Mild Electrocyclization of Heptatrienyl Anions

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Abstract

Carbocycles are prevalent in natural products and drug-like molecules. Despite their importance in medicinal chemistry, functionalized cycloheptanes remain a challenging scaffold to access. We have taken a keen interest in developing a strategy for cycloheptane formation through electrocyclization of heptatrienyl anions. Historically, this strategy has faced many challenges, including the use of strong bases to form the heptatrienyl anion, the lack of product selectivity, and low yields. We aim to overcome these deficiencies by the strategic use of electron withdrawing groups to activate both the heptatriene towards deprotonation and stabilize the resultant heptadienyl anion. In this report we detail the mild catalytic electrocyclization of functionalized heptatrienyl anions.

Acknowledgements

I would like to give thanks to my mom, Yanrong Zhang, who has consistently supported me every step of my life and whose unconditional love has helped me move forward in uncertain times. I wake up everyday grateful for her support, with the understanding that she has sacrificed everything to give me the chance at a better life.

Art, I am grateful to have met you and worked alongside you in your group. You have always gone above and beyond to be a good mentor not just in chemistry but other important aspects of life. We have had many conversations about the state of the world, and I want you to know that you've radically changed the direction of my life for the better.

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List of Abbreviations

HOMO: Highest Occupied Molecular Orbital

LUMO: Lowest Unoccupied Molecular Orbital

EDG: Electron Donating Group

EWG: Electron Withdrawing Group

Boc: Tert-butyloxycarbonyl

TBAF: Tetra-n-butylammonium fluoride

THF: Tetrahydrofuran

tBu: Tertiary Butyl

DBU: 1,8-Diazabicyclo(5.4.0)undec-7-ene

DCM: Dichloromethane

MeCN: Acetonitrile

DMSO: Dimethyl Sulfoxide

Equiv.: Equivalents

Conc.: Concentration

Temp.: Temperature

Rxn: Reaction

r.t.: Room temperature

HWE: Horner-Wadsworth-Emmons

n.a.: Not applicable

1. Chapter 1: Introduction

1.1. The importance of cycloheptanes

Cycloheptanes, like other carbocyclic rings, are a highly prevalent motif in natural products and biologically active compounds. Ingenol mebutate[1], englerin A[2], and cortistatin A[3] are all examples of biologically active natural products containing highly substituted cycloheptanes (**Figure 1**). However, unlike for other common carbocyclic systems, strategies and methods for the construction of cycloheptanes remain limited, preventing their widespread use in pharmaceutical discovery and slowing the synthesis of potentially useful compounds. Therefore, new methods that can facilitate the synthesis of cycloheptanes are likely to have a meaningful impact on the drug discovery process and are a good target for reaction development.

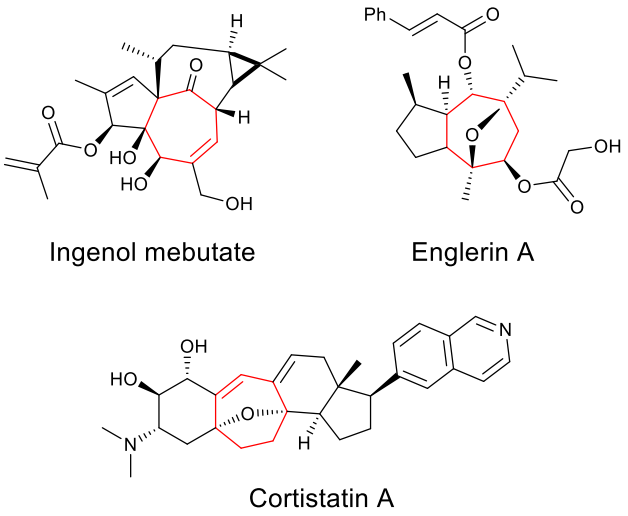


***Figure 1**:Examples of biologically active compounds with 7-membered rings*

1.2. Electrocyclizations in organic chemistry

Pericyclic reactions are a fundamental class of reaction featuring the rearrangement of electrons through a cyclic transition state.[4] They are distinguished into different types by the overall change in sigma (σ) bonds between the reactants and the products.[5]. Electrocyclizations are a type of pericyclic reaction concerned with the formation of a ring system across the termini of a conjugated π system. They are enthalpically driven by the formation of a σ bond at the expense of a pi (π) bond.

1.3. The Woodward-Hoffmann rules for electrocyclization

In 1965, Robert Burns Woodward, and Roald Hoffmann published their seminal paper entitled "*Stereochemistry of electrocyclic reactions*". The paper suggested a relationship between the stereochemical outcome of thermal electrocyclization reactions and the symmetry of the highest occupied molecular orbital (HOMO) of the linear precursor.[6] The symmetry of the frontier molecular orbitals is directly related to the number of electrons participating in the electrocyclization. Systems with (4n) electrons, where n is some integer, have antisymmetrical HOMOs with a point of inversion. Systems with (4n+2) electrons have symmetrical HOMOs with a σ_v plane of reflection. They determined that in order for an electrocyclization reaction to proceed, the symmetry of the frontier molecular orbitals in the substrates and the products must remain unchanged.[7,8] (4n) conjugated systems being antisymmetrical undergo conrotation. Their terminal molecular orbitals rotate in the same direction to preserve orbital symmetry and ensure orbital overlap (**Figure 2**). It is important to note that although the Woodward-Hoffmann rules give guidelines for identifying allowed orbital symmetries, reactions can still fail due to steric, geometric or energic factors.[9]

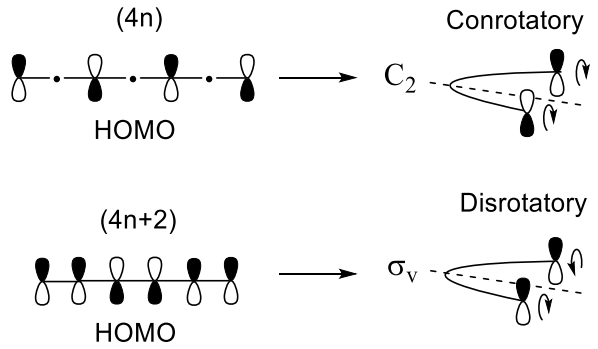


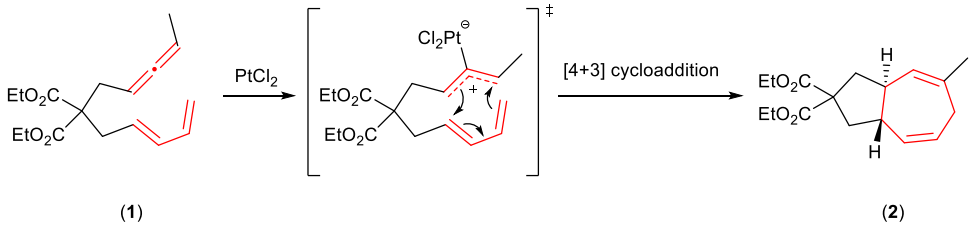
***Figure 2**: HOMO of conjugated systems undergoing conrotatory/disrotatory electrocyclization*

1.4. Existing methods for cycloheptane synthesis

The synthesis of cycloheptanes is an enduring challenge. Many existing methods center around cleavage of bicyclic intermediates or release of ring strain.

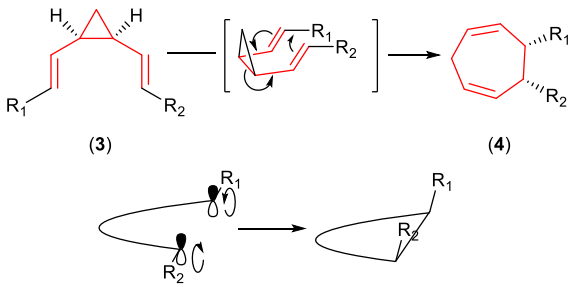
1.4.1. Pericyclic strategies

[4+3] Thermal cycloadditions have been used to generate cycloheptanes. Typically, this method utilizes gold, platinum, or palladium catalysts to generate a cationic allyl intermediate that undergoes a [4+3] cycloaddition with diene (**Scheme 1**).[10]



***Scheme 1**: Cycloheptane formation via [4+3] cycloaddition*

The 3,3-divinyl cyclopropane rearrangement relies on the release of a highly strained cyclopropane ring as the driving force for the sigmatrophic rearrangement (**Scheme 2**).[11] In order for this reaction to proceed the termini of the molecular orbitals must undergo disrotation to ensure proper overlap and maintain orbital symmetry. This results in a stereospecific reaction with stereochemistry of the terminal double bonds determining the stereochemistry of the final product.

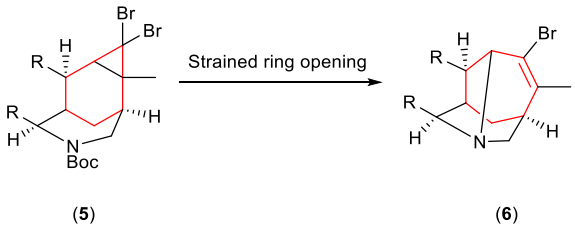


***Scheme 2**: Cycloheptane formation via sigmatropic rearrangement of 3,3-divinyl cyclopropane*

1.4.2. Cyclopropane ring expansion

Ring homologation by cyclopropanation and ring cleavage is widely use for cycloheptane ring formation. This is achieved through the installation of a cyclopropane ring onto an existing cyclohexane. The resulting bicyclic intermediate is then cleaved, expanding the ring by a single carbon. A significant library of work exists for constructing 6- and 3- membered rings,

allowing synthetic chemists easy access to the necessary bicyclic precursor. Nishimura *et al.* utilized this strategy in the synthesis of (+)-Lyconadin A (**Scheme 3**).[12]

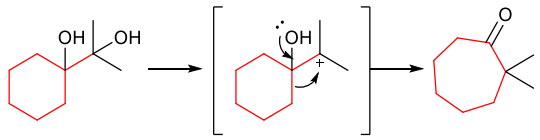


(**5**) (**6**)

Scheme 3*:Cycloheptane formation through cyclopropane ring cleavage*

1.4.3. Pinacol ring expansion

Pinacol ring expansion is another strategy for synthesizing 7-membered rings. Two alcohols groups must be installed adjacent to one another with one on an existing 6-membered ring (**Scheme 4**). An activating group can then be used to induce the ring-adjacent alcohol to leave, generating a carbocation. The resultant cation can subsequently undergo an assisted rearrangement to stabilize the carbocation, forming the cycloheptane (**Scheme 4**).[13]

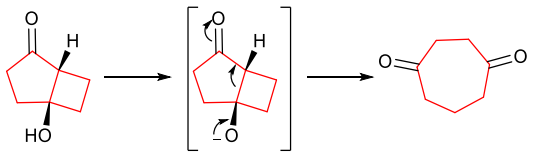


(**7**) (**8**)

Scheme 4*: Cycloheptane formation via the pinacol rearrangement*

1.4.4. De Mayo reaction

The De Mayo reaction involves the retro-aldol cleavage of the internal bridge of an fused bicyclo-[3.2.0]-heptane molecule to give the desired cycloheptane (**Scheme 5**).[14]



(**9**) (**10**)

Scheme 5*: Cycloheptane formation via the De Mayo reaction*

1.5. The electrocyclization of heptatrienyl anions

Heptatrienyl anions are a seven-atom, eight electron conjugated systems that are traditionally formed by deprotonation of heptatrienes with a strong base. The HOMO of this system is antisymmetrical relative to the point of inversion. Therefore, the termini of the molecular orbitals must undergo a conrotatory process to preserve orbital symmetry throughout the reaction (**Figure 3**).

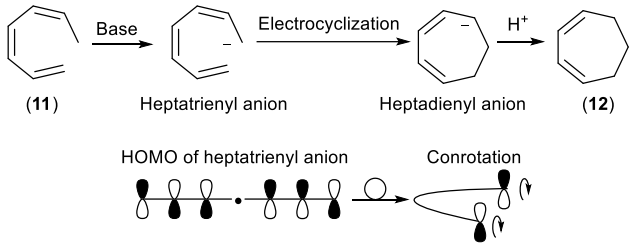
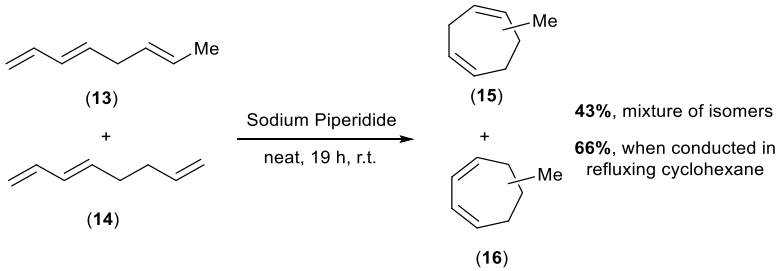


***Figure 3**: 7-atom-8-electron conrotatory electrocyclization*

1.5.1. Original discovery and existing methods

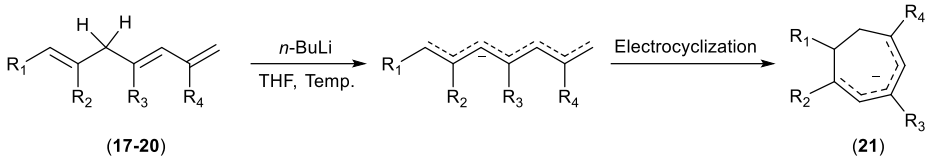
The earliest report on cycloheptane formation by way electrocyclization of heptatrienyl anions was by Zuech *et al.* in 1968.[15] They describe a process where a mixture of linear octatrienes is reacted with sodium piperidide to produce a mixture of cyclic methylcycloheptadienes in 43% yield, improving to 66% when the reaction was conducted in refluxing cyclohexane (**Scheme 6**).



***Scheme 6**: Zuech's initial discovery of cycloheptane formation through electrocyclization*

In 1969, Bates *et al.* conducted a study on the electrocyclization of heptatrienyl anions.[16] A series of heptatrienes **17-20** were deprotonated with *n*-BuLi (pKaH = 50) at reduced temperatures to generate their respective heptatrienyl anions (**Scheme 7**). It was observed that increasing substitution resulted in slower deprotonation. Presumably, the methyl substituents'

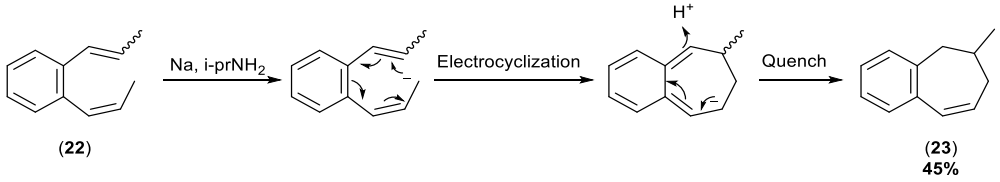
ability to inductively donate electron density destabilizes the heptatrienyl anions, resulting in a slower deprotonation. Electrocyclization of the heptatrienyl anions were observed when anions were warmed to above –30 ℃. The trisubstituted heptatriene only underwent deprotonation at ambient temperature and the acyclic anion could not be observed. This is the earliest instance of substituent groups influencing the rate of heptatrienyl anion formation.



Compound	R_1	R_2	R_3	R_4	Temp.	$t_{\frac{1}{2}}$
17	H	H	H	H	-50 ℃	14 min
18	Me	H	H	H	-50 ℃	300 min
19	H	Me	H	Me	-30 ℃	200 min
20	H	Me	Me	Me	r.t.	

Scheme 7*: Bates' study on the effects of substituents groups on the rate of heptatrienyl anion formation*

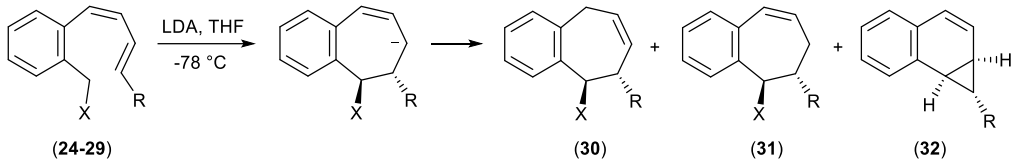
In 1969, Kergomard *et al.* reported the first instance of electrocyclization of heptatriene with a fused benzene moiety (**Scheme 8**).[17] The deprotonation of a terminal propenyl carbon with sodium in isopropyl amine converts a mixture of geometric isomers of ortho-dipropenylbenzene into the respective heptatrienyl anion. The heptatrienyl anion then undergoes an electrocyclization to produce methyl-3,4-benzocycloheptene.



Scheme 8*: Electrocyclization of heptatrienes with a fused benzene moiety*

Matsumoto and colleagues studied the electrocyclization heptatrienes with a fused benzene moiety.[18] In these reactions, the benzylic position is activated by an methoxy or thiomethyl group and deprotonated by LDA to give the respective heptatrienyl anion, which then undergoes electrocyclization to give a mixture of products (**Scheme 9**). The electron withdrawing group plays an important role in activating the benzylic position to deprotonation. Whereas previous methods generated heptatrienyl anions with strong bases, such as *n*-BuLi

(pKaH = 50), at elevated temperatures, Matsumoto's method uses a relatively weaker base LDA (pKaH = 35.7) at –78˚C.

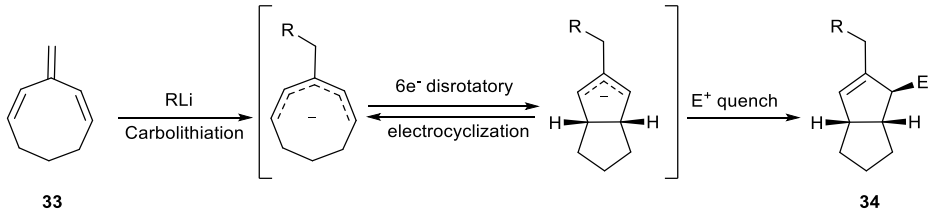


Compound	X	R	**30** (%)	**31** (%)	**32** (%)	Conditions
24	SMe	Ph	65	10	18	–78 ℃, 30 min
25	SMe	Ph	36	4	50	–78 ℃ to r.t., 120 min
26	OMe	Ph	53	4	32	–78 ℃, 30 min
27	OMe	Ph	84	n.a.	n.a.	–78 ℃ to r.t., 120 min
28	OMe	Me[a]	32[b]	2[b]	36	–78 ℃, 30 min
29	OMe	*t*Bu[c]	54	0	0	–78 ℃, 30 min

a) *1:1 ratio of (Z,E)- and (E,E)-isomers used*
b) Obtained as a mixture
c) A 54:46 ratio of (Z,E)- and (E,E)-isomers used

***Scheme 9**: Matsumoto's activated electrocyclization of heptatrienyl anions*

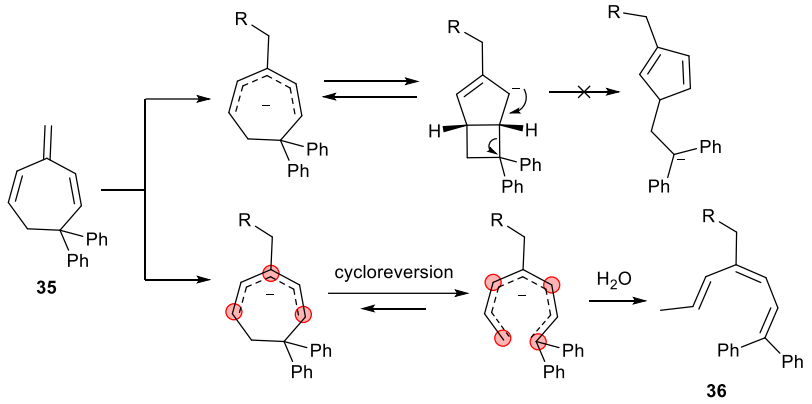
Williams *et al*. studied the electrocyclization of six- through nine- membered cyclodienyl anions formed by carbolithiation of cross conjugated dienes.[19] Cyclooctatrienes **33** and cyclononatrienes were shown to undergo 6-electron disrotatory electrocyclizations to form the corresponding bicyclic rings **34** (**Scheme 10**).



***Scheme 10**: 6-electron disrotatory electrocyclization of cyclooctatrienes and cyclononatrienes*

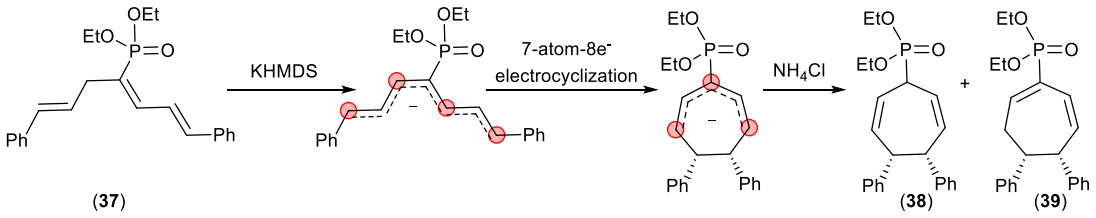
Despite this, carbolithiation of cross-conjugated cycloheptatrienes resulted in formation of linear heptatrienes. To investigate the unexpected result, compound **35** was prepared with the expectation that if the bicyclo[3.2.0]heptane was formed it would be trapped by undergoing an elimination reaction (**Scheme 11**). Instead, they observed the formation of aliphatic heptatriene **36** consistent with the product of a cycloreversion of a cycloheptadienyl anion to an acyclic heptatrienyl anion. Presumably, incorporation of the diphenyl functionality on the

ring system stabilizes the ring open heptatrienyl anion causing the system to favor cycloreversion (**Scheme 11**). The resultant heptatrienyl anion is reminiscent of diphenylmethane (pKaH = 32.3) which is more stable than unstabilized cyclic carbanion (**Scheme 11**).[20] This demonstrates the ability of electron withdrawing groups to stabilize products and influence the equilibrium of 7-atom-8-electron electrocyclizations.



***Scheme 11**: Williams' cycloreversion of functionalized cycloheptadienes*

A recent report by Tanino *et al*. demonstrated the opposite outcome. In their system, a diethylphosphoryl group stabilizes the cyclic heptadienyl anion, shifting the equilibrium of the system to favor electrocyclization and promote ring closure (**Scheme 12**).[21]

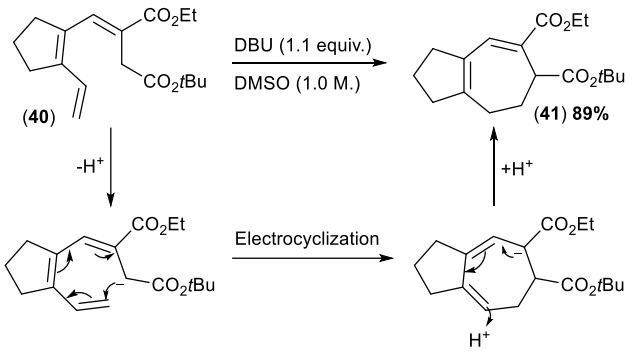


***Scheme 12**: Stabilized electrocyclization of 4-(diethoxyphosphoryl)-1,3,6-heptatriene derivatives*

1.5.2. Previous electrocyclization work by the Orellana group.

Previously, our group's work in this field centered around the electrocyclization of heptatrienes with a fused aliphatic ring and two strategically placed electron withdrawing groups. The fused ring system enforces the necessary all-*cis* arrangement necessary for electrocyclization, while the two electron withdrawing groups act to stabilize the linear heptatrienyl anion and the cyclic heptadienyl anion. It was shown that triene **40** could be electrocyclized to cycloheptane **41** in

89% yield using a stoichiometric amount of DBU (**Scheme 13**). This work is highly innovative as it generates the heptatrienyl anion using DBU (pKaH = 13.5), a substantially weaker base than those used in prior reports *n*-BuLi (pKaH = 50), LDA (pKaH = 35.7).[22] In addition, the use of a second electron withdrawing group stabilizes the cyclic heptadienyl anion, shifting the equilibrium of the reaction to favor electrocyclization. By the strategic use of electron withdrawing groups, the relative stability between the linear and cyclic anions is maintained and the reaction is allowed to be driven by the net gain of a sigma bond at the expense of a π bond.



***Scheme 13**: Optimized conditions for electrocyclization of heptatrienyl anion with fused cyclopentane*

Due to milder nature of the base used, it was hypothesized that the resultant heptadienyl anion could be sufficiently basic to deprotonate the conjugate acid of DBU, thus allowing for a catalytic electrocyclization. Unfortunately, despite the group's best efforts this was never achieved with the aliphatic substrate.

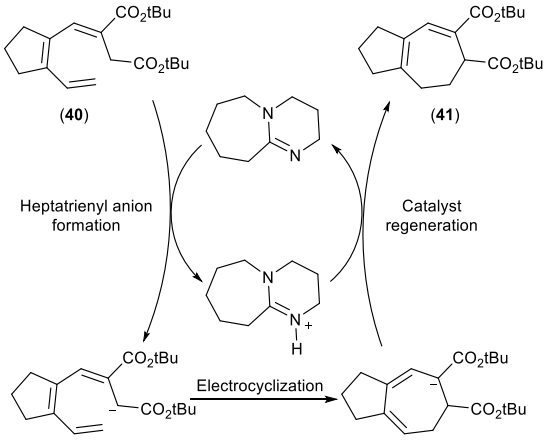
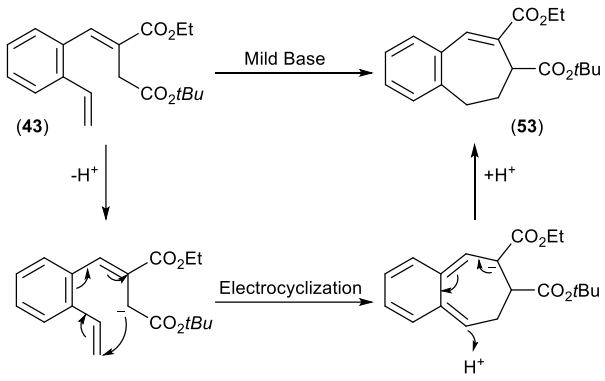


Figure 4**: Hypothetical catalytic electrocyclization of **40

Having optimized the reaction conditions for electrocyclization using stoichiometric base, the group attempted to synthesize a variety of aliphatic rings for electrocyclization starting with the cyclohexane and cycloheptane. Regrettably, carbocycles larger than cyclohexane were found to be unstable and decomposed rapidly.

1.6. Research plan and proposed strategy for electrocyclization of stable heptatrienes

To further advance research into practical electrocyclization reactions, we propose replacing the aliphatic ring system with an aromatic ring (**Scheme 14**). We hope that the inclusion of an aromatic ring will stablize the cycloheptane system and prevent decomposition.



***Scheme 14**: Proposed mild electrocyclization of benzene fused heptatriene*

The replacement of the aliphatic ring with an aromatic ring has subtle but significant effects on the properties of the system. In both the aliphatic and aromatic cases, the resultant heptadienyl anion is stablized by the electron withdrawing ester group and the delocalization of the negative charge across the conjugated system. In the aliphatic case, the cycloheptadienyl anion can be delocalized as normal and receives the full benefit from delocalization (**Figure 5**). This is not the case for the proposed aromatic compound. For the aromatic cycloheptadienyl anion to delocalize its negative charge, it disrupts aromaticity (**Figure 5**). This leads to less effective delocalization compared to the aliphatic case and could increase basicity of the benzylic posion, potentially enabling the catalytic electrocyclization. We hope to develop the catalytic electrocyclization of heptatrienyl anions with fused aromatic ring systems.

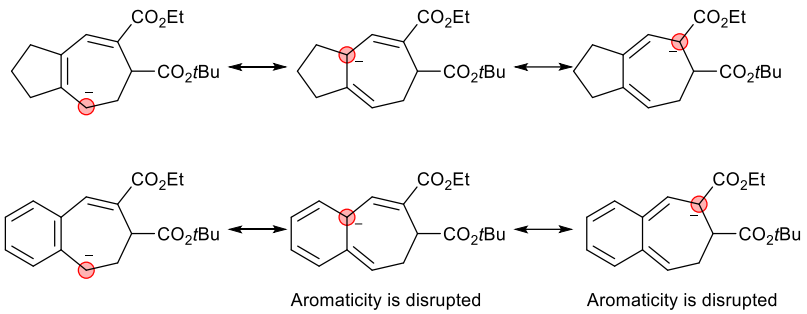
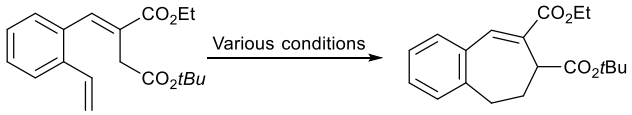


***Figure 5**: Delocalization of negative charge in cyclic heptadienyl anion*

2. Chapter 2: Results and discussion

2.1. Proof of concept and reaction optimization for electrocyclization of aromatic heptatriene

Our initial attempt at the electrocyclization of aromatic heptatrienes utilized stoichiometric TBAF in THF at room temperature (**Table 1**). To our surprise, the reaction did not proceed at room temperature and ultimately required heating to 50˚C to proceed with a yield of 57%. We then attempted the reaction under the best conditions for the aliphatic substrate, using DBU as an organic soluble base at room temperature, and were delighted to discover that the reaction proceeded with 90% yield.

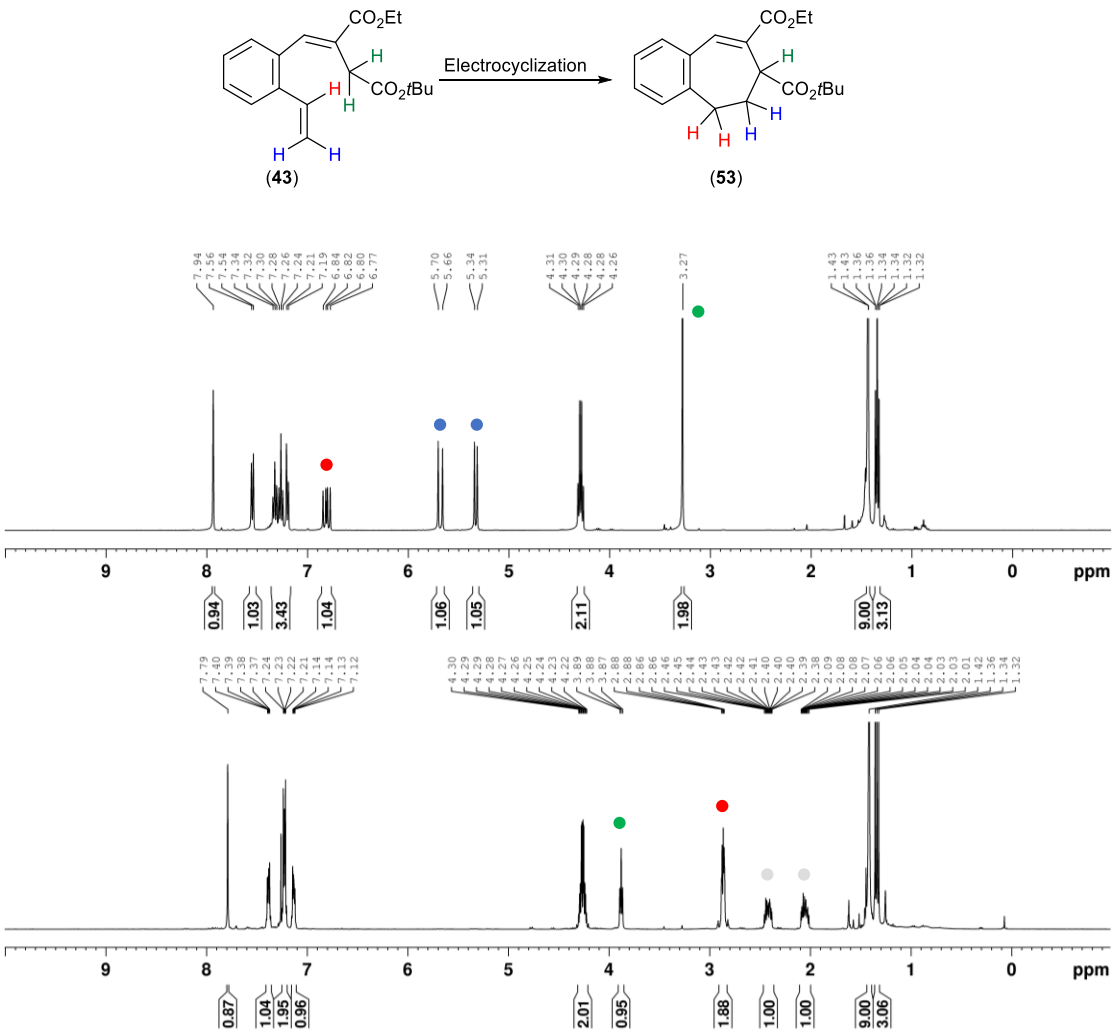


(**43**) (**53**)

Entry	Base	Equiv.	Solvent	Conc. (M)	Temp. (˚C)	Yield (%)
1	TBAF	1.1	THF	0.1	r.t.	No rxn
2	TBAF	1.1	THF	0.1	50	57
3	DBU	1.1	DMSO	0.1	r.t.	90
4	DBU	0.10	DMSO	0.1	r.t.	86
5	DBU	0.10	DMSO	1.0	r.t.	86

***Table 1**: Optimization conditions for aromatic heptatriene*

We knew the reaction was successful because the aromatic triene substrate has several characteristic ^{1}H NMR signals that disappear upon electrocyclization. The quartet at δ6.80 integrating to 1H corresponds to the methine indicated in red on **Figure 6**. Meanwhile the doublets, each integrating to 1H at δ5.68, and δ5.32, correspond to the methene indicated in blue on **Figure 6**. This is further supported by the coupling constants on the quartet and doublet corresponding with one another. Upon electrocyclization, we would expect these protons to shift upfield. This is indeed the case as in the ^{1}H NMR of the product we see the appearance of a triplet integrating to 2H at δ2.86. We believe this correlates to the former methine. In addition, the appearance of two multiplets integrating to 1H at δ2.41, and δ2.05, which correlate to the former methylene, indicating the existence of an adjacent stereogenic center. This is as expected because the electrocyclization would have formed a stereogenic center at the alpha position to the *tert*-butyl ester indicated in green on **Figure 6**.

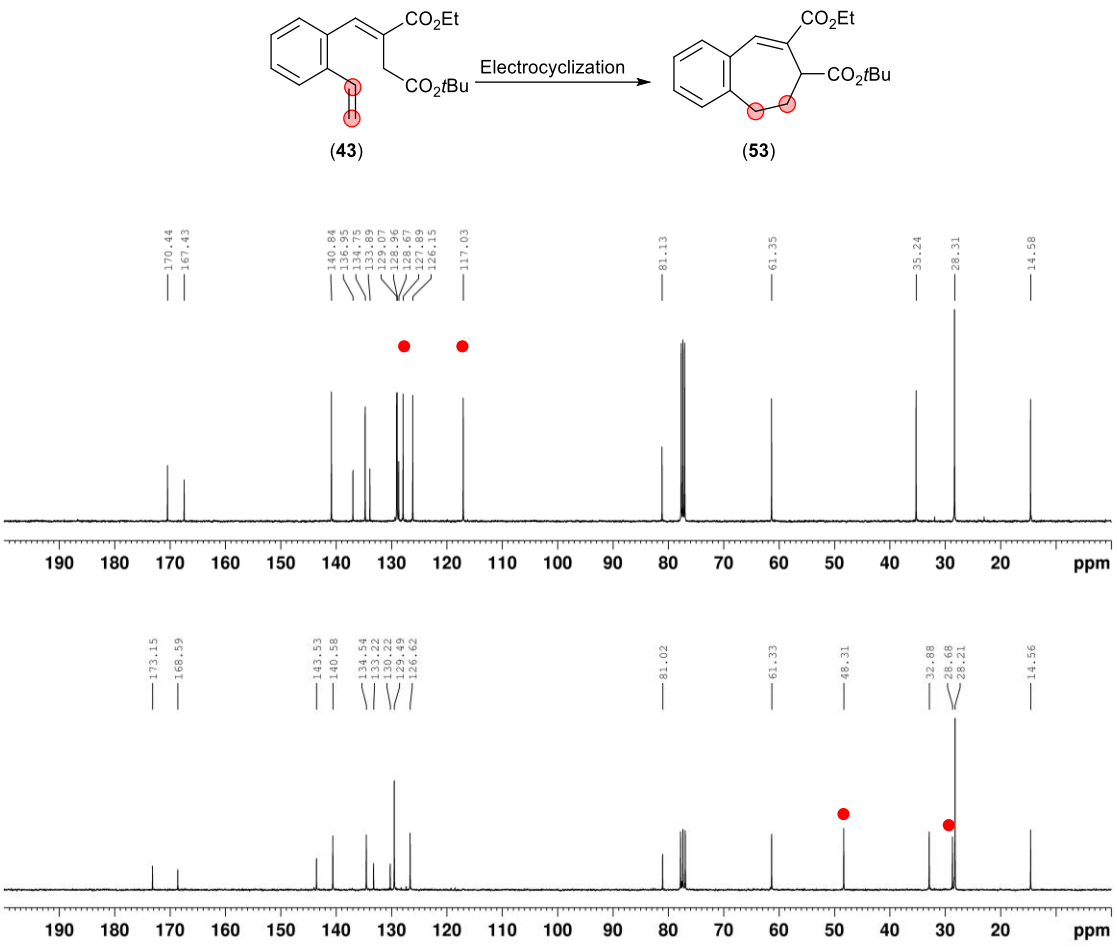


Top: *^{1}H NMR of uncyclized heptatriene **43** highlighting disappearance of diagnostic signal*

Bottom: *^{1}H NMR of cyclized hetadiene **53** highlighting appearance of diagnostic signals*

***Figure 6**: Change in ^{1}H NMR between linear heptatriene and cyclic heptadiene*

This is further supported by the decrease in the number of alkene signals between the ^{13}C NMR of the linear heptatriene and the cyclized heptadiene. Two alkene signals at δ117.0, and 127.9 disappear from the ^{13}C NMR while alkane signals at 48.3 and 28.7 appear (**Figure 7**). This in indicative of electrocyclization reactions as the overall change in unsaturation should lead to a decrease in the number of alkene signals.



Top: *^{13}C NMR of uncyclized heptatriene **43** highlighting disappearance of diagnostic signals*

Bottom: *^{13}C NMR of cyclized hetadiene **53** highlighting appearance of diagnostic signals*

***Figure 7**:Change in ^{13}C NMR between linear heptatriene and cyclic heptadiene*

Having successfully performed the stoichiometric electrocyclization, we attempted the catalytic reaction with DBU in DMSO (**Figure 8**). To our delight, the reaction proceeded in 86% yield to the desired cycloheptane ring. This is the first instance of a catalytic electrocyclization of heptatrienyl anions.

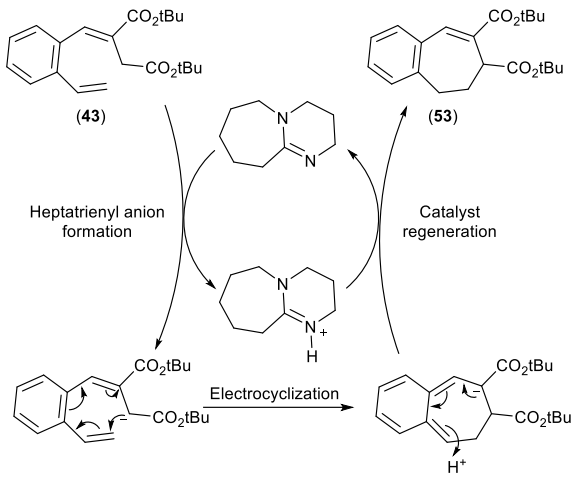
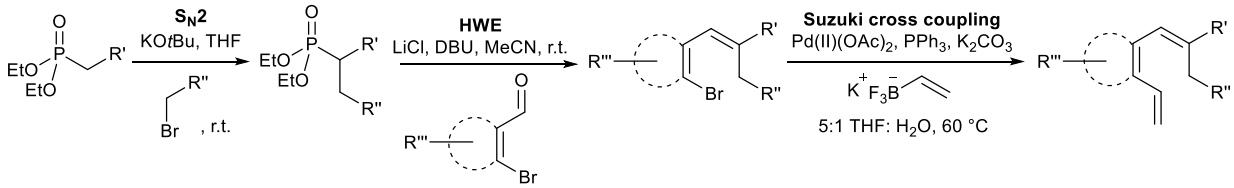


***Figure 8**: Proposed mechanism of catalytic electrocyclization of benzene fused heptatrienyl anions*

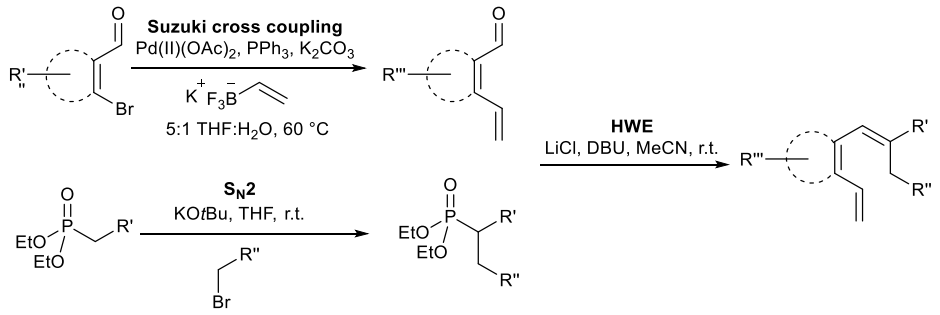
2.2. Substrate synthesis

To streamline our substrate synthesis and minimize waste, we synthesized our heptatriene substrates with two sequences of reactions. Sequence A is a linear synthesis of the triene starting with an S_N2 reaction to synthesize the phosphonate reagent, followed by a Horner-Wadsworth-Emmons (HWE) reaction to install the aromatic moiety, and finally a Suzuki cross coupling to install an alkene (**Scheme 15**). This is the main sequence by which we synthesized our starting materials.



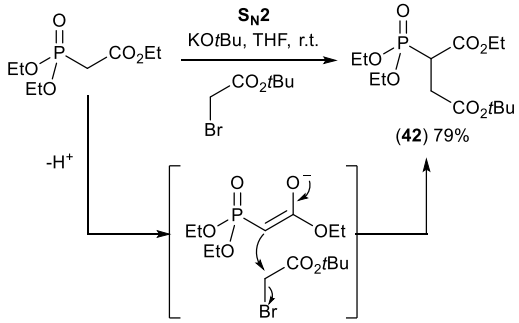
***Scheme 15**: Sequence A - a linear synthesis of heptatrienes*

However, for certain compounds the product of the HWE reaction in sequence A was found to be unstable or difficult to isolate. Therefore, it became necessary to alter the order of reactions. Sequence B is a convergent synthesis of the triene with the Suzuki cross coupling and the S_N2 reaction being carried out independently and coupled together by an HWE reaction (**Scheme 16**).



***Scheme 16**: Sequence B – a convergent synthesis of heptatrienes*

Both sequences require the generation of the phosphonate reagent. To do this, we began by deprotonating triethylphosphonoacetate with potassium *tert*-butoxide, followed by the addition α-bromoacetate (**Scheme 17**).



Scheme 17**: Synthesis of phosphonate **42

Next, we carry out a HWE reaction between the phosphonate and the requisite aldehyde. In order for the electrocyclization reaction to work, the uncyclized heptatriene must be able to adopt an all-*cis* geometry. To ensure that all double bonds in the final triene have the correct orientation relative to one another, we utilized the HWE reaction to install our aromatic moiety. The HWE reaction involves the formation of a phosphonate ylide, followed by coupling with an appropriate aldehyde. For the reaction to produce the desired E isomer, the ylide must be stabilized by an electron withdrawing group. Due to this increased stability, the initial addition reaction is reversible. This allows for the formation of the *cis* and *trans*-oxaphospatane to be under thermodynamic control.[5] The rate of elimination of the *trans*-oxaphosphetane is faster than the rate of reversion back to the starting materials, resulting in the preferential formation of the *E*-isomer. In this case, the stabilized ylide was generated using a soft enolization approach, which employs LiCl as a Lewis acid to activate phosphonoacetate, lowering the pKa of the methine proton and allowing deprotonation with mild amine bases, such as DBU (pKaH

= 13.5) (**Figure 9**).[23] Our choice to use this soft enolization approach was deliberate as the mild conditions would exhibit high functional group tolerance. The resultant ylide then reacts with the appropriate aldehyde forming an oxaphosphetane intermediate which then collapses to give the product (**Figure 9**).

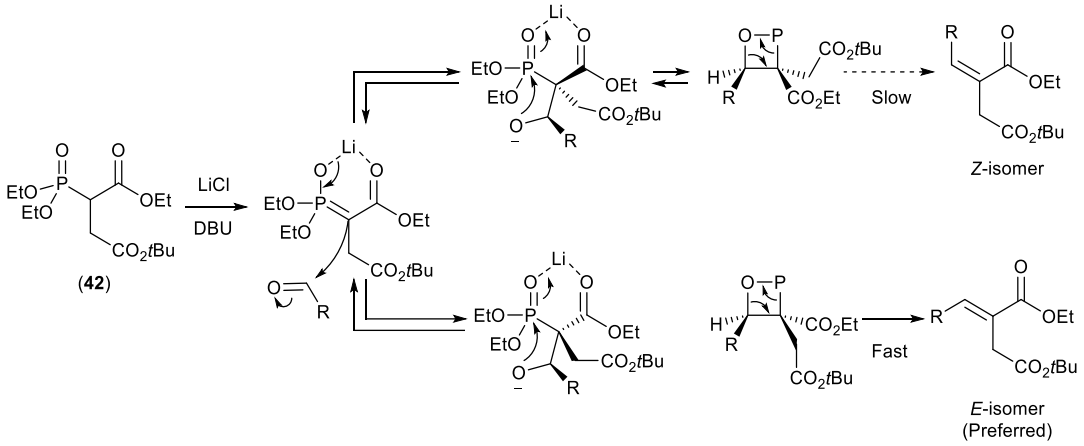


Figure 9*: Mechanism of HWE reaction*

This reaction is used in sequence A to couple the phosphonate backbone to 2-bromobenzaldehyde derivatives to generate intermediates **44**-**47** for Suzuki coupling, and used in sequence B to generate the uncyclized heptatriene **43** (**Figure 10**).

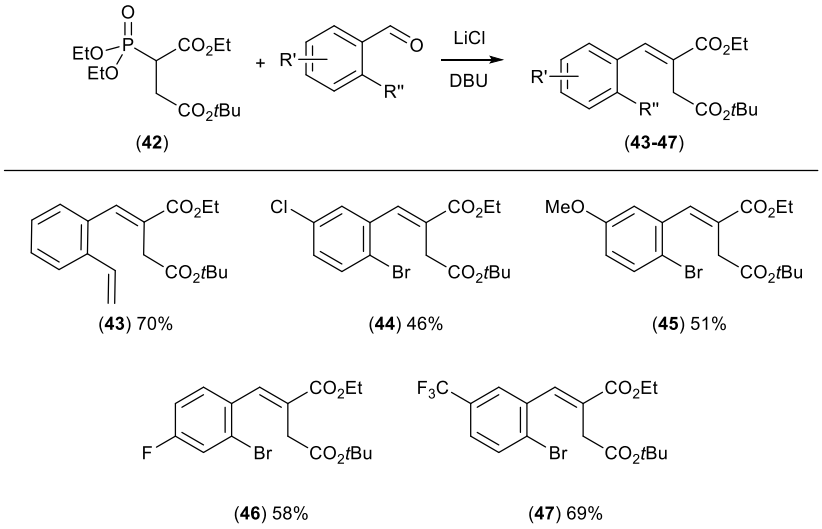


Figure 10*: Products of HWE reactions*

Suzuki reactions were used to install the vinyl functionalities. We generate Pd(0) in situ by reducing Pd(II)$(OAc)_2$ with triphenyl phosphine. The Pd(0) then undergoes an oxidative

addition with the functionalized 2-bromobenzene. The resultant palladium complex then undergoes a transmetallation with the boronic acid. Finally, a reductive elimination takes place, regenerating the Pd(0) catalyst, and releasing the coupling product (**Figure 11**).

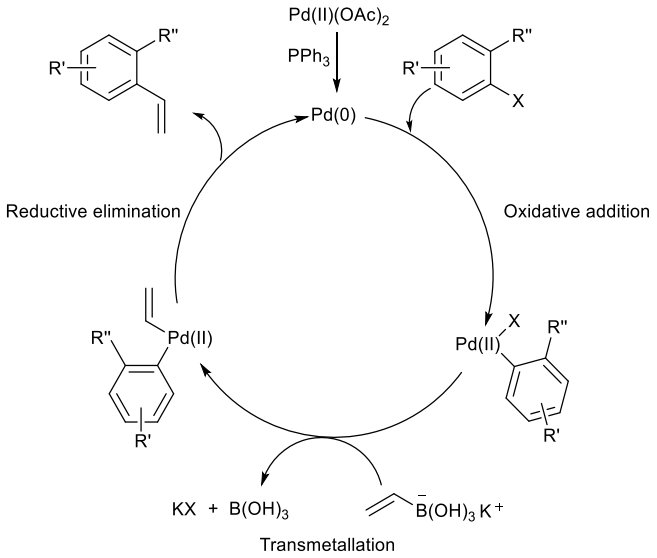


***Figure 11**: Catalytic cycle of Suzuki coupling*

In sequence B, this reaction is used to synthesize 2-vinylbenzaldehyde for the HWE reaction (**Figure 12**). In sequence A, this reaction is carried out after the HWE to synthesize heptatrienes **49**-**52** (**Figure 12**).

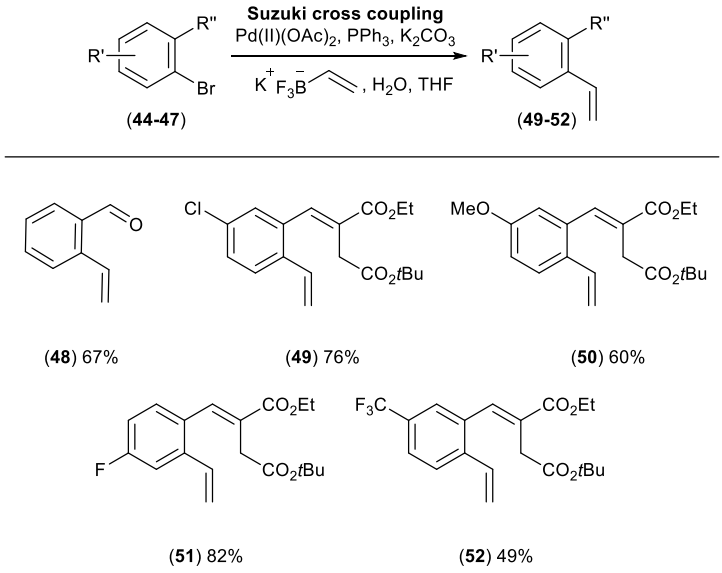


***Figure 12**: Products of Suzuki coupling*

2.3. Substrate scope

Having optimized our catalytic reaction conditions, we began investigating the functional group tolerance of our method. In addition, we also wanted to ascertain the effects of additional electron withdrawing and donating groups on the electrocyclization. The equilibrium of the electrocyclization reaction is dependent on the relative stability between the linear heptatrienyl anion and the cyclized heptadienyl anion. The respective anions delocalize electron density to different sites on the conjugated system and by adding electron donating or electron withdrawing groups to those positions we can disrupt the electrocyclization. In (**Figure 13**) functionalities at position Y can influence the cycloheptadienyl anion and functionalities at position X can influence the stability of the linear heptatrienyl anion.

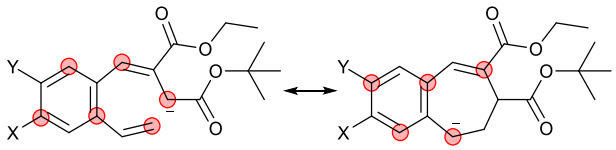


***Figure 13**: Distribution of electron density between linear heptatrienyl anion and cyclized heptadienyl anion*

We began our investigation by synthesizing **54** and **55** (**Figure 14**). Fluorine and trifluoromethyl are important functionalities in medicinal chemistry known to increase the metabolic stability of drug compounds.[24] We also wanted to see if the inductively withdrawing nature of fluorine would interfere with the electrocyclization. Its position on the aromatic ring should stabilize the heptatrienyl anion and favor the ring open form of the system. Fortunately, both electrocyclizations proceeded catalytically in high yield at room temperature. Next, we synthesized compound **56** as a contrast to **54** (**Figure 14**). The position of the chlorine functionality should stabilize the cycloheptadienyl anion. The reaction proceeded catalytically in high yield at room temperature. This result is especially useful as chlorine can be used as a synthetic handle for further functionalization. Taking the yields from **54** and **56**, we can see in both cases the inductively withdrawing effects of the halogens did not have an appreciable effect on the electrocyclization reaction. Having investigated inductive effects, we wanted to see the influence of resonance donating groups. To that end **57** was synthesized, the position of the methoxy functionality destabilizes the cycloheptadienyl anion (**Figure 14**). Additionally, the inclusion of the methoxy group had an impact on ability of the reaction to proceed

catalytically at room temperature. The initial attempt at catalytic electrocyclization did not proceed at room temperature and only produced trace amounts of product when heated to 60 ˚C. A similar result was observed when the reaction was conducted with stoichiometric amount of base with the reaction only proceeding when heated to 60 ˚C.

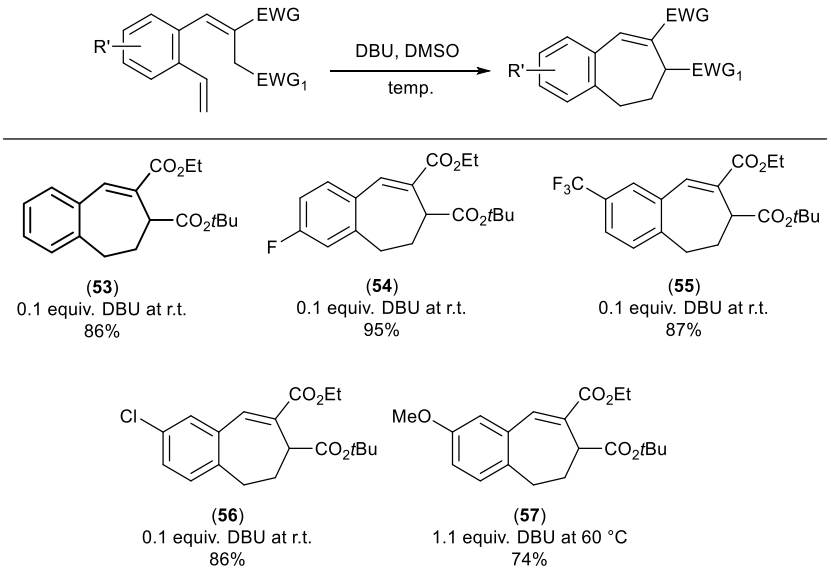


***Figure 14**: Yields and reaction conditions for electrocyclization reaction*

2.4. Conclusion

We have developed a mild catalytic synthesis of cycloheptanes through electrocyclization. Previous works overwhelmingly utilized harsh bases limiting their functional group tolerance and therefor their utility. Our strategic use of electron withdrawing groups to stabilize all intermediates enables the mild formation of heptatrienyl anions without shifting the equilibrium to favour cycloreversion. In addition, the inclusion of an aromatic moiety in our system enables the reaction to proceed catalytically. Our substrate scope studies have demonstrated a tolerance for common functional groups especially those relevant for medicinal chemistry. We have synthesized substrates with additional electron withdrawing and electron donating groups in a variety of positions to try and disrupt/enhance the electrocyclization and have proven that they do not severely hinder the electrocyclization.

3. Chapter 3: Experimental

3.1. General Experimental

All reactions were conducted in flame- or oven-dried glassware under an atmosphere of argon using anhydrous solvents unless specified otherwise. Tetrahydrofuran (THF), diethylether (Et_2O), dichloromethane (DCM) and toluene were dried using an INERT® PureSolv solvent purification system. Commercial reagents were used as received. Thin-layer chromatography was performed on SiliCycle® silica gel 60 F254 plates. Visualization was carried out using UV light (254 nm) and/or $KMnO_4$, $(NH_4)_2Ce(NO_3)_6$, vanillin, or anisaldehyde stains. Flash column chromatography1 was carried out using SiliCycle® SiliaFlash® silica gel (230-400 mesh, 40-63 μ, 60 Å pore size). Hexanes (ACS grade) and ethyl acetate (ACS grade) were used as received. ^{1}H-NMR, ^{13}C-NMR, and ^{19}F NMR spectra were recorded on a Bruker 400 AV, Bruker DRX 600 or Bruker 300 AV spectrometer in chloroform-d (99.8 % deuterated). ^{1}H-NMR, and ^{13}C-NMR were calibrated to 7.26 ppm ^{1}H and 77.36 ppm ^{13}C. Chemical shifts (δ) are reported in ppm and multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), sext (sextet), td (triplet of doublets), tt (triplet of triplets), dd (doublet of doublets), ddd (doublet of doublet of doublets), dddd (doublet of doublet of doublet of doublets), m (multiplet),and br (broad). Coupling constants J are reported in Hertz (Hz). Infrared (IR) spectra were recorded as thin films (neat) using AlphaPlatinum ATR, Bruker, diamond crystal FT-IR instrument.

3.2. General procedure

General procedure A: Horner–Wadsworth–Emmons reaction

Lithium chloride (2 equiv.) was suspended in dry acetonitrile (0.1 M) in a flame-dried round-bottomed flask equipped with a stir bar. The appropriate phosphonate, and aldehyde was added to the round bottom flash. DBU (1.6 equiv.) was then added dropwise to the reaction mixture. The resulting mixture was stirred at room temperature and allowed to stir overnight. The reaction was quenched with water extracted with ethyl acetate, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography.

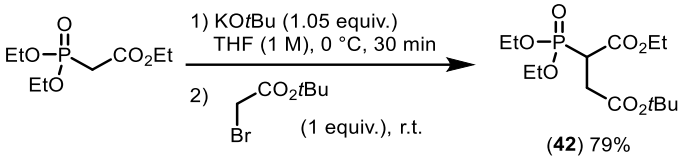
General procedure B: Palladium catalyzed Suzuki cross coupling reaction

$Pd(II)(OAc)_2$ (0.1 equiv.), and PPh_3 (0.2 equiv.) was suspended in dry, de-gassed THF (0.1 M) in a flame-dried round-bottomed flask equipped with a stir bar. The appropriate substrate, inorganic base, trifluoroborate, and H_2O (0.5 M) was added to the round bottom flask. The resulting mixture was heated to 60 °C and allowed to stir overnight. Upon completion, additional water was added. The mixture was extracted with ethyl acetate, dried over anhydrous $MgSO_4$. and concentrated *in vacuo*. The crude product was purified by flash chromatography.

General procedure C: Electrocyclization of activated heptatriene

The appropriate heptatriene was dissolved in dry DMSO (1.0 M) in a flame-dried round-bottomed flask equipped with a stir bar. DBU (0.1 equiv.) was added to the reaction mixture dropwise and allowed to stir at various temperatures. The progress of the reaction was monitored by TLC and upon completion, the reaction was quenched with water, extracted with ethyl acetate, dried over anhydrous $MgSO_4$. and concentrated *in vacuo*. The crude product was purified by flash chromatography.

3.3. Preparation of Substrates: Procedures and Structural Data

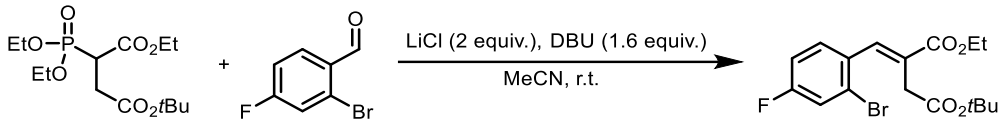


Potassium tert-butoxide (604 mg, 5.38 mmol, 1.05 equiv.) was suspended in dry THF (1 M) in a flame dried round bottom flask equipped with a stir bar and cooled to 0 ˚C. To the round bottom flask, triethyl phosphonoacetate (1149 mg, 5.13 mmol, 1 equiv.) was added and allowed to stir at 0˚C. After 30 minutes, tert-Butyl bromoacetate (1000 mg, 5.13 mmol, 1 equiv.) was added dropwise to the round bottom flask. The solution was stirred overnight and allowed to slowly warm to room temperature. The reaction was quenched with water, extracted with ethyl acetate, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography, to afford **42** (1.37 mg, 4.04 mmol, 79%)

Chromatography: 66% EtOAc in hexanes (Rf = 0.35).

^{1}H-NMR (400 MHz, $CDCl_3$)

δ 4.22 (m, 2 H), 4.14 (m, 4 H), 3.39 (ddd, *J* = 23.8, 11.5, 3.4 Hz, 1 H), 2.98 (m, 1 H), 2.72 (ddd, *J* = 17.5, 9.1, 3.4 Hz, 1 H), 1.41 (s, 9 H), 1.30 (m, 9 H)



42 **46** 56%

42 (500 mg, 1.47 mmol, 1 equiv) was treated with 2-Bromo-4-fluorobenzaldehyde (330 mg, 1.62 mmol, 1.1 equiv) following **General procedure A** to afford **46** (320 mg, 0.82 mmol, 56% yield) as a clear, colorless, oil.

Chromatography: 5% EtOAc in hexanes (Rf = 0.30).

^{1}H-NMR (400 MHz, $CDCl_3$)

δ 7.76 (s, 1 H), 7.34 (m, 2 H), 7.04 (dt, *J* = 8.3, 2.6 Hz, 1 H),
4.28 (q, *J* = 7.1 Hz, 2 H), 3.26 (s, 2 H), 1.44 (s, 9 H), 1.33 (t, *J* = 7.1 Hz, 3 H)

^{13}C-NMR (400 MHz, $CDCl_3$)

δ 170.3, 167.1, 162.6 (d, $^{1}J_{C\text{-}F}$ = 253.0Hz), 139.8, 132.2 (d, $^{4}J_{C\text{-}F}$ = 3.57 Hz),
131.4 (d, $^{3}J_{C\text{-}F}$ = 8.5 Hz), 128.9, 124.7 (d, $^{3}J_{C\text{-}F}$ = 9.5 Hz),
120.5 (d, $^{2}J_{C\text{-}F}$ = 24.6 Hz), 115.0 (d, $^{2}J_{C\text{-}F}$ = 21.2 Hz), 81.5, 61.6, 35.3, 28.3, 14.5

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

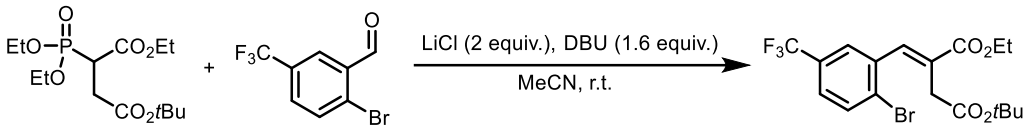
δ −110.49

IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 2979, 2932, 1712, 1482, 1149 cm^{-1}

HRMS ESI-TOF

$(M+H)^+$ calculated for $C_{17}H_{20}BrFO_4$ 387.0601, Found: 387.0601



42 **47** 69%

42 (500 mg, 1.47 mmol, 1 equiv) was treated with 2-Bromo-5-(trifluoromethyl)benzaldehyde (411 mg, 1.62 mmol, 1.1 equiv) following **General procedure A** to afford **47** (443 mg, 1.01 mmol, 69% yield) as a clear, colorless, oil.

Chromatography: 5% EtOAc in hexanes (Rf = 0.36).

^{1}H-NMR (400 MHz, $CDCl_3$)

δ7.80 (s, 1 H), 7.75 (d, J = 8.5 Hz, 1 H), 7.65 (d, J = 1.6 Hz, 1 H), 7.46 (dd, J = 2.2, 8.4 Hz, 1 H). 4.31 (q, J = 7.2 Hz, 2 H), 3.27 (s, 2 H), 1.45 (s, 9 H), 1.35 (t, J = 7.16 Hz, 3 H)

^{13}C-NMR (600 MHz, $CDCl_3$)

δ 169.9, 166.8, 139.3, 137.1, 133.7, 130.4 (q, $^{2}J_{C\text{-}F}$ = 33.0 Hz), 130.1, 127.3 (q, $^{3}J_{C\text{-}F}$ = 3.3 Hz), 126.9 (q, $^{3}J_{C\text{-}F}$ = 3.1 Hz), 123.9 (q, $^{1}J_{C\text{-}F}$ = 272.2 Hz), 81.9, 61.8, 35.5, 28.2, 14.6

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

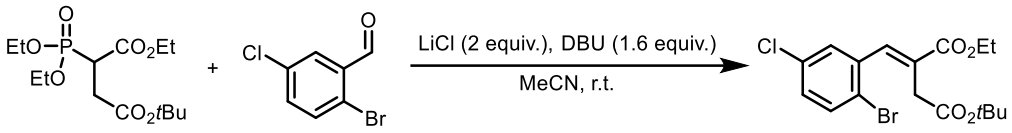
δ − 62.75

IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 2961, 2921, 2850, 1719 cm^{-1}

HRMS ESI-TOF

$(M+H)^+$ calculated for $C_{18}H_{20}BrF_3O_4$ 437.0569, Found: 437.0569



42 **44** 46%

42 (500 mg, 1.47 mmol, 1 equiv) was treated with 2-Bromo-5-chlorobenzaldehyde (357 mg, 1.62 mmol, 1.1 equiv) following **General procedure A** to afford **44** (273 mg, 0.67 mmol, 46% yield) as a clear, colorless, oil.

Chromatography: 5% EtOAc in hexanes (Rf = 0.27).

^{1}H-NMR (400 MHz, $CDCl_3$)

δ 7.74 (s, 1 H), 7.54 (d, *J* = 8.9 Hz, 1 H), 7.35 (d, *J* = 2.9 Hz, 1 H), 7.19 (dd, *J* = 8.9, 2.9 Hz, 1 H), 4.30 (q, *J* = 7.7 Hz, 2 H), 3.29 (s, 2 H), 1.47 (s, 9 H), 1.34 (t, *J* = 7.7 Hz, 3 H)

^{13}C-NMR (400 MHz, $CDCl_3$)

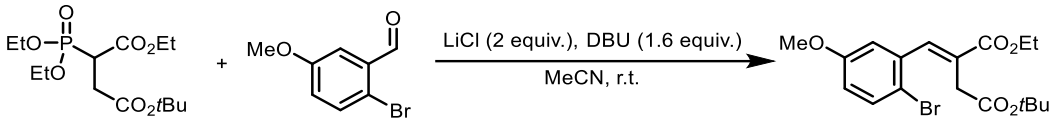
δ 170.0, 166.9, 139.5, 137.6, 134.2, 133.8, 130.3, 130.2, 129.6, 122.2, 81.8, 61.7, 35.4, 28.3, 14.6

IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 2956, 2920, 2851, 1727 cm^{-1}

HRMS ESI-TOF

$(M+H)^+$ calculated for $C_{17}H_{20}BrClO_4$ 403.0306, Found: 403.0305



42 **45** 51%

42 (500 mg, 1.47 mmol, 1 equiv) was treated with 2-Bromo-5-methoxybenzaldehyde (350 mg, 1.62 mmol, 1.1 equiv) following **General procedure A** to afford **45** (301 mg, 0.75 mmol, 51% yield) as a clear, colorless, oil.

Chromatography: 10% EtOAc in hexanes (Rf = 0.30).

^{1}H-NMR (400 MHz, $CDCl_3$)

δ 7.80 (s, 1 H), 7.47 (d, *J* = 8.8 Hz, 1 H), 6.94 (d, *J* = 3.0 Hz, 1 H), δ6.77 (dd, *J* = 8.8, 3.0 Hz, 1 H), δ4.29 (q, *J* = 7.1 Hz, 2 H), δ3.76 (s, 3 H), δ3.32 (s, 2 H), δ1.45 (s, 9 H), δ1.34 (t, *J* = 7.1 Hz, 3 H)

^{13}C-NMR (400 MHz, $CDCl_3$)

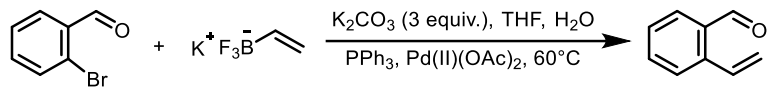
δ 170.6, 167.2, 159.1, 141.0, 136.7, 133.7, 128.7, 116.9, 115.4, 114.6, 81.5, 61.5, 55.9, 35.5, 28.3, 14.6

IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 2977, 2926, 2850, 1713, 1149cm^{-1}

HRMS ESI-TOF

$(M+H)^+$ calculated for $C_{18}H_{23}BrO_4$ 399.0801, Found: 399.0803



48 67%

2-Bromobenzaldehyde (500 mg, 2.70 mmol, 1 equiv) was treated with K_2CO_3 (1120 mg, 8.10 mmol, 3 equiv), and Potassium Vinyl Trifluoroborate (398 mg, 2.97 mmol, 1.1 equiv) following **General Procedure B** to afford compound **48 (**239 mg, 1.81 mmol, 67% yield) as a clear, light-yellow, oil.

Chromatography: 5% EtOAc in hexanes (Rf = 0.35).

^{1}H-NMR (400 MHz, $CDCl_3$)

δ 10.30 (s, 1 H), 7.83 (d, *J* = 7.5 Hz, 1 H), 7.55 (m, 3 H), 7.44 (m, 1 H), 5.70 (dd, *J* = 17.3, 1.1 Hz, 1 H), 5.52 (dd, *J* = 10.9, 1.1 Hz, 1 H)

42 **48** **43** 70%

42 (844 mg, 2.49 mmol, 1 equiv.) was treated with **48** (330 mg, 2.49 mmol, 1 equiv.) following **General procedure A** to afford **43** (552 mg, 1.74 mmol, 70% yield) as a clear, colorless, oil.

Chromatography: 5% EtOAc in hexanes (Rf = 0.30).

^{1}H-NMR (400 MHz, $CDCl_3$)

δ 7.93 (s, 1 H), 7.55 (d, *J* = 7.6 Hz), 7.26 (m, 3 H),
6.80 (dd, *J* = 17.6, 10.8 Hz, 1 H), 5.68 (d, *J* = 17.6 Hz , 1 H),
5.32 (d, *J* = 10.8 Hz, 1 H), 4.28 (q, *J* = 6.9 Hz, 2 H), 3.27 (s, 2 H), 1.43 (s, 9 H),
1.33 (t, *J* = 6.9 Hz, 3 H)

^{13}C-NMR (400 MHz, $CDCl_3$)

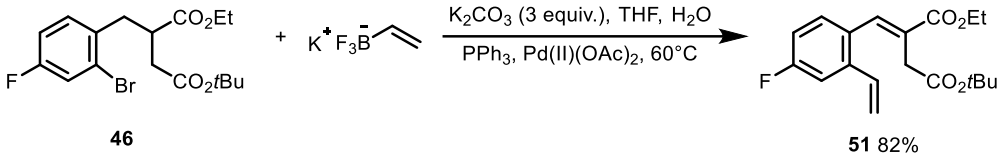
δ 170.4, 167.4, 140.8, 137.0, 134.7, 133.9, 129.1, 128.9, 128.6, 127.9, 126.1,
117.0, 81.1, 61.3, 35.2, 28.3, 14.6

IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 2978, 1714, 1466, 1151 cm^{-1}

HRMS ESI-TOF

$(M+H)^+$ calculated for $C_{19}H_{24}O_4$ 317.1753, Found: 317.1753



46 **51** 82%

46 (281 mg, 0.72 mmol, 1 equiv) was treated with K_2CO_3 (301 mg, 2.1 mmol, 3 equiv), and Potassium Vinyl Trifluoroborate (107 mg, 0.80 mmol, 1.1 equiv) following **General Procedure B** to afford compound **51 (**199 mg, 0.59 mmol, 82% yield) as a clear, light-yellow, oil.

Chromatography: 5% EtOAc in hexanes (Rf = 0.25).

^{1}H-NMR (400 MHz, $CDCl_3$)

δ 7.85 (s, 1 H), 7.20 (m, 2 H), 6.96 (dt, *J* = 8.2, 2.7 Hz, 1 H), 6.75 (ddd, *J* = 17.6, 11.0, 1.3 Hz, 1 H), 5.68 (d, *J* = 17.6 Hz, 1 H), 5.37 (d, *J* = 11.1 Hz, 1 H), 4.27 (q, *J* = 7.1 Hz, 2 H), 3.24 (s, 2 H), 1.42 (s, 9 H), 1.33 (t, *J* = 7.1 Hz, 3 H)

^{13}C-NMR (400 MHz, $CDCl_3$)

δ 170.4, 167.3, 163.2 (d, $^{1}J_{C\text{-}F}$ = 247.6 Hz), 139.8, 139.2 (d, $^{3}J_{C\text{-}F}$ = 7.8 Hz), 133.9 (d, $^{4}J_{C\text{-}F}$ = 1.5 Hz), 130.9 (d, $^{3}J_{C\text{-}F}$ = 8.5 Hz), 129.9 (d, $^{4}J_{C\text{-}F}$ = 3.1 Hz), 129.0, 118.1, 115.0 (d, $^{2}J_{C\text{-}F}$ = 21.6 Hz), 112.7 (d, $^{2}J_{C\text{-}F}$ = 22.0 Hz), 81.3, 61.4, 35.2, 28.3, 14.6

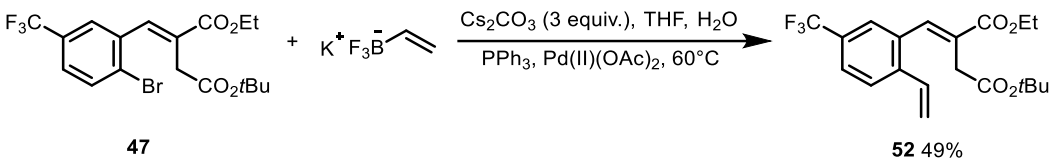
^{19}F-NMR (376 MHz, $CDCl_3$)

IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 2979, 2933, 1716, 1149 cm^{-1}

HRMS ESI-TOF

$(M+H)^+$ calculated for $C_{19}H_{23}FO_4$ 335.1653, Found: 335.1649



47 **52** 49%

47 (443 mg, 1.01 mmol, 1 equiv.) was treated with Cs_2CO_3 (990 mg, 3.04 mmol, 3 equiv.), and Potassium Vinyl Trifluoroborate (149 mg, 1.11 mmol, 1.1 equiv.) following **General Procedure B** to afford compound **52 (**191 mg, 0.50 mmol, 49% yield) as a clear, light-yellow, oil.

Chromatography: 5% EtOAc in hexanes (Rf = 0.3).

^{1}H-NMR (400 MHz, $CDCl_3$)

δ 7.89 (s, 1 H), 7.65 (d, *J* = 8.1 Hz, 1 H), 7.57 (d, *J* = 8.1 Hz, 1 H), 7.53 (s, 1 H), 6.81 (dd, *J* = 17.0, 11.4 Hz, 1 H), 5.78 (d, *J* = 17.0 Hz, 1 H), 5.46 (d, *J* = 11.4 Hz, 1 H), 4.30 (q, *J* = 7.1 Hz, 2 H), 3.24 (s, 2 H), 1.44 (s, 9 H), 1.34 (t, *J* = 7.1 Hz, 3 H)

^{13}C-NMR (400 MHz, $CDCl_3$)

δ 169.6, 166.7, 130.0, 138.9, 134.1, 133.4, 129.7, 129.7 (q, $^{2}J_{C-F}$ = 32.8 Hz), 126.3, 125.8 (q, $^{3}J_{C-F}$ = 3.6 Hz), 125.3 (q, $^{3}J_{C-F}$ = 3.6 Hz), 123.9 (q, $^{1}J_{C-F}$ = 272.2 Hz), 119.1, 81.3, 61.3, 35.0, 27.9, 14.2

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

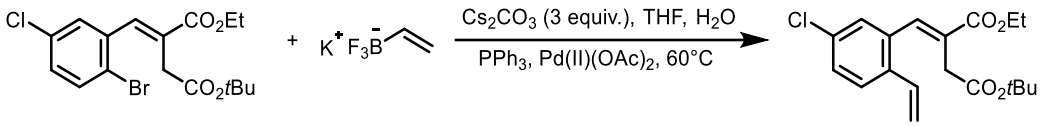
δ − 62.62

IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 2979, 2918, 2849, 1717, cm^{-1}

HRMS ESI-TOF

$(M+H)^+$ calculated for $C_{20}H_{23}F_3O_4$ 285.1621, Found: 385.1622



44 **49** 76%

33 (236 mg, 0.58 mmol, 1 equiv) was treated with Cs_2CO_3 (571 mg, 1.7 mmol, 3 equiv), and Potassium Vinyl Trifluoroborate (86 mg, 0.64 mmol, 1.1 equiv) following **General Procedure B** to afford compound **39 (**157 mg, 0.44 mmol, 76% yield) as a clear, light-yellow, oil.

Chromatography: 5% EtOAc in hexanes (Rf = 0.27).

^{1}H-NMR (400 MHz, $CDCl_3$)

δ 7.83 (s, 1 H), 7.47 (d, *J* = 8.2 Hz, 1 H), 7.29 (dd, *J* = 8.2, 2.3 Hz, 1 H),
7.22 (d, *J* = 2.3 Hz, 1 H), 6.73 (dd, *J* = 17.4, 11.0 Hz, 1 H),
5.66 (dd, *J* = 17.4, 0.8 Hz, 1 H), 5.36 (dd, *J* = 11.0, 0.8 Hz, 1 H),
4.29 (q, *J* = 7.2 Hz, 2 H), 3.25 (s, 2 H), 1.45 (s, 9 H), 1.34 (t, *J* = 7.2 Hz, 3 H)

^{13}C-NMR (400 MHz, $CDCl_3$)

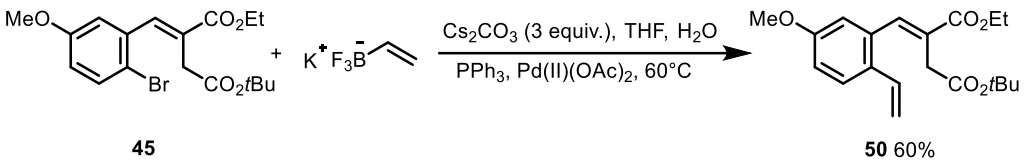
δ 170.1, 167.1, 139.0, 135.4, 135.4, 133.6, 133.6, 129.6, 129.0, 128.9, 127.5,
117.5, 81.5, 61.5, 35.3, 28.3, 14.5

IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 2980, 2933, 1719, 1150 cm^{-1}

HRMS ESI-TOF

$(M+H)^+$ calculated for $C_{19}H_{23}ClO_4$ 351.1347, Found: 351.1358



45 **50** 60%

45 (343 mg, 0.86 mmol, 1 equiv.) was treated with Cs_2CO_3 (840 mg, 2.58 mmol, 3 equiv.), and Potassium Vinyl Trifluoroborate (126 mg, 0.94 mmol, 1.1 equiv.) following **General Procedure B** to afford compound **50 (**178 mg, 0.51 mmol, 60% yield) as a clear, light-yellow, oil.

Chromatography: 10% EtOAc in hexanes (Rf = 0.35).

^{1}H-NMR (400 MHz, $CDCl_3$)

δ 7.92 (s, 1 H), 7.48 (d, *J* = 8.7 Hz, 1 H), 6.87 (dd, *J* = 8.7, 2.6 Hz, 1 H), 6.77 (d, *J* = 2.6 Hz, 1 H), 6.73 (dd, *J* = 17.3, 11.0 Hz, 1 H), 5.55 (d, *J* = 17.3 Hz, 1 H), 5.20 (d, *J* = 11.0 Hz, 1 H), 4.28 (q, *J* = 7.0 Hz, 2 H), 3.78 (s, 3 H), 3.29 (s, 2 H), 1.43 (s, 9 H), 1.34 (t, *J* = 7.0 Hz, 3 H)

^{13}C-NMR (400 MHz, $CDCl_3$)

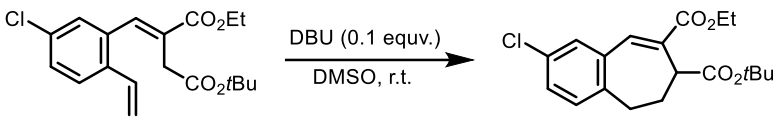
δ 170.3, 167.1, 158.9, 140.6, 134.7, 133.7, 129.3, 128.4, 127.1, 115.1, 114.5, 113.2, 81.0, 61.1, 55.3, 35.1, 28.0, 14.2

IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 2979, 2936, 2970, 2837, 1712 cm^{-1}

HRMS ESI-TOF

$(M+H)^+$ calculated for $C_{20}H_{26}O_5$ 347.1853, Found: 347.1855



49 **56** 86%

49 (59 mg, 0.16 mmol, 1 equiv) was transformed to **56** at room temperature using **General Procedure C**. This provided **56** (50 mg, 0.14 mmol, 86% yield) as a clear, light-yellow, oil.

Chromatography: 5% EtOAc in hexanes (Rf = 0.36).

^{1}H-NMR (400 MHz, $CDCl_3$)

δ 7.67 (s, 1 H), 7.36 (d, *J* = 2.2 Hz, 1 H), 7.18 (dd, *J* = 8.2, 2.2 Hz, 1 H), 7.06 (d, *J* = 8.2 Hz, 1 H), 4.26 (qd, *J* = 7.1, 1.5 Hz, 2 H), 3.87 (t, *J* = 5.6 Hz, 1 H), 2.82 (t, *J* = 5.6 Hz, 2 H), 2.40 (m, 1 H), 2.03 (m, 1 H), 1.41 (s, 9 H), 1.34 (t, *J* = 7.1 Hz, 3 H)

^{13}C-NMR (400 MHz, $CDCl_3$)

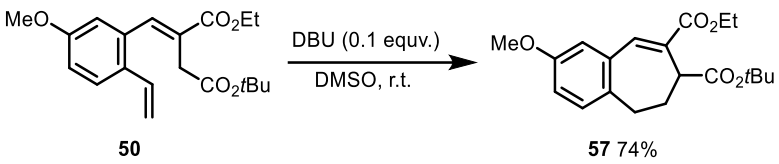
δ 172.9, 168.3, 141.9, 139.0, 135.0, 133.7, 132.3, 131.9, 130.9, 129.2, 81.3, 62.0, 48.2, 32.3, 28.8, 28.3, 14.6

IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 2977, 2932, 2871, 1720, 1706, 1239, 1146cm^{-1}

HRMS ESI-TOF

$(M+H)^+$ calculated for $C_{19}H_{23}ClO_4$ 351.1358, Found: 351.1357



50 **57** 74%

50 (107 mg, 0.31 mmol, 1 equiv) was transformed to **57** at 60 °C using **General Procedure C**. This provided **57** (80 mg, 0.23 mmol, 74% yield) as a clear, light-yellow, oil.

Chromatography: 5% EtOAc in hexanes (Rf = 0.20).

^{1}H-NMR (400 MHz, $CDCl_3$)

δ 7.72 (s, 1 H), 7.03 (d, *J* = 8.2 Hz, 1 H), 6.91 (d, *J* = 2.8 Hz, 1 H), 6.78 (dd, *J* = 8.2, 2.8 Hz, 1 H), 4.26 (m, 2 H), 3.86 (t, *J* = 5.2 Hz, 1 H), 3.08 (s, 3 H), 2.79 (t, *J* = 5.2 Hz, 2 H), 2.38 (m, 1 H), 2.04 (m, 1 H), 1.40 (s, 9 H), 1.33 (t, *J* = 7.3 Hz, 3 H)

^{13}C-NMR (400 MHz, $CDCl_3$)

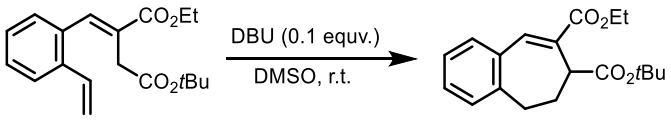
δ 173.2, 168.6, 158.2, 140.5, 136.0, 134.2, 130.8, 130.6, 119.2, 115.3, 81.1, 61.4, 55.7, 48.3, 32.0, 29.2, 28.3, 14.6

IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 2977, 2932, 2849, 1712, 1149 cm^{-1}

HRMS ESI-TOF

$(M+H)^+$ calculated for $C_{20}H_{26}O_5$ 347.1853, Found: 347.1853



43 **53** 86%

43 (170 mg, 0.53 mmol, 1 equiv) was transformed to **53** at room temperature using **General Procedure C**. This provided **53** (146 mg, 0.46 mmol, 86% yield) as a clear, light-yellow, oil.

Chromatography: 5% EtOAc in hexanes (Rf = 0.30).

^{1}H-NMR (400 MHz, $CDCl_3$)

δ 7.78 (s, 1 H), 7.38 (dd, *J* = 4.8, 4.0 Hz, 1 H), 7.23 (d, *J* = 3.4 Hz, 1 H), 7.21 (d, *J* = 3.5 Hz, 1 H), 7.13 (dd, *J* = 4.8, 3.5 Hz, 1 H), 4.26 (m, 2 H), 3.87 (t, *J* = 5.6 Hz, 1 H), 2.86 (m, 2 H), 2.41 (m, 1 H), 2.05 (m, 1 H), 1.41 (s, 9 H), 1.33 (t, *J* = 7.1 Hz, 3 H)

^{13}C-NMR (300 MHz, $CDCl_3$)

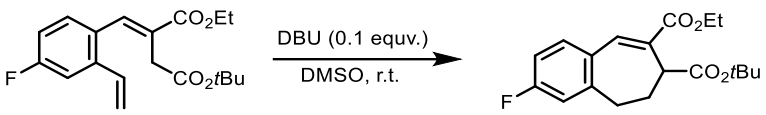
δ 173.2, 168.6, 143.5, 140.6, 134.5, 133.2, 130.2, 129.5, 126.6, 81.0, 61.3, 48.3, 32.9, 28.7, 28.2, 14.6

IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 2977, 2932, 1720, 1702 cm^{-1}

HRMS ESI-TOF

$(M+H)^+$ calculated for $C_{19}H_{24}O_4$ 317.1752 , Found: 317.1746



51 **54** 95%

51 (150 mg, 0.45 mmol, 1 equiv) was transformed to **54** at room temperature using **General Procedure C**. This provided **54** (142 mg, 0.42 mmol, 95% yield) as a clear, light-yellow, oil.[1]

Chromatography: 5% EtOAc in hexanes (Rf = 0.35).

^{1}H-NMR (300 MHz, $CDCl_3$)

δ 7.75 (s, 1 H), 7.36 (dd, *J* = 8.5, 5.9 Hz, 1 H), 6.88 (m, 2 H), 4.25 (qd, *J* = 7.2, 1.7 Hz, 2 H), 3.87 (t, *J* = 5.6 Hz, 1 H), 2.8 (m, 2 H), 2.41 (m, 1 H), 2.04 (m, 1 H), 1.41 (s, 9 H), 1.33 (t, *J* = 7.2 Hz, 3 H)

^{13}C-NMR (300 MHz, $CDCl_3$)

δ 173.0, 168.4, 163.1 (d, $^{1}J_{C\text{-}F}$ = 250.9 Hz), 146.1 (d, $^{3}J_{C\text{-}F}$ = 7.9 Hz), 139.4, 136.5 (d, $^{3}J_{C\text{-}F}$ = 8.8 Hz), 129.5, 129.4, 116.4 (d, $^{2}J_{C\text{-}F}$ = 21.6 Hz), 113.4 (d, $^{2}J_{C\text{-}F}$ = 21.2 Hz) 81.1, 61.4, 48.1, 32.8, 28.3, 28.2, 14.5

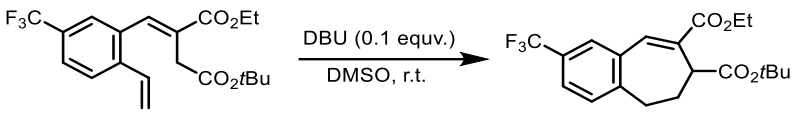
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 2978, 2933, 1722, 1149 cm^{-1}

HRMS ESI-TOF

$(M+H)^+$ calculated for $C_{19}H_{23}FO_4$ 335.1653, Found: 335.1650

[1] Compound prepared by Anmol Dhesi



52 **55** 87%

52 (191 mg, 0.49 mmol, 1 equiv) was transformed to **55** at room temperature using **General Procedure C**. This provided **55** (166 mg, 0.43 mmol, 87% yield) as a clear, light-yellow, oil.[2]

Chromatography: 5% EtOAc in hexanes (Rf = 0.3).

^{1}H-NMR (400 MHz, $CDCl_3$)

δ 7.76 (s, 1 H), 7.62 (s, 1 H), 7.45 (d, *J* = 7.9 Hz, 1 H), 7.25 (d, *J* = 7.9 Hz, 1 H), 4.27 (qd, *J* = 7.1, 2.7 Hz, 2 H), 3.90 (t, *J* = 5.2 Hz, 1 H), 2.90 (t, *J* = 5.7 Hz, 2 H), 2.44 (m, 1 H), 2.05 (m, 1 H), 1.40 (s, 9 H), 1.34 (t, *J* = 7.1 Hz, 3 H)

^{13}C-NMR (400 MHz, $CDCl_3$)

δ 172.7, 168.1, 147.1, 138.9, 134.0, 132.3, 130.7 (q, ^{3}J = 3.6 Hz), 130.0, 129.3 (q, ^{2}J = 32.6 Hz), 125.8 (q, ^{3}J = 3.4 Hz), 124.3 (q, ^{1}J = 271.8 Hz), 81.4, 61.6, 48.1, 32.7, 28.5, 28.2, 14.5

IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 2979, 2934, 2902, 1721 cm^{-1}

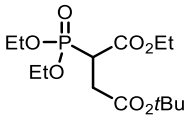
HRMS ESI-TOF

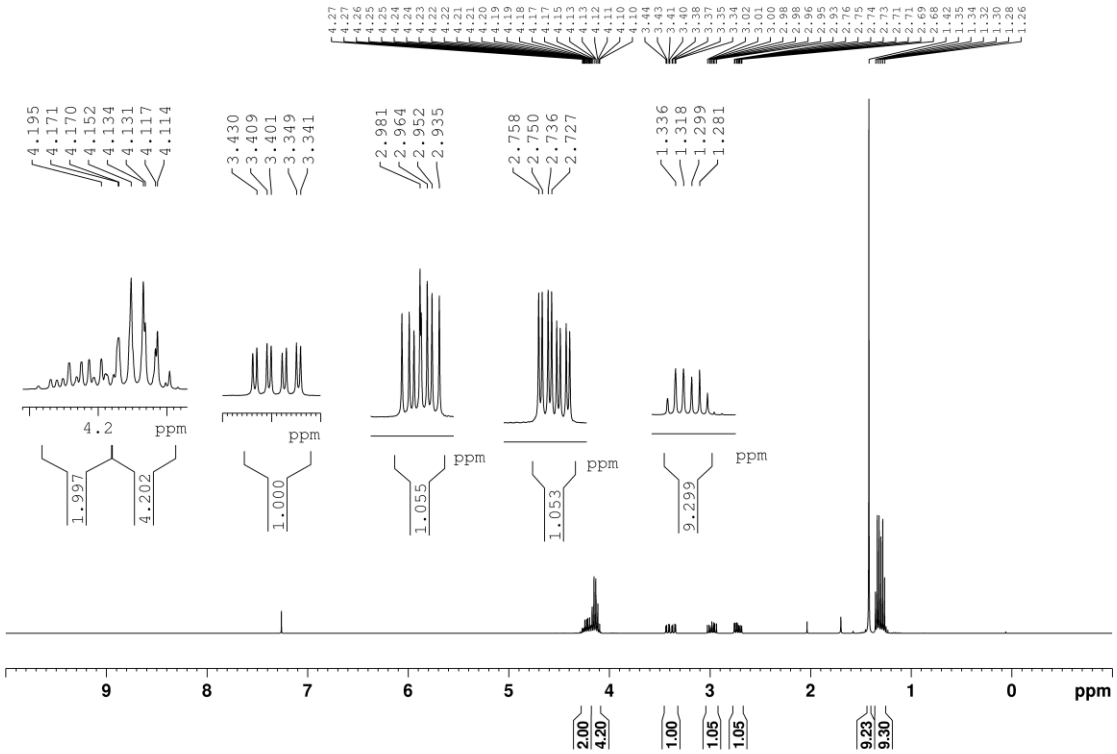
$(M+H)^+$ calculated for $C_{20}H_{23}F_3O_4$ 385.1621, Found: 385.1622

[2] Compound prepared by Anmol Dhesi

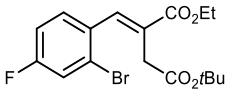
3.4. ^{1}H, ^{13}C, ^{19}F – NMR spectra

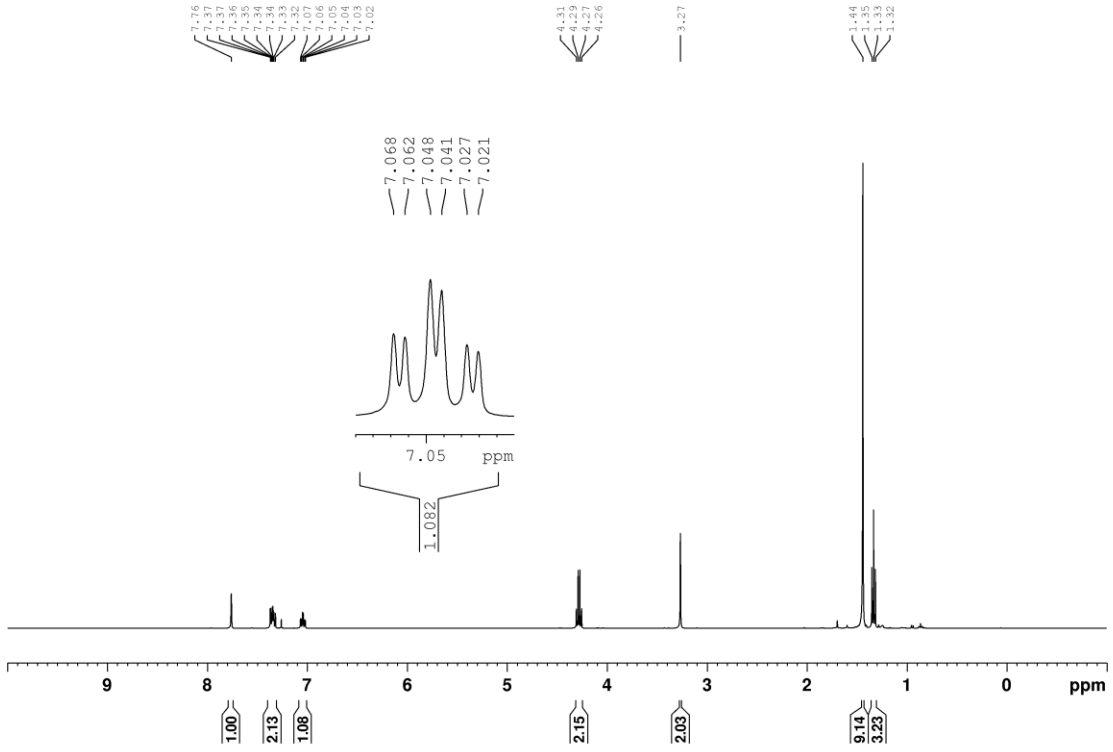
^{1}H NMR (400 MHz, $CDCl_3$) of **42**



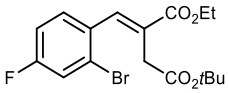


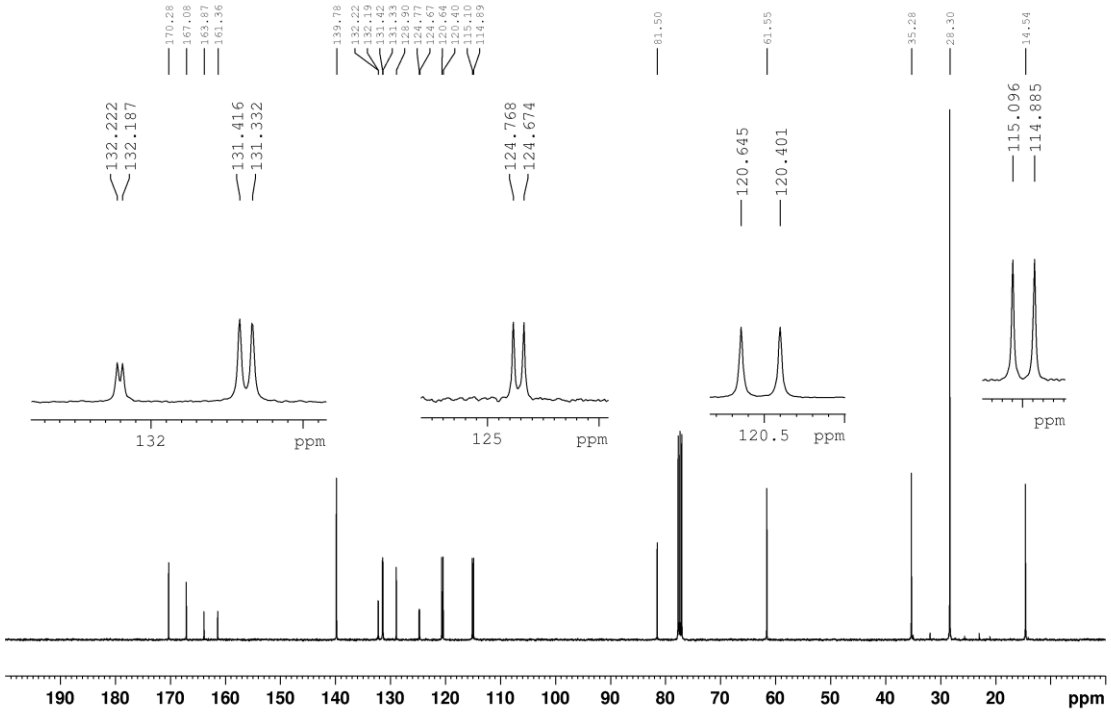
^{1}H NMR (400 MHz, $CDCl_3$) of **46**



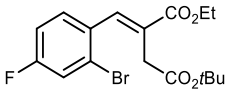


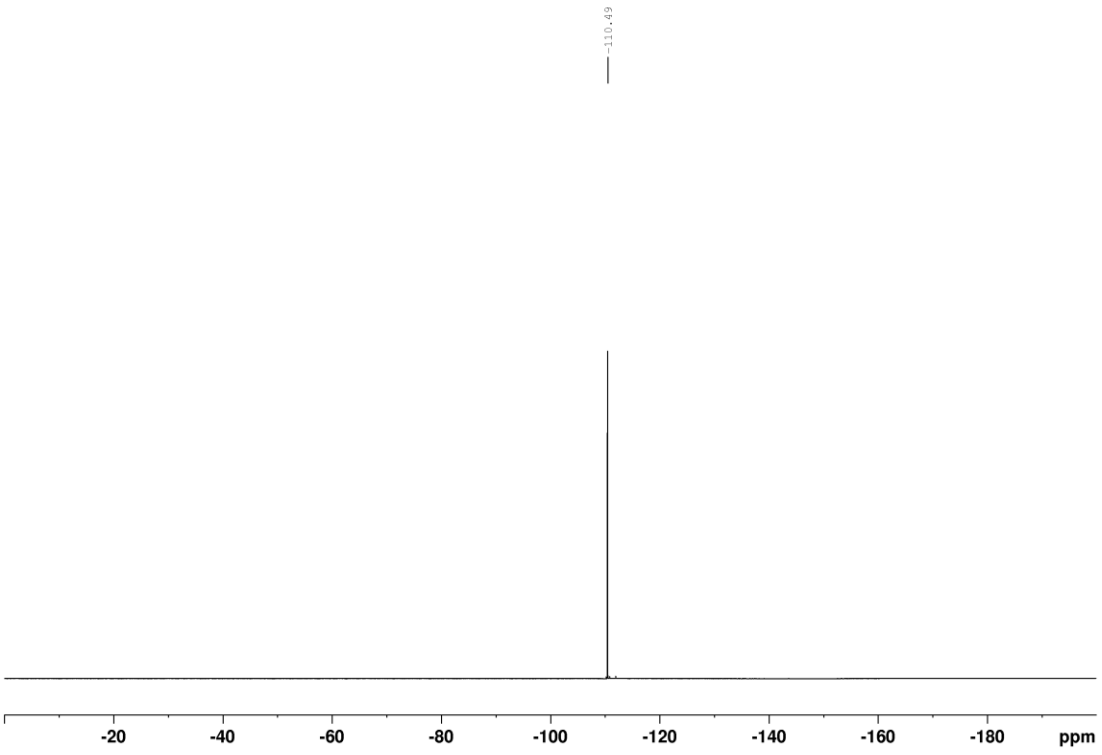
^{13}C NMR (400 MHz, $CDCl_3$) of **46**



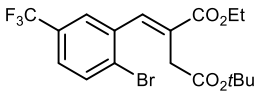


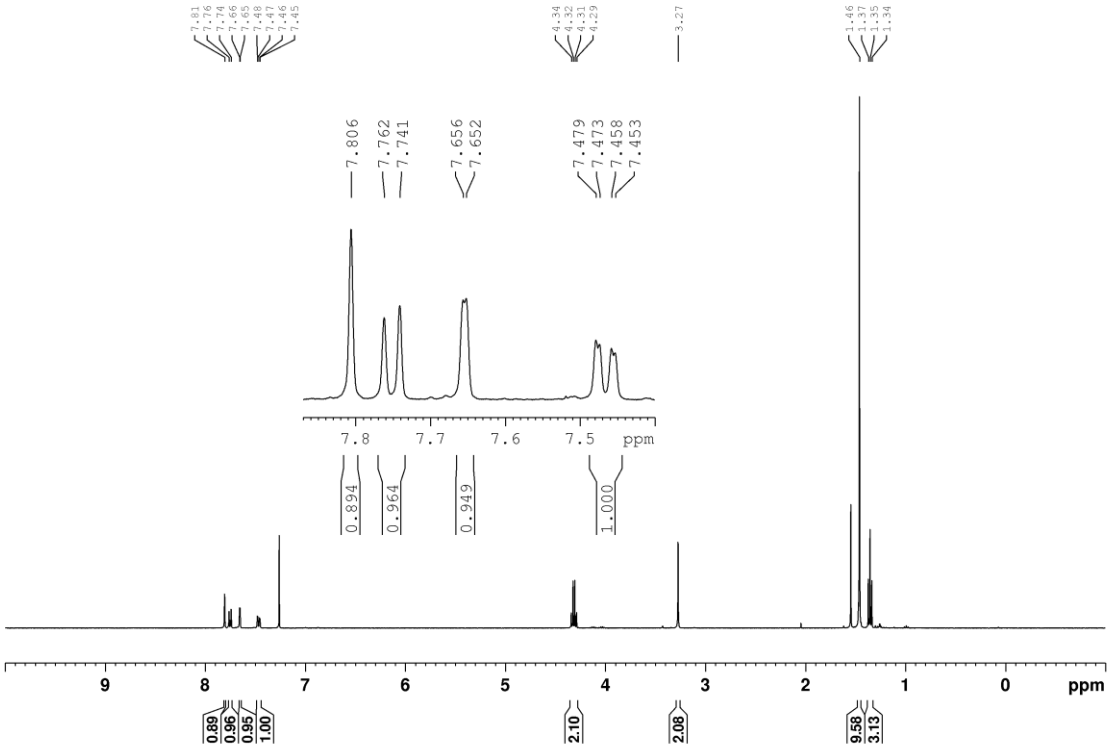
^{19}F NMR (376 MHz, $CDCl_3$) of **46**



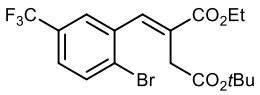


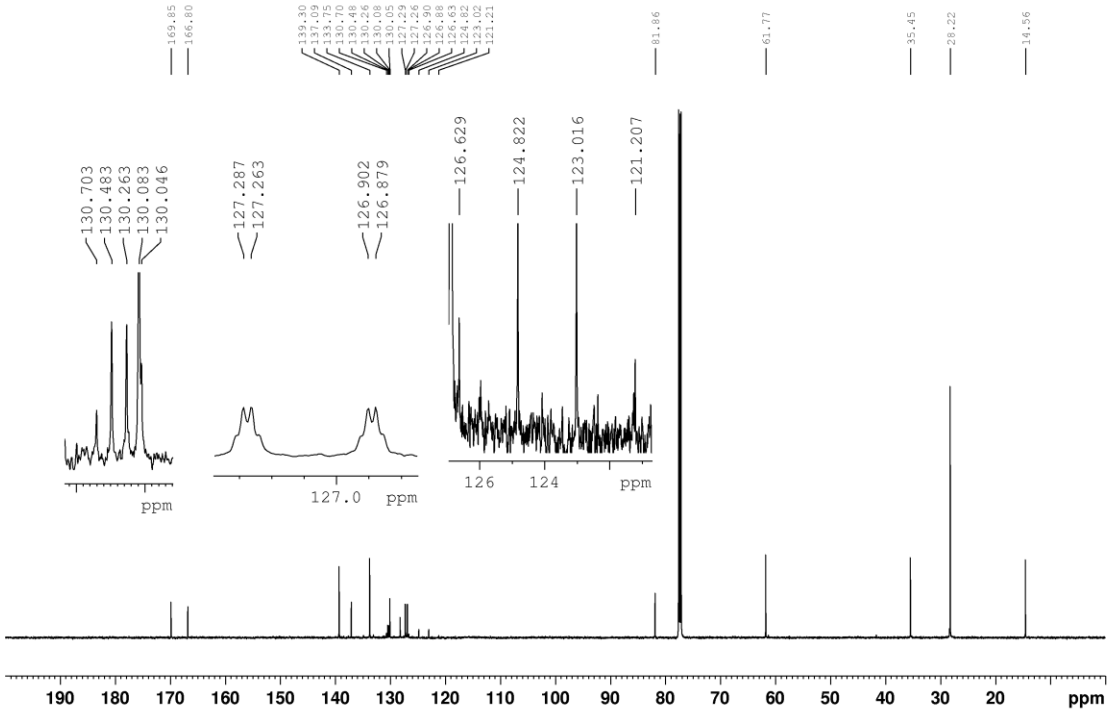
^{1}H NMR (400 MHz, $CDCl_3$) of **47**



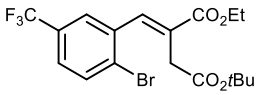


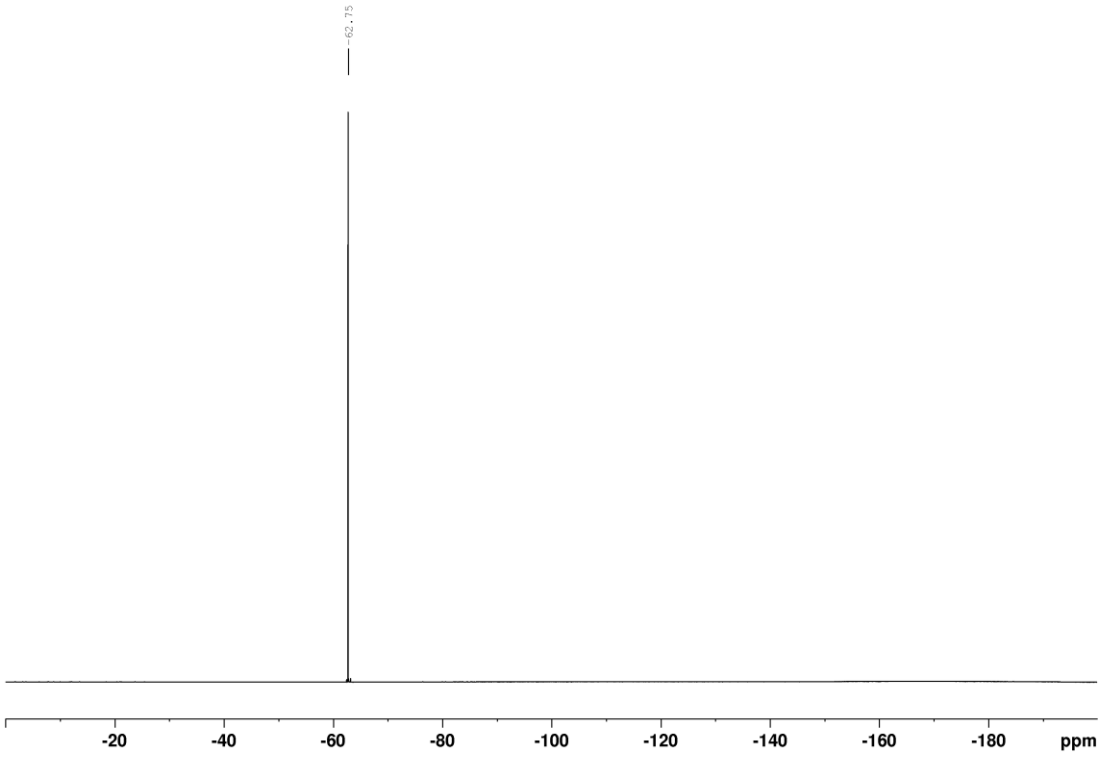
^{13}C NMR (600 MHz, $CDCl_3$) of **47**



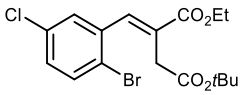


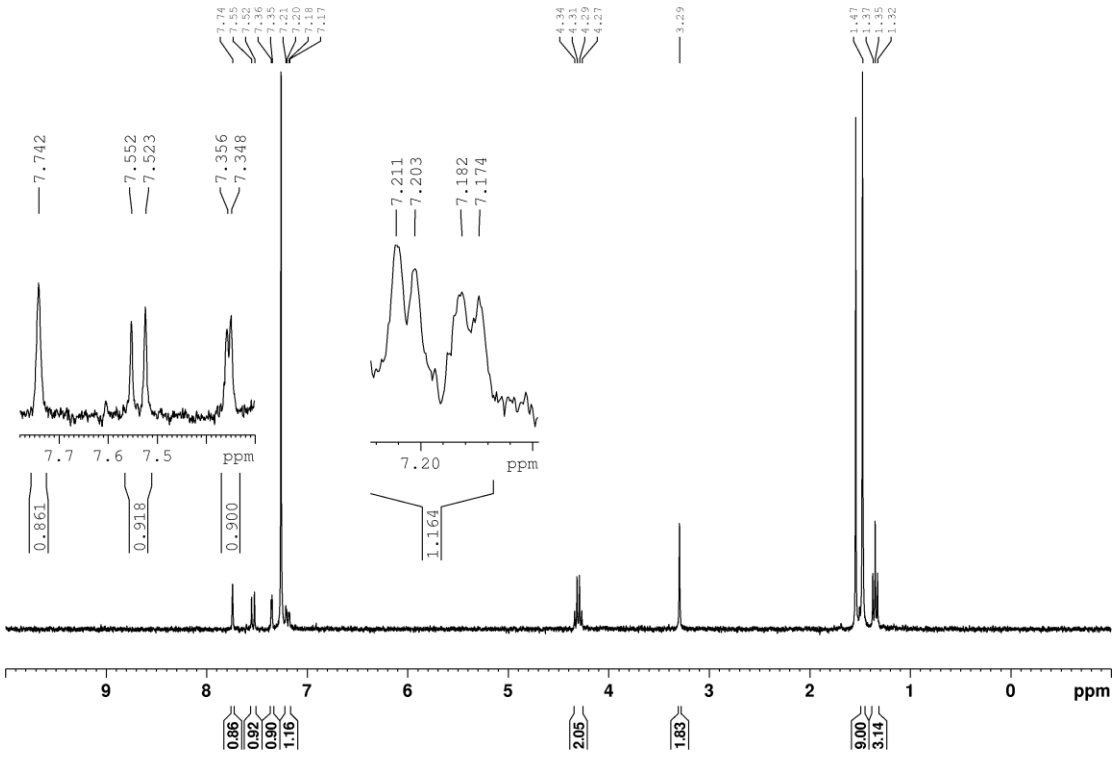
^{19}F NMR (376 MHz, $CDCl_3$) of **47**



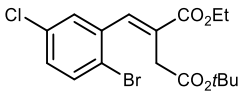


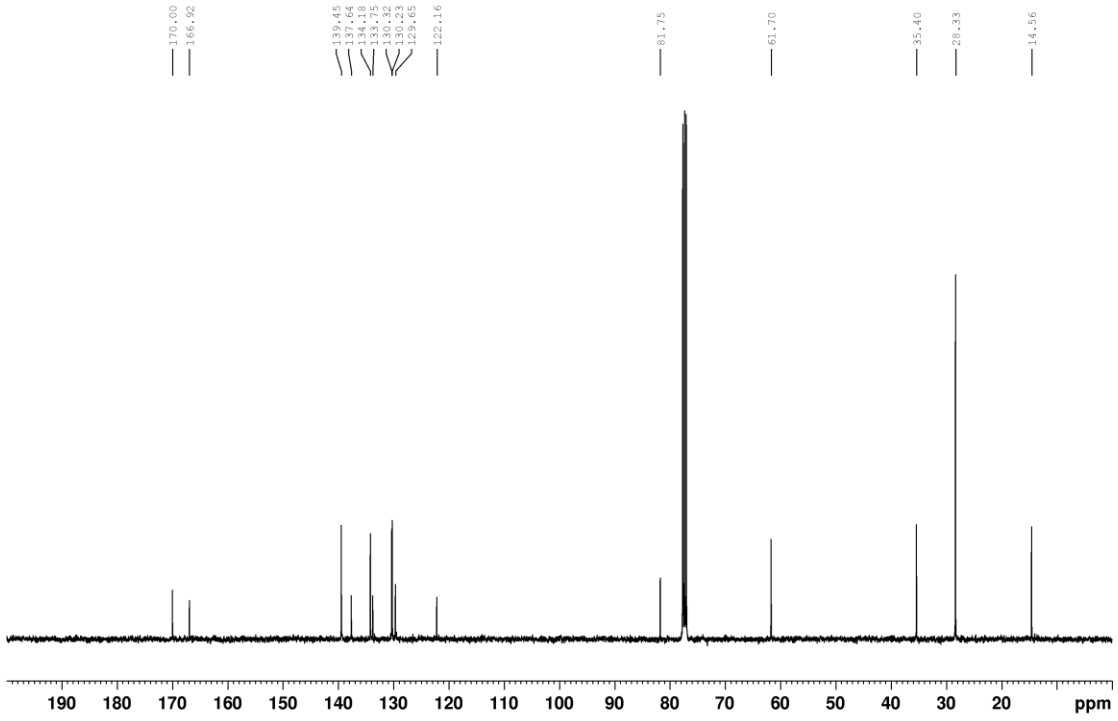
^{1}H NMR (400 MHz, $CDCl_3$) of **44**



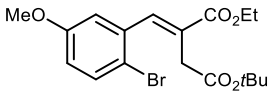


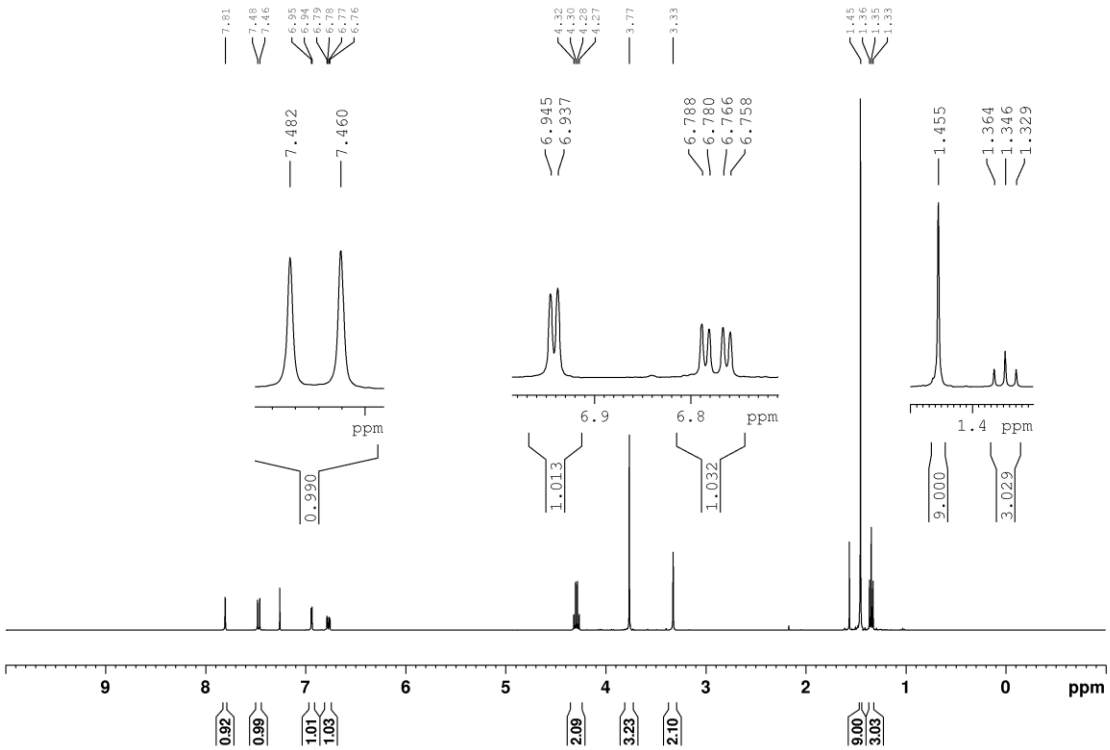
^{13}C NMR (400 MHz, $CDCl_3$) of **44**





^{1}H NMR (400 MHz, $CDCl_3$) of **45**





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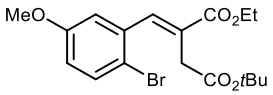
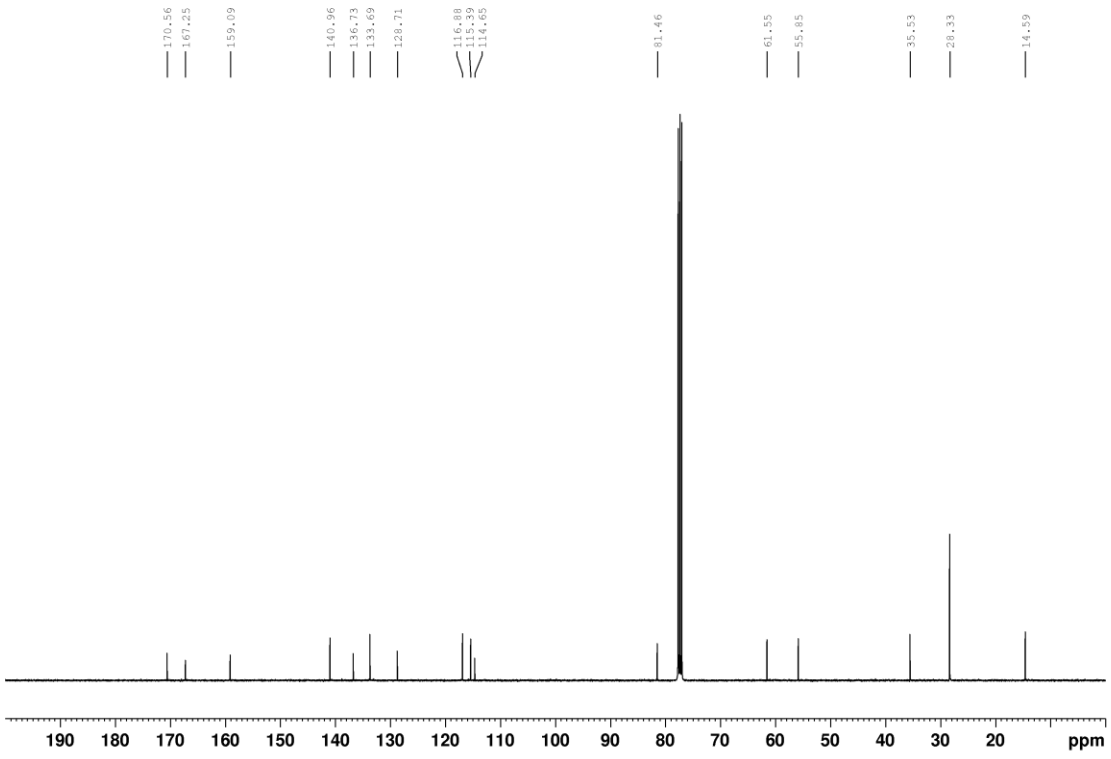
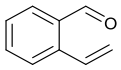
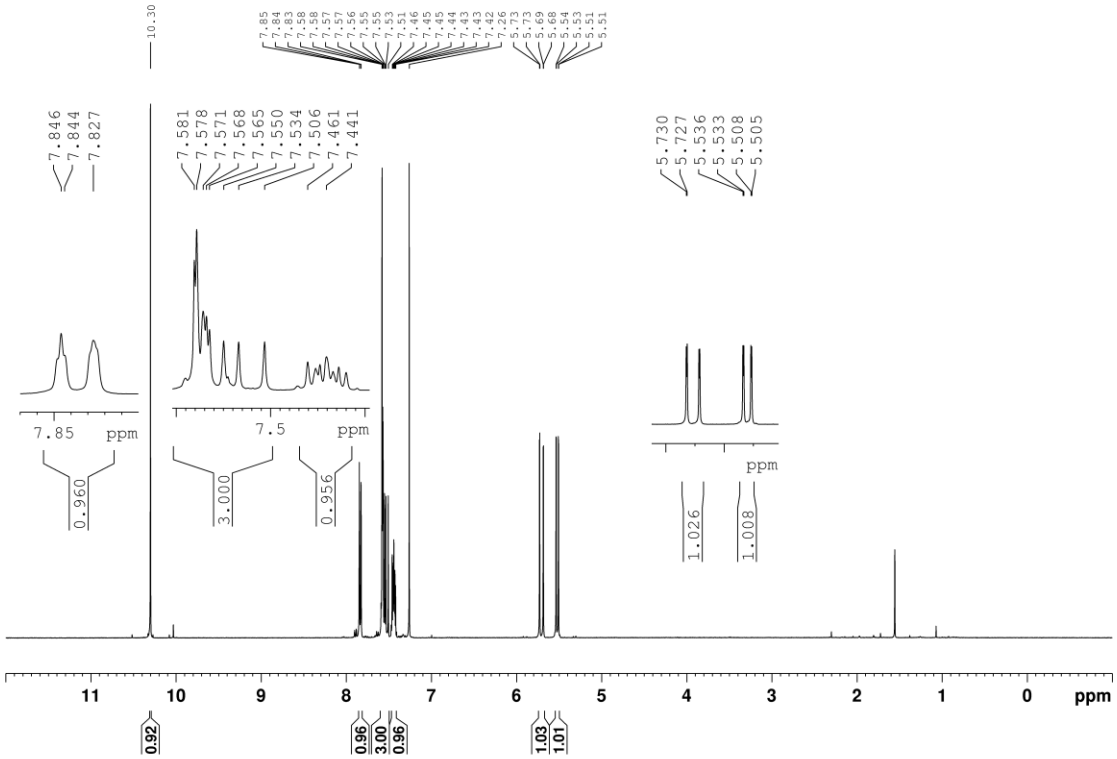


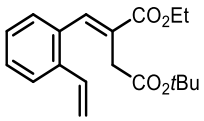


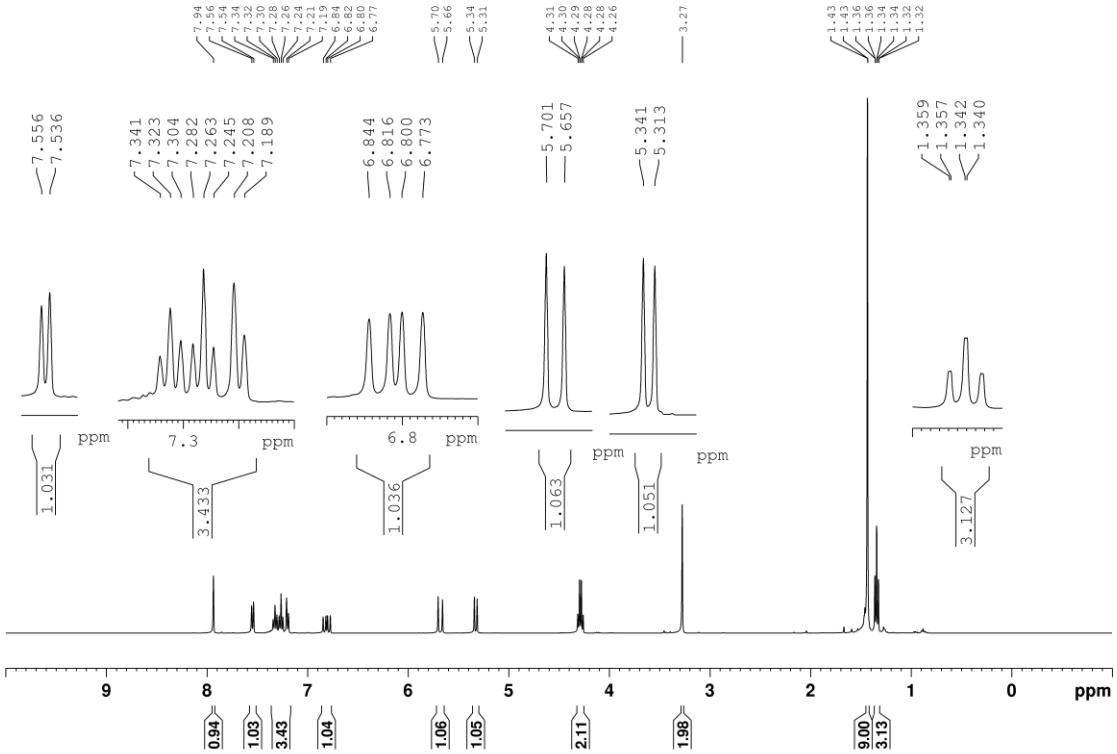
^{1}H NMR (400 MHz, $CDCl_3$) of **48**



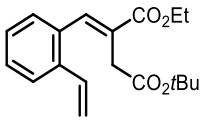


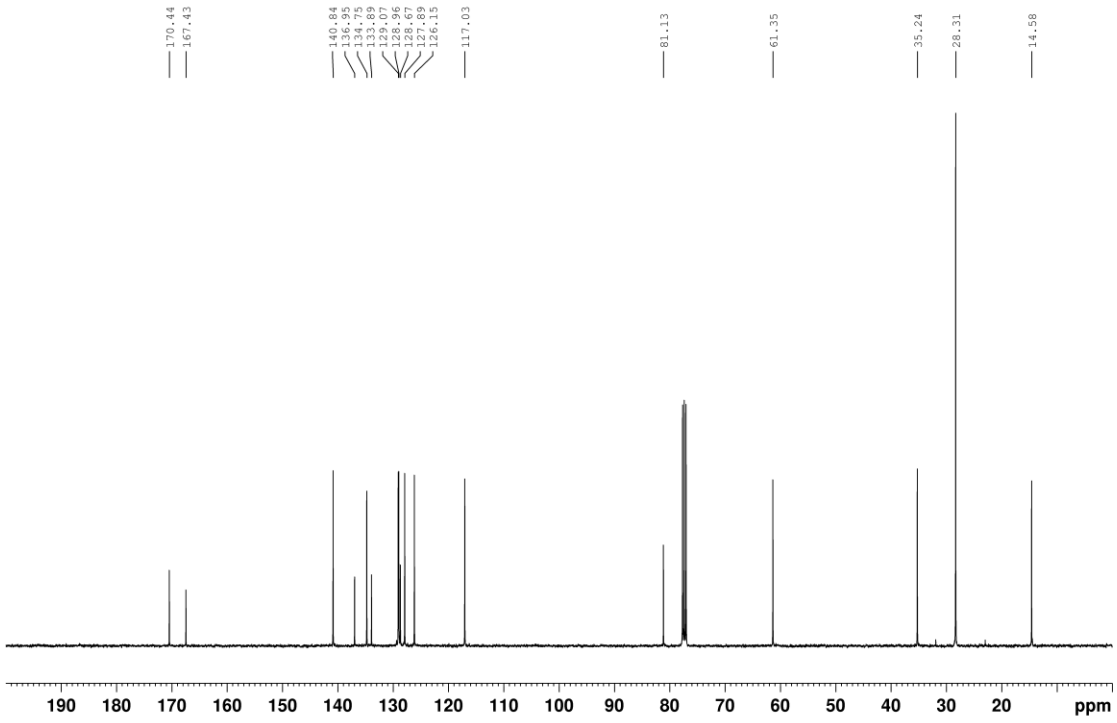
^{1}H NMR (400 MHz, $CDCl_3$) of **43**



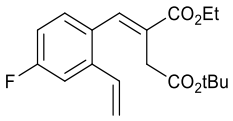


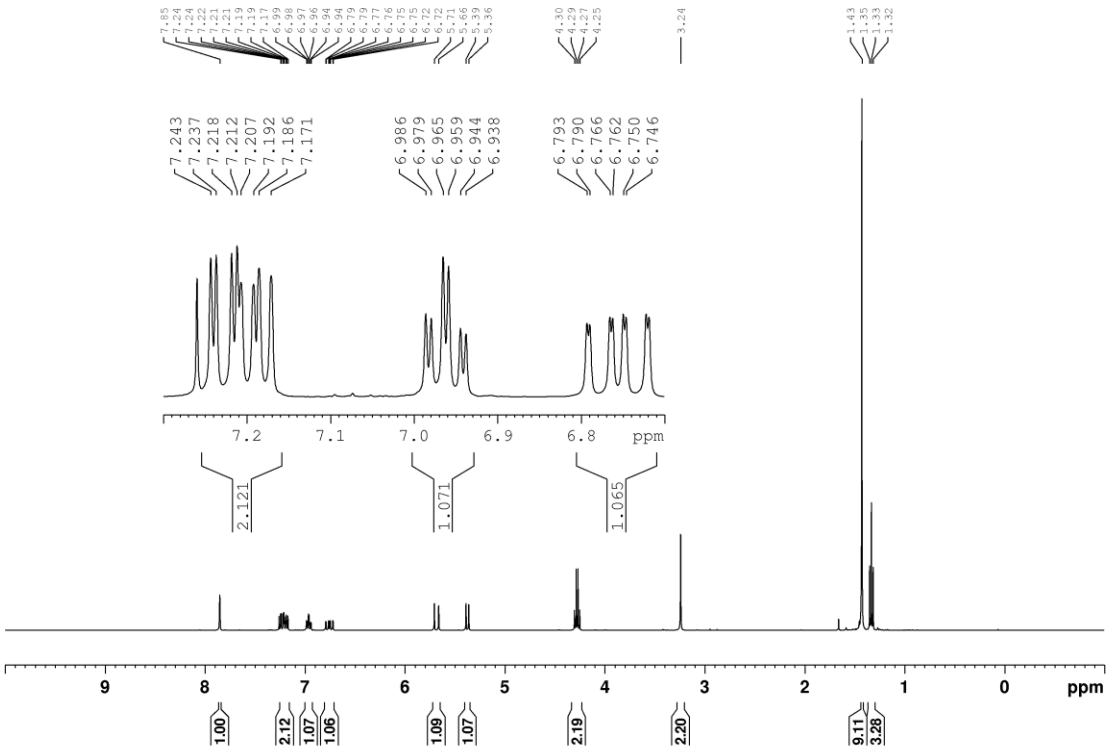
^{13}C NMR (400 MHz, $CDCl_3$) of **43**



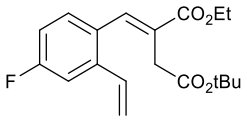


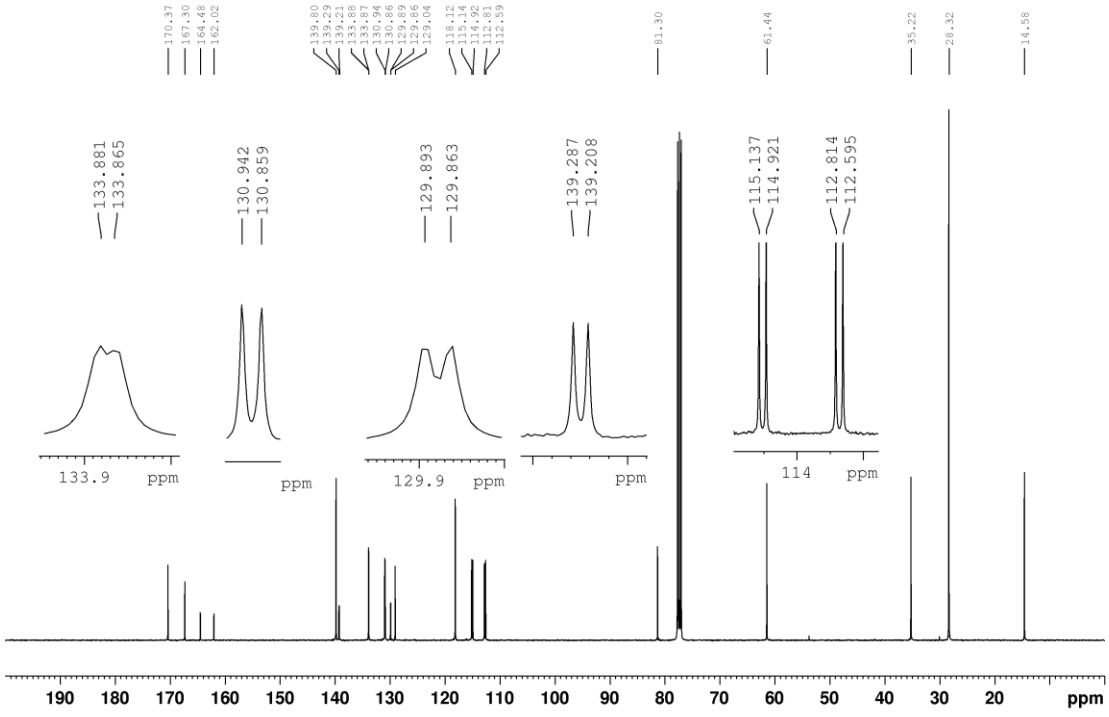
^{1}H NMR (400 MHz, $CDCl_3$) of **51**



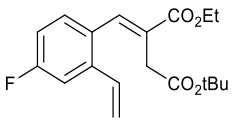


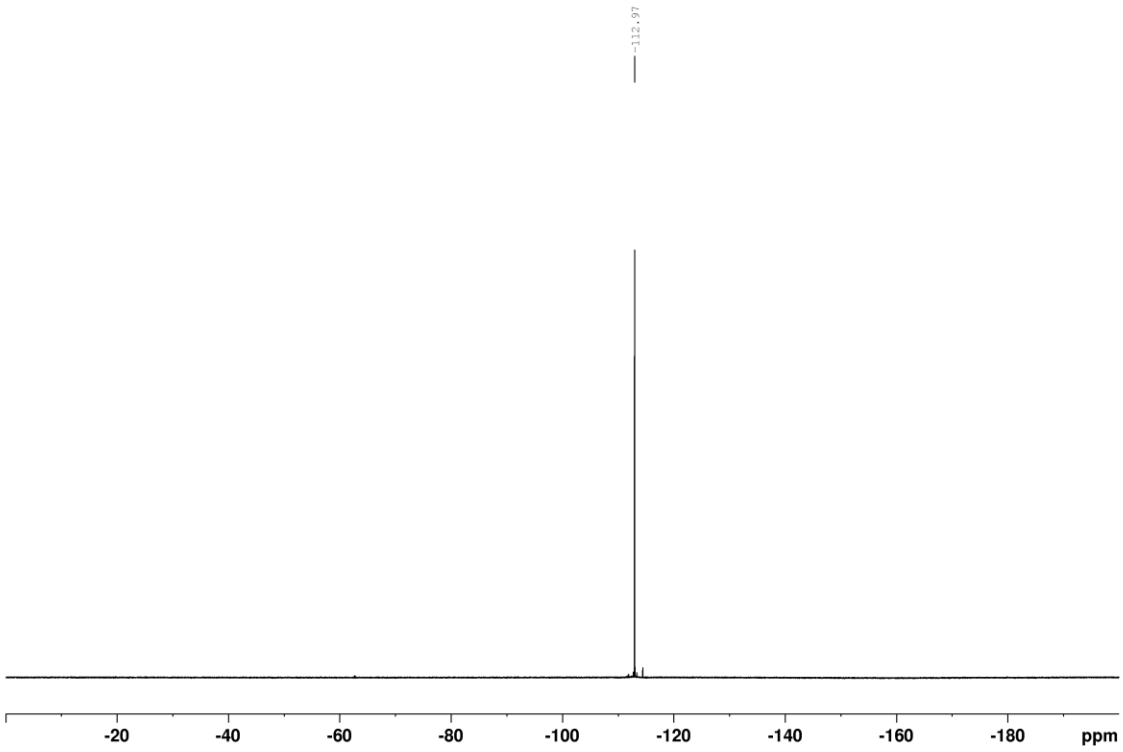
^{13}C NMR (400 MHz, $CDCl_3$) of **51**



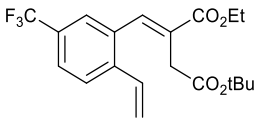


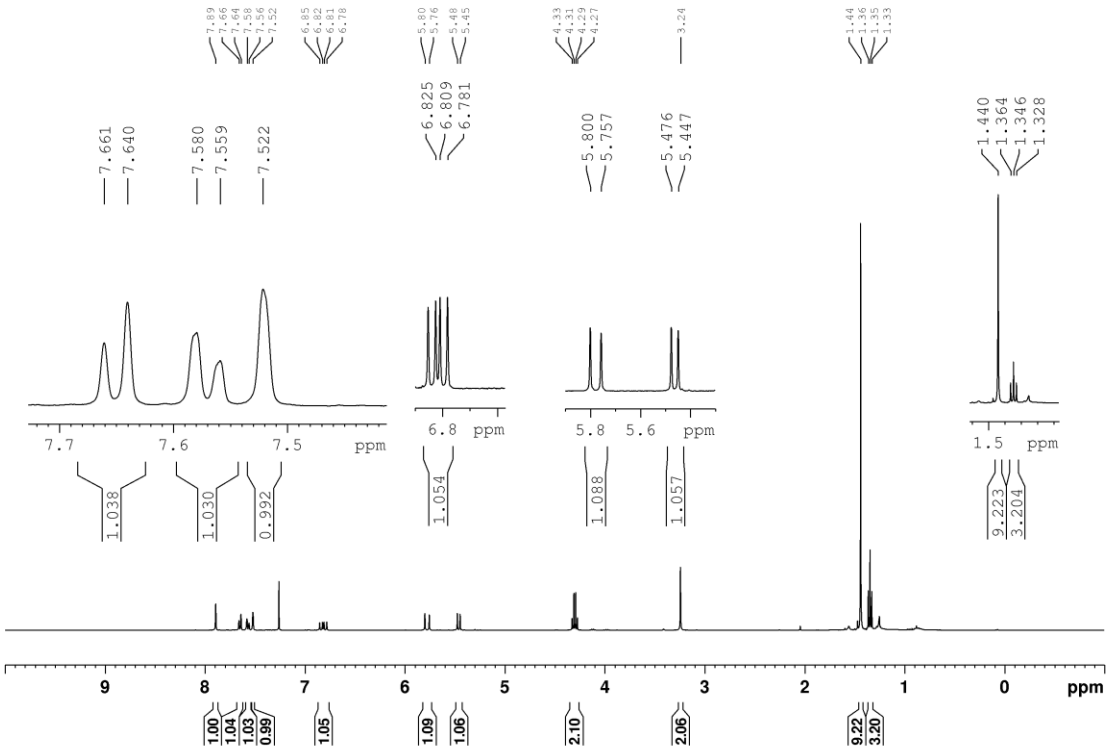
^{19}F NMR (376 MHz, $CDCl_3$) of **51**



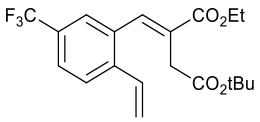


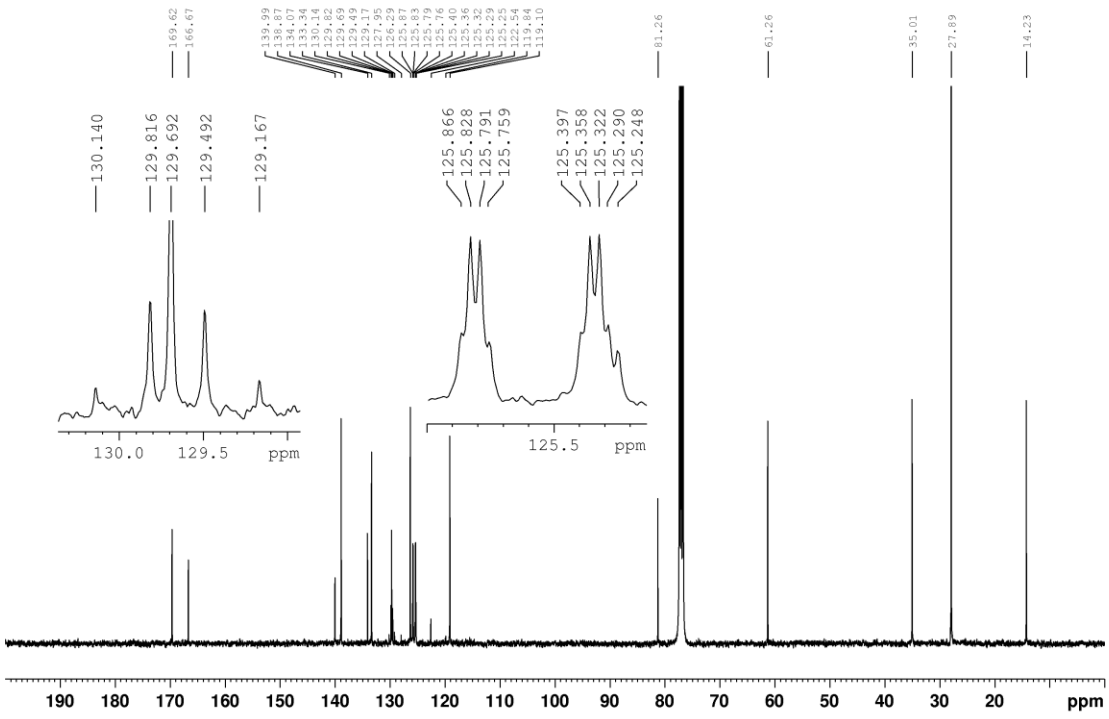
^{1}H NMR (400 MHz, $CDCl_3$) of **52**



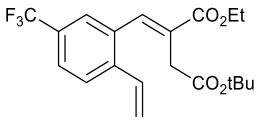


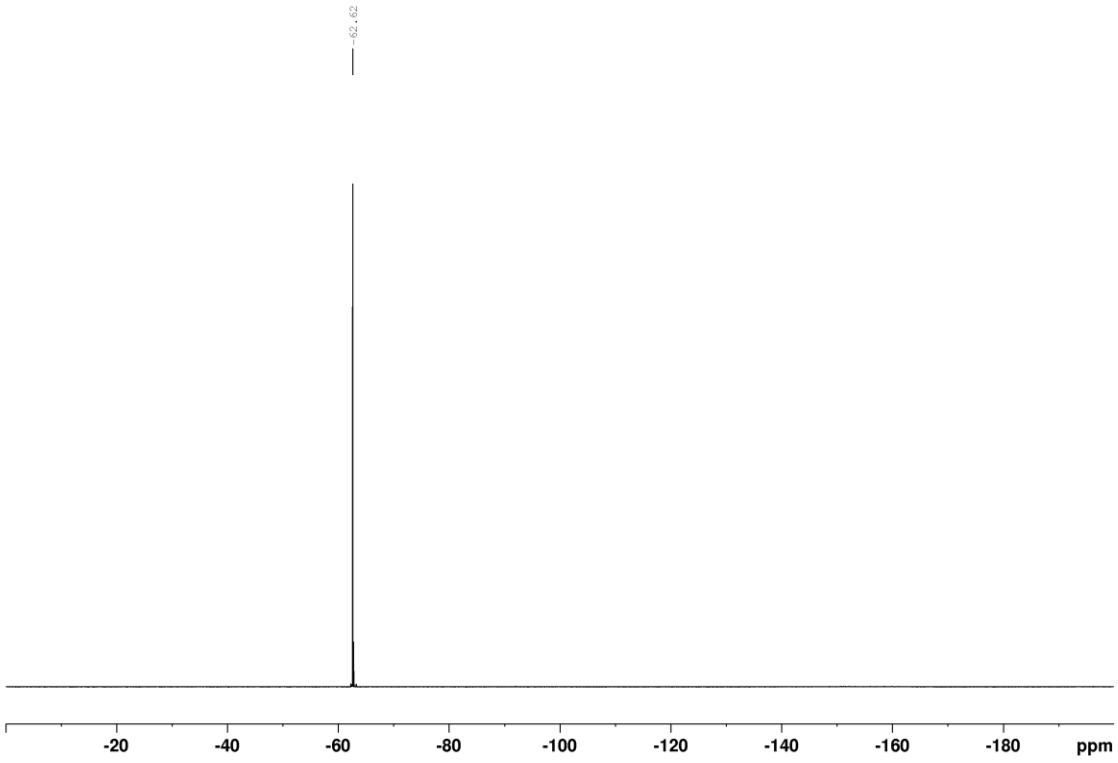
^{13}C NMR (400 MHz, $CDCl_3$) of **52**



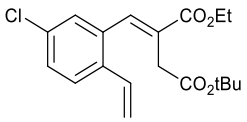


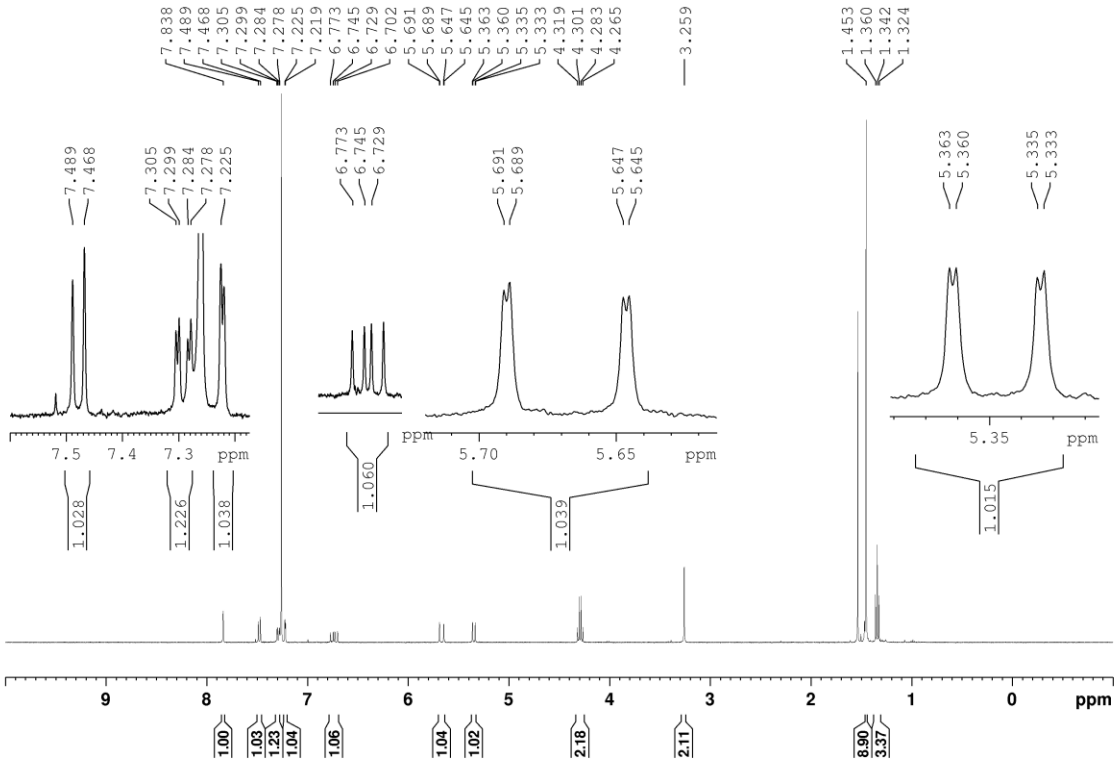
^{19}F NMR (376 MHz, $CDCl_3$) of **52**



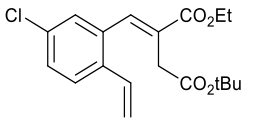


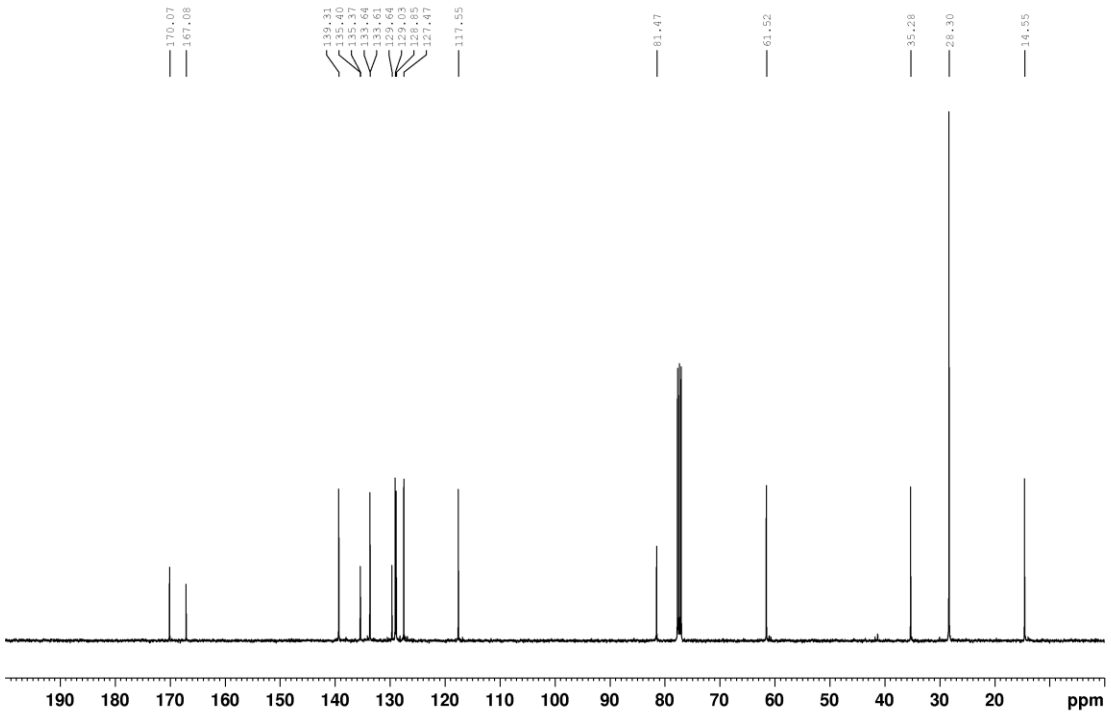
^{1}H-NMR (400 MHz, $CDCl_3$) of **49**



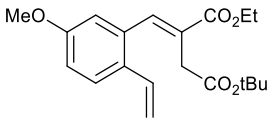


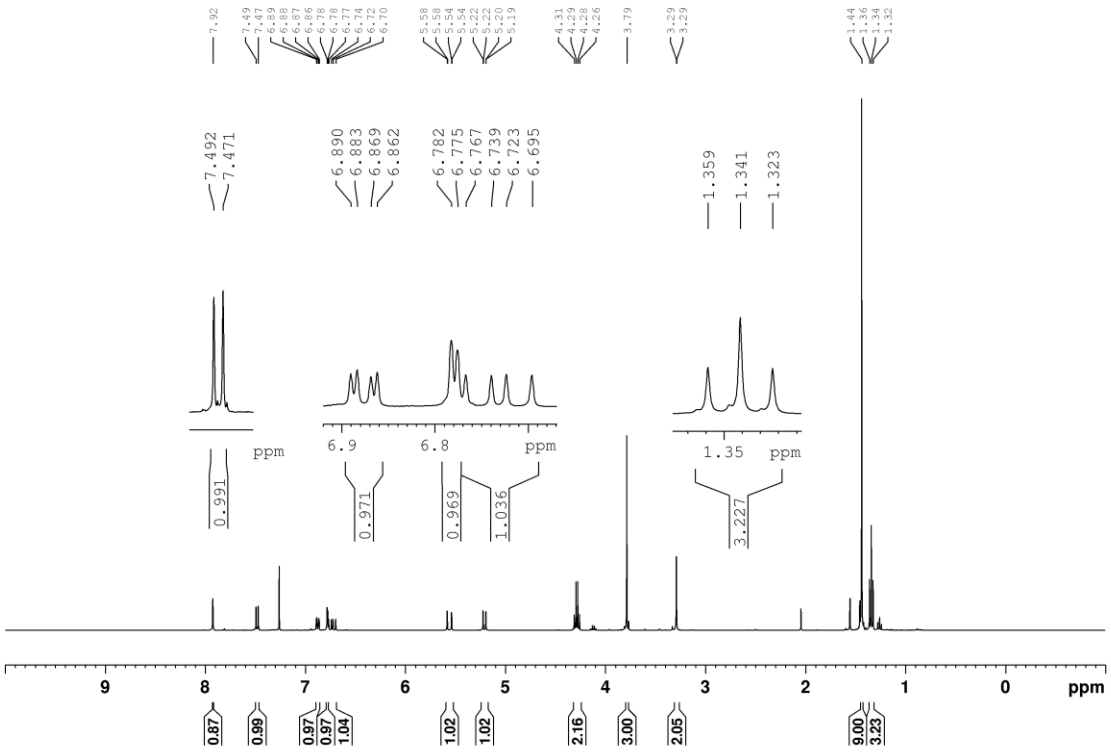
^{13}C-NMR (400 MHz, $CDCl_3$) of **49**



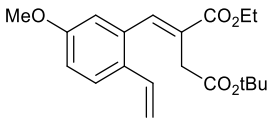


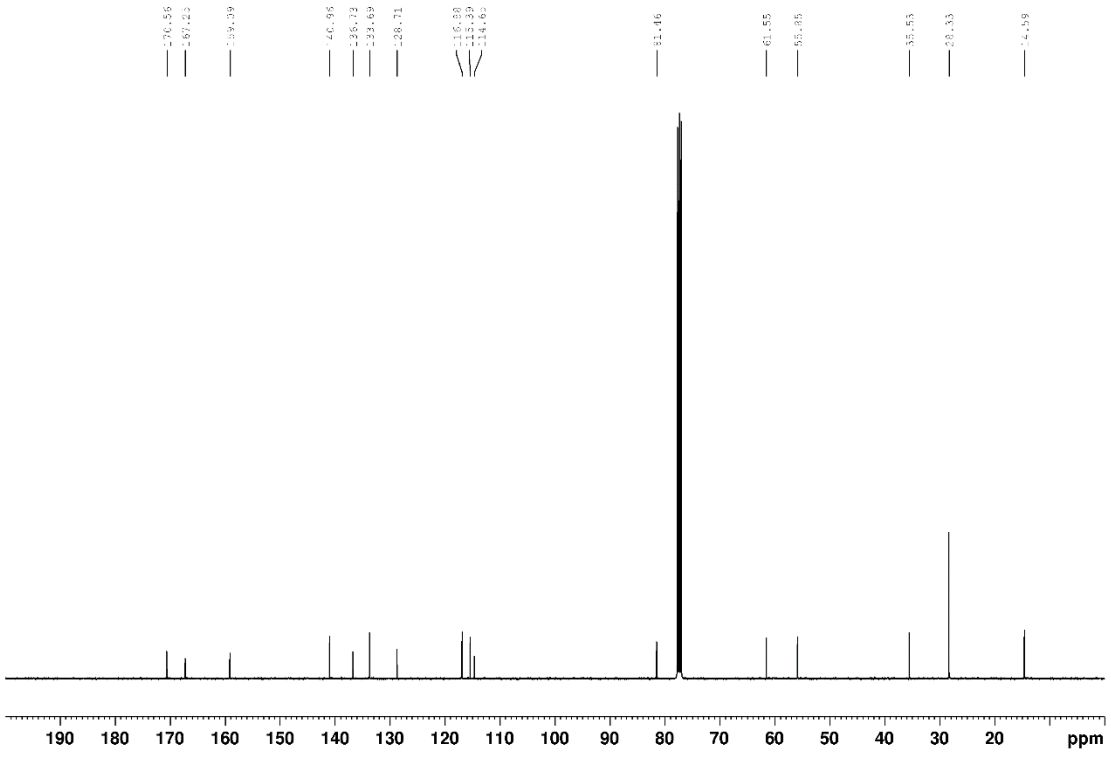
^{1}H-NMR (400 MHz, $CDCl_3$) of **50**



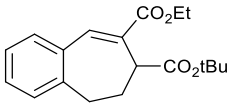


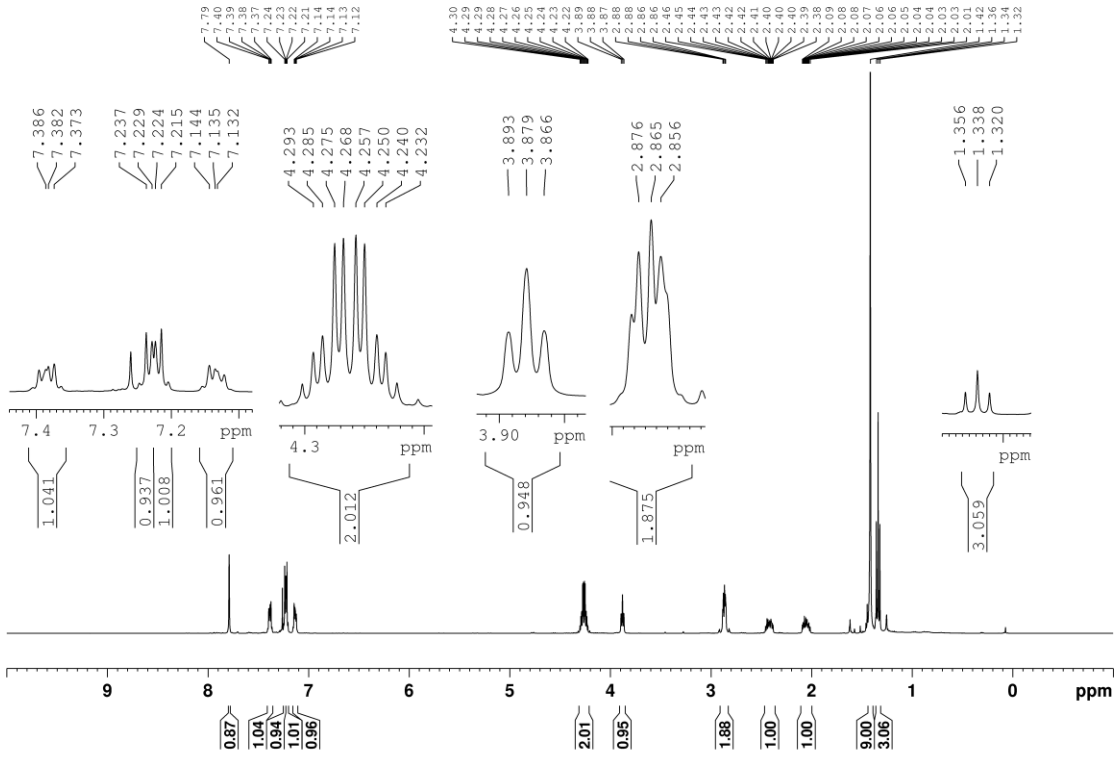
^{13}C-NMR (400 MHz, $CDCl_3$) of **50**



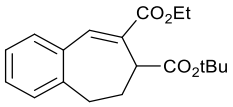


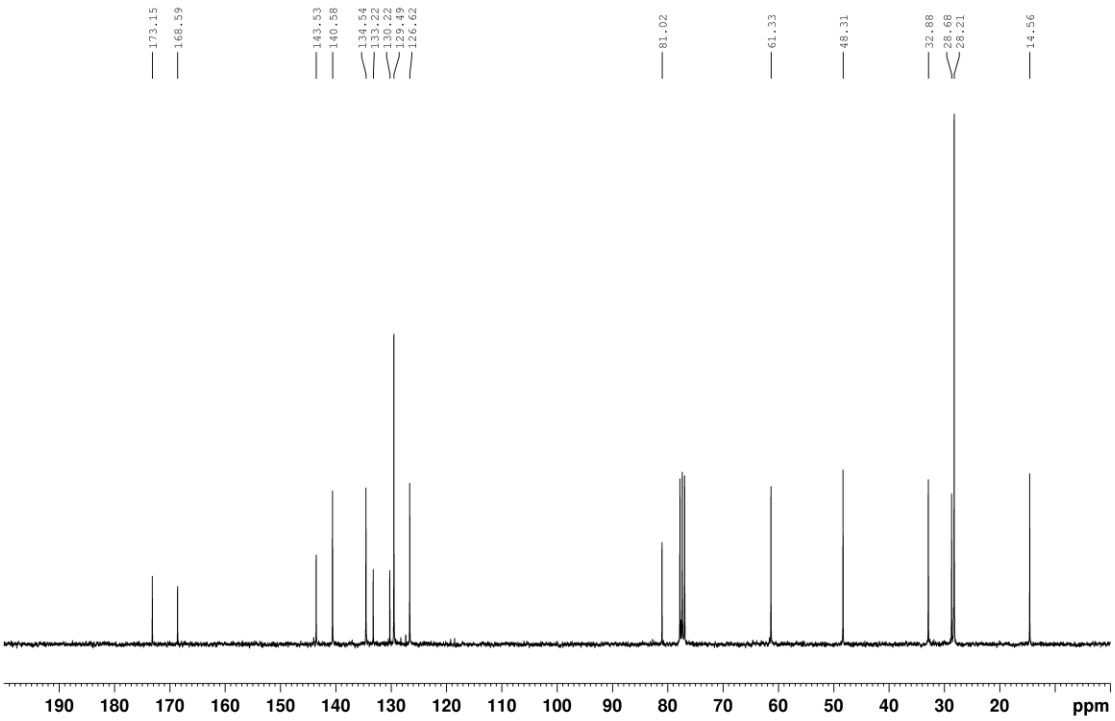
^{1}H NMR (400 MHz, $CDCl_3$) of **53**



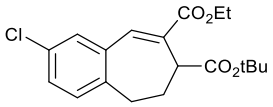


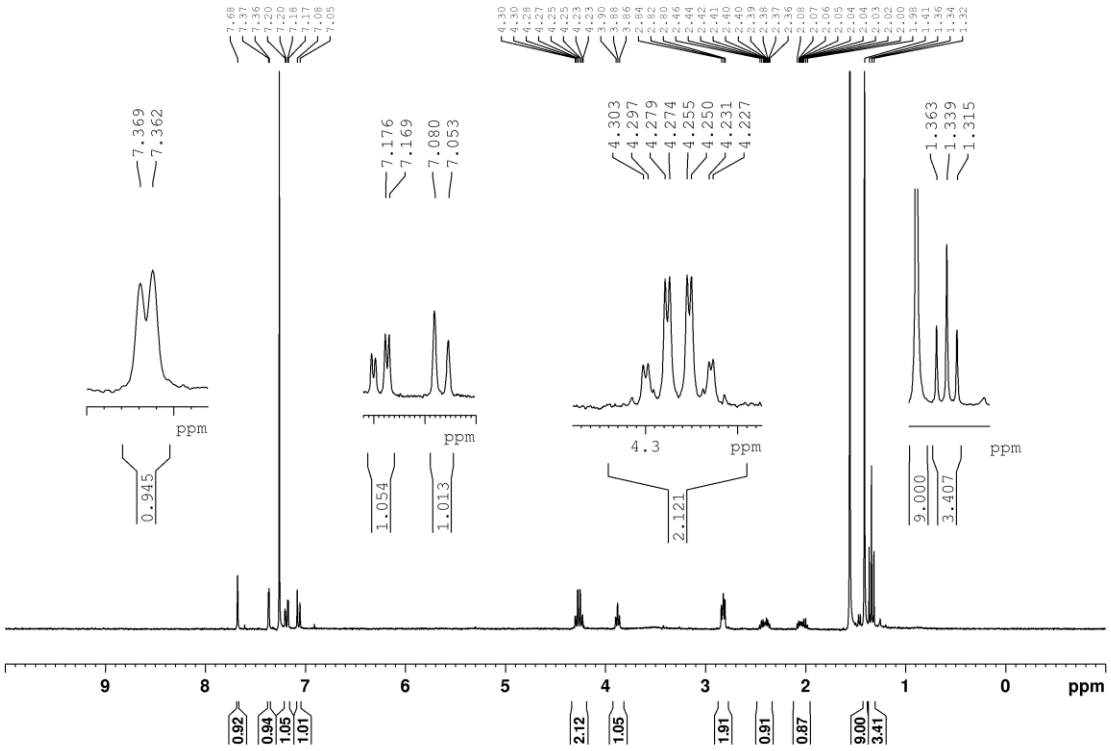
^{13}C NMR (300 MHz, $CDCl_3$) of **53**



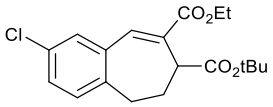


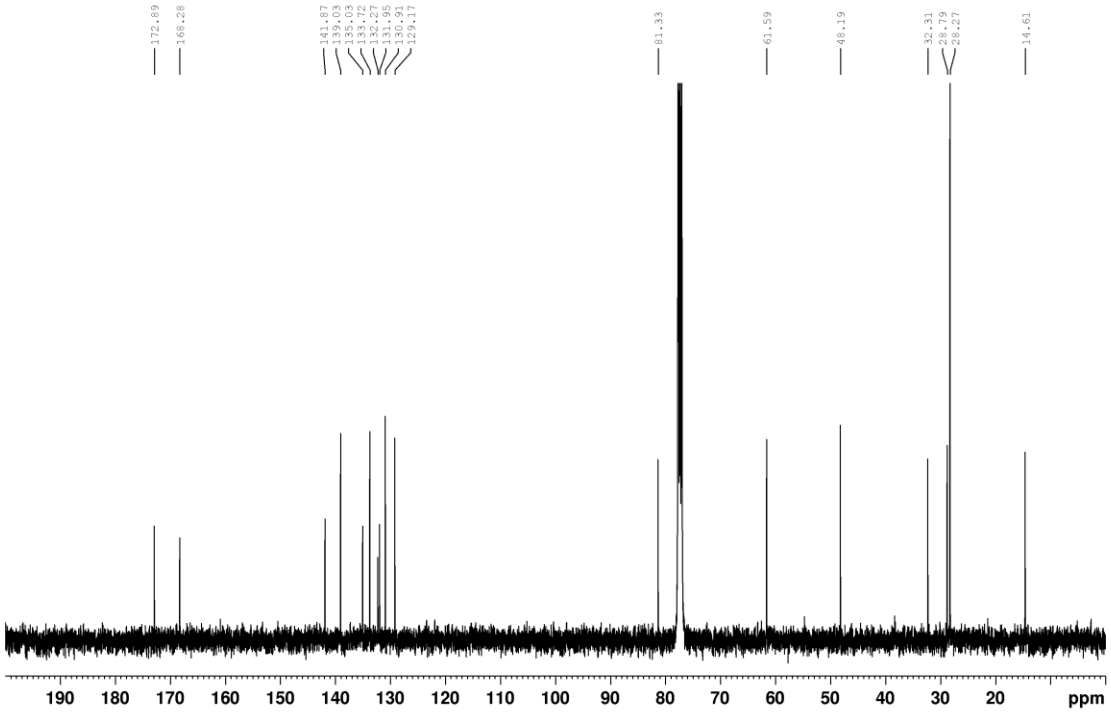
^{1}H NMR (400 MHz, $CDCl_3$) of **56**



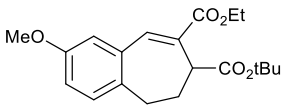


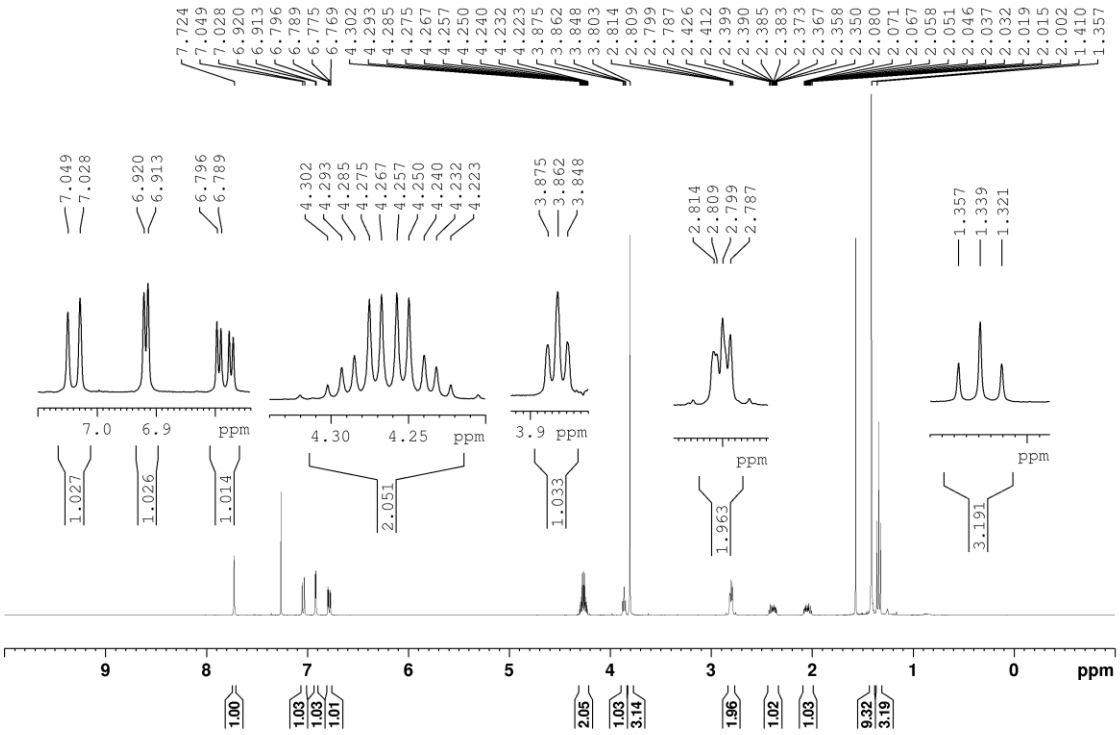
^{13}C NMR (400 MHz, $CDCl_3$) of **56**



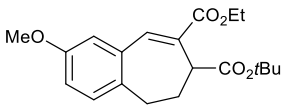


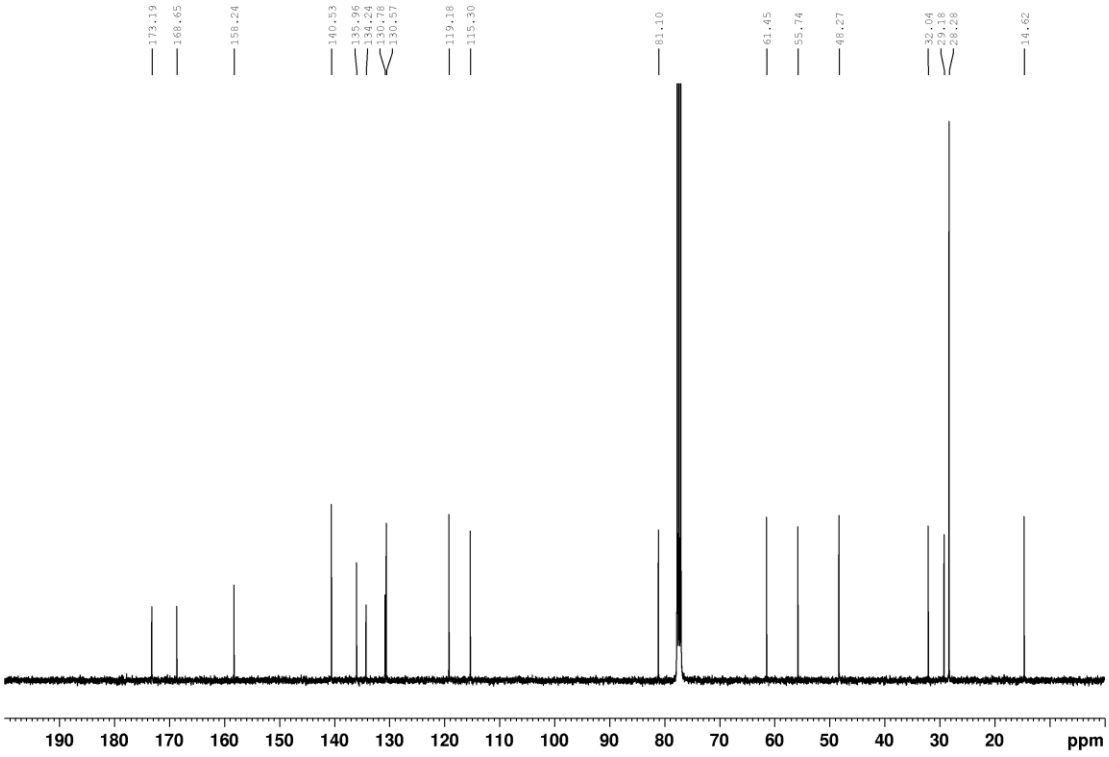
^{1}H NMR (400 MHz, $CDCl_3$) of **57**





^{13}C NMR (400 MHz, $CDCl_3$) of **57**





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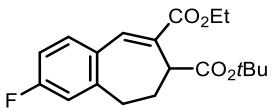
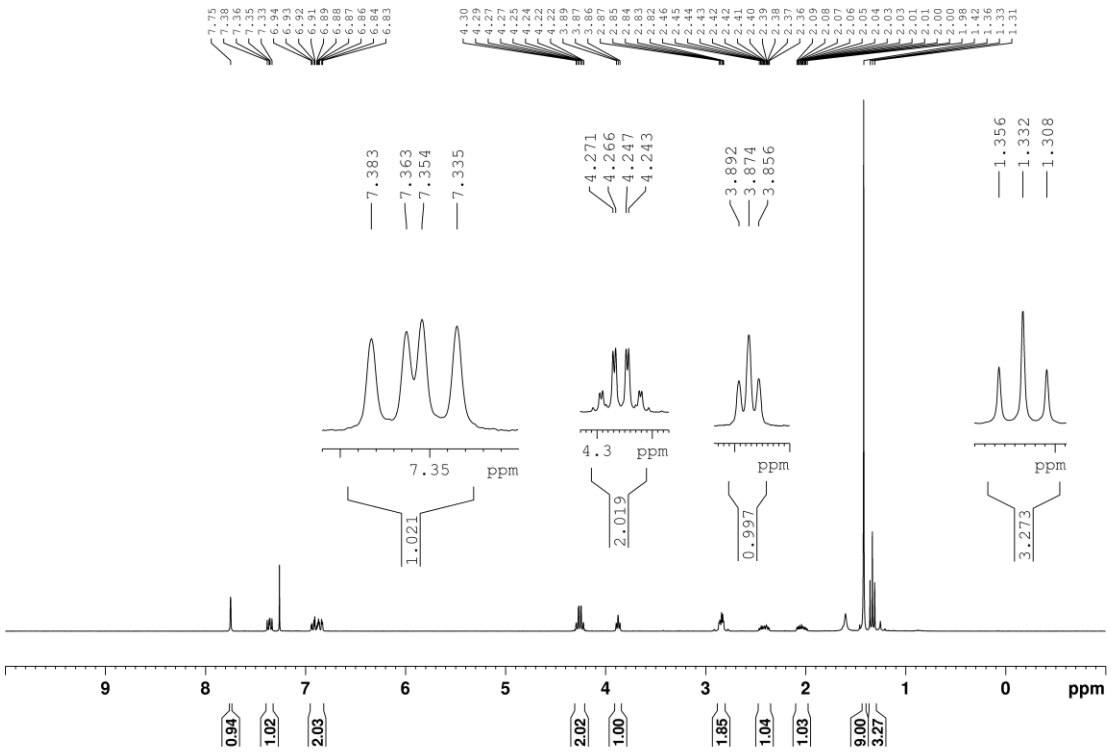
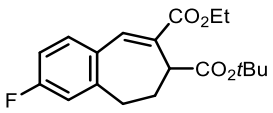


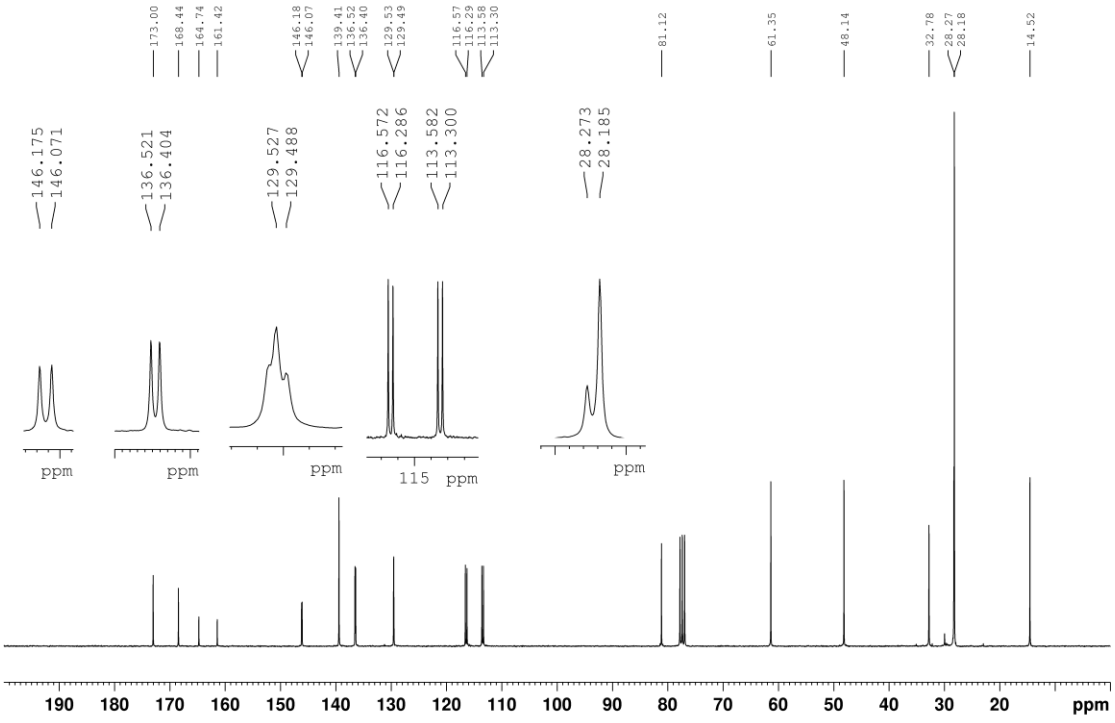
C3
95%



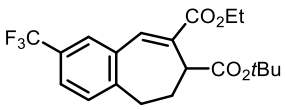
^{13}C NMR (300 MHz, $CDCl_3$) of **54**



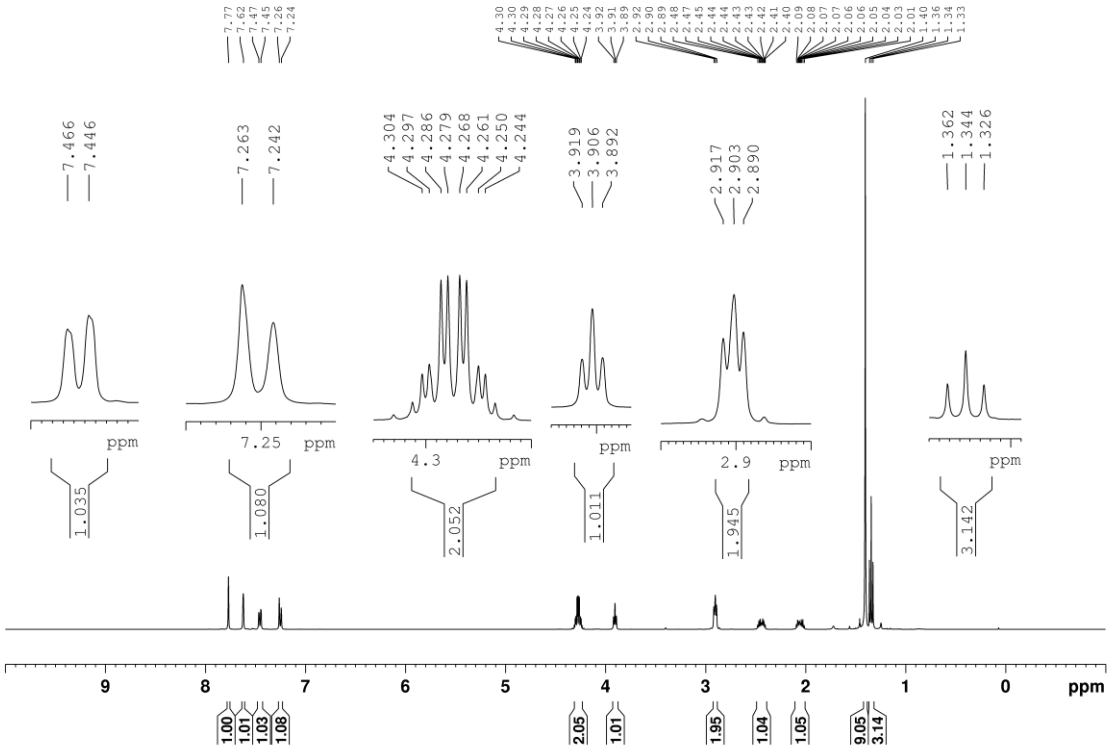
C3
95%



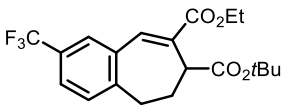
^{1}H NMR (400 MHz, $CDCl_3$) of **55**



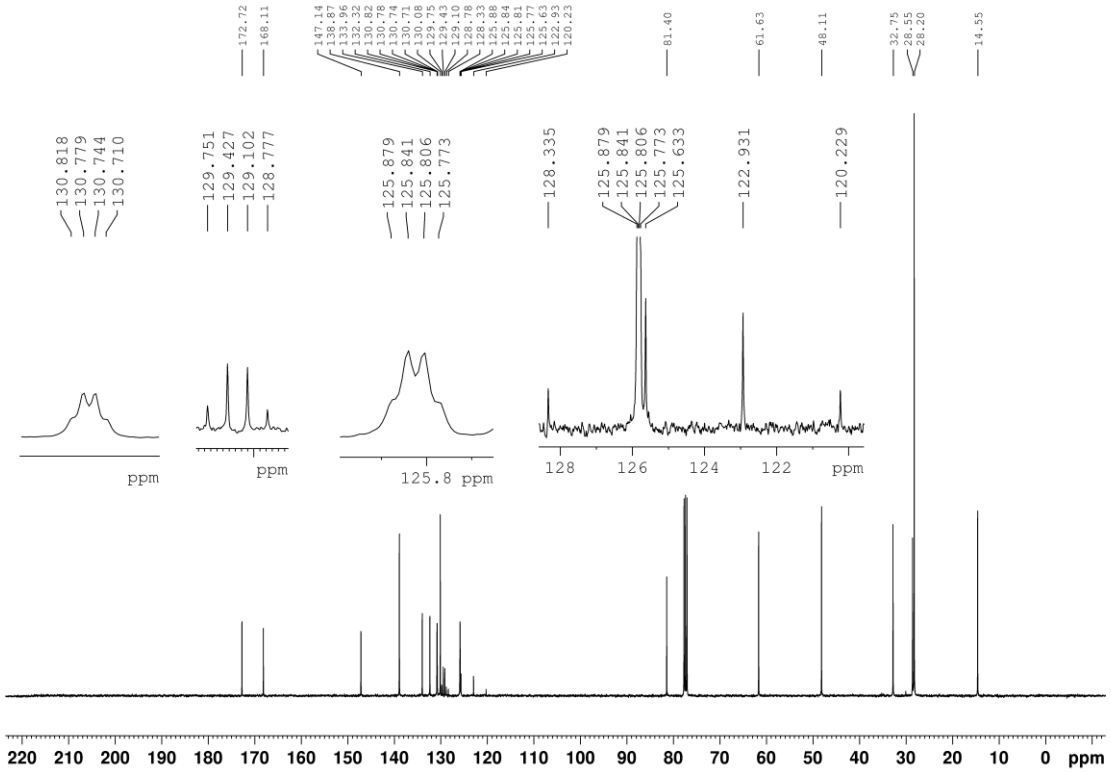
C4
87%



^{13}C NMR (400 MHz, $CDCl_3$) of **55**



C4
87%



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