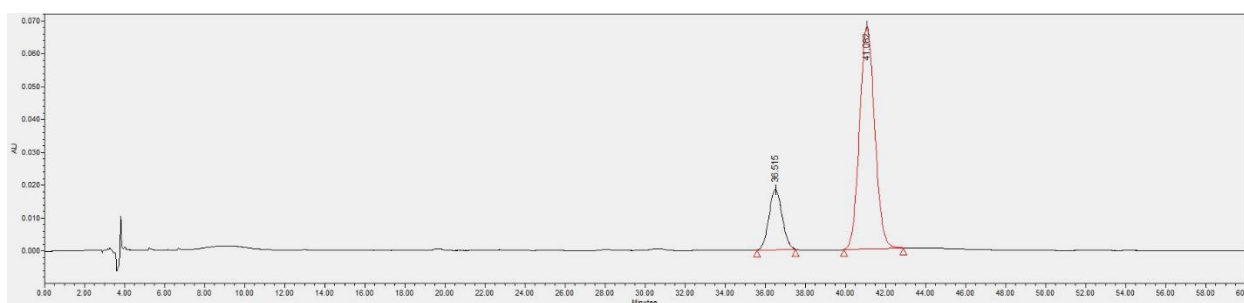
Method: AD3 chiral column, 20% IPA/hexanes 1 mL/min, λ = 300 nm

Racemic:

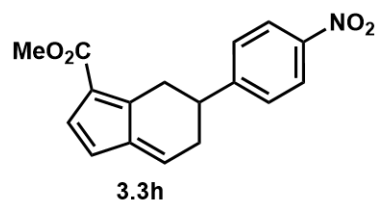


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
36.231	3497024	48.93
40.835	3650375	51.07

Enantioenriched:

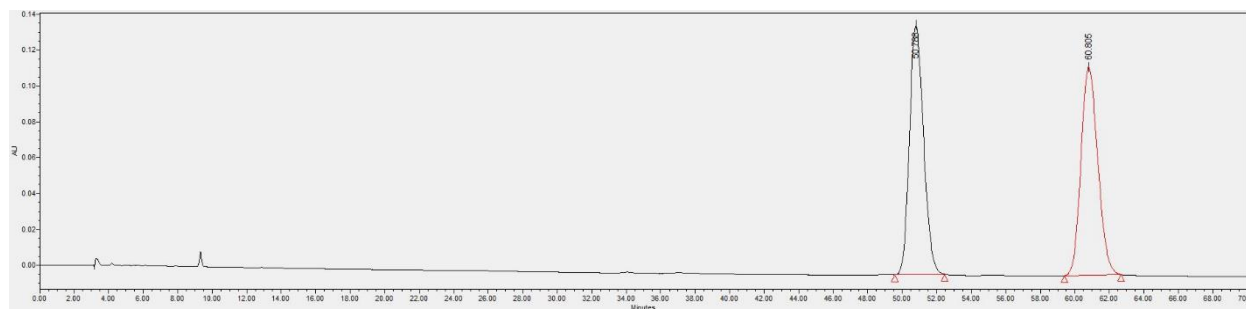


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
36.515	833811	19.03
41.082	3548646	80.97



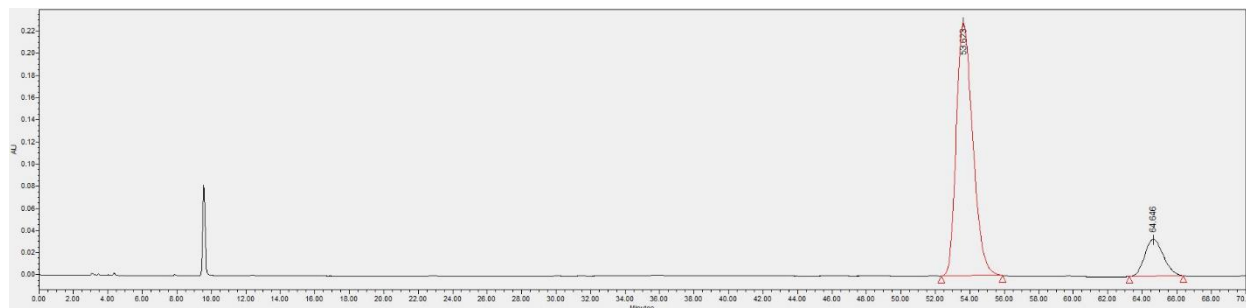
Method: IC3 chiral column, 10% IPA/hexanes 1 mL/min, λ = 300 nm

Racemic:

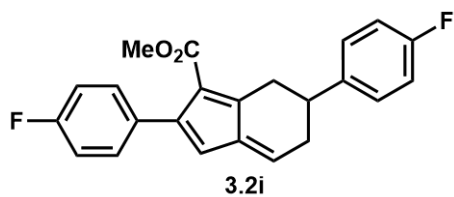


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
50.788	7884483	50.05
60.805	7867752	49.95

Enantioenriched:

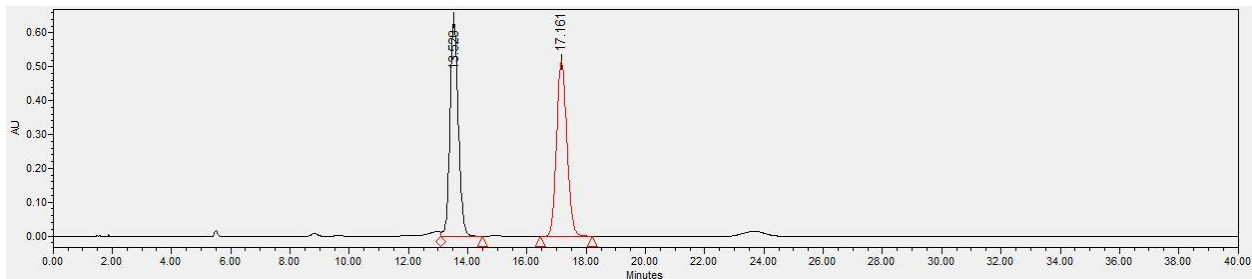


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
53.623	15204151	85.79
64.646	2517547	14.21



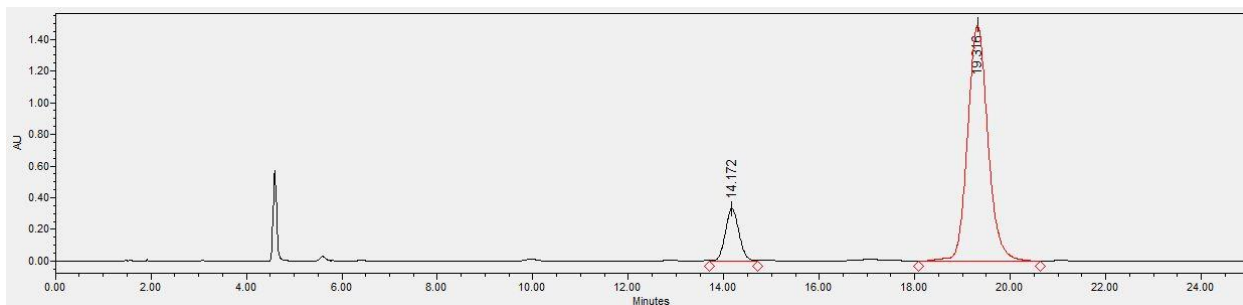
Method: AD3 chiral column, 1% IPA/hexanes 2 mL/min, $\lambda = 254$ nm

Racemic:

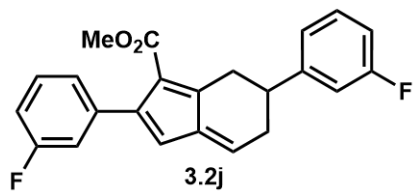


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
13.528	12514684	49.92
17.161	12553489	50.08

Enantioenriched:

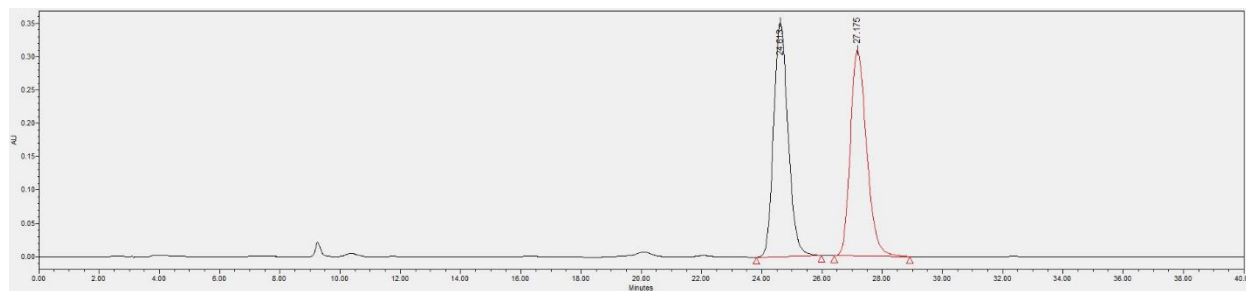


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
14.172	6559553	13.01
19.316	43870177	86.99



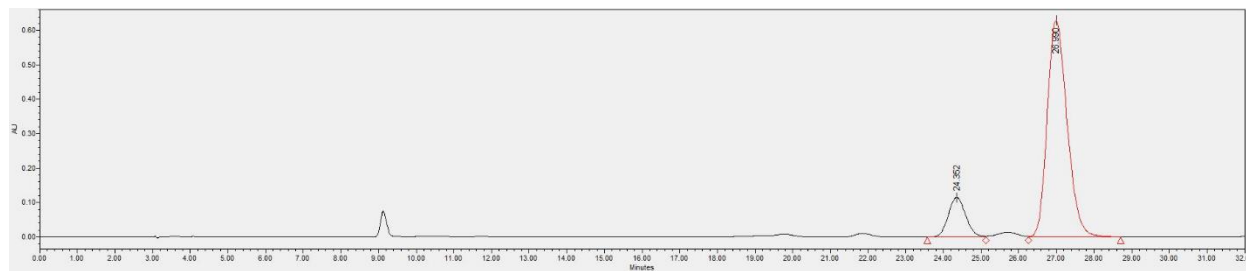
Method: AD3 chiral column, 1% IPA/hexanes 1 mL/min, $\lambda = 254$ nm

Racemic:

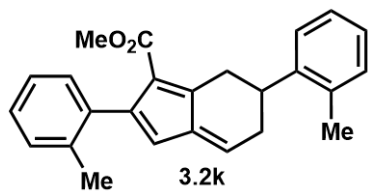


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
24.613	11663305	50.16
27.175	11587976	49.84

Enantioenriched:

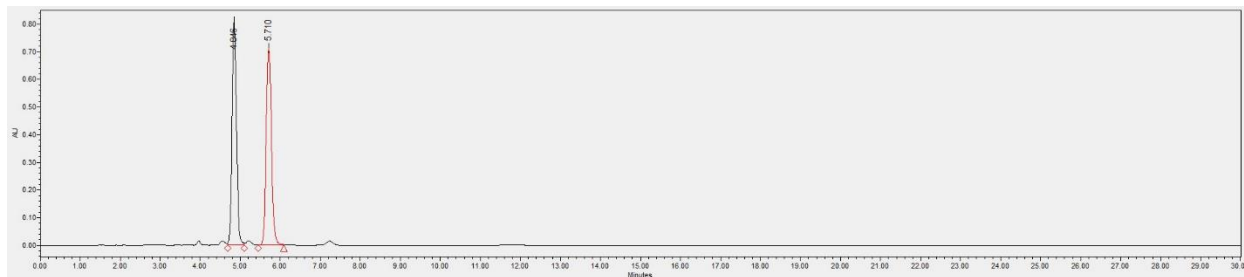


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
24.352	3728105	13.91
26.990	23065599	86.09



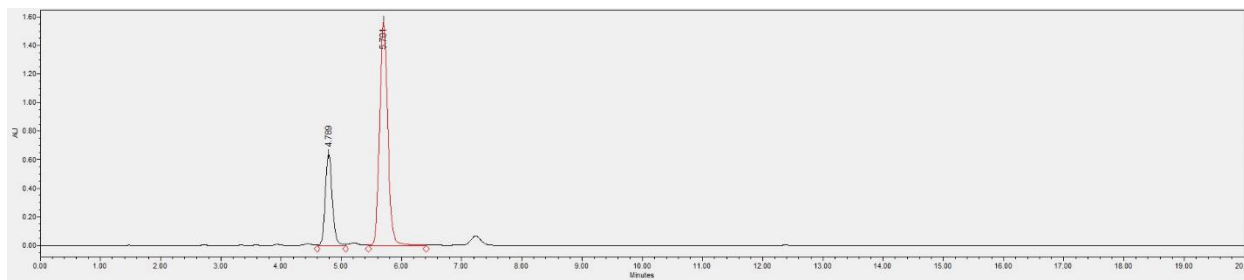
Method: AD3 chiral column, 1% IPA/hexanes 2 mL/min, $\lambda = 254$ nm

Racemic:

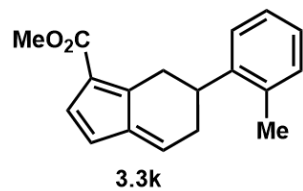


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
4.846	6268940	49.23
5.710	6466074	50.77

Enantioenriched:

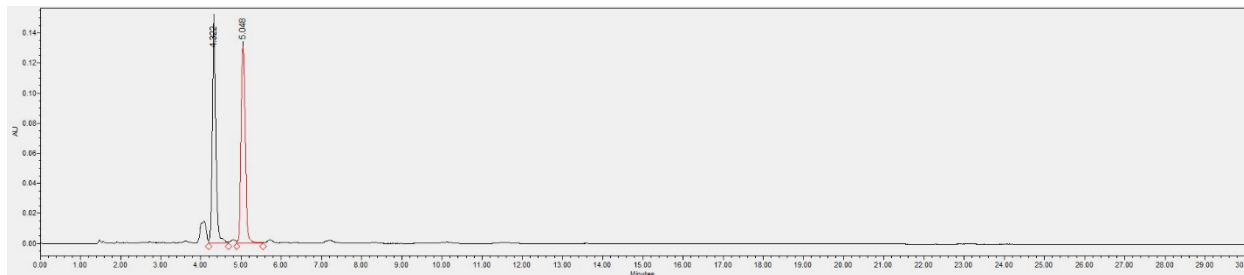


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
4.789	5091885	25.77
5.701	14666872	74.23



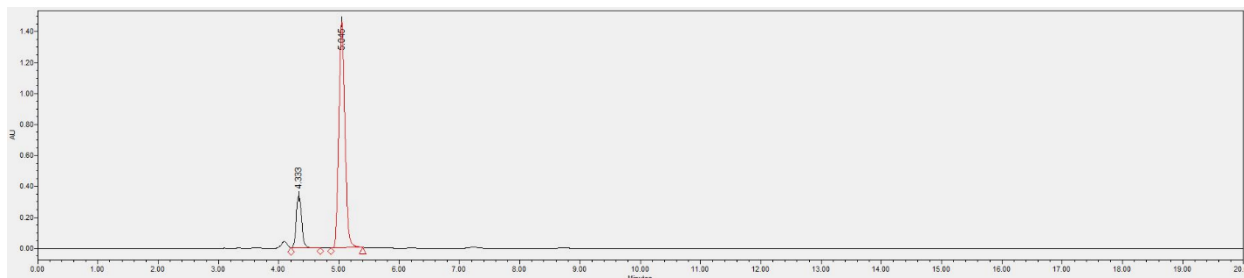
Method: AD3 chiral column, 1% IPA/hexanes 2 mL/min, λ = 254 nm

Racemic:

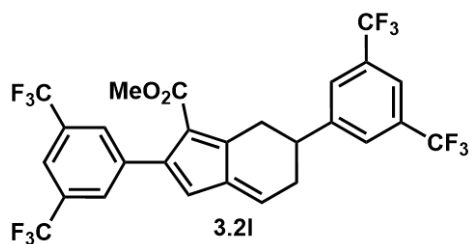


retention time (min)	area (μ V*sec)	% area
4.322	933441	50.29
5.048	922497	49.71

Enantioenriched:

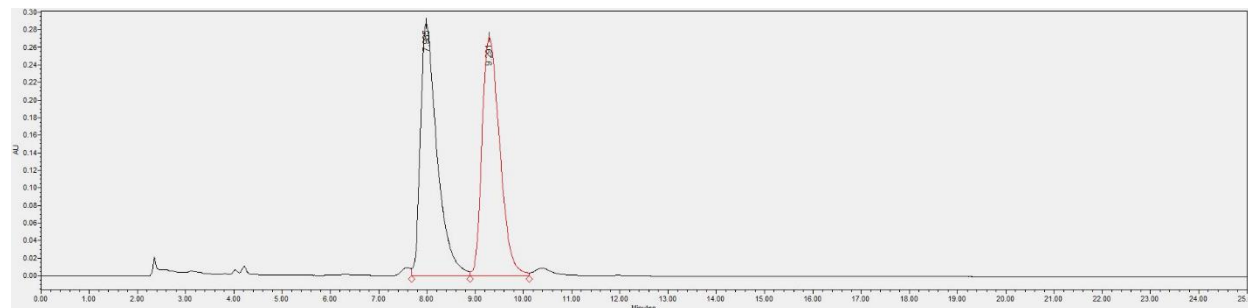


retention time (min)	area (μ V*sec)	% area
4.333	2074475	16.88
5.045	10217293	83.12



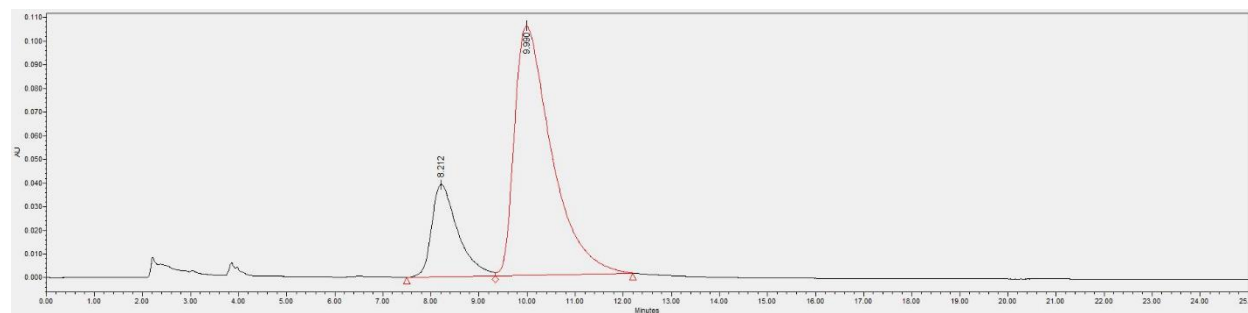
Method: AD3 chiral column, 0.1% IPA/hexanes 2 mL/min, $\lambda = 254$ nm

Racemic:

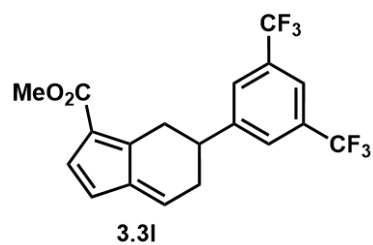


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
7.985	6870120	49.88
9.291	6903733	50.12

Enantioenriched:

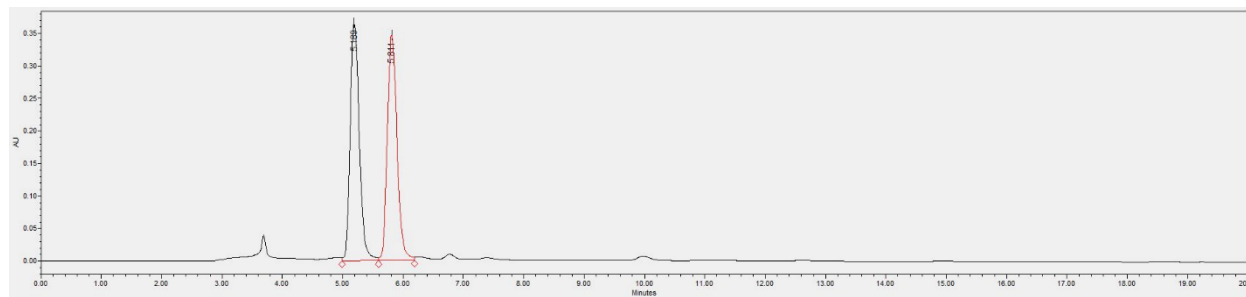


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
8.212	1471906	20.70
9.990	5638367	79.30



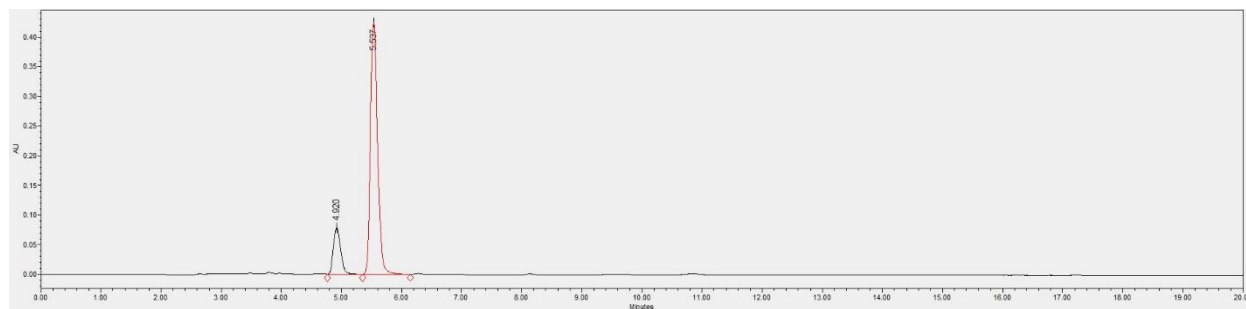
Method: AD3 chiral column, 1% IPA/hexanes 2 mL/min, λ = 254 nm

Racemic:

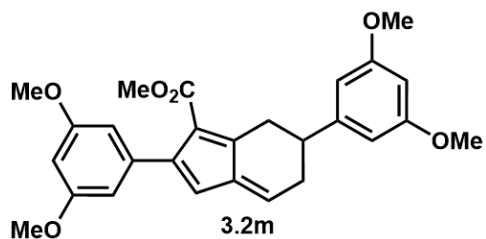


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
5.189	3860051	49.89
5.811	3877174	50.11

Enantioenriched:

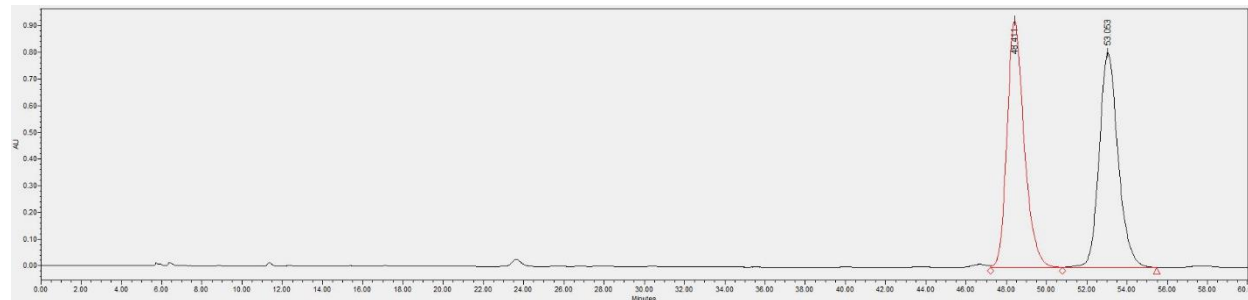


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
4.920	683361	16.23
5.537	3527634	83.77



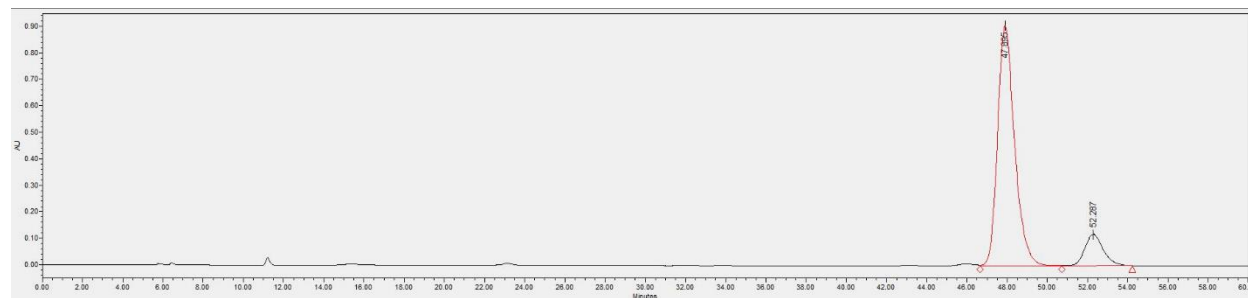
Method: AD3 chiral column, 10% IPA/hexanes 0.5 mL/min, $\lambda = 254$ nm

Racemic:

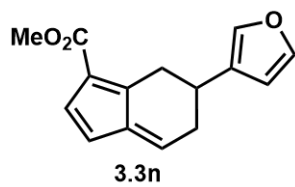


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
48.411	54608707	51.00
53.053	52468745	49.00

Enantioenriched:

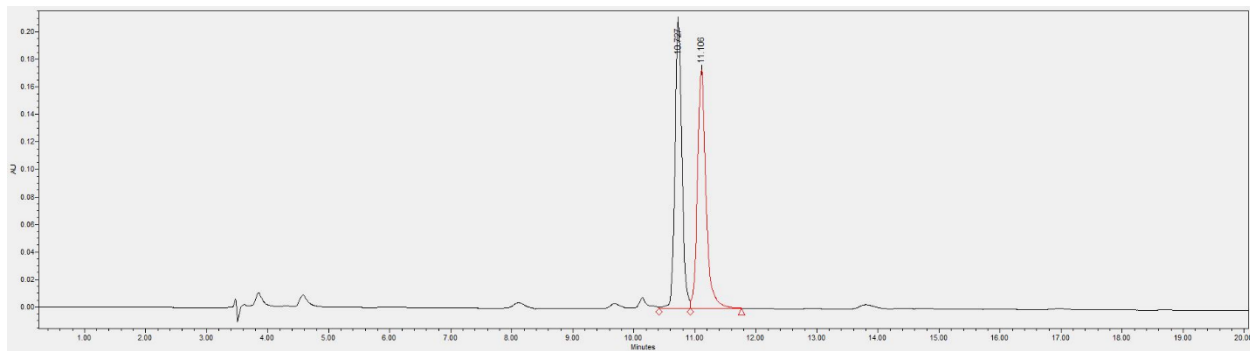


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
47.895	53172216	87.62
52.287	7509946	12.38



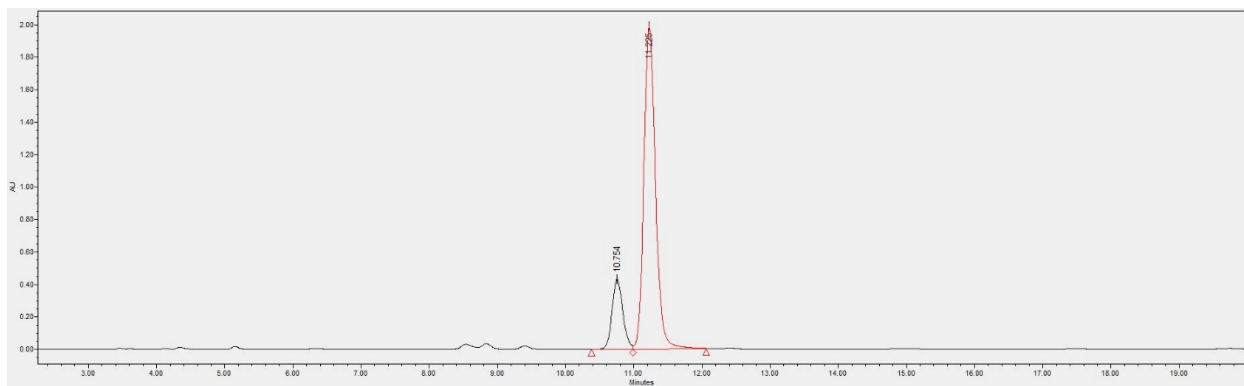
Method: AD3 chiral column, 3% IPA/hexanes 1 mL/min, $\lambda = 254$ nm

Racemic:

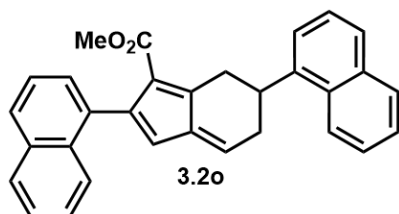


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
10.727	1650568	49.48
11.106	1684933	50.52

Enantioenriched:

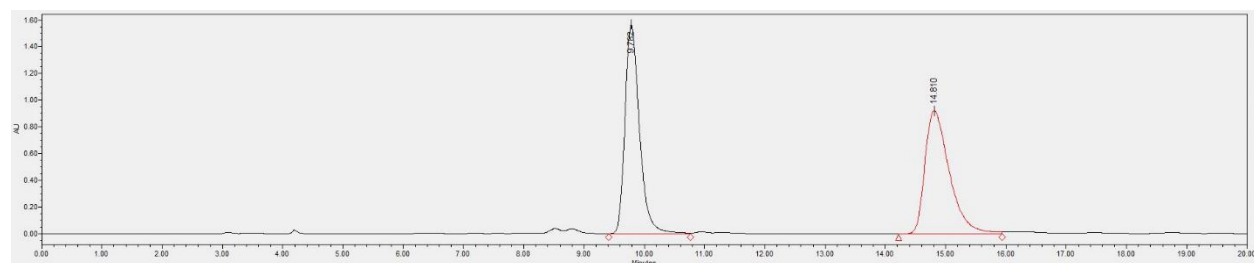


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
10.754	4760779	16.89
11.225	23426907	83.11



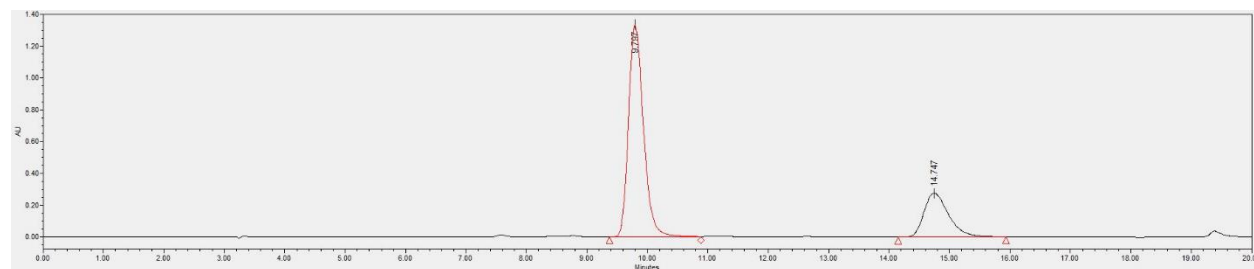
Method: IC3 chiral column, 5% IPA/hexanes 1 mL/min, λ = 254 nm

Racemic:

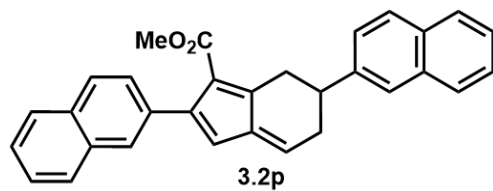


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
9.782	26232252	50.35
14.810	25867050	49.65

Enantioenriched:

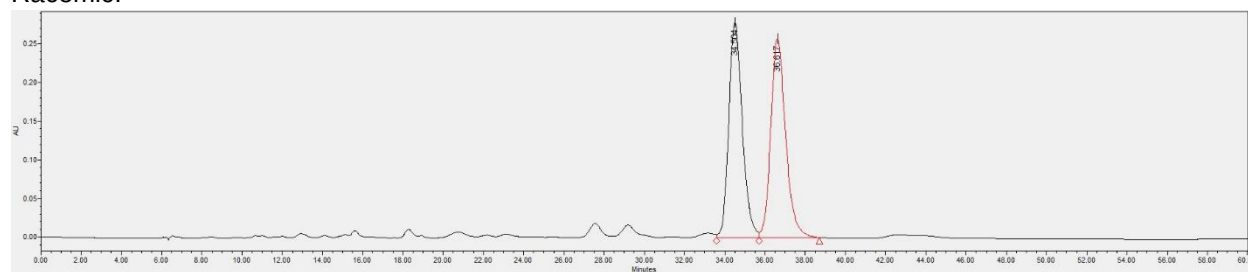


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
9.797	23099233	74.81
14.747	7779830	25.19



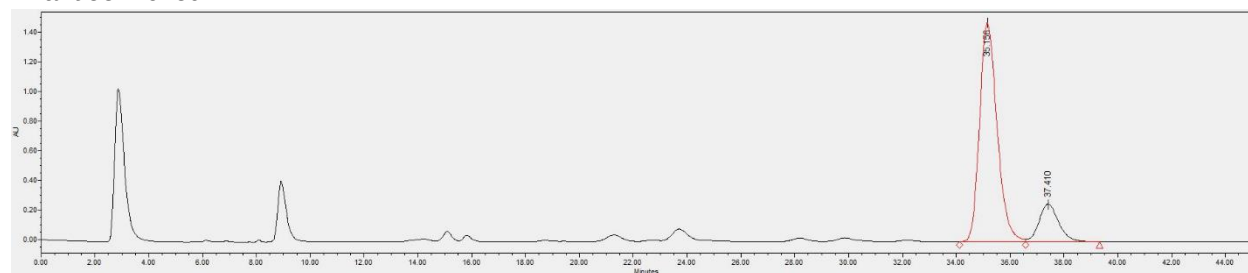
Method: IC3 chiral column, 10% IPA/hexanes 0.5 mL/min, $\lambda = 254$ nm

Racemic:

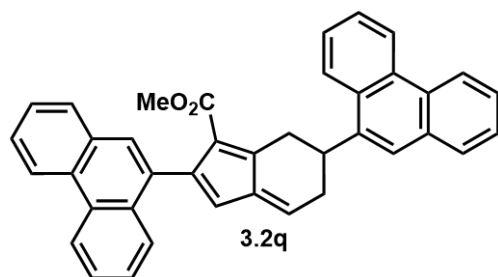


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
34.504	12983708	49.55
36.617	13218519	50.45

Enantioenriched:

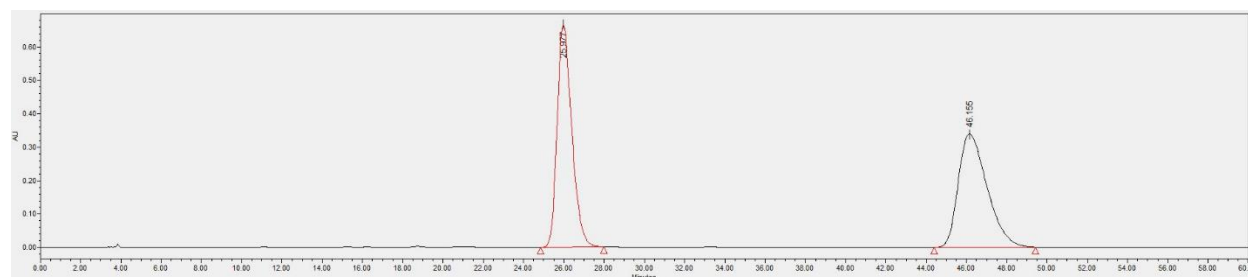


retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
35.156	66720938	83.90
37.410	12800823	16.10



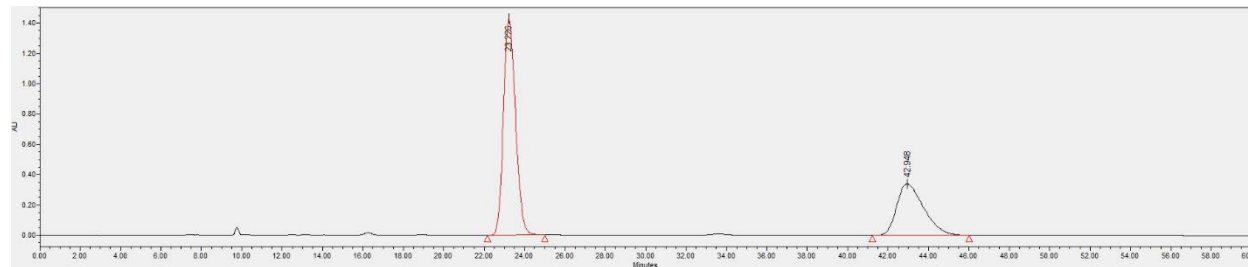
Method: AD3 chiral column, 10% IPA/hexanes 1 mL/min, λ = 254 nm

Racemic:



retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
25.977	33538266	49.96
46.155	33596746	50.04

Enantioenriched:



retention time (min)	area ($\mu\text{V}\cdot\text{sec}$)	% area
23.226	59220409	65.21
42.948	31598331	34.79

3.8.6 Crystallography Data

X-Ray Analysis of 3.1

A colorless block 0.37 x 0.24 x 0.12 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using omega scans. Crystal-to-detector distance was 40 mm and exposure time was 0.50 seconds per frame at low angles and 2.50 seconds at high angles, using a scan width of 0.5°. Data collection was 99% complete to 74.000° in θ . A total of 26165 reflections were collected covering the indices $-21 \leq h \leq 21$, $-9 \leq k \leq 10$, $-39 \leq l \leq 39$. 4271 reflections were founded to be symmetry independent, with an R_{int} of 0.0410. Indexing and unit cell refinement indicated a centered, monoclinic lattice. The space group was found to be C 2/c (No. 15). The data were integrated using the CrysAlis^{Pro} 1.171.40.84a software program and scaled using the SCALE3 ABSPACK scaling algorithm. Solution by intrinsic phasing (SHELXT-2015) produced a heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

[Note: The instruments are supported by an NIH Shared Instrument Grant S10-RR027172.]

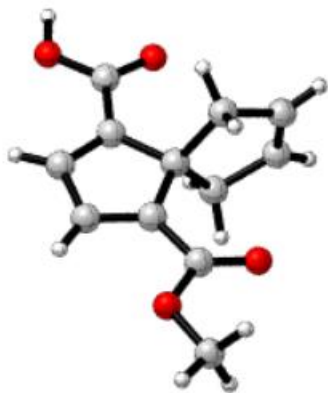


Figure S3.2. CYLview representation of 3.1.

This crystal structure has been deposited at the Cambridge Crystallographic Data Center under CCDC 2245692.

Table S3.10. Crystal data and structure refinement for KGoyal001_Sarpong.

Identification code	KGoyal001_Sarpong
Empirical formula	C ₁₂ H ₁₂ O ₄

Formula weight	220.22	
Temperature	100(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	C 2/c	
Unit cell dimensions	a = 17.1400(2) Å	a = 90°.
	b = 8.09620(10) Å	b = 105.1660(10)°.
	c = 31.5007(4) Å	g = 90°.
Volume	4219.07(9) Å ³	
Z	16	
Density (calculated)	1.387 Mg/m ³	
Absorption coefficient	0.873 mm ⁻¹	
F(000)	1856	
Crystal size	0.370 x 0.240 x 0.120 mm ³	
Theta range for data collection	5.348 to 74.480°.	
Index ranges	-21<=h<=21, -9<=k<=10, -39<=l<=39	
Reflections collected	26165	
Independent reflections	4271 [R(int) = 0.0410]	
Completeness to theta = 74.000°	99.1 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.89090	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	4271 / 0 / 299	
Goodness-of-fit on F ²	1.083	
Final R indices [I>2sigma(I)]	R1 = 0.0423, wR2 = 0.1139	

R indices (all data)	$R_1 = 0.0451$, $wR_2 = 0.1168$
Extinction coefficient	n/a
Largest diff. peak and hole	0.277 and -0.240 e.Å ⁻³

X-Ray Analysis of 3.2a

An orange block 0.33 x 0.19 x 0.12 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using omega scans. Crystal-to-detector distance was 33.00 mm and exposure time was 0.50 seconds per frame using a scan width of 0.5°. Data collection was 100% complete to 74.000° in θ . A total of 31264 reflections were collected covering the indices $-16 \leq h \leq 16$, $-10 \leq k \leq 10$, $-20 \leq l \leq 20$. 6878 reflections were found to be symmetry independent, with an R_{int} of 0.0434. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21 (No. 4). The data were integrated using the CrysAlis^{Pro} 1.172.42.72a software program and scaled using the SCALE3 ABSPACK scaling algorithm. Solution by intrinsic phasing (SHELXT-2015) produced a heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Although a solution was found in P21/n, the presence of an ordered molecule alongside a disordered molecule in the P21 solution likely indicates that P21 is the correct space group, as we would expect both molecules to have the same disorder in the P21 solution if it was meant to be P21/n. However, the Flack parameter is ill-determined due to a lack of noticeable difference in the Friedel pairs, and thus the presence of a single enantiomer cannot be definitively stated.

[Note: The instruments are supported by an NIH Shared Instrument Grant S10-RR027172.]

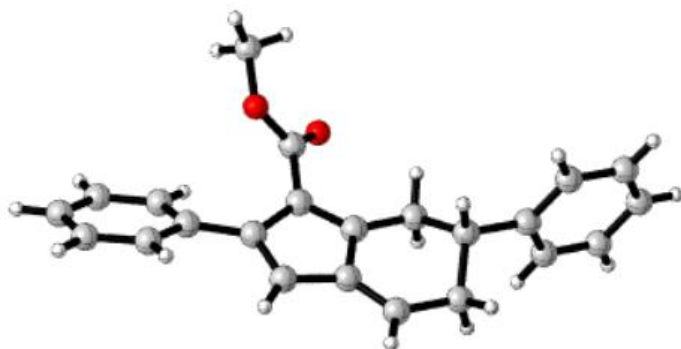


Figure S3.3. CYLview representation of 3.2a.

This crystal structure has been deposited at the Cambridge Crystallographic Data Center under CCDC 2245684.

Table S3.11. Crystal data and structure refinement for KGoyal06_Sarpong.

Identification code	KGoyal06_Sarpong
Empirical formula	C23 H20 O2

Formula weight	328.39	
Temperature	100(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 12.9522(3) Å	a = 90°.
	b = 8.0449(2) Å	b = 98.837(2)°.
	c = 16.5583(4) Å	g = 90°.
Volume	1704.88(7) Å ³	
Z	4	
Density (calculated)	1.279 Mg/m ³	
Absorption coefficient	0.631 mm ⁻¹	
F(000)	696	
Crystal size	0.330 x 0.190 x 0.120 mm ³	
Theta range for data collection	3.453 to 74.502°.	
Index ranges	-16<=h<=16, -10<=k<=10, -20<=l<=20	
Reflections collected	31264	
Independent reflections	6878 [R(int) = 0.0434]	
Completeness to theta = 74.000°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.89267	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	6878 / 79 / 527	
Goodness-of-fit on F ²	1.049	
Final R indices [I>2sigma(I)]	R1 = 0.0513, wR2 = 0.1356	

R indices (all data)	$R_1 = 0.0533$, $wR_2 = 0.1372$
Absolute structure parameter	-0.12(17)
Extinction coefficient	0.0036(6)
Largest diff. peak and hole	0.287 and -0.258 e.Å ⁻³

X-Ray Analysis of 3.4

A colorless block 0.20 x 0.11 x 0.08 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using omega scans. Crystal-to-detector distance was 33.00 mm and exposure time was 0.50 seconds per frame at low and high angles, using a scan width of 0.5°. Data collection was 98% complete to 74.000° in θ . A total of 33501 reflections were collected covering the indices $-12 \leq h \leq 12$, $-13 \leq k \leq 17$, $-25 \leq l \leq 26$. 6110 reflections were founded to be symmetry independent, with an R_{int} of 0.0295. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21/n (No. 14). The data were integrated using the CrysAlis^{Pro} 1.171.41.112a software program and scaled using the SCALE3 ABSPACK scaling algorithm. Solution by intrinsic phasing (SHELXT-2015) produced a heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

[Note: The instruments are supported by an NIH Shared Instrument Grant S10-RR027172.]

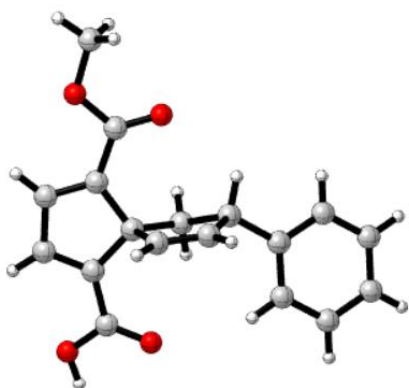


Figure S3.4. CYLview representation of **3.4**.

This crystal structure has been deposited at the Cambridge Crystallographic Data Center under CCDC 2245677.

Table S3.12. Crystal data and structure refinement for KGoyal03_Sarpong.

Identification code	KGoyal03_Sarpong
Empirical formula	C ₁₈ H ₁₆ O ₄
Formula weight	296.31
Temperature	100(2) K
Wavelength	1.54184 Å

Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 10.18740(10) Å	a = 90°.
	b = 13.9611(2) Å	b = 93.5000(10)°.
	c = 21.4180(3) Å	g = 90°.
Volume	3040.54(7) Å ³	
Z	8	
Density (calculated)	1.295 Mg/m ³	
Absorption coefficient	0.748 mm ⁻¹	
F(000)	1248	
Crystal size	0.200 x 0.110 x 0.080 mm ³	
Theta range for data collection	3.781 to 74.502°.	
Index ranges	-12<=h<=12, -13<=k<=17, -25<=l<=26	
Reflections collected	33501	
Independent reflections	6110 [R(int) = 0.0295]	
Completeness to theta = 74.000°	98.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.85005	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	6110 / 0 / 407	
Goodness-of-fit on F ²	1.031	
Final R indices [I>2sigma(I)]	R1 = 0.0351, wR2 = 0.0884	
R indices (all data)	R1 = 0.0405, wR2 = 0.0936	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.240 and -0.222 e.Å ⁻³	

3.8.7. Computational Results

3.8.7.1 Methods

All DFT calculations were performed with the Gaussian 16 package.³⁸ Geometry optimizations were performed in the gas phase using the B3LYP functional, 6-31G(d) basis set³⁹ for all nonmetal atoms and the LANL2DZ^{40,41} basis set with effective core potential (ECP) for Pd. Frequency analyses were carried out at the same level of theory as that used for geometry optimizations to characterize the stationary points as either minima (no imaginary frequencies) or saddle points (one imaginary frequency) on the potential energy surface, and to obtain thermal corrections for Gibbs free energies and enthalpies. All transition states were confirmed to connect reactants and products by intrinsic reaction coordinate (IRC) calculations. Single point energies were calculated with the PBE1PBE^{42,43} functional, the 6-311++G(d,p) basis set for all nonmetal atoms and the SDD^{43,44} for Pd. All calculations used Grimme's dispersion correction, GD3BJ,⁴⁵ and intrinsic dichloroethane solvent via the SMD^{46,47} solvation model (solvent = dichloroethane). Conformational searches were carried out using the CREST conformer-rotamer ensemble sampling tool, version 2.7.1^{48,49} with XTB version 6.2 RC2 (SAW190805)^{50–52}. Molecular structures were visualized using PyMOL.⁵³

3.8.7.2 Optimized TS Structures

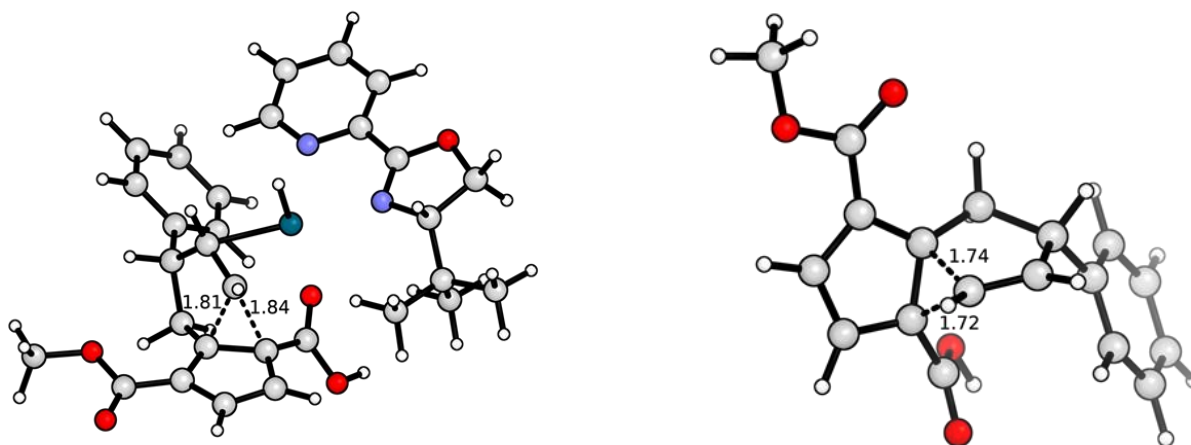


Figure S5. Optimized structure for **TS3.1** (left) and **TS3.2** (right) are shown above.

3.8.7.3 Coordinates and Energies

Table S3.13. Calculated thermochemical data is shown below (in units of a.u.).

Structure	E_SPC	E	ZPE	H_SPC	qh-H_SPC	T.S	T.qh-S	G(T)_SPC	qh-G(T)_SPC
Acetate anion	-228.432394	-228.592382	0.048679	-228.3784	-228.37883	0.03251	0.032046	-228.41091	-228.410876
TFA anion	-525.99598	-526.322888	0.026019	-525.962994	-525.963503	0.038203	0.037386	-526.001197	-526.000889
H ₂	-1.167744	-1.174961	0.010116	-1.154323	-1.154323	0.014793	0.014793	-1.169116	-1.169116
CO ₂	-188.442296	-188.58139	0.01153	-188.427168	-188.427169	0.024319	0.024319	-188.451487	-188.451489
Int1	-1775.124914	-1775.518231	0.585589	-1774.50317	-1774.509205	0.102981	0.096727	-1774.606151	-1774.605932
Int2	-1775.102047	-1775.487989	0.580655	-1774.484353	-1774.491208	0.106298	0.098708	-1774.590651	-1774.589916
TS1	-1775.04595	-1775.427529	0.578519	-1774.4309	-1774.437214	0.103667	0.09732	-1774.534566	-1774.534534
9	-1775.093381	-1775.477135	0.580139	-1774.476263	-1774.483065	0.10658	0.098753	-1774.582843	-1774.581818
4	-995.624092	-995.368171	0.304582	-995.299329	-995.302776	0.069376	0.065851	-995.368705	-995.368627
TS2	-995.576104	-995.319086	0.302491	-995.253922	-995.257129	0.067901	0.064613	-995.321823	-995.321742
5	-995.622326	-995.364755	0.304722	-995.297494	-995.300928	0.070498	0.066057	-995.367993	-995.366985
Int5	-2111.482933	-2112.079202	0.573915	-2110.868036	-2110.876114	0.116126	0.106845	-2110.984162	-2110.98296
TS3	-2111.445356	-2112.033814	0.572035	-2110.83285	-2110.84049	0.114492	0.105675	-2110.947342	-2110.946166
Int6	-2111.497317	-2112.095019	0.574469	-2110.882149	-2110.889869	0.114527	0.105901	-2110.996676	-2110.995771
Int3	-2301.118371	-2301.845578	0.608258	-2300.465457	-2300.474614	0.124405	0.113967	-2300.589862	-2300.588581
Int4	-2299.92657	-2300.660108	0.58882	-2299.293969	-2299.302659	0.124002	0.113112	-2299.417971	-2299.415771
Int7	-2111.506653	-2112.105067	0.574919	-2110.891353	-2110.898897	0.113096	0.104989	-2111.00445	-2111.003886
Int8	-2111.495801	-2112.095385	0.574486	-2110.880436	-2110.88857	0.116377	0.106647	-2110.996813	-2110.995217
TS4	-1775.058231	-1775.45177	0.58128	-1774.44055	-1774.446735	0.104458	0.097474	-1774.545008	-1774.544209
6	-1775.104094	-1775.495859	0.583762	-1774.483532	-1774.489912	0.104126	0.09752	-1774.587658	-1774.587432
Int5-Oac	-1813.930732	-1814.364017	0.597087	-1813.294739	-1813.302008	0.109834	0.102287	-1813.404574	-1813.404296
TS3-Oac	-1813.893178	-1814.31909	0.594923	-1813.259663	-1813.266898	0.108727	0.101427	-1813.368389	-1813.368326
Int6-Oac	-1813.946733	-1814.380312	0.597003	-1813.310784	-1813.31812	0.109669	0.102156	-1813.420453	-1813.420276
IntS1	-2111.477422	-2112.070395	0.574396	-2110.862044	-2110.870112	0.117751	0.107531	-2110.979795	-2110.977643

Table S3.14. The cartesian coordinates of optimized geometries (in units of Å) are given below in the standard XYZ format.

Electronic energy values (in units of Hartrees) for singlepoint calculations are also provided. For cationic structures, the energy of a trifluoroacetate (TFA) anion (or acetate anion for **Int1-OAc**) was calculated separately (not shown).

Counteranions and By-products

C -1.049417 0.005478 -0.025839

Acetate (AcO) (E = -228.432394)

O -1.571297 1.138377 -0.010421

C 0.205511 0.000173 -0.013226

O -1.539867 -1.142872 -0.011076

O 0.745335 1.138710 0.002891

C 0.517245 0.007504 -0.008573

O 0.767022 -1.127550 0.002976

F 1.057953 -0.951444 -0.805950

C -1.350921 -0.010561 -0.003704

F 0.990787 -0.235064 1.248908

H -1.712251 0.068827 1.032160

F 1.071521 1.181850 -0.400907

H -1.761103 0.844657 -0.554617

Dihydrogen (H₂) (E = -1.167744)

H -1.753048 -0.940444 -0.422901

H 0.000000 0.000000 0.371619

Trifluoroacetate (TFA) (E = -525.995980)

H 0.000000 0.000000 -0.371619

Carbon dioxide (CO₂) (E= -188.442296)

C 0.000000 0.000000 0.000000

O 0.000000 0.000000 1.168936

O 0.000000 0.000000 -1.168936

For Figure 3.3A: Int3.1, Int3.2, TS3.1, and 3.9

Structure Int3.1 (E= -1775.124914)

Pd -0.522196 -0.135053 -0.817799

N -1.708499 1.609685 -1.127293

C -3.047608 1.369932 -1.148325

C -3.985250 2.376482 -1.344659

C -3.539677 3.687773 -1.515293

C -2.172782 3.934150 -1.487187

C -1.291355 2.868642 -1.297334

H -0.225564 3.039813 -1.272282

H -1.773510 4.934588 -1.609521

H -4.250062 4.493945 -1.664133

H -5.039801 2.128658 -1.354947

C -3.448762 -0.020141 -0.906945

N -2.607874 -0.951177 -0.633399

C -3.378646 -2.162545 -0.275130

C -3.270798 -2.493576 1.242755

C -3.781445 -1.324028 2.099637

H -4.833095 -1.090558 1.898106

H -3.700287 -1.578240 3.162478

H -3.190133 -0.418235 1.928401

C -4.103203 -3.757644 1.518232

H -5.170588 -3.606841 1.323039

H -4.000086 -4.050010 2.569287

H -3.760812 -4.597031 0.900434

C -1.807494 -2.782294 1.608729

H -1.406602 -3.613629 1.018044

H -1.172416 -1.909897 1.438996

H -1.735735 -3.057378 2.667391

H -2.988894 -3.012196 -0.842023

C -4.802668 -1.786955 -0.755378

H -5.049878 -2.220281 -1.727289

H -5.599270 -1.993471 -0.043436

O -4.749637 -0.331467 -0.931753

C 1.261993 0.855662 -0.919888

C 2.421037 0.008847 -1.432924

H 3.200117 0.682892 -1.806352

H 2.156722 -0.665324 -2.251824

C 2.975363 -0.766165 -0.184467

C 4.485655 -0.803612 -0.097383

C 4.933403 -2.087584 -0.071118

C 3.798652 -2.982523 -0.162268

C 2.657721 -2.241271 -0.237031

C 1.328077 -2.765636 -0.448464

O	0.309675	-2.096675	-0.681962
O	1.232962	-4.098114	-0.405029
H	0.298100	-4.337133	-0.577898
H	3.861765	-4.063552	-0.190140
H	5.966170	-2.403253	0.002989
C	5.315198	0.409409	-0.022533
O	4.873171	1.549035	-0.029478
O	6.627768	0.126687	0.047574
C	7.509185	1.263731	0.115433
H	8.515504	0.847747	0.165673
H	7.297362	1.859447	1.007162
H	7.397774	1.887408	-0.775433
C	2.317266	-0.043986	1.054598
H	3.046247	0.147282	1.844544
H	1.541503	-0.688480	1.472569
C	1.707828	1.255971	0.498228
C	0.650505	1.931229	1.346648
C	0.595681	3.330591	1.379476
C	-0.431543	3.998994	2.049904
C	-1.421300	3.272193	2.714489
C	-1.363766	1.876141	2.713953
C	-0.337072	1.214218	2.038425
H	-0.316508	0.129338	2.045581
H	-2.119843	1.298174	3.238398

H	-2.222816	3.787260	3.236537
H	-0.457073	5.085382	2.052125
H	1.360543	3.901348	0.857947
H	2.534513	1.965392	0.366490
H	1.075578	1.707956	-1.577200

Structure **Int3.2** (E= -1775.102047)

Pd	-0.420181	0.264897	-0.549415
H	-0.596996	0.536072	-2.029507
N	-2.233126	1.524944	-0.221237
C	-2.122434	2.817886	0.102729
C	-3.235799	3.610308	0.385965
C	-4.502661	3.036732	0.324575
C	-4.619639	1.687634	-0.013184
C	-3.458613	0.964446	-0.276043
C	-3.488990	-0.466204	-0.623380
N	-2.444156	-1.188849	-0.767508
C	-2.887353	-2.552290	-1.125303
H	-2.541329	-2.759483	-2.144801
C	-2.275187	-3.631449	-0.196295
C	-0.751739	-3.630725	-0.396521
H	-0.325650	-2.650107	-0.175229
H	-0.276168	-4.368417	0.259700
H	-0.492819	-3.881459	-1.432896
C	-2.609406	-3.334936	1.273549

H	-2.293610	-2.323838	1.547069	H	1.665249	2.977831	2.204819
H	-2.097421	-4.046551	1.930635	H	0.559864	5.146607	2.524654
H	-3.684171	-3.416815	1.472716	H	-0.110798	6.522851	0.560870
C	-2.834741	-5.004936	-0.599975	H	0.359300	5.683143	-1.738870
H	-3.919041	-5.065897	-0.451157	H	1.467450	3.506530	-2.061206
H	-2.373911	-5.793294	0.006399	H	3.298938	1.920705	-0.648895
H	-2.622806	-5.223773	-1.653767	C	2.497731	0.793732	1.010256
C	-4.437166	-2.442634	-1.096319	H	3.463991	0.929792	1.498998
H	-4.911835	-3.032417	-0.310552	H	1.720515	0.985423	1.749298
H	-4.906004	-2.665914	-2.055360	C	2.321418	-0.677746	0.487071
O	-4.696125	-1.034886	-0.795545	C	1.632478	-1.564811	1.502878
H	-5.584535	1.198766	-0.069299	C	2.414022	-2.630982	1.817293
H	-5.389601	3.624930	0.536605	C	3.643779	-2.554766	1.051151
H	-3.096707	4.654339	0.643569	C	3.624527	-1.435618	0.280802
H	-1.119607	3.221999	0.130744	C	4.686362	-0.990708	-0.635833
C	1.582717	-0.493388	-0.848280	O	4.636451	0.026821	-1.309331
C	1.602684	0.851339	-1.219841	O	5.729649	-1.838423	-0.649464
C	2.312461	1.725073	-0.208462	C	6.819549	-1.473229	-1.518047
C	1.636469	3.064009	0.045422	H	6.480732	-1.422773	-2.556132
C	1.265604	3.857786	-1.053068	H	7.236592	-0.507041	-1.222045
C	0.640959	5.091032	-0.872490	H	7.562463	-2.261826	-1.397764
C	0.376862	5.562898	0.417133	H	4.448630	-3.276908	1.102091
C	0.751753	4.790503	1.516243	H	2.171330	-3.415376	2.523719
C	1.377587	3.553096	1.331426	C	0.338291	-1.234871	2.072768

O -0.396835 -0.327208 1.658151

O -0.014532 -1.977514 3.123860

H -0.913097 -1.702425 3.403932

H 1.503573 1.176563 -2.248441

H 1.508762 -1.322598 -1.544281

Transition State TS3.1 (E= -1775.045950)

Pd -0.525560 0.004173 -0.624335

H -0.679099 0.092112 -2.128288

N -2.651287 -0.914388 -0.590618

C -3.581881 -0.031153 -0.537012

C -3.342271 1.418770 -0.483133

N -2.049370 1.783887 -0.579270

C -1.747562 3.083507 -0.613334

C -2.726253 4.077320 -0.525886

C -4.059821 3.700176 -0.401648

C -4.380916 2.341245 -0.386028

H -5.406392 2.001264 -0.305716

H -4.843544 4.446993 -0.326115

H -2.432540 5.120569 -0.553985

H -0.699839 3.333438 -0.716592

O -4.853919 -0.444395 -0.584421

C -4.805696 -1.905423 -0.596575

H -5.427450 -2.249507 -1.422648

H -5.227717 -2.245524 0.350705

C -3.301818 -2.237214 -0.766883

C -2.762388 -3.333179 0.182041

C -2.796544 -2.859252 1.643068

H -2.361232 -3.623924 2.296258

H -3.820822 -2.677968 1.988517

H -2.234542 -1.929343 1.769590

C -1.324825 -3.669713 -0.239378

H -0.876977 -4.384407 0.459189

H -1.306994 -4.117479 -1.240526

H -0.698199 -2.775525 -0.272515

C -3.628816 -4.594111 0.018080

H -4.658765 -4.435345 0.357224

H -3.209854 -5.414618 0.611775

H -3.659735 -4.919640 -1.028911

H -3.102217 -2.559939 -1.795797

C 1.460562 0.577057 -1.031419

C 1.535877 -0.823051 -0.837541

C 2.815700 -0.919074 0.443868

C 1.671972 -1.821714 0.704146

C 2.094664 -3.155858 0.395464

C 3.389179 -3.090310 -0.085214

C 3.853603 -1.751240 -0.060979

C 5.159739 -1.338366 -0.574742

O 6.051932 -2.110482 -0.888497

O	5.273377	0.006221	-0.682500
C	6.538898	0.487537	-1.169103
H	7.351460	0.168843	-0.510966
H	6.725328	0.119669	-2.181636
H	6.455105	1.574653	-1.169815
H	3.967733	-3.921152	-0.470692
H	1.467730	-4.032769	0.467826
C	0.597359	-1.487819	1.666966
O	-0.138898	-0.499428	1.600084
O	0.509967	-2.360814	2.659864
H	-0.238549	-2.097517	3.240090
C	2.870407	0.490085	0.980941
H	3.901054	0.763667	1.203410
H	2.307663	0.543621	1.914810
C	2.281390	1.447342	-0.087867
C	1.614856	2.700028	0.446315
C	1.860995	3.928408	-0.181985
C	1.255266	5.102885	0.271572
C	0.396985	5.066086	1.372349
C	0.144715	3.847096	2.006408
C	0.744425	2.674384	1.545666
H	0.518837	1.736568	2.039552
H	-0.527071	3.806098	2.859312
H	-0.071053	5.977617	1.732823

H	1.461748	6.044305	-0.229894
H	2.538650	3.963573	-1.031631
H	3.119886	1.772529	-0.715892
H	1.614578	-1.546189	-1.639598
H	1.426721	0.911385	-2.066440

Structure 3.9 (E= -1775.093381)

Pd	-0.752959	0.282405	-0.635997
H	-1.167419	0.832933	-1.986861
C	1.229393	0.681055	-1.521294
C	1.029257	-0.694971	-1.346419
C	1.726265	-1.444037	-0.195067
C	2.379805	-2.740101	-0.610772
C	3.705995	-2.651593	-0.408670
C	4.042153	-1.317680	0.126274
C	2.908591	-0.588118	0.276170
C	2.643249	0.836166	0.598805
H	3.538015	1.325965	0.981216
H	1.861766	0.891977	1.365117
C	2.153544	1.550386	-0.686338
C	1.574548	2.942133	-0.446915
C	1.114544	3.695613	-1.539496
C	0.573965	4.967660	-1.358800
C	0.492873	5.522250	-0.077645
C	0.962686	4.791634	1.013014

C	1.497265	3.511769	0.829752	C	-3.038689	3.703679	1.020898
H	1.854516	2.968363	1.696873	C	-4.315419	3.199595	1.250827
H	0.912959	5.210618	2.014111	C	-4.588331	1.871087	0.922214
H	0.074343	6.514423	0.064558	C	-3.568829	1.094973	0.376081
H	0.221758	5.528772	-2.219848	C	-3.777782	-0.314470	0.002516
H	1.185562	3.287936	-2.543965	N	-2.864468	-1.079928	-0.461602
H	3.043102	1.676927	-1.323890	C	-3.481742	-2.397401	-0.730009
C	5.409060	-0.827511	0.401459	H	-3.475514	-2.551390	-1.815652
O	5.693046	0.293113	0.791564	C	-2.693577	-3.569206	-0.090991
O	6.325011	-1.785047	0.166833	C	-2.500311	-3.344007	1.416487
C	7.695313	-1.411473	0.406333	H	-3.457596	-3.313128	1.950028
H	8.284546	-2.295350	0.161497	H	-1.912043	-4.162988	1.846229
H	7.837989	-1.135537	1.454442	H	-1.977809	-2.402894	1.611235
H	7.980132	-0.572597	-0.234029	C	-3.468505	-4.874718	-0.334521
H	4.441715	-3.421252	-0.604835	H	-2.890576	-5.729570	0.035242
H	1.818334	-3.590001	-0.977093	H	-3.653645	-5.031866	-1.404252
C	0.809749	-1.582440	1.014344	H	-4.434359	-4.881880	0.183462
O	-0.075372	-0.764263	1.274645	C	-1.326741	-3.665100	-0.787397
O	1.075454	-2.606971	1.806448	H	-0.709502	-4.441399	-0.321896
H	0.468912	-2.570588	2.578864	H	-1.443774	-3.913865	-1.849308
H	0.715852	-1.303099	-2.189582	H	-0.793025	-2.714685	-0.729691
H	1.000659	1.081746	-2.503245	C	-4.939197	-2.218230	-0.224342
N	-2.331927	1.588537	0.156269	H	-5.691444	-2.391494	-0.994344
C	-2.072088	2.864061	0.467291	H	-5.177839	-2.808573	0.661885

O	-5.017898	-0.810698	0.162688
H	-5.567779	1.437557	1.083322
H	-5.091508	3.826284	1.677884
H	-2.781330	4.730003	1.257297
H	-1.068306	3.212675	0.268264

For Figure 3.3B: 3.4, TS3.2, and 3.5

Structure 3.4 (E= -995.624092)

C	-0.535330	-0.540639	1.590138
C	0.508779	0.282310	1.540186
H	1.032426	0.716584	2.386857
C	0.973222	0.536941	0.114765
C	1.238733	1.998066	-0.155687
C	2.545080	2.192131	-0.464108
C	3.229999	0.918668	-0.445134
C	2.343688	-0.056837	-0.126144
C	2.636485	-1.492783	-0.044186
O	1.803037	-2.367626	0.090835
O	3.949908	-1.742343	-0.151490
C	4.311228	-3.122947	-0.117070
H	5.396173	-3.145720	-0.223638
H	4.015562	-3.576462	0.833067
H	3.838931	-3.667259	-0.939628
H	4.282100	0.777084	-0.663621
H	3.013561	3.144131	-0.686399

C	0.218650	3.041392	-0.044214
O	-0.941568	2.857464	0.273739
O	0.693387	4.264686	-0.337349
H	-0.052669	4.884588	-0.231445
C	-0.177647	-0.094238	-0.726251

H	0.203023	-0.636921	-1.594556
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H	-0.823334	0.710323	-1.085081
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C	-0.982827	-1.008207	0.231214
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C	-2.477140	-0.946686	0.018112
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C	-3.188038	-2.076648	-0.391074
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C	-4.567630	-2.022050	-0.584875
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C	-5.255735	-0.831166	-0.367535
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C	-4.555020	0.303668	0.041827
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C	-3.178055	0.246229	0.233209
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H	-2.629710	1.133267	0.542965
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H	-5.085152	1.237449	0.213321
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H	-6.331498	-0.785748	-0.516699
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H	-5.104215	-2.912017	-0.904439
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H	-2.653244	-3.009322	-0.559520
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H	-0.657808	-2.047342	0.099451
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H	-1.012905	-0.883312	2.504458
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Transition State TS3.2 (E= -995.576104)

C	-0.438520	-0.165531	1.883853
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H	-0.697343	-0.261388	2.934821
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C	-0.905802	-1.164668	0.869911	H	-6.023624	-0.711001	-0.833917
C	0.478522	0.730734	1.469095	C	-0.932209	1.910406	-0.474484
H	-0.836415	-2.154830	1.342259	O	-1.525464	2.832024	0.036583
C	0.167665	-1.106780	-0.263580	O	-1.397600	1.208078	-1.510372
H	1.107443	1.327338	2.119525	C	3.400881	-0.772436	-0.120582
C	1.007768	0.130504	-0.072707	O	3.152326	-1.951607	0.075491
H	-0.296993	-1.092143	-1.252948	O	4.657608	-0.319206	-0.296009
H	0.824909	-1.974945	-0.203691	C	5.675342	-1.314898	-0.238694
C	2.424574	0.302863	-0.195759	H	6.615740	-0.785199	-0.397221
C	0.439772	1.479754	-0.075405	H	5.682957	-1.810248	0.736547
C	2.699646	1.686673	-0.272944	H	5.531177	-2.065940	-1.020935
C	1.525095	2.409531	-0.216112	H	-2.305816	1.521751	-1.689314
H	1.410281	3.486148	-0.209433	<u>Structure 3.5 (E= -995.622326)</u>			
H	3.698118	2.107319	-0.312682	C	1.060654	0.854904	-1.576017
C	-2.345122	-1.019591	0.410060	C	0.106581	1.780399	-1.446457
C	-3.181552	-0.016564	0.902261	C	-0.981868	1.678948	-0.399869
C	-2.861638	-1.922916	-0.525281	C	-2.385544	1.863007	-0.937183
C	-4.498335	0.096069	0.457489	C	-3.088531	0.740025	-0.714905
H	-2.794889	0.697696	1.625142	C	-2.229252	-0.261209	-0.071366
C	-4.173991	-1.812708	-0.972522	C	-0.997742	0.271624	0.133268
H	-2.225438	-2.716954	-0.910829	C	0.297606	-0.319974	0.531918
C	-4.998470	-0.798922	-0.483970	H	0.179222	-1.315431	0.960713
H	-5.131025	0.889442	0.847372	H	0.785546	0.326567	1.272821
H	-4.555790	-2.520472	-1.704023	C	1.202939	-0.382759	-0.730153

C	2.639553	-0.643406	-0.335722
C	3.173417	-1.931780	-0.405317
C	4.484661	-2.180927	-0.005398
C	5.279945	-1.140313	0.469044
C	4.755614	0.149508	0.543207
C	3.444653	0.394411	0.144995
H	3.038311	1.402330	0.203338
H	5.370065	0.967336	0.911072
H	6.303988	-1.332221	0.778457
H	4.885795	-3.189286	-0.068030
H	2.554210	-2.745476	-0.777298
H	0.861019	-1.238407	-1.329794
C	-2.622424	-1.643397	0.241947
O	-1.899024	-2.497178	0.718792
O	-3.908528	-1.863903	-0.067769
C	-4.384748	-3.182888	0.199905
H	-5.430052	-3.187173	-0.110454
H	-3.817195	-3.922024	-0.372202
H	-4.305913	-3.412818	1.266023
H	-4.126065	0.566791	-0.976952
H	-2.728615	2.788287	-1.385416
C	-0.767865	2.751703	0.666345
O	-0.320620	3.851081	0.437940
O	-1.165834	2.354720	1.878976

H	-1.033150	3.109409	2.485836
H	0.079671	2.651910	-2.094856
H	1.809311	0.985181	-2.356215

**For Figure 3.3C: Int3.1 (see above), Int3.5, TS3.3,
and Int3.6**

Structure Int3.5 (E= -2111.482933)

Pd	-0.274528	0.041639	-0.720692
N	-2.478998	-0.174852	-0.340475
C	-2.780650	-1.422427	-0.345382
C	-1.846588	-2.454858	-0.809377
N	-0.607114	-2.002487	-1.128250
C	0.296439	-2.873428	-1.598652
C	0.008066	-4.228967	-1.750974
C	-1.256109	-4.698238	-1.406729
C	-2.203098	-3.792664	-0.929186
H	-3.201604	-4.106259	-0.649899
H	-1.505983	-5.748984	-1.508933
H	0.773535	-4.894240	-2.134392
H	1.263631	-2.462753	-1.856465
O	-3.992747	-1.782905	0.086387
C	-4.615281	-0.549580	0.582528
H	-4.686066	-0.641326	1.667719
H	-5.613503	-0.501797	0.150608
C	-3.653976	0.583851	0.133107

C	-4.222187	1.531839	-0.960349	C	7.669711	0.218603	-0.748750
C	-4.571145	0.750656	-2.236285	H	7.911327	-0.749760	-0.300548
H	-3.677581	0.292964	-2.675382	H	8.299579	0.396598	-1.621710
H	-5.003243	1.425792	-2.983617	H	7.824726	1.006278	-0.005570
H	-5.304063	-0.043074	-2.048252	H	4.382145	0.354465	-2.991385
C	-3.180231	2.611891	-1.289374	H	1.717716	0.300319	-3.272487
H	-2.937944	3.206743	-0.402928	C	2.729402	-1.463904	0.762354
H	-2.252148	2.176787	-1.668751	H	3.760797	-1.783127	0.914599
H	-3.575583	3.292545	-2.052810	H	2.201306	-2.254062	0.228032
C	-5.478645	2.218031	-0.396945	C	2.088336	-1.151088	2.148444
H	-6.290013	1.508132	-0.200412	C	0.677904	-1.706186	2.309778
H	-5.855375	2.955646	-1.114754	C	0.476148	-3.094393	2.233194
H	-5.253191	2.744512	0.538636	C	-0.796357	-3.645434	2.373592
H	-3.335847	1.190263	0.983891	C	-1.898097	-2.815756	2.610445
C	2.194998	0.354123	2.224294	C	-1.707836	-1.437393	2.693286
C	2.557438	0.908301	1.066671	C	-0.432311	-0.885831	2.535701
C	2.750133	-0.117661	-0.038835	H	-0.318270	0.191533	2.558986
C	1.659174	-0.000871	-1.106216	H	-2.554888	-0.779091	2.866263
C	2.233917	0.179861	-2.325665	H	-2.891851	-3.241100	2.718277
C	3.680496	0.217259	-2.175378	H	-0.930427	-4.721429	2.299781
C	4.016023	0.060074	-0.866205	H	1.327741	-3.747915	2.058171
C	5.358320	0.030015	-0.300692	H	2.700949	-1.617633	2.932971
O	5.624181	-0.159378	0.879984	H	2.657093	1.970579	0.872169
O	6.321016	0.234611	-1.237047	H	1.973484	0.909112	3.131442

C -0.426657 2.652448 0.642077

O 0.032955 2.097779 -0.414728

O -1.091782 2.198288 1.569013

C -0.052093 4.156675 0.663229

F -0.421812 4.757977 1.806547

F -0.656819 4.814020 -0.354827

F 1.281313 4.336826 0.522561

Transition State TS3.3 (E= -2111.445356)

Pd -0.196956 0.115728 -0.503257

N -2.204823 -0.736381 -0.480813

C -2.119175 -2.018796 -0.475390

C -0.869995 -2.707903 -0.810824

N 0.190431 -1.879531 -0.989034

C 1.353868 -2.399166 -1.401167

C 1.517413 -3.768986 -1.607708

C 0.443047 -4.625053 -1.382466

C -0.779249 -4.083023 -0.984025

H -1.651055 -4.703289 -0.813722

H 0.547111 -5.695446 -1.525053

H 2.479341 -4.143882 -1.938519

H 2.163537 -1.701278 -1.565880

O -3.213340 -2.723780 -0.183083

C -4.221998 -1.731370 0.211340

H -4.360156 -1.828461 1.289486

H -5.142713 -1.993582 -0.306558

C -3.607713 -0.366638 -0.197668

C -4.291352 0.315893 -1.416694

C -4.237585 -0.590739 -2.656159

H -3.202571 -0.780817 -2.961883

H -4.750159 -0.107634 -3.495676

H -4.726924 -1.556959 -2.485826

C -3.583458 1.643449 -1.727677

H -3.650954 2.334282 -0.881378

H -2.526380 1.493370 -1.962264

H -4.059700 2.125168 -2.590006

C -5.752304 0.617707 -1.040086

H -6.335846 -0.292850 -0.862707

H -6.241542 1.167681 -1.852090

H -5.804404 1.236269 -0.135729

H -3.605214 0.333667 0.639881

C 1.875087 1.022805 2.157038

C 2.151804 1.511561 0.929663

C 2.940242 0.189054 0.093024

C 1.718680 0.697282 -0.551693

C 2.150634 1.465133 -1.692117

C 3.531367 1.413169 -1.775682

C 4.054168 0.643564 -0.703565

C 5.455291 0.438982 -0.394793

O	5.915722	-0.129369	0.592649
O	6.267809	0.961231	-1.357924
C	7.673086	0.805678	-1.129415
H	7.947782	-0.252193	-1.073571
H	8.163384	1.274889	-1.984233
H	7.978043	1.302130	-0.203127
H	4.142718	1.927849	-2.508788
H	1.487779	2.037785	-2.328891
C	2.963815	-0.888483	1.154986
H	3.989920	-0.983069	1.510356
H	2.670096	-1.851807	0.732642
C	2.026365	-0.466819	2.330511
C	0.734729	-1.271462	2.442589
C	0.779273	-2.673975	2.411839
C	-0.384297	-3.430955	2.544356
C	-1.617916	-2.798392	2.729573
C	-1.669745	-1.405671	2.775621
C	-0.504098	-0.649022	2.628627
H	-0.576072	0.431988	2.628290
H	-2.620085	-0.896821	2.908951
H	-2.525275	-3.386958	2.830576
H	-0.328419	-4.515567	2.504644
H	1.731704	-3.180261	2.279644
H	2.568518	-0.637559	3.271557

H	2.329413	2.555801	0.706173
H	1.689724	1.676877	3.004013
C	-1.376170	2.574611	0.629184
O	-0.609105	2.146223	-0.294052
O	-1.974696	1.979544	1.524709
C	-1.568995	4.112867	0.592345
F	-2.885596	4.418972	0.517590
F	-0.957668	4.719904	-0.440939
F	-1.092389	4.669567	1.728752

Structure Int3.6 (E= -2111.497317)

Pd	0.173773	-0.291802	-0.330176
N	1.649932	1.243649	-0.601101
C	1.132596	2.409880	-0.444977
C	-0.311591	2.618236	-0.525397
N	-1.040834	1.473888	-0.601538
C	-2.361143	1.588456	-0.784983
C	-3.006239	2.822993	-0.865882
C	-2.261058	3.990820	-0.749465
C	-0.881039	3.884294	-0.580741
H	-0.246194	4.758368	-0.498634
H	-2.736077	4.965033	-0.795091
H	-4.080143	2.844372	-1.013306
H	-2.912017	0.665846	-0.866874
O	1.957464	3.438359	-0.244978

C	3.291909	2.838714	-0.093078	C	-3.269907	-1.630724	-0.834316
H	3.543504	2.890008	0.968191	C	-4.645003	-1.227556	-1.115624
H	3.983301	3.449327	-0.670199	O	-5.327367	-0.493911	-0.408474
C	3.122258	1.384092	-0.598876	O	-5.104283	-1.746965	-2.279508
C	3.736633	1.102922	-1.999336	C	-6.445412	-1.379728	-2.636161
C	3.172943	2.066330	-3.056083	H	-6.534725	-0.295011	-2.746244
H	2.088904	1.946274	-3.163917	H	-6.640868	-1.872817	-3.589347
H	3.628043	1.857387	-4.030777	H	-7.156461	-1.724478	-1.879924
H	3.380324	3.115779	-2.816971	H	-2.657820	-2.714346	-2.717964
C	3.427188	-0.342019	-2.419546	H	-0.323473	-3.098274	-1.469107
H	3.837527	-1.064593	-1.707974	C	-3.096411	-0.771339	1.621947
H	2.350348	-0.518671	-2.492147	H	-3.917788	-1.409125	1.974932
H	3.874596	-0.545032	-3.399947	H	-3.549892	0.211690	1.462867
C	5.261866	1.269337	-1.888899	C	-2.010622	-0.695061	2.735361
H	5.551399	2.294004	-1.629454	C	-1.267664	0.650191	2.743253
H	5.735768	1.026061	-2.846668	C	-1.999433	1.845114	2.835746
H	5.675942	0.596694	-1.127841	C	-1.358503	3.083281	2.861350
H	3.532468	0.672682	0.119157	C	0.037353	3.154155	2.808532
C	-1.068124	-1.874642	2.661037	C	0.775097	1.974129	2.732032
C	-0.680795	-2.396118	1.484218	C	0.128711	0.734599	2.696645
C	-2.590595	-1.338223	0.333790	H	0.726513	-0.164914	2.615026
C	-1.236664	-1.881134	0.215787	H	1.860410	2.008431	2.687767
C	-1.193532	-2.576598	-1.092118	H	0.539142	4.117679	2.822886
C	-2.387910	-2.389540	-1.720568	H	-1.948900	3.993674	2.922136

H	-3.084569	1.809133	2.889020
H	-2.546974	-0.743523	3.691657
H	0.042792	-3.203362	1.439825
H	-0.648462	-2.252184	3.590108
C	2.428320	-1.889998	0.672944
O	1.537158	-1.863562	-0.243891
O	2.698492	-1.082374	1.557200
C	3.240942	-3.208428	0.595122
F	4.251108	-3.235319	1.479024
F	3.770713	-3.396037	-0.634788
F	2.442558	-4.271638	0.854910

**For Scheme 3.2: Int3.1 (see above), Int3.2 (see above),
Int3.3, Int3.4, Int3.5 (see above), TS3.3 (see above),
Int3.6 (see above), Int3.7, Int3.8**

Structure Int3.3 (E= -2301.118371)

Pd	-0.516190	0.171820	-0.262961
N	-2.545322	1.424762	-0.598393
N	-2.278573	-1.211629	0.176244
C	-2.660306	2.711010	-0.931341
C	-3.663433	0.717990	-0.348488
C	-4.940126	1.273003	-0.411353
H	-5.811606	0.664617	-0.199979
C	-5.054486	2.621927	-0.753361
C	-3.899760	3.351271	-1.023465

H	-3.944312	4.399081	-1.299557
H	-6.032200	3.089648	-0.810672
C	1.278676	1.234062	-0.701853
H	1.172678	1.361997	-1.774958
C	1.709555	2.409199	0.161867
C	1.638400	0.005017	-0.125612
H	2.559840	2.846892	-0.369954
C	2.233128	1.757188	1.467183
H	1.842174	-0.896462	-0.692509
C	2.446956	0.239011	1.167600
H	1.506065	1.845395	2.270296
H	-0.437870	0.619953	1.179169
H	3.159845	2.226772	1.804781
C	3.883124	-0.164819	0.839568
C	2.149645	-0.686386	2.337536
C	4.275549	-1.189986	1.639800
C	3.211781	-1.504420	2.569177
H	3.274830	-2.255143	3.346911
H	5.234956	-1.690330	1.605725
C	0.670613	3.504073	0.333976
C	0.646413	4.564606	-0.583308
C	-0.285869	3.493593	1.359187
C	-0.300418	5.586787	-0.483129
H	1.383363	4.588606	-1.382789

C	-1.227910	4.518201	1.469015	H	-2.021626	-3.100972	-0.649614
H	-0.310323	2.678448	2.074120	C	-1.693296	-3.316824	1.463145
C	-1.239465	5.570398	0.550651	C	-0.183263	-3.189659	1.211722
H	-0.296982	6.398085	-1.206190	H	0.105426	-3.715097	0.294849
H	-1.958621	4.489070	2.272964	H	0.109588	-2.143290	1.096680
H	-1.973058	6.367064	0.638446	H	0.383669	-3.614661	2.046672
C	0.963656	-0.633276	3.195627	C	-2.062448	-4.809007	1.522715
O	0.105721	0.241472	3.188209	H	-1.844751	-5.307640	0.570104
O	0.908289	-1.662131	4.071576	H	-1.478938	-5.309402	2.304224
H	0.097484	-1.534102	4.604319	H	-3.122976	-4.963566	1.753730
C	4.693348	0.437080	-0.231349	C	-2.070930	-2.624738	2.781168
O	4.356553	1.386958	-0.919899	H	-3.146158	-2.691021	2.984990
O	5.884085	-0.180945	-0.366733	H	-1.550486	-3.104468	3.617709
C	6.747442	0.352021	-1.386843	H	-1.795316	-1.566048	2.763252
H	6.274499	0.272015	-2.369346	O	1.272746	-0.434751	-3.518975
H	6.985201	1.399347	-1.181538	C	0.335996	-1.029939	-2.979336
H	7.650961	-0.257153	-1.349905	O	-0.697849	-0.580403	-2.396400
H	-1.736038	3.239946	-1.131321	C	0.461273	-2.582450	-2.945181
C	-3.434084	-0.703418	-0.043497	F	1.039760	-3.083894	-4.054174
C	-2.441714	-2.678746	0.269875	F	1.244419	-2.952767	-1.889797
C	-3.981802	-2.851703	0.280688	F	-0.720596	-3.220477	-2.789299
O	-4.496762	-1.525133	-0.055079	<u>Structure Int3.4 (E= -2299.926570)</u>			
H	-4.348374	-3.548030	-0.473422	C	-4.105948	0.736883	2.066144
H	-4.390899	-3.117904	1.257590	H	-4.245481	1.129234	3.069697

C	-4.101866	1.638667	0.855707	H	-0.418708	5.613581	1.084940
C	-3.906769	-0.546550	1.772843	C	-1.126754	-1.014283	0.269763
H	-5.090746	2.096555	0.729945	O	-0.866399	-0.646711	1.418113
C	-3.834877	0.651664	-0.325609	O	-0.311553	-0.960722	-0.750767
H	-3.864140	-1.368014	2.480485	C	-6.244426	-1.453301	-0.207052
C	-3.757689	-0.796856	0.280913	O	-6.722706	-0.386312	0.150887
H	-2.896555	0.901477	-0.821039	O	-7.002006	-2.494889	-0.622236
H	-4.627030	0.713088	-1.072066	C	-8.419763	-2.264172	-0.631629
C	-4.813129	-1.751746	-0.254121	H	-8.674041	-1.438889	-1.302972
C	-2.476647	-1.538999	-0.076570	H	-8.864562	-3.193313	-0.990118
C	-4.215646	-2.845449	-0.794557	H	-8.781383	-2.035111	0.374828
C	-2.769444	-2.705670	-0.699576	Pd	1.481758	-0.129277	-0.284319
H	-2.051149	-3.431118	-1.064316	N	0.891131	1.677545	-1.052001
H	-4.725887	-3.686355	-1.249428	N	3.222688	1.016162	0.086680
C	-3.074767	2.757017	0.934935	C	-0.275649	1.911348	-1.658788
C	-3.397857	4.056862	0.527438	C	1.798096	2.674660	-0.929238
C	-1.771690	2.501060	1.391058	C	1.552503	3.958313	-1.394686
C	-2.447825	5.081206	0.576851	H	2.302561	4.730943	-1.274406
H	-4.403809	4.269155	0.172360	C	0.324911	4.212739	-2.012143
C	-0.823807	3.522944	1.447552	C	-0.593252	3.176987	-2.152808
H	-1.501449	1.493857	1.692268	H	-1.555005	3.334949	-2.626600
C	-1.157642	4.818128	1.041827	H	0.096269	5.207295	-2.379208
H	-2.718808	6.084391	0.257963	H	-0.941075	1.063294	-1.744760
H	0.179229	3.305002	1.805355	C	3.034937	2.242702	-0.282036

C	4.538786	0.962918	0.797231
C	5.145221	2.330105	0.409174
O	4.001654	3.122562	-0.055639
H	5.601278	2.864582	1.240023
H	5.837237	2.271519	-0.433079
C	2.275780	-2.844488	-0.437759
O	1.999586	-1.963692	0.458294
O	2.431339	-2.714538	-1.645395
C	2.412541	-4.250224	0.198033
F	2.803061	-5.168566	-0.700387
F	1.228778	-4.654415	0.710223
F	3.312664	-4.256240	1.205440
H	4.312408	0.946751	1.869837
C	5.447875	-0.252036	0.471205
C	6.899873	0.100225	0.855986
H	7.342913	0.854957	0.197504
H	6.962408	0.463661	1.889123
H	7.520958	-0.799472	0.783326
C	5.017578	-1.447907	1.334679
H	5.566252	-2.348569	1.035634
H	5.240334	-1.255421	2.391797
H	3.951929	-1.652977	1.245597
C	5.375764	-0.602941	-1.021793
H	6.111031	-1.381563	-1.255303

H	4.387037	-0.979820	-1.299589
H	5.600021	0.265668	-1.653290

Structure Int3.7 (E= -2111.506653)

C	3.533751	-2.108174	-2.851897
C	2.263784	-2.557664	-2.830460
C	1.508501	-2.559520	-1.591927
C	0.165003	-2.711589	-1.345654
C	-0.086154	-2.487964	0.087287
C	1.260314	-2.320020	0.683688
C	2.191627	-2.319272	-0.325448
C	3.678040	-2.154765	-0.306268
H	4.130546	-3.150477	-0.182894
C	4.226609	-1.545144	-1.630217
C	4.168668	-0.017748	-1.594026
C	5.255788	0.694513	-1.068537
C	5.218588	2.084988	-0.956442
C	4.087331	2.789444	-1.375390
C	3.002252	2.090691	-1.907927
C	3.042564	0.699130	-2.016141
H	2.191235	0.167814	-2.427816
Pd	-1.176136	-0.676240	0.035355
N	-2.517921	1.023075	0.009245
C	-3.739033	0.625876	-0.037916
O	-4.702088	1.527794	0.165242

C	-4.000489	2.758384	0.561350	H	-6.209152	-0.495418	-0.400731
H	-4.460482	3.577288	0.012244	H	-6.629993	-2.916595	-0.926986
H	-4.166791	2.887831	1.633007	H	-4.652290	-4.457970	-1.109154
C	-2.514407	2.487056	0.213601	H	-2.377691	-3.545674	-0.737584
H	-1.866351	2.706754	1.064064	O	0.547691	0.351339	0.509670
C	-1.982755	3.252047	-1.030862	C	0.555715	1.007292	1.606077
C	-2.827382	2.939289	-2.276125	O	-0.341578	1.220358	2.418916
H	-2.786098	1.872698	-2.524874	C	1.943408	1.641637	1.885246
H	-3.878902	3.221577	-2.147673	F	2.968592	0.922499	1.400227
H	-2.442253	3.496276	-3.137711	F	2.009922	2.877247	1.323464
C	-0.523322	2.852980	-1.295969	F	2.148738	1.796198	3.209732
H	-0.139010	3.419262	-2.152544	H	2.118934	2.628257	-2.238782
H	0.115695	3.069737	-0.434589	H	4.052198	3.872006	-1.288542
H	-0.429242	1.787388	-1.520152	H	6.072102	2.616840	-0.544023
C	-2.031708	4.758032	-0.719979	H	6.137154	0.149333	-0.737979
H	-1.600463	5.325129	-1.552809	H	5.288052	-1.813298	-1.683440
H	-3.054757	5.121628	-0.570699	H	3.993928	-1.560529	0.553059
H	-1.452659	4.991938	0.181723	C	1.541528	-2.045789	2.085508
C	-4.085538	-0.771185	-0.312600	O	2.651842	-1.908386	2.585509
N	-3.018471	-1.610173	-0.398008	O	0.404662	-1.931406	2.821064
C	-3.243245	-2.899409	-0.677944	C	0.589742	-1.515226	4.180502
C	-4.527823	-3.405336	-0.881247	H	1.094520	-0.547042	4.220261
C	-5.619659	-2.549465	-0.781265	H	1.172322	-2.253203	4.740015
C	-5.393758	-1.203666	-0.489067	H	-0.413600	-1.430873	4.600034

H -0.793595 -3.121641 0.623963

H -0.598665 -2.923376 -2.085936

H 1.780265 -2.900656 -3.743073

H 4.084910 -2.075910 -3.789082

Structure Int3.8 (E= -2111.495801)

C 0.704985 1.796393 0.571068

C 1.496415 2.302608 -0.523244

C 3.431148 0.942407 0.178148

C 2.802546 1.925041 -0.697849

C 3.760295 2.264378 -1.741786

C 4.892288 1.536683 -1.514418

C 4.692087 0.696907 -0.326664

C 5.632416 -0.284283 0.207233

O 5.422032 -1.035260 1.151438

O 6.803145 -0.289775 -0.478241

C 7.781615 -1.236240 -0.024256

H 7.395446 -2.257537 -0.091925

H 8.639203 -1.112661 -0.687120

H 8.071238 -1.029988 1.010226

H 5.804824 1.553952 -2.097093

H 3.587425 2.981902 -2.535057

C 2.667648 0.296061 1.289293

H 3.318990 0.071872 2.138146

H 2.306253 -0.676696 0.931703

C 1.484050 1.172616 1.743165

C 0.537852 0.479265 2.712245

C 0.232193 -0.886506 2.621717

C -0.716694 -1.467100 3.465951

C -1.378307 -0.691514 4.420600

C -1.073116 0.667158 4.530012

C -0.122263 1.241560 3.684468

H 0.105105 2.301638 3.770213

H -1.574598 1.280813 5.273529

H -2.118043 -1.141888 5.076710

H -0.935956 -2.528032 3.375375

H 0.727564 -1.509176 1.885252

H 1.917904 2.033228 2.276413

H 1.024193 2.986478 -1.224282

H -0.047980 2.504331 0.914388

N -1.999077 -1.418031 -0.379013

C -1.225775 -2.444527 -0.408736

C 0.139304 -2.361665 -0.940179

N 0.611925 -1.094654 -1.093811

C 1.770555 -0.921712 -1.736755

C 2.542919 -1.995723 -2.184254

C 2.098047 -3.292807 -1.956801

C 0.862661 -3.480151 -1.332305

H 0.452413 -4.469505 -1.167215

H	2.686085	-4.147518	-2.274143
H	3.480697	-1.796723	-2.690115
H	2.095787	0.098665	-1.882270
O	-1.701247	-3.610785	0.035137
C	-3.036531	-3.312726	0.573037
H	-2.981871	-3.449124	1.654321
H	-3.722198	-4.040286	0.141692
C	-3.306538	-1.839445	0.160813
C	-4.452422	-1.640668	-0.868153
C	-4.166117	-2.412596	-2.165548
H	-4.989266	-2.270484	-2.874881
H	-4.063658	-3.490961	-1.995329
H	-3.247630	-2.053075	-2.643020
C	-4.591632	-0.144419	-1.186927
H	-5.424999	0.013117	-1.882007
H	-4.793534	0.438393	-0.282479
H	-3.686193	0.252492	-1.652668
C	-5.761452	-2.135231	-0.229842
H	-5.738549	-3.209413	-0.012645
H	-6.601653	-1.955222	-0.910112
H	-5.967061	-1.603236	0.707053
H	-3.523863	-1.226277	1.040022
C	-2.917011	2.460166	0.167200
O	-2.182041	1.541668	0.674299

O	-3.948153	2.920898	0.645863
C	-2.421599	3.091838	-1.166622
F	-1.279712	3.799506	-0.961881
F	-3.325074	3.934199	-1.687150
F	-2.144470	2.167840	-2.122626
Pd	-0.675000	0.386027	-0.221513

Scheme S3.1 (β -Carbon Elimination Pathway): Int3.1 (see above), TS3.4, and 3.6

Transition State TS3.4 ($E = -1775.058231$)

Pd	0.132354	-0.383947	0.305560
N	1.188626	-1.845267	1.574859
N	1.964956	-0.820034	-0.845473
C	0.815016	-2.333842	2.762074
C	2.174657	-2.486747	0.898354
C	2.809434	-3.621913	1.390143
H	3.589894	-4.097390	0.808052
C	2.418680	-4.118773	2.634419
C	1.408316	-3.462953	3.330056
H	1.071947	-3.809611	4.300734
H	2.896535	-5.000910	3.047002
C	-1.407100	0.053637	1.687791
H	-0.837007	-0.225267	2.577228
C	-1.920554	1.489576	1.631871
C	-2.425227	-0.871795	1.308201

H	-2.581595	1.630176	2.499953	C	-0.611226	1.513048	-1.827945
C	-2.846888	1.564123	0.351706	O	-0.744612	2.656474	-1.435255
H	-3.478565	-0.646985	1.461687	O	0.110247	1.228059	-2.943310
C	-2.539240	0.396308	-0.538061	H	0.477599	2.077595	-3.261367
H	-2.650880	2.484354	-0.200055	C	-4.747191	-0.916500	-0.658045
H	-2.184738	-1.926567	1.188898	O	-5.307030	-0.430306	0.316009
H	-3.896195	1.536670	0.642485	O	-5.345778	-1.767167	-1.506393
C	-3.351695	-0.651702	-1.048206	C	-6.721424	-2.082114	-1.212513
C	-1.219111	0.284205	-1.246203	H	-6.802639	-2.561258	-0.233433
C	-2.593498	-1.430575	-1.971931	H	-7.331542	-1.175499	-1.228551
C	-1.332285	-0.890992	-2.092442	H	-7.035435	-2.766922	-2.000112
H	-0.553366	-1.234970	-2.758948	H	0.019847	-1.812493	3.281360
H	-2.962337	-2.319641	-2.466451	C	2.552784	-1.864631	-0.374331
C	-0.853050	2.568099	1.726229	C	2.804641	-0.313204	-1.958623
C	0.473669	2.285980	2.076631	C	3.650188	-1.560019	-2.288722
C	-1.209426	3.909070	1.519627	O	3.593552	-2.354714	-1.052925
C	1.423626	3.307948	2.181476	H	3.211024	-2.169962	-3.082417
H	0.785253	1.265702	2.273753	H	4.700273	-1.370521	-2.500118
C	-0.268052	4.929952	1.626002	H	2.163145	-0.033337	-2.794004
H	-2.236026	4.156858	1.264144	C	3.636710	0.931376	-1.515849
C	1.059645	4.632793	1.950915	C	2.698792	2.063586	-1.071784
H	2.449026	3.058981	2.441085	H	2.117281	2.454313	-1.910345
H	-0.569250	5.959670	1.453323	H	2.002186	1.733459	-0.296875
H	1.796386	5.427344	2.029293	H	3.284285	2.895190	-0.664103

C	4.455019	1.409722	-2.726916
H	3.802273	1.627581	-3.581144
H	4.994459	2.329260	-2.472998
H	5.198073	0.670932	-3.047328
C	4.578092	0.590654	-0.347842
H	5.278721	-0.214637	-0.593190
H	5.171757	1.473579	-0.086709
H	4.015407	0.298270	0.546180

Structure 3.6 (E= -1775.104094)

Pd	0.044397	0.654219	-0.438346
N	-1.021070	2.571563	-0.315120
N	-1.929641	0.106377	0.443762
C	-0.537346	3.800808	-0.512776
C	-2.358852	2.399363	-0.219525
C	-3.260085	3.450592	-0.341378
H	-4.325077	3.264247	-0.268943
C	-2.751488	4.735336	-0.544457
C	-1.373188	4.914498	-0.621675
H	-0.939263	5.896966	-0.770146
H	-3.425708	5.580234	-0.636902
C	1.765395	1.303299	-1.703009
H	2.038244	2.301293	-1.373021
C	2.828619	0.223218	-1.655024
C	0.617911	1.176070	-2.480888

H	3.381778	0.290575	-2.605053
C	2.103806	-1.131004	-1.657139
H	0.402023	0.288589	-3.065198
C	0.963547	-1.209954	-0.604117
H	2.796593	-1.960956	-1.488200
H	0.031015	2.058198	-2.719599
H	1.663404	-1.290972	-2.641345
C	0.039080	-2.347658	-0.913307
C	1.433254	-1.548286	0.785413
C	0.089802	-3.267920	0.094415
C	0.964865	-2.778325	1.140940
H	1.132988	-3.273063	2.090005
H	-0.450641	-4.205783	0.129126
C	3.874004	0.370386	-0.550745
C	3.947511	1.474836	0.305513
C	4.845713	-0.633933	-0.411012
C	4.938901	1.561537	1.286147
H	3.213955	2.268876	0.242988
C	5.838646	-0.551758	0.563683
H	4.832310	-1.491436	-1.077773
C	5.886342	0.547133	1.424502
H	4.963585	2.425811	1.944508
H	6.574108	-1.346876	0.650454
H	6.655988	0.614039	2.188429

C	1.983553	-0.577336	1.737427
O	1.580378	0.579683	1.806409
O	2.892450	-1.080361	2.581453
H	3.160855	-0.360337	3.189811
C	-0.751780	-2.461667	-2.144538
O	-0.658256	-1.727590	-3.119467
O	-1.642434	-3.471845	-2.076891
C	-2.472513	-3.654834	-3.238278
H	-3.072649	-2.760213	-3.425591
H	-1.861427	-3.874234	-4.117715
H	-3.117106	-4.501989	-3.002787
H	0.540267	3.890889	-0.591319
C	-2.767013	1.022583	0.084070
C	-2.739238	-1.052619	0.902573
C	-4.092804	-0.757332	0.232458
O	-4.059866	0.700218	0.031581
H	-4.182972	-1.212390	-0.757669
H	-4.972218	-0.982258	0.831548
H	-2.299499	-1.973345	0.518392
C	-2.805456	-1.126095	2.459670
C	-1.389574	-1.219700	3.043111
H	-0.883250	-2.123831	2.697799
H	-0.777523	-0.357458	2.763823
H	-1.441637	-1.260680	4.137300

C	-3.579423	-2.402435	2.832746
H	-3.095895	-3.292107	2.411138
H	-3.606505	-2.518376	3.922064
H	-4.616066	-2.379664	2.478417
C	-3.504341	0.106024	3.060376
H	-4.535307	0.219667	2.709000
H	-3.539245	0.008683	4.151073
H	-2.957649	1.028444	2.833032

Scheme S3.2 (Acetate as X-type Ligand):

Int3.1-OAc (see Int3.1 above), Int3.5-OAc,

TS3.3-OAc, and Int3.6-OAc

Structure **Int3.5-OAc** (E = -1813.930732)

Pd	0.272482	-0.539773	-0.604667
N	2.480189	-0.195766	-0.276145
C	2.738492	1.047877	-0.457429
C	1.778271	1.969773	-1.074628
N	0.558710	1.434184	-1.331612
C	-0.360992	2.192748	-1.943787
C	-0.112340	3.518018	-2.298666
C	1.129540	4.076918	-2.011185
C	2.095750	3.285784	-1.390401
H	3.079449	3.670865	-1.150698
H	1.347894	5.108220	-2.267608
H	-0.890740	4.090868	-2.790135

H	-1.310434	1.715821	-2.149158	C	-2.244917	-1.011754	-2.137747
O	3.931997	1.511950	-0.070719	C	-3.690612	-1.015133	-1.982758
C	4.590021	0.387227	0.603123	C	-4.024529	-0.602698	-0.729529
H	4.648875	0.639217	1.663518	C	-5.363007	-0.460647	-0.175081
H	5.593059	0.310871	0.186645	O	-5.622465	-0.052082	0.950647
C	3.671657	-0.832457	0.319775	O	-6.332473	-0.832103	-1.052434
C	4.289529	-1.913402	-0.610660	C	-7.678046	-0.713434	-0.570627
C	4.642009	-1.321084	-1.983601	H	-7.911790	0.324744	-0.316151
H	3.745600	-0.956245	-2.497498	H	-8.314071	-1.051403	-1.390306
H	5.102859	-2.087780	-2.616839	H	-7.834368	-1.342003	0.311045
H	5.353081	-0.489820	-1.905603	H	-4.393876	-1.308598	-2.755211
C	3.286282	-3.063350	-0.789086	H	-1.731159	-1.317692	-3.043418
H	3.055166	-3.530000	0.174358	C	-2.735302	1.199434	0.581726
H	2.346208	-2.718183	-1.226645	H	-3.764637	1.553049	0.646425
H	3.711542	-3.832367	-1.445225	H	-2.184616	1.871375	-0.076090
C	5.553505	-2.468917	0.068454	C	-2.126811	1.148700	2.016852
H	6.341663	-1.713965	0.168254	C	-0.728093	1.745887	2.106673
H	5.964415	-3.294577	-0.523904	C	-0.556551	3.118487	1.862376
H	5.324189	-2.854935	1.069341	C	0.704224	3.709512	1.927503
H	3.354326	-1.314972	1.246355	C	1.823704	2.937268	2.256811
C	-2.223938	-0.318324	2.362744	C	1.663024	1.574767	2.503621
C	-2.570726	-1.075649	1.321523	C	0.399956	0.980260	2.418782
C	-2.756112	-0.272379	0.045125	H	0.313028	-0.090916	2.563264
C	-1.663546	-0.596104	-0.978793	H	2.524226	0.960058	2.751005

H	2.808434	3.393070	2.309320
H	0.814636	4.771663	1.724855
H	-1.423719	3.727490	1.616138
H	-2.763861	1.740219	2.689646
H	-2.679451	-2.154946	1.324204
H	-2.011860	-0.696245	3.358968
C	0.533969	-2.891804	1.130688
O	0.027386	-2.516302	-0.004456
O	1.154869	-2.183316	1.933146
C	0.282375	-4.367290	1.424409
H	0.587033	-4.984511	0.572600
H	-0.790012	-4.533913	1.581843
H	0.827233	-4.678410	2.318977

Transition State TS3.3-OAc (E= -1813.893178)

Pd	0.288684	-0.603071	-0.376541
N	2.385357	0.015371	-0.433118
C	2.447560	1.280649	-0.648142
C	1.294807	2.035495	-1.147255
N	0.148478	1.313145	-1.219077
C	-0.934971	1.876935	-1.768144
C	-0.931991	3.196459	-2.220664
C	0.229706	3.954287	-2.101263
C	1.370440	3.359334	-1.561667
H	2.305049	3.898868	-1.466031

H	0.255387	4.986799	-2.433025
H	-1.835008	3.610790	-2.654581
H	-1.816289	1.254120	-1.841576
O	3.607831	1.904279	-0.430615
C	4.490370	0.891251	0.160791
H	4.634405	1.164617	1.207444
H	5.438445	0.948320	-0.370743
C	3.724611	-0.447617	-0.013255
C	4.356030	-1.430061	-1.039526
C	4.406908	-0.802534	-2.440972
H	3.398935	-0.594329	-2.816700
H	4.890498	-1.490880	-3.143443
H	4.976923	0.134202	-2.455161
C	3.525588	-2.721648	-1.085064
H	3.520000	-3.214293	-0.106580
H	2.487895	-2.528534	-1.367079
H	3.959009	-3.419114	-1.811979
C	5.776570	-1.780251	-0.562609
H	6.450280	-0.916321	-0.583061
H	6.210004	-2.548156	-1.213638
H	5.761713	-2.176209	0.460321
H	3.608872	-0.965507	0.941022
C	-1.906052	-0.652548	2.365473
C	-2.204370	-1.378461	1.268373

C	-2.852027	-0.209935	0.125125	H	0.621772	-0.186082	2.637233
C	-1.683507	-0.970088	-0.350316	H	2.746292	1.039019	2.730149
C	-2.190792	-1.937817	-1.291589	H	2.814241	3.487877	2.279999
C	-3.557428	-1.771474	-1.425385	H	0.693448	4.698907	1.783242
C	-4.004077	-0.725711	-0.574344	H	-1.452539	3.480500	1.757671
C	-5.378483	-0.322558	-0.359536	H	-2.486719	1.258464	3.057014
O	-5.787925	0.500201	0.457003	H	-2.472875	-2.427062	1.278715
O	-6.234833	-0.974338	-1.199517	H	-1.794974	-1.114775	3.342213
C	-7.618367	-0.637301	-1.051520	C	1.121361	-2.892469	1.265553
H	-7.788020	0.425973	-1.247588	O	0.462399	-2.574695	0.195764
H	-8.148921	-1.242399	-1.788946	O	1.693820	-2.113371	2.039282
H	-7.975954	-0.874791	-0.044838	C	1.125958	-4.395139	1.528437
H	-4.215249	-2.378776	-2.037567	H	0.117218	-4.718560	1.813163
H	-1.585560	-2.704791	-1.758368	H	1.401554	-4.943976	0.621964
C	-2.780776	1.077530	0.917376	H	1.819714	-4.642143	2.335753
H	-3.798761	1.357216	1.188340	<u>Structure Int3.6-OAc (E= -1813.946733)</u>			
H	-2.366207	1.884642	0.310084	Pd	0.295361	-0.724661	-0.117260
C	-1.927391	0.844741	2.205689	N	2.107597	0.318752	-0.611609
C	-0.579731	1.558282	2.209969	C	1.885860	1.575242	-0.766934
C	-0.532442	2.940219	1.966637	C	0.540563	2.089442	-1.013305
C	0.678456	3.631166	1.985653	N	-0.445151	1.163194	-0.888195
C	1.868969	2.952730	2.266606	C	-1.692542	1.538790	-1.193775
C	1.828983	1.582233	2.520429	C	-2.012305	2.835243	-1.598600
C	0.615876	0.887870	2.486389	C	-1.004863	3.789044	-1.689335

C	0.302519	3.404321	-1.394759	C	-1.388616	-1.173758	3.060142
H	1.131150	4.099294	-1.459901	C	-1.100215	-2.041553	2.075529
H	-1.224134	4.808862	-1.987547	C	-2.660336	-0.900474	0.540640
H	-3.044995	3.073397	-1.827546	C	-1.482614	-1.752610	0.678284
H	-2.452517	0.779476	-1.106815	C	-1.566484	-2.738046	-0.423550
O	2.929951	2.405663	-0.729679	C	-2.656037	-2.441146	-1.189177
C	4.071773	1.571218	-0.329598	C	-3.351794	-1.306256	-0.589290
H	4.295980	1.817368	0.710535	C	-4.571097	-0.676267	-1.084576
H	4.909158	1.850084	-0.966373	O	-5.077461	0.345991	-0.633183
C	3.569300	0.116121	-0.505109	O	-5.102928	-1.342486	-2.139251
C	4.146022	-0.628663	-1.741686	C	-6.292856	-0.767987	-2.698727
C	3.856016	0.143880	-3.038200	H	-6.101215	0.245855	-3.062540
H	2.777886	0.232138	-3.213713	H	-6.571288	-1.419306	-3.528413
H	4.290161	-0.385055	-3.894167	H	-7.096324	-0.737323	-1.957092
H	4.284685	1.152700	-3.024611	H	-2.958486	-2.926681	-2.109010
C	3.522113	-2.029383	-1.836164	H	-0.835709	-3.518969	-0.587864
H	3.736876	-2.619078	-0.938911	C	-3.061726	0.061758	1.613698
H	2.436077	-1.980336	-1.950072	H	-4.023266	-0.271834	2.027057
H	3.937456	-2.562705	-2.699713	H	-3.262572	1.052510	1.194573
C	5.664002	-0.779280	-1.541903	C	-2.029371	0.165653	2.775427
H	6.179906	0.187221	-1.514917	C	-0.994305	1.276888	2.542836
H	6.094651	-1.358394	-2.366776	C	-1.433968	2.593601	2.331035
H	5.886356	-1.308201	-0.606997	C	-0.527386	3.634052	2.129467
H	3.763002	-0.473415	0.391542	C	0.847904	3.380474	2.147865

C	1.295904	2.079354	2.369981
C	0.384538	1.036134	2.563071
H	0.765211	0.031696	2.704315
H	2.360615	1.861574	2.382279
H	1.557288	4.187563	1.986277
H	-0.894308	4.642830	1.958990
H	-2.499571	2.809553	2.324566
H	-2.597353	0.471450	3.663523
H	-0.585063	-2.973599	2.284391
H	-1.093366	-1.390132	4.083931
C	2.085639	-2.463546	1.394393
O	1.218681	-2.480452	0.428485
O	2.428177	-1.476258	2.056811
C	2.663247	-3.840581	1.700967
H	2.042684	-4.319364	2.469425
H	2.665340	-4.485445	0.818450
H	3.677293	-3.742633	2.098351

IntS3.1 (initial vinyl palladium species furnished from
decarboxylation of Int3.4) (E= -2111.477422)

Pd	0.457116	0.904026	0.569567
N	2.632639	0.903554	-0.045247
C	2.926970	2.070811	-0.493743
C	1.922745	3.117477	-0.721765
N	0.666002	2.816695	-0.303139

C	-0.293014	3.742796	-0.437425
C	-0.047559	4.988963	-1.013920
C	1.235443	5.292732	-1.456601
C	2.243009	4.340391	-1.299383
H	3.262078	4.533334	-1.612206
H	1.455919	6.253738	-1.909174
H	-0.860983	5.700293	-1.103044
H	-1.270832	3.477282	-0.061013
O	4.209540	2.358188	-0.730916
C	4.968845	1.182722	-0.296881
H	5.580879	1.489669	0.552895
H	5.610042	0.897502	-1.129379
C	3.889716	0.128720	0.078090
C	3.909089	-1.154908	-0.797504
C	3.587074	-0.820641	-2.261364
H	3.654054	-1.724321	-2.877346
H	4.287998	-0.088123	-2.680141
H	2.573845	-0.417005	-2.361822
C	2.887977	-2.161849	-0.249487
H	2.909003	-3.082040	-0.843849
H	3.132097	-2.429958	0.784514
H	1.869701	-1.771165	-0.271119
C	5.308543	-1.788521	-0.692481
H	6.089675	-1.163306	-1.138665

H	5.319566	-2.749987	-1.218298	C	-2.289820	-3.532313	-2.498192
H	5.577975	-1.975809	0.354263	C	-1.417143	-4.475706	-3.046854
H	3.988128	-0.172338	1.124317	C	-0.065845	-4.165835	-3.208789
C	-2.666262	0.120456	-2.117523	C	0.405686	-2.910841	-2.811995
C	-2.576217	1.092349	-1.210368	C	-0.467482	-1.975537	-2.256990
C	-2.595905	0.572285	0.220795	H	-0.093884	-1.003414	-1.942708
C	-1.441906	1.149984	1.041776	H	1.454355	-2.660837	-2.935863
C	-1.933679	1.871897	2.083398	H	0.615618	-4.894103	-3.640102
C	-3.387571	1.827594	2.050330	H	-1.794545	-5.448666	-3.350644
C	-3.810605	1.082191	0.994342	H	-3.343566	-3.774145	-2.379471
C	-5.220657	0.834444	0.705853	H	-3.803718	-1.622022	-1.649032
O	-6.161283	1.313851	1.326287	H	-2.533632	2.155660	-1.423043
O	-5.396414	-0.009959	-0.339349	H	-2.692045	0.272282	-3.193409
C	-6.757958	-0.306635	-0.678569	C	1.157231	-1.237551	2.390070
H	-7.300174	0.605599	-0.943444	O	0.319296	-0.981047	1.455467
H	-6.706863	-0.977383	-1.537297	O	1.978736	-0.510766	2.939967
H	-7.267604	-0.798469	0.155033	C	1.032261	-2.705961	2.869916
H	-4.042334	2.310556	2.768703	F	0.715740	-3.553550	1.870544
H	-1.356454	2.408199	2.829034	F	0.064717	-2.807844	3.810887
C	-2.536487	-0.981097	0.014742	F	2.181479	-3.142690	3.4197
H	-3.274654	-1.490389	0.637391				
H	-1.551316	-1.343179	0.304774				
C	-2.780950	-1.253763	-1.501794				
C	-1.829295	-2.272952	-2.096659				

3.9 References

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Chapter 4: Approaches to Fragment Coupling and Revisions in Strategy

4.1. First-Generation Heck Coupling Approach to Urceoloids A & B

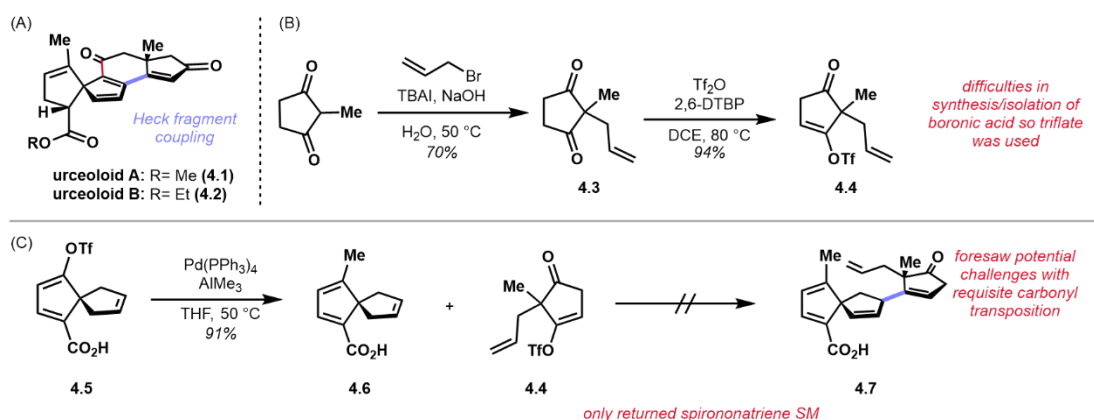


Figure 4.1. (A) conceptual approach to urceoloids A & B. (B) Synthesis of vinyl triflate coupling partner. (C) Modification of spirocyclic fragment and results of initial Heck coupling

Following completion of the work discussed in Chapter 3, we returned to the total synthesis efforts targeting urceoloids¹ A & B (**4.1** & **4.2**, Figure 4.1A), aimed at constructing the carbocyclic core through a key Heck-fragment coupling strategy. Early synthetic progress (see Chapter 2) led to the synthesis of intermediate **4.5**, the triflate of which could be converted to a methyl group upon treatment with Pd(PPh₃)₄ and AlMe₃ to give **4.6** (Figure 4.1C).² With reliable access to a spirocyclic coupling partner, we then pursued the synthesis of a cyclopentenyl coupling partner. This was accomplished through the allylation of 2-methylcyclopentanedione to give **4.3**,³ which, upon reaction with triflic anhydride and 2,6-di-*tert*-butyl pyridine, gave vinyl triflate **4.4** (Figure 4.1B).⁴ At this stage, we sought to convert the cyclopentenyl triflate to a boronic ester in order to accomplish an eventual oxidative Heck⁵ reaction with **4.6**. However, attempts at the synthesis and purification of the corresponding boronic acid were unsuccessful.⁶

As such, we proceeded with the triflate (**4.4**) as a coupling partner under normal Heck reaction conditions. After evaluating an array of different Heck coupling conditions, no product was observed (Figure 4.1C). Under most conditions, recovered spirononene was observed, along with decomposition of the triflate coupling partner. At this stage, the desired transformation appeared to be more challenging than originally expected. Furthermore, subsequent steps such as the proposed carbonyl transposition may also present a formidable challenge. Historically, carbonyl transpositions require multi-step sequences involving α -oxidation, followed by chemoselective deoxygenation of the initial carbonyl.^{7,8} Dong and coworkers have recently published a shorter, two-step sequence to accomplish this which we sought to use.⁹ However, if this method proved unsuccessful in the spirononene system, the efficiency of the overall synthetic route would suffer from a large step-count. Due to the challenges experienced in the intermolecular Heck reaction

and likelihood for further significant challenges along the proposed route, we decided to revise our synthetic strategy at this point.

4.2 Introduction to Second-Generation Heck Coupling Strategy

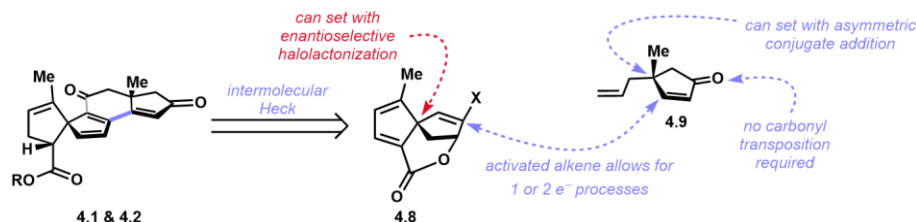


Figure 4.2. Re-designed retrosynthetic approach to natural products **4.1** & **4.2**.

In our new synthetic design, we decided to switch the triflate and alkene motifs of the requisite coupling partners (Figure 4.2). Rather than use the unbiased alkene of the spirononatriene, we hypothesized that the use of a cyclopentenone (**4.9**) would allow for a more facile migratory insertion.¹⁰ Additionally, the enone (**4.9**) could be used for intermolecular fragment coupling through single electron chemistry.¹¹ Importantly, the use of a cyclopentenone allows for proper positioning of the carbonyl moiety relative to the natural product, such that no carbonyl transposition would be required later in the route. An additional benefit of this design is the potential for asymmetric induction in both reaction partners. A chiral, enantioenriched spirononone (**4.8**) may be derived from the product of an asymmetric halolactonization¹² and the quaternary center of the cyclopentenone might be formed through an asymmetric conjugate addition of a methyl group.¹³ With this new route in mind, we set forth on a forward route to first access the desired cyclopentenone.

4.3 Functionalized Cyclopentenone Synthesis

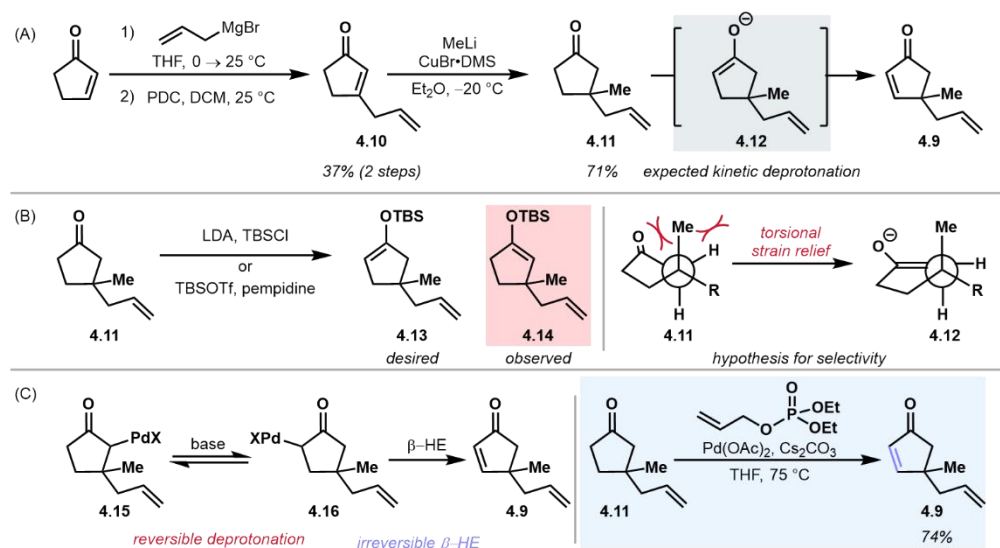


Figure 4.3. (A) Route to desired enone **4.9** (B) Challenges in dehydrogenation of **4.11** (C) Using a reversible reaction system for successful synthesis of **4.9**.

In a two-step sequence, known allyl cyclopentenone¹⁴ (**4.10**) was accessed by 1,2-addition of an allyl Grignard reagent to cyclopentenone, followed by a Babler–Dauben^{15,16} oxidative transposition (Figure 4.3A). Conjugate addition of a methyl Gilman reagent¹⁷ generates the quaternary carbon of substituted cyclopentanone **4.11**. At this point, we sought to dehydrogenate **4.11** to give the desired coupling partner **4.9**. We sought to accomplish this through a kinetic deprotonation of **4.11** to form enolate **4.12**. This enolate could then be trapped as silyl enol ether **4.13** and a subsequent reaction with Pd(II) would effect a Seagusa–Ito oxidation.¹⁸ However, treatment with a bulky base such as LDA and trapping of the enolate with TBSCl only gave the undesired constitutional isomer **4.14** (Figure 4.3B). This was unexpected, as it was hypothesized the desired product would be the product of the more accessible site for deprotonation.

However, Snyder and coworkers reported similar results in a cyclopentenone deprotonation.¹⁹ Unfortunately, their solution of using a bulky amine base such as pentamethyl piperidine did not work for our substrate, and these conditions only give the undesired isomer **4.14**. These results indicated that kinetic deprotonation would not give the desired selectivity. A proposed rationale for the observed selectivity is the ground state destabilization in **4.11**, which is relieved upon deprotonation to form enolate **4.12** (Figure 4.3B, right). In order to circumvent this, we sought to use a thermodynamic reaction manifold, wherein a reversible deprotonation might result in an equilibrium between palladium-enolates **4.15** and **4.16** (Figure 4.3C). Only enolate **4.16** has β -hydrogens which can undergo β -hydrogen elimination and serve as a kinetic sink. Arisha and coworkers²⁰ reported the success of such a method using Pd(OAc)₂ and Na₂CO₃ in simple cyclic enones. Treatment of cyclopentanone **4.11** did, indeed, furnish the desired enone **4.9**, albeit in low (45%) and irreproducible yields. We hypothesized that a less strongly coordinating counter cation may increase the concentration of free enolate which could bind palladium. This hypothesis was tested by substituting the Na₂CO₃ base for Cs₂CO₃, which did, indeed, give **4.9** in a higher and more reproducible yield of 74%.

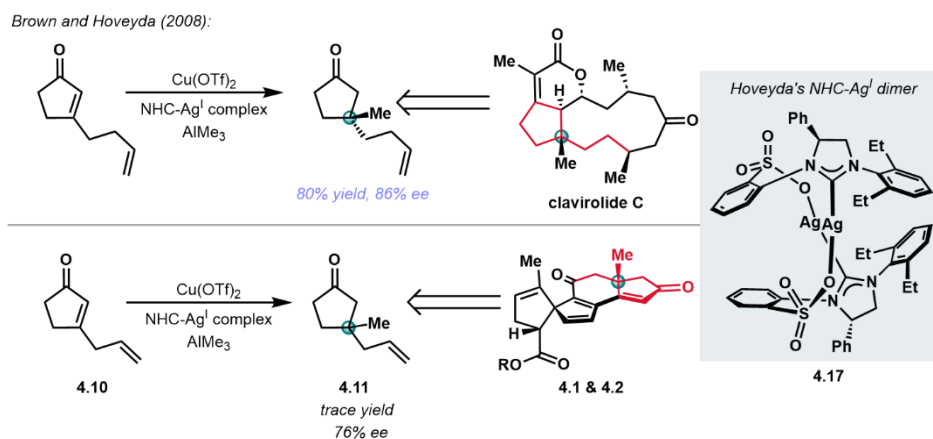


Figure 4.4. Using Hoveyda's Ag-NHC dimer for an asymmetric conjugate addition of a methyl group.

While this route gives **4.9** in a racemic fashion, we ultimately desired enantioenriched material. Precedent by Hoveyda and coworkers has showcased asymmetric conjugate additions of methyl groups into cyclopentenones in high yields and ee's by using a complex consisting of a silver metal center and a N-heterocyclic carbene (NHC) ligand (Figure 4.4, top).^{21,22} Application of Hoveyda's conditions to cyclopentenone gave the expected product in 76% ee but low yield (Figure 4.4, bottom). We hypothesize that the discrepancy between the reported and observed results is likely due to the purity of the synthesized Ag-NHC dimer, as well volatility of the product (**4.9**) which had previously presented issues in isolation. The purity of the complex may be affected by the source of Ag₂O used in the final step in the synthesis of the silver complex. This initial result is encouraging for an eventual asymmetric approach to the natural products, but further investigation is required.

4.4 Using Symmetry to Enable Synthesis of a Spiroononene Coupling Partner

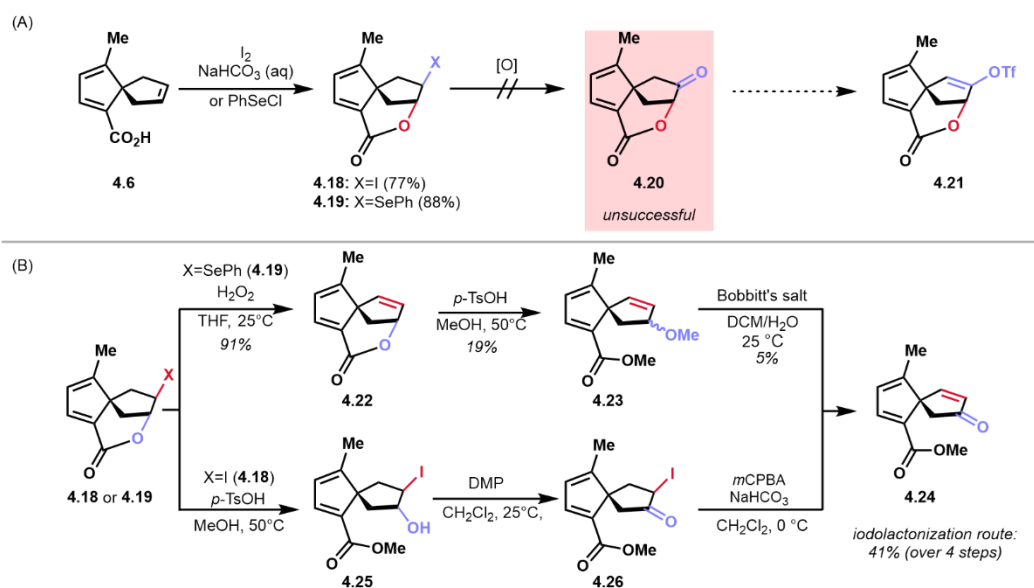


Figure 4.5. (A) Challenges in accessing initially targeted spirocyclic coupling partner (B) Using the symmetry of the spirocyclic system to access spiro-enone **4.24** through two pathways.

With reliable access to **4.9**, we turned our attention to the synthesis of a viable spiroononene coupling partner. Spiroononene **4.6** smoothly underwent iodo- and selenolactonization upon treatment with I₂ or PhSeCl, respectively (Figure 4.5A). At this point, we proposed that the iodide (**4.18**) or phenyl selenide (**4.19**) could be used as a handle for oxidation to ketone **4.20** through Kornblum-type oxidations²³ or seleno-Pummerer^{24,25} reactions. However, this approach was unsuccessful. Kornblum-type oxidations using various silver salts and trapping reagents (e.g. DMSO or N-oxides)²³ only gave decomposition of **4.18**. Additionally, attempts at Pummerer reactions only returned starting material or resulted in Reich oxidation to the allyl lactone (**4.22**).

In order to solve this challenge of oxidation, we decided to use the symmetry of the spirononene system to our advantage. Rather than using the carbon bearing the iodide or selenide for oxidation, the existing oxidation of the lactone alkoxy carbon could be used for further oxidation instead. This approach proved successful for both the selenolactone and iodolactone, albeit through different paths (Figure 4.5B). Reich oxidation²⁶ of selenolactone **4.19** gave allyl lactone **4.22**, which underwent acidic methanolysis to yield allyl ether **4.23** as a mixture of epimers, formed from ionization of a transient alcohol intermediate. Using Leadbeater's method,²⁷ this allyl ether underwent direct oxidation to the ketone (**4.24**) upon treatment with Bobbitt's salt.²⁸ Overall, this sequence proved to be low yielding and as such, an alternate sequence to ketone **4.20**, commencing instead from iodolactone **4.18**, was used.

Acidic methanolysis of iodolactone **4.18** gave halohydrin **4.25**, which was then oxidized to iodoketone **4.26** through treatment with Dess–Martin periodinane (DMP). Attempts at basic elimination of iodoketone **4.26** did not proceed to give the desired product (**4.24**). Despite this, **4.24** was obtained through an oxidative elimination of the iodide through a putative iodoso species.²⁹ This sequence commencing from spirononene **4.6** to spiro-enone **4.24** was telescoped to give an overall 41% yield of **4.24** over four steps. The eastern ring in spiro-enone **4.24** may appear to possess oxidation at the incorrect position relative to the originally targeted compound (**4.20** or **4.21**, Figure 4.5A). However, the two compounds are pseudo-enantiomeric and since the products are formed as racemates, the site of oxidation is ultimately inconsequential (see Figure 4.5A and B, red vs. blue sites).

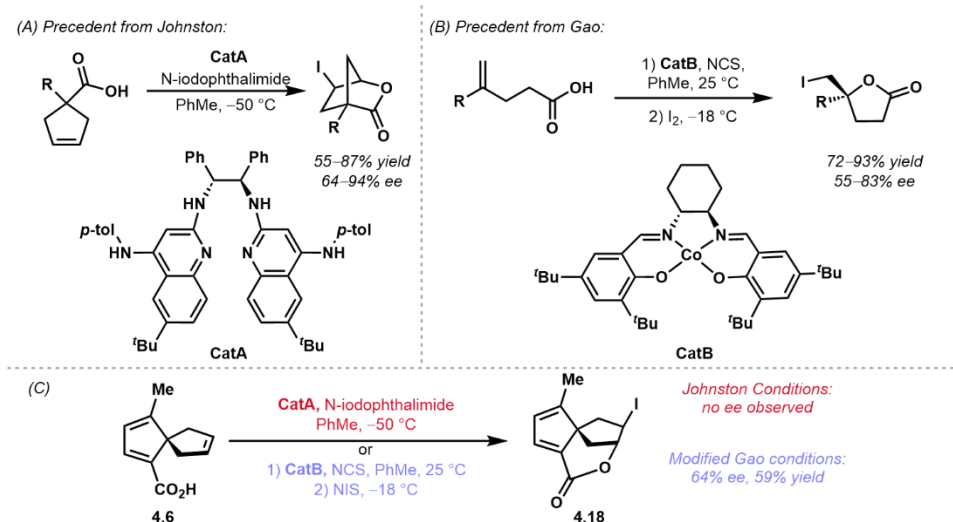


Figure 4.6. Using Johnston's and Gao's iodolactonization conditions to access enantioenriched **4.18**.

Although the compound was synthesized in a racemic fashion, there is potential for access to enantioenriched material through an asymmetric halolactonization.¹² We were inspired by two different catalyst systems for halolactonization reported by Johnston³⁰ and Gao,³¹ respectively (Figure 4.6). Johnston and coworkers used a designer,

chiral bis-amidine (BAM) organocatalyst (**4.26**, Figure 4.6A) to effect the asymmetric iodolactonization of cyclopentenyl carboxylates. Gao and coworkers utilized a chiral Co-salen complex (**CatA**) to induce asymmetry in the iodolactonization of acyclic olefinic acids. Although the reaction system reported by Johnston was more structurally similar to spirononene **4.6**, no enantioinduction was observed using the BAM organocatalyst (Figure 4.6A). Rather, Gao's conditions (Figure 4.6B) gave an encouraging initial result where the iodolactone product (**4.18**) was isolated in 50% ee. Preliminary attempts at optimization of these conditions involved screening different additives, iodine sources, temperatures, and metal centers.³² Among the conditions attempted, the most promising were those using NIS as the iodonium source, giving **4.18** in 67% ee and 59% yield (Figure 4.6C). For further optimization of these reaction parameters, future work may involve modifying the salen ligand backbone.³³

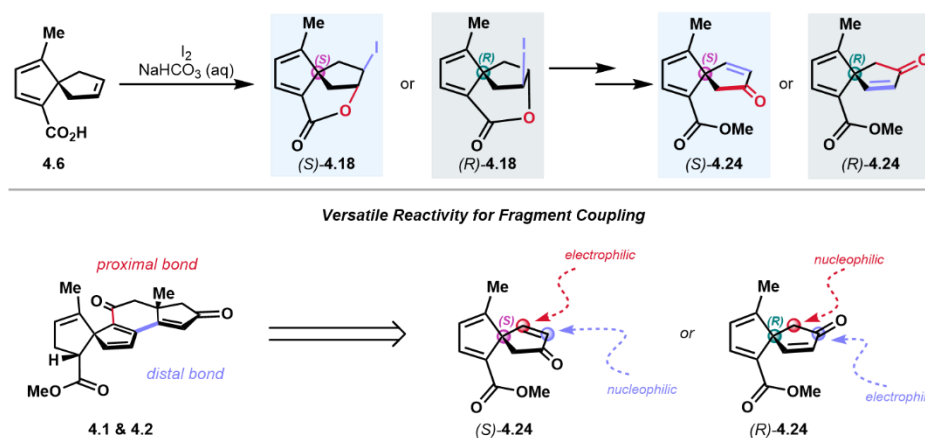


Figure 4.7. Outlining how the symmetry of spirononenes can be leveraged to enable synthesis.

The two enantiomers of spiro-enone **4.24** further exemplify the synthetic utility of symmetric spirononene compounds (Figure 4.7). When considering intermolecular coupling strategies with cyclopentenone **4.9**, the symmetry of spiro-enone **4.24** allows for “equivalent” bond formation at the same carbons of different enantiomers through complementary chemical approaches. In order to construct the framework of natural products **4.1** & **4.2** through intermolecular coupling of cyclopentenone **4.9** and spiro-enone **4.24**, it is helpful to consider the formation of “proximal” and “distal” C–C bonds on the spirononene fragment. When considering (*S*)-**4.24**, proximal bond formation may occur through electrophilic reactivity of the α,β -unsaturated ketone and distal bond formation may occur through the nucleophilic reactivity of the ketone α position through Morita-Baylis-Hillman reactivity. Conversely, (*R*)-**4.24** can undergo proximal bond formation through nucleophilic reactivity of the ketone α carbon and distal bond formation through the electrophilic carbonyl carbon. This symmetry-inspired strategy enables synthesis through the evaluation of numerous pathways toward fragment coupling as discussed in the next section.

4.5 Evaluation of Numerous Fragment Coupling Strategies

The first pathway to be investigated was a Heck cross coupling between cyclopentenone **4.9** and spiro-triflate **4.27**, formed from triflation of **4.24** (Figure 4.8A). Initial evaluation of Heck reaction conditions resulted in consumption of triflate **4.27** but no product was

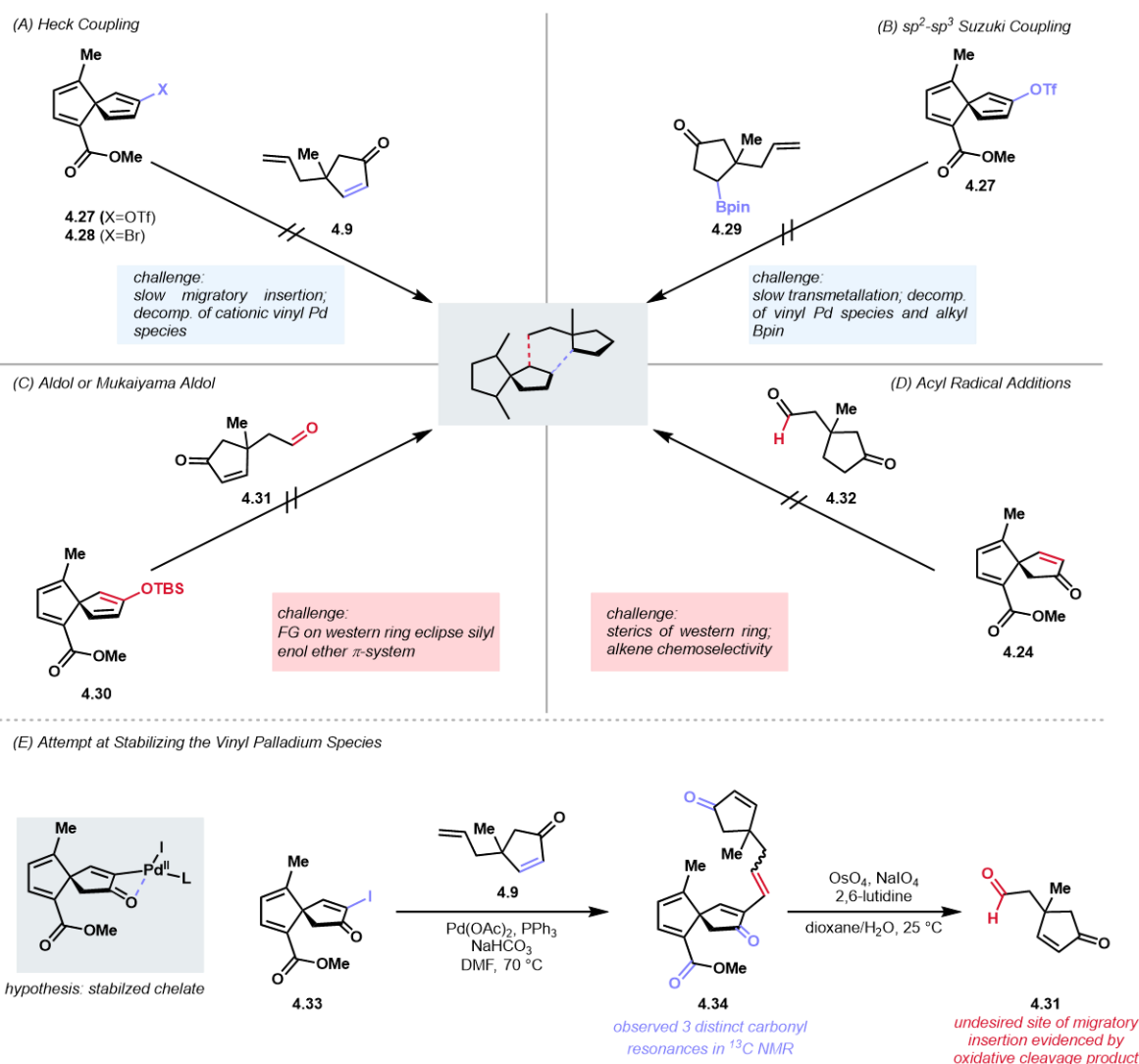


Figure 4.8. The evaluation of various fragment coupling approach is shown above: (A) Heck coupling (B) sp^3 - sp^2 Suzuki coupling (C) Aldol reactions (D) Acyl radical addition. (E) The results of testing the hypothesis of accessing a more stabilized vinyl palladium intermediate.

observed. This might be due to the instability of the more cationic vinyl palladium complex formed from oxidative addition into a vinyl triflate, which has been reported by Stille and Négri³⁴ in related systems. We hypothesized that a more coordinating anion such as a halide may prevent decomposition. This hypothesis was tested by synthesizing the corresponding vinyl bromide (**4.28**), but similar results were obtained. It was also considered that an oxidative Heck reaction may prove successful, as it can occur under

milder conditions (e.g. lower temperature).⁵ However, attempts at the synthesis of spiro-boronic acid or boronate coupling partner from triflate **4.27** were unsuccessful.

Another strategy toward this Heck coupling was to use α -iodo enone **4.33** as the oxidative addition precursor (Figure 4.8E). We hypothesized that the weakly coordinating ability of the adjacent carbonyl oxygen may stabilize the vinyl-palladium intermediate and avoid deleterious reactive pathways. In attempts at Heck reactivity with cyclopentenone **4.9**, trace amounts of some adduct of **4.9** and **4.33** were isolated. However, from the NMR spectra, it was unclear as to where the fragment coupling had occurred. Insight into the identity of the adduct was obtained through ozonolysis. The unknown adduct (**4.34**) was treated with oxidative cleavage conditions³⁵ and in the ¹H NMR of the crude reaction mixture, aldehyde **4.31** was observed. This result indicates that a Heck reaction of α -iodo enone **4.33** and cyclopentenone **4.9** occurred with preferential migratory insertion of the terminal olefin rather than enone. This highlights the challenge that the steric hindrance of the cyclopentenone provides. Despite the lack of immediate success, this result was more encouraging than reactions with spiro-(pseudo)halides **4.27** or **4.28**.

In order to circumvent a challenging migratory insertion, we decided to use a Suzuki coupling which would instead rely on a transmetalation step (Figure 4.8B). To this end, we synthesized cyclopentyl pinacol boronate (Bpin) **4.29** through copper catalyzed boro-cuprate addition of cyclopentenone **4.9**. Attempts at an sp^3 - sp^2 Suzuki coupling,³⁶ however, gave decomposition of both coupling partners. Triflate **4.27** reverted to spiro-enone **4.24**, likely through trapping of vinyl palladium species with water or hydroxide. The alkyl palladium species formed from transmetalation of Bpin **4.29** underwent β -hydride elimination to return cyclopentenone **4.9**.

With unsuccessful intermolecular formation of the distal bond, we turned our attention to first forming the proximal bond and then forming the distal bond in an intramolecular fashion. For proximal bond formation, we sought to use an aldol reaction of **4.24** or Mukaiyama aldol reaction of silyl enol ether **4.30** with aldehyde **4.31** (Figure 4.8C), which was formed through oxidative cleavage of terminal olefin **4.9**. However, reaction conditions involving a variety of Lewis acids were screened and only recovered aldehyde **4.31** and desilylation of **4.30** to spiro-enone **4.24** were observed. In these failed cases of aldol reactivity of spiroenones **4.24** and **4.30**, it is possible that the substituents of the western ring eclipse the π -system of the eastern ring, precluding successful attack of the aldehyde. An umpolung approach was also used wherein aldehyde **4.32** was used as an acyl radical precursor³⁷ for addition into spiro-enone **4.24** (Figure 4.8D), but the sterics of the western ring still prevented success, along with the added issue of alkene chemoselectivity.

In order to reduce the steric encumbrance imposed by the western ring, we posited that reduction of the α,β -unsaturated ester may result in a bisecting angle of the ester

substituent relative to the π -system of the eastern ring (Figure 4.9). Direct reduction of spiro-enone **4.24** presented chemoselectivity issues regarding reduction of the ene-ester over the enone. However, reduction of iodolactone **4.18** cleanly gave the desired reduction product, which was verified through x-ray diffraction of a single crystal of **4.36**. Converting the reduced iodolactone (**4.36**) to the desired spirocycle (**4.35**) did not proceed due to challenges with the oxidative elimination step, (i.e. observation of undesired

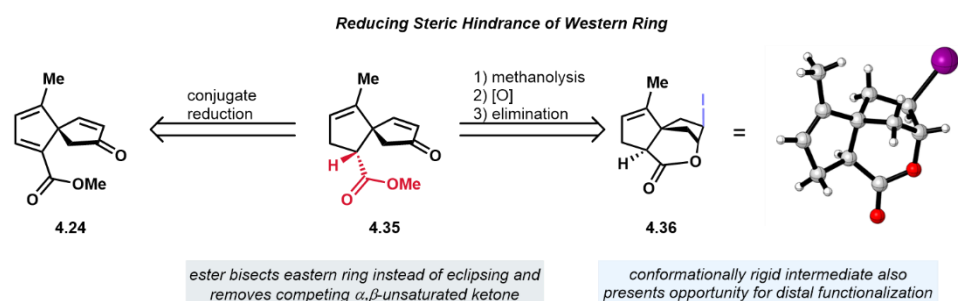


Figure 4.9. Hypothesis for reducing steric encumbrance and a resulting opportunity discovered by analysis of the crystal structure of **4.36**.

epoxidation). Despite this, analysis of the crystal structure of **4.36** indicated that reduction of the ene-ester results in a puckering of the eastern ring, such that the alkyl halide moiety is positioned away from the western ring (Figure 4.9, right). This new steric environment presented an opportunity for distal bond formation which may be less affected by the western ring.

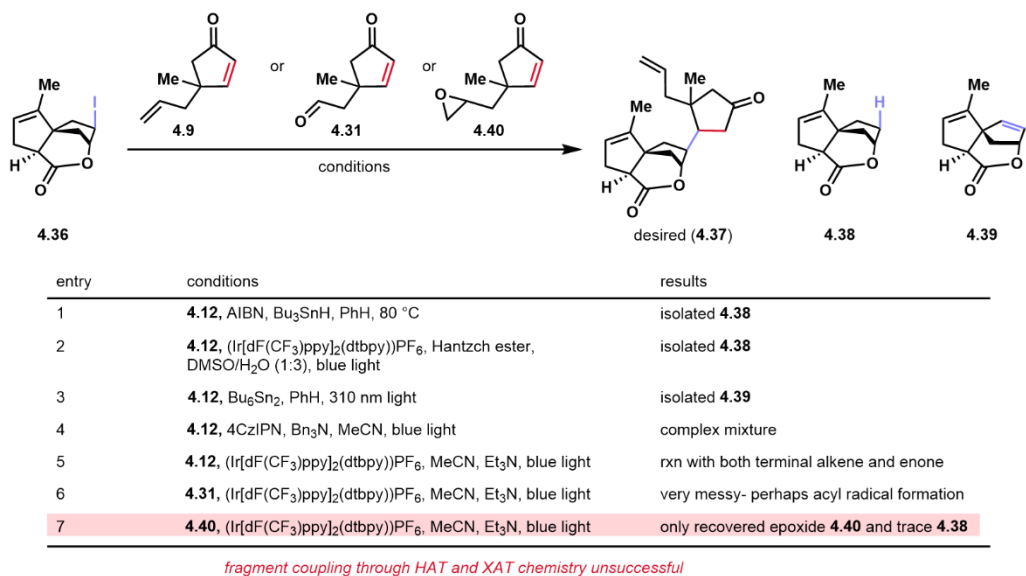


Table 4.1. Using **4.36** for Giese additions with various cyclopentenone partners.

We hypothesized that reduced iodolactone **4.36** would be a good precursor for the generation of an alkyl radical which could perform a Giese addition into cyclopentenone **4.9** (Table 4.1). Treatment of a solution of **4.36** and **4.9** with AIBN and Bu₃SnH resulted in protodehalogenation to give **4.38** (Table 4.1, entry 1), indicating that the desired alkyl radical was indeed formed but trapped by H-atom transfer (HAT) from Bu₃SnH faster than Giese addition with cyclopentenone **4.9**. In order to minimize concentration of reactive stannyl radicals, we turned to photoredox conditions.³⁸ Jiu and coworkers³⁹ reported Giese additions of heteroaryl halides under photoredox conditions method where undesired HAT reactivity was avoided by utilizing a DMSO/H₂O solvent system and Hantzsch ester as the HAT reagent, due to its reduced solubility in water. However, in our system, undesired HAT reactivity was still observed through the isolation of product **4.38** (Table 4.1, entry 2).

We sought to prevent protodehalogenation by using X-atom transfer (XAT) chemistry which avoids the use of a HAT donor. This was first attempted by subjecting iodolactone **4.36** and cyclopentenone **4.9** to Bu₆Sn₂ under irradiation of 310 nm light lamps.⁴⁰ However, under these conditions, the elimination product (**4.39**) was observed rather than desired Giese addition adduct **4.37** (Table 4.1, entry 3). This suggests that once again, an alkyl radical was indeed formed from the iodolactone (**4.36**), but H-atom abstraction by a stannyl radical was faster than addition into cyclopentenone **4.9**. Leonori and coworkers reported XAT conditions using photoredox catalysis which relied on fast and irreversible XAT by α -aminoalkyl radicals.⁴¹ When a mixture of reduced iodolactone **4.36** and cyclopentenone **4.9** was subject to these conditions, an adduct of the two starting materials was indeed observed, as evidenced by three distinct carbonyl resonances in the ¹³C NMR (Table 4.1, entry 5). However, the characteristic ¹H shifts of the alkene protons of both the enone and allyl fragments which would arise from partner **4.9** were not observed. This suggested that although an intermolecular addition of the alkyl radical resulting from reduced iodolactone **4.36** into coupling partner **4.9** occurred, it was accompanied by an additional intramolecular cyclization. At this point, however, it was unclear whether the initial intermolecular reaction occurred with the enone or allyl moiety of cyclopentenone **4.9**. We hypothesized that if addition into the enone preceded an intramolecular cyclization onto the allyl fragment, removing the allyl alkene should prevent this undesired over-reactivity. To this end, the allyl fragment was masked by epoxidation of **4.9** to give epoxide **4.40**. Reaction of **4.36** with epoxide **4.40** under Leonori's conditions unfortunately only returned both starting materials (Table 4.1, entry 7), indicating that intermolecular reaction with the enone was likely slower than reaction with the allyl fragment. The cause of this is likely the persistent challenge of the steric hindrance provided by the quaternary center adjacent to the enone in **4.9**.

4.6 Revising Synthetic Strategy: A Linear Approach to Urceoloids A & B

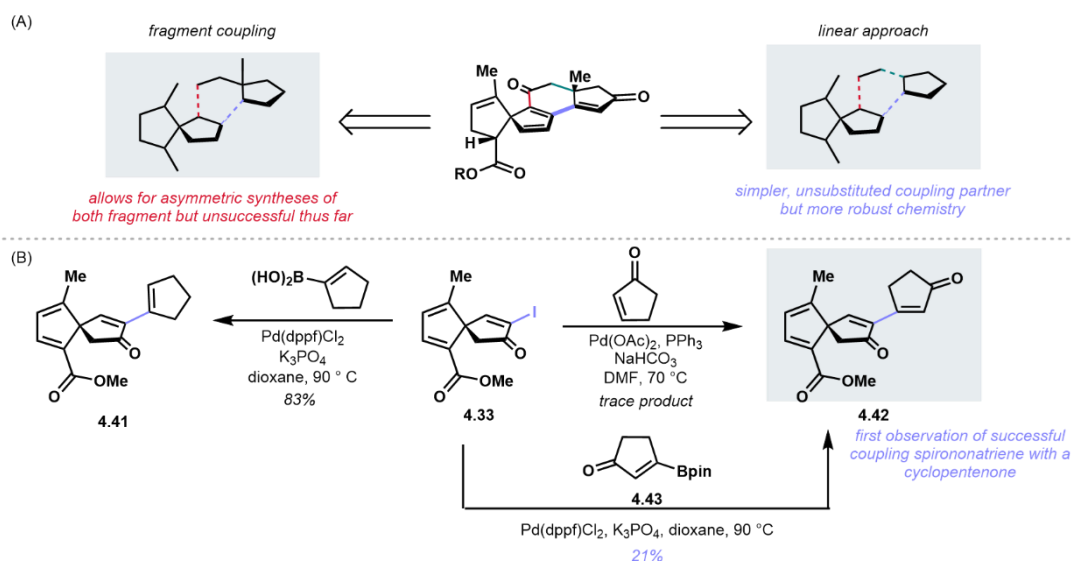


Figure 4.10. (A) Revision of synthetic strategy to a linear approach. (B) Success in cross coupling of simple cyclopentenone coupling partners.

Following these results, we turned to a new synthetic route which would avoid the use of the functionalized, more hindered enone **4.9** and opt for a simpler building block. In this strategy, we envisioned first forming the distal bond between some spirocyclic fragment and a simple cyclopentyl coupling partner and then forging the final six-membered ring of the urceoloid core by connecting a two-carbon fragment (Figure 4.10A). We hypothesized that the best spirocyclic fragment for this would be α -iodo enone **4.33** since it had shown more promising results as compared to other vinyl (pseudo)halides such as **4.27** and **4.28**. Indeed, in an initial reaction with cyclopentenone, a desired

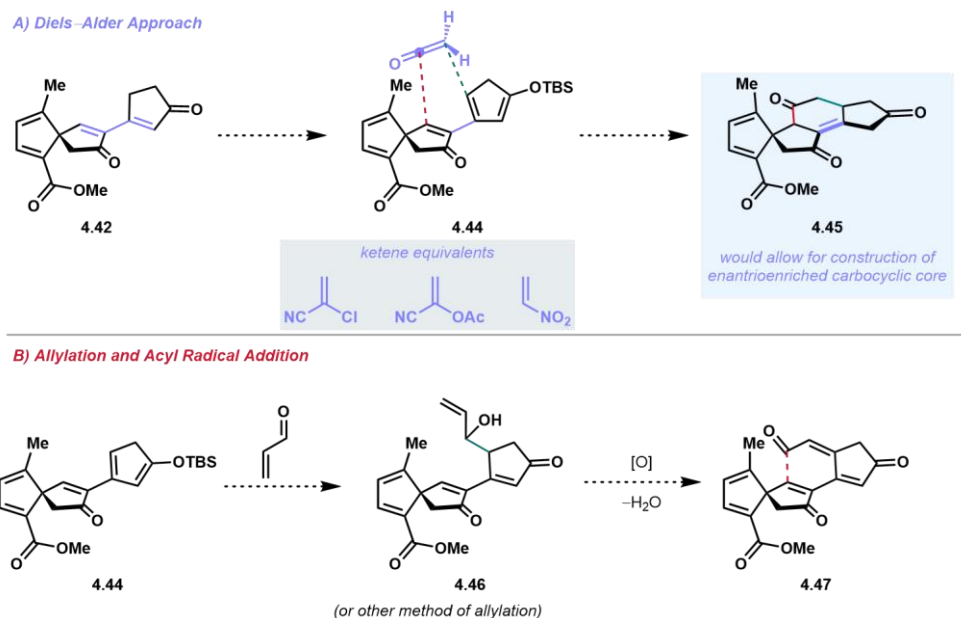


Figure 4.11. Potential paths forward toward construction of the urceoloids core: (A) Diels–Alder strategy. (B) Allylation and intramolecular cyclization approach.

fragment coupling product (**4.42**) was observed for the first time, albeit in trace amounts (Figure 4.10B). Despite removing the steric hindrance, the Heck reaction of cyclic enones remains a synthetic challenge. We hypothesized that an sp^2 - sp^2 Suzuki coupling may be a more robust reaction⁴² and indeed, reaction of **4.33** with simple cyclopentenyl boronic acid gave the desired product (**4.41**) in 83% yield. Following this success, we sought to access greater amounts of the desired “Heck product” (**4.42**) through a Suzuki coupling of **4.33** with β -vinyl Bpin **4.43**. While the yield was still low (21%), the desired product was, indeed, obtained in sufficient amounts for characterization, showcasing a potential for success of this strategy.

This revised, linear approach presents a promising path toward the ultimate synthesis of urceoloids A & B. In order to build the final ring of the urceoloids core, one may envision various methods to connect a two-carbon fragment. The most efficient tactic, in terms of step count, would be a Diels–Alder reaction between a ketene equivalent and the dendralene unit of silyl enol ether **4.44** (Figure 4.11A). In such a reaction, the diene should be sufficiently electronically activated and properly polarized to give the desired product (**4.55**) rather than the undesired reaction with other dienes in the spirononene (**4.44**). One could also consider stepwise approaches of introducing this two-carbon unit (Figure 4.11B). For example, a Mukaiyama aldol reaction of silyl enol ether **4.44** and acrolein could give allyl alcohol **4.46**, which could be carried forward to **4.47** in order to close the six-membered through an intramolecular acyl radical addition.

4.7 Conclusion

Endeavors toward the total synthesis of urceoloids A & B have been a valuable exercise in gaining new insight into spirononenes, an underexplored class of compounds. Failure of an initial Heck coupling strategy led to a second-generation approach which allowed for exploration of various spirocyclic intermediates. Notably, this second-generation strategy led to the realization of how the symmetry of spirononenes can be leveraged to enable synthetic progress through the paradigms of “distal” and “proximal” functionalization, relative to the spirocyclic carbon. This work also led to the first foray into the asymmetric synthesis of spirononenes through an asymmetric halolactonization. Additionally, initial studies have provided an enantioenriched cyclopentenone coupling partner, albeit in low yield. While further investigations regarding enantioinduction in both fragments is still needed, the initial results are encouraging.

After probing various fragment coupling approaches, it was evident that the envisioned strategy was plagued by the challenge of steric hindrance for both coupling partners. This aspect was clearly demonstrated by preferential reactivity of the sterically accessible terminal olefin of **4.9** instead of the electronically activated enone. These results showcase the difficulty of fragment coupling strategies, both generally and specifically with spirononenes.⁴³ This prompted us to enact a final revision in synthetic

strategy – using a linear approach to install a simpler five-membered motif. By relying on a simpler, but more robust approach, we found success in cross-coupling a spirononene bearing α -iodo enone (**4.33**) with β -Bpin cyclopentenone (**4.43**). This new strategy paves the way for further investigations toward the synthesis of urceoloids A & B. Even more notably, this demonstrates the first example of a C–C bond formation with a functionalized spirononene. Such insightful results could only be reached on the heels of many failures, speaking to the merits of total synthesis. While further work remains to be done to complete the first synthesis of the urceoloids A & B, the work presented herein embodies the spirit of exploration in total synthesis that K.C. Nicolau has elegantly stated.⁴⁴ Or as is more colloquially expressed by the adage, “It’s the journey, not the destination.”

4.8 Experimental Contributors

Project design and development was carried out by Prof. Richmond Sarpong (R.S.) and Karan Goyal (K.G.). Experimentation was largely conducted by K.G with guidance from R.S. Rafael Rippel (R.R.) and Nico Homfeldt (N.H.) assisted with scale-up and reaction optimization with guidance from K.G. and R.S.

4.9 Experimental Information

4.9.1 General Information

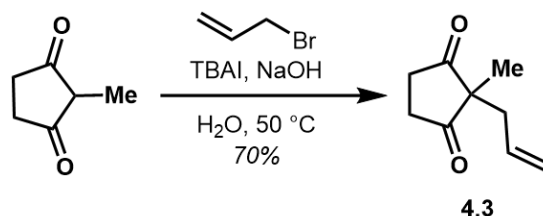
Unless otherwise stated, commercial reagents were purchased and used without purification. Solvents including tetrahydrofuran (THF), diethylether (Et₂O), methanol (MeOH), and benzene (PhH) were dried by passage through activated alumina columns using argon in a Glass Contour solvent purification system. Dichloroethane (DCE, dry and packaged under nitrogen) and dimethylsulfoxide (DMSO, dry and packaged under nitrogen) were used without purification. Dichloromethane (DCM) was freshly distilled over calcium hydride under a N₂ atmosphere. Deuterated solvents were purchased from Cambridge Isotope Laboratories and were used without further purification unless otherwise specified. Deuterated acetic acid was purchased from Sigma Aldrich.

Unless otherwise stated, all reactions were performed in flame-dried or oven-dried glassware under an atmosphere of positive nitrogen pressure using Teflon-coated stir bars. Air and moisture-sensitive liquids were transferred via syringe through rubber septa. Solids were added under inert gas or were dissolved in the appropriate solvent and added via syringe and needle. Reactions ran above room temperature (20–25 °C) were heated in a metal block or oil bath with a thermocouple. Low temperature reactions were carried out in a Dewar flask filled with isopropanol/dry ice (–78 °C) or water/ice (0 °C). Organic solutions were concentrated under reduced pressure on an IKA temperature-controlled rotary evaporator equipped with a dry ice/isopropanol condenser. Reaction progress was monitored by thin layer chromatography (TLC). TLC and preparative TLC were performed on glass-backed Silicycle SiliaPlate 250 μ m thickness, 60 Å porosity F-254 precoated plates. Flash column chromatography was performed with either glass columns using Silicycle silica gel (40– 63 μ m particle size) or with a Yamazen Smart Flash EPCLC W-

Prep 2XY (dual channel) automated flash chromatography system on prefilled, premium, universal columns using ACS grade solvents. Compounds were visualized with UV light (254 nm) and stained with aqueous potassium permanganate (KMnO₄) or *p*-anisaldehyde and heat.

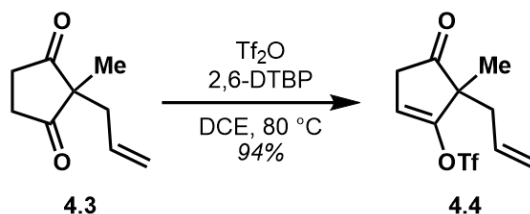
NMR spectral data were obtained using deuterated solvents, obtained from Cambridge Isotope Laboratories, Inc. ¹H NMR, proton-decoupled ¹³C NMR, and ¹⁹F NMR data were recorded on Bruker AV-300, AVQ-400, AVB-400, JEOL-400, NEO-500, AV-600 and AV-700 spectrometers using CDCl₃ as solvent at 20–23 °C. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal (δ 7.26 for ¹H NMR & δ 77.16 for ¹³C NMR in CDCl₃). Data for ¹H, ¹³C, and ¹⁹F spectroscopy are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent), coupling constant (Hz), integration. All raw FID files were processed, and the spectra analyzed, using the program MestReNOVA 11.0 from Mestrelab Research S. L. High-resolution mass spectra (HRMS) were obtained from the Mass Spectral Facility at the University of California, Berkeley, on a Finnigan/Thermo LTQ-FT instrument (ESI). Data acquisition and processing were performed using the Xcalibur™ software. Chiral HPLC analysis was conducted using a Waters Alliance e2695. Separations Module equipped with ChiralPak® columns. Data was processed and analyzed using Empower®3 software. HPLC grade isopropanol (IPA) and hexanes were used for HPLC analysis.

4.9.2 Experimental Procedures and Characterization Data



2-allyl-2-methylcyclopentane-1,3-dione (4.3): This compound was prepared as reported by Han and coworkers³ to give **4.3** as a pale-yellow oil (1.88 g, 60%). The ¹H NMR spectrum was consistent with results reported in the literature.³

¹H NMR (500 MHz, CDCl₃) δ 7.37 (d, *J* = 2.3 Hz, 1H), 5.95 (t, *J* = 1.9 Hz, 1H), 2.97 (d, *J* = 15.0 Hz, 2H), 2.16 (d, *J* = 14.5 Hz, 2H), 1.86 (d, *J* = 1.6 Hz, 3H).



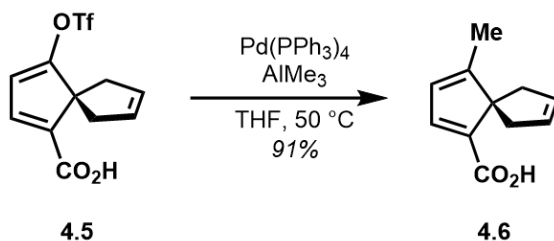
5-allyl-5-methyl-4-oxocyclopent-1-en-1-yl trifluoromethanesulfonate (4.4): This procedure was adapted from the literature.⁴ A stirred mixture of **4.3** (573 mg, 3.76 mmol, 1 equiv) and 2,6-di-*tert*-butylpyridine (1.8 mL, 8.1 mmol, 2.1 equiv) in dry DCE (18.8 mL, 0.2 M) was cooled to 0 °C. To this mixture, a solution of Tf₂O (1.3 mL, 7.9 mmol, 2.1 equiv) in dry DCE (3.3 mL, 1.4 M) was added in a steady stream under an inert atmosphere. The resulting reaction mixture was allowed to warm to ambient temperature (25 °C) and then heated to 80 °C. After stirring for 4 h, the reaction mixture was allowed to cool to room temperature. The mixture was diluted with EtOAc (25 mL) and ice was slowly added. The mixture was poured into a separatory funnel, washed with 4 M HCl (3 x 25 mL) and brine (1 x 25 mL). The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The resulting brown residue was purified by silica gel flash column chromatography (0–20% EtOAc/hexanes gradient) to give 1.0 g (94%) of **4.4** as an orange oil.

¹H NMR (500 MHz, CDCl₃) δ 5.96 (t, *J* = 2.5 Hz, 1H), 5.66 – 5.54 (m, 1H), 5.12 – 5.04 (m, 2H), 3.26 – 2.77 (m, 2H), 2.33 (dddt, *J* = 48.5, 13.9, 7.2, 1.1 Hz, 2H), 1.21 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 212.2, 151.4, 131.4, 120.0, 110.4, 53.8, 41.5, 39.9, 20.1.

¹⁹F NMR (471 MHz, CDCl₃) δ –73.6.

HRMS (EI): Calcd for ([M], C₁₀H₁₁FO₄S)⁺: *m/z* = 284.0325, found 284.0327

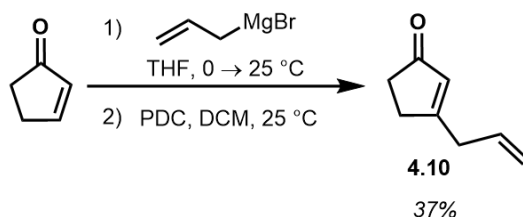


4-methylspiro[4.4]nona-1,3,7-triene-1-carboxylic acid (4.6): This procedure was adapted from a report in the literature.² To a mixture of **4.5** (1.44 g, 4.64 mmol, 1 equiv) and Pd(PPh₃)₄ (268 mg, 0.232 mmol, 0.05 equiv) in THF (46.4 mL, 0.1 M) at 25 °C under an inert atmosphere was added AlMe₃ (9.3 mL, 4.0 equiv, 2.0 M solution in PhMe) in a steady stream. The reaction mixture was heated to 50 °C and stirred for 20 h. The reaction mixture was cooled to 0 °C in an ice bath and then MeOH () was added dropwise to the stirred mixture until bubbling ceased. The mixture was poured into a separatory funnel containing ice and acidified to pH=1 with 1 M HCl. The aqueous layer was extracted with EtOAc (3 x 75 mL). The organic layers were combined, washed with brine (3 x 75 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (5% EtOAc/2% AcOH/hexanes → 10% EtOAc/2% AcOH/hexanes) to give 741 mg (91%) of **4.6** as a yellow powder.

^1H NMR (500 MHz, CDCl_3) δ 7.37 (d, J = 2.3 Hz, 1H), 5.95 (t, J = 1.9 Hz, 1H), 2.97 (d, J = 15.0 Hz, 2H), 2.16 (d, J = 14.5 Hz, 2H), 1.86 (d, J = 1.6 Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 168.8, 166.7, 145.0, 142.3, 130.2, 123.0, 60.4, 38.2, 13.4.

HRMS (ESI): Calcd for $([\text{M}+\text{H}], \text{C}_{11}\text{H}_{13}\text{O}_2)^+$: m/z = 177.0910, found 177.0909

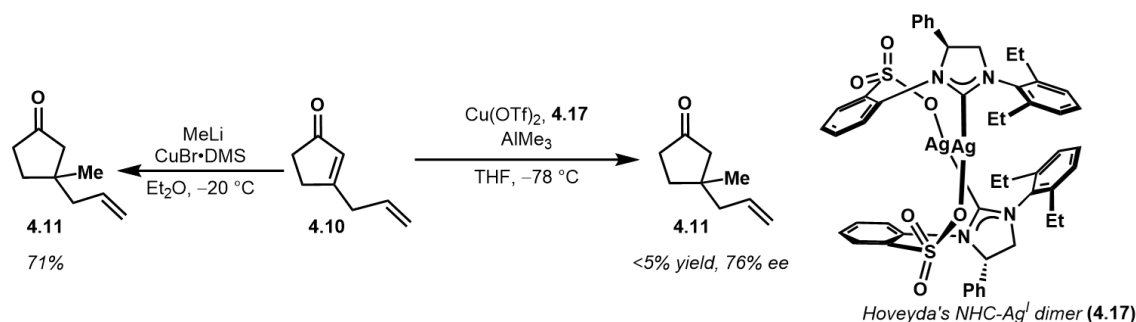


3-allylcyclopent-2-en-1-one (4.10**)**: This procedure was adapted from a report by Whitwood and coworkers.¹⁴ To a solution of 2-cyclopenten-1-one (4.1 mL, 49 mmol, 1 equiv) in THF (8.1 mL, 6 M) cooled to 0 °C in an ice bath was added a solution of allylmagnesium bromide (58 mL, 1.2 equiv, 1.0 M solution in Et_2O) diluted in THF (32 mL) in a slow stream under an inert atmosphere. The reaction mixture was allowed to warm to ambient temperature (25 °C) and stirred for 2 hours. At this point, the reaction mixture was cooled to 0 °C and a saturated solution of aqueous NH_4Cl (50 mL) was slowly added. The resulted heterogenous mixture was decanted into a separatory funnel, diluted with Et_2O (50 mL), and washed with brine (3 x 50 mL). The organic layer was separated, dried over MgSO_4 , and concentrated under reduced pressure. Note: Due to concerns of volatility of the intermediate, heating was not used during rotary evaporation. To the crude yellow oil was added CH_2Cl_2 (75 mL, 0.65 M) and PDC (27 g, 1.5 equiv) under ambient atmosphere. The mixture was stirred for 21 h, diluted with Et_2O (100 mL) and then filtered through a silica pad. The filtrate was concentrated and the resulting residue were purified by silica gel flash column chromatography (20% EtOAc /hexanes – 30% EtOAc /hexanes gradient) to give 2.25 g (37%) of **4.10** as a pale-yellow oil. Note- this compound has a reported boiling point of 110 °C so extended periods under high vacuum were avoided.

^1H NMR (700 MHz, CDCl_3) δ 5.97 (q, J = 1.6 Hz, 1H), 5.87 (ddt, J = 16.1, 10.9, 6.9 Hz, 1H), 5.20 – 5.15 (m, 2H), 3.16 (d, J = 6.9 Hz, 2H), 2.60 (dt, J = 7.1, 1.8 Hz, 2H), 2.44 – 2.40 (m, 2H).

^{13}C NMR (101 MHz, CDCl_3) δ 209.9, 180.6, 132.9, 130.2, 118.4, 60.5, 37.9, 35.5, 31.4, 21.1, 14.3.

HRMS (EI): Calcd for $([\text{M}], \text{C}_8\text{H}_{10}\text{O})^+$: m/z = 122.0732, found 122.0730



3-allyl-3-methylcyclopentan-1-one (4.11): This procedure was adapted from a report in the literature.⁴⁵ To a suspension of CuBr·DMS (4.1 g, 20 mmol, 5 equiv) in THF (84 mL, 0.05 M) cooled to 0 °C in an ice bath was added a solution of methyllithium (24.0 mL, 9.6 equiv, 1.6 M solution in Et₂O) in a slow stream under an inert atmosphere. This mixture was stirred at 0 °C for 20 minutes, then cooled to –20 °C. At this point, a solution of **4.10** (490 mg, 4.0 mmol, 1 equiv) in Et₂O (16.7 mL, 0.2 M) was added in a slow stream and the reaction was stirred at –20 °C for 20 minutes. To this mixture, an aqueous solution of saturated NH₄Cl (100 mL) was slowly added. The resulting heterogenous mixture was then filtered through a celite pad and the filtrate was washed with brine (3 x 100 mL). The organic layer was dried over MgSO₄ and concentrated under reduced pressure without heating the water bath due to volatility concerns. The crude residue was purified by silica gel flash column chromatography (10% Et₂O/hexanes – 20% Et₂O/hexanes gradient) to give 395 mg (71%) of **4.11** as a colorless oil. Note- purification was often not necessary as the crude compound was relatively pure ¹H NMR analysis and could be used in the next step without issues.

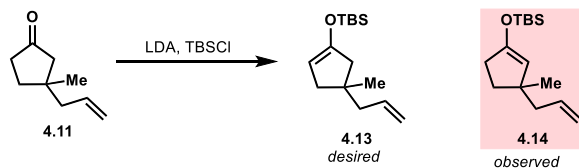
Hoveyda's procedure²² was used to access enantioenriched **4.11** from **4.10**. A solution of chiral silver complex (16.6 mg, 0.0153 mmol, 0.025 equiv), Cu(OTf)₂ (11.1 mg, 0.0307 mmol, 0.050 equiv), and **4.10** (75.0 mg, 0.614 mmol, 1.0 equiv) in THF (6.14 mL, 0.1 M) was stirred at 25 °C for 5 minutes. This solution was then cooled to –78 °C and a solution of AlMe₃ (2.0 in PhMe, 0.92 mL, 1.84 mmol, 3.0 equiv) was added. After stirring for 48 h at –78 °C, a saturated aqueous solution of Rochelle's salt (2 mL) was added and the mixture was allowed to warm to 25 °C. The mixture was stirred for an additional 30 minutes and the aqueous layer was extracted with Et₂O (3 x 5 mL). The organic layer was dried over MgSO₄ and concentrated under reduced pressure without heating the water bath. The resulting residue was purified by preparatory TLC (20% Et₂O/hexanes) to give the product (**4.11**) in trace amounts (0.3 mg, <5%) but 76% ee.

¹H NMR (500 MHz, CDCl₃) δ 5.80 (ddt, *J* = 17.5, 10.2, 7.4 Hz, 1H), 5.13 – 5.02 (m, 2H), 2.33 – 2.26 (m, 2H), 2.18 – 2.10 (m, 3H), 2.04 – 1.96 (m, 1H), 1.87 (dt, *J* = 13.0, 8.5 Hz, 1H), 1.74 (dddd, *J* = 12.9, 7.9, 6.4, 1.3 Hz, 1H), 1.07 (s, 3H).

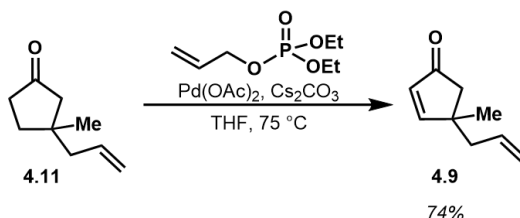
¹³C NMR (151 MHz, CDCl₃) δ 219.8, 134.6, 118.1, 51.7, 45.8, 39.6, 37.0, 34.8, 25.7.

HRMS (EI): Calcd for $([M], C_9H_{14}O)^+$: $m/z = 138.1039$, found 138.1045

Chiral HPLC data: IC3 chiral column, 1% IPA/hexanes, 1 mL/min, $t_R(\text{minor}) = 15.2$ min, $t_R(\text{major}) = 15.6$ min, $\lambda = 300$ nm



((3-allyl-3-methylcyclopent-1-en-1-yl)oxy)(tert-butyl)dimethylsilane (4.14): To a stirred solution of **4.11** (10 mg, 0.072 mmol, 1 equiv) in MeCN (0.7 mL, 0.2 M) was added pempidine (0.026 mL, 0.14 mmol, 2 equiv) and TBSOTf (0.033 mL, 0.14 mmol, 2 equiv) at 25 °C under an inert atmosphere. After 1 h, the mixture was diluted with Et₂O (1 mL) and washed with a saturated solution of aqueous NaHCO₃ (1 x 1 mL) and brine (1 x 1 mL). The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification of the crude residue by preparatory TLC (30% EtOAc/Hex) gave a still impure residue. Despite this, the identity of the constitutional isomer could be confirmed through ¹H-¹H COSY analysis where no correlation was observed between the vinyl singlet (δ 4.50) and resonances in the alkyl region (δ 1.50 – 2.50).

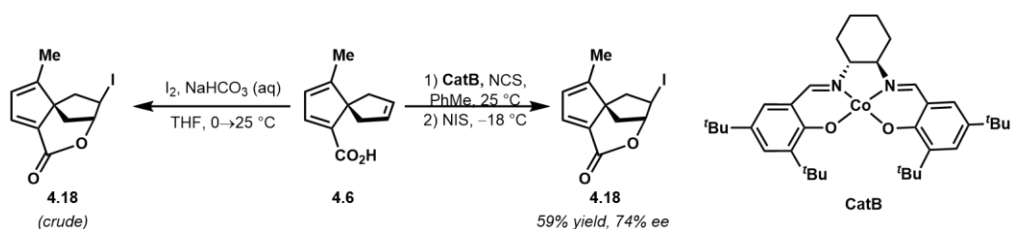


4-allyl-4-methylcyclopent-2-en-1-one (4.9): This procedure was adapted from a report by Arisha and coworkers.²⁰ To a solution of **4.11** (370 mg, 2.68 mmol, 1.0 equiv) and allyl diethyl phosphate (0.95 mL, 5.35 mmol, 2.0 equiv) in THF (13.4 mL, 0.2 M) was added Cs₂CO₃ (1.92 g, 5.89 mmol, 2.2 equiv) and Pd(OAc)₂ (120 mg, 0.535 mmol, 0.2 equiv). The mixture was sparged with Ar for 5 minutes and then heated to reflux (75 °C) for 16 h. The reaction mixture was allowed to cool to 25 °C and then filtered through a silica pad, eluting with Et₂O. The filtrate was concentrated under reduced pressure and the resulting brown oil was purified through silica gel flash column chromatography (10% Et₂O/hexanes – 30% Et₂O/hexanes gradient) to give 257 mg (71%) of **4.9** as a pale-yellow oil.

¹H NMR (500 MHz, CDCl₃) δ 7.43 (d, $J = 5.6$ Hz, 1H), 6.05 (d, $J = 5.6$ Hz, 1H), 5.74 – 5.63 (m, 1H), 5.13 – 5.04 (m, 2H), 2.51 – 2.01 (m, 4H), 1.23 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 209.8, 172.4, 133.6, 132.3, 119.0, 47.4, 44.9, 44.9, 26.2.

HRMS (EI): Calcd for $([M], C_9H_{12}O)^+$: $m/z = 136.0890$, found 136.0890



4-iodo-6-methyl-4,5-dihydro-1H,3H-3,5a-methanocyclopenta[c]oxepin-1-one (**4.18**):

This procedure was adapted from a literature report.⁴⁶ To a solution of **4.6** (1.0 g, 5.7 mmol, 1 equiv) in THF (41 mL, 0.14 M) cooled to 0 °C was added an aqueous solution of saturated NaHCO₃ (76 mL) under ambient atmosphere, followed by the addition of a solution of I₂ in THF (2.16 g I₂ in 21.6 mL THF, 8.5 mmol, 1.5 equiv). The reaction vessel was stirred in the dark at 25 °C for 12 h. The reaction mixture was poured into a separatory funnel containing ice, and an aqueous solution of saturated Na₂S₂O₃ was then added. The aqueous layer was extracted with Et₂O (3 x 100 mL). The organic layers were combined, dried over MgSO₄, and concentrated under reduced pressure to give a 1.67 g (97%) of an off-white wax, which was used in the next step without purification.

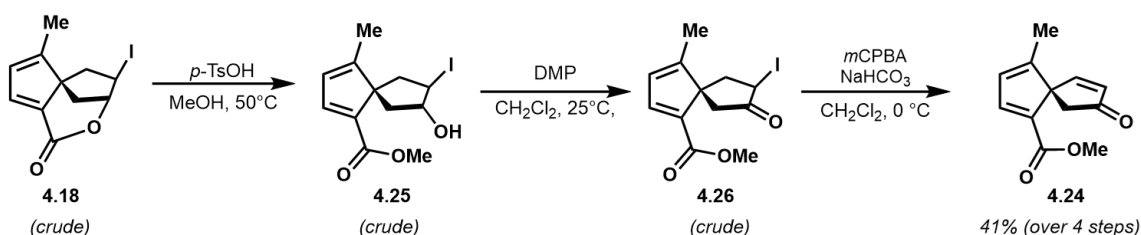
Enantioenriched **4.18** was accessed by adapting Gao's procedure.³¹ A solution of Co-salen complex **Cat1** (13.7 mg, 0.057 mmol, 0.40 equiv) and N-chlorosuccinimide (1.9 mg, 0.014 mmol, 0.25 equiv) in PhMe (2.7 mL, 0.02 M) was stirred for 30 minutes at 25 °C. The resulting black solution was cooled to -18 °C and then N-iodosuccinimide (17.9 mg, 0.080 mmol, 1.4 equiv) was added, followed by **4.6** (10.0 mg, 0.057 mmol, 1.0 equiv). The mixture was stirred at -18 °C for 12 h and then quenched by the addition of saturated aqueous Na₂S₂O₃ solution (1 mL). The aqueous layer was then extracted with EtOAc (3 x 5 mL). The organic layers were combined, dried over MgSO₄, and concentrated under reduced pressure to give a crude off-white wax, which was used in the next step without purification. The crude residue was purified by preparatory TLC (30% EtOAc/hexanes) to give 11.0 mg (59%) of **4.18** as a white residue (64% ee).

¹H NMR (500 MHz, CDCl₃) δ 7.27 (d, *J* = 2.3 Hz, 1H), 6.32 (q, *J* = 1.8 Hz, 1H), 5.21 (d, *J* = 2.7 Hz, 1H), 4.45 (ddd, *J* = 7.7, 5.2, 2.2 Hz, 1H), 2.76 (dd, *J* = 12.4, 2.9 Hz, 1H), 2.58 (dd, *J* = 14.4, 5.1 Hz, 1H), 2.32 (ddd, *J* = 14.4, 8.2, 1.9 Hz, 1H), 2.03 (d, *J* = 1.6 Hz, 3H), 1.74 (dq, *J* = 12.3, 1.8 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 161.2, 155.1, 140.7, 140.5, 128.9, 89.3, 62.9, 43.5, 35.6, 21.3, 13.3.

HRMS (ESI): Calcd for ([M+H], C₁₁H₁₂O₂)⁺: *m/z* = 302.9877, found 302.9875

Chiral HPLC data: ADH chiral column, 3% IPA/hexanes, 1 mL/min, *t_R*(minor) = 17.8 min, *t_R*(major) = 27.3 min, λ = 300 nm



methyl (5*S*,7*S*)-7-hydroxy-8-iodo-4-methylspiro[4.4]nona-1,3-diene-1-carboxylate (4.25): A solution of crude **4.18** (1.67 g, 5.53 mmol, 1 equiv) and *p*-TsOH (1.16 g, 6.08 mmol, 1.1 equiv) in MeOH (55 mL, 0.1 M) was heated to 50 °C and stirred for 23 h. The mixture was then diluted with EtOAc (50 mL), poured into a separatory funnel containing ice, and basified to pH=7–9 with an aqueous solution of saturated NaHCO₃. The mixture was then extracted with EtOAc (3 x 100 mL). The organic layers were combined, dried over MgSO₄, and concentrated under reduced pressure to give a 1.89 g of a crude yellow-brown oil, which was used in the next step without purification. The presence of **4.25** in the crude mixture was confirmed by ¹H NMR analysis.

¹H NMR (500 MHz, CDCl₃) δ 7.20 (d, *J* = 2.3 Hz, 1H), 5.96 (dq, *J* = 3.2, 1.6 Hz, 1H), 4.70 (dt, *J* = 10.0, 8.0 Hz, 1H), 4.49 (q, *J* = 8.0 Hz, 1H), 3.77 (s, 3H), 2.51 (dd, *J* = 14.3, 7.9 Hz, 1H), 2.25 – 2.10 (m, 2H), 2.03 (d, *J* = 1.5 Hz, 3H), 1.92 (dd, *J* = 13.6, 7.5 Hz, 1H).

methyl (5*S*)-7-iodo-4-methyl-8-oxospiro[4.4]nona-1,3-diene-1-carboxylate (4.26): A solution of crude **4.25** (1.89 g, 5.66 mmol, 1 equiv) and Dess–Martin periodinane (4.80 g, 11.3 mmol, 2 equiv) in CH₂Cl₂ was stirred at 25 °C for 7 h. At this point, an aqueous solution of saturated NaHCO₃ (100 mL) was added and the aqueous layer was extracted with EtOAc (3 x 125 mL). The organic layers were combined, washed with brine (3 x 100 mL), dried over MgSO₄, and concentrated under reduced pressure. ¹H NMR analysis of the crude residue confirmed presence of **4.25**, alongside reaction by-products.

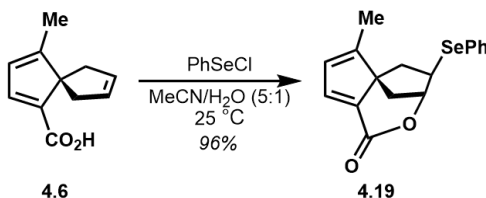
¹H NMR (400 MHz, CDCl₃) δ 7.23 (d, *J* = 2.3 Hz, 1H), 6.11 (dd, *J* = 2.4, 1.6 Hz, 1H), 5.29 (td, *J* = 9.1, 1.6 Hz, 1H), 3.72 (s, 3H), 2.71 – 2.38 (m, 4H), 2.01 (d, *J* = 1.6 Hz, 3H).

methyl-4-methyl-8-oxospiro[4.4]nona-1,3,6-triene-1-carboxylate (4.24): A crude mixture containing **4.25** was dissolved in MeCN (113 mL, 0.05 M) and cooled to 0 °C. To this solution was added NaHCO₃ (4.75 g, 56.6 mmol, 10 equiv) and *m*-CPBA (75 wt % purity, 4.88 g, 28.3 mmol, 5 equiv). The mixture was stirred at 0 °C for 14 h and then quenched by the addition of an aqueous solution of saturated Na₂S₂O₃ (50 mL). The aqueous layer was extracted by EtOAc (3 x 50 mL). The organic layers were combined, washed with a saturated solution of aqueous NaHCO₃ (2 x 50 mL) and then brine (1 x 50 mL), dried over MgSO₄, and then concentrated under reduced pressure. The resulting crude residue was purified by silica gel flash column chromatography (10% EtOAc/hexanes – 30% EtOAc/hexanes gradient) to give 279 mg (41% over 4 steps) of **4.14** as a yellow oil.

¹H NMR (500 MHz, CDCl₃) δ 7.40 (d, *J* = 2.3 Hz, 1H), 6.88 (d, *J* = 5.4 Hz, 1H), 6.38 (d, *J* = 5.4 Hz, 1H), 6.25 (t, *J* = 1.9 Hz, 1H), 3.71 (s, 3H), 2.89 (d, *J* = 18.3 Hz, 1H), 2.34 (d, *J* = 18.3 Hz, 1H), 1.85 (d, *J* = 1.7 Hz, 3H).

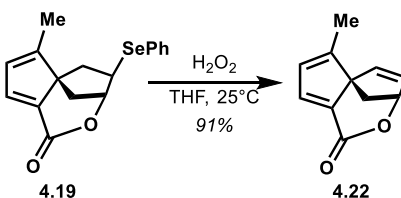
¹³C NMR (126 MHz, CDCl₃) δ 208.6, 165.6, 163.1, 157.3, 144.2, 138.5, 134.6, 127.4, 64.9, 51.4, 38.6, 12.9.

HRMS (ESI): Calcd for ([M+H], C₁₂H₁₃IO₃)⁺: *m/z* = 205.0859, found 205.0859



6-methyl-4-(phenylselanyl)-4,5-dihydro-1H,3H-3,5a-methanocyclopenta[c]oxepin-1-one (4.19): To a stirred solution of **4.6** (30.0 mg, 0.170 mmol, 1 equiv) in MeCN/H₂O (5:1, 0.85 mL, 0.2 M) was added PhSeCl (48.9 mg, 0.266 mmol, 1.5 equiv) under ambient atmosphere at 25 °C. After 1 h, the mixture was diluted with H₂O (1 mL) and extracted with EtOAc (3 x 1 mL). The organic layers were combined, dried over MgSO₄, and then concentrated under reduced pressure. The resulting residue was purified by silica gel flash column chromatography (20% EtOAc/hexanes – 30% EtOAc/hexanes gradient) to give 54.3 mg (96%) of **4.19** as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 7.60 (dd, *J* = 6.6, 3.0 Hz, 2H), 7.42 – 7.32 (m, 4H), 6.36 (d, *J* = 2.4 Hz, 1H), 4.99 (d, *J* = 2.8 Hz, 1H), 3.92 (ddd, *J* = 8.6, 6.1, 2.2 Hz, 1H), 2.51 (dd, *J*



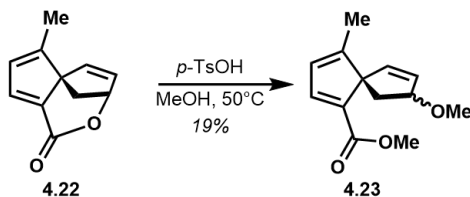
= 12.2, 2.9 Hz, 1H), 2.26 – 2.08 (m, 2H), 2.05 (app d, *J* = 1.5 Hz, 4H), 1.96 (dd, *J* = 13.7, 6.2 Hz, 1H).

6-methyl-1H,3H-3,5a-methanocyclopenta[c]oxepin-1-one (4.22): To a stirred solution of **4.19** (51.8 mg, 0.156 mmol, 1 equiv) in THF (1.56 mL, 0.1 M) was added H₂O₂ (30 wt % solution, 0.18 mL, 1.56 mmol, 10 equiv) under ambient atmosphere at 25 °C. After 4 h, a saturated solution of aqueous NaHCO₃ (5 mL) was added and the aqueous layer was extracted with EtOAc (3 x 5 mL). The organic layers were combined, dried over MgSO₄, and then concentrated under reduced pressure. This gave 24.8 mg (91%) of **4.22** as a white solid which was used without further purification. An analytically pure sample could be obtained through purification by preparatory TLC (30% EtOAc/Hex).

^1H NMR (600 MHz, CDCl_3) δ 7.19 (d, J = 2.2 Hz, 1H), 6.48 (dd, J = 5.4, 2.6 Hz, 1H), 6.40 – 6.30 (m, 1H), 5.99 (d, J = 5.4 Hz, 1H), 5.44 (td, J = 2.7, 1.2 Hz, 1H), 2.43 (dd, J = 11.0, 2.8 Hz, 1H), 2.09 (s, 2H), 1.85 (d, J = 11.0 Hz, 1H).

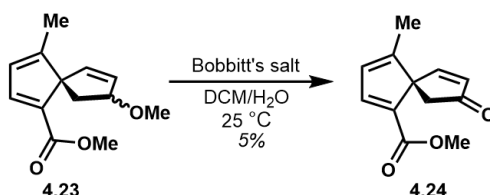
^{13}C NMR (151 MHz, CDCl_3) δ 161.7, 155.5, 140.4, 138.9, 137.5, 134.2, 129.7, 83.4, 65.8, 45.7, 13.8.

HRMS (EI): Calcd for $([\text{M}], \text{C}_7\text{H}_{10}\text{O}_2)^+$: m/z = 174.0765, found 174.0680



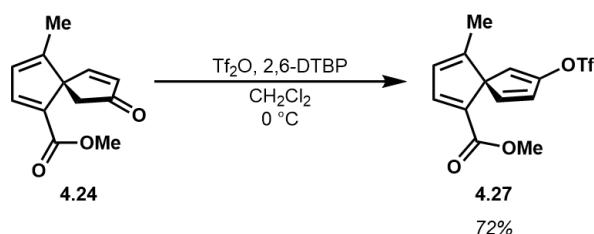
Methyl-8-methoxy-4-methylspiro[4.4]nona-1,3,6-triene-1-carboxylate (4.23): A solution of crude **4.22** (24.8 mg, 0.142 mmol, 1 equiv) and p -TsOH (29.8 mg, 0.157 mmol, 1.1 equiv) in MeOH (1.42 mL, 0.1 M) was heated to 50 °C and stirred for 16 h. The mixture was then diluted with EtOAc (5 mL), poured into a separatory funnel containing ice, and basified to pH=7–9 with an aqueous solution of saturated NaHCO_3 . The mixture was then extracted with EtOAc (3 x 5 mL). The organic layers were combined, dried over MgSO_4 , and concentrated under reduced pressure. The resulting residue was purified by preparatory TLC (30% EtOAc/hexanes) to give 5.9 mg (19%) of **4.23** as a mixture of epimers (approximately 1:1 dr). ^1H NMR data is shown below for one of the epimers.

^1H NMR (700 MHz, CDCl_3) δ 7.29 (d, J = 2.3 Hz, 1H), 6.20 (dd, J = 5.4, 1.9 Hz, 1H), 6.03 (app t, J = 2.0 Hz, 1H), 5.29 (dd, J = 5.4, 1.6 Hz, 1H), 4.85 – 4.80 (m, 1H), 3.73 (s, 3H), 3.42 (s, 3H), 2.57 – 2.49 (m, 1H), 1.92 (d, J = 1.6 Hz, 3H).



methyl-4-methyl-8-oxospiro[4.4]nona-1,3,6-triene-1-carboxylate (4.24): The procedure was adapted from a report by Leadbeater and coworkers.²⁷ To a stirred solution of **4.23** (5.9 mg, 0.027 mmol, 1 equiv) in $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (4:1, 0.67 mL, 0.04 M) was added Bobbitt's salt (17 mg, 0.056 mmol, 2.1 equiv). The resulting mixture was heating to reflux (45 °C) and stirred for 20 h. Another portion (17 mg, 0.056 mmol, 1 equiv) of Bobbitt's salt was added and stirring was continued at 45 °C for an additional 24 h. Then, the reaction mixture was allowed to cool to 25 °C and H_2O (2 mL) was added. The resulting mixture was extracted with Et_2O (3 x 2 mL). The organic layers were combined, washed with a saturated solution of aqueous NaHCO_3 (2 x 50 mL) and then brine (1 x 50 mL), dried over MgSO_4 , and then concentrated under reduced pressure. The resulting crude residue was

purified by preparatory TLC (30% EtOAc/hexanes) to give 0.3 mg (5%) of **4.24**. See above for analytical data.



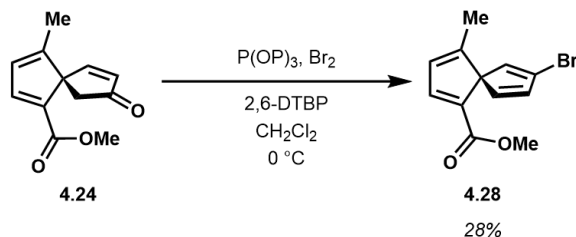
methyl-4-methyl-7-(((trifluoromethyl)sulfonyl)oxy)spiro[4.4]nona-1,3,6,8-tetraene-1-carboxylate (4.27): To a stirred solution of **4.24** (71.3 mg, 0.349 mmol, 1 equiv) and 2,6-di-*tert*-butylpyridine (0.157 mL, 0.698 mmol, 2 equiv) in CH_2Cl_2 (3.5 mL, 0.1 M) was added a 1 M solution of Tf_2O in CH_2Cl_2 (0.70 mL, 0.70 mmol, 2 equiv) under an inert atmosphere at 0 °C. (5.4 g, 36 mmol, 1.0 equiv). The flask was evacuated and refilled with N_2 three times. After 21 h, H_2O (3 mL) was slowly added until bubbling ceased. Hexanes (5 mL) were then added and a brown solid precipitated. The resulting biphasic mixture was filtered through a celite pad. The organic layer was separated, washed with brine (1 x 5 mL), dried over MgSO_4 , filtered, and concentrated under reduced pressure. The resulting crude, black oil which was then purified by silica gel flash column chromatography (0–10% EtOAc/hexanes gradient) to give 84.3 mg (72%) of **4.27** as a yellow oil.

^1H NMR (400 MHz, CDCl_3) δ 7.53 (d, J = 2.2 Hz, 1H), 6.58 (dd, J = 5.5, 1.6 Hz, 1H), 6.41 (dq, J = 3.2, 1.7 Hz, 1H), 5.82 (dd, J = 5.6, 2.6 Hz, 1H), 5.57 (dd, J = 2.6, 1.6 Hz, 1H), 3.66 (s, 3H), 1.67 (d, J = 1.6 Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 162.4, 151.1, 150.9, 145.9, 137.1, 131.3, 129.5, 129.3, 118.7, 72.7, 51.3, 12.3. (CF_3 is not observed here, likely due to ^{13}C - ^{19}F splitting which reduces signal intensity. However, ^{19}F NMR clearly shows evidence for the CF_3 group.)

^{19}F NMR (376 MHz, CDCl_3) δ -72.82.

HRMS (ESI): Calcd for $([\text{M}+\text{H}]^+, \text{C}_{13}\text{H}_{12}\text{F}_3\text{O}_3\text{S})^+$: m/z = 337.0352, found 337.0358.



Methyl-7-bromo-4-methylspiro[4.4]nona-1,3,6,8-tetraene-1-carboxylate (4.28): This procedure was adapted by a report from Prati and coworkers.⁴⁷ To a stirred solution of

P(OPh)₃ (0.135 mL, 0.514 mmol, 2.1 equiv) in CH₂Cl₂ (3 mL, 0.08 M) was added Br₂ (0.025 mL, 0.49 mmol, 2 equiv) dropwise under an inert atmosphere at 0 °C. To this orange solution, 2,6-di-*tert*-butylpyridine (0.11 mL, 0.49 mmol, 2 equiv) and a solution of **4.24** (50.0 mg, 0.245 mmol, 1 equiv) in CH₂Cl₂ (2 mL, 0.12 M) were added. The mixture was allowed to warm to 25 °C and stirred for 12 h. At this point, the mixture was heated to 40 °C for 5 h. The reaction was then quenched with a saturated solution of aqueous Na₂S₂O₃ (5 mL). The aqueous layer was extracted with Et₂O (3 x 5 mL). The organic layers were combined, washed with brine (1 x 10 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by silica gel flash column chromatography (0–10% Et₂O/hexanes gradient) to give 18.6 mg (28%) of **4.28** as a white solid.

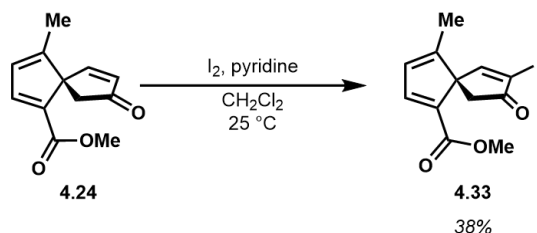
¹H NMR (500 MHz, CDCl₃) δ 7.47 (d, *J* = 2.1 Hz, 1H), 6.56 (dd, *J* = 5.3, 1.4 Hz, 1H), 6.41 – 6.29 (m, 1H), 5.77 (dd, *J* = 2.5, 1.5 Hz, 1H), 5.69 (dd, *J* = 5.3, 2.4 Hz, 1H), 3.66 (s, 3H), 1.65 (d, *J* = 1.6 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 162.5, 152.0, 145.4, 137.4, 135.9, 131.7, 131.6, 128.7, 121.4, 51.3, 12.5. (Note: The OMe carbon resonance is not seen here, likely due to coincidence with the CDCl₃ solvent peak. The resonance at δ 76.8 can be seen in C₆D₆ solvent.)

¹H NMR (600 MHz, C₆D₆) δ 7.33 (d, *J* = 2.2 Hz, 1H), 6.35 (dd, *J* = 5.2, 1.4 Hz, 1H), 5.80 (dt, *J* = 3.3, 1.6 Hz, 1H), 5.56 (dd, *J* = 2.4, 1.4 Hz, 1H), 5.36 (dd, *J* = 5.3, 2.5 Hz, 1H), 3.35 (s, 3H), 1.30 (d, *J* = 1.6 Hz, 3H).

¹³C NMR (151 MHz, C₆D₆) δ 161.5, 150.7, 144.5, 137.0, 135.7, 132.1, 131.7, 128.3, 121.2, 76.8, 50.4, 11.7.

HRMS (ESI): Calcd for ([M+H], C₁₂H₁₂BrO₂)⁺: *m/z* = 267.0015, found 267.0015.



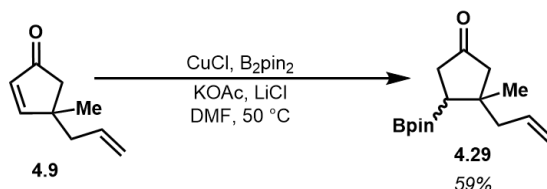
methyl-7-iodo-4-methyl-8-oxospiro[4.4]nona-1,3,6-triene-1-carboxylate (4.33): This procedure was adapted from a report by Banwell and coworkers.⁴⁸ To a stirred solution of **4.24** (39.8 mg, 0.195 mmol, 1 equiv) and pyridine (0.189 mL, 2.34 mmol, 12 equiv) in CH₂Cl₂ (0.97 mL, 0.2 M) was added I₂ (297 mg, 1.17 mmol, 6 equiv) in one portion at 25 °C. After stirring for 20 h, the reaction was quenched with a saturated solution of aqueous Na₂S₂O₃ (3 mL). The aqueous layer was extracted with Et₂O (3 x 5 mL). The organic layers were combined, washed with brine (1 x 10 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by

preparatory TLC (80% Et₂O/hexanes) to give 24.7 mg (38%) of **4.33** as a white solid. A single crystal of **4.33** was grown by slow evaporation from a solution in Et₂O/hexanes.

¹H NMR (600 MHz, CDCl₃) δ 7.40 (d, *J* = 2.3 Hz, 1H), 7.16 (s, 1H), 6.26 (dd, *J* = 2.3, 1.6 Hz, 1H), 3.71 (s, 3H), 2.74 (dd, *J* = 311.5, 18.3 Hz, 2H), 1.85 (d, *J* = 1.6 Hz, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 202.5, 168.5, 162.8, 156.2, 144.4, 137.8, 127.9, 101.5, 66.8, 51.5, 35.9, 13.0.

HRMS (ESI): Calcd for ([M+H], C₁₂H₁₂IO₃)⁺: *m/z* = 330.9826, found 330.9828.



3-allyl-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopentan-1-one

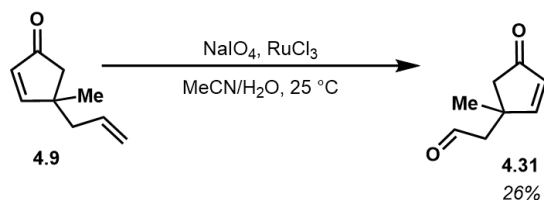
(4.29): This procedure was adapted by a report from Miyaura and coworkers.⁴⁹ To a solution of **4.9** (34.6 mg, 0.254 mmol, 1.0 equiv) in DMF (0.85 mL, 0.3 M) was added B₂pin₂ (129 mg, 0.508 mmol, 2.0 equiv), KOAc (49.9 mg, 0.508 mmol, 2.0 equiv), LiCl (21.5 mg, 0.508 mmol, 2.0 equiv), and CuCl (50.3 mg, 0.508 mmol, 2.0 equiv). The reaction vessel was purged with nitrogen and then heated to 50 °C. After stirring for 20 h, the reaction mixture was diluted with H₂O (2 mL). The aqueous layer was extracted with Et₂O (3 x 5 mL). The organic layers were combined, washed with brine (3 x 5 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by preparatory TLC (80% Et₂O/hexanes) to give 39.8 mg (59%) of **4.29** as a white waxy solid as an unspecified mixture of diastereomers. Due to partially overlapping resonances in both the ¹H and ¹³C spectra, the analytical data for both diastereomers is reported together.

¹H NMR (500 MHz, CDCl₃) δ 5.99 – 5.66 (m, 1H), 5.17 – 4.92 (m, 2H), 2.39 – 2.30 (m, 3H), 2.29 – 2.21 (m, 1H), 2.13 (d, *J* = 6.0 Hz, 1H), 2.06 – 1.83 (m, 1H), 1.60 – 1.52 (m, 1H), 1.25 (d, *J* = 4.8 Hz, 12H).

¹³C NMR (126 MHz, CDCl₃) δ 220.4, 220.4, 134.9, 134.7, 118.2, 118.0, 83.5, 83.5, 52.4, 51.4, 46.1, 42.8, 42.0, 42.0, 39.6, 39.0, 26.8, 25.1, 25.0, 24.8, 24.8, 23.4.

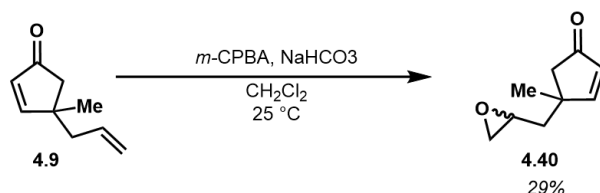
¹¹B NMR (160 MHz, CDCl₃) δ 33.5.

HRMS (ESI): Calcd for ([M+H], C₁₅H₂₆BO₃)⁺: *m/z* = 265.1970, found 265.1971.



2-(1-methyl-4-oxocyclopent-2-en-1-yl)acetaldehyde (4.31): This procedure was adapted by a report from Yang and coworkers.⁵⁰ To a solution of **4.9** (20.0 mg, 0.147 mmol, 1.0 equiv) in MeCN (1.26 mL, 0.13 M) was added NaIO₄ in one portion (78.5 mg, 0.367 mmol, 2.5 equiv) and then a solution of RuCl₃ (1.52 mg, 0.00734 mmol, 0.05 equiv) in H₂O (0.21 mL). The mixture was stirred at 25 °C for 12 h. The reaction mixture was then quenched with a saturated solution of aqueous Na₂S₂O₃ (3 mL). The aqueous layer was extracted with Et₂O (3 x 5 mL). The organic layers were combined, washed with brine (1 x 10 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. This gave 5.3 mg (26%) of a crude residue which was used without further purification.

¹H NMR (500 MHz, CDCl₃) δ 9.84 (t, *J* = 2.2 Hz, 1H), 2.56 (d, *J* = 2.2 Hz, 2H), 2.37 – 2.30 (m, 2H), 2.25 (s, 1H), 2.22 (d, *J* = 1.0 Hz, 1H), 2.02 – 1.89 (m, 2H), 1.22 (s, 3H).

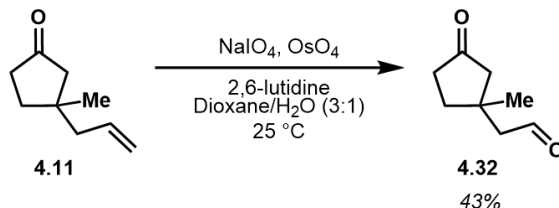


4-methyl-4-(oxiran-2-ylmethyl)cyclopent-2-en-1-one (4.40): A suspension of **4.9** (15.0 mg, 0.110 mmol, 1.0 equiv), *m*-CPBA (75% wt %, 50.7 mg, 0.220 mmol, 2.0 equiv), and NaHCO₃ (18.5 mg, 0.220 mmol, 2.0 equiv) in CH₂Cl₂ (0.55 mL, 0.2 M) was stirred under ambient atmosphere at 25 °C for 12 h. Then, a saturated solution of aqueous NaHCO₃ (1 mL) was added. The aqueous layer was extracted with Et₂O (3 x 2 mL). The organic layers were combined, washed with brine (1 x 5 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The resulting crude mixture was purified by preparatory TLC (60% Et₂O/hexanes) to give 4.8 mg (29%) of **4.40** as an inseparable mixture of diastereomers. Due to partially overlapping resonances in both the ¹H and ¹³C spectra, the analytical data for both diastereomers is reported together.

¹H NMR (500 MHz, CDCl₃) δ 7.54 (app dd, *J* = 8.1, 5.5 Hz, 1H), 6.10 (d, *J* = 5.6 Hz, 1H), 2.89 (dddd, *J* = 11.2, 7.0, 4.1, 2.6 Hz, 1H), 2.77 (ddd, *J* = 11.8, 5.0, 4.0 Hz, 1H), 2.53 – 2.41 (m, 2H), 2.24 (d, *J* = 18.6 Hz, 1H), 1.87 (ddd, *J* = 34.5, 14.3, 4.0 Hz, 1H), 1.65 – 1.49 (m, 1H), 1.32 (app d, *J* = 6.4 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 209.3, 209.2, 172.0, 171.8, 132.5, 132.4, 49.3, 49.0, 48.3, 47.9, 47.0, 46.4, 44.7, 44.4, 43.6, 43.5, 26.7, 26.6.

HRMS (EI): Calcd for $([M], C_9H_{12}O_2)^+$: $m/z = 152.0832$, found 152.0837

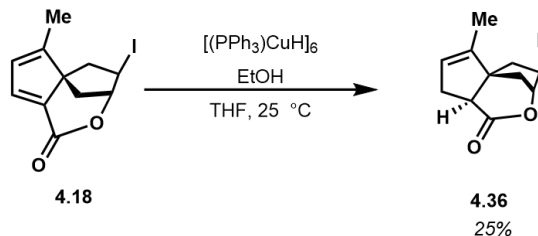


2-(1-methyl-3-oxocyclopentyl)acetaldehyde (4.32): This procedure was adapted from a report by Jin and coworkers.³⁵ To a solution of **4.11** (100.0 mg, 0.724 mmol, 1.0 equiv) and 2,6-lutidine (0.168 mL, 0.145 mmol, 2.0 equiv) in Dioxane/H₂O (3:1, 8.0 mL, 0.1 M) was added NaIO₄ in one portion (78.5 mg, 0.367 mmol, 2.5 equiv) and then a solution of OsO₄ in H₂O (4 wt %, 0.191 mL, 0.0724 mmol, 0.10 equiv). The mixture was stirred at 25 °C for 3 h. The reaction mixture was then diluted with H₂O (10 mL) and the aqueous layer was extracted with Et₂O (3 x 10 mL). The organic layers were combined, washed with brine (1 x 10 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by silica gel flash column chromatography (30–50% Et₂O/hexanes gradient) to give 43.2 mg (43%) of **4.32** as a colorless oil.

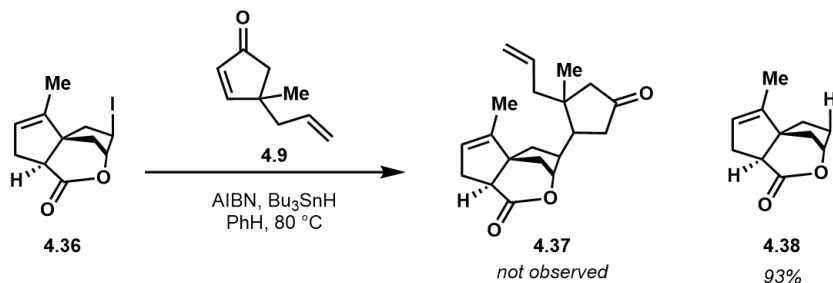
¹H NMR (500 MHz, CDCl₃) δ 9.84 (t, $J = 2.2$ Hz, 1H), 2.56 (d, $J = 2.2$ Hz, 2H), 2.37 – 2.30 (m, 2H), 2.25 (s, 1H), 2.22 (d, $J = 1.0$ Hz, 1H), 2.02 – 1.89 (m, 2H), 1.22 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 218.1, 201.3, 54.4, 51.8, 38.2, 36.3, 35.5, 25.8.

HRMS (EI): Calcd for $([M], C_8H_{12}O_2)^+$: $m/z = 140.0832$, found 140.0836



4-iodo-6-methyl-4,5,8,8a-tetrahydro-1H,3H-3,5a-methanocyclopenta[c]oxepin-1-one (4.36): To a solution of **4.18** (150.0 mg, 0.497 mmol, 1.0 equiv) in THF (5.0 mL, 0.1 M) was added Stryker's reagent ($[(PPh_3)CuH]_6$, 292 mg, 0.149 mmol, 0.3 equiv) and EtOH (0.12 mL, 1.9 mmol, 4.0 equiv). Note: THF was not rigorously dried due to the reported



beneficial effects of adventitious water on some cuprate additions.^{REF} The mixture was stirred at 25 °C for 1 h. The reaction mixture was then filtered through a silica pad, eluting with Et₂O. The filtrate was concentrated under reduced pressure, and the resulting crude residue was purified by silica gel flash column chromatography (20–30% EtOAc/hexanes gradient) to give an impure mixture containing residual PPh₃ and **4.36**. This mixture was again purified by silica gel flash column chromatography (10–20% EtOAc/hexanes gradient) to give 37.2 mg (25%) of **4.36** as a white solid. A single crystal of **4.36** was grown through slow evaporation from a solution in Et₂O/hexanes.

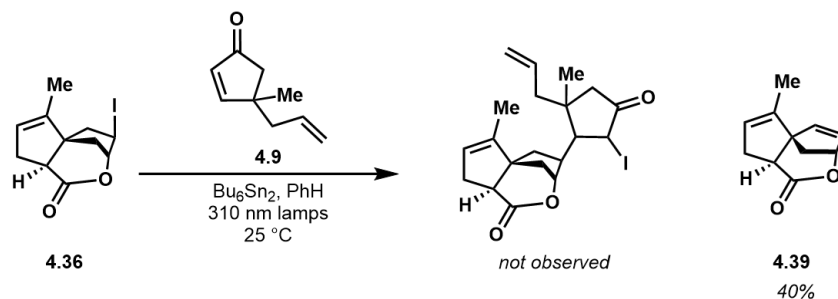
6-methyl-4,5,8,8a-tetrahydro-1H,3H-3,5a-methanocyclopenta[c]oxepin-1-one (4.38):

To a solution of **4.36** (4.1 mg, 0.015 mmol, 1.0 equiv) and **4.9** (5.1 mg, 0.033 mmol, 2.2 equiv) in benzene (0.30 mL, 0.050 M) was added AIBN (2.5 mg, 0.015 mmol, 1.0 equiv) and Bu₃SnH (0.020 mL, 0.076 mmol, 5.0 equiv). The reaction mixture was stirred at 80 °C for 15 h. The reaction mixture was then concentrated under reduced pressure, dissolved in Et₂O (0.5 mL) and a 10% aqueous KF solution (1 mL) was added. This mixture was stirred for 2 h and then extracted with Et₂O (3 x 1 mL). The organic layers were combined, washed with brine (1 x 1 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The resulting crude mixture was purified by preparatory TLC (40% Et₂O/hexanes) to give 2.5 mg (93%) of **4.38** as a white residue.

¹H NMR (500 MHz, CDCl₃) δ 5.42 (q, *J* = 1.5 Hz, 1H), 4.83 (dt, *J* = 4.9, 2.2 Hz, 1H), 2.87 (t, *J* = 9.8 Hz, 1H), 2.75 (dddd, *J* = 16.2, 10.0, 2.8, 1.5 Hz, 1H), 2.44 (dddd, *J* = 19.1, 10.0, 5.1, 2.7 Hz, 1H), 2.20 (dddd, *J* = 18.5, 12.0, 5.3, 2.6 Hz, 1H), 2.12 – 2.06 (m, 1H), 1.94 (td, *J* = 12.2, 7.2 Hz, 1H), 1.68 (d, *J* = 1.4 Hz, 3H), 1.59 – 1.53 (m, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 174.3, 141.2, 124.5, 80.4, 55.7, 53.1, 37.9, 33.7, 33.4, 32.2, 13.0.

HRMS (EI): Calcd for ([M], C₁₁H₁₄O₂)⁺: *m/z* = 178.0988, found 178.0995



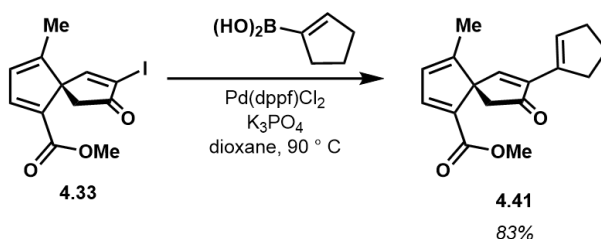
6-methyl-8,8a-dihydro-1H,3H-3,5a-methanocyclopenta[c]oxepin-1-one (4.39): This procedure was adapted from a report by Curran and coworkers.⁴⁰ A solution of **4.36** (10.0 mg, 0.033 mmol, 1.0 equiv) and **4.9** (13.4 mg, 0.099 mmol, 3.0 equiv) and Bu₃Sn₂ (0.003 mL, 0.007 mmol, 0.2 equiv) in benzene (0.33 mL, 0.10 M) was stirred at 25 °C under the irradiation of 310 nm lamps for 14 h. The reaction mixture was concentrated under

reduced pressure and purified by preparatory TLC (60% Et₂O/hexanes) to give 2.2 mg (40%) of **4.39** as an off-white residue.

¹H NMR (500 MHz, CDCl₃) δ 6.48 (dq, *J* = 5.5, 0.7 Hz, 1H), 6.28 (ddd, *J* = 5.6, 2.6, 0.7 Hz, 1H), 5.47 (dt, *J* = 3.0, 1.6 Hz, 1H), 5.24 – 4.97 (m, 1H), 2.99 (td, *J* = 9.8, 1.9 Hz, 1H), 2.77 (dddt, *J* = 13.9, 9.5, 3.1, 1.6 Hz, 1H), 2.54 – 2.36 (m, 1H), 2.00 (ddd, *J* = 11.6, 3.3, 1.8 Hz, 1H), 1.87 – 1.79 (m, 1H), 1.73 (dt, *J* = 3.0, 1.6 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 173.7, 145.7, 140.7, 132.6, 125.5, 81.7, 59.6, 52.6, 41.7, 33.2, 13.4.

HRMS (EI): Calcd for ([M], C₁₁H₁₂O₂)⁺: *m/z* = 176.0832, found 176.0838



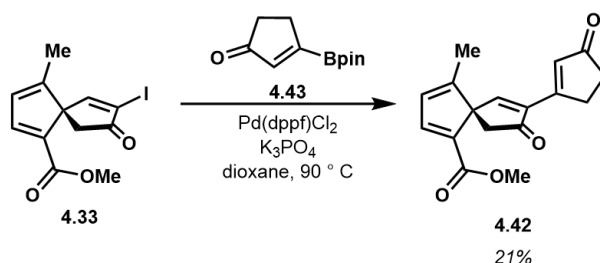
Methyl-7-(cyclopent-1-en-1-yl)-4-methyl-8-oxospiro[4.4]nona-1,3,6-triene-1-

carboxylate (4.41): A flame-dried vial was charged with **4.33** (7.0 mg, 0.021 mmol, 1.0 equiv) and cyclopentene-1-boronic acid (26 mg, 0.023 mmol, 11 equiv), K₃PO₄ (23 mg, 0.021 mmol, 5.0 equiv), and Pd(dppf)Cl₂ (4.2 mg, 0.0057 mmol, 0.27 equiv). The vessel was evacuated and refilled with N₂ three times, then degassed dioxane (0.5 mL, 0.04 M) was added. The mixture was heated to 90 °C and stirred for 4 h. Then, water was added (1 mL) and the aqueous layer was extracted with EtOAc (3 x 1 mL). The organic layers were combined, washed with brine (1 x 1 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The resulting crude mixture was purified by preparatory TLC (40% Et₂O/hexanes) to give 5.1 mg (89%) of **4.41** as a white residue.

¹H NMR (500 MHz, CDCl₃) δ 7.38 (d, *J* = 2.3 Hz, 1H), 6.83 (p, *J* = 2.2 Hz, 1H), 6.43 (d, *J* = 0.9 Hz, 1H), 6.22 (dd, *J* = 2.3, 1.5 Hz, 1H), 3.70 (s, 3H), 2.98 (app d, *J* = 18.2 Hz, 1H), 2.55 – 2.36 (m, 5H), 1.97 – 1.79 (m, 5H).

¹³C NMR (126 MHz, CDCl₃) δ 206.4, 163.2, 158.6, 155.9, 143.9, 140.4, 139.3, 133.2, 132.4, 126.9, 62.3, 51.3, 40.1, 34.0, 33.8, 22.1, 13.1.

HRMS (ESI): Calcd for $[(M+H)^+]$, $C_{17}H_{19}O_3$: m/z = 271.1329, found 271.1330



methyl-4-methyl-8-oxo-7-(3-oxocyclopent-1-en-1-yl)spiro[4.4]nona-1,3,6-triene-1-carboxylate (4.42): A flame-dried vial was charged with **4.33** (10.1 mg, 0.0306 mmol, 1.0 equiv) and Bpin **4.43**⁵¹ (12.7 mg, 0.0612 mmol, 2.0 equiv), K_3PO_4 (13.0 mg, 0.0612 mmol, 2.0 equiv), and $Pd(dppf)Cl_2$ (2.2 mg, 0.0031 mmol, 0.10 equiv). The vessel was evacuated and refilled with N_2 three times, then a solution degassed dioxane/ H_2O (4:1, 0.38 mL mL, 0.080 M) was added. The mixture was heated to 75 °C and stirred for 15 h. Then, water was added (1 mL) and the aqueous layer was extracted with EtOAc (3 x 1 mL). The organic layers were combined, washed with brine (1 x 1 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude mixture was purified by preparatory TLC (50% EtOAc/hexanes) to give 1.8 mg (21%) of **4.42** as a white residue.

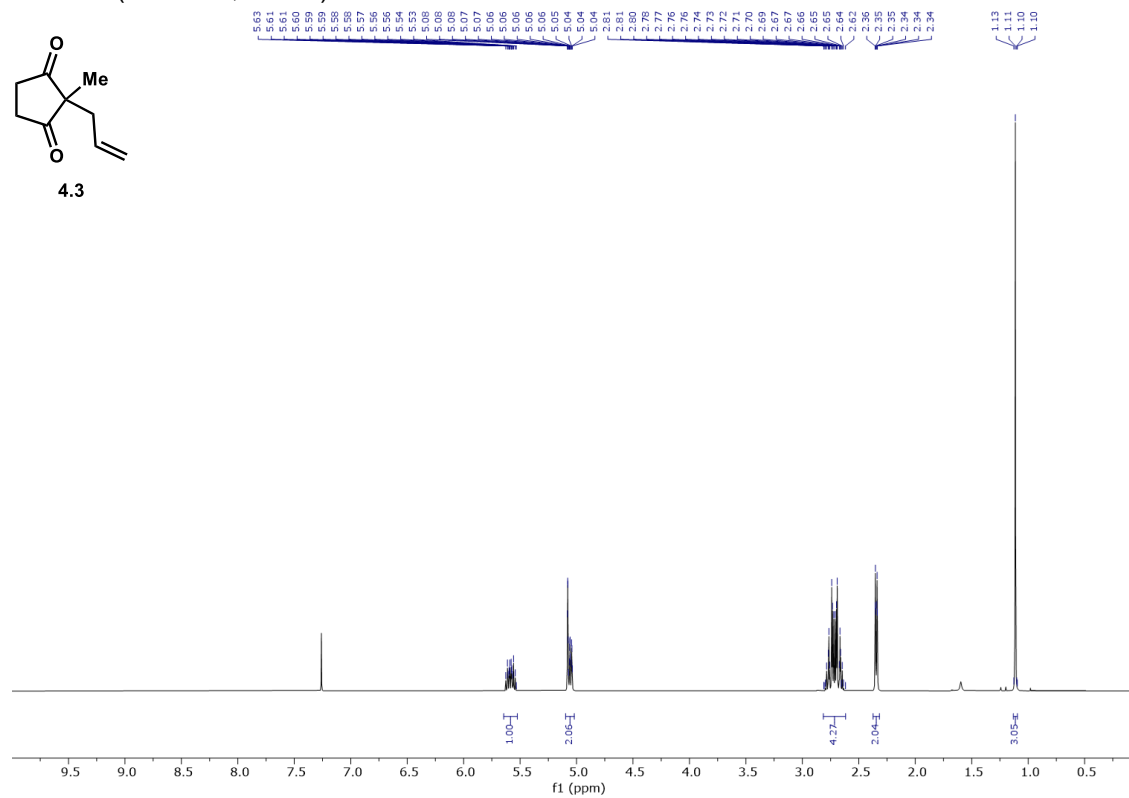
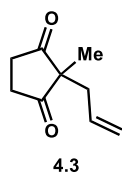
^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J = 2.4 Hz, 1H), 7.07 (s, 1H), 7.04 (t, J = 1.8 Hz, 1H), 6.41 – 6.23 (m, 1H), 3.72 (s, 3H), 2.81 (dd, J = 255.7, 18.5 Hz, 2H), 2.86 – 2.72 (m, 2H), 2.43 (t, J = 5.0 Hz, 2H), 1.88 (d, J = 1.7 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 210.1, 204.0, 163.4, 162.9, 162.1, 157.1, 144.6, 139.8, 138.5, 131.1, 128.4, 62.6, 51.6, 39.8, 33.9, 28.9, 25.0, 13.2. (Note: One extra ^{13}C resonance corresponding to an unknown impurity is observed. Despite this, the remainder of the ^1H NMR, ^{13}C NMR, and HRMS data is consistent with assigned structure.

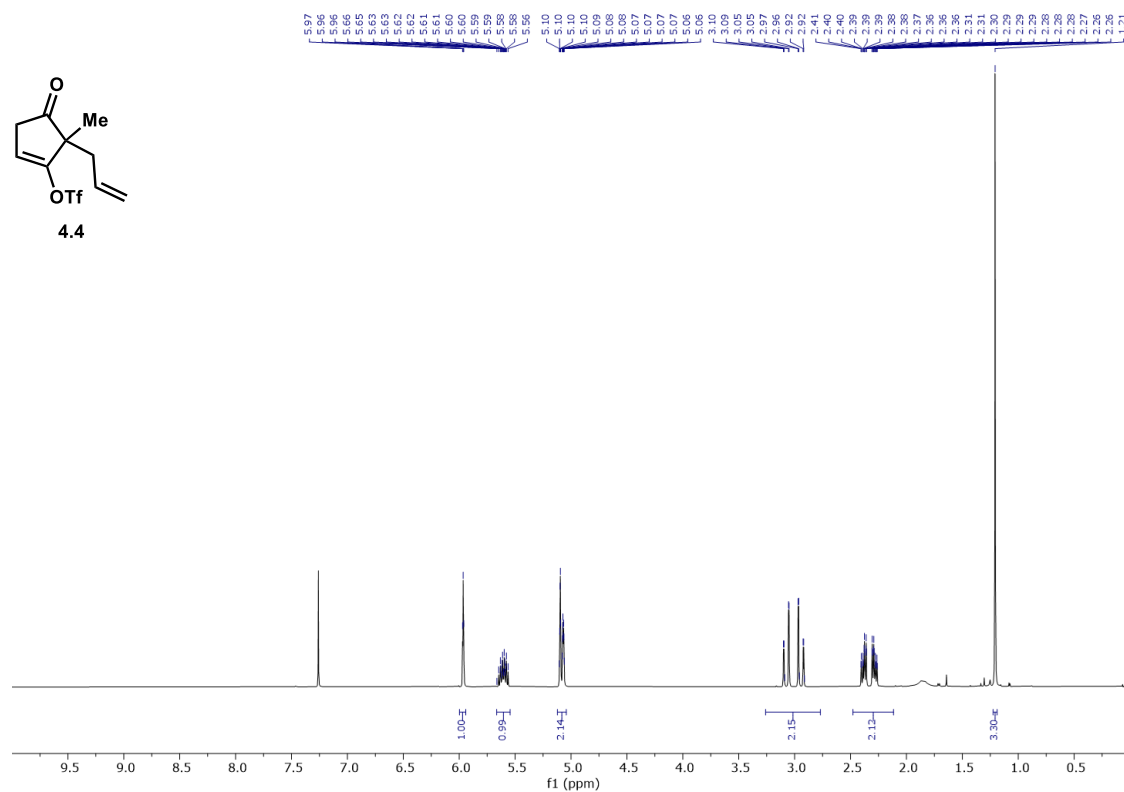
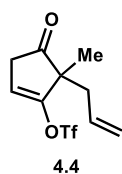
HRMS (ESI): Calcd for $[(M+H)^+]$, $C_{17}H_{17}O_4$: m/z = 285.1121, found 285.1121.

4.9.3 NMR Spectra

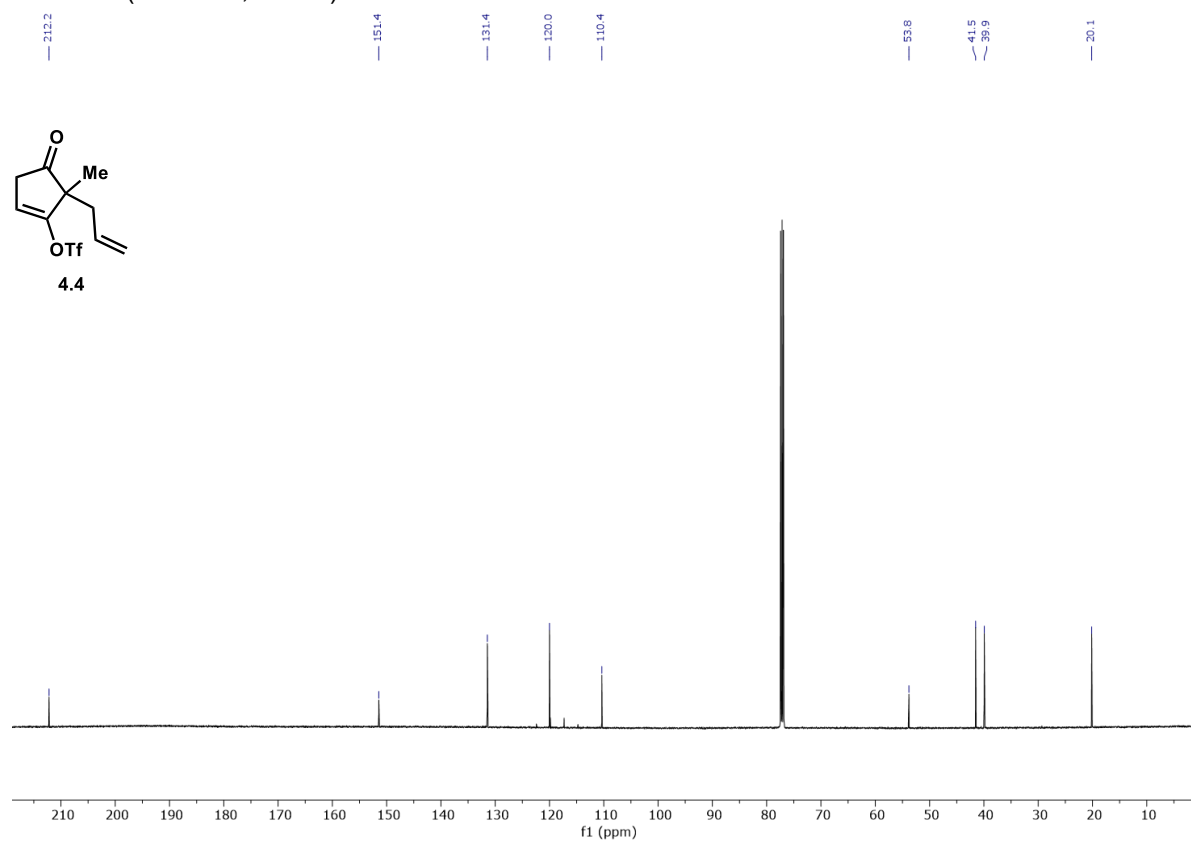
^1H NMR (500 MHz, CDCl_3)



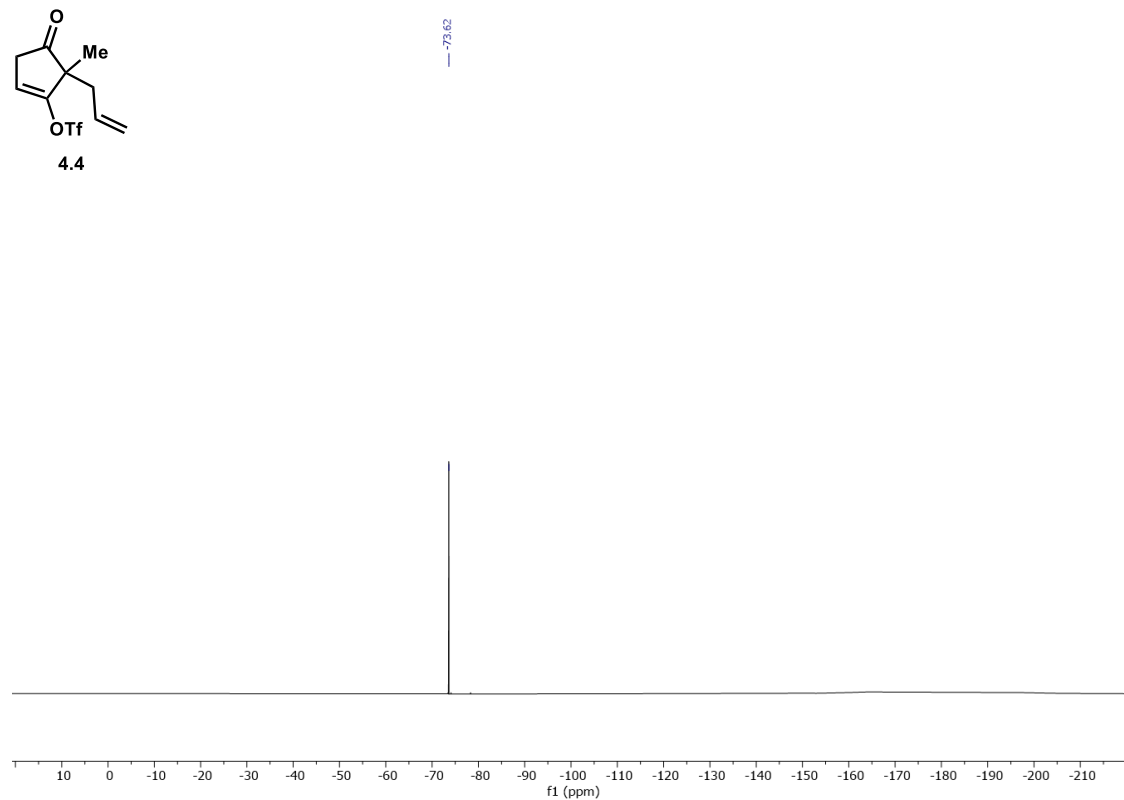
^1H NMR (500 MHz, CDCl_3)



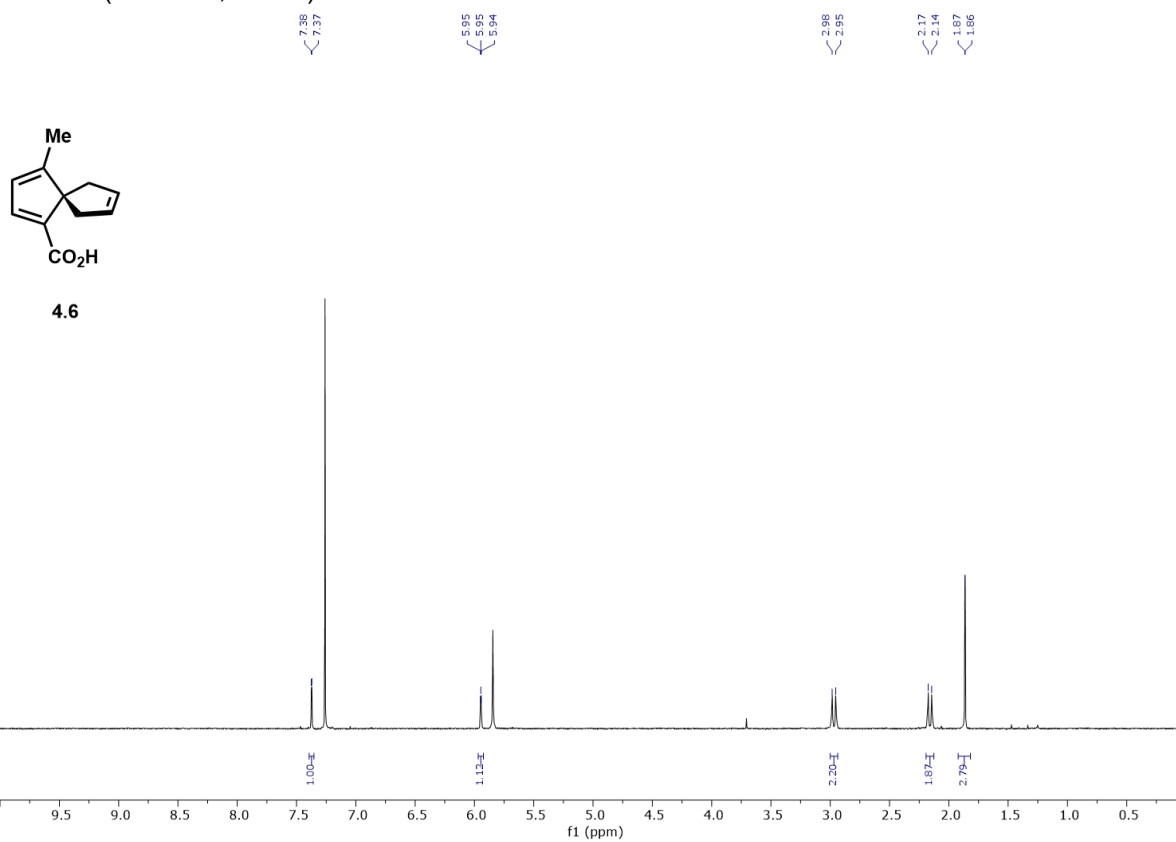
^{13}C NMR (126 MHz, CDCl_3)



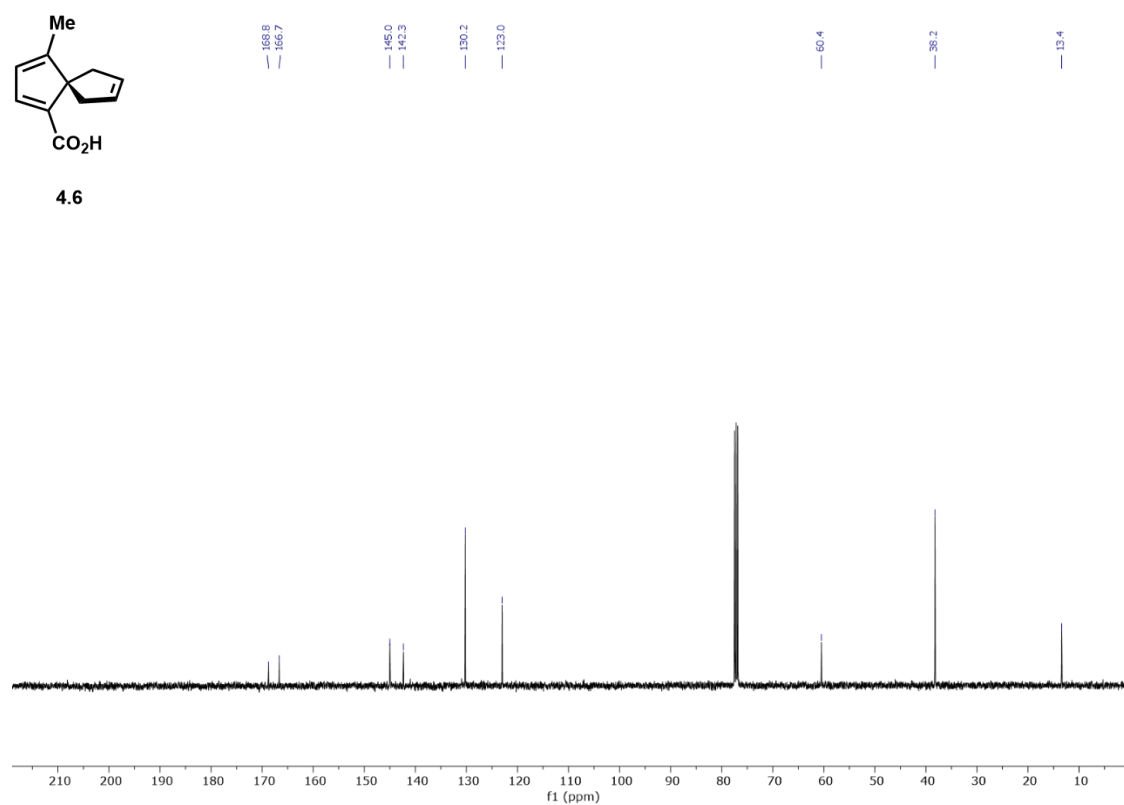
^{19}F NMR (471 MHz, CDCl_3)



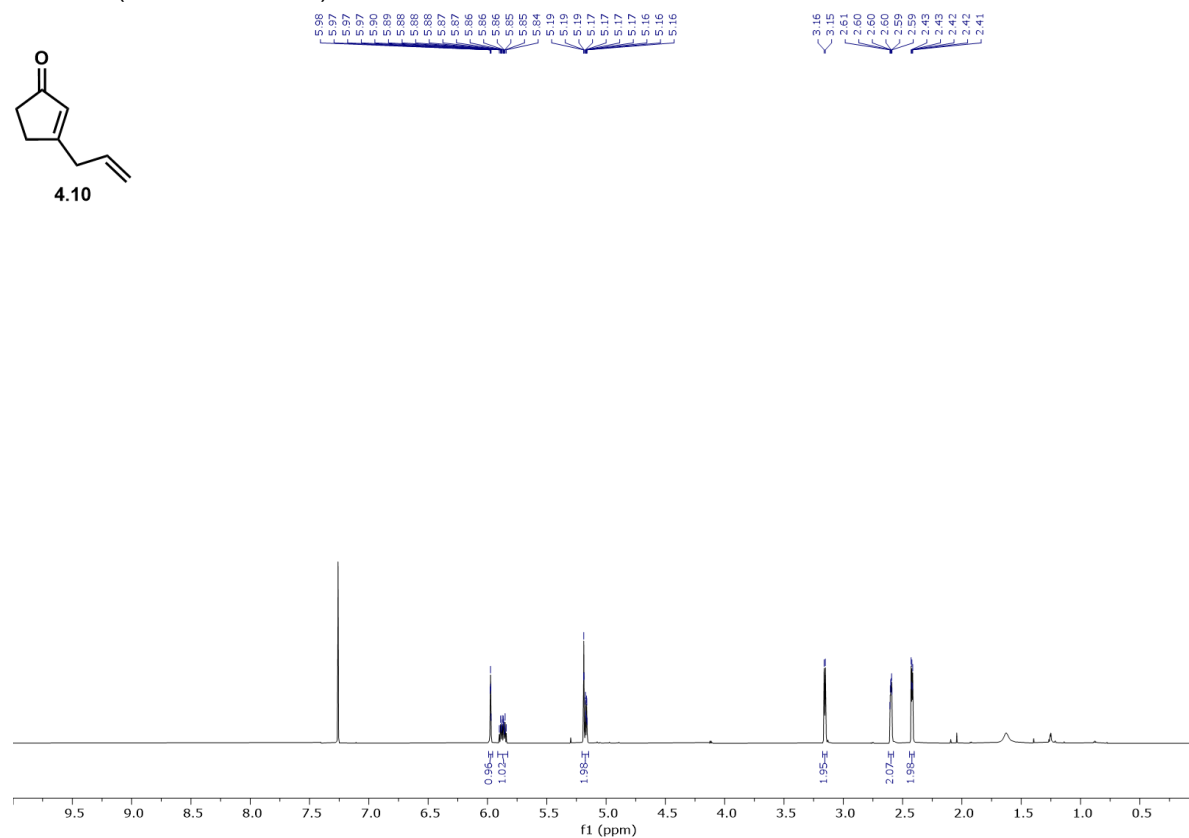
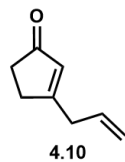
^1H NMR (500 MHz, CDCl_3)



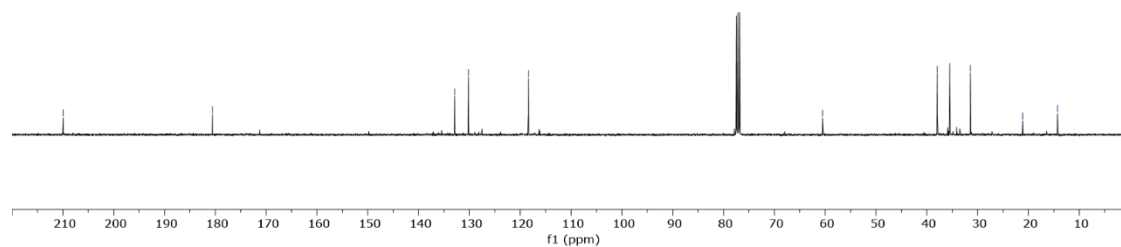
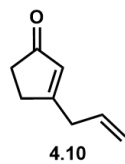
^{13}C NMR (101 MHz, CDCl_3)



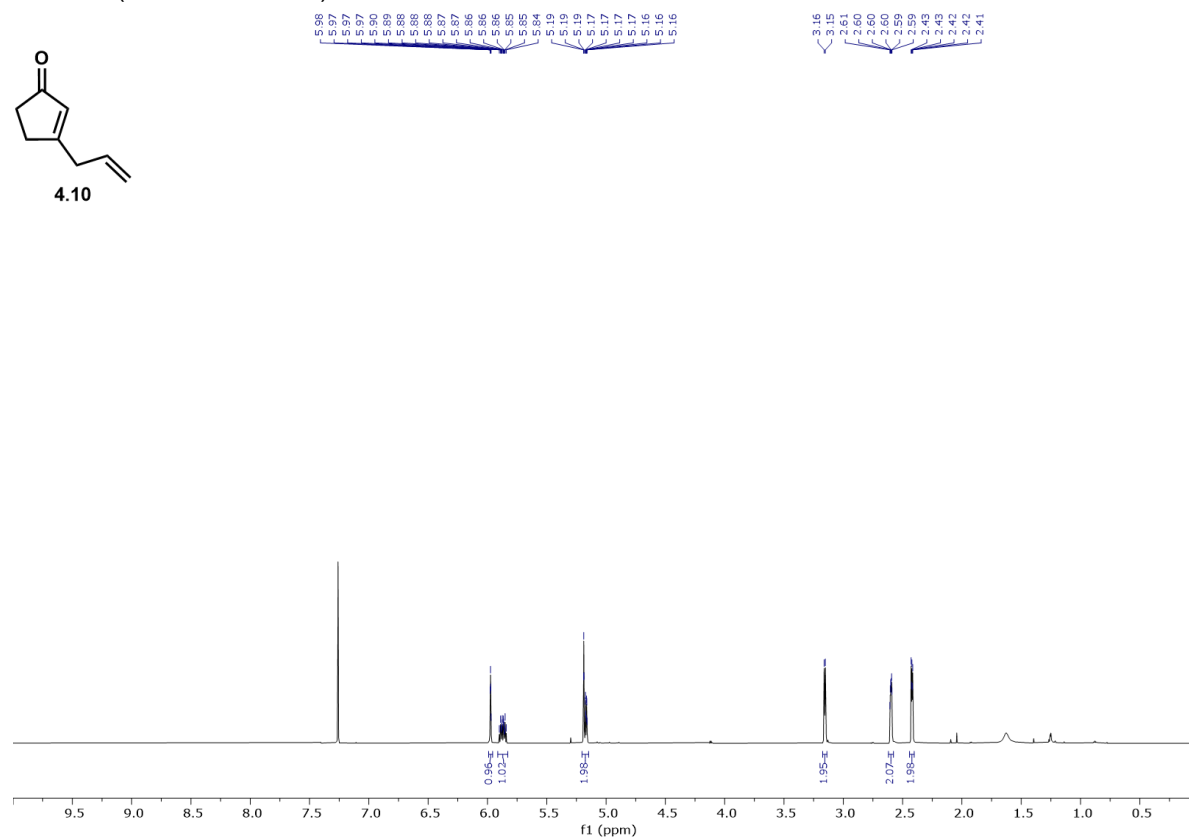
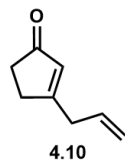
^1H NMR (700 MHz, CDCl_3)



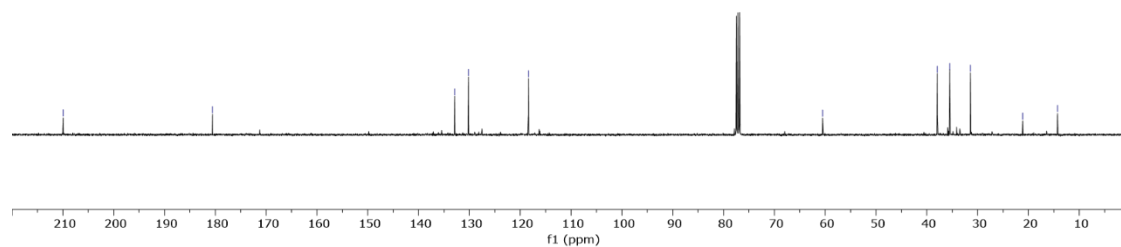
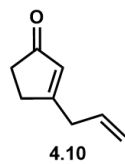
^{13}C NMR (151 MHz, CDCl_3)



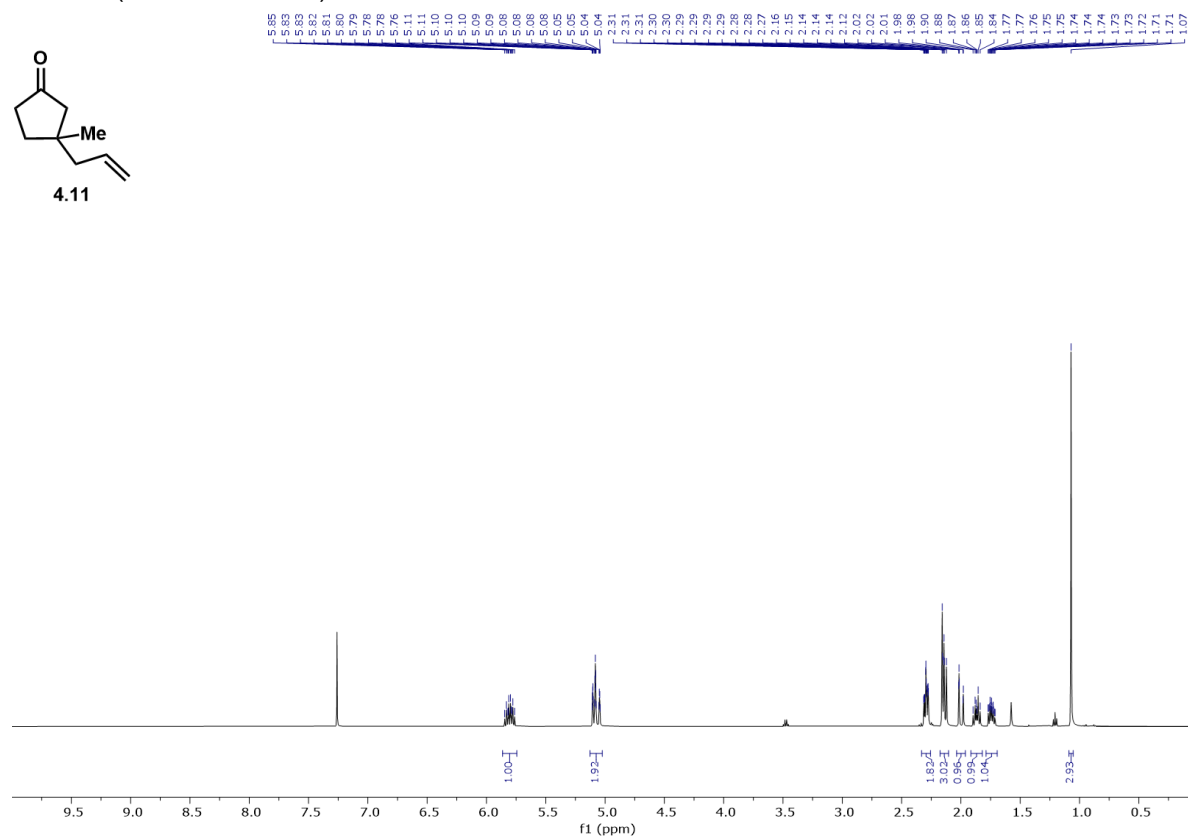
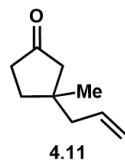
^1H NMR (700 MHz, CDCl_3)



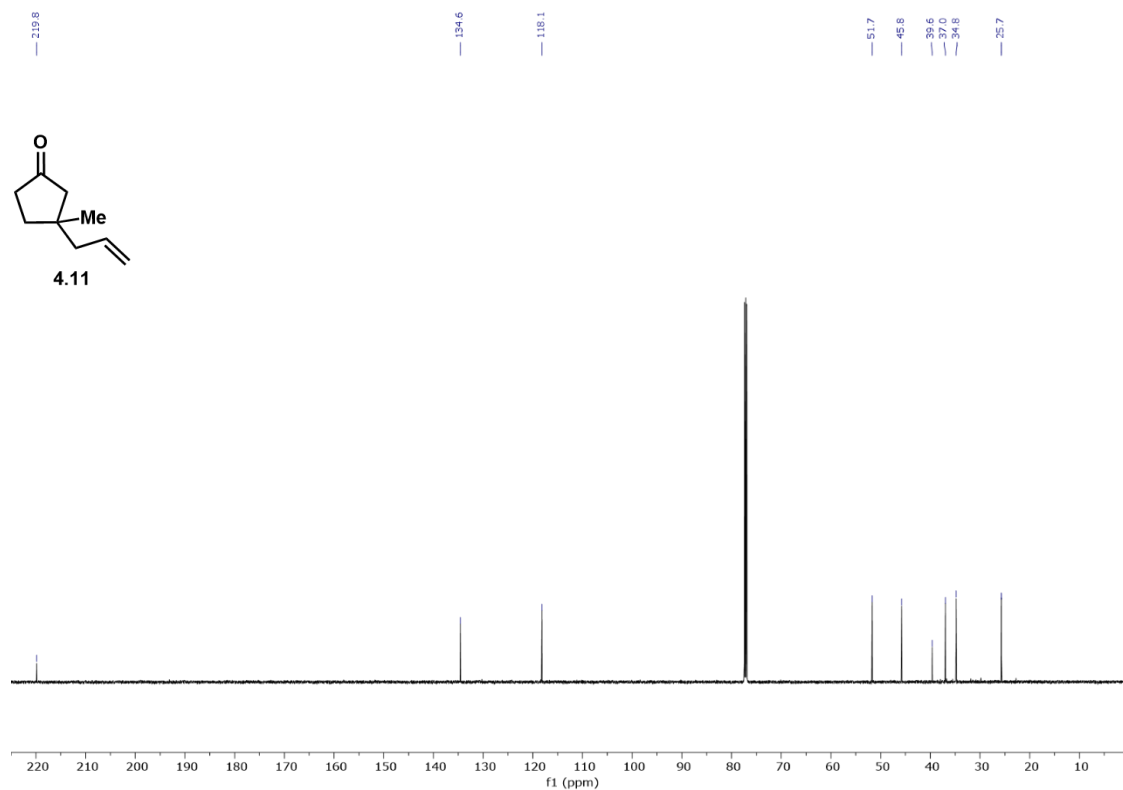
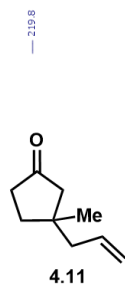
^{13}C NMR (101 MHz, CDCl_3)



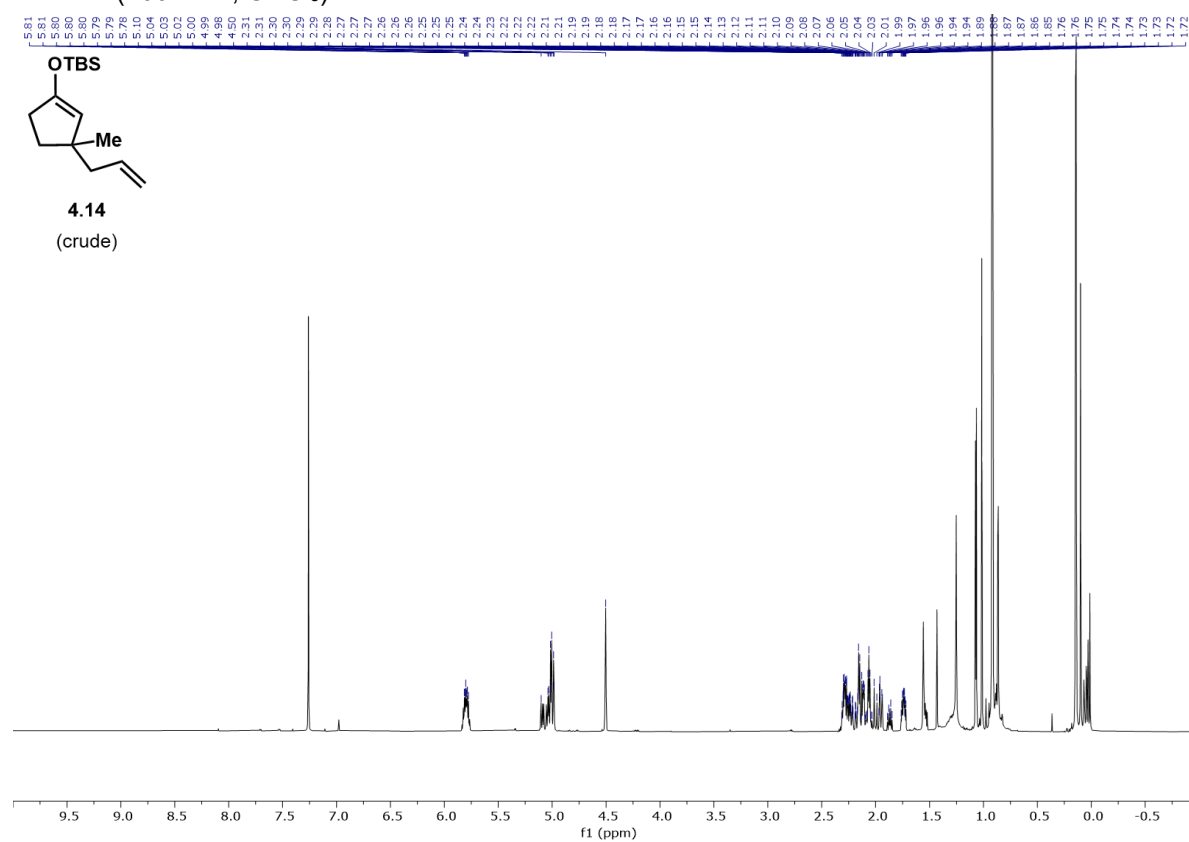
¹H NMR (500 MHz, CDCl₃)



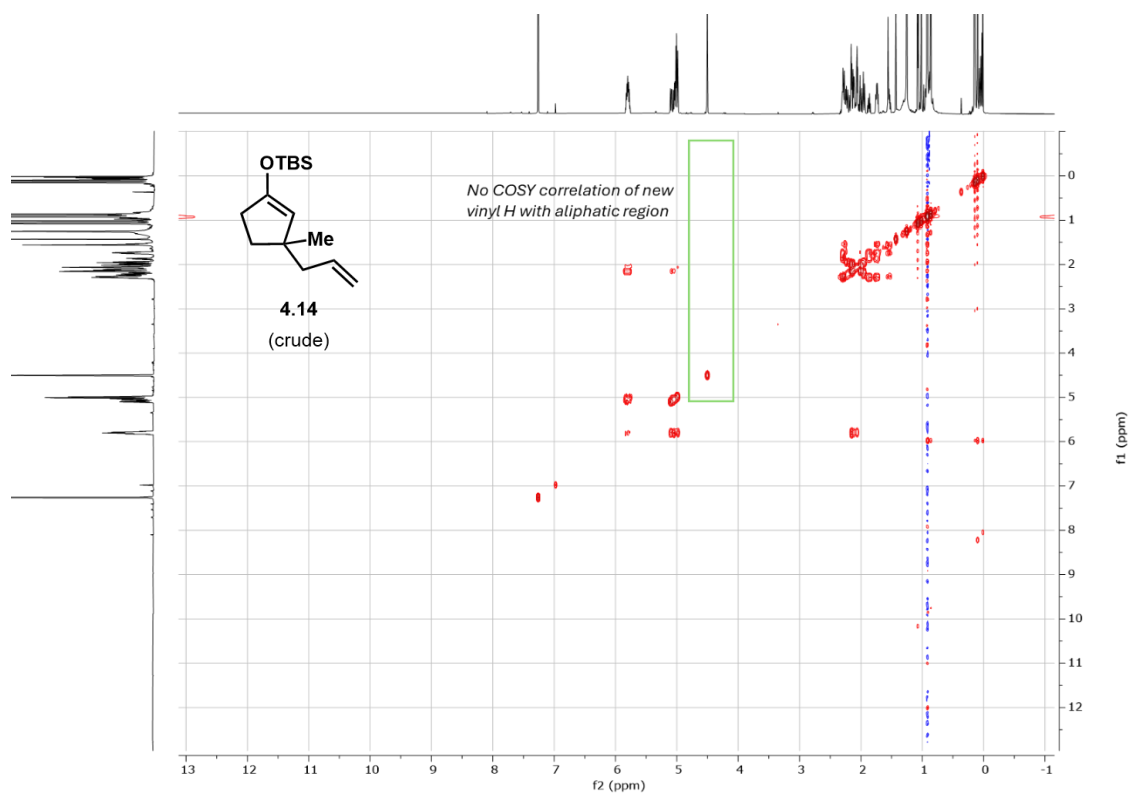
¹³C NMR (151 MHz, CDCl₃)



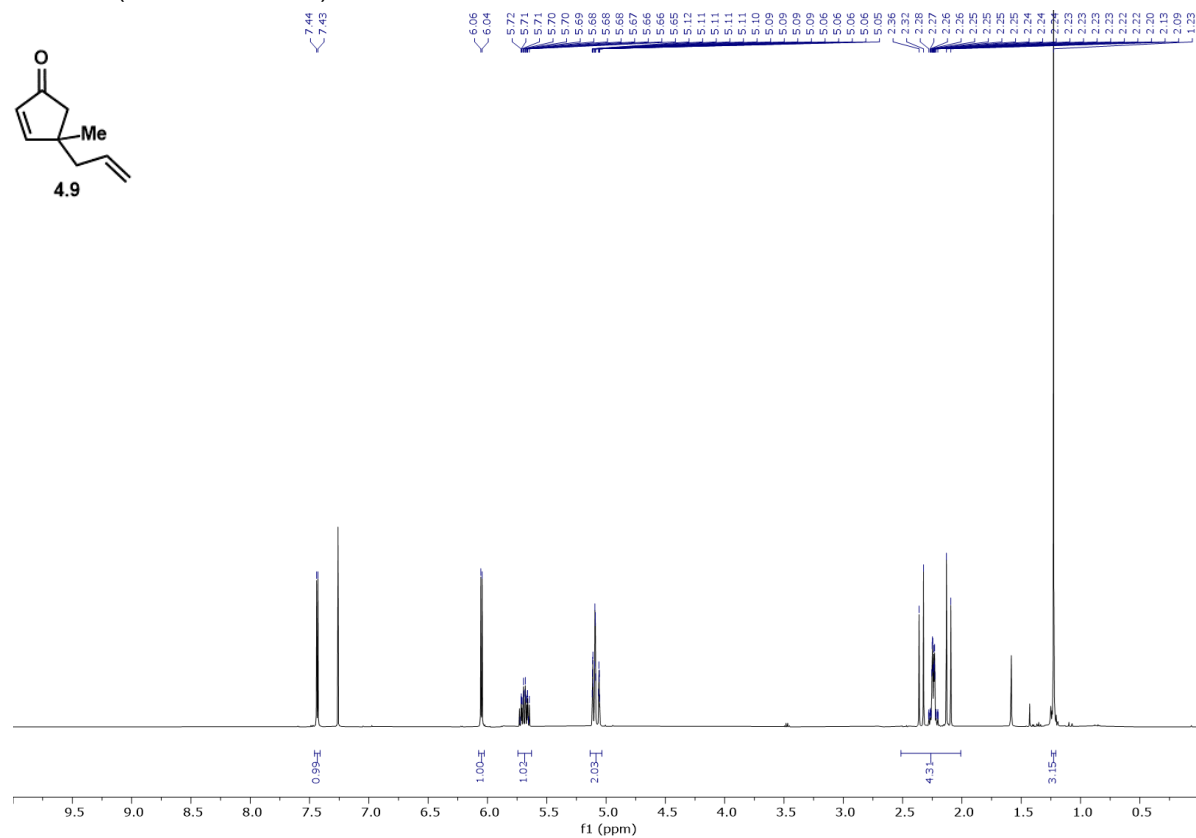
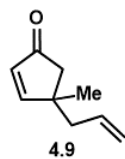
^1H NMR (700 MHz, CDCl_3)



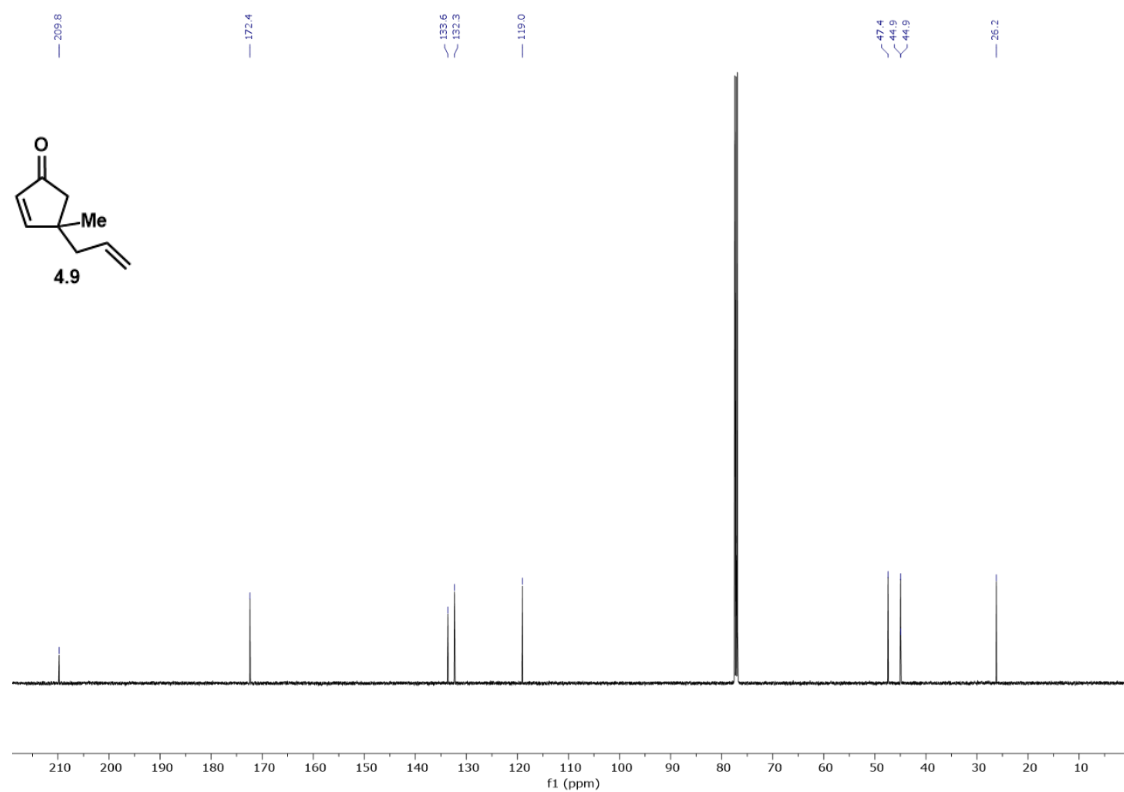
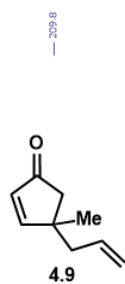
^1H - ^1H COSY NMR (700 MHz, CDCl_3)



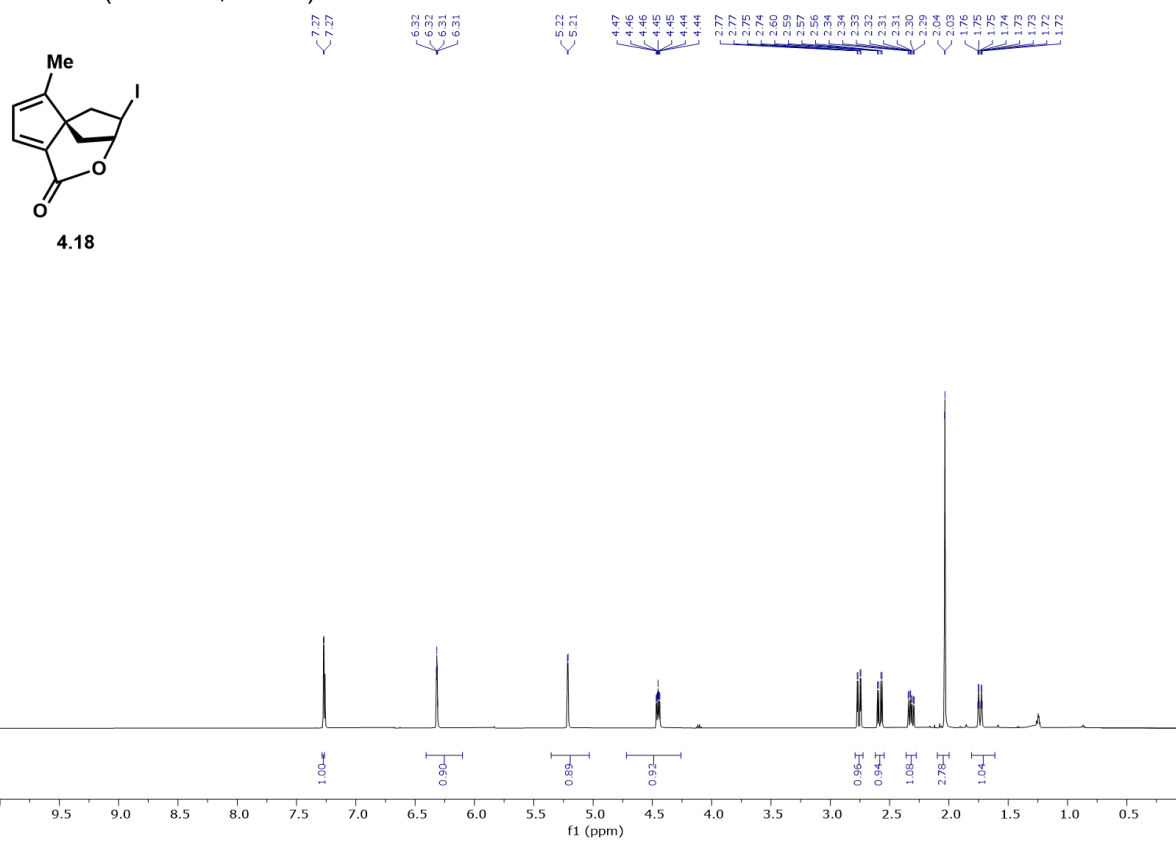
^1H NMR (500 MHz, CDCl_3)



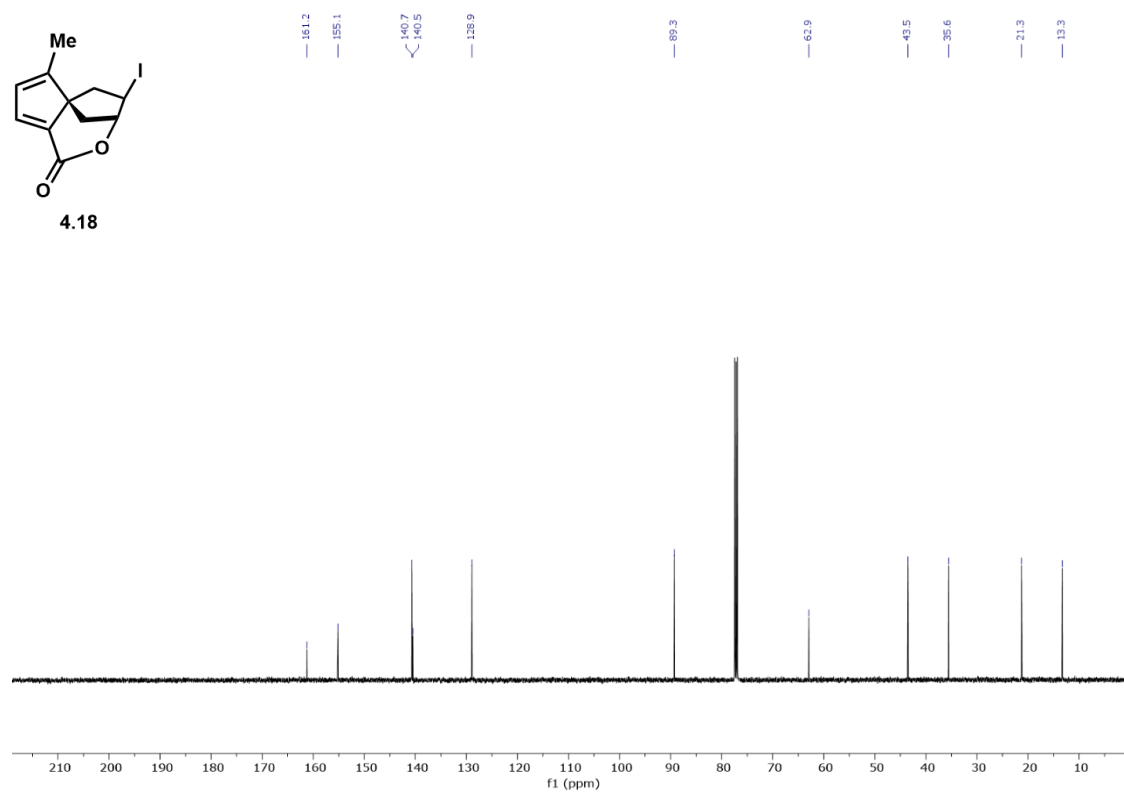
^{13}C NMR (126 MHz, CDCl_3)



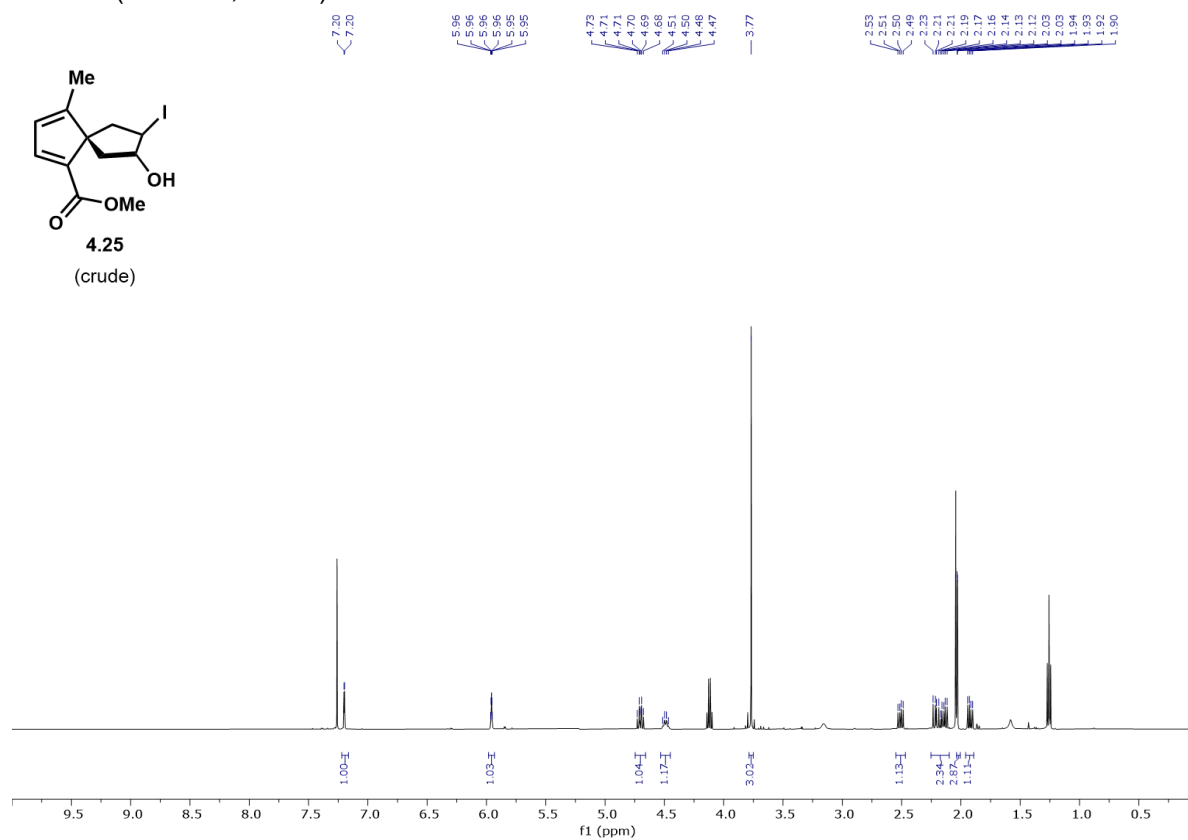
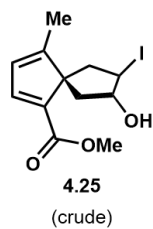
^1H NMR (500 MHz, CDCl_3)



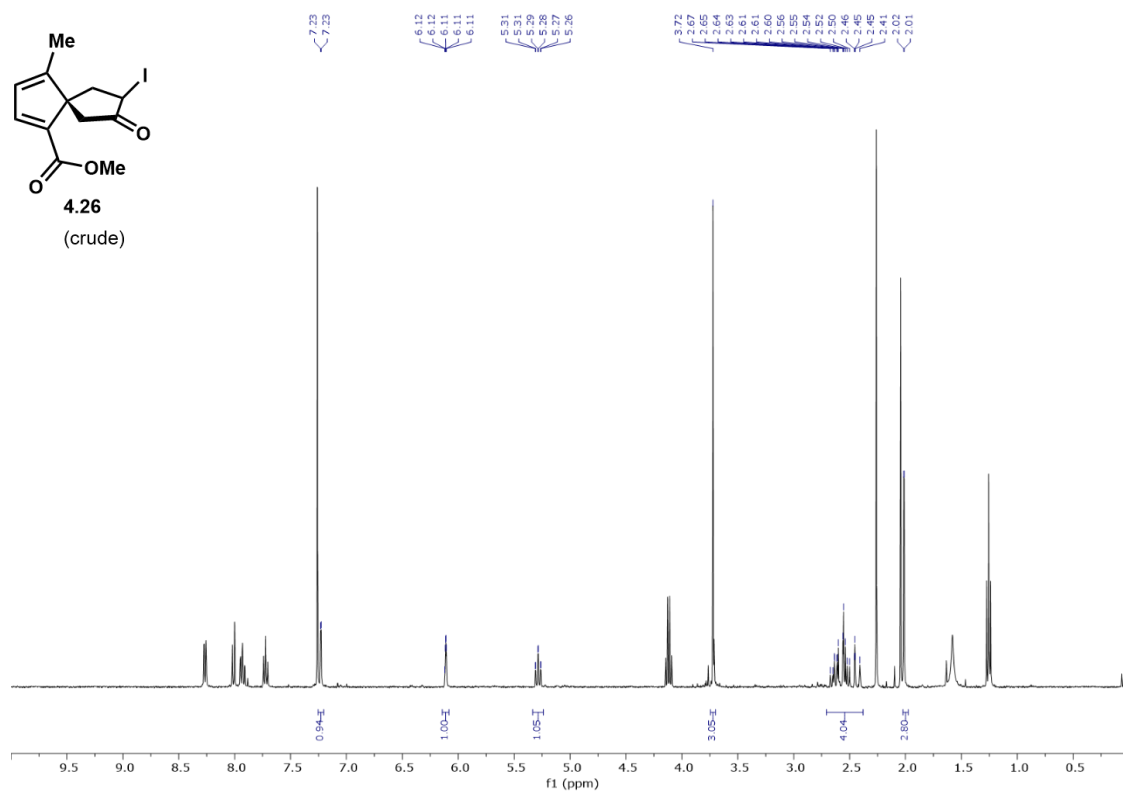
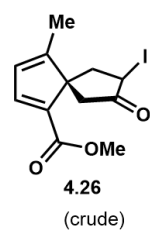
^{13}C NMR (126 MHz, CDCl_3)



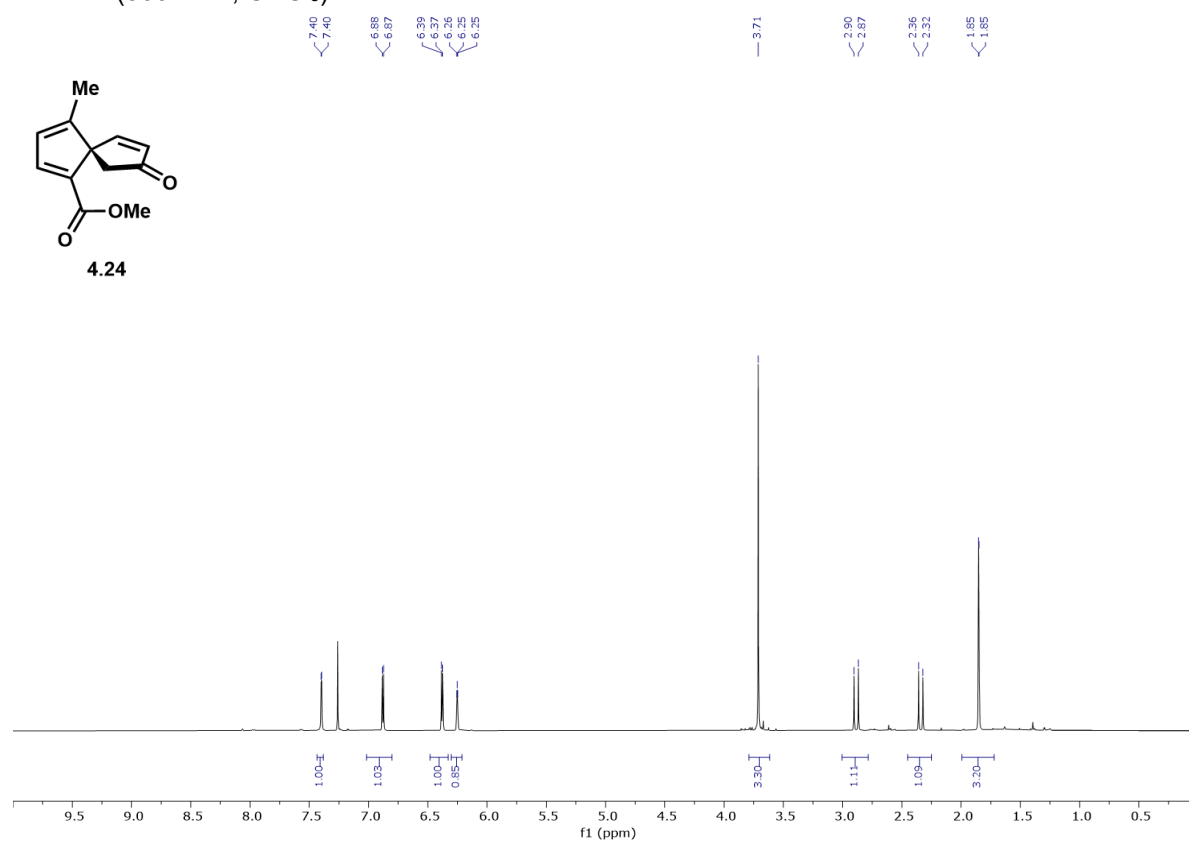
^1H NMR (500 MHz, CDCl_3)



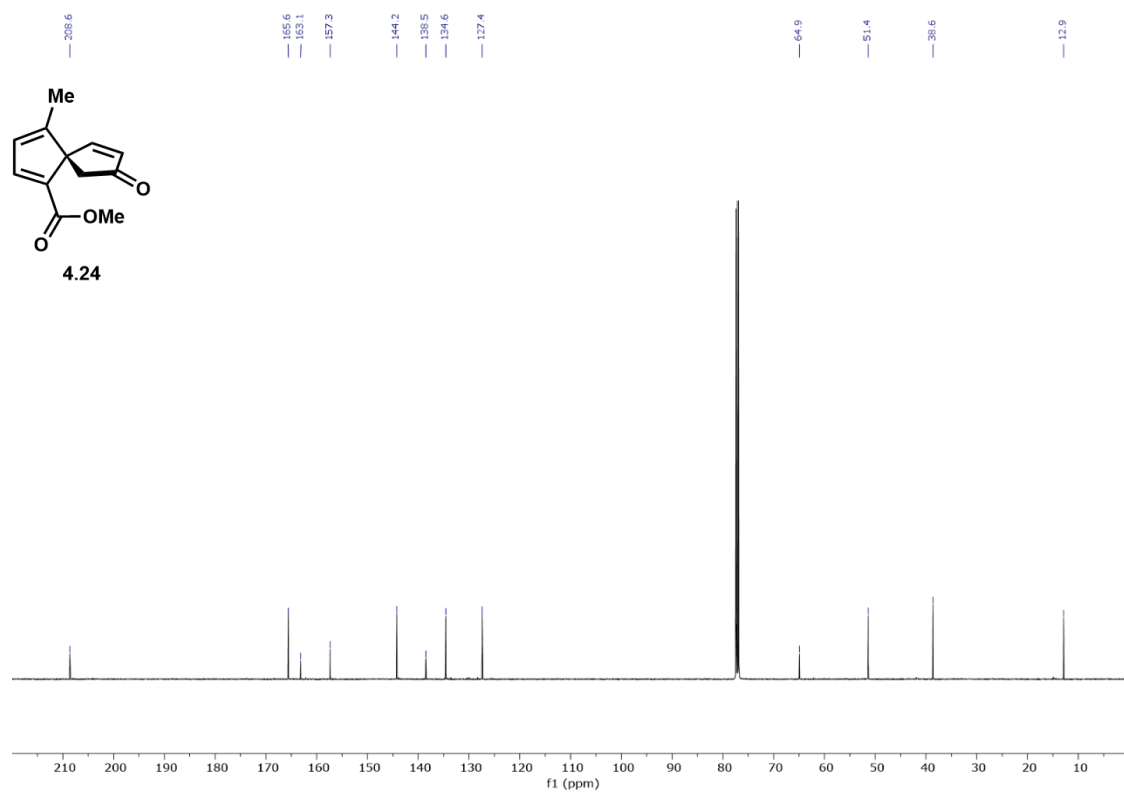
^1H NMR (400 MHz, CDCl_3)



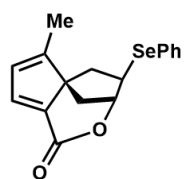
^1H NMR (500 MHz, CDCl_3)



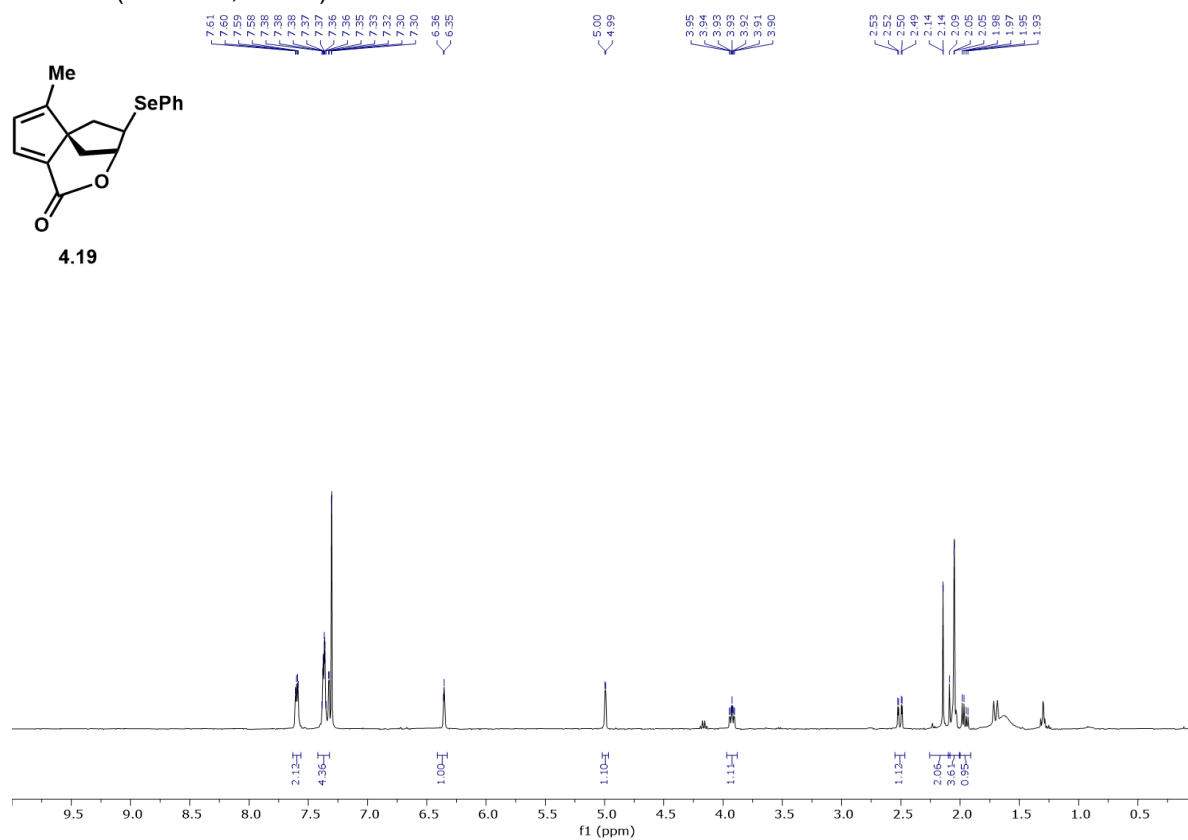
^{13}C NMR (126 MHz, CDCl_3)



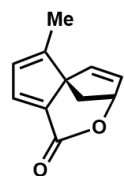
¹H NMR (400 MHz, CDCl₃)



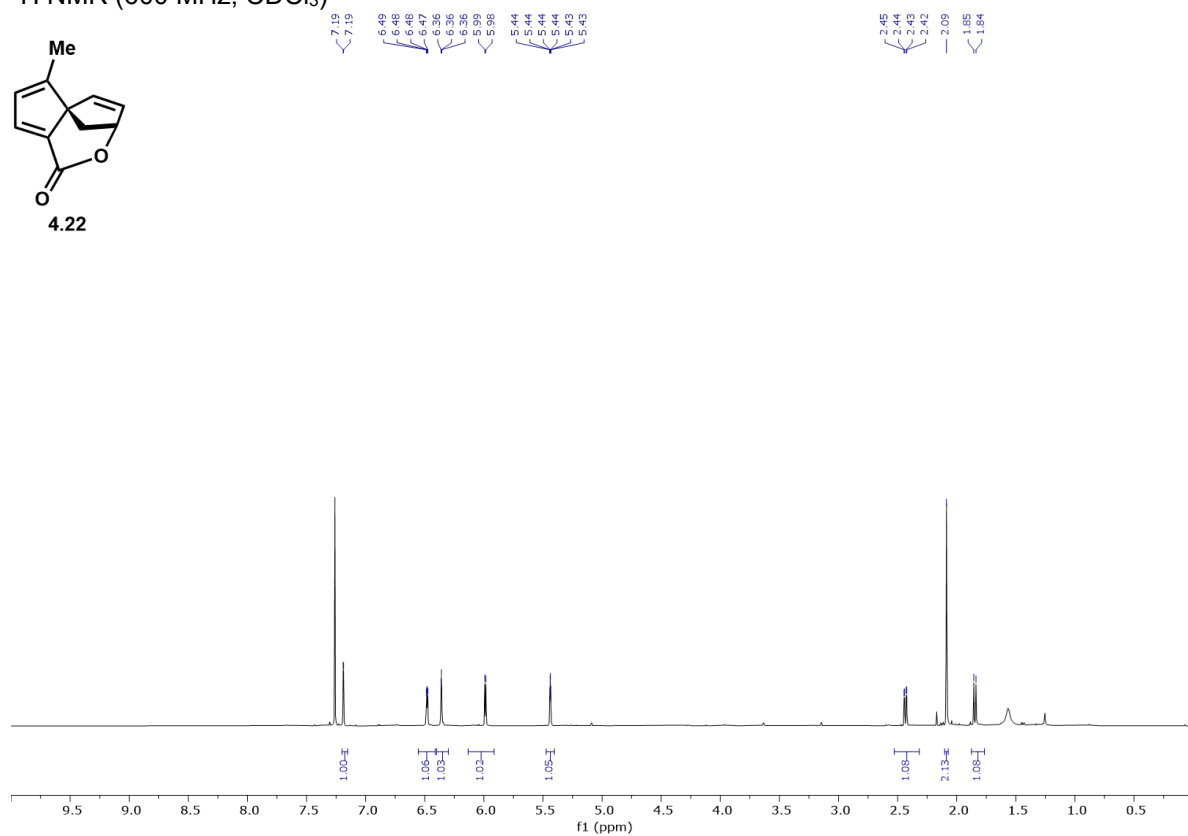
4.19



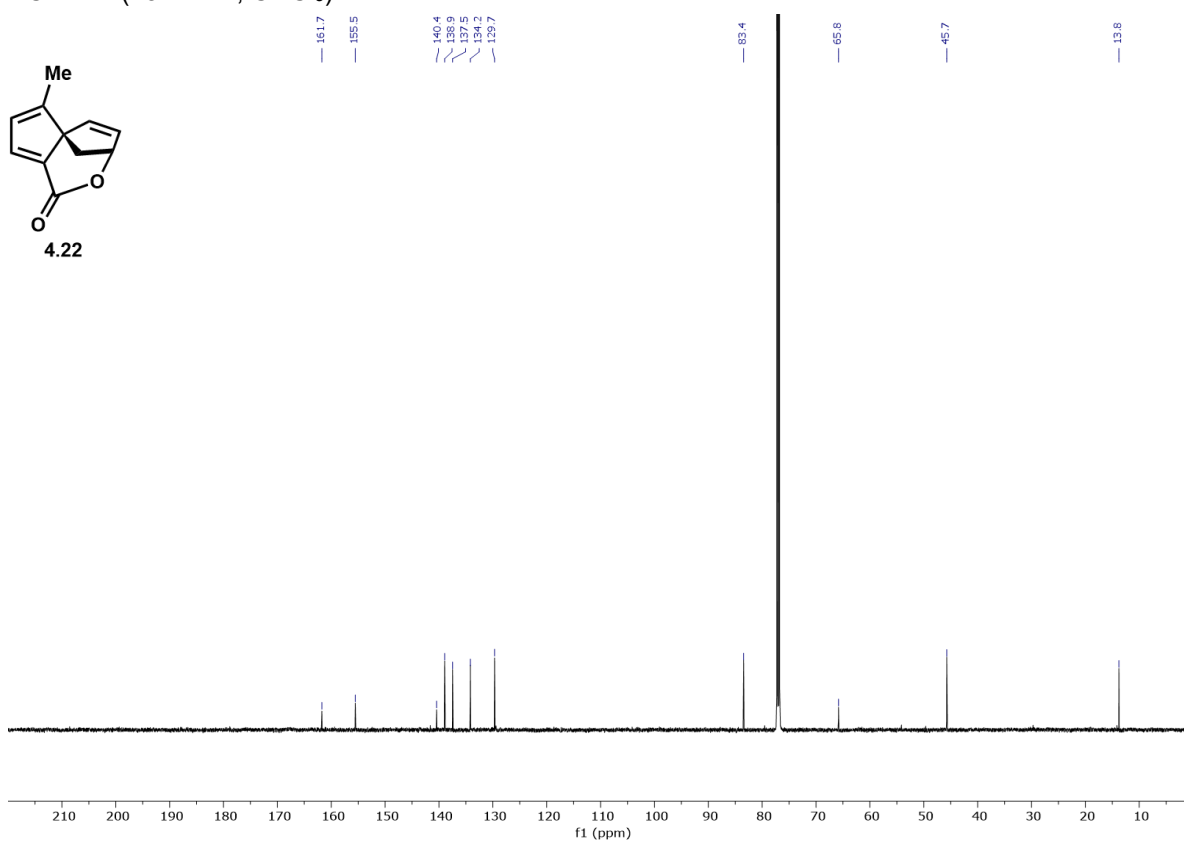
¹H NMR (600 MHz, CDCl₃)



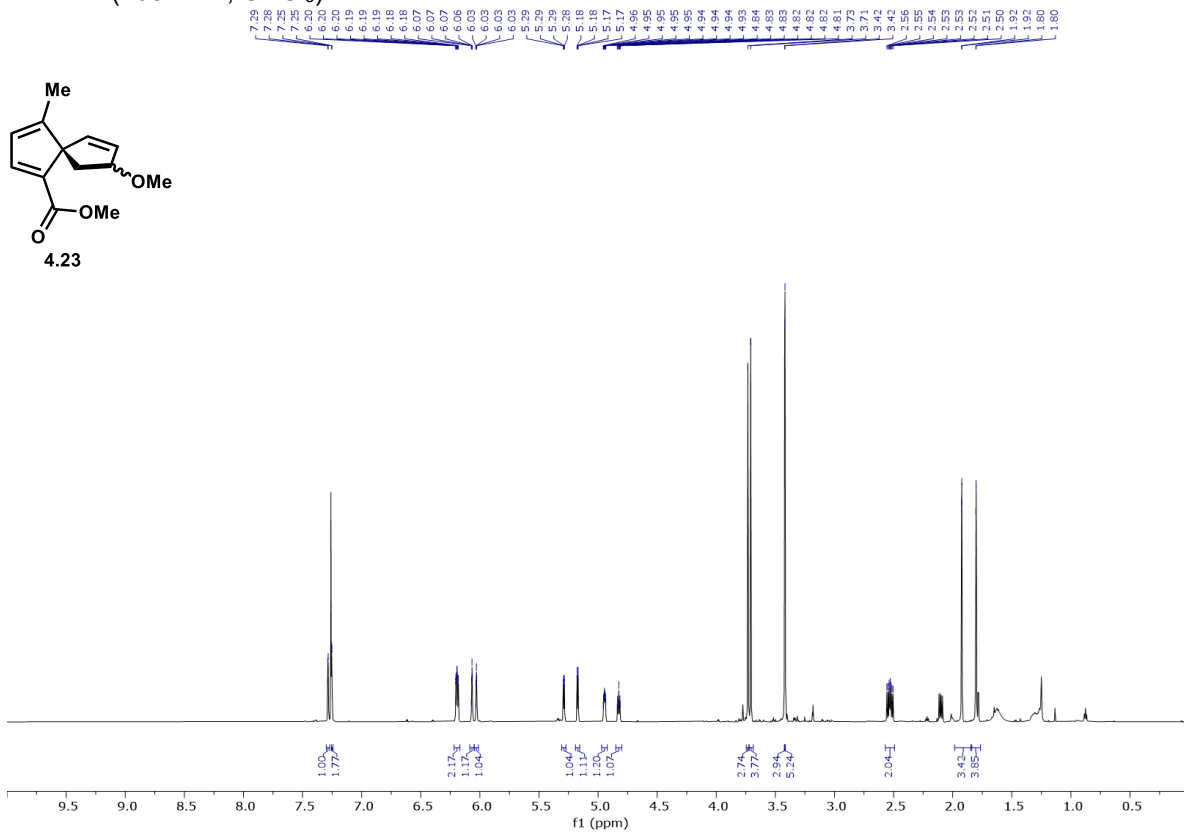
4.22



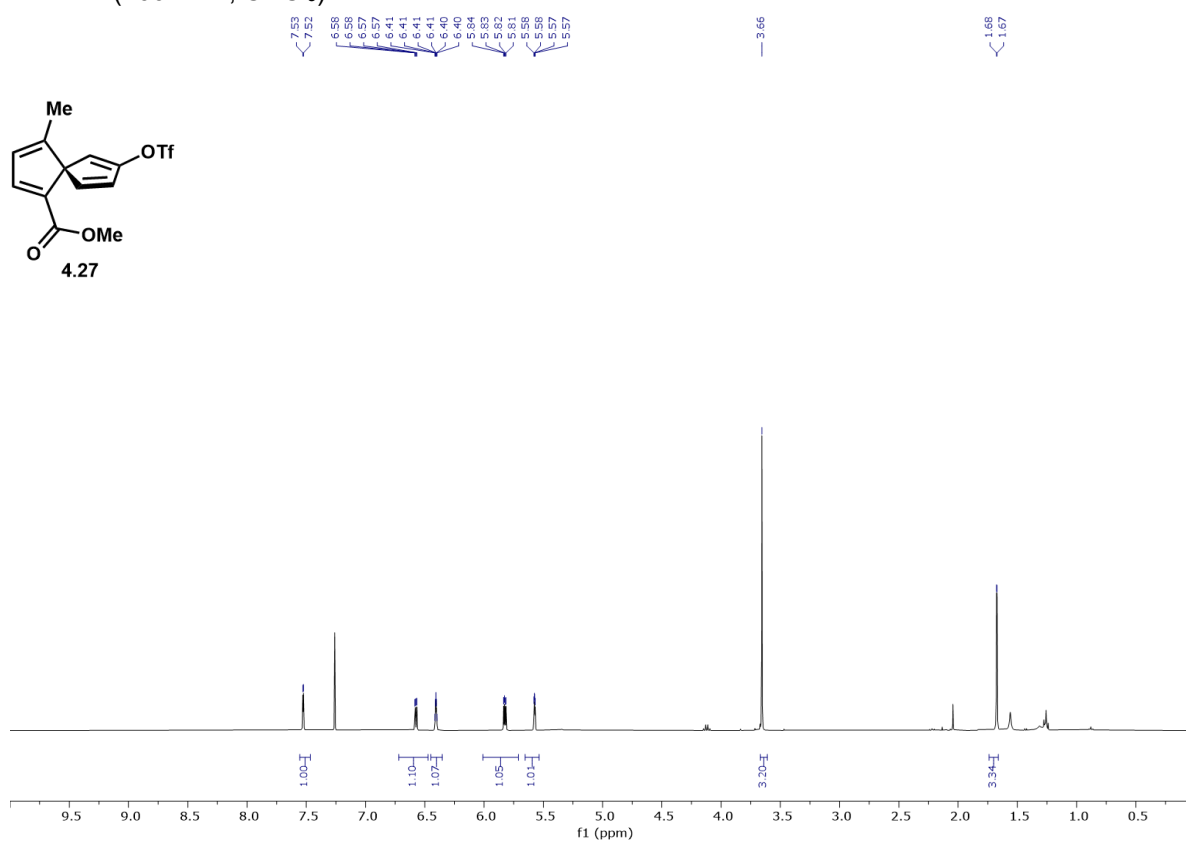
^{13}C NMR (151 MHz, CDCl_3)



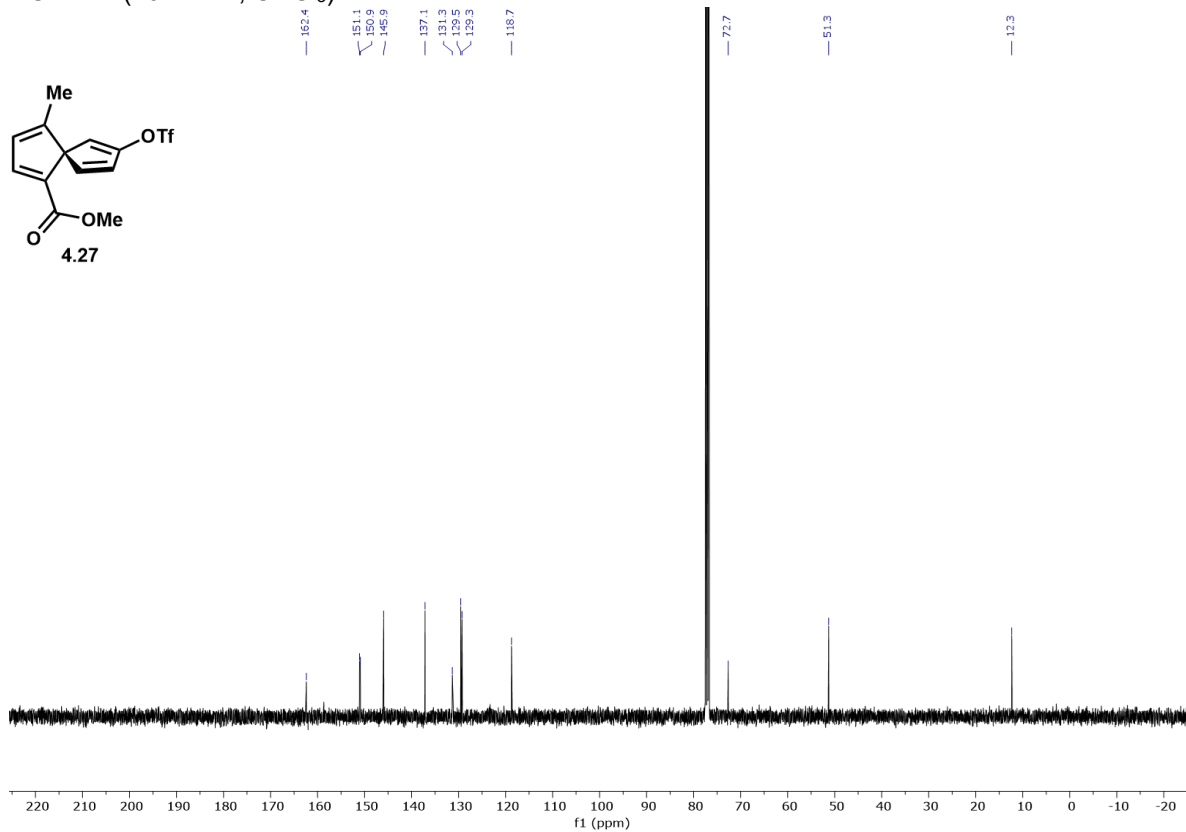
^1H NMR (700 MHz, CDCl_3)



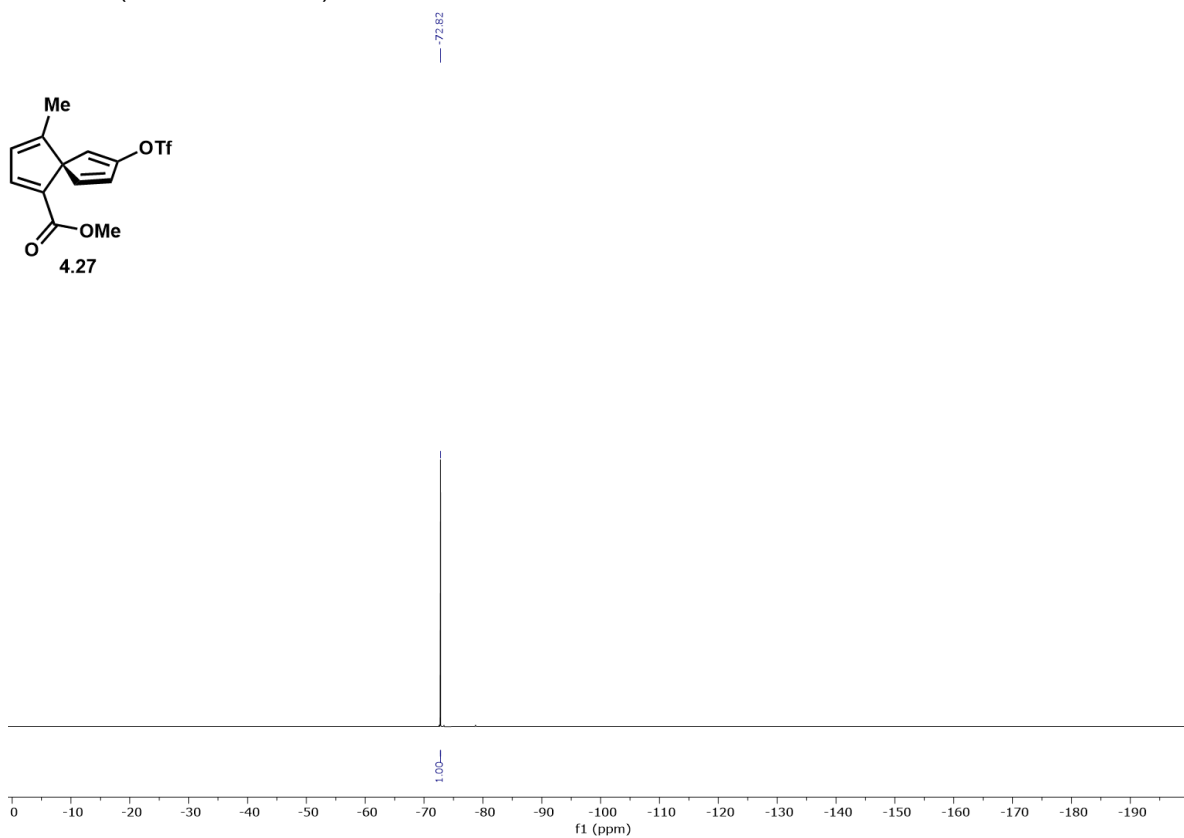
^1H NMR (400 MHz, CDCl_3)



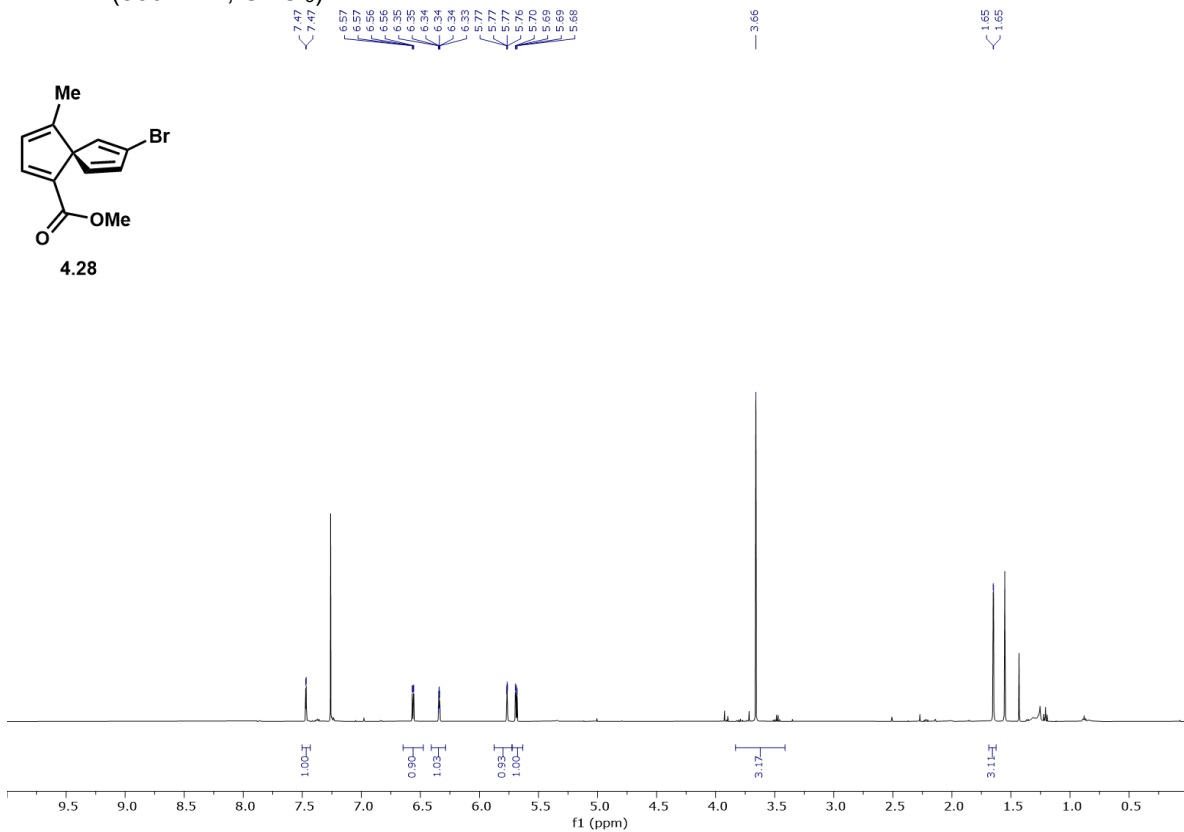
^{13}C NMR (101 MHz, CDCl_3)



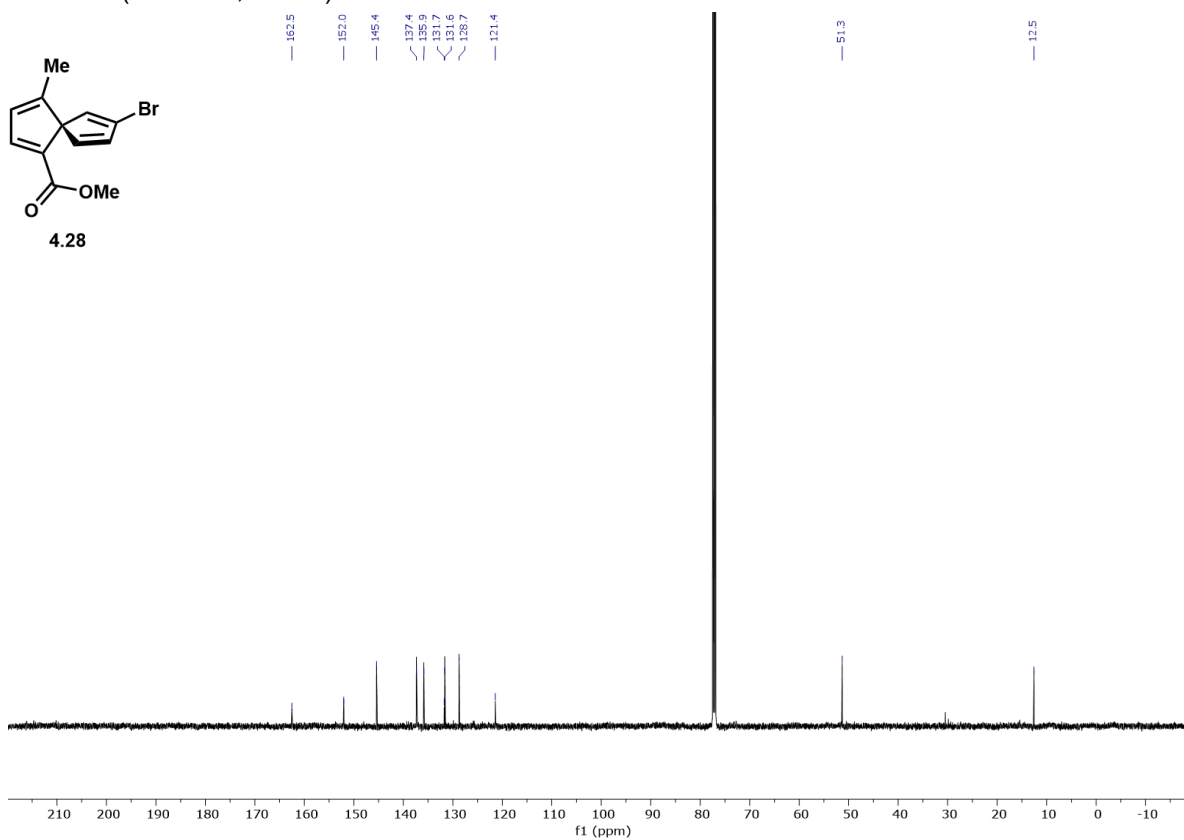
^{19}F NMR (376 MHz, CDCl_3)



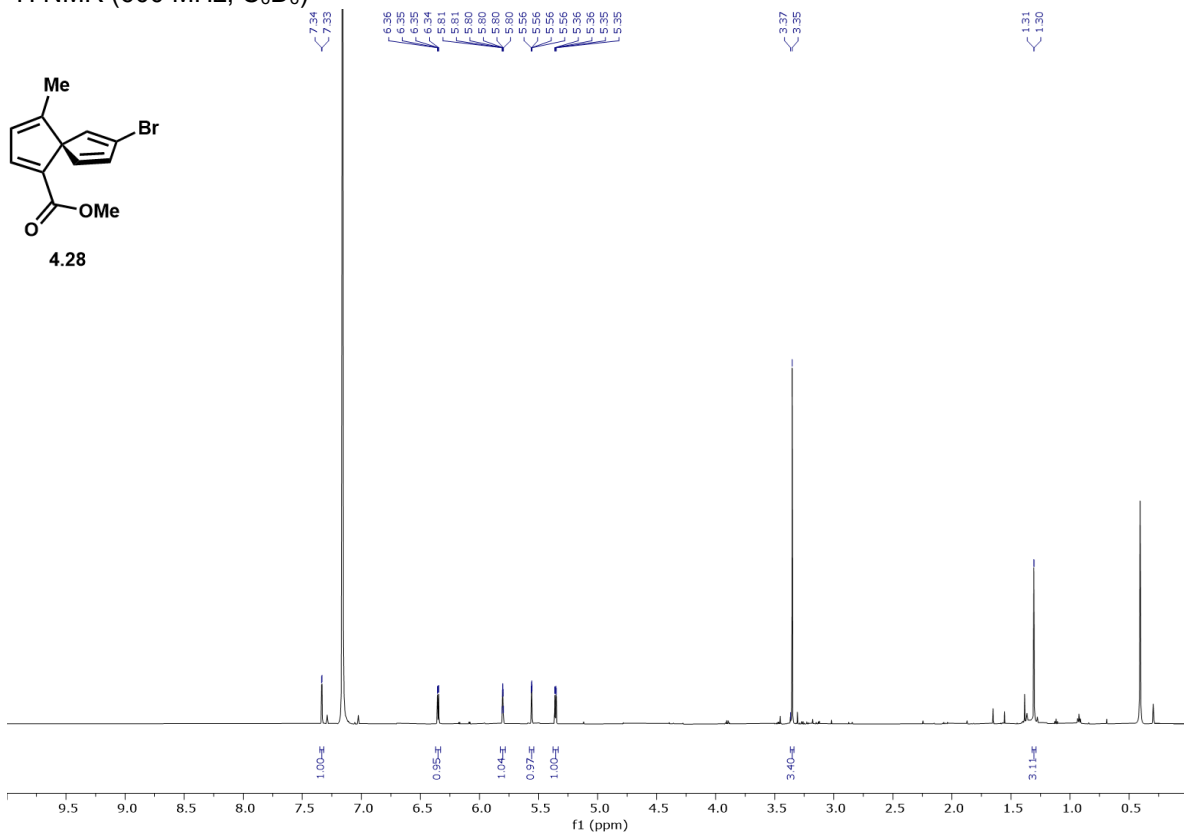
^1H NMR (500 MHz, CDCl_3)



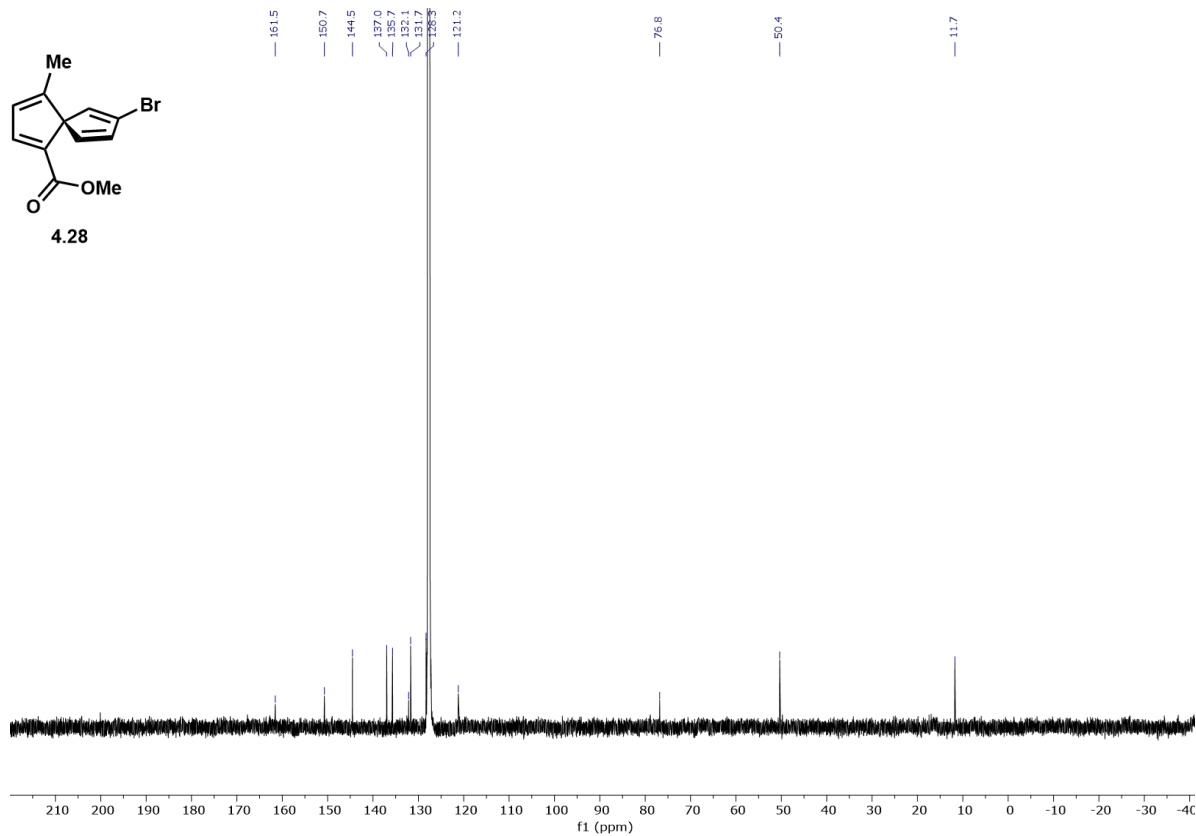
^{13}C NMR (126 MHz, CDCl_3)



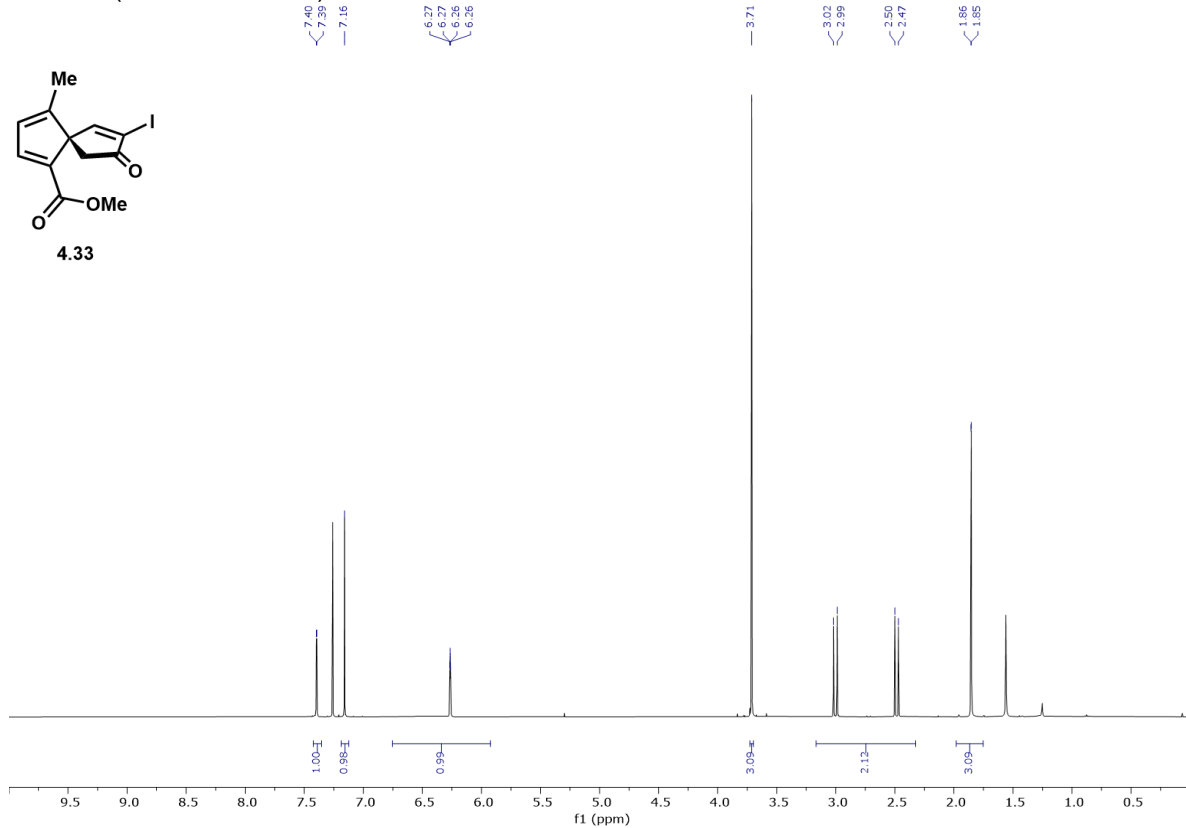
^1H NMR (600 MHz, C_6D_6)



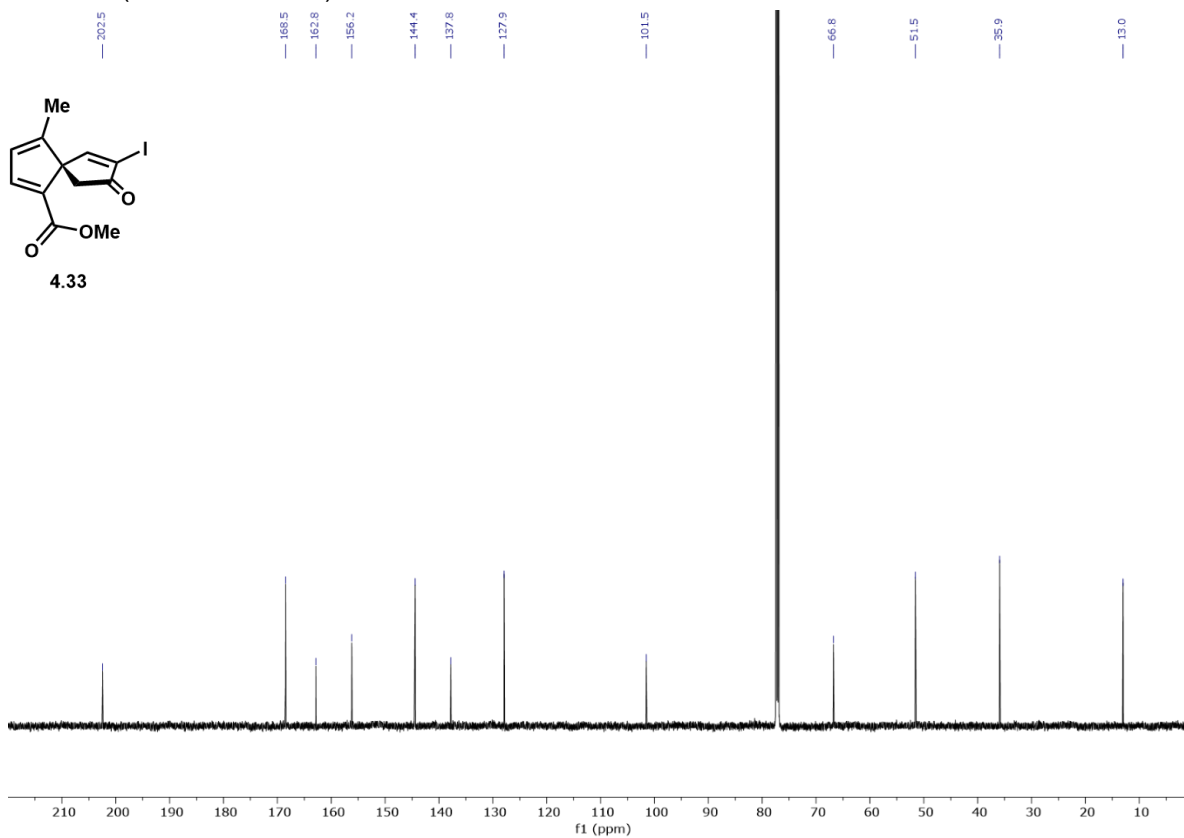
^{13}C NMR (151 MHz, C_6D_6)



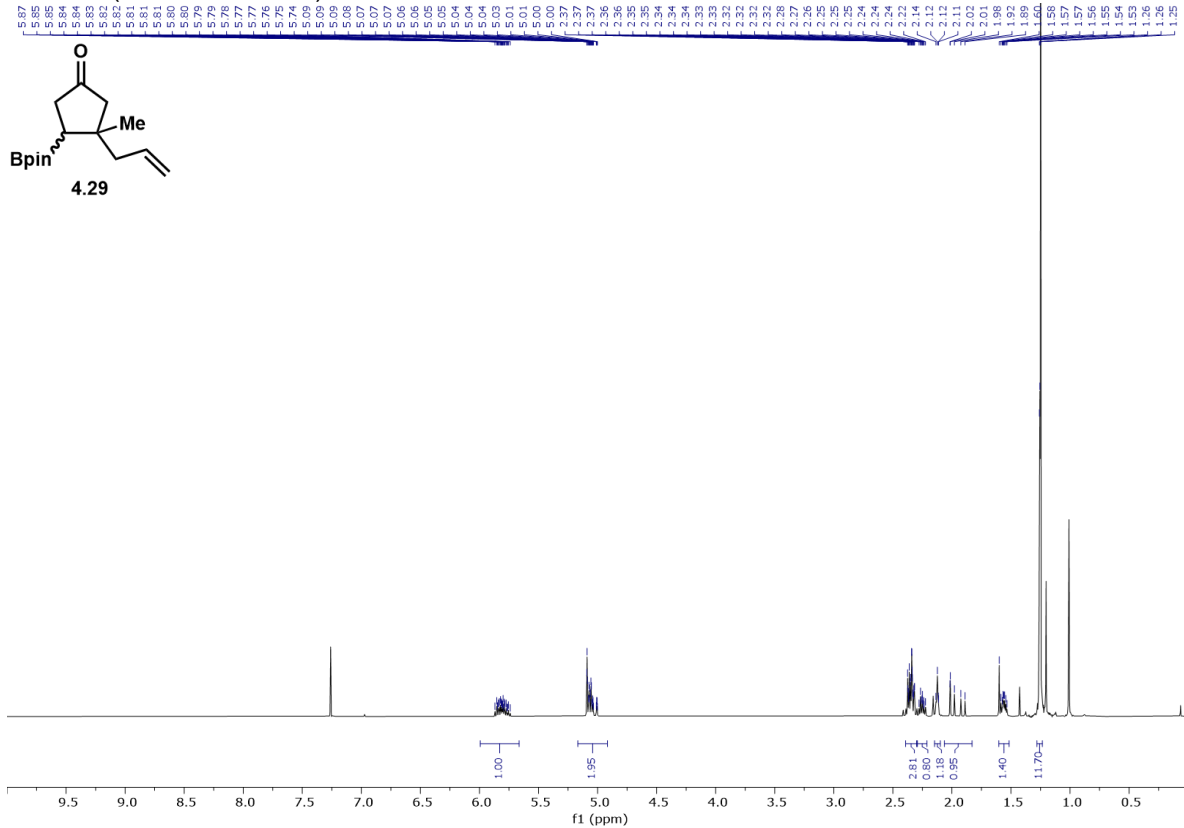
^1H NMR (600 MHz, CDCl_3)



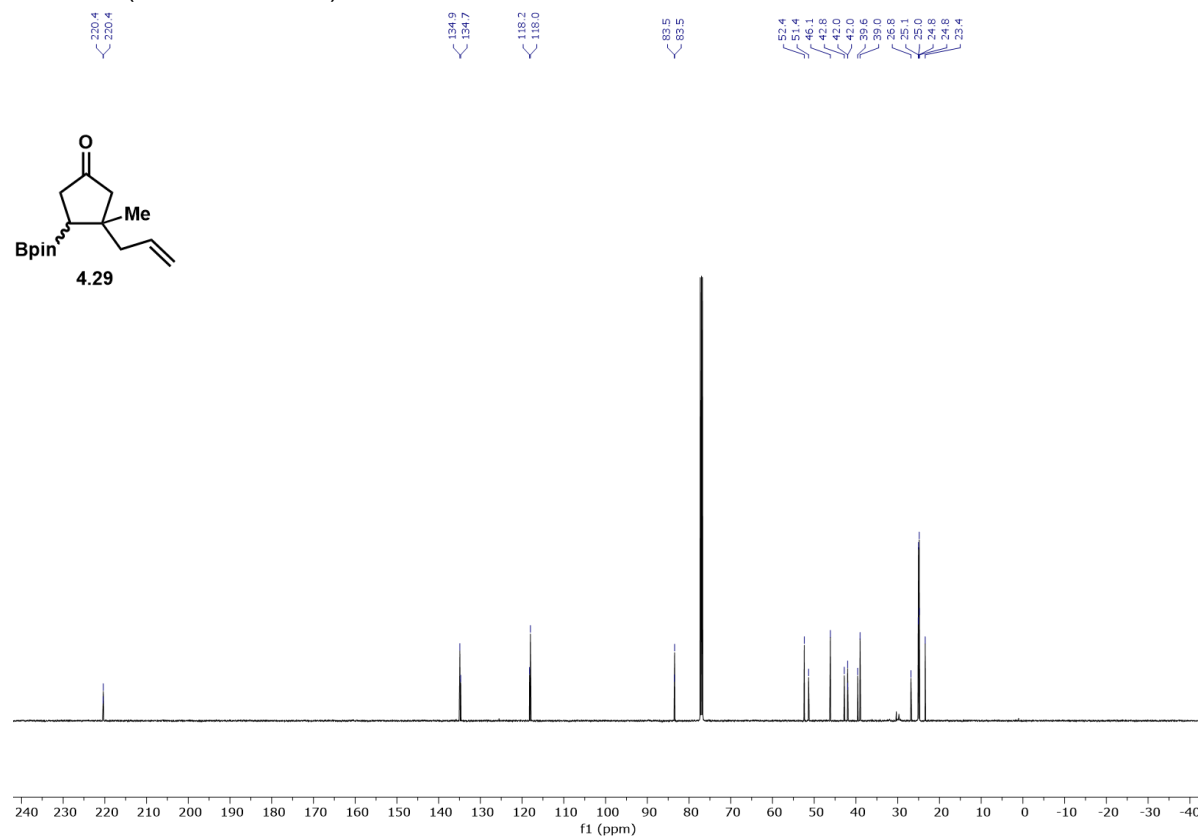
^{13}C NMR (151 MHz, CDCl_3)



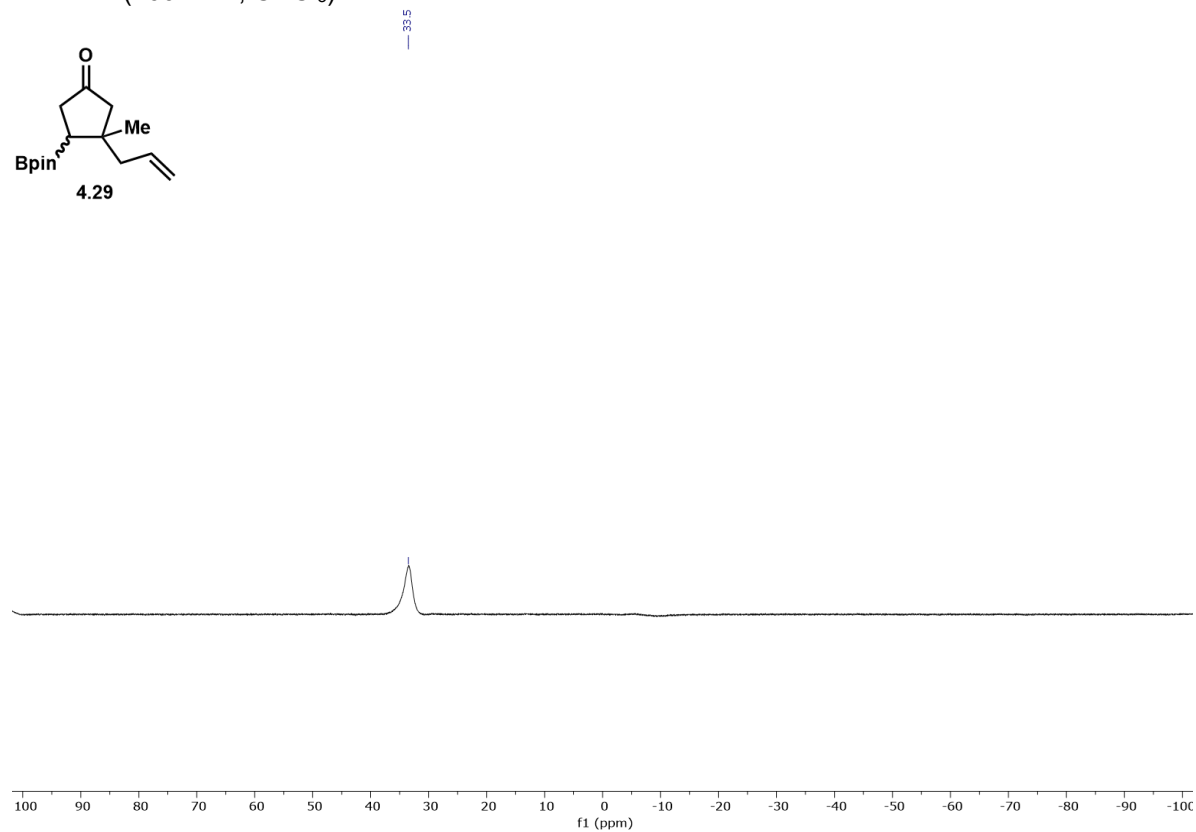
^1H NMR (500 MHz, CDCl_3)



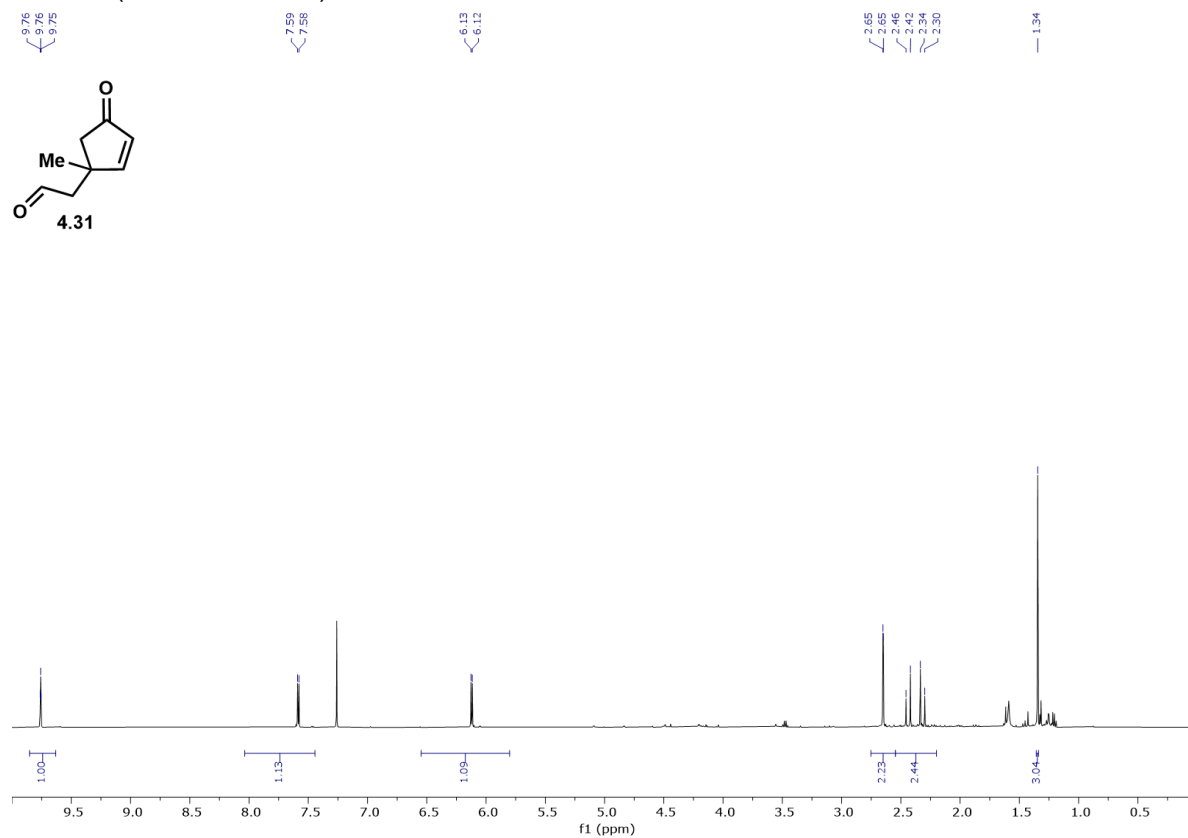
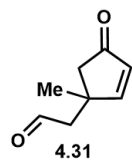
^{13}C NMR (126 MHz, CDCl_3)



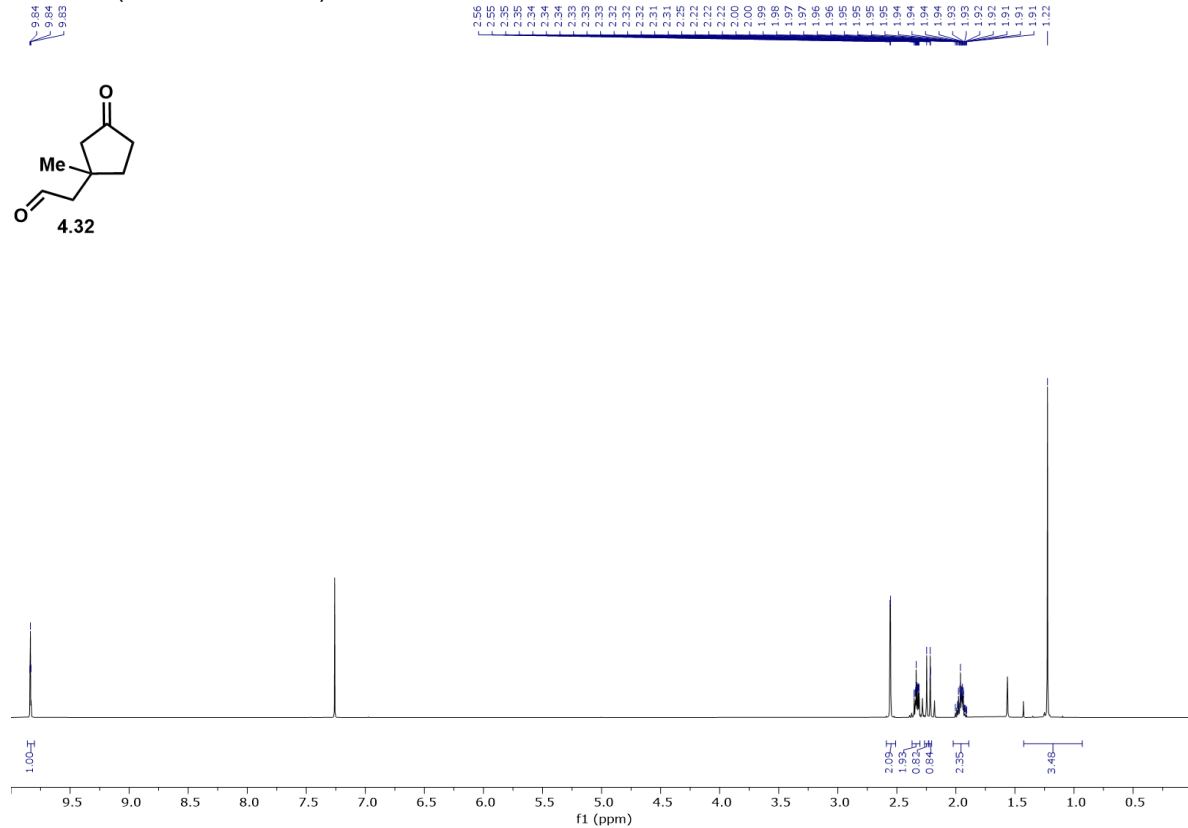
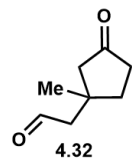
^{11}B NMR (160 MHz, CDCl_3)



9.76
9.76
9.75



9.84
9.84
9.83



4.32

CC1(CCCC1=O)CC=O

218.1 201.3

54.4 51.8 38.2 36.9 35.5 25.8

f1 (ppm)

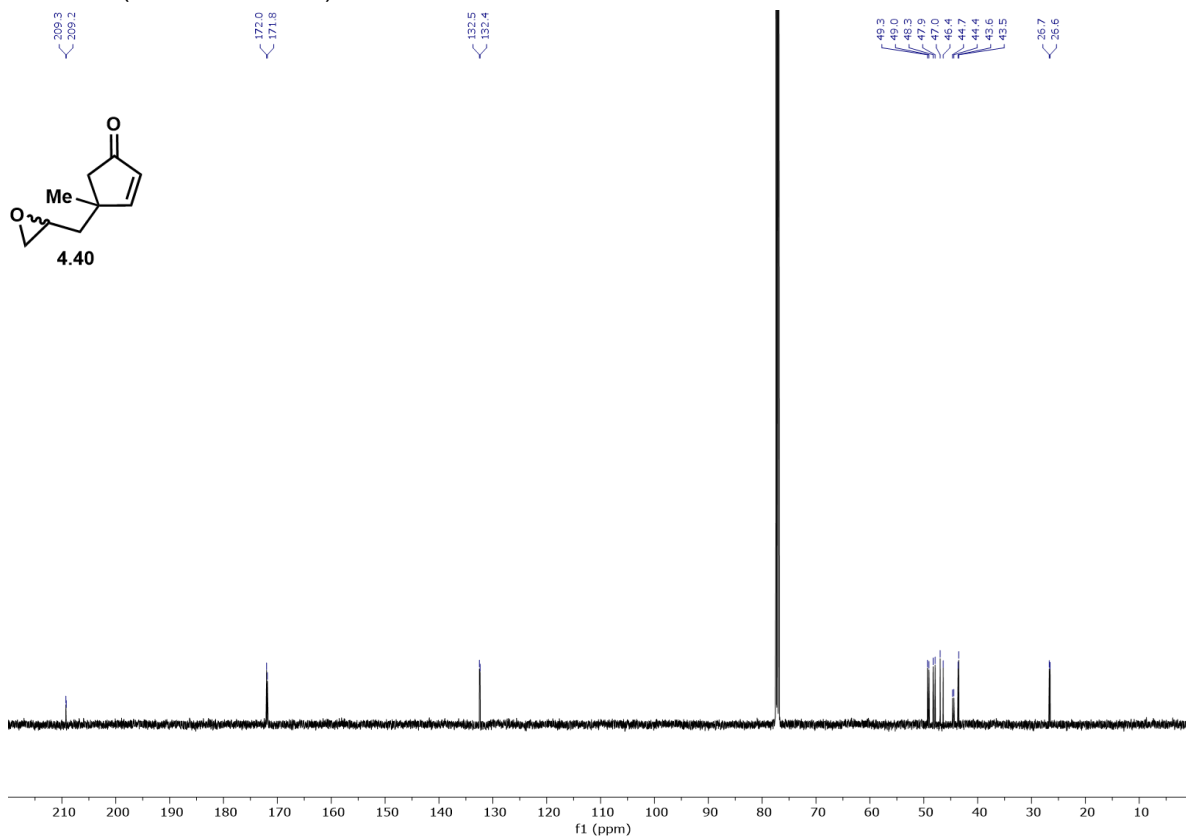
Chemical structure: 2-methyl-2-(oxiran-2-yl)cyclopentan-1-one

¹H NMR spectrum (ppm):

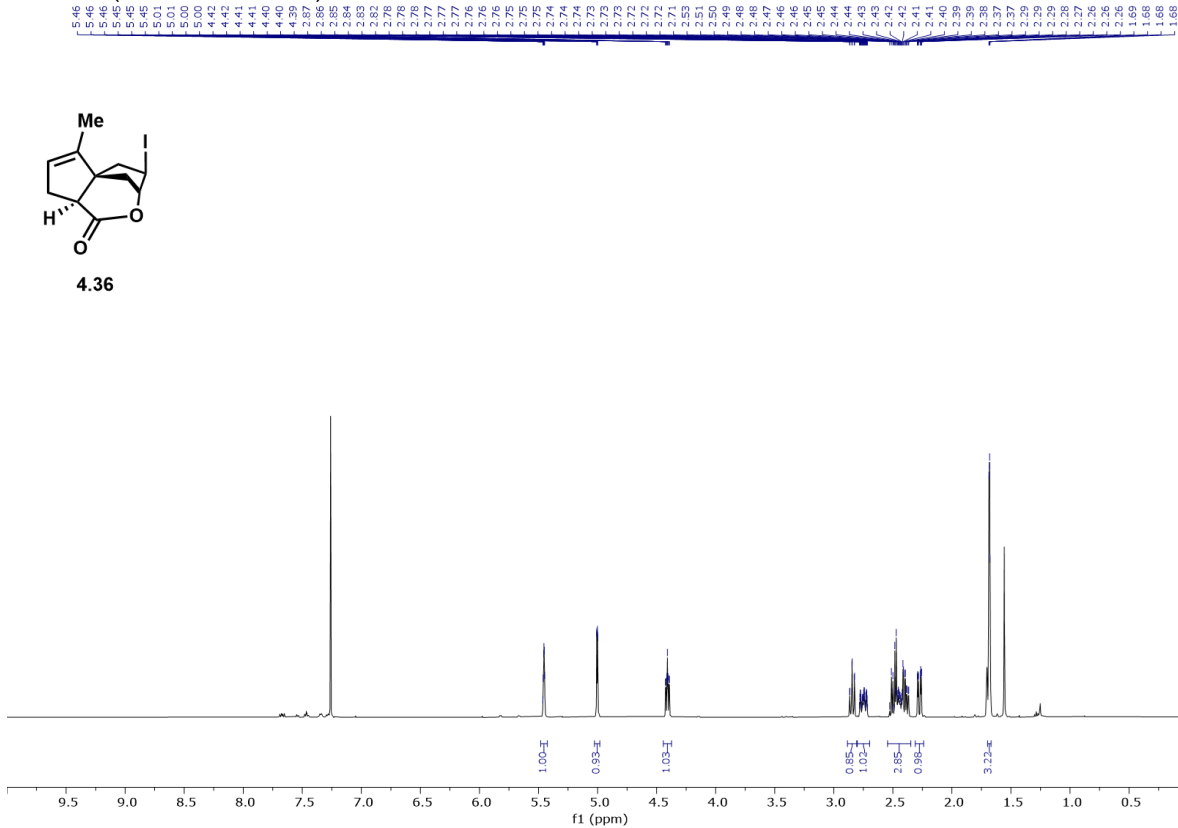
- 7.56, 7.55, 7.53, 7.53 (Aromatic region)
- 6.00 (Singlet)
- 2.90, 2.91, 2.92, 2.93, 2.94, 2.95, 2.96, 2.97, 2.98, 2.99, 3.00 (Multiplet)
- 1.32, 1.33, 1.34, 1.35, 1.36, 1.37, 1.38, 1.39, 1.40, 1.41, 1.42, 1.43, 1.44, 1.45, 1.46, 1.47, 1.48, 1.49, 1.50, 1.51, 1.52, 1.53, 1.54, 1.55, 1.56, 1.57, 1.58, 1.59, 1.60, 1.61, 1.62 (Aliphatic region)

Integration values (from left to right): 1.00, 0.94, 1.00, 1.05, 2.03, 1.06, 1.08, 0.74, 3.17.

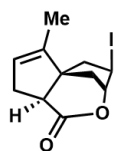
^{13}C NMR (126 MHz, CDCl_3)



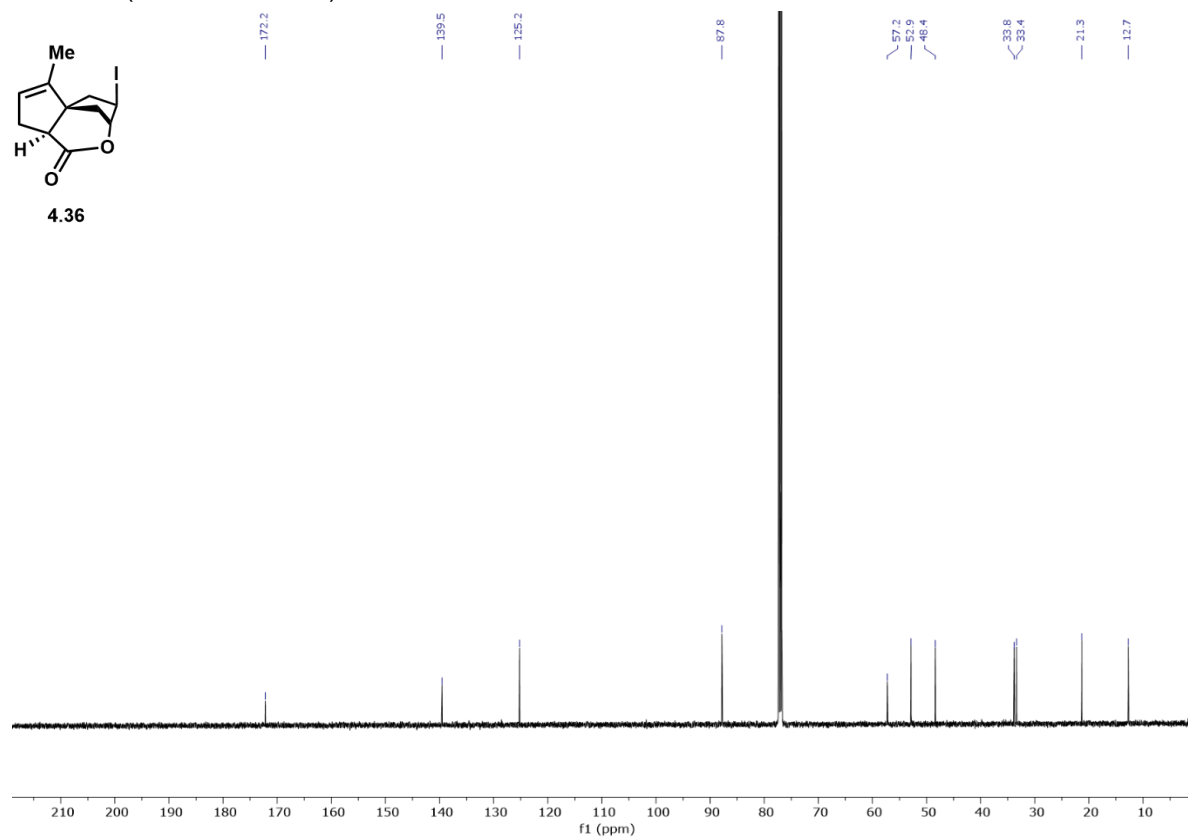
^1H NMR (500 MHz, CDCl_3)



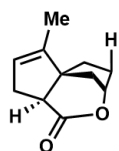
^{13}C NMR (126 MHz, CDCl_3)



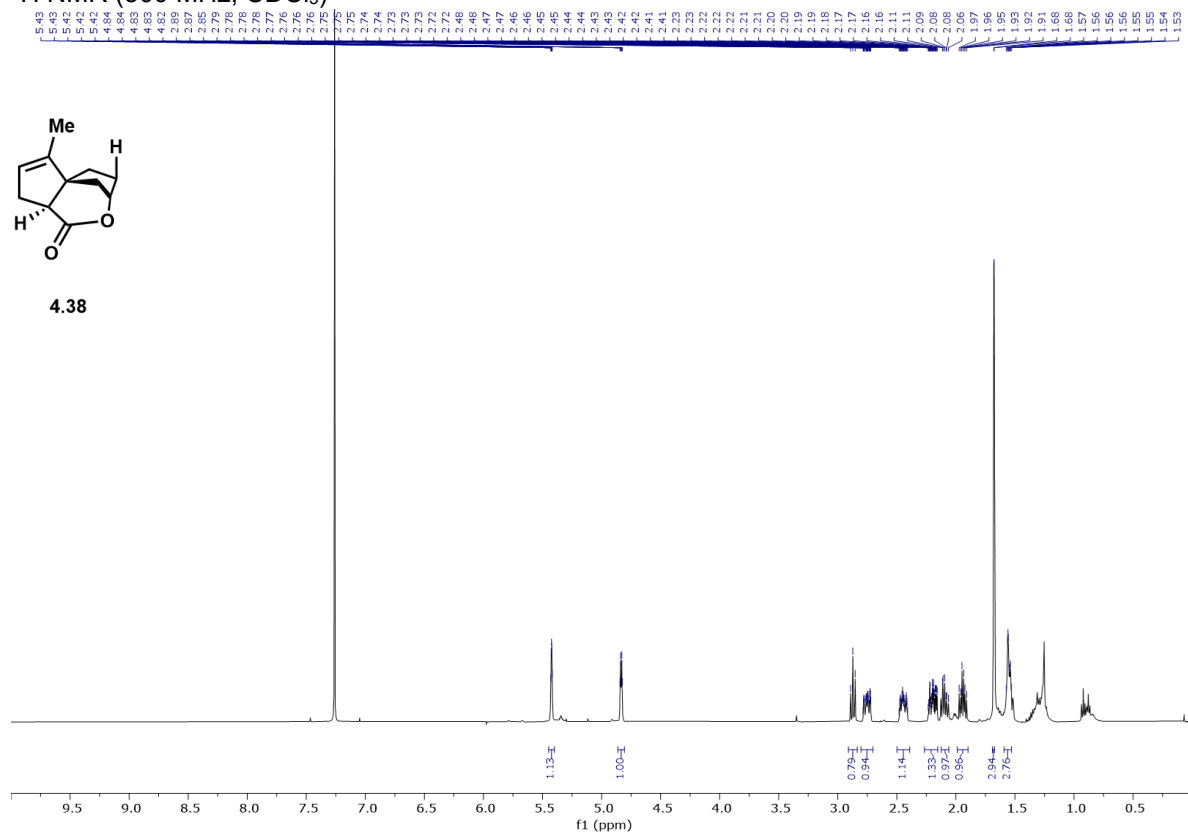
4.36



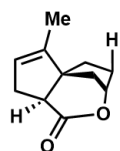
^1H NMR (500 MHz, CDCl_3)



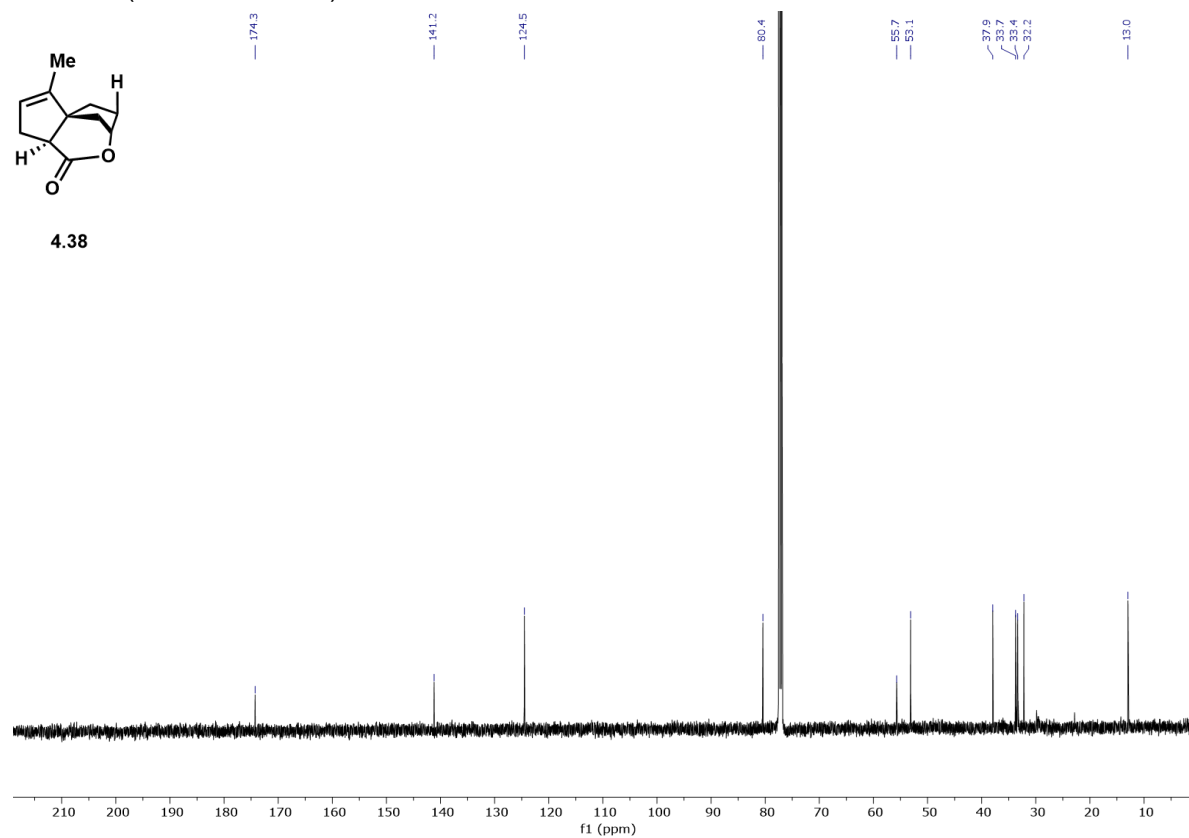
4.38



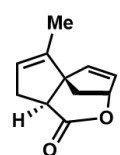
^{13}C NMR (126 MHz, CDCl_3)



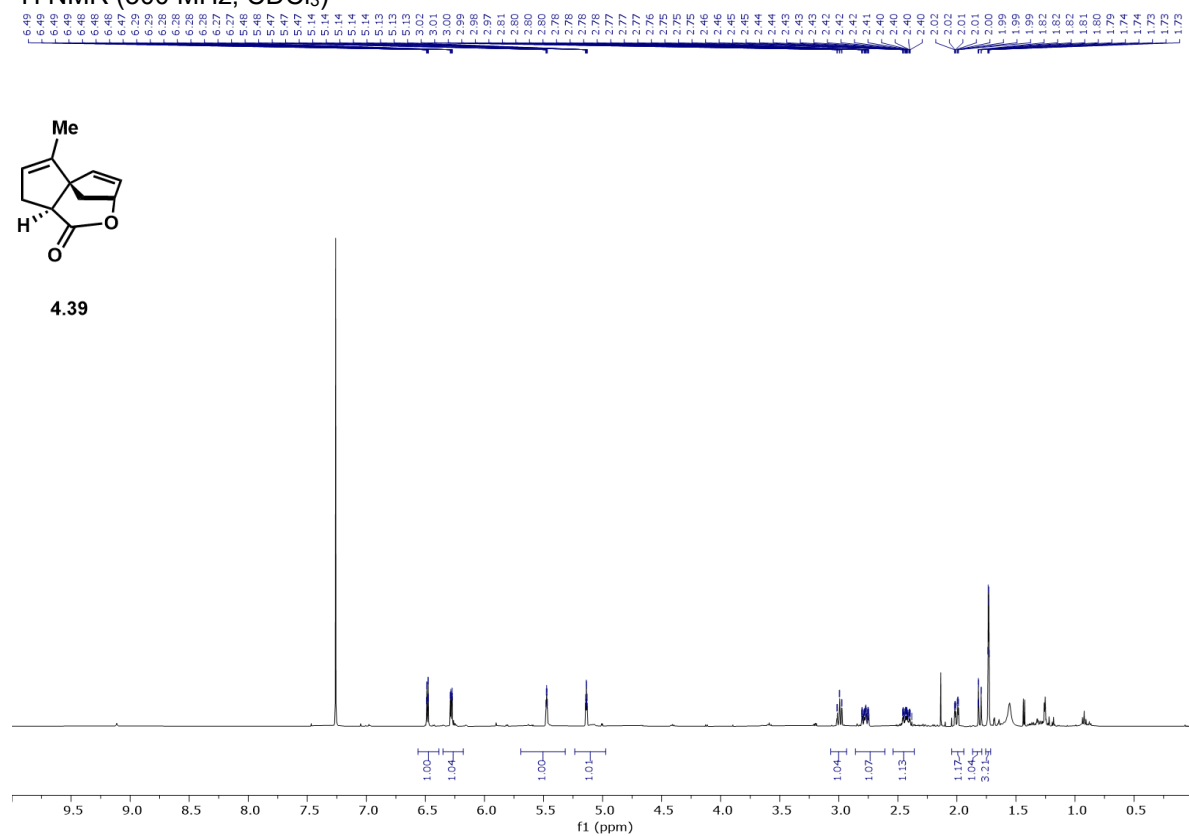
4.38



^1H NMR (500 MHz, CDCl_3)



4.39



4.39

C[C@H]1C=CC(=O)O[C@H]1C=C

The ¹³C NMR spectrum of compound 4.39 shows 11 distinct signals. The chemical structure of 4.39 is a bicyclic enone with a methyl group and a hydrogen atom on the double bond. The spectrum features a carbonyl peak at 173.7 ppm, olefinic and ring quaternary carbon peaks between 125 and 147 ppm, a solvent peak at 81.7 ppm, and aliphatic carbon peaks at 59.6, 52.6, 41.7, 33.2, and 13.4 ppm.

Chemical Shift (ppm)
173.7
145.7
140.7
132.6
125.5
81.7
59.6
52.6
41.7
33.2
13.4

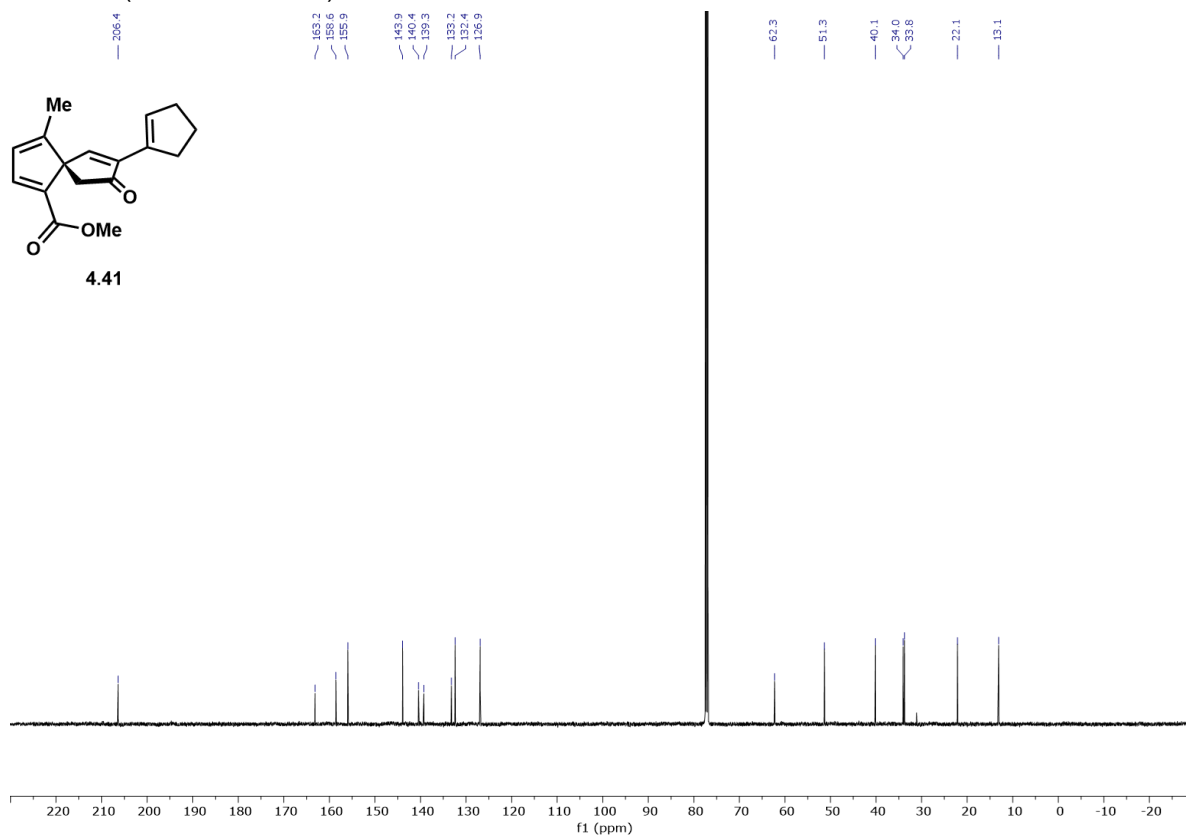
Chemical Structure:

COC(=O)C1=C(C=C(C1C2=CC=CC2C3=CC=CC3))C4=CC=CC=C4

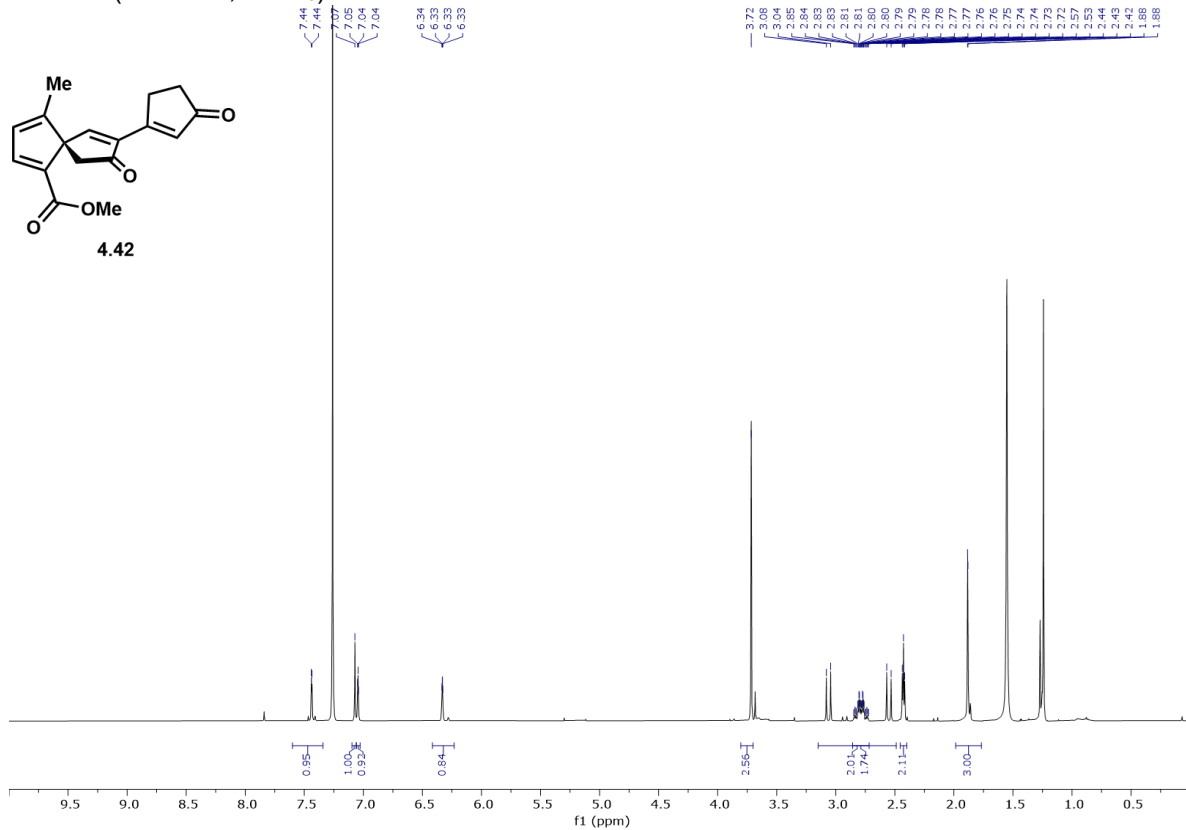
¹H NMR Spectrum (CDCl₃):

Chemical Shift (ppm)	Multiplicity	Integration
~7.3	d	1.03
~7.0	m	1.10
~6.5	d	1.12
~6.2	t	1.00
~3.7	s	3.14
~3.0	m	1.05
~2.5	m	4.83
~1.9	m	5.38

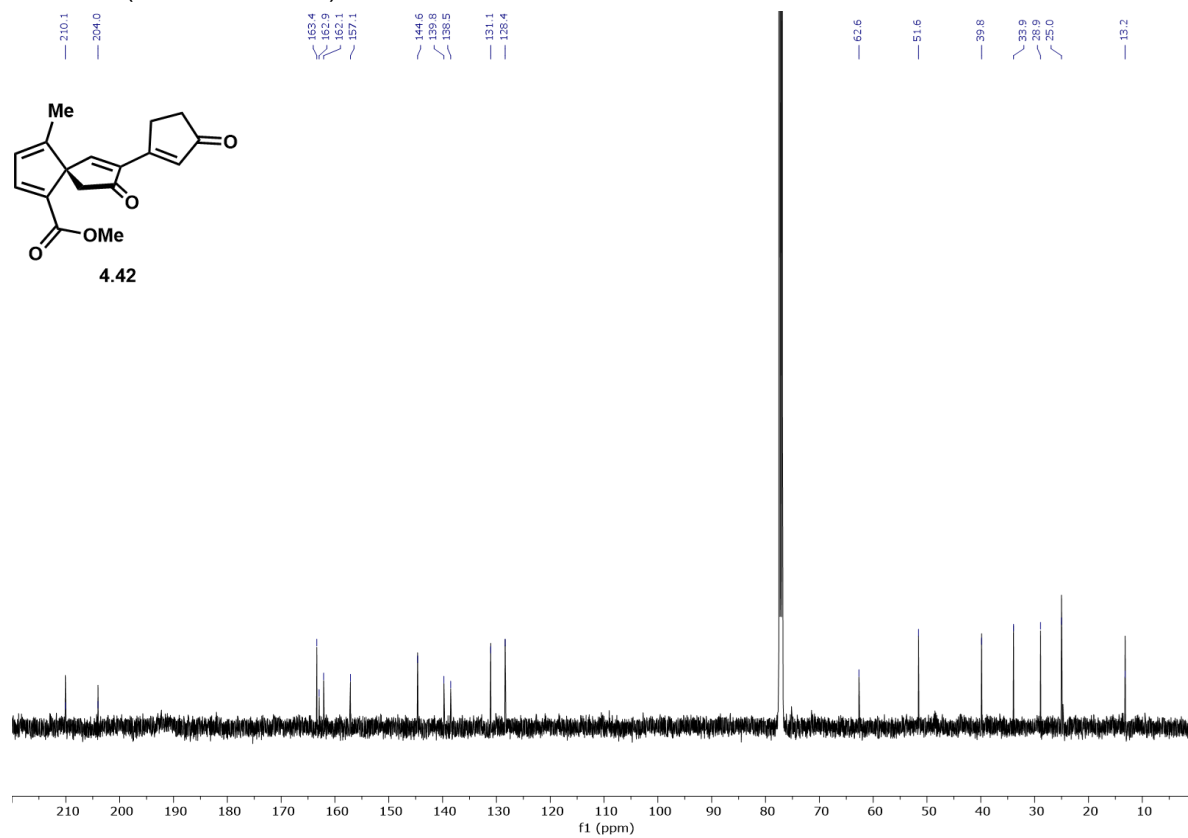
^{13}C NMR (126 MHz, CDCl_3)



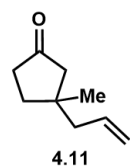
^1H NMR (500 MHz, CDCl_3)



¹³C NMR (126 MHz, CDCl₃)

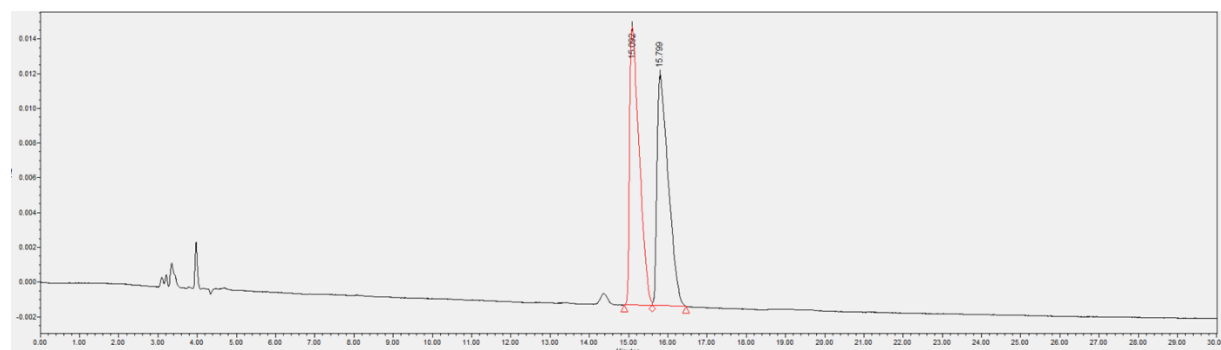


4.9.4 Chiral HPLC Traces



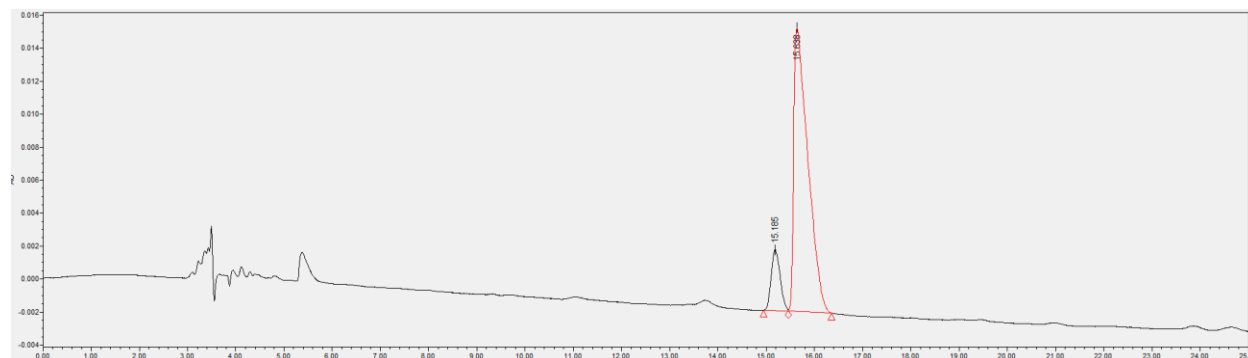
Method: IC3 chiral column, 1% IPA/hexanes, 1 mL/min, t_R (minor)= 15.2 min, t_R (major)= 15.7 min, λ = 300 nm

Racemic:

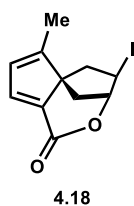


retention time (min)	area (μV*sec)	% area
15.092	272778	50.77
15.799	264483	49.23

Enantioenriched:

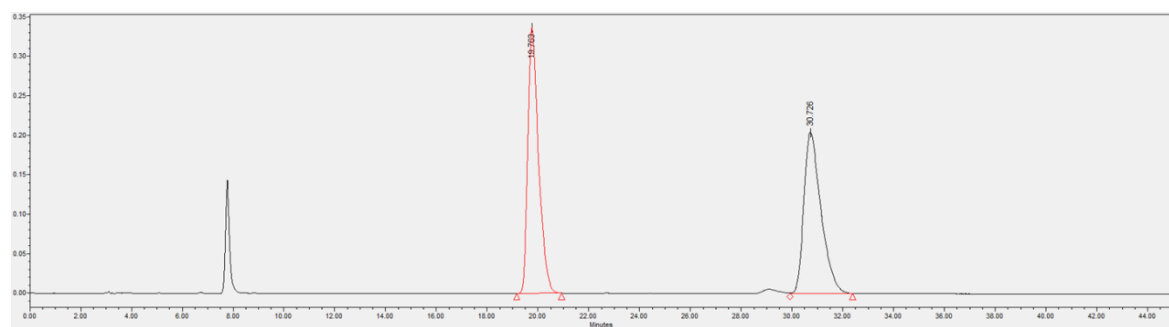


retention time (min)	area (μV*sec)	% area
15.185	47686	12.01
15.638	349212	87.99



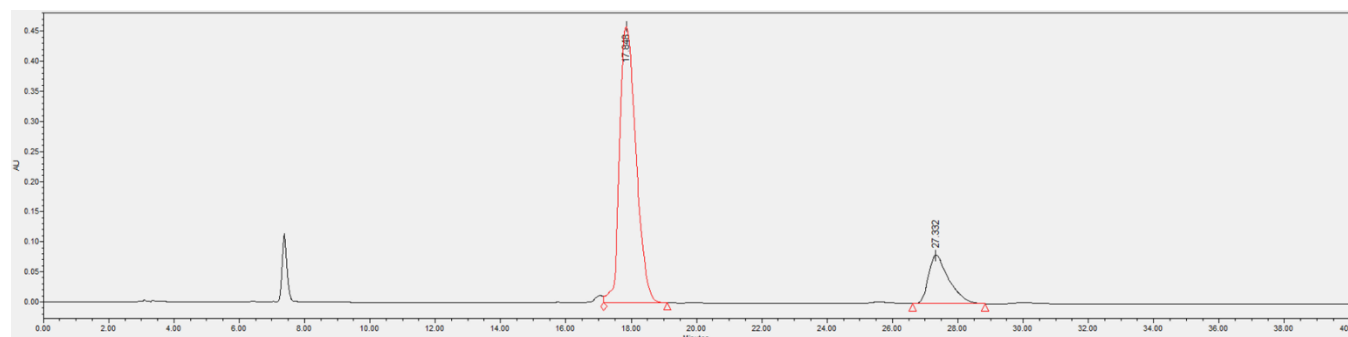
Method: ADH chiral column, 3% IPA/hexanes, 1 mL/min, $t_R(\text{minor}) = 17.8$ min, $t_R(\text{major}) = 27.3$ min, $\lambda = 300$ nm

Racemic:



retention time (min)	area (μV*sec)	% area
19.763	9834854	50.67
30.726	9576316	49.33

Enantioenriched:



retention time (min)	area (μV*sec)	% area
17.848	16046639	82.14
27.332	3489894	17.86

4.9.5 Crystallography Data

X-ray Analysis of 4.33

A colorless block 0.28 x 0.20 x 0.09 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using omega scans. Crystal-to-detector distance was 30.21 mm and exposure time was 0.75 seconds per frame using a scan width of 0.5°. Data collection was 100% complete to 30.500° in θ . A total of 18477 reflections were collected covering the indices $-17 \leq h \leq 16$, $-12 \leq k \leq 12$, $-15 \leq l \leq 15$. 3587 reflections were found to be symmetry independent, with an R_{int} of 0.0300. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be $Pn2_1$ (No. 33). The data were integrated using the CrysAlis^{Pro} 1.172.42.90a software program and scaled using the SCALE3 ABSPACK scaling algorithm. Solution by intrinsic phasing (SHELXT-2015) produced a heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

[Note: The instruments are supported by an NIH Shared Instrument Grant S10-RR027172.]

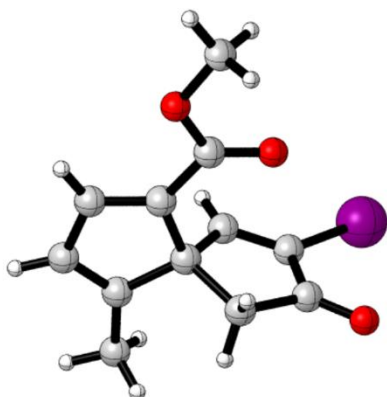


Figure 4.12. CYLview representation of **4.33**.

This crystal structure has been deposited at the Cambridge Crystallographic Data Center under CCDC 2375477.

Table 1. Crystal data and structure refinement for Kgoyal10_Sarpong.

Identification code	KGoyal10_Sarpong	
Empirical formula	C ₁₂ H ₁₁ I O ₃	
Formula weight	330.11	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P n a 21	
Unit cell dimensions	a = 12.2499(4) Å	a = 90°.
	b = 8.9875(3) Å	b = 90°.
	c = 10.9051(3) Å	g = 90°.
Volume	1200.61(7) Å ³	
Z	4	
Density (calculated)	1.826 Mg/m ³	
Absorption coefficient	2.656 mm ⁻¹	
F(000)	640	
Crystal size	0.280 x 0.200 x 0.090 mm ³	
Theta range for data collection	2.937 to 30.507°.	
Index ranges	-17<=h<=16, -12<=k<=12, -15<=l<=15	

Reflections collected	18477
Independent reflections	3587 [R(int) = 0.0300]
Completeness to theta = 30.500°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.81239
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	3587 / 1 / 147
Goodness-of-fit on F ²	1.048
Final R indices [I>2sigma(I)]	R1 = 0.0152, wR2 = 0.0366
R indices (all data)	R1 = 0.0163, wR2 = 0.0370
Absolute structure parameter	-0.040(10)
Extinction coefficient	n/a
Largest diff. peak and hole	0.356 and -0.330 e.Å ⁻³

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for KGoyal10_Sarpong. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
I(1)	6951(1)	-2145(1)	5148(1)	16(1)
O(1)	5022(2)	-1884(2)	2978(2)	24(1)
O(2)	3454(1)	-276(2)	5776(2)	20(1)
O(3)	2500(2)	1671(2)	6521(2)	19(1)
C(1)	5773(2)	902(2)	5031(3)	14(1)
C(2)	5913(2)	-459(2)	4559(2)	14(1)
C(3)	5149(2)	-731(3)	3529(2)	16(1)
C(4)	4564(2)	733(3)	3286(2)	18(1)
C(5)	4890(2)	1774(3)	4360(2)	15(1)
C(6)	3972(2)	2179(2)	5232(4)	14(1)
C(7)	3304(2)	1059(3)	5852(2)	15(1)
C(8)	1801(2)	644(3)	7166(2)	20(1)
C(9)	3913(2)	3672(3)	5341(2)	17(1)
C(10)	4739(2)	4367(3)	4571(2)	20(1)
C(11)	5316(2)	3306(3)	3984(2)	19(1)
C(12)	6238(2)	3500(3)	3108(3)	29(1)

Table 3. Bond lengths [Å] and angles [°] for KGoyal10_Sarpong.

I(1)-C(2)	2.080(2)
O(1)-C(3)	1.208(3)
O(2)-C(7)	1.216(3)
O(3)-C(7)	1.344(3)
O(3)-C(8)	1.443(3)
C(1)-C(2)	1.339(3)
C(1)-C(5)	1.523(3)
C(1)-H(1)	0.9500
C(2)-C(3)	1.482(3)
C(3)-C(4)	1.522(3)
C(4)-C(5)	1.551(3)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-C(6)	1.518(4)
C(5)-C(11)	1.528(3)
C(6)-C(9)	1.349(3)
C(6)-C(7)	1.462(4)
C(8)-H(8A)	0.9800
C(8)-H(8B)	0.9800
C(8)-H(8C)	0.9800
C(9)-C(10)	1.456(4)
C(9)-H(9)	0.9500
C(10)-C(11)	1.349(4)
C(10)-H(10)	0.9500
C(11)-C(12)	1.489(4)
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800
C(7)-O(3)-C(8)	115.97(19)
C(2)-C(1)-C(5)	112.1(2)
C(2)-C(1)-H(1)	124.0
C(5)-C(1)-H(1)	124.0
C(1)-C(2)-C(3)	111.2(2)

C(1)-C(2)-I(1)	128.69(18)
C(3)-C(2)-I(1)	120.01(16)
O(1)-C(3)-C(2)	126.9(2)
O(1)-C(3)-C(4)	126.5(2)
C(2)-C(3)-C(4)	106.66(18)
C(3)-C(4)-C(5)	105.58(17)
C(3)-C(4)-H(4A)	110.6
C(5)-C(4)-H(4A)	110.6
C(3)-C(4)-H(4B)	110.6
C(5)-C(4)-H(4B)	110.6
H(4A)-C(4)-H(4B)	108.8
C(6)-C(5)-C(1)	110.4(2)
C(6)-C(5)-C(11)	101.82(18)
C(1)-C(5)-C(11)	110.52(19)
C(6)-C(5)-C(4)	115.2(2)
C(1)-C(5)-C(4)	103.64(19)
C(11)-C(5)-C(4)	115.39(19)
C(9)-C(6)-C(7)	127.9(3)
C(9)-C(6)-C(5)	109.4(2)
C(7)-C(6)-C(5)	122.60(19)
O(2)-C(7)-O(3)	123.5(2)
O(2)-C(7)-C(6)	124.3(2)
O(3)-C(7)-C(6)	112.2(2)
O(3)-C(8)-H(8A)	109.5
O(3)-C(8)-H(8B)	109.5
H(8A)-C(8)-H(8B)	109.5
O(3)-C(8)-H(8C)	109.5
H(8A)-C(8)-H(8C)	109.5
H(8B)-C(8)-H(8C)	109.5
C(6)-C(9)-C(10)	109.9(2)
C(6)-C(9)-H(9)	125.1
C(10)-C(9)-H(9)	125.1
C(11)-C(10)-C(9)	109.5(2)
C(11)-C(10)-H(10)	125.2
C(9)-C(10)-H(10)	125.2
C(10)-C(11)-C(12)	128.2(2)

C(10)-C(11)-C(5)	109.4(2)
C(12)-C(11)-C(5)	122.4(2)
C(11)-C(12)-H(12A)	109.5
C(11)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
C(11)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for KGoyal10_Sarpong. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
I(1)	16(1)	12(1)	19(1)	1(1)	-1(1)	1(1)
O(1)	27(1)	22(1)	24(1)	-6(1)	-3(1)	-4(1)
O(2)	17(1)	14(1)	29(1)	-2(1)	4(1)	0(1)
O(3)	19(1)	16(1)	21(1)	-1(1)	5(1)	2(1)
C(1)	12(1)	15(1)	15(1)	-1(1)	0(1)	0(1)
C(2)	12(1)	14(1)	14(1)	1(1)	0(1)	0(1)
C(3)	15(1)	19(1)	13(1)	-1(1)	2(1)	-2(1)
C(4)	18(1)	22(1)	15(1)	-2(1)	-3(1)	3(1)
C(5)	14(1)	17(1)	15(1)	-1(1)	0(1)	2(1)
C(6)	13(1)	14(1)	14(1)	-1(1)	-3(1)	1(1)
C(7)	13(1)	16(1)	15(1)	-2(1)	-3(1)	1(1)
C(8)	19(1)	19(1)	21(1)	1(1)	5(1)	-1(1)
C(9)	18(1)	15(1)	19(2)	1(1)	-2(1)	4(1)
C(10)	20(1)	16(1)	24(1)	5(1)	-7(1)	-1(1)
C(11)	18(1)	21(1)	18(1)	6(1)	-3(1)	-2(1)
C(12)	25(1)	33(2)	28(1)	8(1)	6(1)	-3(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for KGoyal10_Sarpong.

	x	y	z	U(eq)
H(1)	6177	1280	5706	17
H(4A)	3763	583	3269	22
H(4B)	4796	1161	2492	22
H(8A)	1365	78	6574	30
H(8B)	1313	1198	7713	30
H(8C)	2249	-42	7651	30
H(9)	3408	4191	5844	21
H(10)	4854	5409	4494	24
H(12A)	6030	3102	2305	43
H(12B)	6880	2966	3414	43
H(12C)	6410	4561	3030	43

Table 6. Torsion angles [°] for KGoyal10_Sarpong.

C(5)-C(1)-C(2)-C(3)	-1.0(3)
C(5)-C(1)-C(2)-I(1)	-177.28(16)
C(1)-C(2)-C(3)-O(1)	-174.2(2)
I(1)-C(2)-C(3)-O(1)	2.4(3)
C(1)-C(2)-C(3)-C(4)	6.5(3)
I(1)-C(2)-C(3)-C(4)	-176.88(15)
O(1)-C(3)-C(4)-C(5)	171.7(2)
C(2)-C(3)-C(4)-C(5)	-9.0(2)
C(2)-C(1)-C(5)-C(6)	119.3(2)
C(2)-C(1)-C(5)-C(11)	-128.9(2)
C(2)-C(1)-C(5)-C(4)	-4.7(3)
C(3)-C(4)-C(5)-C(6)	-112.5(2)
C(3)-C(4)-C(5)-C(1)	8.2(2)
C(3)-C(4)-C(5)-C(11)	129.2(2)
C(1)-C(5)-C(6)-C(9)	116.3(3)
C(11)-C(5)-C(6)-C(9)	-1.1(3)
C(4)-C(5)-C(6)-C(9)	-126.8(3)
C(1)-C(5)-C(6)-C(7)	-62.3(4)
C(11)-C(5)-C(6)-C(7)	-179.7(3)
C(4)-C(5)-C(6)-C(7)	54.7(4)
C(8)-O(3)-C(7)-O(2)	0.1(3)
C(8)-O(3)-C(7)-C(6)	-179.9(2)
C(9)-C(6)-C(7)-O(2)	-174.5(3)
C(5)-C(6)-C(7)-O(2)	3.8(5)
C(9)-C(6)-C(7)-O(3)	5.4(5)
C(5)-C(6)-C(7)-O(3)	-176.3(3)
C(7)-C(6)-C(9)-C(10)	179.3(3)
C(5)-C(6)-C(9)-C(10)	0.8(3)
C(6)-C(9)-C(10)-C(11)	-0.2(3)
C(9)-C(10)-C(11)-C(12)	-179.9(2)
C(9)-C(10)-C(11)-C(5)	-0.6(3)
C(6)-C(5)-C(11)-C(10)	1.0(3)
C(1)-C(5)-C(11)-C(10)	-116.3(2)
C(4)-C(5)-C(11)-C(10)	126.6(2)

C(6)-C(5)-C(11)-C(12)	-179.6(3)
C(1)-C(5)-C(11)-C(12)	63.1(3)
C(4)-C(5)-C(11)-C(12)	-54.1(3)

Symmetry transformations used to generate equivalent atoms:

X-ray Analysis of 4.36

A colorless block 0.25 x 0.13 x 0.12 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using omega scans. Crystal-to-detector distance was 30.21 mm and exposure time was 3.00 seconds per frame using a scan width of 0.5°. Data collection was 100% complete to 30.500° in θ . A total of 19785 reflections were collected covering the indices $-9 \leq h \leq 8$, $-18 \leq k \leq 19$, $-30 \leq l \leq 33$. 3276 reflections were found to be symmetry independent, with an Rint of 0.0309. Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be $P\ b\ c\ a$ (No. 61). The data were integrated using the CrysAlisPro 1.172.42.90a software program and scaled using the SCALE3 ABSPACK scaling algorithm. Solution by intrinsic phasing (SHELXT-2015) produced a heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model or found as Q-peaks. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

[Note: The instruments are supported by an NIH Shared Instrument Grant S10-RR027172.]

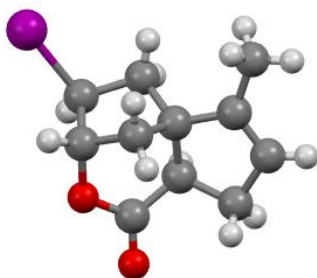


Figure 4.13. CYLview representation of **4.36**. Whole molecule disorder was observed (85:15), the minor component is hidden in this rendering.

This crystal structure has been deposited at the Cambridge Crystallographic Data Center under CCDC 2375478.

Table 1. Crystal data and structure refinement for KGoyal08_Sarpong.

Identification code	KGoyal08_Sarpong		
Empirical formula	C11 H13 I O2		
Formula weight	304.11		
Temperature	100(2) K		
Wavelength	0.71073 Å		
Crystal system	Orthorhombic		
Space group	P b c a		
Unit cell dimensions	a = 6.7797(3) Å $\angle$ = 90°.		
	b = 13.3640(6) Å	$\angle$ = 90°.	
	c = 23.7249(11) Å	$\angle$ = 90°.	
Volume	2149.55(17) Å3		
Z	8		
Density (calculated)	1.879 Mg/m3		

Absorption coefficient 2.951 mm⁻¹
 F(000) 1184
 Crystal size 0.250 x 0.130 x 0.120 mm³
 Theta range for data collection 3.049 to 30.508°.
 Index ranges -9<=h<=8, -18<=k<=19, -30<=l<=33
 Reflections collected 19785
 Independent reflections 3276 [R(int) = 0.0309]
 Completeness to theta = 30.508° 99.9 %
 Absorption correction Semi-empirical from equivalents
 Max. and min. transmission 1.00000 and 0.71874
 Refinement method Full-matrix least-squares on F²
 Data / restraints / parameters 3276 / 2 / 202
 Goodness-of-fit on F² 1.083
 Final R indices [I>2sigma(I)] R1 = 0.0215, wR2 = 0.0486
 R indices (all data) R1 = 0.0267, wR2 = 0.0503
 Extinction coefficient n/a
 Largest diff. peak and hole 0.571 and -0.322 e.Å⁻³

Table 2. Atomic coordinates (x 10⁴) and equivalent isotropic displacement parameters (Å²x 10³) for KGoyal08_Sarpong. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
I(1A)	1828(1)	1811(1)	3115(1)	24(1)
O(2)	5250(2)	3569(1)	5373(1)	33(1)
O(1A)	3283(2)	3216(1)	4670(1)	23(1)
C(4)	6170(3)	3649(1)	3835(1)	18(1)
C(10A)	7808(6)	4295(3)	3618(1)	21(1)
C(1A)	3780(3)	2309(1)	3783(1)	17(1)
C(7)	5104(3)	3449(1)	4871(1)	22(1)

C(9A)	8898(7)	4703(3)	4028(2)	28(1)
C(6A)	6773(3)	3506(2)	4464(1)	20(1)
C(5A)	5831(3)	2615(2)	3558(1)	21(1)
C(2A)	2928(3)	3252(2)	4063(1)	19(1)
C(11A)	8066(7)	4482(4)	3003(1)	39(1)
C(3A)	4109(3)	4102(2)	3812(1)	20(1)
C(8A)	8207(5)	4358(3)	4609(1)	29(1)
C(1B)	3010(16)	2827(9)	3767(4)	17(1)
O(1B)	4278(12)	2632(7)	4698(3)	23(2)
C(6B)	5943(16)	4165(8)	4411(4)	20(2)
C(3B)	6499(17)	2583(8)	3874(5)	19(2)
C(2B)	4478(18)	2269(8)	4121(4)	20(2)
C(5B)	4102(16)	3741(8)	3503(5)	19(2)
I(1B)	1969(8)	1874(4)	3097(2)	38(1)
C(11B)	7900(50)	4320(20)	2856(8)	39(1)
C(8B)	8220(40)	4561(19)	4472(9)	29(1)
C(9B)	8690(50)	4570(20)	3928(12)	28(1)
C(10B)	7800(40)	4280(20)	3473(7)	21(1)

Table 3. Bond lengths [Å] and angles [°] for KGoyal08_Sarpong.

I(1A)-C(1A)	2.168(2)
O(2)-C(7)	1.206(2)
O(1A)-C(7)	1.360(2)
O(1A)-C(2A)	1.461(2)
C(4)-C(3B)	1.445(10)
C(4)-C(10A)	1.498(4)
C(4)-C(3A)	1.524(3)
C(4)-C(6B)	1.539(10)
C(4)-C(5A)	1.547(3)

C(4)-C(6A)	1.560(3)
C(4)-C(5B)	1.613(11)
C(4)-C(10B)	1.63(3)
C(10A)-C(9A)	1.338(4)
C(10A)-C(11A)	1.491(4)
C(1A)-C(2A)	1.536(3)
C(1A)-C(5A)	1.544(3)
C(1A)-H(1A)	1.0000
C(7)-O(1B)	1.293(8)
C(7)-C(6A)	1.489(3)
C(7)-C(6B)	1.559(12)
C(9A)-C(8A)	1.529(6)
C(9A)-H(9A)	0.9500
C(6A)-C(8A)	1.535(4)
C(6A)-H(6A)	1.0000
C(5A)-H(5AA)	0.9900
C(5A)-H(5AB)	0.9900
C(2A)-C(3A)	1.512(3)
C(2A)-H(2A)	1.0000
C(11A)-H(11A)	0.9800
C(11A)-H(11B)	0.9800
C(11A)-H(11C)	0.9800
C(3A)-H(3AA)	0.9900
C(3A)-H(3AB)	0.9900
C(8A)-H(8AA)	0.9900
C(8A)-H(8AB)	0.9900
C(1B)-C(2B)	1.499(15)
C(1B)-C(5B)	1.560(15)
C(1B)-I(1B)	2.156(12)
C(1B)-H(1B)	1.18(15)

O(1B)-C(2B)	1.458(13)
C(6B)-C(8B)	1.64(3)
C(6B)-H(6B)	1.0000
C(3B)-C(2B)	1.548(16)
C(3B)-H(3BA)	0.9900
C(3B)-H(3BB)	0.9900
C(2B)-H(2B)	1.0000
C(5B)-H(5BA)	0.9900
C(5B)-H(5BB)	0.9900
C(11B)-C(10B)	1.465(17)
C(11B)-H(11D)	0.9800
C(11B)-H(11E)	0.9800
C(11B)-H(11F)	0.9800
C(8B)-C(9B)	1.33(4)
C(8B)-H(8BA)	0.9900
C(8B)-H(8BB)	0.9900
C(9B)-C(10B)	1.301(17)
C(9B)-H(9B)	0.9500

C(7)-O(1A)-C(2A)	119.26(15)
C(10A)-C(4)-C(3A)	116.0(2)
C(3B)-C(4)-C(6B)	113.7(6)
C(10A)-C(4)-C(5A)	118.59(19)
C(3A)-C(4)-C(5A)	101.71(15)
C(10A)-C(4)-C(6A)	101.87(16)
C(3A)-C(4)-C(6A)	108.89(15)
C(5A)-C(4)-C(6A)	109.62(15)
C(3B)-C(4)-C(5B)	103.9(6)
C(6B)-C(4)-C(5B)	108.2(6)
C(3B)-C(4)-C(10B)	115.8(11)

C(6B)-C(4)-C(10B)	107.8(9)
C(5B)-C(4)-C(10B)	106.9(9)
C(9A)-C(10A)-C(11A)	125.4(4)
C(9A)-C(10A)-C(4)	113.2(3)
C(11A)-C(10A)-C(4)	121.4(3)
C(2A)-C(1A)-C(5A)	105.72(16)
C(2A)-C(1A)-I(1A)	109.75(13)
C(5A)-C(1A)-I(1A)	112.29(13)
C(2A)-C(1A)-H(1A)	109.7
C(5A)-C(1A)-H(1A)	109.7
I(1A)-C(1A)-H(1A)	109.7
O(2)-C(7)-O(1B)	117.5(4)
O(2)-C(7)-O(1A)	116.89(17)
O(2)-C(7)-C(6A)	124.78(18)
O(1A)-C(7)-C(6A)	118.31(15)
O(2)-C(7)-C(6B)	125.4(4)
O(1B)-C(7)-C(6B)	117.0(5)
C(10A)-C(9A)-C(8A)	111.3(3)
C(10A)-C(9A)-H(9A)	124.3
C(8A)-C(9A)-H(9A)	124.3
C(7)-C(6A)-C(8A)	112.0(2)
C(7)-C(6A)-C(4)	115.28(15)
C(8A)-C(6A)-C(4)	106.83(17)
C(7)-C(6A)-H(6A)	107.5
C(8A)-C(6A)-H(6A)	107.5
C(4)-C(6A)-H(6A)	107.5
C(1A)-C(5A)-C(4)	102.93(15)
C(1A)-C(5A)-H(5AA)	111.2
C(4)-C(5A)-H(5AA)	111.2
C(1A)-C(5A)-H(5AB)	111.2

C(4)-C(5A)-H(5AB)	111.2
H(5AA)-C(5A)-H(5AB)	109.1
O(1A)-C(2A)-C(3A)	108.95(16)
O(1A)-C(2A)-C(1A)	109.74(16)
C(3A)-C(2A)-C(1A)	104.27(16)
O(1A)-C(2A)-H(2A)	111.2
C(3A)-C(2A)-H(2A)	111.2
C(1A)-C(2A)-H(2A)	111.2
C(10A)-C(11A)-H(11A)	109.5
C(10A)-C(11A)-H(11B)	109.5
H(11A)-C(11A)-H(11B)	109.5
C(10A)-C(11A)-H(11C)	109.5
H(11A)-C(11A)-H(11C)	109.5
H(11B)-C(11A)-H(11C)	109.5
C(2A)-C(3A)-C(4)	99.98(15)
C(2A)-C(3A)-H(3AA)	111.8
C(4)-C(3A)-H(3AA)	111.8
C(2A)-C(3A)-H(3AB)	111.8
C(4)-C(3A)-H(3AB)	111.8
H(3AA)-C(3A)-H(3AB)	109.5
C(9A)-C(8A)-C(6A)	102.5(2)
C(9A)-C(8A)-H(8AA)	111.3
C(6A)-C(8A)-H(8AA)	111.3
C(9A)-C(8A)-H(8AB)	111.3
C(6A)-C(8A)-H(8AB)	111.3
H(8AA)-C(8A)-H(8AB)	109.2
C(2B)-C(1B)-C(5B)	107.4(9)
C(2B)-C(1B)-I(1B)	109.7(7)
C(5B)-C(1B)-I(1B)	108.7(7)
C(2B)-C(1B)-H(1B)	106(8)

C(5B)-C(1B)-H(1B)	117(7)
I(1B)-C(1B)-H(1B)	107(7)
C(7)-O(1B)-C(2B)	122.6(7)
C(4)-C(6B)-C(7)	112.5(6)
C(4)-C(6B)-C(8B)	97.4(11)
C(7)-C(6B)-C(8B)	118.7(10)
C(4)-C(6B)-H(6B)	109.2
C(7)-C(6B)-H(6B)	109.2
C(8B)-C(6B)-H(6B)	109.2
C(4)-C(3B)-C(2B)	98.9(7)
C(4)-C(3B)-H(3BA)	112.0
C(2B)-C(3B)-H(3BA)	112.0
C(4)-C(3B)-H(3BB)	112.0
C(2B)-C(3B)-H(3BB)	112.0
H(3BA)-C(3B)-H(3BB)	109.7
O(1B)-C(2B)-C(1B)	107.3(9)
O(1B)-C(2B)-C(3B)	110.3(8)
C(1B)-C(2B)-C(3B)	104.0(9)
O(1B)-C(2B)-H(2B)	111.6
C(1B)-C(2B)-H(2B)	111.6
C(3B)-C(2B)-H(2B)	111.6
C(1B)-C(5B)-C(4)	99.0(7)
C(1B)-C(5B)-H(5BA)	112.0
C(4)-C(5B)-H(5BA)	112.0
C(1B)-C(5B)-H(5BB)	112.0
C(4)-C(5B)-H(5BB)	112.0
H(5BA)-C(5B)-H(5BB)	109.7
C(10B)-C(11B)-H(11D)	109.5
C(10B)-C(11B)-H(11E)	109.5
H(11D)-C(11B)-H(11E)	109.5

C(10B)-C(11B)-H(11F)	109.5
H(11D)-C(11B)-H(11F)	109.5
H(11E)-C(11B)-H(11F)	109.5
C(9B)-C(8B)-C(6B)	98.4(19)
C(9B)-C(8B)-H(8BA)	112.1
C(6B)-C(8B)-H(8BA)	112.1
C(9B)-C(8B)-H(8BB)	112.1
C(6B)-C(8B)-H(8BB)	112.1
H(8BA)-C(8B)-H(8BB)	109.7
C(10B)-C(9B)-C(8B)	134(3)
C(10B)-C(9B)-H(9B)	113.1
C(8B)-C(9B)-H(9B)	113.1
C(9B)-C(10B)-C(11B)	143(3)
C(9B)-C(10B)-C(4)	91.8(18)
C(11B)-C(10B)-C(4)	125(2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for KGoyal08_Sarpong. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
I(1A)	27(1)	23(1)	22(1)	-3(1)	-4(1)	-8(1)
O(2)	35(1)	45(1)	19(1)	-5(1)	-3(1)	3(1)
O(1A)	23(1)	27(1)	17(1)	-3(1)	2(1)	-1(1)
C(4)	17(1)	18(1)	19(1)	1(1)	-1(1)	-1(1)
C(10A)	20(1)	21(1)	23(2)	7(2)	2(2)	-2(1)
C(1A)	19(1)	17(1)	16(1)	-1(1)	-1(1)	0(1)

C(7)	24(1)	22(1)	20(1)	-2(1)	-2(1)	4(1)
C(9A)	18(2)	20(2)	46(2)	-7(1)	-1(1)	-9(1)
C(6A)	19(1)	20(1)	20(1)	-3(1)	-3(1)	2(1)
C(5A)	19(1)	23(1)	20(1)	-3(1)	2(1)	1(1)
C(2A)	18(1)	19(1)	19(1)	-1(1)	-1(1)	1(1)
C(11A)	36(2)	53(2)	29(2)	18(2)	1(2)	-12(1)
C(3A)	20(1)	18(1)	21(1)	1(1)	-4(1)	1(1)
C(8A)	23(1)	36(2)	29(2)	-9(1)	-2(1)	-10(1)
C(1B)	19(1)	17(1)	16(1)	-1(1)	-1(1)	0(1)
O(1B)	23(4)	32(5)	13(3)	4(3)	-3(3)	-9(4)
C(6B)	19(5)	19(5)	21(5)	-8(4)	-7(4)	0(4)
C(3B)	22(5)	14(5)	21(5)	-3(4)	-4(4)	3(4)
C(2B)	32(6)	11(4)	16(5)	2(3)	-8(4)	-4(4)
C(5B)	19(5)	15(5)	23(5)	5(4)	-4(4)	1(4)
I(1B)	55(2)	41(2)	19(1)	0(1)	-7(1)	-30(1)
C(11B)	36(2)	53(2)	29(2)	18(2)	1(2)	-12(1)
C(8B)	23(1)	36(2)	29(2)	-9(1)	-2(1)	-10(1)
C(9B)	18(2)	20(2)	46(2)	-7(1)	-1(1)	-9(1)
C(10B)	20(1)	21(1)	23(2)	7(2)	2(2)	-2(1)

Table 5. Hydrogen coordinates (x 104) and isotropic displacement parameters (Å²x 103)
for KGoyal08_Sarpong.

	x	y	z	U(eq)
H(1A)	3928	1767	4070	21
H(9A)	9964	5151	3965	34
H(6A)	7523	2863	4492	23
H(5AA)	5829	2667	3142	25

H(5AB)	6855	2130	3676	25
H(2A)	1491	3327	3978	22
H(11A)	8338	3848	2810	59
H(11B)	9171	4943	2944	59
H(11C)	6857	4778	2849	59
H(3AA)	4011	4717	4043	24
H(3AB)	3699	4250	3420	24
H(8AA)	7530	4904	4814	35
H(8AB)	9325	4112	4839	35
H(6B)	5045	4754	4371	24
H(3BA)	7602	2419	4131	23
H(3BB)	6741	2278	3500	23
H(2B)	4275	1529	4097	24
H(5BA)	3421	4380	3586	23
H(5BB)	4271	3667	3091	23
H(11D)	8422	3685	2712	59
H(11E)	8763	4869	2742	59
H(11F)	6572	4429	2703	59
H(8BA)	8288	5237	4642	35
H(8BB)	9046	4091	4691	35
H(9B)	9960	4845	3858	34
H(1B)	1700(200)	3000(110)	4060(70)	26

Table 6. Torsion angles [°] for KGoyal08_Sarpong.

C(3A)-C(4)-C(10A)-C(9A)	103.8(4)
C(5A)-C(4)-C(10A)-C(9A)	-134.6(3)
C(6A)-C(4)-C(10A)-C(9A)	-14.2(4)
C(3A)-C(4)-C(10A)-C(11A)	-73.1(4)
C(5A)-C(4)-C(10A)-C(11A)	48.4(5)

C(6A)-C(4)-C(10A)-C(11A) 168.8(4)
 C(2A)-O(1A)-C(7)-O(2) 168.24(17)
 C(2A)-O(1A)-C(7)-C(6A) -13.5(3)
 C(11A)-C(10A)-C(9A)-C(8A) 179.2(4)
 C(4)-C(10A)-C(9A)-C(8A) 2.4(5)
 O(2)-C(7)-C(6A)-C(8A) -39.7(3)
 O(1A)-C(7)-C(6A)-C(8A) 142.2(2)
 O(2)-C(7)-C(6A)-C(4) -162.15(18)
 O(1A)-C(7)-C(6A)-C(4) 19.8(2)
 C(10A)-C(4)-C(6A)-C(7) 145.4(2)
 C(3A)-C(4)-C(6A)-C(7) 22.3(2)
 C(5A)-C(4)-C(6A)-C(7) -88.15(19)
 C(10A)-C(4)-C(6A)-C(8A) 20.3(3)
 C(3A)-C(4)-C(6A)-C(8A)-102.8(2)
 C(5A)-C(4)-C(6A)-C(8A) 146.7(2)
 C(2A)-C(1A)-C(5A)-C(4) 11.2(2)
 I(1A)-C(1A)-C(5A)-C(4) 130.87(13)
 C(10A)-C(4)-C(5A)-C(1A) -166.4(2)
 C(3A)-C(4)-C(5A)-C(1A) -37.81(18)
 C(6A)-C(4)-C(5A)-C(1A) 77.33(18)
 C(7)-O(1A)-C(2A)-C(3A) -35.4(2)
 C(7)-O(1A)-C(2A)-C(1A) 78.2(2)
 C(5A)-C(1A)-C(2A)-O(1A) -96.87(18)
 I(1A)-C(1A)-C(2A)-O(1A) 141.81(13)
 C(5A)-C(1A)-C(2A)-C(3A) 19.7(2)
 I(1A)-C(1A)-C(2A)-C(3A) -101.61(15)
 O(1A)-C(2A)-C(3A)-C(4) 74.05(19)
 C(1A)-C(2A)-C(3A)-C(4) -43.07(19)
 C(10A)-C(4)-C(3A)-C(2A) -179.68(17)
 C(5A)-C(4)-C(3A)-C(2A) 50.14(18)

C(6A)-C(4)-C(3A)-C(2A)-65.54(18)
 C(10A)-C(9A)-C(8A)-C(6A) 10.9(5)
 C(7)-C(6A)-C(8A)-C(9A)-146.2(3)
 C(4)-C(6A)-C(8A)-C(9A)-19.1(3)
 O(2)-C(7)-O(1B)-C(2B) -163.1(7)
 C(6B)-C(7)-O(1B)-C(2B) 13.3(11)
 C(3B)-C(4)-C(6B)-C(7) -28.0(9)
 C(5B)-C(4)-C(6B)-C(7) 86.8(7)
 C(10B)-C(4)-C(6B)-C(7)-157.8(11)
 C(3B)-C(4)-C(6B)-C(8B)97.3(11)
 C(5B)-C(4)-C(6B)-C(8B)-147.8(10)
 C(10B)-C(4)-C(6B)-C(8B) -32.5(14)
 O(2)-C(7)-C(6B)-C(4) 159.9(4)
 O(1B)-C(7)-C(6B)-C(4) -16.1(9)
 O(2)-C(7)-C(6B)-C(8B) 47.2(14)
 O(1B)-C(7)-C(6B)-C(8B) -128.9(13)
 C(6B)-C(4)-C(3B)-C(2B)66.2(9)
 C(5B)-C(4)-C(3B)-C(2B)-51.2(8)
 C(10B)-C(4)-C(3B)-C(2B) -168.1(10)
 C(7)-O(1B)-C(2B)-C(1B) -81.8(11)
 C(7)-O(1B)-C(2B)-C(3B) 30.8(12)
 C(5B)-C(1B)-C(2B)-O(1B) 94.5(10)
 I(1B)-C(1B)-C(2B)-O(1B) -147.5(7)
 C(5B)-C(1B)-C(2B)-C(3B) -22.4(11)
 I(1B)-C(1B)-C(2B)-C(3B) 95.6(8)
 C(4)-C(3B)-C(2B)-O(1B) -68.7(9)
 C(4)-C(3B)-C(2B)-C(1B)46.1(9)
 C(2B)-C(1B)-C(5B)-C(4)-7.4(10)
 I(1B)-C(1B)-C(5B)-C(4) -126.0(6)
 C(3B)-C(4)-C(5B)-C(1B)37.4(9)

C(6B)-C(4)-C(5B)-C(1B)	-83.7(8)
C(10B)-C(4)-C(5B)-C(1B)	160.4(11)
C(4)-C(6B)-C(8B)-C(9B)	23(2)
C(7)-C(6B)-C(8B)-C(9B)	144.0(17)
C(6B)-C(8B)-C(9B)-C(10B)	-6(5)
C(8B)-C(9B)-C(10B)-C(11B)	169(4)
C(8B)-C(9B)-C(10B)-C(4)	-14(4)
C(3B)-C(4)-C(10B)-C(9B)	-100(2)
C(6B)-C(4)-C(10B)-C(9B)	29(2)
C(5B)-C(4)-C(10B)-C(9B)	144.7(19)
C(3B)-C(4)-C(10B)-C(11B)	78(3)
C(6B)-C(4)-C(10B)-C(11B)	-154(3)
C(5B)-C(4)-C(10B)-C(11B)	-38(3)

Symmetry transformations used to generate equivalent atoms:

4.10 References

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