Studies on the Stereoselective Synthesis of Functionalized Quaternary Stereocenters and *E*-3-(Arylmethylidene)-5-(Alkyl/Aryl)-2(3*H*)-Furanones

by

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A thesis submitted to the School of Graduate Studies in partial fulfillment

of the requirements for the degree of Doctor of Philosophy

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To my family and friends

Abstract

An enantioselective synthesis of isolated acyclic quaternary stereocenters was achieved using metal-catalyzed Gosteli-Claisen rearrangements of allyl vinyl ethers. A concise synthesis of 2-*t*-butoxycarbonyl allyl vinyl ethers by regioselective Petasis methylenation and stereoselective Suzuki-Miyaura cross-coupling reactions of iodoallyl *t*-butyl oxalates was developed. Ethers with a terminally unsubstituted vinyl group and a terminally disubstituted allyl portion are readily accessible by this method.

In addition to the metal-catalyzed Gosteli-Claisen rearrangements, organocatalytic variant of the Gosteli-Claisen rearrangement was investigated. A modular synthesis of several new, chiral cyclic phosphoramide-based, thioureas, formamidines and thiosemicarbazides was developed and these phosphoramides were examined for their ability to catalyze the Gosteli-Claisen rearrangement of a selected allyl vinyl ether.

A variety of *E*-3-(arylidene)-5-(alkyl/aryl)-2(3*H*)-furanones were synthesized by employing regioselctive addition of *β*-aryl acrylic acids with iodoacetylenes and subsequent intramolecular Heck reaction of *Z*-acyloxy iodo alkenes. The approach was applied in a formal synthesis of the naturally occurring kinase inhibitor BE-23372M.

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Ac	acetyl
AD	asymmetric dihydroxylation
AIBN	azobisisobutyronitrile
APCI	atmospheric pressure chemical ionization
APPI	atmospheric pressure photoionization
aq.	aqueous
BAIB	bis(acetoxy)iodobenzene
BINOL	1,1′-dinaphthalene-2,2′-diol
BnBr	benzyl bromide
Boc	*tert*-butoxycarbonyl
br	broad
BzCl	benzoyl chloride
CAN	ceric ammonium nitrate
cat.	catalytic
CDI	1,1'-carbonyldiimidazole
CI	chemical ionization
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DCE	1,2-dichloroethylene
DIBAL-H	diisobutylaluminum hydride

DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
EDG	electron donating group
ee	enantiomeric excess
EI	electron impact
eq.	equivalent (s)
ESI	electrospray ionization
esp	$\alpha,\alpha,\alpha',\alpha'$-tetramethyl-1,3-benzenedipropionoate
EtOAc	ethyl acetate
EVK	ethyl vinyl ketone
EWG	electron withdrawing group
g	gram (s)
h	hour (s)
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons
Hz	Hertz

i-Bu	isobutyl
IBX	2-iodoxybenzoic acid
Ipc	diisopinocampheyl
IR	infrared
J	coupling constant
L	ligand
LAH	lithium aluminium hydride
LCPA	lithium *N*-cyclohexyl-*N*-isopropylamide
LDA	lithium diisopropyl amide
LHMDS	lithium hexamethyldisilazide
LICA	lithium isopropyl cyclohexylamide
LiDBB	lithium di-*tert*-butylbiphenylide
LiHMDS	lithium bis(trimethylsilyl)amide
M	molar
M^+	molecular ion
Me	methyl
mg	milligram(s)
MIDA	*N*-methylimidodiacetic
min	minute (s)
mL	milliliter (s)
mmol	millimole (s)
mp	melting point

MS	mass spectrometry
MsCl	methanesulfonyl chloride
MTBD	7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
MVK	methyl vinyl ketone
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
Ph	phenyl
ppm	parts per million
PTSA/*p*-TsOH	*para*-toluenesulfonic acid
R_f	retention factor
rt	room temperature
TBDMS/TBS	*tert*-butyldimethylsilyl
TCA	trichloroacetic acid
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
TMSOTf	trimethylsilyl trifluoromethanesulfonate
UV	ultraviolet

Chapter 1

Modular Synthesis of Allyl Vinyl Ethers for the Enantioselective Construction of Functionalized Quaternary Stereocenters

A portion of the work described in this chapter has been published in *RSC Adv.*:

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Contributions of authors

Muthusamy, G: experimental work, manuscript preparation.

S. V. Pansare: research supervisor, manuscript preparation.

1.1 Introduction

Quaternary stereocenters are attractive structural motifs which present a significant synthetic challenge. They are encountered as structural elements in several biologically active natural products and hence enantioselective approaches to quaternary stereocenters have been intensely investigated in recent years.[1] Many catalytic enantioselective methods have been developed for assembling isolated quaternary stereocenters.[2] Some of these investigations are in the area of natural product synthesis,[1c,d] and other studies highlight methodology for the construction of quaternary stereocenters by employing suitably functionalized starting materials.[1e,2] The following section provides a summary of the catalytic enantioselective syntheses of acyclic quaternary stereocenters reported in recent years. The topic has also been reviewed[1a] very recently.

1.2 Recent Reports on the Synthesis of Isolated Acyclic Quaternary Stereocenters

A review of isolated acyclic quaternary stereocenters reveals that many synthetic strategies have been implemented to synthesize such stereocenters.[2] Since an enormous amount of literature is available on this subject, the focus of the following literature survey is only on the methodologies reported after 2011. The reported synthetic approaches to isolated acyclic quaternary stereocenters can be broadly classified into three categories:

1.2.1 Asymmetric allylic alkylation (AAA) or alkylation reactions

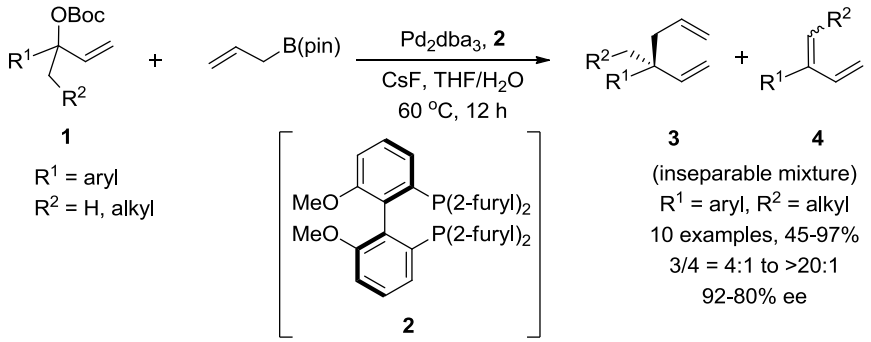
1.2.2 Asymmetric Michael addition approaches

1.2.3 Asymmetric phase transfer catalysis strategies

1.2.1 Asymmetric Allylic Alkylation (AAA) or Alkylation Reactions

1.2.1.1 The Morken Synthesis of Acyclic Quaternary Stereocenters

In 2011, Morken and coworkers[3] reported the enantioselective synthesis of quaternary stereocenters from allyl carbonates. Tertiary allyllic carbonates **1** (Scheme 1.1) were subjected to alkylation with an allylboronate in the presence of Pd_2dba_3 catalyst and (*R*)-MeO-furyl-biphep ligand **2** to afford unsaturated quaternary stereocenters **3** with high enantiomeric excess. Notably, under these reaction conditions, allyl carbonates **1** also furnished the eliminated product, 1,3-dienes **4**, in addition to the required product of allylation **3** (**3**/**4** = 4:1 to >20:1; GC and ^{1}H NMR analysis, Scheme 1.1).

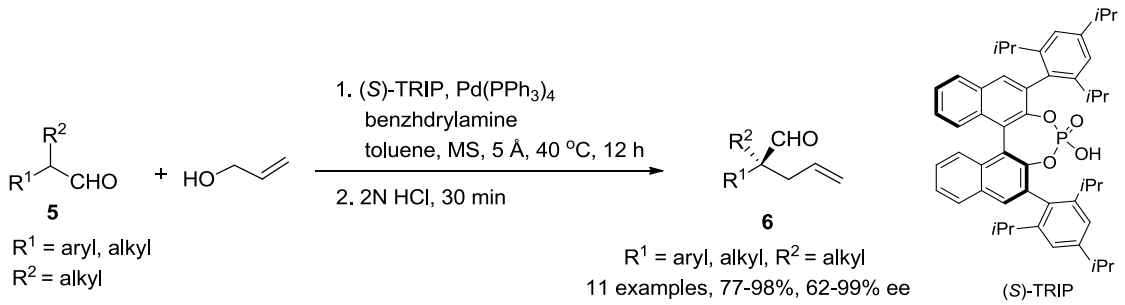


Scheme 1.1

1.2.1.2 The List Synthesis of Acyclic Quaternary Stereocenters

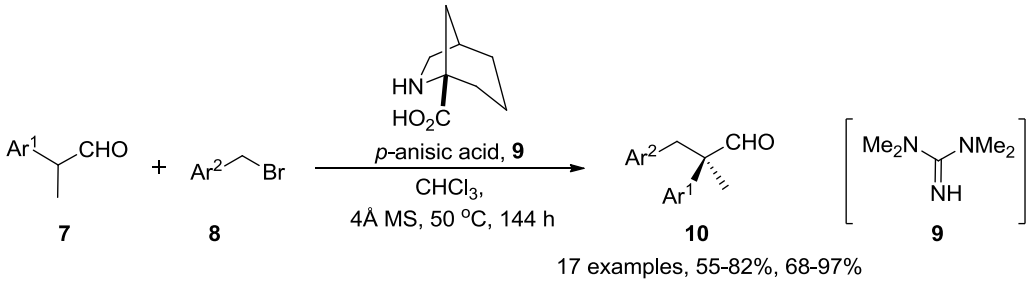
In 2011, List[4] developed the α-allylation of aldehydes **5** with an allylic alcohol to afford the functionalized quaternary stereocenters **6**. Aldehydes **5** underwent α-allylation with allylic alcohol in the presence of (*S*)-TRIP, $Pd(PPh_3)_4$ and benzhydryl amine to give **6** in good yields with moderate to high enantiomeric excess (Scheme 1.2). The authors

stated that the addition of benzhydrylamine plays a crucial role in determining the enantioselectivity of the reactions.



Scheme 1.2

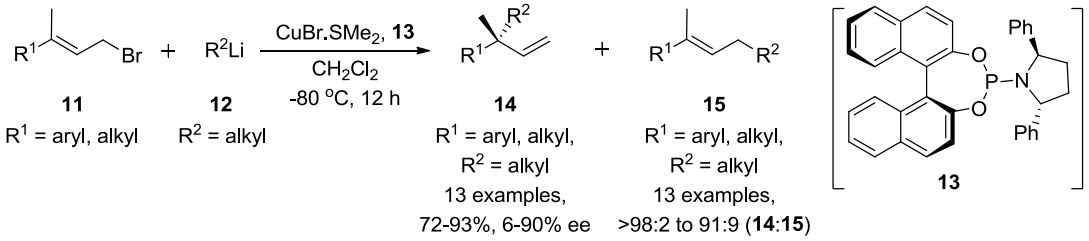
In 2014, the same group[5] introduced asymmetric alkylation of α,α-disubstituted aldehydes **7** with benzyl halides **8** in a dynamic kinetic asymmetric transformation process. Asymmetric S_N2 α-alkylation of **7** with benzyl halides **8** in the presence of a chiral amino acid catalyst afforded the functionalized quaternary stereocenters **10** with high enantiomeric excess (Scheme 1.3). The authors stated that the use of organic mixed acid/base (buffer system) in the reaction conditions favour the formation of compound **10**. The authors suggest that this is due to (i) acceleration of enamine formation through mild acid catalysis, (ii) prevention of *N*-alkylation of the base and the catalyst, (iii) neutralization of the acid by the product. The authors mention that the use of guanidine **9** as an additive increases the catalyst turnover and also furnishes the products **10** in good yields and high enantiomeric excess.



Scheme 1.3

1.2.1.3 The Feringa Synthesis of Acyclic Quaternary Stereocenters

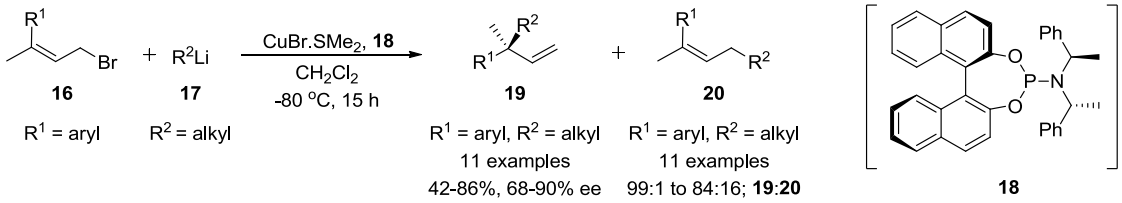
In 2012, Feringa and coworkers[6] developed the copper catalyzed AAA of allyl bromides **11** to afford the unsaturated quaternary stereocenters **14**. An enantioselective S_N2' reaction of (*E*)-allyl bromides **11** with the organocuprate reagent derived *in situ* from the alkyl lithium **12** and the chiral phosphoramidite **13** provided the desired product **14** with low to high enantiomeric excess (Scheme 1.4). Notably, under these reaction conditions, the S_N2 addition product **15** was obtained as the minor product (**14**/**15** >98:2 to 91:9; GC and ^{1}H NMR analysis).



Scheme 1.4

In 2015, the same group[2h] reported the synthesis of quaternary stereocenters from (*Z*)-allyl bromides **16** using the same chemistry described for the (*E*)-allyl bromides in

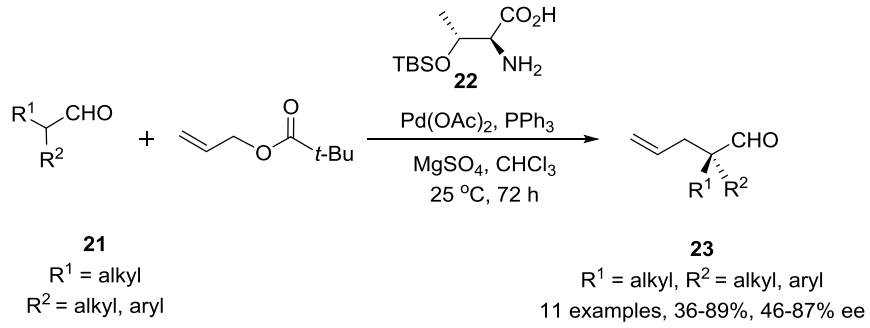
Scheme 1.4. In this case, products **19** were obtained with high enantiomeric excess and the S_N2 addition products **20** were also obtained as minor products (19/20 = 99:1 to 84:16; GC and ^1H NMR analysis, Scheme 1.5).



Scheme 1.5

1.2.1.4 The Yoshida Synthesis of Acyclic Quaternary Stereocenters

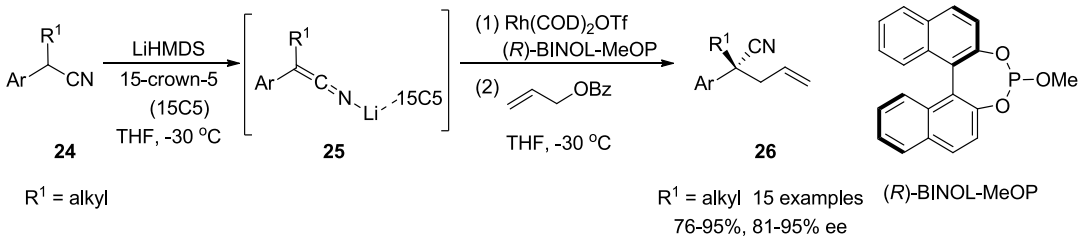
In 2013, Yoshida and coworkers[7] reported the synthesis of acyclic quaternary stereocenters **23** from *α,α*-disubstituted aldehydes **21**. Enantioselective direct *α*-alkylation of aldehydes **21** with allyl pivalate was achieved by using a combination of an organocatalyst **22** and a Pd-based catalyst to afford the functionalized quaternary stereocenters **23** with moderate to high enantiomeric excess (Scheme 1.6).



Scheme 1.6

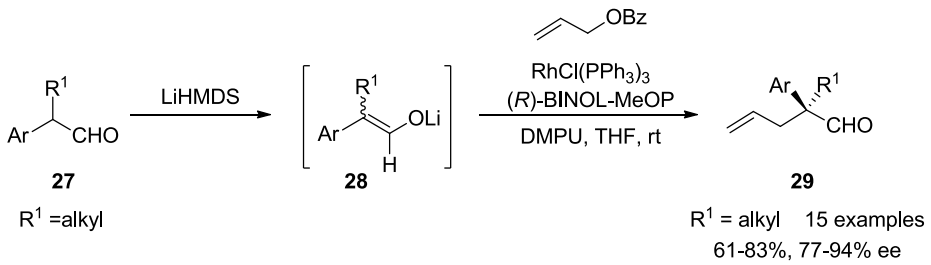
1.2.1.5 The Evans Synthesis of Acyclic Quaternary Stereocenters

In 2015, Evans and coworkers[2e] introduced a method for the synthesis of acyclic quaternary stereocenters from nitriles **24**. Asymmetric allylic alkylation of nitriles **24** with allyl benzoate was achieved in the presence of LiHMDS and a chiral Rh catalyst to afford the functionalized quaternary stereocenters **26** with high enantiomeric excess (Scheme 1.7).



Scheme 1.7

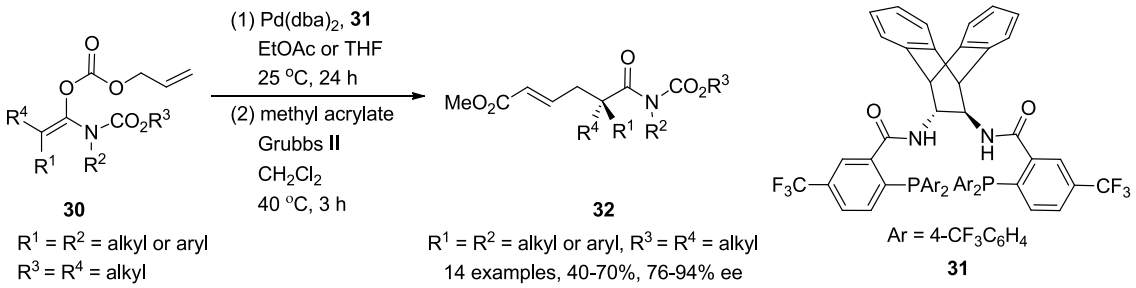
In 2016, the same group[8] reported the direct asymmetric alkylation of aldehydes **27** with allyl benzoates using a chiral Rh catalyst to provide the functionalized quaternary stereocenters **29** with high enantiomeric excess (Scheme 1.8). Reactions of LiHMDS with aldehydes **27** generate lithium enolates **28** and subsequent alkylation of enolates **28** with allyl benzoate in the presence of chiral Rh catalyst affords the desired product **29**. The authors state that (*E*) and (*Z*) enolates **28** produce the same kind of asymmetric induction which avoids the necessity of controlling the geometry of **28** for the enantioselectivity of the reaction.



Scheme 1.8

1.2.1.6 The Stoltz Synthesis of Acyclic Quaternary Stereocenters

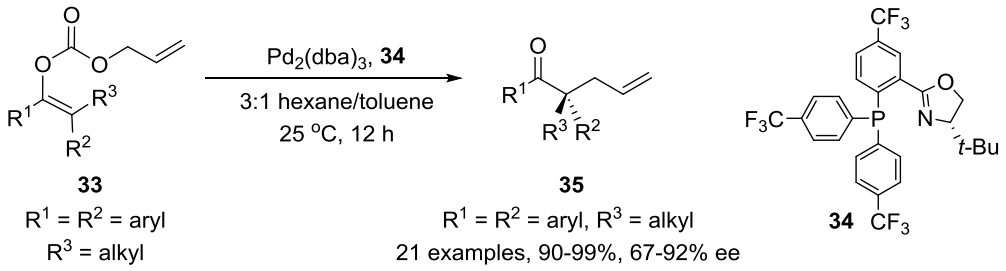
In 2017 Stoltz and coworkers[9] reported the synthesis of acyclic quaternary stereocenters **32** from allyloxy carbonyl trapped amide enolates **30**. Amide enolates **30** were subjected to decarboxylative alkylation in the presence of a chiral phosphine (**31**)-derived Pd catalyst. A subsequent cross metathesis reaction of the alkylation product with methyl acrylate using the Grubbs II catalyst provided the quaternary stereocenters **32** with high enantiomeric excess (Scheme 1.9).



Scheme 1.9

In 2018, the same group[2j] reported the enantioselective decarboxylative allylic alkylation of **33** in the presence of a chiral phosphine ligand (**34**)-derived Pd catalyst to afford functionalized quaternary stereocenters **35** in excellent yields with good

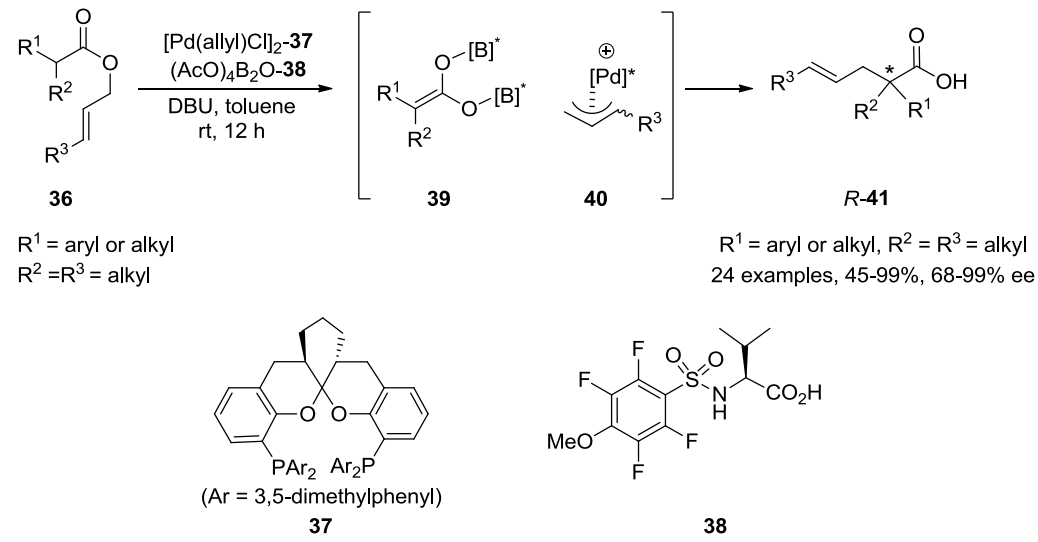
enantiomeric excess (Scheme 1.10). The authors state that ligand **34** plays a crucial role in providing the products **35** in excellent yields and good enantioselectivities.



Scheme 1.10

1.2.1.7 The Kanai Approach to Synthesis of Acyclic Quaternary Stereocenters

In 2018, Kanai and coworkers[10] developed a methodology for the synthesis of isolated quaternary stereocenters from <u>α,α</u>-disubstituted *O*-allyl esters **36**. The methodology relies on the use of Pd and boron-based catalysts that are complexed with the chiral ligands **37** and **38** respectively. *α,α*-Disubstituted *O*-allyl esters **36** in the presence of chiral Pd/Boron catalysts furnished the functionalized quaternary stereocenters **41** with moderate to high enantiomeric excess. The authors state that ionization of esters **36**, during the reaction, generates nucleophilic boron enediolates **39** and electrophilic chiral *π*-allyl palladium complexes **40**. Enantioselective coupling of **39** with **40** provides the desired product **41** (Scheme 1.11).

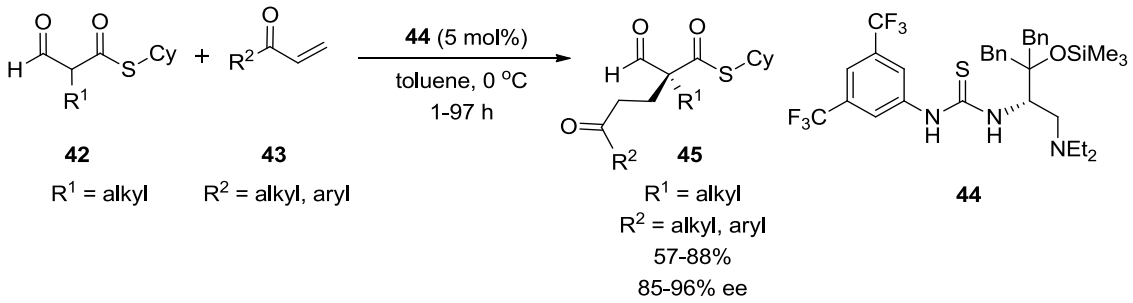


Scheme 1.11

1.2.2 Asymmetric Michael addition Reactions

1.2.2.1 The Misaki Synthesis of Quaternary Stereocenters

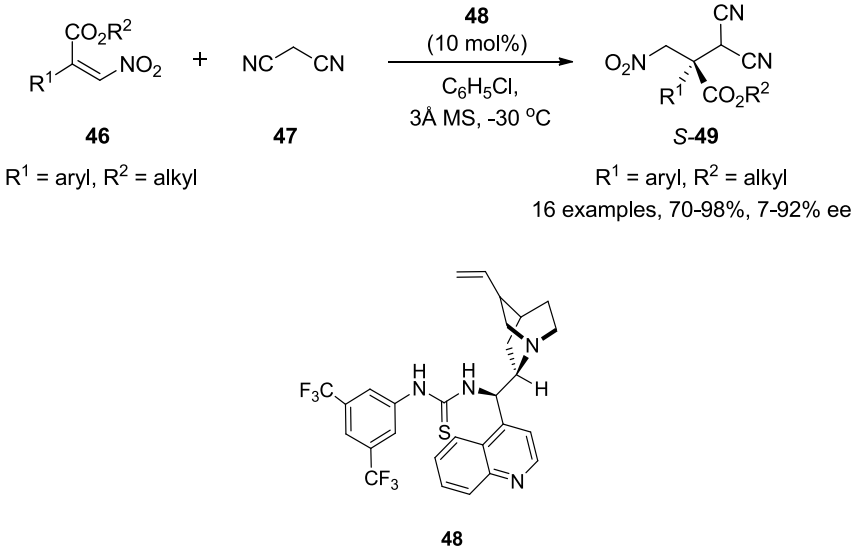
In 2015, Misaki and coworkers[2d] introduced the synthesis of functionalized quaternary stereocenters **45** from thioesters **42**. Enantioselective Michael addition reactions of thioesters **42** to vinyl ketones **43** were achieved by thiourea catalyst **44** to afford the functionalized quaternary stereocenters **45** in good yields with high enantiomeric excess (Scheme 1.12).



Scheme 1.12

1.2.2.2 The Hu Synthesis of Acyclic Quaternary Stereocenters

In 2015, Hu and coworkers[2c] developed a methodology to synthesize functionalized quaternary stereocenters *S*-**49** from nitroalkenes **46**. Michael addition reactions of malononitrile **47** with nitroalkenes **46** in the presence of cinchona alkaloid derived thiourea **48** afforded the functionalized quaternary stereocenters *S*-**49** with low to high enantiomeric excess (Scheme 1.13).



Scheme 1.13

The authors propose a transition state for the Michael addition in which the catalyst **48** is double-hydrogen-bonded with **46** and deprotonated **47** acts as a nucleophile. The *Re* face of the *α*-position of nitroalkene **46** is exposed to the nucleophile **47** and subsequent addition at the *α*-carbon provides *S*-**49** (Figure 1.1) as the major product.

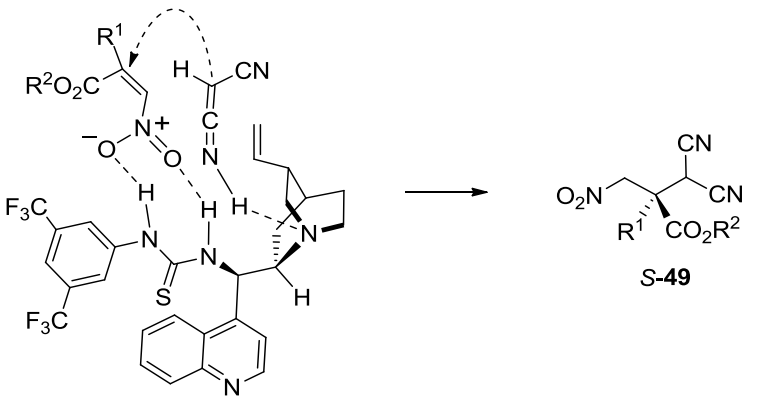
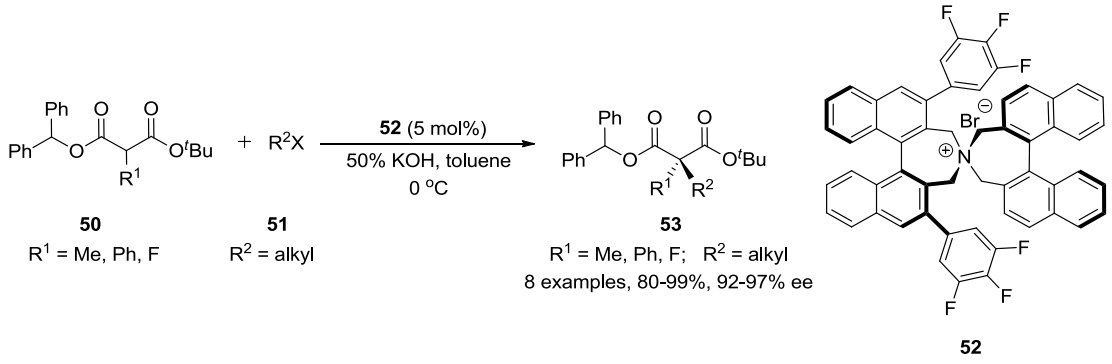


Figure 1.1 Transition state for the formation of *S*-**49**

1.2.3 Chiral Phase Transfer Catalyzed Reaction

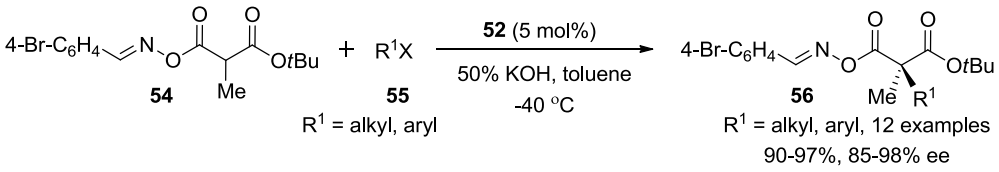
1.2.3.1 The Park Synthesis of Acyclic Quaternary Stereocenters

In 2011, Park and coworkers[11] reported the synthesis of acyclic quaternary stereocenters from malonates **50**. The malonates underwent α-alkylation with alkyl halides **51** in the presence of the chiral phase transfer catalyst **52** to afford the functionalized quaternary stereocenters **53** with high enantiomeric excess (Scheme 1.14).



Scheme 1.14

In 2015, the same group[2a] reported the α-alkylation of malonates **54** to synthesize the functionalized quaternary stereocenters **56**. Malonates **54** reacted with halides **55** in the presence of the chiral catalyst **52** to afford the quaternary stereocenters **56** in good yields with high enantiomeric excess (Scheme 1.15).



Scheme 1.15

1.3 The Gosteli-Claisen Rearrangement

Our interest in the Claisen rearrangement stems from our studies on the asymmetric synthesis of functionalized quaternary stereocenters.[12] The Claisen rearrangement is a cornerstone of synthetic organic chemistry and it is one of the most extensively studied reactions.[13] Applications of the rearrangement range from the construction of key structural elements in natural products to the stereoselective assembly of cyclic and acyclic motifs for applications in other synthetic endeavours.[14] Catalysis of the Claisen rearrangement is of particular interest and catalytic asymmetric versions have also been intensely investigated.[15]

In recent years, allyl vinyl ethers with an alkoxycarbonyl group at the 2-position (the so-called Gosteli-Claisen substrates **57**, Figure 1.2), have attracted attention due to their potential for two-point interaction of these dienes with Lewis acids,[15a,b] and acceleration of the rearrangement by alkoxycarbonyl substituents (Figure 1.2).[16a] The rate

enhancement of the Claisen rearrangement by the electron withdrawing groups such as trifluoromethyl and cyano at C-2 in the allyl vinyl ethers are also studied[16]. This structural feature in the allyl vinyl ethers **57** has therefore enabled the catalysis of their Claisen rearrangement.[17] Hiersemann reported[18] that the Gosteli-Claisen rearrangement is accelerated by metal-triflates (Cu^{+2}, Ln^{+3} and Sc^{+3}) and symmetric variants of the rearrangements were also examined.[15c,18b]

In this context, it may be noted that the rearrangement of allyl vinyl ethers **57** with a terminally unsubstituted vinyl portion and a terminally disubstituted allyl group would generate a functionalized, quaternary stereocenter-containing, acyclic motif **59** (Figure 1.2). Notably, while the Gosteli-Claisen rearrangement has been employed for establishing vicinal stereocenters, only one example has been reported for obtaining isolated quaternary stereocenters.[15a] Nonetheless, other than the sole example, the opportunities for attaining acyclic, functionalized quaternary stereocenters is unexplored.

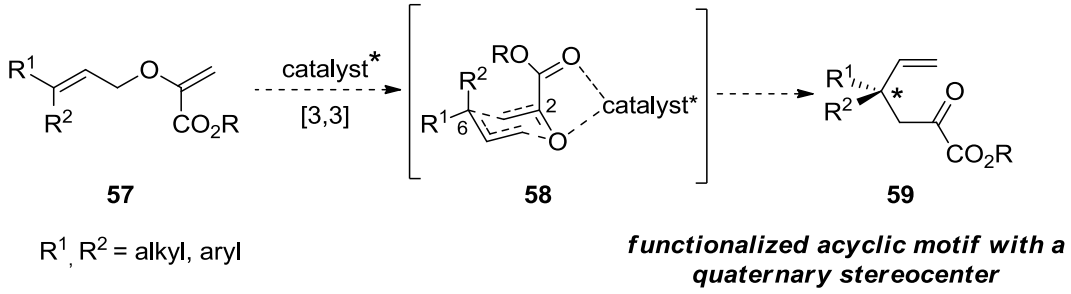


Figure 1.2 Claisen rearrangement of 2-alkoxycarbonyl allyl vinyl ethers

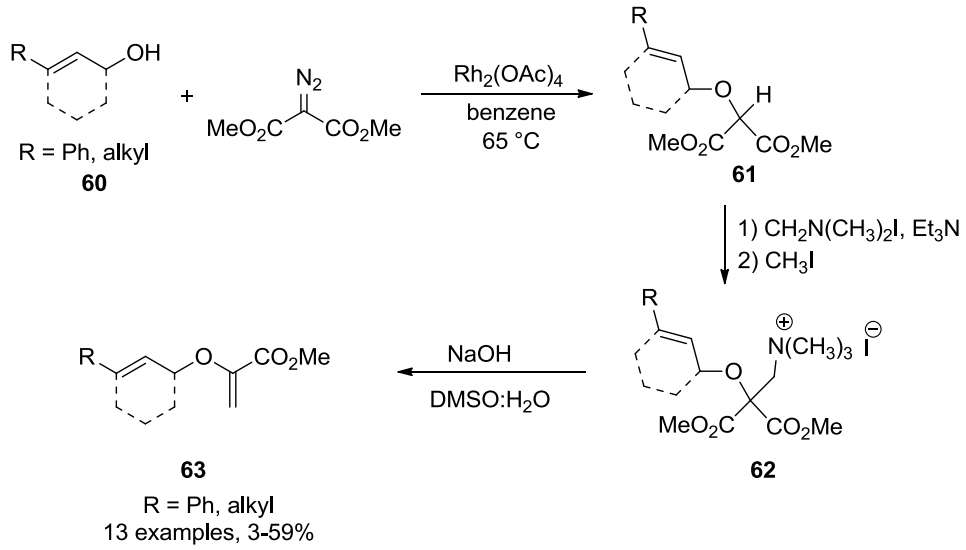
In this context, a convenient synthesis of Gosteli-Claisen substrates of the type **57** would be required for application in the synthesis of quaternary stereocenters. However, only a few syntheses of Gosteli-Claisen substrates are available and a summary of these

methods is provided below. Notably, not all of these methods have been used to prepare dienes of the type **57** with a terminally unsubstituted vinyl portion.

1.4 Known Synthetic Routes to Gosteli-Claisen Substrates

1.4.1 The Gajewski Synthesis of Gosteli-Claisen Substrates

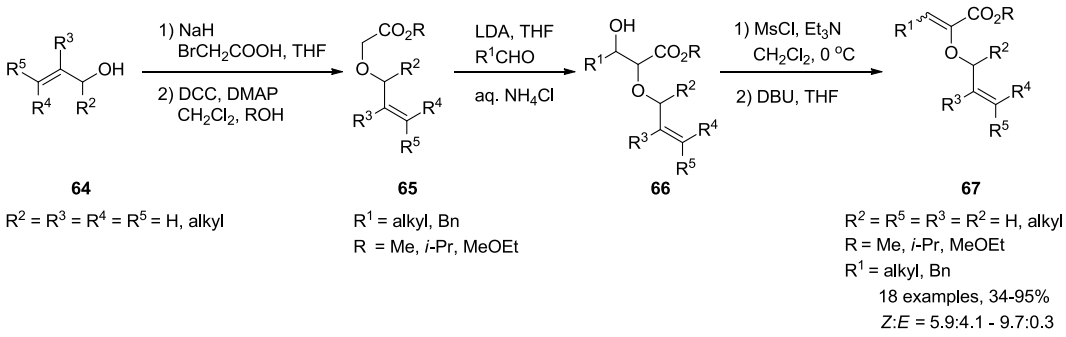
In 1987, Gajewski and coworkers[19] reported the synthesis of Gosteli-Claisen substrates from allylic alcohols. Allylic alcohols **60** reacted with dimethyl diazomalonate in the presence of catalytic amount of rhodium acetate dimer to give the O-H inserted products (allyloxymalonates) **61**. Mannich reaction of **61** with Eschenmoser's salt, followed by quaternization using methyl iodide provided **62**. Thermolysis of **62** in the presence of NaOH in DMSO/H_2O (9:1) resulted in decarboxylative elimination to provide the allyl vinyl ethers **63** (Scheme 1.16) in moderate yields. A limitation of this procedure is that the dienes **63** undergo Claisen rearrangement under the thermolysis conditions and the corresponding products of rearrangement are also always obtained.



Scheme 1.16

1.4.2 The Hiersemann Synthesis of Gosteli-Claisen Substrates

In 2000, Hiersemann[20] developed a synthetic strategy for the synthesis of Gosteli-Claisen substrates. *O*-Alkylation of stereochemically defined allylic alcohols **64** with bromoacetic acid and subsequent Steglich-Hassner esterification with aliphatic alcohols provided *O*-allyl glycolates **65**. The glycolates **65** were subjected to aldol reaction with alkyl aldehydes to afford the *β*-hydroxy esters **66**. Mesylation of **66** followed by a stereorandom E2 elimination in the presence of DBU furnished the Gosetli-Claisen substrates **67** as a mixture of (*Z, E*) and (*E, E*) isomers (Scheme 1.17). Notably, the DBU promoted E2 elimination of mesylates **66** with a benzyl ester functionality also provided the products of Claisen rearrangement (10-12%) in addition to the required dienes **67**.

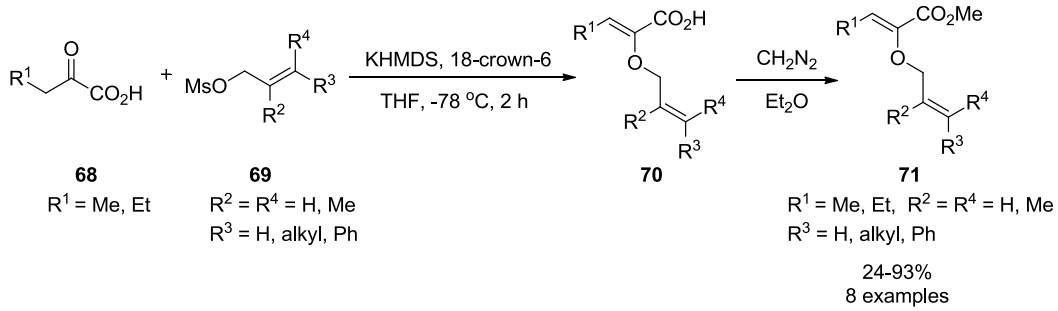


Scheme 1.17

1.4.3 The Jacobsen Synthesis of Gosteli-Claisen Substrates

In 2008, Jacobsen and coworkers[15d] reported a synthesis of Gosteli-Claisen substrates from *α*-ketoacids **68** and allyl mesylates **69**. *O*-Allylation of the enolates generated from **68** with **69** followed by esterification with diazomethane afforded the Gosteli-Claisen substrates **71** in low to excellent yields (Scheme 1.18). Despite the

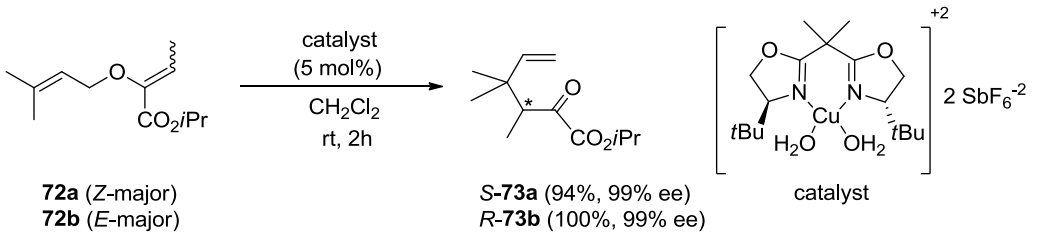
simplicity of this approach, the *O*-allylation of pyruvic acid, which would provide the vinyl-unsubstituted dienes that we required in our studies, is not reported in this study.



Scheme 1.18

1.5 Studies on Metal-Catalyzed Enantioselective Gosteli-Claisen Rearrangements

In 2001, Hiersemann introduced the metal-catalyzed enanatioselective Gosteli-Claisen rearrangement.[18] In these studies, C_2-symmetric bis(oxazoline) (box) ligands were used to prepare chiral complexes[21] from $Cu(H_2O)_2(SbF_6)_2$. From the box ligand/Cu salt combinations examined, the [Cu(*t*-Bu-box)]$(H_2O)_2(SbF_6)_2$ combination was found to provide the optimum catalyst for the Gosteli-Claisen rearrangement.[22a] The rearrangement of the allyl vinyl ether **72** (as a mixture of *Z* and *E* isomers) is shown in Scheme 1.19.[23] Under optimized conditions, the Cu-catalyzed Gosteli-Claisen rearrangement of **72** provided the product **73** in high enantiomeric excess at ambient temperature (Scheme 1.19). The authors propose that the box ligand forms a bidentate chelate with the metal salt and the substitutents at the stereogenic centers in the ligand impose an asymmetric environment for the rearrangement.[22] The stereochemistry of the product is determined by the configuration of the vinylic portions of the ethers and also the chirality of the metal catalysts.



Scheme 1.19

Hiersemann explored the aliphatic Gosteli-Claisen rearrangements for establishing vicinal stereocenters. A variety of substituted Gosteli-Claisen substrates were subjected to [3,3]-sigamatropic rearrangements in the presence of Cu/box catalysts and reaction conditions were optimized to obtain the desired product with high diastereo- and enatiomeric excess as well as to avoid the [1,3]-rearranged product. The authors observed that the rate of the Gosteli-Claisen rearrangements depended on the substituents present on the diene starting materials.[15a,18b]

1.6 Objectives

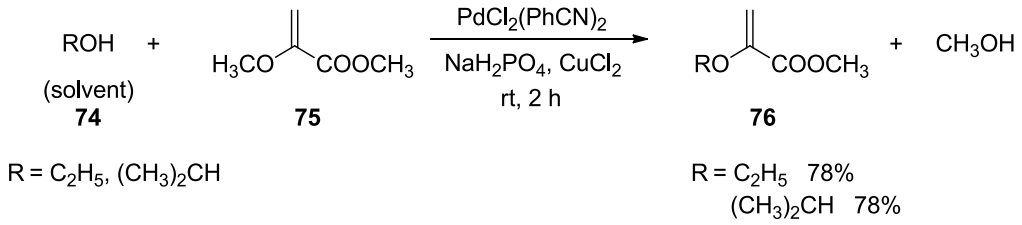
As mentioned in section 1.4, many of the reported syntheses of Gosteli-Claisen substrates require stereochemically defined allylic alcohols as a starting material. The enolate *O*-allylation protocol requires an *α*-keto acid as the starting material and generally provides modest yields. In addition, this method has not been used with esters of pyruvic acid as starting materials.[15d] Importantly, the other syntheses of allyloxy acrylates require multiple steps for installing the vinyl group via Mannich[19] or aldol reactions[20] and the products are sometimes obtained as mixtures with the corresponding Claisen rearrangement product.[19,20] All of these methods are primarily limited by the multiple steps needed to introduce diversity in the allylic portion.[15d,19,20]

One of the objectives of our studies was to develop a synthesis of Gosteli-Claisen substrates that overcome the limitations cited above and, more importantly, provide stereocontrolled access to α-allyloxy acrylates. In addition, we were also interested in the metal-catalyzed enantioselective Gosteli-Claisen rearrangements of dienes **57** to generate functionalized, acyclic quaternary stereocenters.

The following sections describe our investigations on the synthesis of Gosteli-Claisen substrates 57 and their metal-catalyzed enantioselective rearrangements to provide fucntionalized acyclic quaternary stereocenters.

1.7 Results and Discussion

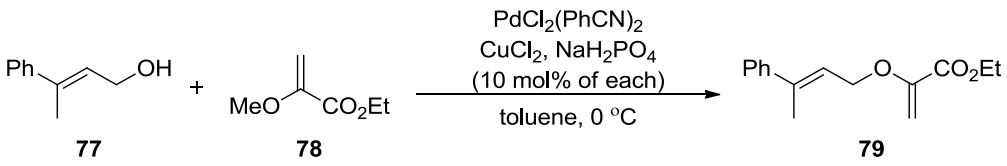
Our initial approach to the synthesis of Gosteli-Claisen substrates was based on the so-called vinyl exchange reaction described by Berchtold. In the original report,[24a] methyl 2-methoxy acrylate **75** was reacted with alcohols **74** in the presence of $PdCl_2(PhCN)_2$ to afford the corresponding vinyl exchange products **76** (Scheme 1.20). The vinyl exchange reaction requires a large excess of the alcohol component which is typically used as the solvent.



Scheme 1.20

We reasoned that a similar vinyl exchange reaction of ethyl 2-methoxy acrylate **78** with allylic alcohol **77** in the presence of $PdCl_2(PhCN)_2$ catalyst could afford the Gosteli-Claisen substrate **79** (Table 1.1). We initially examined the reaction of **77** and **78** under the Berchtold reaction conditions, but with only a slight excess of the alcohol in the presence of toluene as the solvent. Unfortunately, although the desired product **79** was obtained, the yield was very low (7%, Table 1.1, entry 1). Surprisingly, significant decomposition of the starting materials was also observed and **79** was the only identifiable product in this reaction. We therefore examined the exchange reaction under a variety of conditions as shown in Table 1.1. Reaction of **77** with an excess of acrylate **78** (3.5 equiv.) did not improve the yield of (7%, Table 1.1, entry 2). Similarly, the use of an excess of the alcohol **77** was also not beneficial (6% yield of **79**, Table 1.1, entry 3). Somewhat unexpectedly, the reaction of **77** and **78** in the presence of $PdCl_2(PhCN)_2$ but without addition of $CuCl_2$ and NaH_2PO_4 also furnished **79** in 13% over an extended period of time (Table 1.1, entry 4). Although the roles of the additives are not specified in the Berchtold procedure, it is plausible that $CuCl_2$ acts as an oxidant in the Pd-mediated catalytic cycle. Hence we also examined the use of an oxygen atmosphere for the exchange reactions. Unfortunately, this did not improve the product **79** yield (Table 1.1, entry 5 and 6). Since it is possible that small amounts of HCl formed during the reaction (by reduction of $PdCl_2$[24b]) hampers the vinyl exchange step (by catalysing acetal formation[24b] from **78**) we also examined the use of $NaHCO_3$ as an additive instead of NaH_2PO_4. However, this change provided no product and unreacted **77** was recovered (Table 1.1, entry 7).

Table 1.1 Optimization of vinyl exchange reactions of **78** with **77**



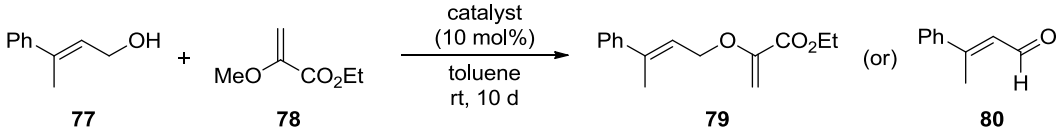
77 **78** **79**

Entry	77 (equiv.)	78 (equiv.)	Atmosphere	Time (d)	Yield (%)
1	1.2	1	N_2	1	7
2	1	3.5	N_2	1	7
3	2	1	N_2	1	6
4[a]	1	1.5	N_2	7	13
5	1	1.5	O_2	1	6
6[b]	1	1.5	O_2	7	8
7[c]	1	1.5	N_2	5	0

[a]Reaction without $CuCl_2$ and NaH_2PO_4. [b]Reaction without NaH_2PO_4. [c]NaH_2PO_4 replaced by $NaHCO_3$.

Since vinyl exchange reactions of enol ethers with alcohols have also been reported with Hg(II) salts as Lewis acids,[24] a survey of other well-known Lewis acid catalysts was conducted for the vinyl exchange reaction of **78** with **77** as shown in Table 1.2.

Table 1.2 Catalyst survey for the vinyl exchange reaction of **78** with **77**



77 **78** **79** **80**

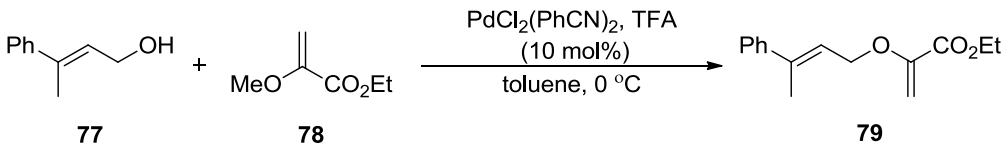
Entry	Catalyst	79(%)	80(%)	77 recovered (%)
1	$Pd(OAc)_2$	-	50	-
2	$Pd(TFA)_2$	-	50	-
3	Pd(1,10-phenanthroline)$(OAc)_2$	-	-	80

4	$PdCl_2(dppf)\cdot CH_2Cl_2$	-	-	82
5	$PdCl_2(PPh_3)_2$	6	-	-
6	$Hg(OAc)_2$	2	-	-
7	$Sc(OTf)_3$	-	-	90
8	$Yb(OTf)_3$	-	-	84
9	$LaCl_3.H_2O$	-	-	86

The attempted vinyl exchange reaction of **77** and **78** in the presence of $Pd(OAc)_2$ or $Pd(TFA)_2$ afforded the oxidation product **80** (Table 1.2, entry 1 and 2). Pd(1,10-phenanthroline)$(OAc)_2$[24b] and $PdCl_2(dppf)\cdot CH_2Cl_2$ did not promote the vinyl exchange reaction and unreacted **77** was recovered (Table 1.2, entry 3 and 4). Although the use of $PdCl_2(PPh_3)_2$ and $Hg(OAc)_2$ afforded **79**, the yields were not synthetically useful (6% and 2% respectively, entries 5 and 6, Table 1.2). No reaction was observed in the presence of $Sc(OTf)_3$, $Yb(OTf)_3$ or $LaCl_3.H_2O$ and unreacted **77** was recovered (Table 1.2, entries 7, 8 and 9).

Previous studies by Nakai[24e] have indicated that the yield of the Pd-catalyzed vinyl exchange reaction of conventional enol ethers with allyl alcohols is significantly increased by the use of trifluoroacetic acid (TFA) as a co-catalyst in the reaction. Hence, the Pd-catalyzed vinyl exchange reaction of **78** with **77** was examined with TFA as an additive (Table 1.3). Unfortunately, none of these reactions provided **79** in improved yield (Table 1.3).

Table 1.3 Optimization of vinyl exchange reaction of **78** with **77**



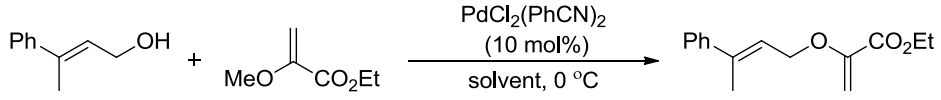
77 **78** **79**

Entry	Time (d)	Yield (%)
1	5	6
2[a]	1	3
3[b]	5	6
4[c]	7	0

[a]Reaction at rt. [b]Reaction with 5 mol% $CuCl_2$. [c]Reaction without addition of $PdCl_2(PhCN)_2$

Based on the optimization studies (Table 1.1 - 1.3) for the vinyl exchange reaction of **78** with **77**, $PdCl_2(PhCN)_2$ catalyst was chosen for the solvent survey (entry 4, Table 1.1). The results of these studies are summarized in Table 1.4.

Table 1.4 Solvent screening for the vinyl exchange reaction of **78** with **77**



77 (1 equiv.) **78** (1.5 equiv.) **79**

Entry	**Solvent**	**Time (d)**	**Yield (%)**
1	Toluene	7	13
1	benzene	7	12
2	CH_2Cl_2	4	10
3	$CHCl_3$	7	10
4	THF	4	6
5	CH_3CN	4	2
6	DMF	7	-

Vinyl exchange reaction of **78** with **77** in benzene provided **79** in 12% (Table 1.4, entry 1). Chlorinated solvents mediated the vinyl exchange reaction of **78** with **77** which furnished **79** in 10% yield (Table 1.4, entry 2 and 3). Only a trace amount of product **79** was obtained for the reactions of **78** with **77** in dipolar aprotic solvents (Table 1.4**,** entry 5 and 6). In all the optimization studies of the vinyl exchange reaction of **78** with **77**, a significant amount of decomposition products (~20-30%) always accompanied the desired product **79**.

Given the difficulties that we faced in the vinyl exchange strategy, we turned our focus to an alternative methodology which could easily functionalize the allylic portion of the allyl vinyl ethers. We decided to explore a strategy that would provide the required 2-alkoxycarbonyl motif of the allyl vinyl ethers in less steps and would also offer access to a variety of terminally disubstituted allyl groups. We reasoned that both of these objectives could be achieved by the chemoselective functionalization of an unsymmetrical dialkyl oxalate. Specifically, we decided to examine the Petasis methylenation[25] of oxalic acid diesters that were derived from *t*-butyl alcohol, for steric control of the regioselectivity[26a] of the methenylation,[26] and from allylic alcohols that could potentially be modified by the introduction of alkyl or aryl groups *via* cross-coupling reactions. Specifically, allylic alcohols with a vinyl halide motif were selected with the objective of conducting cross-coupling reactions involving the vinyl halide at a later stage in our proposed synthesis (Figure 1.3).

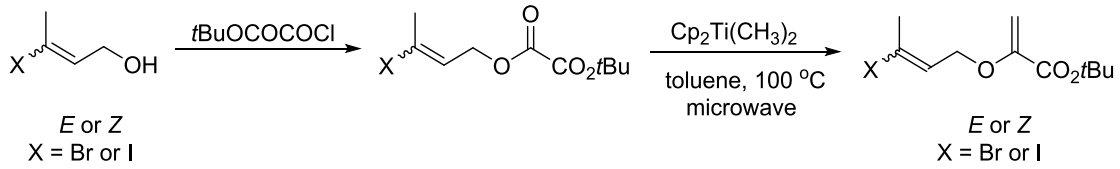
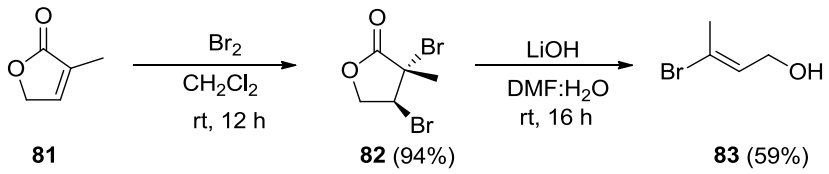


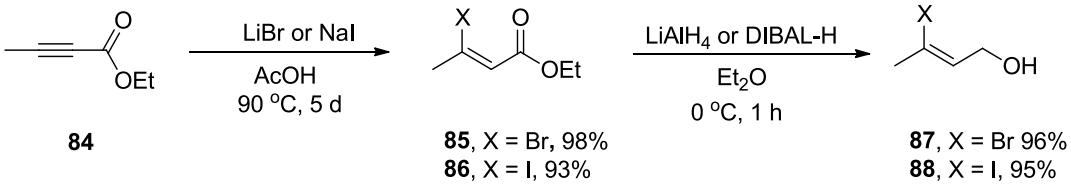
Figure 1.3 Strategy for the synthesis of Gosteli-Claisen substrates

Our studies began with the synthesis of selected bromo allylic alcohols. (*E*)-3-Bromo-2-butenol (**83**) was synthesized from 3-methyl-2-furanone **81** according to the reported procedure.[27] Thus, the reaction of **81** with bromine afforded dibromo compound **82**. Decarboxylative debromination of **82** in the presence of LiOH in DMF/H_2O provided the required alcohol **83** (Scheme 1.21).



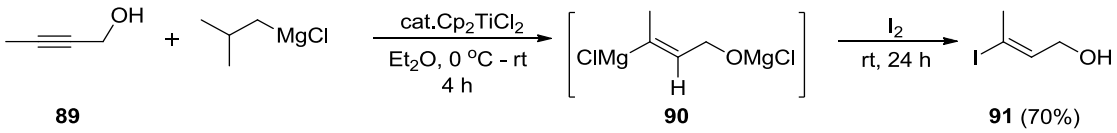
Scheme 1.21

(*Z*)-3-Bromo-2-buten-1-ol **87** and (*Z*)-3-iodo-2-buten-1-ol **88** were synthesized from ethyl-2-butynoate **84**.[28a] Hydrohalogenation of **84** in the presence of LiBr or NaI in acetic acid, afforded the corresponding haloesters **85** or **86**. Reduction of the haloesters with $LiAlH_4$ or DIBAL-H[28b] furnished the allylic alcohols **87** or **88** (Scheme 1.22) in excellent yields.



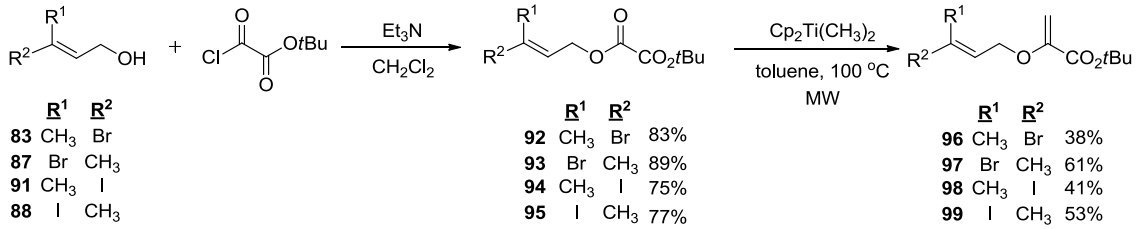
Scheme 1.22

(*Z*)-3-Iodo-2-buten-1-ol (**91**) was prepared from but-2-yn-1-ol **89** by treatment with *iso*-butyl magnesium chloride in the presence of a catalytic amount of titanocene dichloride to afford the *syn*-hydromagnesiation product **90** which upon reaction with iodine afforded **91**[29] (Scheme 1.23).



Scheme 1.23

Esterification of halo allylic alcohols **83**, **87**, **88**, **91** with *t*-butyl oxalyl chloride[30] provided the unsymmetrical dialkyloxalates **92-95** (Scheme 1.24). Pleasingly, the Petasis methylenation of the unsymmetrical dialkyloxalates **92-95**, by heating with dimethyl titanocene under microwave irradiation, provided the corresponding allyl vinyl ethers **96-99** respectively. Notably, the products of methylenation of the more hindered ester functionality were not detected in the crude reaction mixture (Scheme 1.24). In contrast, the ethyl ester analogs of **92** and **93**, prepared from ethyl oxalyl chloride, provided an inseparable mixture of mono-methylenation products (enol ethers) that were obtained by reaction of either the ethyl ester or the allyl ester functionalities of the oxalate.

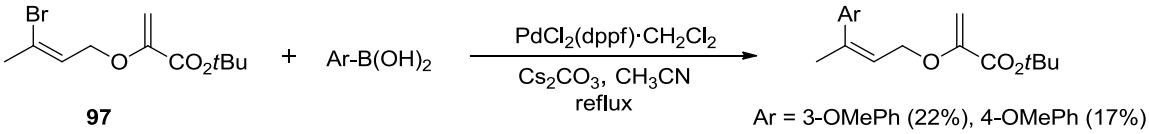


	R¹	R²			
83	CH_3	Br	**92**	CH_3	Br	83%
87	Br	CH_3	**93**	Br	CH_3	89%
91	CH_3	I	**94**	CH_3	I	75%
88	I	CH_3	**95**	I	CH_3	77%

	R¹	R²	
96	CH_3	Br	38%
97	Br	CH_3	61%
98	CH_3	I	41%
99	I	CH_3	53%

Scheme 1.24

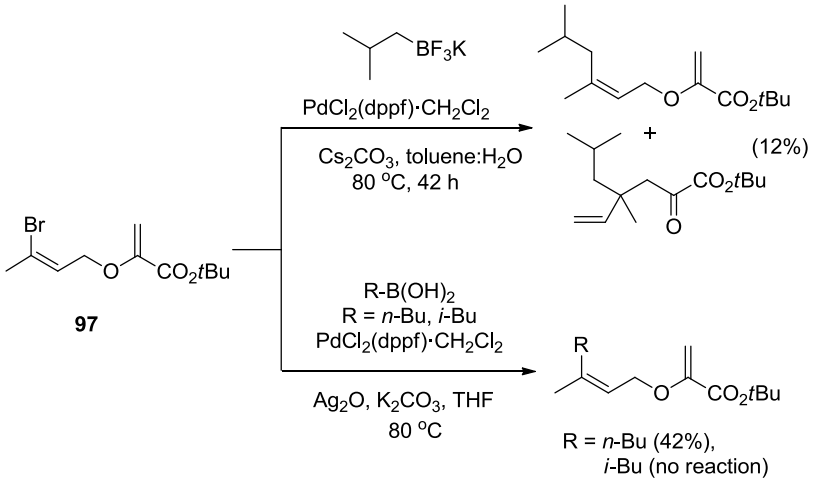
With the required haloallyl vinyl ethers **96-99** in hand we began our studies on the cross coupling reactions of these ethers. Initially, we examined the cross coupling reactions[31a] of the bromo ether **97** with 3-methoxyphenylboronic acid and 4-methoxyphenylboronic acid in the presence of $PdCl_2(dppf)\cdot CH_2Cl_2$. Unfortunately, the desired products were obtained in very low yields (Scheme 1.25). In addition, the attempted cross-coupling of **96** with 3-methoxyphenylboronic acid and 4-methoxyphenylboronic acid under these reaction conditions led to extensive decomposition of **96**.



Scheme 1.25

Although alkyl trifluoroborates are sometimes better cross-coupling reagents than alkyl boronic acids,[12a,31b] the cross-coupling of **97** with potassium isobutyl trifluoroborate provided the expected product either in low yield or as a mixture of the cross-coupled and the rearrangement product as shown in Scheme 1.26. Since Ag_2O is reported to be a beneficial additive in some cross-coupling reactions,[31c,d] its effect as an additive in our reactions was also examined. In these studies, butyl boronic acid performed better than

$BuBF_3K$. Thus, the cross-coupling of **97** with butyl boronic acid afforded the expected product in 42% yield, whereas no cross-coupling was observed with isobutyl boronic acid (Scheme 1.26).



Scheme 1.26

After a brief survey of solvents and reaction conditions, it was evident that the cross-coupling reactions of the bromo ethers **96** and **97** either failed or provided very low yields of the required products. Hence, further studies were done with the iodo derivatives **98** and **99**.

Since the introduction of an alkyl group in **96** and **97** via cross-coupling was particularly challenging, initial studies with **98** and **99** focused on their cross-coupling reactions with butyl boronic acid derivatives. The attempted cross-coupling of $BuBF_3K$ with either **98** or **99** in the presence of $PdCl_2(dppf)\cdot CH_2Cl_2$ and Cs_2CO_3 in toluene/H_2O led to complete decomposition of the vinyl halide. Interestingly, while no cross-coupling was observed with **99** and $BuBF_3K$, the use of $BuB(OH)_2$ provided **101a** (16%) when $PdCl_2(dppf)\cdot CH_2Cl_2$, and Ag_2O were used in THF, and $NaHCO_3$ was employed as the

base. Hence, all subsequent cross-coupling reactions of **98** and **99** were conducted in the presence of Ag_2O as an additive. The yield of **101a** improved significantly (67%) when $PdCl_2(dppf)\cdot CH_2Cl_2$ was replaced with $Pd(PPh_3)_4$ and K_2CO_3 was used as the base.[31e] Using these conditions, **98** provided **100a** (63%). Similarly, the cross-coupling of **98** with isobutyl- and cyclopropylboronic acids provided **100b** (61%) and **100c** (65%) respectively (Figure 1.4).

Although the use of Ag_2O as an additive was beneficial for cross-coupling reactions of **98** with aryl boronic acids, some modification of the conditions used for the cross-coupling with alkylboronic acids was also necessary. Thus, while the unoptimized cross-coupling of **98** and 2-naphthyl boronic acid ($PdCl_2(dppf)\cdot CH_2Cl_2$, Cs_2CO_3 in CH_3CN) provided **100d** in low yield (22%) in initial studies, the use of Ag_2O as an additive and KOH as the base in dioxane[31f] considerably improved the yield of **100d** (68%). With the optimized reaction conditions in hand, several alkyl as well as arylboronic acids were coupled with **98** and **99** to provide the functionalized allyl vinyl ethers **100a-j** and **101a-h** and these results are summarized in Figure 1.4.

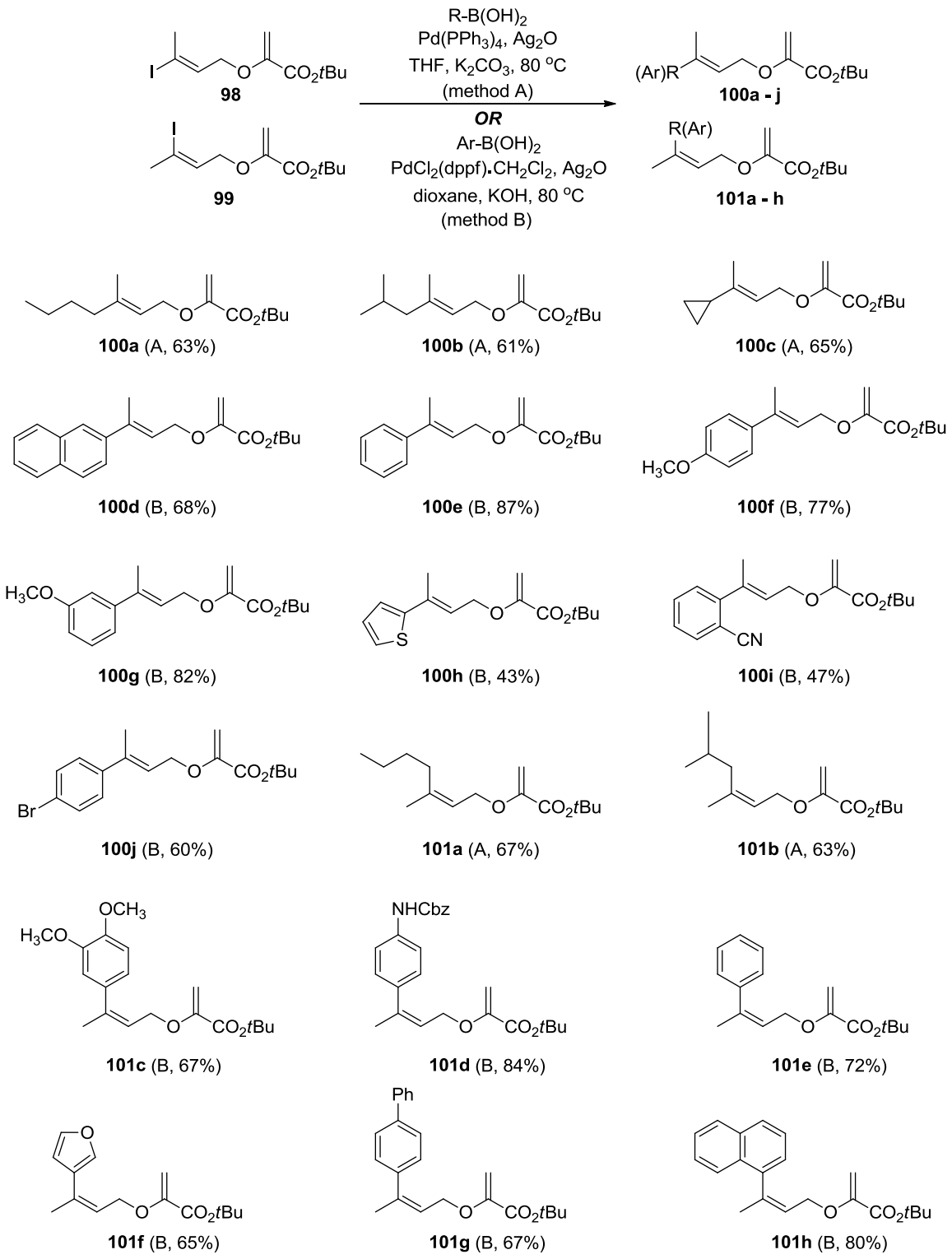


Figure 1.4 Synthesis of allyl vinyl ethers

Notably, although both Pd(0)[32a,b] and Pd(II)[32c-f] derived catalysts are reported to catalyze the Claisen rearrangement of allyl vinyl ethers at ambient temperature, rearrangement of **98** and **99** was not observed under the optimized cross-coupling conditions. However, it is also known that the Pd(II) catalyzed Claisen rearrangement reactions are sensitive to the nature of the ligand in the Pd catalyst.[32d] The success of the cross-coupling reactions in the present study, despite the presence of transient Pd(II) species, underscores the importance of the ligand effect and it may be attributed to the use of a diphosphine ligand on the palladium. Although this effect has not been investigated for the Claisen rearrangements with Pd(0)-derived catalytic species, the results of the present study suggest that either the nature of the Pd(0) species or the electronic properties of the substrate are critical for the rearrangement. Alternatively, it is plausible that the cross-coupling reactions of **98** and **99** are faster than the Pd-catalyzed Claisen rearrangement of **100** and **101**.

1.8 Metal-catalyzed Enantioselective Gosteli-Claisen Rearrangement

After developing new methodologies for the synthesis of allyl vinyl ethers, their asymmetric Gosteli-Claisen rearrangements were examined with chiral metal-catalysts. A selection of bisoxazoline ligands was employed in this study. Ligands that differed in the spacer group between two oxazoline rings as well as the substituents at the stereogenic centers (**L1**-**L6**, Figure 1.5) were prepared. Three metal salts, $Yb(OTf)_3$, $Cu(OTf)_2$ and $Mg(NTf)_2$ were chosen for preparing chiral metal complexes with ligands **L1**-**L6** with the objective of identifying the best metal-ligand combination and the results of these studies are summarized in Table 1.5. All of the chiral metal complexes were prepared *in situ* by

adding the salt to a solution of the ligand in a suitable solvent followed by stirring the mixture at ambient temperature for 1 h to provide a homogeneous solution. A solution of the diene was then added to this catalyst solution.

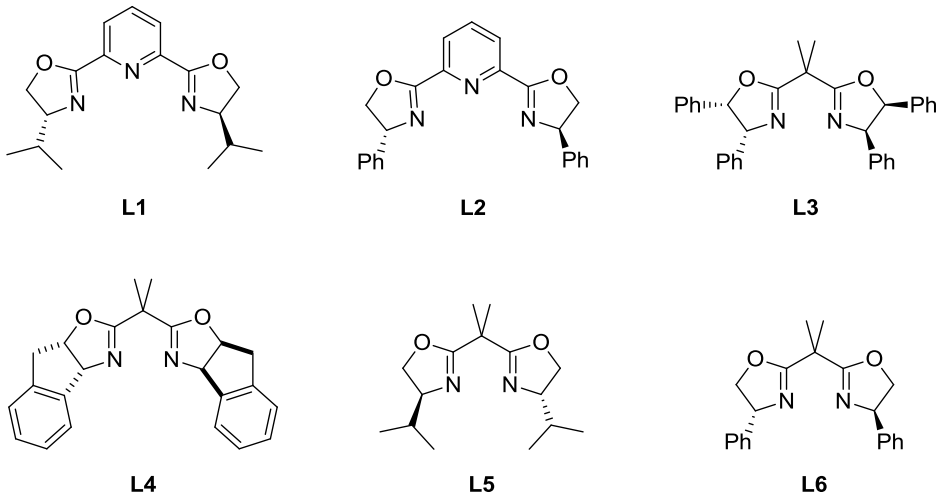
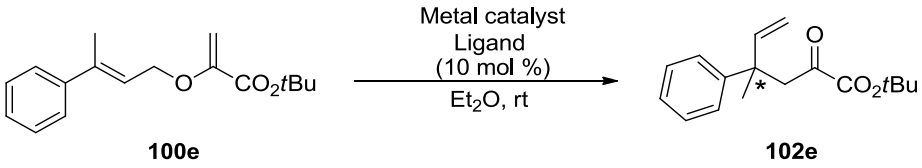


Figure 1.5 List of bis(oxazoline) ligands

Initial studies of the Gosteli-Claisen rearrangement were conducted with the allyl vinyl ether **100e** in diethyl ether as the solvent. Notably, only some of the selected metal salt/ligand combinations provided the rearrangement product **102e** at ambient temperature. Exposure of **100e** to the $Yb(OTf)_3$/**L1** chiral complex afforded the Claisen rearrangement product **102e** in low yield (25%) and also low enantiomeric excess (11% ee, Table 1.5, entry 1). Metal complexes derived from a combination of Cu or Mg salts and the ligand **L1** did not promote the Gosteli-Claisen rearrangement (Table 1.5, entry 2 and 3). No product was obtained for the reactions of **100e** with metal salts/**L2** (Table 1.5, entry 4-6). The use of $Yb(OTf)_3$/**L3** furnished the product **102e** with 6% ee (Table 1.5, entry 7). Allyl vinyl ether **100e** decomposed in the presence of $Cu(OTf)_2$/**L3** at ambient

temperature and hence the reaction was also conducted at 0 ^{o}C (Table 1.5, entry 8 and 9). Unfortunately, lowering the temperature resulted in complete inhibition of the reaction and no product was obtained. When the $Mg(NTf)_2$/**L3** catalyst was used, **102e** was obtained with 3% ee (Table 1.5, entry 10). The combination metal salts with a sterically hindered box ligand such as **L4** provided **102e** with low enantiomeric excess (Table 1.5, entry 11-13). Reaction of **100e** with $Yb(OTf)_3$/**L5** afforded **102e** with 19% ee (Table 1.5, entry 14). **100e** did not undergo rearrangement in the presence of $Cu(OTf)_2$/**L5** and $Mg(NTf)_2$/**L5** catalysts (Table 1.5, entry 15 and 16). Catalyst $Yb(OTf)_3$/**L6** and $Mg(NTf)_2$/**L6** did not afford the rearrangement product **102e** (Table 1.5, entry 17 and 20). Gratifyingly, the Cu complex derived from $Cu(OTf)_2$ and **L6** effectively catalyzed the rearrangement to provide **102e** in 53% yield with 45% ee (Table 1.5, entry 18). The reaction of **100e** with $Cu(OTf)_2$/**L6** at 0 ˚C provided no product and unreacted **100e** was recovered (Table 1.5, entry 19).

Table 1.5 Ligand screening for the metal-catalyzed Gosteli-Claisen rearrangement of **100e**



100e **102e**

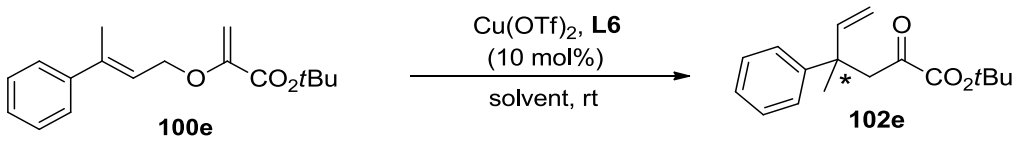
Entry	Metal catalyst	Ligand	Time (d)	Yield (%)	100e recovered (%)	ee (%)
1	$Yb(OTf)_3$	**L1**	5	25	0	11
2	$Cu(OTf)_2$	**L1**	10	0	63	-
3	$Mg(NTf)_2$	**L1**	10	0	55	-

4	$Yb(OTf)_3$	**L2**	10	0	68	-
5	$Cu(OTf)_2$	**L2**	10	0	71	-
6	$Mg(NTf)_2$	**L2**	10	0	76	-
7	$Yb(OTf)_3$	**L3**	10	33	0	6
8	$Cu(OTf)_2$	**L3**	1 h	0	0	-
9	$Cu(OTf)_2$	**L3**[a]	6 h	0	69	-
10	$Mg(NTf)_2$	**L3**	10	13	0	3
11	$Yb(OTf)_3$	**L4**	10	11	0	5
12	$Cu(OTf)_2$	**L4**	10	7	0	4
13	$Mg(NTf)_2$	**L4**	10	9	0	8
14	$Yb(OTf)_3$	**L5**	5	10	-	19
15	$Cu(OTf)_2$	**L5**	11	0	52	-
16	$Mg(NTf)_2$	**L5**	6	0	65	-
17	$Yb(OTf)_3$	**L6**	6	0	76	-
18	$Cu(OTf)_2$	**L6**	3	53	0	45
19	$Cu(OTf)_2$	**L6**[a]	7	0	66	-
20	$Mg(NTf)_2$	**L6**	6	0	74	-

[a]Reaction at 0 ^{o}C

Having identified a suitable metal salt/ligand combination, solvent screening was carried out for the rearrangement of **100e** with the catalyst derived from $Cu(OTf)_2$ and the ligand **L6**. Unfortunately, none of the other solvents improved the enantiomeric excess of the product **102a** (Table 1.6).

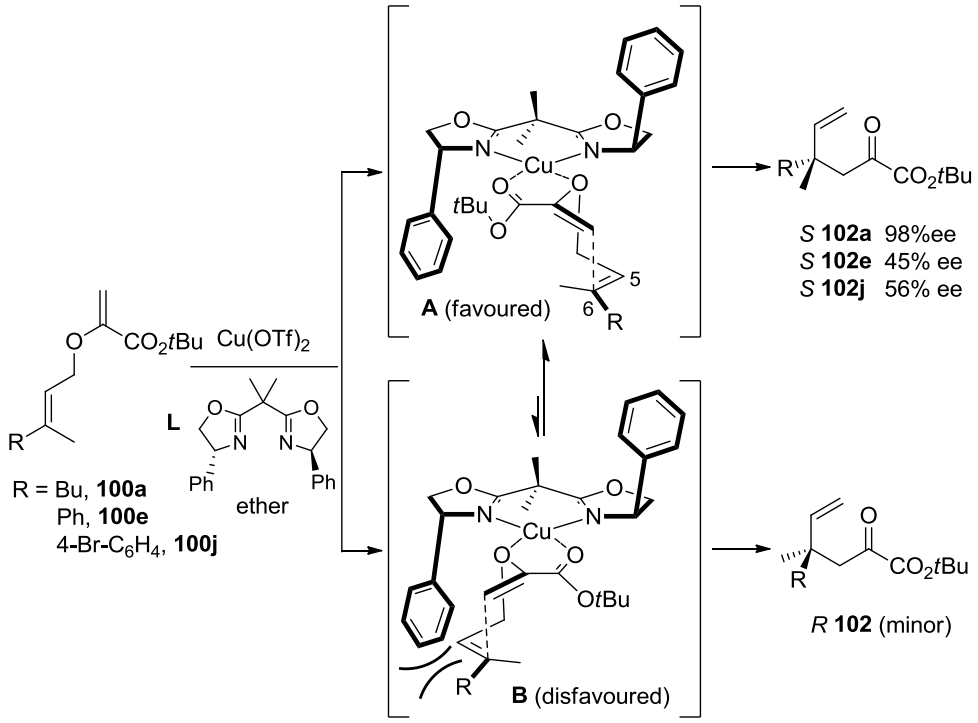
Table 1.6 Solvent screening for the Gosteli-Claisen rearrangement of **100e**



Entry	solvent	Time (d)	Yield (%)	ee (%)
1	toluene	4	53	43
2	$CHCl_3$	1	52	39
3	CH_2Cl_2	2	64	38
4	DCE	22 h	77	40
5	EtOAc	7	20	41
6	THF	7	17	42
7	Et_2O	3	53	45

Consequently, the substrate scope of the rearrangement reaction was examined with $Cu(OTf)_2$/**L6** in ether as the solvent. Ethers in which the allyl portion was substituted with butyl (**100a**), phenyl (**100e**) and 4-bromophenyl (**100j**) substituents were examined. Under the optimized reaction conditions, the ethers **100a**, **100e** and **100j** provided the α-keto esters **102a** (58% yield, 97% ee), **102e** (53%, 45% ee) and **102j** (48%, 56% ee) respectively. The results suggest that dialkyl substitution at C-6 in the allyl vinyl ether is beneficial for enantioselectivity.

The formation of *S*-**102a** as the major enantiomer is based on a transition state assembly for related rearrangements proposed by Hiersemann[23] and a tentative mechanistic rationale for the Gosteli-Claisen rearrangement of the dienes **100** is shown in Scheme 1.27.



Scheme 1.27 Enantioselective Claisen rearrangement of **100** to **102**

The allyl vinyl ether forms a bidentate chelate with the Cu(II)-box complex to generate the sterically favoured distorted square planar complex **A** (Scheme 1.27) in which one face (*Re* for **100a** and *Si* for **100e** and **100j**) of the terminal carbon in the allyl group (C6) is exposed to the terminal carbon in the vinyl group (C1) in a chair-like conformation of the diene. The diastereomeric complex **B** is disfavored due to steric interactions between the R substituent in the allyl portion and the phenyl ring in the box

ligand. Subsequent rearrangement from complex **A** would generate the *S* enantiomer of **102**.

The precise reasons for the lower enantioselectivity of the rearrangement of **100e** and **100j** are not known at this time. It is plausible that, for these substrates, the difference in energy of the complexes **A** and **B** is less than the corresponding difference in energy for the complexes of **100a**, presumably due to the greater steric requirements of a butyl group in **100a** compared to a phenyl group in **100e** and **100j**. Alternatively, in the case of **100e** and **100j**, resonance stabilization of the positive charge at C6 (benzylic carbocation) may favor more the polar transition state assemblies **A′** and **A″** in which there is significantly more C-O bond cleavage than C-C bond formation (Figure 1.6). Notably, polar transition states for the Claisen rearrangement have been proposed on the basis of computational studies as well as experimentally observed substituent effects.[33] Rotation of the C5-C6 bond in the transition state **A′** will lead to the assembly **A″** in which the *Re* face of C6 in the vinyl group is exposed for bond formation. Subsequent rearrangement via **A″** will generate the *R* enantiomer of **102e** and **102j** (Figure 1.6), thus reducing the enantiomeric excess of the *S* enantiomer in these products.

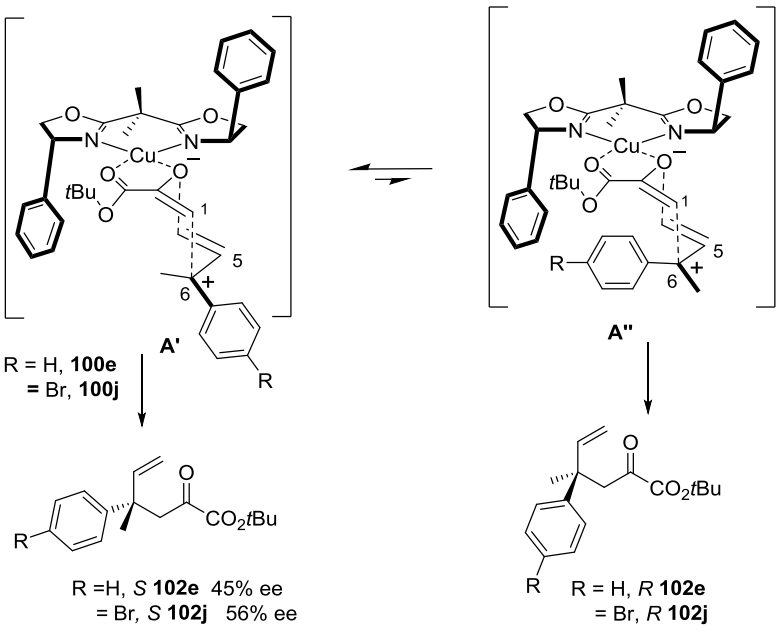


Figure 1.6. Enantioselective Gosteli-Claisen rearrangement of **100**

1.9 Conclusions

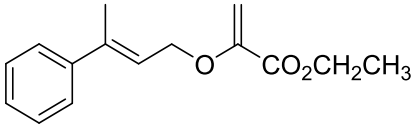
In conclusion, we have developed a modular synthesis of 2-*t*-butoxycarbonyl allyl vinyl ethers that are unsubstituted at C1 (vinyl portion) and disubstituted at C6 (allyl portion). The methodology offers a one-step construction of the functionalized vinyl portion of the ether and enables stereospecific synthesis of the terminally disubstituted allyl functionality. Metal-catalyzed enantioselective Claisen rearrangement of the allyl vinyl ethers generates a functionalized, acyclic motif with a quaternary stereocenter. Studies on the organocatalytic variant of the enantioselective Gosteli-Claisen rearrangement are discussed in the following chapter.

1.10 Experimental Section

General:

All commercially available reagents were used without purification. All reactions requiring anhydrous conditions were performed under an atmosphere of dry nitrogen using oven dried glassware. CH_2Cl_2 and THF were distilled from CaH_2 and sodium/benzophenone respectively. Commercial precoated silica gel plates were used for TLC. Silica gel for flash column chromatography was 230-400 mesh. IR spectra were recorded on a Bruker TENSOR 27 FT-IR instrument. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE III 300 or an AVANCE 500 instrument. Mass spectra were obtained on an Agilent 1100 series LC/MSD (Trap) or an Agilent 6200 LC/MSD (TOF) chromatographic system. High-resolution (HR) mass spectra (EI or ESI) were obtained on a Waters GCT Premier Micromass mass spectrometer.

(E)-*E*thyl 2-((3-phenylbut-2-en-1-yl)oxy)acrylate (79):



To a solution of allylic alcohol **77**[34] (100 mg, 0.68 mmol) in toluene (2 mL) were added enol pyruvate **78**[35] (130 mg, 1.00 mmol) and $PdCl_2(PhCN)_2$ (25 mg, 0.06 mmol) at 0 ^oC and the mixture was stirred at 0 ^oC for 7 days. Water (2 mL) was added and the mixture was extracted with EtOAc (3 x 5 mL). The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash

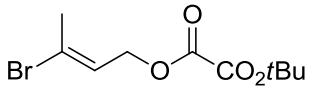
chromatography on silica gel (hexane:EtOAc, 96:4) to provide 21 mg (13%) of allyl vinyl ether **79** as a colorless oil.

IR (neat): 2982, 2926, 2870, 1733, 1620, 1311, 1184, 1165, 1020, 852, 757, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44-7.39 (m, 2H, Ar*H*), 7.36-7.26 (m, 3H, Ar*H*), 5.99 (tq, 1H, *J* = 6.3, 1.3, CH_3C=C*H*), 5.40 (d, 1H, *J* = 2.6, C=CH_2), 4.66 (d, 1H, *J* = 2.6, C=CH_2), 4.57 (br d, 2H, *J* = 6.3, OCH_2), 4.28 (q, 2H, *J* = 7.1, CH_2CH_3), 2.13-2.07 (m, 3H, CH_3C=CH), 1.34 (t, 3H, *J* = 7.1, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4 (*C*=O), 151.3 (*C*=CH_2), 142.6 (ArC_{ipso}), 139.1 (CH_3C=CH), 128.4 (2 x Ar*C*), 127.6 (Ar*C*), 125.9 (2 x Ar*C*), 122.2 (ArC=*C*H), 94.6 (C=*C*H_2), 66.1 (O*C*H_2), 61.6 (*C*H_2CH), 16.5 (*C*H_3C=CH), 14.3 (CH_2CH_3); HRMS (APPI, pos.): *m/z* (246.1258 (246.1256 calc. for $C_{15}H_{18}O_3$ (M^+) and 269.1149 (269.1154 calc. for $C_{15}H_{18}NaO_3$ $(M+Na)^+$).

General procedure for the synthesis of allyl *tert*-butyl oxalates 92-95:

To a solution of the 3-halo-2-butenol[27-29] in dichloromethane was added triethyl amine. The mixture was stirred for 5 min at ambient temperature and then cooled to 0 ^{o}C. A solution of *tert*-butyl 2-chloro-2-oxoacetate in dichloromethane was added over 5 min and the mixture was stirred at 0 ^{o}C for the specified time. Water was added and the mixture was extracted with dichloromethane. The combined extracts were washed with aqueous HCl (0.1 M), saturated aqueous sodium bicarbonate, brine, dried over Na_2SO_4 and concentrated under reduced pressure to provide the corresponding allyl *tert*-butyl oxalates. These were used in the next step without purification.

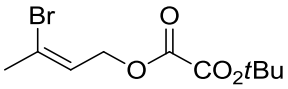
(*E*)-3-Bromobut-2-enyl *tert*-butyl oxalate (92):



The reaction of (*E*)-3-bromo-2-butenol (310 mg, 2.06 mmol), triethylamine (0.350 mL, 2.48 mmol) and *tert*-butyl 2-chloro-2-oxoacetate (405 mg, 2.48 mmol) in dichloromethane (5 mL) for 3 h, according to the general procedure, provided 478 mg (83%) of **92**; R_f = 0.20 (hexanes/EtOAc, 96:4).

IR (neat): 2983, 2920, 1760, 1736, 1371, 1327, 1260, 1194, 1138, 943, 841 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.09 (tq, 1H, *J* = 7.8, 1.4, CH_3C=C*H*), 4.68 (br d, 2H, *J* = 7.8, OCH_2), 2.38-2.35 (m, 3H, CH_3C=CH), 1.56 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.2 (*C*$O_2(CH_3)_3$ or *C*O_2CH_2), 156.6 (*C*O_2CH_2 or *C*$O_2(CH_3)_3$), 128.5 (Br*C*=CH), 124.6 (BrC=*C*H), 85.2 (*C*$(CH_3)_3$, 62.5 (OCH_2), 27.7 (C(*C*H_3)$_3$), 23.9 (*C*H_3C=CH); HRMS (ESI, pos.): *m/z* 278.0156 (278.0154 calc. for $C_{10}H_{15}{}^{79}BrO_4$ (M^+)).

(*Z*)-3-Bromobut-2-enyl *tert*-Butyl oxalate (93):

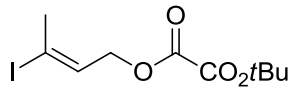


The reaction of (*Z*)-3-bromo-2-butenol (2.60 g, 17.3 mmol), triethylamine (2.89 mL, 20.7 mmol) and *tert*-butyl 2-chloro-2-oxoacetate (3.41 g, 20.8 mmol) in dichloromethane (25 mL) for 2 h, according to the general procedure, provided 4.31 g (89%) of **93**; R_f = 0.24 (hexanes/EtOAc, 95:5).

IR (neat): 2982, 1762, 1736, 1371, 1320, 1194, 1135, 950, 843 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.92 (tq, 1H, *J* = 6.3, 1.3, CH_3C=C*H*), 4.84 (dq, 2H, *J* = 6.3, 1.3, OCH_2), 2.35

(apparent q, 3H, *J* = 1.3, C*H*$_3$C=CH), 1.56 (s, 9H, C(C*H*$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.3 (*C*O$_2$(CH$_3$)$_3$ or *C*O$_2$CH$_2$), 156.7 (*C*O$_2$CH$_2$ or *C*O$_2$(CH$_3$)$_3$), 127.8 (Br*C*=CH), 122.3 (BrC=*C*H), 85.0 (*C*(CH$_3$)$_3$, 66.0 (O*C*H$_2$), 29.0 (*C*H$_3$C=CH), 27.7 (C(*C*H$_3$)$_3$); HRMS (APPI, pos.): *m/z* 278.0155 (278.0154 calc. for $C_{10}H_{15}{}^{79}BrO_4$ (M^+)).

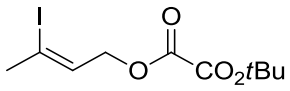
(*E*)-3-Iodobut-2-enyl *tert*-Butyl oxalate (94):



The reaction of (*E*)-3-iodo-2-butenol (1.75 g, 8.85 mmol), triethylamine (1.48 mL, 10.6 mmol) and *tert*-butyl 2-chloro-2-oxoacetate (1.74 g, 10.6 mmol) in dichloromethane (10 mL) for 1 h, according to the general procedure, provided 2.10 g (75%) of **94**; R_f = 0.21 (hexanes/EtOAc, 95:5).

IR (neat): 2983, 1761, 1737, 1371, 1329, 1310, 1263, 1193, 1139, 945, 842 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.38 (tq, 1H, *J* = 7.4, 1.5, CH$_3$C=C*H*), 4.64 (br d, *J* = 7.4, OC*H*$_2$), 2.55-2.49 (m, 3H, C*H*$_3$C=CH), 1.56 (s, 9H, C(C*H*$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.1 (*C*O$_2$(CH$_3$)$_3$ or *C*O$_2$CH$_2$), 156.5 (*C*O$_2$CH$_2$ or *C*O$_2$(CH$_3$)$_3$), 133.1 (IC=*C*H), 102.9 (I*C*=CH), 85.2 (*C*(CH$_3$)$_3$, 62.5 (O*C*H$_2$), 28.3 (*C*H$_3$C=CH), 27.8 (C(*C*H$_3$)$_3$; HRMS (ESI, pos.): *m/z* 326.0015 (326.0015 calc. for $C_{10}H_{15}IO_4$ (M^+)).

(*Z*)-3-Iodobut-2-enyl *tert*-Butyl oxalate (95):



The reaction of (*Z*)-3-iodo-2-butenol (1.58 g, 7.98 mmol), triethylamine (1.34 mL, 9.57 mmol) and *tert*-butyl 2-chloro-2-oxoacetate (1.57 g, 9.57 mmol) in dichloromethane (10 mL) for 1 h, according to the general procedure, provided 2.01 g (77%) of **95**; R_f = 0.28 (hexanes/EtOAc, 95:5).

IR (neat): 2981, 1763, 1735, 1658, 1394, 1370, 1258, 1193, 1139, 1082, 950, 843 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.81 (tq, 1H, *J* = 6.1, 1.4, $CH_3C=CH$), 4.77 (dq, 2H, *J* = 6.1, 1.4, OCH_2), 2.57 (apparent q, 3H, *J* = 1.4, $CH_3C=CH$), 1.56 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.3 ($CO_2(CH_3)_3$ or CO_2CH_2), 156.7 (CO_2CH_2 or $CO_2(CH_3)_3$), 128.5 ($C=CH-CH_2$), 105.6 ($C=CH-CH_2$), 85.1 ($C(CH_3)_3$, 70.7 (OCH_2), 33.9 ($CH_3C=CH$), 27.7 ($CH_3)_3$; HRMS (ESI, pos.): *m/z* 326.0006 (326.0015 calc. for $C_{10}H_{15}IO_4$ (M^+)).

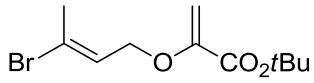
General procedure for the synthesis of allyl vinyl ethers:

A CEM Discover® microwave reactor was used for the microwave experiments. All reactions involving microwave heating were conducted in sealed reaction vessels. The temperature of the reaction mixture was monitored with an infrared sensor and the mixture was at the preset temperature (100 °C) in approximately 60 s.

To a solution of the allyl *tert*-butyl oxalate in toluene in a 35 mL microwave vial was added a solution of the Petasis reagent (2.2 equiv.) in toluene.[36] The vial was sealed and the mixture was heated with stirring at 100 °C until completion of the reaction. The

mixture was then cooled to ambient temperature, hexane (10 mL) was added, and the mixture was stirred for 5 min. The precipitated solids were removed by filtration through a pad of Celite® and the filtrate was concentrated under reduced pressure (for the iodo compounds, this residue was briefly treated with aqueous HCl as described). The residue was purified by flash chromatography on silica gel (hexane:EtOAc, 99:1) to provide the allyl vinyl ethers.

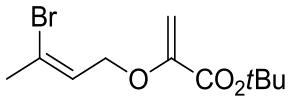
***tert*-Butyl (*E*)-2-((3-bromobut-2-enyl)oxy)acrylate (96):**



The reaction of **92** (478 mg, 1.71 mmol) and the Petasis reagent (5.60 mL of 0.67 M solution in toluene, 3.76 mmol) for 15 min according to the general procedure, provided after purification by flash column chromatography 178 mg (38 %) of **96** as a yellow oil; R_f = 0.26 (hexanes/EtOAc, 96:4).

IR (neat): 2979, 2932, 1729, 1370, 1209, 1153, 1125, 845 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.12 (tq, 1H, *J* = 6.8, 1.3, CH_3C=C*H*), 5.29 (d, 1H, *J* = 2.6, C=C*H*H), 4.53 (d, 1H, *J* = 2.6, C=CH*H*), 4.26 (br d, 2H, *J* = 6.8, OCH_2), 2.32-2.29 (m, 3H, CH_3C=CH), 1.52 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.0 (*C*=O), 151.7 (*C*=CH_2), 126.5 (C=*C*H-CH_2), 125.2 (*C*=CH-CH_2), 94.0 (C=*C*H_2), 82.0 *C*(CH_3)$_3$), 65.0 (O*C*H_2), 28.0 (C(*C*H_3)$_3$), 24.0 (*C*H_3C=C); HRMS (ESI, pos.): *m/z* 276.0362 (276.0361 calc. for $C_{11}H_{17}{}^{79}BrO_3$ (M^+)).

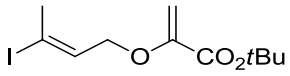
***tert*-Butyl (*Z*)-2-((3-bromobut-2-enyl)oxy)acrylate (97):**



The reaction of **93** (900 mg, 3.22 mmol) and the Petasis reagent (10.6 mL of 0.67 M solution in toluene, 7.08 mmol) for 15 min according to the general procedure, provided after purification by flash column chromatography 540 mg (61 %) of **97** as a yellow oil; R_f = 0.27 (hexanes/EtOAc, 95:5).

IR (neat): 2978, 2930, 1727, 1620, 1392, 1368, 1207, 1152, 1036, 849 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.97-5.90 (m, 1H, CH_3C=C*H*), 5.28 (d, 1H, *J* = 2.6, C=C*H*H), 4.58 (d, 1H, *J* = 2.6, C=CH*H*), 4.45-4.39 (m, 2H, OCH_2), 2.33 (apparent q, 3H, *J* = 1.3, CH_3C=CH), 1.52 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.1 (*C*=O), 151.5 (*C*=CH_2), 124.9 (*C*=CH-CH_2), 124.5 (C=*C*H-CH_2), 93.9 (C=*C*H_2), 82.0 (*C*(CH_3)$_3$, 68.2 (O*C*H_2), 28.8 (*C*H_3C=C), 28.0 (C(*C*H_3)$_3$; HRMS (ESI, pos.): *m/z* 276.0356 (276.0361 calc. for $C_{11}H_{17}{}^{79}BrO_3$ (M^+)).

***tert*-Butyl (*E*)-2-((3-iodobut-2-en-1-yl)oxy)acrylate (98):**

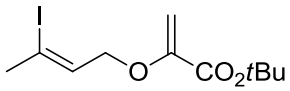


The reaction of **94** (100 mg, 0.30 mmol) and the Petasis reagent (1 mL of 0.67 M solution in toluene, 0.67 mmol) for 5 min according to the general procedure provided the crude product. This was dissolved in dichloromethane (5 mL), the solution was washed with aqueous HCl (0.2 M, 2 x 3 mL) and the organic phase was concentrated. The residue

was purified by flash column chromatography to provide 54 mg (56%) of **98** a yellow oil; R_f = 0.21 (hexanes/EtOAc, 96:4).

IR (neat): 2979, 2931, 1727, 1619, 1369, 1328, 1284, 1254, 1149, 1069, 1023, 996, 842 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.41 (tq, 1H, *J* = 6.5, 1.5, $CH_3C=CH$), 5.28 (d, 1H, *J* = 2.6, C=C*H*H), 4.53 (d, 1H, *J* = 2.6, C=CH*H*), 4.24 (br d, 2H, *J* = 6.5, OCH_2), 2.47 (m, 3H, $CH_3C=CH$), 1.50 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.9 (*C*=O), 151.5 ($C=CH_2$), 135.2 ($C=CH-CH_2$), 99.1 ($C=CH-CH_2$), 93.8 ($C=CH_2$), 82.0 $C(CH_3)_3$), 65.2 (OCH_2), 28.3 ($CH_3C=C$), 28.0 ($C(CH_3)_3$); HRMS (APPI, pos.): *m/z* 324.0236 (324.0222 calc. for $C_{11}H_{17}IO_3$ (M^+)).

***tert*-Butyl (*Z*)-2-((3-iodobut-2-en-1-yl)oxy)acrylate (99):**



The reaction of **95** (270 mg, 0.83 mmol) and the Petasis reagent (2.8 mL of 0.67 M solution in toluene, 1.87 mmol) for 5 min according to the general procedure provided the crude product. This was dissolved in dichloromethane (10 mL) and the solution was washed with aqueous HCl (0.2 M, 2 x 10 mL) and the organic phase was concentrated. The residue was purified by flash column chromatography to provide 153 mg (57%) of **99** a yellow oil; R_f = 0.24 (hexanes/EtOAc, 96:4).

IR (neat): 2978, 2934, 1724, 1618, 1392, 1368, 1254, 1206, 1148, 1085, 1031, 847 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.89-5.82 (m, 1H, $CH_3C=CH$), 5.28 (d, 1H, *J* = 2.6, C=C*H*H), 4.57 (d, 1H, *J* = 2.6, C=CH*H*), 4.36-4.30 (m, 2H, OCH_2), 2.54 (apparent q, 3H, *J* = 1.5, $CH_3C=CH$), 1.52 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.0 (*C*=O),

151.5 (*C*=CH_2), 130.7 (C=*C*H-CH_2), 102.3 (*C*=CH-CH_2), 94.1 (C=*C*H_2), 82.0 *C*$(CH_3)_3$), 73.0 (O*C*H_2), 33.6 (*C*H_3C=C), 28.0 (C(*C*$H_3)_3$); HRMS (APPI, pos.): *m/z* 324.0231 (324.0222 calc. for $C_{11}H_{17}IO_3$ (M^+)).

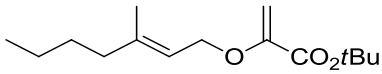
General Procedure 1 for Suzuki-Miyaura cross-coupling of 98 and 99 with arylboronic acids:

To the iodoallyl vinyl ether were added the arylboronic acid, KOH, Ag_2O and dioxane (purged with N_2 for 15 min) at room temperature followed by $PdCl_2(dppf)\cdot CH_2Cl_2$. The mixture was heated with stirring at 80 ^oC until consumption of the iodo allyl vinyl ether (TLC). After cooling to ambient temperature, diethyl ether was added and the resulting solution was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel.

General Procedure 2 for Suzuki-Miyaura cross-coupling of 98 and 99 with alkylboronic acids:

To the iodoallyl vinyl ether were added the alkylboronic acid, K_2CO_3, Ag_2O and THF (purged with N_2 for 15 min) at room temperature followed by freshly prepared $Pd(PPh_3)_4$. The mixture was heated to reflux until consumption of the iodo allyl vinyl ether (TLC). After cooling to ambient temperature, H_2O (1 mL) was added and the mixture was extracted with diethyl ether (3 x 2 mL) and the combined extracts were washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel.

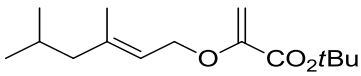
***tert*-Butyl (*E*)-2-(3-methylhept-2-enyloxy)acrylate (100a):**



The reaction of **98** (82 mg, 0.25 mmol), butylboronic acid (28 mg, 0.27 mmol), $Pd(PPh_3)_4$ (29 mg, 0.025 mmol), Ag_2O (145 mg, 0.62 mmol) and K_2CO_3 (103 mg, 0.74 mmol) in THF (1 mL) for 1 h according to General Procedure 2 provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 95:5), 39 mg (63%) of **100a** as a clear oil; R_f = 0.23 (hexanes/EtOAc, 97:3).

IR (neat): 2932, 1726, 1617, 1263, 1153, 909 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.42 (tq, 1H, *J* = 6.4, 1.3, CH_3C=C*H*), 5.23 (d, 1H, *J* = 2.3, C=CH*H*), 4.53 (d, 1H, *J* = 2.3, C=C*H*H), 4.31 (br d, 2H, *J* = 6.6, OCH_2), 2.06-1.98 (m, 2H, C=CCH_2), 1.67 (s, 3H, CH_3C=C), 1.51 (s, 9H, C(CH_3)$_3$), 1.46-1.24 (m, 4H, CH_2CH_2), 0.90 (t, 3H, *J* = 7.2, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.3 (*C*=O), 152.1 (*C*=CH_2), 141.0 (CH_3C=CH), 118.8 (CH_3C=*C*H), 93.1 (C=*C*H_2), 81.6 (*C*(CH_3)$_3$, 65.5 (O*C*H_2), 39.2 (C=C*C*H_2CH_2), 29.8 ($CH_3CH_2CH_2$ or $CH_3CH_2CH_2$), 28.0 (C(*C*H_3)$_3$, 22.4 ($CH_3CH_2CH_2$ or $CH_3CH_2CH_2$), 16.6 (*C*H_3C=CH or *C*$H_3CH_2CH_2$), 14.0 (*C*$H_3CH_2CH_2$ or *C*H_3C=CH); HRMS (APPI, neg.): *m/z* 254.1875 (254.1882 calc. for $C_{15}H_{26}O_3$ (M^+)).

***tert*-Butyl (*E*)-2-(3,5-dimethylhex-2-enyloxy)acrylate (100b):**

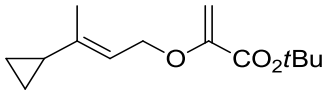


The reaction of **98** (80 mg, 0.25 mmol), (2-methylpropyl)boronic acid (28 mg, 0.27 mmol), $Pd(PPh_3)_4$ (28 mg, 0.025 mmol), Ag_2O (142 mg, 0.61 mmol) and K_2CO_3

(102 mg, 0.74 mmol) in THF (1 mL) for 2h according to General Procedure 2 provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 95:5), 37mg (61%) of **100b** as a clear oil; R_f = 0.24 (hexanes/EtOAc, 97:3).

IR (neat): 2957, 2928, 2871, 1726, 1617, 1369, 1316, 1206, 1150, 1026, 847 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.40 (br t, 1H, *J* = 6.4, CH_3C=C*H*), 5.23 (d, 1H, *J* = 2.3, C=CH*H*), 4.53 (d, 1H, *J* = 2.3, C=C*H*H), 4.33 (br d, 2H, *J* = 6.4, OCH_2), 1.89 (br d, 2H, *J* = 7.4, CH_2CH(CH_3)$_2$), 1.81-1.71 (m, 1H, C*H*(CH_3)$_2$, 1.66-1.62 (br s, 3H, CH_3C=C), 1.51 (s, 9H, C(CH_3)$_3$), 0.85 (d, 6H, *J* = 6.5, CH(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.3 (*C*=O), 152.1 (*C*=CH_2), 139.8 (*i*-Bu*C*=CH), 120.3 (CH_3C=CH), 93.1 (C=*C*H_2), 81.6 (*C*(CH_3)$_3$, 65.5 (O*C*H_2), 49.2 (*C*H_2CH(CH_3)$_2$, 28.0 (C(*C*H_3)$_3$, 26.0 (*C*H(CH_3)$_2$, 22.4 (CH(*C*H_3)$_2$, 16.5 (*C*H_3C=C); HRMS (APPI, pos.): *m/z* 254.1875 (254.1882 calc. for $C_{15}H_{26}O_3$ (M^+)).

***tert*-Butyl (*E*)-2-(3-cyclopropylbut-2-enyloxy)acrylate (100c):**

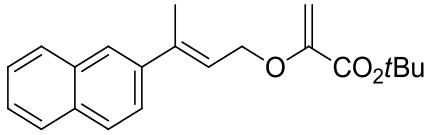


The reaction of **98** (80 mg, 0.25 mmol), cyclopropylboronic acid (23 mg, 0.27 mmol), $Pd(PPh_3)_4$ (28 mg, 0.024 mmol), Ag_2O (142 mg, 0.61 mmol) and K_2CO_3 (102 mg, 0.74 mmol) in THF (1 mL) for 1 h according to General Procedure 2 provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 95:5), 37 mg (65%) of **100c** as a clear oil; R_f = 0.23 (hexanes/EtOAc, 97:3).

IR (neat): 2978, 2932, 1725, 1616, 1368, 1319, 1206, 1148, 1019 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.51-5.43 (br t, 1H, *J* = 6.8, CH_3C=C*H*), 5.23 (d, 1H, *J* = 2.3, C=CH*H*),

4.53 (d, 1H, *J* = 2.3, C=C*H*H), 4.31 (d, 2H, *J* = 6.5, OCH_2), 1.57 (s, 3H, CH_3C=C), 1.51 (s, 9H, C(CH_3)$_3$), 1.45-1.36 (m, 1H, C*H*CH_2CH_2), 0.64-0.54 (m, 2H, CH_2CH_2), 0.53-0.44 (m, 2H, CH_2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.3 (*C*=O), 152.0 (*C*=CH_2), 141.5 (CH_3*C*=CH), 117.3 (CH_3C=*C*H), 93.1 (C=*C*H_2), 81.7 (*C*(CH_3)$_3$, 65.4 (OCH_2), 28.0 (C(*C*H_3)$_3$, 18.7 (*C*HCH_2CH_2 or *C*H_3), 14.4 (*C*H_3 or *C*HCH_2CH_2), 4.74 (*C*H_2*C*H_2); HRMS (APPI, neg.): *m/z* 238.1569 (238.1569 calc. for $C_{14}H_{22}O_3$ (M^+)).

***tert*-Butyl (*E*)-2-(3-(naphthalen-2-yl)but-2-enyloxy)acrylate (100d):**

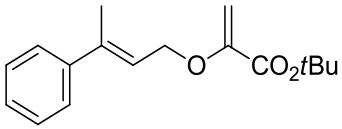


The reaction of **98** (110 mg, 0.34 mmol), 2-naphthylboronic acid (58 mg, 0.34 mmol), $PdCl_2$(dppf)·CH_2Cl_2 (4.10 mg, 0.005 mmol), Ag_2O (79 mg, 0.34 mmol) and KOH (19 mg, 0.34 mmol) in dioxane (1.2 mL) for 40 min according to General Procedure 1 provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 95:5), 75 mg (68%) of **100d** as a clear oil; R_f = 0.22 (hexanes/EtOAc, 95:5).

IR (neat): 2978, 2932, 1724, 1616, 1368, 1349, 1327, 1206, 1148, 1022, 850, 812 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86-7.77 (m, 4H, Ar*H*), 7.6 (dd, 1H, *J* = 8.6, 1.9, Ar*H*), 7.50-7.40 (m, 2H, Ar*H*), 6.17 (tq, 1H, *J* = 6.1, 1.3, CC=C*H*), 5.31 (d, 1H, *J* = 2.4, C=CH*H*), 4.64 (d, 1H, *J* = 2.4, C=C*H*H), 4.59 (d, 2H, *J* = 6.1, OCH_2), 2.20 (m, 3H, CH_3C=C), 1.54 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.3 (*C*=O), 152.0 (*C*=CH_2), 139.7 (ArC_{ipso}), 138.4 (Ar*C*=C), 133.4 (ArC_{ipso}), 132.8 (ArC_{ipso}), 128.2 (Ar*C*), 127.8 (Ar*C*), 127.5 (Ar*C*), 126.2 (Ar*C*), 125.9 (Ar*C*), 124.5 (Ar*C*), 124.2 (Ar*C*), 122.9

(ArC=*C*H), 93.6 (C=*C*H_2), 81.9 (*C*(CH_3)$_3$), 66.1 (O*C*H_2), 28.0 (*C*H_3)$_3$, 16.3 (*C*H_3); HRMS (APPI, pos.): *m/z* 324.1722 (324.1725 calc. for $C_{21}H_{24}O_3$ (M^+)).

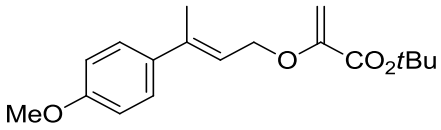
***tert*-Butyl (*E*)-2-(3-phenylbut-2-enyloxy)acrylate (100e):**



The reaction of **98** (100 mg, 0.31 mmol), phenylboronic acid (38 mg, 0.31 mmol), $PdCl_2$(dppf)·CH_2Cl_2 (3.70 mg, 0.004 mmol), Ag_2O (72 mg, 0.31 mmol) and KOH (56 mg, 0.31 mmol) in dioxane (1.1 mL) for 20 min according to General Procedure 1 provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 95:5), 73 mg (87%) of **100e** as a clear oil; R_f = 0.21 (hexanes/EtOAc, 97:3).

IR (neat): 2979, 2931, 1726, 1618, 1369, 1337, 1317, 1207, 1150, 1032, 848 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44-7.38 (m, 2H, Ar*H*), 7.36-7.26 (m, 3H, Ar*H*), 6.00 (tq, 1H, *J* = 6.2, 1.3, CC=C*H*), 5.29 (d, 1H, *J* = 2.4, C=CH*H*), 4.60 (d, 1H, *J* = 2.4, C=C*H*H), 4.53 (d, 2H, *J* = 6.2, OCH_2), 2.11-2.07 (m, 3H, CH_3C=C), 1.52 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.2 (*C*=O), 152.0 (*C*=CH_2), 142.5 (ArC_{ipso}), 138.6 (Ph*C*=CH), 128.3 (2 x Ar*C*), 127.4 (Ar*C*), 125.8 (2 x Ar*C*), 122.3 (PhC=*C*H), 93.5 (C=*C*H_2), 81.8 (*C*(CH_3)$_3$, 66.0 (O*C*H_2), 28.0 (C(*C*H_3)$_3$, 16.4 (*C*H_3C=CH); HRMS (APPI, pos.): *m/z* 274.1581 (274.1569 calc. for $C_{17}H_{22}O_3$ (M^+)).

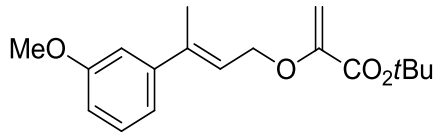
***tert*-Butyl (*E*)-2-((3-(4-methoxyphenyl)but-2-en-1-yl)oxy)acrylate (100f):**



The reaction of **98** (85 mg, 0.26 mmol), 4-methoxyphenylboronic acid (39 mg, 0.26 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (3.30 mg, 0.004 mmol), Ag_2O (60 mg, 0.26 mmol) and KOH (14 mg, 0.26 mmol) in dioxane (1 mL) for 35 min according to General Procedure 1 provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 9:1), 60 mg (77%) of **100f** as a clear oil; R_f = 0.21 (hexanes/EtOAc, 93:7).

IR (neat): 2978, 2932, 1726, 1613, 1512, 1370, 1248, 1207, 1152, 1032 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36 (d, 2H, *J* = 8.8, Ar*H*), 6.85 (d, 2H, *J* = 8.8, Ar*H*), 5.93 (tq, 1H, *J* = 6.3, 1.3, CC=C*H*), 5.28 (d, 1H, *J* = 2.4, C=CH*H*), 4.60 (d, 1H, *J* = 2.4, C=C*H*H), 4.51 (d, 2H, *J* = 6.3, OCH_2), 3.81 (s, 3H, OCH_3), 2.07 (m, 3H, CH_3C=C), 1.52 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.3 (*C*=O), 159.1 (ArC_{ipso}), 152.0 ($C=CH_2$), 138.1 (ArC_{ipso}), 135.0 (Ar*C*=CH), 126.9 (2 x Ar*C*), 120.6 (ArC=*C*H), 113.6 (2 x Ar*C*), 93.4 ($C=CH_2$), 81.8 ($C(CH_3)_3$), 66.0 (OCH_2), 55.3 (OCH_3), 28.0 ($CH_3)_3$, 16.3 (CH_3); HRMS (APPI, neg.): *m/z* 304.1669 (304.1675 calc. for $C_{18}H_{24}O_4$ (M^+)).

***tert*-Butyl (*E*)-2-(3-(3-methoxyphenyl)but-2-enyloxy)acrylate (100g):**

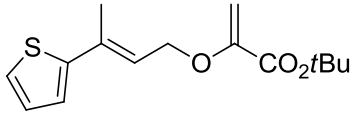


The reaction of **98** (114 mg, 0.35 mmol), 3-methoxyphenylboronic acid (53 mg, 0.35 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (4.10 mg, 0.005 mmol), Ag_2O (81 mg, 0.35 mmol) and

KOH (20 mg, 0.35 mmol) in dioxane (1.2 mL) for 20 min according to General Procedure 1 provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 93:7), 87 mg (82%) of **100g** as a clear oil; R_f = 0.22 (hexanes/EtOAc, 93:7).

IR (neat): 2979, 2936, 1725, 1614, 1580, 1370, 1319, 1288, 1207, 1149, 1038 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.23 (t, 1H, *J* = 8.0, Ar*H*), 7.03-6.99 (m, 1H, Ar*H*), 6.96-6.94 (m, 1H, Ar*H*), 6.81 (br dd, 1H, *J* = 8.2, 2.5, Ar*H*), 6.01 (tq, 1H, *J* = 6.1, 1.3, CH_3C=C*H*), 5.29 (d, 1H, *J* = 2.4, C=CH*H*), 4.60 (d, 1H, *J* = 2.4, C=C*H*H), 4.52 (br d, 2H, *J* = 6.1, OCH_2), 3.82 (s, 3H, OCH_3), 2.09-2.06 (m, 3H, CH_3C=CH), 1.52 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.2 (*C*=O), 159.5 (ArC_{ipso}), 152.0 (*C*=CH_2), 144.1 (ArC_{ipso}), 138.4 (CH_3C=CH), 129.2 (Ar*C*), 122.5 (CH_3C=*C*H), 118.3 (Ar*C*), 112.8 (Ar*C*), 111.6 (Ar*C*), 93.5 C=*C*H_2), 81.8 (*C*(CH_3)$_3$), 65.9 (O*C*H_2), 55.3 (O*C*H_3), 28.0 (*C*H_3)$_3$, 16.4 (*C*H_3); HRMS (APPI, neg.): *m/z* 304.1668 (304.1675 calc. for $C_{18}H_{24}O_4$ (M^+)).

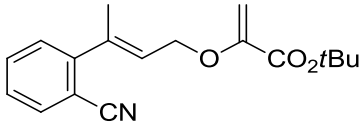
***tert*-Butyl (*E*)-2-((3-(thiophen-2-yl)but-2-en-1-yl)oxy)acrylate (100h):**



The reaction of **98** (101 mg, 0.31 mmol), 2-thienylboronic acid (40 mg, 0.31 mmol), $PdCl_2$(dppf)·CH_2Cl_2 (3.30 mg, 0.004 mmol), Ag_2O (72 mg, 0.31 mmol) and KOH (17 mg, 0.31 mmol) in dioxane (1.1 mL) for 4h according to General Procedure 1 provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 95:5), 37 mg (43%) of **100h** as clear oil; R_f = 0.20 (hexanes/EtOAc, 97:3).

IR (neat): 2979, 1723, 1617, 1369, 1315, 1206, 1148, 849 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16 (dd, 1H, *J* = 5.1, 1.2, Ar*H*), 7.05 (dd, 1H, *J* = 3.6, 1.2, Ar*H*), 6.97 (dd, 1H, *J* = 5.1, 3.6, Ar*H*), 6.13 (tq, 1H, *J* = 6.4, 1.3, CH_3C=C*H*), 5.29 (d, 1H, *J* = 2.5, C=CH*H*), 4.59 (d, 1H, *J* = 2.5, C=C*H*H), 4.50 (br d, 2H, *J* = 6.4, OCH_2), 2.12-2.09 (m, 3H, CH_3C=CH), 1.52 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.2 (*C*=O), 152.0 (*C*=CH_2), 146.4 (ArC_{ipso}), 132.7 (CH_3*C*=CH), 127.3 (CH_3C=*C*H), 124.3 (Ar*C*), 123.4 (Ar*C*), 120.5 (Ar*C*), 93.6 (C=*C*H_2), 81.9 (*C*(CH_3)$_3$), 65.5 (O*C*H_2), 28.0 (*C*H_3)$_3$, 16.3 (*C*H_3); HRMS (APPI, neg.): *m/z* 280.1120 (280.1133 calc. for $C_{15}H_{20}O_3S$ (M^+)).

***tert*-Butyl (*E*)-2-((3-2-cyanophenyl)but-2-en-1-yl)oxy)acrylate (100i):**

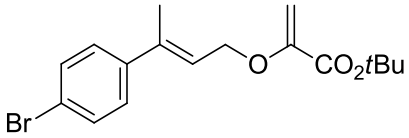


The reaction of **98** (90 mg, 0.27 mmol), 2-cyanophenylboronic acid (40 mg, 0.27 mmol), $PdCl_2$(dppf)·CH_2Cl_2 (3.30 mg, 0.004 mmol), Ag_2O (63 mg, 0.27 mmol) and KOH (15 mg, 0.27 mmol) in dioxane (1 mL) for 4h according to General Procedure 1 provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 9:1), 38 mg (47%) of **100i** as clear oil; R_f = 0.20 (hexanes/EtOAc, 93: 7).

IR (neat): 2979, 2933, 2225, 1724, 1619, 1370, 1336, 1317, 1288, 1206, 1148, 1030 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (dd, 1H, *J* = 8.0, 1.4, Ar*H*), 7.54 (dt, 1H, *J* = 7.7, 1.4, Ar*H*), 7.38-7.32 (m, 1H, Ar*H*), 5.87 (tq, 1H, *J* = 6.0, 1.4, CC=C*H*), 5.32 (d, 1H, *J* = 2.6, C=CH*H*), 4.64 (d, 1H, *J* = 2.6, C=C*H*H), 4.55 (d, 2H, *J* = 6.0, OCH_2), 3.81 (s, 3H, OCH_3), 2.16-2.12 (m, 3H, CH_3C=C), 1.52 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$):

δ 162.1 (*C*=O), 151.8 (*C*=CH_2), 148.2 (ArC_{ipso}), 136.9 (Ar*C*=CH), 133.3 (Ar*C*), 132.6 (Ar*C*), 128.5 (Ar*C*), 127.6 (ArC=*C*H or Ar*C*), 127.5 (Ar*C* or ArC=*C*H), 118.4 (*C*N), 110.6 (ArC_{ipso} (*C*-CN)), 93.8 (C=*C*H_2), 81.9 (*C*$(CH_3)_3$), 65.4 (O*C*H_2), 28.0 (*C*$H_3)_3$, 18.0 (*C*H_3); HRMS (APPI, neg.): *m/z* 299.1520 (299.1521 calc. for $C_{18}H_{21}NO_3$ (M^+)).

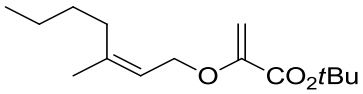
***tert*-Butyl (*E*)-2-((3-(4-bromophenyl)but-2-en-1-yl)oxy)acrylate (100j):**



The reaction of **98** (97 mg, 0.30 mmol), 4-bromophenylboronic acid (60 mg, 0.30 mmol), $PdCl_2$(dppf)·CH_2Cl_2 (3.30 mg, 0.004 mmol), Ag_2O (69 mg, 0.30 mmol) and KOH (17 mg, 0.30 mmol) in dioxane (1.1 mL) for 40 min according to General Procedure 1 provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 9:1), 63 mg (60%) of **100j** as a clear oil; R_f = 0.26 (hexanes/EtOAc, 92:8).

IR (neat): 2979, 2932, 1724, 1617, 1484, 1368, 1335, 1316, 1206, 1148, 1007, 848, 812 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43 (d, 2H, *J* = 8.5, Ar*H*), 7.27 (d, 2H, *J* = 8.5, Ar*H*), 6.00 (tq, 1H, *J* = 6.1, 1.3, CC=C*H*), 5.29 (d, 1H, *J* = 2.5, C=CH*H*), 4.59 (d, 1H, *J* = 2.5, C=C*H*H), 4.50 (d, 2H, *J* = 6.1, OCH_2), 2.08-2.03 (m, 3H, CH_3C=C), 1.52 (s, 9H, C(C$H_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.1 (*C*=O), 151.9 (*C*=CH_2), 141.4 (ArC_{ipso}), 137.6 (Ar*C*=CH), 131.4 (2 x Ar*C*), 127.4 (2 x Ar*C*), 122.9 (ArC_{ipso} (C-Br) or ArC=*C*H), 121.3 (ArC=*C*H or ArC_{ipso} (C-Br)), 93.5 (C=*C*H_2), 81.9 (*C*$(CH_3)_3$), 65.8 (O*C*H_2), 28.0 (*C*$H_3)_3$, 16.3 (*C*H_3); HRMS (APPI, neg.): *m/z* 352.0684 (352.0674 calc. for $C_{17}H_{21}BrO_3$ (M^+)).

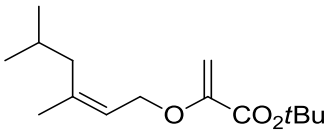
***tert*-Butyl (*Z*)-2-(3-methylhept-2-enyloxy)acrylate (101a):**



The reaction of **99** (75 mg, 0.23 mmol), butylboronic acid (26 mg, 0.25 mmol), $Pd(PPh_3)_4$ (26 mg, 0.023 mmol), Ag_2O (133 mg, 0.57 mmol) and K_2CO_3 (95 mg, 0.69 mmol) in THF (1 mL) for 1 h according to General Procedure 2 provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 95:5), 38 mg (67%) of **101a** as a clear oil; R_f = 0.24 (hexanes/EtOAc, 97:3).

IR (neat): 2961, 2931, 2867, 1729, 1617, 1370, 1324, 1207, 1154, 848 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.46-5.41 (br t, 1H, *J* = 6.3, CH_3C=C*H*), 5.23 (d, 1H, *J* = 2.3, C=CH*H*), 4.53 (d, 1H, *J* = 2.3, C=C*H*H), 4.28 (d, 2H, *J* = 6.7, OCH_2), 2.06 (t, 2H, *J* = 7.4, C=CCH_2), 1.77-1.71 (m, 3H, C=CCH_3), 1.51 (s, 9H, C(CH_3)$_3$), 1.44-1.26 (m, 4H, CH_2CH_2), 0.90 (t, 3H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.2 (*C*=O), 152.1 (*C*=CH_2), 141.7 (Bu*C*=C), 119.4 (C=*C*H), 92.9 (C=*C*H_2), 81.6 (*C*(CH_3)$_3$), 65.0 (OCH_2), 32.0, 30.2, 27.9, 23.4, 22.6, 13.9; HRMS (APPI, neg.): *m/z* 254.1879 (254.1882 calc. for $C_{15}H_{26}O_3$ (M^+)).

***tert*-Butyl (*Z*)-2-(3,5-dimethylhex-2-enyloxy)acrylate (101b):**

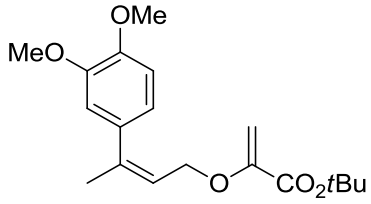


The reaction of **99** (50 mg, 0.15 mmol), (2-methylpropyl)boronic acid (17 mg, 0.16 mmol), $Pd(PPh_3)_4$ (17 mg, 0.014 mmol), Ag_2O (87 mg, 0.37 mmol) and K_2CO_3 (62

mg, 0.45 mmol) in THF (1 mL) for 3 h according to General Procedure 2 provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 95:5), 24 mg (63%) of **101b** as a clear oil; R_f = 0.24 (hexanes/EtOAc, 97:3).

IR (neat): 2957, 2930, 2871, 1727, 1616, 1460, 1369, 1317, 1254, 1206, 1150, 1019 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.54-5.46 (br t, 1H, *J* = 6.5, $CH_3C=CH$), 5.23 (d, 1H, *J* = 2.3, C=CH*H*), 4.53 (d, 1H, *J* = 2.4, C=C*H*H), 4.28 (br d, 2H, *J* = 6.6, OCH_2), 1.94 (d, 2H, 7.3, $CH_2CH(CH_3)_2$), 1.85-1.75 (m, 1H, $CH(CH_3)_2$, 1.75-1.70 (m, 3H, $CH_3C=C$), 1.51 (s, 9H, $C(CH_3)_3$), 0.88 (d, 6H, *J* =6.5, $CH(CH_3)_2$; ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.3 (*C*=O), 152.1 ($CH_3C=CH_2$), 140.4 (*i*Bu*C*=CH), 120.7 (*C*=CH), 93.0 ($C=CH_2$), 81.7 ($C(CH_3)_3$, 65.1 (OCH_2), 41.6 ($CH_2CH(CH_3)_2$, 28.0 ($C(CH_3)_3$, 26.7 ($CH(CH_3)_2$ or $CH_3C=C$), 23.7 ($CH_3C=C$ or $CH(CH_3)_2$), 22.5 ($CH(CH_3)_2$; HRMS (APPI, pos.): *m/z* 254.1880 (254.1882 calc. for $C_{15}H_{26}O_3$ (M^+)).

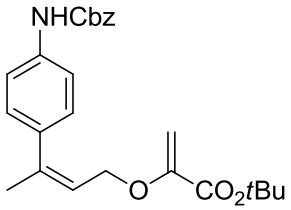
***tert*-Butyl (*Z*)-2-(3-(3,4-dimethoxyphenyl)but-2-enyloxy)acrylate (101c):**



The reaction of **99** (88 mg, 0.27 mmol), 3,4-dimethoxyphenylboronic acid (49 mg, 0.27 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (3.30 mg, 0.004 mmol), Ag_2O (62 mg, 0.27 mmol) and KOH (15 mg, 0.27 mmol) in dioxane (1 mL) for 30 min according to General Procedure 1 provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 93:7), 60 mg (67%) of **101c** as a clear oil; R_f = 0.21 (hexanes/EtOAc, 95:5).

IR (neat): 2976, 2937, 1724, 1616, 1513, 1460, 1370, 1318, 1255, 1205, 1146, 1025, 911, 849 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.88-6.81 (d, 1H, *J* = 8.0, Ar*H*), 6.79-6.72 (m, 2H, Ar*H*), 5.78-5.72 (tq, 1H, *J* = 7.0, 1.4, CC=C*H*), 5.16 (d, 1H, *J* = 2.3, C=CH*H*), 4.37 (d, 1H, *J* = 2.3, CC=C*H*H), 4.20 (br dd, 2H, *J* = 7.0, 1.1, CCH_2), 3.89 (s, 3H, ArOCH_3), 3.85 (s, 3H, ArOCH_3), 2.12-2.07 (m, 3H, C=CCH_3), 1.51 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.2 (*C*=O), 151.7 (ArC_{ipso}), 148.5 (ArC_{ipso}), 148.3 (*C*=CH_2), 142.4 (Ph*C*=CH), 133.2 (ArC_{ipso}), 121.0 (ArC=*C*H), 120.0 (Ar*C*), 111.2 (Ar*C*), 110.9 (Ar*C*), 93.2 (C=*C*H_2), 81.7 (*C*(CH_3)$_3$, 66.1 (*C*H_2-O), 55.87 (O*C*H_3), 55.80 (O*C*H_3), 28.0 (*C*H_3)$_3$, 25.3 (*C*H_3); HRMS (APPI, pos.): *m/z* 334.1778 (334.1780 calc. for $C_{19}H_{26}O_5$ (M^+)).

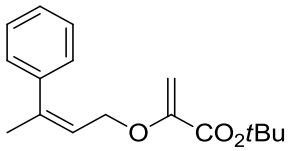
***tert*-Butyl (*Z*)-2-(3-(4-(benzyloxycarbonylamino)phenyl)but-2-enyloxy)acrylate (101d):**



The reaction of **99** (95 mg, 0.29 mmol), 4-Cbz-aminophenylboronic acid boronic acid (79 mg, 0.29 mmol), $PdCl_2$(dppf)·CH_2Cl_2 (3.60 mg, 0.004 mmol), Ag_2O (67 mg, 0.29 mmol) and KOH (16 mg, 0.29 mmol) in dioxane (1.1 mL) for 30 min according to General Procedure 1 provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 85:15), 102 mg (84 %) of **101d** as a clear oil; R_f = 0.25 (hexanes/EtOAc, 85:15); IR (neat): 3350, 2977, 1710, 1614, 1593, 1525, 1316, 1208,

1149, 1050 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.27 (br m, 7H, Ar*H*), 7.12 (br d, 2H, Ar*H*, *J* = 6.8), 6.95-6.65 (br, 1H, N*H*) 5.73 (br t, 1H, *J* = 6.8, C=C*H*), 5.20 (br s, 2H, ArCH_2O), 5.15 (d, 1H, 2.3, C=CH*H*), 4.33 (d, 1H, 2.3, CC=C*H*H), 4.20 (br d, 2H, *J* = 6.8, OCH_2), 2.07 (br s, 3H, C=CCH_3), 1.50 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.3 (*C*=O), 153.4 (*C*(O)NH_2), 151.6 (*C*=CH_2), 141.2 (ArC_{ipso}), 137.1 (ArC_{ipso}), 136.0 (ArC_{ipso}), 135.6 (Ph*C*=CH), 128.6 (2 x Ar*C*) 128.5 (2 x Ar*C*), 128.38 (2 x Ar*C*), 128.33 (2 x Ar*C*), 121.6 (ArC=*C*H), 118.4 (Ar*C*), 93.3 (C=*C*H_2), 81.7 (*C*$(CH_3)_3$, 67.0 (Ph*C*H_2 or O*C*H_2), 66.0 (O*C*H_2 or Ph*C*H_2), 28.0 (*C*$H_3)_3$, 25.1 (*C*H_3); HRMS (APPI, pos.): *m/z* 254.1875 (254.1882 calc. for $C_{15}H_{26}O_3$ (M^+)).

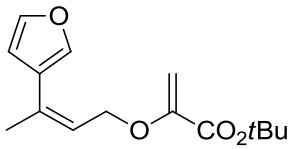
tert-Butyl (*Z*)-2-(3-phenylbut-2-enyloxy)acrylate (101e):



The reaction of **99** (100 mg, 0.30 mmol), phenylboronic acid (36 mg, 0.30 mmol), $PdCl_2$(dppf)·CH_2Cl_2 (3.30 mg, 0.004 mmol), Ag_2O (69 mg, 0.30 mmol) and KOH (17 mg, 0.30 mmol) in dioxane (1.1 mL) for 20 min according to General Procedure 1 provided, after purification by flash chromatography on silica gel (hexanes/Et_2O, 9:1), 59 mg (72%) of **101e** as a clear oil; R_f = 0.22 (hexanes/Et_2O, 96:4); IR (neat): 2978, 2935, 1723, 1617, 1368, 1319, 1205, 1148, 912 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.23 (m, 3H, Ar*H*), 7.21-7.14 (m, 2H, Ar*H*), 5.77 (tq, 1H, *J* = 6.7, 1.4, C=CC*H*CH_2), 5.14 (d, 1H, *J* = 2.3, C=CH*H*), 4.33 (d, 1H, *J* = 2.3, C=C*H*H), 4.21 (br dq, 2H, *J* = 6.7, 1.4 OCH_2), 2.12-2.09 (m, 3H, CH_3C=C), 1.51 (s, 9H, COC(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ

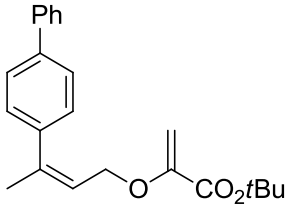
162.2 (*C*=O), 151.7 (*C*=CH_2), 141.8 (Ph*C*=CH), 140.5 (ArC_{ipso}), 128.2 (2 x Ar*C*), 127.7 (2 x Ar*C*), 127.4 (Ar*C*), 121.7 (PhC=*C*H), 93.2 (C=*C*H_2), 81.7 (*C*$CH_3)_3$, 66.1 (*C*H_2O), 28.0 (*C*$H_3)_3$, 25.3 (C=C*C*H_3); HRMS (APPI, neg.): *m/z* 274.1556 (274.1569 calc. for $C_{17}H_{22}O_3$ (M^+)).

***tert*-Butyl (*Z*)-2-((3-(furan-3-yl)but-2-en-1-yl)oxy)acrylate (101f):**



The reaction of **99** (99 mg, 0.30 mmol), 3-furanylboronic acid (34 mg, 0.30 mmol), $PdCl_2$(dppf)·CH_2Cl_2 (3.67 mg, 0.004 mmol), Ag_2O (69 mg, 0.30 mmol) and KOH (17 mg, 0.30 mmol) in dioxane (1.2 mL) for 3h according to General Procedure 1 provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 97:3), 51 mg (65%) of **101f** as a clear oil; R_f = 0.24 (hexanes/EtOAc, 97:3); IR (neat): 2923, 2853, 1727, 1619, 1456, 1368, 1320, 1256, 1206, 1152, 1023, 956, 873 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (d, 2H, *J* = 1.4, Ar*H*), 6.41 (t, 1H, *J* = 1.4, Ar*H*), 5.71 (tq, 1H, *J* = 6.6, 1.3, CH_3C=C*H*), 5.23 (d, 1H, *J* = 2.4, C=CH*H*), 4.48 (d, 1H, *J* = 2.4, C=C*H*H), 4.41-4.34 (br m, 2H, *J* = 6.6, OCH_2), 2.04 (br q, 3H, *J* = 1.3, CH_3C=CH), 1.52 (s, 9H, C(C$H_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.2 (*C*=O), 151.7 (*C*=CH_2), 143.0 (Ar*C*), 140.4 (Ar*C*), 132.2 (CH_3*C*=CH or ArC_{ipso}), 124.3 (ArC_{ipso} or CH_3*C*=CH), 121.7 (CH_3C=*C*H), 110.1 (Ar*C*), 93.4 (C=*C*H_2), 81.8 (*C*$(CH_3)_3$), 65.8 (O*C*H_2), 28.0 (C(*C*$H_3)_3$), 24.1 (*C*H_3C=CH); HRMS (APPI, pos.): *m/z* 264.1345 (264.1362 calc. for $C_{15}H_{20}O_4$ (M^+)).

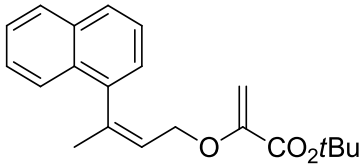
***tert*-Butyl (*Z*)-2-(3-(biphenyl-4-yl)but-2-enyloxy)acrylate (101g):**



The reaction of **99** (98 mg, 0.30 mmol), 4-biphenylboronic acid (59 mg, 0.30 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (3.70 mg, 0.004 mmol), Ag_2O (69 mg, 0.30 mmol) and KOH (17 mg, 0.30 mmol) in dioxane (1.1 mL) for 30 min according to General Procedure 1 provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 93:7), 70 mg (67%) of **101g** as a clear oil; R_f = 0.25 (hexanes/EtOAc, 93:7).

IR (neat): 2976, 2935, 1724, 1616, 1368, 1318, 1205, 1147, 1012 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.63-7.53 (m, 4H, Ar*H*), 7.47-7.40 (m, 2H, Ar*H*), 7.37-7.25 (m, 3H, Ar*H*), 5.81 (tq, 1H, *J* = 6.7, 1.4, C=C*H*), 5.17 (d, 1H, *J* = 2.3, C=CH*H*), 4.37 (d, 1H, *J* = 2.3, C=C*H*H), 4.27 (br dd, 2H, *J* = 6.7, 1.2, OCH_2), 2.16-2.11 (m, 3H, C=CCH_3), 1.51 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.3 (*C*=O), 151.7 (*C*=CH_2), 141.4 (ArC_{ipso}), 140.7 (ArC_{ipso}), 140.2 (ArC_{ipso}), 139.5 (Ph*C*=CH), 128.8 (2 x Ar*C*), 128.2 (2 x Ar*C*), 127.4 (Ar*C*), 127.0 (2 x Ar*C*), 126.9 (2 x Ar*C*), 122.0 (ArC=*C*H), 93.3 (C=*C*H_2), 81.7 (*C*$(CH_3)_3$, 66.1 (O*C*H_2), 28.0 (*C*H_3)$_3$, 25.2 (*C*H_3); HRMS (APPI, neg.): *m/z* 423.2047 (423.2046 calc. for $C_{25}H_{29}NO_5$ (M^+)).

***tert*-Butyl (*Z*)-2-(3-(naphthalen-1-yl)but-2-enyloxy)acrylate (101h):**



The reaction of **99** (101 mg, 0.31 mmol), 1-naphthylboronic acid (53 mg, 0.31 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (3.80 mg, 0.004 mmol), Ag_2O (72 mg, 0.31 mmol) and KOH (17 mg, 0.31 mmol) in dioxane (1.1 mL) for 1 h according to General Procedure 1 provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 93:7), 80 mg (80%) of **101h** as clear oil; R_f = 0.22 (hexanes/EtOAc, 93:7).

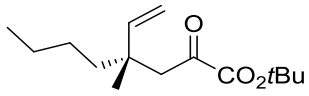
IR (neat): 2975, 2934, 1724, 1617, 1369, 1316, 1205, 1147, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.90-7.74 (m, 3H, Ar*H*), 7.51-7.40 (m, 3H, Ar*H*), 7.27-7.22 (m, 1H, Ar*H*), 6.02 (tq, 1H, *J* = 6.4, 1.5, CH_3C=C*H*), 5.04 (d, 1H, *J* = 2.4, C=CH*H*), 4.19 (d, 1H, *J* = 2.4, C=C*H*H), 3.99-3.91 (br m, 2H, OCH_2), 2.16 (br q, 3H, *J* = 1.4, CH_3C=C), 1.48 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.2 (*C*=O), 151.7 (*C*=CH_2), 140.0 (ArC_{ipso}), 138.8 (Ar*C*=C), 133.7 (ArC_{ipso}), 130.6 (ArC_{ipso}), 128.4 (Ar*C*), 127.5 (Ar*C*), 126.2 (Ar*C*), 125.9 (Ar*C*), 125.5 (Ar*C*), 125.2 (Ar*C*), 124.9 (Ar*C*), 123.9 (ArC=*C*H), 93.2 (C=CH_2), 81.6 *C*(CH_3)$_3$), 66.4 (OCH_2), 28.0 (C(*C*H_3)$_3$), 26.1 (*C*H_3C=C); HRMS (APPI, neg.): *m/z* 324.1721 (324.1725 calc. for $C_{21}H_{24}O_3$ (M^+)).

General procedure for the rearrangement of 100 to 102:

To a suspension of $Cu(OTf)_2$ in ether was added **L6** and the mixture was stirred at ambient temperature for 1 h. To the resulting solution was added a solution of the allyl vinyl ether in ether (1 mL). The resulting solution was stirred at ambient temperature for

the specified time. The solution was concentrated and the residue was purified by flash chromatography on silica gel to provide **102**.

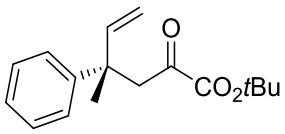
***tert*-Butyl (*S*)-4-methyl-2-oxo-4-vinyloctanoate (102a):**



Treatment of **100a** (60 mg, 0.24 mmol) with the complex derived from $Cu(OTf)_2$ (8.7 mg, 0.024 mmol) and (*R*,*R*)-2,2'-isopropylidene-bis(4-phenyl-2-oxazoline) (8 mg, 0.024 mmol) in ether (1 mL) for 92 h according to the general procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 97:3), 35 mg (58%) of **102a** as a clear oil; R_f = 0.27 (hexanes/EtOAc, 97:3).

IR (neat): 3084, 2958, 2930, 1720, 1460, 1370, 1283, 1257, 1155, 1056, 1008, 914, 866 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.81 (dd, 1H, *J* = 17.5, 10.8, C*H*=CH_2), 5.00 (dd, 1H, *J* = 10.8, 1.0, CH=C*H*$_2$), 4.93 (dd, 1H, *J* = 17.5, 1.0, CH=C*H*$_2$), 2.90 (d, 1H, *J* = 14.2, C*H*$_2$C(O)), 2.68 (d, 1H, *J* = 14.2, C*H*$_2$C(O)), 1.54 (s, 9H, C(C*H*$_3$)$_3$), 1.45-1.35 (m, 2H, C*H*$_2$CH$_2$), 1.30-1.15 (m, 4H, C*H*$_2$CH$_2$), 1.09 (s, 3H, C*H*$_3$), 0.88 (t, 3H, *J* = 7.0, CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.2 (*C*(O)CO$_2$*t*Bu), 161.3 (*C*O$_2$*t*Bu), 145.1 (*C*H=CH$_2$), 112.6 (CH=*C*H2), 83.7 (*C*(CH$_3$)$_3$), 47.9 (*C*H$_2$C(O)), 40.7 (*C*H$_2$), 39.8 (*C*quat.), 27.8 (C(*C*H$_3$)$_3$), 26.2 (*C*H$_2$), 23.2 (*C*H$_2$), 22.7 (*C*H$_3$), 14.0 (*C*H$_3$); HRMS (APPI, pos.): *m/z* 254.1875 (254.1882 calc. for $C_{15}H_{26}O_3$ (M^+)); HPLC: Chiralpak AS-H (hexane/*i*-PrOH, 99.5:0.5, flow rate 1 mL min^{-1}, λ= 254 nm): t_{major} = 3.74; t_{minor} 3.45 min; 97% ee.

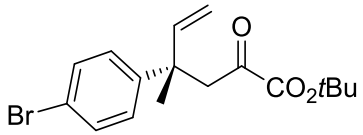
***tert*-Butyl (*S*)-4-methyl-2-oxo-4-phenylhex-5-enoate (102e):**



Treatment of **100e** (30 mg, 0.11 mmol) with the complex derived from $Cu(OTf)_2$ (4 mg, 0.011 mmol) and (*R*,*R*)-2,2'-isopropylidenebis(4-phenyl-2-oxazoline) (3.70 mg, 0.011 mmol) in ether (0.5 mL) for 67 h according to the general procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 98:2), 16 mg (53%) of **102e** as a clear oil; R_f = 0.21 (hexanes/EtOAc, 98:2).

IR (neat): 2980, 1720, 1413, 1289, 1257, 1155, 1055, 1008, 920, 838 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32-7.28 (m, 4H, Ar*H*), 7.23-7.15 (m, 1H, Ar*H*), 6.15 (dd, 1H, *J* = 17.4, 10.7, C*H*=CH_2), 5.14 (dd, 1H, *J* = 10.7, 0.8, CH=C*H*H), 5.09 (dd, 1H, *J* = 17.4, 0.8, CH=CH*H*), 3.29 (s, 2H, CH_2C(O)), 1.52 (s, 3H, CH_3), 1.45 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.3 (*C*(O)CO_2*t*Bu), 160.8 (*C*O_2*t*Bu), 145.6 (ArC_{ipso}), 145.0 (*C*H=CH_2), 128.4 (2 x Ar*C*), 126.5 (Ar*C*), 126.3 (2 x Ar*C*), 112.8 (CH=*C*H_2), 83.7 (*C*(CH_3)$_3$), 48.0 (*C*H_2C(O)), 43.6 (Ar-*C*-CH_3), 27.7 (C(*C*H_3)$_3$), 25.2 (Ar-C-*C*H_3); HRMS (APPI, pos.): *m/z* 274.1575 (274.1569 calc. for $C_{17}H_{22}O_3$ (M^+)); HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 99.6/0.4, flow rate 1 mL min^{-1}, λ= 254 nm): t_{major} = 6.77; t_{minor} 7.50 min; 45% ee.

***tert*-Butyl (*S*)-4-(4-bromophenyl)-4-methyl-2-oxohex-5-enoate (102j):**



Treatment of **100j** (50 mg, 0.14 mmol) with the complex derived from $Cu(OTf)_2$ (5.2 mg, 0.014 mmol) and (*R*,*R*)-2,2'-isopropylidenebis(4-phenyl-2-oxazoline) (4.8 mg, 0.014 mmol) in ether (0.5 mL) for 120 h according to the general procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 98:2), 24 mg (48%) of **102j** as a clear oil; R_f = 0.22 (hexanes/EtOAc, 98:2).

IR (neat): 2979, 2935, 1720, 1490, 1396, 1370, 1290, 1256, 1155, 1054, 1008, 921, 824 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.41 (d, 2H, *J* = 8.7, Ar*H*), 7.18 (d, 2H, *J* = 8.7, Ar*H*), 6.08 (dd, 1H, *J* = 17.4, 10.7, C*H*=CH_2), 5.15 (dd, 1H, *J* = 10.7, 0.7, CH=C*H*H), 5.08 (dd, 1H, *J* = 17.4, 0.7, CH=CH*H*), 3.26 (AB system, 2H, *J* = 15.3, CH_2C(O)), 1.49 (s, 3H, CH_3), 1.46 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.8 (*C*(O)CO_2*t*Bu), 160.7 (*C*O_2*t*Bu), 144.57 (*C*H=CH_2), 144.52 (ArC_{ipso}), 131.4 (2 x Ar*C*), 128.3 (2 x Ar*C*), 120.5 (Ar*C*-Br), 113.2 (CH=*C*H2), 84.0 (*C*(CH_3)$_3$), 47.8 (*C*H_2C(O)), 43.3 (Ar-*C*-CH_3), 27.7 (C(*C*H_3)$_3$), 25.2 (Ar-C-*C*H_3); HRMS (APPI, pos.): *m/z* 352.0667 (352.0674 calc. for $C_{17}H_{21}BrO_3$ (M^+)); HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 99.6/0.4, flow rate 1 mL min^{-1}, λ= 254 nm): t_{major} = 8.06; t_{minor} 9.04 min; 56% ee.

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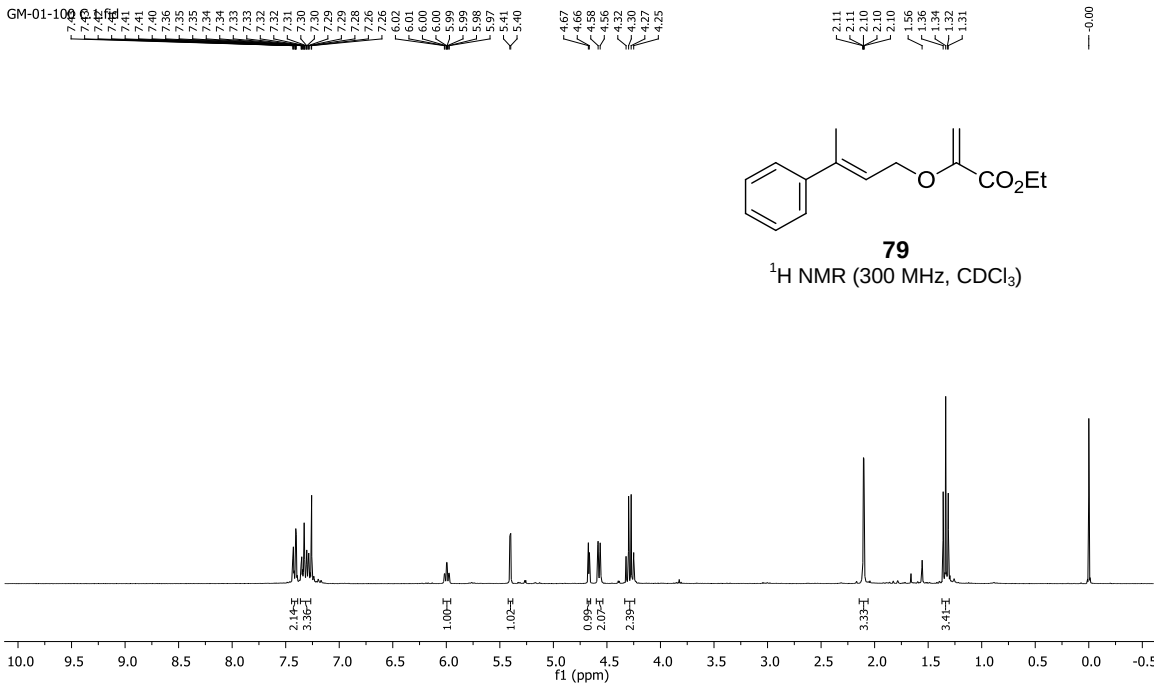
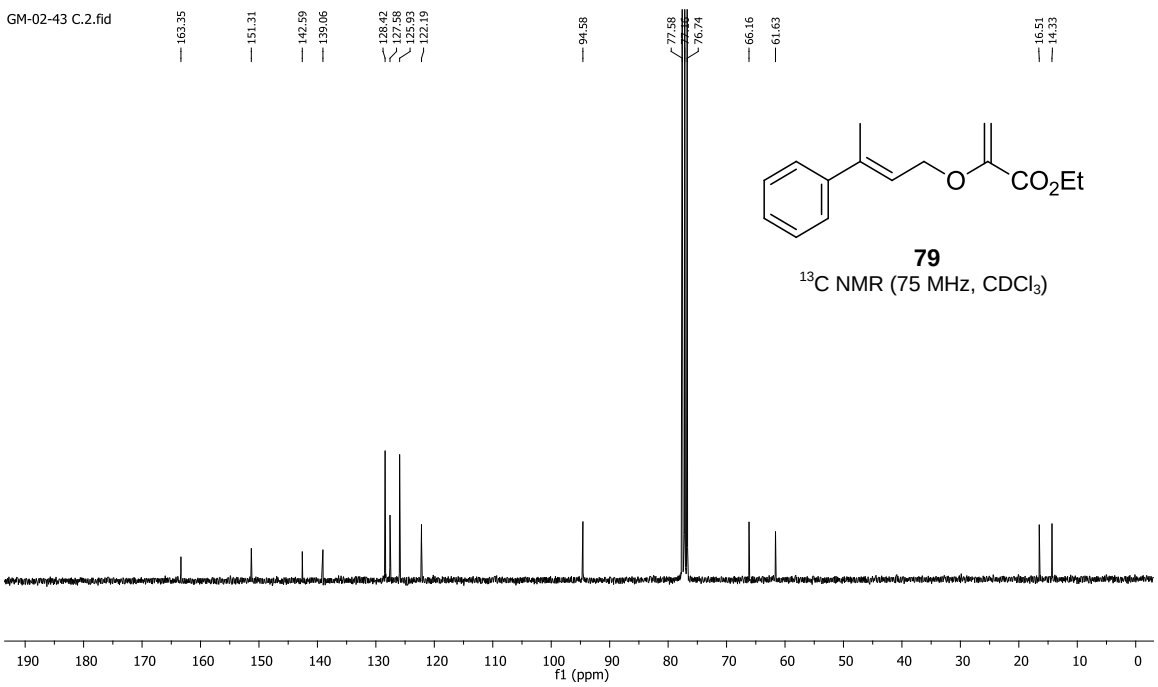
1.12 APPENDIX 1 (^{1}H, ^{13}C NMR and HPLC traces)



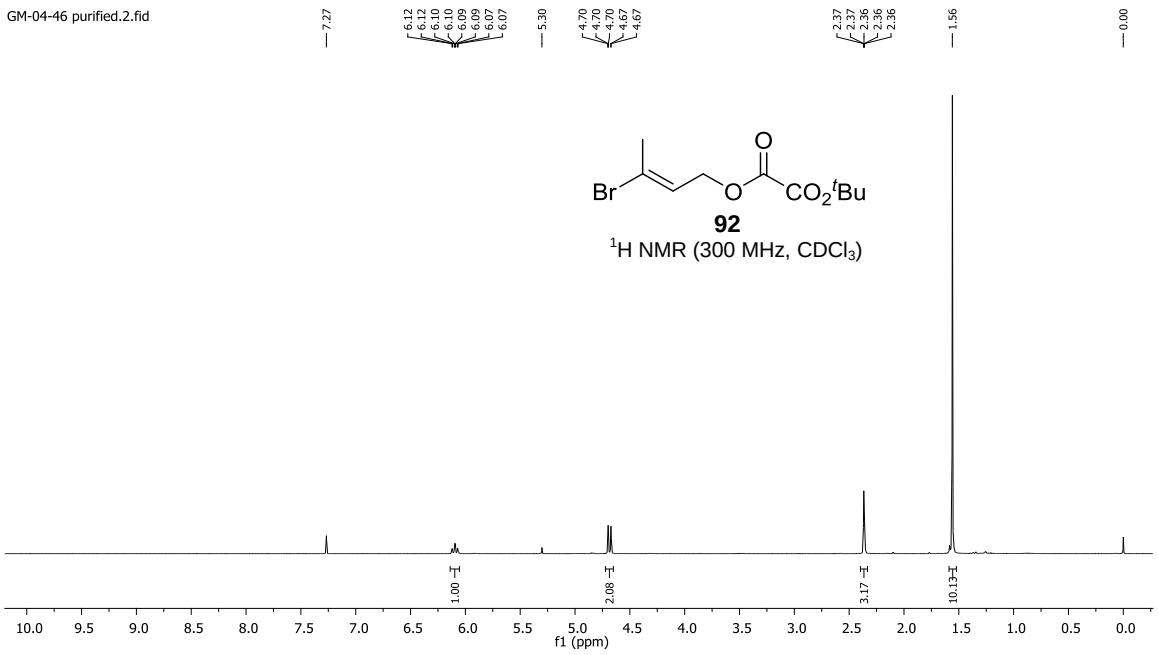
79

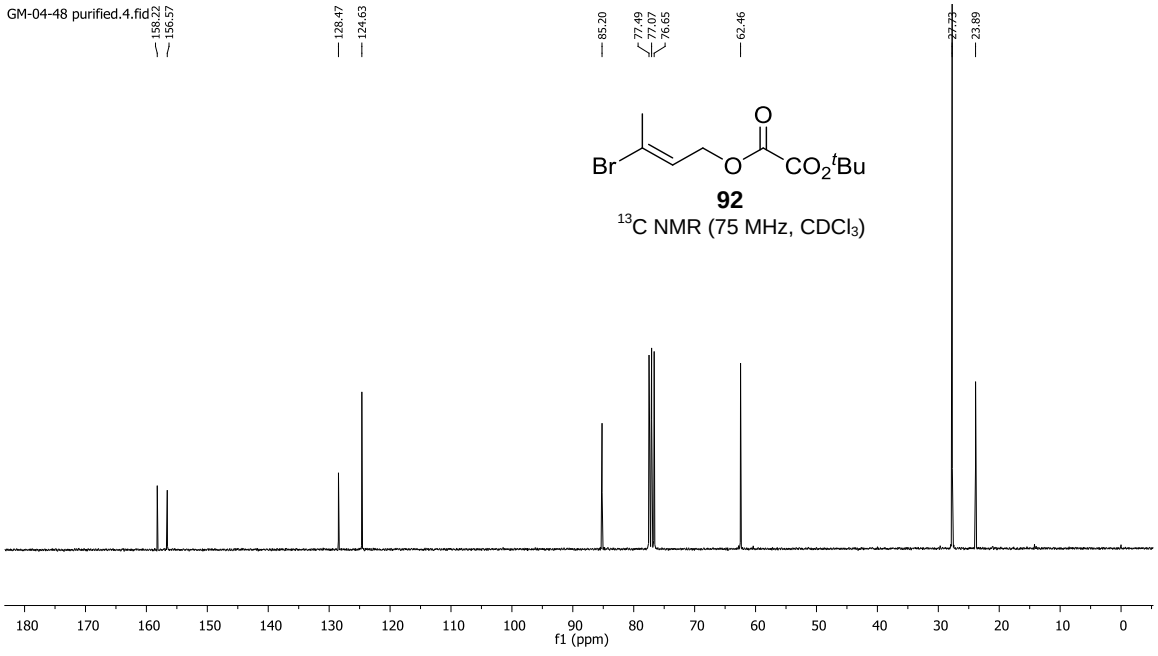
^{1}H NMR (300 MHz, $CDCl_3$)

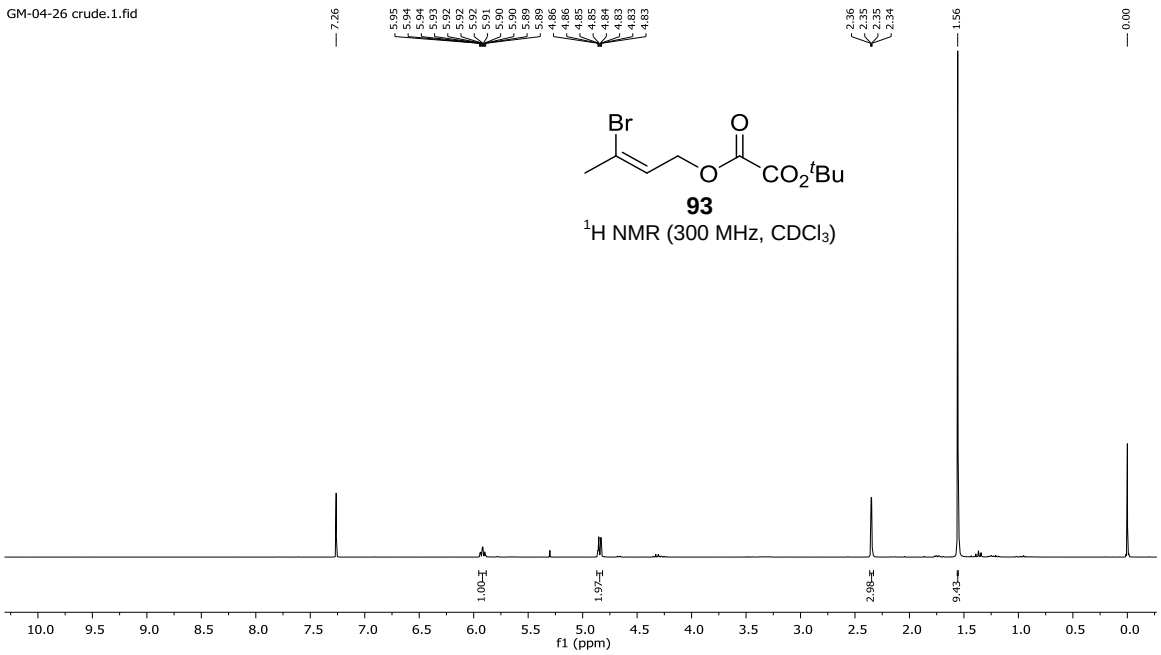


79

^{13}C NMR (75 MHz, $CDCl_3$)

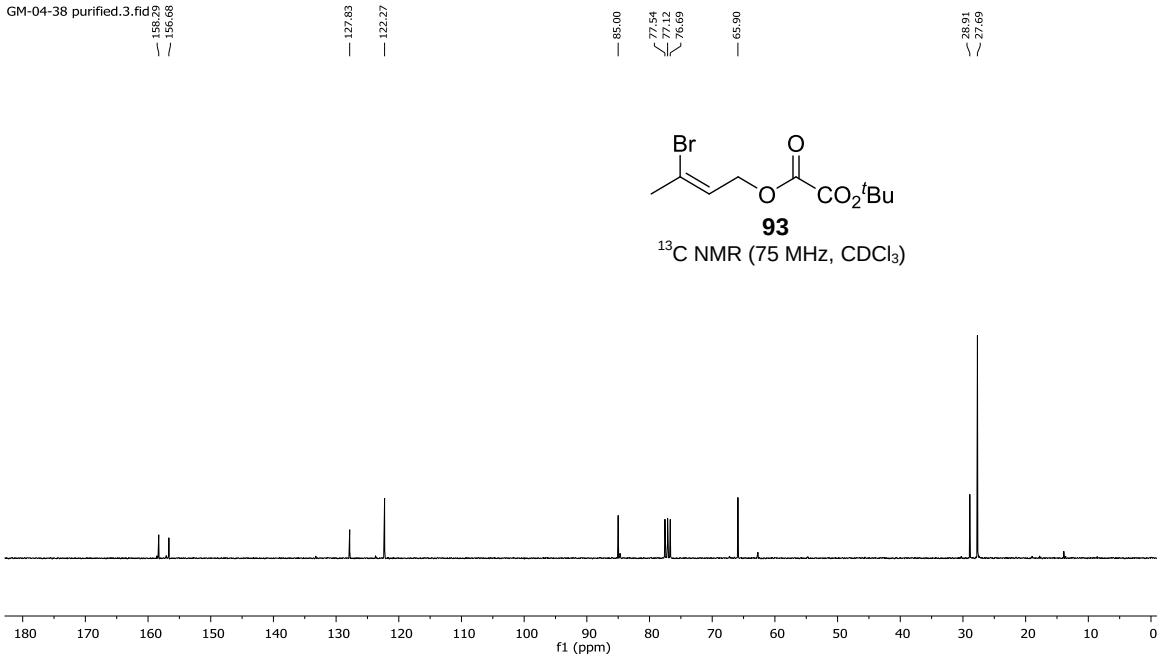

GM-04-46 purified.2.fid
7.27
6.12
6.12
6.10
6.10
6.09
6.09
6.07
6.07
5.30
4.70
4.70
4.70
4.67
4.67
2.37
2.37
2.36
2.36
2.36
1.56
0.00
Br
O
O
CO2tBu
92
1H NMR (300 MHz, CDCl3)
1.00
2.08
3.17
10.13
f1 (ppm)


GM-04-48 purified.4.fid
158.22
156.57
128.47
124.63
85.20
77.49
77.07
76.65
62.46
27.73
23.89
Br
O
O
CO2tBu
92
13C NMR (75 MHz, CDCl3)
f1 (ppm)



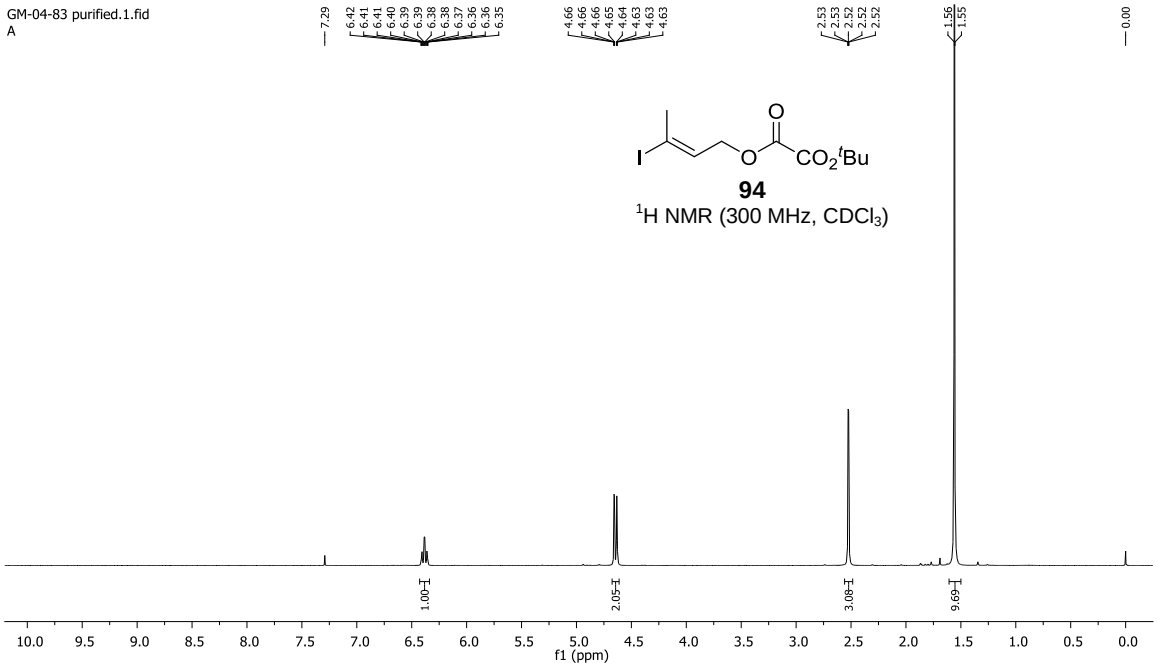
93

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



93

^{13}C NMR (75 MHz, $CDCl_3$)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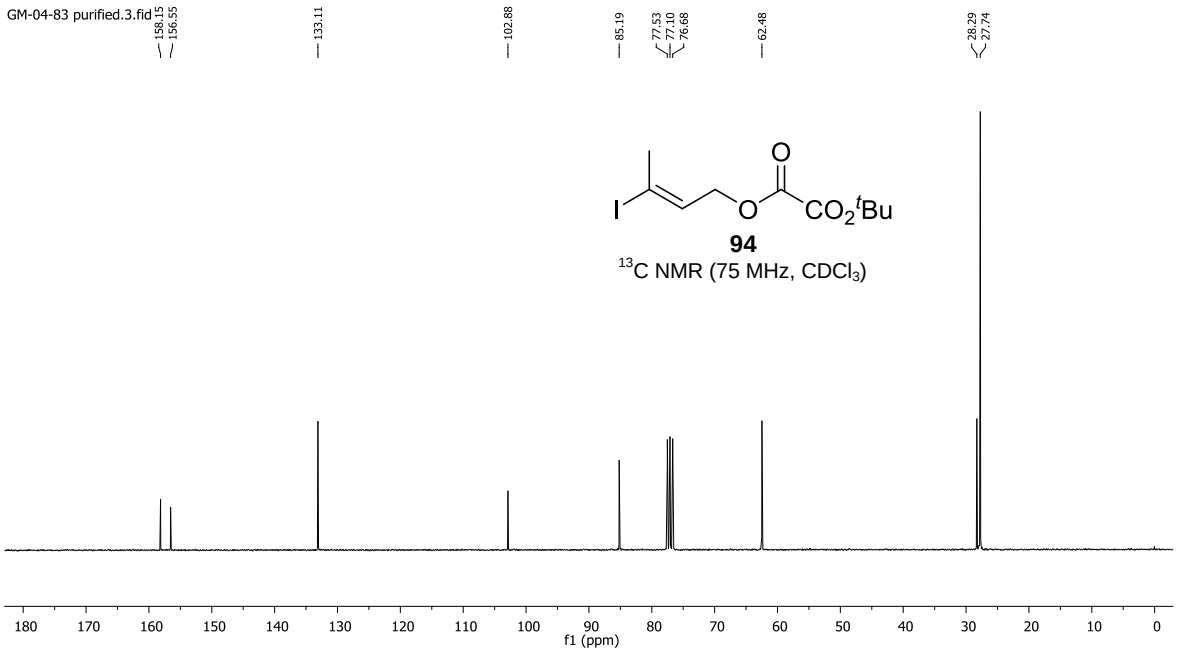
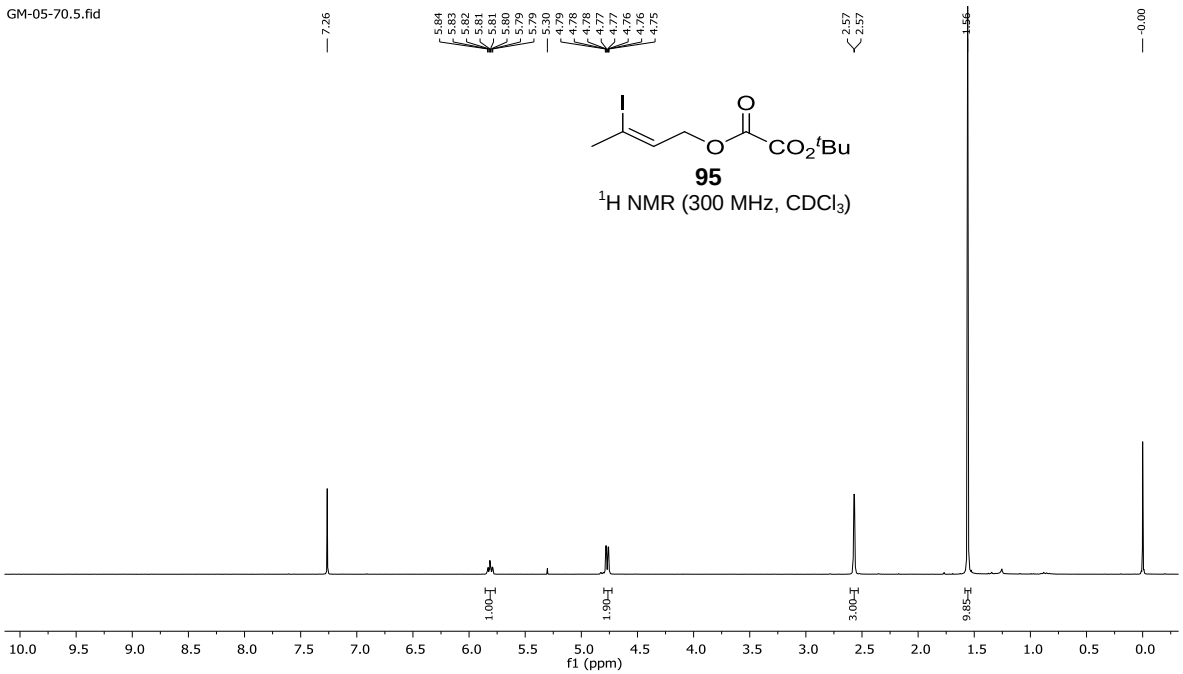
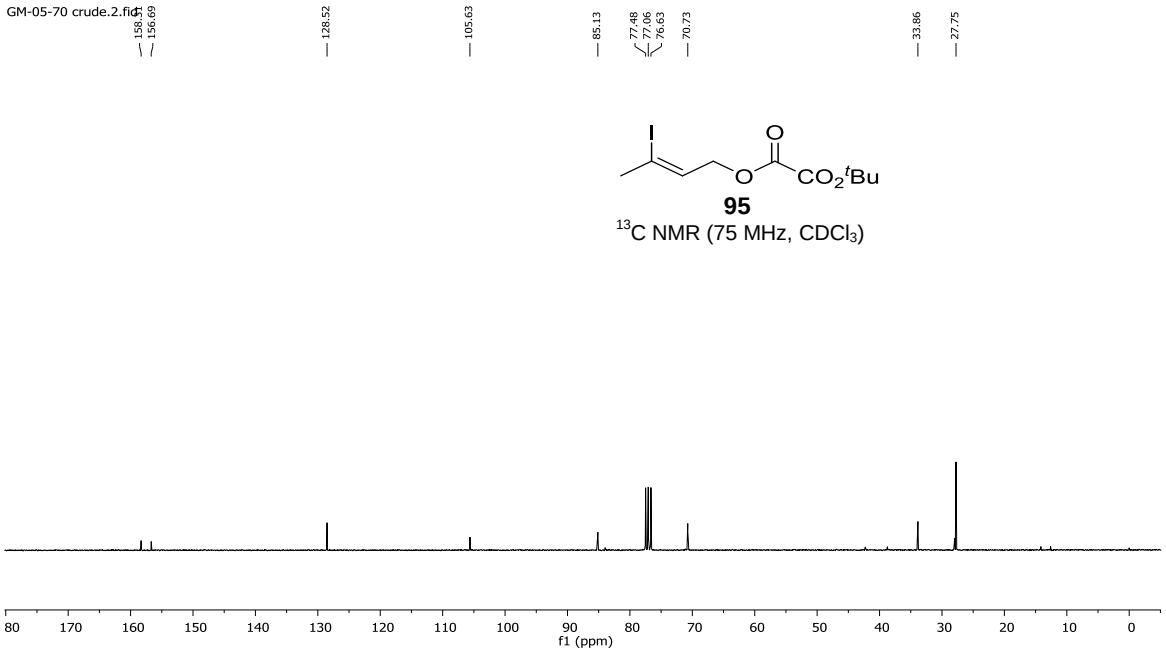
A
7.29
6.42
6.41
6.41
6.40
6.39
6.39
6.38
6.38
6.37
6.36
6.36
6.35
4.66
4.66
4.66
4.65
4.64
4.63
4.63
4.63
2.53
2.53
2.52
2.52
2.52
1.56
1.55
0.00
O
I
O
CO2tBu
94
1H NMR (300 MHz, CDCl3)
1.00
2.05
3.08
9.69
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


GM-04-83 purified.3.fid
158.15
156.55
133.11
102.88
85.19
77.53
77.10
76.68
62.48
28.29
27.74
O
I
O
CO2tBu
94
13C NMR (75 MHz, CDCl3)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



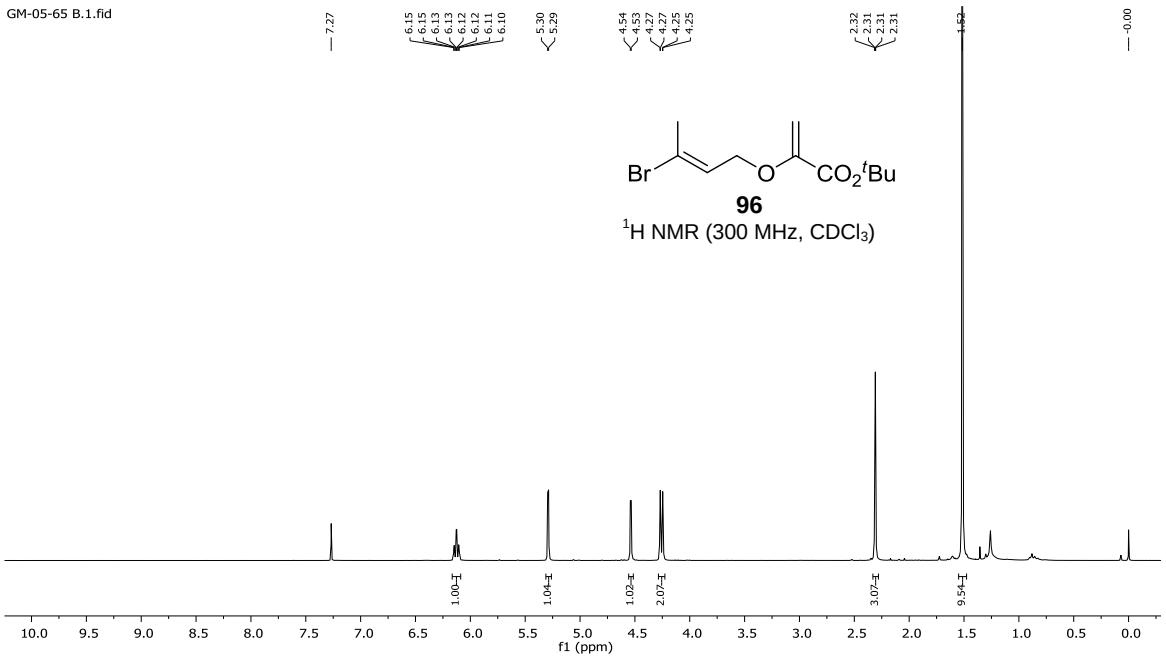
95

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



95

^{13}C NMR (75 MHz, $CDCl_3$)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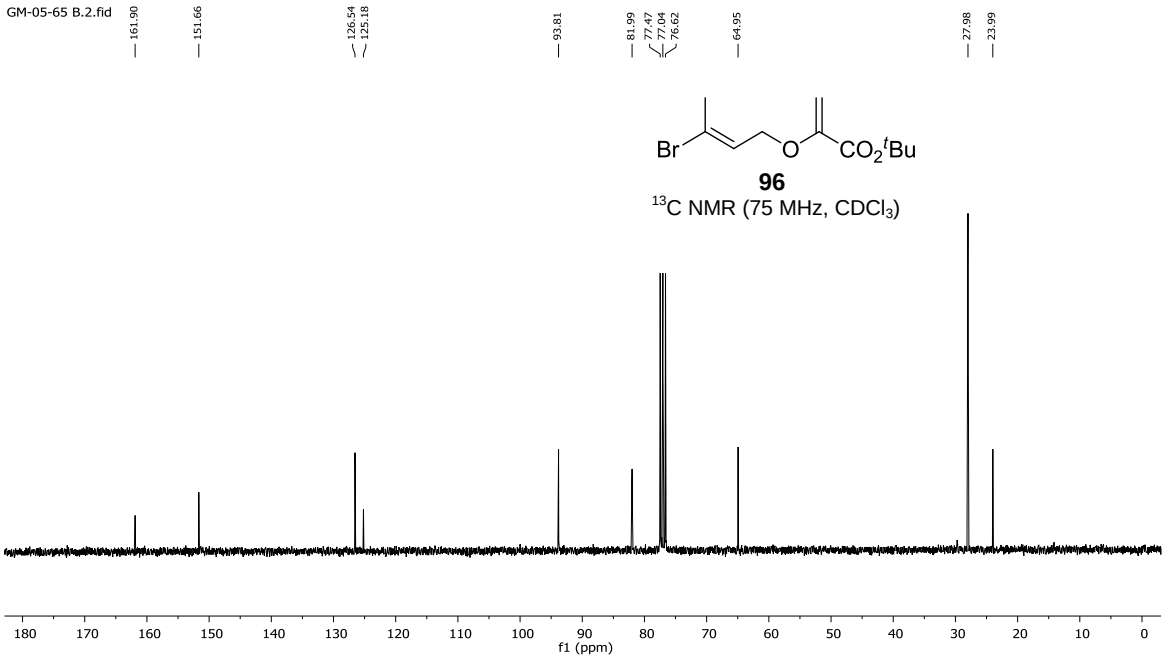
6.15
6.15
6.13
6.13
6.12
6.12
6.11
6.10
5.30
5.29
4.54
4.53
4.27
4.27
4.25
4.25
2.32
2.31
2.31
2.31
1.52
0.00
Br
O
CO2tBu
96
1H NMR (300 MHz, CDCl3)
1.00
1.04
1.02
2.07
3.07
9.54
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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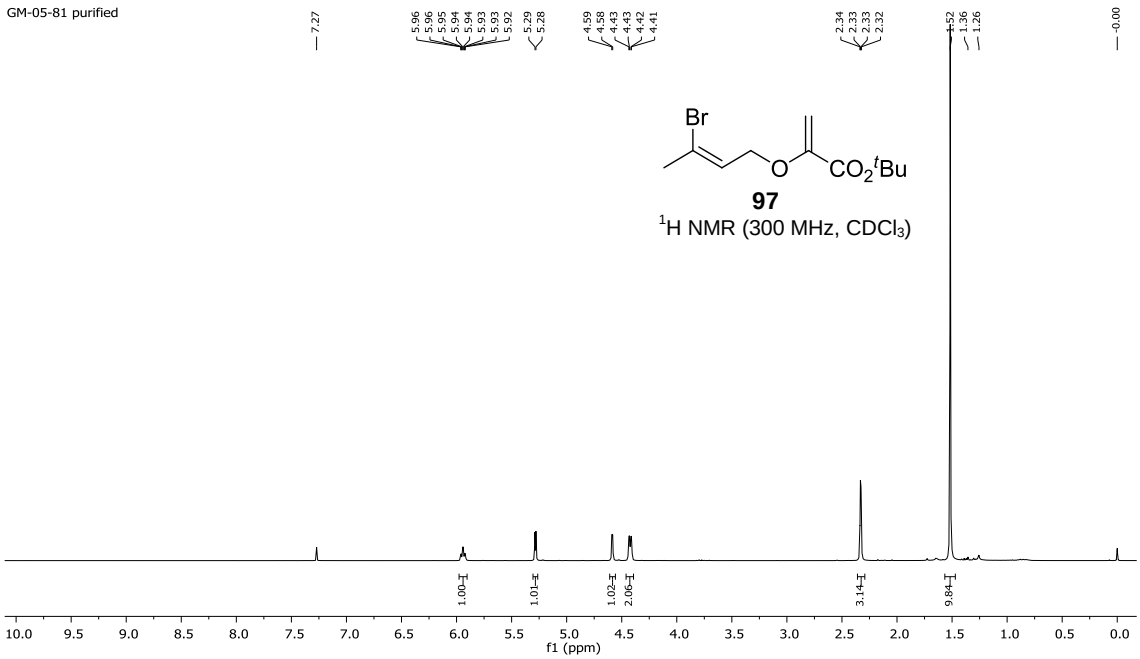
161.90
151.66
126.54
125.18
93.81
81.99
77.47
77.04
76.62
64.95
27.98
23.99
Br
O
CO2tBu
96
13C NMR (75 MHz, CDCl3)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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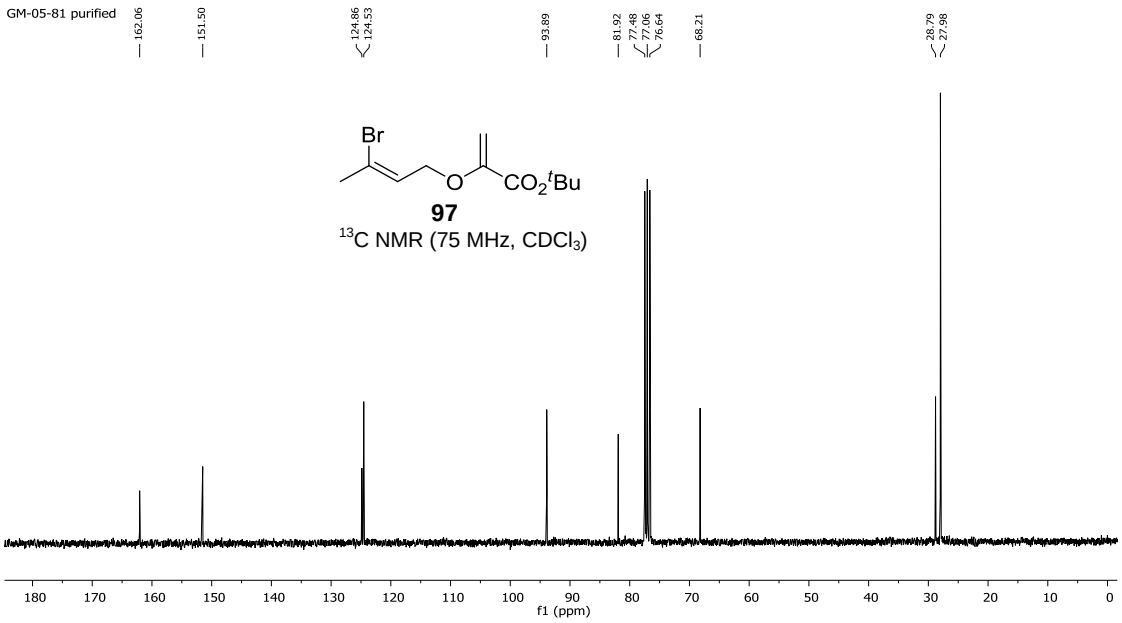
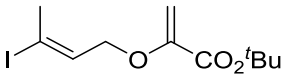
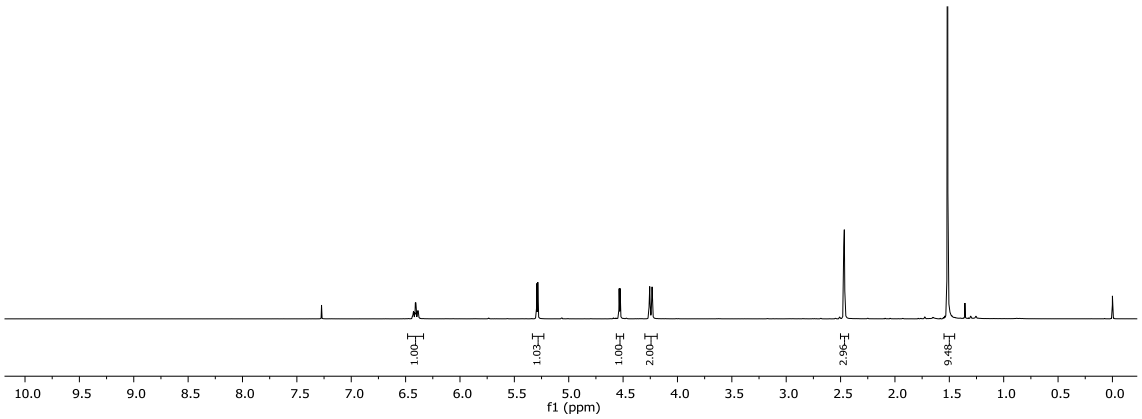
5.96
5.96
5.95
5.94
5.94
5.93
5.93
5.92
5.29
5.28
4.59
4.58
4.43
4.43
4.42
4.41
2.34
2.33
2.33
2.32
1.52
1.36
1.26
0.00
Br
O
CO2tBu
97
1H NMR (300 MHz, CDCl3)
1.00
1.01
1.02
2.06
3.14
9.84
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


GM-05-81 purified
162.06
151.50
124.86
124.53
93.89
81.92
77.48
77.06
76.64
68.21
28.79
27.98
Br
O
CO2tBu
97
13C NMR (75 MHz, CDCl3)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

GM-06-86 A.2.fid



98



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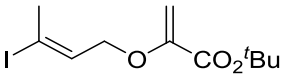
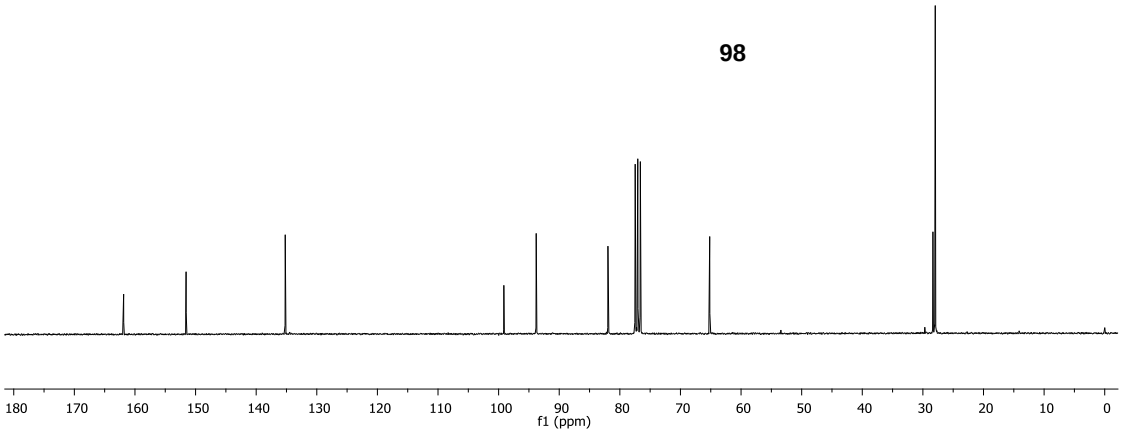
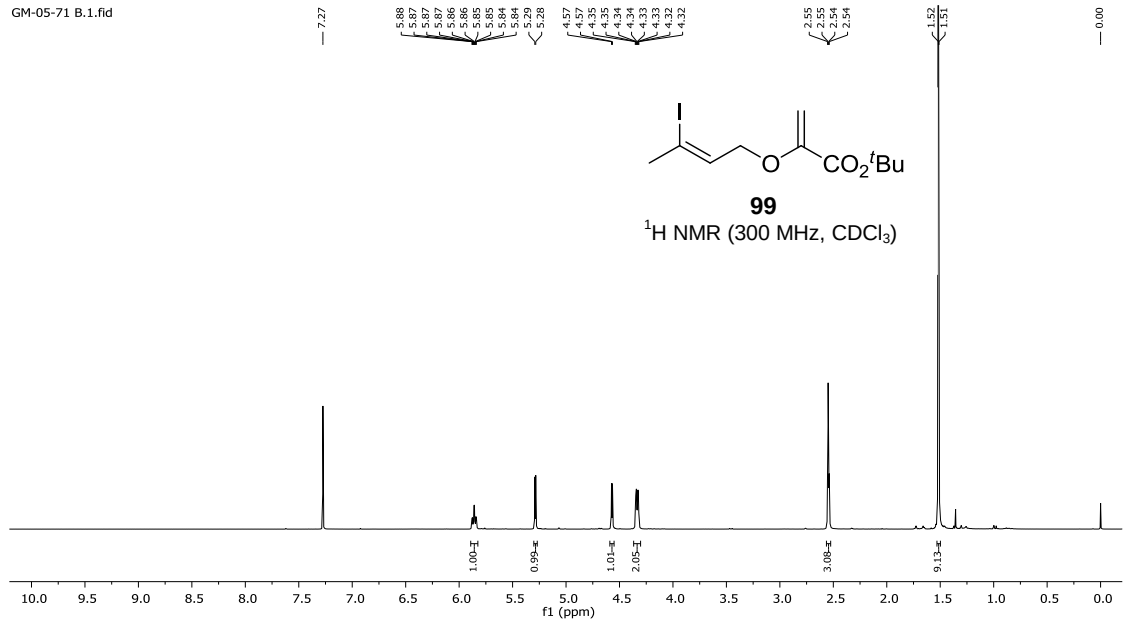


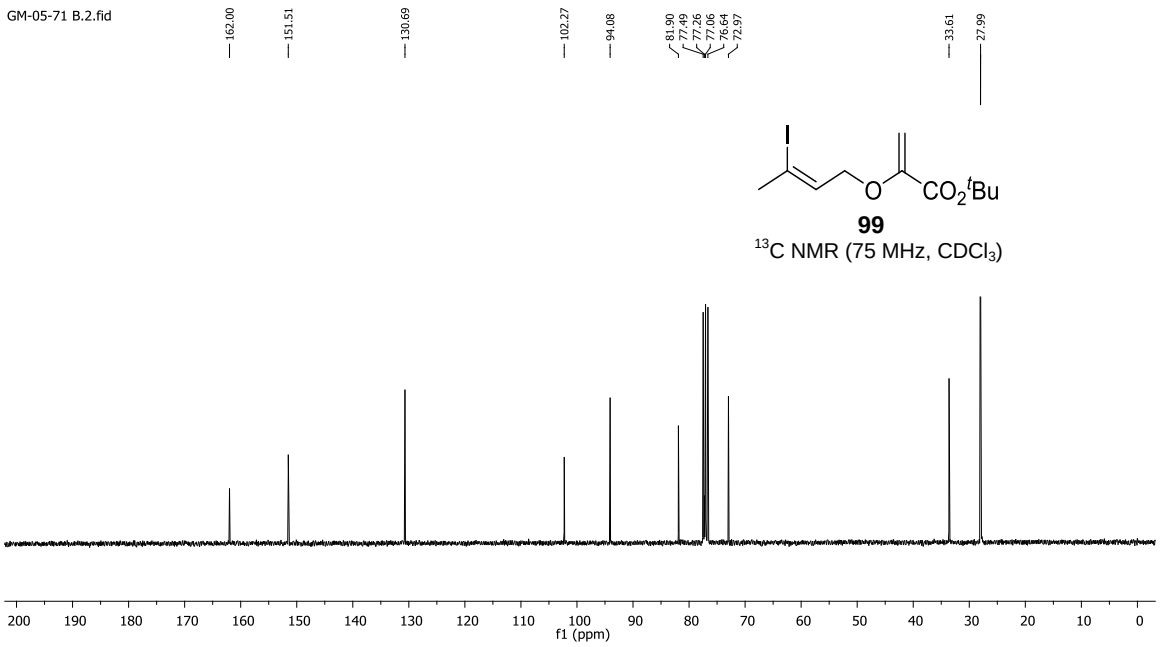
98





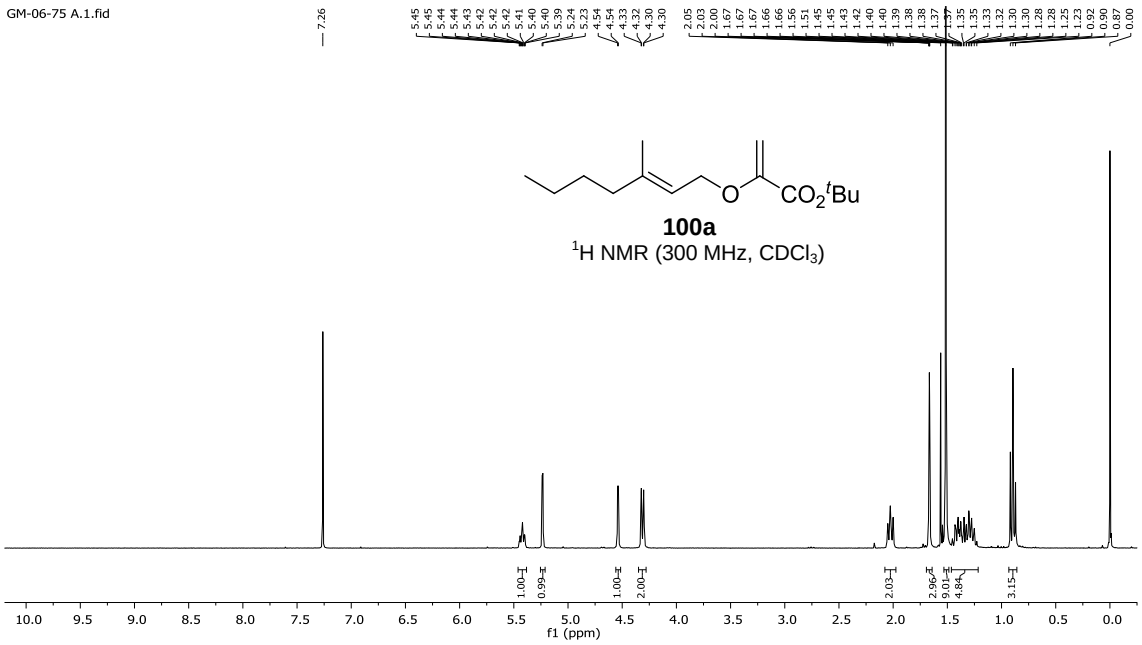
99

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



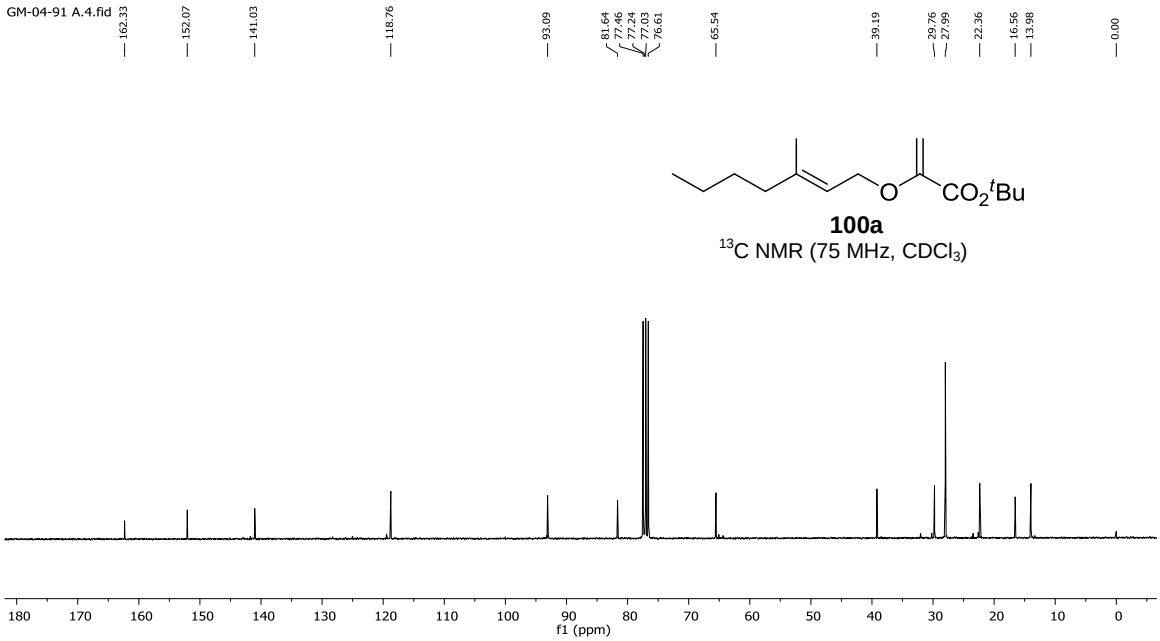
99

^{13}C NMR (75 MHz, $CDCl_3$)



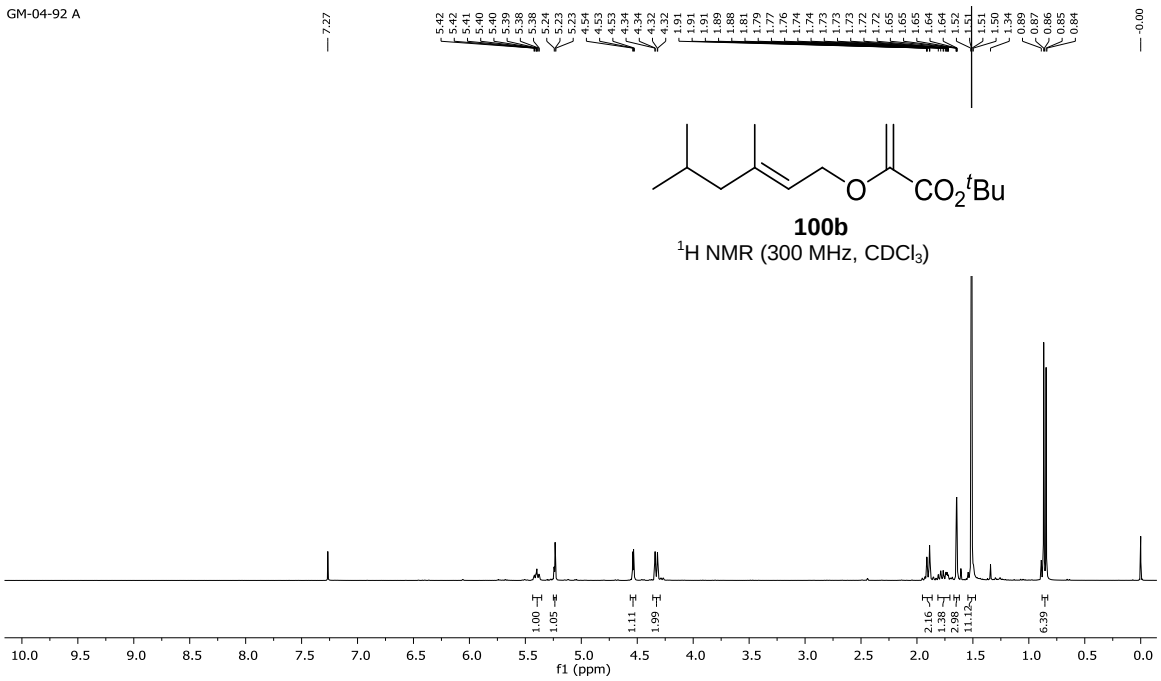
100a

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



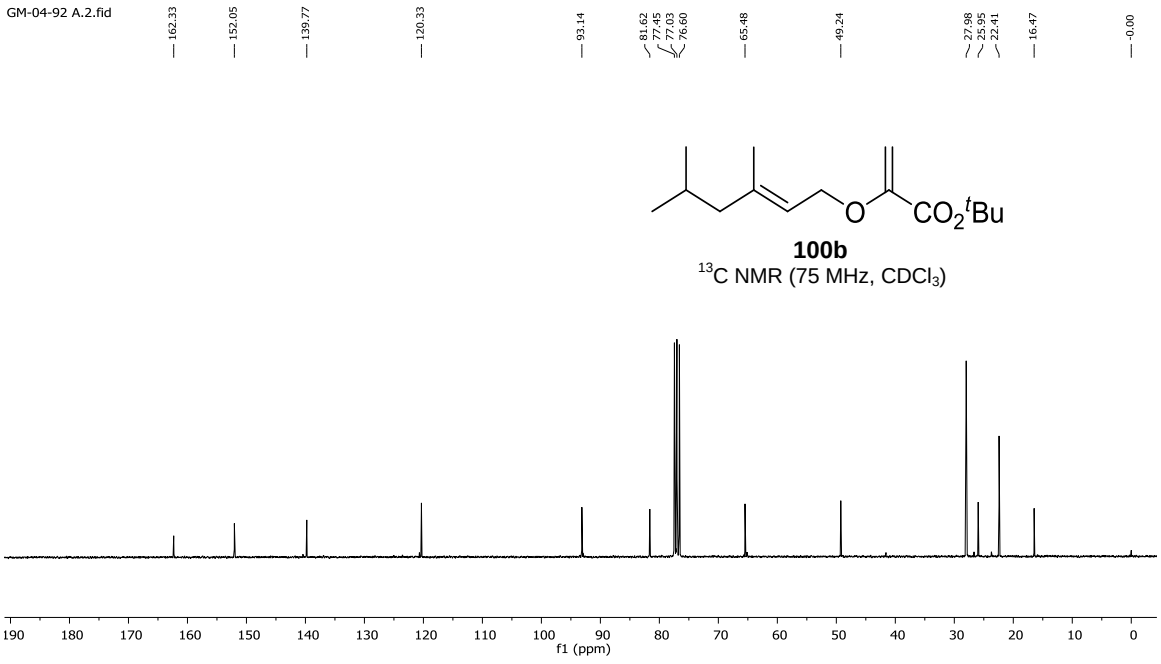
100a

^{13}C NMR (75 MHz, $CDCl_3$)



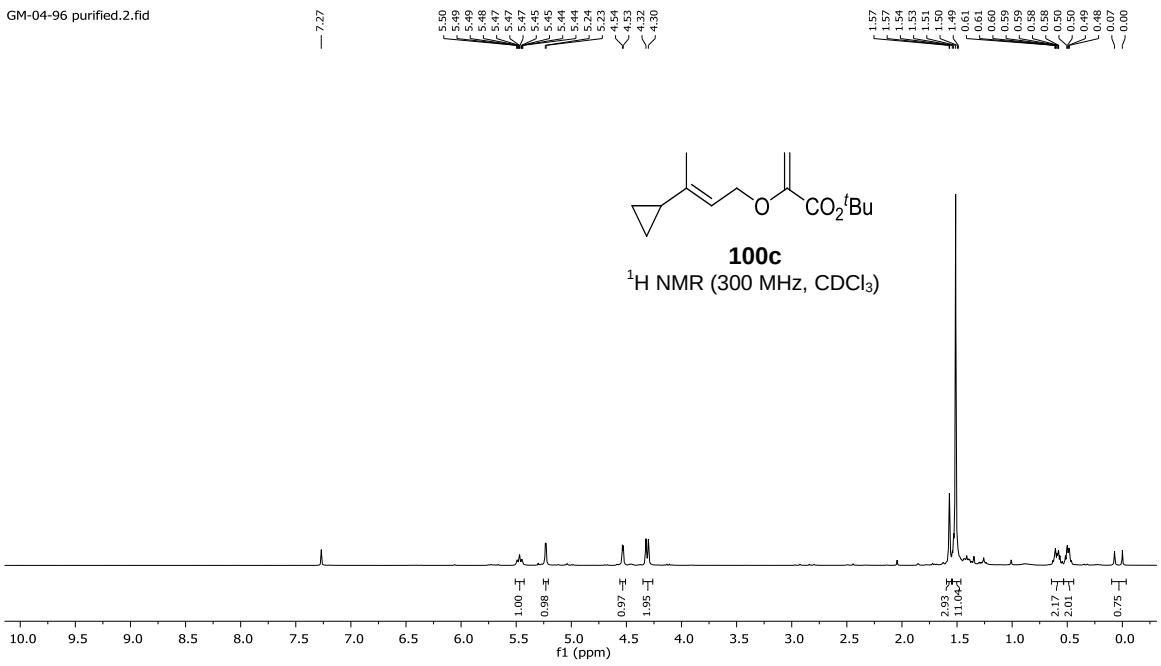
100b

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



100b

^{13}C NMR (75 MHz, $CDCl_3$)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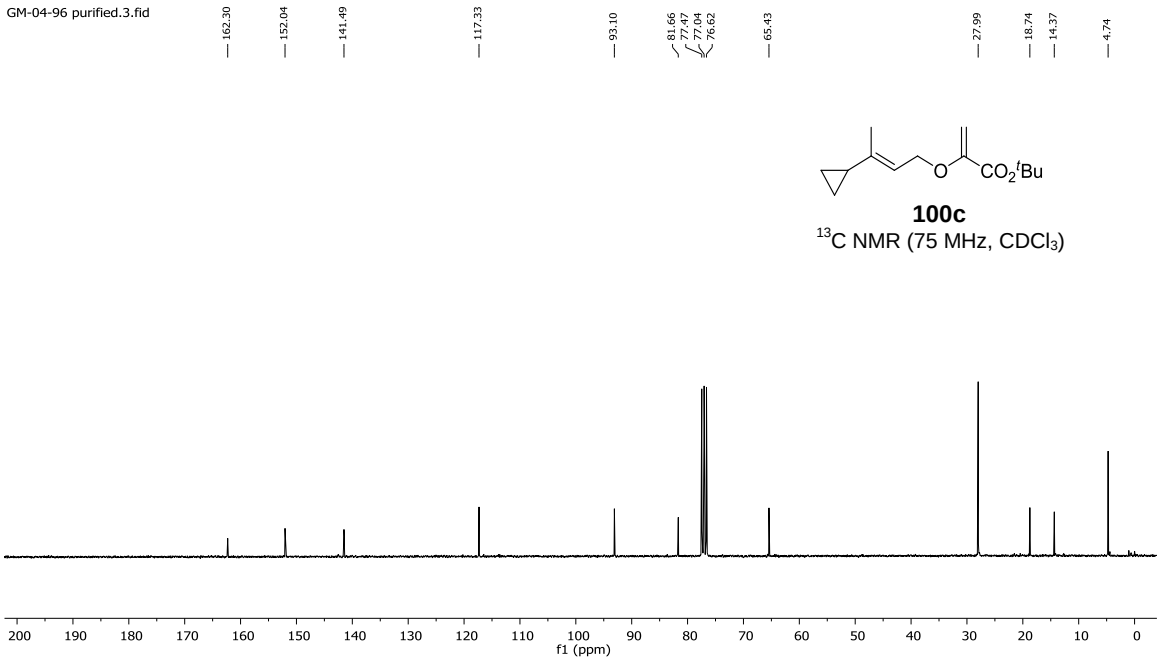
5.50
5.49
5.49
5.48
5.47
5.47
5.47
5.45
5.45
5.44
5.44
5.24
5.23
4.54
4.53
4.32
4.30
1.57
1.57
1.54
1.53
1.51
1.50
1.49
0.61
0.60
0.59
0.59
0.58
0.58
0.50
0.50
0.49
0.48
0.07
0.00
O
CO2tBu
100c
1H NMR (300 MHz, CDCl3)
1.00
0.98
0.97
1.95
2.93
11.04
2.17
2.01
0.75
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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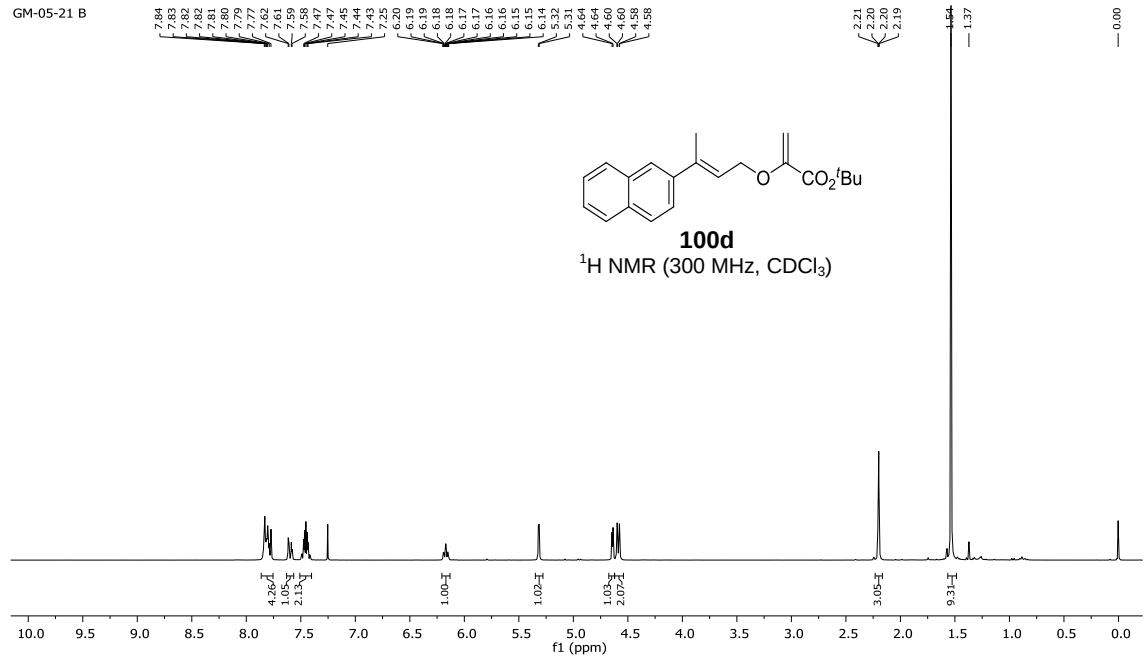
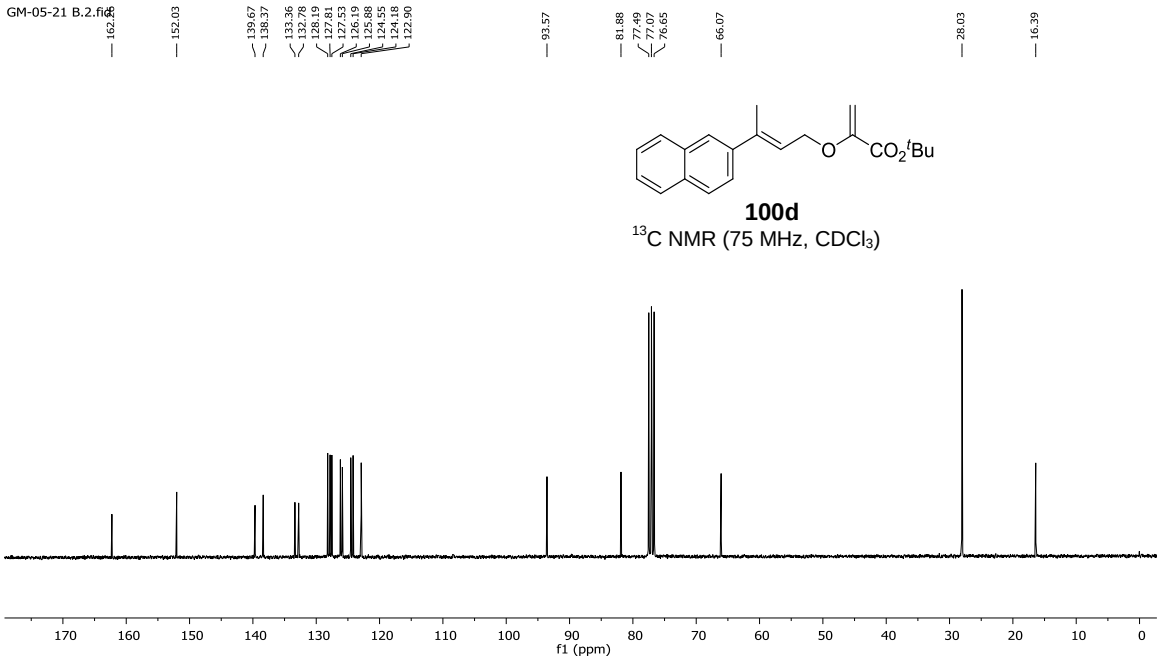
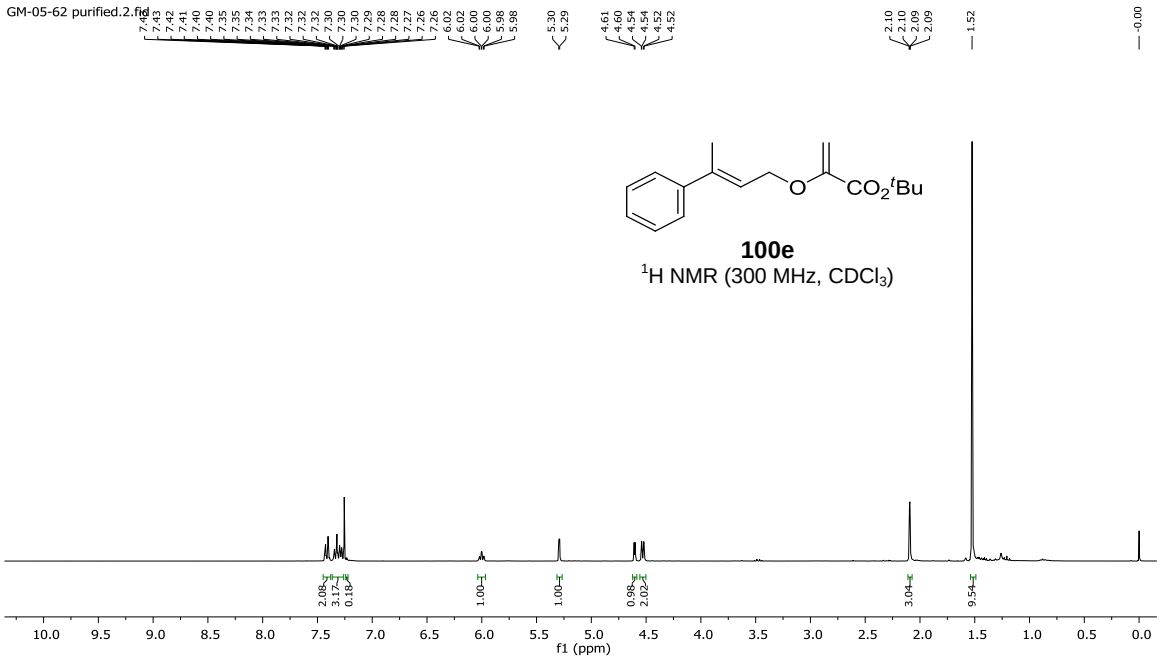
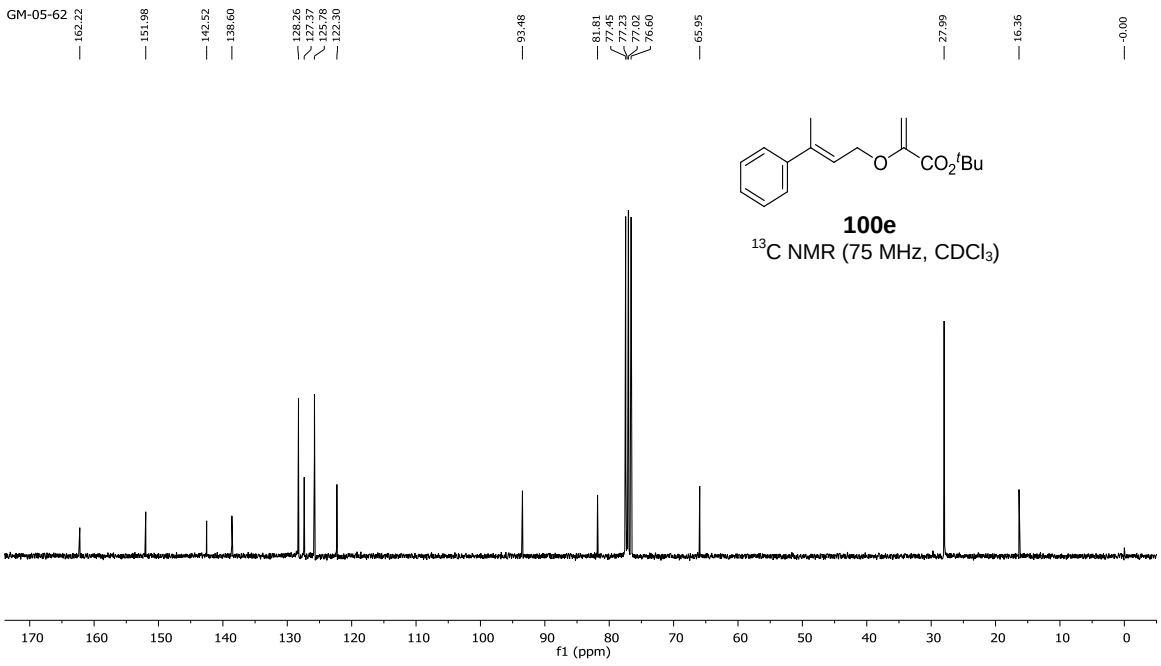
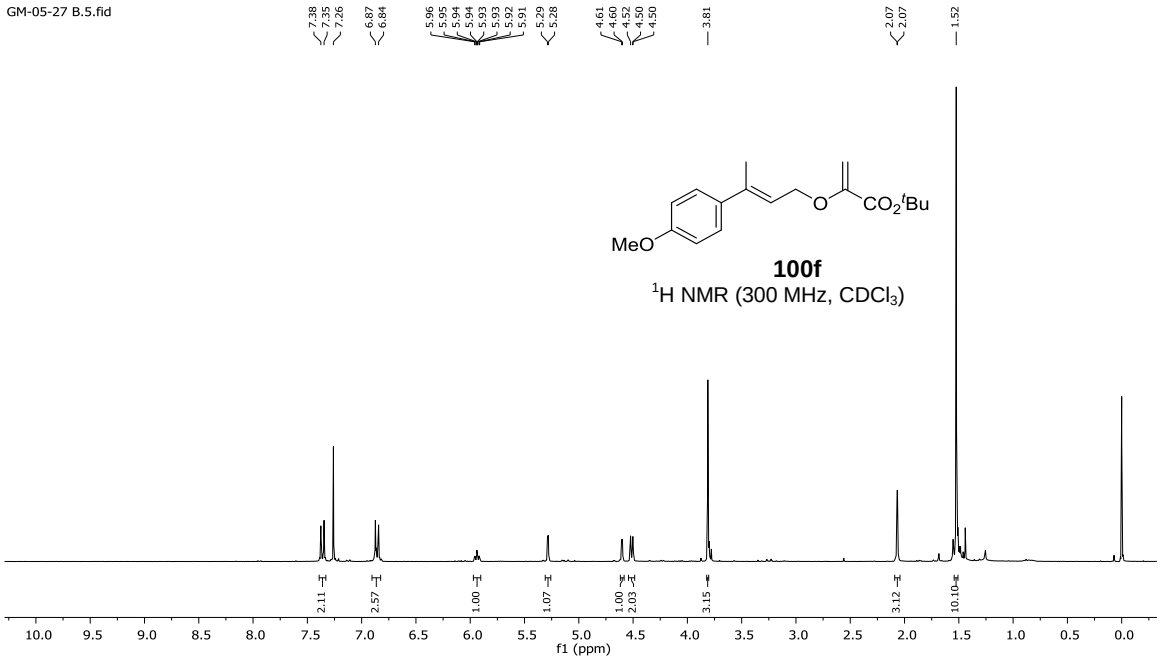
162.30
152.04
141.49
117.33
93.10
81.66
77.47
77.04
76.62
65.43
27.99
18.74
14.37
4.74
O
CO2tBu
100c
13C NMR (75 MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

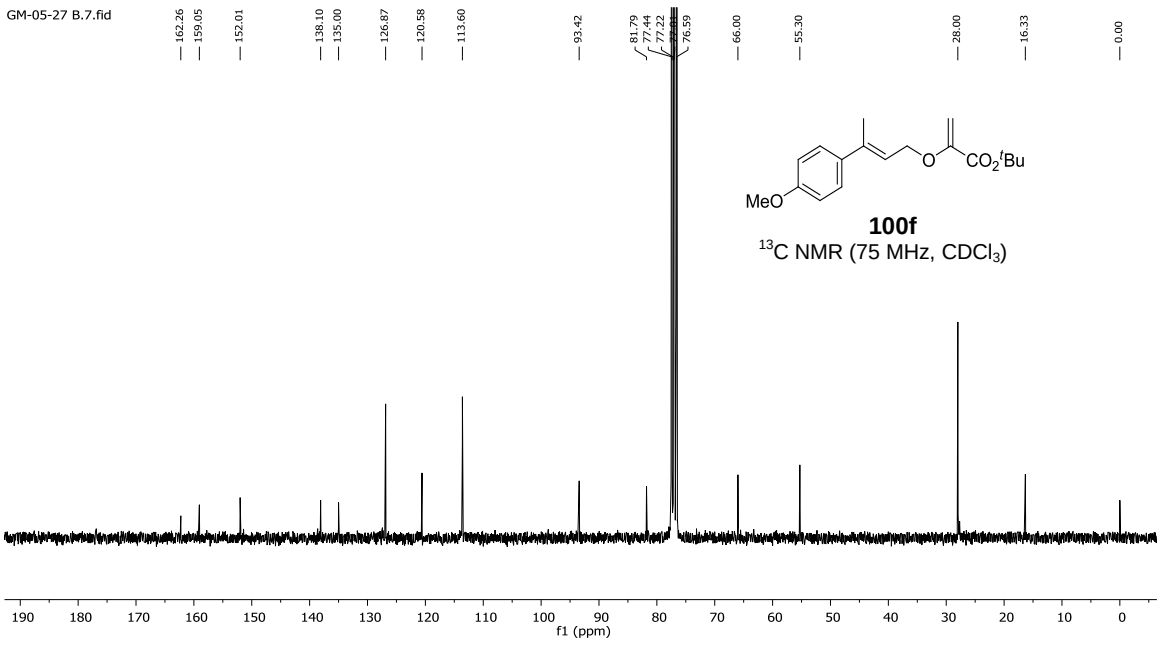

GM-05-21 B
7.84 7.83 7.82 7.82 7.81 7.80 7.79 7.77 7.62 7.61 7.59 7.58 7.47 7.47 7.45 7.44 7.43 7.25 6.20 6.19 6.19 6.18 6.18 6.17 6.17 6.16 6.16 6.15 6.15 6.14 5.32 5.31 4.64 4.64 4.60 4.60 4.58 4.58
2.21 2.20 2.20 2.19 1.64 1.37 0.00
O
CO2tBu
100d
1H NMR (300 MHz, CDCl3)
4.26 1.05 2.13 1.00 1.02 1.03 2.07 3.05 9.31
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

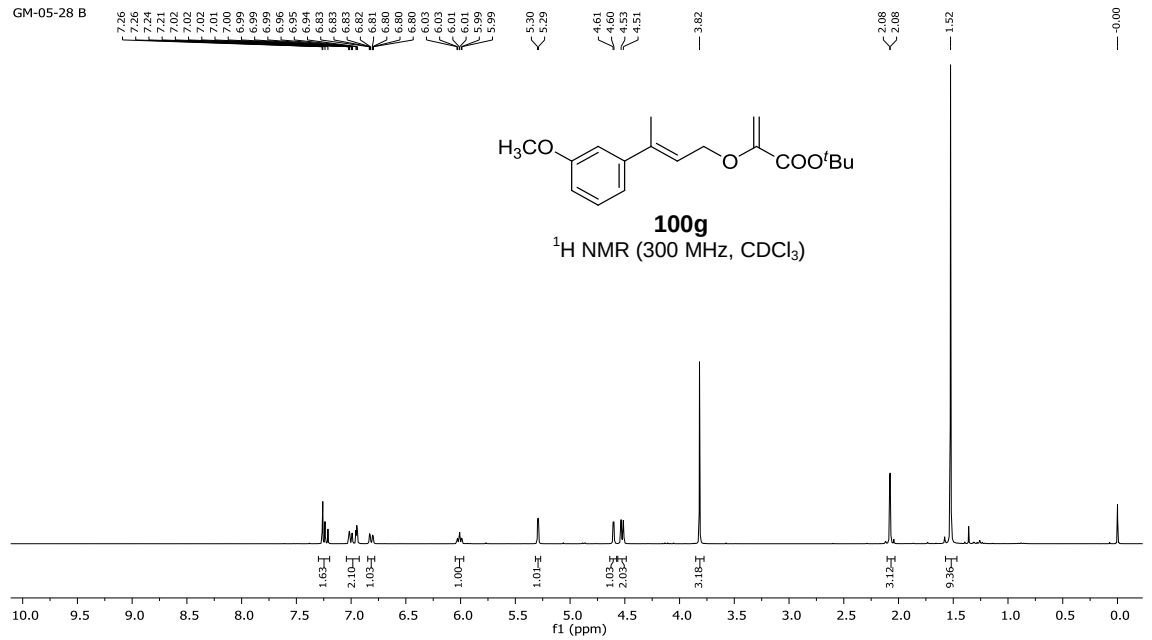

GM-05-21 B.2.fid
162.86 152.03 139.67 138.37 133.36 132.78 128.19 127.81 127.53 126.19 125.88 124.55 124.18 122.90 93.57 81.88 77.49 77.07 76.65 66.07 28.03 16.39
O
CO2tBu
100d
13C NMR (75 MHz, CDCl3)
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


GM-05-62 purified.2.fid
7.45 7.43 7.42 7.41 7.40 7.40 7.35 7.35 7.34 7.33 7.33 7.32 7.32 7.32 7.30 7.30 7.30 7.29 7.28 7.28 7.27 7.26 7.26 6.02 6.02 6.00 6.00 5.98 5.98 5.30 5.29 4.61 4.60 4.54 4.54 4.52 4.52 2.10 2.10 2.09 2.09 1.52 -0.00
O
CO2tBu
100e
1H NMR (300 MHz, CDCl3)
2.08 3.17 0.18 1.00 1.00 0.98 2.02 3.04 9.54
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


GM-05-62
162.22 151.98 142.52 138.60 128.26 127.37 125.78 122.30 93.48 81.81 77.45 77.23 77.02 76.60 65.95 27.99 16.36 -0.00
O
CO2tBu
100e
13C NMR (75 MHz, CDCl3)
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

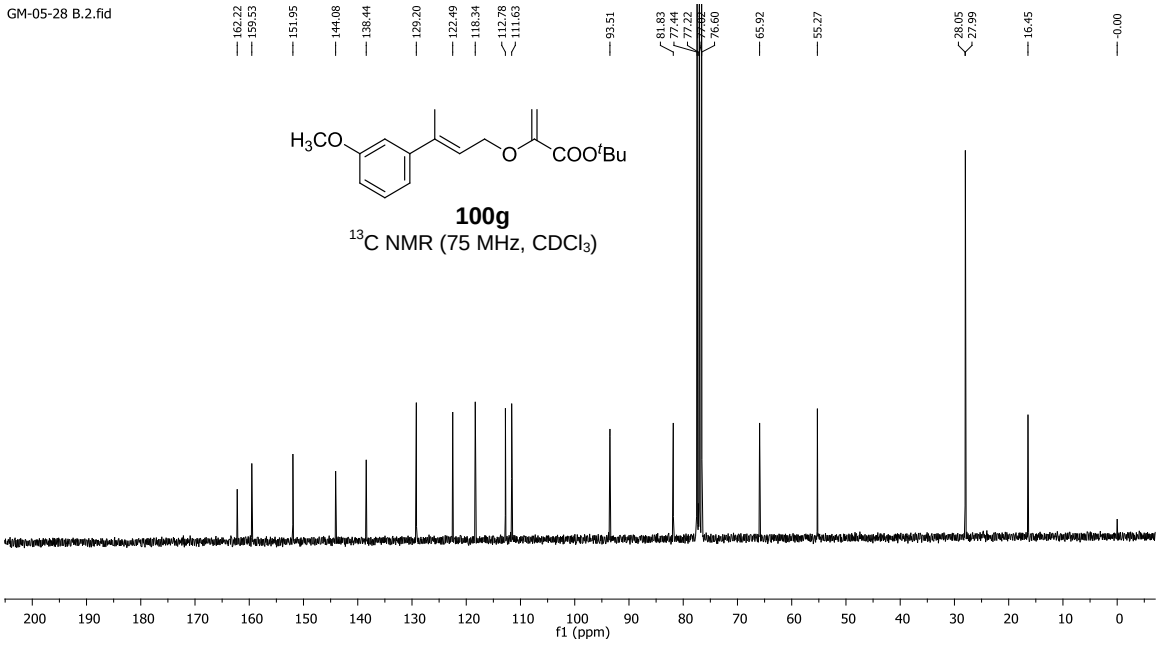

GM-05-27 B.5.fid
7.38
7.35
7.26
6.87
6.84
5.96
5.95
5.94
5.94
5.93
5.93
5.92
5.91
5.29
5.28
4.61
4.60
4.52
4.50
4.50
3.81
2.07
2.07
1.52
MeO
O
CO2tBu
100f
1H NMR (300 MHz, CDCl3)
2.11
2.57
1.00
1.07
1.00
2.03
3.15
3.12
10.10
f1 (ppm)


GM-05-27 B.7.fid
162.26
159.05
152.01
138.10
135.00
126.87
120.58
113.60
93.42
81.79
77.44
77.22
76.59
66.00
55.30
28.00
16.33
0.00
MeO
O
CO2tBu
100f
13C NMR (75 MHz, CDCl3)
f1 (ppm)



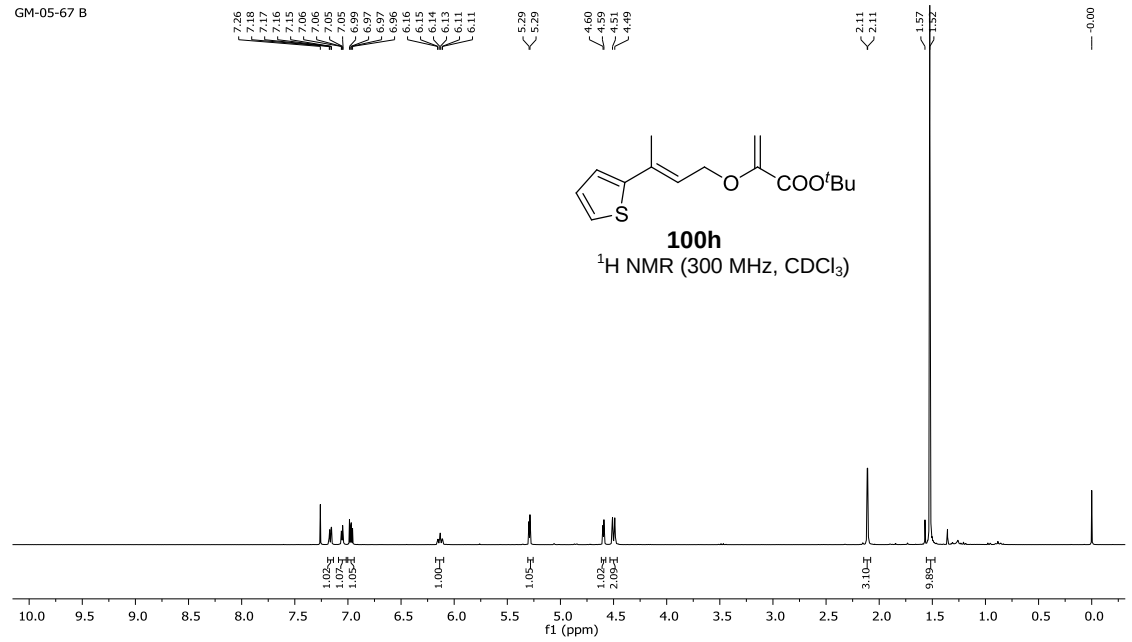
100g

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



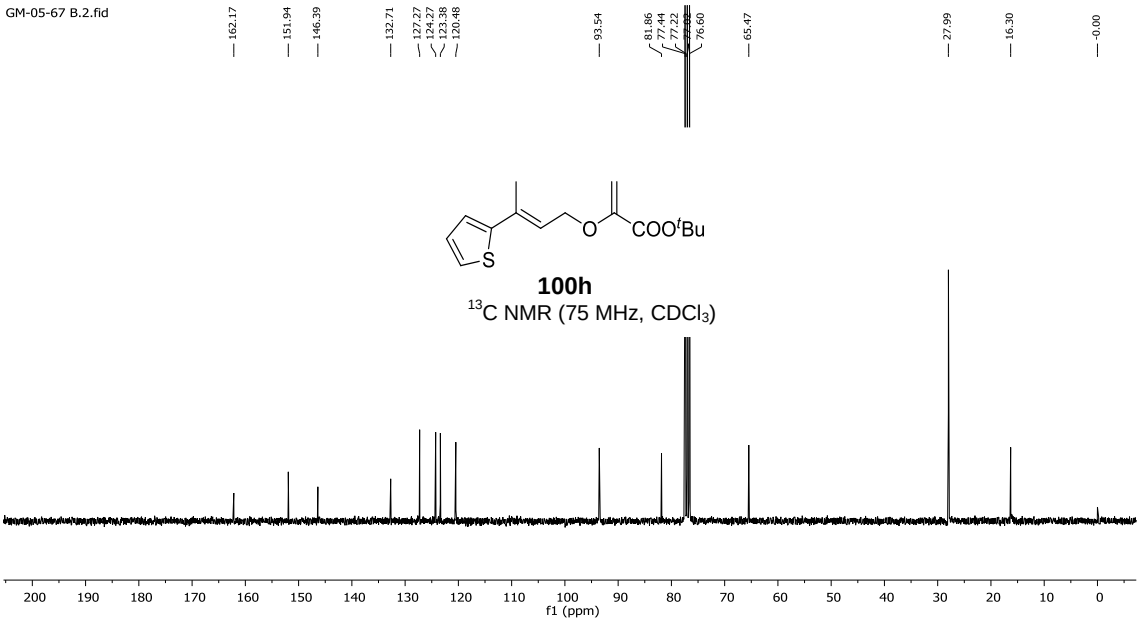
100g

^{13}C NMR (75 MHz, $CDCl_3$)



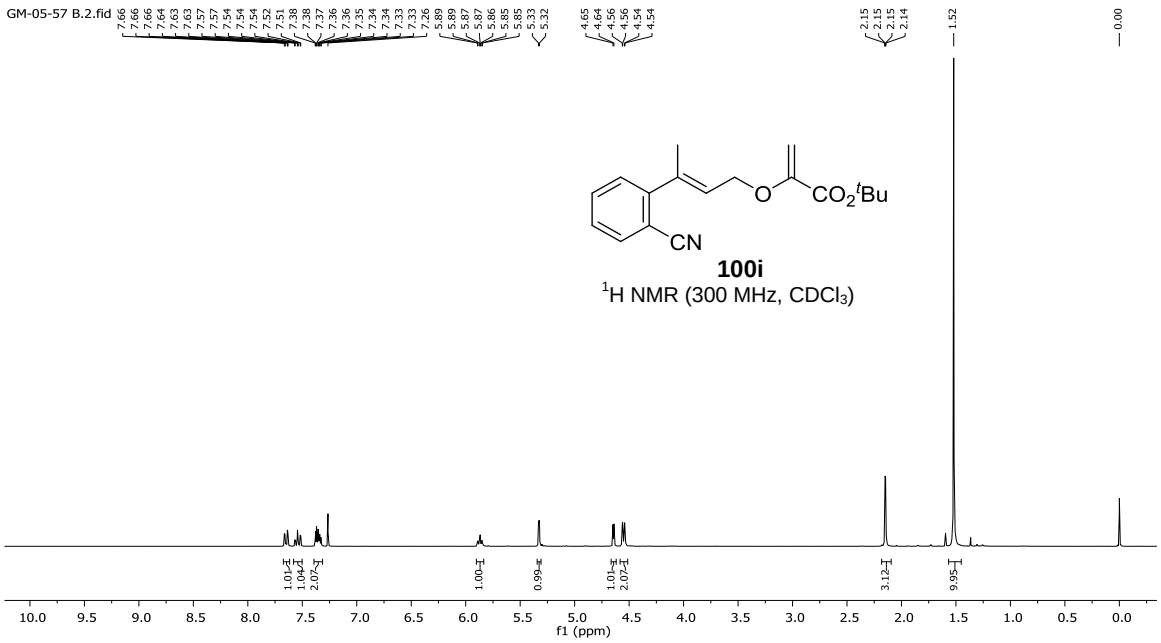
100h

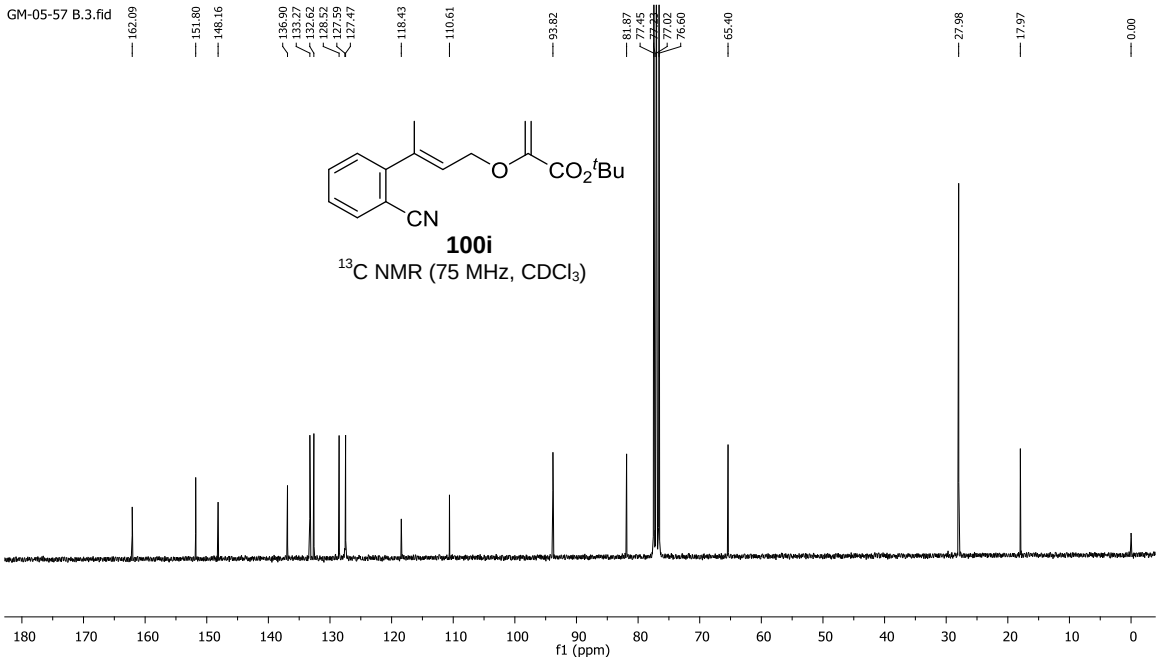
^{1}H NMR (300 MHz, $CDCl_3$)

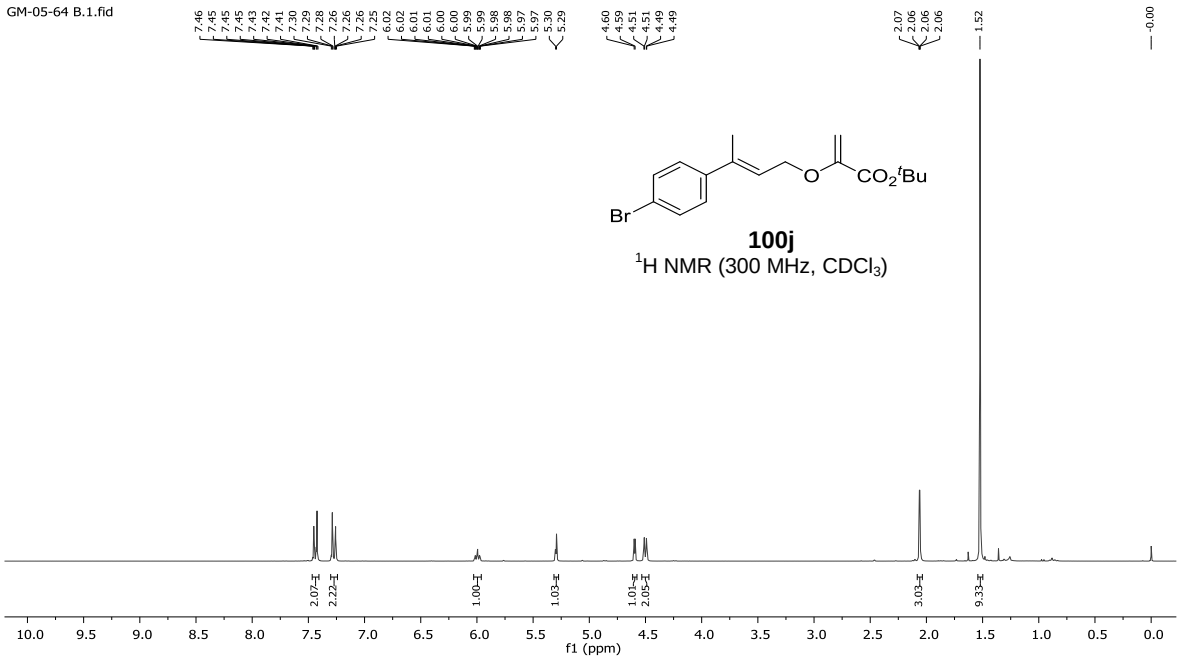


100h

^{13}C NMR (75 MHz, $CDCl_3$)

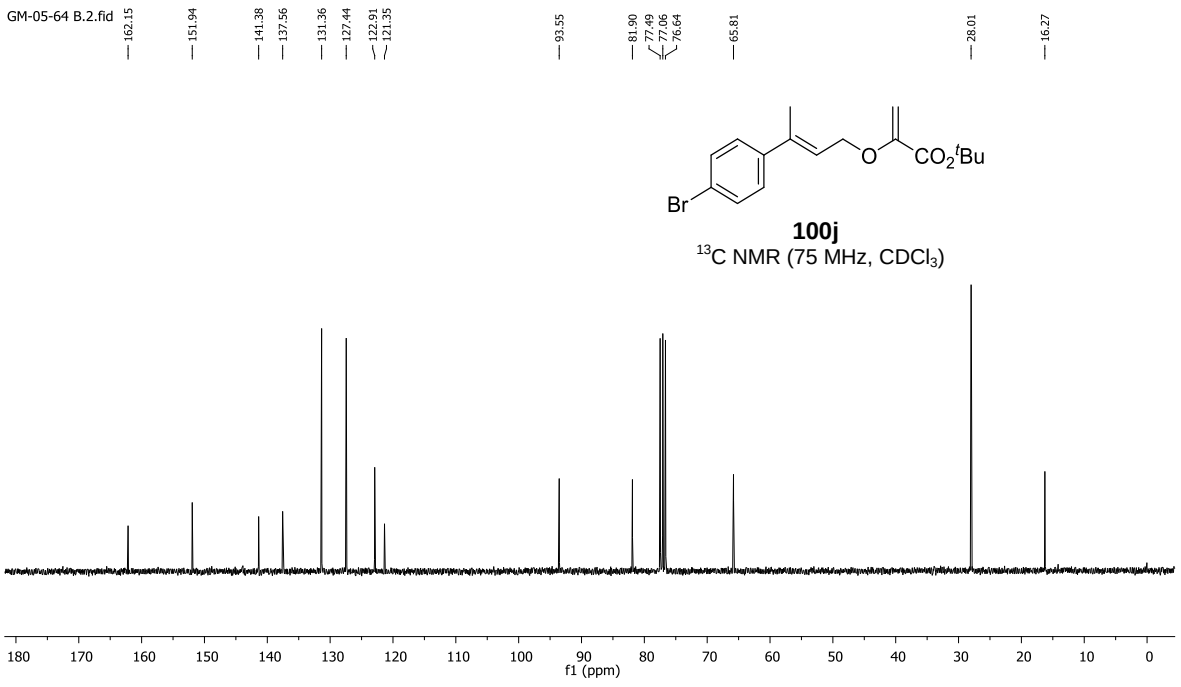

GM-05-57 B.2.fid
CN
O
CO2tBu
100i
1H NMR (300 MHz, CDCl3)
f1 (ppm)


GM-05-57 B.3.fid
CN
O
CO2tBu
100i
13C NMR (75 MHz, CDCl3)
f1 (ppm)



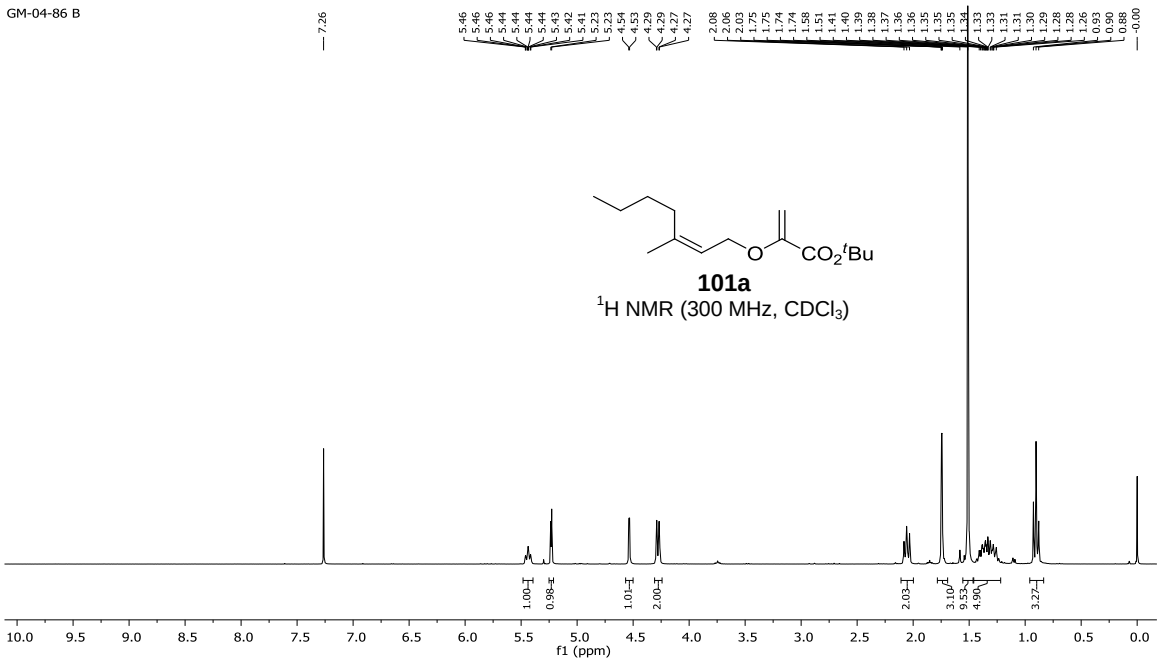
100j

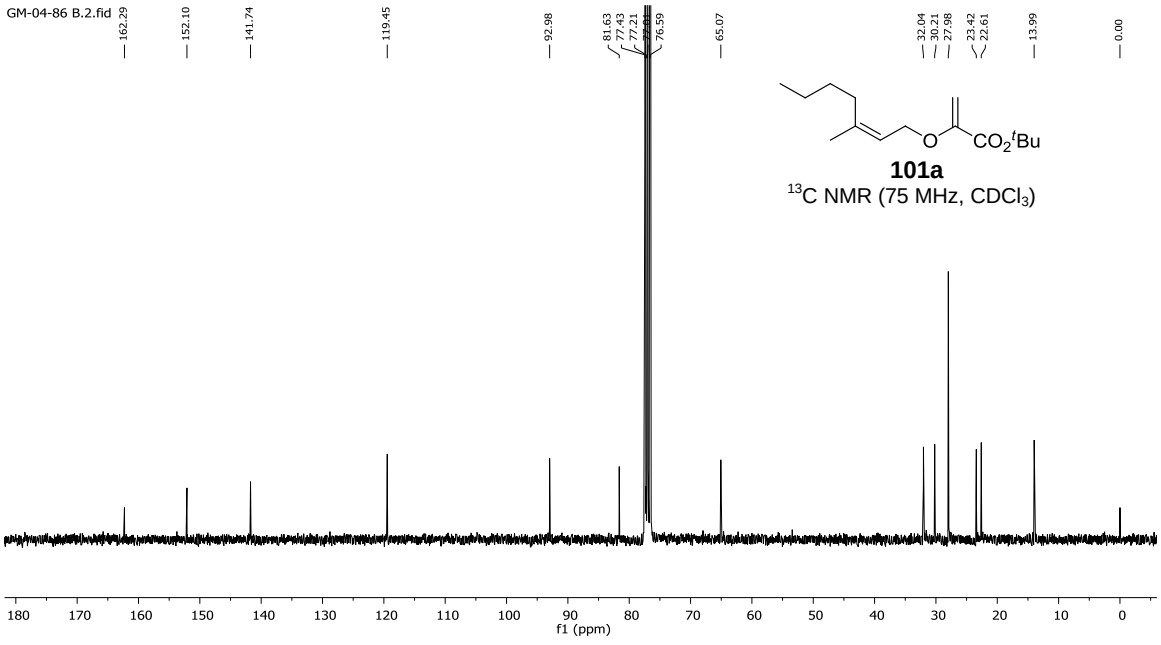
^{1}H NMR (300 MHz, $CDCl_3$)

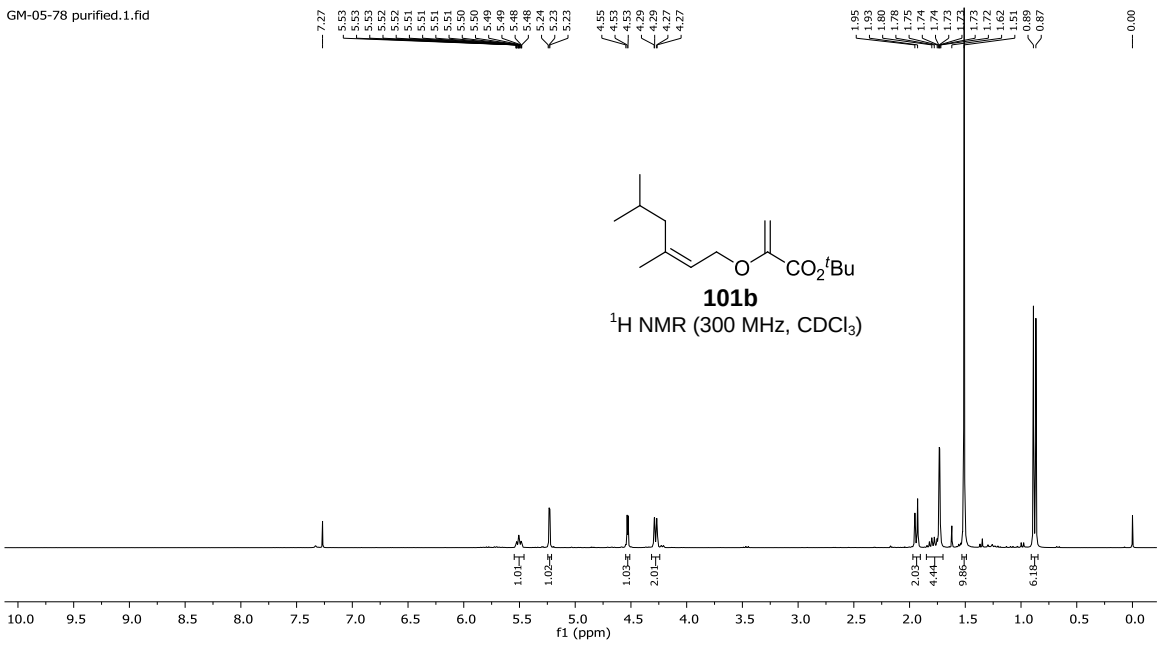


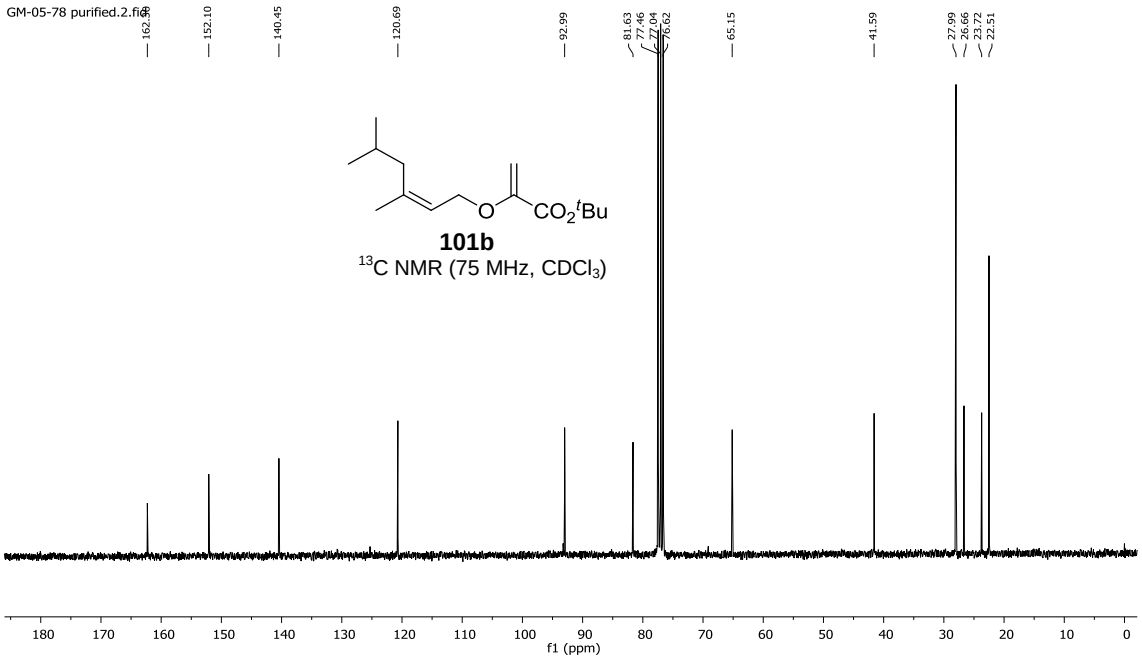
100j

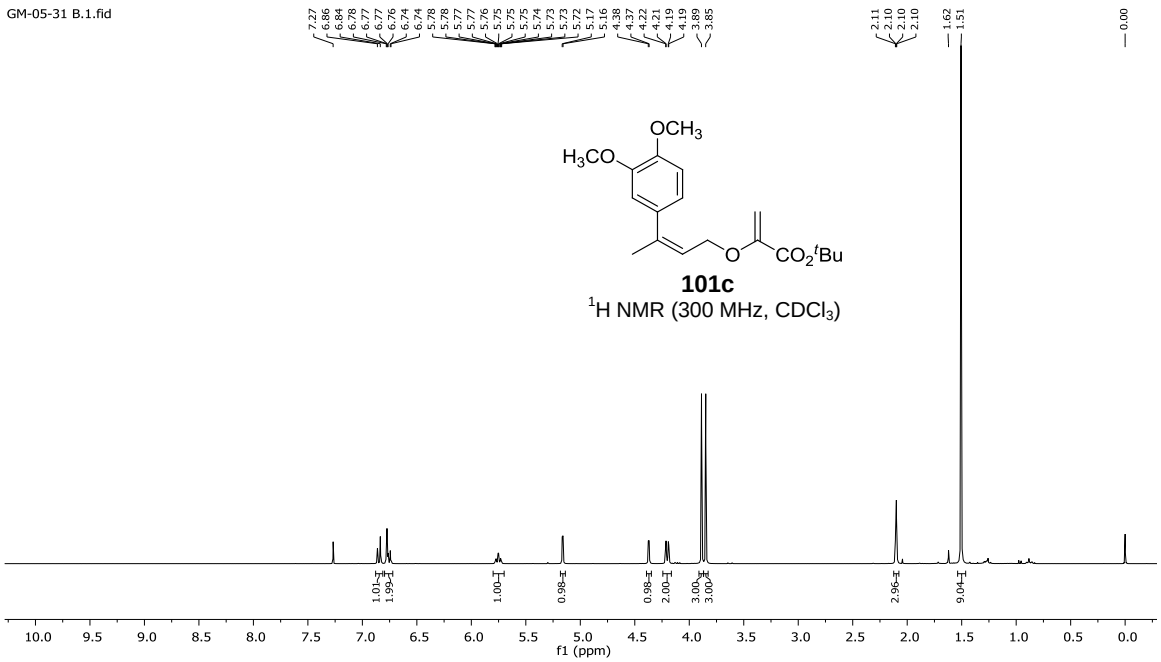
^{13}C NMR (75 MHz, $CDCl_3$)

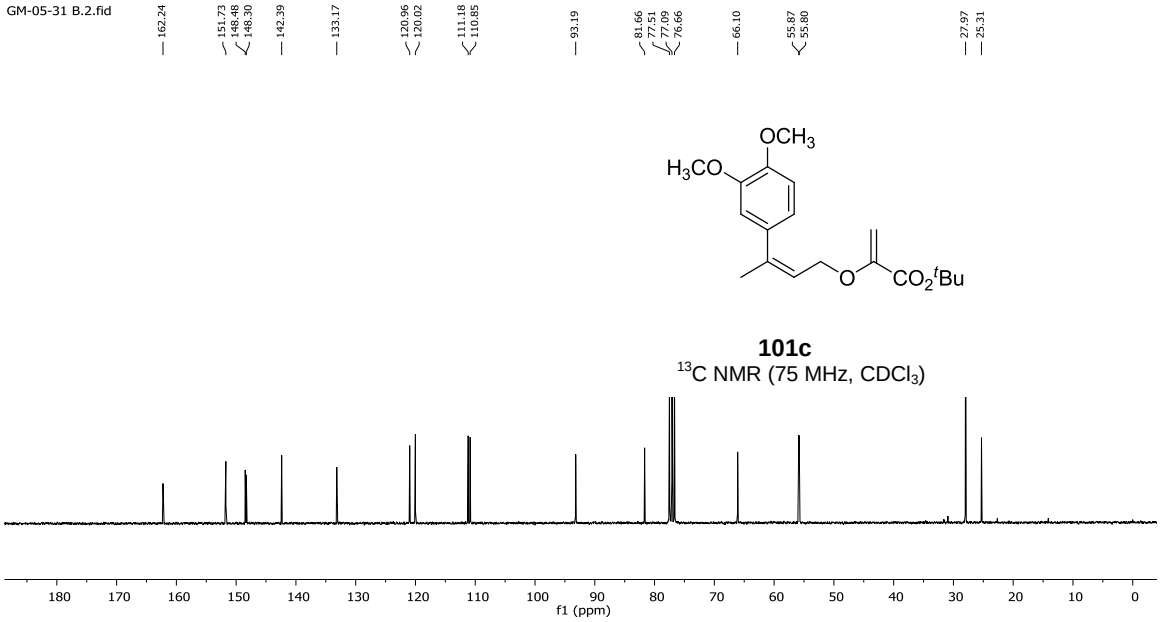

GM-04-86 B
7.26
5.46
5.46
5.46
5.44
5.44
5.44
5.44
5.43
5.42
5.41
5.23
5.23
4.54
4.53
4.29
4.29
4.27
4.27
2.08
2.06
2.03
1.75
1.75
1.74
1.74
1.58
1.51
1.41
1.40
1.39
1.38
1.37
1.36
1.36
1.35
1.35
1.35
1.34
1.33
1.33
1.31
1.31
1.30
1.29
1.28
1.28
1.26
0.93
0.90
0.88
-0.00
O
CO2tBu
101a
1H NMR (300 MHz, CDCl3)
1.00
0.98
1.01
2.00
2.03
3.10
9.55
4.90
3.27
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

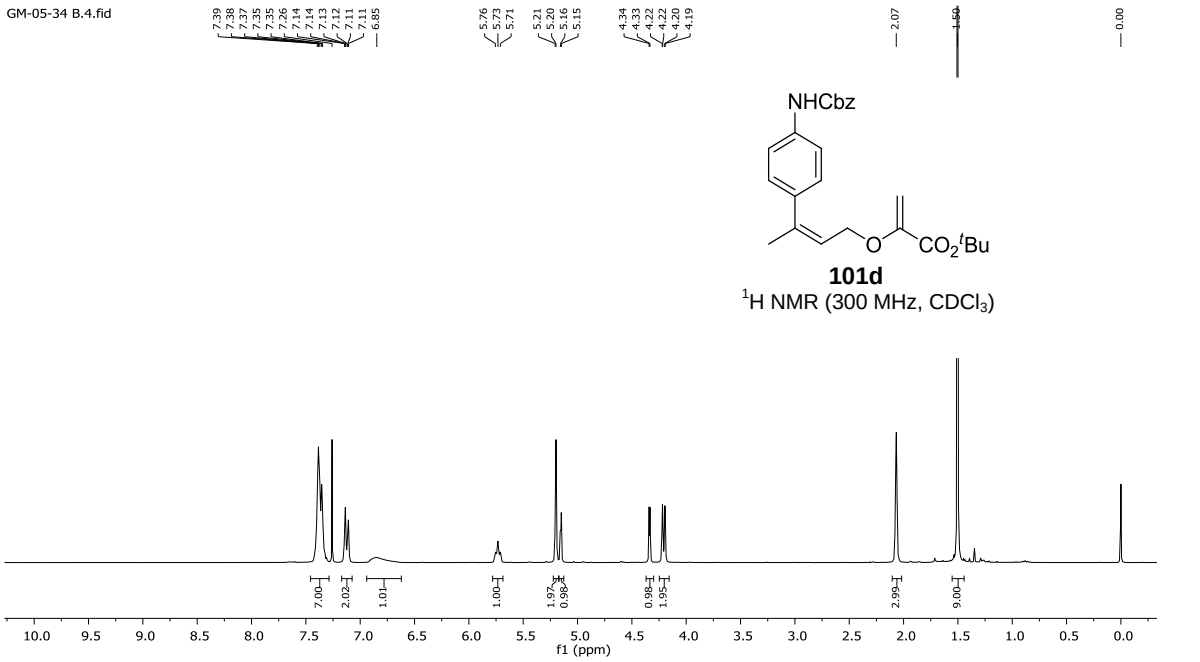

GM-04-86 B.2.fid
162.29
152.10
141.74
119.45
92.98
81.63
77.43
77.21
76.79
76.59
65.07
32.04
30.21
27.98
23.42
22.61
13.99
0.00
O
CO2tBu
101a
13C NMR (75 MHz, CDCl3)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

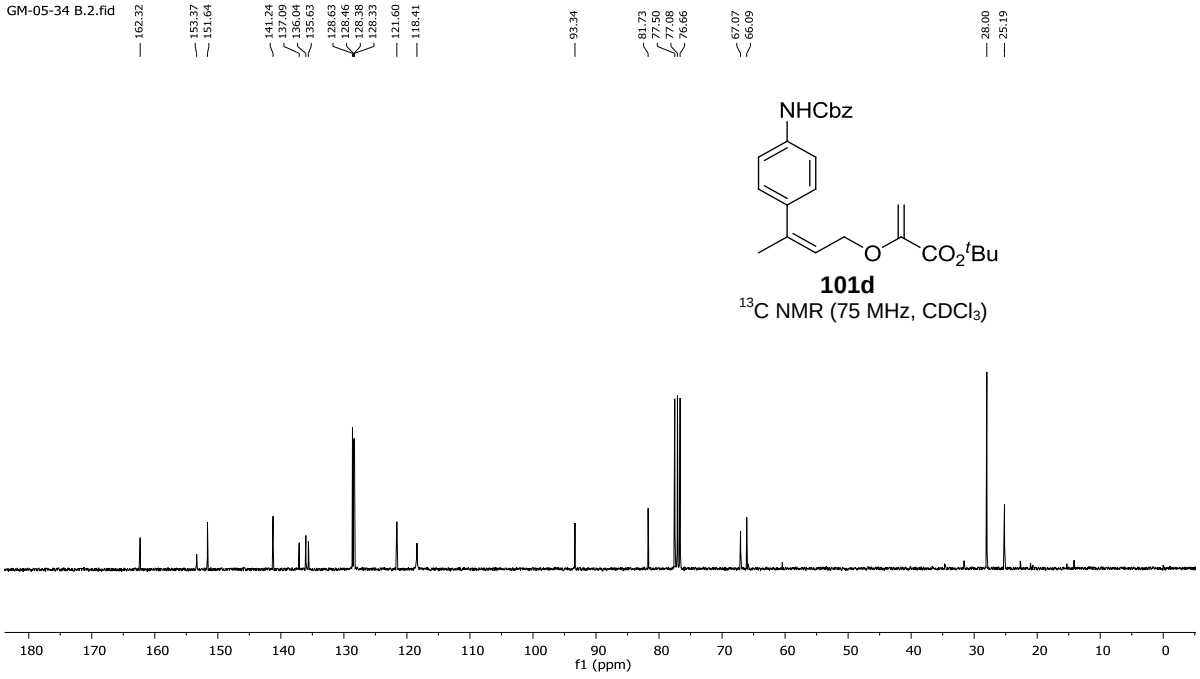

GM-05-78 purified.1.fid
7.27
5.53
5.53
5.53
5.52
5.52
5.51
5.51
5.51
5.51
5.50
5.50
5.49
5.49
5.48
5.48
5.24
5.23
5.23
4.55
4.53
4.53
4.30
4.29
4.27
4.27
1.95
1.93
1.80
1.78
1.75
1.74
1.74
1.73
1.73
1.72
1.72
1.62
1.51
0.89
0.87
0.00
O
CO2tBu
101b
1H NMR (300 MHz, CDCl3)
1.01
1.02
1.03
2.01
2.03
4.44
9.86
6.18
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

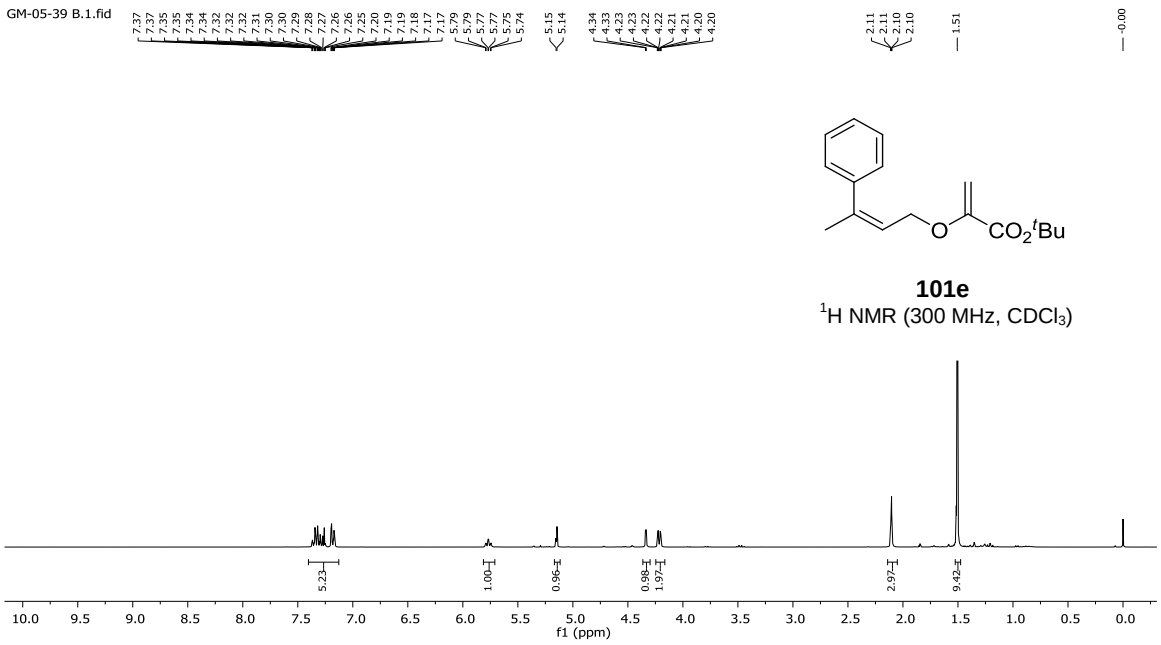

GM-05-78 purified.2.fid
162.83
152.10
140.45
120.69
92.99
81.63
77.46
77.04
76.62
65.15
41.59
27.99
26.66
23.72
22.51
O
CO2tBu
101b
13C NMR (75 MHz, CDCl3)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


GM-05-31 B.1.fid
OCH3
H3CO
O
CO2tBu
101c
1H NMR (300 MHz, CDCl3)
f1 (ppm)


GM-05-31 B.2.fid
OCH3
H3CO
O
CO2tBu
101c
13C NMR (75 MHz, CDCl3)
f1 (ppm)

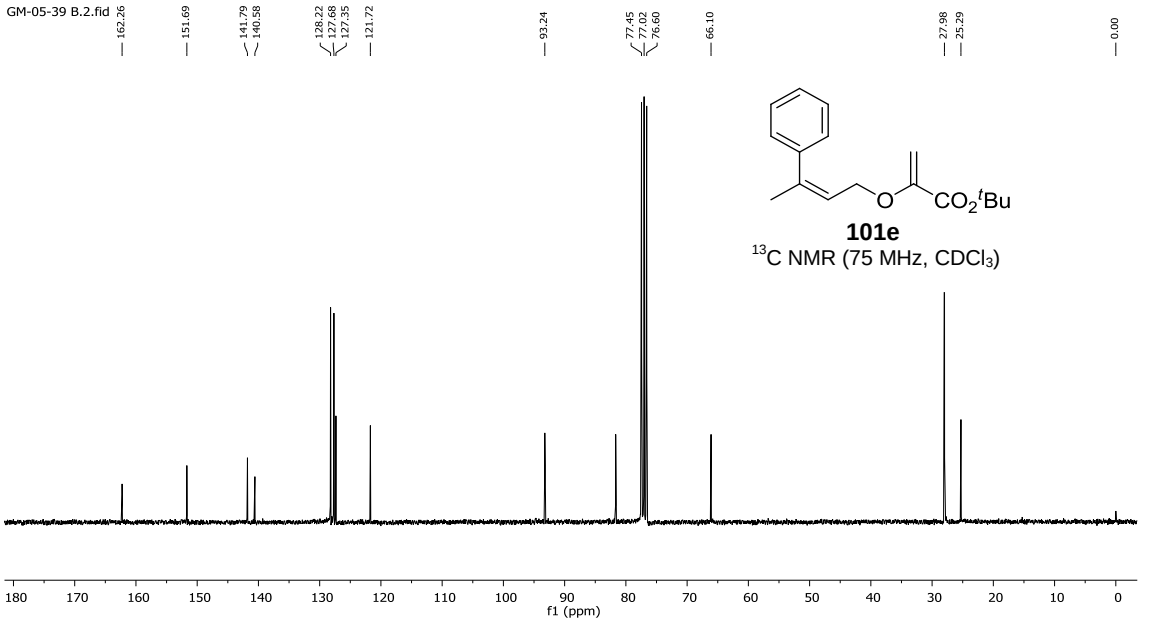

GM-05-34 B.4.fid
NHCbz
O
CO2tBu
101d
1H NMR (300 MHz, CDCl3)
f1 (ppm)


GM-05-34 B.2.fid
NHCbz
O
CO2tBu
101d
13C NMR (75 MHz, CDCl3)
f1 (ppm)



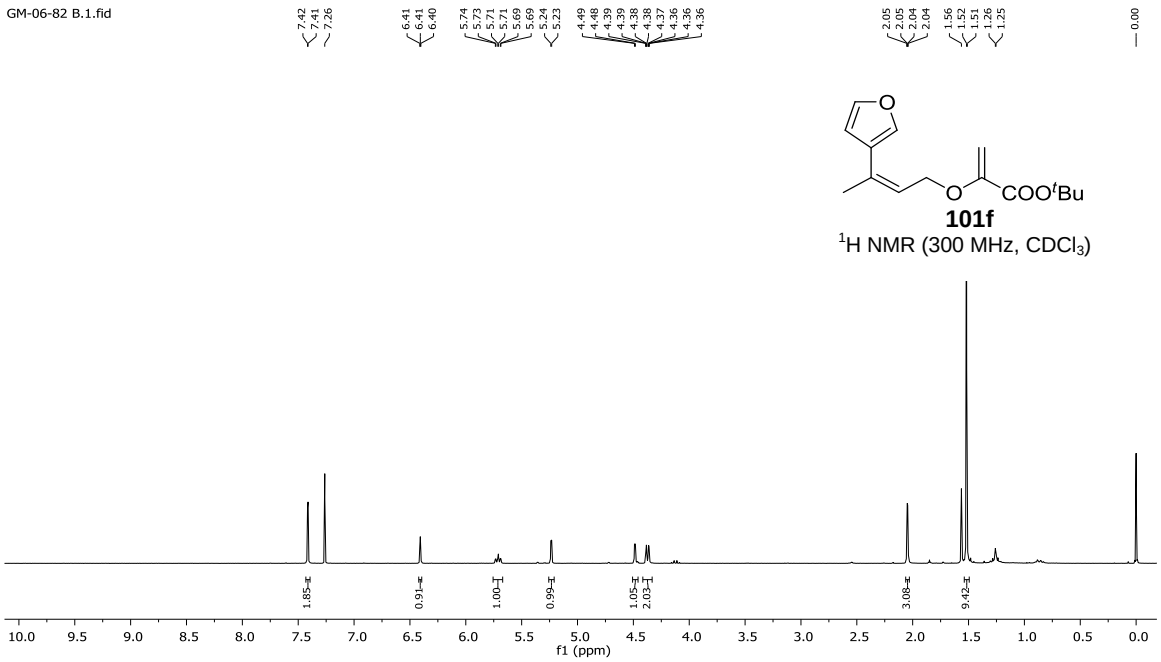
101e

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



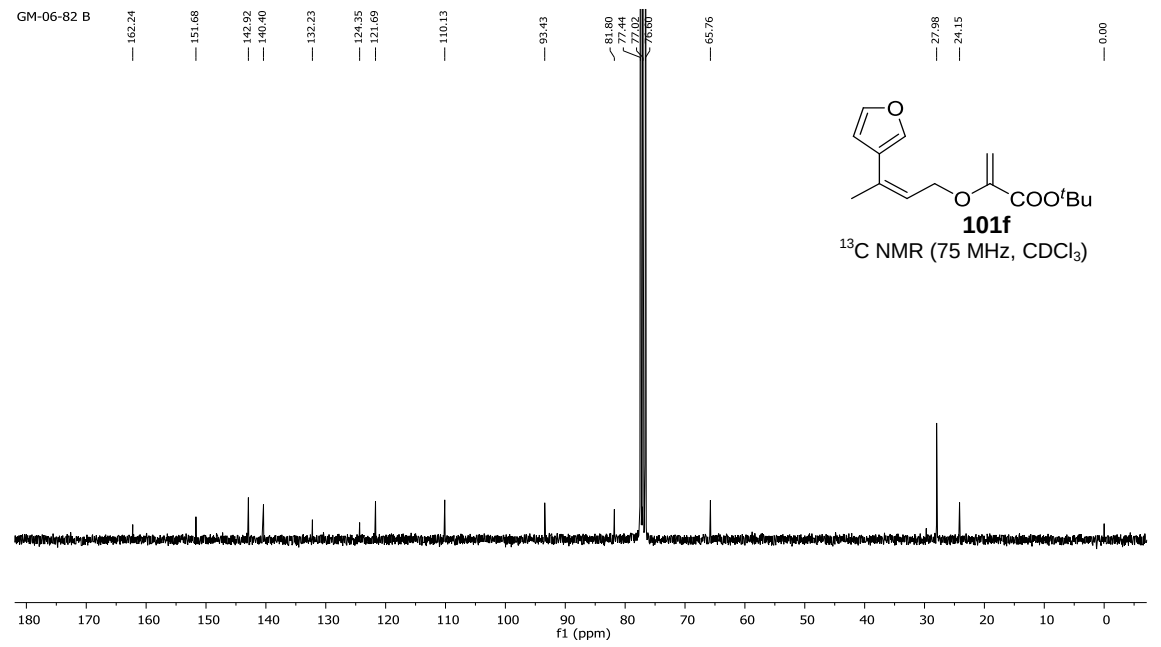
101e

^{13}C NMR (75 MHz, $CDCl_3$)



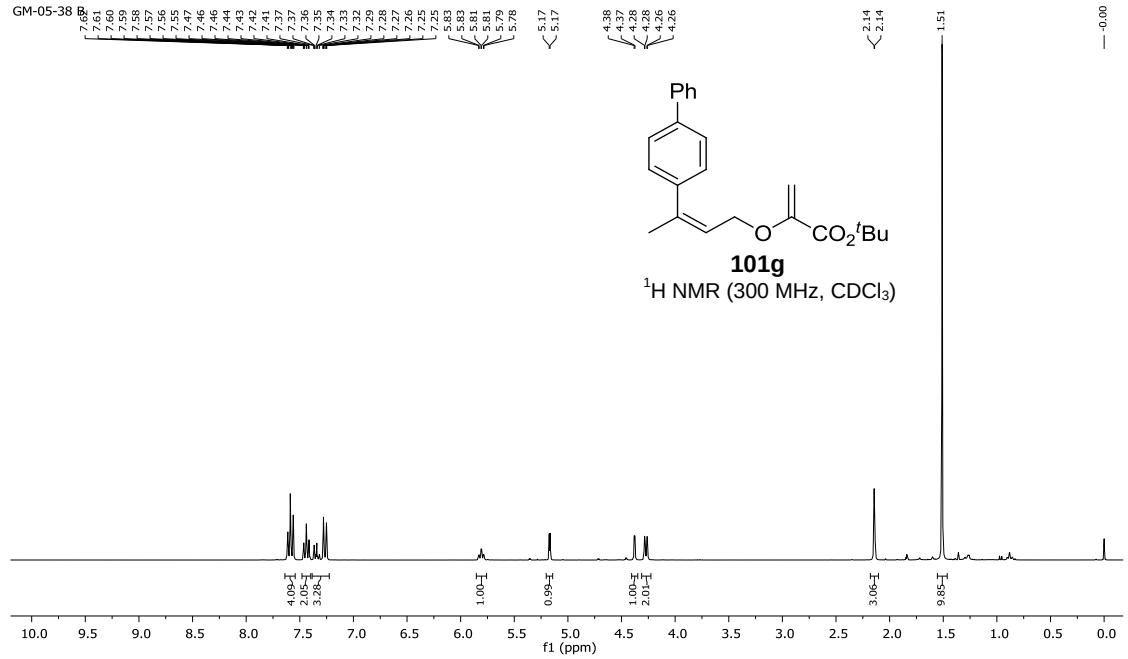
101f

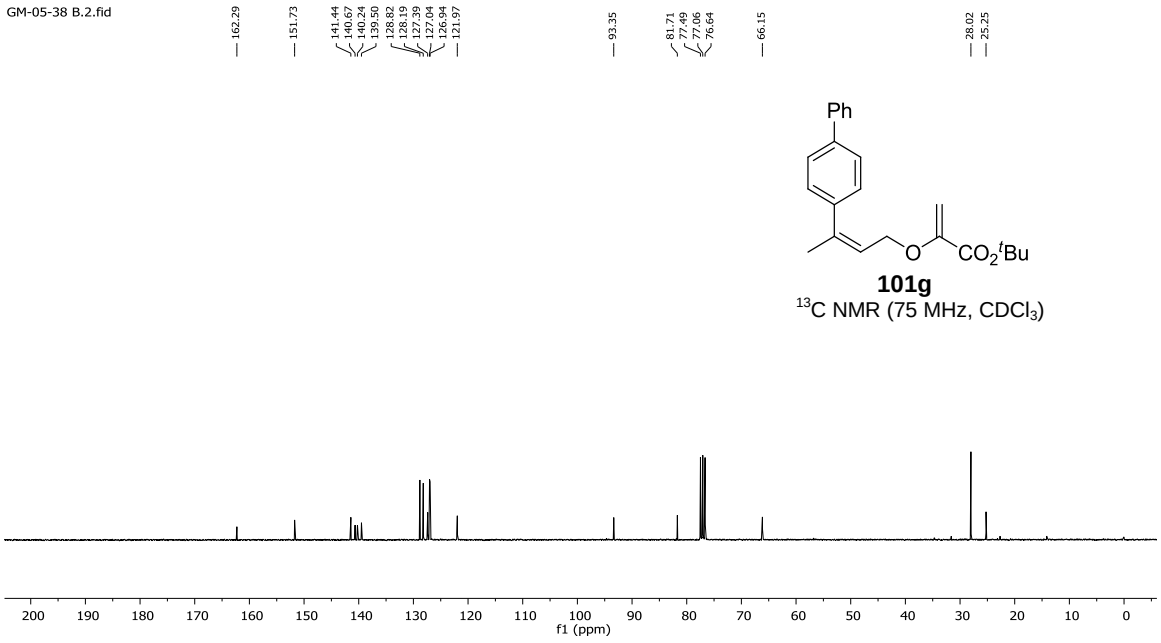
^{1}H NMR (300 MHz, $CDCl_3$)

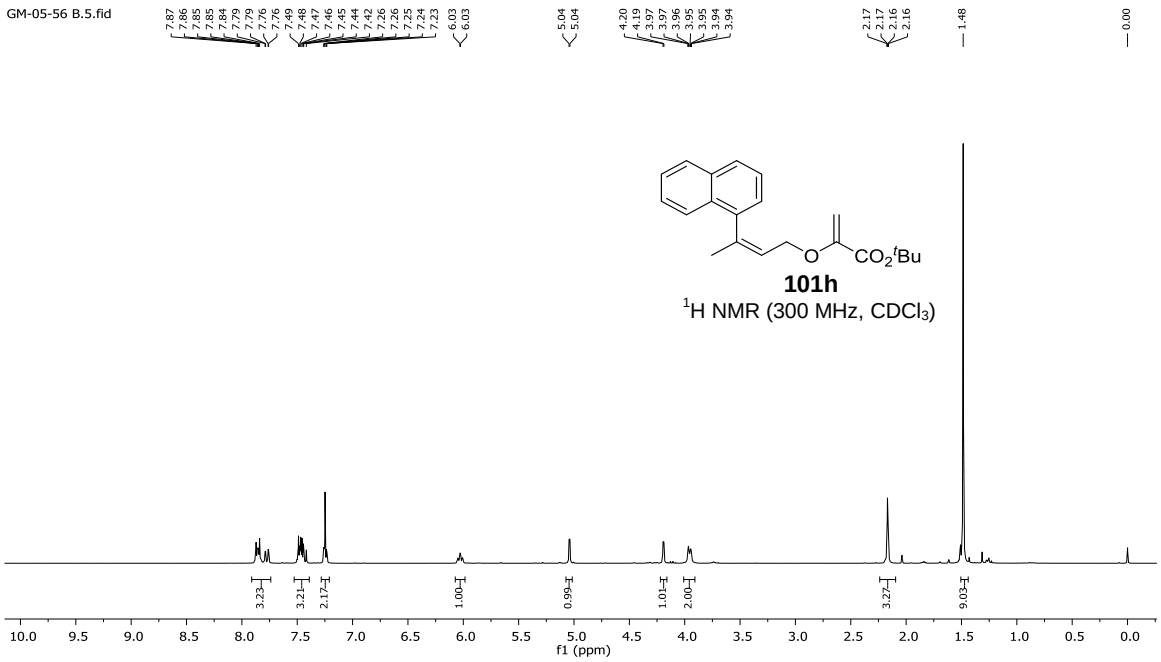


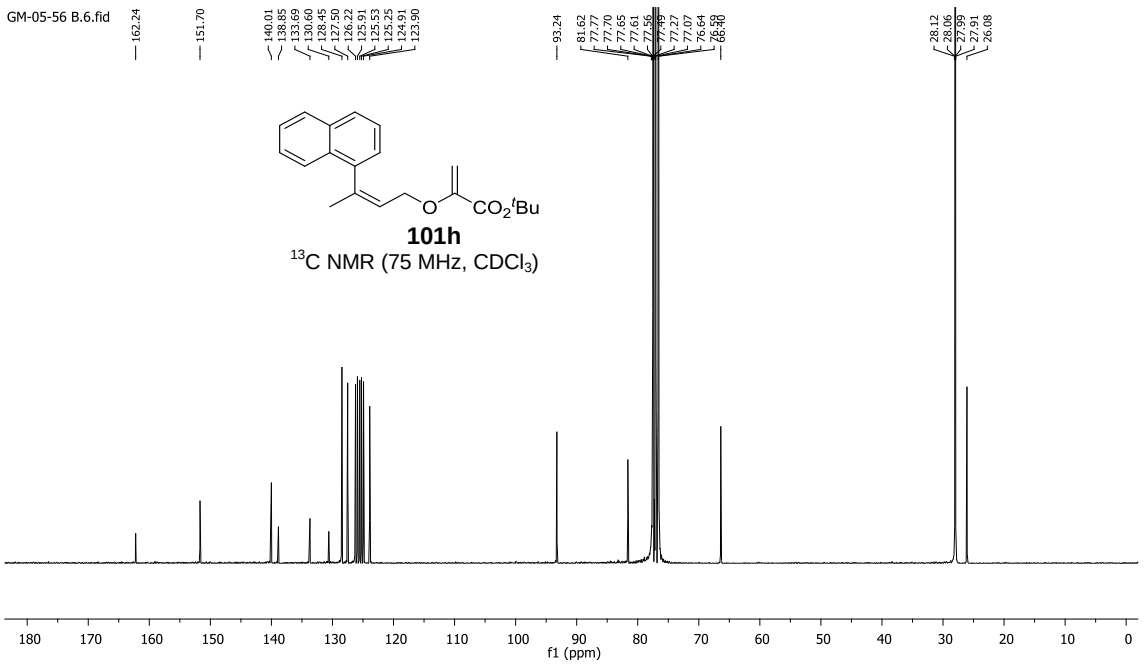
101f

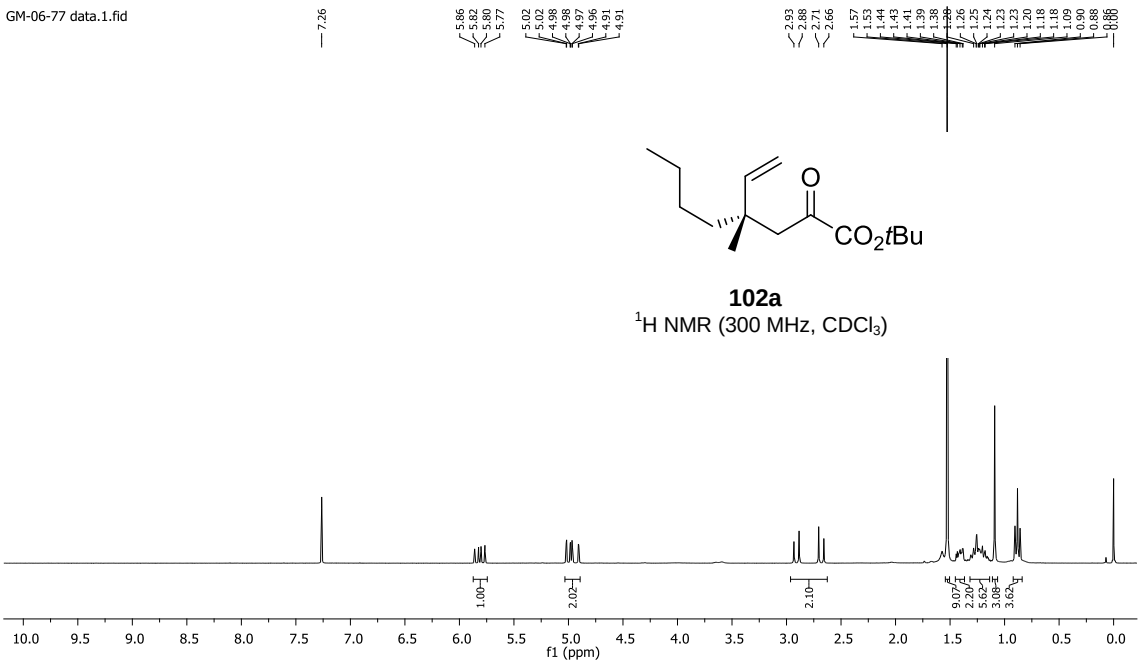
^{13}C NMR (75 MHz, $CDCl_3$)


GM-05-38 B
Ph
O
CO2tBu
101g
1H NMR (300 MHz, CDCl3)
f1 (ppm)


GM-05-38 B.2.fid
Ph
O
CO2tBu
101g
13C NMR (75 MHz, CDCl3)
f1 (ppm)

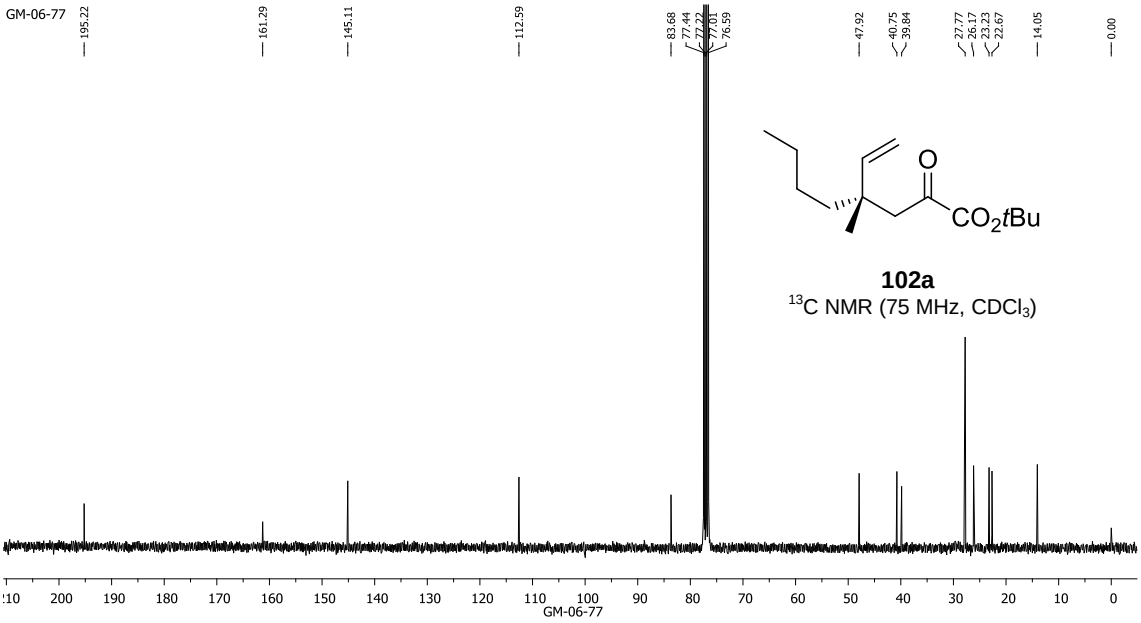

GM-05-56 B.5.fid
7.87
7.86
7.85
7.85
7.84
7.79
7.79
7.76
7.76
7.49
7.48
7.47
7.46
7.45
7.44
7.42
7.26
7.26
7.25
7.24
7.23
6.03
6.03
5.04
5.04
4.20
4.19
3.97
3.97
3.96
3.95
3.95
3.94
3.94
2.17
2.17
2.16
2.16
1.48
0.00
3.23
3.21
2.17
1.00
0.99
1.01
2.00
3.27
9.03
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
O
CO2tBu
101h
1H NMR (300 MHz, CDCl3)


GM-05-56 B.6.fid
162.24
151.70
140.01
138.85
133.69
130.60
128.45
127.50
126.22
125.91
125.53
125.35
124.91
123.90
93.24
81.62
77.77
77.70
77.65
77.61
77.56
77.49
77.27
77.07
76.64
65.50
65.40
28.12
28.06
27.96
27.91
26.08
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)
O
CO2tBu
101h
13C NMR (75 MHz, CDCl3)



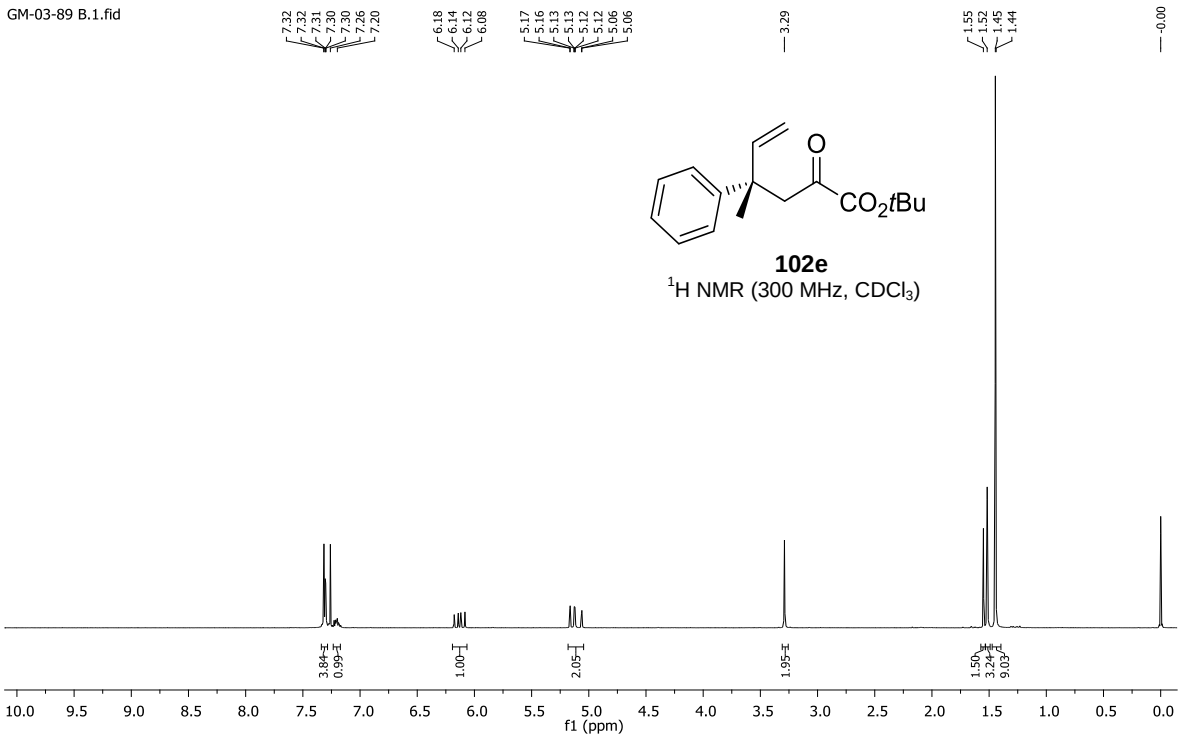
102a

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



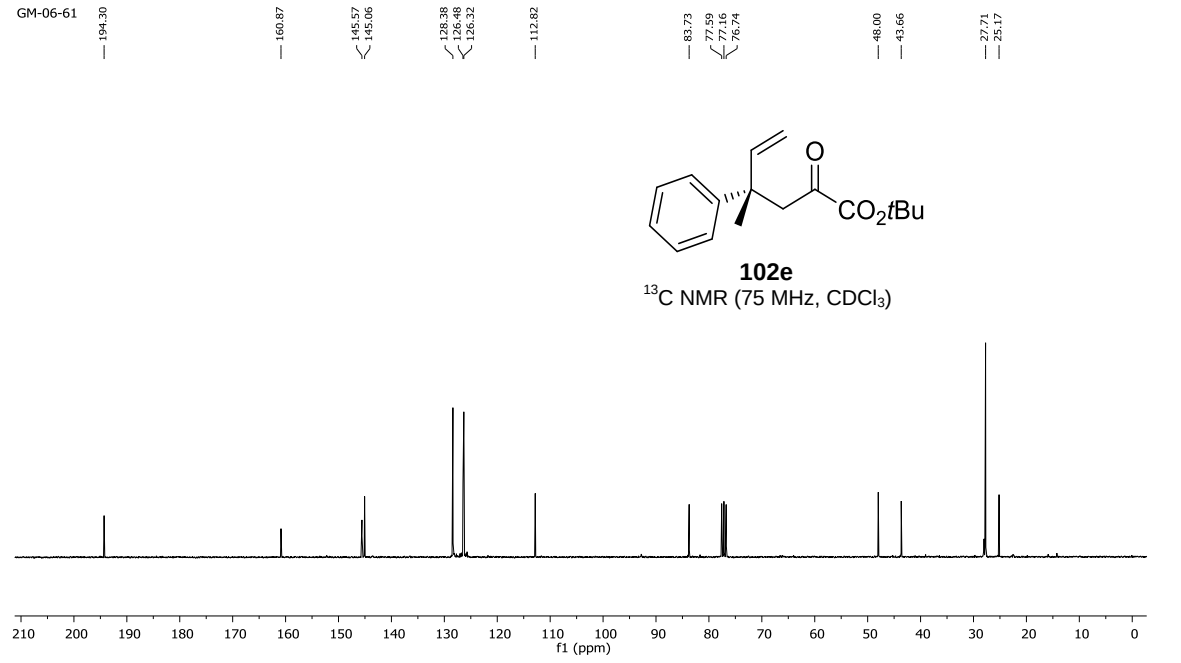
102a

^{13}C NMR (75 MHz, $CDCl_3$)



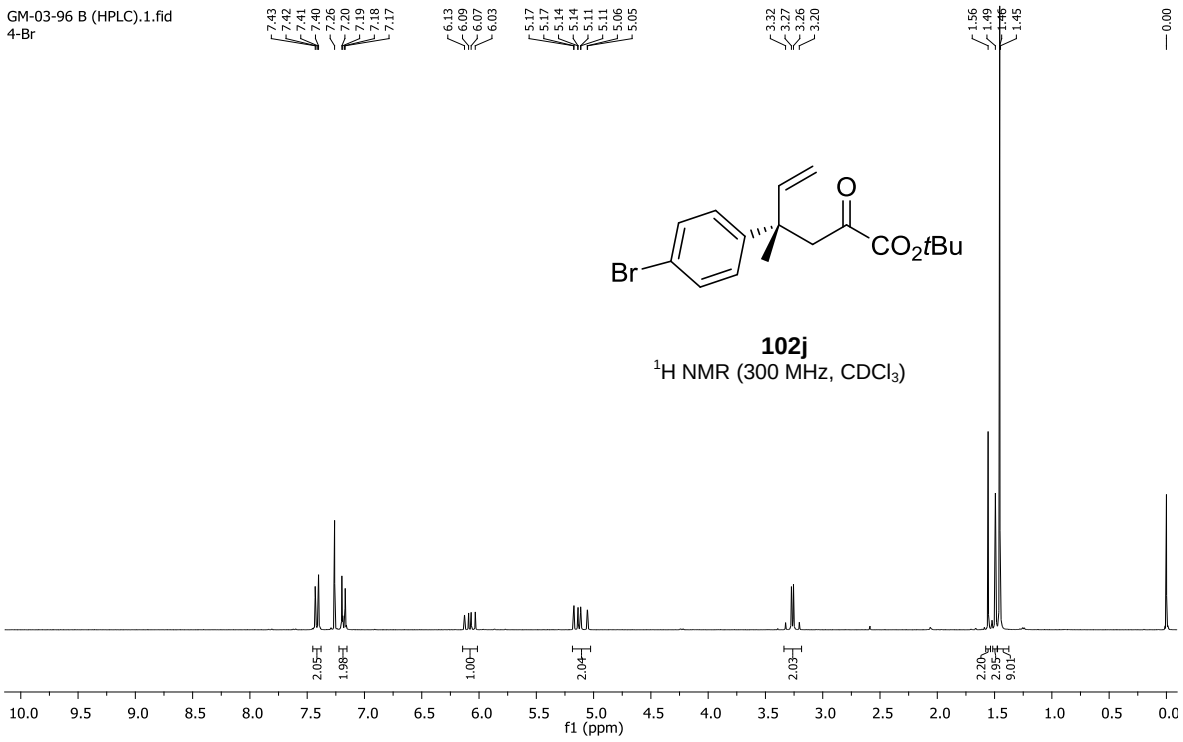
102e

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



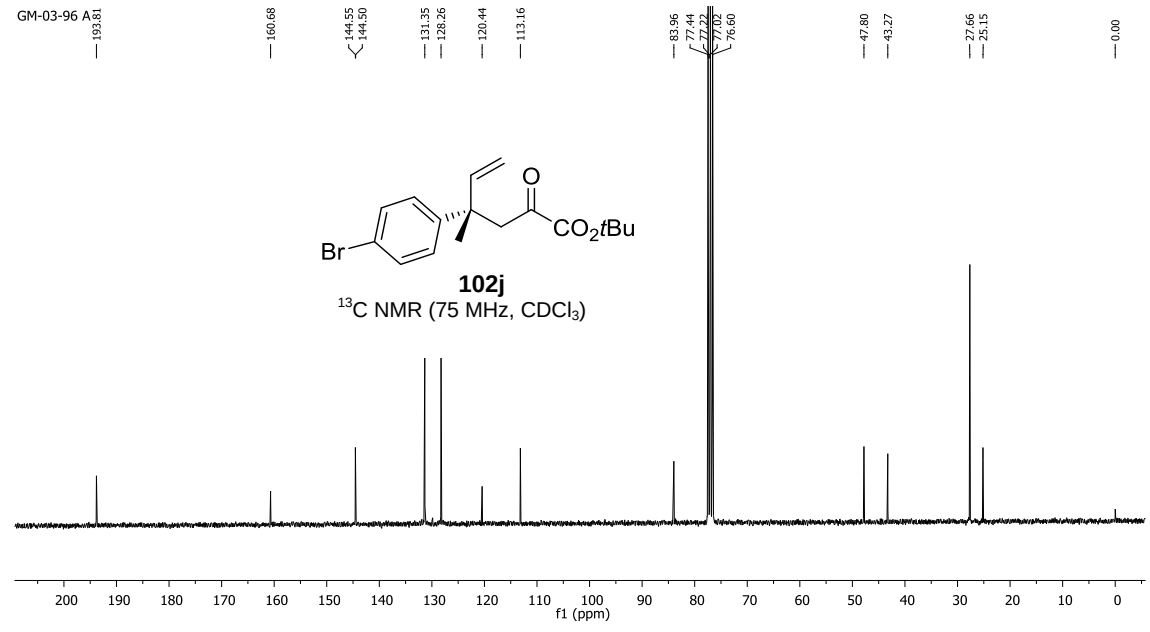
102e

^{13}C NMR (75 MHz, $CDCl_3$)



102j

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



102j

^{13}C NMR (75 MHz, $CDCl_3$)

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Project Name Gopinathan

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

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Sample Type:	Unknown	Date Acquired:	14/10/2016 7:41:07 PM NDT
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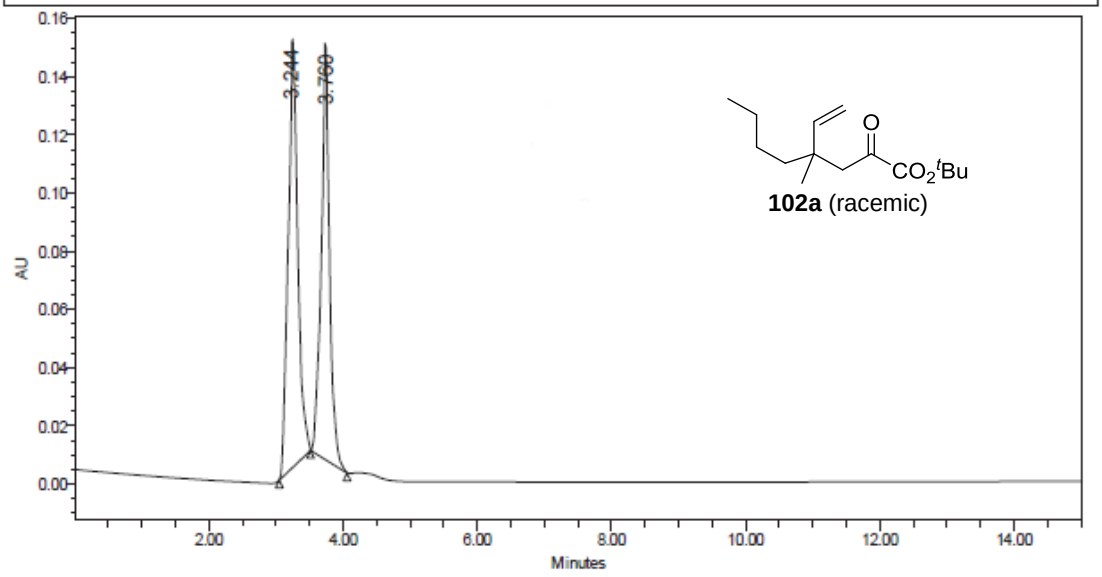
Run Time:	15.00 Minutes	Sample Set Name	



102a (racemic)

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	3.244	1367045	54.64	139092	48.41
2	3.760	1134656	45.36	148232	51.59

Report Method: Untitled

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Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	GM-06-97	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	18/10/2016 4:05:18 PM NDT
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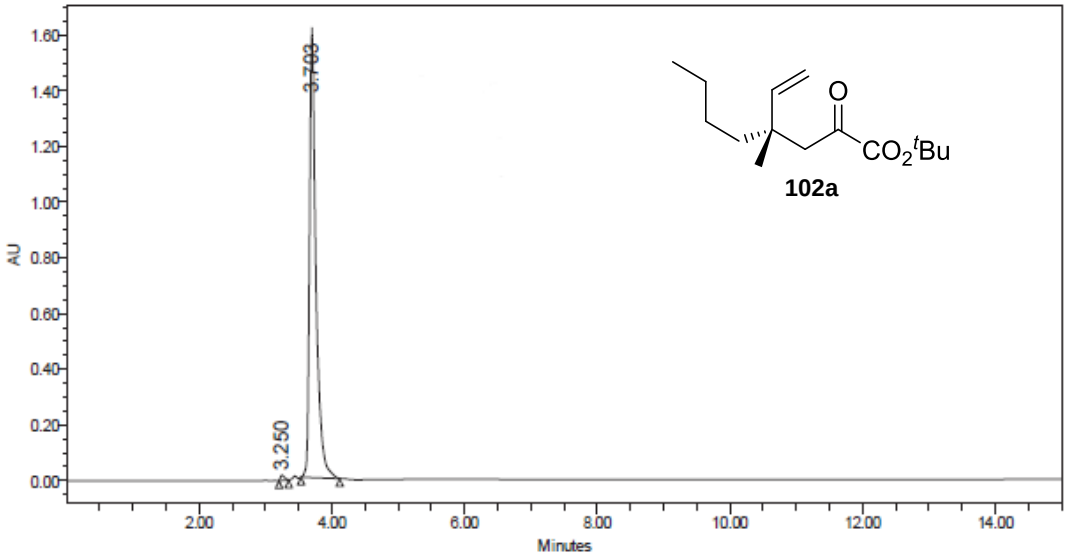

102a

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	3.250	97998	0.95	21496	1.35
2	3.703	10239846	99.05	1574798	98.65

Report Method: Untitled

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Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

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Sample Type:	Unknown	Date Acquired:	08/09/2016 4:01:43 PM NDT
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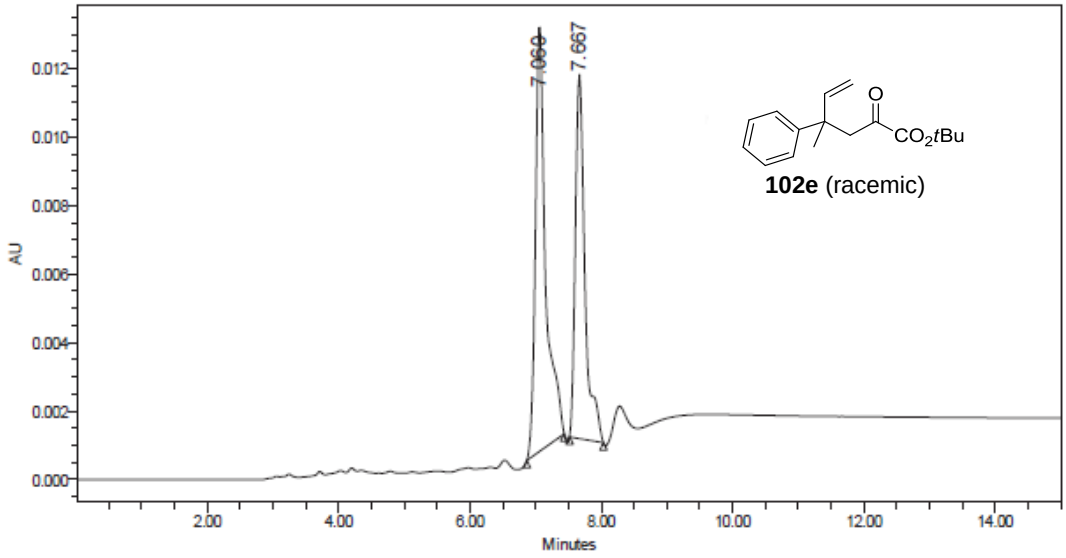
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	15.00 Minutes	Sample Set Name	



102e (racemic)

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	7.060	135885	55.90	12434	53.96
2	7.667	107196	44.10	10610	46.04

Report Method: Untitled

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Project Name Gopinathan

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

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Sample Type:	Unknown	Date Acquired:	26/08/2016 12:33:50 PM NDT
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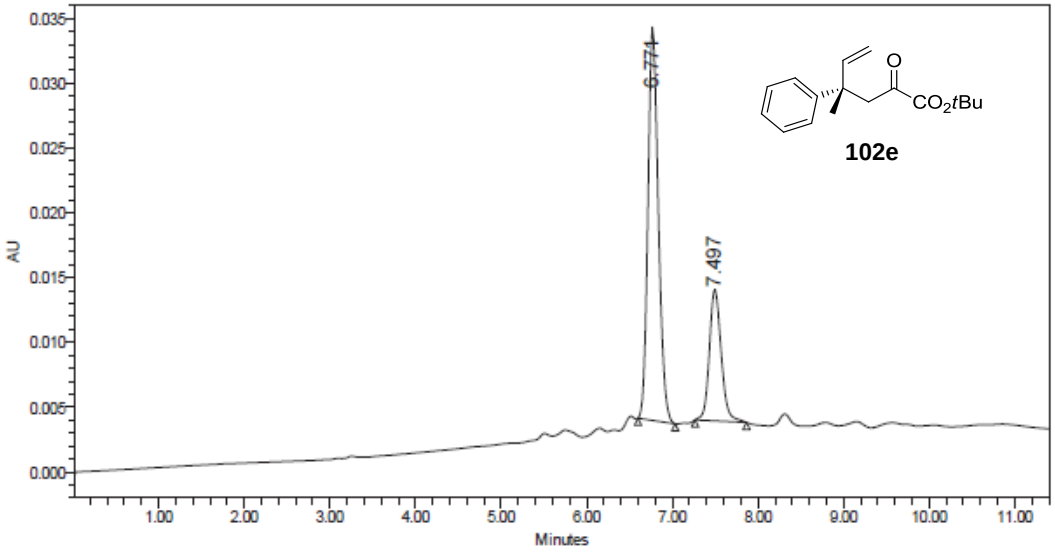
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	15.00 Minutes	Sample Set Name	



102e

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1	6.771	255610	72.51	30347	74.97
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Report Method: Untitled

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Memorial University

Project Name Gopinathan

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

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Injection #:	1	Date Processed:	23/08/2016 8:38:36 PM NDT
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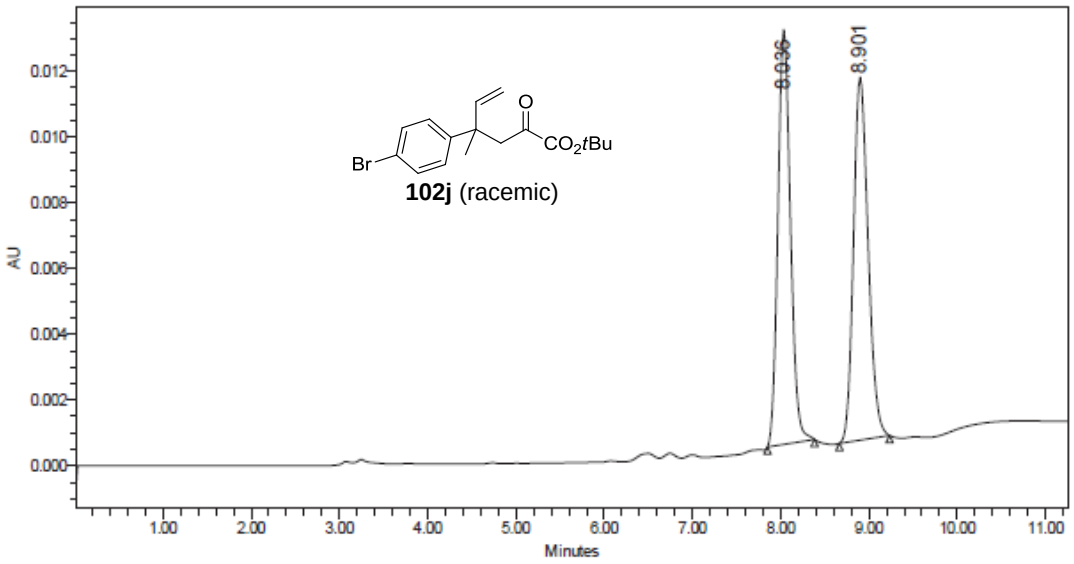

102j (racemic)

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1	8.036	124362	49.47	12619	53.33
2	8.901	127043	50.53	11043	46.67

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Project Name Gopinathan

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

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Sample Type:	Unknown	Date Acquired:	16/08/2015 10:06:48 PM NDT
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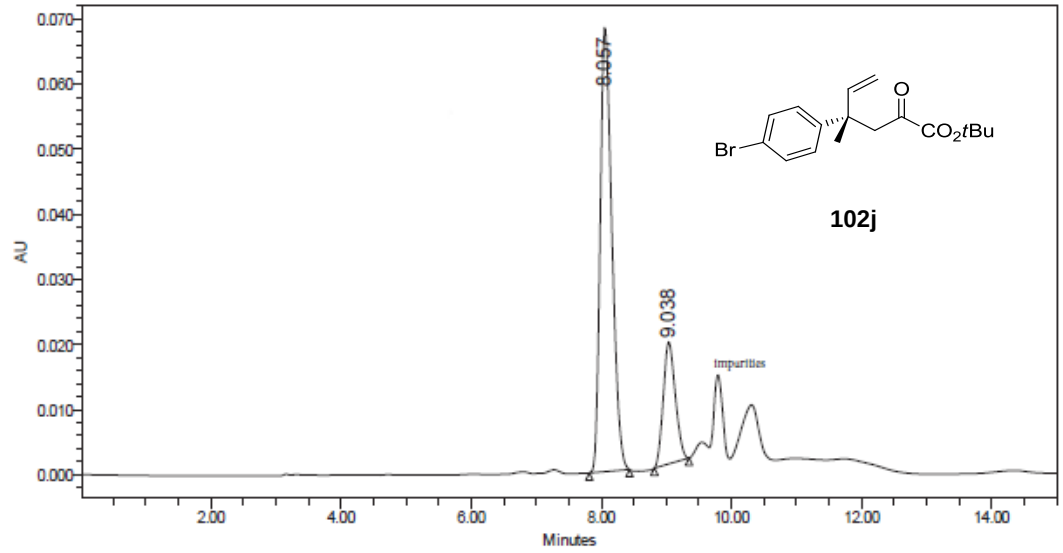
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	15.00 Minutes	Sample Set Name	



102j

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	8.057	851673	77.91	68520	78.49
2	9.038	241468	22.09	18781	21.51

Report Method: Untitled

Page: 1 of 1

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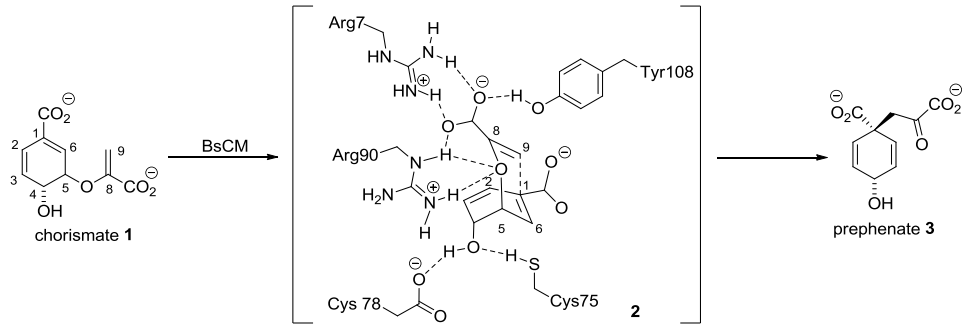
Chapter 2

Organocatalytic Enantioselective Gosteli-Claisen Rearrangement

2.1 Introduction

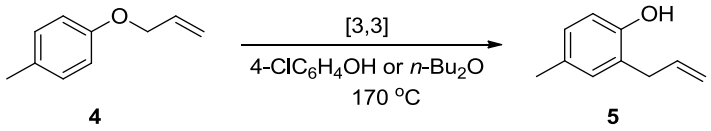
In addition to the metal-catalyzed Gosteli-Claisen rearrangements described in Chapter 1 in this thesis, we have also investigated an organocatalytic variant of the Gosteli-Claisen rearrangement. The following sections describe previous studies in this area as well as the synthesis of several new organocatalysts based on chiral cyclic phosphoramides (diazaphospholidines) and studies on their application in the Gosteli-Claisen rearrangement.

Acceleration of the Claisen rearrangement of suitably functionalized dienes in the presence hydrogen bond donors is well known.[1,2] A spectacular example of such a rate enhancement is the enzyme-catalyzed Claisen rearrangement of chorismic acid to prephenic acid in the shikimic acid biosynthesis pathway. The enzyme chorismate mutase (BsCM) catalyzes the Claisen rearrangement of chorismate **1** to prephenate **3** with a 10^6-fold rate enhancement compared to the uncatalyzed thermal reaction (Scheme 2.1). Computational studies of this reaction have suggested that hydrogen bonding of chorismate with hydrogen bond donor groups in the enzyme active site plays a crucial role in this rate enhancement.[1]



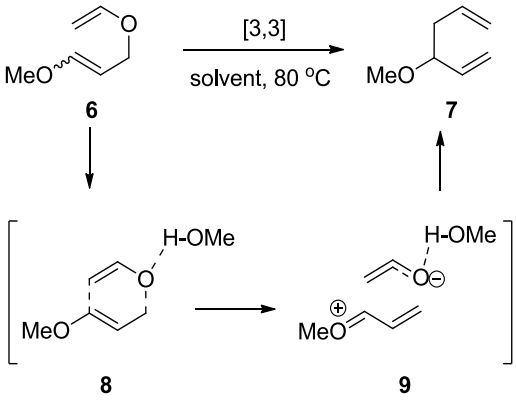
Scheme 2.1

A significant rate acceleration is also observed when the Claisen rearrangement is conducted in protic solvents.[2] For example, White studied[2a] the effect of solvents on the reaction rate of Claisen rearrangement of allyl vinyl ether **4** and observed that rearrangement of **4** in a protic medium (4-ClC_6H_4OH) proceeds 300 times faster than in an aprotic medium such as Bu_2O (Scheme 2.2).



Scheme 2.2

Curran also reported[2b] solvent effects on the Claisen rearrangement of allyl vinyl ether **6**. Rearrangement of **6** is 68 times faster in methanol-d_4 compared to benzene-d_6. The authors suggest that the ether oxygen of the substrate **6** forms a hydrogen bond with the protic solvent as shown in **8**, which generates enolate-oxonium ion pair **9** (Scheme 2.3). The formation of ion pair **9** stabilizes the transition state more than the ground state and promotes the rate of the reaction.



Scheme 2.3

Studies on rate enhancement of the aqueous Claisen rearrangement by Jorgensen, using quantum mechanical computational methods, have revealed that bis hydrogen bonding of an allyl vinyl ether with two water molecules is responsible for the rate acceleration (Figure 2.1).[3]

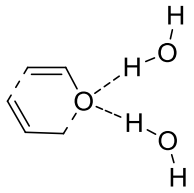


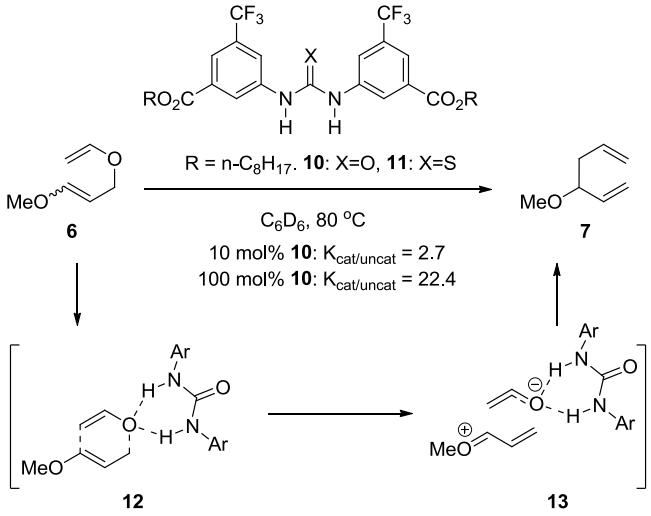
Figure 2.1

2.2 Previous Reports on Organocatalytic Claisen rearrangements

2.2.1 Catalysis of the Organocatalytic Claisen Rearrangement by Ureas and Thioureas

Catalysis of the Claisen rearrangement using ureas and thioureas as hydrogen bond donor catalysts was first reported by Curran.[4] The mechanism suggested by the authors is not a concerted [3,3]-sigmatropic rearrangement, but a dissociation/recombination mechanism instead. For example, rearrangement of allyl vinyl ether **6** was accelerated in the presence of urea catalyst **10** to provide the rearrangement product **7** (Scheme 2.4). The use of stoichiometric amount of the urea catalyst increased the reaction rate 22-fold over the uncatalyzed reaction. The authors propose that the allyl vinyl ether **6** participates in bis hydrogen bonding with **10** to generate **12** (Scheme 2.4) which generates the ion pair **13**. Recombination of the ions in **13** proceeds with carbon-carbon bond formation to

provide the product **7**.[2b] The thiourea catalyst **11** decomposed under the reaction conditions (refluxing benzene, Scheme 2.4).

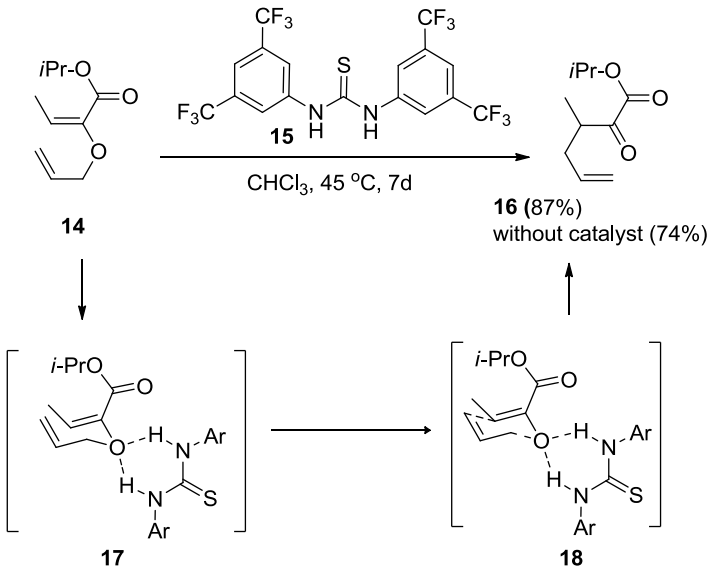


Scheme 2.4

2.2.2 Studies on the Organocatalytic Gosteli-Claisen Rearrangement

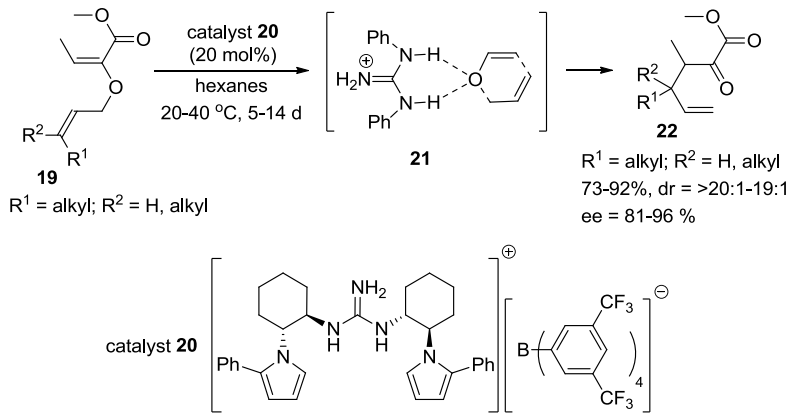
The thiourea catalyzed Gosteli-Claisen rearrangement was studied by Hiersemann and coworkers.[5] The allyl vinyl ether **14** afforded the rearrangement product **16** in 87% yield in the presence of 1 equiv. of thiourea catalyst **15**. However, **14** underwent the Claisen rearrangement even in the absence of catalyst **15** and provided **16** in 74% under the conditions used for the thiourea-containing reaction (Scheme 2.5). This suggested that there was only marginal catalysis of the rearrangement by the thiourea **15**. Computational studies indicated that **15** forms bis hydrogen bonds with the ether oxygen of allyl vinyl ether to generate **17**. However, stabilization of the transition state resulting from **17**, achieved by hydrogen bonding, is insufficient to overcome the energy barrier for

conformational changes in **14** as well as the complexation required to form **17**, both of which are necessary for the Claisen rearrangement.



Scheme 2.5

In 2008, Jacobsen reported[6] the Gosteli-Claisen rearrangement of dienes **19** (Scheme 2.6) using the guanidinium catalyst **20** derived from *trans*-1-pyrrolo-2-aminocyclohexane. When hexane was used as the solvent, the rearrangement products **22** were obtained in good yields with excellent diastereo and enantiomeric excess (Scheme 2.6).



Scheme 2.6

The authors mentioned that the pK_a of the catalyst **20** is 14, which is similar to the pK_a of *N*,*N*′-diphenylthiourea. The catalyst **20** engages in bis-hydrogen-bonding with the substrate **19** to generate **21**, which undergoes rearrangement to give the product **22** with high diastero and enantiomeric excess.

2.3 Objective

As discussed in Section 2.2, only a few reports are available for the organocatalytic Claisen rearrangement. Notably, while a sole report is available for the organocatalytic enantioselective Gosteli-Claisen rearrangement for obtaining vicinal stereocenters,[6] its utility for establishing isolated quaternary stereocenters is unexplored.

Our objective was to develop new chiral, dual hydrogen bond donor organocatalysts for the enantioselective Gosteli-Claisen rearrangement. Asymmetric induction as well as high hydrogen bond donor ability of the catalysts could be obtained by introducing a chiral cyclic phosphoramide moiety.[7] Bis-hydrogen-bonding interaction

of allyl vinyl ether **23** with organocatalyst could accelerate the [3,3]-rearrangement to provide the functionalized quaternary stereocenters **25** (Figure 2.2).

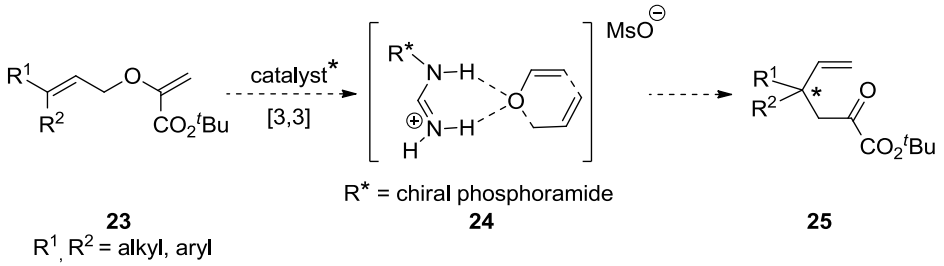


Figure 2.2. Bis-hydrogen-bonding of allyl vinyl ether with catalyst

2.4 Results and Discussion

We have designed new small molecules containing functionality that is potentially capable of binding to a Lewis base via bis-hydrogen-bonding, and are thus potentially capable of catalyzing the Gosteli-Claisen rearrangement of allyl vinyl ethers (Figure 2.3). A common structural feature in these molecules (Figure 2.3, **26**-**30**) is a chiral cyclic phosphoramide portion that is derived from a C_2-symmetric vicinal diamine. It may be noted that while the thiourea functionality in **26** and the 2-aminopyridine motif in **30** are known double hydrogen bond donors,[7,8] the thiosemicarbazone imine, as in **27**, is reported only recently[9] and the protonated amidine functionality **28** and **29** have not been examined as double hydrogen bond donors.

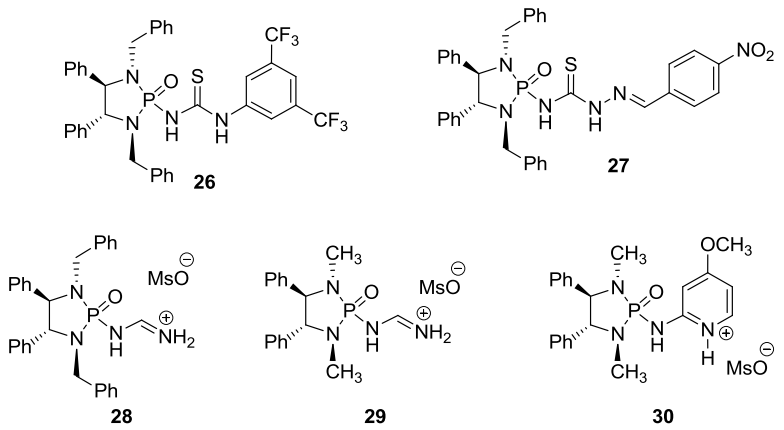
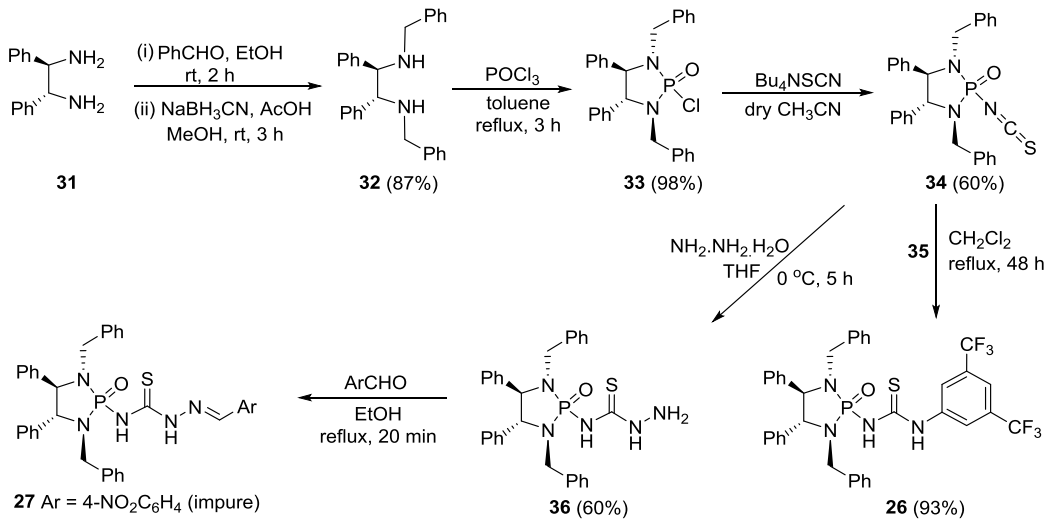


Figure 2.3. Chiral cyclic phosphoramide derived organocatalysts

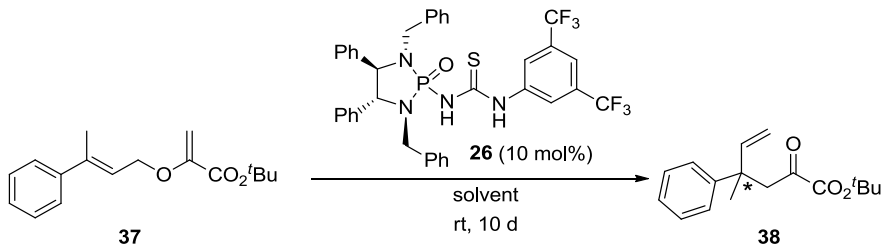
Our studies began with synthesis of catalyst **26** from the commercially available (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (**31**). Reductive amination[10] of benzaldehyde with **31** afforded **32** (87%) which furnished **33** (98%) upon reaction with $POCl_3$. Treatment of **33** with Bu_4NSCN afforded isothiocyanate **34** (60%). Subsequent reaction of **34** with 3,5-bis(trifluoromethyl)aniline (**35**) furnished thiourea catalyst **26** in 93%. Thiosemicarbazide **36** was obtained from **34** by reacting with hydrazinemonohydrate. Thiosemicarbazide **36** was converted to thiosemicarbazone **27** by reacting with 4-nitrobenzaldehyde. The product **27** was obtained as an impure material along with unidentified side products. Further attempts to purify the crude material were unsuccessful (Scheme 2.7).



Scheme 2.7 Synthesis of thiourea catalyst **26**

With the catalyst **26** in hand, we examined its catalytic activity for the Gosteli-Claisen rearrangement of allyl vinyl ether **37**. A solvent screening was performed for this reaction as shown in Table 2.1. The reaction of **37** in the presence of catalyst **26** in CF_3CH_2OH as the solvent furnished the product **38** in 20% yield and 4% ee (Table 2.1, entry 1). However, a similar reaction in the absence of **26** also provided the product **38** in 22% yield (Table 2.1, entry 2). This observation suggests that the solvent (CF_3CH_2OH) catalyzes the rearrangement, presumably by hydrogen bonding with **37**, and that this reaction pathway does not allow any significant participation of catalyst **26**. Unfortunately, the reaction did not proceed in any of the other solvents that were examined. This suggests that **26** is not a suitable catalyst for the conversion of **37** to **38** (Table 2.1, entry 3-9).

Table 2.1: Solvent screening for the Gosteli-Claisen rearrangement of **37** with catalyst **26**.



Entry	Solvent	Yield (%)	37 Recovered (%)
1	CF_3CH_2OH	20 (4% ee)	52
2[a]	CF_3CH_2OH	22	48
3	CH_2Cl_2	-	65
4	$CHCl_3$	-	62
5	EtOAc	-	71
6	Et_2O	-	67
7	hexanes	-	75
8	toluene	-	66
9	DMF	-	42

[a]Reaction without addition of catalyst **26**.

Given the lack of reactivity of **26**, we reasoned that addition of a metal salt could potentially generate a complex in which the acidity of the *N*-H functionality in **26** is enhanced, thus making it a better H-bond donor. The activated form of **26** could bind more effectively to **37** and hopefully accelerate the Gosteli-Claisen rearrangement (Figure 2.4).

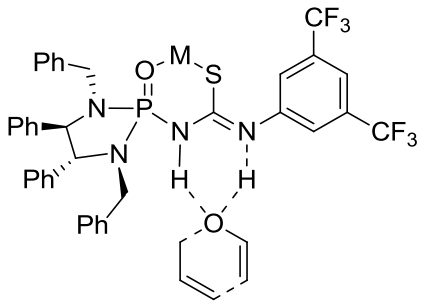
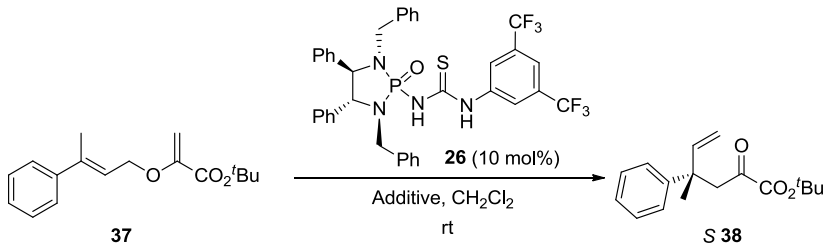


Figure 2.4. Bis-hydrogen-bonding of **37** with organocatalyst

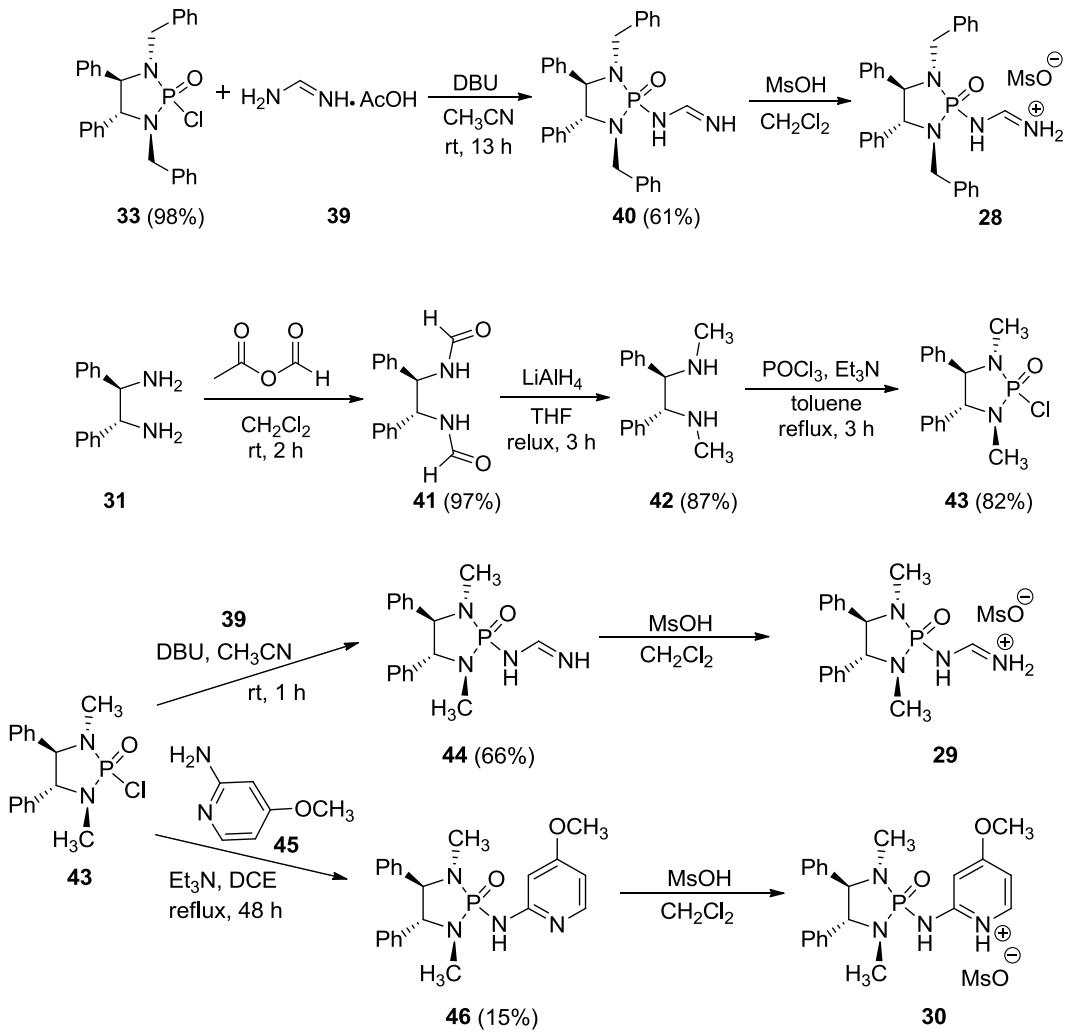
To this effect, an additive survey was conducted for this reaction as shown in Table 2.2. The allyl vinyl ether **37** was used in this study with CH_2Cl_2 as the solvent. Notably, only some of the selected thiourea/additive combinations provided the rearrangement product **38** at ambient temperature. Exposure of **37** to the **26**/$HgCl_2$ led to decomposition of **37** (Table 2.2 entry 1). Metal complexes derived from **26**/$Mg(ClO_4)_2$ and **26**/TiF_4 afforded the desired product **38** in low enantiomeric excess (Table 2.2, entry 2 and 3). No product was obtained for the reaction of **37** with metal complexes **26**/LiBr and **26**/$ZnCl_2$. Decomposition of **37** was observed in the presence of **26**/$Cu(OTf)_2$. Reaction of **26**/$Sc(OTf)_3$ complex with **37** provided the product **38** as a racemate (Table 2.2, entry 7).

Table 2.2: Additive survey for Gosteli-Claisen rearrangement of **37** with **38**.



Entry	Additive	Time (d)	Yield (%)	ee (%)	37 recovered (%)
1	$HgCl_2$	3	-	-	**37** decomposed
2	$Mg(ClO_4)_2$	10	8	7	36
3	TiF_4	10	12	6	42
4	$LiBr.H_2O$	10	-	-	55
5	$ZnCl_2$	10	-	-	26
6	$Cu(OTf)_2$	2	-	-	**37** decomposed
7	$Sc(OTf)_3$	9	13	rac	10

Since the thiourea catalyzed reactions were inefficient (very low yield as well as enantioselectivity), we turned our focus to the synthesis and application of phosphoramide containing amidinium salts as bis-hydrogen-bond donor catalysts (**28**-**30**, Scheme 2.8). Reaction of compound **33** with commercially available formamidine acetate **39** in the presence of DBU afforded the amidine **40** in 61% yield (Scheme 2.8).



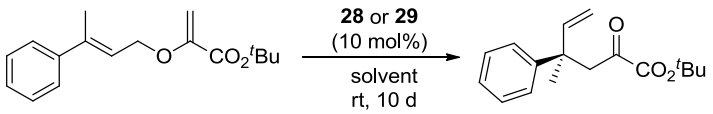
Scheme 2.8

The effect of modifying the *N*-alkyl group, in compound **28**, from benzyl to methyl was also examined. The synthesis of the *N*-methyl analogue **29** starts from (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine **31**. Formylation of diamine provided diamide **41**, which was subsequently reduced with $LiAlH_4$ to give **42** in 87% yield.[11] Treatment of **42** with $POCl_3$ furnished **43** in 82% yield.[12] Reaction of **43** with formamidine acetate (**39**) provided **44** in 66% yield. Compound **43** reacted with 4-methoxy aminopyridine (**45**) in the presence of Et_3N provided **46** in 15% yield. The salts **28**-**30** were prepared by the *in*

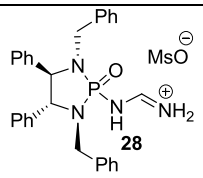
situ reaction of the amidines **40**, **44** and **46** respectively with one equivalent of methanesulfonic acid (Scheme 2.8).

The chiral amidinium salts **28** and **29** (Scheme 2.08) were selected as catalyst candidates in this study. A solvent survey was conducted for the Gosteli-Claisen rearrangement of **37** with amidinium salt **28** and **29** (Table 2.3). Allyl vinyl ether **37** in the presence of catalyst **28** or **29** at ambient temperature afforded the rearrangement product **38** with 12% ee (Table 2.3, entry 1 and 9). Unfortunately, no rearrangement product was obtained when other solvents were examined (Table 2.3) and hence a solvent optimization study could not be conducted.

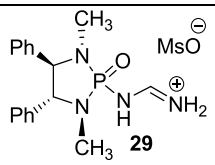
Table 2.3: Solvent screening for the Gosteli-Claisen rearrangement of **37** with catalyst **28** and **29**



37 *R* **38**

Entry	Catalyst	Solvent	Yield (%)	ee (%)	37 recovered (%)
1		CH_2Cl_2	20	12	27
2		$CHCl_3$	0	-	58
3		EtOAc	0	-	62
4		Et_2O	0	-	66
5		hexanes	0	-	63

28

6		DMF	0	-	-
7		CH_3CN	0	-	38
8		toluene	0	-	42
9	 **29**	CH_2Cl_2	15	12	23
10		$CHCl_3$	0	-	43
11		EtOAc	0	-	39
12		Et_2O	0	-	44
13		hexanes	0	-	62
14		DMF	0	-	-
15		CH_3CN	0	-	46
16		toluene	0	-	32

Next, we examined the catalyst effect of **30** for the Gosteli-Claisen rearrangement of allyl vinyl ether **37**. A solvent screening was performed for the Gosteli-Claisen rearrangement of **37** with catalyst **30** (Table 2.4). Unfortunately, none of these reactions provided the rearrangement product **38**.

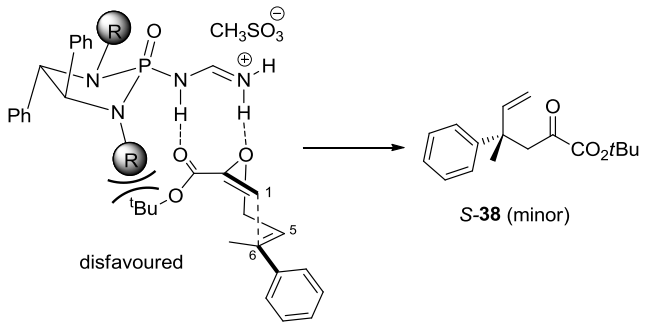
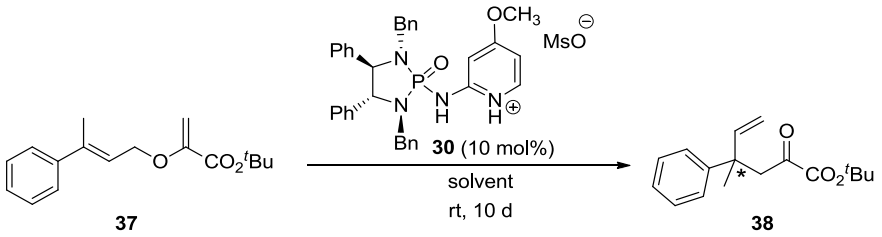


Figure 2.5. Proposed transition state for the organocatalytic Gosteli-Claisen rearrangement of **37** with catalysts **28** and **29**

Table 2.4: Solvent screening for the Gosteli-Claisen rearrangement of **37** with catalyst **30**

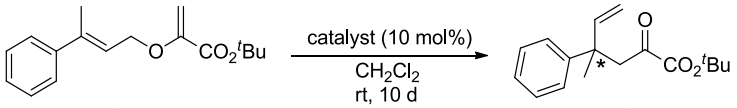


Entry	Solvent	37 Recovered (%)
1	CH_2Cl_2	68
2	$CHCl_3$	74
3	EtOAc	61
4	Et_2O	65
5	hexanes	76
6	toluene	55
7	DMF	36

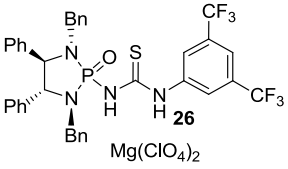
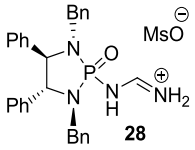
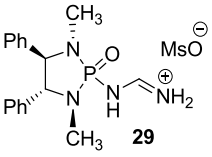
2.5 Summary of results for the organocatalytic Gosteli-Claisen rearrangement

The best results obtained for the Gosteli-Claisen rearrangement in terms of enantioselectivity are summarized in Table 2.5. Allyl vinyl ether **37** in the presence of thiourea catalyst **26**/$Mg(ClO_4)_2$ afforded the product with 7% ee (Table 2.5, entry 1). Reactions of allyl vinyl ether **37** with amidinium catalyst **26** and **29** provided the rearrangement product **38** with 12% ee (Table 2.5, entry 2 and 3). Notably, modifying the amine protecting group benzyl (**28**) to methyl (**29**) did not affect the enantiomeric excess of the product.

Table 2.5. Summary of best results obtained for organocatalytic Gosteli-Claisen rearrangements of **37**



37 **38**

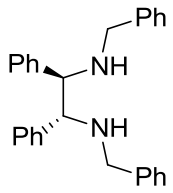
Entry	Catalyst	Product	ee (%)
1		*S* **38**	7
2		*R* **38**	12
3		*R* **38**	12

2.6 Conclusion

In summary, we developed a simple synthesis of several new types of organocatalysts that contain a chiral phosphoramide functionality. These catalysts were examined for the enantioselective Gosteli-Claisen rearrangement of the allyl vinyl ether **37**. Some of these catalysts accelerated the [3,3]-sigmatropic rearrangement of **37** and afforded the quaternary stereocenter but with low enantiomeric excess. Structural changes in the organocatalysts as well as optimization of the reactions are required, and these studies are continuing in the Pansare group.

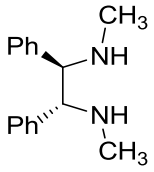
2.7 Experimental Section

(1*R*,2*R*)-N^1,N^2-Dibenzyl-1,2-diphenylethane-1,2-diamine (32):



Prepared from (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine and benzaldehyde according to the literature procedure.[10] Spectroscopic data for **32** was identical to the reported data.[10]

(1*R*,2*R*)-N^1,N^2-Dimethyl-1,2-diphenylethane-1,2-diamine (42):



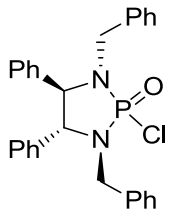
Prepared from (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine and acetic formic anhydride according to the literature procedure.[11] Spectroscopic data for **42** was identical to the reported data.[11]

General procedure for the synthesis of phosphoryl chlorides 33 and 43:

To a solution of the diamine in toluene was added triethyl amine. The solution was cooled to 0 ˚C and $POCl_3$ was added dropwise. The mixture was then warmed to room temperature, heated to reflux for 4 h and then cooled to room temperature. The white precipitate that was formed was removed by filtration, and the filter cake was washed toluene (10 mL). The combined filtrates were concentrated under reduced

pressure and the residue was purified by flash chromatography on silica gel (hexane/EtOAc, 9:1) to provide the phosphoryl chlorides.

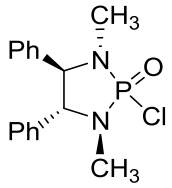
(4*R*,5*R*)-1,3-Dibenzyl-2-chloro-4,5-diphenyl-1,3,2-diazaphospholidine 2-oxide (33):



The reaction of **32** (1.00 g, 2.55 mmol), NEt_3 (0.710 mL, 5.10 mmol) and $POCl_3$ (0.24 mL, 2.55 mmol) according to the general procedure provided, after purification by flash column chromatography on silica gel, 950 mg (79%) of **33** as a colorless oil; R_f = 0.21 (hexanes/EtOAc, 9:1).

IR (neat): 3061, 3031, 2924, 2906, 2866, 1494, 1452, 1273, 1255, 1212, 1108, 1028, 765, 734, 698, 517, 493 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35-7.12 (m, 16H, Ar*H*), 7.06-6.96 (m, 4H, Ar*H*), 4.58 (dd, 1H, *J* = 14.8, 10.5, PhC*H*), 4.16 (t, 1H, *J* = 14.7, PhCH_2), 4.10-3.94 (m, 3H, PhCH_2) 3.65 (dd, 1H, *J* = 14.8, 10.9, PhC*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.7 (d, $^3J_{CP}$ = 3.5, ArC_{ipso}), 137.3 (d, $^3J_{CP}$ = 8.9, ArC_{ipso}), 135.37 (d, $^3J_{CP}$ = 3.6, ArC_{ipso}), 135.32 (d, $^3J_{CP}$ = 2.9, ArC_{ipso}), 129.4 (2 x Ar*C*), 129.1 (2 x Ar*C*), 128.9 (2 x Ar*C*), 128.8 (2 x Ar*C*), 128.69 (Ar*C*), 128.64 (Ar*C*), 128.60 (2 x Ar*C*), 128.3 (2 x Ar*C*), 128.1 (2 x Ar*C*), 127.94 (2 x Ar*C*), 127.89 (Ar*C*), 127.7 (Ar*C*), 68.2 (d, $^2J_{CP}$ = 13.6, PhCH_2), 66.7 (d, $^2J_{CP}$ = 12.8, PhCH_2), 47.6 (d, *J* = 4.6, Ph*C*H), 45.7 (d, *J* = 6.0, Ph*C*H); ^{31}P NMR (121 MHz, $CDCl_3$): 25.7; HRMS (ESI, pos.): *m/z* 472.1471 (472.1471 calc. for $C_{28}H_{26}ClN_2OP$, M^+) and 473.1543 (473.1550 calc. for $C_{28}H_{27}ClN_2OP$, $(M+H)^+$).

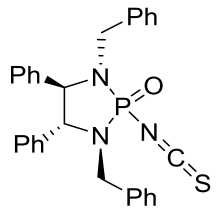
(4*R*,5*R*)-2-Chloro-1,3-dimethyl-4,5-diphenyl-1,3,2-diazaphospholidine 2-oxide (43):



The reaction of **42** (1.00 g, 4.16 mmol), NEt_3 (1.20 mL, 8.32 mmol) and $POCl_3$ (0.400 mL, 4.16 mmol) according to the general procedure, provided after purification by flash column chromatography 1.11 g (82%) of **43** as a colorless oil; R_f = 0.23 (hexanes/EtOAc, 9:1).

IR (neat): 3004, 2936, 2866, 2826, 1452, 1273, 1209, 1152, 1109, 741, 697, 513, 491 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.28 (m, 6H, Ar*H*), 7.17-7.11 (m, 2H, Ar*H*), 7.10-7.04 (m, 2H, Ar*H*), 4.15 (dd, 1H, *J* = 8.6, 4.3, PhC*H*), 3.85 (d, 1H, *J* = 8.6, PhC*H*), 2.60 (d, 3H, *J* = 10.5, CH_3), 2.46 (d, 3H, *J* = 14.4, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.8 (d, $^3J_{CP}$ = 5.5, ArC_{ipso}), 135.8 (d, $^3J_{CP}$ = 12.8, ArC_{ipso}), 128.75 (2 x Ar*C*), 128.73 (Ar*C*), 128.69 (2 x Ar*C*), 128.5 (Ar*C*), 127.8 (2 x Ar*C*), 127.6 (2 x Ar*C*), 70.8 (d, $^2J_{CP}$ = 12.1, Ph*C*H), 70.2 (d, $^2J_{CP}$ = 12.0, Ph*C*H), 29.9 (d, $^2J_{CP}$ = 2.6, *C*H_3), 29.0 (d, $^2J_{CP}$ = 5.3, *C*H_3); ^{31}P NMR (121 MHz, $CDCl_3$): δ 29.9; HRMS (APPI, pos.): *m/z* 320.0854 (320.0845 calc. for $C_{16}H_{18}ClN_2OP$, $(M)^+$) and 321.0928 (321.0924 calc. for $C_{16}H_{19}ClN_2OP$, $(M+H)^+$).

(4*R*,5*R*)-1,3-Dibenzyl-2-isothiocyanato-4,5-diphenyl-1,3,2-diazaphospholidine 2-oxide (34):

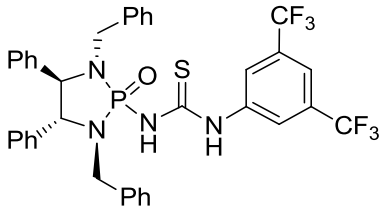


To a solution of phosphoryl chloride **33** (300 mg, 0.634 mmol) in dry CH_3CN was added tetrabutylammonium thiocyanate (571 mg, 1.90 mmol), the solution was heated to reflux for 24 h and then cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 8:2) to provide 210 mg (67%) of isothiocyanate **34** as colorless oil; R_f = 0.2 (hexanes/EtOAc, 8:2).

IR (neat): 3063, 3030, 2918, 2036, 1986, 1494, 1455, 1361, 1257, 1208, 1173, 1139, 1097, 1067, 759, 740, 480 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35-7.17 (m, 14H, Ar*H*), 7.16-7.08 (m, 2H, Ar*H*), 7.08-6.96 (m, 4H, Ar*H*), 4.47 (dd, 1H, *J* = 14.7, 10.8, PhCH_2), 4.30 (dd, 1H, *J* = 14.9, 11.4, PhCH_2), 4.08 (t, 1H, *J* = 5.7, PhC*H*), 3.95 (dd, 1H, *J* = 7.7, 5.7, PhC*H*), 3.84 (dd, 1H, *J* = 14.9, 12.2, PhC*H*), 3.68 (dd, 1H, *J* = 14.7, 11.0, PhCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.1 (d, $^2J_{CP}$ = 9.2, *C*=S), 137.9 (d, $^3J_{CP}$ = 3.9, ArC_{ipso}), 137.3 (d, $^3J_{CP}$ = 6.6, ArC_{ipso}), 135.1 (d, $^3J_{CP}$ = 2.4, ArC_{ipso}), 134.9 (d, $^3J_{CP}$ = 2.8, ArC_{ipso}), 128.91 (3 x Ar*C*), 128.89 (3 x Ar*C*), 128.76 (2 x Ar*C*), 128.50 (Ar*C*), 128.46 (3 x Ar*C*), 128.41 (2 x Ar*C*), 127.7 (2 x Ar*C*), 127.48 (2 x Ar*C*), 127.43 (2 x Ar*C*), 67.1 (d, $^2J_{CP}$ = 14.6, Ph*C*H), 66.5 (d, $^2J_{CP}$ = 14.0, Ph*C*H), 46.6 (d, $^2J_{CP}$ = 4.8, Ph*C*H_2), 45.9 (d, $^2J_{CP}$ = 5.7,

Ph*C*H_2); HRMS (APPI, pos.): *m/z* 495.1557 (495.1534 calc. for $C_{29}H_{26}N_3OPS$ $(M)^+$) and 496.1629 (496.1612 calc. for $C_{29}H_{27}N_3OPS$ $(M+H)^+$).

1-(3,5-bis(Trifluoromethyl)phenyl)-3-((4*R*,5*R*)-1,3-dibenzyl-2-oxido-4,5-diphenyl-1,3,2-diazaphospholidin-2-yl)thiourea (26):

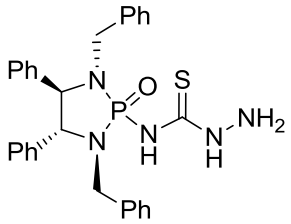


To a solution of isothiocyanate **34** (140 mg, 0.283 mmol) in CH_2Cl_2 (7 mL) was added aniline **35** (45 µL, 0.30 mmol) and the solution was heated to reflux for 48 h. The solution was then cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes/CH_2Cl_2, 1:1) to provide 191 mg (93%) of the thiourea **26** as a semi-solid; R_f = 0.20 (hexanes/CH_2Cl_2, 1:1).

IR (neat): 3090, 3066, 3033, 2927, 1492, 1473, 1456, 1384, 1344, 1317, 1278, 1238, 1176, 1134, 1066, 852, 762, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 11.72 (s, 1H, P(O)N*H*CSNH), 8.11 (s, 2H, Ar*H*), 7.67 (s, 1H, Ar*H*), 7.38-7.30 (m, 6H, Ar*H*), 7.28-7.15 (m, 12H, Ar*H*), 7.06-6.96 (m, 2H, Ar*H*), 6.78 (br s, 1H, P(O)NHCSN*H*), 4.26 (t, 1H, *J* = 13.1, PhCH_2 or PhC*H*), 4.21-4.13 (m, 2H, PhCH_2 and PhC*H*), 4.09 (dd, 1H, *J* = 6.8, 2.9, PhCH_2 or PhC*H*), 3.86 (dd, 1H, *J* =14.2, 11.5, PhCH_2), 3.75 (dd, 1H, *J* = 14.0, 8.8, PhCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.5 (d, $^2J_{CP}$ = 4.3, *C*=S), 139.9 (ArC_{ipso}), 137.1 (ArC_{ipso}), 137.0 (d, $^3J_{CP}$ = 0.9, ArC_{ipso}), 134.7 (d, $^3J_{CP}$ = 0.9, ArC_{ipso}), 134.6 (d, $^3J_{CP}$ = 2.0,

ArC_{ipso}), 131.6 (q, J_{CF} = 33.6, 2 x CF_3), 129.4 (2 x Ar*C*), 129.3 (2 x Ar*C*), 129.1 (2 x Ar*C*), 129.0 (2 x Ar*C*), 128.9 (Ar*C*), 128.8 (Ar*C*), 128.7 (2 x Ar*C*), 128.6 (2 x Ar*C*), 128.1 (Ar*C*), 128.0 (Ar*C*), 127.7 (2 x Ar*C*), 127.6 (2 x Ar*C*), 125.0 (ArC_{ipso}), 123.40-123.36 (br, 2 x Ar*C*), 121.3 (ArC_{ipso}), 118.8-118.57 (m, Ar*C*), 68.8 (d, $^2J_{CP}$ = 12.5, Ph*C*H), 67.5 (d, $^2J_{CP}$ = 13.1, Ph*C*H), 47.8 (d, $^2J_{CP}$ = 4.5, Ph*C*H_2), 47.1 (d, $^2J_{CP}$ = 4.1, Ph*C*H_2); ^{31}P NMR (121 MHz, $CDCl_3$): 16.4; HRMS (APPI, pos.): *m/z* 724.1838 (724.1860 calc. for $C_{37}H_{31}F_6N_4OPS$, $(M)^+$) and 725.1913 (725.1939 calc. for $C_{37}H_{32}F_6N_4OPS$, $(M+H)^+$).

***N*-((4*R*,5*R*)-1,3-Dibenzyl-2-oxido-4,5-diphenyl-1,3,2-diazaphospholidin-2-yl)hydrazine carbothioamide (36):**



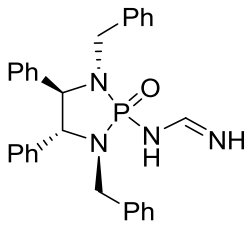
To a solution of isothiocyanate **34** (100 mg, 0.20 mmol) in THF (3.0 mL) was added hydrazine monohydrate (0.32 mL, 3.50 mmol) at 0 ˚C and the solution was stirred for 5 h at 0 ˚C. Water (1.0 mL) was added at 0 ˚C, the resulting mixture was warmed to room temperature and then extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes:EtOAc, 6:4) to provide 63 mg (60%) of thiosemicarbazide **36** as a semi-solid; R_f = 0.22 (hexanes:EtOAc, 6:4).

IR (neat): 3217, 3087, 3062, 3030, 2922, 1605, 1493, 1455, 1358, 1233, 1200, 1169, 1128, 1098, 1067, 1030, 993, 760, 739, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.39 (br s, 1H, P(O)N*H*CSNH), 7.34-7.17 (m, 13H, Ar*H*), 7.16-7.04 (m, 5H, Ar*H*), 6.98-6.89 (m, 2H, Ar*H*), 6.41 (d, 1H, *J* = 8.4, P(O)N*H*CSN*H*), 4.33 (br s, 2H, NH_2), 4.30-4.14 (m, 2H, PhC*H* or PhCH_2), 4.14-4.06 (m, 1H, PhC*H* or PhCH_2), 3.99 (dd, 1H, *J* = 6.6, 3.3, PhC*H* or PhCH_2), 3.79 (dd, 1H, *J* = 14.4, 9.8, PhC*H* or PhCH_2), 3.66 (dd, 1H, *J* = 14.4, 12.2, PhC*H* or PhCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.6 (d, $^{2}J_{CP}$ = 2.5, *C*=S), 137.4 (d, $^{3}J_{CP}$ = 6.8, ArC_{ipso}), 137.2 (d, $^{3}J_{CP}$ = 5.8, ArC_{ipso}), 135.0 (d, $^{3}J_{CP}$ = 0.5, ArC_{ipso}), 134.9 (d, $^{3}J_{CP}$ = 2.3, ArC_{ipso}), 129.3 (2 x Ar*C*), 129.2 (2 x Ar*C*), 128.9 (2 x Ar*C*), 128.8 (2 x Ar*C*), 128.7 (Ar*C*), 128.6 (Ar*C*), 128.5 (2 x Ar*C*), 128.4 (2 x Ar*C*), 127.9 (Ar*C*), 127.8 (2 x Ar*C*), 127.7 (Ar*C*), 127.6 (2 x Ar*C*), 68.2 (d, $^{2}J_{CP}$ = 12.7, Ph*C*H), 67.1 (d, $^{2}J_{CP}$ = 13.2, Ph*C*H), 47.1 (d, $^{2}J_{CP}$ = 5.2, Ph*C*H_2), 46.7 (d, $^{2}J_{CP}$ = 4.2, Ph*C*H_2); ^{31}P NMR (121 Hz, CDCl): 15.9; HRMS (APPI, neg.): *m/z* 527.1889 (527.1909 calc. for $C_{29}H_{30}N_5OPS$, $(M)^-$).

General procedure for the synthesis of amidines 40, 44 and 46:

To a solution of formamidine acetate (**39**) in CH_3CN was added DBU. The mixture was stirred for 5 min at room temperature and a solution of the phosphoryl chloride in CH_3CN was added dropwise. The solution was stirred until complete consumption of the phosphoryl chloride. Water was added and the mixture was extracted with EtOAc (3 x 5 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH) to provide the required amidines.

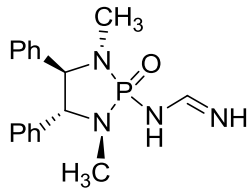
***N*-((4*R*,5*R*)-1,3-Dibenzyl-2-oxido-4,5-diphenyl-1,3,2-diazaphospholidin-2-yl)formimidamide (40):**



The reaction of **33** (80.0 mg, 0.170 mmol), DBU (51.0 µL, 0.340 mmol) and formamidine acetate (**39)** (19.4 mg, 0.190 mmol) according to the general procedure provided, after purification by flash column chromatography on silica gel ($MeOH/CH_2Cl_2$, 5:95) 50 mg (61%) of **40** as a semi-solid; R_f = 0.20 ($MeOH/CH_2Cl_2$, 5:95).

IR (neat): 3393, 3129, 3061, 3028, 2971, 2911, 2847, 1646, 1582, 1492, 1452, 1356, 1252, 1174, 1154, 1117, 1099, 792, 730, 697, 561, 480 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.97 (d, 1H, *J* = 30.5, NHC*H*NH), 7.35-7.08 (m, 20H, Ar*H*), 5.60 (br s, 1H, N*H*CHNH), 4.13 (t, 1H, *J* = 13.7, PhCH_2), 4.12-4.05 (m, 1H, PhCH_2), 4.02 (d, 2H, *J* = 4.5, 2 x PhC*H*), 3.76 (dd, 1H, *J* = 9.6, 4.7, PhCH_2), 3.71 (dd, 1H, *J* = 9.6, 4.7, PhCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.1 (NH*C*HNH), 139.9 (d, $^3J_{CP}$ = 5.5, ArC_{ipso}), 139.2 (d, $^3J_{CP}$ = 5.4, ArC_{ipso}), 137.4 (d, $^3J_{CP}$ = 2.5, ArC_{ipso}), 137.2 (d, $^3J_{CP}$ = 1.5, ArC_{ipso}), 129.2 (2 x Ar*C*), 128.9 (2 x Ar*C*), 128.3 (3 x Ar*C*), 128.0 (3 x Ar*C*), 127.9 (6 x Ar*C*), 127.8 (2 x Ar*C*), 127.0 (Ar*C*), 126.9 (Ar*C*), 68.7 (d, $^2J_{CP}$ = 10.7, Ph*C*H), 68.1 (d, $^2J_{CP}$ = 13.3, Ph*C*H), 47.0 (d, $^2J_{CP}$ = 4.8, Ph*C*H_2), 46.9 (d, *J* = 5.1, Ph*C*H_2); ^{31}P NMR (121 MHz, $CDCl_3$): δ 27.3; HRMS (APPI, pos.): *m/z* 480.2098 (480.2079 calc. for $C_{29}H_{29}N_4OP$, $(M)^+$) and 481.2173 (481.2157 calc. for $C_{29}H_{30}N_4OP$, $(M+H)^+$).

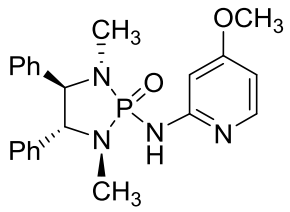
***N*-((4*R*,5*R*)-1,3-Dimethyl-2-oxido-4,5-diphenyl-1,3,2-diazaphospholidin-2-yl)formimidamide (44):**



The reaction of **43** (80.0 mg, 0.25 mmol), DBU (75.0 µL, 0.50 mmol) and formamidine acetate (**39**, 28.6 mg, 0.280 mmol) according to the general procedure, provided after purification by flash column chromatography ($MeOH/CH_2Cl_2$, 5:95) 54 mg (66%) of **44** as a semi-solid; R_f = 0.20 ($MeOH/CH_2Cl_2$, 5:95).

IR (neat): 3132, 3031, 2950, 2813, 1650, 1597, 1493, 1453, 1336, 1232, 1149, 993, 868, 813, 730, 699, 551, 459 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.32 (d, 1H, *J* = 27.6, NHC*H*NH), 7.33-7.20 (m, 6H, Ar*H*), 7.19-7.07 (m, 4H, Ar*H*), 6.57 (br s, 1H, N*H*CHNH), 3.94 (dd, 2H, *J* = 8.5, 2 x PhC*H*), 2.44 (d, 3H, *J* = 10, CH_3N), 2.31 (d, 3H, *J* = 10.2, CH_3N); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.1 (NH*C*HNH), 138.6 (d, $^3J_{CP}$ = 8.4, ArC_{ipso}), 137.9 (d, J_{CP} = 9.1, ArC_{ipso}), 128.4 (2 x Ar*C*), 128.3 (2 x Ar*C*), 128.03 (2 x Ar*C*), 128.01 (2 x Ar*C*), 127.9 (2 x Ar*C*), 71.8 (d, $^2J_{CP}$ = 3.1, Ph*C*H), 71.6 (d, $^2J_{CP}$ = 3.7, Ph*C*H), 30.2 (d, $^2J_{CP}$ = 3.9, *C*H_3), 30.1 (d, $^2J_{CP}$ = 2.9, *C*H_3); ^{31}P NMR (121 MHz, $CDCl_3$): δ 30.0; HRMS (ESI, neg.): *m/z* 329.1299 (329.1293 calc. for $C_{17}H_{20}N_3O_2P$, (M^- for the *N*-formyl analogue of **44** obtained by imine hydrolysis) and 328.1226 (328.1215 calc. for $C_{17}H_{19}N_3O_2P$, $(M-H)^-$ for *N*-formyl analogue of **44**).

(4*R*,5*R*)-2-((4-Methoxypyridin-2-yl)amino)-1,3-dimethyl-4,5-diphenyl-1,3,2-diazaphospholidine 2-oxide (46):



To a solution of **43** (500.00 mg, 1.56 mmol) in 1,2-dichloroethane (5.00 mL) was added Et_3N (0.430 mL, 3.12 mmol) and the solution was heated to reflux for 48 h. The mixture was cooled to room temperature, water (5 mL) was added and the resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified using preparative TLC (silica gel, CH_2Cl_2/MeOH, 95:5) to give **46** as a semi-solid; R_f = 0.20 (CH_2Cl_2/MeOH, 95:5).

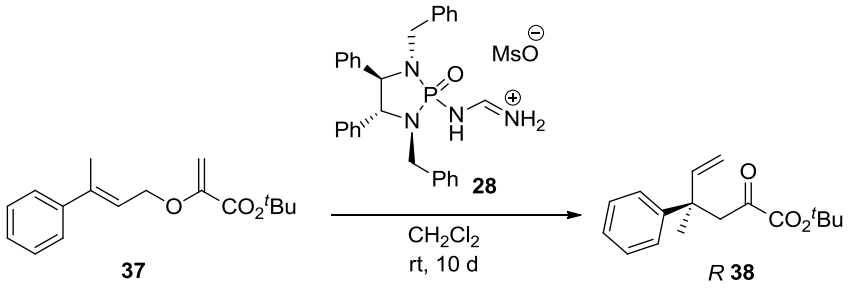
IR (neat): 3061, 2951, 2903, 2817, 1594, 1453, 1305, 1260, 1209, 1160, 1209, 1160, 1073, 1041, 1009, 978, 701, 497 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.08 (dd, 1H, *J* = 5.6, 0.7, Ar*H*), 7.32-7.26 (m, 4H, Ar*H*), 7.26-7.16 (m, 6H, Ar*H*), 6.52-6.46 (m, 2H, Ar*H*), 6.28 (br s, 1H, N*H*), 4.53 (d, 1H, *J* = 8.9, PhC*H*), 4.06 (d, 1H, *J* = 8.9, PhC*H*), 3.86 (s, 3H, OCH_3), 2.45 (d, 3H, *J* = 10.4, CH_3), 2.38 (d, 3H, *J* = 10.4, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3 (d, $^2J_{CP}$ = 1.9, ArC_{ipso}), 156.1 (ArC_{ipso}), 148.9 (Ar*C*), 138.3 (d, $^3J_{CP}$ = 9.0, ArC_{ipso}), 138.2 (d, $^3J_{CP}$ = 8.0, ArC_{ipso}), 128.42 (2 x Ar*C*), 128.36 (2 x Ar*C*), 128.26 (2 x Ar*C*), 128.2 (2 x Ar*C*), 128.05 (Ar*C*), 128.01 (Ar*C*), 105.0 (Ar*C*), 95.5 (d, $^3J_{CP}$ = 7.5, Ar*C*), 71.6 (d, $^2J_{CP}$ = 12.3, PhCH), 71.1 (d, $^2J_{CP}$ = 12.2, PhCH), 55.2 (OCH_3), 30.0 (d, $^2J_{CP}$ =3.1, CH_3), 29.2 (d, $^2J_{CP}$ = 4.2, CH_3); ^{31}P NMR (121 Hz, $CDCl_3$): 21.4; HRMS (ESI,

pos.): *m/z* 408.1695 (408.1715 calc. for $C_{22}H_{25}N_4O_2P$, $(M)^+$) and 409.1767 (409.1793 calc. for $C_{22}H_{26}N_4O_2P$, $(M+H)^+$).

General procedure for the rearrangement of 37 to 38:

To a solution of **40** or **44** in dichloromethane was added methanesulfonic acid and the mixture was stirred at ambient temperature for 5 min. To the resulting solution was added a solution of the allyl vinyl ether **37** in dichloromethane. The resulting solution was stirred at ambient temperature for 10 days. Water (1 mL) was added and the solution was extracted with DCM (3 x 2 mL). The combined fractions were concentrated and the residue was purified by flash chromatography on silica gel to provide **38.**

***tert*-Butyl (*R*)-4-methyl-2-oxo-4-phenylhex-5-enoate (38):**



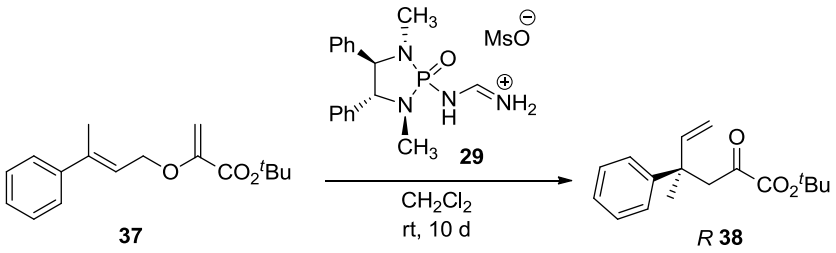
The reaction of amidine **40** (5.3 mg, 0.011 mmol), methanesulfonic acid (0.1 M solution in CH_2Cl_2, 0.11 mL, 0.011 mmol) and allyl vinyl ether **37** (30 mg, 0.11 mmol) according to the general procedure provided, after purification by flash column

chromatography on silica gel (Et_2O/hexanes, 2:98) 6 mg (20%) of **38** as a clear oil; R_f = 0.21 (Et_2O/hexanes, 4:96)

Spectroscopic data for **38** were identical to the reported data of **102e** from Chapter 1 in this thesis.

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 99.6/0.4, flow rate 1 mL min^{-1}, λ= 254 nm): t_{minor} = 7.01; t_{major} = 7.61 min; 12% ee.

***tert*-Butyl (*R*)-4-methyl-2-oxo-4-phenylhex-5-enoate (38):**



The reaction of amidine **44** (3.6 mg, 0.011 mmol), methanesulfonic acid (0.1 M solution in CH_2Cl_2, 0.1 mL, 0.11 mmol) and allyl vinyl ether **37** (30 mg, 0.11 mmol) according to the general procedure provided, after purification by flash column chromatography on silica gel (Et_2O/hexanes, 2:98) 5 mg (15%) of **38** as a clear oil ; R_f = 0.21 (Et_2O/hexanes, 4:96)

HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 99.6/0.4, flow rate 1 mL min^{-1}, λ= 254 nm): t_{minor} = 6.84 ; t_{major} = 7.41 min; 12% ee.

2.8 References

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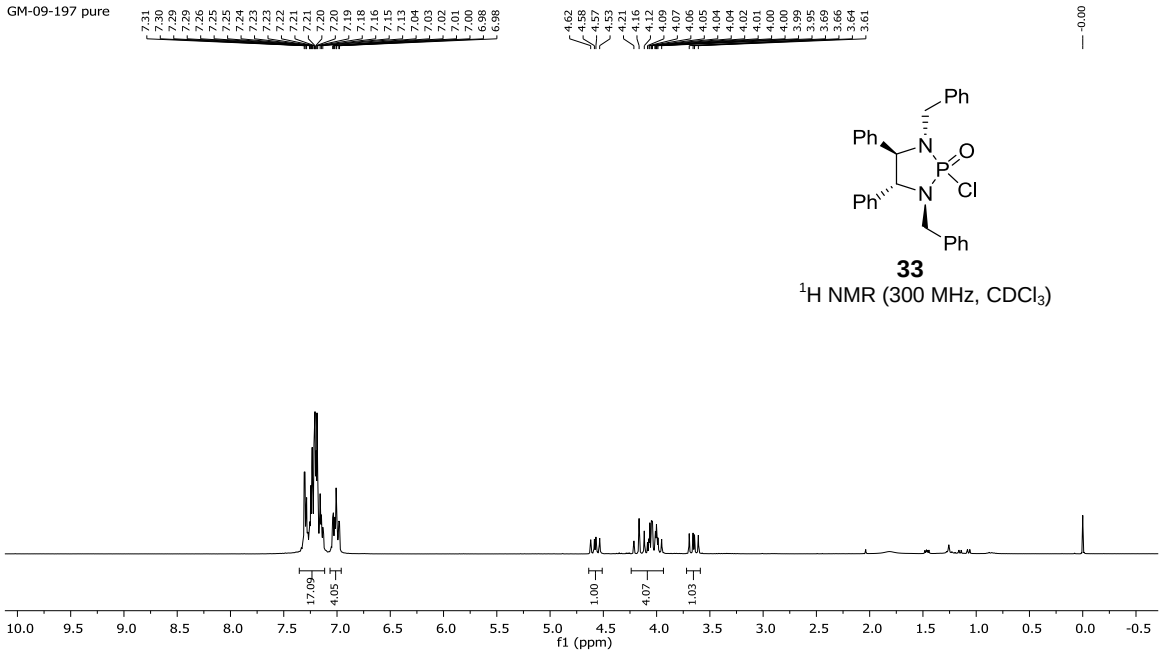
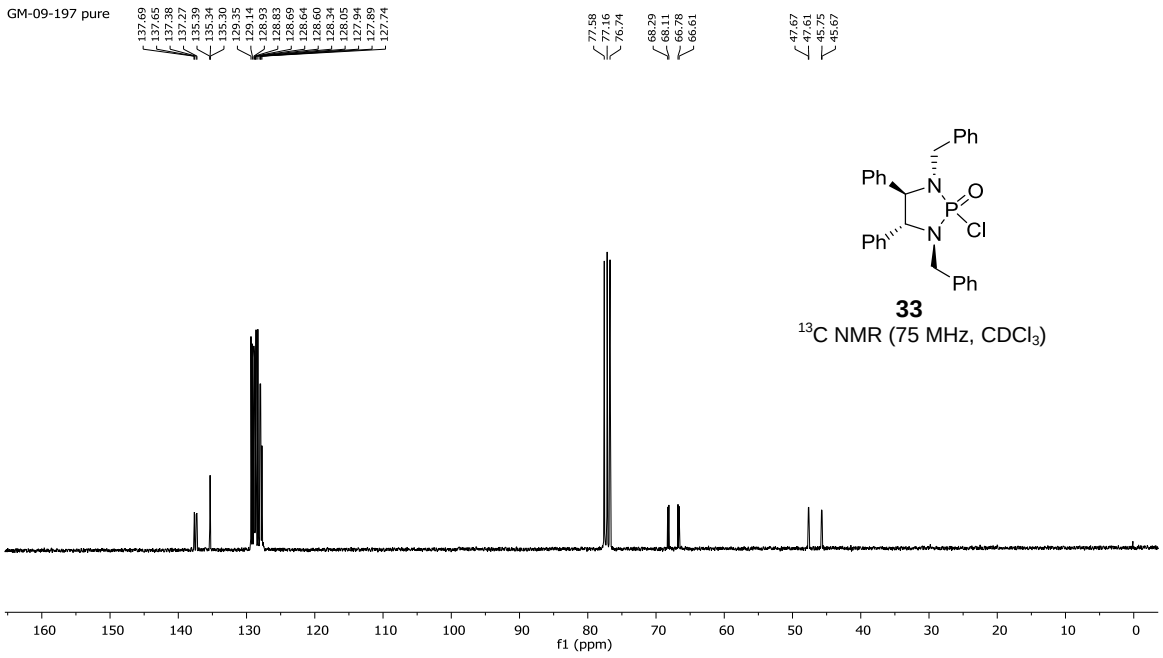
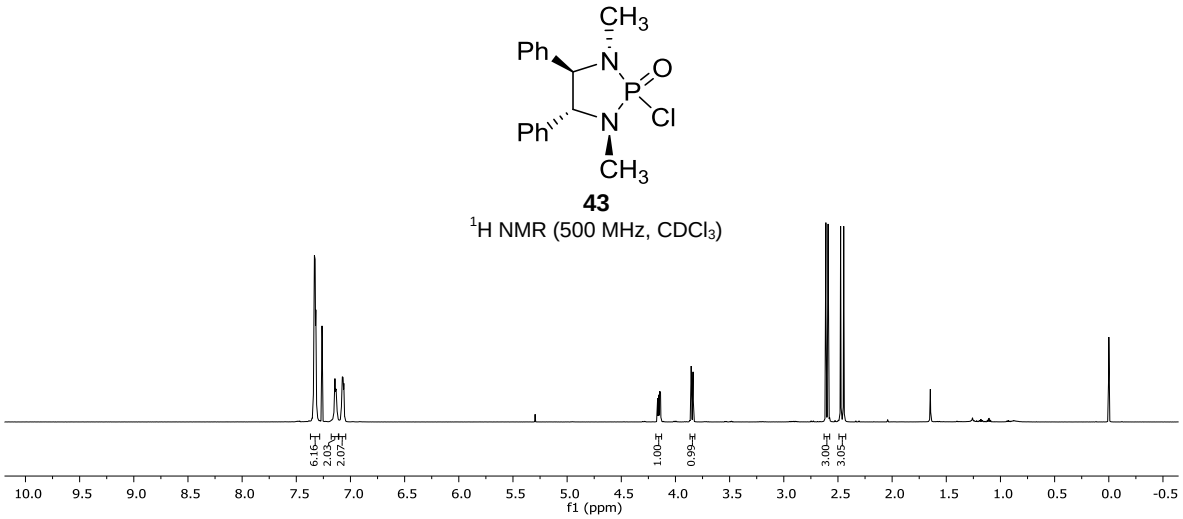
2.9 APPENDIX 2 (^{1}H, ^{13}C NMR spectras and HPLC traces)


GM-09-197 pure
7.31 7.30 7.29 7.29 7.26 7.25 7.25 7.24 7.23 7.23 7.22 7.21 7.21 7.20 7.20 7.19 7.18 7.16 7.15 7.13 7.04 7.03 7.02 7.01 7.00 6.98 6.98
4.62 4.58 4.57 4.53 4.21 4.16 4.12 4.09 4.07 4.06 4.05 4.04 4.04 4.02 4.01 4.00 4.00 3.99 3.95 3.69 3.66 3.64 3.61
-0.00
Ph
Ph
N
P
O
Cl
Ph
N
Ph
Ph
33
^{1}H NMR (300 MHz, CDCl$_3$)
17.09
4.05
1.00
4.07
1.03
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


GM-09-197 pure
137.69 137.65 137.38 137.27 135.39 135.34 135.30 129.35 129.14 128.93 128.83 128.69 128.64 128.60 128.34 128.05 127.94 127.89 127.74
77.58 77.16 76.74
68.29 68.11 66.78 66.61
47.67 47.61 45.75 45.67
Ph
Ph
N
P
O
Cl
Ph
N
Ph
Ph
33
^{13}C NMR (75 MHz, CDCl$_3$)
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

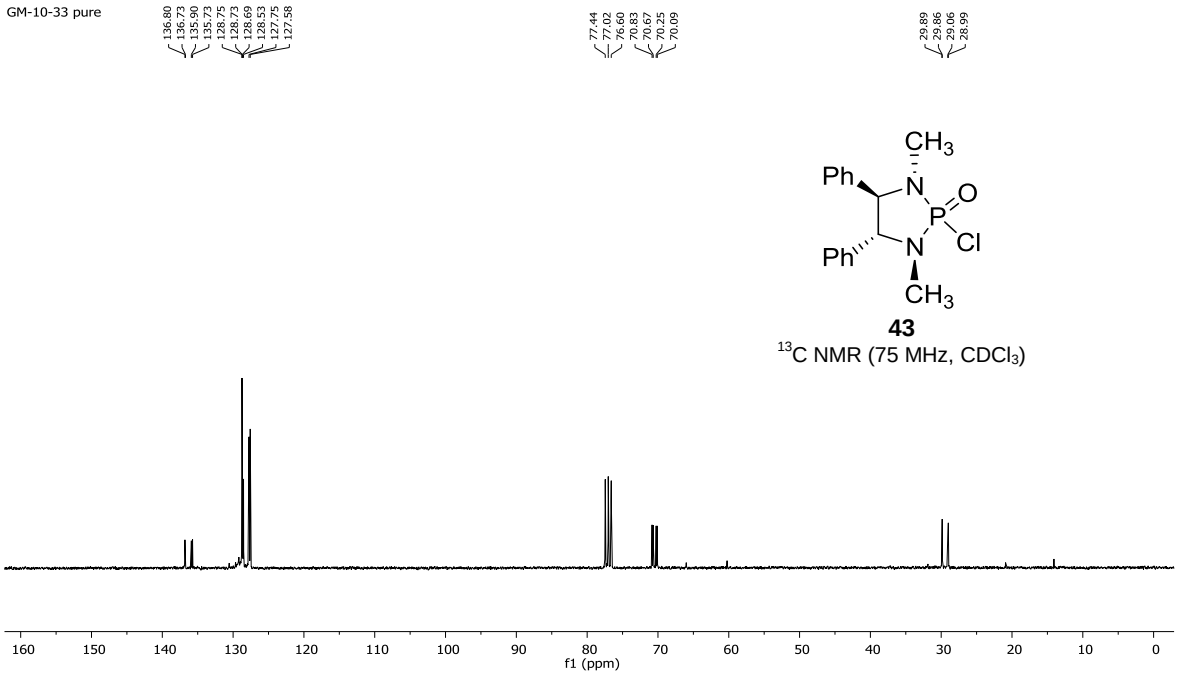
RAA-07-035 pure.1.fid



43

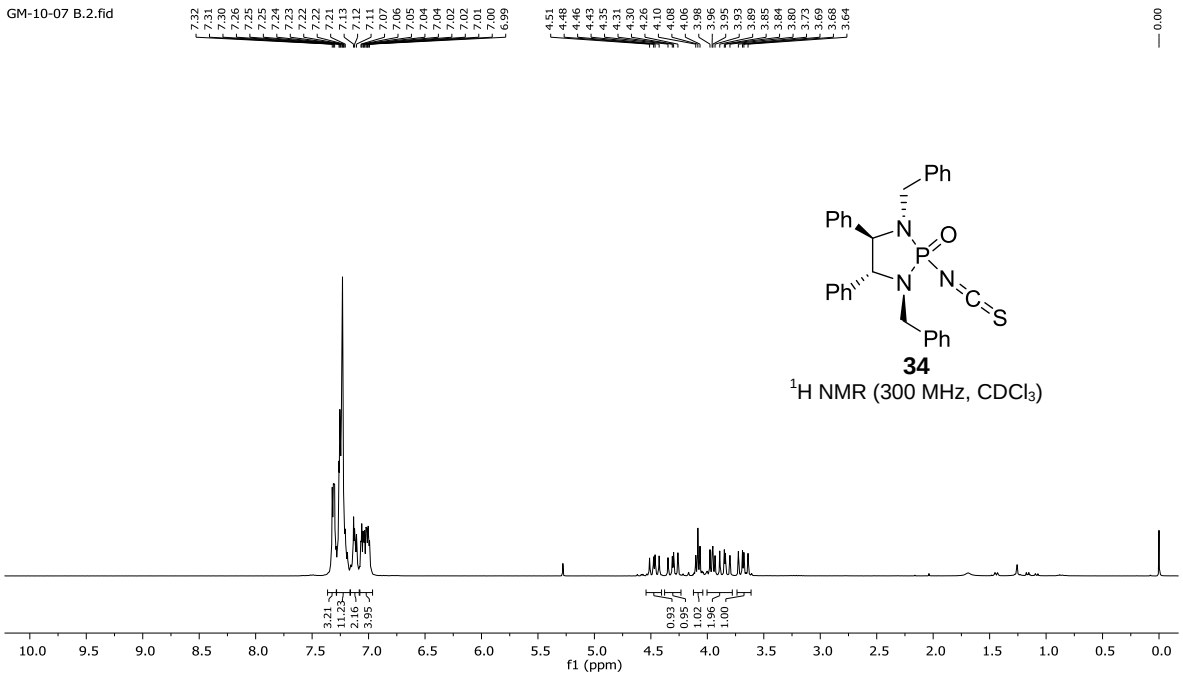
^{1}H NMR (500 MHz, $CDCl_3$)

GM-10-33 pure



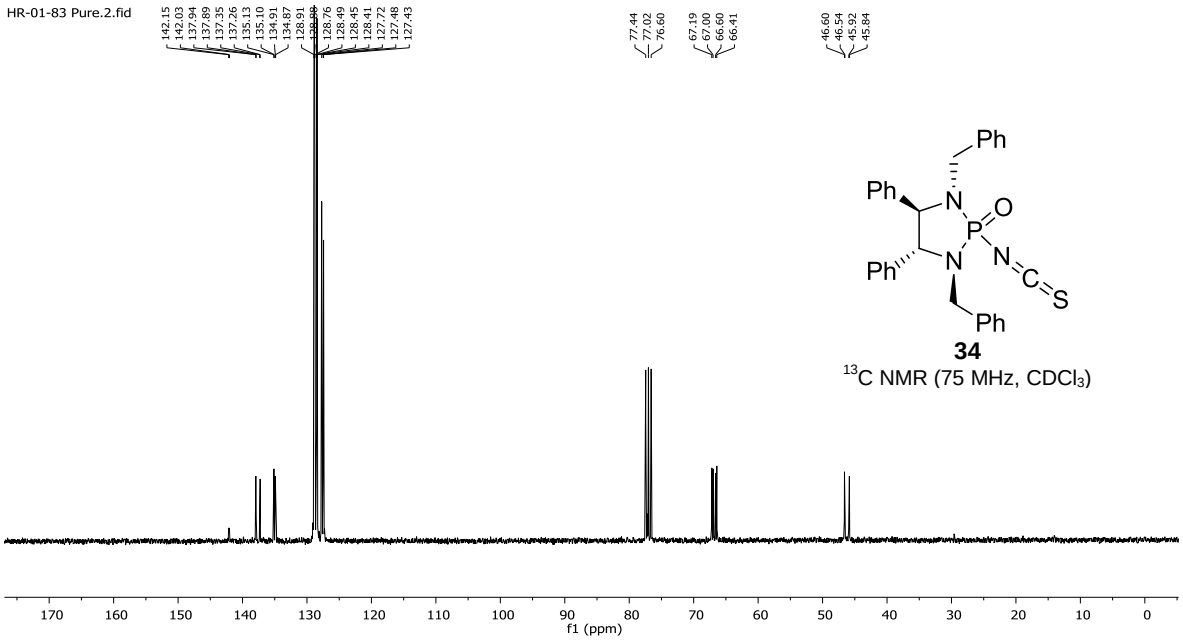
43

^{13}C NMR (75 MHz, $CDCl_3$)



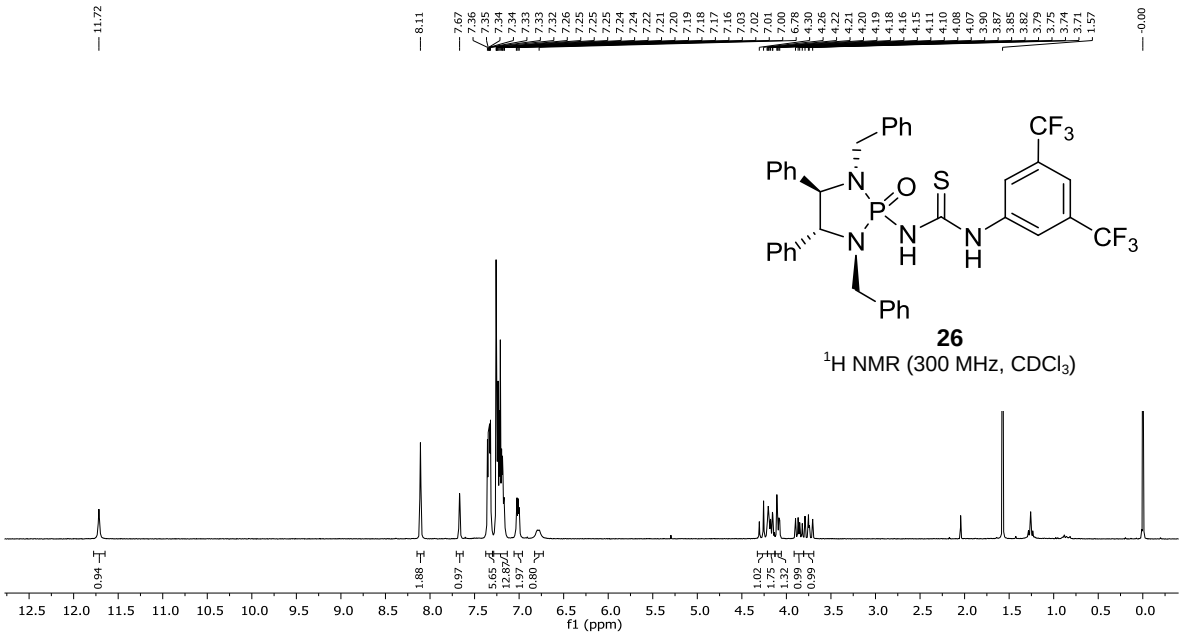
34

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



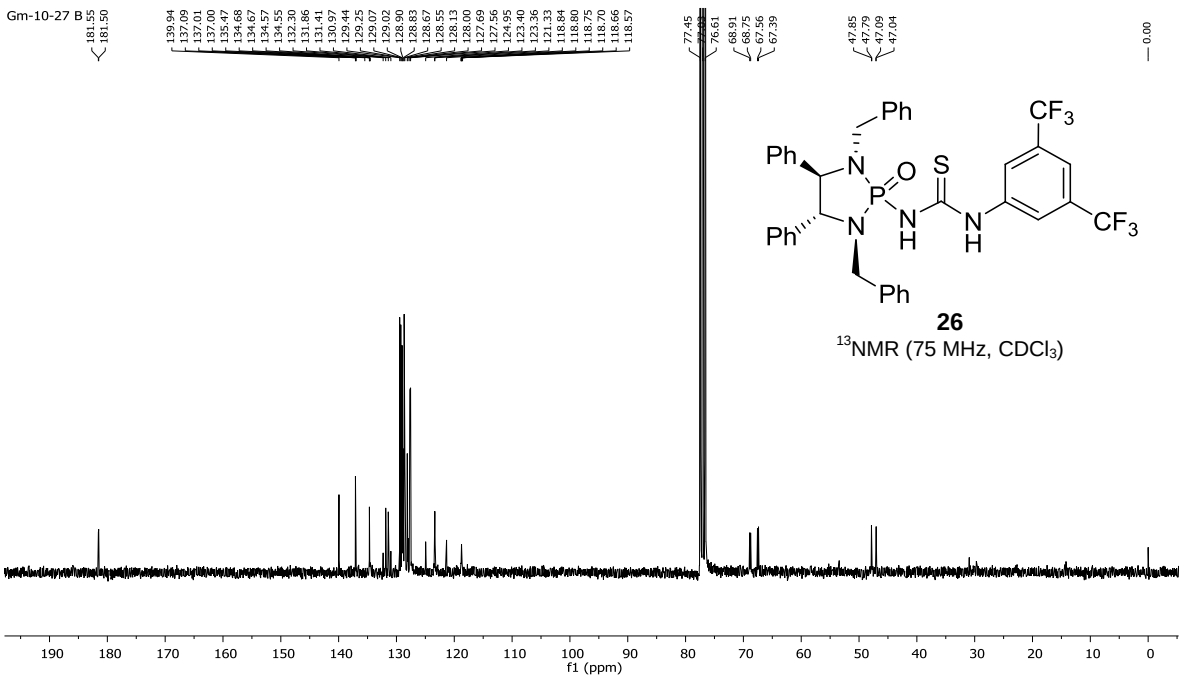
34

^{13}C NMR (75 MHz, $CDCl_3$)



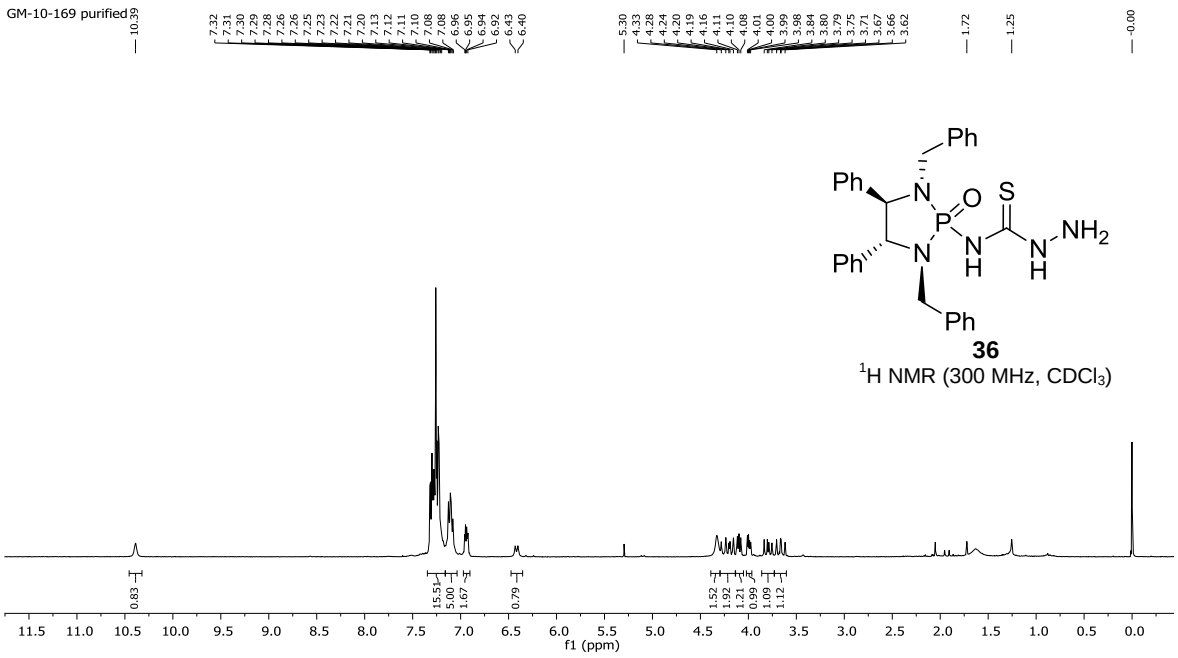
26

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



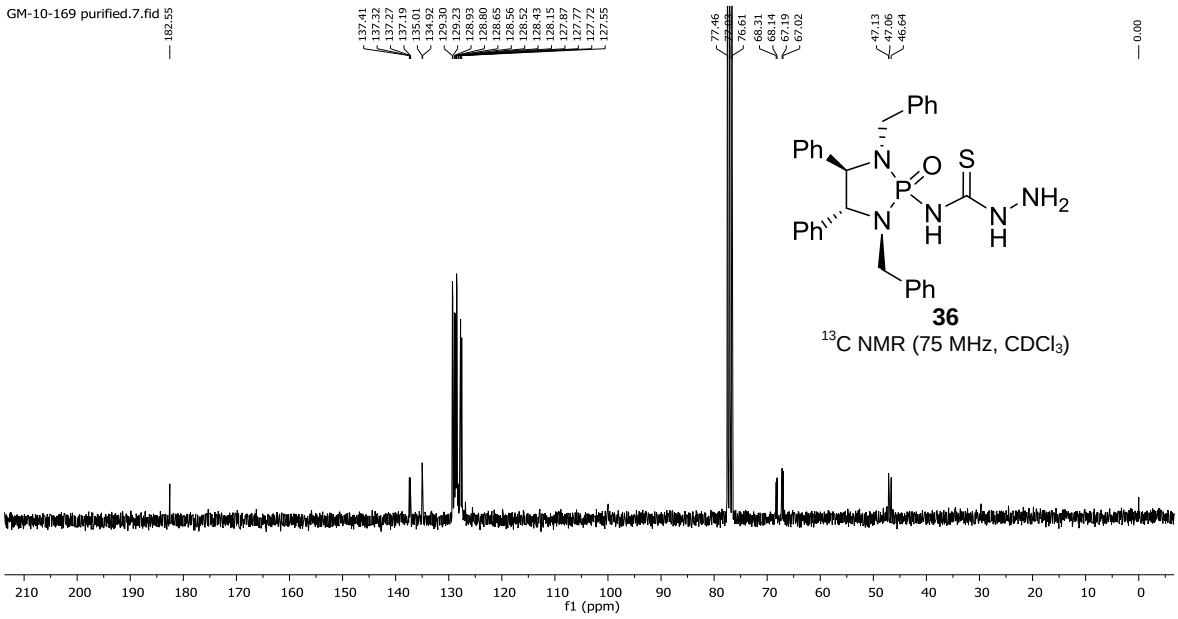
26

^{13}NMR (75 MHz, $CDCl_3$)



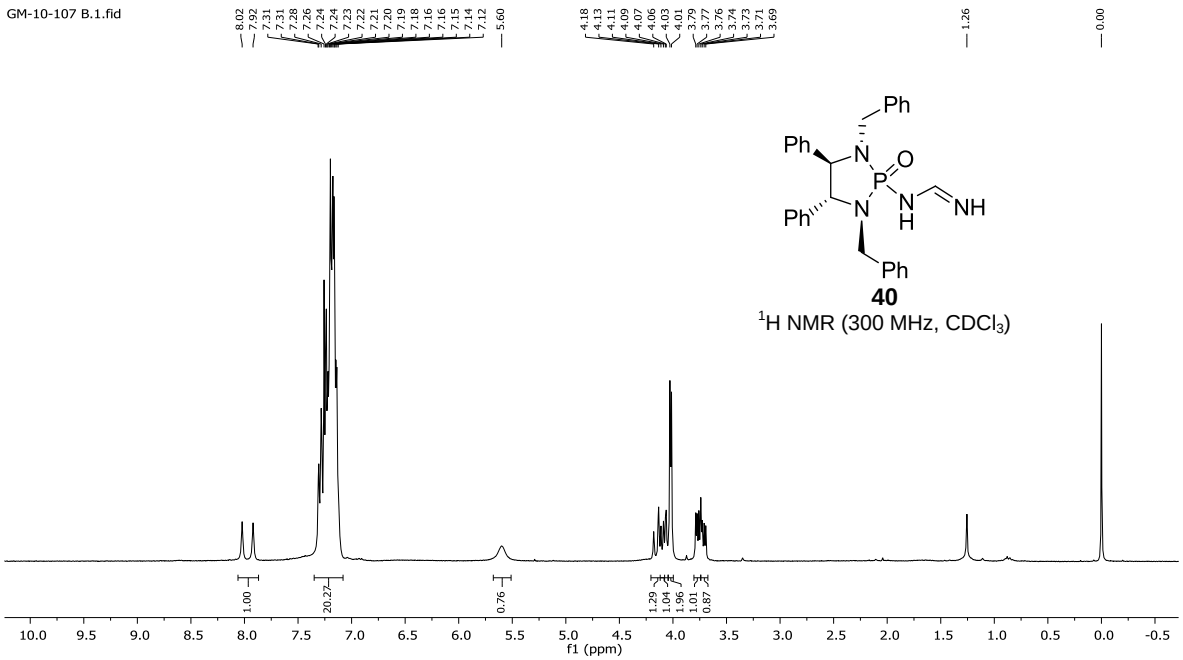
36

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



36

^{13}C NMR (75 MHz, $CDCl_3$)


GM-10-107 B.1.fid
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7.92
7.31
7.31
7.28
7.26
7.24
7.24
7.23
7.22
7.21
7.20
7.19
7.18
7.16
7.16
7.15
7.14
7.12
5.60
4.18
4.13
4.11
4.09
4.07
4.06
4.03
4.01
3.79
3.77
3.76
3.74
3.73
3.71
3.69
1.26
0.00
Ph
Ph
N
O
P
N
H
NH
Ph
N
Ph
40
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20.27
0.76
1.29
1.04
1.96
1.01
0.87
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9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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3.0
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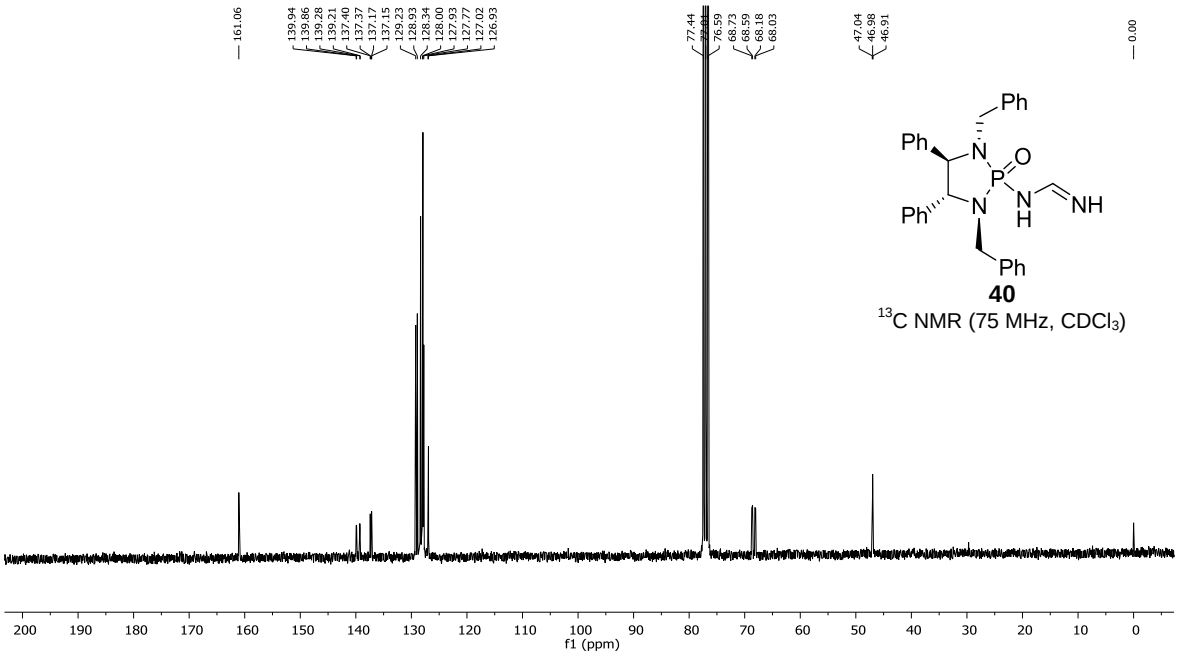
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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68.59
68.18
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200
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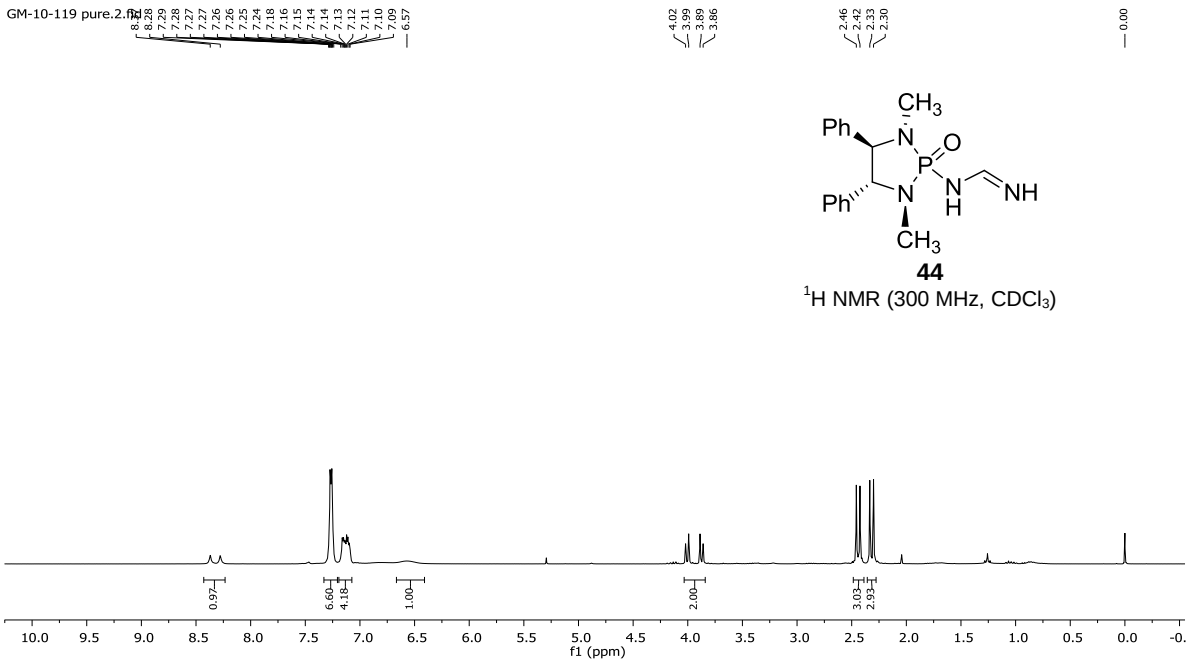

44

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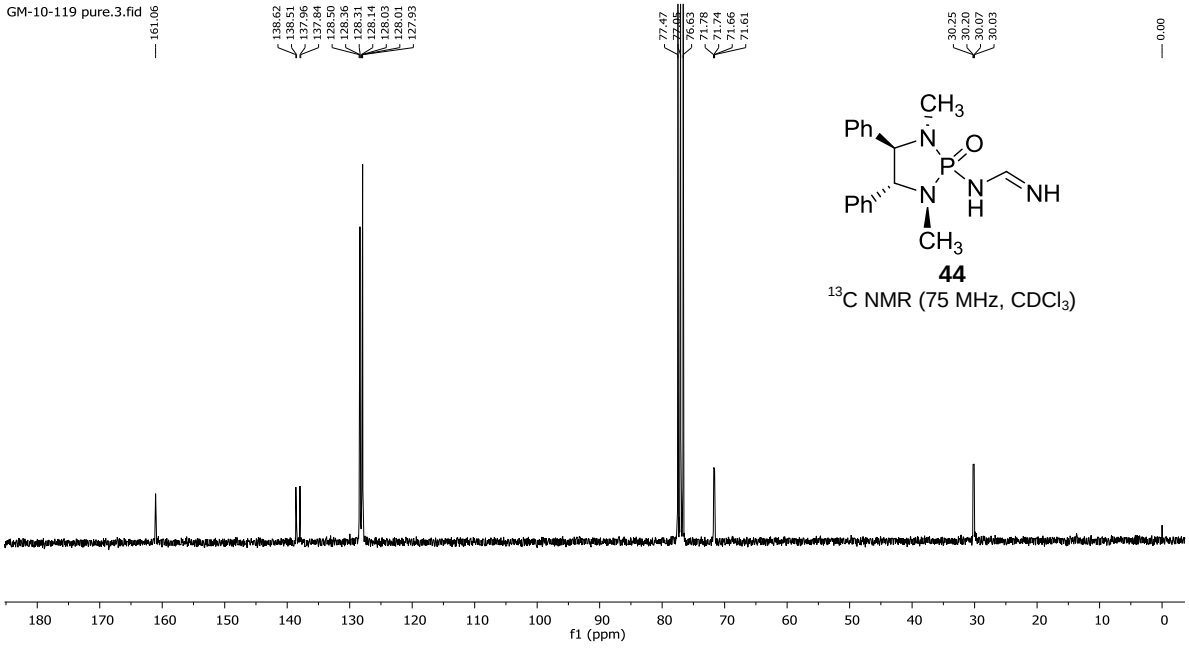

44

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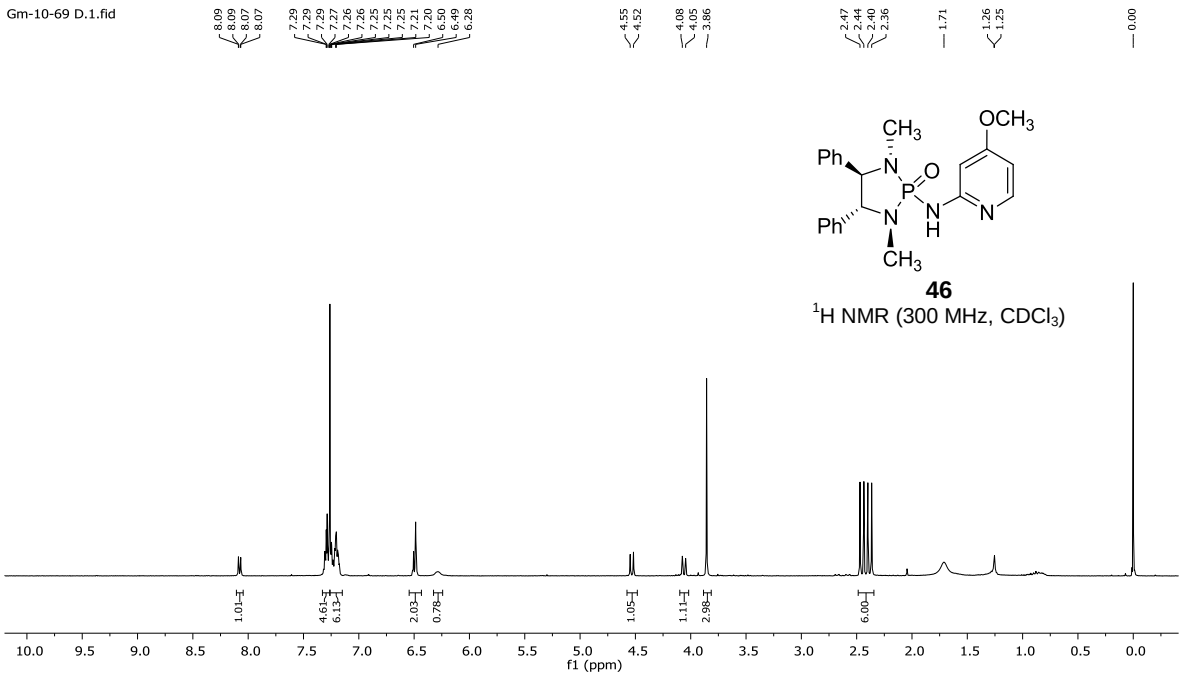

46

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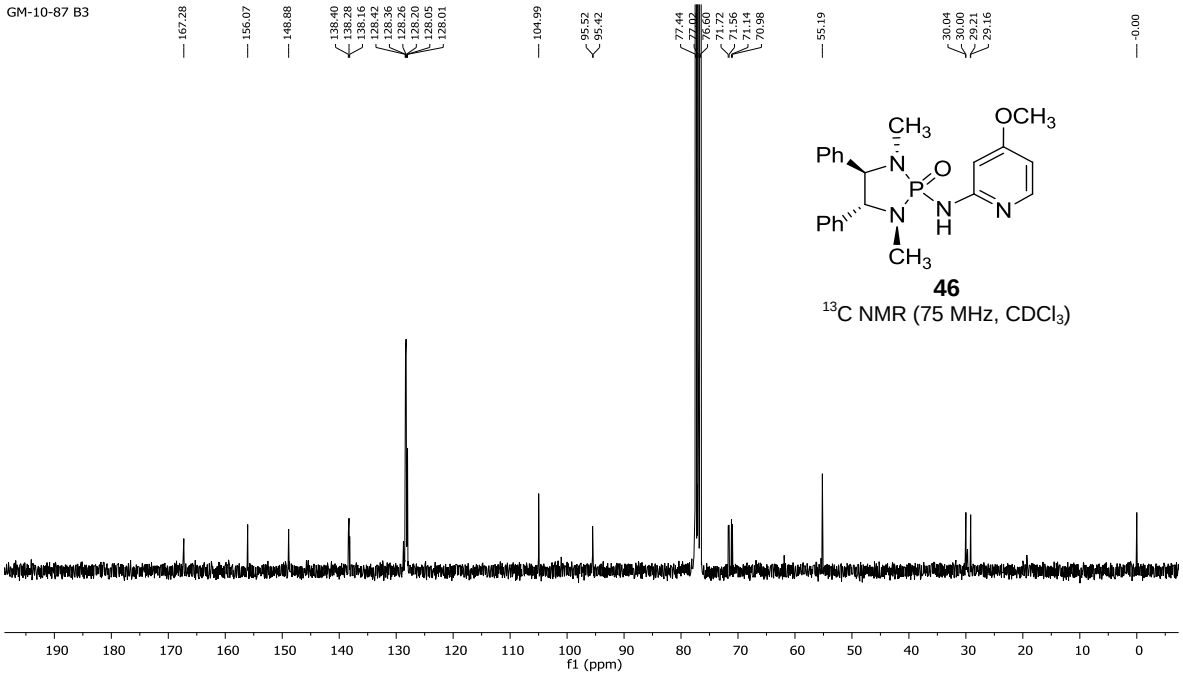

46

^{13}C NMR (75 MHz, $CDCl_3$)

Memorial University

Project Name Gopinathan

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

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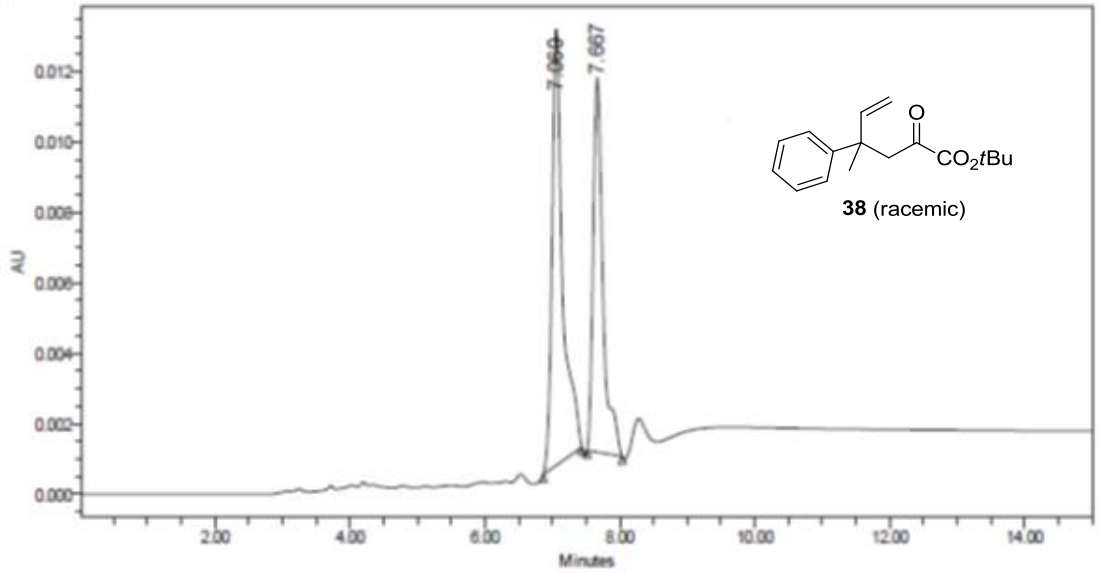
Sample Type:	Unknown	Date Acquired:	08/09/2016 4:01:43 PM NDT
Vial:	1	Acq. Method:	AD_H 99_6% Hex 0_4% IPA
Injection #:	1	Date Processed:	08/09/2016 4:18:02 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	15.00 Minutes	Sample Set Name	



38 (racemic)

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Report Method: Untitled

Page: 1 of 1

Printed: 26/09/2016

10:30:16 AM Canada/Newfoundland

Memorial University

Project Name Gopinathan

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

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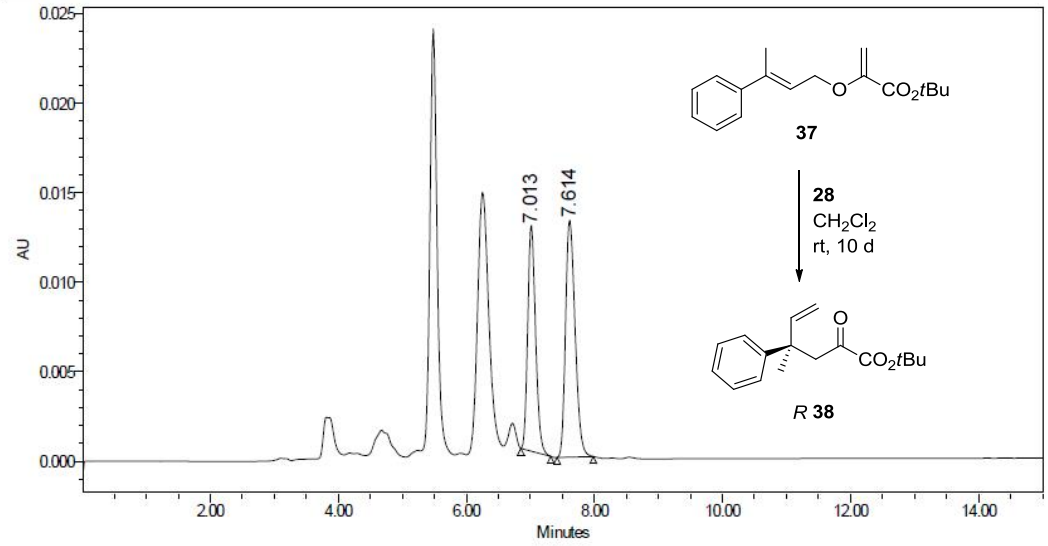
Run Time:	15.00 Minutes	Sample Set Name	



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Report Method: Untitled

Page: 1 of 1

Printed: 20/02/2019

1:23:34 PM Canada/Newfoundland

Memorial University

Project Name Gopinathan

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

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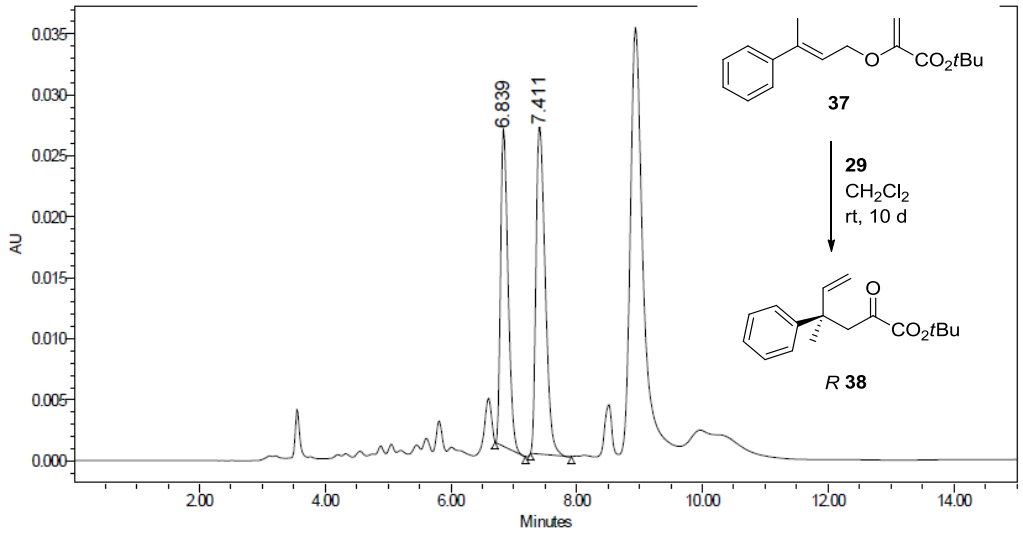
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	15.00 Minutes	Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	6.839	215298	44.01	26122	49.29
2	7.411	273857	55.99	26876	50.71

Chapter 3

Stereoselective Synthesis of *E*-3-(Arylmethylidene)-5-(Alkyl/Aryl)-2(3*H*)-Furanones by Sequential Hydroacyloxylation-Heck Reaction of Iodoalkynes

A portion of the work described in this chapter has been published in *Organic & Biomolecular Chemistry*:

Muthusamy, G.; Pansare, S. V. *Org. Biomol. Chem.* **2018**, *16*, 7971-7983.

Contributions of authors

Muthusamy, G: experimental work, manuscript preparation.

S. V. Pansare: research supervisor, manuscript preparation.

3.1 Introduction

The 3-(arylidene/alkylidene)-5-(aryl/alkyl) 2(3*H*)-furanone motif is encountered in several natural products and biologically relevant molecules.[1a] Representative examples of such furanones are the protein kinase inhibitor BE-23372M (**1**, Figure 3.1)[2] isolated from *Rhizoctonia* strain F23372, furanone **2** (*Z* isomer of **1**)[3] and ralfuranone I (**3**).[4] The related 3-alkylidene 2(3*H*)-furanone motif (unsubstituted at C5) also occurs as a component of terpenoid natural products such as peronemin D_1 (**4**)[5] and guttoside (**5**).[6] Other *E*-3-(arylidene/alkylidene)-5-(aryl/alkyl) furanones have attracted significant interest due to their interesting biological profile which includes antitubercular (inhibition of Mycobacterium sulfotransferase),[7] antimalarial (selective inhibition of falcipain-2),[8] analgesic[9] and anti-inflammatory[10] activity. In addition, 2(3*H*)-furanones are useful starting materials for the synthesis of a variety of oxacycles[11] and azacycles.[12]

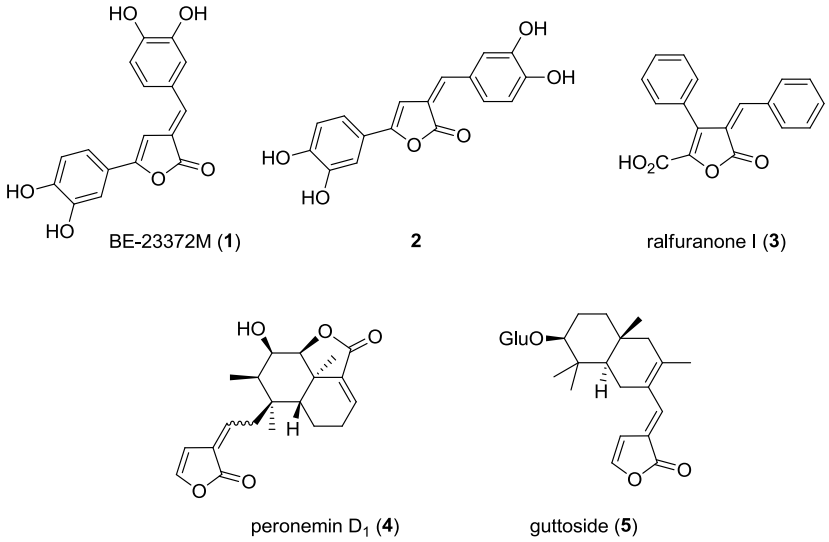


Figure 3.1. Naturally occurring 3-(arylidene/alkylidene)-5-(aryl/alkyl) furanones

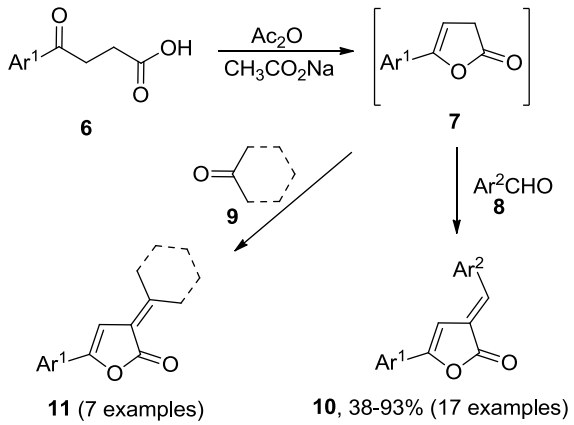
Given their natural occurrence and biological activity, the synthesis of 3-(arylidene/alkylidene)-5-(aryl/alkyl) furanones is of interest, but only a handful of

methods are currently available. The following sections provide a summary of the reported syntheses of 3- (arylidene/alkylidene)-5-(aryl/alkyl) furanones.

3.2 Known syntheses of *E*-3-(aryl/alkyl)-5-(aryl/alkyl)-2(3*H*)-furanones

3.2.1 The Perkin-Erlenmeyer synthesis of 2(3*H*)-furanones

The classical approach for the synthesis of 2(3*H*)-furanones involves condensation of γ-keto acids with aldehydes or ketones under Perkin-Erlenmeyer reaction conditions.[1] Acids **6** were subjected to lactonization in the presence of sodium acetate and acetic anhydride to give lactones **7**. Subsequent condensation of lactones **7** with aldehydes **8**[1b] or ketones **9**[1c] afforded the furanones **10** or **11** (scheme 3.1).

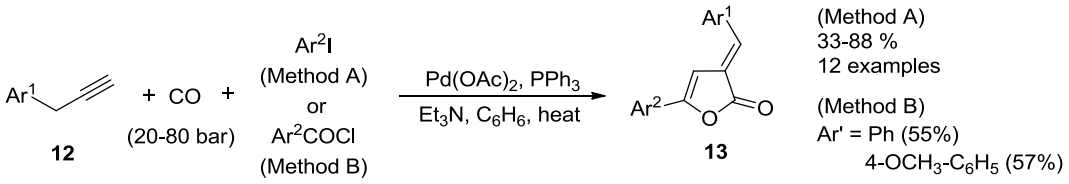


Scheme 3.1

3.2.2 The Alper synthesis of 2(3*H*)-furanones

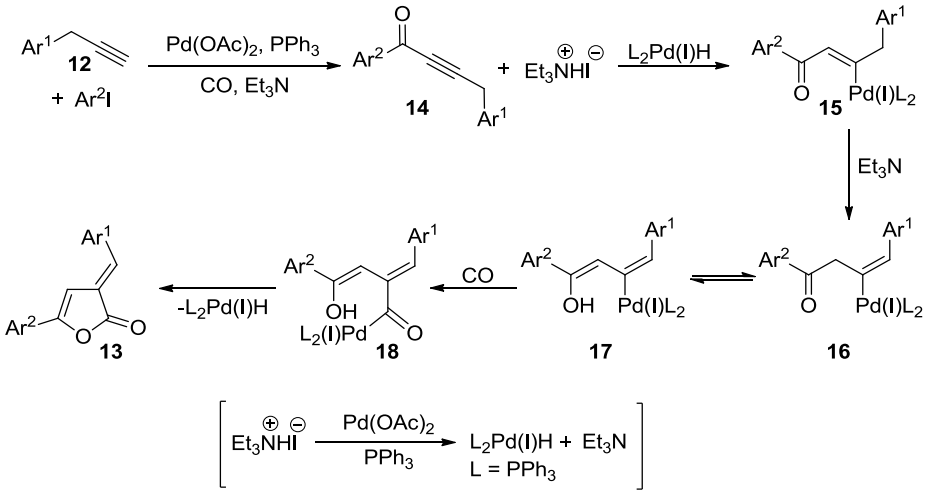
In 1991, Alper and co-workers[13] introduced a methodology for the synthesis of furanones **13** from benzyl acetylenes **12**. Their strategy relies on cyclocarbonylation of benylacetylenes **12** with aryl halides or acid chlorides in the presence of $Pd(OAc)_2$ and

CO gas under high pressure (20-80 bar) to provide furanones **13** in low to moderate yields (Scheme 3.2).



Scheme 3.2

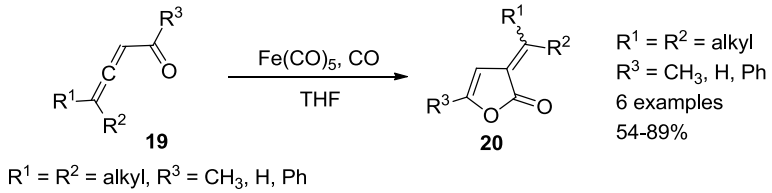
A mechanism has been proposed for the carbonylation method (Scheme 3.3). In the initial step, a carbonylative cross-coupling reaction of the aryl halide with benzyl acetylene **12** affords the alkynone **14**. Addition of palladium hydride to **14** provides **15** which isomerizes to **16** (Pd and the aryl group *trans* to minimize steric interactions) in the presence of Et_3N. Enolization of **16** provides **17** which undergoes carbonylation to provide **18** which cyclizes to **13** with concomitant reductive elimination to regenerate the Pd catalyst (Scheme 3.3).



Scheme 3.3

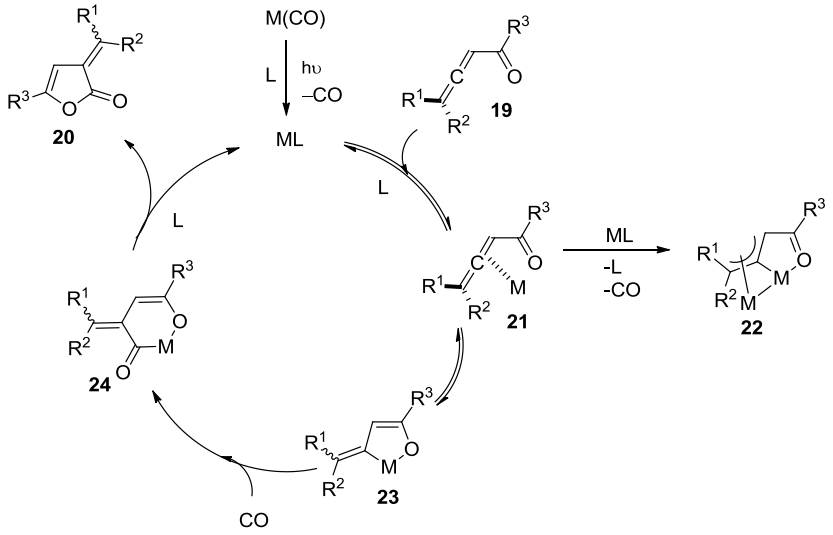
3.2.3 The Eaton synthesis of 2(3*H*)-furanones

In 1993, Eaton and co-workers[14] reported the synthesis of 2(3*H*)-furanones. The synthesis relies on the photochemical [4+1] reactions of allenyl ketones **19** with CO in the presence of $Fe(CO)_5$ as the catalyst to afford the furanones **20** as a mixture of *E* and *Z* isomers (Scheme 3.4).



Scheme 3.4

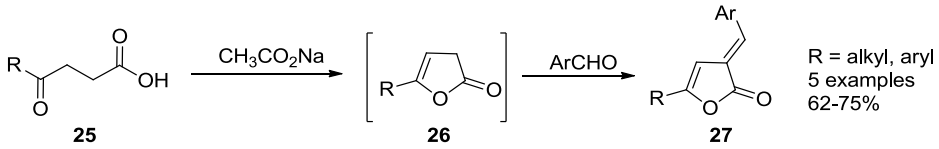
A mechanism has been proposed for the [4+1] reaction (Scheme 3.5). Photolysis of M(CO) (M = metal) results in loss of CO and generation of the active catalyst ML (L = solvent). Complexation of ML with **19** provides **21**, which is in equilibrium with **23**. Carbonylation of **23** provide **24** which furnishes the furanones **20** by a reductive elimination process. Irradiation of **19** (where $R^1 = R^2 = R^3 = CH_3$) at lower energy (λ = 350 nm) gave the products **20** in 86% yield whereas irradiation at higher energy (λ = 254 nm) provided **20** in 50% yield. The authors state that the higher energy irradiation of **19** could generate a greater concentration of the catalytic species ML which reacts with the intermediate **21** to provide catalytically inactive metal clusters **22** (Scheme 3.5).



Scheme 3.5

3.2.4 The Yu synthesis of 2(3*H*)-furanones

In 1997, Yu and co-workers[15] reported the synthesis of furanones **27** from 4-oxoalkanoic acids **25**. Lactonization of acids **25** in the presence of sodium acetate provided the lactones **26**. Subsequent aldol condensation of **26** with aldehydes afforded the furanones **27** in 62-75% yield (Scheme 3.6).



Scheme 3.6

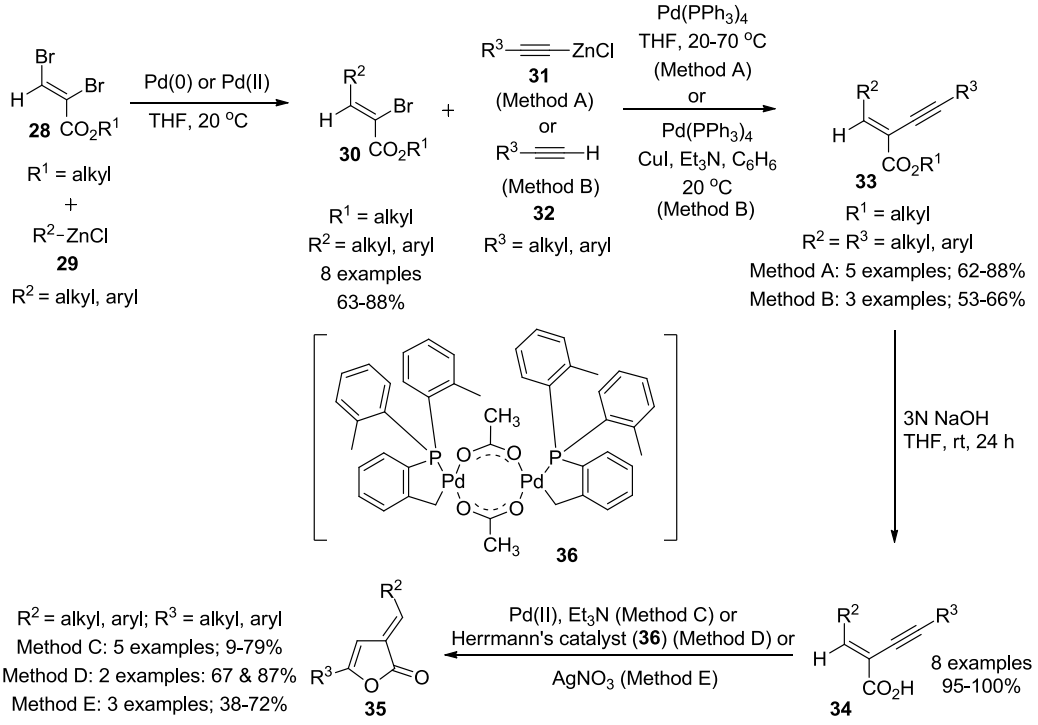
3.2.5 The Rossi synthesis of 2(3*H*)-furanones

In 1998, Rossi and co-workers[16] reported the synthesis of *E*-3-(aryl/alkyl)-5-(aryl/alkyl)-2(3*H*)-furanones **35** from (*Z*)-2,3-dibromopropenoates **28**. The synthesis starts with regio and stereoselective Negishi cross-coupling reactions of 2,3-

dibromopropenoates **28** with alkylzinc chlorides **29** to provide the mono cross-coupled products **30**. Enynes **33** were obtained from Negishi cross-coupling reactions of **30** with **31** (Method A) or Sonogashira cross coupling reactions of **30** with **32** (Method B) as shown in Scheme 3.7. Hydrolysis of **33** afforded the acids **34**.

Furanones **35** were prepared from **34** by employing three different methods (Scheme 3.7). Intramolecular oxypalladation of acids **34** in the presence of $PdCl_2(PhCN)_2$ provided the furanones **35** in low to moderate yields (Method C).

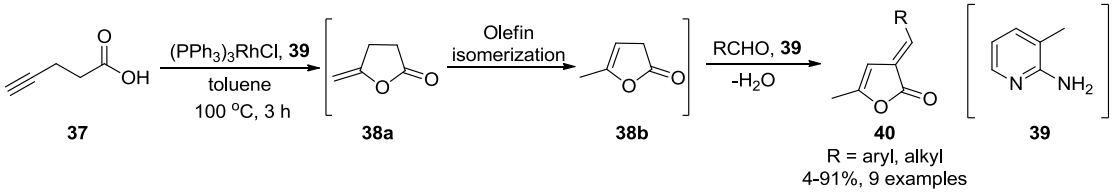
Alternatively, reaction of **34** in the presence of Herrmann's catalyst (**36**) afforded **35** in moderate yields (Method D). In the third procedure, the acids **34** were subjected to cyclization in the presence of $AgNO_3$ to provide the furanones **35** in low to moderate yields (Method E) (Scheme 3.7).



Scheme 3.7

3.2.6 The Jun synthesis of 2(3*H*)-furanones

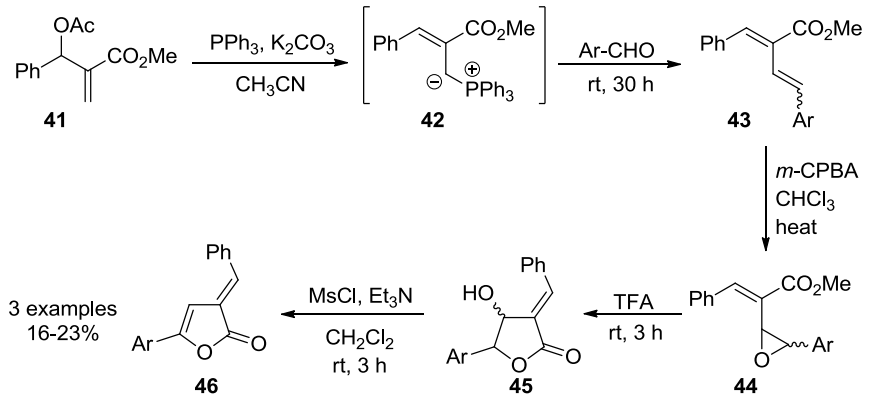
In 2005, Jun and coworkers[17] developed a methodology to synthesize furanones **40** from 4-pentynoic acid **37**. The acid **37** reacted with aldehydes in the presence of Wilkinson's catalyst ($(PPh_3)_3RhCl$) and 2-amino-3-picoline (**39**) to provide the furanones **40** in low to excellent yields (Scheme 3.8). Acid **37** undergoes lactonization in the presence of $(PPh_3)_3RhCl$ catalyst to provide **38a**. Olefin isomerization in **38a** and subsequent aldol condensation with aldehydes affords furanones **40**.



Scheme 3.8

3.2.7 The Kim synthesis of 2(3*H*)-furanones

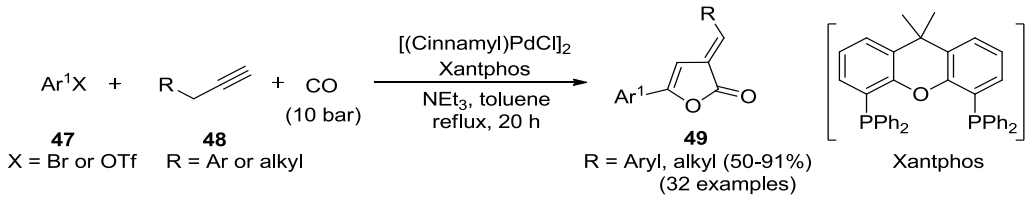
In 2007, Kim and co-workers[18] reported a synthesis of furanones **46** from Baylis-Hilman adducts **41**. In this methodology, ylide **42** was generated *in situ* from the Baylis-Hilman adduct **41**. Subsequent Wittig reactions of **42** with aryl aldehydes afforded the dienes **43**. Epoxidation of **43** with *m*-CPBA gave **44** which provided the hydroxy lactones **45** upon treatment with TFA. The lactones **45** were dehydrated, by elimination of the corresponding mesylates, to furnish the furanones **46** in low yields (Scheme 3.9).



Scheme 3.9

3.2.8 The Beller synthesis of 2(3*H*)-furanones

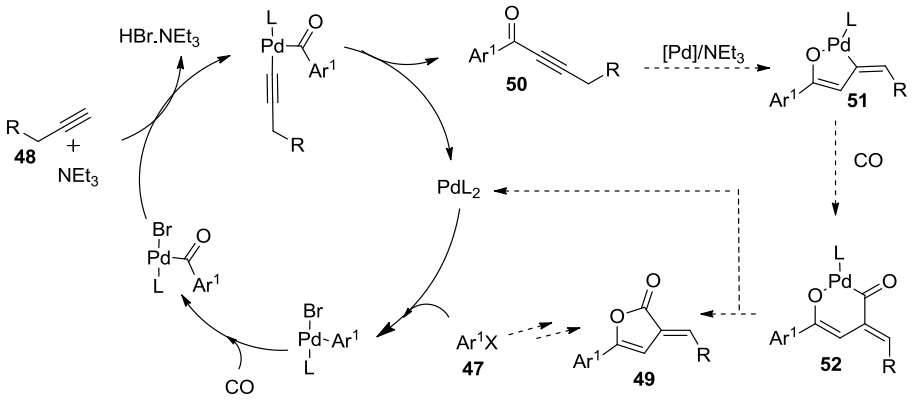
In 2011, Beller and coworkers[19a] modified the Alper carbonylation method (Scheme 3.2) in a synthesis of furanones **49**. Carbonylative cross-coupling reactions of aryl halides or aryl triflates **47** with benzyl acetylenes **48** was performed under high pressure of CO (10 bar) in the presence of a Pd catalyst in refluxing toluene to afford the furanones **49** in moderate to good yields (Scheme 3.10).



Scheme 3.10

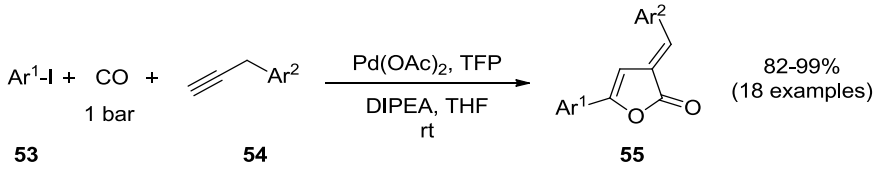
A mechanism has been proposed for the double carbonylation step (Scheme 3.11). Carbonylative Sonogashira cross coupling of aryl halides **47** with benzyl acetylenes **48** provide the alkynones **50**. Alkynones **50** react with Pd catalyst, and the resulting products

isomerize to give **51** (see Scheme 3.2). A second carbonylation of **51** furnish **52** which undergo reductive elimination to provide the furanones **49** (Scheme 3.11).



Scheme 3.11

In 2012, the same group reported[19b] a carbonylation method to synthesize the furanones **55** under mild reaction conditions that avoided the high pressure (of CO) as well as heating that was required in the earlier synthesis (Scheme 3.10). Thus, the carbonylative cross coupling of halides **53** with benzyl acetylenes **54** were conducted at ambient temperature in the presence a Pd catalyst and CO under atmospheric pressure to provide the furanones **55** in excellent yields (Scheme 3.12).



Scheme 3.12

3.3 Objective

As discussed in section 3.2, many of the known syntheses of *E*-3-(aryl/alkyl)-5-(aryl/alkyl)-2(3*H*)-furanones utilize toxic CO gas as a reagent. Some of the other reported procedures are limited by the multiple steps required or a narrow substrate scope for the furanone synthesis. Our objective was to develop a methodology for the stereoselective synthesis of *E*-3-(aryl/alkyl)-5-(aryl/alkyl)-2(3*H*)-furanones under mild reaction conditions, which could overcome the above limitations.

Our strategy for the synthesis of 2(3*H*)-furanones relies on the subsequent intramolecular *E*-selective Mizoroki-Heck reaction of iodoenol acrylates which, in turn, can be obtained by the *Z*-selective addition of cinnamic acids to iodoacetylenes (Figure 3.2).

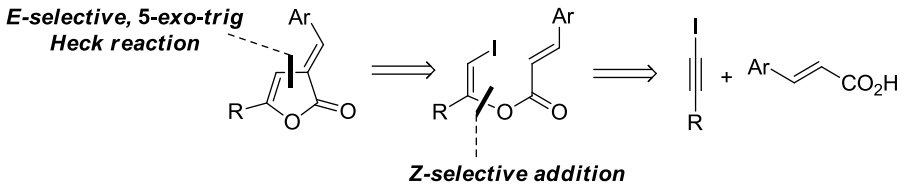
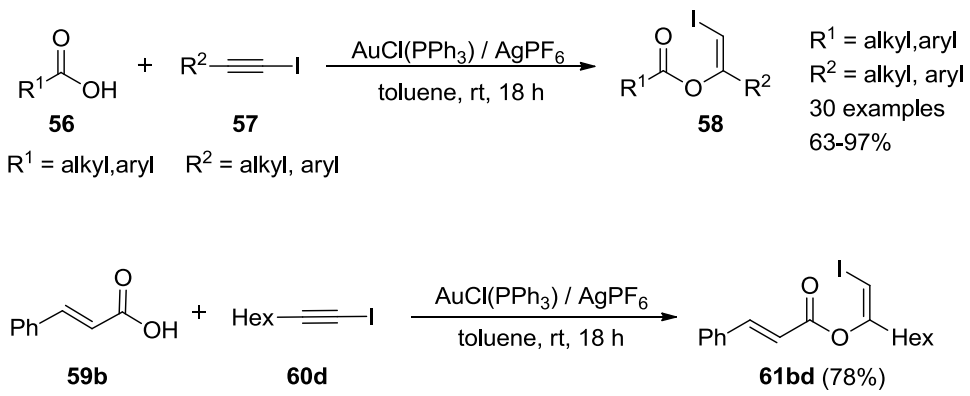


Figure 3.2 Two-step synthesis of 2(3*H*)-furanones from iodoacetylenes and cinnamic acids

A brief analysis of the individual stereoselective steps proposed in our retrosynthetic analysis is instructive. It may be noted that extensive studies on the regioselective addition of carboxylic acids to haloacetylenes are available,[20a-d] but a *Z*-selective version of this reaction employing either aliphatic or substituted benzoic acids as nucleophiles was reported only recently.[20e]

In 2017, Cadierno and coworkers[20e] reported the regio and stereoselective synthesis of (*Z*)-*β*-iodoenol acrylates from iodoacetylenes. Intermolecular addition of carboxylic acids **56** to iodoacetylenes **57** in the presence of $(PPh_3)_3AuCl/AgPF_6$ afforded iodoenol acrylates **58** in good yields (Scheme 3.13). The authors also reported a sole example of the addition of a cinnamic acid to an iodoacetylene in which the (*Z*)-*β*-iodoenol acrylate **61bd** was prepared from cinnamic acid **59b** and iodoacetylene **60d**. However, other than compound **61bd**, the scope of the addition of *α*,*β*- unsaturated acids to iodoacetylenes was not examined.



Scheme 3.13

Also, even though intramolecular Mizoroki-Heck reactions[21] of aryl halides are well known, the corresponding version involving vinyl halides is less well known. In addition, the stereochemical outcome (formation of *E* or *Z* products)[22] and the regiochemistry (5-*exo*-*trig* vs 6-*endo*-*trig*)[23] of the proposed intramolecular Mizoroki-Heck reaction can vary with substrate structure and the reaction conditions (Figure 3.3).

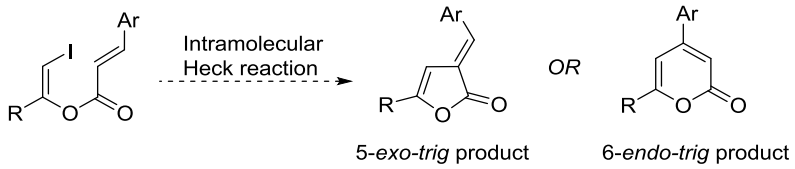


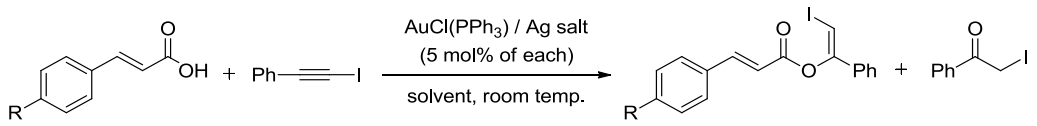
Figure 3.3 Regiochemistry of intramolecular Heck reaction of (*Z*)-*β*-iodoenol acrylate

3.4 Results and Discussion

Our studies began with an investigation of the Au(I)-catalyzed addition of 4-methoxy cinnamic acid (**59a**) to (iodoethynyl)benzene (**60a**) to provide the iodoenol cinnamate **61aa**. Although previous studies on related reactions had employed Au(I)-based catalytic systems,[20] the combination of reactants that we wanted to examine (cinnamic acids and aryl- or alkyl-substituted iodoacetylenes), and the scope of this reaction, had not been studied previously, Nonetheless, we first investigated a combination of $AuCl(PPh_3)$ and $AgPF_6$ in toluene, conditions that are reported to efficiently catalyze the addition of aliphatic carboxylic acids to iodoalkynes.[20e] Although this reaction worked when **59a** and **60a** were used, the yield of **61aa** was disappointing (38%, entry 1, Table 3.1). Significant amounts of unreacted **60a** and the iodomethyl ketone **62a**, derived from the iodoacetylene **60a**, were also obtained in this reaction. Since **62a** could have been formed by the hydrolysis of **61aa** due to adventitious moisture in the toluene, we examined anhydrous toluene as the solvent. Surprisingly, this decreased the yield of **61aa** (Table 3.1, entry 2, 24%) but the amount of **62a** was only marginally affected. Clearly, a survey of additives and solvents for the reaction of **59a** and **60a** was necessary and, accordingly, a combination of $AuCl(PPh_3)$ and selected silver salts was

examined in toluene as the solvent. Unfortunately, the use of AgOTf or $AgSbF_6$ as the co-catalysts did not improve the yield of **61aa** even after extended reaction times (entries 3 and 4, Table 3.1). These observations prompted a survey of solvents for the reaction with the $AuCl(PPh_3)/AgPF_6$ catalytic system. The reaction failed when DMF or acetonitrile was used (entries 5 and 6, Table 3.1) as the solvent and ethereal solvents significantly slowed the reaction to provide **61aa** in very low yield (6% and 8%, entries 7 and 8, Table 3.1). Notably, significant decomposition of **60a** was also observed in these reactions (only 17% and 21% of **61aa** based on recovery of **60a**). Although a similar trend was also observed in dichloromethane (entries 9 and 10, Table 3.1), the use of chloroform as the solvent was beneficial (**61aa** (70%) and **62a** (10%) entry 11, Table 3.1). As was observed for the reactions with anhydrous toluene, the use of anhydrous chloroform was also not beneficial (68% yield of **61aa**). We also ascertained that the reaction required both $AuCl(PPh_3)$ and $AgPF_6$ (entries 13 and 14, Table 3.1) and that it was not catalyzed by protic acids in the absence of $AuCl(PPh_3)/AgPF_6$ (entries 15 and 16, Table 3.1). Thus, the optimum conditions for preparing **61aa** involve the use of $AuCl(PPh_3)/AgPF_6$ in $CHCl_3$ at ambient temperature. These conditions also provided **61ba** (83%, entry 17, Table 3.1) from the reaction of **60b** and **59a**.

Table 3.1. Optimization of hydroacyloxylation of **60a**



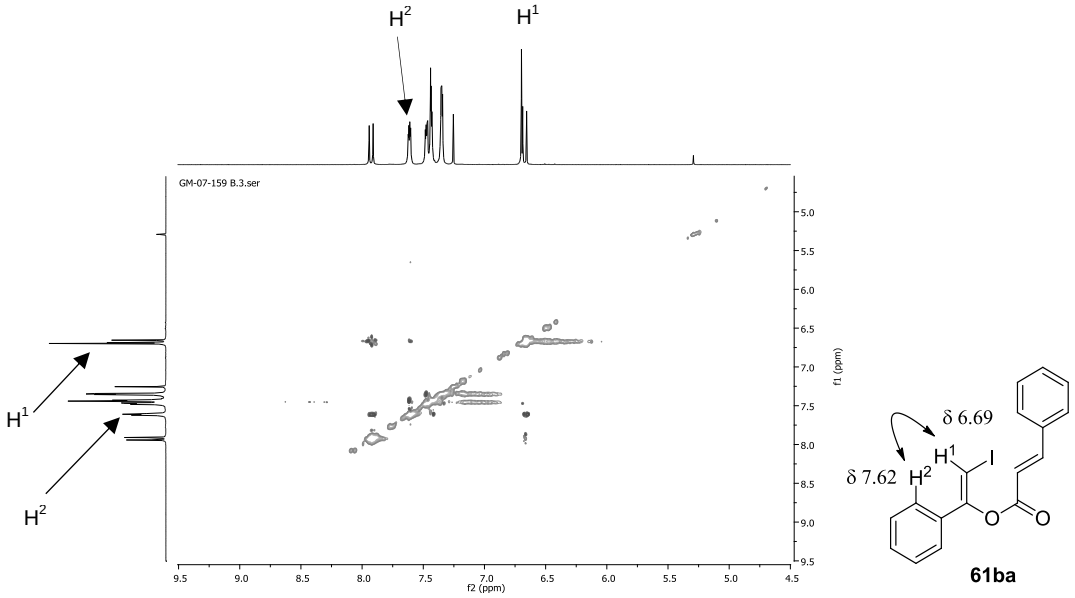
Entry	Solvent	Additive	Time (h)	61aa (%)	60a (% unreacted)	62a (%)
1	toluene	$AgPF_6$	76	38 (47)[a]	18	20
2	dry toluene	$AgPF_6$	76	24 (36)[a]	29	17
3	toluene	AgOTf	62	29 (38)[a]	24	28
4	toluene	$AgSbF_6$	62	25 (37)[a]	25	21
5	DMF	$AgPF_6$	75	-		-
6	dry CH_3CN	$AgPF_6$	75	-		-
7	dioxane	$AgPF_6$	120	6 (17)[a]	44	4
8	dry THF	$AgPF_6$	144	8 (21)[a]	60	7
9	dry CH_2Cl_2	$AgPF_6$	1	16 (26)[a]	37	11
10	dry CH_2Cl_2[b]	$AgPF_6$	4	12 (25)[a]	50	9
11	$CHCl_3$	$AgPF_6$	23	70	-	10
12	dry $CHCl_3$	$AgPF_6$	23	68	-	8
13	$CHCl_3$[c]	$AgPF_6$	72	-		-
14	$CHCl_3$	-	70	-		-
15	$CHCl_3$[d]	CF_3CO_2H	75	-		-
16	$CHCl_3$[d]	CH_3SO_3H	75	-		-

17	$CHCl_3$	$AgPF_6$	37	83[e]	-

[a]Yield based on recovered **60a**. [b]Reaction at 0 [o]C. [c]reaction without $AuCl(PPh)_3$.

[d]Reaction without $AuCl(PPh_3)$ and Ag salt. [e]Yield of **61ba**.

The stereochemistry of **61aa** and **61ba** was confirmed by NOESY (interaction of the iodomethylidene hydrogen (H^1) and the *ortho* hydrogen (H^2) of the adjacent phenyl ring as shown in the Figure 3.4).



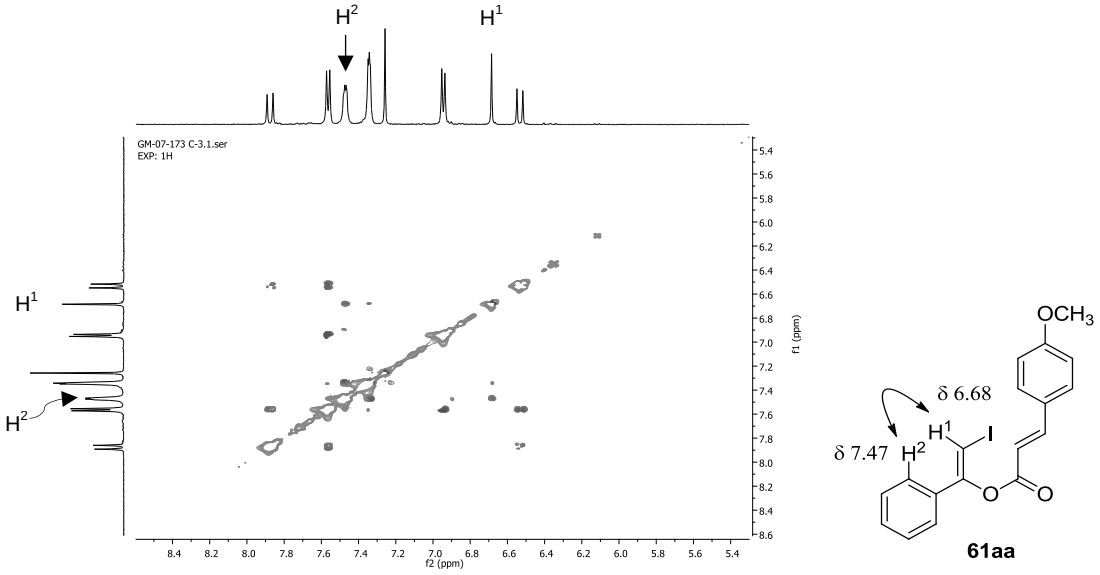
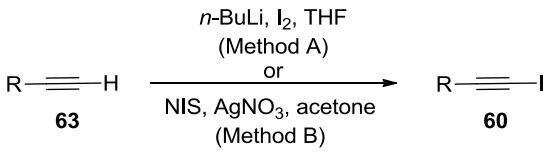
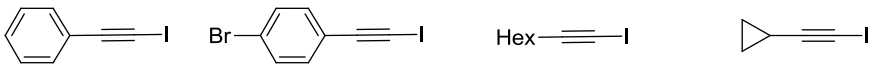


Figure 3.4 ^{1}H-^{1}H NOESY spectrum for **61ba** and **61aa**

A series of iodoacetylenes were synthesized from acetylenes (Figure 3.5) or aldehydes (Figure 3.6) in order to explore the substrate scope of the hydroacyloxylation reactions. Iodoacetylenes (**60a**, **60b**, **60d** and **60f**) were synthesized from corresponding acetylene derivatives **63** using method A or method B as shown in Figure 3.5.





60a (90%) (Method A) | **60b** (73%) (Method B) | **60d** (93%) (Method A) | **60f** (91%) (Method A)

Figure 3.5 Synthesis of iodoacetylenes from acetylenes

A few other iodoacetylenes (**60c**, **60e**, **60g**, **60h**) were synthesized from the corresponding aldehydes using Corey-Fuchs reactions (Figure 3.6). Bromination of aldehydes **64** with tetrabromomethane in the presence of PPh_3 afforded the dibromo compounds **65**. Sequential treatment of **65** with *n*-BuLi and iodine provided iodoacetylenes **60** (Figure 3.6).

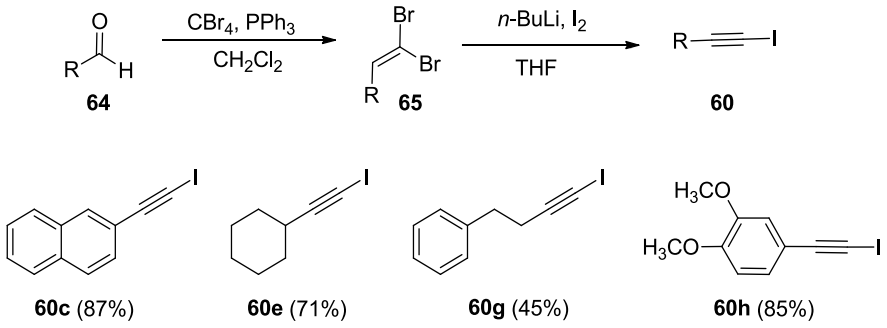


Figure 3.6. Synthesis of iodoacetylenes from aldehydes

To our delight, a variety of *Z*-*β*-iodoenol acrylates were synthesized from hydroacyloxylation of acids **59** to iodoacetylenes **60** (Figure 3.7) using the optimized reaction conditions. In all these reactions, a minor amount of iodomethyl ketones **62** (~10%) always accompanied the desired product **61**.

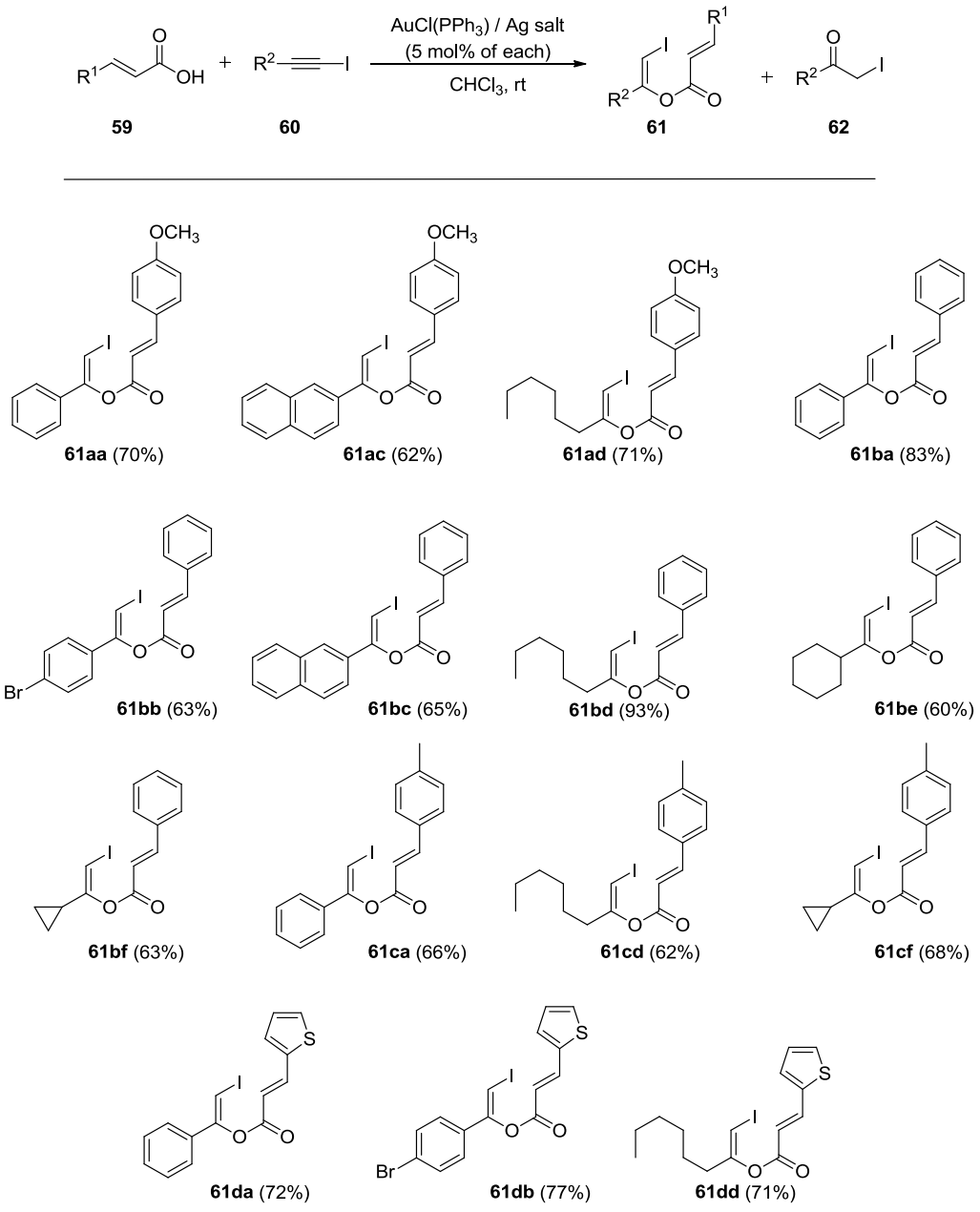
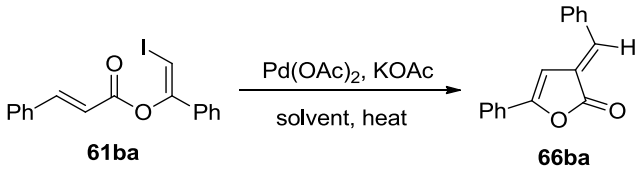


Figure 3.7. Hydroacyloxylation of **60**

With the *Z*-*β*-iodoenol acrylates **61** in hand, their intramolecular Heck reactions were examined to achieve the target 2(3*H*)-furanones **66**. Since our objective was to develop an operationally simple, and preferably a one-pot procedure we initially chose to examine the reaction of **61ba** in the presence of $Pd(OAc)_2$ and KOAc in $CHCl_3$ or

toluene, since these solvents were suitable for the synthesis of **61ba**. However, the reaction of **61ba** in $CHCl_3$ provided **66ba** in very low yield (10%) and the reaction failed when toluene, toluene/H_2O or toluene/DMF were used as the solvents. Nonetheless, when the reaction was conducted in DMF as the solvent, **66ba** was obtained in an excellent yield (91%, Table 3.2).

Table 3.2. 5-*exo-trig* cyclization of **61ba** to **66ba**



61ba **66ba**

Entry	Solvent	Temp (˚C)	Time (h)	Yield (%)[a]
1	$CHCl_3$	61	5	10
2	toluene/H_2O	100	5	-
3	toluene/H_2O (3/1)	100	2	-
4	toluene/DMF (1/1)	100	3	-
5	DMF	80	1	91

[a]10 mol% of $Pd(OAc)_2$

Notably, only the *E*-isomer of **66ba** was obtained and its spectroscopic data was in agreement with that reported in the literature.[19] The *E*-stereochemistry of the exocyclic double bond in **66ba** was also confirmed by a NOESY experiment in which the interaction of the C4 methine (H^1) and the *ortho* hydrogens of the phenyl rings (H^2 and H^3) in **66ba** was observed (Figure 3.8). In addition, none of the isomeric pyranone

product that would arise from the alternative 6-*endo-trig* cyclization (see Figure 3.3) of **61ba** was formed. The conversion of **61ba** to **66ba** is thus an example of an *E*-selective, 5-*exo-trig* Mizoroki-Heck reaction.

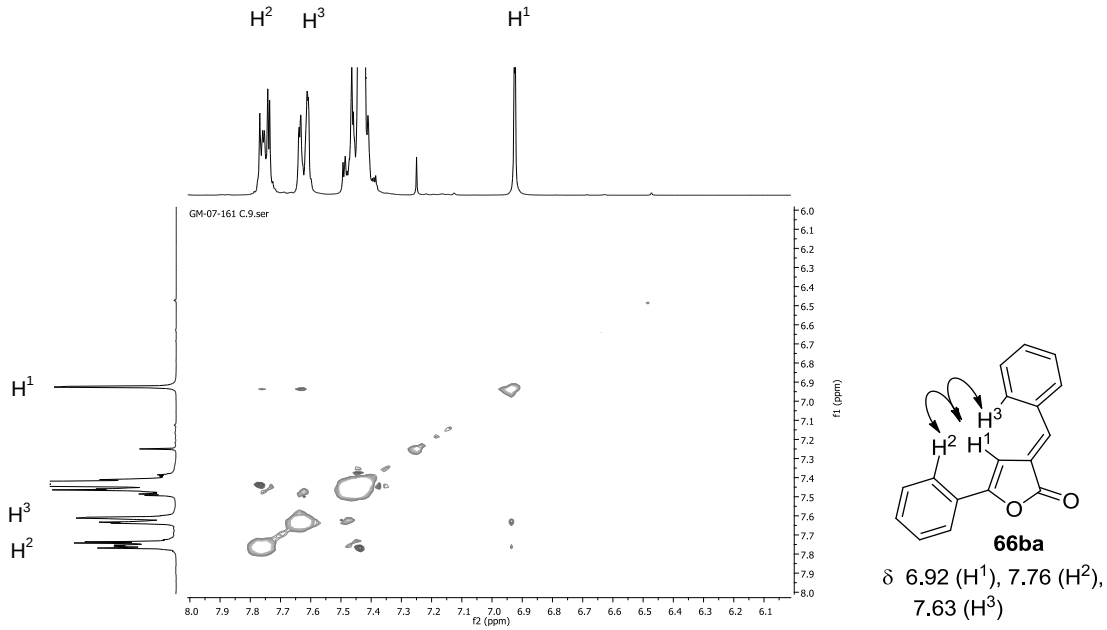


Figure 3.8. ^{1}H-^{1}H NOESY spectrum for **66ba**

Encouraged by the successful conversion of **61ba** to **66ba**, we further simplified the synthesis of **66ba** by developing a protocol which avoided the chromatographic purification of **61ba**. Thus, after the completion of the Au-catalyzed addition of **59b** to **60a** (TLC analysis), the reaction mixture was directly filtered through a plug of silica gel, the filtrate was concentrated and the residue (mixture of the hydroacyloxylation product **61** and some iodomethyl ketone **62**) was used for the subsequent Heck reaction. Pleasingly, this modified procedure provided **66ba** in 72% yield, which is comparable to the yield of **66ba** obtained from chromatographed **61ba** (75% over two steps). This simplified protocol proved to be successful for a variety of β-aryl acrylic acids (**59a-d**)

and aryl (**60a-c**) or alkyl substituted 1-iodo-1-alkynes (**60d-g**). Thus, the 2(3*H*)-furanones **66** were obtained (17%-59% over 2 steps, Figure 3.9) by successive hydroacyloxylation, Mizoroki-Heck reactions of the iodoacetylenes without isolation and purification of the intermediate *Z*-*β*-iodoenol acrylates **61**. The *E*-stereochemistry of the exocyclic double bond in **66ad** was also confirmed by a NOESY experiment (interaction of the C4 methine (H^1) and the ortho hydrogen (H^2) of the phenyl ring in **66ad** was observed (Figure 3.10). In all cases, only the 2(3*H*)-furanone product **66** was obtained and the isomeric pyranone was not detected. The Mizoroki-Heck reaction for the aryl-substituted acetylene-derived substrates were conducted at 80 ^{o}C, but the reactions for the alkyl-acetylene-derived substrates are conducted at a lower temperature (40 ^{o}C) to prevent decomposition of the iodoenol cinnamates intermediate. The methodology works for several combinations of the carboxylic acids **59** and the acetylenes **60** (Figure 3.9). All of the furanones **66** were assigned the *E* stereochemistry by analogy to **66ba** and **66ad**. *β*-Alkyl acrylic acids were not examined in this study.

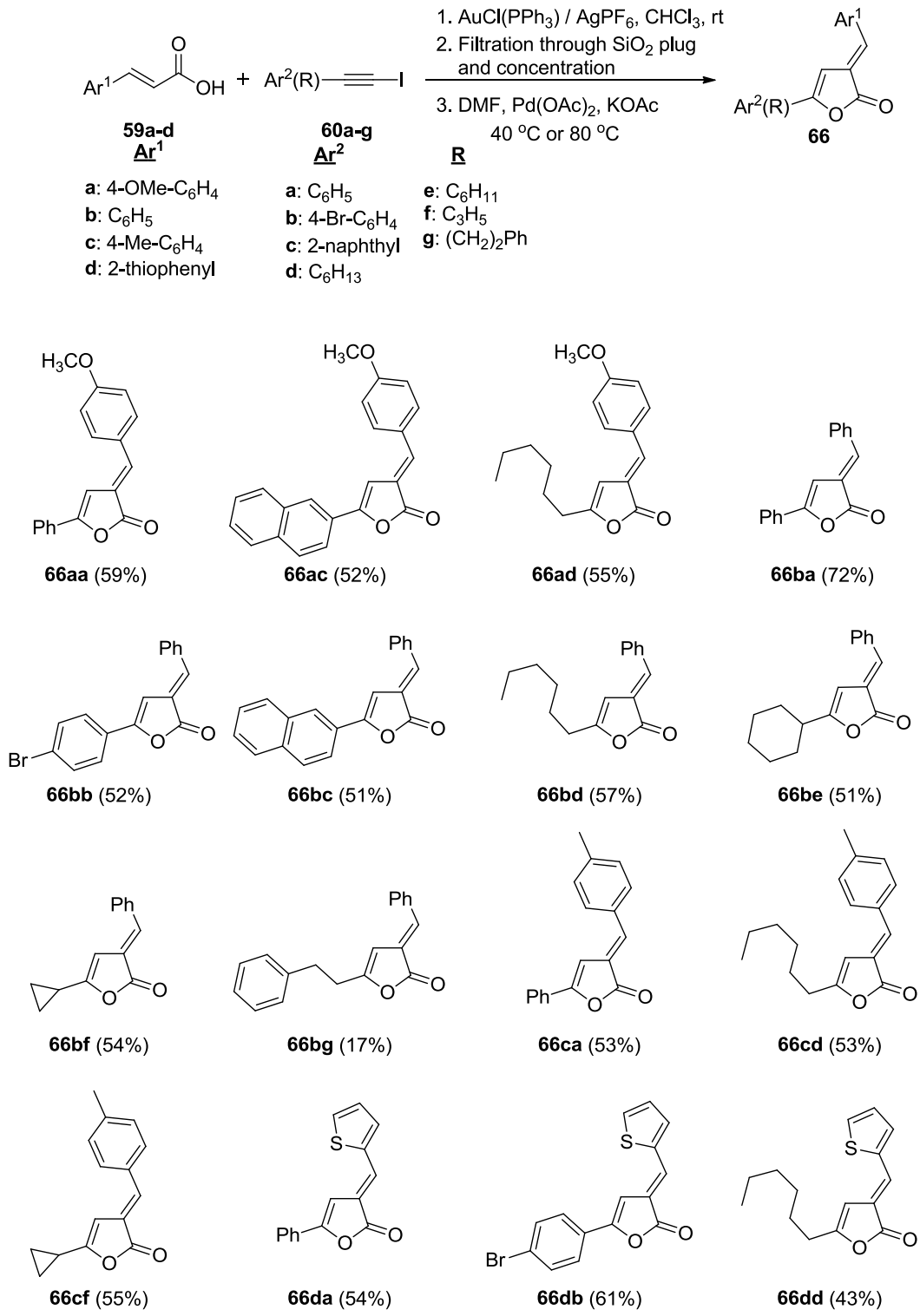


Figure 3.9. Synthesis of furanones from *β*-aryl acrylic acids and iodoacetylenes

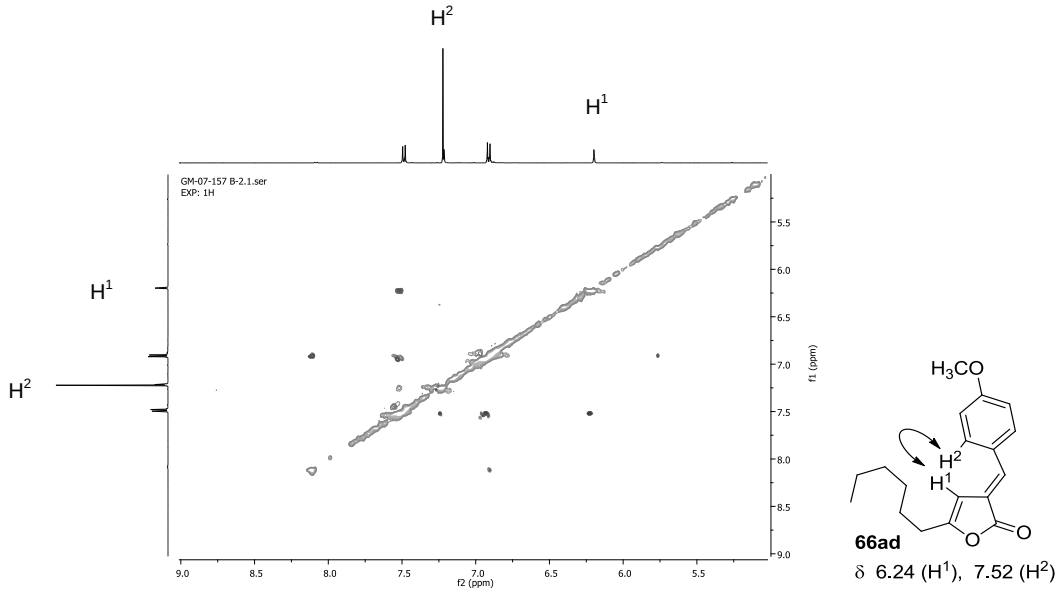


Figure 3.10. ^{1}H-^{1}H NOESY spectrum for **66ad**

We also examined the possibility of preparing (*Z*)-arylidene furanones from (*Z*)-cinnamic acids. We anticipated that the reaction of (*Z*)-**59b** with **60a** using our simplified protocol would give (*Z*)-**66ba** as shown in Figure 3.11.

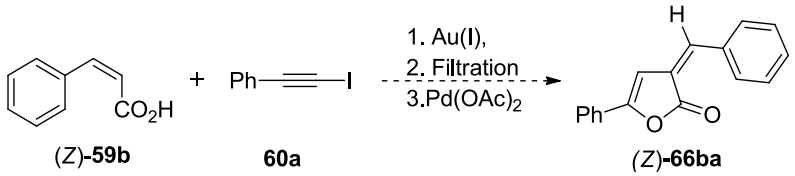
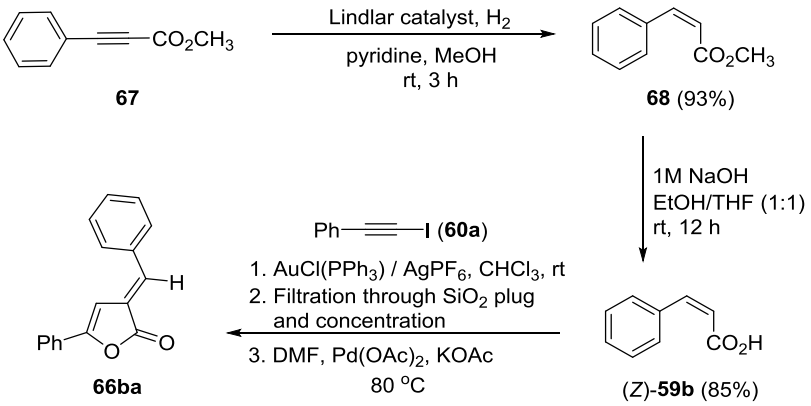


Figure 3.11. Synthesis of (*Z*)-**66ba**

The required starting material ((*Z*)-**59b**) was synthesized from methyl 3-phenylpropiolate (**67**). Hydrogenation of **67** in the presence of Lindlar catalyst (5% Pd on $CaCO_3$, poisoned with lead) afforded the (*Z*)-methylcinnamate **68**, which was hydrolyzed to furnish (*Z*)-**59b**. Surprisingly, the reaction of **60a** with (*Z*)-**59b** using our simplified protocol provided only the *E*-isomer of furanone **66ba** (Scheme 3.14). This observation

suggests that, in our studies, the reductive elimination step in the Mizoroki-Heck reaction provides the thermodynamically more stable (*E*)-alkene.

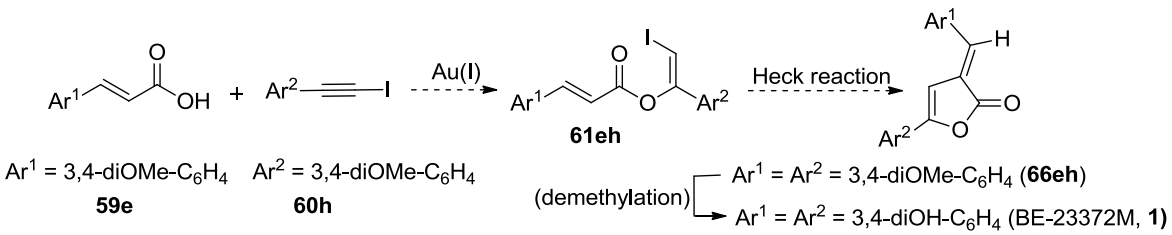


Scheme 3.14. Synthesis of **59b** and application in hydroacyloxylation/Mizoroki-Heck reactions with **60a**.

The potential for further simplification of our methodology to a one pot protocol (definition of one-pot synthesis)[24] by avoiding the silica plug filtration of the iodoenol acrylate, was also investigated. Thus, for the reactions of **59b** with **60a** and **60d**, concentration of the reaction mixture (after the Au-catalyzed reaction) and replacement of the solvent ($CHCl_3$) with DMF for the subsequent Mizoroki-Heck reaction provided **66ba** (61%) and **66bd** (64%). Notably, the yield of **66bd** obtained by the one pot modification is higher than obtained previously (57%, Figure 3.9). Marginally higher loading of $Pd(OAc)_2$ (15% compared to 10% for the protocol in Figure 3.9) is required for the one pot version of the synthesis of **66**.

3.4.1 Synthesis of BE-23372M

The furanone synthesis methodology was applied in a formal synthesis of BE-23372M (**1**),[25] a potent tyrosine kinase inhibitor, which inhibits A431 human epidermoid carcinoma and MKN-7 human stomach cancer cell lines. Our initial approach to the synthesis of BE-23372M was started with hydroacyloxylation of iodoaceytlene **60h** (Scheme 3.15). Hydroacyloxylation of **60h** with **59e** could give the iodoenol acrylate **61eh**. Intramolecular Heck reaction of **61eh**, followed by demethylation of **61eh** would provide BE-23372M (**1**) (Scheme 3.15).

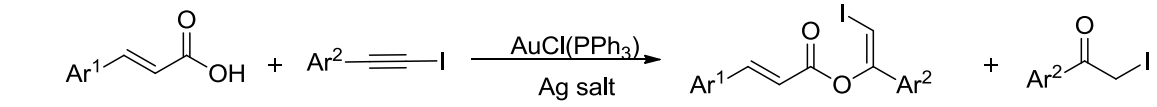


Scheme 3.15. Planned synthetic strategy for the synthesis of BE-23372M (**1**)

We initially examined the reaction of **59e** with **60h** using our previously optimized hydroacyloxylation reaction conditions (Table 3.3, entry 1). Unfortunately, a significant amount of decomposition of starting materials was observed and unidentified impurities were obtained in addition to the desired product **61eh** (11%, Table 3.3, entry 1). A similar trend was observed when lowering the temperature (Table 3.3, entry 2). Hence, an optimization of hydroacyloxylation of the **60h** was conducted by varying the solvents and co-catalyst (Table 3.3). Reactions in other chlorinated solvents provided

only a trace amount of products (Table 3.3, entry 3 and 4). Also, the reaction with toluene as solvent provided a very low yield of **61eh** and no product was obtained when THF was used (Table 3.3, entry 5 and 6).

Table 3.3 Optimization of the hydroacyloxylation of **60h**



Ar^1 = 3,4-diOMe-C_6H_4 **59e** + Ar^2 = 3,4-diOMe-C_6H_4 **60h** → Ar^1 = Ar^2 = 3,4-diOMe-C_6H_4 (**61eh**) + **62h**

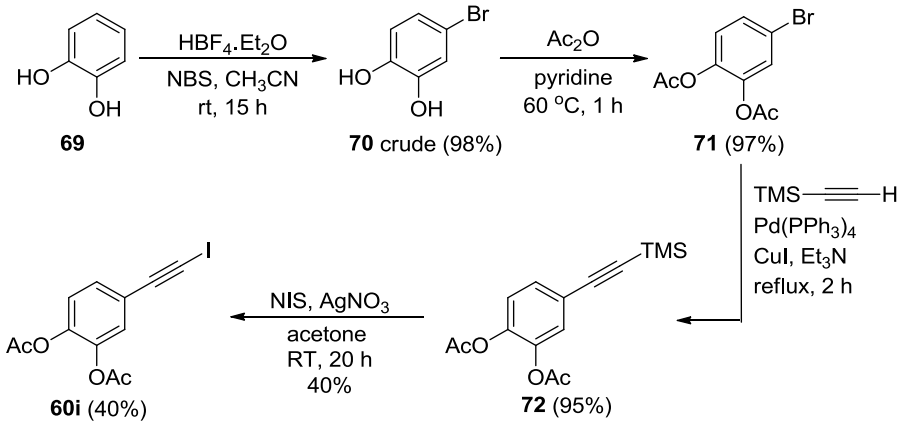
Entry	Ag salt	Solvent	Time (h)	61eh (%)	62h (%)
1	$AgPF_6$	$CHCl_3$	15	11	28
2[a]		$CHCl_3$	36	5	11
3		DCE	48	2	-
4		CH_2Cl_2	24	3	-
5		toluene	18	2	7
6		THF	72	0	-
7	AgOTf	$CHCl_3$	3	6	49
8		CH_2Cl_2	4	5	-
9		DCE	10	2	-

[a]Reaction was conducted at 0 ^oC

Reaction of **60h** with **59e** in the presence of AgOTf additive and in $CHCl_3$ as solvent provided **61eh** in 6% and **62h** in 49% (Table 3.3, entry 7). None of the other chlorinated solvents improved the desired product yield (Table 3.3, entry 8 and 9). We

have also examined the hydroacyloxylation reactions of **60a** with **59e** and **60h** with **59b**; unfortunately, no products were obtained and unreacted starting materials were recovered. The reasons for the failure of electron rich reaction partners are not well understood.

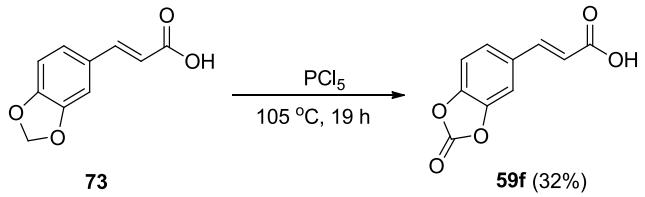
Based on the above results, we reasoned that replacing the strongly activating (dimethoxy) substituents on the aryl ring (**59e** and **60h**) with a weaker activating group might be beneficial for the hydroacyloxylation reaction. The 3,4-diacetoxyphenyl iodoacetylene **60i** was selected as an alternative to **60h** and it was prepared from catechol as shown in Scheme 3.16.



Scheme 3.16. Synthesis of **60i**

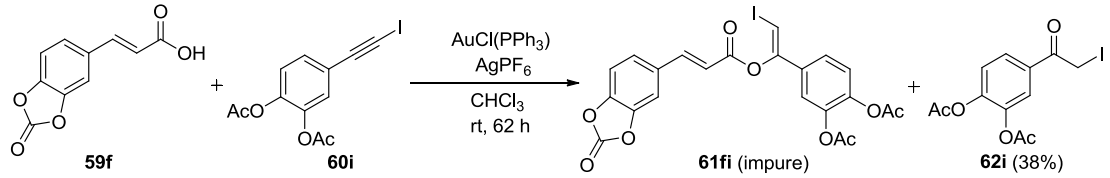
Monobromination of catechol **69** in the presence of $HBF_4 \cdot Et_2O$ and NBS afforded the bromoarene **70**. Treatment of **70** with Ac_2O furnished the diacetoxy derivative **71**. Pleasingly, Sonogashira cross coupling reaction of **71** with TMS-acetylene provided the alkyne **72** in 95% yield. Compound **72** was subjected to iododesilylation in the presence of NIS and $AgNO_3$ to give iodoacetylene **60i** (40%, Scheme 3.16).

The electron deficient cinnamic acid **59f** was chosen for the hydroacyloxylation reaction of **60i**. Reaction of PCl_5 with acid **73** according to the literature procedure[25] afforded **59f** in 32% yield as shown in Scheme 3.17.



Scheme 3.17. Synthesis of cinnamic acid **59f**

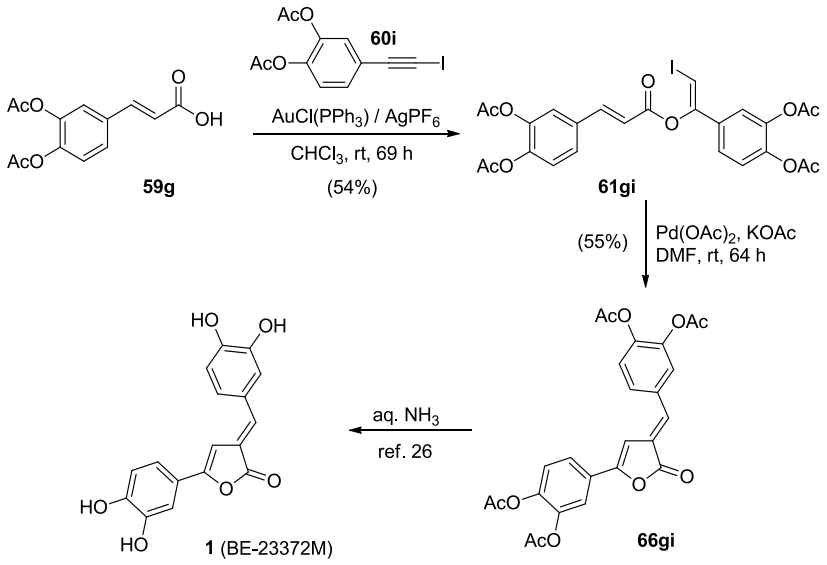
With the required starting materials in hand, the hydroacyloxylation reaction of 3,4-diacetoxyphenyl iodoacetylene **60i** with **59f** was conducted under our optimized reaction conditions. Surprisingly, this reaction generated a complex mixture of products from which only a small amount of the desired product **61fi** could be isolated as a mixture with an unidentifiable impurity (Scheme 3.18).



Scheme 3.18. Hydroacyloxylation of **60i** with **59f**

Clearly, a change in the nucleophilic partner or the electrophilic partner or both was necessary. However, having prepared **60i**, we decided to change the nucleophilic component (the carboxylic acid) since that would involve a simple protection of the phenolic groups in caffeic acid. Accordingly, caffeic acid was diacetylated to provide the acid **59g** which was then used in a hydroacyloxylation reaction with **60i** (Scheme 3.18). Gratifyingly, reaction of the acid **59g** and the iodoacetylene **60i** according to our

optimized protocol provided the iodoenol acrylate **61gi** in 55% yield. Intramolecular Heck reaction of **61gi** provided the tetraacetoxy 2(3*H*)-furanone derivative **66gi** (55%), which can be deacetylated to provide **1** (Scheme 3.19),[26] thereby completing a formal synthesis of **1**.



Scheme 3.19 Formal synthesis of BE-23372M

3.5 Conclusion

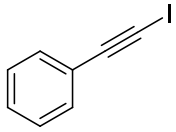
In conclusion, a short synthesis of *E*-3-(arylidene)-5-(alkyl/aryl)-2(3*H*)-furanones was developed from readily available *β*-aryl acrylic acids and iodoacetylenes as the starting materials. The modular, two step methodology is easily modified to a one pot protocol which makes it particularly attractive for preparing libraries of structurally diverse furanones for further applications.

3.6 Experimental Section

General procedure for the synthesis of iodoalkynes from alkyl or aryl acetylenes:

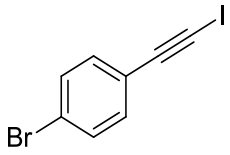
To a solution of alkyl or aryl acetylene (1.0 equiv.) in anhydrous THF (10 mL) was added *n*-BuLi (1.3 equiv.) at -78 ^{o}C. The reaction mixture was stirred at -78 ^{o}C for 30 min. A solution of iodine (1.05 equiv.) in anhydrous THF (5 mL) was added at -78 ^{o}C and the mixture was warmed to room temperature and stirred until complete consumption of the acetylene (verified by TLC). Water (5 mL) was added and the mixture was extracted with pentane (3 x 10 mL). The combined organic fractions were washed with saturated aqueous $Na_2S_2O_3$ (1 x 10 mL), brine (1 x 10 mL) and dried over Na_2SO_4. The organic fractions were concentrated under reduced pressure.

(Iodoethynyl)benzene (60a)[27]



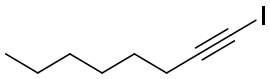
The reaction of ethynylbenzene (1.00 g, 9.80 mmol), *n*-BuLi (1.80 M solution in hexanes, 7.00 mL, 12.7 mmol) and iodine (2.60 g, 10.3 mmol) in THF for 10 min according to General Procedure provided 2.0 g (90%) of **60a** as a clear oil. R_f = 0.67 (hexanes); IR (neat): 3056, 3029, 2925, 2170, 1596, 1486, 1441, 751, 686, 520 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46-7.39 (m, 2H, Ar*H*), 7.35-7.26 (m 3H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.5 (2 x Ar*C*), 128.9 (Ar*C*), 128.4 (2 x Ar*C*), 123.5 (ArC_{ipso}), 94.3 (*C*≡C-I), 6.30 (C≡*C*-I).

1-Bromo-4-(iodoethynyl)benzene (60b)[28]



To a solution of 1-bromo-4-ethynylbenzene (200 mg, 1.10 mmol) in acetone (5 mL) were added *N*-iodosuccinimide (285 mg, 1.27 mmol) and silver nitrate (18.7 mg, 0.110 mmol). The reaction flask was wrapped with aluminium foil and the mixture was stirred at room temperature for 2h. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 95:5) to provide 246 mg (73%) of **60b** as a white solid. R_f = 0.44 (hexanes); mp: 95-97 ^{o}C; IR (neat): 3053, 2984, 2161, 1481, 1389, 1264, 1228, 1067, 1009, 818, 738, 632, 516 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (d, 2H, *J* = 8.3, Ar*H*), 7.28 (d, 2H, *J* = 8.3, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$): 133.9 (2 x Ar*C*), 131.7 (2 x Ar*C*), 123.3 (ArC_{ipso}), 122.4 (ArC_{ipso}), 93.2 (Ar-*C*≡C), 8.1 (C≡*C*-I).

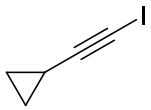
1-Iodooct-1-yne (60d)[20e]



The reaction of oct-1-yne (2.00 g, 18.1 mmol), *n*-BuLi (1.17 M solution in hexanes, 20.0 mL, 23.6 mmol) and iodine (4.80 g, 19.1 mmol) in THF for 10 min according to General Procedure provided 3.98 g (93%) of **60d** as a clear oil. R_f = 0.66

(hexanes); IR (neat): 2955, 2928, 2857, 1461, 1428 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (t, 2H, *J* = 7.0, C≡C-C*H*$_2$), 1.57-1.45 (m, 2H, C*H*$_2$), 1.44-1.21 (m, 6H, (C*H*$_2$)$_3$), 0.89 (t, 3H, *J* = 6.8, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 95.0 (*C*≡C-I), 31.4 (*C*H$_2$), 28.6 (2 x *C*H$_2$), 22.7 (*C*H$_2$), 21.0 (*C*H$_2$), 14.2 (*C*H$_3$), -7.5 (*C*≡*C*-I).

(Iodoethynyl)cyclopropane (60f)[20e]



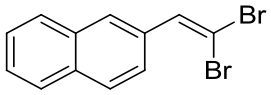
The reaction of ethynylcyclopropane (1.00 g, 15.2 mmol), *n*-BuLi (1.80 M solution in hexanes, 11.0 mL, 19.7 mmol) and iodine (4.02 g, 15.9 mmol) in THF for 10 min according to General Procedure provided 2.65 g (91%) of **60f** as a clear oil. R_f = 0.65 (hexanes); IR (neat): 2956, 2926, 2857, 2210, 1725, 1577, 1425, 1053, 1028, 816, 499 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41-1.31 (m, 1H, C*H*), 0.80-0.68 (m, 4H, C*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 97.4 (*C*≡CI), 8.4 (2 x *C*H$_2$), 1.7 (*C*H), -11.7 (*C*-I).

General Procedure for the synthesis of 1,1-dibromo-1-alkenes:

To a solution of the aldehyde (1 equiv.) in anhydrous CH_2Cl_2 was added tetrabromomethane (2 equiv.). The resulting solution was cooled to 0 ^{o}C, triphenylphosphine (4 equiv.) was added and the mixture was stirred at room temperature until complete consumption of the aldehyde (verified by TLC). The mixture was then

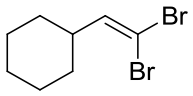
concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel.

2-(2,2-Dibromovinyl)naphthalene (65c)[29]



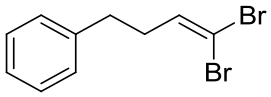
The reaction of 2-naphthaldehyde (2.00 g, 12.8 mmol), tetrabromomethane (8.50 g, 25.6 mmol) and triphenylphosphine (13.4 g, 51.2 mmol) in CH_2Cl_2 (25 mL) for 2 h according to the general procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 9:1), 3.70 g (93%) of **65c** as a white solid. R_f = 0.21 (hexanes/EtOAc, 8:2); mp: 95-97 ^oC (Lit.[26] 94-96 ^oC); IR (neat): 3053, 3008, 1502, 831, 813, 745, 640, 584 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.00 (br s, 1H, Ar*H*), 7.88-7.78 (m, 3H, Ar*H* and C*H*=C(Br)$_2$), 7.66-7.60 (m, 2H, Ar*H*), 7.54-7.45 (m, 2H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.0 (*C*=C(Br)$_2$, 133.04 (Ar*C*$_{ipso}$), 133.02 (Ar*C*$_{ipso}$), 132.8 (Ar*C*$_{ipso}$), 128.3 (Ar*C*), 128.2 (Ar*C*), 128.0 (Ar*C*), 127.8 (Ar*C*), 126.8 (Ar*C*), 126.6 (Ar*C*), 125.7 (Ar*C*), 89.9 (*C*-Br).

(2,2-Dibromovinyl)cyclohexane (65e)[29]



The reaction of cyclohexanecarbaldehyde (1.50 g, 13.4 mmol), tetrabromomethane (8.90 g, 26.8 mmol) and triphenylphosphine (14.0 g, 53.6 mmol) in CH_2Cl_2 (20 mL) for 3 h according to the general procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 9:1), 3.23 g (90%) of **65e** as a clear oil. R_f = 0.71 (hexanes); IR (neat): 2923, 2850, 1610, 965, 894, 813, 763, 570 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.23 (d, 1H, *J* = 9.0, C*H*=C(Br)$_2$), 2.35-2.20 (m, 1H, C*H*-CH=C), 1.80-1.58 (m, 5H, CH_2), 1.40-1.03 (m, 5H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.7 (*C*=C(Br)$_2$), 87.0 (C=*C*(Br)$_2$), 42.4 (*C*H), 31.2 (2 x *C*H_2), 25.7 (*C*H_2), 25.5 (2 x *C*H_2).

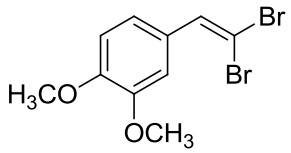
(4,4-Dibromobut-3-en-1-yl)benzene (65g)[29]



The reaction of 3-phenylpropanal (1.00 g, 7.45 mmol), tetrabromomethane (4.95 g, 14.9 mmol) and triphenylphosphine (7.82 g, 29.8 mmol) in CH_2Cl_2 (15 mL) for 2 h according to the general procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 9:1), 1.33 g (62%) of **65g** as a clear oil. R_f = 0.71 (hexanes); IR (neat): 3062, 3026, 2924, 1783, 1495, 1452, 796, 746, 697, 595 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34-7.26 (m, 2H, Ar*H*), 7.24-7.15 (m, 3H, Ar*H*), 6.41 (t, 1H,

J = 7.6, C*H*=C(Br)$_2$, 2.73 (t, 2H, *J* = 7.6, PhC*H*$_2$), 2.46-2.37 (m, 2H, PhCH$_2$C*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.6 (Ar*C*$_{ipso}$), 137.7 (C*H*=C(Br)$_2$), 128.6 (2 x Ar*C*), 128.4 (2 x Ar*C*), 126.3 (Ar*C*), 89.6 (C=*C*(Br)$_2$), 34.7 (Ph*C*H$_2$), 33.9 (PhCH$_2$*C*H$_2$).

4-(2,2-Dibromovinyl)-1,2-dimethoxybenzene (65h)[29]

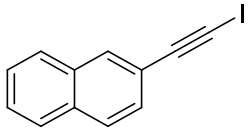


The reaction of 3,4-dimethoxybenzaldehyde (1.50 g, 9.00 mmol), tetrabromomethane (5.97 g, 18.0 mmol) and triphenylphosphine (9.43 g, 36.0 mmol) in CH_2Cl_2 (20 mL) for 3 h according to the general procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 9:1), 2.36 g (82%) of **65h** as a yellow oil. R_f = 0.25 (hexanes/EtOAc, 93:7); IR (neat): 3001, 2955, 2932, 2905, 2834, 1598, 1510, 1258, 1234, 1140, 1022, 629 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (br s, 1H, C*H*=C(Br)$_2$, 7.19 (br s, 1H, Ar*H*), 7.09 (dd, 1H, *J* = 8.4, 0.7, Ar*H*), 6.85 (d, 1H, *J* = 8.4, Ar*H*), 3.89 (s, 6H, 2 x OC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.3 (Ar*C*$_{ipso}$), 148.6 (Ar*C*$_{ipso}$), 136.4 (*C*H=C(Br)$_2$, 128.0 (Ar*C*$_{ipso}$), 121.9 (Ar*C*), 111.1 (Ar*C*), 110.8 (Ar*C*), 87.4 (CH=*C*(Br)$_2$, 55.91 (O*C*H$_3$), 55.89 (O*C*H$_3$).

General procedure for the one-pot synthesis of iodoalkynes from 1,1-dibromo-1-alkenes:

To a solution of 1,1-dibromo-1-alkene (1 equiv.) in anhydrous THF (10 mL) was added *n*-BuLi (2.2 equiv.) at -78 ^{o}C. The reaction mixture was stirred at -78 ^{o}C until consumption of the 1,1-dibromo-1-alkene (TLC) and a solution of iodine (1.05 equiv.) in anhydrous THF (5 mL) was added at -78 ^{o}C. The mixture was stirred at -78 ^{o}C until complete consumption of the acetylene (verified by TLC). Water (5mL) was added, the mixture was warmed to room temperature and extracted with pentane (3 x 10 mL). The combined extracts were washed with saturated aqueous $Na_2S_2O_3$ (2 x 10 mL), brine (1 x 10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to provide the iodoalkyne that was pure by ^{1}H NMR.

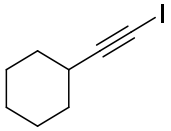
2-(Iodoethynyl)naphthalene (60c)[30]



The reaction of 2-(2,2-Dibromovinyl)naphthalene **65c** (710 mg, 4.66 mmol), *n*-BuLi (1.07 M solution in hexanes, 9.60 mL, 10.3 mmol) and iodine (1.24 g, 4.90 mmol) for 3 h according to General Procedure provided 1.13 g (87%) of **60c** as a yellow oil. R_f = 0.65 (100% hexanes); IR (neat): 3053, 2956, 2926, 2856, 2168, 1568, 1499, 813, 743, 471 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (s, 1H, Ar*H*), 7.82-7.73 (m, 3H, Ar*H*), 7.51-7.44 (m, 3H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$): 133.0 (ArC_{ipso}), 132.7 (ArC_{ipso}),

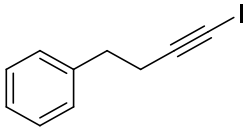
132.6 (Ar*C*), 128.7 (Ar*C*), 128.0 (Ar*C*), 127.8 (Ar*C*), 127.7 (Ar*C*), 127.0 (Ar*C*), 126.6 (Ar*C*), 120.6 (ArC_{ipso}), 94.5 (*C*≡CI), 6.5 (*C*-I).

(Iodoethynyl)cyclohexane (60e)[20e]



The reaction of (2,2-dibromovinyl)cyclohexane **65e** (1.00 g, 3.73 mmol), *n*-BuLi (0.90 M solution in hexanes, 9.0 mL, 8.2 mmol) and iodine (990 mg, 3.91 mmol) in THF for 1 h according General Procedure provided 620 mg (71%) of **60e** as a clear oil. R_f = 0.63 (hexanes); IR (neat): 2926, 2852, 2181, 1446, 498 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.59-2.47 (m, 1H, C*H*-C≡CI), 1.84-1.63 (m, 4H, CH_2), 1.56-1.38 (m, 3H, CH_2), 1.38-1.19 (m, 3H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 99.2 (*C*≡CI), 32.6 (3 x *C*H_2), 31.4 (*C*H-C≡CI), 25.9 (*C*H_2), 24.9 (*C*H_2), -7.3 (*C*-I).

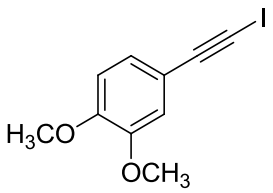
(4-Iodobut-3-yn-1-yl)benzene (60g)[31]



The reaction of (2,2-dibromovinyl)cyclohexane **65g** (1.50 g, 5.20 mmol), *n*-BuLi (1.07 M solution in hexanes, 12.1 mL, 13.0 mmol) and iodine (1.38 g, 5.45 mmol) in THF for 4 h according General Procedure provided 600 mg (45%) of **60g** as a clear oil. R_f =

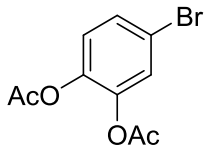
0.67 (hexanes); IR (neat): 3026, 2926, 1452, 1425, 697, 507 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-7.26 (m, 2H, Ar*H*), 7.24-7.16 (m, 3H, Ar*H*), 2.83 (t, 2H, *J* = 7.5, PhC*H*$_2$CH$_2$), 2.67-2.60 (m, 2H, PhCH$_2$C*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.4 (Ar*C*$_{ipso}$), 128.6 (2 x Ar*C*), 128.5 (2 x Ar*C*), 126.5 (Ar*C*), 94.0 (*C*≡CI), 35.1 (Ph*C*H$_2$), 23.2 (PhCH$_2$*C*H$_2$), -5.9 (*C*-I).

4-(Iodoethynyl)-1,2-dimethoxybenzene (60h)



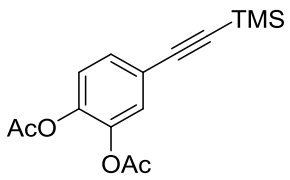
Reaction of 4-(2,2-Dibromovinyl)-1,2-dimethoxybenzene **65h** (886 mg, 5.46 mmol), *n*-BuLi (1.07 M solution in hexanes, 11.20 mL, 12.01 mmol) and iodine (1.45 g, 5.73 mmol) in THF for 4 h according to General Procedure (extracted with EtOAc) provided 1.33 g (85%) of **60h** as a yellow solid. R_f = 0.21 (hexanes/EtOAc, 8:2); mp: 120-122 ^{o}C; IR (neat): 2994, 2957, 2929, 2856, 2831, 1597, 1578, 1507, 1236, 1133, 1021, 843, 801,764 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.03 (dd, 1H, *J* = 8.3, 1.9, Ar*H*), 6.92 (d, 1H, *J* = 1.9, Ar*H*), 6.77 (d, 1H, *J* = 8.3, Ar*H*), 3.87 (s, 3H, OC*H*$_3$), 3.85 (s, 3H, OC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.0 (Ar*C*$_{ipso}$), 148.5 (Ar*C*$_{ipso}$), 125.8 (Ar*C*), 115.6 (Ar*C*$_{ipso}$), 114.9 (Ar*C*), 110.8 (Ar*C*), 94.2 (Ar-*C*≡C), 55.9 (2 x O*C*H$_3$), 4.1 (C≡*C*-I); HRMS (APPI, pos.): *m/z* 287.9644 (287.9647 calc. for $C_{10}H_9IO_2$, (M^+)) and 288.9715 (288.9725 calc. for $C_{10}H_{10}IO_2$, $(M+H)^+$).

4-Bromo-1,2-phenylene diacetate (71)[32a,b]



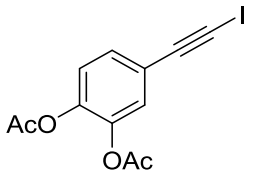
To a solution of 4-bromobenzene-1,2-diol **70** [32c] (1.37 g, 7.25 mmol) in pyridine (0.7 mL) was added acetic anhydride (1.44 mL, 15.9 mmol) and the mixture was stirred at 60 ^{o}C for 3h. The mixture was cooled to room temperature and then acidified with aqueous HCl (1M, 5 mL) and then extracted with EtOAc (3 x 5 mL). The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure to provide **71** (1.92 g, 97 %) as a clear oil. This material was used without any purification. R_f =0.21 (hexanes/EtOAc, 8:2); IR (neat): 3100, 2939, 1766, 1485, 1369, 1193, 1160, 1111, 1008, 922, 898, 585 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.35 (m, 2H, Ar*H*), 7.10-7.05 (m, 1H, Ar*H*), 2.29 (s, 3H, OCOC*H*$_3$), 2.28 (s, 3H, OCOC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9 (*C*=O), 167.8 (*C*=O), 142.7 (Ar*C*$_{ipso}$), 141.4 (Ar*C*$_{ipso}$), 129.7 (Ar*C*), 126.8 (Ar*C*), 124.7 (Ar*C*), 118.7 (Ar*C*$_{ipso}$), 20.59 (*C*H$_3$), 20.55 (*C*H$_3$); HRMS (ESI, pos.): *m/z* 271.9684 (271.9684 calc. for $C_{10}H_9BrO_4$, (M^+)) and 272.9753 (272.9762 calc. for $C_{10}H_{10}{}^{79}BrO_4$, $(M+H)^+$).

4-((Trimethylsilyl)ethynyl)-1,2-phenylene diacetate (72)



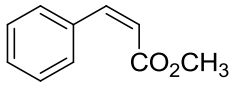
To a solution of 4-bromo-1,2-phenylene diacetate **71** (700 mg, 2.56 mmol) in Et_3N (8 mL) were added ethynyltrimethylsilane (0.54 mL, 3.85 mmol), $Pd(PPh_3)_4$ (59 mg, 0.050 mmol), CuI (20 mg, 0.10 mmol) and the mixture was heated to reflux for 2 h. The mixture was then cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in EtOAc (10 mL) and the solution was filtered through a pad of Celite.® Water (5 mL) was added to the filtrate and the mixture was extracted with EtOAc (3 x 7 mL). The combined extracts were washed with brine (1 x 10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 8:2) to provide 703 mg (95%) of **72** as a white solid. R_f = 0.22 (hexanes/EtOAc, 8:2); mp: 61-63 ^oC; IR (neat): 2959, 2900, 2160, 1762, 1496, 1372, 1252, 1205, 1173, 1139, 1107, 1013, 962, 894, 838 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.33 (dd, 1H, *J* = 8.3, 1.9, Ar*H*), 7.29 (d, 1H, *J* = 1.9, Ar*H*), 7.12 (d, 1H, *J* = 8.3, Ar*H*), 2.28 (s, 6H, 2 x OCOCH_3), 0.23 (s, 9H, Si(CH_3)$_3$; ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.09 (*C*=O), 168.08 (*C*=O), 142.5 (ArC_{ipso}), 141.9 (ArC_{ipso}), 130.4 (Ar*C*), 127.1 (Ar*C*), 123.5 (Ar*C*), 122.0 (ArC_{ipso}), 103.4 (Ar-*C*≡C), 95.4 (C≡*C*-Si), 20.8 (OCO*C*H_3), 20.7 (OCO*C*H_3), 0.0 (Si(*C*H_3)$_3$; HRMS (APPI, pos.): *m/z* 290.0979 (290.0974 calc. for $C_{15}H_{18}O_4Si$, (M^+)) and 291.1052 (291.1053 (calc. for $C_{15}H_{19}O_4Si$, $(M+H)^+$).

4-(Iodoethynyl)-1,2-phenylene diacetate (60i)



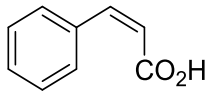
To a solution of TMS protected alkyne **70** (440 mg, 1.51 mmol) in acetone (10 mL) were added *N*-iodosuccinimide (850 mg, 3.78 mmol) and silver nitrate (103 mg, 0.604 mmol). The reaction flask was wrapped with aluminium foil and the mixture was stirred at room temperature for 20 h. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 7:3) to provide 223 mg (43%) of **60i** as a clear oil. R_f = 0.28 (hexanes/EtOAc, 7:3); IR (neat): 2923, 2852, 1766, 1498, 1369, 1261, 1199, 1176, 1108, 1011, 895, 835, 649 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.31 (dd, 1H, *J* = 8.4, 1.8, Ar*H*), 7.26 (d, 1H, *J* = 1.8, Ar*H*), 7.13 (d, 1H, *J* = 8.4, Ar*H*), 2.28 (s, 6H, 2 x OCOCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.0 (2 x *C*=O), 142.9 (ArC_{ipso}), 141.9 (ArC_{ipso}), 130.8 (Ar*C*), 127.5 (Ar*C*), 123.6 (Ar*C*), 122.1 (ArC_{ipso}), 92.5 (*C*≡CI), 20.76 (*C*H_3), 20.70 (*C*H_3), 8.0 (C≡*C*-I); HRMS (ESI, pos.): 343.9553 (343.9546 calc. for $C_{12}H_9IO_4$, (M^+)) and 344.9627 (344.9624 calc. for $C_{12}H_{10}IO_4$, $(M+H)^+$).

(*Z*)-methyl 3-phenylacrylate (68)[33]



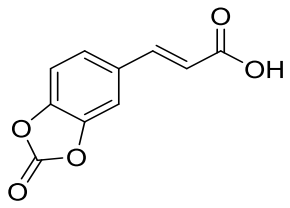
To a solution of methyl 3-phenylpropiolate **67** (390 mg, 2.43 mmol) in methanol (10 mL) were added Lindlar catalyst (5% Pd on $CaCO_3$, poisoned with lead; 258 mg, 2.43 mmol) and pyridine (195 μL, 2.43 mmol). The reaction mixture was stirred H_2 (balloon) at room temperature for 3 h and then filtered through a pad of Celite.® The pad was washed with EtOAc (10 mL) and the combined filtrates were washed with aqueous HCl (1M, 1 x 10 mL), brine (1 x 10 mL) and concentrated under reduced pressure to provide 366 mg (93%) of **68**. R_f = 0.21 (hexanes/EtOAc, 9:1); IR (neat): 3028, 2951, 1720, 1629, 1451, 1195, 1161, 826, 767, 694 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 7.62-7.55 (m, 2H, Ar*H*), 7.40-7.31 (m, 3H, Ar*H*), 6.96 (d, 1H, *J* = 12.6, Ar-C*H*=CH), 5.96 (d, 1H, *J* = 12.6, Ar-CH=C*H*), 3.71 (s, 3H, COOCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 166.6 (*C*=O), 143.4 (Ar-*C*H=CH), 134.8 (ArC_{ipso}), 129.7 (2 x Ar*C*), 129.1 (Ar*C*), 128.0 (2 x Ar*C*), 119.3 (Ar-CH=*C*H), 51.4 (COO*C*H_3).

(*Z*)-3-Phenylacrylic acid (*Z*-50b)[34]



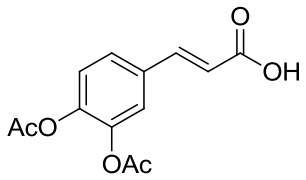
To a solution of (*Z*)-methyl 3-phenylacrylate (**68**) (370 mg, 2.28 mmol) in EtOH/THF (1:1, 4 mL) was added aqueous NaOH (1M, 4.50 mL, 4.50 mmol). The reaction mixture was stirred at room temperature for 12 h. The mixture was then concentrated under reduced pressure, acidified with aqueous HCl (1M, 6 mL) and extracted with EtOAc (3 x 5 mL). The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure to provide *Z*-**50b** (286 mg, 85%) as a clear oil. R_f = 0.22 (hexanes/EtOAc, 8:2); IR (neat): 3028, 2970, 2739, 2575, 1687, 1623, 1433, 1225, 924, 826, 762, 694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 11.8 (br s, 1H, COO*H*), 7.62-7.54 (m, 2H, Ar*H*), 7.35-7.29 (m, 3H, Ar*H*), 7.03 (d, 1H, *J* = 12.7, Ar-C*H*=CH), 5.94 (d, 1H, *J* = 12.7, Ar-CH=C*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9 (*C*OOH), 146.0 (Ar-*C*=C), 134.5 (ArC_{ipso}), 130.1 (2 x Ar*C*), 129.5 (Ar*C*), 128.2 (2 x Ar*C*), 118.8 (Ar-C=*C*).

(*E*)-3-(2-Oxobenzo[d][1,3]dioxol-5-yl)acrylic acid (59f)[25]



A mixture of (*E*)-3-(benzo[d][1,3]dioxol-5-yl)acrylic acid (**71**) (1.90 g, 9.88 mmol) and PCl_5 (7.20 g, 34.6 mmol) in a 250 mL round bottomed flask (equipped with a drying tube) was stirred at 105 ^oC for 19 h. The mixture was cooled to room temperature and the volatiles were removed under reduced pressure. Formic acid (5mL) was added to the residue and the mixture was stirred until the gas evolution ceased. The precipitated solid was filtered and washed with cold formic acid (1 x 5mL), acetic acid (1 x 5 mL), hexanes (1 x 10 mL) and dried under reduced pressure to provide 652 mg (32%) of **59f** as a tan powder. R_f = 0.22 (hexanes/EtOAc, 6:4); mp: 254-256 ^oC (Lit.[11] 260-261 ^oC); IR (neat): 3341, 2960, 2582, 1832, 1681, 1438, 1237, 1213, 1160 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 12.45 (br s, 1H, COO*H*), 7.95 (d, 1H, *J* = 1.5, Ar*H*), 7.62 (d, 1H, *J* = 16, Ar-C*H*=CH), 7.60 (dd, *J* = 8.4, 1.5, Ar*H*), 7.51 (d, 1H, *J* = 8.4, Ar*H*), 6.59 (d, 1H, *J* = 16, Ar-CH=C*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.4 (*C*=O), 150.8 (O-*C*O), 144.2 (ArC_{ipso}), 143.7 (ArC_{ipso}), 142.9 (Ar-*C*H=CH), 131.5 (ArC_{ipso}), 126.1 (Ar*C*), 119.8 (Ar*C*), 110.6 (Ar*C*), 108.9 (Ar-CH=*C*H); HRMS (APPI, pos.): 206.0207 (206.0215 calc. for $C_{10}H_6O_5$, (M^+)) and 229.0097 (229.0113 calc. for $C_{10}H_6NaO_5$, $(M+Na)^+$).

(*E*)-3-(3,4-Diacetoxyphenyl)acrylic acid (59g)[35]

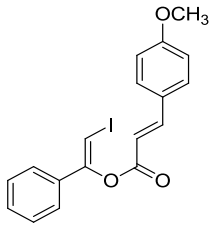


To a solution of caffeic acid (1.56 g, 8.66 mmol) in pyridine (10 mL) were added acetic anhydride (1.64 mL, 17.3 mmol) and DMAP (211 mg, 1.73 mmol) at 0 ^{o}C and the reaction mixture was stirred at room temperature for 14 h. Water (5 mL) was added and the mixture was extracted with EtOAc (3 x 10 mL). The combined extracts were washed with aqueous HCl (1M, 1 x 10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to provide **59g** (2.05 g, 89%) as a white solid. R_f = 0.22 (hexanes/EtOAc, 4:6); mp: 190-192 ^{o}C; IR (neat): 2943, 2902, 2599, 1753, 1676, 1629, 1501, 1432, 1375, 1251, 1206, 1185, 1114, 1014, 986, 910, 879, 825 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, 1H, *J* = 16.0, Ar-C*H*=CH), 7.43 (dd, 1H, *J* = 8.4, 2.0, Ar*H*), 7.39 (d, 1H, *J* = 2.0, Ar*H*), 7.24 (d, 1H, *J* = 8.4, Ar*H*), 6.39 (d, 1H, *J* = 16.0, Ar-CH=C*H*), 2.32 (s, 3H, OCOCH_3), 2.31 (s, 3H, OCOCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4 (*C*OOH), 168.1 (*C*(O)CH_3), 168.0 (*C*(O)CH_3), 145.1 (Ar-*C*H=CH), 143.9 (ArC_{ipso}), 142.5 (ArC_{ipso}), 132.9 (ArC_{ipso}), 126.7 (Ar*C*), 124.1 (Ar*C*), 123.0 (Ar*C*), 118.4 (Ar-CH=*C*H), 20.7 (*C*H_3), 20.6 (*C*H_3).

General Procedure for the synthesis of (*Z*)-*β*-iodoenol cinnamates (61):

To a solution of the cinnamic acid (1 equiv.) and the iodoalkyne (1 equiv.) in $CHCl_3$ were added $AuCl(PPh_3)$ (5 or 10 mol%) and $AgPF_6$ (5 or 10 mol%) at room temperature. The reaction flask was wrapped with aluminium foil and the reaction mixture was stirred at room temperature until consumption of the iodoalkyne (TLC). The mixture was then concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel. In some cases, traces of the the iodomethyl ketone byproduct co-eluted with **62**. This impurity was easily removed by dissolving the mixture in a minimum volume of pentane, cooling the solution to -78 ^oC and decanting the supernatant to provide pure **61** as a residual semisolid or oil.

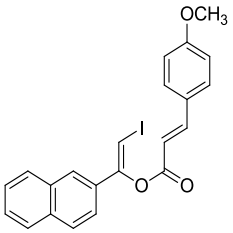
(*E*)-((*Z*)-2-Iodo-1-phenylvinyl) 3-(4-methoxyphenyl)acrylate (61aa):



The reaction of (*E*)-3-(4-methoxyphenyl)acrylic acid (**59a)** (53 mg, 0.30 mmol), iodoalkyne **60a** (68 mg, 0.30 mmol), $AuCl(PPh_3)$ (7.4 mg, 0.015 mmol) and $AgPF_6$ (3.8 mg, 0.015 mmol) in $CHCl_3$ (1.5 mL) for 23 h according to General Procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 9:1), 85 mg (70%) of **61aa** as a pale yellow solid and 7 mg (10%) of **62a** as a colourless gum. R_f = 0.20 (hexanes/EtOAc, 9:1); mp: 101-103 ^oC; IR (neat): 3080, 2918, 2849, 2837, 1721,

1625, 1598, 1571, 1508, 1492, 1249, 1169, 1102, 1016, 982, 825, 744, 521 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.87 (d, 1H, *J* = 15.9, Ar-C*H*=CH), 7.56 (d, 2H, *J* = 8.7, Ar*H*), 7.50- 7.45 (m, 2H, Ar*H*), 7.38-7.31 (m, 3H, Ar*H*), 6.94 (d, 2H, *J* = 8.7, Ar*H*), 6.68 (s, 1H, C*H*I=C), 6.53 (d, 1H, *J* = 15.9, Ar-CH=C*H*), 3.86 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.6 (*C*-O), 161.9 (ArC_{ipso}), 155.1 (*C*=O), 147.2 (Ar-*C*=C), 133.8 (ArC_{ipso}), 130.2 (2 x Ar*C*), 129.3 (Ar*C*), 128.7 (2 x Ar*C*), 126.8 (ArC_{ipso}), 125.2 (2 x Ar*C*), 114.5 (2 x Ar*C*), 113.8 (Ar-C=*C*), 68.1 (O*C*H_3), 55.4 (*C*-I); HRMS (APPI, pos.): *m/z* 406.0066 (406.0066 calc. for $C_{18}H_{15}IO_3$, $(M)^+$), 407.0133 (407.0144 (calc. for $C_{18}H_{16}IO_3$, $(M+H)^+$). Spectroscopic data for **62a** is in agreement with the reported data.[36]

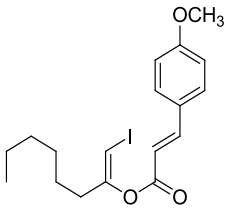
(*E*)-(*Z*)-2-Iodo-1-(naphthalen-2-yl)vinyl-3-(4-methoxyphenyl)acrylate (61ac):



The reaction of (*E*)-3-(4-methoxyphenyl)acrylic acid (**59a**) (54 mg, 0.30 mmol), iodoalkyne **60c** (83 mg, 0.30 mmol), AuCl(PPh_3) (7.40 mg, 0.015 mmol) and $AgPF_6$ (3.80 mg, 0.015 mmol) in $CHCl_3$ (1.5 mL) for 15 h according to General Procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 9:1), 85 mg (62%) of **61ac** as a semisolid. R_f = 0.23 (hexanes/EtOAc, 95:5); IR (neat): 2920, 2840, 1733, 1709, 1629, 1597, 1570, 1244, 1217, 1167, 1106, 1028, 823, 756, 547, 475 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.92 (d, 1H, *J* = 15.9, Ar-C*H*=CH), 7.90 (d, 1H, *J* = 1.4, Ar*H*), 7.85-7.77 (m, 3H, Ar*H*), 7.58 (apparent d, 3H, *J* = 8.8, Ar*H*), 7.52-7.42 (m,

2H, Ar*H*), 6.95 (d, 2H, *J* = 8.8, Ar*H*), 6.83 (s, 1H, C=C*H*I), 6.59 (d, 1H, *J* = 15.9, Ar-CH=C*H*), 3.86 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.8 (*C*-O), 162.1 (ArC_{ipso}), 155.2 (*C*=O), 147.5 (Ar-*C*=C), 133.6 (ArC_{ipso}), 133.2 (ArC_{ipso}), 131.2 (ArC_{ipso}), 130.4 (2 x Ar*C*), 128.7 (2 x Ar*C*), 127.8 (Ar*C*), 127.0 (ArC_{ipso}), 126.9 (Ar*C*), 126.8 (Ar*C*), 124.7 (Ar*C*), 122.8 (Ar*C*), 114.6 (2 x Ar*C*), 114.0 (Ar-C=*C*), 68.9 (C=*C*I), 55.6 (O*C*H_3); HRMS (APPI, pos.): *m/z* 456.0210 (456.0222 calc. for $C_{22}H_{17}IO_3$, (M^+) and 457.0282 (457.0301 calc. for $C_{22}H_{18}IO_3$, $(M+H)^+$).

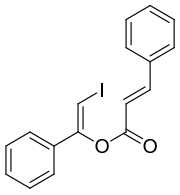
(*E*)-(*Z*)-1-Hexyl-2-iodovinyl 3-(4-methoxyphenyl)acrylate (61ad):



The reaction of (*E*)-3-(4-methoxyphenyl)acrylic acid (**59a**) (89 mg, 0.50 mmol), iodoalkyne (**60d**) (118 mg, 0.50 mmol), AuCl(PPh_3) (12.4 mg, 0.025 mmol) and $AgPF_6$ (6.30 mg, 0.025 mmol) in $CHCl_3$ (2 mL) for 18 h according to General Procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 93:7), 147 mg (71%) of **61ad** as a clear oil. R_f = 0.22 (hexanes/EtOAc, 93:7); IR (neat): 2953, 2927, 2856, 1722, 1629, 1510, 1251, 1170, 1123, 1110, 1029, 980, 825,519cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, 1H, *J* = 16.0, ArC*H*=CH), 7.53 (d, 2H, *J* = 8.7, Ar*H*), 6.93 (d, 2H, *J* = 8.7, Ar*H*), 6.40 (d, 1H, *J* = 16.0, ArCH=C*H*), 5.86 (t, 1H, *J* = 1.1, C=C*H*I), 3.86 (s, 3H, OCH_3), 2.43 (td, 2H, *J* = 7.6, 1.1, IHC=CCH_2CH_2), 1.54-1.44 (m, 2H, IHC=CCH$_2$CH_2), 1.38-1.23 (m, 6H, (CH_2)$_3$CH$_3$), 0.91-0.83 (m, 3*H*, (CH$_2$)$_3$CH_3); ^{13}C

NMR (75 MHz, $CDCl_3$): δ 163.7 (*C*=C-I), 161.8 (ArC_{ipso}), 158.1 (*C*=O), 146.6 (Ar-*C*=C), 130.1 (2 x Ar*C*), 126.9 (ArC_{ipso}), 114.4 (2 x Ar*C*), 114.2 (Ar-C=*C*), 64.9 (O*C*H_3), 55.4 (C=*C*-I), 34.6 (C=C-*C*H_2), 31.5 (*C*H_2), 28.6 (*C*H_2), 26.4 (*C*H_2), 22.5 (*C*H_2), 14.0 (*C*H_3); HRMS (APPI, pos.): *m/z* 414.0699 (414.0692 calc. for ($C_{18}H_{23}IO_3$, $(M)^+$) and 415.0775 (415.0770 calc. for $C_{18}H_{24}IO_3$, $(M+H)^+$).

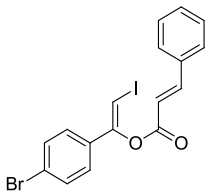
(*Z*)-2-Iodo-1-phenylvinyl cinnamate (61ba):



The reaction of (*E*)-cinnamic acid (**59b**) (44 mg, 0.30 mmol), iodoalkyne **60a** (68 mg, 0.30 mmol), $AuCl(PPh_3)$ (14.8 mg, 0.030 mmol) and $AgPF_6$ (7.6 mg, 0.030 mmol) in $CHCl_3$ (1.5 mL) for 45 h according to General Procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 95:5), 94 mg (83%) of **61ba** as a white solid. R_f = 0.22 (hexanes/EtOAc, 93:7); mp: 102-104 ^oC; IR (neat): 3106, 3085, 3051, 3000, 1731, 1633, 1309, 1261, 1186, 1126, 1015, 984, 861, 763, 733, 680, 488 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.92 (d, 1H, *J* = 16.0, ArC*H*=CH), 7.64-7.56 (m, 2H, Ar*H*), 7.50-7.39 (m, 5H, Ar*H*), 7.37-7.31 (m, 3H, Ar*H*), 6.69 (s, 1H, ArC=C*H*I), 6.66 (d, 1H, *J* = 16.0, Ar-C*H*=CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4 (*C*=C-I), 155.1 (*C*=O), 147.6 (Ar-*C*=C), 134.0 (ArC_{ipso}), 133.8 (ArC_{ipso}), 131.0 (Ar*C*), 129.4 (Ar*C*), 129.1 (2 x Ar*C*), 128.8 (2 x Ar*C*), 128.5 (2 x Ar*C*), 125.3 (2 x Ar*C*), 116.5 (Ar-C=*C*), 68.3 (C=*C*-I);

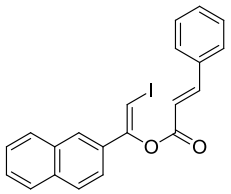
HRMS (APPI, pos.): *m/z* 375.9970 (375.9960 calc. for $C_{17}H_{13}IO_2$, $(M)^+$) and 394.0309 (394.0304 calc. for $C_{17}H_{17}INO_2$, $(M+NH_4)^+$).

(*Z*)-1-(4-Bromophenyl)-2-iodovinyl cinnamate (61bb):



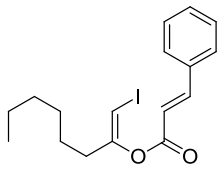
The reaction of **59b** (44 mg, 0.30 mmol), **60b** (92 mg, 0.30 mmol), $AuCl(PPh_3)$ (7.4 mg, 0.015 mmol) and $AgPF_6$ (3.8 mg, 0.015 mmol) in $CHCl_3$ (1.5 mL) for 64 h according to the General Procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 98:2), 86 mg (63%) of **61bb** as a semisolid. R_f = 0.26 (hexanes/EtOAc, 98:2); IR (neat): 3082, 2923, 2853, 1733, 1677, 1634, 1584, 1485, 1123, 1005, 764, 485 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.92 (d, 1H, *J* = 16.0, Ar-C*H*=CH), 7.65-7.57 (m, 2H, Ar*H*), 7.51-7.40 (m, 5H, Ar*H*), 7.33 (d, 2H, *J* = 8.7, Ar*H*), 6.72 (s, 1H, C=C*H*I), 6.65 (d, 1H, *J* = 16.0, Ar-CH=C*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4 (*C*-O), 154.2 (*C*=O), 148.0 (Ar-*C*=C), 134.0 (ArC_{ipso}). 132.9 (ArC_{ipso}), 132.1 (2 x Ar*C*), 131.2 (Ar*C*), 129.2 (2 x Ar*C*), 128.6 (2 x Ar*C*), 126.9 (2 x Ar*C*), 123.7 (Ar*C*), 116.4 (Ar-C=*C*), 69.2 (C=*C*HI); HRMS (APPI, pos.): *m/z* 453.9040 (453.9065 calc. for $C_{17}H_{12}BrIO_2$, (M^+) and 454.9109 (454.9144 calc. for $C_{17}H_{13}BrIO_2$, $(M+H)^+$).

(*Z*)-2-Iodo-1-(naphthalen-2-yl)vinyl cinnamate (61bc):



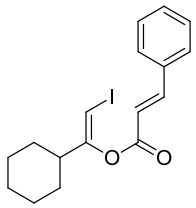
The reaction of **59b** (44 mg, 0.30 mmol), **60c** (83 mg, 0.30 mmol), $AuCl(PPh_3)$ (7.40 mg, 0.015 mmol) and $AgPF_6$ (3.80 mg, 0.015 mmol) in $CHCl_3$ (1.5 mL) for 67 h according to the General Procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 95:5), 83 mg (65%) of **61bc** as a semisolid. R_f = 0.23 (hexanes/EtOAc, 98:2); IR (neat): 3082, 3058, 2923, 2853, 1732, 1633, 1188, 1122, 980, 760, 475 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.97 (d, 1H, *J* = 16, Ar-C*H*=CH), 7.90 (d, 1H, *J* = 1.8, Ar*H*), 7.86-7.77 (m, 3H, Ar*H*), 7.68-7.61 (m, 2H, Ar*H*), 7.59 (dd, 1H, *J* = 8.7, 1.9, Ar*H*), 7.54-7.40 (m, 5H, Ar*H*), 6.85 (s, 1H, C=C*H*I), 6.73 (d, 1H, Ar-CH=C*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4 (*C*-O), 155.0 (*C*=O), 147.6 (Ar-*C*=C), 134.1 (2 x ArC_{ipso}), 133.5 (ArC_{ipso}), 133.1 (ArC_{ipso}), 131.0 (Ar*C*), 129.1 (2 x Ar*C*), 128.7 (Ar*C*), 128.6 (Ar*C*), 128.5 (2 x Ar*C*), 127.7 (Ar*C*), 126.9 (Ar*C*), 126.7 (Ar*C*), 124.6 (Ar*C*), 122.7 (Ar*C*), 116.5 (Ar-C=*C*), 68.8 (C=*C*HI); HRMS (APPI, pos.): *m/z* 426.0112 (426.0117 calc. for $C_{21}H_{15}IO_2$, (M^+) and 427.0184 (427.0195 calc. for $C_{21}H_{16}IO_2$, $(M+H)^+$).

(*Z*)-1-Iodooct-1-en-2-yl cinnamate (61bd):



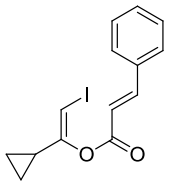
The reaction of (*E*)-cinnamic acid (**59b**) (74 mg, 0.50 mmol), iodoalkyne **60d** (118 mg, 0.500 mmol), AuCl(PPh_3) (12.4 mg, 0.025 mmol) and $AgPF_6$ (6.30 mg, 0.025 mmol) in $CHCl_3$ (2.5 mL) for 18 h according to General Procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 95:5), 178 mg (93%) of **61bd** as a clear oil. R_f = 0.27 (hexanes/EtOAc, 95:5); IR (neat): 3082, 3028, 2953, 2927, 2856, 1729, 1632, 1328, 1308, 1194, 1129, 979, 763, 501 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.83 (d, 1H, *J* = 16.0, Ar-C*H*=CH), 7.63-7.51 (m, 2H, Ar*H*), 7.46-7.35 (m, 3H, Ar*H*), 6.54 (d, 1H, *J* = 16.0, Ar-CH=C*H*), 5.87 (br t, 1H, *J* = 1.2, C=C*H*I), 2.44 (td, 2H, *J* = 7.6, 1.2, CH_2-C=C*H*I), 1.60-1.44 (m, 2H, IHC=CCH_2CH_2), 1.40-1.20 (m, 6H, (CH_2)$_3$$CH_3$, 0.95-0.80 (m, 3H, C$H_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.5 (*C*-O), 158.2 (*C*=O), 147.0 (Ar-*C*=C), 134.2 (ArC_{ipso}), 130.9 (Ar*C*), 129.1 (2 x Ar*C*), 128.5 (2 x Ar*C*), 117.0 (Ar-C=*C*), 65.2 (C=*C*I), 34.7 (*C*H_2), 31.6 (*C*H_2), 28.7 (*C*H_2), 26.5 (*C*H_2), 22.6 (*C*H_2), 14.2 (*C*H_3); HRMS (APPI, pos.): *m/z* 384.0596 (384.0586 calc. for $C_{17}H_{21}IO_2$, $(M)^+$) and 385.0668 (385.0664 calc. for $C_{17}H_{22}IO_2$, $(M+H)^+$).

(*Z*)-1-Cyclohexyl-2-iodovinyl cinnamate (61be):



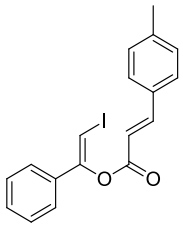
The reaction of **59b** (45 mg, 0.30 mmol), **60e** (70 mg, 0.30 mmol), $AuCl(PPh_3)$ (7.4 mg, 0.015 mmol) and $AgPF_6$ (3.8 mg, 0.015 mmol) in $CHCl_3$ (1.5 mL) for 47 h according to the General Procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 98:2), 69 mg (60%) of **61be** as a clear oil. R_f = 0.24 (hexanes/EtOAc, 98:2); IR (neat): 2925, 2852, 1728, 1632, 1448, 1306, 1190, 1120, 1006, 978, 761, 702, 680, 484 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.83 (d, 1H, *J* = 16.0, Ar-C*H*=CH), 7.62-7.53 (m, 2H, Ar*H*), 7.45-7.38 (m, 3H, Ar*H*), 6.55 (d, 1H, *J* = 16.0, Ar-CH=C*H*), 5.92 (d, 1H, *J* = 1.1, C=C*H*I), 2.43-2.27 (m, 1H, C*H*CH_2), 2.00-1.85 (m, 2H, CH_2), 1.84-1.73 (m, 2H, CH_2), 1.37-1.13 (m, 6H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4 (*C*-O), 162.0 (*C*=O), 146.9 (Ar-*C*=C), 134.2 (ArC_{ipso}), 130.8 (Ar*C*), 129.1 (2 x Ar*C*), 128.4 (2 x Ar*C*), 117.1 (Ar-C=*C*), 65.2 (C=*C*HI), 43.8 (*C*H), 30.7 (2 x *C*H_2), 26.05 (*C*H_2), 26.01 (2 x *C*H_2); HRMS (APPI, pos.): *m/z* 382.0413 (382.0430calc. for $C_{17}H_{19}IO_2$, (M^+) and 383.0486 (383.0508 calc. for $C_{17}H_{20}IO_2$, $(M+H)^+$).

(*Z*)-1-Cyclopropyl-2-iodovinyl cinnamate (61bf):



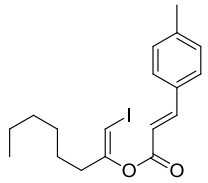
The reaction of **59b** (45 mg, 0.30 mmol), **60f** (58 mg, 0.30 mmol), $AuCl(PPh_3)$ (7.4 mg, 0.015 mmol) and $AgPF_6$ (3.8 mg, 0.015 mmol) in $CHCl_3$ (1.5 mL) for 24 h according to General Procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 98:2), 64 mg (63%) of **61bf** as a clear oil. R_f = 0.22 (hexanes/EtOAc, 98:2); IR (neat): 3083, 3008, 2921, 1729, 1632, 1190, 1124, 1048, 762 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.83 (d, 1H, *J* = 16.0, Ar-C*H*=CH), 7.62-7.52 (m, 2H, Ar*H*), 7.46-7.36 (m, 3H, Ar*H*), 6.53 (d, 1H, *J* = 16.0, Ar-CH=C*H*), 5.94 (d, 1H, *J* = 0.7, C=C*H*I), 1.85-1.73 (m, 1H, C*H*$(CH_2)_2$), 0.83-0.68 (m, 4H, CH$(CH_2)_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4 (*C*-O), 158.2 (*C*=O), 147.2 (Ar-*C*=C), 134.2 (ArC_{ipso}), 130.9 (Ar*C*), 129.1 (2 x Ar*C*), 128.5 (2 x Ar*C*), 116.8 (Ar-C=*C*), 63.9 (C=*C*HI), 15.1 *C*H$(CH_2)_2$), 5.8 CH$(CH_2)_2$); HRMS (APPI, pos.): *m/z* 339.9970 (339.9960 calc. for $C_{14}H_{13}IO_2$, (M^+) and 341.0042 (341.0038 calc. for $C_{14}H_{14}IO_2$, $(M+H)^+$).

(*E*)-(*Z*)-2-Iodo-1-phenylvinyl 3-(*p*-tolyl)acrylate (61ca):



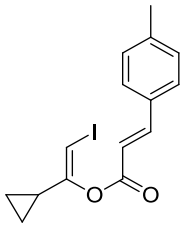
The reaction of **59c** (49 mg, 0.30 mmol), **60a** (68 mg, 0.30 mmol), $AuCl(PPh_3)$ (14.8 mg, 0.0300 mmol) and $AgPF_6$ (7.6 mg, 0.030 mmol) in $CHCl_3$ (1.5 mL) for 47 h according to the General Procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 98:2), 77 mg (66%) of **61ca** as a semisolid. R_f = 0.26 (hexanes/EtOAc, 98:2); IR (neat): 2955, 2923, 2854, 1734, 1633, 1607, 1267, 1224, 1199, 1177, 1124, 812, 752, 725, 495 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, 1H, *J* = 16.0, Ar-C*H*=CH), 7.54-7.43 (m, 4H, Ar*H*), 7.40-7.30 (m, 3H, Ar*H*), 7.23 (d, 2H, *J* = 7.9, Ar*H*), 6.69 (s, 1H, C=C*H*I), 6.62 (d, 1H, *J* = 16.0, Ar-CH=C*H*), 2.40 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.6 (*C*-O), 155.2 (*C*=O), 147.7 (Ar-*C*H=CH), 141.6 (ArC_{ipso}), 133.9 (ArC_{ipso}), 131.5 (ArC_{ipso}), 129.9 (2 x Ar*C*), 129.5 (Ar*C*), 128.9 (2 x Ar*C*), 128.6 (2 x Ar*C*), 125.4 (2 x Ar*C*), 115.5 (Ar-CH=*C*H), 68.3 (C=*C*HI), 21.7 (*C*H_3); HRMS (APPI, pos.): *m/z* 390.0121 (390.0117 calc. for $C_{18}H_{15}IO_2$, (M^+) and 391.0193 (391.0195 calc. for $C_{18}H_{16}IO_2$, $(M+H)^+$).

(*E*)-(*Z*)-1-Iodooct-1-en-2-yl 3-(*p*-tolyl)acrylate (61cd):



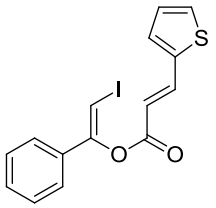
The reaction of **59c** (49 mg, 0.30 mmol), **60d** (71 mg, 0.30 mmol), $AuCl(PPh_3)$ (7.4 mg, 0.015 mmol) and $AgPF_6$ (3.8 mg, 0.015 mmol) in $CHCl_3$ (1.5 mL) for 27 h according to the General Procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 95:5), 74 mg (62%) of **61cd** as a clear oil. R_f = 0.22 (hexanes/EtOAc, 97:3); IR (neat): 2954, 2927, 2857, 1729, 1632, 1608, 1195, 1179, 1131, 982, 812, 498 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.80 (d, 1H, *J* = 16.0, Ar-C*H*=CH), 7.47 (d, 2H, *J* = 7.9, Ar*H*), 7.22 (d, 2H, *J* = 7.9, Ar*H*), 6.49 (d, 1H, *J* = 16.0, Ar-CH=C*H*), 5.86 (s, 1H, C=C*H*I), 2.43 (t, 2H, *J* = 7.5, CH_2C-O), 2.39 (s, 3H, Ar-CH_3), 1.51 (quint, 2H, *J* = 7.5, $CH_2CH_2CH_2$C-O), 1.37-1.23 (m, 6H, $(CH_2)_3CH_3$), 0.88 (t, 3H, *J* = 6.7, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.6 (*C*-O), 158.1 (*C*=O), 146.9 (Ar-*C*=C), 141.3 (ArC_{ipso}), 131.4 (ArC_{ipso}), 129.7 (2 x Ar*C*), 128.4 (2 x Ar*C*), 115.7 (Ar-C=*C*), 65.0 (C=*C*HI), 34.6 (*C*H_2), 31.5 (*C*H_2), 28.6 (*C*H_2), 26.4 (*C*H_2), 22.5 (*C*H_2), 21.5 (Ar-*C*H_3), 14.1 (CH_2*C*H_3); HRMS (APPI, pos.): *m/z* 398.0741 (398.0743 calc. for $C_{18}H_{23}IO_2$, (M^+) and 399.0813 (399.0821 calc. for $C_{18}H_{24}IO_2$, $(M+H)^+$).

(*E*)-(*Z*)-1-Cyclopropyl-2-iodovinyl 3-(*p*-tolyl)acrylate (61cf):



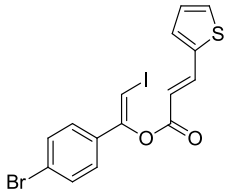
The reaction of **59c** (49 mg, 0.30 mmol), **60f** (58 mg, 0.30 mmol), $AuCl(PPh_3)$ (7.4 mg, 0.015 mmol) and $AgPF_6$ (3.8 mg, 0.015 mmol) in $CHCl_3$ (1.5 mL) for 24 h according to the General Procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 95:5), 72 mg (68%) of **61cf** as a clear oil. R_f = 0.20 (hexanes/EtOAc, 98:2); IR (neat): 3083, 3011, 2919, 2854, 1725, 1692, 1629, 1607, 1191, 1177, 1111, 1045, 809, 750, 495 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, 1H, *J* = 16.0, Ar-C*H*=CH), 7.47 (d, 2H, *J* = 8.1, Ar*H*), 7.21 (d, 2H, *J* = 8.1, Ar*H*), 6.48 (d, 1H, *J* = 16.0, Ar-CH=C*H*), 5.93 (d, 1H, *J* = 0.7, C=C*H*I), 2.39 (s, 3H, CH_3), 1.85-1.73 (m, 1H, C*H*$(CH_2)_2$), 0.82-0.68 (m, 4H, (CH_2)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.6 (*C*-O), 158.3 (*C*=O), 147.2 (Ar-*C*=C), 141.5 (ArC_{ipso}), 131.5 (ArC_{ipso}), 129.9 (2 x Ar*C*), 128.5 (2 x Ar*C*), 115.7 (Ar-C=*C*), 63.8 (C=*C*HI), 21.7 (*C*H_3), 15.2 *C*H$(CH_2)_2$), 5.7 (2 x *C*H_2); HRMS (APPI, pos.): *m/z* 354.0120 (354.0117 calc. for $C_{15}H_{15}IO_2$, (M^+) and 355.0193 (355.0195 calc. for $C_{15}H_{16}IO_2$, $(M+H)^+$).

(*E*)-(*Z*)-2-Iodo-1-phenylvinyl 3-(thiophen-2-yl)acrylate (61da):



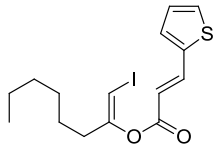
The reaction of **59d** (77 mg. 0.50 mmol), **60a** (114 mg, 0.500 mmol), $AuCl(PPh_3)$ (12.4 mg, 0.025 mmol) and $AgPF_6$ (6.3 mg, 0.025 mmol) in $CHCl_3$ (2.5 mL) for 50 h according to the General Procedure provided**,** after purification by flash chromatography on silica gel (hexanes/EtOAc, 9:1), 138 mg (72%) of **61da** as a semisolid. R_f = 0.28 (hexanes/EtOAc, 95:5); IR (neat): 3082, 2922, 2853, 1725, 1673, 1619, 1266, 1218, 1199, 1174, 1115, 1040, 1019, 969, 748, 485 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.00 (br dt, 1H, *J* = 15.6, 0.7, Ar-C*H*=CH), 7.51-7.41 (m, 3H, Ar*H*), 7.39-7.30 (m, 4H, Ar*H*), 7.09 (dd, 1H, *J* = 5.1, 3.7, Ar*H*), 6.68 (s, 1H, C=C*H*I), 6.45 (d, 1H, *J* = 15.6, Ar-CH=C*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.3 (*C*-O), 155.1 (*C*=O), 139.9 (Ar-*C*=C), 139.3 (ArC_{ipso}), 133.8 (ArC_{ipso}), 132.1 (Ar*C*), 129.6 (Ar*C*), 129.5 (Ar*C*), 128.9 (2 x Ar*C*), 128.4 (Ar*C*), 125.3 (2 x Ar*C*), 115.2 (Ar-C=*C*), 68.4 (C=*C*HI); HRMS (APPI, pos.): *m/z* 381.9506 (381.9524 calc. for $C_{15}H_{11}IO_2S$, (M^+) and 382.9578 (382.9603 calc. for $C_{15}H_{12}IO_2S$, $(M+H)^+$).

(*E*)-(*Z*)-1-(4-Bromophenyl)-2-iodovinyl-3-(thiophen-2-yl)acrylate (61db):



The reaction of **59d** (46 mg, 0.30 mmol), **60b** (92 mg, 0.30 mmol), $AuCl(PPh_3)$ (7.4 mg, 0.015 mmol) and $AgPF_6$ (3.8 mg, 0.015 mmol) in $CHCl_3$ (1.5 mL) for 66 h according to the General Procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 97:3), 106 mg (77%) of **61db** as a semisolid. R_f = 0.20 (hexanes/EtOAc, 98:2); IR (neat): 3082, 1728, 1620, 1218, 1200, 1174, 1119, 1006, 831, 709, 468 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.00 (d, 1H, *J* = 15.7, Ar-C*H*=CH), 7.51-7.44 (m, 3H, Ar*H*), 7.38-7.29 (m, 3H, Ar*H*), 7.10 (dd, 1H, *J* = 5.1, 3.7, Ar*H*), 6.71 (s, 1H, C=C*H*I), 6.43 (d, 1H, *J* = 15.7, Ar-CH=C*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.2 (*C*-O), 154.2 (*C*=O), 140.2 (Ar-*C*=C), 139.2 (ArC_{ipso}), 132.9 (Ar*C*), 132.3 (Ar*C*), 132.1 (2 x Ar*C*), 129.8 (Ar*C*), 128.5 (Ar*C*), 126.8 (2 x Ar*C*), 123.7 (ArC_{ipso}), 114.9 (Ar-*C*=C), 69.2 (C=*C*HI); HRMS (APPI, pos.): *m/z* 459.8622 (459.8630 calc. for $C_{15}H_{10}BrIO_2S$, (M^+) and 460.8685 (460.8708 calc. for $C_{15}H_{11}BrIO_2S$, $(M+H)^+$).

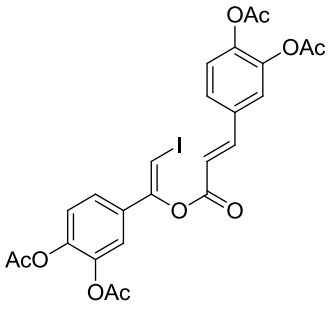
(*E*)-(*Z*)-1-Iodooct-1-en-2-yl-3-(thiophen-2-yl)acrylate (61dd):



The reaction of **59d** (46 mg, 0.30 mmol), **60d** (71 mg, 0.300 mmol), $AuCl(PPh_3)$ (7.4 mg, 0.015 mmol) and $AgPF_6$ (3.80 mg, 0.015 mmol) in $CHCl_3$ (1.5 mL) for 50 h

according to the General Procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 95:5), 83 mg (71%) of **61dd** as a clear oil. R_f = 0.26 (hexanes/EtOAc, 98:2); IR (neat): 2953, 2926, 2856, 1724, 1620, 1199, 1182, 1122, 1044, 968, 856, 828, 704, 489 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.92 (dt, 1H, *J* = 15.7, 0.8, Ar-C*H*=CH), 7.43 (dt, 1H, 5.1, 0.8, Ar*H*), 7.31 (br m, 1H, Ar*H*), 7.08 (dd, 1H, *J* = 5.1, 3.6, Ar*H*), 6.32 (d, 1H, *J* = 15.7, Ar-CH=C*H*), 5.86 (t, 1H, *J* = 1.1, C=C*H*I), 2.46-2.38 (m, 2H, CH_2-C=C*H*I), 1.56-1.43 (m, 2H, CH_2CH_2C=C*H*I), 1.39-1.21 (m, 6H, (CH_2)$_3$CH_3), 0.92-0.83 (m, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.3 (*C*-O), 158.1 (*C*=O), 139.4 (ArC_{ipso}), 139.3 (Ar-*C*=C), 131.8 (Ar*C*), 129.4 (Ar*C*), 128.4 (Ar*C*), 115.6 (Ar-C=*C*), 65.2 (C=*C*I), 34.7 (CH_2), 31.6 (*C*H$_2$), 28.7 (*C*H$_2$), 26.5 (*C*H$_2$), 22.6 (*C*H$_2$), 14.2 (*C*H$_3$); HRMS (APPI, pos.): *m/z* 390.0141 (390.0150 calc. for $C_{15}H_{19}IO_2S$, (M^+) and 391.0214 (391.0229 calc. for $C_{15}H_{20}IO_2S$, $(M+H)^+$).

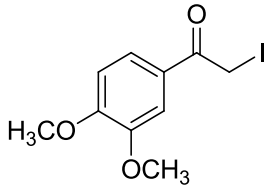
4-((*E*)-3-(((*Z*)-1-(3,4-Diacetoxyphenyl)-2-iodovinyl)oxy)-3-oxoprop-1-en-1-yl)-1,2-phenylene diacetate (61gi)[26]



The reaction of cinnamic acid **59g** (198 mg, 0.750 mmol), iodoalkyne **60i** (258 mg, 0.750 mmol), AuCl(PPh_3) (56 mg, 0.15 mmol) and $AgPF_6$ (28 mg, 0.15 mmol) in $CHCl_3$ (5 mL) for 69 h according to General Procedure provided, after purification by flash

chromatography on silica gel (CH_2Cl_2/MeOH, 99.8:0.2), 246 mg (54%) of **61gi** as a clear oil. R_f = 0.26 (hexanes/EtOAc, 6:4); IR (neat): 3084, 2925, 2853, 1769, 1735, 1637, 1503, 1370, 1201, 1186, 1111, 1041, 902, 516 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.84 (d, 1H, *J* = 16.0, Ar-C*H*=CH), 7.52-7.42 (m, 2H, Ar*H*), 7.34 (dd, 1H, *J* = 8.5, 2.2, Ar*H*), 7.30-7.26 (m, 2H, Ar*H*), 7.19 (d, 1H, *J* = 8.5, Ar*H*), 6.72 (s, 1H, C*H*I), 6.58 (d, 1H, *J* = 16.0, Ar-CH=C*H*) 2.32 (s, 3H, C(O)CH_3), 2.31 (s, 3H, C(O)CH_3), 2.28 (s, 6H, 2 x C(O)CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.0 (*C*(O)CH_3), 167.91 (*C*(O)CH_3), 167.87 (*C*(O)CH_3), 167.85 (*C*(O)CH_3), 162.6 (C=*C*-O), 153.4 (CH-*C*=O), 145.7 (Ar-*C*H=CH), 144.1 (ArC_{ipso}), 142.9 (ArC_{ipso}), 142.6 (ArC_{ipso}), 142.2 (ArC_{ipso}), 132.7 (ArC_{ipso}), 132.4 (ArC_{ipso}), 126.9 (Ar*C*), 124.1 (Ar*C*), 123.8 (Ar*C*), 123.4 (Ar*C*), 123.1 (Ar*C*), 120.5 (Ar*C*), 117.5 (Ar-CH=*C*H), 69.6 (*C*-I), 20.7 (2 x *C*(O)CH_3), 20.6 (2 x *C*(O)CH_3); HRMS (APPI, neg.): *m/z* 608.0199 (608.0179 calc. for $C_{25}H_{21}IO_{10}$, $(M)^-$) and 607.0128 (607.0101 calc. for $C_{25}H_{20}IO_{10}$, $(M-H)^-$).

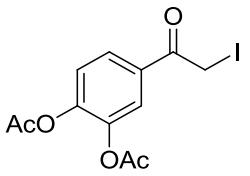
1-(3,4-Dimethoxyphenyl)-2-iodoethanone (62h)[37]



The reaction of 3,4-dimethoxy cinnamic acid **59e** (48 mg, 0.23 mmol), iodoalkyne **60h** (65 mg, 0.23 mmol), AuCl(PPh_3) (5.7 mg, 0.011 mmol) and $AgPF_6$ (3.0 mg, 0.011 mmol) in $CHCl_3$ (1.5 mL) for 5 h according to General Procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 6:4), 20 mg (28%) of **62h** as a clear

oil. R_f = 0.21 (hexanes/EtOAc, 6:4); IR (neat): 2932, 2838, 1659, 1582, 1512, 1459, 1419, 1265, 1221, 1140, 1097, 1017, 877, 808, 726, 508 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.62 (dd, 1H, *J* = 8.4, 2.1, Ar*H*), 7.54 (d, 1H, *J* = 2.1, Ar*H*), 6.90 (d, 1H, *J* = 8.4, Ar*H*), 4.33 (s, 2H, CH_2I), 3.97 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.8 (*C*=O), 154.0 (ArC_{ipso}), 149.5 (ArC_{ipso}), 126.7 (ArC_{ipso}), 124.0 (Ar*C*), 111.1 (Ar*C*), 110.2 (Ar*C*), 56.3 (OCH_3), 56.2 (OCH_3), 1.3 (CH_2).

4-(2-Iodoacetyl)-1,2-phenylene diacetate (62i)



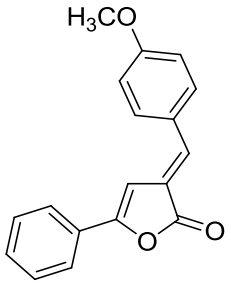
The reaction of cinnamic acid **59g** (198 mg, 0.750 mmol), iodoalkyne **60i** (258 mg, 0.750 mmol), AuCl(PPh_3) (56 mg, 0.15 mmol) and $AgPF_6$ (28 mg, 0.15 mmol) in $CHCl_3$ (5 mL) for 69 h according to General Procedure 1 provided, after purification by flash chromatography on silica gel (CH_2Cl_2/MeOH, 99.8:0.2), 27 mg (10%) of **62i** as a clear oil. R_f = 0.26 (CH_2Cl_2/hexanes, 8:2); IR (neat): 2936, 1766, 1675, 1587, 1501, 1369, 1285, 1263, 1192, 1164, 1117, 1087, 1007, 895 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.90 (dd, 1H, *J* = 8.5, 2.1, Ar*H*), 7.83 (d, 1H, *J* = 2.1, Ar*H*), 7.33 (d, 1H, *J* = 8.5, Ar*H*), 4.32 (s, 2H, CH_2I), 2.33 (s, 3H, C(O)CH_3), 2.32 (s, 3H, C(O)CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.9 (*C*=O), 167.0 (O*C*OCH_3), 166.6 (O*C*OCH_3), 145.6 (ArC_{ipso}), 141.5 (ArC_{ipso}), 131.0 (ArC_{ipso}), 126.7 (Ar*C*), 123.6 (Ar*C*), 123.0 (Ar*C*), 19.8 (CH_3), 19.7 (CH_3); HRMS (APPI, neg.): *m/z* 361.9636 (361.9651 calc. for $C_{12}H_{11}IO_5$, $(M)^-$).

General Procedure for the synthesis of furanones from cinnamic acids and iodoalkynes:

To a solution of the cinnamic acid (1 equiv.) and the iodoalkyne (1 equiv.) in $CHCl_3$ were added $AuCl(PPh_3)$ (5 or 10 mol%) and $AgPF_6$ (5 or 10 mol%) at room temperature. The reaction flask was wrapped with aluminium foil and the reaction mixture was stirred at room temperature until consumption of the iodoalkyne (TLC). The mixture was directly applied to a short column of flash silica (5 cm height in a standard Pasteur pipette, approximately 600 mg of flash silica) packed in CH_2Cl_2. The column was then washed with CH_2Cl_2 (5 x 1 mL) and the combined eluates were concentrated under reduced pressure to provide the crude (*Z*)-*β*-iodoenol acrylate.

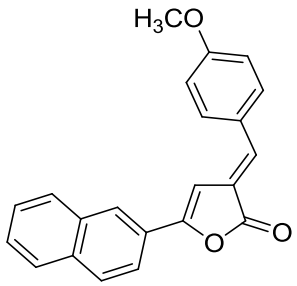
To a solution of the (*Z*)-*β*-iodoenol acrylate (1 equiv.) and $Pd(OAc)_2$ (10 mol%) in DMF (purged with N_2 for 15 min) was added KOAc (2.5 equiv.) at room temperature. The mixture was stirred at 40 ^oC or at 80 ^oC until consumption of the iodoenol cinnamate (TLC). The reaction mixture was then cooled to ambient temperature, H_2O (1 mL) was added and the mixture was extracted with EtOAc (3 x 2 mL). The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel.

(*E*)-3-(4-Methoxybenzylidene)-5-phenylfuran-2(3*H*)-one (66aa):



The reaction of **59a** (54 mg, 0.30 mmol), **60a** (68 mg, 0.30 mmol), $AuCl(PPh_3)$ (7.4 mg, 0.015 mmol) and $AgPF_6$ (3.8 mg, 0.015 mmol) in $CHCl_3$ (1.5 mL) for 15 h according to the General Procedure provided 138 mg of the crude iodoenol cinnamate**.** Reaction of the crude iodoenol cinnamate (122 mg, 0.30 mmol), KOAc (74 mg, 0.75 mmol) and $Pd(OAc)_2$ (6.70 mg. 0.03 mmol) in DMF at 80 ^oC for 5 h according to the General Procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 8:2), 49 mg (59%) of **66aa** as a yellow solid. R_f = 0.29 (hexanes/EtOAc, 8:2); mp: 170-172 ^oC; IR (neat): 2927, 2836, 1753, 1600, 1582, 1509, 1247, 1163, 1027, 999, 829, 741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ δ 7.79-7.72 (m, 2H, Ar*H*), 7.61 (d, 2H, *J* = 8.7, Ar*H*), 7.48-7.37 (m, 4H, Ar*H* and Ar-C*H*=C), 6.99 (d, 2H, *J* = 8.7, Ar*H*), 6.92 (br d, 1H, *J* = 1.2, C*H*=C-O), 3.88 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9 (*C*=O), 161.5 (ArC_{ipso}), 156.0 (CH=*C*-O), 135.5 (Ar-*C*H=C), 132.1 (2 x Ar*C*), 130.2 (Ar*C*), 128.9 (2 x Ar*C*), 128.3 (ArC_{ipso} or *C*-C=O), 128.0 (*C*-C=O or ArC_{ipso}), 125.2 (2 x Ar*C*), 123.0 (ArC_{ipso}), 114.7 (2 x Ar*C*), 99.9 (Ph-C=*C*H), 55.5 (O*C*H_3); HRMS (APPI, pos.): *m/z* 278.0947 (278.0943 calc. for $C_{18}H_{14}O_3$, $(M)^+$) and 279.1018 (279.1021 calc. for $C_{18}H_{15}O_3$, $(M+H)^+$).

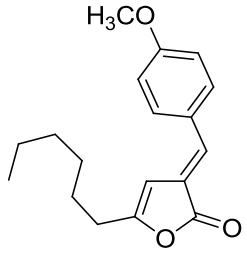
(*E*)-3-(4-Methoxybenzylidene)-5-(naphthalen-2-yl)furan-2(3*H*)-one (66ac):[10]



The reaction of **59a** (54 mg. 0.30 mmol), **60c** (83 mg, 0.30 mmol), AuCl(PPh_3) (7.4 mg, 0.015 mmol) and $AgPF_6$ (3.8 mg, 0.015 mmol) in $CHCl_3$ (1.5 mL) for 15 h according to the General Procedure provided 138 mg of the crude iodoenol cinnamate**.** Reaction of the crude iodoenol cinnamate (138 mg, 0.30 mmol), KOAc (74 mg, 0.75 mmol) and $Pd(OAc)_2$ (6.7 mg. 0.030 mmol) in DMF at 80 ^oC for 1 h according to the General Procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 9:1), 51 mg (52%) of **66ac** as a yellow solid. R_f = 0.29 (hexanes/EtOAc, 9:1); mp: 121-122 ^oC (Lit.[10] 123-124 ^oC); IR (neat): 2954, 2912, 2833, 1755, 1592, 1567, 1510, 1246, 1169, 1012, 814, 746 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.26 (br s, 1H, Ar*H*), 7.94-7.81 (m, 3H, Ar*H*), 7.77 (dd, 1H, *J* = 8.7, 1.7, Ar*H*), 7.64 (d, 2H, *J* = 8.7, Ar*H*), 7.58-7.48 (m, 2H, Ar*H*), 7.43 (s, 1H, C*H*=C-O), 7.03 (s, 1H, Ph-C*H*=C), 7.00 (d, 2H, *J* = 8.7, Ar*H*), 3.89 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9 (*C*=O), 161.5 (ArC_{ipso}), 156.0 (CH=*C*-O), 135.5 (Ar-*C*H=C), 134.0 (ArC_{ipso}), 133.2 (ArC_{ipso}), 132.2 (2 x Ar*C*), 128.8 (Ar*C*), 128.7 (Ar*C*), 128.1 (Ar*C*), 127.8 (Ar*C*), 127.4 (Ar*C*), 127.0 (ArC_{ipso}), 125.4 (*C*-C=O), 125.3 (Ar*C*), 123.0 (ArC_{ipso}), 121.9 (Ar*C*), 114.8 (2 x Ar*C*),

100.5 (*C*H=C-O), 55.5 (O*C*H_3); HRMS (APPI, pos.): 328.1098 (328.1099 calc. for $C_{22}H_{16}O_3$, $(M)^+$) and 329.1169 (329.1178 calc. for $C_{22}H_{17}O_3$ $(M+H)^+$).

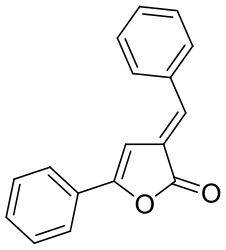
(*E*)-5-Hexyl-3-(4-methoxybenzylidene)furan-2(3*H*)-one (66ad):



The reaction of **59a** (89 mg, 0.50 mmol), **60d** (118 mg, 0.50 mmol), AuCl(PPh_3) (12.4 mg, 0.025 mmol) and $AgPF_6$ (6.3 mg, 0.025 mmol) in $CHCl_3$ (2 mL) for 18 h according to the General Procedure provided 208 mg of the crude iodoenol cinnamate. Reaction of the crude iodoenol cinnamate (208 mg, 0.50 mmol), KOAc (123 mg, 1.25 mmol) and $Pd(OAc)_2$ (11.2 mg. 0.05 mmol) in DMF at 40 ^oC for 54 h according to the General Procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 9:1), 79 mg (55%) of **66ad** as a clear oil. R_f = 0.21 (hexanes/EtOAc, 9:1); IR (neat): 2954, 2928, 2856, 1763, 1628, 1593, 1511, 1304, 1252, 1165, 1028, 924, 827 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.52 (d, 2H, *J* = 8.7, Ar*H*), 7.25 (s, 1H, ArC*H*=C), 6.94 (d, 2H, *J* = 8.7, Ar*H*), 6.24 (br q, 1H, *J* = 0.9, C*H*=C-CH_2), 3.86 (s, 3H, OCH_3), 2.47 (t, 2H, *J* = 7.1, CH_2C=CH), 1.65 (quint, 2H, *J* = 7.1, CH_2CH_2C=CH), 1.45-1.23 (m, 6H, $CH_3(CH_2)_3$), 0.90 (br t, *J* = 6.7, 3H, $CH_3(CH_2)_3$; ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4 (*C*=O), 161.2 (C=*C*-O or ArC_{ipso}) 161.1 (ArC_{ipso} or C=*C*-O), 133.9 (Ar-*C*H=C), 131.8 (2 x Ar*C*), 127.9 (*C*-C=O), 122.9 (ArC_{ipso}), 114.5 (2 x Ar*C*), 100.9 (*C*H=C-O), 55.4 (O*C*H_3), 31.5 (CH=C-*C*H_2), 28.9 (*C*H_2), 28.8 (*C*H_2), 26.0 (*C*H_2), 22.5

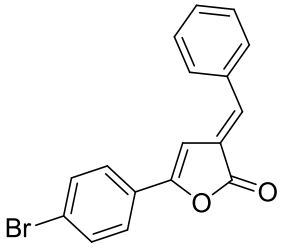
(*C*H_2), 14.1 (*C*H_3); HRMS (APPI, pos.): *m/z* 286.1569 (286.1569 calc. for $C_{18}H_{22}O_3$, (M^+)) and 287.1642 (287.1647 calc. for $C_{18}H_{23}O_3$, $(M+H)^+$).

(*E*)-3-Benzylidene-5-phenylfuran-2(3*H*)-one (66ba):[19a]



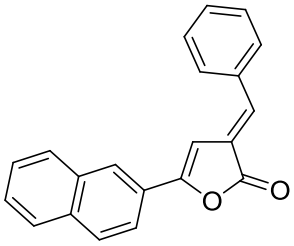
The reaction of **59b** (30 mg, 0.20 mmol), **60a** (46 mg, 0.20 mmol), AuCl(PPh_3) (10 mg, 0.020 mmol) and $AgPF_6$ (5.0 mg, 0.020 mmol) in $CHCl_3$ (1 mL) for 43 h according to the General Procedure provided 75 mg of the crude iodoenol cinnamate. Reaction of the crude iodoenol cinnamate (75 mg, 0.20 mmol), KOAc (49 mg, 0.50 mmol) and $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) in DMF at 80 ^oC for 1 h according to General Procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 9:1), 36 mg (72%) of **66ba** as a yellow solid. R_f = 0.21 (hexanes/EtOAc, 95:5); mp: 153-155 ^oC; IR (neat): 3120, 3025, 2999, 1754, 1625, 1450, 1278, 1003, 756, 733, 682 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.79-7.71 (m, 2H, Ar*H*), 7.65-7.59 (m, 2H, Ar*H*), 7.50-7.37 (m, 7H, 6 x Ar*H* and Ph-C*H*=C), 6.92 (d, 1H, *J* = 1.1, Ph-C*H*=C); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4 (*C*=O), 157.0 (*C*-O), 135.5 (Ph-*C*H=C), 135.2 (ArC_{ipso}), 130.6 (Ar*C*), 130.3 (Ar*C*), 130.1 (2 x Ar*C*), 129.2 (2 x Ar*C*), 128.9 (2 x Ar*C*), 128.1 (*C*-C=O), 125.5 (ArC_{ipso}), 125.4 (2 x Ar*C*), 99.9 (*C*H=C-O); HRMS (APPI, pos.): *m/z* 248.0849 (248.0837 calc. for $C_{17}H_{12}O_2$, $(M)^+$) and 249.0921 (249.0916 calc. for $C_{17}H_{13}O_2$, $(M+H)^+$).

(*E*)-3-Benzylidene-5-(4-bromophenyl)furan-2(3*H*)-one (66bb):[19b]



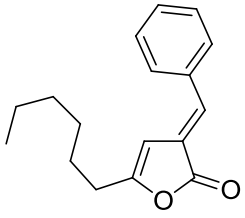
The reaction of **59b** (44 mg. 0.30 mmol), **60b** (92 mg, 0.30 mmol), $AuCl(PPh_3)$ (7.4 mg, 0.015 mmol) and $AgPF_6$ (3.8 mg, 0.015 mmol) in $CHCl_3$ (1.5 mL) for 64 h according to the General Procedure provided 137 mg of the crude iodoenol cinnamate**.** Reaction of the crude iodoenol cinnamate (137 mg, 0.30 mmol), KOAc (74 mg, 0.75 mmol) and $Pd(OAc)_2$ (6.7 mg. 0.030 mmol) in DMF at 80 ^oC for 45 min according to the General Procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 9:1), 51 mg (52%) of **66bb** as a yellow solid. R_f = 0.27 (hexanes/EtOAc, 9:1); mp: 208- 210 ^oC; IR (neat): 3128, 3026, 2921, 1752, 1619, 1585, 1449, 1278, 1170, 1067, 991, 823, 801, 755, 730, 675, 540 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.66-7.55 (m, 6H, Ar*H* and Ar-C*H*=C), 7.52-7.40 (m, 4H, Ar*H*), 6.94 (d, 1H, *J* = 1.0, C*H*=C-O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.0 (*C*=O), 156.0 (*C*-O), 136.2 (Ar-*C*H=C), 135.1 (ArC_{ipso}), 132.2 (2 x Ar*C*), 130.5 (*C*-C=O), 130.2 (2 x Ar*C*), 129.2 (2 x Ar*C*), 127.0 (ArC_{ipso}), 126.7 (2 x Ar*C*), 125.2 (ArC_{ipso}), 124.9 (ArC_{ipso}), 100.4 (*C*H=C-O); HRMS (APPI, pos.): *m/z* 325.9932 (325.9942 calc. for $C_{17}H_{11}{}^{79}BrO_2$, $(M)^+$) and 327.0014 (327.0021 calc. for $C_{17}H_{12}{}^{79}BrO_2$, $(M+H)^+$), 328.9996 (328.9999 calc. for $C_{17}H_{11}{}^{81}BrO_2$, $(M+H)^+$).

(*E*)-3-Benzylidene-5-(naphthalen-2-yl)furan-2(3*H*)-one (66bc):[10,19a]



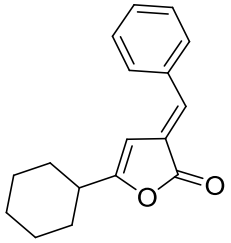
The reaction of **59b** (44 mg. 0.30 mmol), **60c** (83 mg, 0.30 mmol), $AuCl(PPh_3)$ (7.4 mg, 0.015 mmol) and $AgPF_6$ (3.8 mg, 0.015 mmol) in $CHCl_3$ (1.5 mL) for 67 h according to the General Procedure provided 128 mg of the crude iodoenol cinnamate. Reaction of the crude iodoenol cinnamate (128 mg, 0.30 mmol), KOAc (74 mg, 0.75 mmol) and $Pd(OAc)_2$ (6.7 mg. 0.030 mmol) in DMF at 80 ^oC for 1 h according to the General Procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 9:1), 45 mg (51%) of **66bc** as a yellow solid. R_f = 0.29 (hexanes/EtOAc, 9:1); mp: 173-174 ^oC (Lit.[10] mp: 172-173 ^oC); IR (neat): 3057, 3025, 1758, 1623, 1302, 1261, 1015, 803, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.27 (br s, 1H, Ar*H*), 7.95-7.81 (m, 3H, Ar*H* and Ph-C*H*=C), 7.77 (dd, 1H, *J* = 8.6, 1.6, Ar*H*), 7.70-7.62 (m, 2H, Ar*H*), 7.58-7.39 (m, 6H, Ar*H*), 7.04 (s, 1H, C*H*=C-O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4 (*C*=O), 157.0 (*C*-O), 135.5 (Ph-*C*H=C), 135.3 (naphthylC_{ipso}), 134.2 (ArC_{ipso} or *C*-C=O), 133.1 (*C*-C=O or ArC_{ipso}), 130.3 (Ar*C*) , 130.2 (2 x Ar*C*), 129.2 (2 x Ar*C)*, 128.9 (Ar*C*), 128.8 (Ar*C*), 127.9 (Ar*C*), 127.6 (Ar*C*), 127.0 (Ar*C*), 125.7 (Ar*C*), 125.5 (Ar*C*), 125.2 (Ar*C*), 122.0 (Ar*C*), 100.5 (C=C-O); HRMS (APPI, pos.): *m/z* 298.0998 (298.0994 calc. for $C_{21}H_{14}O_2$, $(M)^+$) and 299.1066 (299.1072 calc. for $C_{21}H_{15}O_2$, $(M+H)^+$).

(*E*)-3-Benzylidene-5-hexylfuran-2(3*H*)-one (66bd):



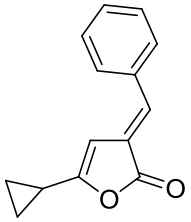
The reaction of **59b** (74 mg, 0.50 mmol), **60d** (118 mg, 0.500 mmol), $AuCl(PPh_3)$ (12.4 mg, 0.0250 mmol) and $AgPF_6$ (6.30 mg, 0.0250 mmol) in $CHCl_3$ (2.5 mL) for 24 h according to the General Procedure provided 178 mg of the crude iodoenol cinnamate. Reaction of the crude iodoenol cinnamate (178 mg, 0.460 mmol), KOAc (113 mg, 1.15 mmol) and $Pd(OAc)_2$ (10 mg, 0.046 mmol) in DMF at 40 ^oC for 24 h according to the General Procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 95:5), 73 mg (57%) of **66bd** as a yellow oil. R_f = 0.27 (hexanes/EtOAc, 95:5); IR (neat): 2954, 2928, 2857, 1770, 1629, 1451, 1173, 1156, 1028, 961, 762, 689 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.58-7.52 (m, 2H, Ar*H*), 7.47-7.34 (m, 3H, Ar*H*), 7.30 (br s, 1H, ArC*H*), 6.26 (br q, 1H, *J* = 1.1, CH_2C=C*H*), 2.48 (br t 2H, *J* = 7.5, C*H*$_2$C=CH), 1.65 (quint, 2H, *J* = 7.5, C*H*$_2$CH$_2$C-O), 1.45-1.23 (m, 6H, $CH_3(CH_2)_3CH_2$), 0.94-0.84 (br t, 3H, *J* = 6.8, C*H*$_3$(CH$_2$)$_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9 (*C*=O), 162.3 (*C*-O), 135.2 (ArC_{ipso}), 133.9 (Ar-*C*H=C), 129.9 (3 x Ar*C*), 129.0 (2 x Ar*C*), 125.4 (*C*-C=O), 101.1 (*C*H=C-CH$_2$), 31.5 (CH=C-*C*H$_2$), 28.9 (*C*H$_2$), 28.8 (*C*H$_2$), 25.9 (*C*H$_2$), 22.5 (*C*H$_2$), 14.0 (*C*H$_3$); HRMS (APPI, pos.): *m/z* 256.1461 (256.1463 calc. for $C_{17}H_{20}O_2$, $(M)^+$) and 274.1812 (274.1807 calc. for $C_{17}H_{24}NO_2$, $(M+NH_4)^+$).

(*E*)-3-Benzylidene-5-cyclohexylfuran-2(3*H*)-one (66be):



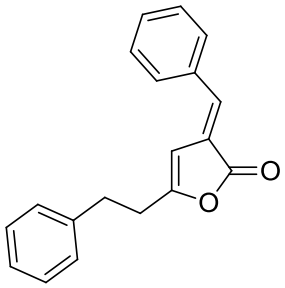
The reaction of **59b** (45 mg. 0.30 mmol), **60e** (70 mg, 0.30 mmol), $AuCl(PPh_3)$ (7.4 mg, 0.015 mmol) and $AgPF_6$ (3.8 mg, 0.015 mmol) in $CHCl_3$ (1.5 mL) for 47 h according to the General Procedure provided 115 mg of the crude iodoenol cinnamate. Reaction of the crude iodoenol cinnamate (115 mg, 0.30 mmol), KOAc (74 mg, 0.75 mmol) and $Pd(OAc)_2$ (6.7 mg. 0.030 mmol) in DMF at 40 ^oC for 118 h according to the General Procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 9:1), 39 mg (51%) of **66be** as a clear oil. R_f = 0.26 (hexanes/EtOAc, 9:1); IR (neat): 3051, 2923, 2851, 1762, 1621, 1447, 1157, 1126, 990, 929, 760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.58-7.52 (m, 2H, Ar*H*), 7.46-7.34 (m, 3H, Ar*H*), 7.31 (br s, 1H, Ph-C*H*=C), 6.21 (t, 1H, *J* = 1.1, (C*H*=C-O), 2.51–2.37 (m, 1H, (CH_2C*H*C-O), 2.06-1.96 (m, 2H, CH_2), 1.87-1.68 (m, 3H, CH_2), 1.46-1.18 (m, 5H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.0 (*C*=O), 166.2 (*C*-O), 135.2 (ArC_{ipso}), 134.0 (Ar-*C*H=C), 129.9 (3 x Ar*C*), 129.0 (2 x Ar*C*), 125.4 (*C*-C=O), 96.8 (*C*H=C-O), 37.6 (CH_2-*C*H), 29.7 (2 x *C*H_2), 25.9 (*C*H_2), 25.6 (2 x *C*H_2); HRMS (APPI, pos.): *m/z* 254.1311 (254.1307 calc. for $C_{17}H_{18}O_2$, $(M)^+$) and 255.1383 (255.1385 calc. for $C_{17}H_{19}O_2$, $(M+H)^+$).

(*E*)-3-Benzylidene-5-cyclopropylfuran-2(3*H*)-one (66bf):



The reaction of **59b** (45 mg, 0.30 mmol), **60f** (58 mg, 0.30 mmol), $AuCl(PPh_3)$ (7.4 mg, 0.015 mmol) and $AgPF_6$ (3.8 mg, 0.015 mmol) in $CHCl_3$ (1.5 mL) for 24 h according to General Procedure 3 provided 102 mg of the crude iodoenol cinnamate. Reaction of the crude iodoenol cinnamate (102 mg, 0.30 mmol), KOAc (74 mg, 0.75 mmol) and $Pd(OAc)_2$ (6.7 mg, 0.030 mmol) in DMF at 40 ^oC for 72 h according to the General Procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 9:1), 34 mg (54%) of **66bf** as a clear oil. R_f = 0.25 (hexanes/EtOAc, 9:1); IR (neat): 3090, 3015, 1769, 1631, 1300, 1048, 1022, 966, 759, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.57-7.51 (m, 2H, Ar*H*), 7.46-7.33 (m, 3H, Ar*H*), 7.21 (s, 1H, Ar-C*H*=C), 6.32 (s, 1H, C*H*=C-O), 1.83-1.71 (m, 1H, CH_2CHCH_2), 1.09-0.93 (m, 4H, CH_2CHCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7 (*C*=O), 162.9 (*C*-O), 135.3 (ArC_{ipso}), 132.5 (Ar-*C*H=C), 129.8 (2 x Ar*C*), 129.7 (Ar*C*), 129.0 (2 x Ar*C*), 125.4 (*C*-C=O), 99.6 (*C*H=C-O), 10.2 (*C*H), 7.1 (2 x CH_2); HRMS (APPI, pos.): *m/z* 212.0836 (212.0837 calc. for $C_{14}H_{12}O_2$, $(M)^+$) and 213.0909 (213.0916 calc. for $C_{14}H_{13}O_2$, $(M+H)^+$).

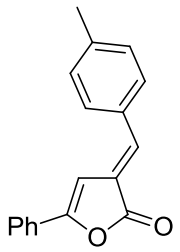
(*E*)-3-Benzylidene-5-phenethylfuran-2(3*H*)-one (66bg)



The reaction of (*E*)-cinnamic acid **59b** (44 mg. 0.30 mmol), iodoalkyne **60g** (77 mg, 0.30 mmol), $AuCl(PPh_3)$ (7.4 mg, 0.025 mmol) and $AgPF_6$ (3.8 mg, 0.025 mmol) in $CHCl_3$ (1.5 mL) for 7 h according to General Procedure provided 120 mg of the crude iodoenol cinnamate**.** Reaction of the crude iodoenol cinnamate (120 mg, 0.30 mmol), KOAc (74 mg, 0.75 mmol) and $Pd(OAc)_2$ (6.70 mg. 0.03 mmol) in DMF at 40 ^oC for 72 h according to General Procedure 6 provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 9:1), 14 mg (17%) of **66bg** as a clear oil.

R_f = 0.28 (hexanes/EtOAc, 9:1); IR (neat): 3027, 2926, 1769, 1630, 1451, 1174, 1159, 1030, 931, 763, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.55-7.49 (m, 2H, Ar*H*), 7.46-7.36 (m, 3H, 3 x Ar*H* or 2 x Ar*H* and Ph-C*H*=C), 7.34-7.27 (m, 3H, m, 3H, 3 x Ar*H* or 2 x Ar*H* and Ph-C*H*=C), 7.25-7.18 (m, 3H, Ar*H*), 6.24 (br q, *J* = 1.1, 1H, C*H*=C-O), 3.02-2.93 (m, 2H, C*H*$_2$CH$_2$Ph), 2.84-2.76 (m, 2H, CH$_2$C*H*$_2$Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7 (*C*=O), 160.9 (*C*-O), 140.1 (Ar*C*$_{ipso}$), 135.0 (Ar*C*$_{ipso}$), 134.6 (Ar-*C*H=C), 130.0 (Ar*C*), 129.9 (2 x Ar*C*), 129.0 (2 x Ar*C*), 128.6 (2 x Ar*C*), 128.3 (2 x Ar*C*), 126.5 (Ar*C*), 125.1 (*C*-C=O), 101.8 (*C*H=C-O), 32.2 (*C*H$_2$CH$_2$Ph), 30.9 (CH$_2$C*H*$_2$Ph); HRMS (APPI, pos.): 276.1148 (276.1150 calc. for $C_{19}H_{16}O_2$, (M^+)) and 294.1492 (294.1494 calc. for $C_{19}H_{20}NO_2$, $(M+NH_4)^+$).

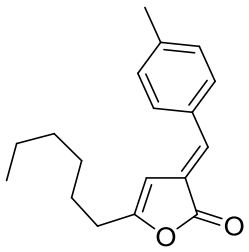
(*E*)-3-(4-Methylbenzylidene)-5-phenylfuran-2(3*H*)-one (66ca):[19a]



The reaction of **59c** (49 mg. 0.30 mmol), **60a** (68 mg, 0.30 mmol), $AuCl(PPh_3)$ (14.8 mg, 0.0300 mmol) and $AgPF_6$ (7.6 mg, 0.030 mmol) in $CHCl_3$ (1.5 mL) for 47 h according to the General Procedure provided 117 mg of the crude iodoenol cinnamate. Reaction of the crude iodoenol cinnamate (117 mg, 0.30 mmol), KOAc (74 mg, 0.75 mmol) and $Pd(OAc)_2$ (6.7 mg. 0.030 mmol) in DMF at 80 ^oC for 1 h according to the General Procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 95:5), 43 mg (53%) of **66ca** as a yellow solid.

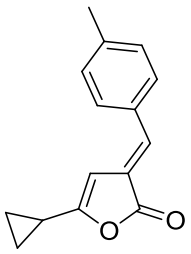
R_f = 0.27 (hexanes/EtOAc, 95:5); mp: 150-152 ^oC; IR (neat): 3043, 2913, 2852, 1753, 1448, 1278, 1169, 1001, 883, 802, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.79-7.73 (m, 2H, Ar*H*), 7.54 (d, 2H, *J* = 8.3, Ar*H*), 7.48-7.38 (m, 4H, Ar*H* and Ar-C*H*=C), 7.27 (d, 2H, *J* = 8.3, Ar*H*), 6.93 (d, 1H, *J* = 0.9, C*H*=C-O), 2.42 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6 (*C*=O), 156.5 (*C*-O), 141.0 (ArC_{ipso}), 135.7 (Ar-*C*H=C), 132.5 (ArC_{ipso}), 130.4 (Ar*C*), 130.2 (2 x Ar*C*), 129.9 (2 x Ar*C*), 128.9 (2 x Ar*C*), 128.2 (ArC_{ipso}), 125.3 (2 x Ar*C*), 124.5 (Ar*C*), 100.0 (*C*H=C-O), 21.6 (O*C*H_3); HRMS (APPI, pos.): *m/z* 262.1001 (262.0994 calc. for $C_{18}H_{14}O_2$, $(M)^+$) and 263.1074 (263.1072 calc. for $C_{18}H_{15}O_2$, $(M+H)^+$).

(*E*)-5-Hexyl-3-(4-methylbenzylidene)furan-2(3*H*)-one (66cd):



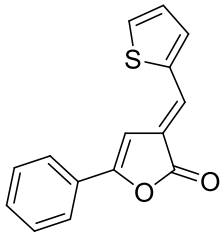
The reaction of **59c** (49 mg, 0.30 mmol), **60d** (71 mg, 0.30 mmol), $AuCl(PPh_3)$ (7.4 mg, 0.015 mmol) and $AgPF_6$ (3.8 mg, 0.015 mmol) in $CHCl_3$ (1.5 mL) for 27 h according to the General Procedure provided 120 mg of the crude iodoenol cinnamate. Reaction of the crude iodoenol cinnamate (120 mg, 0.30 mmol), KOAc (74 mg, 0.75 mmol) and $Pd(OAc)_2$ (6.70 mg. 0.03 mmol) in DMF at 40 ^oC for 72 h according to the General Procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 95:5), 43 mg (53%) of **66cd** as a yellow semisolid. R_f = 0.27 (hexanes/EtOAc, 95:5); IR (neat): 2954, 2925, 2856, 1763, 1630, 1601, 1169, 1031, 928, 812 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, 2H, *J* = 8.0, Ar*H*), 7.27 (s, 1H, Ar-C*H*=C), 7.23 (d, 2H, *J* = 8.0, Ar*H*), 6.25 (br m, 1H, C*H*=C-O), 2.47 (t, 2H, *J* = 7.5, CH_2C-O), 2.39 (s, 3H, CH_3), 1.64 (quint, 2H, *J* = 7.5, CH_2CH_2C-O), 1.42-1.26 (m, 6H, $CH_3(CH_2)_3CH_2$), 0.89 (br t, 3H, *J* = 6.7, $CH_3(CH_2)_3CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2 (*C*=O), 161.7 (*C*-O), 140.5 (ArC_{ipso}), 134.1 (Ar-*C*H=C), 132.4 (ArC_{ipso}), 130.0 (2 x Ar*C*), 129.8 (2 x Ar*C*), 124.4 (*C*-C=O), 101.1 (*C*H=C-O), 31.5 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 25.9 (CH_2), 22.5 (CH_2), 21.6 (CH_3), 14.0 (CH_3); HRMS (APPI, pos.): *m/z* 270.1627 (270.1620 calc. for $C_{18}H_{22}O_2$, $(M)^+$) and 271.1701 (271.1698 calc. for $C_{18}H_{23}O_2$, $(M+H)^+$).

(*E*)-5-Cyclopropyl-3-(4-methylbenzylidene)furan-2(3*H*)-one (66cf):



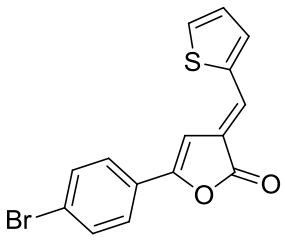
The reaction of **59c** (49 mg, 0.30 mmol), **60f** (58 mg, 0.30 mmol), $AuCl(PPh_3)$ (7.4 mg, 0.015 mmol) and $AgPF_6$ (3.8 mg, 0.015 mmol) in $CHCl_3$ (1.5 mL) for 24 h according to the General Procedure provided 106 mg of the crude iodoenol cinnamate. Reaction of the crude iodoenol cinnamate (106 mg, 0.30 mmol), KOAc (74 mg, 0.75 mmol) and $Pd(OAc)_2$ (6.7 mg. 0.030 mmol) in DMF at 40 ^oC for 70 h according to the General Procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 9:1), 35 mg (55%) of **66cf** as a clear oil. R_f = 0.25 (hexanes/EtOAc, 9:1); IR (neat): 3093, 3015, 2923, 1773, 1631, 1246, 1045, 1021, 967, 812 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.44 (d, 2H, *J* = 8.2, Ar*H*), 7.22 (d, 2H, *J* = 8.2, Ar*H*), 7.19 (s, 1H, Ar-C*H*=C), 6.30 (s, 1H, C*H*=C-O), 2.39 (s, 3H, CH_3), 1.82-1.71 (m, 1H, CH_2CHCH_2), 1.07-0.91 (m, 4H, CH_2CHCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9 (*C*=O), 162.2 (*C*-O), 140.3 (ArC_{ipso}), 132.8 (Ar-*C*H=C), 132.6 (ArC_{ipso}) 129.9 (2 x Ar*C*), 129.7 (2 x Ar*C*), 124.4 (*C*-C=O), 99.7 (*C*=C-O), 21.5 (*C*H_3), 10.1 (*C*H), 7.0 (2 x *C*H_2); HRMS (APPI, pos.): 226.1000 (226.0994 calc. for $C_{15}H_{14}O_2$, $(M)^+$) and 227.1073 (227.1072 calc. for $C_{15}H_{15}O_2$, $(M+H)^+$).

(*E*)-5-Phenyl-3-(thiophen-2-ylmethylene)furan-2(3H)-one (66da):[38]



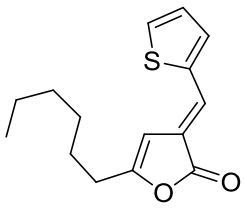
The reaction of **59d** (77 mg. 0.50 mmol), **60a** (114 mg, 0.500 mmol), $AuCl(PPh_3)$ (12.4 mg, 0.0250 mmol) and $AgPF_6$ (6.3 mg, 0.025 mmol) in $CHCl_3$ (2.5 mL) for 50 h according to the General Procedure 3 provided 191 mg of the crude iodoenol cinnamate. Reaction of the crude iodoenol cinnamate (191 mg, 0.500 mmol), KOAc (122 mg, 1.25 mmol) and $Pd(OAc)_2$ (11 mg. 0.050 mmol) in DMF at 80 ^oC for 1 h according to the General Procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 9:1), 69 mg (54%) of **66da** as a brown solid. R_f = 0.28 (hexanes/EtOAc, 9:1); mp: 130-132 ^oC; IR (neat): 3118, 3103, 3054, 1752, 1618, 1583, 1418, 1277, 1257, 1197, 996, 881, 734, 680 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.79-7.72 (m, 2H, Ar*H*), 7.58 (dt, 1H, *J* = 5.1, 1.0, Ar*H*), 7.56 (d, 1H, *J* = 1.0, Ar-C*H*=C),), 7.48-7.37 (m, 2H), 7.43 (d, 1H, *J* = 1.4), 7.4 (dt, 1H, *J* = 3.8, 0.8), 7.14 (dd, 1H, *J* = 5.1, 3.7, Ar*H*), 6.91 (d, 1H, *J* = 1.0, C*H*=C-O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5 (*C*=O), 156.1 (*C*-O), 139.5 (ArC_{ipso}), 134.1 (Ar-*C*H=C), 131.2 (Ar*C*), 130.6 (Ar*C*), 129.0 (2 x Ar*C*), 128.5 (Ar*C*), 128.2 (*C*-C=O), 127.4 (Ar*C*), 125.5 (2 x Ar*C*), 122.9 (ArC_{ipso}), 100.5 (*C*H=C-O); HRMS (APPI, pos.): *m/z* 254.0412 (254.0402 calc. for $C_{15}H_{10}O_2S$, $(M)^+$) and 255.0487 (255.0480 calc. for $C_{15}H_{11}O_2S$, $(M+H)^+$).

(*E*)-5-(4-Bromophenyl)-3-(thiophen-2-ylmethylene)furan-2(3*H*)-one (66db):



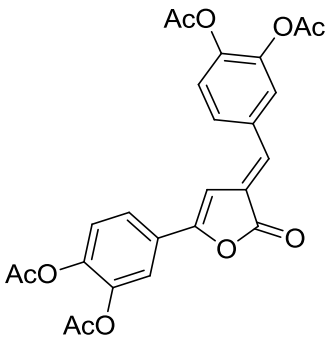
The reaction of **59d** (46 mg. 0.30 mmol), **60b** (92 mg, 0.30 mmol), $AuCl(PPh_3)$ (7.4 mg, 0.015 mmol) and $AgPF_6$ (3.8 mg, 0.015 mmol) in $CHCl_3$ (1.5 mL) for 66 h according to the General Procedure provided 138 mg of the crude iodoenol cinnamate. Reaction of the crude iodoenol cinnamate (138 mg, 0.300 mmol), KOAc (74 mg, 0.75 mmol) and $Pd(OAc)_2$ (6.7 mg. 0.030 mmol) in DMF at 80 ^oC for 20 min according to the General Procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 9:1), 61 mg (61%) of **66db** as a yellow semisolid. R_f = 0.27 (hexanes/EtOAc, 9:1); IR (neat): 2920, 2851, 1750, 1615, 1400, 992, 822, 805, 739, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.65-7.54 (m, 6H, Ar*H* and Ar-C*H*=C), 7.45-7.41 (m, 1H, Ar*H*), 7.16 (dd, 1H, *J* = 5.1, 3.8, Ar*H*), 6.94 (d, 1H, *J* = 0.8, C*H*=C-O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.0 (*C*=O), 154.9 (*C*-O), 139.3 (ArC_{ipso}), 134.3 (Ar-*C*H=C), 132.2 (2 x Ar*C*), 131.4 (Ar*C*), 128.5 (Ar*C*), 127.9 (Ar*C*), 127.0 (*C*-C=O), 126.7 (2 x Ar*C*), 124.7 (ArC_{ipso}), 122.5 (ArC_{ipso}), 100.9 (*C*H=C-O); HRMS (APPI, pos.): *m/z* 331.9511 (331.9507 calc. for $C_{15}H_9{}^{79}BrO_2S$, (M^+)), 333.9470 (333.9486 calc. for $C_{15}H_9{}^{81}BrO_2S$).

(*E*)-5-Hexyl-3-(thiophen-2-ylmethylene)furan-2(3*H*)-one (66dd):



The reaction of **59d** (46 mg, 0.30 mmol), **60d** (71 mg, 0.30 mmol), $AuCl(PPh_3)$ (7.4 mg, 0.025 mmol) and $AgPF_6$ (3.8 mg, 0.025 mmol) in $CHCl_3$ (1.5 mL) for 50 h according to the General Procedure provided 117 mg of the crude iodoenol cinnamate. Reaction of the crude iodoenol cinnamate (117 mg, 0.30 mmol), KOAc (74 mg, 0.75 mmol) and $Pd(OAc)_2$ (6.70 mg. 0.03 mmol) in DMF at 40 ^oC for 96 h according to the General Procedure provided, after purification by flash chromatography on silica gel (hexanes/EtOAc, 9:1), 24 mg (43%) of **66dd** as a white semisolid. R_f = 0.29 (hexanes/EtOAc, 9:1); IR (neat): 2952, 2927, 2854, 1759, 1625, 1604, 1147, 1020, 925, 847, 731, 707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.53 (dt, 1H, *J* = 5.1, 1.0, Ar*H*), 7.43 (q, 1H, *J* = 1.0, Ar-C*H*=CH), 7.35 (dt, 1H, *J* = 3.7, 1.0, Ar*H*), 7.11 (dd, 1H, *J* = 5.1, 3.7, Ar*H*), 6.26 (q, 1H, *J* = 1.0, C*H*=C-O), 2.49 (t, 2H, *J* = 7.6, 2H, CH_2-C-O), 1.66 (quint, 2H, *J* = 7.6, CH_2), 1.45-1.23 (m, 6H, (CH_2)$_3$, 0.90 (br t, 3H, *J* = 7.0, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9 (*C*=O), 161.5 (*C*-O), 139.4 (ArC_{ipso}), 133.4 (Ar-*C*H=C), 130.5 (Ar*C*), 128.2 (Ar*C*), 126.0 (Ar*C*), 122.8 (*C*-C=O), 101.6 (*C*H=C-O), 31.5 (*C*H_2-C-O), 29.0 (*C*H_2), 28.8 (*C*H_2), 26.0 (*C*H_2), 22.5 (*C*H_2), 14.1 (*C*H_3); HRMS (APPI, pos.): *m/z* 262.1031 (262.1028 calc. for $C_{15}H_{18}O_2S$, $(M)^+$) and 263.1102 (263.1106 calc. for $C_{15}H_{19}O_2S$, $(M+H)^+$).

(*E*)-4-(4-(3,4-Diacetoxybenzylidene)-5-oxo-4,5-dihydrofuran-2-yl)-1,2-phenylene diacetate (66gi):[26]

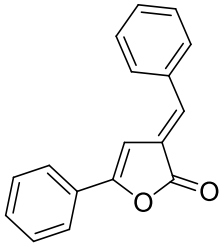


The reaction of iodoenol cinnamate **61gi** (237 mg, 0.390 mmol), KOAc (96 mg, 0.97 mmol) and $Pd(OAc)_2$ (8.8 mg, 0.039 mmol) in DMF at room temperature for 64 h according to the General Procedure provided, after purification by flash chromatography on silica gel (CH_2Cl_2/EtOAc, 98:2), 103 mg (55%) of **66gi** as a yellow solid. R_f = 0.27 (CH_2Cl_2/EtOAc, 96:4); mp: 157-158 ^oC (Lit.[24] 157-159 ^oC); IR (neat): 2927, 1764, 1499, 1428, 1370, 1194, 1170, 1114, 1010, 947, 900 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.64 (dd, 1H, *J* = 8.5, 1.8, Ar*H*), 7.58 (d, 1H, *J* = 1.8, Ar*H*), 7.48 (dd, 1H, *J* = 8.5, 1.8, Ar*H*), 7.44 (d, 1H, *J* = 1.8, Ar*H*), 7.38 (s, 1H, Ar-C*H*=C), 7.30 (d, 2H, *J* = 8.5, Ar*H*), 6.83 (s, 1H, C*H*=C-O), 2.34 (s, 3H, OCOCH_3), 2.32 (br s, 6H, 2 x OCOCH_3), 2.31 (s, 3H, OCOCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.5 (*C*=O), 168.05 (*C*=O), 168.02 (*C*=O), 167.91 (*C*=O), 167.89 (*C*=O), 156.0 (*C*-O), 143.9 (ArC_{ipso}), 143.5 (ArC_{ipso}), 142.60 (ArC_{ipso}), 142.57 (ArC_{ipso}), 134.0 (Ar-*C*H=C), 133.7 (ArC_{ipso}), 128.4 (Ar*C*), 126.7 (ArC_{ipso} or *C*-C=O), 126.1 (*C*-C=O or ArC_{ipso}), 124.6 (Ar*C*), 124.22 (Ar*C*), 124.20 (Ar*C*), 123.7 (Ar*C*), 120.7 (Ar*C*), 100.2 (*C*H=C-O), 20.73 (*C*H_3), 20.69 (*C*H_3), 20.68 (*C*H_3),

20.62 (*C*H_3); HRMS (APPI, neg.): *m/z* 480.1065 (480.1057 calc. for $C_{25}H_{20}O_{10}$, $(M)^-$) and 539.1136 (539.1190 calc. for $C_{27}H_{23}O_{12}$, $(M+OAc)^-$).

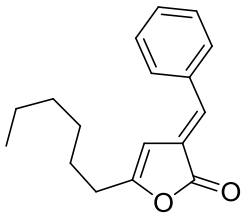
General procedure for the one-pot synthesis of furanones from cinnamic acids and iodoalkynes: To a solution of the cinnamic acid (1 equiv.) and the iodoalkyne (1 equiv.) in $CHCl_3$ (1.5 mL) were added $AuCl(PPh_3)$ (5 or 10 mol%) and $AgPF_6$ (5 or 10 mol%) at room temperature. The reaction flask was wrapped with aluminium foil and the reaction mixture was stirred at room temperature until consumption of the iodoalkyne (TLC). The reaction mixture was concentrated under reduced pressure. To a solution of the residue (crude (*Z*)-*β*-iodoenol cinnamate) and $Pd(OAc)_2$ (15 mol%) in DMF (1.5 mL, purged with N_2 for 15 min) was added KOAc (2.5 equiv.) at room temperature. The mixture was heated at the specified temperature until consumption of the iodoenol cinnamate (TLC). The reaction mixture was then cooled to ambient temperature, H_2O (1 mL) was added and the mixture was extracted with EtOAc (3 x 2 mL). The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel.

(*E*)-3-Benzylidene-5-phenylfuran-2(3*H*)-one (66ba):[19]



The reaction of (*E*)-cinnamic acid **59b** (44 mg. 0.30 mmol), iodoalkyne **60a** (68 mg, 0.30 mmol), $AuCl(PPh_3)$ (15 mg, 0.030 mmol), $AgPF_6$ (7.6 mg, 0.030 mmol) in $CHCl_3$ (stirred for 45 h), followed by reaction of $Pd(OAc)_2$ (10.0 mg, 0.044 mmol), KOAc (74 mg, 0.750 mmol) and DMF at 80 ^oC for 50 min according to general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 9:1), 45 mg (61%) of **66ba** as a yellow solid.

(*E*)-3-Benzylidene-5-hexylfuran-2(3*H*)-one (66bd):



The reaction of (*E*)-cinnamic acid **59b** (44 mg. 0.30 mmol), iodoalkyne **60d** (71 mg, 0.30 mmol), $AuCl(PPh_3)$ (7.4 mg, 0.015 mmol) and $AgPF_6$ (3.8 mg, 0.015 mmol) in $CHCl_3$ (stirred for 24 h), followed by reaction of $Pd(OAc)_2$ (10.0 mg, 0.044 mmol) and KOAc (74 mg, 0.75 mmol) in DMF at 40 ^oC for 27 h according to general procedure

provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 95:5), 49 mg (64%) of **66bd** as a yellow oil.

3.7 References

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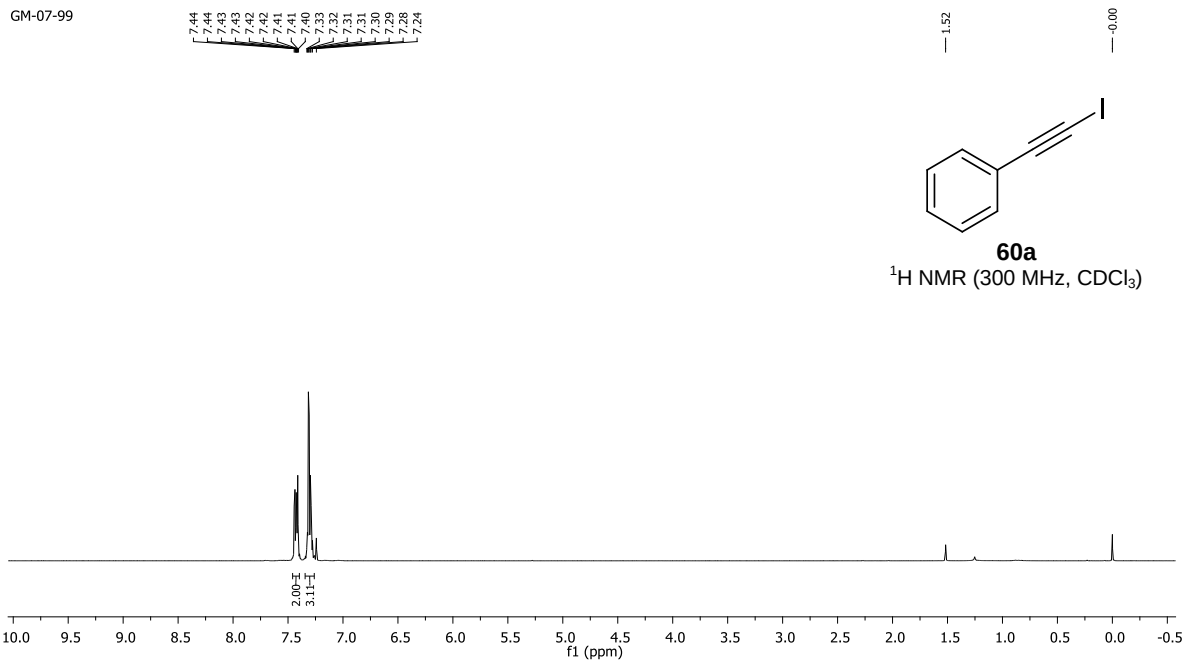
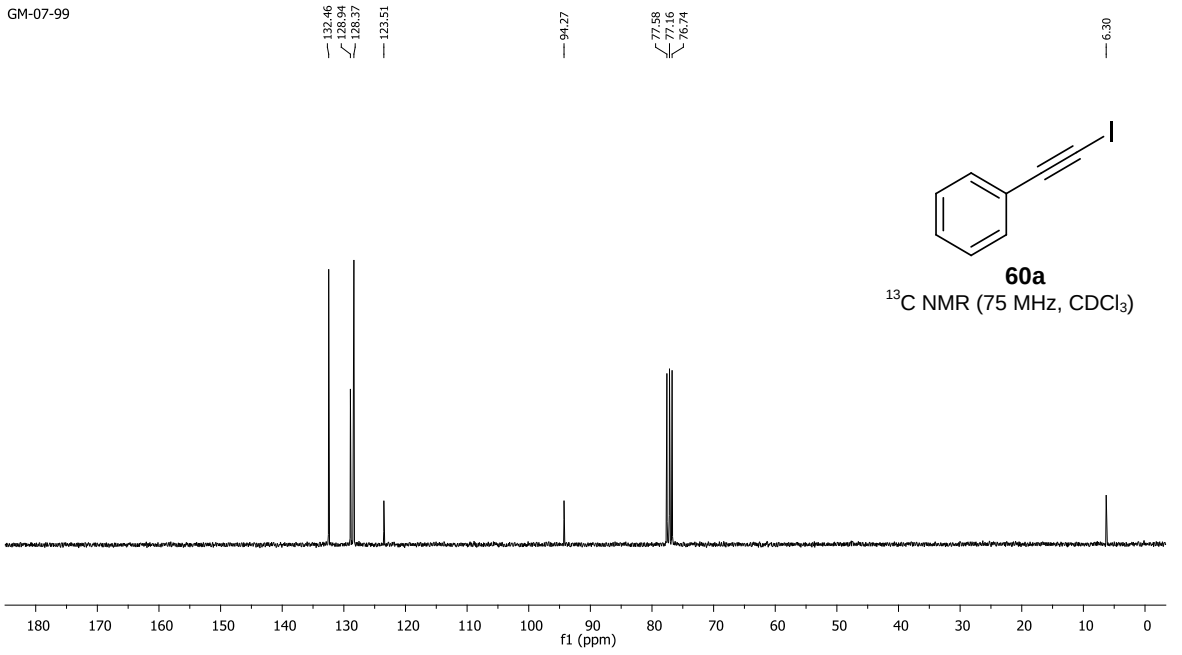
3.9 APPENDIX 3 (^{1}H and ^{13}C NMR spectras)



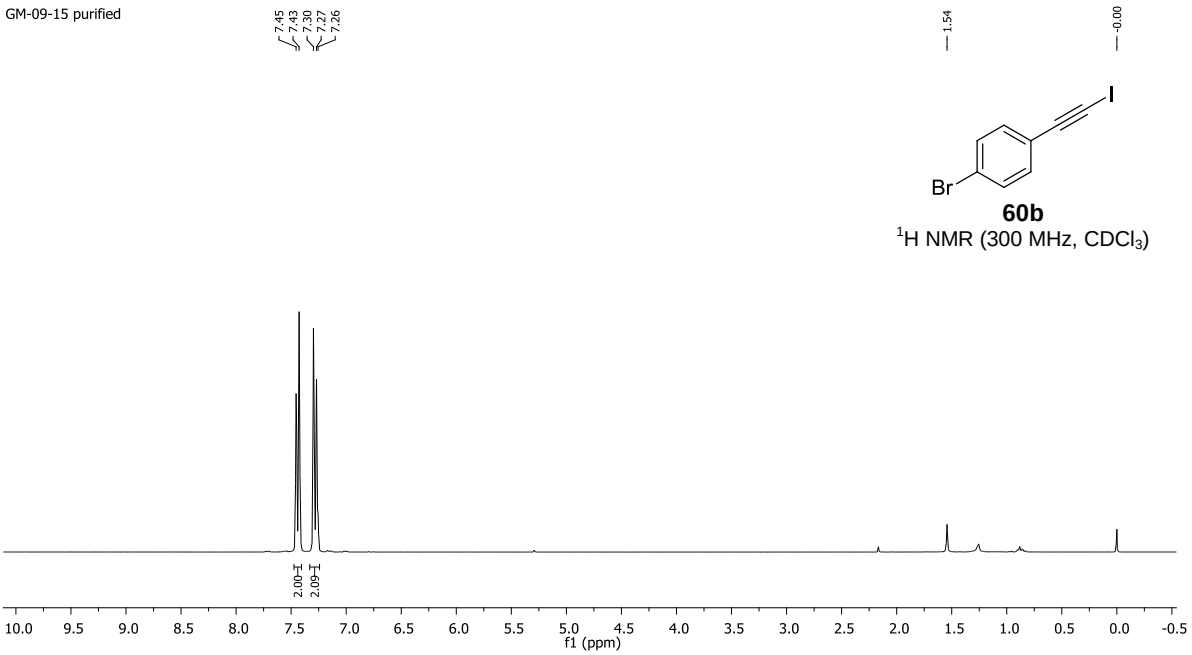
60a

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



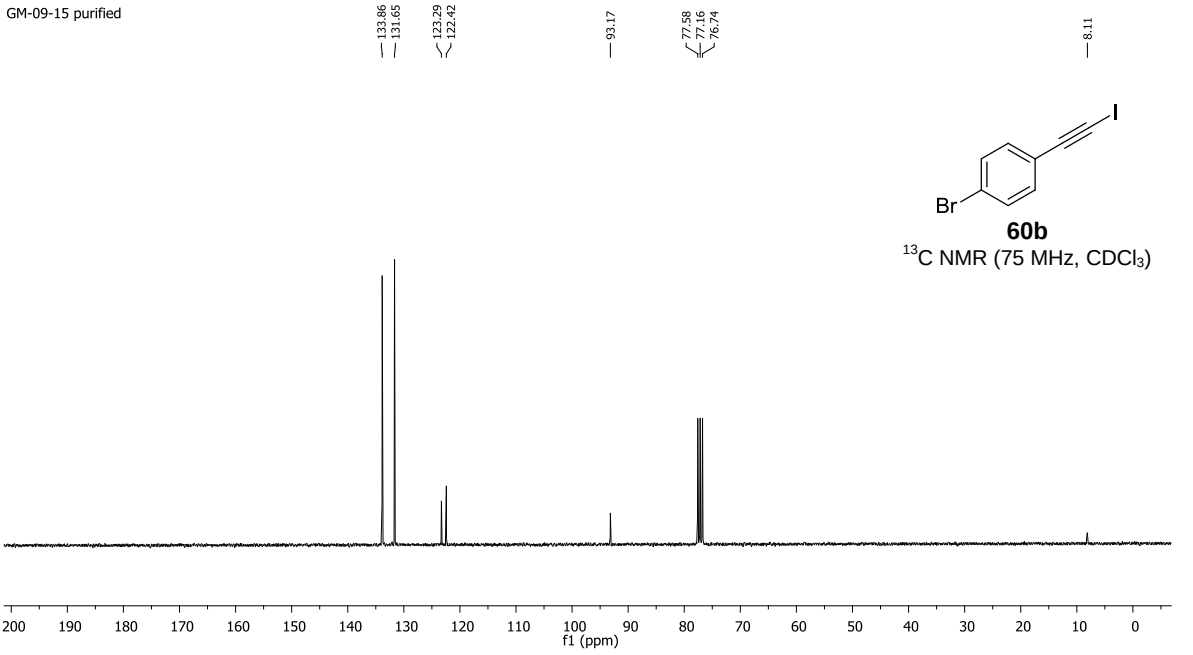
60a

^{13}C NMR (75 MHz, $CDCl_3$)



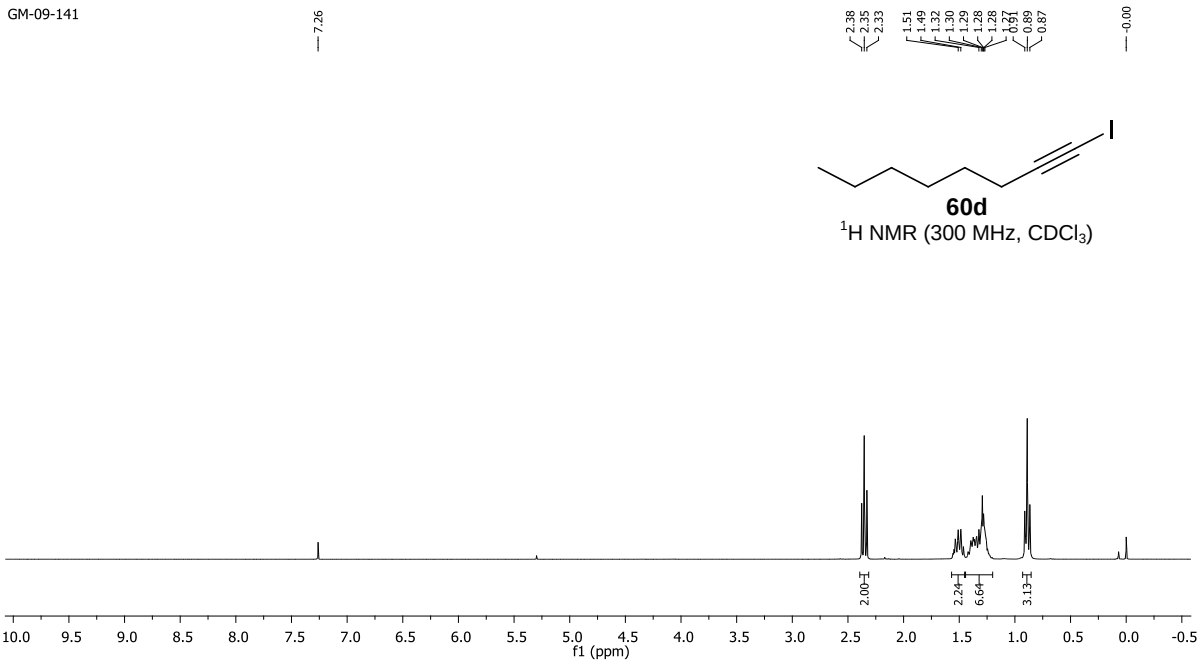
60b

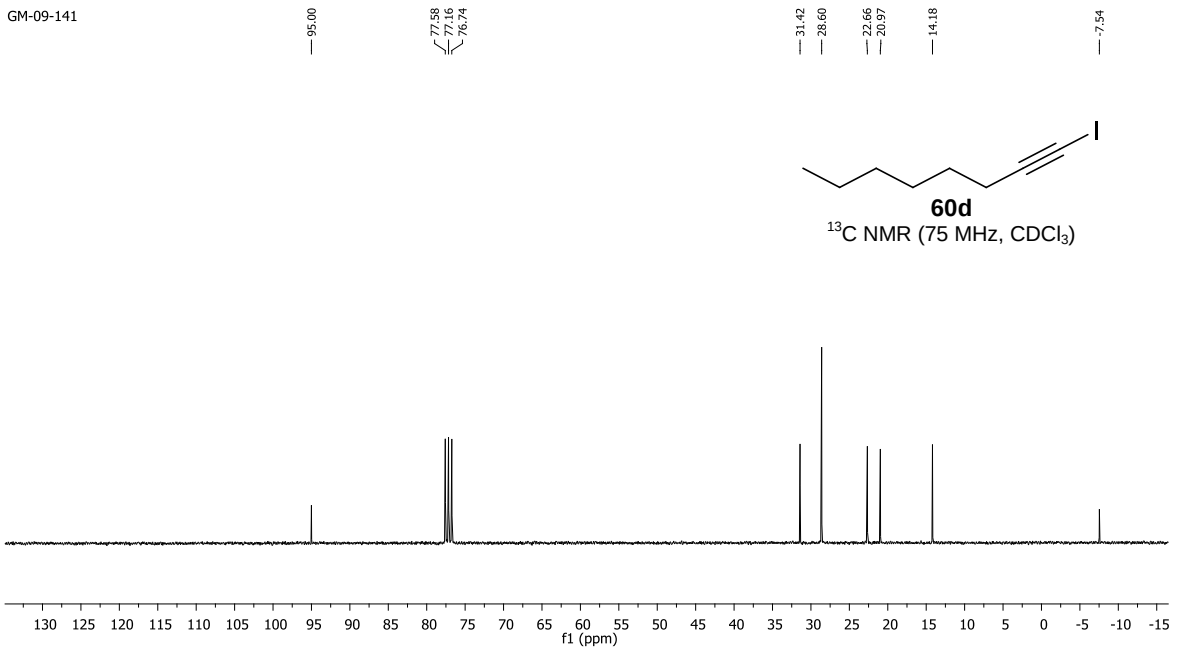
^{1}H NMR (300 MHz, $CDCl_3$)



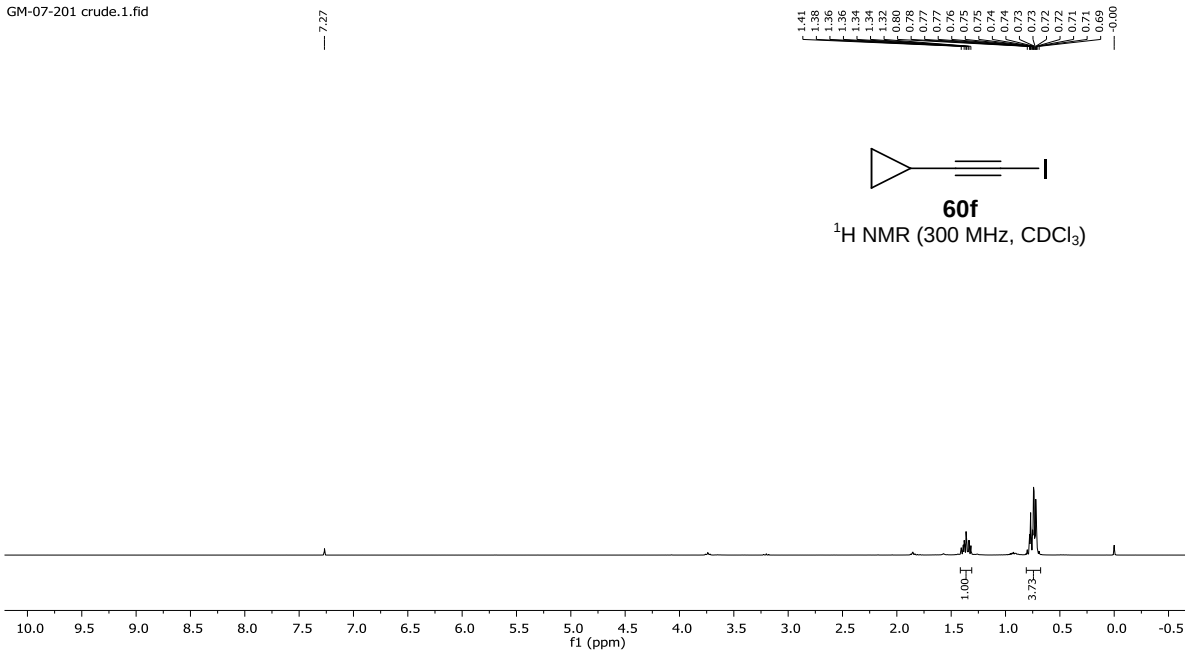
60b

^{13}C NMR (75 MHz, $CDCl_3$)


GM-09-141
7.26
2.38
2.35
2.33
1.51
1.49
1.32
1.30
1.29
1.28
1.28
1.27
0.91
0.89
0.87
-0.00
I
60d
1H NMR (300 MHz, CDCl3)
2.00
2.24
6.64
3.13
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


GM-09-141
95.00
77.58
77.16
76.74
31.42
28.60
22.66
20.97
14.18
-7.54
I
60d
13C NMR (75 MHz, CDCl3)
130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5 -10 -15
f1 (ppm)

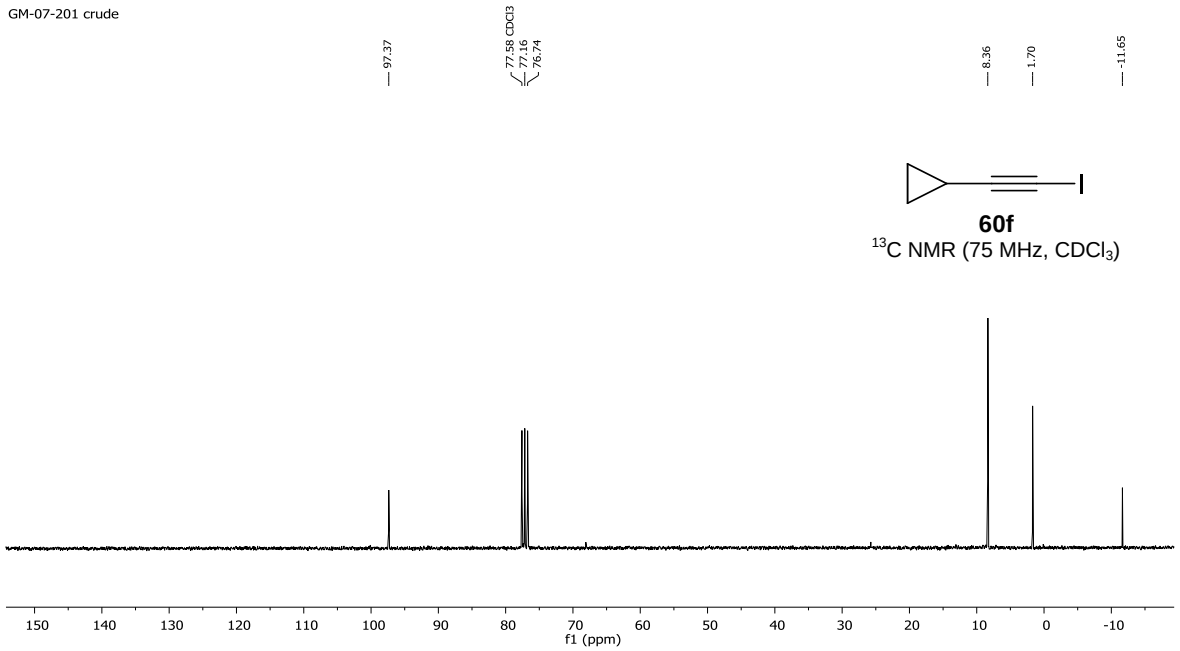
GM-07-201 crude.1.fid



60f

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

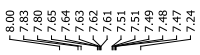
GM-07-201 crude

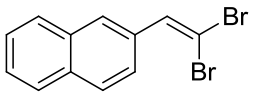


60f

^{13}C NMR (75 MHz, $CDCl_3$)

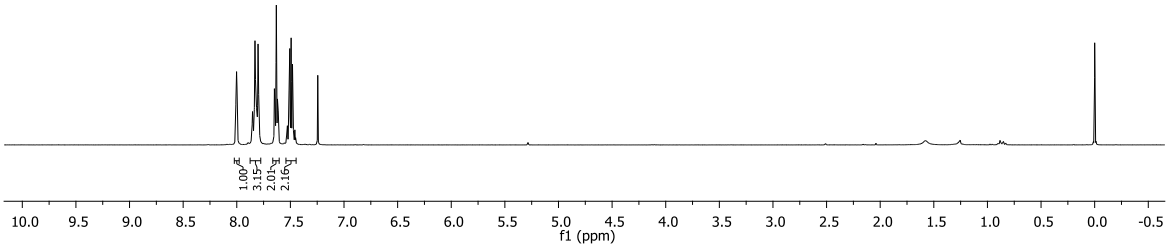
GM-08-87



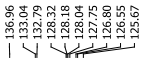


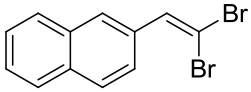
65c

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



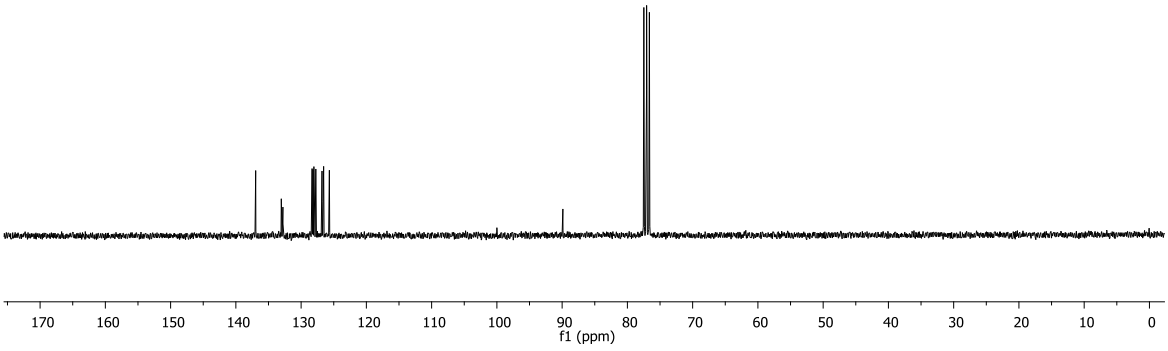
GM-08-87

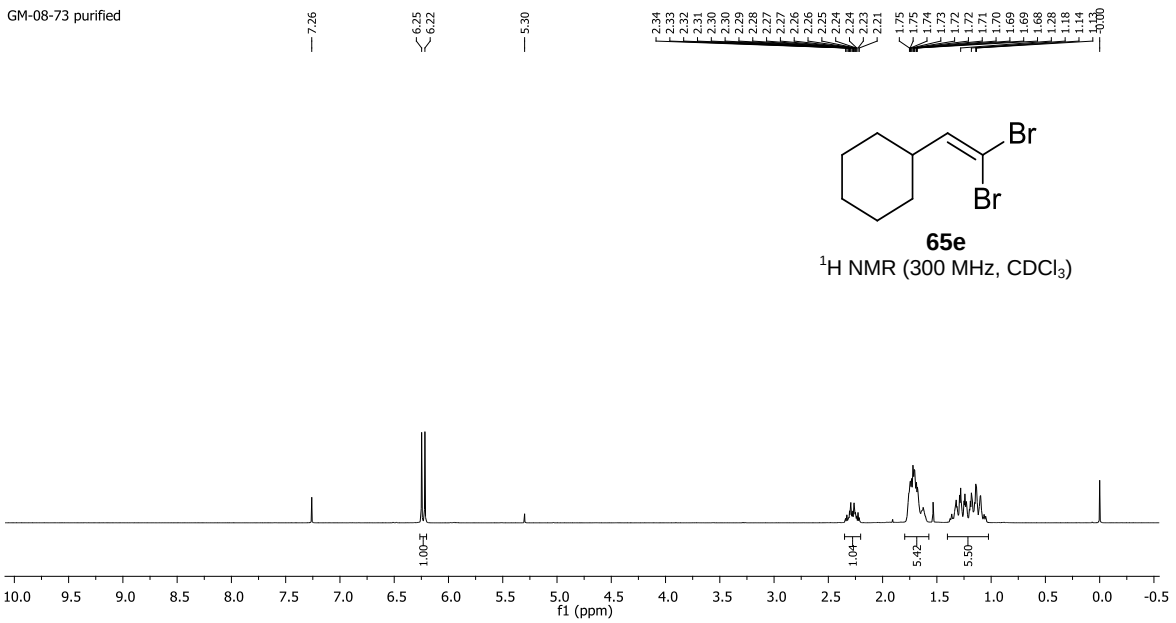




65c

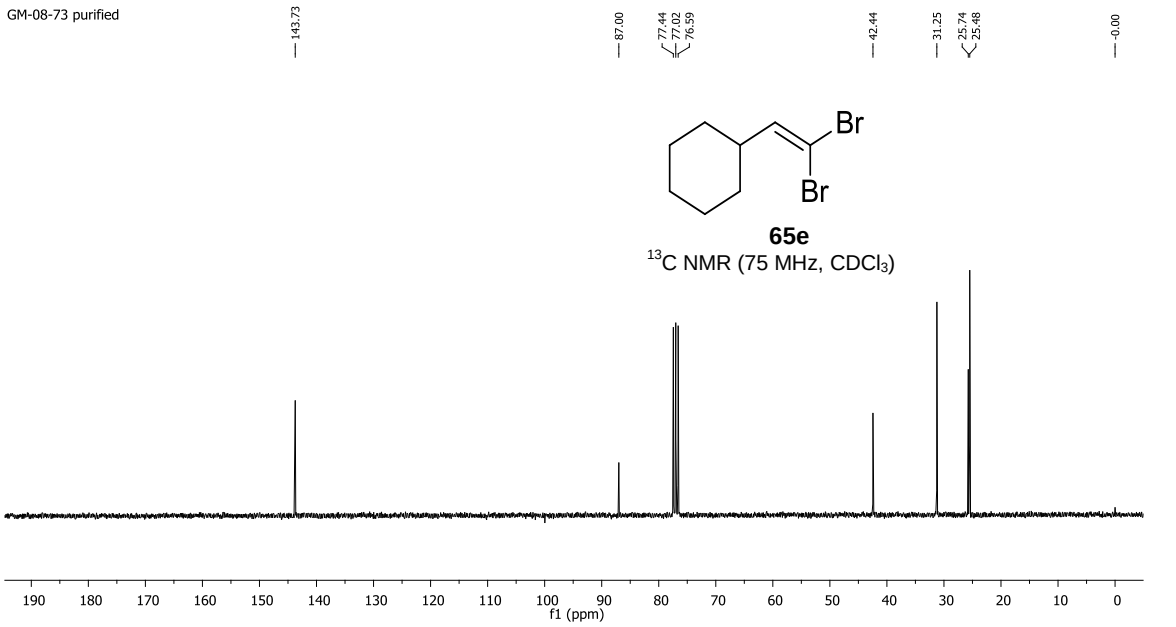
^{13}C NMR (75 MHz, $CDCl_3$)





65e

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



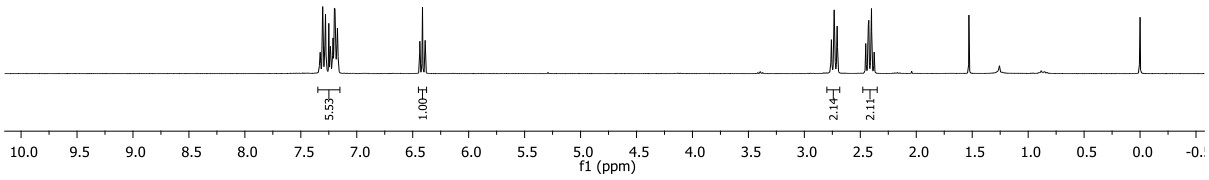
65e

^{13}C NMR (75 MHz, $CDCl_3$)

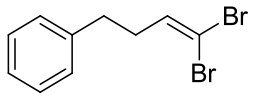
GM-08-57 purified.1.fid

65g

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

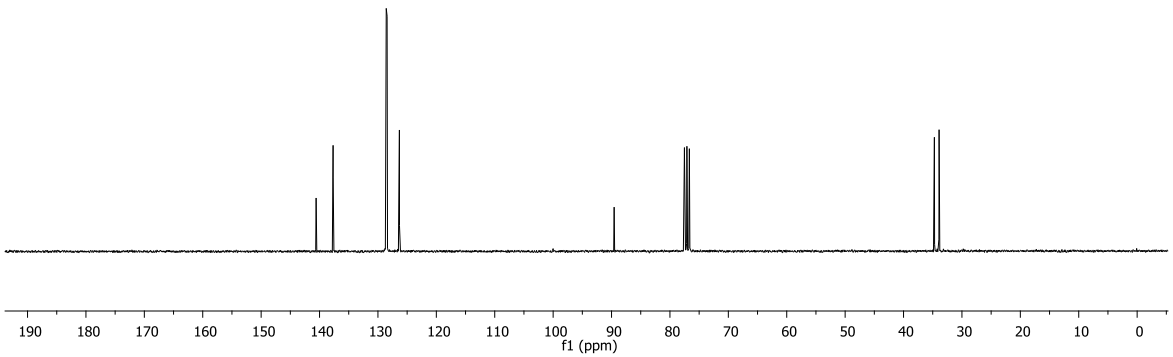


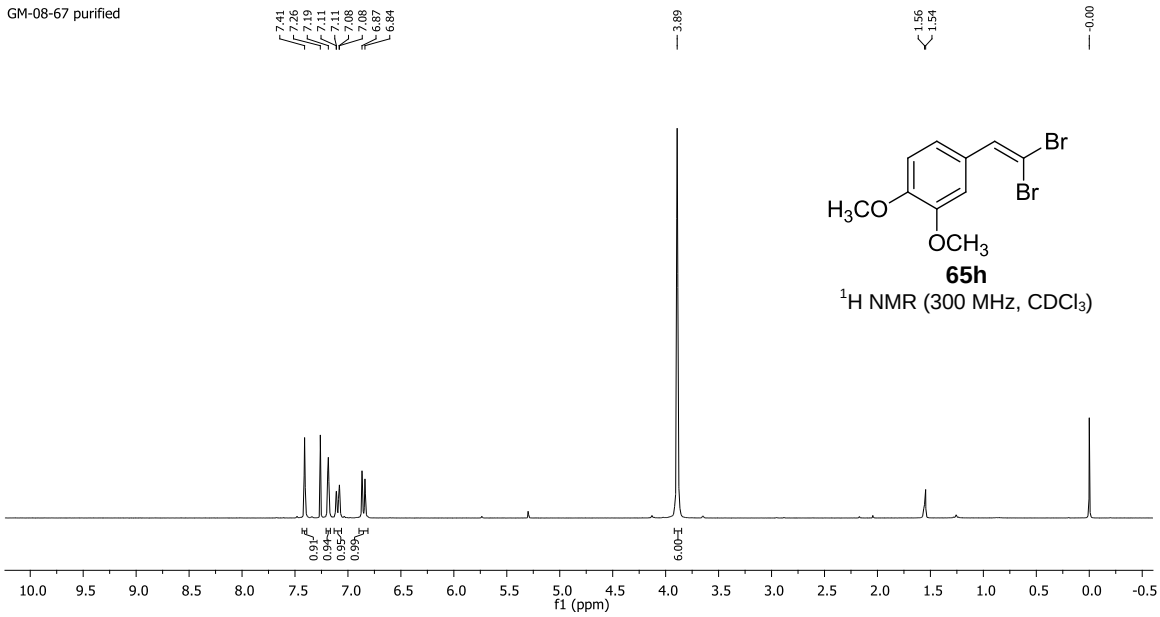
GM-08-57 purified



65g

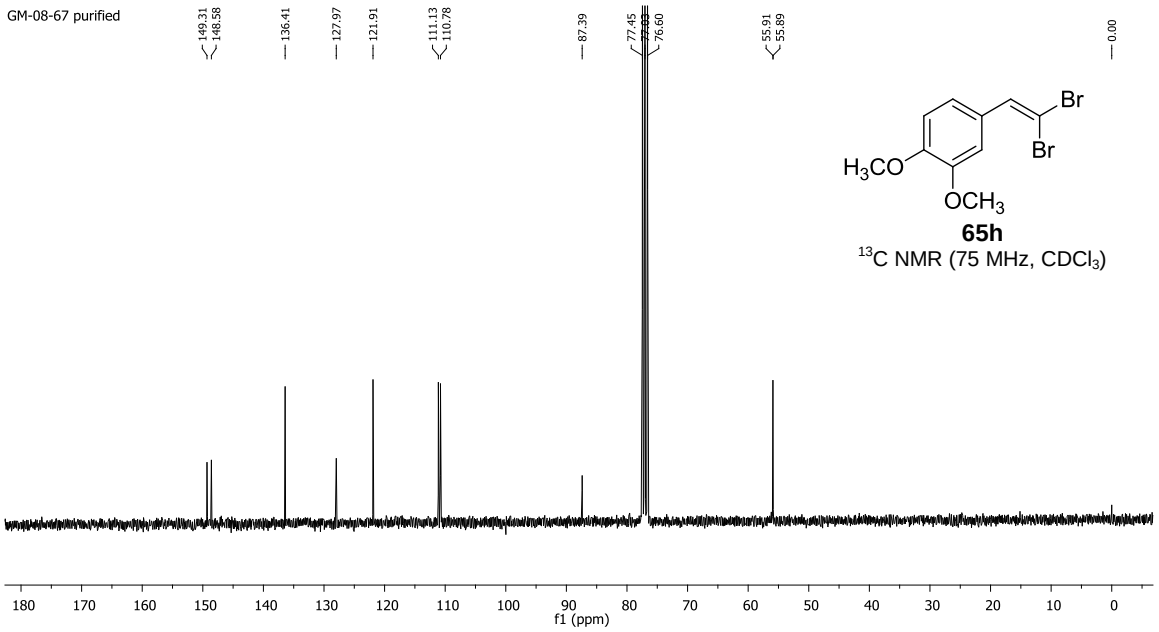
^{13}C NMR (75 MHz, $CDCl_3$)





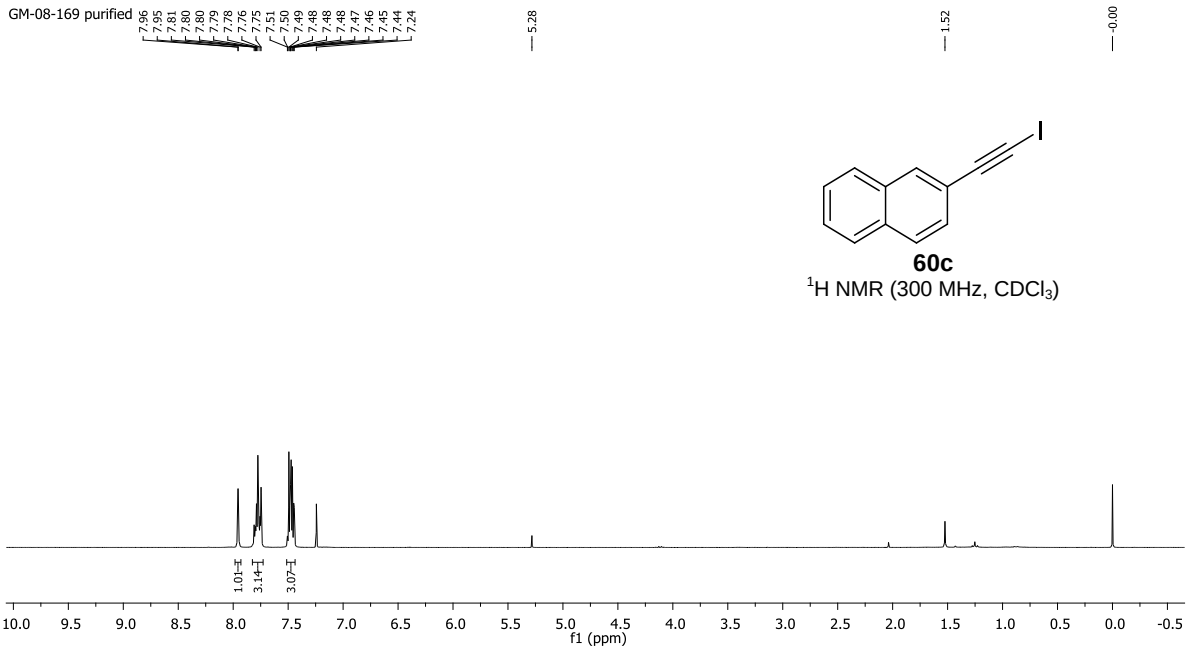
65h

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



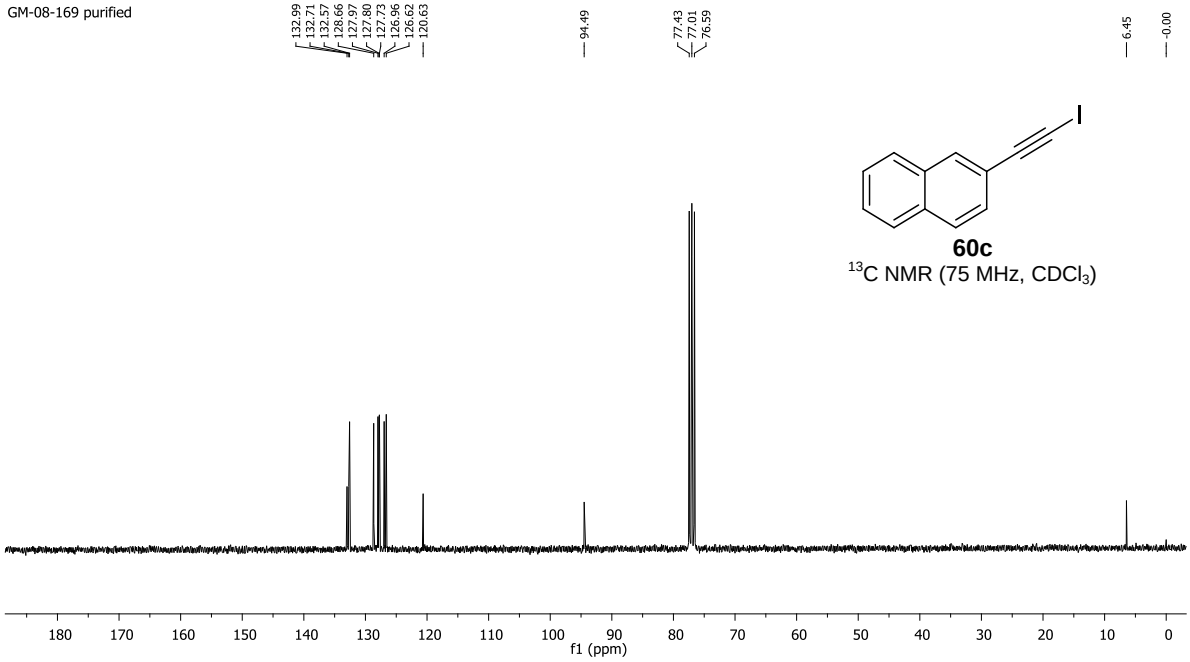
65h

^{13}C NMR (75 MHz, $CDCl_3$)



60c

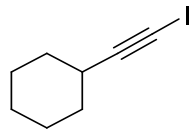
^{1}H NMR (300 MHz, $CDCl_3$)



60c

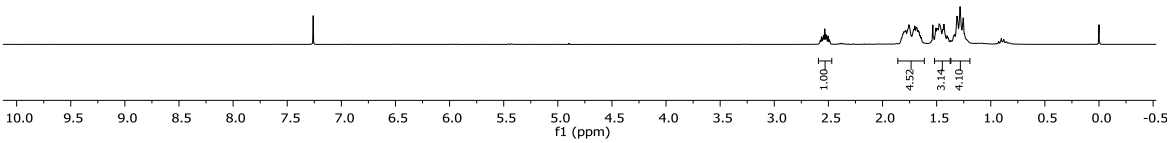
^{13}C NMR (75 MHz, $CDCl_3$)

GM-08-177 purified

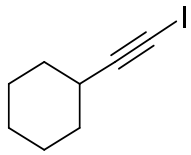


60e

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

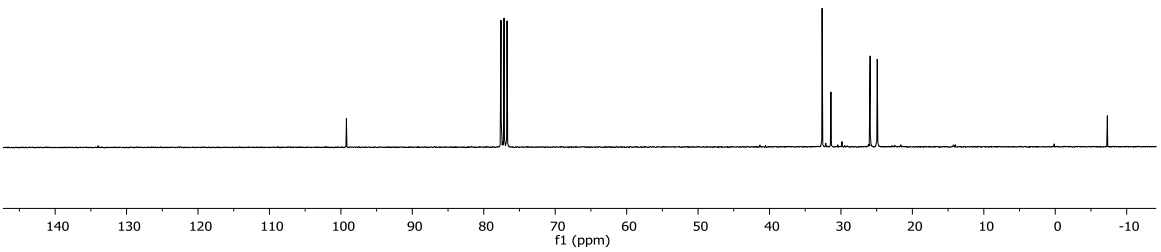


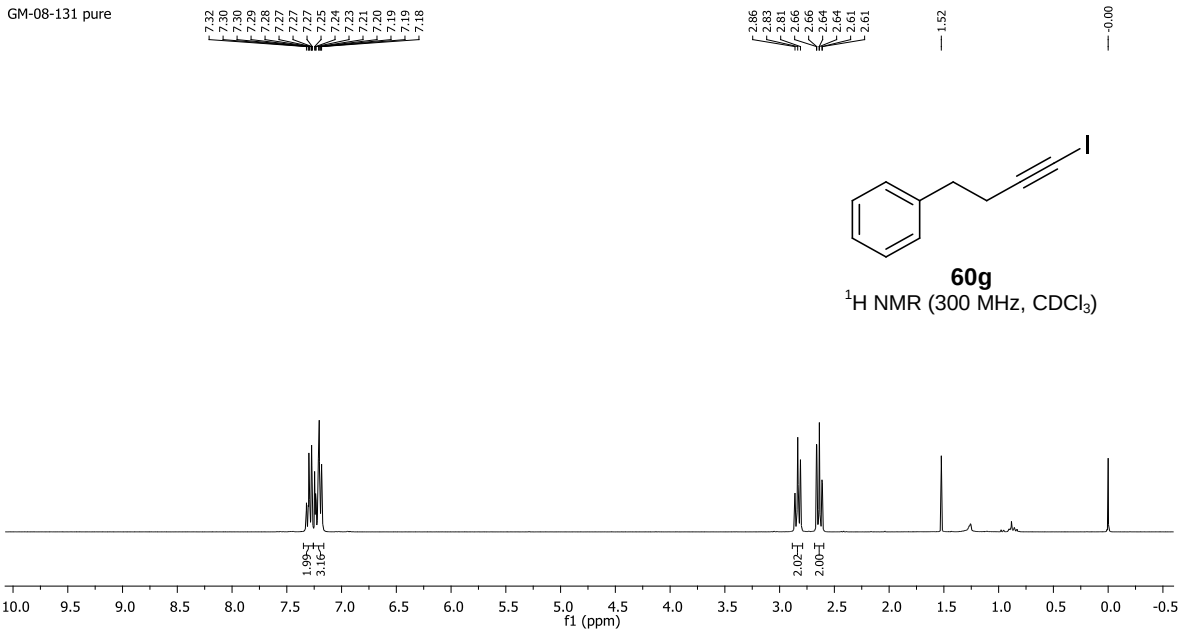
GM-08-177 purified

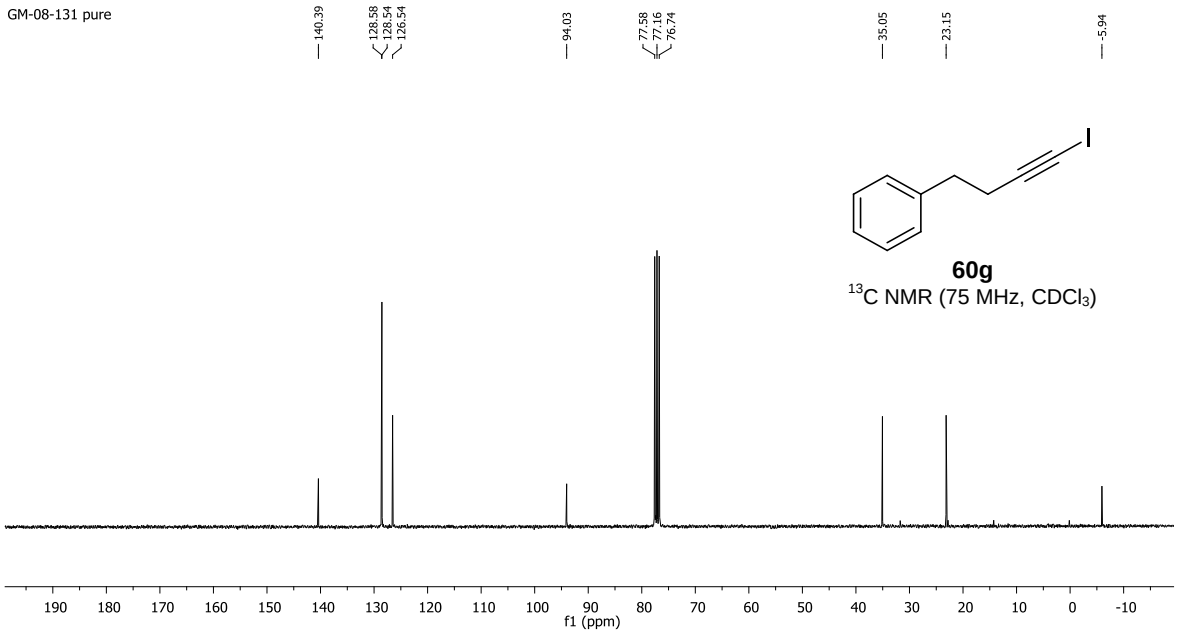


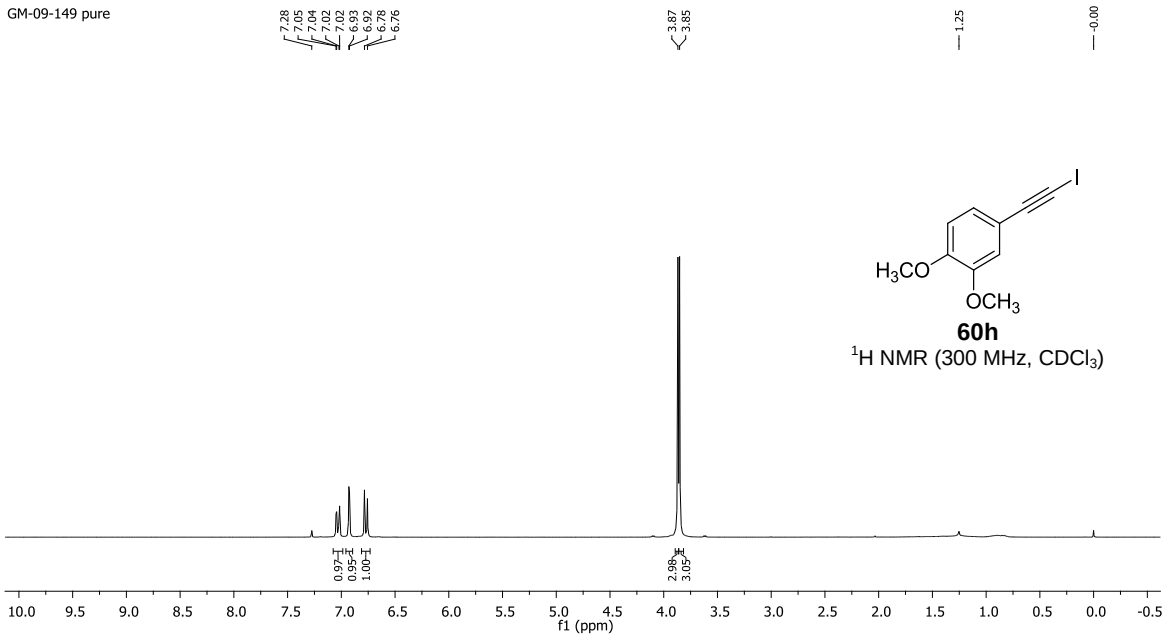
60e

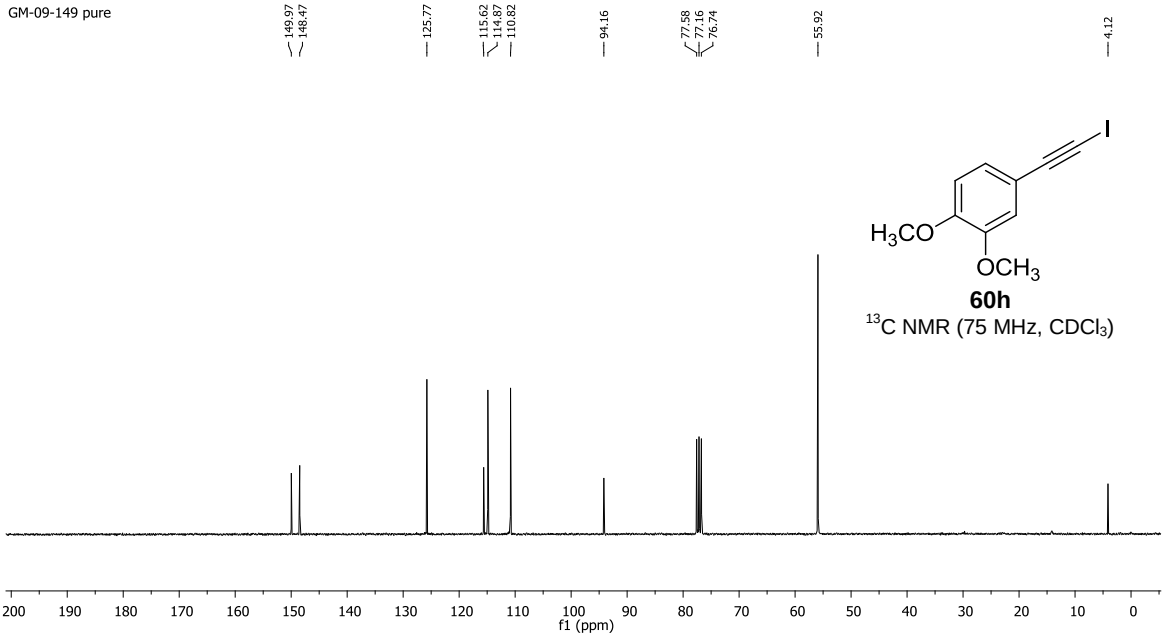
^{13}C NMR (75 MHz, $CDCl_3$)

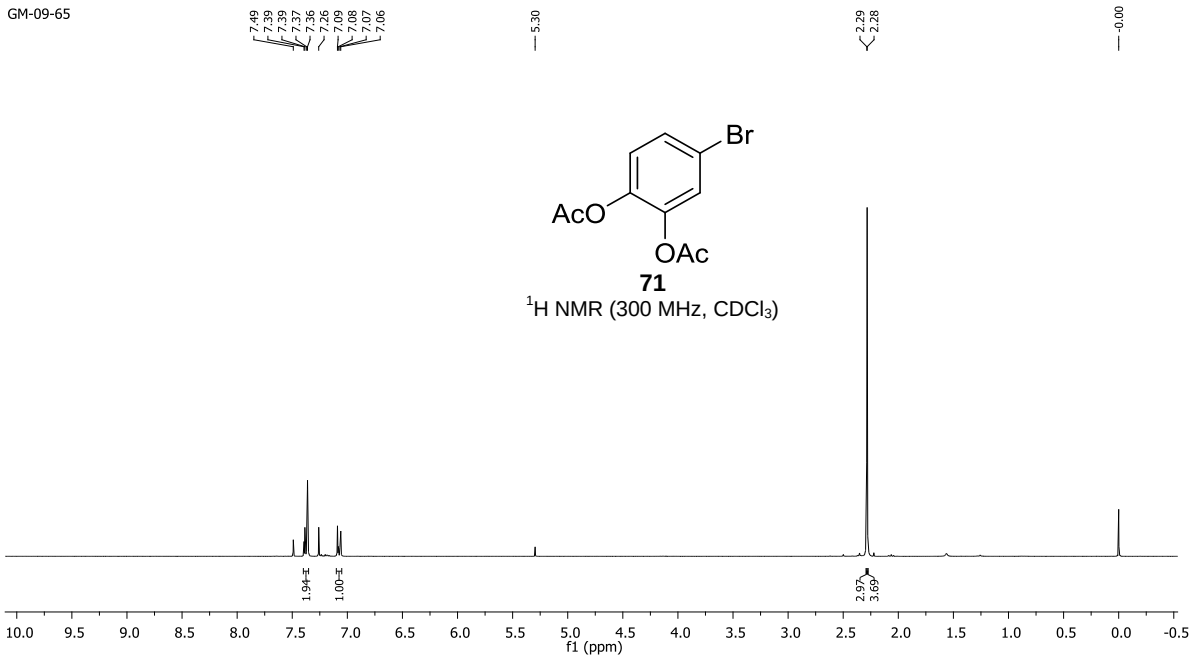


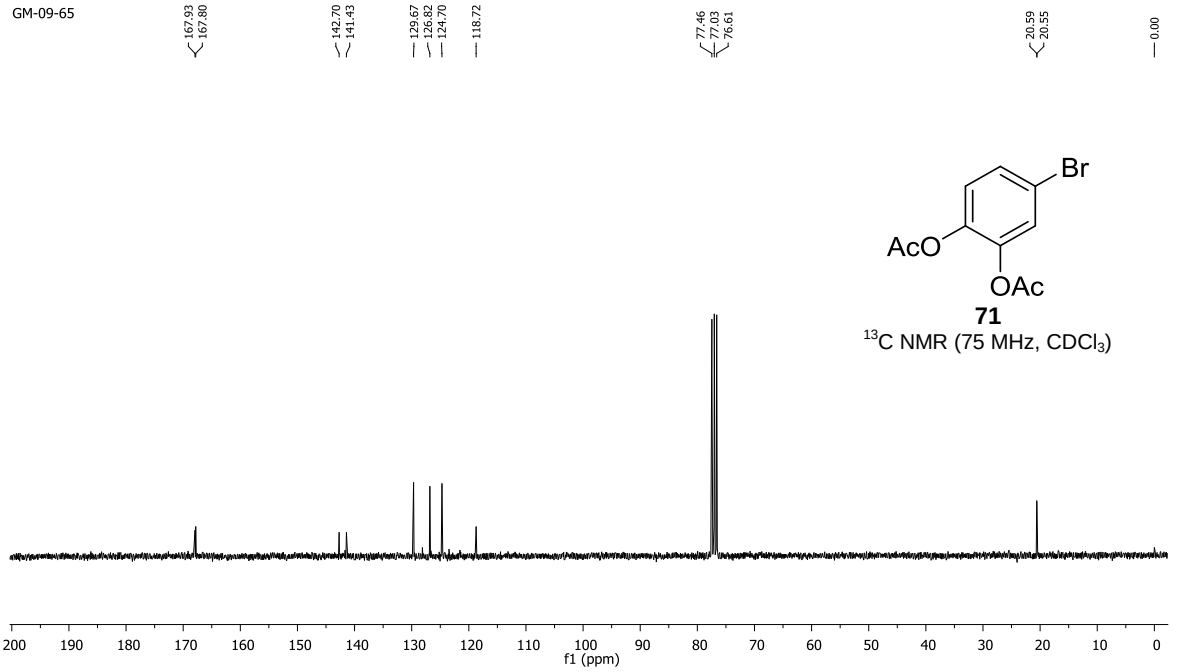

GM-08-131 pure
7.32
7.30
7.30
7.29
7.28
7.27
7.27
7.27
7.25
7.24
7.23
7.21
7.20
7.19
7.19
7.18
2.86
2.83
2.81
2.66
2.66
2.64
2.64
2.61
2.61
1.52
-0.00
I
60g
1H NMR (300 MHz, CDCl3)
1.99
3.16
2.02
2.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

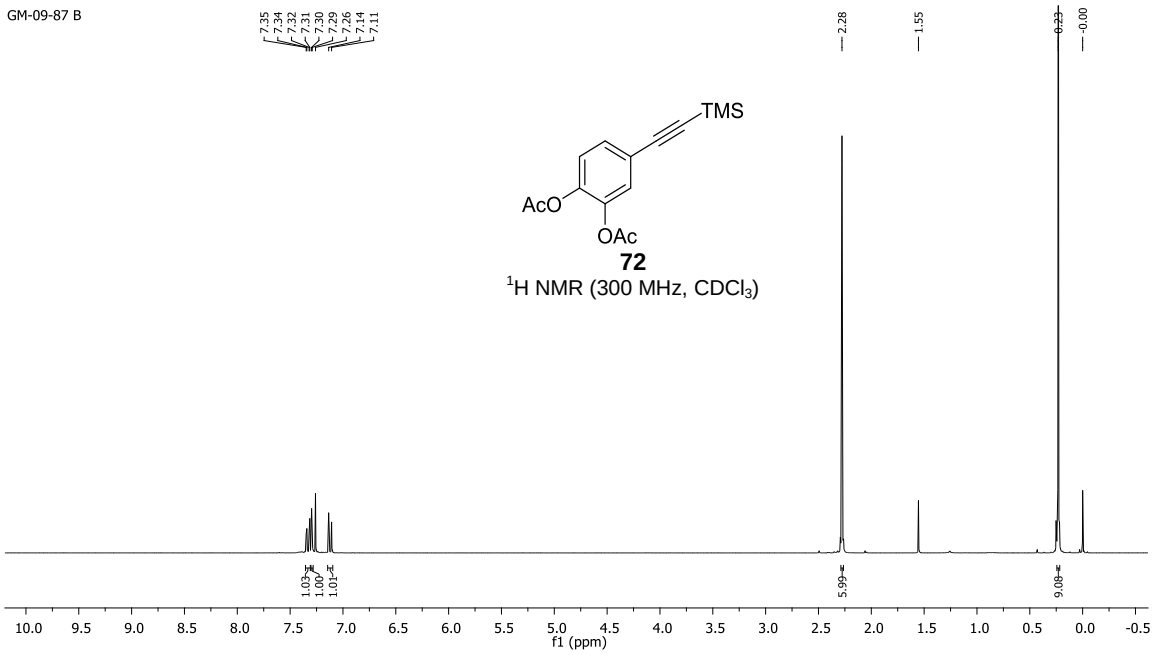

GM-08-131 pure
140.39
128.58
128.54
126.54
94.03
77.58
77.16
76.74
35.05
23.15
-5.94
I
60g
13C NMR (75 MHz, CDCl3)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

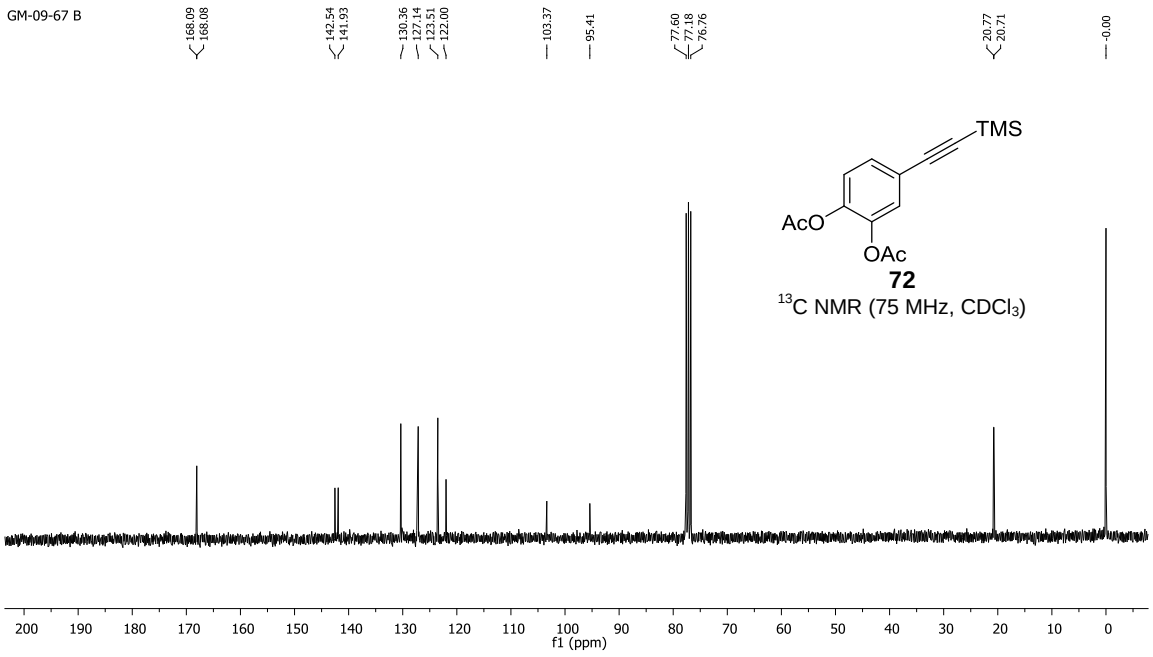

GM-09-149 pure
7.28
7.05
7.04
7.02
7.02
6.93
6.92
6.78
6.76
3.87
3.85
1.25
-0.00
I
H3CO
OCH3
60h
1H NMR (300 MHz, CDCl3)
0.97
0.97
1.00
2.98
3.09
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

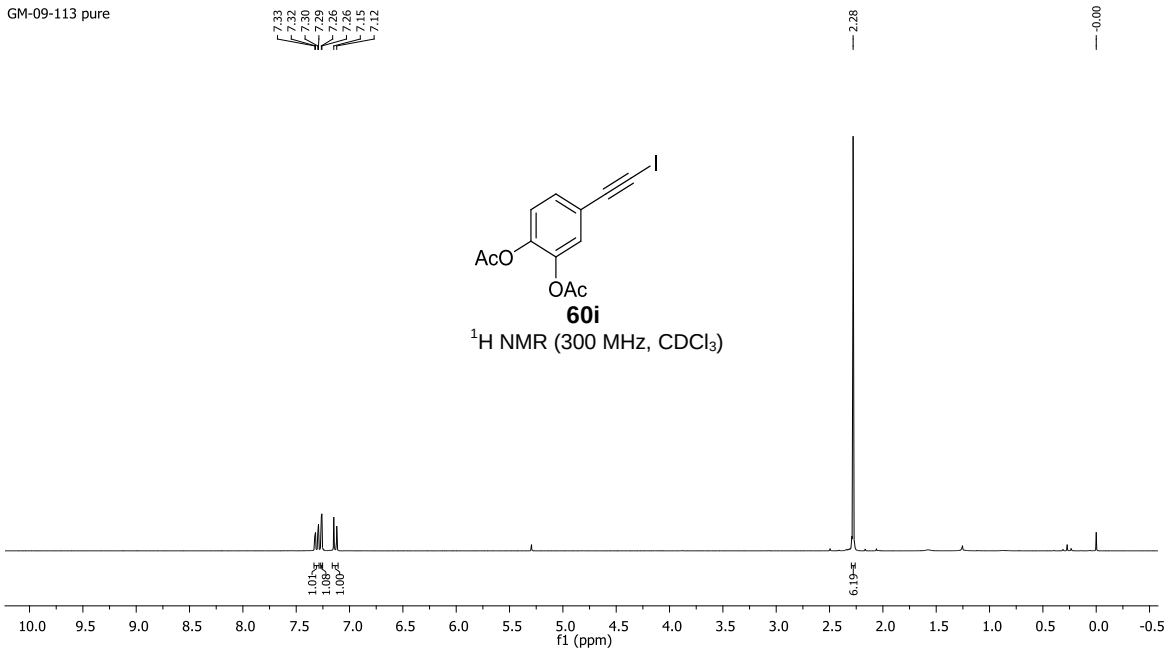

GM-09-149 pure
149.97
148.47
125.77
115.62
114.87
110.82
94.16
77.58
77.16
76.74
55.92
4.12
I
H3CO
OCH3
60h
13C NMR (75 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

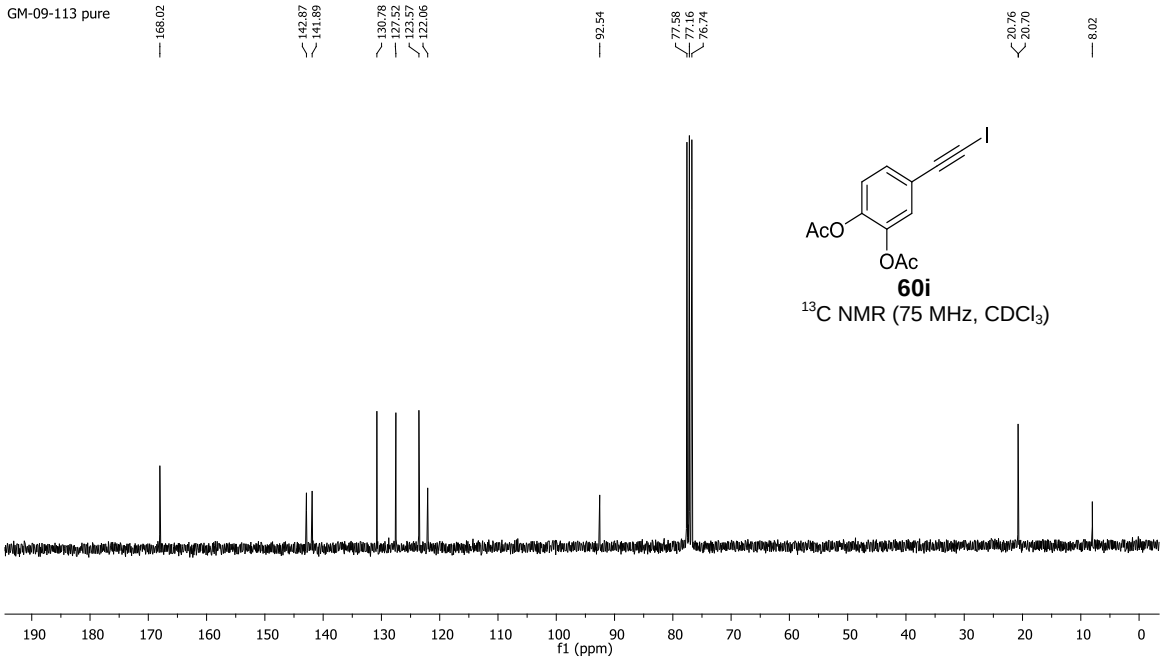

GM-09-65
7.49
7.39
7.39
7.37
7.36
7.26
7.09
7.08
7.07
7.06
5.30
2.29
2.28
0.00
Br
AcO
OAc
71
1H NMR (300 MHz, CDCl3)
1.94
1.00
2.97
3.69
f1 (ppm)

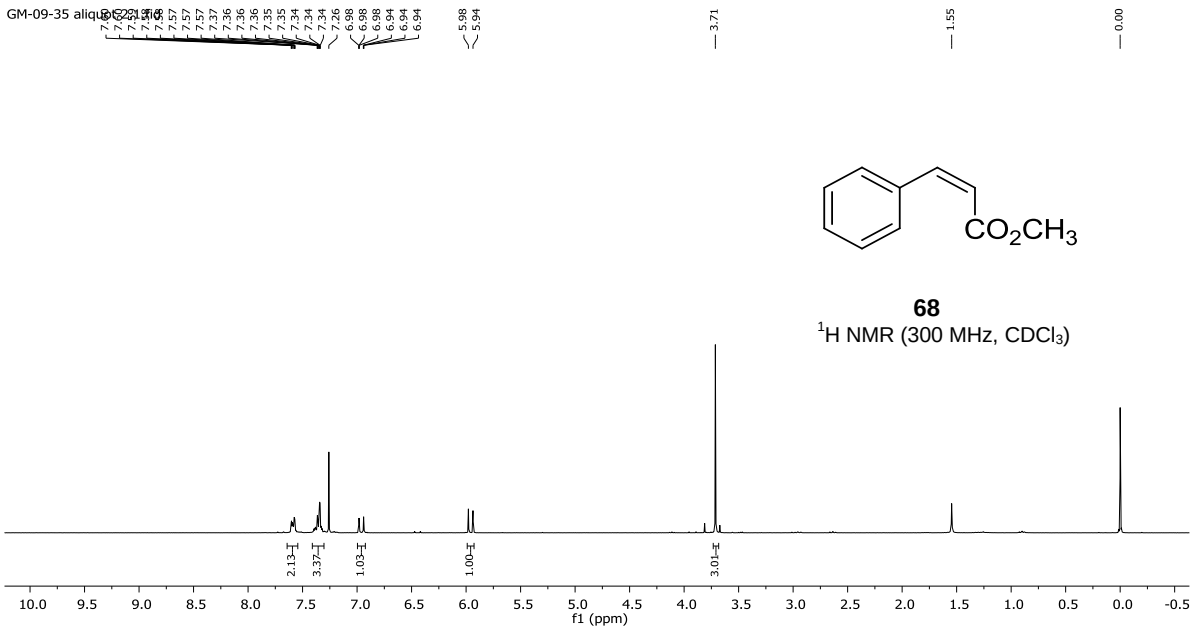

GM-09-65
167.93
167.80
142.70
141.43
129.67
126.82
124.70
118.72
77.46
77.03
76.61
20.59
20.55
0.00
Br
AcO
OAc
71
13C NMR (75 MHz, CDCl3)
f1 (ppm)


GM-09-87 B
7.35
7.34
7.32
7.31
7.30
7.29
7.26
7.14
7.11
2.28
1.55
6.23
-0.00
TMS
AcO
OAc
72
1H NMR (300 MHz, CDCl3)
1.03
1.00
1.01
5.99
9.08
f1 (ppm)


GM-09-67 B
168.09
168.08
142.54
141.93
130.36
127.14
123.51
122.00
103.37
95.41
77.60
77.18
76.76
20.77
20.71
-0.00
TMS
AcO
OAc
72
13C NMR (75 MHz, CDCl3)
f1 (ppm)

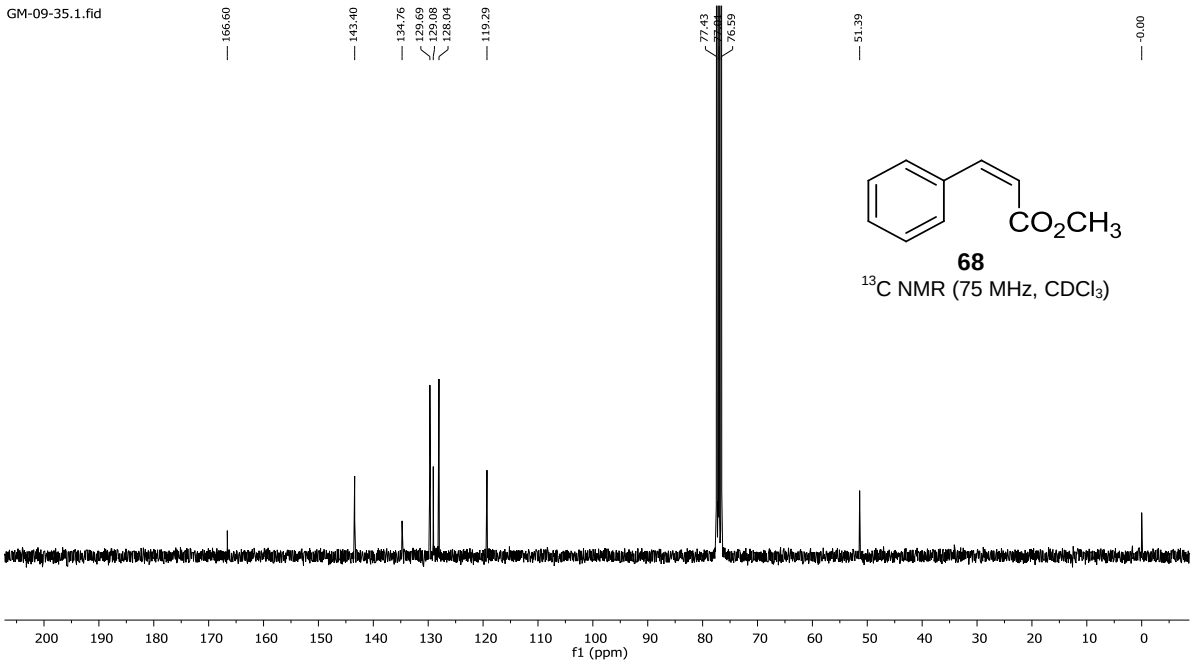

GM-09-113 pure
7.33
7.32
7.30
7.29
7.26
7.26
7.15
7.12
2.28
-0.00
I
AcO
OAc
60i
1H NMR (300 MHz, CDCl3)
1.01
1.08
1.00
6.19
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


GM-09-113 pure
168.02
142.87
141.89
130.78
127.52
123.57
122.06
92.54
77.58
77.16
76.74
20.76
20.70
8.02
I
AcO
OAc
60i
13C NMR (75 MHz, CDCl3)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



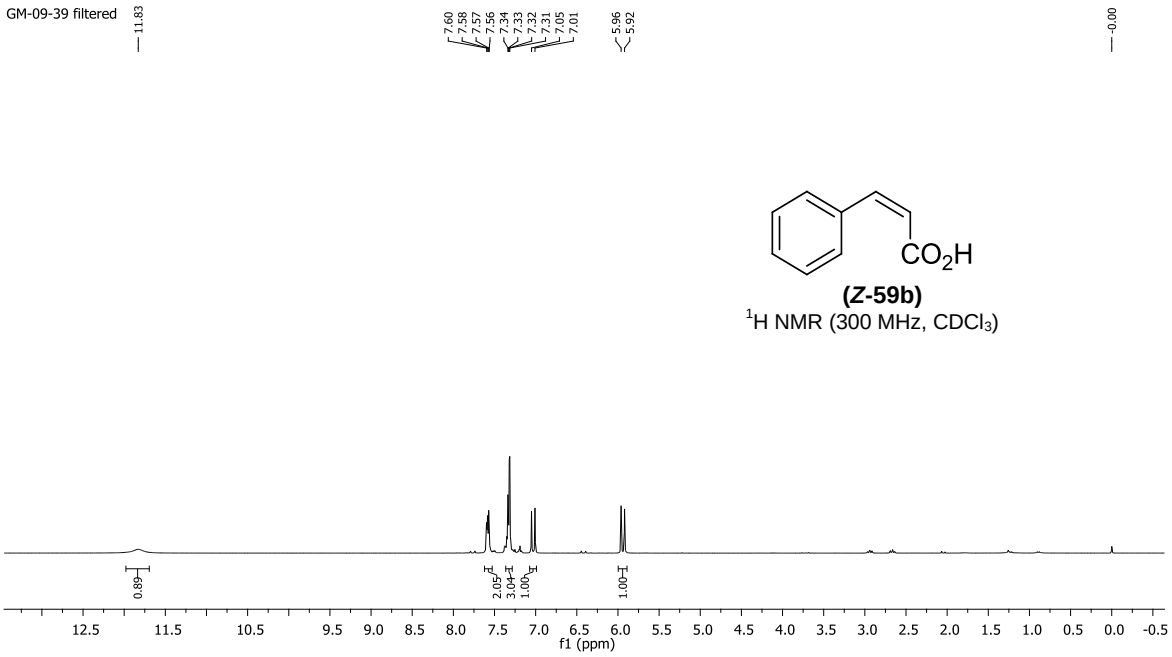
68

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



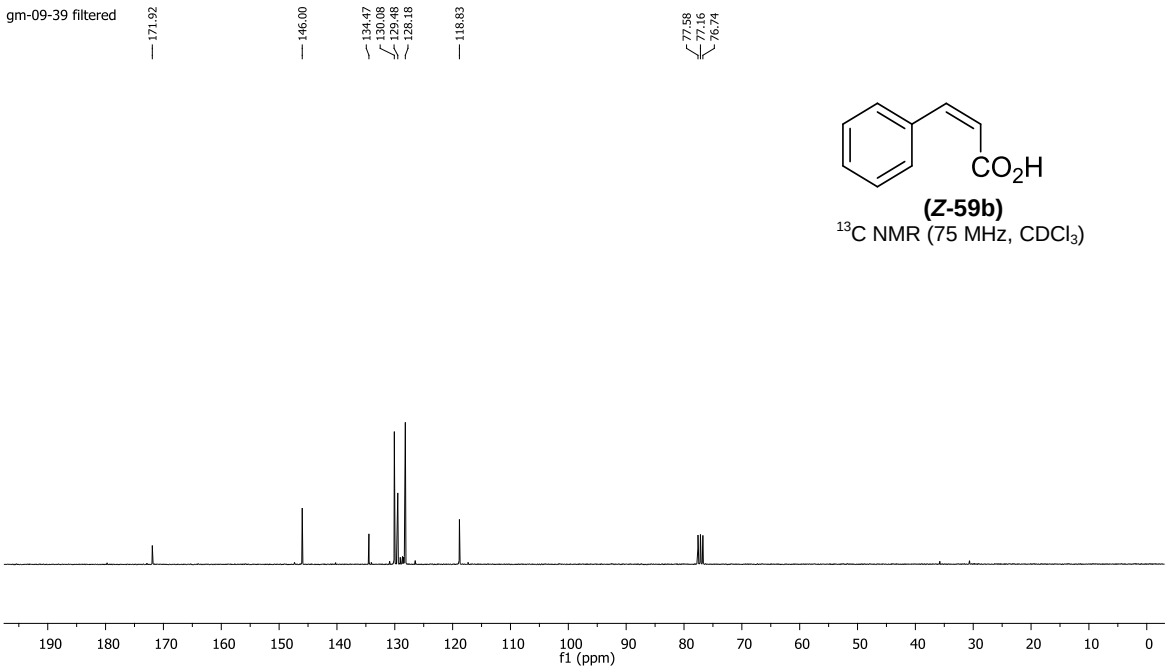
68

^{13}C NMR (75 MHz, $CDCl_3$)



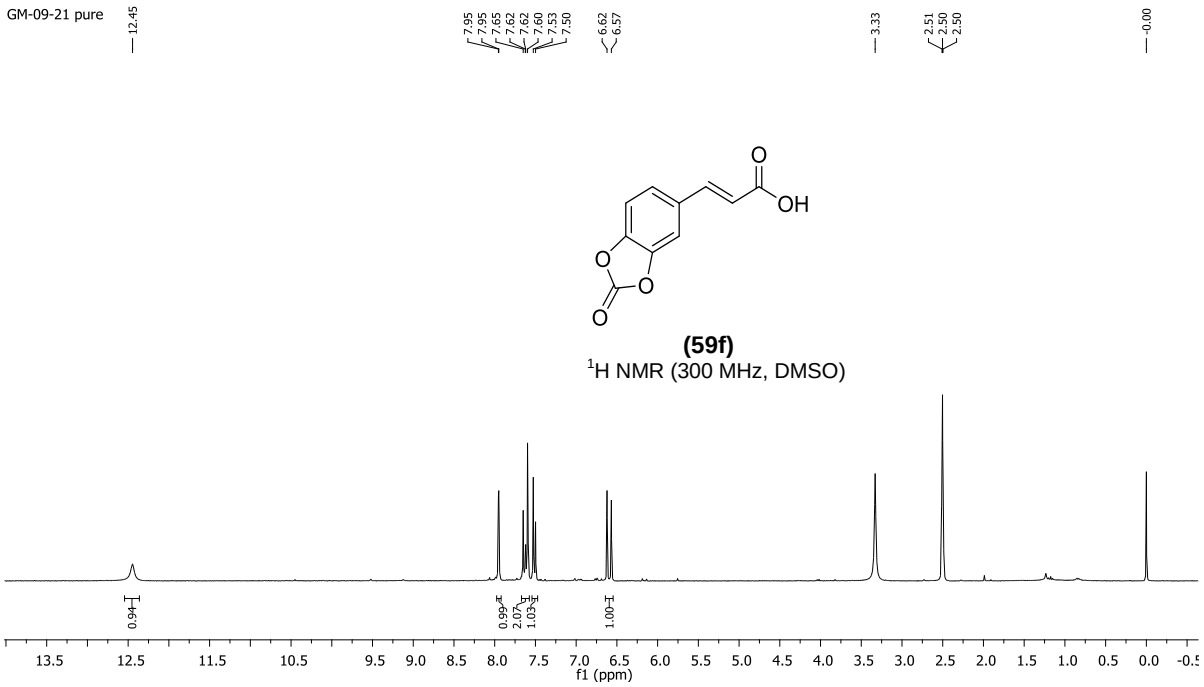
(*Z*-59b)

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



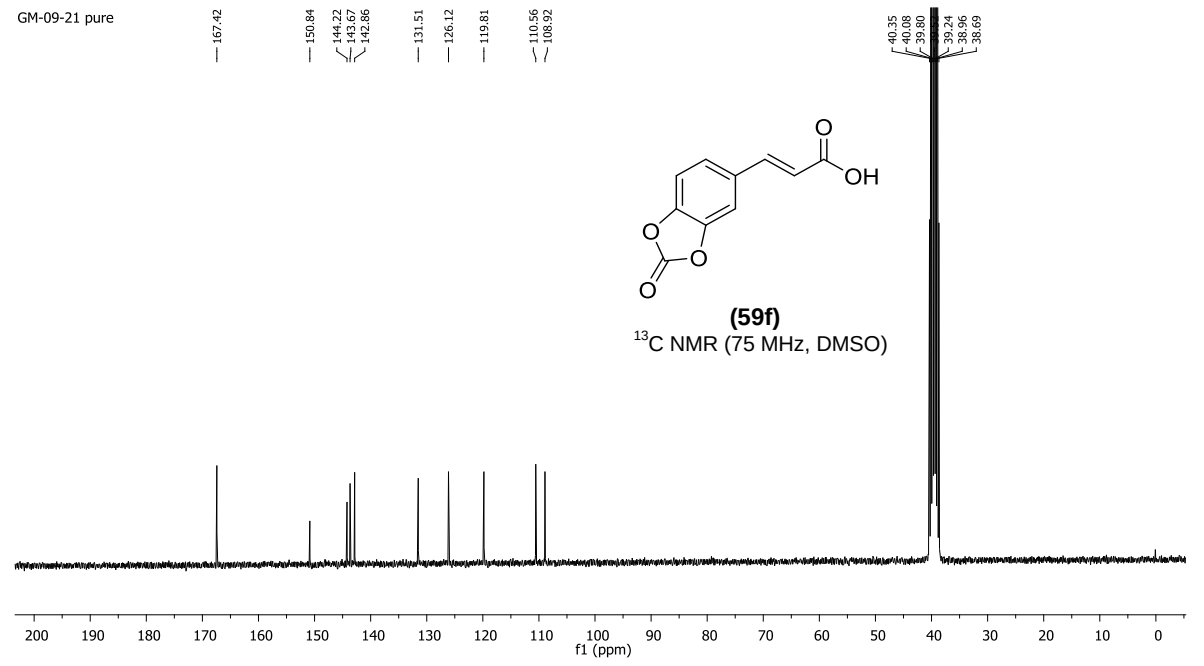
(*Z*-59b)

^{13}C NMR (75 MHz, $CDCl_3$)



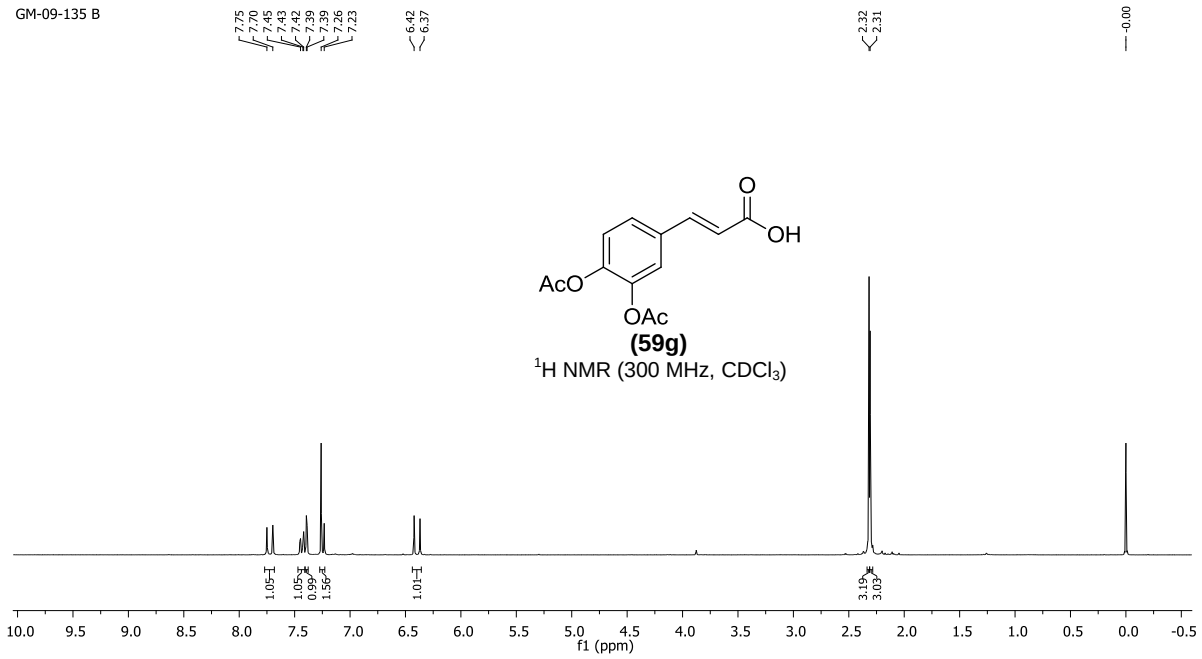
(59f)

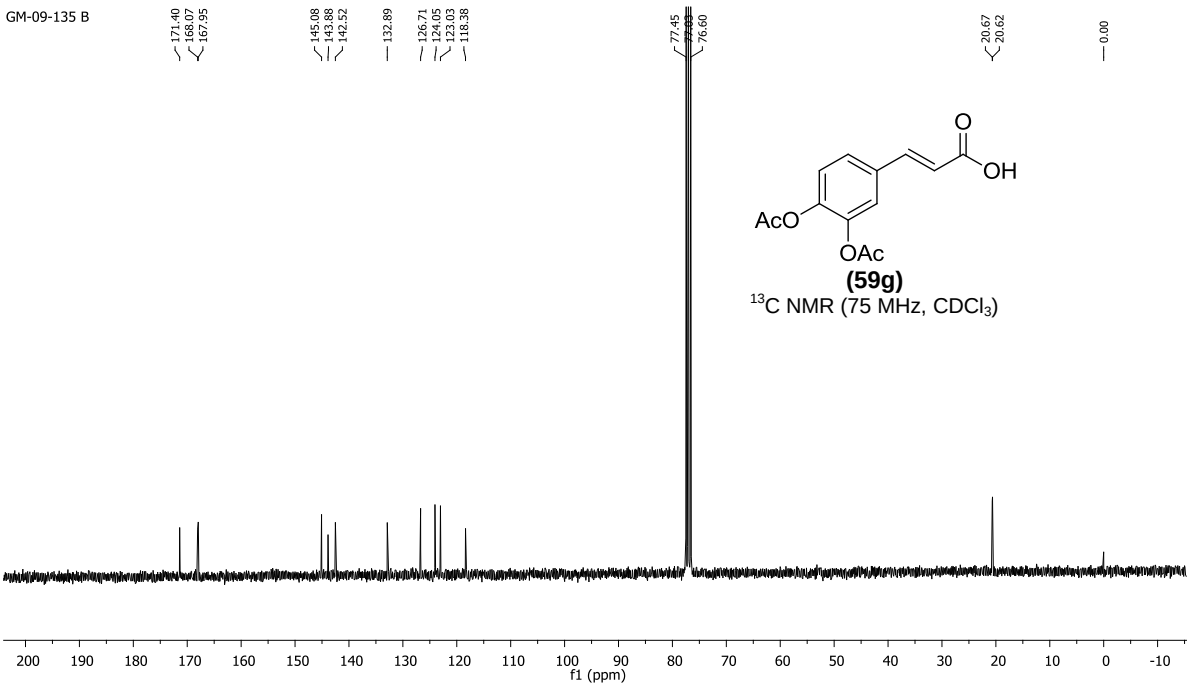
^{1}H NMR (300 MHz, DMSO)

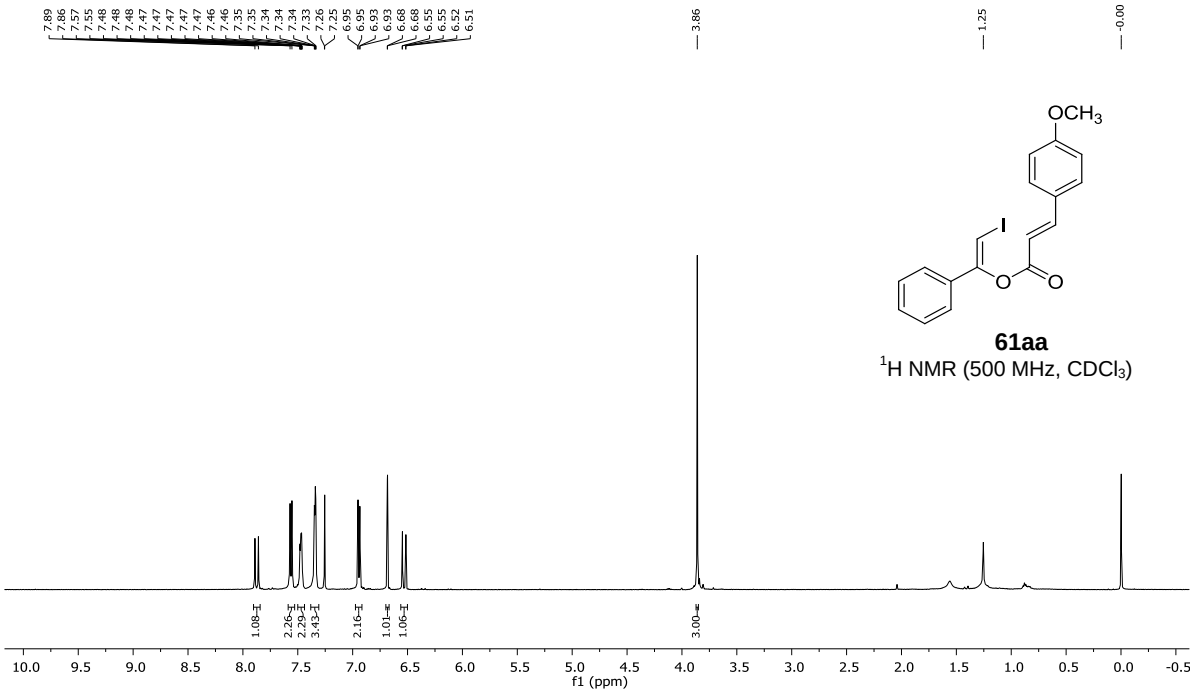


(59f)

^{13}C NMR (75 MHz, DMSO)

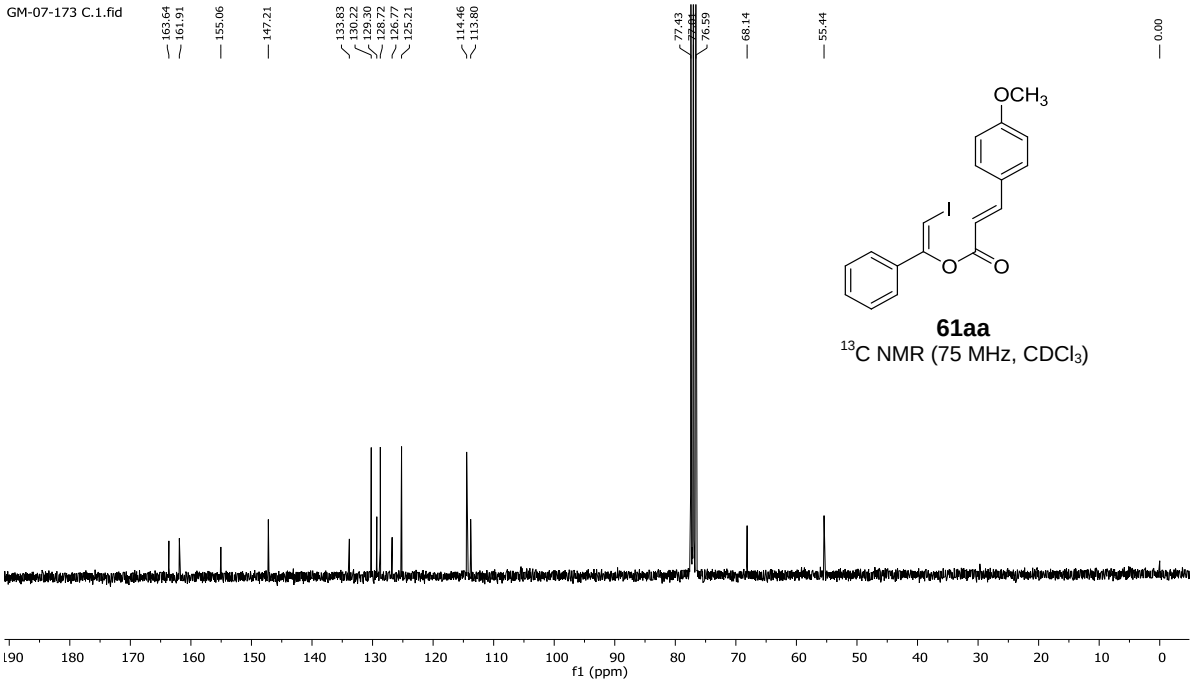

GM-09-135 B
7.75
7.70
7.45
7.43
7.42
7.39
7.39
7.26
7.23
6.42
6.37
2.32
2.31
-0.00
O
OH
AcO
OAc
(59g)
1H NMR (300 MHz, CDCl3)
1.05
1.05
0.99
1.56
1.01
3.19
3.03
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


GM-09-135 B
171.40
168.07
167.95
145.08
143.88
142.52
132.89
126.71
124.05
123.03
118.38
77.45
77.03
76.60
20.67
20.62
0.00
O
OH
AcO
OAc
(59g)
13C NMR (75 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



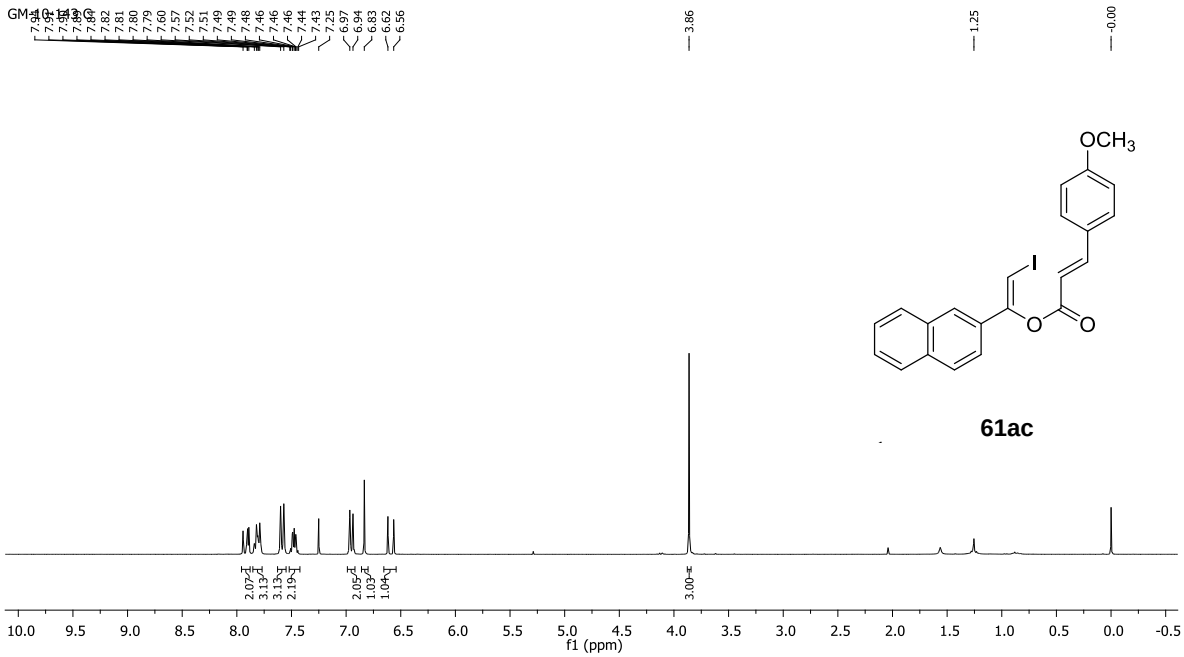
61aa

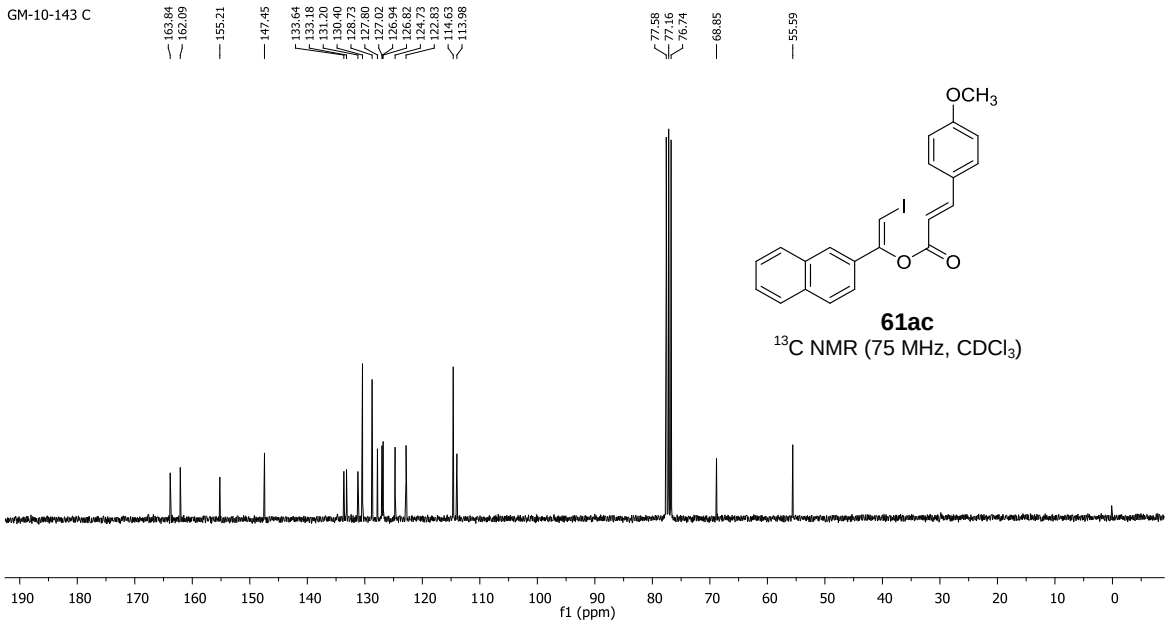
^{1}H NMR (500 MHz, $CDCl_3$)

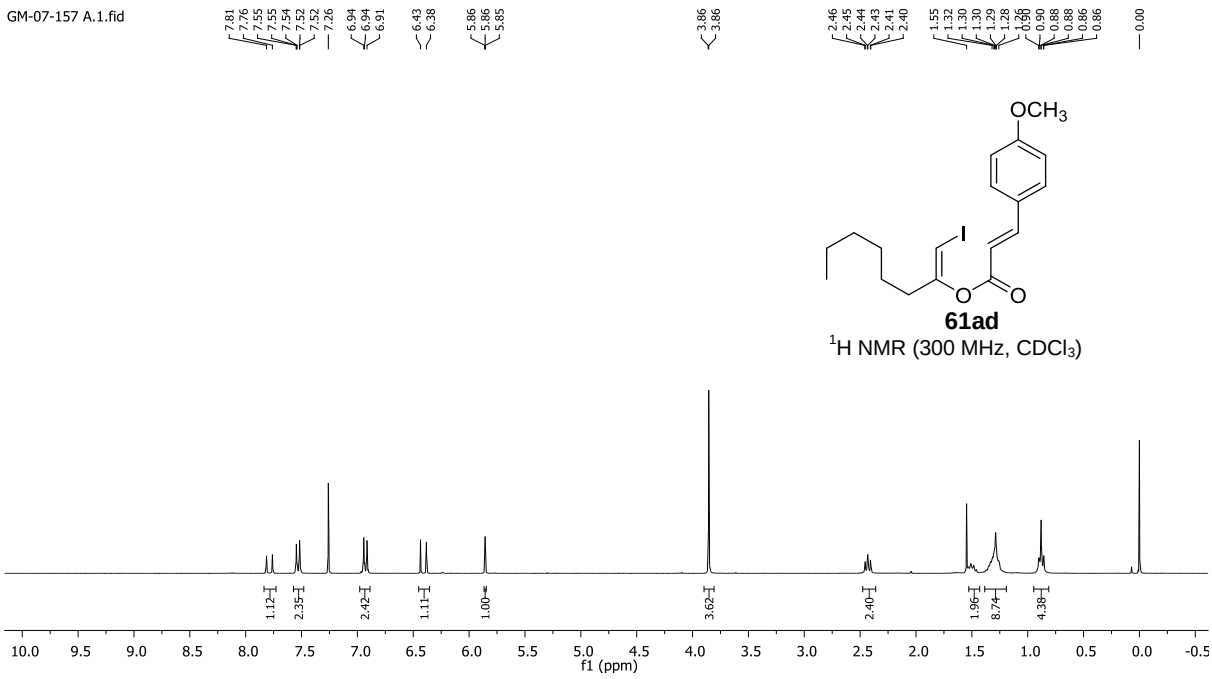


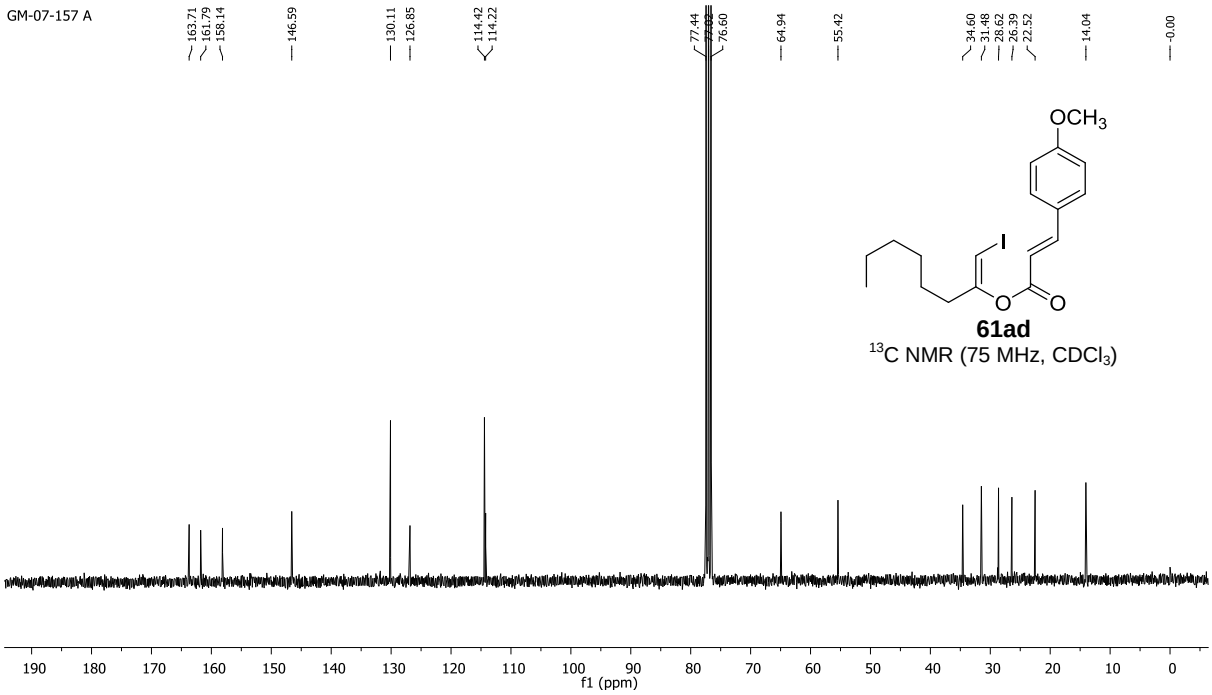
61aa

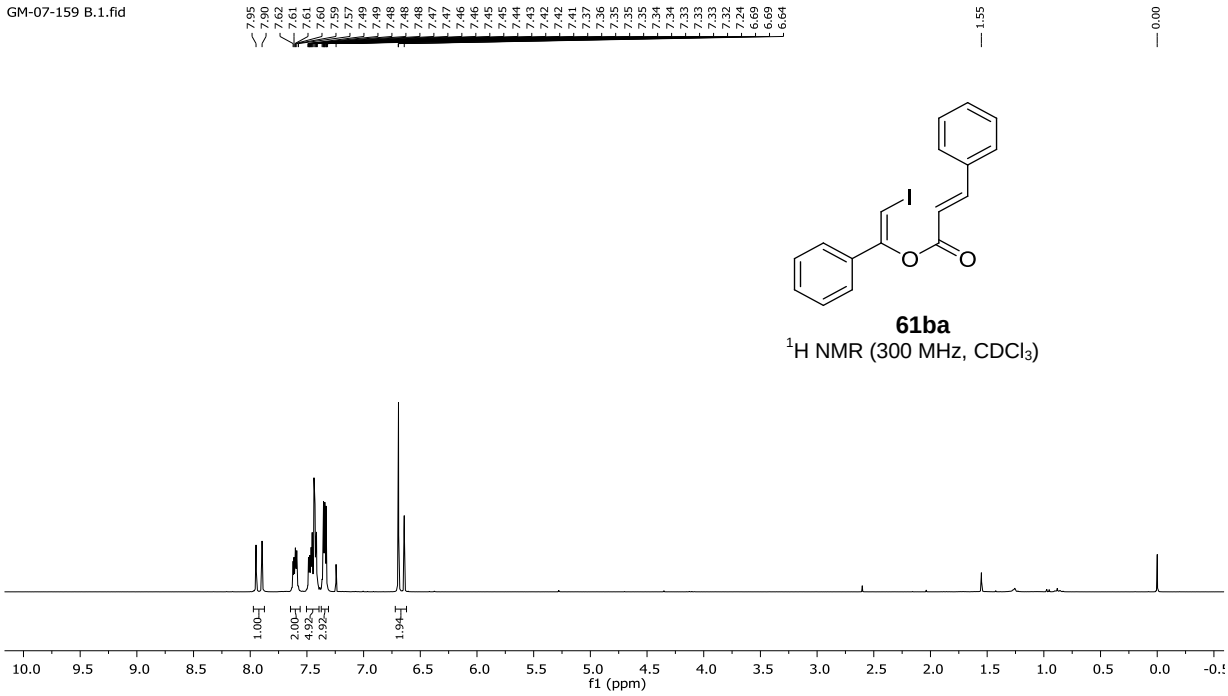
^{13}C NMR (75 MHz, $CDCl_3$)


3.86
1.25
-0.00
OCH3
I
O
O
61ac
2.07
3.13
3.13
2.19
2.05
1.03
1.04
3.00
f1 (ppm)


GM-10-143 C
163.84
162.09
155.21
147.45
133.64
133.18
131.20
130.40
128.73
127.80
127.02
126.94
126.62
124.73
121.63
114.63
113.98
77.58
77.16
76.74
68.85
55.59
OCH3
I
O
O
61ac
13C NMR (75 MHz, CDCl3)
f1 (ppm)

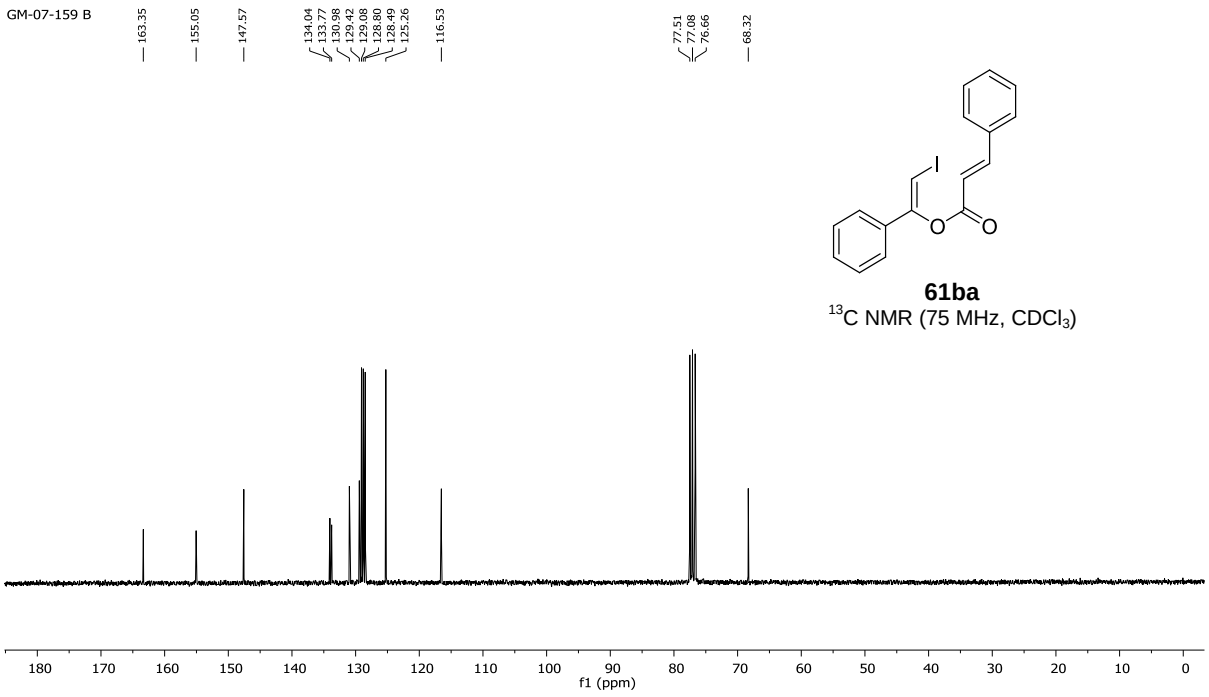

GM-07-157 A.1.fid
7.81
7.76
7.55
7.55
7.54
7.52
7.52
7.26
6.94
6.94
6.91
6.43
6.38
5.86
5.86
5.85
3.86
3.86
2.46
2.45
2.44
2.43
2.41
2.40
1.55
1.32
1.30
1.30
1.29
1.28
0.90
0.90
0.88
0.88
0.86
0.86
0.00
OCH3
I
O
O
61ad
1H NMR (300 MHz, CDCl3)
1.12
2.35
2.42
1.11
1.00
3.62
2.40
1.96
8.74
4.38
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


GM-07-157 A
163.71
161.79
158.14
146.59
130.11
126.85
114.42
114.22
77.44
77.02
76.60
64.94
55.42
34.60
31.48
28.62
26.39
22.52
14.04
-0.00
OCH3
I
O
O
61ad
13C NMR (75 MHz, CDCl3)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



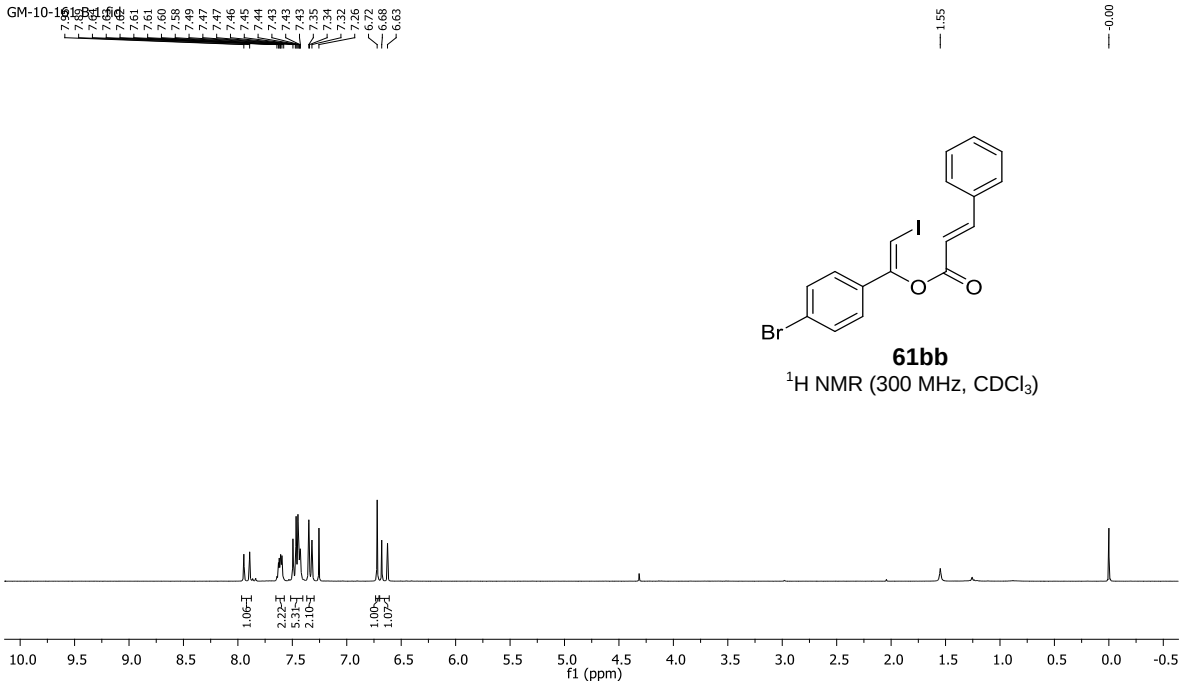
61ba

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



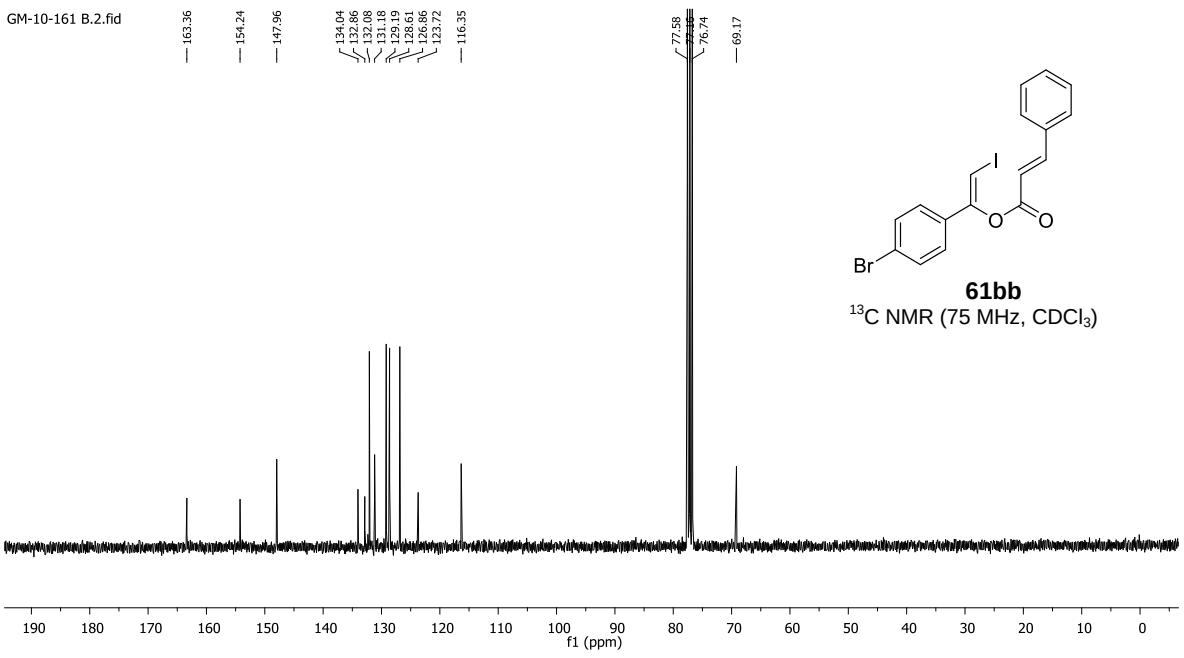
61ba

^{13}C NMR (75 MHz, $CDCl_3$)



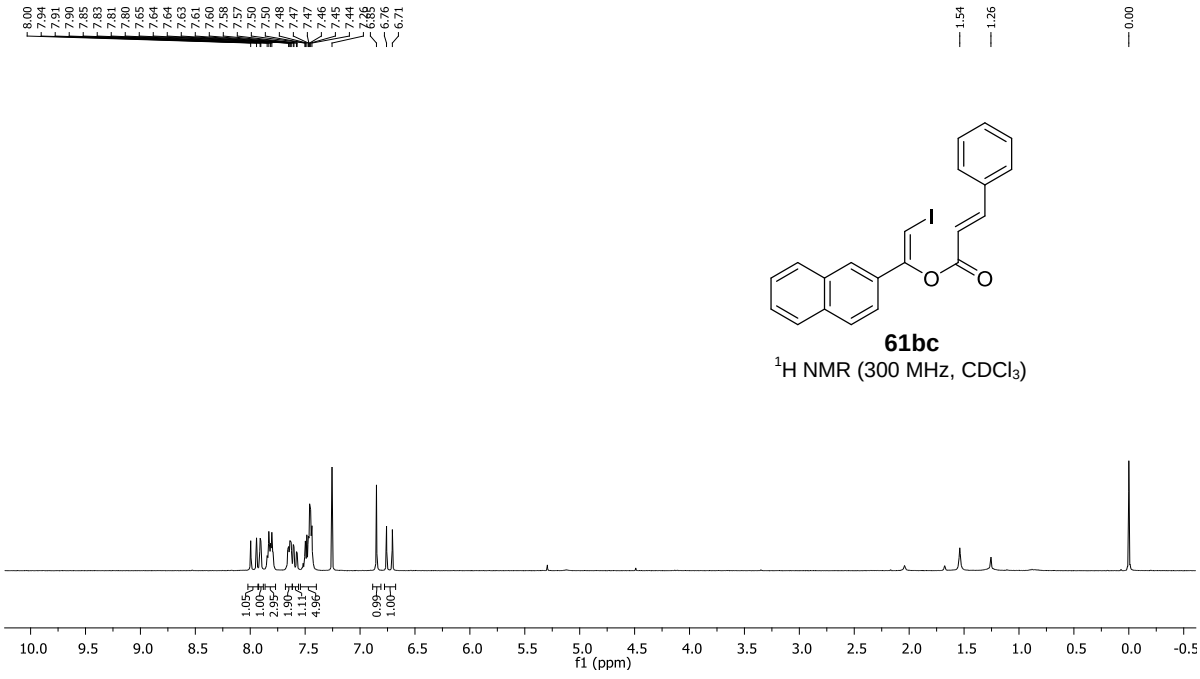
61bb

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



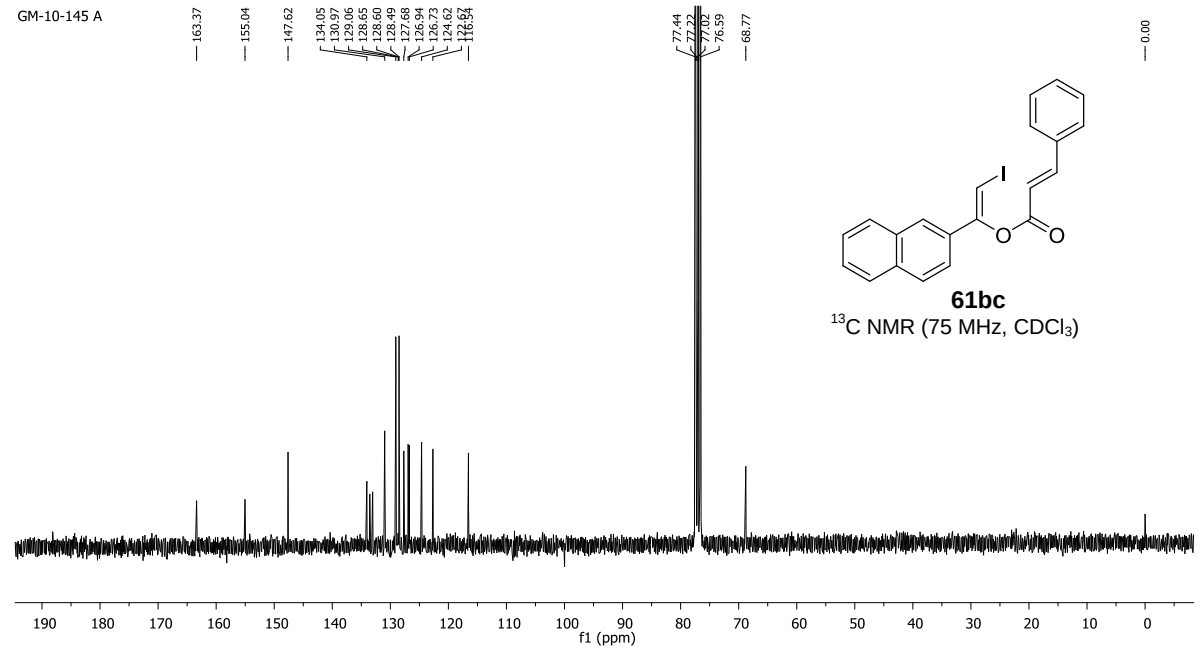
61bb

^{13}C NMR (75 MHz, $CDCl_3$)



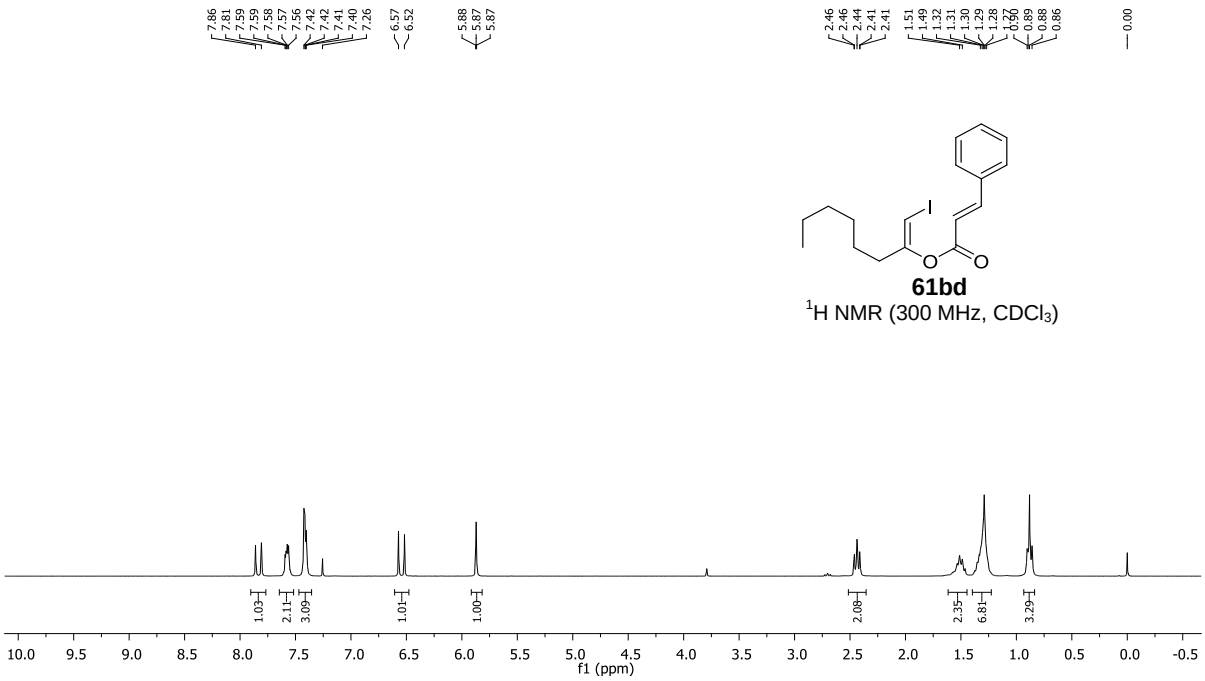
61bc

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



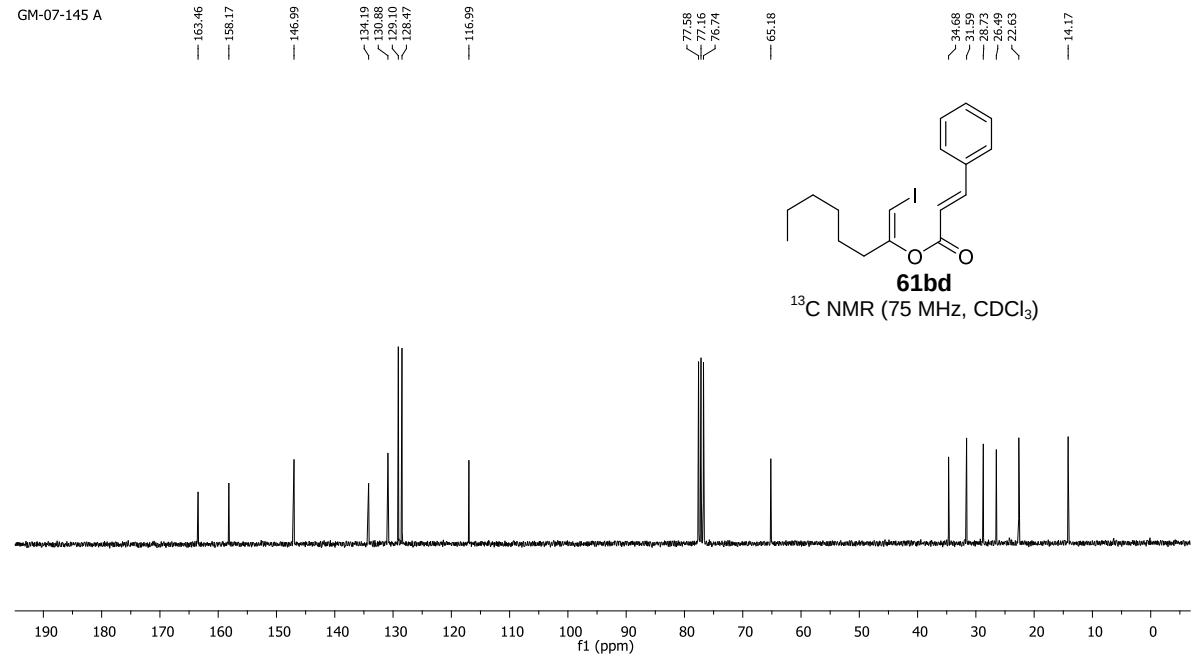
61bc

^{13}C NMR (75 MHz, $CDCl_3$)



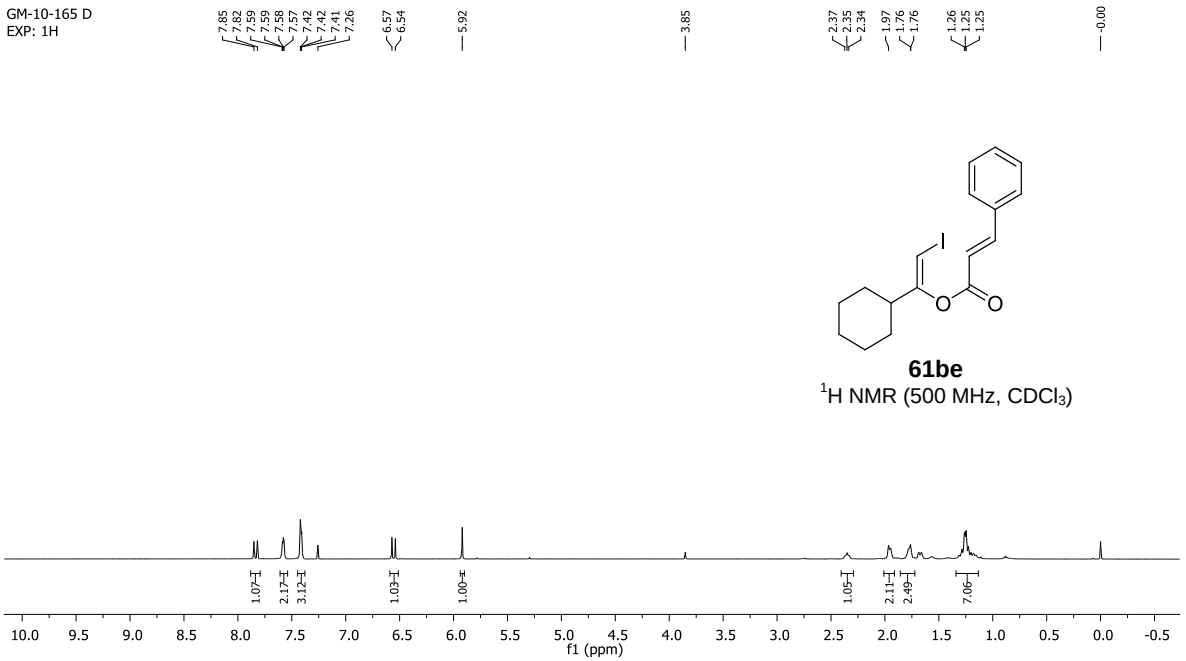
61bd

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



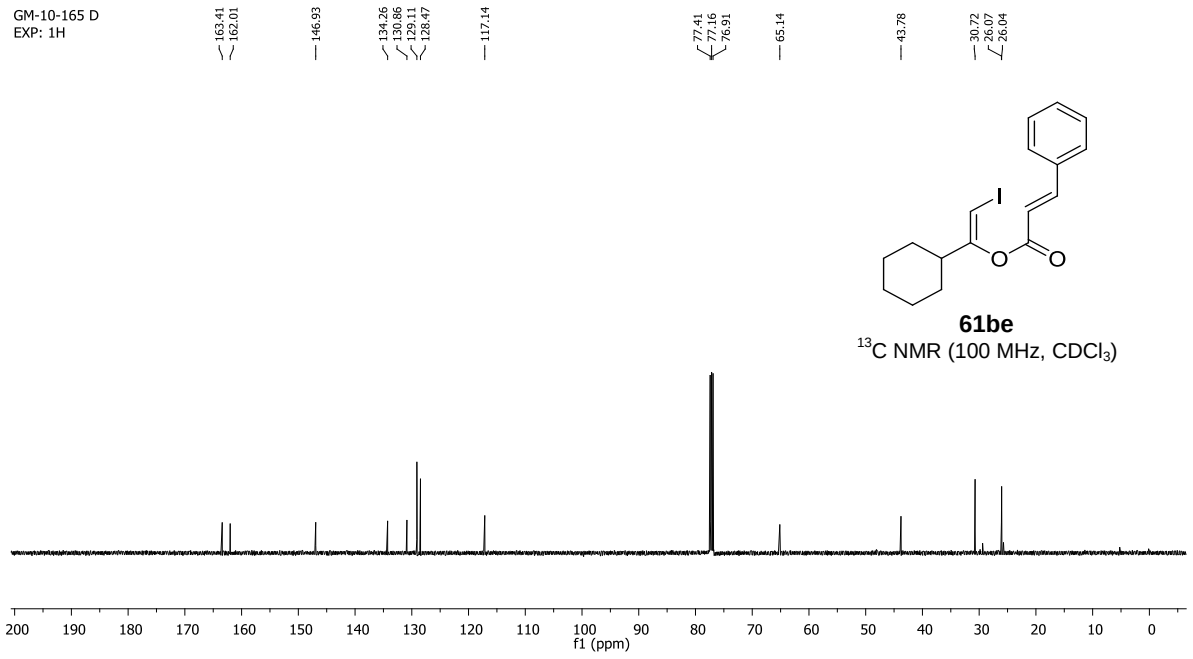
61bd

^{13}C NMR (75 MHz, $CDCl_3$)



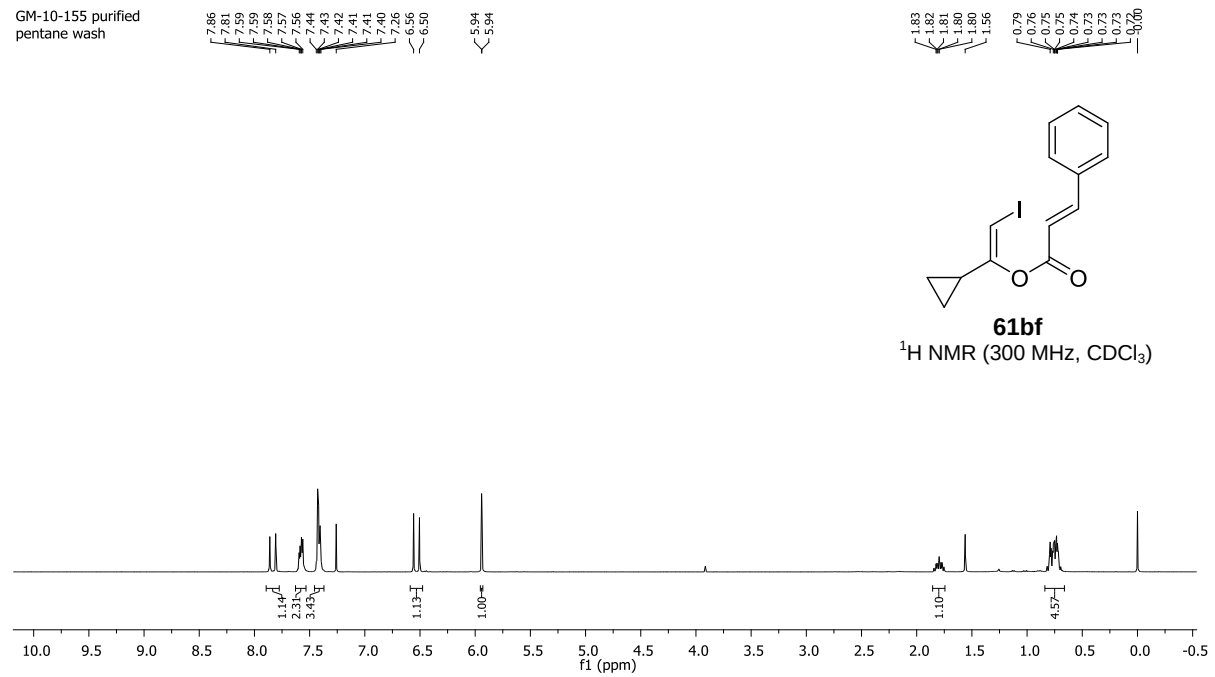
61be

^{1}H NMR (500 MHz, $CDCl_3$)



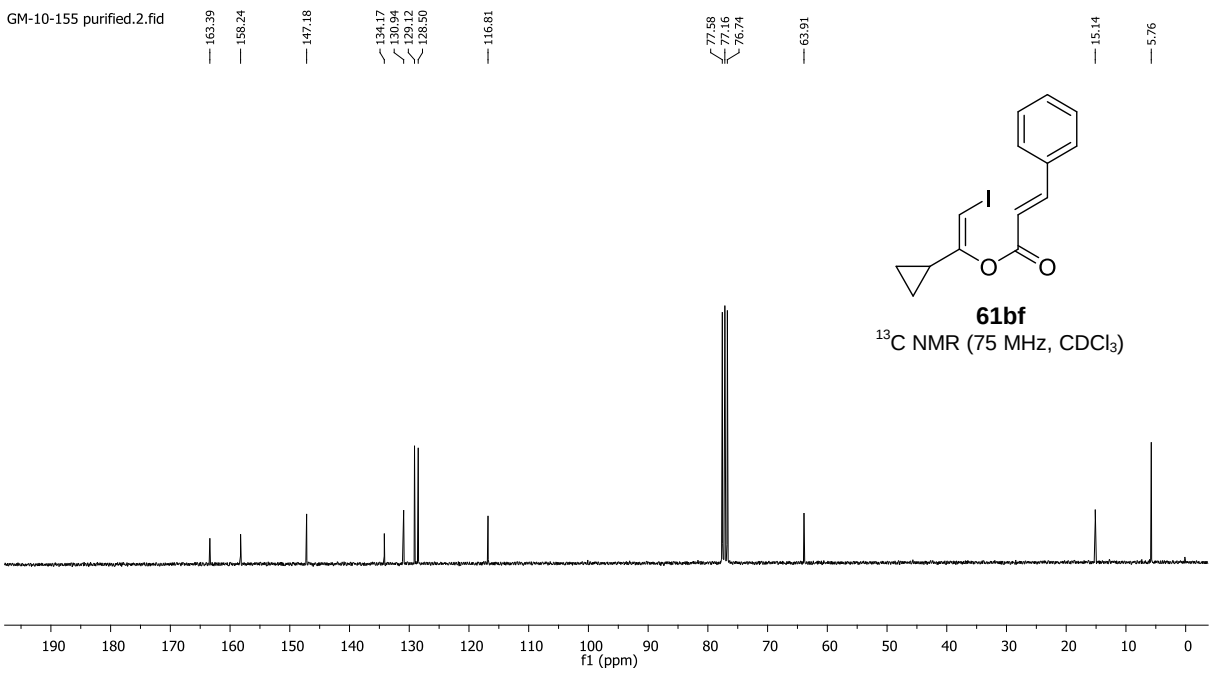
61be

^{13}C NMR (100 MHz, $CDCl_3$)



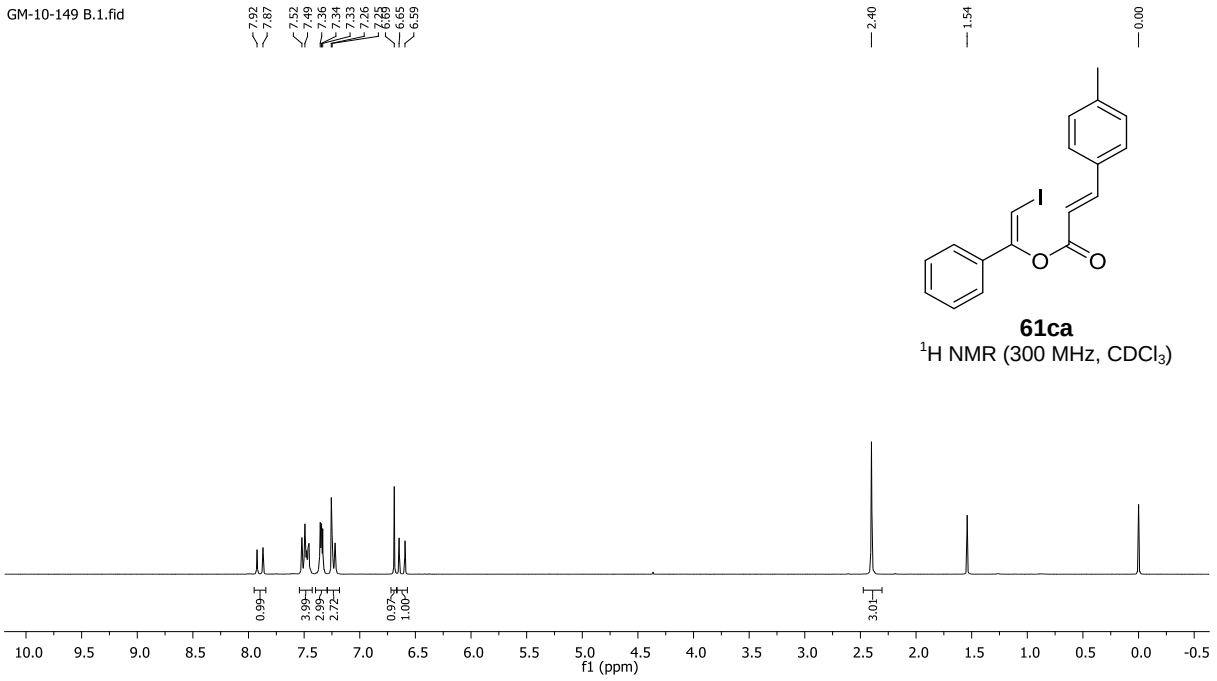
61bf

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



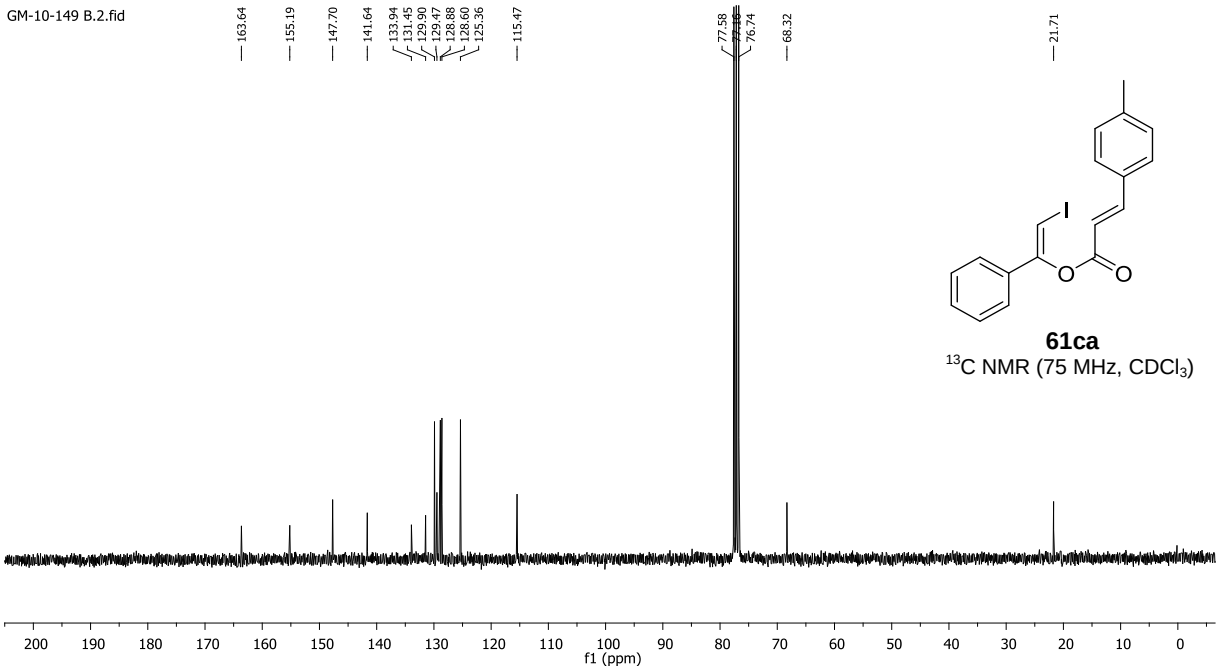
61bf

^{13}C NMR (75 MHz, $CDCl_3$)



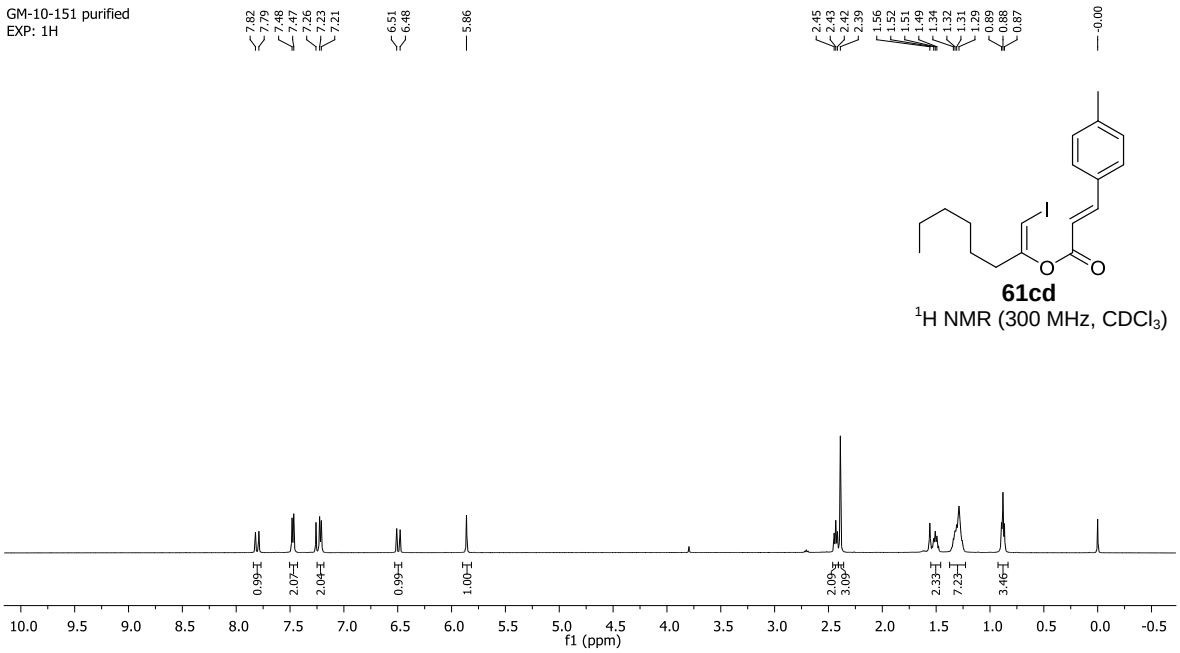
61ca

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



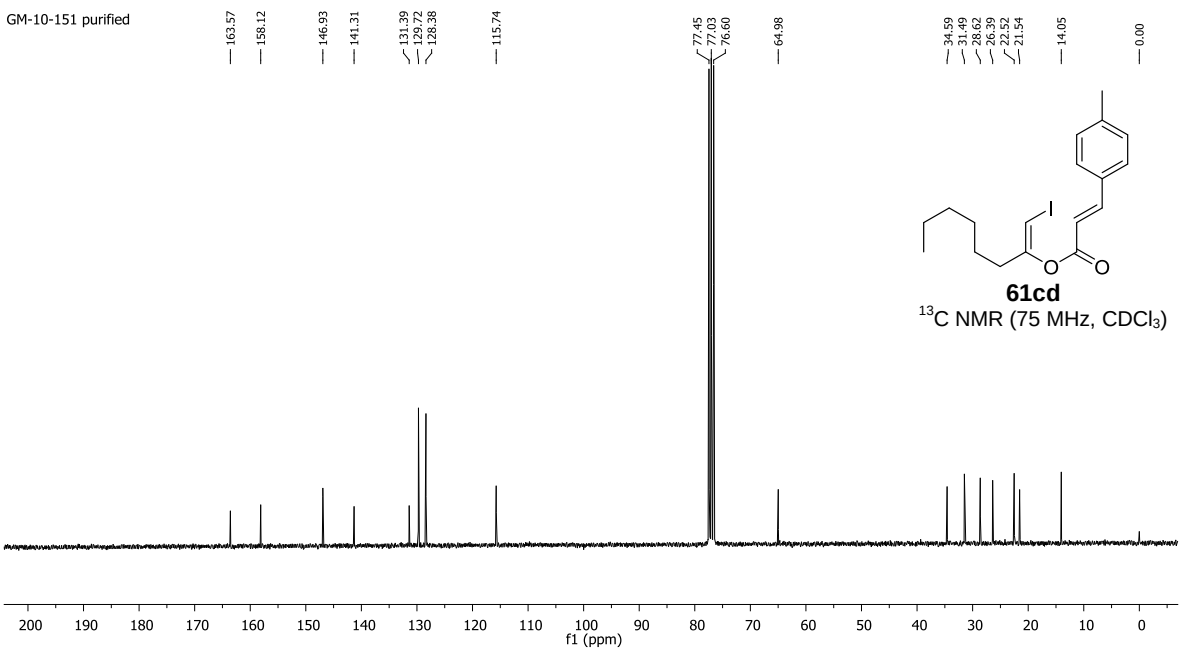
61ca

^{13}C NMR (75 MHz, $CDCl_3$)



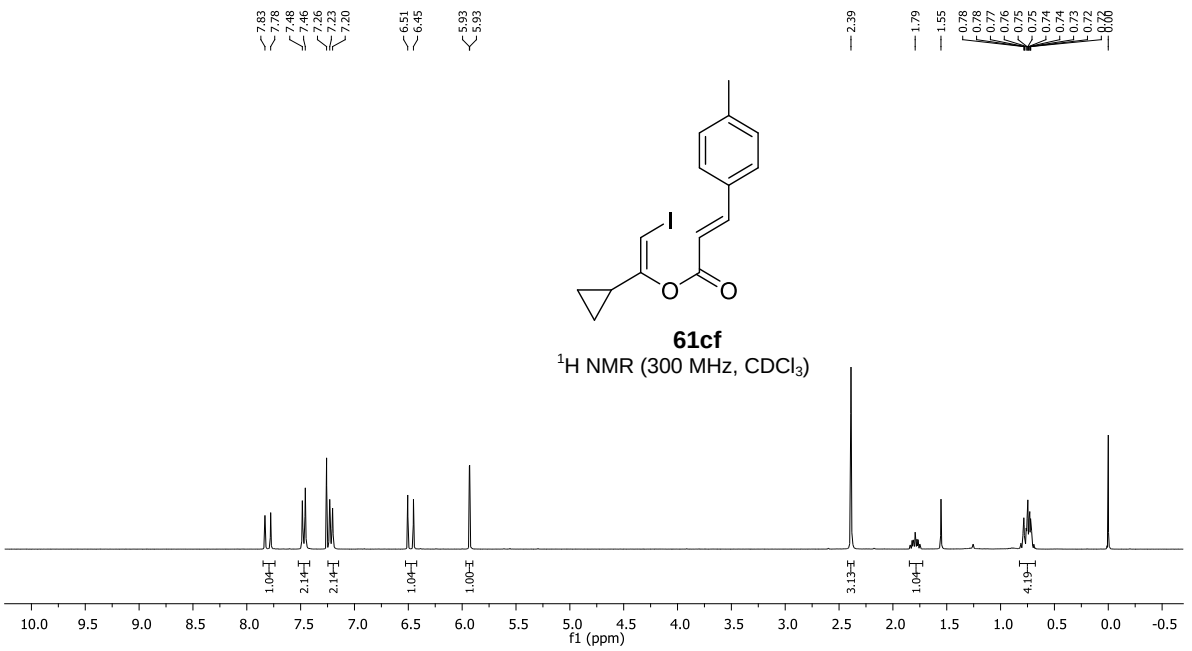
61cd

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



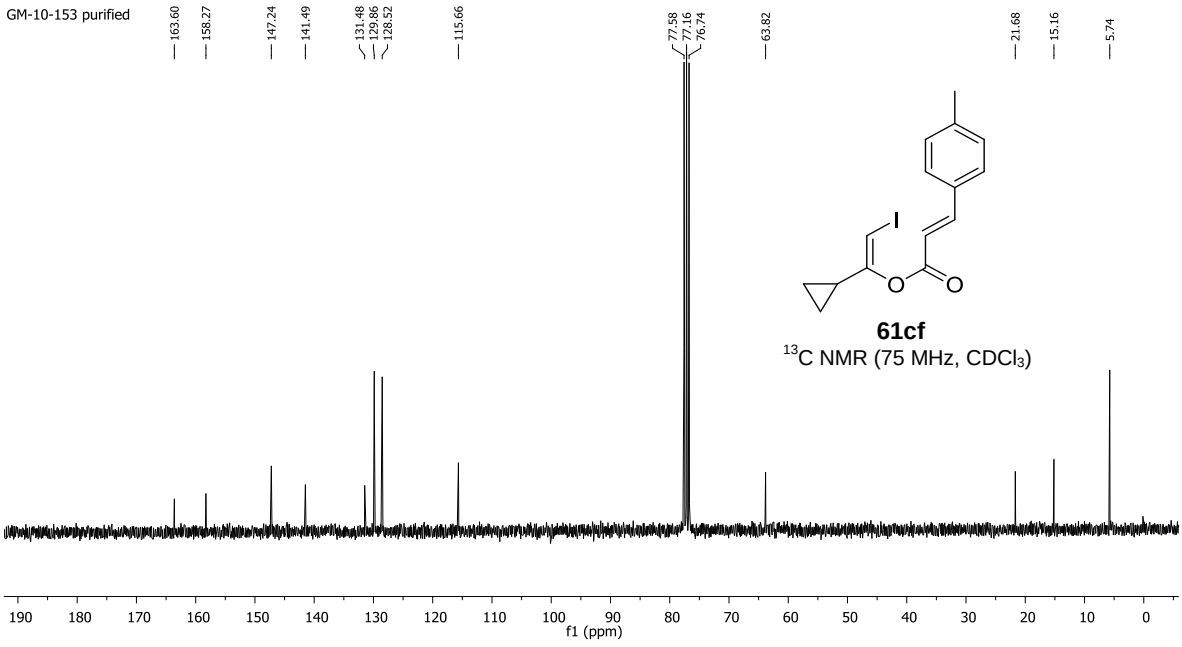
61cd

^{13}C NMR (75 MHz, $CDCl_3$)



61cf

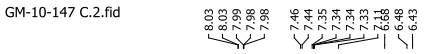
^{1}H NMR (300 MHz, $CDCl_3$)

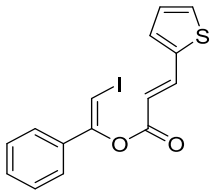


61cf

^{13}C NMR (75 MHz, $CDCl_3$)

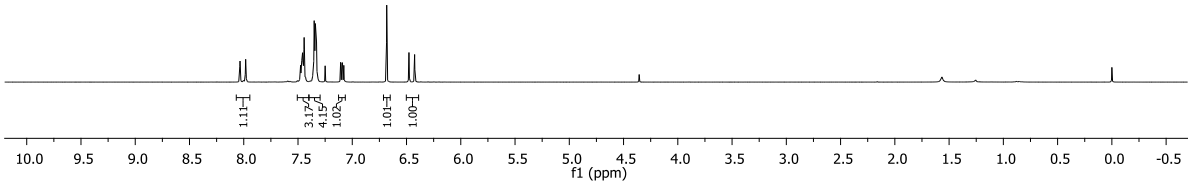
GM-10-147 C.2.fid



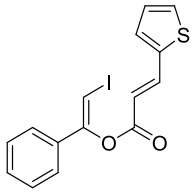


61da

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

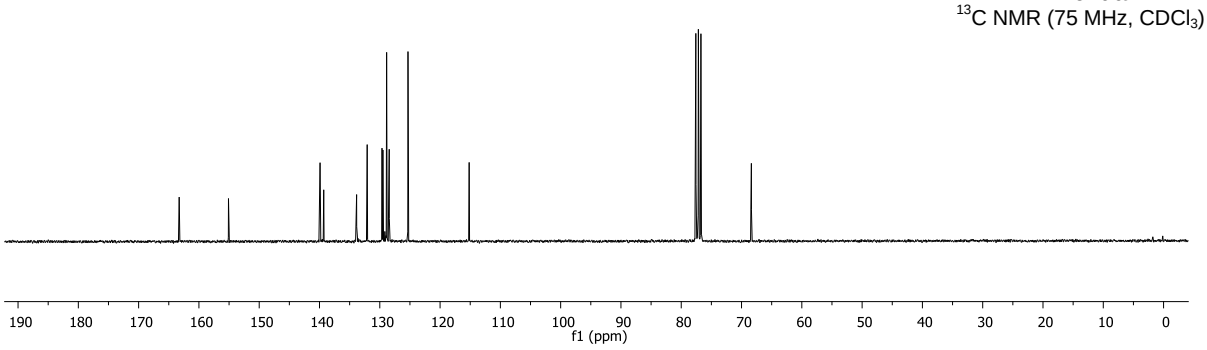


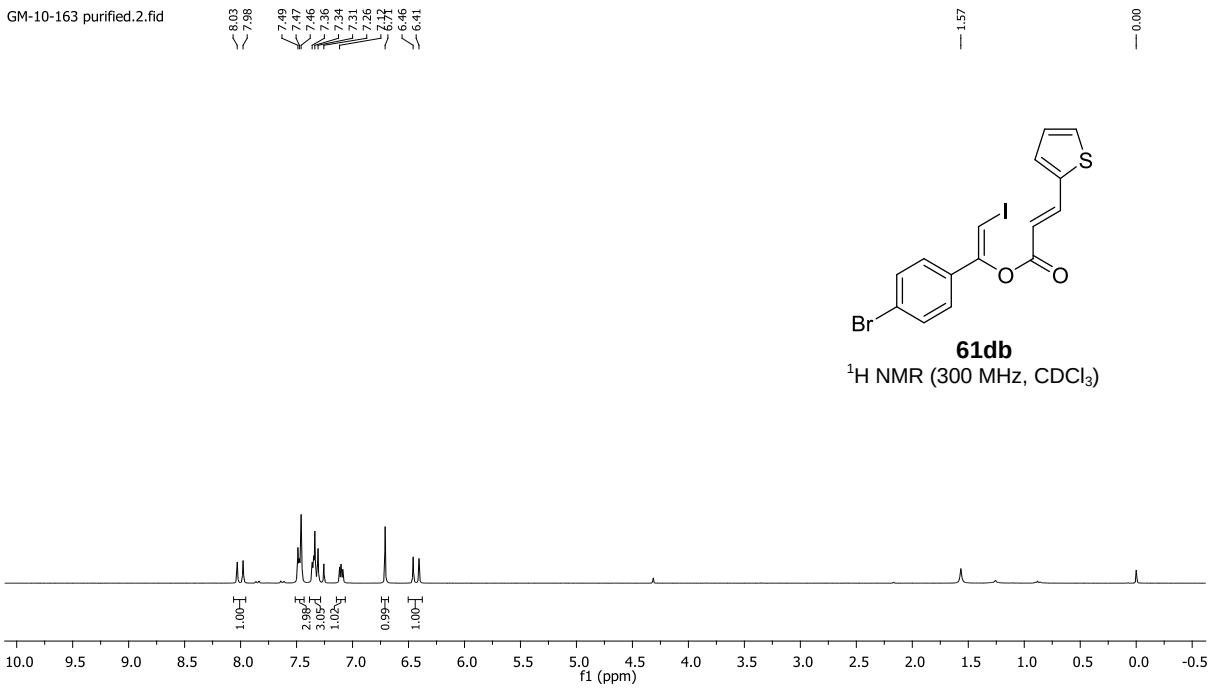
GM-10-147 C.3.fid



61da

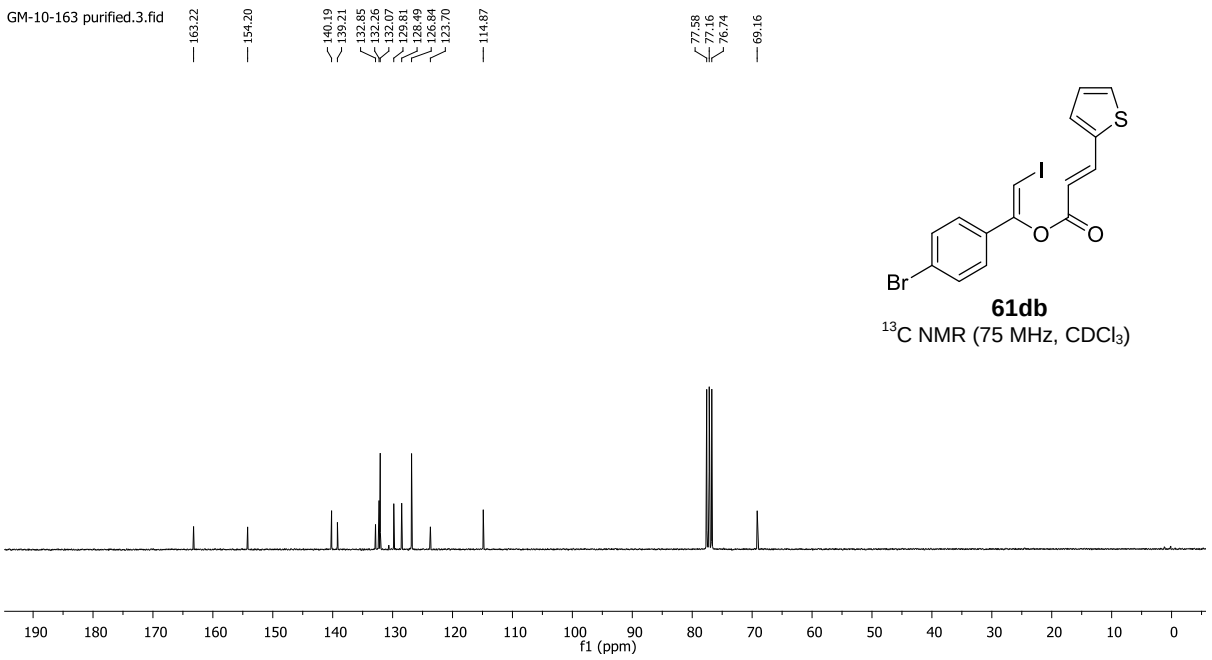
^{13}C NMR (75 MHz, $CDCl_3$)





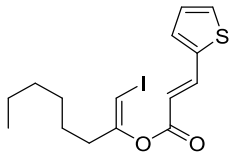
61db

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



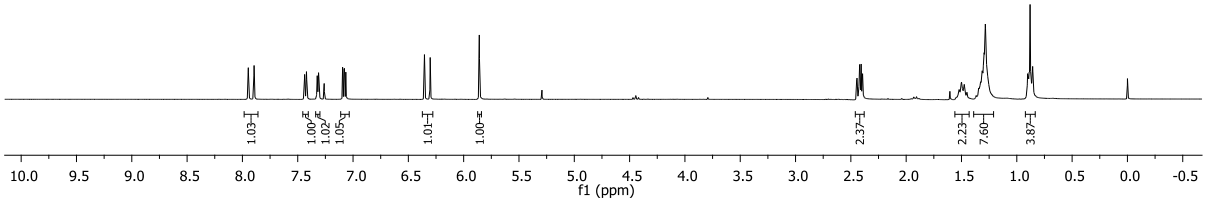
61db

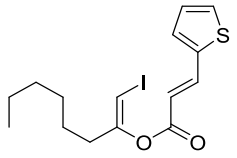
^{13}C NMR (75 MHz, $CDCl_3$)



61dd

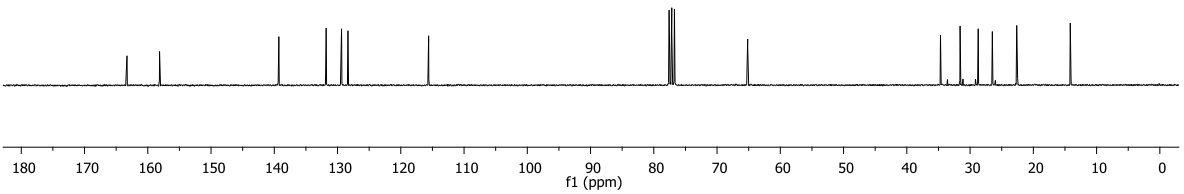
^{1}H NMR (300 MHz, $CDCl_3$)

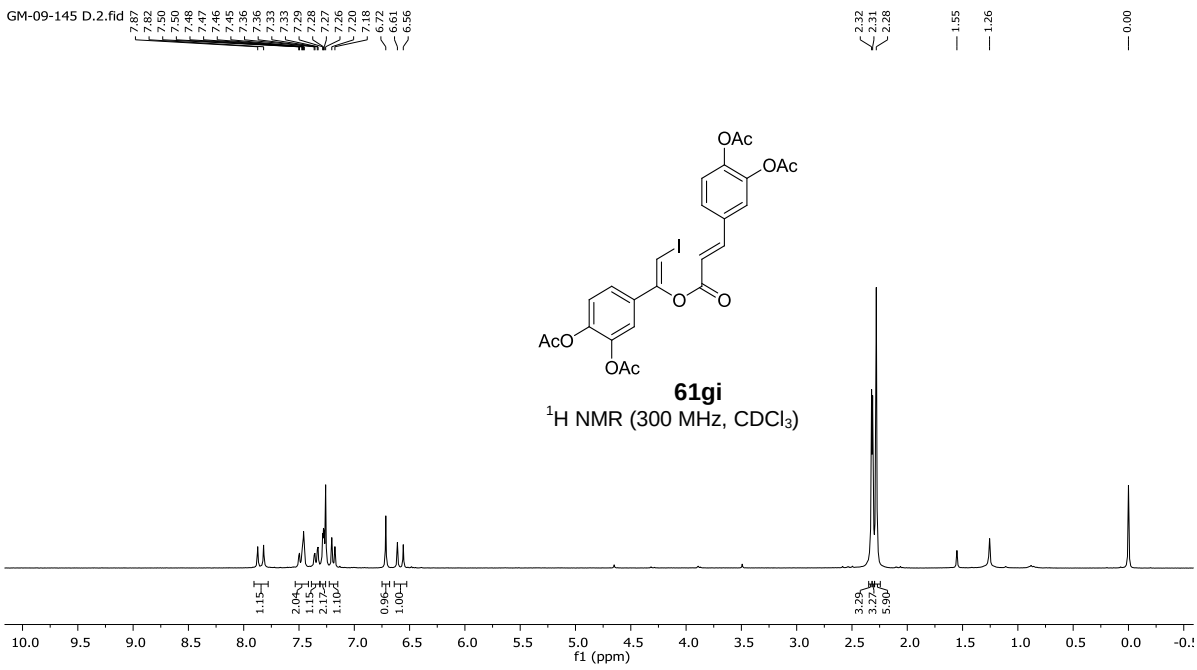




61dd

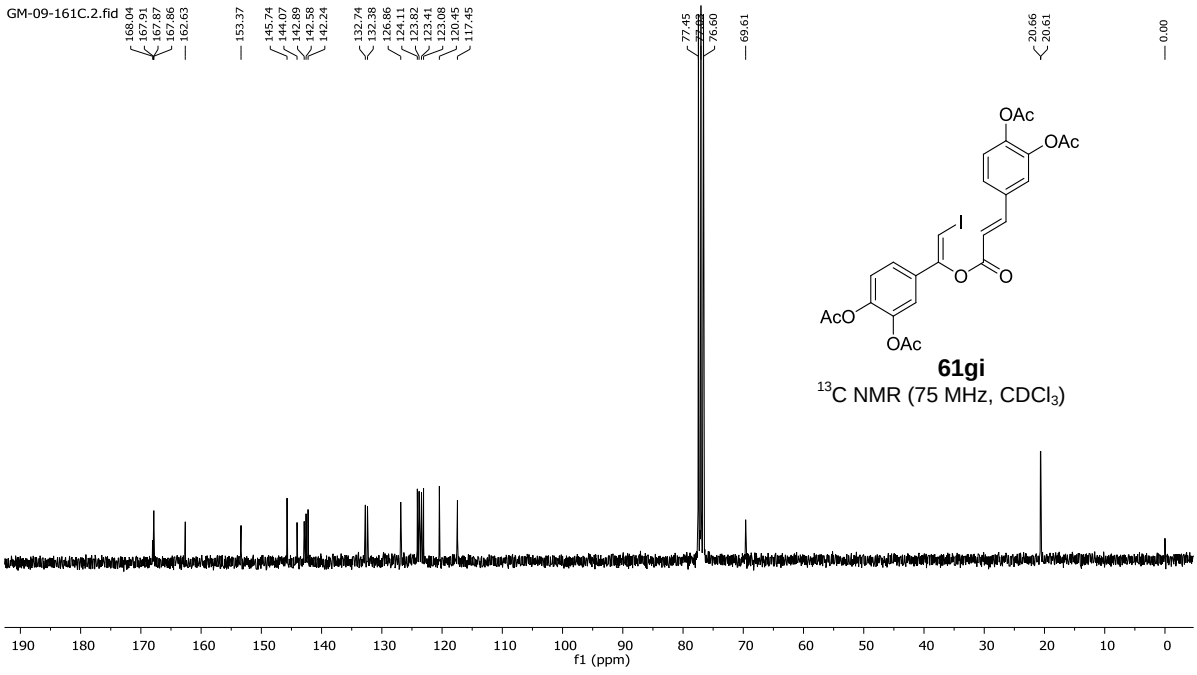
^{13}C NMR (75 MHz, $CDCl_3$)





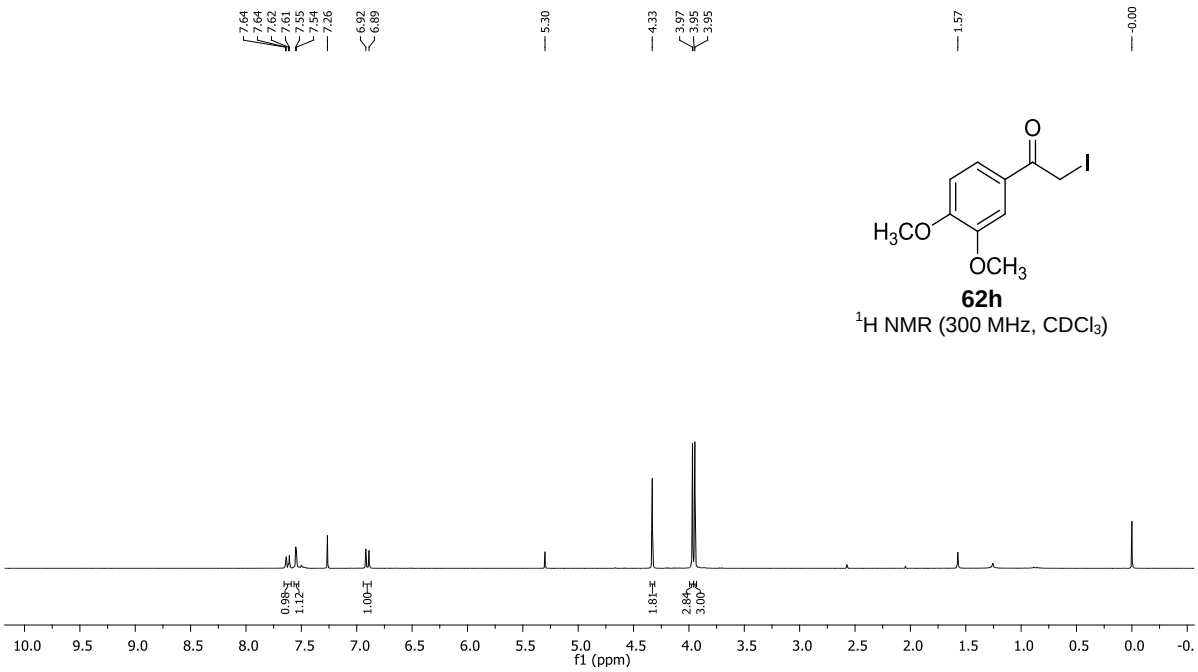
61gi

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



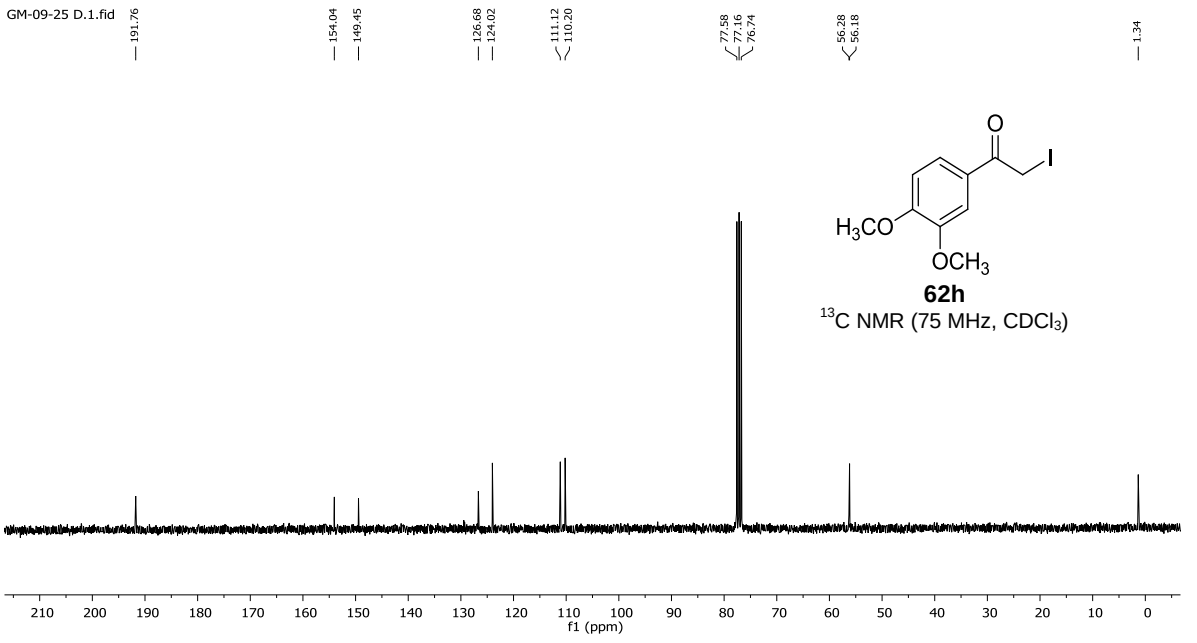
61gi

^{13}C NMR (75 MHz, $CDCl_3$)



62h

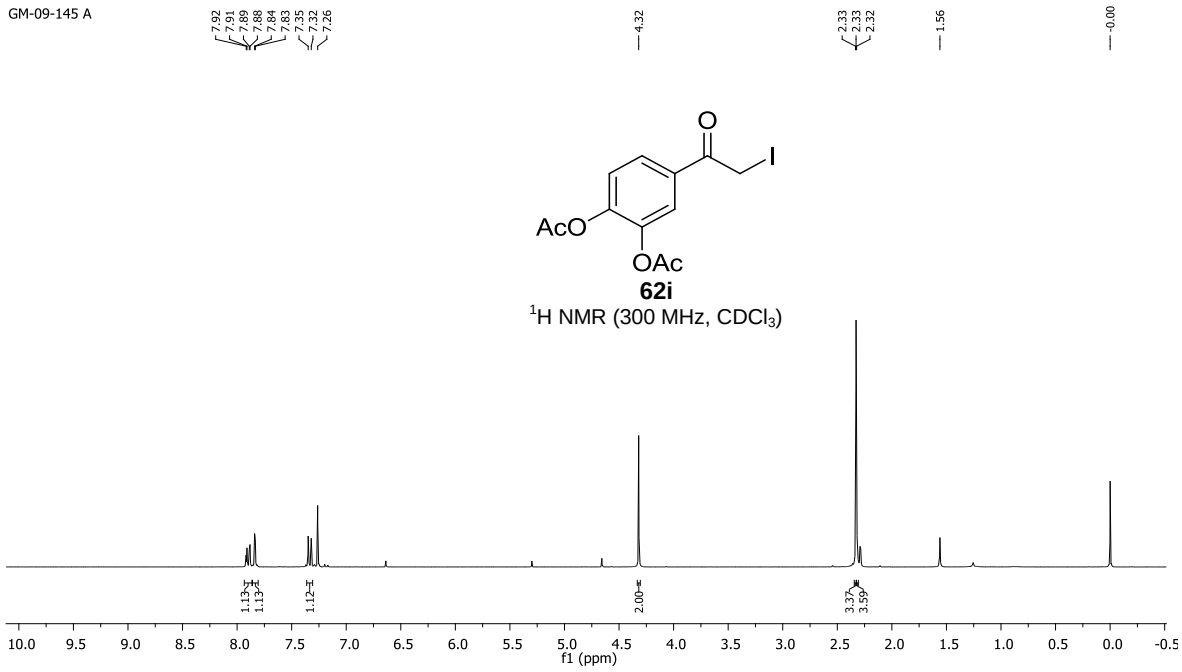
^{1}H NMR (300 MHz, $CDCl_3$)



62h

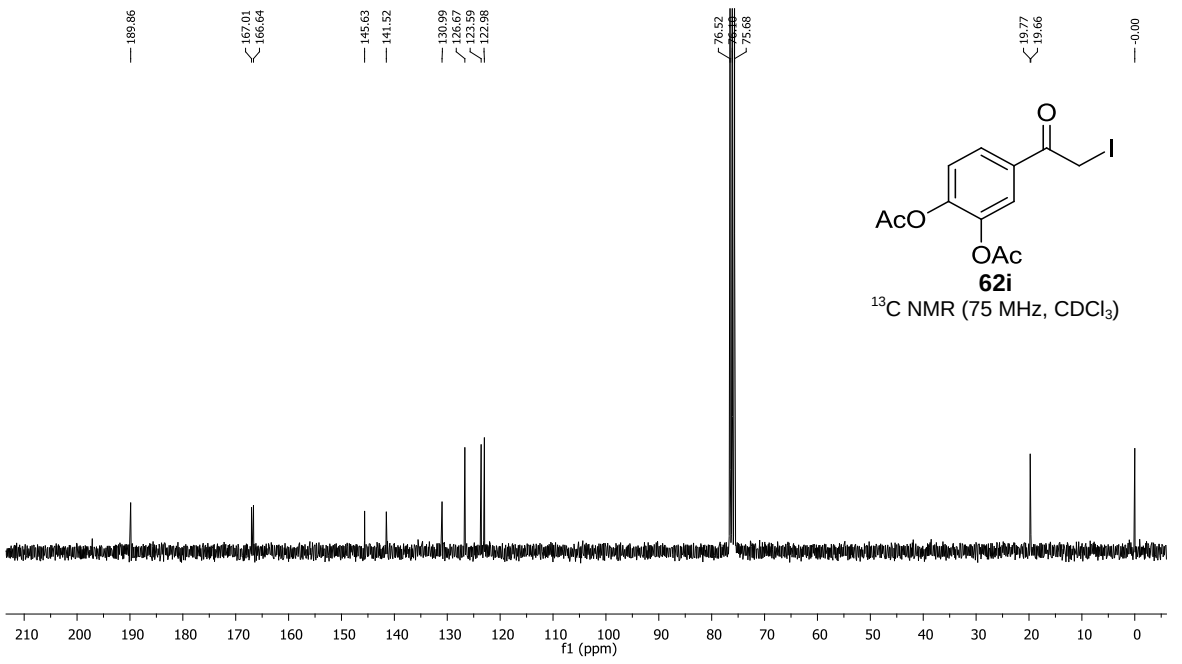
^{13}C NMR (75 MHz, $CDCl_3$)

GM-09-145 A



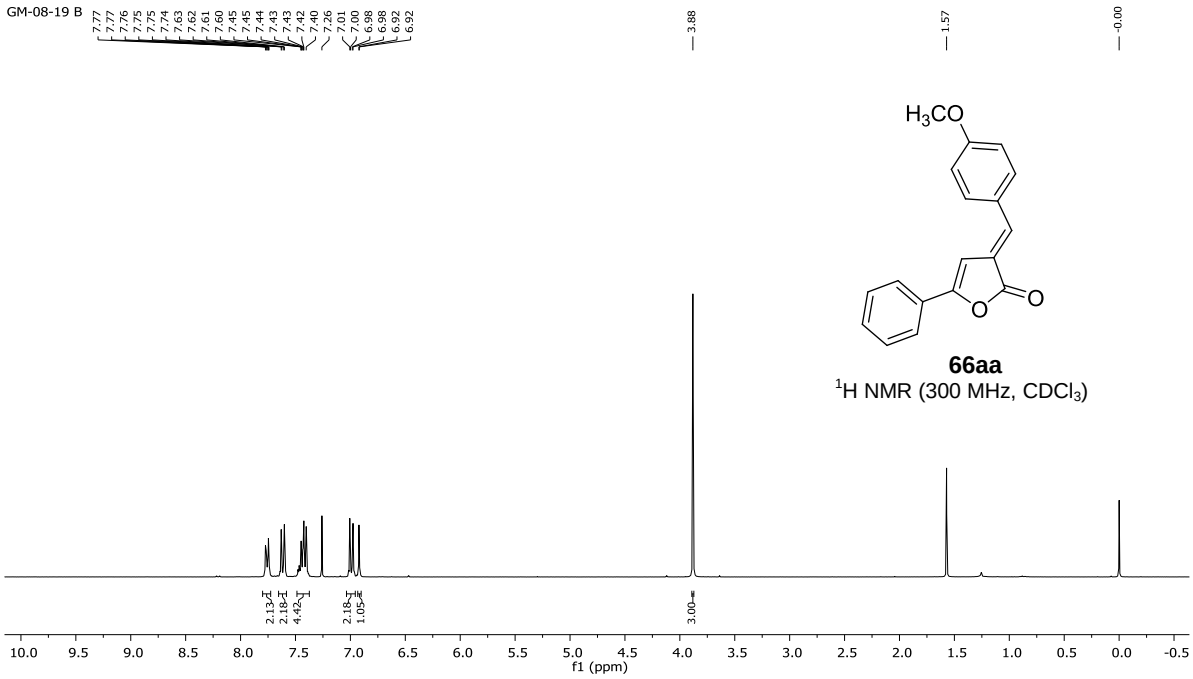
62i

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



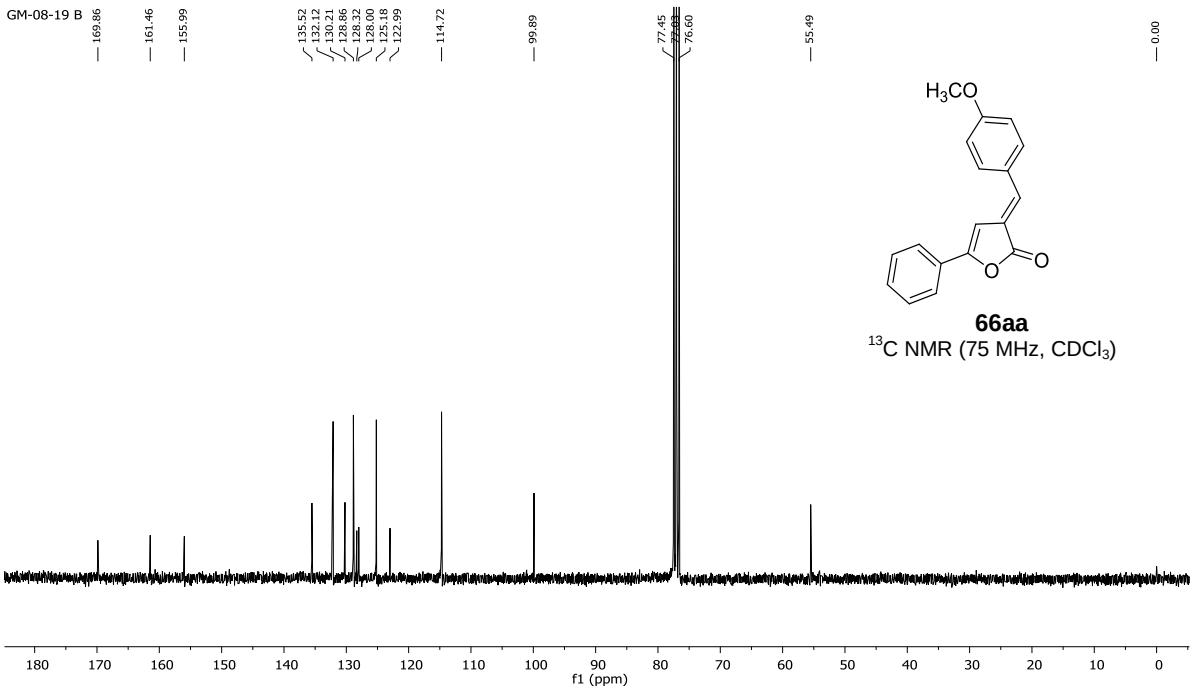
62i

^{13}C NMR (75 MHz, $CDCl_3$)



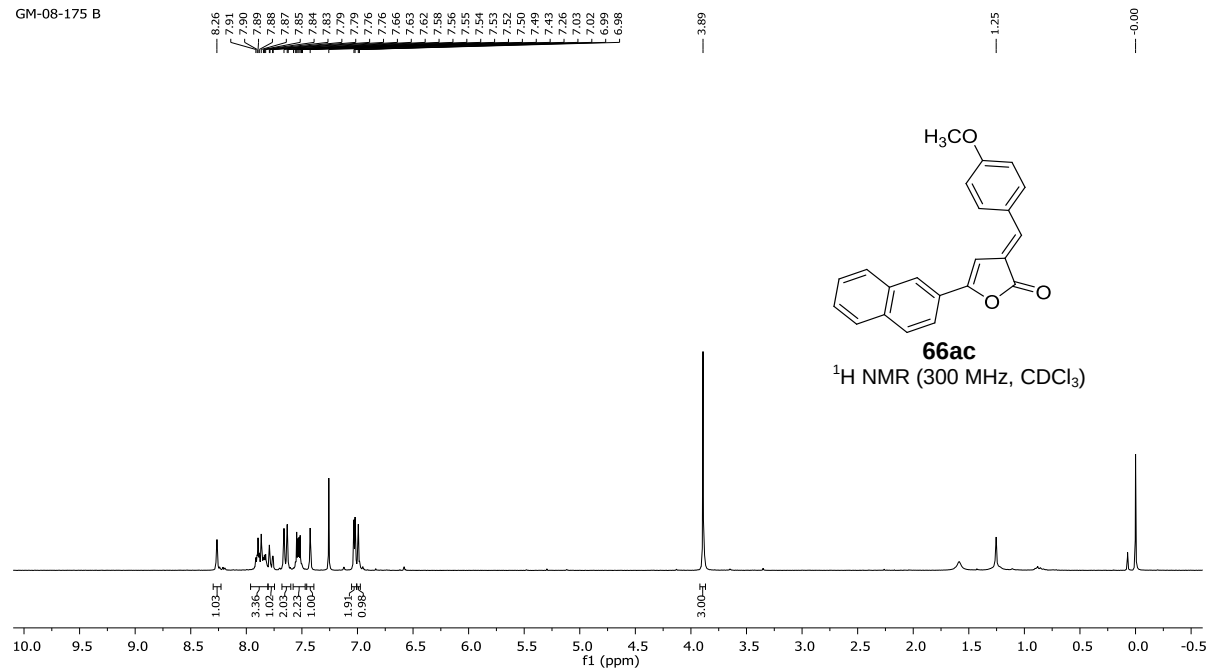
66aa

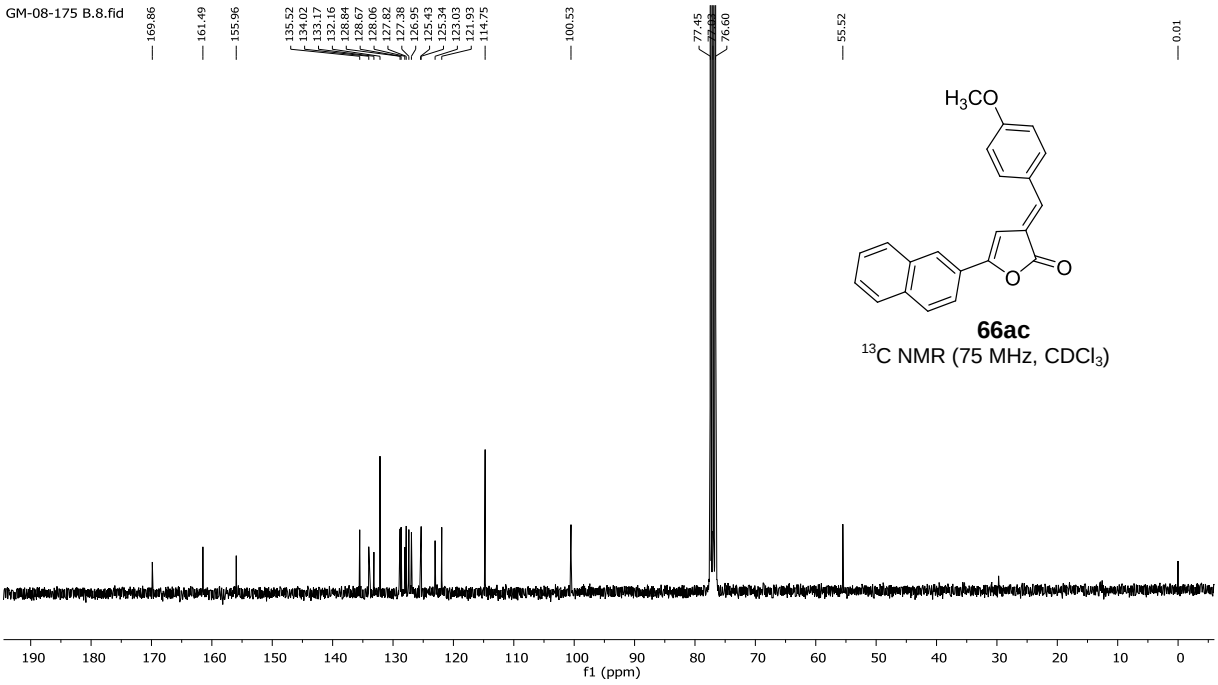
^{1}H NMR (300 MHz, $CDCl_3$)

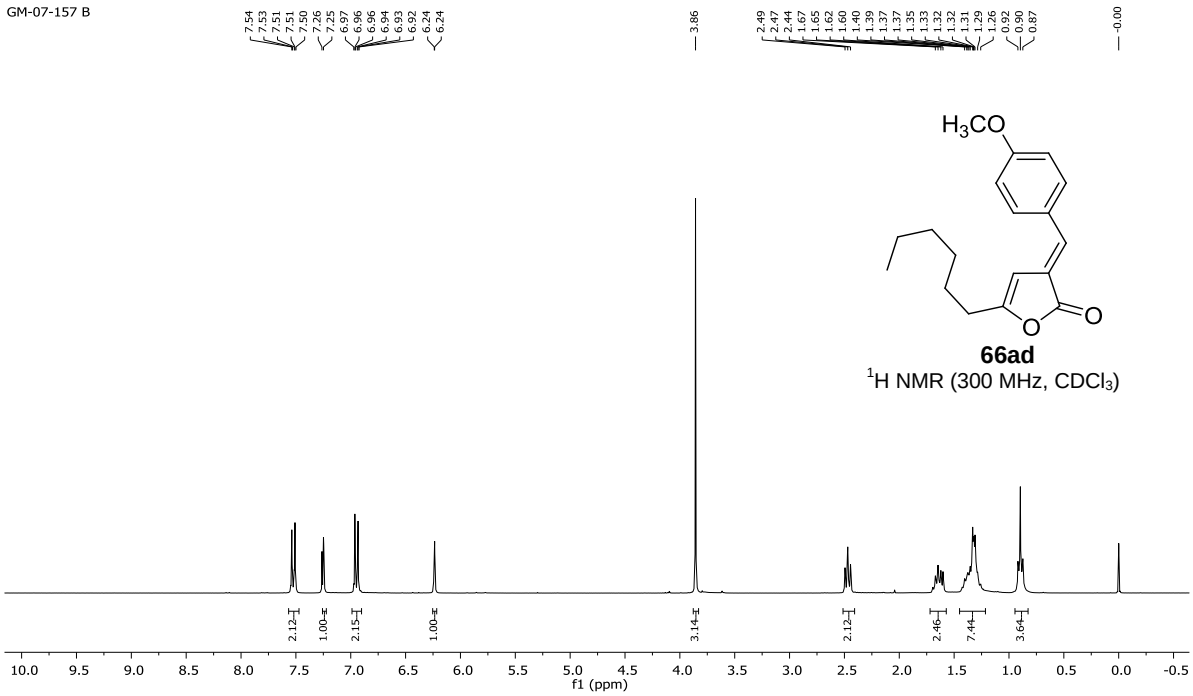


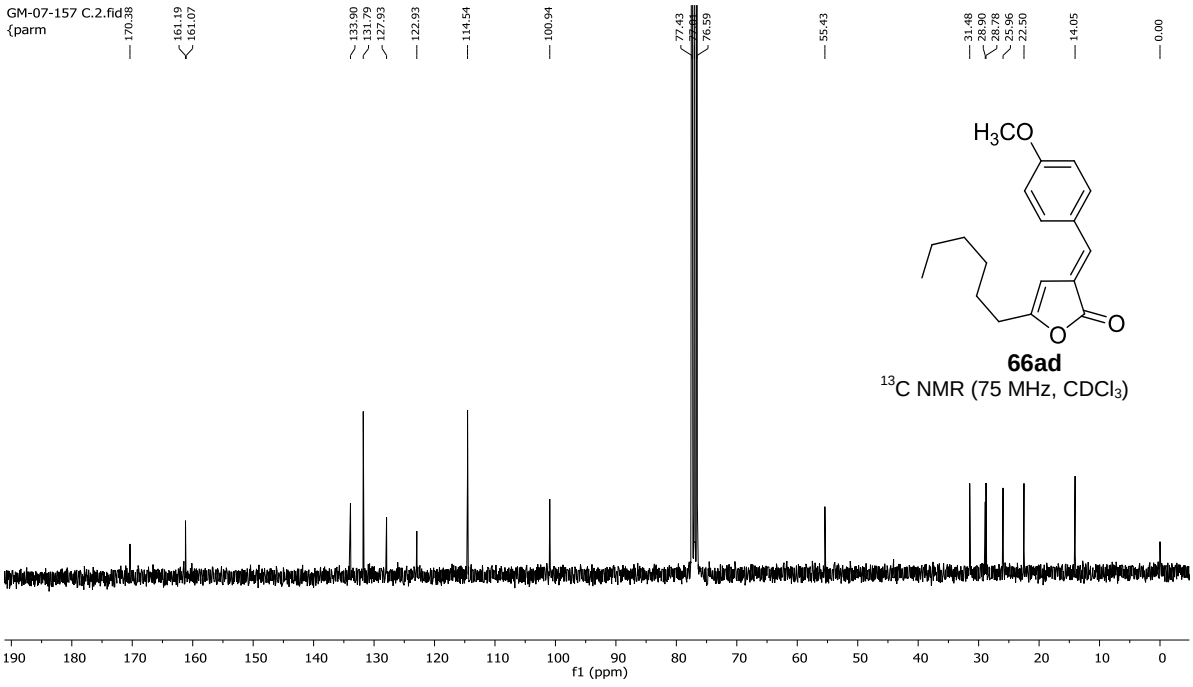
66aa

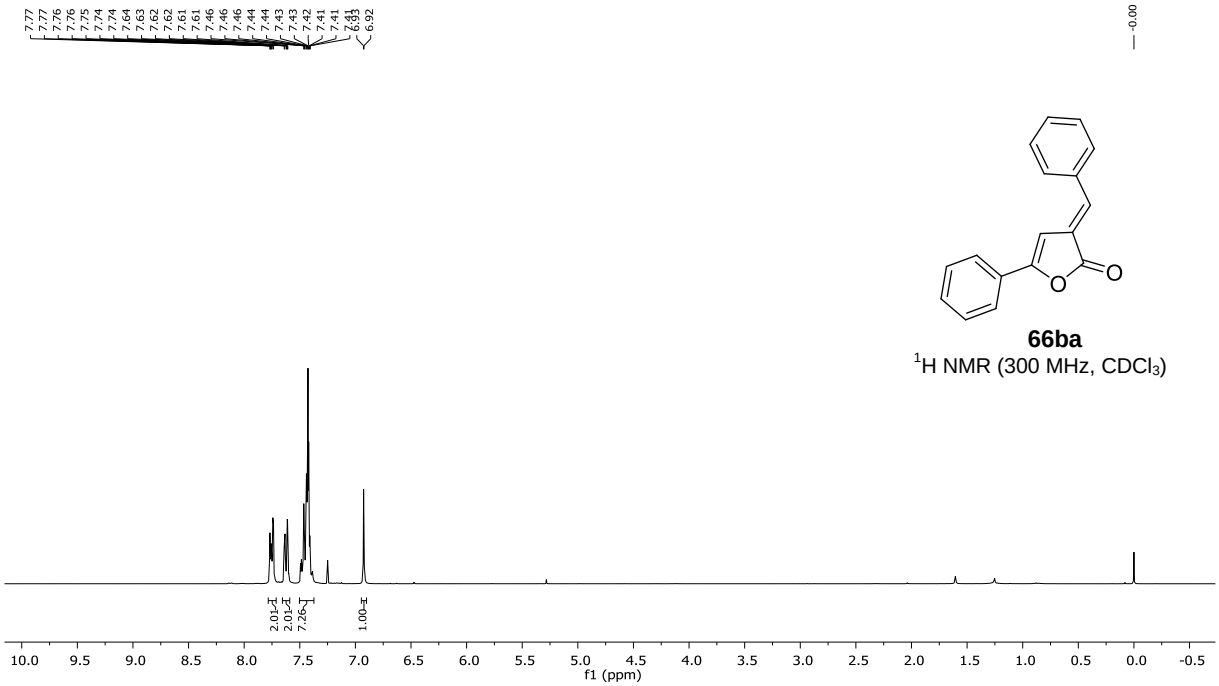
^{13}C NMR (75 MHz, $CDCl_3$)


GM-08-175 B
8.26
7.91
7.90
7.89
7.88
7.87
7.85
7.84
7.83
7.79
7.79
7.76
7.76
7.66
7.63
7.62
7.58
7.56
7.55
7.54
7.53
7.52
7.50
7.49
7.43
7.26
7.03
7.02
6.99
6.98
3.89
1.25
0.00
H3CO
O
O
66ac
1H NMR (300 MHz, CDCl3)
1.03
3.36
1.02
2.03
2.23
1.00
1.91
0.98
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


GM-08-175 B.8.fid
169.86
161.49
155.96
135.52
134.02
133.17
132.16
128.84
128.67
128.06
127.82
127.38
126.95
125.43
125.34
123.03
121.93
114.75
100.53
77.45
77.20
76.60
55.52
0.01
H3CO
O
O
66ac
13C NMR (75 MHz, CDCl3)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

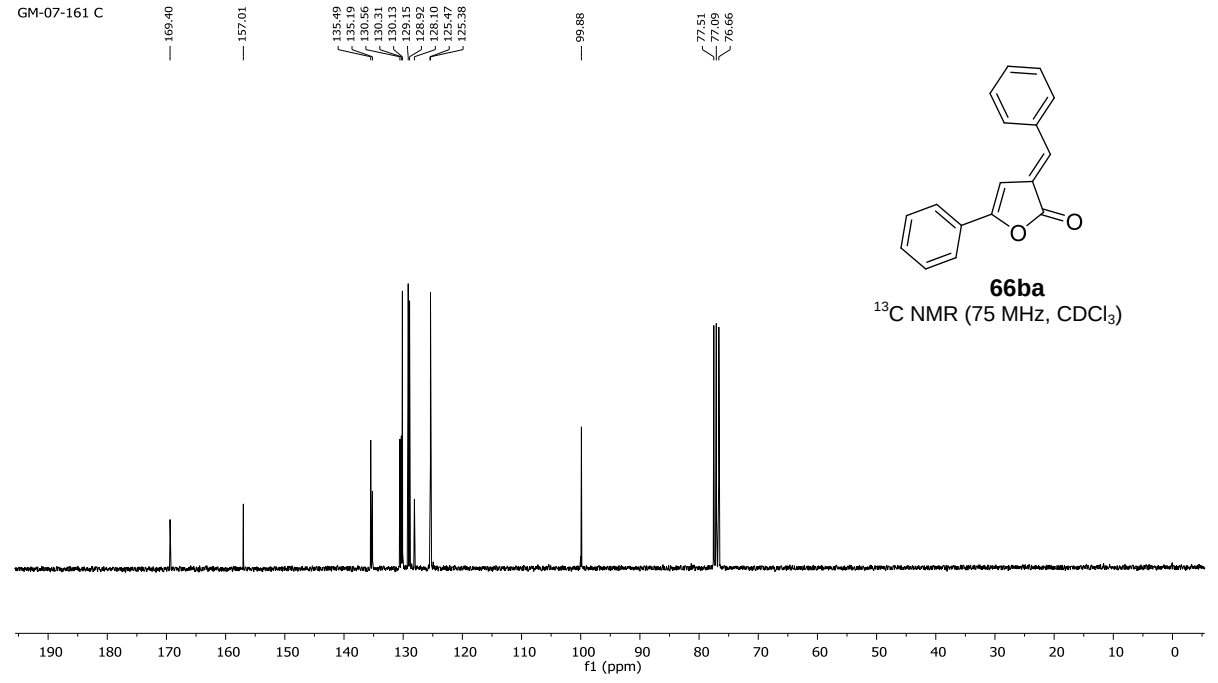

GM-07-157 B
7.54
7.53
7.51
7.51
7.50
7.26
7.25
6.97
6.96
6.96
6.94
6.93
6.92
6.24
6.24
3.86
2.49
2.47
2.44
1.67
1.65
1.62
1.60
1.40
1.39
1.37
1.37
1.35
1.33
1.32
1.32
1.31
1.29
1.26
0.92
0.90
0.87
0.00
H3CO
O
O
66ad
1H NMR (300 MHz, CDCl3)
2.12
1.00
2.15
1.00
3.14
2.12
2.46
7.44
3.64
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


GM-07-157 C.2.fid
{parm
170.38
161.19
161.07
133.90
131.79
127.93
122.93
114.54
100.94
77.43
77.01
76.59
55.43
31.48
28.90
28.78
25.96
22.50
14.05
0.00
H3CO
O
O
66ad
13C NMR (75 MHz, CDCl3)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



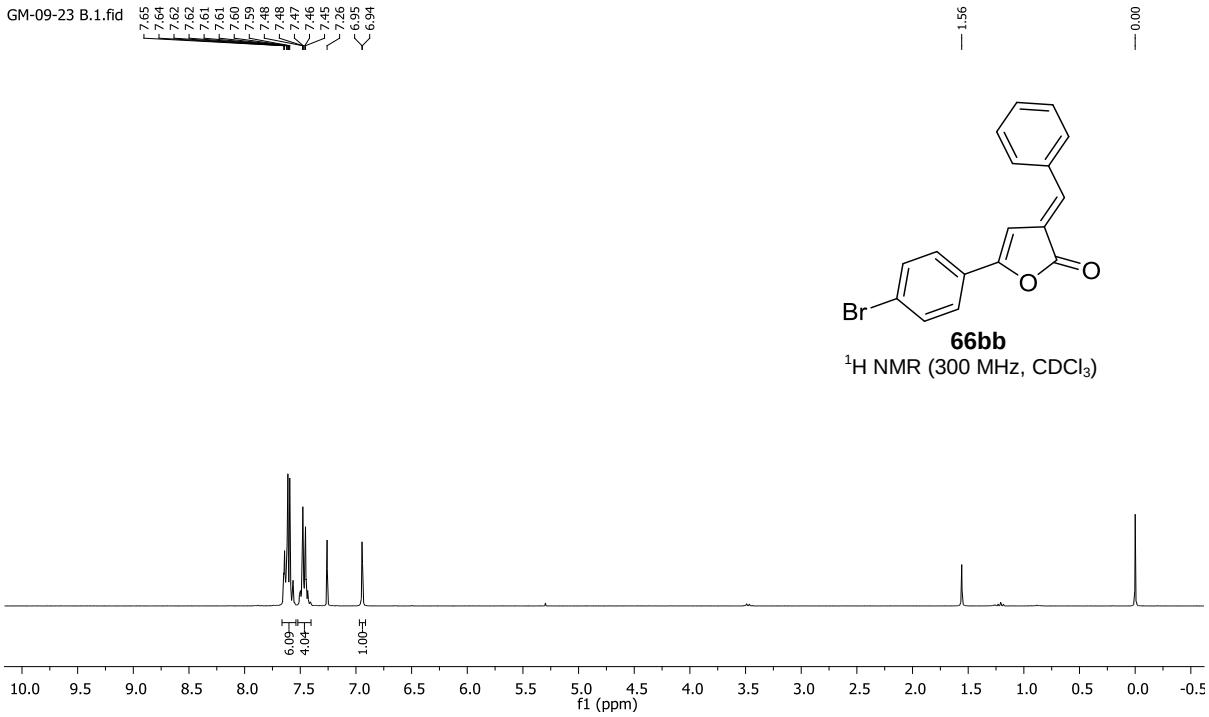
66ba

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



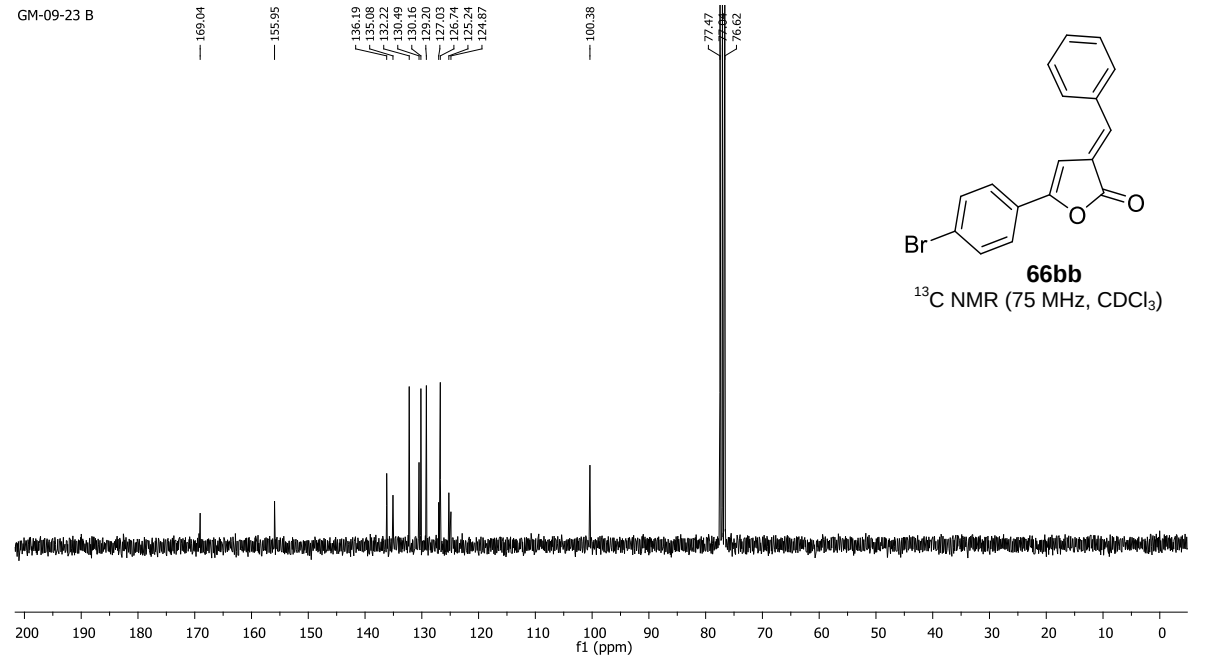
66ba

^{13}C NMR (75 MHz, $CDCl_3$)



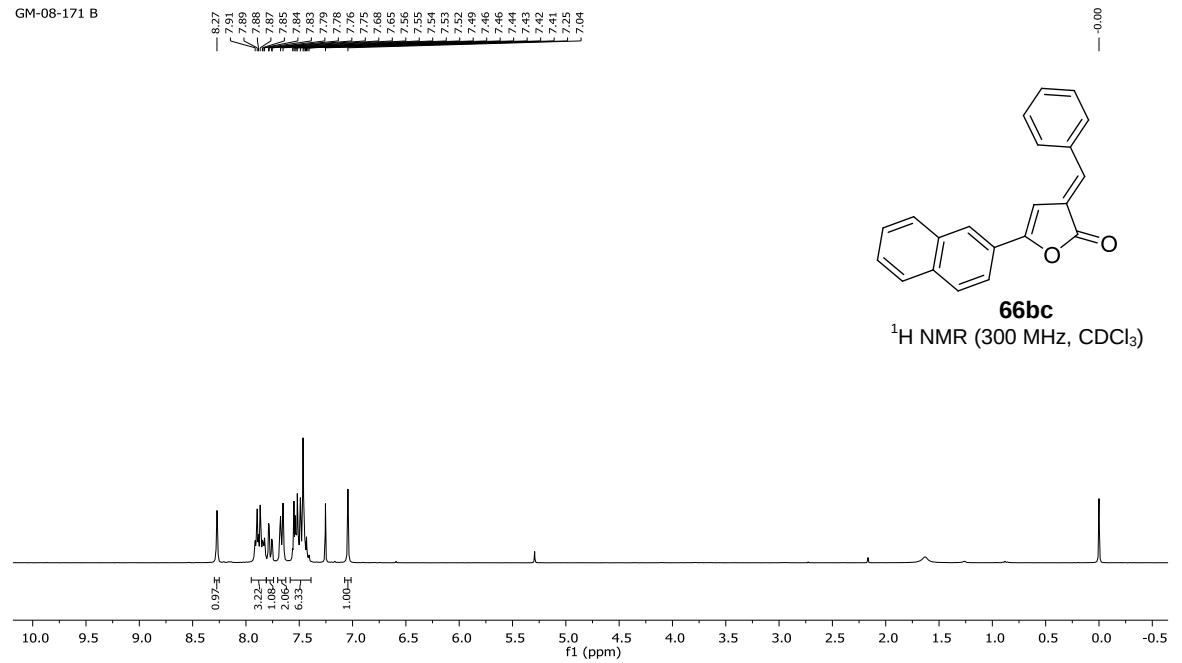
66bb

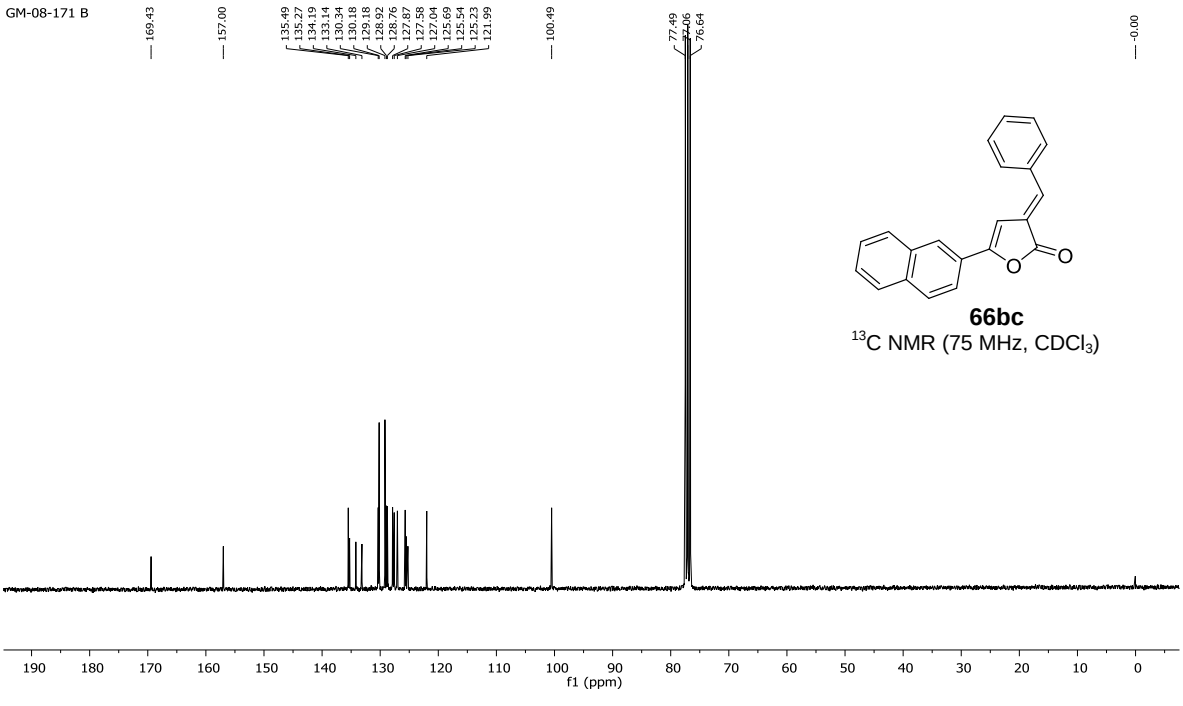
^{1}H NMR (300 MHz, $CDCl_3$)

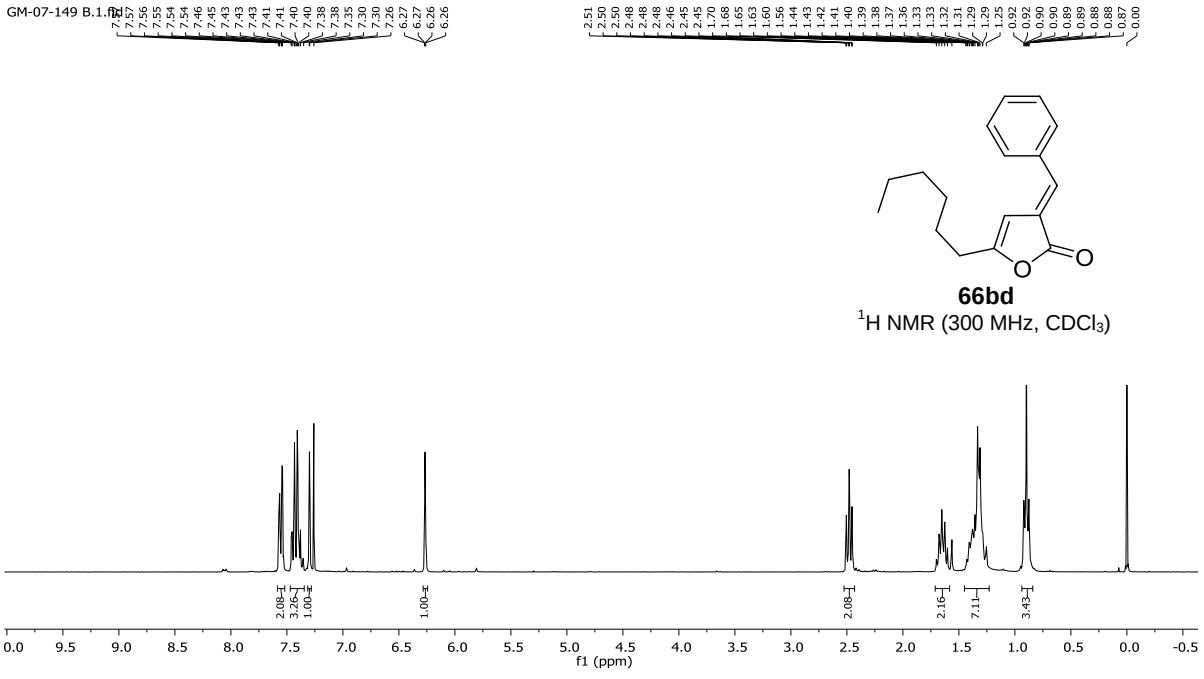


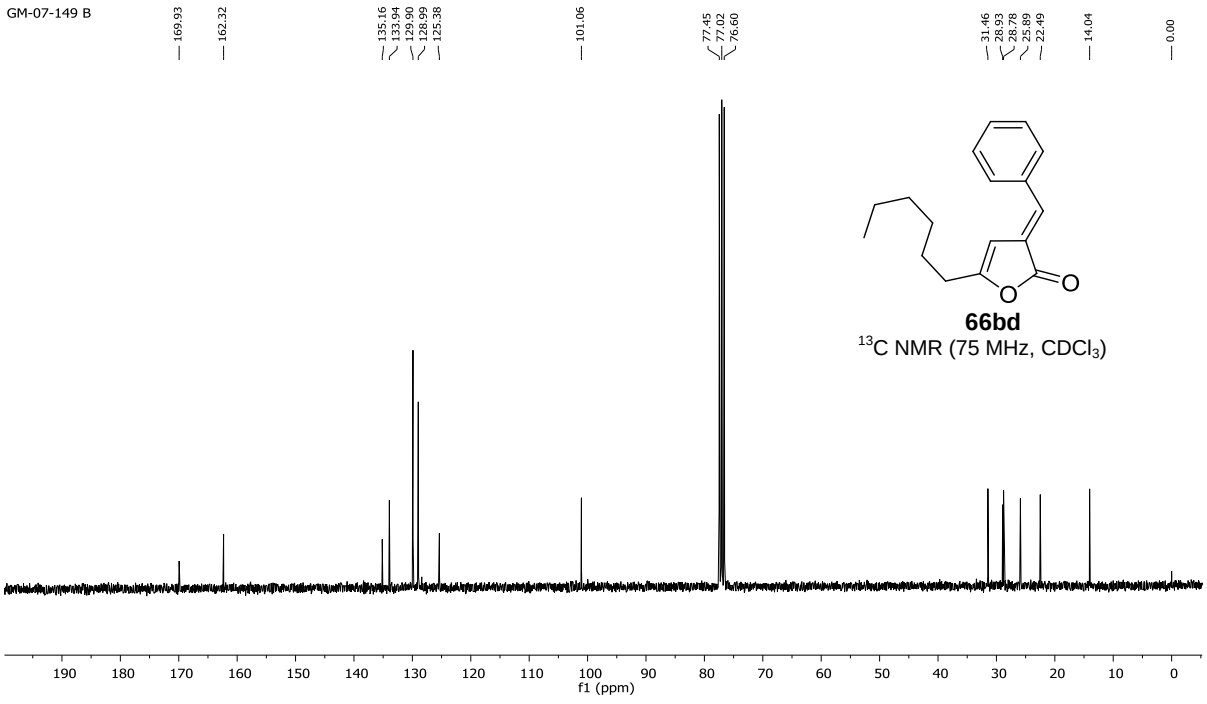
66bb

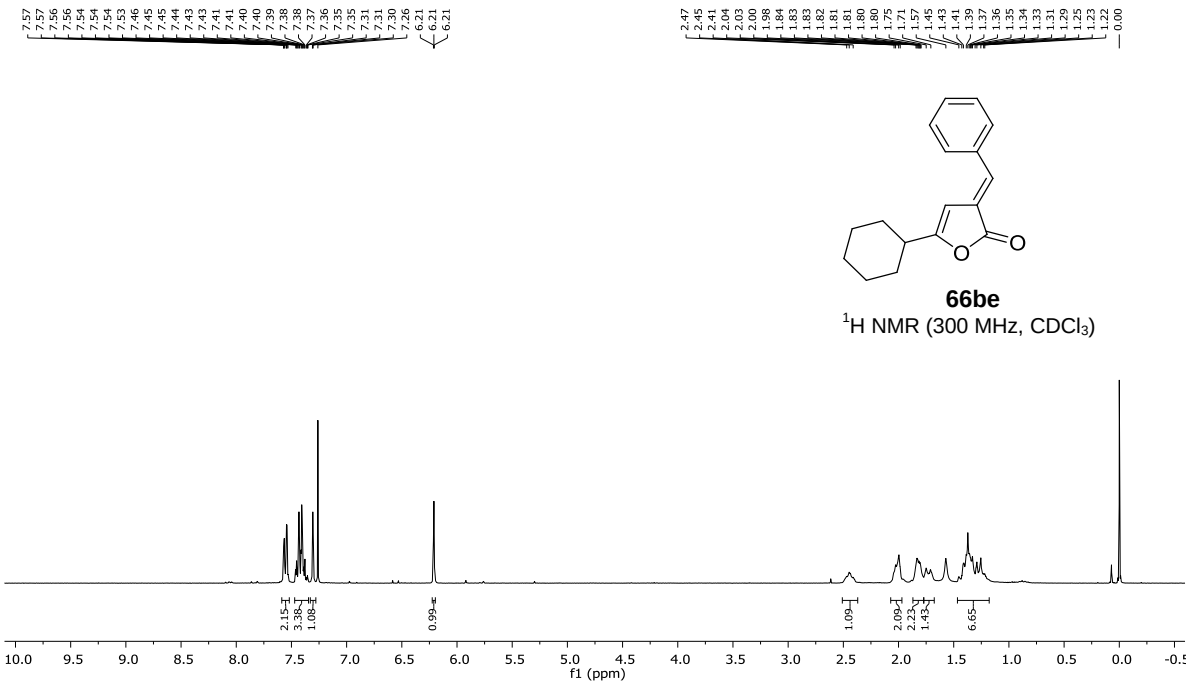
^{13}C NMR (75 MHz, $CDCl_3$)


GM-08-171 B
8.27
7.91
7.89
7.88
7.87
7.85
7.84
7.83
7.79
7.78
7.76
7.75
7.68
7.65
7.56
7.55
7.54
7.53
7.52
7.49
7.46
7.46
7.44
7.43
7.42
7.41
7.25
7.04
-0.00
O
O
66bc
1H NMR (300 MHz, CDCl3)
0.97
3.22
1.08
2.06
6.33
1.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


GM-08-171 B
169.43
157.00
135.49
135.27
134.19
133.14
130.34
130.18
129.18
128.92
128.76
127.87
127.58
127.04
125.69
125.54
125.23
121.99
100.49
77.49
77.06
76.64
-0.00
O
O
66bc
13C NMR (75 MHz, CDCl3)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

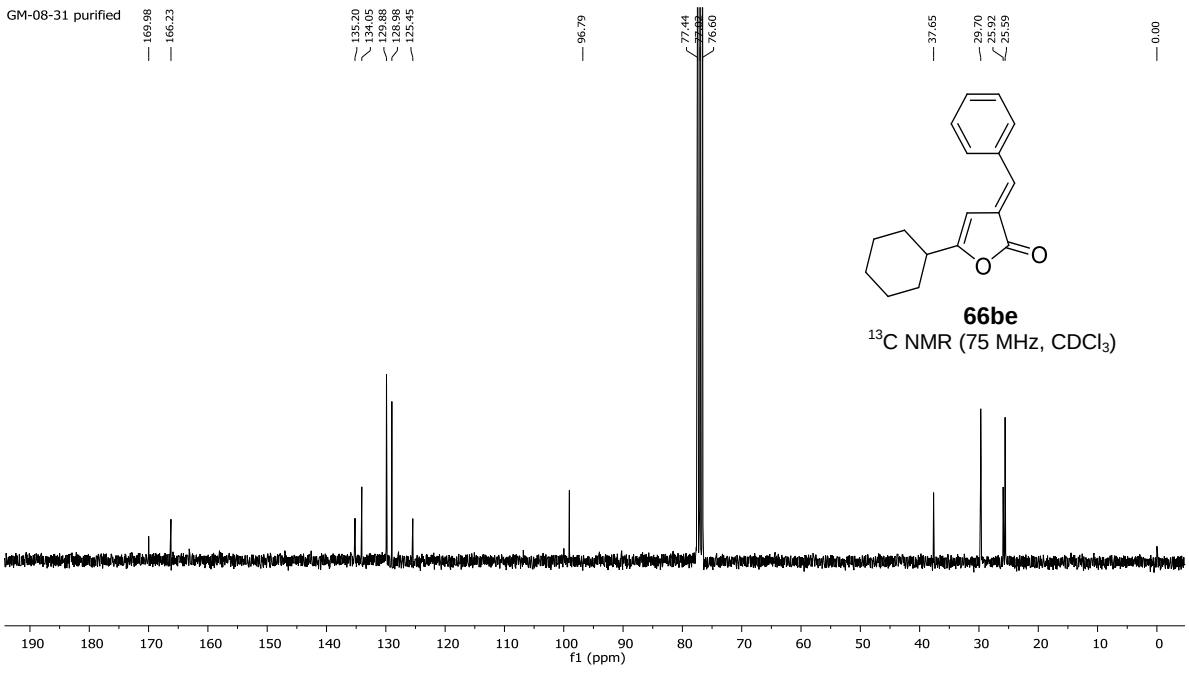

GM-07-149 B.1.fid
O
O
66bd
1H NMR (300 MHz, CDCl3)
f1 (ppm)


GM-07-149 B
O
O
66bd
13C NMR (75 MHz, CDCl3)
f1 (ppm)



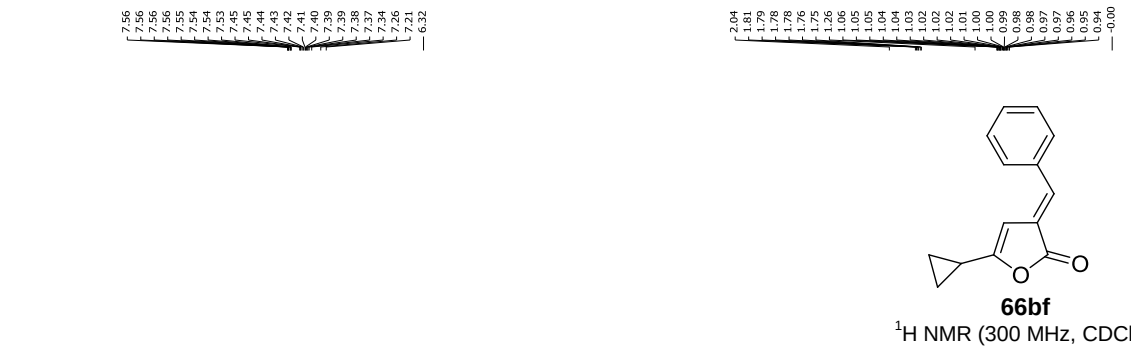
66be

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



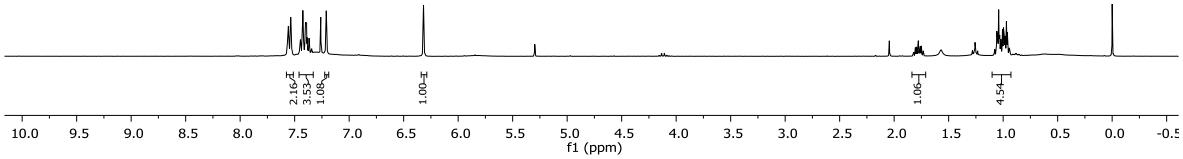
66be

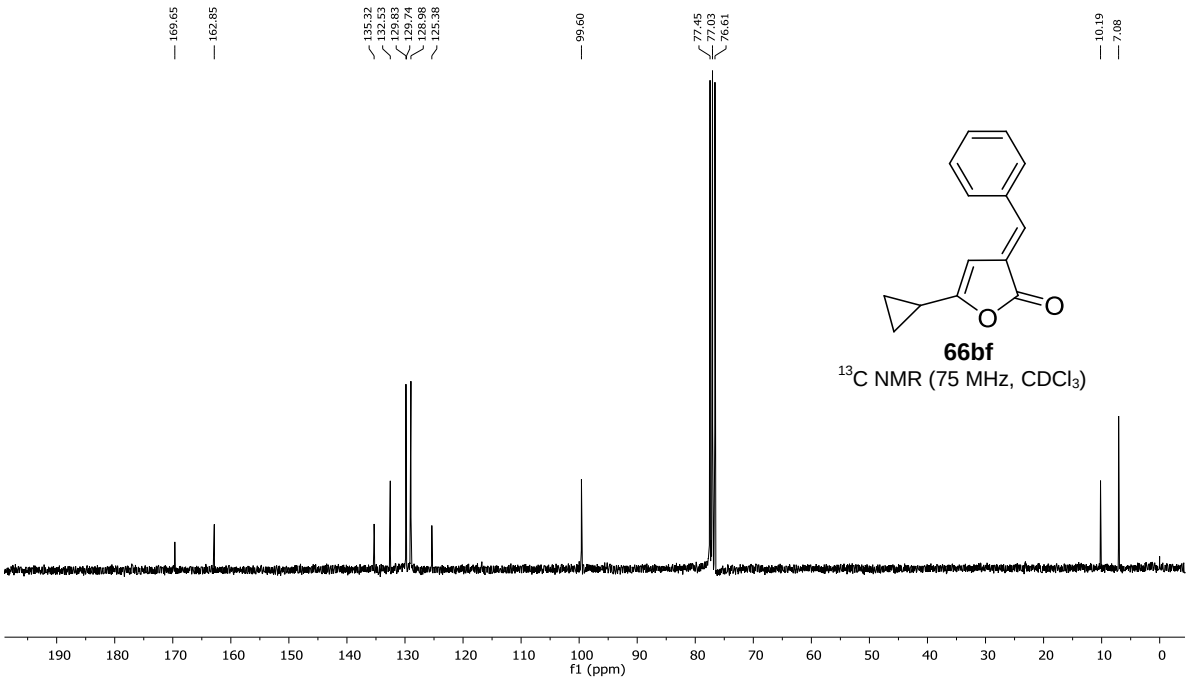
^{13}C NMR (75 MHz, $CDCl_3$)



66bf

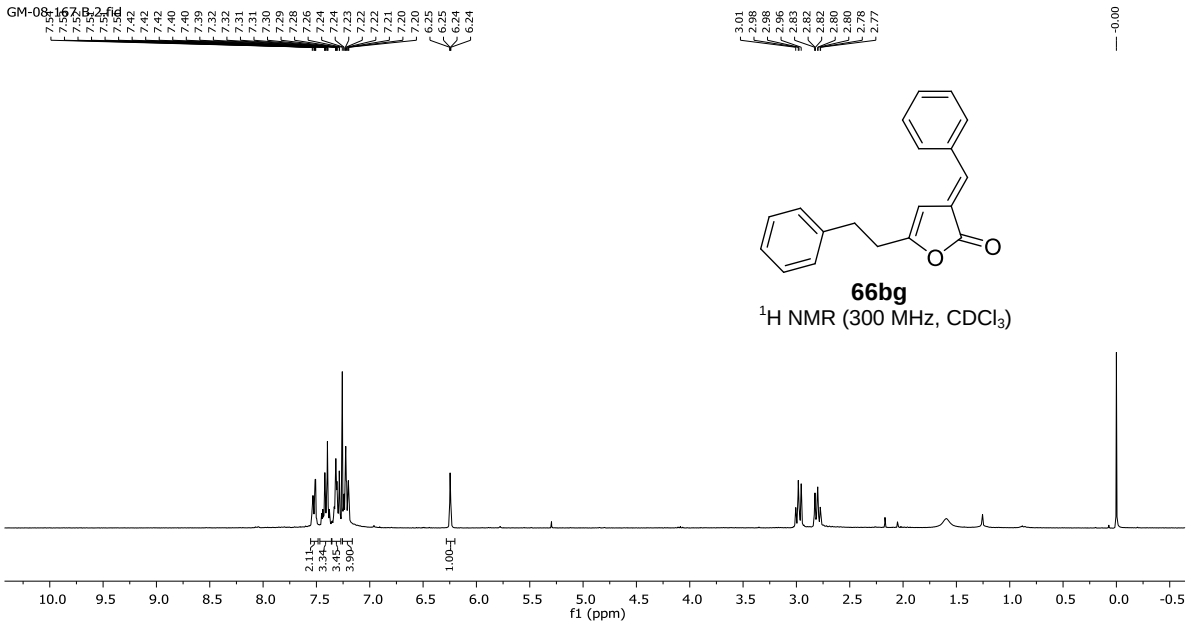
^{1}H NMR (300 MHz, $CDCl_3$)

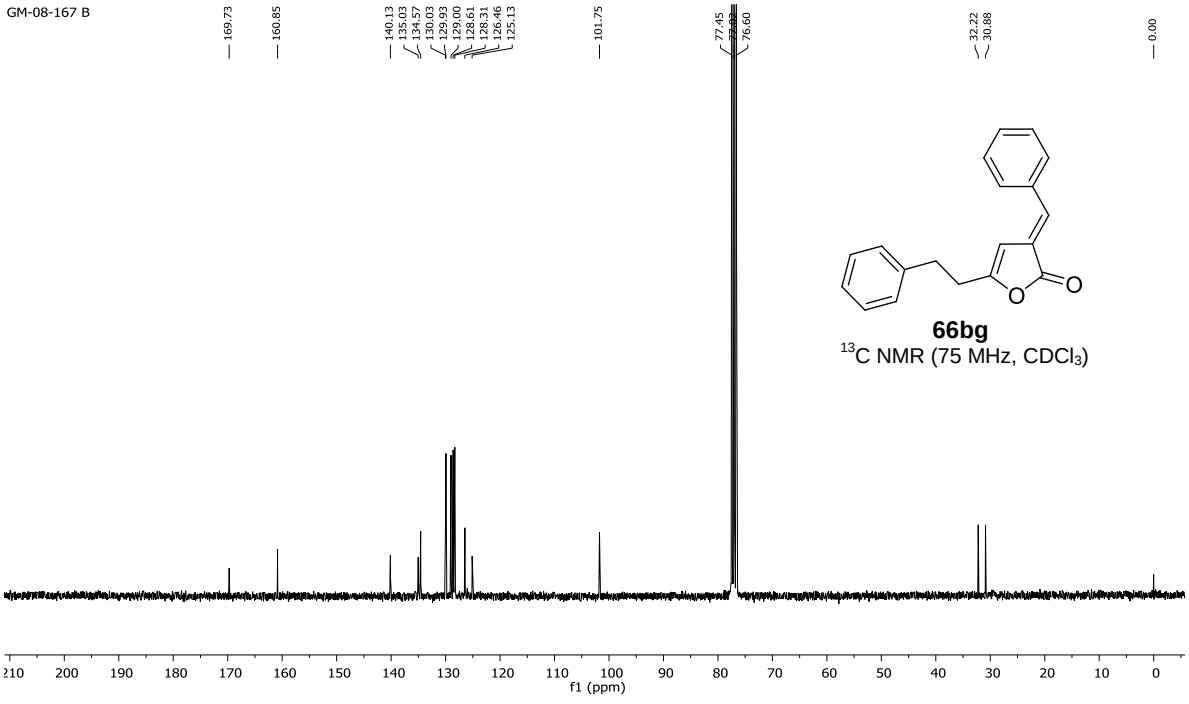


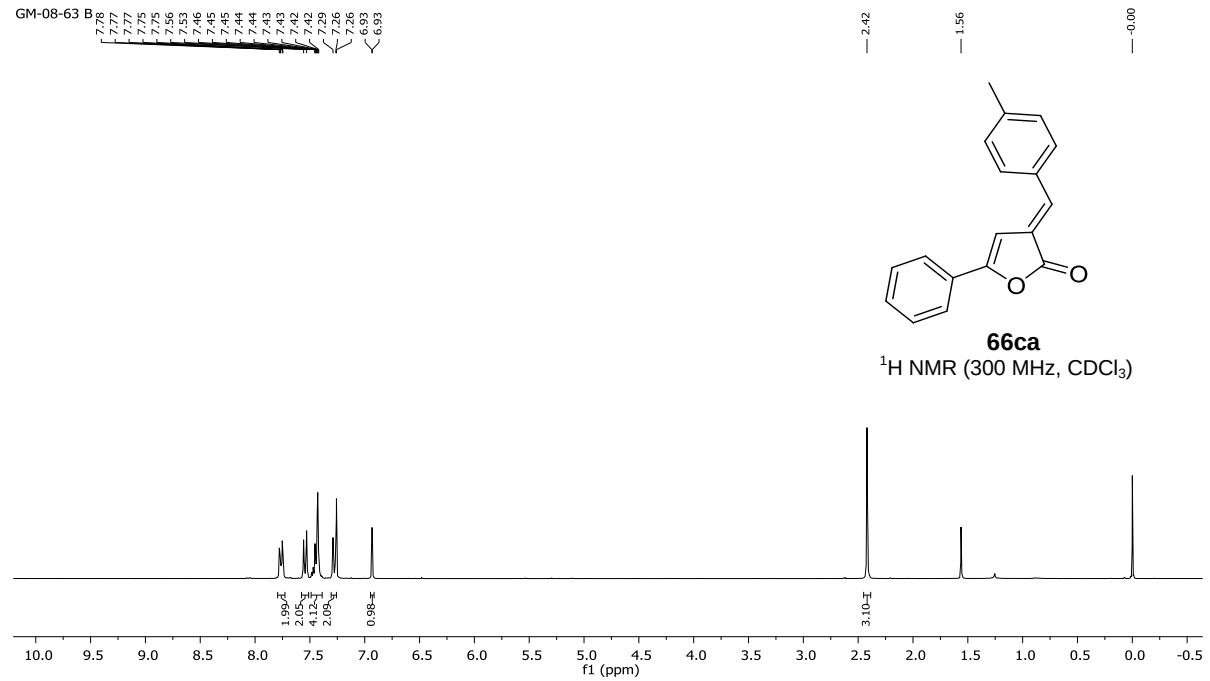


66bf

^{13}C NMR (75 MHz, $CDCl_3$)

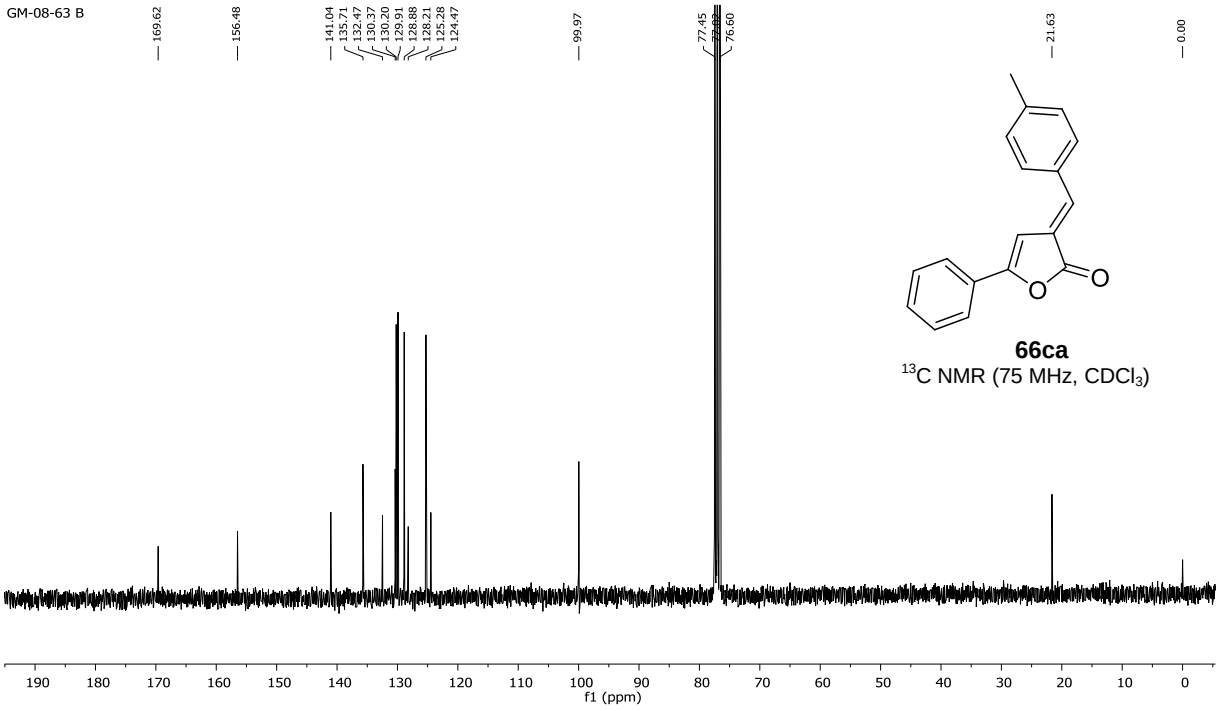

GM-08-167-B-2.fid
7.55 7.54 7.53 7.53 7.52 7.50 7.42 7.42 7.40 7.40 7.39 7.32 7.32 7.31 7.31 7.30 7.29 7.28 7.26 7.24 7.24 7.23 7.22 7.21 7.21 7.20 6.25 6.25 6.24 6.24
3.01 2.98 2.98 2.96 2.96 2.83 2.82 2.82 2.80 2.80 2.78 2.77
-0.00
O
O
66bg
1H NMR (300 MHz, CDCl3)
2.11 3.34 3.45 3.90 1.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


GM-08-167 B
169.73 160.85 140.13 135.03 134.57 130.03 129.93 129.00 128.61 128.31 126.46 125.13 101.75 77.45 77.03 76.60 32.22 30.88 0.00
O
O
66bg
13C NMR (75 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



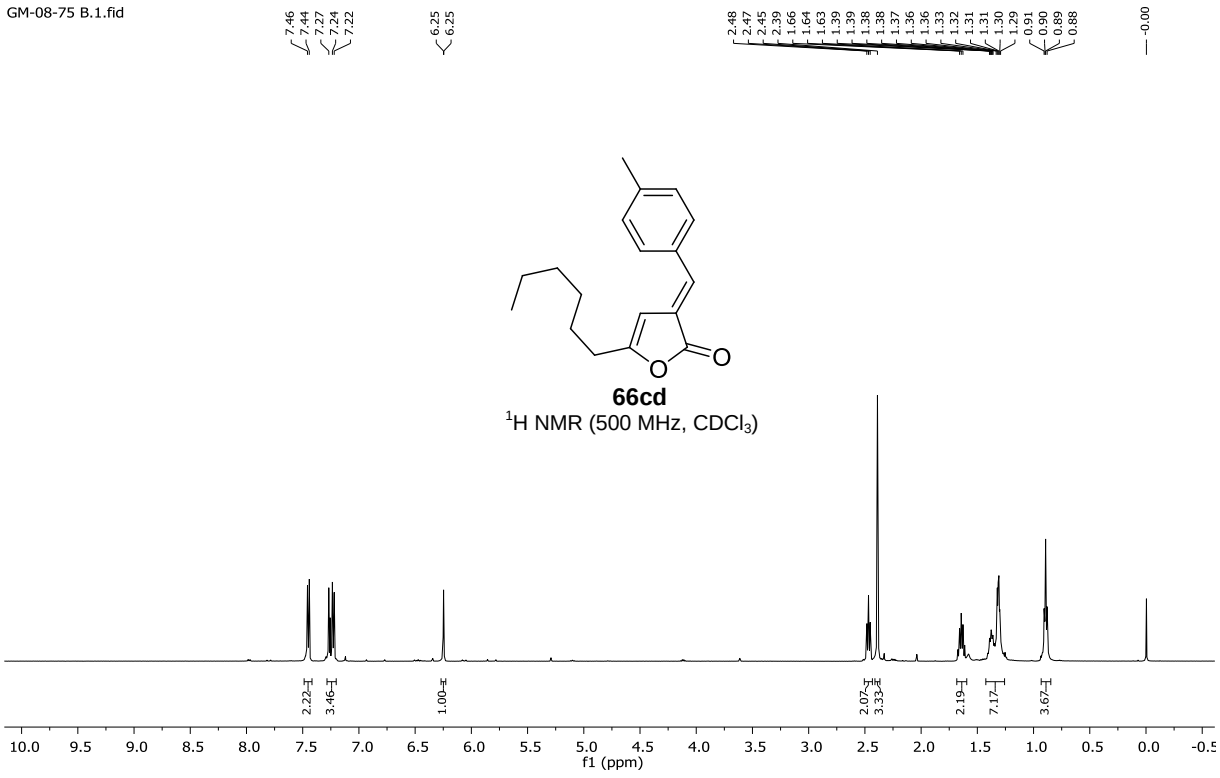
66ca

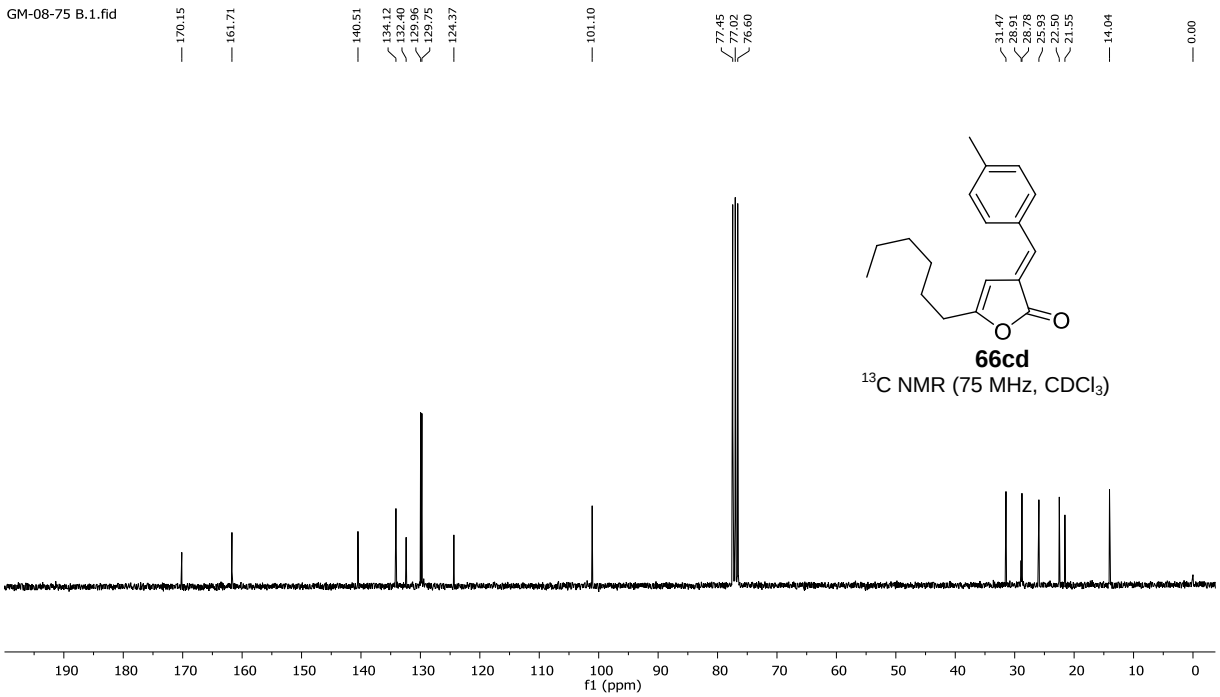
^{1}H NMR (300 MHz, $CDCl_3$)

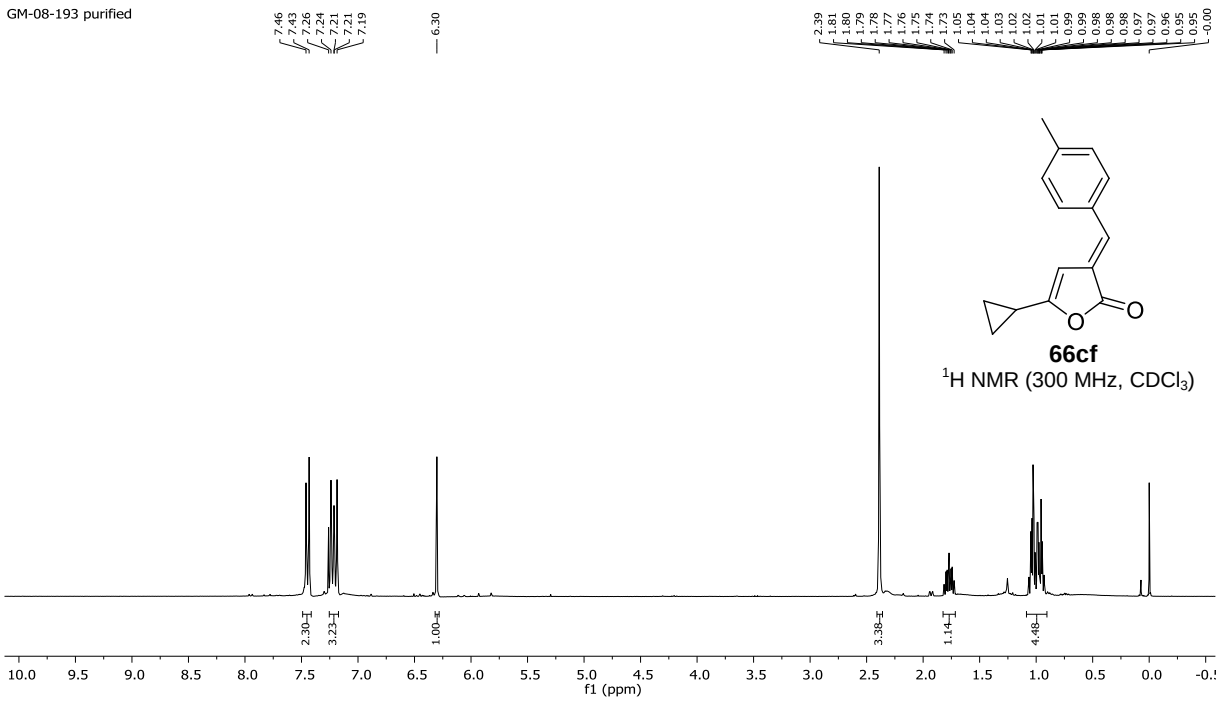


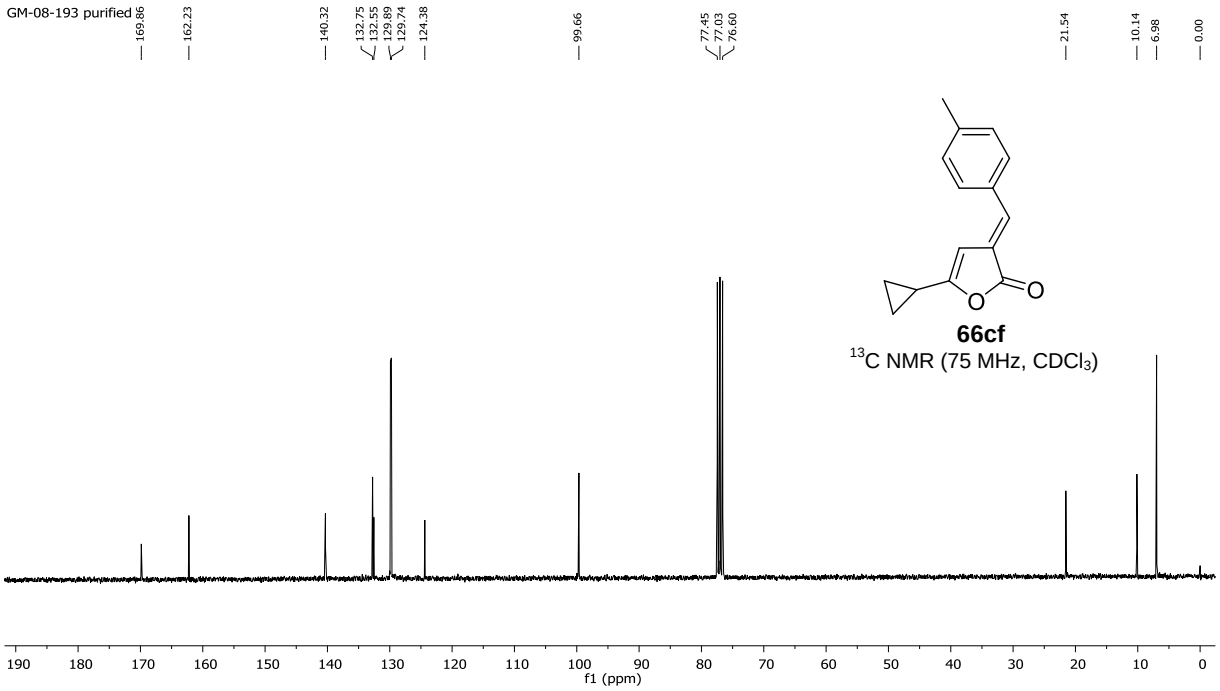
66ca

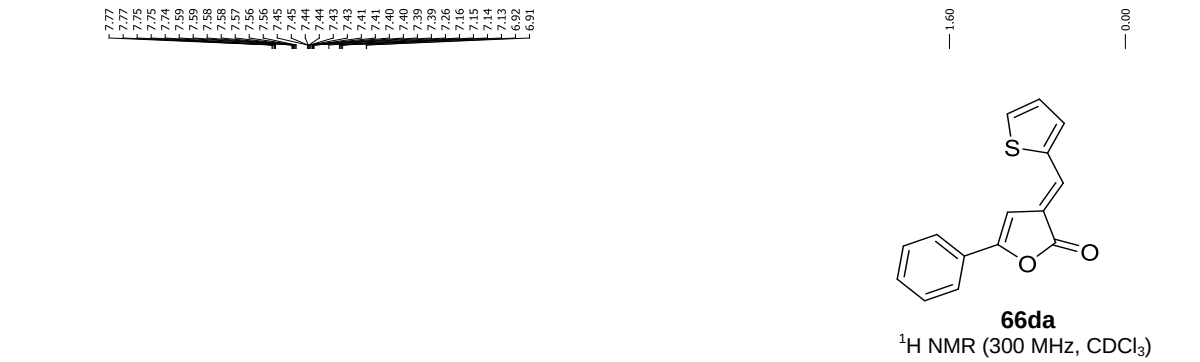
^{13}C NMR (75 MHz, $CDCl_3$)


GM-08-75 B.1.fid
7.46
7.44
7.27
7.24
7.22
6.25
6.25
2.48
2.47
2.45
2.39
1.66
1.64
1.63
1.39
1.39
1.38
1.38
1.37
1.36
1.36
1.33
1.32
1.31
1.31
1.30
1.29
0.91
0.90
0.89
0.88
-0.00
66cd
1H NMR (500 MHz, CDCl3)
2.22
3.46
1.00
2.07
3.33
2.19
7.17
3.67
f1 (ppm)


GM-08-75 B.1.fid
170.15
161.71
140.51
134.12
132.40
129.96
129.75
124.37
101.10
77.45
77.02
76.60
31.47
28.91
28.78
25.93
22.50
21.55
14.04
0.00
66cd
13C NMR (75 MHz, CDCl3)
f1 (ppm)

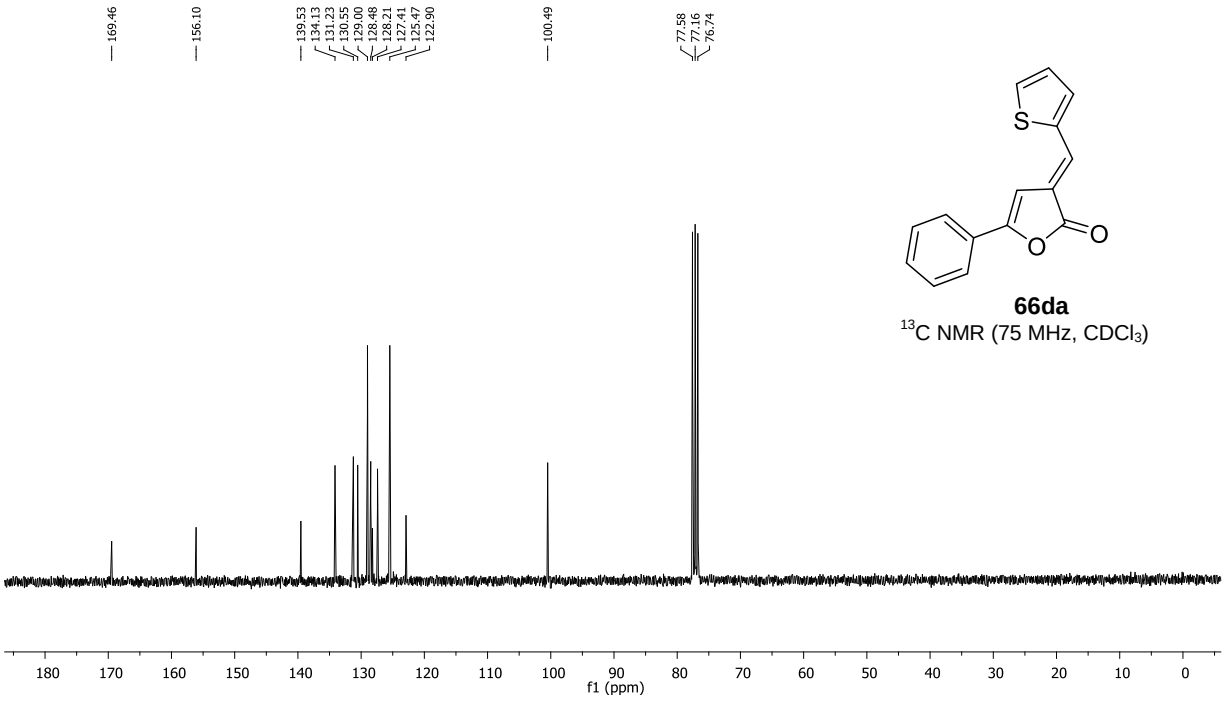

GM-08-193 purified
7.46
7.43
7.26
7.24
7.21
7.21
7.19
6.30
2.39
1.81
1.80
1.79
1.78
1.77
1.76
1.75
1.74
1.73
1.05
1.04
1.04
1.03
1.02
1.02
1.01
1.01
0.99
0.99
0.98
0.98
0.98
0.97
0.97
0.96
0.95
0.95
0.00
O
O
66cf
1H NMR (300 MHz, CDCl3)
2.30
3.23
1.00
3.38
1.14
4.48
f1 (ppm)


GM-08-193 purified
169.86
162.23
140.32
132.75
132.55
129.89
129.74
124.38
99.66
77.45
77.03
76.60
21.54
10.14
6.98
0.00
O
O
66cf
13C NMR (75 MHz, CDCl3)
f1 (ppm)



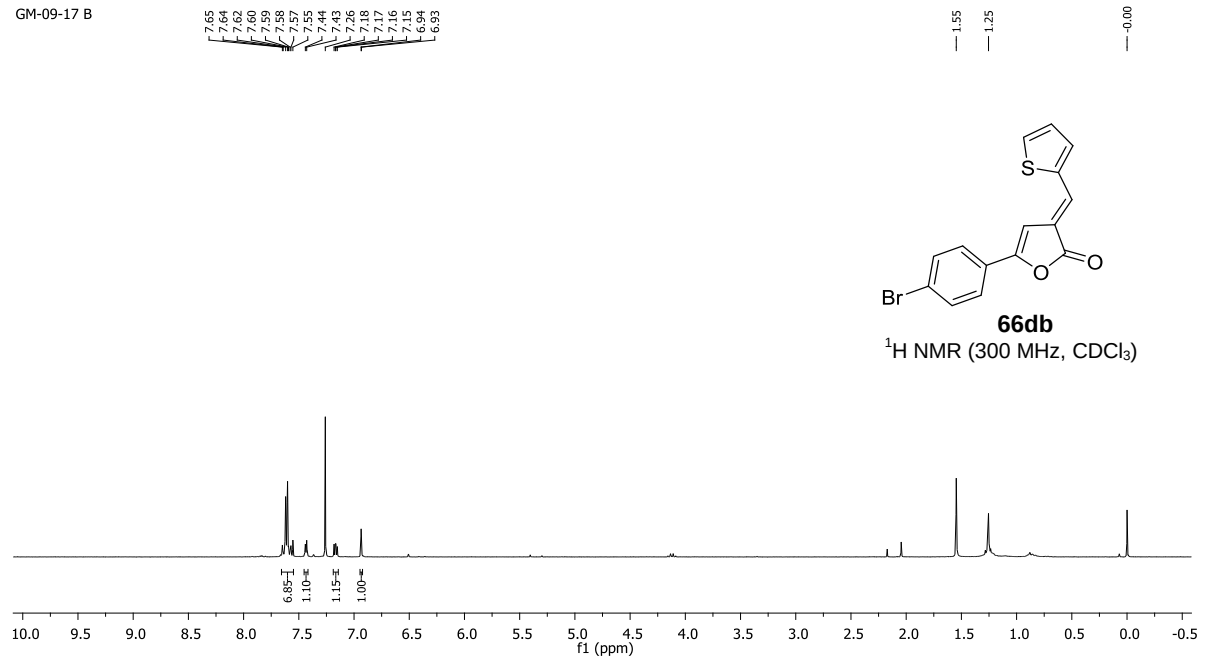
66da

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



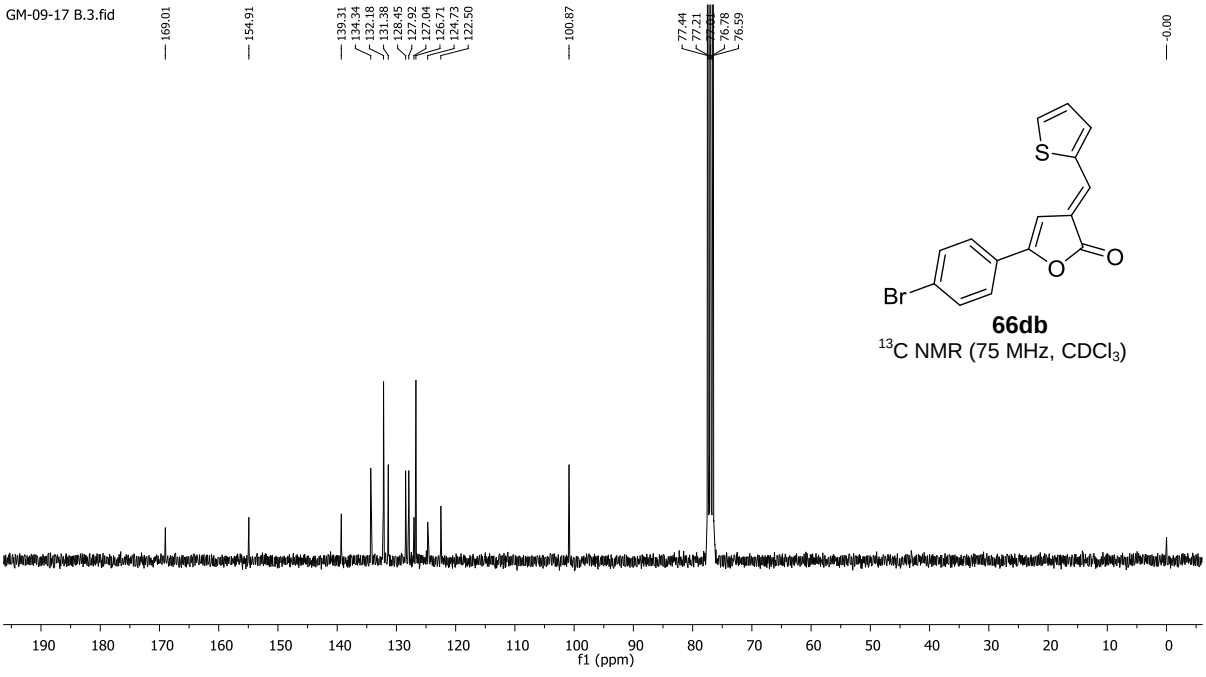
66da

^{13}C NMR (75 MHz, $CDCl_3$)



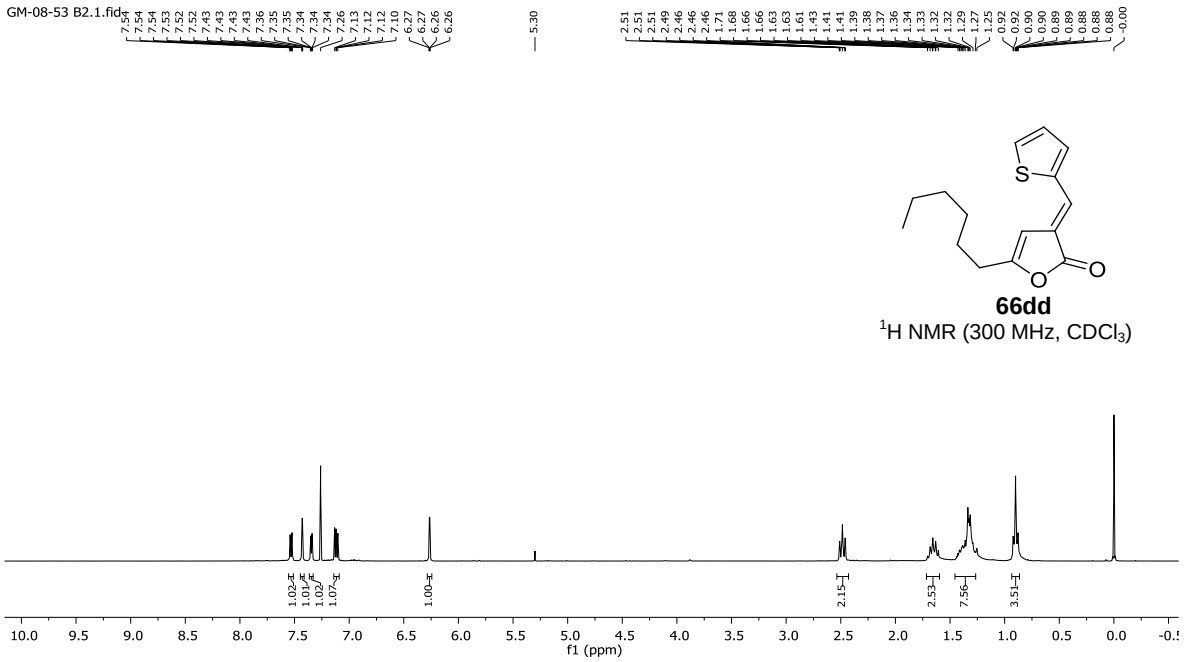
66db

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



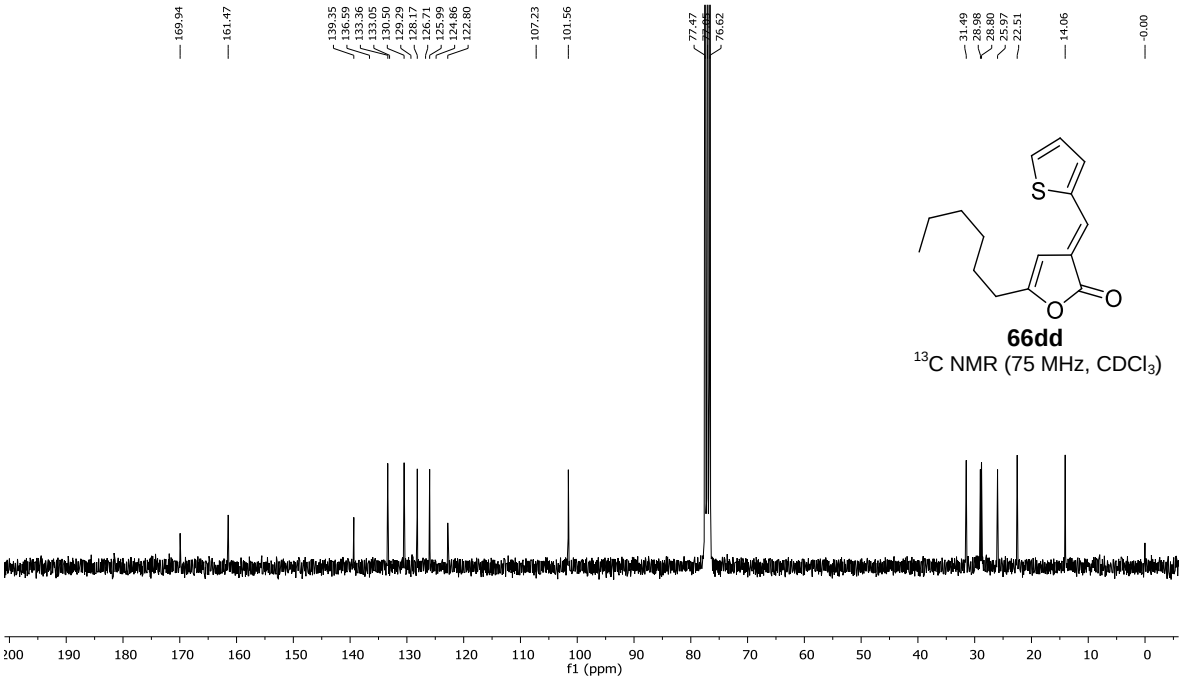
66db

^{13}C NMR (75 MHz, $CDCl_3$)



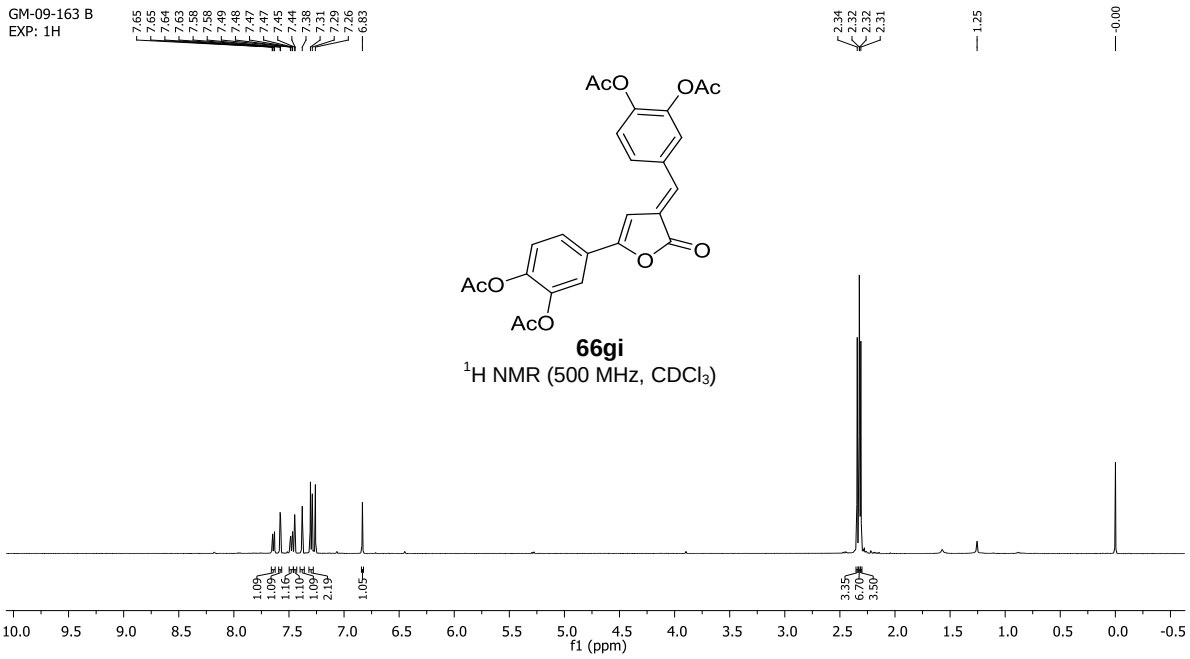
66dd

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



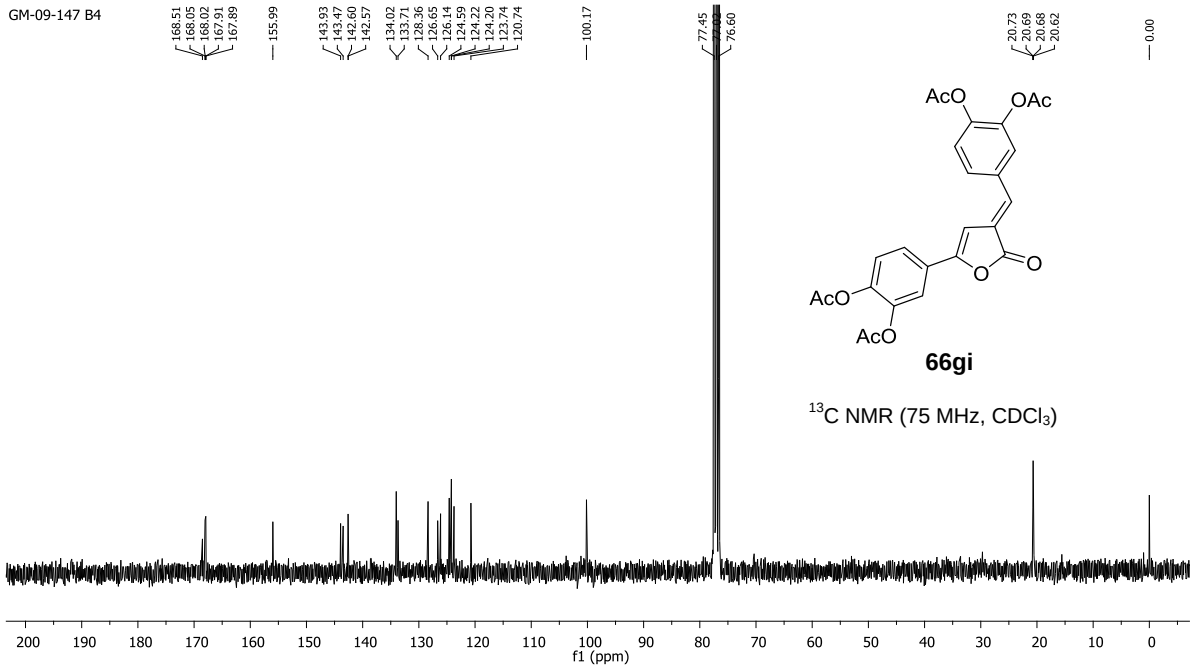
66dd

^{13}C NMR (75 MHz, $CDCl_3$)



66gi

^{1}H NMR (500 MHz, $CDCl_3$)



66gi

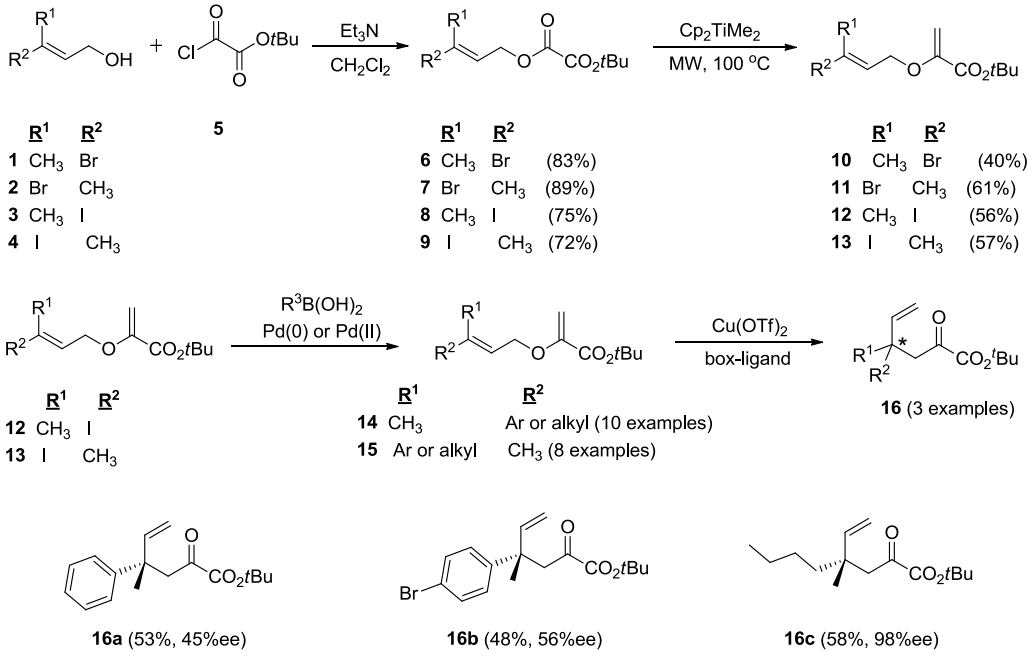
^{13}C NMR (75 MHz, $CDCl_3$)

Chapter 4

Conclusions

4.1 Summary of the thesis

An enantioselective synthesis of isolated acyclic quaternary stereocenters was developed using metal-catalyzed Gosteli-Claisen rearrangements. Esterfication of alcohols **1-4** with *t*-butyl oxalyl chloride **5** provided unsymmetrical dialkyloxalates **6-9** in 72-89% yields. Subsequent regioselctive Petasis methylenation of stereochemically pure unsymmetrical oxalates **6-9** furnished the corresponding allyl vinyl ethers **10-13** in 40-61% yields. The allyl portion was then elaborated by the introduction of aryl and alkyl substituents by stereoselective Suzuki-Miyaura cross-coupling to afford a variety of substituted allyl vinyl ethers **14** and **15**. The catalytic enantioselective Claisen rearrangement of **14** and **15** to provide **16** was investigated using chiral bis(oxazoline) complexes of $Cu(OTf)_2$ (Scheme 4.1). Details of the studies are provided in Chapter 1 of this thesis.



Scheme 4.1

In addition to the metal-catalyzed Gosteli-Claisen rearrangements, we have investigated organocatalytic version of Gosteli-Claisen rearrangement. We developed a modular synthesis of several new types of chiral cyclic phosphoramide-based organocatalysts that contain functionality that is potentially capable of double hydrogen bonding (Figure 4.1) and examined their catalytic activity for the Gosteli-Claisen rearrangements. The results of these studies are described in Chapter 2.

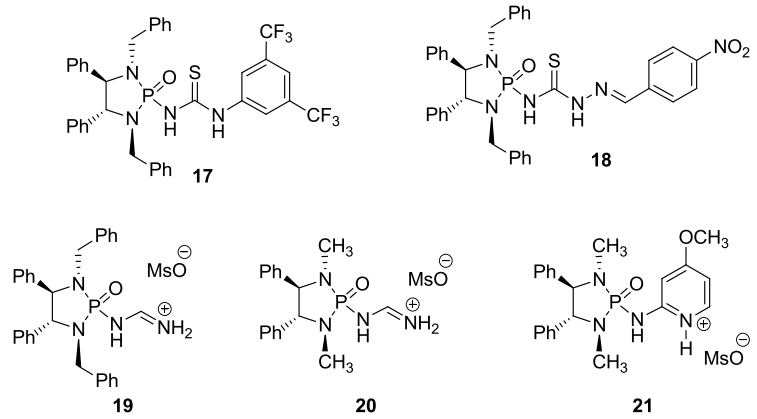
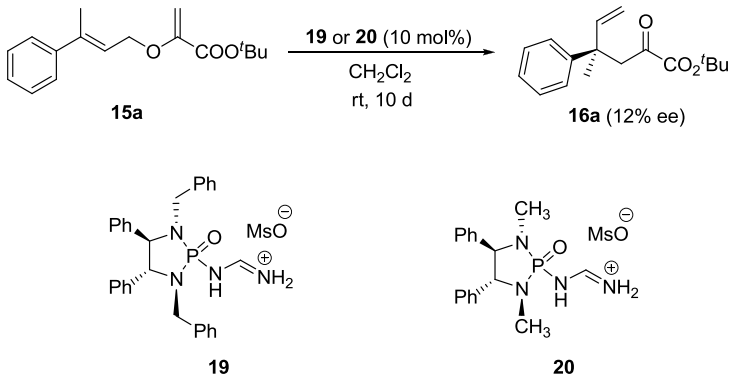


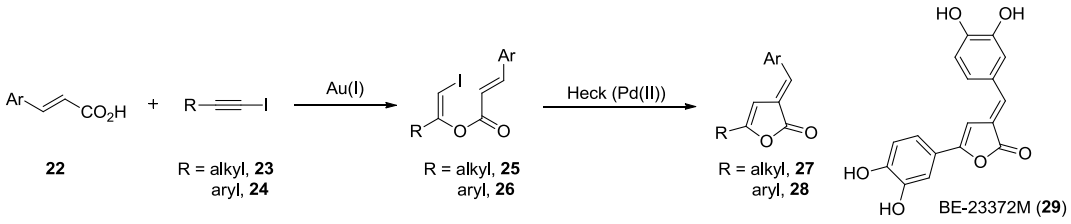
Figure 4.1

Organocatalysts **19** and **20** accelerated the Gosteli-Claisen rearrangement of **15a** and provided the **16a** containing a quaternary stereocenter, but with low enantiomeric excess (Scheme 4.2). Structural changes in the organocatalysts as well as optimization of the reactions are required, and these studies are continuing in the Pansare group.



Scheme 4.2

The *E*-3-(arylidene)-5-(alkyl/aryl)-2(3*H*)-furanone motif is found in several biologically relevant natural products. We have developed a modular, stereoselective synthesis of such furanones. The methodology features regioselective addition of *β*-aryl acrylic acids **22** to iodoalkynes **23**, **24** to furnish the *Z*-acyloxy iodoalkenes **25** and **26**. A stereoselective *5-exo-trig* Heck reaction of the enol esters generates the target *E*-3-(arylmethylidene)-5-(alkyl/aryl)-2(3*H*)-furanones **27**, **28**. The approach was applied in a formal synthesis of the naturally occurring kinase inhibitor BE-23372M **29** (Scheme 4.3). The details of the synthesis are reported in Chapter 3 of this thesis.



Scheme 4.3

4.2 Future work

It is plausible that increasing the acidity of the organocatalyst **19** by structural modification in the formamidine moiety could facilitate the binding ability of the catalyst with allyl vinyl ethers. Introducing an electron-withdrawing substituent (CCl_3) in the formamidine moiety as shown in **30** could increase the acidity of the N-H protons. Alternatively, addition of a metal salt to the organocatalyst **31** could potentially generate a metal-complex **32** in which the rigidity of the catalyst as well as the acidity of the N-H functionality are improved. The catalyst **32** would bind more effectively to the oxygen in an allyl vinyl ether and is therefore anticipated accelerate the Gosteli-Claisen rearrangement (Figure 4.2).

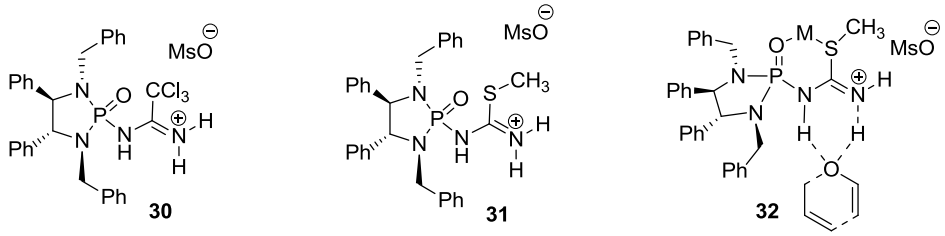
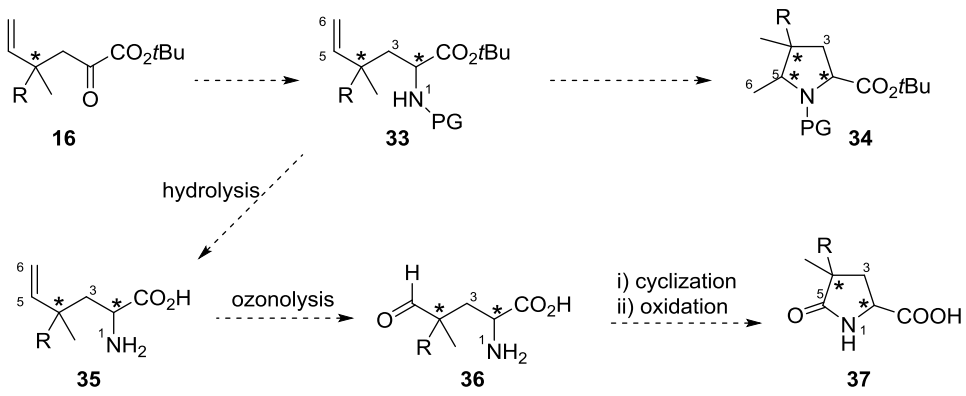


Figure 4.2

Functionalized stereocenters **16**, which were obtainded from organocatalytic Gosteli-Claisen rearrangements, may be useful for the synthesis of a variety of potentially biologically relevant molecules. For example, **16** could be converted to unnatural amino acids such as **33** by stereoselctive reductive amination. Intramolecular hydroamination of **33** would give functionalized pyrrolidines such as **34**. Hydrolysis of compound **33** followed by ozonolysis could afford amino acids **36**, from which pyroglutamic acid derivatives such as **37** could be accesible in two steps (Scheme 4.4).


CO2tBu
R
O
16
6
5
3
1
HN
PG
33
N
34
hydrolysis
CO2H
NH2
35
ozonolysis
H
36
i) cyclization
ii) oxidation
COOH
37

Scheme 4.4