Generation and Trapping of Highly Strained Reactive Intermediate: Ethyl 1,2-Cyclohexadienecarboxylate

by

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A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science

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Abstract

Highly strained reactive intermediates can initiate chemical reactions and afford unique products. Cyclic allenes are important examples of such intermediates. Within the cyclic allene family, 1,2-cyclohexadiene was intensively studied over the years. In this dissertation, the investigation of developing practical methodology to generate and trap 1-substituted-1,2-cyclohexadiene will be detailed.

In Chapter 1, a brief history of strained reactive intermediates family is discussed, including benzynes and cycloalkynes, in addition to the development of 1,2-cyclohexadiene chemistry. The discovery of 1,2-cyclohexadiene, the study on its structure and properties and some known 1-substituted cyclohexa-1,2-dienes will be discussed.

A brief introduction of existing methods to generate and trap 1-subsituted cyclohexa-1,2-diene is described at the beginning of Chapter 2. Investigation of practical generation and trapping of ethyl 1,2-cyclohexadienecarboxylate, including systematic optimization of reaction conditions and exploration of the reaction scopes, is then discussed. The attempt to investigate the mechanism of newly discovered [2+2] cycloaddition between ethyl 1,2-cyclohexadienecarboxylate and alkynes will also be included.

To Yumin Zhou and Xian Sun

Acknowledgements

I would like to express my deepest gratitude to Professor F. G. West for all the support and understanding along my program. Thank you for your suggestions and feedback to my research project.

Also, I would like to acknowledge past and present West group members who made my graduate study so rewarding, not only your encouragement and helpful suggestions in my research topic but also for the valuable life experiences you shared with me.

The department has very knowledgeable, experienced support staff members. I must acknowledge the help and inspiration I received from them, including Bernie Hippel from chemical stores, Jason Dibbs from the glass shop, Mark Miskolzie from Nuclear the Magnetic Resonance Laboratory, Jing Zheng from the Mass Spectrometry Laboratory, Wayne Moffat from the Analytical and Instrumentation Laboratory, and the many others in the department

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List of Symbols and Abbreviations

1D	one dimensional
2D	two dimensional
^{1}H	proton
^{13}C	carbon-13
^{14}C	carbon-14
^{35}C	chloride-35
Å	angstrom
aq	aqueous solution
Ar	aryl
br	broad (NMR)
Bu	butyl
ºC	degrees celsius
Calcd	calculated
cm^{-1}	wave numbers
d	day(s), doublet (spectral)
DBU	1,8-diazabicyclo[5.4,0]undec-7-ene
DCM	dichloromethane
dd	doublet of doublets (NMR)
ddd	doublet of doublet of doublets (NMR)
DIBF	1,3-diphenylbenzo[4,2,0]furan
DME	1,2-dimethoxyethane
DMS	dimethyl sulfide
DMSO	diemthylsulfoxide
dr	disastereomeric ratio

EDG	electron-donating group
EI	electron impact (mass spectrometry)
ESI	electrospray ionization (mass spectrometry)
Et	ethyl
EtOAc	ethyl acetate
equiv.	equivalent(s)
EWG	electron-withdrawing group
^{19}F	fluorine -19
g	gram(s)
GC-MS	gas chromatography–mass spectrometry
h	hour(s)
HMBC	heteronuclear multiple bond coherence (NMR)
HRMS	high resolution mass spectrometry
Hz	hertz
IR	infrared
J	coupling constant unit
kcal	kilocalories
LDA	lithium aluminum hydride
M	molar
m	multiplet (NMR)
M^+	molar ion (mass spectrometry)
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter(s)
mmol	millimole(s)

MS	mass spectrometry
m/z	mass to charge ratio (mass spectrometry)
NMR	nuclear magnetic resonance
NOE	Nuclear Overhauser Effect
ppm	parts per million (NMR)
R	generalized substituent
R_f	retention factor (flash chromatography)
rt	room temperature
s	singlet (NMR)
T	temperature
t	triplet (NMR)
^{t}Bu	*tert*-butyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
Tol	tolyl
δ	chemical shift

Chapter 1

Highly Strained Reactive Intermediates

1.1 Reactive Intermediates

Reactive intermediates are high-energy and short-lived species generated in reactions that are never present in high concentrations because they tend to react quickly upon their generation. Most reaction mechanisms involve reactive intermediates and therefore, the study of reactive intermediates is important to organic chemistry.[1] High reactivity and instability are two characteristic features of reactive intermediates, and the instability can be considered as the origin of high reactivity. Reactive intermediates can be further divided into two types based on the source of instability (Figure 1).

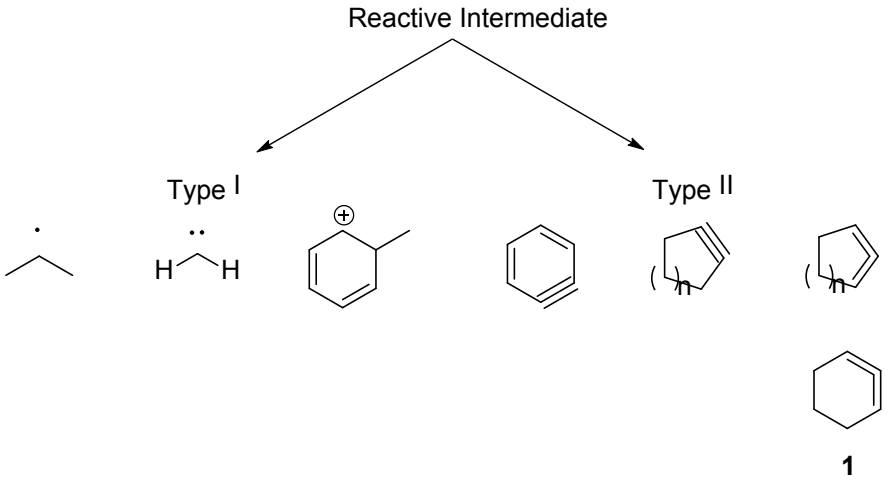


Figure 1. Two Types of Reactive Intermediate

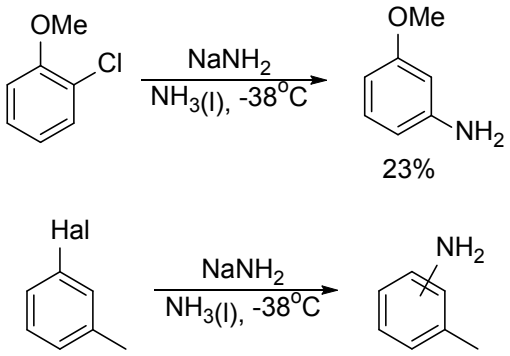
Instability of Type I reactive intermediates is driven by their incomplete valence shell. Carbocations, free radicals and carbenes are the most representative Type I reactive intermediates. This type of reactive intermediates contains nonbonding electrons on carbon or has divalent or trivalent carbon atoms. Such species tend to give more stable products with tetravalent carbon atoms by reacting with other molecules. Type I reactive

intermediates are very common in organic chemistry.

Benzyne is the most representative example of Type II reactive intermediates, whose instability is mainly driven by strain, especially ring strain and angle strain. Benzyne suffers huge strain due to the conflict between the bond angle requirement of the alkyne moiety and the geometric constraints of a six-membered ring. Due to this huge strain, benzyne is highly reactive and tends to release the strain via further transformations. Similarly cycloalkynes and cyclic allenes are highly reactive due to the strain generated from the allene or alkyne moiety in the ring. The scale of strain in cycloalkynes and cyclic allenes is closely associated with ring size. Large rings are less rigid and able to accommodate either an alkyne or allene moiety. Large ring cyclic allenes and alkynes normally are not considered as reactive intermediates, and some of them are stable enough to be isolated. For small ring cyclic allenes and alkynes, they are highly reactive and unable to be isolated under regular laboratory condition. This thesis will focus on cyclic allenes in small rings, especially 1,2-cyclohexadiene **1**.

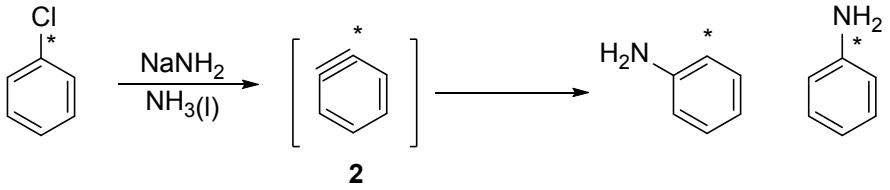
1.2 Strained Reactive Intermediates: Benzynes and Cycloalkynes

The discovery of benzyne was associated with a series of unusual rearrangements observed in the 1940s.[2] In 1945, Gilman and Avakian treated *o*-chloroanisole with sodium amide in liquid ammonia, and obtained 23% of *m*-anisidine (Scheme 1).[3] Similar rearrangement was also observed by Bergstrom and Horning in 1946.[4] A mixture of isomers of tolylamines was observed when they treated m-tolyl halide with sodium amide.



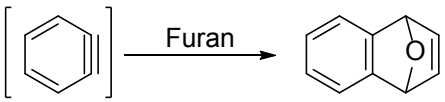
Scheme 1. The Unusual Rearrangements Observed in the 1940s

In order to explain these unusual rearrangements, Roberts did ^{14}C tracer experiment in 1953.[5] He prepared chlorobenzene-1-^{14}C and treated it under sodium amide in liquid ammonia (Scheme 2). At the end of reaction, equal amounts of aminobenzenes with the ^{14}C at C-1 and C-2 were formed. Based on this observation, he hypothesized that benzyne intermediate **2** was involved in this reaction.



Scheme 2. ^{14}C Tracer Experiment by Roberts in 1953

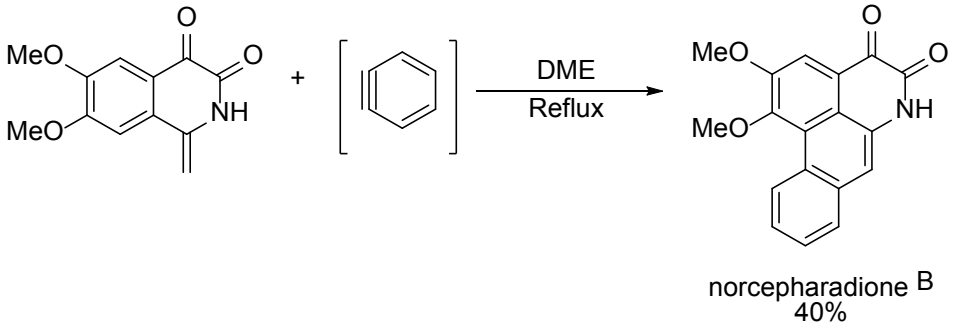
Roberts' hypothesis was proved by Wittig two years later. In 1955, Wittig and Pohmer successfully trapped benzyne with furan and afforded [4+2] cycloadduct **3** with unreported yield (eq 1), and similar result has been reported by Huisgen and Knorr later in 1967.[6] These experimental results served as important experimental evidence for the existence of benzyne.



(1)

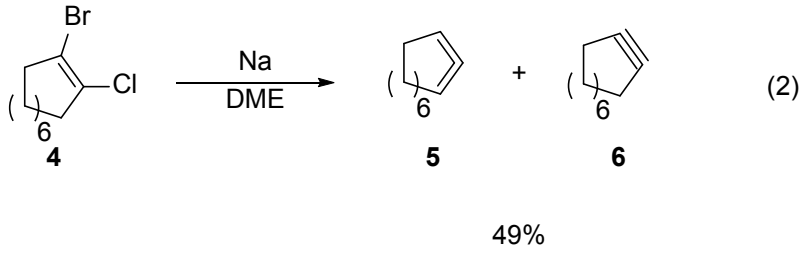
3

During the last 60 years, chemists built up a good understanding of benzyne, which allowed benzyne to be widely used in synthetic chemistry, especially in cycloaddition and substitution reactions.[7] Benzyne chemistry has been proved as a reliable method in natural product synthesis.[8] For example, one of the key steps in the total synthesis of isoquinoline alkaloids is the intermolecular cycloaddition of benzyne (Scheme 3).[9] The application of benzyne illustrates the potential synthetic application of Type II reactive intermediates.

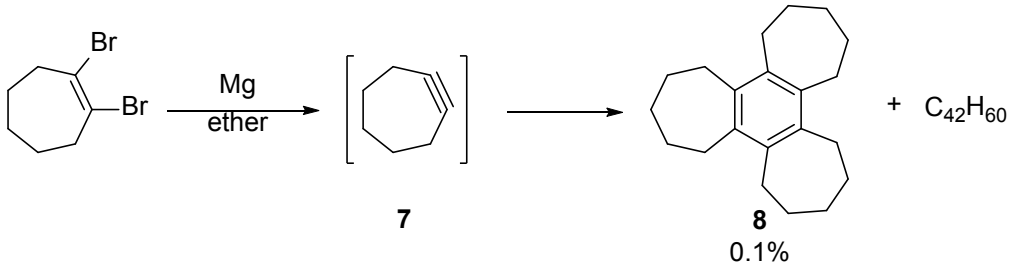


Scheme 3. Benzyne in the Total Synthesis of Nocepharadione B

The discovery of cycloalkynes can be traced back to the mid-1930s, when Favorskii claimed to generate five- to eight-membered cyclic alkynes by treating the corresponding 1-bromo-2-chlorocycloalkenes with sodium in ether solution.[10] However his results were not well accepted by other chemists, since most of these results were irreproducible. In 1953, Blomquist treated the 1-bromo-2-chlorocyclodecene **4** with sodium in ether solution and he was able to isolate 1,2-cyclodecadiene **5** as the major product and cyclodecyne **6** as the minor product in 49% combined yield(eq 2).[11]



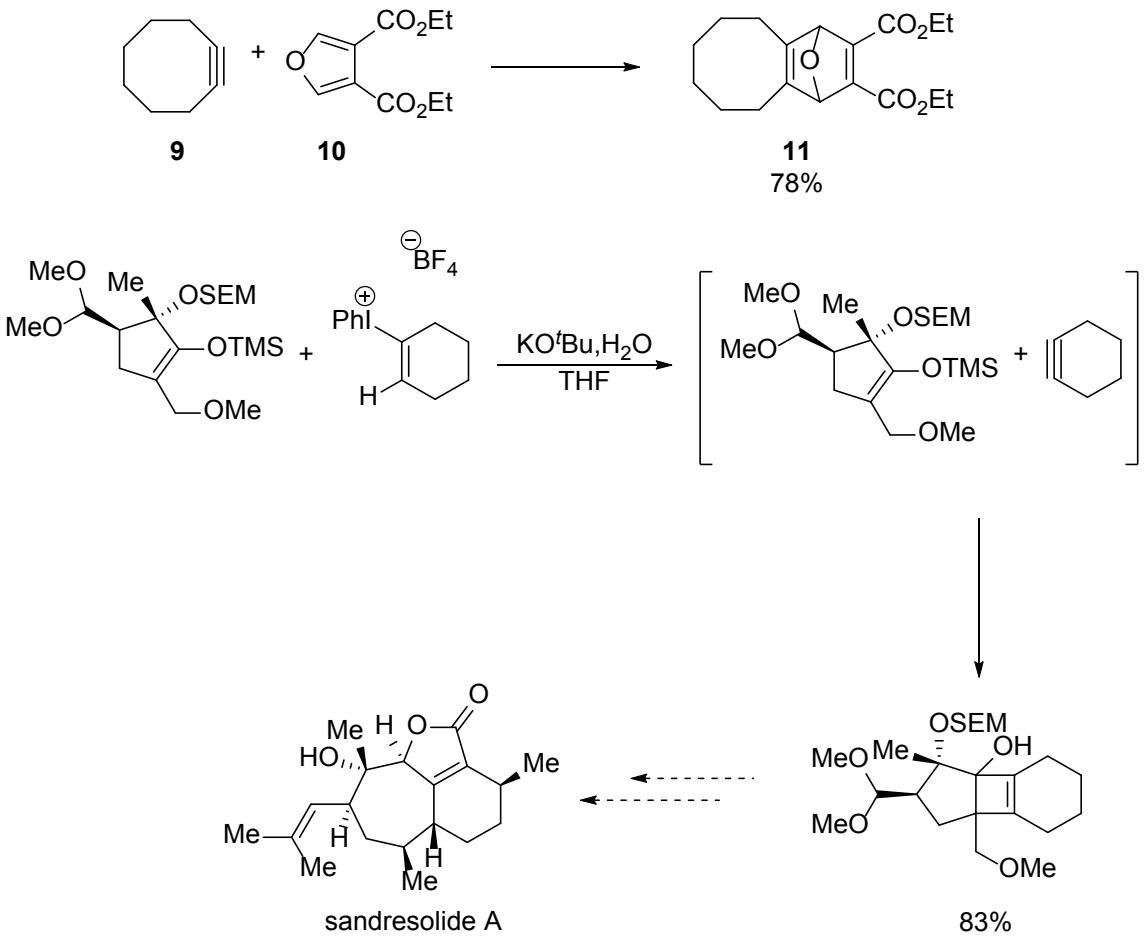
Cyclooctyne is the smallest cycloalkyne to be isolated and it is air sensitive and tends to rearrange and polymerize.[12] For the cycloalkynes smaller than cyclooctyne, oligomers were commonly observed. In 1969, Wittig and coworkers reported the generation of cycloheptyne **7** by treating 1,2-dibromocycloheptene with magnesium in ether (Scheme 4).[13] They were unable to observe **7** directly, but obtained a mixture of trace trimer **8**, $C_{21}H_{30,}$ and an uncharacterized compound with molecular formula of $C_{42}H_{60}$. Medium and small sized cycloalkynes are found to be unstable and tended to oligomerize, presumably driven by relief of ring strain.



Scheme 4. Generation and Oligomerization of Cycloheptyne

Other than oligomerization, cycloalkynes can be trapped by dienes or olefins to afford the corresponding cycloadducts.[14] In 1980, Tochtermann reported the trapping of cyclooctyne **9** with diethyl 3,4-furandicarboxylate **10** to afford [4+2] cycloadduct **11** in 78% yield (Scheme 5).[15] Cycloaddition of cycloalkynes is a powerful tool to build up complex molecules.[16] In 2010, Carreira and coworkers applied cycloaddition of cyclohexyne to generate the advance intermediate toward the synthesis of sandresolide

A.[16,17]



Scheme 5. Application of Cycloalkynes in Organic Synthesis

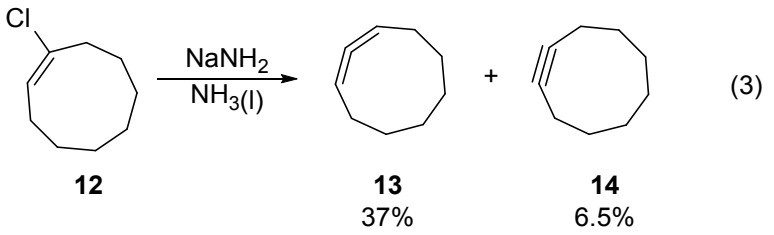
1.3 Cyclic Allenes

1.3.1 The Early Study on Cyclic Allenes

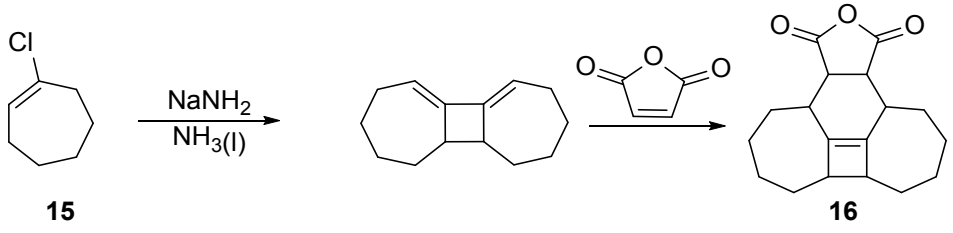
As isomers of cycloalkynes, cyclic allenes are cumulene type molecules. The initial study of cyclic allenes was closely associated with cyclic alkynes, since the early generation methods often could not selectively generate one in preference to the other.

The discovery of cyclic allenes was also claimed by Favorskii in 1936. He believed cyclic allenes were synthesized along with cycloalkynes when

1-bromo-2-chlorocycloalkenes were treated with sodium in ether solution.[18] Later the generation and isolation of 1,2-cycloheptadiene with his method was proved to be irreproducible by his student Domnin.[18,19] After 1,2-cyclodecadiene **5** was synthesized by Blomquist in 1953,[11] Ball and Landor isolated 1,2-cyclonondiene **13** in 1962.[20] Vinyl halide **12** was treated with sodium amide in liquid ammonia; however, the cyclic alkyne **14** remained as a minor product (eq 3).



During the course of these studies, Ball and Landor found that they were unable to isolate any cyclic allenes smaller than 1,2-cyclooctadiene. They didn't directly observe 1,2-cycloheptadiene when 1-chlorocycloheptene **15** was treated with sodium amide in liquid ammonia. What they observed was a dimer product, which was trapped by maleic anhydride to afford cycloadduct **16**, the yield was unreported due to the inseparable impurity (Scheme 6). When cyclic allenes are too strained to be isolated, they tend to oligomerize similar to cycloalkynes.

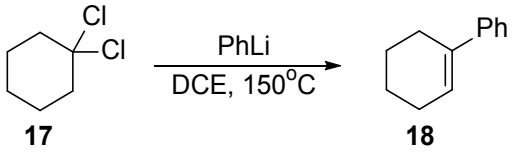


Scheme 6. Dimerization of 1,2-Cycloheptadiene

The generation of small ring cyclic allenes had two problems. The first problem

was the generation of undesired cyclic alkynes as side products. The second problem was the oligomerization of cyclic allenes, especially in small ring systems. Due to these two problems, generation of 1,2-cyclohexadiene **1** was considered to be an especially hard target.

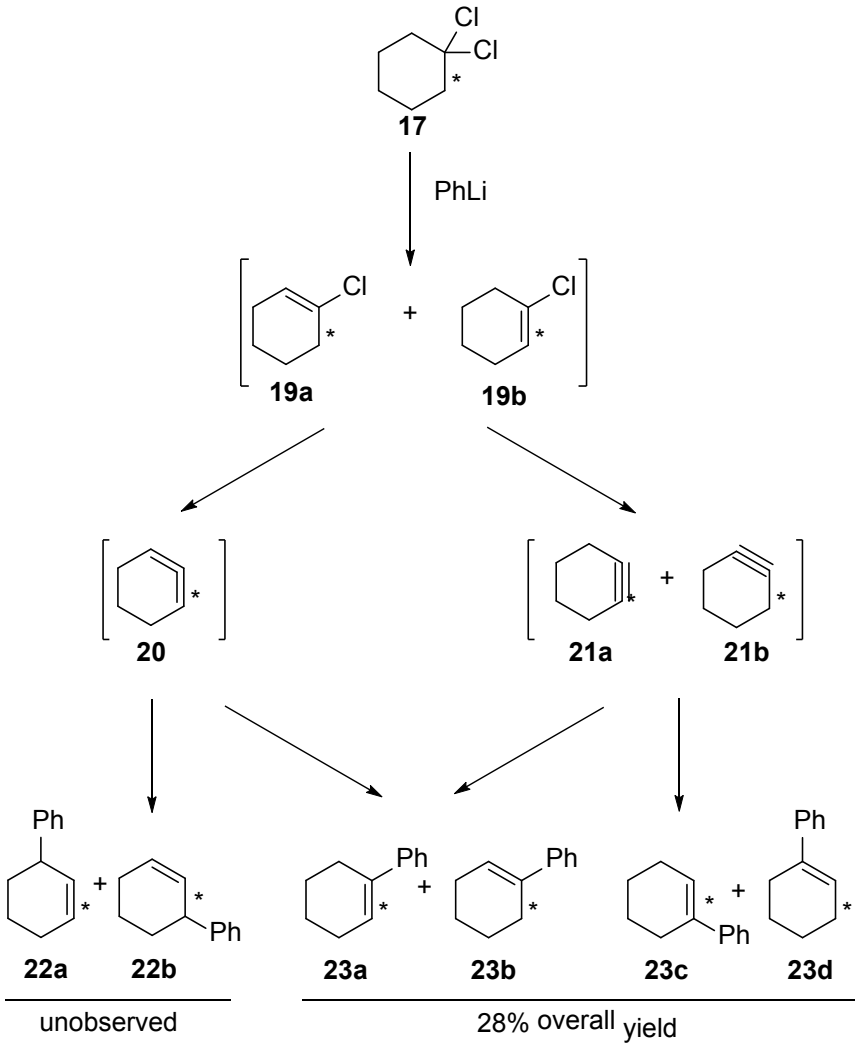
In 1957, Scardiglia and Roberts reported a ^{14}C labeling experiment to confirm whether the coupling reaction of phenyllithium and 1,1-dichlorocyclohexane **17** involved a cycloalkyne intermediate. (eq 4).[21]



17 **18** (4)

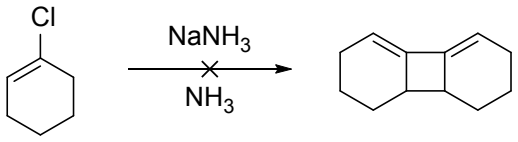
Based on their hypothesis, cyclohexyne-1-^{14}C **21a** and cyclohexyne-3-^{14}C **21b** would be generated after base-induced elimination of vinyl chloride intermediates **19a** and **19b**. Cycloalkynes **21a** and **21b** would couple with phenyllithium to afford the product **23a** to **23d** in 1:1:1:1 ratio (Scheme 7). To examine their hypothesis, they prepared 1,1-dichlorocyclohexane **17** and treated it with phenyllithium in ether in a steel bomb at 150 ˚C. A mixture of coupling products was isolated in 28% overall yield. 1-Phenylcyclohexene-1-^{14}C **23c** was isolated from the mixture in 6.5 % yield, which was about 25% of the whole mixture and very close to the expected value. Allene intermediate **20** was also considered by the authors. If phenyl coupled on the central carbon of allene, **23a** and **23b** would be generated in equal amounts; however, **23c** was about 25% of the whole mixture of coupling products. Thus, even if the coupling reaction did involve cyclic allene **20**, it should be a neglectable amount compared with **21a** and **21b**. If phenyl coupled on the terminal carbon of allene, compounds **22a** and **22b** would be formed; however, these two products were not observed by authors. Based on these results, Scardiglia and Roberts concluded that the coupling reaction of 1,1-dichlorocyclohexane **17** and phenyllithium involved cyclohexyne as an intermediate,

which was apparently generated preferentially over 1,2-cyclohexadiene.



Scheme 7. Scardiglia and Roberts' ^{14}C Labeling Experiment

When Ball and Landor attempted to generate 1,2-cyclohexadiene from 1-chlorocyclohexene **24** with sodium amide, they observed the recovered starting material **24** and two fractions of nitrogen containing high boiling liquid. They did not observe the formation of dimer product **25** (eq 5).[20]

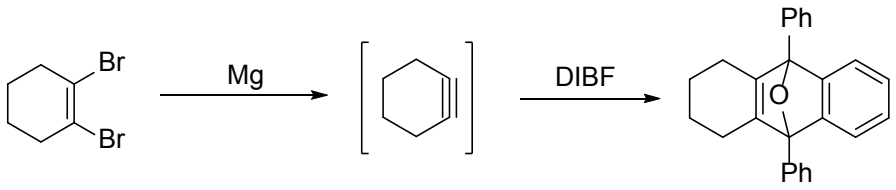


24 **25** (5)

Ball and Landor considered their experimental results to be in agreement with Scardiglia and Roberts's hypothesis that the generation of 1,2-cyclohexadiene was unpreferred compared with cyclohexyne. They believed linear allene system should be left intact in six-membered ring to make 1,2-cyclohexadiene, which caused 1,2-cyclohexadiene was not formed preferentially to cyclohexyne. However, the authors also didn't observe any indication for the generation of cyclohexyne in the reaction. The misunderstanding of 1,2-cyclohexadiene was due to the limited understanding of its structure. Later, in the 1960s, 1,2-cyclohexadiene was generated and allowed chemists to go deep into the structure and property strain reactive intermediate.

1.3.2 The Discovery of 1,2-Cyclohexadiene

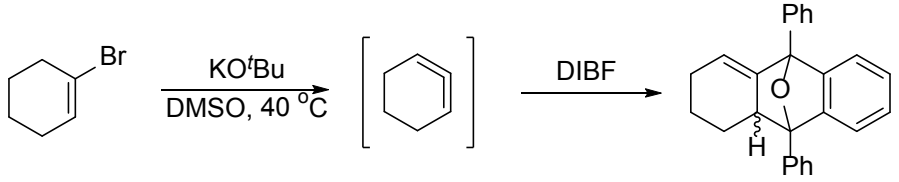
The existence of 1,2-cyclohexadiene was not confirmed until 1966. In 1961, Wittig managed to generate cyclohexyne by treating 1,2-dibromocyclohexene **26** with magnesium. Upon generation, cyclohexyne was trapped by 1,3-diphenylbenzo[*c*]furan (DIBF) to afford [4+2] cycloadduct **27** (Scheme 8).[22] Wittig also considered cyclic allene as a possible intermediate, which could afford the same trapping product after isomerization. To prove that the cycloadduct **27** is generated directly from cyclohexyne instead of isomerization of the cycloadduct from 1,2-cyclohexadiene, he had to generate and trap the cyclic allene via an independent route.



26 **27**

Scheme 8. Trapping of Cyclohexyne with DIBF

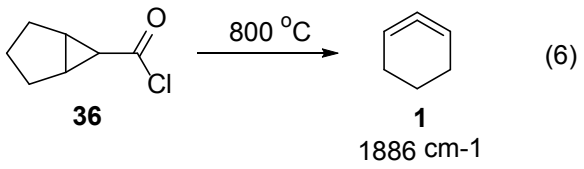
In 1966, Wittig treated 1-bromocyclohexene **28** with potassium *tert*-butoxide in dimethyl sulfoxide (DMSO). Upon deprotonation and elimination, 1,2-cyclohexadiene **1** was generated and trapped by DIBF to afford [4+2] cycloadduct **29** in a mixture of endo-/exo-isomers with 37% overall yield (Scheme 9).[23] When cycloadduct **27** was subjected to the same condition, it did not isomerize to **29**, which further confirmed cycloadduct **29** was generated from 1,2-cyclhexadiene instead of cycloalkyne.



28 **1** **29**
37%

Scheme 9. Generation and Trapping of 1,2-Cyclohexadiene

Wittig's result was considered as the first conclusive demonstration of the existence of 1,2-cyclohexadiene **1**. In 1983, Wentrup and co-workers obtained direct spectroscopic data of **1**.[24] 1,2-Cyclohexadiene **1** was generated by vacuum pyrolysis of bicycle- [3.1.0]hexane-6-carbonyl chloride **29** under 10^{-4} torr at 800 ˚C (eq 6). With increasing temperature, they observed an increasing intensity of an ion (*m/z* =80) by mass spectrometry monitoring. They were also able to trap **1** in an Ar matrix (< 170 ˚C), and an absorption was observed at 1886 cm^{-1} in the IR spectrum.



1.3.3 The Structure of 1,2-Cyclohexadiene

The opinions on the preferred structure of 1,2-cyclohexadiene were mixed before the 1980s. The allene structure **1** was expected to be bent and twisted due to the requirement of putting a linear allene into the ring. Thus the planar diradical **30a** and zwitterions **30b**/**30c** were considered as preferred structures of 1,2-cyclohexadiene (Figure 2). Bottini and coworkers suggested **1** isomerizes rapidly to planar diradical **30a**, which was proposed to be the active species in the stepwise [2+2] cycloadditions.[25] Zwitterions **30b**/**30c** were preferred by Moore and Moser based on INDO-MO calculations.[26]

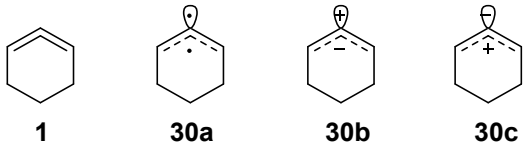
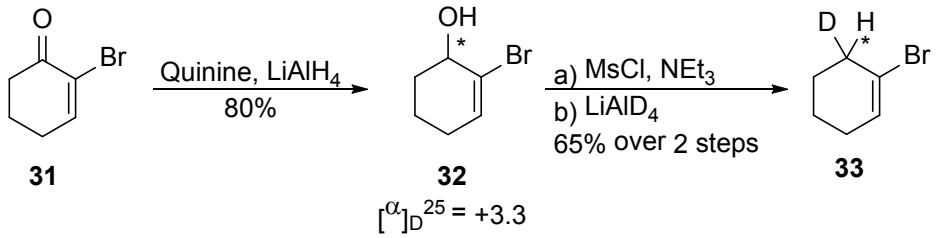


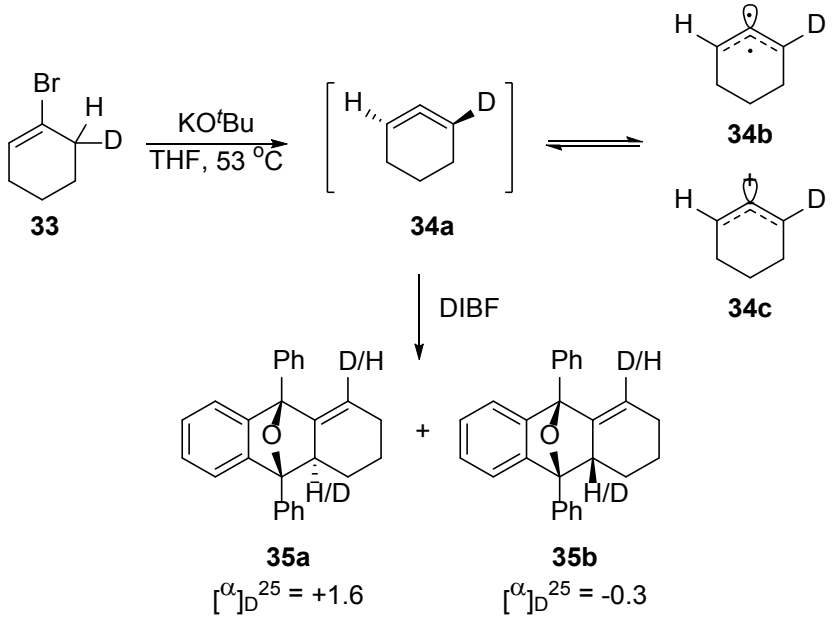
Figure 2. Possible Structures of 1,2-Cyclohexadiene

In 1980, Jones and Balci determined the structure of 1,2-cyclohexadiene with experimental results.[27] They synthesized the optically active allylic alcohol **32** via the reduction of the enone **31** with lithium aluminum hydride-quinine complex (Scheme 10).[28] After mesylation and S_N2 attack of lithium aluminum deuteride, the optically active allene precursor **33** was generated. They hypothesized enantiomeric rich cycloadducts would be afforded if the optically active allene was trapped by dienes.



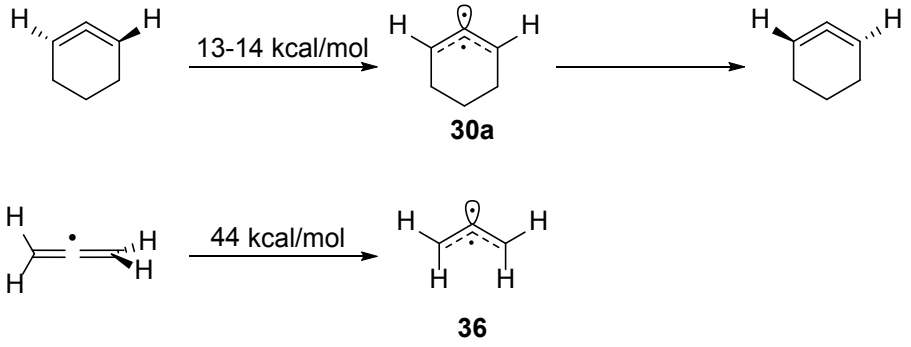
Scheme 10. The Preparation of Optically Active Allene Precursor **33**

Jones and Balci treated optically active allene precursor **33** with KO^{t}Bu in THF and isolated enantiomeric rich cycloadducts **35a** and **35b** (Scheme 11). Although the degree of optical rotation of cycloadduct **35b** was -0.3˚, which was low, this value should be meaningful, especially considered the optically active compound **32** was +3.3˚. In addition, when the reaction temperature was increased to 100 ˚C, a racemic mixture was observed, which gave 0˚ of optical rotation. These observations demonstrated the cycloaddition occurred on a non-plannar allene intermediate, which underwent racemization at higher temperature. Based on this result, Jones and Balci concluded the structure of **1** was nonplanar and best represented as bent allene.



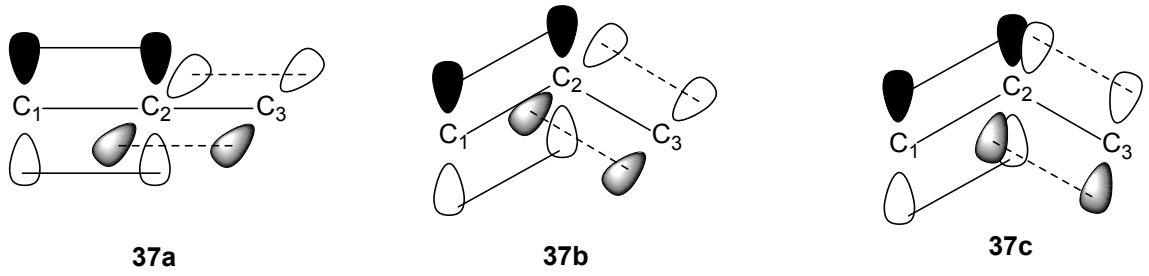
Scheme 11. The Trapping of Enantiomerical Cycloadducts from Optically Active Allene Precursor

Jones and Balci's result was also supported by computational studies. In 1982, Johnson reported the ab initio study of 1,2-cyclohexadiene and his result also supported the bent allene structure.[29] Based on ab initio MCSCF calculations, they found the equilibrium geometry of 1,2-cyclohexadiene is strongly bent and chiral, which can racemize though a diradical intermediate **30a,** and this singlet diradical was found to be 13.1 kcal/mol above **1** (Scheme 12). A similar result, 14.3 kcal/mol, was reported by Engels, Munster and Christl in 2002, where they used DFT calculations.[30] The diradical **36** was found to be 44 kcal/mol above 1,2-propadiene, which is significantly higher than 1,2-cyclohexadiene. Johnson's computational results are also in line with Jones and Balci's experimental result, where a racemic mixture was obtained when temperature increased from 53 ˚C to 100 ˚C.



Scheme 12. Energy Required to Racemize Allene via Diradical Intermediate

To accommodate an allene structure into six-membered ring, the linear allene **37a** has to be bent at C_2 to make the C_1-C_2-C_3 bond angle close to 120°, like structure **37b** (Figure 3).[31] This deformation will break the linear allene structure and maintain two π bonds orthogonal to each other. For structure **37b**, the C_1-C_2 is closer to π bond of C_2-C_3 and the σ bond of C_1-C_2 can hyperconjugate with the π bond and presumably weakens it. Of course, twisting may occur on C_2-C_3 axis to rotate the π bond away from C_1-C_2, like **37c**, to minimize the hyperconjugation and break the orthogonal double bonds.



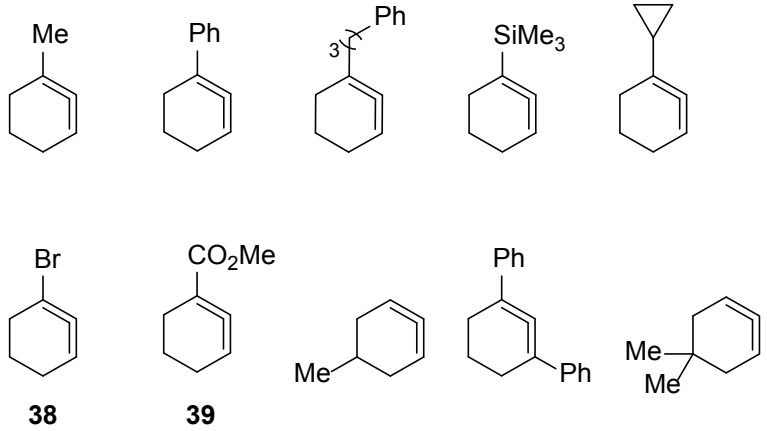
37a **37b** **37c**

Figure 3. Molecular Orbital of 1,2-Cyclohexadiene

Based on these experimental and computational results, the structure of **1** is best represented as a chiral bent allene, which will racemized via **30a**. On the other hand zwitterions **30b/30c** are the exited states much higher in energy than **30a**.[32]

1.4 Electron Withdrawing Group Substituted 1,2-Cyclohexadienes

Since the initial report by Wittig and Fritze in 1966, various substituted 1,2-cyclohexadienes have been reported (Figure 4).[2,25,33]

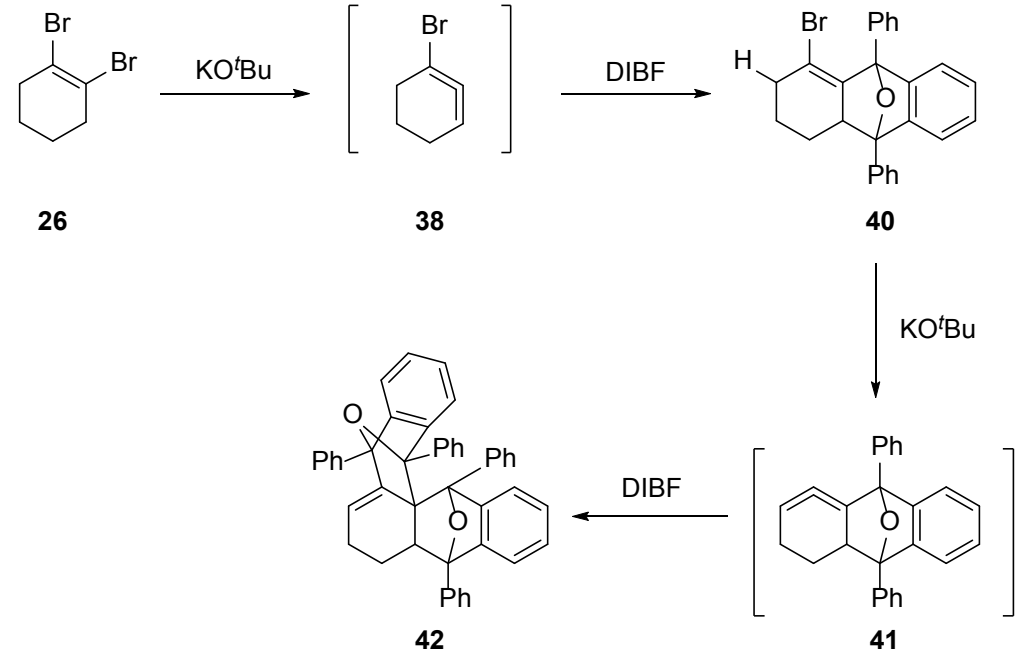


38 **39**

Figure 4. Substituted Cyclohexa-1,2-dienes Reported

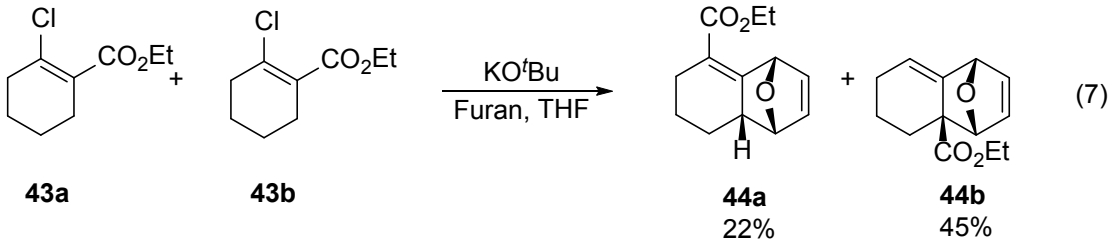
Among these substituted allenes, 1-substituted cyclohexa-1,2-dienes were more attractive targets since the electronic property of allene could be varied by different

substituents. However, most studies focused on alkyl or aryl substituted cyclohexa-1,2-dienes, and only two examples of electron-deficient cyclic allenes have been reported: 1-bromo-cyclohexa-1,2-diene **38** and methyl cyclohexa-1,2-diene-1-carboxylate **39**. Allene **38** is electron-deficient due to the inductive effect of the bromine on the allene, while **39** is through the conjugation with ester group. However, choosing electron withdrawing halogen had a problem in the presence of base (Scheme 13). 1,2-Dibromocyclohexene **26** was treated with base in the presence of DIBF, and the cycloadduct **40** was formed after the generation and trapping of cyclic allene **38**. Cycloadduct **40** still contained a vinyl bromide moiety and underwent base-induced elimination again to generate cyclic allene **41,** which was trapped with DIBF to afford product **42**. Installation of halogen on the 1-position of 1,2-cyclohexadiene resulted in the undesired deprotonation and elimination of cycloadduct. Based on this result, to prevent the further elimination on the corresponding trapped product, the electron withdrawing group on 1-subsituted cyclohexa-1,2-diene should not be a good leaving group.



Scheme 13. Generation and Trapping of Electron-deficient 1,2-Cyclohexadienes

In 1999, Houk, Tolbert and coworkers reported the generation and trapping of **39** (eq 7).[33e] The vinyl chloride precursors **43a, 43b** were treated with KO^{t}Bu to generate cyclic allene **39**, which was trapped by furan *in situ* to afford [4+2] cycloadducts **44a** and **44b**. Although they were able to afford a functionalized fused ring structure, the authors didn't make any further investigations on this reaction. Due to the incomplete study, the reactivity of **39** has not been fully explored. The investigation on conjugated 1,2-cyclohexadiene will help us to have better understanding of this reactive intermediate and novel reactivity might be rewarded during the course of study.



1.5 Conclusion

Alkyl cyclohexa-1,2-diene-1-carboxylate is a novel cumulene type reactive intermediate, with the potential to access functionalized fused cyclic structures upon trapping. The primary goal of the investigation of 1,2-cyclohexadiene can be divided into two parts: one is the allene generation and another is the trapping of allene. For the generation of allene, a number of methods has been established to generate 1,2-cyclohexadiene. The West group is particularly interested in using base-induced elimination and fluoride-induced elimination to generate substituted 1,2-cyclohexadiene. Verner Lofstrand has focused on the generation of electron rich allenes via fluoride-induced elimination.[34] Exploring new reactivity of 1,2-cyclohexaidene by expanding the scope of trapping agent is another focus of the West group. Upon building up enough experimental results on these reactive intermediates, we will be able to gain deep understanding of the properties of cyclic allene. This thesis will describe the

progress of developing a practical method to generate and trap electron deficient 1-substituted cyclohexa-1,2-diene via base-induced elimination and the discovery of new reactivity of this type reactive intermediate.

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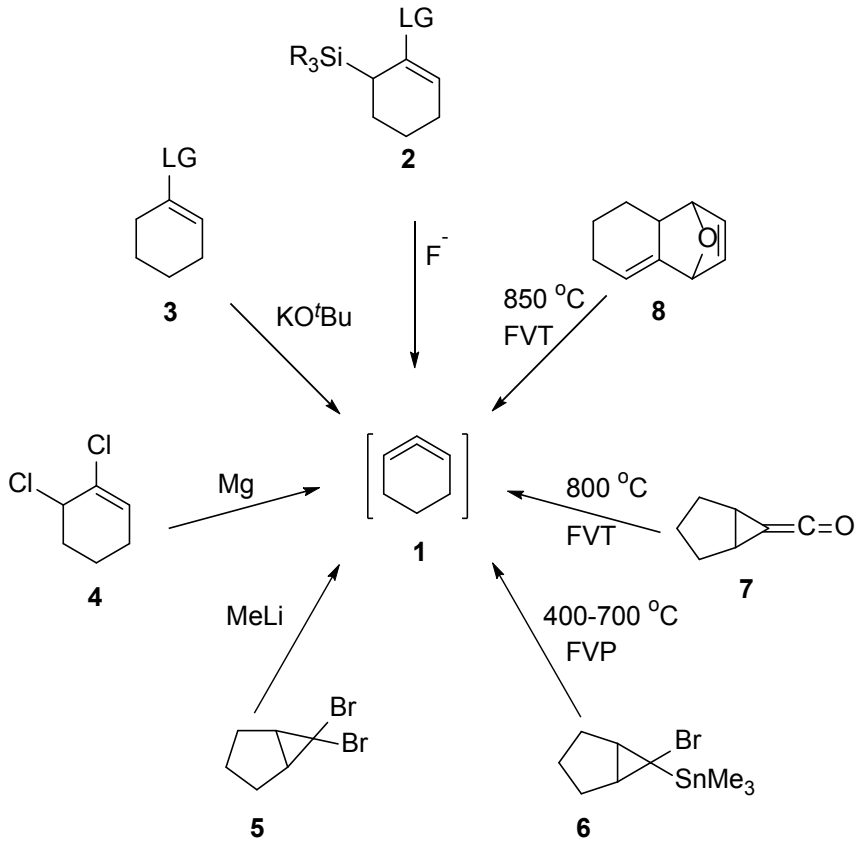
Chapter 2

Generation and Trapping of Electron Deficient Cyclic Allenes

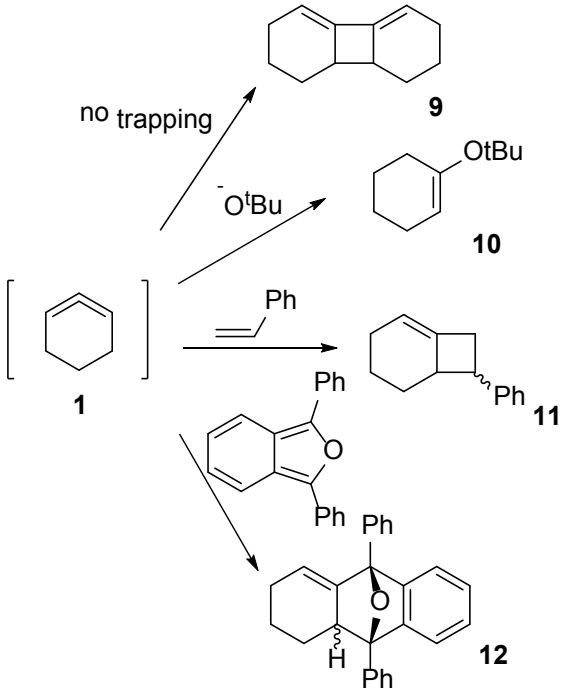
2.1 Generation and Trapping of 1,2-Cyclohexadienes

Since the initial discovery of 1,2-cyclohexadiene **1** in 1966, various methods were established to generate **1** (Scheme 1). 1,2-Cyclohexadiene **1** could be generated by elimination of corresponding vinyl precursors **2**, **3** or **4**.[1] Bicyclo[3,1,0]hexane derivates **5**, **6** or **7** also afforded **1** upon treatment under different conditions.[2] 1,2-Cyclohexadiene could also be synthesized from **8** via retrocycloaddition by flash vacuum thermolysis (FVT) at 850 °C.[2b]



Scheme 1. Different Methods to Generate 1,2-Cyclohexadiene **1**

Due to its instability, **1** readily undergoes dimerization to generate dimer **9** (Scheme 2). This oligomerization process could be diverted by cycloaddition or nucleophilic substitution to afford corresponding products **10, 11** and **12.**[1a, 3] However with the simple unsubstituted 1,2-cyclohexadiene, it is challenging to increase molecular complexity and perform further transformation on products due to the lack of functional groups on **1**. In order to build up complex molecules with cyclic allene building blocks, substituted cyclohexa-1,2-dienes were studied. 1-Subsituted cyclohexa-1,2-diene was the most studied substrate among all substituted cyclohexa-1,2-dienes. The following sections highlights these methods used to generate and trap 1-substituted cyclohexa-1,2-diene.

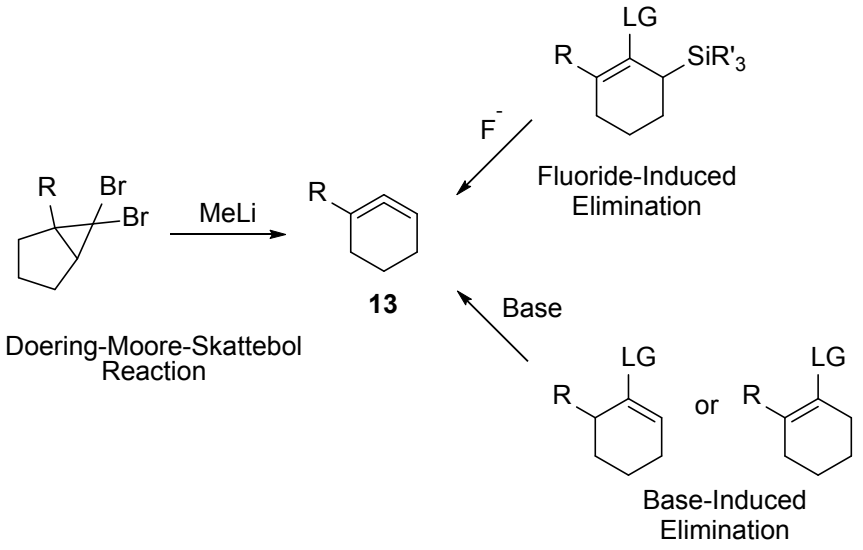


Scheme 2. Trapping of 1,2-Cyclohexadiene **1**

2.1.1 Generation of 1-Substituted Cyclohexa-1,2-dienes

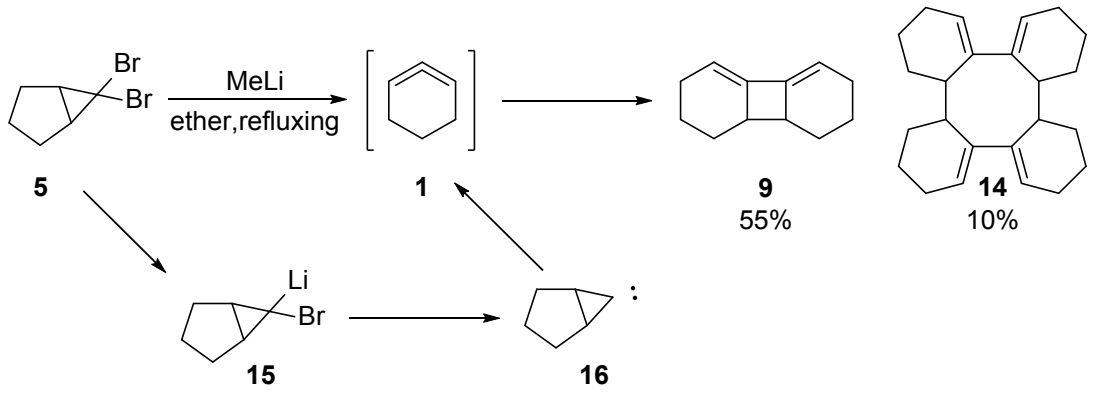
As been mentioned, various methods have been developed to generate **1**; however, for the generation of 1-substituted cyclohexa-1,2-diene **13**, only three methods have been frequently

used: the Doering–Moore–Skattebøl reaction, fluoride-induced elimination and base-induced elimination (Scheme 3).



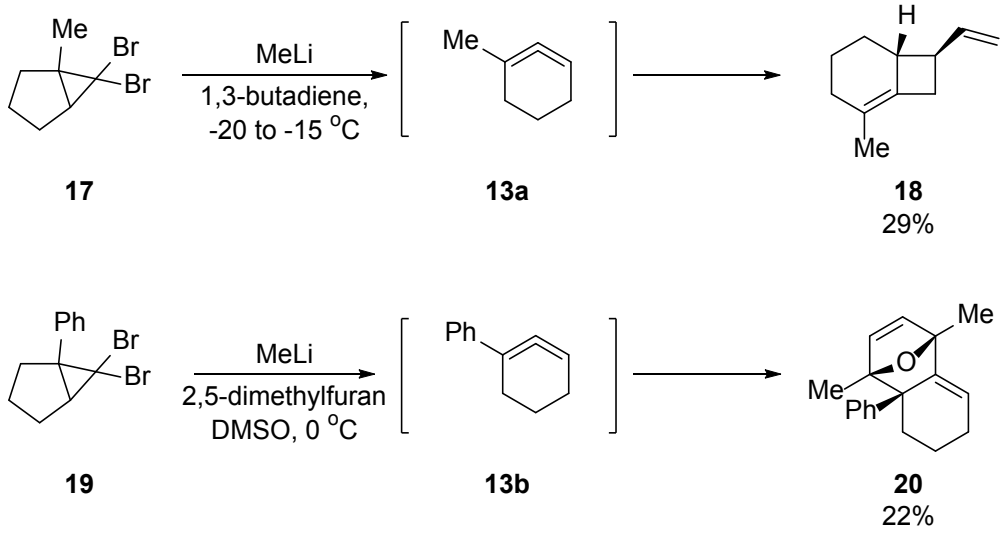
Scheme 3. Three Major Generation Methods of 1-Substituted Cyclohexa-1,2-diene **13**

The Doering–Moore–Skattebøl reaction was first introduced by Moore and Moser in 1970.[2a] 6,6-Dibromobicyclo[3.1.0]hexane **5** was treated with methyllithium in refluxing diethyl ether, affording 55% of dimer **9** and 10% of tetramer **14** (Scheme 4). Moore and Moser explained the generation of **1** via the relief of strain in carbene intermediate **16**.



Scheme 4. Cyclic Allene Generation via Doering–Moore–Skattebøl Reaction

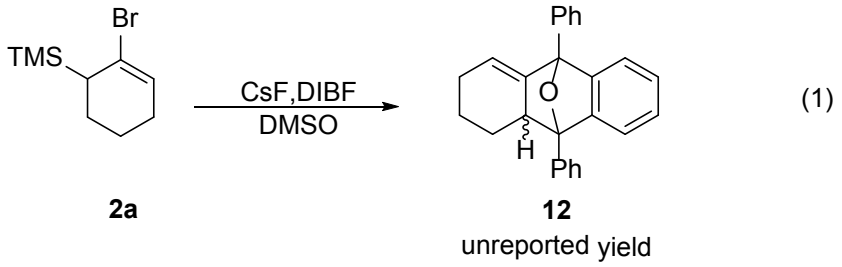
1-Substituted cyclohexa-1,2-diene **13** could also be generated by Doering–Moore–Skattebøl reaction. In 1987, Christl and co-workers reported the generation of 1-methylcyclohexa-1,2-diene **13a** from its dibromo precursor **17** and trapped the allene with 1,3-butadiene to generate [2+2] cycloadduct **18** in 29% yield (Scheme 5).[4] In 2009, Christl, Stalke and co-workers reported the generation of 1-phenylcyclohexa-1,2-diene **13b** via the Doering–Moore–Skattebøl reaction. They generated **13b** by treating dibromo precursor **19** with methyllithium. In the presence of 2,5-dimethylfuran, 22% of [4+2] cycloadduct **20** was obtained (Scheme 5).[5] The highlight of this allene generation method was that the trapping product could be obtained without the requirement of large excess of trap. The biggest drawback of this method was the use of alkyllithium reagent, which limited the scope of trap due to the harsh reaction condition.



Scheme 5. Generation of **13** via Doering–Moore–Skattebøl Reaction

Fluoride-induced elimination has emerged as a mild method to generate short-lived reactive intermediates such as benzynes and strained alkenes over the past few decades.[6] The application of this method in the generation of cyclic allenes was first introduced by Shakespeare and Johnson.[1b] In 1990, they successfully generated **1** by treating allene precursor **2a** with cesium

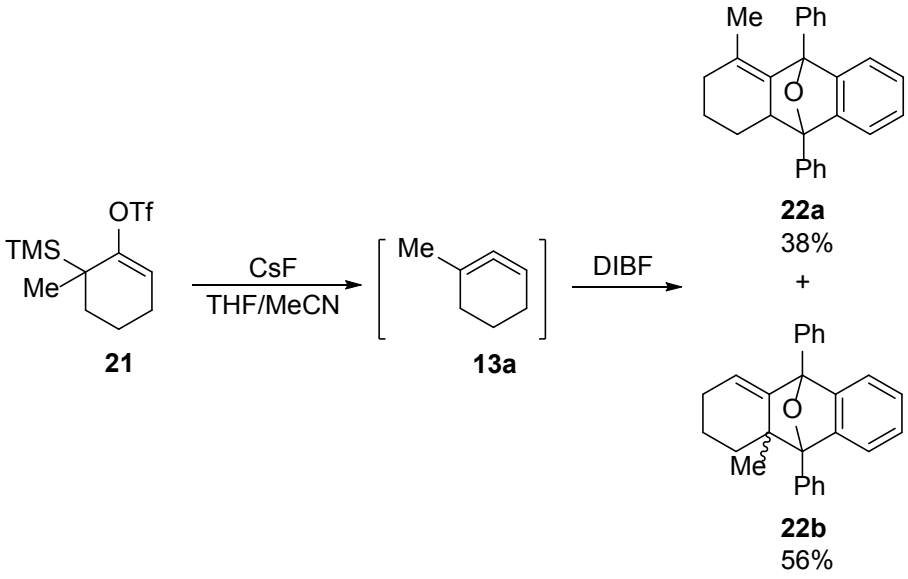
fluoride in DMSO, and isolated **12** upon trapping with 1,3-diphenylbenzo[4,2,0]furan (DIBF) (eq 1).



2a **12**

unreported yield (1)

In 2009, Peña, Guitián and co-workers reported the generation and trapping of 1-methylcyclohexa-1,2-diene **13a** via fluoride-induced elimination (Scheme 6).[7] Cyclic allene **13a** was generated after desilylation and elimination of precursor **21 i**n the presence of CsF, and was trapped with 1.5 equivalents of DIBF to afford cycloadducts **22a**/**22b** in 94% combined yield.



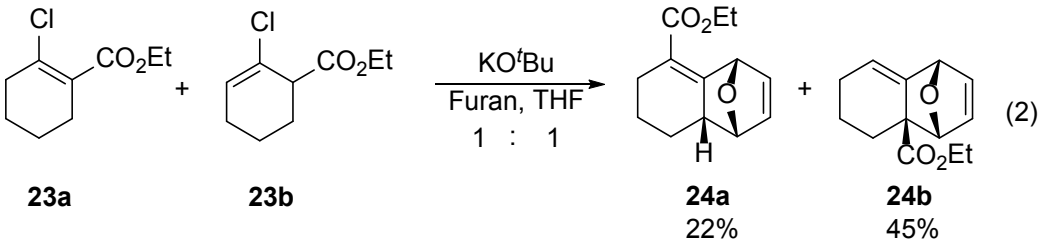
21 **13a** **22a** 38% + **22b** 56%

Scheme 6. Generation of **13** via Fluoride-Induced Elimination

Fluoride-induced elimination served as a reliable method to generate both substituted and

unsubstituted cyclohexa-1,2-dienes. Compared with the Doering–Moore–Skattebøl reaction, fluoride-induced elimination was able to generate and trap cyclic allenes under much milder conditions. With the insight of the potential of this allene generation method, the West group has also studied to this chemistry.[8]

Base-induced elimination was the oldest method known to generate cyclic allenes, and contributed a great deal to the development of cyclic allene chemistry.[9] 1-Substituted cyclohexa-1,2-diene has also been generated via this method, and it is widely reported in the literature.[3a,10] However, only few bases have been used in the generation of cyclic allenes: sodium amide and potassium *tert*-butoxide. In addition, the choice of base was not studied systematically. The major drawback of this method was the requirement to use a huge excess of trapping reagent as solvent (eq 2).[11] Due to this disadvantage, the scope of trap was narrower than the other methods, and mainly used to facilitate theoretical investigation rather than developing synthetic methodology.



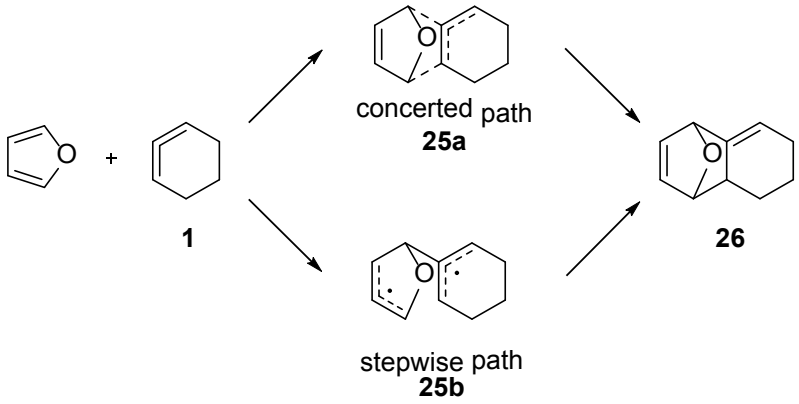
2.1.2 Trapping of 1-Substituted Cyclohexa-1,2-dienes

Due to the high reactivity and instability of 1,2-cyclohexadienes, they are normally trapped *in situ* upon generation; otherwise, they undergo oligomerization to afford dimer, trimer and tetramer.[12] In most cases, cyclic allenes are trapped via [4+2] or [2+2] cycloaddition with diene or olefin to afford corresponding fused cycloadduct.

The classic method to trap 1,2-cyclohexadiene **1** is [4+2] cycloaddition, and the corresponding cycloadduct is considered as evidence to support a cyclic allene intermediate.

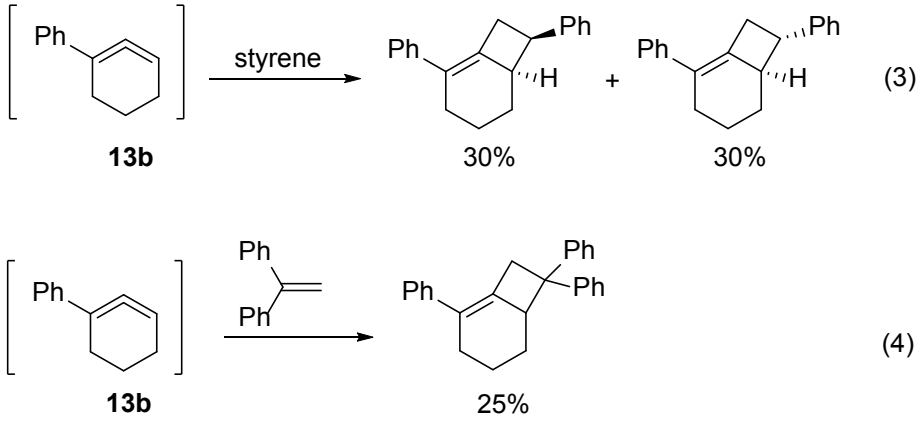
[4+2] Cycloaddition was commonly used in the study of 1-subsituted cyclohexa-1,2-dienes. However, only furan and 1,3-diphenylisobenzofuran were reported as traps in most literature examples.[7,11,13]

In 1999, Houk and Tolbert collaborated to investigate the mechanism of the [4+2] cycloaddtion of 1,2-cyclohexadiene **1**. They proposed the mechanism of the cycloaddition could be either concerted or stepwise (Scheme 7). Based on the computational results, they found in the [4+2] cycloaddition between **1** and furan, the concerted transition structures are highly asynchronous. The two forming bond have a significant length difference about 0.8 Å in endo and 1.0 Å in exo structure. On the other hand, in the stepwise mechanism the intermediate **25b** was found to be 23.2 kcal/mol lower than the concerted path. In addition, no transition structure was found in the stepwise pathway. Based on the computational results, [4+2] cycloaddition of **1** with diene is more likely under a stepwise mechanism.

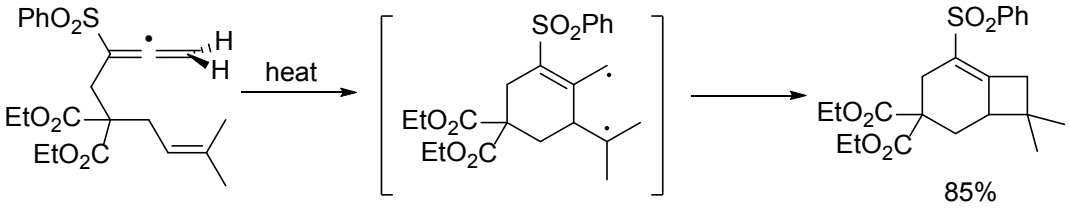


Scheme 7. Two Possible Pathways of Cycloaddition between **1** and Furan

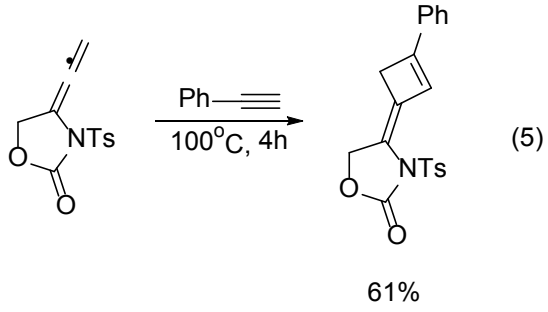
1-Subsituted cyclohexa-1,2-dienes could be trapped by olefins via [2+2] cycloaddition to afford 4,6-fused bicyclic products (eqs 3, 4).[3b,4,5] [2+2] Cycloaddition of **13b** with styrene or 1,1-diphenylethylene had high regioselectivity and only occurred on the least substituted double bond.



There were no direct computational or experimental study on the mechanism of [2+2] cycloaddition of 1,2-cyclohexadiene. Based on the experience from the thermal [2+2] cycloaddition of acyclic allene (Scheme 8), it might be a stepwise mechanism involving a diradical intermediate.[14] Acyclic allenes can undergo thermal [2+2] cycloaddition with alkyne to form cyclobutene derivates (eq 5).[15] However, [2+2] cycloaddition between 1,2-cyclohexadiene and alkyne has not been reported yet.

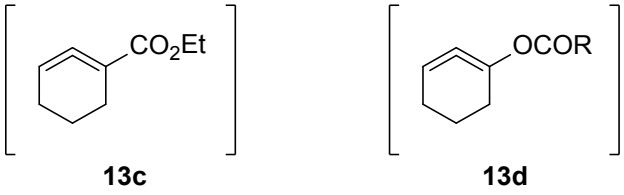


Scheme 8. Stepwise Mechanism for [2+2] Cycloaddition between Acyclic Allene and Olefin



2.2 Results and Discussions

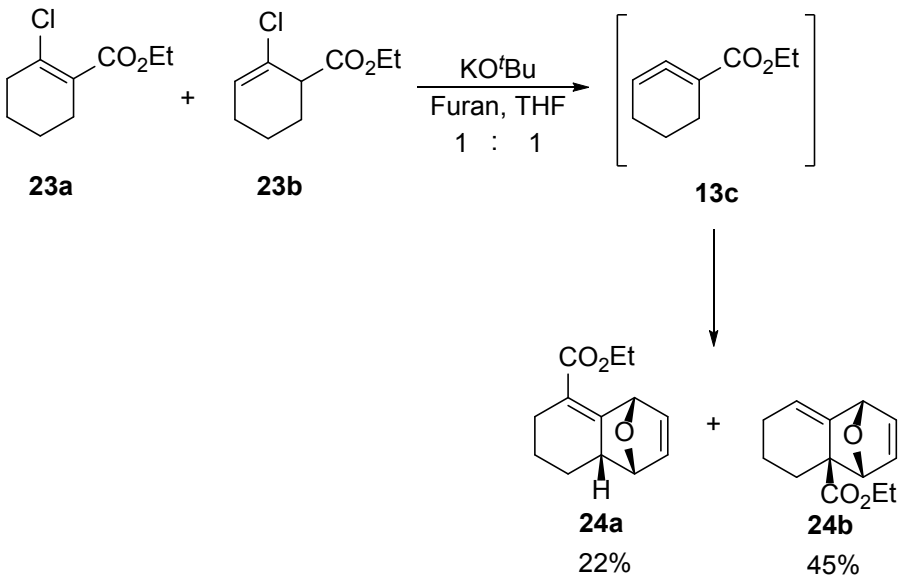
1-Substituted cyclohexa-1,2-dienes **13** are attractive research targets as they should build up molecular complexity from relatively simple precursors. In this regard, the West group engaged in this field and focused on the generation and trapping of both electron deficient and electron rich 1-substituted cyclohexa-1,2-dienes **13c** and **13d** (Figure 1). The electron rich cyclic allene **13d** was investigated by Verner Lofstrand. In this thesis, the study on electron deficient cyclic allene **13c** will be described.



13c **13d**

Figure 1. Two Type of 1-Subsititued Cyclohexa-1,2-dienes Studied in the West Laboratory

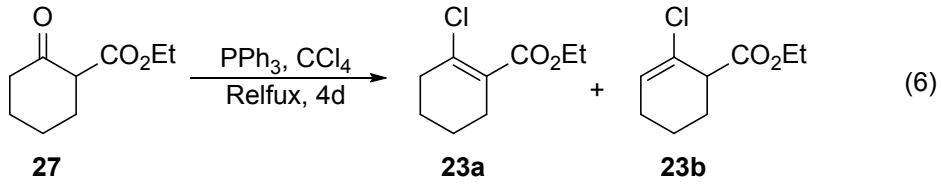
Ethyl cyclohexa-1,2-diene-1-carboxylate **13c** was first reported by Tolbert and Houk in 1999 (Scheme 9).[11] Compared with alkyl or aryl substituted cyclic allenes, the ester functional group potentially allowed further transformations on the corresponding cycloadducts. However, the biggest drawback was the requirement of a huge excess of furan as solvent (550 equiv.) to trap the allene, which restricted the further exploration in this methodology due to the cost of reagents. I present herein my investigation on the generation and trapping of **13c** via base-induced elimination and [2+2] cycloaddition with alkynes.



Scheme 9. Tolbert's Generation and Trapping of **13c**

2.2.1 Optimization

The allene precursors **23a** and **23b** were obtained in about 60% yield as a 1.5 : 1 mixture by chlorodeoxygenation of ethyl cyclohexanone-2-carboxylate **27** with triphenylphosphine in refluxing carbon tetrachloride over 4 days (eq 6).[16] Regioisomers **23a** and **23b** have very close R_f value on flash column and they should have the same reactivity toward allene generation. In the generation and trapping of allene **13c**, the mixture of **23a** and **23b** was used without further separation.

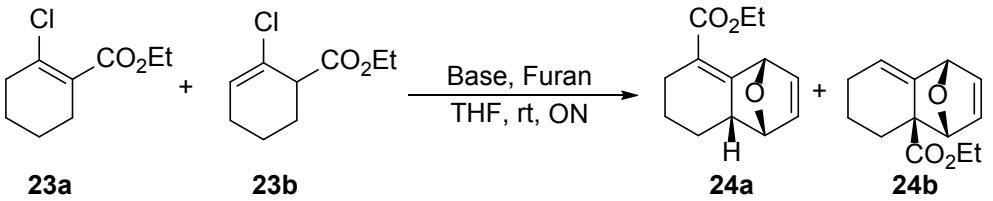


The initial optimization started with base screening under Tolbert's condition (Table 1). A diluted reaction mixture was applied to minimize the background reaction, such as oligomerization of the cyclic allene. The organic base DBU gave no reaction and starting

material was recovered (entry 1), which indicated DBU is not basic enough to deprotonate allylic proton on the allene precursor. Cycloadducts **24a** and **24b** could be obtained by using a stronger silylamide base (entries 2-3). The starting material was fully consumed and yielded 20-30% product, which was isolated from a complex mixture. Noticeably, potassium bis(trimethylsilyl)amide (KHMDS) gave slightly higher yield than sodium bis(trimethylsilyl)amide (NaHMDS), which may be due to the cation effect in which the anion is more naked and reactive in KHMDS. The pKa value of KO^{t}Bu was around 32 in DMSO, close to NaHMDS and KHMDS, 26 to 30 in THF.[17]

KO^{t}Bu afforded **24a**/**b** in 61% yield, which was much higher than the other bases (entry 4) , and the difference in yields may be due to the fact that silylamide is considerably more bulky. A stronger base has also been tested. When LDA was also subjected to the reaction conditions, starting material was fully consumed while only 22% cycloadduct was isolated (entry 5). The reaction crude mixture was very complex, which may be due occurrence of side reactions in the presence of such strong base. In the case of NaH, although all starting material was consumed, only 8% product was isolated (entry 6). It's hard to conclude which factor resulted in the high yield of KO^{t}Bu, since the overall yield was affected by both allene generation and trapping. Based on base screening, KO^{t}Bu is optimal for the generation and trapping of **13c**.

Table 1. Base Screening of Cyclic Allene Generation and Trapping[a]



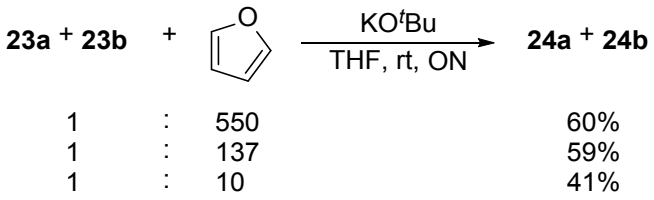
23a **23b** **24a** **24b**

Entry	Base	Equiv.	Yield[b]
1	DBU	1.5	No reaction
2	NaHMDS	1.5	20.5%
3	KHMDS	1.5	28%
4	KO^{t}Bu	1.5	61%
5	LDA	1.5	22%
6	NaH[c]	3	8%

[a]Standard procedure: To a stirred solution of precursors **23a** and **23b** (0.2 mmol) and furan (8 mL) in THF (4 mL), solution of base in THF (4 mL) was added over 30 minutes. After stirring overnight, the reaction mixture was quenched with H_2O, followed by extraction with diethyl ether, drying through $MgSO_4$, and chromatographic purification. [b] Combined yield of **24a** and **24b**. [c] 60 % Dispersion in mineral oil.

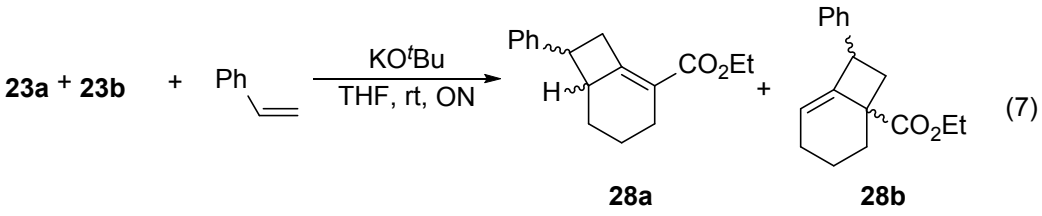
As mentioned above, Tolbert's conditions required use of a huge excess of furan as solvent to trap **13c**. However, use of excess traps has two major problems associated. First is the cost of reaction, which limits the scale of reaction and the choice of traps. The second problem is that excess traps will complicate the work up and purification steps, especially with high boiling point traps. To achieve a practical generation and trapping of **13c**, lowering the load of trap was essential. In order to prevent the oligomerization of **13c**, the volume of solvent was fixed when the amount of furan was optimized (Scheme 10). The yield was almost unchanged when the ratio of precursors to furan dropped from 1:550 to 1:137. When 10 equivalents of furan were used, 41% of product was obtained. A further decline of yield was expected with continued lowering of the trap loading. These experiments suggested at least 10 equivalents of traps were required to obtain

cycloadducts in trap screening.

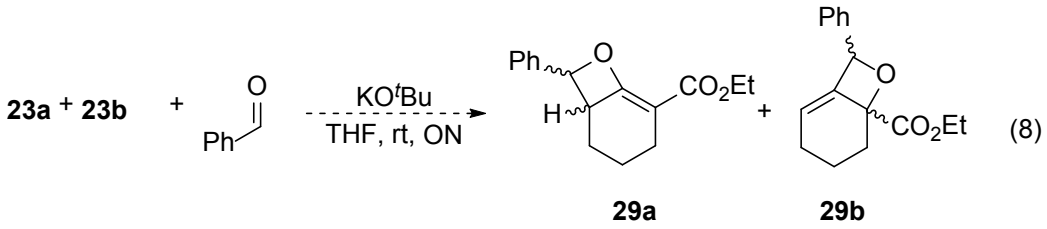


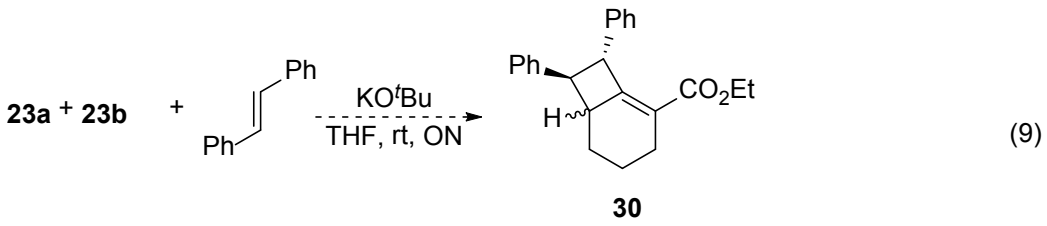
Scheme 10. Optimization of Trap Loading

Other than [4+2] cycloaddition, cyclic allenes can also be trapped via [2+2] cycloaddition. It was well presented in the literature that [2+2] cycloaddition of **13** with alkenes afforded single regioisomers, which would simplify the analysis of the crude reaction.[3a,18] As a relatively cheap commercial reagent, styrene was used as solvent of reaction; however, unlike furan, styrene has a high boiling point and it cannot be removed during workup. To isolate the product, a distillation or large scale flash chromatography was required to separate the crude product from unreacted styrene. Upon chromatographic purification, cycloadducts **28a**, **28b** and their diastereomers were obtained as an inseparable mixture (eq 7). Benzaldehyde (25 equiv.) and *trans*-stilbene (20 equiv.) afforded complex mixtures and failed to afford any clean fractions upon flash chromatography (eqs 8-9). The corresponding cycloadducts **29a**, **29b** and **30** could not be identified by crude ^{1}H NMR, due to the overlapping peaks and lack of characteristic proton resonances. Therefore, the existence of these cycloadducts remained unproved.

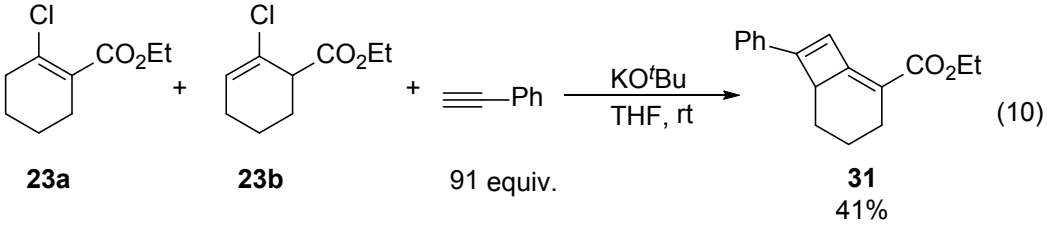


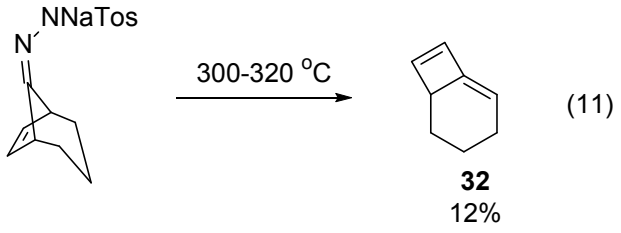
(7)





When phenylacetylene (91 equiv.) was used as trap, the [2+2] cycloadduct **31** was obtained in 41% yield (eq 10). The structure of **31** was proposed based on analysis of the ^{1}H and ^{13}C NMR spectra.





The structural determination of **31** was also aided by the known compound, bicyclo[4.2.0]octa-1,7-diene **32**, reported by Brinker and co-workers in 2012 (eq 11).[19] By comparing the ^{1}H NMR spectra of **31** and **32**, it was found that ^{1}H signals of cycloadduct **31** were distributed in a similar pattern as **32** with more downfield shift due to the extra ester group

and phenyl group. For example, in the case of the bridgehead hydrogens H_a and H_b (Fig 2), H_b was about 0.8 ppm downfield of H_a. The regiochemistry was determined by a 1D NOE experiment (Fig 3). Bridgehead hydrogen H_b correlated to a signal in the aromatic region (presumably the ortho protons) indicating a close contact. Examination of the two possible regioisomers, **31** and **31a**, indicates a significant difference in the through-space distance from H_b to the ortho aromatic protons. Inspection of Dreiding models indicates that this distance is ca. 3 Å for **31** and 4.5 Å for **31a**.[20] Molecular modeling calculations arrived at similar values for the optimized geometry of the two possible isomers.[21] Given the approximate upper limit of 4 Å required for observation of an strong NOE contact in such rigid fused ring system, this result strongly supports the structural assignment as **31** rather than **31a**.[22] The assignment of region chemistry of **31** was also supported by other evidence. In a 2D HMBC experiment, the alkene proton H_c is found to couple with one sp^3 carbon corresponding to the bridgehead carbon and four sp^2 carbons corresponding to one aromatic carbon and three alkene carbons. This observation fits the structure of **31**(Fig 4). In the opposite regioisomer **31a**, H_d is expected to couple with two sp^3 carbons, including the bridgehead carbon and the adjacent carbon on the ring, and three sp^2 carbon corresponding to one aromatic and two alkene carbons. Although **31** did not form crystals for X-ray diffraction analysis, the structure of **31** gets sufficient support from the NMR experiments. Compound **32**, mentioned by Brinker in his paper, was found to be thermally unstable and polymerized within a few hours at room temperature. On the other hand, cycloadduct **31** was bench stable at room temperature over weeks. The stability of **31** could be rationalized by the phenyl and ester groups conjugated to diene, which provided extra stability through electron delocalization across the fused ring.

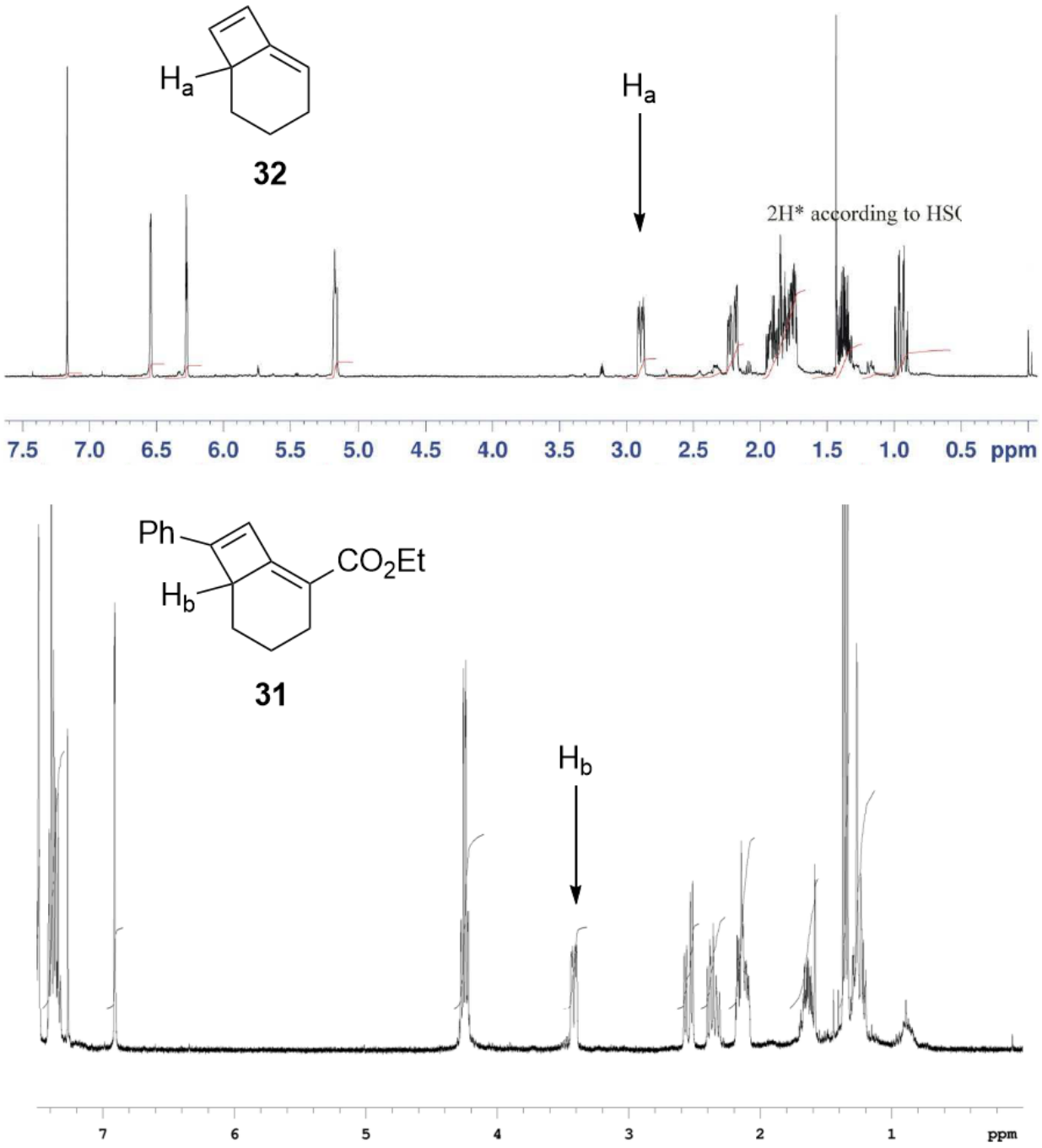


Figure 2. [1]H NMR Spectrum of Bicyclo[4.2.0]octa-1,7-diene **32** and Cycloadduct **31** (Portions of **Figure 2.** Adapeted by the authors from *J. Org. Chem.* **2012**, *77*, 3800.)

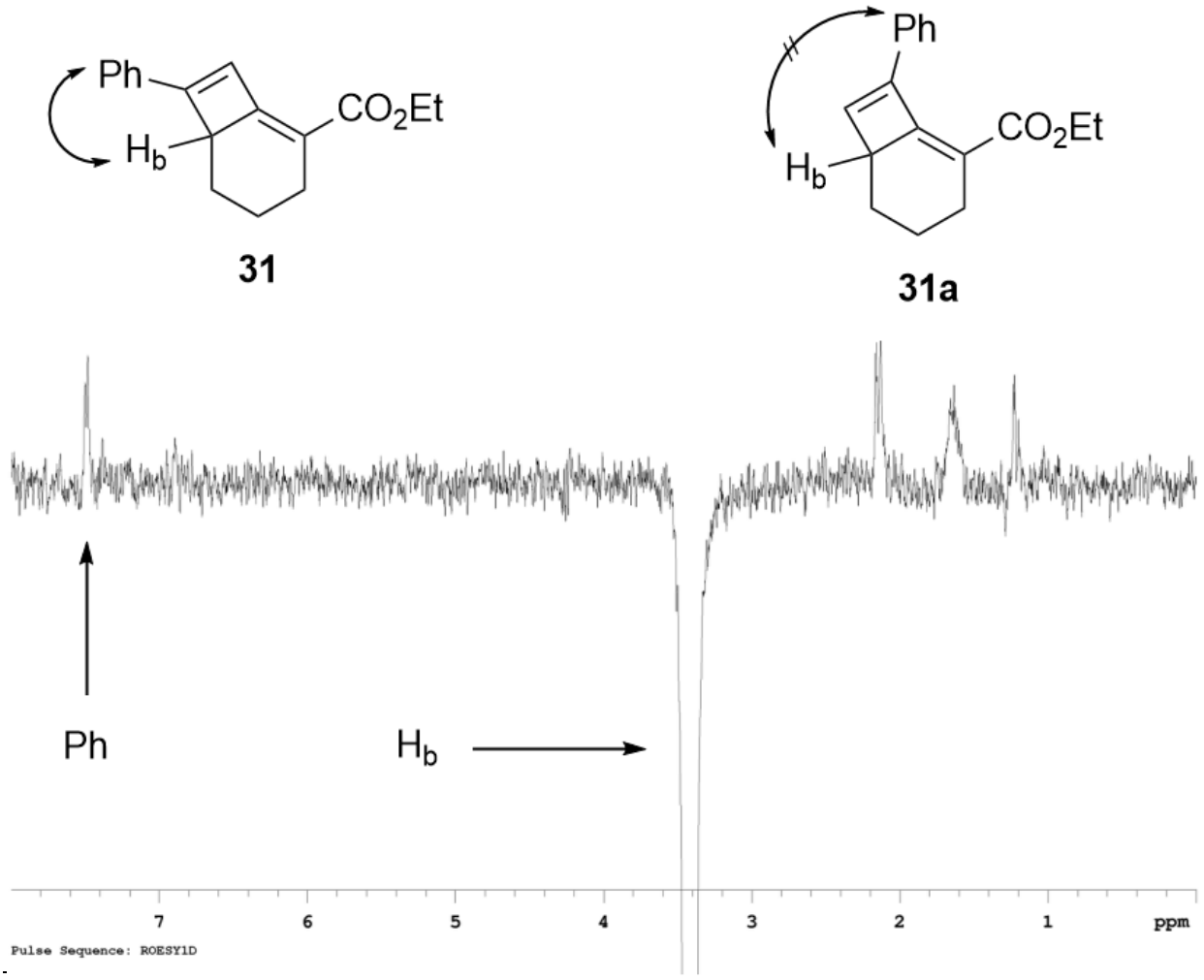


Figure 3. 1D NOE Spectrum of Cycloadduct **31**

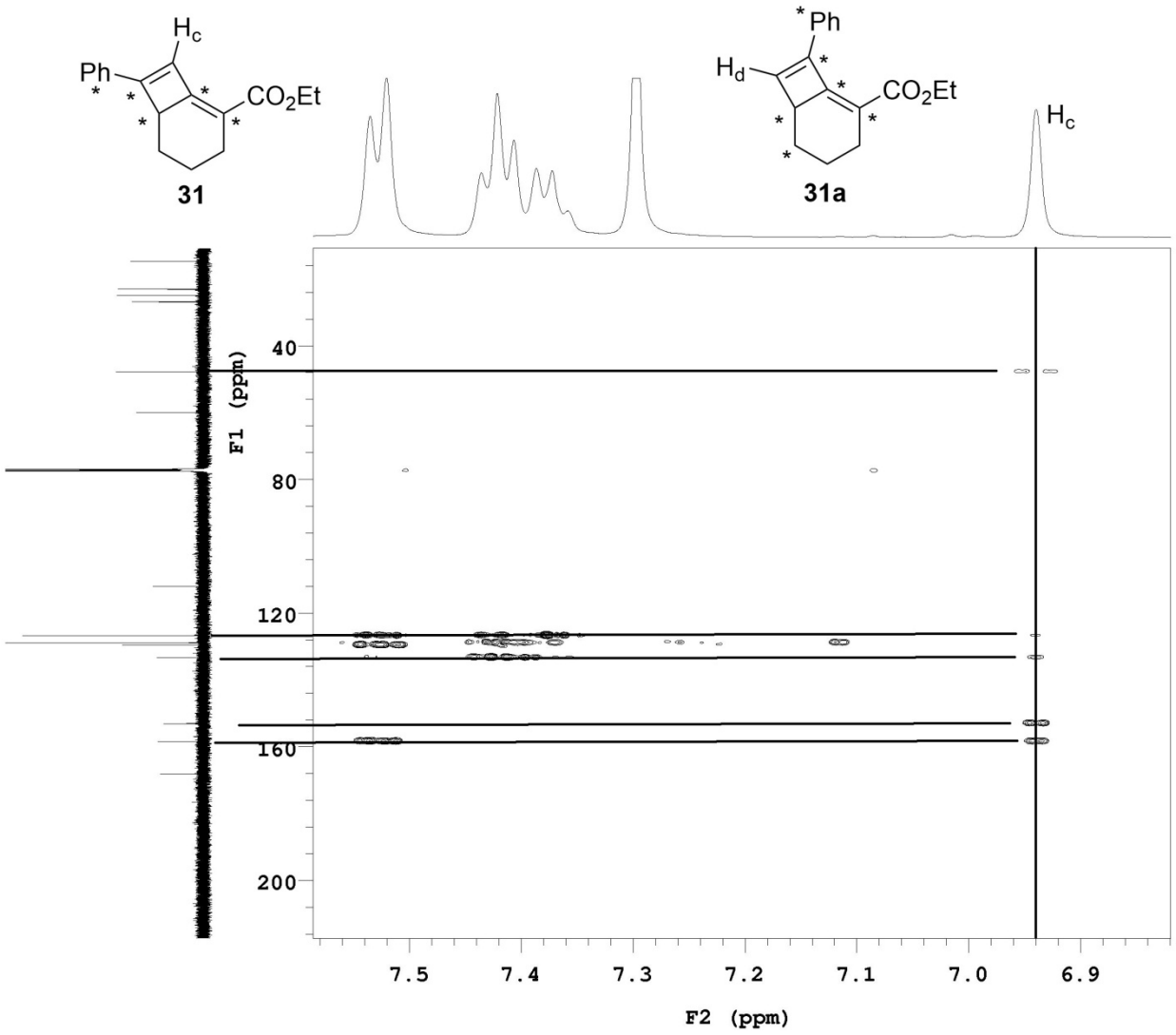
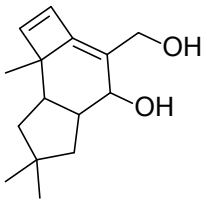


Figure 4. 2D HMBC Spectrum of Cycloadduct **31**

This bicyclo[4,2,0]octadiene skeleton is also present in the natural product, 4,5-dehydro-5-deoxyarmillol **33**, which was isolated from terrestrial fungi and characterized by Pettit and coworkers in 2010 (Fig 5).[23] This indicated that [2+2] cycloadducts such as **31** may have potential application in natural product synthesis.

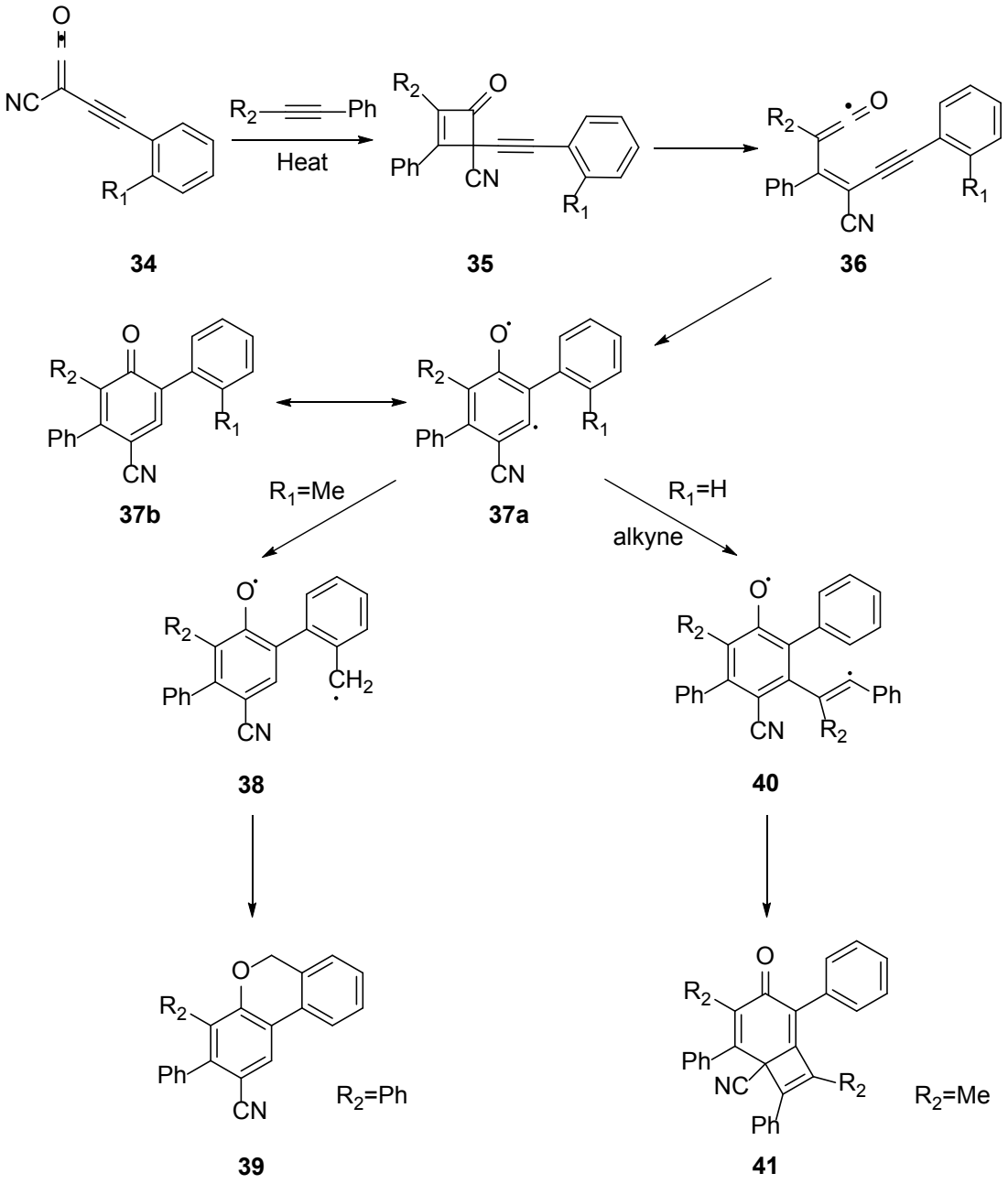


33

4,5-dehydro-5-deoxyarmillol

Figure 5. Natural Product Isolated from Terrestrial Fungi.

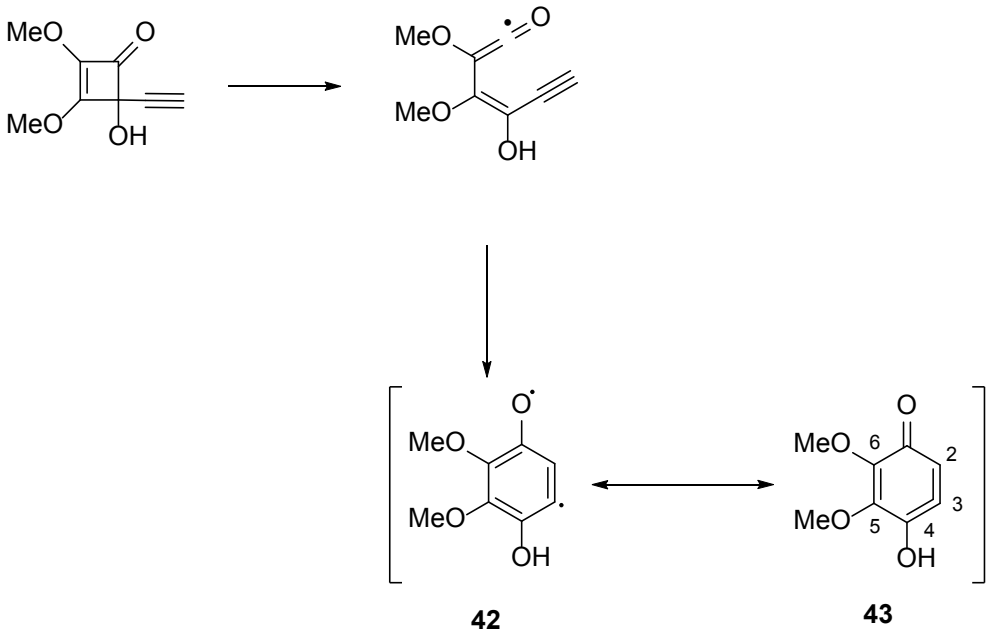
At the time of these studies, there had been no reports of the [2+2] cycloaddition between 1,2-cyclohexadiene and alkynes. A similar reactivity had been observed with 2,4,5-cyclohexatrien-1-one. [24] In 1990, Moore and coworkers investigated the [2+2] cycloaddition between alkynylcyanoketenes and alkynes. They observed unusual transformations generating polycyclic aromatic compound **39** and bicyclo[4.2.0]octa-1,4,7-trien-3-ones **41,** depending on substrates (Scheme 11). They proposed after [2+2] cycloaddition of **34**, cyclobutenone **35** underwent ring opening to generate enynylketene **36**. Subsequent ring closure gave diradical intermediate **37a**, which was the key intermediate leading to both products **39** and **41**. Upon hydrogen atom abstraction from the adjacent methyl on the phenyl ring, intermediate **38** would be generated. After diradical ring closure, tricyclic product **39** was obtained. When the phenyl ring did not have an *ortho*-methyl group, hydrogen abstraction would not occur in **37a** (R_1=H). It reacted with another equivalent of alkyne to generate **41** via the formation of diradical intermediate **40**. Although Moore and coworkers invoked diradical **37a** following cyclization of **36**, it should be noted that the closed-shell resonance form **37b** is also plausible. In this context, formation of [2+2] adduct **41** is quite analogous to the formation of **31** from **13c**.



Scheme 11. Proposed Mechanisms for the Generation of **39** and **41**

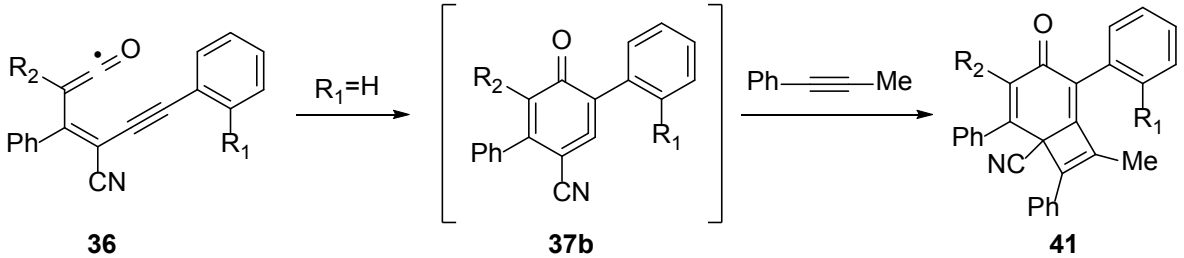
In 2002, based on Moore's report, Fernández and co-workers investigated the possibility of a cyclohexatrienone intermediate via a computational study.[25] They calculated the relative energy of the diradical intermediate and 2,4,5-cyclohexatrien-1-one. To simplify computations, they chose **42** and **43** as models (Scheme 12). The trieneone **43** intermediate was about 19.6 Kcal/mol

lower in energy than triplet diradical **42**. The structure of **43** was also calculated and it was found that the six-membered ring is not planar, and C_1 and C_4 were out of the plane. The bond lengths of C_2-C_3, C_3-C_4 and C_5-C_6 were found to be 1.34, 1.35 and 1.37 Å respectively, which are very close to typical double bond lengths and suggested the cyclic trienone structure.



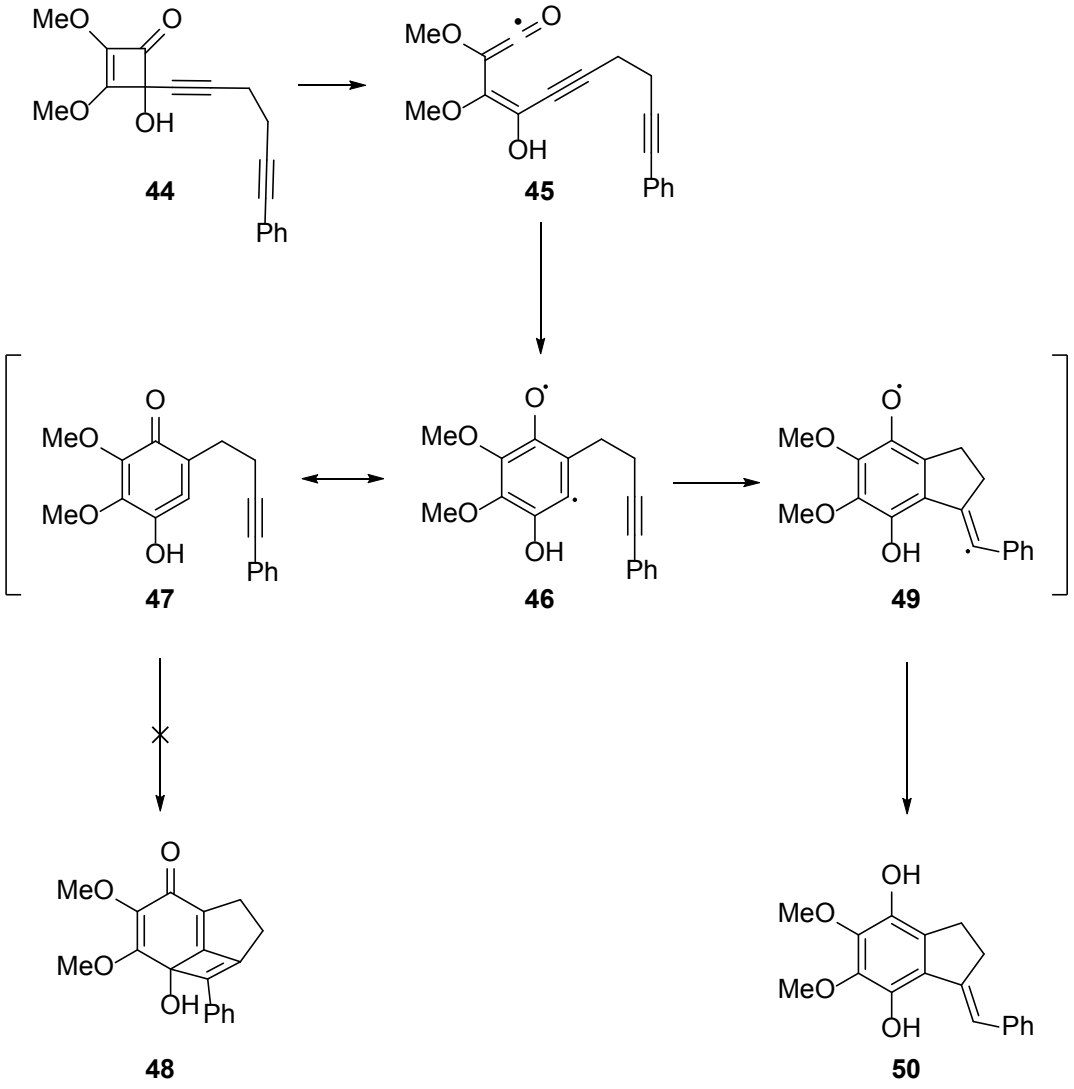
Scheme 12. Computational Study on Relative Energy of Diradical and Trienone Intermediate

Based on Fernández's computational work, the generation of bicyclo[4.2.0]otadiene **39,** observed by Moore in 1990, could be rationalized by [2+2] cycloaddition of trienone **37b** and alkyne (Scheme 13).



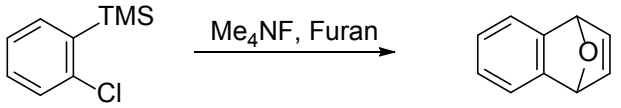
Scheme 13. Generation of **39** via [2+2] cycloaddition of **35b** and alkyne

However, not all experimental results supported this hypothesis. In 1996, Moore prepared ketene **45** from cyclobutenone **44**, which was already tethered to an alkyne. The [2+2] cycloadduct **48** was not observed, but the bicyclic product **50** was isolated and characterized (Scheme 14). This result could be explained by radical 5-exo-dig cyclization of **46** to afford intermediate **49**. The absence of **48** suggested that trienone **47** was not the preferred resonance form, or that the intramolecular [2+2] cycloaddition might not occur due to the strain in product **48**. A longer tethered carbon chain might be required to allow intramolecular [2+2] cycloaddition.

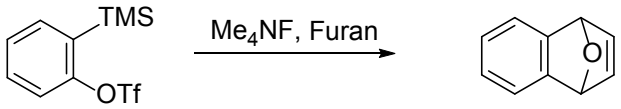


Scheme 14. Unsuccessful Internal Trapping of **47**

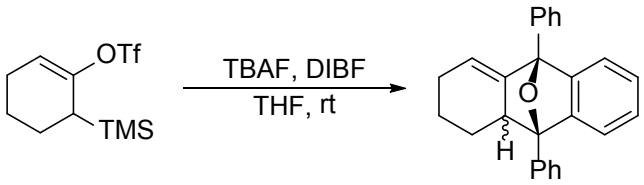
[2+2] Cycloaddition between **13c** and alkyne is a novel reaction to be further investigated. However, with vinyl chloride precursors **23a**/**23b**, it still requires a large excess of phenylacetylene to afford a low yield. It was found in the literature that the overall yields of generation and trapping of reactive intermediates were affected by the leaving group on the precursors. In 1983, Kobayashi reported the use of triflate as leaving group to generate and trap benzyne. Aryl triflate precursor **51b** can afford [4+2] cycloadduct in a higher yield than the corresponding Aryl chloride **51a** under the same conditions (eqs 12, 13). In 2009, Guitián and Peña applied the same strategy to cyclic allene chemistry and were able to afford a good yield of cycloadduct **12** via fluoride-induced elimination of vinyl triflate precursor **52** (eq 14).[7] Based on these experiences, changing the leaving group from chloride to triflate might also improve the overall yield of [2+2] cycloaddition between **13c** and alkynes.



51a 32% (12)

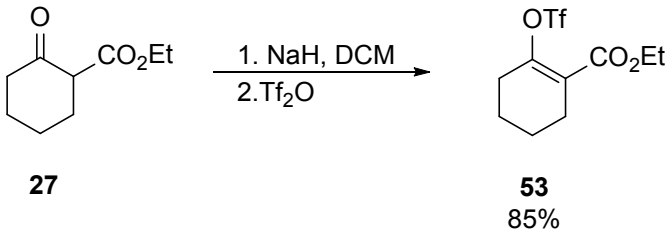


51b 76% (13)



52 **12** 66% (14)

Vinyl triflate precursor **53** was synthesized from **27** based on literature procedures (eq 15).[26] Precursor **53** was thermally stable and used in the optimization of the [2+2] cycloaddition.

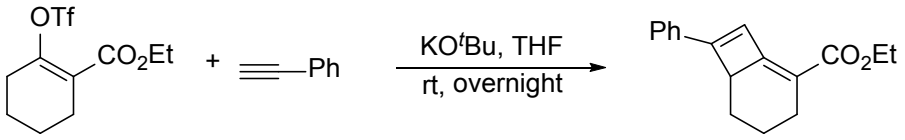


(15)

27 **53**
85%

In the presence of 32 equivalents of phenylacetylene, 43% yield of **31** was obtained upon treating **53** with KO^{t}Bu in 2 mL THF. (Table 2, entry 1). The yield dropped significantly when the ratio of **53** to alkyne was reduced to 1: 6, while the volume of solvent remained the same (entry 2). Increasing the concentration of **53** by reducing the volume of solvent returned the yield to 35% (entry 3), which suggested the efficiency of allene generation and trapping is concentration dependent. A dilute reaction mixture was normally applied to minimize the oligomerization of cyclic allene; however, in our system the concentrated reaction mixture was critical for lowering the trap loading. The optimized condition gave 34% yield with only 2 equivalents of acetylene (entry 6). When vinyl chloride precursors **23a**/**23b** were subjected to the same condition, only 19% yield of product was obtained (entry 8). Based on these results, changing the leaving group from chloride to triflate improved the overall yield of generation and trapping of **13c**.

Table 2. Optimization of Trap Loading[a]



53 **31**

Entry	Alkyne (equiv.)	Solvent (mL)	[Trap] (M)	[Precursor] (M)	yield[b]
1	43	2	3.7	0.085	32%
2	6	2	0.5	0.085	7%
3	6	0.4	2.6	0.43	35%
4	2	0.4	0.9	0.43	30%
5	0.67	0.4	0.3	0.43	27%
6	2	0.2	1.7	0.85	34%
7	4	0.2	3.4	0.85	33%
8	2	0.6	0.6	0.28	19%[c]

[a] Standard procedure: To a stirred solution of precursor **53** (0.17 mmol) and phenylacetylene in THF, a solution of KO^{t}Bu (0.3 mmol) in THF was added over 15 minutes. After stirring overnight, the reaction mixture was quenched with H_2O, followed by extraction with diethyl ether, drying through $MgSO_4$, and chromatographic purification. [b] Isolated yield. [c] Vinyl chloride precursor **23a**/**23b** were used in place of **53.**

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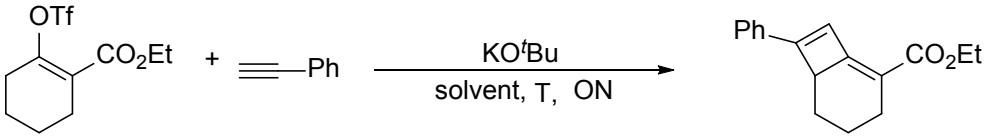
The effect of solvent and temperature were also studied (Table 3). Using a given amount of KO^{t}Bu, it required more volume of toluene and acetonitrile to dissolve the base. A dilute solution was undesired for allene generation and trapping, as shown in the previous optimization. As the result, only a trace amount of **31** was observed (entries 2,3). If a more concentrated solution was applied, acetonitrile still afforded only a trace amount of product, while 21% yield was obtained with toluene (entries 4-6). Diethyl ether and DCM were also screened and gave similar yields around 16% (entries 7, 8). Among the solvents screened, THF gave the best yield which may be due to the high solubility of KO^{t}Bu in THF (entry 1).

When the reaction mixture was cooled to 0 °C, the yield increased to 41% (entry 10). However, the yield dropped to 12% at -78 °C, though the starting material was fully consumed (entry 11). This suggested the rate of [2+2] cycloaddition is too slow to compete with side

reactions at this temperature and 0 °C is the optimized temperature for allene generation and trapping.

Table 3. Screening of Solvent and Temperature. [a]



53 **31**

Entry	Temperature	Solvent	Volume (mL)	yield[b]
1	rt	THF	0.2	34%
2	rt	MeCN	1.6	Trace
3	rt	Toluene	1.5	Trace
4	rt	MeCN	0.4	Trace [c]
5	rt	Toluene	0.4	11%[c]
6	rt	Toluene	0.2	21%[c]
8	rt	Ether	0.2	16%
9	rt	DCM/ THF	0.2 + 0.2	16%
10	0 °C to rt	THF	0.2	41%
11	-78 °C to rt	THF	0.2	12%

[a] Standard procedure: To a stirred mixture of precursor **53** (0.17 mmol) and phenylacetylene (0.34 mmol), solution of KO^{t}Bu (0.3 mmol) in given solvent was added over 15 to 30 minutes under given temperature. After stirring overnight, the reaction mixture was quenched with H_2O, followed by extraction with diethyl ether, drying through $MgSO_4$, and chromatographic purification. [b] Isolated yield. [c] KO^{t}Bu was not fully dissolved.

Investigation of byproducts was critical to improve the generation and trapping of **13c**. The reaction mixture was hard to purify on silica gel due to overlapping spots and tailing. Furthermore, some components decomposed on silica gel. Therefore, the study of side reactions had to be done by other analytical methods. Based on GC/LC-MS, ketone ester **27** was frequently observed as a minor product. It is known that vinyl triflates can be hydrolyzed back to the corresponding ketone in the presence of base and water.[27] Therefore the hydrolysis of **53** may be due to the moisture entering the reaction mixture. Other than **27**, high molecular weight compounds were observed by GC-MS. However the molecular weight did not match with any

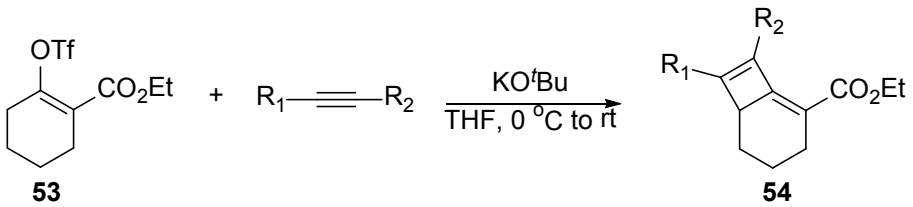
predicted oligomers of **13c** and the structure of these components was not determined.

2.2.2 Reaction Scope

With the optimized conditions in hand, the scope of [2+2] cycloaddition between cyclic allene **13c** and alkynes was tested (Table 4).

Various alkynes were examined. While aliphatic terminal alkynes achieved limited success, they mainly resulted in intractable mixture and desired products could only be identified by crude ^{1}H NMR spectra and GC/LC-MS analysis (entries 1-3). Ethynyltrimethylsilane was the only exception, and afforded **54a** in a 10% isolated yield (entry 4). Cycloadduct **54a** was found to be thermally unstable and decomposed at 0 °C over a few days, after it has been fully characterized. As Brinker mentioned, bicyclo[4.2.0]octa-1,7-diene **32** is not thermally stable, and the low yield might also due to decomposition of cycloadducts. Benefiting by the conjugation to the bicyclo[4,2,0]octadiene skeleton, terminal arylalkynes gave low to moderate yields from 8% to 41% (entries 5-14). Electron-rich acetylene afforded a better yield than electron deficient one (entries 9-11 and entries 12-13). However, the discrepancy in yields and regiochemistry between ethynyltoluene and ethynylanisole trapping cannot be explained with the data in hand (entries 6-8 and entries 9-11). With internal alkynes, intractable mixtures were observed in all cases (entries 15-17). Based on the analysis of GC-MS and LC-MS, no desired product was formed and a portion of allene precursor was hydrolyzed back to the ketoester **27**. This observation can be explained by steric effect: extra substitution on alkyne raises the transition state energy for the cycloaddition due to steric repulsion, which slows down or inhibits the cycloaddition. In general, the scope of intermolecular [2+2] cycloaddition between **53** and alkyne is restricted to the terminal aryl alkynes.

Table 4. Scope of [2+2] Cycloaddition of **13c** with Alkynes[a]

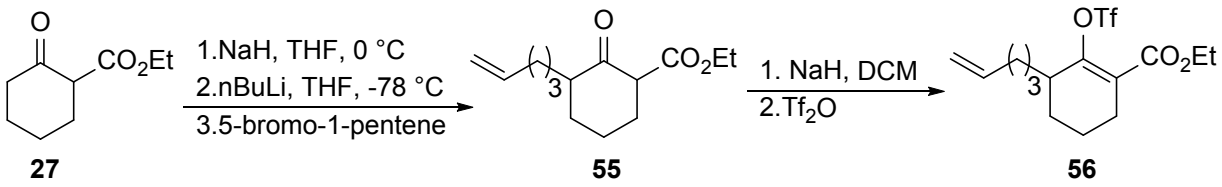


53 **54**

Entry	R_1	R_2	Product (yield %)
1	CO_2Et	H	Trace
2	Bu	H	Trace
3	OEt	H	Intractable mixture
4	TMS	H	**54a** (10)
5	Ph	H	**31** (41)
6	2-toyl	H	**54b** (29)
7	3- toyl	H	**54c** (24)
8	4- toyl	H	**54d** (22)
9	2- methoxyphenyl	H	**54e** (21)
10	3- methoxyphenyl	H	**54f** (27)
11	4- methoxyphenyl	H	**54g** (40)
12	2-chlorophenyl	H	**54h** (8)
13	3-chlorophenyl	H	Decomposition[b]
14	4-*t*-butyl phenyl	H	Decomposition
15	Ph	Ph	Intractable mixture[c]
16	Me	Me	Intractable mixture
17	CO_2Et	CO_2Et	Recovered starting material

[a] Standard procedure: To a stirred mixture of precursor **53** (0.17 mmol) and alkyne (0.34 mmol), a solution of KO^{t}Bu (0.3 mmol) in THF (0.2 mL) was added over 15 minutes at 0˚C. After stirring overnight, the reaction mixture was allowed to warm up to room temperature and quenched with H_2O, followed by extraction with diethyl ether, drying through $MgSO_4$, and chromatographic purification. [b] Product can be observed by ^{1}H NMR, but decomposes upon column purification. [c] Desired product was not observed by ^{1}H NMR and GC-MS analysis.

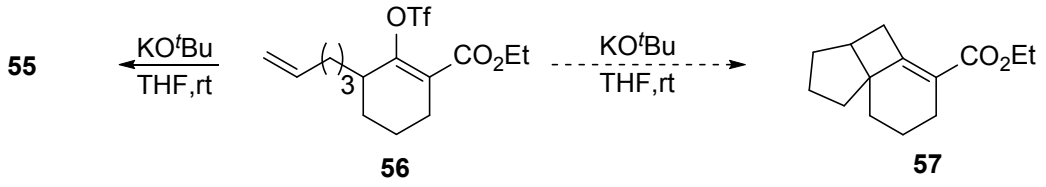
To expand the scope of the reaction, an intramolecular [2+2] cycloaddition was proposed. Intramolecular trapping of cyclic allene can afford products with higher molecular complexity and improve the efficiency of trapping to compete over the side reactions. In regard to Moore's cyclic triene result, a longer tethered carbon chain may be necessary to avoid excessive ring strain and allow [2+2] cycloaddition.[24] However, the influence of allylic substitution on the allene generation and trapping was unclear. As a test reaction, internal alkene trapping experiments were designed. Alkenes are known to trap cyclic allenes and the corresponding purcursor for intramolecular alkene trapping should take fewer steps to prepare. The allene precursor **56** was prepared from commercial available source. (Scheme 15).



27 **55** **56**

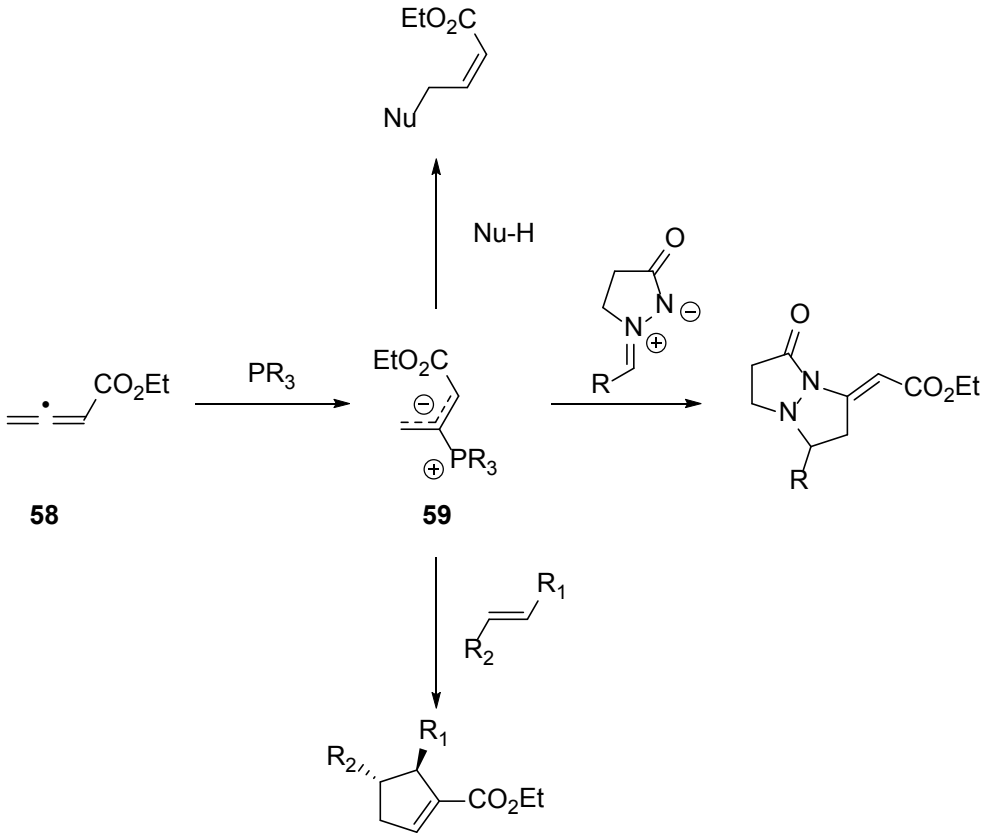
Scheme 15. Preparation of Allene Precursor **56** for Intramolecular Allene Trapping

The tricyclic product **57** was expected if the intermolecular trapping worked; however, the major product was ketoester **55,** and the starting material was not fully consumed after 12-16 hours (Scheme 16). Due to the extra substitution on the allylic position, the allylic proton may be too hindered for easy deprotonation by KO^{t}Bu. The extra substitution on the allylic position surely had negative influence on the generation of cyclic allene. It is possible that due to the slow deprotonation, **56** is hydrolyzed back to **55** in the presence of moisture. Other than allene generation, the trapping of allene might also cause problems. Although it is known that simple alkenes can react with unsubstituted 1,2-cyclohexadiene **13a**, the nature of **13c** might be different and the trapping of alkene might not be efficient. [4,13a] Based on these experimental results, the attempts at intramolecular trapping were unsuccessful.



Scheme 16. Intramolecular Trapping of Cyclic Allene

In the literature, phosphines are known react with ester substituted allene **58** to generate phosphonium dienolate **59** after the addition of phosphine to the central carbon of the allene. Intermediate **59** can undergo various reactions with different partners, including cycloaddition (Scheme 17).[28]

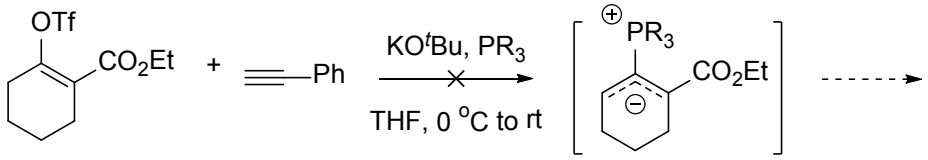


Scheme 17. Phosphine Catalyzed Acyclic Allene Reactions

Since cyclic allene **13c** shares the ester substitution with **58**, phosphine should also be able

to react with **13c** to afford cyclic phosphonium dienolate **60** and undergo further transformation. If the addition of phosphine to allene is efficient and faster than the allene trapping, the [2+2] cycloadduct **31** may not be observed. However, when triphenylphosphine or tributylphosphine were added under standard condition, a significant amount of starting material was recovered together with a complex mixture (Table 5, entries 1 and 2). Similar results were obtained in the absence of acetylene (entries 3 and 4). Based on these control experiments, phosphines were found to have a negative effect on the allene generation under standard reaction conditions.

Table 5. Control Experiments of Phoshpine Additive[a]



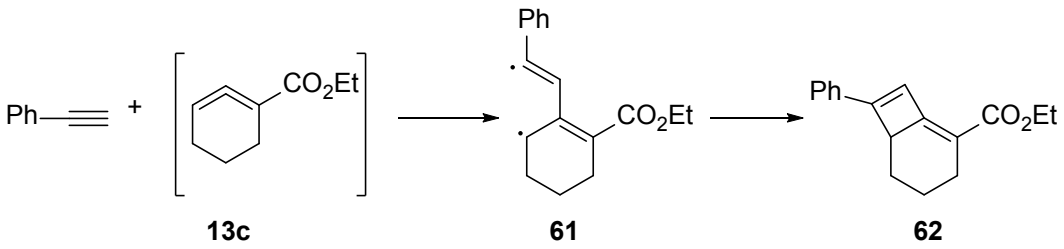
53 **60**

Entry	Phosphine[b]	Precursor	Acetylene	Observation
1	PPh_3	**53**	Phenylacetylene	**53** Recoverd
2	PBu_3	**53**	Phenylacetylene	**53** Recoverd
3	PPh_3	**53**	Absence	**53** Recoverd
4	PBu_3	**53**	Absence	**53** Recoverd

[a] Standard procedure: To a stirred mixture of precursor **53** (0.17 mmol), phosphine (0.17 mmol) and phenylacetylene (0.34 mmol), a solution of KO^{t}Bu (0.3 mmol) in THF (0.2mL) was added over 15 minutes at 0˚C. After stirring overnight, the reaction mixture was quenched with H_2O, followed by extraction with diethyl ether, drying through $MgSO_4$.

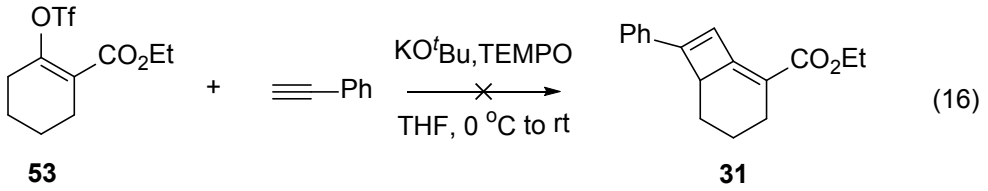
2.2.3 Mechanism Study

The mechanism of [2+2] cycloaddition was proposed to be a stepwise diradical mechanism and involving a diradical intermediate **61** (Scheme 18). [11, 18]



Scheme 18. Proposed Mechanism of [2+2] Cycloaddition between **13c** and Phenylacetylene

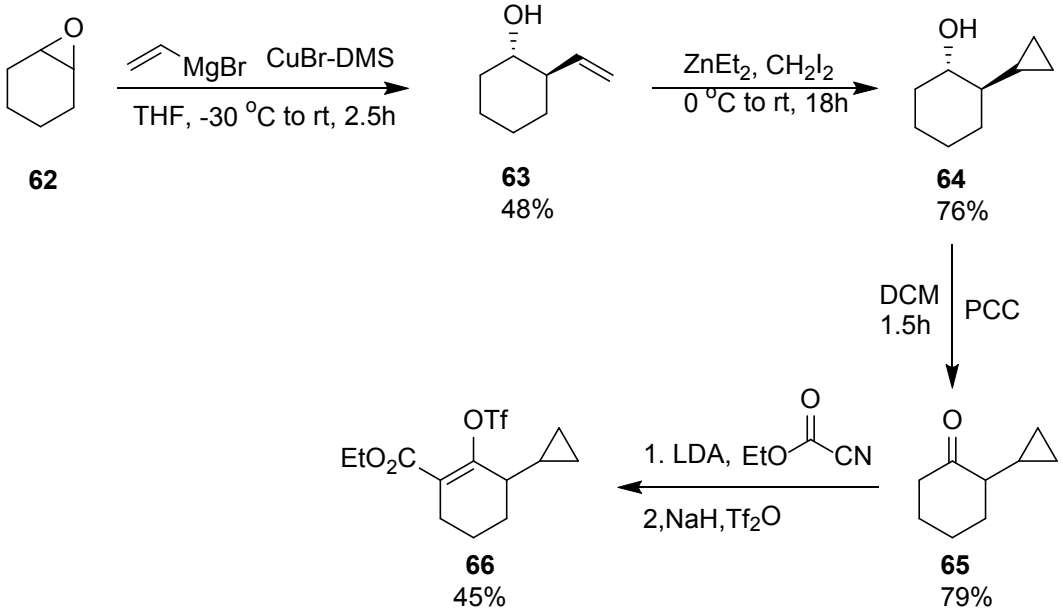
This hypothesis could be proved if the existence of diradical intermediate **61** were confirmed. The initial attempt was based on interrupting cycloaddition with external radical scavengers including TEMPO. When TEMPO (0.8 equiv.) was added under standard reaction conditions, the allene precursor **53** (1 equiv.) was fully consumed and a complex mixture resulted (Eq 16). Cycloadduct **31** was not observed by GC-MS and ^{1}H NMR.



The external radical scavengers were shown to interrupt [2+2] cycloaddition. This suggested a radical species could be involved in the allene generation or trapping. However, this experiment did not provide enough evidence of the existence of **61** to support the hypothesis.

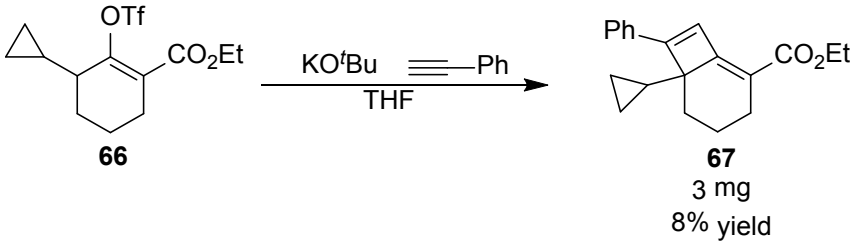
Based on the proposed mechanism, an allylic radical would be generated in intermediate **61**, which could be trapped by installing a radical clock on the allylic position. Following this idea, cyclopropane substituted precursor **66** was proposed to examine the hypothesis. The preparation of **66** started from the epoxide opening of cyclopentene oxide to afford **63** (Scheme 19).[29] The alkene was converted to cyclopropane **64** by applying the Furukawa modified Simmons–Smith reaction.[30] Compound **65** was obtained after the oxidation of **64**. The ester group was installed by enolate attack on ethyl cyanoformate to generate a cyclic ketoester, which was converted to

vinyl triflate **66** directly and the overall yield over two steps was 45%. If [2+2] cycloaddition of cyclic allene and alkyne involves radical intermediate, in the case of **66**, the cyclopropane group could undergo ring opening rearrangement, in which case other products besides [2+2] cycloadduct would be observed.



Scheme 19. Preparation of Internal Radical Trap Precursor **66**

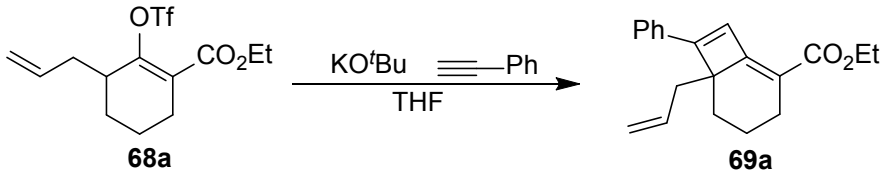
Allene precursor **66** was subjected to the standard reaction condition, and resulted in a complex mixture. After two column purifications over silica, 3 mg of [2+2] cycloadduct **67** was isolated and characterized (8% yield) (eq 17).



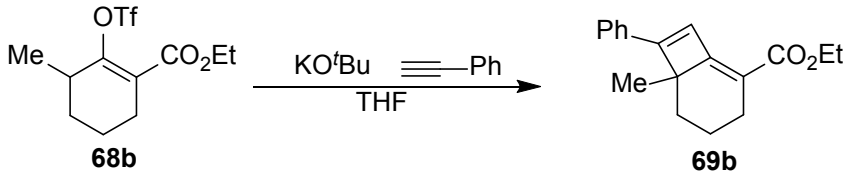
(17)

It was unclear whether the low yield resulted from partial cyclopropane ring opening to

give products that were not characterizable, or incomplete generation and trapping of allylic substituted 1,2-cyclohexadiene. To examine the effect of allylic substitution, allene precursors **68a** and **68b** were prepared under the similar procedures as **56**. When **68a** was subjected under the standard conditions, a complex mixture was obtained (eq 18). Although the corresponding diene and alkene protons were observed by ^{1}H NMR analysis; however, due to the low yield and complex reaction mixture, a pure product was unable to be obtained after two chromatographic purifications. The byproducts of the reaction could not be fully characterized, and one of major byproducts was the hydrolyzed ketoester. For **68b**, similar result was observed and the product **96b** could not be characterized due to the low yield and inseparable impurities.

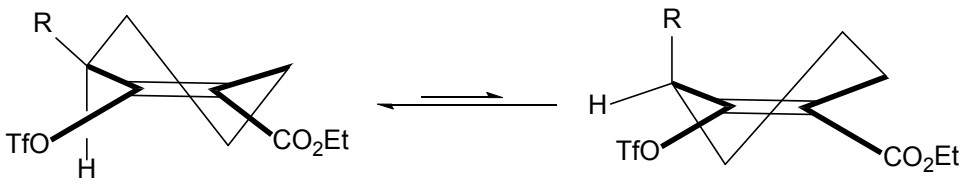


68a **69a** (18)



68b **69b** (19)

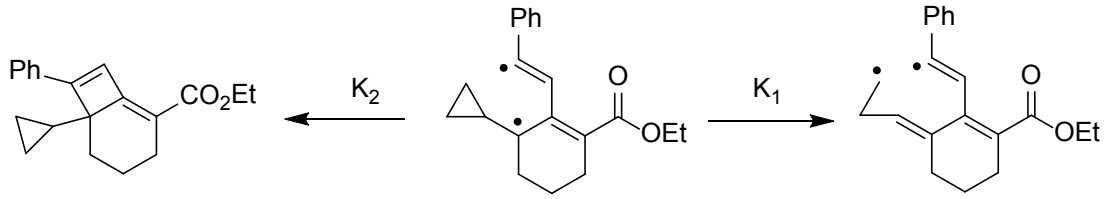
Substitution on the allylic position of the vinyl triflate precursor resulted in a low yield of cycloadduct. In the allene precursor, the allylic substituent should prefer to be in the pseudo-equatorial position to achieve the most stable conformer **70a** (Scheme 20). However, in order to generate the cyclic allene, the allylic hydrogen needs to be orientated coplanar with leaving group to form the new double bond. The conflict between these two facts may be the reason for low yield of 1,3-subsituted cyclohexa-1,2-diene.



70a **70b**

Scheme 20. Effect of Allylic Substation in Allene Generation

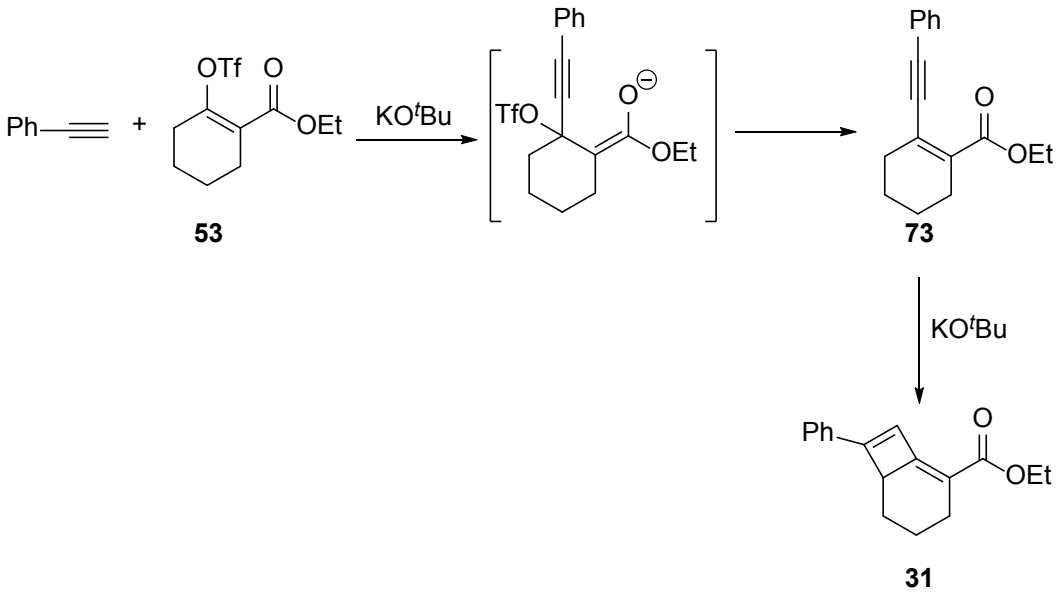
The isolation of **67** is not sufficient evidence to rule out the radical intermediate. Intermediate **70** can experience cyclopropane ring opening to generate diradical **72**, which could then undergo a variety of further reactions. Another reaction pathway of **71** is the cyclobutene ring closure to afford cycloadduct **67**. If the rate of cyclobutene ring closure (K_2) was much faster than cyclopropane ring opening (K_1), which is about 1.5 x 10^7 s^{-1},[31] **67** could be formed without cyclopropane ring opening. s



67 **71** **72**

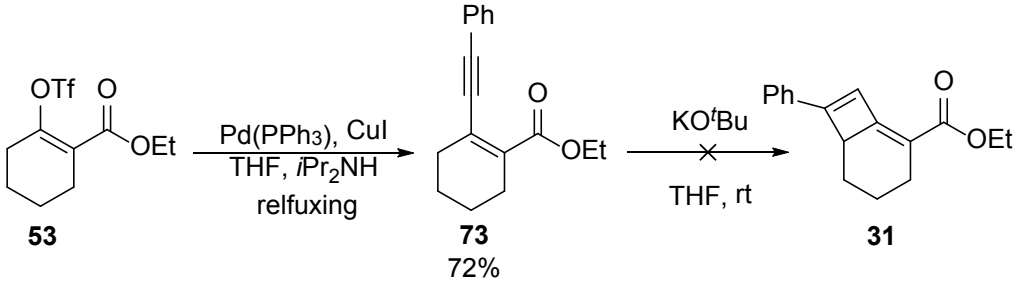
Scheme 21. Two Possible Reaction Pathways of Intermediate **70**

Another possible stepwise mechanism was considered (Scheme 22), which involved Micheal addition of acetylene anion to vinyl triflate **53**. Intermediate **73** could form after elimination of triflate. The allylic proton could then be deprotonate and may undergo nucleophilic cyclization to give cycloadduct **31**. However, this type of nucleophilic 4-endo-dig cyclization has not been reported in literature.[32]



Scheme 22. Alternative Stepwise Reaction Pathway to cycloadduct **31**

To examine this potential pathway, compound **73** was synthesized by Sonogashira coupling.[33] No cycloadduct **31** was observed, when **73** was subjected to standard reaction condition (Scheme 23). Based on this experiment, this alternative pathway could be eliminated.



Scheme 23. Examine the Alterative Reaction Pathway

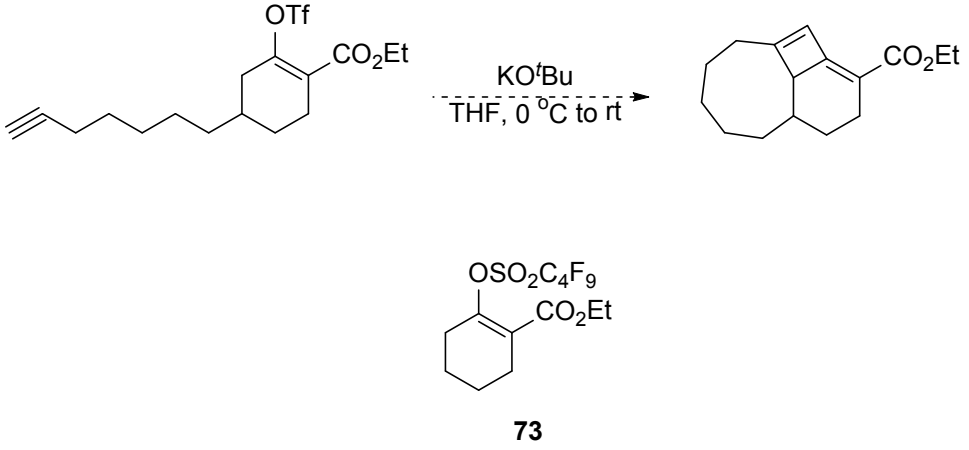
2.3 Conclusion

We have found a practical method to generate **13c** and trap it with various alkynes to afford unique [2+2] cycloadducts. Compared with previous methods, the new method can afford acceptable yields without the requirement of using a huge excess of trapping agents. Based on

substrate screening, terminal aryl alkynes are found to be good traps for **13c** and afford isolable products. The resulting cycloadducts share the carbon skeleton with certain types of natural products and have potential synthetic application. The mechanism of [2+2] cycloaddition requires further investigation to be fully understood. Due to the highly reactive nature of cyclic allenes, the yield of reaction remains to be improved and continued study is required to enhance the efficiency of this methodology.

2.4 Future plans

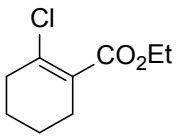
The biggest drawback of this work is the low yield of the cycloaddition. In order to improve this part, there are two possible approaches. One is increasing the rate of trapping reaction to afford more of the desired products before the allene can undergo undesired decomposition pathways. The second approach is elimination of the known side reactions. Intramolecular trapping should increase the rate of a trapping reaction. Although reaction of **59** was not successful, installation of a trapping group on other ring carbons may still be worth of considering (Scheme 24). Hydrolysis of the vinyl triflate precursor is one of the major side reactions that has been characterized. The vinyl nonaflate **73** can be used as the allene precursor and it is known to be less prone to hydrolysis to ketone.[34]



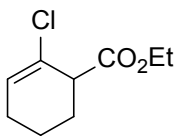
Scheme 24. Alternative Approach to Improve Yield of [2+2] Cycloaddition

2.5 Experimental

General Information. All reactions were performed out in flame-dried glassware under inert atmosphere unless otherwise stated. Anhydrous solvents and reagents were transferred via oven-dried syringes or cannulae. Solvents were distilled before use: dichloromethane and acetonitrile from calcium hydride, tetrahydrofuran, diethyl ether from sodium metal and benzophenone, and toluene from sodium metal. Other solvents and commercially available reagents were used directly from bottle unless otherwise stated. Thin layer chromatography was performed on glass plates precoated with 0.25 mm silica gel and visualized using either UV or 2.5 % *p*-anisaldehyde in AcOH-H_2SO_4-EtOH (1:3:85) with heating. Flash chromatography was performed on silica gel SI 60 (40−63 μm) with the indicated eluents. Nuclear magnetic resonance (NMR) spectra were measured in indicated deuterated solvents at 400/500 MHz for ^{1}H and 100/125 MHz for ^{13}C. For ^{1}H NMR, the residual solvent protons are used as internal standards for chemical shifts, reported in ppm, and coupling constants (*J*) were reported in Hertz (Hz). Multiplicity of signals in ^{1}H NMR spectra was described as following: broad (br), singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), etc. For ^{13}C NMR, the solvent carbons were used as internal standards for chemical shifts, reported in ppm. Infrared (IR) spectra were measured with Thermo Scientific Nicolet 8700 FT-IR or Continuum FT-IR. All samples were prepared as neat film or DCM cast film on silicon (Si) wafer and absorbances were reported in cm^{-1}. High-resolution mass spectrometry (HRMS) was performed on a double-focusing mass spectrometer with electron impact (EI) ionization source.



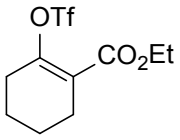
23a



23b

Ethyl 2-chlorocyclohexenecarboxylate 23a and its regioisomer 23b. To a flame-dried round bottom flask containing a magnetic stirring bar was added **27** (1.8 mL, 12.8 mmol) and CCl_4 (16

mL) under inert atmosphere. Triphenylphosphine (9.92g, 34 mmol) was poured into the stirring reaction mixture at room temperature. The reaction was heated to reflux under inert atmosphere. After 4 days at reflux, hexane (50 mL) was added to reaction flask after cool down. The reaction was allowed to stir for another day. The reaction mixture was filtered and washed with hexane (100 mL), and sticky yellow oil was formed after evaporation of solvent. Crude product was purified by flash column chromatography (1:9 EtOAc:Hexane) to afford 1.52 g of **23a** and **23b** as light yellow oil with 60% overall yield. Further distillation was applied if there was significant amount of triphenylphosphine oxide remaining. The spectral data of products agreed with literature reports.[11]

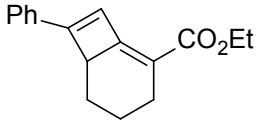


53

Ethyl 2-(trifluoromethanesulfonyloxy)cyclohexenecarboxylate 53. To a flame-dried round bottom flask containing a magnetic stirring bar was added NaH (356 mg, 8.8 mmol, 60 % dispersion in mineral oil) under inert atmosphere. DCM (24 mL) was added to the flask. The reaction mixture was cooled to 0 ˚C, followed by slow addition of **27** (1.36g, 8 mmol). After 20 to 30 min, Tf_2O (1.36 mL, 9.5 mmol) was added at same temperature dropwise. The reaction mixture was allowed to stir at 0 °C for 1 h. 1M HCl (50 mL) was added to the solution and the aqueous layer was extracted with DCM (100 mL). The organic layer passed through a short column filled with anhydrous $MgSO_4$. Upon filtration through a thin pad of SiO_2, colorless oil **53** was obtained (2.05g, 85% yield) as single product: IR (film) 2948, 2871, 2736, 1670, 1423 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.28 (q, J = 7.2 Hz , 2H), 2.51-2.45 (m, 2H), 2.43-2.37 (m, 2H), 1.82-1.75 (m, 2H), 1.70-1.63 (m, 2H), 1.33 (t, J = 7.2 Hz , 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, , 151.3, 123.3, 118.3 (q, J_{C-F} = 318 Hz), 61.6, 28.5, 26.2, 22.3, 21.1, 13.9; HRMS (EI, M^+) for $C_{10}H_{13}O_5F_3S$ calcd. 302.0436, found: *m/z* 302.0437.

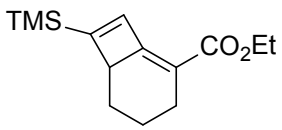
General Procedure for Cyclic Allene Generation and Trapping.

Allene precursor **53** (1 equiv.) and alkyne (2 equiv.) were added to flame-dried round bottom flask containing a magnetic stirring bar under inert atmosphere. The reaction mixture was cooled to 0 °C in ice bath, followed by the syringe addition of KO^{t}Bu in THF(0.3 mmol in 0.2 mL, 1.8 equiv.) over 10-15 min. The reaction was allowed to stir in ice bath overnight and quenched with distilled waster (2-3mL). The aqueous layer was extracted with ether (3 x 15 mL). The combined organic layer was washed with brine solution (5 mL) and passed through a short column filled with anhydrous $MgSO_4$. The solvent was removed by rotary evaporation and the crude product was purified by flash column chromatography to afford the desired product.



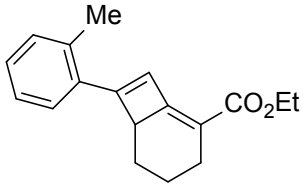
31

Ethyl 7-phenylbicyclo[4.2.0]octa-1,7-diene-2-carboxylate 31. The reaction was performed with phenylacetylene following the general procedure. Flash column chromatography (1:19 EtOAc:Hexane, R_f= 0.2), **31** (21 mg, 41%) was isolated as a single product: IR (film) 2933, 2858, 1698,1679, 1282 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.47 (m, 2H), 7.41-7.36 (m, 2H), 7.36-7.31 (m, 1 H), 6.90 (br d, J = 1.3 Hz, 1H), 4.31-4.24 (ABX$_3$, H_A= 4.29 ppm, H_B= 4.26 ppm, $J_{A\text{-}B}$ = 17.8 Hz, $J_{A\text{-}X}$= $J_{B\text{-}X}$ = 7.2 Hz; simulated by spin-works 2.5.5. 2H), 3.42 (br dd, J = 3.4, 11.5 Hz, 1H), 2.54 (dd, J = 7.0, 18.5 Hz, 1H), 2.40-2.30 (m, 1H), 2.18-2.07 (m, 2H), 1.68-1.57 (m, 1H), 1.35 (t, J = 7.2 Hz, 3H), 1.28-1.25 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 158.5, 153.1, 133.4, 129.6, 128.9, 128.9, 126.7, 112.0, 60.1, 47.8, 26.9, 25.0, 23.1, 14.8; HRMS (EI, M$^+$) for $C_{17}H_{18}O_2$ calcd. 254.1307, found: *m/z* 254.1306.



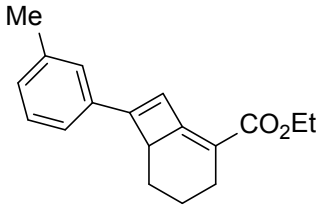
54a

Ethyl 7-trimethylsilylbicyclo[4.2.0]octa-1,7-diene-2-carboxylate 54a. The reaction was performed with ethynyltrimethylsilane following the general procedure. Flash column chromatography (1:19 EtOAc:Hexane, R_f= 0.5) gave an inseparable mixture. After another column purification (1 :1 DCM:Hexane, R_f= 0.3), **54a** (8.2 mg, 10%) was isolated as a single product: IR (film) 2938, 1734, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, *J* = 2 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.13 (br dd, *J* = 4.5, 12 Hz, 1H), 2.43 (dd, *J* = 6.8, 18.8 Hz, 1H), 2.23 (ddd, *J* = 8, 10.5, 18.8 Hz, 1H), 2.08-1.97 (m,1H), 1.91-1.82 (m, 1H), 1.55-1.44 (m, 1H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.05-0.94 (m, 1H), 0.14 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 167.7, 154.9, 146.9, 110.3, 60.0, 50.9, 27.5, 24.7, 23.2, 14.7, -1.67; HRMS (EI, M^+) for $C_{14}H_{22}O_2Si$ calcd. 250.1489, found: *m/z* 250. 1388.



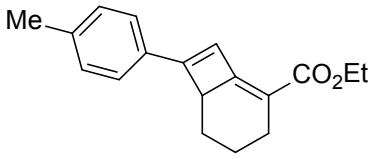
54b

Ethyl 7-(2-methylphenyl)bicyclo[4.2.0]octa-1,7-diene-2-carboxylate 54b. The reaction was performed with 2-ethynyltoluene following the general procedure. Flash column chromatography (1:1 DCM:Hexane, R_f= 0.5 in 100% DCM), **54b** (13 mg, 29%) was isolated as a single product: IR (film) 2978, 2934, 2861, 1698, 1247 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.38 (m, 1H), 7.26-7.20 (m, 3H), 6.79 (br s, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 3.48 (br dd, *J* = 3.9, 11.8 Hz, 1H), 2.55 (dd, *J* = 7.0, 18.2 Hz, 1H), 2.46 (s, 3H), 2.42-2.31 (m, 1H), 2.22-2.06 (m, 2H), 1.71-1.58 (m, 1H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.29-1.24 (m, 1H); ^{13}C NMR (125 MHz, CD_2Cl_3) δ 167.9, 158.4, 153.8, 138.9, 132.4, 132.1, 131.3, 129.5, 129.0, 126.3, 112.2, 60.1, 49.4, 27.6, 25.3, 23.3, 22.1, 14.7; HRMS (EI, M^+) for $C_{18}H_{20}O_2$ calcd. 268.1463, found: *m/z* 268.1463.



54c

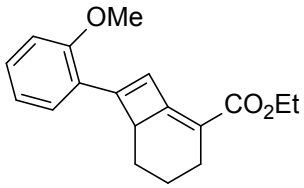
Ethyl 7-(3-methylphenyl)bicyclo[4.2.0]octa-1,7-diene-2-carboxylate 54c. The reaction was performed with 3-ethynyltoluene following the general procedure. Flash column chromatography (2:1 DCM:Hexane, R_f = 0.6), **54c** (11 mg, 24%) was isolated as a single product: IR (film) 2977, 2932, 2859, 1699, 1603, 1271 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28-7.25 (m, 2H), 7.24-7.22 (m, 1H), 7.14-7.10 (m, 1H), 6.85 (d, *J* = 2 Hz, 1H), 4.20 (m, 2H), 3.36 (ddd, *J* = 2, 4.8, 12 Hz, 1H), 2.50 (dd, *J* = 7.2, 18 Hz, 1H), 2.37-2.22 (m, 4H), 2.15-2.02 (m, 2H), 1.64-1.55 (m, 1H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.26-1.20 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 158.7, 153.2, 138.6, 133.3, 130.5, 128.8, 128.7, 127.4, 124.0, 111.8, 60.0, 47.8, 27.0, 25.0, 23.1, 21.6, 14.8; HRMS (EI, M^+) for $C_{18}H_{20}O_2$ calcd. 268.1463, found: *m/z* 268.1463.



54d

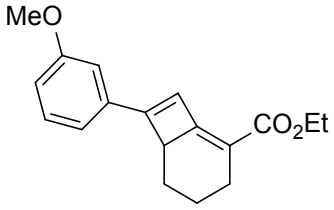
Ethyl 7-(4-methylphenyl)bicyclo[4.2.0]octa-1,7-diene-2-carboxylate 54d. The reaction was performed with 4-ethynyltoluene following the general procedure. Flash column chromatography (1:19 EtOAc:Hexane, R_f = 0.25), **54d** (10 mg, 22%) was isolated as a single product: IR (film) 3031, 2936, 2850, 1726, 1606, 1266 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8 Hz, 2H), 7.22 (d, *J* = 8 Hz, 2H), 6.87 (d, *J* = 2 Hz, 1H), 4.27 (m, 2H), 3.42 (ddd, *J* = 2, 4.8, 7.2 Hz, 1H), 2.56 (dd, *J* = 7.2, 18.8 Hz, 1H), 2.43-2.32 (m, 4H), 2.20-2.08 (m, 2H), 1.69-1.62 (m, 1H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.32-1.26 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 158.4, 153.1, 139.7, 130.4, 129.4, 127.7, 126.6, 111.2, 59.8, 47.6, 26.7, 24.8, 22.9, 21.6, 14.6; HRMS (EI, M^+) for

$C_{18}H_{20}O_2$ calcd. 268.1463, found: *m/z* 268.1458.



54e

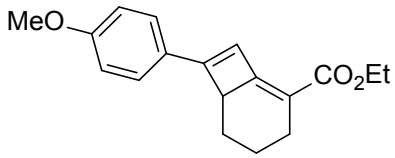
Ethyl 7-(2-methoxyphenyl)bicyclo[4.2.0]octa-1,7-diene-2-carboxylate 54e. The reaction was performed with 2-ethynylanisole following the general procedure. Flash column chromatography (1:9 EtOAc:Hexane, R_f= 0.25), **54e** (20 mg, 21%) was isolated as a single product: IR (film) 2933, 2838, 1696,1269,1251 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.29 (m, 2H), 6.98-6.91 (m, 3H), 4.24 (q, *J* = 7.2 Hz, 2H), 3.92 (s, 3H), 3.43 (ddd, *J* = 1.8, 4.4, 12 Hz, 1H), 2.52 (dd, *J* = 8, 19 Hz, 1H), 2.39-2.28 (m, 1H), 2.18-2.04 (m, 2H), 1.67-1.57 (m, 1H), 1.34 (t, *J* = 7.2Hz, 3H), 1.26-1.21 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 159.3, 155.1, 154.8, 132.7, 130.9, 129.2, 122.4, 120.6, 111.4, 110.9, 69.9, 55.5, 48.7, 27.3, 25.0, 23.2, 14.8; HRMS (EI, M^+) for $C_{18}H_{20}O_3$ calcd. 284.1412, found: *m/z* 284.1417.



54f

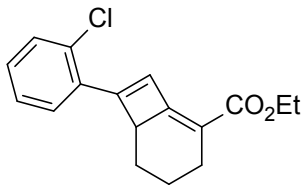
Ethyl 7-(3-methoxyphenyl)bicyclo[4.2.0]octa-1,7-diene-2-carboxylate 54f. The reaction was performed with 3-ethynylanisole following the general procedure. Flash column chromatography (1:14 to 1:9 EtOAc:Hexane, R_f= 0.55 in1:9 EtOAc:Hexane), **54f** (8 mg, 17%) was isolated as a single product: IR (film) 2933, 2857, 1698,1275 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, *J* = 8 Hz, 1H), 7.09 (d, *J* = 8 Hz, 1H), 7.01-6.99 (m, 1 H), 6.91-6.88 (m, 2H), 4.24 (q, *J* = 7.2 Hz, 2H), 3.84 (s, 3H), 3.39 (dd, *J* = 4, 12 Hz, 1H), 2.54 (dd, *J* = 7.2, 18.8 Hz, 1H), 2.40-2.30 (m, 1H),

2.17-2.06 (m, 2H), 1.69-1.56 (m, 1H), 1.34 (t, J = 7.2 Hz, 3H), 1.27-1.23 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 160.0, 158.4, 152.9, 134.6, 129.9, 129.2, 119.5, 115.5, 112.2, 111.8, 60.1, 55.5, 47.8, 26.9, 25.0, 23.1, 14.8; HRMS (EI, M^+) for $C_{18}H_{20}O_3$ calcd. 284.1412, found: *m/z* 284.1408.



54g

Ethyl 7-(4-methoxyphenyl)bicyclo[4.2.0]octa-1,7-diene-2-carboxylate 54g. The reaction was performed with 4-ethynylanisole following the general procedure. Flash column chromatography (1:19 EtOAc:Hexane, R_f= 0.2), **54g** (20 mg, 40%) was isolated as a single product: IR (film) 2934, 2839, 1697,1602, 1496,1252 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 6.77 (d, J = 1.9 Hz, 1H), 4.23 (m, 2H), 3.84 (s, 3H), 3.37 (ddd, J = 1.9, 4.0, 11.6 Hz, 1H), 2.53 (dd, J = 7.2, 18.4 Hz, 1H), 2.34 (ddd, J = 7.2, 10.8, 18.4 Hz, 1H), 2.18-2.04 (m, 2H), 1.70-1.58 (m, 1H), 1.34 (t, J = 7.2 Hz, 3H), 1.29-1.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 160.7, 158.2, 153.2, 128.2, 126.4, 126.1, 114.2, 110.5, 59.7, 55.3, 47.6, 26.7, 24.7, 22.9, 14.5; HRMS (EI, M^+) for $C_{18}H_{20}O_3$ calcd. 284.1412, found: *m/z* 284.1405.

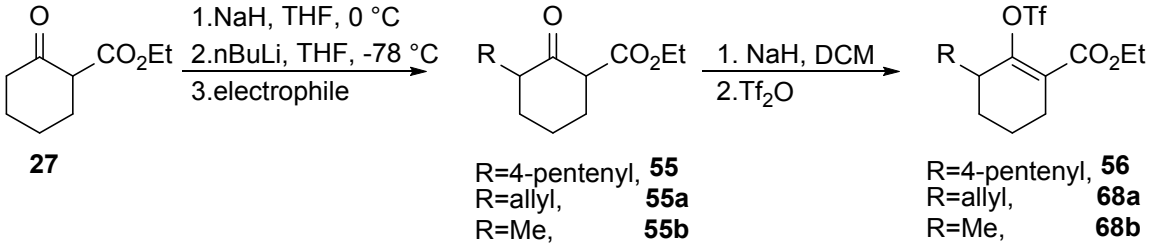


54h

Ethyl 7-(2-chlorophenyl)bicyclo[4.2.0]octa-1,7-diene-2-carboxylate 54h. The reaction was performed with 1-chloro-2-ethynylbenzene following the general procedure. Flash column chromatography (1:1 DCM:Hexane, R_f= 0.2) gave an inseparable mixture. After another column purification (100% DCM, R_f= 0.5), **54h** (8 mg, 8%) was isolated as a single product: IR (film)

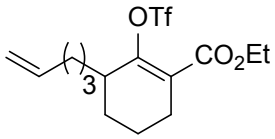
3060, 2979, 2862, 1698, 1276, 1220 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 7.45 (dd, *J* = 1.9, 7.5 Hz, 1H), 7.41 (dd, *J* = 1.5, 7.5 Hz, 1H), 7.29 (dt, *J* = 1.5, 7.5 Hz 1H), 7.25 (dt, *J* = 1.9, 7.5 Hz, 1H), 7.15 (d, *J* = 1.9 Hz, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 3.49 (dd, *J* = 4.8, 12 Hz, 1H), 2.51 (dd, *J* = 7.0 , 19 Hz, 1 H), 2.33 (ddd, *J* = 8, 10.5, 19 Hz, 1H), 2.20-2.14 (m, 1H), 2.14-2.07 (m, 1H), 1.70-1.59 (m, 1H), 1.32 (t, *J* = 7 Hz, 3H), 1.25-1.21 (m, 1H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 168.2, 155.6, 153.6, 135.0, 134.7, 131.9, 131.5, 130.7, 130.6, 127.7, 114.1, 60.6, 49.8, 27.9, 25.8, 23.7, 15.1; HRMS (EI, M^+) for $C_{17}H_{17}O_2{}^{35}Cl$ calcd. 288.0917, found: *m/z* 288.0918.

Standard Procedure for the Preparation of Allylic Subsituted Allene Precursors.



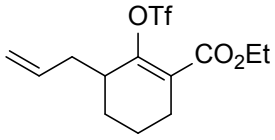
To a flame-dried round bottom flask containing a magnetic stirring bar was added **27** (1 equiv.) and THF (0.5 M). The solution was cooled to 0 °C, followed by the addition of NaH (1.2 equvi., 60 % dispersion in mineral oil). The mixture was allowed to stir for 20 min and cooled to -78 °C. A solution of *n*Buli in hexane (1.2-1.3 equiv.) was added slowly into the mixture. The reaction mixture was allowed to stir for another 10-20 min, followed by the addition of electrophile (1.5 equiv.) The reaction was warmed up and monitored by TLC. NH_4Cl was added to quench the reaction upon completion. The mixture was extracted with diethyl ether and the combined organic layer was passed through a short column filled with anhydrous $MgSO_4$. After filtration, the solvent was removed by rotary evaporation and the crude product was purified by flash column chromatography to afford alkylated ketoester **55**, which is a mixture of tautomers.

To a flame-dried round bottom flask containing a magnetic stirring bar was added NaH (1.1 equiv, 60 % dispersion in mineral oil) under inert atmosphere. DCM (0.3M) was added to the flask. The reaction mixture was cooled to 0 ˚C, followed by slow addition of **55** (1 equiv.). After 20 to 30 min, Tf_2O (1.2 equiv.) was added at same temperature dropwise. Reaction mixture was allowed to stir at 0 °C for one hour. 1M HCl was added to the solution and the aqueous layer was extracted with DCM. The organic layer passed through a short column filled with anhydrous $MgSO_4$. After filtration, the solvent was removed by rotary evaporation and the crude product was purified by flash column chromatography to afford vinyl triflate precursors **56**, **68a**, **68b**.



56

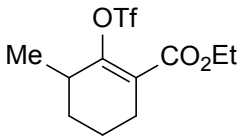
Ethyl 3-(4-pentenyl)-2-(trifluoromethanesulfonyloxy)cyclohexenecarboxylate 56. The reaction was performed with 4-pentenyl bromide as electrophile following the general procedure. After flash column chromatography (1:1 DCM:Hexane, R_f= 0.2), **54h** (48 mg, 5% over 2 steps) was isolated as a single product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 ($AFMX_2$, *J*= 17,0, 10.2, 6.8 Hz, 1H), 5.06-4.97 (m, 2H), 4.34-4.22 (m, 2H), 2.61-2.35 (m, 4H), 2.13-2.03 (m, 2H), 1.94-1.85 (m, 2H), 1.83-1.57 (m, 5H), 1.36-1.30 (t, *J*= 7.2 Hz, 3H).



68a

Ethyl 3-(2-propenyl)-2-(trifluoromethanesulfonyloxy)cyclohexenecarboxylate 68a. The reaction was performed with allyl bromide as electrophile following the general procedure. After flash column chromatography (1:1 DCM: Hexane, R_f= 0.3), product contained some impurities. After another column purification (1:9 EtOAc:Hexane, R_f= 0.45), **68a** (1.04 mg, 58% over 2

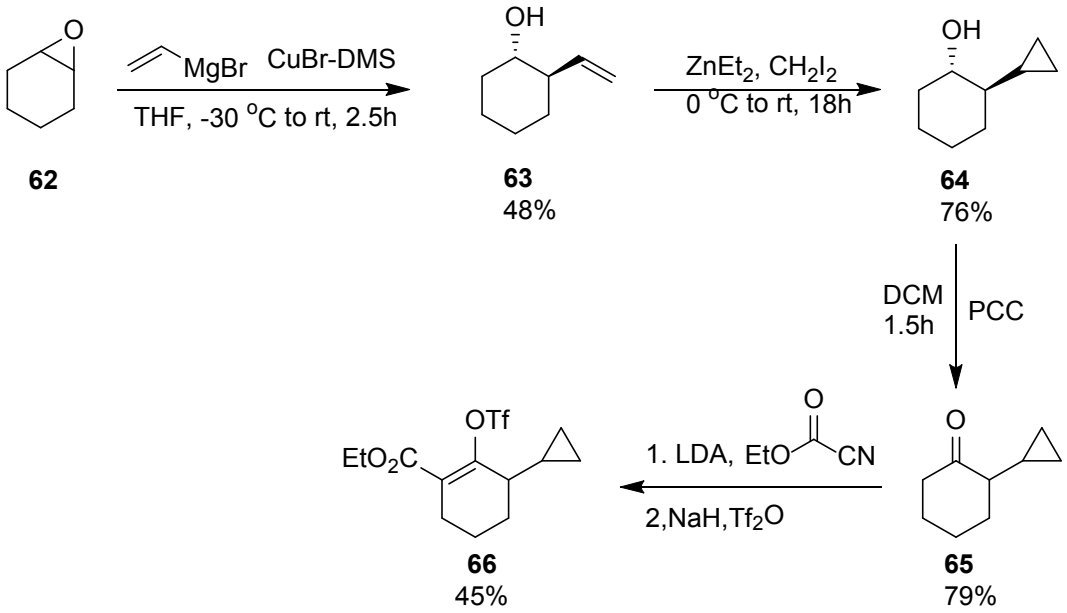
steps) was isolated as a single product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74-5.61 (m, 1H), 5.09-5.03 (m, 2H), 4.30-4.18 (m, 2H), 2.60-2.32 (m, 4H), 2.16-2.07 (m, 1H), 1.85-1.73 (m,1H), 1.70-1.53 (m, 3H), 1.29 (t, *J*= 7.2 Hz, 3H).



68b

Ethyl 3-methyl-2-(trifluoromethanesulfonyloxy)cyclohexenecarboxylate 68b. The reaction was performed with iodomethane as electrophile following the general procedure. After flash column chromatography (1:9 EtOAc:Hexane, R_f = 0.45), product contained some impurities. After another column purification (1:1 DCM:Hexane, R_f= 0.3), **54h** (0.85 g, 54% over two steps) was isolated as a single product: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.31-4.26 (m, 2H), 2.66-2.40 (m, 4H), 2.00-1.93 (m,1H), 1.83-1.59 (m, 3H), 1.54-1.47 (m, 1H), 1.35 (t, *J*= 7.2 Hz, 3H), 1.21 (d, *J*= 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 154.7, 123.4, 118.3 (q, $J_{C\text{-}F}$ = 318 Hz), 61.6, 33.2, 31.1, 26.9, 18.8, 17.8, 13.9.

Procedure for the Preparation of Allene precursor 66.



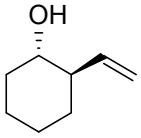
62

63
48%

64
76%

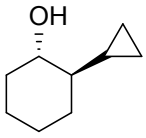
65
79%

66
45%



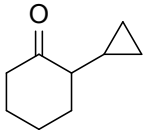
63

2-Ethenylcyclohexanol 63. To a flame-dried round bottom flask containing a magnetic stirring bar was added CuBr·DMS (0.412 g, 2 mmoles) and THF (52 mL). The solution was cooled to -30 °C, followed by the addition of vinylmagnesium bromide solution (34 mL, 0.77 M in THF, 26 mmol). The mixture was allowed to stir for 20 minutes, followed by the addition of cyclopentene oxide (2 mL, 20 mmoles). The solution turned dark yellow and was warmed up to room temperature. After 2 h, the reaction was complete and was quenched with NH_4Cl (aq). The mixture was extracted with diethyl ether and the combined organic layer was washed with brine solution and passed through a short column filled with anhydrous $MgSO_4$. After filtration, the solvent was removed by rotary evaporation and the crude product was purified by flash column chromatography (1:9 EtOAc:Hexane, R_f= 0.15) to afford **63** (1.2 g, 48%) as a single product. Characterization data is available through the literature. The spectral data of products agreed with literature reports.[35]



64

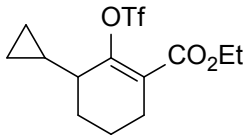
2-Cyclopropylcyclohexanol 64. To a flame-dried round bottom flask containing a magnetic stirring bar was added **63** (1.3 g, 10.5 mmol) and CH_2I_2 (2.5 mL, 31 mmol). The solution was cooled to 0 °C, followed by the addition of Et_2Zn (31 mL, 31 mmol, 1M in hexane). The reaction mixture was allowed to warm up to room temperature and stirred for 1.5 h. Subsequently, air was blown through the mixture for 30 min then the solution was allowed to stir overnight. Toluene (20 mL) was added to the mixture and the organic layer was washed with NaOH solution (aq, 3 x 20 mL). The combined aqueous layer was back extracted with Et_2O (3 x 50 mL). The combined organic layer was washed with brine solution and passed through a short column filled with anhydrous Na_2SO_4. After filtration, the solvent was removed by rotary evaporation and the crude product was purified by flash column chromatography (1:9 EtOAc:Hexane, R_f= 0.2) to afford **64** (1.1 g, 76%) as a single product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.51-3.41 (m, 1H), 2.30 (s, 1H), 2.02-1.96 (m, 1H), 1.83-1.64 (m, 3H), 1.35-1.03 (m, 4H), 0.62-0.31 (m, 5H), 0.05-0.00 (m,1H).



65

2-Cyclopropylcyclohexanone 65. To a round bottom flask containing a magnetic stirring bar was added **64** (1.1 g, 7.9 mmol) and DCM (16 mL). Pyridinium chlorochromate (2.9 g, 13.4 mmol) was added to the reaction. The reaction mixture was allowed to stir at room temperature. After one hour, diethyl ether (20 mL) was added to the reaction flask, the organic solution was poured to another container. The remaining solid was washed with extra ether (3 x 20 mL). The

combined organic solution was filtered through a plug of silica gel. After filtration, the solvent was removed by rotary evaporation and afford **65** (0.86g, 79%) as a single product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52-2.42 (m, 1H), 2.34-2.24 (m, 1H), 2.19-2.07 (m, 1H), 2.06-1.96 (m, 1H), 1.95-1.84 (m, 1H), 1.83-1.71 (m, 1H), 1.70-1.53 (m, 3H), 1.10-0.90 (m, 1H), 0.67-0.59 (m, 1H), 0.52-0.44 (m, 1H), 0.18-0.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.0, 56.2, 41.7, 33.7, 27.9, 24.5, 11.2, 4.3, 2.5.

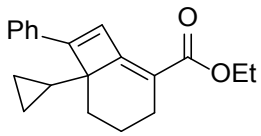


66

Ethyl 3-cyclopropyl-2-(trifluoromethanesulfonyloxy)cyclohexenecarboxylate 66. A solution of LDA (0.44 mmol) in ether (4 mL) was prepared in a flame-dried round bottom flask containing a magnetic stirring bar under inert atmosphere. 2-Cyclopropylcyclohexen-1-one **65** (56 mg, 0.4 mmol) was added into the solution at -78 °C via syringe. The reaction was allowed to stir over 40 min at -78 °C. Ether (3 mL) was added to the reaction mixture, followed by addition of ethyl cyanoformate at -78 °C. After 1 h, the reaction was warmed up to 0 °C and allowed to stir another 15 h. The reaction was quenched with H_2O (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layer was washed with brine solution (5 mL) and passed through a short column filled with anhydrous $MgSO_4$. After filtration, the solvent was removed by rotary evaporation and the crude product was carried to next step without further purification.

To a flame-dried round bottom flask containing a magnetic stirring bar was added NaH (17.6 g, 0.44 mmol, 60% in mineral oil) and DCM (2 mL) under inert atmosphere. The crude ketoester precursor was added into the stirring reaction mixture via syringe at 0 °C. After stirring over 15 min, trifluoromethanesulfonic anhydride (0.080 mL, 0.48 mmol) was added dropwise to the solution via syringe at 0 °C. The reaction was warmed up and allowed to stir at 0 °C for another

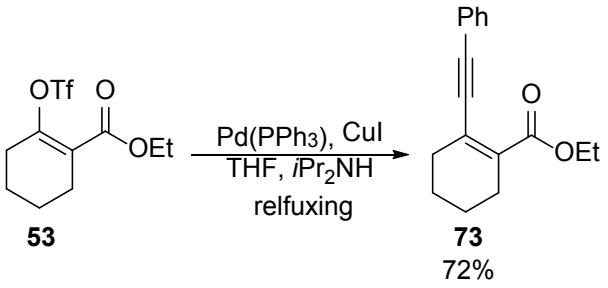
2 h. The reaction was quenched with 1M HCl (3 mL) and extracted with DCM (3 x 10 mL). The combined organic layer was washed with brine solution (5 mL) and passed through a short column filled with anhydrous $MgSO_4$. After filtration, the solvent was removed by rotary evaporation and the crude product was purified by flash column chromatography (1:1DCM:Hexane, R_f = 0.3) to afford **53c** (62 mg, 45% over 2 steps) as a single product: IR (microscope) 2945, 1726, 1661, 1211 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.26 (m, 2H), 2.64-2.46, (m, 2H), 1.92-1.6 (m, 5H), 1.32 (t, *J* = 7.2 Hz, 3H), 0.92-0.83 (m, 1H), 0.72-0.63 (m, 1H), 0.54-0.45 (m, 2H), 0.18-0.08 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 153.7, 123.6, 118.4 (q, $J_{c\text{-}f}$ = 317 Hz), 61.8, 43.0, 29.3, 27.3, 18.8, 14.9, 14.1, 5.5, 2.6; HRMS (EI, M^+) for $C_{13}H_{17}O_5F_3S$ calcd. 342.0759, found: *m/z* 342.0748.



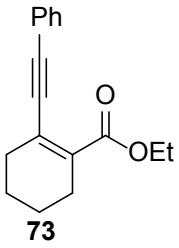
60

Ethyl 6-cyclopropyl-7-phenylbicyclo[4.2.0]octa-1,7-diene-2-carboxylate 60. The reaction was performed with phenylacetylene following general procedure on page 60. Flash chromatography (1:14 EtOAc:Hexane, R_f = 0.25) gave an inseparable mixture. After another column purification (100% toluene, R_f = 0.2), **60** (3 mg, 8%) was isolated as a single product: IR (film) 3078, 2979, 2936, 2852, 1697, 1483, 1268 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52-7.48 (m, 2H), 7.42-7.32 (m, 3H), 6.90 (s, 1H), 4.23 (m, 2H), 2.47-2.40 (m, 2H), 2.38-2.28 (m, 1H), 2.23-2.16 (m, 1H), 2.08-2.00 (m, 1H), 1.72 (dt, *J* = 13, 4.6 Hz, 1H), 1.35 (t, *J* = 7 Hz, 3H), 1.26-1.18 (m, 1H), 0.69-0.6 (m, 1H), 0.44-0.31 (m, 2H), 0.17-0.08 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 160.1, 154.9, 132.6, 129.6, 129.2, 128.7, 126.8, 112.3, 59.8, 54.4, 32.2, 23.2, 20.8, 15.7, 14.5, 6.5, 1.7; HRMS (EI, M^+) for $C_{20}H_{22}O_2$ calcd. 294.1620, found: *m/z* 294.1620.

Procedure for the Preparation of 73.



53 **73** 72%



73

Ethyl 2-(2-phenylethynyl)cyclohexenecarboxylate 73. To a flame-dried round bottom flask containing a magnetic stirring bar was added **53** (320 mg, 1.25 mmol), $Pd(PPh_3)_4$ (71 mg, 0.062 mmol) and CuI (36 mg, 0.18 mmol) under inert atmosphere. A solution of phenylacetylene (0.21 mL, 1.86 mmol) in $i Pr_2NH$ (0.83 mL) and THF (0.25 mL) was added into the reaction mixture at room temperature. The reaction mixture was allowed to stir at reflux overnight. The reaction was quenched with H_2O and extracted with diethyl ether. The combined organic layer was filtered through Celite® and passed through a short column filled with anhydrous $MgSO_4$. After filtration, the solvent was removed by rotary evaporation and the crude product was purified by flash column chromatography (1:1 DCM:Hexane, R_f = 0.2) afforded a mixture of product and trace impurity. After another column purification (1:3 Hexane: Toluene, R_f = 0.2) to afford **73** (230 mg, 72%) as a single product: IR (film) 3078, 2979, 2936, 2852, 1697, 1483, 1268 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48-7.44 (m, 2H), 7.33-7.29 (m, 3H), 4.26 (q, J = 7 Hz, 2H), 2.46-2.40 (m, 4H), 1.71-1.65 (m, 4H), 1.32 (t, J = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 134.7, 131.8, 128.5, 128.4, 128.2, 123.7, 96.2, 89.7, 60.7, 32.5, 26.6, 22.1, 21.9, 14.6; HRMS (EI, M^+) for $C_{17}H_{18}O_2$ calcd. 254.1306, found: *m/z* 254.1303.

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21 Molecular mechanics calculations (all-atom MM method employing the Tripos 5.2 force field) were carried out using Ghemical (ver. 2.99.2). I thank Mark Miskolzie (Nuclear Magnetic Resonance Laboratory, Department of Chemistry, University of Alberta) for assistance in carrying out these calculations.

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20 Professor Derrick L. J. Clive, personal communication.

21 Molecular mechanics calculations (all-atom MM method employing the Tripos 5.2 force field) were carried out using Ghemical (ver. 2.99.2). I thank Mark Miskolzie (Nuclear Magnetic Resonance Laboratory, Department of Chemistry, University of Alberta) for assistance in carrying out these calculations.

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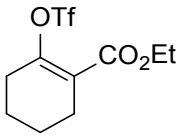
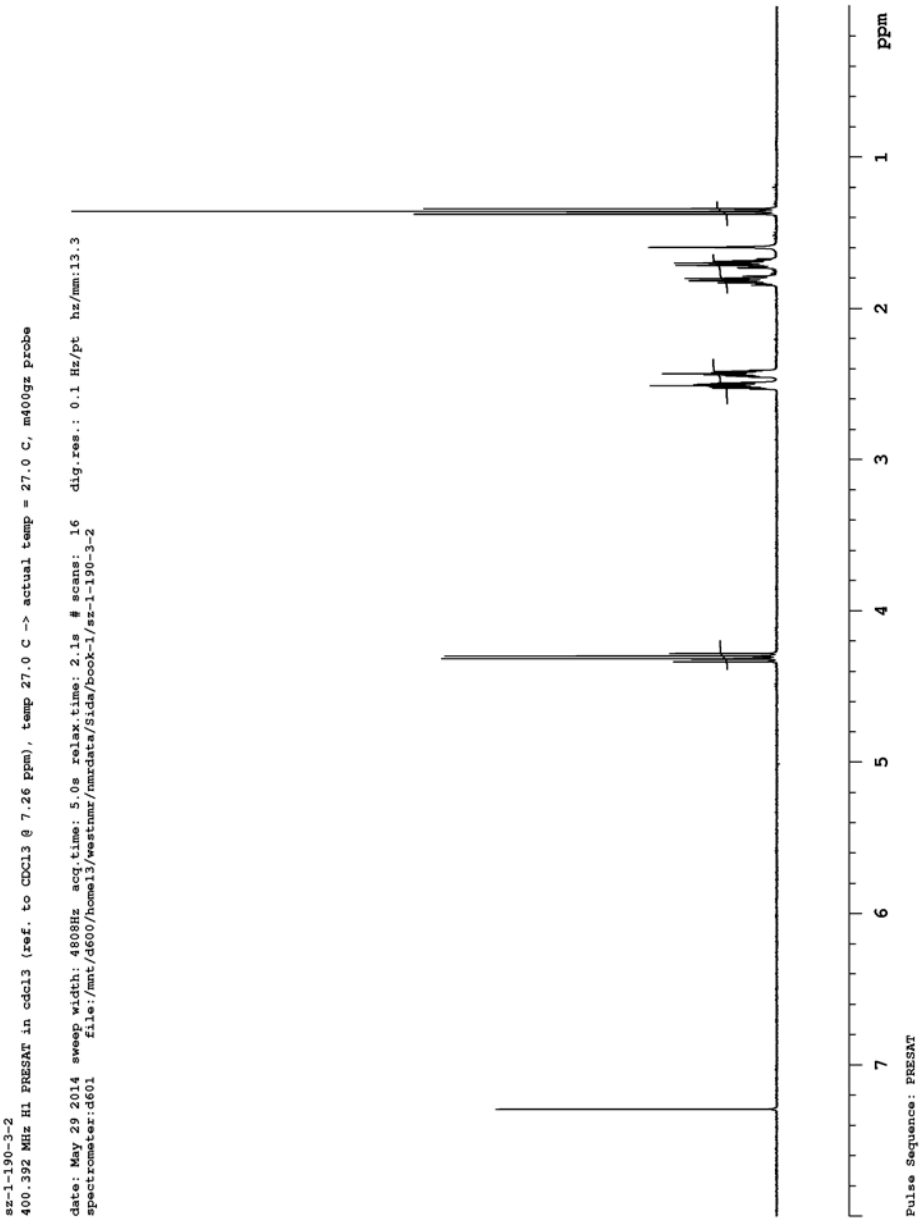
Appendix:

Selected NMR spectra (Chapter 2)


OTf
CO2Et

53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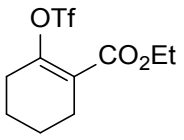
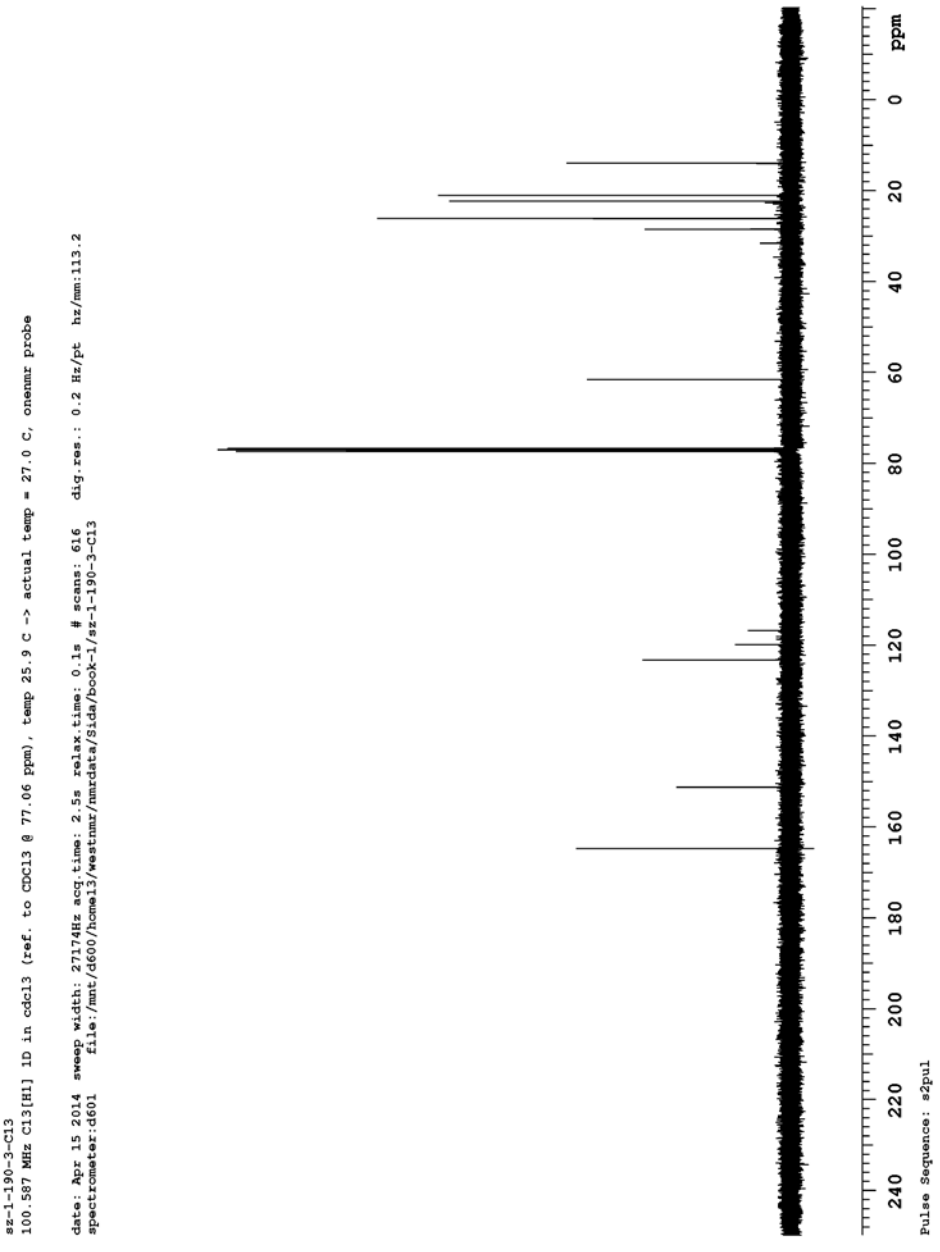
date: May 29 2014 sweep width: 4808Hz acq.time: 5.0s relax.time: 2.1s # scans: 16 dig.res.: 0.1 Hz/pt hz/mm:13.3
spectrometer:d601 file:/mnt/d600/home13/westnmr/nmrdata/Sida/book-1/sz-1-190-3-2
7
6
5
4
3
2
1
ppm
Pulse Sequence: PRESAT


OTf
CO2Et

53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date: Apr 15 2014 sweep width: 27174Hz acq.time: 2.5s relax.time: 0.1s # scans: 616 dig.res.: 0.2 Hz/pt hz/mm:113.2
spectrometer::d601 file:/mnt/d600/home13/westnmr/nmrdata/Sida/book-1/sz-1-190-3-C13
240 220 200 180 160 140 120 100 80 60 40 20 0 ppm
Pulse Sequence: s2pul

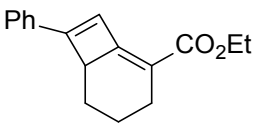
53

sz-1-190-3-2
376.708 MHz F19 1D in cdcl3, temp 27.0 C -> actual temp = 27.0 C, m400gz probe

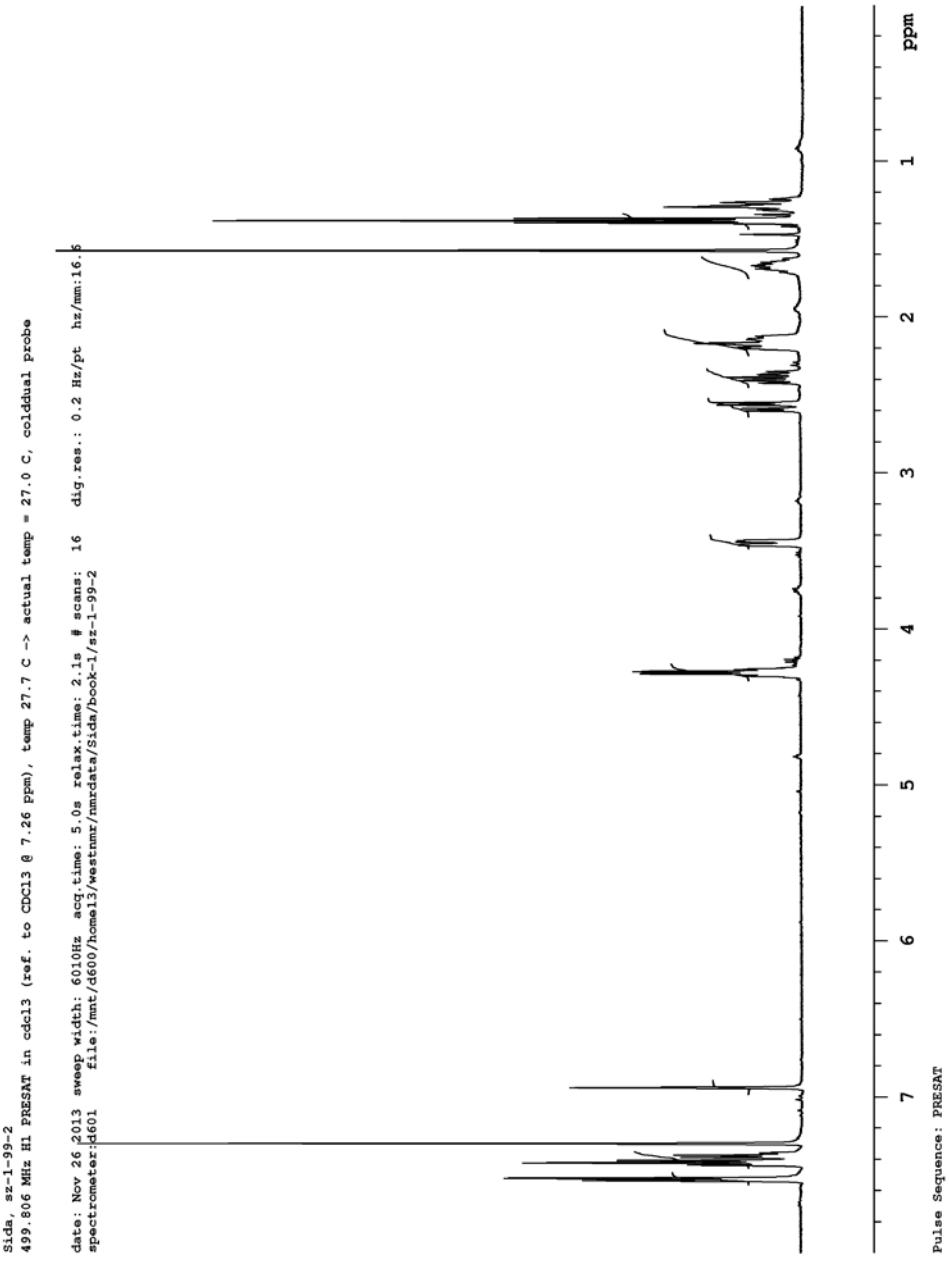
data: May 29 2014 sweep width: 79365Hz acq.time: 0.8s relax.time: 4.2s # scans: 32 dig.res.: 0.3 Hz/pt hz/mm:33.6
spectrometer:d601 file:/mnt/d600/home13/westnmr/nmrdata/Sida/book-1/sz-1-190-3-2-F19

-62 -64 -66 -68 -70 -72 -74 -76 -78 -80 ppm

Pulse Sequence: s2pul


Ph
CO2Et

31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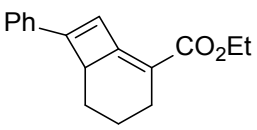
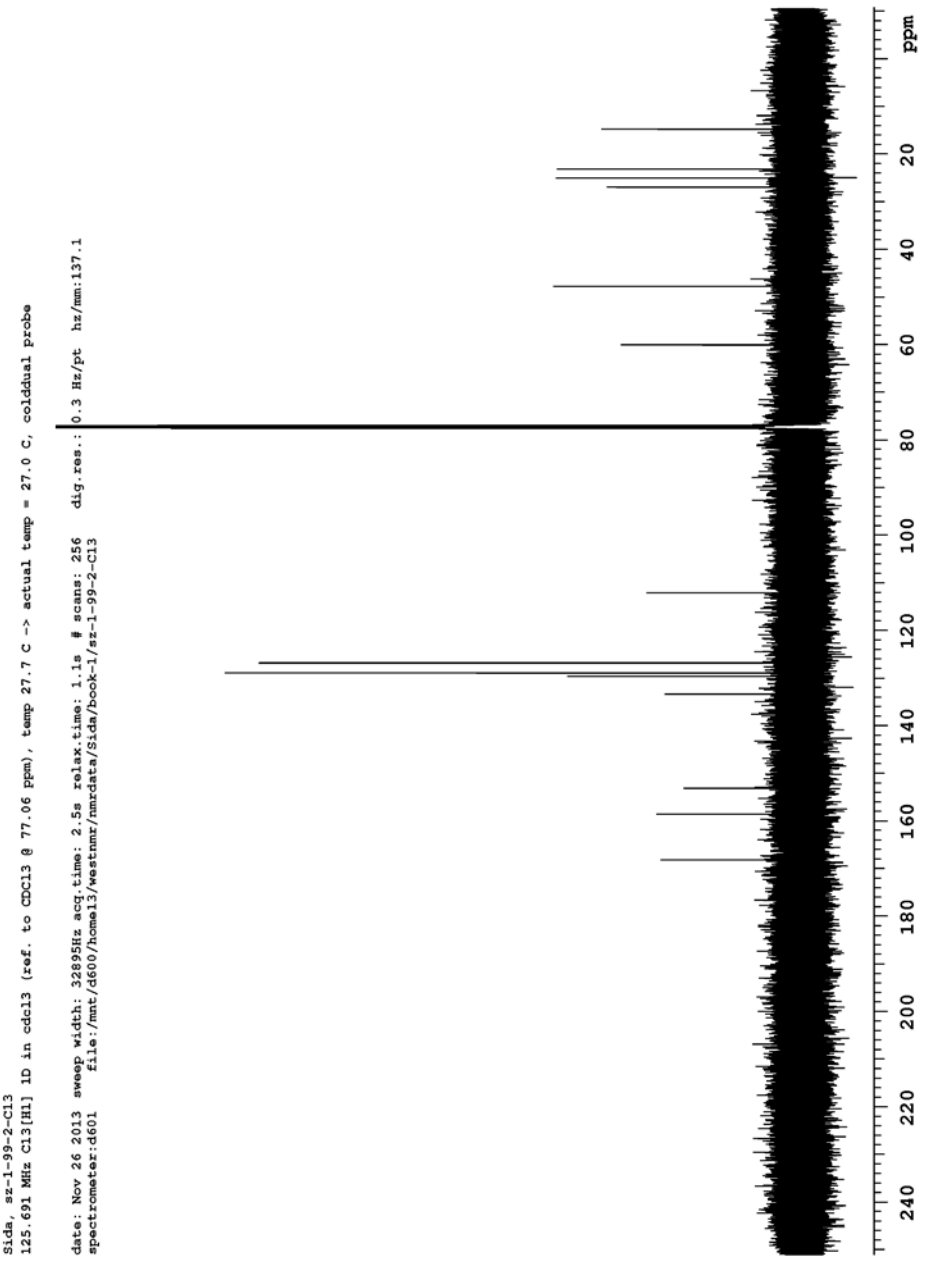
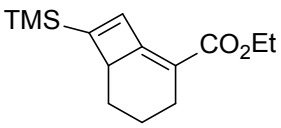
date: Nov 26 2013 sweep width: 6010Hz acq.time: 5.0s relax.time: 2.1s # scans: 16 dig.res.: 0.2 Hz/pt hz/mm:16.5
spectrometer:d601 file:/mnt/d600/home13/westnmr/nmrdata/Sida/book-1/sz-1-99-2
7
6
5
4
3
2
1
ppm
Pulse Sequence: PRESAT

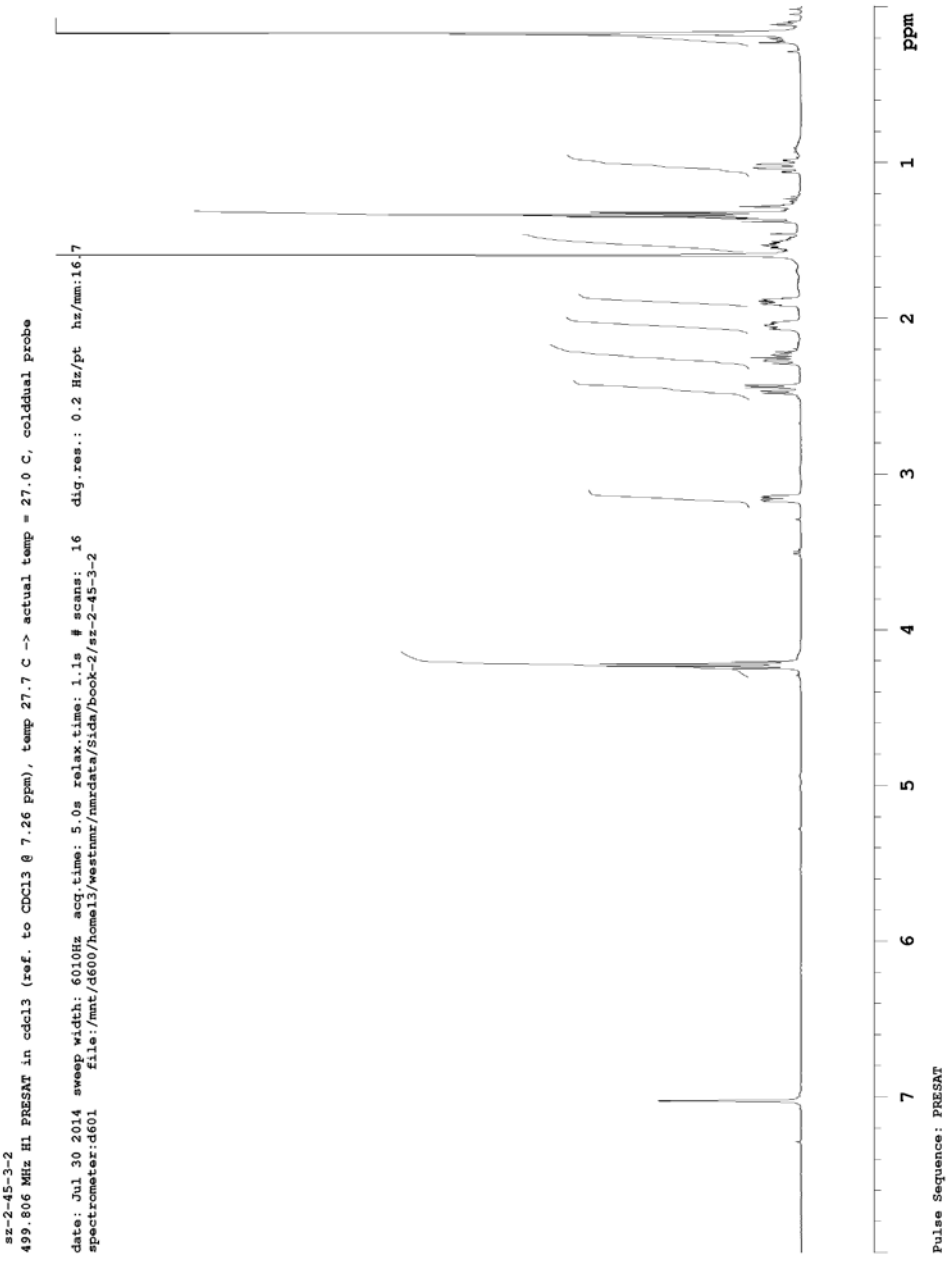

Ph
CO2Et

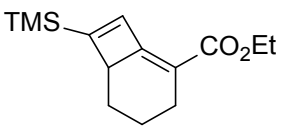
31


Sida, sz-1-99-2-C13
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
data: Nov 26 2013 sweep width: 32895Hz acq.time: 2.5s relax.time: 1.1s # scans: 256 dig.res.: 0.3 Hz/pt hz/mm:137.1
spectrometer:d601 file:/mnt/d600/home13/westnmr/nmrdata/Sida/book-1/sz-1-99-2-C13
240 220 200 180 160 140 120 100 80 60 40 20
ppm
Pulse Sequence: s2pul

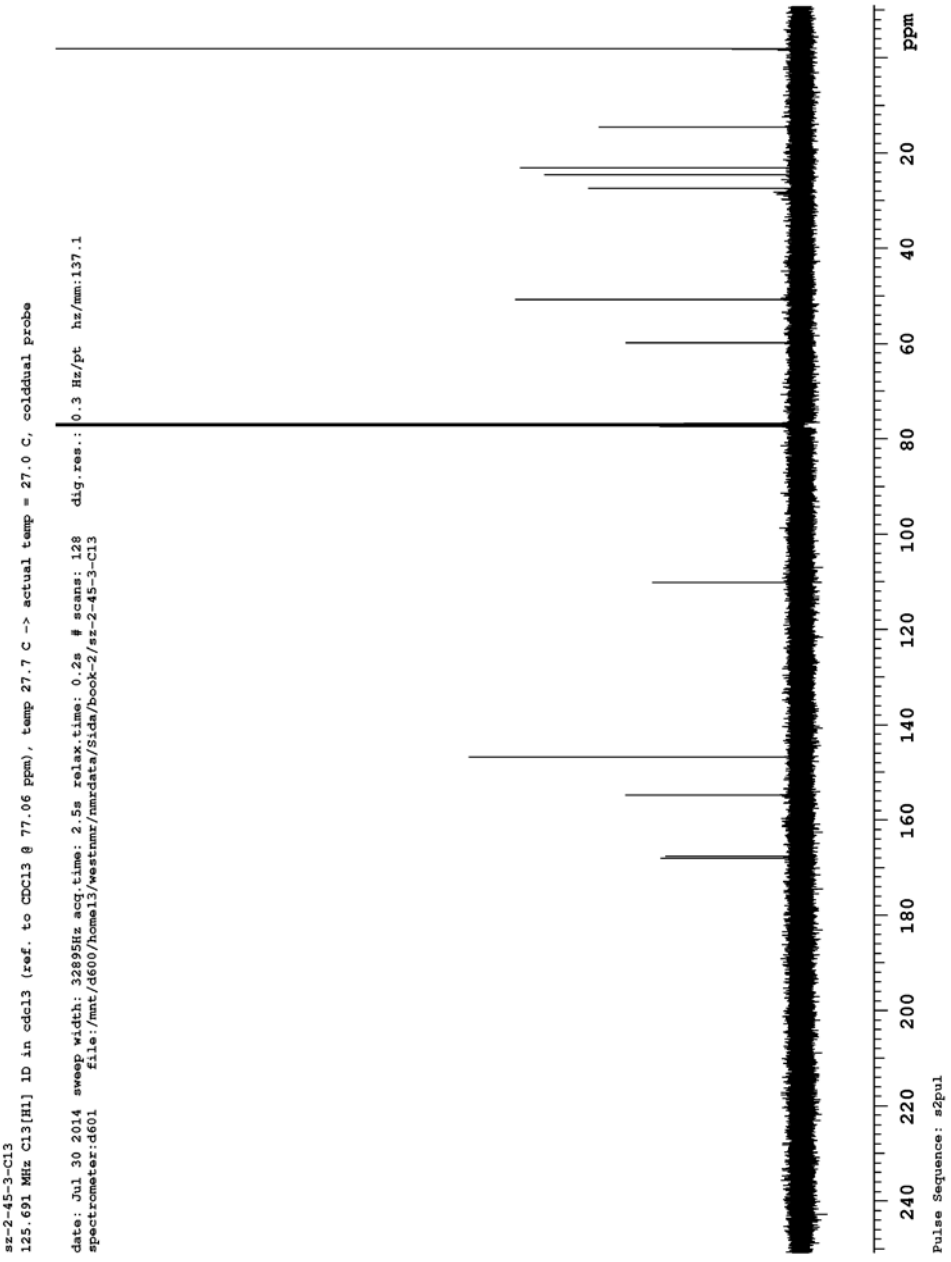

TMS
CO2Et

54a


sz-2-45-3-2
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
data: Jul 30 2014 sweep width: 6010Hz acq.time: 5.0s relax.time: 1.1s # scans: 16 dig.res.: 0.2 Hz/pt hz/mm:16.7
spectrometer:d601 file:/mnt/d600/home13/westnmr/nmrdata/Sida/book-2/sz-2-45-3-2
7
6
5
4
3
2
1
ppm
Pulse Sequence: PRESAT


TMS
CO2Et

54a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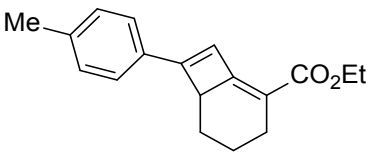
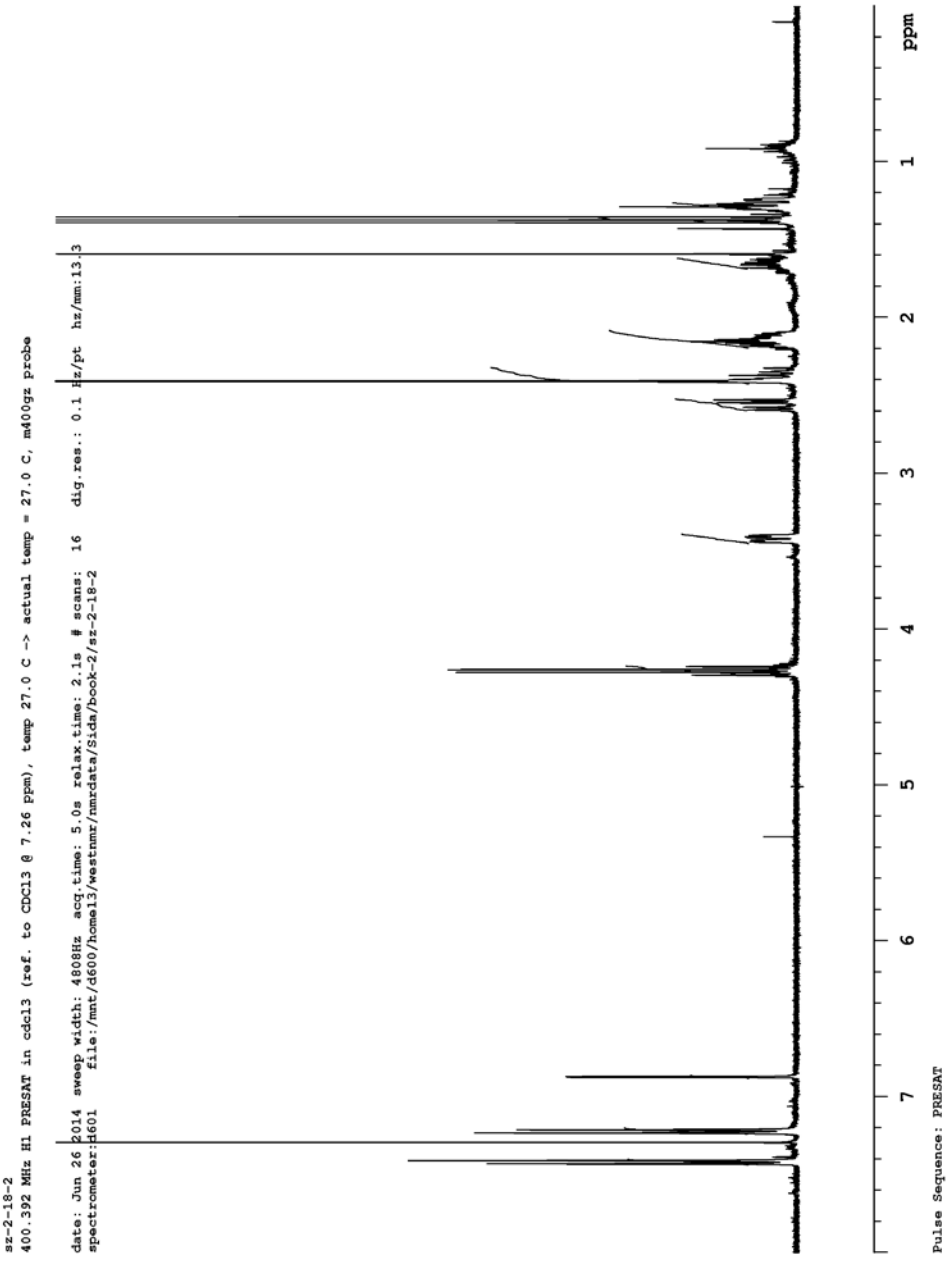
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
data: Jul 30 2014 sweep width: 32895Hz acq.time: 2.5s relax.time: 0.2s # scans: 128 dig.res.: 0.3 Hz/pt hz/mm:137.1
spectrometer:d601 file:/mnt/d600/home13/westnmr/nmrdata/Sida/book-2/sz-2-45-3-C13
240 220 200 180 160 140 120 100 80 60 40 20
ppm
Pulse Sequence: s2pul


Me
CO2Et

54d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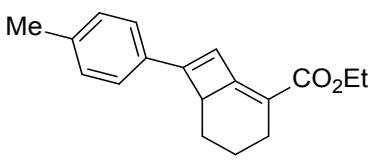
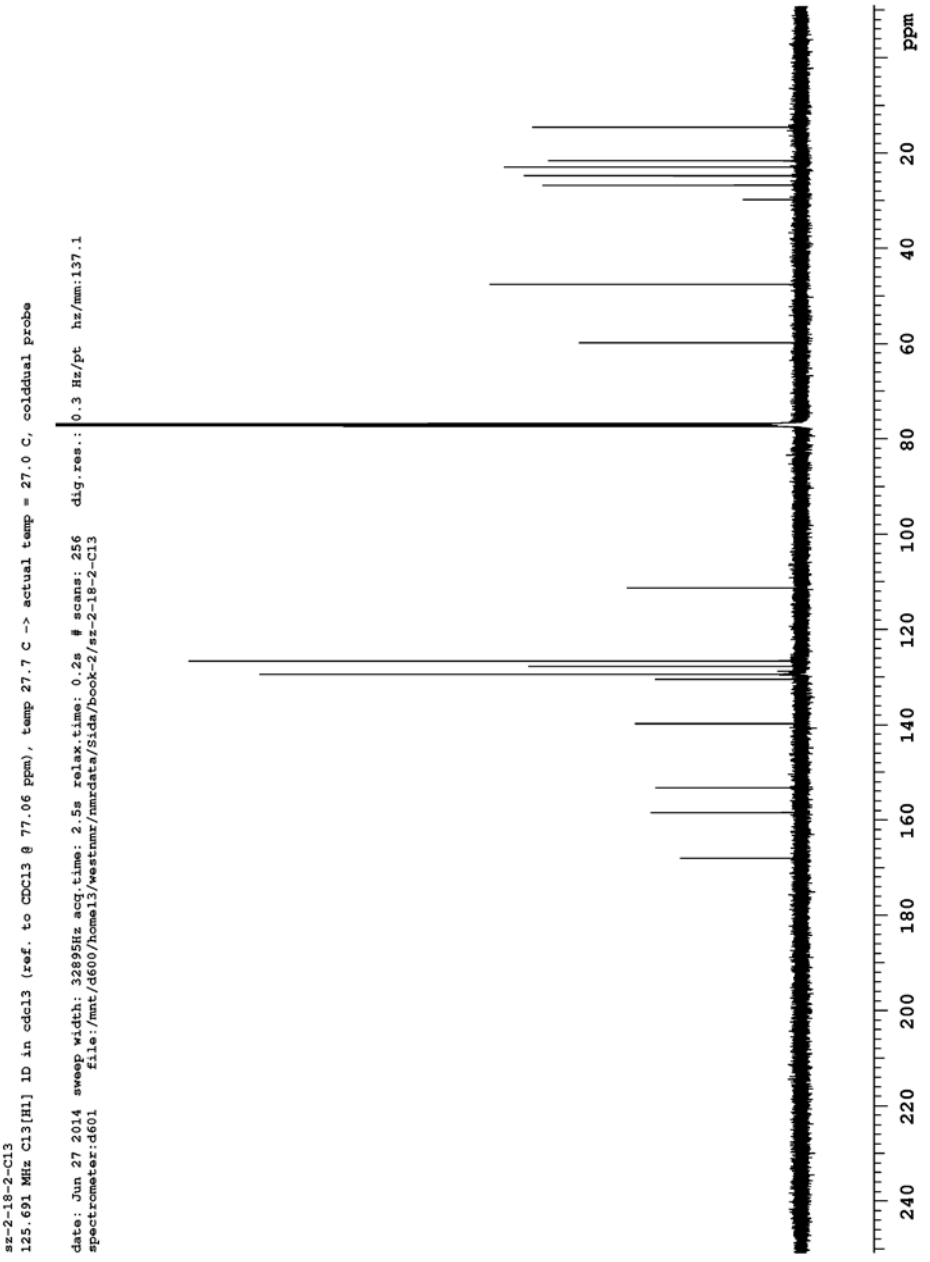
data: Jun 26 2014 sweep width: 4808Hz acq.time: 5.0s relax.time: 2.1s # scans: 16 dig.res.: 0.1 hz/pt hz/mm:13.3
spectrometer:H601 file:/mnt/d600/home13/westnmr/nmrdata/Sida/book-2/sz-2-18-2
7
6
5
4
3
2
1
ppm
Pulse Sequence: PRESAT


Me
CO2Et

54d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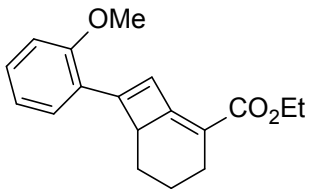
date: Jun 27 2014 sweep width: 32895Hz acq.time: 2.5s relax.time: 0.2s # scans: 256 dig.res.: 0.3 Hz/pt hz/mm:137.1
spectrometer:d601 file:/mnt/d600/home13/westnmr/nmrdata/Sida/book-2/sz-2-18-2-C13
240 220 200 180 160 140 120 100 80 60 40 20
ppm
Pulse Sequence: s2pul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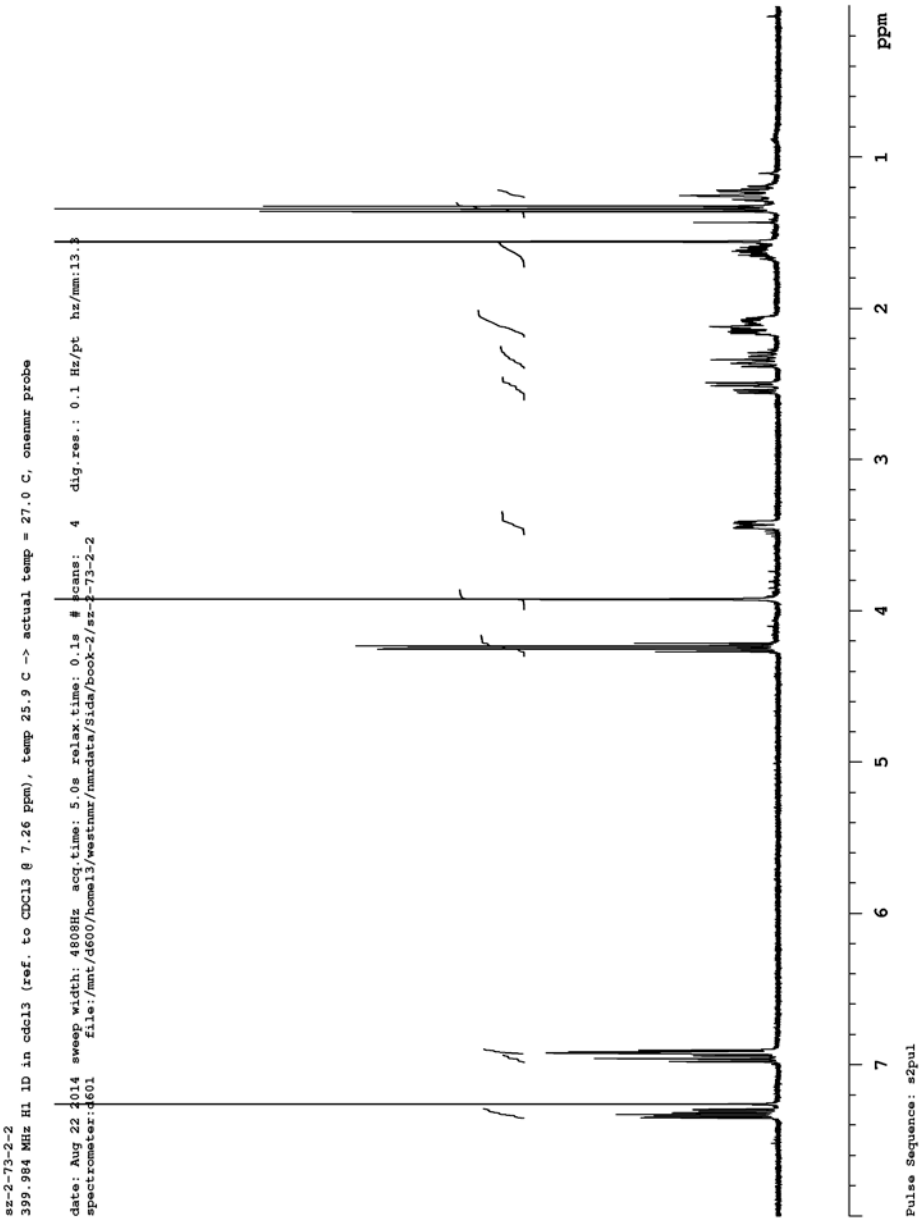
CO2Et

54e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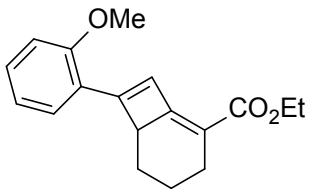
date: Aug 22 2014 sweep width: 4808Hz acq.time: 5.0s relax.time: 0.1s # scans: 4 dig.res.: 0.1 Hz/pt hz/mm:13.3
spectrometer:d601 file:/mnt/d600/home13/westnmr/nmrdata/Sida/book-2/sz-2-73-2-2
7
6
5
4
3
2
1
ppm
Pulse Sequence: s2pul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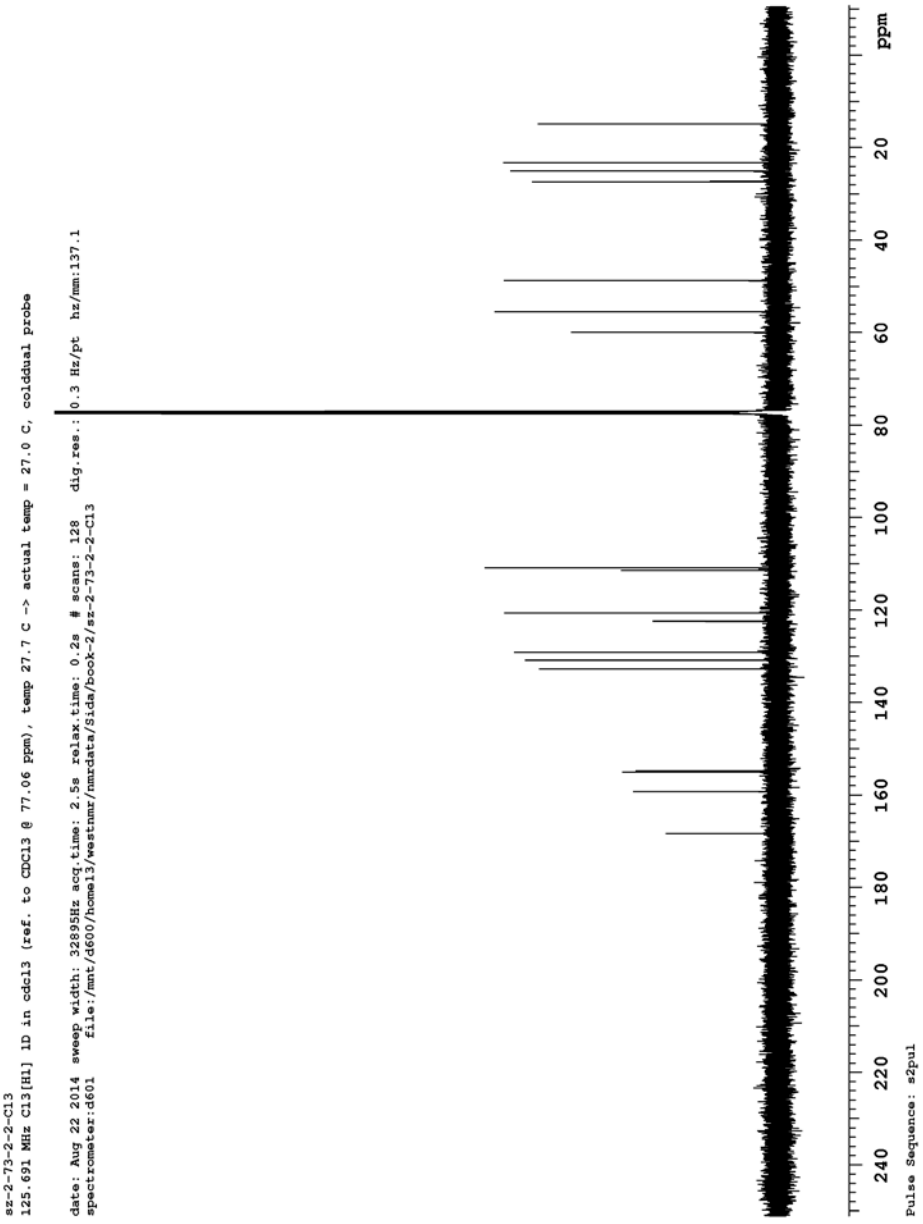
CO2Et

54e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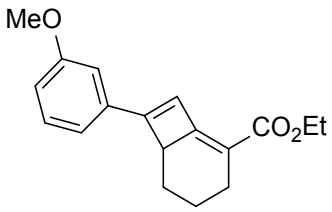
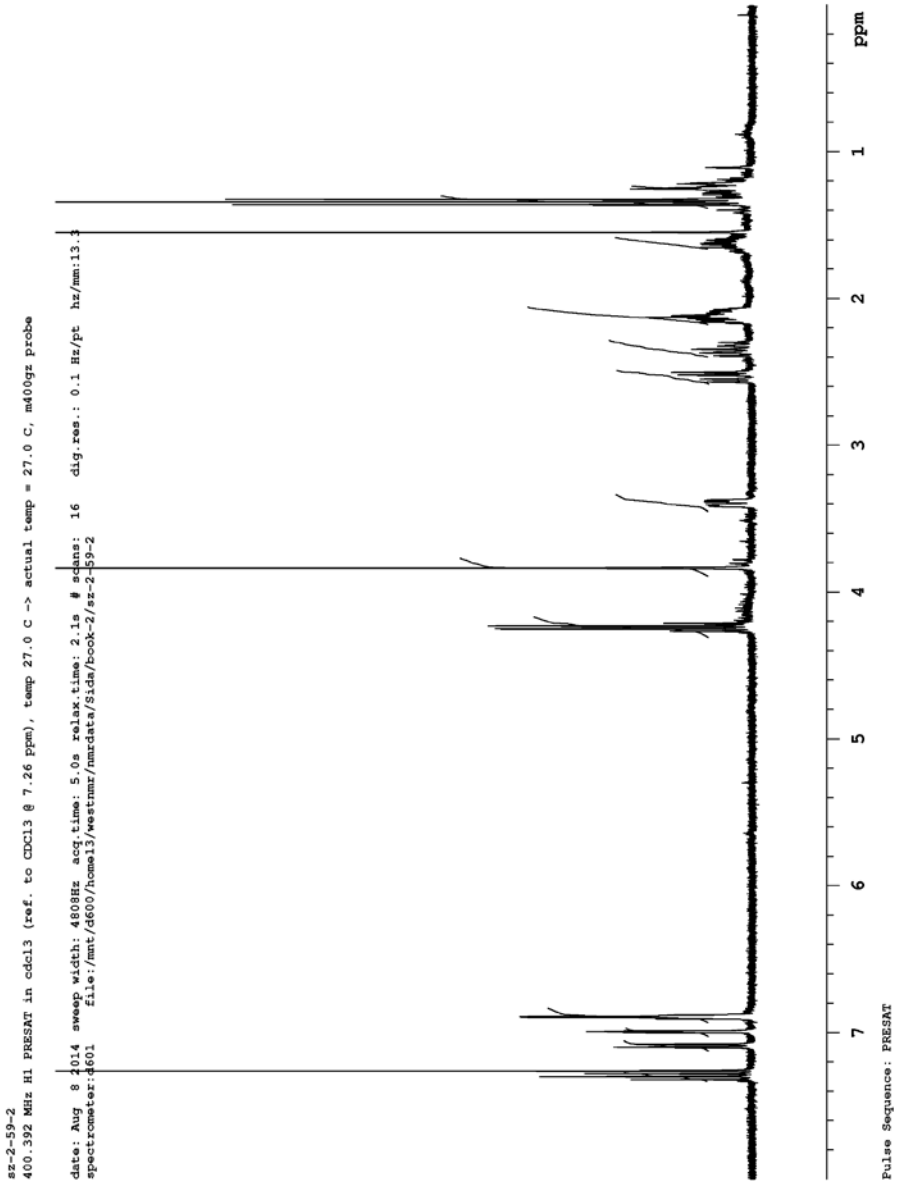
date: Aug 22 2014 sweep width: 32895Hz acq.time: 2.5s relax.time: 0.2s # scans: 128 dig.res.: 0.3 Hz/pt hz/mm:137.1
spectrometer:d601 file:/mnt/d600/home13/westnmr/nmrdata/Sida/book-2/sz-2-73-2-2-C13
240 220 200 180 160 140 120 100 80 60 40 20 ppm
Pulse Sequence: s2pul


MeO
CO2Et

54f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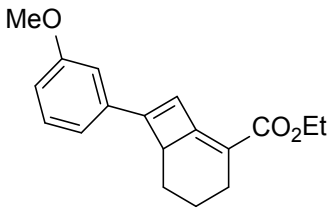
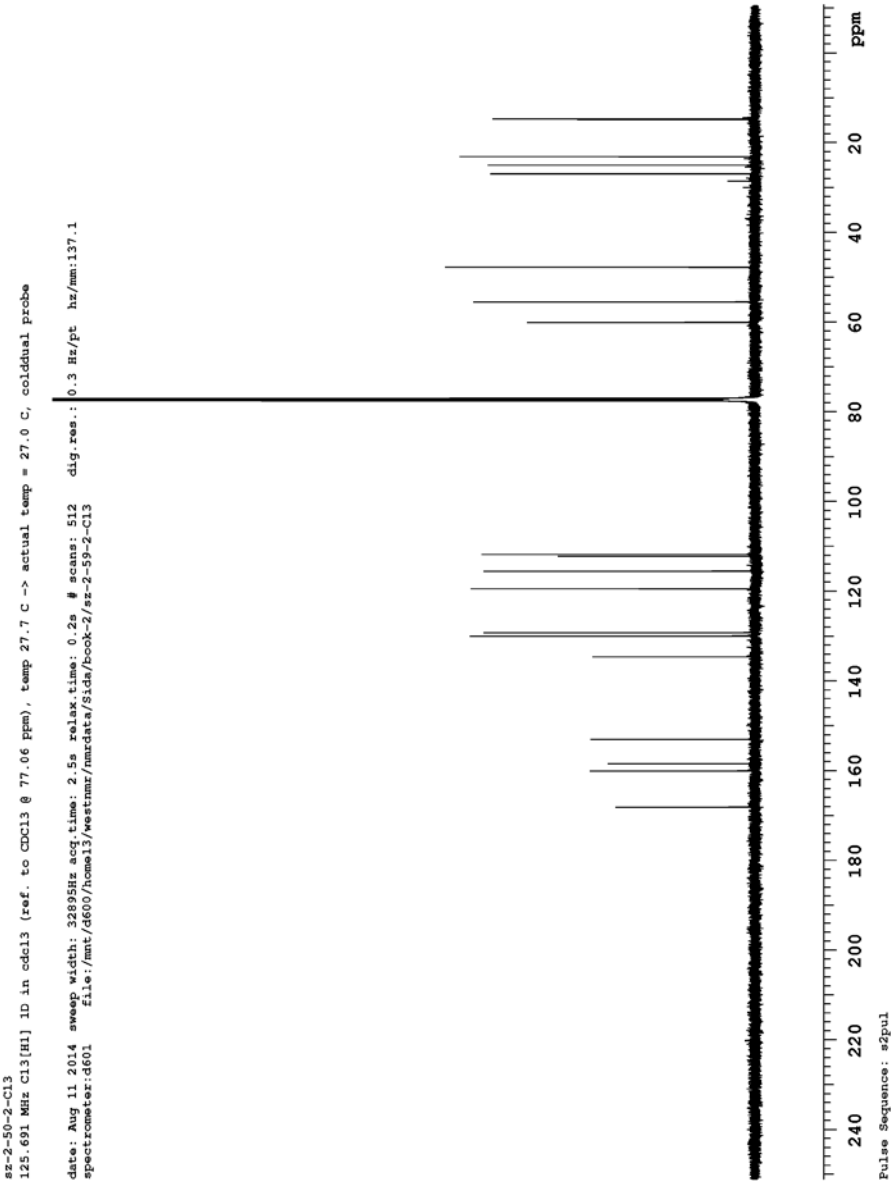
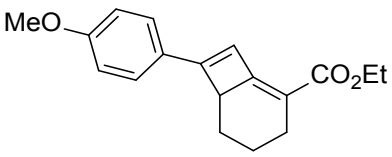
date: Aug 8 2014 sweep width: 4809Hz acq.time: 5.0s relax.time: 2.1s # scans: 16 dig.res.: 0.1 Hz/pt hz/mm:13.3
spectrometer:d601 file:/mnt/d600/home13/westnmr/nmrdata/Sida/book-2/sz-2-59-2
7
6
5
4
3
2
1
ppm
Pulse Sequence: PRESAT

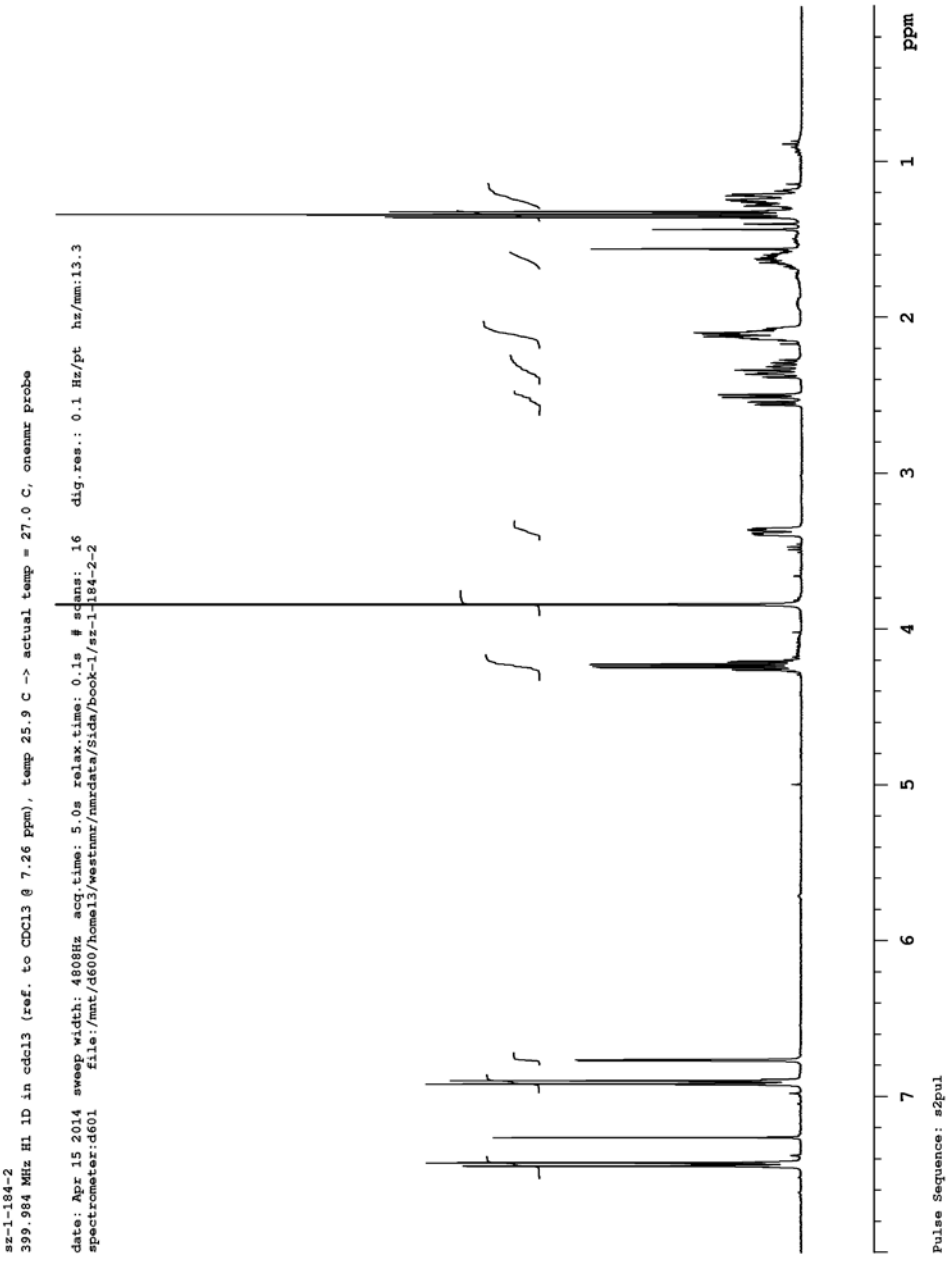

MeO
CO2Et

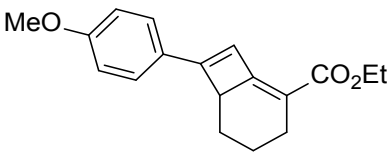
54f


sz-2-50-2-C13
125.691 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: Aug 11 2014 sweep width: 32895Hz acq.time: 2.5s relax.time: 0.2s # scans: 512 dig.res.: 0.3 Hz/pt hz/mm:137.1
spectrometer:d601 file:/mnt/d600/home13/westnmr/nmrdata/Sida/book-2/sz-2-59-2-C13
240 220 200 180 160 140 120 100 80 60 40 20 ppm
Pulse Sequence: s2pul

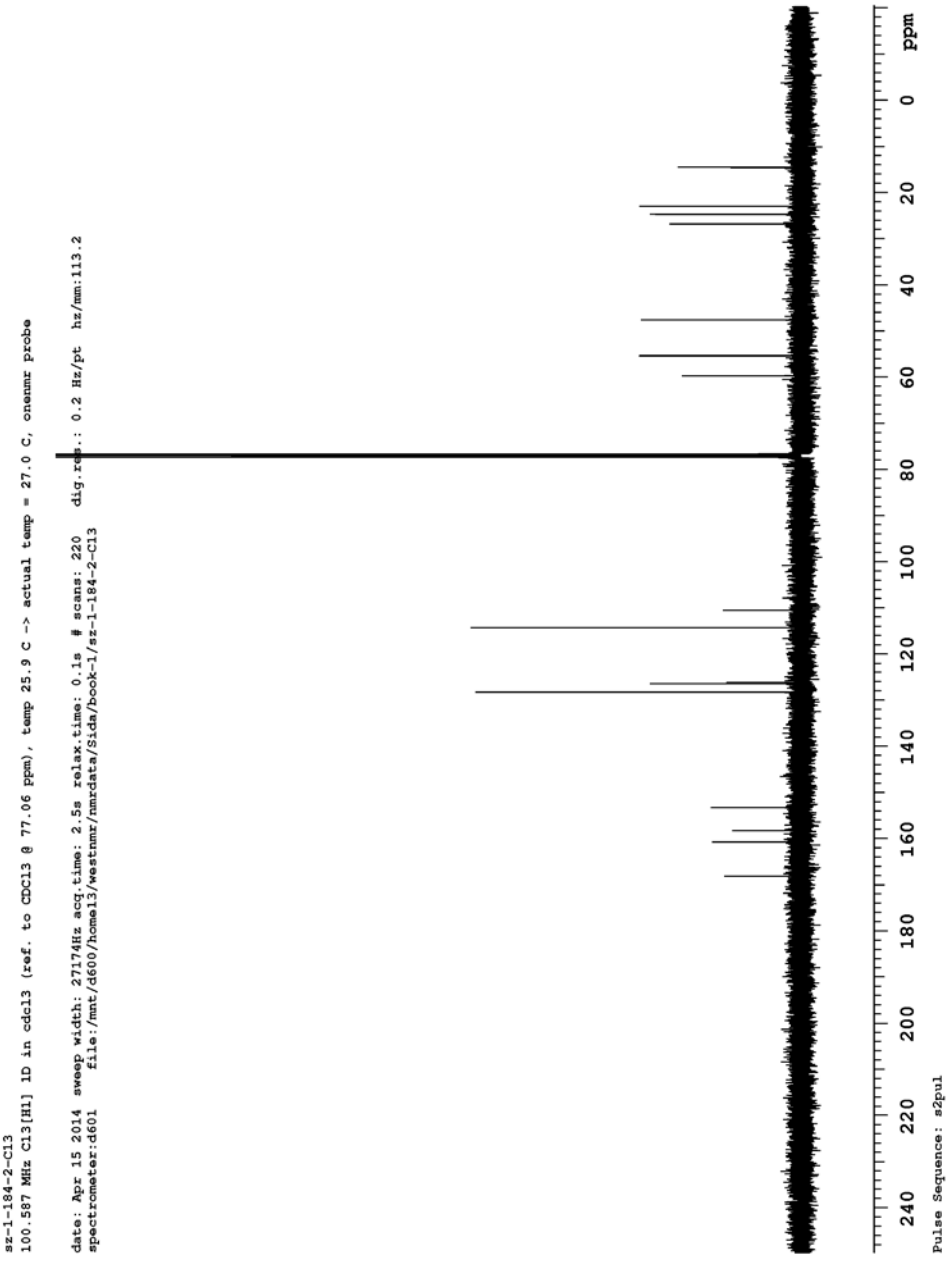

MeO
CO2Et

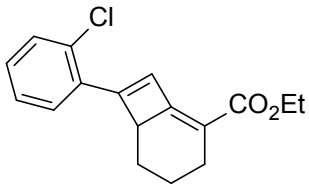
54g


sz-1-184-2
399.984 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 25.9 C --> actual temp = 27.0 C, onenmr probe
data: Apr 15 2014 sweep width: 4808Hz acq.time: 5.0s relax.time: 0.1s # scans: 16 dig.res.: 0.1 Hz/pt hz/mm:13.3
spectrometer:d601 file:/mnt/d600/home13/westnmr/nmrdata/Sida/book-1/sz-1-184-2-2
7
6
5
4
3
2
1
ppm
Pulse Sequence: s2pul

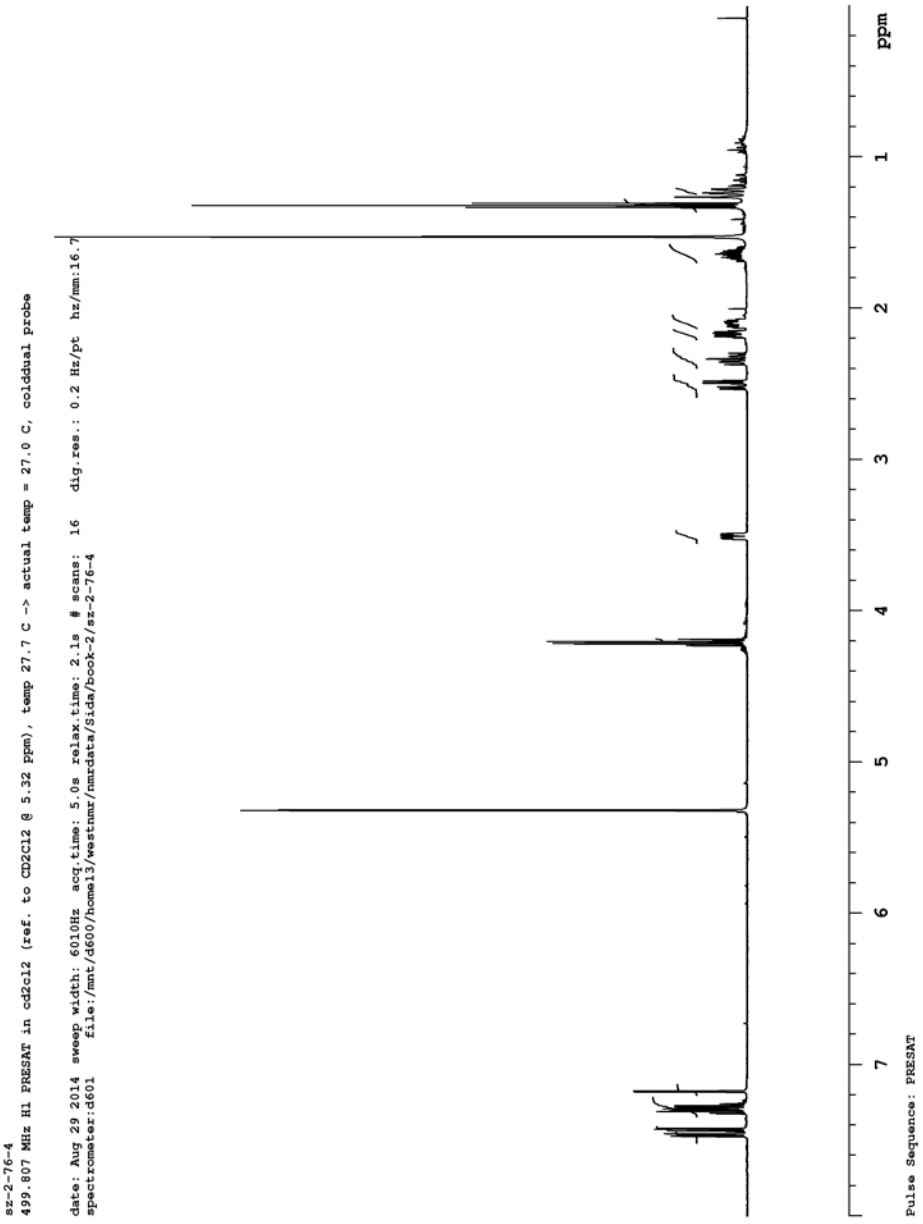

MeO
CO2Et

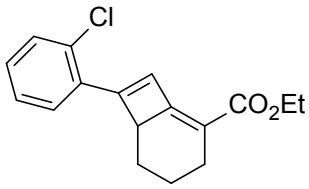
54g


sz-1-184-2-C13
100.587 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 25.9 C -> actual temp = 27.0 C, onenmr probe
data: Apr 15 2014 sweep width: 27174Hz acq.time: 2.5s relax.time: 0.1s # scans: 220 dig.res.: 0.2 Hz/pt hz/mm:113.2
spectrometer:d601 file:/mnt/d600/home13/westnmr/nmrdata/Sida/book-1/sz-1-184-2-C13
240 220 200 180 160 140 120 100 80 60 40 20 0 ppm
Pulse Sequence: s2pul

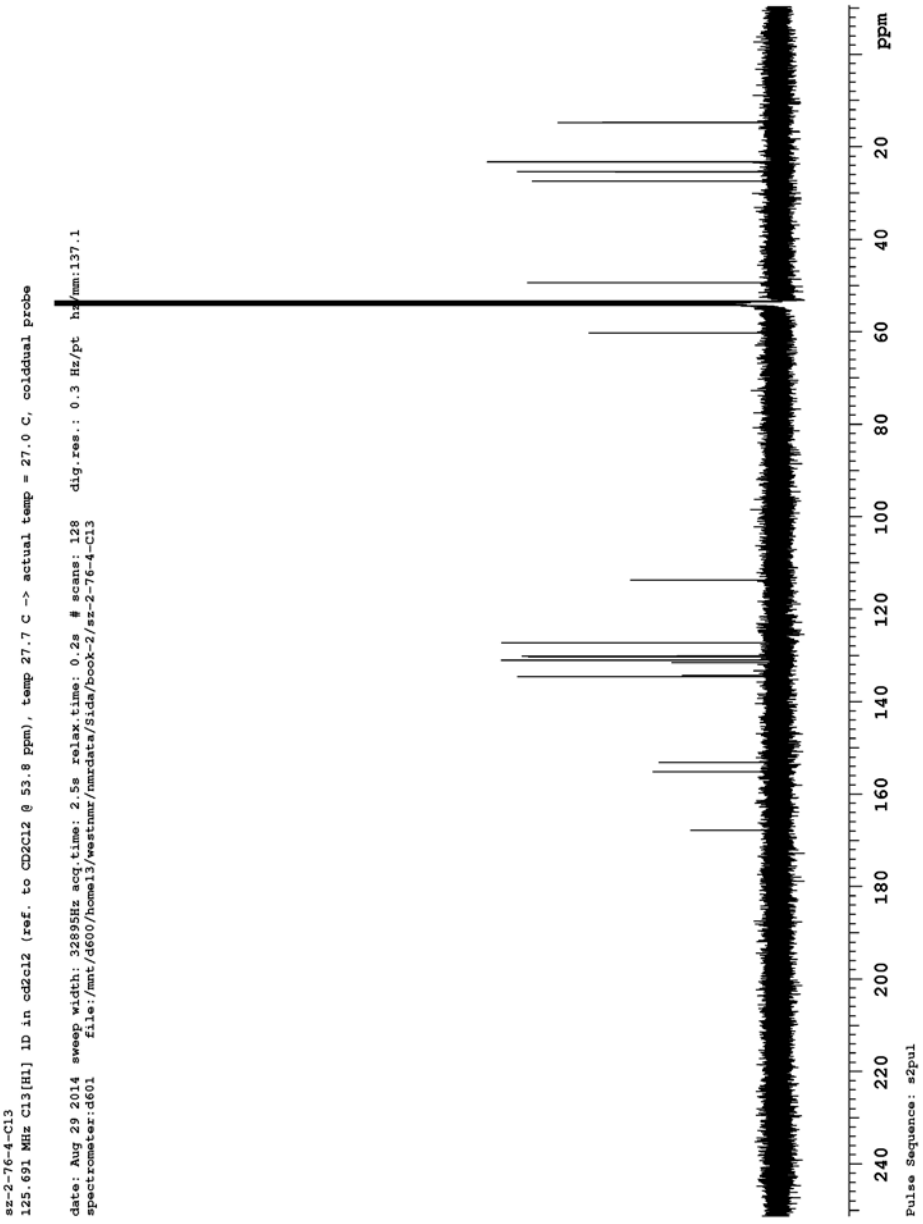

Cl
CO2Et

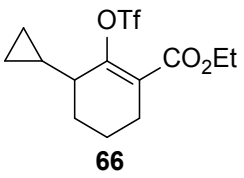
54h


sz-2-76-4
499.807 MHz H1 PRESAT in cd2cl2 (ref. to CD2Cl2 @ 5.32 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: Aug 29 2014 sweep width: 6010Hz acq.time: 5.0s relax.time: 2.1s # scans: 16 dig.res.: 0.2 Hz/pt hz/mm:16.7
spectrometer:d601 file:/mnt/d600/home13/westnmr/nmrdata/Sida/book-2/sz-2-76-4
7
6
5
4
3
2
1
ppm
Pulse Sequence: PRESAT

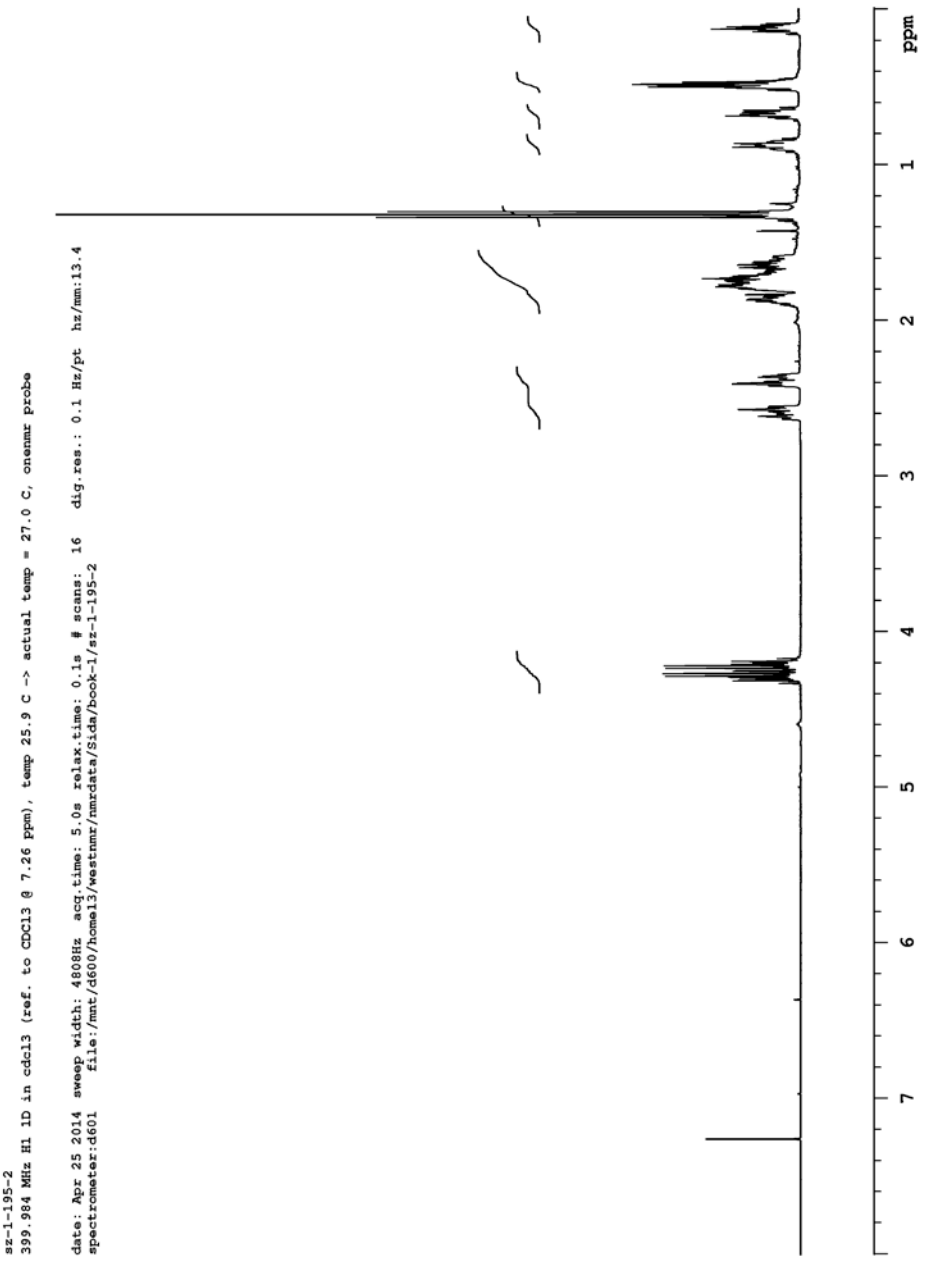

Cl
CO2Et

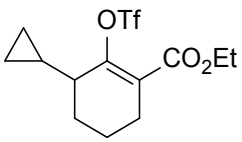
54h


sz-2-76-4-C13
125.691 MHz C13[H1] 1D in cd2cl2 (ref. to CD2Cl2 @ 53.8 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: Aug 29 2014 sweep width: 32895Hz acq.time: 2.5s relax.time: 0.2s # scans: 128 dig.res.: 0.3 Hz/pt hz/mm:137.1
spectrometer:d601 file:/mnt/d600/home13/westnmr/nmrdata/Sida/book-2/sz-2-76-4-C13
240 220 200 180 160 140 120 100 80 60 40 20 ppm
Pulse Sequence: s2pul

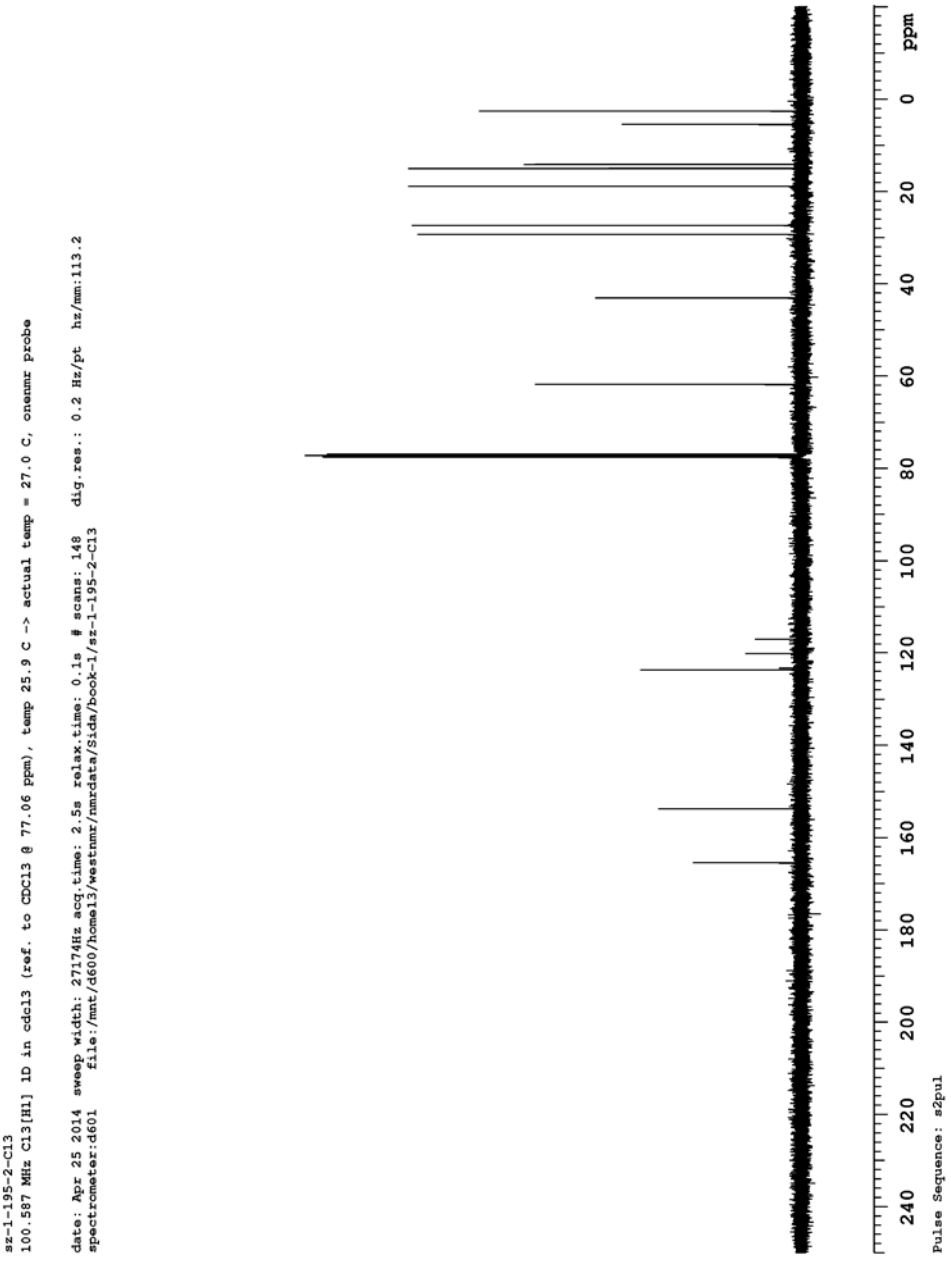

OTf
CO2Et

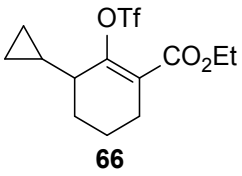
66


sz-1-195-2
399.984 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 25.9 C --> actual temp = 27.0 C, onenmr probe
data: Apr 25 2014 sweep width: 4808Hz acq.time: 5.0s relax.time: 0.1s # scans: 16 dig.res.: 0.1 Hz/pt hz/mm:13.4
spectrometer:d601 file:/mnt/d600/home13/westnmr/nmrdata/Sida/book-1/sz-1-195-2
7
6
5
4
3
2
1
ppm
Pulse Sequence: s2pul

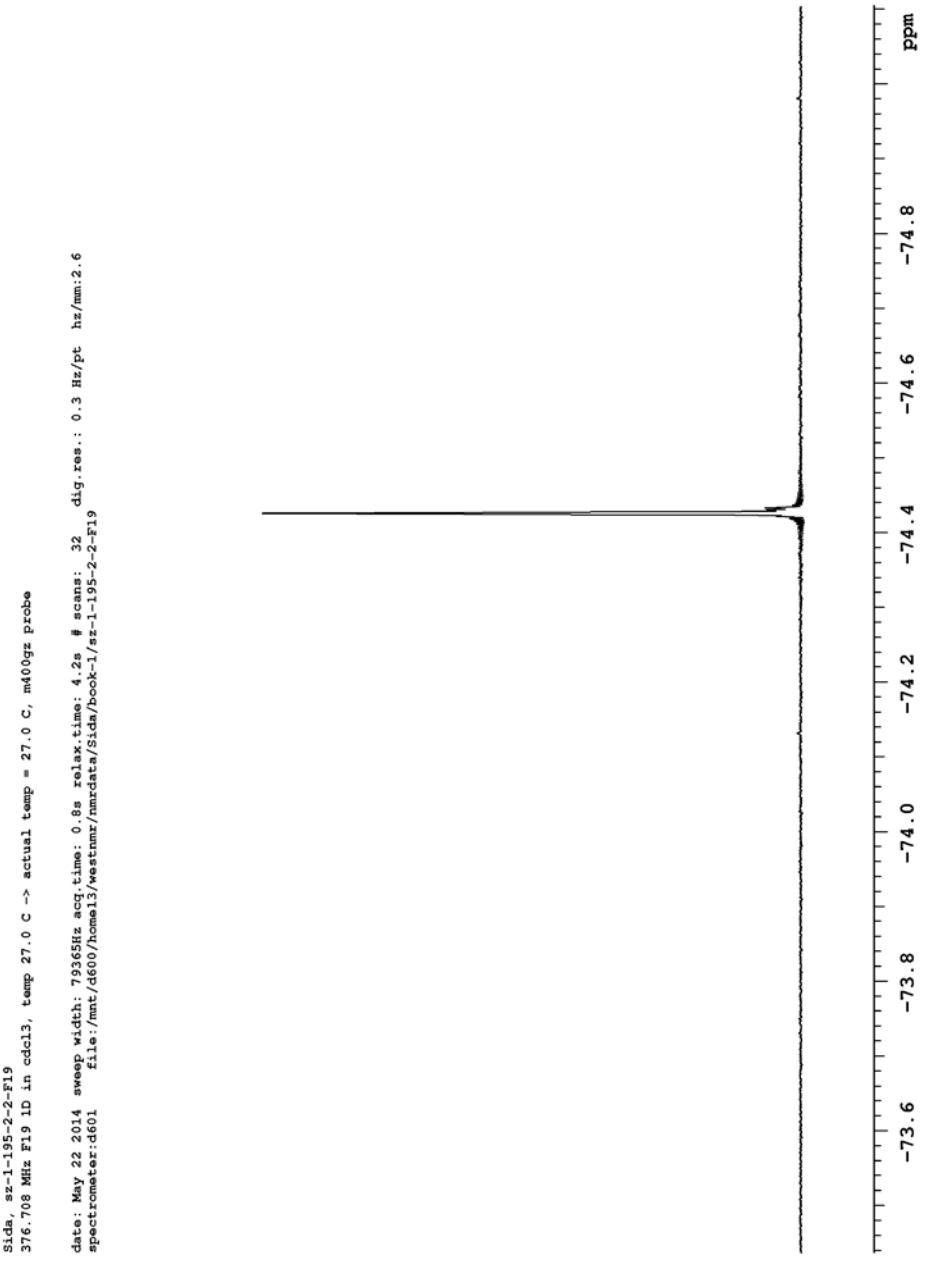

OTf
CO2Et

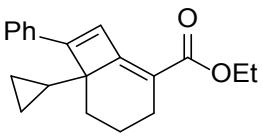
66


sz-1-195-2-C13
100.587 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 25.9 C -> actual temp = 27.0 C, onenmr probe
data: Apr 25 2014 sweep width: 27174Hz acq.time: 2.5s relax.time: 0.1s # scans: 148 dig.res.: 0.2 Hz/pt hz/mm:113.2
spectrometer:d601 file:/mnt/d600/home13/westnmr/nmrdata/Sida/book-1/sz-1-195-2-C13
240 220 200 180 160 140 120 100 80 60 40 20 0 ppm
Pulse Sequence: s2pul

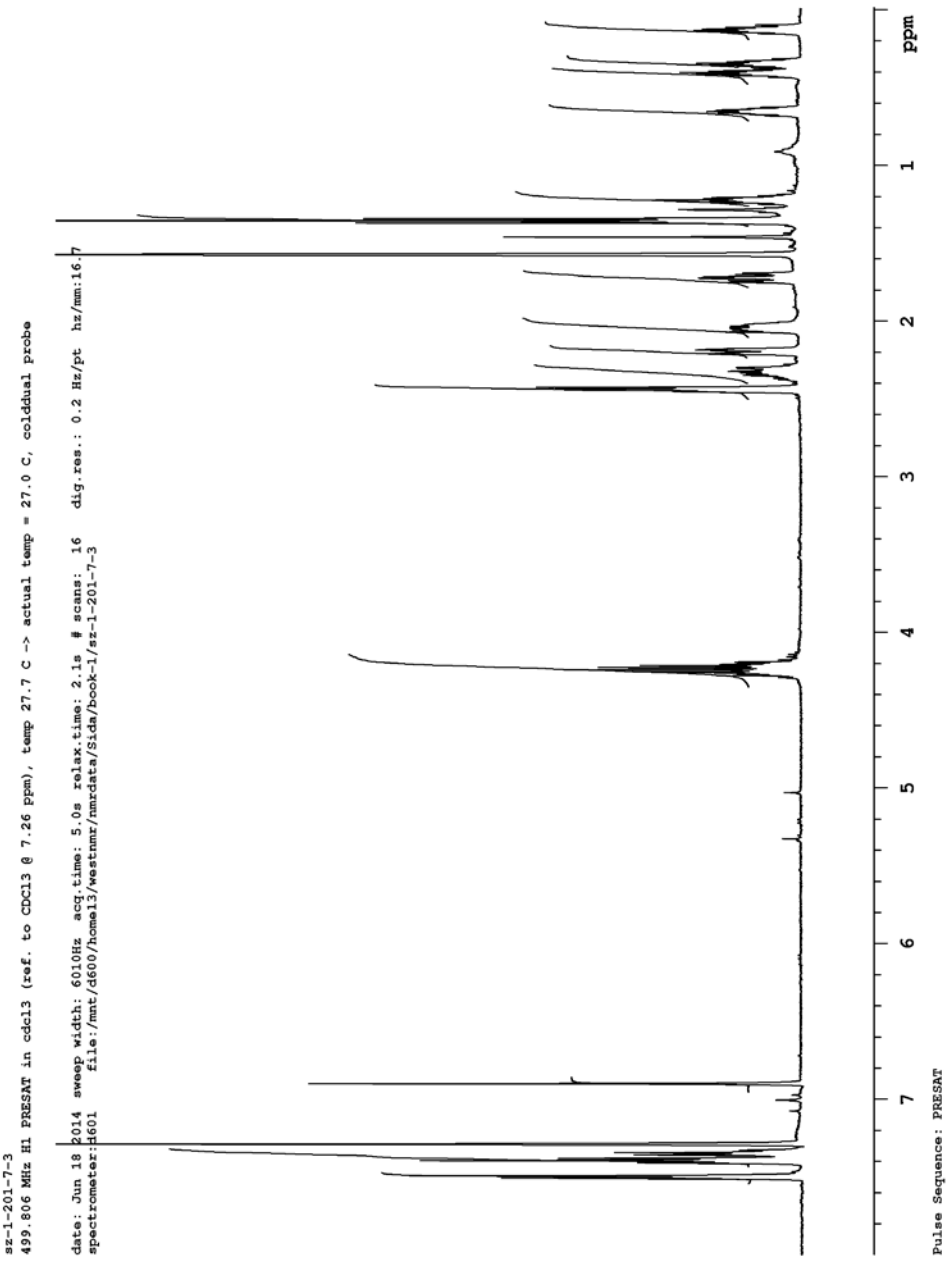

OTf
CO2Et

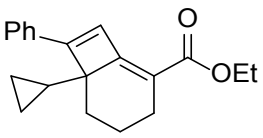
66


Sida, sz-1-195-2-2-F19
376.708 MHz F19 1D in cdcl3, temp 27.0 C -> actual temp = 27.0 C, m400gz probe
data: May 22 2014 sweep width: 79365Hz acq.time: 0.8s relax.time: 4.2s # scans: 32 dig.res.: 0.3 Hz/pt hz/mm:2.6
spectrometer:d601 file:/mnt/d600/home13/westnmr/nmrdata/Sida/book-1/sz-1-195-2-2-F19
-73.6
-73.8
-74.0
-74.2
-74.4
-74.6
-74.8
ppm
Pulse Sequence: s2pul

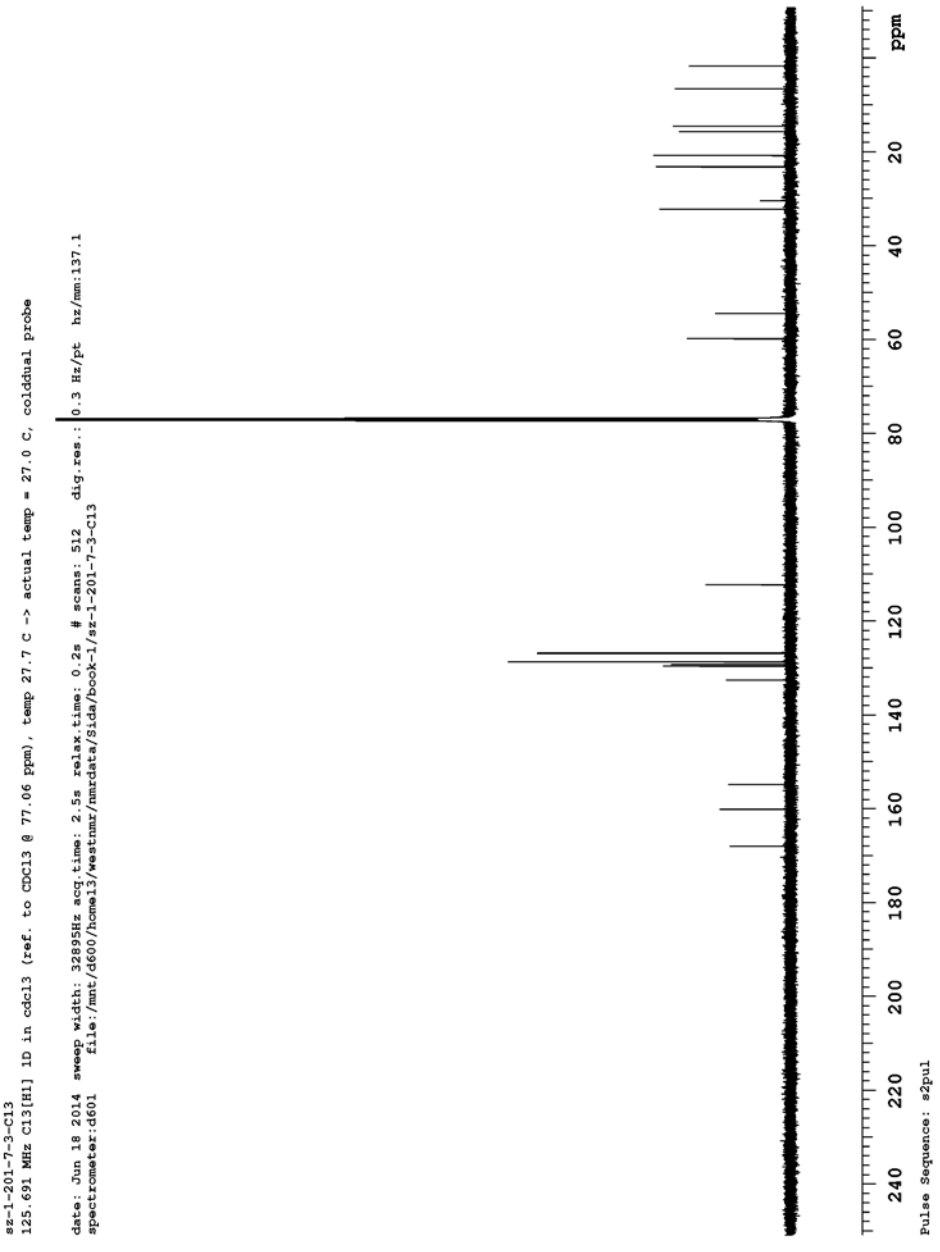

Ph
O
OEt

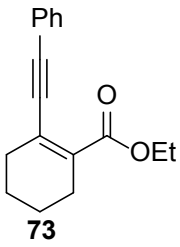
60


sz-1-201-7-3
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: Jun 18 2014 sweep width: 6010Hz acq.time: 5.0s relax.time: 2.1s # scans: 16 dig.res.: 0.2 Hz/pt hz/mm:16.7
spectrometer:H601 file:/mnt/d600/home13/westnmr/nmrdata/Sida/book-1/sz-1-201-7-3
7
6
5
4
3
2
1
ppm
Pulse Sequence: PRESAT

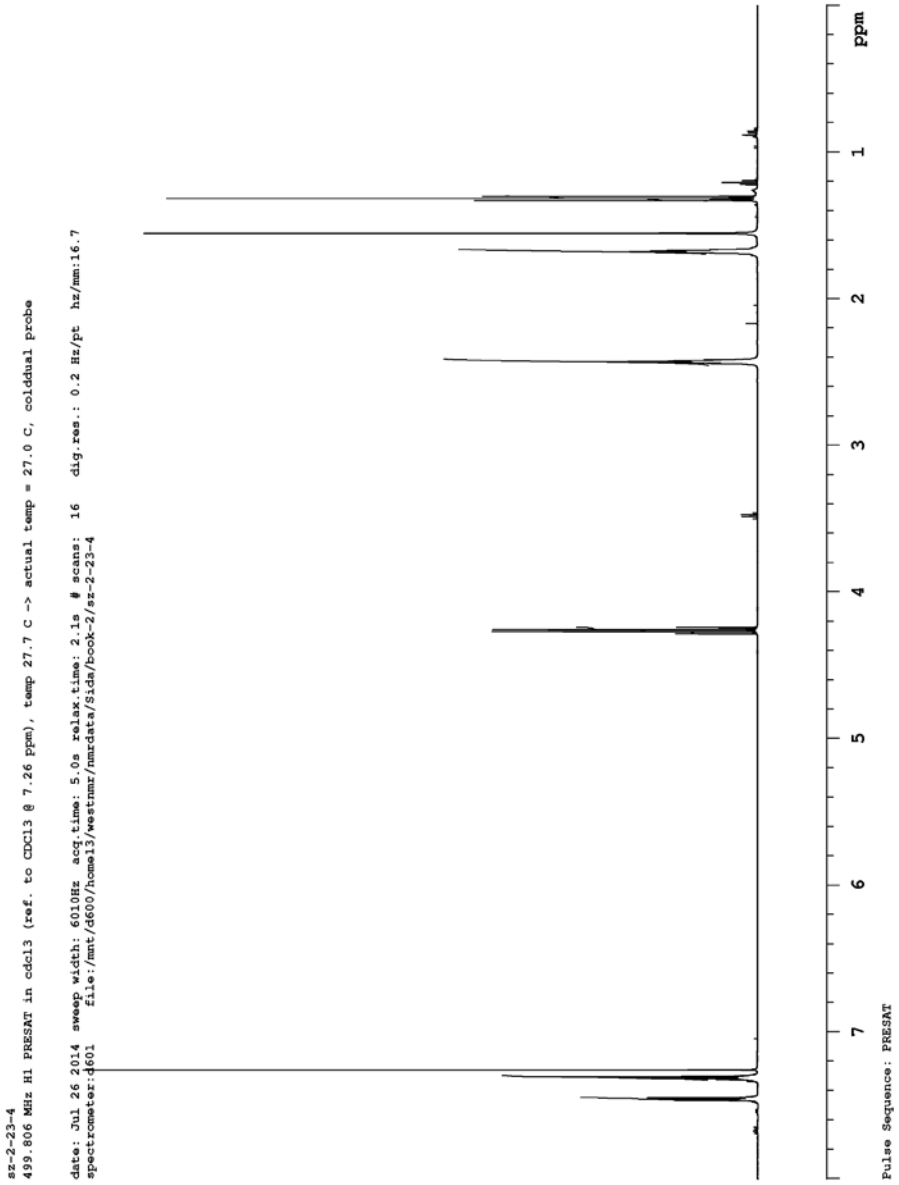

Ph
O
OEt

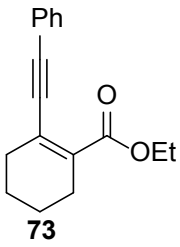
60


sz-1-201-7-3-C13
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: Jun 18 2014 sweep width: 32895Hz acq.time: 2.5s relax.time: 0.2s # scans: 512 dig.res.: 0.3 Hz/pt hz/mm:137.1
spectrometer:d601 file:/mnt/d600/home13/westnmr/nmrdata/Sida/book-1/sz-1-201-7-3-C13
240 220 200 180 160 140 120 100 80 60 40 20 ppm
Pulse Sequence: s2pul

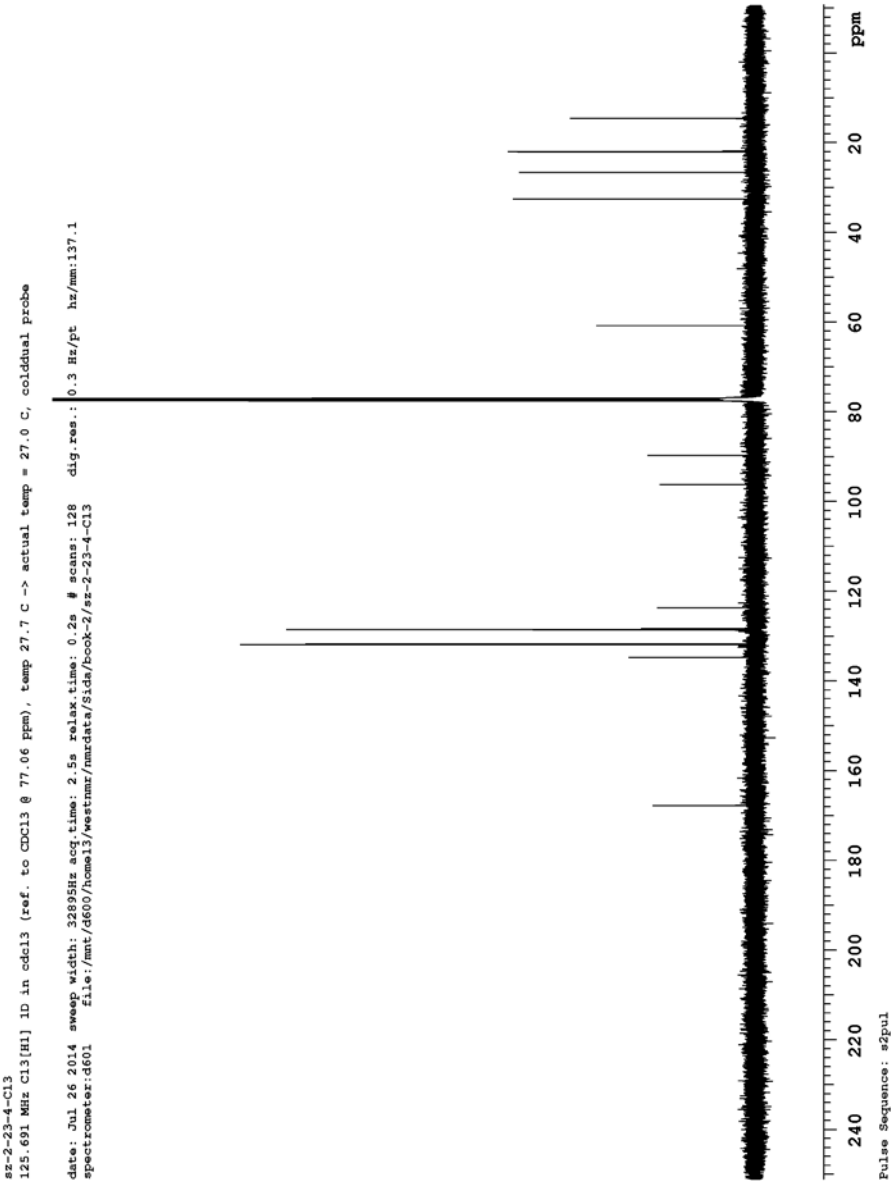

Ph
O
OEt

73


sz-2-23-4
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: Jul 26 2014 sweep width: 6010Hz acq.time: 5.0s relax.time: 2.1s # scans: 16 dig.res.: 0.2 Hz/pt hz/mm:16.7
spectrometer:d601 file:/mnt/d600/home13/westnmr/nmrdata/Sida/book-2/sz-2-23-4
7
6
5
4
3
2
1
ppm
Pulse Sequence: PRESAT


Ph
O
OEt

73


sz-2-23-4-C13
125.691 MHz C13{H1} 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
date: Jul 26 2014 sweep width: 32895Hz acq.time: 2.5s relax.time: 0.2s # scans: 128 dig.res.: 0.3 Hz/pt hz/mm:137.1
spectrometer:d601 file:/mnt/d600/home13/westnmr/nmrdata/Sida/book-2/sz-2-23-4-C13
240 220 200 180 160 140 120 100 80 60 40 20 ppm
Pulse Sequence: s2pul